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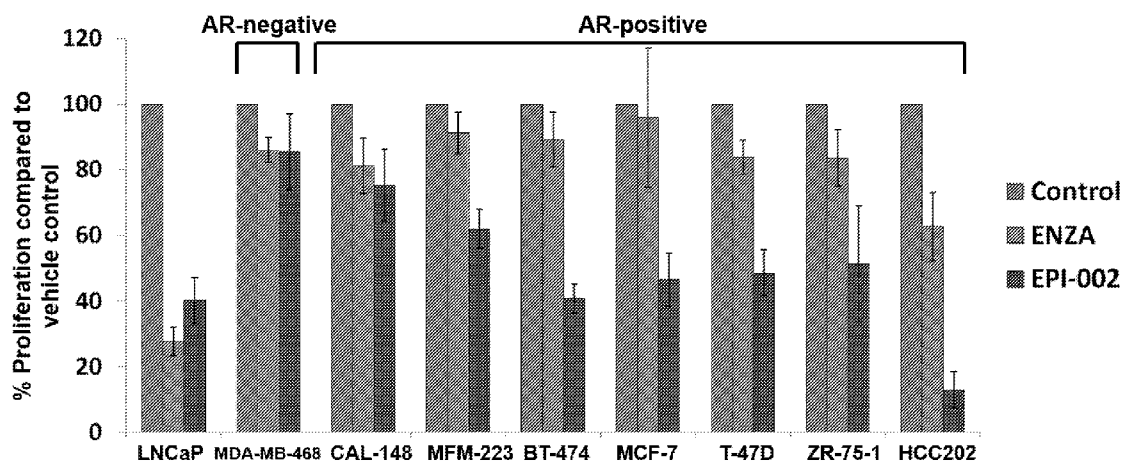
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(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

(54) **Title:** PHARMACEUTICAL COMPOSITIONS AND COMBINATIONS COMPRISING INHIBITORS OF THE ANDROGEN RECEPTOR AND USES THEREOF

FIG. 1



(57) **Abstract:** The present disclosure generally relates to pharmaceutical compositions and combinations comprising an androgen receptor N-terminal domain inhibitor or an inhibitor and a second therapeutically active agent, such as an CDK4/6 inhibitor, a Pin1 inhibitor (inhibitor of peptidyl-prolyl cis/trans isomerases), or an antiandrogen. In particular, the present disclosure relates to pharmaceutical compositions and combinations useful for treatment of various cancers, for example breast cancer and prostate cancer. Further, the present disclosure relates administering an androgen receptor N-terminal domain inhibitor in combination with radiation therapy for treatment of various cancers.



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PHARMACEUTICAL COMPOSITIONS AND COMBINATIONS COMPRISING INHIBITORS OF THE ANDROGEN RECEPTOR AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[1] This application claims priority to U.S. Provisional Application No. 62/825,440, filed March 28, 2019, U.S. Provisional Application No. 62/825,450, filed March 28, 2019, U.S. Provisional Application No. 62/842,980, filed May 3, 2019, and U.S. Provisional Application No. 62/857,519, filed June 5, 2019, the disclosures of which are hereby incorporated by reference in their entireties for all purposes.

STATEMENT REGARDING SEQUENCE LISTING

[2] The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is ESSA_042_01WO_SeqList_ST25.txt. The text file is ~2.4 KB, and was created on March 27, 2020, and is being submitted electronically.

FIELD OF THE INVENTION

[3] The present disclosure generally relates to pharmaceutical compositions and combinations comprising an androgen receptor N-terminal domain inhibitor or an inhibitor and an additional therapeutic agent, such as a cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor, a Pin1 inhibitor (inhibitor of peptidyl-prolyl cis/trans isomerases), or an antiandrogen. In particular, the present disclosure relates to pharmaceutical compositions and combinations useful for treatment of various cancers, for example breast cancer and prostate cancer. Further, the present disclosure relates to administration of an androgen receptor N-terminal domain inhibitor in combination with radiation therapy for treating various cancers.

BACKGROUND OF THE INVENTION

[4] 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. Essenhight, *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, also known as androgen ablation therapy (ABT) or androgen deprivation therapy (ADT).

[5] Androgen receptor (AR) is a transcription factor that plays dual roles in breast cancer cells: promoting or inhibiting proliferation depending on expression and activity of estrogen receptor-alpha. Expression of AR is detected in up to 90% of all breast cancers.

[6] 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.

[7] 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.

[8] 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).

[9] 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.

[10] Other relevant AR antagonists 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).

[11] 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).

[12] 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, potentially through interaction with NTD domain, 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; WO 2016/112455; WO 2016/141458; WO 2017/177307;

WO 2017/210771; and WO 2018/045450, and which are hereby incorporated by reference in their entireties.

[13] 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).

[14] The intrinsically disordered AR NTD is essential for its transcriptional activity. It harbors six putative binding sites for Pin1, a proline isomerase that regulates protein conformation at specific phosphorylated-Ser/Thr-Pro motifs. All-trans retinoic acid (ATRA) is a validated and potent Pin1 inhibitor. Since conformational changes within the AR NTD are required for transactivation, perturbation of its structure may be a promising approach to block its activity.

[15] While significant advances have been made in this field, there remains a need for improved treatment for AR-mediated disorders including breast cancer and prostate cancer. Currently there is no FDA-approved targeted therapy for triple-negative breast cancer (TNBC). AR plays a role in the proliferation of breast cancer cells by either promoting proliferation or inhibiting proliferation depending on the expression of estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2). AR expression is detected in up to 90% of all

breast cancers and in up to approximately 35% of TNBC. AR-Vs have been detected in primary breast cancer specimens and in breast cancer cell lines. AR-V7 expression was detected in circulating-tumor cells of patients with metastatic breast cancer and was associated with bone metastases. Targeting AR is a potential therapeutic strategy for AR-positive TNBC.

[16] Cyclin-dependent kinases 4 and 6 (CDK4/6) are activated by cyclin D1 to phosphorylate Rb and are critical in the transition from G1 to S phase in cell cycle. Luminal AR subtype of triple negative breast cancer is particularly sensitive to CDK4/6 inhibitors and this sensitivity is associated with AR expression. Thus, androgen receptor N-terminal domain inhibitors in combination with CDK4/6 inhibitors can be a way to target treatment of AR-mediated diseases and conditions.

[17] In addition, targeting Pin1 activity with an Pin1 inhibitor that may disrupt the AR NTD could enhance inhibition the AR NTD by androgen receptor modulators which bind to Tau-5 in the NTD.

[18] In addition, a combination approach using AR modulating therapeutics with radiation could provide a promising option for the treatment of metastatic castration resistant prostate cancer (mCRPC) as targeted radiotherapy with radium 223 dichloride for mCRPC has been shown to increase overall survival (OS) of patients with bone metastases by approximately 3 months. All currently approved AR modulating drugs, such as enzalutamide and abiraterone, either directly or indirectly target the AR C-terminus ligand-binding domain (LBD). Such drugs are often unsuccessful due to the emergence of AR splice variants (ARV-7, ARv567es) that are constitutively active and lack a LBD. The presently disclosed method explores the use of androgen receptor N-terminal domain inhibitors that can bind to full-length AR and/or truncated AR splice variants in combination with radiation therapy.

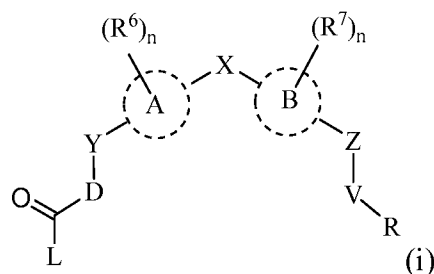
SUMMARY OF THE INVENTION

[19] The present disclosure relates to pharmaceutical compositions and combinations comprising an androgen receptor N-terminal domain inhibitor and a second therapeutically active agent. In one embodiment, the pharmaceutical composition comprises a CDK4/6 inhibitor and an androgen receptor N-terminal domain inhibitor. In one embodiment, the pharmaceutical composition comprises an androgen receptor N-terminal domain inhibitor and an androgen receptor ligand-binding domain inhibitor. In one embodiment, the pharmaceutical composition comprises an androgen receptor N-terminal domain inhibitor and a Pin1 inhibitor. In one embodiment, the pharmaceutical composition comprises an androgen receptor N-terminal domain inhibitor and a Pin1 inhibitor, wherein the androgen receptor N-

terminal domain inhibitor is not 3-(4-(2-(4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol, 3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate, or stereoisomers thereof.

[20] The present disclosure also relates to a method of treating cancer comprising administering an androgen receptor N-terminal domain inhibitor and a radiation therapy. In one embodiment, the radiation therapy is ionizing radiation therapy.

[21] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the androgen receptor N-terminal domain inhibitor has the structure of formula (i):



[22] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[23] A and B are each independently aryl or heteroaryl;

[24] X is a bond, $-(CR^8R^9)_t-$, $-O-$, $-C(=O)-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

[25] Y and Z are each independently a bond, $-(CR^8R^9)_t-$, $-O-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

[26] V is a bond, optionally substituted $-(CR^{11}R^{12})_m-$, $-C(=O)-$, $-N(R^{10})CO-$, $-CONR^{10}-$, or $-NSO_2R^{10}-$;

[27] R is $-(CR^{4a}R^{4b})-(CR^{5a}R^{5b})-W$ or W;

[28] W is hydrogen, halogen, $-CF_3$, $-CF_2R^{10}$, $-CN$, $-OR^{13}$, $-NR^{13}R^{14}$, optionally substituted $-CONR^{13}R^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[29] D is $-(CR^{1a}R^{1b})_q-$, $-O-$, or $-NR^{10}-$;

[30] L is $-(CR^{2a}R^{2b})-R^3$ or $-E-R^3$;

[31] E is $-(CR^{2a}R^{2b})_g-$, $-O-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$;

[32] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-$

OCO(C₁–C₆ alkyl), –NR¹³R¹⁴, optionally substituted –(C₁–C₆ alkyl)–NR¹³R¹⁴, –NR¹⁴COR¹⁶, optionally substituted –(C₁–C₆ alkyl)–NR¹⁴COR¹⁶, –CONR¹⁴R¹⁵, optionally substituted –(C₁–C₆ alkyl)–CONR¹⁴R¹⁵, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[33] or alternatively, R^{1a} and R^{1b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[34] or alternatively, R^{2a} and R^{2b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[35] or alternatively, R^{1a}, R^{1b}, R^{2a} and R^{2b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[36] R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1–6} alkyl, optionally substituted C_{2–6} alkenyl, optionally substituted C_{2–6} alkynyl, optionally substituted C_{1–6} alkoxy, optionally substituted –OCO(C₁–C₆ alkyl), –NR¹³R¹⁴, optionally substituted –(C₁–C₆ alkyl)–NR¹³R¹⁴, –NR¹⁴COR¹⁶, optionally substituted –(C₁–C₆ alkyl)–NR¹⁴COR¹⁶, –CONR¹⁴R¹⁵, optionally substituted –(C₁–C₆ alkyl)–CONR¹⁴R¹⁵, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[37] or alternatively, R^{4a} and R^{4b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[38] or alternatively, R^{4a}, R^{4b}, R^{5a} and R^{5b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[39] R³ is absent, hydrogen, –CN, –CF₃, –OH, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted –OR¹⁵, optionally substituted C₁–C₆ alkoxy, –NH₂, –NR¹⁶R¹⁷, –NR¹⁶COR¹⁸, –NR¹⁶S(O)_pR¹⁸, –CONR¹⁴R¹⁵, –SONR¹⁴R¹⁵, –SO₂NR¹⁴R¹⁵, optionally substituted –S(O)_pR¹⁸, –N₃, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[40] or alternatively, R^{2a} , R^{2b} and R^3 taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[41] or alternatively, R^{2a} and R^{10} taken together form an optionally substituted heterocyclyl;

[42] R^6 and R^7 are each independently H, methyl, methoxy, $-\text{CN}$, F, Cl, Br, I, ^{123}I , $-\text{CF}_3$, $-\text{OH}$, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-(\text{C}_1\text{--C}_6 \text{ alkoxy})$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{OH}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{SO}_2\text{R}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})\text{NR}^{14}\text{SO}_2\text{R}^{16}$, $-\text{NR}^{14}\text{COR}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-\text{SO}_2\text{R}^{16}$, or optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{SO}_2\text{R}^{16}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[43] R^8 , R^9 , R^{11} and R^{12} are each independently hydrogen, $-\text{OH}$, halogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$ alkynyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, optionally substituted $\text{C}_1\text{--C}_6$ alkylamino, optionally substituted $-\text{OCO}(\text{C}_1\text{--C}_6 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[44] or alternatively, R^8 and R^9 taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

[45] or alternatively, R^{11} and R^{12} , on a same carbon atom or a different carbon atom, taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[46] R^{10} is hydrogen, halogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, $-\text{CO}(\text{C}_1\text{--C}_6 \text{ alkyl})$, optionally substituted $\text{C}_1\text{--C}_6$ alkylamino, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[47] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$

alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[48] or alternatively, R^{14} and R^{15} are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

[49] or alternatively, R^{16} and R^{17} are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

[50] m is 0, 1, 2, 3, or 4;

[51] each n is independently 0, 1 or 2;

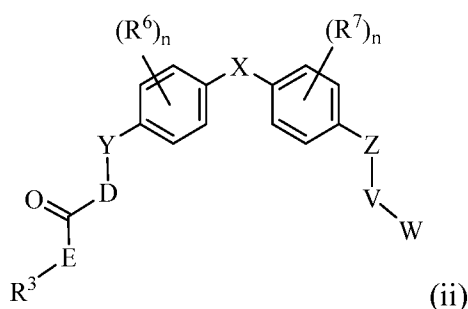
[52] each p is independently 0, 1 or 2;

[53] q is 0, 1 or 2;

[54] each g is independently 0, 1, 2, 3, or 4; and

[55] each t is independently 1 or 2.

[56] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the androgen receptor N-terminal domain inhibitor has the structure of formula (ii):



[57] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[58] X is a bond, $-NR^{10}-$, or $-(CR^{8a}R^{9a})_t-$;

[59] Y and Z are each independently a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$;

[60] V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$;

[61] W is halogen, $-NH_2$, or $-CF_3$.

[62] D is $-NR^{10}-$ and E is $-(CR^{2a}R^{2b})_g-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$;

[63] or alternatively, E is $-NR^{10}-$ or $-NR^{10}-(CR^{2a}R^{2b})_g-$, and D is $-(CR^{1a}R^{1b})_q-$ or $-NR^{10}-$;

[64] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-$

C₃ alkyl)-NR¹³R¹⁴, -NR¹⁴COR¹⁶, -(C₁-C₃ alkyl)-NR¹⁴COR¹⁶, -CONR¹⁴R¹⁵, or -(C₁-C₆ alkyl)-CONR¹⁴R¹⁵; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo (=O), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[65] R³ is selected from hydrogen, -C₁-C₆ alkyl, -OR¹⁵, -SR¹⁸, -C₁-C₆ alkoxy, -NR¹⁶R¹⁷, -NR¹⁶SR¹⁸, -NR¹⁶SOR¹⁸, -NR¹⁶SO₂R¹⁸, -NR¹⁶COR¹⁸, -CONR¹⁴R¹⁵, -SONR¹⁴R¹⁵, -SO₂NR¹⁴R¹⁵, -SOR¹⁸, or -SO₂R¹⁸;

[66] R⁶ and R⁷ are each independently H, halogen, -CN, -CF₃, -OH, or C₁-C₃ alkyl;

[67] R^{8a} and R^{9a} are each independently hydrogen, halogen, -OH, or C₁-C₃ alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

[68] R¹⁰ is each independently hydrogen, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or -CO(C₁-C₃ alkyl);

[69] R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are each independently hydrogen, C₁-C₃ alkyl, C₂-C₃ alkenyl, or C₂-C₃ alkynyl; or R¹⁴ and R¹⁵ taken together form an optionally substituted 5- or 6- membered heterocyclyl;

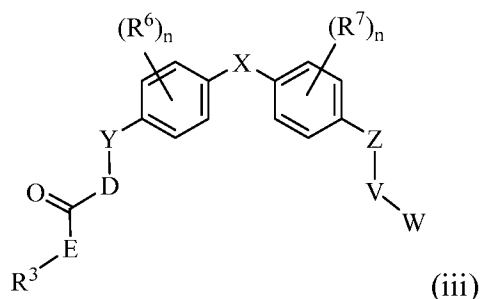
[70] each n is independently 0, 1 or 2;

[71] q is 0, 1 or 2;

[72] each g is independently 0, 1, 2, 3, or 4; and

[73] each t is independently 1 or 2.

[74] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the androgen receptor N-terminal domain inhibitor has the structure of formula (iii):



[75] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

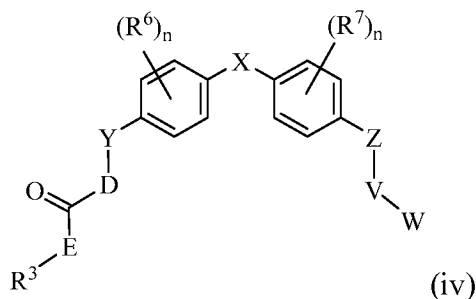
[76] X is a bond, -NR¹⁰-, or -(CR^{8a}R^{9a})_t;

[77] Y and Z are each independently a bond, -CH₂-, -C(CH₃)H-, -O-, -S-, -NH-, -NCH₃-, or -N(COCH₃)-

[78] V is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH(OH)CH₂-, or -CH₂C(OH)(CH₃)CH₂-;

- [79] W is halogen, $-\text{NH}_2$ or $-\text{CF}_3$;
- [80] D is $-\text{O}-$ or $-\text{NR}^{10}-$ and E is $-(\text{CR}^{2a}\text{R}^{2b})_{\text{gg}}-$;
- [81] or alternatively, E is $-\text{O}-$, $-\text{NR}^{10}-$ or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_{\text{g}}-$, and D is $-(\text{CR}^{1a}\text{R}^{1b})_{\text{q}}-$;
- [82] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, $\text{C}_1\text{--C}_3$ alkoxy, $-\text{OCO}(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1\text{--C}_3 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1\text{--C}_3 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$; or $(\text{R}^{1a}$ and $\text{R}^{1b})$ or $(\text{R}^{2a}$ and $\text{R}^{2b})$ taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;
- [83] R^3 is selected from hydrogen, $-\text{C}_1\text{--C}_6$ alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1\text{--C}_6$ alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;
- [84] R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, $\text{C}_1\text{--C}_3$ alkyl;
- [85] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;
- [86] R^{10} is each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, or $-\text{CO}(\text{C}_1\text{--C}_3 \text{ alkyl})$;
- [87] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, or $\text{C}_2\text{--C}_3$ alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;
- [88] m is 0, 1, 2, 3, or 4;
- [89] each n is independently 0, 1 or 2;
- [90] q is 1 or 2;
- [91] g is 0, 1, 2, 3, or 4;
- [92] gg is 1, 2, 3, or 4; and
- [93] t is 1 or 2.

[94] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the androgen receptor N-terminal domain inhibitor has the structure of formula (iv):



[95] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[96] X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

[97] Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

[98] V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

[99] W is $-\text{CF}_2\text{R}^{10}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[100] D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$;

[101] E is $-(\text{CR}^{2a}\text{R}^{2b})_g-$;

[102] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, C_2 – C_3 alkynyl, C_1 – C_3 alkoxy, $-\text{OCO}(\text{C}_1$ – C_3 alkyl), $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1$ – C_3 alkyl) $-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1$ – C_3 alkyl) $-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1$ – C_6 alkyl) $-\text{CONR}^{14}\text{R}^{15}$, or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[103] R^3 is selected from hydrogen, C_1 – C_6 alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, C_1 – C_6 alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;

[104] R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or C_1 – C_3 alkyl;

[105] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or C_1 – C_3 alkyl; or R^{8a} and R^{9a} taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

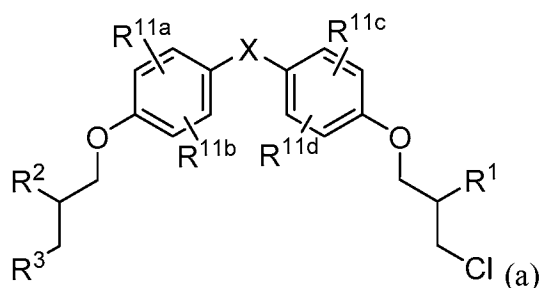
[106] R^{10} is each independently hydrogen, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, C_2 – C_3 alkynyl, or $-\text{CO}(\text{C}_1$ – C_3 alkyl);

[107] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, or C_2 – C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6-membered heterocyclyl;

- [108] m is 0, 1, 2, 3, or 4;
 [109] each n is independently 0, 1 or 2;
 [110] q is 0, 1 or 2;
 [111] g is 0, 1, 2, 3, or 4; and
 [112] t is 1 or 2.

[113] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the androgen receptor is selected from Table A.

[114] In one embodiment (a):



- [115] wherein:
 [116] X is $-S(O)_n-$ or $-C(R^8R^9)-$;
 [117] R^1 is H, hydroxyl or $-OC(=O)R^{13}$;
 [118] R^2 is hydroxyl or $-OC(=O)R^{13}$;
 [119] R^3 is halo, $-OH$, $-OR^4$, $-OC(=O)R^{13}$, $-NH_2$, $-NHC(=O)R^{13}$, $-N(C(=O)R^{13})_2$, $-NHS(O)_nR^5$, $-N(C(=O)R^{13})(S(O)_nR^5)$, $-N(C_1-C_6 \text{ alkyl})(S(O)_nR^5)$, $-S(O)_nR^5$, $-N_3$, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;
 [120] R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;
 [121] R^5 is each independently C_1-C_6 alkyl or aryl which are optionally substituted with one or more R^6 ;
 [122] R^6 is each independently selected from the group consisting of H, F, Cl, Br, I, ^{123}I , hydroxyl, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_6-C_{12} aryl, wherein each R^6 is optionally substituted with one or more of halogen, ^{123}I , ^{18}F , hydroxyl, $-OS(O)_2$ -aryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;
 [123] R^8 and R^9 are each independently H or C_1-C_6 alkyl;
 [124] R^{11a} , R^{11b} , R^{11c} and R^{11d} are each independently H, methyl, $-CN$, F, Cl, Br, I, or ^{123}I ;
 [125] R^{13} is C_1-C_6 alkyl; and

[126] n is 0, 1, or 2;

[127] wherein at least one of R^{11a}, R^{11b}, R^{11c} and R^{11d} is methyl, -CN, F, Cl, Br, I, or ¹²³I.

[128] In one embodiment the compounds of formula (a), the compound has at least two of R^{11a}, R^{11b}, R^{11c} and R^{11d} are methyl, -CN, F, Cl, Br, I, or ¹²³I. In one embodiment, R^{11c} and R^{11d} are each independently methyl, -CN, Cl, or Br. In some embodiments, R^{11c} and R^{11d} are each Cl or -CN.

[129] In one embodiment the compounds of formula (a), X is -C(R⁸R⁹)- and R⁸ and R⁹ are each independently C₁-C₃ alkyl.

[130] In one embodiment the compounds of formula (a), R⁸ and R⁹ are each methyl.

[131] In one embodiment the compounds of formula (a), R¹ and R² are both hydroxyl.

[132] In one embodiment the compounds of formula (a), R³ is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom.

[133] In one embodiment the compounds of formula (a), R³ is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrroline, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine. In one embodiment, R³ is -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -N(C(=O)R¹³)(S(O)_nR⁵), -N(C₁-C₆ alkyl)(S(O)_nR⁵) or -S(O)_nR⁵. In some embodiments, R³ is -NH₂, -NHC(=O)(C₁-C₄ alkyl), -N[(C(=O)(C₁-C₄ alkyl)]₂, -NHS(O)_n(C₁-C₃ alkyl), -N[C(=O)(C₁-C₄ alkyl)][(S(O)_n(C₁-C₃ alkyl))], -N[C₁-C₆ alkyl][S(O)_n(C₁-C₃ alkyl)], or -S(O)_n(C₁-C₃ alkyl).

[134] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the androgen receptor N-terminal domain inhibitor is selected from Table B.

[135] In one embodiment of the method of treating cancer, the method further comprises administering a second therapeutically active agent.

[136] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the second therapeutically active agent is selected from a poly (ADP-ribose) polymerase (PARP) inhibitor, an androgen receptor ligand-binding domain inhibitor, an inhibitor of CYP17, a microtubule inhibitor, a modulator of PD-1 or PD-L1, a gonadotropin releasing hormone agonist, a 5-alpha reductase inhibitor, a vascular endothelial growth factor

inhibitor, a histone deacetylase inhibitor, an integrin α -v- β -3 inhibitor, a receptor tyrosine kinase, a phosphoinositide 3-kinase inhibitor, an anaplastic lymphoma kinase (ALK) inhibitor, an endothelin receptor A antagonist, an anti-CTLA4 inhibitor, an heat shock protein 27 (HSP27) inhibitor, an androgen receptor degrader, a androgen receptor DNA-binding domain inhibitor, a bromodomain and extra-terminal motif (BET) inhibitor, an androgen receptor N-terminal domain inhibitor, an α -particle emitting radioactive therapeutic agent, niclosamide, a selective estrogen receptor modulator (SERM), a selective estrogen receptor degrader (SERD), an aromatase inhibitor, selective progesterone receptor modulator (SPRM), a glucocorticoid receptor inhibitor, a CDK4/6 inhibitor, a HER2 receptor antagonist, a mammalian target of rapamycin (mTOR) inhibitor, an AKT inhibitor, a B-cell lymphoma-2 (Bcl-2) inhibitor, an aurora kinase inhibitor, a Wnt-targeting antagonist, a CYP11a inhibitor, a selective androgen receptor N-terminal domain inhibitor, or enhancer of zeste homolog 2 (EZH2) inhibitor.

[137] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the CDK4/6 inhibitor is selected from palbociclib, ribociclib, trilaciclib or abemaciclib. In one embodiment, the CDK4/6 inhibitor is Palbociclib.

[138] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the androgen receptor ligand-binding domain inhibitor is enzalutamide, apalutamide, darolutamide, bicalutamide, nilutamide, flutamide, ODM-204, or TAS3681. In one embodiment, the androgen receptor ligand-binding domain inhibitor is enzalutamide.

[139] In one embodiment of the pharmaceutical compositions or combinations of the present disclosure, the Pin1 inhibitor is selected from juglone, plumbagin, PiB, PiJ, epigallocatechin gallate (EGCG), all-trans retinoic acid (ATRA), dipentamethylene thiauram monosulfide, TME-001 (2-(3-chloro-4-fluoro-phenyl)-isothiazol-3-one), KPT-6566, API-1, buparvaquone, or a pharmaceutically acceptable salt thereof.

[140] In one embodiment of the pharmaceutical compositions or combinations of the present disclosure, the Pin1 inhibitor is selected from Table C or a pharmaceutically acceptable salt thereof. In one embodiment of the pharmaceutical compositions or combinations of the present disclosure, the Pin1 inhibitor is selected from Table D or a pharmaceutically acceptable salt thereof.

[141] In one embodiment of the pharmaceutical compositions or combinations of the present disclosure, the Pin1 inhibitor is CRYPEVEIC, wherein the cysteine residues of said peptide are cyclized by a disulfide bond (SEQ ID NO: 1); Ac-Lys(N-biotinoyl)-Ala-Ala-Bth-D-

Thr(PO₃H₂)-Pip-Nal-Gln-NH₂ (SEQ ID NO: 2); Ac-Phe-D-Thr(PO₃H₂)-Pip-Nal-Gln-NH₂ (SEQ ID NO: 3); and Ac-Phe-Phe-pSer-Ψ[(Z)CHdC-Pro-Arg-NH₂ (SEQ ID NO: 4).

[142] In one embodiment of the pharmaceutical compositions or combinations of the present disclosure, the Pin1 inhibitor is selected from 5-hydroxy-1,4-naphthledione, (1-piperidinecarbodithioic acid, anhydrosulfide), or diethyl-1,3,6,8-tetrahydro-1,3,6,8-tetraoxobenzo[lmn] phenanthroline-2,7-diacetate, or a pharmaceutically acceptable salt thereof.

[143] In one embodiment of the pharmaceutical compositions or combinations of the present disclosure, the Pin1 inhibitor is ATRA.

[144] In one embodiment, the pharmaceutical compositions or combinations of the present disclosure comprises Compound 13a and enzalutamide. In one embodiment, the pharmaceutical compositions or combinations of the present disclosure comprises Compound 13a and Palbociclib. In one embodiment, the pharmaceutical compositions or combinations of the present disclosure comprises Compound 13a and ATRA.

[145] In one embodiment of the pharmaceutical compositions or combinations or the methods of the present disclosure, the composition or the combination further comprises a pharmaceutically acceptable carrier is provided.

[146] In one embodiment, the present disclosure relates to methods for modulating androgen receptor activity, comprising administering the pharmaceutical compositions or combinations of the present disclosure, to a subject in need thereof.

[147] In one embodiment of any one of the method as disclosed herein, the modulating androgen receptor activity is for treating a condition or disease selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration.

[148] In one embodiment, the present disclosure relates to methods for treating cancer, comprising administering the pharmaceutical compositions or combinations of the present disclosure, to a subject in need thereof. In one embodiment, the cancer is selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, or salivary gland carcinoma. In one embodiment, the cancer is prostate cancer.

[149] In one embodiment of the methods as disclosed herein, the cancer is breast cancer. In one embodiment, the breast cancer is AR-positive triple negative breast cancer.

[150] In one embodiment of the methods as disclosed herein, the prostate cancer is primary or localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, advanced prostate cancer, metastatic prostate cancer, metastatic castration-resistant prostate cancer, and hormone-sensitive prostate cancer. In some embodiments, the prostate cancer is metastatic castration-resistant prostate cancer. In other embodiments, the prostate cancer expresses full-length androgen receptor or truncated androgen receptor splice variant. In one embodiment, the prostate cancer is resistant to enzalutamide monotherapy.

[151] In one embodiment of the methods as disclosed herein comprising administering the pharmaceutical compositions or combinations comprising an androgen receptor N-terminal domain inhibitor and a second therapeutically active agent, the methods further comprising administering radiation therapy to the subject.

[152] In one embodiment of the method of administering radiation lutetium-177 is administered concurrently with radiation. In one embodiment, lutetium-177 is targeted to prostate cancer cells.

[153] In one embodiment of any one of the methods disclosed herein, the radiation therapy is ionizing radiation therapy. In one embodiment, the administering the androgen receptor N-terminal domain inhibitor or a pharmaceutical composition thereof and the administering radiation therapy occurs during same treatment period or during different treatment period.

BRIEF DESCRIPTION OF THE DRAWINGS

[154] **Fig. 1** shows cell proliferation assay results for breast cancer and prostate cancer cell lines treated with control, enzalutamide (ENZ), or EPI-002.

[155] **Fig. 2A** shows cell viability of SUM-159PT cells treated with Compound 13a with and without palbociclib (Palbo).

[156] **Fig. 2B** shows cell viability of MDA-MB-468 cells treated with Compound 13a with and without palbociclib (Palbo).

[157] **Fig. 2C** shows cell viability of LNCaP cells treated with Compound 13a or enzalutamide (ENZ) with and without palbociclib (Palbo).

[158] **Fig. 2D** shows cell viability of LNCaP95 cells treated with Compound 13a or enzalutamide (ENZ) with and without palbociclib (Palbo).

[159] **Fig. 3** shows % cells in each cell cycle phase for AR-positive SUM-159PT cells in a cell cycle study.

[160] **Fig. 4** shows % cells in each cell cycle phase for LNCaP95 cells in a cell cycle study.

- [161] **Fig. 5** shows % cells in each cell cycle phase for C4-2B-MDVR cells in a cell cycle study.
- [162] **Fig. 6** shows colony numbers in C4-2B-MDVR cells treated with EPI-002 or Compound 13a, alone or in combination with enzalutamide.
- [163] **Fig. 7A** shows Compound 13a and/or enzalutamide effects on levels of *PSA* mRNA in C4-2B-MDVR. **Fig. 7B** shows Compound 13a and/or enzalutamide effects on levels of *UBE2C* mRNA in C4-2B-MDVR. **Fig. 7C** shows Compound 13a and/or enzalutamide effects on levels of *FKBP5* mRNA in C4-2B-MDVR. **Fig. 7D** shows Compound 13a and/or enzalutamide effects on levels of *Cyclin A2* mRNA in C4-2B-MDVR. **Fig. 7E** shows Compound 13a and/or enzalutamide effects on levels of *TMPRSS2* mRNA in C4-2B-MDVR. **Fig. 7F** shows Compound 13a and/or enzalutamide effects on levels of *CDC20* mRNA in C4-2B-MDVR.
- [164] **Fig. 8** shows protein levels of AR-FL and AR-V7 from C4-2B-MDVR cells treated with Compound 13a alone or in combination with enzalutamide, normalized to β -actin
- [165] **Fig. 9A** shows effects of Compound 13a and/or enzalutamide on androgen-induced *PSA*-luciferase activity in LNCaP cells. **Fig. 9B** shows effects of Compound 13a and/or enzalutamide on AR-V7 induced *PSA*-luciferase activity in LNCaP cells.
- [166] **Fig. 9C** shows effects of Compound 13a and/or enzalutamide on levels of V7BS3-luciferase activity in LNCaP cells. **Fig. 9D** shows effects of Compound 13a and/or enzalutamide on AR-V7-induced V7BS3-luciferase activity in LNCaP cells.
- [167] **Fig. 10** shows cell proliferation assay results for VCaP-MDVR cell lines treated enzalutamide (ENZ) alone or in combination with Compound 13a.
- [168] **Fig. 11A** shows cell proliferation assay results for C4-2B-MDVR cell lines treated enzalutamide (ENZ) alone or in combination with Compound 13a in the absence of R1881.
- [169] **Fig. 11B** shows cell proliferation assay results for C4-2B-MDVR cell lines treated enzalutamide (ENZ) alone or in combination with Compound 13a in the presence of R1881.
- [170] **Fig. 12A** shows Western blot analyses for γ H2AX in protein lysates from LNCaP95 cells treated with DMSO (control), EPI-002 (35 μ M), Compound 13a (8 μ M), or enzalutamide (ENZ, 5 μ M) with or without irradiation (4Gy) harvested after 48 h incubation.
- [171] **Fig. 12B** shows percent of LNCaP95 cells positive for γ H2AX after treatment with DMSO (control), EPI-002, or enzalutamide (ENZ) with or without irradiation (2 Gy or 4Gy).
- [172] **Fig. 12C** shows percent of γ H2AX foci in LNCaP95 cells treated with DMSO (control), EPI-002, Compound 13a, or enzalutamide (ENZ) with or without irradiation (4Gy).
- [173] **Fig. 12D** shows representative images of γ H2AX foci in LNCaP95 cells treated with DMSO (control), EPI-002, Compound 13a, or enzalutamide (ENZ) with irradiation (4Gy).

[174] **Fig. 13** shows inhibitory dose-response curve for juglone and ATRA in PSA(6.1kb)-luciferase assay.

[175] **Fig. 14** is a Western blot showing the levels PSA and AR protein in lysates prepared from LNCaP cells treated with juglone (20 μ M) or ATRA (10 μ M), and R1881 (1 nM) or vehicle for 24h.

[176] **Fig. 15** shows transcriptional activity of AR-V7 in LNCaP cells measured with luciferase reporter gene regulated by *UBE2C* promoter.

[177] **Fig. 16** is a Western blot showing the levels AR-V7 expression in lysates prepared from LNCaP cells.

[178] **Fig. 17** shows inhibitory dose-response curve for EPI-002 and Compound **13a** with or without ATRA in PSA(6.1kb)-luciferase assay.

[179] **Fig. 18A and 18B** are Western blots showing the levels altered expression of proteins regulating senescence in lysates prepared from the cells after 3 or 6 days of treatment with ATRA, EPI-002, or the combination thereof.

[180] **Fig. 19A and 19B** shows cell cycle analysis of LN95-D3 cells after treating with combination of ATRA and EPI-002 or Compound 13a or Enzalutamide (EnZ), in 1.5% charcoal-tripped serum.

[181] **Fig. 20** shows Western blots showing stability of Cylin D1 and Pin 1 with the treatment with ATRA or 13CisRA.

DETAILED DESCRIPTION

[182] All publications, patents and patent applications, including any drawings and appendices therein are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent or patent application, drawing, or appendix was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

Definitions

[183] While the following terms are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter.

[184] Throughout the present specification, the terms “about” and/or “approximately” may be used in conjunction with numerical values and/or ranges. The term “about” is understood to mean those values near to a recited value. 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” may be used interchangeably.

[185] 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 may 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.).

[186] The term “a” or “an” refers to one or more of that entity; for example, “a androgen receptor N-terminal domain inhibitor” refers to one or more androgen receptor N-terminal domain inhibitors or at least one androgen receptor N-terminal domain inhibitor. As such, the terms “a” (or “an”), “one or more” and “at least one” are used interchangeably herein. In addition, reference to “an inhibitor” by the indefinite article “a” or “an” does not exclude the possibility that more than one of the inhibitors is present, unless the context clearly requires that there is one and only one of the inhibitors.

[187] As used herein, the verb “comprise” as is used in this description and in the claims and its conjugations are used in its non-limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. The present invention may suitably “comprise”, “consist of”, or “consist essentially of”, the steps, elements, and/or reagents described in the claims.

[188] It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely”, “only” and the like in connection with the recitation of claim elements, or the use of a “negative” limitation.

[189] The term “pharmaceutically acceptable salts” includes both acid and base addition salts. Pharmaceutically acceptable salts include those obtained by reacting the active compound functioning as a base, with an inorganic or organic acid to form a salt, for example, salts of hydrochloric acid, sulfuric acid, phosphoric acid, methanesulfonic acid, camphorsulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, carbonic acid, etc. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods.

[190] The term “treating” means one or more of relieving, alleviating, delaying, reducing, improving, or managing at least one symptom of a condition in a subject. The term “treating”

may also mean one or more of arresting, delaying the onset (i.e., the period prior to clinical manifestation of the condition) or reducing the risk of developing or worsening a condition.

[191] 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 disclosure 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.

[192] 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 disclosure contemplates various stereoisomers and mixtures thereof and includes “enantiomers”, which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another.

[193] A “tautomer” refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present disclosure includes tautomers of any said compounds.

[194] A “prodrug” refers to a derivative of a compound of the present disclosure that will be converted to the compound *in vivo*. In one embodiment of the present disclosure, a prodrug includes a compound of formula (i)-(iii) and (a), having a free hydroxyl group (-OH) that is acetylated (-OCOMe) or acylated at one or more positions.

[195] An “effective amount” means the amount of a formulation according to the invention that, when administered to a patient for treating a state, disorder or condition is sufficient to effect such treatment. The “effective amount” will vary depending on the active ingredient, the state, disorder, or condition to be treated and its severity, and the age, weight, physical condition and responsiveness of the mammal to be treated.

[196] The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical formulation that is sufficient to result in a desired clinical benefit after administration to a patient in need thereof.

[197] As used herein, the term "ionizing radiation" refers to ionizing radiation from any source that is capable of ionizing atoms or molecules of a cell. Non-limiting examples of ionizing radiation include: X-rays, ultraviolet light, gamma rays, alpha particles, beta particles, and neutrons. Depending on the wavelength, ultraviolet light may be considered either ionizing or non-ionizing radiation.

[198] 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, bladder cancer, pancreatic cancer, hepatocellular 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, bladder cancer, pancreatic cancer, hepatocellular 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.

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

[200] All weight percentages (i.e., "% by weight" and "wt. %" and w/w) referenced herein, unless otherwise indicated, are measured relative to the total weight of the pharmaceutical composition.

[201] As used herein, "substantially" or "substantial" refers to the complete or nearly complete extent or degree of an action, characteristic, property, state, structure, item, or result. For example, an object that is "substantially" enclosed would mean that the object is either completely enclosed or nearly completely enclosed. The exact allowable degree of deviation

from absolute completeness may in some cases depend on the specific context. However, generally speaking, the nearness of completion will be so as to have the same overall result as if absolute and total completion were obtained. The use of "substantially" is equally applicable when used in a negative connotation to refer to the complete or near complete lack of action, characteristic, property, state, structure, item, or result. For example, a composition that is "substantially free of" other active agents would either completely lack other active agents, or so nearly completely lack other active agents that the effect would be the same as if it completely lacked other active agents. In other words, a composition that is "substantially free of" an ingredient or element or another active agent may still contain such an item as long as there is no measurable effect thereof

[202] "Electrophile" as used herein relates to species that is attracted to an electron rich center. In chemistry, an electrophile is a reagent attracted to electrons. It participates in a chemical reaction by accepting an electron pair in order to bond to a nucleophile. Because electrophiles accept electrons, they are Lewis acids. Most electrophiles are positively charged, have an atom that carries a partial positive charge, or have an atom that does not have an octet of electrons.

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

[204] "Amino" refers to the -NH_2 radical.

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

[206] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo radical, including their radioisotopes. " ^{123}I " refers to the radioactive isotope of iodine having atomic mass 123. The compounds of Formula I can comprise at least one ^{123}I moiety. Throughout the present application, where structures depict a ^{123}I moiety at a certain position it is meant that the I moiety at this position is enriched for ^{123}I . In other words, the compounds contain more than the natural abundance of ^{123}I at the indicated position(s). It is not required that the compounds comprise 100% ^{123}I at the indicated positions, provided ^{123}I is present in more than the natural abundance. Typically the ^{123}I isotope is enriched to greater than 50%, greater than 60%, greater than 70%, greater than, 80% or greater than 90%, relative to ^{127}I . " ^{18}F " refers to the radioactive isotope of fluorine having atomic mass 18. " F " or " ^{19}F " refers to the abundant, non-radioactive fluorine isotope having atomic mass 19. The compounds of Formula I can comprise at least one ^{18}F moiety. Throughout the present application, where structures depict a ^{18}F moiety at a certain position it is meant that the F moiety at this position is enriched for ^{18}F . In other words, the compounds contain more than the natural abundance of ^{18}F at the indicated position(s). It

is not required that the compounds comprise 100% ^{18}F at the indicated positions, provided ^{18}F is present in more than the natural abundance. Typically the ^{18}F isotope is enriched to greater than 50%, greater than 60%, greater than 70%, greater than 80% or greater than 90%, relative to ^{19}F .

[207] “Hydroxy” or “hydroxyl” refers to the -OH radical.

[208] “Imino” refers to the =NH substituent.

[209] “Nitro” refers to the -NO₂ radical.

[210] “Oxo” refers to the =O substituent.

[211] “Thioxo” refers to the =S substituent.

[212] “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 C₁-C₁₂ alkyl, an alkyl comprising up to 10 carbon atoms is a C₁-C₁₀ alkyl, an alkyl comprising up to 6 carbon atoms is a C₁-C₆ alkyl and an alkyl comprising up to 5 carbon atoms is a C₁-C₅ alkyl. A C₁-C₅ alkyl includes C₅ alkyls, C₄ alkyls, C₃ alkyls, C₂ alkyls and C₁ alkyl (i.e., methyl). A C₁-C₆ alkyl includes all moieties described above for C₁-C₅ alkyls but also includes C₆ alkyls. A C₁-C₁₀ alkyl includes all moieties described above for C₁-C₅ alkyls and C₁-C₆ alkyls, but also includes C₇, C₈, C₉ and C₁₀ alkyls. Similarly, a C₁-C₁₂ alkyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkyls. Non-limiting examples of C₁-C₁₂ 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.

[213] “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 C₁-C₁₂ alkylene include methylene, ethylene, propylene, n-butylenes, ethenylene, propenylene, n-butenylene, propynylene, n-butylnylene, 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.

[214] “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 C₂-C₁₂ alkenyl, an alkenyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkenyl, an alkenyl group comprising up to 6 carbon atoms is a C₂-C₆ alkenyl and an alkenyl comprising up to 5 carbon atoms is a C₂-C₅ alkenyl. A C₂-C₅ alkenyl includes C₅ alkenyls, C₄ alkenyls, C₃ alkenyls, and C₂ alkenyls. A C₂-C₆ alkenyl includes all moieties described above for C₂-C₅ alkenyls but also includes C₆ alkenyls. A C₂-C₁₀ alkenyl includes all moieties described above for C₂-C₅ alkenyls and C₂-C₆ alkenyls, but also includes C₇, C₈, C₉ and C₁₀ alkenyls. Similarly, a C₂-C₁₂ alkenyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkenyls. Non-limiting examples of C₂-C₁₂ 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.

[215] “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 C₂-C₁₂ 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.

[216] “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 C₂-C₁₂ alkynyl, an alkynyl comprising up to 10 carbon atoms is a C₂-C₁₀ alkynyl, an alkynyl group comprising up to 6 carbon atoms is a C₂-C₆ alkynyl

and an alkynyl comprising up to 5 carbon atoms is a C₂-C₅ alkynyl. A C₂-C₅ alkynyl includes C₅ alkynyls, C₄ alkynyls, C₃ alkynyls, and C₂ alkynyls. A C₂-C₆ alkynyl includes all moieties described above for C₂-C₅ alkynyls but also includes C₆ alkynyls. A C₂-C₁₀ alkynyl includes all moieties described above for C₂-C₅ alkynyls and C₂-C₆ alkynyls, but also includes C₇, C₈, C₉ and C₁₀ alkynyls. Similarly, a C₂-C₁₂ alkynyl includes all the foregoing moieties, but also includes C₁₁ and C₁₂ alkynyls. Non-limiting examples of C₂-C₁₂ alkenyl include ethynyl, propynyl, butynyl, pentynyl and the like. Unless stated otherwise specifically in the specification, an alkyl group can be optionally substituted.

[217] “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 C₂-C₁₂ 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.

[218] “Alkoxy” refers to a radical of the formula -OR_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, an alkoxy group can be optionally substituted.

[219] “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.

[220] “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 “C_w-C_z acyl” where w and z depicts the range of the number of carbon in R_a, as defined above. For example, “C₁-C₁₀ acyl” refers to alkylcarbonyl group as defined above, where R_a is C₁-C₁₀ alkyl, C₁-C₁₀ alkenyl, or C₁-C₁₀ alkynyl radical as defined above. Unless stated otherwise specifically in the specification, an alkyl carbonyl group can be optionally substituted.

[221] “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.

[222] “Aralkyl” or “arylalkyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene 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.

[223] “Aralkenyl” or “arylalkenyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkenylene group as defined above and R_c is one or more aryl radicals as defined above. Unless stated otherwise specifically in the specification, an aralkenyl group can be optionally substituted.

[224] “Aralkynyl” or “arylalkynyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkynylene group as defined above and R_c is one or more aryl radicals as defined above. Unless stated otherwise specifically in the specification, an aralkynyl group can be optionally substituted.

[225] “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.

[226] “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, decalyl, 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.

[227] “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.

[228] “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.

[229] “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.

[230] “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.

[231] “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.

[232] “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.

[233] “Heterocyclyl,” “heterocyclic ring” or “heterocycle” refers to a stable 3- to 20-membered non-aromatic, partially aromatic, or 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. Heterocyclyl 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, imidazolynyl, imidazolidynyl, isothiazolidynyl, isoxazolidynyl, morpholynyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazynyl, 2-oxopiperidynyl, 2-oxopyrrolidynyl, oxazolidynyl, piperidynyl, piperazynyl, 4-piperidonyl, pyrrolidynyl, pyrazolidynyl, quinuclidynyl, thiazolidynyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholynyl, thiamorpholynyl, 1-oxo-thiomorpholynyl, and 1,1-dioxo-thiomorpholynyl. Unless stated otherwise specifically in the specification, a heterocyclyl group can be optionally substituted.

[234] “Heterocyclylalkyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene group as defined above and R_c is a heterocyclyl radical as defined above. Unless stated otherwise specifically in the specification, a heterocycloalkylalkyl group can be optionally substituted.

[235] “Heterocyclylalkenyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkenylene group as defined above and R_c is a heterocyclyl radical as defined above. Unless stated otherwise specifically in the specification, a heterocycloalkylalkenyl group can be optionally substituted.

[236] “Heterocyclylalkynyl” refers to a radical of the formula $-R_b-R_c$ where R_b is an alkynylene group as defined above and R_c is a heterocyclyl radical as defined above. Unless stated otherwise specifically in the specification, a heterocycloalkylalkynyl group can be optionally substituted.

[237] “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.

[238] “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, azepynyl, acridynyl, 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 (benzothiophene), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophene, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1H-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 thiophene (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group can be optionally substituted.

[239] “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.

[240] “Heteroarylalkyl” refers to a radical of the formula $-R_b-R_f$ where R_b is an alkylene 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.

[241] “Heteroarylalkenyl” refers to a radical of the formula $-R_b-R_f$ where R_b is an alkenylene chain as defined above and R_f is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkenyl group can be optionally substituted.

[242] “Heteroarylalkynyl” refers to a radical of the formula $-R_b-R_f$ where R_b is an alkynylene chain as defined above and R_f is a heteroaryl radical as defined above. Unless stated otherwise specifically in the specification, a heteroarylalkynyl group can be optionally substituted.

[243] “Ring” refers to a cyclic group which can be fully saturated, partially saturated, or fully unsaturated. A ring can be monocyclic, bicyclic, tricyclic, or tetracyclic. Unless stated otherwise specifically in the specification, a ring can be optionally substituted.

[244] “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.

[245] 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, alkyl diarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups.

[246] “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 $-\text{NR}_g\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{NR}_g\text{C}(=\text{O})\text{OR}_h$, $-\text{NR}_g\text{SO}_2\text{R}_h$, $-\text{OC}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{OR}_g$, $-\text{SR}_g$, $-\text{SOR}_g$, $-\text{SO}_2\text{R}_g$, $-\text{OSO}_2\text{R}_g$, $-\text{SO}_2\text{OR}_g$, $=\text{NSO}_2\text{R}_g$, and $-\text{SO}_2\text{NR}_g\text{R}_h$. “Substituted” also means any of the above groups in which one or more hydrogen atoms are replaced with $-\text{C}(=\text{O})\text{R}_g$, $-\text{C}(=\text{O})\text{OR}_g$, $-\text{C}(=\text{O})\text{NR}_g\text{R}_h$, $-\text{CH}_2\text{SO}_2\text{R}_g$, $-\text{CH}_2\text{SO}_2\text{NR}_g\text{R}_h$. 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.

[247] 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, “ $\text{XY}-\text{$ ”

” 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 $\text{CH}_3\text{-R}^3$, wherein R^3 is H or “

$\text{XY}-\text{---}$ ” 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 .

[248] “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.

[249] The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed inventions, or that any publication specifically or implicitly referenced is prior art.

Androgen Receptor N-Terminal Domain Inhibitors of the Present Disclosure

[250] The pharmaceutical compositions or combinations of the present disclosure can be useful for modulating (including inhibiting) androgen receptors. Further, the pharmaceutical compositions or combinations of the present disclosure can be useful for treating various diseases and conditions including, but not limited to, cancer.

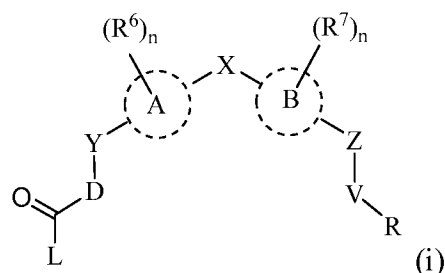
[251] In one embodiment of the present disclosure, the pharmaceutical compositions or combinations comprises an androgen receptor N-terminal domain inhibitor and a CDK4/6 inhibitor.

[252] In one embodiment, the pharmaceutical composition comprises an androgen receptor N-terminal domain inhibitor and a Pin1 inhibitor. In one embodiment, the pharmaceutical composition comprises an androgen receptor N-terminal domain inhibitor and a Pin1 inhibitor, wherein the androgen receptor N-terminal domain inhibitor is not 3-(4-(2-(4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol, 3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate, or stereoisomers thereof.

[253] In one embodiment of the present disclosure, the pharmaceutical compositions or combinations comprises an androgen receptor N-terminal domain inhibitor and an androgen receptor ligand-binding domain inhibitor.

[254] The androgen receptor N-terminal domain inhibitors of the present disclosure can, alone, be useful for treating various diseases and conditions including, but not limited to, cancer. In some embodiments, the cancer is prostate cancer.

[255] In one embodiment, the present disclosure provides androgen receptor N-terminal domain inhibitors selected from compounds of formula (i):



[256] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[257] A and B are each independently aryl or heteroaryl;

[258] X is a bond, $-(CR^8R^9)_t-$, $-O-$, $-C(=O)-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

[259] Y and Z are each independently a bond, $-(CR^8R^9)_t-$, $-O-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

[260] V is a bond, optionally substituted $-(CR^{11}R^{12})_m-$, $-C(=O)-$, $-N(R^{10})CO-$, $-CONR^{10}-$, or $-NSO_2R^{10}-$;

[261] R is $-(CR^{4a}R^{4b})-(CR^{5a}R^{5b})-W$ or W;

[262] W is hydrogen, halogen, $-CF_3$, $-CF_2R^{10}$, $-CN$, $-OR^{13}$, $-NR^{13}R^{14}$, optionally substituted $-CONR^{13}R^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[263] D is $-(CR^{1a}R^{1b})_q-$, $-O-$, or $-NR^{10}-$;

[264] L is $-(CR^{2a}R^{2b})-R^3$ or $-E-R^3$;

[265] E is $-(CR^{2a}R^{2b})_g-$, $-O-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$;

[266] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[267] or alternatively, R^{1a} and R^{1b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[268] or alternatively, R^{2a} and R^{2b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[269] or alternatively, R^{1a} , R^{1b} , R^{2a} and R^{2b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[270] R^{4a} , R^{4b} , R^{5a} , and R^{5b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[271] or alternatively, R^{4a} and R^{4b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[272] or alternatively, R^{4a} , R^{4b} , R^{5a} and R^{5b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[273] R^3 is absent, hydrogen, $-CN$, $-CF_3$, $-OH$, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted $-OR^{15}$, optionally substituted C_{1-6} alkoxy, $-NH_2$, $-NR^{16}R^{17}$, $-NR^{16}COR^{18}$, $-NR^{16}S(O)_pR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-S(O)_pR^{18}$, $-N_3$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[274] R^{2a} , R^{2b} and R^3 taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[275] R^6 and R^7 are each independently H, halogen, $-CN$, $-CF_3$, $-OH$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-(C_{1-6} \text{ alkyl})-(C_{1-6} \text{ alkoxy})$, optionally substituted $-(C_{1-6} \text{ alkyl})-OH$, $-NR^{13}R^{14}$, optionally

substituted $-(C_1-C_6 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}SO_2R^{16}$, optionally substituted $-(C_1-C_6 \text{ alkyl})NR^{14}SO_2R^{16}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-SO_2NR^{14}R^{15}$, optionally substituted $-SO_2R^{16}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-SO_2R^{16}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[276] R^8 , R^9 , R^{11} and R^{12} are each independently hydrogen, $-OH$, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, optionally substituted C_1-C_6 alkylamino, optionally substituted $-OCO(C_1-C_6 \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[277] or alternatively, R^8 and R^9 taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

[278] or alternatively, R^{11} and R^{12} , on a same carbon atom or a different carbon atom, taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[279] R^{10} is hydrogen, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 alkoxy, $-CO(C_1-C_6 \text{ alkyl})$, optionally substituted C_1-C_6 alkylamino, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[280] or alternatively, R^{2a} and R^{10} taken together form an optionally substituted heterocyclyl;

[281] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

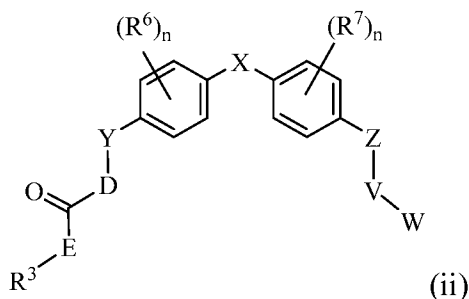
[282] or alternatively, R^{14} and R^{15} are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

[283] or alternatively, R^{16} and R^{17} are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

[284] m is 0, 1, 2, 3, or 4;

- [285] each n is independently 0, 1 or 2;
 [286] each p is independently 0, 1 or 2;
 [287] q is 0, 1 or 2;
 [288] each g is independently 0, 1, 2, 3, or 4; and
 [289] each t is independently 1 or 2.

[290] In one embodiment, the present disclosure provides androgen receptor N-terminal domain inhibitors selected from compounds of formula (ii):



[291] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

- [292] X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;
 [293] Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;
 [294] V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;
 [295] W is halogen, $-\text{NH}_2$, or $-\text{CF}_3$.
 [296] D is $-\text{NR}^{10}-$ and E is $-(\text{CR}^{2a}\text{R}^{2b})_g-$, $-\text{NR}^{10}-$, or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$;
 [297] or alternatively, E is $-\text{NR}^{10}-$ or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$, and D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$ or $-\text{NR}^{10}-$;
 [298] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-\text{OCO}(\text{C}_1-\text{C}_3 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$; or $(\text{R}^{1a}$ and $\text{R}^{1b})$ or $(\text{R}^{2a}$ and $\text{R}^{2b})$ taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;
 [299] R^3 is selected from hydrogen, $-\text{C}_1-\text{C}_6$ alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1-\text{C}_6$ alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;
 [300] R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, C_1-C_3 alkyl;
 [301] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or C_1-C_3 alkyl;

[302] R^{10} is each independently hydrogen, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, C_2 – C_3 alkynyl, $-\text{CO}(C_1$ – C_3 alkyl);

[303] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, or C_2 – C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

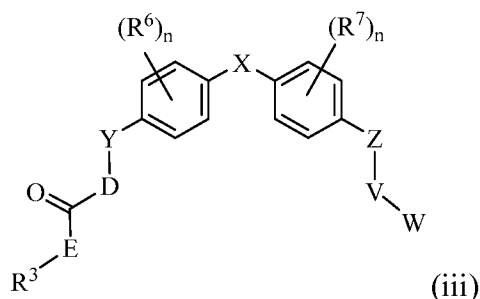
[304] each n is independently 0, 1 or 2;

[305] q is 0, 1 or 2;

[306] each g is independently 0, 1, 2, 3, or 4; and

[307] each t is independently 1 or 2.

[308] In one embodiment, the present disclosure provides androgen receptor N-terminal domain inhibitors selected from compounds of formula (iii):



[309] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[310] X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

[311] Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

[312] V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

[313] W is halogen, $-\text{NH}_2$ or $-\text{CF}_3$;

[314] D is $-\text{NR}^{10}-$ and E is $-(\text{CR}^{2a}\text{R}^{2b})_{gg}-$;

[315] or alternatively, E is $-\text{NR}^{10}-$ or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$, and D is $-(\text{CR}^{1a}\text{R}^{1b})_{qq}-$;

[316] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, C_2 – C_3 alkynyl, C_1 – C_3 alkoxy, $-\text{OCO}(C_1$ – C_3 alkyl), $-\text{NR}^{13}\text{R}^{14}$, $-(C_1$ – C_3 alkyl) $-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(C_1$ – C_3 alkyl) $-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(C_1$ – C_6 alkyl) $-\text{CONR}^{14}\text{R}^{15}$; or $(R^{1a}$ and $R^{1b})$ or $(R^{2a}$ and $R^{2b})$ taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[317] R^3 is selected from hydrogen, $-C_1-C_6$ alkyl, $-OR^{15}$, $-SR^{18}$, $-C_1-C_6$ alkoxy, $-NR^{16}R^{17}$, $-NR^{16}SR^{18}$, $-NR^{16}SOR^{18}$, $-NR^{16}SO_2R^{18}$, $-NR^{16}COR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-SOR^{18}$, or $-SO_2R^{18}$;

[318] R^6 and R^7 are each independently H, halogen, $-CN$, $-CF_3$, $-OH$, or C_1-C_3 alkyl;

[319] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-OH$, or C_1-C_3 alkyl;

[320] R^{10} is each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or $-CO(C_1-C_3$ alkyl);

[321] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

[322] m is 0, 1, 2, 3, or 4;

[323] each n is independently 0, 1 or 2;

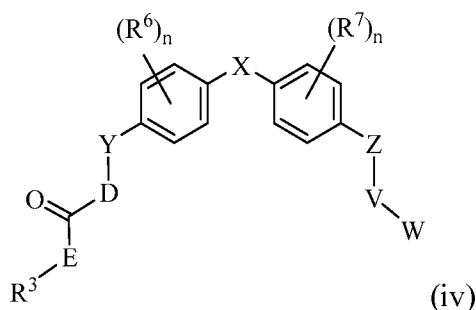
[324] q is 1 or 2;

[325] g is 0, 1, 2, 3, or 4;

[326] gg is 1, 2, 3, or 4; and

[327] t is 1 or 2.

[328] In one embodiment, the present disclosure provides androgen receptor N-terminal domain inhibitors selected from compounds of formula (iv):



[329] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[330] X is a bond, $-NR^{10}-$, or $-(CR^{8a}R^{9a})_t-$;

[331] Y and Z are each independently a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$;

[332] V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$;

[333] W is $-CF_2R^{10}$, $-NR^{13}R^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[334] D is $-(CR^{1a}R^{1b})_q-$;

[335] E is $-(CR^{2a}R^{2b})_g-$;

[336] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=O$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[337] R^3 is selected from hydrogen, $-C_1-C_6$ alkyl, $-OR^{15}$, $-SR^{18}$, $-C_1-C_6$ alkoxy, $-NR^{16}R^{17}$, $-NR^{16}SR^{18}$, $-NR^{16}SOR^{18}$, $-NR^{16}SO_2R^{18}$, $-NR^{16}COR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-SOR^{18}$, or $-SO_2R^{18}$;

[338] R^6 and R^7 are each independently H, halogen, $-CN$, $-CF_3$, $-OH$, or C_1-C_3 alkyl;

[339] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-OH$, or C_1-C_3 alkyl; or R^{8a} and R^{9a} taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

[340] R^{10} is each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or $-CO(C_1-C_3 \text{ alkyl})$;

[341] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

[342] m is 0, 1, 2, 3, or 4;

[343] each n is independently 0, 1 or 2;

[344] q is 0, 1 or 2;

[345] g is 0, 1, 2, 3, or 4; and

[346] t is 1 or 2.

[347] In one embodiment of the compounds of formula (i), R is W.

[348] In one embodiment of the compounds of formula (i), W is hydrogen, halogen, $-CF_3$, or $-NR^{13}R^{14}$. In one embodiment, W is hydrogen, halogen, $-CF_3$, or $-NH_2$. In some embodiments, W is aryl, optionally substituted with halogen, C_1-C_3 alkyl, $-CN$, $-CF_3$, $-OH$, C_1-C_3 alkoxy, $-NR^{13}R^{14}$, or $-SO_2R^{16}$. In another embodiment, W is a phenyl, optionally substituted with halogen, C_1-C_3 alkyl, $-CN$, $-CF_3$, $-OH$, or C_1-C_3 alkoxy.

[349] In one embodiment of the compounds of formula (i)-(iii), W is hydrogen, halogen, $-CF_3$, or $-NH_2$. In one embodiment, W is a halogen. In one embodiment, W is Cl, Br, I, or F. In other embodiments, W is Cl.

[350] In one embodiment of the compounds of formula (i), L is $-E-R^3$.

[351] In one embodiment of the compounds of formula (i)-(iv), X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$. In one embodiment, X is a bond. In other embodiments, X is $-(\text{CR}^8\text{R}^9)_t-$ or $-\text{NR}^{10}-$. In another embodiment, X is $-\text{NR}^{10}-$.

[352] In one embodiment of the compounds of formula (i)-(iv), X is $-\text{NR}^{10}-$, wherein R^{10} is hydrogen or optionally substituted C_1 - C_6 alkyl. In another embodiment, R^{10} is hydrogen. In some embodiments, X is $-\text{NR}^{10}-$, wherein R^{10} is methyl. In one embodiment, X is $-\text{NR}^{10}-$, wherein R^{10} is H, C_1 - C_6 alkyl, or $-\text{CO}(\text{C}_1$ - C_6 alkyl). In one embodiment, X is $-\text{NR}^{10}-$, wherein R^{10} is H, C_1 - C_6 alkyl, or $-\text{CO}(\text{C}_1$ - C_6 alkyl). In one embodiment, X is $-\text{NR}^{10}-$, wherein R^{10} is H, C_1 - C_3 alkyl, or $-\text{CO}(\text{C}_1$ - C_3 alkyl).

[353] In one embodiment of the compounds of formula (i)-(iv), X is $-(\text{CR}^8\text{R}^9)_t-$. In one embodiment, X is $-(\text{CR}^8\text{R}^9)-$, wherein R^8 and R^9 are each selected from H, halogen, $-\text{OH}$, or C_1 - C_6 alkyl. In one embodiment, X is a bond or $-(\text{CR}^{8a}\text{R}^{9a})_t-$, wherein R^{8a} and R^{9a} are each selected from H, halogen, $-\text{OH}$, or C_1 - C_6 alkyl and t is 1, or 2. In some embodiments, X is $-(\text{CR}^8\text{R}^9)_t-$, wherein each R^8 and R^9 are independently hydrogen or optionally substituted C_1 - C_6 alkyl. In some embodiments, X is $-(\text{CR}^8\text{R}^9)_t-$, wherein each R^8 and R^9 are hydrogen. In some embodiments, X is $-(\text{CR}^8\text{R}^9)_t-$, wherein each R^8 and R^9 are methyl.

[354] In one embodiment of the compounds of formula (i)-(iv), X is a bond or $-(\text{CR}^{8a}\text{R}^{9a})_t-$, wherein t is 1, or 2.

[355] In one embodiment of the compounds of formula (i)-(iv), the instance of t when X is $-(\text{CR}^8\text{R}^9)_t-$ is 1. In other embodiments, the instance of t when X is $-(\text{CR}^8\text{R}^9)_t-$ is 2.

[356] In one embodiment of the compounds of formula (i)-(iv), X $-(\text{CR}^{8a}\text{R}^{9a})_t-$, wherein R^{8a} and R^{9a} taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl. In one embodiment, X $-(\text{CR}^{8a}\text{R}^{9a})_t-$, wherein R^{8a} and R^{9a} taken together form an optionally substituted 3- to 6-membered carbocyclyl or an optionally substituted 3- to 6-membered heterocyclyl containing one heteroatom selected from O, S, or N. In one embodiment, X $-(\text{CR}^{8a}\text{R}^{9a})_t-$, wherein R^{8a} and R^{9a} taken together form a 3- to 6-membered carbocyclyl or a 3- to 6-membered heterocyclyl containing one heteroatom selected from O, S, or N. In one embodiment, X $-(\text{CR}^{8a}\text{R}^{9a})_t-$, wherein R^{8a} and R^{9a} taken together form a 4-membered heterocyclyl containing one O.

[357] In one embodiment of the compounds of formula (i)-(iv), X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$. In one embodiment, X is a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$, $-\text{N}(i\text{Pr})-$, or $-\text{N}(\text{COCH}_3)-$. In other embodiments, X is a bond, $-\text{NH}-$, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2-$, or $-\text{CH}_2\text{CH}_2-$. In other embodiments, X is a bond, $-\text{NH}-$, $-\text{N}(\text{COCH}_3)-$, $-\text{N}(\text{C}_1$ - C_3 alkyl)-, $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{OH})-$, $-\text{CHF}-$, or $-\text{CHF}_2-$. In other

embodiments, X is a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$, $-\text{N}(\text{iPr})-$, or $-\text{N}(\text{COCH}_3)-$.

[358] In one embodiment of the compounds of formula (i), Y is $-(\text{CR}^8\text{R}^9)_t-$, $-\text{O}-$, or $-\text{NR}^{10}-$. In other embodiments, Y is $-\text{O}-$. In another embodiment, Y is $-(\text{CR}^8\text{R}^9)_t-$. In another embodiment, Y is $-(\text{CR}^8\text{R}^9)_t-$, wherein each R^8 and R^9 are hydrogen.

[359] In one embodiment of the compounds of formula (i), the instance of t when Y is $-(\text{CR}^8\text{R}^9)_t-$ is 1.

[360] In one embodiment of the compounds of formula (i), Y is $-\text{NR}^{10}-$. In another embodiment, Y is $-\text{NR}^{10}-$, wherein R^{10} is hydrogen or optionally substituted C_1 – C_6 alkyl. In another embodiment, Y is $-\text{NR}^{10}-$, R^{10} is hydrogen. In another embodiment, Y is $-\text{NR}^{10}-$, R^{10} is methyl.

[361] In one embodiment of the compounds of formula (i)-(iv), Y is a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$. In one embodiment, Y is a $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$. In one embodiment, Y is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$, or $-\text{NCH}_3-$. In some embodiments, Y is a bond, $-\text{CH}_2-$, $-\text{O}-$, or $-\text{NCH}_3-$. In some embodiments, Y is a bond, $-\text{CH}_2-$, $-\text{O}-$, or $-\text{NH}-$. In some embodiments, Y is $-\text{O}-$.

[362] In one embodiment of the compounds of formula (i), Z is $-(\text{CR}^8\text{R}^9)_t$, O, or NR^{10} . In one embodiment, Z is O. In some embodiments, Z is $-(\text{CR}^8\text{R}^9)_t$. In another embodiment, Z is $-(\text{CR}^8\text{R}^9)_t$, wherein each R^8 and R^9 are hydrogen.

[363] In one embodiment of the compounds of formula (i), the instance of t when Z is $-(\text{CR}^8\text{R}^9)_t$ is 1.

[364] In one embodiment of the compounds of formula (i), Z is $-\text{NR}^{10}-$. In some embodiments, Z is $-\text{NR}^{10}-$, wherein R^{10} is hydrogen or optionally substituted C_1 – C_6 alkyl. In some embodiments, Z is $-\text{NR}^{10}-$, wherein R^{10} is hydrogen. In some embodiments, Z is $-\text{NR}^{10}-$, wherein R^{10} is methyl.

[365] In one embodiment of the compounds of formula (i)-(iii), Z is a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$. In one embodiment, Z is $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$. In one embodiment, Z is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$. In some embodiments, Z is a bond, $-\text{CH}_2-$, $-\text{O}-$, or $-\text{NCH}_3-$. In some embodiments, Z is a bond, $-\text{CH}_2-$, $-\text{O}-$, or $-\text{NH}-$. In some embodiments, Z is $-\text{O}-$.

[366] In one embodiment of the compounds of formula (i), V is a bond, $-(\text{CR}^{11}\text{R}^{12})_m-$, $-\text{C}(=\text{O})-$, $-\text{N}(\text{R}^{10})\text{CO}-$, $-\text{CONR}^{10}-$, or $-\text{NSO}_2\text{R}^{10}-$. In one embodiment, V is a bond. In other embodiments, V is optionally substituted $-\text{C}(\text{R}^{11}\text{R}^{12})_m-$. In one embodiment, is optionally

substituted $-C(R^{11}R^{12})_m-$, wherein each R^{11} and R^{12} are hydrogen. In some embodiments, V is $-(CR^{11}R^{12})_m-$.

[367] In one embodiment of the compounds of formula (i), V is $-(CR^{11}R^{12})_m-$, wherein m is 1, 2, or 3. In some embodiments, V is $-(CR^{11}R^{12})_m-$, wherein R^{11} and R^{12} are each selected from H, halogen, -OH, or C₁-C₆ alkyl. In some embodiments, V is $-(CR^{11}R^{12})_m-$, wherein m is 1, 2, or 3. In some embodiments, V is $-(CR^{11}R^{12})_m-$, wherein R^{11} and R^{12} are each selected from H, halogen, -OH, or C₁-C₃ alkyl.

[368] In one embodiment of the compounds of formula (i)-(iv), V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$.

[369] In one embodiment of the compounds of formula (i), Z is a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$; and V is $-(CR^{11}R^{12})_m-$.

[370] In one embodiment of the compounds of formula (i)-(iv), Z is a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$; V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$; and W is halogen, $-NH_2$, or $-CF_3$.

[371] In one embodiment of the compounds of formula (i)-(iv), Z is a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$; V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$; and W is halogen, $-NH_2$, or $-CF_3$.

[372] In one embodiment of the compounds of formula (i), m is 1 or 2. In some embodiments, m is 1.

[373] In one embodiment of the compounds of formula (i), each R^8 and R^9 are independently hydrogen or optionally substituted C₁-C₆ alkyl.

[374] In one embodiment of the compounds of formula (i), R^{1a} and R^{1b} are each hydrogen or optionally substituted C₁₋₆ alkyl. In other embodiments, R^{1a} and R^{1b} are each hydrogen.

[375] In one embodiment of the compounds of formula (i), R^{2a} and R^{2b} are each hydrogen or optionally substituted C₁₋₆ alkyl. In other embodiments, R^{2a} and R^{2b} are each hydrogen.

[376] In one embodiment of the compounds of formula (i)-(iv), R^3 is selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted $-OR^{15}$, optionally substituted $-SR^{18}$, optionally substituted C₁-C₆ alkoxy, $-NR^{16}R^{17}$, $-NR^{16}SR^{18}$, $-NR^{16}SOR^{18}$, $-NR^{16}SO_2R^{18}$, $-NR^{16}COR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-SOR^{18}$, or optionally substituted $-SO_2R^{18}$. In one embodiment, R^3 is selected from hydrogen, $-C_1-C_3$ alkyl, $-NR^{16}SO(C_1-C_3 \text{ alkyl})$, $-NR^{16}SO_2(C_1-C_3 \text{ alkyl})$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-SOR^{18}$,

or $-\text{SO}_2\text{R}^{18}$. In other embodiments, R^3 is selected from $-\text{NHSO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NCH}_3\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, or $-\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$.

[377] In one embodiment of the compounds of formula (i)-(iv), R^3 is $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{NR}^{16}\text{S}(\text{O})_p\text{R}^{18}$, $-\text{S}(\text{O})_p\text{R}^{18}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In other embodiments, R^3 is $-\text{NR}^{16}\text{R}^{17}$. In one embodiment, R^3 is $-\text{NR}^{16}\text{S}(\text{O})_p\text{R}^{18}$ or $-\text{S}(\text{O})_p\text{R}^{18}$.

[378] In one embodiment of the compounds of formula (i)-(iv), R^3 is hydrogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$ alkynyl, optionally substituted $-\text{OR}^{15}$, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, $-\text{NH}_2$, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{NR}^{16}\text{S}(\text{O})_p\text{R}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-\text{S}(\text{O})_p\text{R}^{18}$, $-\text{N}_3$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In some embodiments, R^3 is hydrogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, optionally substituted $\text{C}_1\text{--C}_3$ alkyl, optionally substituted $\text{C}_2\text{--C}_3$ alkenyl, optionally substituted $\text{C}_2\text{--C}_3$ alkynyl, optionally substituted $-\text{OR}^{15}$, optionally substituted $\text{C}_1\text{--C}_3$ alkoxy, $-\text{NH}_2$, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{NR}^{16}\text{S}(\text{O})_p\text{R}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-\text{S}(\text{O})_p\text{R}^{18}$, $-\text{N}_3$, optionally substituted 3- to 7-membered carbocyclyl, optionally substituted 3- to 7-membered heterocyclyl, optionally substituted 6- to 12-membered aryl, or optionally substituted 5- to 12-membered heteroaryl. In other embodiments, R^3 is hydrogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, optionally substituted $\text{C}_1\text{--C}_3$ alkyl, optionally substituted $\text{C}_2\text{--C}_3$ alkenyl, optionally substituted $\text{C}_2\text{--C}_3$ alkynyl, optionally substituted $-\text{OR}^{15}$, optionally substituted $\text{C}_1\text{--C}_3$ alkoxy, $-\text{NH}_2$, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{NR}^{16}\text{S}(\text{O})_p\text{R}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-\text{S}(\text{O})_p\text{R}^{18}$, or $-\text{N}_3$. In one embodiment, R^3 is optionally substituted 3- to 7-membered carbocyclyl, optionally substituted 3- to 7-membered heterocyclyl, optionally substituted 6-membered aryl, or optionally substituted 5- to 6-membered heteroaryl.

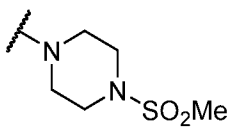
[379] In one embodiment of the compounds of formula (i)-(iv), R^3 is selected from hydrogen, $\text{C}_1\text{--C}_6$ alkyl, $\text{C}_1\text{--C}_6$ alkoxy, $-\text{NHSO}_2(\text{C}_1\text{--C}_6 \text{ alkyl})$, $-\text{NCH}_3\text{SO}_2(\text{C}_1\text{--C}_6 \text{ alkyl})$, $-\text{SO}_2(\text{C}_1\text{--C}_6 \text{ alkyl})$, $-\text{NHCO}(\text{C}_1\text{--C}_6 \text{ alkyl})$, or $-\text{N}(\text{C}_1\text{--C}_6 \text{ alkyl})\text{CO}(\text{C}_1\text{--C}_6 \text{ alkyl})$. In another embodiment, R^3 is hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_1\text{--C}_3$ alkoxy, $-\text{NHSO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NCH}_3\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NHCO}(\text{C}_1\text{--C}_3 \text{ alkyl})$, or $-\text{N}(\text{C}_1\text{--C}_3 \text{ alkyl})\text{CO}(\text{C}_1\text{--C}_3 \text{ alkyl})$. In other embodiments, R^3 is selected from $-\text{NHSO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NCH}_3\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, or $-\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$. In one embodiment, R^3 is selected from hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, $\text{C}_1\text{--C}_3$ alkoxy, $-\text{S}(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{SO}(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NHSO}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{NHSO}_2\text{CH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)\text{SO}_2\text{CH}_3$, $-\text{SO}_2\text{NH}_2$, $-\text{CONH}_2$,

-CON(C₁-C₃ alkyl)₂, -CONH(C₁-C₃ alkyl), -NHCO(C₁-C₃ alkyl), or -N(CH₃)CO(C₁-C₃ alkyl). In one embodiment, R³ is selected from hydrogen, methyl, ethyl, propyl, isopropyl, methoxy, -SO₂CH₃, -NHSO₂CH₃, or -N(CH₃)SO₂CH₃. In one embodiment, R³ is selected from -SO₂CH₃, -NHSO₂CH₃, or -N(CH₃)SO₂CH₃.

[380] In one embodiment of the compounds of formula (i)-(iv), R³ is C₁-C₆ alkyl.

[381] In one embodiment of the compounds of formula (i)-(iv), R³ is -NR¹⁶R¹⁷, wherein R¹⁶ and R¹⁷ are taken together to form an 3- to 7-membered optionally substituted heterocyclyl. In one embodiment, R³ is -NR¹⁶R¹⁷, wherein R¹⁶ and R¹⁷ are taken together to form a 6-membered optionally substituted heterocycle. In one embodiment, R³ is -NR¹⁶R¹⁷, wherein R¹⁶ and R¹⁷ are taken together to form a 6-membered optionally substituted heterocycle. In one embodiment, R³ is -NR¹⁶R¹⁷, wherein R¹⁶ and R¹⁷ are taken together to form an optionally substituted piperazine. In one embodiment, R³ is -NR¹⁶R¹⁷, wherein R¹⁶ and R¹⁷ are taken together to form a piperazine, optionally substituted with -SO₂CH₃, -NHSO₂CH₃, or -

N(CH₃)SO₂CH₃. In one embodiment, R³ is



[382] In one embodiment of the compounds of formula (i)-(iv), R¹⁶ and R¹⁷ are taken together with the intervening atom to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R¹⁶ and R¹⁷ are taken together to form an optionally substituted heterocyclyl. In some embodiments, R¹⁶ and R¹⁷ are taken together to form an 3- to 7-membered optionally substituted heterocyclyl. In some embodiments, R¹⁶ and R¹⁷ are taken together to form an 3- to 7-membered optionally substituted heterocyclyl, comprising one or more heteroatoms selected from N, O, or S.

[383] In one embodiment of the compounds of formula (i)-(iv), R¹⁶ is hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, R¹⁶ is hydrogen or optionally substituted C₁-C₆ alkyl. In some embodiments, R¹⁶ is hydrogen or C₁-C₆ alkyl. In some embodiments, R¹⁶ is hydrogen or C₁-C₃ alkyl.

[384] In one embodiment of the compounds of formula (i)-(iv), R¹⁷ is hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, R¹⁷ is hydrogen or

optionally substituted C₁–C₆ alkyl. In some embodiments, R¹⁷ is hydrogen or C₁–C₆ alkyl. In some embodiments, R¹⁷ is hydrogen or C₁–C₃ alkyl.

[385] In one embodiment of the compounds of formula (i)–(iv), R¹⁸ is hydrogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, R¹⁸ is hydrogen or optionally substituted C₁–C₆ alkyl. In some embodiments, R¹⁸ is hydrogen or C₁–C₆ alkyl. In some embodiments, R¹⁸ is hydrogen or C₁–C₃ alkyl.

[386] In one embodiment of the compounds of formula (i), R¹⁸ is C₁–C₆ alkyl; and p is 2.

[387] In one embodiment of the compounds of formula (i), R^{2a}, R^{2b} and R³ taken together with the intervening atom are optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In other embodiments, R^{2a}, R^{2b} and R³ taken together with the intervening atom are optionally substituted heteroaryl. In some embodiments, R^{2a}, R^{2b} and R³ taken together with the intervening atom are optionally substituted tetrazolyl, imidazolyl, 1,2,3–triazolyl, oxazole, pyrazinyl, pyrimidinyl, or 1,3,5–triazinyl.

[388] In one embodiment of the compounds of formula (i), R^{4a} is hydrogen, halogen, optionally substituted C_{1–6} alkyl, or optionally substituted C_{1–6} alkoxy. In some embodiments, R^{4a} is optionally substituted C_{1–6} alkyl or hydrogen. In other embodiments, R^{4a} is hydroxy.

[389] In one embodiment of the compounds of formula (i), R^{4b} is hydrogen, halogen, optionally substituted C_{1–6} alkyl, or optionally substituted C_{1–6} alkoxy. In some embodiments, R^{4b} is hydrogen.

[390] In one embodiment of the compounds of formula (i), R^{5a} is hydrogen, halogen, optionally substituted C_{1–6} alkyl, or optionally substituted C_{1–6} alkoxy. In one embodiment, R^{5a} is hydrogen.

[391] In one embodiment of the compounds of formula (i), R^{5b} is hydrogen, halogen, optionally substituted C_{1–6} alkyl, or optionally substituted C_{1–6} alkoxy. In one embodiment, R^{5b} is hydrogen.

[392] In one embodiment of the compounds of formula (i), n is 1. In other embodiments, n is 2.

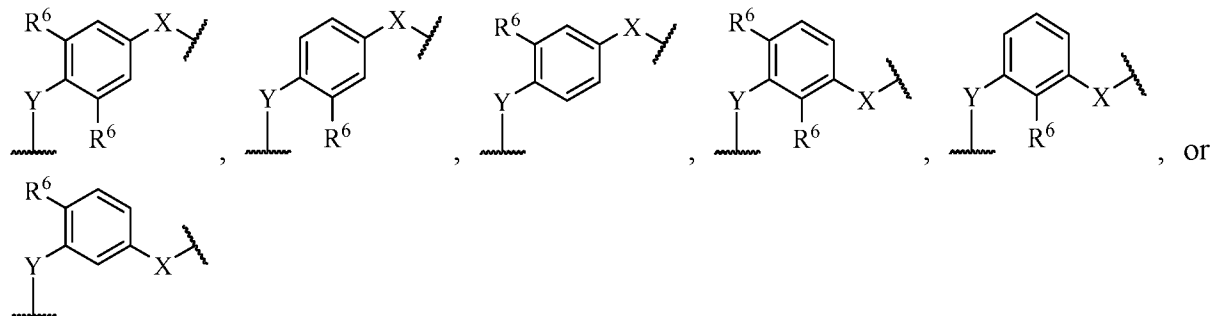
[393] In one embodiment of the compounds of formula (i), R⁶ and R⁷ are each independently halogen, –CN, –CF₃, –OH, optionally substituted C₁–C₆ alkyl, optionally substituted C₁–C₆ alkoxy, optionally substituted –(C₁–C₆ alkyl)–(C₁–C₆ alkoxy), optionally substituted –(C₁–C₆ alkyl)–OH, –NR¹³R¹⁴, optionally substituted –(C₁–C₆ alkyl)–NR¹³R¹⁴, –NR¹⁴SO₂R¹⁶,

optionally substituted $-(C_1-C_6 \text{ alkyl})NR^{14}SO_2R^{16}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-SO_2NR^{14}R^{15}$, optionally substituted $-SO_2R^{16}$, or optionally substituted $-(C_1-C_6 \text{ alkyl})-SO_2R^{16}$. In one embodiment, R^6 and R^7 are each independently halogen, $-CN$, $-CF_3$, $-OH$, optionally substituted C_1-C_3 alkyl, C_1-C_3 alkoxy, optionally substituted $-(C_1-C_3 \text{ alkyl})-(C_1-C_3 \text{ alkoxy})$, optionally substituted $-(C_1-C_3 \text{ alkyl})-OH$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}SO_2R^{16}$, optionally substituted $-(C_1-C_3 \text{ alkyl})NR^{14}SO_2R^{16}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_1-C_3 \text{ alkyl})-CONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-(C_1-C_3 \text{ alkyl})-SO_2NR^{14}R^{15}$, $-SO_2R^{16}$, or optionally substituted $-(C_1-C_3 \text{ alkyl})-SO_2R^{16}$. In one embodiment, R^6 and R^7 are each independently halogen, $-CN$, $-CF_3$, $-OH$, C_1-C_3 alkyl, C_1-C_3 alkoxy, $-(C_1-C_3 \text{ alkyl})-(C_1-C_3 \text{ alkoxy})$, $-(C_1-C_3 \text{ alkyl})-OH$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}SO_2R^{16}$, $-(C_1-C_3 \text{ alkyl})NR^{14}SO_2R^{16}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, $-(C_1-C_3 \text{ alkyl})-CONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-(C_1-C_3 \text{ alkyl})-SO_2NR^{14}R^{15}$, $-SO_2R^{16}$, or $-(C_1-C_3 \text{ alkyl})-SO_2R^{16}$. In one embodiment, R^6 and R^7 are each independently halogen, $-CN$, $-CF_3$, $-OH$, C_1-C_3 alkyl, or $-CONR^{14}R^{15}$. In some embodiments, R^6 and R^7 are each independently halogen, $-CN$, $-CF_3$, $-OH$, methyl, methoxy, or $-CONH_2$. In one embodiment, R^6 and R^7 are each independently Cl, $-CN$, $-CF_3$, $-OH$, methyl, methoxy, or $-CONH_2$.

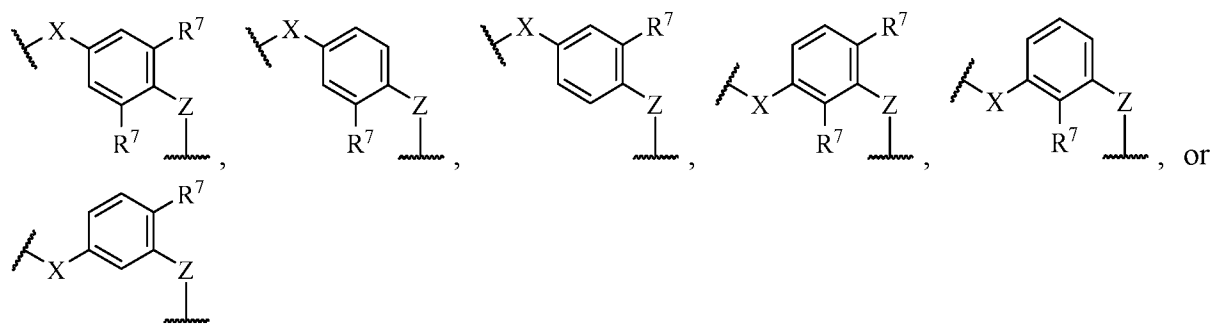
[394] In one embodiment of the compounds of formula (i), R^6 and R^7 are each independently optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, R^6 and R^7 are each independently 3- to 7-membered carbocyclyl, 3- to 7-membered heterocyclyl, phenyl, or 5- to 6-membered heteroaryl.

[395] In one embodiment of the compounds of formula (i)-(iv), R^6 and R^7 is each independently halogen, $-CN$, $-CF_3$, $-OH$, methyl, or methoxy. In one embodiment, R^6 and R^7 are each independently halogen, $-CN$, $-CF_3$, $-OH$, or methyl. In one embodiment, R^6 and R^7 are each independently H, halogen, $-CN$, or methyl. In another embodiment, R^6 and R^7 is each independently Cl, $-CN$, $-CF_3$, $-OH$, methyl, or methoxy. In one embodiment, R^6 and R^7 is each independently H, methyl, methoxy, CN, F, Cl, Br, or I. In one embodiment of the compounds of formula (i)-(iv), R^6 and R^7 is independently H, methyl, methoxy, CN, F, Cl, Br, I, ^{123}I or CF_3 . In other embodiments, R^6 and R^7 is F, Cl, Br, or I. In one embodiment, each occurrence of R^6 and R^7 is Cl.

[396] In one embodiment of the compounds of formula (i)-(iv), R^6 have one of the connectivity as shown below with respect to X and Y:



[397] In one embodiment of the compounds of formula (i)-(iv), R^7 have one of the connectivity as shown below with respect to X and Z:



[398] In one embodiment of the compounds of formula (i)-(iv), n in $-(R^6)_n$ is 0, 1, or 2. In some embodiments, n is 0 or 1. In other embodiments, n is 0. In some embodiments, n is 1.

[399] In one embodiment of the compounds of formula (i)-(iv), n in $-(R^7)_n$ is 0, 1, or 2. In some embodiments, n is 0 or 1. In other embodiments, n is 0. In some embodiments, n is 1.

[400] In one embodiment of the compounds of formula (i)-(iv), the sum of n in $-(R^6)_n$ and $-(R^7)_n$ is 0, 1, 2, 3, or 4. In some embodiments, the sum of n in $-(R^6)_n$ and $-(R^7)_n$ is 1, 2, 3, or 4. In some embodiments, the sum of n in $-(R^6)_n$ and $-(R^7)_n$ is 2 or 4. In some embodiments, the sum of n in $-(R^6)_n$ and $-(R^7)_n$ is 2.

[401] In one embodiment of the compounds of formula (i), A and B are each independently 5- or 6-membered aryl or heteroaryl. In other embodiments, A and B are each independently selected from phenyl, pyridyl, pyrimidyl, or thiophene. In one embodiment, A and B are each phenyl.

[402] In one embodiment of the compounds of formula (i), A has a meta or para connectivity with X and Y. In one embodiment of the compounds of formula (i), B has a meta or para connectivity with X and Z.

[403] In one embodiment of the compounds of formula (i)-(iv), D is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, or $-\text{CH}_2\text{CH}_2-$. In one embodiment, D is $-(\text{CH}_2)_2-$.

[404] In one embodiment of the compounds of formula (i), D is $-(CR^{1a}R^{1b})_q-$; E is $-O-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$; and q is 1 or 2.

[405] In one embodiment of the compounds of formula (i), D is $-O-$ or $-NR^{10}-$; E is $-(CR^{2a}R^{2b})_g-$; and g is 1, 2, 3, or 4.

[406] In one embodiment of the compounds of formula (i), D is $-O-$ or $-NR^{10}-$; and E is $-O-$, $-NR^{10}-$ or $-NR^{10}-(CR^{2a}R^{2b})_g-$.

[407] In one embodiment of the compounds of formula (i), R^{8b} and R^{9b} are each independently hydrogen, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_1-C_6 alkoxy, $-NR^{13}R^{14}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, R^{11} and R^{12} are not $-OH$.

[408] In one embodiment of the compounds of formula (i), R^{11} and R^{12} are each independently hydrogen, halogen, $-OH$, or C_1-C_3 alkyl.

[409] In one embodiment of the compounds of formula (i), g is independently 0, 1, 2, or 3.

[410] In one embodiment of the compounds of formula (i), R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=O$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl.

[411]

[412] In one embodiment of the compounds of formula (i)-(iii), q is 0.

[413] In one embodiment of the compounds of formula (i)-(iii), E is $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$.

[414] In one embodiment of the compounds of formula (i)-(iii), g is 0.

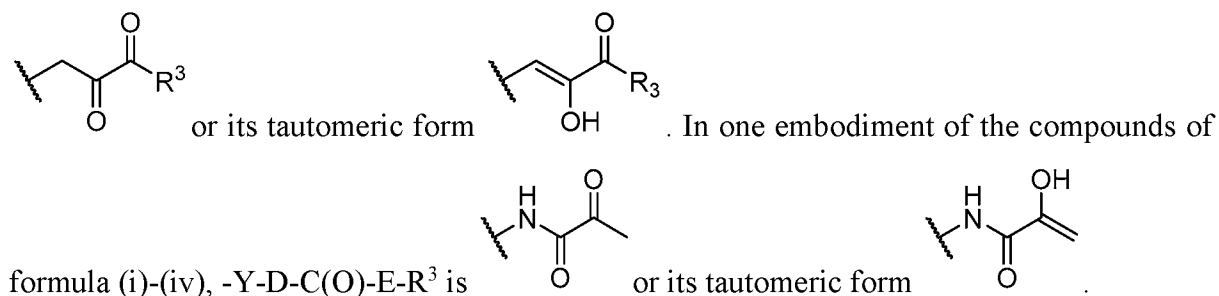
[415] In one embodiment of the compounds of formula (i)-(iii), at least one of Z and Y is $-O-$.

[416] In one embodiment of the compounds of formula (i) or (iv), Y is $-O-$, D is $-(CR^{1a}R^{1b})_q-$, L is $-(CR^{2a}R^{2b})-R^3$, and R^3 is $-NR^{16}S(O)_pR^{18}$. In one embodiment, Y is $-O-$, D is $-(CR^{1a}R^{1b})-$, L is $-(CR^{2a}R^{2b})-R^3$, and R^3 is $-NR^{16}S(O)_2(C_1-C_3 \text{ alkyl})$. In one embodiment, Y is $-O-$, D is $-CH_2-$, $-CH(CH_3)-$, or $-C(CH_3)_2-$, L is $-CH_2-R^3$, and R^3 is $-NHS(O)_2CH_3$.

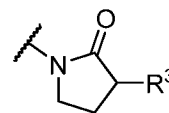
[417] In one embodiment of the compounds of formula (i)-(iii), when E is $-O-$, R^3 is hydrogen, $-CF_3$, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In other embodiments, when E is $-O-$, R^3 is hydrogen, $-CF_3$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl.

[418] In one embodiment of the compounds of formula (i)-(iv), at least one of Z and Y is $-O-$.

[419] In one embodiment of the compounds of formula (i)-(iv), $-D-C(O)-E-R^3$ is



[420] In one embodiment of the compounds of formula (i), $-D-C(O)-E-R^3$ is



[421] In one embodiment of the compounds of formula (i)-(iv), R^{1a} , and R^{1b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$; or R^{1a} and R^{1b} taken together form an oxo ($=O$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl. In some embodiments, R^{1a} , and R^{1b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$. In one embodiment, R^{1a} and R^{1b} are each hydrogen or R^{1a} and R^{1b} taken together form an oxo ($=O$).

[422] In one embodiment of the compounds of formula (i)-(iv), R^{2a} and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$; or R^{2a} and R^{2b} taken together form an oxo ($=O$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl. In some embodiments, R^{2a} and R^{2b} are each independently hydrogen, halogen, $-$

OH, C₁–C₃ alkyl, C₂–C₃ alkenyl, C₂–C₃ alkynyl, C₁–C₃ alkoxy, –OCO(C₁–C₃ alkyl), –NR¹³R¹⁴, –(C₁–C₃ alkyl)–NR¹³R¹⁴, –NR¹⁴COR¹⁶, –(C₁–C₃ alkyl)–NR¹⁴COR¹⁶, –CONR¹⁴R¹⁵, or –(C₁–C₆ alkyl)–CONR¹⁴R¹⁵. In one embodiment, R^{2a} and R^{2b} are each hydrogen or R^{2a} and R^{2b} taken together form an oxo (=O).

[423] In one embodiment of the compounds of formula (ii)-(iii) R^{8a} and R^{9a} are each independently hydrogen, halogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted C₁–C₆ alkoxy, –NR¹³R¹⁴, optionally substituted –(C₁–C₆ alkyl)–NR¹³R¹⁴, –NR¹⁴COR¹⁶, optionally substituted –(C₁–C₆ alkyl)–NR¹⁴COR¹⁶, –CONR¹⁴R¹⁵, optionally substituted –(C₁–C₆ alkyl)–CONR¹⁴R¹⁵, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, R^{8a} and R^{9a} are each independently hydrogen, halogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted C₁–C₆ alkoxy, –NR¹³R¹⁴, optionally substituted –(C₁–C₆ alkyl)–NR¹³R¹⁴, –NR¹⁴COR¹⁶, optionally substituted –(C₁–C₆ alkyl)–NR¹⁴COR¹⁶, –CONR¹⁴R¹⁵, or optionally substituted –(C₁–C₆ alkyl)–CONR¹⁴R¹⁵. In one embodiment, R^{8a} and R^{9a} hydrogen, halogen, –OH, or C₁–C₃ alkyl. In one embodiment, R^{8a} and R^{9a} hydrogen, halogen, –OH, or methyl. In one embodiment, R^{8a} and R^{9a} hydrogen, F, –OH, or methyl.

[424] In one embodiment of the compounds of formula (i)-(iv), R¹⁰ is hydrogen, halogen, optionally substituted C₁–C₆ alkyl, or optionally substituted C₁–C₆ alkoxy. In some embodiments, R¹⁰ is hydrogen, C₁–C₆ alkyl, or C₁–C₆ alkoxy. In some embodiments, R¹⁰ is hydrogen, C₁–C₃ alkyl, or C₁–C₃ alkoxy.

[425] In one embodiment of the compounds of formula (i), R^{2a} and R¹⁰ taken together form an optionally substituted heterocyclyl. In one embodiment, R^{2a} and R¹⁰ taken together form an optionally substituted 5- or 6-membered heterocyclyl.

[426] In one embodiment of the compounds of formula (i)-(iv), R¹³ is hydrogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, R¹³ is hydrogen or optionally substituted C₁–C₆ alkyl. In some embodiments, R¹³ is hydrogen or C₁–C₆ alkyl. In some embodiments, R¹³ is hydrogen or C₁–C₃ alkyl.

[427] In one embodiment of the compounds of formula (i)-(iv), R¹⁴ is hydrogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally

substituted aryl, or optionally substituted heteroaryl. In one embodiment, R¹⁴ is hydrogen or optionally substituted C₁–C₆ alkyl. In some embodiments, R¹⁴ is hydrogen or C₁–C₆ alkyl. In some embodiments, R¹⁴ is hydrogen or C₁–C₃ alkyl.

[428] In one embodiment of the compounds of formula (i)-(iv), R¹⁵ is hydrogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In one embodiment, R¹⁵ is hydrogen or optionally substituted C₁–C₆ alkyl. In some embodiments, R¹⁵ is hydrogen or C₁–C₆ alkyl. In some embodiments, R¹⁵ is hydrogen or C₁–C₃ alkyl.

[429] In one embodiment of the compounds of formula (i)-(iv), R¹⁴ and R¹⁵ are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R¹⁴ and R¹⁵ are taken together to form an optionally substituted heterocyclyl. In some embodiments, R¹⁴ and R¹⁵ are taken together to form an 3- to 7-membered optionally substituted heterocyclyl. In some embodiments, R¹⁴ and R¹⁵ are taken together to form an 3- to 7-membered optionally substituted heterocyclyl, comprising one or more heteroatoms selected from N, O, or S.

[430] In one embodiment of the compounds of formula (i)-(iv), R¹¹ and R¹² are each independently hydrogen, halogen, –OH, or C₁–C₃ alkyl. In one embodiment, R¹¹ and R¹² are each independently hydrogen, halogen, or C₁–C₃ alkyl. In one embodiment, R¹¹ and R¹² are not –OH.

[431] In one embodiment of the compounds of formula (i)-(iv), g is independently 0, 1, 2, or 3. In one embodiment, g is 0. In another embodiment, g is 1, 2, or 3. In some embodiments, g is 1 or 2.

[432] In one embodiment of the compounds of formula (i), n is S(O)_n is 2. In another embodiment, n is 1 or 2. In some embodiments, n is 0.

[433] In one embodiment of the compounds of formula (i)-(iv), p is 2. In another embodiment, p is 1 or 2. In some embodiments, p is 0.

[434] In one embodiment of the compounds of formula (i)-(iv), q is 0. In another embodiment, q is 1. In one embodiment, q is 2.

[435] In one embodiment of the compounds of formula (i)-(iv), t is 1. In one embodiment, t is 2.

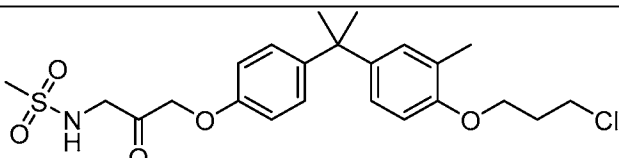
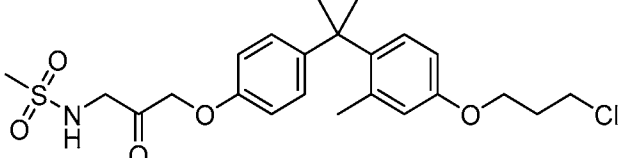
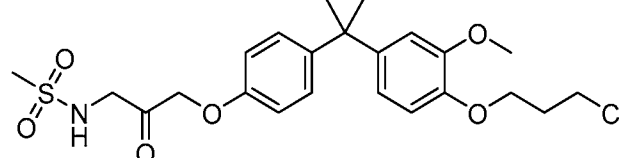
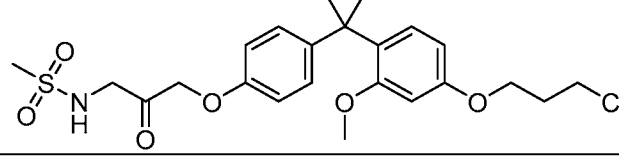
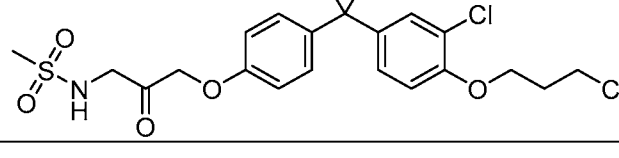
[436] In one embodiment of the compounds of formula (iii), gg is 1, 2, or 3. In some embodiments, gg is 1 or 2.

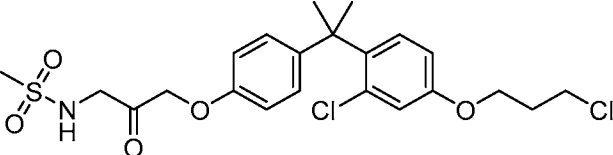
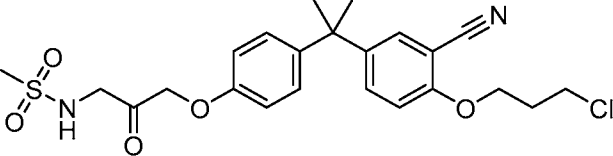
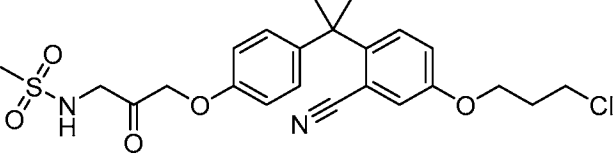
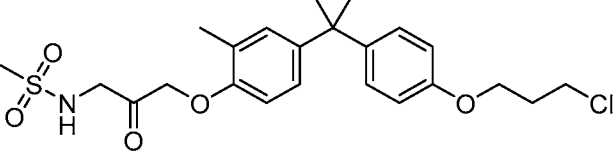
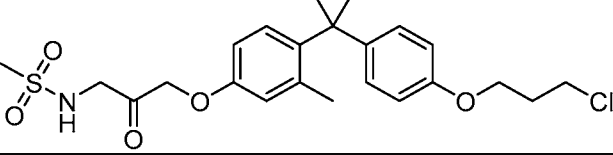
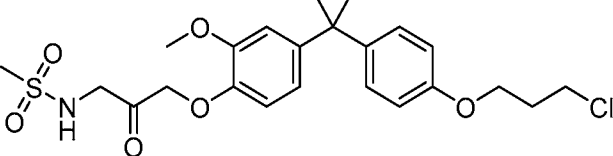
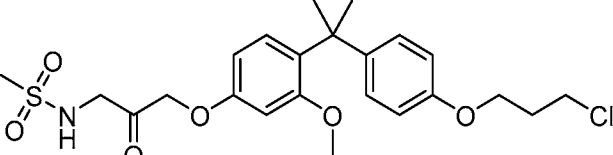
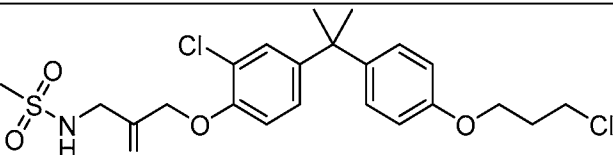
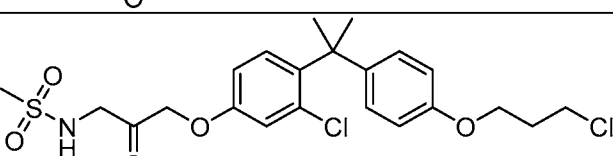
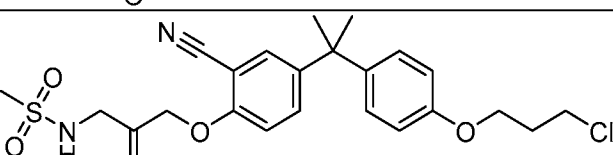
[437] In one embodiment of the compounds of formula (i), Z and V are not both a bond or absent (e.g., m is 0 in $-(CR^{11}R^{12})_m-$).

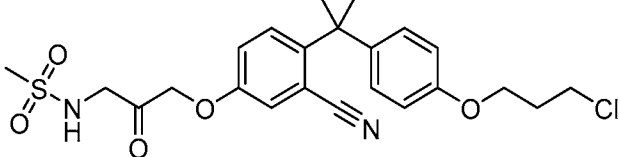
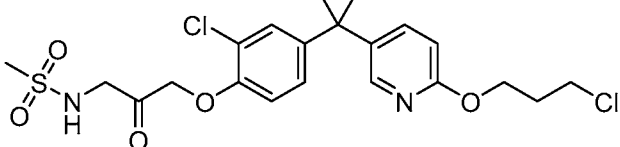
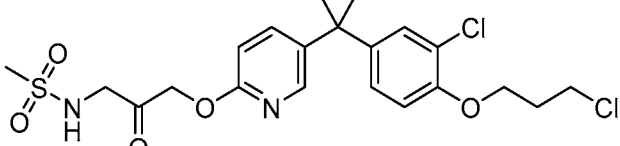
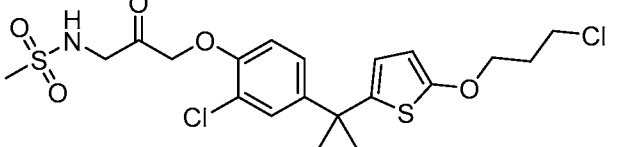
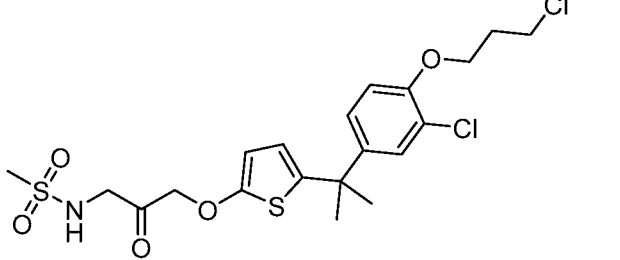
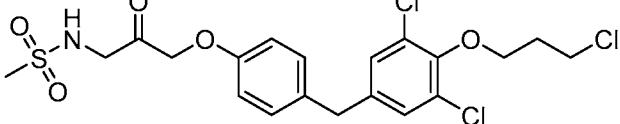
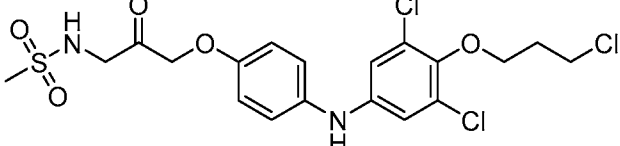
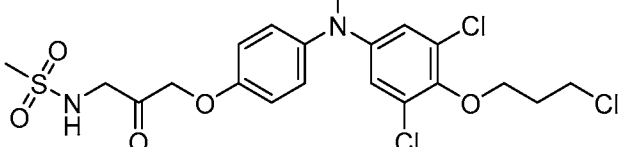
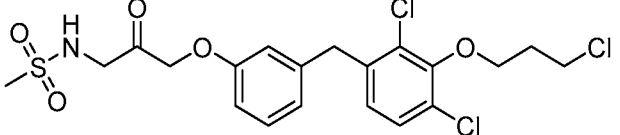
[438] In one embodiment, the present disclosure provides compounds as disclosed in Table A or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof. In one embodiment, the present disclosure provides androgen receptor N-terminal domain inhibitors selected from Compounds **AA1-AA98**, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof. In one embodiment, the present disclosure provides androgen receptor N-terminal domain inhibitors selected from Compounds **AA99-AA104**, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof. In one embodiment, the present disclosure provides androgen receptor N-terminal domain inhibitors selected from Compounds **AA1-AA104**, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof.

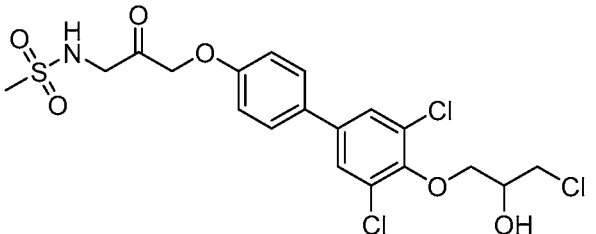
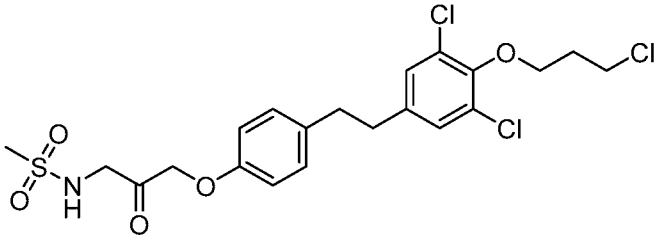
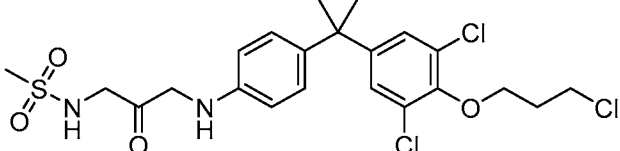
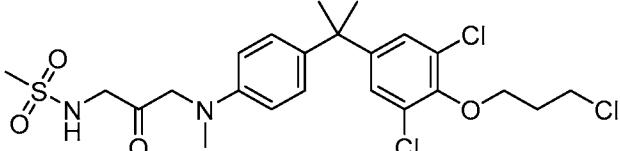
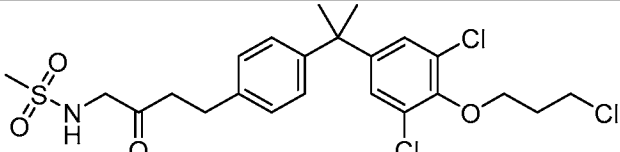
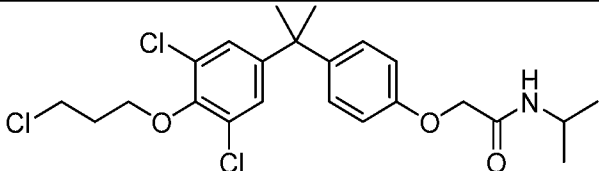
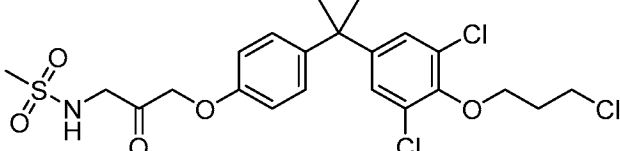
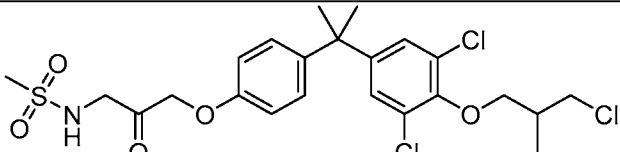
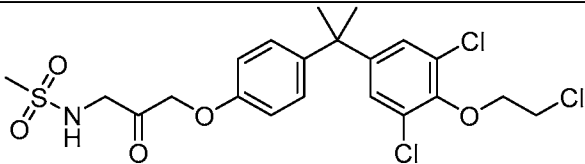
[439] The compounds disclosed in WO 2019/226991 can be useful androgen receptor N-terminal domain inhibitors for the present invention. The disclosure of WO 2019/226991 is incorporated by reference in its entirety for all purposes.

[440] **Table A.** Androgen Receptor Modulators

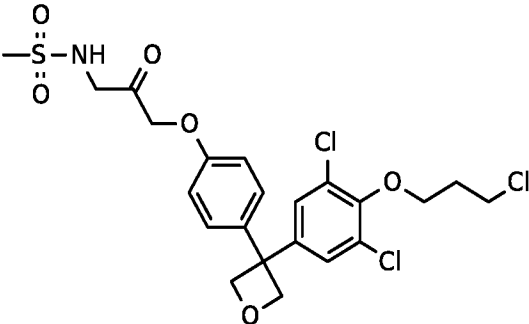
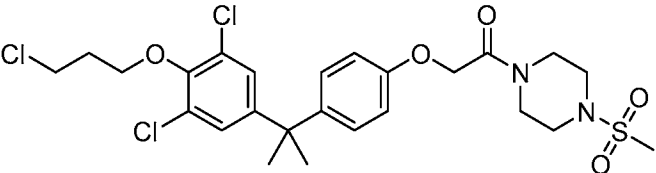
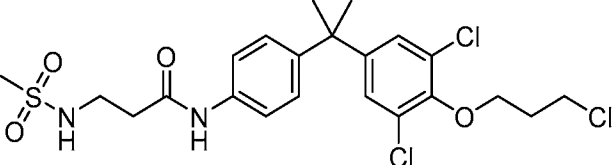
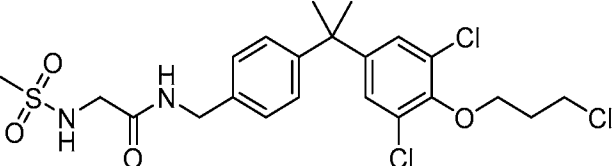
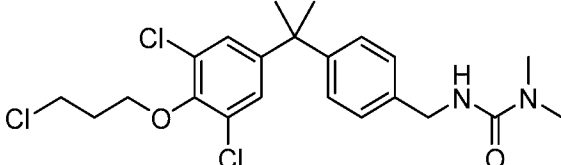
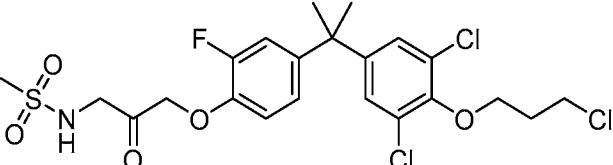
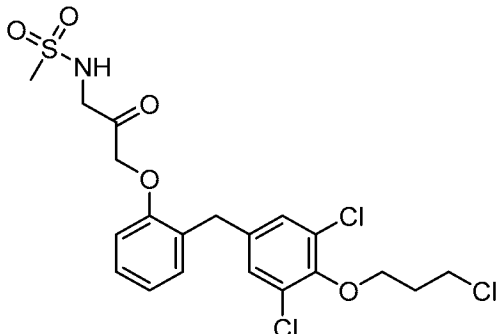
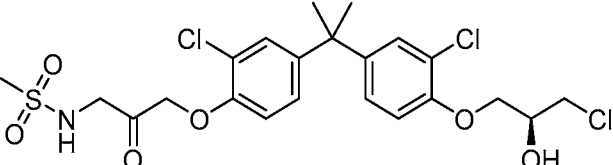
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AA2	
AA3	
AA4	
AA5	

Compound ID	Structure
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AA7	
AA8	
AA9	
AA10	
AA11	
AA12	
AA13	
AA14	
AA15	

Compound ID	Structure
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AA18	
AA19	
AA20	
AA21	
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AA23	
AA24	

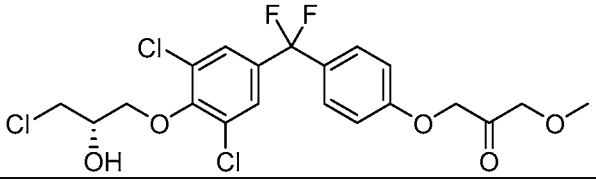
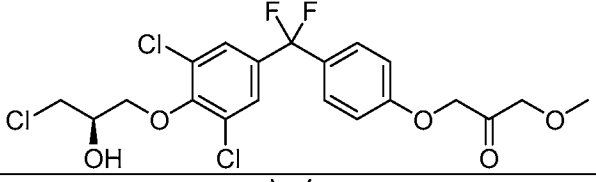
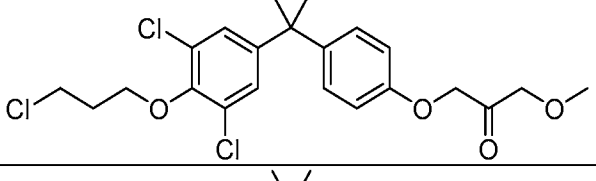
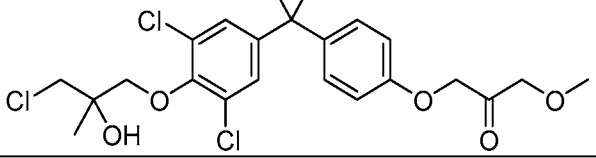
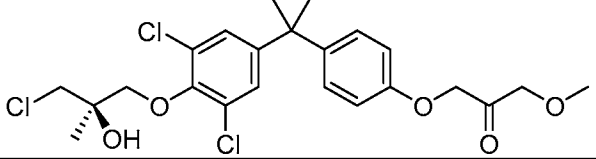
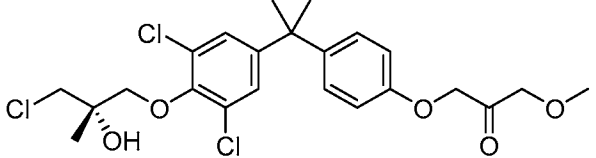
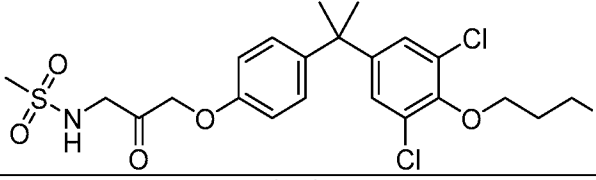
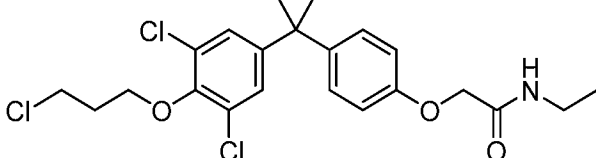
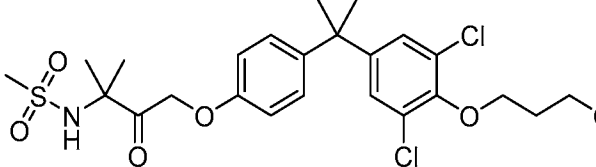
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AA33	

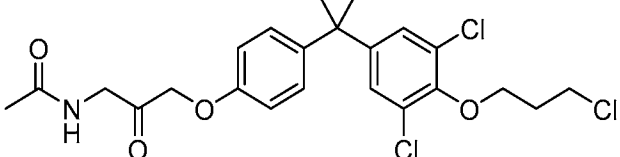
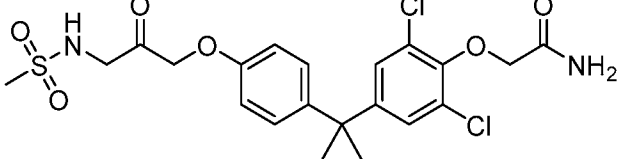
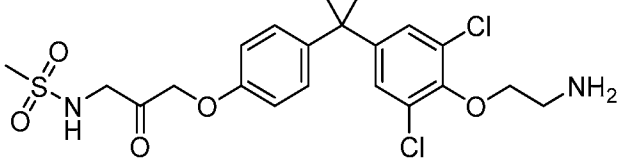
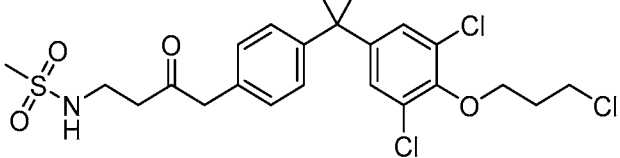
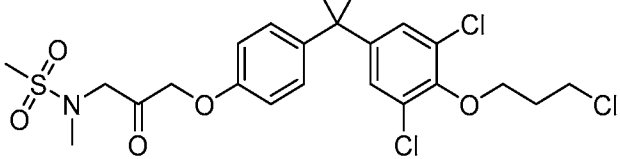
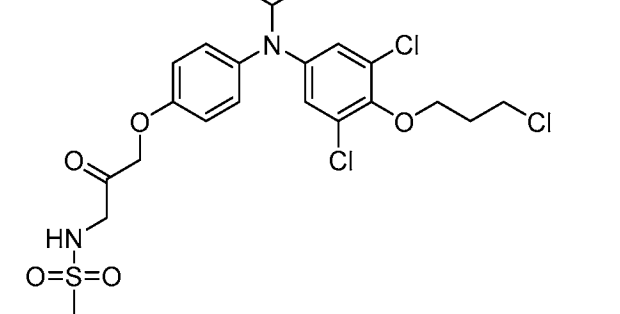
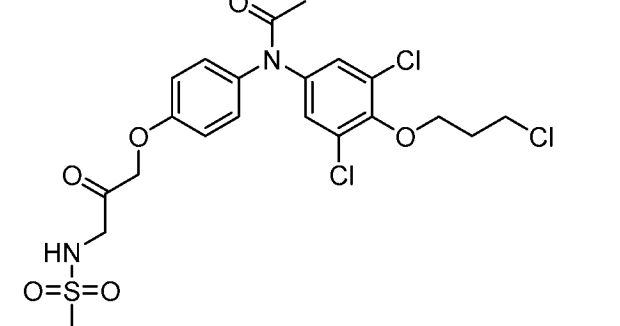
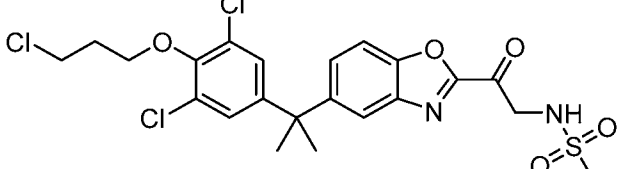
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AA42	

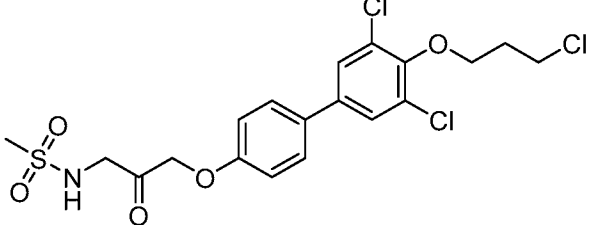
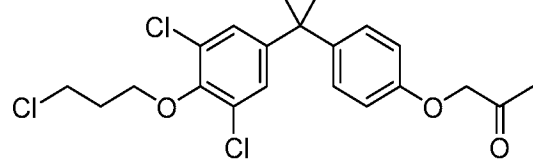
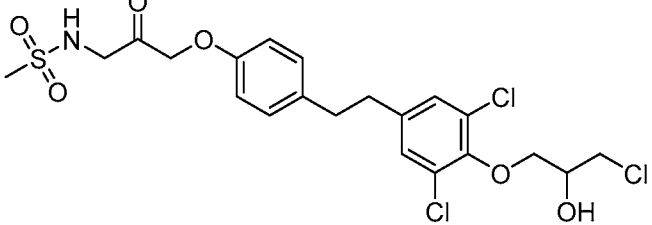
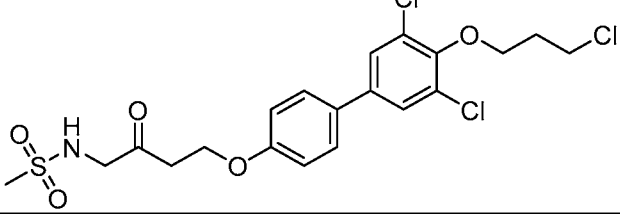
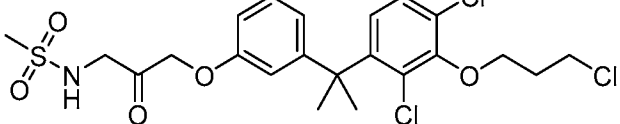
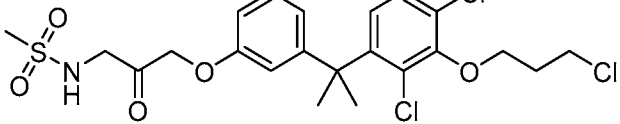
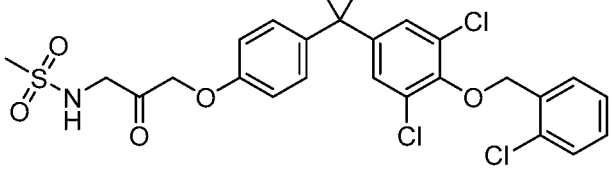
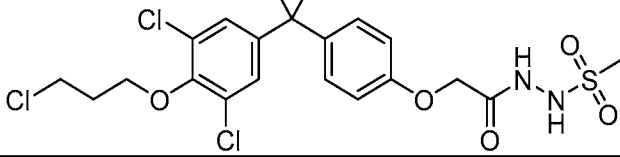
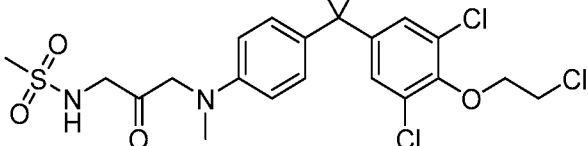
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AA49	
AA50	

Compound ID	Structure
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AA51(R)	
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AA52(S)	
AA52(R)	
AA53	
AA53(S)	
AA53(R)	
AA54	

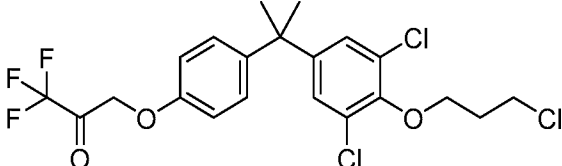
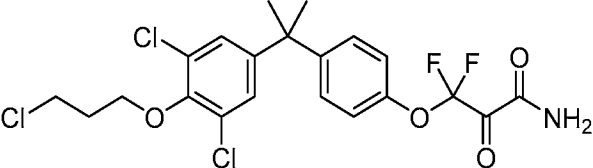
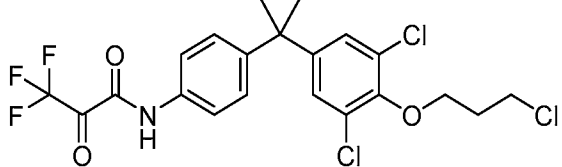
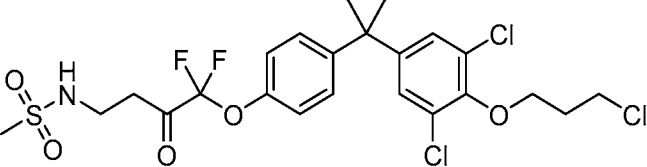
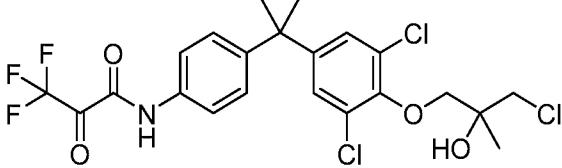
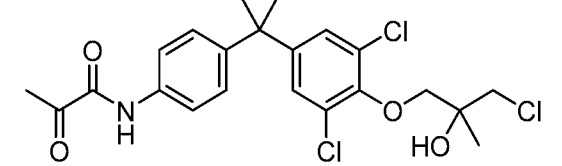
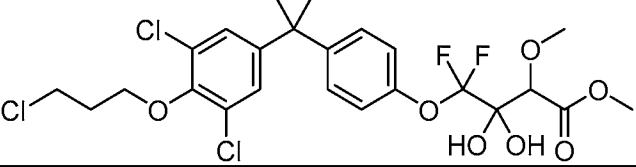
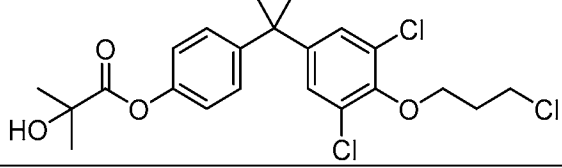
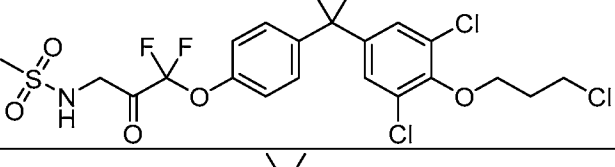
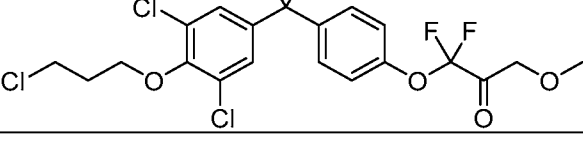
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AA54(R)	
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AA56	
AA56(S)	
AA56(R)	
AA57	
AA57(S)	
AA57(R)	
AA58	

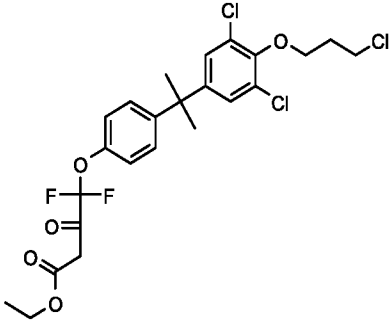
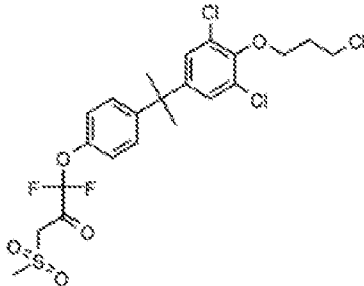
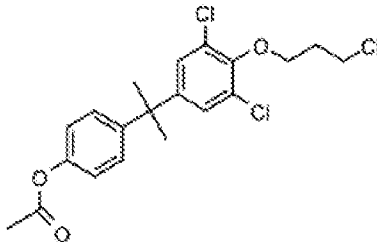
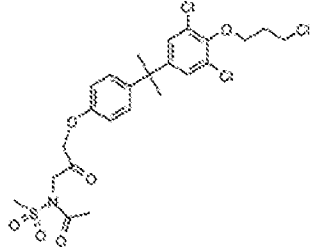
Compound ID	Structure
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AA58(R)	
AA59	
AA60	
AA60(S)	
AA60(R)	
AA61	
AA62	
AA63	
AA64	

Compound ID	Structure
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AA66	
AA67	
AA68	
AA69	
AA70	
AA71	
AA72	

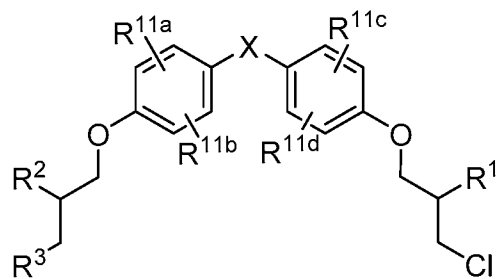
Compound ID	Structure
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AA74	
A75	
AA76	
AA77	
A78	
AA79	
AA80	
AA81	

Compound ID	Structure
AA82	
AA83	
AA84	
AA85	
AA86	
AA87	
AA88	
AA89	
AA90	

Compound ID	Structure
AA91	
AA92	
AA93	
AA94	
AA95	
AA96	
AA97	
AA98	
AA99	
AA100	

Compound ID	Structure
AA101	
AA102	
AA103	
AA104	

[441] In one embodiment, the present disclosure provides androgen receptor N-terminal domain inhibitors selected from compounds of formula (a):



(a)

[442] or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

[443] X is $-S(O)_n-$ or $-C(R^8R^9)-$;

[444] R^1 is H, $-OH$, or $-OC(=O)R^{13}$;

[445] R^2 is $-OH$, or $-OC(=O)R^{13}$;

[446] R^3 is halo, $-OH$, $-OR^4$, $-OC(=O)R^{13}$, $-NH_2$, $-NHC(=O)R^{13}$, $-N(C(=O)R^{13})_2$, $-NHS(O)_nR^5$, $-N(C(=O)R^{13})(S(O)_nR^5)$, $-N(C_1-C_6 \text{ alkyl})(S(O)_nR^5)$, $-S(O)_nR^5$, $-N_3$, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

[447] R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

[448] R^5 is each independently C_1-C_6 alkyl or aryl which are optionally substituted with one or more R^6 ;

[449] R^6 is each independently selected from the group consisting of H, F, Cl, Br, I, ^{123}I , $-OH$, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_6-C_{12} aryl, wherein each R^6 is optionally substituted with one or more of halogen, ^{123}I , ^{18}F , $-OH$, $-OS(O)_2$ -aryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

[450] R^8 and R^9 are each independently H or C_1-C_6 alkyl;

[451] R^{11a} , R^{11b} , R^{11c} and R^{11d} are each independently H, methyl, $-CN$, F, Cl, Br, I, or ^{123}I ;

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

[453] n is 0, 1, or 2;

[454] wherein at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is methyl, $-CN$, F, Cl, Br, I, or ^{123}I .

[455] In one embodiment of the compounds of formula (a), X is $-C(R^8R^9)-$. In one embodiment X is $-C(R^8R^9)-$, wherein R^8 and R^9 are each independently H or C_1-C_3 alkyl. In another embodiment, X is $-C(R^8R^9)-$, wherein R^8 and R^9 are each C_1 alkyl. In some embodiments, X is $-S(O)_2-$ or $-C(CH_3)_2-$.

[456] In one embodiment of the compounds of formula (a), R^1 is $-OH$. In another embodiment, R^1 is $-OC(=O)R^{13}$. In some embodiments, R^1 is $-OC(=O)R^{13}$, wherein R^{13} is C_1-C_4 alkyl. In other embodiments, R^1 is $-OC(=O)R^{13}$, wherein R^{13} is methyl. In one embodiment, R^1 is H.

[457] In one embodiment of the compounds of formula (a), R^2 is $-OH$. In another embodiment, R^2 is $-OC(=O)R^{13}$. In some embodiments, R^2 is $-OC(=O)R^{13}$, wherein R^{13} is C_1-C_4 alkyl. In other embodiments, R^2 is $-OC(=O)R^{13}$, wherein R^{13} is methyl.

[458] In one embodiment of the compounds of formula (a), at least one of R^1 , R^2 , or R^3 is -OH. In some embodiments, at least two of R^1 , R^2 , or R^3 are each -OH. In other embodiments, R^1 and R^2 are each -OH.

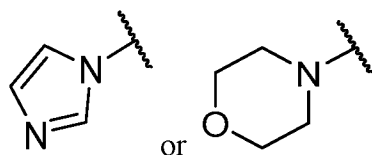
[459] In one embodiment of the compounds of formula (a), at least one of R^1 , R^2 , or R^3 is $-\text{OC}(=\text{O})\text{R}^{13}$, wherein R^{13} is C₁-C₄ alkyl. In another embodiment, at least one of R^1 , R^2 , or R^3 is $-\text{OC}(=\text{O})\text{R}^{13}$, wherein R^{13} is methyl. In some embodiments, at least two of R^1 , R^2 , or R^3 are each $-\text{OC}(=\text{O})\text{R}^{13}$, wherein R^{13} is C₁-C₄ alkyl. In another embodiment, at least two of R^1 , R^2 , or R^3 are each $-\text{OC}(=\text{O})\text{R}^{13}$, wherein R^{13} is methyl. In other embodiments, R^1 and R^2 are each $-\text{OC}(=\text{O})\text{R}^{13}$, wherein R^{13} is methyl.

[460] In one embodiment of the compounds of formula (a), R^3 is $-\text{NH}_2$, $-\text{NHC}(=\text{O})\text{R}^{13}$, $-\text{N}(\text{C}(=\text{O})\text{R}^{13})_2$, $-\text{NHS}(\text{O})_n\text{R}^5$, $-\text{N}(\text{C}(=\text{O})\text{R}^{13})(\text{S}(\text{O})_n\text{R}^5)$, or $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{S}(\text{O})_n\text{R}^5)$. In one embodiment, R^3 is a $-\text{NH}_2$. In one embodiment, R^3 is a $-\text{NHC}(=\text{O})\text{R}^{13}$. In one embodiment, R^3 is a $-\text{N}(\text{C}(=\text{O})\text{R}^{13})_2$. In another embodiment, R^3 is a $-\text{NHS}(\text{O})_n\text{R}^5$. In some embodiments, R^3 is a $-\text{NHS}(\text{O})_2\text{R}^5$. In other embodiments, R^3 is a $-\text{NHS}(\text{O})_2\text{R}^5$, wherein R^5 is C₁-C₃ alkyl. In one embodiment, R^3 is a $-\text{NHS}(\text{O})_2\text{R}^5$, wherein R^5 is C₁ alkyl. In one embodiment, R^3 is a $-\text{N}(\text{C}(=\text{O})\text{R}^{13})(\text{S}(\text{O})_n\text{R}^5)$. In one embodiment, R^3 is a $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{S}(\text{O})_n\text{R}^5)$. In one embodiment, R^3 is a $-\text{NHS}(\text{O})_2\text{CH}_3$.

[461] In one embodiment of the compounds of formula (a), R^3 is $-\text{NH}_2$, $-\text{NHC}(=\text{O})(\text{C}_1\text{-C}_4 \text{ alkyl})$, $-\text{N}[(\text{C}(=\text{O})(\text{C}_1\text{-C}_4 \text{ alkyl}))_2]$, $-\text{NHS}(\text{O})_n(\text{C}_1\text{-C}_3 \text{ alkyl})$, $-\text{N}[\text{C}(=\text{O})(\text{C}_1\text{-C}_4 \text{ alkyl})][(\text{S}(\text{O})_n(\text{C}_1\text{-C}_3 \text{ alkyl}))]$, or $-\text{N}[\text{C}_1\text{-C}_6 \text{ alkyl}][(\text{S}(\text{O})_n(\text{C}_1\text{-C}_3 \text{ alkyl}))]$. In some embodiments, R^3 is $-\text{NH}(\text{C}(=\text{O})\text{CH}_3)$ or $-\text{N}(\text{C}(=\text{O})\text{CH}_3)_2$. In other embodiments, R^3 is $-\text{NHS}(\text{O})_2\text{CH}_3$. In other embodiments, R^3 is $-\text{N}(\text{C}(=\text{O})\text{CH}_3)(\text{S}(\text{O})_2\text{CH}_3)$.

[462] In one embodiment of the compounds of formula (a), R^3 is a $-\text{S}(\text{O})_n\text{R}^5$. In one embodiment, R^3 is a $-\text{S}(\text{O})_2\text{R}^5$. In another embodiment, R^3 is a $-\text{S}(\text{O})_2(\text{C}_1\text{-C}_3 \text{ alkyl})$. In other embodiments, R^3 is a $-\text{S}(\text{O})_2\text{CH}_3$. In other embodiments, R^3 is a $-\text{S}(\text{O})_2\text{CH}_2\text{CH}_3$.

[463] In one embodiment of the compounds of formula (a), R^3 is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom in the ring. In one embodiment, R^3 is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrroline, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine. In a certain embodiment, R^3 is



[464] In one embodiment of the compounds of formula (a), R^3 is $-OR^4$. In one embodiment, R^3 is $-OR^4$, wherein R^4 is C_1 - C_6 alkyl. In another embodiment, R^3 is $-OR^4$, wherein R^4 is C_1 - C_3 alkyl. In one embodiment, R^3 is $-OR^4$, wherein R^4 is methyl, ethyl, *n*-propyl, or *i*-propyl. In one embodiment, R^3 is $-OR^4$, wherein R^4 is methyl. In another embodiment, R^3 is $-OR^4$, wherein R^4 is *i*-propyl.

[465] In one embodiment of the compounds of formula (a), R^3 is a halogen. In other embodiments, R^3 is F, Cl, Br, or I. In one embodiment, R^3 is F.

[466] In one embodiment of the compounds of formula (a), at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is Cl. In another embodiment, at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is Br. In some embodiments, at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is methyl. In some embodiments, at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is $-CN$.

[467] In one embodiment of the compounds of formula (a), at least two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are methyl, F, Cl, Br, I, or ^{123}I . In another embodiment, exactly two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are methyl, F, Cl, Br, I, or ^{123}I .

[468] In one embodiment of the compounds of formula (a), R^{11a} and R^{11b} are each H and R^{11c} and R^{11d} are each independently methyl, F, Cl, Br, I, or ^{123}I . In one embodiment, R^{11a} and R^{11b} are each H, and R^{11c} and R^{11d} are each Cl. In one embodiment, R^{11a} and R^{11b} are each H, and R^{11c} and R^{11d} are each Br. In one embodiment, R^{11a} and R^{11b} are each H, and R^{11c} and R^{11d} are each methyl.

[469] In one embodiment of the compounds of formula (a), R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each independently methyl, F, Cl, Br, I, or ^{123}I . In one embodiment, R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each Cl. In one embodiment, R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each Br. In one embodiment, R^{11a} and R^{11c} are each H, and R^{11b} and R^{11d} are each methyl.

[470] In one embodiment of the compounds of formula (a), R^{13} is C_1 - C_3 alkyl. In other embodiments, R^{13} is methyl, ethyl, or propyl. In one embodiment, R^{13} is a methyl.

[471] In one embodiment of the compounds of formula (a), *n* is 0. In another embodiment *n* is 1. In some embodiments, *n* is 2.

[472] In one embodiment of the compounds of formula (a), the compound comprises one or more of F, Cl, Br, I or ^{123}I substitutions for R^3 . In one embodiment, the compound comprises one or more of I or ^{123}I substitutions for R^3 .

[473] In one embodiment of the compounds of formula (a), the compound comprises at least one R^6 substituent on R^3 , wherein at least one R^6 is further substituted with at least one of F, Cl, Br, I or ^{123}I . In another embodiment, R^6 substituent on R^3 is further substituted with at least one of I or ^{123}I .

[474] In some more specific embodiments of the compounds of Formula (a), the compound has one of the following structures from **Table B**, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof. In one embodiment, the compounds of Formula (a) is selected from Compounds 1, 1a, 1A, 1aA, 5, 5a, 5A, 5aA, 7, 7a, 7A, 7aA, 8, 8a, 8A, 8aA, 9, 9a, 9A, 9aA, 11, 11a, 11A, 11aA, 12, 12a, 13, 13a, 13A, 13aA, 14, 14a, 14A, 14aA, 22, or 22a, or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

[475] The compounds disclosed in WO 2017/177307 can be useful androgen receptor modulators for the present invention. The disclosure of WO 2017/177307 is incorporated by reference in its entirety for all purposes.

[476] **Table B.** Androgen receptor N-terminal domain inhibitors

Comp ID	Structure	Comp ID	Structure
1		1A	
1a		1aA	
5		5A	

Comp ID	Structure	Comp ID	Structure
5a		5aA	
7		7A	
7a		7aA	
8		8A	
8a		8aA	
9		9A	

Comp ID	Structure	Comp ID	Structure
9a		9aA	
11		11A	
11a		11aA	
12			
12a			
13		13A	

Comp ID	Structure	Comp ID	Structure
13a		13aA	
14		14A	
14a		14aA	
22			
22a			

[477] In one embodiment, the compounds as disclosed herein is an androgen receptor N-terminal domain inhibitor. In one embodiment, the compounds as disclosed herein binds to androgen receptor. In another embodiment, the compounds as disclosed herein binds to androgen receptor N-terminal domain.

[478] In one embodiment, the pharmaceutical compositions and the pharmaceutical combinations of present disclosure comprises a compound of formula (i)-(iv) or (a), or a pharmaceutically acceptable salt thereof and a second therapeutically active agent. In one embodiment, the pharmaceutical compositions and the pharmaceutical combinations of present disclosure comprises a compound of formula (i)-(iv) or a compound of Table A, or a

pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a CDK4/6 inhibitor or an androgen receptor ligand-binding domain inhibitor. In one embodiment, the pharmaceutical compositions and the pharmaceutical combinations of present disclosure comprises a compound of formula (i)-(iv) or a compound of Table A, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a CDK4/6 inhibitor or an androgen receptor ligand-binding domain inhibitor. In one embodiment, the pharmaceutical compositions and the pharmaceutical combinations of present disclosure comprises a compound selected from Compounds AA1-AA98, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a CDK4/6 inhibitor or an androgen receptor ligand-binding domain inhibitor. In one embodiment, the pharmaceutical compositions and the pharmaceutical combinations of present disclosure comprises a compound selected from Compounds AA1-AA104, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a CDK4/6 inhibitor or an androgen receptor ligand-binding domain inhibitor. In one embodiment, the pharmaceutical compositions and the pharmaceutical combinations of present disclosure comprises a compound of formula (a) or a compound of Table B, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a CDK4/6 inhibitor or an androgen receptor ligand-binding domain inhibitor. In one embodiment, the pharmaceutical compositions and the pharmaceutical combinations of present disclosure comprises a compound is selected from Compounds 1, 1a, 1A, 1aA, 5, 5a, 5A, 5aA, 7, 7a, 7A, 7aA, 8, 8a, 8A, 8aA, 9, 9a, 9A, 9aA, 11, 11a, 11A, 11aA, 12, 12a, 13, 13a, 13A, 13aA, 14, 14a, 14A, 14aA, 22, or 22a, or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, and a CDK4/6 inhibitor or an androgen receptor ligand-binding domain inhibitor.

[479] In one embodiment, the pharmaceutical compositions and the pharmaceutical combinations of present disclosure further comprises a pharmaceutically acceptable carrier or a pharmaceutically acceptable excipient.

[480] *CDK4/6 Inhibitors*

[481] The G1/S transition is a stage in the cell cycle between the G1 (GAP 1) phase, when the cell grows, and the S (Synthesis) phase, when DNA is replicated. The G1/S transition is a cell cycle check point where DNA integrity is assessed and the cell cycle can pause, for example, in response to improperly or partially replicated DNA. During this transition the cell can decide to become quiescent (enter G0), differentiate, make DNA repairs, or proliferate based on molecular signaling inputs and environmental inputs. The G1/S transition occurs late

in G1 phase and the absence or improper application of this highly regulated check point can lead to cellular transformation and disease states such as cancer by deregulated state of proliferation.

[482] The retinoblastoma tumor suppressor protein (Rb) governs this key cell-cycle checkpoint (at G1/S transition) that normally prevents G1 phase cells from entering S phase in the absence of appropriate mitogenic signals. Cancer cells frequently overcome or bypass Rb-dependent growth suppression via constitutive phosphorylation and inactivation of Rb function by cyclin-dependent kinase (CDK) 4 or CDK6 partnered with D-type cyclins (cyclin D).

[483] During this G1/S transition, G1 cyclin D-CDK4/6 dimer complex phosphorylates Rb (phosphorylated Rb = pRb) releasing transcription factor E2F, which then drives the transition from G1 to S phase. Once the G1 cyclin D-CDK4/6 dimer complex causes pRb to release E2F by conformational change in E2F-bounded Rb upon phosphorylation, E2F drives the expression of other cyclins, such as cyclin E and cyclin A, which push the cell through the cell cycle by activating cyclin-dependent kinases, and a molecule called proliferating cell nuclear antigen, or PCNA, which speeds DNA replication and repair by helping to attach polymerase to DNA.

[484] Thus, the activity/expression level of cyclin D and control of the G1/S transition by Rb and/or pRb is critical for cell proliferation. Many cancers harbor mutations in the protein present in this Rb checkpoint pathway that controls progression of the cell cycle. Thus, there is a need for treatment of cancer which is effective for treating subjects who have abnormally high expression levels in the Rb checkpoint pathway or harbor mutations in the protein present in the Rb checkpoint pathway.

[485] Cyclin D1 activates CDK4/6 to phosphorylate Rb and other proteins involved in the transition from G1 phase to S phase during cell cycle. Luminal androgen receptor (LAR) subtype of TNBC is particularly sensitive to CDK4/6 inhibitors. This sensitivity is associated with AR expression and low cyclin E1 levels.

[486] In one embodiment, any known CDK4/6 inhibitors can be used in the pharmaceutical compositions and combinations of the present disclosure.

[487] In one embodiment, the CDK4/6 inhibitors useful for the pharmaceutical compositions and combinations as disclosed herein, is selected from palbociclib, ribociclib, trilaciclib or abemaciclib. In one embodiment, the CDK4/6 inhibitor is selected from palbociclib, abemaciclib, or ribociclib. In one embodiment, the CDK4/6 inhibitor is palbociclib.

[488] *Androgen Receptor Ligand-Binding Domain Inhibitor*

[489] In one embodiment, the androgen receptor N-terminal domain inhibitor compound of formula (i)-(iv) or (a), or a pharmaceutically acceptable salt thereof are androgen receptor N-terminal domain inhibitors. In one embodiment, androgen receptor N-terminal domain inhibitors can be useful when used in combination with an androgen receptor ligand-binding domain inhibitor. In some embodiments, an androgen receptor N-terminal domain inhibitor and an androgen receptor ligand-binding domain inhibitor can act synergistically.

[490] In one embodiment, the androgen receptor ligand-binding domain inhibitor is enzalutamide, apalutamide, darolutamide, bicalutamide, nilutamide, flutamide, ODM-204, or TAS3681. In one embodiment, the androgen receptor ligand-binding domain inhibitor is enzalutamide.

[491] *Pin1 Inhibitors*

[492] Pin1 is a unique isomerase that regulates the proline conformation of a phosphorylated motif (pSer/Thr-Pro). Pin1 levels are often elevated in prostate cancer and correlate with risk for developing castration-resistant prostate cancer (CRPC).

[493] Since the *cis/trans* conformations of proline are dramatically different, they may influence protein structure and function. There are several putative Pin1 sites located on the AR (androgen receptor), and many are within the intrinsically disordered N-terminal domain (NTD).

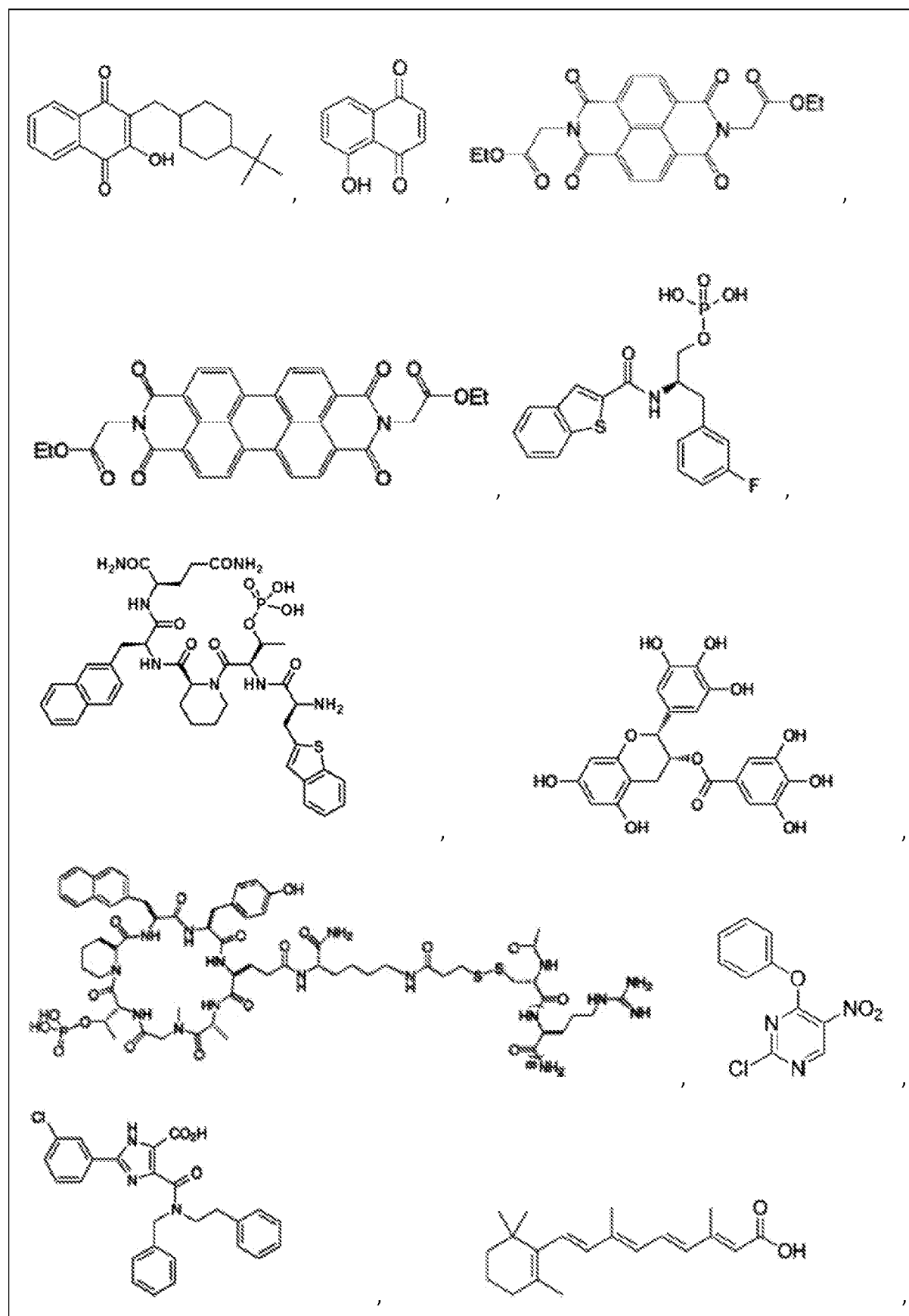
[494] The intrinsically disordered AR NTD (androgen receptor N-terminal domain) is essential for its transcriptional activity. It harbors six putative binding sites for Pin1, a proline isomerase that regulates protein conformation at specific phosphorylated-Ser/Thr-Pro motifs. Since conformational changes within the AR NTD are required for transactivation, perturbation of its structure can lead to blocking AR NTD activity. Thus, Pin1 inhibitors used in combination with an androgen receptor N-terminal domain inhibitor can lead to enhanced inhibition of the androgen receptor, including AR NTD.

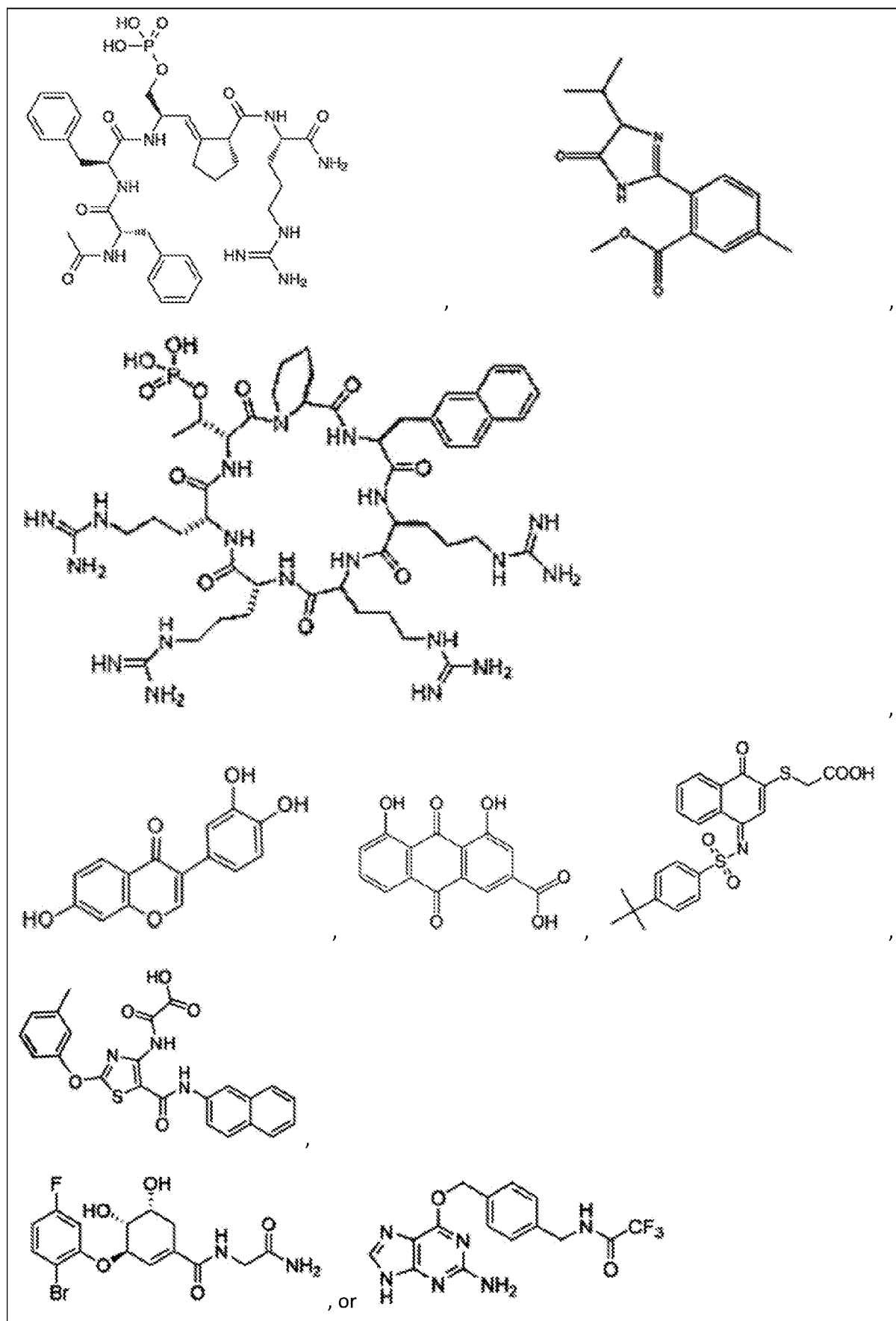
[495] In one embodiment, any known Pin1 inhibitors can be used in combination with androgen receptor N-terminal domain inhibitor as disclosed herein.

[496] In one embodiment, Pin1 inhibitor is selected from juglone, plumbagin, PiB, PiJ, epigallocatechin gallate (EGCG), all-trans retinoic acid (ATRA), dipentamethylene thiauram monosulfide, TME-001 (2-(3-chloro-4-fluoro-phenyl)-isothiazol-3-one), KPT-6566, API-1, buparvaquone, or a pharmaceutically acceptable salt thereof.

[497] In one embodiment, Pin1 inhibitor is selected from Table C or a pharmaceutically acceptable salt thereof.

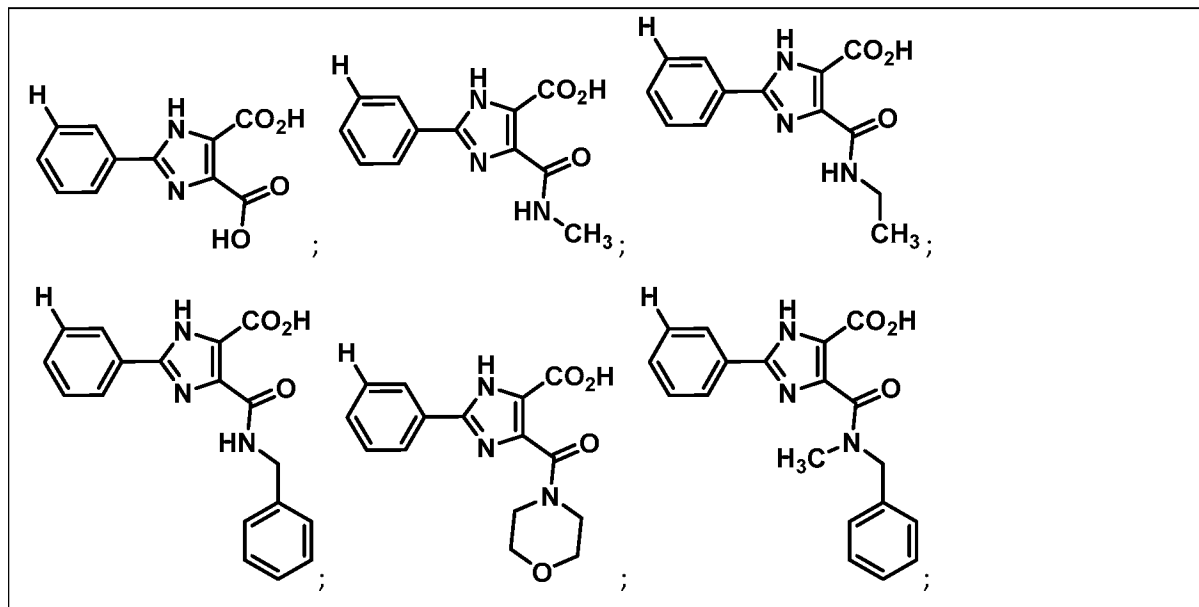
[498] Table C. Pin1 Inhibitors

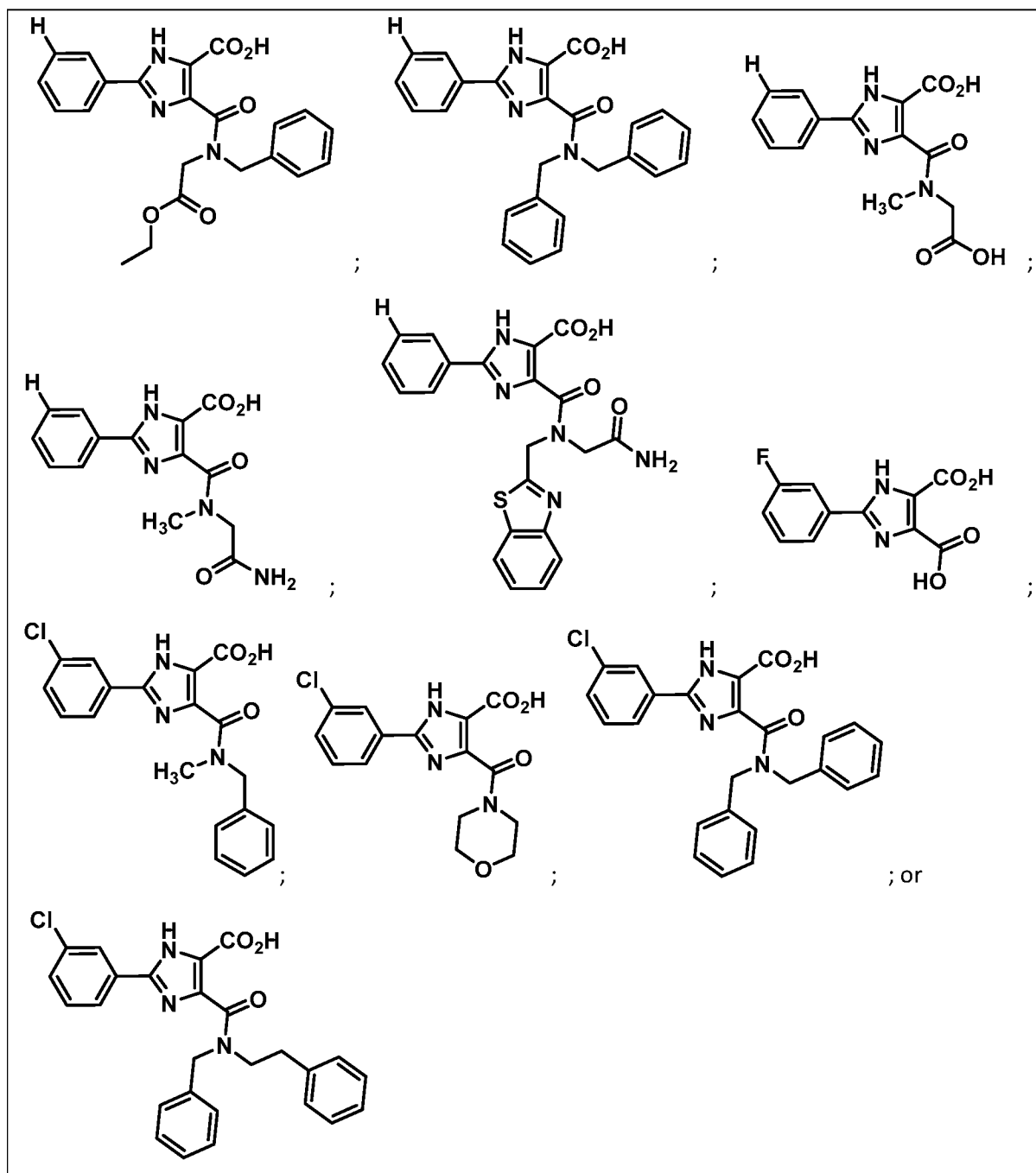




[499] In some embodiments, the Pin1 inhibitor is an analogue of retinoic acid. In yet other embodiments, the Pin1 inhibitor is selected from Table D, or a pharmaceutically acceptable salt thereof.

[500] **Table D.** Pin1 inhibitors





[501] In yet other embodiments, the Pin1 inhibitor is a peptide. In some such embodiments, the peptide is selected from: CRYPEVEIC, wherein the cysteine residues of said peptide are cyclized by a disulfide bond (SEQ ID NO: 1); Ac-Lys(N-biotinoyl)-Ala-Ala-Bth-D-Thr(PO₃H₂)-Pip-Nal-Gln-NH₂ (SEQ ID NO: 2); Ac-Phe-D-Thr(PO₃H₂)-Pip-Nal-Gln-NH₂ (SEQ ID NO: 3); and Ac-Phe-Phe-pSer-Ψ[(Z)CHdC-Pro-Arg-NH₂ (SEQ ID NO: 4).

[502] In one embodiment, Pin1 inhibitor is selected from 5-hydroxy-1,4-naphthlenedione, (1-piperidinecarbodithioic acid, anhydrosulfide), or diethyl-1,3,6,8-tetrahydro-

1,3,6,8-tetraoxobenzo[lmn]phenanthroline-2,7-diacetate, or a pharmaceutically acceptable salt thereof.

[503] In one embodiment, Pin1 inhibitor is juglone or ATRA. In one embodiment, Pin1 inhibitor is ATRA.

[504] *Other Therapeutically Active Agents*

[505] The pharmaceutical composition of the present disclosure comprises a second therapeutically active agent. The second therapeutically active agent can be selected from from a poly (ADP-ribose) polymerase (PARP) inhibitor, an androgen receptor ligand-binding domain inhibitor, an inhibitor of CYP17, a microtubule inhibitor, a modulator of PD-1 or PD-L1, a gonadotropin releasing hormone agonist, a 5-alpha reductase inhibitor, a vascular endothelial growth factor inhibitor, a histone deacetylase inhibitor, an integrin alpha-v-beta-3 inhibitor, a receptor tyrosine kinase, a phosphoinositide 3-kinase inhibitor, an anaplastic lymphoma kinase (ALK) inhibitor, an endothelin receptor A antagonist, an anti-CTLA4 inhibitor, an heat shock protein 27 (HSP27) inhibitor, an androgen receptor degrader, a androgen receptor DNA-binding domain inhibitor, a bromodomain and extra-terminal motif (BET) inhibitor, an androgen receptor N-terminal domain inhibitor, an alpha-particle emitting radioactive therapeutic agent, niclosamide, a selective estrogen receptor modulator (SERM), a selective estrogen receptor degrader (SERD), an aromatase inhibitor, selective progesterone receptor modulator (SPRM), a glucocorticoid receptor inhibitor, a CDK4/6 inhibitor, a HER2 receptor antagonist, a mammalian target of rapamycin (mTOR) inhibitor, an AKT inhibitor, a B-cell lymphoma-2 (Bcl-2) inhibitor, an aurora kinase inhibitor, a Wnt-targeting antagonist, a CYP11a inhibitor, a selective androgen receptor N-terminal domain inhibitor, or enhancer of zeste homolog 2 (EZH2) inhibitor.

[506] The pharmaceutical composition of the present disclosure comprises a second therapeutically active agent. The second therapeutically active agent can be selected from from a poly (ADP-ribose) polymerase (PARP) inhibitor, an androgen receptor ligand-binding domain inhibitor, an inhibitor of CYP17, a microtubule inhibitor, a modulator of PD-1 or PD-L1, a gonadotropin releasing hormone agonist, a 5-alpha reductase inhibitor, a vascular endothelial growth factor inhibitor, a histone deacetylase inhibitor, an integrin alpha-v-beta-3 inhibitor, a receptor tyrosine kinase, a phosphoinositide 3-kinase inhibitor, an anaplastic lymphoma kinase (ALK) inhibitor, an endothelin receptor A antagonist, an anti-CTLA4 inhibitor, an heat shock protein 27 (HSP27) inhibitor, an androgen receptor degrader, a androgen receptor DNA-binding domain inhibitor, a bromodomain and extra-terminal motif

(BET) inhibitor, an androgen receptor N-terminal domain inhibitor, an alpha-particle emitting radioactive therapeutic agent, niclosamide, a selective estrogen receptor modulator (SERM), a selective estrogen receptor degrader (SERD), an aromatase inhibitor, selective progesterone receptor modulator (SPRM), a glucocorticoid receptor inhibitor, a CDK4/6 inhibitor, a HER2 receptor antagonist, or a mammalian target of rapamycin (mTOR) inhibitor.

[507] In one embodiment, the second therapeutically active agent is selected from a poly (ADP-ribose) polymerase (PARP) inhibitor including but not limited to olaparib, niraparib, rucaparib, talazoparib; an androgen receptor ligand-binding domain inhibitor including but not limited to enzalutamide, apalutamide, darolutamide, bicalutamide, nilutamide, flutamide, ODM-204, TAS3681; an inhibitor of CYP17 including but not limited to galeterone, abiraterone, abiraterone acetate; a microtubule inhibitor including but not limited to docetaxel, paclitaxel, cabazitaxel (XRP-6258); a modulator of PD-1 or PD-L1 including but not limited to pembrolizumab, durvalumab, nivolumab, atezolizumab; a gonadotropin releasing hormone agonist including but not limited to cyproterone acetate, leuprolide; a 5-alpha reductase inhibitor including but not limited to finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260, SKF105,111; a vascular endothelial growth factor inhibitor including but not limited to bevacizumab (Avastin); a histone deacetylase inhibitor including but not limited to OSU-HDAC42; an integrin alpha-v-beta-3 inhibitor including but not limited to VITAXIN; a receptor tyrosine kinase including but not limited to sunitumib; a phosphoinositide 3-kinase inhibitor including but not limited to alpelisib, buparlisib, idealisib; an anaplastic lymphoma kinase (ALK) inhibitor including but not limited to crizotinib, alectinib; an endothelin receptor A antagonist including but not limited to ZD-4054; an anti-CTLA4 inhibitor including but not limited to MDX-010 (ipilimumab); an heat shock protein 27 (HSP27) inhibitor including but not limited to OGX 427; an androgen receptor degrader including but not limited to ARV-330, ARV-110; a androgen receptor DNA-binding domain inhibitor including but not limited to VPC-14449; a bromodomain and extra-terminal motif (BET) inhibitor including but not limited to BI-894999, GSK25762, GS-5829; an N-terminal domain inhibitor including but not limited to a sintokamide; an alpha-particle emitting radioactive therapeutic agent including but not limited to radium 233 or a salt thereof; niclosamide; or related compounds thereof; a selective estrogen receptor modulator (SERM) including but not limited to tamoxifen, raloxifene, toremifene, arzoxifene, bazedoxifene, pipindoxifene, lasofoxifene, enclomiphene; a selective estrogen receptor degrader (SERD) including but not limited to fulvestrant, ZB716, OP-1074, elacestrant, AZD9496, GDC0810, GDC0927, GW5638, GW7604; an aromatase inhibitor including but not limited to anastrozole,

exemestane, letrozole; selective progesterone receptor modulators (SPRM) including but not limited to mifepristone, lonaprisone, onaprisone, asoprisnil, lonaprisnil, ulipristal, telapristone; a glucocorticoid receptor inhibitor including but not limited to mifepristone, COR108297, COR125281, ORIC-101, PT150; CDK4/6 inhibitors including palbociclib, abemaciclib, ribociclib; HER2 receptor antagonist including but not limited to trastuzumab, neratinib; or a mammalian target of rapamycin (mTOR) inhibitor including but not limited to everolimus, temsirolimus, an AKT inhibitor including but not limited to MK-2206; a Bcl-2 inhibitor including but not limited to venetoclax; an aurora kinase inhibitor including but not limited to alisertib; a Wnt-targeting antagonist including but not limited to DKK-1-4 proteins (Dikhopf), secreted Frazzle related proteins (sFRP); a CYP11a inhibitor including but not limited to ODM-208; a selective androgen receptor N-terminal domain inhibitor including but not limited to LY2452473; or EZH2 inhibitor including but not limited to CPI-1205.

[508] In one embodiment, the second therapeutically active agent is selected from a poly (ADP-ribose) polymerase (PARP) inhibitor including but not limited to olaparib, niraparib, rucaparib, talazoparib; an androgen receptor ligand-binding domain inhibitor including but not limited to enzalutamide, apalutamide, darolutamide, bicalutamide, nilutamide, flutamide, ODM-204, TAS3681; an inhibitor of CYP17 including but not limited to galeterone, abiraterone, abiraterone acetate; a microtubule inhibitor including but not limited to docetaxel, paclitaxel, cabazitaxel (XRP-6258); a modulator of PD-1 or PD-L1 including but not limited to pembrolizumab, durvalumab, nivolumab, atezolizumab; a gonadotropin releasing hormone agonist including but not limited to cyproterone acetate, leuprolide; a 5-alpha reductase inhibitor including but not limited to finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260, SKF105,111; a vascular endothelial growth factor inhibitor including but not limited to bevacizumab (Avastin); a histone deacetylase inhibitor including but not limited to OSU-HDAC42; an integrin alpha-v-beta-3 inhibitor including but not limited to VITAXIN; a receptor tyrosine kinase including but not limited to sunitinib; a phosphoinositide 3-kinase inhibitor including but not limited to alpelisib, buparlisib, idealisib; an anaplastic lymphoma kinase (ALK) inhibitor including but not limited to crizotinib, alectinib; an endothelin receptor A antagonist including but not limited to ZD-4054; an anti-CTLA4 inhibitor including but not limited to MDX-010 (ipilimumab); an heat shock protein 27 (HSP27) inhibitor including but not limited to OGX 427; an androgen receptor degrader including but not limited to ARV-330, ARV-110; a androgen receptor DNA-binding domain inhibitor including but not limited to VPC-14449; a bromodomain and extra-terminal motif (BET) inhibitor including but not limited to BI-894999, GSK25762, GS-5829; an N-terminal

domain inhibitor including but not limited to a sintokamide; an alpha-particle emitting radioactive therapeutic agent including but not limited to radium 233 or a salt thereof; niclosamide; or related compounds thereof; a selective estrogen receptor modulator (SERM) including but not limited to tamoxifen, raloxifene, toremifene, arzoxifene, bazedoxifene, pipindoxifene, lasofoxifene, enclomiphene; a selective estrogen receptor degrader (SERD) including but not limited to fulvestrant, ZB716, OP-1074, elacestrant, AZD9496, GDC0810, GDC0927, GW5638, GW7604; an aromatase inhibitor including but not limited to anastrozole, exemestane, letrozole; selective progesterone receptor modulators (SPRM) including but not limited to mifepristone, lonaprisone, onaprisone, asoprisnil, lonaprisnil, ulipristal, telapristone; a glucocorticoid receptor inhibitor including but not limited to mifepristone, COR108297, COR125281, ORIC-101, PT150; CDK4/6 inhibitors including palbociclib, abemaciclib, ribociclib; HER2 receptor antagonist including but not limited to trastuzumab, neratinib; or a mammalian target of rapamycin (mTOR) inhibitor including but not limited to everolimus, temsirolimus.

[509] In one embodiment, the second therapeutically active agent is a microtubule inhibitor. In one embodiment, the microtubule inhibitor is selected from docetaxel, paclitaxel, or cabazitaxel (XRP-6258). In one embodiment, the microtubule inhibitor is docetaxel.

[510] In one embodiment, the second therapeutically active agent is a Bcl-2 inhibitor. In one embodiment, the Bcl-2 inhibitor is venetoclax.

Therapeutic Use

[511] The pharmaceutical compositions and combinations of the present disclosure find use in any number of methods. For example, in some embodiments the compounds are useful in methods for modulating androgen receptor (AR). In some embodiments the compounds are useful in methods for inhibiting androgen receptor (AR). In some embodiments the compounds are useful in methods for inhibiting AR N-terminal domain. In some embodiments, inhibiting androgen receptor (AR) activity is in a mammalian cell. In some embodiments, inhibiting 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.

[512] In other embodiments, inhibiting androgen receptor (AR) activity is for treatment of at least one indication selected from the group consisting of: prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular 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 other embodiments, the prostate cancer is primary/localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, metastatic prostate cancer, advanced prostate cancer, or metastatic castration-resistant prostate cancer (CRPC), or hormone-sensitive prostate cancer. While in other embodiments, the prostate cancer is androgen dependent prostate cancer. In other embodiments, the spinal and bulbar muscular atrophy is Kennedy's disease.

[513] 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, comprising administering a pharmaceutical composition or a combination as disclosed herein, comprising a CDK4/6 inhibitor and an androgen receptor N-terminal domain inhibitor having the structure of formula (i)-(iv) or (a), or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, to a subject in need thereof. 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. In another embodiment, the present invention provides a method of treating prostate cancer.

[514] In one embodiment of the present disclosure, a method of reducing, inhibiting, or ameliorating proliferation, comprising administering a therapeutically effective amount of a pharmaceutical composition or a combination comprising a CDK4/6 inhibitor and an androgen receptor N-terminal domain inhibitor having the structure of formula (i)-(iv) or (a), or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, is provided. 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*.

[515] 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 cured with 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.

[516] In one embodiment, the condition or disease associated with cell proliferation is cancer. In one embodiment of any one of the methods disclosed herein, the cancer 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. In one embodiment, the breast cancer is triple negative breast cancer. In some embodiments, the breast cancer is AR-positive triple negative breast cancer.

[517] In another embodiment of the present disclosure, a method for reducing or preventing tumor growth, comprising contacting tumor cells with a pharmaceutical composition or a combination as disclosed herein, comprising a CDK4/6 inhibitor and an androgen receptor N-terminal domain inhibitor having the structure of formula (i)-(iv) or (a), or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof is provided.

[518] 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 (r_1) is faster than the rate of tumor growth after said treatment (r_2) such that $r_1 > r_2$.

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

[520] 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 embodiments, the prostate cancer is androgen-dependent prostate cancer or androgen-independent prostate cancer. In another embodiment, the tumor cells are breast cancer tumor cells.

[521] The present disclosure also relates to use of the androgen receptor N-terminal domain inhibitors or compositions thereof as disclosed herein for treatment of cancer in combination with radiation therapy.

[522] In one embodiment of the methods with radiation therapy, the type of radiation can include X-rays gamma rays, high energy electrons and high LET (Linear Energy Transfer) radiation, such as, protons, neutron, and alpha particles. The ionizing radiation can be employed by techniques well known to those skilled in the art. For example, X-rays and gamma rays are applied by external and/or interstitial means from linear accelerators or radioactive sources. High-energy electrons can be produced by linear accelerators and high LET radiation is also applied from radioactive sources implanted interstitially. The total dose of radiation employed by one skilled in the art can range from 18 to 160 Gray (Gy). (One Gray unit of measure is equal to 100 rads) The total dose of radiation can be divided into 5 to 7 continuous weeks of therapy. In one embodiment, one week of radiation is divided into 5 daily fractions. A daily fraction of radiation consists of a dose from 1.2 to 2.5 Gray. The total amount of radiation used in brachytherapy may be 160 Gy. The exact dosage of radiation can depend on a variety of factors including but not limited to the volume of the cancerous tissue to be irradiated, normal tissue surrounding the cancerous tissue, age of the patient, medical history of the patient, and other clinical factors. *See*, R. Arriagada, Hematology/Oncology Clinics of North America, Vol. 11, pgs. 461-472 (1997) and S. Hellman, Principles of Cancer Management: Radiation Therapy, in Cancer: Principles and Practice of Oncology, 5th Ed., Lippincott Publishers, pgs. 307-332 (1997); the disclosure of which is herein incorporated by reference.

[523] In one embodiment of the method with radiation therapy, the radiation therapy is administered in the same treatment period as the androgen receptor N-terminal domain inhibitor or the composition/combination thereof. That is, the subject receives radiation therapy on the same day or the same week as the androgen receptor N-terminal domain inhibitor or the composition/combination thereof. In one embodiment, the radiation therapy is administered within 24 hours of administration of the androgen receptor N-terminal domain inhibitor or a composition/combination thereof.

[524] In one embodiment of the method with radiation therapy, the radiation therapy is administered in a different treatment period as the androgen receptor N-terminal domain

inhibitor or the composition/combination thereof. That is, the subject first receives treatment with the androgen receptor N-terminal domain inhibitor or the composition/combination thereof for a duration as prescribed by a medical professional and upon completion of the androgen receptor modulator treatment, is administered radiation therapy, or vice versa.

[525] In one embodiment of the methods disclosed herein, radiation therapy is administered concurrently with lutetium-177 or other alpha emitters, to a subject who has been treated or in treatment with the androgen receptor N-terminal domain inhibitor or the composition/combination thereof as disclosed herein. In one embodiment lutetium-177 is targeted for prostate cancer cells.

[526] In one embodiment of the methods disclosed herein, radiation therapy is administered concurrently with a prostate specific membrane antigen (PSMA) ligand. In one embodiment, PSMA ligand is targeted for prostate cancer cells.

[527] In one embodiment of the methods disclosed herein, Compound 13a is administered in a patient in need thereof in combination with radiation therapy. In one embodiment, the method of combining administration of Compound 13a with radiation therapy increases accumulation of DNA damage. In one embodiment, the method of combining administration of Compound 13a with radiation therapy increases accumulation of DNA damage.

Pharmaceutical Compositions and Formulations

[528] The pharmaceutical composition or a combination as disclosed herein, can further comprise a pharmaceutically acceptable carrier or excipient.

[529] In one embodiment, pharmaceutical composition or a combination comprises an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, a second therapeutically effective agent, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a Pin1 inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, pharmaceutical composition or a combination comprises ATRA, an androgen receptor modulator selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a CDK4/6 inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the

pharmaceutical composition or the combination comprises palbociclib, an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a Bcl-2 inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises venetoclax, an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises an androgen receptor ligand-binding domain inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a) enzalutamide, apalutamide, or darolutamide, b) an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and c) a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a microtubule inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises docetaxel, an androgen receptor N-terminal domain inhibitor selected from Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient.

[530] In one embodiment, pharmaceutical composition or a combination comprises an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, a second therapeutically effective agent, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a Pin1 inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, pharmaceutical composition or a combination comprises ATRA, an androgen receptor modulator selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a CDK4/6 inhibitor, an androgen receptor N-

terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises palbociclib, an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a Bcl-2 inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises venetoclax, an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises an androgen receptor ligand-binding domain inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a) enzalutamide, apalutamide, or darolutamide, b) an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and c) a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises a microtubule inhibitor, an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, the pharmaceutical composition or the combination comprises docetaxel, an androgen receptor N-terminal domain inhibitor selected from Table B, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient.

[531] In one embodiment, pharmaceutical composition or a combination comprises ATRA, Compound 13a, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, pharmaceutical composition or a combination comprises pablociclib, Compound 13a, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient. In one embodiment, pharmaceutical composition or a combination comprises venetoclax, Compound 13a, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient.

[532] In one embodiment, pharmaceutical composition or a combination comprises enzalutamide, Compound 13a, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier or excipient.

[533] In one embodiment, a pharmaceutical composition, as described herein, further comprises one or more additional therapeutically active agents. In one embodiment, one or more additional therapeutically active agents are selected from therapeutics useful for treating cancer, neurological disease, a disorder characterized by abnormal accumulation of α -synuclein, a disorder of an aging process, cardiovascular disease, bacterial infection, viral infection, mitochondrial related disease, mental retardation, deafness, blindness, diabetes, obesity, autoimmune disease, glaucoma, Leber's Hereditary Optic Neuropathy, and rheumatoid arthritis.

[534] In some embodiments, the one or more additional therapeutic agents is a poly (ADP-ribose) polymerase (PARP) inhibitor including but not limited to olaparib, niraparib, rucaparib, talazoparib; an androgen receptor ligand-binding domain inhibitor including but not limited to enzalutamide, apalutamide, darolutamide, bicalutamide, nilutamide, flutamide, ODM-204, TAS3681; an inhibitor of CYP17 including but not limited to galeterone, abiraterone, abiraterone acetate; a microtubule inhibitor including but not limited to docetaxel, paclitaxel, cabazitaxel (XRP-6258); a modulator of PD-1 or PD-L1 including but not limited to pembrolizumab, durvalumab, nivolumab, atezolizumab; a gonadotropin releasing hormone agonist including but not limited to cyproterone acetate, leuprolide; a 5- α reductase inhibitor including but not limited to finasteride, dutasteride, turosteride, bexlosteride, izonsteride, FCE 28260, SKF105,111; a vascular endothelial growth factor inhibitor including but not limited to bevacizumab (Avastin); a histone deacetylase inhibitor including but not limited to OSU-HDAC42; an integrin α -v- β -3 inhibitor including but not limited to VITAXIN; a receptor tyrosine kinase including but not limited to sunitumib; a phosphoinositide 3-kinase inhibitor including but not limited to alpelisib, buparlisib, idealisib; an anaplastic lymphoma kinase (ALK) inhibitor including but not limited to crizotinib, alectinib; an endothelin receptor A antagonist including but not limited to ZD-4054; an anti-CTLA4 inhibitor including but not limited to MDX-010 (ipilimumab); an heat shock protein 27 (HSP27) inhibitor including but not limited to OGX 427; an androgen receptor degrader including but not limited to ARV-330, ARV-110; a androgen receptor DNA-binding domain inhibitor including but not limited to VPC-14449; a bromodomain and extra-terminal motif (BET) inhibitor including but not limited to BI-894999, GSK25762, GS-5829; an N-terminal domain inhibitor including but not limited to a sintokamide; an alpha-particle emitting

radioactive therapeutic agent including but not limited to radium 233 or a salt thereof; niclosamide; or related compounds thereof; a selective estrogen receptor modulator (SERM) including but not limited to tamoxifen, raloxifene, toremifene, arzoxifene, bazedoxifene, pipindoxifene, lasofoxifene, enclomiphene; a selective estrogen receptor degrader (SERD) including but not limited to fulvestrant, ZB716, OP-1074, elacestrant, AZD9496, GDC0810, GDC0927, GW5638, GW7604; an aromatase inhibitor including but not limited to anastrozole, exemestane, letrozole; selective progesterone receptor modulators (SPRM) including but not limited to mifepristone, lonaprisone, onaprisone, asoprisnil, lonaprisnil, ulipristal, telapristone; a glucocorticoid receptor inhibitor including but not limited to mifepristone, COR108297, COR125281, ORIC-101, PT150; CDK4/6 inhibitors including palbociclib, abemaciclib, ribociclib; HER2 receptor antagonist including but not limited to trastuzumab, neratinib; a mammalian target of rapamycin (mTOR) inhibitor including but not limited to everolimus, temsirolimus.

[535] In a further embodiment of the present disclosure, a pharmaceutical composition or combination as disclosed herein comprises a pharmaceutically acceptable carrier, excipient or adjuvant is provided. The pharmaceutically acceptable carriers, excipients and adjuvants are added to the composition or formulation for a variety of purposes. In one embodiment, a pharmaceutically acceptable carrier includes a pharmaceutically acceptable excipient, binder, and/or diluent. In one embodiment, suitable pharmaceutically acceptable excipients include, but are not limited to, water, salt solutions, alcohol, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic acid, viscous paraffin, hydroxymethylcellulose and polyvinylpyrrolidone.

[536] In certain embodiments, the pharmaceutical compositions of the present disclosure may additionally contain other adjunct components conventionally found in pharmaceutical compositions, at their art-established usage levels. Thus, for example, the pharmaceutical compositions may contain additional, compatible, pharmaceutically-active materials such as, for example, antipruritics, astringents, local anesthetics or anti-inflammatory agents, or may contain additional materials useful in physically formulating various dosage forms of the compositions of the present invention, such as dyes, flavoring agents, preservatives, antioxidants, opacifiers, thickening agents and stabilizers. However, such materials, when added, should not unduly interfere with the biological activities of the components of the compositions of the present invention. The formulations can be sterilized and, if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers,

salts for influencing osmotic pressure, buffers, colorings, flavorings and/or aromatic substances and the like which do not deleteriously interact with the oligonucleotide(s) of the formulation.

[537] For the purposes of this disclosure, the compounds of the present disclosure can be formulated for administration by a variety of means including orally, parenterally, by inhalation spray, topically, or rectally in formulations containing pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used here includes subcutaneous, intravenous, intramuscular, and intraarterial injections with a variety of infusion techniques. Intraarterial and intravenous injection as used herein includes administration through catheters.

[538] The compounds disclosed herein can be formulated in accordance with the routine procedures adapted for desired administration route. Accordingly, the compounds disclosed herein can take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compounds disclosed herein can also be formulated as a preparation for implantation or injection. Thus, for example, the compounds can be formulated with suitable polymeric or hydrophobic materials (e.g., as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives (e.g., as a sparingly soluble salt). Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. Suitable formulations for each of these methods of administration can be found, for example, in Remington: The Science and Practice of Pharmacy, A. Gennaro, ed., 20th edition, Lippincott, Williams & Wilkins, Philadelphia, PA.

[539] In certain embodiments, a pharmaceutical composition of the present disclosure is prepared using known techniques, including, but not limited to mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[540] In one embodiment, suitable pharmaceutically acceptable carriers include, but are not limited to, inert solid fillers or diluents and sterile aqueous or organic solutions. Pharmaceutically acceptable carriers are well known to those skilled in the art and include, but are not limited to, from about 0.01 to about 0.1 M and preferably 0.05M phosphate buffer or 0.8% saline. Such pharmaceutically acceptable carriers can be aqueous or non-aqueous solutions, suspensions and emulsions. Examples of non-aqueous solvents suitable for use in the present application include, but are not limited to, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate.

[541] Aqueous carriers suitable for use in the present application include, but are not limited to, water, ethanol, alcoholic/aqueous solutions, glycerol, emulsions or suspensions, including saline and buffered media. Oral carriers can be elixirs, syrups, capsules, tablets and the like.

[542] Liquid carriers suitable for use in the present application can be used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compounds. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators.

[543] Liquid carriers suitable for use in the present application include, but are not limited to, water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also include an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form comprising compounds for parenteral administration. The liquid carrier for pressurized compounds disclosed herein can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

[544] Solid carriers suitable for use in the present application include, but are not limited to, inert substances such as lactose, starch, glucose, methyl-cellulose, magnesium stearate, dicalcium phosphate, mannitol and the like. A solid carrier can further include one or more substances acting as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier can be a finely divided solid which is in admixture with the finely divided active compound. In tablets, the active compound is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active compound. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins. A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free flowing form such as a powder or granules, optionally mixed with a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface active or dispersing agent. Molded tablets may be made by molding in a

suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropyl methylcellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

[545] Parenteral carriers suitable for use in the present application include, but are not limited to, sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's and fixed oils. Intravenous carriers include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose and the like. Preservatives and other additives can also be present, such as, for example, antimicrobials, antioxidants, chelating agents, inert gases and the like.

[546] Carriers suitable for use in the present application can be mixed as needed with disintegrants, diluents, granulating agents, lubricants, binders and the like using conventional techniques known in the art. The carriers can also be sterilized using methods that do not deleteriously react with the compounds, as is generally known in the art.

[547] Diluents may be added to the formulations of the present invention. Diluents increase the bulk of a solid pharmaceutical composition and/or combination, and may make a pharmaceutical dosage form containing the composition and/or combination easier for the patient and care giver to handle. Diluents for solid compositions and/or combinations include, for example, microcrystalline cellulose (e.g., AVICEL), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrans, 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.

[548] Additional embodiments relate to the pharmaceutical formulations wherein the formulation is selected from the group consisting of a solid, powder, liquid and a gel. In certain embodiments, a pharmaceutical composition of the present invention is a solid (e.g., a powder, tablet, a capsule, granulates, and/or aggregates). In certain of such embodiments, a solid pharmaceutical composition comprising one or more ingredients known in the art, including, but not limited to, starches, sugars, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[549] Solid pharmaceutical compositions 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.

[550] The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition and/or combination. 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.

[551] Glidants can be added to improve the flowability of a non-compacted solid composition and/or combination 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.

[552] 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 and/or combination 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.

[553] 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 and/or combination of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

[554] 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.

[555] In certain embodiments, a pharmaceutical composition of the present invention is a liquid (e.g., a suspension, elixir and/or solution). In certain of such embodiments, a liquid pharmaceutical composition is prepared using ingredients known in the art, including, but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents.

[556] Liquid pharmaceutical compositions can be prepared where the solid or amorphous components are dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol, or glycerin.

[557] For example, formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. In particular, biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers can be useful excipients to control the release of active compounds. Other potentially useful parenteral delivery systems include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-auryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration.

[558] Liquid pharmaceutical compositions can contain emulsifying agents to disperse uniformly throughout the composition and/or combination 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.

[559] Liquid pharmaceutical compositions can 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.

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

[561] 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.

[562] A liquid composition can 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.

[563] In one embodiment, a pharmaceutical composition is prepared for administration by injection (e.g., intravenous, subcutaneous, intramuscular, etc.). In certain of such embodiments, a pharmaceutical composition comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (e.g., ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical compositions for injection are presented in unit dosage form, e.g., in ampoules or in multi-dose containers. Certain pharmaceutical compositions for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical compositions for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the pharmaceutical agents to allow for the preparation of highly concentrated solutions.

[564] The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile

fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables. Formulations for intravenous administration can comprise solutions in sterile isotonic aqueous buffer. Where necessary, the formulations can also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachet indicating the quantity of active agent. Where the compound is to be administered by infusion, it can be dispensed in a formulation with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the compound is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients can be mixed prior to administration.

[565] Suitable formulations further include aqueous and non-aqueous sterile injection solutions that can contain antioxidants, buffers, bacteriostats, bactericidal antibiotics and solutes that render the formulation isotonic with the bodily fluids of the intended recipient; and aqueous and non-aqueous sterile suspensions, which can include suspending agents and thickening agents.

[566] In certain embodiments, a pharmaceutical composition of the present invention is formulated as a depot preparation. Certain such depot preparations are typically longer acting than non-depot preparations. In certain embodiments, such preparations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, depot preparations are prepared using suitable polymeric or hydrophobic materials (for example an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[567] In certain embodiments, a pharmaceutical composition of the present invention comprises a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical compositions including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

[568] In certain embodiments, a pharmaceutical composition of the present invention comprises a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-

limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80 and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g., polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[569] In certain embodiments, a pharmaceutical composition of the present invention comprises a sustained-release system. A non-limiting example of such a sustained-release system is a semi-permeable matrix of solid hydrophobic polymers. In certain embodiments, sustained-release systems may, depending on their chemical nature, release pharmaceutical agents over a period of hours, days, weeks or months.

[570] Appropriate pharmaceutical compositions of the present disclosure can be determined according to any clinically-acceptable route of administration of the composition to the subject. The manner in which the composition is administered is dependent, in part, upon the cause and/or location. One skilled in the art will recognize the advantages of certain routes of administration. The method includes administering an effective amount of the agent or compound (or composition comprising the agent or compound) to achieve a desired biological response, e.g., an amount effective to alleviate, ameliorate, or prevent, in whole or in part, a symptom of a condition to be treated, e.g., oncology and neurology disorders. In various aspects, the route of administration is systemic, e.g., oral or by injection. The agents or compounds, or pharmaceutically acceptable salts or derivatives thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally, intraportally, and parenterally. Alternatively or in addition, the route of administration is local, e.g., topical, intra-tumor and peri-tumor. In some embodiments, the compound is administered orally.

[571] In certain embodiments, a pharmaceutical composition of the present disclosure is prepared for oral administration. In certain of such embodiments, a pharmaceutical composition is formulated by combining one or more agents and pharmaceutically acceptable carriers. Certain of such carriers enable pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral

ingestion by a subject. Suitable excipients include, but are not limited to, fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). In certain embodiments, such a mixture is optionally ground and auxiliaries are optionally added. In certain embodiments, pharmaceutical compositions are formed to obtain tablets or dragee cores. In certain embodiments, disintegrating agents (e.g., cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate) are added.

[572] In certain embodiments, dragee cores are provided with coatings. In certain such embodiments, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings.

[573] In certain embodiments, pharmaceutical compositions for oral administration are push-fit capsules made of gelatin. Certain of such push-fit capsules comprise one or more pharmaceutical agents of the present invention in admixture with one or more filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, pharmaceutical compositions for oral administration are soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In certain soft capsules, one or more pharmaceutical agents of the present invention are dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

[574] In certain embodiments, pharmaceutical compositions are prepared for buccal administration. Certain of such pharmaceutical compositions are tablets or lozenges formulated in conventional manner.

[575] In certain embodiments, a pharmaceutical composition is prepared for transmucosal administration. In certain of such embodiments penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[576] In certain embodiments, a pharmaceutical composition is prepared for administration by inhalation. Certain of such pharmaceutical compositions for inhalation are prepared in the form of an aerosol spray in a pressurized pack or a nebulizer. Certain of such pharmaceutical compositions comprise a propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain embodiments using a pressurized aerosol, the dosage unit may be determined with a valve that delivers a metered

amount. In certain embodiments, capsules and cartridges for use in an inhaler or insufflator may be formulated. Certain of such formulations comprise a powder mixture of a pharmaceutical agent of the invention and a suitable powder base such as lactose or starch.

[577] In other embodiments the compound of the present disclosure are administered by the intravenous route. In further embodiments, the parenteral administration may be provided in a bolus or by infusion.

[578] In certain embodiments, a pharmaceutical composition is prepared for rectal administration, such as a suppository or retention enema. Certain of such pharmaceutical compositions comprise known ingredients, such as cocoa butter and/or other glycerides.

[579] In certain embodiments, a pharmaceutical composition is prepared for topical administration. Certain of such pharmaceutical compositions comprise bland moisturizing bases, such as ointments or creams. Exemplary suitable ointment bases include, but are not limited to, petrolatum, petrolatum plus volatile silicones, and lanolin and water in oil emulsions. Exemplary suitable cream bases include, but are not limited to, cold cream and hydrophilic ointment.

[580] In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

[581] In certain embodiments, one or more compounds of formula (i)-(iv) or (a), or a pharmaceutically acceptable salt or solvate thereof are formulated as a prodrug. In certain embodiments, upon in vivo administration, a prodrug is chemically converted to the biologically, pharmaceutically or therapeutically more active form. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (e.g., through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, prodrugs are less water soluble than the corresponding active form. In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, a prodrug is an ester. In certain such embodiments, the ester is metabolically hydrolyzed to carboxylic acid upon administration. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a prodrug comprises a short peptide (polyaminoacid) bound to an acid

group. In certain of such embodiments, the peptide is cleaved upon administration to form the corresponding active form.

[582] In certain embodiments, a prodrug is produced by modifying a pharmaceutically active compound such that the active compound will be regenerated upon in vivo administration. The prodrug can be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism in vivo, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, e.g., Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

[583] In various aspects, the androgen receptor N-terminal domain inhibitors in the pharmaceutical composition or combination as disclosed herein can be administered at about 0.001 mg/kg to about 100 mg/kg body weight (e.g., about 0.01 mg/kg to about 10 mg/kg or about 0.1 mg/kg to about 5 mg/kg).

[584] The concentration of a disclosed compound in a pharmaceutically acceptable mixture will vary depending on several factors, including the dosage of the compound to be administered, the pharmacokinetic characteristics of the compound(s) employed, and the route of administration. The agent may be administered in a single dose or in repeat doses. The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. Treatments may be administered daily or more frequently depending upon a number of factors, including the overall health of a patient, and the formulation and route of administration of the selected compound(s). An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[585] The compounds or pharmaceutical compositions of the present disclosure may be manufactured and/or administered in single or multiple unit dose forms.

[586] Having now generally described the invention, the same will be more readily understood through reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

[587] The disclosure now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

[588] Synthetic Preparation

[589] The novel compounds of the present invention can be prepared in a variety of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods as hereinafter described below, together with synthetic methods known in the art of synthetic organic chemistry or variations thereon as appreciated by those skilled in the art.

[590] Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene and Wuts, *Protective Groups in Organic Synthesis*, 44th. Ed., Wiley & Sons, 2006, as well as in Jerry March, *Advanced Organic Chemistry*, 4th edition, John Wiley & Sons, publisher, New York, 1992 which are incorporated herein by reference in their entirety.

[591] Compounds of the present invention can be prepared by the literature methods cited in the following text. The following schemes depict established, known syntheses of these scaffolds.

[592] The groups and/or the substituents of the compounds of the present invention can be synthesized and attached to these scaffolds by the literature methods cited in the following text. The following schemes depict the known techniques for accomplishing this joinder.

[593] General Synthesis

[594] Compounds of the present invention can be synthesized using the following methods. General reaction conditions are given, and reaction products can be purified by general known methods including crystallization, silica gel chromatography using various organic solvents such as hexane, cyclohexane, ethyl acetate, methanol and the like, preparative high pressure liquid chromatography or preparative reverse phase high pressure liquid chromatography.

[595] Representative Synthesis of Androgen Receptor N-terminal domain inhibitors

[596] For synthesis of Compounds in Table A, see WO 2019/226991 for procedures. The disclosures of WO 2019/226991 are hereby incorporated by reference in their entireties.

[597] Example 1: (S)-N-(3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-oxopropyl)methanesulfonamide (**AA51(S)**):

[598] To a solution of (R)-N-(3-(4-(2-(3,5-dichloro-4-(oxiran-2-ylmethoxy)phenyl)propan-2-yl)phenoxy)-2-oxopropyl)methanesulfonamide (**1g**) (30 mg, 0.06 mmol, 1.0 eq.) in MeCN (6 mL) was added $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (34 mg, 0.09 mmol, 1.5 eq.) and the solution was heated to reflux for 16 hours. The resulting white paste was collected by filtration and washed with ethyl acetate and the clear suspension was concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography (elution: ethyl acetate in hexane) to provide (S)-N-(3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-oxopropyl)methanesulfonamide (**AA51(S)**): (13.7 mg, 42.4 %) as a colorless oil. LRMS ($\text{M} + \text{Na}^+$) m/z : calcd 560.05; found 560.0. ^1H NMR (400 MHz, DMSO-d_6): δ 7.44 (t, $J = 5.6$ Hz, 1H), 7.23 (s, 2H), 7.15 (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 5.55 (d, $J = 5.2$ Hz, 1H), 4.91 (s, 2H), 4.01-4.10 (m, 3H), 3.96 (d, $J = 5.6$ Hz, 2H), 3.82 (dd, $J = 4.0, 11.2$ Hz, 2H), 3.70 (dd, $J = 4.0, 11.2$ Hz, 2H), 2.93 (s, 3H), 1.60 (s, 6H).

[599] Example 2: N-(3-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-2-oxopropyl)methanesulfonamide (**AA31**). To a solution of (R)-N-(3-(4-(2-(3,5-dichloro-4-(3-CHloropropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide (**2a**) (25.0 mg, 0.048 mmol, 1.0 eq.) in anhydrous dichloromethane (3 mL) was treated Dess-Martin periodinane (41 mg, 0.096 mmol, 2.0 eq.) at 0 °C for 10 minutes. Then it was warmed to the room temperature for 16 hours. The reaction was quenched by the addition of a saturated solution of ammonium chloride (2 ml) and the mixture was extracted with ethyl acetate (2 x 30 ml). The combined organic layers were washed with deionized water (2 x 30 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash silica gel column chromatography (elution: acetate in hexane) to provide N-(3-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-2-oxopropyl)methanesulfonamide (**AA31**) (30 mg, 88 % yield) as a colorless oil. LRMS ($\text{M} + \text{Na}^+$) m/z : calcd 544.06; found 544.2. ^1H NMR (400 MHz, DMSO-d_6): δ 7.44 (t, $J = 5.6$ Hz, 1H), 7.24 (s, 2H), 7.15 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 8.8$ Hz, 2H), 4.91 (s, 2H), 4.01 (m, 4H), 3.86 (t, $J = 6.4$ Hz, 2H), 2.93 (s, 3H), 2.19 (m, 2H), 1.60 (s, 6H).

[600] Example 3: 1-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)phenoxy)-3-(methylsulfonyl)propan-2-one (**AA55**). Compound (**AA55**) was synthesized according to

Compound (AA31) by using (S)-2,6-dichloro-4-(2-(4-(2-hydroxy-3-(methylsulfonyl)propoxy)phenyl)propan-2-yl)phenol (**3d**) Yield (94.1%). LRMS (M + Na⁺) m/z: calcd 529.06; found 529.3. ¹H NMR (400 MHz, DMSO-d₆): δ 7.24 (s, 2H), 7.15 (d, J = 9.2 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 4.96 (s, 2H), 4.59 (s, 2H), 4.08 (t, J = 6.0 Hz, 2H), 3.86 (t, J = 6.0 Hz, 2H), 3.11 (s, 3H), 2.19 (m, 2H), 1.61 (s, 6H).

[601] Example 4: N-(3-(4-(3-(3,5-dichloro-4-(3-chloropropoxy)phenyl)oxetan-3-yl)phenoxy)-2-oxopropyl)methanesulfonamide (**AA43**). To a solution of tert-butyl N-(3-(4-(3-(3,5-dichloro-4-(3-chloropropoxy)phenyl)oxetan-3-yl)phenoxy)-2-oxo-propyl)-N-methylsulfonyl-carbamate (60 mg, 0.1 mmol) in DCM (2 mL) was added formic acid (1 mL) and the solution was stirred at 25 °C for 15 min. TLC showed the reaction was completed. The reaction was concentrated under reduced pressure. The residue was purified by prep-HPLC (HCO₂H) to give N-(3-(4-(3-(3,5-dichloro-4-(3-chloropropoxy)phenyl)oxetan-3-yl)phenoxy)-2-oxopropyl)methanesulfonamide (6.7 mg, yield: 13.2 %) as colorless oil. LCMS purity (220 nm): 94.5%. ¹H NMR (400MHz, CHCl₃-d) δ 7.18-7.10 (m, 4H), 6.93 (br d, J=7.7 Hz, 2H), 5.20 (br d, J=5.1 Hz, 2H), 5.12 (br d, J=5.3 Hz, 2H), 5.05 (br s, 1H), 4.69 (s, 2H), 4.41 (br d, J=4.2 Hz, 2H), 4.21-4.14 (m, 2H), 3.87 (br t, J=5.8 Hz, 2H), 3.01 (s, 3H), 2.30 (br t, J=5.8 Hz, 2H). %. LRMS (M + H⁺) m/z: calcd 535.0; found 535.

[602] Example 5: Synthesis of N-(4-(2-(3,5-dichloro-4-(3-chloropropoxy)phenyl)propan-2-yl)benzyl)-2-(methylsulfonylamido)acetamide (**AA46**). To a solution of 2-bromo-N-[[4-[1-[3,5-dichloro-4-(3-chloropropoxy)phenyl]-1-methyl-ethyl]phenyl]methyl]acetamide (**5**) (100 mg, 0.20 mol) and Cs₂CO₃ (321 mg, 0.98 mmol) in DMF (5 mL) was added methanesulfonamide (37.5 mg, 0.39 mmol). Then the resulting solution was stirred at 25 °C for 2 hours. LCMS showed the reaction was completed. The solution was poured into water (5 mL) and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 mL x 4). The combined organic layers were washed with brine (4 mL x 3), dried over Na₂SO₄, filtered and concentrated. The crude product was purified by prep-HPLC (TFA) to give the N-[[4-[1-[3,5-dichloro-4-(3-chloropropoxy)phenyl]-1-methyl-ethyl]phenyl]methyl]-2-(methanesulfonamido)acetamide (24.1 mg, yield: 23.4 %) as a yellow gum. HPLC purity (220 nm): 98.3%. ¹H NMR (400MHz, CHCl₃-d) δ 7.26-7.18 (m, 4H), 7.14 (s, 2H), 6.34 (br s, 1H), 5.02 (br s, 1H), 4.49 (d, J=5.7 Hz, 2H), 4.18 (t, J=5.8 Hz, 2H), 3.92-3.85 (m, 4H), 3.03 (s, 3H), 2.31 (quin, J=6.1 Hz, 2H), 1.66 (s, 6H). LCMS (M + H⁺) m/z: clcd 522.1; found 523.0.

[603] Example 6: Synthesis of N-(3,5-dichloro-4-(3-chloropropoxy)phenyl)-N-(4-(3-(methylsulfonamido)-2-oxopropoxy)phenyl)acetamide (**AA71**). A solution of tert-butyl (3-(4-(N-(3,5-dichloro-4-(3-chloropropoxy)phenyl)acetamido)phenoxy)-2-oxopropyl)(methylsulfonyl)carbamate (200 mg, 0.2 mmol) in HCl/EtOAc (4 M, 4 mL) was stirred at 25 °C for 15 min. TLC showed the reaction was completed. The reaction was concentrated under reduced pressure. The residue was purified by prep-HPLC (HCl) to give N-(3,5-dichloro-4-(3-chloropropoxy)phenyl)-N-(4-(3-(methylsulfonamido)-2-oxopropoxy)phenyl)acetamide (69 mg, yield: 59.0 %) as yellow oil. HPLC purity (220 nm): 93.5%. ¹H NMR (400 MHz, CHCl₃-d) δ = 7.26 - 7.21 (m, 4H), 7.01 - 6.92 (m, 2H), 5.05 (br s, 1H), 4.70 (s, 2H), 4.40 (d, *J* = 5.1 Hz, 2H), 4.15 (br s, 2H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.02 (s, 3H), 2.28 (quin, *J* = 6.0 Hz, 2H), 2.10 - 2.01 (m, 3H). LCMS (M + H⁺) *m/z*: clcd: 538.0; found: 539.0.

[604] Example 7: Synthesis of N-(3-((3',5'-dichloro-4'-(3-chloropropoxy)-[1,1'-biphenyl]-4-yl)oxy)-2-oxopropyl)methanesulfonamide (**AA73**). A solution of tert-butyl (3-((3',5'-dichloro-4'-(3-chloropropoxy)-[1,1'-biphenyl]-4-yl)oxy)-2-oxopropyl)(methylsulfonyl)carbamate (**7**) (70.0%, 0.13 g, 0.15 mol) in HCl/EtOAc (2 mL) was stirred at 20 °C for 0.5 hour. LCMS showed the reaction was completed. The solution was concentrated under reduced pressure. The crude product was purified by prep-HPLC (HCl) to give N-(3-((3',5'-dichloro-4'-(3-chloropropoxy)-[1,1'-biphenyl]-4-yl)oxy)-2-oxopropyl)methanesulfonamide (29 mg, yield: 27.0 %) as brown oil. HPLC purity (220 nm): 90.5%. ¹H NMR (400MHz, CHCl₃-d) δ = 7.51 - 7.48 (d, *J*=8.8 Hz, 2H), 7.47 (s, 2H), 7.00 - 6.96 (d, *J*=8.6 Hz, 2H), 5.12 - 4.99 (m, 1H), 4.72 (s, 2H), 4.46 - 4.37 (d, *J*=5.2 Hz, 2H), 4.25 - 4.17 (t, *J*=5.7 Hz, 2H), 3.96 - 3.83 (t, *J*=6.4 Hz, 2H), 3.02 (s, 3H), 2.38 - 2.25 (m, 2H). LCMS (M + H⁺) *m/z*: clcd: 480.0; found 480.0.

[605] Example 8: Synthesis of N-(3-(4-(3,5-dichloro-4-(3-chloro-2-hydroxypropoxy)phenethyl)phenoxy)-2-oxopropyl)methanesulfonamide (**AA75**). A solution of tert-butyl N-(3-(4-(2-(3,5-dichloro-4-(3-chloro-2-(methoxymethoxy)propoxy)phenyl)ethyl)phenoxy)-2-oxo-propyl)-N-methylsulfonyl-carbamate (**9**) (180 mg, 0.27 mmol) in TFA (2 mL) and DCM (10 mL) was stirred at 20 °C for 3 hours. LCMS showed the reaction was completed. The resulting solution was concentrated under reduced pressure. The residue was purified by prep-HPLC (HCl) to give N-(3-(4-(2-(3,5-dichloro-4-(3-chloro-2-hydroxy-propoxy)phenyl)ethyl)phenoxy)-2-oxo-propyl)methanesulfonamide (13.9 mg, yield: 9.84%) as white solid. HPLC purity (220 nm): 92%. ¹H NMR (400

MHz, CHCl₃-d) δ ppm 7.06-7.11 (m, 4 H), 6.80-6.86 (m, 2 H), 5.02 (br s, 1 H), 4.63-4.69 (m, 2 H), 4.40 (d, J=5.14 Hz, 2 H), 4.23 (br s, 1 H), 4.12-4.20 (m, 2 H), 3.74-3.90 (m, 2 H), 3.00 (s, 3 H), 2.83-2.86 (m, 2 H), 2.79-2.83 (m, 2 H).

[606] Example 9: Synthesis of N-(3-((4-(2-(3,5-dichloro-4-(2-chloroethoxy)phenyl)propan-2-yl)phenyl)(methylamino)-2-oxopropyl)methanesulfonamide hydrochloride (**AA81**). A solution of tert-butyl (3-((4-(2-(3,5-dichloro-4-(2-chloroethoxy)phenyl)propan-2-yl)phenyl)(methylamino)-2-oxopropyl) (methylsulfonyl)carbamate (100 mg, 0.2 mmol) in HCl/EtOAc (2 mL) was stirred at 25 °C for 15 min. TLC showed the reaction was completed. The reaction was concentrated under reduced pressure. The residue was purified by prep-HPLC (HCl) to give N-(3-((4-(2-(3,5-dichloro-4-(2-chloroethoxy)phenyl)propan-2-yl)phenyl)(methylamino)-2-oxopropyl)methanesulfonamide hydrochloride (7.6 mg, yield: 9.1 %) as yellow oil. ¹H NMR (400MHz, CHCl₃-d) δ 7.16 (br s, 2H), 7.12 (s, 2H), 6.95 (br s, 2H), 5.70 (br s, 1H), 4.49-4.22 (m, 4H), 4.15-3.81 (m, 4H), 3.18 (br s, 3H), 2.94 (br s, 3H), 1.62 (s, 6H). LCMS (M + H⁺) m/z: clcd: 520.1; found 521.0.

[607] For synthesis of Compounds in Table B, see WO 2017/177307 for procedures. The disclosures of WO 2017/177307 are hereby incorporated by reference in their entireties.

[608] Example 10: Synthesis of (R)-3-(4-(2-(3,5-dichloro-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (Compound **1a**). To a solution of (S)-4-((4-(2-(3,5-dichloro-4-(((R)-oxiran-2-yl)methoxy)phenyl)propan-2-yl)phenoxy)methyl)-2,2-dimethyl-1,3-dioxolane (560 mg, 1.2 mmol, 1.0 equiv) in MeCN (12 mL) was added CeCl₃·7H₂O (1118 mg, 3.0 mmol, 2.5 equiv) and the mixture was heated to reflux for 16 h. The resulting white paste was collected by filtration and washed with ethyl acetate and the clear suspension was concentrated under reduced pressure. The resulting residue was purified by column chromatography to provide the titled compound (512 mg, 92%) as a sticky oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.15-7.12 (m, 4H), 6.86 (d, J = 9.0 Hz, 2H), 4.26-4.23 (m, 1H), 4.21-4.15 (m, 2H), 4.15-4.11 (m, 1H), 4.08-4.03 (m, 2H), 3.86 (dd, J = 4.8 Hz, 10.8 Hz, 2H), 3.78 (dd, J = 6.6 Hz, 12.6 Hz, 2H), 1.64 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 156.76, 149.30, 148.26, 141.84, 128.52, 127.87, 127.67, 114.35, 73.69, 70.48, 69.26, 63.78, 45.55, 42.34, 30.79; ESI-LRMS calcd for [M + Na]⁺ 485.1, found 485.4.

[609] Example 11: Synthesis of (R)-3-(4-(2-(3,5-dibromo-4-((S)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol (Compound **3a**). Compound

3a was synthesized by a similar procedure used to prepare Compound **1a** in Example 10. ¹H NMR (400 MHz, DMSO-D₆) δ (ppm) = 7.39 (s, 1H), 7.30 (dd, J = 2.0 Hz, 34.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.57-5.54 (m, 1H), 4.91 (d, J = 4.8 Hz, 1H), 4.64 (t, J = 5.6 Hz, 1H), 4.10-4.08 (m, 1H), 3.98-3.92 (m, 3H), 3.86-3.81 (m, 2H), 3.79-3.76 (m, 1H), 3.71 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.45-3.42 (m, 2H), 1.60 (s, 6H).

[610] Example 12: Synthesis of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-((*R*)-2-hydroxy-3-methoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **5a**). To a solution of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-(((*R*)-oxiran-2-yl)methoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (15 mg, 0.034 mmol, 1.0 equiv) in anhydrous methanol (2 mL) was added Erbium (III) trifluoromethanesulfonate (2.1 mg, 0.0034 mmol, 0.1 equiv) and the mixture was stirred at room temperature for 40 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (0.5 ml) and the mixture was extracted with ethyl acetate (2 x 10 ml). The organic layer was washed with deionized water (2 x 10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on silica gel (elution: 30% ethyl acetate in hexane to 50% ethyl acetate in hexane) to provide Compound **5a** (12.5 mg, 77.1%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.14-7.10 (m, 4H), 6.87 (d, J = 6.0 Hz, 2H), 4.26-4.22 (m, 1H), 4.21-4.15 (m, 3H), 4.06-4.01 (m, 2H), 3.87 (dd, J = 6.0 Hz, 11.4 Hz, 1H), 3.79 (dd, J = 5.4 Hz, 11.4 Hz, 1H), 3.61 (dd, J = 4.2 Hz, 9.6 Hz, 1H), 3.57 (dd, J = 6.0 Hz, 9.6 Hz, 1H), 3.44 (s, 3H), 1.64 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 156.37, 148.81, 147.69, 141.04, 127.95, 127.25, 127.05, 113.81, 73.13, 73.00, 69.93, 68.58, 68.44, 58.88, 45.00, 41.78, 30.25.

[611] Example 13: Synthesis of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-((*R*)-2-hydroxy-3-isopropoxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **7a**). Compound **7a** was synthesized by a similar procedure used to prepare Compound **3a** in Example 11. ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.13-7.10 (m, 4H), 6.86 (d, J = 8.8 Hz, 2H), 4.25-4.12 (m, 4H), 4.03-3.98 (m, 2H), 3.85 (dd, J = 5.2 Hz, 10.8 Hz, 1H), 3.77 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.67-3.53 (m, 3H), 2.83 (s, 1H), 2.57 (s, 1H), 1.62 (s, 6H), 1.18 (d, J = 6.0 Hz, 6H).

[612] Example 14: Synthesis of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-((*S*)-3-fluoro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **8a**). To a solution of Compound **1a** (1 equiv; synthesized according to Example 10) in dichloromethane were

successively added triethylamine trihydrofluoride (2 equiv) and XtalFluor-M (2 equiv). After 3 h, the reaction mixture was quenched at room temperature with a 5% aqueous sodium bicarbonate solution and stirred for 15 min, and the resulting mixture was extracted twice with dichloromethane. The organic phases were combined, dried over anhydrous magnesium sulfate, and filtered. Solvents were evaporated, and the resulting crude material was purified by silica gel chromatography to provide Compound **8a**. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.16-7.14 (m, 4H), 6.87 (d, J = 8.4 Hz, 2H), 4.69-4.56 (m, 2H), 4.30-4.22 (m, 2H), 4.22-4.16 (m, 2H), 4.10-4.09 (m, 2H), 3.87 (dd, J = 6.0 Hz, 11.4 Hz, 1H), 3.79 (dd, J = 5.4 Hz, 10.8 Hz, 1H), 1.64 (s, 6H).

[613] Example 15: Synthesis of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-((*R*)-2-hydroxy-3-(1*H*-imidazol-1-yl)propoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **9a**). To a solution of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-(((*R*)-oxiran-2-yl)methoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (12.6 mg, 0.028 mmol, 1.0 equiv) in anhydrous MeCN (2 mL) was added Bismuth (III) trifluoromethanesulfonate (1.8 mg, 0.0028 mmol, 0.1 equiv) and the mixture was stirred at room temperature for 40 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (0.5 ml) and the mixture was extracted with ethyl acetate (2 x 10 ml). The organic layer was washed with deionized water (2 x 10 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography to provide Compound **9a** (8.7 mg, 60.4%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.56 (s, 1H), 7.16-7.14 (m, 4H), 7.04 (s, 1H), 7.01 (s, 1H), 6.86 (d, J = 8.4 Hz, 2H), 4.29-4.23 (m, 3H), 4.22-4.13 (m, 3H), 3.98-3.92 (m, 2H), 3.87 (dd, J = 6.0 Hz, 11.4 Hz, 1H), 3.79 (dd, J = 4.8 Hz, 10.8 Hz, 1H), 1.65 (s, 6H).

[614] Example 16: Synthesis of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-((*R*)-2-hydroxy-3-morpholinopropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **11a**). Compound **11a** was synthesized by a similar procedure used to prepare Compound **9a** in Example 15. ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.16-7.11 (m, 4H), 6.88 (d, J = 8.8 Hz, 2H), 4.27-4.13 (m, 4H), 4.07-3.98 (m, 2H), 3.90-3.77 (m, 6H), 2.84-2.80 (m, 2H), 2.73-2.72 (m, 2H), 2.71-2.67 (m, 2H), 1.65 (s, 6H); ESI-LRMS calcd for [M + H]⁺ 532.1, found 534.6.

[615] Example 17: Synthesis of (*R*)-1-amino-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **12a**) and *N*-((*R*)-3-(4-

(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide (Compound **13a**)

[616] Synthesis of (*R*)-1-amino-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **12a**). To a solution of (*R*)-1-azido-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (57 mg, 0.117 mmol, 1.0 equiv) in MeCN (6 mL) was added triphenylphosphine (36.7 mg, 0.14 mmol, 1.2 equiv) and the mixture was heated to reflux for 16 h. The reaction was quenched by deionized water (2 ml) and the mixture was extracted with ethyl acetate (2 x 30 ml). The organic layer was washed with deionized water (2 x 30 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on Si gel (elution: 2% methanol in dichloromethane to 30% methanol in dichloromethane) to provide Compound **12a** (24.3 mg, 44.9%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.12-7.09 (m, 4H), 6.84 (d, J = 8.4 Hz, 2H), 4.24-4.21 (m, 1H), 4.17-4.13 (m, 2H), 3.97 (m, 3H), 3.84 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.76 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.00-2.85 (m, 2H), 1.61 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 157.00, 149.35, 148.31, 141.60, 128.52, 127.81, 127.61, 114.37, 73.78, 70.47, 70.42, 70.14, 45.65, 44.11, 42.34, 30.25; ESI-LRMS calcd for [M + H]⁺ 462.1, found 463.9.

[617] Synthesis of *N*-((*R*)-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)-2-hydroxypropyl)methanesulfonamide (Compound **13a**). To a solution of (*R*)-1-azido-3-(4-(2-(3,5-dichloro-4-((*S*)-3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (14.3 mg, 0.031 mmol, 1.0 equiv) in anhydrous dichloromethane (3 mL) was treated triethylamine (12.5 mg, 0.124 mmol, 4.0 equiv) and methane sulfonyl chloride (3.6 mg, 0.031 mmol, 1.0 equiv) sequentially at 0 °C for 10 minutes. Then it was warmed to room temperature for 16 hours. The reaction was quenched by the addition of a saturated solution of ammonium chloride (2 ml) and the mixture was extracted with ethyl acetate (2 x 20 ml). The organic layer was washed with deionized water (2 x 20 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on silica gel (elution: 50% ethyl acetate in hexane to 75% ethyl acetate in hexane) to provide Compound **13a** (9.7 mg, 57.9%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.15-7.13 (m, 4H), 6.87 (d, J = 5.4 Hz, 2H), 4.93-4.90 (m, 1H), 4.26-4.23 (m, 1H), 4.21-4.13 (m, 3H), 4.06-4.01 (m, 2H), 3.87 (dd, J = 5.4 Hz, 11.4 Hz, 1H), 3.79 (dd, J = 5.4 Hz, 10.8 Hz, 1H), 3.50-3.45 (m, 1H), 3.26-3.31 (m, 1H), 3.03 (s, 3H), 1.64

(s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ (ppm) = 155.94, 148.69, 147.73, 141.57, 127.99, 127.39, 127.05, 113.81, 73.14, 69.92, 68.85, 68.54, 45.19, 44.99, 41.81, 39.98, 30.22.

[618] Example 18: Synthesis of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-((*S*)-3-(ethylsulfonyl)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (Compound **14a**). To a solution of (*S*)-1-chloro-3-(2,6-dichloro-4-(2-(4-((*S*)-3-(ethylthio)-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propan-2-ol (14.6 mg, 0.029 mmol, 1.0 equiv) in anhydrous dichloromethane (3 mL) was treated 3-chloroperbenzoic acid (14.0 mg, 0.081 mmol, 2.8 equiv) at 0 °C for 10 minutes. Then it was warmed to room temperature for 3 hours. The reaction was quenched by the addition of a saturated solution of ammonium chloride (2 mL) and the mixture was extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with saturated NaHCO_3 (20 mL), deionized water (2 x 20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by gradient flash column chromatography on Si gel (elution: 30% ethyl acetate in hexane to 75% ethyl acetate in hexane) to provide Compound **14a** (4.7 mg, 31.0%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.18-7.15 (m, 4H), 6.88 (d, J = 8.8 Hz, 2H), 4.69-4.67 (m, 1H), 4.27-4.15 (m, 3H), 4.10-4.07 (m, 2H), 3.88 (dd, J = 5.2 Hz, J = 11.2 Hz, 1H), 3.80 (dd, J = 5.2 Hz, J = 10.8 Hz, 1H), 3.39-3.20 (m, 4H), 1.66 (s, 6H), 1.48 (t, J = 7.2 Hz, 3H); ESI-LRMS calcd for $[\text{M} + \text{Na}]^+$ 561.1, found 561.5.

[619] Example 19: Synthesis of (*R*)-3-(4-(2-(4-((*S*)-3-chloro-2-hydroxypropoxy)-3-methylphenyl)propan-2-yl)-2-methylphenoxy)propane-1,2-diol (Compound **22a**). Compound **22a** was synthesized by a similar procedure used to prepare Compound **1a** in Example 10. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) = 6.97-6.94 (m, 4H), 6.81-6.76 (m, 2H), 5.50 (d, J = 4.8 Hz, 1H), 4.86 (s, 1H), 4.61 (s, 1H), 4.06-4.00 (m, 1H), 3.97-3.89 (m, 3H), 3.86-3.76 (m, 3H), 3.69 (dd, J = 5.6 Hz, 11.2 Hz, 1H), 3.50-3.44 (m, 2H), 2.10 (s, 6H), 1.55 (s, 6H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ (ppm) = 155.14, 154.74, 143.23, 142.75, 129.32, 129.23, 125.66, 125.62, 125.22, 125.16, 111.28, 111.16, 70.67, 70.02, 69.48, 69.32, 63.43, 55.50, 47.53, 31.42, 16.86, 16.79.

[620] Example 20: Synthesis (*R*)-1-(4-(2-(4-((*R*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate (Compound **5dA**). Ac₂O (128 mg, 1.26 mmol, 6.0 equiv.), Et₃N (127 mg, 1.26 mmol, 6.0 equiv.) and DMAP (26 mg, 0.21 mmol, 1.0 equiv.) were added to a solution of Compound **5a** (100 mg, 0.21 mmol, 1.0 equiv., see Example 12) in anhydrous DCM (5 mL) at room temperature and the resultant mixture was stirred at the same temperature overnight. The mixture was diluted with EtOAc (30 mL) and the organic layer was washed with water (15 mL) and brine (15 mL). The organic layer was further dried over anhydrous MgSO₄ and evaporated under reduced pressure. The crude was loaded onto a silica gel column and eluted with Hexane/EtOAc (13/1 to 6/1) to give 111 mg of the titled compound as colorless oil (yield: 95.0%). ¹H NMR (600 MHz, CHLOROFORM-*d*) δ 7.11 - 7.12 (m, 2H), 7.09 - 7.11 (m, 2H), 6.82 - 6.87 (m, 2H), 5.32 - 5.35 (m, 1H), 5.28 - 5.32 (m, 1H), 4.18 - 4.26 (m, 2H), 4.09 - 4.16 (m, 2H), 3.97 (dd, *J* = 5.14, 11.74 Hz, 1H), 3.88 (dd, *J* = 5.14, 11.74 Hz, 1H), 3.66 (dd, *J* = 2.20, 4.40 Hz, 2H), 3.40 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H), 1.61 (s, 6H). ¹³C NMR (151 MHz, CHLOROFORM-*d*) δ 170.8, 170.4, 156.9, 149.4, 148.4, 141.8, 128.7, 127.9, 127.7, 114.5, 71.9, 71.1, 70.9, 66.4, 59.6, 42.7, 42.4, 30.9, 21.4, 21.2.

[621] Example 21: Synthesis (*R*)-1-(4-(2-(4-((*S*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-methoxypropan-2-yl acetate (Compound **5aA**). Acetic Anhydride (4.1 mg, 0.04 mmol, 4.0 equiv) was added to a solution of Compound **5a** (5.0 mg, 0.01 mmol, 1.0 equiv, see Example 12), DMAP (0.1 mg, 0.001 mmol, 0.1 equiv) and Et₃N (4.1 mg, 0.04 mmol, 4.0 equiv) in anhydrous dichloromethane (1 mL). The resulting solution was stirred overnight at room temperature. Dichloromethane was removed under reduced pressure and the residue was purified by column chromatography to afford the title compound as a colorless oil (5.8 mg, 98.6%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.11-7.08 (m, 4H), 6.83 (d, *J*=8.8, 2H), 5.35-5.26 (m, 2H), 4.26-4.17 (m, 2H), 4.16-4.07 (m, 2H), 3.96 (dd, *J*=5.2 Hz, 11.6 Hz, 1H), 3.86 (dd, *J*=5.6 Hz, 11.6 Hz, 1H), 3.66-3.61 (m, 2H), 3.38 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.60 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.80, 170.45, 156.96, 149.41, 148.39, 141.80, 128.69, 127.90, 127.70, 114.54, 71.91, 71.12, 70.54, 66.44, 59.62, 42.73, 42.43, 30.90, 21.38, 21.18; ESI-LRMS calcd for [M + H]⁺ 561.1, found 561.1.

[622] Example 22: Synthesis of (*R*)-1-(4-(2-(4-((*S*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-isopropoxypropan-2-yl acetate (Compound **7aA**).

Compound **7aA** was synthesized by a similar procedure used to prepare Compound **5aA** in Example 21 by using Compound **7a** prepared according to Example 13. Compound **7aA** was obtained as a colorless oil (6.4 mg, 96.2%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.12-7.08 (m, 4H), 6.85 (d, J=8.8, 2H), 5.36-5.30 (m, 1H), 5.28-5.22 (m, 1H), 4.27-4.09 (m, 4H), 3.97 (dd, J=5.2 Hz, 11.6 Hz, 1H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 3.71-3.57 (m, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 1.61 (s, 6H), 1.15 (dd, J=2.0 Hz, 6.0 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.16, 169.78, 156.42, 148.77, 147.72, 141.03, 128.02, 127.20, 127.03, 113.91, 71.97, 71.25, 70.98, 70.30, 66.01, 65.72, 42.06, 41.76, 30.24, 21.60, 21.54, 20.74, 20.52; ESI-LRMS calcd for [M + Na]⁺ 611.1, found 611.1.

[623] Example 23: Synthesis of (*S*)-1-(4-(2-(4-((*S*)-2-acetoxy-3-(ethylsulfonyl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate (Compound **14aA**). Compound **14aA** was synthesized by a similar procedure used to prepare Compound **5aA** in Example 21 by using Compound **14a** prepared according to Example 18. Compound **14aA** was obtained as a colorless oil (3.4 mg, 97.3%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.13-7.08 (m, 4H), 6.84 (d, J=8.8, 2H), 5.63-5.57 (m, 1H), 5.36-5.30 (m, 1H), 4.29-4.18 (m, 4H), 3.97 (dd, J=5.2 Hz, 12.0 Hz, 1H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 3.54-3.40 (m, 2H), 3.10 (q, J=7.2 Hz, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 1.61 (s, 6H), 1.44 (t, J=7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.41, 170.16, 158.50, 154.94, 142.86, 142.39, 128.70, 128.03, 127.66, 114.48, 71.87, 71.46, 67.79, 67.05, 52.48, 48.82, 42.69, 42.44, 30.86, 21.15, 20.90, 6.80; ESI-LRMS calcd for [M + Na]⁺ 645.1, found 645.1.

[624] Example 24: Synthesis of (*R*)-1-(4-(2-(4-((*S*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-morpholinopropan-2-yl acetate (Compound **11aA**). Compound **11aA** was synthesized by a similar procedure used to prepare Compound **5aA** in Example 21 by using Compound **11a** prepared according to Example 16. Compound **11aA** was obtained as a colorless oil (6.8 mg, 97.6%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.14-7.07 (m, 4H), 6.83 (d, J=8.8, 2H), 5.72-5.70 (m, 1H), 5.36-5.30 (m, 1H), 4.47-4.40 (m, 1H), 4.39-4.32 (m, 1H), 4.29-4.14 (m, 4H), 3.99-3.94 (m, 3H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 3.58-3.37 (m, 4H), 2.97 (m, 2H), 2.23 (s, 3H), 2.14 (s, 3H), 1.61 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.54, 170.37, 156.02, 149.12, 148.39, 142.61, 128.67, 128.06, 127.60, 114.34, 71.81, 70.90, 67.26, 65.89, 63.60, 58.52, 53.17, 52.58, 42.64, 42.40, 30.78, 29.87, 21.56, 21.11; ESI-LRMS calcd for [M + H]⁺ 616.1, found 616.1.

[625] Example 25: Synthesis of (*S*)-1-(4-(2-(4-((*R*)-2-acetoxy-3-(1*H*-imidazol-1-yl)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate (Compound **9aA**). Compound **9aA** was synthesized by a similar procedure used to prepare Compound **5aA** in Example 21 by using Compound **9a** prepared according to Example 15. Compound **9aA** was obtained as a colorless oil (5.6 mg, 93.6%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 9.40 (s, 1H), 7.39 (s, 1H), 7.20 (s, 1H), 7.14-7.10 (m, 4H), 6.82 (d, J=8.4, 2H), 5.50 (m, 1H), 5.35-5.31 (m, 1H), 4.78-4.70 (m, 2H), 4.27-4.18 (m, 4H), 3.96 (dd, J=5.6 Hz, 11.6 Hz, 1H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 2.14 (s, 3H), 2.11 (s, 3H), 1.61 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.21, 169.67, 155.72, 148.93, 142.61, 136.02, 128.53, 127.97, 127.46, 121.62, 120.13, 114.19, 71.66, 70.76, 69.72, 65.27, 49.70, 42.49, 42.26, 30.65, 20.96, 20.91; ESI-LRMS calcd for [M + H]⁺ 597.1, found 597.1.

[626] Example 26: Synthesis of (*S*)-1-(4-(2-(4-((*R*)-2-acetoxy-3-(*N*-(methylsulfonyl)acetamido)propoxy)phenyl)propan-2-yl)-2,6-dichlorophenoxy)-3-chloropropan-2-yl acetate (Compound **13aA**). Compound **13aA** was synthesized according to Example 21 by using Compound **13a**. Compound **13aA** was obtained as a colorless oil (6.0 mg, 100%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.13-7.08 (m, 4H), 6.82 (d, J=8.4, 2H), 5.47-5.42 (m, 1H), 5.36-5.30 (m, 1H), 4.29-4.07 (m, 6H), 3.97 (dd, J=5.2 Hz, 11.6 Hz, 1H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 3.33 (s, 3H), 2.44 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.61 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 171.33, 170.47, 170.29, 156.42, 149.13, 148.29, 142.17, 128.58, 127.88, 127.54, 114.33, 71.74, 70.82, 70.36, 67.19, 46.69, 42.66, 42.57, 42.31, 30.73, 24.49, 21.07, 20.03; ESI-LRMS calcd for [M + H]⁺ 666.1, found 666.1.

[627] Example 27: Synthesis of (*S*)-1-(4-(2-(4-((*S*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)-3-fluoropropan-2-yl acetate (Compound **8aA**). Compound **8aA** was synthesized according to Example 21 by using Compound **8a** prepared according to Example 14. Compound **8aA** was obtained as a colorless oil (5.8 mg, 95.9%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) = 7.13-7.10 (m, 4H), 6.84 (d, J=8.8 Hz, 2H), 5.39-5.29 (m, 2H), 4.79-4.71 (m, 1H), 4.67-4.59 (m, 1H), 4.27-4.18 (m, 2H), 4.16-4.14 (m, 2H), 3.97 (dd, J=5.2 Hz, 11.6 Hz, 1H), 3.87 (dd, J=5.6 Hz, 11.6 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 1.61 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.58, 170.46, 156.65, 149.33, 148.43, 142.14, 128.73, 127.99, 127.70, 114.48, 82.13, 80.99 (d, J=513.0 Hz), 71.92, 70.98, 70.77, 70.64 (d, J=19.5 Hz), 65.19, 65.15 (d, J=6.0 Hz), 42.73, 42.46, 30.91, 21.22, 21.19; ESI-LRMS calcd for [M + H]⁺ 549.1, found 549.1.

[628] **Example 28:** Synthesis of (*S*)-3-(4-(2-(4-((*S*)-2-acetoxy-3-chloropropoxy)-3,5-dichlorophenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate (Compound **1aA**). Compound **1aA** was synthesized according to Example 21 by using Compound **1a** prepared according to Example 10. Compound **1aA** was obtained as a colorless oil (63.0 mg, 97.1%). ¹H NMR (600 MHz, CDCl₃) δ (ppm) = 7.14-7.11 (m, 4H), 6.85 (d, J=12.0 Hz, 2H), 5.39-5.33 (m, 2H), 4.45 (dd, J=4.2 Hz, 12.0 Hz, 1H), 4.32 (dd, J=6.0 Hz, 12.0 Hz, 1H), 4.26 (dd, J=4.8 Hz, 10.2 Hz, 1H), 4.22 (dd, J=4.8 Hz, 10.2 Hz, 1H), 4.13-4.12 (m, 2H), 3.98 (dd, J=5.4 Hz, 12.0 Hz, 1H), 3.89 (dd, J=5.4 Hz, 12.0 Hz, 1H), 2.16 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 1.63 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ (ppm) = 170.21, 169.90, 169.77, 156.07, 148.66, 147.76, 141.40, 128.04, 127.28, 127.02, 113.88, 71.24, 70.31, 69.30, 65.55, 62.10, 42.05, 41.77, 30.23, 20.56, 20.50, 20.35; ESI-LRMS calcd for [M + Na]⁺ 611.1, found 611.0.

[629] **Biological Assays**

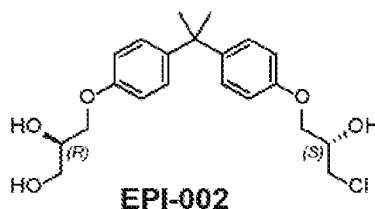
[630] **Example 29:** Activity of Exemplary Compounds in Cellular Assays

[631] LNCaP cells were transiently transfected with the PSA (6.1 kb)-luciferase reporter for 24 h, and then treated with indicated concentration of representative compounds with synthetic androgen, R1881 (1 nM) for 24 h. After 24 h of incubation with R1881, the cells were harvested, and relative luciferase activities were determined. To determine the IC₅₀, treatments were normalized to the maximum activity with androgen-induction (in the absence of test compounds, vehicle only) (Table 1).

[632] Luciferase Assay: Lysates were thawed on ice then collected into V-bottom 96-well tissue culture plates. Lysates were centrifuged at 4°C for 5 minutes at 4000 rpm. To measure luminescence of LNCaP cell lysates the Firefly Luciferase Assay System (Promega) was employed, according to manufacturer's protocol.

[633] Statistical analyses were performed using GraphPad Prism (Version 6.01 for Windows; La Jolla, CA, USA). Comparisons between treatment and control groups were compared using Two-Way ANOVA with post-hoc Dunnett's and Tukey's tests. Differences were considered statistically significant at P values less than 0.05. Densitometric quantification of relative AR levels was determined by Image.

[634] Table 1 shows the IC₅₀ of representative Compounds from Tables A-B from androgen-induced PSA luciferase assay. EPI-002 has the following structure:



[635] Table 1. IC₅₀ of Representative Compounds on Androgen-Induced PSA Luciferase Activity

Compound ID	Androgen-induced PSA-luciferase IC ₅₀ (nM)	n
AA31	51	5
AA33	38	6
AA52	74	3
AA56	344	3
AA85	368	1
1a	1410	11
5a	1030	6
9a	3120	11
11a	1050	10
12a	2260	4
13a	1054	3
14a	950	11
EPI-002	9580	2
Enzalutamide	189	8
Bicalutamide	306	2

[636] Material and Methods for Examples 30-33

[637] Western Blot Analysis: Cell lysates (20 µg) were run on 8% SDS-PAGE and transferred to nitrocellulose membrane for Western blot with anti-AR antibody (N20 from Santa Cruz) and anti-b-actin antibody.

[638] Cell Proliferation and Viability Assay: Each breast cancer cell line was plated at 5,000 cells per well in a 96-well plate in culture medium containing 5% or 10% fetal bovine serum. LNCaP and LNCaP95 (resistance to enzalutamide) prostate cancer cell lines were included as controls. The next day, cells were treated with vehicle control, enzalutamide, EPI-002 or Compound 13a at indicated concentrations with or without Palbociclib. For proliferation assay, cells were treated for 4 days and labeled with BrdU for 2 hours. Incorporation of BrdU was measured by enzyme-linked immunosorbent assay (ELISA; Cell Proliferation ELISA, BrdU (colorimetric) from Roche). For cell viability assays, alamarBlue was used for assess cell viability after 2 or 3 days of treatment.

[639] *Cell Cycle Analysis*: Breast cancer or prostate cancer cell lines were plated at 150,000 – 300,000 cells per 60-mm culture dish in medium containing 5% or 10% fetal bovine serum (5% charcoal-stripped serum for LNCaP95). Next day cells were treated with vehicle control, Enzalutamide or an androgen receptor N-terminal domain inhibitor with or without Palbociclib. At indicated time points, cells were labeled with BrdU for 2 hours and harvested for cell cycle analysis. Collected cells were stained with anti-BrdU-FTIC antibody and 7-aminoactinomycin D, and analyzed by flow cytometry using FACSCalibur.

[640] *Colony Forming Assay*: Cell lines were plated at 400 (SUM-159PT) or 500 (LNCaP95) cells per well of 24-well plates in medium containing 5% fetal bovine serum (or charcoal-stripped serum for LNCaP95). Next day cells were treated with vehicle control, Enzalutamide, an androgen receptor N-terminal domain inhibitor or Palbociclib at indicated concentrations. After 7 days (SUM-159PT) or 15 days (LNCaP95) of treatments, cells were fixed and stained with crystal violet.

[641] Example 30. Cell Proliferation and Cell Viability Assays

[642] Breast cancer cell lines and a prostate cancer cell line LNCaP were treated with vehicle control, enzalutamide (ENZA; 10 μ M) or EPI-002 (35 μ M) for 4 days. BrdU incorporation was used to assess cell proliferation. Data from each treatments were normalized to vehicle control as shown in **Fig. 1**. Results are presented as mean $\pm$ SEM ($n \geq 3$ except $n=2$ for MDA-MB-468).

[643] Breast cancer and prostate cancer cell lines were treated with vehicle control, various concentrations of Compound **13a** or Enzalutamide (ENZA), with or without 0.25 mM Palbociclib (Palbo) for 2 or 3 days. AlamarBlue was used to assess cell viability. Data from each treatments were normalized to vehicle control as shown in **Figs. 2A-2D**. Results are presented as mean $\pm$ SEM ($n = 3$ except $n = 6$ for LNCaP).

[644] These assays demonstrated that cell proliferation and viability of AR-positive breast cancer cell lines were significantly inhibited by treatment with EPI-002 or Compound **13a**. Anti-androgen such as enzalutamide had no or negligible effects.

[645] Example 31. Cell Cycle Analysis

[646] Breast cancer and prostate cancer cell lines were treated with vehicle control, 5 μ M or 10 μ M of Compound **13a** or Enzalutamide (ENZA), with or without 0.25 μ M Palbociclib (Palbo) for 2, 3 or 4 days. Representative data are shown. $n \geq 3$. Stacked columns show average results from 3-4 experiments. **Fig. 3** shows % cells in each cell cycle phase for AR-positive

SUM-159PT cells and **Fig. 4** shows % cells in each cell cycle phase for LNCaP95 prostate cancer cells.

[647] Results demonstrated that Compound **13a** caused cell cycle disruption. Combination with palbociclib resulted in cell accumulation in G1 phase and cell reduction in early S phase for AR-positive SUM-159PT cells, while the combination resulted in cell accumulation in G1 and G2/M phases and almost complete elimination in S phase for LNCaP95 prostate cancer cells.

[648] Enzalutamide resistant human prostate cancer cell line C4-2B-MDVR was treated with vehicle control (DMSO), 2.5 μ M or 3.5 μ M of Compound **13a** with or without Enzalutamide (ENZA). Stacked columns, **Fig. 5** shows % cells in each cell cycle phase for C4-2B-MDVR.

[649] Results demonstrated that Compound **13a** in combination with enzalutamide lead to G1 arrest in C4-2B-MDVR.

[650] **Example 32. Colony Formation**

[651] Breast cancer and prostate cancer cell lines were treated with vehicle control, various concentrations of Compound **13a**, Enzalutamide (ENZA), or Palbociclib (Palbo) for 7 days (SUM-159PT) or for 15 days (LNCaP95). Representative data are shown. $n \geq 3$.

[652] Combination of Compound **13a** and palbociclib reduced colony formation in AR-positive SUM159-PT breast and LNCaP95 prostate cancer cells. This inhibitory effect is reversible.

[653] Enzalutamide resistant human prostate cancer cell line C4-2B-MDVR was treated with vehicle control (DMSO), various concentration of EPI-002, Compound **13a**, Enzalutamide (ENZA), or combination of EPI-002 or Compound 13a with Enzalutamide. The combination reduced colony formation (**Fig. 6**).

[654] Results from Examples 30-32 demonstrate targeting AR NTD with androgen receptor N-terminal domain inhibitor, such as Compound 13a, may benefit patients with breast cancer that express AR. Without bound to any theory, a targeted, combination therapeutic approach could allow more specific and effective treatments for breast cancer patients and prostate cancer patients.

[655] **Example 33. Effect of Compound 13a and Enzalutamide on FI-AR and AR-V7 Regulated Genes**

[656] Transcript levels of *PSA*, *UBE2C*, *FKBP5*, *CYCLIN A2*, *TMPRSS2*, and *CDC20*, were measured in enzalutamide resistant human prostate cancer cell line C4-2B-MDVR.

Enzalutamide increased the expression of UBE2C and cyclin A2 in the presence of androgen (**Fig 7B, Fig 7D**) and had no effect on CDC20 (**Fig 7F**). Compound 13a decreased transcript expression of the M-phase cell cycle genes *UBE2C*, *CYCLIN A2*, *CDC20* and *PSA*, *FKBP5*, and *CDC20* (**Figs. 7B, 7D, and 7F**). While Compound 13a alone did not decrease transcript expression in *PSA*, *FKBP5*, and *CDC20* but not *TMPRSS23* (**Figs. 7A-7F**), in R1881 treated cells, Compound 13a in combination with enzalutamide decreased the transcript expression more than monotherapies. **Fig. 8** shows protein levels of AR-FL and AR-V7 from C4-2B-MDVR cells treated with Compound 13a alone or in combination with enzalutamide, normalized to β -actin.

[657] As shown in **Figs. 9B-9D**, Compound 13a inhibited transcriptional activities of ectopic AR-V7.

[658] Without bound to any theory, targeting AR-NTD in addition to AR-LBD to block both FL-AR and AR-Vs could be a potential treatment option for CRPC.

[659] Example 34. Effect of Compound 13a and Enzalutamide on Cell Proliferation

[660] Prostate cancer cell line VCaP were treated with vehicle control, Enzalutamide (ENZA; 0.05, 0.5, or 5 μ M) with or without Compound 13a (6 or 12 μ M). BrdU incorporation was used to assess cell proliferation. Data from each treatments were normalized to vehicle control as shown in **Fig. 10**. IC₅₀ was determined as shown in Table 2.

[661] **Table 2.** IC₅₀ for blocking proliferation of VCaP cells

Compound ID	IC ₅₀ (μ M)
Enzalutamide	163.6
Enzalutamide + 13a (6 μ M)	3.350
Enzalutamide + 13a (6 μ M)	0.2060

[662] Enzalutamide resistant human prostate cancer cell line C4-2B-MDVR were treated with vehicle control, Enzalutamide (ENZA; 0.75, 1.5, or 1.25 μ M) with or without Compound 13a (1.5 or 2.5 μ M) in cells treated with R1881 and in cells not treated with R1881. BrdU incorporation was used to assess cell proliferation. Data from each treatments were normalized to vehicle control as shown in **Fig. 11A and 11B**. IC₅₀ was determined as shown in Table 3.

[663] As shown in **Fig. 10, 11A and 11B** and Tables 3-4, synergistic effect of Compound 13a and enzalutamide was observed in cell proliferation assay.

[664] **Table 3.** IC₅₀ in C4-2B-MDVR 1.5% CSS cell proliferation assay

Compound ID	IC ₅₀ (μM) +R1881	IC ₅₀ (μM) -R1881
Enzalutamide + 13a (1.5 μM)	15.98	30.16
Enzalutamide + 13a (2.5 μM)	5.91	15.98

[665] Example 35. Combination of Compound 13a and Radiation

[666] LNCaP95 cells treated with DMSO (control), EPI-002 (35 μM), Compound 13a (8 μM), or enzalutamide (ENZ, 5 μM) with or without irradiation (4Gy) and harvested after 48 h incubation. Western blot analyses measuring γH2AX protein is shown in **Fig. 12A**.

[667] Further, cells were labelled for γH2AX and 7AAD and analyzed by flow cytometry (**Fig. 12B**). The percent of cells positive for γH2AX are shown in **Fig. 12B**. The percentage of cells containing above 10 γH2AX foci (mean ± SD from three independent experiments) are represented in **Fig. 12C**. Enzalutamide had no effect whereas Compound 13a did.

[668] **Fig. 12D** shows representative images of foci of DNA damage.

[669] Flow Cytometry: Cell cycle analysis was conducted by flow cytometry using BrdU-FITC and 7-AAD. DNA damage was analyzed using γH2AX antibody (CST) and 7-AAD. Cells were analyzed on FACScalibur flow cytometer.

[670] Immunofluorescence staining: γH2AX antibody (Millipore mouse), Alexa488 anti-mouse antibody were used for staining. Cells were analyzed on Axio observer (x20 magnification) equipped with apotome 2.

[671] Statistical analysis: Graphs represent the means ± SEM from three independent experiments performed with three technical replicates. Statistical significance was determined using GraphPad Prism software with a one-way ANOVA; *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

[672] Without bound to any theory, this experiment shows combination of Compound 13a and radiation therapy increases accumulation of DNA damage *in vitro*.

[673] Material and Methods for Examples 36-38

[674] Compounds: Juglone and all-trans retinoic acid (ATRA) were purchased from Sigma-Aldrich. EPI-002 was provided by NAEJA, Compound 13a was prepared in house, and enzalutamide (ENZ) was purchased from OmegaChem.

[675] Pin1 activity assay: Pin1 PPIase activity assay was measured using the Fluorimetric Green Pin1 Assay kit (AnaSpec) using 500 ng of recombinant human Pin1 protein (Abcam) incubated at 37°C for 60 min.

[676] Transfections and luciferase assays: Plasmids and transfections have been previously described elsewhere in Andersen et al., *Cancer Cell*. 2010, and Myung et al., *J Clin Invest*. 2013.

[677] Flow cytometry: Fixed cells were probed with anti-BrdU-FITC antibody (BD Biosciences) and stained with 7-AAD (Sigma). Data was acquired on a FACSCalibur flow cytometer (BD Biosciences) with CellQUEST Pro and later analyzed using FlowJo V10 software.

[678] β -galactosidase staining: Cells grown in chamber slides and treated with compounds were fixed at room temperature with 2% formaldehyde/0.2% glutaraldehyde, and then incubated at 37°C with fresh β -gal staining solution (Cell Signaling) titrated to pH 6.0. Staining was optimal after incubating the slides overnight for 16-18 hours.

[679] Statistical analyses: Statistical significance was determined with GraphPad Prism 8 software using two-way ANOVA with Dunnett's multiple comparisons test unless indicated otherwise; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; ns, not significant.

[680] Example 36. Effect of Pin1 Inhibitors on Transcriptional Activity of AR

[681] LNCaP cells were transfected with the PSA (6.1 kb)-luciferase reporter for 24 h, and then treated with indicated concentration of juglone, ATRA, or 13CisRA (inactive conformation) with synthetic androgen, R1881 (1 nM) for 24 h as described in Example 35. After 24 h of incubation with R1881, the cells were harvested, and relative luciferase activities were determined. **Fig. 13** shows inhibitory dose-response curve for juglone and ATRA on PSA (6.1 kb)-luciferase activity. **Fig. 14** is a Western blot showing the levels PSA and AR protein in lysates prepared from LNCaP cells treated with juglone (20 μ M) or ATRA (10 μ M), and R1881 (1 nM) or vehicle for 24h. Data shown in Figures are the means $\pm$ SE from 4 independent experiments.

[682] No inhibitory effects were observed for reporter constructs regulated by CMV promoter or AP-1 binding sites with juglone, ATRA, or 13CisRA.

[683] Transcriptional activity of AR-V7 was measured using a luciferase reporter gene regulated by *UBE2C* promoter (**Fig. 15**). In LNCaP cells, *UBE2C* is selectively activated by ectopic AR-V7 expression. Cells transfected with V7 and *UBE2C*-luciferase were incubated with enzalutamide (ENZ, 10 μ M), EPI-002 (25 μ M), juglone (JUG, 20 μ M), or ATRA (10 μ M) for 24h. **Fig. 16** is a Western blot showing equal levels of V7 expression between treatment groups. Results shown in **Figs. 15** and **16** are the means $\pm$ SE from 3 independent experiments.

[684] The above-described assays demonstrated that inhibiting Pin1 with ATRA decreased the transcriptional activity of AR and androgen-induced expression of PSA protein. Further, the assays demonstrated that ATRA also reduced the transcriptional activity of AR-V7 and androgen-independent growth of LN95 cells expressing both full-length AR and V7.

[685] Example 37. Effect of Compound 13a and ATRA on Transcriptional Activity of AR

[686] LNCaP cells were transfected with the PSA (6.1 kb)-luciferase reporter for 24 h, and then treated with indicated concentration of ATRA and EPI-002 or ATRA and Compound **13a** with synthetic androgen, R1881 (1 nM) for 24 h as described in Example 35. After 24 h of incubation with R1881, the cells were harvested, and relative luciferase activities were determined. **Fig. 17** shows inhibitory dose-response curve on PSA (6.1 kb)-luciferase activity. Table 4 shows the calculated IC₅₀ in the above-described luciferase assay.

[687] ATRA and EPI-002 or Compound **13a** demonstrated a synergistic effect on inhibiting AR transcriptional activity. In the presence of ATRA, the dose-response curves for EPI-002 and Compound **13a** shifted to the left, resulting in a 2-fold decrease in their IC₅₀ values.

[688] Table 4. IC₅₀ in Luciferase Assay

	IC ₅₀ ± SE (μM)	R ²
EPI-002	7.9 ± 1.2	.94
EPI-002 (+ATRA)	4.4 ± 1.1	.97
Compound 13a	0.74 ± 1.2	.96
Compound 13a (+ATRA)	0.42 ± 1.2	.93

[689] This experiment demonstrated that ATRA enhanced the potency of androgen receptor inhibitors/modulators. Pharmaceutical combination of Pin1 and androgen receptor modulators can be a new therapeutic strategy for the treatment of prostate cancer, including CRPC.

[690] Example 38. Cell Cycle Analysis and Cellular Senescence

[691] Cell cycle analysis of LN95-D3 cells after treating with combinations of ATRA and AR NTD modulators (EPI-002, Compound **13a**) or antiandrogen (ENZ, enzalutamide), in 1.5% charcoal-stripped serum. After incubating with the compounds, cells were labelled with BrdU for 2h and then processed for flow cytometry. ATRA arrested cells in G1 and decreased the S phase population in a dose-dependent manner. These effects were synergistic with EPI-002 and with Compound **13a**, but not with ENZ (**Figs. 19A and 19B**). Further, Western blot analysis

shows that ATRA inhibits Pin1 and leads to its degradation, which in turn affects the stability of Cyclin D1, a Pin1 substrate (**Fig. 20**).

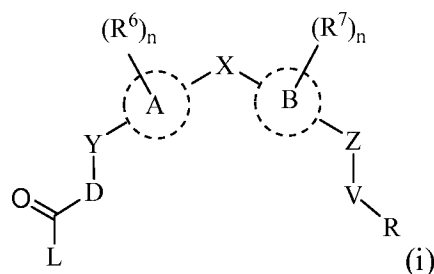
[692] Senescence-associated β -gal staining of LN95 cells were observed after incubating in 1.5% charcoal-stripped serum with EPI-002, ATRA, or combination for 3 days. Combining EPI-002 and ATRA showed synergy for increasing the percentage of β -gal-positive cells. **Figs 18A and 18B** are Western blots of lysates prepared from the cells after 3 or 6 days of treatment showed altered expression of proteins regulating senescence. Results shown are representative of 3 independent experiments. Without bound to any theory, a more potent androgen receptor modulators of the present disclosure in combination with Pin1 inhibitors, e.g., ATRA, would also demonstrate synergy for increasing the percentage of β -gal-positive cells.

[693] Numbered Embodiments

[694] Embodiment 1. A pharmaceutical composition comprising an androgen receptor N-terminal domain inhibitor and a second therapeutically active agent.

[695] Embodiment 2. A pharmaceutical composition comprising a Pin1 inhibitor and an androgen receptor N-terminal domain inhibitor, wherein the androgen receptor N-terminal domain inhibitor is not 3-(4-(2-(4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol, 3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate, or stereoisomers thereof.

[696] Embodiment 3. The pharmaceutical composition of Embodiment 1 or 2, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (i):



[697] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[698] A and B are each independently aryl or heteroaryl;

[699] X is a bond, $-(CR^8R^9)_t-$, $-O-$, $-C(=O)-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

[700] Y and Z are each independently a bond, $-(CR^8R^9)_t-$, $-O-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

[701] V is a bond, optionally substituted $-(CR^{11}R^{12})_m-$, $-C(=O)-$, $-N(R^{10})CO-$, $-CONR^{10}-$, or $-NSO_2R^{10}-$;

[702] R is $-(CR^{4a}R^{4b})-(CR^{5a}R^{5b})-W$ or W;

[703] W is hydrogen, halogen, $-CF_3$, $-CF_2R^{10}$, $-CN$, $-OR^{13}$, $-NR^{13}R^{14}$, optionally substituted $-CONR^{13}R^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[704] D is $-(CR^{1a}R^{1b})_q-$, $-O-$, or $-NR^{10}-$;

[705] L is $-(CR^{2a}R^{2b})-R^3$ or $-E-R^3$;

[706] E is $-(CR^{2a}R^{2b})_g-$, $-O-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$;

[707] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[708] or alternatively, R^{1a} and R^{1b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[709] or alternatively, R^{2a} and R^{2b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[710] or alternatively, R^{1a} , R^{1b} , R^{2a} and R^{2b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[711] R^{4a} , R^{4b} , R^{5a} , and R^{5b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[712] or alternatively, R^{4a} and R^{4b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[713] or alternatively, R^{4a} , R^{4b} , R^{5a} and R^{5b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[714] R^3 is absent, hydrogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$ alkynyl, optionally substituted $-\text{OR}^{15}$, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, $-\text{NH}_2$, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{NR}^{16}\text{S}(\text{O})_p\text{R}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-\text{S}(\text{O})_p\text{R}^{18}$, $-\text{N}_3$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[715] or alternatively, R^{2a} , R^{2b} and R^3 taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[716] or alternatively, R^{2a} and R^{10} taken together form an optionally substituted heterocyclyl;

[717] R^6 and R^7 are each independently H, methyl, methoxy, $-\text{CN}$, F, Cl, Br, I, ^{123}I , $-\text{CF}_3$, $-\text{OH}$, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-(\text{C}_1\text{--C}_6 \text{ alkoxy})$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{OH}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{SO}_2\text{R}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})\text{NR}^{14}\text{SO}_2\text{R}^{16}$, $-\text{NR}^{14}\text{COR}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-\text{SO}_2\text{R}^{16}$, or optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{SO}_2\text{R}^{16}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[718] R^8 , R^9 , R^{11} and R^{12} are each independently hydrogen, $-\text{OH}$, halogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$ alkynyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, optionally substituted $\text{C}_1\text{--C}_6$ alkylamino, optionally substituted $-\text{OCO}(\text{C}_1\text{--C}_6 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$, optionally substituted

carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[719] or alternatively, R⁸ and R⁹ taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

[720] or alternatively, R¹¹ and R¹², on a same carbon atom or a different carbon atom, taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[721] R¹⁰ is hydrogen, halogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₁–C₆ alkoxy, -CO(C₁–C₆ alkyl), optionally substituted C₁–C₆ alkylamino, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[722] R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are each independently hydrogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[723] or alternatively, R¹⁴ and R¹⁵ are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

[724] or alternatively, R¹⁶ and R¹⁷ are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

[725] m is 0, 1, 2, 3, or 4;

[726] each n is independently 0, 1 or 2;

[727] each p is independently 0, 1 or 2;

[728] q is 0, 1 or 2;

[729] each g is independently 0, 1, 2, 3, or 4; and

[730] each t is independently 1 or 2.

[731] **Embodiment 4.** The pharmaceutical composition of Embodiment 3, wherein R is W.

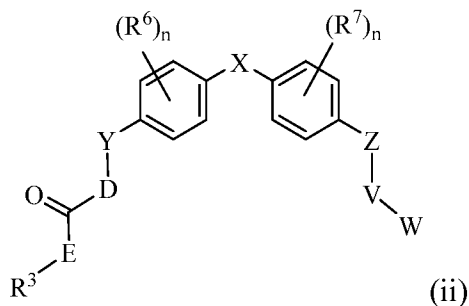
[732] **Embodiment 5.** The pharmaceutical composition of Embodiment 3 or 4, wherein W is hydrogen, halogen, -CF₃, or -NR¹³R¹⁴.

[733] **Embodiment 6.** The pharmaceutical composition of any one of Embodiments 3-5, wherein L is -E-R³.

[734] **Embodiment 7.** The pharmaceutical composition of any one of Embodiments 3-6, wherein R³ is selected from hydrogen, -C₁–C₃ alkyl, -NR¹⁶SO(C₁–C₃ alkyl), -NR¹⁶SO₂(C₁–C₃ alkyl), -SONR¹⁴R¹⁵, -SO₂NR¹⁴R¹⁵, -SOR¹⁸, or -SO₂R¹⁸.

[735] **Embodiment 8.** The compound of any one of Embodiments 3-7, wherein R^3 is selected from $-\text{NH}\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NCH}_3\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, or $-\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$.

[736] **Embodiment 9.** The pharmaceutical composition of Embodiment 3, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (ii):



[737] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[738] X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

[739] Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

[740] V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

[741] W is halogen, $-\text{NH}_2$, or $-\text{CF}_3$.

[742] D is $-\text{NR}^{10}-$ and E is $-(\text{CR}^{2a}\text{R}^{2b})_g-$, $-\text{NR}^{10}-$, or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$;

[743] or alternatively, E is $-\text{NR}^{10}-$ or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$, and D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$ or $-\text{NR}^{10}-$;

[744] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, $\text{C}_1\text{--C}_3$ alkoxy, $-\text{OCO}(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1\text{--C}_3 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1\text{--C}_3 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[745] R^3 is selected from hydrogen, $-\text{C}_1\text{--C}_6$ alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1\text{--C}_6$ alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;

[746] R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl;

[747] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

[748] R^{10} is each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, or $-\text{CO}(\text{C}_1\text{--C}_3 \text{ alkyl})$;

[749] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, or C_2 – C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

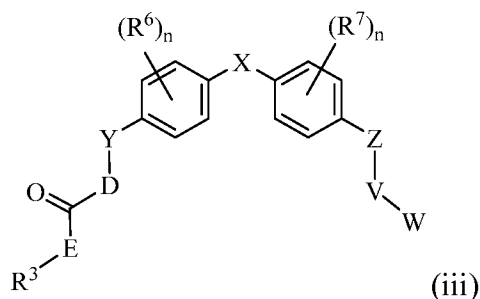
[750] each n is independently 0, 1 or 2;

[751] q is 0, 1 or 2;

[752] each g is independently 0, 1, 2, 3, or 4; and

[753] each t is independently 1 or 2.

[754] **Embodiment 10.** The pharmaceutical composition of Embodiment 3, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (iii):



[755] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[756] X is a bond, $-NR^{10}-$, or $-(CR^{8a}R^{9a})_t-$;

[757] Y and Z are each independently a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$;

[758] V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$;

[759] W is halogen, $-NH_2$ or $-CF_3$;

[760] D is $-O-$ or $-NR^{10}-$ and E is $-(CR^{2a}R^{2b})_{gg}-$;

[761] or alternatively, E is $-O-$, $-NR^{10}-$ or $-NR^{10}-(CR^{2a}R^{2b})_g-$, and D is $-(CR^{1a}R^{1b})_q-$;

[762] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, C_2 – C_3 alkynyl, C_1 – C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$, or $(R^{1a}$ and $R^{1b})$ or $(R^{2a}$ and $R^{2b})$ taken together form an oxo ($=O$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[763] R^3 is selected from hydrogen, $-C_1$ – C_6 alkyl, $-OR^{15}$, $-SR^{18}$, $-C_1$ – C_6 alkoxy, $-NR^{16}R^{17}$, $-NR^{16}SR^{18}$, $-NR^{16}SOR^{18}$, $-NR^{16}SO_2R^{18}$, $-NR^{16}COR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-SOR^{18}$, or $-SO_2R^{18}$;

[764] R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl;

[765] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

[766] R^{10} is each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, or $-\text{CO}(\text{C}_1\text{--C}_3 \text{ alkyl})$;

[767] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, or $\text{C}_2\text{--C}_3$ alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

[768] m is 0, 1, 2, 3, or 4;

[769] each n is independently 0, 1 or 2;

[770] q is 1 or 2;

[771] g is 0, 1, 2, 3, or 4;

[772] gg is 1, 2, 3, or 4; and

[773] t is 1 or 2.

[774]

[775] **Embodiment 11.** The pharmaceutical composition of Embodiment 9 or 10, wherein W is Cl, Br, I, or F.

[776] **Embodiment 12.** The pharmaceutical composition of any one of Embodiments 9-11, wherein D is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, or $-\text{CH}_2\text{CH}_2-$.

[777] **Embodiment 13.** The pharmaceutical composition of Embodiment 9, wherein q is 0.

[778] **Embodiment 14.** The pharmaceutical composition of any one of Embodiments 9-13, wherein E is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

[779] **Embodiment 15.** The pharmaceutical composition of any one of Embodiments 9-14, wherein g is 0.

[780] **Embodiment 16.** The pharmaceutical composition of any one of Embodiments 9-15, wherein R^3 is selected from $-\text{NHSO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NCH}_3\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$, or $-\text{SO}_2(\text{C}_1\text{--C}_3 \text{ alkyl})$.

[781] **Embodiment 17.** The pharmaceutical composition of any one of Embodiments 9-16, wherein R^6 and R^7 are each independently H, halogen, $-\text{CN}$, or methyl.

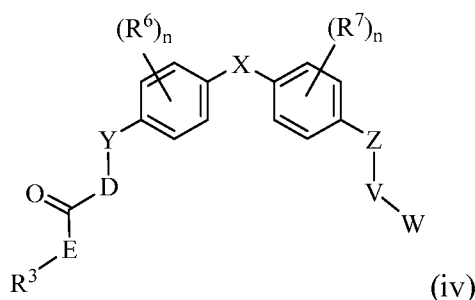
[782] **Embodiment 18.** The pharmaceutical composition of any one of Embodiments 9-17, wherein X is a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$, $-\text{N}(i\text{Pr})-$, or $-\text{N}(\text{COCH}_3)-$.

[783] **Embodiment 19.** The pharmaceutical composition of any one of Embodiments 9-18, Z is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$.

[784] **Embodiment 20.** The pharmaceutical composition of any one of Embodiments 9-19, Y is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$, or $-\text{NCH}_3-$.

[785] **Embodiment 21.** The pharmaceutical composition of any one of Embodiments 9-20, wherein at least one of Z and Y is $-\text{O}-$.

[786] **Embodiment 22.** The pharmaceutical composition of Embodiment 3, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (iv):



[787] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[788] X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

[789] Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

[790] V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

[791] W is halogen, $-\text{CF}_2\text{R}^{10}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[792] D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$;

[793] E is $-(\text{CR}^{2a}\text{R}^{2b})_g-$;

[794] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-\text{OCO}(\text{C}_1-\text{C}_3 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$; or $(\text{R}^{1a}$ and $\text{R}^{1b})$ or $(\text{R}^{2a}$ and $\text{R}^{2b})$ taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[795] R^3 is selected from hydrogen, $-\text{C}_1-\text{C}_6$ alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1-\text{C}_6$ alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;

[796] R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or C_1-C_3 alkyl;

[797] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-OH$, or C_1-C_3 alkyl; or R^{8a} and R^{9a} taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

[798] R^{10} is each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or $-CO(C_1-C_3 \text{ alkyl})$;

[799] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

[800] m is 0, 1, 2, 3, or 4;

[801] each n is independently 0, 1 or 2;

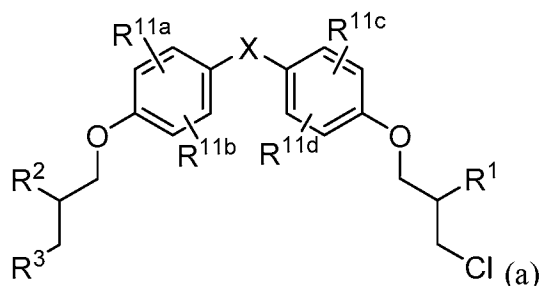
[802] q is 0, 1 or 2;

[803] g is 0, 1, 2, 3, or 4; and

[804] t is 1 or 2.

[805] **Embodiment 23.** The pharmaceutical composition of Embodiment 1 or 2, wherein the androgen receptor N-terminal domain inhibitor is selected from Table A.

[806] **Embodiment 24.** The pharmaceutical composition of Embodiment 1 or 2, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (a):



[807] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[808] X is $-S(O)_n-$ or $-C(R^8R^9)-$;

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

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

[811] R^3 is halo, $-OH$, $-OR^4$, $-OC(=O)R^{13}$, $-NH_2$, $-NHC(=O)R^{13}$, $-N(C(=O)R^{13})_2$, $-NHS(O)_nR^5$, $-N(C(=O)R^{13})(S(O)_nR^5)$, $-N(C_1-C_6 \text{ alkyl})(S(O)_nR^5)$, $-S(O)_nR^5$, $-N_3$, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

[812] R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

[813] R⁵ is each independently C₁-C₆ alkyl or aryl which are optionally substituted with one or more R⁶;

[814] R⁶ is each independently selected from the group consisting of H, F, Cl, Br, I, ¹²³I, hydroxyl, oxo, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₆-C₁₂ aryl, wherein each R⁶ is optionally substituted with one or more of halogen, ¹²³I, ¹⁸F, hydroxyl, -OS(O)₂-aryl, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

[815] R⁸ and R⁹ are each independently H, or C₁-C₆ alkyl;

[816] R^{11a}, R^{11b}, R^{11c} and R^{11d} are each independently H, methyl, -CN, F, Cl, Br, I, or ¹²³I;

[817] R¹³ is C₁-C₆ alkyl; and

[818] n is 0, 1, or 2;

[819] wherein at least one of R^{11a}, R^{11b}, R^{11c} and R^{11d} is methyl, -CN, F, Cl, Br, I, or ¹²³I.

[820] **Embodiment 25.** The pharmaceutical composition of Embodiment 24, wherein at least two of R^{11a}, R^{11b}, R^{11c} and R^{11d} are methyl, -CN, F, Cl, Br, I, or ¹²³I.

[821] **Embodiment 26.** The pharmaceutical composition of Embodiment 24, wherein R^{11c} and R^{11d} are each independently methyl, -CN, Cl, or Br.

[822] **Embodiment 27.** The pharmaceutical composition of Embodiment 24, wherein R^{11c} and R^{11d} are each Cl or -CN.

[823] **Embodiment 28.** The pharmaceutical composition of any one of Embodiments 24-27, wherein X is -C(R⁸R⁹)- and R⁸ and R⁹ are each independently C₁-C₃ alkyl.

[824] **Embodiment 29.** The pharmaceutical composition of Embodiment 28, wherein R⁸ and R⁹ are each methyl.

[825] **Embodiment 30.** The pharmaceutical composition of any one of Embodiments 24-29, wherein R¹ and R² are both hydroxyl.

[826] **Embodiment 31.** The pharmaceutical composition of any one of Embodiments 24-30, wherein R³ is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom.

[827] **Embodiment 32.** The pharmaceutical composition of any one of Embodiments 24-30, wherein R³ is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrroline, imidazoline,

imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine.

[828] Embodiment 33. The pharmaceutical composition of any one of Embodiments 24-30, wherein R^3 is $-NH_2$, $-NHC(=O)R^{13}$, $-N(C(=O)R^{13})_2$, $-NHS(O)_nR^5$, $-N(C(=O)R^{13})(S(O)_nR^5)$, $-N(C_1-C_6 \text{ alkyl})(S(O)_nR^5)$ or $-S(O)_nR^5$.

[829] Embodiment 34. The pharmaceutical composition of any one of Embodiments 24-30, wherein R^3 is $-NH_2$, $-NHC(=O)(C_1-C_4 \text{ alkyl})$, $-N[(C(=O)(C_1-C_4 \text{ alkyl}))_2]$, $-NHS(O)_n(C_1-C_3 \text{ alkyl})$, $-N[C(=O)(C_1-C_4 \text{ alkyl})][(S(O)_n(C_1-C_3 \text{ alkyl}))]$, $-N[C_1-C_6 \text{ alkyl}][S(O)_n(C_1-C_3 \text{ alkyl})]$, or $-S(O)_n(C_1-C_3 \text{ alkyl})$.

[830] Embodiment 35. The pharmaceutical composition of Embodiment 1 or 2, wherein the androgen receptor N-terminal domain inhibitor is selected from Table B.

[831] Embodiment 36. The pharmaceutical composition of any one of Embodiments 1 and 3-35, wherein the second therapeutically active agent is selected from a poly (ADP-ribose) polymerase (PARP) inhibitor, an androgen receptor ligand-binding domain inhibitor, an inhibitor of CYP17, a microtubule inhibitor, a modulator of PD-1 or PD-L1, a gonadotropin releasing hormone agonist, a 5- α reductase inhibitor, a vascular endothelial growth factor inhibitor, a histone deacetylase inhibitor, an integrin α -v- β -3 inhibitor, a receptor tyrosine kinase, a phosphoinositide 3-kinase inhibitor, an anaplastic lymphoma kinase (ALK) inhibitor, an endothelin receptor A antagonist, an anti-CTLA4 inhibitor, an heat shock protein 27 (HSP27) inhibitor, an androgen receptor degrader, a androgen receptor DNA-binding domain inhibitor, a bromodomain and extra-terminal motif (BET) inhibitor, an androgen receptor N-terminal domain inhibitor, an α -particle emitting radioactive therapeutic agent, niclosamide, a selective estrogen receptor modulator (SERM), a selective estrogen receptor degrader (SERD), an aromatase inhibitor, selective progesterone receptor modulator (SPRM), a glucocorticoid receptor inhibitor, a CDK4/6 inhibitor, a HER2 receptor antagonist, a mammalian target of rapamycin (mTOR) inhibitor, an AKT inhibitor, a B-cell lymphoma-2 (Bcl-2) inhibitor, an aurora kinase inhibitor, a Wnt-targeting antagonist, a CYP11a inhibitor, a selective androgen receptor N-terminal domain inhibitor, or enhancer of zeste homolog 2 (EZH2) inhibitor.

[832] Embodiment 37. The pharmaceutical composition of any one of Embodiments 1 and 3-35, wherein the CDK4/6 inhibitor is selected from palbociclib, ribociclib, trilaciclib or abemaciclib.

[833] Embodiment 38. The pharmaceutical composition of any one of Embodiments 1 and 3-35, wherein the CDK4/6 inhibitor is palbociclib.

[834] Embodiment 39. The pharmaceutical composition of any one of Embodiments 1 and 3-35, wherein the androgen receptor ligand-binding domain inhibitor is enzalutamide, apalutamide, darolutamide, bicalutamide, nilutamide, flutamide, ODM-204, or TAS3681.

[835] Embodiment 40. The pharmaceutical composition of any one of Embodiments 1 and 3-35, wherein the androgen receptor ligand-binding domain inhibitor is enzalutamide.

[836] Embodiment 41. The pharmaceutical composition of any one of Embodiments 2-35, wherein the Pin1 inhibitor is selected from juglone, plumbagin, PiB, PiJ, epigallocatechin gallate (EGCG), all-trans retinoic acid (ATRA), dipentamethylene thiauram monosulfide, TME-001 (2-(3-chloro-4-fluoro-phenyl)-isothiazol-3-one), KPT-6566, API-1, buparvaquone, or a pharmaceutically acceptable salt thereof.

[837] Embodiment 42. The pharmaceutical composition of any one of Embodiments 2-35, wherein the Pin1 inhibitor is selected from **Table C** or a pharmaceutically acceptable salt thereof.

[838] Embodiment 43. The pharmaceutical composition of any one of Embodiments 2-35, wherein the Pin1 inhibitor is selected from **Table D** or a pharmaceutically acceptable salt thereof.

[839] Embodiment 44. The pharmaceutical composition of any one of Embodiments 2-35, wherein the Pin1 inhibitor is CRYPEVEIC, wherein the cysteine residues of said peptide are cyclized by a disulfide bond (SEQ ID NO: 1); Ac-Lys(N-biotinoyl)-Ala-Ala-Bth-D-Thr(PO₃H₂)-Pip-Nal-Gln-NH₂ (SEQ ID NO: 2); Ac-Phe-D-Thr(PO₃H₂)-Pip-Nal-Gln-NH₂ (SEQ ID NO: 3); and Ac-Phe-Phe-pSer-Ψ[(Z)CHdC-Pro-Arg-NH₂ (SEQ ID NO: 4).

[840] Embodiment 45. The pharmaceutical composition of any one of Embodiments 2-35, wherein the Pin1 inhibitor is selected from 5-hydroxy-1,4-naphthledione, (1-piperidinecarbodithioic acid, anhydrosulfide), or diethyl-1,3,6,8-tetrahydro-1,3,6,8-tetraoxobenzo[lmn] phenanthroline-2,7-diacetate, or a pharmaceutically acceptable salt thereof.

[841] Embodiment 46. The pharmaceutical composition of any one of Embodiments 2-35, wherein the Pin1 inhibitor is ATRA.

[842] Embodiment 47. The pharmaceutical composition of any one of Embodiments 1-46, further comprising a pharmaceutically acceptable carrier.

[843] Embodiment 48. A method for inhibiting androgen receptor activity, comprising administering a pharmaceutical composition of any one of Embodiments 1-47, to a subject in need thereof.

[844] **Embodiment 49.** The method of Embodiment 48, wherein the inhibiting androgen receptor activity is for treating a condition or disease selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration.

[845] **Embodiment 50.** A method for treating cancer, comprising administering the pharmaceutical composition of any one of Embodiments 1-47, to a subject in need thereof.

[846] **Embodiment 51.** The method of Embodiment 50, wherein the cancer is breast cancer.

[847] **Embodiment 52.** The method of Embodiment 51, wherein the breast cancer is triple negative breast cancer.

[848] **Embodiment 53.** The method of Embodiment 50, wherein the cancer is selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, or salivary gland carcinoma.

[849] **Embodiment 54.** The method of Embodiment 50, wherein the cancer is prostate cancer.

[850] **Embodiment 55.** The method of Embodiment 54, wherein the prostate cancer is primary or localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, advanced prostate cancer, metastatic prostate cancer, metastatic castration-resistant prostate cancer, and hormone-sensitive prostate cancer.

[851] **Embodiment 56.** The method of Embodiment 54, wherein the prostate cancer is metastatic castration-resistant prostate cancer.

[852] **Embodiment 57.** The method of Embodiment 54, wherein the prostate cancer expresses full-length androgen receptor or truncated androgen receptor splice variant.

[853] **Embodiment 58.** The method of any one of Embodiments 50-54, further comprising administering radiation therapy the subject.

[854] **Embodiment 59.** The method of Embodiment 58, wherein the radiation therapy is ionizing radiation therapy.

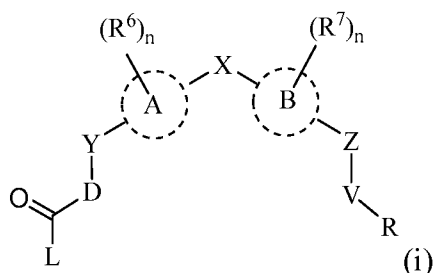
[855] **Embodiment 60.** The method of Embodiment 58 or 59, wherein the administering the pharmaceutical composition and the administering radiation therapy occurs during same treatment period or during different treatment period.

[856] **Embodiment 61.** The method of any one of Embodiments 58-60, wherein the subject has prostate cancer.

[857] **Embodiment 62.** The method of any one of Embodiments 50-61, wherein the prostate cancer is resistant to enzalutamide monotherapy.

[858] Embodiment 63. A method of treating cancer, comprising administering a therapeutically effective amount of an androgen receptor modulator and a radiation therapy to a subject in need thereof.

[859] Embodiment 64. The method of Embodiment 63, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (i):



[860] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[861] A and B are each independently aryl or heteroaryl;

[862] X is a bond, $-(CR^8R^9)_t-$, $-O-$, $-C(=O)-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

[863] Y and Z are each independently a bond, $-(CR^8R^9)_t-$, $-O-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

[864] V is a bond, optionally substituted $-(CR^{11}R^{12})_m-$, $-C(=O)-$, $-N(R^{10})CO-$, $-CONR^{10}-$, or $-NSO_2R^{10}-$;

[865] R is $-(CR^{4a}R^{4b})-(CR^{5a}R^{5b})-W$ or W;

[866] W is hydrogen, halogen, $-CF_3$, $-CF_2R^{10}$, $-CN$, $-OR^{13}$, $-NR^{13}R^{14}$, optionally substituted $-CONR^{13}R^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[867] D is $-(CR^{1a}R^{1b})_q-$, $-O-$, or $-NR^{10}-$;

[868] L is $-(CR^{2a}R^{2b})-R^3$ or $-E-R^3$;

[869] E is $-(CR^{2a}R^{2b})_g-$, $-O-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$;

[870] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[871] or alternatively, R^{1a} and R^{1b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[872] or alternatively, R^{2a} and R^{2b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[873] or alternatively, R^{1a} , R^{1b} , R^{2a} and R^{2b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[874] R^{4a} , R^{4b} , R^{5a} , and R^{5b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[875] or alternatively, R^{4a} and R^{4b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[876] or alternatively, R^{4a} , R^{4b} , R^{5a} and R^{5b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[877] R^3 is absent, hydrogen, $-CN$, $-CF_3$, $-OH$, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted $-OR^{15}$, optionally substituted C_{1-6} alkoxy, $-NH_2$, $-NR^{16}R^{17}$, $-NR^{16}COR^{18}$, $-NR^{16}S(O)_pR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-S(O)_pR^{18}$, $-N_3$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[878] or alternatively, R^{2a} , R^{2b} and R^3 taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[879] or alternatively, R^{2a} and R^{10} taken together form an optionally substituted heterocyclyl;

[880] R^6 and R^7 are each independently H, methyl, methoxy, $-\text{CN}$, F, Cl, Br, I, ^{123}I , $-\text{CF}_3$, $-\text{OH}$, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-(\text{C}_1\text{--C}_6 \text{ alkoxy})$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{OH}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{SO}_2\text{R}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})\text{NR}^{14}\text{SO}_2\text{R}^{16}$, $-\text{NR}^{14}\text{COR}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-\text{SO}_2\text{R}^{16}$, or optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{SO}_2\text{R}^{16}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[881] R^8 , R^9 , R^{11} and R^{12} are each independently hydrogen, $-\text{OH}$, halogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$ alkynyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, optionally substituted $\text{C}_1\text{--C}_6$ alkylamino, optionally substituted $-\text{OCO}(\text{C}_1\text{--C}_6 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[882] or alternatively, R^8 and R^9 taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

[883] or alternatively, R^{11} and R^{12} , on a same carbon atom or a different carbon atom, taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[884] R^{10} is hydrogen, halogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, $-\text{CO}(\text{C}_1\text{--C}_6 \text{ alkyl})$, optionally substituted $\text{C}_1\text{--C}_6$ alkylamino, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[885] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[886] or alternatively, R^{14} and R^{15} are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

[887] or alternatively, R^{16} and R^{17} are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

[888] m is 0, 1, 2, 3, or 4;

[889] each n is independently 0, 1 or 2;

[890] each p is independently 0, 1 or 2;

[891] q is 0, 1 or 2;

[892] each g is independently 0, 1, 2, 3, or 4; and

[893] each t is independently 1 or 2.

[894] **Embodiment 64.** The method of Embodiment 63, wherein R is W .

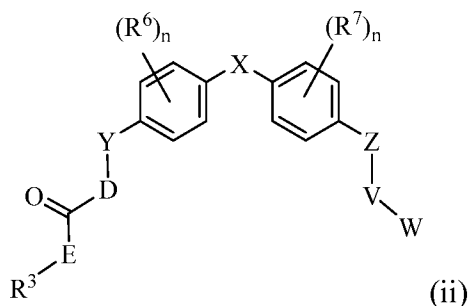
[895] **Embodiment 65.** The method of Embodiment 63 or 64, W is hydrogen, halogen, $-CF_3$, or $-NR^{13}R^{14}$.

[896] **Embodiment 66.** The method of any one of Embodiments 63-65, wherein L is $-E-R^3$.

[897] **Embodiment 67.** The method of any one of Embodiments 63-66, wherein R^3 is selected from hydrogen, $-C_1-C_3$ alkyl, $-NR^{16}SO(C_1-C_3 \text{ alkyl})$, $-NR^{16}SO_2(C_1-C_3 \text{ alkyl})$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-SOR^{18}$, or $-SO_2R^{18}$.

[898] **Embodiment 68.** The method of any one of Embodiments 63-67, wherein R^3 is selected from $-NH SO_2(C_1-C_3 \text{ alkyl})$, $-NCH_3SO_2(C_1-C_3 \text{ alkyl})$, or $-SO_2(C_1-C_3 \text{ alkyl})$.

[899] **Embodiment 69.** The method of Embodiment 63, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (ii):



[900] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[901] X is a bond, $-NR^{10}-$, or $-(CR^{8a}R^{9a})_t-$;

[902] Y and Z are each independently a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$;

[903] V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$;

[904] W is halogen, $-NH_2$, or $-CF_3$.

[905] D is $-\text{NR}^{10}-$ and E is $-(\text{CR}^{2a}\text{R}^{2b})_g-$, $-\text{NR}^{10}-$, or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$;

[906] or alternatively, E is $-\text{NR}^{10}-$ or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$, and D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$ or $-\text{NR}^{10}-$;

[907] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-\text{OCO}(\text{C}_1-\text{C}_3 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[908] R^3 is selected from hydrogen, $-\text{C}_1-\text{C}_6$ alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1-\text{C}_6$ alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;

[909] R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or C_1-C_3 alkyl;

[910] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or C_1-C_3 alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

[911] R^{10} is each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or $-\text{CO}(\text{C}_1-\text{C}_3 \text{ alkyl})$;

[912] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

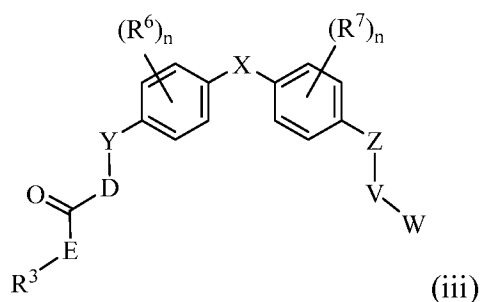
[913] each n is independently 0, 1 or 2;

[914] q is 0, 1 or 2;

[915] each g is independently 0, 1, 2, 3, or 4; and

[916] each t is independently 1 or 2.

[917] **Embodiment 70.** The method of Embodiment 63, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (iii):



[918] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[919] X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

[920] Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

[921] V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

[922] W is halogen, $-\text{NH}_2$ or $-\text{CF}_3$;

[923] D is $-\text{O}-$ or $-\text{NR}^{10}-$ and E is $-(\text{CR}^{2a}\text{R}^{2b})_{\text{gg}}-$;

[924] or alternatively, E is $-\text{O}-$, $-\text{NR}^{10}-$ or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_{\text{g}}-$, and D is $-(\text{CR}^{1a}\text{R}^{1b})_{\text{q}}-$;

[925] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-\text{OCO}(\text{C}_1-\text{C}_3 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$; or $(\text{R}^{1a}$ and $\text{R}^{1b})$ or $(\text{R}^{2a}$ and $\text{R}^{2b})$ taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[926] R^3 is selected from hydrogen, $-\text{C}_1-\text{C}_6$ alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1-\text{C}_6$ alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;

[927] R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or C_1-C_3 alkyl;

[928] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or C_1-C_3 alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

[929] R^{10} is each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or $-\text{CO}(\text{C}_1-\text{C}_3 \text{ alkyl})$;

[930] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

[931] m is 0, 1, 2, 3, or 4;

[932] each n is independently 0, 1 or 2;

[933] q is 1 or 2;

[934] g is 0, 1, 2, 3, or 4;

[935] gg is 1, 2, 3, or 4; and

[936] t is 1 or 2.

[937] **Embodiment 71.** The method of Embodiment 69 or 70, wherein W is Cl, Br, I, or F.

[938] **Embodiment 72.** The method of any one of Embodiments 134-136, wherein D is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, or $-\text{CH}_2\text{CH}_2-$.

[939] **Embodiment 73.** The method of Embodiment 69, wherein q is 0.

[940] **Embodiment 74.** The method of any one of Embodiments 69-73, wherein E is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, or $-\text{CH}_2\text{CH}_2\text{CH}_2-$.

[941] **Embodiment 75.** The method of any one of Embodiments 69-74, wherein g is 0.

[942] **Embodiment 76.** The method of any one of Embodiments 69-75, wherein R^3 is selected from $-\text{NHSO}_2(\text{C}_1-\text{C}_3 \text{ alkyl})$, $-\text{NCH}_3\text{SO}_2(\text{C}_1-\text{C}_3 \text{ alkyl})$, or $-\text{SO}_2(\text{C}_1-\text{C}_3 \text{ alkyl})$.

[943] **Embodiment 77.** The method of any one of Embodiments 69-76, wherein R^6 and R^7 are each independently H, halogen, $-\text{CN}$, or methyl.

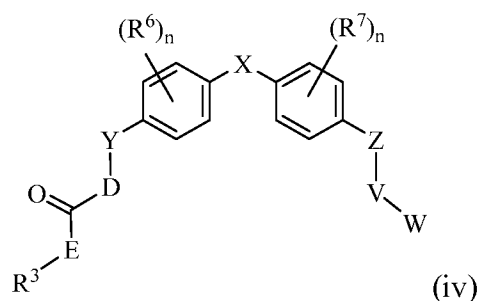
[944] **Embodiment 78.** The method of any one of Embodiments 69-77, wherein X is a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$, $-\text{N}(i\text{Pr})-$, or $-\text{N}(\text{COCH}_3)-$.

[945] **Embodiment 79.** The method of any one of Embodiments 69-78, Z is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$.

[946] **Embodiment 80.** The method of any one of Embodiments 69-79, Y is $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$, or $-\text{NCH}_3-$.

[947] **Embodiment 81.** The method of any one of Embodiments 69-80, wherein at least one of Z and Y is $-\text{O}-$.

[948] **Embodiment 82.** The method of Embodiment 63, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (iv):



[949] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[950] X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

[951] Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

[952] V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

[953] W is halogen, $-\text{CF}_2\text{R}^{10}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

[954] D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$;

[955] E is $-(CR^{2a}R^{2b})_g-$;

[956] R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=O$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

[957] R^3 is selected from hydrogen, $-C_1-C_6$ alkyl, $-OR^{15}$, $-SR^{18}$, $-C_1-C_6$ alkoxy, $-NR^{16}R^{17}$, $-NR^{16}SR^{18}$, $-NR^{16}SOR^{18}$, $-NR^{16}SO_2R^{18}$, $-NR^{16}COR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-SOR^{18}$, or $-SO_2R^{18}$;

[958] R^6 and R^7 are each independently H, halogen, $-CN$, $-CF_3$, $-OH$, or C_1-C_3 alkyl;

[959] R^{8a} and R^{9a} are each independently hydrogen, halogen, $-OH$, or C_1-C_3 alkyl; or R^{8a} and R^{9a} taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

[960] R^{10} is each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or $-CO(C_1-C_3 \text{ alkyl})$;

[961] R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

[962] m is 0, 1, 2, 3, or 4;

[963] each n is independently 0, 1 or 2;

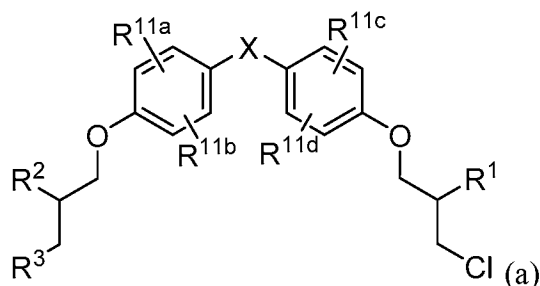
[964] q is 0, 1 or 2;

[965] g is 0, 1, 2, 3, or 4; and

[966] t is 1 or 2.

[967] **Embodiment 83.** The method of Embodiment 63 wherein the androgen receptor N-terminal domain inhibitor is selected from Table A.

[968] **Embodiment 84.** The method of Embodiment 63, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (a):



[969] or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

[970] X is $-S(O)_n-$ or $-C(R^8R^9)-$;

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

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

[973] R^3 is halo, $-OH$, $-OR^4$, $-OC(=O)R^{13}$, $-NH_2$, $-NHC(=O)R^{13}$, $-N(C(=O)R^{13})_2$, $-NHS(O)_nR^5$, $-N(C(=O)R^{13})(S(O)_nR^5)$, $-N(C_1-C_6 \text{ alkyl})(S(O)_nR^5)$, $-S(O)_nR^5$, $-N_3$, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

[974] R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

[975] R^5 is each independently C_1-C_6 alkyl or aryl which are optionally substituted with one or more R^6 ;

[976] R^6 is each independently selected from the group consisting of H, F, Cl, Br, I, ^{123}I , hydroxyl, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_6-C_{12} aryl, wherein each R^6 is optionally substituted with one or more of halogen, ^{123}I , ^{18}F , hydroxyl, $-OS(O)_2$ -aryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

[977] R^8 and R^9 are each independently H, or C_1-C_6 alkyl;

[978] R^{11a} , R^{11b} , R^{11c} and R^{11d} are each independently H, methyl, $-CN$, F, Cl, Br, I, or ^{123}I ;

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

[980] n is 0, 1, or 2;

[981] wherein at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is methyl, $-CN$, F, Cl, Br, I, or ^{123}I .

[982] **Embodiment 85.** The method of Embodiment 84, wherein at least two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are methyl, $-CN$, F, Cl, Br, I, or ^{123}I .

[983] **Embodiment 86.** The method of Embodiment 84, wherein R^{11c} and R^{11d} are each independently methyl, $-CN$, Cl, or Br.

[984] **Embodiment 87.** The method of Embodiment 84, wherein R^{11c} and R^{11d} are each Cl or -CN.

[985] **Embodiment 88.** The method of any one of Embodiments 84-87, wherein X is -C(R^8R^9)- and R^8 and R^9 are each independently C_1 - C_3 alkyl.

[986] **Embodiment 89.** The method of Embodiment 88, wherein R^8 and R^9 are each methyl.

[987] **Embodiment 90.** The method of any one of Embodiments 84-89, wherein R^1 and R^2 are both hydroxyl.

[988] **Embodiment 91.** The method of any one of Embodiments 84-90, wherein R^3 is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom.

[989] **Embodiment 92.** The method of any one of Embodiments 84-91, wherein R^3 is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrroline, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine.

[990] **Embodiment 93.** The method of any one of Embodiments 84-92, wherein R^3 is -NH₂, -NHC(=O) R^{13} , -N(C(=O) R^{13})₂, -NHS(O)_n R^5 , -N(C(=O) R^{13})(S(O)_n R^5), -N(C_1 - C_6 alkyl)(S(O)_n R^5) or -S(O)_n R^5 .

[991] **Embodiment 94.** The method of any one of Embodiments 84-93, wherein R^3 is -NH₂, -NHC(=O)(C_1 - C_4 alkyl), -N[(C(=O)(C_1 - C_4 alkyl)]₂, -NHS(O)_n(C_1 - C_3 alkyl), -N[C(=O)(C_1 - C_4 alkyl)][(S(O)_n(C_1 - C_3 alkyl))], -N[C_1 - C_6 alkyl][S(O)_n(C_1 - C_3 alkyl)], or -S(O)_n(C_1 - C_3 alkyl).

[992] **Embodiment 95.** The method of Embodiment 63, wherein the androgen receptor N-terminal domain inhibitor is selected from Table B.

[993] **Embodiment 96.** The method of any one of Embodiments 48-95, further comprising administering a second therapeutically active agent.

[994] **Embodiment 97.** The method of Embodiment 96, wherein the second therapeutically active agent is selected from a poly (ADP-ribose) polymerase (PARP) inhibitor, an androgen receptor ligand-binding domain inhibitor, an inhibitor of CYP17, a microtubule inhibitor, a modulator of PD-1 or PD-L1, a gonadotropin releasing hormone agonist, a 5- α reductase inhibitor, a vascular endothelial growth factor inhibitor, a histone deacetylase inhibitor, an integrin α -v- β -3 inhibitor, a receptor tyrosine kinase, a phosphoinositide 3-kinase

inhibitor, an anaplastic lymphoma kinase (ALK) inhibitor, an endothelin receptor A antagonist, an anti-CTLA4 inhibitor, an heat shock protein 27 (HSP27) inhibitor, an androgen receptor degrader, a androgen receptor DNA-binding domain inhibitor, a bromodomain and extra-terminal motif (BET) inhibitor, an androgen receptor N-terminal domain inhibitor, an alpha-particle emitting radioactive therapeutic agent, niclosamide, a selective estrogen receptor modulator (SERM), a selective estrogen receptor degrader (SERD), an aromatase inhibitor, selective progesterone receptor modulator (SPRM), a glucocorticoid receptor inhibitor, a CDK4/6 inhibitor, a HER2 receptor antagonist, a mammalian target of rapamycin (mTOR) inhibitor, an AKT inhibitor, a B-cell lymphoma-2 (Bcl-2) inhibitor, an aurora kinase inhibitor, a Wnt-targeting antagonist, a CYP11a inhibitor, a selective androgen receptor N-terminal domain inhibitor, or enhancer of zeste homolog 2 (EZH2) inhibitor.

[995] Embodiment 98. The method of Embodiment 97, wherein the CDK4/6 inhibitor is selected from palbociclib, ribociclib, trilaciclib or abemaciclib.

[996] Embodiment 99. The method of Embodiment 97, wherein the CDK4/6 inhibitor is palbociclib.

[997] Embodiment 100. The method of Embodiment 97, wherein the androgen receptor ligand-binding domain inhibitor is enzalutamide, apalutamide, darolutamide, bicalutamide, nilutamide, flutamide, ODM-204, or TAS3681.

[998] Embodiment 101. The method of Embodiment 97, wherein the androgen receptor ligand-binding domain inhibitor is enzalutamide.

[999] Embodiment 102. The method of Embodiment 97, wherein the PSMA antibody contains lutetium-177.

[1000] Embodiment 103. The method of any one of Embodiments 98-102, wherein the cancer is selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, or salivary gland carcinoma.

[1001] Embodiment 104. The method of Embodiment 103, wherein the cancer is prostate cancer.

[1002] Embodiment 105. The method of Embodiment 103, wherein the prostate cancer is primary or localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, advanced prostate cancer, metastatic prostate cancer, metastatic castration-resistant prostate cancer, and hormone-sensitive prostate cancer.

[1003] Embodiment 106. The method of Embodiment 103, wherein the prostate cancer is metastatic castration-resistant prostate cancer.

[1004] Embodiment 107. The method of Embodiment 103, wherein the prostate cancer expresses full-length androgen receptor or truncated androgen receptor splice variant.

[1005] Embodiment 108. The method of any one of Embodiments 103-107, wherein the prostate cancer is resistant to enzalutamide used with LHRH (luteinizing hormone-releasing hormone) analogues.

[1006] Embodiment A. The method of Embodiment 103, wherein the cancer is breast cancer.

[1007] Embodiment 110. The method of Embodiment 109, wherein the breast cancer is triple negative breast cancer.

[1008] Embodiment 111. The method of any one of Embodiments 63-110, wherein the radiation therapy is ionizing radiation therapy.

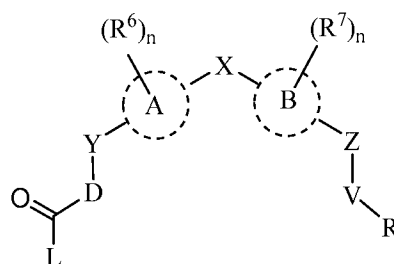
[1009] Embodiment 112. The method of any one of Embodiments 63-110, wherein the administering the androgen receptor N-terminal domain inhibitor and the administering radiation therapy occurs during same treatment period or during different treatment period.

[1010] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

[1011] While the invention has been described in connection with proposed specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth and as follows in the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an androgen receptor N-terminal domain inhibitor and a second therapeutically active agent.
2. A pharmaceutical composition comprising a Pin1 inhibitor and an androgen receptor N-terminal domain inhibitor, wherein the androgen receptor N-terminal domain inhibitor is not 3-(4-(2-(4-(3-chloro-2-hydroxypropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diol, 3-(4-(2-(4-(2-acetoxy-3-chloropropoxy)phenyl)propan-2-yl)phenoxy)propane-1,2-diyl diacetate, or stereoisomers thereof.
3. The pharmaceutical composition of claim 1 or 2, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (i):



(i)

or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

A and B are each independently aryl or heteroaryl;

X is a bond, $-(CR^8R^9)_t-$, $-O-$, $-C(=O)-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

Y and Z are each independently a bond, $-(CR^8R^9)_t-$, $-O-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

V is a bond, optionally substituted $-(CR^{11}R^{12})_m-$, $-C(=O)-$, $-N(R^{10})CO-$, $-CONR^{10}-$, or $-NSO_2R^{10}-$;

R is $-(CR^{4a}R^{4b})-(CR^{5a}R^{5b})-W$ or W;

W is hydrogen, halogen, $-CF_3$, $-CF_2R^{10}$, $-CN$, $-OR^{13}$, $-NR^{13}R^{14}$, optionally substituted $-CONR^{13}R^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

D is $-(CR^{1a}R^{1b})_q-$, $-O-$, or $-NR^{10}-$;

L is $-(CR^{2a}R^{2b})-R^3$ or $-E-R^3$;

E is $-(CR^{2a}R^{2b})_g-$, $-O-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$;

R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{1a} and R^{1b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{2a} and R^{2b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{1a} , R^{1b} , R^{2a} and R^{2b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^{4a} , R^{4b} , R^{5a} , and R^{5b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{4a} and R^{4b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{4a} , R^{4b} , R^{5a} and R^{5b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^3 is absent, hydrogen, $-CN$, $-CF_3$, $-OH$, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted $-OR^{15}$, optionally substituted C_{1-6} alkoxy, $-NH_2$, $-NR^{16}R^{17}$, $-NR^{16}COR^{18}$, $-NR^{16}S(O)_pR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-S(O)_pR^{18}$, $-N_3$, optionally

substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{2a} , R^{2b} and R^3 taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{2a} and R^{10} taken together form an optionally substituted heterocyclyl;

R^6 and R^7 are each independently H, methyl, methoxy, $-\text{CN}$, F, Cl, Br, I, ^{123}I , $-\text{CF}_3$, $-\text{OH}$, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-(\text{C}_1\text{--C}_6 \text{ alkoxy})$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{OH}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{SO}_2\text{R}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})\text{NR}^{14}\text{SO}_2\text{R}^{16}$, $-\text{NR}^{14}\text{COR}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, optionally substituted $-\text{SO}_2\text{R}^{16}$, or optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{SO}_2\text{R}^{16}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^8 , R^9 , R^{11} and R^{12} are each independently hydrogen, $-\text{OH}$, halogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$ alkynyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, optionally substituted $\text{C}_1\text{--C}_6$ alkylamino, optionally substituted $-\text{OCO}(\text{C}_1\text{--C}_6 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, optionally substituted $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^8 and R^9 taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

or alternatively, R^{11} and R^{12} , on a same carbon atom or a different carbon atom, taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^{10} is hydrogen, halogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_1\text{--C}_6$ alkoxy, $-\text{CO}(\text{C}_1\text{--C}_6 \text{ alkyl})$, optionally substituted $\text{C}_1\text{--C}_6$ alkylamino, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, optionally substituted $\text{C}_1\text{--C}_6$ alkyl, optionally substituted $\text{C}_2\text{--C}_6$ alkenyl, optionally substituted $\text{C}_2\text{--C}_6$ alkynyl,

optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{14} and R^{15} are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

or alternatively, R^{16} and R^{17} are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

m is 0, 1, 2, 3, or 4;

each n is independently 0, 1 or 2;

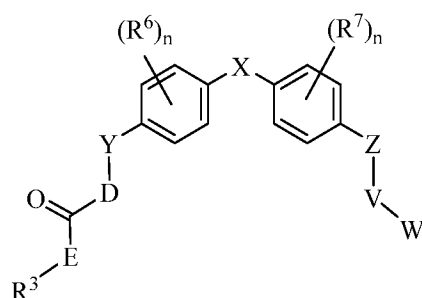
each p is independently 0, 1 or 2;

q is 0, 1 or 2;

each g is independently 0, 1, 2, 3, or 4; and

each t is independently 1 or 2.

4. The pharmaceutical composition of claim 3, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (ii):



(ii)

or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

X is a bond, $-NR^{10}-$, or $-(CR^{8a}R^{9a})_t-$;

Y and Z are each independently a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$;

V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$;

W is halogen, $-NH_2$, or $-CF_3$.

D is $-NR^{10}-$ and E is $-(CR^{2a}R^{2b})_g-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$;

or alternatively, E is $-NR^{10}-$ or $-NR^{10}-(CR^{2a}R^{2b})_g-$, and D is $-(CR^{1a}R^{1b})_q-$ or $-NR^{10}-$;

R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_6 \text{ alkyl})-$

CONR¹⁴R¹⁵, or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo (=O), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

R³ is selected from hydrogen, -C₁-C₆ alkyl, -OR¹⁵, -SR¹⁸, -C₁-C₆ alkoxy, -NR¹⁶R¹⁷, -NR¹⁶SR¹⁸, -NR¹⁶SOR¹⁸, -NR¹⁶SO₂R¹⁸, -NR¹⁶COR¹⁸, -CONR¹⁴R¹⁵, -SONR¹⁴R¹⁵, -SO₂NR¹⁴R¹⁵, -SOR¹⁸, or -SO₂R¹⁸;

R⁶ and R⁷ are each independently H, halogen, -CN, -CF₃, -OH, or C₁-C₃ alkyl;

R^{8a} and R^{9a} are each independently hydrogen, halogen, -OH, or C₁-C₃ alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

R¹⁰ is each independently hydrogen, C₁-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or -CO(C₁-C₃ alkyl);

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are each independently hydrogen, C₁-C₃ alkyl, C₂-C₃ alkenyl, or C₂-C₃ alkynyl; or R¹⁴ and R¹⁵ taken together form an optionally substituted 5- or 6- membered heterocyclyl;

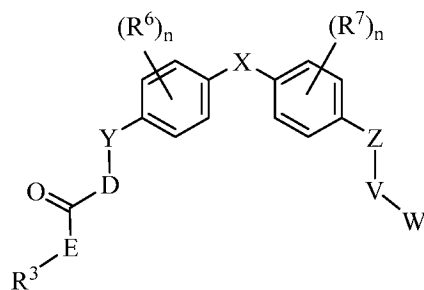
each n is independently 0, 1 or 2;

q is 0, 1 or 2;

each g is independently 0, 1, 2, 3, or 4; and

each t is independently 1 or 2.

5. The pharmaceutical composition of claim 3, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (iii):



(iii)

or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

X is a bond, -NR¹⁰-, or -(CR^{8a}R^{9a})_t;

Y and Z are each independently a bond, -CH₂-, -C(CH₃)H-, -O-, -S-, -NH-, -NCH₃-, or -N(COCH₃)-

V is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH(OH)CH₂-, or -CH₂C(OH)(CH₃)CH₂-;

W is halogen, -NH₂ or -CF₃;

D is $-\text{O}-$ or $-\text{NR}^{10}-$ and E is $-(\text{CR}^{2a}\text{R}^{2b})_{\text{gg}}-$;

or alternatively, E is $-\text{O}-$, $-\text{NR}^{10}-$ or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_{\text{g}}-$, and D is $-(\text{CR}^{1a}\text{R}^{1b})_{\text{q}}-$;

R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, $\text{C}_1\text{--C}_3$ alkoxy, $-\text{OCO}(\text{C}_1\text{--C}_3 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1\text{--C}_3 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1\text{--C}_3 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1\text{--C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

R^3 is selected from hydrogen, $-\text{C}_1\text{--C}_6$ alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1\text{--C}_6$ alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;

R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl;

R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

R^{10} is each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, or $-\text{CO}(\text{C}_1\text{--C}_3 \text{ alkyl})$;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, or $\text{C}_2\text{--C}_3$ alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6- membered heterocyclyl;

m is 0, 1, 2, 3, or 4;

each n is independently 0, 1 or 2;

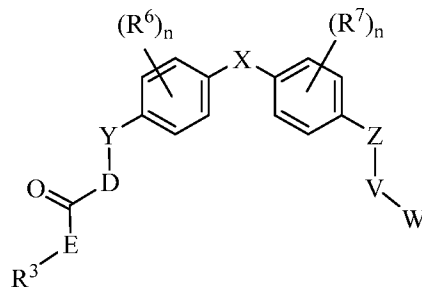
q is 1 or 2;

g is 0, 1, 2, 3, or 4;

gg is 1, 2, 3, or 4; and

t is 1 or 2.

6. The pharmaceutical composition of claim 3, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (iv):



(iv)

or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

W is halogen, $-\text{CF}_2\text{R}^{10}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$;

E is $-(\text{CR}^{2a}\text{R}^{2b})_g-$;

R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, C_2 – C_3 alkynyl, C_1 – C_3 alkoxy, $-\text{OCO}(\text{C}_1$ – C_3 alkyl), $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1$ – C_3 alkyl)– $\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1$ – C_3 alkyl)– $\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1$ – C_6 alkyl)– $\text{CONR}^{14}\text{R}^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

R^3 is selected from hydrogen, $-\text{C}_1$ – C_6 alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1$ – C_6 alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;

R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or C_1 – C_3 alkyl;

R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or C_1 – C_3 alkyl; or R^{8a} and R^{9a} taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^{10} is each independently hydrogen, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, C_2 – C_3 alkynyl, or $-\text{CO}(\text{C}_1$ – C_3 alkyl);

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, or C_2 – C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6-membered heterocyclyl;

m is 0, 1, 2, 3, or 4;

each n is independently 0, 1 or 2;

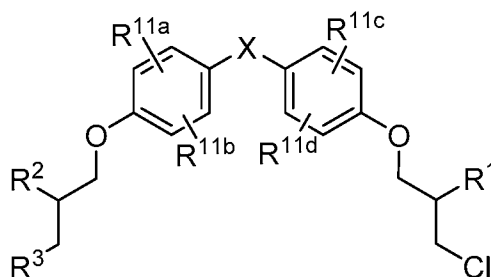
q is 0, 1 or 2;

g is 0, 1, 2, 3, or 4; and

t is 1 or 2.

7. The pharmaceutical composition of claim 1 or 2, wherein the androgen receptor N-terminal domain inhibitor is selected from Table A.

8. The pharmaceutical composition of claim 1 or 2, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (a):



(a)

wherein:

X is $-S(O)_n-$ or $-C(R^8R^9)-$;

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

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

R^3 is halo, $-OH$, $-OR^4$, $-OC(=O)R^{13}$, $-NH_2$, $-NHC(=O)R^{13}$, $-N(C(=O)R^{13})_2$, $-NHS(O)_nR^5$, $-N(C(=O)R^{13})(S(O)_nR^5)$, $-N(C_1-C_6 \text{ alkyl})(S(O)_nR^5)$, $-S(O)_nR^5$, $-N_3$, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

R^4 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

R^5 is each independently C_1-C_6 alkyl or aryl which are optionally substituted with one or more R^6 ;

R^6 is each independently selected from the group consisting of H, F, Cl, Br, I, ^{123}I , hydroxyl, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_6-C_{12} aryl, wherein each R^6 is optionally substituted with one or more of halogen, ^{123}I , ^{18}F , hydroxyl, $-OS(O)_2$ -aryl, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

R^8 and R^9 are each independently H, or C_1-C_6 alkyl;

R^{11a} , R^{11b} , R^{11c} and R^{11d} are each independently H, methyl, $-CN$, F, Cl, Br, I, or ^{123}I ;

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

n is 0, 1, or 2;

wherein at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is methyl, $-CN$, F, Cl, Br, I, or ^{123}I .

9. The pharmaceutical composition of claim 8, wherein at least two of R^{11a}, R^{11b}, R^{11c} and R^{11d} are methyl, -CN, F, Cl, Br, I, or ¹²³I.
10. The pharmaceutical composition of claim 8, wherein R^{11c} and R^{11d} are each independently methyl, -CN, Cl, or Br.
11. The pharmaceutical composition of claim 8, wherein R^{11c} and R^{11d} are each Cl or -CN.
12. The pharmaceutical composition of any one of claim 8-11, wherein X is -C(R⁸R⁹)- and R⁸ and R⁹ are each independently C₁-C₃ alkyl.
13. The pharmaceutical composition of claim 12, wherein R⁸ and R⁹ are each methyl.
14. The pharmaceutical composition of any one of claims 8-13, wherein R¹ and R² are both hydroxyl.
15. The pharmaceutical composition of any one of claims 8-14, wherein R³ is an optionally substituted 5 or 6 membered heteroaryl or an optionally substituted 3 to 7 membered heterocyclyl, wherein said heteroaryl or said heterocyclyl respectively comprise at least one N atom.
16. The pharmaceutical composition of any one of claims 8-14, wherein R³ is selected from a group consisting of pyrrole, furan, thiophene, pyrazole, pyridine, pyridazine, pyrimidine, imidazole, thiazole, isoxazole, oxadiazole, thiadiazole, oxazole, triazole, isothiazole, oxazine, triazine, azepine, pyrrolidine, pyrroline, imidazoline, imidazolidine, pyrazoline, pyrazolidine, piperidine, dioxane, morpholine, dithiane, thiomorpholine, piperazine, and tetrazine.
17. The pharmaceutical composition of any one of claims 8-14, wherein R³ is -NH₂, -NHC(=O)R¹³, -N(C(=O)R¹³)₂, -NHS(O)_nR⁵, -N(C(=O)R¹³)(S(O)_nR⁵), -N(C₁-C₆ alkyl)(S(O)_nR⁵) or -S(O)_nR⁵.
18. The pharmaceutical composition of any one of claims 8-14, wherein R³ is -NH₂, -NHC(=O)(C₁-C₄ alkyl), -N[(C(=O)(C₁-C₄ alkyl)]₂, -NHS(O)_n(C₁-C₃ alkyl), -N[C(=O)(C₁-

C4 alkyl)][(S(O)_n(C1-C3 alkyl)], -N[C₁-C₆ alkyl)][S(O)_n(C1-C3 alkyl)], or -S(O)_n(C1-C3 alkyl).

19. The pharmaceutical composition of claim 1 or 2, wherein the androgen receptor N-terminal domain inhibitor is selected from Table B.

20. The pharmaceutical composition of any one of claims 1 and 3-19, wherein the second therapeutically active agent is selected from a poly (ADP-ribose) polymerase (PARP) inhibitor, an androgen receptor ligand-binding domain inhibitor, an inhibitor of CYP17, a microtubule inhibitor, a modulator of PD-1 or PD-L1, a gonadotropin releasing hormone agonist, a 5- α reductase inhibitor, a vascular endothelial growth factor inhibitor, a histone deacetylase inhibitor, an integrin α -v- β -3 inhibitor, a receptor tyrosine kinase, a phosphoinositide 3-kinase inhibitor, an anaplastic lymphoma kinase (ALK) inhibitor, an endothelin receptor A antagonist, an anti-CTLA4 inhibitor, an heat shock protein 27 (HSP27) inhibitor, an androgen receptor degrader, a androgen receptor DNA-binding domain inhibitor, a bromodomain and extra-terminal motif (BET) inhibitor, an androgen receptor N-terminal domain inhibitor, an α -particle emitting radioactive therapeutic agent, niclosamide, a selective estrogen receptor modulator (SERM), a selective estrogen receptor degrader (SERD), an aromatase inhibitor, selective progesterone receptor modulator (SPRM), a glucocorticoid receptor inhibitor, a CDK4/6 inhibitor, a HER2 receptor antagonist, a mammalian target of rapamycin (mTOR) inhibitor, an AKT inhibitor, a B-cell lymphoma-2 (Bcl-2) inhibitor, an aurora kinase inhibitor, a Wnt-targeting antagonist, a CYP11a inhibitor, a selective androgen receptor N-terminal domain inhibitor, or enhancer of zeste homolog 2 (EZH2) inhibitor.

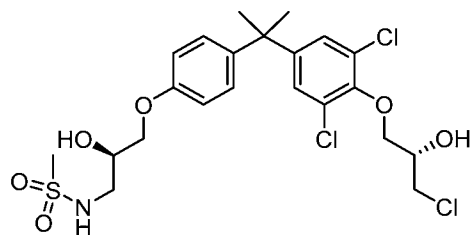
21. The pharmaceutical composition of claim 20, wherein the CDK4/6 inhibitor is selected from palbociclib, ribociclib, trilaciclib or abemaciclib.

22. The pharmaceutical composition of claim 20 or 21, wherein the CDK4/6 inhibitor is palbociclib.

23. The pharmaceutical composition of claim 20, wherein the androgen receptor ligand-binding domain inhibitor is enzalutamide, apalutamide, darolutamide, bicalutamide, nilutamide, flutamide, ODM-204, or TAS3681.

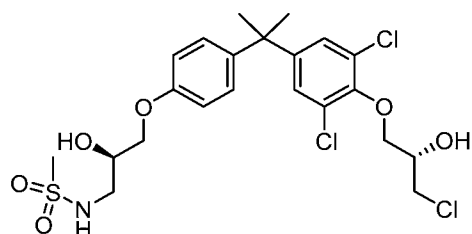
24. The pharmaceutical composition claim 20 or 23, wherein the androgen receptor ligand-binding domain inhibitor is enzalutamide.

25. A pharmaceutical composition comprising enzalutamide and



or a pharmaceutically acceptable salt thereof.

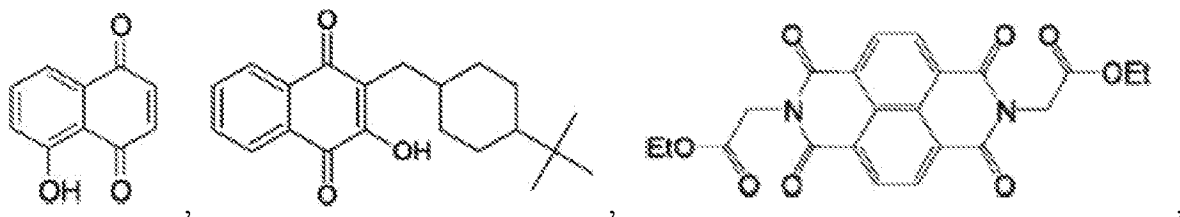
26. A pharmaceutical composition comprising palbociclib and

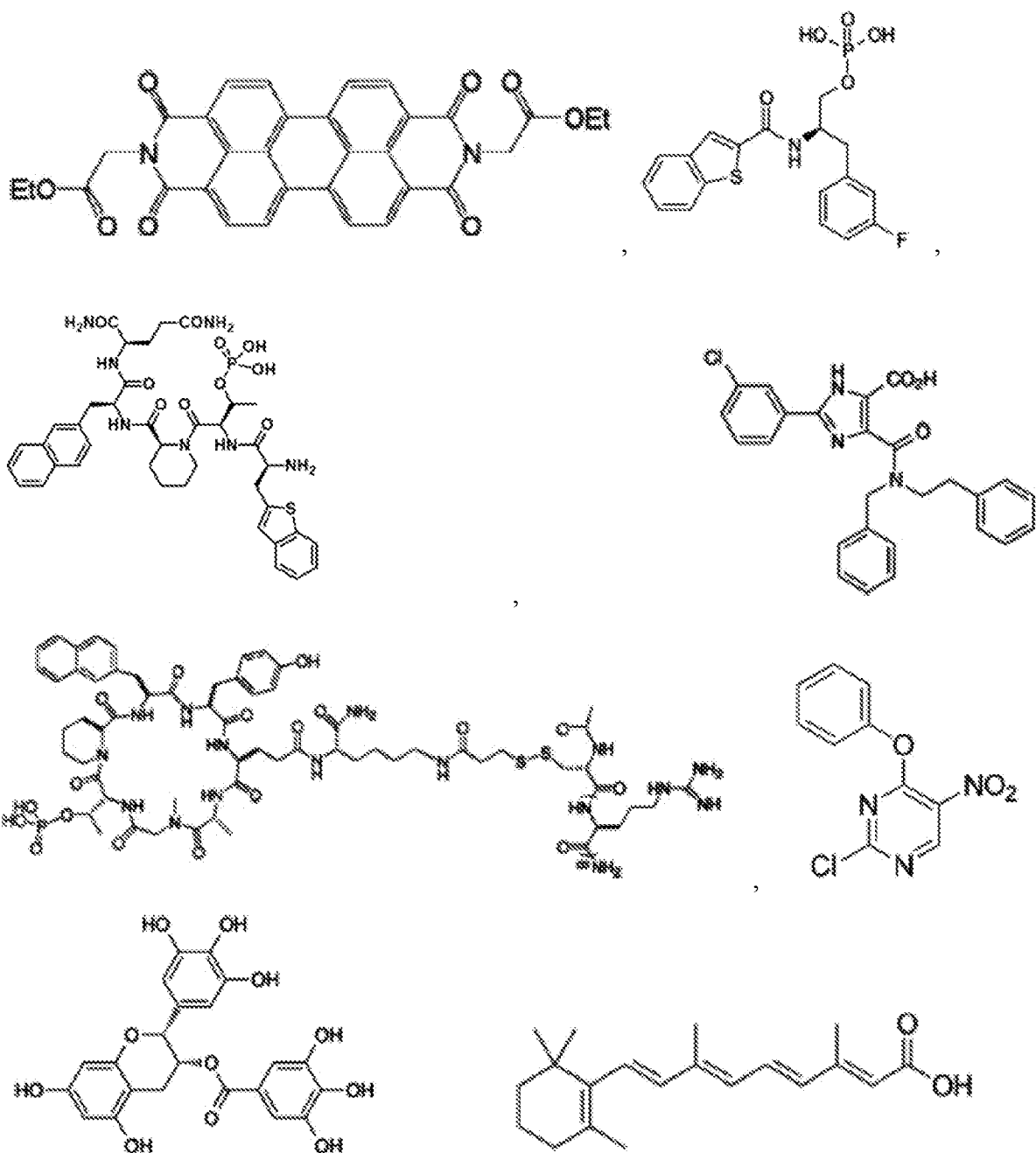


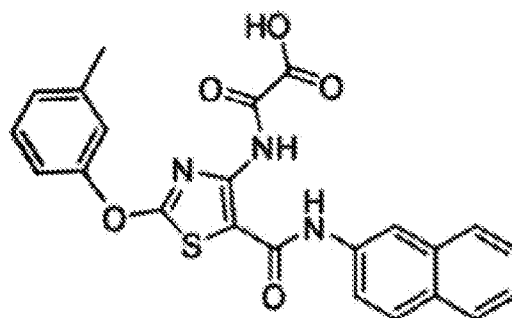
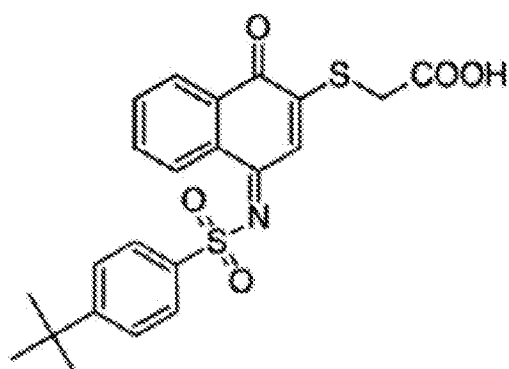
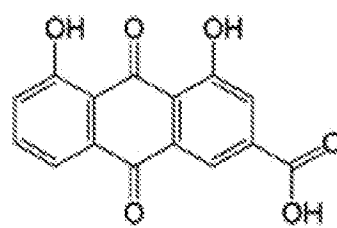
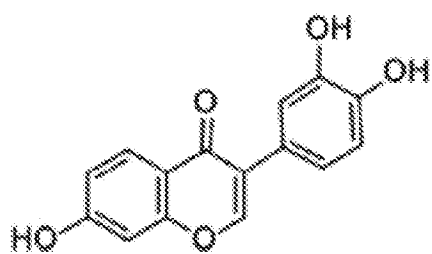
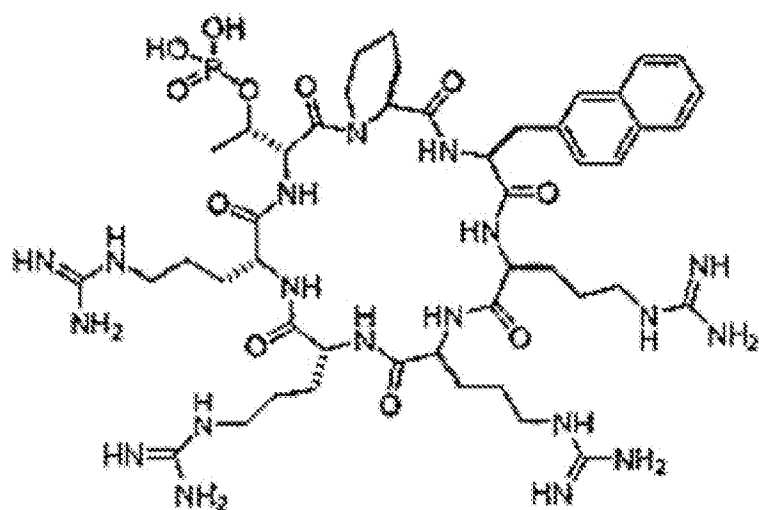
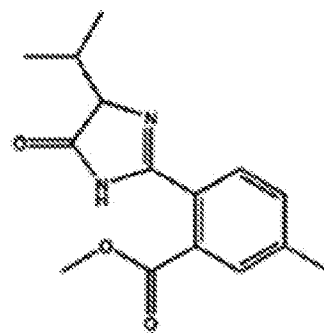
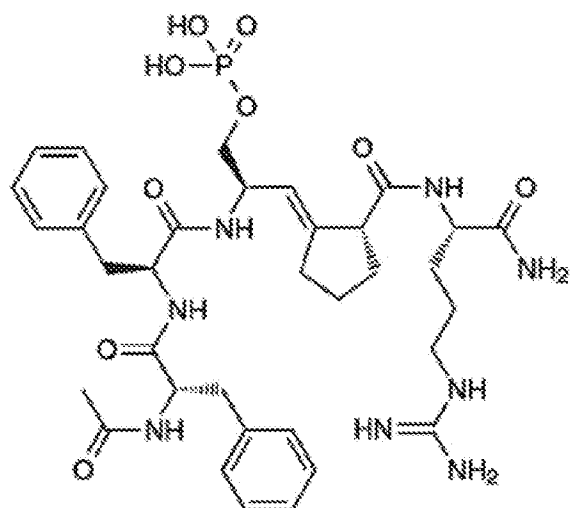
or a pharmaceutically acceptable salt thereof.

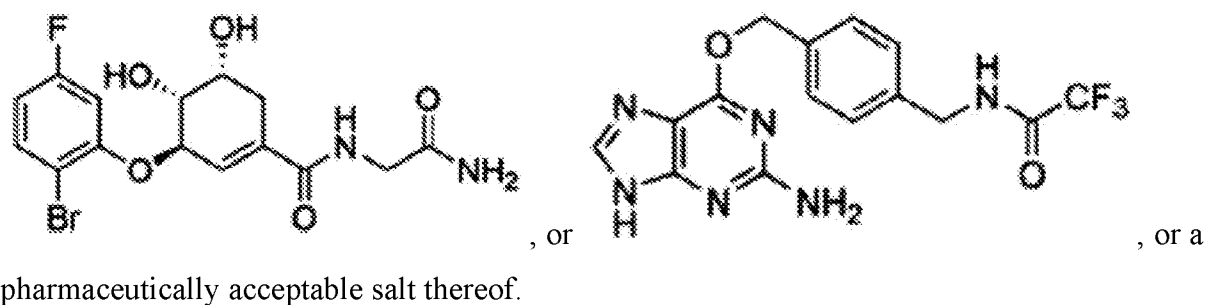
27. The pharmaceutical composition of any one of claims 2-19, wherein the Pin1 inhibitor is selected from juglone, plumbagin, PiB, PiJ, epigallocatechin gallate (EGCG), all-trans retinoic acid (ATRA), dipentamethylene thiauram monosulfide, TME-001 (2-(3-chloro-4-fluoro-phenyl)-isothiazol-3-one), KPT-6566, API-1, buparvaquone, or a pharmaceutically acceptable salt thereof.

28. The pharmaceutical composition of any one of claims 2-19, wherein the Pin1 inhibitor is selected from

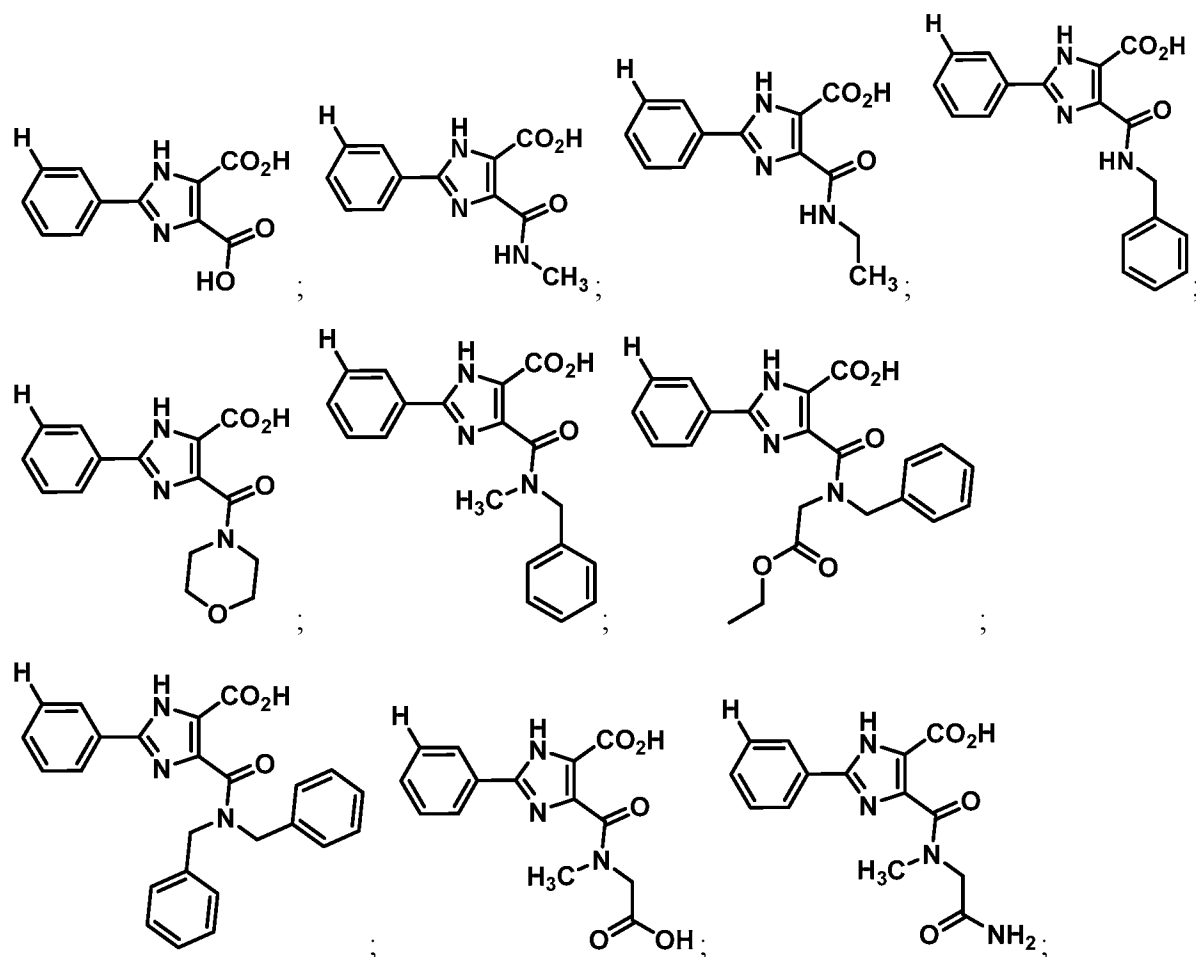


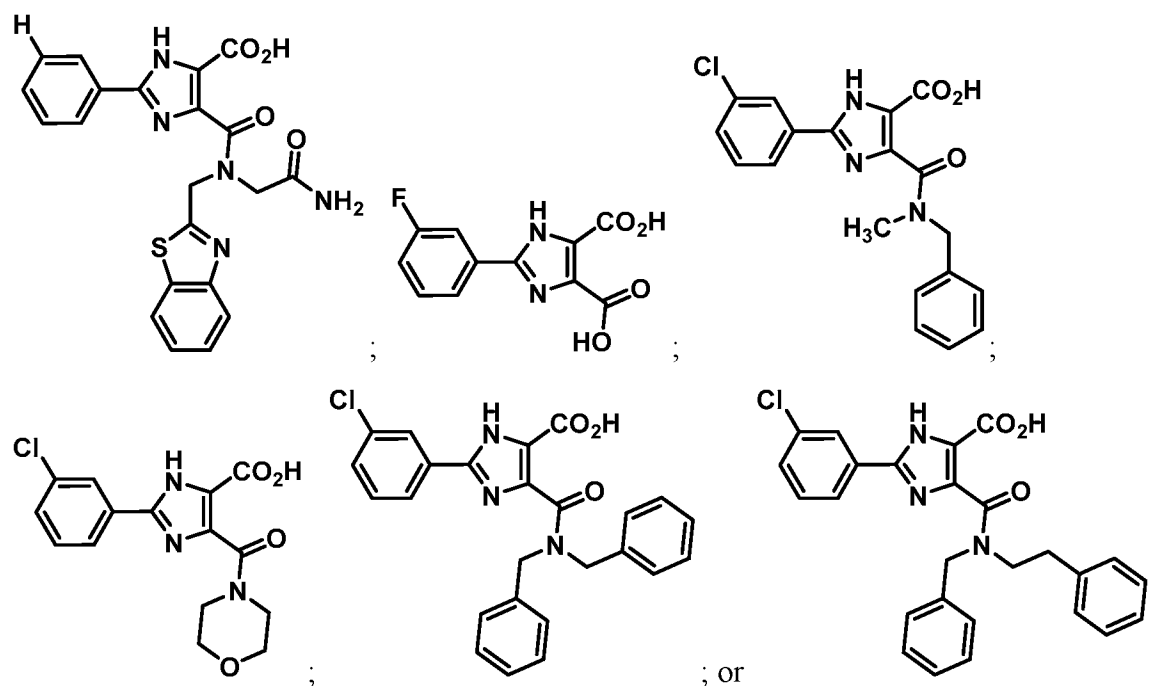






29. The pharmaceutical composition of any one of claims 2-19, wherein the Pin1 inhibitor is selected from





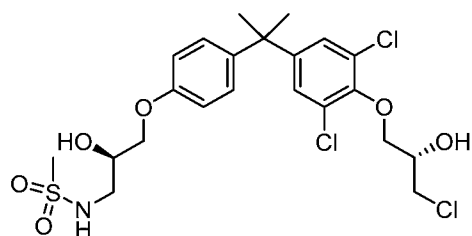
or a pharmaceutically acceptable salt thereof.

30. The pharmaceutical composition of any one of claims 2-19 wherein the Pin1 inhibitor is CRYPEVEIC, wherein the cysteine residues of said peptide are cyclized by a disulfide bond (SEQ ID NO: 1); Ac-Lys(N-biotinoyl)-Ala-Ala-Bth-D-Thr(PO₃H₂)-Pip-Nal-Gln-NH₂ (SEQ ID NO: 2); Ac-Phe-D-Thr(PO₃H₂)-Pip-Nal-Gln-NH₂ (SEQ ID NO: 3); and Ac-Phe-Phe-pSer-Ψ[(Z)CHdC-Pro-Arg-NH₂ (SEQ ID NO: 4).

31. The pharmaceutical composition of any one of claims 2-19, wherein the Pin1 inhibitor is selected from 5-hydroxy-1,4-naphthledione, (1-piperidinecarbodithioic acid, anhydrosulfide), or diethyl-1,3,6,8-tetrahydro-1,3,6,8-tetraoxobenzo[lmn] phenanthroline-2,7-diacetate, or a pharmaceutically acceptable salt thereof.

32. The pharmaceutical composition of any one of claims 2-19, wherein the Pin1 inhibitor is ATRA.

33. A pharmaceutical composition comprising ATRA and



or a pharmaceutically acceptable salt thereof.

34. The pharmaceutical composition of any one of claims 1-33, further comprising a pharmaceutically acceptable carrier.

35. A method for inhibiting androgen receptor activity, comprising administering a pharmaceutical composition of any one of claims 1-34, to a subject in need thereof.

36. The method of 35, wherein the inhibiting androgen receptor activity is for treating a condition or disease selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, salivary gland carcinoma, hair loss, acne, hirsutism, ovarian cysts, polycystic ovary disease, precocious puberty, spinal and bulbar muscular atrophy, or age-related macular degeneration.

37. A method for treating cancer, comprising administering the pharmaceutical composition of any one of claims 1-34, to a subject in need thereof.

38. The method of claim 37, wherein the cancer is breast cancer.

39. The method of claim 38, wherein the breast cancer is triple negative breast cancer.

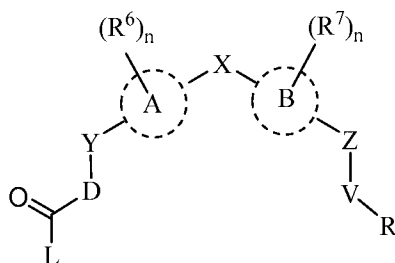
40. The method of claim 37, wherein the cancer is selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, or salivary gland carcinoma.

41. The method of claim 37, wherein the cancer is prostate cancer.

42. The method of claim 41, wherein the prostate cancer is primary or localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, advanced prostate cancer,

metastatic prostate cancer, metastatic castration-resistant prostate cancer, and hormone-sensitive prostate cancer.

43. The method of claim 42, wherein the prostate cancer is metastatic castration-resistant prostate cancer.
44. The method of claim 41, wherein the prostate cancer expresses full-length androgen receptor or truncated androgen receptor splice variant.
45. The method of any one of claims 37-44, further comprising administering radiation therapy the subject.
46. The method of claim 45, wherein the radiation therapy is ionizing radiation therapy.
47. The method of claim 45 or 46, wherein the administering the pharmaceutical composition and the administering radiation therapy occurs during same treatment period or during different treatment period.
48. The method of any one of claims 45-47, wherein the subject has prostate cancer.
49. The method of any one of claims 41-48, wherein the prostate cancer is resistant to enzalutamide monotherapy.
50. A method of treating cancer, comprising administering a therapeutically effective amount of an androgen receptor N-terminal domain inhibitor and a radiation therapy to a subject in need thereof.
51. The method of claim 50, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (i):



or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

A and B are each independently aryl or heteroaryl;

X is a bond, $-(CR^8R^9)_t-$, $-O-$, $-C(=O)-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

Y and Z are each independently a bond, $-(CR^8R^9)_t-$, $-O-$, $-S(O)_n-$, $-NR^{10}-$, $-CONR^{10}-$, $-NR^{10}CO-$, $-SO_2NR^{10}-$, or $-NR^{10}SO_2-$;

V is a bond, optionally substituted $-(CR^{11}R^{12})_m-$, $-C(=O)-$, $-N(R^{10})CO-$, $-CONR^{10}-$, or $-NSO_2R^{10}-$;

R is $-(CR^{4a}R^{4b})-(CR^{5a}R^{5b})-W$ or W;

W is hydrogen, halogen, $-CF_3$, $-CF_2R^{10}$, $-CN$, $-OR^{13}$, $-NR^{13}R^{14}$, optionally substituted $-CONR^{13}R^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

D is $-(CR^{1a}R^{1b})_q-$, $-O-$, or $-NR^{10}-$;

L is $-(CR^{2a}R^{2b})-R^3$ or $-E-R^3$;

E is $-(CR^{2a}R^{2b})_g-$, $-O-$, $-NR^{10}-$, or $-NR^{10}-(CR^{2a}R^{2b})_g-$;

R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, hydroxy, optionally substituted C_{1-6} alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted C_{1-6} alkoxy, optionally substituted $-OCO(C_{1-6} \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_{1-6} \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_{1-6} \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{1a} and R^{1b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{2a} and R^{2b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{1a}, R^{1b}, R^{2a} and R^{2b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R^{4a}, R^{4b}, R^{5a}, and R^{5b} are each independently hydrogen, halogen, hydroxy, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted C₁₋₆ alkoxy, optionally substituted -OCO(C₁₋₆ alkyl), -NR¹³R¹⁴, optionally substituted -(C₁₋₆ alkyl)-NR¹³R¹⁴, -NR¹⁴COR¹⁶, optionally substituted -(C₁₋₆ alkyl)-NR¹⁴COR¹⁶, -CONR¹⁴R¹⁵, optionally substituted -(C₁₋₆ alkyl)-CONR¹⁴R¹⁵, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{4a} and R^{4b} taken together form a CO, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{4a}, R^{4b}, R^{5a} and R^{5b} taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R³ is absent, hydrogen, -CN, -CF₃, -OH, optionally substituted C₁₋₆ alkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, optionally substituted -OR¹⁵, optionally substituted C₁₋₆ alkoxy, -NH₂, -NR¹⁶R¹⁷, -NR¹⁶COR¹⁸, -NR¹⁶S(O)_pR¹⁸, -CONR¹⁴R¹⁵, -SONR¹⁴R¹⁵, -SO₂NR¹⁴R¹⁵, optionally substituted -S(O)_pR¹⁸, -N₃, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{2a}, R^{2b} and R³ taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R^{2a} and R¹⁰ taken together form an optionally substituted heterocyclyl;

R⁶ and R⁷ are each independently H, methyl, methoxy, -CN, F, Cl, Br, I, ¹²³I, -CF₃, -OH, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ alkoxy, optionally substituted -(C₁₋₆ alkyl)-(C₁₋₆ alkoxy), optionally substituted -(C₁₋₆ alkyl)-OH, -NR¹³R¹⁴, optionally substituted -(C₁₋₆ alkyl)-NR¹³R¹⁴, -NR¹⁴SO₂R¹⁶, optionally substituted -(C₁₋₆ alkyl)NR¹⁴SO₂R¹⁶, -NR¹⁴COR¹⁶, optionally substituted -(C₁₋₆ alkyl)-NR¹⁴COR¹⁶, -

CONR¹⁴R¹⁵, optionally substituted $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-SO_2NR^{14}R^{15}$, optionally substituted $-SO_2R^{16}$, or optionally substituted $-(C_1-C_6 \text{ alkyl})-SO_2R^{16}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R⁸, R⁹, R¹¹ and R¹² are each independently hydrogen, $-OH$, halogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted C₁–C₆ alkoxy, optionally substituted C₁–C₆ alkylamino, optionally substituted $-OCO(C_1-C_6 \text{ alkyl})$, $-NR^{13}R^{14}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, optionally substituted $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R⁸ and R⁹ taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

or alternatively, R¹¹ and R¹², on a same carbon atom or a different carbon atom, taken together form an optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R¹⁰ is hydrogen, halogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₁–C₆ alkoxy, $-CO(C_1-C_6 \text{ alkyl})$, optionally substituted C₁–C₆ alkylamino, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are each independently hydrogen, optionally substituted C₁–C₆ alkyl, optionally substituted C₂–C₆ alkenyl, optionally substituted C₂–C₆ alkynyl, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

or alternatively, R¹⁴ and R¹⁵ are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

or alternatively, R¹⁶ and R¹⁷ are taken together to form an optionally substituted heterocyclyl, or optionally substituted heteroaryl;

m is 0, 1, 2, 3, or 4;

each n is independently 0, 1 or 2;

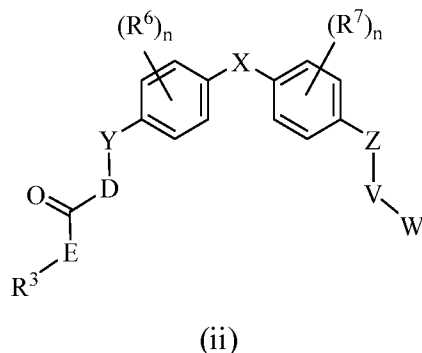
each p is independently 0, 1 or 2;

q is 0, 1 or 2;

each g is independently 0, 1, 2, 3, or 4; and

each t is independently 1 or 2.

52. The method of claim 50, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (ii):



or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

W is halogen, $-\text{NH}_2$, or $-\text{CF}_3$.

D is $-\text{NR}^{10}-$ and E is $-(\text{CR}^{2a}\text{R}^{2b})_g-$, $-\text{NR}^{10}-$, or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$;

or alternatively, E is $-\text{NR}^{10}-$ or $-\text{NR}^{10}-(\text{CR}^{2a}\text{R}^{2b})_g-$, and D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$ or $-\text{NR}^{10}-$;

R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-\text{OH}$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-\text{OCO}(\text{C}_1-\text{C}_3 \text{ alkyl})$, $-\text{NR}^{13}\text{R}^{14}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{14}\text{COR}^{16}$, $-(\text{C}_1-\text{C}_3 \text{ alkyl})-\text{NR}^{14}\text{COR}^{16}$, $-\text{CONR}^{14}\text{R}^{15}$, or $-(\text{C}_1-\text{C}_6 \text{ alkyl})-\text{CONR}^{14}\text{R}^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=\text{O}$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

R^3 is selected from hydrogen, $-\text{C}_1-\text{C}_6$ alkyl, $-\text{OR}^{15}$, $-\text{SR}^{18}$, $-\text{C}_1-\text{C}_6$ alkoxy, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{SR}^{18}$, $-\text{NR}^{16}\text{SOR}^{18}$, $-\text{NR}^{16}\text{SO}_2\text{R}^{18}$, $-\text{NR}^{16}\text{COR}^{18}$, $-\text{CONR}^{14}\text{R}^{15}$, $-\text{SONR}^{14}\text{R}^{15}$, $-\text{SO}_2\text{NR}^{14}\text{R}^{15}$, $-\text{SOR}^{18}$, or $-\text{SO}_2\text{R}^{18}$;

R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or C_1-C_3 alkyl;

R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or C_1-C_3 alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

R^{10} is each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or $-\text{CO}(\text{C}_1-\text{C}_3 \text{ alkyl})$;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, or C_2 – C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6-membered heterocyclyl;

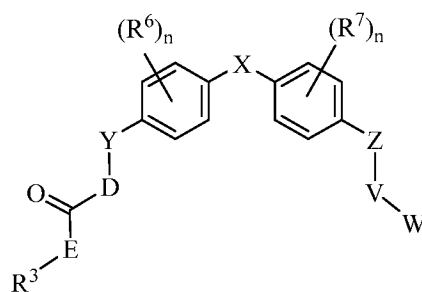
each n is independently 0, 1 or 2;

q is 0, 1 or 2;

each g is independently 0, 1, 2, 3, or 4; and

each t is independently 1 or 2.

53. The method of claim 50, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (iii):



(iii)

or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

X is a bond, $-NR^{10}-$, or $-(CR^{8a}R^{9a})_t-$;

Y and Z are each independently a bond, $-CH_2-$, $-C(CH_3)H-$, $-O-$, $-S-$, $-NH-$, $-NCH_3-$, or $-N(COCH_3)-$;

V is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, $-CH_2CH(OH)CH_2-$, or $-CH_2C(OH)(CH_3)CH_2-$;

W is halogen, $-NH_2$ or $-CF_3$;

D is $-O-$ or $-NR^{10}-$ and E is $-(CR^{2a}R^{2b})_{gg}-$;

or alternatively, E is $-O-$, $-NR^{10}-$ or $-NR^{10}-(CR^{2a}R^{2b})_g-$, and D is $-(CR^{1a}R^{1b})_q-$;

R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1 – C_3 alkyl, C_2 – C_3 alkenyl, C_2 – C_3 alkynyl, C_1 – C_3 alkoxy, $-OCO(C_1$ – C_3 alkyl), $-NR^{13}R^{14}$, $-(C_1$ – C_3 alkyl)– $NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1$ – C_3 alkyl)– $NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1$ – C_6 alkyl)– $CONR^{14}R^{15}$; or $(R^{1a}$ and $R^{1b})$ or $(R^{2a}$ and $R^{2b})$ taken together form an oxo ($=O$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

R^3 is selected from hydrogen, $-C_1$ – C_6 alkyl, $-OR^{15}$, $-SR^{18}$, $-C_1$ – C_6 alkoxy, $-NR^{16}R^{17}$, $-NR^{16}SR^{18}$, $-NR^{16}SOR^{18}$, $-NR^{16}SO_2R^{18}$, $-NR^{16}COR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-SOR^{18}$, or $-SO_2R^{18}$;

R^6 and R^7 are each independently H, halogen, $-\text{CN}$, $-\text{CF}_3$, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl;

R^{8a} and R^{9a} are each independently hydrogen, halogen, $-\text{OH}$, or $\text{C}_1\text{--C}_3$ alkyl; or R^{8a} and R^{9a} taken together form an 3- to 6-membered carbocyclyl or heterocyclyl;

R^{10} is each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, $\text{C}_2\text{--C}_3$ alkynyl, or $-\text{CO}(\text{C}_1\text{--C}_3 \text{ alkyl})$;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, $\text{C}_1\text{--C}_3$ alkyl, $\text{C}_2\text{--C}_3$ alkenyl, or $\text{C}_2\text{--C}_3$ alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6-membered heterocyclyl;

m is 0, 1, 2, 3, or 4;

each n is independently 0, 1 or 2;

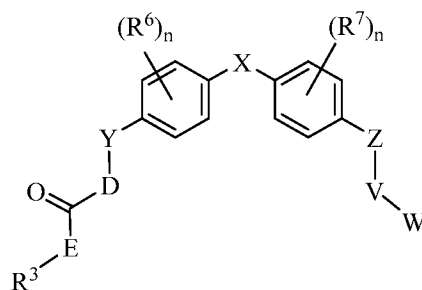
q is 1 or 2;

g is 0, 1, 2, 3, or 4;

gg is 1, 2, 3, or 4; and

t is 1 or 2.

54. The method of claim 50, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (iv):



(iv)

or a pharmaceutically acceptable salt, tautomer, stereoisomer or prodrug thereof, wherein:

X is a bond, $-\text{NR}^{10}-$, or $-(\text{CR}^{8a}\text{R}^{9a})_t-$;

Y and Z are each independently a bond, $-\text{CH}_2-$, $-\text{C}(\text{CH}_3)\text{H}-$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{NCH}_3-$, or $-\text{N}(\text{COCH}_3)-$;

V is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2-$, or $-\text{CH}_2\text{C}(\text{OH})(\text{CH}_3)\text{CH}_2-$;

W is halogen, $-\text{CF}_2\text{R}^{10}$, $-\text{NR}^{13}\text{R}^{14}$, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

D is $-(\text{CR}^{1a}\text{R}^{1b})_q-$;

E is $-(\text{CR}^{2a}\text{R}^{2b})_g-$;

R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each independently hydrogen, halogen, $-OH$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_3 alkoxy, $-OCO(C_1-C_3 \text{ alkyl})$, $-NR^{13}R^{14}$, $-(C_1-C_3 \text{ alkyl})-NR^{13}R^{14}$, $-NR^{14}COR^{16}$, $-(C_1-C_3 \text{ alkyl})-NR^{14}COR^{16}$, $-CONR^{14}R^{15}$, or $-(C_1-C_6 \text{ alkyl})-CONR^{14}R^{15}$; or (R^{1a} and R^{1b}) or (R^{2a} and R^{2b}) taken together form an oxo ($=O$), an optionally substituted carbocyclyl, or an optionally substituted heterocyclyl;

R^3 is selected from hydrogen, $-C_1-C_6$ alkyl, $-OR^{15}$, $-SR^{18}$, $-C_1-C_6$ alkoxy, $-NR^{16}R^{17}$, $-NR^{16}SR^{18}$, $-NR^{16}SOR^{18}$, $-NR^{16}SO_2R^{18}$, $-NR^{16}COR^{18}$, $-CONR^{14}R^{15}$, $-SONR^{14}R^{15}$, $-SO_2NR^{14}R^{15}$, $-SOR^{18}$, or $-SO_2R^{18}$;

R^6 and R^7 are each independently H, halogen, $-CN$, $-CF_3$, $-OH$, or C_1-C_3 alkyl;

R^{8a} and R^{9a} are each independently hydrogen, halogen, $-OH$, or C_1-C_3 alkyl; or R^{8a} and R^{9a} taken together form an optionally substituted carbocyclyl or optionally substituted heterocyclyl;

R^{10} is each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, or $-CO(C_1-C_3 \text{ alkyl})$;

R^{13} , R^{14} , R^{15} , R^{16} , R^{17} and R^{18} are each independently hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl; or R^{14} and R^{15} taken together form an optionally substituted 5- or 6-membered heterocyclyl;

m is 0, 1, 2, 3, or 4;

each n is independently 0, 1 or 2;

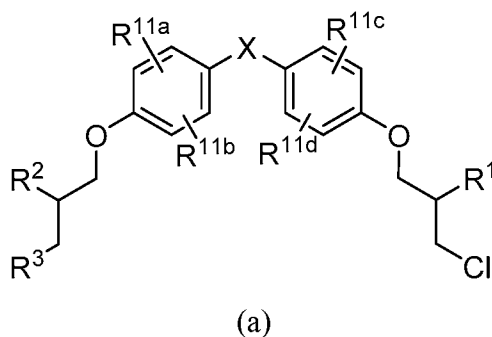
q is 0, 1 or 2;

g is 0, 1, 2, 3, or 4; and

t is 1 or 2.

55. The method of claim 50, wherein the androgen receptor N-terminal domain inhibitor is selected from Table A.

56. The method of claim 50, wherein the androgen receptor N-terminal domain inhibitor is a compound of formula (a):



wherein:

X is $-\text{S}(\text{O})_n-$ or $-\text{C}(\text{R}^8\text{R}^9)-$;

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

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

R^3 is halo, $-\text{OH}$, $-\text{OR}^4$, $-\text{OC}(=\text{O})\text{R}^{13}$, $-\text{NH}_2$, $-\text{NHC}(=\text{O})\text{R}^{13}$, $-\text{N}(\text{C}(=\text{O})\text{R}^{13})_2$, $-\text{NHS}(\text{O})_n\text{R}^5$, $-\text{N}(\text{C}(=\text{O})\text{R}^{13})(\text{S}(\text{O})_n\text{R}^5)$, $-\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})(\text{S}(\text{O})_n\text{R}^5)$, $-\text{S}(\text{O})_n\text{R}^5$, $-\text{N}_3$, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

R^4 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, aryl, carbocyclyl, heteroaryl or heterocyclyl which are optionally substituted with one or more R^6 ;

R^5 is each independently $\text{C}_1\text{-C}_6$ alkyl or aryl which are optionally substituted with one or more R^6 ;

R^6 is each independently selected from the group consisting of H, F, Cl, Br, I, ^{123}I , hydroxyl, oxo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_6\text{-C}_{12}$ aryl, wherein each R^6 is optionally substituted with one or more of halogen, ^{123}I , ^{18}F , hydroxyl, $-\text{OS}(\text{O})_2\text{-aryl}$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, or $\text{C}_2\text{-C}_6$ alkynyl;

R^8 and R^9 are each independently H, or $\text{C}_1\text{-C}_6$ alkyl;

R^{11a} , R^{11b} , R^{11c} and R^{11d} are each independently H, methyl, $-\text{CN}$, F, Cl, Br, I, or ^{123}I ;

R^{13} is $\text{C}_1\text{-C}_6$ alkyl; and

n is 0, 1, or 2;

wherein at least one of R^{11a} , R^{11b} , R^{11c} and R^{11d} is methyl, $-\text{CN}$, F, Cl, Br, I, or ^{123}I .

57. The method of claim 56, wherein at least two of R^{11a} , R^{11b} , R^{11c} and R^{11d} are methyl, $-\text{CN}$, F, Cl, Br, I, or ^{123}I .

58. The method of claim 56 or 57, wherein X is $-\text{C}(\text{R}^8\text{R}^9)-$ and R^8 and R^9 are each independently $\text{C}_1\text{-C}_3$ alkyl.

59. The method of any one of claim 56-58, wherein R^1 and R^2 are both hydroxyl.
60. The method of any one of claim 56-59, wherein R^3 is $-NH_2$, $-NHC(=O)R^{13}$, $-N(C(=O)R^{13})_2$, $-NHS(O)_nR^5$, $-N(C(=O)R^{13})(S(O)_nR^5)$, $-N(C_1-C_6 \text{ alkyl})(S(O)_nR^5)$ or $-S(O)_nR^5$.
61. The method of any one of claim 26-59, wherein R^3 is $-NH_2$, $-NHC(=O)(C_1-C_4 \text{ alkyl})$, $-N[(C(=O)(C_1-C_4 \text{ alkyl}))_2]$, $-NHS(O)_n(C_1-C_3 \text{ alkyl})$, $-N[C(=O)(C_1-C_4 \text{ alkyl})][(S(O)_n(C_1-C_3 \text{ alkyl}))]$, $-N[C_1-C_6 \text{ alkyl}][S(O)_n(C_1-C_3 \text{ alkyl})]$, or $-S(O)_n(C_1-C_3 \text{ alkyl})$.
62. The method of claim 50, wherein the androgen receptor N-terminal domain inhibitor is selected from Table B.
63. The method of any one of claims 50-62, further comprising administering a second therapeutically active agent.
64. The method of claim 63, wherein the second therapeutically active agent is selected from a poly (ADP-ribose) polymerase (PARP) inhibitor, an androgen receptor ligand-binding domain inhibitor, an inhibitor of CYP17, a microtubule inhibitor, a modulator of PD-1 or PD-L1, a gonadotropin releasing hormone agonist, a 5-alpha reductase inhibitor, a vascular endothelial growth factor inhibitor, a histone deacetylase inhibitor, an integrin alpha-v-beta-3 inhibitor, a receptor tyrosine kinase, a phosphoinositide 3-kinase inhibitor, an anaplastic lymphoma kinase (ALK) inhibitor, an endothelin receptor A antagonist, an anti-CTLA4 inhibitor, an heat shock protein 27 (HSP27) inhibitor, an androgen receptor degrader, a androgen receptor DNA-binding domain inhibitor, a bromodomain and extra-terminal motif (BET) inhibitor, an androgen receptor N-terminal domain inhibitor, an alpha-particle emitting radioactive therapeutic agent, niclosamide, a selective estrogen receptor modulator (SERM), a selective estrogen receptor degrader (SERD), an aromatase inhibitor, selective progesterone receptor modulator (SPRM), a glucocorticoid receptor inhibitor, a CDK4/6 inhibitor, a HER2 receptor antagonist, a mammalian target of rapamycin (mTOR) inhibitor, an AKT inhibitor, a B-cell lymphoma-2 (Bcl-2) inhibitor, an aurora kinase inhibitor, a Wnt-targeting antagonist, a CYP11a inhibitor, a selective androgen receptor N-terminal domain inhibitor, or enhancer of zeste homolog 2 (EZH2) inhibitor.

65. The method of any one of claims 50-64, wherein the radiation therapy is administered concurrently with lutetium-177 or other alpha emitters.
66. The method of claim 65, wherein the lutetium-177 is targeted for prostate cancer cells.
67. The method of any one of claim 50-66, wherein the cancer is selected from prostate cancer, breast cancer, ovarian cancer, bladder cancer, pancreatic cancer, hepatocellular cancer, endometrial cancer, or salivary gland carcinoma.
68. The method of claim 67, wherein the cancer is prostate cancer.
69. The method of claim 68, wherein the prostate cancer is primary or localized prostate cancer, locally advanced prostate cancer, recurrent prostate cancer, advanced prostate cancer, metastatic prostate cancer, metastatic castration-resistant prostate cancer, and hormone-sensitive prostate cancer.
70. The method of claim 68, wherein the prostate cancer is metastatic castration-resistant prostate cancer.
71. The method of claim 68, wherein the prostate cancer expresses full-length androgen receptor or truncated androgen receptor splice variant.
72. The method of any one of claims 68-71, wherein the prostate cancer is resistant to enzalutamide used with luteinizing hormone-releasing hormone (LHRH) analogues.
73. The method of claim 67, wherein the cancer is breast cancer.
74. The method of claim 73, wherein the breast cancer is triple negative breast cancer.
75. The method of any one of claims 50-74, wherein the radiation therapy is ionizing radiation therapy.

76. The method of any one of claims 50-75, wherein the administering the androgen receptor N-terminal domain inhibitor and the administering radiation therapy occurs during same treatment period or during different treatment period.

FIG. 1

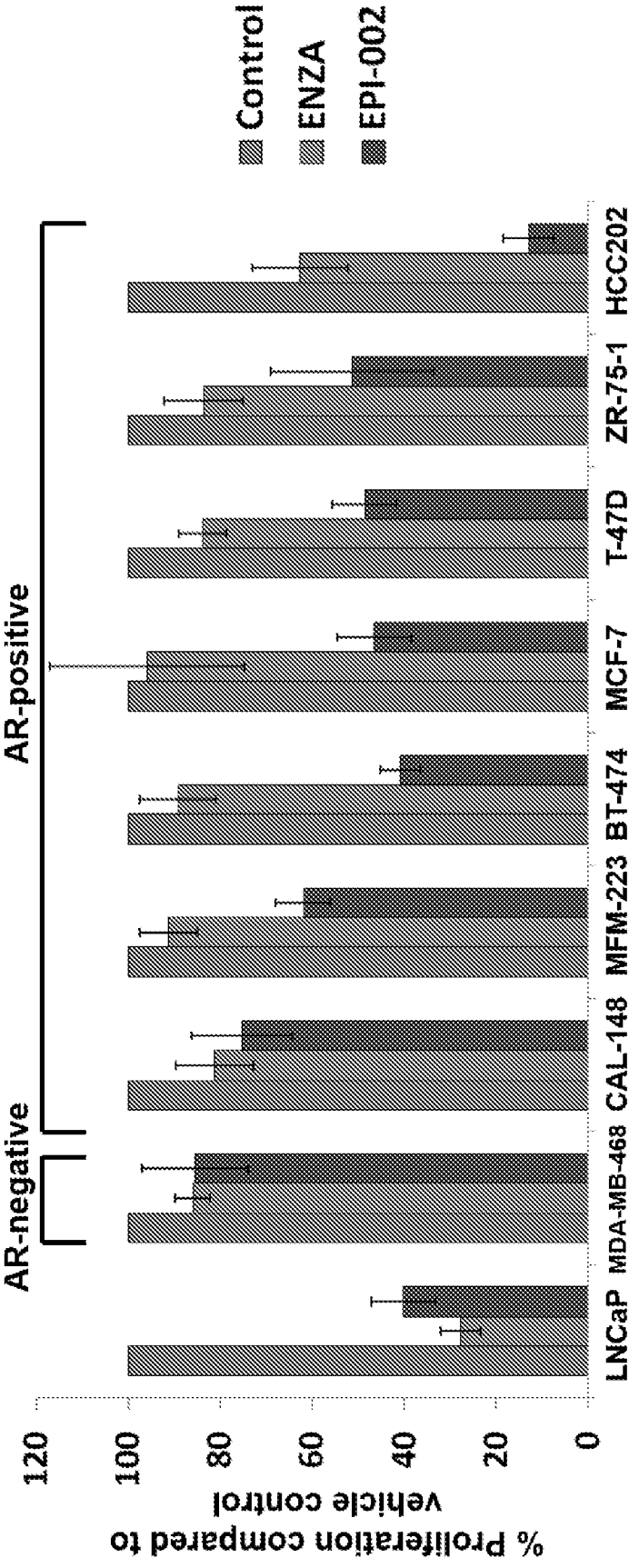


FIG. 2A

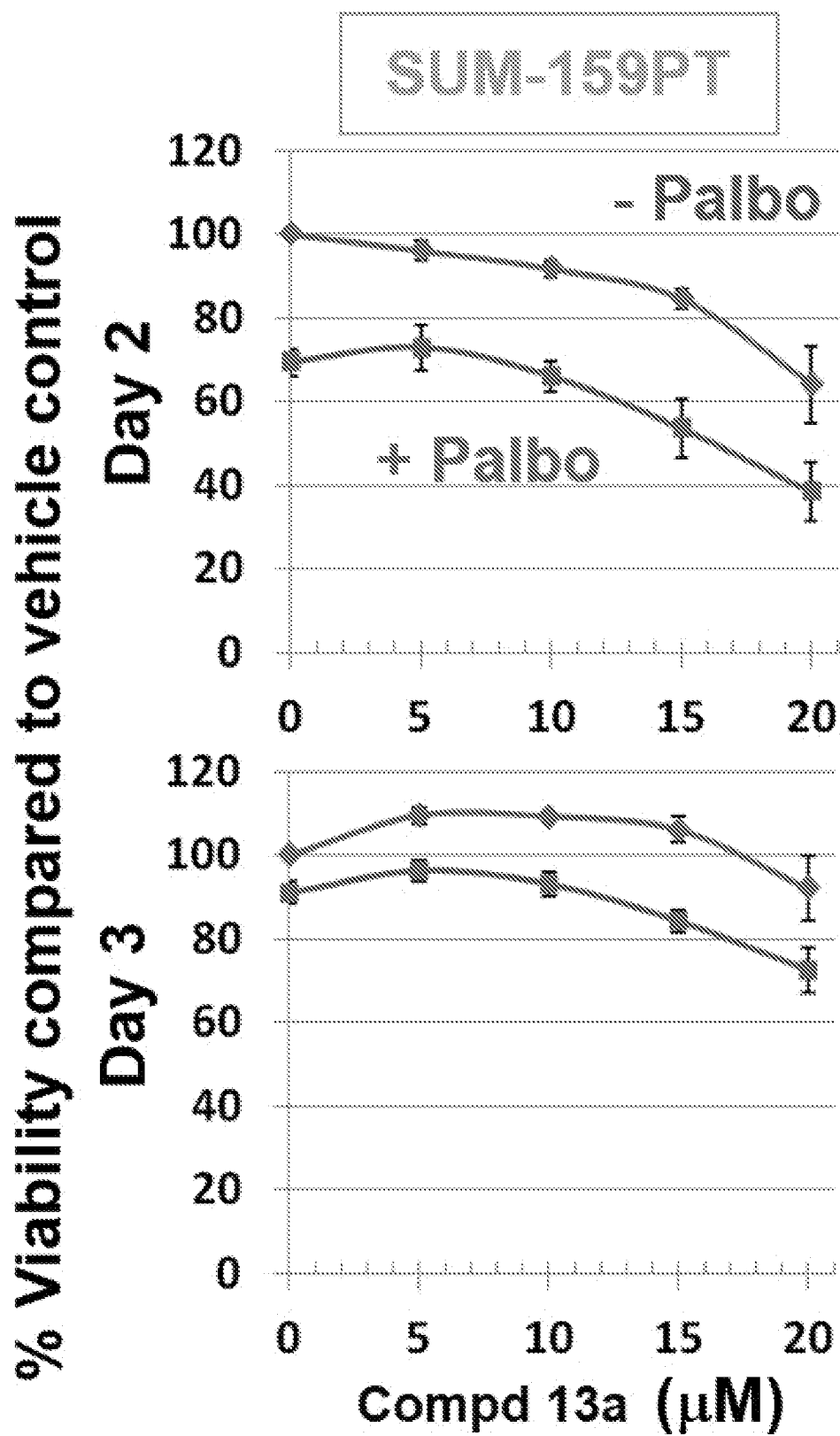


FIG. 2B

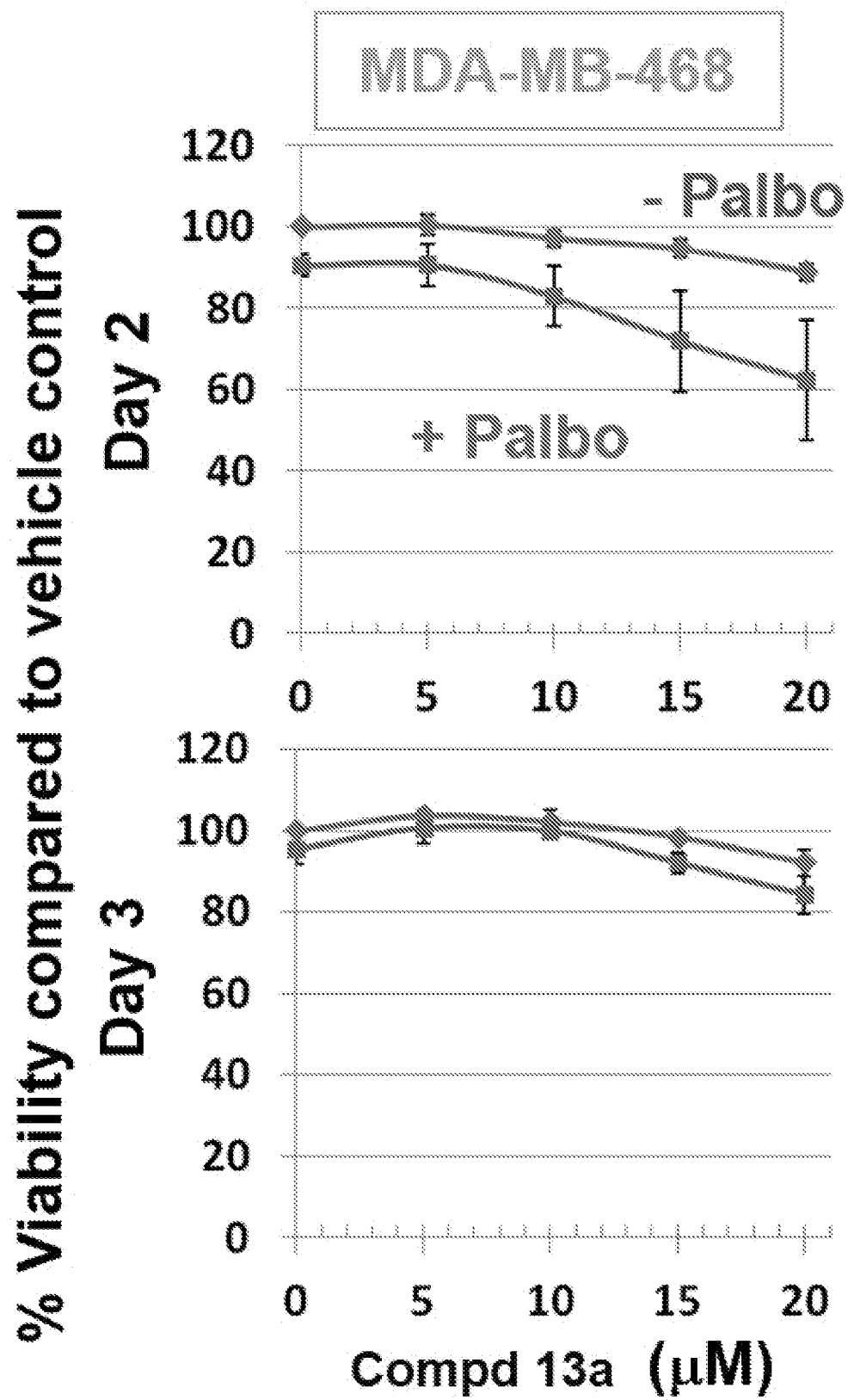


FIG. 2C

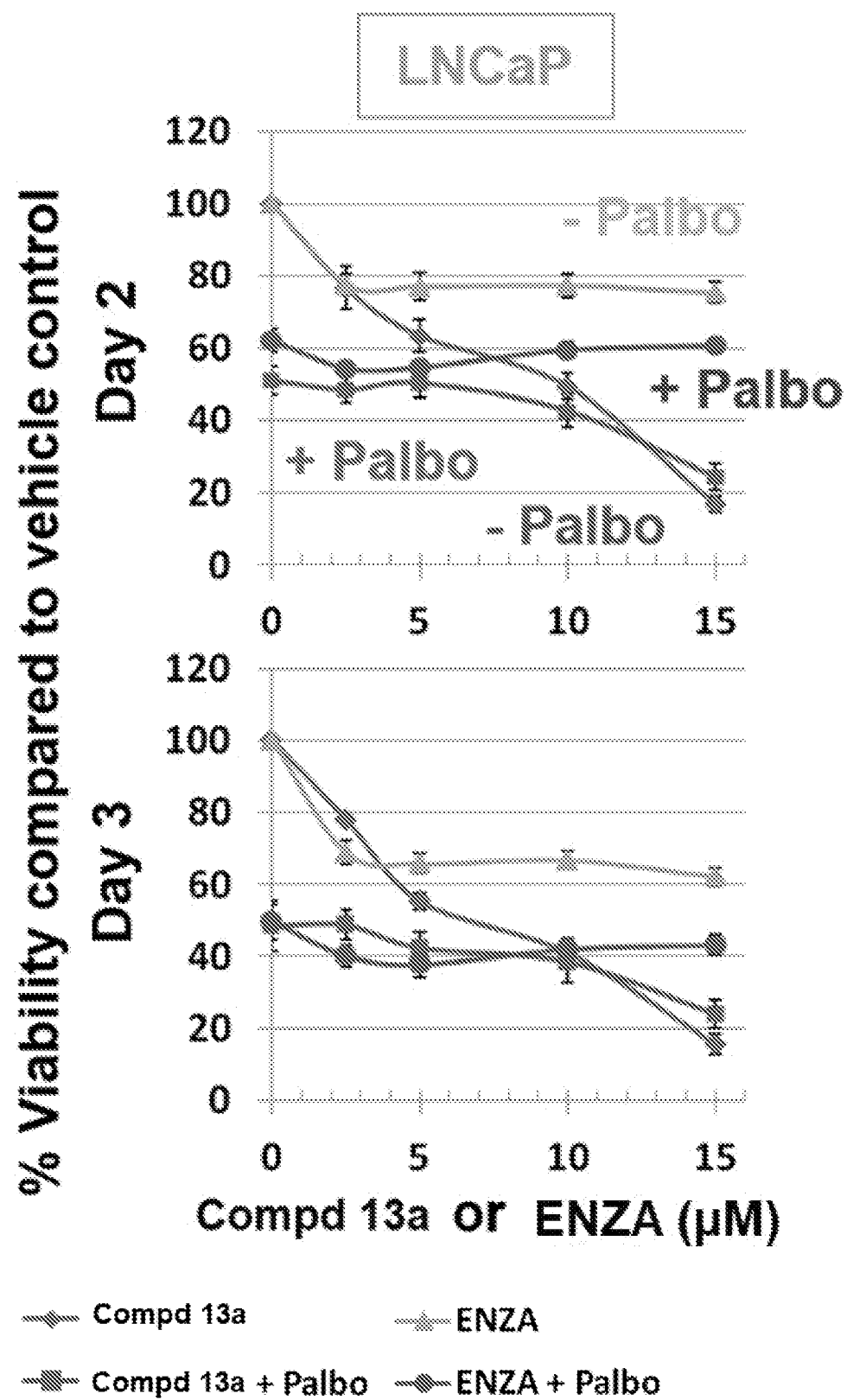


FIG. 2D

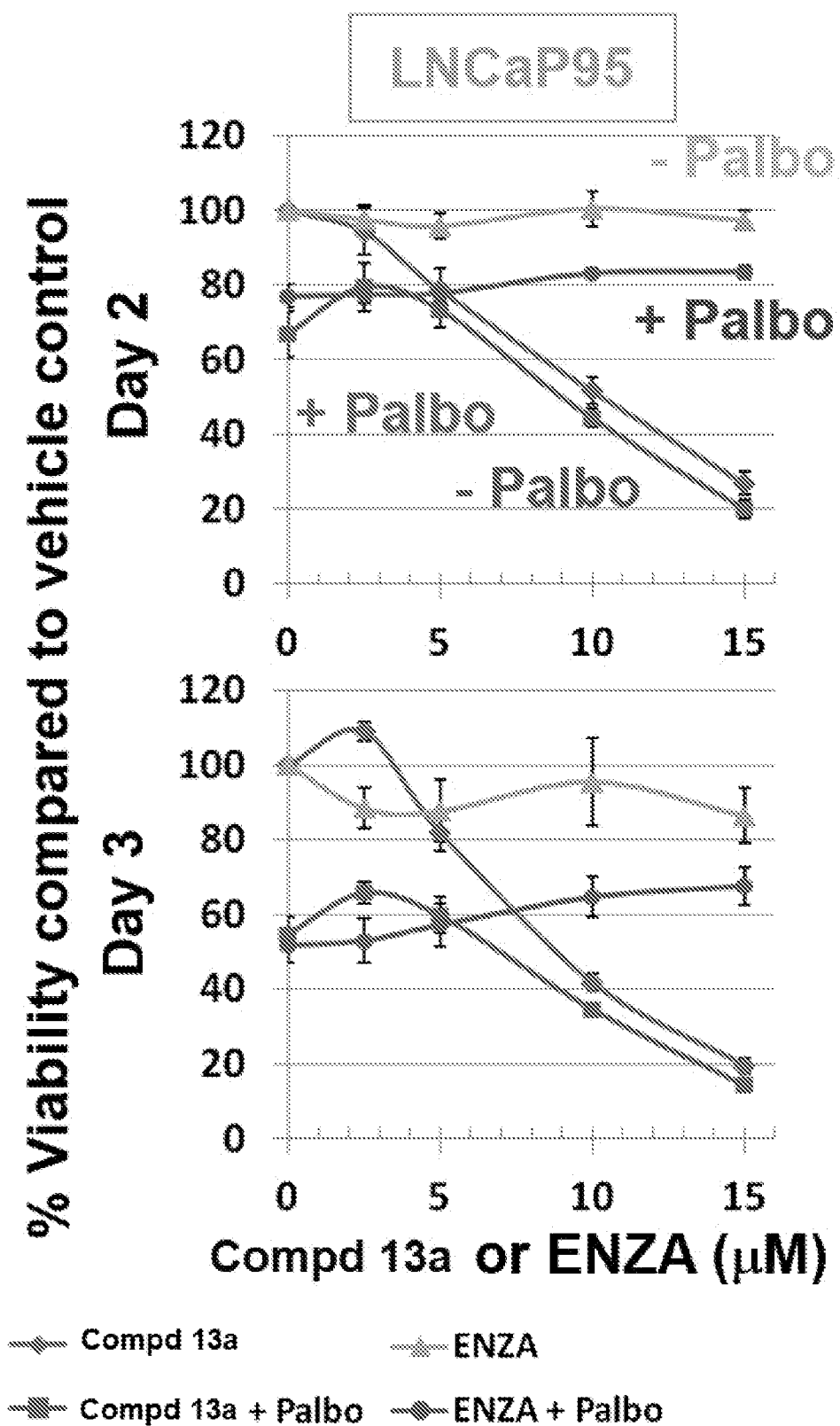


FIG. 3

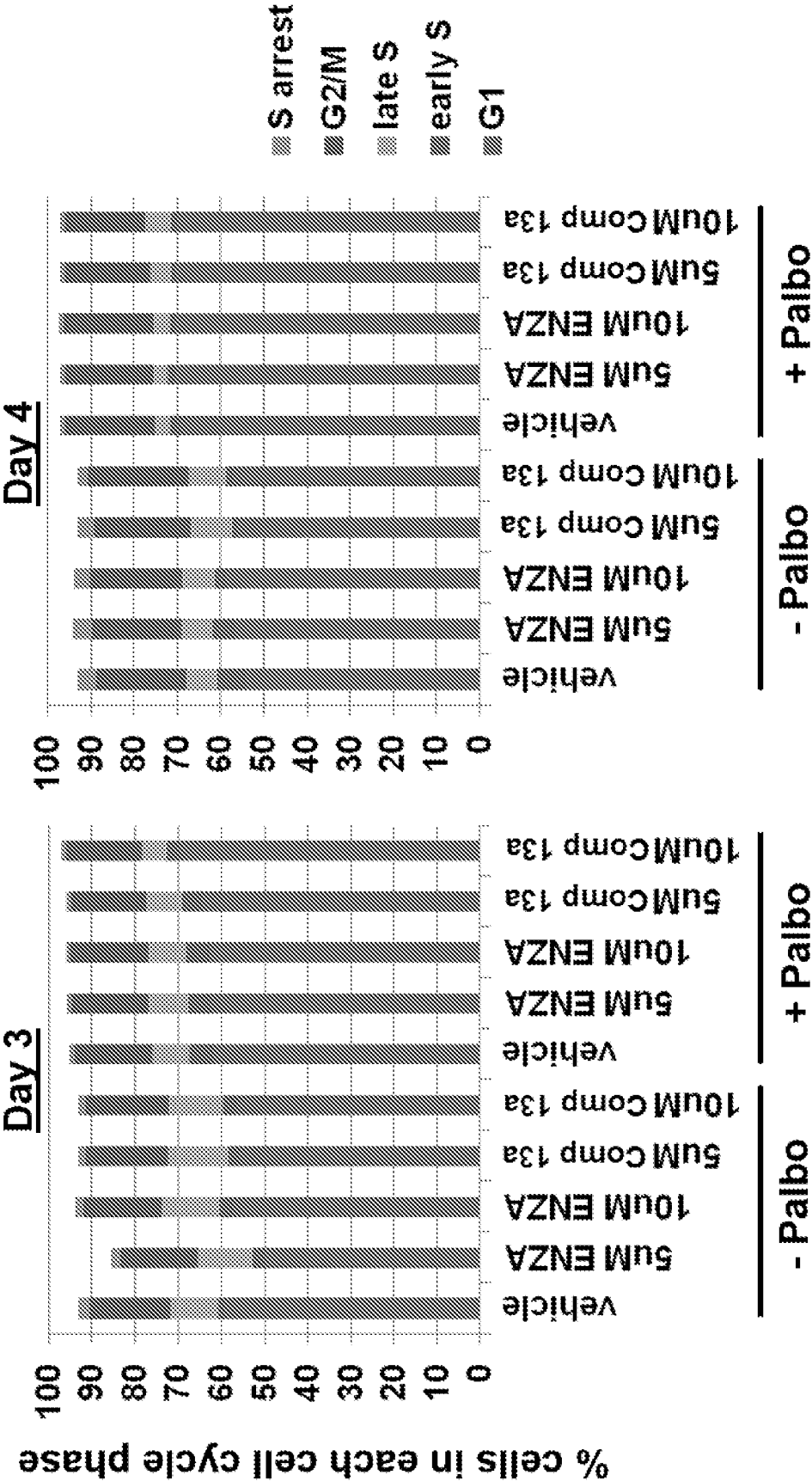
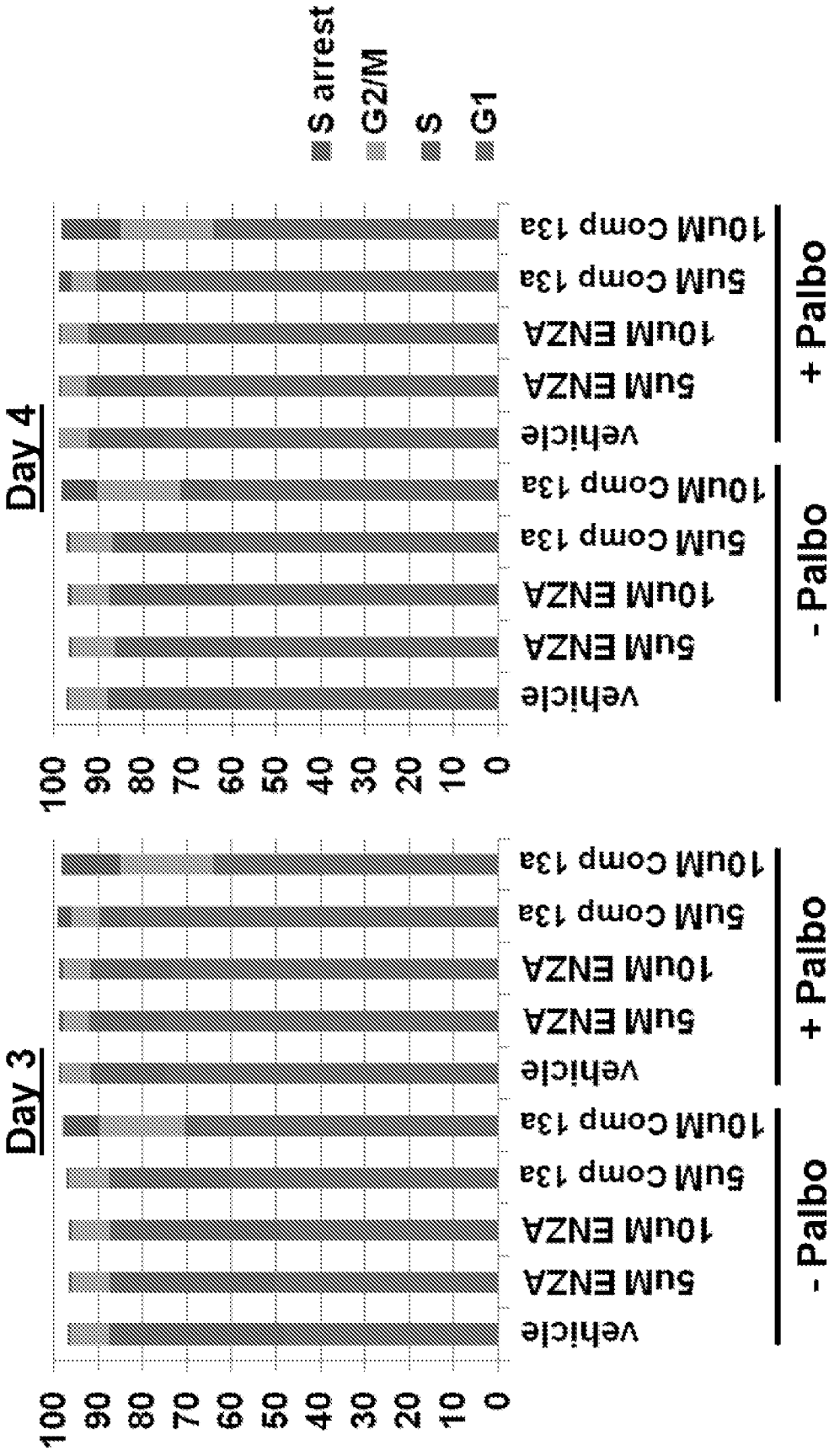
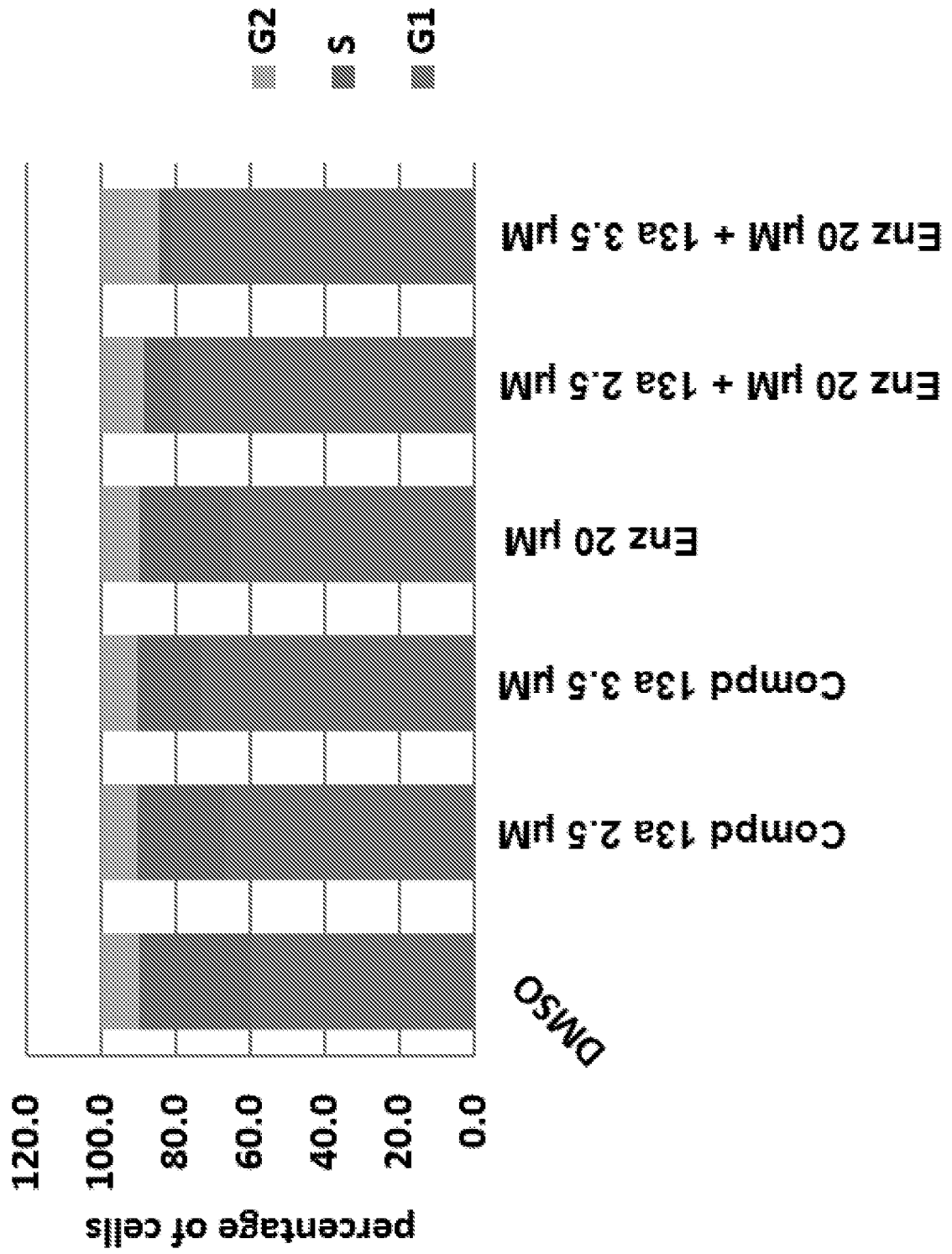


FIG. 4





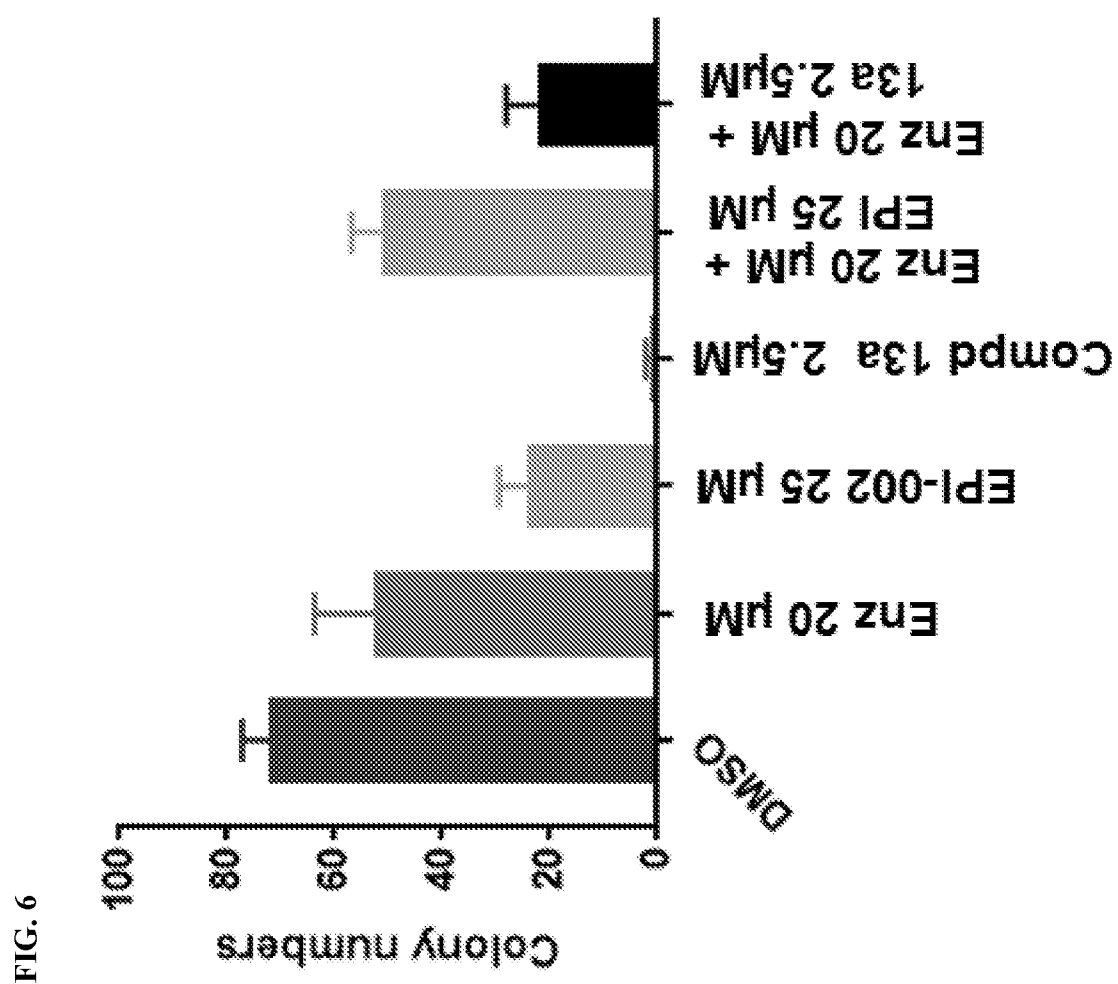


FIG. 7A

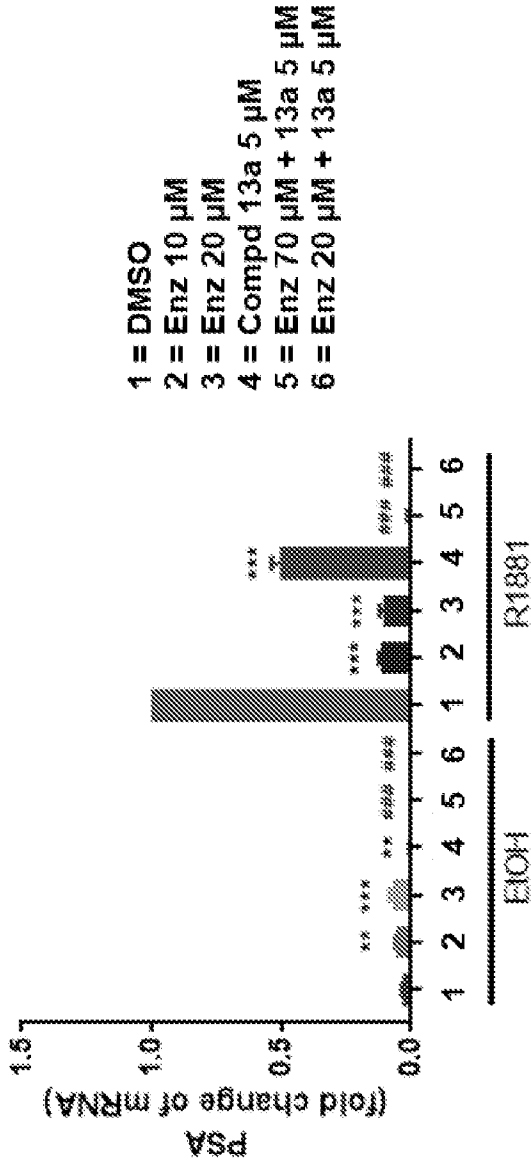


FIG. 7B

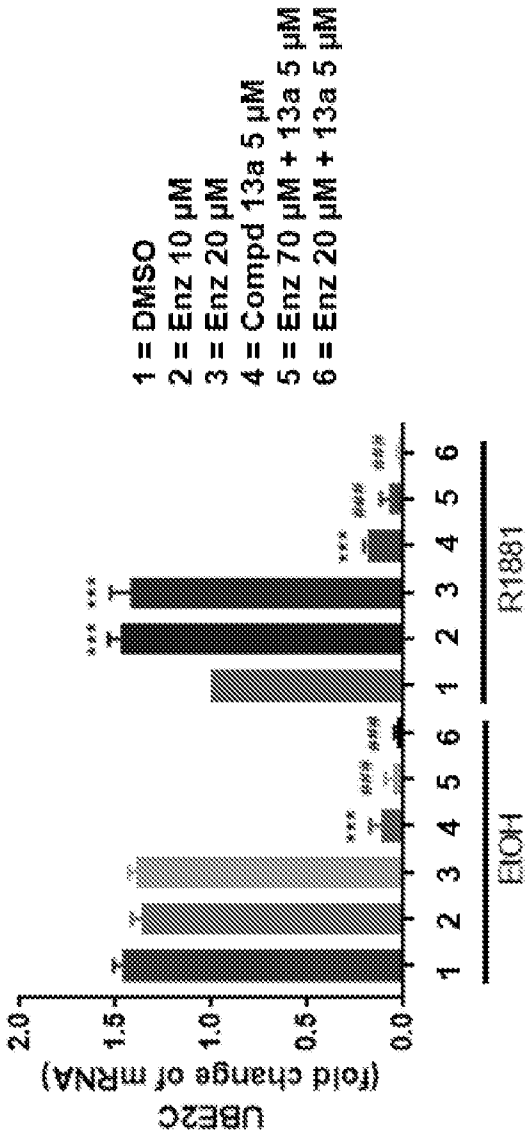


FIG. 7C

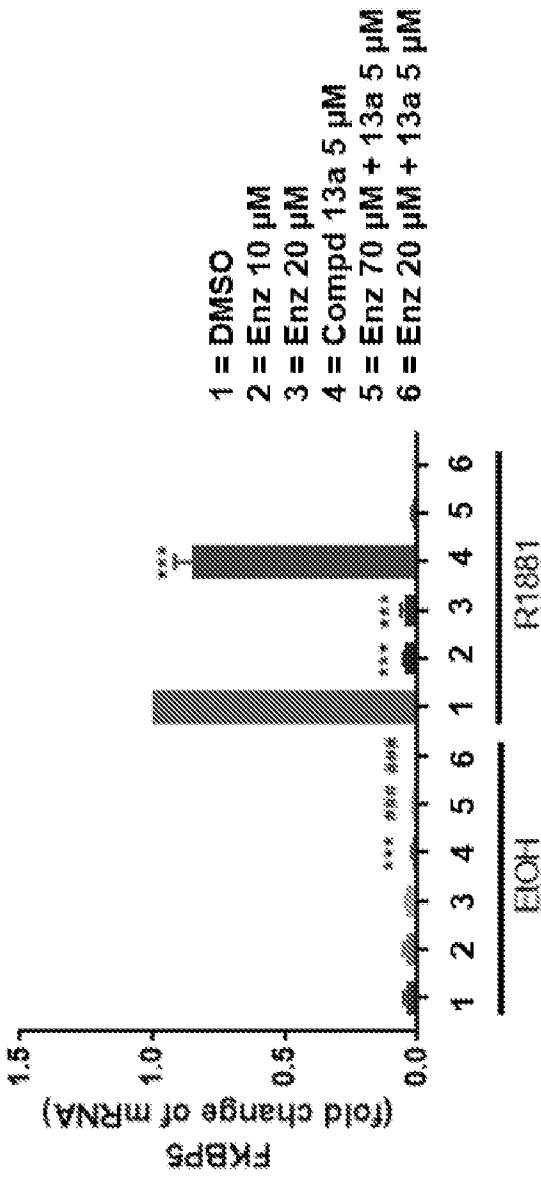
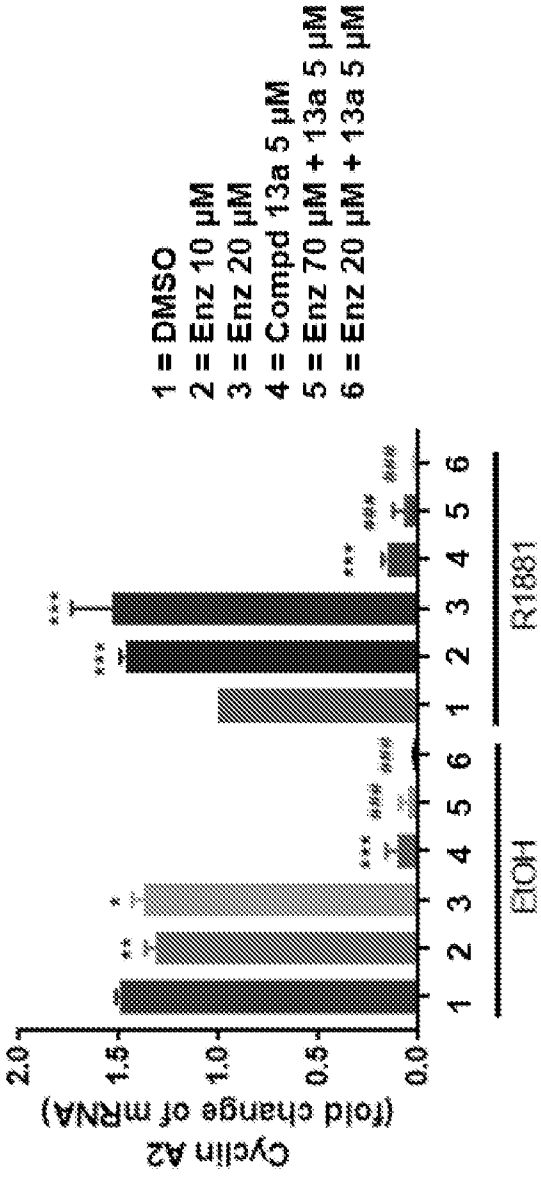


FIG. 7D



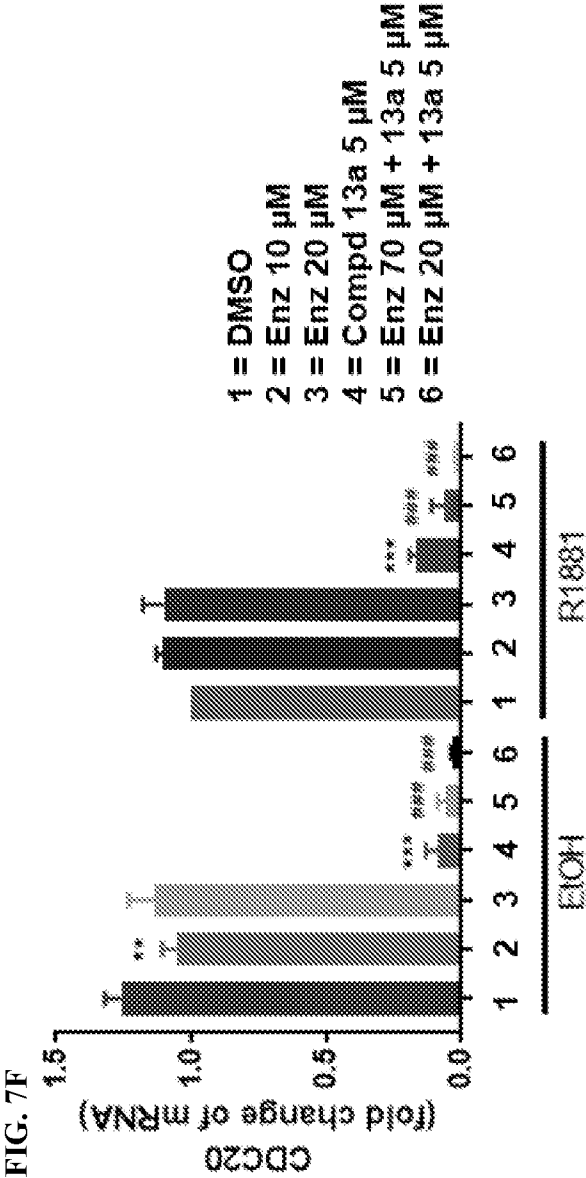
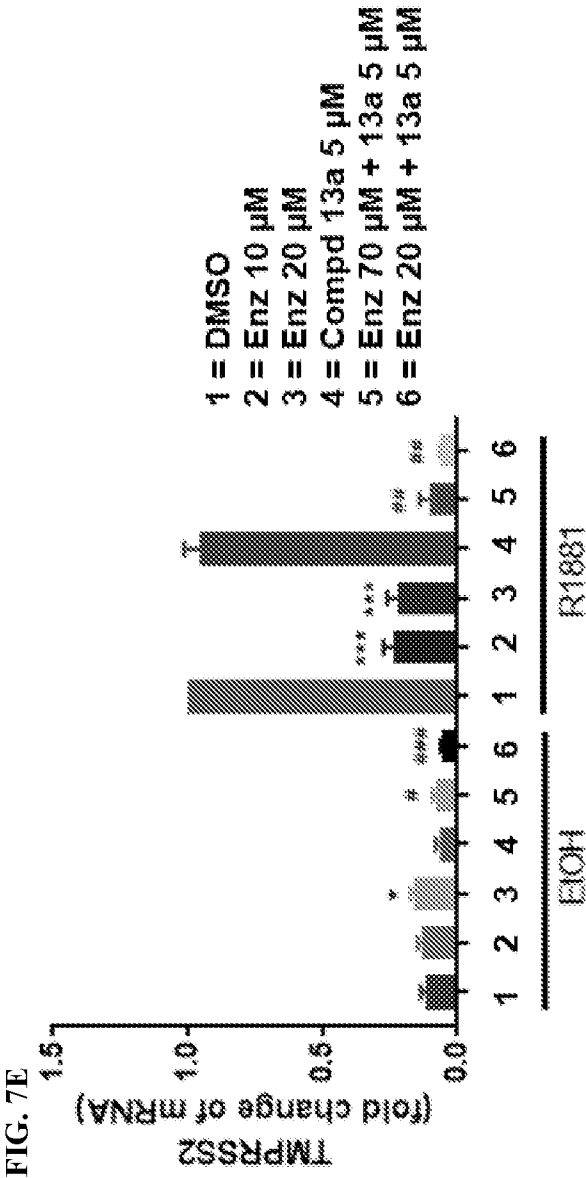
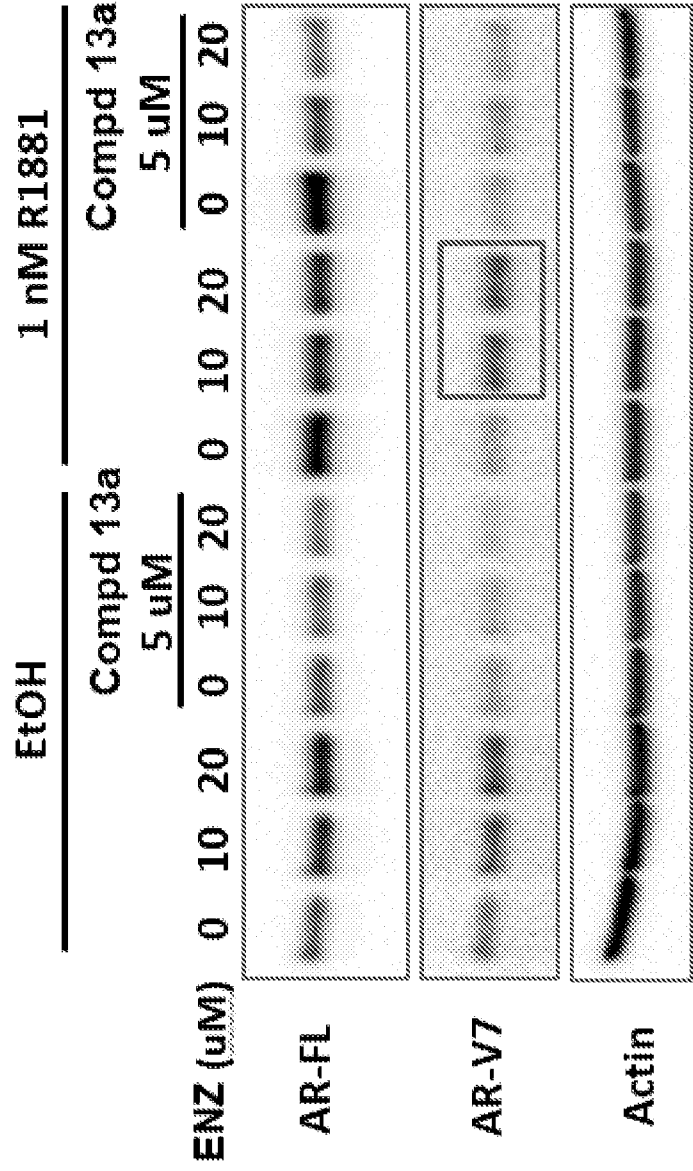
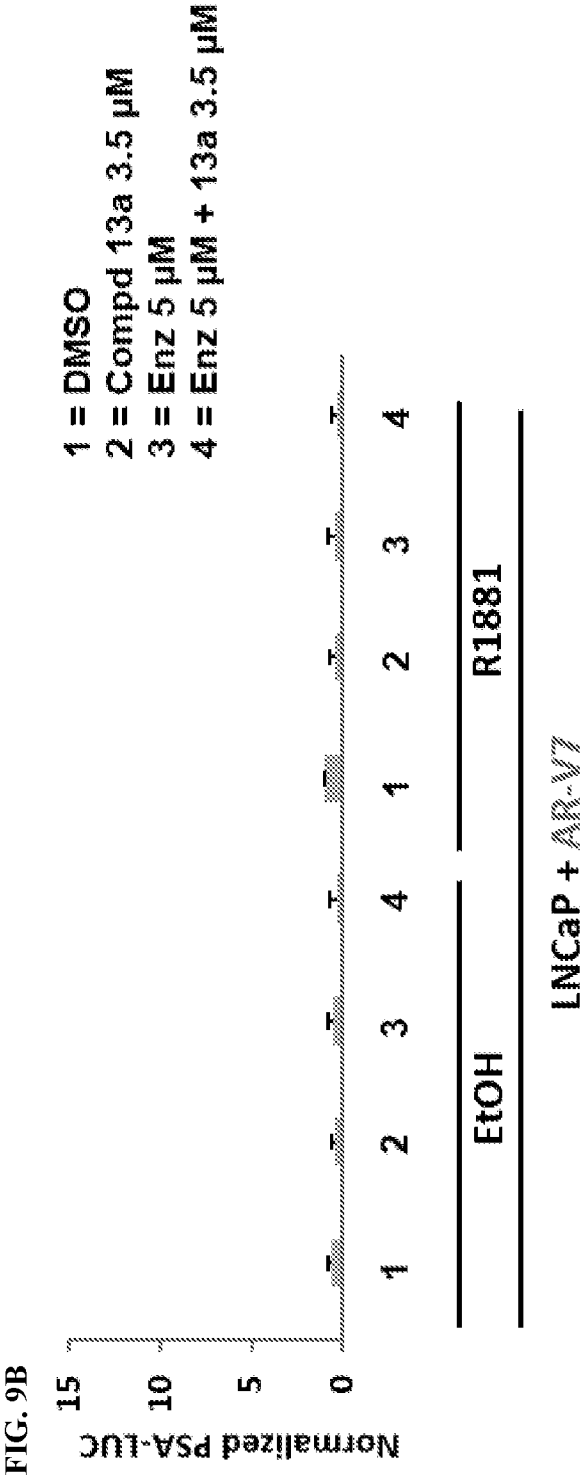
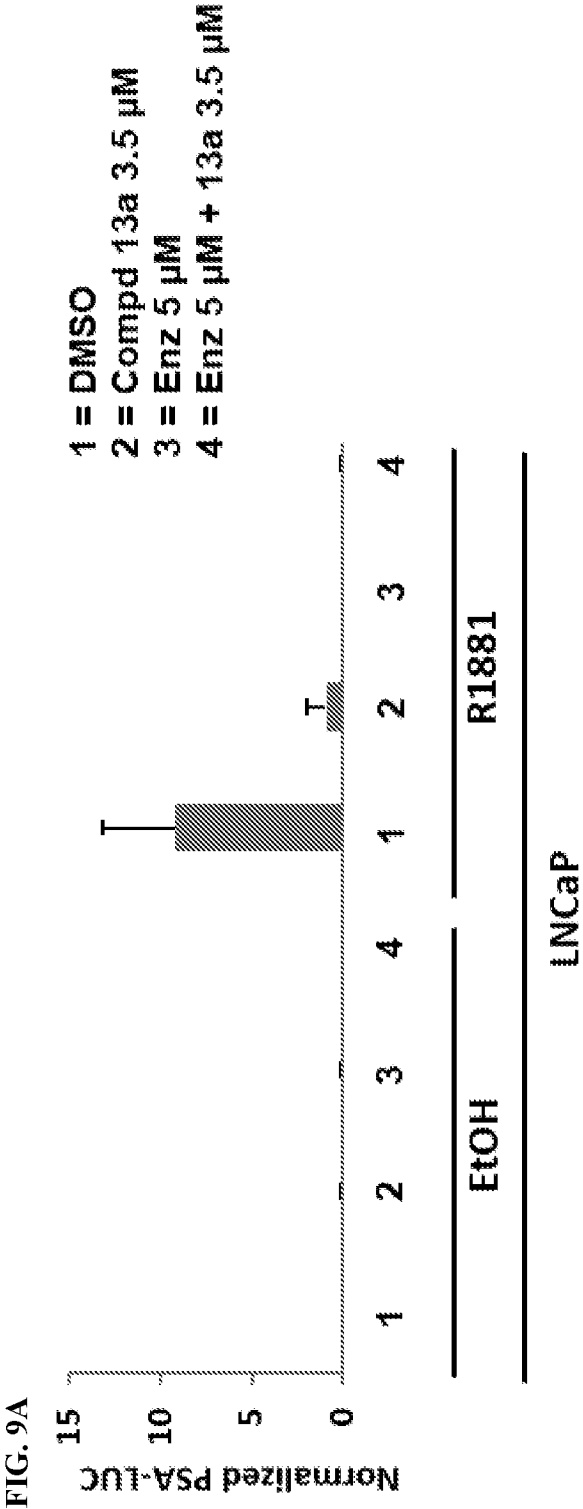


FIG. 8





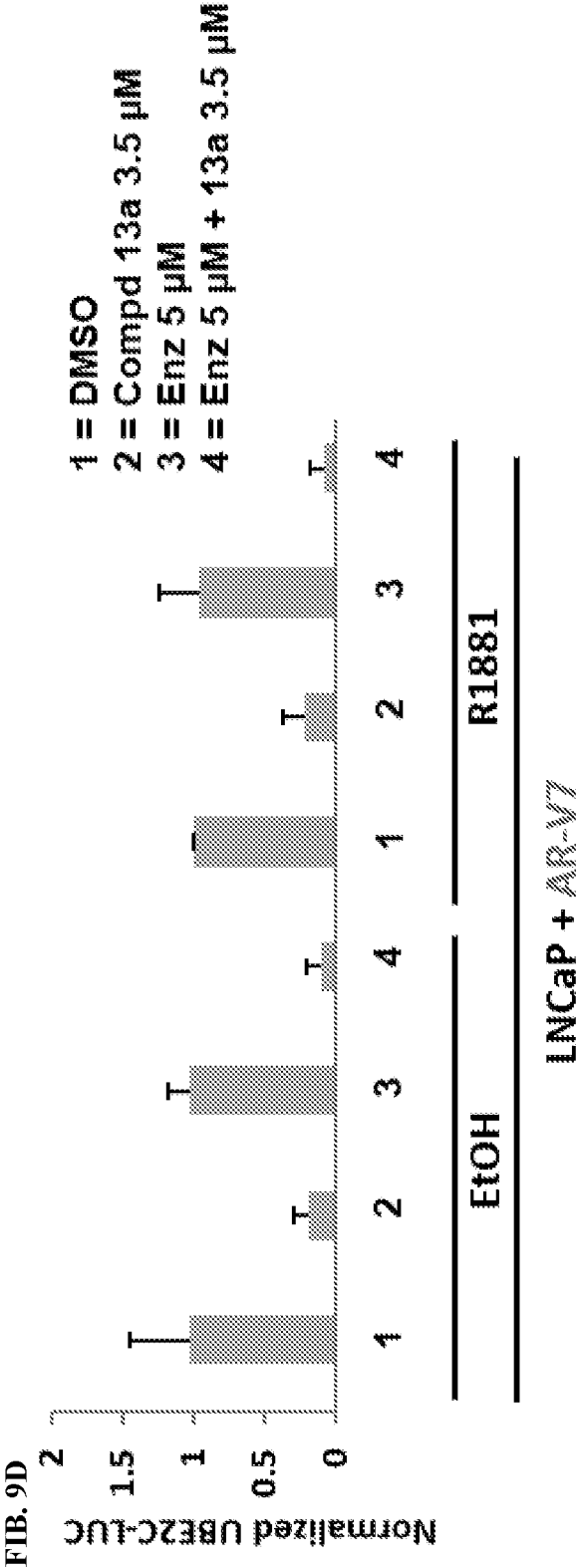
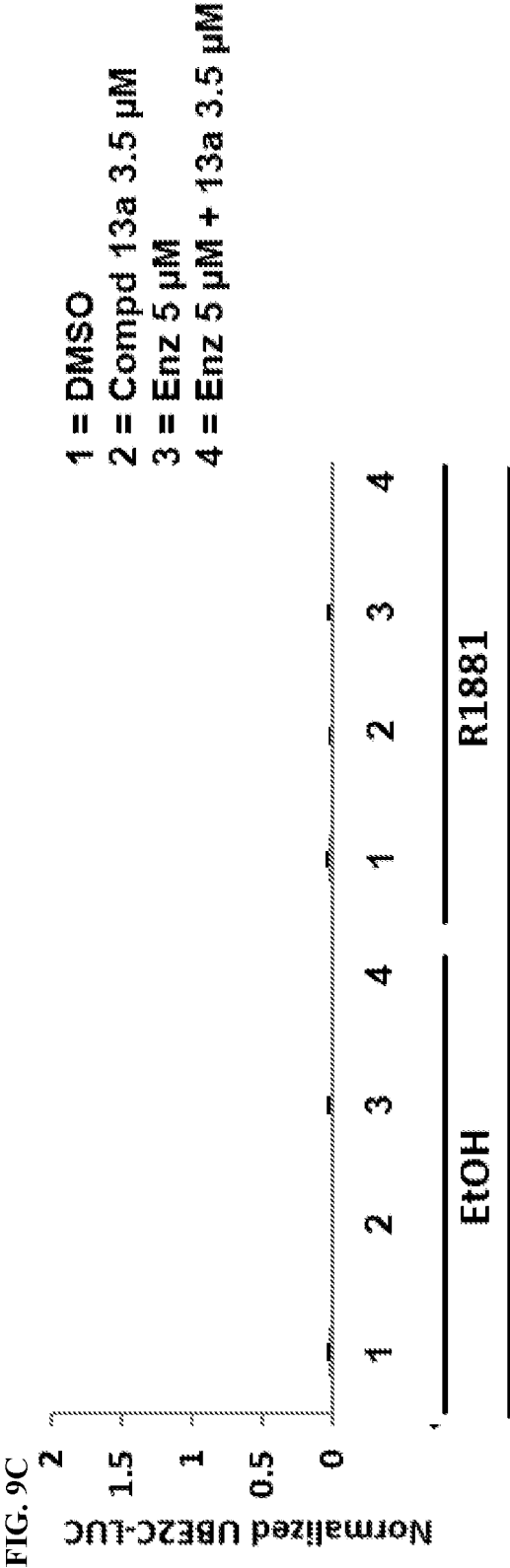


FIG. 10A

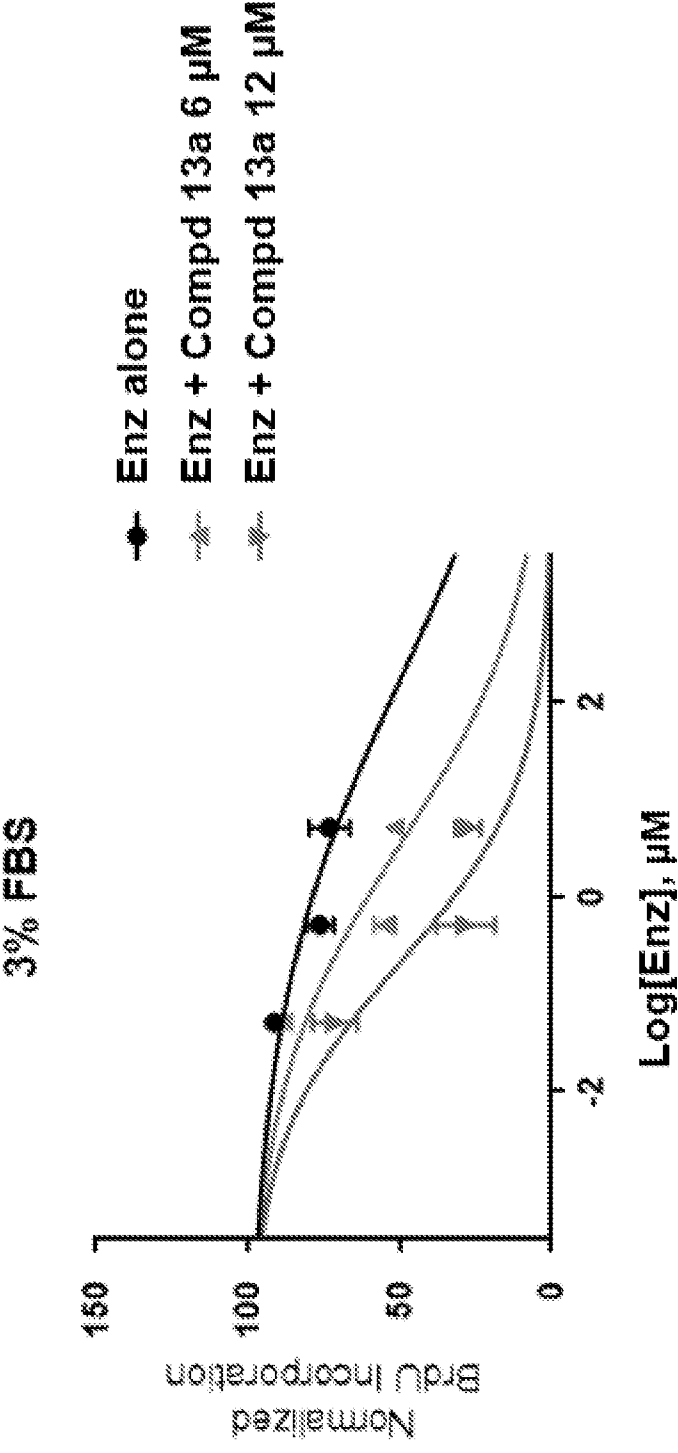


FIG. 11A

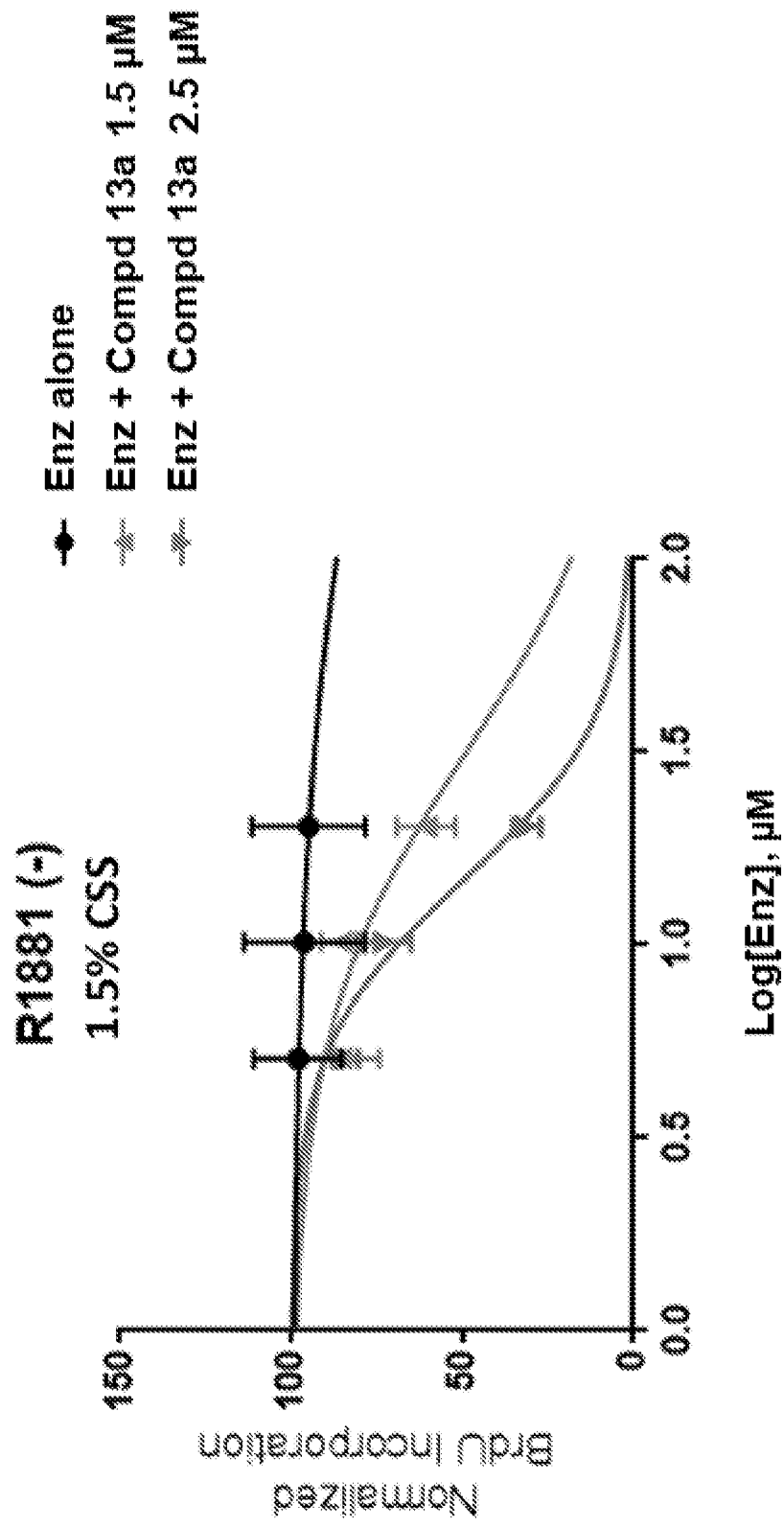


FIG. 11B

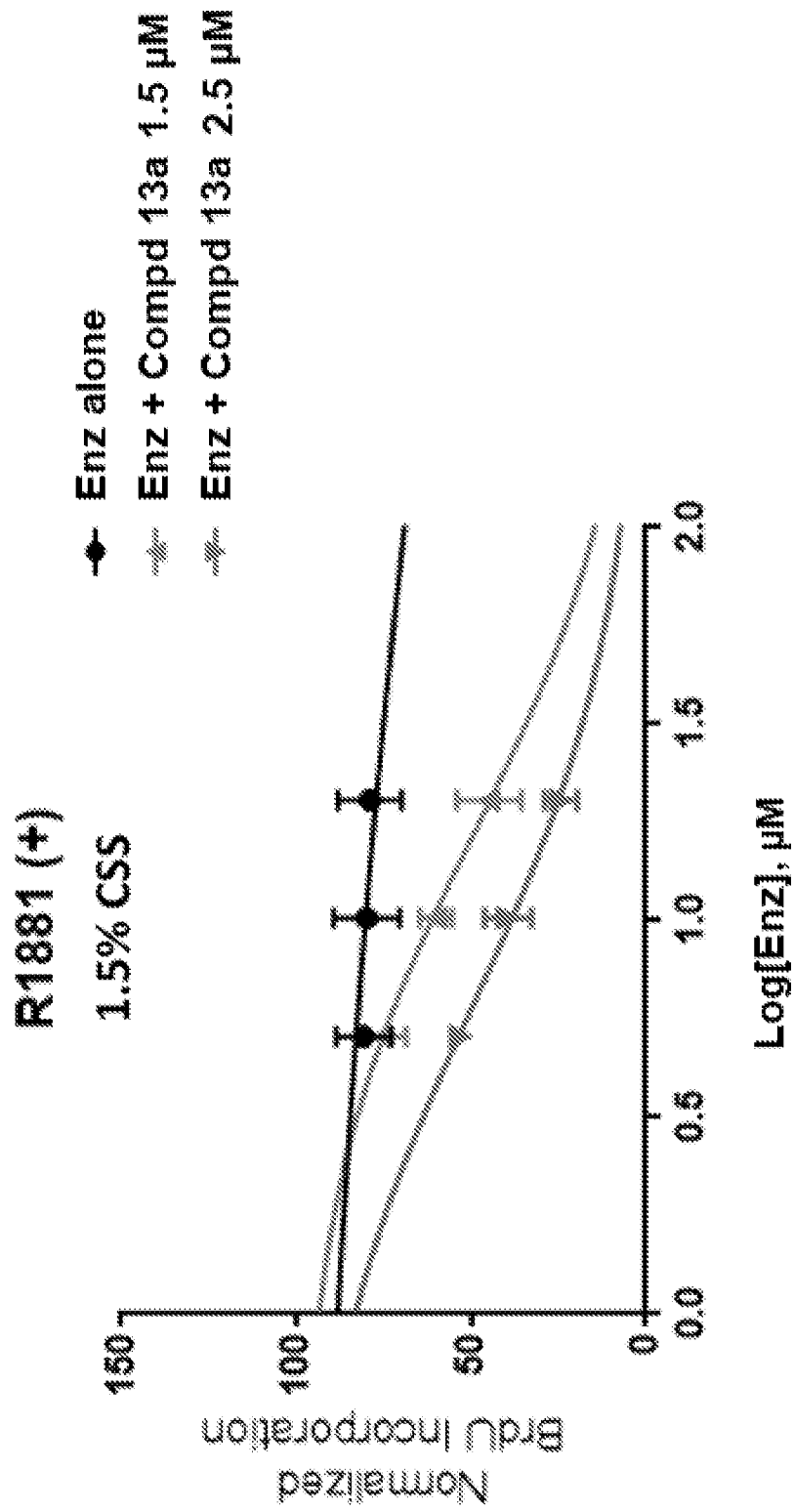


FIG. 12A

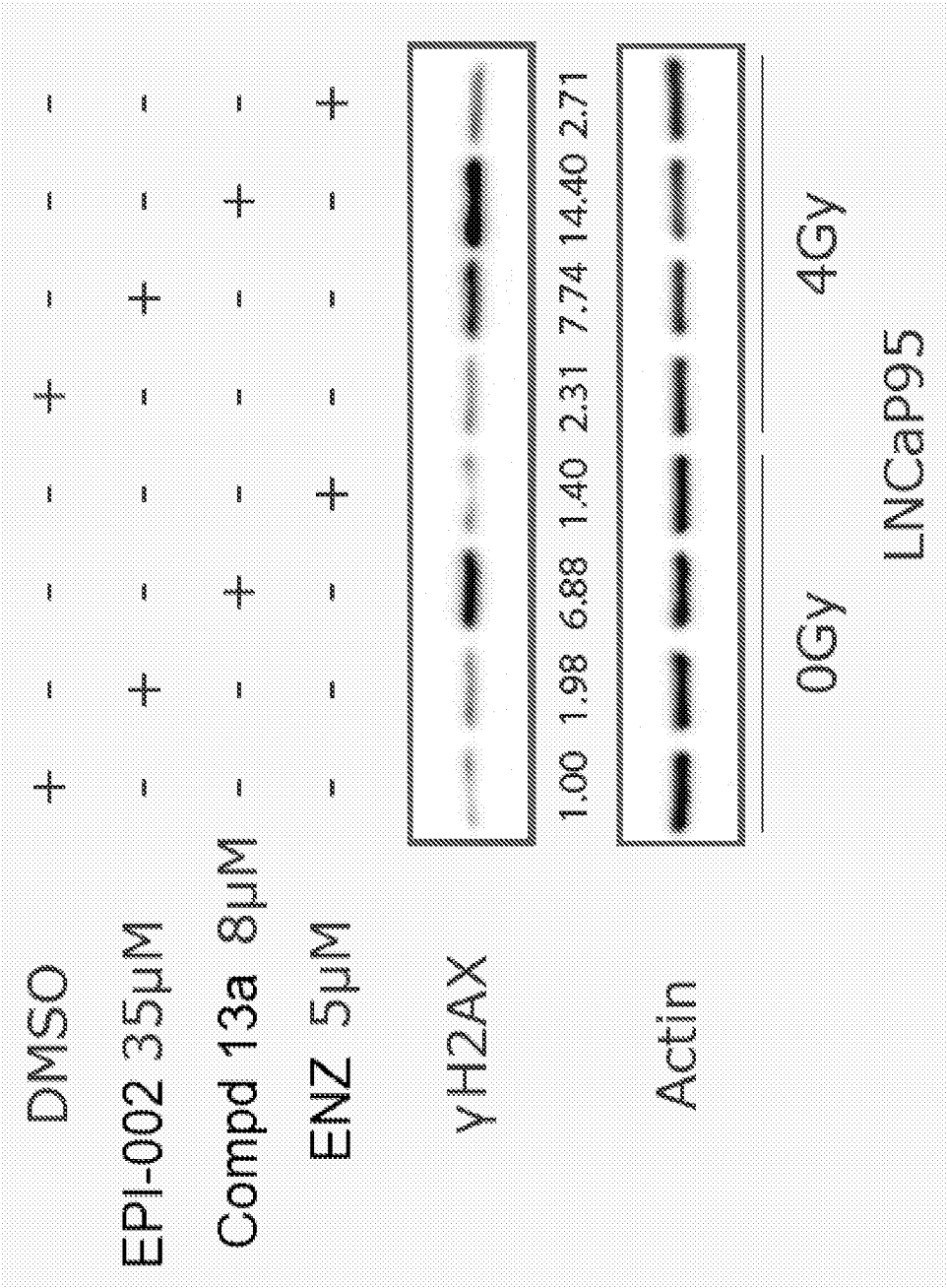


FIG. 12B

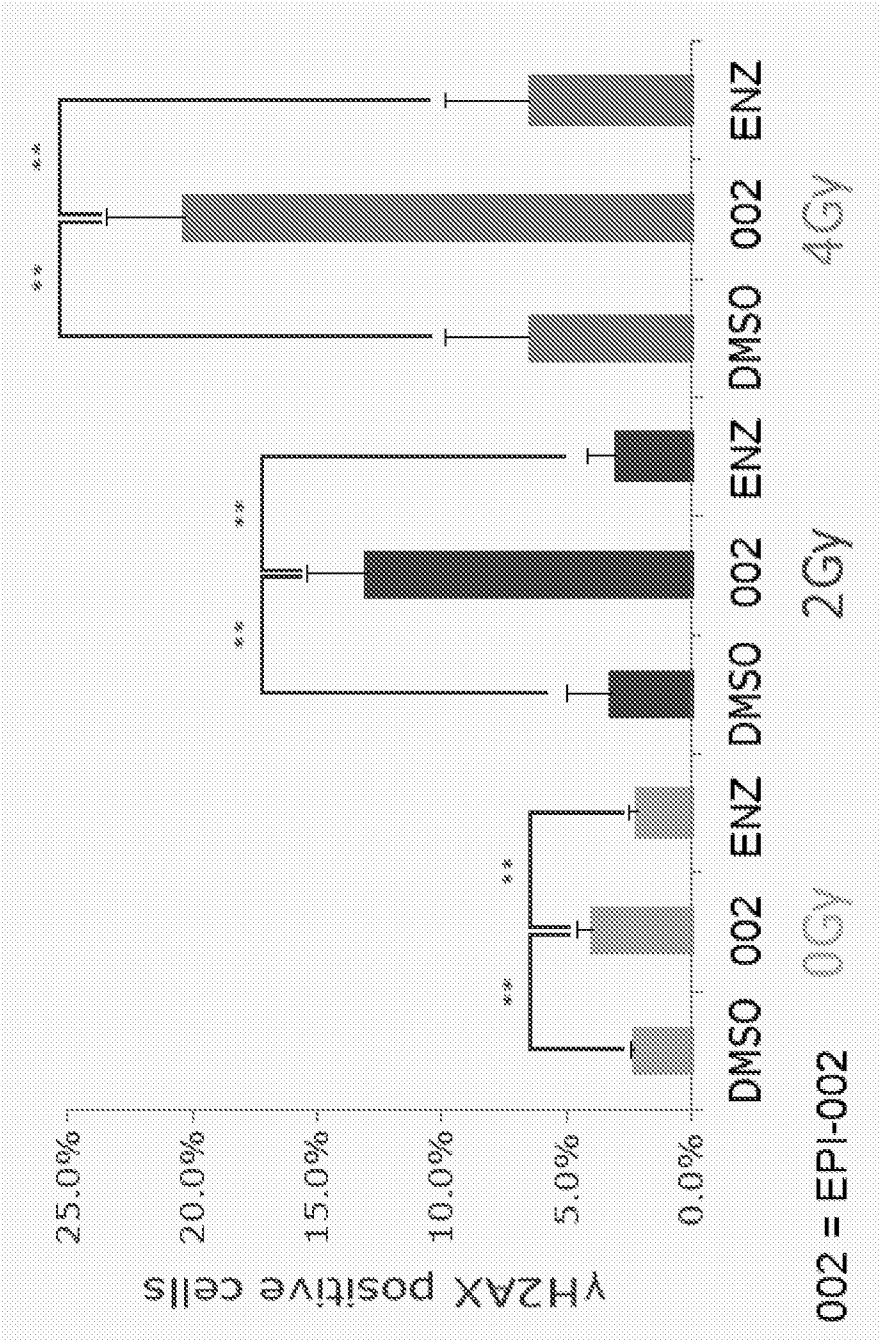
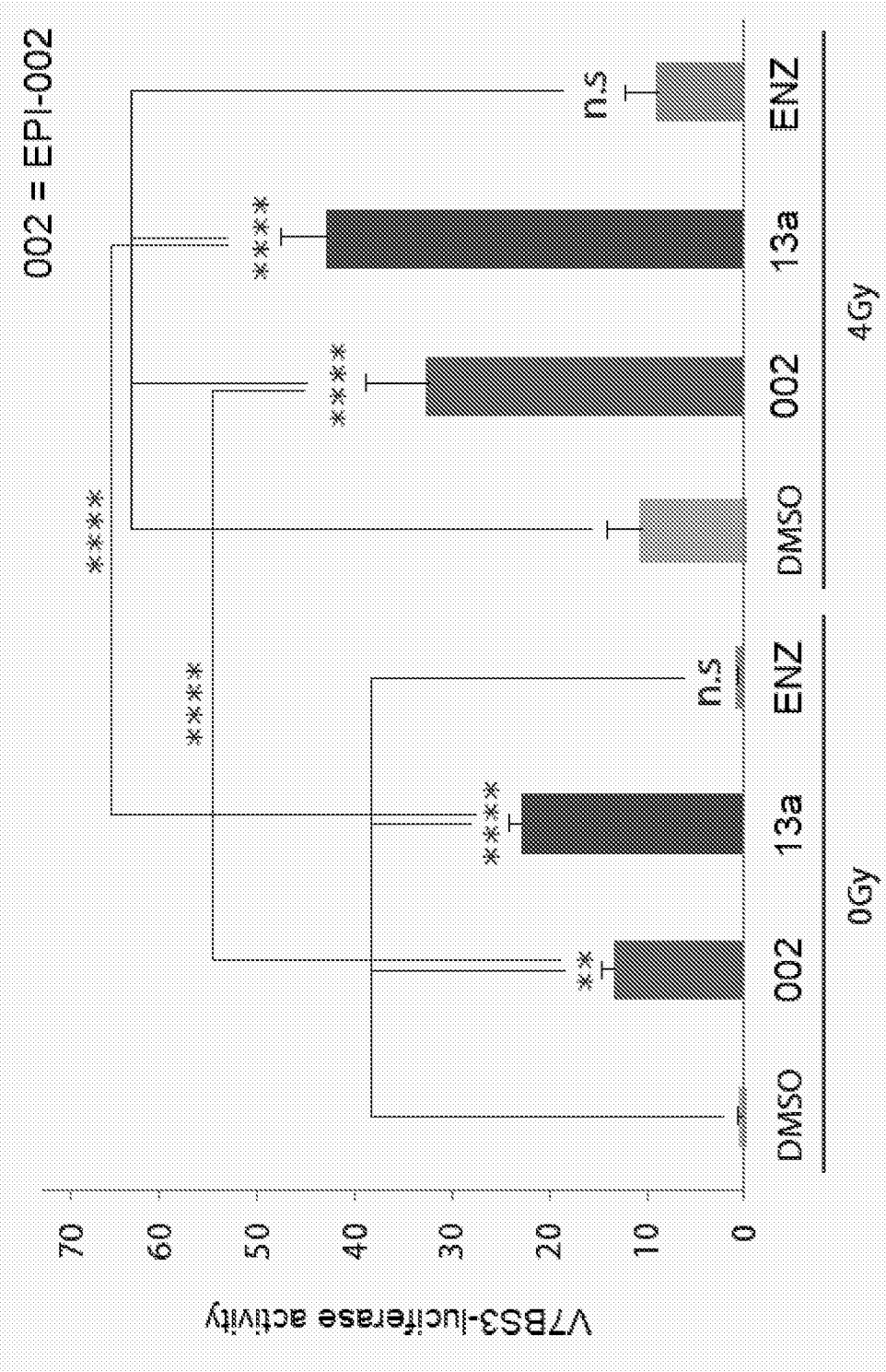


FIG. 12C



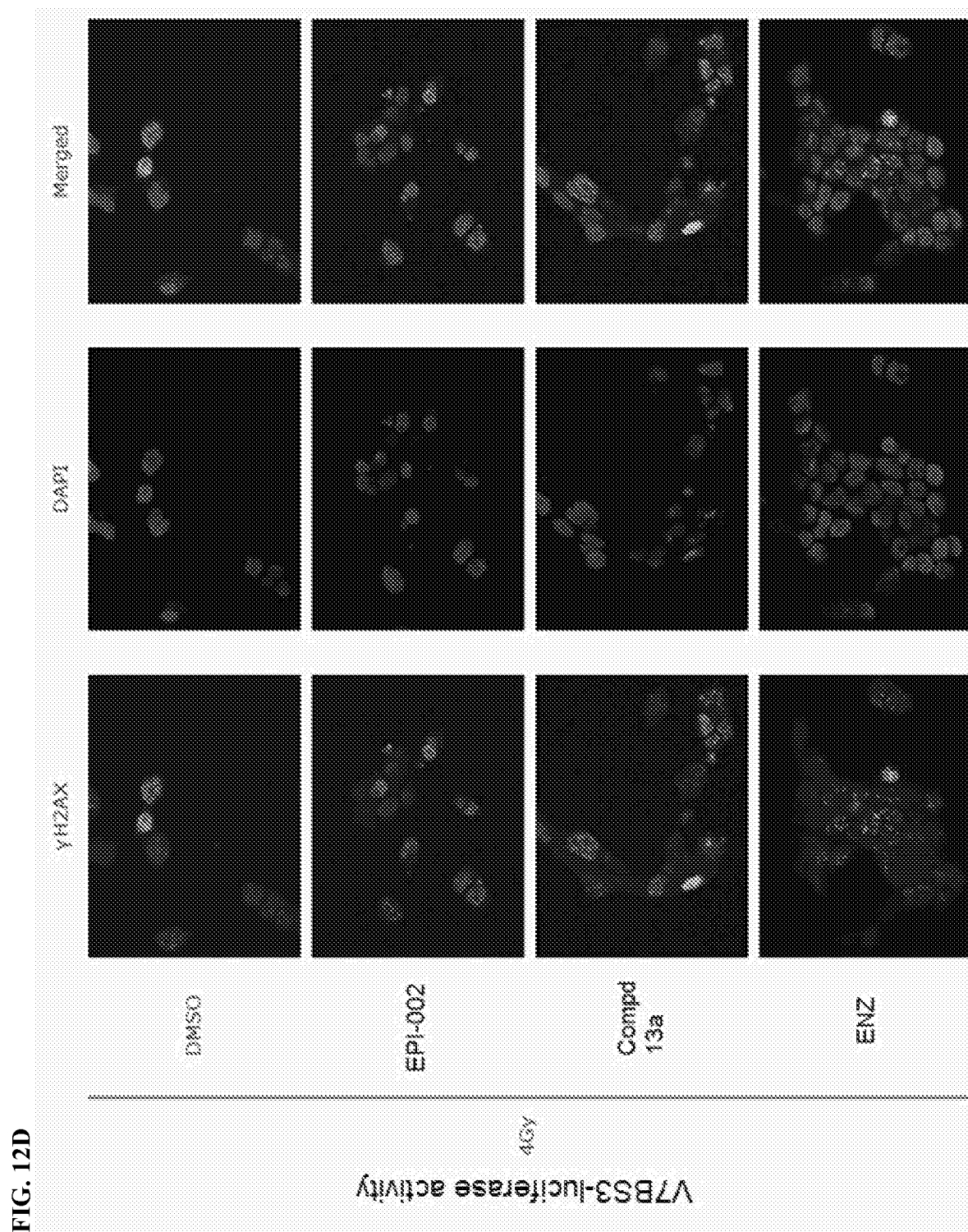


FIG. 13

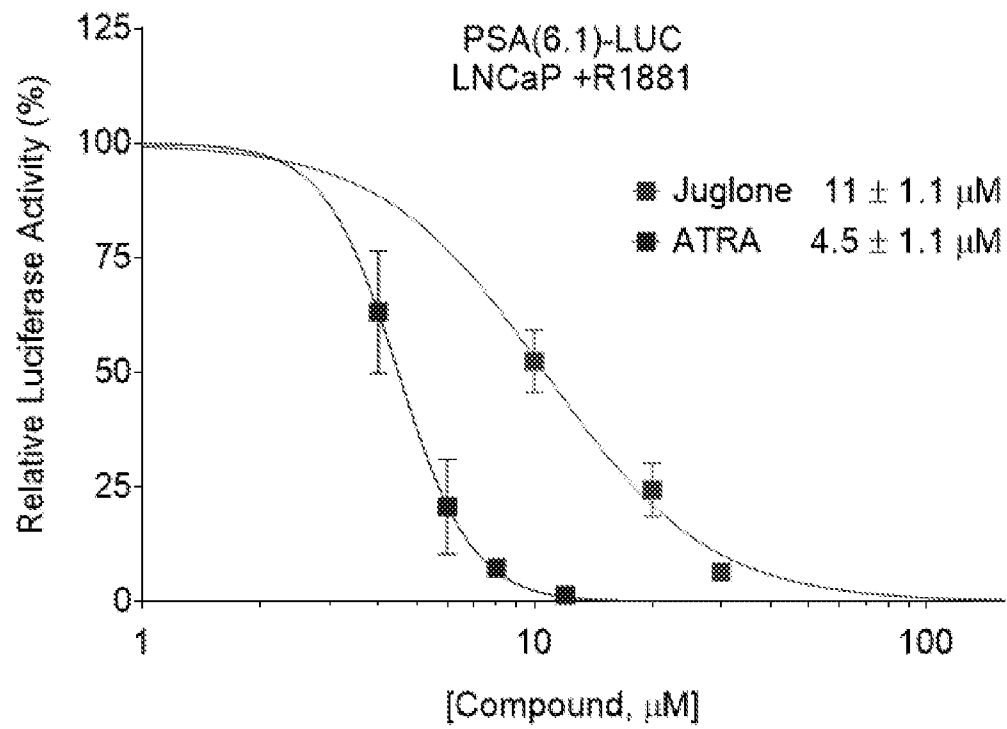


FIG. 14

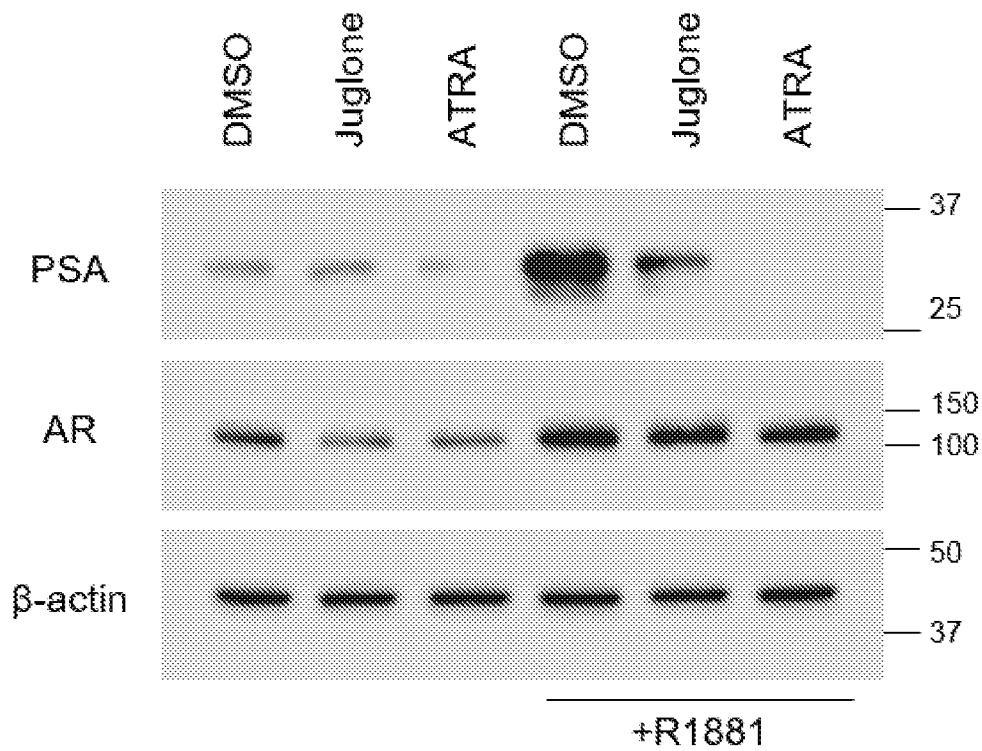


FIG. 15

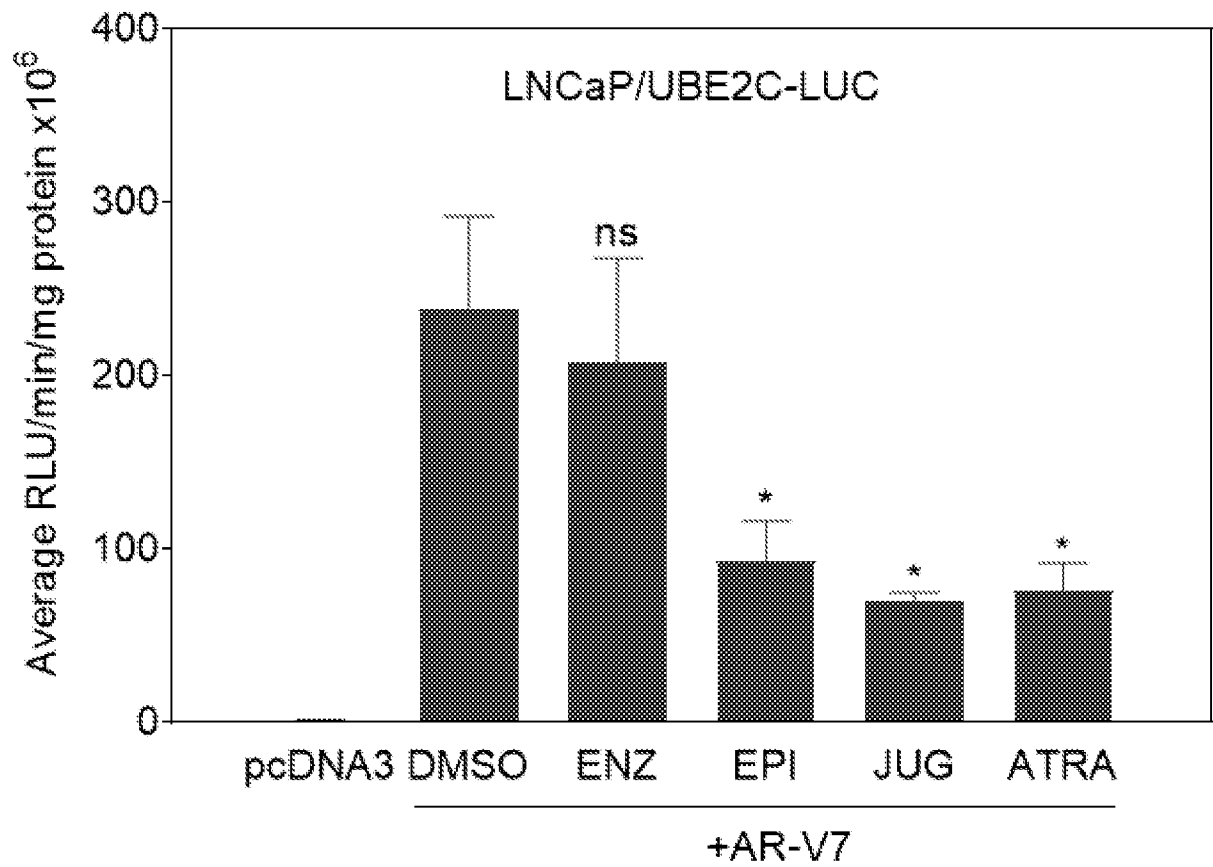


FIG. 16

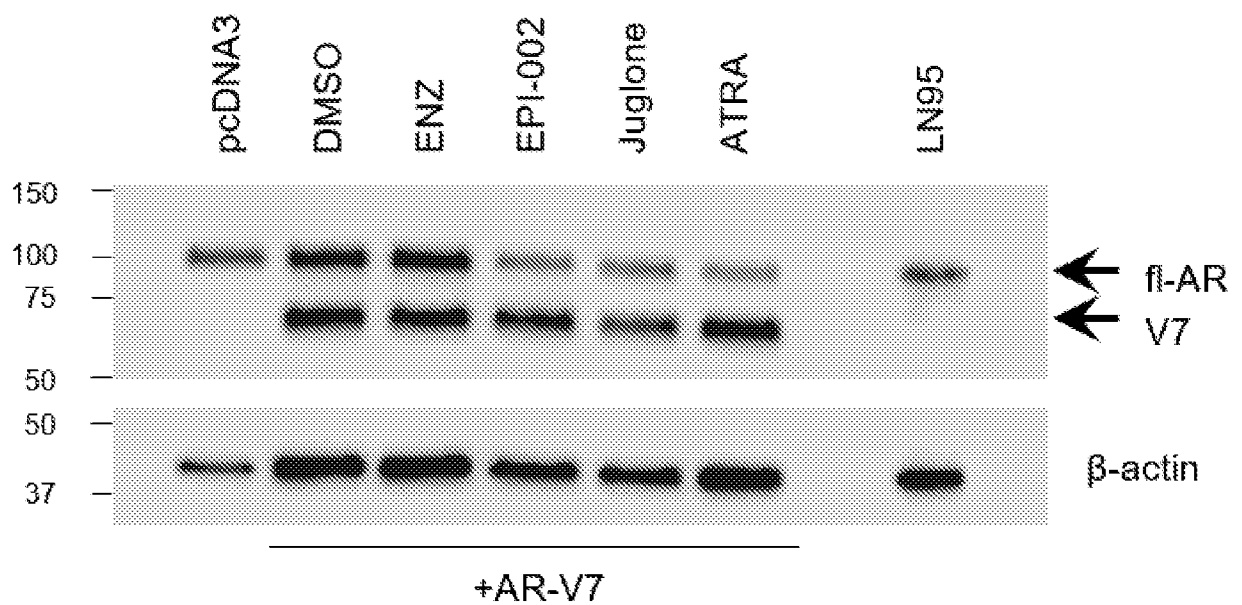


FIG. 17

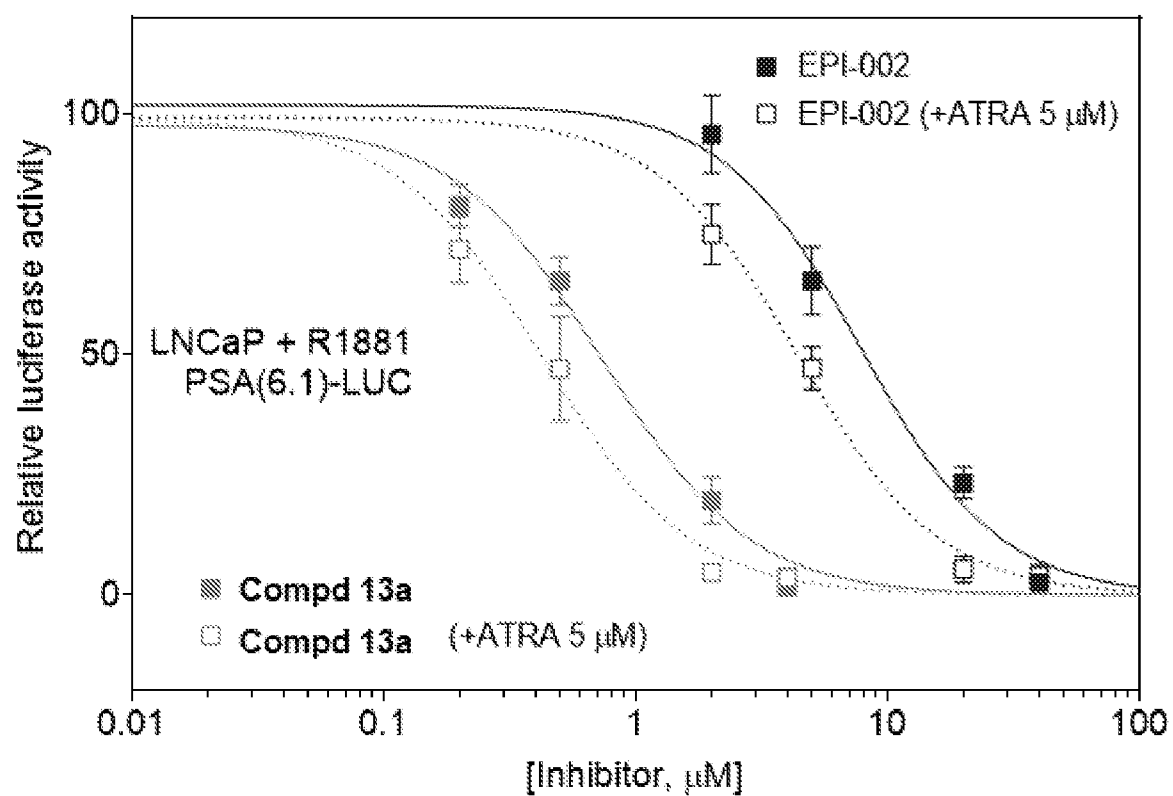


FIG. 18A

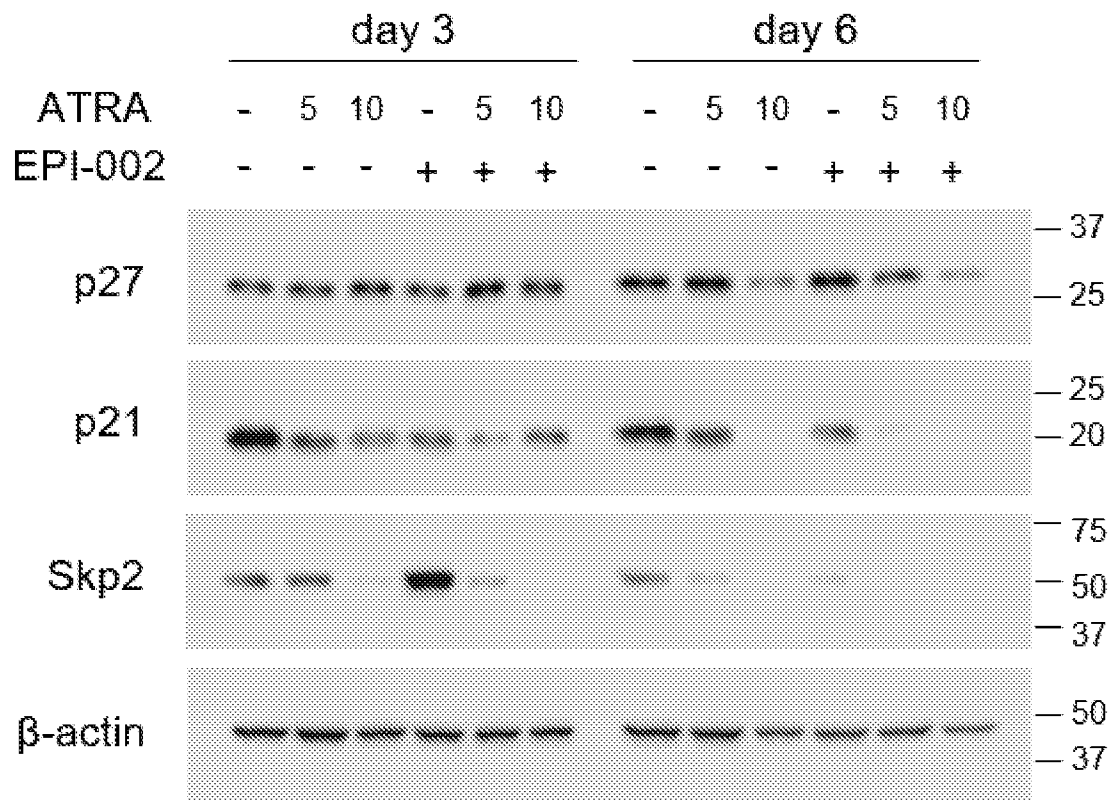


FIG. 18B

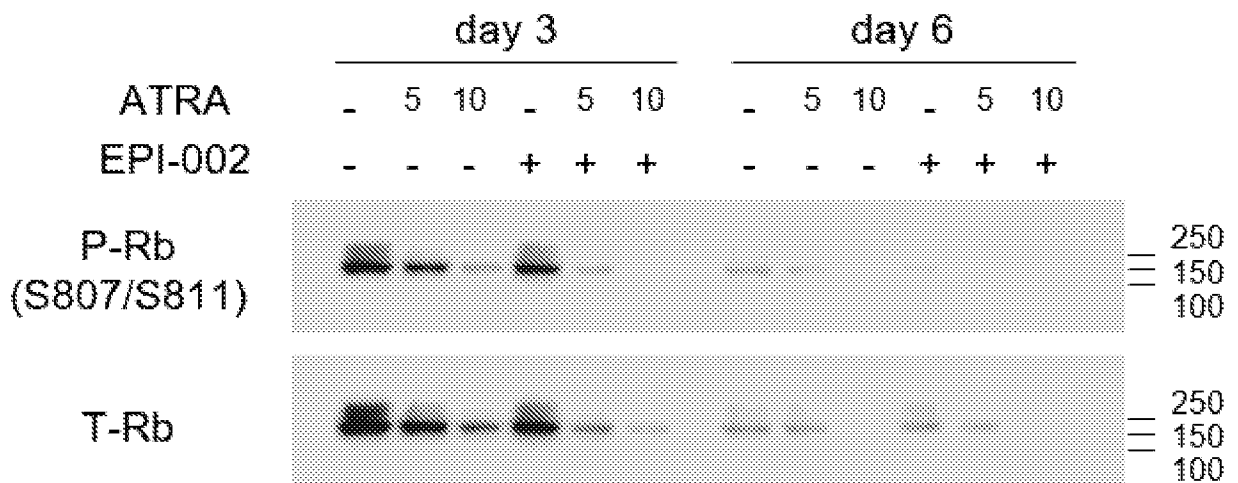


FIG. 19A

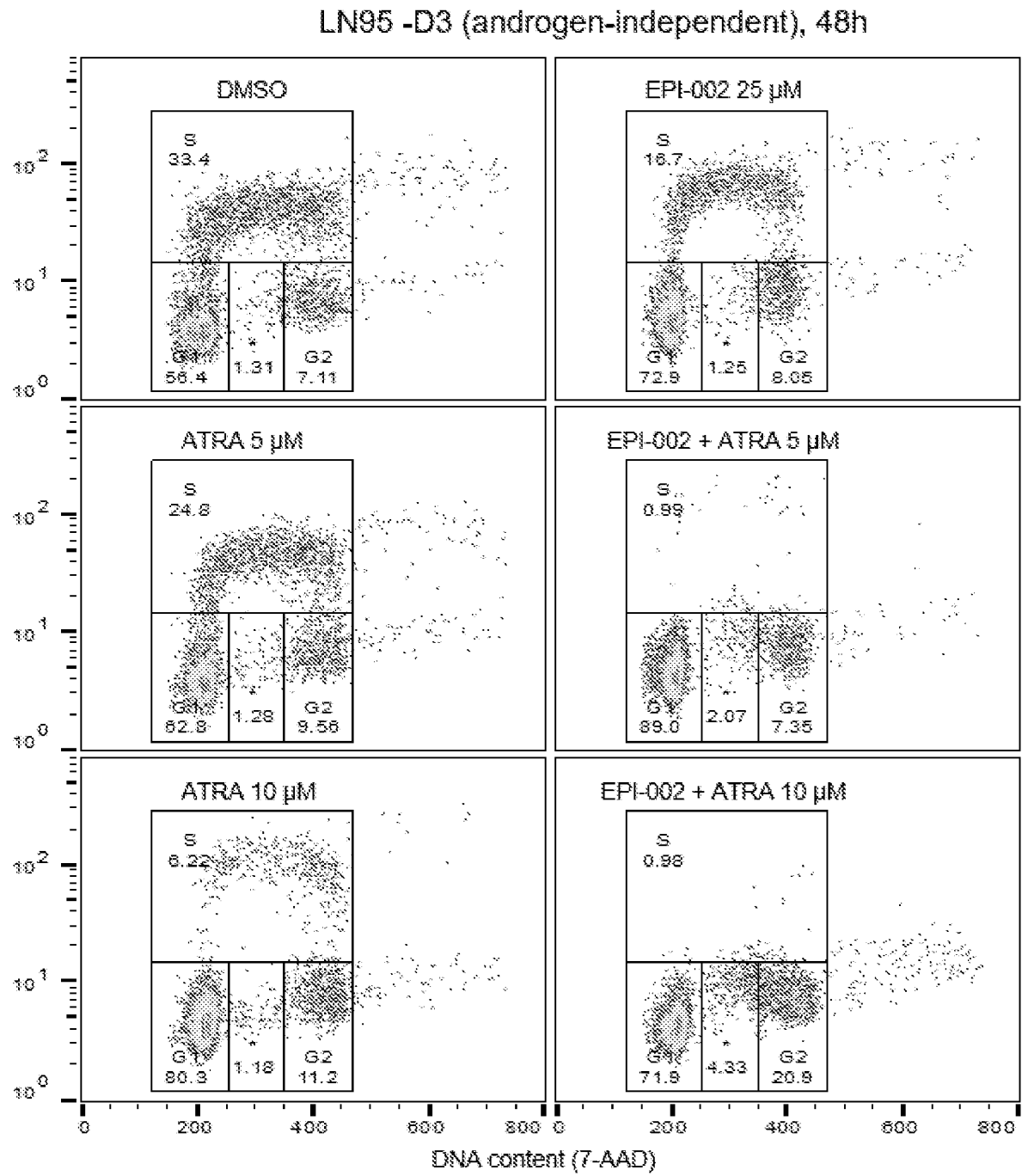
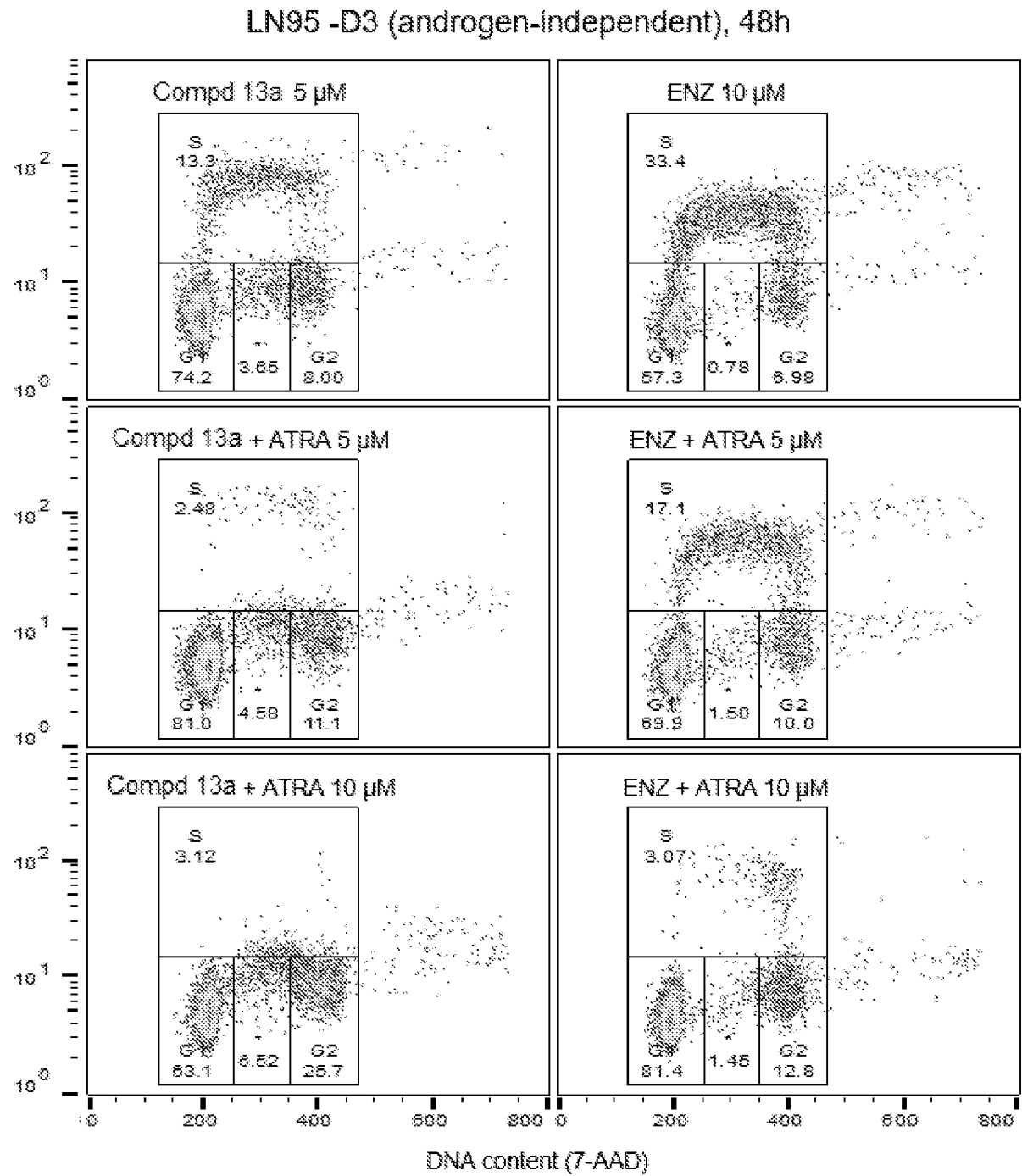


FIG. 19B



Western blot analysis of Pin1, Cyclin D1, and β -actin in LN95 cells treated with 13cisRA or ATRA. The blot shows protein levels for Pin1 (15-20 kDa), Cyclin D1 (25-37 kDa), and β -actin (37-50 kDa) across concentrations of 0, 1, 5, and 10 μ M for both treatments. Pin1 levels increase with 13cisRA treatment, while Cyclin D1 levels decrease. β -actin serves as a loading control.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/25545

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/075; C07C 43/164; A61P 5/26; A61P 5/28 (2020.01)

CPC - A61K 31/075; C07C 43/164; A61K 2300/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y -- A	WO 2018/157232 A1 (British Columbia Cancer Agency Branch) 07 September 2018 (07.09.2018) pg. 5, ln 1-10, formula I; pg. 13, ln 16 to pg.16. ln 5	1;50 ----- 2;3/1;3/2;8-11;19;33;51; 56-58;62 ----- 4-7;52-55
X -- Y -- A	US 2017/0298033 A1 (The UNIVERSITY of BRITISH COLUMBIA) 19 October 2017 (19.10.2017) para [0055]-[0056];[0133];[0136]; pg. 16, pg. 17, pg. 26, pg. 34, Table 1	25; 26 ----- 2;3/2;8-11;19;33;56-58;62 ----- 4-7; 52-55
Y --- A	PUBCHEM 15305867 deposited 09 February 2007 (09.02.2007) pp. 1-11. pg. 2	3/1; 3/2; 51 ----- 4-7; 52-55
A	US 2016/0068466 A1 (The University of British Columbia) 10 March 2016 (10.03.2016) pg. 14, Table 1	4-7; 52-55

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

14 JUNE 2020

Date of mailing of the international search report

09 JUL 2020

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Lee Young

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/25545

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

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

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

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

3. ☒ Claims Nos.: 12-18, 20-24, 27-32, 34-49, 59-61 and 63-76
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.