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Potent benzimidazolone based human β_3-adrenergic receptor agonists

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Abstract—The synthesis and biological evaluation of a series of benzimidazolone β_3 adrenergic receptor agonists are described. A trend toward the reduction of rat atrial tachycardia upon increasing steric bulk at the 3-position of the benzimidazolone moiety was observed.

The β_3 adrenergic receptor plays an important role in mediating lipolysis in white adipose tissue[1] and thermogenesis in brown adipose tissue.[2] It has been reported that stimulation of this receptor induces a variety of pharmacological effects such as an increase in fat oxidation, enhancement of energy expenditure, and improvement of glucose uptake in rodent models of obesity and diabetes.[3] It may not, however, play as dominant a role in humans[4] and despite the interest in this target, there have only been mixed reports of clinical efficacy in humans.[5] Recent reports suggest the use of β_3 agonists as therapeutics for gastrointestinal[6] and urinary disease.[7]

Although activation of β_1 receptors is known to increase heart rate, evidence has accumulated to suggest that some β_3 agonists may produce a chronotropic effect in rat atria,[8] and there has been considerable debate in the literature as to the underlying mechanism of the effect.[9] The presence of a fourth β adrenoceptor was postulated,[10] though this is now widely believed to be a low-affinity state of the β_1 receptor.[11] One of the goals of this SAR was to minimize this in vitro atrial tachycardia.

As part of our β_3 agonist program, we utilized parallel synthesis to quickly synthesize and screen a number of compounds. We identified compound **1** (Fig. 1) as a agonist at the human β_3 adrenergic receptor and were interested in understanding the SAR around the benzimidazolone ring.

2-Amino-3-nitrophenol (**2**, Scheme 1) was reacted with (2*S*)-glycidyl 3-nitrobenzenesulfonate to provide the epoxide (**3**) which was opened using dibenzylamine. The aromatic nitro group was reduced to provide the dianiline which was treated with triphosgene in a biphasic solvent mixture (toluene/aqueous acid) to form the benzimidazolone (**5**). The alcohol was protected as the TBS ether. This material was deprotonated with sodium hydride and treated with 1.5 equivalents of iodomethane. Three methylated products (**6**–**8**) were isolated by flash chromatography and the structures of the monomethyl regioisomers assigned by NOESY and ROESY NMR experiments. These compounds were desilylated and debenzylated to give the desired amines

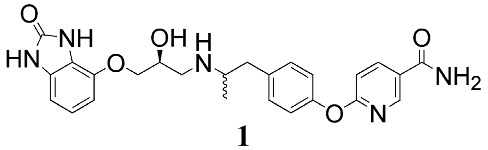

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Figure 1. Initial hit.

Keywords: Beta 3 agonists; Obesity; Benzimidazolone; Tachycardia; Beta 1 receptors.

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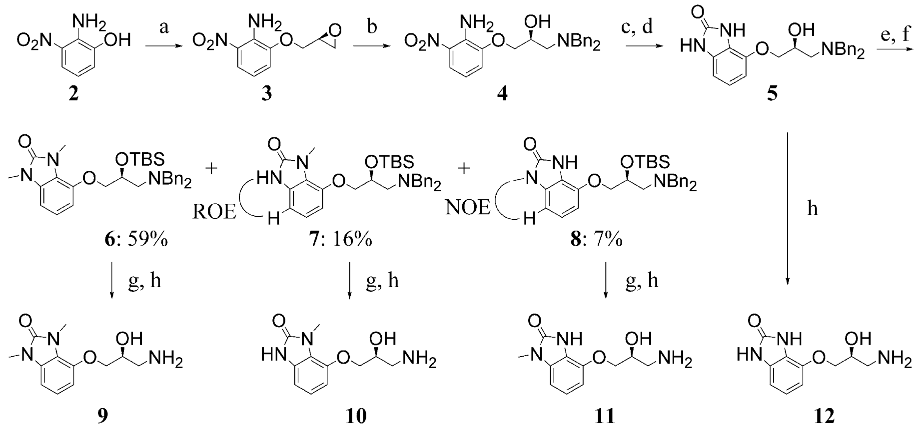
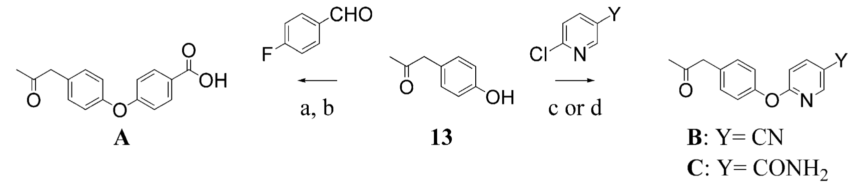
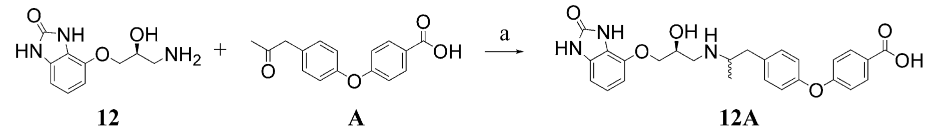


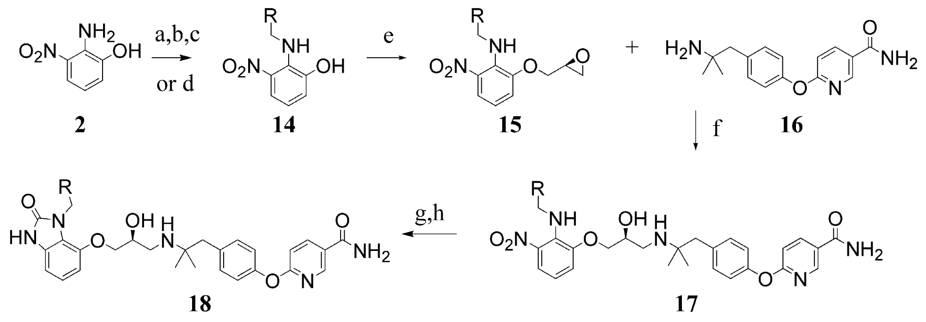
Scheme 1. Reagents and conditions: (a) (2*S*)-glycidyl 3-nitrobenzenesulfonate, K_2CO_3, acetone, reflux, 18 h, 99%; (b) Bn_2NH, MeOH, reflux, 10 h, 78%; (c) $Na_2S_2O_4$, $NaHCO_3$, EtOH/H_2O (2:1), rt, 16 h, 81%; (d) triphosgene, toluene/2 N HCl (3:5), rt, 14 h, 93%; (e) TBSCl, imidazole, DMF, rt, 18 h, 96%; (f) NaH, MeI, THF, 0 °C, rt, 18 h, see yields above; (g) TBAF, THF, 0 °C, 3–5 h, 60–96%; (h) 10% Pd/C, ammonium formate, MeOH, 1 h, 75–85%.



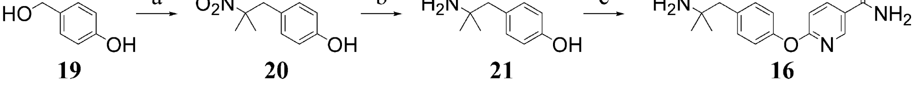
Scheme 2. Reagents and conditions: (a) Cs_2CO_3, DMF, rt, 18 h, 79%; (b) $NaClO_2$, Me_2SO, rt, 18 h, 31%; (c) NaH, DMF, 90 °C, 3 h, 32%; (d) K_2CO_3, DMAC, 130 °C, 2.5 h, 44%.



Scheme 3. Reagents and conditions: (a) $NaCNBH_3$, acetic acid, MeOH, rt, 24 h.



Scheme 4. Reagents and conditions: (a) ROCl or $(RCO)_2O$, Et_3N, CH_2Cl_2, 0 °C, rt, 18 h; (b) K_2CO_3, MeOH, rt, 2 h, 56–94%(two steps); (c) BH_3-Me_2S, THF, 0 °C, rt, 2 h, 54–57%; (d) $NaBH(OAc)_3$, HOAc, 1,2 dichloroethane, 18 h, 11–49%; (e) (2*S*)-glycidyl 3-nitrobenzenesulfonate, K_2CO_3, acetone, reflux, 18 h, 60–73%; (f) EtOH, reflux, 18 h, 42–58%; (g) $Na_2S_2O_4$, $NaHCO_3$, EtOH/H_2O (2:1), rt, 2 h; (h) triphosgene, toluene/2 N HCl (3:5), rt, 18–72 h, 33–58% (two steps).



Scheme 5. Reagents and conditions: (a) 2-nitropropane, potassium *tert*-butoxide, diglyme, 130–150 °C, 4 h, 71%; (b) H_2 (50 psi), 5% Pd/C, HOAc, MeOH, 50 °C, 16 h, 86%; (c) 6-chloronicotinamide, K_2CO_3, DMAC/iso-octane (5:1), 140 °C, 6 h, 93%.

(**9**–**11**). Debenzylation of the protected amine (**5**) provided 4-(3-amino-2-hydroxy-propoxy)-1,3-dihydro-benzoimidazol-2-one (**12**) as a comparator.

The ketones were synthesized as described in Scheme 2. 1-(4-Hydroxy-phenyl)-propan-2-one (**13**) was treated with cesium carbonate and 4-fluorobenzaldehyde, and the resulting aldehyde was then oxidized to give acid (**A**). Similarly, nucleophilic aromatic substitution reactions of the phenol (**13**) with 6-chloro-nicotinonitrile and 6-chloro-nicotinamide provided ketones **B** and **C**, respectively. A standard reductive amination protocol between these amines and ketones was conducted in a parallel fashion in combination with ion exchange purification as illustrated for fragments **12** and **A** in Scheme 3.[12] An excess of the ketone (2 equiv) was utilized to ensure complete consumption of the starting amine (1 equiv), so that the resulting product amine could be obtained in >85% purity after ion exchange chromatography.

A general synthetic route to allow for variation of the substituent on the nitrogen is described in Scheme 4. 2-Amino-3-nitrophenol (**2**) was treated with excess acid chloride or anhydride,[13] and then the ester was selectively hydrolyzed to provide the amide, which was reduced with borane-dimethylsulfide complex to yield the substituted aniline (**14**). Alternatively, a reductive amination of 2-amino-3-nitrophenol (**2**) with the corresponding aldehyde yielded the aniline (**14**) in one chemical operation. This phenol was further elaborated to the epoxide (**15**) as previously described, and this epoxide was opened using amine **16**. The benzimidazolone ring was formed in an identical manner to that described in Scheme 1 to yield the desired compounds (**18**).

The synthesis of the amine (**16**) is detailed in Scheme 5. 4-hydroxybenzyl alcohol (**19**) was treated with potassium *tert*-butoxide and 2-nitropropane to afford 4-(2-methyl-2-nitropropyl)phenol (**20**). The nitro group was reduced by hydrogenation to provide the amine (**21**). This phenol was then further elaborated via nucleophilic aromatic substitution to the desired amine (**16**).

The biological results of the compounds prepared in this parallel synthesis effort are reported in Table 1. The compounds derived from amine **9** (i.e., 4-hydroxy-1,3-dimethyl-1,3-dihydro-benzoimidazol-2-one), as well as from amine **11** (i.e., 4-hydroxy-1-methyl-1,3-dihydro-benzoimidazol-2-one) lose most of the β_3 agonist activity of the parent unsubstituted compounds derived from

Table 1. Agonist activity of compounds at a concentration of 100 nM expressed as % of the maximal response to isoproterenol[a]

Amine	% of the maximal response to isoproterenol		
	Ketone		
	A	**B**	**C**
12	99	88	97
9	28	11	25
10	84	83	87
11	30	29	33

[a] Values are means of three experiments.

Table 2. In vitro agonist activity[a] at human β adrenergic receptors and rat β_3 adrenergic receptor for variations in R

Compound	R	Human β_3		Rat β_3		Human β_2		Human β_1		Rat atrial tachycardia[b]
		EC_{50} (nM) (*n*)	E_{max} (%) (*n*)	EC_{50} (nM) (*n*)	E_{max} (%) (n)	EC_{50} (nM) (*n*)	E_{max} (%) (*n*)	EC_{50} (nM) (*n*)	E_{max} (%) (*n*)	% increase in heart rate (*n*)
18a	H	7.1 ± 0.6 (129)	79.7 ± 8.4 (129)	24.5 ± 2.7 (13)	59.6 ± 2.0 (13)	>10,000 (41)	<10 (41)	8.7 ± 2.5 (41)	18.0 ± 0.8 (41)	17.7 ± 3.7 (4)
18b	$-CH_3$	5.2 ± 1.3 (3)	65.1 ± 7.7 (3)	NA[c]	NA[c]	>10,000 (3)	<10 (3)	>10,000 (3)	<10 (3)	20.8 ± 1.8 (3)
18c	$-CH_2CH_3$	5.2 ± 1.1 (3)	73.9 ± 1.8 (3)	NA[c]	NA[c]	>10,000 (3)	<10 (3)	>10,000 (3)	<10 (3)	19.9 ± 2.4 (4)
18d	$-CH_2(CH_3)_3$	8.9 ± 3.2 (8)	65.5 ± 9.3 (8)	62.6 ± 12.7 (12)	57.7 ± 2.0 (12)	>10,000 (8)	<10 (8)	>10,000 (9)	<10 (9)	4.6 ± 0.2 (4)
18e	$-CH_2$–cyclopropyl	5.4 ± 0.2 (3)	67.9 ± 11.1 (3)	6.8 ± 2.7 (3)	42.7 ± 5.0 (3)	>10,000 (3)	<10 (3)	>10,000 (3)	<10 (3)	8.9 ± 1.2 (3)
18f	$-CH_2$–cyclobutyl	10.1 ± 0.7 (3)	58.2 ± 3.5 (3)	28.7 ± 15.5 (3)	49.6 ± 0.6 (3)	>10,000 (3)	<10 (3)	>10,000 (3)	<10 (3)	6.5 ± 2.2 (3)
18g	$-CH_2$–cyclopentyl	11.7 ± 1.8 (4)	63.7 ± 2.6 (4)	NA[c]	NA[c]	2.4 ± 0.5 (3)	20.2 ± 3.5 (3)	>10,000 (3)	<10 (3)	9.9 ± 0.3 (3)

[a] β agonist activities are expressed by a measurement of cAMP levels in CHO cells expressing the human β adrenergic receptors or the rat β_3 adrenergic receptors. Intrinsic activity was determined as the maximal response of the compound as a percentage of the maximal response of isoproterenol at 10 mM.

[b] Maximal rat atrial tachycardia or response to 0.1 mM agonist if maximal response was not attained.

[c] Data not available.

Table 3. Acute in vivo studies in diet-induced obese Long Evans rats

Compound	Dose (mg/kg po)	Respiratory quotient % reduction over vehicle (20 h)	Energy expenditure % increase over vehicle (20 h)	Exposure[b] $AUC_{(0-6h)}$ (ng-h/mL)
18d	10	22%[a]	9%[a]	342[c]
18f	10	29%[a]	18%[a]	112

[a] $p < 0.05$.

[b] Area under the plasma concentration curve determined over the duration 0–6 h in obese Long Evans rats following a 10 mg/kg po dose.

[c] Rat oral bioavailability (F344 rats) was found to be 8%.

amine **12**. In contrast, the compounds derived from the other monomethyl regioisomer (i.e., from amine **10**) retain most of the β_3 agonist activity of the unsubstituted benzimidazolone.

Further exploration of the substitution on this nitrogen of this regioisomer yielded some interesting results. The β adrenergic agonist data of these compounds are shown in Table 2. These compounds are still potent agonists of the β_3 receptor with little or no agonist activity at the β_1 or β_2 receptors. However, these compounds showed differential activity in their propensity to cause atrial tachycardia in vitro.[14] This effect is dependent on the size of the substituent on the nitrogen with larger groups showing a reduced propensity to cause tachycardia.

The pharmacological profiles of compounds **18d** and **18f** were further assessed by measuring carbohydrate and fat utilization in diet-induced obese Long Evans rats by indirect calorimetry, measuring respiratory quotient over a 24-h period.[15] A single oral dose of these compounds induced a decrease in respiratory quotient as well as an increase in energy expenditure (Table 3). Despite this encouraging data, these compounds were shown to have poor oral exposure (Table 3) and further optimization to improve the in vivo properties of these molecules will be reported in due course.

Acknowledgments

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