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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2018 (15.03.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/045450 A1

(51) International Patent Classification:
A61K 31/09 (2006.01) *C07C 43/23* (2006.01)
A61P 35/00 (2006.01)

(21) International Application Number:
PCT/CA2017/000201

(22) International Filing Date:
08 September 2017 (08.09.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/385,648 09 September 2016 (09.09.2016) US

(71) Applicants: **BRITISH COLUMBIA CANCER AGENCY BRANCH** [CA/CA]; 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6 (CA). **THE UNIVERSITY OF BRITISH COLUMBIA** [CA/CA]; University-Industry Liaison Office, #103-6190 Agronomy Road, Vancouver, British Columbia V6T 1ZE (CA).

(72) Inventors: **SADAR, Marianne Dorothy**; 4091 Bayridge Avenue, West Vancouver BC V7V 3J9 (CA). **MAWJI, Nasrin R.**; 203-3421 Curle Avenue, Burnaby BC V5G 4P4 (CA). **OBST, Jonathon Kyle**; 328 East 19th Avenue, Vancouver BC V5V 1J5 (CA). **ANDERSEN, Raymond John**; 4048 West 32nd Avenue, Vancouver, BC V6S 1Z6 (CA). **WILLIAMS, David E.**; 1472 East 20th Avenue, Vancouver BC V5N 2K6 (CA). **JIAN, Kunzhong**; 2660 Tennis Crescent, Vancouver, BC V6T 2E1 (CA).

(74) Agent: **DEETH WILLIAMS WALL LLP**; 150 York Street, Suite 400, Toronto, Ontario M5H 3S5 (CA).

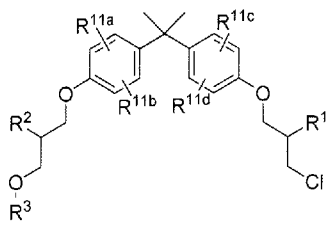
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2018/045450 A1

(54) Title: BISPHENOL A COMPOUNDS AND METHODS FOR TREATING DRUG-RESISTANT ANDROGEN RECEPTOR MEDIATED CANCERS



(I)

(57) Abstract: The present invention provides methods for treating cancer comprising a compound of formula (I) or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein the cancer, cancer cells, or tumour cells are resistant to a cancer agent which is susceptible to glucuronidation. R^1, R^2, R^3, R^{11a}, R^{11b}, R^{11c}, and R^{11d} are as defined herein. (Formula (I))

BISPHENOL A COMPOUNDS AND METHODS FOR TREATING DRUG-RESISTANT ANDROGEN RECEPTOR MEDIATED CANCERS

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims the priority benefit of U.S. Provisional Application No. 62/385,648, filed on September 9, 2016, the disclosure of which is incorporated by reference herein in its entirety

STATEMENT OF GOVERNMENT INTEREST

[002] This invention was made in part with government support under Grant No. 2R01 CA105304 awarded by the U.S. National Cancer Institute. The United States Government has certain rights in this invention.

FIELD OF THE DISCLOSURE

[003] The present disclosure generally relates to bisphenol-type compounds and their use for treatment of androgen receptor mediated disorders including cancer. Cancer can be prostate cancer, including but not limited to, primary/localized prostate cancer (newly diagnosed), locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, metastatic castration-resistant prostate cancer (CRPC), and hormone-sensitive prostate cancer. This disclosure also relates to bisphenol-related compounds which can be effective in the treatment of cells which display overexpression of *UGT2B* genes and/or compounds resistant to glucuronidation.

BACKGROUND OF THE DISCLOSURE

[004] Androgens mediate their effects through the androgen receptor (AR). Androgens play a role in a wide range of developmental and physiological responses and are involved in male sexual differentiation, maintenance of spermatogenesis, and male gonadotropin regulation (R. K. Ross, G. A. Coetzee, C. L. Pearce, J. K. Reichardt, P. Bretsky, L. N. Kolonel, B. E. Henderson, E. Lander, D. Altshuler & G. Daley, *Eur Urol* 35, 355-361 (1999); A. A. Thomson, *Reproduction* 121, 187-195 (2001); N. Tanji, K. Aoki & M. Yokoyama, *Arch Androl* 47, 1-7 (2001)). Several lines of evidence show that androgens are associated with the development of prostate

carcinogenesis. Firstly, androgens induce prostatic carcinogenesis in rodent models (R. L. Noble, *Cancer Res* 37, 1929-1933 (1977); R. L. Noble, *Oncology* 34, 138-141 (1977)) and men receiving androgens in the form of anabolic steroids have a higher incidence of prostate cancer (J. T. Roberts & D. M. Essenhigh, *Lancet* 2, 742 (1986); J. A. Jackson, J. Waxman & A. M. Spiekerman, *Arch Intern Med* 149, 2365-2366 (1989); P. D. Guinan, W. Sadoughi, H. Alsheik, R. J. Ablin, D. Alrenga & I. M. Bush, *Am J Surg* 131, 599-600 (1976)). Secondly, prostate cancer does not develop if humans or dogs are castrated before puberty (J. D. Wilson & C. Roehrborn, *J Clin Endocrinol Metab* 84, 4324-4331 (1999); G. Wilding, *Cancer Surv* 14, 113-130 (1992)). Castration of adult males causes involution of the prostate and apoptosis of prostatic epithelium while eliciting no effect on other male external genitalia (E. M. Bruckheimer & N. Kyprianou, *Cell Tissue Res* 301, 153-162 (2000); J. T. Isaacs, *Prostate* 5, 545-557 (1984)). This dependency on androgens provides the underlying rationale for treating prostate cancer with chemical or surgical castration (androgen ablation), also known as androgen ablation therapy (ABT) or androgen depravation therapy (ADT).

[005] Androgens also play a role in female diseases such as polycystic ovary syndrome as well as cancers. One example is ovarian cancer where elevated levels of androgens are associated with an increased risk of developing ovarian cancer (K. J. Helzlsouer, A. J. Alberg, G. B. Gordon, C. Longcope, T. L. Bush, S. C. Hoffman & G. W. Comstock, *JAMA* 274, 1926-1930 (1995); R. J. Edmondson, J. M. Monaghan & B. R. Davies, *Br J Cancer* 86, 879-885 (2002)). The AR has been detected in a majority of ovarian cancers (H. A. Risch, *J Natl Cancer Inst* 90, 1774-1786 (1998); B. R. Rao & B. J. Slotman, *Endocr Rev* 12, 14-26 (1991); G. M. Clinton & W. Hua, *Crit Rev Oncol Hematol* 25, 1-9 (1997)), whereas estrogen receptor-alpha (ERa) and the progesterone receptor are detected in less than 50% of ovarian tumors.

[006] The only effective treatment available for advanced prostate cancer is the withdrawal of androgens which are essential for the survival of prostate luminal cells. Androgen ablation therapy causes a temporary reduction in tumor burden concomitant with a decrease in serum prostate-specific antigen (PSA). Unfortunately prostate cancer can eventually grow again in the absence of testicular androgens (castration-resistant disease) (Huber *et al* 1987 *Scand J. Urol Nephrol.* 104, 33-39). Castration-resistant prostate cancer that is still driven by AR is biochemically characterized before the onset of symptoms by a rising titre of serum PSA (Miller

et al 1992 *J. Urol.* 147, 956-961). Once the disease becomes castration-resistant most patients succumb to their disease within two years.

[007] The AR has distinct functional domains that include the carboxy-terminal ligand-binding domain (LBD), a DNA-binding domain (DBD) comprising two zinc finger motifs, and an N-terminus domain (NTD) that contains two transcriptional activation units (tau1 and tau5) within activation function-1 (AF-1). Binding of androgen (ligand) to the LBD of the AR results in its activation such that the receptor can effectively bind to its specific DNA consensus site, termed the androgen response element (ARE), on the promoter and enhancer regions of "normally" androgen regulated genes, such as PSA, to initiate transcription. The AR can be activated in the absence of androgen by stimulation of the cAMP-dependent protein kinase (PKA) pathway, with interleukin-6 (IL-6) and by various growth factors (Culig *et al* 1994 *Cancer Res.* 54, 5474-5478; Nazareth *et al* 1996 *J. Biol. Chem.* 271, 19900-19907; Sadar 1999 *J. Biol. Chem.* 274, 7777-7783; Ueda *et al* 2002 A *J. Biol. Chem.* 277, 7076-7085; and Ueda *et al* 2002 B *J. Biol. Chem.* 277, 38087-38094). The mechanism of ligand-independent transformation of the AR has been shown to involve: 1) increased nuclear AR protein suggesting nuclear translocation; 2) increased AR/ARE complex formation; and 3) the AR-NTD (Sadar 1999 *J. Biol. Chem.* 274, 7777-7783; Ueda *et al* 2002 A *J. Biol. Chem.* 277, 7076-7085; and Ueda *et al* 2002 B *J. Biol. Chem.* 277, 38087-38094). The AR can be activated in the absence of testicular androgens by alternative signal transduction pathways in castration-resistant disease, which is consistent with the finding that nuclear AR protein is present in secondary prostate cancer tumors (Kim *et al* 2002 *Am. J. Pathol.* 160, 219-226; and van der Kwast *et al* 1991 *Inter. J. Cancer* 48, 189-193).

[008] Clinically available inhibitors of the AR include nonsteroidal antiandrogens such as bicalutamide (Casodex™), nilutamide, flutamide, and enzalutamide. There is also a class of steroidal antiandrogens, such as cyproterone acetate and spironolactone. Both steroidal and non-steroidal antiandrogens target the LBD of the AR and predominantly fail presumably due to poor affinity and mutations that lead to activation of the AR by these same antiandrogens (Taplin, M.E., Bubley, G.J., Kom Y.J., Small E.J., Uptonm M., Rajeshkumarm B., Balkm S.P., *Cancer Res.*, 59, 2511-2515 (1999)), and constitutively active AR splice variants. Antiandrogens have no effect on the constitutively active AR splice variants that lack the ligand-binding domain (LBD) and are associated with castration-recurrent prostate cancer (Dehm SM, Schmidt LJ, Heemers HV, Vessella RL, Tindall DJ., *Cancer Res* 68, 5469-77, 2008; Guo Z, Yang X, Sun F, Jiang R, Linn

DE, Chen H, Chen H, Kong X, Melamed J, Tepper CG, Kung HJ, Brodie AM, Edwards J, Qiu Y., *Cancer Res.* 69, 2305-13, 2009; Hu et al 2009 Cancer Res. 69, 16-22; Sun et al 2010 *J Clin Invest.* 2010 120, 2715-30) and resistant to abiraterone and enzalutamide (Antonarakis et al., *N Engl J Med.* 2014, 371, 1028-38; Scher et al *JAMA Oncol.* 2016 doi: 10.1001). Conventional therapy has concentrated on androgen-dependent activation of the AR through its C-terminal domain.

[009] AR antagonists other than the bisphenol ether derivatives previously reported (*see*, WO 2010/000066, WO 2011/082487; WO 2011/082488; WO 2012/145330; WO 2015/031984; WO 2016/058080; and WO 2016/058082) that bind to full-length AR and/or truncated AR splice variants that are currently being developed include: AR degraders such as niclosamide (Liu C et al 2014), galeterone (Njar et al 2015; Yu Z at al 2014), and ARV-330/Androgen receptor PROTAC (Neklesa et al 2016 *J Clin Oncol* 34 suppl 2S; abstr 267); AR DBD inhibitor VPC-14449 (Dalal K et al 2014 *J Biol Chem.* 289(38):26417-29; Li H et al 2014 *J Med Chem.* 57(15):6458-67); antiandrogens apalutamide (Clegg NJ et al 2012), ODM-201 (Moilanen AM et al 2015), ODM-204 (Kallio et al *J Clin Oncol* 2016 vol. 34 no. 2_suppl 230), TAS3681 (Minamiguchi et al 2015 *J Clin Oncol* 33, suppl 7; abstr 266); and AR NTD inhibitors 3E10-AR441bsAb (Goicochea NL et al 2015), and sintokamide (Sadar et al 2008; Banuelos et al 2016).

[010] The AR-NTD is also a target for drug development (e.g. WO 2000/001813; Myung *et al. J. Clin. Invest* **2013**, *123*, 2948), since the NTD contains Activation-Function-1 (AF-1) which is the essential region required for AR transcriptional activity (Jenster et al 1991. *Mol Endocrinol.* 5, 1396-404). The AR-NTD importantly plays a role in activation of the AR in the absence of androgens (Sadar, M.D. 1999 *J. Biol. Chem.* 274, 7777-7783; Sadar MD *et al* 1999 *Endocr Relat Cancer.* 6, 487-502; Ueda *et al* 2002 *J. Biol. Chem.* 277, 7076-7085; Ueda 2002 *J. Biol. Chem.* 277, 38087-38094; Blaszczyk *et al* 2004 *Clin Cancer Res.* 10, 1860-9; Dehm *et al* 2006 *J Biol Chem.* 28, 27882-93; Gregory *et al* 2004 *J Biol Chem.* 279, 7119-30). The AR-NTD is important in hormonal progression of prostate cancer as shown by application of decoy molecules (Quayle *et al* 2007, *Proc Natl Acad Sci U S A.* 104,1331-1336).

[011] While the crystal structure has been resolved for the AR C-terminus LBD, this has not been the case for the NTD due to its high flexibility and intrinsic disorder in solution (Reid *et al* 2002 *J. Biol. Chem.* 277, 20079-20086) thereby hampering virtual docking drug discovery approaches. Compounds that modulate AR include the bisphenol compounds disclosed in published PCT Nos: WO 2010/000066, WO 2011/082487; WO 2011/082488; WO 2012/145330; WO 2012/139039;

WO 2012/145328; WO 2013/028572; WO 2013/028791; WO 2014/179867; WO 2015/031984; WO 2016/058080; WO 2016/058082; WO2016/112455; and WO 2016/141458, which are hereby incorporated by reference in their entireties, to the British Columbia Cancer Agency Branch and The University of British Columbia.

[012] Transcriptionally active androgen receptor plays a major role in CRPC in spite of reduced blood levels of androgen (Karantanos, T. *et al Oncogene* **2013**, *32*, 5501-5511; Harris, W. P. *et al Nature Clinical Practice Urology*, **2009**, *6*, 76-85). AR mechanisms of resistance to ADT include: overexpression of AR (Visakorpi, T. *et al Nature Genetics* **1995**, *9*, 401-406; Koivisto, P. *et al Scandinavian Journal of Clinical and Laboratory Investigation Supplementum* **1996**, *226*, 57-63); gain-of-function mutations in the AR LBD (Culig Z. *et al Molecular Endocrinology* **1993**, *7*, 1541-1550); intratumoral androgen synthesis (Cai, C. *et al Cancer Research* **2011**, *71*, 6503-6513); altered expression and function of AR coactivators (Ueda, T. *et al The Journal of Biological Chemistry* **2002**, *277*, 38087-38094; Xu J. *et al Nature Reviews Cancer* **2009**, *9*, 615-630); aberrant post-translational modifications of AR (Gioeli D. *et al Molecular and Cellular Endocrinology* **2012**, *352*, 70-78; van der Steen T. *et al International Journal of Molecular Sciences* **2013**, *14*, 14833-14859); and expression of AR splice variants (AR-Vs) which lack the ligand-binding domain (LBD) (Karantanos, T. *et al Oncogene* **2013**, *32*, 5501-5511; Andersen R. J. et al Cancer Cell 2010, 17, 535-546; Myung J. K. *et al The Journal of Clinical Investigation* **2013**, *123*, 2948-2960; Sun S. *et al The Journal of Clinical Investigation* **2010**, *120*, 2715-2730). Anti-androgens such as bicalutamide and enzalutamide target AR LBD, but have no effect on truncated constitutively active AR-Vs such as AR-V7 (Li Y. *et al Cancer Research* **2013**, *73*, 483-489). Expression of AR-V7 is associated with resistance to current hormone therapies (Li Y. *et al Cancer Research* **2013**, *73*, 483-489; Antonarakis E. S. *et al The New England Journal of Medicine* **2014**, *371*, 1028-1038).

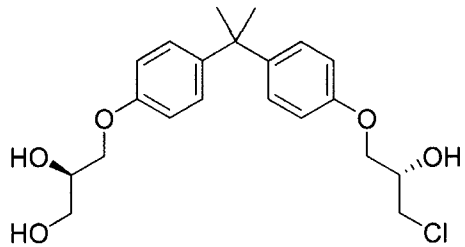
[013] While significant advances have been made in this field, especially the development of AR NTD targeting compounds, there remains a need to understand if and how resistance to AR NTD inhibitors will develop and impact cancer treatments, especially castration-resistant prostate cancer. The present disclosure provides a resistance model for a known AR NTD inhibitor and demonstrates that certain compounds show efficacy in the treatment of AR NTD resistance model cell lines.

BRIEF SUMMARY

[014] In one embodiment of the present disclosure, a method of treating a condition associated with cell proliferation in a patient in need thereof is provided. In one embodiment, the present invention provides a method of treating cancer or tumors. In another embodiment, the present invention provides a method of treating prostate cancer or breast cancer.

[015] In one embodiment, the methods described herein are useful in treating a condition, a disease, a cancer, a tumor, or various cells that have become resistant to one or more therapeutically active compounds. In one embodiment, the present methods are useful in treating a condition, a disease, a cancer, a tumor, or various cells that has become resistant to one or more AR NTD modulators. In another embodiment, the present methods are useful in treating a condition, a disease, a cancer, a tumor, or various cells that has become resistant to a therapeutically active compound that is susceptible to metabolism. In another embodiment, the present methods are useful in treating a condition, a disease, a cancer, a tumor, or various cells that has become resistant to a therapeutically active compound that is susceptible to glucuronidation.

[016] In one embodiment, the present methods are useful in treating a condition, a disease, a cancer, a tumor, or various cells that has become resistant to Compound A:



Compound A.

[017] In one embodiment, the present disclosure provides a method of reducing, inhibiting, or ameliorating proliferation of resistant cells, comprising administering a therapeutically effective amount of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is provided. In one embodiment, the cells are resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

[018] In one embodiment, the reducing, inhibiting, or ameliorating in the method disclosed herein, is *in vivo*. In another embodiment, the reducing, inhibiting, or ameliorating is *in vitro*.

[019] In one embodiment, the cells in the method disclosed herein, are a cancer cells. In one embodiment, the cancer cells are a prostate cancer cells. In one embodiment, the prostate cancer

cells are cells of primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. In another embodiment, the prostate cancer cells are a metastatic castration-resistant prostate cancer. In other embodiments, the prostate cancer cells are an androgen-dependent prostate cancer cells or an androgen-independent prostate cancer cells. In one embodiment, the cancer cells are breast cancer cells.

[020] In another embodiment of the present disclosure, a method for treating a condition or disease that is responsive to modulation of androgen receptor activity, comprising administering to the subject, a therapeutically effective amount of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is provided. In one embodiment, the cells are resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

[021] In one embodiment, the treating in the method disclosed herein is *in vivo*. In another embodiment, the treating is *in vitro*.

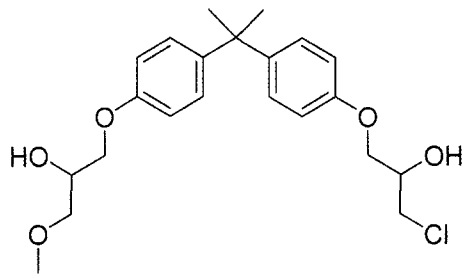
[022] In one embodiment, the condition or disease in the method disclosed herein is selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration. In one embodiment, the condition or disease is prostate cancer. In one embodiment, the prostate cancer is selected from primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. In another embodiment, the prostate cancer is a metastatic castration-resistant prostate cancer. In some embodiments, the prostate cancer is an androgen-dependent prostate cancer cells or an androgen-independent prostate cancer. In one embodiment, the condition or disease is breast cancer.

[023] In another embodiment of the present disclosure, a method for reducing or preventing tumor growth, comprising contacting tumor cells with a therapeutically effective amount of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is provided. In one embodiment, the cells are resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

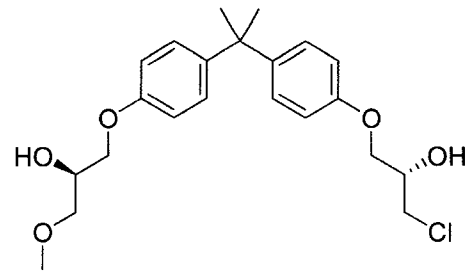
[024] In one embodiment, the reducing or preventing in the method disclosed herein is *in vivo*. In another embodiment, the treating is *in vitro*.

[025] In one embodiment, the tumor cell in the method disclosed herein is selected from prostate cancer, breast cancer, ovarian cancer, endometrial cancer, or salivary gland carcinoma. In one embodiment, the tumor cells are prostate cancer tumor cells. In one embodiment, the prostate cancer is selected from primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. In other embodiments, the prostate cancer is a metastatic castration-resistant prostate cancer. In some embodiment, the prostate cancer is androgen-dependent prostate cancer or androgen-independent prostate cancer. In another embodiment, the tumor cells are is breast cancer tumor cells.

[026] In one embodiment of any one of the methods disclosed herein, The method of claim 1, the compound of formula (I) is



[027] In one embodiment of any one of the methods disclosed herein, The method of claim 1, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC) is



Compound B.

[028] In one embodiment of any one of the methods disclosed herein, the AR NTD modulator is an AR NTD inhibitor. In another embodiment, AR NTD modulator is an AR NTD binder. In one

embodiment, the AR NTD modulator that the condition, disease, tumor, cancer, or cells have become resistant to is to Compound A.

[029] In one embodiment of any one of the methods disclosed herein, the AR NTD modulator is susceptible to glucuronidation. In another embodiment, the AR NTD modulator is not glucuronidation resistant.

DESCRIPTION OF THE FIGURES

[030] **Figure 1A** shows measurement of LNCaP cell proliferation which were treated with DMSO, Compound A, or enzalutamide (ENZ) in the presence of synthetic androgen R1881.

[031] **Figure 1B** shows measurement of LNCaP-EPI^R cell proliferation which were treated with DMSO, Compound A, or enzalutamide (ENZ) in the presence of synthetic androgen R1881.

[032] **Figure 1C** shows measurement of LNCaP and LNCaP-EPI^R cell proliferation at 96 hours after treatment with DMSO, Compound A, enzalutamide (ENZ), or bicalutamide (BIC) in the presence of synthetic androgen R1881.

[033] **Figure 2A** shows measurement of tumor volume in LNCaP xenografts in response to treatment with Compound A or a vehicle (control).

[034] **Figure 2B** shows measurement of tumor volume in LNCaP-EPI^R xenografts in response to treatment with Compound A, enzalutamide (ENZ), or a vehicle (control).

[035] **Figure 3A** shows *UGT2B7* gene expression in LNCaP and LNCaP-EPI^R cells treated with DMSO, Compound A, or enzalutamide (ENZ) with or without the presence of synthetic androgen R1881.

[036] **Figure 3B** shows *UGT2B15* gene expression in LNCaP and LNCaP-EPI^R cells treated with DMSO, Compound A, or enzalutamide (ENZ) with or without the presence of synthetic androgen R1881.

[037] **Figure 4A** shows *UGT2B17* gene expression in LNCaP and LNCaP-EPI^R cells treated with DMSO, Compound A, or enzalutamide (ENZ) with or without the presence of synthetic androgen R1881.

[038] **Figure 4B** shows *UGT2B28* gene expression in LNCaP and LNCaP-EPI^R cells treated with DMSO, Compound A, or enzalutamide (ENZ) with or without the presence of synthetic androgen R1881.

[039] **Figure 5** shows endogenous *UGT2B* in LNCaP-EPI^R cells and LNCaP cells.

[040] **Figure 6** shows UGT2B enzyme activity with Compounds A and B in competition with luciferin in mouse liver microsomes.

[041] **Figure 7** shows HPLC traces of Compounds A and B and their glucuronide metabolites when incubated with mouse liver microsomes and UDPGA cofactor or with mouse liver microsomes, UDPGA cofactor, and β-glucuronidase.

[042] **Figure 8A** shows measurement of LNCaP cell proliferation which were treated with DMSO, Compound A, or Compound B in the presence of synthetic androgen R1881.

[043] **Figure 8B** shows measurement of LNCaP-EPI^R cell proliferation which were treated with DMSO, Compound A, or Compound B in the presence of synthetic androgen R1881.

[044] **Figure 9A** shows *FKBP5* gene expression in LNCaP and LNCaP-EPI^R cells treated with DMSO, Compound A, Compound B, or enzalutamide (ENZ) in the presence of synthetic androgen R1881.

[045] **Figure 9B** shows *RHOU* gene expression in LNCaP and LNCaP-EPI^R cells treated with DMSO, Compound A, Compound B, or enzalutamide (ENZ) in the presence of synthetic androgen R1881.

[046] **Figure 9C** shows *KLK2* gene expression in LNCaP and LNCaP-EPI^R cells treated with DMSO, Compound A, Compound B, or enzalutamide (ENZ) in the presence of synthetic androgen R1881.

[047] **Figure 9D** shows *KLK3* gene expression in LNCaP and LNCaP-EPI^R cells treated with DMSO, Compound A, Compound B, or enzalutamide (ENZ) in the presence of synthetic androgen R1881.

[048] **Figure 10A** shows anti-tumor activity for Compounds A and B in LNCaP xenografts.

[049] **Figure 10B** shows anti-tumor activity for Compounds A and B in LNCaP-EPI^R xenografts.

[050] **Figure 10C** shows tumor sample sizes collected after experiment as described in Figure 10B.

DETAILED DESCRIPTION

I. Definitions

[051] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention can be practiced without these details. In other instances, well-known structures

have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[052] Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics can be combined in any suitable manner in one or more embodiments. Also, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly dictates otherwise. It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

[053] The terms below, as used herein, have the following meanings, unless indicated otherwise:

[054] "Amino" refers to the $-NH_2$ radical.

[055] "Cyano" refers to the -CN radical.

[056] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo radical.

[057] "Hydroxy" or "hydroxyl" refers to the -OH radical.

[058] "Imino" refers to the =NH substituent.

[059] "Nitro" refers to the $-NO_2$ radical.

[060] "Oxo" refers to the =O substituent.

[061] "Thioxo" refers to the =S substituent.

[062] "Alkyl" or "alkyl group" refers to a fully saturated, straight or branched hydrocarbon chain radical having from one to twelve carbon atoms, and which is attached to the rest of the molecule by a single bond. Alkyls comprising any number of carbon atoms from 1 to 12 are included. An alkyl comprising up to 12 carbon atoms is a C_1-C_{12} alkyl, an alkyl comprising up to 10 carbon atoms is a C_1-C_{10} alkyl, an alkyl comprising up to 6 carbon atoms is a C_1-C_6 alkyl and an alkyl comprising up to 5 carbon atoms is a C_1-C_5 alkyl. A C_1-C_5 alkyl includes C_5 alkyls, C_4 alkyls, C_3 alkyls, C_2 alkyls and C_1 alkyl (*i.e.*, methyl). A C_1-C_6 alkyl includes all moieties described above

for C_1-C_5 alkyls but also includes C_6 alkyls. A C_1-C_{10} alkyl includes all moieties described above for C_1-C_5 alkyls and C_1-C_6 alkyls, but also includes C_7, C_8, C_9 and C_{10} alkyls. Similarly, a C_1-C_{12} alkyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkyls. Non-limiting examples of C_1-C_{12} alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *sec*-propyl, *n*-butyl, *i*-butyl, *sec*-butyl, *t*-butyl, *n*-pentyl, *t*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, and *n*-dodecyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[063] "Alkylene" or "alkylene chain" refers to a fully saturated, straight or branched divalent hydrocarbon chain radical, and having from one to twelve carbon atoms. Non-limiting examples of C_1-C_{12} alkylene include methylene, ethylene, propylene, *n*-butylene, ethenylene, propenylene, *n*-butenylene, propynylene, *n*-butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkylene chain can be optionally substituted.

[064] "Alkenyl" or "alkenyl group" refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Each alkenyl group is attached to the rest of the molecule by a single bond. Alkenyl group comprising any number of carbon atoms from 2 to 12 are included. An alkenyl group comprising up to 12 carbon atoms is a C_2-C_{12} alkenyl, an alkenyl comprising up to 10 carbon atoms is a C_2-C_{10} alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C_2-C_6 alkenyl and an alkenyl comprising up to 5 carbon atoms is a C_2-C_5 alkenyl. A C_2-C_5 alkenyl includes C_5 alkenyls, C_4 alkenyls, C_3 alkenyls, and C_2 alkenyls. A C_2-C_6 alkenyl includes all moieties described above for C_2-C_5 alkenyls but also includes C_6 alkenyls. A C_2-C_{10} alkenyl includes all moieties described above for C_2-C_5 alkenyls and C_2-C_6 alkenyls, but also includes C_7, C_8, C_9 and C_{10} alkenyls. Similarly, a C_2-C_{12} alkenyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkenyls. Non-limiting examples of C_2-C_{12} alkenyl include ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl,

5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, 9-decenyl, 1-undecenyl, 2-undecenyl, 3-undecenyl, 4-undecenyl, 5-undecenyl, 6-undecenyl, 7-undecenyl, 8-undecenyl, 9-undecenyl, 10-undecenyl, 1-dodecenyl, 2-dodecenyl, 3-dodecenyl, 4-dodecenyl, 5-dodecenyl, 6-dodecenyl, 7-dodecenyl, 8-dodecenyl, 9-dodecenyl, 10-dodecenyl, and 11-dodecenyl. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[065] "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain radical, having from two to twelve carbon atoms, and having one or more carbon-carbon double bonds. Non-limiting examples of C_2-C_{12} alkenylene include ethene, propene, butene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkenylene chain can be optionally substituted.

[066] "Alkynyl" or "alkynyl group" refers to a straight or branched hydrocarbon chain radical having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Each alkynyl group is attached to the rest of the molecule by a single bond. Alkynyl group comprising any number of carbon atoms from 2 to 12 are included. An alkynyl group comprising up to 12 carbon atoms is a C_2-C_{12} alkynyl, an alkynyl comprising up to 10 carbon atoms is a C_2-C_{10} alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C_2-C_6 alkynyl and an alkynyl comprising up to 5 carbon atoms is a C_2-C_5 alkynyl. A C_2-C_5 alkynyl includes C_5 alkynyls, C_4 alkynyls, C_3 alkynyls, and C_2 alkynyls. A C_2-C_6 alkynyl includes all moieties described above for C_2-C_5 alkynyls but also includes C_6 alkynyls. A C_2-C_{10} alkynyl includes all moieties described above for C_2-C_5 alkynyls and C_2-C_6 alkynyls, but also includes C_7, C_8, C_9 and C_{10} alkynyls. Similarly, a C_2-C_{12} alkynyl includes all the foregoing moieties, but also includes C_{11} and C_{12} alkynyls. Non-limiting examples of C_2-C_{12} alkenyl include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[067] "Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain radical, having from two to twelve carbon atoms, and having one or more carbon-carbon triple bonds. Non-limiting examples of C_2-C_{12} alkynylene include ethynylene, propargylene and

the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, an alkynylene chain can be optionally substituted.

[068] "Alkoxy" refers to a radical of the formula -OR_a where R_a is an alkyl, alkenyl or alknyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group can be optionally substituted.

[069] "Alkylamino" refers to a radical of the formula -NHR_a or -NR_aR_a where each R_a is, independently, an alkyl, alkenyl or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkylamino group can be optionally substituted.

[070] "Alkylcarbonyl" refers to the –C(=O)R_a moiety, wherein R_a is an alkyl, alkenyl or alkynyl radical as defined above. A non-limiting example of an alkyl carbonyl is the methyl carbonyl ("acetal") moiety. Alkylcarbonyl groups can also be referred to as "Cw-Cz acyl" where w and z depicts the range of the number of carbon in R_a, as defined above. For example, "C1-C_{10} acyl" refers to alkylcarbonyl group as defined above, where R_a is C_1-C_{10} alkyl, C_1-C_{10} alkenyl, or C_1-C_{10} alkynyl radical as defined above. Unless stated otherwise specifically in the specification, an alkyl carbonyl group can be optionally substituted.

[071] "Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. For purposes of this invention, the aryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" is meant to include aryl radicals that are optionally substituted.

[072] "Aralkyl" refers to a radical of the formula -R_b-R_c where R_b is an alkylene, alkenylene or alkynylene group as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. Unless stated otherwise specifically in the specification, an aralkyl group can be optionally substituted.

[073] "Carbocyclyl," "carbocyclic ring" or "carbocycle" refers to a rings structure, wherein the atoms which form the ring are each carbon. Carbocyclic rings can comprise from 3 to 20 carbon atoms in the ring. Carbocyclic rings include aryls and cycloalkyl. cycloalkenyl and cycloalkynyl as defined herein. Unless stated otherwise specifically in the specification, a carbocyclyl group can be optionally substituted.

[074] "Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic fully saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkyl group can be optionally substituted.

[075] "Cycloalkenyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon double bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkenyl radicals include, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like. Polycyclic cycloalkenyl radicals include, for example, bicyclo[2.2.1]hept-2-enyl and the like. Unless otherwise stated specifically in the specification, a cycloalkenyl group can be optionally substituted.

[076] "Cycloalkynyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having one or more carbon-carbon triple bonds, which can include fused or bridged ring systems, having from three to twenty carbon atoms, preferably having from three to ten carbon atoms, and which is attached to the rest of the molecule by a single bond. Monocyclic cycloalkynyl radicals include, for example, cycloheptynyl, cyclooctynyl, and the like. Unless otherwise stated specifically in the specification, a cycloalkynyl group can be optionally substituted.

[077] "Cycloalkylalkyl" refers to a radical of the formula $-R_b-R_d$ where R_b is an alkylene, alkenylene, or alkynylene group as defined above and R_d is a cycloalkyl, cycloalkenyl,

cycloalkynyl radical as defined above. Unless stated otherwise specifically in the specification, a cycloalkylalkyl group can be optionally substituted.

[078] "Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl, and the like. Unless stated otherwise specifically in the specification, a haloalkyl group can be optionally substituted.

[079] "Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 1-fluoropropenyl, 1,1-difluorobutenyl, and the like. Unless stated otherwise specifically in the specification, a haloalkenyl group can be optionally substituted.

[080] "Haloalkynyl" refers to an alkynyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, 1-fluoropropynyl, 1-fluorobutynyl, and the like. Unless stated otherwise specifically in the specification, a haloalkenyl group can be optionally substituted.

[081] "Heterocyclyl," "heterocyclic ring" or "heterocycle" refers to a stable 3- to 20-membered non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Heterocyclycl or heterocyclic rings include heteroaryls as defined below. Unless stated otherwise specifically in the specification, the heterocyclyl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized; and the heterocyclyl radical can be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocyclyl group can be optionally substituted.

[082] "*N*-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule

is through a nitrogen atom in the heterocyclyl radical. Unless stated otherwise specifically in the specification, a *N*-heterocyclyl group can be optionally substituted.

[083] "Heterocyclylalkyl" refers to a radical of the formula $-R_b-R_e$ where R_b is an alkylene, alkenylene, or alkynylene chain as defined above and R_e is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl can be attached to the alkyl, alkenyl, alkynyl radical at the nitrogen atom. Unless stated otherwise specifically in the specification, a heterocyclylalkyl group can be optionally substituted.

[084] "Heteroaryl" refers to a 5- to 20-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. For purposes of this invention, the heteroaryl radical can be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which can include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical can be optionally oxidized; the nitrogen atom can be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted.

[085] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. Unless stated otherwise specifically in the specification, an *N*-heteroaryl group can be optionally substituted.

[086] "Heteroarylalkyl" refers to a radical of the formula $-R_b-R_f$ where R_b is an alkylene, alkenylene, or alkynylene chain as defined above and R_f is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkyl group can be optionally substituted.

[087] "Thioalkyl" refers to a radical of the formula $-SR_a$ where R_a is an alkyl, alkenyl, or alkynyl radical as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, a thioalkyl group can be optionally substituted.

[088] The term "substituted" used herein means any of the above groups (*i.e.,* alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, alkoxy, alkylamino, alkylcarbonyl, thioalkyl, aryl, aralkyl, carbocyclyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl) wherein at least one hydrogen atom is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyldiarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. "Substituted also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which

one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkynyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In addition, each of the foregoing substituents can also be optionally substituted with one or more of the above substituents.

[089] As used herein, the symbol "  " (hereinafter can be referred to as "a point of attachment bond") denotes a bond that is a point of attachment between two chemical entities, one of which is depicted as being attached to the point of attachment bond and the other of which is not depicted as being attached to the point of attachment bond. For example, "  " indicates that the chemical entity "XY" is bonded to another chemical entity via the point of attachment bond. Furthermore, the specific point of attachment to the non-depicted chemical entity can be specified by inference. For example, the compound CH_3-R^3, wherein R^3 is H or "  " infers that when R^3 is "XY", the point of attachment bond is the same bond as the bond by which R^3 is depicted as being bonded to CH_3.

[090] "Fused" refers to any ring structure described herein which is fused to an existing ring structure in the compounds of the invention. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring can be replaced with a nitrogen atom.

[091] The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed compounds. Such products can result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising administering a compound of this invention to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabelled compound of the invention in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples.

[092] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[093] As used herein, a "subject" can be a human, non-human primate, mammal, rat, mouse, cow, horse, pig, sheep, goat, dog, cat and the like. The subject can be suspected of having or at risk for having a cancer, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, or suspected of having or at risk for having acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration. Diagnostic methods for various cancers, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, and diagnostic methods for acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration and the clinical delineation of cancer, such as prostate cancer, breast cancer, ovarian cancer, salivary gland carcinoma, or endometrial cancer, diagnoses and the clinical delineation of acne, hirsutism, alopecia, benign prostatic hyperplasia, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration are known to those of ordinary skill in the art. The terms "subject" and "patient" are used interchangeably throughout the present application.

[094] "Mammal" includes humans and both domestic animals such as laboratory animals and household pets (*e.g.*, cats, dogs, swine, cattle, sheep, goats, horses, rabbits), and non-domestic animals such as wildlife and the like.

[095] "Optional" or "optionally" means that the subsequently described event of circumstances can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical can or cannot be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[096] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

[097] "Pharmaceutically acceptable salt" includes both acid and base addition salts.

[098] Compounds as described herein can be in the free form or in the form of a salt thereof. In some embodiments, compounds as described herein can be in the form of a pharmaceutically acceptable salt, which are known in the art (Berge et al., *J. Pharm. Sci.* 1977, 66, 1). "Pharmaceutically acceptable salt" as used herein includes, for example, salts that have the desired pharmacological activity of the parent compound (salts which retain the biological effectiveness and/or properties of the parent compound and which are not biologically and/or otherwise undesirable). Compounds as described herein having one or more functional groups capable of forming a salt can be, for example, formed as a pharmaceutically acceptable salt. Compounds containing one or more basic functional groups can be capable of forming a "pharmaceutically acceptable acid addition salt" with, for example, a pharmaceutically acceptable organic or inorganic acid. Pharmaceutically acceptable salts can be derived from, for example, and without limitation, acetic acid, adipic acid, alginic acid, aspartic acid, ascorbic acid, benzoic acid, benzenesulfonic acid, butyric acid, cinnamic acid, citric acid, camphoric acid, camphorsulfonic acid, cyclopentanepropionic acid, diethylacetic acid, digluconic acid, dodecylsulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, glucoheptanoic acid, gluconic acid, glycerophosphoric acid, glycolic acid, hemisulfonic acid, heptanoic acid, hexanoic acid, hydrochloric acid, hydrobromic acid, hydriodic acid, 2-hydroxyethanesulfonic acid, isonicotinic acid, lactic acid, malic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-napthalenesulfonic acid, naphthalenedisulphonic acid, p-toluenesulfonic acid, nicotinic acid, nitric acid, oxalic acid, pamoic acid, pectinic acid, 3-phenylpropionic acid, phosphoric acid, picric acid, pimelic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, succinic acid, sulfuric acid, sulfamic acid, tartaric acid, thiocyanic acid or undecanoic acid.

[099] Compounds containing one or more acidic functional groups can be capable of forming "Pharmaceutically acceptable base addition salt" with a pharmaceutically acceptable base, for example, and without limitation, inorganic bases based on alkaline metals or alkaline earth metals or organic bases such as primary amine compounds, secondary amine compounds, tertiary amine compounds, quaternary amine compounds, substituted amines, naturally occurring substituted amines, cyclic amines or basic ion-exchange resins. Pharmaceutically acceptable salts can be derived from, for example, and without limitation, a hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation such as ammonium, sodium, potassium, lithium,

calcium, magnesium, iron, zinc, copper, manganese or aluminum, ammonia, benzathine, meglumine, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, glucamine, methylglucamine, theobromine, purines, piperazine, piperidine, procaine, *N*-ethylpiperidine, theobromine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, *N*,*N*-dimethylaniline, *N*-methylpiperidine, morpholine, *N*-methylmorpholine, *N*-ethylmorpholine, dicyclohexylamine, dibenzylamine, *N*,*N*-dibenzylphenethylamine, 1-ephenamine, *N*,*N*'-dibenzylethylenediamine or polyamine resins. In some embodiments, compounds as described herein can contain both acidic and basic groups and can be in the form of inner salts or zwitterions, for example, and without limitation, betaines. Salts as described herein can be prepared by conventional processes known to a person skilled in the art, for example, and without limitation, by reacting the free form with an organic acid or inorganic acid or base, or by anion exchange or cation exchange from other salts. Those skilled in the art will appreciate that preparation of salts can occur *in situ* during isolation and purification of the compounds or preparation of salts can occur by separately reacting an isolated and purified compound.

[100] Often crystallizations produce a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent can be water, in which case the solvate can be a hydrate. Alternatively, the solvent can be an organic solvent. Thus, the compounds of the present invention can exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The compound of the invention can be true solvates, while in other cases, the compound of the invention can merely retain adventitious water or be a mixture of water plus some adventitious solvent.

[101] In some embodiments, compounds and all different forms thereof (e.g. free forms, salts, polymorphs, isomeric forms) as described herein can be in the solvent addition form, for example, solvates. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent in physical association the compound or salt thereof. The solvent can be, for example, and without

limitation, a pharmaceutically acceptable solvent. For example, hydrates are formed when the solvent is water or alcoholates are formed when the solvent is an alcohol.

[102] In some embodiments, compounds and all different forms thereof (e.g. free forms, salts, solvates, isomeric forms) as described herein can include crystalline and amorphous forms, for example, polymorphs, pseudopolymorphs, conformational polymorphs, amorphous forms, or a combination thereof. Polymorphs include different crystal packing arrangements of the same elemental composition of a compound. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability and/or solubility. Those skilled in the art will appreciate that various factors including recrystallization solvent, rate of crystallization and storage temperature can cause a single crystal form to dominate.

[103] In some embodiments, compounds and all different forms thereof (e.g. free forms, salts, solvates, polymorphs) as described herein include isomers such as geometrical isomers, optical isomers based on asymmetric carbon, stereoisomers, tautomers, individual enantiomers, individual diastereomers, racemates, diastereomeric mixtures and combinations thereof, and are not limited by the description of the formula illustrated for the sake of convenience.

[104] A "pharmaceutical composition" refers to a formulation of a compound of the invention and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium includes all pharmaceutically acceptable carriers, diluents or excipients therefor.

[105] "An "effective amount" refers to a therapeutically effective amount or a prophylactically effective amount. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result, such as reduced tumor size, increased life span or increased life expectancy. A therapeutically effective amount of a compound can vary according to factors such as the disease state, age, sex, and weight of the subject, and the ability of the compound to elicit a desired response in the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the compound are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result, such as smaller tumors, increased life span, increased life expectancy or prevention of the

progression of prostate cancer to a castration-resistant form. Typically, a prophylactic dose is used in subjects prior to or at an earlier stage of disease, so that a prophylactically effective amount can be less than a therapeutically effective amount.

[106] The term "patient" or "subject" as used herein, includes humans and animals, preferably mammals.

[107] "Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or condition of interest, and includes:

(i) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, i.e., arresting its development;

(iii) relieving the disease or condition, i.e., causing regression of the disease or condition; or

(iv) relieving the symptoms resulting from the disease or condition, i.e., relieving pain without addressing the underlying disease or condition. As used herein, the terms "disease" and "condition" can be used interchangeably or can be different in that the particular malady or condition cannot have a known causative agent (so that etiology has not yet been worked out) and it is therefore not yet recognized as a disease but only as an undesirable condition or syndrome, wherein a more or less specific set of symptoms have been identified by clinicians.

[108] "Drug resistance", "resistance" or "resistant" refers to the circumstance when a disease, a condition, or cells affected by a disease or a condition does not respond to a treatment of a drug or drugs or a circumstance where the response has significantly diminished from previously. The above terms also refers to circumstances where the disease/condition or cells affected by the disease/condition ceases responding to a drug or drugs that the disease/condition or cells affected by the disease/condition had previously responded.

[109] The compounds of the invention, or their pharmaceutically acceptable salts can contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms whether or not they are specifically depicted herein. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers can be prepared using

chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

[110] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

[111] A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds.

[112] The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program, ChemDraw Ultra Version 11.0.1 and/or ChemDraw Ultra Version 14.0 software naming program (CambridgeSoft), or any subsequent versions thereof. For complex chemical names employed herein, a substituent group is named before the group to which it attaches. For example, cyclopropylethyl comprises an ethyl backbone with cyclopropyl substituent. Except as described below, all bonds are identified in the chemical structure diagrams herein, except for some carbon atoms, which are assumed to be bonded to sufficient hydrogen atoms to complete the valency.

[113] Throughout the present specification, the terms "about" and/or "approximately" can be used in conjunction with numerical values and/or ranges. The term "about" is understood to mean those values near to a recited value. For example, "about 40 [units]" can mean within ± 25% of 40 (*e.g.*, from 30 to 50), within ± 20%, ± 15%, ± 10%, ± 9%, ± 8%, ± 7%, ± 6%, ± 5%, ± 4%, ± 3%, ± 2%, ± 1%, less than ± 1%, or any other value or range of values therein or therebelow. Furthermore, the phrases "less than about [a value]" or "greater than about [a value]" should be understood in view of the definition of the term "about" provided herein. The terms "about" and "approximately" can be used interchangeably.

[114] Throughout the present specification, numerical ranges are provided for certain quantities. It is to be understood that these ranges comprise all subranges therein. Thus, the range "from 50 to 80" includes all possible ranges therein (*e.g.*, 51-79, 52-78, 53-77, 54-76, 55-75, 60-70, *etc.*). Furthermore, all values within a given range can be an endpoint for the range encompassed thereby (*e.g.*, the range 50-80 includes the ranges with endpoints such as 55-80, 50-75, *etc.*).

II. Compounds

[115] The present invention provides bisphenol-related compounds of formula (I), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof. The compounds disclosed herein can be used in a combination with at least one additional therapeutically active agent (combination therapy). The bisphenol-related compounds as disclosed herein were developed to specifically target the AR amino-terminal domain (NTD) to block the transcriptional activities of FL-AR (full-length androgen receptor) and AR-Vs (AR-splice variants), which results in antitumor activity in CRPC xenografts (Andersen, R. J. *et. al.*, *Cancer Cell* **2010**, *17*, 535-546; Myung, J. K. *et al., J. Clin. Invest.* **2013**, *123*, 2948-2960; Martin, S. K. *et al. Molecular Oncology* **2015**, *9*, 628-639).

[116] As noted above, certain embodiments of the present invention are directed to compounds useful for treatment of various cancers, including various types of prostate cancers. While not wishing to be bound by any theory, it is believed that binding of the compounds to the androgen receptor (for example at the N-terminal domain) can contribute to the activity of the disclosed compounds.

[117] In one embodiment the invention includes compounds which form covalent bonds with the androgen receptor (AR) (e.g., at the N-terminal domain), thus resulting in irreversible (or substantially irreversible) inhibition of the same. In this regard, the certain compounds of the present invention are designed to include functional groups capable of forming covalent bonds with a nucleophile under certain *in vivo* conditions. For example, in some embodiments the reactivity of compounds of the present invention is such that they will not substantially react with various nucleophiles (e.g., glutathione) when the compounds are free in solution. However, when the free mobility of the compounds is restricted, and an appropriate nucleophile is brought into close proximity to the compound, for example when the compounds associate with, or bind to, the

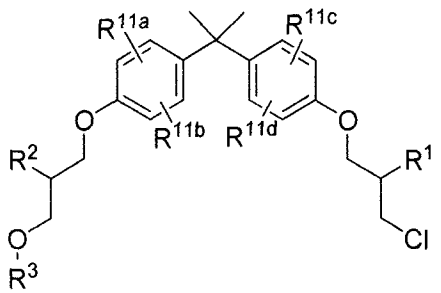
androgen receptor, the compounds are capable of forming covalent bonds with certain nucleophiles (e.g., thiols).

[118] In one embodiment, the invention includes compound which are resistant to metabolism. As used herein, the term "metabolism" can include but is not limited to, oxidation, reduction, hydrolysis, hydration, glucuronidation, acetylation, methylation, and sulfation.

[119] In one embodiment, the invention includes compound which are resistant to glucuronidation. Glucuronidation (or glucuronosylation) is a process of an addition of a glucuronic acid to a substrate, which is often involved in xenobiotic metabolism of compounds such as drugs. The human body uses glucuronidation to metabolize compounds into more water-soluble compounds that can subsequently be eliminated or excreted from the body. Thus, glucuronidation is one of the main routes of biotransformation.

[120] Glucuronidation of a compound does not always cause decreased biological activity or detoxification; however, it often leads to modulation of the efficacy of a compound or a drug.

[121] The present invention includes all compounds which have the above described properties (i.e., binding to androgen receptor (AR)). In one embodiment, the present invention is directed to a compound having a structure of Formula (I):



(I),

[122] or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof; wherein

[123] R^1 is hydroxyl or $-OC(=O)R^{13}$;

[124] R^2 is hydroxyl or $-OC(=O)R^{13}$;

[125] R^3 is C_1-C_6 alkyl;

[126] R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, or halogen; and

[127] R^{13} is C_1-C_6 alkyl.

[128] In one embodiment, a compound of formula (I) is resistant to glucuronidation.

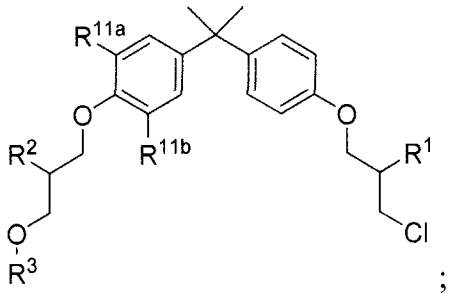
[129] In one embodiment, a compound of formula (I) is an AR N-terminal domain inhibitor.

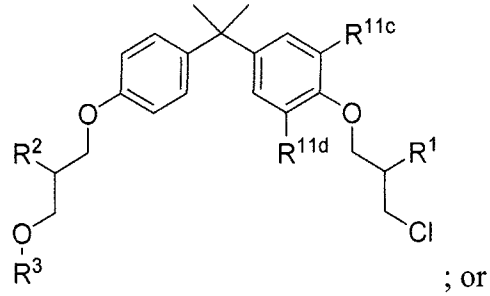
[130] In another embodiment, a compound of formula (I) is an AR N-terminal domain binder.

[131] In one embodiment, R^1 and R^2 are each hydroxyl or -OC(=O)CH_3.

[132] In one embodiment, R^3 is C_1-C_3 alkyl. In one embodiment R^3 is methyl, ethyl, or propyl. In one embodiment, R^3 is methyl.

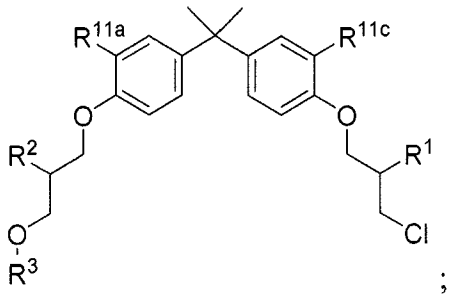
[133] In one embodiment, compound of formula (I) has the following structures:



; 

; or

(IA) (IB)



;

(IC)

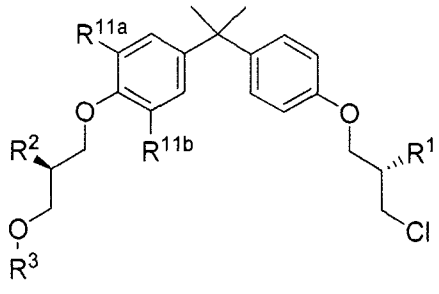
or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof; wherein R^1, R^2, R^3, R^{11a}, R^{11b}, R^{11c} and R^{11d} are as defined previously.

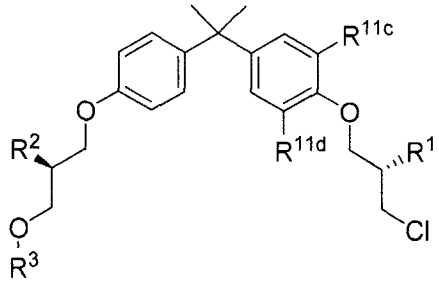
[134] In one embodiment, R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, Cl, or methyl.

[135] In one embodiment, R^{13} is methyl. In one embodiment, R^{13} is ethyl.

[136] In some more specific embodiments of the compound of formula (I), (IA), (IB), or (IC) is a racemate. In another embodiment, the compound of formula (I), (IA), (IB), or (IC) is a stereoisomer where the stereochemistry at the carbon atoms bearing R^1 and R^2 are defined as (*S*) or (*R*).

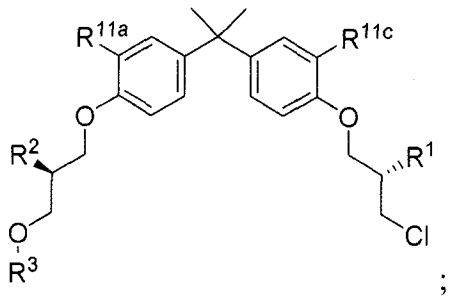
[137] In one embodiment, compound of formula (I) has the following structures:



; 

; or

(IIA) (IIB)

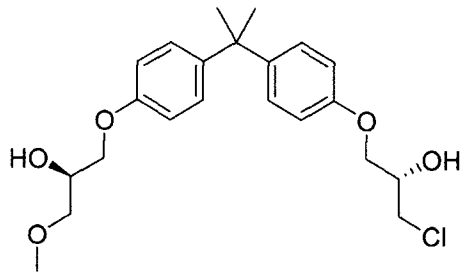


;

(IIC)

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof; wherein R^1, R^2, R^3, R^{11a}, R^{11b}, R^{11c} and R^{11d} are as defined previously.

[138] In some specific embodiments of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC) is:



Compound B;

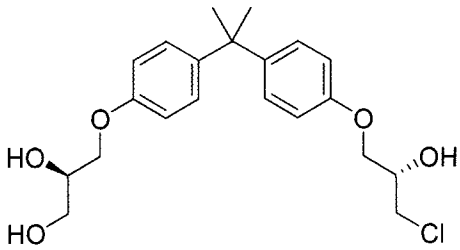
or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

III. Therapeutic Use

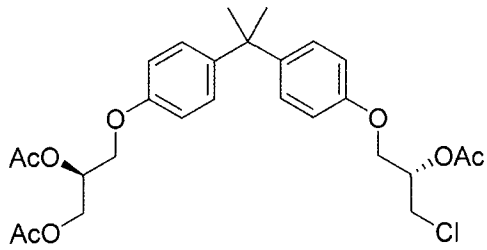
[139] In one embodiment of the present disclosure, a method of treating a condition associated with cell proliferation in a patient in need thereof is provided. In one embodiment, the present invention provides a method of treating cancer or tumors. In another embodiment, the present invention provides a method of treating prostate cancer or breast cancer.

[140] In one embodiment, the methods described herein are useful in treating a condition, a disease, a cancer, a tumor, or various cells that has become resistant to a therapeutically active compound. In one embodiment, the present methods are useful in treating a condition, a disease, a cancer, a tumor, or various cells that has become resistant to one or more AR NTD modulators. In another embodiment, the present methods are useful in treating a condition, a disease, a cancer, a tumor, or various cells that has become resistant to a therapeutically active compound that is susceptible to glucuronidation.

[141] In one embodiment, the present methods are useful in treating a condition, a disease, a cancer, a tumor, or various cells that has become resistant to Compound A and/or Compound C:



Compound A



Compound C.

[142] In one embodiment of the present disclosure, a method of reducing, inhibiting, or ameliorating proliferation of resistant cells, comprising administering a therapeutically effective amount of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is provided. In one embodiment, the cells are resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

[143] In one embodiment, the reducing, inhibiting, or ameliorating in the method disclosed herein, is *in vivo*. In another embodiment, the reducing, inhibiting, or ameliorating is *in vitro*.

[144] In one embodiment, the cells in the method disclosed herein, are a cancer cells. In one embodiment, the cancer cells are a prostate cancer cells. In one embodiment, the prostate cancer cells are cells of primary/localized prostate cancer (newly diagnosed or early stage), locally advanced prostate cancer, recurrent prostate cancer (*e.g.*, prostate cancer which was not responsive to primary therapy), metastatic prostate cancer, advanced prostate cancer (*e.g.*, after castration for recurrent prostate cancer), metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. In another embodiment, the prostate cancer cells are cells of a metastatic castration-resistant prostate cancer. In other embodiments, the prostate cancer cells are an

androgen-dependent prostate cancer cells or an androgen-independent prostate cancer cells. In one embodiment, the cancer cells are breast cancer cells.

[145] In another embodiment of the present disclosure, a method for treating a condition or disease that is responsive to modulation of androgen receptor activity, comprising administering to the subject, a therapeutically effective amount of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is provided. In one embodiment, the cells are resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

[146] In one embodiment, the treating in the method disclosed herein is *in vivo*. In another embodiment, the treating is *in vitro*.

[147] In one embodiment, the condition or disease in the method disclosed herein is selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration. In one embodiment, the condition or disease is prostate cancer. In one embodiment, prostate cancer is selected from primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. In another embodiment, the prostate cancer is a metastatic castration-resistant prostate cancer. In some embodiments, the prostate cancer is an androgen-dependent prostate cancer cells or an androgen-independent prostate cancer. In one embodiment, the condition or disease is breast cancer.

[148] In another embodiment of the present disclosure, a method for reducing or preventing tumor growth, comprising contacting tumor cells with a therapeutically effective amount of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is provided. In one embodiment, the cells are resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

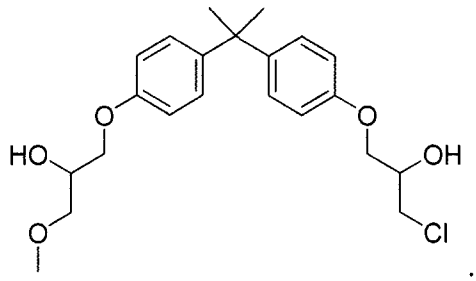
[149] In one embodiment, reducing or preventing tumor growth includes reduction in tumor volume. In one embodiment, reducing or preventing tumor growth includes complete elimination of tumors. In one embodiment, reducing or preventing tumor growth includes stopping or halting the existing tumor to grow. In one embodiment, reducing or preventing tumor growth includes reduction in the rate of tumor growth. In one embodiment, reducing or preventing tumor growth

includes reduction in the rate of tumor growth such that the rate of tumor growth before treating a patient with the methods disclosed herein (r1) is faster than the rate of tumor growth after said treatment (r2) such that r1 > r2.

[150] In one embodiment, the reducing or preventing in the method disclosed herein is *in vivo*. In another embodiment, the treating is *in vitro*.

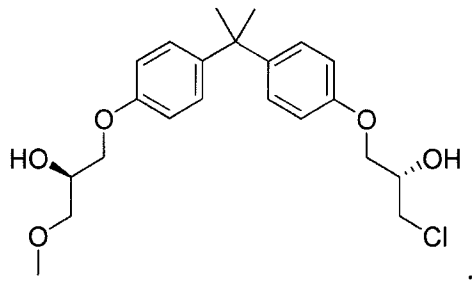
[151] In one embodiment, the tumor cell in the method disclosed herein is selected from prostate cancer, breast cancer, ovarian cancer, endometrial cancer, or salivary gland carcinoma. In one embodiment, the tumor cells are prostate cancer tumor cells. In one embodiment, the prostate cancer tumor cells are tumor cells of primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. In other embodiments, the prostate cancer is a metastatic castration-resistant prostate cancer. In some embodiment, the prostate cancer is androgen-dependent prostate cancer or androgen-independent prostate cancer. In another embodiment, the tumor cells are is breast cancer tumor cells.

[152] In one embodiment of any one of the methods disclosed herein, The method of claim 1, the compound of formula (I) is



.

[153] In one embodiment of any one of the methods disclosed herein, The method of claim 1, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC) is



.

[154] In one embodiment of any one of the methods disclosed herein, the AR NTD modulator is an AR NTD inhibitor. In another embodiment, AR NTD modulator is an AR NTD binder. In one embodiment, the AR NTD modulator that the condition, disease, tumor, cancer, or cells have become resistant to is to Compound A.

[155] In one embodiment of any one of the methods disclosed herein, the AR NTD modulator is susceptible to glucuronidation. In another embodiment, the AR NTD modulator is not glucuronidation resistant.

[156] The present disclosure also provides methods for modulating androgen receptor (AR). Accordingly, in one embodiment, the present disclosure provides the use of any one of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as disclosed herein, for modulating androgen receptor (AR) activity. For example in some embodiments, modulating androgen receptor (AR) activity is in a mammalian cell. Modulating androgen receptor (AR) can be in a subject in need thereof (e.g., a mammalian subject) and for treatment of any of the described conditions or diseases. In one embodiment, the combination of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent, as disclosed herein, is useful in modulating androgen receptor. In one embodiment, said modulation of AR occurs at the N-terminal domain (NTD).

[157] In other embodiments, modulating androgen receptor (AR) activity is for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, age related macular degeneration, and combinations thereof. For example in some embodiments, the indication is prostate cancer. In another embodiment, prostate cancer is selected from primary/localized prostate cancer (newly diagnosed or early stage), locally advanced prostate cancer, recurrent prostate cancer (*e.g.,* prostate cancer which was not responsive to primary therapy), metastatic prostate cancer, advanced prostate cancer (*e.g.,* after castration for recurrent prostate cancer), metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. In other embodiments, the spinal and bulbar muscular atrophy is Kennedy's disease.

[158] In one embodiment, the present disclosure provides a method for treating a condition or disease that is responsive to modulation of androgen receptor activity, comprising administering to the subject, a therapeutically effective amount of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as described herein. In one embodiment, the composition of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent, as disclosed herein, is provided in the use of a method for treating conditions or diseases that is responsive to modulation of androgen receptor activity. In some embodiments, said conditions or disease that is responsive to modulation of androgen receptor activity is selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, age related macular degeneration, and combinations thereof.

[159] In some embodiments, compounds as described herein can be administered to a subject. In one embodiment, the present invention is directed to a method of treating castration resistant prostate cancer comprising administering a pharmaceutical composition comprising a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent, as disclosed herein. In some embodiments, the present invention is directed to a method of treating androgen-dependent prostate cancer comprising administering a pharmaceutical composition comprising a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent. In other embodiments, the present invention is directed to a method of treating androgen-independent prostate cancer comprising administering a pharmaceutical composition comprising a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent. In one embodiment, the at least one therapeutically active agent is selected from the group consisting of inhibitors of PI3K/AKT/mTOR pathway, active agents associated with the treatment of prostate cancer, and anticancer agents. In one embodiment, the at least one therapeutically active agent is a PI3K/mTOR dual inhibitor.

[160] In other embodiments, the present disclosure provides a method of modulating androgen receptor (AR) activity, the method comprising administering a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, pharmaceutically acceptable salt thereof, or pharmaceutical composition of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof as described herein (including compositions comprising at least one additional therapeutically active agent), to a subject (e.g., mammal) in need thereof. In some embodiments, modulating androgen receptor (AR) activity is in a mammalian cell. In other embodiments, modulating androgen receptor (AR) activity is in a mammal. In one embodiment, modulating androgen receptor (AR) activity is in a human.

[161] The modulating androgen receptor (AR) activity can be for inhibiting AR N-terminal domain activity. The modulating androgen receptor (AR) activity can be for inhibiting androgen receptor (AR) activity. The modulating can be *in vivo*. The modulating androgen receptor (AR) activity can be for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy (e.g., Kennedy's disease), and age related macular degeneration. The indication can be prostate cancer. The prostate cancer can be selected from primary/localized prostate cancer (newly diagnosed or early stage), locally advanced prostate cancer, recurrent prostate cancer (*e.g.*, prostate cancer which was not responsive to primary therapy), metastatic prostate cancer, advanced prostate cancer (*e.g.*, after castration for recurrent prostate cancer), metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. In one embodiment, the prostate cancer is CRPC.

[162] In accordance with another embodiment, there is provided a use of compounds of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, and at least one additional therapeutically active agent, as described herein for preparation of a medicament for modulating androgen receptor (AR) or for preparation of a medicament for treatment of cancer, such as prostate cancer and breast cancer.

[163] Alternatively, in one embodiment, a method of modulating androgen receptor activity, comprising administering a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof in combination therapy with at

least one additional therapeutically active agent. In some embodiments, the administration can be to a mammal. In other embodiments, the administering can be to a mammal in need thereof and in an effective amount for the treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy (e.g., Kennedy's disease), age related macular degeneration, and combinations thereof. In one embodiment, the method as disclosed herein is to treat prostate cancer selected from primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer.

[164] In one embodiment, the compound of the present disclosure (e.g., compounds of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof) can be used at various stages of the treatment of AR-related diseases or conditions, including prostate cancer. In one embodiment, the compound of the present disclosure can be useful in a neoadjuvant therapy. In another embodiment, the compound of the present disclosure can be useful in a primary therapy. In other embodiments, the compound of the present disclosure can be useful alone or in combination with different therapies or with administration of additional pharmaceutical active agents. In one embodiment, the compound of the present disclosure can be useful in an adjuvant therapy. An "adjuvant therapy" is a therapy that is administered in addition to a primary, main, or initial therapy in order to maximize the effectiveness of treatment.

[165] In one embodiment, the compound of the present disclosure (e.g., compounds of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof) can be useful in an adjuvant therapy following an androgen ablation therapy. In another embodiment, the compound of the present disclosure can be useful in an adjuvant therapy to prevent recurrence of the disease after primary therapy or previous treatments.

[166] Androgen ablation therapy causes a temporary reduction in prostate cancer tumor burden, but the malignancy will begin to grow again in the absence of testicular androgens to form castrate resistant prostate cancer (CRPC). A rising titer of serum prostate-specific antigen (PSA) after androgen ablation therapy indicates biochemical failure, the emergence of CRPC, and re-initiation

of an androgen receptor (AR) transcription program. Most patients succumb to CRPC within two years of biochemical failure.

[167] AR is a transcription factor and a validated target for prostate cancer therapy. Current therapies include androgen ablation and administration of antiandrogens. Most CRPC is suspected to be AR-dependent. AR has distinct functional domains that include the C-terminus ligand-binding domain (LBD), a DNA-binding domain (DBD), and an amino-terminal domain (NTD). AR NTD contains the activation function- 1 (AF-1) that contributes most of the activity to the AR. Recently, splice variants of the AR that lack the LBD have been reported in prostate cancer cell lines (VCaP and 22Rv1), and in CRPC tissues. To date more than 20 splice variants of AR have been detected. Splice variants V7 and V567es are clinically relevant with levels of expression correlated to poor survival and CRPC. AR V567es is solely expressed in 20% of metastases. Abiraterone resistance is associated with expression of AR splice variants. Enzalutamide also increases levels of expression of these constitutively active AR splice variants. These splice variants lack LBD and thereby would not be inhibited by current therapies that target the AR LBD such as antiandrogens or androgen ablation therapy. A single patient with advanced prostate cancer can have many lesions throughout the body and skeleton and each tumor can have differing levels of expression of AR.

[168] In one embodiment, the present disclosure also provides method of treating, reducing, and ameliorating cell proliferation. In one embodiment, the method comprises contacting cancer and/or tumor cells with the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as disclosed herein. In another embodiment, the method comprises contacting cancer and/or tumor cells with the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent is administered to the patient in need thereof. Said administration of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent can be simultaneous administration, sequential administration, overlapping administration, interval administration, continuous administration, or a combination thereof.

[169] In another embodiment, the method of contacting cancer and/or tumor cells with the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable

salt, tautomer or stereoisomer thereof, as disclosed herein, may induce cell apoptosis or alleviate or prevent the progression of the disorder. In one embodiment, the method of contacting cancer and/or tumor cells with the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent, as disclosed herein, may induce cell apoptosis or alleviate or prevent the progression of the disorder.

[170] Additionally, disclosed are methods for treating cancers, cancer cells, tumors, or tumor cells. Non limiting examples of cancer that may be treated by the methods of this disclosure include cancer or cancer cells of: colorectum, breast, ovary, cervix, lung, liver, pancreas, lymph node, colon, prostate, brain, head and neck, skin, kidney, bone (e.g., Ewing's sarcoma) and blood and heart (e.g., leukemia, lymphoma, carcinoma). In one embodiment, the methods of this disclosure include treatment of cancer or cancer cells of prostate or breast cancer. Non limiting examples of tumors that may be treated by the methods of this disclosure include tumors and tumor cells of: colorectum, breast, ovary, cervix, lung, liver, pancreas, lymph node, colon, prostate, brain, head and neck, skin, kidney, bone (e.g., Ewing's sarcoma) and blood and heart (e.g., leukemia, lymphoma, carcinoma). In one embodiment, the methods of this disclosure include treatment of tumors and tumor cells of prostate or breast.

[171] The present invention also provides methods of treating, preventing, ameliorating and/or alleviating the progression of disorders or conditions characterized by cell proliferation in a subject. More particularly, the methods of the present invention involve administration of an effective amount of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, in a subject to treat a disorder or a condition characterized by cell proliferation. In one embodiment, the methods of the present disclosure involve administration of an effective amount of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent in a subject to treat a disorder or a condition characterized by cell proliferation.

[172] As used herein, administering can be effected or performed using any of the various methods known to those skilled in the art. The compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, can be administered, for example, subcutaneously, intravenously, parenterally, intraperitoneally,

intradermally, intramuscularly, topically, enteral (e.g., orally), rectally, nasally, buccally, sublingually, vaginally, by inhalation spray, by drug pump or via an implanted reservoir in dosage formulations containing conventional non-toxic, physiologically acceptable carriers or vehicles.

[173] Further, the presently disclosed compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, can be administered to a localized area in need of treatment or by means of a medical device or appliances. This can be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, transdermal patches, by injection, by catheter, by suppository, by implant (the implant can optionally be of a porous, non-porous, or gelatinous material), graft, prosthesis, or stent, including membranes, such as sialastic membranes or fibers.

[174] The form in which the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, is administered (e.g., syrup, elixir, capsule, tablet, foams, emulsion, gel, etc.) will depend in part on the route by which it is administered. For example, for mucosal (e.g., oral mucosa, rectal, intestinal mucosa, bronchial mucosa) administration, nose drops, aerosols, inhalants, nebulizers, eye drops or suppositories can be used. The compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, can also be used to coat bioimplantable materials to enhance neurite outgrowth, neural survival, or cellular interaction with the implant surface. The compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, disclosed herein can be administered together with other biologically active agents, such as anticancer agents, analgesics, anti-inflammatory agents, anesthetics and other agents which can control one or more symptoms or causes of a disorder or a condition characterized by cell proliferation. In one embodiment, the present disclosure provides a pharmaceutical composition comprising a combination therapy comprising a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent.

[175] In one embodiment, at least one additional therapeutically active agent can be selected from PI3K/AKT/mTOR pathway inhibitors, which include but are not limited to, BEZ-235 (2-methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-ylimidazo[4,5-c]quinolin-1-yl)phenyl]propanenitrile), XL-765 (N-[4-[[3-(3,5-dimethoxyanilino)quinoxalin-2-yl]sulfamoyl]phenyl]-3-methoxy-4-methylbenzamide), PF- 4691502 (2-amino-8-[4-(2-hydroxyethoxy)cyclohexyl]-6-(6-

methoxypyridin-3-yl)-4-methylpyrido[2,3-d]pyrimidin-7-one), PKI-402 (1-[4-(3-ethyl-7-morpholin-4-yltriazolo[4,5-d]pyrimidin-5-yl)phenyl]-3-[4-(4-methylpiperazine-1-carbonyl)phenyl]urea), GSK-2126458 (Omipalisib; 2,4-difluoro-N-[2-methoxy-5-(4-pyridazin-4-ylquinolin-6-yl)pyridin-3-yl]benzenesulfonamide), GDC-0980 (1-[4-[[2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholin-4-ylthieno[3,2-d]pyrimidin-6-yl]methyl]piperazin-1-yl]-2-hydroxypropan-1-one or Apitolisib; (2S)-1-[4-[[2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholin-4-ylthieno[3,2-d]pyrimidin-6-yl]methyl]piperazin-1-yl]-2-hydroxypropan-1-one and PKI-587 (gedatolisib; 1-[4-[4-(dimethylamino)piperidine-1-carbonyl]phenyl]-3-[4-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)phenyl]urea).

[176] In one embodiment, In one embodiment, at least one additional therapeutically active agent can be selected from AR ligand-binding domain (LBD) inhibitors, which include but are not limited to bicalutamide (Casodex™; (N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide), nilutamide (5,5-dimethyl-3-[4-nitro-3-(trifluoromethyl)phenyl] imidazolidine-2,4-dione), flutamide (2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]-propanamide), galeterone, enzalutamide (4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide), apalutamide (ARN-509), ODM-201 (BAY-1841788), abiraterone (or CB-7630; (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl) 2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol), and steroidal antiandrogens such as cyproterone acetate (6-chloro-1β,2β-dihydro-17-hydroxy-3'*H*-cyclopropa[1,2]pregna-4,6-diene-3,20-dione).

[177] In one embodiment, In one embodiment, at least one additional therapeutically active agent can be selected from cancer agents associated with the treatment of prostate cancer, which include but are not limited to docetaxel (Taxotere; 1,7β,10β-trihydroxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoate}), Bevacizumab (Avastin), OSU-HDAC42 ((S)-(+)-N-hydroxy-4-(3-methyl-2-phenylbutyrylamino)-benzamide), VITAXIN, sunitumib (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide), ZD-4054 (N-(3-Methoxy-5-methylpyrazin-2-yl)-2-[4-(1,3,4-oxadiazol-2-yl)phenyl]pyridin-3-sulfonamid), Cabazitaxel (XRP-6258), MDX-010 (Ipilimumab), OGX 011, finasteride (Proscar, Propecia; *N*-(1,1-dimethylethyl)-3-oxo-(5α,17β)-4-azaandrost-1-ene-17-carboxamide), dutasteride (Avodart;

5α, 17β)-*N*-{2,5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide), turosteride ((4aR,4bS,6aS,7S,9aS,9bS,11aR)-1,4a,6a-trimethyl-2-oxo-N-(propan-2-yl)-N-(propan-2 ylcarbamoyl)hexadecahydro-1H-indeno[5,4-f]quinoline-7-carboxamide), bexlosteride (LY-191,704; (4aS,10bR)-8-chloro-4-methyl-1,2,4a,5,6,10b-hexahydrobenzo[f]quinolin-3-one), izonsteride (LY-320,236; (4aR,10bR)-8-[(4-ethyl-1,3-benzothiazol-2-yl)sulfanyl]-4,10b-dimethyl-1,4,4a,5,6,10b-hexahydrobenzo[f]quinolin-3(2H)-one), FCE 28260, and SKF105,111.

[178] In one embodiment, at least one additional therapeutic agent is selected from: enzalutamide, Galeterone, ARN-509; abiraterone, bicalutamide, nilutamide, flutamide, cyproterone acetate, docetaxel, Bevacizumab (Avastin), OSU-HDAC42, VITAXIN, sunitumib, ZD-4054, Cabazitaxel (XRP-6258), MDX-010 (Ipilimumab), OGX 427, OGX 011, finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260, SKF105,111, ODM-201, ODM-204, radium 233, niclosamide, apalutamide, ARV-330, VPC-14449, TAS3681, 3E10-AR441bsAb, sintokamide or related compounds thereof.

[179] In one embodiment, at least one additional therapeutically active agent can be selected from various known cancer agents including alkylating agents, anti-metabolites, plant alkaloids and terpenoids (e.g., taxanes), topoisomerase inhibitors, anti-tumor antibiotics, kinase inhibitors, hormonal therapies, molecular targeted agents, and the like. Generally such an anticancer agent is an alkylating agent, an anti-metabolite, a vinca alkaloid, a taxane, a topoisomerase inhibitor, an anti-tumor antibiotic, a tyrosine kinase inhibitor, an immunosuppressive macrolide, an Akt inhibitor, an HDAC inhibitor an Hsp90 inhibitor, a CDK (cyclin-dependent kinase) inhibitor, CHK (checkpoint kinase) inhibitor, PARP (poly (DP-ribose)polymerase) inhibitors, and the like.

[180] Additionally, administration can comprise administering to the subject a plurality of dosages over a suitable period of time. Such administration regimens can be determined according to routine methods, upon a review of the instant disclosure.

[181] The compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof of the invention are generally administered in a dose of about 0.01 mg/kg/dose to about 100 mg/kg/dose. Alternately the dose can be from about 0.1 mg/kg/dose to about 10 mg/kg/dose; or about 1 mg/kg/dose to 10 mg/kg/dose. Time release preparations may be employed or the dose may be administered in as many divided doses as is convenient. When other methods are used (e.g. intravenous administration), the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer

or stereoisomer thereof, are administered to the affected tissue at a rate from about 0.05 to about 10 mg/kg/hour, alternately from about 0.1 to about 1 mg/kg/hour. Such rates are easily maintained when the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, are intravenously administered as discussed herein. Generally, topically administered formulations are administered in a dose of about 0.5 mg/kg/dose to about 10 mg/kg/dose range. Alternately, topical formulations are administered at a dose of about 1 mg/kg/dose to about 7.5 mg/kg/dose or even about 1 mg/kg/dose to about 5 mg/kg/dose.

[182] A range of from about 0.1 to about 100 mg/kg is appropriate for a single dose. Continuous administration is appropriate in the range of about 0.05 to about 10 mg/kg.

[183] Drug doses can also be given in milligrams per square meter of body surface area rather than body weight, as this method achieves a good correlation to certain metabolic and excretionary functions. Moreover, body surface area can be used as a common denominator for drug dosage in adults and children as well as in different animal species (Freireich et al., (1966) Cancer Chemother Rep. 50, 219-244). Briefly, to express a mg/kg dose in any given species as the equivalent mg/sq m dose, the dosage is multiplied by the appropriate km factor. In an adult human, 100 mg/kg is equivalent to 100 mg/kgx37 kg/sq m=3700 mg/m^2.

[184] A dosage form of the present invention may contain a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as disclosed herein, in an amount of about 5 mg to about 500 mg. That is, a dosage form of the present invention may contain in a compound of the present disclosure in an amount of about 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 55 mg, 60 mg, 65 mg, 70 mg, 75 mg, 80 mg, 85 mg, 90 mg, 95 mg, 100 mg, 110 mg, 120 mg, 125 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 175 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 225 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 275 mg, 280 mg, 290 mg, 300 mg, 310 mg, 320 mg, 325 mg, 330 mg, 340 mg, 350 mg, 360 mg, 370 mg, 375 mg, 380 mg, 390 mg, 400 mg, 410 mg, 420 mg, 425 mg, 430 mg, 440 mg, 450 mg, 460 mg, 470 mg, 475 mg, 480 mg, 490 mg, or 500 mg.

[185] The ratio of the doses of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof to that of the one or more additional therapeutically active agents can be about 1:1 or can vary, e.g., about 2:1, about 3:1, about 4:1, about 5:1, about 6:1, about 7:1, about 8:1, about 9:1, about 10:1, about 1:2, about

1:3, about 1:4, about 1:5, about 1:6, about 1:7, about 1:8, about 1:9, about 1:10, and can be varied accordingly to achieve the optimal therapeutic benefit.

[186] A dosage form of the present invention may be administered, hourly, daily, weekly, or monthly. The dosage form of the present invention may be administered twice a day or once a day. The dosage form of the present invention may be administered with food or without food.

[187] Insofar as the compounds of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof disclosed herein can take the form of a mimetic or fragment thereof, it is to be appreciated that the potency, and therefore dosage of an effective amount can vary. However, one skilled in the art can readily assess the potency of the compounds of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof of the type presently envisioned by the present application.

[188] In settings of a gradually progressive disorder or condition characterized by cell proliferation, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent are generally administered on an ongoing basis. In certain settings administration of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent disclosed herein can commence prior to the development of disease symptoms as part of a strategy to delay or prevent the disease. In other settings the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent disclosed herein is administered after the onset of disease symptoms as part of a strategy to slow or reverse the disease process and/or part of a strategy to improve cellular function and reduce symptoms.

[189] It will be appreciated by one of skill in the art that dosage range will depend on the particular compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent, and its potency. The dosage range is understood to be large enough to produce the desired effect in which the neurodegenerative or other disorder and the symptoms associated therewith are ameliorated and/or survival of the cells is achieved, but not be so large as to cause unmanageable adverse side effects. It will be understood, however, that the specific dose level for any particular

patient will depend on a variety of factors including the activity of the specific compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs which have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those skilled in the art. The dosage can also be adjusted by the individual physician in the event of any complication. No unacceptable toxicological effects are expected when compounds of the present disclosure are used in accordance with the present application.

[190] An effective amount of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent disclosed herein comprise amounts sufficient to produce a measurable biological response. Actual dosage levels of active ingredients of the present application can be varied so as to administer an amount of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent that is effective to achieve the desired therapeutic response for a particular subject and/or application. Preferably, a minimal dose is administered, and the dose is escalated in the absence of dose-limiting toxicity to a minimally effective amount. Determination and adjustment of a therapeutically effective dose, as well as evaluation of when and how to make such adjustments, are known to those of ordinary skill in the art.

[191] Further with respect to the methods of the present application, a preferred subject is a vertebrate subject. A preferred vertebrate is warm-blooded; a preferred warm-blooded vertebrate is a mammal. The subject treated by the presently disclosed methods is desirably a human, although it is to be understood that the principles of the present application indicate effectiveness with respect to all vertebrate species which are included in the term "subject." In this context, a vertebrate is understood to be any vertebrate species in which treatment of a neurodegenerative disorder is desirable. As used herein, the term "subject" includes both human and animal subjects. Thus, veterinary therapeutic uses are provided in accordance with the present application.

[192] As such, the present application provides for the treatment of mammals such as humans, as well as those mammals of importance due to being endangered, such as Siberian tigers; of economic importance, such as animals raised on farms for consumption by humans; and/or animals

of social importance to humans, such as animals kept as pets or in zoos or farms. Examples of such animals include but are not limited to: carnivores such as cats and dogs; swine, including pigs, hogs, and wild boars; ruminants and/or ungulates such as cattle, oxen, sheep, giraffes, deer, goats, bison, and camels; and horses. Also provided is the treatment of birds, including the treatment of those kinds of birds that are endangered and/or kept in zoos, as well as fowl, and more particularly domesticated fowl, i.e., poultry, such as turkeys, chickens, ducks, geese, guinea fowl, and the like, as they are also of economical importance to humans. Thus, also provided are the treatment of livestock, including, but not limited to, domesticated swine, ruminants, ungulates, horses (including race horses), poultry, and the like.

[193] In general, compounds of the invention should be used without causing substantial toxicity. Toxicity of the compounds of the invention can be determined using standard techniques, for example, by testing in cell cultures or experimental animals and determining the therapeutic index, *i.e.*,, the ratio between the LD50 (the dose lethal to 50% of the population) and the LD100 (the dose lethal to 100% of the population). In some circumstances, such as in severe disease conditions, substantial excesses of the compositions can be administered for therapeutic effects. Some compounds of this invention can be toxic at some concentrations. Titration studies can be used to determine toxic and non-toxic concentrations. Toxicity can be evaluated by examining a particular compound's or composition's specificity across cell lines using PC3 or DU145 cells as possible negative controls since these cells do not express functional AR. Animal studies can be used to provide an indication if the compound has any effects on other tissues. Systemic therapy that targets the AR will not likely cause major problems to other tissues since antiandrogens and androgen insensitivity syndrome are not fatal.

[194] Compounds for use in the present invention can be obtained from medical sources or modified using known methodologies from naturally occurring compounds. In addition, methods of preparing or synthesizing compounds of the present invention will be understood by a person of skill in the art having reference to known chemical synthesis principles. For example, Auzou *et al* 1974 *European Journal of Medicinal Chemistry* 9(5), 548-554 describes suitable synthetic procedures that can be considered and suitably adapted for preparing compounds of any one of the compounds of structure (I) as set out above. Other references that can be helpful include: Debasish Das, Jyh-Fu Lee and Soofin Cheng "Sulfonic acid functionalized mesoporous MCM-41 silica as a convenient catalyst for Bisphenol-A synthesis" *Chemical Communications*, (2001) 2178–2179;

US Patent 2571217 Davis, Orris L.; Knight, Horace S.; Skinner, John R. (Shell Development Co.) "Halohydrin ethers of phenols." (1951); and Rokicki, G.; Pawlicki, J.; Kuran, W. "Reactions of 4-chloromethyl-1,3-dioxolan-2-one with phenols as a new route to polyols and cyclic carbonates." Journal fuer Praktische Chemie (Leipzig) (1985) 327, 718-722.

[195] In some embodiments, compounds and all different forms thereof as described herein can be used, for example, and without limitation, in combination with other treatment methods for at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age related macular degeneration. For example, compounds and all their different forms as described herein can be used as neoadjuvant (prior), adjunctive (during), and/or adjuvant (after) therapy with surgery, radiation (brachytherapy, external beam, RIT), or other therapies (eg. HIFU), and in combination with chemotherapies, androgen ablation, antiandrogens or any other therapeutic approach.

[196] The compounds described herein can be used for *in vivo* or *in vitro* research uses (i.e. non-clinical) to investigate the mechanisms of orphan and nuclear receptors (including steroid receptors such as androgen receptor (AR)). Furthermore, these compounds can be used individually or as part of a kit for in vivo or in vitro research to investigate signal transduction pathways and/or the activation of orphan and nuclear receptors using recombinant proteins, cells maintained in culture, and/or animal models.

IV. Pharmaceutical Formulations

[197] In another embodiment, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as disclosed herein, as the active ingredient, combined with a pharmaceutically acceptable excipient or carrier. The excipients are added to the formulation for a variety of purposes.

[198] In some embodiments, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent may be formulated into a single pharmaceutical composition. In some embodiments, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a

pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent are formulated into a separate pharmaceutical composition comprising a pharmaceutically acceptable excipient or a carrier.

[199] In one embodiment, the pharmaceutical composition comprising the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent.

[200] Suitable pharmaceutical compositions can be formulated by means known in the art and their mode of administration and dose determined by the skilled practitioner. Many suitable formulations are known, including, polymeric or protein microparticles encapsulating a compound to be released, ointments, pastes, gels, hydrogels, or solutions which can be used topically or locally to administer a compound. A sustained release patch or implant can be employed to provide release over a prolonged period of time. Many techniques known to one of skill in the art are described in *Remington: the Science & Practice of Pharmacy* by Alfonso Gennaro, 20th ed., Lippencott Williams & Wilkins, (2000).

[201] Diluents may be added to the formulations of the present invention. Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition n easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g., AVICEL), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g., EUDRAGIT(r)), potassium chloride, powdered cellulose, sodium chloride, sorbitol, and talc.

[202] Solid pharmaceutical compositions and/or combinations that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions and/or combinations include acacia, alginic acid, carbomer (e.g., carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, gum tragacanth, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g., KLUCEL), hydroxypropyl methyl cellulose (e.g., METHOCEL), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g., KOLLIDON, PLASDONE), pregelatinized starch, sodium alginate, and starch.

[203] The dissolution rate of a compacted solid pharmaceutical composition a in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g., AC-DI-SOL and PRIMELLOSE), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g., KOLLIDON and POLYPLASDONE), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g., EXPLOTAB), potato starch, and starch.

[204] Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, and tribasic calcium phosphate.

[205] When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

[206] Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

[207] Solid and liquid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

[208] In liquid pharmaceutical compositions may be prepared using the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, of the present invention and any other solid excipients where the components are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol, or glycerin.

[209] Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions and/or combinations of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol, and cetyl alcohol.

[210] Liquid pharmaceutical compositions may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, and xanthan gum.

[211] Sweetening agents such as aspartame, lactose, sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol, and invert sugar may be added to improve the taste.

[212] Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxyl toluene, butylated hydroxyanisole, and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

[213] A liquid composition may also contain a buffer such as guconic acid, lactic acid, citric acid or acetic acid, sodium guconate, sodium lactate, sodium citrate, or sodium acetate. Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

[214] The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions and/or combinations. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts. For example, a compound can be dissolved in sterile water or saline or a pharmaceutically acceptable vehicle used for administration of non-water soluble compounds such as those used for vitamin K, for a parenteral administration. For enteral administration, the compound can be administered in a tablet, capsule

or dissolved in liquid form. The tablet or capsule can be enteric coated, or in a formulation for sustained release.

[215] Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and lozenges, as well as liquid syrups, suspensions, aerosols and elixirs.

[216] The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

[217] A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water that causes the powders to clump into granules. The granulate is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may be tableted, or other excipients may be added prior to tableting, such as a glidant and/or a lubricant.

[218] A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

[219] As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

[220] A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting; however, they are not subjected to a final tableting step.

[221] The active ingredient and excipients may be formulated into compositions and/or combinations and dosage forms according to methods known in the art.

[222] In one embodiment, a dosage form may be provided as a kit comprising a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and pharmaceutically acceptable excipients and carriers as separate components. In one embodiment, a dosage form may be provided as a kit comprising a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof at least one additional therapeutically active agent, and pharmaceutically acceptable excipients and carriers as separate components. In some embodiments, the dosage form kit allow physicians and patients to formulate an oral solution or injection solution prior to use by dissolving, suspending, or mixing the compound of formula ((I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof with pharmaceutically acceptable excipients and carriers. In one embodiment, a dosage form kit which provides a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof which has improved stability when compared to pre-formulated formulations a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof.

[223] In one embodiment, a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof is used in the formulation. The compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, of the present invention may be used in pharmaceutical formulations or compositions as single components or mixtures together with other forms of a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof. In one embodiment, pharmaceutical formulations or compositions of the present invention contain 25-100% or 50-100% by weight, of at least one compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, as described herein, in the formulation or composition.

[224] In one embodiment, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, is administered at a dose from about 5 mg/day to about 500 mg/day. In one embodiment, at least one additional therapeutically active agent is administered at about 1 mg/day to about 500 mg/day. In another embodiment, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and/or at least one additional

therapeutically active agent is administered at a dose from about 1 mg/m^2 to about 3 g/m^2, from about 5 mg/m^2 to about 1 g/m^2, or from about 10 mg/m^2 to about 500 mg/m^2.

[225] The administered dose may be expressed in units of mg/m^2/day in which a patient's body surface area (BSA) may be calculated in m^2 using various available formulae using the patient's height and weight. The administered dose may alternatively be expressed in units of mg/day which does not take into consideration the patient's BSA. It is straightforward to convert from one unit to another given a patient's height and weight.

[226] The term "co-administration" or "coadministration" refers to administration of (a) a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and (b) at least one additional therapeutically active agent, together in a coordinated fashion. For example, the co-administration can be simultaneous administration, sequential administration, overlapping administration, interval administration, continuous administration, or a combination thereof. In one embodiment, a compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent are formulated into a single dosage form. In another embodiment, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one additional therapeutically active agent are provided in a separate dosage forms.

[227] In one embodiment, the co-administration is carried out for one or more treatment cycles. By "treatment cycle", it is meant a pre-determined period of time for co-administering the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent. Typically, the patient is examined at the end of each treatment cycle to evaluate the effect of the present combination therapy. In one embodiment, the co-administration is carried out for 1 to 48 treatment cycles. In another embodiment, the co-administration is carried out for 1 to 36 treatment cycles. In another embodiment, the co-administration is carried out for 1 to 24 treatment cycles.

[228] In one embodiment, each of the treatment cycle has about 3 or more days. In another embodiment, each of the treatment cycle has from about 3 days to about 60 days. In another embodiment, each of the treatment cycle has from about 5 days to about 50 days. In another embodiment, each of the treatment cycle has from about 7 days to about 28 days. In another embodiment, each of the treatment cycle has 28 days. In one embodiment, the treatment cycle has

about 29 days. In another embodiment, the treatment cycle has about 30 days. In another embodiment, the treatment cycle has about a month-long treatment cycle. In another embodiment, the treatment cycle has from about 4 to about 6 weeks.

[229] Depending on the patient's condition and the intended therapeutic effect, the dosing frequency for each of the c compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent may vary from once per day to six times per day. That is, the dosing frequency may be once per day, twice per day, three times per day, four times per day, five times per day, or six times per day. In some embodiments, dosing frequency may be one to six times per week or one to four times per month. In one embodiment, dosing frequency may be once a week, once every two weeks, once every three weeks, once every four weeks, or once a month.

[230] There may be one or more void days in a treatment cycle. By "void day", it is meant a day when neither the compound of formula(I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof or at least one therapeutically active agent is administered. In other words, none of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent is administered on a void day. Any treatment cycle must have at least one non-void day. By "non-void day", it is meant a day when at least one of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent is administered.

[231] By "simultaneous administration", it is meant that the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent are administered on the same day. For the simultaneous administration, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent can be administered at the same time or one at a time.

[232] In one embodiment of the simultaneous administration, the c compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, is administered from 1 to 4 times per day, 1 to 4 times per week, once every two weeks, once every three weeks, once every four weeks or 1 to 4 times per month; and the at least one additional therapeutically active agent is administered 1 to 4 times per day, 1 to 4 times

per week, once every two weeks, once every three weeks, once every four weeks or 1 to 4 times per month. In another embodiment of the simultaneous administration, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, is administered once a week, once every two weeks, once every three weeks, once every four weeks, or once a month; and the at least one additional therapeutically active agent is administered 1 to 4 times per day, 1 to 4 times per week, once every two weeks, once every three weeks, once every four weeks or 1 to 4 times per month.

[233] By "sequential administration", it is meant that during a period of two or more days of continuous co-administration without any void day, only one of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent is administered on any given day.

[234] In one embodiment of the sequential administration, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, is administered from 1 to 4 times per day, 1 to 4 times per week, once every two weeks, once every three weeks, once every four weeks or 1 to 4 times per month; and at least one additional therapeutically active agent is administered 1 to 4 times per day, 1 to 4 times per week, once every two weeks, once every three weeks, once every four weeks or 1 to 4 times per month. In another embodiment of the sequential administration, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, is administered from once a week, once every two weeks, once every three weeks, once every four weeks, or once a month; and at least one additional therapeutically active agent is administered 1 to 4 times per day, 1 to 4 times per week, once every two weeks, once every three weeks, once every four weeks or 1 to 4 times per month.

[235] By "overlapping administration", it is meant that during a period of two or more days of continuous co-administration without any void day, there is at least one day of simultaneous administration and at least one day when only one of the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent is administered.

[236] By "interval administration", it is meant a period of co-administration with at least one void day. By "continuous administration", it is meant a period of co-administration without any

void day. The continuous administration may be simultaneous, sequential, or overlapping, as described above.

[237] In the present method, the co-administration comprises oral administration, parenteral administration, or a combination thereof. Examples of the parenteral administration include, but are not limited to intravenous (IV) administration, intraarterial administration, intramuscular administration, subcutaneous administration, intraosseous administration, intrathecal administration, or a combination thereof. The compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent can be independently administered orally or parenterally. In one embodiment, the compound of formula (I), (IA), (IB), (IC), (IIA), (IIB), or (IIC), or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof and at least one therapeutically active agent is administered parenterally. The parenteral administration may be conducted via injection or infusion.

EXAMPLES

Material and Methods

[238] *Cells and reagents*: LNCaP have been described previously. Compound A and Compound B were from inventors or NAEJA (Edmonton, Alberta). Enzalutamide was purchased from Omega Chem (St-Romuald, Quebec). The synthetic androgen, R1881, was purchased from Perkin-Elmer (Woodbridge, ON).

[239] *Cell proliferation based on crystal violet staining:* LNCaP cells or LNCaP-EPI^R cells were seeded in a 96-well plate and pre-treated for 1 h with DMSO, Compound A (25 μM), Compound B (25 μM), or enzalutamide (10 μM), in serum-free conditions prior to addition of 0.1 nM R1881or EtOH.

[240] *Gene expression analysis*: LNCaP cells or LNCaP-EPI^R cells were treated with DMSO, Compound A (25 μM), Compound B (25 μM), or enzalutamide (10 μM) for 1 h prior to the addition of R1881 (1nM) or EtOH for 48 h. Total RNA was isolated and reverse transcribed to cDNA. Quantitative real-time RT-PCR was performed in triplicates for each biological sample. Expression levels were normalized to SDHA housekeeping gene.

[241] *Animal studies*: Six to eight weeks old male NOD-SCID mice were maintained in the Animal Care Facility in the British Columbia Cancer Research Centre. All animal experiments

were approved by the University of British Columbia Animal Care Committee. Mice were castrated when subcutaneous xenografts were approximately 100 mm^3. Seven days after castration, mice were dosed by either oral gavage or tail vein injection. Tumor volumes were measured twice a week using a caliper by the formula length x width x height x 0.52.

[242] **EXAMPLE 1**: Compound A resistant LNCaP cell line generation (LNCaP-EPI^R).

[243] LNCaP cells were continuously exposed, once a week, in RPMI 1640 media containing 5% FBS (fetal bovine serum) and 25 μM Compound A for approximately 18 months to provide potentially Compound A resistant LNCaP cells. The media was replenished every three days.

[244] **EXAMPLE 2**: Demonstration of Compound A resistance following chronic treatment.

[245] LNCaP cells and Compound A resistant LNCaP cells (LNCaP-EPI^R) were treated with DMSO, Compound A, or enzalutamide (ENZ) for 1 h prior to the addition of R1881 (0.1 nM) for up to 96 h. Proliferation was measured by crystal violet staining.

[246] Compound A and enzalutamide (anti-androgen) demonstrated similar inhibition in cell proliferation of LNCaP cells (Fig. 1A); however, LNCaP-EPI^R cells stimulated with R1881 (synthetic androgen) are able to proliferate in the presence of Compound A (Fig. 1B). In addition, bicalutamide (also an anti-androgen) demonstrated similar activity to enzalutamide as shown in the cell proliferation data point at 96 hours in the resistant line (Fig. 1C), indicating cross-resistance had not developed. The effect of anti-androgens enzalutamide and bicalutamide on LNCaP cells indicates that the AR plays a fundamental role in providing mitogenic signals. Figures 1A-1C: Two-way ANOVA (Dunnett's test applied *post hoc*), error bars represent mean +/- SEM, n=3 independent experiments. n.s.; not statistically significant; ****$p < 0.0001$.

[247] **EXAMPLE 3**: An *in vivo* study on tumour volume in mice inoculated with LNCAP or LNCaP-EPI^R.

[248] Male mice were inoculated subcutaneously with LNCaP or LNCaP-EPI^R cells. Once tumours reached ~100 mm^3 mice were castrated and 7 days after castration were treated daily for 28 days with Compound A (200 mg/kg), enzalutamide (10 mg/kg), or vehicle (CMC, VEH).

[249] LNCaP xenograft show growth inhibition in response to Compound A (Fig 2A); however this phenomenon is lost in LNCaP-EPI^R xenografts (Fig. 2B). Significant sensitivity to anti-

androgen enzalutamide was also seen *in vivo*, validating *in vitro* observations (Example 2). Figures 2A-2B: One-way ANOVA (Bonferroni test applied *post hoc*), error bars represent mean +/- SEM, n=8 tumours. *p < 0.05; ** p < 0.01; *** p < 0.001; ****p < 0.0001.

[250] **EXAMPLE 4**: Levels of Expression of *UGT2B* genes.

[251] qRT-PCR of mRNA isolated from *in vitro* treated samples (DMSO, Compound A, or enzalutamide, with or without R1881) were evaluated for levels of expression of *UGT2B* genes.

[252] In Figures 3A, 3B, 4A, and 4B, all transcripts were normalized to transcript levels of *SDHA*. qPCR data (Figs. 3A, 3B, 4A, and 4B) confirm *UGT2B* overexpression in LNCaP-EPI^R cells. Error bars represent mean +/- SEM, n=3 independent experiments. Increased levels of UGT2B mRNA were measured in the resistant cell line. This is important as Compound A has three hydroxyl groups which could be putative targets for glucuronidation.

[253] **EXAMPLE 5**: *UGT2B* activity.

[254] Endogenous *UGT2B* activity was measured in LNCaP cells and LNCaP-EPI^R cells by percent substrate (luciferin) consumption. Figure 5 demonstrates that LNCaP-EPI^R cells display nearly 7-fold higher *UGT2B* activity compared to LNCaP cells. Figure 5: T-test (two-tailed, unpaired) error bars represent mean +/- SEM, n=4 independent experiments.

[255] Endogenous *UGT2B* activity was measured in mouse liver microsomes for Compounds A and B in competition with luciferin substrate. Figure 6 demonstrates that Compound A competes with luciferin whereas Compound B does not. Figure 6: Two-way ANOVA (Dunnett's test applied post hoc), error bars represent mean +/- SEM, n=3 independent experiments.

[256] Compounds A and B were separately incubated in the presence of mouse liver microsomes and UDPGA (uridine 5'-diphospho-glucuronic acid) cofactor. Glucuronidation reaction consists of transferring glucuronosyl group from UDPGA to substrates, e.g., Compound A or B. Compound A showed metabolism by glucuronidation whereas Compound B appeared to form some glucuronide conjugates but in much lower degree than Compound A. In both experiments, the presence of β-glucuronidase liberated glucuronic acid and released Compounds A and B. Figure 7 shows HPLC traces from the incubation experiment with UDPGA and UDPGA with β-glucuronidase.

[257] **EXAMPLE 6**: Inhibiting cell proliferation and AR signaling in LNCaP- EPI^R cells.

[258] Compound B is resistant to glucuronidation. LNCaP cells and LNCaP-EPI^R were treated with DMSO, Compound A, or Compound B for 1 h prior to the addition of R1881 (0.1 nM) for up to 96 h. Proliferation was measured by crystal violet staining.

[259] LNCaP-EPI^R cells show significant sensitivity to Compound B but not to Compound A, which implies that glucuronidation may drive resistance to Compound A (Figs. 8A-8B). Figures 8A-8B: Two-way ANOVA (Dunnett's test applied *post hoc*), error bars represent mean +/- SEM, n=3 independent experiments. *$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; ****$p < 0.0001$.

[260] **EXAMPLE 7**: Blocking AR transcriptional activity.

[261] qRT-PCR of mRNA samples generated from *in vitro* treated samples (DMSO, Compound A, Compound B, or enzalutamide with or without R1881) were analyzed for AR transcriptional activity. Compound B showed enhanced efficacy in blocking AR transcriptional activity as measured using AR-target genes in response to androgen (Figs. 9A-9D). In Figures 9A-9D, all transcripts were normalized to transcript levels of *SDHA*. Error bars represent mean +/- SEM, n=3 independent experiments.

[262] **EXAMPLE 8**: Anti-tumor activity in LNCaP and LNCaP-EPI^R xenografts.

[263] Male mice were inoculated subcutaneously with LNCaP or LNCaP-EPI^R cells. Once tumours reached ~100 mm^3 mice were castrated and 7 days after castration were treated by tail vein injection every other day for 14 days with Compound A (50 mg/kg), Compound B (50 mg/kg), or vehicle (15% DMSO/25.5% PEG-400, VEH).

[264] Figure 10A demonstrates Compounds A and B having similar anti-tumor activity in LNCaP xenografts. Figure 10B demonstrates Compound B having enhanced anti-tumor activity when compared to Compound A in LNCaP-EPI^R xenografts. Figure 10C shows the tumor size at from experiments in LNCaP-EPI^R xenografts. Figures 10A-10B: Two-way ANOVA (Dunnett's test applied post hoc), error bars represent mean +/- SEM, n=18 (VEH/Compound B); n=7 (Compound A).

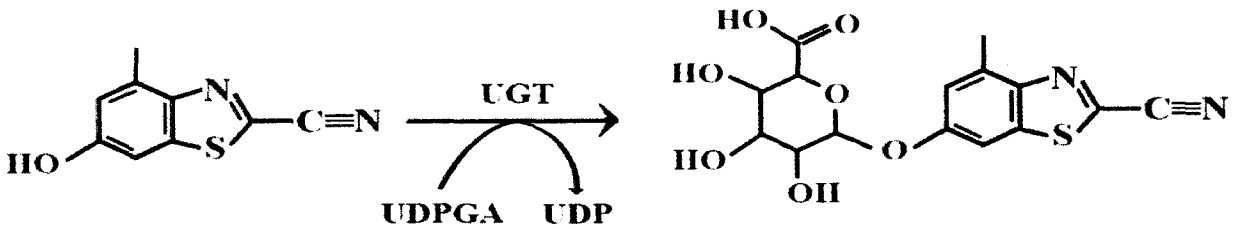
Discussions

[265] Parental LNCaP cells have shown evidence of becoming resistant to Compound A as demonstrated by studies described herein involving LNCaP-EPI^R cell lines. However, LNCaP-EPI^R remains to be sensitive to anti-androgens targeting the LBD (such as enzalutamide and bicalutamide) *in vitro* and *in vivo* (Examples 2-3).

[266] Furthermore, Compound A is significantly less effective at blocking AR-mediated transcription as measured by target genes such as *FKBP5*, *RHOU*, *KLK2*, and *KLK3*. This may be, without bound to any theory, due to overexpression of *UGT2B* genes which facilitates the metabolism and excretion of Compound A via glucuronidation.

[267] *UGT2B* genes mediate transfer of glucuronic acid to exposed hydroxyl groups on target substrates as shown in Scheme 1. Compound A contains three putative glucuronidation sites (free hydroxyl groups) which, without bound to any theory, may facilitate the metabolism and excretion by glucuronidation.

[268] **Scheme 1**: Glucuronidation of 2-Benzothiazolecarbonitrile



[269] Endogenous *UGT2B* activity is displayed nearly 7-fold higher in LNCaP-EPI^R cells compared to LNCaP cells (Fig. 7).

[270] Compound B is resistant to glucuronidation and showed significant efficacy in the cell proliferation assay for both LNCaP and LNCaP-EPI^R cells as well as anti-tumor activity in LNCaP and LNCaP-EPI^R xenografts. These studies which shows Compound B to inhibit cell proliferation of LNCaP-EPI^R cells and demonstrating anti-tumor activity, can support the hypothesis that the resistance to Compound A in LNCaP-EPI^R cells is due to overexpression of *UGT2B* genes.

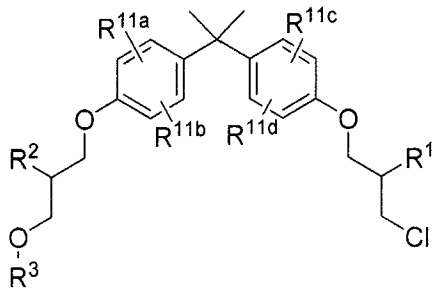
[271] In conclusion, our findings demonstrate that AR NTD inhibitors that are also resistant to glucuronidation may find usefulness in treatment of cells that became resistant, in some embodiment due to over expression of *UGT2B* genes. These AR NTD inhibitors that are glucuronidation resistant may be used in monotherapy or in combination therapy for treatment of various diseases including cancer.

[272] Although various embodiments of the invention are disclosed herein, many adaptations and modifications can be made within the scope of the invention in accordance with the common general knowledge of those skilled in this art. Such modifications include the substitution of known equivalents for any aspect of the invention in order to achieve the same result in substantially the same way. Numeric ranges are inclusive of the numbers defining the range. The word "comprising" is used herein as an open-ended term, substantially equivalent to the phrase "including, but not limited to", and the word "comprises" has a corresponding meaning. As used herein, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a thing" includes more than one such thing. Citation of references herein is not an admission that such references are prior art to the present invention. Any priority document(s) and all publications, including but not limited to patents and patent applications, cited in this specification are incorporated herein by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein and as though fully set forth herein. The invention includes all embodiments and variations substantially as hereinbefore described and with reference to the examples and drawings.

CLAIMS

What is claimed is:

1. A method of reducing, inhibiting, or ameliorating proliferation of resistant cells, comprising administering a therapeutically effective amount of a compound of formula (I):



(I),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof; wherein

R^1 is hydroxyl or $-OC(=O)R^{13}$;

R^2 is hydroxyl or $-OC(=O)R^{13}$;

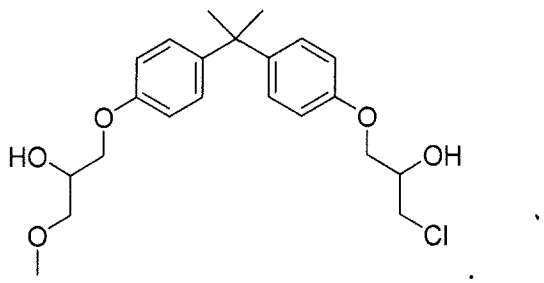
R^3 is C_1-C_6 alkyl;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, or halogen;

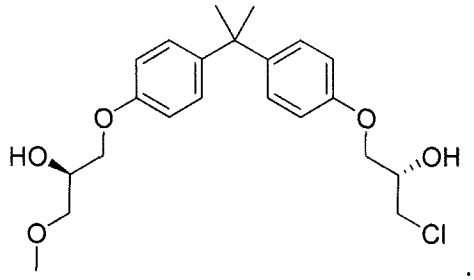
R^{13} is C_1-C_6 alkyl; and

wherein the cells are resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

2. The method of claim 1, wherein the compound of formula (I) is



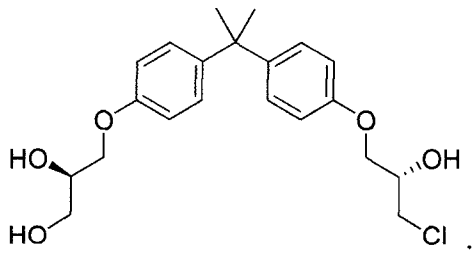
3. The method of claim 1 or 2, wherein the compound of formula (I) is



4. The method of any one of claims 1-3, wherein the AR NTD modulator is an AR NTD inhibitor.

5. The method of any one of claims 1-3, wherein the AR NTD modulator is an AR NTD binder.

6. The method of any one of claims 1-3, wherein the AR NTD modulator is



7. The method of any one of claims 1-6, wherein the reducing, inhibiting, or ameliorating is *in vivo*.

8. The method of any one of claims 1-6, wherein the reducing, inhibiting, or ameliorating is *in vitro*.

9. The method of any one of claims 1-8, wherein the cells are a cancer cells.

10. The method of claim 9, wherein the cancer cells are a prostate cancer cells.

11. The method of claim 10, wherein the prostate cancer cells are selected from cells of primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer.

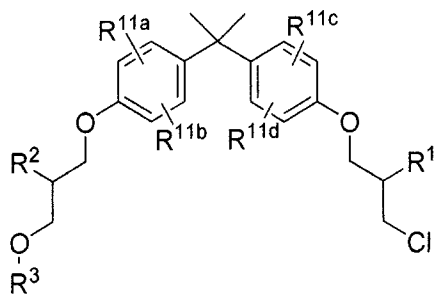
12. The method of claim 10, wherein the prostate cancer cells are metastatic castration-resistant prostate cancer (CRPC) cells.

13. The method of any one of claims 1-12, wherein the AR NTD modulator is susceptible to glucuronidation.

14. The method of any one of claims 1-12, wherein the AR NTD modulator is not glucuronidation resistant.

15. The method of claim 9, wherein the cancer cells are a breast cancer cells.

16. A method for treating a condition or disease that is responsive to modulation of androgen receptor activity, comprising administering to the subject, a therapeutically effective amount of a compound of formula (I);



(I),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof; wherein

R^1 is hydroxyl or –OC(=O)R^{13};

R^2 is hydroxyl or -OC(=O)R^{13};

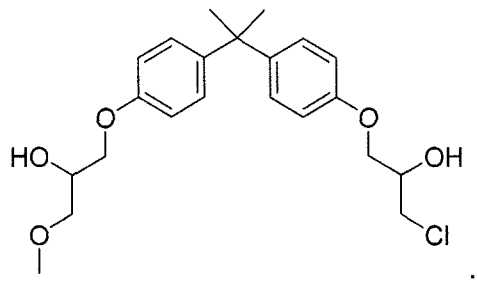
R^3 is C_1-C_6 alkyl;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, or halogen;

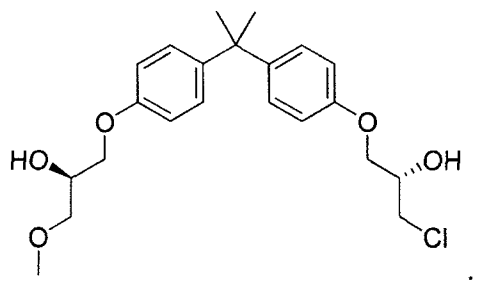
R^{13} is C_1-C_6 alkyl; and

wherein the condition or disease is resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

17. The method of claim 16, wherein the compound of formula (I) is



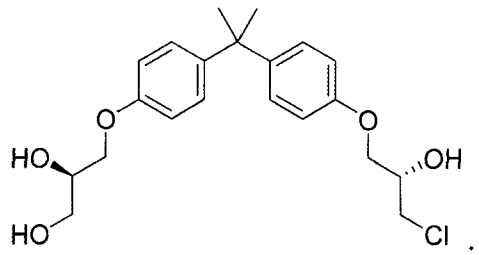
18. The method of claim 16 or 17, wherein the compound of formula (I) is



19. The method of any one of claims 16-18, wherein the AR NTD modulator is an AR NTD inhibitor.

20. The method of any one of claims 16-19, wherein the AR NTD modulator is an AR NTD binder.

21. The method of any one of claims 16-19, wherein the AR NTD modulator is



22. The method of any one of claims 16-21, wherein the treating is *in vivo*.

23. The method of any one of claims 16-21, wherein the treating is *in vitro*.

24. The method of any one of claims 16-21, wherein the condition or disease is selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, and age-related macular degeneration.

25. The method of any one of claims 16-24, wherein the condition or disease is prostate cancer.

26. The method of claim 25, wherein the prostate cancer is selected from primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer.

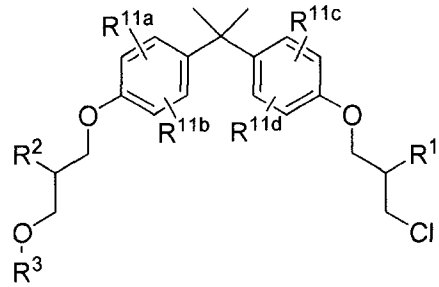
27. The method of claim 25, wherein the prostate cancer is a metastatic castration-resistant prostate cancer.

28. The method of claim 24, wherein the condition or disease is breast cancer.

29. The method of any one of claims 16-28, wherein the AR NTD modulator is susceptible to glucuronidation.

30. The method of any one of claims 16-28, wherein the AR NTD modulator is not glucuronidation resistant.

31. A method for reducing or preventing tumor growth, comprising contacting tumor cells with a therapeutically effective amount of a compound of formula (I);



(I),

or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof; wherein

R^1 is hydroxyl or $-OC(=O)R^{13}$;

R^2 is hydroxyl or $-OC(=O)R^{13}$;

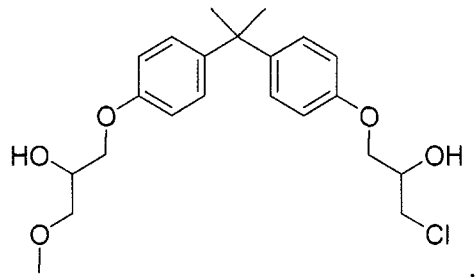
R^3 is C_1-C_6 alkyl;

R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, or halogen;

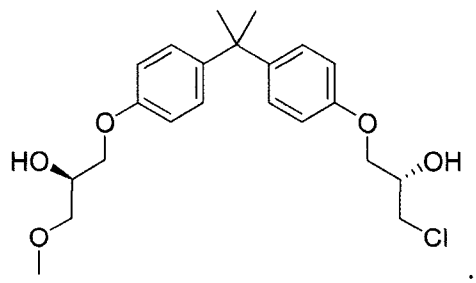
R^{13} is C_1-C_6 alkyl; and

wherein the condition or disease is resistant to an androgen receptor N-terminal domain (AR NTD) modulator.

32. The method of claim 31, wherein the compound of formula (I) is



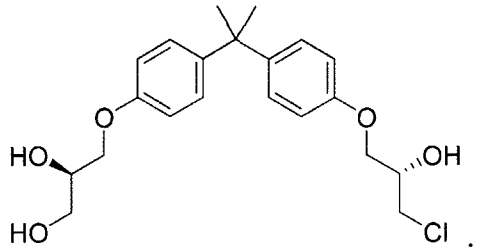
33. The method of claim 31 or 32, wherein the compound of formula (I) is



34. The method of any one of claims 31-33, wherein the AR NTD modulator is an AR NTD inhibitor.

35. The method of any one of claims 31-33, wherein the AR NTD modulator is an AR NTD binder.

36. The method of any one of claims 31-33, wherein the AR NTD modulator is



37. The method of any one of claims 31-36, wherein the reducing or preventing is *in vivo*.

38. The method of any one of claims 31-36, wherein the reducing or preventing is *in vitro*.

39. The method of any one of claims 31-38, wherein the tumor cell is selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, endometrial cancer, and salivary gland carcinoma.

40. The method of claim 39, wherein the tumor cells are prostate cancer tumor cells.

41. The method of claim 40, wherein the prostate cancer is selected from primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer.

42. The method of claim 40, wherein the prostate cancer is a castration resistant prostate cancer.

43. The method of claim 39, wherein the tumor cells are is breast cancer tumor cells.

44. The method of any one of claims 31-43, wherein the AR NTD modulator is susceptible to glucuronidation.

45. The method of any one of claims 31-43, wherein the AR NTD modulator is not glucuronidation resistant.

FIG. 1A

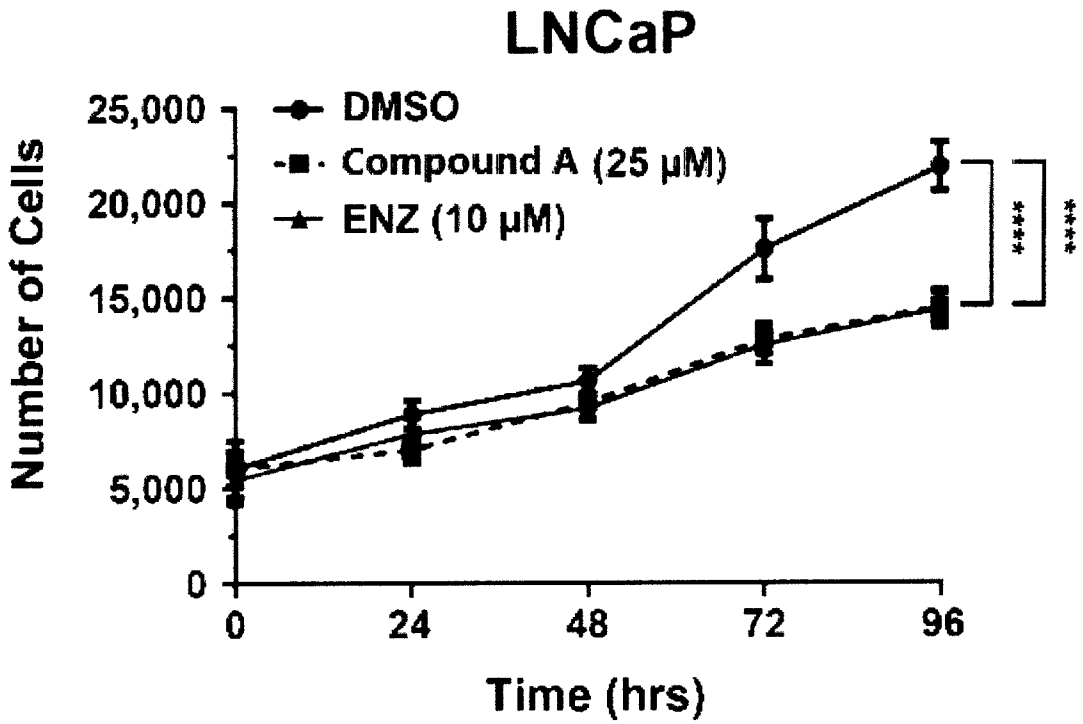

LNCaP
DMSO
Compound A (25 μM)
ENZ (10 μM)
Number of Cells
25,000
20,000
15,000
10,000
5,000
0
0
24
48
72
96
Time (hrs)
****
****

FIG. 1B

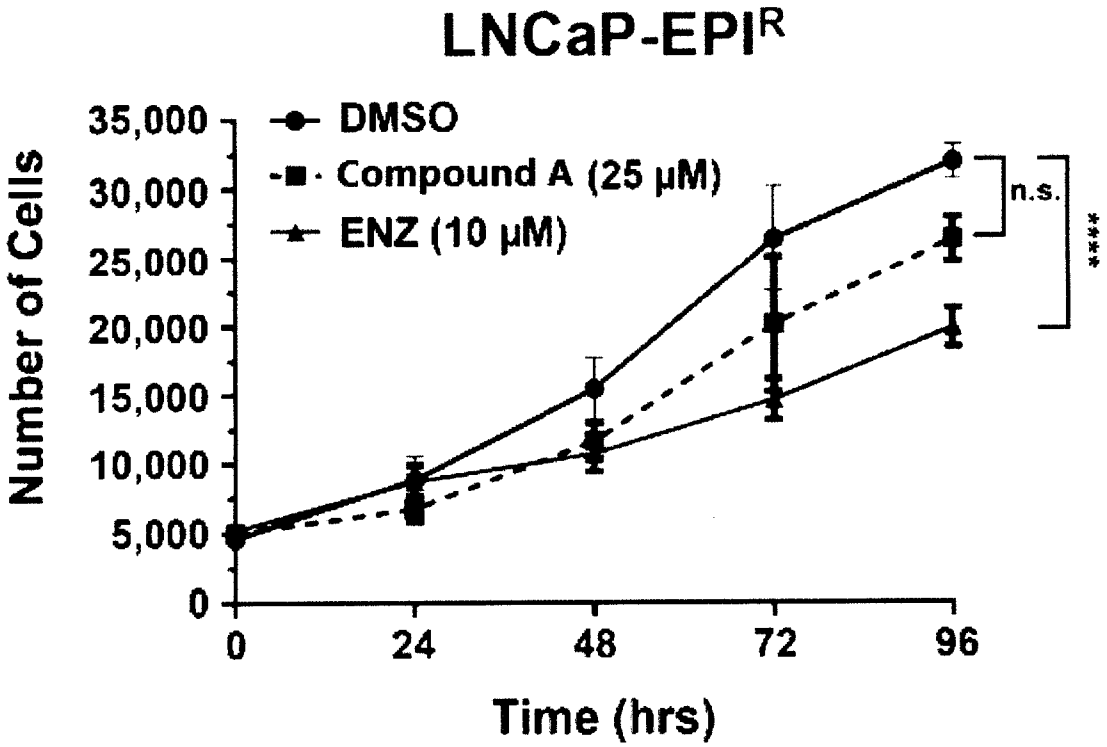

LNCaP-EPI^R
DMSO
Compound A (25 μM)
ENZ (10 μM)
Number of Cells
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
0
24
48
72
96
Time (hrs)
n.s.
****

FIG. 1C

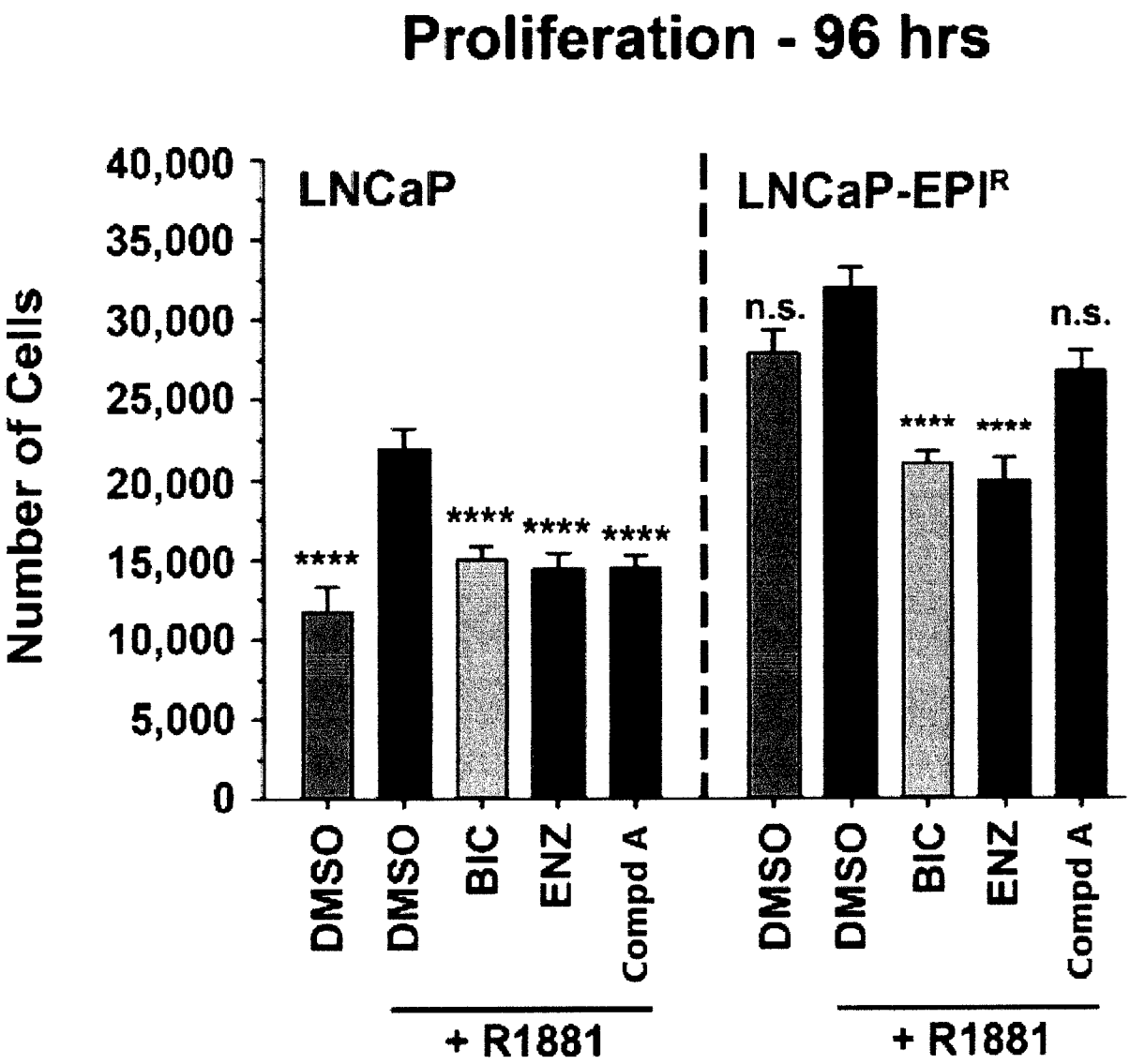

Proliferation - 96 hrs
LNCaP
LNCaP-EPI^R
Number of Cells
40,000
35,000
30,000
25,000
20,000
15,000
10,000
5,000
0
****
****
****
****
n.s.
****
****
n.s.
DMSO
DMSO
BIC
ENZ
Compd A
DMSO
DMSO
BIC
ENZ
Compd A
+ R1881
+ R1881

FIG. 2A

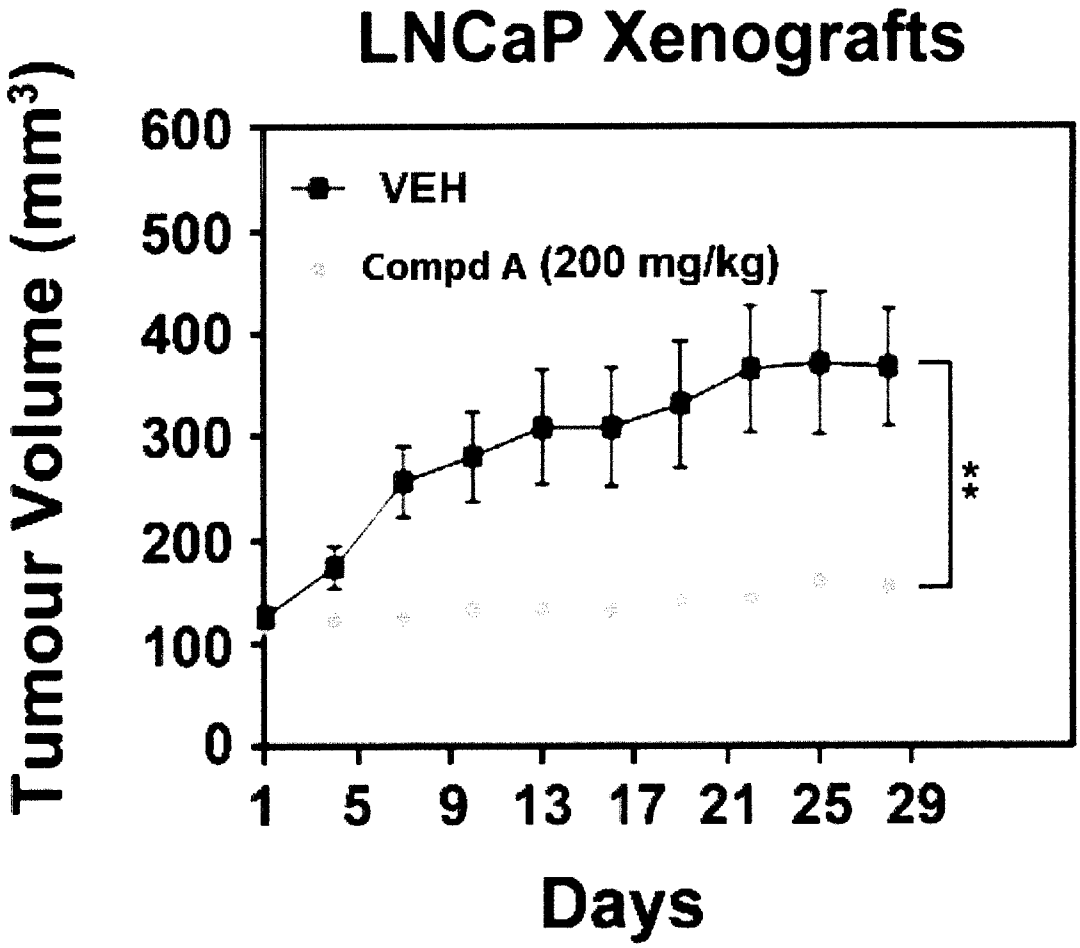

LNCaP Xenografts
Tumour Volume (mm3)
600
500
400
300
200
100
0
VEH
Compd A (200 mg/kg)
**
1
5
9
13
17
21
25
29
Days

FIG. 2B

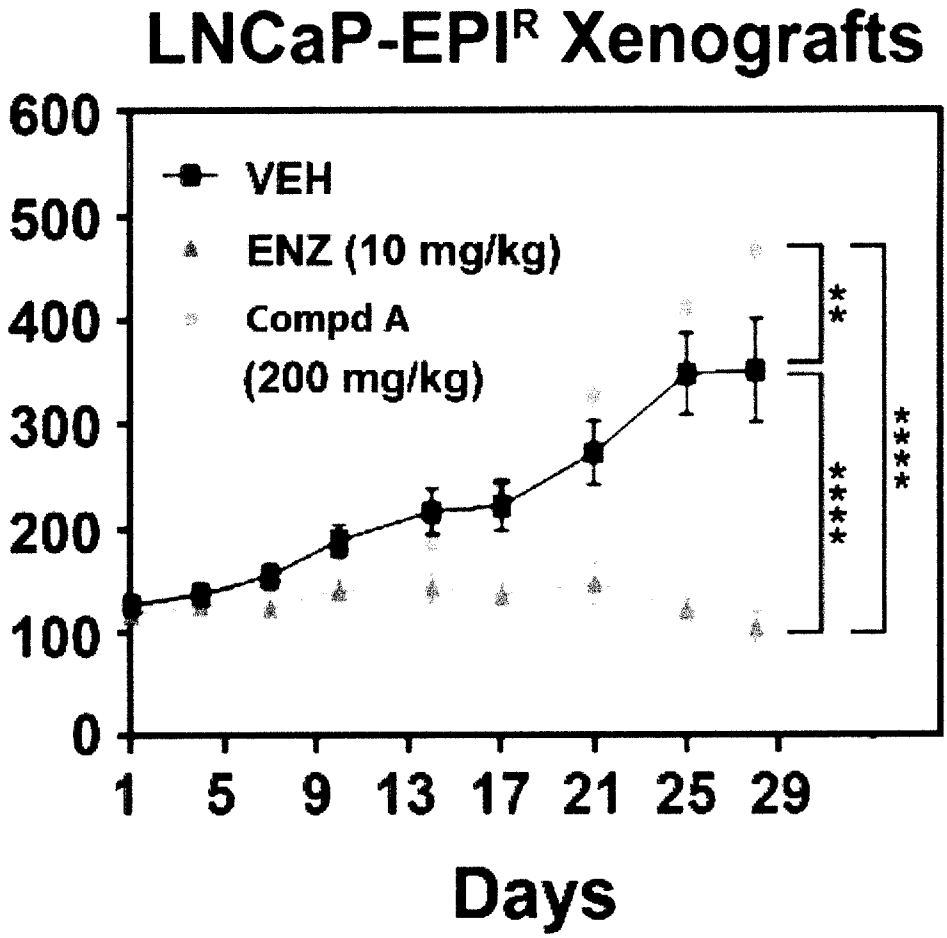

LNCaP-EPI^R Xenografts
600
500
400
300
200
100
0
VEH
ENZ (10 mg/kg)
Compd A
(200 mg/kg)
**
****
****
1
5
9
13
17
21
25
29
Days

FIG. 3A

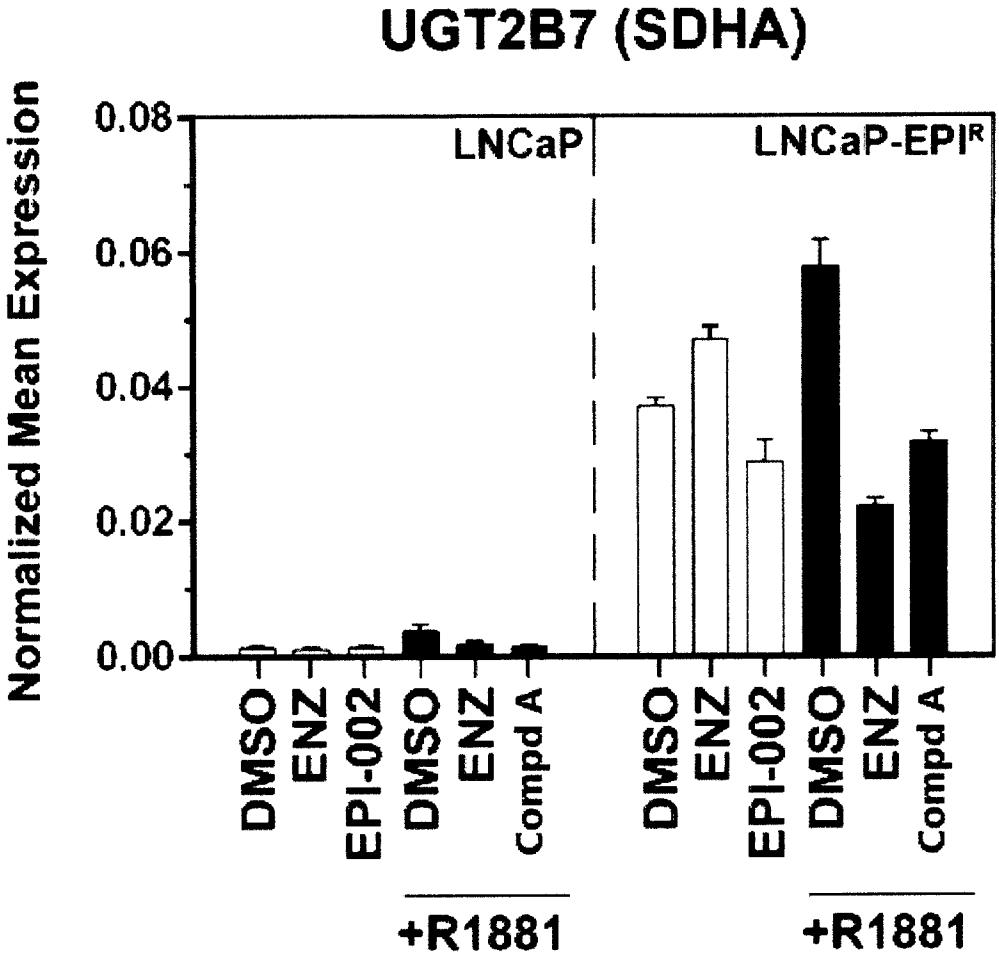

UGT2B7 (SDHA)
Normalized Mean Expression
0.08
0.06
0.04
0.02
0.00
LNCaP
LNCaP-EPI^R
DMSO
ENZ
EPI-002
DMSO
ENZ
Compd A
DMSO
ENZ
EPI-002
DMSO
ENZ
Compd A
+R1881
+R1881

FIG. 3B

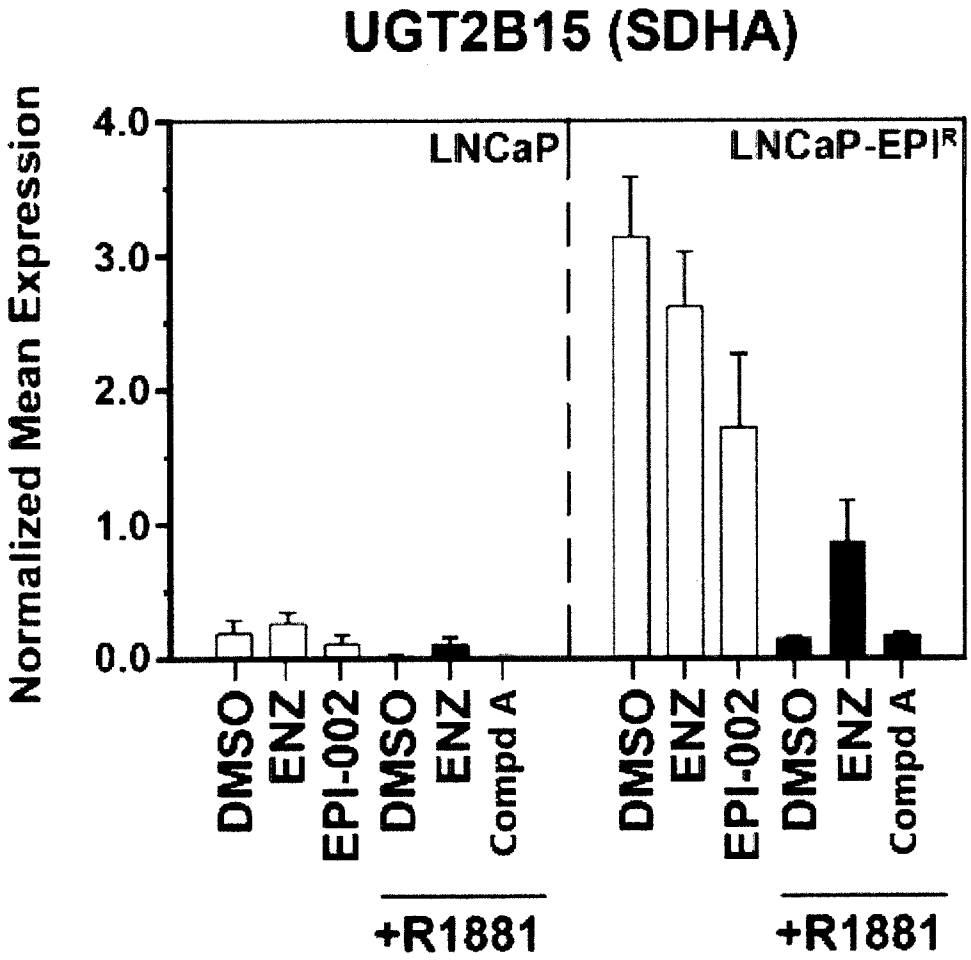

UGT2B15 (SDHA)
Normalized Mean Expression
4.0
3.0
2.0
1.0
0.0
LNCaP
LNCaP-EPI^R
DMSO
ENZ
EPI-002
DMSO
ENZ
Compd A
DMSO
ENZ
EPI-002
DMSO
ENZ
Compd A
+R1881
+R1881

FIG. 4A

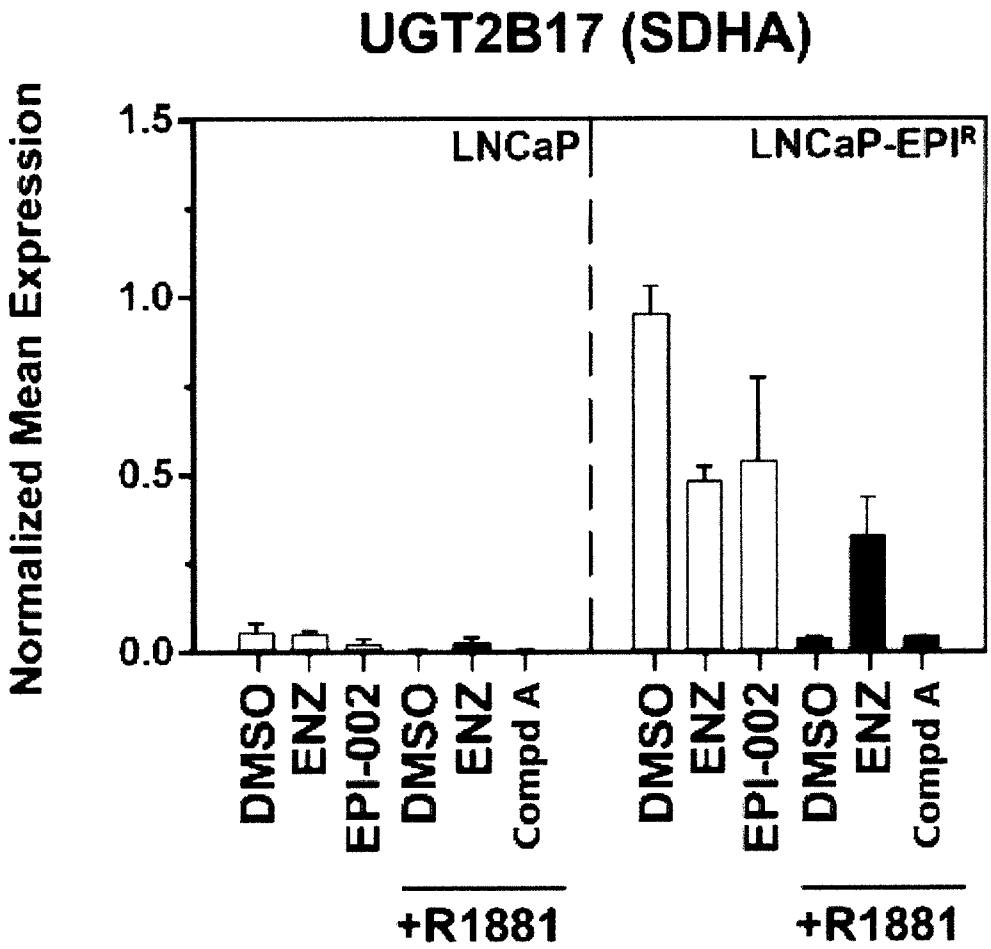

UGT2B17 (SDHA)
Normalized Mean Expression
1.5
1.0
0.5
0.0
LNCaP
LNCaP-EPI^R
DMSO
ENZ
EPI-002
DMSO
ENZ
Compd A
DMSO
ENZ
EPI-002
DMSO
ENZ
Compd A
+R1881
+R1881

FIG. 4B

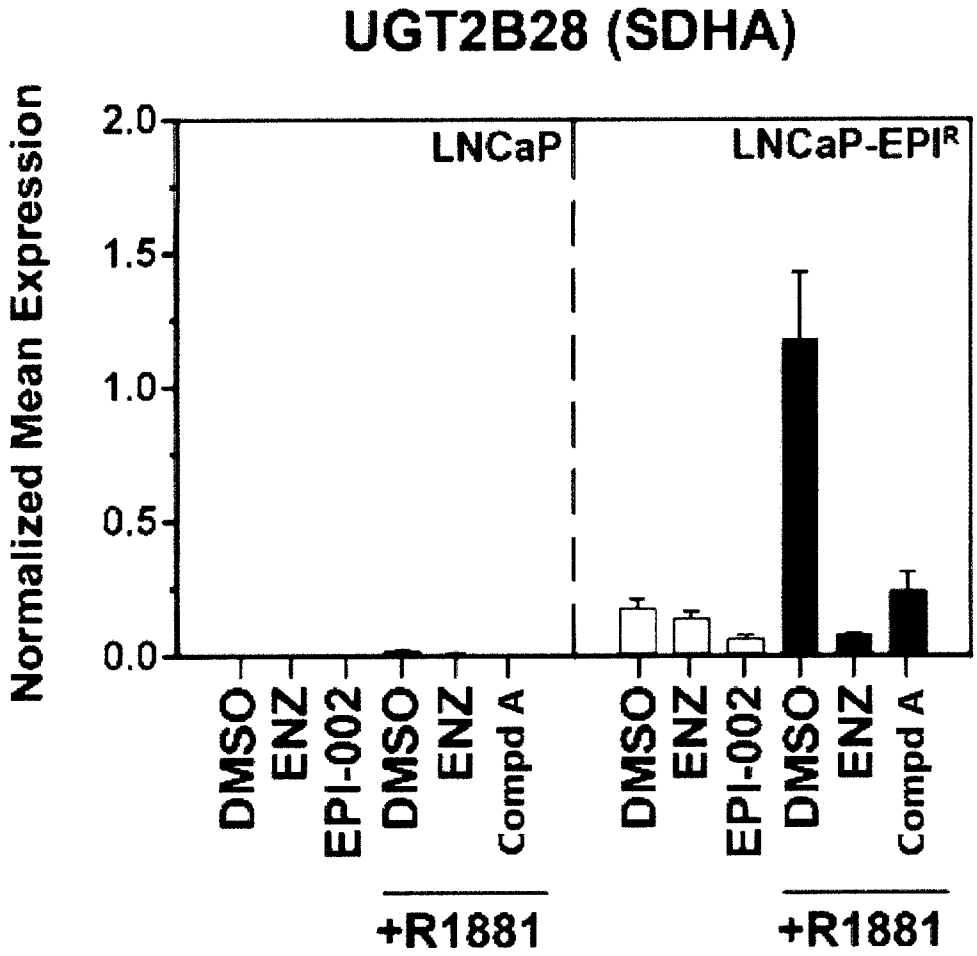

UGT2B28 (SDHA)
Normalized Mean Expression
2.0
1.5
1.0
0.5
0.0
LNCaP
LNCaP-EPI^R
DMSO
ENZ
EPI-002
DMSO
ENZ
Compd A
DMSO
ENZ
EPI-002
DMSO
ENZ
Compd A
+R1881
+R1881

FIG. 5

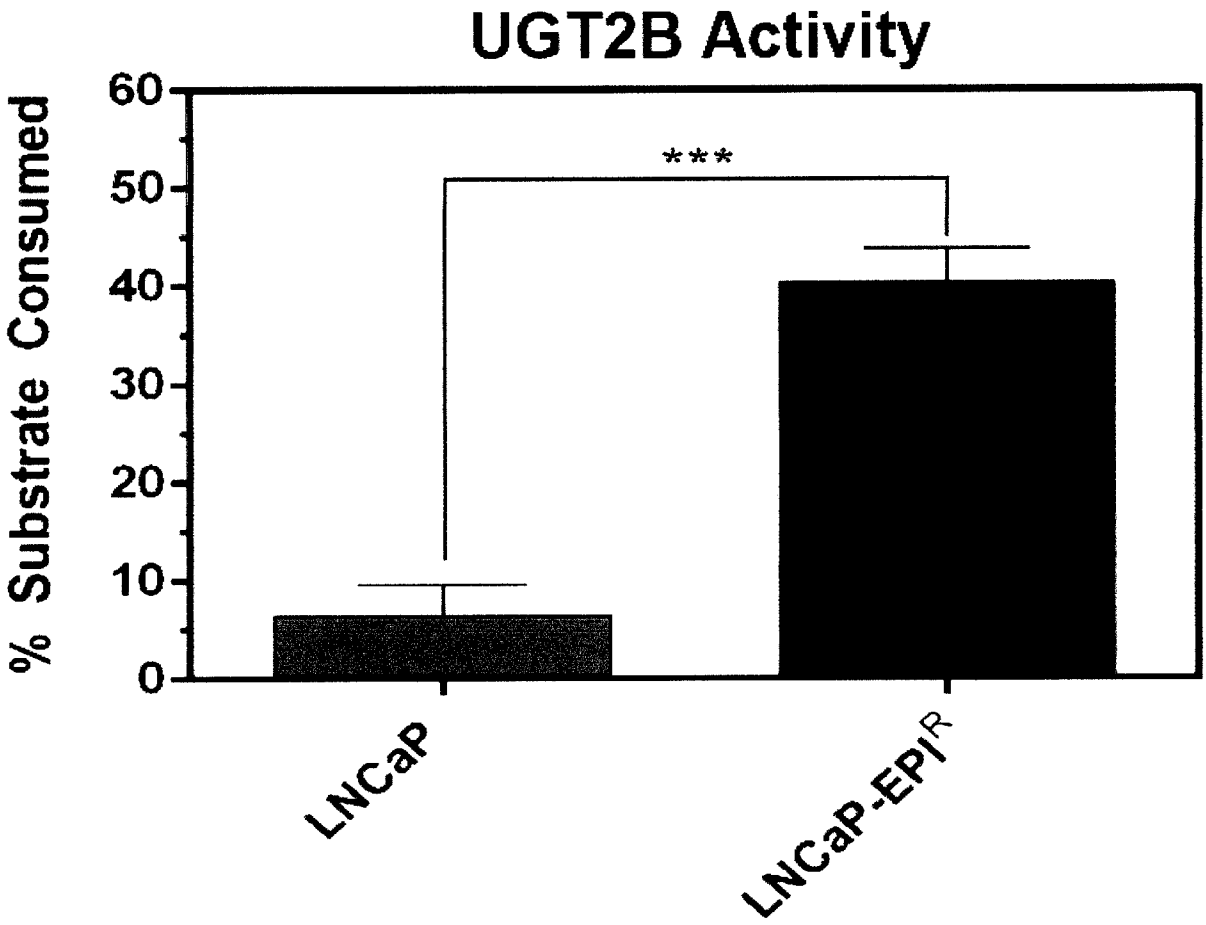
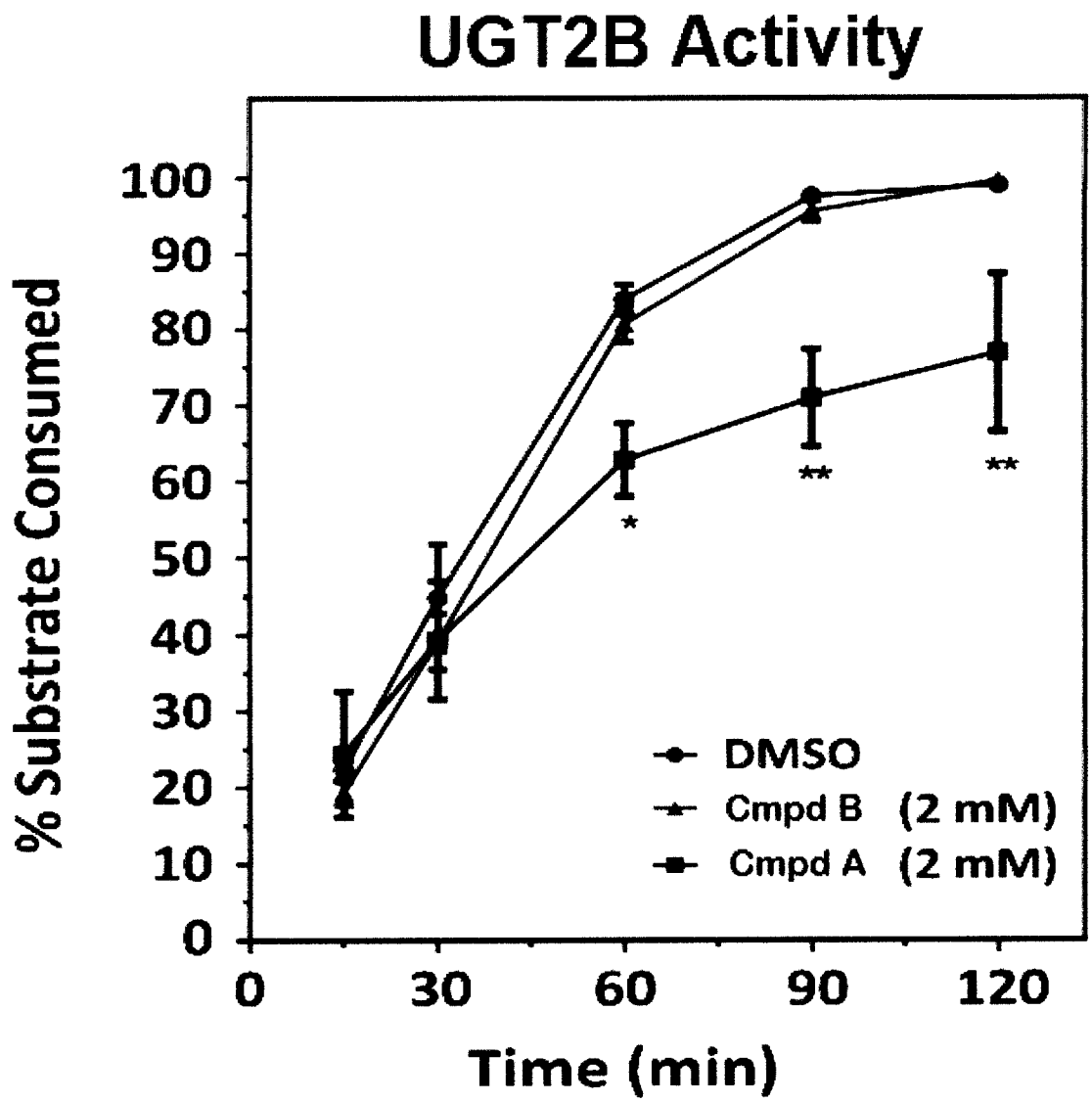

UGT2B Activity
% Substrate Consumed
60
50
40
30
20
10
0
***
LNCaP
LNCaP-EPI^R

FIG. 6


UGT2B Activity
% Substrate Consumed
100
90
80
70
60
50
40
30
20
10
0
0
30
60
90
120
Time (min)
DMSO
Cmpd B (2 mM)
Cmpd A (2 mM)
*
**
**

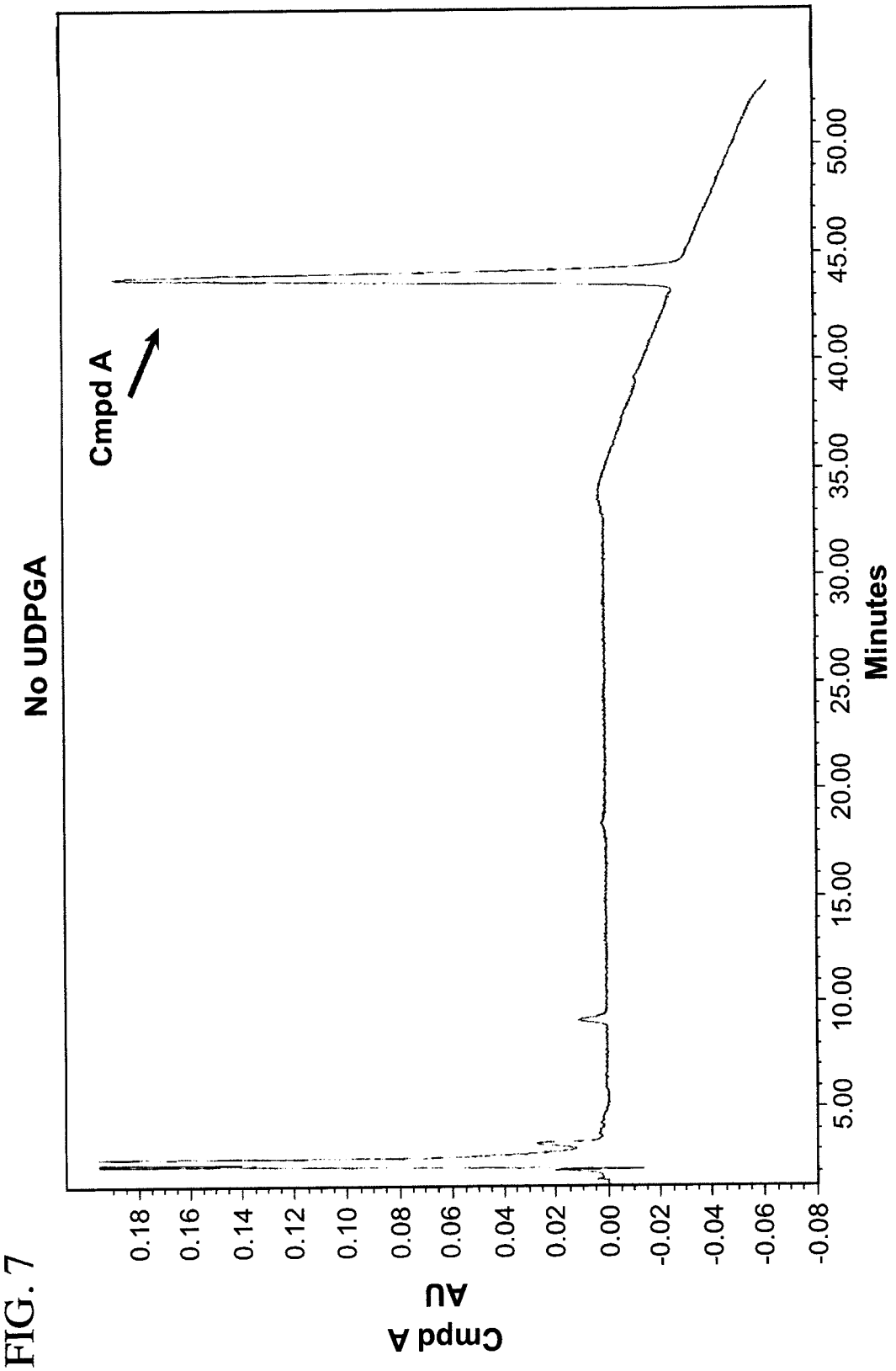

No UDPGA
Cmpd A
Cmpd A
AU
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
-0.06
-0.08
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
45.00
50.00
Minutes

FIG. 7

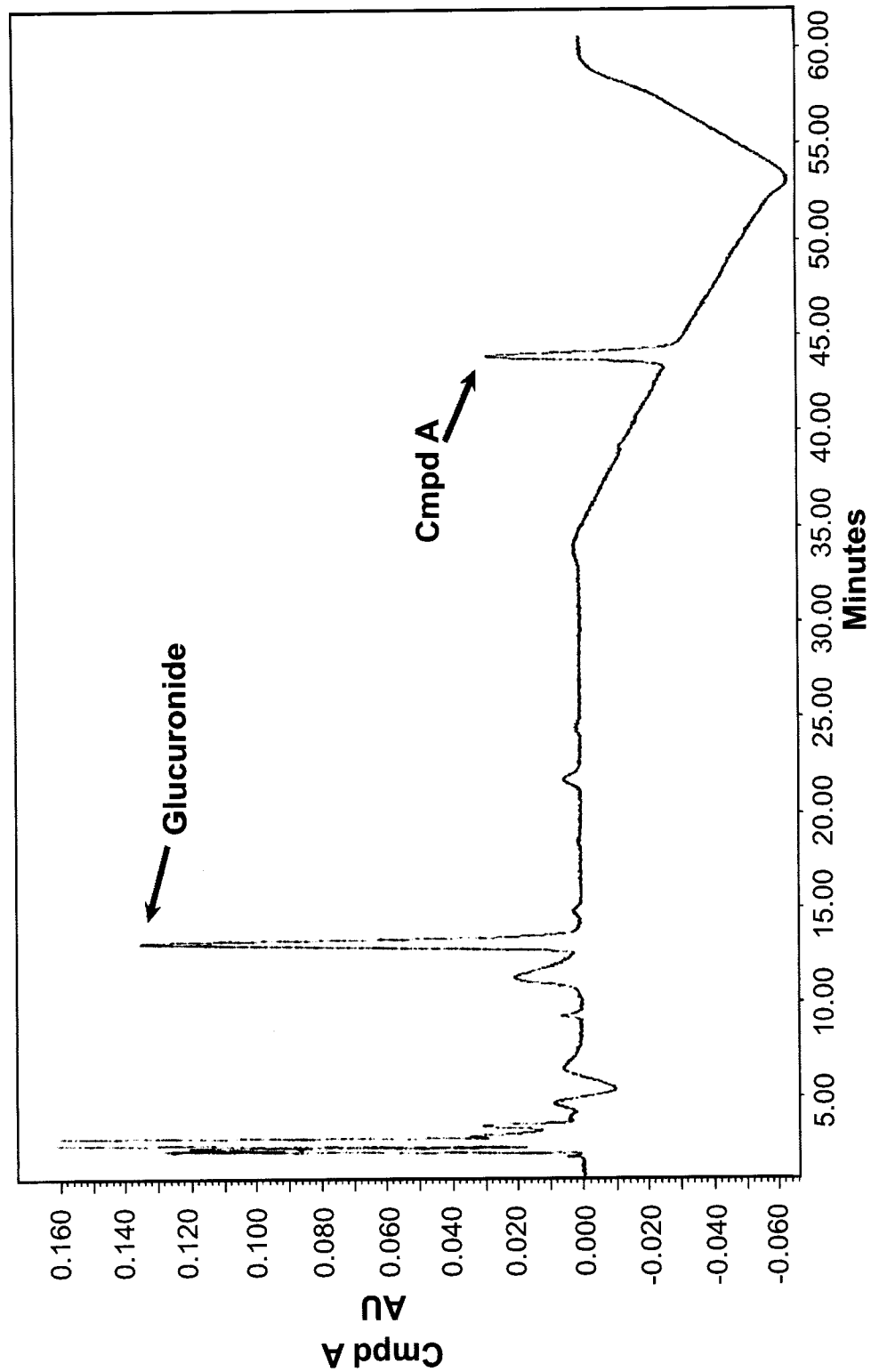

+ UDPGA
Glucuronide
Cmpd A
Cmpd A AU
0.160
0.140
0.120
0.100
0.080
0.060
0.040
0.020
0.000
-0.020
-0.040
-0.060
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
45.00
50.00
55.00
60.00
Minutes

FIG. 7 Cont.

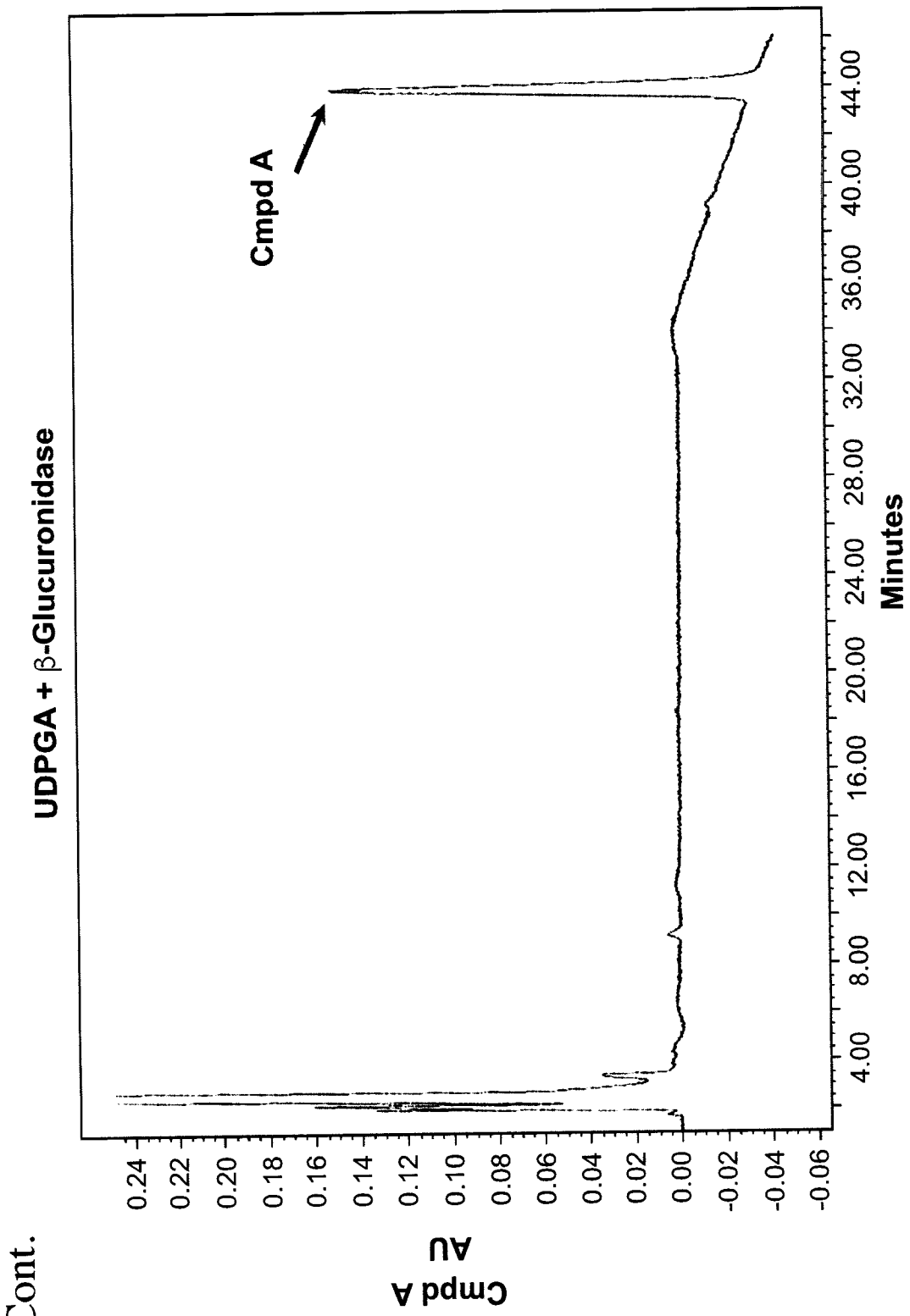

UDPGA + β-Glucuronidase
Cmpd A
Cmpd A
AU
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
-0.04
-0.06
4.00
8.00
12.00
16.00
20.00
24.00
28.00
32.00
36.00
40.00
44.00
Minutes

FIG. 7 Cont.

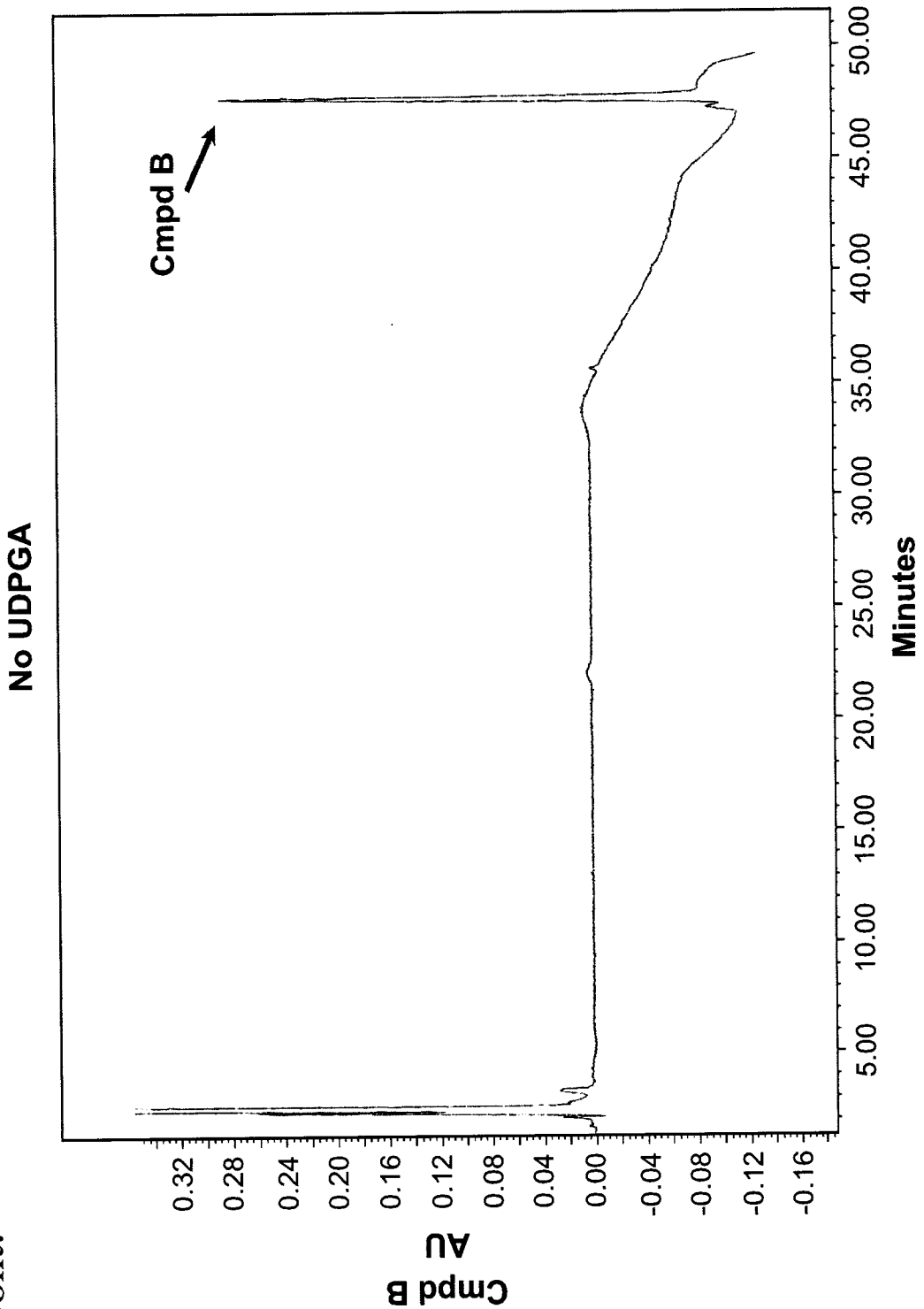

No UDPGA
Cmpd B
Cmpd B
AU
0.32
0.28
0.24
0.20
0.16
0.12
0.08
0.04
0.00
-0.04
-0.08
-0.12
-0.16
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
45.00
50.00
Minutes

FIG. 7 Cont.

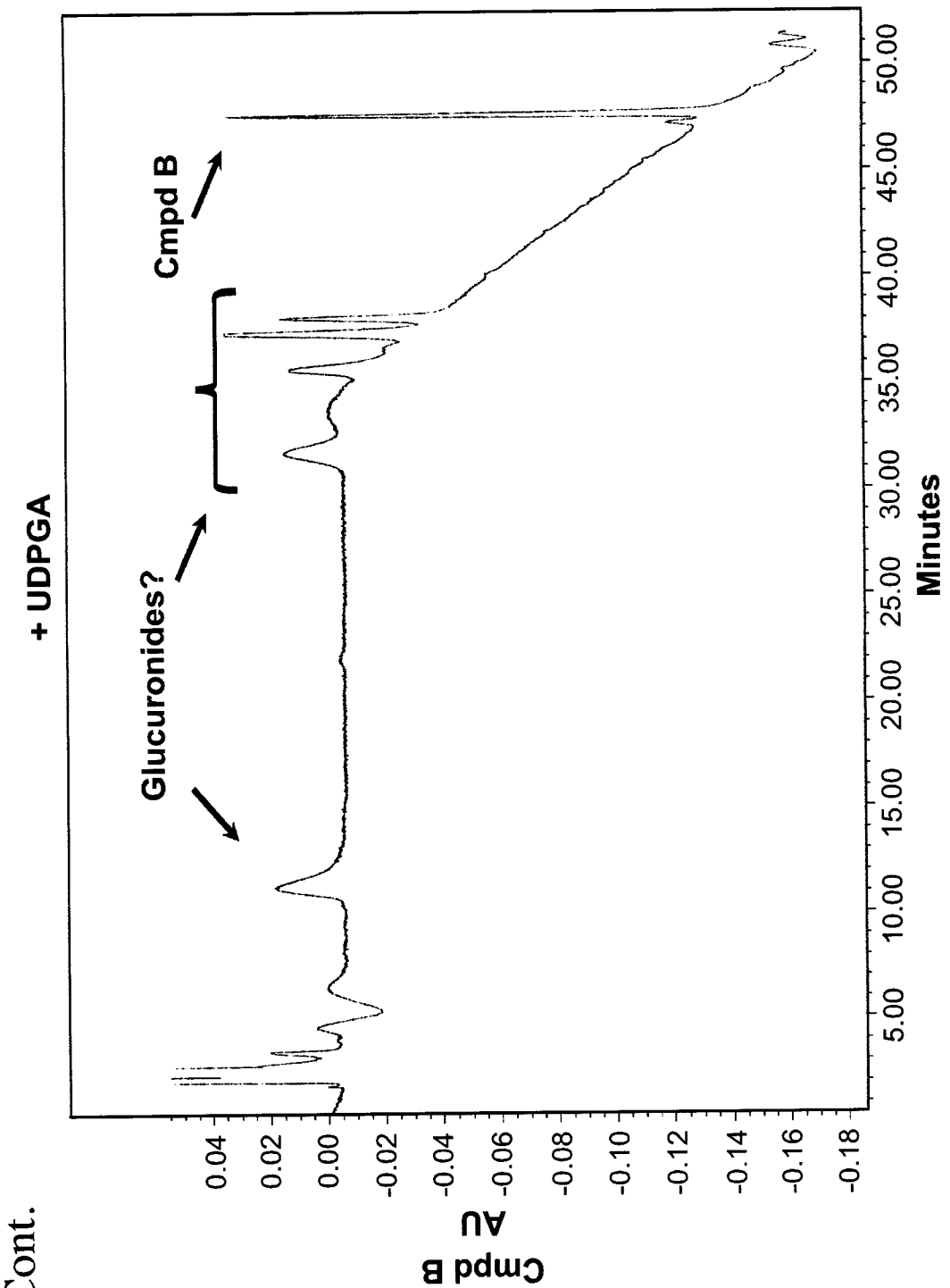

+ UDPGA
Glucuronides?
Cmpd B
Cmpd B AU
0.04
0.02
0.00
-0.02
-0.04
-0.06
-0.08
-0.10
-0.12
-0.14
-0.16
-0.18
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
45.00
50.00
Minutes

FIG. 7 Cont.

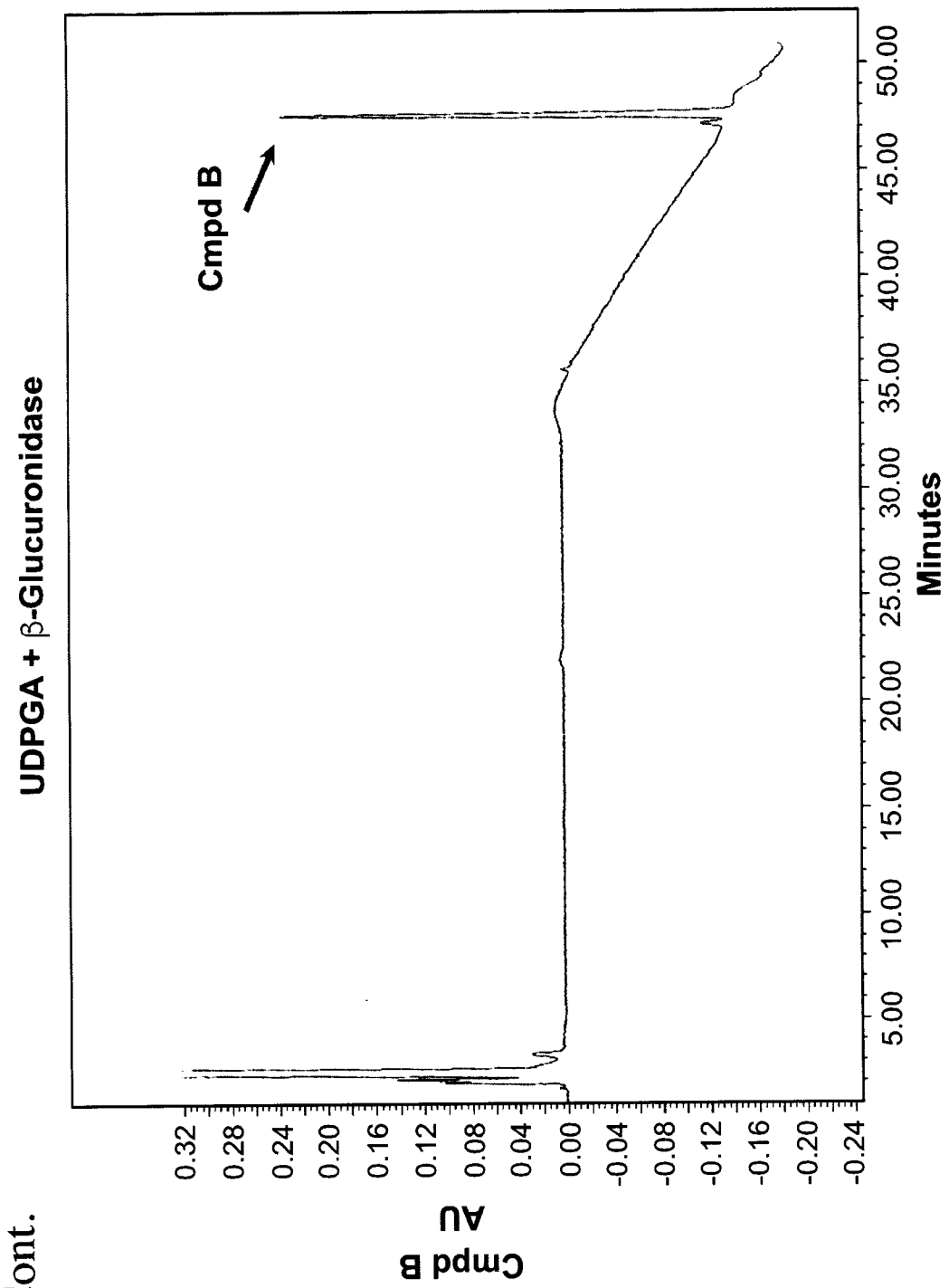

UDPGA + β-Glucuronidase
Cmpd B
Cmpd B
AU
0.32
0.28
0.24
0.20
0.16
0.12
0.08
0.04
0.00
-0.04
-0.08
-0.12
-0.16
-0.20
-0.24
5.00
10.00
15.00
20.00
25.00
30.00
35.00
40.00
45.00
50.00
Minutes

FIG. 7 Cont.

FIG. 8A

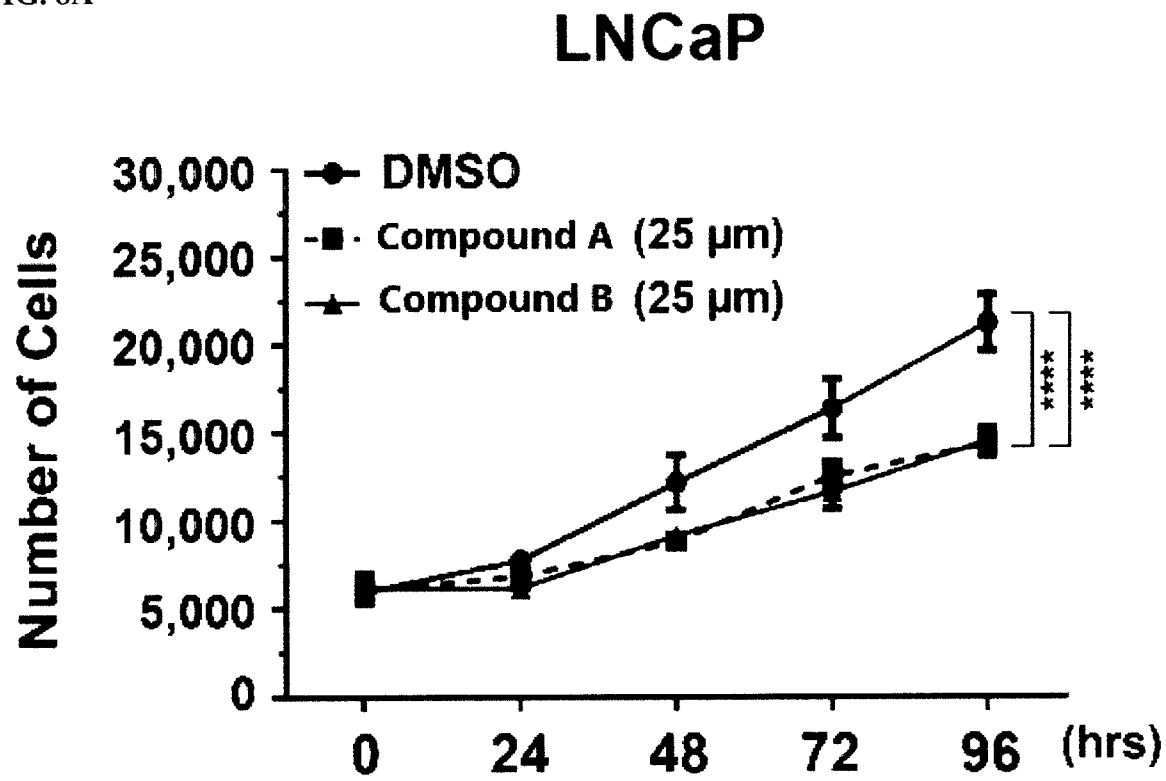

LNCaP
DMSO
Compound A (25 µm)
Compound B (25 µm)
Number of Cells
30,000
25,000
20,000
15,000
10,000
5,000
0
0
24
48
72
96
(hrs)
****
****

FIG. 8B

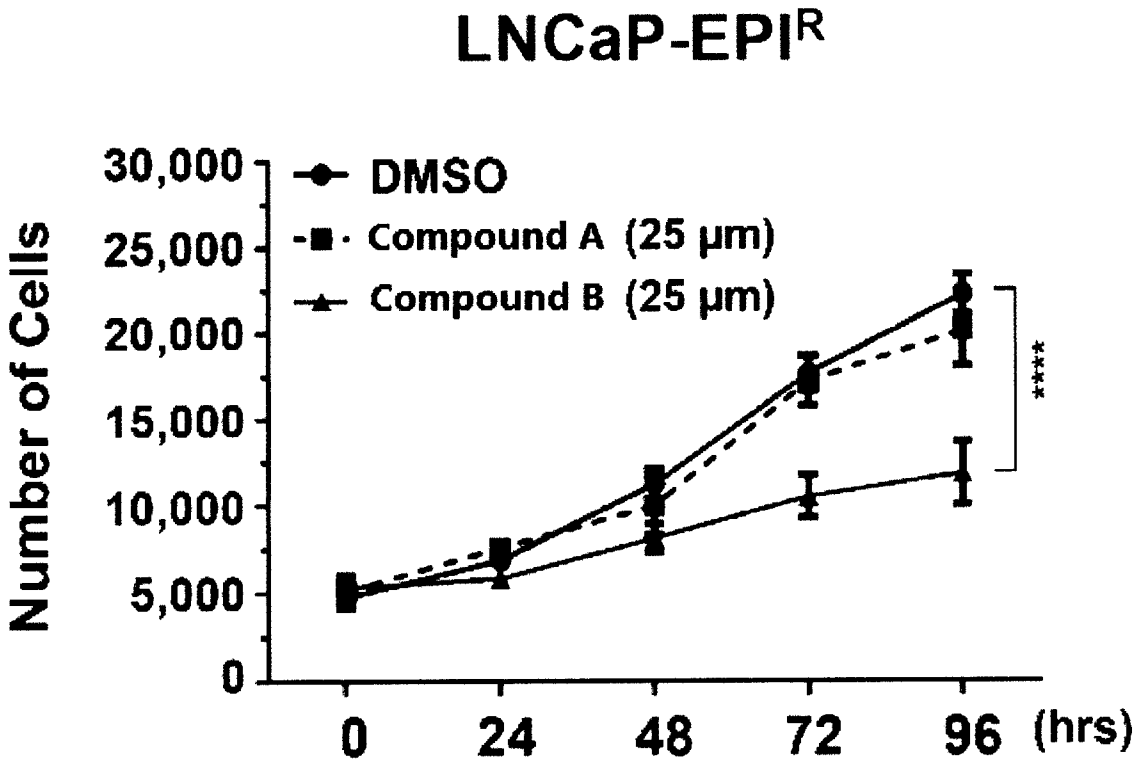

LNCaP-EPI^R
DMSO
Compound A (25 µm)
Compound B (25 µm)
Number of Cells
30,000
25,000
20,000
15,000
10,000
5,000
0
0
24
48
72
96
(hrs)
****

FIG. 9A

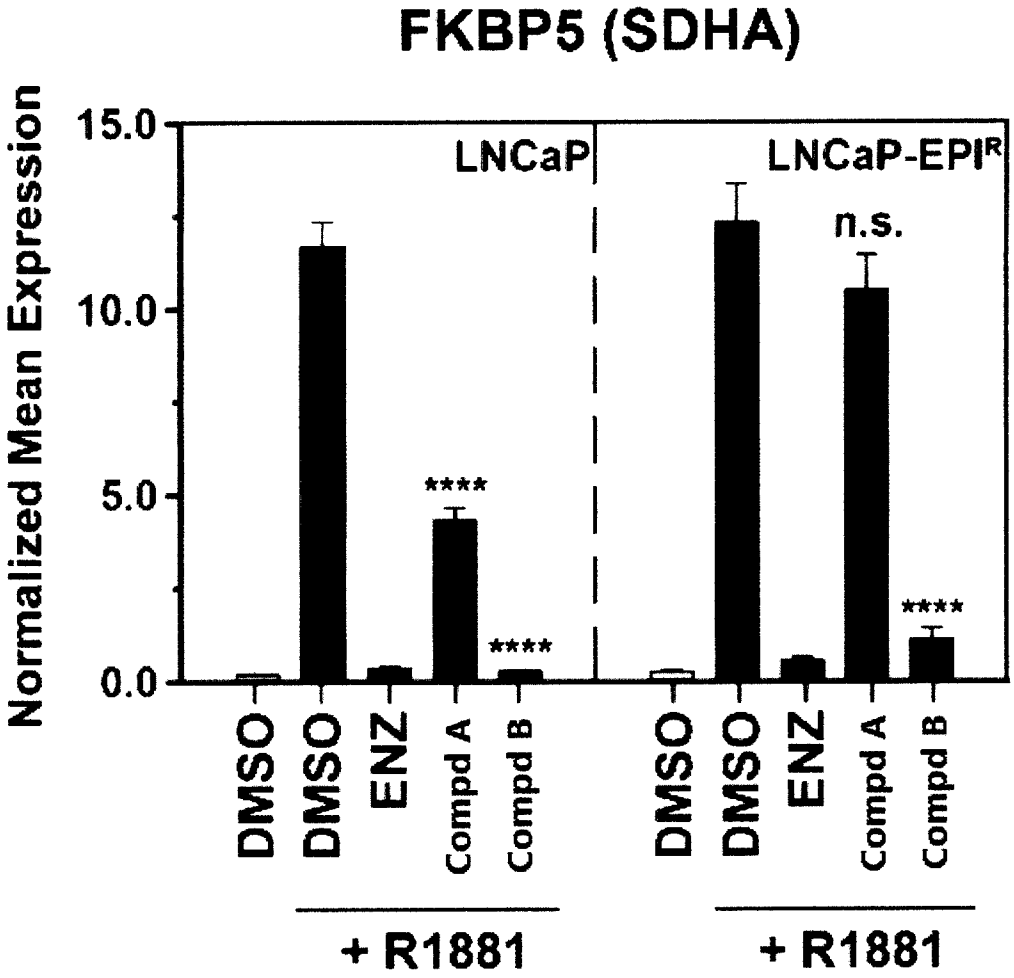

FKBP5 (SDHA)
Normalized Mean Expression
15.0
10.0
5.0
0.0
LNCaP
LNCaP-EPI^R
n.s.
****
****
****
DMSO
DMSO
ENZ
Compd A
Compd B
DMSO
DMSO
ENZ
Compd A
Compd B
+ R1881
+ R1881

FIG. 9B

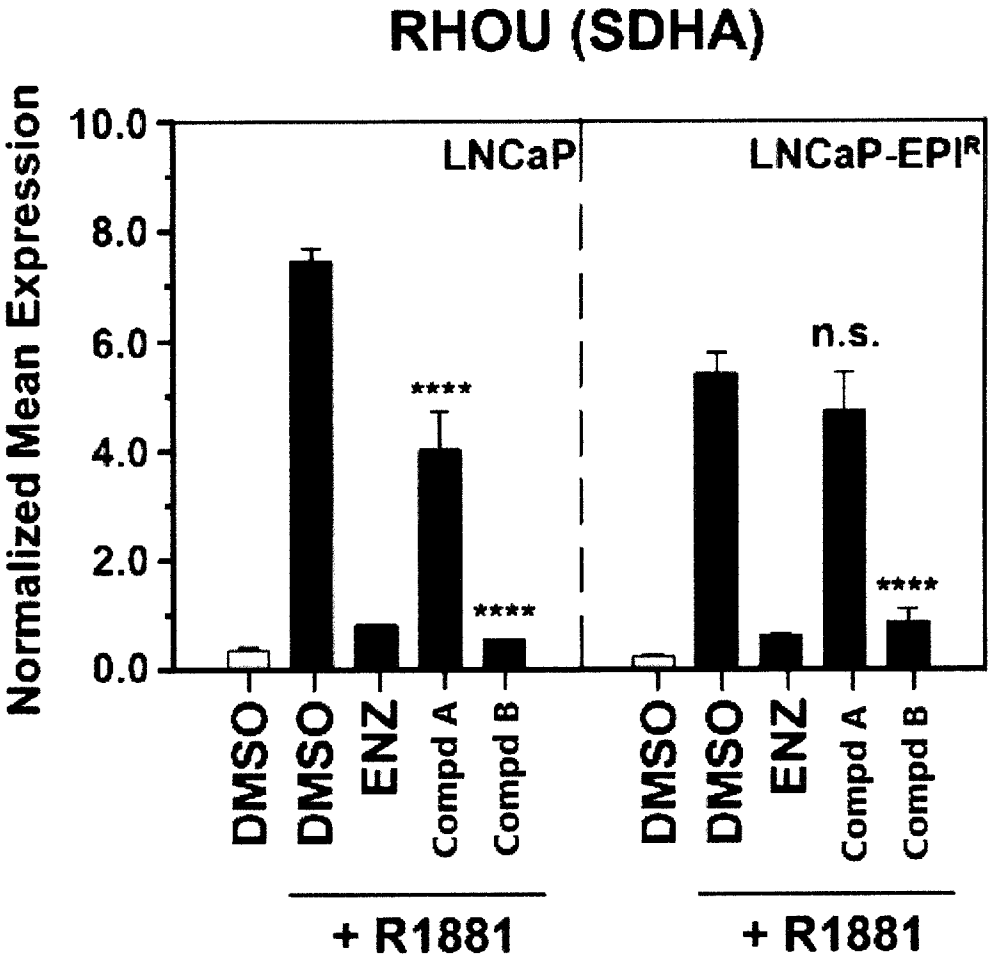

RHOU (SDHA)
Normalized Mean Expression
10.0
8.0
6.0
4.0
2.0
0.0
LNCaP
LNCaP-EPI^R
****
****
n.s.
****
DMSO
DMSO
ENZ
Compd A
Compd B
DMSO
DMSO
ENZ
Compd A
Compd B
+ R1881
+ R1881

FIG. 9C

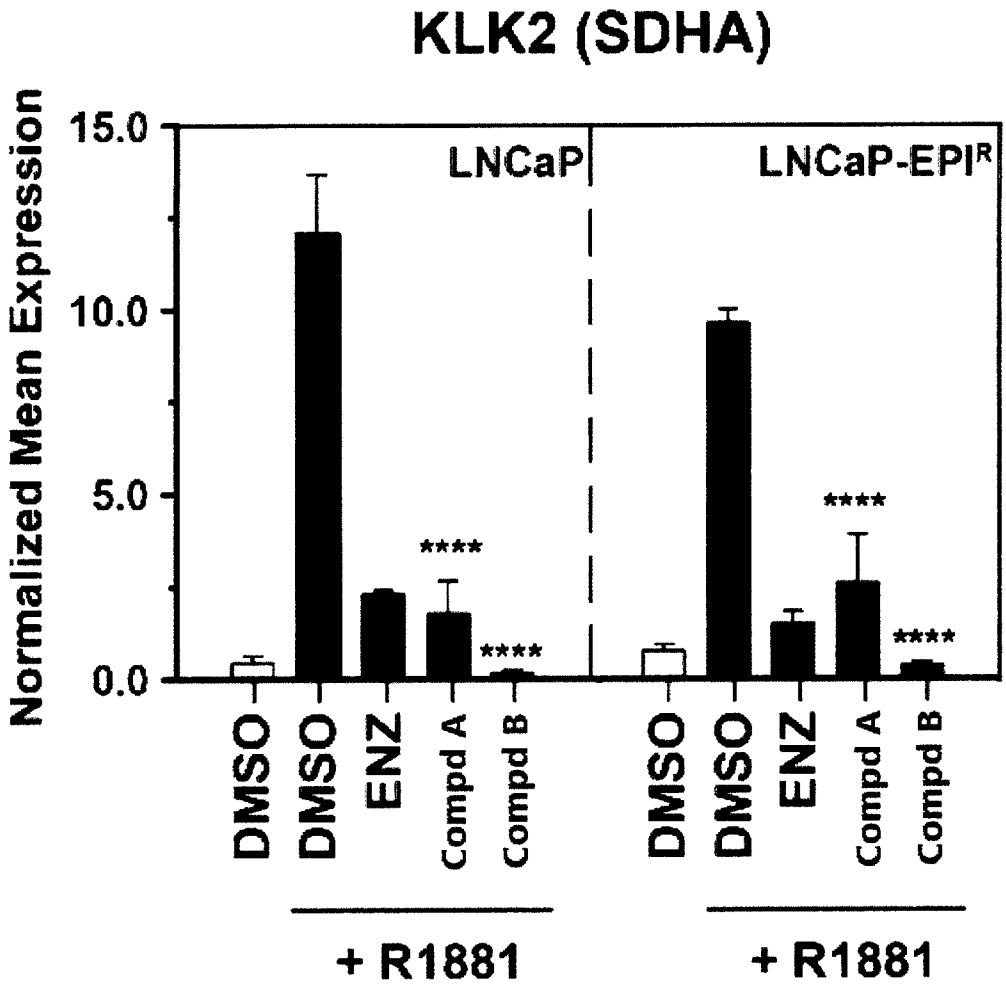

KLK2 (SDHA)
Normalized Mean Expression
15.0
10.0
5.0
0.0
LNCaP
LNCaP-EPI^R
****
****
****
****
DMSO
DMSO
ENZ
Compd A
Compd B
DMSO
DMSO
ENZ
Compd A
Compd B
+ R1881
+ R1881

FIG. 9D

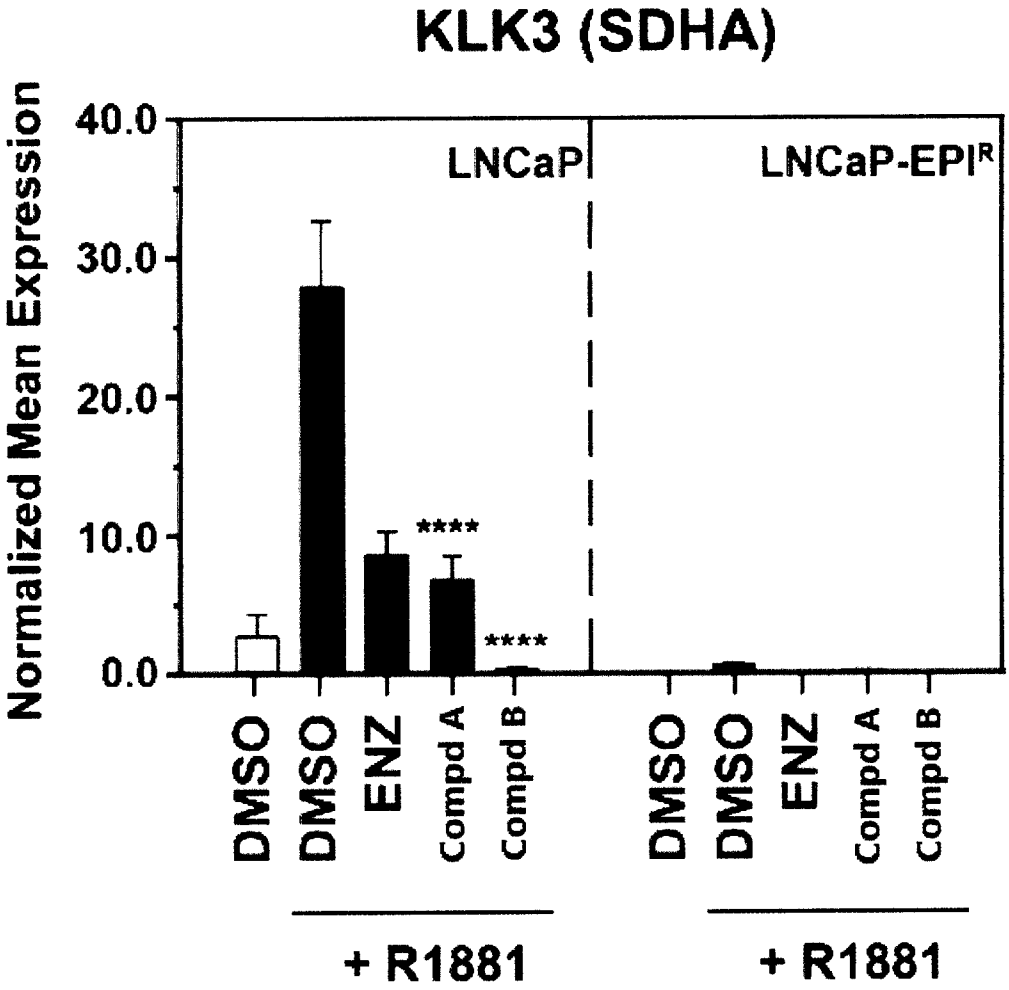

KLK3 (SDHA)
Normalized Mean Expression
40.0
30.0
20.0
10.0
0.0
LNCaP
LNCaP-EPI^R
****
****
DMSO
DMSO
ENZ
Compd A
Compd B
DMSO
DMSO
ENZ
Compd A
Compd B
+ R1881
+ R1881

FIG. 10A

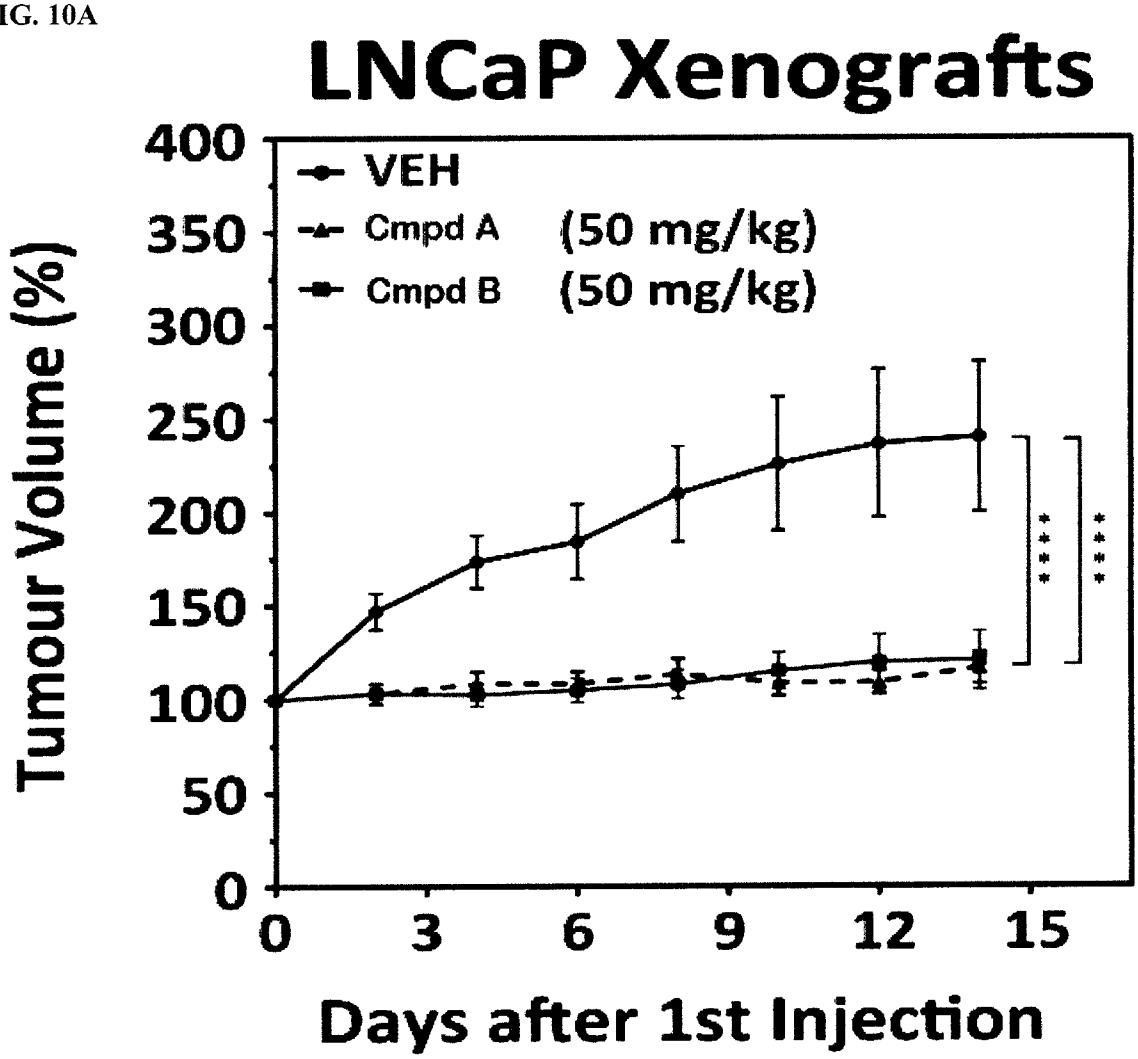

LNCaP Xenografts
Tumour Volume (%)
400
350
300
250
200
150
100
50
0
VEH
Cmpd A (50 mg/kg)
Cmpd B (50 mg/kg)
****
****
0
3
6
9
12
15
Days after 1st Injection

FIG. 10B

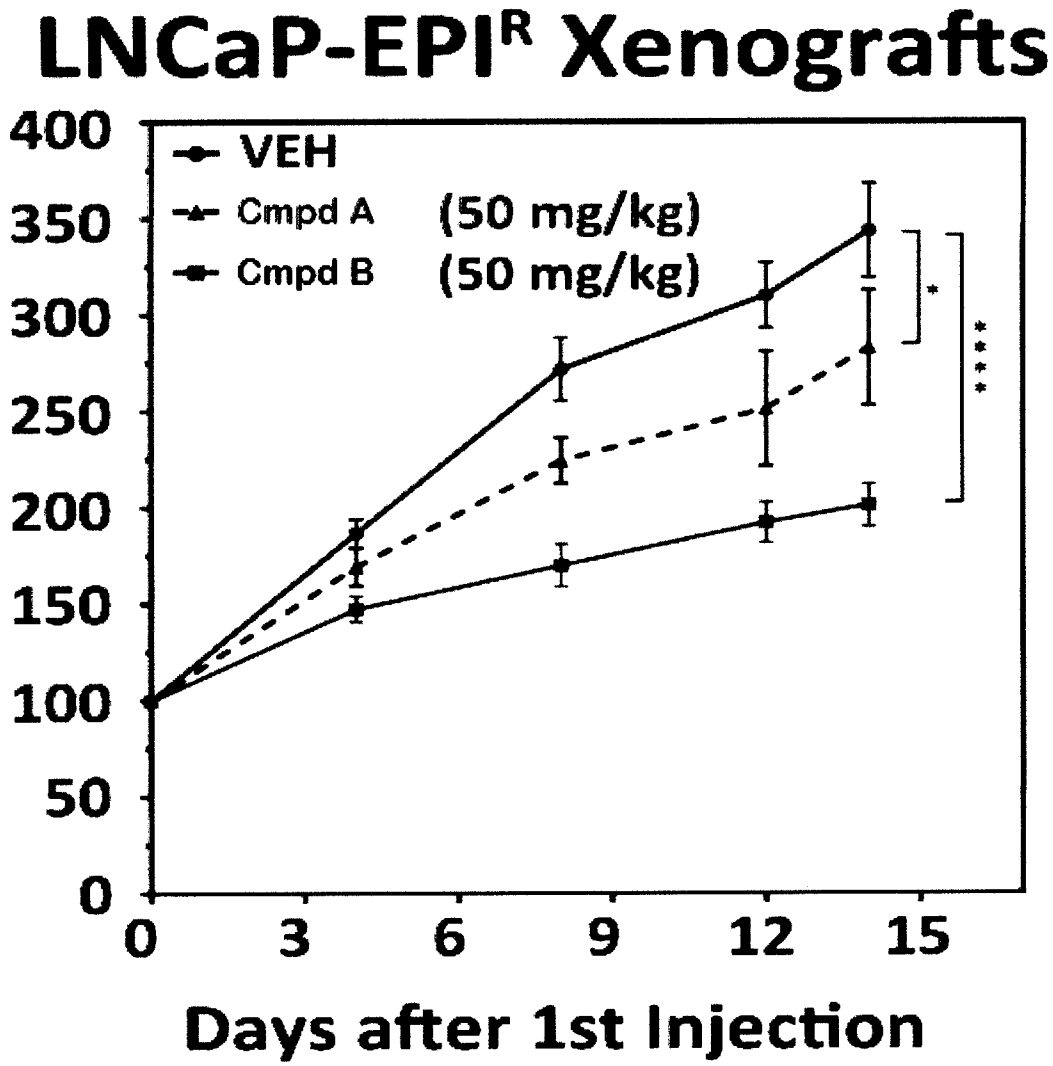
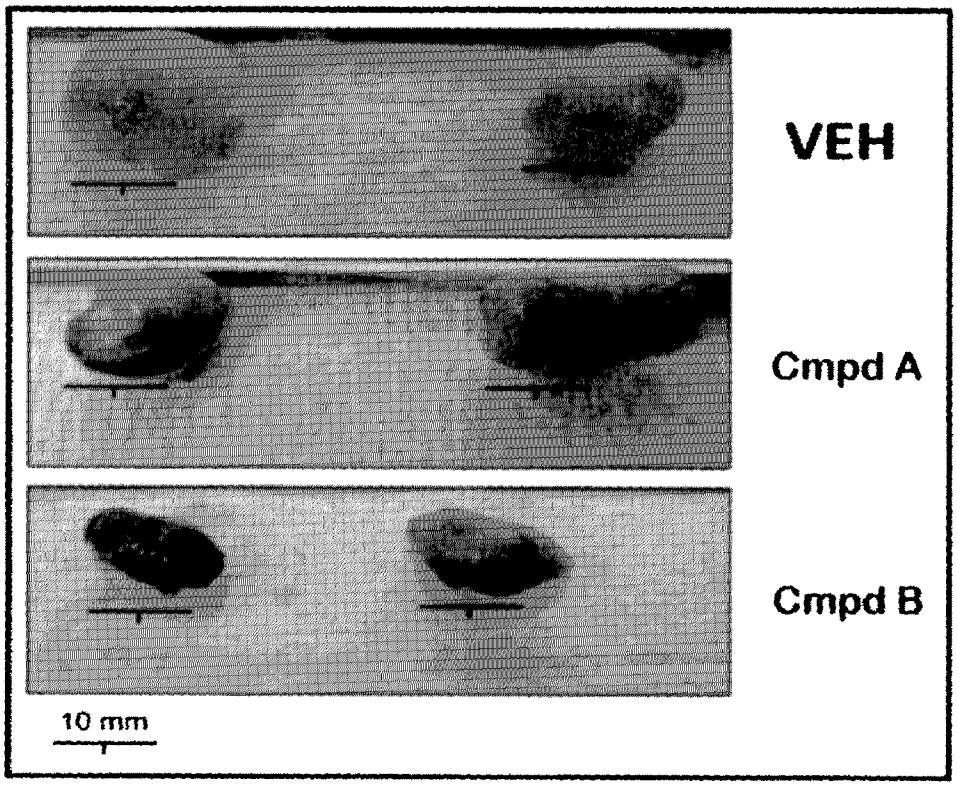

LNCaP-EPI^R Xenografts
VEH
Cmpd A (50 mg/kg)
Cmpd B (50 mg/kg)
400
350
300
250
200
150
100
50
0
0
3
6
9
12
15
Days after 1st Injection
*
****

FIG. 10C



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2017/000201

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***A61K 31/09*** (2006.01) , ***A61P 35/00*** (2006.01) , ***C07C 43/23*** (2006.01)

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)
IPC: ***A61K 31/09*** (2006.01) , ***A61P 35/00*** (2006.01) , ***C07C 43/23*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Questel-Orbit, Canadian Patent Databse (Intellect)
Keywords: bisphenol, bis-phenol, cancer, AR NTD, androgen receptor N-terminal domain

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2012/139039 A2 (ANDERSEN, R. J., et al.) – 11 October 2012 (11.10.2012) See compounds 30, 34-38 (Table 2), chlorinated derivatives on page 36 (last line) and on page 37 (2^{nd} compound on row 3).	1-45 1-45
X	WO 2014/179867 A1 (MAWJI, N. R., et al) – 13 November 2014 (13.11.2014) See compounds of claim 28 on page 86, Examples 15, 16, 19-21, compound B on page 69, compounds (7c) and (13b) on page 70, compound (3c) on page 71	
P, X	US 2017/0298033 Al (ANDERSEN, R., et al.) – 19 October 2017 (19.10.2017) Abstract and claims	1-45

☐ Further documents are listed in the continuation of Box C.

☑ See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"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		

Date of the actual completion of the international search 17 November 2017 (17-11-2017)	Date of mailing of the international search report 08 December 2017 (08-12-2017)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Cristina Belyea (819) 639-6987

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2017/000201

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2012139039A2	11 October 2012 (11-10-2012)	WO2012139039A2	11 October 2012 (11-10-2012)
		WO2012139039A3	25 April 2013 (25-04-2013)
		EP2693875A2	12 February 2014 (12-02-2014)
		EP2693875A4	22 October 2014 (22-10-2014)
		US2014248263A1	04 September 2014 (04-09-2014)
WO2014179867A1	13 November 2014 (13-11-2014)	WO2014179867A1	13 November 2014 (13-11-2014)
		AU2014262333A1	19 November 2015 (19-11-2015)
		AU2014262333B2	16 June 2016 (16-06-2016)
		AU2016228233A1	06 October 2016 (06-10-2016)
		CA2911352A1	13 November 2014 (13-11-2014)
		CL2015003271A1	22 April 2016 (22-04-2016)
		CN105358522A	24 February 2016 (24-02-2016)
		EP2994451A1	16 March 2016 (16-03-2016)
		EP2994451A4	05 October 2016 (05-10-2016)
		HK1221712A1	09 June 2017 (09-06-2017)
		JP2016518394A	23 June 2016 (23-06-2016)
		JP6100439B2	22 March 2017 (22-03-2017)
		JP2017125036A	20 July 2017 (20-07-2017)
		KR20160013072A	03 February 2016 (03-02-2016)
		KR101739800B1	25 May 2017 (25-05-2017)
		KR20170060162A	31 May 2017 (31-05-2017)
		MX2015015509A	12 August 2016 (12-08-2016)
		MX347705B	09 May 2017 (09-05-2017)
		PE00912016A1	03 March 2016 (03-03-2016)
		PH12015502525A1	28 March 2016 (28-03-2016)
		SG10201607177XA	28 October 2016 (28-10-2016)
		SG11201509038UA	30 December 2015 (30-12-2015)
		US2014335080A1	13 November 2014 (13-11-2014)
		US9173939B2	03 November 2015 (03-11-2015)
		US2016068466A1	10 March 2016 (10-03-2016)
US2017298033A1	19 October 2017 (19-10-2017)	US2017298033A1	19 October 2017 (19-10-2017)
		WO2017177307A1	19 October 2017 (19-10-2017)