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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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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

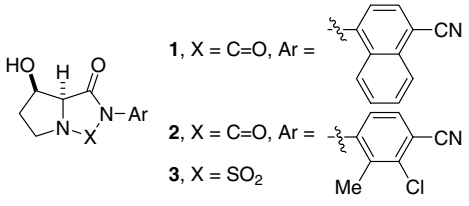

Figure 1. BMS SARM scaffolds incorporating 4-cyanoanilines.

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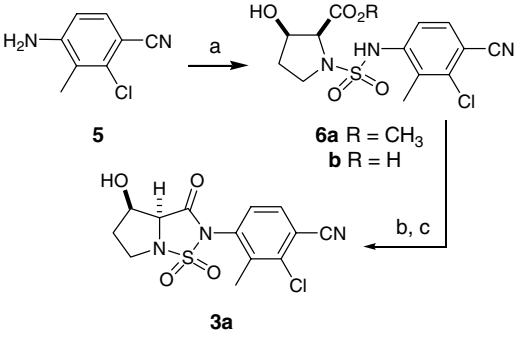
the 3-oxo group of **2** with a sulfonyl group (e.g., **3**) as a means of reducing the potential for aniline release in vivo. This is based in part on the fact that a sulfamide N–S bond is expected to be significantly more resistant to hydrolysis than the corresponding acyl urea N–C bond.

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.

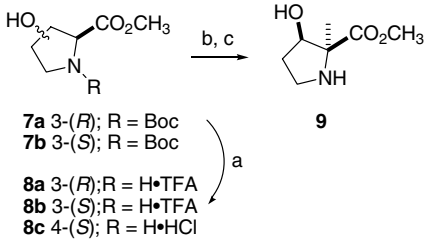
The prerequisite hydroxyprolines **8a**, **8b** and **9** were obtained from the Boc-protected precursors **7a**, **7b** (Scheme 2).[12] Boc deprotection of prolines **7a** and **7b** afforded **8a** and **8b**. Proline **8c**, used in the preparation of **3d**, was commercially available. Alkylation 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.

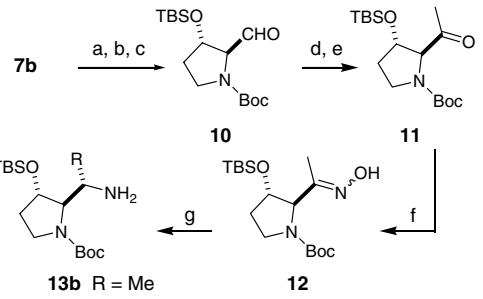
Descarbonyl analogues **4a** and **4b** were prepared from the proline derivatives **10** and **13b** (Scheme 4). Sodium triacetoxyborohydride-mediated reductive amination of aldehyde **10** with aniline **5** followed by Boc deprotection generated the pyrrolidine **14a**. Alkyl-substituted variants 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



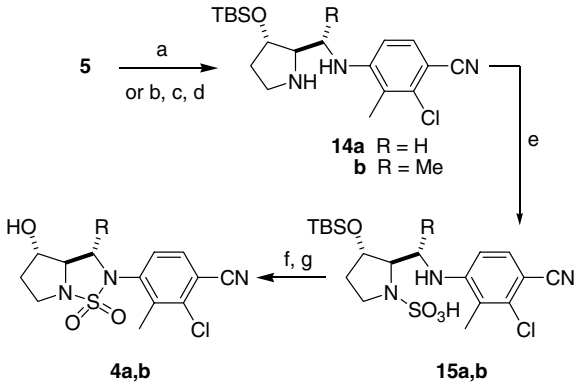
Scheme 1. Reagents and conditions: (a) (1) $ClSO_3H$ (1.1 equiv), PCl_5, CH_2Cl_2, reflux; (2) DIEA (2 equiv), **8a** (1.1 equiv), CH_2Cl_2, 0 °C; 43%; (b) 1.6 N NaOH, rt; 92%; (c) DCC, *p*-NO_2PhOH (2 equiv), CH_3CN, reflux; 78%.



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%.