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Potent oxindole based human β_3 adrenergic receptor agonists

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Abstract—The synthesis and biological evaluation of a series of oxindole β_3 adrenergic receptor agonists is described. A modulation of rat atrial tachycardia was observed with substitution at the 3-position of the oxindole moiety.

The β_3 adrenoceptor is expressed predominantly in the adipose tissue and is known to be involved 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]; however, there have only been mixed reports of clinical efficacy in humans.[4] This receptor is also expressed in the gastrointestinal tract[5] and bladder[6] where it mediates relaxation and may be of therapeutic value for gastrointestinal[7] and urinary disease.[8]

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,[9] and there has been considerable debate in the literature as to the underlying mechanism of the effect.[10] Reports suggesting the existence of a fourth β adrenoceptor[11] observed in cardiac and white adipose tissue have now been modified since this phenotype disappears in β_1 and β_1/β_2 adrenoceptor knockout mice.[12] This unique pharmacology observed is probably due to the interaction of these compounds with a low affinity state of the β_1 receptor. One of the goals of this SAR was to minimize this in vitro atrial tachycardia.

As described earlier, we identified a compound containing a benzimidazolone moiety (**1**, Fig. 1) which exhibited potent β_3 agonist activity (EC_{50} = 7.1 nM, E_{max} = 80%).[13] Our previous SAR studies also indicated that one of the NHs of the benzimidazolone was more critical for β_3 activity. We thus considered the replacement of the benzimidazolone moiety with an oxindole and also further explored the role of steric bulk in the 3-position of this moiety in modulating rat atrial tachycardia in vitro.

4-Methoxyoxindole (**2**, Scheme 1)[14] was demethylated to yield the corresponding phenol (**3a**, R^1, R^2 = H). This phenol was reacted with (2*S*)-glycidyl 3-nitrobenzenesulfonate to provide the epoxide (**4a**, R^1, R^2 = H) which was opened using 2 equivalents of the amine (**5**)[13] to yield the desired propanolamine (**6a**, R^1, R^2 = H).

In order to introduce substituents at the 3-position of the oxindole, 4-methoxyoxindole (**2**, Scheme 1) was treated with two equivalents of *n*-butyl lithium in the presence of TMEDA[15] followed by alkyl iodides to give the desired monoalkylated product (**7b–d**). These products could be resubjected to the same alkylation conditions to yield the desired dialkylated oxindoles (**8e–g**). Alternatively, the dilakylated compounds could be

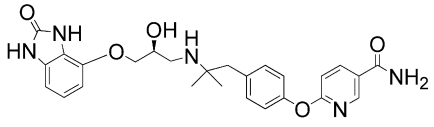

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Figure 1. Initial compound.

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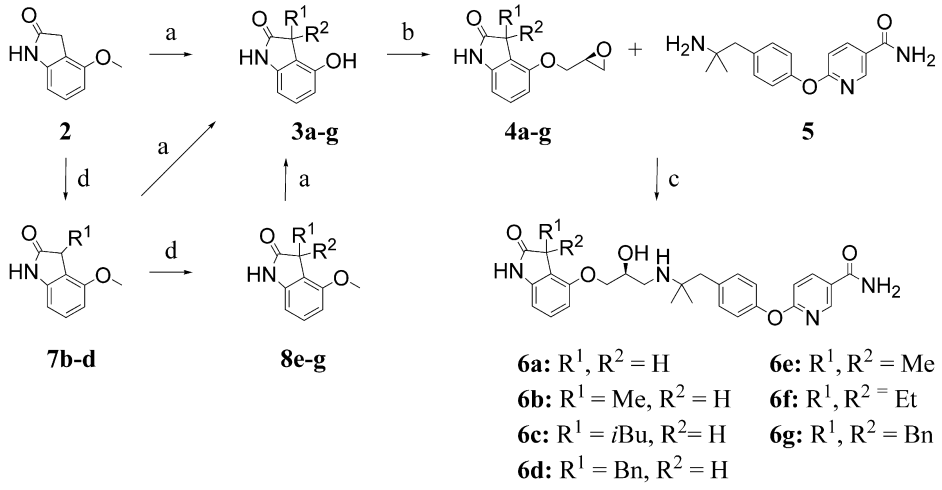
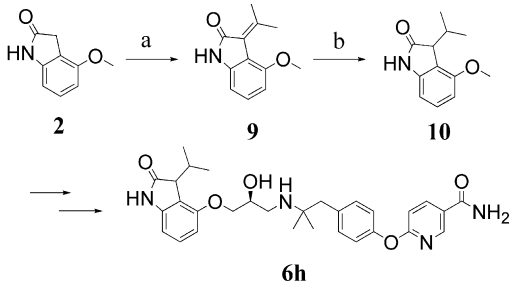


Scheme 1. Reagents and conditions: (a) pyridine hydrochloride, 180 °C (40–90%); (b) (2*S*)-glycidyl 3-nitrobenzenesulfonate, K_2CO_3, acetone, reflux, 18 h; (c) EtOH, reflux, 18 h; (d) 2 equiv *n*-BuLi, TMEDA, RI, THF, −78 °C to rt (30–70%).

obtained in one step by adding excess alkylating agent. These intermediates (**7b–d**) and (**8e–g**) could be further elaborated as described for compound **6a** to provide the final compounds (**6b–g**).[16]

The 3-isopropyloxindole derivative (**6h**) was prepared as described in Scheme 2. 4-Methoxyoxindole (**2**) was converted to the 3-isopropylidine substituted compound (**9**) by reaction with acetone.[17] The resulting double bond was hydrogenated to yield the desired branched alkyl oxindole (**10**) which can be converted to the desired propanolamine (**6h**) as detailed in Scheme 1.

The 4-methoxyoxindole (**2**) was also alkylated with alkyl diiodides in a similar manner to form spirofused oxindole intermediates (**11a–c**, Scheme 3) which were further elaborated to yield the desired final compounds (**12**).

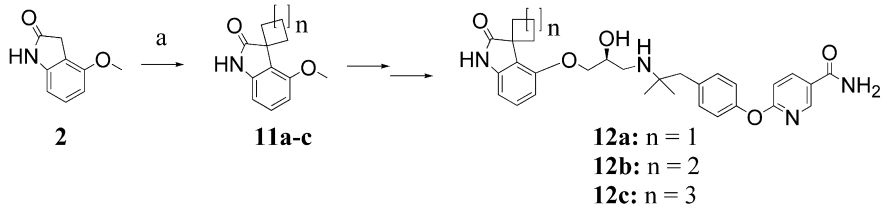


Scheme 2. Reagents and conditions: (a) acetone, piperidine, reflux, 17%; (b) H_2, 50 psi, PtO_2, EtOH, 38%.

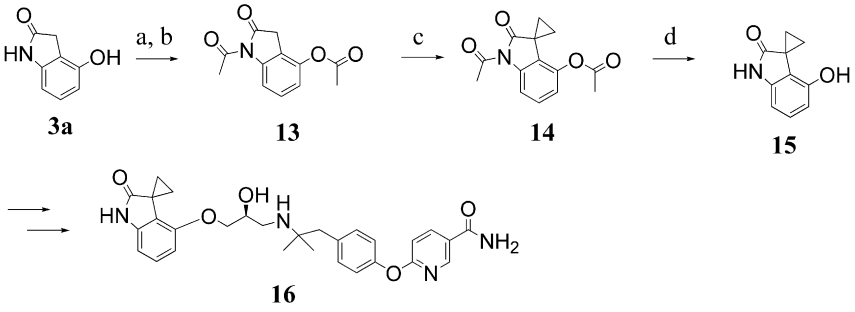
The synthesis of the cyclopropyl analog is outlined in Scheme 4. 4-Hydroxyoxindole (**3a**) was treated with acetic anhydride to give the diacetate (**13**).[18] Milder alkylating conditions using potassium carbonate provided the cyclopropyl analog (**14**), which was deprotected under acidic conditions to provide the necessary phenol (**15**) for further elaboration to compound (**16**).

The replacement of the benzimidazolone with the oxindole moiety resulted in a compound (**6a**) which was slightly less potent than compound **1**. We then explored substitution at the 3-position of the oxindole, and found that the 3-methyl and 3,3-dimethyl substitution resulted in compounds (**6b** and **6e**) that were more active than the unsubstituted compound (**6a**). However, larger substituents led to a decrease in the efficacy of these compounds as agonists at the β_3 adrenergic receptor as shown in Table 1. We further investigated forming 3,3-fused spirocycles instead of the dialkylated compounds.

A marked difference in both β_3 adrenergic activity and rat atrial tachycardia was seen between the 3,3-diethyl compound (**6f**; Table 1) and the cyclopentyl fused spirocyclic compound (**12b**; Table 2), alluding to the spatial requirements of this site. We have demonstrated in our earlier publication that the differences in potency at the rat β_3 receptor do not account for the differences we see in rat atrial tachycardia.[13] The β adrenergic agonist data of these compounds are shown in Table 2. These compounds are also agonists of the β_3 receptor with little or no agonist activity at the β_1 or β_2 receptors,



Scheme 3. Reagents and conditions: (a) 2 equiv *n*-BuLi, TMEDA, I–$(CH_2)_n$–I, THF, −78 °C to rt (33–45%).



Scheme 4. Reagents and conditions: (a) Ac_2O, AcOH, reflux; (b) Ac_2O, Na_2CO_3, THF, 16% two steps; (c) 1,2-dibromoethane, K_2CO_3, DMSO, rt, 79%; (d) 3 N H_2SO_4, THF, reflux, 2 h, 50%.

Table 1. In vitro agonist activity[a] at human β adrenergic receptors for variations in R

Compound	R^1, R^2	Human 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*)	% increase in heart rate (*n*)
6a	H, H	24.4 ± 5.6 (*n* = 6)	50.5 ± 4.4 (*n* = 6)	>10,000 (*n* = 4)	<10 (*n* = 4)	>10,000 (*n* = 4)	<10 (*n* = 4)	19.5 ± 4.1 (*n* = 4)
6b	Me, H	12.0 ± 3.5 (*n* = 5)	72.6 ± 5.4 (*n* = 3)	>10,000 (*n* = 4)	<10 (*n* = 4)	>10,000 (*n* = 4)	<10 (*n* = 4)	10.4 ± 2.1 (*n* = 3)
6h	*i*-Pr, H	13.9 ± 7.2 (*n* = 3)	41.7 ± 8.4 (*n* = 3)	>10,000 (*n* = 3)	<10 (*n* = 3)	>10,000 (*n* = 3)	<10 (*n* = 3)	NT[c]
6c	*i*-Bu, H	14.0 ± 2.8 (*n* = 4)	49.4 ± 5.7 (*n* = 4)	>10,000 (*n* = 5)	<10 (*n* = 5)	>10,000 (*n* = 5)	<10 (*n* = 5)	NT[c]
6d	Bn, H	12.3 ± 4.4 (*n* = 2)	15.6 ± 0.6 (*n* = 2)	>10,000 (*n* = 2)	<10 (*n* = 2)	>10,000 (*n* = 2)	<10 (*n* = 2)	NT[c]
6e	Me, Me	5.2 ± 2.1 (*n* = 6)	67.9 ± 2.0 (*n* = 6)	>10,000 (*n* = 5)	<10 (*n* = 5)	>10,000 (*n* = 6)	<10 (*n* = 6)	9.7 ± 1.7 (*n* = 7)
6f	Et, Et	2.7 (*n* = 1)	14.2 (*n* = 1)	>10,000 (*n* = 1)	<10 (*n* = 1)	>10,000 (*n* = 1)	<10 (*n* = 1)	2.0 ± 0.6 (*n* = 3)
6g	Bn, Bn	268.1 ± 21.3 (*n* = 2)	48.5 ± 2.3 (*n* = 2)	>10,000 (*n* = 2)	<10 (*n* = 2)	>10,000 (*n* = 2)	<10 (*n* = 2)	NT[c]

[a] β agonist activities are expressed by a measurement of cAMP levels in CHO cells expressing the human β 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 obtained.
[c] Not tested.

Table 2. In vitro agonist activity[a] at human β adrenergic receptors for variations in ring size

Compound	*n*	Human 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*)	% increase in heart rate (*n*)
16	0	6.6 ± 0.2 (*n* = 3)	76.8 ± 3.2 (*n* = 3)	35.2 ± 30.6 (*n* = 3)	13.5 ± 0.4 (*n* = 3)	58.3 ± 35.5 (*n* = 3)	21.4 ± 4.2 (*n* = 3)	13.2 ± 2.8 (*n* = 3)
12a	1	17.6 ± 4.6 (*n* = 3)	71.2 ± 3.9 (*n* = 3)	>10,000 (*n* = 3)	<10 (*n* = 3)	>10,000 (*n* = 3)	<10 (*n* = 3)	14.8 ± 5.1 (*n* = 3)
12b	2	10.6 ± 1.2 (*n* = 9)	66.3 ± 2.8 (*n* = 9)	>10,000 (*n* = 9)	<10 (*n* = 9)	>10,000 (*n* = 9)	<10 (*n* = 9)	8.6 ± 1.4 (*n* = 9)
12c	3	8.3 ± 0.8 (*n* = 3)	41.0 ± 5.8 (*n* = 3)	>10,000 (*n* = 3)	<10 (*n* = 3)	>10,000 (*n* = 3)	<10 (*n* = 3)	16.0 ± 2.3 (*n* = 3)

[a] β agonist activities are expressed by a measurement of cAMP levels in CHO cells expressing the human β 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 obtained.

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

Compound	Dose (mg/kg) po[b]	Respiratory quotient % reduction over vehicle (20 h)	Energy expenditure % increase over vehicle (20 h)	Food consumption (g)
6e	10	45%[a]	14%[a]	11.8 ± 1.7[a]
6e	1	31%[a]	8%	13.7 ± 1.8
Vehicle	0	—	—	19.9 ± 2.1

[a] $p < 0.05$.
[b] Rat oral bioavailability (F344 rats) was found to be 10%.

though the efficacy appears to fall off with increasing ring size. Interestingly, we found that introducing bulk at the 3-position did appear to modulate the in vitro rat atrial tachycardia exhibited by these compounds.[19]

The pharmacological profile of compound **6e** (rat β_3 EC_{50} = 6.5 ± 2.5 nM, E_{max} = 67.8 ± 4.2%) was further assessed by measuring carbohydrate and fat utilization in diet-induced obese Long Evans rats by indirect calo-

rimetry, measuring respiratory quotient over a 24-h period.[20] A single oral dose of this compound induced a decrease in respiratory quotient as well as an increase in energy expenditure (Table 3). Food consumption was lower in both treated groups but only statistically significant in the higher 10 mg/kg dose group. Despite this encouraging data, this compound was shown to only have an oral bioavailability of 10% and further optimization to improve the in vivo properties of these molecules will be reported in due course.

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