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Bioorganic & Medicinal Chemistry Letters 17 (2007) 955–958
Bioorganic & Medicinal Chemistry Letters

2-(2,2,2-Trifluoroethyl)-5,6-dichlorobenzimidazole derivatives as potent androgen receptor antagonists

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Received 26 October 2006; revised 13 November 2006; accepted 14 November 2006
Available online 18 November 2006

Abstract—The synthesis and in vivo SAR of *N*-benzyl, *N*-aceto, and *N*-ethylene ether derivatives of 2-(2,2,2-trifluoroethyl)-5,6-dichloro-benzimidazole as novel androgen receptor antagonists are described. SAR studies led to the discovery of 4-bromo-benzyl benzimidazole **17** as a more potent androgen receptor antagonist in the rat prostate (ID_{50} = 0.13 mg/day), compared with bicalutamide (ID_{50} = 0.23 mg/day).

Testosterone and dihydrotestosterone mediate protein anabolism and affect basal metabolism through the upregulation of the androgen receptor (AR).[1] Androgens have also been shown to increase libido in animal models.[2] Although androgens have many beneficial effects and are important for gender dimorphism[3] and male development, endogenous androgens such as testosterone stimulate hyperplasia of the prostate and exacerbate androgen-dependent prostate cancer.[4]

Prostate cancer is the third leading cause of death for the US men, behind heart disease and stroke. Early treatment of the disease during the hormone-responsive stage benefits patients with a 99.8% 5-year survival rate.[5] Bicalutamide and flutamide, two non-steroidal antiandrogens, are currently used for the treatment of androgen-dependent prostate cancer[6] (Chart 1).

We are interested in selective androgen receptor ligands[7] and have recently described the discovery of 5,6-dichlorobenzimidazole scaffold as androgen antagonists, of which 2-(2,2,2-trifluoroethyl) derivatives (**1**) were more potent than bicalutamide in both immature and mature rat models.[7f] In this paper, we wish to report the results of our studies on the synthesis and in vivo activity[8] of N-substituted 2-(2,2,2-trifluoroethyl)-5,6-dichloro-benzimidazoles (Chart 2).

Target benzimidazoles were prepared by alkylation of **1** or **2** with substituted benzyl halides and potassium carbonate in DMF to afford compounds **6**–**12a** and **16**–**52**.

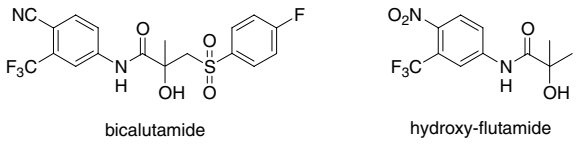

Chart 1.

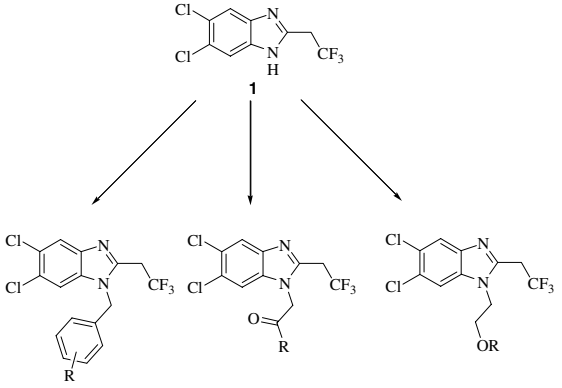

Chart 2.

Keywords: Benzimidazoles; Androgen receptor antagonists; Bicalutamide.
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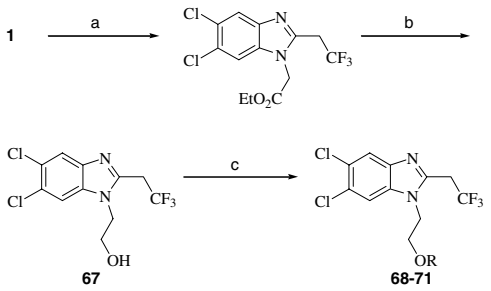
doi:10.1016/j.bmcl.2006.11.047

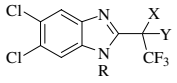


Scheme 1. Synthesis of **66–70**. Reagents and conditions: (a) $BrCH_2CO_2Et$, NaH, DMF (62%); (b) $LiBH_4$, THF, EtOH (63%); (c) ArOH, DBAD, PPh_3, PhMe (65–74%).

Compounds **53–66** were similarly synthesized from the reaction of **1** with α-halo ketones in the presence of sodium hydride in DMF (Scheme 1).

Previously, we reported the discovery of compounds **1**, **2**, and **5**, which possess high (90–96%) prostate weight inhibition in both immature and mature rats.[7f] Replacement of the hydroxyl in **2** with a fluorine also gave a potent compound (**3**) (81% prostrate weight inhibition at 1 mg/day). Compound **3** was tested in a dose-dependent manner and the ID_{50} was 0.15 mg/d that is the same as compound **2**. However, toxicity was observed at the 3 mg/day dose (Table 1). Pentafluoro ethyl derivative **4** was exceedingly toxic and could not be tested. Having completed the SAR studies on the side-chain modifications, we turned our attention to the effect of N-alkylation on potency in our series. Based on the literature evidence for bicalutamide and flutamide, N-alkylation usually leads to inactive or less-active analogs. Much to our delight, N-benzylation of **1** provided a compound that possessed good efficacy (**6**, 79% prostrate weight inhibition). Although N-benzylation of **2** diminished activity, the *N*-benzyl derivative of the ketone hydrate **5** (compound **8)** showed good activity. Alkylation with CH_2-2-pyridinyl showed good activity as well (**9**, **10**). Interestingly, neither *N*-methyl nor *N*-ethyl derivative of compound **13** showed efficacy, indicating that the efficacy of the benzyl analogs was not due to the potential metabolic cleavage of the benzyl moiety since methyl and ethyl are more prone to oxidative cleavage by P450s.

Table 1.



Compound	R	X	Y	PW inhibition %[a]
1	H	H	H	90
2	H	H	OH	96
3	H	H	F	81[b]
4	H	F	F	Toxic
5	H	OH	OH	94
6	Bn	H	H	79
7	Bn	H	OH	49
8	Bn	OH	OH	85
9	CH_2–2-pyr	H	H	89
10	CH_2–2-pyr	H	OH	84
11	CH_2CN	Me	OH	54
12	CH_2OMe	Me	OH	88
13	H	Me	OH	74
14	Me	Me	OH	na
15	Et	Me	OH	na
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).

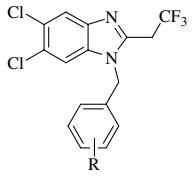
[b] Dose = 1 mg/day.

The finding that the N-substituted benzimidazoles are efficacious is quite significant. It further demonstrated the divergent SARs between our series and bicalutamide/flutamide. To achieve our goal to identify androgen receptor antagonists that have comparable efficacy in inhibiting prostate growth to that of bicalutamide, we decided to further explore the substituent effect on the phenyl ring of the benzyl group on the nitrogen of the benzimidazole. A variety of substitutions around the aromatic ring was next explored.

Halogens such as Br, Cl, or F were tolerated at the 2- or 4-position, but not at the 3-position. Pentafluoro benzyl derivative **24** abolished activity. Electron-donating groups such as methyl or methoxy substituents generally reduced activity. Trifluoromethyl substitution is well tolerated, with the most active (86% prostrate weight inhibition) in the 2-position. Di-trifluoromethyl analog **30**, however, is inactive. Electron-withdrawing groups such as nitro or nitrile were best at the 2-position. Interestingly, a phenyl group is also well tolerated at the 2-position (**49**). Pyridinyl derivatives were also prepared with the nitrogen at the 2-position, showing the best activity (**50**, 89% prostrate weight inhibition). Selected compounds were tested in a dose-dependent manner, which gives a more accurate assessment of activity. To our delight, most compounds tested showed comparable efficacy to that of the benchmark, bicalutamide. Unsubstituted benzyl derivative **6** had an ID_{50} of 0.37 mg/day, compared to an ID_{50} of 0.23 mg/day for bicalutamide. 4-Bromobenzyl analog **17** (ID_{50} = 0.13 mg/day) is the most active among the halogen-substituted analogs. Based on single dose (2 mg/day) testing, pyridin-2-yl analog **50** showed an 89% prostate weight inhibition, and had an ID_{50} of 0.40 mg/day (Table 2).

Next, we extended the side chain off the benzimidazole nitrogen by inserting a carbonyl group between the nitrogen and the R-group (Table 3). Moderate activity was observed when R-group is simple alkyl such as ethyl ketone **53**. Although unsubstituted acetophenone analog **55** had low activity (38% prostrate weight inhibition), substitution with electron-withdrawing groups such as nitro or fluorine at the 4-position restored activity (67–71% prostrate weight inhibition). An electron-donating group such as a methoxy substituent abolished activity. Pyridin-2-yl analog **63** showed better activity than the pyridin-3-yl analog **64**. Thiophen-2-yl analog **65** showed moderate activity. The most active compound in the *N*-aceto series, pyridin-2-yl analog **63** was tested in a

Table 2. Effect of benzyl substitution



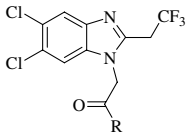
Compound	R	PW inhibition %[a]	ID_{50}s
6	H	79	0.37
16	2-Br	84	0.38
17	4-Br	75	0.13
18	2-Cl	90	0.26
19	3-Cl	35	
20	4-Cl	77	0.28
21	2-F	77	0.82
22	3-F	55	
23	4-F	80	0.19
24	2,3,4,5,6-F	19	
25	2-CH_3	73	
26	3-CH_3	31	
27	2-CF_3	86	
28	3-CF_3	74	0.40
29	4-CF_3	75	
30	2-CF_3, 4-CF_3	13	
31	2-OCH_3	51	
32	3-OCH_3	na	
33	4-OCH_3	51	
34	3-OCF_3	26	
35	4-OCF_3	35	
36	4-SCF_3	13	
37	4-SO_2Me	32	
38	2-CH_2SO_2Ph	74	
39	4-OCH_2Ph	46	
40	2-NO_2	81	0.95
41	3-NO_2	49	
42	4-NO_2	61	
43	4-OH	28	
44	4-CO_2Et	56	
45	4-CO_2H	38	
46	2-CN	74	
47	3-CN	70	
48	4-CN	68	
49	2-Ph	79	0.55
50	Pyridin-2-yl	89	0.40
51	Pyridin-3-yl	80	
52	Pyridin-4-yl	42	
Bicalutamide		70	0.23

[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).

dose-dependent manner and the ID_{50} was 0.47 mg/day (Table 4).

Since methylene methyl ether **11** showed good activity (90% prostrate weight inhibition), extension of the side chain to ethylene ether derivatives was briefly explored. The preparation of compounds **67**–**71** begins with N-alkylation of **1** with ethyl bromoacetate and sodium hydride in DMF. Reduction of the ethyl ester was carried out with lithium borohydride. Initial attempts to carry out a Mitsunobu displacement using diethylazodicarboxylate (DEAD) were plagued with difficult separation of the product from the hydrazide by-product. Switching from DEAD to di-*tert*-butylazodicarboxylate (DBAD) alleviated this problem.

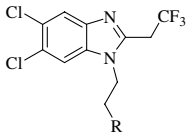
Table 3. Effect of *N*-aceto substitution



Compound	R	PW inhibition %[a]
53	Et	64
54	Ph	38
55	Ph, 3-NO_2	14
56	Ph, 4-NO_2	71
57	Ph, 4-Br	27
58	Ph, 4-Cl	33
59	Ph, 4-F	67
60	Ph, 2-OMe	10
61	Ph, 3-OMe	na
62	Ph, 2-OMe, 4-OMe	na
63	Pyridin-2-yl	76
64	Pyridin-3-yl	na
65	Thiophen-2-yl	43
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 4. Effect of ethylene aryl ether substitution



Compound	R	PW inhibition %[a]
66	OH	54
67	OPh(4-Cl)	48
68	OPh(3-F)	22
69	OPh(4-F)	40
70	OPh(4-CN)	86
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).

Ethylene alcohol **66** showed moderate activity (54% prostrate weight inhibition). 4-Fluoro-phenyl ether **69** was more active than the 3-fluoro-phenyl analog **68**. In general, extension of the side chain with an ethylene aryl ether did not yield very active compounds, with the exception of 4-cyano-phenyl ether **70** (86% prostrate weight inhibition).

In summary, *N*-alkyl substitution, such as benzyl, aceto, and ethylene ether side chains was explored. *N*-Aceto and ethylene aryl ether derivatives generally did not improve prostate antagonist activity. N-Benzylation of our initial lead, **1**, was well tolerated, particularly with halogen (Cl, Br, F) substitution at the 2- or 4 position. 4-Bro-

mobenzyl analog, **17**, has an ID_{50} of 0.13 mg/d, which is more potent than bicalutamide. The superior in vivo efficacy of the novel benzimidazoles in reducing prostate weight provided us with an excellent opportunity to select a development candidate. Further biological evaluations of the most potent compounds are underway.

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