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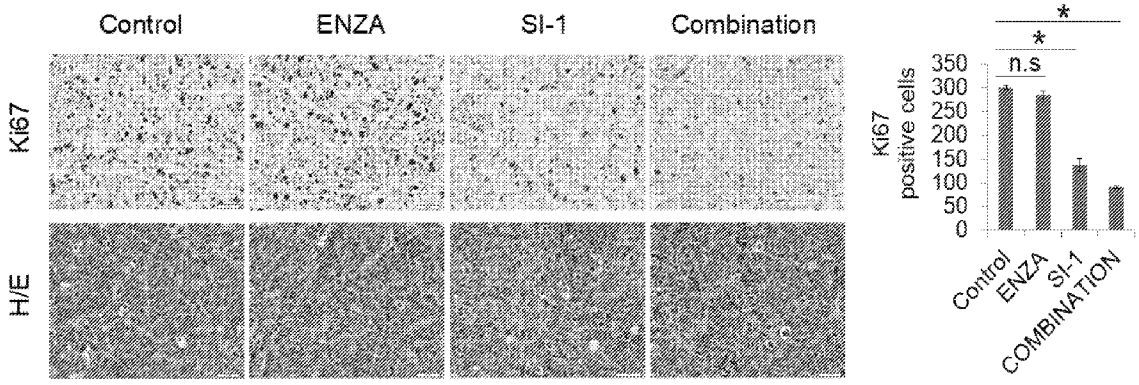
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(54) Title: COMPOUNDS, COMPOSITIONS, AND METHODS FOR TREATMENT OF ANDROGEN-MEDIATED DISEASE

FIG. 9F



(57) Abstract: Provided herein are steroid sulfatase inhibitor compounds and androgen receptor inhibitor compounds that can be useful in, for example, the treatment of cancers such as prostate cancer and breast cancer. Pharmaceutical compositions and kits including the compounds are described, as well as methods for the treatment of cancer such as prostate cancer and breast cancer.

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COMPOUNDS, COMPOSITIONS, AND METHODS FOR TREATMENT OF ANDROGEN-MEDIATED DISEASE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application claims priority to U.S. Provisional Patent Application No. 62/754,487, filed November 01, 2018, which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Prostate cancer is the second leading cause of cancer-related deaths and the most commonly diagnosed cancer in men with an estimated 220,800 new cases yearly in the United States [Ferlay, et al., Eur J Cancer, 2013. **49**(6): 1374-403; Siegel, et al., *Cancer statistics, 2015.* CA Cancer J Clin, 2015. **65**(1): 5-29]. First line treatments for prostate cancer aim to reduce circulating androgen levels through the use of androgen deprivation therapies (ADT). This is accomplished using one of two methods: surgical bilateral orchiectomy which inhibits androgen synthesis by the testes or through the use of castration-inducing drugs to reduce androgen levels and androgen receptor (AR) activation. While ADT is initially effective at reducing prostate cancer growth, after 2-3 years of treatment the majority of patients will progress to castration resistant prostate cancer (CRPC) and tumor growth will proceed even in the presence of castrate levels of androgen. At this point of disease progression, the number of therapeutic options is currently limited but is the focus of intense research to improve the outcome for patients [Harris, et al., Nat Clin Pract Urol, 2009. **6**(2): 76-85].

[0003] Clinically, CRPC is defined as progression of prostate cancer in the presence of castrate levels of circulating testosterone [Cookson, et al., J Urol, 2013. **190**(2): 429-38; Saad, et al., Can Urol Assoc J, 2010. **4**(6): p. 380-4]. Often times, the AR is either overexpressed, hyper-activated, or both leading to the transcription of downstream target genes which ultimately promotes tumor progression despite the patient having negligible levels of androgen present. The mechanisms which lead to the development of CRPC from hormone-sensitive prostate cancer are widely studied. The identified mechanisms, including AR amplification and mutation, AR co-activator and co-repressor modifications, aberrant

activation and/or post-translational modification, AR splice variants, and altered steroidogenesis, each result in an increase in AR activation and signaling. This can be due to an increased amount of androgen, enhanced response to existing androgen, and activation of the AR by non-classical ligands or no ligand at all among other methods [*see*, Dehm, et al., Cancer Res, 2008. **68**(13): 5469-77; Chang, et al., Br J Cancer, 2014. **111**(7): 1249-54; Chang, et al., Proc Natl Acad Sci U S A, 2011. **108**(33): 13728- 33; Shtivelman, et al., Oncotarget, 2014. **5**(17): 7217-59; Steketee, et al., Int J Cancer, 2002. **100**(3): p. 309-17].

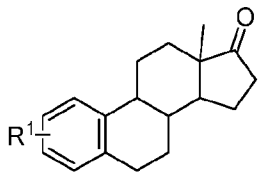
[0004] Treatment of CRPC is currently achieved with the administration of taxanes, such as docetaxel and cabazitaxel, which interrupt the growth of fast-dividing cells through disruption of microtubule function, or with next-generation antiandrogen therapies including enzalutamide and abiraterone. The primary mechanism of antiandrogens is to inhibit AR activation either directly, by antagonizing the receptor, or indirectly by blocking androgen synthesis. Unfortunately, it is estimated that one third of patients given abiraterone and one fourth of patients given enzalutamide will fail to respond to initial treatment with these drugs [de Bono, et al., N Engl J Med, 2011. **364**(21): 1995-2005; Scher, et al., N Engl J Med, 2012. **367**(13): p. 1187-97]. Furthermore, within 12-24 months of initiating treatment, even those who initially respond to the drugs will develop resistance.

[0005] Targeting androgen signaling via androgen deprivation therapy including recent approved therapies such as abiraterone and enzalutamide has been the mainstream of clinical interventions in castration resistant prostate cancer (CRPC). Despite these advances that provide temporary respite, there is still no cure for CRPC. Development of resistance to enzalutamide/abiraterone is eventually inevitable, with the development of several potential pathways of resistance [Scher, et al., Lancet, 2010. **375**(9724): 1437-46; Kim, et al., Curr Treat Options Oncol, 2012. **13**(2): 189-200.]. Recent studies have linked AR alternative splicing, particularly AR-V7, to the development of enzalutamide/abiraterone resistance [*see*, Nadiminty, et al., Mol Cancer Ther, 2013. **12**: 1629- 1637; Joseph, et al., Cancer Discov, 2013. **3**(9): 1020-9; Korpal, et al., Cancer Discov, 2013. **3**(9): 1030- 43; Nyquist, et al., Proc Natl Acad Sci U S A, 2013. **110**(43): 17492-7]. Previous studies demonstrate that uncontrolled intraprostatic androgen synthesis and elevated levels of cholesterol and its subsequent product dehydroepiandrosterone (DHEA) are observed in enzalutamide resistance cells [Liu, et al., Cancer Res, 2015. **75**(7): 1413-1422]. DHEA synthesized from cholesterol is sulfonated by DHEA sulfotransferase to DHEAS. The conversion of DHEAS to biologically active DHEA is mediated by steroid sulfatase (STS) [Purohit, et al., **212**(2): 99-

110]. Once unconjugated, DHEA is further metabolized to the active androgens that bind the androgen receptor (AR) leading to cell proliferation.

BRIEF SUMMARY OF THE INVENTION

[0006] Provided herein are compounds according to Formula I:



(I),

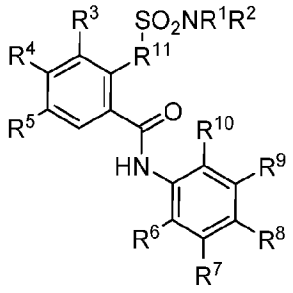
and pharmaceutically acceptable salts thereof, wherein

R^1 is $-X(SO_2)Y-$;

X is O and Y is NH, or X is NH and Y is O; and

R^1 is combined with two carbons of the phenyl group to which it is attached to form an oxathiazolidine dioxide.

[0007] Also provided herein are compounds according to Formula III



(III),

and pharmaceutically acceptable salts thereof, wherein

R^1 and R^2 are each independently hydrogen or C_{1-6} alkyl;

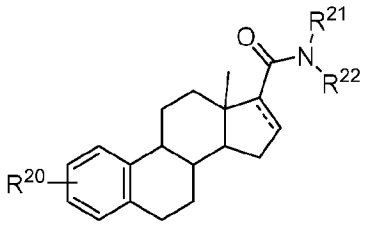
R^3, R^4, and R^5 are each independently hydrogen, halogen,-OH, C_{1-6} alkyl, or C_{1-6} alkoxy;

R^6, R^7, R^8, R^9, and R^{10} are each independently hydrogen, halogen, -OH, $-NH_3$, $-NO_2$, -CN, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkoxy;

R^{11} is a bond, C_{1-6} alkylene, NR^{12} , or O; and

R^{12} is hydrogen or C_{1-6} alkyl.

[0008] Also provided herein are pharmaceutical compositions comprising an antiandrogen drug and a compound according to Formula II:



(II),

or a pharmaceutically acceptable salt thereof, wherein:

the dashed line represents a single bond or a double bond;

R^{20} is $-O(SO_2)NR^{23}R^{24}-$, which is combined with two carbons of the phenyl group to which it is attached to form a 4- to 10-membered heterocycle, or

R^{20} is $-O(SO_2)NR^{23}R^{25}$;

R^{21}, R^{22}, R^{23}, and R^{25} are each independently hydrogen or C_{1-6} alkyl; and

R^{24} is a bond, C_{1-6} alkylene, or C_{1-6} alkenylene.

[0009] Steroid sulfatase inhibitors (STSi's, e.g., compounds and according to Formula I and/or Formula II) and androgen receptor inhibitors (e.g., compounds according to Formula II) can be used to enhance the therapeutic benefit of antiandrogens (e.g., bicalutamide, enzalutamide, abiraterone, darolutamide, and the like) and chemotherapeutics such as docetaxel. Also provided herein are methods for treating conditions such as cancer (e.g., prostate cancer or breast cancer). The methods include administering a compound of Formula I, Formula II, or Formula III to a subject in need thereof. In some embodiments, the methods also include administration of an antiandrogen.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1A shows the structures of STSi's Si-1 to Si-5.

[0011] FIG. 1B shows the structures of STSi's Si-6 to Si-10.

[0012] FIG. 2 shows that STSi's inhibit STS activity. VCaP cells were treated with increasing doses of either Si-1 (left panel) or Si-2 (right panel) and STS activity was measured by microtiter plate cellular assay using fluorescence readout.

[0013] FIG. 3 shows the characterization of STSi's (Si-1 to Si-10) on STS enzymatic activity in VCaP cells. VCaP cells were treated with 5 μM of different STSi, and STS activity was measured by microtiter plate cellular assay using fluorescence readout.

[0014] FIG. 4 shows that STSi's inhibit prostate cancer cell growth. LNCaP, C4-2B, CWR22rv1 (rv1), DU145, PC3, and VCaP Prostate cancer cells were treated with increasing

doses of either Si-1 (left panel) or Si-2 (right panel) for 48 hrs and the cell number were counted.

[0015] FIG. 5 shows the growth effects of STSi's on C4-2B cells. C4-2B prostate cancer cells were treated with increasing doses of different STSi for 48 hrs and the cell number were counted.

[0016] FIG. 6 shows that STSi's enhance enzalutamide treatment. Enzalutamide resistant C4-2BMDVR cells (left panels) and CWR22rv1 cells (right panels) were treated Si-1 (top panels) or Si-2 (bottom panels) either alone or with enzalutamide and cell number was counted.

[0017] Fig 7 shows that STSi's enhance abiraterone treatment. Abiraterone resistant C4-2BAbiR cells (left panels) and CWR22rv1 cells (right panels) were treated Si-1 (top panels) or Si-2 (bottom panels) either alone or with abiraterone and cell number was counted.

[0018] FIG. 8A shows tumor volume in mice after VCaP xenografting, castration and tumor relapse, plotted over a 3-week course of treatment with vehicle control, Si-1 (25 mg/Kg i.p) or Si-2 (25mg/Kg i.p).

[0019] FIG. 8B shows images of tumors collected from the treatment groups after 3 weeks.

[0020] FIG. 8C shows a plot of tumor weight collected after 3 weeks of treatment.

[0021] FIG. 8D shows a plot of body weight across treatment groups, monitored twice weekly.

[0022] FIG. 8E shows the PSA level in mouse serum, collected after 3 weeks of treatment, determined for each treatment group ELISA assay.

[0023] FIG 8F shows IHC staining for Ki67, AR and H/E in each group. Numerical data obtained from the micrographs at left are shown at right. * $p<0.05$. Taken together FIGS. 8A-8E demonstrate that STSi's inhibit resistant VCaP tumor growth.

[0024] FIG. 9A. shows total cell numbers determined in VCaP cell culture, treated with 10 μM or 25 μM Si-1 or Si-2 with or without 20 μM enzalutamide for 3 days.

[0025] FIG. 9B shows the quantitation of luciferase expression in VCaP cells transiently transfected with control siRNA, STS siRNA, and PSA luciferase plasmid, following treated with 10 μM enzalutamide for 24 hours.

[0026] FIG. 9C. shows a Western blot analysis of VCaP cell lysates, prepared from cells treated with 25 μM Si-1 or Si-2 with or without 20 μM enzalutamide for 3 days.

[0027] FIG. 9D shows tumor volume in mice after VCaP xenografts, castration, and tumor relapse, plotted over a 3-week course of treatment with vehicle control, enzalutamide (25 mg/Kg p.o), Si-1 (25 mg/Kg i.p) or their combination. Tumor volumes were determined twice weekly.

[0028] FIG. 9E shows a plot of tumor weight collected from the treatment groups after 3 weeks.

[0029] FIG. 9F shows IHC staining for Ki67 and H/E staining in each group. Numerical data obtained from micrographs at left are shown at right. * $p<0.05$. Taken together, FIGS. 9E-9F demonstrate that STSi's improve enzalutamide treatment *in vitro* and *in vivo*.

[0030] Fig 10 shows that STSi's inhibit breast cancer cell growth. MCF-7, MDA-MB-468, and MDA-MB-231 breast cancer cells were treated with increasing doses of either Si-1 (left panel) or Si-2 for 48 hrs (right panel), and the cell numbers were counted.

[0031] FIG. 11 shows the structure of niclosamide-sulfamate.

[0032] FIG. 12A shows total cell number in CWR22Rv1 culture treated with 0.5 μM niclosamide sulfamate (Nic-S) with or without 20 μM enzalutamide (ENZA) or 5 μM abiraterone acetate (AA), determined at 3 and 5 days.

[0033] FIG. 12B shows a Western blot analysis of C4-2B MDVR cell lysates prepared after treatment with different concentrations of Nic-S.

[0034] FIG. 12C shows a plot of tumor volume in mice bearing CWR22-rv1 tumors, over the course of combination treatment with Nic-S and enzalutamide.

[0035] FIG. 12D shows a blot of body weight measured for mice bearing CWR22-rv1 tumors, treated with enzalutamide, abiraterone acetate, or a combination thereof. *$p<0.05$. Taken together, FIGS. 12A-12D demonstrate that Nic-S synergistically enhances Enza/AA treatment and suppresses Wnt5A expression.

DETAILED DESCRIPTION OF THE INVENTION

[0036] The present invention is based, in part, on the development of new compounds that can be used as steroid sulfatase inhibitors and androgen receptor inhibitors in the treatment of cancers including, without limitation, prostate cancer and breast cancer. It has also been discovered that these compounds are surprisingly effective when used in conjunction with antiandrogen drugs such as enzalutamide. The therapeutic agents and methods provided herein have been found to be effective in treating castration resistant prostate cancer and improving the efficacy of enzalutamide treatment.

I. Definitions

[0037] As used herein, the term "alkyl," by itself or as part of another substituent, refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{1-6}, C_{1-7}, C_{1-8}, C_{1-9}, C_{1-10}, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{3-4}, C_{3-5}, C_{3-6}, C_{4-5}, C_{4-6}, and C_{5-6}. For example, C_{1-6} alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc. Alkyl can also refer to alkyl groups having up to 20 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Alkyl groups can be substituted or unsubstituted. Unless otherwise specified, "substituted alkyl" groups may be substituted with one or more groups selected from halo, hydroxy, amino, alkylamino, amido, acyl, nitro, cyano, and alkoxy.

[0038] As used herein, the term "alkoxy," by itself or as part of another substituent, refers to a group having the formula –OR, wherein R is alkyl as described above.

[0039] As used herein, the term "alkylene" refers to an alkyl group, as defined above, linking at least two other groups (*i.e.*, a divalent alkyl radical such as "methylene" having the structure $–CH_2–$). The two moieties linked to the alkylene group can be linked to the same carbon atom or different carbon atoms of the alkylene group.

[0040] As used herein, the term "alkenyl," by itself or as part of another substituent, refers to a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one double bond. Alkenyl can include any number of carbons, such as C_2, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{2-7}, C_{2-8}, C_{2-9}, C_{2-10}, C_3, C_{3-4}, C_{3-5}, C_{3-6}, C_4, C_{4-5}, C_{4-6}, C_5, C_{5-6}, and C_6. Alkenyl groups can have any suitable number of double bonds, including, but not limited to, 1, 2, 3, 4, 5 or more. Examples of alkenyl groups include, but are not limited to, vinyl (ethenyl), propenyl, isopropenyl, 1-butenyl, 2-butenyl, isobutenyl, butadienyl, 1-pentenyl, 2-pentenyl,

isopentenyl, 1,3-pentadienyl, 1,4-pentadienyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,5-hexadienyl, 2,4-hexadienyl, or 1,3,5-hexatrienyl. Alkenyl groups can be substituted or unsubstituted. Unless otherwise specified, "substituted alkenyl" groups may be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, alkoxy, haloalkyl, carboxy, amido, nitro, oxo, and cyano.

[0041] As used herein, the term "alkenylene" refers to an alkenyl group, as defined above, linking at least two other groups (*i.e.*, a divalent alkenyl radical such as "methine" having the structure –CH=). The two moieties linked to the alkenylene group can be linked to the same carbon atom or different carbon atoms of the alkenylene group.

[0042] As used herein, the term "alkynyl," by itself or as part of another substituent, refers to either a straight chain or branched hydrocarbon having at least 2 carbon atoms and at least one triple bond. Alkynyl can include any number of carbons, such as C_2, C_{2-3}, C_{2-4}, C_{2-5}, C_{2-6}, C_{2-7}, C_{2-8}, C_{2-9}, C_{2-10}, C_3, C_{3-4}, C_{3-5}, C_{3-6}, C_4, C_{4-5}, C_{4-6}, C_5, C_{5-6}, and C_6. Examples of alkynyl groups include, but are not limited to, acetylenyl, propynyl, 1-butynyl, 2-butynyl, isobutynyl, sec-butynyl, butadiynyl, 1-pentynyl, 2-pentynyl, isopentynyl, 1,3-pentadiynyl, 1,4-pentadiynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 1,3-hexadiynyl, 1,4-hexadiynyl, 1,5-hexadiynyl, 2,4-hexadiynyl, or 1,3,5-hexatriynyl. Alkynyl groups can be substituted or unsubstituted. Unless otherwise specified, "substituted alkynyl" groups may be substituted with one or more moieties selected from halo, hydroxy, amino, alkylamino, alkoxy, haloalkyl, carboxy, amido, nitro, oxo, and cyano.

[0043] As used herein, the terms "halo" and "halogen" refer to fluorine, chlorine, bromine and iodine.

[0044] As used herein, the term "haloalkyl," by itself or as part of another substituent, refers to an alkyl group where some or all of the hydrogen atoms are replaced with halogen atoms. As for alkyl groups, haloalkyl groups can have any suitable number of carbon atoms, such as C_{1-6}. For example, haloalkyl includes trifluoromethyl, fluoromethyl, *etc.* In some instances, the term "perfluoro" can be used to define a compound or radical where all the hydrogens are replaced with fluorine. For example, perfluoromethyl refers to 1,1,1-trifluoromethyl.

[0045] As used herein the term "heterocyclyl," by itself or as part of another substituent, refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. Additional heteroatoms can also be useful, including, but not

limited to, B, Al, Si and P. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -$S(O)_2$-. Heterocyclyl groups can include any number of ring atoms, such as, C_{3-6}, C_{4-6}, C_{5-6}, C_{3-8}, C_{4-8}, C_{5-8}, C_{6-8}, C_{3-9}, C_{3-10}, C_{3-11}, or C_{3-12}, wherein at least one of the carbon atoms is replaced by a heteroatom. Any suitable number of carbon ring atoms can be replaced with heteroatoms in the heterocyclyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. The heterocyclyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. The heterocyclyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline. Heterocyclyl groups can be unsubstituted or substituted. Unless otherwise specified, "substituted heterocyclyl" groups can be substituted with one or more groups selected from halo, hydroxy, amino, oxo (=O), alkylamino, amido, acyl, nitro, cyano, and alkoxy.

[0046] The heterocyclyl groups can be linked via any position on the ring. For example, aziridine can be 1- or 2-aziridine, azetidine can be 1- or 2- azetidine, pyrrolidine can be 1-, 2- or 3-pyrrolidine, piperidine can be 1-, 2-, 3- or 4-piperidine, pyrazolidine can be 1-, 2-, 3-, or 4-pyrazolidine, imidazolidine can be 1-, 2-, 3- or 4-imidazolidine, piperazine can be 1-, 2-, 3- or 4-piperazine, tetrahydrofuran can be 1- or 2-tetrahydrofuran, oxazolidine can be 2-, 3-, 4- or 5-oxazolidine, isoxazolidine can be 2-, 3-, 4- or 5-isoxazolidine, thiazolidine can be 2-, 3-, 4- or 5-thiazolidine, isothiazolidine can be 2-, 3-, 4- or 5- isothiazolidine, and morpholine can be 2-, 3- or 4-morpholine.

[0047] When heterocyclyl includes 3 to 8 ring members and 1 to 3 heteroatoms, representative members include, but are not limited to, pyrrolidine, piperidine, tetrahydrofuran, oxane, tetrahydrothiophene, thiane, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, morpholine, thiomorpholine, dioxane and dithiane. Heterocyclyl can also form a ring having 5 to 6 ring members and 1 to 2 heteroatoms, with representative members including, but not limited to, pyrrolidine, piperidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, and morpholine.

[0048] As used herein, the term "hydroxy" refers to the moiety –OH.

[0049] As used herein, the term "oxo" refers to an oxygen atom that is double-bonded to a compound (*i.e.*, O=).

[0050] As used herein, the term "amino" refers to a moiety $–NR_2$, wherein each R group is H or alkyl. An amino moiety can be ionized to form the corresponding ammonium cation. "Alkylamino" refers to an amino moiety wherein at least one of the R groups is alkyl.

[0051] As used herein, the term "amido" refers to a moiety –NRC(O)R or $–C(O)NR_2$, wherein each R group is H or alkyl.

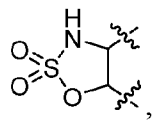
[0052] As used herein, the term "acyl" refers to the moiety –C(O)R, wherein each R group is alkyl.

[0053] As used herein, the term "nitro" refers to the moiety $–NO_2$.

[0054] As used herein, the term "cyano" refers to a carbon atom triple-bonded to a nitrogen atom (*i.e.*, the moiety –C≡N).

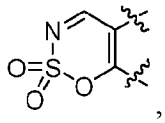
[0055] As used herein, the term "carboxy" refers to the moiety –C(O)OH.

[0056] As used herein, the term "oxathiazolidine dioxide" refers to a moiety having the structure:



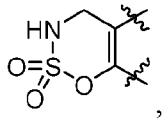
wherein the wavy lines indicate points of attachment to other atoms in the molecule containing the oxathiazolidine dioxide.

[0057] As used herein, the term "oxathiazine dioxide" refers to a moiety having the structure:



wherein the wavy lines indicate points of attachment to other atoms in the molecule containing the oxathiazine dioxide.

[0058] As used herein, the term "dihydro-oxathiazine dioxide" refers to a moiety having the structure:



wherein the wavy lines indicate points of attachment to other atoms in the molecule containing the dihydro-oxathiazine dioxide.

[0059] As used herein, the term "salt" refers to an acid salt or base salt of an active agent such as a steroid sulfatase inhibitor or an androgen receptor inhibitor. Acid salts of basic active agents include mineral acid salts (*e.g.*, salts formed by using hydrochloric acid, hydrobromic acid, phosphoric acid, and the like), organic acid salts (*e.g.*, salts formed using acetic acid, propionic acid, glutamic acid, citric acid, and the like), and quaternary ammonium salts (*e.g.*, salts formed via reaction of an amine with methyl iodide, ethyl iodide, or the like). It is understood that the pharmaceutically acceptable salts are non-toxic.

[0060] Acidic active agents may be contacted with bases to provide base salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

[0061] The neutral forms of the active agents can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner if desired. In some embodiments, the parent form of the compound may differ from various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts forms may be equivalent to the parent form of the compound.

[0062] By "pharmaceutically acceptable," it is meant that the excipient is compatible with the other ingredients of the formulation and is not deleterious to the recipient thereof. As used herein, the term "pharmaceutically acceptable excipient" refers to a substance that aids the administration of an active agent to a subject. Useful pharmaceutical excipients include, but are not limited to, binders, fillers, disintegrants, lubricants, glidants, coatings, sweeteners, flavors and colors.

[0063] As used herein, the terms "effective amount" and "therapeutically effective amount" refer to a dose of a compound such a steroid sulfatase inhibitor, an androgen receptor inhibitor, or an antiandrogen that produces therapeutic effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see*, *e.g.*, Lieberman, *Pharmaceutical Dosage*

Forms (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition, 2006, Brunton, Ed., McGraw-Hill; and *Remington: The Science and Practice of Pharmacy*, 21st Edition, 2005, Hendrickson, Ed., Lippincott, Williams & Wilkins).

[0064] As used herein, the term "cancer" is intended to include any member of a class of diseases characterized by the uncontrolled growth of aberrant cells. The term includes all known cancers and neoplastic conditions, whether characterized as malignant, benign, recurrent, soft tissue, or solid, and cancers of all stages and grades including advanced, recurrent, pre- and post-metastatic cancers. Additionally, the term includes androgen-independent, castrate-resistant, castration recurrent, hormone-resistant, drug-resistant, and metastatic castrate-resistant cancers. Examples of different types of cancer include, but are not limited to, prostate cancer (*e.g.*, prostate adenocarcinoma); breast cancers (*e.g.*, triple-negative breast cancer, ductal carcinoma *in situ*, invasive ductal carcinoma, tubular carcinoma, medullary carcinoma, mucinous carcinoma, papillary carcinoma, cribriform carcinoma, invasive lobular carcinoma, inflammatory breast cancer, lobular carcinoma *in situ*, Paget's disease, Phyllodes tumors); gynecological cancers (*e.g.*, ovarian, cervical, uterine, vaginal, and vulvar cancers); lung cancers (*e.g.*, non-small cell lung cancer, small cell lung cancer, mesothelioma, carcinoid tumors, lung adenocarcinoma); digestive and gastrointestinal cancers such as gastric cancer (*e.g.*, stomach cancer), colorectal cancer, gastrointestinal stromal tumors (GIST), gastrointestinal carcinoid tumors, colon cancer, rectal cancer, anal cancer, bile duct cancer, small intestine cancer, and esophageal cancer; thyroid cancer; gallbladder cancer; liver cancer; pancreatic cancer; appendix cancer; renal cancer (*e.g.*, renal cell carcinoma); cancer of the central nervous system (*e.g.*, glioblastoma, neuroblastoma); skin cancer (*e.g.*, melanoma); bone and soft tissue sarcomas (*e.g.*, Ewing's sarcoma); lymphomas; choriocarcinomas; urinary cancers (*e.g.*, urothelial bladder cancer); head and neck cancers; and bone marrow and blood cancers (*e.g.*, chronic lymphocytic leukemia, lymphoma). As used herein, a "tumor" comprises one or more cancerous cells.

[0065] As used herein, the terms "antiandrogen" and "antiandrogen drug" refer to compounds that alter the androgen pathway by blocking the androgen receptors, competing for binding sites on the cell's surface, or affecting or mediating androgen production. Antiandrogens are useful for treating several diseases including, but not limited to, prostate

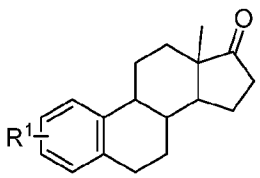
cancer. Examples of antiandrogens include, but are not limited to, enzalutamide, abiraterone, bicalutamide, and darolutamide..

[0066] As used herein, the terms "about" and "around" indicate a close range around a numerical value when used to modify that specific value. If "X" were the value, for example, "about X" or "around X" would indicate a value from 0.9X to 1.1X, *e.g.*, a value from 0.95X to 1.05X, or a value from 0.98X to 1.02X, or a value from 0.99X to 1.01X. Any reference to "about X" or "around X" specifically indicates at least the values X, 0.9X, 0.91X, 0.92X, 0.93X, 0.94X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, 1.05X, 1.06X, 1.07X, 1.08X, 1.09X, and 1.1X, and values within this range.

II. Steroid Sulfatase Inhibitors

[0067] Development of resistance to enzalutamide/abiraterone is eventually inevitable Emerging clinical evidence showed the serum level of DHEAS concentration is highly elevated in advanced prostate cancer, and may serve as an ample pool for intracrine androgen synthesis. STS is an enzyme involved in the local production of androgens and estrogens in target organs [Purohit, *supra*]. The present invention was developed, in part, to identify new steroid sulfatase inhibitors for blocking STS activity as a therapeutic approach to treat STS-activated hormone related cancers, including resistant prostate and breast cancers. As described in more detail below, several STS inhibitors (STSi's) were synthesized and found to inhibit STS activity in prostate cancer cells. Inhibition of STS by STSi's inhibited the growth of enzalutamide-resistant C4-2B MDVR cells, abiraterone-resistant C4-2BAbiR cells, and VCaP and CWR22Rv1 cells. STSi resensitized enzalutamide-resistant C4-2B MDVR and CWR22Rv1 cells to enzalutamide treatment. Similarly, STSi's also resensitized abiraterone resistant cells to abiraterone treatment. Furthermore, STSi's significantly inhibited tumor growth of resistant VCaP prostate tumor growth in castrated male mice. Additionally, it was demonstrated that STSi's inhibited the growth of resistant MDA-MB-231 breast cancer cells.

[0068] Accordingly, provided herein are compounds according to Formula I:



(I),

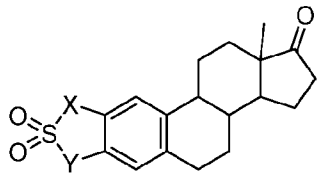
and pharmaceutically acceptable salts thereof, wherein:

R^1 is $-X(SO_2)Y-$;

X is O and Y is NH, or X is NH and Y is O; and

R^1 is combined with two carbons of the phenyl group to which it is attached to form an oxathiazolidine dioxide.

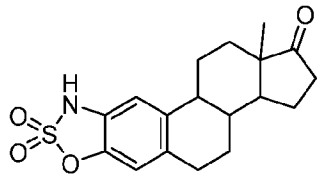
[0069] In some embodiments, the compound has a structure according to Formula Ia:



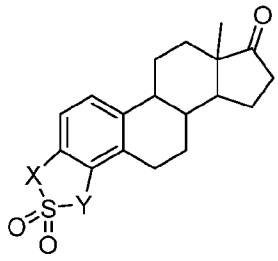
(Ia),

wherein one of X and Y is NH, and wherein the other of X and Y is O.

[0070] In some embodiments, the compound is:



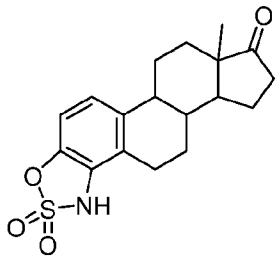
[0071] In some embodiments, the compound has a structure according to Formula Ib:



(Ib),

wherein one of X and Y is NH, and wherein the other of X and Y is O.

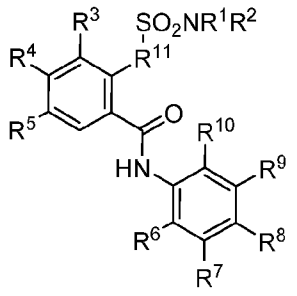
[0072] In some embodiments, the compound of Formula Ib is



III. Androgen Receptor Inhibitors

[0073] Androgen receptor (AR) variants are known to be upregulated in certain cancers such as castration-resistant prostate cancer (CRPC). Expression of AR variants is associated with prostate cancer progression and resistance to AR-targeted therapy (Mostaghel et al., Clin Cancer Res 2011; 17:5913–25; Schrader et al., Eur Urol 2013; 64:169–70; Zhang et al., PLoS One 2011; 6:e27970; Sun et al., J Clin Invest 2010; 120:2715–30). AR variant AR-V7, which is encoded by contiguous splicing of AR exons 1/2/3/CE3, is known for its prevalence in prostate cancer samples (7, 12, 16) and can induce castration resistant cell growth in vitro and in vivo (7, 17). The present inventors previously found that niclosamide (2′,5-dichloro-4′-nitrosalicylanilide) can be used as an AR inhibitor to overcome enzalutamide resistance and enhances enzalutamide therapy in prostate cancer cells.

[0074] Also provided herein are compounds according to Formula III:



(III),

and pharmaceutically acceptable salts thereof, wherein:

R^1 and R^2 are each independently hydrogen or C_{1-6} alkyl;

R^3, R^4, and R^5 are each independently hydrogen, halogen,-OH, C_{1-6} alkyl, or C_{1-6} alkoxy;

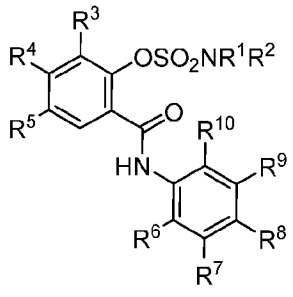
R^6, R^7, R^8, R^9, and R^{10} are each independently hydrogen, halogen, -OH, $-NH_3$, $-NO_2$, -CN, C_{1-6} haloalkyl (*e.g.*, $-CF_3$ or $-CCl_3$), C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkoxy;

R^{11} is a bond, C_{1-6} alkylene, NR^{12} , or O; and

R^{12} is hydrogen or C_{1-6} alkyl.

[0075] In some embodiments, R^{11} is C_{1-6} alkylene (*e.g.*, methylene, ethylene, or *n*-propylene). In some embodiments, R^{11} is NR^{12} or O. In some embodiments, R^{11} is NR^{12} and R^{12} is H. In some embodiments, R^{11} is NR^{12} and R^{12} is C_{1-6} alkyl (*e.g.*, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, or branched hexyl).

[0076] In some embodiments, R^{11} is a bond. In some embodiments, the compound has a structure according to Formula IIIa:



(IIIa),

wherein, R^1 and R^2 are each independently hydrogen or C_{1-6} alkyl; R^3, R^4, and R^5 are each independently hydrogen, halogen,-OH, C_{1-6} alkyl, or C_{1-6} alkoxy; and R^6, R^7, R^8, R^9, and R^{10} are each independently hydrogen, halogen, -OH, $-NH_3$, $-NO_2$, -CN, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkoxy.

[0077] In some embodiments, R^1 and R^2 is H. In some embodiments, R^1 is H and R^2 is C_{1-6} alkyl (*e.g.*, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, *sec*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, or branched hexyl). In some embodiments R^1 and R^2 are C_{1-6} alkyl.

[0078] In some embodiments, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are each independently hydrogen, halogen, or $-NO_2$. In some embodiments, R^5 is halogen (*e.g.*, fluoro, chloro, or bromo) and R^3, R^4, R^6, R^7, R^8, R^9, and R^{10} are each independently hydrogen, halogen, or $-NO_2$. In some embodiments, R^5 is halogen (*e.g.*, fluoro, chloro, or bromo) and R^3 and R^4 are each independently hydrogen or halogen. In some such embodiments, R^8 is $-NO_2$.

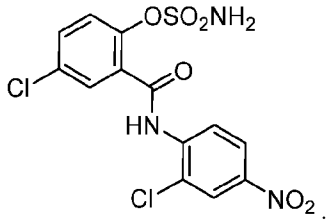
[0079] In some embodiments, R^8 is $-NO_2$ and R^3, R^4, R^5, R^6, R^7, R^9, and R^{10} are each independently hydrogen or halogen. In some embodiments, R^8 is halogen (*e.g.*, fluoro, chloro, or bromo) and R^6, R^7, R^9, and R^{10} are each independently hydrogen or halogen. In some such embodiments, R^8 is $-NO_2$., R^6 is halogen, and R^7, R^9, and R^{10} are H. In some such embodiments, R^5 is halogen and R^3 and R^4 are each independently hydrogen or halogen.

[0080] In some embodiments, R^1 and R^2 are hydrogen in compounds of Formula III or IIIa; and R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are each independently hydrogen, halogen, or $-NO_2$.

[0081] In some embodiments, compounds of Formula III or IIIa are provided wherein: one of R^3, R^4, and R^5 is halogen and two of R^3, R^4, and R^5 are hydrogen; and one of R^6, R^7, R^8, R^9, and R^{10} is halogen, one of R^6, R^7, R^8, R^9, and R^{10} is $-NO_2$, and three of R^6, R^7, R^8, R^9, and R^{10} are hydrogen. In some such embodiments, R^1 and R^2 are hydrogen.

[0082] In some embodiments, compounds of Formula III or IIIa are provided wherein: one of R^3, R^4, and R^5 is chloro and two of R^3, R^4, and R^5 are hydrogen; and one of R^6, R^7 ,R^8, R^9, and R^{10} is chloro, one of R^6, R^7 ,R^8, R^9, and R^{10} is $-NO_2$, and three of R^6, R^7 ,R^8, R^9, and R^{10} are hydrogen. In some such embodiments, R^1 and R^2 are hydrogen.

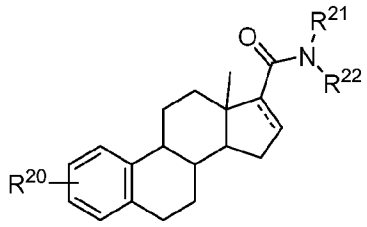
[0083] In some embodiments, the compound of Formula III or IIIa is:



IV. Antiandrogen Compositions and other Pharmaceutical Compositions

[0084] Advantageously, compounds according to the present disclosure can be used in conjunction with antiandrogen drugs for the synergistic treatment of diseases such as cancer. Use of the compounds can result, for example, in the re-sensitization of antiandrogen-resistant cancer (*e.g.*, antiandrogen-resistant prostate cancer or breast cancer) to antiandrogen therapy. Combination therapies according to the present disclosure may employ steroidal antiandrogens (*e.g.*, cyproterone acetate, abiraterone, and the like) and/or non-steroidal antiandrogens (*e.g.*, enzalutamide, flutamide, nilutamide, and bicalutamide). These and other antiandrogens are described, for example by Schröder et al. ((2009) "Steroidal Antiandrogens." In: Jordan V.C., Furr B.J. (eds) *Hormone Therapy in Breast and Prostate Cancer. Cancer Drug Discovery and Development.* Humana Press) and Kolvenbag, et al. ((2009) "Nonsteroidal Antiandrogens." In: Jordan V.C., Furr B.J. (eds) *Hormone Therapy in Breast and Prostate Cancer. Cancer Drug Discovery and Development.* Humana Press).

[0085] Some embodiments of the present disclosure provide a pharmaceutical composition comprising an antiandrogen drug and a compound according to Formula II:



(II),

wherein:

the dashed line represents a single bond or a double bond;

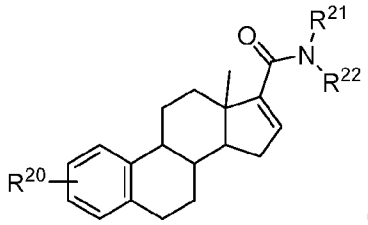
R^{20} is $–O(SO_2)NR^{23}R^{24}–$, which is combined with two carbons of the phenyl group to which it is attached to form a 4- to 10-membered heterocycle, or

R^{20} is $–O(SO_2)NR^{23}R^{25}$;

R^{21}, R^{22}, R^{23}, and R^{25} are each independently hydrogen or C_{1-6} alkyl; and

R^{24} is a bond, C_{1-6} alkylene, or C_{1-6} alkenylene.

[0086] In some embodiments, the compound has a structure according to Formula IIa:

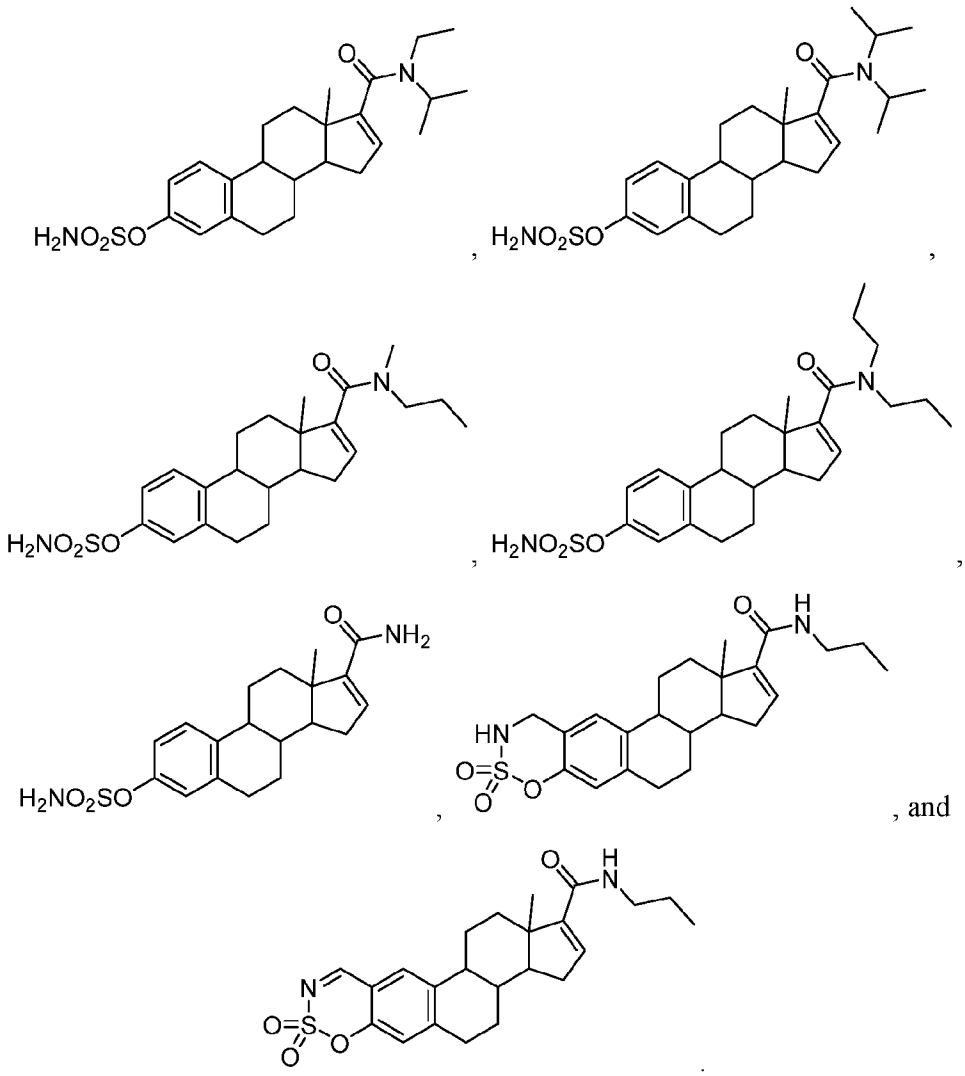


(IIa).

[0087] In some embodiments, R^{21} and R^{22} are each independently hydrogen or C_{1-3} alkyl in compounds of Formula II or Formula IIa. In some embodiments, R^{21} is hydrogen, methyl, ethyl, propyl, isopropyl in compounds of Formula II or Formula IIa; and R^{22} is hydrogen, propyl, or isopropyl. In some such embodiments, R^{20} is $–O(SO_2)NR^{23}R^{24}–$, and R^{24} is C_{1-6} alkylene or C_{1-6} alkenylene. In some embodiments, R^{20} is combined with two carbons of the phenyl group to which it is attached to form an oxathiazine dioxide or a dihydro-oxathiazine dioxide. In some embodiments, R^{20} is $–O(SO_2)–NR^{23}R^{25}$ in compounds of Formula II and Formula IIa.

[0088] In some embodiments, R^{21} is hydrogen, methyl, ethyl, propyl, or isopropyl; and R^{22} is hydrogen, propyl, or isopropyl. Compounds according to Formula II and Formula IIa can be prepared as described below and, for example, in U.S. Pat. No. 6,399,595.

[0089] In some embodiments, the steroid sulfatase inhibitor compound has a structure selected from the group consisting of:



[0090] In some embodiments, the antiandrogen drug is selected from the group consisting of bicalutamide, apalutamide, enzalutamide, abiraterone, darolutamide, and a combination thereof.

[0091] Also provided herein are compositions comprising: (i) compounds of Formula I, Formula III, or a combination thereof, and (ii) an antiandrogen drug as set forth above.

[0092] Typically, pharmaceutical compositions will contain one or more pharmaceutically acceptable excipients in combination with the steroid sulfatase inhibitor and/or the androgen receptor inhibitor.

[0093] The pharmaceutical compositions are generally made by admixing an STS inhibitor (*e.g.*, a compound according to Formula I or II) and/or an AR inhibitor (*e.g.*, a compound according to Formula III), optionally an antiandrogen drug (*e.g.*, bicalutamide, apalutamide,

enzalutamide, darolutamide, abiraterone acetate, or a combination thereof), and a pharmaceutically acceptable carrier and/or excipient or diluent. Such compositions are suitable for pharmaceutical use in a human or other animal. The pharmaceutical compositions may be prepared by any of the methods well-known in the art of pharmacy (*see, e.g.,* Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); and *Remington: The Science and Practice of Pharmacy*, 21st Edition, 2005, Hendrickson, Ed., Lippincott, Williams & Wilkins). Pharmaceutically acceptable carriers include any of the standard pharmaceutical carriers, buffers and excipients, including phosphate-buffered saline solution, water, and emulsions (such as an oil/water or water/oil emulsion), and various types of wetting agents and/or adjuvants. Preferred pharmaceutical carriers will depend, in part, upon the intended mode of administration of the active agent.

[0094] The pharmaceutical compositions can include a combination of drugs (*e.g.,* compounds according to Formulas I, II, and/or III and an antiandrogen drug such as enzalutamide, abiraterone, bicalutamide, darolutamide, and/or apalutamide), or any pharmaceutically acceptable salts thereof, as active ingredients and a pharmaceutically acceptable carrier and/or excipient or diluent. A pharmaceutical composition may optionally contain other therapeutic ingredients.

[0095] The compositions (*e.g.,* combinations of STS inhibitors, AR inhibitors, and/or antiandrogen drugs) can be combined as the active ingredients in intimate admixture with a suitable phrmaceutical carrier and/or excipient according to conventional pharmaceutical compounding techniques. Any carrier and/or excipient suitable for the form of preparation desired for administration is contemplated for use with the compounds disclosed herein.

[0096] The pharmaceutical compositions include those suitable for topical, parenteral, pulmonary, nasal, rectal, or oral administration. The most suitable route of administration in any given case will depend in part on the nature and severity of the cancer (*e.g.,* prostate or breast cancer) condition and also optionally the stage of the cancer.

[0097] Other pharmaceutical compositions include those suitable for systemic (enteral or parenteral) administration. Systemic administration includes oral, rectal, sublingual, or sublabial administration. Parenteral administration includes, *e.g.,* intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations,

intravenous infusion, transdermal patches, *etc.* In particular embodiments, pharmaceutical compositions may be administered intratumorally.

[0098] Compositions for pulmonary administration include, but are not limited to, dry powder compositions consisting of the powder of a compound described herein, or a salt thereof, and the powder of a suitable carrier and/or lubricant. The compositions for pulmonary administration can be inhaled from any suitable dry powder inhaler device known to a person skilled in the art.

[0099] The pharmaceutical compositions may be in a form suitable for oral use. Suitable compositions for oral administration include, but are not limited to, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups, elixirs, solutions, buccal patches, oral gels, chewing gums, chewable tablets, effervescent powders, and effervescent tablets. Such compositions can contain one or more agents selected from sweetening agents, flavoring agents, coloring agents, antioxidants, and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

[0100] Tablets generally contain the active ingredients in admixture with non-toxic pharmaceutically acceptable excipients, including: inert diluents, such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate, and sodium phosphate; granulating and disintegrating agents, such as corn starch and alginic acid; binding agents, such as polyvinylpyrrolidone (PVP), cellulose, polyethylene glycol (PEG), starch, gelatin, and acacia; and lubricating agents such as magnesium stearate, stearic acid, and talc. The tablets can be uncoated or coated, enterically or otherwise, by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Tablets can also be coated with a semi-permeable membrane and optional polymeric osmogents according to known techniques to form osmotic pump compositions for controlled release. Compositions for oral administration can be formulated as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (such as calcium carbonate, calcium phosphate, or kaolin), or as soft gelatin capsules wherein the active ingredients are mixed with water or an oil medium (such as peanut oil, liquid paraffin, or olive oil).

[0101] The pharmaceutical compositions can also be in the form of an injectable aqueous or oleaginous solution or suspension. Sterile injectable preparations can be formulated using non-toxic parenterally-acceptable vehicles including water, Ringer's solution, and isotonic sodium chloride solution, and acceptable solvents such as 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0102] Aqueous suspensions contain the active agents in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include, but are not limited to: suspending agents such as sodium carboxymethylcellulose, methylcellulose, oleagino-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin, polyoxyethylene stearate, and polyethylene sorbitan monooleate; and preservatives such as ethyl, *n*-propyl, and *p*-hydroxybenzoate. Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid. Dispersible powders and granules (suitable for preparation of an aqueous suspension by the addition of water) can contain the active ingredients in admixture with a dispersing agent, wetting agent, suspending agent, or combinations thereof. Additional excipients can also be present.

[0103] The pharmaceutical compositions can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, such as gum acacia or gum tragacanth; naturally-occurring phospholipids, such as soy lecithin; esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate; and condensation products of said partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate.

[0104] Transdermal delivery can be accomplished by means of iontophoretic patches and the like. The active ingredients can also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the active agents with a suitable non-irritating excipient which is solid at ordinary temperatures but

liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0105] Controlled release parenteral formulations of the compositions can be made as implants, oily injections, or as particulate systems. For a broad overview of delivery systems see, Banga, A.J., THERAPEUTIC PEPTIDES AND PROTEINS: FORMULATION, PROCESSING, AND DELIVERY SYSTEMS, Technomic Publishing Company, Inc., Lancaster, PA, (1995) incorporated herein by reference. Particulate systems include microspheres, microparticles, microcapsules, nanocapsules, nanospheres, and nanoparticles.

[0106] Polymers can be used for ion-controlled release of active agents. Various degradable and nondegradable polymeric matrices for use in controlled drug delivery are known in the art (Langer R., Accounts Chem. Res., 26:537-542 (1993)). For example, the block copolymer, polaxamer 407 exists as a viscous yet mobile liquid at low temperatures but forms a semisolid gel at body temperature. It has shown to be an effective vehicle for formulation and sustained delivery of recombinant interleukin 2 and urease (Johnston et al., Pharm. Res., 9:425-434 (1992); and Pec et al., J. Parent. Sci. Tech., 44(2):58 65 (1990)). Alternatively, hydroxyapatite has been used as a microcarrier for controlled release of proteins (Ijntema et al., Int. J. Pharm., 112:215-224 (1994)). In yet another aspect, liposomes are used for controlled release as well as drug targeting of the lipid-capsulated drug (Betageri et al., LIPOSOME DRUG DELIVERY SYSTEMS, Technomic Publishing Co., Inc., Lancaster, PA (1993)). Numerous additional systems for controlled delivery of therapeutic proteins are known. *See, e.g.,* U.S. Pat. No. 5,055,303, 5,188,837, 4,235,871, 4,501,728, 4,837,028 4,957,735 and 5,019,369, 5,055,303; 5,514,670; 5,413,797; 5,268,164; 5,004,697; 4,902,505; 5,506,206, 5,271,961; 5,254,342 and 5,534,496, each of which is incorporated herein by reference.

V. Methods of Treating Cancer

[0107] Also provided herein are methods for the treatment of disorders such as cancer. The methods include administering to a therapeutically effective amount of a compound according to Formulas I, II, and/or III, optionally in combination with an antiandrogen drug.

[0108] In some embodiments, the disorder is a cancer. The cancer may be, for example, an androgen-independent cancer, a metastatic cancer, a castrate-resistant cancer, a castration recurrent cancer, a hormone-resistant cancer, a metastatic castrate-resistant cancer, or a combination thereof. In some embodiments, the cancer is prostate cancer or breast cancer.

[0109] In some embodiments, the method includes administration of an antiandrogen (e.g., enzalutamide, abiraterone, bicalutamide, darolutamide, and/or apalutamide). In some embodiments, the method includes administration of the antiandrogen and an STS inhibitor according to Formula I or Formula Ia as described above. In some embodiments, the method includes administration of the antiandrogen and an AR inhibitor according to Formula III or Formula IIIa as described above. In some embodiments, the method includes administration of a composition containing an antiandrogen and a compound according to Formula II or Formula IIa as described above. The active agents may be administered concomitantly or sequentially.

[0110] In some embodiments, the antiandrogen drug is a non-steroidal AR antagonist, a CYP17A1 inhibitor, or a combination thereof. Suitable non-steroidal AR antagonists include bicalutamide (Casodex, Cosudex, Calutide, Kalumid), flutamide, nilutamide, apalutamide (ARN-509, JNJ-56021927), darolutamide, enzalutamide (Xtandi), cimetidine and topilutamide. Suitable CYP17A1 inhibitors include abiraterone acetate (Zytiga), ketoconazole, and seviteronel. Any combination of antiandrogen drugs can be used in methods of the present invention.

[0111] The compounds and/or pharmaceutical compositions as described herein can be administered at any suitable dose in the methods. In general, the compound and/or composition is administered at a dose ranging from about 0.1 milligrams to about 1000 milligrams per kilogram of a subject's body weight (*i.e.*, about 0.1-1000 mg/kg). In some embodiments, the compound and/or composition is administered at a dose ranging from about 1 milligram to about 100 milligrams per kilogram of a subject's body weight (*i.e.*, about 1-100 mg/kg). The dose can be, for example, about 0.1-1000 mg/kg, or about 1-10 mg/kg, or about 10-50 mg/kg, or about 25-50 mg/kg, or about 50-75 mg/kg, or about 1-75-100 mg/kg, or about 1-500 mg/kg, or about 25-250 mg/kg, or about 50-100 mg/kg. The dose can be about 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 mg/kg. The dosages can be varied depending upon the requirements of the patient, the severity of the disorder being treated, and the particular formulation being administered. The dose administered to a patient should be sufficient to result in a beneficial therapeutic response in the patient. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of the drug in a particular patient. Determination of the proper dosage for a particular situation is within the

skill of the typical practitioner. The total dosage can be divided and administered in portions over a period of time suitable to treat to the cancer or other disease/condition.

[0112] In some embodiments, the methods include administering the antiandrogen in an amount ranging from about 0.5 mg/kg/day to about 100 mg/kg/day (e.g., from about 1 mg/kg/day to about 10 mg/kg/day). As a non-limiting example, enzalutamide may be administered in an amount ranging from about 1 mg/kg/day to about 5 mg/kg day. In some embodiments, the methods include administering abiraterone or abiraterone acetate in an amount ranging from about 5 mg/kg/day to about 50 mg/kg/day.

[0113] The compounds and/or compositions can be administered for periods of time which will vary depending upon the nature of the particular disorder, its severity, and the overall condition of the subject to whom the compounds and/or compositions are administered. Administration can be conducted, for example, hourly, every 2 hours, three hours, four hours, six hours, eight hours, or twice daily including every 12 hours, or any intervening interval thereof. Administration can be conducted once daily, or once every 36 hours or 48 hours, or once every month or several months. Following treatment, a subject can be monitored for changes in his or her condition and for alleviation of the symptoms of the disorder. The dosage can either be increased in the event the subject does not respond significantly to a particular dosage level, or the dose can be decreased if an alleviation of the symptoms of the disorder is observed, or if the disorder has been remedied, or if unacceptable side effects are seen with a particular dosage. A therapeutically effective amount can be administered to the subject in a treatment regimen comprising intervals of at least 1 hour, or 6 hours, or 12 hours, or 24 hours, or 36 hours, or 48 hours between dosages. Administration can be conducted at intervals of at least 72, 96, 120, 144, 168, 192, 216, or 240 hours (*i.e.*, 3, 4, 5, 6, 7, 8, 9, or 10 days).

[0114] In some embodiments, the methods further include administration of one or more additional anti-cancer agents. Examples of anti-cancer agents include, but are not limited to, chemotherapeutic agents (*e.g.*, carboplatin, paclitaxel, pemetrexed, or the like), tyrosine kinase inhibitors (*e.g.*, erlotinib, crizotinib, osimertinib, or the like), poly (ADP-ribose) polymerase inhibitors (*e.g.*, olaparib, rucaparib, and the like), and immunotherapeutic agents (*e.g.*, pembrolizumab, nivolumab, durvalumab, atezolizumab, or the like). In some embodiments, the methods include administration of radiotherapy, *e.g.*, external beam radiation; intensity modulated radiation therapy (IMRT); brachytherapy (internal or implant

radiation therapy); stereotactic body radiation therapy (SBRT)/stereotactic ablative radiotherapy (SABR); stereotactic radiosurgery (SRS); or a combination of such techniques.

[0115] In some of these embodiments, the cancer is advanced stage cancer. In some of these embodiments, the cancer is drug resistant. In some of these embodiments, the cancer is antiandrogen drug resistant or androgen independent. In some of these embodiments, the cancer is metastatic. In some of these embodiments, the cancer is metastatic and drug resistant (*e.g.*, antiandrogen drug resistant). In some of these embodiments, the cancer is castration resistant. In some of these embodiments, the cancer is metastatic and castration resistant. In some of these embodiments, the cancer is enzalutamide resistant. In some of these embodiments, the cancer is enzalutamide and arbiraterone resistant. In some of these embodiments, the cancer is enzalutamide, arbiraterone, darolutamide, and bicalutamide resistant. In some of these embodiments, the cancer is enzalutamide, arbiraterone, bicalutamide, darolutamide, and apalutamide resistant. In other embodiments, the cancer is resistant (*e.g.*, docetaxel, cabazitaxel, paclitaxel). The cancer (*e.g.*, prostate or breast cancer) can be resistant to any combination of these drugs.

[0116] In some embodiments, treatment comprises inhibiting cancer cell (*e.g.*, prostate or breast cancer cell) growth, inhibiting cancer cell proliferation, inhibiting cancer cell migration, inhibiting cancer cell invasion, ameliorating the symptoms of cancer, reducing the size of a cancer tumor, reducing the number of cancer tumors, reducing the number of cancer cells, inducing cancer cell necrosis, pyroptosis, oncosis, apoptosis, autophagy, or other cell death, or enhancing the therapeutic effects of a composition or pharmaceutical composition comprising a niclosamide analog and an antiandrogen drug. In particular instances, the subject does not have cancer.

[0117] In particular methods of treating cancer (*e.g.*, prostate cancer, breast cancer, androgen-independent cancer, or drug-resistant cancer), described herein, treatment comprises enhancing the therapeutic effects of an antiandrogen drug (*e.g.*, a non-steroidal adrogen recept antagonist or a CYP17A1 inhibitor). In certain embodiments, treatment comprises enhancing the therapeutic effects of enzalutamide. In certain other embodiments, treatment comprises enhancing the therapeutic effects of abiraterone. In yet other embodiments, treatment comprises enhancing the therapeutic effects of apalutamide. In some other embodiments, treatment comprises enhancing the therapeutic effects of bicalutamide. The enhancement can be synergistic or additive.

[0118] In certain embodiments of the methods set forth herein, treatment comprises reversing, reducing, or decreasing cancer cell (*e.g.*, prostate cancer cell or breast cancer cell) resistance to antiandrogen drugs. In certain embodiments of the methods set forth herein, treatment comprises resensitizing cancer cells (*e.g.*, prostate cancer cells or breast cancer cells) to antiandrogen drugs. In any of the methods described herein, the antiandrogen drug is a compound selected from the group consisting of a non-steroidal androgen receptor antagonist, a CYP17A1 inhibitor, and a combination thereof. In certain embodiments, the antiandrogen drug is enzalutamide, apalutamide, bicalutamide, and/or abiraterone acetate.

[0119] In any of the aforementioned methods, treatment may comprise reversing cancer cell (*e.g.*, prostate or breast cancer cell) resistance to an antiandrogen drug (*e.g.*, a non-steroidal androgen receptor antagonist or CYP17A1 inhibitor); reducing or decreasing cancer cell resistance to an antiandrogen drug; or resensitizing cancer cells to an antiandrogen drug. In some embodiments, treatment comprises reversing cancer cell (*e.g.*, prostate or breast cancer cell) resistance to enzalutamide, apalutamide, bicalutamide, darolutamide, abiraterone acetate, or a combination thereof. In some other embodiments, treatment comprises reducing or decreasing cancer cell resistance to enzalutamide, apalutamide, bicalutamide, darolutamide, abiraterone acetate, or a combination thereof. In some embodiments, treatment comprises resensitizing cancer cells to enzalutamide, apalutamide, bicalutamide, abiraterone acetate, darolutamide, or a combination thereof.

[0120] In any of the methods described herein, the cancer is selected from the group consisting of castration-resistant cancer, metastatic castration-resistant cancer, advanced stage cancer, drug-resistant cancer, antiandrogen-resistant cancer, bicalutamide resistant cancer, enzalutamide-resistant cancer, abiraterone acetate-resistant cancer, apalutamide-resistant cancer, darolutamide-resistant cancer, AR-V1-, AR-V3-, AR-V7-, AR-V9-, and/or AR-V12-induced drug-resistant cancer, AR-V1-, AR-V3-, AR-V7-, AR-V9-, and/or AR-V12-induced antiandrogen drug-resistant cancer, AR-V1-, AR-V3-, AR-V7-, AR-V9-, and/or AR-V12-induced enzalutamide-resistant cancer, AR-V1-, AR-V3-, AR-V7-, AR-V9-, and/or AR-V12-induced abiraterone acetate-resistant cancer, AR-V1-, AR-V3-, AR-V7-, AR-V9-, and/or AR-V12-induced apalutamide-resistant cancer, AR-V1-, AR-V3-, AR-V7-, AR-V9-, and/or AR-V12-induced bicalutamide-resistant cancer, and combinations thereof.

[0121] In some embodiments, a test sample is obtained from the subject. The test sample can be obtained before and/or after the STS inhibitor(s) and antiandrogen drug(s) are

administered to the subject. Non-limiting examples of suitable samples include blood, serum, plasma, cerebrospinal fluid, tissue, saliva, and urine. In some instances, the sample comprises normal tissue. In other instances, the sample comprises cancer tissue. The sample can also be made up of a combination of normal and cancer cells.

[0122] In some embodiments, a reference sample is obtained. The reference sample can be obtained, for example, from the subject and can comprise normal tissue. The reference sample can be also be obtained from a different subject and/or a population of subjects. In some instances, the reference sample is either obtained from the subject, a different subject, or a population of subjects before and/or after the STS inhibitor(s) and antiandrogen drug(s) are administered to the subject, and comprises normal tissue. However, in some instances the reference sample comprises cancer tissue and is obtained from the subject and/or from a different subject or a population of subjects.

[0123] In some embodiments, the level of one or more biomarkers is determined in the test sample and/or reference sample. Non-limiting examples of suitable biomarkers include prostate-specific antigen (PSA), alpha-methylacyl-CoA racemase (AMACR), endoglin (CD105), engrailed 2 (EN-2), prostate-specific membrane antigen (PSMA), caveolin-1, interleukin-6 (IL-6), CD147, members of the S100 protein family (*e.g.,* S100A2, S100A4, S100A8, S100A9, S100A11), annexin A3 (ANXA3), human kallikrein-2 (KLK2), TGF-Beta1, beta-microseminoprotein (MSMB), estrogen receptor (ER), progesterone receptor (PgR), HER2, Ki67, cyclin D1, and cyclin E.

[0124] Prostate-specific antigen (PSA) is a protein produced primarily by prostate cells. Most PSA is released into the semen, but some PSA is also released into the blood. In the blood, PSA exists in unbound and complexed (cPSA) forms. Conventional laboratory tests can measure unbound and/or total (unbound and complexed) PSA. Elevated PSA levels can be caused by benign prostatic hyperplasia (BPH) and inflammation of the prostate, but can also be caused by prostate cancer. Determining PSA levels may also include one or more determinations of PSA velocity (*i.e.,* the change in PSA level over time), PSA doubling time (*i.e.,* how quickly the PSA level doubles), PSA density (*i.e.,* a comparison of the PSA concentration and the volume of the prostate (which can be evaluated, for example, by ultrasound)), and age-specific PSA ranges.

[0125] Typically, the level of the one or more biomarkers in one or more test samples is compared to the level of the one or more biomarkers in one or more reference samples.

Depending on the biomarker, and increase or a decrease relative to a normal control or reference sample can be indicative of the presence of cancer or a higher risk for cancer. As a non-limiting example, levels of one or biomarkers in test samples taken before and after the STS inhibitor(s) and antiandrogen drug(s) are administered to the subject are compared to the level of the one or more biomarkers in a reference sample that is either normal tissue obtained from the subject, or normal tissue that is obtained from a different subject or a population of subjects. In some instances, the biomarker is serum, and the level of PSA in a test sample obtained from the subject before the STS inhibitor(s) and antiandrogen drug(s) are administered to the subject is higher than the level of PSA in the reference sample. In other instances, the level of PSA in a test sample obtained from the subject after administration of the STS inhibitor(s) and antiandrogen drug(s) is decreased relative to the level of PSA in a test sample obtained prior to administration. Alternatively, as another non-limiting example, the difference in PSA level between a sample obtained from the subject after administration and a reference sample is smaller than a difference between the PSA level in a sample obtained from the subject prior to administration and the reference sample (*i.e.*, administration results in a decrease in PSA in the test sample such that the difference between the level measured in the test sample and the level measured in the reference sample is diminished or eliminated).

[0126] The differences between the reference sample or value and the test sample need only be sufficient to be detected. In some embodiments, an increased level of a biomarker (*e.g.*, PSA) in the test sample, and hence the presence of cancer or increased risk of cancer, is determined when the biomarker levels are at least, *e.g.*, about 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold, or 20-fold higher in comparison to a negative control. In other embodiments, a decreased level of a biomarker in the test sample, and hence the presence of cancer or increased risk of cancer, is determined when the biomarker levels are at least, *e.g.*, about 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold, or 20-fold lower in comparison to a negative control.

[0127] The biomarker levels can be detected using any method known in the art, including the use of antibodies specific for the biomarkers. Exemplary methods include, without limitation, PCR, Western Blot, dot blot, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunofluorescence, FACS analysis,

electrochemiluminescence, and multiplex bead assays (*e.g.*, using Luminex or fluorescent microbeads). In some instances, nucleic acid sequencing is employed.

[0128] In certain embodiments, the presence of decreased or increased levels of one or more biomarkers is indicated by a detectable signal (*e.g.*, a blot, fluorescence, chemiluminescence, color, radioactivity) in an immunoassay or PCR reaction (*e.g.*, quantitative PCR). This detectable signal can be compared to the signal from a control sample or to a threshold value. In some embodiments, a decreased presence is detected, and the presence or increased risk of cancer is indicated, when the detectable signal of biomarker(s) in the test sample is at least, *e.g.*, about 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold, or 20-fold lower in comparison to the signal of antibodies in the reference sample or the predetermined threshold value. In other embodiments, an increased presence is detected, and the presence or increased risk of cancer is indicated, when the detectable signal of biomarker(s) in the test sample is at least, *e.g.*, about 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold, or 20-fold greater in comparison to the signal of antibodies in the reference sample or the predetermined threshold value.

VI. Kits

[0129] Also provided herein are kits for preventing or treating cancer in a subject. The kits are useful for treating any cancer, some non-limiting examples of which include prostate cancer, breast cancer, uterine cancer, ovarian cancer, colorectal cancer, stomach cancer, pancreatic cancer, lung cancer (*e.g.*, mesothelioma, lung adenocarcinoma), esophageal cancer, head and neck cancer, sarcomas, melanomas, thyroid carcinoma, CNS cancers (*e.g.*, neuroblastoma, glioblastoma), chronic lymphocytic leukemia, and any other cancer described herein. The kits are also suitable for treating androgen-independent, castrate-resistant, castration recurrent, hormone-resistant, drug-resistant, and metastatic castrate-resistant cancers.

[0130] In some embodiments, the kits comprise a STS inhibitor and an antiandrogen drug. In some other embodiments, the kits further comprise a pharmaceutically acceptable carrier. In particular embodiments, the STS inhibitor is a compound according to Formulas I, II, and/or III.

[0131] In some embodiments, the antiandrogen drug is a non-steroidal androgen receptor antagonist, a CYP17A1 inhibitor, or a combination thereof. Suitable non-steroidal AR antagonists include bicalutamide (Casodex, Cosudex, Calutide, Kalumid), flutamide, nilutamide, apalutamide (ARN-509, JNJ-56021927), darolutamide, enzalutamide (Xtandi), cimetidine and topilutamide. Suitable CYP17A1 inhibitors include abiraterone acetate (Zytiga), ketoconazole, and seviteronel. Any combination of antiandrogen drugs can be used in the kits.

[0132] Materials and reagents to carry out the various methods described above can be provided in kits to facilitate execution of the methods. As used herein, the term "kit" includes a combination of articles that facilitates a process, assay, analysis, or manipulation. The kits may be utilized in a wide range of applications including, for example, diagnostics, prognostics, therapy, and the like.

[0133] Kits can contain chemical reagents as well as other components. In addition, the kits can include, without limitation, instructions to the kit user, apparatus and reagents for sample collection and/or purification, apparatus and reagents for product collection and/or purification, apparatus and reagents for administering STS inhibitor(s) and/or antiandrogen drug(s), apparatus and reagents for determining the level(s) of biomarker(s), sample tubes, holders, trays, racks, dishes, plates, solutions, buffers or other chemical reagents, suitable samples to be used for standardization, normalization, and/or control samples. Kits can also be packaged for convenient storage and safe shipping, for example, in a box having a lid.

[0134] In some embodiments, the kits also contain negative and positive control samples for detection of biomarkers. Non-limiting examples of suitable biomarkers include prostate-specific antigen (PSA), alpha-methylacyl-CoA racemase (AMACR), endoglin (CD105), engrailed 2 (EN-2), prostate-specific membrane antigen (PSMA), caveolin-1, interleukin-6 (IL-6), CD147, members of the S100 protein family (*e.g.*, S100A2, S100A4, S100A8, S100A9, S100A11), annexin A3 (ANXA3), human kallikrein-2 (KLK2), TGF-Beta1, beta-microseminoprotein (MSMB), estrogen receptor (ER), progesterone receptor (PgR), HER2, Ki67, cyclin D1, and cyclin E. In some instances, the one or more biomarkers comprises PSA. In some embodiments, the negative control samples are obtained from individuals or groups of individuals who do not have cancer. In other embodiments, the positive control samples are obtained from individuals or groups of individuals who have cancer. In some embodiments, the kits contain samples for the preparation of a titrated curve of one or more

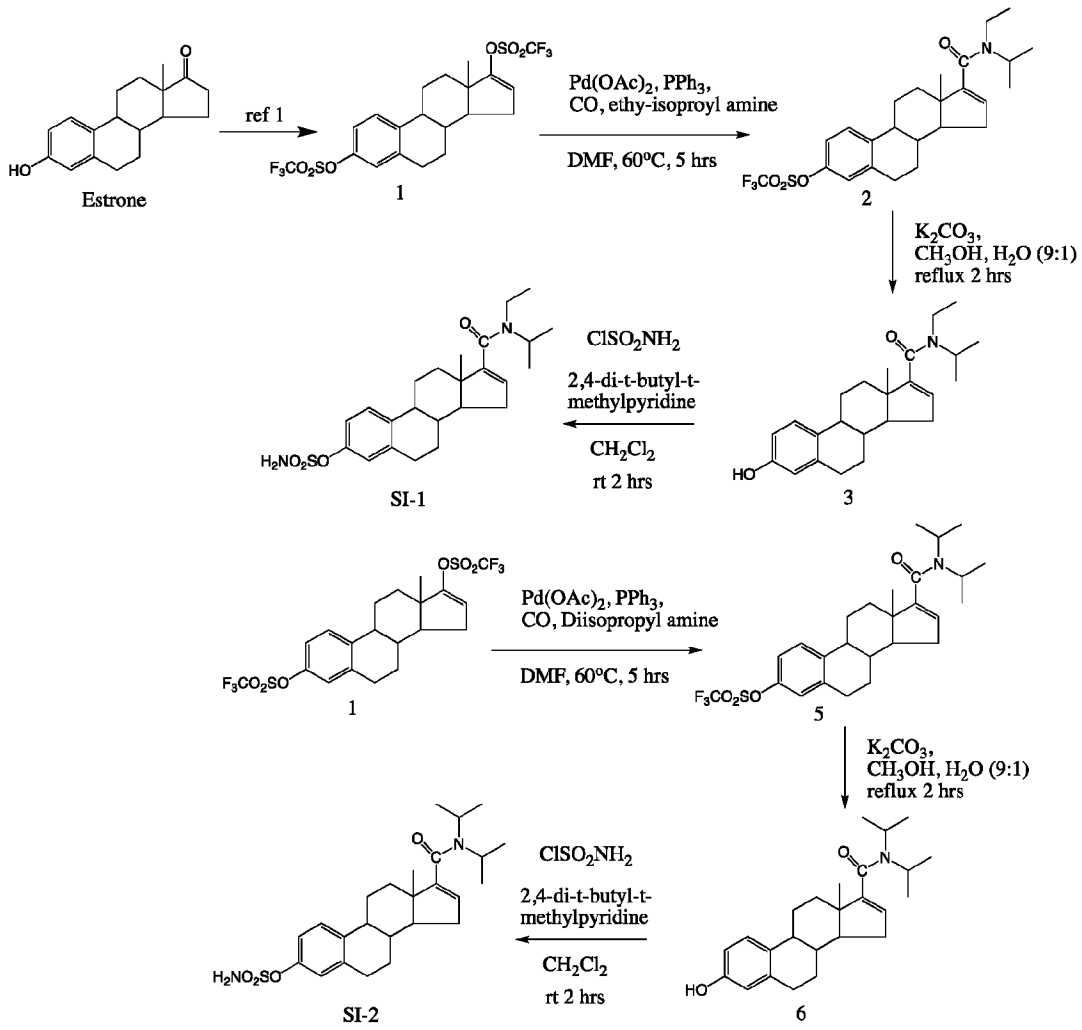
biomarkers in a sample, to assist in the evaluation of quantified levels of the one or more biomarkers in a test biological sample.

VII. Examples

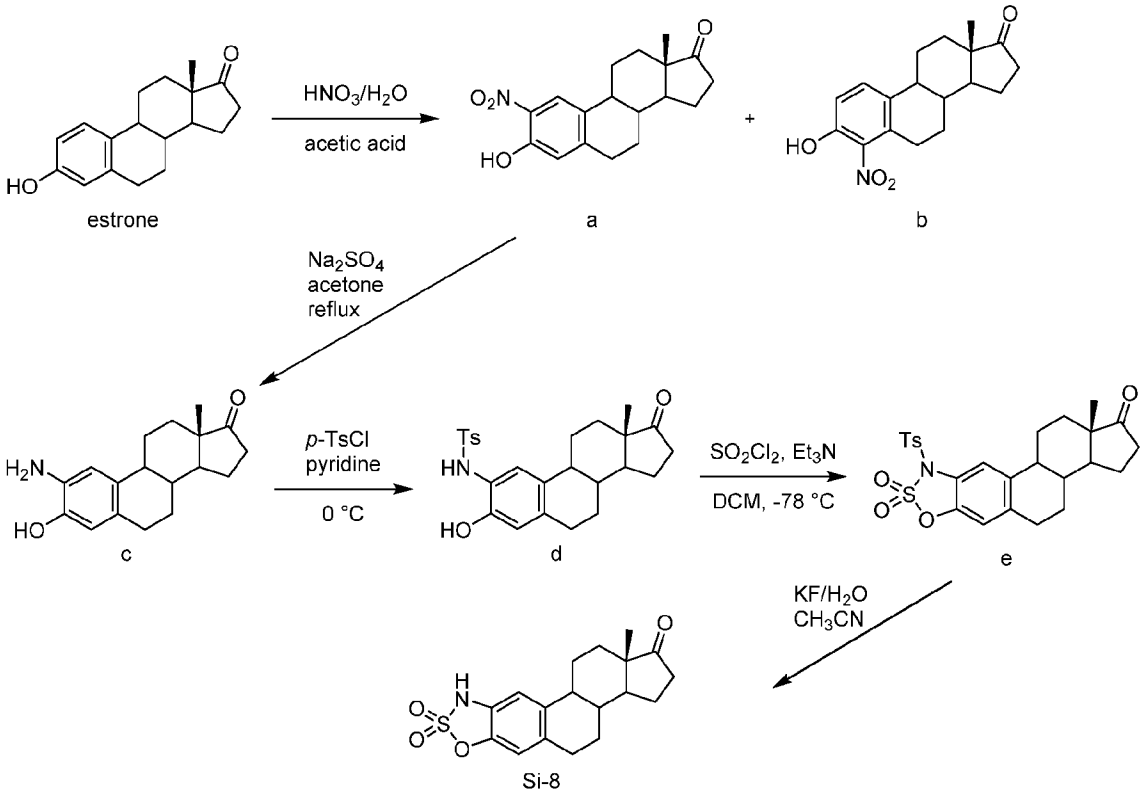
[0135] The present invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes only, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

Example 1. Synthesis of STSi Compounds.

[0136] *Synthesis of Si-1 and Si-2:* A representative synthesis of STSi compounds Si-1 and Si-2 is shown below. Estrone was converted to the ditriflate (1). Select insertion of the substituted carboxamide into the D ring afforded compound (2). Removal of the triflate to yield (3) and sulfamoylation of (3) yielded Si-1. The synthesis of Si-2 was similar to Si-1 except diisopropyl amine was used instead of ethyl-isopropyl amine. A total of 10 STSi compounds (Si-1 to Si-10) were synthesized and are shown in FIG. 1A and FIG. 1B.



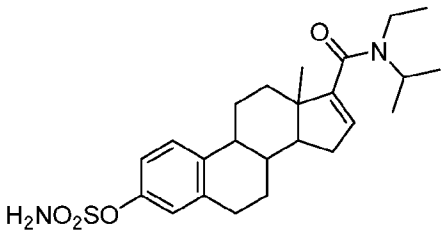
[0137] *Synthesis of Si-8 and Si-9*: The synthesis of STSi compound Si-8 is shown in the scheme below. Nitration of estrone provided a mixture of regioisomers (a) and (b). Reduction of compound (a) afforded amine (c). Protection of the amine with toysyl chloride yielded protected compound (d) with was further treated with sulfuryl chloride to obtain protected oxathiazolidine dioxide (e). Deprotection with aqueous base afforded the STSi compound Si-8. The analogous synthesis was performed using compound (b) to afford STSi compound Si-9. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.02 (d, J = 4.6 Hz, 1H), 6.94 (d, J = 4.7 Hz, 1H), 2.82 (dt, J = 9.4, 4.5 Hz, 2H), 2.55 – 2.16 (m, 6H), 2.16 – 1.83 (m, 3H), 1.77 (dd, J = 9.5, 3.8 Hz, 1H), 1.67 – 1.15 (m, 6H), 0.83 (d, J = 4.6 Hz, 3H). Si-9: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.05 (q, J = 8.6 Hz, 2H), 2.68 (dtd, J = 24.0, 17.5, 6.2 Hz, 2H), 2.48 – 2.31 (m, 1H), 2.24 (td, J = 10.5, 4.2 Hz, 1H), 2.16 – 1.86 (m, 3H), 1.86 – 1.68 (m, 1H), 1.68 – 1.08 (m, 5H), 0.83 (s, 3H).



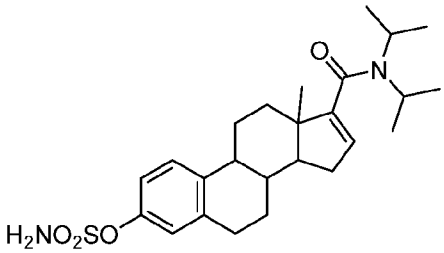
Example 2. STSi Activity Study

[0138] The sensitivity of prostate cancer cells to STS inhibitors was tested using cell growth assays and clonogenic assays. Quantitative reverse transcription-PCR, and Western blotting were performed to detect expression levels of STS and AR. Expression of STS was downregulated using siRNA specific to STS. Steroid profile including DHEA and androgens was analyzed by Liquid Chromatography-Mass Spectrometry (LC-MS). STS activity was determined by 4-Methylumbelliferyl sulfate assay through a fluorescence microtiter plate reader. PSA secretion was determined by ELISA and PSA-luciferase activity was measured by reporter assay. Eleven potent STS inhibitors were synthesized and characterized. The in vivo efficacy of two novel STS inhibitors was tested in castration relapsed VCaP xenograft tumor models.

[0139] STS was found to be overexpressed in CRPC patients and cells. Inhibiting STS by siRNA was shown to suppress cell growth and AR signaling. Selected from 11 potential STS inhibitors, two novel small molecule inhibitors (Si-1 and Si-2) inhibited the STS activity and the growth of C4-2B and VCaP cells.



(Si-1)



(Si-2)

[0140] Additionally, Si-1 and Si-2 significantly suppressed AR expression and its transcriptional activity, suggesting that inhibition of STS activity by Si-1 and Si-2 downregulates the AR signaling. Both Si-1 and Si-2 significantly suppressed relapsed VCaP tumor growth and tumor AR levels in vivo. Furthermore, Si-1 increased the efficacy of enzalutamide treatment in vitro and in vivo.

Example 3. Characterization of STSi in prostate cancer cells.

[0141] To evaluate the ability of STSi in inhibition of STS enzymatic activity, VCaP prostate cancer cells were treated with two synthesized STSi and STS enzymatic activity was measured. The activity assay was carried as described by Wolff, et al. (Anal Biochem, 2003. **318**(2): p. 276-284). FIG. 2 shows that both STSi significantly inhibited STS enzymatic activity in a dose dependent manner. FIG. 3 shown the effects of other STSi on STS enzymatic activity in VCaP cells.

Example 4. STSi inhibits prostate cancer cell growth in vitro.

[0142] To examine the effects of STSi on the growth of prostate cancer cells, C4-2B, LNCaP, DU145, PC3, CWR22rv1 and VCaP cells were treated with increasing doses of STSi for 48 hrs and cell numbers were counted. As shown in FIG. 4, Si-1 and Si-2 inhibited cell growth in a dose dependent manner. FIG. 5 shows the effects of other STSi on the growth of C4-2B cells. To examine the effects of STSi on the growth of resistant prostate cancer cells, enzalutamide-resistant C4-2B MDVR and abiraterone-resistant C4-2BAbiR cells were treated with different doses of both STSi, and the cell numbers were counted. As shown in FIG. 6 and FIG. 7, the STSi's inhibit the growth of C4-2BMDVR and C4-2BAbiR cells, while

combination with enzalutamide or abiraterone further decreased cell growth in both C4-2BMDVR and C4-2BAbiR cells.

Example 5. STSi's inhibit prostate cancer tumor growth in vivo.

[0143] To determine whether these compounds inhibit enzalutamide/abiraterone resistance tumor growth in vivo, A VCaP tumor model that expresses endogenous STS was employed. VCaP tumors were allowed to develop in intact SCID mice and the animals were castrated after tumors reached 80-100 mm^3 of size. This setting allowed VCaP, a CRPC line, to relapse after castration and STS inhibitor to be tested for their efficacy. As shown in FIG. 8A, after one week of castration, the VCaP tumors started to relapse and the treatments with Si-1 and Si-2 (25 mg/kg/d i.p.) significantly diminished tumor progression. Si-1 and Si-2 showed similar tumor suppression compared with control (around 60% tumor suppression) (FIG. 8B-8C). Both Si-1 and Si-2 significantly decreased the tumor weight after 3 weeks treatment ($p=0.00155$ and $p=0.00061$ respectively). However, the mice body weight was not affected by the Si-1 and Si-2 treatment compared with control group (FIG. 8D). The serum PSA level was also significantly decreased after 3 weeks of treatment. As shown in FIG. 8E, in a control group expressing 300 ng/mL PSA at 3 weeks of treatment time point, Si-1 decreased by 50% of PSA ($p=0.00267$) and Si-2 decreased by 55% of PSA ($p=0.000692$). Tumor proliferation and AR expression by IHC was also examined. As shown in FIG. 8E, both Si-1 and Si-2 showed less Ki67 and AR staining in VCaP tumors. The relapsed VCaP tumors expressed strong AR nuclear and cytoplasm staining. However, Si-1 and Si-2 significantly suppressed the tumor AR expression. Taken together, these in vivo results further confirm that Si-1 and Si-2 showed excellent anti-tumor efficacy *in vivo*.

Example 6. STSi improves enzalutamide treatment *in vitro* and *in vivo*.

[0144] To further test if STS inhibition could improve enzalutamide treatment, Si-1 and Si-2 were tested in combination with enzalutamide in VCaP cells. As shown in FIG. 9A, enzalutamide slightly suppressed VCaP cell growth *in vitro*, and cell growth was reduced with addition of Si-1 and Si-2. Combination with Si-1 or Si-2 with enzalutamide further reduced cell numbers. The AR transcriptional activity was also determined, as shown in FIG. 9B. Enzalutamide treatment slightly decreased PSA luciferase activity in VCaP cells, STSi suppressed the AR activity, and in combination with enzalutamide further reduced the AR transcriptional activity. The AR expression was also determined by western blot. As shown in FIG. 9C, enzalutamide treatment decreased AR expression, both Si-1 and Si-2 significantly

decreased AR expression, and combination treatment with Si-1 or Si-2 with enzalutamide completely suppressed AR expression.

[0145] The VCaP tumor model was then used to validate the efficacy of combination therapy. As shown in FIG. 9D-E, enzalutamide treatment alone only slighted delayed tumor growth and produced a tumor growth curve very similar to the control. Si-1 significantly suppressed tumor growth and tumor weight, and combined with enzalutamide further suppressed the tumor growth in vivo. IHC staining confirmed that enzalutamide did not affect the Ki67 expression in relapsed VCaP tumors, Si-1 significantly decreased the Ki67 expression, while combination treatment further lowered Ki67 expression (FIG. 9F). Taken together, these data demonstrate that Si-1 improved enzalutamide treatment in vivo.

Example 7. STSi inhibits breast cancer cell growth in vitro.

[0146] To examine the effects of STSi on the growth of breast cancer cells, MCF-7, MDA-MB-468 and MDA-MB-231 cells were treated with different doses of STSi for 48 hrs and cell numbers were counted. As shown in FIG 10, Si-1 and Si-2 inhibits cell growth in a dose dependent manner.

Example 8. Synthesis of Niclosamide Sulfamate.

[0147] Niclosamide (3.27 g, 0.01 mol), triethylamine (TEA) (15.4 ml, 0.11 mol) and 4-(dimethylamino)pyridine (DMAP) (0.25 g) were dissolved in dichloromethane (DCM, CH_2Cl_2) (120 ml) at 0 °C. Chlorosulfonamide (12.23 g, 0.105 mol) was then added to the reaction mixture and the resulting solution was stirred for 30 min at 0 °C. The solution was then washed with water and the dichloromethane layer was obtained, dried and evaporated to yield a brownish solid. The solid was purified by silica column chromatography to obtain the white pure niclosamide sulfamate (0.64 g, 15.8% yield). ^{1}H NMR (300 MHz, Acetone-d_6) δ 8.81 (d, J = 9.2 Hz, 1H), 8.40 (d, J = 2.6 Hz, 1H), 8.32 (dd, J = 9.2, 2.6 Hz, 1H), 8.01 (d, J = 2.7 Hz, 1H), 7.75 (dd, J = 8.8, 2.7 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H).

Example 9. Niclosamide Sulfamate inhibits Wnt5A signaling and enhances enzalutamide treatment.

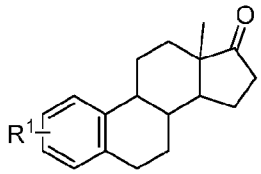
[0148] Niclosamide suffers from low solubility and oral bioavailability, which is believed to be due in part to the formation of intra-molecular hydrogen bonding between the phenolic OH group with the ketone group of niclosamide. The phenolic group was converted to a sulfamate to form the prodrug niclosamide sulfamate (Nic-S), which can be cleaved by

steroid sulfatase after oral administration. Niclosamide sulfamate (Nic-S) was found to inhibit Wnt5A expression (FIG. 12B) and synergistically enhance enzalutamide treatment *in vitro* and *in vivo* without obvious toxicity (FIG. 12 A, C, D).

[0149] Although the foregoing has been described in some detail by way of illustration and example for purposes of clarity and understanding, one of skill in the art will appreciate that certain changes and modifications can be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound according to Formula I:



(I),

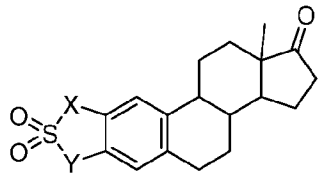
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $–X(SO_2)Y–$;

X is O and Y is NH, or X is NH and Y is O; and

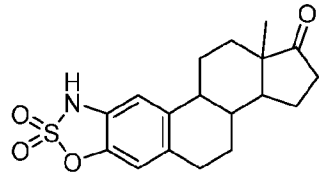
R^1 is combined with two carbons of the phenyl group to which it is attached to form an oxathiazolidine dioxide.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having a structure according to Formula Ia:



(Ia).

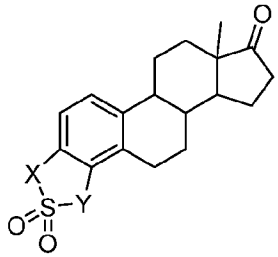
3. The compound of claim 2, which is:



,

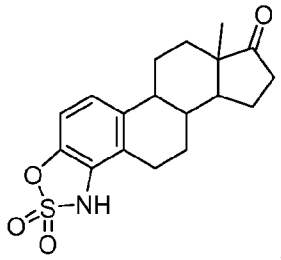
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having a structure according to Formula Ib:



(Ib).

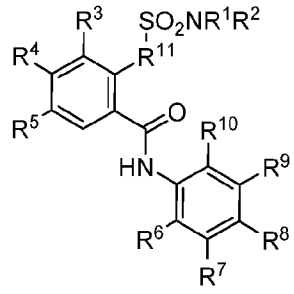
5. The compound of claim 4, which is:



,

or a pharmaceutically acceptable salt thereof.

6. A compound according to Formula III:



(III),

or pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently hydrogen or C_{1-6} alkyl;

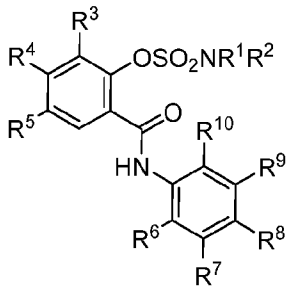
R^3, R^4, and R^5 are each independently hydrogen, halogen,-OH, C_{1-6} alkyl, or C_{1-6} alkoxy;

R^6, R^7, R^8, R^9, and R^{10} are each independently hydrogen, halogen, -OH, $-NH_3$, $-NO_2$, -CN, C_{1-6} haloalkyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} alkoxy;

R^{11} is a bond, C_{1-6} alkylene, NR^{12} , or O; and

R^{12} is hydrogen or C_{1-6} alkyl.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, having a structure according to Formula IIIa:



(IIIa).

8. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 are hydrogen; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} are each independently hydrogen, halogen, or $-NO_2$.

9. The compound of any one of claims 6-8, or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 are hydrogen;

one of R^3, R^4, and R^5 is halogen, and two of R^3, R^4, and R^5 are hydrogen; and

one of R^6, R^7 ,R^8, R^9, and R^{10} is halogen, one of R^6, R^7 ,R^8, R^9, and R^{10} is $-NO_2$, and three of R^6, R^7 ,R^8, R^9, and R^{10} are hydrogen.

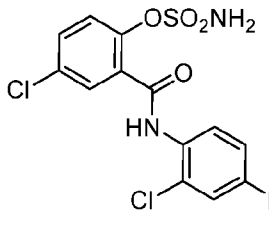
10. The compound of any one of claims 6-9, or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 are hydrogen;

one of R^3, R^4, and R^5 is chloro, and the others of R^3, R^4, and R^5 are hydrogen; and

one of R^6, R^7 ,R^8, R^9, and R^{10} is chloro, another of R^6, R^7 ,R^8, R^9, and R^{10} is $-NO_2$, and the others of R^6, R^7 ,R^8, R^9, and R^{10} are hydrogen.

11. The compound of any one of claims 6-10, which is:



or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

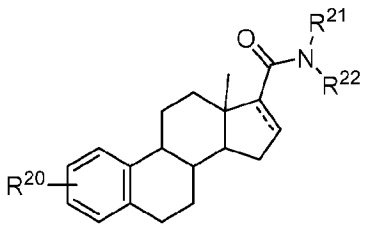
13. The pharmaceutical composition of claim 12, further comprising an antiandrogen drug.

14. The pharmaceutical composition of claim 13, wherein the antiandrogen drug is selected from the group consisting of enzalutamide, abiraterone, bicalutamide, apalutamide, darolutamide, and combinations thereof.

15. A pharmaceutical composition comprising the compound of any one of claims 2-11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

16. The pharmaceutical composition of claim 15, further comprising an antiandrogen drug.

17. A pharmaceutical composition comprising an antiandrogen drug and a compound according to Formula II:



(II),

or a pharmaceutically acceptable salt thereof, wherein:

the dashed line represents a single bond or a double bond;

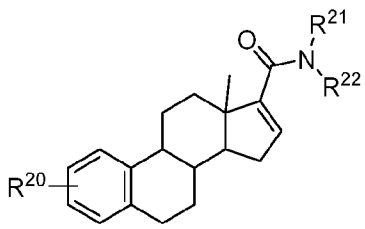
R^{20} is $–O(SO_2)NR^{23}R^{24}–$, which is combined with two carbons of the phenyl group to which it is attached to form a 4- to 10-membered heterocycle, or

R^{20} is $–O(SO_2)NR^{23}R^{25}$;

R^{21}, R^{22}, R^{23}, and R^{25} are each independently hydrogen or C_{1-6} alkyl; and

R^{24} is a bond, C_{1-6} alkylene, or C_{1-6} alkenylene.

18. The pharmaceutical composition of claim 17, wherein the compound has a structure according to Formula IIa:



(IIa).

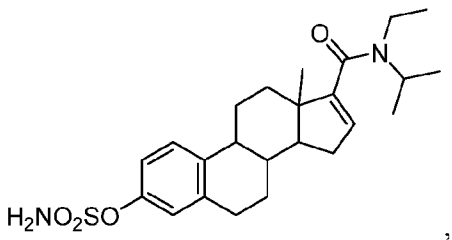
19. The pharmaceutical composition of claim 17 or claim 18, wherein R^{20} is $–O(SO_2)NR^{23}R^{24}–$, and R^{24} is C_{1-6} alkylene or C_{1-6} alkenylene.

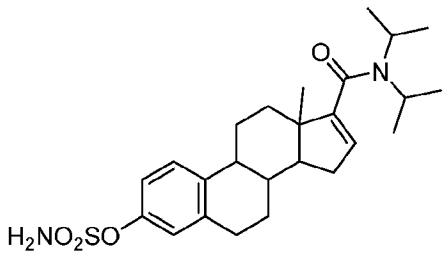
20. The pharmaceutical composition of any one of claims 17-19, wherein R^{20} is combined with two carbons of the phenyl group to which it is attached to form an oxathiazine dioxide or a dihydro-oxathiazine dioxide.

21. The pharmaceutical composition of claim 17 or claim 18, wherein R^{20} is $–O(SO_2)–NR^{23}R^{25}$.

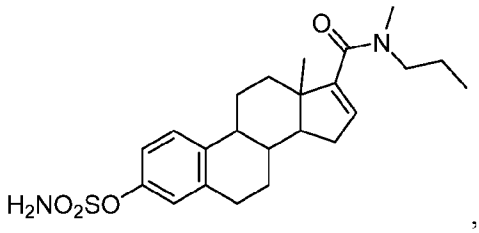
22. The pharmaceutical composition of any one of claims 17-21, wherein:
R^{21} is hydrogen, methyl, ethyl, propyl, or isopropyl; and
R^{22} is hydrogen, propyl, or isopropyl.

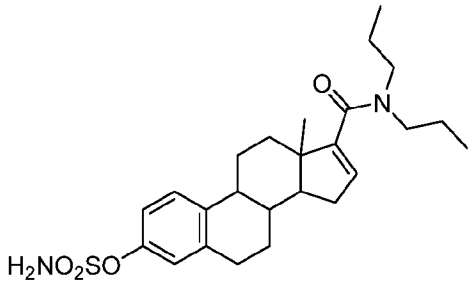
23. The pharmaceutical composition of any one of claims 17-22, wherein the steroid sulfatase inhibitor compound is selected from the group consisting of:



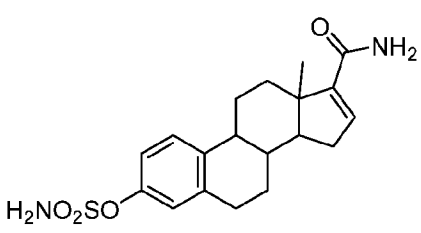
,


,

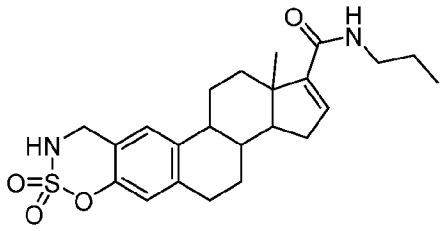


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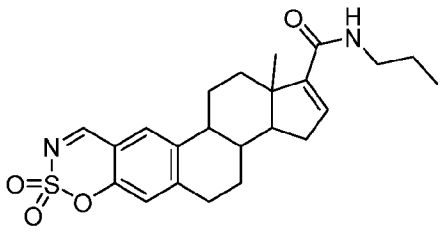
,



,



, and



.

24. The pharmaceutical composition of any one of claims 16-23, wherein the antiandrogen drug is selected from the group consisting of enzalutamide, abiraterone, bicalutamide, apalutamide, darolutamide, and combinations thereof.

25. A method of treating a disorder, the method comprising administering to a subject in need thereof a therapeutically effective amount of the compound of any one of claims 1-11, or a therapeutically effective amount of a pharmaceutical composition of any one of claims 12-24.

26. The method of claim 25, wherein the disorder is a cancer.

27. The method of claim 26, wherein the cancer is selected from the group consisting of an androgen-independent cancer, a metastatic cancer, a castrate-resistant cancer, a castration recurrent cancer, a hormone-resistant cancer, a metastatic castrate-resistant cancer, and combinations thereof.

28. The method of claim 26 or 27, wherein the cancer is prostate cancer or breast cancer.

29. The method of any one of claims 26-28, whrein the cancer is prostate cancer.

30. The method of any one of claims 25-29, wherein the compound of Formula I or the compound of Formula III is administered, and wherein the method further comprises administering to the subject an antiandrogen drug.

31. The method of any one of claims 25-29, wherein the composition comprising the compound of Formula II and the antiandrogen drug is administered.

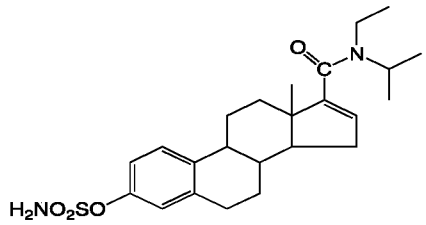
32. The method of any one of claims 25-31, wherein the antiandrogen drug is selected from the group consisting of enzalutamide, abiraterone, bicalutamide, apalutamide, darolutamide, and a combination thereof.

33. The method of any one of claims 25-32 further comprising determining the level of one or more biomarkers in a test sample obtained from the subject.

34. The method of claim 33, wherein the one or more biomarkers comprises prostate-specific antigen (PSA).

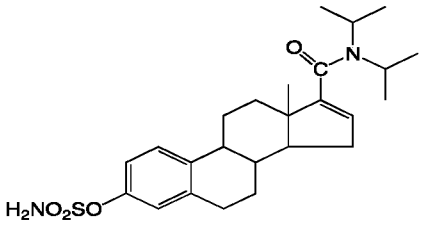
35. The method of claim 34, wherein administration of the compound of any one of claims 1-11, or the pharmaceutical composition of any one of claims 12-24, results in a decrease in the level of PSA in a test sample obtained from the subject the administration as compared to the level of PSA in a test sample obtained from the subject before the administration.

FIG. 1A



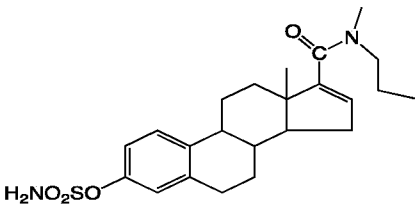
SI-1

(MW - 446.6)



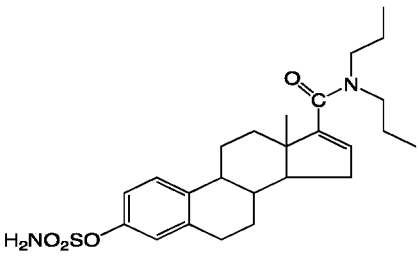
SI-2

(MW - 460.6)



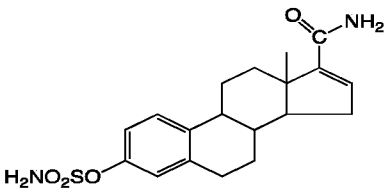
SI-3

(MW - 432.6)



SI-4

(MW - 460.6)



SI-5

(MW - 376.5)

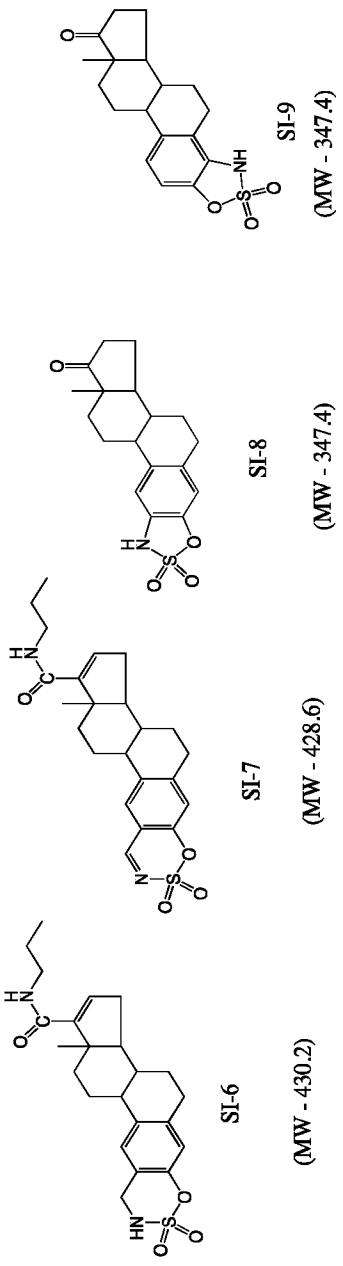


FIG. 1B

FIG. 2

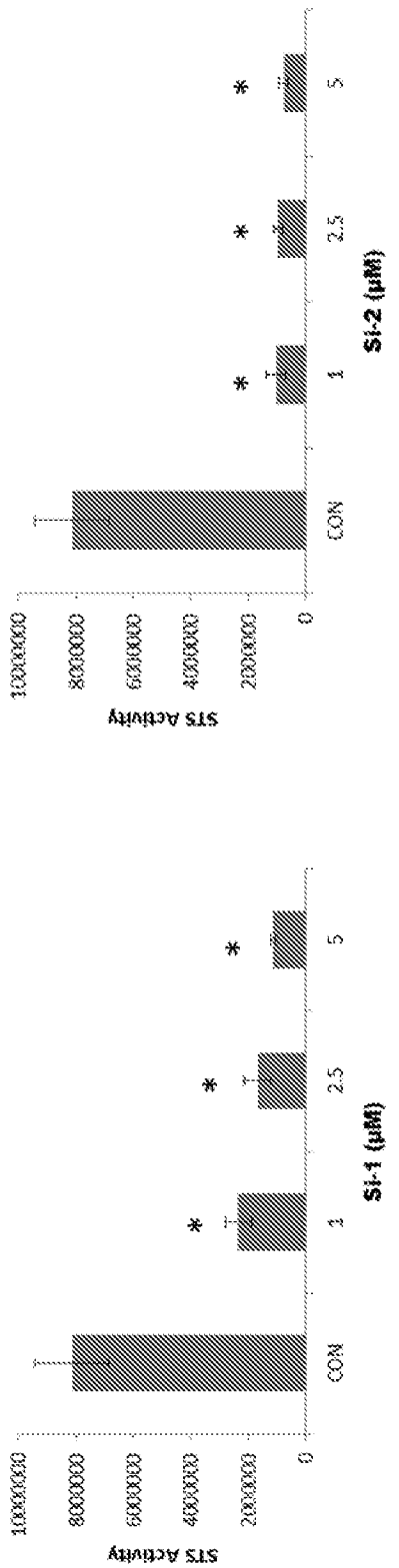

STS Activity of VCaP Treated with Si-1
STS Activity
10000000
8000000
6000000
4000000
2000000
0
CON
1
2.5
5
Si-1 (μM)
*
STS Activity of VCaP Treated with Si-2
STS Activity
10000000
8000000
6000000
4000000
2000000
0
CON
1
2.5
5
Si-2 (μM)
*

FIG. 3

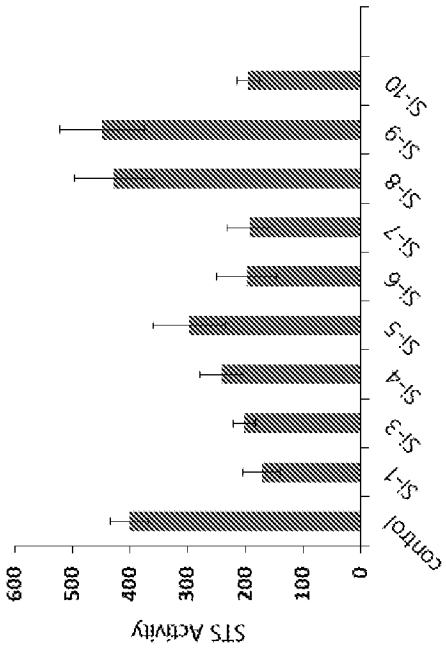
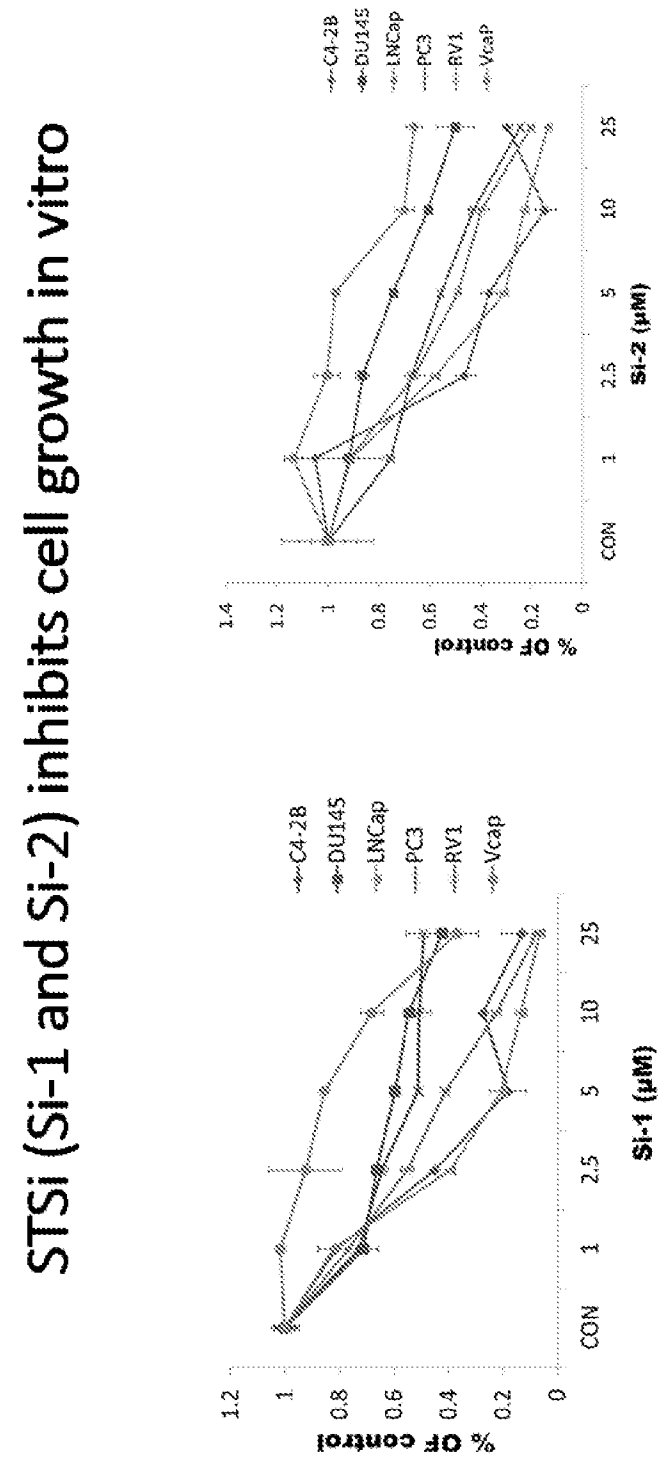

Characterization of STSi (5 uM) activity in VCaP cells
STS Activity
600
500
400
300
200
100
0
control
Si-1
Si-2
Si-3
Si-4
Si-5
Si-6
Si-7
Si-8
Si-9
Si-10

FIG. 4


STSi (Si-1 and Si-2) inhibits cell growth in vitro
% OF control
Si-1 (μM)
Si-2 (μM)
CON
C4-2B
DU145
LNCap
PC3
RV1
Vcap

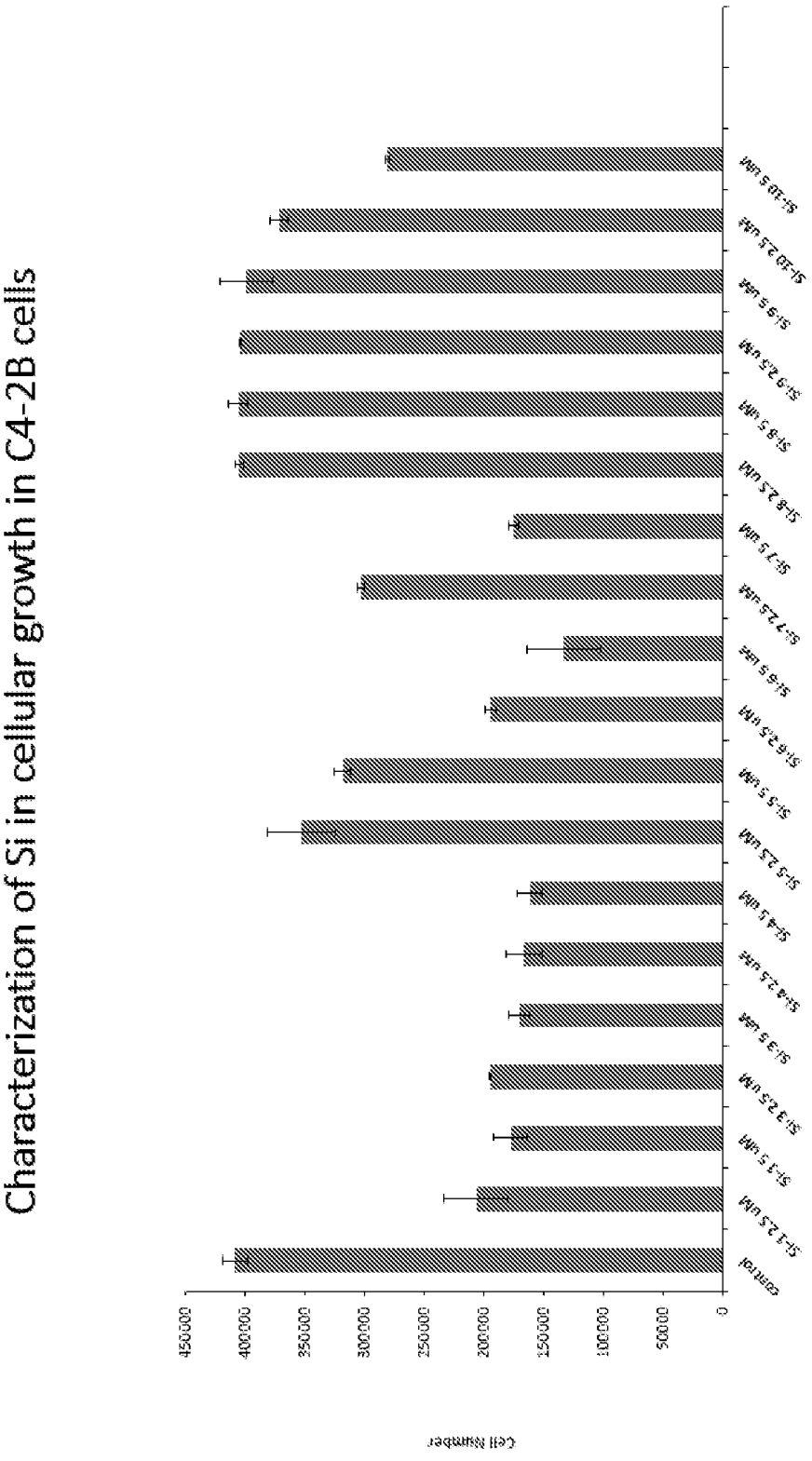

Characterization of Si in cellular growth in C4-2B cells
Cell Number
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
control
Si-1 2.5 uM
Si-1 5 uM
Si-2 2.5 uM
Si-2 5 uM
Si-3 2.5 uM
Si-3 5 uM
Si-4 2.5 uM
Si-4 5 uM
Si-5 2.5 uM
Si-5 5 uM
Si-6 2.5 uM
Si-6 5 uM
Si-7 2.5 uM
Si-7 5 uM
Si-8 2.5 uM
Si-8 5 uM
Si-9 2.5 uM
Si-9 5 uM
Si-10 2.5 uM
Si-10 5 uM

FIG. 5

FIG. 6

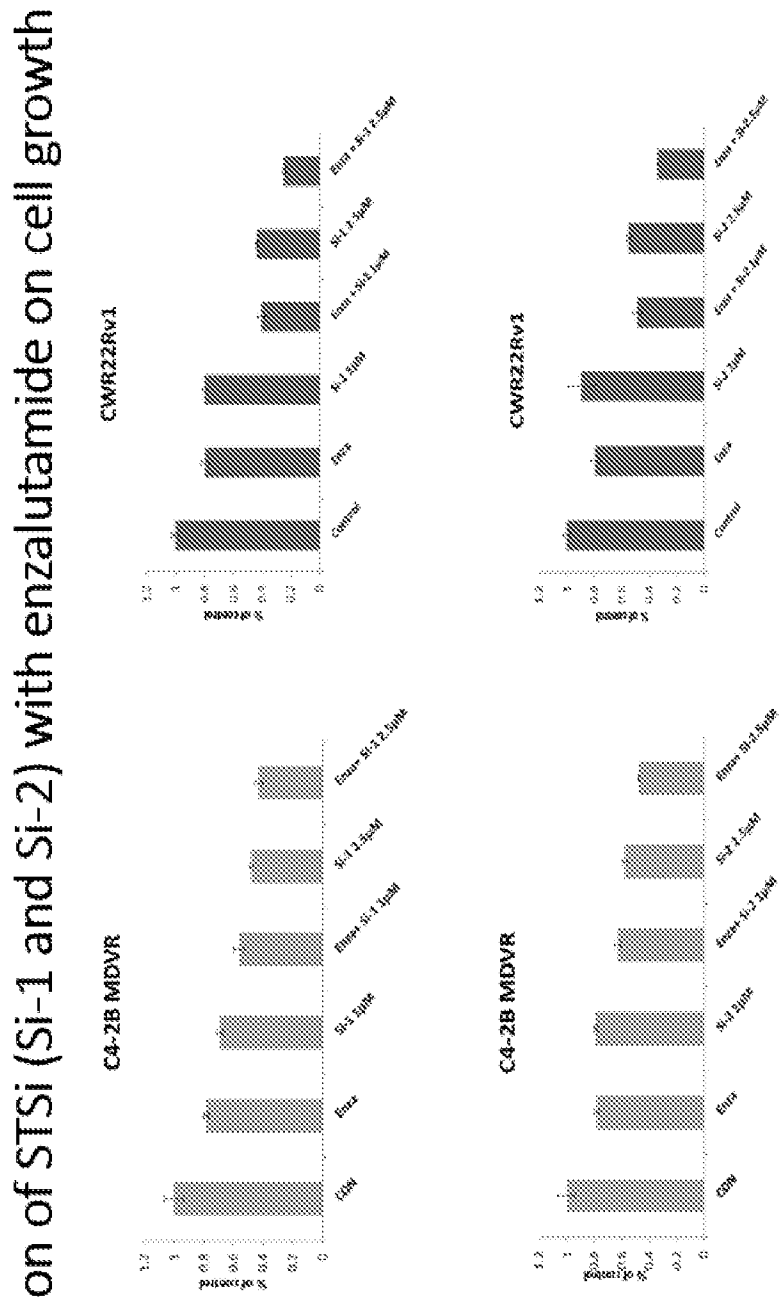

Combination of STSi (Si-1 and Si-2) with enzalutamide on cell growth
C4-2B MDVR
CWR22Rv1
C4-2B MDVR
CWR22Rv1
Control
Enza
Si-1 5μM
Si-2 5μM
Enza + Si-1 1μM
Enza + Si-1 2.5μM
Enza + Si-2 2.5μM
Enza + Si-2 5μM
CON
Enza
Si-1 5μM
Si-2 5μM
Enza+ Si-1 1μM
Enza+ Si-1 2.5μM
Enza+ Si-2 2.5μM
Enza+ Si-2 5μM

FIG. 7

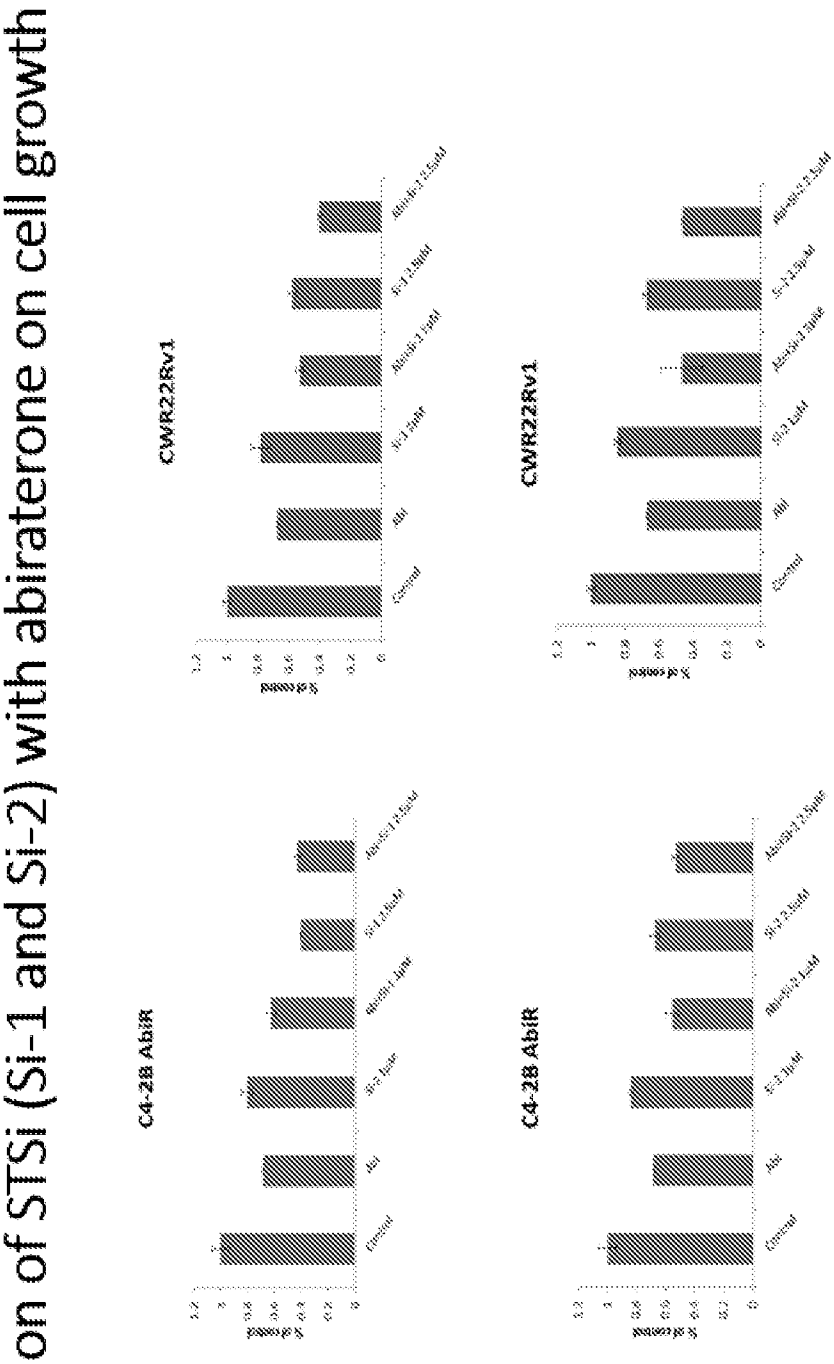

Combination of STSi (Si-1 and Si-2) with abiraterone on cell growth
CWR22Rv1
C4-2B AbiR
CWR22Rv1
C4-2B AbiR

FIG. 8A

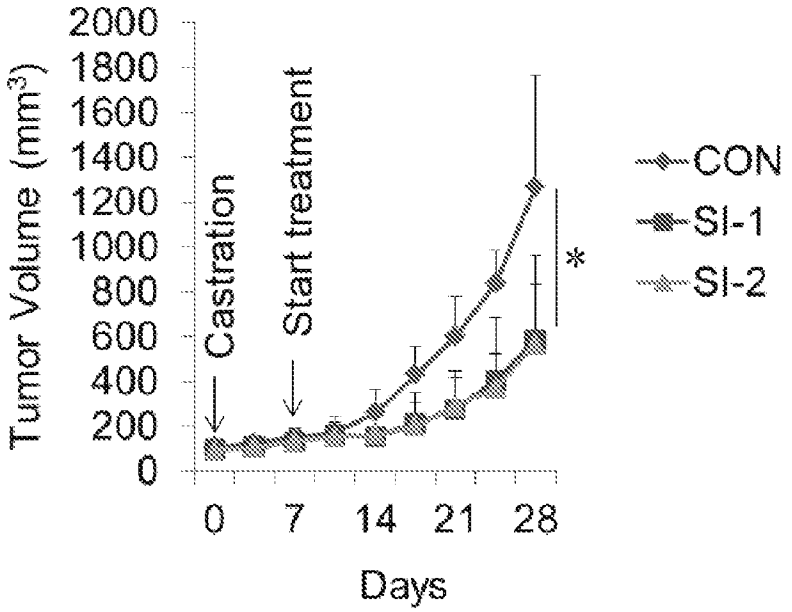

Tumor Volume (mm3)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Castration
Start treatment
*
CON
SI-1
SI-2
0
7
14
21
28
Days

FIG. 8B

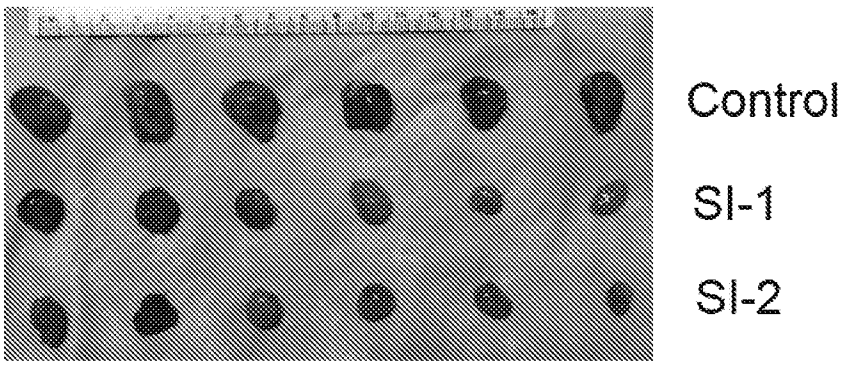

Control
SI-1
SI-2

FIG. 8C

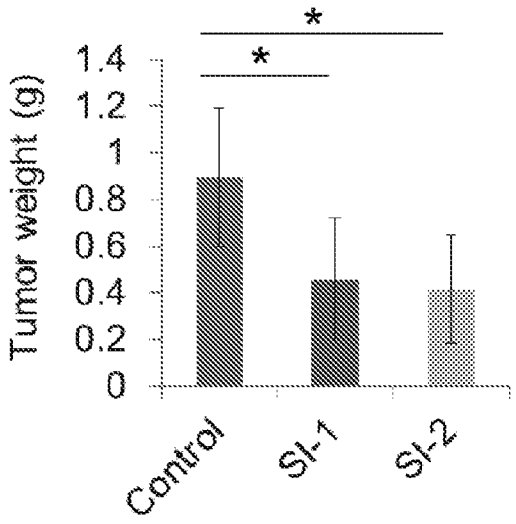

*
*
Tumor weight (g)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Control
SI-1
SI-2

FIG. 8D

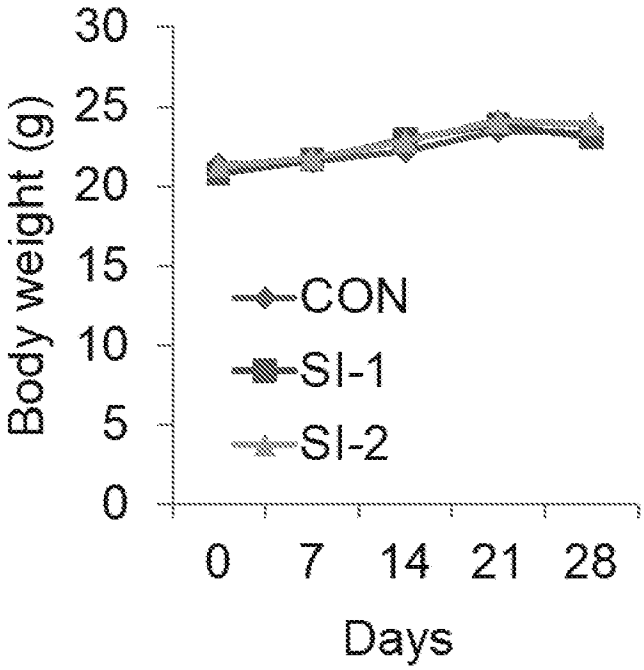

Body weight (g)
30
25
20
15
10
5
0
CON
SI-1
SI-2
0
7
14
21
28
Days

FIG. 8E

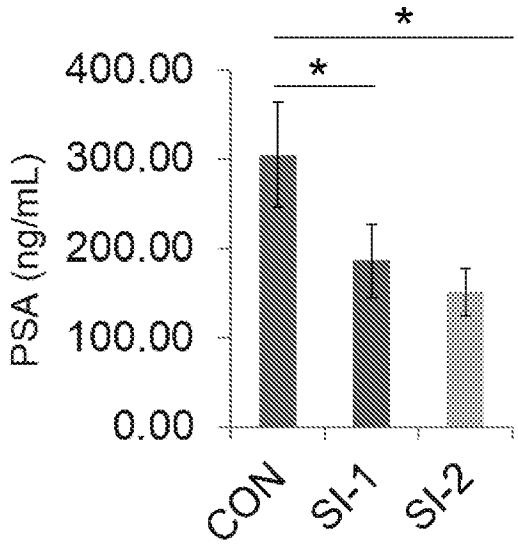

*
*
400.00
300.00
200.00
100.00
0.00
PSA (ng/mL)
CON
SI-1
SI-2

FIG. 8F

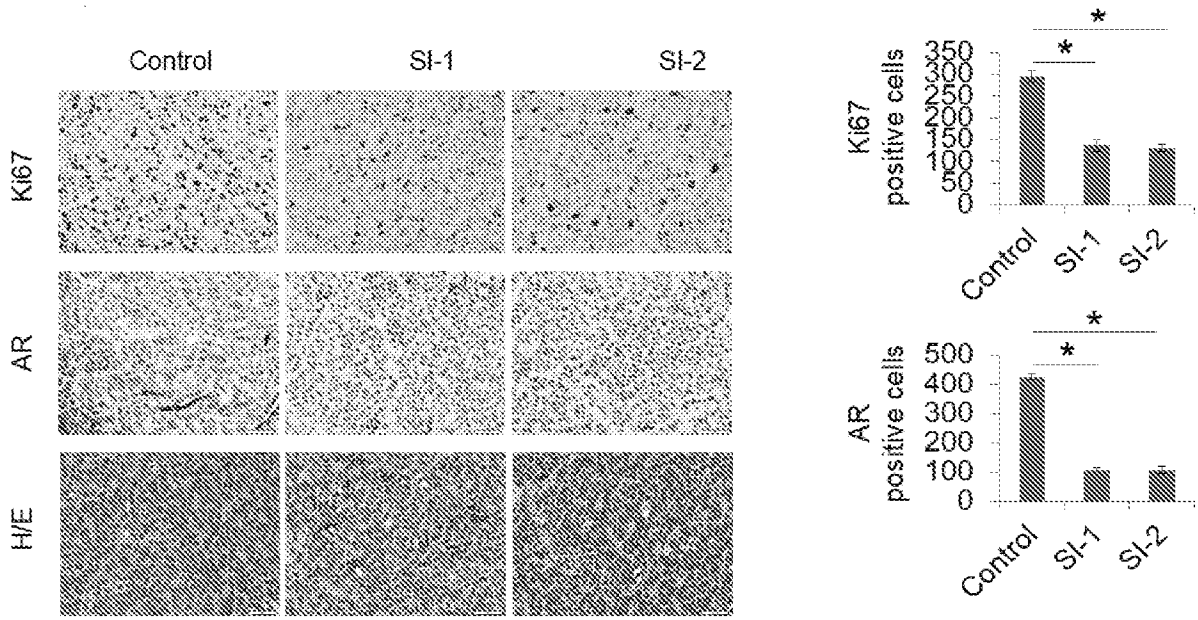

Control
SI-1
SI-2
Ki67
AR
H/E
Ki67 positive cells
AR positive cells
Control
SI-1
SI-2

FIG. 9A

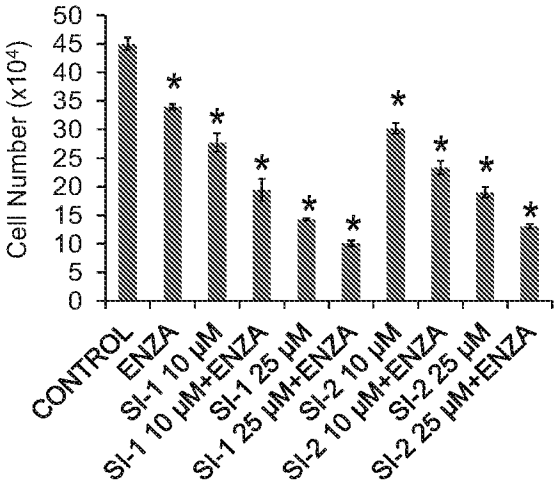

Cell Number (x10⁴)
50
45
40
35
30
25
20
15
10
5
0
CONTROL
ENZA
SI-1 10 μM
SI-1 10 μM+ENZA
SI-1 25 μM
SI-1 25 μM+ENZA
SI-2 10 μM
SI-2 10 μM+ENZA
SI-2 25 μM
SI-2 25 μM+ENZA

FIG. 9B

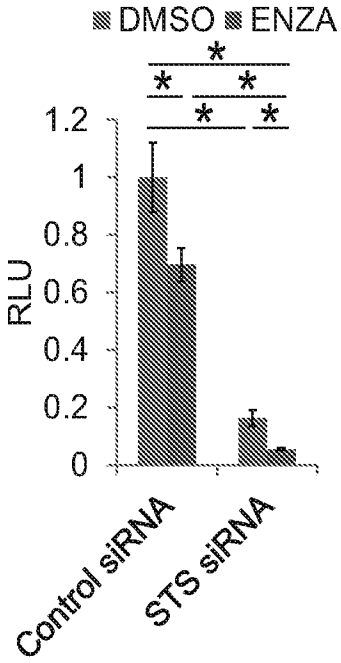

DMSO
ENZA
RLU
1.2
1
0.8
0.6
0.4
0.2
0
Control siRNA
STS siRNA

FIG. 9C

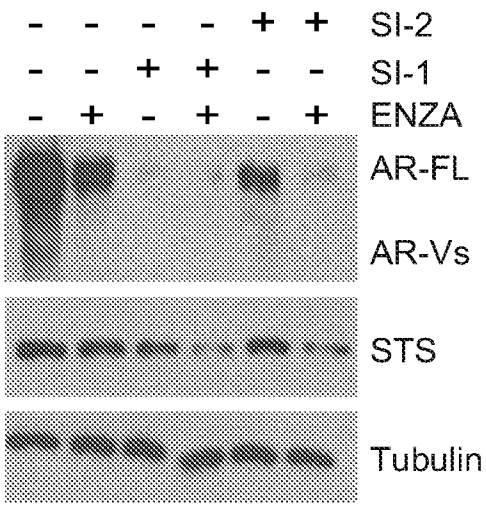

- - - - + + SI-2
- - + + - - SI-1
- + - + - + ENZA
AR-FL
AR-Vs
STS
Tubulin

FIG. 9D

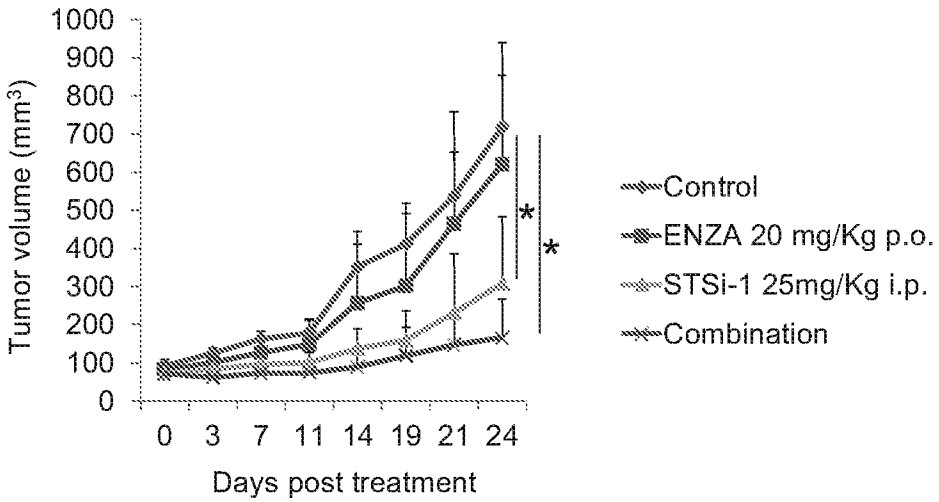
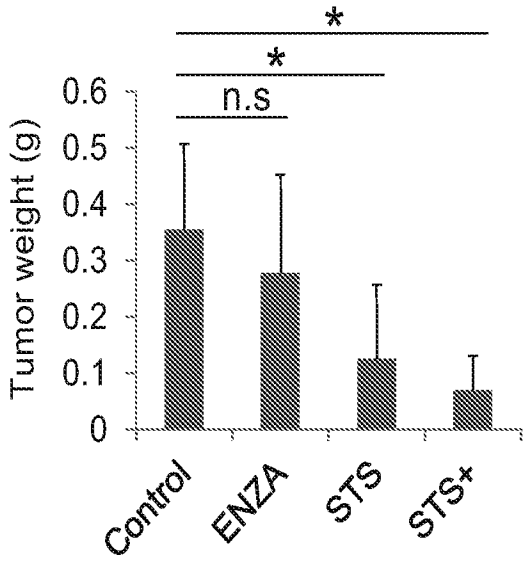

Tumor volume (mm3)
1000
900
800
700
600
500
400
300
200
100
0
0 3 7 11 14 19 21 24
Days post treatment
*
*
Control
ENZA 20 mg/Kg p.o.
STSi-1 25mg/Kg i.p.
Combination

FIG. 9E



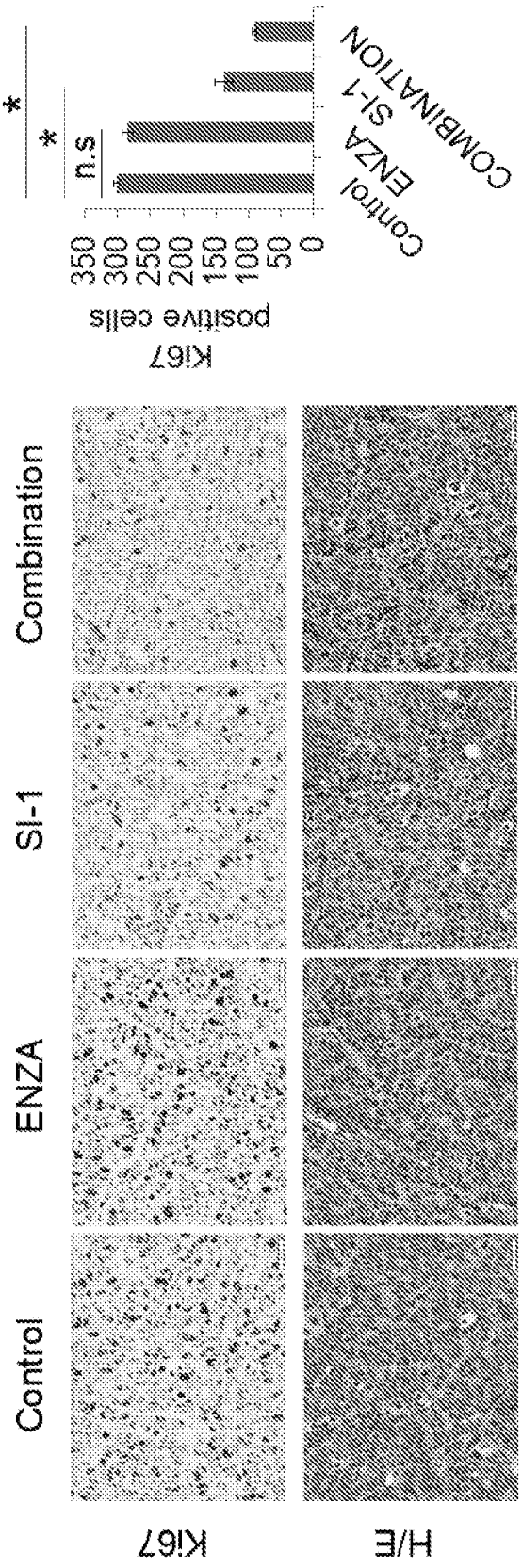

Control
ENZA
SI-1
Combination
KI67
H/E
KI67
positive cells
350
300
250
200
150
100
50
0
Control
ENZA
SI-1
COMBINATION
n.s
*
*

FIG. 9F

FIG. 10

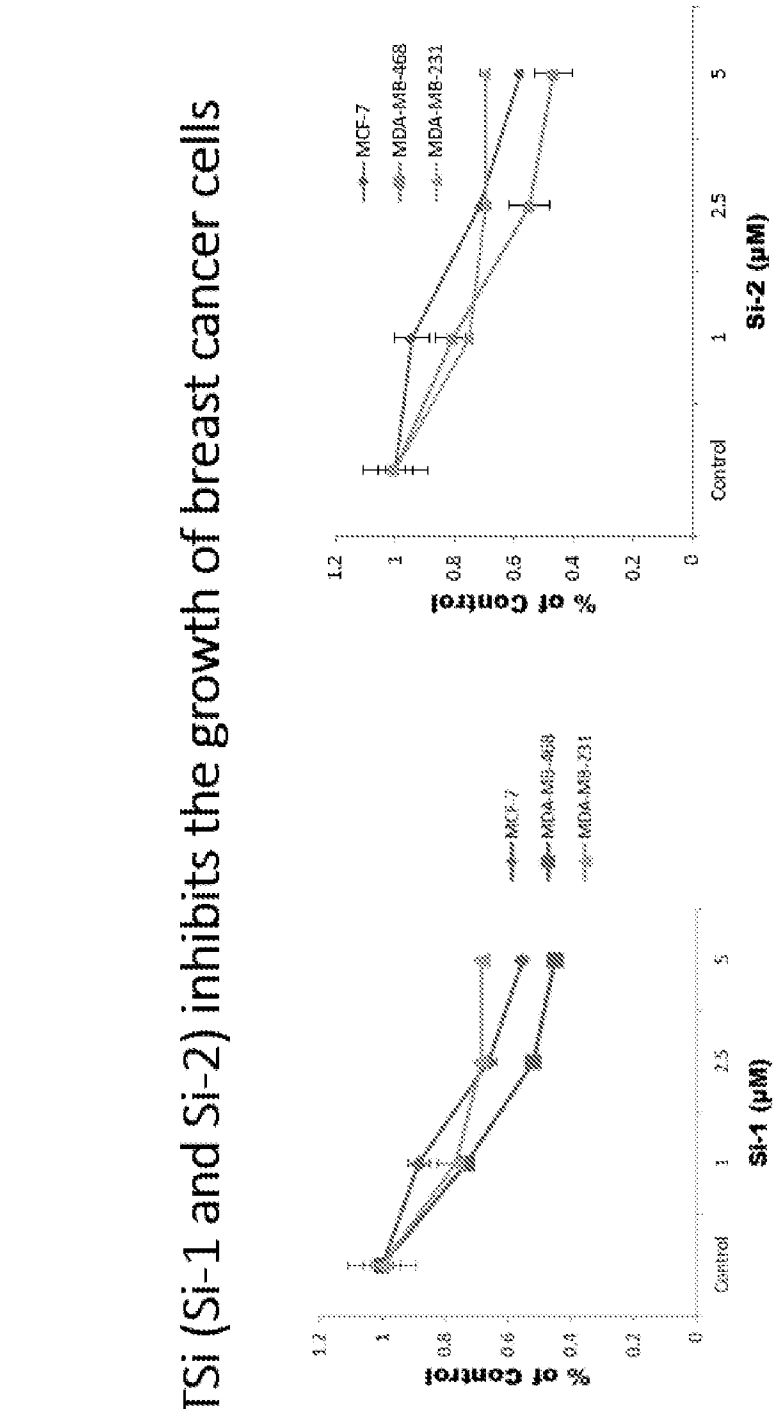
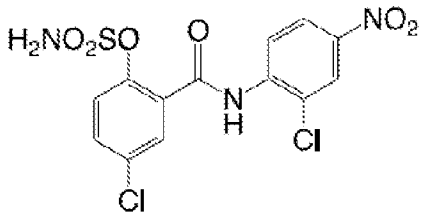

STSi (Si-1 and Si-2) inhibits the growth of breast cancer cells
% of Control
1.2
1
0.8
0.6
0.4
0.2
0
Control
1
2.5
5
Si-1 (μM)
MCF-7
MDA-MB-468
MDA-MB-231
% of Control
1.2
1
0.8
0.6
0.4
0.2
0
Control
1
2.5
5
Si-2 (μM)
MCF-7
MDA-MB-468
MDA-MB-231

FIG. 11



Niclosamide sulfamate

(MW – 406.2)

FIG. 12A

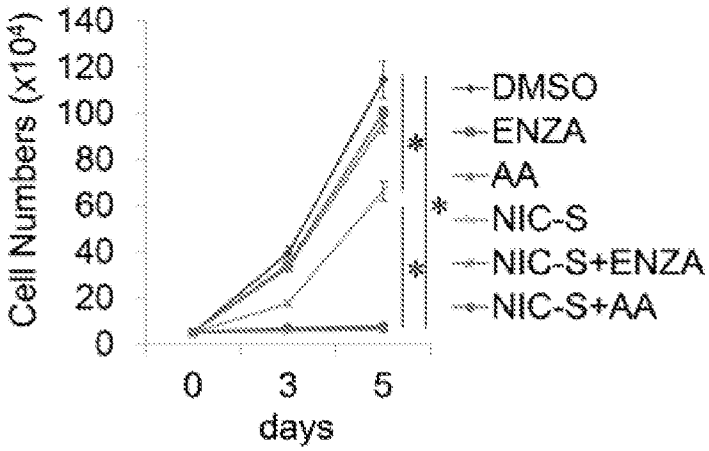


FIG. 12B

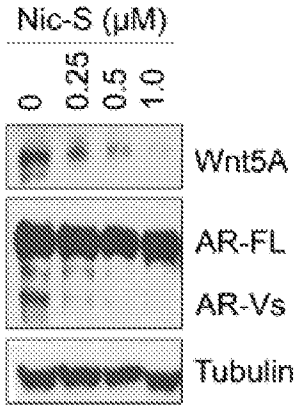


FIG. 12C

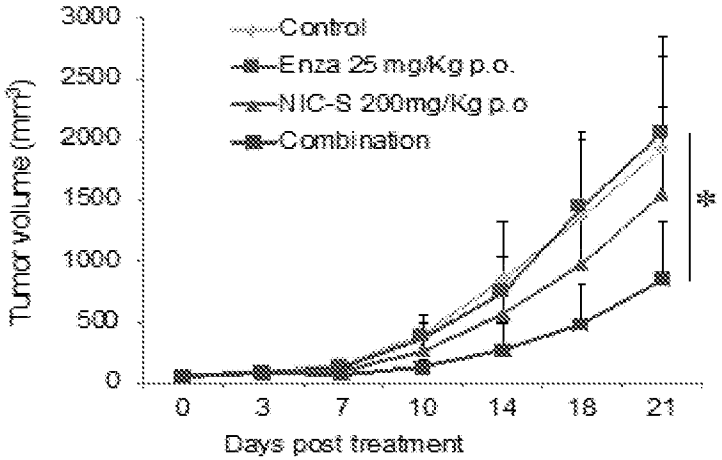
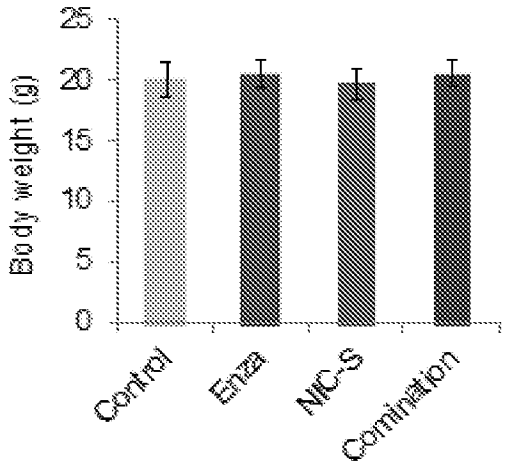


FIG. 12D



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/059491

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/566; A61K 31/565; A61P 35/00; C07J 71/00 (2020.01)
CPC - A61K 31/566; A61K 31/565; A61P 35/00; C07J 71/00 (2020.01)

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WOO et al. Synthesis and evaluation of analogues of estrone-3-O-sulfamate as potent steroid sulfatase inhibitors, Bioorganic & Medicinal Chemistry, Vol. 20, Iss. 8, 15 April 2012, [retrieved on 05 February 2020]. Retrieved from the Internet. <URL: https://www.sciencedirect.com/science/article/pii/S0968089612001861>, abstract	1-3 --- 12-14
Y	US 2006/0035875 A1 (SHIOTSU et al) 16 February 2006 (16.02.2006) entire document	12-14
A	PUBCHEM. Compound Summary for SID 160859304, Available Date: 27 February 2013 [retrieved on 09 December 2019]. Retrieved from the Internet: <URL: https://pubchem.ncbi.nlm.nih.gov/substance/160859304> entire document	1-3, 12-14
A	US 2017/0112843 A1 (THE SCRIPPS RESEARCH INSTITUTE) 27 April 2017 (27.04.2017) entire document	1-3, 12-14

☐ Further documents are listed in the continuation of Box C. ☐ 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 application or patent 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
06 February 2020	21 FEB 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/059491

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: 10, 11, 15, 16, 20, 22-35
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:
See extra sheet(s).

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

2. ☐ As all searchable claims could be searched without effort justifying 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 report covers 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.:
1-3, 12-14

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

International application No.
PCT/US2019/059491

Continued from Box No. III Observations where unity of invention is lacking

Claims 1-3 and 12-14 have been analyzed subject to the restriction that the claims read on a compound according to Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound is as shown in claim 3 of the instant invention.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-5 and 12-14 are drawn to compounds according to Formula I, and pharmaceutical compositions thereof.

Group II+: claims 6-9 are drawn to compounds according to Formula III.

Group III+: claims 17-19 and 21 are drawn to pharmaceutical composition comprising an antiandrogen drug and a compound according to Formula II.

The first invention of Group I+ is restricted to a compound according to Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound is as shown in claim 3 of the instant invention, and pharmaceutical compositions thereof. It is believed that claims 1-3 and 12-14 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

The first invention of Group II+ is restricted to a compound according to Formula III, or a pharmaceutically acceptable salt thereof, wherein: R1 and R2 are each hydrogen; R3, R4, and R5 are each hydrogen; R6, R7, R8, R9, and R10 are each hydrogen; R11 is a bond; and R12 is hydrogen.

The first invention of Group III+ is restricted to a pharmaceutical composition comprising an antiandrogen drug and a compound according to Formula II: or a pharmaceutically acceptable salt thereof, wherein: the dashed line represents a single bond; R20 is –O(SO2)NR23R24-, which is combined with two carbons of the phenyl group to which it is attached to form a 5-membered heterocycle, wherein O is attached to the top carbon adjacent to the six-membered ring and N is attached to the next carbon; R21, R22, R23, and R25 are each hydrogen; and R24 is a bond.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound according to Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound is as shown in claim 5 of the instant invention, and pharmaceutical compositions thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+, II+, and III+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, compounds according to Formula I, and pharmaceutical compositions thereof, are not present in Groups II+ and III+; the special technical features of Group II+, compounds according to Formula III, are not present in Groups I+ and III+; and the special technical features of Group III+, pharmaceutical composition comprising an antiandrogen drug and a compound according to Formula II, are not present in Groups I+ and II+.

The Groups I+, II+, and III+ formulae do not share a significant structural element requiring the selection of alternatives for R1, R2,R3, R4, R5, R6, R7, R8, R9, R10, R20, R21, and R22 and accordingly these groups lack unity a priori.

Additionally, even if Groups I+, II+, and III+ were considered to share the technical features of a compound according to Formula I, or a pharmaceutically acceptable salt thereof, pharmaceutical compositions thereof; a compound according to Formula III, or a pharmaceutically acceptable salt thereof ; and a pharmaceutical composition comprising an antiandrogen drug and a compound according to Formula II: or a pharmaceutically acceptable salt thereof, these shared technical features do not represent a contribution over the prior art as disclosed by Substance Record for SID 160859304 to PubChem, US 2017/0112843 A1 to The Scripps Research Institute, and US 2006/0035875 A1 to Shiotsu et al.

Substance Record for SID 160859304 to PubChem teaches a compound according to Formula I, wherein R1 is –X(SO2)Y-; X is O and Y is NH; and R1 is combined with two carbons of the phenyl group to which it is attached to form a oxathiazolidine dioxide (Pg. 2, see structure shown) pharmaceutical compositions thereof (Pg. 3;...see shown structure...).

Additionally, US 2017/0112843 A1 to The Scripps Research Institute teaches a compound according to Formula III, wherein: R1 is hydrogen and R2 is C1 alkyl; R3, R4, and R5 are each hydrogen; R6, R7, R9, and R10 are each hydrogen; R8 is –CN; and R11 is a bond (Drawings Sheet 14 of 18, FIG. 8, compound on the bottom left, see shown structure); and pharmaceutical compositions (Para. [0020])

Further, US 2006/0035875 A1 to Shiotsu et al. teach a pharmaceutical composition comprising an antiandrogen drug (Claims 25-29) and a compound according to Formula II: wherein the dashed line represents a double bond; R20 is –O(SO2)NR23R25; R21, R22 are each independently C3 alkyl; R23 and R25 are hydrogen; (Para. [0096], compound 1, see structure shown).

The inventions listed in Groups I+, II+, and III+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.