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Synthesis, Structure−Activity Relationships, and Characterization of Novel Nonsteroidal and Selective Androgen Receptor Modulators

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Herein we describe the discovery of ACP-105 (**1**), a novel and potent nonsteroidal selective androgen receptor modulator (SARM) with partial agonist activity relative to the natural androgen testosterone. Compound **1** was developed from a series of compounds found in a HTS screen using the receptor selection and amplification technology (R-SAT). In vivo, **1** improved anabolic parameters in a 2-week chronic study in castrated male rats. In addition to compound **1**, a number of potent antiandrogens were discovered from the same series of compounds whereof one compound, **13**, had antagonist activity at the AR T877A mutant involved in prostate cancer.

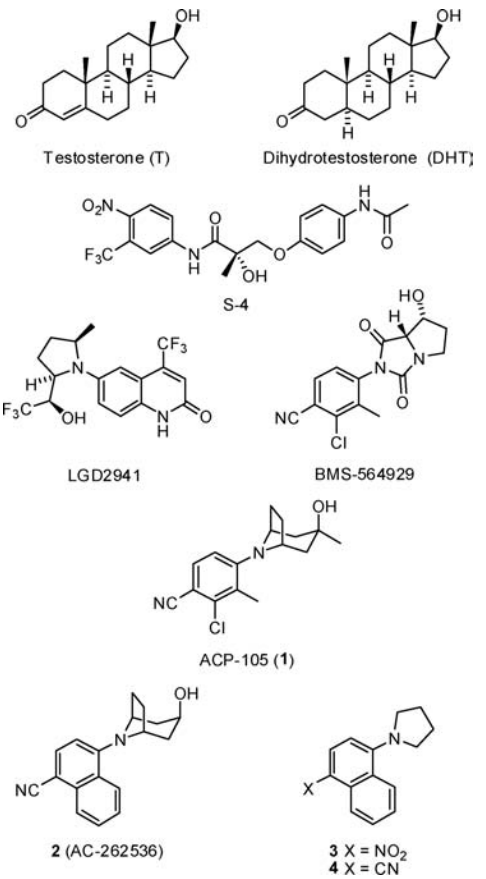
Introduction

The design of nonsteroidal androgen receptor (AR[a]) ligands with specific pharmacological profiles will expand the clinical applications of androgens in diseases of the prostate, hormone-replacement therapy, osteoporosis, and male contraception.[1] Physiologically, AR is predominantly activated by testosterone (T) and its metabolite dihydrotestosterone (DHT) (Chart 1). In addition, various synthetic androgen steroidal ligands have been developed for the treatment of, for example, male hypogonadism, muscle wasting, anemia, benign prostate hyperplasia, and prostate cancer.[2] However, the use of steroidal androgens has been limited because of the risk of serious side effects, e.g., cardiovascular events, hepatotoxicity, and the potential of prostatic hyperplasia or cancer.[2,3] In particular, the lack of discrimination between anabolic and androgenic effects of the current forms of testosterone is of major concern and has driven the search for selective AR modulators (SARMs).

A number of nonsteroidal selective AR agonists that are under preclinical or clinical development has been reported, e.g., BMS-564929, S-4 (andarine), and LGD-2941.[1,4] Several of these compounds have revealed potent and efficacious anabolic activity and acted as partial agonists in androgenic tissues in animal models.[5]

Recently we reported on the pharmacological characterization of compound **2** (AC-262536) as a novel, potent, and selective AR ligand that shows partial agonistic activity relative to T.[6] The partial agonistic activity was suggested to have beneficial implications, (e.g., differences in tissue selective actions could be enhanced because of distinct receptor reserve contents in androgen-responsive tissues).Furthermore, in tissues with high natural androgen content, such as the prostate, a partial AR agonist could act as a functional

Chart 1



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[a] Abbreviations: AR, androgen receptor; DHT, dihydrotestosterone; F, flutamide; HF, hydroxyflutamide; LBD, ligand binding domain; o/n, overnight; PTSA, *p*-toluenesulfonic acid; rt, room temperature; R-SAT, receptor selection and amplification technology; SAR, structure−activity relationship; SARM, selective androgen receptor modulator; SLR; structure−liability relationship; T, testosterone.

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antagonist of androgen action by effectively competing with both T and DHT. Tropanol **2** was developed in a hit-to-lead optimization effort starting from the hit compound **3** identified in an in-house screen using the receptor selection and amplification technology (R-SAT).[7] R-SAT is a functional cell-based assay that allows one to monitor receptor-dependent proliferative responses of various receptor classes, including G-protein-coupled receptors and nuclear receptors.[8] In vivo experiments in castrated rats showed that **2** significantly improved anabolic parameters in these animals while only having minimal effects on the androgenic tissues.

Herein we report on the structure−activity relationship (SAR) studies first leading to **2** and further to the discovery of ACP-105 (**1**), an orally available, selective, and potent SARM. Furthermore, we also describe how small changes in the structures led to intrinsic receptor activities ranging from full agonistic to antagonistic activities including an antiandrogen with antagonist activity at the AR T877A mutant involved in prostate cancer.

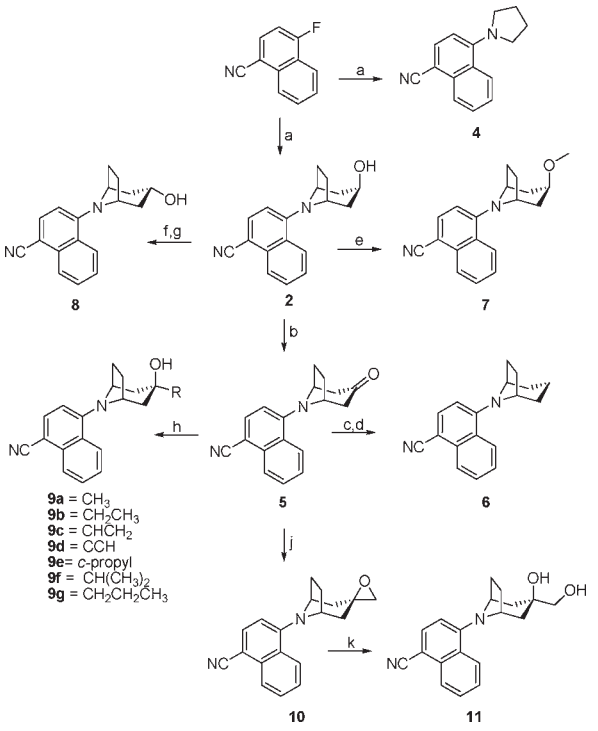
Chemistry

The syntheses of naphthalene **4** and a series of tropane analogues are outlined in Scheme 1. Compounds **2** and **4** were synthesized from 4-fluoro-1-naphthonitrile and nortropine or pyrrolidine, respectively, in a microwave assisted nucleophilic aromatic substitution. The methoxytropanol analogue **7** was obtained by alkylation of **2** with methyl iodide and sodium hydride. The *exo*-tropanol analogue **8** was obtained from the *endo*-derivative **2** using Mitsunobu conditions. Swern oxidation of **2** afforded the ketone **5** which served as a useful synthetic intermediate to prepare a number of different derivatives. Ketone **5** was converted to the corresponding *p*-toluenesulfonylhydrazone derivative and subsequently reduced using sodium cyanoborohydride and *p*-toluenesulfonic acid to yield tropane **6**. Compounds **9a**−**g** were synthesized using the protocol developed by Knochel and coworkers wherein Grignard reagents were added to ketones using $CeCl_3 \cdot 2LiCl$ as an additive.[9] This protocol gave both high chemoselectivity and regioselectivity, with a preferential *exo*-attack on the ketone, dr > 9:1 (**9a**−**g**).[9b] Tropanone **5** was subjected to a Corey−Chaykovsky reaction to obtain epoxide **10** with complete diastereoselectivity. Aqueous H_2SO_4 was used to ring-open epoxide **10**, affording diol **11**. Compound **12** was obtained by a nucleophilic aromatic substitution between nortropine and 2,3-dimethyl-4-nitrophenol triflate (Scheme 2). Syntheses of compounds **13** and **14** were carried out by a nucleophilic aromatic substitution of nortropine with 2-chloro-4-fluorobenzonitrile and 2-chloro-4-fluoro-3-methylbenzonitrile, respectively, in pyridine. An efficient convergent synthesis was developed to prepare compound **1** from 2-chloro-4-fluoro-3-methylbenzonitrile and endo-3-*exo*-methyl-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (**15**). Tropanol **15** was synthesized in three steps from N-Boc-tropinone via a complete diastereoselective epoxidation followed by a reduction and a subsequent trituration as HCl salt.

Results and Discussion

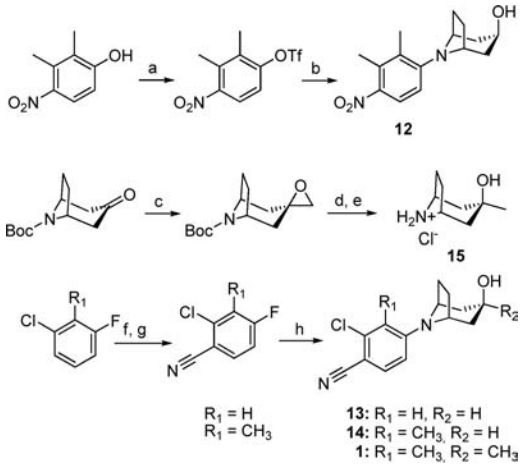
In vitro functional activity determined with R-SAT assays and radioligand binding data at the AR receptor and the intrinsic clearance values in human and rat liver microsomes of compounds **1**−**14** are summarized in Table 1. The first step in the hit-to-lead optimization was to turn our attention to the potential toxic functionality of **3**. The aromatic nitro group was exchanged with a cyano group to give compound **4**. Other functional group exchanges (e.g., chlorine, amides, acetamide,

Scheme 1[a]



[a] (a) Nortropine or pyrrolidine, pyridine, microwave, 220 °C, 5 min, 92% and 62% yields, respectively; (b) (i) $(COCl)_2$, DMSO, dichloromethane, −60 °C; (ii) NEt_3, rt, o/n, 86% yield; (c) $pTsNHNH_2$, EtOH, reflux, 1 h, 92% yield; (d) $NaBH_3CN$, PTSA, DMF/sulfolane, 1:1, cyclohexane, 110 °C, 7 h, 40% yield; (e) MeI, NaH, 60 °C DMF, o/n, 8% yield; (f) DIAD, PPh_3, *p*-nitrobenzoic acid, THF, rt, o/n, then 40 °C, 3 h, 50% yield; (g) 2 M LiOH, THF, o/n, 89% yield; (h) RMgX, $CeCl_3 \cdot 2LiCl$, THF, −10 °C to rt, o/n, 23−63% yields; (j) $(CH_3)_3SOI$, DMSO, NaH, rt, o/n, 61% yield; (k) 0.2 M H_2SO_4, THF, rt, 3 h, 31% yield.

Scheme 2[a]



[a] (a) $(CF_3SO_2)_2O$, NEt_3, CH_2Cl_2, 0 °C to rt, 98% yield; (b) nortropine, pyridine, 110 °C, 16 h, 7% yield; (c) $(CH_3)_3SOI$, DMSO, NaH, rt, 20 h, used without further purification; (d) superhydride, THF, 0 °C, rt, 77% yield; (e) 4 M HCl in dioxane, Et_2O, rt, 2 h, 77% yield; (f) Br_2, Fe(0), 30 °C, 1 h; (g) $Pd(PPh_3)_4$, $Zn(CN)_2$, DMF, 120 °C, 2 h, 40% yield, two steps; (h) **15** or nortropine, pyridine, 110 °C, 18 h, 63% yield (**13**), 18% yield (**14**), 40% yield (**1**).

Table 1. Ligand Activities at AR Wild Type and T877A Mutant and Intrinsic Microsomal Clearance[a]

	AR			AR, mutation T877A			Cl_{int} (μL/(mL·mg))	
compd	pEC_{50}	% eff	pK_i	pEC_{50}	% eff	pK_i	$Cl_{Int,human}$	$Cl_{Int,rat}$
T	8.7 ± 0.2	102 ± 11						
DHT	8.4 ± 0.2	107 ± 19		8.9 ± 0.3	100 ± 5			
F		NA	6.2 ± 0.6	4.7 ± 0.2	36 ± 5	6.4 ± 0.3		
HF		NA	7.3 ± 0.2	7.0 ± 0.4	97 ± 8	NA		
1 (ACP-105)	9.0 ± 0.3	81 ± 6		9.4 ± 0.3	37 ± 5	5.5 ± 0.4	28	72
2	7.9 ± 0.3	73 ± 11					70	148
3	8.2 ± 0.5	96 ± 22						
4	7.8 ± 0.6	67 ± 14					528	1177
5	7.0 ± 0.3	66 ± 10					49	189
6	8.4 ± 0.3	95 ± 11					114	591
7	7.7 ± 0.3	60 ± 24						
8	7.0 ± 0.4	47 ± 3					7	57
9a	8.7 ± 0.1	88 ± 14					22	95
9b	8.4 ± 0.4	44 ± 2						
9c	8.7 ± 0.1	48 ± 3						
9d		NA	7.0 ± 0.5	8.1 ± 0.2	66 ± 7	6.4 ± 0.2	19	97
9e	8.7 ± 0.1	56 ± 1						
9f	8.3 ± 0.8	42 ± 6						
9g	7.8 ± 0.6	42 ± 6						
10		Na	7.4 ± 0.3	7.9 ± 0.3	39 ± 8	6.8 ± 0.2		
11		Na	6.9 ± 0.1	7.4 ± 0.1	58 ± 10	NA	28	35
12	7.9 ± 0.2	76 ± 8						
13		NA	7.0 ± 0.1		NA	7.0 ± 0.2		
14	8.7 ± 0.1	81 ± 3					69	214

[a] R-SAT was performed as described in ref 6. Agonist efficacies were compared to that of DHT (100%). Values represent the mean ± SEM of three or more independent experiments (n > 3). NA = not active. T = testosterone. DHT = dihydrotestosterone. F = flutamide. HF = hydroxyflutamide.

and carboxylic acid) were also screened; however, the replacement with any of these groups gave compounds devoid of activity in R-SAT (results not shown). Pyrrolidine **4** showed a somewhat lower activity than **3** and turned out to have an unacceptably high metabolic in vitro clearance. In general, cyclic amines are known to be readily subject to metabolic transformations, one of those paths being oxidation at the α-positions. We therefore looked at the possibility of blocking this path by introducing another ring system, which would inhibit the metabolism at the two positions neighboring the nitrogen. Replacing the pyrrolidine with a tropane (**6**) gave, in addition to an increased stability in both human and rat liver microsomes, a significant increase in potency compared to **4**. Although a clear improvement was achieved, the in vitro clearance for **6** was still suboptimal. The synthetic intermediate **5** provided the knowledge that the AR receptor pharmacophore shows a certain tolerance toward the presence of polar groups, i.e., carbonyl. Whereas **5** was approximately 50 times less potent than **6** (the pEC_{50} decreases from 8.4 for **6** to 7.0 for **5**), a significant increase in metabolic stability was observed. Therefore, insertion of a hydroxyl group at the 3-position of the tropane ring could have several benefits, first blocking the 3-position toward metabolism and second by potentially improving binding interactions by capturing H-bonds with asparagine 705 (N705) and threonine 877 (T877) at the ligand binding domain (LBD) of the AR, as has been suggested for the endogenous ligands.[10] Tropanol **2** was therefore synthesized and indeed showed an improved liver microsomal stability. The AR agonistic activity of **2** was slightly lower than for **6**, suggesting that hydrogen bond interactions with the LBD are not crucial for the activity for this class of compounds.

To improve the metabolic stability further and to explore changes in the tropane, other functional groups, e.g., amine, hydroxylamine, and amide derivatives in the 3-position of the tropane, were investigated, but all were devoid of activity (results not shown). Epoxide **10** and diol **11** were prepared to test whether additional polar groups may be acceptable. These compounds showed significant antagonistic activity instead of the expected agonistic activity. Whereas methylation of the 3-hydroxyl gave a compound (**7**) that was approximately equipotent with the parent tropanol **2**, the *exo*-tropanol **8** showed a significant decrease in both potency and efficacy compared to the *endo*-tropanol **2**. Nevertheless, **8** displayed a further improvement in microsomal stability compared to **2**. The reduction of clearance seen with *exo*-alcohol **8** could be due to steric hindrance by the tropane bridge limiting the accessibility of hydrogen on the methine carbon. Thus, by removal of the *exo*-hydrogen, a potential oxidation path may be avoided. Furthermore, although the accessibility to the *endo*-alcohol group is limited by the carbon bridge of the tropane, phase II metabolism, i.e., conjugation, may still represent a potential problem. Hence, introducing a sterically crowded environment around the alcohol may decrease both potential phase I and phase II metabolic pathways. Therefore, a series of tropanol derivatives (**9a**−**g**) bearing varying alkyl substituents in 3-*exo*-position was synthesized. The *exo*-methyl tropanol **9a** displayed about 10-fold increase in potency (pEC = 8.7) compared to **2** (pEC = 7.9). In addition, **9a** showed increased stability in both rat and human liver microsomes compared to **2**.

The increased microsomal stability for **9a** and **2** corroborated with the results from stability studies in cryopreserved rat hepatocytes, where half-lives of 96 and 3 min, respectively, were observed. When the chain length was extended with one carbon from methyl to ethyl (**9b**), a decrease in both potency and efficacy was observed compared to **9a**. Further elongation of the alkyl chain from ethyl (**9b**) to propyl (**9g**) denoted a trend of decreased activity with longer alkyl chain. Thus, in this series a steric component can be observed going from

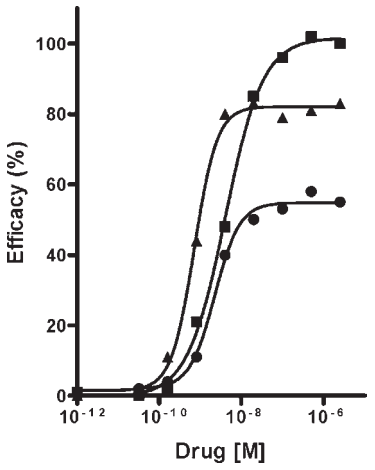


Figure 1. Receptor activity for DHT and the partial agonists **1** and **9e**. Each compound was tested in concentration−response experiments in R-SAT assay: (■) DHT, (▲) **1**, and (●) **9e**.

methyl (**9a**, $pEC_{50} = 8.7$) to ethyl (**9b**, $pEC_{50} = 8.4$) to propyl (**9g**, $pEC_{50} = 7.8$). The vinyl analogue **9c** showed potency comparable with the methyl analogue **9a** and somewhat higher than the ethyl derivative **9b**. The introduction of a cyclopropyl group (**9e**) led to a more active compound than **9f** bearing an isopropyl group. The acetylene analogue **9d** on the other hand showed no AR agonistic activity; instead **9d** displayed antagonistic activity. The reversal of activity for ethyne **9d**, going from agonistic to antagonistic activity, could be due the rigidity of the ethyne part. What might occur is that the ethyne part interacts unfavorably, for agonistic activity, with T877 in the AR. With the exception of compound **9a** and the antagonist **9d**, all 3-alkyl substituted compounds prepared in this series showed partial agonist activity in the cell-proliferation assay R-SAT.

Next, we focused on the aromatic moiety, with the purpose of replacing the naphthalene scaffold with a substituted phenyl.[11] A number of substituted phenyl derivatives were synthesized, and a representative set of analogues (**12**−**14**, **1**) is outlined in Scheme 2. 2,3-Dimethyl substituted nitrobenzene **12** was prepared as the first representative of the phenyl series and showed potent AR agonistic activity, which indicated that the established SAR in the naphthalene series may be applicable to the phenyl series as well. Indeed, exchanging the nitro group in **12** with cyano functionality and the 2-methyl with chlorine gave compound **14**, which displayed an in vitro activity ($pEC_{50} = 8.7$, 81% eff) comparable to **9a** and significantly higher than the activity observed for **12** or the corresponding naphthalene analogue **2**. Furthermore, introduction of the 3-*exo*-methyl group on the tropanol (**1**) led to a highly potent and metabolically stable compound (Figure 1). Interestingly, the 2-chlorobenzonitrile **13**, not having a substituent in the 3-position of the phenyl, was a potent antagonist and did not display any agonistic activity. This may be explained by the absence of a steric interaction between a substituent at the neighboring position with the tropane ring, leading to small conformation changes necessary for agonist activity. This result also confirms that small modifications of the compound, in particular introduction of more polar groups on the tropane moiety, switch the intrinsic receptor activity from full agonist via partial agonism to antagonist activity.

The antiandrogens **9d**, **10**, **11**, and **13** found in this SAR study were further examined for their activities at the AR mutant T877A. Antiandrogens are used clinically for the treatment of cancer, e.g., flutamide (Euxlin). However, these compounds often give rise to mutations in the AR, resulting in drug resistance.[12] The AR T877A mutation has been found in cases of advanced prostate cancer and provide a selective growth and survival advantage in a cell-based model.[13] The T877A mutant, resulting from replacement of threonine 877 with alanine, possesses a larger LBD that compensates for a bulkier antagonist compared to an agonist compound. Thus, the antagonist allows the adoption of an AR-LBD agonist conformation in the T877A mutant. Hydroxyflutamide (HF) is an antagonist at the wild type AR and an agonist at the T877A AR mutant. In line with this, ethyne **9d**, speculated to be an antagonist due to steric reasons, was the most potent agonist at the AR T877A mutant with a pEC_{50} of 8.1 ± 0.2, whereas the benzonitrile **13** retained its antagonist activity at the mutant. The result for **13** may be expected, as we hypothesized that its antagonist activity does not result from bulkiness but rather from a slight conformation change. Both **10** and **11** showed partial agonist activity at the T877A mutant. These results could provide an insight in designing antiandrogens based on agonists that retain antagonist activity at the AR T877A mutant.

AR agonists **1** and **2** together with testosterone were also tested in an AR transcriptional activity luciferase reporter gene assay (for testosterone, $pEC_{50} = 8.5 \pm 0.6$, efficacy $104 \pm 24\%$; for **2**, $pEC_{50} = 8.8 \pm 0.1$, efficacy $72 \pm 9\%$; for **1**, $pEC_{50} = 9.6 \pm 0.1$, efficacy $86 \pm 11\%$), and the results obtained corroborated those seen using R-SAT.

As part of establishing a structure−liability relationship (SLR) investigating off-target activities, **1** was further evaluated in a number of in vitro receptor assays and no agonism activity at the other 47 nuclear receptors and no significant binding affinity for 31 selected G-protein-coupled receptors were observed.

In addition to the metabolic clearance determined in liver microsomes, the half-lives of **9a** and **1** in human hepatocytes were measured and found to be 8.4 and 5.0 h, respectively. Pharmacokinetic studies of both compounds were performed showing high oral bioavailability in both rats and dogs ($F_{oral,rat}$ = 41% and 38% in rats and $F_{oral,dog}$ = 52% and 56% in dogs, **9a** and **1**, respectively). Compound **1** was further assessed for efficacy and selectivity in the stimulation of muscle vs prostate tissue growth in castrated male rats. This pharmacological model has been widely used for the assessment of anabolic and androgenic activities. **1** was delivered via subcutaneous osmotic pumps for 14 days at doses of 0.1−3 (mg/kg)/day to ORX rats. Testosterone propionate was administered at a dose of 0.75 (mg/kg)/day. After 2 weeks of dosing, levator ani muscle and ventral prostate tissues were weighed and compared to those of a sham-operated vehicle-treated control group. The principal finding from this study was that **1** produced a robust anabolic effect on the levator ani muscle (67% reversal of ORX-induced atrophy at 1 (mg/kg)/day) while having lesser androgenic effects on prostate (21% reversal; T, 48%).[14] Furthermore, to test if **1** was a partial AR agonist in vivo, the ability of **1** to reverse the androgenic actions of testosterone was evaluated. ORX rats were dosed daily with either testosterone propionate, 1 mg/kg sc, alone or together with **1**, 10 mg/kg po, for 14 days. Twenty-four hours after the last dosing, animals were sacrificed and the weights of their prostate measured. Testosterone propionate produced androgenic effects in the prostate that were attenuated by **1** (Figure 2).

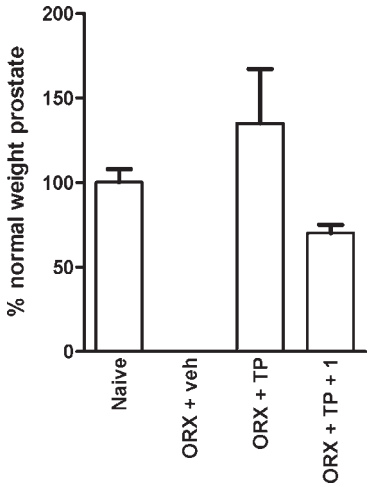


Figure 2. Compound **1** attenuated the androgenic effects of testosterone propionate (TP) in an animal model of orchidectomy (ORX).

Conclusion

In conclusion, we have presented herein the discovery of a new class of highly potent, nonsteroidal SARMs. In particular compound **1** showed promising overall pharmacological, pharmacokinetic, and in vivo properties, making it suitable for further clinical development.

Experimental Section

All procedures were carried out under a nitrogen atmosphere unless otherwise indicated using anhydrous solvents purchased from commercial sources without further purification. The microwave-assisted reactions were carried out using a SmithCreator or Initiator 60EXP single mode cavity, producing continuous irradiation at 2450 MHz. Reaction temperatures and pressures were determined using the built-in, online IR and pressure sensors. Thin layer chromatography (TLC) was performed on precoated Merck silica gel 60 F_{254}, which was visualized by UV light or by staining with a solution of $KMnO_4$ (1%) and Na_2CO_3 (5%). Flash chromatography was performed using SiO_2 60 (0.040−0.063 mm). All ^1H and ^{13}C NMR spectra were recorded using a Varian XL 400 MHz spectrometer. NMR spectra were recorded in CD_3OD, $CDCl_3$, or DMSO-d_6; chemical shifts are given in ppm relative to CH_3OH (^1H, 3.31 ppm; ^{13}C, 49.00 ± 0.01 ppm), $CHCl_3$ (^1H, 7.26 ppm; ^{13}C, 77.16 ± 0.06 ppm), or DMSO (^1H, 2.50 ppm; ^{13}C, 39.52 ± 0.06 ppm), respectively. Liquid chromatography/mass spectrometry was performed on a Waters/Micromass ZQ2000 LC/MS instrument consisting of a ZQ single quadropole mass spectrometer equipped with an electrospray ionization interface, and a Waters Alliance HT with a 2795 separation module and 996 photodiode array detector (PDA). HPLC method and parameters were as follows. Mobile phase: (A) 10 mM NH_4OAc H_2O; (B) 10 mM NH_4OAc, CH_3CN-H_2O (95:5). Column: Waters Xterra MS C_{18} 3.5 μm, 30 mm × 4.6 mm i.d. with a guard column cartridge system. Program: 5 min gradient starting at 30% B (initial hold for 0.5 min), to 100% B, hold for 1.5 min, over 0.5 min to 30% B, hold for 2.5 min. The flow rate was 1 mL/min. PDA range: 190−450 nm. HRMS analyses were recorded in FAB(+) mode using direct inlet, at the University of Lund, Sweden. Elemental analysis was determined on a "2400 CHN elemental analyzer" by Perkin-Elmer in the microanalytical laboratory of the Fakultät für Chemie, Universität Wien, Austria. The purity of compounds **1**−**14** are >98% based on HPLC analysis and elemental analysis.

2-Chloro-4-(3-*endo*-hydroxy-3-*exo*-methyl-8-azabicyclo[3.2.1]-oct-8-yl)-3-methylbenzonitrile Hydrochloride (1). 2-Chloro-4-fluoro-3-methylbenzonitrile (2.48 g, 14.6 mmol), *endo*-3-*exo*-methyl-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (**15**) (3.37 g, 19.0 mmol), and K_2CO_3 (6.67 g, 48.2 mmol) were dissolved in dimethyl sulfoxide (40 mL), and the mixture was stirred under argon at 80 °C for 18 h. The reaction mixture was poured into water (200 mL) and stirred for 30 min. The off-white solid was filtered off and recrystallized twice from toluene, giving a white powder (1.53 g). The mother liquor was evaporated and the residue recrystallized to yield a second batch of compound (210 mg), giving an overall yield of 40%. The hydrochloride salt was prepared by dissolving the product in diethyl ether and adding HCl (1 equiv, 4 M solution in 1,4-dioxane). The mixture was allowed to stir for 15 min and the precipitated salt was filtered off, washed with diethyl ether, and dried. The title compound was obtained as a colorless solid. Mp = 160 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 8.6 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 3.82 (m, 2H), 2.36 (s, 3H), 2.32−2.22 (m, 2H), 2.17−1.98 (m, 2H), 1.92−1.77 (m, 4H), 1.26 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.8, 138.4, 132.0, 129.7, 117.9, 115.5, 105.1, 69.6, 59.3, 45.9, 34.7, 27.4, 17.9. LCMS m/z 291 $[M+H]^+$. Anal. ($C_{16}H_{19}ClN_2O$) C, H, N.

General Procedure (GP) for Compounds 9a−g. In a flame-dried Schlenk flask under argon atmosphere was placed a $CeCl_3 \cdot 2LiCl$ solution in anhydrous THF (~0.6 M, 1.0 mL, 0.6 mmol). Ketone **5** (0.50 mmol) was added neat, and the resulting mixture was stirred for 1 h at rt. The reaction mixture was cooled to 0 °C, Grignard reagent (0.6 mmol) was added dropwise, and the reaction mixture was allowed to stir at the same temperature. Upon full conversion of starting material (checked by TLC and/or analytical HPLC/MS), saturated ammonium chloride (1.0 mL) and ethyl acetate (2.0 mL) were added. The aqueous layer was extracted with more ethyl acetate (2 × 10 mL), and the combined extracts were dried over sodium sulfate, filtered, and concentrated to dryness. The residues were purified by column chromatography on silica gel to give pure products.

4-(3-*endo*-Hydroxy-3-*exo*-methyl-8-azabicyclo[3.2.1]oct-8-yl)-naphthalene-1-carbonitrile (9a). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (**5**) (138 mg, 0.50 mmol) and methylmagnesium bromide (3.0 M in diethyl ether, 0.2 mL, 0.6 mmol). The crude product was purified by preparative TLC (DCM/EtOAc, 3:1, two runs) to yield the title compound (42 mg, 29%) as a colorless solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.16 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.1 Hz, 1H), 7.66−7.59 (m, 1H), 7.56−7.49 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 4.17−4.08 (m, 2H), 2.35−2.23 (m, 4H), 2.02−1.88 (m, 4H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 134.6, 133.8, 128.5, 128.0, 126.2, 126.1, 125.6, 119.3, 111.2, 102.2, 69.9, 60.6, 46.2, 34.7, 26.9. LCMS m/z 293 $[M+H]^+$. Anal. ($C_{19}H_{20}N_2O$) C, H, N.

4-(3-*endo*-Hydroxy-3-*exo*-cyclopropyl-8-azabicyclo[3.2.1]oct-8-yl)naphthalene-1-carbonitrile (9e). The title compound was prepared according to GP from 4-(3-oxo-8-azabicyclo[3.2.1]-oct-8-yl)naphthalene-1-carbonitrile (**5**) (138 mg, 0.50 mmol) and cyclopropylmagnesium bromide (0.5 M in THF, 1.2 mL, 0.60 mmol). Purification by reverse phase preparative HPLC yielded the title compound (39 mg, 25%) as a pale-yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19−8.14 (m, 2H), 7.73 (d, J = 8.1 Hz, 1H), 7.63 (ddd, J = 1.2, 6.9, 8.4 Hz, 1H), 7.57−7.50 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 4.17−4.12 (m, 2H), 2.31−2.22 (m, 4H), 1.98−1.91 (m, 2H), 1.80 (dd, J = 1.8, 15.7, 2H), 1.02−0.95 (m, 2H), 0.46−0.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 134.4, 133.6, 128.3, 127.7, 125.9, 125.8, 125.4, 119.1, 110.8, 101.8, 70.0, 60.1, 44.1, 26.9, 24.7, 0.15. LCMS m/z 319 $[M+H]^+$. Anal. ($C_{21}H_{22}N_2O$) C, H, N.

R-SAT Assays. Receptor selection and amplification technology (R-SAT) is a functional cell-based assay that allows one to monitor receptor-dependent proliferative responses of various receptor classes including nuclear receptors. This process is achieved by partial cellular transformation via loss of contact inhibition and growth factor dependency. Monitoring is achieved by transfecting the cells with a β-galactosidase reporter

gene vector whose expression is under a constitutively active promoter. Briefly, mouse NIH-3T3 fibroblasts were plated overnight in 96-well plates in DMEM 10% calf serum (Hyclone) and grown to 60−70% confluency prior to transfection. Transient transfections were performed using Polyfect (Qiagen) according to the manufacturer's instructions. Typically, a transfection mix would consist of expression vectors encoding the androgen receptor (200 ng), β-galactosidase (500 ng), and the coactivators SRC1, DRIP205, and GRIP1 (10 ng each). Such a transfection mix would be sufficient to transfect 30 96-wells. Sixteen hours after transfection, cells were incubated with different doses of ligand in DMEM containing 30% ultraculture (Hyclone) and 0.4% calf serum (Hyclone) to generate a dose−response curve. After 5 days, plates were developed by adding onto the washed cells a solution containing the β-galactosidase substrate *o*-nitrophenyl β-galactose (ONPG) (in phosphate-buffered saline with 5% Nonidet P-40 detergent). Plates were read using a microplate reader at 420 nm. Data from R-SAT assays were fit to the equation $r = A + B(x/(x + c))$, where A = minimum response, B = maximum response minus minimum response, c = EC50, r = response, and x = concentration of ligand. Curves were generated using the curve fitting softwares Excel Fit and GraphPad Prism (San Diego, CA).

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Supporting Information Available: Synthetic procedures for all compounds and biological methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Full data of this study will be presented elsewhere.