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Perspective

Therapeutic Strategies to Target the Androgen Receptor

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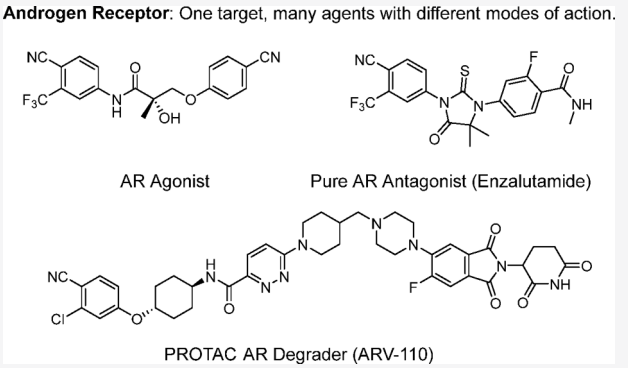
ABSTRACT: The androgen receptor (AR) plays a key role in the maintenance of muscle and bone and the support of male sexual-related functions, as well as in the progression of prostate cancer. Accordingly, AR-targeted therapies have been developed for the treatment of related human diseases and conditions. AR agonists are an important class of drugs in the treatment of bone loss and muscle atrophy. AR antagonists have also been developed for the treatment of prostate cancer, including metastatic castration-resistant prostate cancer (mCRPC). Additionally, selective AR degraders (SARDs) have been reported. More recently, heterobifunctional degrader molecules of AR have been developed, and four such compounds are now in clinical development for the treatment of human prostate cancer. This review attempts to summarize the different types of compounds designed to target AR and the current frontiers of research on this important therapeutic target.



1. INTRODUCTION

The androgen receptor (AR) is a transcriptional factor that is essential for the growth, survival, and proliferation of cells.[1] Testosterone and its more active metabolite, 5α-androstan-17β-ol-3-one, or dihydrotestosterone (DHT), are endogenous androgens.[2] Androgens and AR signaling are essential in the male sexual system, for secondary sexual characteristics, and for muscle and skeleton development and maintenance in both males and females.[3−6] Androgen deficiency leads to decreasing libido and dysfunction in males, which causes loss of muscle mass and strength and a depressed mood. AR agonists are therefore useful in treating age- and disease-related androgen deficiency, muscle atrophy, and bone loss.

AR signaling is important in prostate development and homeostasis,[7] and AR proteins are necessary for the function, survival, and differentiation of prostatic tissue in the normal prostate.[8,9] However, the functions of ARs and their signaling can switch during prostate carcinogenesis from tumor suppressive to tumor promotional.[8,10,11] Androgens and ARs also play a critical role in the initiation and progression of prostate cancer and a subset of breast cancer.[12,13] Androgen deprivation therapy (ADT), achieved either by surgical castration or with drugs that block androgen synthesis, has proved to be effective in the treatment of androgen-dependent advanced and metastatic prostate cancer, which is also termed androgen-dependent prostate cancer.[14,15] Unfortunately, the therapeutic efficacy of castration is not long-lasting, and after a few years of treatment, prostate cancer progresses into what is termed castration-resistant prostate cancer (CRPC).[16] However, AR signaling continues to play an important role in CRPC, and blocking AR signaling is therefore a useful therapeutic strategy in the treatment of CRPC.[17]

The current clinical paradigm for the treatment of prostate cancer, even in the castration-resistant state, is focused on blocking AR signaling. Potent AR-directed therapies, such as the second generation, pure AR-antagonist enzalutamide, can effectively block AR signaling. However, resistances to AR-directed therapies rapidly develop in the clinic. AR gene amplification, activating mutations of the AR receptor on the AR ligand-binding domain (LBD), and splice variants (ARVs)—particularly the constitutively active AR-variants that lack the LBD[12,13,18−24]—are some of the important resistance mechanisms to AR-directed therapies.

AR exerts its function in both androgen-dependent and androgen-independent mechanisms (Figure 1).[25,26] In the androgen-dependent pathway, androgen binding to AR causes conformational changes in the AR to make AR dissociate from heat shock proteins (HSP), followed by the recruitment of coregulators and subsequent dimerization and translocation into the nucleus to bind to targeted DNAs for gene transcription. In the androgen-independent AR pathway, AR and AR variants (ARV) can dimerize without initiation by an androgen. In the latter scenario, AR can be activated in the absence of androgens

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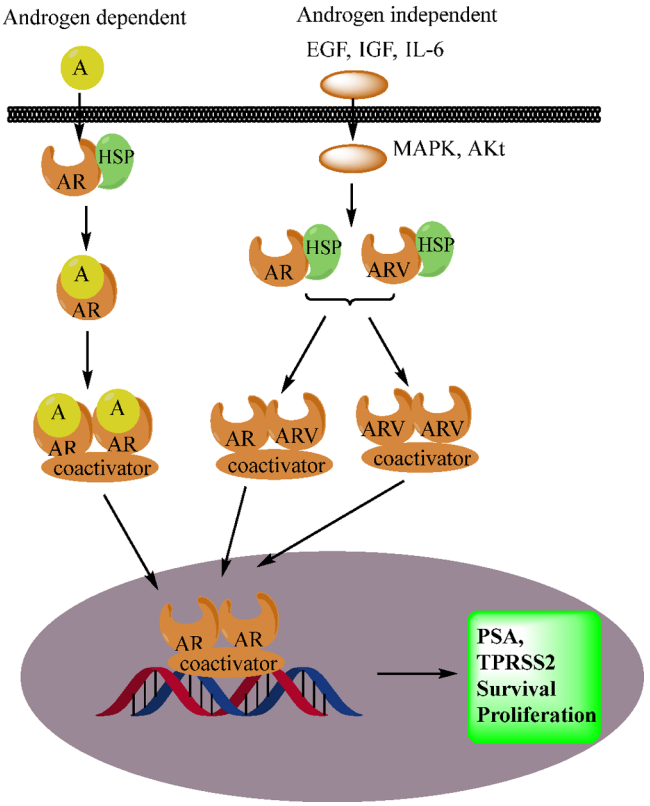

Figure 1. Androgen-dependent and -independent gene expression pathways. A, androgen; AR, androgen receptor; HSP, heat shock protein; ARV, androgen receptor variant.

by epidermal growth factor (EGF), insulin-like growth factor (IGF), and interleukin-6 (IL-6) signaling pathways via phosphorylation, which leads to increased nuclear translocation and gene transcription.[27]

AR exists in different forms: full-length AR (FLAR), AR variants (ARV), and mutant forms (Figure 2).[28−31] Full-length

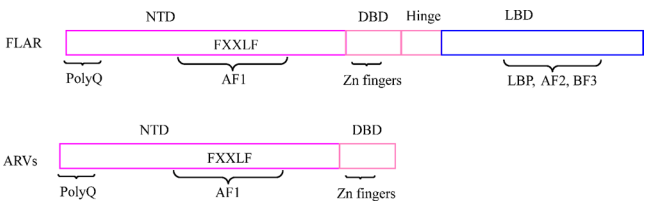

Figure 2. Illustration of structures of FLAR and ARVs. NTD, N-terminal domain; DBD, DNA-binding domain; LBD, ligand-binding domain; PolyQ, poly glutamines; AF1, activation function 1; LBP, ligand-binding pocket; AF2, activation function 2; BF3, binding function 3.

AR is a 110 kDa 919-amino acid protein that consists of an N-terminal transcriptional domain (NTD), a C-terminal ligand-binding domain (LBD), and a DNA-binding domain (DBD) that links the N- and C-terminal domains through a hinge region. The N-terminal domain is capped by polyglutamines and polyglycines. The average number of polyglutamines is 21, and they comprise a region that is responsible for the interaction with AR coregulators. The NTD contains a transcriptional activation function 1 (AF1), and FXXLF is the signature motif of AF1. This FXXLF motif interacts with the LBD upon androgen binding to AR, known as an N/C interaction. DBD binds to an androgen response element (ARE) during gene transcription and has two zinc fingers that are attached to the hinge region. The LBD includes a ligand-binding pocket (LBP), a transcriptional activation function 2 (AF2) domain, and a binding function 3 (BF3) domain. ARVs, lacking a LBD at the C-terminal, are alternative spliced ARs.[32] More than 20 ARVs have been identified in human prostate cancers, including in cell lines and clinical specimens. Indeed, overexpression of ARV7 has been found in enzalutamide-resistant mCRPC patients. Among numerous mutations of AR (http://androgendb.mcgill.ca), F877L, T878A, H875Y, and W742L/C point mutants have been associated with resistance to the prostate cancer drugs abiraterone, bicalutamide, enzalutamide, and apalutamide.[33−36]

2. AR DRUGGABLE POCKETS

AR contains a number of potential druggable pockets within different domains. The ligand-binding domain (LBD) contains the well-known internal ligand-binding pocket (LBP).[37,38] The AF1 (activation function 1), AF2 (activation function 2),[39,40] DBD (DNA-binding domain),[41,42] and BF3 (the binding function 3)[43] each contain a potentially druggable pocket. A number of cocrystal structures revealing these pockets, with the exception of AF1, have been determined.

The LBP pocket is formed by 5 helices (H3, H5, H10, H11, and H12). Agonists and antagonists compete with testosterone or DHT for binding to the LBP pocket (Figure 3A,B). Agonists and antagonists induce different conformational changes in AR, which leads to different poses of the H12 helix. Molecular dynamics simulations of AR with agonists and antagonists have been performed on the basis of the estrogen receptor,[44] but precise experimental details of these conformational changes for the H12 helix remain to be determined.

The AF1 domain consists of residues 142−485 of the N-terminal transactivation domain (NTD),[47] and its crystal structure remains to be solved. The AF2 domain contains an androgen-dependent activation site, located near the LBP pocket on the LBD (Figure 3A).[48] After androgen binds to LBP on AR, the H12 folds back to enclose the LBP and create a surface pocket formed by helices H3, H4, and H12, which together comprise the AF2 pocket. BF3 (Figure 3B) contains an allosteric site located on LBD in the vicinity of, but distinct from, the LBP and AF2 pockets.[49] Small molecule binding to the BF3 site leads to conformational change in AR, which renders it inaccessible to AR coactivators. The interface between DBD and DNA generates another pocket (Figure 3C).[50] Compared with estrogen receptor (ER), progesterone receptor (PR), and other nuclear receptors, AR DBD has two unique amino acids Q592 and Y594 that may provide an opportunity to design AR DBD-selective inhibitors.[46]

Several mechanisms of action of small molecules targeting AR have been established. All agonists and most antagonists discovered to date bind to the LBP, initiating or disrupting gene transcription process. Compounds binding to the AF1 site can be either inhibitors or selective AR degraders (SARD), but their precise mechanisms of action remain to be established.[51,52] Compounds, which bind to the AF2, BF3, and DBD pockets, can inhibit AR gene transcription, thus functioning as antagonists.[53] More recently, heterobifunctional small-molecules based upon the proteolysis-targeting chimera (PROTAC) technology have been designed to induce the degradation of AR.[54] This review summarizes and analyzes different therapeutic approaches targeting AR, including AR agonists, antagonists, SARDs, and PROTACs.

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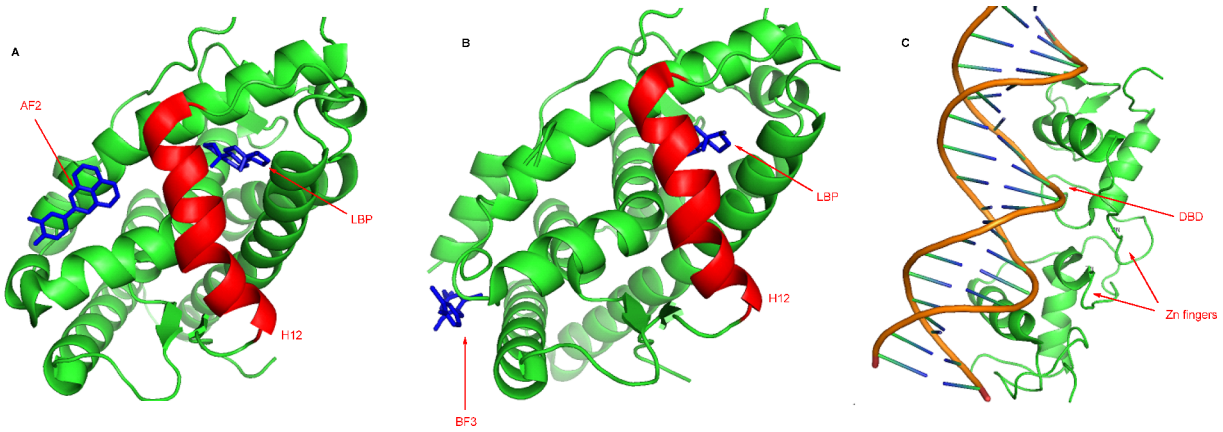

Figure 3. (A) Binding pocket of LBP and AF2 (PDB ID: 2YHD). H12 is illustrated in the agonist position (red). (B) Binding pocket of LBP and BF3 (PDB ID: 2PKL). H12 is illustrated in the agonist position (red). (C) Interaction of DBD with DNA (PDB ID: 1R4I). The vicinity of the DBD pocket and Zn fingers are illustrated in red. Panel A generated from Axerio-Celies et al.[45] Panel B generated from Estébanez-Perpiñá et al.[43] Panel C generated from Shaffer et al.[46]

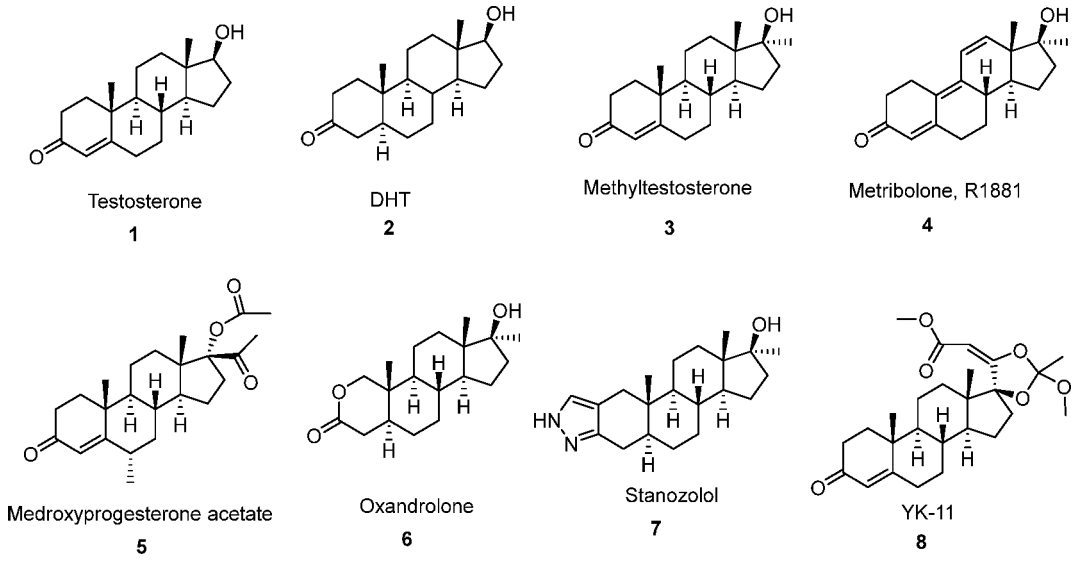

Figure 4. Structures of testosterone, dihydrotestosterone (DHT), and synthetic AR agonists.

3. AR AGONISTS

3.1. Steroid-Based AR Agonists. Testosterone was isolated and synthesized in 1935.[55] It has a K_d value of 0.4−1.0 nM to human AR (hAR), and DHT has a higher affinity with a K_d value of 0.25−0.5 nM (Figure 4). With its EC_{50} of 0.1−0.2 nM, dihydrotestosterone (DHT) is approximately 10 times more potent than testosterone in the activation of AR.[56,57] Testosterone and DHT have short half-lives of 50 and 30 min, respectively.[58] Testosterone is metabolized by aromatases into estrogens, and DHT is metabolized by 3α-hydroxysteroid dehydrogenase reduction within the cells of androgen sensitive tissues.[58] Both testosterone and DHT are quickly metabolized in the GI tract,[58,59] and consequently, they are not useful as oral drugs.

Introduction of a 17α-methyl into a steroid prevents the oxidation of the hydroxyl group at C17 and greatly increases the metabolic stability and bioavailability of the compound (Figure 4).[60] Methyl testosterone (**3**) has a half-life of approximately 3 h, significantly longer than that of testosterone, but its affinity is 4 times lower than that of testosterone.[61] Metribolone (R1881, **4**), also with a 17α-methyl substituent, has a 1.5−2 times greater affinity for AR than DHT.[62] However, metribolone leads to severe liver toxicity in animals and has not been used clinically. Medroxyprogesterone acetate (MPA, **5**) is a full AR agonist with a K_d value of 1 nM, but it is a pan-nuclear hormone agonist for PR and GR, among others.[63] Although it is a potent AR agonist, MPA is used as a birth control agent, and its activity is primarily related to its PR agonist effect. Oxandrolone (**6**) is an anabolic-selective AR agonist that has approximately 10 times greater selectivity for anabolic AR than androgenic AR. Oxandrolone has a K_i value of 62 nM against AR.[64] Stanozolol (**7**), with a pyrazoline moiety has greater solubility and a binding affinity similar to that of testosterone[65] but no selectivity for anabolic AR over androgenic AR. YK-11 (**8**) is an anabolic-selective AR agonist that activates AR without an N/C interaction and induces C2C12 myoblast cell division more significantly than DHT.[66,67]

All these steroid AR agonists have common side effects, including acne, abnormal hair growth, increased sexual desire, and liver damage. Most of them were used as performance-enhancing drugs and are therefore controlled substances.

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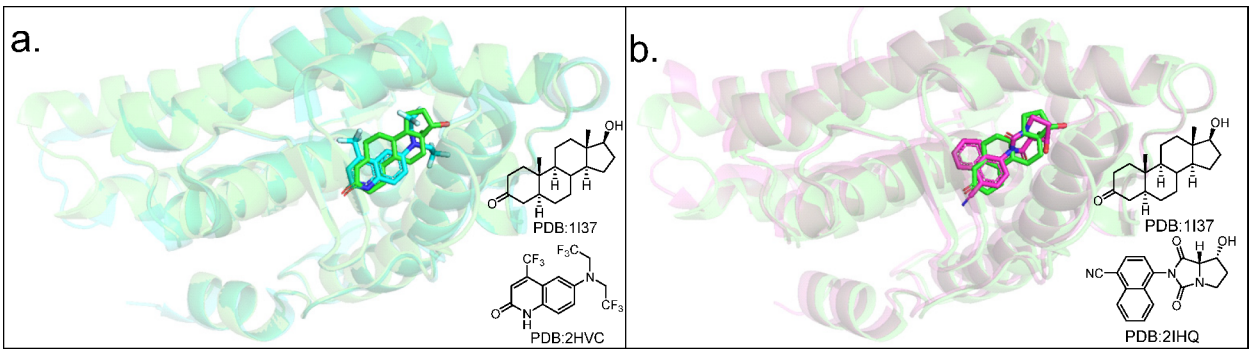

Figure 5. Alignment of DHT with nonsteroid AR agonists in AR. (a) Alignment of DHT (PDB ID: 1I37)[68] with a nonsteroid LGD2226 (PDB ID: 2HVC)[69] in a cocrystal structure. (b) Alignment of DHT (PDB ID: 1I37) with a cyano aromatic agonist (PDB ID: 2IHQ)[70] in a cocrystal structure.

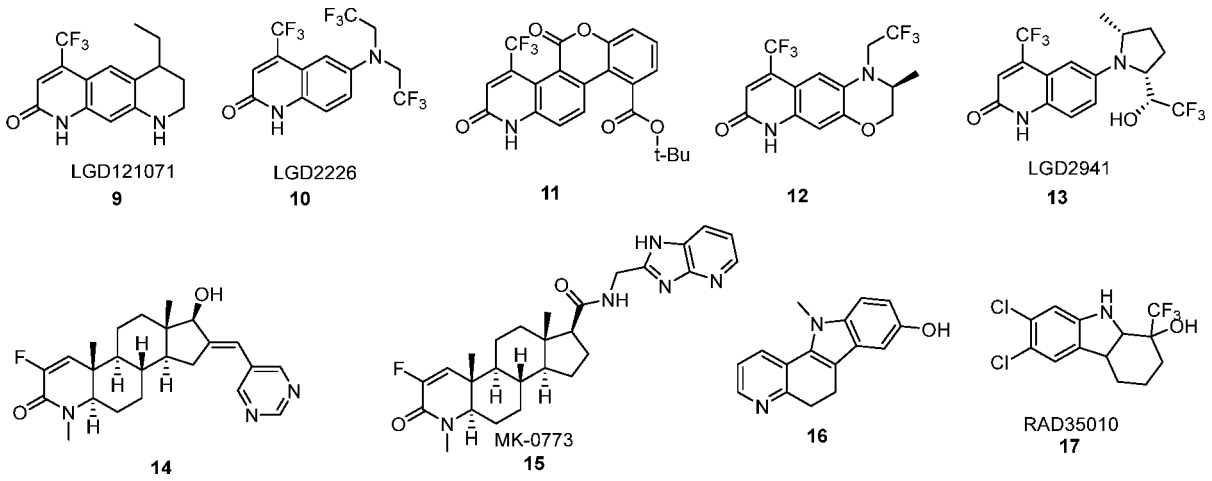

Figure 6. Structures of orally available polycyclic AR agonists.

Steroid-based AR agonists are being gradually phased out and replaced by nonsteroidal agonists.

3.2. Nonsteroidal AR Agonists. Early nonsteroid AR agonists were testosterone mimetics obtained from ligand-based drug design efforts. These compounds usually contain a hydrogen bond acceptor moiety that mimics the carbonyl group at C3 in DHT, a group that mimics the 17-hydroxy group in DHT, and a polycyclic ring (bicyclic, tricyclic, or tetracyclic) as epitomized by DHT and LGD2226 in Figure 5a.[68,69] The determination of AR agonist cocrystal structures led to the discovery of cyano- or nitrophenyl-based compounds. The cyano motif mimics the carbonyl group at C3 in DHT, as illustrated in Figure 5b.[70]

3.2.1. Polycyclic AR agonists. On the basis of a systematic SAR study, Ligand Pharmaceuticals reported a series of trifluoromethyl quinolinone compounds (**9**−**13**) (Figure 6).[71−80] These compounds have K_i values for binding against human AR (hAR) protein from 0.9 to 17 nM, a low-digit EC_{50} agonist potency against hAR in cell, and 82−132% efficacy compared with that of DHT (Table 1). In a mouse model, these compounds selectively target anabolic AR and are capable of stimulating muscle and bone marrow growth. Among them, **13** (LGD2941) had been in phase I clinical trials by Ligand Pharmaceuticals for the treatment of hypogonadism, female sexual dysfunction, and menopausal syndrome.[81]

Compounds **14** and **15** were developed by Merck as orally available full AR agonists.[82,83] Compound **14** has an AR protein binding IC_{50} of 59 nM, an agonist EC_{50} in the TAMAR cells of 17 nM, and efficacy of 141% compared with that of DHT.

Table 1. Activities of Compounds from Ligand Pharmaceuticals Incorporated

compound no.	hAR agonist EC_{50} nM (CV-1)	hAR agonist efficacy % (DHT 100%)	hAR K_i (nM) ($K_{i\text{-DHT}}$= 0.2)	reference
9	4	100	17	71, 72
10	0.2	95	4.6	73−75
11	1.1	132	8.7	76
12	1.1	82	0.9	77−79
13	7.1	109	6.5	80

Compound **15** (MK0773) is an analogue of **14** and has an AR binding IC_{50} of 6.6 nM.[84] The heteroaromatic ring in **14** or **15** improved the pharmokinetic (PK) profile and oral bioavailability. In a rat study, compound **14** was reported to exhibit osteoblastic and muscle tissue selectivity as an oral agent. Compound **15** was selected for clinical study and, in a phase II clinical trials for sarcopenia in women, it was found to increase lean body mass but failed to improve muscle strength and function.[83] Compound **16** is a tetracyclic indole disclosed by Johnson & Johnson with a pyridine nitrogen mimicking the carbonyl at C3 in DHT.[85] Compound **16** has an IC_{50} of 29 nM in the rat AR COS-7 whole-cell binding assay, whereas R1881 (compound **4** in Figure 5) has an IC_{50} of 1.5 nM in the same assay. The carbazole derivative (**17**) (RAD35010) is an anabolic-selective agonist with an AR binding IC_{50} of 27 nM.[86] In a castrated male rat model, **17** as an oral agent was able to restore levator ani weight to the sham level without increasing the weight of the prostate.

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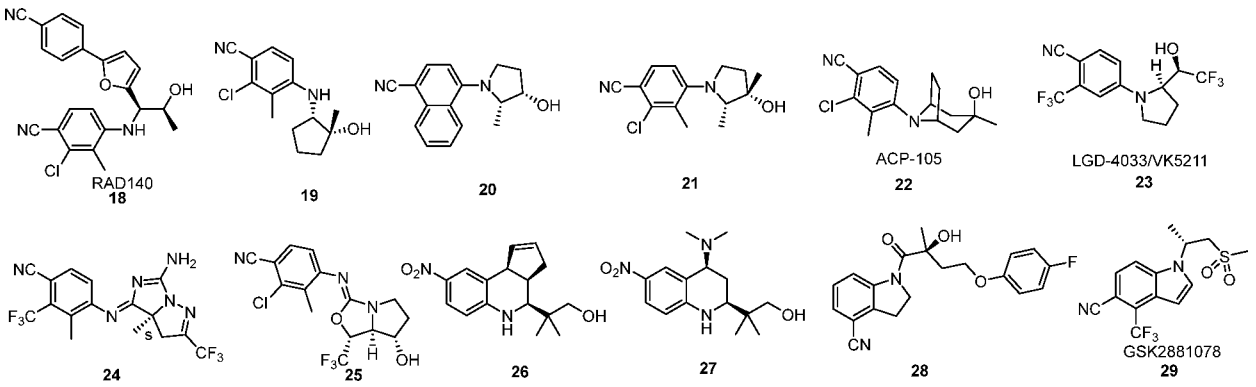

Figure 7. Structures of cyanoaniline AR agonists.

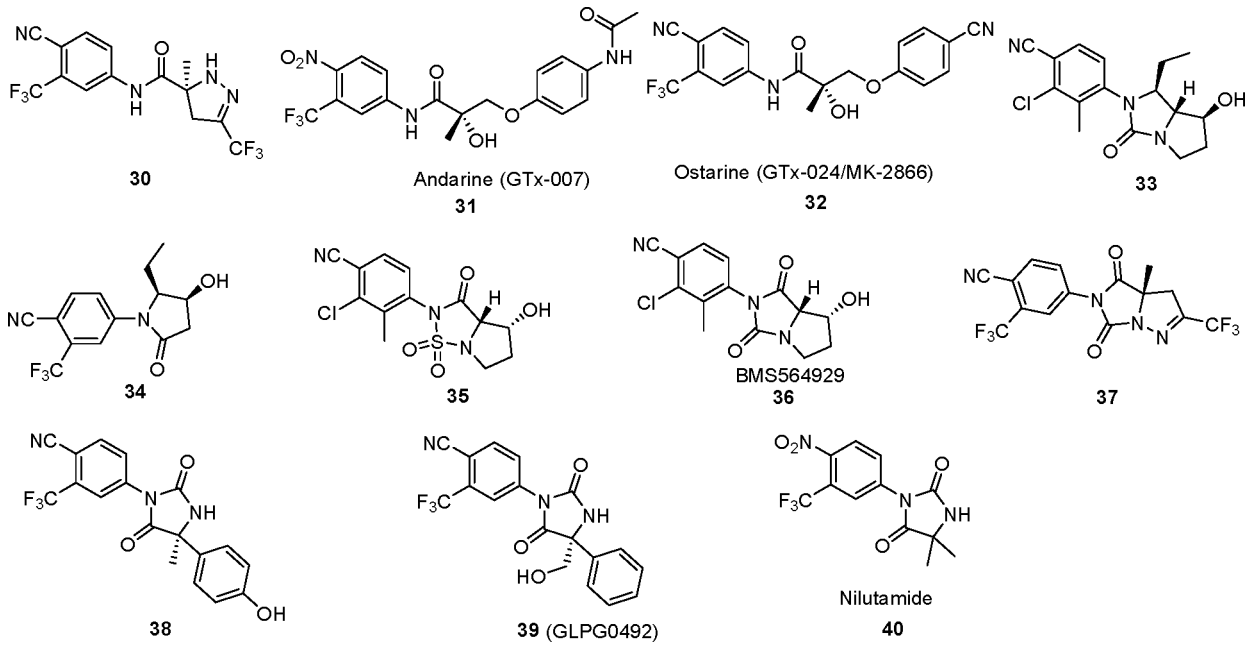

Figure 8. Structures of cyano acylaniline AR agonists.

3.2.2. Cyano/Nitroanilines. RAD140 (**18**) is a tissue-selective anabolic AR agonist with an AR binding K_i of 7 nM (Figure 7).[87] Interestingly, it binds to AR in breast cancer cells but not to AR in prostate cancer cells.[87] RAD140 significantly increases fat and lean body mass in rats and monkeys at 0.1 mg/kg or higher with oral administration. In an AR+/ER+ breast cancer PDX model, RAD140 activates AR and suppresses ER. RAD140 has been evaluated as a single agent in a phase I clinical trial in patients with AR+/ER+ breast cancer.[88] Compound **19**, a compound developed by Eli Lilly, has a K_i value of 2 nM against AR and an EC_{50} of 0.5 nM in AR-expressing C2C12 cells. It demonstrates an ED_{50} of 0.14 mg/kg in muscle but has little effect on the prostate.[89] Compound **19** has high skin permeability, which makes it suitable as a transdermal AR agonist.

Compounds **20**−**21** were developed by the Takeda Corp. as tissue-selective agonists (Figure 7).[90−92] Compound **20** has an IC_{50} value of 2.4 nM to hAR and an EC_{50} of 0.32 nM in an hAR luciferase reporter assay in the Cos-7 cell line, and compound **21** has the corresponding values of 1.0 and 0.29 nM, respectively. In the male rat, compounds **20** [3 mg/kg, subcutaneous (SQ), 4 days] or **21** (1.5 mg/kg, SQ, 4 days) double the weight of the levator ani muscle but have no influence in prostate or seminal vesicles. Both compounds, however, demonstrate high brain concentrations in a rat tissue distribution study and are therefore unsuitable for further clinical development. Compound **22** was developed by Acadia Pharma.[93] It has an AR binding IC_{50} of 1 nM and efficacy equal to 81% of DHT. It also showed good oral bioavailability in rats and dogs. It was found to be tissue-selective in a male rat efficacy study, in which the levator ani weight increased by 68% compared with a 21% increase of the prostate after oral administration of 0.75 mg/kg for 14 days. LGD4033/VK5211 (**23**), an agonist developed by Ligand Pharmaceuticals, has a K_i value of 1 nM against hAR.[94,95] In rats, it shows anabolic selectivity in muscle and bone over prostate. Compound **23** is currently being developed by Viking Pharmaceutics for the treatment of acute hip fractures in male patients over 65 years old.

Compound **24** is a full agonist with an imidazolopyrazole scaffold that was developed by Johnson & Johnson (Figure 7).[96] During lead compound optimization, compounds were evaluated in a male rat model following PO administration. Compound **24** increases levator ani weight by 91% and prostate weight by 36% after 2 mg/kg dosing for 5 days. Compound **25** from BMS is a highly affinitive AR agonist with a K_i of 0.3 nM and an EC_{50} of 0.2 nM,[97] but no tissue selectivity in a male

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J. Med. Chem. 2022, 65, 8772−8797

castrated rat model. After 0.1 mg/kg PO (by mouth) of **25** for 14 days, the weight of both the levator ani muscle and the prostate increased by 100%. In addition to the absence of tissue selectivity, cyano phenylimino compounds (**24**, **25**) are thought to have stability concerns, and this has hindered their further development.[97]

Compounds **26** and **27** from Karen Pharmaceuticals are designed to match the pharmacophore of DHT (Figure 7).[98,99] The distances between the nitro group and the dimethyl in **26** and **27** are similar to that between the 3-carbonyl and the 18-methyl in DHT. Both compounds are pure agonists with rat AR binding IC_{50} values of 13 and 26 nM, and agonist EC_{50} values of 9.2 and 13 nM respectively. Although **26** and **27** bind selectively to AR better than other nuclear receptors, they lack tissue selectivity for the levator ani muscle over the prostate. The cyanodihydroindole compound (**28**) developed by Pfizer has an AR binding IC_{50} of 12.7 nM and an EC_{50} of 2.5 nM in an androgen response element luciferase assay (ARE-LUC).[100] In a rat efficacy study, it selectively stimulated growth of the levator ani muscle without impact on prostate and seminal vesicle tissue after 10 mg/kg SQ dosing for 14 days. GSK2881078 (**29**) is an orally available tissue-selective agonist from GlaxoSmithKline (GSK) that restores the levator ani muscle to the sham level in a castrated rat model after 0.3 mg/kg PO for 28 days, but has little impact on prostate tissue. In a phase I clinical trial for the muscle atrophy of COPD patients, GSK2881078 was well tolerated and capable of increasing lean body mass in a dose-dependent manner. It has also completed the phase II clinical trial, but the results are yet to be released.[101,102]

Compound **30**, a pyrazoline amide, shows pure agonist effects in both anabolic and androgenic systems (Figure 8).[103] In rats, at 0.11 mg/day PO over 14 days, compound **30** achieves 90% of levator ani muscle stimulation compared with testosterone. At 0.76 mg/day, it demonstrates 51% prostate stimulation compared with testosterone, thereby indicating low tissue selectivity. Andarine (GTx-007) (**31**) and ostarine (GTx-024/MK-2866) (**32**) are AR agonists with AR binding K_i values of 4.0 and 0.55 nM, respectively.[104,105] Ostarine modulates skeletal muscle through the selective potentiation of anabolic AR. In several phase II double-blind clinical trials, ostarine significantly improved total lean body mass and physical function.[106]

Compound **33** is a potent cyanophenyl cyclourea AR agonist developed by Bristol Meyers Squibb (BMS). It binds to AR with a K_i of 0.9 nM and an EC_{50} of 1.8 nM (Figure 8).[107] In rats, it achieves a levator ani muscle ED_{50} of 0.09 mg/kg PO and exhibits a >50-fold difference of muscle over prostate selectivity. Furthermore, this compound demonstrated a 5.5 h plasma half-life and 65% oral bioavailability in a rat PK study. Compound **34** is a cyano phenylactam agonist developed by the Takeda Corp.[92] It demonstrates an AR binding IC_{50} of 3.6 nM and EC_{50} of 4.7 nM. It also shows selectivity for muscle over prostate. Although both these compounds present overall promising profiles as drug candidates, to date, neither compound has been evaluated in clinical trials.

Compounds **35**, an acyl and sulfonyl imide, and BMS564929 (**36**), a diacyl imide, were designed by BMS using a structure-based drug design approach (Figure 8).[70,108,109] Both compounds bind tightly to AR with a K_i of 0.45 and 3.2 nM, and an EC_{50} of 11.9 and 2.3 nM, respectively. Both compounds demonstrate tissue selectivity in rat with a simulation of levator ani muscle to prostate of >250- and >50-fold, respectively. However, **35** achieves good rat PK with iv administration while **36** is orally available. Compound **36** has been evaluated in a clinical trial, in which the side effect of an enlarged prostate was observed. Compound **37** is a hydantoin derivative developed by Johnson & Johnson.[110] During the SAR study, the compounds were directly evaluated in a castrated rat model without *in vitro* assessment. Compound **37** stimulates levator ani muscle growth of 75% but only 11% growth of prostate after 2 mg/day for 5 days PO, which indicates it is a muscle-selective and orally available agonist.

The hydantoin compounds (**38**, **39**) were obtained by modification of the AR antagonist nilutamide (**40**) (Figure 8).[111,112] Compound **38** is a partial agonist with an AR binding IC_{50} of 0.9 nM. In a rat castrated model, it shows strong levator ani muscle stimulation and a weak antiandrogenic effect on ventral prostate with 30 mg/kg PO. Compound **39** (GLPG0492) is also a partial agonist with an AR IC_{50} of 13 nM. Compound **39** achieves >50% bioavailability compared with 9% of compound **38**. Compound **39** has been evaluated in a phase I clinical trial, but its further clinical development was not reported.[113]

Compound **41**, developed by Novartis, is a full agonist with an hAR binding IC_{50} of 0.7 nM and an EC_{50} of 0.5 nM in an AR functional assay (Figure 9).[114] It demonstrates excellent human

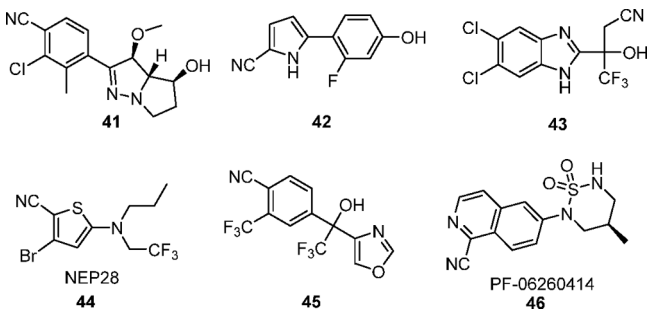

Figure 9. Structures of miscellaneous AR agonists.

skin permeation in the absence of a penetration enhancer. In the Hershberger rat model, it completely restores skeletal muscle without any effect on the prostate. Compound **42** is an AR agonist developed by Pfizer to treat osteoporosis and frailty.[115] It has an EC_{50} of 0.34 nM in ARE-Luciferase transfected CV-1 cells, but a low N/C (N-terminal/C-terminal) interaction with an EC_{50} of 1206 nM. In a rat efficacy study, **42** selectively stimulated the levator ani muscle over the prostate but achieved only modest efficacy at 10 mg/kg IP (intraperitoneal). The benzimidazole (**43**) is an agonist lacking cyano substitution on the phenyl ring, developed by Johnson & Johnson.[116] Compound **43** exerts an agonist effect in muscle but an antagonist effect in the prostate. It has an AR binding IC_{50} of 2 nM and an ED_{50} of 0.01 mg/kg in rat. NEP28 (**44**) has a thiophene ring in place of the phenyl ring and has an IC_{50} of ∼10 nM in 22RV1 pARE-LUC.[117] It is selective for levator ani muscle over prostate in a rat castration model. However, it is capable of penetrating the CNS and modulating the amyloid-β degradation enzyme neprilysin, which indicates that it is not purely an AR agonist. Compound **45** was developed by GSK with optimized potency and physiochemical properties and has a high oral availability of 83%.[118] The isoquinoline derivative (**46**) was developed by Pfizer to treat muscle weakness and has been evaluated in a phase 1 clinical trial.[119]

Stimulation of the levator ani over prostate in male rat is the standard method to evaluate the AR agonists' *in vivo* anabolic- to androgenic-selectivity. High *in vivo* efficacy and high selectivity

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J. Med. Chem. 2022, 65, 8772−8797

Table 2. *In vivo* Selectivity of AR Agonists on Levator Ani over Prostate Tissue

compound no.	impact on levator ani muscle and prostate	reference
17	in castrated male rat model, restores levator ani muscle weight to sham level and no weight change on prostate	86
20	in male rat 3 mg/kg, SQ, 4 days, doubles the weight of levator ani muscle but has no influence in prostate or seminal vesicles	90, 91
21	in male rat 1.5 mg/kg, SQ, 4 days, doubles the weight of levator ani muscle but has no influence in prostate or seminal vesicles	92
22	in male rat 0.75 mg/kg, PO, 14 days, the levator ani weight increases by 68%, and prostate weight increases by 21%	93
24	in male rat 2 mg/kg, PO, 5 days, the levator ani weight increases by 91%, and prostate weight increases by 36%	96
25	in male rat 0.1 mg/kg, PO, 25 days, the levator ani weight increases by 100%, and prostate weight increases by 100%	97
28	in male rat 10 mg/kg, PO, 14 days, the levator ani weight increases, and prostate weight stays the same	100
29	in castrated male rat 0.3 mg/kg, PO, 28 days, the levator ani weight restores to sham level, and no weight change on prostate	101
30	in male rat 0.11 mg/day, PO, 14 days, the levator ani weight achieves 90% stimulation compared with testerone	103
33	in male rat 0.09 mg/kg, PO, 14 days, >50-fold increase of levator ani weight compared with prostate	107
35	>250-fold stimulation of levator ani weight compared with prostate	70, 108, 109
36	>50-fold stimulation of levator ani weight compared with prostate	70, 108, 109
37	in castrated male rat 2 mg/day, PO, 5 days, the levator ani weight increases 75%, and prostate weight increases 11%	110
38	in castrated male rat 30 mg/kg/day, PO, strength stimulation on levator ani muscle, and weak effect on prostate	111, 112
42	in male rat 10 mg/kg IP, selectively stimulates levator ani muscle over prostate	115

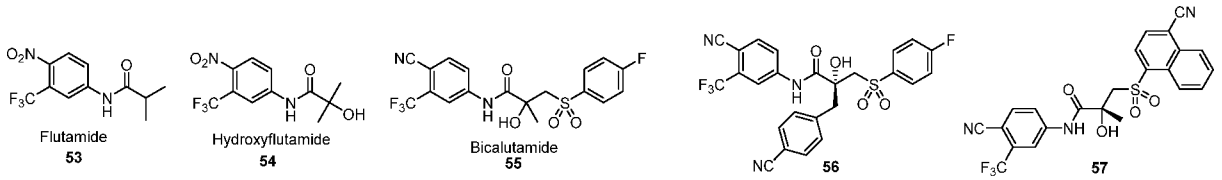

Figure 10. Structures of cyano acylaniline AR antagonists.

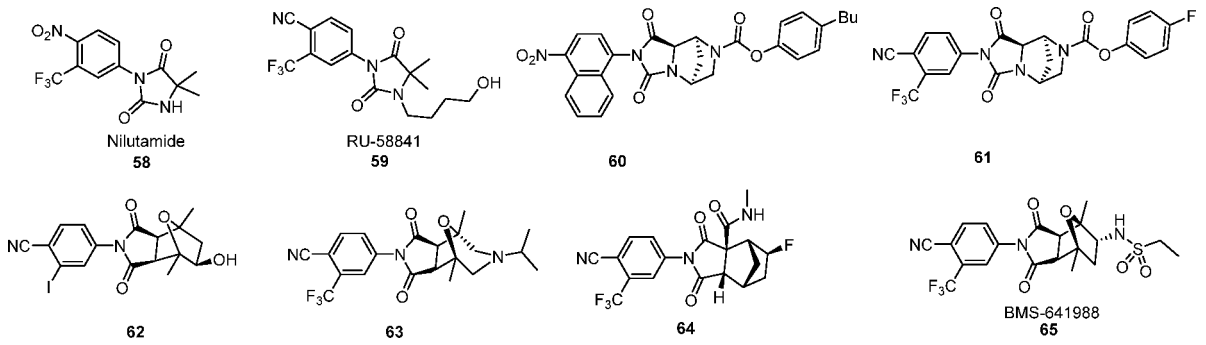

Figure 11. Structures of cyano phenyl hydantoin and cyclodiacylimide AR antagonists.

of the levator ani over prostate are necessary for further evaluation. Some of the aforementioned AR agonists have been studied for their *in vivo* effects on the levator ani and prostate, and their results are summarized in Table 2.

4. ANDROGEN-COMPETITIVE ANTAGONISTS

Unlike agonists, which bind to AR and initiate gene transcription, antagonists bind to AR and recruit coregulators that inactivate AR gene transcription. Antagonists that bind to LBP are androgen-competitive AR inhibitors. AR antagonists have been developed for the treatment of human prostate cancer and other human conditions such as acne.

4.1. AR Antagonists for Prostate Cancer. Flutamide (**53**) and hydroxyflutamide (**54**) are two of the early AR antagonists reported (Figure 10).[120,121] Flutamide is a prodrug and metabolizes to an active form, hydroxyflutamide. Hydroxyflutamide has an IC_{50} of 84 nM in androgen-sensitive SEM-107 Shionogi cells and an IC_{50} of 45 nM in T-47D breast cells. Both drugs are not tissue-selective and are used to treat prostate cancer as well as acne, excessive hair growth, and high androgens in women. However, because of their metabolically susceptible nitro group, both drugs have a very short half-life *in vivo* and must be taken three times a day. Both drugs have been replaced by new generation antagonists. Bicalutamide (**55**) is an antagonist drug used along with other androgen-deprived therapies.[122] The IC_{50} of bicalutamide in LNCaP cells is 160 nM. The activity of bicalutamide is from the *R*-isomer, which binds to AR with a K_i value of 11 nM. The *S*-isomer is less active with an AR binding K_i of 365 nM. However, development of resistance has plagued bicalutamide. One resistance mechanism for bicalutamide is a switch from antagonist to agonist after AR mutation. Hence, modifications of bicalutamide to develop newer antagonists to overcome mutation-related resistance have been undertaken by different groups. Guerrini et al.[123] introduced a benzyl ring to the hydroxyl carbon of *R*-bicalutamide to generate **56**, which has an AR binding affinity and LNCaP-inhibitory activity similar to that of *R*-bicalutamide. It demonstrates inhibitory activity in bicalutamide-resistant CRPC- and AIPC-mutated cells and in androgen-independent PC-3 and DU145 cells. However, **56** is less effective than *R*-bicalutamide in the suppression of tumor growth in mouse xenograft models. GTx corp. found that replacement of the

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J. Med. Chem. 2022, 65, 8772−8797

Table 3. Activities of BMS Antagonists 60-65

compound no.	^{3}H-DHT displacement (MDA-453) K_i (nM)	MDA-453 IC_{50} (nM)	LNCaP IC_{50} (nM)	seminal vesicle and prostate weight decrease	PO CWR22R mice dose (24 h exposure)	reference
60	73	60	4750			127
61	18	350	3920			127
62	2.4	19			30 mg/kg (6 μM) 90 mg/kg (24 μM)	128
63	14	32	125			129
64	8	91		35% (15 mg/kg)	15 mg/kg (2.8 μM)	130
65	1.7	16	153	42% (1 mg/kg) 74% (10 mg/kg)	1 mg/kg (0.79 μM) 10 mg/kg (4 μM)	131

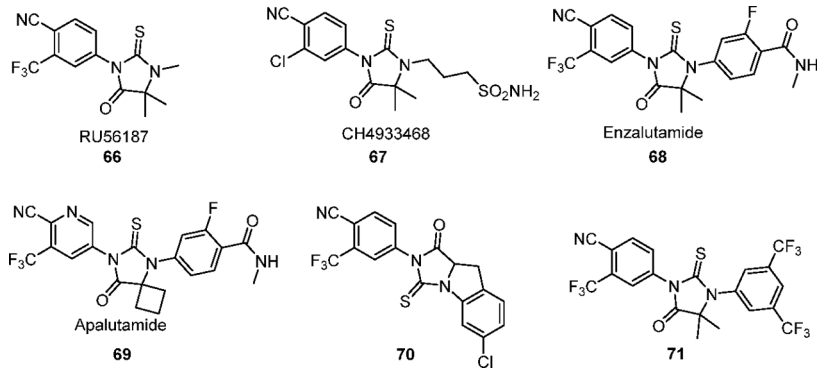

Figure 12. Structures of cyano phenyl thioxoimidzaolidine AR antagonists.

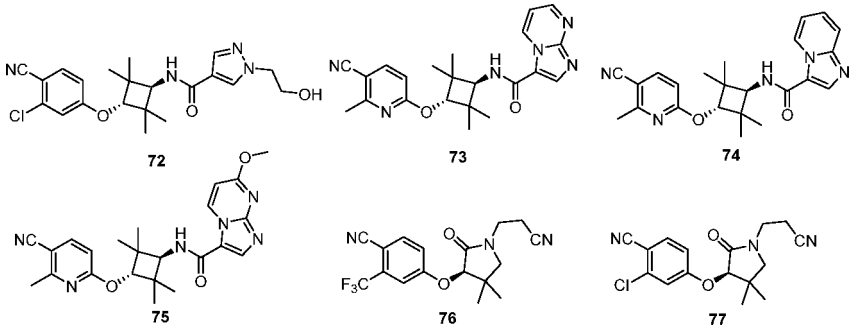

Figure 13. Structures of cyano phenyl cycloalkyl ether AR antagonists.

phenyl ring by a bulkier aromatic naphthyl ring, as in **57**, increased the potency against wild-type and W742L- and T878A-mutated AR.[124−126]

Nilutamide (**58**) was discovered in 1977 and is used together with other androgen-deprived therapies (Figure 11).[132] In the Shionogi cell proliferation assay, nilutamide has an IC_{50} of 412 nM while the IC_{50} of bicalutamide is 243 nM. Nilutamide is not tissue-selective and has been replaced by a new generation of antagonists, which include bicalutamide and enzalutamide. Substituents on the N of nilutamide appear to be tolerated and increase the AR binding affinity. RU-58441 (**59**) is 4 times more potent than nilutamide, but it is not orally available and has never been evaluated in clinical trials.[133] BMS developed compounds **60** and **61** by extending the five-membered ring in nilutamide.[127] Compounds **60** and **61** have K_i values of 73 and 18 nM, respectively, in displacement of ^{3}H-DHT in the AR+ MDA-MB-453 breast cancer cell line (Table 3). These two compounds show IC_{50} values of 6 and 35 nM, respectively, in MDA-MB-453 cells, and 4.75 and 3.92 μM, respectively, in LNCaP cells. Further modifications of **60** and **61** by altering the bicyclic ring and introducing heteroatoms and optimizing the tail substitution led to compounds **62−65**. In MDA-453 cells, compounds **62−65** have K_i values ranging from 1.7 to 14 nM, and IC_{50} values from 16 to 91 nM.[128−131,134] Compounds **62**, **64**, and **65** achieve micromolar activity in CWR22R cells. Compound **65** reduces seminal vesicle weight by 42% with 1 mg/kg PO dosing and by 74% at 10 mg/kg. As a result, **65** was evaluated in phase I dose escalation trials in CRPC but failed to reach phase II.[135]

RU56187 (**66**), obtained by modification of nilutamide, is a prodrug that undergoes N-demethylation to produce an active compound (Figure 12).[136,137] RU56187 is slightly less potent than DHT in binding to AR and is 3-fold more potent than bicalutamide in rat efficacy studies. However, RU56187 was used simply as a proof of concept of the thioxoimidazolidine scaffold and was not evaluated in clinical trials. In a follow-up study, Chugai Pharmaceuticals extended the substitution to obtain **67**, which is stable in microsomes and does not undergo dealkylation.[138] Compound **67** has an IC_{50} of 440 nM in AR binding and 410 nM in LNCaP. In the LNCaP xenograft mouse model, **67** demonstrates efficacy comparable with that of bicalutamide.

Enzalutamide (**68**) and apalutamide (**69**) were both discovered by the Michael E. Jung group and have a similar

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J. Med. Chem. 2022, 65, 8772−8797

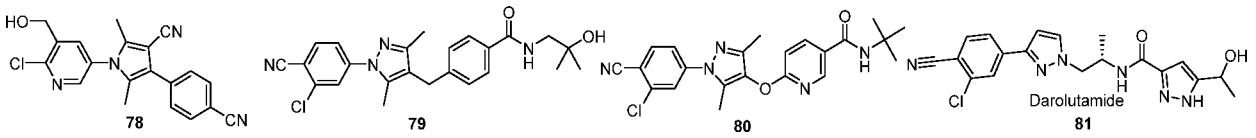

Figure 14. Structures of phenyl pyrrole and pyrazole AR antagonists.

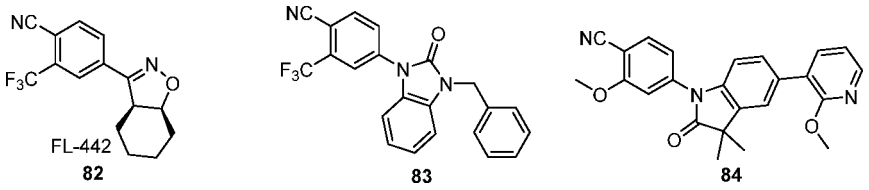

Figure 15. Structures of cyano phenyl bicyclic AR antagonists.

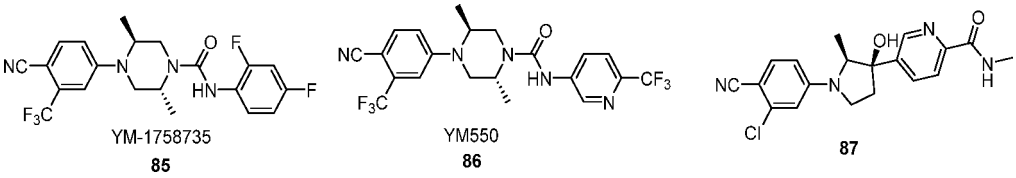

Figure 16. Structures of cyano phenyl cycloamine AR antagonists.

scaffold.[139] Enzalutamide has an IC_{50} of 36 nM in LNCaP cells. In mechanistic studies, it inhibits AR nuclear translocation, DNA binding, and gene transcription. In a mouse LNCaP xenograft model with overexpressed AR, enzalutamide achieves tumor regression at 10 mg/kg.[139] Apalutamide has a similar binding affinity compared with enzalutamide but an approximately 2-fold lower IC_{50} in LNCaP than enzalutamide.[139]

Several groups have pursued further modifications of enzalutamide. Cyclization of the five-membered enzalutamide ring with the second phenyl ring leads to a rigid compound (**70**), which is 2-fold less potent in LNCaP cells than enzalutamide is.[140,141] Bassetto et al.[142,143] introduced 3,5-bis-trifluoromethyl groups onto the second phenyl ring of enzalutamide to produce **71**, which was discovered to have a 60-fold increase in potency in LNCaP. However, both **70** and **71** have significantly higher lipophilicity than enzalutamide and neither has been assessed *in vivo*.

Pfizer reported a series of cyanophenyl cycloalkyl ether compounds (**72**−**77**) as AR antagonists (Figure 13).[144−146] Compounds **72** and **73** inhibit cell growth in AR-overexpressed LNCaP with IC_{50} values of 59 and 144 nM, respectively. Both compounds possess good druglike properties including solubilities of 12 and 11.4 μM and calculated cLogP values of 3.8 and 4.5, respectively. In an LNCaP xenograft mouse model, with 100 mg/kg SQ administration for **72** and 25 mg/kg SQ administration for **73**, both compounds strongly inhibited tumor growth after 5 weeks, at which time point both groups showed a prostate-specific antigen (PSA) decrease of >90%. However, **73** is rapidly metabolized by aldehyde oxidases, and consequently, two optimized compounds (**74** and **75**) were identified and proved to be unsusceptible to aldehyde oxidase. The lactam phenyl ether scaffold (**76**) has an AR antagonist IC_{50} of 131 nM but it also demonstrates 89% of the agonist effect at 1 μM. In a rat PK study, **76** shows 64% oral bioavailability. Replacing the trifluoromethyl group in **76** with a chlorine afforded 77, which has an AR antagonist IC_{50} of 68 nM and 89% of agonist effect at 1 μM.

The Takeda Corp. discovered a series of phenyl pyrrolo and pyrazolo compounds (**78**−**80**) (Figure 14).[147,148] Unlike **79** and **80**, compound **78** has hydroxymethyl and chlorine substituents on the phenyl ring. Compounds **78**−**80** have wild-type AR binding IC_{50} values of 0.037, 0.034, and 0.43 μM and bicalutamide-resistant T877A AR binding IC_{50} values of 0.1, 0.16, and 0.34 μM, respectively. In a COS-7 gene transcriptional assay, compounds **78**−**80** have antagonist IC_{50} values of 0.025, 0.59, and 1.0 μM against wild-type AR and 0.11, 1.1, and 0.19 μM against T877A AR mutant, respectively. In an LNCaP-cxD2 xenograft mouse model, **78** at 25 mg/kg after 28 days PO administration achieves 15% T/C (treatment group/control group), **79** at 40 mg/kg achieves 23% T/C, and **80** at 50 mg/kg achieves 17% T/C.

Darolutamide (**81**), which contains a central pyrazole, was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of CRPC. Darolutamide is a mixture of two diastereomers, which are interconvertible through a ketone form. Both diastereomers and the ketone form are active AR antagonists. *In vitro*, darolutamide has 8−10 times stronger affinity in AR binding than enzalutamide and apalutamide.[149] It inhibits N/C interactions and AR homodimerization in both wild-type and W742C/L-mutated AR. *In vivo*, darolutamide inhibits tumor growth in VCaP, MR49F, and other AR mutant xenograft animal models.[149]

Poutiainen et al.[150] reported a cyclohexyl isoxazole compound (**82**) as an AR antagonist that inhibits 99.2% of DHT binding to AR (Figure 15). It has a PIC_{50} of 7.56 in COS-1 cells, measured with bicalutamide as a control at PIC_{50} = 6.92, and strongly inhibits the growth of AR W742L- and T878A-mutated COS-1 cells. Pfizer reported a cyanophenyl-substituted benzimidazole (**83**) and an indole (**84**) as potent AR antagonists.[151] These two compounds demonstrate IC_{50} values of 170 and 79.6 nM in refractory prostate cancer cells but have not been evaluated *in vivo* and have not been further optimized.

Two piperidine ureas (**85**, **86**) have been reported by Astellas as AR-selective antagonists (Figure 16).[152] Compound **86** binds to hAR with a K_i of 4.6 nM and to rat AR with a K_i of 6.2 nM. In

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J. Med. Chem. 2022, 65, 8772−8797

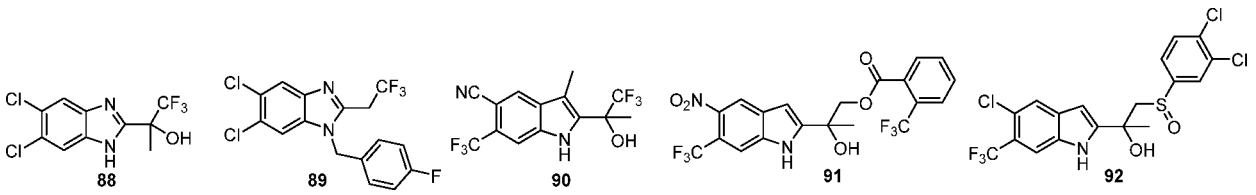

Figure 17. Structures of indole and benzimidazole AR antagonists.

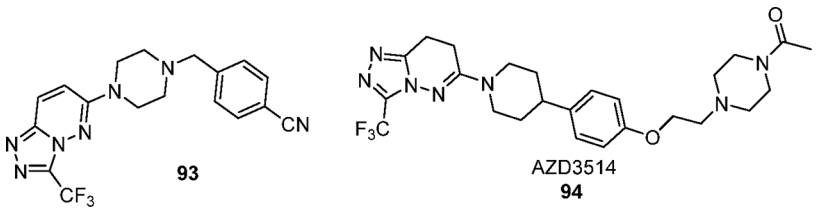

Figure 18. Structures of AstraZeneca AR antagonists.

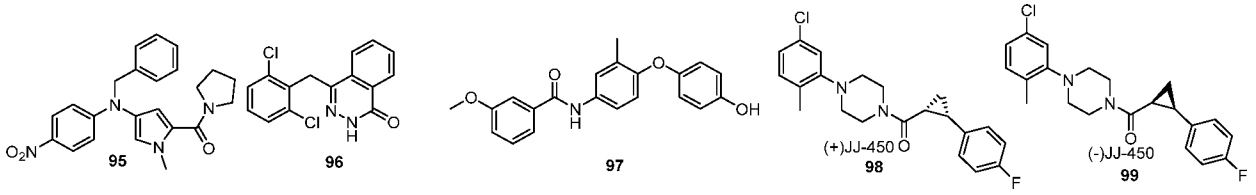

Figure 19. Structures of uncommon AR antagonists.

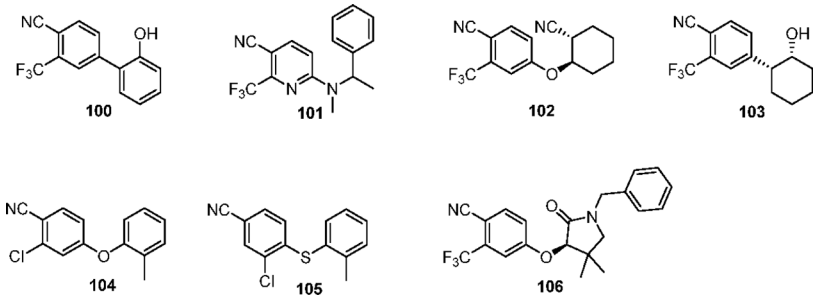

Figure 20. Structures of topical AR antagonists from Pfizer.

an AR-mediated transcriptional activation assay, **85** has an IC_{50} of 0.2 μM, and **86** has an IC_{50} of 0.11 μM. In a male Wistar rat efficacy study of 10 mg/kg for 15 days PO, **85** failed to decrease ventral prostate weight, but **86** reduced it by 67%. A further rat efficacy study determined the ED_{50} of **86** to be 2.2 mg/kg/day. Compound **87** is an antagonist designed by the Takeda Corp. on the basis of its in-house agonist (**21**).[153] Compound **87** binds to wild-type AR with an IC_{50} of 0.83 μM and to T878A-mutated AR with an IC_{50} of 1.7 μM. In an LNCaP cell growth study, **87** was found to have an IC_{50} of 0.29 μM in wild-type and 1.7 μM in T878A mutation. At 1 μM concentration, it inhibits PSA expression by >60% in LNCaP cells. In an LNCaP xenograft mouse model, **87** at 30 mg/kg PO twice daily for 4 weeks has a minimal effect on tumor growth, consistent with no PSA reduction.

A series of benzimidazoles (**88**−**89**) and indoles (**90**−**92**) have been developed by Johnson & Johnson (Figure 17).[154−157] Compounds **88**−**90** were directly evaluated *in vivo* without any *in vitro* assessment. In testosterone-treated castrated rats with dosing of 2 mg/day PO for 5 days, **88**−**90** reduced prostate weight by 96, 84, and 80%, respectively, which resulted in calculated ID_{50} values of 0.32, 0.13, and 0.13 mg/day. Compounds **91** and **92** were evaluated *in vitro* and have AR binding IC_{50} values of 140 and 100 nM compared with the bicalutamide value of 1300 nM.

AstraZeneca identified a trifluoromethyl triazolopyridazine (**93**) as a novel antagonist, with a PIC_{50} in AR binding of <4.1 and a PIC_{50} in AR downregulation of <5.8 (Figure 18).[158] Compound **93** demonstrates 100% rat oral availability and reduces rat seminal vesicle weight by about 80% after dosing of 258 μM/kg twice daily PO for 7 days. Further optimization of **93** yielded AZD3514 (**94**).[159] AZD3514 shows a PIC_{50} in AR downregulation of <5.75. In a PK study, AZD3514 demonstrates 74% oral availability in rats and 75% in dogs. In addition to inhibiting AR, AZD3514 induces AR degradation at 1 μM, which indicates that it has more than one mechanism of action. AZD3514 has been evaluated in a phase I clinical trial for CRPC. It provides modest efficacy and reduces PSA in patents but has significant side effects.[160]

Compounds **95** and **96** are examples from two different series of antagonists reported by the Tanatani research group (Figure 19).[161,162] Compound **95** has a binding K_i of 0.11 μM in wild-type AR, 0.006 μM in T878A-mutated AR, and an IC_{50} in SC-3 cells of 0.44 μM. Compound **96** has IC_{50} values of 0.18 μM in

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J. Med. Chem. 2022, 65, 8772−8797

SC-3 cells and 0.56 μM in LNCaP and is capable of reducing ~80% of PSA expression in LNCaP. Compound **97**, developed by Astellas, has IC_{50} values of 0.75 μM in SC-3, 0.043 μM in T887A-mutated LNCaP, 0.22 μM in H874Y-mutated 22RV1, and >10 μM in AR-independent PC-3.[163,164] The Wipf group[165] identified JJ-450 after systemic optimization of a high-throughput screening lead compound. The dextrorotary enantiomer (**98**) has an EC_{50} of 1.7 μM in C4-2-PSA-rl cell PSA luciferase assay, in which enzalutamide had an EC_{50} of 1.1 μM. The levorotary enantiomer **99** is 10 times less active. The binding site of this compound has not been identified and it may be involved in multiple mechanisms of action. It inhibits AR transcriptional activity by retarding AR translocation and also inhibits ARV7 transcriptional activity and ARV7 gene expression.[166]

4.2. AR Antagonists for Topical Use. Pfizer reported a series of AR antagonists (**100**−**106**) (Figure 20).[167−174] These compounds have hAR binding IC_{50} values of 20 to 100 nM and AR MDA-kb2 cell function IC_{50} values from 0.2 to 90 nM (Table 4). Most of these compounds reduce wax ester in an animal topical sebum model, but none of them has been evaluated in the clinic.

Table 4. Activities of Pfizer Preclinical Compounds

compound no.	hAR binding IC_{50} (nM)	AR function IC_{50} (MDA-kb2) (nM)	cLogP	in vivo wax ester inhibition (3% formulation, 2 weeks)	reference
100	39.9	0.2	3.55	86%	167
101	20	45		83%	168
102	60	12		64%	169
103	26	90		85%	170
104	60	57		>80%	171
105	43	78		>80%	172
106	100	38	4.70	(1% formulation) 78%	173, 174

5. RELATION BETWEEN AGONIST AND ANTAGONIST

5.1. Methyl on the Phenyl Ring. As summarized above, cyanophenyl-based AR agonists may or may not possess a methyl at the *meta* position relative to the cyano group in the phenyl ring. However, none of the AR antagonists has a methyl substituent. The methyl moiety on the cyanophenyl ring may have certain functions contributing to the AR agonist effect. Sunden et al.[175] proposed that the methyl groups could lead to a conformational difference in the whole molecule illustrated by compounds **108** and **109** (Figure 21). The methyl compound (**109**) is an AR agonist, while the desmethyl compound (**108**) is an AR antagonist. Sunden et al. suggests[176] that the methyl dictates the conformation of the molecule (**109**), which allows H12 to flip back to the agonist position. However, the desmethyl compound (**108**) remains in a stable conformation that prevents H12 from switching back to the agonist position.

The methyl moiety may also have other functions that contribute to the agonist effect. Antagonists for prostate cancer are designed to target androgenic AR, and agonists are designed to target anabolic AR. It is possible that the difference between androgenic AR and anabolic AR may the methyl-containing compound better suited for anabolic AR.[176] An example is RAD140 (**18**), which comprises a methyl moiety and is selective for AR in breast tissue over AR prostate tissue.

5.2. Size of the Molecule. Theoretically, agonists bind to AR and induce H12 to flip back to enclose the LBP, while antagonists bind to AR, and H12 remains open. Therefore, it may be thought that antagonists should be bulkier than agonists. However, this size theory is not necessarily correct. Hydroxyflutamide is an antagonist of androgenic AR (Figure 22). Andarine, which is significantly larger than hydroxyflutamide, is an agonist in anabolic AR and a partial agonist in androgenic AR.[104,105]

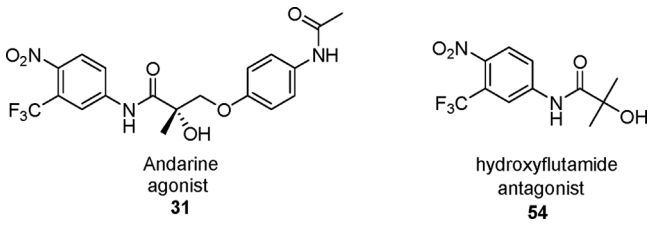

Figure 22. An example in which the size of an agonist is bulkier than that of the antagonist.

5.3. Antagonist−Agonist switch. One of the resistance mechanisms to AR antagonists involves the antagonist−agonist switch. Upon AR mutation, an antagonist can turn into an agonist for the mutated AR (Figure 23). Bicalutamide is an antagonist for wild-type AR, but it becomes an agonist for T878A- and T878S-mutated AR.[177] Similarly, enzalutamide and apalutamide are weak agonists for F877L and F876L AR, but strong agonists in F877L/T878A-mutated AR.[23,178]

6. CLINICAL DEVELOPMENT OF SECOND-GENERATION AR ANTAGONISTS

Among the many AR antagonists discussed above, enzalutamide, apalutamide, and darolutamide have been recently approved by the FDA for the treatment of human prostate cancer and are regarded as second-generation AR antagonists.[179] These antagonists are AR-selective and have also eliminated the agonist effects associated with those first-generation AR antagonists such as flutamide and bicalutamide. The second-generation antagonists achieve improvements in potency and efficacy and have diminished side effects.

Enzalutamide (**68**) was the first second-generation antagonist approved by the FDA (Figure 24). In a preclinical study,

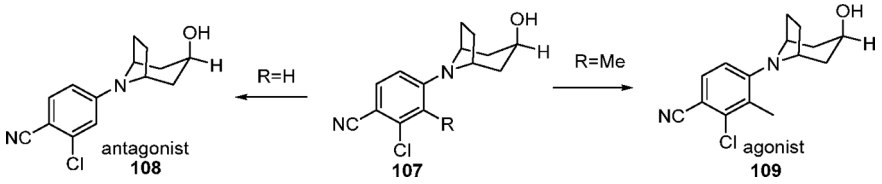

Figure 21. A methyl on the phenyl ring defines agonist and antagonist.

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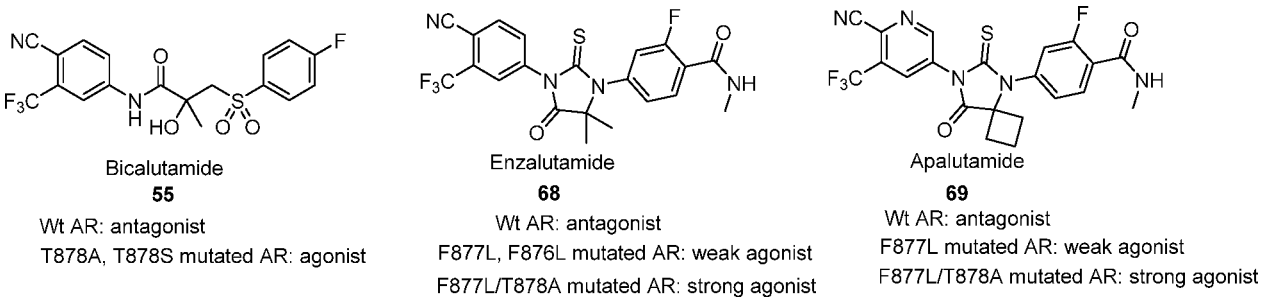

Figure 23. AR mutation and antagonist agonist switch.

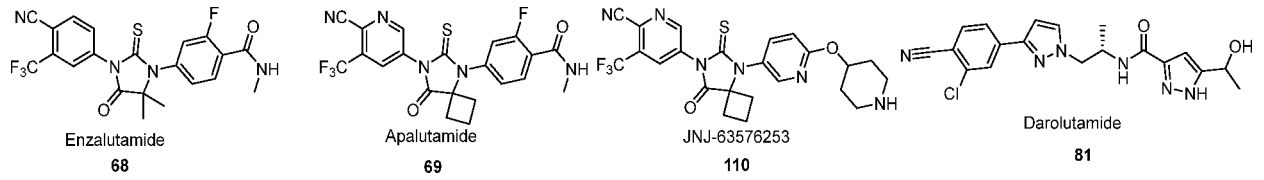

Figure 24. Second-generation AR antagonists.

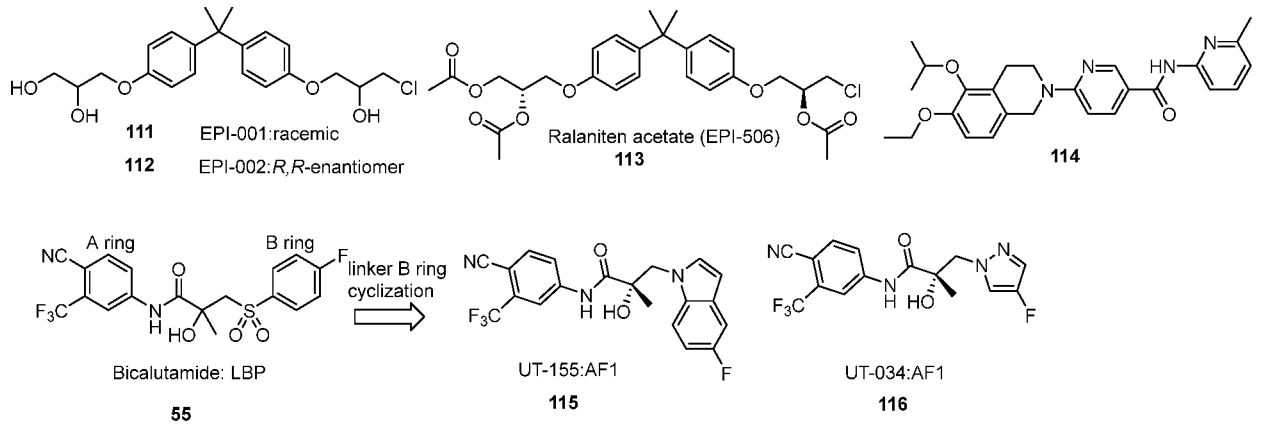

Figure 25. AF1 site antagonists.

enzalutamide demonstrated high potency, efficacy, favorable oral PK, and few adverse effects (Section 4.1).[180] In phase I/II studies, it is well tolerated for up to 4 years, with fatigue as the major side effect.[181] It also demonstrates durable antitumor efficacy in naïve and post chemotherapeutic CRPC, as measured by a reduction of PSA levels and tumor radiography. In phase II trials, >90% of patients who are eligible for ADT on a treatment cohort achieved more than 80% reduction of PSA at week 25.[182] In a phase III study, enzalutamide afforded a significant survival benefit and improved quality of life over a placebo in prostate cancer patients. This was observed in androgen-sensitive prostate cancer and pre- and postdocetaxel mCRPC.[183] Currently, combinations of enzalutamide with different classes of drugs are being extensively evaluated in clinical trials.

An uncommon but lethal side effect with enzalutamide is seizure resulting from its ability to cross the blood brain barrier (BBB) and bind to the GABA-gated chloride channel.[184] Apalutamide and enzalutamide have a similar GABA binding affinity and IC_{50} values of ∼3 μM. Apalutamide, with a polar nitrogen on the phenyl ring, is more hydrophilic than enzalutamide and, thus, has less BBB penetration. The concentration of apalutamide in brain tissue is four times lower than that of enzalutamide.[185] A phase I study in mCRPC showed that apalutamide is capable of reducing the median PSA level >85% at week 12.[186] A phase II study with apalutamide demonstrated durable activity in non-mCRPC, pre- and post-abiraterone acetate, and prednisone mCRPC arms with a median PSA level at week 12 decreasing to 85%, 88%, and 22%, respectively.[187] Apalutamide in phase III trials of CRPC achieved median metastasis-free survival of 40 months compared with 16 months for the placebo.[188] A common side effect of apalutamide is skin rash, which can be attributed to the cyano pyrimidine moiety, which is capable of attaching to cysteine residues in proteins through a reversible covalent bond.[189]

JNJ-63576253 (**110**) is a clinical stage second-generation AR antagonist capable of overcoming a subset of enzalutamide and apalutamide resistance.[190] It has an IC_{50} of 54 nM in LNCaP cells in a transcriptional reporter assay. It is also capable of inhibiting enzalutamide- and apalutamide-resistant F877L mutant LNCaP with an IC_{50} of 37 nM in the transcriptional reporter assay. In addition, it inhibits VCaP proliferation with an IC_{50} of 290 nM. JNJ-63576253 achieves 45% oral availability in mouse. In an *in vivo* efficacy study in an LNCaP F877L xenograft mouse model, JNJ-63576253 achieved 87% tumor growth inhibition with daily dosing of 30 mg/kg PO. This compound is currently being evaluated in phase I/II clinical trials in CRPC patients with F877L mutation.[191]

A preclinical study of darolutamide revealed multiple advantages over enzalutamide, including higher potency, the

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J. Med. Chem. 2022, 65, 8772−8797

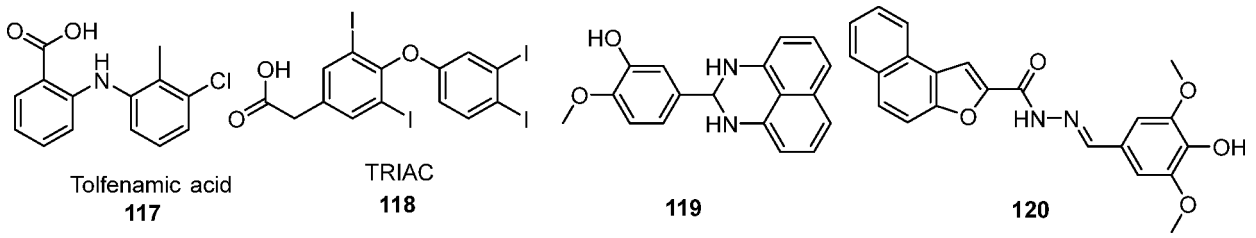

Figure 26. AF2 site antagonists.

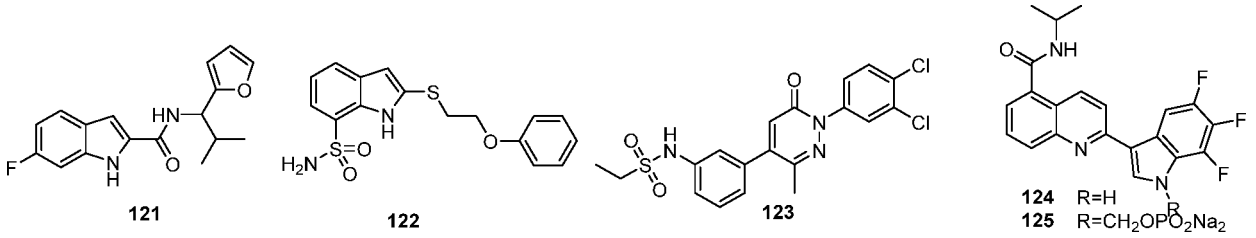

Figure 27. BF3 site antagonists.

ability to overcome W742L mutation, and efficacy in various murine xenograft models (Section 4.1).[192] Darolutamide is also capable of suppressing testosterone levels that are induced by ADT in CNS, while enzalutamide and apalutamide both fail to do so. Furthermore, darolutamide exhibits very poor BBB permeation with the ratio of brain-to-blood concentration in mice >10-fold lower than for enzalutamide.[193] phase I/II studies demonstrate that darolutamide is well tolerated and effective in mCRPC and reduces PSA by >50% in 70% of patients at week 12.[193] In a phase III study, darolutamide provided, on average, 40 metastasis-free months versus 18 months with a placebo, as well as other benefits such as overall survival, progression-free time, and quality of life.[194]

Despite its clinical success, resistance to enzalutamide is observed in the clinic within 3 to 6 months that is cross-resistant with abiraterone.[195] The mechanisms of resistance to enzalutamide have been reviewed elsewhere.[196] Because of their similar mechanisms, it is expected that resistance to apalutamide and darolutamide will be reported in the future.

7. NONANDROGEN COMPETITIVE AGENTS

7.1. AF1 Site. EPI-001 (**111**) is a biphenyl derivative and the first compound known to inhibit the AF1 of NTD (Figure 25).[197] It blocks the N/C interaction required for the transcriptional activity of AR and its splice variants by covalently inhibiting transcriptional activation units 1 and 5 on NTD. EPI-001 has an IC_{50} of ∼6 μM for the inhibition of AR NTD transactivation. However, as a covalent inhibitor, EPI-001 also modulates peroxisome proliferator-activated receptor gamma, which indicates multiple mechanisms of action (MOAs) may contribute to its activity.[198] EPI-002 is an enantiomerically pure version of EPI-001.[199] EPI-506 is the acetate prodrug of EPI-002 and it inhibits AR NTD transcription with an IC_{50} of ∼9.6 μM. A phase I/II clinical trial for EPI-506 in CRPC patients failed to achieve its end point.[200] An optimized compound, EPI-7386, with an undisclosed structure, is a member of the latest generation of bisphenol NTD inhibitors. It has an IC_{50} of 535 nM for AR NTD transactivation.[201]

The dihydroisoquinolinicotinamide compound (**114**) is a novel scaffold that binds to the AF1 site.[202] At a concentration of 10 μM, it demonstrates a >95% AR antagonist effect and a <5% DHT agonist effect and inhibits LNCaP cell growth by >90%. Compound **114** has an IC_{50} of 0.78 μM in NTD-overexpressed HEK293T cells. Western blotting assays showed this compound reduced AR and ARV levels in LNCaP, CWR22rv, DU145, PPC1, and HEK293T cell lines at a concentration of 10 μM. In a cellular proliferative assay, this compound has IC_{50} values around 1 μM in AR-independent C4-2 and CWR22rv cell lines. Compound **114** inhibits tumors with 10 mg/kg of 21 days IP dosing in CWR22rv xenograft mouse with T/C of 65%.

The Miller group cyclized the linker and the B-ring in bicalutamide and obtained UT-155 (**115**) and UT-034 (**116**). Both UT-155 and UT-034 bind to the AF1 site and function as SARDs.[203−205] Although they are derivatives of bicalutamide, UT-155 and UT-034 do not bind to the LBP pocket with LBP K_i values greater than 10 μM; both reduce full-length AR and ARV at a 1 μM concentration in LNCaP and 22RV1 cell lines and inhibit cellular growth >70% in an enzalutamide-resistant MR49F cell line. In a mouse efficacy study with 100 mg/kg dosing, both compounds suppressed tumor growth in both an LNCaP castrated model and an MR49F model.

7.2. AF2 Site. Compounds **117** to **120** were identified by virtual screening and have micromolar IC_{50} values in the inhibition of AR and coregulatory SRC2 and SRC3 interactions (Figure 26).[43,45,206] Compound **120** has IC_{50} values of 26.3 μM against wild-type AR and 33.2 μM in T878A-mutated AR.[206] At a 10 μM concentration, it inhibits LNCaP cell growth by ∼30% and also reduces PSA expression by ∼30%. However, **120** consists of an acylhydrazone moiety that is known to be labile in the acidic environment found in cancer cells.

7.3. BF3 Site. Similar to AF2 binders, BF3 binders (**121**−**123**) are tool compounds (Figure 27).[207−210] In an enhanced green fluorescent protein transcriptional (eGFPT) assay, the IC_{50} values are 0.43 μM for **121** and 1.5 μM for **122**.[208,209] Compound **122** decreases PSA in LNCaP with an IC_{50} of 0.53 μM. At a 6 μM concentration, **122** reduces PSA > 80% in LNCaP cells and >60% in enzalutamide-resistant LNCaP. Compound **123** has an IC_{50} of 6.26 μM in an AR luciferase activity binding assay, whereas that of bicalutamide is 0.27 μM. Compound **123** has an IC_{50} of 11.57 μM in LNCaP, compared with bicalutamide whose IC_{50} is 23.79 μM.[210] Compound **124** was identified from virtual screening, and **125** is an orally bioavailable prodrug of **124**.[211] Compound **125** inhibits the PSA level in LNCaP cell line with an IC_{50} of 0.66 μM. Compound

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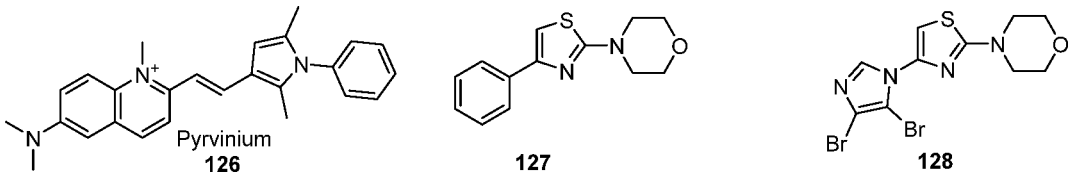

Figure 28. DBD site antagonists.

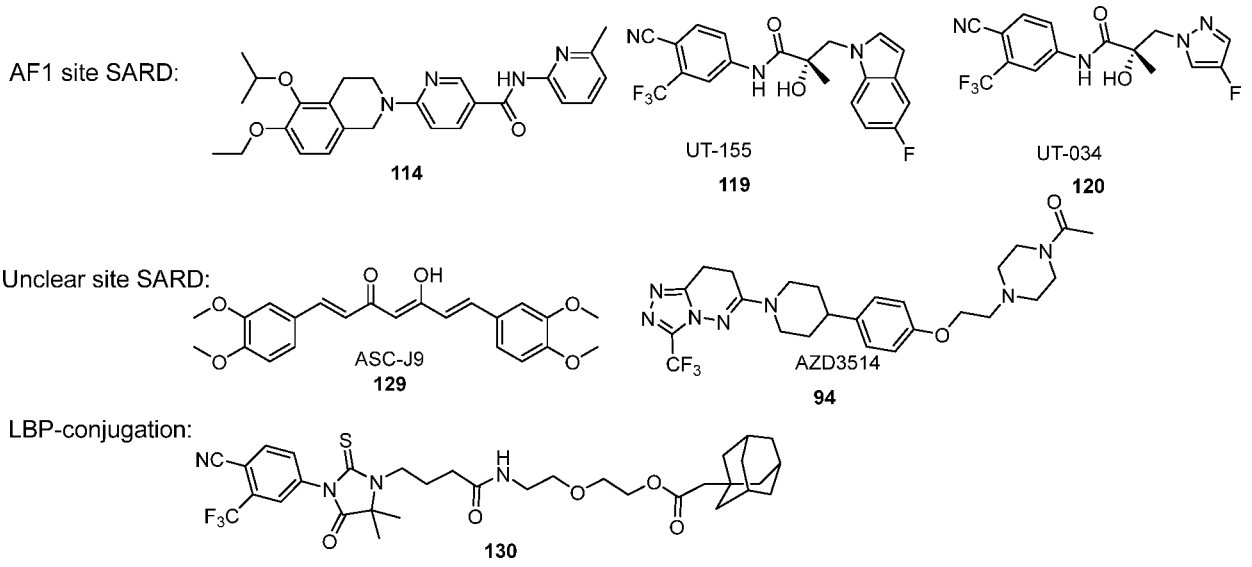

Figure 29. Structures of SARD.

125 inhibits tumor growth in LNCaP xenograft mice, but is less efficacious than enzalutamide.

7.4. DBD. Pyrvinium (**126**) was identified as the first DBD inhibitor with an IC_{50} of 0.19 μM in AR transcriptional activity (Figure 28).[212] Compound **127** is a lead compound obtained from virtual screening and has an IC_{50} of 0.33 μM in an eGFPT assay and an IC_{50} of 0.28 μM in reducing PSA in LNCaP. An SAR study and optimization of **127** led to **128**, which has IC_{50} values of 0.10 μM in an enhanced green fluorescence cellular AR transcription assay and 0.17 μM in an LNCaP PSA assay. In a cell proliferation assay, the IC_{50} values for **128** were <0.5 μM in LNCaP and <0.5 μM in MR47F.[213]

8. SARD

The rapid emergence of resistance to AR antagonists in the clinic has necessitated new approaches of targeting AR. Taking a page from selective estrogen receptor degraders (SERD) in the estrogen receptor arena, the selective androgen receptor degrader (SARD) is thought to be a potentially promising strategy with which to treat prostate cancer.[214] SARD is proposed to disrupt the AR coregulatory protein−protein interaction and lead to a proteasome-dependent degradation of the AR protein, potentially through an enhanced association of AR with MDM2, which is an E3 ligase.[215] However, the exact mechanism of SARDs is still not clear.

Some compounds, such as **114**, **119**, and **120** described above, when binding to the AF1 site, are found to be able to degrade full-length AR and ARVs. Further clinical evaluation of these compounds, which may help to understand the role of ARV in CRPC, is awaited.

Compounds **129** and **94** are also identified as SARDs, but their binding site is unknown. At 7.5 μM, ASC-J9 degrades >80% of AR and ARV3, completely inhibits DHT (1 nM and 10 nM), and inhibits the growth of C4-2, C81, CWR22RV1, and LNCaP cells at a concentration of 5 μM (Figure 29).[216] A mechanism of action study showed that ASC-J9 interrupts the AR-AR70 and AR-SRC interactions in LNCaP cells and it interrupts the AR-AR5 interaction in WPMY-1 cells. ASC-J9 inhibits C81, C4-2, and LNCaP xenograft mouse tumor growth with 75 mg/kg dosing. It is currently being evaluated in a phase II clinical trial as an acne cream. As discussed above, AZD3514 can be classified as a SARD, but its mechanism is unknown.

Compound **130**, a derivative of RU56187 can also degrade AR. It achieves a maximum of >50% of AR degradation in LNCaP cells. It also blocks cell growth in LNCaP and MR49F at a 3 μM concentration.[217] Although **130** is a weak degrader, it validates a concept that AR can be degraded by AR inhibitor conjugates.

9. PROTACs

In 2001, the laboratories of Deshaies at the California Institute of Technology and Crews at Yale University published their groundbreaking paper, which formally documented the concept of proteolysis-targeting chimeras (PROTACs).[218] A PROTAC is a bifunctional small molecule consisting of a ligand for the protein of interest (POI) and a ligand to bind to and recruit an E3 ligase or an E3 ligase complex, tethered together through a linker. A PROTAC molecule brings the POI to close proximity of the E3 ligase/E3 ligase complex for ubiquitination, followed by proteosome-dependent degradation. In the past few years, major progresses have been made in the discovery and development of PROTAC degraders for a large number of proteins, including AR.

For the design of PROTAC degraders against AR, the AR ligand can be agonists, antagonists, or AR allosteric site binders, as described above. E3 ligase systems, such as inhibitors of

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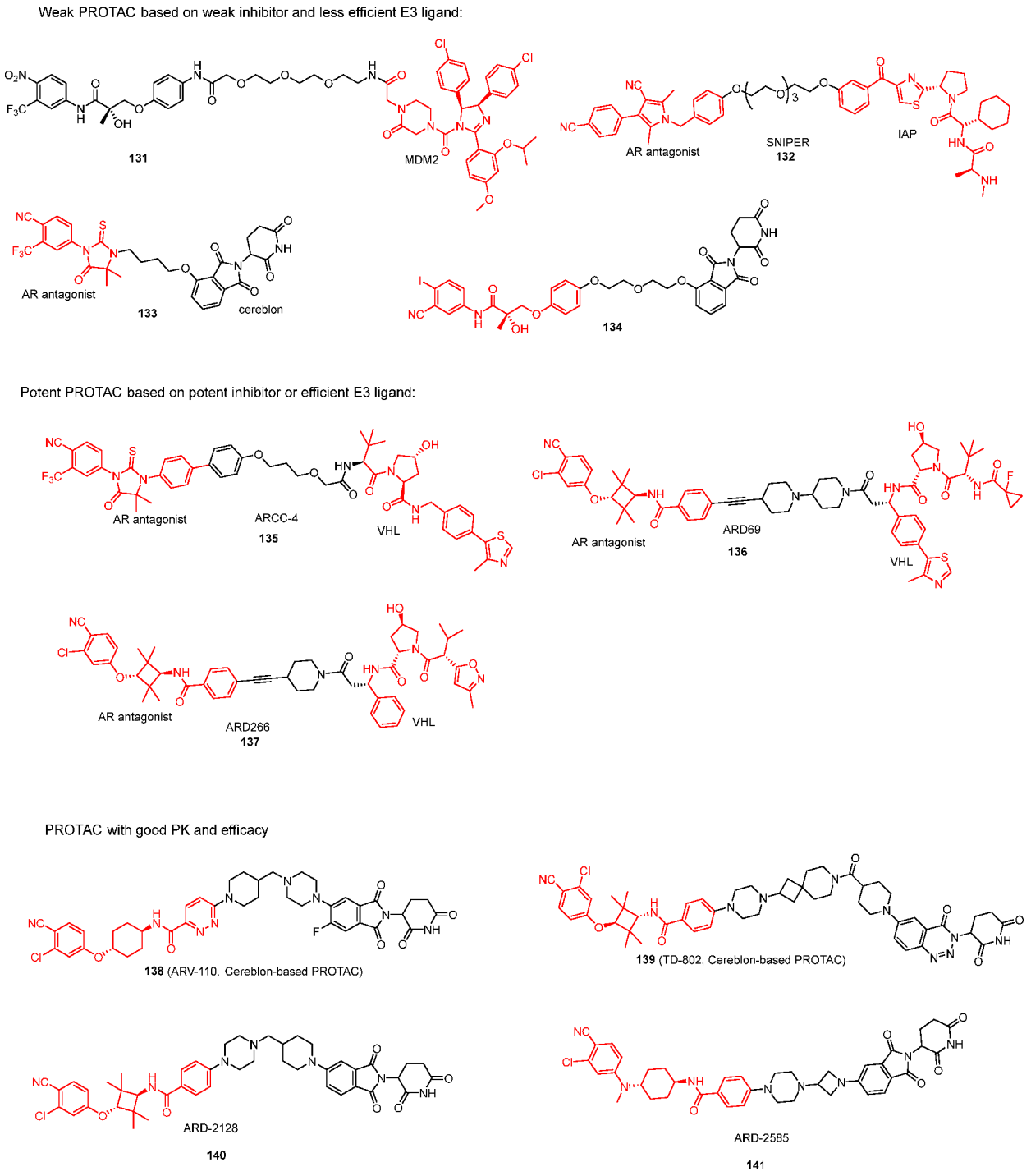

Figure 30. Chemical structures of AR PROTACs.

MDM2, apoptosis proteins (IAP), the von Hippel−Lindau (VHL)/cullin 2, and the cereblon/cullin 4A, have been used in the design of PROTAC degrader molecules. The E3 ligase systems and their utilities in PROTACs have been recently reviewed.[219]

In 2008, the Crews laboratory reported the first PROTAC AR degrader (**131**), which was designed using an MDM2 inhibitor as the E3 ligase ligand and bicalutamide as the AR antagonist.[220] While compound **131** only degraded AR protein in cells at micromolar concentrations, it provided an important proof-of-concept (Figure 30).

Scientists from the Takeda Corp. employed IAP ligands for the design of bifunctional degraders, which they named specific and nongenetic inhibitors of apoptosis protein-dependent protein erasers (SNIPERs). Compound **132** was one such SNIPER molecule for AR.[221] This compound (**132**) reduces AR at 1 μM in 22RV1 and VCaP cells. In the VCaP cell line, it also inhibits AR-mediated gene expression and suppresses cell growth. In addition to AR degradation, **132** induces the degradation of cIAP1 protein by binding to cIAP1, which leads to the activation of caspase and the apoptosis of VCaP cell line.

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PROTAC **133** is obtained by linking the cereblon ligand thalidomide to a relatively weak AR antagonist RU56187.[222] PROTAC **133** demonstrates AR degradation in LNCaP and VCaP in a dose- and time-dependent manner. It also inhibits LNCaP cell proliferation, migration, and invasion, but it is a weak AR degrader with potency or efficacy not superior to that of enzalutamide. Kim et al. designed the PROTAC **134** using a bicalutamide derivative as the AR ligand and thalidomide as a cereblon ligand. Compound **134**, however, is a weak AR PROTAC with a DC_{50} value of 5.2 μM in LNCaP cells.[223]

Highly potent AR PROTACs were designed using potent AR antagonists and VHL ligands, represented by compounds **135**–**137**. Crews et al.[224] reported an enzalutamide VHL-based AR PROTAC ARCC-4 (**135**), which achieves low nanomolar degradation potencies in VCaP, LNCaP, 22RV1, and other AR+ prostate cancer cell lines, as well as in the AR+/ER+ T47D breast cancer cell line. It also inhibits the growth of prostate cancer cells. Our group[225] discovered ARD69 after a systematic optimization of the VHL ligand portion by testing different AR antagonists and optimizations of the linker. ARD69 achieves a DC_{50} value of <1 nM in LNCaP and VCaP cells. It also reduces AR-related gene expression in low nanomolar concentrations and inhibits LNCaP and VCaP cell growth at nM concentrations. In a mouse VCaP xenograft model, a single dose of ARD69 reduces AR and PSA effectively. In a follow-up study, a weak VHL ligand was used for the successful design of a potent and efficacious AR PROTAC ARD266 (**137**).[226] Despite their exceptional degradation potency, compounds **136**–**137** have low oral bioavailability in animals, which limits their further development. ARD69 and ARD266 showed that PROTACs with highly rigid linkers not only are feasible but also may provide better potency.

AR PROTACs designed from a potent AR ligand and cereblon ligand with rigid linkers have demonstrated excellent AR degradation potency, potent cell growth inhibitory activity, good PK profiles, and efficacious antitumor efficacy. ARV-110 from Arvinas is the first AR PROTAC evaluated in clinical trials.[227] ARV110 utilized a potent AR antagonist, which is derivative of **72** (Section 4) and a thalidomide analogue. In a preclinical study, ARV-110 degrades AR at low nM concentrations in LNCaP, VCaP, and AR-mutated VCaP (F877L, T878A, M897V, and H875Y) cell lines. It also blocks PSA expression and inhibits cell growth in AR-dependent wild-type and enzalutamide-resistant VCaP cell line.[228] ARV-110 effectively reduces AR protein in VCaP and LNCaP xenograft tumor tissues. Importantly, ARV-110 inhibits tumor growth and is more efficacious than enzalutamide in AR+ prostate cancer xenograft models in mice with oral administration. Initial clinical data showed that ARV-110 is well tolerated, effectively reduces AR protein in tumor tissue in patents, and achieves clinical objective responses with oral administration.[229] TD-802 (**139**), which was made from a derivative of the AR antagonist **72** (Section 4), a cereblon ligand, and a rigid linker, potently degrades AR protein and inhibits cancer cell growth in AR+ cancer cells. TD-802 also has good microsomal stability and *in vivo* pharmacokinetic (PK) properties and is capable of retarding tumor growth in the VCaP xenograft model in mice upon intraperitoneal (IP) injection.[230] Our group recently reported two series of orally available AR PROTACs.[231,232] We employed thalidomide as the cereblon ligand and systematic optimization of the AR antagonist and linker portions to obtain two series of exceptionally potent and efficacious degraders exemplified by ARD-2128 and ARD-2585 (**140** and **141**, respectively).[231,232] ARD-2128 achieves DC_{50} values of 0.28 and 8.3 nM in VCaP and LNCaP cell lines, respectively. ARD-2128 achieves an excellent PK profile and 67% oral bioavailability in mice. It effectively reduces AR protein and suppresses AR-regulated genes in tumor tissues with oral administration, which leads to the effective inhibition of tumor growth in mice without signs of toxicity.

ARD-2585 is an even more potent AR degrader than ARD-2128. ARD-2528 achieves DC_{50} values of less than 0.1 nM in both VCaP and LNCaP cell lines. ARD-2585 inhibits VCaP and LNCaP cellular growth with IC_{50} values of 1.5 and 16.2 nM, respectively. ARD2585 demonstrates excellent PK in mice and 51% oral bioavailability. It is more efficacious than enzalutamide in suppressing tumor growth in mice VCaP xenograft without any sign of toxicity.

The data on ARV-110, ARD-2128, and ARD-2585 showed that highly potent and orally active AR PROTAC molecules can be successfully designed using a potent AR antagonist and a cereblon ligand.

PROTACs based on inhibitors binding to NTD pockets should be able to degrade ARV and full-length AR simultaneously. AF1 and DBD are the two known binding sites in NTD. Some of the AF1 site inhibitors are SARDs (Section 8). Hence, an AR PROTAC based on a DBD site inhibitor would be a good choice for an ARV degrader. MTX-23 is the first PROTAC based on a derivative of **128** (section 7.4) and a VHL ligand.[233] MTX-23 degrades ARV7 and full-length AR with DC_{50} values of 0.37 and 2 μM, respectively (Figure 31).

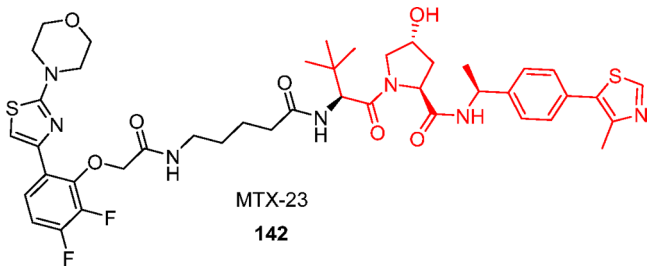

Figure 31. Chemical Structure of AR PROTAC MTX-23.

MTX-23 inhibits cellular growth of apalutamide- and darolutamide-resistant 22RV1 and VCaP cell lines at a concentration of 1 μM and suppresses tumor growth in enzalutamide-resistant 22RV1 mouse xenografts. Although a modestly potent degrader of ARV7 and full-length AR, MTX-23 is a useful tool compound with which to validate the concept of ARV PROTACs.

10. FUTURE PERSPECTIVES

In the past half century, significant efforts from pharmaceutical companies and academic research laboratories have been invested in the development of AR agonists. Besides the early achievements in steroid-based AR agonists, no nonsteroid AR agonist has been approved by the FDA to date. However, exploration at the molecular level of nonsteroid AR agonists with LBP has led to great progress in AR antagonists since the year 2000. Second-generation AR antagonists enzalutamide, apalutamide, and darolutamide are selective, potent, and efficacious and have fewer side effects in the clinic. However, the rapid emergence of resistance to these drugs necessitates new strategies to target AR.

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The recently established surface druggable pockets, AF2, BF3, and DBD, may allow circumvention of some of the LBP-related drug resistance mechanisms. Some tool compounds have been identified for each binding site. More potent and selective compounds for these sites may be needed to further understand their MOAs. With the cocrystal structures of the AF2, BF3, and DBD binding pockets, structure-based drug design is feasible.

Although the cocrystal structure of the AF1 site is still unavailable, compounds **115** and **116** from the Miller group shed some light in this direction.[203−205] These compounds are minor modifications of bicalutamide but bind to the AF1 site and act as SARD molecules. Given the success in selective estrogen receptor degraders (SERD), AF1-binding SARDs are an important direction in AR research.

In the past few years, AR PROTACs have become a hot topic in AR research and AR-targeted therapy. Interestingly, despite a large number of agonists and antagonists, reported AR PROTACs have employed only a few AR inhibitors and their derivatives, including bicalutamide, enzalutamide, and compound **72** from Pfizer. Ligands for VHL and cereblon have been successful in designing potent AR PROTACs, but only cereblon ligands afford a good oral bioavailability. ARV-110 was the first orally active PROTAC AR degrader advanced into clinical development. ARV-766 was the second PRTOAC AR degrader evaluated in phase I clinical studies. Currently, both ARV-110 and ARV-766 are focused on a subset of enzalutamide-resistant CRPCs. Most recently, AC-0176 from Accutar and CC-94676 from Celgene/BMS were also being evaluated for safety, tolerability, pharmacokinetics, and pharmacodynamics in phase I human clinical trials. With the enthusiasm of pharmaceutical companies and academic research groups, more PROTAC AR degraders are expected to enter clinical development in the near future.

Compounds binding to AF1 and DBD sites are capable of inhibiting ARV7. PROTACs like MTX-23, based on a DBD inhibitor, can degrade ARV7. Further optimization of MTX-23 may provide an opportunity to develop a therapy for the treatment of a subset of CRPC that is dependent on ARV7 and will provide research tools to study ARV7 in CRPC.

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Notes

The authors declare the following competing financial interest(s): The University of Michigan has filed patent applications on AR degraders, which have been licensed to Oncopia Therapeutics, Inc. W. Xiang and S. Wang are co-inventors on these patent applications and receive royalties from the University of Michigan. S. Wang was a co-founder and served as a paid consultant to Oncopia. S. Wang and the University of Michigan also owned equity in Oncopia, which was acquired by Roivant Sciences. S. Wang is a paid consultant to Proteovant Therapeutics/Roivant Sciences and owns equity in Roivant Sciences. The University of Michigan has received a research contract from Oncopia/Proteovant Therapeutics/Roivant Sciences for which S. Wang serves as the principal investigator.

Biographies

Weiguo Xiang received his Ph.D. in Medicinal Chemistry from Duquesne University in 2016. After graduation, Weiguo joined Dr. Shaomeng Wang's laboratory at the University of Michigan as a postdoctoral fellow and is currently a research investigator. Weiguo has been working on the discovery and development of PROTAC degraders against different proteins in the past few years.

Shaomeng Wang received his B.S. degree in Chemistry from Peking University in 1986 and his Ph.D. in Chemistry from Case Western Reserve University in 1993, followed by a postdoctoral fellowship at the NIH, USA. Dr. Wang was assistant and then associate professor between 1996−2001 at Georgetown University Medical Center. Dr. Wang joined the University of Michigan, Ann Arbor in 2001 and is currently the Warner-Lambert/Parke-Davis Professor in Medicine and Professor of Internal Medicine, Pharmacology and Medicinal Chemistry. Dr. Wang served as the Co-Editor-in-Chief for the *Journal of Medicinal Chemistry* from 2012−2020. Dr. Wang has published more than 320 peer-reviewed papers, is an inventor of 66 granted US patents, and has advanced 9 compounds into phase 1−3 clinical development.

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ABBREVIATIONS USED

ADT, androgen deprived therapy; AF1, activation function 1; AF2, activation function 2; AR, androgen receptor; ARV, androgen receptor splice variant; ARE, androgen response element; BF3, binding function 3; DBD, DNA binding domain; DHT, dihydrotestosterone; EGF, epidermal growth factor; ER, estrogen receptor; FLAR, full length AR; HSP, heat shock protein; IAP, inhibitor of apoptosis; IGF, insulin-like growth factor; IL-6, interleukin-6; LBD, ligand binding domain; LBP, ligand binding pocket; mCRPC, metastatic castration-resistant prostate cancer; NTD, N-terminal transcriptional domain; PR, progestogen receptor; PROTAC, proteolysis targeting chimera; SARD, selective AR degrader; SERD, selective estrogen receptor degrader; ; SNIPER, inhibitor of apoptosis protein-dependent protein eraser; VHL, von Hippel−Lindau

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