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Synthesis of potent and tissue-selective androgen receptor modulators (SARMs): 2-(2,2,2)-Trifluoroethyl-benzimidazole scaffold

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Abstract—The synthesis and in vivo SAR of 2-(2,2,2)-trifluoroethyl-benzimidazoles are described. Prostate antagonism and/or *levator ani* agonism can be modulated by varying the substitution at the 2-position of 5,6-dichloro-benzimidazoles. Potent androgen agonists on the muscle were discovered that strongly bind to the androgen receptor (2–17 nM) and show potent in vivo efficacy (0.03–0.11 mg/day). True SARMs showing both prostate antagonism and *levator ani* agonism were revealed.

The two major endogenous androgens, testosterone and dihydrotestosterone, mediate protein anabolism and affect basal metabolism through the activation of the androgen receptor (AR).[1] Serum androgen levels in the male start rising exponentially at the advent of puberty. The increase in androgen production is important for the development of male sexual and physiological characteristics.[2] As men age, serum androgen levels decrease from 600–700 ng/dL (18–40 years old) to 450–500 ng/dL (70–80 years old).[3]

Although androgens have many beneficial effects on muscle development, steroidal androgens such as testosterone show agonism on the prostate and exacerbate androgen-dependent prostate cancer.[4] Tissue-selective androgen receptor modulators (SARMs) that are agonists in muscle and antagonists in the prostate could be used to treat hypogonadism, cachexia, and aid in burn recovery without increasing the risk of prostate hyperplasia. Largely due to success in SERMs, the interest in finding selective androgen receptor modulators has significantly increased in the recent years.[5] In comparison to SERMs, SARMs have less defined pharmacophores. In estrogen receptor ligands, introducing an aromatic side chain that bears a basic functional group, such as 4-diethylaminoethoxyphenyl, at the position corresponding to 11-position of estradiol usually converts an agonist to an antagonist in some tissues. Such an antagonist often exhibits certain level of tissue selectivity by maintaining agonistic activity in certain tissues. In contrast, recent reported androgen receptor ligands that may display tissue selectivity represent a wide variety of structural classes without well-defined structural moiety that might interact with helix 12 of the receptor.[5a] We have been interested in identifying androgen receptor ligands for some time and have generated a library of compounds in this area.[6] In order to identify a tissue-selective androgen receptor modulator, we decided to modify the structures of the potent benzimidazole androgen receptor antagonists we reported recently.[6f,g] In this paper, we describe the findings of this effort. Chart 1 summarizes the target compounds and Schemes 1–3 outline the synthesis.

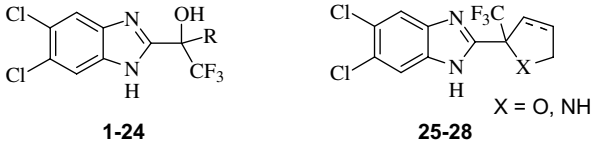

Chart 1.

Keywords: SARM; Benzimidazoles; In vivo screening.
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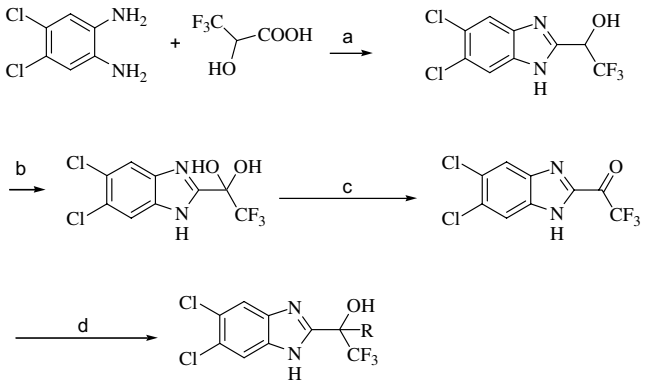
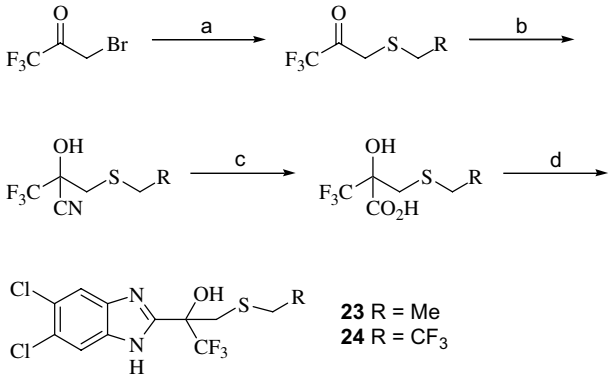
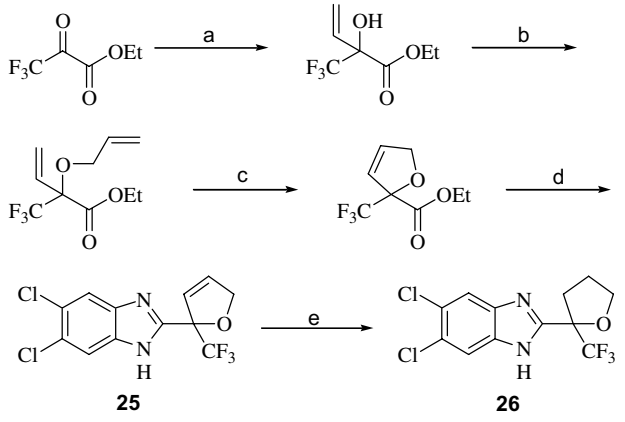


Scheme 1. Synthesis of **1**–**22**. Reagents and conditions: (a) 6 N HCl, reflux, 18 h; (b) 4-methoxy-TEMPO (cat.), NaBr (cat.), and 10–13% NaOCl (4 equiv) in THF, −10 °C to rt; (c) drying in vacuum oven, 80 °C, 4 days; and (d) R-MgBr or R-Li, THF or in dust, R-Br, NH_4Cl (aq).



Scheme 2. Synthesis of **23** and **24**. Reagents: (a) EtSH or CF_3CH_2SH, K_2CO_3; (b) HCl, NaCN, H_2O, THF; (c) H_2SO_4, HCl; and (d) 5,6-dichloro-1,2-phenylenediamine, 6 N HCl.



Scheme 3. Synthesis of **25** and **26**. Reagents: (a) vinyl-MgBr, THF; (b) allyl bromide, NaH, THF; (c) Grubbs' catalyst II, CH_2Cl_2; (d) 5,6-dichloro-1,2-phenylenediamine, Et_2AlCl, PhMe; and (e) H_2 (g), 5% Rh on alumina, MeOH.

Benzimidazoles **1**–**4**, **6**–**14**, and **17**–**22** were prepared by addition of excess (2.5–3.0 equivalents) Grignard or lithium reagent to trifluoromethylketone (Scheme 1). The ketone favors the hydrate form in the presence of water. In order to carry out the subsequent organometallic addition, pre-drying in a heated oven under vacuum for 3–4 days was necessary. Compounds **5**, **15**, and **16** were prepared via indium-mediated Barbier reaction in aqueous conditions (1).[7]

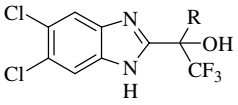
Compounds **23** and **24** were synthesized by displacement of 3-bromo-1,1,1-trifluoroacetone with ethane- or trifluoroethanethiol, followed by cyanohydrin formation and hydrolysis to afford the acid (Scheme 2). Condensation of the acid with 5,6-dichloro-1,2-phenylendiamine under Phillips' conditions[8] gave benzimidazoles **23** and **24**.

Compounds **25** and **26** were prepared using a ring-closing metathesis (RCM) strategy (Scheme 3). Addition of vinyl magnesium bromide to ethyl trifluoropyruvate, followed by O-alkylation with allyl bromide, provided the RCM precursor. Treatment of the diene with 2nd generation Grubbs' catalyst afforded the dihydrofuran. Condensation of this ester with 5,6-dichloro-1,2-phenylene diamine in the presence of Et_2AlCl[9] afforded benzimidazole **25**, which was further subjected to hydrogenation with 5% Rhodium on alumina to give tetrahydrofuran **26**. The amino analogs **27** and **28** were prepared similarly from BOC-protected imine of ethyl trifluoropyruvate.[10]

Similar to our AR antagonist program, we have adopted a direct in vivo screening protocol for the AR agonist program by measuring *levator ani* weight in a 5-day once daily dosing in immature rats. To assess tissue selectivity at the screening stage, both prostate weight inhibition and *levator ani* stimulation were measured at the same dose for all target compounds in the antagonist and agonist modes, respectively. To our delight, many compounds demonstrated AR agonist activity on muscle and AR antagonism on prostate. Data for the acyclic analogs (compounds **1**–**24**) are summarizes in Table 1. Compound **1** (R = Et) showed very potent stimulatory activity on muscle, but unfortunately displayed toxicity (showing signs of lethargy) at the 3 mg/day dose. Interestingly, *n*-propyl analog, **2**, showed both modest prostate inhibition (63%) and *levator ani* stimulation (67%), a sign of a truly tissue-selective androgen receptor modulator. Branched alkyl group such as isopropyl (**3**) imparted strong muscle stimulation without any observed toxicity. Further branching such as in 1,1-dimethylpropyl analog, **4**, abolished stimulatory activity in the muscle.

It seems that small substitution is favored for AR agonist activity on muscle so we next explored small unsaturated substitution. Interestingly, simple vinyl analog, **7** was found to be a muscle agonist (82% L.A. stimulation) while the corresponding isopropenyl analog, **8** was a pure prostate antagonist (127% prostate inhibition) with no apparent anabolic activity. Compound **8** serves as an excellent lead for our AR antagonist program which will be discussed elsewhere. AR agonist **7** was found to have an ED_{50} of 0.04 mg/day (L.A.) in immature rats and later confirmed $ED_{50} < 0.3$ mg/kg (L.A.) in the mature rats. The *cis*-propenyl analog, **9**, showed combined 70% prostate inhibition with 73% L.A. stimulation. The *trans*-

Table 1. AR antagonist and agonist activities of acyclic analogs



Compound	R	P.W. Inh.[a] (%)	L.A. Stim.[b] (%)
1	Et	25	106[c]
2	*n*-Pr	63	67
3	*i*-Pr	33	87
4	1,1-Dimethylpropyl	42	11
5	Propargyl	68	71
6	CH_2CN	9	126
7	Vinyl	56	82
8	Isopropenyl	127	na
9	*cis*-Propenyl	70	73
10	*trans*-Propenyl	61	23
11	2-Methylpropen-1-yl	45	13
12	1,2-Dimethylpropen-1-yl	47	na
13	Phenyl	61	na
14	Propynyl	79	na
15	Propa-1,2-dienyl	85	99
16	1-Methyl-propa-1,2-dienyl	78	15
17	Allyl	87	34
18	2-Methy-allyl	59	17
19	Benzyl	86	na
20	4-F-benzyl	72	na
21	3-Methyl-allyl	74	10
22	3,3-Dimethylallyl	71	na
23	CH_2SEt	31	96
24	$CH_2SCH_2CF_3$	na	26
bicalutamide		70	na

[a] Prostate Weight Inhibition % in testosterone treated castrated immature Sprague Dawley rats. Dose = 2 mg/day including bicalutamide. The control group administered with testosterone (0.1 mg/day sc) was set to 100% (N = 3/group).

[b] *Levator ani* weight stimulation % in castrated immature Sprague Dawley rats. Dose = 2 mg/day. Testosterone treated (1 mg/day) control group is set at 100% (N = 3/group).

[c] Toxicity observed at 3 mg/day dose in a follow-up study (na, not active).

propenyl analog, **10**, showed moderate prostate inhibition (61%) and no significant muscle agonism. Additional placement of methyl substituents on the olefin such as in **11** and **12** knocked down activity in both prostate and muscle. Allenyl analog, **15**, shows promise as a true SARM with 85% prostate inhibition and 99% L.A. stimulation in the immature rats. Placement of a methyl substituent on the allene, as in **16**, abolished agonist activity on muscle but retained antagonist activity on the prostate. A similar observation was noted in vinyl analog, **7**, and isopropenyl analog, **8**. Phenyl analog, **13**, and propynyl analog, **14**, were pure antagonists with prostate inhibition of 61% and 79%, respectively.

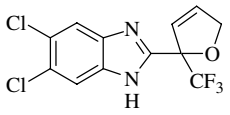
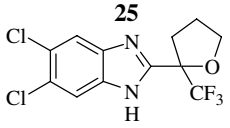
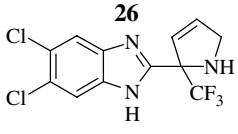
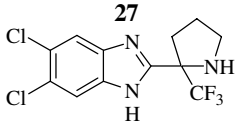
Allyl analog, **17**, showed 87% prostate inhibition and weak muscle stimulation (34%). A dose–response study confirmed the ID_{50} to be 0.67 mg/d on prostate and the ED_{50} to be 1.4 mg/d in muscle. Methallyl analog, **18**, exhibited decreased prostate inhibition (59%) and muscle stimulation (17%). Further α-branching on methallyl (**21**, **22**) raised prostate inhibition activity without effect on muscle. Benzyl (**19**) or a 4-fluoro-benzyl (**20**) substitution produced pure prostate antagonists with inhibition of 86% and 72%, respectively. Introduction of an ethylthio group (**23**) imparted very good muscle agonism while the trifluoroethyl thioether, **24**, displayed little effect on muscle or prostate.

Annulation of the alkyl or alkenyl group onto the hydroxyl group to form an ether was next explored (Table 2). Dihydrofuran **25** showed modest muscle agonism and no effect on the prostate. Saturation of the olefin produced tetrahydrofuran **26**, which showed modest activity in both muscle and prostate. Replacement of the oxygen with NH knocked down muscle agonism while preserving modest prostate inhibition.

Dose–response of the effect on muscle for selected compounds was determined in the in vivo model. Many analogs showed excellent potency in stimulating muscle growth. To verify that the activity was mediated through AR, androgen receptor binding of a few representative compounds was also determined in a cell-based binding assay. Compound **3** (R = *i*-Pr) showed 2 nM binding affinity for the androgen receptor and ED_{50} = 0.05 mg/day on *levator ani*. Moreover, compounds **6** (R = CH_2CN) and **7** (R = vinyl) showed ED_{50} of 0.03 and 0.04 mg/day, respectively (Table 3).

Compounds **7** (R = vinyl), **9** (R = *cis*-propenyl), and **15** (R = allenyl) showed prostate inhibition and *levator ani* stimulation. The dose where the compounds display AR antagonism on prostate is in the same range as their agonism on the muscle, indicating that at therapeutic doses as AR agonists, they might exhibit antagonist

Table 2. AR antagonist and agonist activities of cyclic analogs

Compound	P.W. Inh.[a] (%)	L.A. Stim.[b] (%)
 **25**	na	50
 **26**	55	64
 **27**	57	8
 **28**	35	4

[a] Prostate Weight Inhibition % in testosterone treated castrated immature Sprague Dawley rats. Dose = 2 mg/day. Normalized to control group administered with vehicle (N = 3/group).

[b] *Levator ani* weight stimulation % in castrated immature Sprague Dawley rats. Dose = 2 mg/day. Testosterone treated (1 mg/day) control group is set at 100% (N = 3/group) (na, not active).

Table 3. AR binding affinity and efficacy on muscles

Compound	IC_{50}[a] (nM)	ED_{50}[b] (mg/day)
3	2	0.05
6	nt	0.03
7	7	0.04
9	nt	0.11
15	nt	0.075
23	17	0.10

[a] In nM; COS AR whole cell binding assay.

[b] In mg/day; tested in castrated immature Sprague Dawley rats. 5-day doses = 3, 1, 0.3, 0.1, 0.03 mg/day. Normalized to 1 mg/day testosterone set to 100% (N = 3/group) (nt, not tested).

activity on prostate. For example, compound **15** had an ID_{50} of 0.80 mg/kg in prostate and ED_{50} of 0.075 mg/day (ca. 1.5 mg/kg) in *levator ani*. Ethyl thioether **23** also showed comparable in vivo efficacy (ED_{50} = 0.10 mg/day) and binding affinity (IC_{50} = 17 nM). In this series, all compounds with good in vivo efficacy were strong AR binders.

In summary, we have identified a series of novel benzimidazoles that demonstrated characteristics of true SARMs, agonism on muscle and antagonism on prostate. To our knowledge, AR agonists disclosed in the literature to date either showed weak stimulation or no effect on prostate growth. In particular, substitution with conformationally bent groups such as vinyl (**7**), CH_2CN (**6**), and allenyl (**15**) imparts strong *levator ani* stimulation. α-Branching on the vinyl or allenyl group switched muscle agonists to prostate antagonists. Some alkyl groups such as ethyl, isopropyl, and ethyl methylthioether were effective in turning on muscle agonism. Most promising compounds (**2**, **7**, **9**, and **15**) showed both good muscle agonism and good prostate inhibition. These compounds could potentially be used to treat hypogonadism and cachexia without causing androgenic complications, or to treat BPH and prostate cancer with added advantages of muscle stimulation. Since many of these diseases and conditions often co-exist in older populations, we believe our compounds possessing true SARM characteristics may offer unique opportunities for clinical development. Further pharmacology, ADME, PK, safety, and toxicology on the lead candidates will be reported in due course.

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