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Novel Arylpiperazines as Selective α_1-Adrenergic Receptor Antagonists

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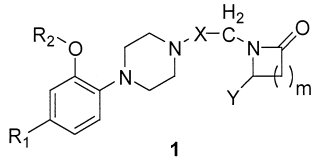
Abstract—A novel series of arylpiperazines has been synthesized and identified as antagonists of α_{1a} adrenergic receptor (α_{1a}-AR) implicated in benign prostatic hyperplasia. These compounds selectively bind to membrane bound α_{1a}-AR with K_is as low as 0.66 nM. As such, these potentially represent a viable treatment for BPH without the side effects associated with known α_1-adrenergic antagonists.

Benign prostatic hyperplasia (BPH), a nonmalignant enlargement of the prostate, is the most common benign tumor in men. There are two components of BPH, a static and a dynamic component. The static component is due to enlargement of the prostate gland, which may result in compression of the urethra and obstruction to the flow of urine from the bladder. The dynamic component is due to increased smooth muscle tone of the bladder neck and the prostate itself (which interferes with emptying of the bladder) and is regulated by alpha 1 adrenergic receptors (α_1-ARs). The medical treatments available for BPH address these components to varying degrees, and the therapeutic choices are expanding.

The use of α_1-AR antagonists in the treatment of BPH is related to their ability to decrease the tone of prostatic smooth muscle, leading to relief of the obstructive symptoms. Adrenergic receptors are found throughout the body and play a dominant role in the control of blood pressure, nasal congestion, prostate function and other processes.[1] There are a number of cloned α_1-AR receptor subtypes: α_{1a}-, α_{1b}-, and α_{1d}-AR.[2] It has been shown that the α_{1a}-AR subtype comprises the majority of α_1-ARs in human prostatic smooth muscle and mediates contraction in this tissue. These findings suggest that the development of a subtype-selective α_{1a}-AR antagonist might result in a therapeutically effective agent with reduced side effects, such as orthostatic hypotension, for the treatment of BPH.

Herein we report on a series of substituted arylpiperazines **1** that are effective as antagonists of α_{1a}-AR.



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The general structure **1** requires the assembly of arylpiperazine **2** with the lactam derivative **5** through a linker (Schemes 1 and 2).

Amine **3** was synthesized in two steps in 76% yield by the alkylation of piperazine nitrogen with either Boc-protected bromoalkylamine or bromoalkyl-phthalimide in the presence of potassium carbonate in acetonitrile. The Boc group was removed by treatment with trifluoroacetic acid in dichloromethane, while phthalimide group was cleaved with methylhydrazine in ethanol. Acid **5** was prepared in two steps (92% yield) by alkylation of compound **4** with *tert*-butyl bromoacetate in the presence of sodium hydride in toluene. The *tert*-butyl group was removed with trifluoroacetic acid in dichloromethane. Compound **3** was then coupled with **5** by standard peptide coupling conditions using EDCI/HOBt in the presence of DMAP in dichloromethane affording compound **1(b–h)** in 35–78% yield (Table 1).[3] Compound **1a** was prepared by alkylation of **1c** with iodomethane in the presence of sodium hydride in THF (Scheme 2).

Compound **8** was synthesized in a similar fashion (Scheme 3). Amine **2** was alkylated in 92% yield by bromoethanol in the presence of potassium carbonate in acetonitrile affording alcohol **6**. Acid chloride **7** was prepared by treatment of acid **5** with oxalyl chloride in

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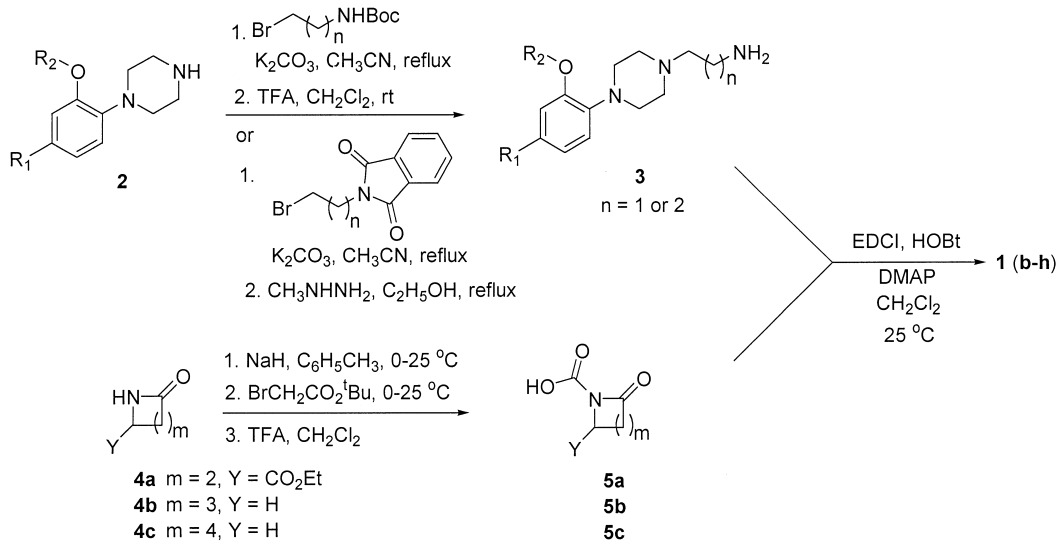
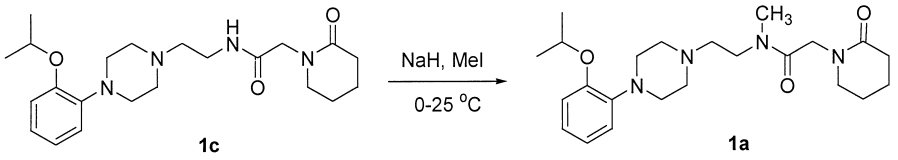


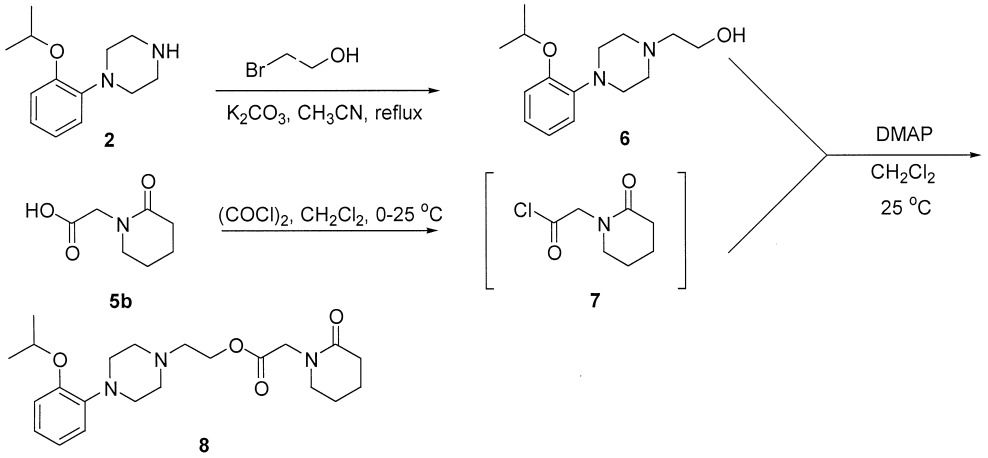
Scheme 1.



Scheme 2.

Table 1.

Compd	R_1	R_2	X	Y	m	K_i			**1b/1a**	**1d/1a**	pA_2
						a_{1a}	a_{1b}	a_{1d}			
1a	H	*i*-Pr	$C_2H_4N(CH_3)CO$	H	3	53	10,000	650	187	12	
1b	H	Me	$(CH_2)_3NHCO$	H	3	98	10,000	10,000	102	102	
1c	H	*i*-Pr	C_2H_4NHCO	H	3	8.7	46,120	372	5301	43	7.50
1d	H	*i*-Pr	C_2H_4NHCO	CO_2Et	2	20	26,310	260	1315	13	7.79
1e	H	*i*-Pr	C_2H_4NHCO	H	4	18	3536	505	196	28	6.69
1f	F	*i*-Pr	C_2H_4NHCO	H	3	83	10,000	4500	120	54	
1g	F	CH_2CF_3	C_2H_4NHCO	H	3	129	10,000	5350	77	41	
1h	H	*i*-Pr	$(CH_2)_3NHCO$	H	3	0.66	10,000	80	15,152	121	
8	H	*i*-Pr	$(CH_2)_2OCO$	H	3	38	2244	108	59	3	
11	H	*i*-Pr	CH_2COCH_2CO	H	3	417	10,000	6043	24	14	
14	H	*i*-Pr	$CH_2CH(OH)CH_2CO$	H	3	28	10,000	253	556	9	
15	H	*i*-Pr	$CH_2CHCHCO$	H	3	18	5316	602	295	33	



Scheme 3.

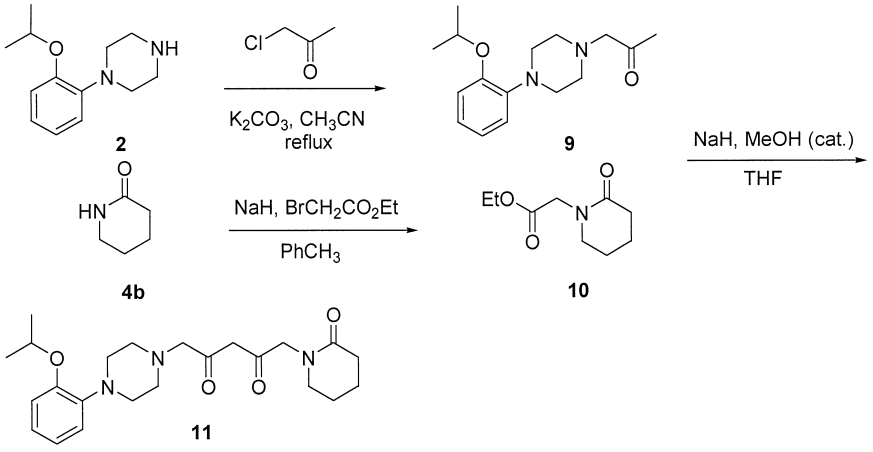
dichloromethane and it was used without further purification. Reaction of compounds **6** and **7** in the presence of base such as DMAP or TEA in dichloromethane provided the desired product **8** in 88% yield.

The preparation of compound **11** is illustrated in Scheme 4. When amine **2** was treated with chloroacetone in the presence of potassium carbonate, compound **9** was obtained in 98% yield. It was then condensed with ester **10** using sodium hydride as base in the presence of catalytic amount of methanol in THF providing dione **11** in quantitative yield.

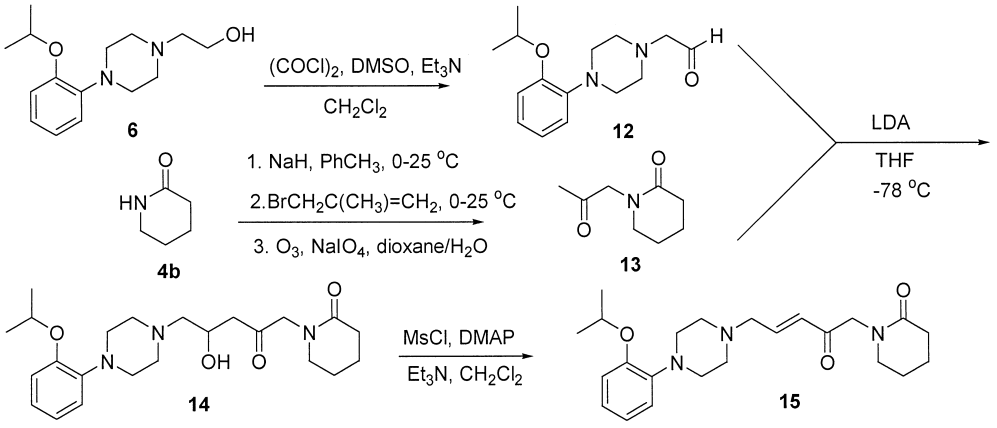
Compounds **14** and **15** were derived from an aldol condensation (Scheme 5). Alcohol **6** was oxidized to the corresponding aldehyde **12** in quantitative yield using standard Swern conditions.[4] This aldehyde was unstable and used without further purification. Ketone **13** was synthesized in 2 steps in 85% overall yield from lactam **4** by firstly *N*-alkylation with 3-bromo-2-methylpropene using sodium hydride as base in dry toluene followed by oxidation with osmium tetroxide and sodium periodate in dioxane–water mixed solvent. Aldol condensation of **12** and **13** was achieved by treatment of **13** with LDA in THF at −78 °C for 30 min followed by addition of a solution of aldehyde **12** in THF affording β-hydroxy ketone derivative **14** in only 6% yield. No simultaneous elimination was observed; however, upon treatment with mesyl chloride in the presence of triethylamine in dichloromethane, compound **14** was easily converted to α,β-unsaturated ketone **15** in 32% yield.

The biological data of selected compounds are outlined in Table 1.[5] K_i data expressed in nanomolar concentration (nM) are determined by a radioligand binding assay which tested the binding affinity of these compounds to COS cell membranes expressing the human adrenergic receptor subtypes: α_{1a}-AR, α_{1b}-AR, and α_{1d}-AR. The pA_2 data is generated by evaluation of tissue contractions in isolated rat prostatic tissue strips (Panlabs, Inc.). The difference in proportionality between K_i and pA_2 could simply be a distribution or solubility effect due to one being a binding assay and the other a biological tissue prep.

A number of the compounds discussed are highly potent and selective antagonists of the α_{1a}-AR. It appears that potency and selectivity are optimal when R_2 is an isopropyl group. Compounds **11** and **14** were synthesized to introduce polarity into the chain to potentially enhance bioavailability and change the metabolic profile. Compound **15** was made to rigidify the chain. Furthermore, compound **1h** is thirteen times more potent than its analogue **1c**, which has a shorter carbon linker.



Scheme 4.



Scheme 5.

While some of the comparators and currently marketed tamsulosin/Flomax® show greater absolute affinity for all α1-AR subtypes, none are as selective as compounds **1c** and **1h**. Expanded biological profiling of key activities is presently underway.

Acknowledgement

We wish to thank Dr. Gee-Hong Kuo for helpful discussions.

References and Notes

1. Harrison, J. K.; Pearson, W. R.; Lynch, K. R. *Trends Pharmacol. Sci.* **1991**, *12*, 62.
2. Goetz, A. S.; King, H. K.; Ward, S. D.; True, T. A.; Rimele, T. J.; Saussy, D. L., Jr. *Eur. J. Pharmacol.* **1995**, *272*, R5.
3. General procedure for the synthesis of compounds **1b**–**h**: **Compound 3c**: A mixture of 2-isopropoxyphenylpiperazine (**2a**, 6.6 g, 30 mmol), *N*-(2-bromoethyl)-phthalimide (7.6 g, 30 mmol) and potasssium carbonate (6.2 g, 45 mmol) in acetonitrile (100 mL) was allowed to heat at reflux overnight (ca. 12 h). The reaction mixture was cooled to room temperature, the precipitate was filtered off and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel using 30% ethyl acetate/hexanes as eluent afforded the desired product as a light-yellow solid (9.0 g, 23 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.71 (m, 2H), 6.89 (m, 4H), 4.59 (m, 1H), 3.87 (t, $J=6.7$ Hz, 2H), 3.05 (bs, 4H), 2.70 (2t, $J=6.6$ Hz, 6H), 1.34 (d, $J=6.0$ Hz, 6H). MS *m*/*z* (MH+) 394.

The light-yellow solid (7.5 g, 19 mmol) was then dissolved in warm ethanol (70.0 mL), methyl hydrazine (20.0 mL) was added and the reaction mixture was allowed to heat at reflux for 3 h. It was then cooled to room temperature and concentrated in vacuo affording the desired crude product **3c** as an oil (5.0 g. 19 mmol, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 4.60 (m, 1H), 3.12 (bs, 4H), 2.86 (t, $J=6.2$ Hz, 2H), 2.64 (bs, 4H), 2.51 (t, $J=6.2$ Hz, 2H), 2.31 (bs, 2H), 1.34 (d, $J=6.1$ Hz, 6H). MS *m*/*z* (MH+) 264.

Compound 5b: To a solution of δ-Valerolactam **4b** (6.1g, 61 mmol) in 100 mL toluene at 0 °C under N_2 was added NaH (95% tech, 1.7 g, 71 mmol) and the resulting suspension was stirred for 1 h. *tert*-Butyl-bromoacetate (9.5 mL, 64 mmol) was added slowly and the reaction mixture was warmed to room temperature. After 10 h saturated ammonium chloride solution was added and the organic layer was separated. It was washed with brine (3×) and water, dried over sodium sulfate, filtered and concentrated to give a colorless oil (13.0 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 2H), 3.34 (t, $J=5.9$ Hz, 2H), 2.42 (m, 2H), 1.85 (m, 4H), 1.47 (s, 9H). MS *m*/*z* (MH+) 214.

The oil (13.0 g, 61 mmol) was dissolved in methylene chloride (40 mL) followed by addition of trifluoroacetic acid (20 mL) and the reaction mixture was stirred under nitrogen for 4 h. Volatiles were removed in vacuo affording 8.8 g of **5b** as light-brown oil in 92% yield. This oil is used without further purification. ^{1}H NMR (300 MHz, CD_3OD) δ 4.08 (s, 2H), 3.40 (t, $J=5.7$ Hz, 2H), 2.38 (t, $J=5.7$ Hz, 2H), 1.85 (m, 4H). MS *m*/*z* (MH+) 158.

Compound 1c: A mixture of acid **5** (4.2 g, 27 mmol), amine **3c** (7.1 g, 27 mmol), EDCI (5.6 g, 30 mmol), HOBt (4.0 g, 30 mmol) and DMAP (0.3 g, 1.5 mmol) in dichloromethane (100 mL) was allowed to stir at room temperature under nitrogen atmosphere overnight. Saturated aqueous solution of potassium carbonate was added and the organic layer was separated. It was then washed with water (×3), dried (over sodium sulfate), filtered, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluting with 2–3% MeOH in CH_2Cl_2 providing the title compound in 78% yield as a white solid (8.4 g, 21 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89 (m, 4H), 6.68 (bs, 1H), 4.58 (m, 1H), 4.01 (s, 2H), 3.38 (m, 4H), 3.10 (bs, 4H), 2.63 (bs, 4H), 2.54 (t, $J=6.1$ Hz, 2H), 2.43 (m, 2H), 1.82 (m, 4H), 1.33 (d, $J=6.1$ Hz, 6H). MS *m*/*z* (MH+) 403.

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