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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 4487–4490

Synthesis and SAR of tetrahydropyrrolo[1,2-*b*][1,2,5]thiadiazol-2(3*H*)-one 1,1-dioxide analogues as highly potent selective androgen receptor modulators

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Received 7 May 2007; revised 31 May 2007; accepted 1 June 2007
Available online 6 June 2007

Abstract—Replacement of the 3-oxo group of 2-chloro-4-[(7*R*,7a*S*)-7-hydroxy-1,3-dioxotetrahydro-1*H*-pyrrolo[1,2*c*]imidazol-2(3*H*)-yl]-3-methylbenzonitrile resulted in a sulfamide series of selective androgen receptor modulator (SARM) agonists.

Sarcopenia is the slow, progressive loss of muscle mass which occurs with advancing age as a result of a decrease in circulating levels of the androgens testosterone (T) and dihydrotestosterone (DHT), as well as growth hormone.[1] Associated with this decline in muscular mass and strength is an increase in the risk of injury and the reliance of the frail elderly on assistance with daily tasks. Since sarcopenia is not considered a disease per se, very few drugs have been developed specifically for this condition. Many recent therapies for sarcopenia are based on the hypothesis that increasing the circulating levels of T and/or DHT will have a beneficial effect on muscle function.[2–5] However, studies have shown that these anabolic hormones may increase the risk of prostate cancer and cardiovascular disease[6] as well as cause additional side effects.[7,8] Therefore, therapeutic agents are being sought which might maintain muscle size and strength, thereby improving quality of life in this segment of the population.

Androgens regulate many physiological processes through androgen receptor (AR)-mediated signaling. The AR is a member of the nuclear receptor superfamily of ligand dependent transcription factors.[9] Selective androgen receptor modulators (SARMs) have been the subject of preclinical investigation for almost a decade, and some of the first of these agents have recently entered human clinical trials for the treatment and prevention of sarcopenia.[10] These and other SARMs are expected to deliver muscle and bone enhancing effects while minimizing the risks of those side effects associated with T therapy.[11]

Our previous efforts directed toward the discovery of novel SARMs led to the identification of the potent and muscle selective *N*-aryl bicyclic hydantoins **1** and **2** (Fig. 1).[12,13] These compounds have potency in vitro and in vivo comparable to or greater than that of the native hormones, and exhibit a wide separation between anabolic and androgenic effects in classic rodent models. Subsequent reports from these laboratories have detailed the SAR surrounding the aryl fragment of this chemotype.[4] Herein, we report the effects of replacing

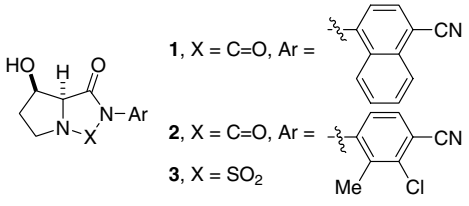

Figure 1. BMS SARM scaffolds incorporating 4-cyanoanilines.

Keywords: Selective androgen receptor modulator; Thiadiazol; Sarcopenia.
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doi:10.1016/j.bmcl.2007.06.007

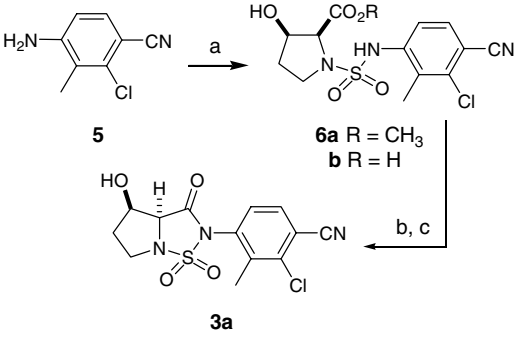
the 3-oxo group of **2** with a sulfonyl group (e.g., **3**) as a means of reducing the potential for aniline release in vivo. This is based in part on the fact that a sulfamide N–S bond is expected to be significantly more resistant to hydrolysis than the corresponding acyl urea N–C bond.

Synthesis of acyl sulfamide SARM agonists **3a–d** was achieved by condensation of aniline **5**[12] with the appropriate proline and pyrrolidine precursors (Scheme 1). This involved generation of the corresponding sulfamyl chloride of aniline **5** by treatment with $ClSO_3H$ and PCl_5 in refluxing CH_2Cl_2,[14] followed immediately by treatment with hydroxyproline ester **8a** in the presence of DIEA to give sulfamide ester **6a**. Ester hydrolysis, and finally, DCC/*p*-nitrophenol-mediated cyclization of the resulting acid gave prototype acyl sulfamide SARM compound **3a**.[15] Compounds **3b–d** were synthesized in a similar fashion from the appropriate precursors.

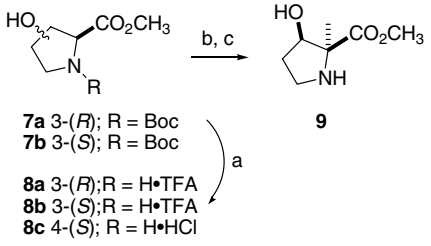
The prerequisite hydroxyprolines **8a**, **8b** and **9** were obtained from the Boc-protected precursors **7a**, **7b** (Scheme 2).[12] Boc deprotection of prolines **7a** and **7b** afforded **8a** and **8b**. Proline **8c**, used in the preparation of **3d**, was commercially available. Alkylation of **7a** using LDA and CH_3I according to the procedure of Williams,[16] followed by deprotection, provided the TFA salt of 2-methyl proline **9**.

Synthesis of the pyrrolidine precursors to compounds **4a–c** began with TBS protection of the hydroxyl group of proline **7b**, subsequent reduction of the ester with $LiHBEt_3$, followed by oxidation of the resultant alcohol with NMO and TPAP to generate aldehyde **10** (Scheme 3). Addition of MeMgBr to **10** followed by a second NMO/TPAP oxidation yielded acetyl pyrrolidine **11**. After conversion of **11** to oxime **12** using $HON{\cdot}H_2{\cdot}HCl$, subsequent Pd(C)/Raney-Ni hydrogenation at 70 psi produced aminoethyl pyrrolidine **13** in high overall yield.

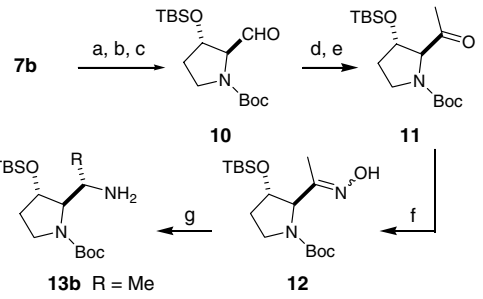
Descarbonyl analogues **4a** and **4b** were prepared from the proline derivatives **10** and **13b** (Scheme 4). Sodium triacetoxyborohydride-mediated reductive amination of aldehyde **10** with aniline **5** followed by Boc deprotection generated the pyrrolidine **14a**. Alkyl-substituted variants necessitated conversion of aniline **5** to the corresponding iodide using *t*-butyl nitrite and CuI, and the resultant aryliodide was then coupled with amine **13b** following the protocol of Buchwald to yield the methyl-substituted **14b**. Conversion of **14a** and **14b** to the sulfonic acids using $ClSO_3H$ resulted in **15a** and **15b**, which were



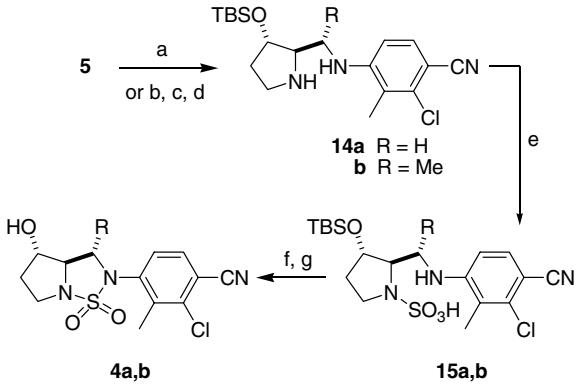
Scheme 1. Reagents and conditions: (a) (1) $ClSO_3H$ (1.1 equiv), PCl_5, CH_2Cl_2, reflux; (2) DIEA (2 equiv), **8a** (1.1 equiv), CH_2Cl_2, 0 °C; 43%; (b) 1.6 N NaOH, rt; 92%; (c) DCC, *p*-NO_2PhOH (2 equiv), CH_3CN, reflux; 78%.



Scheme 2. Reagents and conditions: (a) TFA, CH_2Cl_2, 0 °C, 100%; (b) LDA (3 equiv), CH_3I (1.5 equiv), HMPA, THF, −50 °C, 62%; (c) TFA, CH_2Cl_2, 0 °C, 100%.



Scheme 3. Reagents and conditions: (a) Imidazole (2.5 equiv), TBSCl (1.3 equiv), DMF, rt; 95%; (b) $LiBHEt_3$ (5 equiv), THF, −78 °C to rt; 83%; (c) NMO (2.5 equiv), TPAP (8.5 mol %), CH_3CN, CH_2Cl_2, rt; 89%; (d) MeMgBr (3 equiv), THF, −78 °C to rt; (e) NMO (2 equiv), TPAP (5 mol %), CH_3CN, CH_2Cl_2, rt; (f) $NH_2OH{\cdot}HCl$ (3.8 equiv), CH_3OH, H_2O, pyridine, rt; 72%; (g) 10% Pd(C), Raney-Ni, H_2, NH_3, CH_3OH, H_2O, 70 psi, rt, 64%.

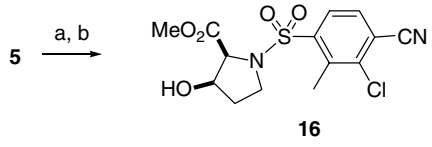


Scheme 4. Reagents and conditions: (a) (1) $NaBH(OAc)_3$ (1.6 equiv), **10** (0.9 equiv), CH_2Cl_2, DMF, rt; (2) TFA, CH_2Cl_2, rt, 24%; (b) CuI (1.1 equiv), *t*-BuONO (1.3 equiv), CH_3CN, 65 °C, 43%; (c) Cs_2CO_3 (2 equiv), **13b**, $Pd_2(dba)_3$, (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine, DMSO, toluene, 110 °C (sealed tube), 99%; (d) TFA, CH_2Cl_2, rt, 44%; (e) $ClSO_3H$ (1.4 equiv), DIEA, CH_2Cl_2, rt, 83%; (f) $POCl_3$ (2.3 equiv), pyridine, CH_2Cl_2, rt–50 °C, 4–40%; (g) TBAF, THF, rt, 38–100%.

isolated as their respective DIEA salts. The corresponding sulfonyl chlorides, generated by $POCl_3$ treatment, cyclized in situ to generate, after deprotection of the silyl protecting group using TBAF, sulfamides **4a** and **4b**. Compound **4c**, a diastereomer of **4a**, was synthesized in the same manner.

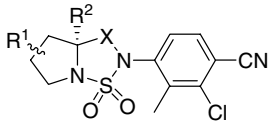
Synthesis of abbreviated compound **16** involved reaction of the aryl sulfonic acid derived from aniline **5** with thionyl chloride and subsequent coupling of the resulting sulfonyl chloride with proline **8a** to afford the sulfonamide (Scheme 5).

Binding affinities for the SARM analogues were determined using a whole cell binding assay in the human breast carcinoma cell line MDA-453 as previously reported.[12] Functional agonist activity was determined using AR transactivation assays in the mouse myoblast C2C12 cell line (Table 1). The most potent compound in this series, **3a**, exhibits sub-nanomolar binding affinity, although functional activity (EC_{50} = 12 nM) was at least 20-fold weaker than the parent **2**. Its diastereomer, **3b**, loses over 60-fold potency in the binding assay and almost 250-fold activity in the functional assay. Methylation at the ring juncture as in **3c** causes a greater than 15- and 100-fold decrease in binding affinity and functional activity, respectively. Activity in both assays is decreased >100-fold for compound **3d**, a regioisomer of **3b** in which the hydroxyl group has been shifted by one position. Reduction of the carbonyl group to a methylene (**4a**) resulted in a 400-fold loss in activity relative to that of **3a**. This impact was attenuated 10-fold for the *R*-diastereomer **4c**. Methylation at the C-3 position of the bicyclic ring system to generate **4b** also regained 10-fold binding affinity when compared to **4a**. For this set of analogues, the *R*-configured hydroxyl group confers substantially increased activity relative to compounds with hydroxyl groups bearing the *S*-configuration. Additionally, the importance of the bicyclic motif for activity of **3a** is readily apparent upon comparison to the acyclic ester **6a** or acid **6b**, where the thiadiazolidine 1,1-dioxide ring is replaced with an open chain version, reducing functional activity by >250-fold. Furthermore, replacement of the sulfamide moiety of **6a** with a sulfonamide group as in **16** fails to restore agonist activity.



Scheme 5. Reagents and conditions: (a) (1) $NaNO_2$ (1.04 equiv), 6 N HCl, rt, (2) SO_2, $CuCl_2{\cdot}2\ H_2O$ (1.2 equiv), AcOH, rt; 44%; (b) (1) $SOCl_2$, DMF (cat), rt; (2) **8a** (2 equiv), pyridine, rt, 62%.

Table 1. Androgen receptor binding and transactivation assay data for SARM compounds and testosterone control



Compound	R^1	R^2	X	K_i[a] (nM)	EC_{50}[b] (nM)
T	—	—	—	0.25	2.8
1	—	—	—	3.2	2.3
2	—	—	—	2.11	0.44
3a	4-(*R*)-OH	H	C=O	0.45	11.9
3b	4-(*S*)-OH	H	C=O	29	2959[c]
3c	4-(*R*)-OH	CH_3	C=O	8.2	1251[c]
3d	5-(*S*)-OH	H	C=O	44	3517[c]
4a	4-(*S*)-OH	H	CH_2	189	ND
4b	4-(*S*)-OH	H	$CHCH_3$	20	8962[c]
4c	4-(*R*)-OH	H	CH_2	14	7729[c]
6a	—	—	—	ND	7459
6b	—	—	—	ND	>3000
16	—	—	—	36	>3000[d]

ND, no data.

[a] Binding determined through direct displacement of [^{3}H]-DHT in the MDA-453 cell line.

[b] Functional agonist activity determined in stably transfected mouse myoblast C2C12 cells using a luciferase reporter.

[c] Partial agonist (I.A. ⩽50%).

[d] Antagonist IC_{50} = 278 nM.

Compound **3a** exhibited acceptable pharmacokinetic properties,[17] and was evaluated in a standard in vivo model measuring prostate and levator ani muscle growth in mature castrated male rats after two weeks of once daily oral treatment compared with testosterone propionate (TP) given subcutaneously (Fig. 2). In this study, where dosing began 14 days after castration, the

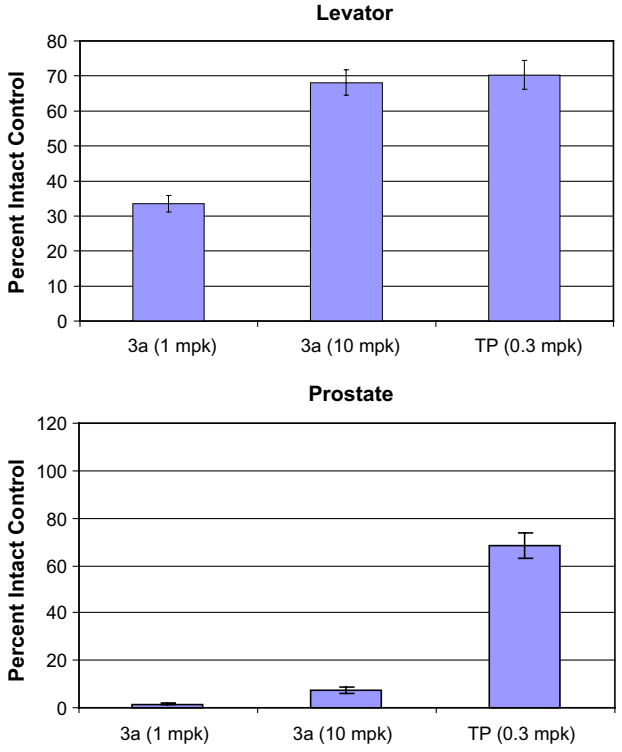


Figure 2. Levator ani and prostate growth response in mature castrated male rats given once daily doses of **3a** (1 or 10 mg/kg, po) or testosterone propionate (TP, 0.3 mg/kg sc) for 14 days.

10 mg/kg dose of **3a** restored levator ani weights to those of TP treated animals, both groups achieving approximately 70% that of intact, vehicle-treated, sham-operated controls. However, the effect on prostate at this dose was substantially weaker than that for TP, giving only a 10% response relative to intact controls compared with 70% induced by TP. This observed muscle selectivity for **3a** is consistent with the desired pharmacological profile of a SARM which might be suitable for treatment of sarcopenia.

High affinity androgen agonists were obtained upon substitution of the bicyclic imide moiety of **2** with a sulfamide group, exemplified by compound **3a**. Further modification of **3a** to invert the hydroxyl group stereochemistry, reduce the bridging carbonyl or hydrolyze the ring resulted in dramatic loss of biological activity. In this system, hydroxyl substitution at C4 is preferred over C5, and the 4-(*R*) diastereomers are more active than the corresponding 4-(*S*)-isomers. Structural changes to **3a** caused substantial decreases in functional activity in cell-based assays while in many cases retaining comparable to moderately reduced binding affinity. In most cases, switching from a carbonyl to an isosteric sulfonyl moiety resulted in compounds with weak partial agonist profiles. In general, the acyl sulfamide core appeared less tolerant of significant structural modifications than the corresponding hydantoin compounds.[4,18] Nonetheless, investigation of the acyl sulfamide scaffold yielded in vivo active, muscle-selective AR agonists, and this template provides a potential alternative to the hydantoin SARMs previously reported.

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15. A typical procedure for preparation of SARM **3a** follows: to a solution of **5** (100 mg, 0.60 mmol) in 3 mL of CH_2Cl_2 at rt was added chlorosulfonic acid (44 μL, 0.66 mmol) followed by PCl_5 (125 mg, 0.60 mmol) and the suspension refluxed for 30 min. The suspension was cooled to rt and added dropwise to a solution of 0.25 mL of NEt_3 in 1 mL of CH_2Cl_2 cooled to 0 °C. Diisopropylethylamine (0.21 mL, 1.20 mmol) was added followed by **8a** (120 mg, 0.660 mmol) and the solution stirred at 0 °C for 30 min. The reaction mixture was washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/CH_3OH, 98:2, 95:5, and 90:10) to afford **6a**. A solution of **6a** (109 mg, 0.29 mmol) in 15 mL of 1.6 N NaOH was stirred at rt for 1 h. The reaction mixture was acidified to pH 2 with 10% HCl and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford **6b**. To a suspension of **6b** (82 mg, 0.23 mmol) in 5 mL of CH_3CN at rt was added DCC (47 mg, 0.23 mmol) followed by *p*-nitrophenol (63 mg, 0.46 mmol). The suspension was refluxed for 1 h, cooled to rt, and filtered. The filtrate was concentrated and the residue dissolved in EtOAc, washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc/hexanes, 50:50 and 75:25) to afford **3a** (61 mg). ^1H NMR (400 MHz, CD_3OD) δ 2.21–2.23 (m, 2H), 2.37, 2.39 (s, 3H), 3.61–3.64 (m, 1H), 3.97–4.04 (m, 1H), 4.66, 4.68 (s, 1H), 4.79 (d, J = 3.85 Hz, 1H), 7.45, 7.55 (d, J = 8.25 Hz, 1H), 7.83 (d, J = 8.25 Hz, 1H); HPLC:Phenomenex C18 4.6 × 50 mm, 4 min gradient, 10% MeOH/90% H_2O/0.1% TFA to 90% MeOH/10% H_2O/0.1% TFA; 1 min hold, 4 mL/min UV detection at 220 nm, 2.65 min retention time; MS (ES): *m*/*z* 340 $[M-H]^-$.
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