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Novel Heterocycles as Selective α_1-Adrenergic Receptor Antagonists

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Abstract—A novel series of aryl piperazine substituted heterocycles has been synthesized and identified as antagonists of the α_{1a}-adrenergic receptor (α_{1a}-AR), which has been implicated in benign prostatic hyperplasia (BPH). These compounds selectively inhibit binding to the α_{1a}-AR with K_is as low as 2.1 nM. © 2000 Elsevier Science Ltd. All rights reserved.

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 α_1-adrenergic receptors (α_1-ARs). The medical treatments available for BPH address these components to varying degrees, and 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-AR mRNAs and expressed protein in human prostatic smooth muscle and mediates contraction in this tissue.[3–7] 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.[8,9]

Herein we report on a novel heterocyclic series of substituted arylpiperazines (Fig. 1) that selectively bind to the α_{1a}-AR receptor.

The compounds of Figure 1, when A is pyrazole or substituted pyrazole derivatives may be prepared according to Scheme 1; Scheme 2 illustrates those compounds when A is 2-aminopyrinidine, and Scheme 3 when A is isoxazole or isoxazoline.

We have previously reported the synthesis of dione **5**,[10] in which compound **1** reacts with chloroacetone at a reflux temperature in the presence of potassium carbon-

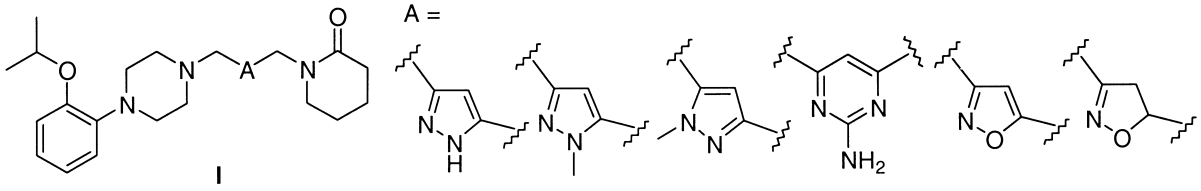

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Figure 1.

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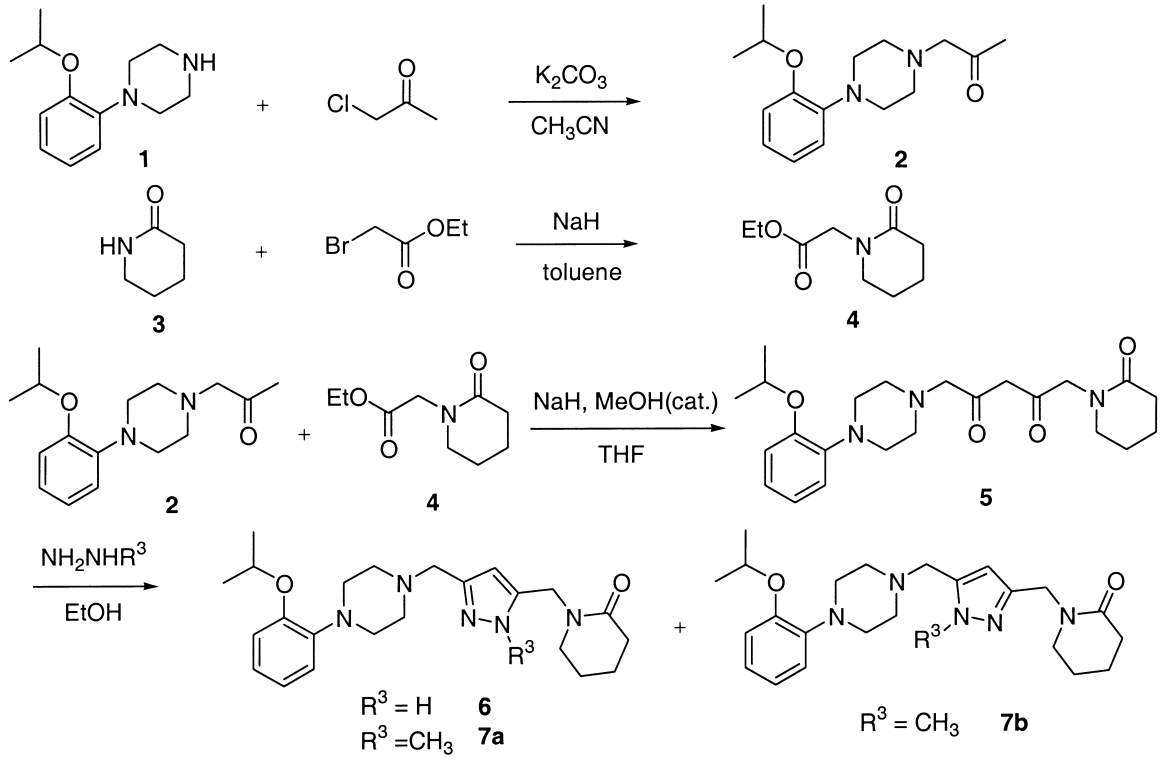
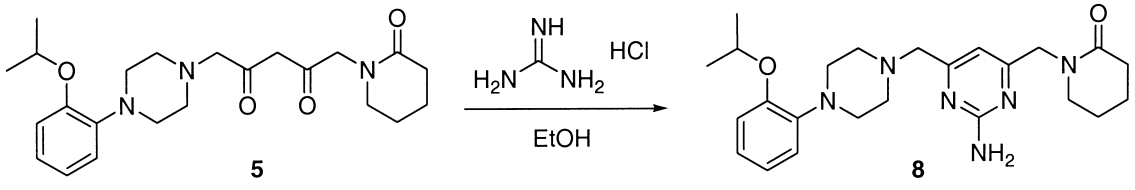
ate in acetonitrile affording compound **2**, which is condensed with ester **4** using sodium hydride as base. A catalytic amount of methanol is crucial in this condensation reaction. Dione **5** is then treated with hydrazine or methylhydrazine at room temperature to give the pyrazole **6** or the methyl pyrazoles **7a** and **7b** (Scheme 1). The regiochemistry of **7a** and **7b** was confirmed by NOE studies.

Dione **5** may also be treated with guanidine hydrochloride in the presence of a weak base, such as sodium acetate, in ethanol at 50 °C to give the 2-aminopyrimidine derivative **8** (Scheme 2).

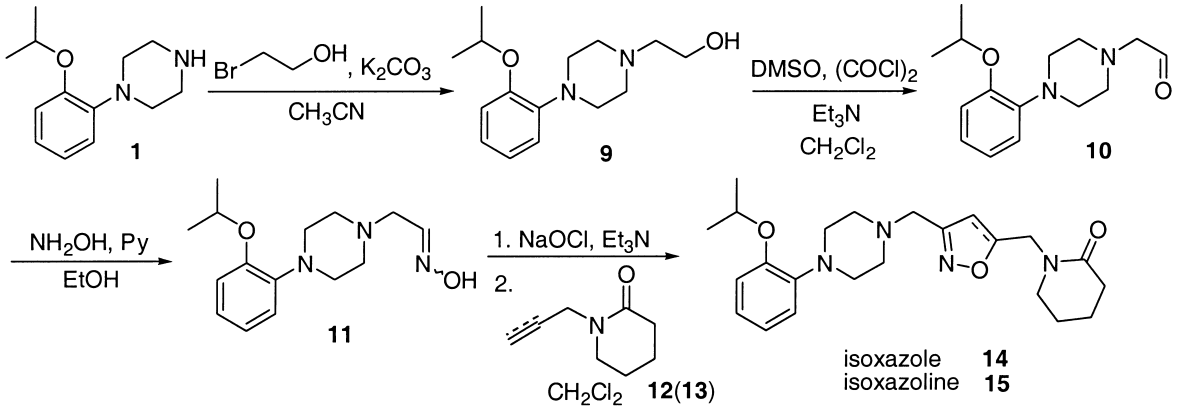
Scheme 3 illustrates the preparation of both isoxazole **14** and isoxazoline derivative **15**.[11,12] The strategy involves a 1,3-dipolar cycloaddition reaction of a nitrile oxide,



Scheme 1.



Scheme 2.



Scheme 3.

Table 1.

Compounds	K_i (nM)			Ratio (1b/1a)	Ratio (1d/1a)
	α_{1a}	α_{1b}	α_{1d}		
6	2.1	3915	177	1864	84
7a	3.7	3080	52	832	14
7b	9	2770	44	308	5
8	79	>10,000	>10,000	>127	>127
14	3.8	4456	272	1172	72
15	89	>10,000	1517	>112	17

generated in situ from the corresponding oxime **11**, with an alkyne or an alkene derivative. Treatment of compound **1** with bromoethanol and potassium carbonate at a reflux temperature in acetonitrile gives the alcohol **9** in quantitative yield. The alcohol is oxidized under Swern oxidation conditions affording the corresponding aldehyde **10**.[11,13] Subsequent treatment of **10** with hydroxylamine hydrochloride in the presence of pyridine in ethanol at room temperature gives the oxime **11** in good yield. Reaction of oxime **11** with *N*-propargyl-δ-valerolactam **12** or *N*-allyl-δ-valerolactam **13**, aqueous NaOCl and triethylamine in dichloromethane at room temperature gives the isoxazole **14** or isoxazoline **15** exclusively in moderate yield.

The biological data[14] of selected compounds[15] can be seen in Table 1. 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}-, α_{1b}-, and α_{1d}-AR.[14]

Radioligand binding studies showed that a number of the compounds discussed have significantly higher affinity for the α_{1a}-AR subtype than for the α_{1b}-AR or α_{1d}-AR subtype and displayed a higher level of receptor selectivity than some of the comparators and currently marketed tamsulosin (Flomax®). Some of these compounds were more potent in inhibiting (±)-norepinephrine-induced contractions of isolated rat prostate tissue than those of isolated rat aorta tissue, whereas tamsulosin had the reversed tissue selectivity.[14] Pyrazole derivative **6** shows the best potency and selectivity among this series of heterocyclic compounds. Expanded biological profiling of key active compounds is underway.

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. Faure, C.; Pimoule, C.; Vallancien, G.; Langer, S. Z.; Graham, D. *Life Sci.* **1994**, *54*, 1595.
4. Schwinn, D. A.; Kwatra, M. M. *Adv. Pharmacol.* **1998**, *42*, 390.
5. Lepor, H.; Tang, R.; Kobayashi, S.; Sharpiro, E.; Forray, C.; Wetzel, J. M.; Gluchowski, C. *J. Urol.* **1995**, *154*, 2096.
6. Michel, M. C.; Grubbel, B.; Taguchi, K.; Verfurth, F.; Otto, T.; Kropfl, D. *J. Auton Pharmacol.* **1996**, *16*, 21.
7. Price, D. T.; Schwinn, D. A.; Lomasney, J. W.; Allen, L. F.; Caron, M. G.; Lefkowitz, R. J. *J. Urol.* **1993**, *150*, 546.
8. Brune, M. E.; Katwala, S. P.; Milicic, I.; Buckner, S. A.; Ireland, L. M.; Kerwin, J. F., Jr.; Hancock, A. A. *Pharmacology* **1996**, *53*, 356.
9. Kenny, B. A.; Miller, A. M.; Williamson, I. J. R.; O'Connell, J.; Chalmers, D. H.; Naylor, A. M. *Br. J. Pharmacol.* **1996**, *118*, 871.
10. Li, X.; Murray, W. V.; Jolliffe, L.; Pulito, V. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1093.
11. Gribble, A. D.; Dolle, R. E.; Shaw, A.; McNair, D.; Novelli, R.; Novelli, C. E.; Slingsby, B. P.; Shah, V. P.; Tew, D.; Saxty, B. A.; Allen, M.; Groot, P. H.; Pearce, N.; Yates, J. *J. Med. Chem.* **1996**, *39*, 3569.
12. Curran, D. P. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI: Greenwich, 1988; Vol. 1, pp 129–189.
13. Swern, D.; Mancuso, A. J.; Huang, S.-L. *J. Org. Chem.* **1978**, *43*, 2480.
14. Pulito, V. L.; Li, X.; Varga, S. S.; Mulcahy, L. S.; Clark, K. S.; Pekow, C. A.; Halbert, S. A.; Reitz, A. B.; Murray, W. V.; Jolliffe, L. K. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 224.

15. ^{1}H NMR and mass spectrum data for selected compounds: Compound **2** (yield 98%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 4.59 (m, 1H), 3.25 (s, 2H), 3.15 (bt, 4H), 2.67 (bt, 4H), 2.19 (s, 3H), 1.34 (d, 6H, J = 6.03 Hz). MS m/z 277 (MH+). **4** (yield 76%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (q, 2H, J = 7.22 Hz), 4.10 (s, 2H), 3.36 (m, 2H), 2.43 (m, 2H), 1.86 (m, 4H), 1.28 (t, 3H, J = 7.25 Hz). **5** (yield 100%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 4.59 (m, 1H), 4.26 & 4.18 (2s, 2H), 3.69 & 3.30 (2s, 2H), 3.35 (m, 2H), 3.20 (bs, 2H), 3.14 (bs, 4H), 2.69 (m, 4H), 2.46 (m, 2H), 1.86 (m, 4H), 1.34 (2d, 6H, J = 6.06 Hz). MS m/z 416 (MH+). **6** (yield 62%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 6.17 (s, 1H), 4.59 (m, 1H), 4.48 (s, 2H), 3.61 (s, 2H), 3.34 (m, 2H), 3.12 (bs, 4H), 2.67 (bs, 4H), 2.42 (m, 2H), 1.78 (m, 4H), 1.34 (d, 6H, J = 6.10 Hz). MS m/z 412 (MH+). **7a** (yield 40%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 6.18 (s, 1H), 4.64 (s, 2H), 4.59 (m, 1H), 3.83 (s, 3H), 3.57 (s, 2H), 3.22 (m, 2H), 3.14 (bs, 4H), 2.69 (bs, 4H), 2.43 (m, 2H), 1.79 (m, 4H), 1.34 (d, 6H, J = 6.02 Hz). MS m/z 426 (MH+). **7b** (yield 8%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 6.11 (s, 1H), 4.59 (m, 1H), 4.53 (s, 2H), 3.87 (s, 3H), 3.50 (s, 2H), 3.30 (m, 2H), 3.08 (bs, 4H), 2.59 (bs, 4H), 2.42 (m, 2H), 1.77 (m, 4H), 1.34 (d, 6H, J = 6.00 Hz). MS m/z 426 (MH+). **8** (yield 20%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 6.70 (s, 1H), 5.07 (bs, 2H), 4.59 (m, 1H), 4.50 (s, 2H), 3.48 (s, 2H), 3.34 (m, 2H), 3.14 (bs, 4H), 2.66 (bs, 4H), 2.49 (m, 2H), 1.85 (m, 4H), 1.34 (d, 6H, J = 6.06 Hz). MS m/z 439 (MH+). **9** (yield 92%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 4.59 (m, 1H), 3.68 (t, 2H, J = 5.43 Hz), 3.27 (bs, 1H), 3.12 (bs, 4H), 2.68 (bs, 4H), 2.60 (t, 2H, J = 5.40 Hz), 1.34 (d, 6H, J = 6.03 Hz). MS m/z 265 (MH+). **11** (yield 86% from **9**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (t, 1H, J = 6.06 Hz), 6.91 (m, 4H), 4.59 (m, 1H), 3.72 (dd, 1H, J = 7.02 Hz), 3.23 (d, 1H, J = 6.08 Hz), 3.15 (m, 6H), 2.73 (bs, 4H), 1.34 (d, 6H, J = 6.08 Hz). MS m/z 278 (MH+). **14** (yield 14%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 6.26 (s, 1H), 4.67 (s, 2H), 4.59 (m, 1H), 3.64 (s, 2H), 3.41 (t, 2H, J = 5.65 Hz), 3.12 (bs, 4H), 2.68 (bs, 4H), 2.43 (t, 2H, J = 5.65), 1.83 (m, 4H), 1.34 (d, 6H, J = 6.04 Hz). MS m/z 413 (MH+). **15** (yield 16%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 4.86 (m, 1H), 4.59 (m, 1H), 3.87 (dd, 1H, J = 3.33 Hz), 3.57 (m, 1H), 3.41 (m, 1H), 3.30 (s, 2H), 3.17 (m, 2H), 3.11 (bs, 4H), 2.84 (dd, 1H, J = 7.58 Hz), 2.63 (t, 4H, J = 3.28 Hz), 2.40 (m, 2H), 1.79 (m, 4H), 1.34 (d, 6H, J = 6.06 Hz). MS m/z 415 (MH+).