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Cyclic Imides as Potent and Selective α-1A Adrenergic Receptor Antagonists

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Abstract—We disclose a new compound class of potent and selective α-1A adrenergic receptor antagonists exemplified by the geminally, disubstituted cyclic imide **7**. The optimization of lead compounds resulting in the cyclic imide motif is highlighted. The results of in vitro and in vivo studies of selected compounds are presented.

Benign prostatic hyperplasia (BPH) is a pathological disorder in men that develops in response to the action of dihydrotestosterone on the aging prostate gland.[1] It is a disease that causes voiding difficulties and impacts the quality of life. One contributory component to the origin of symptoms is the contraction of smooth muscles under α-1 adrenergic receptor-mediated sympathetic stimulation.[2] Among the three α-1 receptor subtypes (α-1A, α-1B, and α-1D), it is the α-1A receptor that is chiefly responsible for the contractile tone of the prostatic urethra.[3–6] This has led to an intensive effort to develop uroselective α-1A adrenergic receptor antagonists with the expectation that such agents would have the potential to offer an improved side-effect profile compared to currently available drugs.[7,8]

The starting point for this investigation was the phenyl acetamide **1**, which we had previously shown to be a useful structural motif for designing potent and selective, low molecular weight α-1A adrenergic receptor antagonists.[9] We supposed that the physicochemical properties of **1** and its congeners, as well as their pharmacokinetic (PK) properties, might be improved by incorporating structural features that altered their log P and also imparted more rigidity. The concept was to modify previously identified regions of the phenyl acetamides that had the highest potential to impact α-1A receptor binding potency and metabolic stability. Our findings are disclosed herein.

The requisite 4-aryl piperidines were synthesized employing a bis-alkylation reaction between benzylnitrile **11** and *N*-Boc-bis-chloroethylamine **12** (Scheme 1).[10] Deprotection, alkylation, and a subsequent deprotection completed the assembly of intermediate **13**. The corresponding 4-carboxymethyl piperidines were obtained by hydrolyzing the initial 4-cyanopiperidine alkylation product, followed by esterification of the resulting carboxylic acid. The condensation of amine **13** with the diphenylacetic acid **14** was carried out in the standard way utilizing a soluble carbodiimide reagent. The conversion of **5** to **6** was effected with *p*-nitrophenyl chloroformate and sodium hydride; thus, acylation at ambient temperature was followed by ring formation, which was induced by heating the mixture of intermediates.

The cyclic imides were prepared according to the general route outlined in Scheme 2. Ditolylacetic acid was converted to the half-acid ester **15** in the following three-step operation: (1) esterification, (2) α-alkylation, and (3) debenzylation via catalytic hydrogenation.

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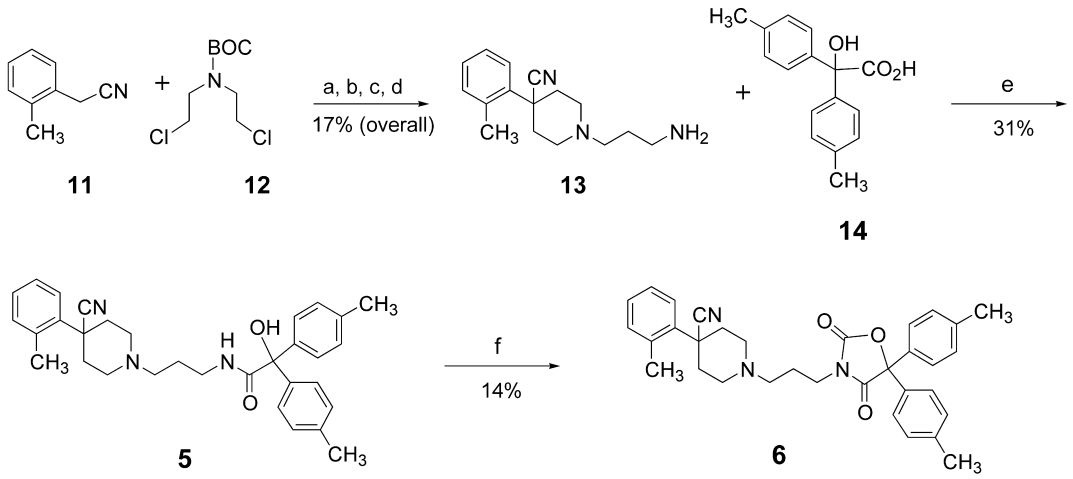
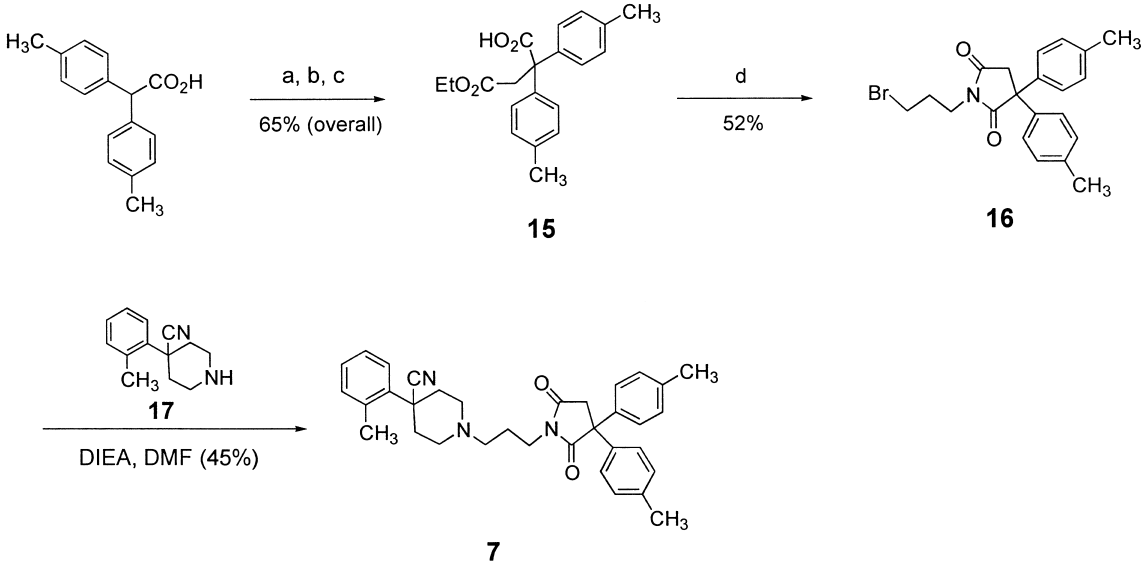
Reaction of 3-bromopropylamine with **15** yielded the intermediate amide-ester, which spontaneously cyclized to give imide **16**. Standard *N*-alkylation of 4-(2-methylphenyl)-4-cyanopiperidine **17** or its 2-chloro analogue **18** with bromide **16** delivered **7** and **8**, respectively. The latter compound was transformed to the thioimide **10** with Lawesson's reagent. The half-acid ester **15** was converted to the amide-ester and heated to provide the corresponding imide. This material was reacted with epichlorohydrin to give the epoxide, which served as substrate for the alkylation with **17** to provide compound **9**.

The binding affinity of synthetic compounds to human α-1 receptors was measured utilizing cloned receptor binding assays (Table 1).[4] These data are provided in Table 1.

We have previously shown that phenylacetamides, exemplified by compound **1**, are potent and selective α-1A receptor antagonists.[9] It was further determined that diphenylacetamide analogues displayed improved binding affinities for all α-1 receptor subtypes (cf. **2**). Functional group manipulation of **2** to give **3** led to further potency gains. While this trend was encouraging, representative compounds in this structural series showed poor pharmacokinetic (PK) properties (rat and dog: F $<10\%$; $t_{1/2}<1$ h; $C_{max}<100$ nM). We reasoned that one plausible explanation for these properties was facile metabolism and the rapid clearance of these compounds. A probable locus of metabolism in the diphenylacetamide structure is the benzylic position.[11] This prompted the preparation of **4** and the more potent homologue **5**. Although the α-1a receptor binding affinity of the latter compound was improved relative to its precursors, its PK properties remained poor (Table 2). Our next strategy was to reduce the number of hydrogen bond donating groups in **5** and to simultaneously bias the conformation of the diphenylacetamide fragment by forming an oxazolidinedione ring. This led to **6** and a reduction in α-1a receptor binding affinity. However, the exchange of oxygen in the oxazolidine ring

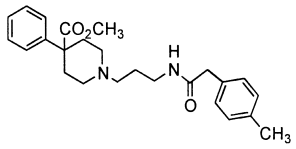
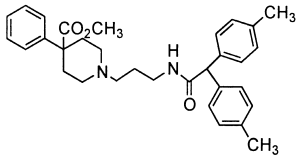
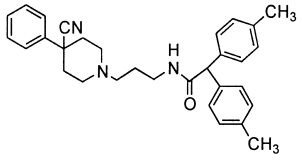
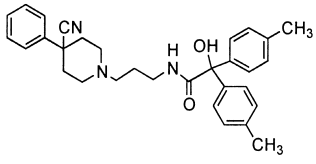
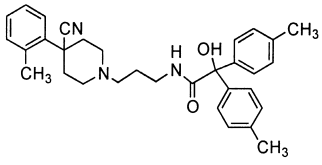
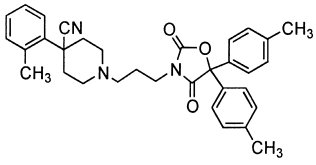
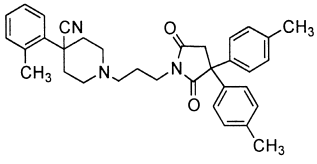
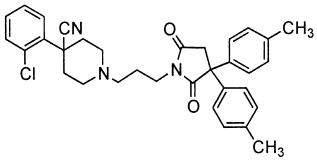
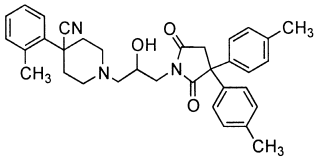
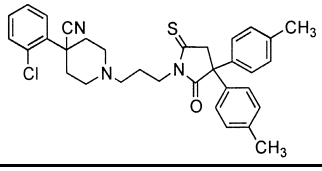


Scheme 1. (a) NaH, DMF, 60 °C or Cs_2CO_3, DMSO; (b) HCl (g), EtOAc, 0 °C; (c) $Br(CH_2)_3NHBOC$, DMF, NEt_3, 23 °C; (d) HCl (g), EtOAc, 0 °C; (e) EDC, HOBt, DIEA, DMF, 23 °C; (f) 4-nitrophenylchloroformate, NaH, THF, 65 °C.



Scheme 2. (a) BnBr, K_2CO_3, DMF, 23 °C; (b) LHMDS, $BrCH_2CO_2Et$; (c) H_2, 10% Pd/C, EtOH; (d) $Br(CH_2)_3NH_2$, EDC, HBT, $NaHCO_3$, DMF.

Table 1.

		K_i (nM)[a]		
		α-1a	α-1b	α-1d
1		74	>3000	3400
2		17	170	975
3		7.3	>2000	1400
4		5.7	1800	4800
5		2.0	570	1500
6		77	>2000	>5000
7		1.7	1900	1500
8		0.48	98	220
9		9.7	1500	4100
10		220	>2000	>5000

[a]All K_i values are calculated for competition binding assays (I ^{125}-HEAT) utilizing cloned human α-1 receptors and are the geometric mean of at least two experiments.

Table 2.

	Rat[a]		Dog[b]	
	F	$t_{1/2}$ (h)	F	$t_{1/2}$ (h)
5	<1	1.3	ND	ND
7	18	2.5	8	1.3
8	19	0.66	11	1.7

ND, not determined.
[a]Male Sprague–Dawley rats (0.2–0.25) kg were dosed with 1–3 mg/kg iv and 3–10 mg/kg po (3–4 animals). Plasma samples were analyzed from 0.08 to 24 h using LC–MS/MS quantification.
[b]Male beagle dogs (ca. 8 kg) were dosed with 1–3 mg/kg iv and 3–10 mg/kg po (2–3 animals). Plasma samples were analyzed by LC–MS/MS; computation of pharmacokinetic parameters was performed with the aid of TOPFIT software.

with methylene led to a dramatic change in the receptor binding profile. The resulting imide, **7**, showed excellent affinity for the α-1a receptor subtype with greater than 1000- and 880-fold selectivity for the α-1b and α-1d receptors, respectively. Additional α-1a receptor binding potency was gained by modifying the *ortho*-substituent on the 4-aryl ring of piperidine **8** (cf. **7** and **8**). Other structural modifications connected with the propyl chain linking unit [e.g., incorporation of OH for solubility, (**9**)] and the imide carbonyl groups (**10**) proved detrimental to α-1a receptor binding affinity relative to **7** and **8**.

Three key compounds, **5**, **7**, and **8**, were dosed in rats (1 mg/kg, iv and 3 mg/kg, po) and dogs (3 mg/kg, iv and 10 mg/kg, po). Plasma levels were measured by LC–MS from 0.3 to 6 h in rats and from 1 to 24 h in dogs. Selected PK data are collated in Table 2, from which it is evident that the pharmacokinetic profiles of these analogues were modestly improved compared to the precursor phenylacetamides (vide supra).

We successfully designed a series of potent, cyclic imide α-1A receptor antagonists exemplified by compounds **7** and **8**. Analogue **7** shows greater than 1100- and 880-fold selectivity versus the α-1b and α-1d receptor subtypes. This compound also displayed >100-fold selectivity against other G-protein coupled receptors (α-2a, α-2b, α-2c, dopamine-1, -2, -3, -5, H-1, H-2, and 5HT-1a) tested. Inroads were made in improving the pharmacokinetic properties of the prototype phenylacetamide α-1A antagonists by incorporating this structural motif in a cyclic imide scaffold.

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