Synthesis and Evaluation of Small Molecule Inhibitors of the Androgen Receptor N-Terminal Domain

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ABSTRACT: The androgen receptor (AR) is central to prostate cancer pathogenesis and has been extensively validated as a drug target. However, small-molecule anti-androgen therapies remain limited due to resistance and will eventually fail to suppress tumor growth, resulting in progression to castration-resistant prostate cancer (CRPC). The intrinsically disordered N-terminal domain (NTD) is crucial for AR transactivation and has been investigated as a suitable target in the presence of ligand binding domain mutations. A screening campaign identified biaryl isoxazole compound 7 as a weak inhibitor of the AR NTD. A library of biaryl analogues were synthesized, and their biological activities were assessed in a VCaP cell-based luciferase reporter gene assay. A structure−activity relationship (SAR) study revealed that indazole analogue 16 exhibited increased potency and favorable physicochemical properties with a benchmarked pharmacokinetic profile, providing a suitable starting point for further optimization of 16 as a CRPC therapeutic in the presence of AR mutations.

KEYWORDS: Prostate cancer, Androgen receptor, Intrinsically disordered protein

Prostate cancer remains the second most common cancer, with one in eight men receiving a diagnosis in their lifetime and almost 400,000 deaths worldwide in 2020 alone. Despite significant advances in localized prostate cancer therapies, around 20−30% of patients will subsequently present with advanced and metastatic forms of the disease and will require systemic treatment. While effective at inducing remission and offering a relief from symptoms, treatments such as androgen deprivation therapy (ADT) ultimately only slow the course of the disease before almost inevitable progression to castration-resistant prostate cancer (CRPC), which is associated with a poor prognosis. Central to prostate cancer pathogenesis is the nuclear androgen receptor (AR), a 110 kDa transcription factor which is primarily responsible for androgen-mediated regulation of gene expression. In common with all nuclear receptors, the AR protein consists of the ligand-binding domain (LBD), in which the ligand binding pocket (LBP) is located; the DNA-binding domain (DBD); the N-terminal domain (NTD); and a hinge region which connects the LBD with the DBD. Due to the critical role of the AR protein in the progression of prostate cancer, AR antagonists that compete with androgens for binding in the LBP are used clinically and have traditionally been the primary focus of drug discovery campaigns. In this regard, the second-generation nonsteroidal anti-androgens (NSAAs) enzalutamide (1), apalutamide (2), and darolutamide (3) have all been approved within the past decade for the treatment of CRPC. However, anti-androgen therapies will eventually fail to suppress tumor growth due to a complex array of resistance mechanisms, which inevitably leads to reactivation of the AR signaling axis. For this reason, alternative small-
molecule CRPC therapies have been sought that do not rely on binding to the canonical LBD but instead target other domains of the AR. 20–22 It has been shown that the NTD is critical for the transactivation and function of AR, in which the modular activation function (AF-1) is of particular importance for gene expression and in facilitating protein–protein interactions. 23,24 However, due to the intrinsically disordered nature of this domain, it is not amenable to structure-based drug design and has therefore garnered less attention as a potential target for therapeutic intervention in the past. 25 Despite this, in the past decade, several small molecules have been developed which act on the AR via the disordered NTD. 26–30 For example, the EPI family of compounds, 31–33 including racemic EPI-001 (7), have been reported to block AR transcription via interaction with the AF-1 region of the AR-NTD, while other EPI analogues (EPI-002 (5) and EPI-7170 (6)) have been shown to induce conformation changes within the NTD and disrupt interactions between the AF1 and essential protein coactivators. 40 Furthermore, EPI-7386 (structure not disclosed) is currently in phase-1 clinical trials and has effectively demonstrated that AR NTD inhibitors could be potential therapeutics in the presence of LBD-driven resistance in the context of CRPC. 41,42

Herein we report our work toward the design, synthesis, and biological evaluation of a novel series of biaryl small-molecule antagonists of the AR receptor NTD. Previous work within our laboratories identified compound 7 as a weak binder of AR splice variants (ARVs) lacking the LBD using a high-throughput screen utilizing a functional cell-based assay developed in our group, with hits from this assay counterscreened for cytoxicity and inhibition of luciferase activity to confirm specific activity. 43 In an effort to develop understanding of the structure–activity relationship (SAR) and identify more potent AR-NTD inhibitor analogues, we synthesized analogues of 7 focusing largely on changes to the LHS heterocyclic region, alternative substituents on the RHS aromatic ring, and replacement of the potentially metabolically labile thioether functional group (Figure 2a).

Our current work began with the validation of our screening-derived hit compound 7 in a cell-based reporter gene assay. This required the synthesis of compound 7 from readily available starting materials, which is shown in Figure 2b. Aniline 7a was converted to the corresponding diazoniun salt by treatment with sodium nitrite, which was followed by a Sandmeyer-type reaction with sodium methanethiolate that provided thioether 7b in 86% yield. Hydrolysis of the ester group followed by amidation via in situ formation of the Vilsmier reagent afforded primary carbamate 7d. Palladium-catalyzed Heck reaction with ethyl vinyl ether gave the intermediate enol ether, which was hydrolyzed under acidic conditions to afford ketone 7e in 43% yield. Finally, formylation of the -position of the carbonyl in the presence of sodium hydride followed by ring closure with hydroxylamine afforded isoazole 7 in 25% yield over two steps. Compound 7 was then evaluated in our VCaP cell-based GRE2-luciferase reporter gene assay and was found to have an IC50 of 7.4 μM.

For reference, the benchmark AR antagonist enzalutamide (1) and EPI-001 (4) were also examined for their effect against GRE2-luciferase activity in our hands (Figure 1). In this assay, enzalutamide was very potent, with an IC50 of 0.34 μM, while EPI-001 had an IC50 of 37.4 μM.

As shown in Figure 2a, the four main regions of the template were targeted for further SAR study. In our initial investigations into modifications of the LHS region, the biaryl C–C bond was used as a linchpin disconnection, with alternative heterocyclic groups being introduced via Suzuki–Miyaura cross-coupling with aryl bromide 7d and a range of boronic acids under thermal or microwave conditions (Table 1; see the Supporting Information for further details). Compound 8 with an unfunctionalized phenyl ring was inactive in our assay.

Following this, the LHS region was explored via the introduction of smaller, five-membered heterocyclic motifs. Thiophene 9 showed robust activity (IC50 = 0.60 μM), while dimethylisooxazole 10 was weakly active (IC50 = 4.7 μM) and pyrrole 11 retained no activity. Next, benzannulated heterocycles bearing hydrogen-bond donors (HBDs) were examined. Indazole 12 showed good activity, with an IC50 of 0.70 μM, while indole 13 displayed a 10-fold decrease in activity (IC50 = 10.3 μM). Interestingly, indazole 14 featuring different connectivity compared with analogue 12, such that the HBD is oriented in a different direction, was less potent (IC50 = 2.2 μM). Activity was recovered with imidazole 15, which displayed an IC50 of 0.92 μM. Removing the HBD from the RHS heterocycle by blocking the free NH group of indazole 12 with a methyl substituent gave compound 16, which exhibited excellent potency (IC50 = 0.12 μM). This represents a 60-fold increase in potency over our initial hit compound 7 and compares favorably with enzalutamide (IC50 = 0.34 μM). Deletion of a nitrogen atom resulted in approximately similar potency in -methylindole 17 (IC50 = 0.09 μM). Imidazopyridine 18 and oxindole 19 were tested; however, both displayed no activity. Quinoline 20 and isoquinoline 21 were active, both with an IC50 of 0.80 μM, demonstrating that the position of the nitrogen atom has no effect on the activity. However, deleting the aryl ring resulted in a loss of activity of pyridine analogues 22 and 23. The addition of a nitrogen atom in pyrimidine analogue

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**Figure 2.** Proposed structural modifications and synthesis of initial HTS hit compound 7. Reagents and conditions: (a) NaNO2, 1 M HCl, rt, 1 h, then NaSMe, rt, 2 h, 86%; (b) 4 M NaOH, THF/EtOH (1:1), rt, 16 h, quant.; (c) (COCl)2, DMF, THF, rt, 1 h, then NH4OH, 0 °C, 2 h, 74%; (d) ethyl vinyl ether, Pd(dppf)Cl2, K2CO3, DMF/H2O (9:1), 90 °C, 64 h, then 2 M HCl, rt, 0.5 h, 43%; (e) NaH, EtOCH2, rt, 24 h; (f) H2NOH·HCl, EtOH, 85 °C, 1 h, 25% over two steps.
resulted in recovery of activity with an IC\textsubscript{50} of 0.27 μM. Our attention next focused on more lipophilic benzannulated heterocycles such as benzo[b]furan \textit{25}, benzoxazole \textit{26}, and 2,3-dihydrobenzofuran \textit{27}. Of these compounds, only unsaturated benzo[b]furan \textit{25} displayed activity (IC\textsubscript{50} = 0.60 μM). Activity was abolished in electron-rich acyclic ether analogue \textit{28} but recovered to an extent with the incorporation of a fluorine atom in analogue \textit{29} (IC\textsubscript{50} = 0.76 μM). Increasing the electron density of the ring and increasing the number of HBDs via the replacement of a methoxy group with an aryl amine resulted in loss of activity in compound \textit{30}. We next examined fluorinated phenol isomers \textit{31}, \textit{32}, and \textit{33}. Interestingly, the position of the fluorine atom on the aromatic ring significantly influenced the bioactivity, as \textit{ortho} and \textit{meta} analogues \textit{31} and \textit{32} were inactive while \textit{para} derivative \textit{33} was potent (IC\textsubscript{50} = 0.12 μM).

Subsequently, in an effort to improve solubility and other physicochemical properties, a π-deficient pyridine ring was introduced into our scaffold in analogues \textit{34}−\textit{37} (Table 2). It is clear from matched molecular pairs \textit{34} and \textit{16} that the pyridine ring is not tolerated on the RHS, resulting in a loss of activity, perhaps due to unfavorable conformation changes or a decrease in electron density. Substitution of a hydrogen atom for a fluorine atom at the \textit{ortho} position with respect to the thioether in compound \textit{38} gave activity (IC\textsubscript{50} = 0.24 μM) similar to that of compound \textit{16}. Moving the thioether group around the ring to furnish \textit{meta} substitution relative to the biaryl C−C bond resulted in an inactive compound (\textit{39}).

Replacement of the methyl thioether functionality was next investigated, as it was reasoned that this could be a potential metabolic liability (Table 3). This required \textit{de novo} synthesis from prefunctionalized starting materials (see the Supporting Information for experimental details). For example, ether starting materials were prepared by O-alkylation, while nitrogen functionality was introduced via nucleophilic aromatic substitution with the desired amine. Compounds \textit{40}−\textit{57} were then delivered by subjecting these starting materials to a palladium-catalyzed Suzuki−Miyaura cross-coupling with methylindazole boronic acid, as detailed previously. First, replacement of the methyl group with a bulkier, more lipophilic benzyl group resulted in moderately potent compound \textit{40} (IC\textsubscript{50} = 2.2 μM), while substitution of the thioether with alkyl functionality (methyl \textit{41} and ethyl \textit{42}) resulted in loss of activity. Similarly, no bioactivity was observed for compound \textit{43} after removal of the thioether and replacement with a hydrogen atom. While fluorinated analogue \textit{44} was inactive, compound \textit{45} bearing a trifluoromethyl group was weakly active, with an IC\textsubscript{50} of 8.6 μM. Attempts to introduce ether functionality resulted in complete loss of activity, with methyl ether \textit{46}, benzyl ether \textit{47}, and trifluoromethyl ether \textit{48} all displaying IC\textsubscript{50} > 30 μM. Furthermore, a similar lack of activity was observed with free phenol derivative \textit{49}, while

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Table 1. Region 1 Investigations into Alternative RHS Heterocyclic Scaffolds

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Table 2. Region 2 Investigations into Alternative Substitutions of the LHS Aromatic Ring

24 resulted in recovery of activity with an IC\textsubscript{50} of 0.27 μM. Our attention next focused on more lipophilic benzannulated heterocycles such as benzo[b]furan \textit{25}, benzoxazole \textit{26}, and 2,3-dihydrobenzofuran \textit{27}. Of these compounds, only unsaturated benzo[b]furan \textit{25} displayed activity (IC\textsubscript{50} = 0.60 μM). Activity was abolished in electron-rich acyclic ether analogue \textit{28} but recovered to an extent with the incorporation of a fluorine atom in analogue \textit{29} (IC\textsubscript{50} = 0.76 μM). Increasing the electron density of the ring and increasing the number of HBDs via the replacement of a methoxy group with an aryl amine resulted in loss of activity in compound \textit{30}. We next examined fluorinated phenol isomers \textit{31}, \textit{32}, and \textit{33}. Interestingly, the position of the fluorine atom on the aromatic ring significantly influenced the bioactivity, as \textit{ortho} and \textit{meta} analogues \textit{31} and \textit{32} were inactive while \textit{para} derivative \textit{33} was potent (IC\textsubscript{50} = 0.12 μM).

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bulkier ether analogues 50 and 51 were all inactive in our assay. Changing the C−O linkage to a C−N bond in compound 52 resulted in modest activity, with an IC_{50} of 0.94 μM. Alternative N-linked analogues were synthesized, including cyclic morpholine compound 53 and acyclic derivatives 54e−57. Only analogue 56 featuring a morpholine ring attached to the LHS aryl ring via a linear propyl amine chain was active in the assay, with an IC_{50} of 0.80 μM.

For reasons of synthetic tractability, molecular matched pairs of pyrimidine analogue 24 were investigated where the primary carboxamide was replaced with tertiary amides via coupling of carboxylic acid 58 with cyclic secondary amines (Table 4). In the VCaP GRE2-luciferase assay, carboxylic acid 58 was active, with an IC_{50} value of 0.12 μM, while tertiary amides 59 and 60 exhibited IC_{50} values of 0.13 and 0.26 μM, respectively. Compounds 59 and 60 displayed comparable potency to matched pair 24, which suggests that the HBD capabilities of the primary amide are not crucial for binding to the AR.

During the SAR investigation of the core scaffold, control of lipophilicity was maintained with the aim of keeping this parameter in the desired Lipinski-type space. A ligand lipophilicity (LLE) plot showing the effects of changes by region revealed no significant correlation between cellular potency and cLogP (see the Supporting Information for further information). The in vitro activity (IC_{50} = 0.12 μM) and favorable physicochemical properties placed methylindazole 16 within lead-like chemical space (Table 5). The lipophilicity (cLogP = 2.3), topological polar surface area (TPSA = 86), and numbers of HBDs (2) and hydrogen bond acceptors (HBAs) (4) were all within the desired property space associated with lead assets.44 The intrinsic property forecast index (iPFI), a metric proposed by Young and co-workers,45 is the sum of cLogP and the aromatic ring count, which is a predictor of important considerations such as solubility and off-target effects and should be kept <7. The iPFI of compound 16 is in the acceptable range, with a value of 5.3. Moreover, compound 16 has a ligand efficiency of 0.33 and a ligand-lipophilic efficiency of 4.7.

Having demonstrated robust in vitro and physicochemical properties, we next sought to further probe the pharmacology of emerging lead compound 16. To this end, AR-v splice variant activity was determined through transfection of PC3 cells with an ARNTD−DBD expression plasmid and a GRE2-luciferase reporter gene (Figure 3).43 This construct retains the constitutively active NTDDDBD core; however, it is insensitive to LBD antagonists such as enzalutamide. Compound 16 shows 35% inhibition of AR-v activity at 10 μM, whereas enzalutamide is not active in this assay. In addition to this, we evaluated hormone-dependent expression of prostate-specific antigen (PSA) in VCaP cells (see the Supporting Information). This showed a similar level of inhibition (34%), confirming pathway-relevant pharmacological effects.

We next explored the potential developability of this compound as a potent AR inhibitor with an investigation of the in vitro pharmacokinetic properties of 16 (Table 5). Compound 16 exhibited a moderate thermodynamic aqueous
promising intrinsic clearance (CL \times \text{efflux ratio} = 1.2). Furthermore, compound 16 displayed promising intrinsic clearance (Cl\text{int}) in human liver microsomes and a half-life of 5.4 min. The plasma protein binding of 16 was determined and showed a free fraction of 9.9%. The potential for drug–drug interactions was next investigated, and no inhibition of CYP450 was observed (with both 34A and 2D6 isoforms), while no hERG channel inhibition was observed via a Q-patch clamp assay.

Encouraged by the promising in vitro profile, compound 16 was advanced, and a pharmacokinetic (PK) profile was obtained in male CD-1 mice (Table 6). When compound 16 was administered intravenously (iv) at 1 mg/kg, a short half-life ($t_{1/2}$) of 0.29 h was observed along with a high clearance of 126 mL min$^{-1}$ kg$^{-1}$. The maximum plasma concentration ($C_{\text{max}}$) was 432 ng/mL, while the area under the curve (AUC) was 131 h·ng/mL (as can be seen in the $C_{\text{max}}$ versus time profile in Figure 4). Following an oral dose (p.o) of compound 16 at 10 mg/kg, a mean half-life of 4 h was observed along with adequate plasma exposure ($C_{\text{max}} = 195$ ng/mL) and measurable exposure (AUC = 173 h·ng/mL) with oral bioavailability ($F$) of 16%, suggesting that target engagement may be difficult to achieve when considering the potency and exposure data.

In summary, after identification and validation of initial hit 7 as a weak binder of the AR NTD, 50 analogues were synthesized to explore the SAR and optimize potency. Investigations into region 1 revealed that several benzannulated N-heterocycles were tolerated and had elevated activity compared to the initial hit. In particular, the N-methylindazole analogue 16 showed a 60-fold increase in potency over the progenitor compound 7. Furthermore, compound 16 compared favorably in terms of potency to the clinically deployed AR antagonist enzalutamide (IC$_{50} = 0.34$ μM) and was more potent than known AR-NTD AP1 binder EPI-001 (IC$_{50} = 37.4$ μM) under the assay conditions. Together, the excellent potency, favorable physicochemical properties, and benchmarked pharmacokinetic profile offer a starting point for the further optimization of compound 16 as a tool compound to investigate the pharmacology and engagement of the AR NTD. Further optimization of this emerging chemical equity is underway in our laboratories, focusing on tuning the metabolic profile to attain exposure consistent with target engagement as well as biophysical studies of the interaction with the AR-NTD, and will be reported in due course.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.3c00426.

Preparative details of all compounds and requisite intermediates, associated spectral data, and bioassay procedures (PDF)

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**Figure 3.** Small-molecule inhibition of androgen receptor transcriptional activity of compound 16 and enzalutamide (enza.).

**Figure 4.** $C_{\text{max}}$ versus time profile for compound 16.
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Author Contributions
M.C.H. and C.M.R. contributed equally. All of the authors approved the final version of the manuscript.

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Notes
The authors declare no competing financial interest.

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ABBREVIATIONS
ADT, androgen deprivation therapy; AF-1, activation function-1; AR, androgen receptor; AUC, area under the curve; Clint, intrinsic clearance; CRPC, castration-resistant prostate cancer; CYP, cytochrome P; DBD, DNA binding domain; HBA, hydrogen-bond acceptor; HBD, hydrogen-bond donor; LBD, ligand binding domain; LBP, ligand binding pocket; NSAA, nonsteroidal anti-androgen; NTD, N-terminal domain; iPFI, intrinsic property forecast index; SAR, structure–activity relationship; TPSA, topological polar surface area.

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