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Brief Article

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2-Chloro-4-[[(1*R*,2*R*)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonitrile: A Transdermal Selective Androgen Receptor Modulator (SARM) for Muscle Atrophy

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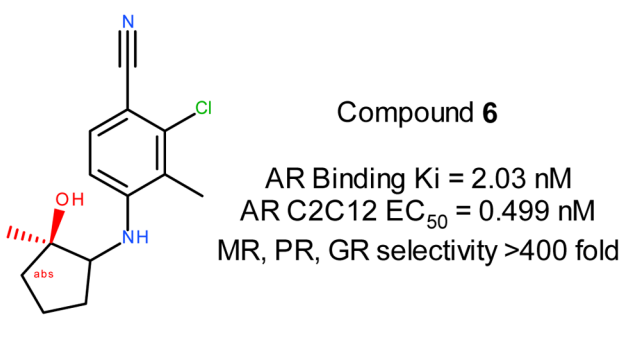
Supporting Information



ABSTRACT: A transdermal SARM has a potential to have therapeutic benefit through anabolic activity in muscle while sparing undesired effects of benign prostate hyperplasia (BPH) and liver-mediated decrease in HDL-C. 2-Chloro-4-[(2-hydroxy-2-methyl-cyclopentyl)amino]-3-methyl-benzonitrile **6** showed the desired muscle and prostate effects in a preclinical ORX rat model. Compound **6** had minimal effect on HDL-C levels in cynomolgus monkeys and showed human cadaver skin permeability, thus making it an effective tool for proof-of-concept studies in a clinical setting.

INTRODUCTION

Androgens are key steroidal sex hormones which play a critical role in the male reproductive system, e.g., in prostatic and testicular development.[1] Androgens also cause increases in skeletal muscle mass and bone mineral density. These hormones, including testosterone (T), which is primarily produced in the testes, and its active metabolite dihydrotestosterone (DHT), induce their effect through binding to the androgen receptor (AR).[1] AR belongs to a subfamily of classical nuclear steroid hormone receptors (NHRs) consisting of the estrogen (ER), progesterone (PR), glucocorticoid (GR), and mineralocorticoid (MR) receptors.[1] Interaction of androgens with AR triggers a series of complex and cell type specific signaling pathways, leading to the androgenic effect which acts primarily on the reproductive system and anabolically on muscle and bone. Expanding the therapeutic application of androgens relies on the pharmacological separation of these two effects.[2−5] SARMs having beneficial effects on bone and muscle with minimal benign prostate hyperplasia (BPH), prostate cancer, and CV risks associated with oral androgens and/or SARMs are highly desirable.[6,7]

The mechanism of AR action is similar to that of other NHRs. Ligand-free AR is mainly located in the cytoplasm and associated with a complex of heat shock proteins (HSPs). Upon ligand binding, the AR dissociates from the HSPs, undergoes a conformational change, translocates to the nucleus, and dimerizes. In the nucleus, the AR binds to androgen response element on the promoter or enhancer regions of androgen responsive genes. The activated AR recruits various coregulators, which subsequently leads to transcription of the target genes.[1,8]

While the tissue-selectivity mechanism remains unclear, in literature various SARMs, such as GTx-007, LGD-2226, BMS-564929, and ACP-105, have been identified (Chart 1).[7−9] These SARMs have been found to have beneficial effect on muscle with lower BPH and prostate cancer risks. The clinical potential of these as systemically administered agents has been limited due to unfavorable plasma lipoproteins changes, such as lowering of HDL-C.[10]

Orally administered androgens and SARMs reduce level of circulating HDL-C in humans, which is considered to increase cardiovascular risk due to potentially antiatherogenic effects of HDL-C.[10] However, androgen and SARM induced decrease in

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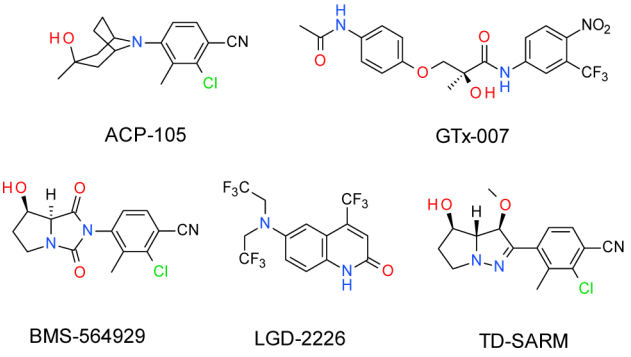
Chart 1. Reported Selective Androgen Receptor Modulators (SARMs)



circulating HDL-C may not automatically be considered proatherogenic because it could be reflective of accelerated reverse cholesterol transport pathway.[11] Topical testosterone (T) formulations are not associated with these risks.[10−15] However, both topical and oral T increase the risk of BPH and prostate cancer.[6] It is reported that decreased plasma HDL-C is mediated through engagement of AR in the liver.[13] Therefore, we hypothesized that a transdermal SARM would minimize first pass liver exposure, mitigating CV risk while maintaining favorable muscle effect and minimal prostate risks seen with an oral SARM. Ullrich et. al recently reported a transdermal SARM (TD-SARM, Chart 1), however, HDL-C effect of these SARMs are not known.[16]

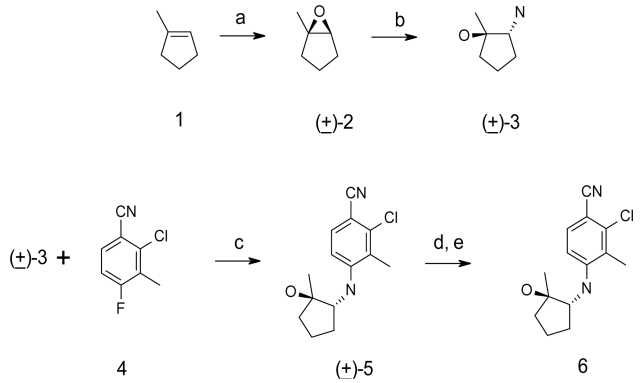
Our overarching structure activity relationship (SAR) strategy for the SARM chemistry effort focused on designing and developing compounds that would be suitable for transdermal delivery. These compounds would maintain favorable in vitro and in vivo activities with minimum effect on the prostate.

RESULTS AND DISCUSSION

Many active AR compounds were identified from Lilly collection which emerged during our prior NHR ligand discovery efforts screen. In the early phase of the SAR investigation, a few of these active chemical scaffolds were evaluated and optimized for transdermal permeability. This required optimization of physicochemical properties such as molecular weight,[17] cLogP, number of H-bond donors and acceptors, and aqueous and ethanol solubilities.[17−19] Ultimately, the *N*-arylhydroxyalkyl series was identified and optimized, leading to 2-chloro-4-[[(1*R*,2*R*)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonotrile, compound **6**. Herein we report the synthesis, in vitro, and in vivo data for compound **6** as well as the crystal structure of the AR ligand binding domain:compound **6** complex.

Compound **6** was synthesized as shown in Scheme 1. Commercially available 1-methylcyclopentene **1** was oxidized to epoxide **2** using MCPBA. Treatment of epoxide **2** with ammonium hydroxide at 90 °C resulted in ring opening to give desired *trans*-hydroxylamine **3** as a racemic compound. SNAr reaction of Amine **3** with 2-chloro-4-fluoro-3-methyl-benzonitrile under basic condition and at 130 °C yielded the racemic mixture of target compound **5**. The racemate **5** was purified using chiral chromatography to provide 2-chloro-4-[[(1*R*,2*R*)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonotrile, compound **6**. Absolute stereochemistry of **6** was

Scheme 1. Synthesis of Compound 6[a]



[a]Reagents and conditions: (a) *m*-CPBA, DCM, rt; (b) NH_4OH, ethanol, water, 90 °C; (c) $LiCO_3$, DMSO, water, 130 °C; (d) CHIRALPAK AD-H column, 20% 2-propanol/carbon dioxide; (e) crystallization.

determined by X-ray crystallization (Figure 3B). Compounds **7**, **8**, and **9** were synthesized as reported previously.[20]

Compounds **6**−**9** were first tested in vitro for their ability to bind AR and other closely related NHRs such as GR, MR, and PR.[19] The compounds were also evaluated for their in vitro functional activity using a C2C12 cell-based assay with methyltrienolone as the standard (Table 1).

Compound **6** and its corresponding *cis*-isomer **7** bound to AR with a K_i of 2.03 and 0.68 nM and showed significant selectivity (>400-fold) over PR, GR, and MR. Compounds **6** and **7** also demonstrated potent agonist activity in the aforementioned C2C12 cellular assay with an EC_{50} of 0.499 and 0.039 nM, respectively. Expansion of the ring to cyclohexyl analogue **8** or incorporation of an oxygen as in analogue **9** resulted in significant decrease in AR binding and functional activities of these compounds. The AR binding and selectivity data justified further investigation of **6** and **7**.

Considering potent in vitro activity of compounds **6** and **7** in binding and functional assays, we tested these in vivo for their anabolic muscle activities using transdermal (TD) administration.[19] For this study, we measured the mass of the highly androgen-responsive levator ani muscle of the rat. This muscle is a striated perineal muscle that supports the organs that reside within the pelvis. To demonstrate that **6** and **7** acted as SARM and had minimal effect on prostate, the prostate weight was also measured in these animals. In an in vivo study (data not shown), **6** and **7** both significantly increased LA muscle mass at 1 mg/kg/day (mpk) when compared to the ORX control group. While **6** had no significant effect on prostate, **7** significanty increased its weight. Considering its SARM like activity, **6** was chosen for a full dose response study. The results of this study are shown in Figure 1.

A significant increase in LA muscle mass was observed in the animals treated with compound **6** relative to the orchidectomized (ORX) control group (Vehicle) at 0.3 mpk and higher doses. In contrast, the increases in prostate wet weight at all doses were minimal and not significant with **6** when compared to the vehicle treated group. Projected muscle ED_{50} dose for **6** was determined to be 0.14 mpk. The results thus clearly indicated that **6** acted as a true tissue selective SARM in vivo.

We next evaluated the PK profile of compound **6** from the rat LA muscle efficacy study. A highly sensitive bioanalytical

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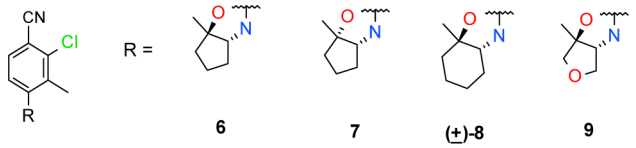
Table 1. In Vitro Binding and Functional Activities of Methyltrienolone, Compound 6, and Related Compounds[a]



compd	AR (K_i nM)	GR (K_i nM)	MR (K_i nM)	PR (K_i nM)	AR C2C12 (EC_{50} nM)
methyltrienolone	0.40 ± 0.25	9.65 ± 4.29	0.54 ± 0.11	0.49 ± 0.31	0.013 ± 0.010
6	2.03 ± 0.98	>6020	1450 ± 897	872 ± 63	0.499 ± 0.416
7	0.68 ± 0.38	462 ± 122	1840 ± 1450	448 ± 104	0.0398 ± 0.026
(±)-8	16.9	>3120	415	520	4.88
9	5.21	2390	>7010	1220	73.7

[a]HEK293 lysate stable transfection was used as source of AR, GR, PR, and MR binding assays. All data are reported as mean ± SD from at least three independent determinations except data for compounds **8** and **9**, which were run only once.

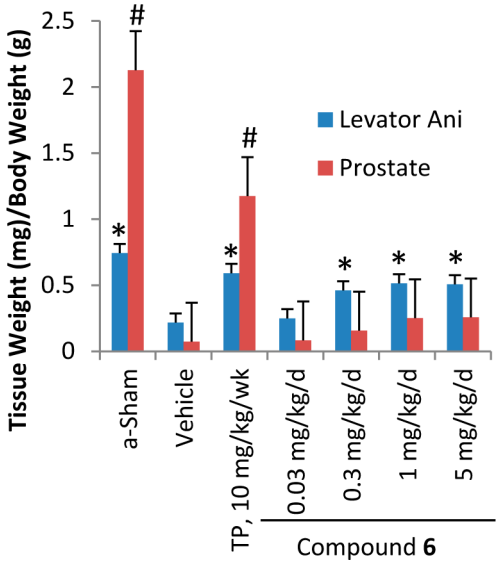


Figure 1. Delayed rat ORX model. Sexually mature 8-week-old SD rats were castrated and allowed to waste LA muscle for 6 weeks, followed by treatment with compound **6** (daily TD) across a dose range for 2 weeks. Animals (n = 6) were sacrificed, and wet weights for the levator ani muscle and the ventral prostate were measured. TP = (testosterone propionate). # p-value <0.05 vs prostate ORX vehicle; * p-value <0.05 vs levator ani ORX vehicle.

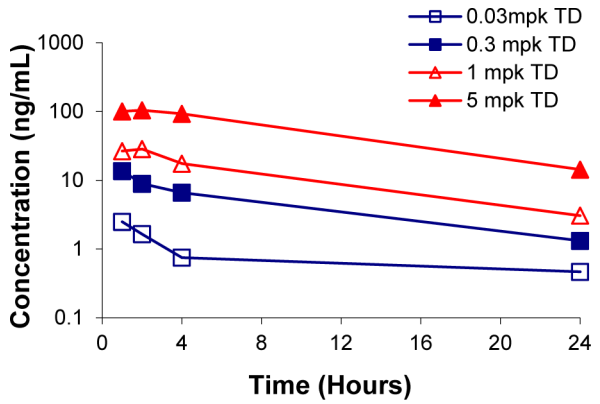


Figure 2. Delayed rat ORX model. Sexually mature 8-week-old SD rats were castrated and allowed to waste LA muscle for 6 weeks, followed by treatment with compound **6** (daily TD) across a dose range for 2 weeks. Plasma concentrations of **6** were measured over 24 h after last dose before sacrifice.

assay (0.1−500 ng/mL) was employed for PK evaluations as the potency of **6** led to low efficacious doses thus resulting in low exposures. Absorption of **6** was rapid (T_{max} ~ 1−2 h) with the efficacy exposure ($EAUC_{50}$) of 39.9 ng·h/mL and EC_{max} of 3.24 ng/mL measured by AUC_{0-24h} in the 2-week study (Figure 2).

Compound **6** was evaluated for its effect on HDL-C lowering in vivo in intact (i.e., nongonadectomized) young adult female cynomolgus monkeys. A TD PK evaluation of the compound confirmed its skin permeability in the cynomolgus monkey (data not shown). This animal model has been shown to respond to androgens with a lowering of HDL-C and is considered predictive of a similar human response.[21,22] Doses of 0.035 and 0.18 mg/kg of **6** as a gel formulation were applied transdermally once daily for 14 days. The group mean decrease in HDL-C after 14 days relative to the mean of the two baseline determinations was 10% at the 0.035 mg/kg dose (Table 2). At 0.18 mg/kg, the HDL-C decrease from baseline was 33%. In a separate 14-day study in cynomolgus monkey, conducted under essentially the same experimental conditions as described for compound **6**, **T** at TD dose of 1 mg/kg (AUC 145 ng·h/mL) lowered HDL-C about 15%. At similar AUC, T in humans has a ~2−4% decrease in plasma HDL-C, suggesting monkeys as being more sensitive species with regard to HDL-C changes.[5] Considering significantly greater sensitivity of monkeys relative to humans, the HDL-C data demonstrate that **6** has no significant effect on HDL-C at 0.035 mg/kg/day. However, the translation of 33% decrease in plasma HDL-C observed at 0.18 mg/kg/day from monkeys to humans remains to be seen. The AUC of **6** at 0.18 mg/kg/day was 42.5 ng·h/mL, which was over 1-fold the $EAUC_{50}$ observed in rat ORX study.

Following encouraging HDL-C results in cynomolgus monkeys for compound **6**, we next evaluated percutaneous absorption across human cadaver skin, in vitro, using the finite dose technique and Franz diffusion chamber. Application volume and dose per unit area were chosen to simulate anticipated human clinical volume and dose. The data from this study are presented in Table 3. At a dose of 0.2 mg/cm^2, percutaneous absorption of **6** was comparable to **T**, with delivery of 13.17 and 12.47 μg/cm^2/48 h, respectively. We tested **6** at a higher dose of 0.7 mg/cm^2 and observed an increase in amount crossing the skin, although the relationship between amount crossing and applied dose was not proportionally greater. These data suggest acceptable absorption of **6** across human cadaver skin and allows further evaluation of the compound in the clinic to study correlation of muscle efficacy,

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Table 2. Decrease in Plasma HDL-C Relative to Baseline (Day 1) after Transdermal Application of Testosterone (T) and Compound 6 in Cynomolgus Monkeys

			after 3 doses HDL-C		after 7 doses HDL-C		after 14 doses HDL-C		
compd	dose (mg/kg/d)	baseline day 1 HDL-C (mg/dL)	mg/dL	decrease (%)	mg/dL	decrease (%)	mg/dL	decrease (%)	AUC after 14 doses (ng·h/mL)
T	1.00[a]	52.0 ± 3.6					44.3 ± 2.1	15	145
6	0.035	77.02 ± 9.18	68.2 ± 8.6	13	72.4 ± 8.2	7.1	70.2 ± 7.8	10	12.0 ± 2.2
6	0.18	75.37 ± 7.38	62.2 ± 8.1	16	52.9 ± 7.6	29	49.7 ± 5.6	33	42.5 ± 6.1

[a]At this dose of **T**, an AUC which is comparable to normal human AUC was obtained.

Table 3. Human Cadaver Skin Permeability of Testosterone (T) and Compound 6

compd	conc (mg/mL)	applied volume (μL/cm^2)	applied dose (mg/cm^2)	amount crossing 1 cm^2[a] (μg)
T	20	10	0.2	12.47 ± 1.02
6	20	10	0.2	13.17 ± 4.01
6	35	20	0.7	19.60 ± 2.51

[a]Mean amount crossing to the receptor after 48 h obtained from three independent donors, each with n = 3 determinations. The individual diffusion cell values per donor were averaged to obtain a within donor mean (±SD). The population (across donor) mean (±SE) was obtained by averaging the donor means (shown).

prostate, and HDL-C effects using transdermal route of administration.

The tertiary structure of the AR ligand binding domain (LBD) is similar to that observed in previous AR LBD crystal structures. Compound **6** is bound in the canonical steroid binding site with the nitrile pointing upward between helices α-3 and α-6 and the pentane ring at the base of the pocket sandwiched between helices α-3 and α-11 (Figure 3). Only one hydrogen bond is found between **6** and the AR LBD: the hydroxyl of the cyclopentane ring forms a hydrogen bond with the side chain of N705 at the base of α-3 (check for side chain flip, Figure 3). The remainders of the contacts are van der Waals interactions in this region. The chlorophenyl is encased within a hydrophobic cage formed by the side chains of L704, W741, M742, M745, M749, F764, L873, and M895 (Supporting Information, Figure 3) similar to A ring of **T**. Interestingly, the linker nitrogen in **6** is surrounded by a hydrophobic groove formed by M742, M780, and L873, a generally unfavorable environment for a hydrogen bond donor. While the 17-hydroxyl of **T** forms a similar hydrogen bond with the N705 side chain, it also forms an additional hydrogen bond with the side chain oxygen of T877 of α-11 (Figure 3).

To satisfy this hydrogen bond, the side chain rotates clockwise ~120° relative to its orientation in the **6**-bound form. Another point of contrast is observed in the orientation of the W741 side chain, the orientation of which is flipped when the two structures are compared, with the indole more proximal to the α-3 helix in the **6**-bound form. This flexibility of side chains in the binding pocket, especially that of W741, allowed hits within this scaffold to be discovered in the screen. The side chain movement of W741 was subsequently observed in X-ray cocrystal structure with compound **6** (Figure 3A,B). The overall pose of the two ligands are similar where the D ring of the steroid overlays approximately with the cyclopentane of **6** and the A ring of the steroid overlays on top of the 3-chloro-4-C*N*-phenyl ring of **6**.

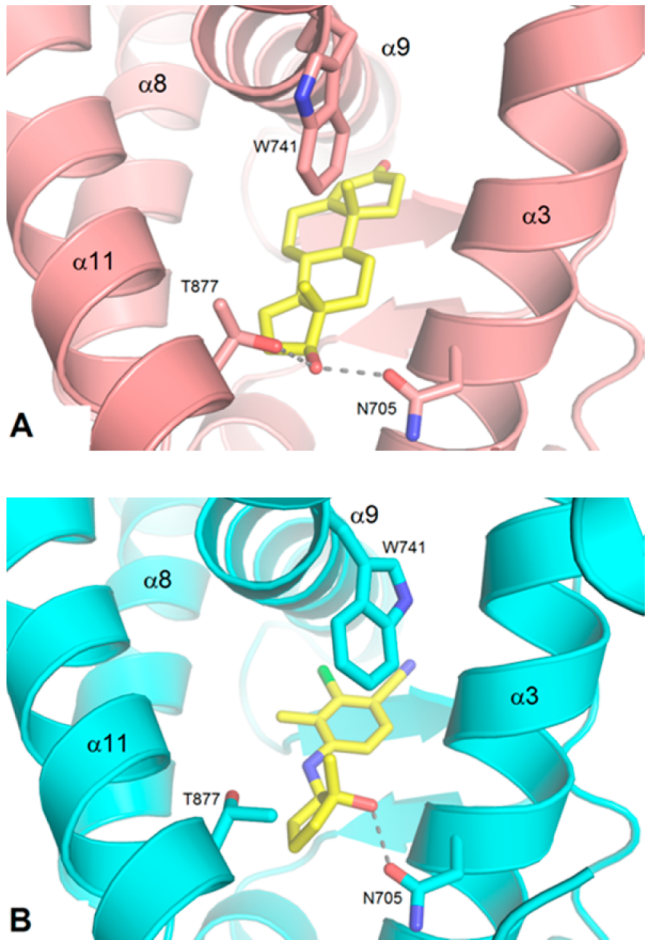

Figure 3. X-ray cocrystal structure of (A) testosterone and (B) compound **6** with AR ligand binding domain.

CONCLUSION

Herein, we have described the synthesis and biological evaluation of compound **6**, a transdermal SARM, as a potential drug for the treatment of muscle atrophy. Our SAR effort applying structure-based design and the incorporation of desired physicochemical properties led to discovery of **6** as a SARM with a nanomolar K_i in binding and less than a nanomolar EC_{50} in functional assays. Compound **6** also showed excellent selectivity over other NHRs, including GR, MR, and PR. When tested in the in vivo ORX rat model, **6** exhibited efficacy in muscle with an ED_{50} of 0.14 mpk and with minimal effect on prostate, thus behaving as a SARM. Compound **6** was highly permeable in monkey skin, allowing the team to study its effect on HDL-C lowering in the cynomolgus monkey model. Because of its marginal effect on HDL-C lowering in monkeys

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when applied topically and high human cadaver skin permeability, **6** has emerged as a valuable TD SARM for further clinical studies to understand muscle efficacy vs HDL-C correlations.

EXPERIMENTAL SECTION

All solvents were purchased from Sigma-Aldrich (Hy-Dry anhydrous solvents), and commercially available reagents were used as received. All reactions were followed by TLC analysis (TLC plates GF254, Merck) or liquid chromatography mass spectrometry (LCMS) using Agilent 1100 equipped with a solvent degasser, binary pump, auto sampler, thermostated column compartment with 2-position/10-port valve, and a diode array detector (Agilent Technologies, Waldbronn, Germany). The UV wavelength was set at 214 nm. Electrospray mass spectrometry measurements were performed on a MSD quadrupole mass spectrometer (Agilent Technologies, Palo Alto, CA, USA) interfaced to the above HPLC system. MS measurements were acquired in positive ionization mode over the mass range of 100−700. Data acquisition and integration for LC/UV and MS detection was performed using Chemstation software (Agilent Technologies). GCMS measurements were acquired in GC_MS Agilent 7890A equipment using HP-Chiral 30m, 0.25 mm, 0.25 mm (β-cyclodextrin in (35% phenyl)-methylpolixiloxane) column, and mass measurements were performed in EI ionization mode over the mass range of 50−500. NMR spectra were recorded at ambient temperature using standard pulse methods on any of the following spectrometers and signal frequencies: Bruker Advance DPX 300 MHz (^{1}H = 300 MHz, ^{13}C = 75 MHz) and 400 MHz spectrometers (^{1}H = 400 MHz, ^{13}C = 100 MHz). Chemical shifts are reported in ppm and are referenced to the following solvent peaks: $CDCl_3$ (^{1}H = 7.27 ppm, ^{13}C = 77.00 ppm), DMSO-d_6 (^{1}H = 2.50 ppm, ^{13}C = 39.51 ppm), and MeOH-d_4 (^{1}H = 3.31 ppm, ^{13}C = 49.15 ppm). Coupling constants are quoted to the nearest 0.1 Hz, and multiplicities are given by the following abbreviations and combinations thereof: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Optical rotations were recorded using a PerkinElmer 343 polarimeter with fixed wavelength (589 nm). The purity of all compounds tested was determined by LCMS and ^{1}H NMR to be >95%.

(±)-Methyl-6-oxabicyclo[3.1.0]hexane (2). To a solution of 1-methylcyclopentene **1** (25 mL; 236.7 mmol) and methylene chloride (770 mL) cooled to 5 °C, *m*-chloroperoxybenzoic acid (87.5 g ; 355.1 mmol) was added portionwise during 30 min and the mixture was stirred and warmed to rt overnight. The mixture was filtered over a Celite and then filtrates neutralized with sodium bicarbonate aqueous solution 7% w/w until adjusted pH = 8. Then the organic layer was separated and treated with sodium sulfite 10% aqueous solution until negative oxidant strips test control. Then the organic layer was dried over sodium sulfate, filtered, and the filtrates evaporated to afford **2** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (s, 1H), 1.81−1.99 (m, 2H), 1.38−1.65 (m, 4H), 1.42 (s, 3H). GC-MS: 98 (M+).

(±)-2-Amino-1-methyl-cyclopentanol (3). To a solution of1-methyl-6-oxabicyclo[3.1.0]hexane (24 g equiv; 244.7 mmol) in ethanol (100 mL) and water (50 mL), ammonium hydroxide 30% w/w (50 mL; 359.5 mmol) was added. Then solution was heated in a pressure reactor at 90 °C during 4 h and then cooled to rt. Solvent was evaporated and residue was diluted with *i*-propyl alcohol (100 mL) three times and evaporated. Residue was dried under vacuum to constant weight and then crude oil purified by distillation (20 mbar/25 °C) to afford (28.4 g, 60%, two steps). Used without additional purification in next step.

2-Chloro-4-fluoro-3-methyl-benzonitrile (4). To a solution of diisopropylamine (474 mL, 3.35 mol) in dry THF (5.8L) cooled at −5 °C under nitrogen, *n*-BuLi (2.5 M in hexane) (1.24 L, 3.097 mol) was added. In a separate flask, a solution of **1** (400g, 2.58 mol) in dry THF (5.8L) was cooled to −70 °C under nitrogen. Then the freshly prepared LDA solution was added via cannula keeping −70 °C. After addition, MeI (643 mL, 10.32 mol) was added, keeping −70 °C, and then reaction was allowed to raise the temperature from −70 to −5 °C for 17 h. Reaction mixture was treated with ammonium chloride aqueous solution (3 L), diluted with water (3.5 L), and finally extracted with diethyl ether (2 × 2L). Organic phases were separated, combined, and dried over sodium sulfate. Then mixture was filtered and filtrate concentrated to dryness, yielding a black solid which is purified by silica gel pad eluting with hexane−AcOEt 40:1 to yield 323g (74%) of 2-chloro-4-fluoro-3-methyl-benzonitrile (**4**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (dd, J = 8.6, 8.6 Hz, 1 H), 7.54 (dd, J = 8.6, 5.6 Hz, 1H), 2.36 (d, J = 2.4, 3H).

2-Chloro-4-[[(±)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonitrile (±5). To a solution of 2-chloro-4-fluoro-3-methyl-benzonitrile (**4**) (30 g; 176.9 mmol) and (±)-2-amino-1-methyl-cyclopentanol (34 g, 212.3 mmol) in dimethyl sulfoxide (270 mL) was added lithium carbonate (26.1 g, 353.8 mmol) and water (30 mL). Reaction mixture was degassed bubbling nitrogen during 15 min and then was heated in a pressure reactor at 130 °C during 48 h. Reaction was cooled at rt and diluted with water (9 L) and MTBE (1 L). Layers were separated and the aqueous layer washed twice with MTBE (2 × 1 L). Organics were combined, dried over sodium sulfate, and filtered. Filtrate was concentrated to dryness, yielding a black solid which is purified by silica gel pad eluting with CH_2Cl_2−AcOEt 40:1 to yield 46 g (96%) of 2-chloro-4-[[(±)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonitrile (**±5**).

Chiral HPLC Purification of ±5. Chiralpak AD 11 cm × 35 cm; 75/25 heptane/IPA; 800 mL/min; 310 nm. 2-Chloro-4-[[(±)-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonitrile **5** (280 g) as purified under the above conditions to afford 137 g of desired **6**. Chiral analysis was carried out with Chiralpak AD-H 4.6 mm × 150 mm; 75/25 heptane/IPA; 0.6 mL/min; 270 nm. Specific rotation: $[\alpha]_D^{25}$ = 20.2 (c = 10, EtOH). ^{1}H NMR (400 MHz, DMSO-d_6): 7.46 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.47 (d, J = 7.8 Hz, 1H), 4.64 (s, 1H), 3.72−3.66 (m, 1H), 2.19 (s, 3H), 2.06 (s, 1H), 1.70−1.57 (m, 4H), 1.03 (s, 3H). LC-MS/ES: m/z (^{35}Cl/^{37}Cl) 265.2/267.2 (M + 1).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b01168.

Complete experimental data of the crystallographic studies; biological assays and tests associated with compound **6** (PDF)

Molecular formula strings (CSV)

Accession Codes

Coordinates and structure factors of compound **6** in complex with the binding domain of AR have been deposited to the Protein Data Bank with accession: 5CJ6.

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Author Contributions

The manuscript was written through contributions of all authors. A.S., G.V., K.G., D.M., J.G., P.G.L., and P.J. contributed to chemistry, while H.B., N.C., N.P., S.S., V.K., and J.H. contributed to in vitro and in vivo studies. J.L. and Y.W. contributed to structure biology. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

AR androgen receptor; ER estrogen receptor; PR progesterone receptor; GR glucocorticoid receptor, and MR mineralocorticoid receptor; SARM selective androgen receptor modulators

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