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Synthesis and SAR of potent and selective androgen receptor antagonists: 5,6-Dichloro-benzimidazole derivatives

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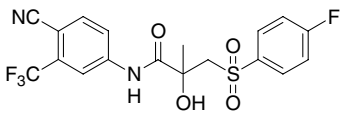
Abstract—The synthesis and in vivo SAR of 5,6-dichloro-benzimidazole derivatives as novel selective androgen receptor antagonists are described. During screening of 2-alkyl benzimidazoles, it was found that a trifluoromethyl group greatly enhances antagonist activity in the prostate. Benzimidazole **1** is a potent AR antagonist in the rat prostate (ID_{50} = 0.15 mg/day).

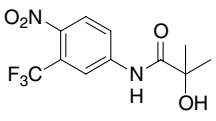
Testosterone, the predominant endogenous ligand to the androgen receptor[1] (AR), is synthesized in the testes and the adrenal cortex. In some tissues, testosterone is rapidly converted to a higher affinity ligand, dihydrotestosterone (DHT). During the early stages of prostate cancer, androgen activation of AR exacerbates the disease and stimulates hyperplasia of the prostate.[2] The American Cancer Society estimates that 232,090 men in the U.S. will be diagnosed with prostate cancer and 30,350 men will die of prostate cancer in 2005.[3] Early treatment of the disease during the hormone responsive stage with a non-steroidal androgen receptor (AR) prostate-selective antagonist benefits patients with a 99.8% 5-year survival rate.[3] Bicalutamide, a non-steroidal antiandrogen, is currently the predominant antiandrogen used for treatment of androgen-dependent prostate cancer.[4]

In conjunction with our ongoing interest in androgen receptor ligands,[5] a program was initiated to explore the use of a benzimidazole scaffold in place of the propionanilide motif found in the bicalutamide and flutamide structures. Unfortunately, as noted in the literature, in vitro AR binding does not correlate well with in vivo efficacy.[6] Therefore, compounds were screened in vivo in immature three-week-old orchidectomized male Sprague–Dawley rats. In this paper, we describe the results of our studies on the synthesis and pharmacology of 5,6-dichloro-benzimidazole derivatives.

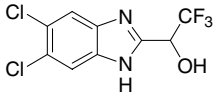
Chart 1



bicalutamide



hydroxy-flutamide



1

Initially benzimidazoles **2**–**5** were prepared by condensation of phenylene 1,2-diamines with 2-hydroxy-2-methyl-propionic acid under Phillips' conditions [4 N HCl (aq), 100 °C].[7] The 5-fluoro-6-chloro benzimidazole showed modest activity (Table 1). The 5,6-dichloro substitution (**3**) was superior to **2** and either the 5-chloro-6-trifluoromethyl (**4**) or the 5-cyano-6-trifluoromethyl (**5**) substitution, reducing prostate weight by 77% in the orchidectomized immature rat model.[8] The 5,6-dichloro substitution was chosen for further derivatization.

Since flutamide is metabolically oxidized to pharmacologically active 2-hydroxyflutamide,[9] des-hydroxy derivatives were explored. Compound **6** showed little effect on the prostate weight (Table 2), indicating that it may not be hydroxylated to compound **3** in vivo or

Keywords: Androgen receptor antagonists; Benzimidazoles; Prostate weight.
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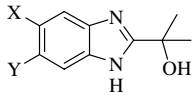
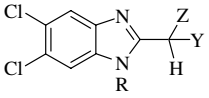
Table 1. Effect of benzene substitution



Compound	X	Y	P.W. inh. %[a]
2	F	Cl	57
3	Cl	Cl	77
4	Cl	CF_3	42
5	CN	CF_3	63
Bicalutamide			70

[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).

Table 2. Effect of 2-alkyl substitution



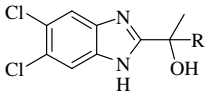
Compound	R	Y	Z	P.W. inh. %[a]
6	H	Me	Me	11
7	H	Et	Me	88
8	H	*n*-Pr	Me	32
9	H	Et	Et	80
10	Me	Me	Me	93
11	Me	Et	Me	na
12	Me	*n*-Pr	Me	23
13	Me	Et	Et	77
14	Et	Me	Me	82
15	Et	Et	Et	3
Bicalutamide				70

[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) (na, not active).

may possess poor pharmacokinetic properties. Extension of the alkyl substitution by one or two carbons restored activity as seen with compounds **7** and **9**. Interestingly, N-methylation of **6** provided compound **10**, which showed potent activity (93% pros. inh.). Compound **10** was found to reduce prostate weight in a dose-dependent manner and the ID_{50} was 0.26 mg/day. Bicalutamide has similar potency (ID_{50} = 0.23 mg/d) in this model. N-Methylation of **7** knocked out activity completely, while there was no significant difference in activity between compounds **8** and **9** versus **12** and **13**, respectively. N-Ethylation did not improve activity over the N-methylated analogs. Only small alkyl chains are tolerated.

Varying the side chain in 1*H*-benzimidazoles did not lead to improvements in activity (Table 3). Replacement of one methyl group in compound **3** with a trifluoromethyl group (**17**) gave comparable activity. However, **17** was found to be toxic at the 3 mg/d dose. Installing a methylene hydroxyl (**18**) or a methylene nitrile (**19**) reduced activity. Sulfone analogs, including **21** (bicalutamide side chain), showed little activity, indicating

Table 3. Effect of side chain in 1*H*-benzimidazoles



Compound	R	P.W. inh. %[a]
16	H	na
3	Me	77
17	CF_3	74
18	CH_2OH	67
19	CH_2CN	64
20	$CH_2S(O)_2Me$	na
21	$CH_2S(O)_2Ph$(4-F)	29
22	$CH_2S(O)_2Ph$(4-Me)	11
23	2-Furanyl	20
24	2-Thiophene	16
Bicalutamide		70

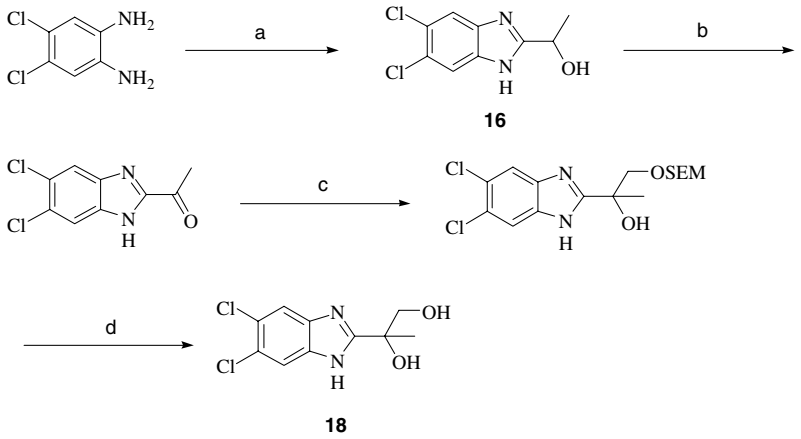
[a] Prostate weight inhibition % in testosterone treated castrated immature Sprague–Dawley rats. Dose = 2 mg/day. Normalized to control group administered with vehicle (N = 3/group) (na, not active).

divergent SAR from that of bicalutamide. Substitution with a heteroaromatic ring, such as 2-furan (**23**) and 2-thiophene (**24**), also diminished activity.

Installation of the side chain was carried out according to Scheme 1. Phillip's condensation of 4,5-dichloro-1,2-phenylene diamine with lactic acid afforded alcohol **16**, which was subsequently oxidized with potassium dichromate in dilute sulfuric acid. Addition to the methyl ketone with 3 equivalents of the lithium reagent derived from the metallation of trimethyl-(2-tributylstannanyl-methoxy-methoxy-ethyl)-silane afforded the SEM ether.[10] Initial attempt to desilylate with TBAF in THF failed to remove the SEM group. Deprotection with $LiBF_4$ in wet CH_3CN gave diol **18**.[11] Compounds **19**–**24** were prepared similarly by addition of a lithium or Grignard organometallic to the methyl ketone.

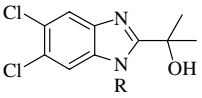
The effect of N-substitution on compound **3** was briefly explored (Table 4). *N*-Methyl analog, **25**, showed enhanced activity over **3**. Sequential lengthening from *N*-methyl to *N*-butyl decreased activity. Compounds **3** and **25** were 100% orally bioavailable and had a po half-life of 4 and 3 h, respectively. Interestingly, insertion of an oxygen (**29**) or sulfur (**30**) into the alkyl group gave potent compounds, while methylene nitrile (**31**) substitution knocked out activity. Since **29** and **30** may be sensitive to acid hydrolysis, introduction of sulfide and sulfone side chains off C2 of the benzimidazole was carried out on the *N*-methyl benzimidazole scaffold.

Benzimidazole **3** was prepared similarly as **16**, using the Phillips' procedure. Selective N-methylation was carried out with dimethylsulfate in the presence of a phase transfer catalyst (Scheme 2). The sulfide or sulfone side chain was introduced by dehydration of alcohol **25** with Burgess' inner salt. Hydroxychlorination[12] with trichloroisocyanuric acid was followed by displacement with ethanethiol to afford sulfide **33**. Hydroxychlorination failed on 1*H*-benzimidazole substrates. Subsequent oxidation with *m*-CPBA afforded sulfone **40**. With the



Scheme 1. Synthesis of **16** and **18**. Reagents and conditions: (a) lactic acid, HCl (aq), 100 °C, 35%; (b) K_2CrO_7, 25% (v/v) H_2SO_4, 49% (aq); (c) Bu_4SnCH_2OSEM, *n*-BuLi, THF, 26%; (d) $LiBF_4$, CH_3CN, H_2O, 29%.

Table 4. Effect of N-substitution on **3**



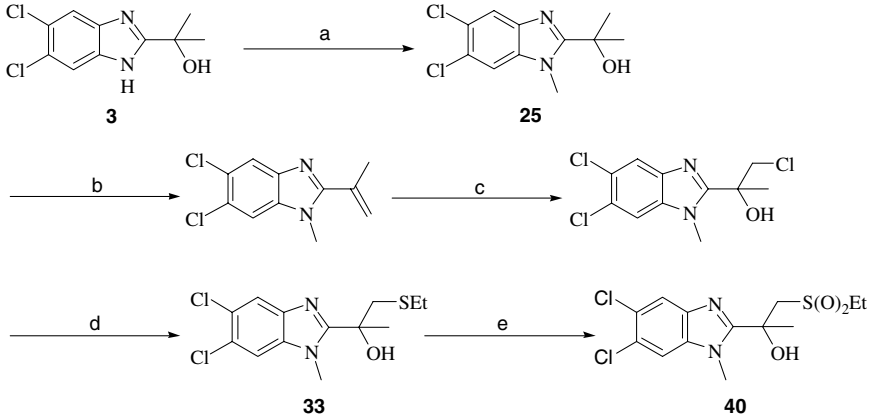
Compound	R	P.W. inh. %[a]
3	H	77
25	Me	91
26	Et	82
27	*n*-Pr	53
28	*n*-Bu	na
29	CH_2OMe	90
30	CH_2SMe	96
31	CH_2CN	5
Bicalutamide		70

[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) (na, not active).

appropriate sulfide, compounds **33**–**45** were prepared similarly.

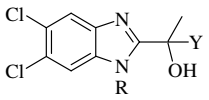
Ethyl thioether **33** inhibited prostate weight by 86%, while bulkier alkyl thioethers **35**–**37** decreased activity (Table 5). Interestingly, trifluoroethyl thioether **38** abolished activity. Benzyl thioether **37** showed moderate activity, weaker than **33**. In contrast to **33**, ethyl ether **32** had low activity. Installation of a 4-fluoro phenyl thioether (**39**) also did not show significant activity. Since sulfides can be oxidized in vivo to the corresponding sulfones (vide supra), sulfone derivatives were synthesized and compared. In general, the sulfones had weaker activity than the sulfides, with the exception of the sulfone derived from oxidation of trifluorothioether, which showed slightly better activity. *N*-Ethyl analogs, **34** and **41**, had similar activity as **33** and **40**. Compound **34** had low oral bioavailability (15%) and a short half-life (1 h). Thioether **34** was quickly converted in vivo to the corresponding sulfone **41**, which has high bioavailability (99%) and a longer half-life of 15 h.

Although compound **17** showed some toxicity, further investigation revealed that the trifluoromethyl group imparts greater activity on prostate weight inhibition (Table 6). 2-Ethyl benzimidazole **46**, as expected, is inactive. However, 2-(2,2,2-trifluoro-ethyl)-benzimidazole **47** is a potent prostate antagonist with an ID_{50} of 0.097 mg/d (more potent than bicalutamide) (Table 7). Moreover, compound **47** has high oral bioavailability with a half-



Scheme 2. Synthesis of **25**, **33**, and **40**. Reagents and conditions: (a) Me_2SO_4, NaOH, CH_3CN, benzyltriethylammonium chloride, 52%; (b) Burgess' inner salt, THF, 68%; (c) trichloroisocyanuric acid, acetone, H_2O, 35%; (d) EtSH, NaOMe, MeOH, 97%; (e) *m*-CPBA, CH_2Cl_2, 47%.

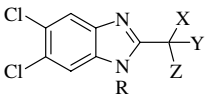
Table 5. Sulfide and sulfone derivatives



Compound	R	Y	P.W. inh. %[a]
32	Me	CH_2OEt	10
33	Me	CH_2SEt	86
34	Et	CH_2SEt	79
35	Me	CH_2S*n*-Pr	40
36	Me	CH_2S*i*-Bu	9
37	Me	CH_2SBn	63
38	Me	$CH_2SCH_2CF_3$	6
39	Me	$CH_2SPh(4\text{-}F)$	6
40	Me	$CH_2S(O)_2Et$	79
41	Et	$CH_2S(O)_2Et$	74
42	Me	$CH_2S(O)_2$*n*-Pr	26
43	Me	$CH_2S(O)_2$*i*-Bu	7
44	Me	$CH_2S(O)_2Bn$	16
45	Me	$CH_2S(O)_2CH_2CF_3$	38
Bicalutamide			70

[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).

Table 6. Trifluoromethyl group increases activity



Compound	R	X	Y	Z	P.W. inh. %[a]
46	H	H	H	Me	na
16	H	H	OH	Me	na
47	H	H	H	CF_3	90
1	H	H	OH	CF_3	96
(+)-**1**					81[b]
(−)-**1**					80[b]
48	Me	H	H	CF_3	60
49	Me	H	OMe	CF_3	60
50	H	OH	OH	CF_3	94
17	H	Me	OH	CF_3	74
Bicalutamide					70

[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) (na, not active).

[b] Dose = 0.3 mg/day.

life of 5.3 h. Compound **47** is converted to compound **1** in vivo. The hydroxyl analog **1** is also very potent (ID_{50} = 0.15 mg/d), compared to **16** (inactive). Compound **1** has high po bioavailability (132%) and a half-life of 14.7 h. N-Methylation and/or O-methylation decreased activity. The enantiomers of **1** were chemically resolved by making the corresponding Mosher esters. Both (+)-**1** and (−)-**1** were potent antagonists (80% pros. wgt. inh. at 0.3 mg/day). It was speculated that the hydrate of the corresponding trifluoromethyl ketone may be active. Oxidation of **1** with TEMPO and bleach gave ketone hydrate (**50**), which is a potent AR antagonist on the prostate (ID_{50} = 0.17 mg/d). In a 6-week-old intact mature rat (2-month-old) model, compounds **47** and

Table 7. ID_{50}s of select compounds

Compound	ID_{50}[a] (immature rat)	ID_{50}[b] (mature rat)
47	0.097	18
1	0.15	30
(+)-**1**	0.032	NT
(−)-**1**	0.12	NT
50	0.17	23
Bicalutamide	0.23	30

[a] In mg/day; tested in testosterone propionate treated (0.1 mg/day sc) castrated immature Sprague–Dawley rats. Five-day doses = 3, 1, 0.3, 0.1, 0.03 mg/day. Normalized to control group administered with vehicle (N = 3/group).

[b] In mg/kg; tested in testosterone propionate treated (0.4 mg/kg) castrated mature Sprague–Dawley rats. Six-week doses = 30, 10, 3, 1, and 0.3 mg/kg. Normalized to control group administered with vehicle. (N = 3/group) (NT, not tested).

50 had an ID_{50} of 18 and 23 mg/kg, respectively, which are more efficacious than bicalutamide (ID_{50} = 30 mg/kg). Racemate **1** had an ID_{50} of 30 mg/kg, similar to bicalutamide.

Selected compounds were tested in a COS AR whole-cell binding assay. Compound **3** showed 90% inhibition of binding at 3000 nM (ID_{50} = 80 nM). Sulfone **41**, which had similar in vivo activity (74% P.W. inh.) as **3** (77% P.W. inh.), only showed 20% inhibition of binding at 3000 nM. One of the most effective antagonists discovered in this series, **47**, also showed weak binding (30% inhibition of binding at 3000 nM). Similar to other investigators' findings, we also do not see a correlation between in vitro binding and in vivo efficacy.[6]

We have designed and synthesized AR ligands containing a benzimidazole core in place of the propionanilide found in the bicalutamide structure. The 5,6-dichloro substitution was found to be superior to the 5-cyano-6-trifluoromethyl substitution pattern found in bicalutamide. Small alkyl groups at *N*1, such as methyl and ethyl, were tolerated, while larger alkyl groups eroded activity. Installation of sulfide or sulfone side chains off *C*2 did not lead to more potent antagonists. The trifluoromethyl group in compounds **1**, **47**, and **50** imparted good efficacy on the prostate. Moreover, compounds **47** and **50** were found to be more efficacious than bicalutamide in mature rats.

Acknowledgments

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