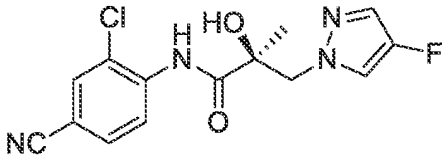
a wheelchair in some cases. The mutation results in a protracted polyglutamine tract added to the N-terminal domain of the androgen receptor (polyQ AR). Binding and activation of this lengthened polyQ AR by endogeneous androgens (testosterone and DHT) results in unfolding and nuclear translocation of the mutant androgen receptor. The androgen-induced toxicity and androgen- dependent nuclear accumulation of polyQ AR protein seems to be central to the pathogenesis. Therefore, the inhibition of the androgen-activated polyQ AR might be a therapeutic option (A. Baniahmad. Inhibition of the androgen receptor by antiandrogens in spinobulbar muscle atrophy. J. Mol. Neurosci.201658(3), 343-347). These steps are required for pathogenesis and result in partial loss of transactivation function (*i.e.*, an androgen insensitivity) and a poorly understood neuromuscular degeneration. Support of the use of antiandrogens comes in a report in which the antiandrogen flutamide protects male mice from androgen-dependent toxicity in three models of spinal bulbar muscular atrophy (Renier KJ, *et al.* Endocrinology 2014, 155(7), 2624-2634). Currently there are no disease-modifying treatments, but rather only symptom directed treatments. Efforts to target the polyQ AR of Kennedy's disease as the proximal mediator of toxicity by harnessing cellular machinery to promote its degradation, *i.e.*, through the use of a SARD, hold promise for therapeutic intervention. Selective androgen receptor degraders such as those reported herein bind to and degrade all androgen receptors tested (full length, splice variant, antiandrogen resistance mutants, etc.) so degradation of polyQ AR polymorphism is also expected, indicating that they are promising leads for treatment of SBMA.

[0023] Here selective androgen receptor degrader (SARD) compounds are described that may bind to the LBD and/or an alternate binding and degradation domain (BDD) located in the NTD, antagonize AR, and degrade AR thereby blocking ligand-dependent and ligand-independent AR activities. This novel mechanism produces improved efficacy when dosed systemically (*e.g.*, for prostate cancer) or topically (*e.g.*, dermatological diseases).

SUMMARY

[0024] One aspect of the disclosure encompasses a selective androgen receptor degrader (SARD) compound, or its isomer, optical isomer, or any mixture of optical isomers,



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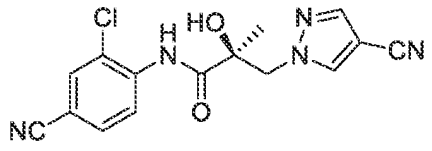

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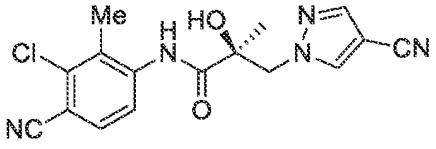

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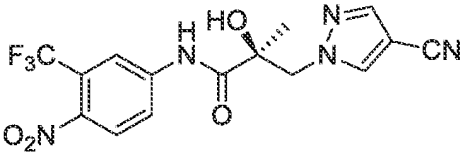

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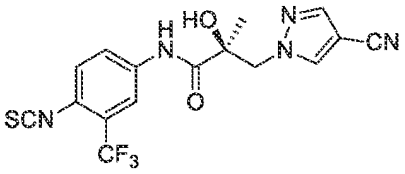

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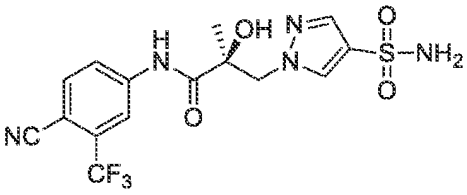

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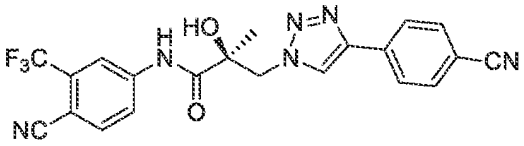

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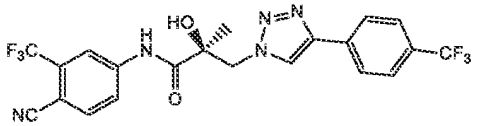

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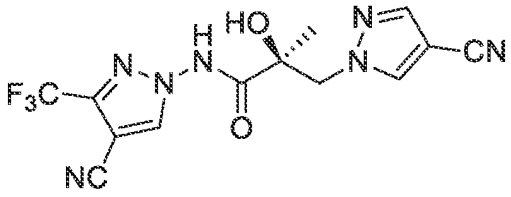


1094.

[0025] One example of the disclosure encompasses the SARD compound having at least one of the following properties: binding to the AR through an alternate binding domain in the NTD; binds to the AR through the AR ligand binding domain (LBD); exhibits AR-splice variant (AR-SV) degradation activity; exhibits AR-full length (AR-FL) degradation activity including pathogenic mutations thereof; exhibits AR-SV inhibitory activity (*i.e.*, is an AR-SV antagonist); exhibits AR- FL inhibitory activity (*i.e.*, is an AR-FL antagonist) including pathogenic mutations thereof; possesses dual AR-SV degradation and AR-SV inhibitory functions; dual AR-FL degradation and AR-FL inhibitory functions and/or AR antagonism in vivo of an AR target organ.

[0026] Another aspect of the disclosure encompasses pharmaceutical compositions comprising a SARD compound according to this disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, polymorph, hydrate or any combination thereof, and a pharmaceutically acceptable carrier. The pharmaceutical composition may be formulated for topical use. The topical pharmaceutical composition may be a solution, lotion, salve, cream, ointment, liposome, spray, gel, foam, roller stick, cleansing soap or bar, emulsion, mousse, aerosol, or shampoo. The pharmaceutical composition may be formulated for oral use.

[0027] In another example, the disclosure provides a method of treating an androgen receptor dependent disease or condition or an androgen 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 as described herein. In one example, an "androgen receptor dependent disease or condition" is a medical condition that is, in part or in full, dependent on, or is sensitive to, the presence of androgenic activity or activation of the AR-axis in the body. In one example, an androgen dependent disease or condition is used interchangeably with an androgen receptor dependent disease or condition.

[0028] In one example, the androgen receptor dependent disease or condition 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.

[0028a] In another aspect, the disclosure provides a SARD compound as defined herein, 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.

[0028b] In another aspect, the disclosure provides use of a SARD compound as defined herein, 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.

[0028c] In another aspect, the disclosure provides use of a SARD compound as defined herein, 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.

[0028d] In another aspect, the disclosure provides use of a SARD compound as defined herein, 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 darolutamide resistant prostate cancer in a subject.

[0028e] In another aspect, the disclosure provides use of a SARD compound as defined herein, 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 enzalutamide resistant prostate cancer in a subject.

[0028f] In another aspect, the disclosure provides use of a SARD compound as defined herein, 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 apalutamide resistant prostate cancer in a subject.

[0028g] In another aspect, the disclosure provides use of a SARD compound as defined herein, 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 abiraterone resistant prostate cancer.

[0029] The disclosure 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 defined by formulas 48-51, 53-58, 99A-99H, 120, 1072-1076, 1078-1080, and 1082-1094. 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 of the disclosure 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 example, the method may treat

enzalutamide resistant prostate cancer. In another example, the method may treat apalutamide resistant prostate cancer. In another example, the method may treat abiraterone resistant prostate cancer. In another example, the method may treat darolutamide resistant prostate cancer. Yet another example of the disclosure encompasses a method of treating prostate or other AR antagonist resistant cancer with a SARD compound of the disclosure 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.

[0030] In some examples, the prostate cancer is AR antagonist resistant prostate cancer which overexpresses the glucocorticoid receptor (GR). In some examples, activation of the GR provides support for growth of the prostate cancer and/or confers antiandrogen resistance to the prostate cancer. In some examples, SARDs of this disclosure can be used to treat GR-dependent or GR-overexpressing prostate cancers, whether antiandrogen resistant or not. In some examples, SARDs of this disclosure can be used to treat PR-dependent or PR-overexpressing prostate cancers, whether antiandrogen resistant or not. In some examples, activation of GR and/or PR leads to reactivation of the AR-axis, which is preventable or treatable by use of the SARDs of this disclosure.

[0031] Yet another example of the disclosure encompasses a method of treating prostate or other AR-expressing cancers using a SARD compound of the disclosure 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 example, the breast cancer is triple negative breast cancer (TNBC).

[0031a] In another aspect, the disclosure provides use of a SARD compound as defined herein, 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 triple negative breast cancer in a subject.

[0032] The 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 disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, polymorph, hydrate or any combination thereof. The method may comprise further reducing the levels of AR-full length in the subject.

[0032a] In another aspect, the disclosure provides use of a SARD compound as defined herein, 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.

[0033] Another example of the disclosure encompasses a method of treating Kennedy's disease in a subject comprising administering to the subject a compound of formulas 48-51, 53-58, 99A- 99H, 120, 1072-1076, 1078-1080, and 1082-1094.

[0034] Yet another example of the disclosure encompasses a method of: (a) treating acne in a subject, *e.g.*, acne vulgaris; (b) decreasing sebum production in a subject, *e.g.*, treats sehorrhea, seborrheic dermatitis, or acne; (c) treating hirsutism in a subject, *e.g.*, female facial hair; (d) treating alopecia in a subject, *e.g.*, androgenic alopecia, alopecia areata, alopecia secondary to chemotherapy, alopecia secondary to radiation therapy, alopecia induced by scarring, or alopecia induced by stress; (e) treating a hormonal condition in female, *e.g.*, precocious puberty, early 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; (f) treating sexual perversion, hypersexuality, or paraphilias in a subject; (g) treating androgen psychosis in a subject; (h) treating virilization in a subject; (i) treating complete or partial

androgen insensitivity syndrome in a subject; (j) increasing or modulating ovulation in an animal; (k) treating of cancer in a subject; or any combination thereof, by administering a compound of this disclosure or a pharmaceutical composition thereof.

[0035] One example of the disclosure encompasses methods of reducing the levels of polyglutamine (polyQ) AR polymorphs in a subject comprising administering a compound according to this disclosure. The method may inhibit, degrade, or both the function of the polyglutamine (polyQ) AR polymorphs (polyQ-AR). The polyQ-AR may be a short polyQ polymorph or a long polyQ polymorph. When the polyQ-AR is a short polyQ polymorph, the

method further treats dermal disease. When the polyQ-AR is a long polyQ polymorph, the method further treats Kennedy's disease.

[0036] Another example of the disclosure encompasses methods of treating amyotrophic lateral sclerosis (ALS) in a subject by administering a therapeutically effective amount of the compound of the disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, polymorph, hydrate or any combination thereof; or a pharmaceutical composition thereof.

[0037] Another example of the disclosure encompasses methods of treating abdominal aortic aneurysm (AAA) in a subject by administering a therapeutically effective amount of the compound of the disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, polymorph, hydrate or any combination thereof; or a pharmaceutical composition thereof.

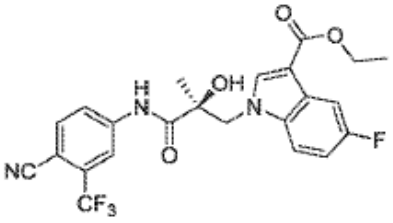
[0038] Yet another example of the disclosure encompasses methods of treating uterine fibroids in a subject by administering a therapeutically effective amount of the compound of this disclosure, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, polymorph, hydrate or any combination thereof; or a pharmaceutical composition thereof.

[0039] In yet another example, the disclosure provides a method of treating, suppressing, reducing the incidence, reducing the severity, or inhibiting the progression of a hormonal condition in a male in need thereof, comprising administering to the subject a therapeutically effective amount of a selective androgen receptor degrader (SARD) compound of the disclosure. In one example, the condition in the method of the disclosure is hypergonadism, hypersexuality, sexual dysfunction, gynecomastia, precocious puberty in a male, alterations in cognition and mood, depression, hair loss, hyperandrogenic dermatological disorders, precancerous lesions of the prostate, benign prostate hyperplasia, prostate cancer and/or other androgen-dependent cancers.

[0040] It will be appreciated that for simplicity and clarity of illustration, elements shown in the figures have not necessarily been drawn to scale. For example, the dimensions of some of the elements may be exaggerated relative to other elements for clarity. Further, where considered

WHAT IS CLAIMED IS:

1. A selective androgen receptor degrader (SARD) compound, or its isomer, optical isomer, or any mixture of optical isomers, pharmaceutically acceptable salt, pharmaceutical product, hydrate or any combination thereof, wherein said SARD compound is represented by a compound of the following structures:



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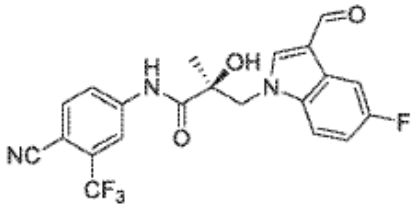

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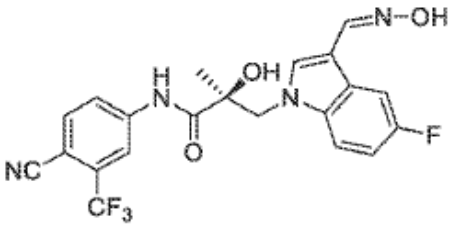

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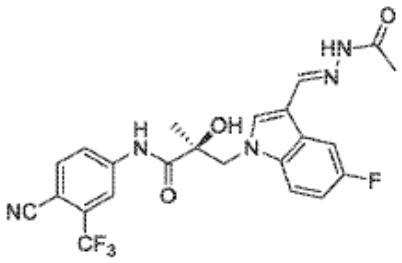

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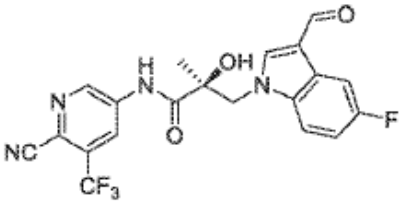

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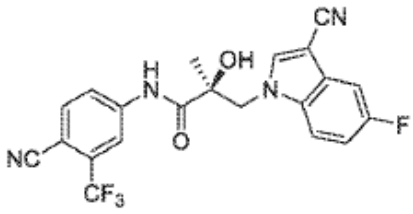

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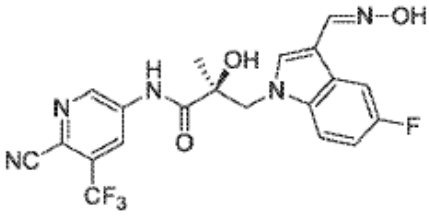

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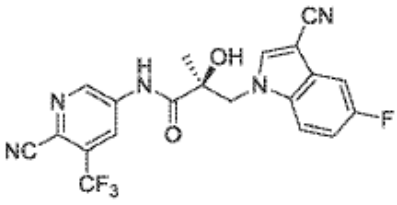

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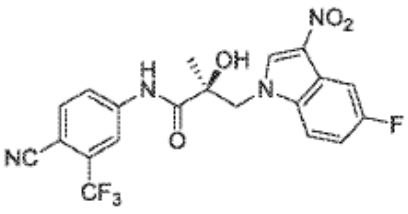

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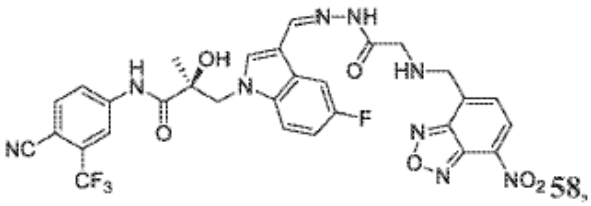

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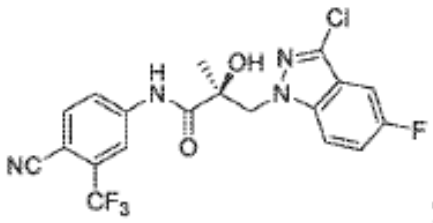

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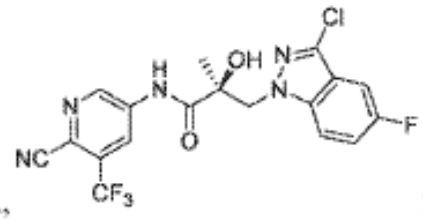

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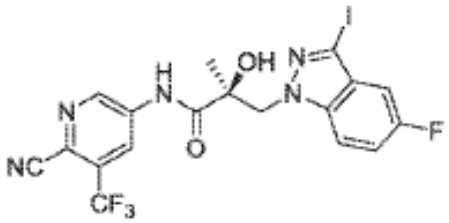

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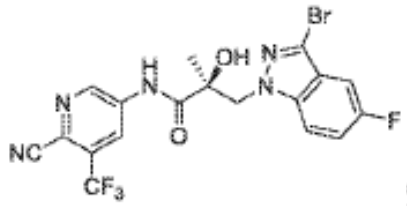

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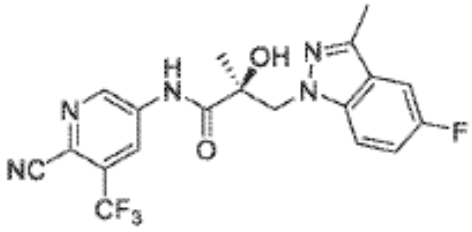

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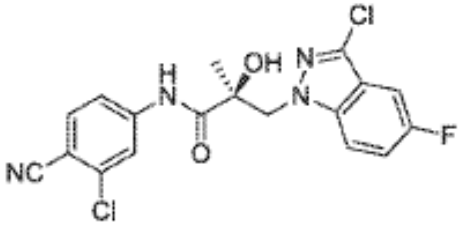

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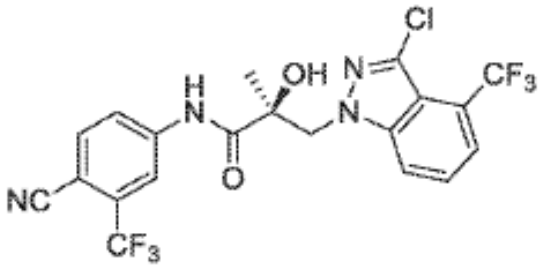

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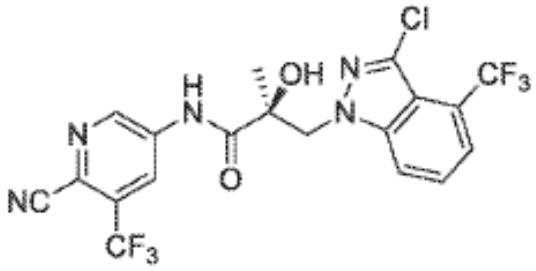

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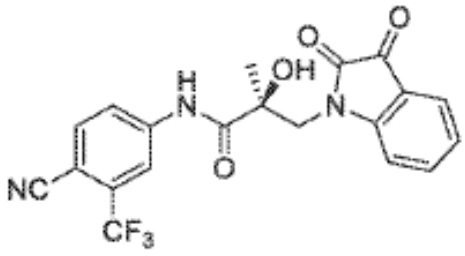

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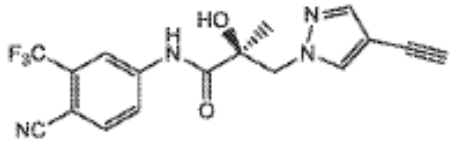

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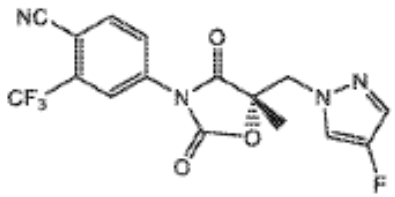

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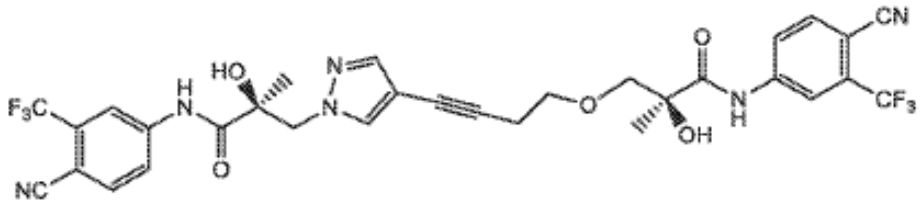

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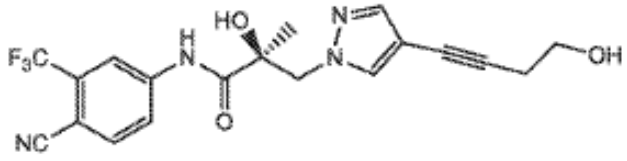

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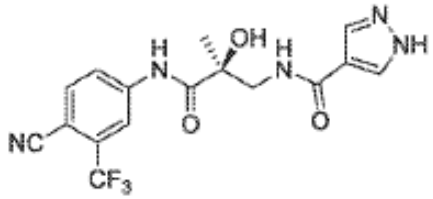

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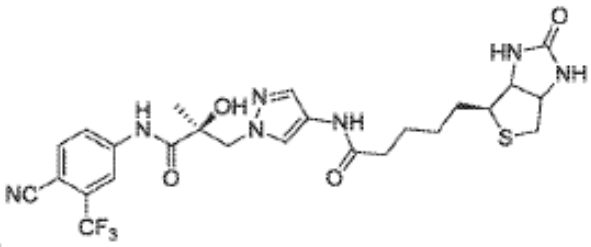

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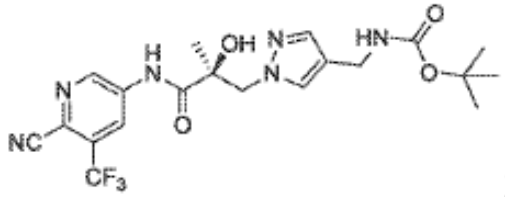

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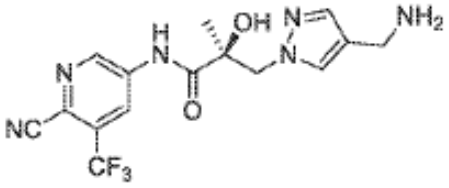

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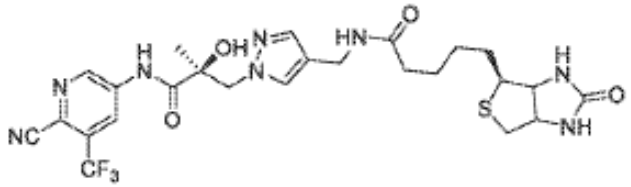

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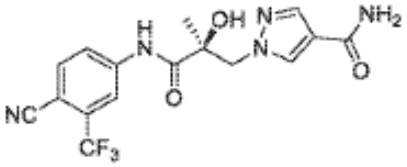

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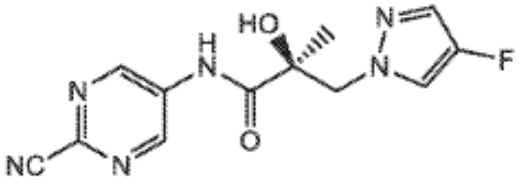

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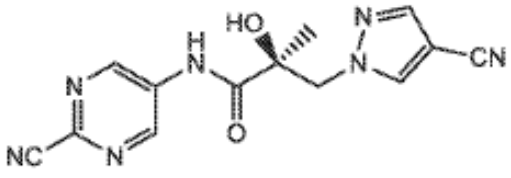

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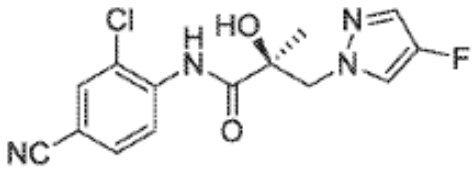

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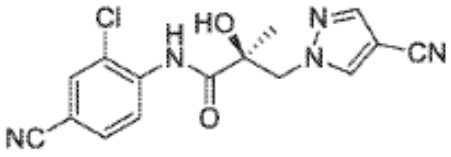

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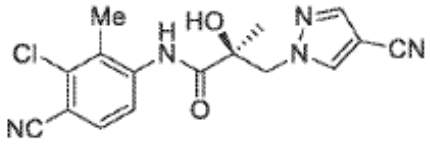

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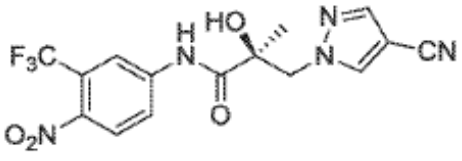

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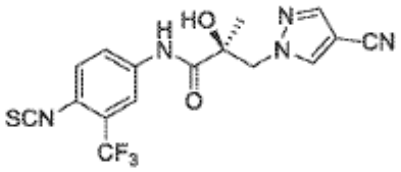

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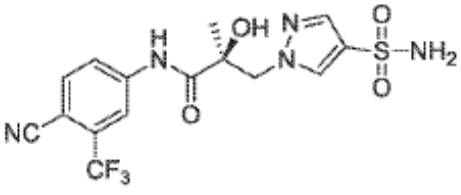

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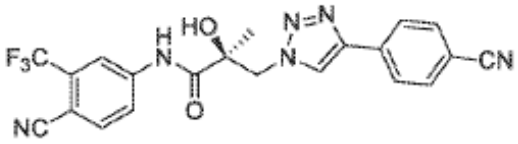

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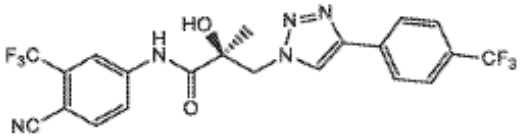

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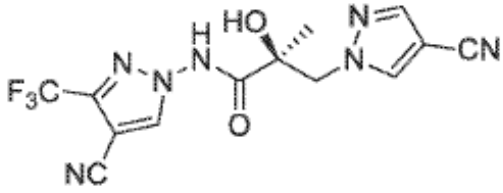

1094.

2. The compound according to claim 1, wherein the compound exhibits at least one of binding to the AR through an alternate binding domain in the NTD, AR-splice variant (AR-SV) degradation activity, full length (AR-FL) degradation activity, AR-SV inhibitory activity, AR-FL inhibitory activity, or AR antagonism *in vivo* of an AR target organ.

3. A pharmaceutical composition comprising a SARD compound according to claim 1, 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.

4. The pharmaceutical composition according to claim 3, wherein the composition is formulated for topical use.

5. The pharmaceutical composition according to claim 4, wherein 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.

6. The pharmaceutical composition according to claim 3, wherein the composition is formulated for oral use.

7. A SARD compound according to claim 1, 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.

8. Use of a SARD compound according to claim 1, 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.

9. The use of claim 8, 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.

10. The use of claim 8, wherein said androgen receptor dependent disease or condition is breast cancer in said subject.

11. The use of claim 10, wherein said subject has AR expressing breast cancer, AR-SV expressing breast cancer, and/or AR-V7 expressing breast cancer.

12. The use of claim 8, wherein said androgen receptor dependent disease or condition is Kennedy's disease in said subject.

13. The use of claim 8, wherein said androgen receptor dependent disease or condition is acne in said subject.

14. The use of claim 13, wherein said acne is acne vulgaris.

15. The use of claim 8, wherein said androgen receptor dependent disease or condition is overproduction of sebum in said subject.

16. The use of claim 15, wherein reducing said overproduction of sebum treats at least one of seborrhea seborrheic dermatitis or acne

17. The use of claim 8, wherein said androgen receptor dependent disease or condition is hirsutism or alopecia in said subject.

18. The use of claim 17, wherein said 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.

19. The use of claim 8, wherein said androgen receptor dependent disease or condition is a hormonal disease or condition in a female in said subject.

20. The use of claim 19, 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.

21. The use of claim 8, wherein said androgen receptor dependent disease or condition is hormonal disease or condition in a male in said subject.

22. The use of claim 21, 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.

23. The use of claim 8, wherein said androgen receptor dependent disease or condition is sexual perversion, hypersexuality, or paraphilias in said subject.

24. The use of claim 8, wherein said androgen receptor dependent disease or condition is androgen psychosis in said subject.

25. The use of claim 8, wherein said androgen receptor dependent disease or condition is virilization in said subject.

26. The use of claim 8, wherein said androgen receptor dependent disease or condition is androgen insensitivity syndrome in said subject.

27. The use of claim 8, wherein said androgen receptor dependent disease or condition is AR-expressing cancer in said subject.

28. The use of claim 27, wherein said 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.

29. The use of claim 8, wherein said androgen receptor dependent disease or condition is amyotrophic lateral sclerosis (ALS) in said subject.

30. The use of claim 8, wherein said androgen receptor dependent disease or condition is uterine fibroids in said subject.

31. The use of claim 8, wherein said androgen receptor dependent disease or condition is abdominal aortic aneurysm (AAA) in said subject.

32. The use of claim 8, wherein said androgen receptor dependent disease or condition is caused by polyglutamine (polyQ) AR polymorphs in a subject.

33. The use according to claim 32, wherein the polyQ-AR is a short polyQ polymorph or a long polyQ polymorph.

34. The use according to claim 33, wherein the polyQ-AR is a short polyQ polymorph and the use is further for treatment of a dermal disease.

35. The use according to claim 34, wherein the dermal disease is at least one of alopecia, seborrhea, seborrheic dermatitis, or acne.

36. The use according to 33 32, wherein the polyQ-AR is a long polyQ polymorph and the use is further for treatment of Kennedy's disease.

37. Use of a SARD compound according to claim 1, 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.

38. The use according to claim 37, wherein the prostate cancer is at least one of advanced prostate cancer, refractory prostate cancer, castration resistant prostate cancer (CRPC), metastatic CRPC (mCRPC), non-metastatic CRPC (nmCRPC), or high-risk nmCRPC.

39. The use according to claim 37, wherein further, androgen deprivation therapy (ADT) is to be administered.

40. The use according to claim 37, wherein the prostate cancer is resistant to treatment with an androgen receptor antagonist(s).

41. The use according to claim 40, wherein the androgen receptor antagonist is at least one of darolutamide, enzalutamide, apalutamide, bicalutamide, abiraterone, EPI-001, EPI-506, AZD-3514, galeterone, ASC-J9, flutamide, hydroxyflutamide, nilutamide, cyproterone acetate, ketoconazole, or spironolactone.

42. Use of a SARD compound according to claim 1, 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 darolutamide resistant prostate cancer in a subject.

43. Use of a SARD compound according to claim 1, 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 enzalutamide resistant prostate cancer in a subject.

44. Use of a SARD compound according to claim 1, 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 apalutamide resistant prostate cancer in a subject.

45. Use of a SARD compound according to claim 1, 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 abiraterone resistant prostate cancer.

46. Use of a SARD compound according to claim 1, 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 triple negative breast cancer in a subject.

47. Use of a SARD compound according to claim 1, 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.

48. The use according to claim 47, wherein the use further reduces the levels of AR-full length (AR-FL) in the subject.