CHAPTER 12

RECENT ADVANCES IN TARGETING THE ANDROGEN RECEPTOR WITH PROTACS

Weiguo Xiang, Xin Han, Lijie Zhao, and Shaomeng Wang

Departments of Internal Medicine, Pharmacology, and Medicinal Chemistry, University of Michigan

Contents

1. INTRODUCTION

The androgen receptor (AR) is a nuclear transcription factor that is essential for growth, survival and proliferation of prostate cells.[1] AR also plays a key role in the initiation and progression of human prostate cancer and a subset of human breast cancer.[2,3] Androgen deprivation therapy (ADT), achieved either by surgical castration or with drugs that block androgen synthesis, has proven to be effective in the treatment of androgen-dependent advanced and metastatic prostate cancer.[4,5] Unfortunately, after a few years of castration, prostate cancer progresses into what is now termed castration-resistant prostate cancer (CRPC).[6] AR and AR signaling continue to play important roles in CRPC, and effective inhibition of AR and AR signaling has been pursued for the treatment of CRPC.[7]

2022 Medicinal Chemistry Reviews, Volume 57
ISSN 2575-9175
http://dx.doi.org/10.1021/mc-2022-vol57.ch12

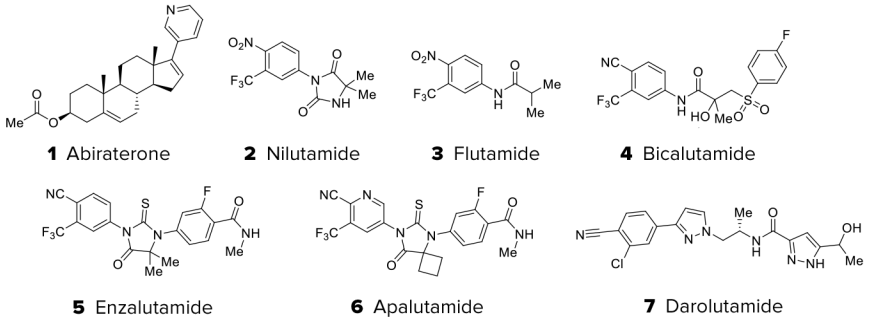


Figure 1 Drugs that block AR and AR signaling.

New therapies targeting AR and AR signalling have been developed for the treatment of advanced prostate cancer, including metastatic CRPC (mCRPC). These therapies include a new anti-androgen drug, abiraterone, and second-generation pure AR antagonists (Figure 1).[8,9] Abiraterone (**1**) is a CYP17 inhibitor that blocks the biosynthesis of testosterone and dihydrotestosterone. The first-generation AR antagonists nilutamide (**2**) and flutamide (**3**) have low selectivity of prostate over other tissues and organs.[10] They only partially suppress AR activity and were largely replaced by bicalutamide (**4**).[11] More recently, second-generation AR antagonists with no agonist effects, improved potency and efficacy, and diminished side effects were developed.[12] In the past decade, three second-generation AR antagonists, namely enzalutamide (**5**), apalutamide (**6**) and darolutamide (**7**), have been approved for the treatment of prostate cancer. Enzalutamide and apalutamide have a similar chemical scaffold.[13] Enzalutamide was the first second-generation pure AR antagonist approved by the U.S. FDA and is currently the standard first-line treatment for CRPC. An uncommon but serious side effect of enzalutamide is seizure resulting from its ability to cross the blood brain barrier (BBB) and bind to the GABA-gated chloride channel.[14] Although apalutamide and enzalutamide have a similar GABA binding affinity, apalutamide has lower brain exposure than enzalutamide and causes fewer incidences of induced seizure.[15] A common side effect of apalutamide is skin rash, which is possibly due to the cyano pyrimidine moiety undergoing reversible covalent bond formation with cysteine residues in proteins.[16]

Darolutamide (**7**) was recently approved by the FDA to treat CRPC.[17] Darolutamide is a mixture of two diastereomers that are interconvertible through a ketone metabolite.[17] Both alcohol diastereomers and the ketone form of darolutamide are active AR antagonists. *In vitro*, darolutamide has 8-10 times stronger affinity to AR than enzalutamide or apalutamide.[18] Furthermore, darolutamide exhibits reduced brain penetration with the ratio of brain-to-blood concentration in mice >10-fold lower than that for enzalutamide.[19] Consequently, darolutamide is less prone to inducing seizures.

Despite the clinical benefits of these second-generation AR antagonists, patients with prostate cancer can develop resistance to these drugs, with AR and AR signaling continuing to play an important role for cancer growth.[20] Some of the major resistance mechanisms involving AR include activation of point mutations, gene amplification, and expression of splicing variants.[21] Consequently, new strategies are being pursued to target AR.

Learning from the successful development of selective estrogen receptor degraders (SERDs) for the treatment of ER-positive breast cancer,[22] selective androgen receptor degraders (SARDs) have been pursued as a potential new therapeutic strategy targeting AR. SARDs are proposed to disrupt the interactions of AR and its coregulators, leading to activation of a proteasome-dependent pathway to promote AR degradation.[23] Several classes of SARD molecules have been reported. Compounds **8** and **9** are derivatives of bicalutamide. They are reported to bind to the AF1 (activation function-1) transactivation domain in AR and are capable of degrading full-length AR and AR variants (Figure 2).[24] ASC-J9 (**10**) was shown to induce degradation of wild-type AR and ARV3 variants, but its binding site on AR was not identified.[25] It is currently being evaluated in a Phase II clinical trial for the treatment of acne. AZD3514 (**11**) reduces the expression of AR, but its precise mechanism of action has not been determined.[26] Compound **12** was designed using an AR ligand and a hydrophobic tag that mimics the partially denatured protein state and leads to the degradation of AR.[27] Compared with SERD molecules, current SARD molecules lack the desired potencies, and further optimization is needed toward the development of SARD molecules as a new class of therapeutic agents for the treatment of prostate cancer.

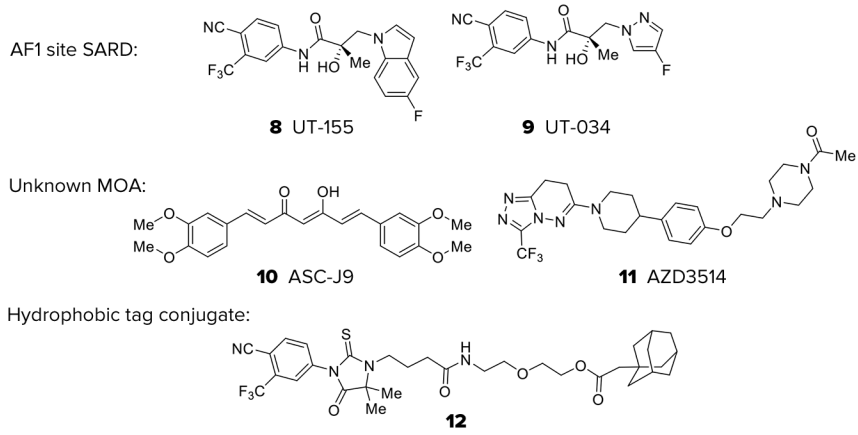


Figure 2 Chemical structures of selective AR degraders (SARDs).

In the last few years, induction of protein degradation by employing the proteolysis-targeting chimera (PROTAC) technology has gained considerable momentum for the discovery and development of new therapeutic agents. In this chapter, we will review recent progress on the discovery and development of PROTAC AR degraders.

1.1 Basic Concept of Proteolysis-Targeting Chimera (PROTAC) Technology

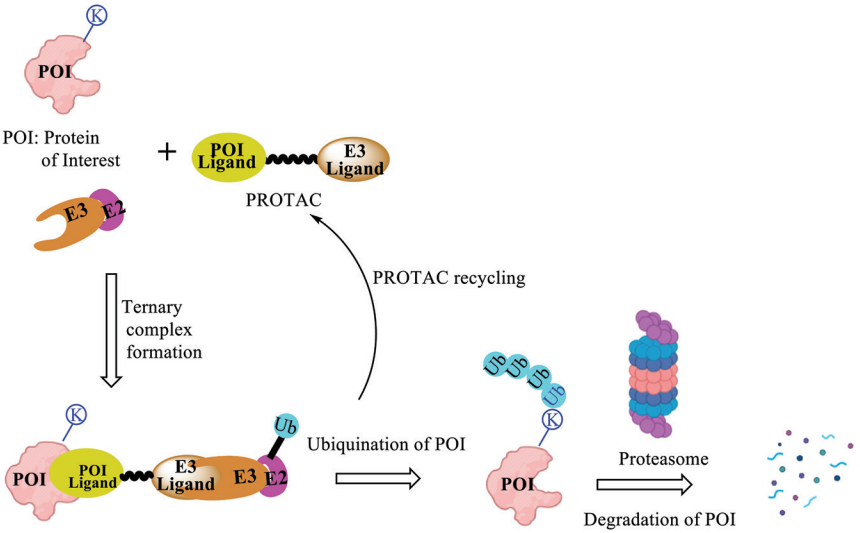


Figure 3 Illustration of the PROTAC technology platform.

PROTACs were initially introduced in 2001 by Deshaies and Crews.[28] The general concept is outlined in Figure 3. Although the PROTAC research field progressed slowly for the first decade since the initial publication, tremendous progress has been made in recent years in investigating the therapeutic potential of this approach. PROTAC degraders have several major advantages over traditional small-molecule agents. First, it has been demonstrated that one PROTAC degrader molecule has the capability of inducing degradation of more than one protein of interest (POI) by functioning as a "catalyst" which can be recycled multiple times (Figure 3). This behavior is also referred to as "event driven" for a degrader molecule instead of "occupancy driven" for a traditional small-molecule drug.[29] PROTAC degraders can achieve exceptional degradation potencies on POIs and therefore can have more profound pharmacological effects against POIs than their corresponding small-molecule inhibitors. Second, a PROTAC degrader requires the formation of a ternary complex, consisting of the PROTAC molecule itself, the POI, and the E3 ligase complex.[30] The formation of a ternary complex by a PROTAC degrader not only involves the binding pocket residues on the POI but also engages POI protein and E3 ligase protein interactions. Hence, PROTAC degraders are capable of achieving high degradation selectivity. Third, for the design of a PROTAC degrader, a ligand for the POI is needed, but the ligand does not need to target a functional site in the POI.[31] This provides the opportunity to expand druggable protein targets beyond those susceptible to traditional small molecules, which typically target a functional site in a protein to be therapeutically effective. Finally, by effectively reducing the levels of a protein through degradation, a PROTAC degrader has the ability to shut down a POI more profoundly than a traditional small-molecule inhibitor, particularly for those proteins with multiple domains encoding different biological functions. Hence, a PROTAC degrader can have an augmented pharmacological effect and be more efficacious than a traditional small-molecule inhibitor.[32]

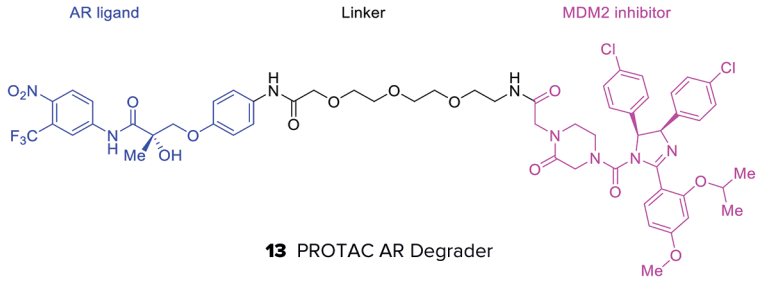
Compared to traditional small molecules, PROTAC degrader molecules have major limitations in the context of drug development. Since a PROTAC degrader consists of two small-molecule ligands and a linker, it typically has a molecular weight (MW) above 700.[33] Such high MW compounds have intrinsic challenges in achieving good cell permeability and oral bioavailability. Therefore, while PROTAC degraders can be readily designed as research tool compounds for *in vitro* studies, extensive optimization

efforts are needed to achieve good tissue penetration and, especially, oral bioavailability.

To date, ligands for four different E3 ligases have been employed in the design of PROTAC AR degraders. Below we discuss PROTAC AR degraders designed using each of these four E3 ligases.

2. MDM2-BASED AR PROTAC DEGRADERS

The first PROTAC AR degrader (**13**) was reported by the Crews Laboratory in 2008 using MDM2 (murine double minute 2) as the targeted E3 ligase (Figure 4).[34] In a physiological setting, MDM2 binds to p53 and induces p53 degradation. Although targeting the MDM2-p53 protein-protein interaction was proposed as a therapeutic strategy to reactivate p53, discovery of potent and selective MDM2 inhibitors was found to be difficult. A breakthrough was reported in 2004 by scientists at Roche, who discovered nutlins as first-in-class potent and selective inhibitors of the MDM2-p53 interaction with *in vivo* activity.[35] In their design of PROTAC AR degraders, the Crews Laboratory employed a nutlin with an IC_{50} value of 90 nM for binding to MDM2 linked to a bicalutamide analog with a K_i value of 4 nM to AR. Despite the use of high-affinity ligands to both MDM2 and AR, compound **13** was found to degrade the AR protein in cells only at micromolar concentrations, suggesting that the MDM2 E3 ligase is not very efficient in inducing degradation of AR. Nevertheless, the study by the Crews Laboratory provided important proof-of-concept that the AR protein can be degraded by a bifunctional small molecule through the PROTAC mechanism.

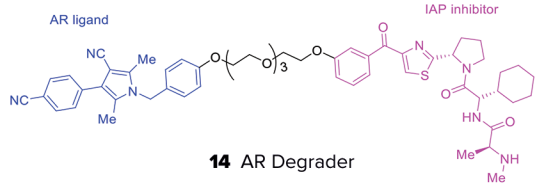


13 PROTAC AR Degrader

Figure 4 Chemical structure of an MDM2-based AR PROTAC molecule.

3. IAP-BASED AR PROTAC DEGRADERS

Inhibitors of apoptosis proteins (IAPs) were initially identified as a class of proteins that play a key role in regulating apoptosis, which is a form of programmed cell death. Several IAP protein members in mammalian cells, including cellular IAP1 (cIAP1), cIAP2, and X-linked IAP (XIAP) also possess a ring domain, which encodes an E3 ligase function.[36] Smac (second mitochondria-derived activator of caspase), also known as DIABLO (direct IAP-binding protein with low pI), was identified as an endogenous antagonist of IAP proteins.[37] Smac binds to IAP proteins using an Ala-Val-Pro-Ile tetrapeptide binding motif. Based upon the Smac-IAP protein-protein interaction, small-molecule inhibitors of IAP proteins, often called Smac mimetics, have been developed, and a number of them are currently in clinical development.[38] Scientists from Takeda have employed Smac mimetics to recruit IAP proteins as the E3 ligases in the design of bifunctional PROTAC degraders, which they named SNIPERs (specific and non-genetic inhibitor of apoptosis protein [IAP]-dependent protein erasers).[39] Compound **14** is a SNIPER that was designed using a high-affinity IAP inhibitor and a pyrrole-based potent AR antagonist (Figure 5) and was found to be capable of reducing AR protein in AR-positive VCaP and 22RV1 cell lines at low micromolar concentrations. Compound **14** consistently and effectively suppresses AR-mediated gene expression and inhibits cell growth in the VCaP cell line. It was demonstrated that although SNIPER molecules bind to XIAP and cIAP1/2, cIAP1 is the primary E3 ligase engaged in the induction of degradation of the target protein.[40] A major weakness of SNIPER degrader molecules is that by binding to cIAP1, they also induce rapid degradation of cIAP1 in cells, potentially limiting their degradation potency and efficacy against the POI.[39]

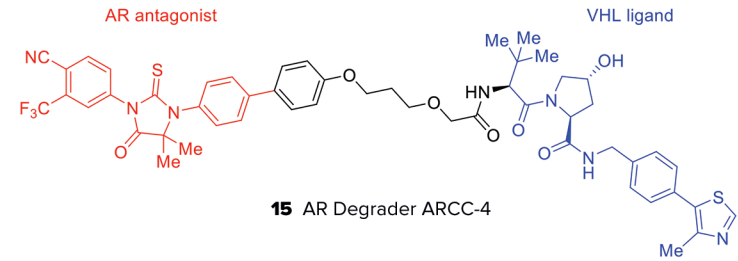


14 AR Degrader

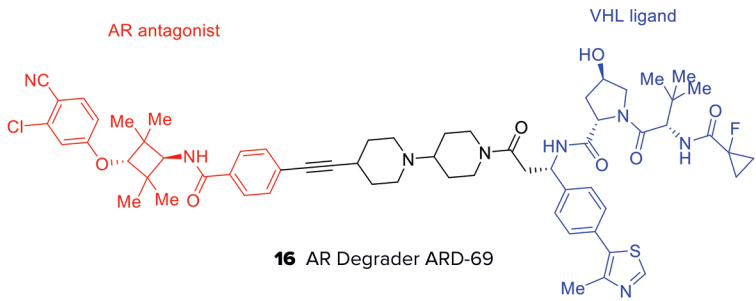
Figure 5 Structure of IAP-based AR PROTAC molecules.

4. VHL-BASED AR PROTAC DEGRADERS

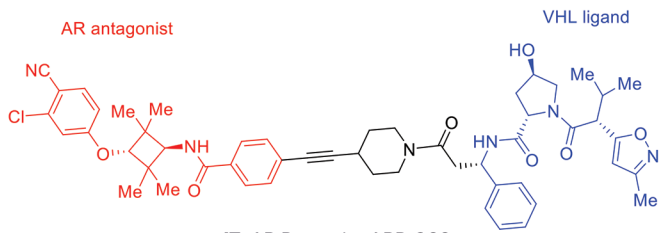
The von Hippel-Lindau (VHL) E3 ubiquitin ligase complex has played a critical role in the advances of the PROTAC field. The VHL complex consists of VHL itself, elongins B and C, cullin 2, and ring box protein 1 (Rbx1).[41] Hypoxia-inducible factor 1α (HIF-1α) is the primary endogenous substrate of the VHL E3 ligase. Co-crystal structures of VHL in a complex with a HIF-1α peptide show that VHL contains a single, conserved pocket that interacts with a short HIF-1α peptide containing a hydroxyproline residue.[42] Based upon the short HIF-1α peptide that is responsible for its binding with VHL, a large number of peptidomimetics have been developed in the laboratories of Ciulli at the University of Dundee and Crews at Yale University.[43,44] These



15 AR Degrader ARCC-4



16 AR Degrader ARD-69



17 AR Degrader ARD-266

Figure 6 Chemical structures of representative VHL-based AR PROTAC molecules.

peptidomimetics have much improved binding affinity, cell permeability, and microsomal stability over that of the initial HIF-1α peptide. These potent and cell-permeable peptidomimetic ligands for VHL have enabled the design of highly potent PROTAC degraders for AR and many other proteins.[45]

ARCC-4 (**15**) was the first AR PROTAC degrader designed using a high-affinity VHL ligand (Figure 6).[46] ARCC-4 achieves a DC_{50} (half maximal degradation concentration) of 5 nM in the AR+ VCaP cell line, which has AR gene amplification. It also achieves low nanomolar degradation potencies in the LNCaP, 22RV1, and other AR+ prostate cancer cell lines, as well as in the AR+/ER+ T47D breast cancer cell line. Importantly, ARCC-4 efficiently degrades clinically relevant AR mutants containing a point mutation such as F876L, T877A, L702H, H874Y, or M896V. These results demonstrate that AR PROTAC molecules have the potential to overcome some important resistance mechanisms to some of the second-generation AR antagonists such as enzalutamide. ARCC-4 also potently inhibits cell growth in a number of AR+ prostate cancer cell lines, being 10-times more potent than enzalutamide.

Our group[47] reported ARD-69 (**16**, Figure 6) as a highly potent AR degrader with *in vivo* activity. ARD-69 was discovered through extensive optimization efforts (Figure 7). First, a set of initial AR PROTAC degraders was obtained by tethering enzalutamide to a high-affinity peptidomimetic VHL ligand with flexible linkers of various lengths. This led to the identification of compound **19** which was shown to reduce the levels of AR protein by 48% at 100 nM and by 88% at 1000 nM in the LNCaP cell line. Compound **20** was obtained by partial rigidification of the linker as well as by using a pyridinylpiperazine moiety that improves its physicochemical properties. Compound **20** was found to achieve similar AR degradation potencies as compound **19**. Changing the linking position in the VHL ligand and employing a highly rigid linker yielded compound **21**, which was found to reduce AR in the LNCaP cell line by 20, 81, and 97% at 10, 100, and 1000 nM, respectively. Finally, employment of a more potent AR antagonist with a high-affinity VHL ligand and a similar rigid linker afforded ARD-69 (**16**). ARD-69 achieves a DC_{50} value of <1 nM in the LNCaP and VCaP cell lines. It also potently suppresses AR-regulated gene expression, inhibits LNCaP and VCaP cell growth at low nM concentrations, and is >100-fold more potent than its corresponding AR antagonist. In a mouse VCaP xenograft

model, a single IP dose of ARD-69 effectively reduces the AR protein level and suppresses prostate-specific antigen (PSA) expression. ARD-69 inhibits tumor growth in the LNCaP and VCaP xenograft models in mice at well tolerated doses.[47] In a follow-up study, a weaker VHL ligand was used in the successful design of a highly potent AR PROTAC degrader ARD266 (**17**), demonstrating that effective PROTAC degraders do not necessarily require the most potent E3 ligase ligands.[48]

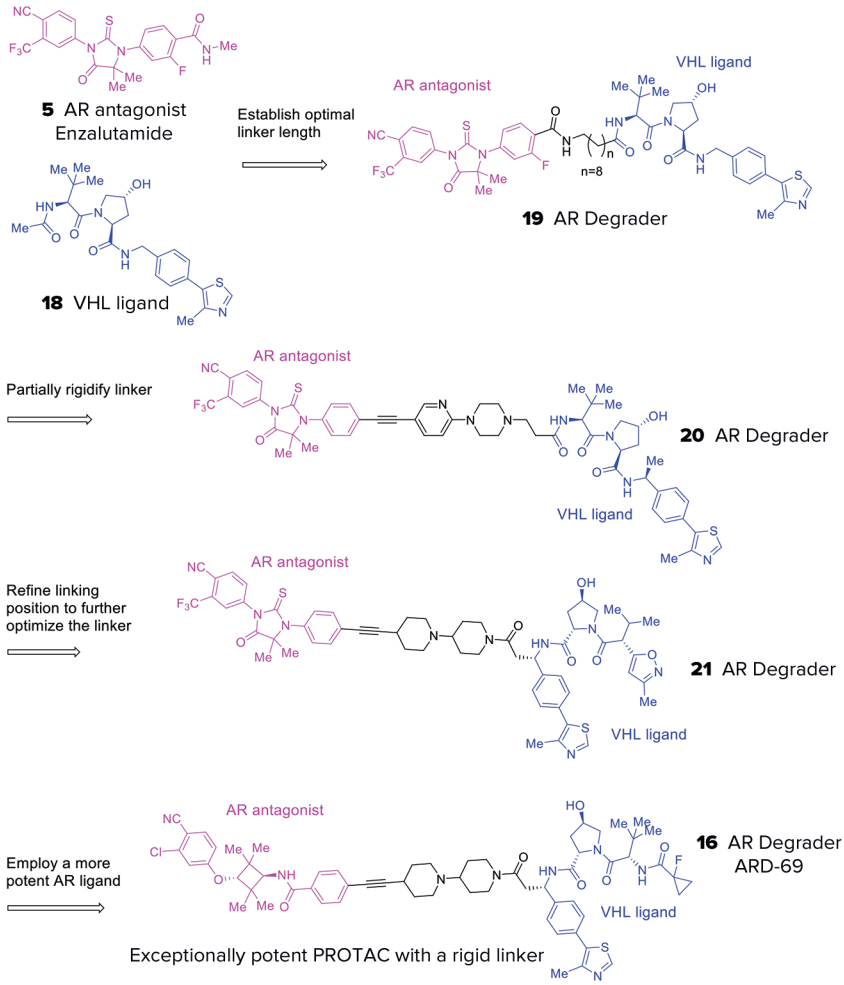


Figure 7 Stepwise design of an exceptionally potent VHL-based AR PROTAC ARD-69 with *in vivo* activity.

ARD-69 has a MW of 1129 and a calculated polar surface of 197 Å^2, and ARD-266 has a MW of 916 and a calculated polar surface of 174 Å^2. Both compounds employ a peptidomimetic VHL ligand. It is therefore not surprising that both compounds lack oral bioavailability, an important limitation for their further development as oral drugs.

5. CEREBLON-BASED AR PROTAC DEGRADERS

In 2010, Ito et al. made a landmark discovery that the protein cereblon is a primary target of thalidomide.[49] Cereblon is a substrate recognition receptor for the cullin 4A E3 ligase complex, consisting of cereblon, DDB1, and cullin 4A.[50-53] By binding to cereblon, thalidomide and its derivatives recruit non-native substrates (neo-substrates) to the cullin 4A/cereblon E3 complex for ubiquitination, followed by subsequent proteasomal degradation. Since thalidomide and its analogs lenalidomide and pomalidomide have low MW and excellent druglike properties, incorporating them as E3 ligase ligands in bifunctional PROTAC degraders offers an increased chance of achieving favorable drug properties. Bradner and his colleagues were the first to employ a cereblon ligand for the design of PROTAC degraders.[54] Cereblon ligands have been extensively used for the design of PROTAC degraders of AR.

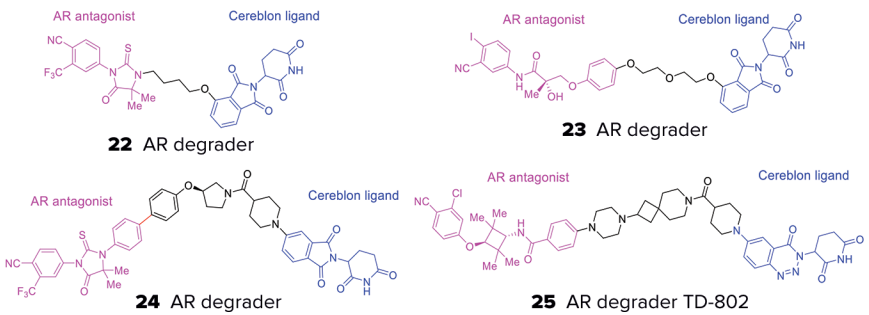


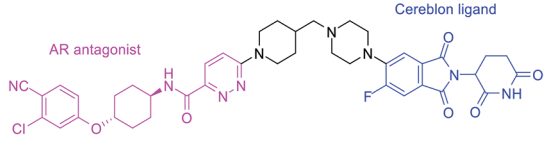
Figure 8 Chemical structures of representative cereblon-based AR PROTAC molecules.

Compounds **22** and **23** are two early PROTAC AR degraders designed using a cereblon ligand (Figure 8).[55,56] Although both **22** and **23** only degrade AR proteins at micromolar concentrations in AR+ prostate cancer cells and have demonstrated no superiority to enzalutamide in cell growth inhibition against AR+ prostate cancer cells, these compounds provided proof-of-

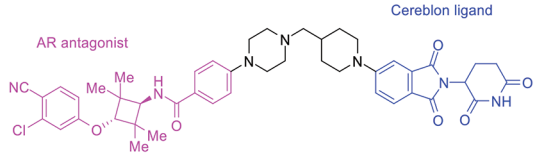
concept that the cereblon/cullin 4A E3 ligase can be employed for the design of PROTAC degraders against AR.

The PROTAC **24** was recently reported as a PROTAC AR degrader, employing an enzalutamide derivative as the AR ligand, a thalidomide derivative as the cereblon ligand, and a rigid linker. PROTAC **24** achieved a DC_{50} value of 77 nM in the AR+ LNCaP cell line.[57] TD-802 (**25**) was designed using a high-affinity AR ligand, which was initially discovered by scientists at Pfizer, together with a new cereblon ligand and a different rigid linker.[58] TD-802 was shown to potently degrade AR with a DC_{50} value of 12.5 nM in the LNCaP cell line. The compound has good microsomal stability and achieves reasonable pharmacokinetics (PK) after intraperitoneal (IP) injection in mice. Importantly, upon IP injection, TD-802 slowed tumor growth in the VCaP xenograft model in mice.

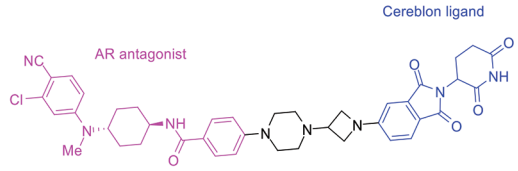
5.1 Discovery of Orally Bioavailable AR PROTAC Degraders



26 AR degrader Bavdegalutamide (ARV-110)



27 AR degrader ARD-2128



28 AR degrader ARD-2585

Figure 9 Three representative cereblon-based orally bioavailable AR PROTACs.

As mentioned above, a typical PROTAC degrader has a MW above 700 and falls outside of Lipinski's "rule of five," posing challenges to achieving

oral bioavailability.[59] Despite these properties, orally active AR PROTAC degraders have been successfully obtained through extensive optimization efforts, with three representative compounds shown in Figure 9.

Bavdegalutamide (ARV-110, **26**) was the first reported orally bioavailable AR PROTAC degrader with its structure included in a patent publication by Arvinas[60] and later disclosed in the 2021 AACR national meeting.[61] The optimization strategy used for the discovery of bavdegalutamide was presented in the AACR meeting and shown in Figure 10. Scientists at Arvinas started their efforts by screening different AR ligands and E3 ligands and chose an AR inhibitor reported by Pfizer[62] with thalidomide as the cereblon ligand, which yielded degrader **29** employing a flexible linker. Compound **29** achieves a DC_{50} value between 1 to 10 nM and D_{max} (maximal degradation) value <50% in in the LNCaP cell line. Compound **29** was found to have encouraging oral bioavailability, but it is reported to show high clearance in a PK study in an undisclosed species. Further optimization of the linker in **29** yielded compound **30**, which has a DC_{50} value < 1 nM and a D_{max} value >50%. Compound **30** was found to have suboptimal *in vivo* efficacy and a high melting point, suggesting challenges for formulation. Conformational restriction of the linker in **30** afforded **31**, which achieved a DC_{50} value < 1nM and D_{max} value >50%. Compound **31** was shown to auto-induce AR signaling, indicating that it might have some other mechanism of action in addition to its PROTAC mode of action. Replacing the pyrimidine in **31** with a phenyl provided **32**, which retains high AR degradation potency but had suboptimal oral exposure in a PK study in undisclosed species. Replacement of the AR ligand in compound **32** with a different AR antagonist and installation of a fluorine substituent on thalidomide led to the discovery of bavdegalutamide (ARV-110, **26**) as a candidate for clinical development.

In the LNCaP cell line, bavdegalutamide has a DC_{50} value of 0.24 nM and a D_{max} of 82%. Bavdegalutamide was shown to degrade AR at low nM concentrations in the parental VCaP cell line and other engineered VCaP cell lines containing a mutated AR (F877L, T878A, M897V, and H875Y), and effectively blocks PSA synthesis. Bavdegalutamide inhibits cell growth in the parental VCaP cell line and in an enzalutamide-resistant VCaP cell line.[63] Although bavdegalutamide has a MW of 812, it is reported to achieve sufficient oral bioavailability in mice, rats, and non-rodent species to support oral dosing in preclinical PD and efficacy models, preclinical toxicology studies, and in human clinical trials. Oral administration of bavdegalutamide effectively reduces AR protein in VCaP and LNCaP xenograft tumor tissues.

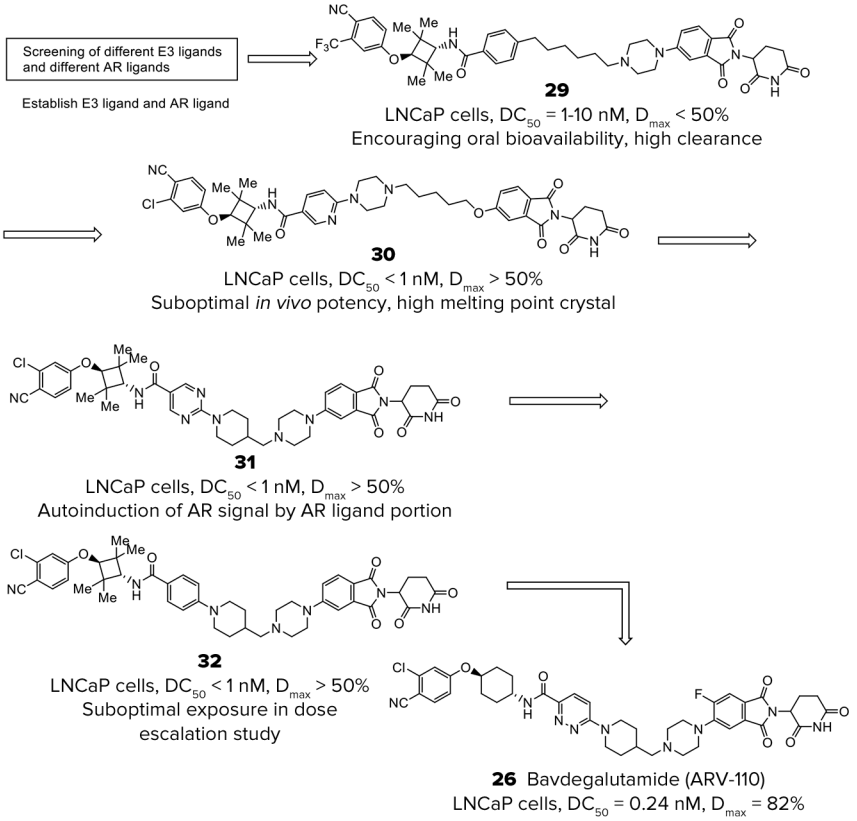


Figure 10 Medicinal chemistry campaign for the discovery of the potent and orally active AR degrader ARV-110.[60,61]

Bavdegalutamide effectively inhibits tumor growth and is more efficacious than enzalutamide in multiple AR+ prostate cancer xenograft models in mice with oral administration.[64]

Our group recently reported two series of orally bioavailable and potent AR PROTAC degraders, represented by ARD-2128 (**27**) and ARD-2585 (**28**) (Figure 9).[65,66] ARD-2128 employs a potent AR ligand reported by Pfizer scientists, with a rigid linker and thalidomide-type cereblon ligand. ARD-2128 achieves DC_{50} values of 0.28 nM and 8.3 nM in the VCaP and LNCaP cell lines, respectively, as well as an excellent PK profile in mice, including low clearance and good volume of distribution, and 67% oral bioavailability. Oral administration of ARD-2128 effectively reduces AR protein and

suppresses AR-regulated genes in tumor tissues, leading to the effective inhibition of tumor growth in mice. The chemical structure of ARD-2128 was independently included in a patent from Arvinas.[60]

ARD-2585 was obtained through a multiple-step optimization process, as shown in Figure 11.[66] First, the AR antagonist **33** was linked to thalidomide **34** through a linear linker to determine the optimal linker length, which led to identification of the potent degrader **35**. In the next stage, linker rigidification using different ring systems was investigated, yielding a potent degrader **36**. Finally, optimization of the AR antagonist portion of **36** and fine-tuning of the rigid linker resulted in the discovery of ARD-2585 (**28**). ARD-2585 achieves DC_{50} values below 0.1 nM in both the VCaP and LNCaP cell lines. It inhibits VCaP and LNCaP cellular growth with IC_{50} values of 1.5 and 16 nM, respectively, and demonstrates an excellent PK profile in mice with an oral bioavailability of 51%. ARD-2585 is more effective than enzalutamide in suppressing tumor growth in the VCaP xenograft tumor model in mice at well-tolerated doses.

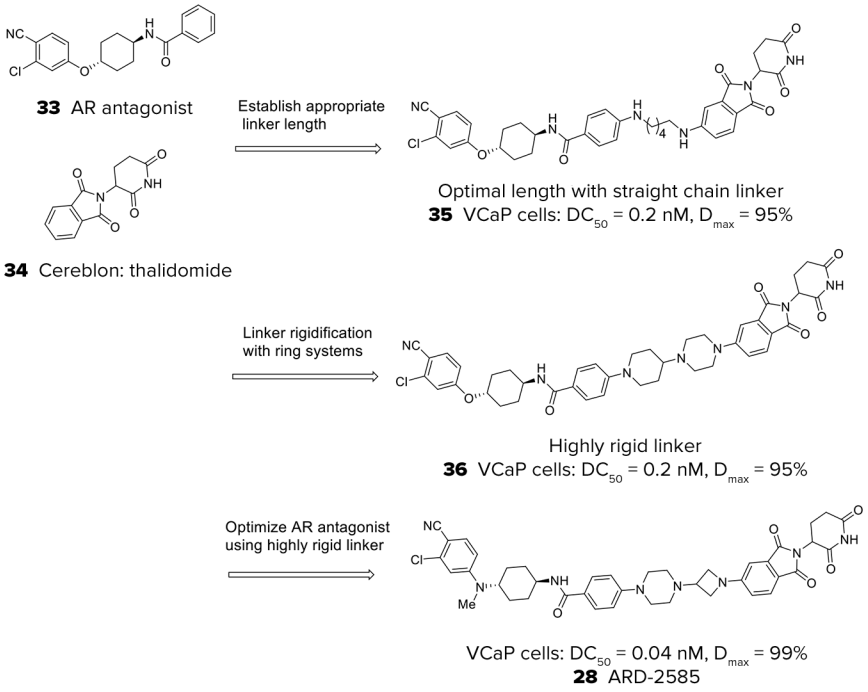
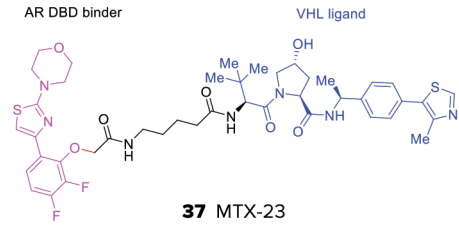


Figure 11 Stepwise design of ARD-258 as a highly potent and orally bioavailable AR PROTAC.

Bavdegalutamide, ARD-2128 and ARD-2585 have MWs of 812, 820, and 763, respectively, which puts them clearly outside the "rule-of-five" space. However, these AR degraders are able to achieve a good PK profile in mice and excellent oral bioavailabilities. Examination of the chemical structures of ARV-110, ARD-2128, and ARD-2585 highlights some of the common features and physicochemical properties of these orally bioavailable PROTAC degraders. Each of them employs a rigid, aliphatic linker containing a positively charged group, a thalidomide derivative as the E3 ligand, and a low MW AR ligand. Their calculated polar surface areas are between 149 and 180 $Å^2$, and their calculated clogP values are in the range of 4.3-6.7. The discovery of these highly potent and orally active AR PROTAC degraders suggests that despite the expected challenges in achieving good oral bioavailability with bifunctional PROTAC molecules, careful selection of ligands for the POI, employment of highly rigid linkers with good physicochemical properties, and use of cereblon ligands can deliver orally active PROTAC degraders.

6. PROTAC DEGRADERS TARGETING AR VARIANTS

It has been proposed that PROTAC degraders designed using inhibitors that bind to the N-terminal domain (NTD) should be able to induce degradation of both full-length AR as well as AR variants (ARV).[67] AF1 and DBD (DNA binding domain) are the two known binding sites located in the NTD of AR. MTX-23 (**37**) is the first ARV7 PROTAC based on an AR DBD ligand and a VHL ligand (Figure 12).[68] MTX-23 was shown to degrade ARV7 and full-length AR with DC_{50} values of 0.37 and 2.0 μM, respectively. It further inhibits cellular growth of apalutamide-resistant and darolutamide-resistant 22RV1 and VCaP cell lines at low μM concentrations and suppresses tumor growth in an enzalutamide-resistant 22RV1 resistant mouse xenograft model. Although MTX-23 is still a relatively weak degrader against ARV7 or full-length AR, it provides a clear proof-of-concept that PROTAC degraders against ARVs can be obtained.



37 MTX-23

Figure 12 Chemical structure of PROTAC MTX-23 targeting wild-type AR and AR variant 7 (ARV7).

7. CLINICAL DEVELOPMENT OF PROTAC AR DEGRADERS

To date, five orally bioavailable AR degraders, bavdegalutamide (**26**) and ARV-766 from Arvinas, AC-0176 from Accutar, HP518 from Hinova, CC-94676 from Celgene/BMS) and one topical gel AR degrader (GT20029 from Kintor), have been advanced into clinical development, and early clinical data for bavdegalutamide has been reported.[64] The structure of bavdegalutamide is the only one that has been disclosed. Bavdegalutamide was evaluated in patients with metastatic prostate cancer and either once-daily or twice-daily oral administration in the Phase I trial with the dose range of 35-700 mg QD or 210-420 mg BID. The exposures of bavdegalutamide were dose-proportional, and at a dose of 420 mg QD, the AUC_{0-24} reached 10,000 ng/ml*h, exceeding its preclinical efficacious exposure in mice. Based on combined safety, pharmacokinetics, and activity data, a dose of 420 mg QD was selected as the recommended Phase II dose (RP2D).

Bavdegalutamide was found to be well tolerated. No grade ≥4 treatment-related adverse events (TRAEs) were found in 138 patients treated at the RP2D, and grade 3 TRAEs were rare. The most common TRAEs of any grade at the RP2D were nausea (48%), fatigue (36%), vomiting (26%), decreased appetite (25%), diarrhea (20%), and alopecia (14%). Treatment was discontinued as a result of adverse events in 12 patients (9%).

Efficacy was analyzed in biomarker-defined subgroups based upon AR status. Across biomarker-evaluable patients in Phase I and Phase II who had at least one month of PSA follow-up, 46% of patients with AR T878A/S and/or H875Y mutations had the best PSA decline of ≥50% (PSA50). Of the seven patients with AR T878A/S and/or H875Y mutations who were RECIST-evaluable, six had tumor shrinkage, and two patients had confirmed partial responses, defined as tumor shrinkage by 30% or greater. PSA decline was also observed in other subgroups, including patients with AR wild-type, L702H mutation/AR-V7 variant expression, and with either abiraterone or enzalutamide pretreatment. Overall, bavdegalutamide demonstrated clinical activity in a post-novel hormonal agent (NHA), heavily pretreated mCRPC patient population. Biomarker selection of patients with AR T878 and/or H875 mutations enriches bavdegalutamide sensitivity.

ARV-766 was advanced into Phase I human clinical trials in October 2021.[69] To date, its chemical structure and preclinical data have not been

disclosed. However, it was stated by Arvinas that ARV-766 works better than bavdegalutamide "at blunting the growth of cancer cells with L702H alterations, the most frequent mutation associated with resistance to abiraterone and other AR-targeted therapies."[69] AC-0176 from Accutar, HP518 from Hinova, GT20029 from Kintor, and CC-94676 from Celgene/BMS are also being evaluated in Phase I human clinical trials for their safety, tolerability, pharmacokinetics, and pharmacodynamics recently, although no preclinical or clinical data has been reported for these AR degraders.

8. FUTURE PERSPECTIVES

AR has been extensively pursued as a therapeutic target for the treatment of human prostate cancer and other human diseases or conditions. Second-generation AR antagonists have been developed, and in the last decade, three of them have received regulatory approval for the treatment of advanced prostate cancer, including metastatic disease. Despite their clinical successes, resistance to these AR-targeted agents develops in treated patients, typically within 18 months. In patients who have become resistant to these AR antagonists, AR and AR signaling continue to play a major role in fueling prostate cancer growth and metastases. Some of the major resistance mechanisms include activation of AR point mutations, AR gene amplification and expression of AR splicing variants. Therefore, AR and AR signaling remain attractive therapeutic targets for advanced prostate cancer, even when the disease evolves into resistance to second-generation AR antagonists.

Several new therapeutic approaches have been pursued against AR, including the development of selective SARDs and inhibitors targeting different domains of AR. Recently, major progress has been made in the discovery and development of bifunctional PROTAC degraders against full-length AR. Several classes of AR ligands and four different types of ligands for E3 ligases (MDM2, IAP, VHL/cullin 2, cereblon/cullin 4A) have been employed for the design of PROTAC AR degraders. While PROTAC AR degraders employing ligands for MDM2 or IAP only showed degradation potencies in the micromolar ranges, highly potent AR degraders using ligands for VHL and cereblon have been discovered. In particular, potent and orally active AR degraders using ligands for cereblon have been obtained. These AR degraders not only effectively induce degradation of wild-type AR but also of AR mutants known to be resistant to AR antagonists. They also

outperform enzalutamide in preclinical efficacy studies both *in vitro* and *in vivo*. To date, five orally active PROTAC AR degraders, bavdegalutamide, ARV-766, AC-0176, HP518, and CC-94676, have been advanced into clinical development. Early clinical data on bavdegalutamide demonstrate a good safety profile and the ability to achieve predicted efficacious plasma exposures. Importantly, bavdegalutamide shows antitumor activity in post-NHA, heavily pretreated mCRPC patients and has the best response in patients with AR T878 and/or H875 mutations. This early clinical data for bavdegalutamide provides evidence that PROTAC AR degraders have potential in the treatment of mCRPC. With the early clinical success for bavdegalutamide, it is expected that more PROTAC AR degraders will be advanced into clinical development in the future. Furthermore, PROTAC AR degraders have the potential to treat not only mCRPC patients who fail second-generation AR antagonists, but also patients with early prostate cancer given the excellent safety profile demonstrated by bavdegalutamide.

References

1. Aurilio, G.; Cimadamore, A.; Mazzucchelli, R.; Lopez-Beltran, A.; Verri, E.; Scarpelli, M.; Massari, F.; Cheng, L.; Santoni, M.; Montironi, R. Androgen receptor signaling pathway in prostate cancer: From genetics to clinical applications. *Cells* **2020**, *9*, 2653.
2. Lonergan, P. E.; Tindall, D. J. Androgen receptor signaling in prostate cancer development and progression. *J. Carcinog*. **2011**, *10*, 20.
3. Anestis, A.; Zoi, I.; Papavassiliou, A. G.; Karamouzis, M. V. Androgen receptor in breast cancer-clinical and preclinical research insights. *Molecules* **2020**, *25*, 358.
4. Fujimoto, N. Role of the androgen-androgen receptor axis in the treatment resistance of advanced prostate cancer: From androgen-dependent to castration resistant and further. *J. UOEH*. **2016**, *38*, 129-138.
5. Kahn, B.; Collazo, J.; Kyprianou, N. Androgen receptor as a driver of therapeutic resistance in advanced prostate cancer. *Int. J. Biol. Sci*. **2014**, *10*, 588-595.
6. Beltran, H.; Beer, T. M.; Carducci, M. A.; de Bono, J.; Gleave, M.; Hussain, M.; Kelly, W. K.; Saad, F.; Sternberg, C.; Tagawa, S. T.; Tannock, I. F. New therapies for castration-resistant prostate cancer: Efficacy and safety. *Eur. Urol*. **2011**, *60*, 279-90.
7. Nadiminty, N.; Gao, A. C. Mechanisms of persistent activation of the androgen receptor in CRPC: Recent advances and future perspectives. *World J. Urol*. **2012**, *30*, 287-295.
8. Mostaghel, E. A. Abiraterone in the treatment of metastatic castration-resistant prostate cancer. *Cancer Manag. Res*. **2014**, *6*, 39-51.
9. Nowakowska, M. K.; Lei, X.; Wehner, M. R.; Corn, P. G.; Giordano, S. H.; Nead, K. T. Association of second-generation antiandrogens with depression among patients with prostate cancer. *JAMA Network Open* **2021**, *4*, e2140803.
10. Brown, T. R. Nonsteroidal selective androgen receptors modulators (SARMs): Designer androgens with flexible structures provide clinical promise. *Endocrinology* **2004**, *145*, 5417-5419.
11. Gao, W.; Kim, J.; Dalton, J. T. Pharmacokinetics and pharmacodynamics of nonsteroidal androgen receptor ligands. *Pharm Res*. **2006**, *23*, 1641-58.
12. Rice, M. A.; Malhotra, S. V.; Stoyanova, T. Second-generation antiandrogens: From discovery to standard of care in castration resistant prostate cancer. *Front. Oncol*. **2019**, *9*, 801.

13. Jung, M. E.; Ouk, S.; Yoo, D.; Sawyers, C. L.; Chen, C.; Tran, C.; Wongvipat, J. Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). *J. Med. Chem*. **2010**, *53*, 2779-2796.
14. Crona, D. J.; Whang, Y. E. Posterior reversible encephalopathy syndrome induced by enzalutamide in a patient with castration-resistant prostate cancer. *Invest. New Drugs* **2015**, *33*, 751-754.
15. Ryan, C.; Wefel, J. S.; Morgans, A. K. A review of prostate cancer treatment impact on the CNS and cognitive function. *Prostate Cancer P. D*. **2020**, *23*, 207-219.
16. Ji, C.; Guha, M.; Zhu, X.; Whritenour, J.; Hemkens, M.; Tse, S.; Walker, G. S.; Evans, E.; Khan, N. K.; Finkelstein, M. B.; Callegari, E.; Obach, R. S. Enzalutamide and apalutamide: In vitro chemical reactivity studies and activity in a mouse drug allergy model. *Chem. Res. Toxicol*. **2020**, *33*, 211-222.
17. Crawford, E. D.; Stanton, W.; Mandair, D. Darolutamide: An evidenced-based review of its efficacy and safety in the treatment of prostate cancer. *Cancer Manag. Res*. **2020**, *12*, 5667-5676.
18. Moilanen, A.-M.; Riikonen, R.; Oksala, R.; Ravanti, L.; Aho, E.; Wohlfahrt, G.; Nykänen, P. S.; Törmäkangas, O. P.; Palvimo, J. J.; Kallio, P. J. Discovery of ODM-201, a new-generation androgen receptor inhibitor targeting resistance mechanisms to androgen signaling-directed prostate cancer therapies. *Sci. Rep*. **2015**, *5*, 12007.
19. Fizazi, K.; Smith, M. R.; Tombal, B. Clinical development of darolutamide: A novel Androgen receptor antagonist for the treatment of prostate cancer. *Clin. Genitourin. Cancer* **2018**, *16*, 332-340.
20. Alumkal, J. J.; Sun, D.; Lu, E.; Beer, T. M.; Thomas, G. V.; Latour, E.; Aggarwal, R.; Cetnar, J.; Ryan, C. J.; Tabatabaei, S.; Bailey, S.; Turina, C. B.; Quigley, D. A.; Guan, X.; Foye, A.; Youngren, J. F.; Urrutia, J.; Huang, J.; Weinstein, A. S.; Friedl, V.; Rettig, M.; Reiter, R. E.; Spratt, D. E.; Gleave, M.; Evans, C. P.; Stuart, J. M.; Chen, Y.; Feng, F. Y.; Small, E. J.; Witte, O. N.; Xia, Z. Transcriptional profiling identifies an androgen receptor activity-low, stemness program associated with enzalutamide resistance. *Proc. Natl. Acad. Sci. U.S.A*. **2020**, *117*, 12315-12323.
21. Watson, P. A.; Arora, V. K.; Sawyers, C. L. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat. Rev. Cancer* **2015**, *15*, 701-711.
22. Gombos, A. Selective oestrogen receptor degraders in breast cancer: A review and perspectives. *Curr. Opin. Oncol*. **2019**, *31*, 424-429.
23. Narayanan, R.; Ponnusamy, S.; Miller, D. D. Destroying the androgen receptor (AR)-potential strategy to treat advanced prostate cancer. Oncoscience **2017**, 4, 175-177.
24. Hwang, D.-J.; He, Y.; Ponnusamy, S.; Mohler, M. L.; Thiyagarajan, T.; McEwan, I. J.; Narayanan, R.; Miller, D. D. New generation of selective androgen receptor degraders: Our initial design, synthesis, and biological evaluation of new compounds with enzalutamide-resistant prostate cancer activity. *J. Med. Chem*. **2019**, *62*, 491-511.
25. Lai, K. P.; Huang, C. K.; Chang, Y. J.; Chung, C. Y.; Yamashita, S.; Li, L.; Lee, S. O.; Yeh, S.; Chang, C. New therapeutic approach to suppress castration-resistant prostate cancer using ASC-J9 via targeting androgen receptor in selective prostate cells. *Am. J. Pathol*. **2013**, *182*, 460-473.
26. Loddick, S. A.; Ross, S. J.; Thomason, A. G.; Robinson, D. M.; Walker, G. E.; Dunkley, T. P. J.; Brave, S. R.; Broadbent, N.; Stratton, N. C.; Trueman, D.; Mouchet, E.; Shaheen, F. S.; Jacobs, V. N.; Cumberbatch, M.; Wilson, J.; Jones, R. D. O.; Bradbury, R. H.; Rabow, A.; Gaughan, L.; Womack, C.; Barry, S. T.; Robson, C. N.; Critchlow, S. E.; Wedge, S. R.; Brooks, A. N. AZD3514: A small molecule that modulates androgen receptor signaling and function in vitro and in vivo. *Mol. Cancer Ther*. **2013**, *12*, 1715-1727.
27. Gustafson, J. L.; Neklesa, T. K.; Cox, C. S.; Roth, A. G.; Buckley, D. L.; Tae, H. S.; Sundberg, T. B.; Stagg, D. B.; Hines, J.; McDonnell, D. P.; Norris, J. D.; Crews, C. M. Small-molecule-mediated degradation of the androgen receptor through hdrophobic tagging. *Angew. Chem. Int. Ed. Engl*. **2015**, *54*, 9659-9662.

28. Sakamoto, K. M.; Kim, K. B.; Kumagai, A.; Mercurio, F.; Crews, C. M.; Deshaies, R. J. Protacs: Chimeric molecules that target proteins to the Skp1-Cullin–F box complex for ubiquitination and degradation. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 8554-8559.
29. Mares, A.; Miah, A. H.; Smith, I. E. D.; Rackham, M.; Thawani, A. R.; Cryan, J.; Haile, P. A.; Votta, B. J.; Beal, A. M.; Capriotti, C.; Reilly, M. A.; Fisher, D. T.; Zinn, N.; Bantscheff, M.; MacDonald, T. T.; Vossenkamper, A.; Dace, P.; Churcher, I.; Benowitz, A. B.; Watt, G.; Denyer, J.; Scott-Stevens, P.; Harling, J. D. Extended pharmacodynamic responses observed upon PROTAC-mediated degradation of RIPK2. *Commun. Biol.* **2020**, *3*, 140.
30. Smith, B. E.; Wang, S. L.; Jaime-Figueroa, S.; Harbin, A.; Wang, J.; Hamman, B. D.; Crews, C. M. Differential PROTAC substrate specificity dictated by orientation of recruited E3 ligase. *Nat. Commun.* **2019**, *10*, 131.
31. Paiva, S.-L.; Crews, C. M. Targeted protein degradation: Elements of PROTAC design. *Curr. Opin. Chem. Biol.* **2019**, *50*, 111-119.
32. Beveridge, R.; Kessler, D.; Rumpel, K.; Ettmayer, P.; Meinhart, A.; Clausen, T. Native mass spectrometry can effectively predict PROTAC efficacy. *ACS. Cent. Sci.* **2020**, *6*, 1223-1230.
33. Klein, V. G.; Townsend, C. E.; Testa, A.; Zengerle, M.; Maniaci, C.; Hughes, S. J.; Chan, K. H.; Ciulli, A.; Lokey, R. S. Understanding and improving the membrane permeability of VH032-based PROTACs. *ACS Med. Chem. Lett.* **2020**, *11*, 1732-1738.
34. Schneekloth, A. R.; Pucheault, M.; Tae, H. S.; Crews, C. M. Targeted intracellular protein degradation induced by a small molecule: En route to chemical proteomics. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5904-5908.
35. Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. *Science* **2004**, *303*, 844-848.
36. Oberoi-Khanuja, T. K.; Rajalingam, K. IAPs as E3 ligases of Rac1: Shaping the move. *Small GTPases* **2012**, *3*, 131-136.
37. Martinez-Ruiz, G.; Maldonado, V.; Ceballos-Cancino, G.; Grajeda, J. P. R.; Melendez-Zajgla, J. Role of Smac/DIABLO in cancer progression. *J. Exp. Clin. Cancer Res.* **2008**, *27*, 48.
38. Bai, L.; Smith, D. C.; Wang, S. Small-molecule SMAC mimetics as new cancer therapeutics. *Pharmacol. Ther.* **2014**, *144*, 82-95.
39. Shibata, N.; Nagai, K.; Morita, Y.; Ujikawa, O.; Ohoka, N.; Hattori, T.; Koyama, R.; Sano, O.; Imaeda, Y.; Nara, H.; Cho, N.; Naito, M. Development of protein degradation inducers of androgen receptor by conjugation of androgen receptor ligands and inhibitor of apoptosis protein ligands. *J. Med. Chem.* **2018**, *61*, 543-575.
40. Naito, M.; Ohoka, N.; Shibata, N. SNIPERs—hijacking IAP activity to induce protein degradation. *Drug Discov. Today: Technol.* **2019**, *31*, 35-42.
41. Stebbins, C. E.; Kaelin, W. G., Jr.; Pavletich, N. P. Structure of the VHL-ElonginC-ElonginB complex: Implications for VHL tumor suppressor function. *Science* **1999**, *284*, 455-461.
42. Buckley, D. L.; Van Molle, I.; Gareiss, P. C.; Tae, H. S.; Michel, J.; Noblin, D. J.; Jorgensen, W. L.; Ciulli, A.; Crews, C. M. Targeting the von Hippel-Lindau E3 ubiquitin ligase using small molecules to disrupt the VHL/HIF-1α interaction. *J. Am. Chem. Soc.* **2012**, *134*, 4465-4468.
43. Buckley, D. L.; Gustafson, J. L.; Van Molle, I.; Roth, A. G.; Tae, H. S.; Gareiss, P. C.; Jorgensen, W. L.; Ciulli, A.; Crews, C. M. Small-molecule inhibitors of the interaction between the E3 ligase VHL and HIF1α. *Angew. Chem. Int. Ed.* **2012**, *51*, 11463-11467.
44. Soares, P.; Gadd, M. S.; Frost, J.; Galdeano, C.; Ellis, L.; Epemolu, O.; Rocha, S.; Read, K. D.; Ciulli, A. Group-based optimization of potent and cell-active inhibitors of the von Hippel-Lindau (VHL) E3 ubiquitin ligase: Structure-activity relationships leading to the chemical probe (2S,4R)-1-((S)-2-(1-cyanocyclopropanecarboxamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (VH298). *J. Med. Chem.* **2018**, *61*, 599-618.

45. Bricelj, A.; Steinebach, C.; Kuchta, R.; Gütschow, M.; Sosič, I. E3 ligase ligands in successful PROTACs: An overview of syntheses and linker attachment points. *Front. Chem*. **2021**, *9*, 707317.
46. Salami, J.; Alabi, S.; Willard, R. R.; Vitale, N. J.; Wang, J.; Dong, H.; Jin, M.; McDonnell, D. P.; Crew, A. P.; Neklesa, T. K.; Crews, C. M. Androgen receptor degradation by the proteolysis-targeting chimera ARCC-4 outperforms enzalutamide in cellular models of prostate cancer drug resistance. *Commun. Biol*. **2018**, *1*, 100.
47. Han, X.; Wang, C.; Qin, C.; Xiang, W.; Fernandez-Salas, E.; Yang, C.-Y.; Wang, M.; Zhao, L.; Xu, T.; Chinnaswamy, K.; Delproposto, J.; Stuckey, J.; Wang, S. Discovery of ARD-69 as a highly potent proteolysis targeting chimera (PROTAC) degrader of androgen receptor (AR) for the treatment of prostate cancer. *J. Med. Chem*. **2019**, *62*, 941-964.
48. Han, X.; Zhao, L.; Xiang, W.; Qin, C.; Miao, B.; Xu, T.; Wang, M.; Yang, C.-Y.; Chinnaswamy, K.; Stuckey, J.; Wang, S. Discovery of highly potent and efficient PROTAC degraders of androgen receptor (AR) by employing weak binding affinity VHL E3 ligase ligands. *J. Med. Chem*. **2019**, *62*, 11218-11231.
49. Ito, T.; Ando, H.; Suzuki, T.; Ogura, T.; Hotta, K.; Imamura, Y.; Yamaguchi, Y.; Handa, H. Identification of a primary target of thalidomide teratogenicity. *Science* **2010**, *327*, 1345-1350.
50. Krönke, J.; Udeshi, N. D.; Narla, A.; Grauman, P.; Hurst, S. N.; McConkey, M.; Svinkina, T.; Heckl, D.; Comer, E.; Li, X.; Ciarlo, C.; Hartman, E.; Munshi, N.; Schenone, M.; Schreiber, S. L.; Carr, S. A.; Ebert, B. L. Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells. *Science* **2014**, *343*, 301-305.
51. Lu, G.; Middleton, R. E.; Sun, H.; Naniong, M.; Ott, C. J.; Mitsiades, C. S.; Wong, K.-K.; Bradner, J. E.; Kaelin, W. G. The myeloma drug Lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. *Science* **2014**, *343*, 305-309.
52. Krönke, J.; Fink, E. C.; Hollenbach, P. W.; MacBeth, K. J.; Hurst, S. N.; Udeshi, N. D.; Chamberlain, P. P.; Mani, D. R.; Man, H. W.; Gandhi, A. K.; Svinkina, T.; Schneider, R. K.; McConkey, M.; Järås, M.; Griffiths, E.; Wetzler, M.; Bullinger, L.; Cathers, B. E.; Carr, S. A.; Chopra, R.; Ebert, B. L. Lenalidomide induces ubiquitination and degradation of CK1α in del(5q) MDS. *Nature* **2015**, *523*, 183-188.
53. Matyskiela, M. E.; Lu, G.; Ito, T.; Pagarigan, B.; Lu, C.-C.; Miller, K.; Fang, W.; Wang, N.-Y.; Nguyen, D.; Houston, J.; Carmel, G.; Tran, T.; Riley, M.; Nosaka, L. A.; Lander, G. C.; Gaidarova, S.; Xu, S.; Ruchelman, A. L.; Handa, H.; Carmichael, J.; Daniel, T. O.; Cathers, B. E.; Lopez-Girona, A.; Chamberlain, P. P. A novel cereblon modulator recruits GSPT1 to the CRL4CRBN ubiquitin ligase. *Nature* **2016**, *535*, 252-257.
54. Winter, G. E.; Buckley, D. L.; Paulk, J.; Roberts, J. M.; Souza, A.; Dhe-Paganon, S.; Bradner, J. E. Phthalimide conjugation as a strategy for in vivo target protein degradation. *Science* **2015**, *348*, 1376-1381.
55. Da, Y.; Liu, S.; Lin, P.; Wang, F.; Yan, R.; Shu, Y.; Lin, J. Design, synthesis, and biological evaluation of small molecule PROTACs for potential anticancer effects. *Med. Chem. Res*. **2020**, *29*, 334-340.
56. Kim, G. Y.; Song, C. W.; Yang, Y. S.; Lee, N. R.; Yoo, H. S.; Son, S. H.; Lee, S. J.; Park, J. S.; Lee, J. K.; Inn, K. S.; Kim, N. J. Chemical degradation of androgen receptor (AR) using bicalutamide analog-thalidomide PROTACs. *Molecules* **2021**, *26*, 2525.
57. Gockel, L. M.; Pfeifer, V.; Baltes, F.; Bachmaier, R. D.; Wagner, K. G.; Bendas, G.; Gutschow, M.; Sosic, I.; Steinebach, C. Design, synthesis, and characterization of PROTACs targeting the androgen receptor in prostate and lung cancer models. *Arch. Pharm*. **2022**, *355*, e202100467.
58. Takwale, A. D.; Jo, S.-H.; Jeon, Y. U.; Kim, H. S.; Shin, C. H.; Lee, H. K.; Ahn, S.; Lee, C. O.; Ha, J. D.; Kim, J.-H.; Hwang, J. Y. Design and characterization of cereblon-mediated androgen receptor proteolysis-targeting chimeras. *Eur. J. Med. Chem*. **2020**, *208*, 112769.

59. Edmondson, S. D.; Yang, B.; Fallan, C. Proteolysis targeting chimeras (PROTACs) in 'beyond rule-of-five' chemical space: Recent progress and future challenges. *Bioorg. Med. Chem. Lett*. **2019**, *29*, 1555-1564.
60. Crew, A. P.; Hornberger, K. R.; Snyder, L. B.; Zimmermann, K.; Wang, J.; Berlin, M.; Crews, C. M.; Dong, H. Compounds and methods for the targeted degradation of androgen receptor. US20180099940A1, Apr. 12, 2018.
61. Snyder, L. B.; Neklesa, T. K.; Chen, X.; Dong, H.; Ferraro, C.; Gordon, D. A.; Macaluso, J.; Pizzano, J.; Wang, J.; Willard, R. R.; Vitale, N.; Peck, R.; Moore, M. D.; Crews, C. M.; Houston, J.; Crew, A. P.; Taylor, I. Abstract 43: Discovery of ARV-110, a first in class androgen receptor degrading PROTAC for the treatment of men with metastatic castration resistant prostate cancer. *Cancer Res*. **2021**, *81 (13_Supplement)*, 43.
62. Guo, C.; Linton, A.; Kephart, S.; Ornelas, M.; Pairish, M.; Gonzalez, J.; Greasley, S.; Nagata, A.; Burke, B. J.; Edwards, M.; Hosea, N.; Kang, P.; Hu, W.; Engebretsen, J.; Briere, D.; Shi, M.; Gukasyan, H.; Richardson, P.; Dack, K.; Underwood, T.; Johnson, P.; Morell, A.; Felstead, R.; Kuruma, H.; Matsimoto, H.; Zoubeidi, A.; Gleave, M.; Los, G.; Fanjul, A. N. Discovery of aryloxy tetramethylcyclobutanes as novel androgen receptor antagonists. *J. Med. Chem*. **2011**, *54*, 7693-7704.
63. Neklesa, T.; Snyder, L. B.; Willard, R. R.; Vitale, N.; Pizzano, J.; Gordon, D. A.; Bookbinder, M.; Macaluso, J.; Dong, H.; Ferraro, C.; Wang, G.; Wang, J.; Crews, C. M.; Houston, J.; Crew, A. P.; Taylor, I. ARV-110: An oral androgen receptor PROTAC degrader for prostate cancer. *J. Clin. Oncol*. **2019**, *37 (7_suppl)*, 259.
64. Gao, X.; Burris Iii, H. A.; Vuky, J.; Dreicer, R.; Sartor, A. O.; Sternberg, C. N.; Percent, I. J.; Hussain, M. H. A.; Rezazadeh Kalebasty, A.; Shen, J.; Heath, E. I.; Abesada-Terk, G.; Gandhi, S. G.; McKean, M.; Lu, H.; Berghorn, E.; Gedrich, R.; Chirnomas, S. D.; Vogelzang, N. J.; Petrylak, D. P. Phase 1/2 study of ARV-110, an androgen receptor (AR) PROTAC degrader, in metastatic castration-resistant prostate cancer (mCRPC). *J. Clin. Oncol*. **2022**, *40 (6_suppl)*, 17.
65. Han, X.; Zhao, L.; Xiang, W.; Qin, C.; Miao, B.; McEachern, D.; Wang, Y.; Metwally, H.; Wang, L.; Matvekas, A.; Wen, B.; Sun, D.; Wang, S. Strategies toward discovery of potent and orally bioavailable proteolysis targeting chimera degraders of androgen receptor for the treatment of prostate cancer. *J. Med. Chem*. **2021**, *64*, 12831-12854.
66. Xiang, W.; Zhao, L.; Han, X.; Qin, C.; Miao, B.; McEachern, D.; Wang, Y.; Metwally, H.; Kirchhoff, P. D.; Wang, L.; Matvekas, A.; He, M.; Wen, B.; Sun, D.; Wang, S. Discovery of ARD-2585 as an exceptionally potent and orally active PROTAC degrader of androgen receptor for the treatment of advanced prostate cancer. *J. Med. Chem*. **2021**, *64*, 13487-13509.
67. Yu, X.; Yi, P.; Hamilton, R. A.; Shen, H.; Chen, M.; Foulds, C. E.; Mancini, M. A.; Ludtke, S. J.; Wang, Z.; O'Malley, B. W. Structural insights of transcriptionally active, full-length androgen receptor coactivator complexes. *Mol. Cell*. **2020**, *79*, 812-823.e4.
68. Lee, G. T.; Nagaya, N.; Desantis, J.; Madura, K.; Sabaawy, H. E.; Kim, W. J.; Vaz, R. J.; Cruciani, G.; Kim, I. Y. Effects of MTX-23, a novel PROTAC of androgen receptor splice variant-7 and androgen receptor, on CRPC resistant to second-line antiandrogen therapy. *Mol. Cancer Ther*. **2021**, *20*, 490-499.
69. Dolgin, E. PROTAC shrinks mutated prostate tumors. *Cancer Discov*. **2022**, *12*, OF2.