N-Aryl-oxazolidin-2-imine Muscle Selective Androgen Receptor Modulators Enhance Potency through Pharmacophore Reorientation[†,△]

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A novel selective androgen receptor modulator (SARM) scaffold was discovered as a byproduct obtained during synthesis of our earlier series of imidazolidin-2-ones. The resulting oxazolidin-2-imines are among the most potent SARMs known, with many analogues exhibiting sub-nM in vitro potency in binding and functional assays. Despite the potential for hydrolytic instability at gut pH, compounds of the present class showed good oral bioavailability and were highly active in a standard rodent pharmacological model.

Introduction

The search for alternatives to testosterone (T[a]) and its analogues to address a range of unmet medical needs from age-related functional decline related to decreased T in aging men[1,2] to muscle wasting conditions[3] and cognitive disorders including Alzheimer's disease[4] has been attracting greater attention from the biomedical community. From the first disclosure of an orally active nonsteroidal androgen nearly a decade ago,[5] a growing number of novel chemical structural motifs have emerged from several groups.[6−8] In connection with our long-standing interest in identifying potent and muscle selective agonists of the androgen receptor (AR), which might show clinical promise for the treatment of age-related functional decline in elderly men, we have continued to explore structure−activity and structure−selectivity relationships around our previously disclosed bicyclohydantoin selective androgen receptor modulator (SARM) scaffold.[9,10] Our preclinical discovery program previously identified BMS-564929 (Figure 1) as an orally active, highly potent muscle SARM, and this compound is one of several agents that have advanced to clinical studies.[11−13] In our subsequent efforts, we wished to maintain the hydroxy-substituted [5,5] bicyclic scaffold for its optimal receptor binding features but to make other modifications to the molecules that might enhance pharmaceutics and/or formulation properties of the lead compound, including aqueous solubility.[14] Recognizing that subtle changes in nuclear receptor ligand structure and binding motifs can lead to profound changes in phenotype, we also hoped to broaden our understanding of factors governing tissue selectivity through application of structural biology tools to evaluate novel ligands.[15] To that end, we set out to explore C1 des-carbonyl analogues of our earlier bicyclohydantoins, including both bridgehead and C1-alkylated imidazolidin-2-ones, as they were envisioned to sterically and/or electronically block possible metabolic oxidation at C1. In the course of chemical syntheses of molecules in support of these investigations,[14] side-products were observed that led to the discovery of a conformationally novel SARM scaffold. Subsequent targeted synthesis of analogues sharing this novel architecture yielded compounds that are among the most potent SARMs identified to date and that possess moderately wide separation between muscle and prostate activity in vivo.

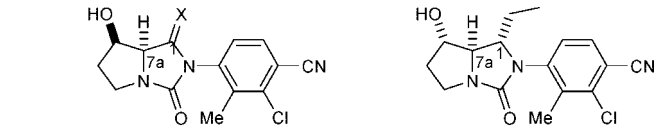

Figure 1. Bicyclic *N*-arylurea selective androgen receptor modulators.

Chemistry

The first compounds in the present angularly configured series of SARMs were discovered through isolation and characterization of side products obtained in a cyclization sequence designed to close the central ring of the aryl-substituted bicyclic scaffold. Under the conditions we had previously employed to access C1-trifluoromethyl-substituted analogues in the imidazolidin-2-one series from hydroxy urea intermediates **4**[14] (*t*BuOK, THF, −78 °C, followed by *p*TsCl),[16] followed by desilylation with fluoride, we observed variable amounts of side products with the same molecular mass as the expected N-cyclized products **5** (Scheme 1). The side products were rigorously characterized

[†] The X-ray coordinates for the complex of compound **6c** and androgen receptor have been deposited to the Protein Data Bank, PDB ID code 3G0W.

[△] The authors dedicate this paper to the memory of John DiMarco.

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[a] Abbreviations: SARM: selective androgen receptor modulator; T: testosterone; AR: androgen receptor; ER: estrogen receptor; PR: progesterone receptor; GR: glucocorticoid receptor; MR: mineralocorticoid receptor.

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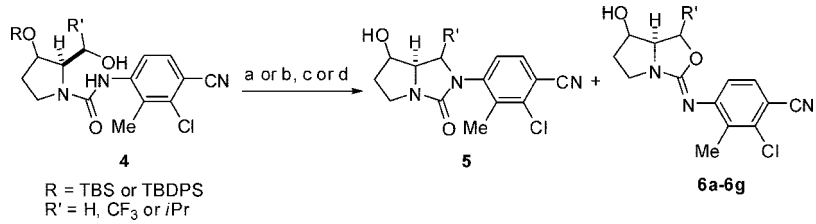
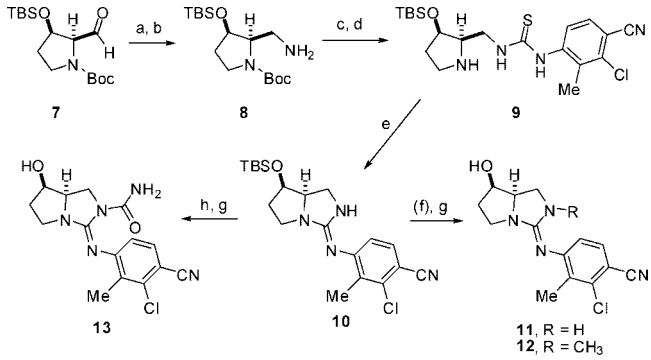
Scheme 1[a]



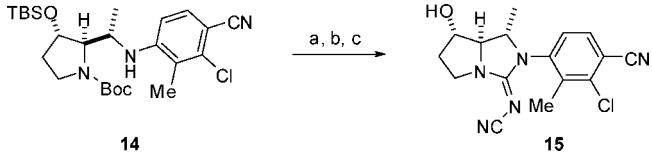
[a] Reagents and conditions: (a) KO*t*-Bu (2.5 equiv), *p*-Tos-Cl, THF, 0 °C (8−12%); (b) PPh_3, CCl_4, Et_3N (11−77%); (c) TBAF, THF (26−83%); (d) HF·py, THF, 0 °C to rt (45−92%).

Scheme 2[a]



[a] Reagents and conditions: (a) 4 Å molecular sieves, MeOH, 0 °C; $BnNH_2$, $NaCNBH_3$; (b) H_2, $Pd(OH)_2$/C, EtOH (55%, 2 steps); (c) 2-chloro-4-isocyanato-3-methylbenzonitrile, THF (82%); (d) TFA, CH_2Cl_2, $NaHCO_3$ (100%); (e) $HgCl_2$, THF, 55 °C (33%); (f) NaH, DMF, MeI (50%); (g) HF·py, THF; (h) NaH, DMF, BrCN (32%).

Scheme 3[a]



[a] Reagents and conditions: (a) 15% TFA in CH_2Cl_2; (b) diphenyl cyanocarbonimidate, DIPEA, sealed tube, 160 °C, 2 h; (c) TBAF, THF (72%, 3 steps).

through extensive NMR experiments and X-ray crystallography, revealing the O-cyclized *Z*-oxazolidin-2-imine products **6**. Upon biological testing of a prototype analogue in this O-cyclized series, we were surprised to learn of the exquisite potency exhibited by this alternative pharmacophoric arrangement. Consequently, we optimized conditions to favor the O-cyclization pathway in order to generate other members of this series to better understand the pharmacologic properties associated with this alternative scaffold. We found that treatment of ureas **4** with Ph_3P and NEt_3 in $CHCl_3$ provided O-cyclized *Z*-imine compounds as the major products (sole products in the cases where R′ in cyclization precursor **4** = CF_3) in moderate to good yields.[17] Desilylation of the secondary alcohols of the cyclization products by use of either TBAF or HF/pyridine provided the O-cyclized targets **6a**−**g**.

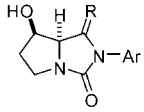
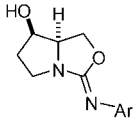
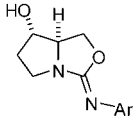
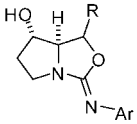
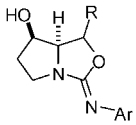
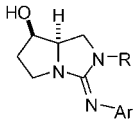
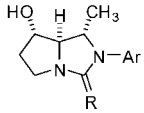
Guanidine derivatives **11**−**13** were derived from aldehyde **7** (Scheme 2), beginning with a 2-step conversion to primary amine **8**. Reaction with 2-chloro-4-isocyanato-3-methylbenzonitrile (prepared in one step via treatment with thiophosgene) provided thiourea **9**. Boc-deprotection and $HgCl_2$-mediated cyclization yielded the desired cyclic guanidine **10**, which was desilylated to provide **11**, or alternatively *N*-methylated, followed by desilylation to provide **12**. A third analogue was prepared from **10** by treatment with NaH and CNBr in DMF prior to deprotection to give acylguanidine **13**. A cyanoguanidine analogue **15** was prepared in three steps from Boc-protected diamine **14** by Boc removal, followed by treatment with diphenyl cyanocarbonimidate and Hünig's base in a sealed tube at 160 °C and subsequent desilylation with TBAF.

Biological Results and Discussion

Our initial discovery of side products in the synthetic step to complete the heterobicyclic imidazolidin-2-one ring formation of earlier SARMs led us to first elucidate the structure of these isomeric species and to then characterize the in vitro pharmacological profile of these compounds. Much to our surprise, the *N*-aryl imine prototype compound **6a** exhibited both receptor binding (0.8 nM) and functional activity (4.8 nM) within the potency range of the corresponding bicyclohydantoin clinical compound **1** and its descarbonyl analogue **2** (Table 1). This finding was particularly unexpected due to the seemingly altered structural alignment of key pharmacophoric elements in the imine scaffold relative to the imidazolone core and due to detailed analysis of binding interactions of compound **1** obtained through an X-ray cocrystal structure.[11] Diastereomeric alcohol **6b** was found to have similar potency. A series of alkyl and haloalkyl substitutions were then evaluated at C1 of the bicyclic skeleton, as these groups had imparted potent activity and favorable physical properties in the earlier series. While all five compounds in this grouping (**6c**−**6g**) had very tight binding affinity (K_is 200−700 pM), the compounds were more differentiated in their agonist potencies in transcriptional assays. The strongest correlation of structural features with functional agonist potency in this series appears to be that alignment of the hydroxyl and alkyl groups on the same face of the puckered bicyclic scaffold is preferred, and this parameter supersedes any direct impact of absolute configuration at the two steroecenters adjacent to the ring-fused carbon. Several guanidine analogues were also prepared to explore the effects of oxygen replacement. Unsubstituted guanidine **11**, as well as the *N*-methyl (**12**) and *N*-acyl (**13**) versions and the transposed cyanoguanidine **15** exhibited AR binding affinity within range of the parent **2**. However, it is interesting to note that none of these compounds showed robust agonist activity in cellular assays but rather exhibited a partial agonist (**12**, **13**, **15**) or antagonist (**11**) phenotype.

Despite the potential for chemical instability of the oxazolidin-2-imines at gut pH (we found **6c** to be unstable in solution, 0.1 N HCl, 37 °C, 24 h, 0.41% remaining), we chose to advance **6c** to rodent studies in order to evaluate the anabolic efficacy and tissue selectivity. In a preliminary rat PK screen, **6c** was found to have a surprisingly high AUC (5800 nM × h after a 5 mg/kg po dose) considering its acid instability. In a subsequent standard two week castrated rat model in recovery mode,[18,19] once daily **6c** exhibited a muscle ED_{50} of 0.9 μg/kg po and a

Table 1. Androgen Receptor Binding (K_i) and Functional (EC_{50}) Potency[b]

cmpd	structure[a]	R	K_i (nM)	EC_{50} (nM)
1		O	14 ± 3	7.8 ± 2
2		H_2	6 ± 2	6.4 ± 12
6a		-	0.8 ± 0.5	4.8 ±0.6
6b		-	0.3 ± 0.1	14 ± 0.5
6c		(*R*)-CF_3	0.3 ± 0.1	0.2 ± 0.1
6d		(*S*)-CF_3	0.2 ± 0.5	19 ± 3
6e		(*S*)-CF_3	2.3 ± 0.3	1.1 ± 0.1
6f		(*R*)-CF_3	0.3 ± 0.1	1.4 ± 0.2
6g		(*R*)-*i*-Pr	0.7 ± 0.2	3.7 ± 0.6
11		H	10 ± 2	1800[c]
12		CH_3	1.9 ± 0.1	44
13		$C(O)NH_2$	19 ± 2	IA
15		N-CN	17	1109
16		O	1.6	5.4 ± 1

[a] Ar = 2-chloro-3-methylbenzonitrile. [b] In vitro data are at least two separate measurements, see ref 11 for detailed assay conditions. [c] IC_{50}, antagonist mode.

Table 2. Growth of Levator Ani Muscle and Prostate in Castrated Male Rats

6c (mg/kg, po)	LA % intact ± SE	P % intact ± SE
0.00001	21.0 ± 1.2	2.6 ± 0.54
0.0001	25.0 ± 2.73	3.6 ± 0.48
0.001	59.0 ± 1.72	9.5 ± 1.05
0.01	109.3 ± 9.02	38.8 ± 6.96
0.03	103.5 ± 2.94	72.9 ± 8.2
0.1	100.5 ± 2.85	103.0 ± 10.7
0.3	103.9 ± 6.72	104.5 ± 5.2
ED_{50}, μg/kg	0.9	14.3
TP ED_{50}, μg/kg	210	420

prostate ED_{50} of 14.3 μg/kg, exhibiting 16-fold selectivity for muscle over prostate (Table 2). This high level of anabolic drive is comparable to the most potent known agents, although the muscle selectivity observed is an order of magnitude lower than previously seen with hydantoin **1**.[11] Compound **6c** was shown to be selective for androgen receptor and had no significant activity in the related steroidal nuclear hormone receptors ER, PR, GR, and MR.

An X-ray cocrystal structure of compound **6c** with AR (Figure 2A) and compound **1** from its complex with AR[11] can be superimposed (protein only) and compared (Figure 2B) to reveal key differences. The combined binding interactions of a nonclassical H-bond with R752 and the π−edge−face interaction with F764 of the AR between the nitrile and aryl rings of **6c**, respectively, appear to be the predominating

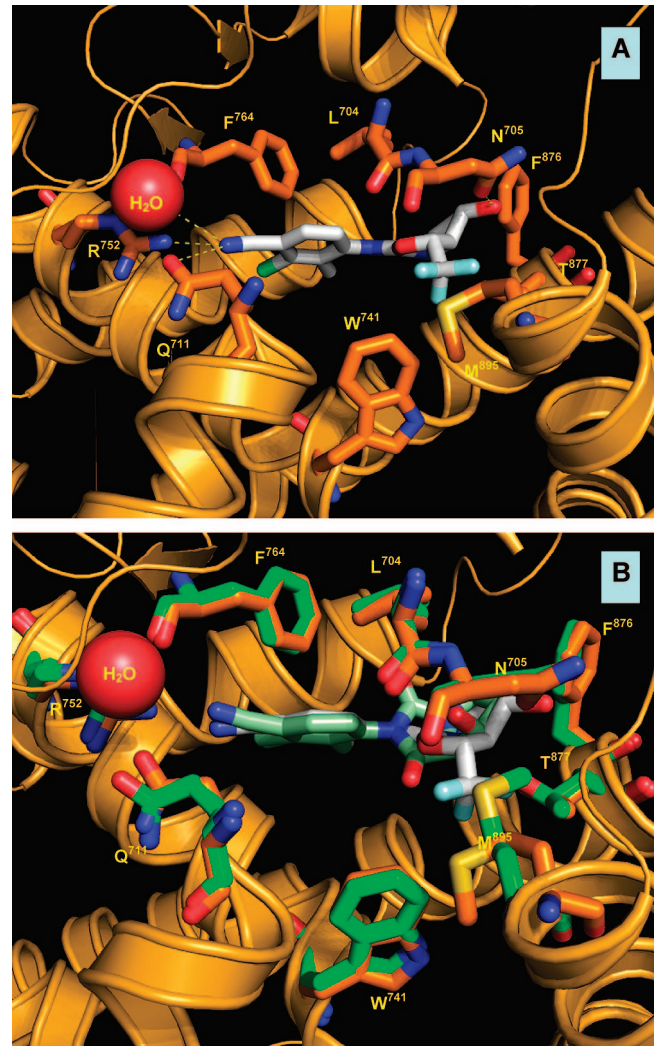


Figure 2. (A) X-ray cocrystal structure of **6c** bound to the human androgen receptor ligand binding domain at 2.0 Å resolution. There are several hydrogen bonds (dashed lines) seen in the complex of **6c** and AR LBD: the CN group of **6c** can form a hydrogen bond with R752 at 2.81 Å; the CN group of **6c** and a bound water molecule can also form a hydrogen bond; the hydroxyl group of **6c** can form a hydrogen bond with N705 at 2.75 Å. (B) Superimposition of X-ray co crystal structures of **1** and **6c**. The protein backbone is displayed in the orange ribbon. The C atoms of compound **6c** are colored white, and C atoms of compound **1** are colored green.

anchoring contacts, and sufficient plasticity in the LBD exists to accommodate maintaining a productive H-bond with T877 and/or N705 through the hydroxy group of **6c**. There is also a water molecule bound to the CN group of **6c** that has not been observed with our previous AR structures. This water is analogous to that seen for progesterone bound to its receptor. In addition, the CF_3 moiety from **6c** projects toward helix 12 of AR, causing M895 to rearrange so as to create a small cavity between W741 and helix 12. Interestingly, unlike the highly tissue selective compound **1** but similar to that seen with the native hormones T and DHT, **6c** experiences a bifurcated H-bond to both T877 and N705. It is not yet clear whether the empirical correlation of this binding feature to reduced tissue selectivity in vivo is mechanistically linked. It is envisioned that with a larger collection of suitable tool molecules of varying binding modes, a deeper understanding of this relationship might be achieved.

As a result of characterization of side products obtained during the synthesis of SARM analogues, modifications to the vectorial orientation of key pharmacophoric elements in an earlier series were achieved and confirmed through analysis of X-ray cocrystal structures of a prototype ligand bound to the AR. Relative to those more linearly oriented compounds previously disclosed from these laboratories, the modified ligand shape appears to correlate with enhanced in vitro potency. This novel scaffold may provide an alternative ligand design template for further drug discovery efforts to identify improved SARMs for a range of indications.

Experimental Section

General Chemistry Methods. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a JEOL 400 or 500 MHz, or on a Bruker 400 MHz instrument. Analytical HPLC were performed on a Shimadzu instrument using YMC C18 5 μm 4.6 mm × 50 mm column with a 4 min gradient of 0−100% solvent A (90% MeOH/90% H_2O/0.2% H_3PO_4) and 100−0% of solvent B (10% MeOH/90% H_2O/0.2% H_3PO_4) with a 1 min hold. LC-MS spectra were obtained on a Shimadzu HPLC and Micromass platform using electrospray ionization. HRMS were obtained on a Micromass LCT in lockspray with electrospray ionization. The preparative HPLC was done on an automated Shimadzu system using the YMC ODS C18 5 μm preparative columns with mixtures of solvent C (90% MeOH/10% H_2O/0.2% TFA) and solvent D (10% MeOH/90% H_2O/0.2% TFA) or mixtures of solvent E (90% CH_3CN/10%H_2O/0.2% TFA) and solvent F (10% CH_3CN/90% H_2O/ 0.2% TFA). Other reagents and solvents were obtained from commercial sources and were used without further purification. All reactions were carried out under a nitrogen atmosphere unless otherwise noted.

Methods for Preparation of 6c: (2*R*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(1*R*)-((2,2,2-trifluoro-1-hydroxyethyl)]-pyrrolidine-1-carboxylic Acid (3-Chloro-4-cyano-2-methylphenyl)-amide (4c). Compound **4c** was prepared in 8% overall yield according to our previously reported method.[14] MS *m*/*z* 492 $[M + H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 and 0.07 (br s, total 6 H), 0.84 (br s, 9 H), 1.94−2.21 (m, 2 H), 2.29 (br s, 3 H), 3.46−3.48 (m, 1 H), 3.52 (br. s., 1 H), 3.65 (br s, 1 H), 3.70−3.83 (m, 1 H), 4.11 (br s, 1 H), 4.42 (br s, 1 H), 5.21 (br s, 1 H), 7.49 (d, J = 8.8 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.98, 14.54, 17.81, 25.60, 32.81, 44.56, 67.69, 72.28, 72.50, 116.66, 119.49, 126.50, 131.90, 136.95, 141.78, 156.67.

Typical Procedures for Cyclizations to Compounds 6a−g. Method A: To a solution of hydroxy urea **4** (0.140 mmol, 1.00 equiv) in THF (3 mL) at 0 °C was added a 1 M solution of *t*-BuOK in THF (0.230 mmol, 1.60 equiv) and *p*-TsCl (0.470 mmol, 3.30 equiv). The mixture was stirred at 0 °C for 30 min and was diluted with EtOAc. The layers were separated, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine and then dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography provided a mixture of silyl-protected **5** (major) and silyl-protected **6** (minor) products. Method B: To a solution of hydroxy urea **4** (0.250 mmol) in CH_3CN (2 mL) at 0 °C was added Ph_3P (1.0 mmol, 4.0 equiv), CCl_4 (2.0 mmol, 8.0 equiv), and NEt_3 (1.0 mmol, 4.0 equiv), and the mixture was stirred at rt overnight. The reaction was diluted with CH_2Cl_2 (ca. 20 mL) and then washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography provided the silyl-protected **6** as the major products. The silyl groups were removed by one of the two following methods. Method C: To a solution of silyl protected **6** (0.025 mmol, 1 equiv) in THF (1 mL) at 0 °C was added a 1.0 M TBAF solution in THF (0.250 mmol, 10 equiv). After stirring at rt for 1 h, saturated aqueous NH_4Cl and EtOAc were added. The layers were separated, and the organic layer was washed with brine and then dried over $MgSO_4$, filtered, and concentrated. Method D: To a solution of silyl-protected **6** (0.055 mmol) in THF (2 mL) at 0 °C was added HF/pyridine mixture (∼2.3:1, 0.120 mL), and the reaction was stirred at rt overnight. Saturated aqueous $NaHCO_3$ (5 mL) was added, and the product was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and then filtered and concentrated. Purification via flash chromatography provided **6a−g**.

***Z*-4-[(1*R*,7*S*,7a*S*)-7-Hydroxy-1-trifluoromethyl-tetrahydropyrrolo[1,2-*c*]oxazol-3-ylideneamino]-2-chloro-3-methylbenzonitrile (6c).** Compound **6c** was prepared in two steps from **4c** by following the general cyclization method B (60% yield, sole product isolated) and deprotection method D (93% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 1.98 (dd, 1 H), 2.30 (dd, J = 12.6, 5.5 Hz, 1 H), 3.49 (br s, 1 H), 3.61−3.77 (m, 1 H), 3.81 (dd, J = 6.6, 3.8 Hz, 1 H), 4.19 (q, J = 7.1 Hz, 1 H), 5.09 (dd, J = 6.6, 3.8 Hz, 1 H), 5.48 (s, 0 H), 6.97 (d, J = 8.2 Hz, 1 H), 7.47 (d, J = 8.2 Hz, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ 15.3, 35.0, 48.5, 68.1, 74.6, 108.1, 117.9, 123.1, 124.4 (q, J = 279), 132.3, 132.5, 137.6, 152.8; MS: *m*/*z* 360 $[M + H]^+$. HRMS calcd for (M + H) 360.0727, found 360.0724. HPLC 100% purity (Zorbax SB C18 4.6 mm × 75 mm; 8 min gradient eluting with solvent A: 10% MeOH/90% water/0.2% H_3PO_4 and solvent B: 90% MeOH/10% water/0.2% H_3PO_4; retention time = 6.48 min); 99% purity (Chiracel OD 4.6 mm × 250 mm; isocratic eluting with 20% isopropanol in heptane; retention time = 5.79 min). HRMS calcd for (M + H) 360.0727, found 360.0724. Anal. calcd: ($C_{15}H_{13}ClF_3N_3O_2$) C, 50.08; H, 3.64; N, 11.68. Found: C, 49.97; H, 3.37; N, 11.42. Stereochemistry was confirmed via X-ray analysis, and this data can be found in the Supporting Information for this article.

X-ray Crystallography. The AR LBD−**6c** complex was crystallized at 20 °C by vapor diffusion in the hanging drop mode using a 3 mg/mL concentration of **6c** as previously described.[15] Data to 1.95 Å resolution were collected at beamline ID32 at the APS synchrotron and reduced with program HKL2000, and the structure was refined with program BUSTER. The His-Tag and the first six residues of the N-terminal and the last residue of the C-terminal were not visible in the electron density and have been excluded from the model. The final structure has an *R*-factor = 20.1% (R_{free} = 23.8%) and contains 2229 atoms (2034 protein atoms, 24 ligand atoms, and 171 solvent atoms).

Acknowledgment. We thank the department of Pharmaceutical Candidate Optimization for bioanalytical and physicochemical profiling support.

Supporting Information Available: Preparation of and characterization data for intermediates and final compounds **6a**, **6b**, **6d**, **6e**, **6f**, **6g**, **11**, **12**, **13**, and **15** and single crystal X-ray structural data for compound **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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