Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 2443–2446

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

# Arylpiperazine Substituted Heterocycles as Selective $\alpha_{1a}$ Adrenergic Antagonists

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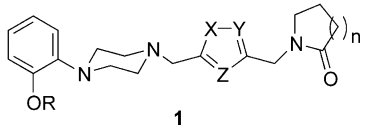
Received 10 December 2001; accepted 13 May 2002

**Abstract**—Antagonists of the $\alpha_1$-adrenergic receptors ($\alpha_1$-ARs) are useful for the treatment of benign prostatic hyperplasia. A series of potent and subtype-selective $\alpha_{1a}$-AR antagonists has been synthesized, displaying in vitro binding affinity in the low the nanomolar range. 

Benign prostatic hyperplasia (BPH) is characterized by nonmalignant enlargement of the prostate.[1] A number of urological symptoms are associated with it, including poor urine flow from the bladder, increased frequency in urination, nocturia and hesitancy or delay in starting urine flow. These symptoms of BPH result from a combination of two components. The mechanical constriction of the urethra is due to the increased prostatic mass. The dynamic component of BPH is regulated by $\alpha_1$ adrenergic receptors ($\alpha_1$-ARs), which cause increased smooth muscle tone in the bladder neck and prostate.

$\alpha_1$-ARs belong to the superfamily of membrane-bound G-protein coupled receptors (GPCRs), and stimulate predominantly phospholipase C-β, resulting in mobilization of $Ca^{2+}$ from intracellular stores, and ultimately, smooth muscle contraction.[2] $\alpha_1$-ARs are involved in the regulation of cardiovascular and central nervous systems (CNS).[3] The three native $\alpha_1$-AR subtypes ($\alpha_{1a}$, $\alpha_{1b}$, and $\alpha_{1d}$) have been cloned from a number of species, including human.[4] The use of selective $\alpha_1$-AR blockers is a potential therapeutic choice for the treatment of BPH.[1,5]

Several non-subtype selective $\alpha_1$-AR antagonists of the quinazoline class, such as prazosin, terazosin and doxazosin, have been approved for the treatment of BPH. These agents work by relaxing the smooth muscle of the prostate and other urinary tract tissues.[6] These non-subtype selective $\alpha_1$-antagonists have shown a greater incidence of side effects than those agents with improved $\alpha_{1a}$-AR selectivity.[7,8] Substantial efforts at designing $\alpha_{1a}$-AR antagonists have been shown.[9] In this report we wish to present a new series of potent and selective $\alpha_{1a}$-AR antagonists.




**1**

In a previous study,[10] we have shown that compound **1** (where R = O$^i$Pr, $X$ = S, $Y$ = $Z$ = CH, and $n$ = 2) is a potent and selective $\alpha_{1a}$-AR antagonist. We observed that the 1-(2-alkoxyaryl)piperazinyl unit was required for its binding affinity and selectivity, and 1-(2-isopropoxyphenyl)-piperazinyl moiety was optimal. We also decided to modify the thiophene ring to other five-membered heteroaromatic ring systems. (Formula **1** where $X$ = O, S; $Y$ = N, CH; $Z$ = CH, N).

In order to evaluate the effects of differing amide groups on $\alpha_1$-activity, we initially explored the isoxazole analogues (Scheme 1). Isoxazole **6**[11] was prepared by reaction of 1-(2-isopropoxyphenyl)-piperazine (**2**) with propargyl bromide to afford acetylene **4** which was submitted to

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0960-894X/02/$ - see front matter 
PII: S0960-894X(02)00436-5

[3 + 2]-dipolar cyclo-addition conditions followed by aqueous HCl treatment. Compound **6** was then reacted sequentially with excess $SOCl_2$ to generate the corresponding chloro derivative in the form of its HCl salt and lactam anions to furnish the *N*-alkylated products (**10a** and **10b**). Oxazoles **11a–c** was prepared from 1-(2-phenoxyphenyl)-piperazine[12] (**3**) in a similar fashion.

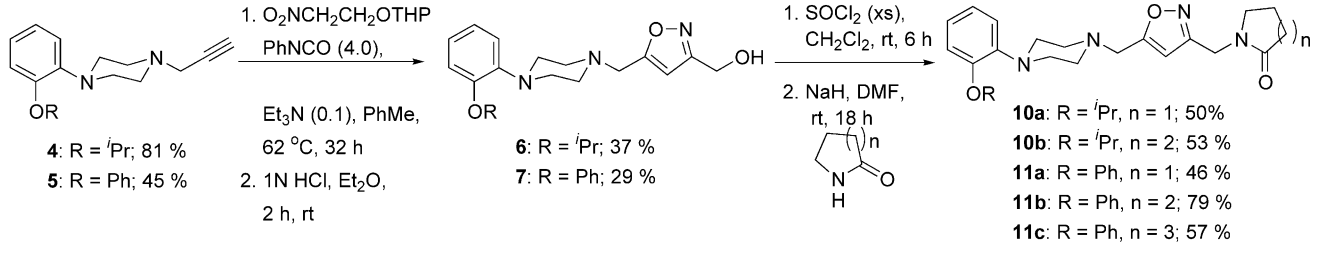
The oxazole **12**[13] was converted to the ester **14** as depicted in Scheme 2. The ester functionality was reduced to the alcohol **15**. Compound **15** was allowed to react with excess $SOCl_2$ to produce, upon workup, the corresponding chloro derivative in 57% yield in two steps The chloride was subsequently displaced with a number of lactams and cyclic imides to generate compounds **16a–e** in moderate yields.

The thiazole analogues were prepared in the same manner as the oxazole derivatives (Scheme 3). Thiazole **17**[14] was brominated and the product (**18**) was heated with piperazine **2** in 1-methyl-2-pyrrolidinone (NMP). The resulting ester **19** was converted to the lactam derivatives **21a** and **21b** employing the previous protocol.[15,16]

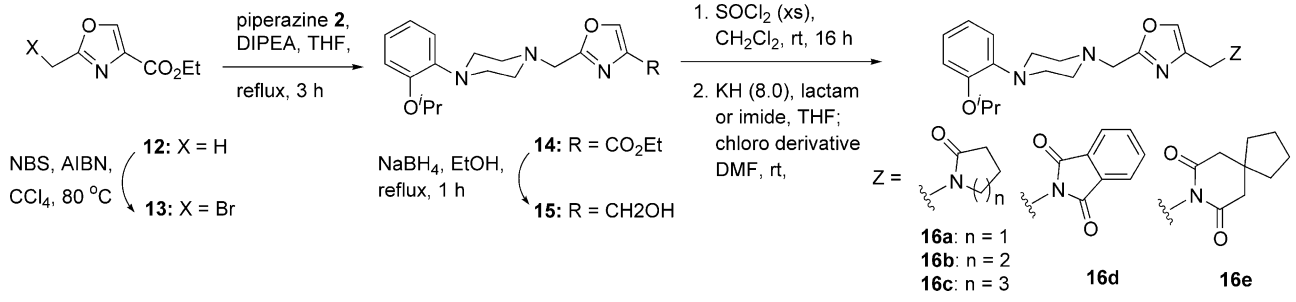
Binding data ($K_i$)[17] were determined utilizing a $^{125}$I-HEAT [(±)-(β-(([$^{125}$I] 3-iodo-4-hydroxyphenyl)-ethyl)-aminomethyl)-tetralone] radioligand binding assay. In this assay the binding affinities of compounds to COS cell membranes expressing the human adrenergic receptor subtypes ($\alpha_{1a}$-AR, $\alpha_{1b}$-AR, and $\alpha_{1d}$-AR), were evaluated (Table 1).

The binding affinities of the derivatives **10a** and **10b** against the $\alpha_{1a}$ subtype remained comparable. This indicated that the lactam ring size was not critical but favored a five-membered ring. The selectivity among the subtypes $\alpha_{1b}$ and $\alpha_{1d}$ were excellent, $>500$-fold and $>50$-fold, respectively. Upon changing the isopropyl group to the phenyl at the aryl-piperazine moiety (see **11a–c**), the binding affinity and selectivity decreased dramatically. Nonetheless, the selectivity pattern remained. The activity was lost when the lactam moiety was omitted (see **7**). The compounds having isopropyl (**10a** and **10b**) substituents were more potent than the corresponding phenoxy analogues (**11a–c**). Therefore, we decided to maintain the 1-(2-isopropoxyphenyl)-piperazine moiety constant and modify other parts of the lead molecule.

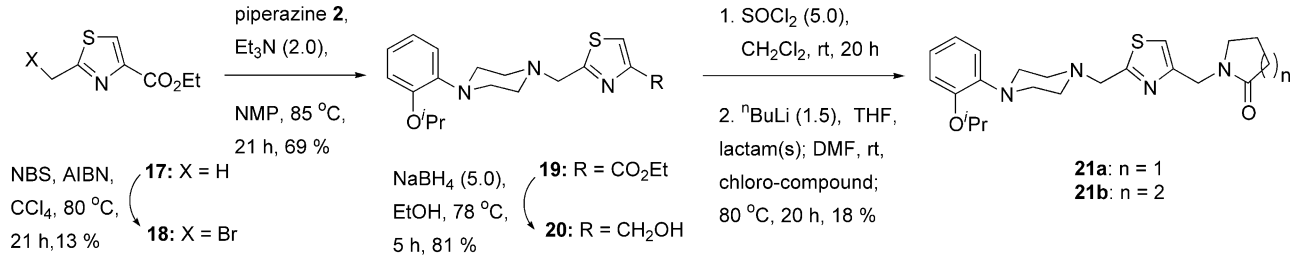
Oxazole derivatives were subsequently examined. It was clear that the oxazole moiety is not well tolerated, and resulted in a substantial decrease in binding affinity. We did find that the introduction of a thiazole was well tolerated. The binding affinities of the thiazole compounds (**21a** and **21b**) towards the $\alpha_{1a}$ subtype was in the 1.0 nM range, comparable to the isoxazole analogues.




**Scheme 1.** Synthesis of 3,5-disubstituted isoxazole tethered lactams.




**Scheme 2.** Preparation of 2,4-disubstituted oxazole tethered lactams and cyclic imides.




**Scheme 3.** Synthesis of 2,4-disubstituted thiazole tethered lactams.

**Table 1.** Binding affinities[a] to the human $\alpha_1$-ARs

| Compd | $K_i$ (nM) | | | $K_i$ ratio | |
|---|---|---|---|---|---|
| | $\alpha_{1a}$ | $\alpha_{1b}$ | $\alpha_{1d}$ | $\alpha_{1b}/\alpha_{1a}$ | $\alpha_{1d}/\alpha_{1a}$ |
| **7** | 1502 | 3719 | 3064 | 2.5 | 2 |
| **10a** | 1.1 | 2992 | 65.5 | 2720 | 60 |
| **10b** | 8.4 | >5000 | 1435 | >595 | 174 |
| **11a** | 28 | >5000 | 34.5 | >170 | 1.2 |
| **11b** | 15 | 2205 | 170 | 147 | 11.3 |
| **11c** | 86 | >5000 | 285 | >58 | 3.3 |
| **16a** | 1298 | >5000 | >5000 | >3.8 | >3.8 |
| **16b** | 2321 | >5000 | >5000 | >2.2 | >2.2 |
| **16c** | 3466 | >5000 | >5000 | >1.4 | >1.4 |
| **16d** | 297 | >5000 | 1107 | >16.8 | 3.7 |
| **16e** | 82 | >5000 | 4142 | >61 | 50 |
| **21a** | 0.9 | 4251 | 105 | 4522 | 112 |
| **21b** | 1.2 | 1735 | 39.5 | 1446 | 33 |

[a]Values are means of three experiments, there was $\leq 5\%$ standard error.

In summary, a novel series of '1,3-disubstuted' isoxazole-, oxazole-, and thiazole- compounds were prepared. The study of the SAR of these series has led to the discovery of a family of potent and selective $\alpha_{1a}$-AR inhibitors.

## Acknowledgements

We wish to thank Drs. Peter Connolly and Allen Reitz for their helpful comments.

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15. **General procedure A.** A mixture of propargyl bromide (3.98 g, 3.5 mmol), piperazine **3** (7.09 g, 27.9 mmol) and $K_2CO_3$ (5.01 g, 36.3 mmol) in $CH_3CN$ (50 mL) was heated at 60 °C for 18 h. Then, the reaction was allowed to cool to rt and worked up with EtOAc. The crude was chromatographed ($SiO_2$, 5–10% EtOAc/hexane) to produce **5** (3.70 g, 45%). To a solution of acetylene **5** (3.60 g, 12.3 mmol) in toluene (200 mL) were added 2-(2-nitroethoxy)-tetrahydropyran (4.32 g, 24.6 mmol), PhNCO (6.61 g, 55.5 mmol) and $Et_3N$ (0.34 mL, 2.46 mmol) in that order, and heated at 62 °C for 24 h. Standard workup and silica gel chromatography yielded a THP-protected derivative (2.26 g, 41%). The latter (4.91 g) was taken in $Et_2O$ (25 mL) and treated with 1 N HCl (aq, 25 mL) at rt overnight to furnish isoxazole **7** in 71% (2.85 g) yield. The alcohol **7** (0.25 g, 0.68 mmol) was stirred with $SOCl_2$ (1 mmol, 13.5 mmol) in $CH_2Cl_2$ (2 mL) at rt for 6 h. The volatile materials then were removed in vacuo to obtain a yellowish foam. The latter was used immediately. 2-Pyrrolidinone (0.11 g, 1.3 mmol) was added to a suspension of NaH (0.062 g, 2.6 mmol) in DMF (2 mL) and stirred for 0.5 h. Then a solution of the above chloro compound (DMF, 2 mL) was added, followed by addition of KI (0.02 g, 0.13 mmol), and stirred for 24 h. Upon aqueous work up with EtOAc and chromatography ($SiO_2$, 10–40% EtOAc in hexane), pure **11a** (0.13 g, 46%) was obtained.

**General procedure B.** A mixture of piperazine **2** (1.87 g, 8.50 mmol), bromide **18** (1.94 g, 7.76 mmol) and $Et_3N$ (1.57 g, 15.52 mmol) in 1-methyl-2-pyrrolidinone (15 mL) was stirred at 85 °C for 21 h. The reaction was quenched with water, extracted with $Et_2O$ and dried ($Na_2SO_4$) and concentrated in vacuo. The product **19** was purified by column chromatography on silica gel (EtOAc/haxane) to obtain as red oil (2.27 g, 69%). A mixture of compound **19** and $NaBH_4$ was stirred in EtOH at 78 °C for 5 h. Water was added and the mixture was acidified to pH 7.0 with 1 N HCl (aq). The n extracted several times with $Et_2O$ and the dried ($Na_2SO_4$) and concentrated. The residue was purified by on silica gel ($CH_2Cl_2$/acetone) to give compound **20** (1.64 g, 81%) as yellow oil. A mixture of compound **20** (1.0 g, 2.9 mmol) and $SO_2Cl_2$ (1,7 g, 14.3 mmol) in $CH_2Cl_2$ (5 mL) was stirred at rt for 20 h. Ice was added and the mixture was basified to a pH of 7–8 by adding $NaHCO_3$ (aq). Extracted with $CH_2Cl_2$ then dried ($Na_2SO_4$) and concentrated in vacuo to the crude chloride as dark-red oil. 2-Pyrrolidinone (0.03 g, 0.36 mmol) was dissolved in THF (10 mL) ans treated with *n*-BuLi (0.23 mL, 1.6 M, 0.36 mmol) at rt for 15 min. A solution of the crude chloride (0.087 g, 0.24 mmol) in DMF (1 mL) was added and the resulting mixture was stirred at 80 °C for 3 h. The reaction mixture was quenched with water and extracted with $Et_2O$. The organic layer was dried and concentrated. Purification ($SiO_2$, EtOAc/hexane) afforded compound **21a** (0.018 g, 18%).

16. $^1$H NMR [(300 MHz, $CDCl_3$), δ (ppm)] and mass spectral data for selected compounds: Compound **11a**: 6.90–7.31 (m, 9H), 6.13 (s, 1H), 4.50 (s, 2H), 3.61 (s, 2H), 3.37 (t, $J=7.0$ Hz, 2H), 3.12 (br s, 4H), 2.49 (br s, 4H), 2.42 (t, $J=8.1$ Hz, 2H), 2.03 (quintet, $J=7.5$ Hz, 2H). MS (ES): $m/z$ 433 $[M+H]^+$, 865 $[2M+H]^+$. Compound **16b**: 7.40 (s, 1H), 6.85–6.93 (m, 2H), 6.75–6.80 (m, 2H), 4.41 (s, 2H), 4.32 (septet, $J=6.0$ Hz, 1H), 3.50 (s, 2H), 3.05 (br m, 6H), 2.60 (br m, 4H), 2.15 (br m, 2H), 1.14–1.34 (m, 4H), 1.12 (d, $J=6.0$ Hz, 6H). LCMS (CI): $m/z$ 413 $[M+H]^+$. Compound **21a**: 7.54 (s, 1H), 6.92 (m, 4H), 4.62 (s, 2H), 4.59 (m, 1H), 3.87 (s, 2H), 3.36 (t, $J=6.9$ Hz, 2H), 3.14 (br s, 4H), 2.77 (m, 4H), 2.42 (t, $J=8.0$ Hz, 2H), 2.02 (m, 2H), 1.33 (d, $J=6.0$ Hz, 6H); MS (ES): $m/z$ 415 $[M+H]^+$. Compound **21b**: 7.55 (s, 1H), 6.90 (m, 4H), 4.68 (s, 2H), 4.59 (m, 1H), 3.87 (s, 2H), 3.30 (br s, 2H), 3.14 (br s, 4H), 2.75 (br s, 4H), 2.42 (br s, 2H), 1.79 (m, 4H), 1.33 (d, $J=6.0$ Hz, 6H); MS (ES): $m/z$ 429 $[M+H]^+$.

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