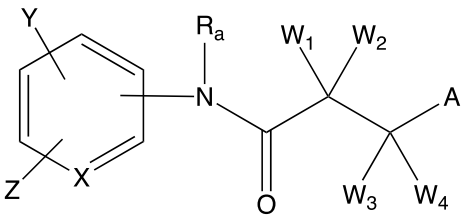
in the androgen biosynthetic pathways, not nuclear receptors.

[0025] The unique property of degrading AR-SV has extremely important health consequences. Only few molecules are reported to bind and inhibit the AR-NTD or DNA binding domains (DBD). No irreversible AR antagonists have been approved yet. Most small molecule antagonists or inhibitors bind to the target protein by hydrophobic and hydrogen bonds and function as competitive antagonists. The bonds are weak and can be easily displaced by excess competitors. It is highly desirable to discover molecules that bind covalently (covalent bonds have at least 10 fold higher energy than hydrogen bonds) and irreversibly. It is important to discover irreversible AR antagonists that can provide sustained inhibition of the AR, for example, the inhibition of enzalutamide (Enza)-resistant -AR and -PCa tumors and treatment-refractory BC with selective AR covalent antagonists (SARCAs) as described herein. Furthermore, a wide variety of androgen-dependent diseases and conditions are described herein to be susceptible to treatment with AR antagonists. The SARCAs of this invention, in addition to alkylating the AR, further provide potent inhibition of wtAR *in vitro* (see IC_{50} values in Tables 1 and 2) and hence will be effective in the same scope of diseases as traditional AR antagonists. I.e., the novel properties possessed by the SARCAs of this invention, e.g., binding of AF-1 in the NTD, alkylation of AR at NTD or LBD, or degradation of AR do not limit the scope of diseases susceptible to the AR antagonists of this invention. Instead, these novel AR antagonistic properties serve to expand the scope of androgen dependent diseases and conditions that are susceptible as fewer resistance mechanisms will be able to overcome treatment with the SARCAs of this invention.

SUMMARY ~~OF THE INVENTION~~

[0026] In one aspect, the ~~invention~~ disclosure provides a compound represented by the structure of formula I



I

wherein

X is CH or N;

Y is H, CF_3, F, Br, Cl, I, CN, or $C(R)_3$;

Z is H, NO_2, CN, F, Br, Cl, I, COOH, COR, NHCOR, or CONHR;

or Y and Z form a 5 to 8 membered fused ring;

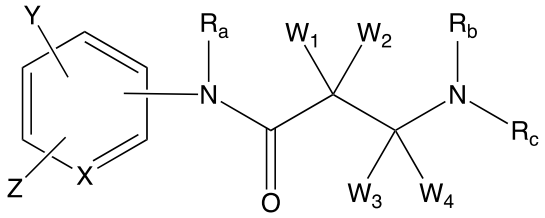
R is H, alkyl, alkenyl, CH_2CH_2OH, CF_3, CH_2Cl, CH_2CH_2Cl, aryl, F, Cl, Br, I, or OH;

R_a is H, alkyl-NCO, alkyl-NCS, alkyl-SCN, alkyl-OCN, alkyl-N_3, alkyl-SO_2F, alkyl-

membered saturated or unsaturated heterocyclic ring having at least one nitrogen atom and 0, 1, or 2 double bonds, optionally substituted with at least one of Q^1, Q^2, Q^3 and Q^4, each independently selected from hydrogen, keto, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, haloalkyl, CF_3, substituted or unsubstituted aryl, F, Cl, Br, I, CN, NO_2, hydroxyl, alkoxy, OR, benzyl, NCS, maleimide, NHCOOR, $N(R)_2$, NHCOR, CONHR, COOR, COR, -NCO, -NCS, -SCN, -OCN, -N_3, -SO_2F, -CH_2halide, -NHCOCH$_2$-halide, -NHSO$_2$CH$_2$-halide, -CH$_2$-CH=CH-COOR, -CH$_2$-C(COOR)=CH$_2$, -CH$_2$-CH=CH-CONHR, -CH$_2$-C(CONHR)=CH$_2$, -CH$_2$-CH=CH-CONHCOR, -CH$_2$-C(CONHCOR)=CH$_2$, -CH$_2$-CH=CH-CON(R)$_2$, or -CH$_2$-C(CON(R)$_2$)=CH$_2$;

or its isomer, optical isomer, racemic mixture, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof.

[0027] In one ~~embodiment~~example, the compound of the disclosure ~~invention~~ is represented by the structure of formula II



II

wherein

X is CH or N;

Y is H, CF_3, F, Br, Cl, I, CN, or $C(R)_3$;

Z is H, NO_2, CN, F, Br, Cl, I, COOH, COR, NHCOR, or CONHR;

or Y and Z form a 5 to 8 membered fused ring;

R is H, alkyl, alkenyl, CH_2CH_2OH, CF_3, CH_2Cl, CH_2CH_2Cl, aryl, F, Cl, Br, I, or OH;

R_a is H, alkyl-NCO, alkyl-NCS, alkyl-SCN, alkyl-OCN, alkyl-N_3, alkyl-SO_2F, alkyl-CH_2halide, alkyl-NHCOCH$_2$halide, alkyl-NHSO$_2$CH$_2$halide, -CH$_2$-CH=CH-COOR, -CH$_2$-C(COOR)=CH$_2$, -CH$_2$-CH=CH-CONHR, -CH$_2$-C(CONHR)=CH$_2$, -CH$_2$-CH=CH-CONHCOR, -CH$_2$-C(CONHCOR)=CH$_2$, -CH$_2$-CH=CH-CON(R)$_2$, or -CH$_2$-C(CON(R)$_2$)=CH$_2$, wherein halide is F, Cl, Br, or I;

W_1 is H or OR_d, wherein R_d is H, alkyl-NCO, alkyl-NCS, alkyl-SCN, alkyl-OCN, alkyl-N_3, alkyl-SO_2F, alkyl-CH_2halide, alkyl-NHCOCH$_2$halide, alkyl-NHSO$_2$CH$_2$halide, -CH$_2$-CH=CH-COOR, -CH$_2$-C(COOR)=CH$_2$, -CH$_2$-CH=CH-CONHR, -CH$_2$-C(CONHR)=CH$_2$, -CH$_2$-CH=CH-CONHCOR, -CH$_2$-C(CONHCOR)=CH$_2$, -CH$_2$-CH=CH-CON(R)$_2$, or -CH$_2$-

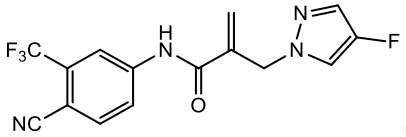
CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2;

or its isomer, optical isomer, racemic mixture, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof.

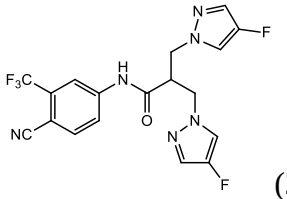
[0028] In one ~~embodiment~~example, the compound of the disclosure ~~invention~~ represented by the structure of formula I or formula II contains at least one nucleophile acceptor group. In one example~~embodiment~~, the compound of the disclosure ~~invention~~ represented by the structure of formula I or formula II contains at least one functional group with an α, β-unsaturated carbonyl. In one example~~embodiment~~, such α, β-unsaturated carbonyl functional groups include but are not limited to α, β-unsaturated ketones, amides, esters, thioesters, acid anhydrides, carboxylic acids, carboxylates, acid halides, imides, and the like. In one example~~embodiment~~, the α, β-unsaturated functional group serves as a Michael addition reaction acceptor for nucleophiles within the AR.

[0029] In one example~~embodiment~~, the compound of the disclosure ~~invention~~ represented by the structure of formula I or formula II contains at least one nucleophile acceptor group. In one example~~embodiment~~, the nucleophile acceptor group is at least one of isocyanato (-NCO), isothiocyanato (-NCS), cyanato (-CNO), thiocyanato (-CNS), azido (N_3), sulfonyl fluoride (-SO_2F), halomethyl (-CH_2-halide), 2-haloacetyl (-NHCOCH_2-halide), halosulfonyl (-NHSO_2CH_2-halide), and the like. In one example~~embodiment~~, the nucleophile acceptor group serves as a nucleophile acceptor for nucleophiles within the AR. In one example~~embodiment~~, said AR nucleophile is within the NTD. In another example~~embodiment~~, said AR nucleophile is within the AF-1 domain. In another example~~embodiment~~, said AR nucleophile is within the LBD. In one embodiment, the nucleophile acceptor group is present in the R_a group. In one example~~embodiment~~, the nucleophile acceptor group is present in the W_1 group. In one example~~embodiment~~, the nucleophile acceptor group is present in the W_3 or W_4 group. In one example~~embodiment~~, the nucleophile acceptor group is present in any one of the Q^1, Q^2, Q^3, or Q^4 groups.

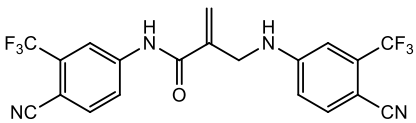
[0030] In one example~~embodiment~~, the compound of the disclosure ~~invention~~ is represented by the structure of any one of the following compounds:



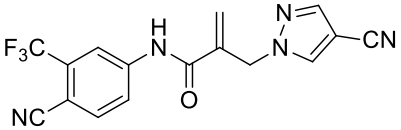
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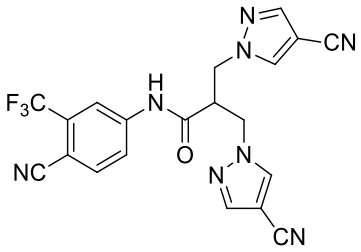
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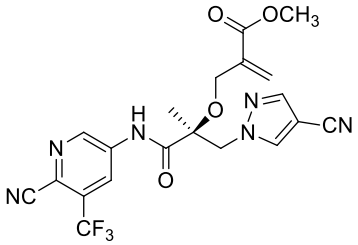
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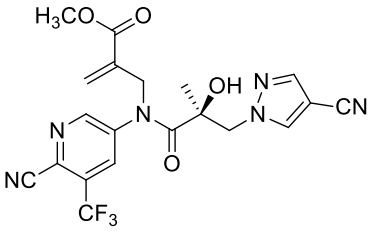
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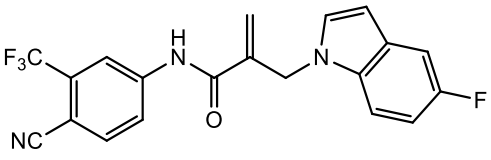
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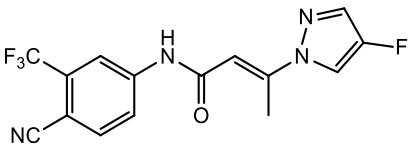
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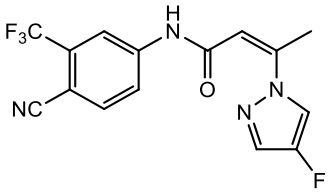
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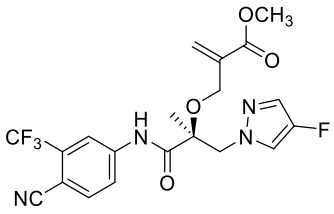
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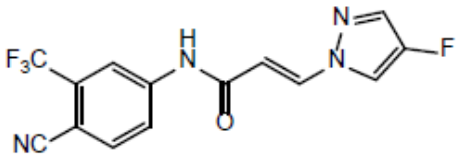
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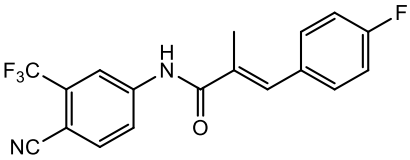
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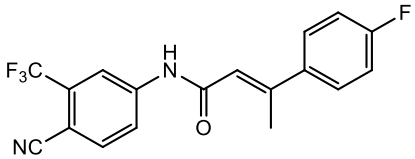
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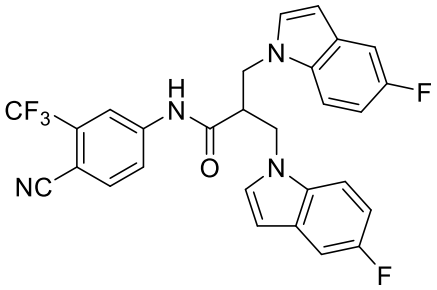
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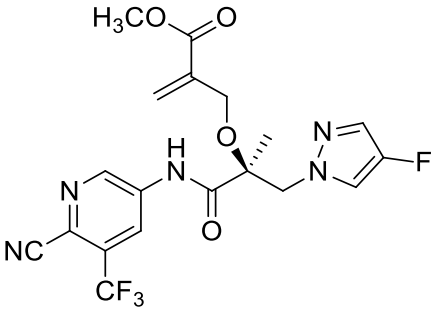
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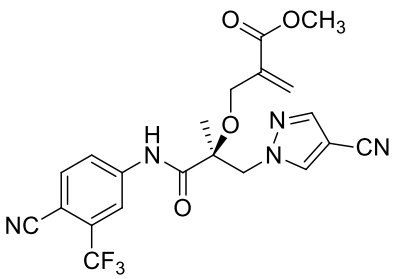
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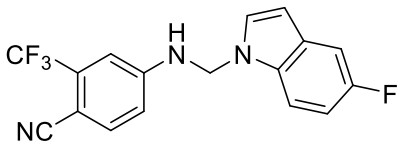
(17), or



(18).

[0031] In ~~one embodiment~~another aspect, the compound of the disclosure ~~invention~~ is represented by the structure of

compound **15**



(**15**).

[0032] In ~~one~~ another aspect, the disclosure ~~invention~~ provides a pharmaceutical composition comprising a compound of the disclosure~~invention~~, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, and a pharmaceutically acceptable carrier. In one example~~embodiment~~, the composition is formulated for topical use. In one example~~embodiment~~, the composition is in the form of a solution, lotion, salve, cream, ointment, liposome, spray, gel, foam, roller stick, cleansing soap or bar, emulsion, mousse, aerosol, or shampoo. In another example~~embodiment~~, the composition is formulated for oral use.

[0032a] In another aspect, the disclosure provides a compound of the disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, for use in therapy.

[0032b] In another aspect, the disclosure provides use of a compound of the disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, in the manufacture of a medicament for the treatment of an androgen receptor dependent disease or condition in a subject.

[0033] In another ~~aspect~~example, the disclosure ~~invention~~ provides a method of treating an androgen receptor dependent disease or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of the disclosure ~~invention~~ as described herein. In one example~~embodiment~~, the compound of the disclosure ~~invention~~ binds irreversibly to androgen receptor (AR).

[0034] In one example~~embodiment~~, the androgen receptor dependent disease or condition in the subject responds to at least one of AR-splice variant (AR-SV) degradation activity, AR full length (AR-FL) degradation activity, irreversible or reversible AR-SV inhibitory activity, or irreversible or reversible AR-FL inhibitory activity.

[0035] In one example~~embodiment~~, the androgen receptor dependent disease or condition is breast cancer.

[0036] In one example~~embodiment~~, the subject has AR expressing breast cancer, AR-SV expressing breast cancer, and/or AR-V7 expressing breast cancer.

[0037] In one example~~embodiment~~, the androgen receptor dependent disease or condition is Kennedy's disease.

[0038] In one exampleembodiment, the androgen receptor dependent disease or condition is acne. In one exampleembodiment, the acne is acne vulgaris.

[0039] In one exampleembodiment, the androgen receptor dependent disease or condition is overproduction of sebum. In one exampleembodiment, reducing the overproduction of sebum treats at least one of seborrhea, seborrheic dermatitis, or acne.

[0040] In one exampleembodiment, the androgen receptor dependent disease or condition is hirsutism or alopecia.

[0041] In one exampleembodiment, the alopecia is at least one of androgenic alopecia, alopecia areata, alopecia secondary to chemotherapy, alopecia secondary to radiation therapy, alopecia induced by scarring, or alopecia induced by stress.

[0042] In one exampleembodiment, the androgen receptor dependent disease or condition is a hormonal disease or condition in a female. In one exampleembodiment, the hormonal disease or condition in a female is at least one of precocious puberty, dysmenorrhea, amenorrhea, multilocular uterus syndrome, endometriosis, hysteromyoma, abnormal uterine bleeding, early menarche, fibrocystic breast disease, fibroids of the uterus, ovarian cysts, polycystic ovary syndrome, pre-eclampsia, eclampsia of pregnancy, preterm labor, premenstrual syndrome, or vaginal dryness.

[0043] In one exampleembodiment, the androgen receptor dependent disease or condition is hormonal disease or condition in a male. In one exampleembodiment, the hormonal disease or condition in a male is at least one of hypergonadism, hypersexuality, sexual dysfunction, gynecomastia, precocious puberty in a male, alterations in cognition and mood, depression, hair loss, hyperandrogenic dermatological disorders, pre-cancerous lesions of the prostate, benign prostate hyperplasia, prostate cancer and/or other androgen-dependent cancers.

[0044] In one exampleembodiment, the androgen receptor dependent disease or condition is sexual perversion, hypersexuality, or paraphilias.

[0045] In one exampleembodiment, the androgen receptor dependent disease or condition is androgen psychosis.

[0046] In one exampleembodiment, the androgen receptor dependent disease or condition is virilization.

[0047] In one exampleembodiment, the androgen receptor dependent disease or condition is androgen insensitivity syndrome.

[0048] In one exampleembodiment, the androgen receptor dependent disease or condition is AR-expressing cancer in said subject. In one exampleembodiment, the AR-expressing cancer is at least one of breast cancer, testicular cancer, cancers associated with partial androgen insensitivity syndromes (PAIS) such as gonadal tumors and seminoma, uterine cancer, ovarian cancer, cancer of the fallopian tubes or peritoneum, salivary gland cancer, bladder cancer, urogenital cancer, brain cancer, skin cancer, lymphoma, mantle cell lymphoma, liver cancer, hepatocellular carcinoma, renal cancer, renal cell carcinoma, osteosarcoma, pancreatic cancer, endometrial cancer, lung cancer, non-small cell lung cancer (NSCLC), gastric cancer, colon cancer, perianal adenoma, or central nervous system cancer.

[0049] In one exampleembodiment, the androgen receptor dependent disease or condition is amyotrophic lateral sclerosis (ALS).

[0050] In one exampleembodiment, the androgen receptor dependent disease or condition is uterine fibroids.

[0051] In one exampleembodiment, the androgen receptor dependent disease or condition is abdominal aortic aneurysm (AAA).

[0052] In one exampleembodiment, the androgen receptor dependent disease or condition is caused by polyglutamine (polyQ) AR polymorphs in a subject. In one exampleembodiment, the polyQ-AR is a short

polyQ polymorph or a long polyQ polymorph. In one exampleembodiment, the polyQ-AR is a short polyQ polymorph and the method further treats dermal disease. In one exampleembodiment, the dermal disease is at least one of alopecia, seborrhea, seborrheic dermatitis, or acne. In another exampleembodiment, the polyQ-AR is a long polyQ polymorph and the method further treats Kennedy's disease.

[0052a] In another aspect, the disclosure provides use of a compound of the disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, in the manufacture of a medicament for the treatment of a prostate cancer (PCa) or increasing the survival of a male subject suffering from prostate cancer.

[0053] In another aspectexample, the disclosure invention encompasses a method of treating prostate cancer (PCa) or increasing survival in a male subject in need of treatment comprising administering to the subject a therapeutically effective amount of a compound of the disclosure invention as described herein. The prostate cancer includes, but is not limited to, advanced prostate cancer, castration resistant prostate cancer (CRPC), metastatic CRPC (mCRPC), non-metastatic CRPC (nmCRPC), high-risk nmCRPC or any combination thereof. Another example embodiment of the disclosure invention encompasses the method further comprising administering androgen deprivation therapy (ADT). Alternatively, the method may treat a prostate or other cancer that is resistant to treatment with known androgen receptor antagonist(s) or ADT. In another exampleembodiment, the method may treat enzalutamide resistant prostate cancer. In another exampleembodiment, the method may treat apalutamide resistant prostate cancer. In another exampleembodiment, the method may treat abiraterone resistant prostate cancer. In another exampleembodiment, the method may treat darolutamide resistant prostate cancer. Yet another exampleembodiment of the disclosure invention encompasses a method of treating prostate or other AR antagonist resistant cancer with a compound of the disclosure invention as described herein, wherein the androgen receptor antagonist(s) is at least one of darolutamide, apalutamide, enzalutamide, bicalutamide, abiraterone, EPI-001, EPI-506, AZD-3514, galeterone, ASC-J9, flutamide, hydroxyflutamide, nilutamide, cyproterone acetate, ketoconazole, or spironolactone.

[0054] Yet another example embodiment of the disclosure invention encompasses a method of treating prostate or other AR-expressing cancers using a compound of the disclosure invention wherein the other cancers are selected from breast cancer such as triple negative breast cancer (TNBC), testicular cancer, cancers associated with partial androgen insensitivity syndromes (PAIS) such as gonadal tumors and seminoma, uterine cancer, ovarian cancer, cancer of the fallopian tubes or peritoneum, salivary gland cancer, bladder cancer, urogenital cancer, brain cancer, skin cancer, lymphoma, mantle cell lymphoma, liver cancer, hepatocellular carcinoma, renal cancer, renal cell

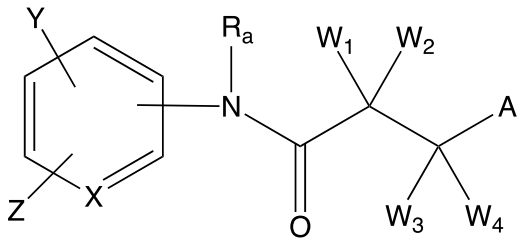
carcinoma, osteosarcoma, pancreatic cancer, endometrial cancer, lung cancer, non-small cell lung cancer (NSCLC), gastric cancer, colon cancer, perianal adenoma, or central nervous system cancer. In another exampleembodiment, the breast cancer is triple negative breast cancer (TNBC).

[0054a] In another aspect, the disclosure provides use of a compound of the disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, in the manufacture of a medicament for the reduction of levels of AR-splice variants in a subject.

[0055] The invention disclosure encompasses a method of reducing the levels of AR-splice variants in a subject comprising administering to the subject a therapeutically effective amount of a compound of this inventiondisclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically

WHAT IS CLAIMED IS:

1. A compound represented by the structure of formula I



I

wherein

X is CH or N;

Y is H, CF_3, F, Br, Cl, I, CN, or $C(R)_3$;

Z is H, NO_2, CN, F, Br, Cl, I, COOH, COR, NHCOR, or CONHR;

or Y and Z form a 5 to 8 membered fused ring;

R is H, alkyl, alkenyl, CH_2CH_2OH, CF_3, CH_2Cl, CH_2CH_2Cl, aryl, F, Cl, Br, I, or OH;

R_a is H, alkyl-NCO, alkyl-NCS, alkyl-SCN, alkyl-OCN, alkyl-N_3, alkyl-SO_2F, alkyl-CH_2halide, alkyl-$NHCOCH_2$halide, alkyl-$NHSO_2CH_2$halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-$CON(R)_2$, or -CH_2-$C(CON(R)_2)$=CH_2, wherein halide is F, Cl, Br, or I;

W_1 is H or OR_d, wherein R_d is H, alkyl-NCO, alkyl-NCS, alkyl-SCN, alkyl-OCN, alkyl-N_3, alkyl-SO_2F, alkyl-CH_2halide,-alkyl-$NHCOCH_2$halide, alkyl-$NHSO_2CH_2$halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-$CON(R)_2$, or -CH_2-$C(CON(R)_2)$=CH_2;

W_2 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, CF_2CF_3, or CH_2A;

or W_1 and W_2, together with the carbon atom to which they are attached, form a $C=CW_5W_6$ group, wherein W_5 and W_6 are each H or alkyl;

W_3 and W_4 are individually H, OH, alkyl, wherein the alkyl is optionally substituted with OR, NO_2, CN, F, Br, Cl, I, COR, NHCOR, CONHR, -NCO, -NCS, -SCN, -OCN, -N_3, -SO_2F, -CH_2halide, -$NHCOCH_2$halide, -$NHSO_2CH_2$halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -

CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2;

or one of W_1 and W_2 with one of W_3 and W_4, together with the carbon atoms to which they are attached, form a C=C bond;

A is NR_bR_c or a 5 to 10-membered aryl or heteroaryl group, optionally substituted with at least one of Q^1, Q^2, Q^3 and Q^4, each independently selected from hydrogen, keto, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, haloalkyl, CF_3, substituted or unsubstituted aryl, F, Cl, Br, I, CN, NO_2, hydroxyl, alkoxy, OR, benzyl, NCS, maleimide, NHCOOR, N$(R)_2$, NHCOR, CONHR, COOR, COR, -NCO, -NCS, -SCN, -OCN, -N_3, -SO_2F, -CH_2halide, -NHCOCH_2-halide, -NHSO_2CH_2-halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2;

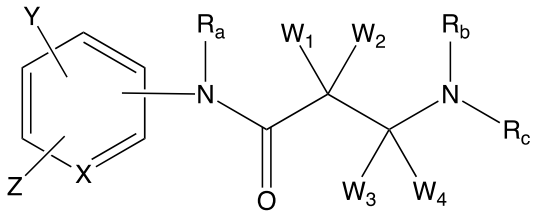
R_b is H or alkyl, wherein the alkyl is optionally substituted with OR, NO_2, CN, F, Br, Cl, I, COR, NHCOR, or CONHR;

R_c is alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein said alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups are optionally substituted with CN, NO_2, CF_3, F, Cl, Br, I NHCOOR, N$(R)_2$, NHCOR, COR, alkyl, or alkoxy;

or R_b and R_c, together with the nitrogen atom to which they are attached, form a 5 to 10-membered saturated or unsaturated heterocyclic ring having at least one nitrogen atom and 0, 1, or 2 double bonds, optionally substituted with at least one of Q^1, Q^2, Q^3 and Q^4, each independently selected from hydrogen, keto, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, haloalkyl, CF_3, substituted or unsubstituted aryl, F, Cl, Br, I, CN, NO_2, hydroxyl, alkoxy, OR, benzyl, NCS, maleimide, NHCOOR, N$(R)_2$, NHCOR, CONHR, COOR, COR, -NCO, -NCS, -SCN, -OCN, -N_3, -SO_2F, -CH_2halide, -NHCOCH_2-halide, -NHSO_2CH_2-halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2;

or its isomer, optical isomer, racemic mixture, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof.

2. The compound of claim 1, wherein said compound is represented by the structure of formula II



II

wherein

X is CH or N;

Y is H, CF_3, F, Br, Cl, I, CN, or $C(R)_3$;

Z is H, NO_2, CN, F, Br, Cl, I, COOH, COR, NHCOR, or CONHR;

or Y and Z form a 5 to 8 membered fused ring;

R is H, alkyl, alkenyl, CH_2CH_2OH, CF_3, CH_2Cl, CH_2CH_2Cl, aryl, F, Cl, Br, I, or OH;

R_a is H, alkyl-NCO, alkyl-NCS, alkyl-SCN, alkyl-OCN, alkyl-N_3, alkyl-SO_2F, alkyl-CH_2halide, alkyl-$NHCOCH_2$halide, alkyl-$NHSO_2CH_2$halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2, wherein halide is F, Cl, Br, or I;

W_1 is H or OR_d, wherein R_d is H, alkyl-NCO, alkyl-NCS, alkyl-SCN, alkyl-OCN, alkyl-N_3, alkyl-SO_2F, alkyl-CH_2halide, alkyl-$NHCOCH_2$halide, alkyl-$NHSO_2CH_2$halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2;

W_2 is CH_3, CH_2F, CHF_2, CF_3, CH_2CH_3, CF_2CF_3, or CH_2A;

or W_1 and W_2, together with the carbon atom to which they are attached, form a C=CW_5W_6 group, wherein W_5 and W_6 are each H or alkyl;

W_3 and W_4 are individually H, OH, alkyl, wherein the alkyl is optionally substituted with OR, NO_2, CN, F, Br, Cl, I, COR, NHCOR, CONHR, -NCO, -NCS, -SCN, -OCN, -N_3, -SO_2F, -CH_2halide, -$NHCOCH_2$halide, -$NHSO_2CH_2$halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-

C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2;

or one of W_1 and W_2 with one of W_3 and W_4, together with the carbon atoms to which they are attached, form a C=C bond;

A is NR_bR_c or a 5 to 10-membered aryl or heteroaryl group, optionally substituted with at least one of Q^1, Q^2, Q^3 and Q^4, each independently selected from hydrogen, keto, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, haloalkyl, CF_3, substituted or unsubstituted aryl, F, Cl, Br, I, CN, NO_2, hydroxyl, alkoxy, OR, benzyl, NCS, maleimide, NHCOOR, N$(R)_2$, NHCOR, CONHR, COOR, COR, -NCO, -NCS, -SCN, -OCN, -N_3, -SO_2F, -CH_2halide, -NHCOCH_2-halide, -NHSO_2CH_2-halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2;

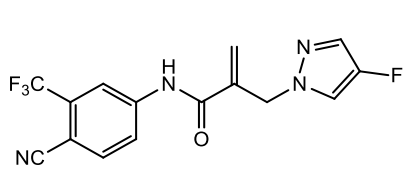
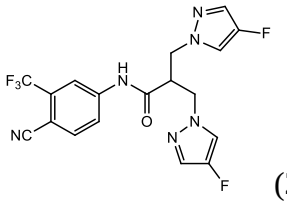
R_b is H or alkyl, wherein the alkyl is optionally substituted with OR, NO_2, CN, F, Br, Cl, I, COR, NHCOR, or CONHR;

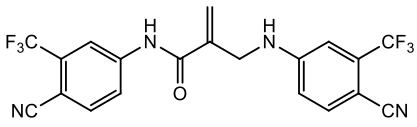
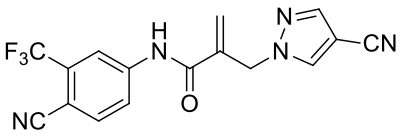
R_c is alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein said alkyl, haloalkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups are optionally substituted with CN, NO_2, CF_3, F, Cl, Br, I NHCOOR, N$(R)_2$, NHCOR, COR, alkyl, or alkoxy;

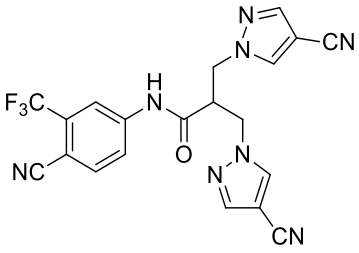
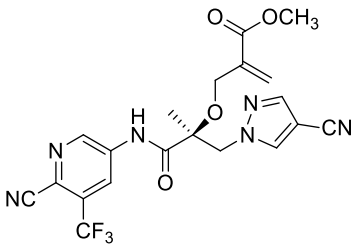
or R_b and R_c, together with the nitrogen atom to which they are attached, form a 5 to 10-membered saturated or unsaturated heterocyclic ring having at least one nitrogen atom and 0, 1, or 2 double bonds, optionally substituted with at least one of Q^1, Q^2, Q^3 and Q^4, each independently selected from hydrogen, keto, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, haloalkyl, CF_3, substituted or unsubstituted aryl, F, Cl, Br, I, CN, NO_2, hydroxyl, alkoxy, OR, benzyl, NCS, maleimide, NHCOOR, N$(R)_2$, NHCOR, CONHR, COOR, COR, -NCO, -NCS, -SCN, -OCN, -N_3, -SO_2F, -CH_2halide, -NHCOCH_2-halide, -NHSO_2CH_2-halide, -CH_2-CH=CH-COOR, -CH_2-C(COOR)=CH_2, -CH_2-CH=CH-CONHR, -CH_2-C(CONHR)=CH_2, -CH_2-CH=CH-CONHCOR, -CH_2-C(CONHCOR)=CH_2, -CH_2-CH=CH-CON$(R)_2$, or -CH_2-C(CON$(R)_2$)=CH_2;

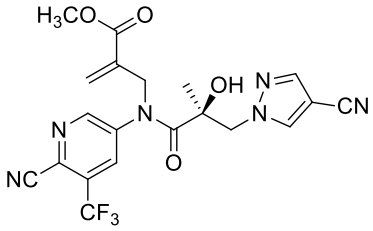
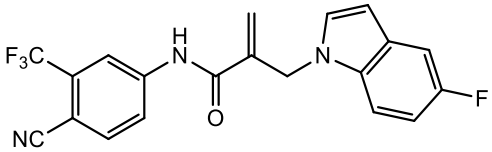
or its isomer, optical isomer, racemic mixture, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof.

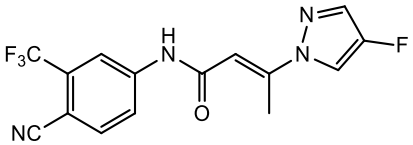
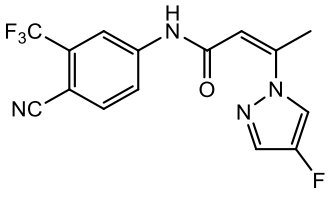
3. The compound of claim 1, wherein said compound is represented by the structure of any one of the following compounds:

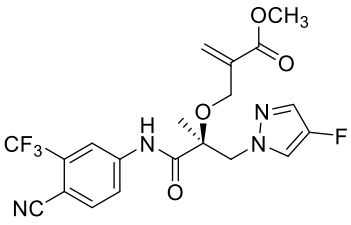

(**1**),

(**2**),

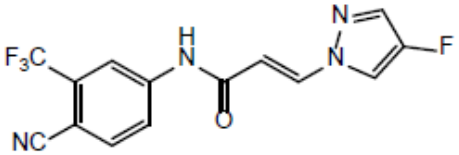

(**3**),

(**4**),


(**5**),

(**6**),

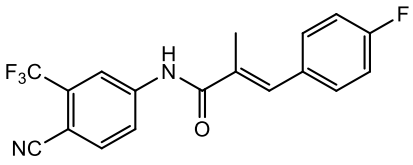

(**7**),

(**8**),

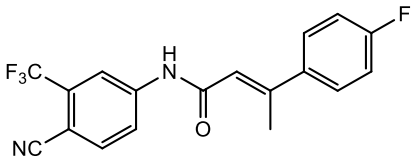

(**9**),

(**10**),



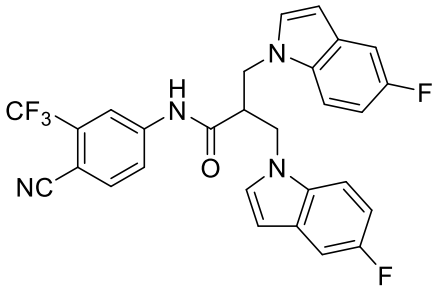
(**11**),


(**12**),

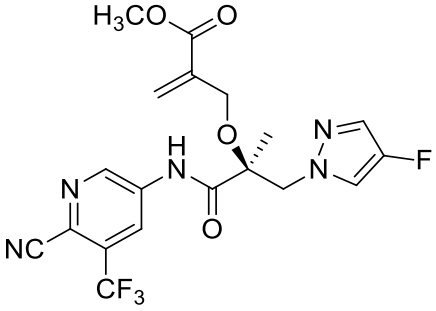


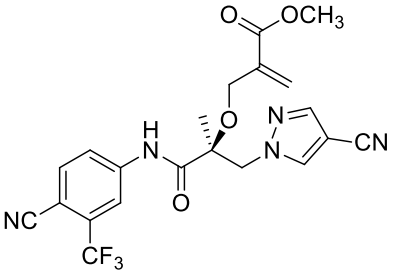
(**13**),


(**14**),



(**16**)



(17), or


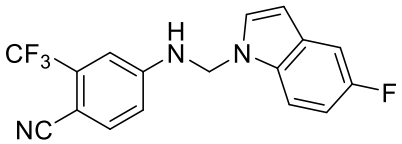
(18)

4. The compound of claim 1, wherein said compound is a selective androgen receptor covalent antagonist (SARCA) compound containing at least one nucleophile acceptor group.

5. The compound of claim 4, where said nucleophile acceptor group is a Michael addition reaction acceptor or at least one of -NCO, -NCS, -N_3, 2-haloacetyl, or halomethyl.

6. The compound of claim 1 or 2, wherein R_a and R_d are not H at the same time.

7. A compound represented by the structure of compound **15**



(**15**).

8. A pharmaceutical composition comprising a compound of any one of claims 1-7, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, and a pharmaceutically acceptable carrier.

9. A compound of any one of claims 1-7, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, for use in therapy.

~~9~~10. Use of a compound of any one of claims 1-7, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, in the manufacture of a medicament for the treatment of ~~A method of treating~~ an androgen receptor dependent disease or condition in a subject ~~in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-7~~.

~~10~~11. The ~~method~~ use of claim ~~9~~10, wherein said compound binds irreversibly to androgen receptor (AR).

~~11~~12. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition in said subject responds to at least one of AR-splice variant (AR-SV) degradation activity, full length (AR-FL) degradation activity, AR-SV inhibitory, or AR-FL inhibitory activity.

~~12~~13. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition is breast cancer in said subject.

~~13~~14. The use ~~method~~ of claim 10~~9~~, wherein said subject has AR expressing breast cancer, AR-SV expressing breast cancer, and/or AR-V7 expressing breast cancer.

~~14~~15. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition is Kennedy's disease, acne, overproduction of sebum, hirsutism or alopecia in said subject.

~~15~~16. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition is a hormonal disease or condition in a female in said subject.

~~16~~17. The use ~~method~~ of claim ~~15~~16, wherein said hormonal disease or condition in a female is at least one of precocious puberty, dysmenorrhea, amenorrhea, multilocular uterus syndrome, endometriosis, hysteromyoma, abnormal uterine bleeding, early menarche, fibrocystic

breast disease, fibroids of the uterus, ovarian cysts, polycystic ovary syndrome, pre-eclampsia, eclampsia of pregnancy, preterm labor, premenstrual syndrome, or vaginal dryness.

~~17~~18. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition is hormonal disease or condition in a male in said subject.

~~18~~19. The use ~~method~~ of claim ~~17~~18, wherein said hormonal disease or condition in a male is at least one of hypergonadism, hypersexuality, sexual dysfunction, gynecomastia, precocious puberty in a male, alterations in cognition and mood, depression, hair loss, hyperandrogenic dermatological disorders, pre-cancerous lesions of the prostate, benign prostate hyperplasia, prostate cancer and/or other androgen-dependent cancers.

~~19~~20. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition is sexual perversion, hypersexuality, paraphilias, androgen psychosis, virilization, or androgen insensitivity syndrome in said subject.

~~20~~21. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition is AR-expressing cancer in said subject.

~~21~~22. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition is amyotrophic lateral sclerosis (ALS), uterine fibroids. or abdominal aortic aneurysm (AAA) in said subject.

~~22~~23. The use ~~method~~ of claim ~~9~~10, wherein said androgen receptor dependent disease or condition is caused by polyglutamine (polyQ) AR polymorphs in a subject.

~~23~~24. Use of a compound of any one of claims 1-7, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, in the manufacture of a medicament for the treatment of a ~~A method of treating~~ prostate cancer (PCa) or increasing the survival of a male subject suffering from prostate cancer ~~comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-7, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof~~.

~~24~~25. Use of a compound of any one of claims 1-7, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, in the manufacture of a medicament for the reduction of ~~A method of reducing the~~ levels of AR-splice variants in a subject ~~comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-7, or its isomer, optical~~

~~isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof~~.