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Design and synthesis of selective α_{1B} adrenoceptor antagonists

Ryoji Hayashi,* Eiji Ohmori, Masafumi Isogaya, Mitsuhiro Moriwaki and Hiroki Kumagai

Pharmaceutical Research Laboratories, Toray Industries, Inc., 1111 Tebiro, Kamakura, Kanagawa 248-8555, Japan

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Abstract—A series of novel indolylpiperidine derivatives were synthesized and assessed for their pharmacological profiles at α_1 adrenoceptor subtypes by in vitro binding studies at rat α_{1A} and α_{1B} receptors. Compound **11** was a potent (K_i = 0.63 nM) and selective (approximately 30-fold more selective for the α_{1B} receptor than for the α_{1A} receptor) α_{1B} adrenoceptor antagonist.

The existence of multiple adrenoceptors has been firmly established and the receptors have been classified as follows: α_1 (α_{1A}, α_{1B}, α_{1D}), α_2 (α_{2A}, α_{2B}, α_{2C}), β_1, β_2, and β_3.[1] Of these adrenoceptors, the α_1 receptor has received much attention as a target for the treatment of hypertension or benign prostatic hyperplasia (BPH).

Each of the α_1 receptor subtypes is considered to exhibit pharmacological and tissue specificities. It is very important to provide compounds that are selective for each of the α_1 receptor subtypes in order to elucidate the physiological activities mediated by them and treat the diseases in which they are involved.

Presently, prazosin is widely used as a therapeutic agent for hypertension and has already been known to exhibit no selectivity for the α_1 receptor subtypes.

Subsequently, a multiplicity of compounds have been synthetically obtained; for example, 5-methylurapidil and KMD-3213 have been developed as compounds that have a high selectivity for the α_{1A} receptor.[2,3] Experiments that used these compounds suggested that the α_{1A} receptor is deeply involved in urethral smooth muscle contraction.[4]

In contrast, a large number of compounds show high affinity for the α_{1B} receptor and consequently poor selectivity.[5] Therefore, the physiological roles of the α_{1B} receptor remain undefined. However, recent experiments using α_{1B} transgenic mice have suggested that the α_{1B} receptor is involved in cardiac hypertrophy and neurodegeneration.[6,7] In addition, experiments using α_{1B} receptor knockout mice have suggested that the α_{1B} receptor is involved in vasopressor responses.[8] These findings have resulted in an intensive effort to develop selective α_{1B} receptor antagonists.

Some quinazoline derivatives have been discovered as selective α_{1B} adrenoceptor antagonists, for example, cyclazosin and the Merck compound.[9,10] However, we tried to use other structural motifs for designing potent and selective α_{1B} adrenoceptor antagonists. Our starting point for this investigation was risperidone, a well-known D_2 antagonist.[11] Risperidone also displays a high affinity for α_1 adrenoceptors and was 120-fold more selective for the α_{1B} receptor than for the α_{1A} receptor.[12] Our strategy was to create novel α_{1B} adrenoceptor antagonists by simplifying the structure of risperidone to obtain a lead compound and then carry out a variety of structural modifications of this lead compound.

First, compound **1** was designed by a method used to simplify risperidone, as illustrated in Scheme 1.

Compound **1** was prepared from the corresponding piperidine by N-alkylation with 3-chloropropyl-piperidine (Scheme 2). [13] Compound **1** displayed moderate binding affinity for the α_1 receptors and slight selectivity for the α_{1B} receptor in comparison with the α_{1A} receptor. Hence, we regarded compound **1** as a promising lead compound.

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* Corresponding author. E-mail: ryoji_hayashi2@nts.toray.co.jp

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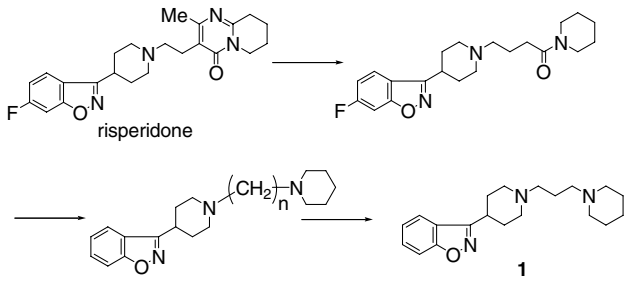
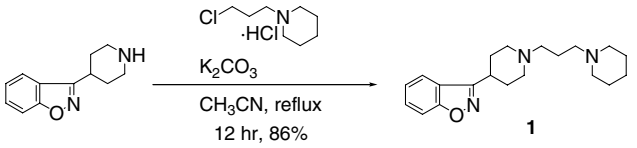


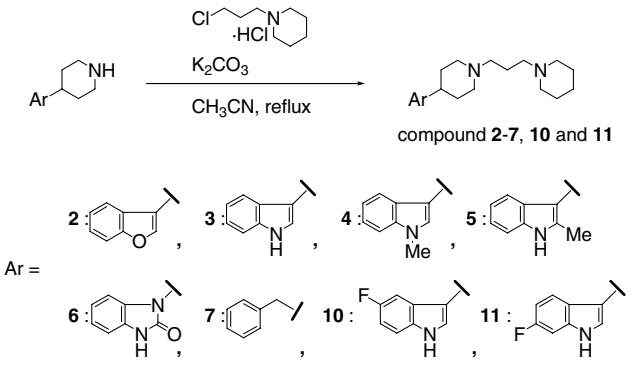
Scheme 1.



Scheme 2.

Then, the benzo[*d*]isoxazole moiety of compound **1** was replaced with other aryl moieties. Compounds **2**–**7**, **10**, and **11** were prepared in the same manner (Scheme 3).[14]

The obtained compounds were converted into the corresponding dihydrochloride salts for pharmacological tests. These synthetic compounds were evaluated for their binding affinity to the α_{1A} receptor and α_{1B} receptor using radioligand binding assays (Table 1). The specific ligands and tissue sources used were as



Scheme 3.

Table 1. Binding affinities of compounds **1**–**11** and prazosin

Compound	K_i[a] (nM) α_{1A} (rat)	K_i[a] (nM) α_{1B} (rat)	α_{1B} ratio[b]
1	57	14	4.0
2	60	7.7	7.8
3	120	3.0	40
4	480	60	8.0
5	1900	71	27
6	900	70	13
7	nt	1120	
8	56	1.1	51
9	57	1.5	38
10	690	16	43
11	21	0.63	33
Prazosin	0.23	0.10	2.3

[a] Values are means of two experiments (nt, not tested).
[b] α_{1B} selectivity (α_{1A} K_i/α_{1B} K_i).

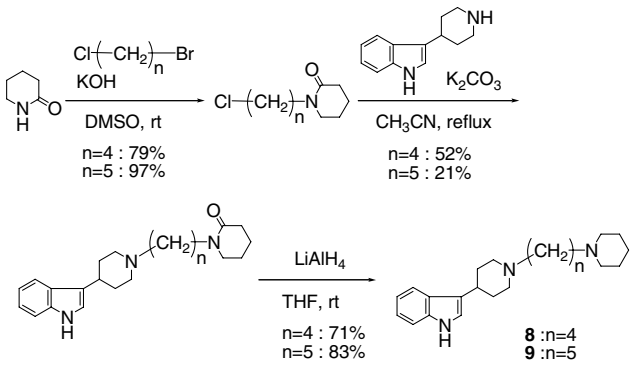
follows: α_{1A} receptor, [^{3}H]prazosin and rat submaxillary gland membranes; α_{1B}, [^{3}H]prazosin and rat liver membranes. Compounds **1**–**6** that have a fused benzene ring system as an aryl moiety showed moderate or high affinity for the α_{1B} receptor (K_i < 100 nM). In particular, the indole derivative, that is, compound **3**, was a potent and selective ligand (K_i = 3.0 nM, 40-fold more selective for the α_{1B} receptor than for the α_{1A} receptor). The hydrogen-donating ability of indole may contribute to an improvement in the α_{1B} receptor selectivity because compound **3** was more selective for the α_{1B} receptor than compound **2**. This hypothesis could explain why compounds **5** and **6** were more selective for the α_{1B} receptor than compounds **1**, **2**, and **4**. Compounds **4**, **5**, and **6** were less potent for the α_{1B} receptor than compound **3**. It was speculated that a steric hindrance at 1- or 2- position of indole was unfavorable for the binding of the α_{1B} receptor.

Subsequently, we focused our attention on further modification of the indole derivative **3**. We first determined the optimal alkylene chain length between two piperidine rings. The target compounds were prepared as shown in Scheme 4.

Elongation of the carbon chain by one or two carbons had desirable effect on the affinity for the α_{1B} receptor (compounds **8** and **9** vs **3**). Fluorine was then introduced in the indole moiety as in risperidone. Though the potency of the 5-fluoro derivative for the α_{1A} and α_{1B} receptors was reduced, the 6-fluoro derivative, that is, compound **11**, exhibited the highest affinity (K_i = 0.63 nM) for the α_{1B} receptor in the synthesized compounds and good selectivity (approximately 30-fold more selective for the α_{1B} receptor than for the α_{1A} receptor) for the α_{1B} receptor.

Table 2 shows the binding affinities of representative compounds for the other adrenoceptors. These compounds have moderate affinity for the α receptors and poor affinity for the β receptors. The binding affinities in Tables 1 and 2 suggest that our indolylpiperidine derivatives are selective α_{1B} receptor ligands.

In addition, the compounds in Table 1 were regarded as α_{1B} adrenoceptor antagonists because they inhibited norepinephrine-induced contraction of the dog carotid artery.[15]



Scheme 4.

Table 2. Binding affinities of representative compounds for the other adrenoceptors[a]

Compound	K_i[b] (nM) α_{1D} (human)	K_i[b] (nM) α_2 non-selective (rat)	K_i[b] (nM) β non-selective (rat)
3	69	370	>1000
9	37	355	>1000
11	22	140	>1000

[a] These assays were performed by MDS Pharma Services.
[b] Values are means of two experiments.

In conclusion, we successfully designed a new class of α_{1B} adrenoceptor antagonists bearing an indolylpiperidine structure. In particular, among the compounds synthesized in this study, compound **11** exhibited the highest affinity ($K_i = 0.63$ nM) and a good selectivity (approximately 30-fold more selective for the α_{1B} receptor than for the α_{1A} receptor) for the α_{1B} receptor. A more extensive study on the structure–activity relationship of the indolylpiperidine derivatives is in progress and will be reported in the future.

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14. All compounds were fully characterized by spectral methods. Representative data of compound **11** (free base); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44–1.45 (2H, m), 1.56–1.63 (4H, m), 1.74–1.86 (4H, m), 2.02–2.14 (4H, m), 2.31–2.42 (6H, m), 2.76–2.83 (1H, m), 3.04–3.08 (2H, br d), 6.87 (1H, ddd, $J = 2.2$, 8.7, 9.6 Hz), 6.95 (1H, d, $J = 1.6$ Hz), 7.03 (1H, dd, $J = 2.2$, 9.6 Hz), 7.54 (1H, dd, $J = 5.5$, 8.7 Hz), 7.91–8.01 (1H, br s); EI-MS *m/z*: 343 $[MH]^+$.
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