overexpressing pathogenic states with sufficient potency to maintain suppression of the AR axis as PC becomes progressively more refractory to treatment.

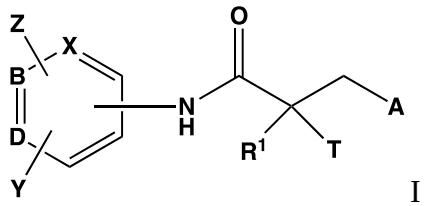
[007] Binding to a non-LBD site and degradation of the AR protein are promising preclinical approaches to rationally target CRPC. Degradation of AR can be achieved by genetic knockdown technologies, such as antisense oligonucleotides, RNA interference, and DNA editing. Despite genetic approaches having great therapeutic potential, it remains clinically challenging due to technical difficulties in delivering oligonucleotides (polyanionic macromolecules) to the prostate and metastatic tumors. Further, oligonucleotide uptake into the tumor cells is poor. Alternatively, targeted destruction of the AR by protein knockdown technologies which degrade AR via the ubiquitin proteasome system (UPS) remain promising options yet to be tested definitively in the clinical setting.

[008] In recent antitumor studies, the discovery and characterization of AR antagonists have been reported that selectively inhibit tumor growth and degrade the AR (full-length) and AR SVs (truncated) within these tumors (Ponnusamy, *et al. Cancer Res*. 2017, 77, 6282−6298). A series of aryl indol-1-yl propanamides and aryl indolin-1-yl propanamides has been reported as selective androgen receptor degraders (SARDs) (Hwang, *et al. J. Med. Chem*. 2019, 62, 491−511). These SARD activities were mediated through the UPS as determined by UPS inhibitor studies (Ponnusamy, *et al*. *Cancer Res*. 2017, 77, 6282−6298; Ponnusamy, *et al*. *Clin. Cancer Res*. 2019, 25, 6764−6780). The SARDs have been found to degrade AR and inhibit AR function and exhibit *in vitro* inhibitory potency in screening assays (*e.g.*, LBD binding, transcriptional inhibition, AR degradation, and antiproliferative assays) and greater *in vivo* efficacy (Hershberger assay and various AR-dependent CPRC xenografts) than the approved AR antagonists.

[009] Pyrazolylpropanamide compounds as described herein are selective androgen receptor degraders (SARDs) and pan-antagonists. These compounds exhibit potent AR antagonist activities, including promising distribution, metabolism, and pharmacokinetic properties, and broad-spectrum AR antagonist properties, including potent *in vivo* antitumor activity.

SUMMARY

[0010] The present disclosure provides a method of treating prostate cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound represented by the structure of formula I



I

wherein

T is OH;

R^1 is CH_3;

Y is H, CF_3, F, I, Br, Cl, or CN;

Z is H, NO_2, CN, halogen, COOR, COR, NHCOR, or CONHR;

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

X and D are each CH or N;

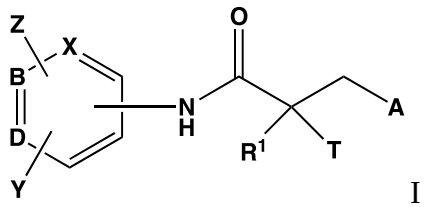
B is a bond or CH, and when B is a bond, D=B-X is represented by D-X;

R is H, alkyl, haloalkyl, alkyl-OH, aryl, F, Cl, Br, I, or OH;

A is a five-membered unsaturated 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 linear or branched alkyl, haloalkyl, CF_3, aryl, F, Cl, Br, I, CN, NO_2, OR, benzyl, alkynyl, $SO_2N(R)_2$, NHCOOR, $N(R)_2$, NHCOR, CONHR, COOR, or COR; wherein said alkyl, alkynyl, and aryl are each optionally substituted with halogen, CN, or OH,

or its optical isomer, pharmaceutically acceptable salt, hydrate or any combination thereof.

[0010a] In one aspect, the present disclosure provides use of a compound represented by the structure of formula I



I

wherein

T is OH;

R^1 is CH_3;

Y is H, CF_3, F, I, Br, Cl, or CN;

Z is H, NO_2, CN, halogen, COOR, COR, NHCOR, or CONHR;

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

X and D are each CH or N;

B is a bond or CH, and when B is a bond, D=B-X is represented by D-X;

R is H, alkyl, haloalkyl, alkyl-OH, aryl, F, Cl, Br, I, or OH;

A is a five-membered unsaturated heteroaryl having at least one nitrogen atom, optionally substituted with at least one of Q^1, Q^2, Q^3 and Q^4, each independently selected from linear or branched alkyl, haloalkyl, CF_3, aryl, F, Cl, Br, I, CN, NO_2, OR, benzyl, alkynyl, $SO_2N(R)_2$, NHCOOR, $N(R)_2$, NHCOR, CONHR, COOR, or COR; wherein said alkyl, alkynyl, and aryl are each optionally substituted with halogen, CN, or OH,

or its optical isomer, pharmaceutically acceptable salt, hydrate or any combination thereof,

in the manufacture of a medicament for the treatment of prostate cancer.

[0011] In some examples, the prostate cancer is advanced prostate cancer, refractory prostate cancer, AR overexpressing prostate cancer, castration-resistant prostate cancer, castration-sensitive prostate cancer, AR-V7 expressing prostate cancer, or d567ES expressing prostate cancer.

[0012] In some examples, the castration resistant prostate cancer (CRPC) is metastatic CRPC (mCRPC), non-metastatic CRPC (nmCRPC), or high-risk nmCRPC.

[0013] In some examples, the castration-resistant prostate cancer is AR overexpressing castration-resistant prostate cancer, F876L mutation expressing castration-resistant prostate cancer, F876L_T877A double mutation expressing castration-resistant prostate cancer, AR-V7 expressing castration-resistant prostate cancer, d567ES expressing castration-resistant prostate cancer, and/or castration-resistant prostate cancer characterized by intratumoral androgen synthesis.

[0014] In some examples, the castration-sensitive prostate cancer is F876L mutation expressing castration-sensitive prostate cancer, F876L_T877A double mutation castration-sensitive prostate cancer, and/or castration-sensitive prostate cancer characterized by intratumoral androgen synthesis. In some examples, the treating of castration-sensitive prostate cancer is conducted in a non-castrate setting, or as monotherapy, or when castration-sensitive prostate cancer tumor is resistance to enzalutamide, apalutamide, and/or abiraterone.

[0015] In some examples, the disclosure further comprises administering androgen deprivation therapy (ADT).

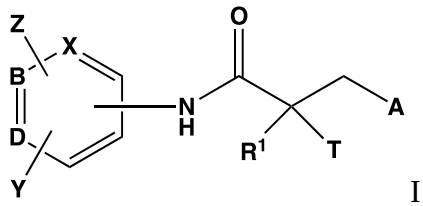
[0016] In some examples, the prostate cancer is resistant to treatment with an androgen receptor antagonist. In some examples, the androgen receptor antagonist is at least one of darolutamide, enzalutamide, apalutamide, bicalutamide, abiraterone, EPI-001, EPI-506, AZD-3514, galeterone, ASC-J9, flutamide, hydroxyflutamide, nilutamide, cyproterone acetate, ketoconazole, or spironolactone.

[0017] In some examples, the prostate cancer is darolutamide resistant prostate cancer, enzalutamide resistant prostate cancer, apalutamide resistant prostate cancer, or abiraterone resistant prostate cancer. In some examples, the prostate cancer is darolutamide resistant prostate cancer. In some examples, the prostate cancer is enzalutamide resistant prostate cancer. In other examples, the prostate cancer is apalutamide resistant prostate cancer. In some examples, the prostate cancer is abiraterone resistant prostate cancer.

[0018] 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. Use of a compound represented by the structure of formula I



I

wherein

T is OH;

R^1 is CH_3;

Y is H, CF_3, F, I, Br, Cl, or CN;

Z is H, NO_2, CN, halogen, COOR, COR, NHCOR, or CONHR;

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

X and D are each CH or N;

B is a bond or CH, and when B is a bond, D=B-X is represented by D-X;

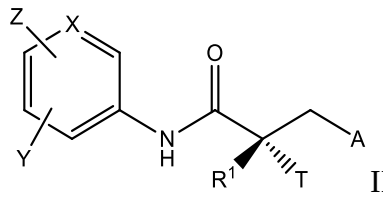
R is H, alkyl, haloalkyl, alkyl-OH, aryl, F, Cl, Br, I, or OH;

A is a five-membered unsaturated heteroaryl having at least one nitrogen atom, optionally substituted with at least one of Q^1, Q^2, Q^3 and Q^4, each independently selected from linear or branched alkyl, haloalkyl, CF_3, aryl, F, Cl, Br, I, CN, NO_2, OR, benzyl, alkynyl, $SO_2N(R)_2$, NHCOOR, $N(R)_2$, NHCOR, CONHR, COOR, or COR; wherein said alkyl, alkynyl, and aryl are each optionally substituted with halogen, CN, or OH,

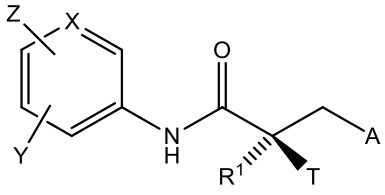
or its optical isomer, pharmaceutically acceptable salt, hydrate or any combination thereof,

in the manufacture of a medicament for the treatment of prostate cancer.

2. The use according to claim 1, wherein said compound is represented by a compound of formula IIA or formula IIB:

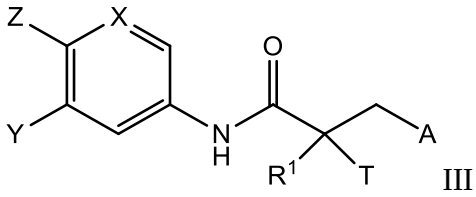


IIA



IIB.

3. The use according to claim 1, wherein said compound is represented by a compound of formula III:



III

wherein

T is OH;

R^1 is CH_3;

Y is H, CF_3, F, I, Br, Cl, or CN;

Z is H, NO_2, CN, halogen, COOR, COR, NHCOR, or CONHR;

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

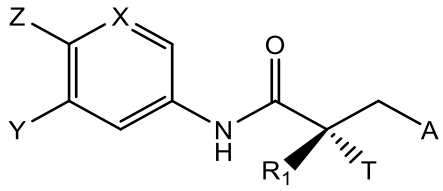
X is CH or N;

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

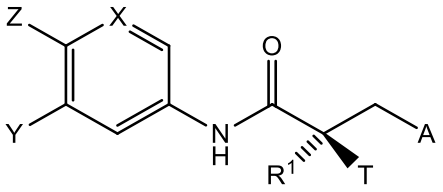
A is a pyrrole, pyrazole, triazole, or imidazole, each optionally substituted with at least one of Q^1, Q^2, Q^3 and Q^4, each independently selected from linear or branched alkyl, haloalkyl, CF_3, aryl, F, Cl, Br, I, CN, NO_2, OR, benzyl, alkynyl, $SO_2N(R)_2$, NHCOOR, $N(R)_2$, NHCOR, CONHR, COOR, or COR; wherein said alkyl, alkynyl, and aryl are each optionally substituted with halogen, CN, or OH,

or its optical isomer, pharmaceutically acceptable salt, hydrate or any combination thereof.

4. The use according to claim 3, wherein said compound is represented by the structure of formula IIIA or formula IIIB:

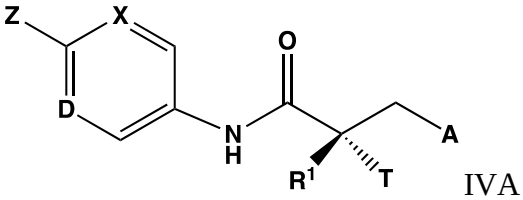


IIIA

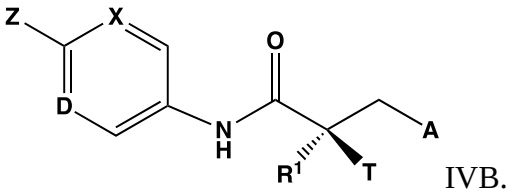


IIIB.

5. The use according to claim 1, wherein said compound is represented by the structure of formula IVA or formula IVB:

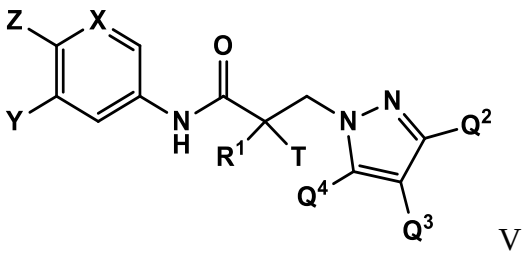


IVA



IVB.

6. The use according to claim 1, wherein said compound is represented by the structure of formula V:



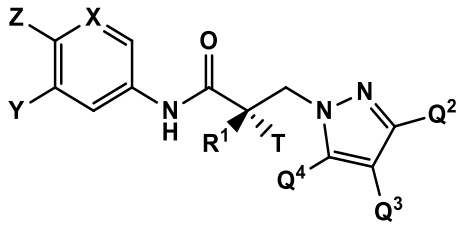
V

wherein

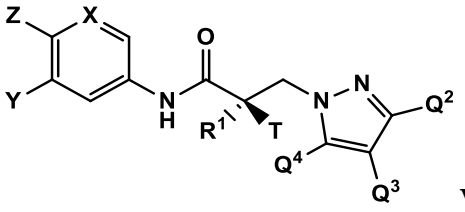
Q^2, Q^3 and Q^4 are each independently selected from linear or branched alkyl, haloalkyl, CF_3, aryl, F, Cl, Br, I, CN, NO_2, OR, benzyl, alkynyl, $SO_2N(R)_2$, NHCOOR, $N(R)_2$, NHCOR, CONHR, COOR, or COR; wherein said alkyl, alkynyl, and aryl are each optionally substituted with halogen, CN, or OH,

or its optical isomer, pharmaceutically acceptable salt, hydrate or any combination thereof.

7. The use according to claim 6, wherein said compound is represented by the structure of formula VA or formula VB:



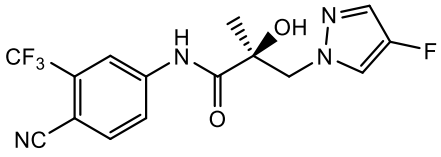
VA



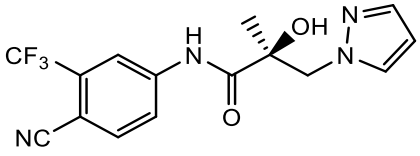
VB.

8. The use according to claim 1, wherein Q^1, Q^2, Q^3 and Q^4 is CN, NO_2, CF_3, F, Cl, Br, I, alkynyl, $SO_2N(R)_2$, NHCOOR, $N(R)_2$, NHCOR, COR, or phenyl, wherein said phenyl is optionally substituted with halogen, CN, or OH.

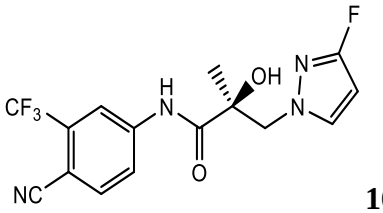
9. The use according to claim 1, wherein said compound is represented by any one of the following compounds:



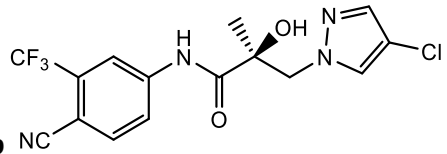
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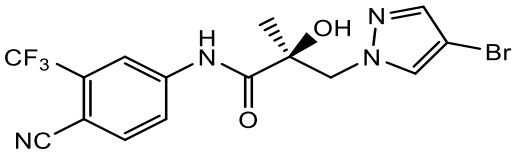
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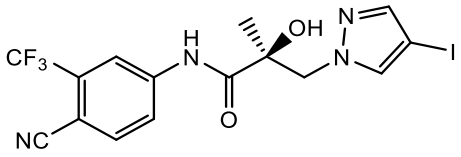
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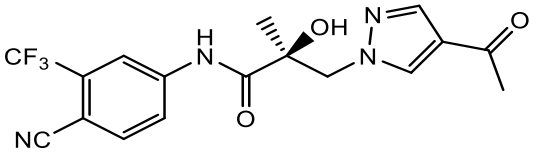
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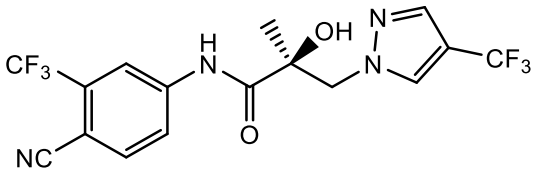
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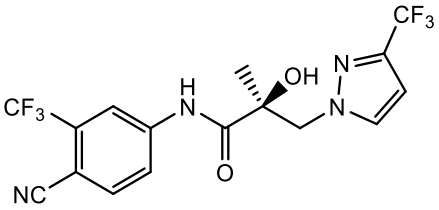
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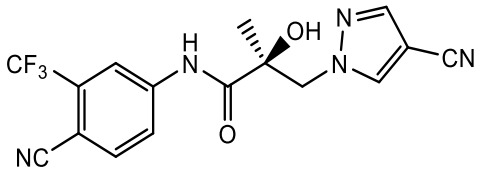
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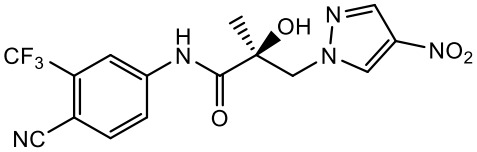
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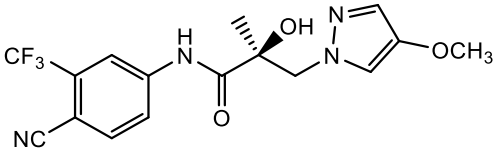
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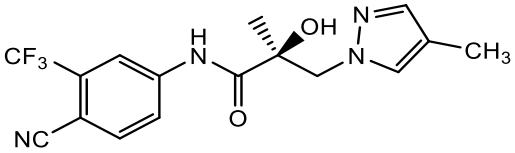
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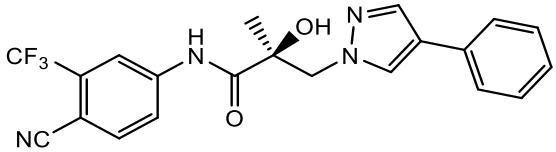
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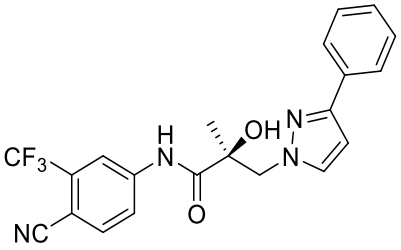
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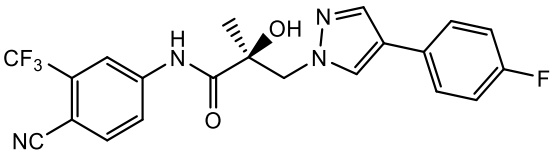
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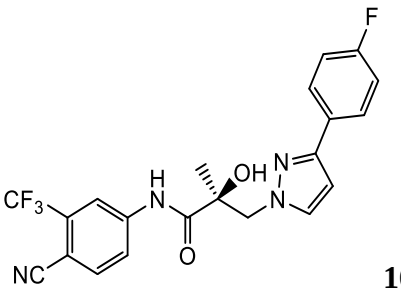
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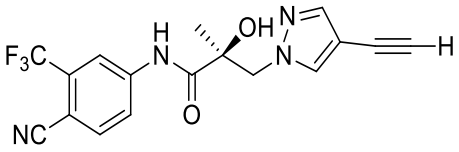
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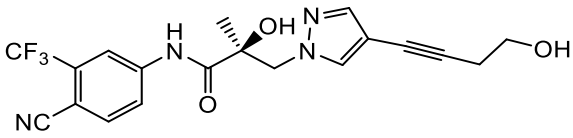
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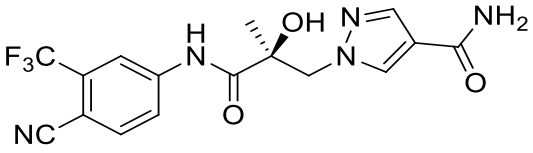
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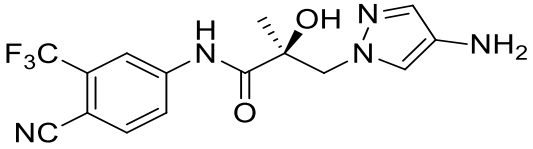
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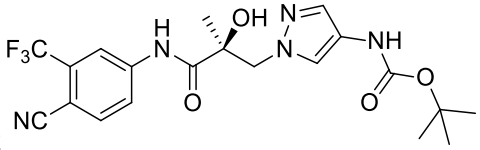
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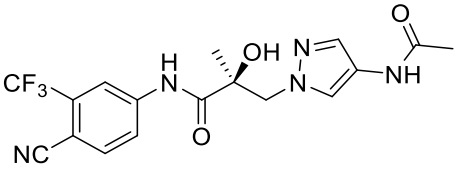
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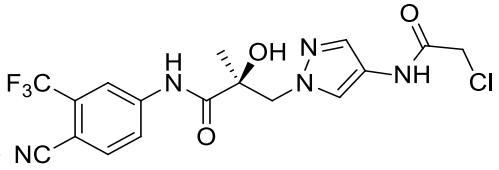
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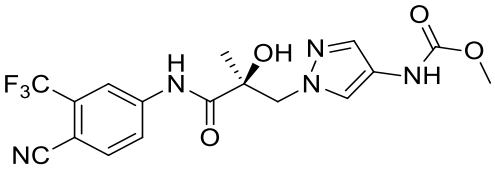
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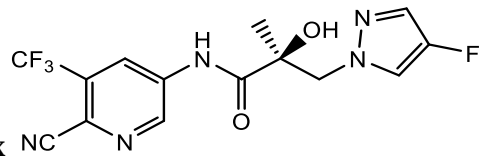
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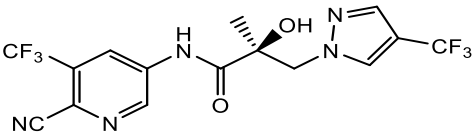
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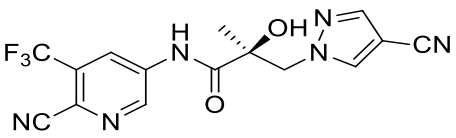
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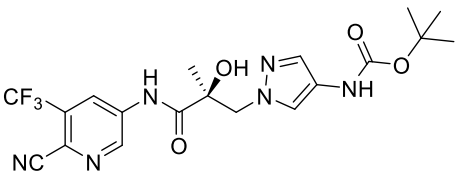
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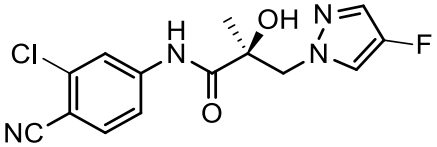
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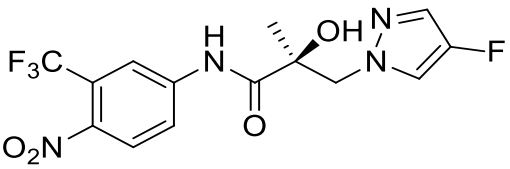
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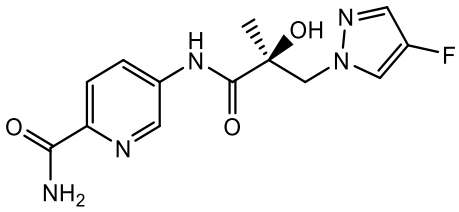
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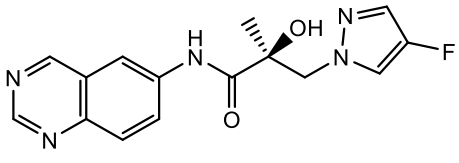
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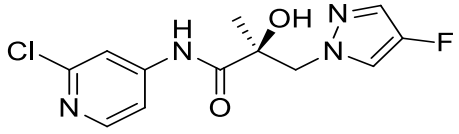
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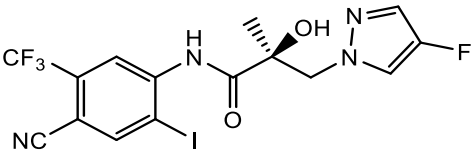
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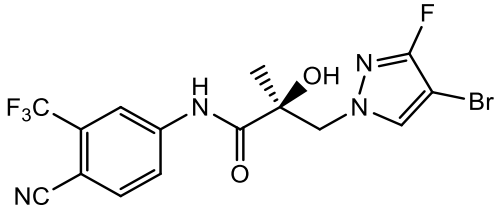
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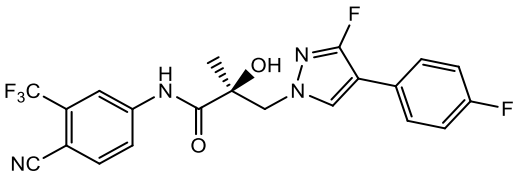
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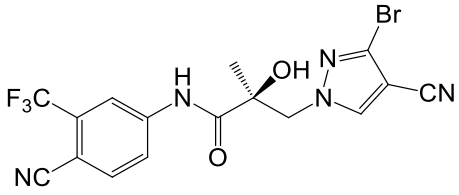
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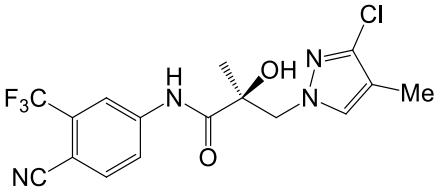
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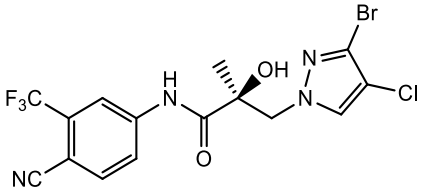
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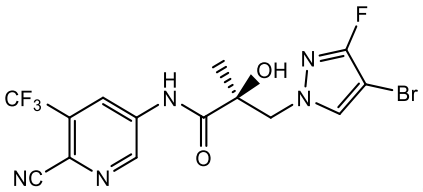
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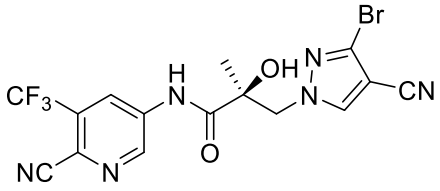
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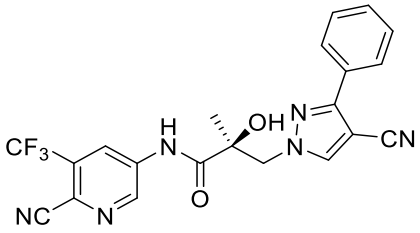
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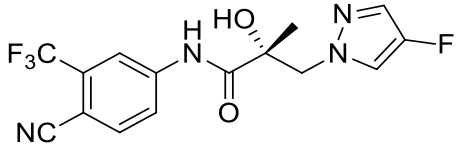
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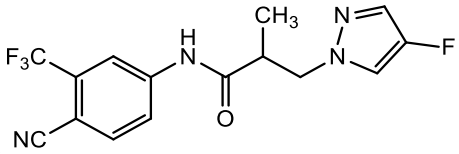
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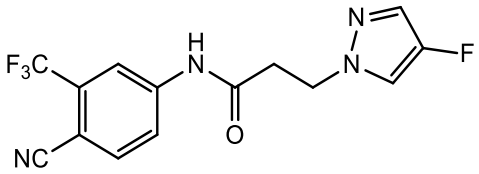
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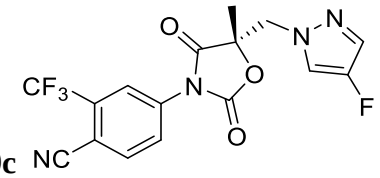
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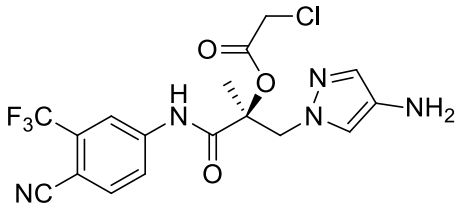
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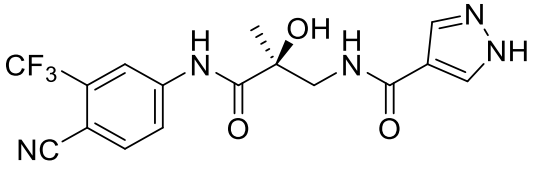
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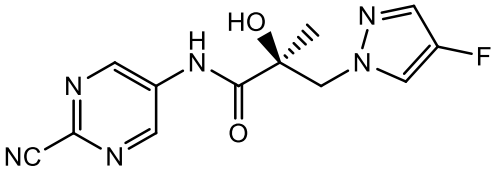
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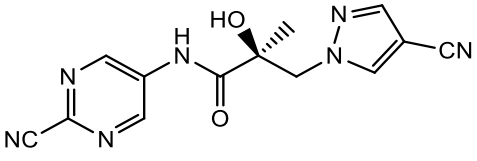
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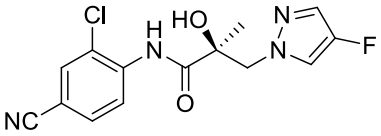
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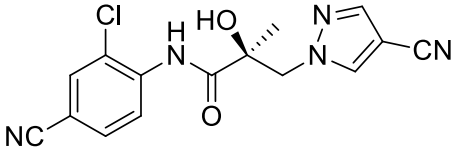
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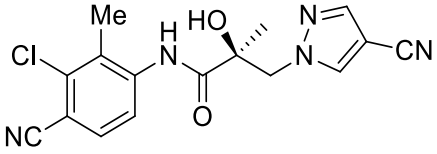
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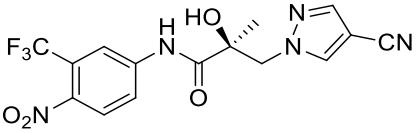
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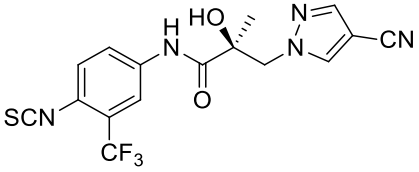
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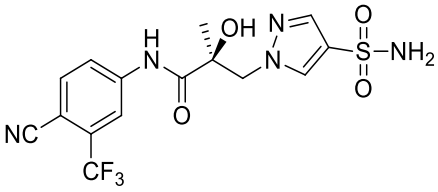
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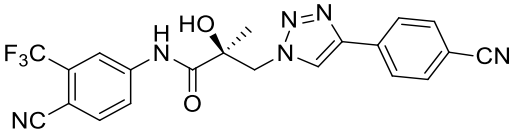
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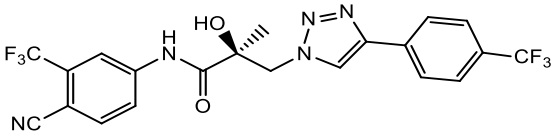
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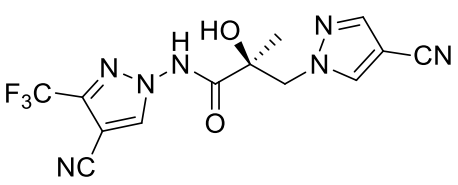
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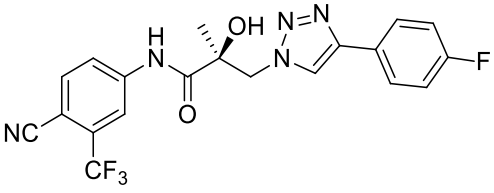
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29p

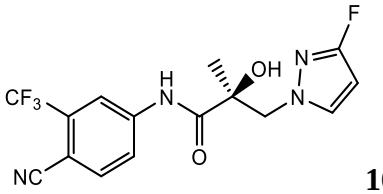
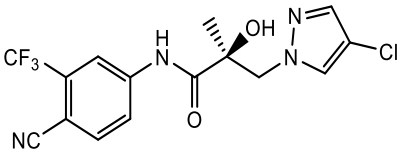
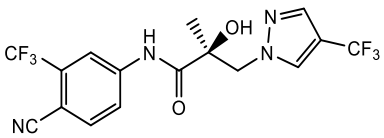
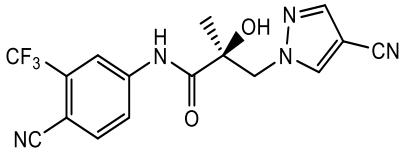
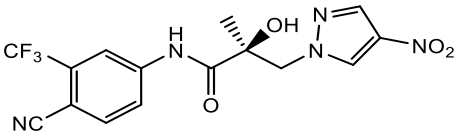


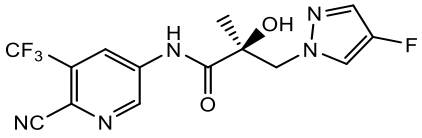
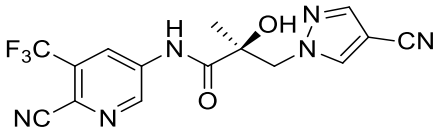
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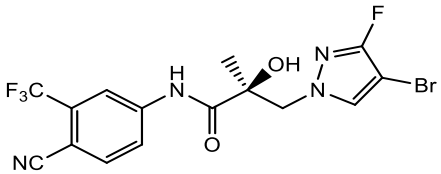
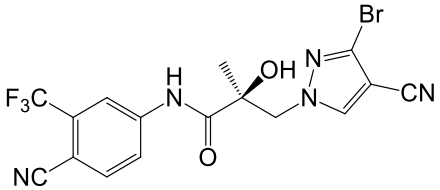
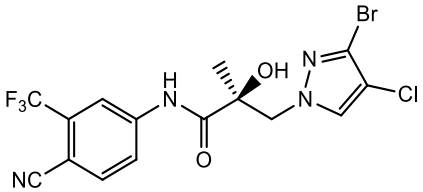
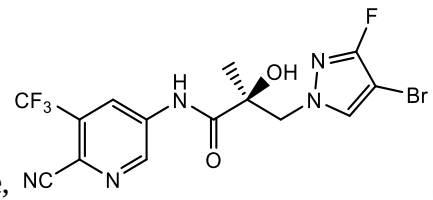
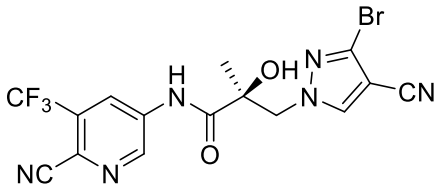


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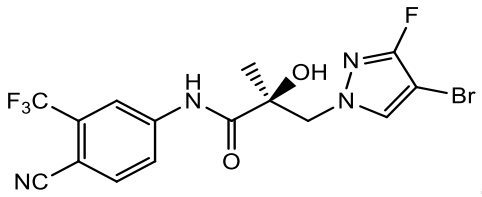
10. The use according to claim 1, wherein said compound is represented by any one of the following compounds


16b,

16c,

16g,

16i, and

16j.


21a or

21c.


26a,

26c,

26e,

26f, and

26g.

11. The use according to claim 1, wherein said compound is represented by compound 26a



26a.

12. The use according to claim 1, wherein said prostate cancer is advanced prostate cancer, refractory prostate cancer, AR overexpressing prostate cancer, castration-resistant prostate cancer, castration-sensitive prostate cancer, AR-V7 expressing prostate cancer, or d567ES expressing prostate cancer.

13. The use according to claim 12, wherein said castration-resistant prostate cancer is AR overexpressing castration-resistant prostate cancer, F876L mutation expressing castration-resistant prostate cancer, F876L_T877A double mutation expressing castration-resistant prostate cancer, AR-V7 expressing castration-resistant prostate cancer, d567ES expressing castration-resistant prostate cancer, and/or castration-resistant prostate cancer characterized by intratumoral androgen synthesis.

14. The use according to claim 12, wherein said castration-sensitive prostate cancer is F876L mutation expressing castration-sensitive prostate cancer, F876L_T877A double mutation castration-sensitive prostate cancer, and/or castration-sensitive prostate cancer characterized by intratumoral androgen synthesis.

15. The use according to claim 12, wherein said treatment of castration-sensitive prostate cancer is to be conducted in a non-castrate setting, or as monotherapy, or when castration-sensitive prostate cancer tumor is resistance to enzalutamide, apalutamide, and/or abiraterone.

16. The use according to claim 12, wherein the castration resistant prostate cancer (CRPC) is metastatic CRPC (mCRPC), non-metastatic CRPC (nmCRPC), or high-risk nmCRPC.

17. The use according to claim 1, wherein an androgen deprivation therapy (ADT) is to be further administered.

18. The use according to claim 1, wherein the prostate cancer is resistant to treatment with an androgen receptor antagonist.

19. The use according to claim 18, 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.

20. The use according to claim 1, wherein said prostate cancer is darolutamide resistant prostate cancer, enzalutamide resistant prostate cancer, apalutamide resistant prostate cancer, or abiraterone resistant prostate cancer.

21. The use according to claim 1, wherein said prostate cancer is darolutamide resistant prostate cancer.

22. The use according to claim 1, wherein said prostate cancer is enzalutamide resistant prostate cancer.

23. The use according to claim 1, wherein said prostate cancer is apalutamide resistant prostate cancer.

24. The use according to claim 1, wherein said prostate cancer is abiraterone resistant prostate cancer.