Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 15 (2005) 3216–3219
Bioorganic & Medicinal Chemistry Letters

# Pharmacophore-based design, synthesis, biological evaluation, and 3D-QSAR studies of aryl-piperazines as $\alpha_1$-adrenoceptor antagonists

Min-Yong Li,[a] Hao Fang[b] and Lin Xia[a,*]

[a]*Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China*
[b]*School of Pharmacy, Shandong University, Jinan 250012, China*

Received 15 March 2005; revised 27 April 2005; accepted 2 May 2005

**Abstract**—Phenyl-piperazines were designed and synthesized based on pharmacophore for uro-selective $\alpha_1$-adrenoceptor antagonists and 3D chemical database searching. Within this series, three compounds, **2**, **3**, and **13**, showed similar or better $\alpha_1$-AR antagonistic activity compared with prazosin. The 3D-QSAR study of these compounds may provide useful information for the development of novel aryl-piperazines as uro-selective $\alpha_1$-adrenoceptor antagonists, which can be used for the treatment of BPH with fewer side effects.


Benign prostatic hyperplasia (BPH) is a common disease in aging male population, and a substantial percentage of men with BPH develop bladder outlet obstruction (BOO) as part of age-related urological disorder.[1] Recent studies provide that BPH is primarily mediated by $\alpha_1$-adrenoceptor ($\alpha_1$-AR) in prostatic tissue, and as a result, some $\alpha_1$-AR antagonists, such as terazosin, doxazosin, and alfuzosin, are clinically used for their treatment.[2] However, these agents have side effects, such as hypotension, dizziness, muscle fatigue, and so on, which are presumably due to an inability of these antagonists to adequately discriminate between the $\alpha_1$-AR in the vascular and lower urinary tracts.[3] These observations suggest that a powerful uro-selective $\alpha_1$-AR antagonist could alleviate the symptoms associated with BPH within minimal cardiovascular side effects.

Recently, we reported a three-point pharmacophore for some uro-selective $\alpha_1$-AR antagonists, such as tamsulosin, silodosin, indoramin, GG-818, and RS-100975, using the Apex-3D program.[4] This pharmacophore model contained an aromatic ring (A), a positive ionizable center (P), and a hydrogen bond donor (HBD). The distances of A–P, A–HBD, and P–HBD are 5.296–5.477, 5.429–6.823, and 3.000 Å, respectively.

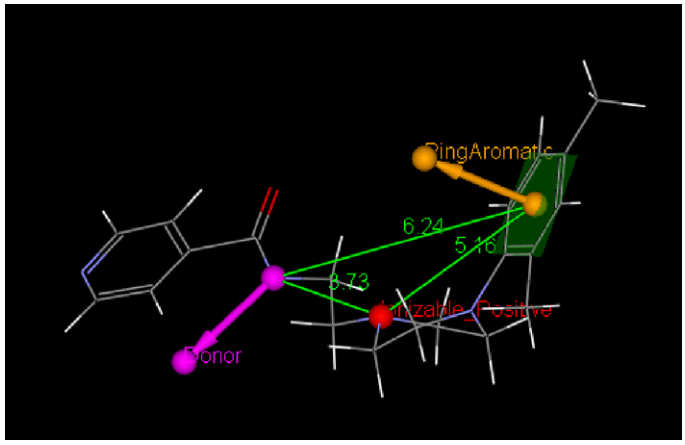
In an on-going study, the previously generated pharmacophore model was used to search our in-house chemical database using the 3DFS flexible searching program.[5] One hit (**1**) with an aryl-piperazine skeleton was found. Compound **1** has an excellent fit of the pharmacophore model. The mapping picture with distance is shown in Figure 1.

In our first trial, compound **1** was evaluated for its $\alpha_1$-AR antagonistic activity to phenylphrine-reduced contractions of isolated Sprague–Dawley rat *anococcygeal* muscles. The results showed that **1** had moderate $\alpha_1$-AR antagonistic activity ($pA_2 = 7.07$). Such preliminary results suggest that compound **1** can be used as a lead compound, and aryl-piperazine can be used as scaffold of $\alpha_1$-AR antagonists for further development.

To improve the $\alpha_1$-AR antagonistic activity for this aryl-piperazine lead compound, we decided to modify the structure based on pharmacophore features. Compounds **2**–**22** were designed by replacing the pyridine ring with other heterocycles and changing the substituent on the phenyl ring of the aryl-piperazine structure. These compounds (**2**–**22**) have been synthesized via the route outlined in Scheme 1. The alkylation of

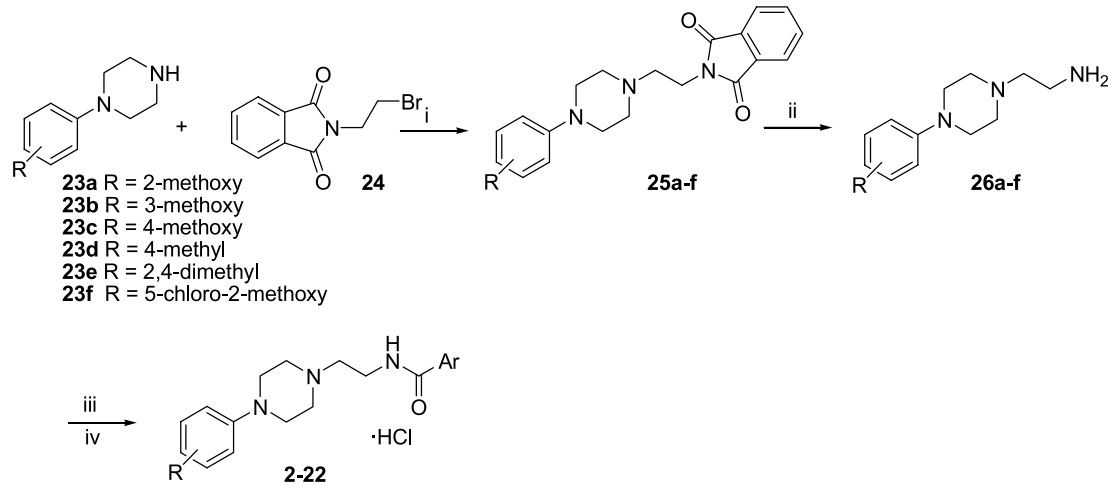
*Keywords*: Pharmacophore-based design; $\alpha_1$-Adrenoceptor; Antagonists; 3D-QSAR.
* Corresponding author. Tel.: +86 25 8327 1440; fax: +86 25 8330 1606; e-mail: phenopro@cpu.edu.cn

0960-894X/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2005.05.003




**1**

**Figure 1.** Pharmacophore model mapped to **1**.




**Scheme 1.** Reagents and conditions: (i) $Et_3N$, $CH_3CN$, 100 °C; (ii) $N_2H_4 \cdot H_2O$, EtOH, 80 °C; (iii) ArCOCl, $K_2CO_3$, $CH_3CN$, 100 °C; (iv) ethanolic HCl.

phenylpiperazine **23a**–**f** with 2-(2-bromoethyl)phthalimide **24** in the presence of $Et_3N$ in acetonitrile yielded **25a**–**f**. Compounds **25a**–**f** were then converted into **26a**–**f** by deprotecting the phthalimide groups with hydrazine hydrate. Finally, **26a**–**f** were acylated with aroyl chloride and then converted to water-soluble hydrochloride salts to give target compounds **2**–**22**.[6]

The target compounds were evaluated for their $\alpha_1$-AR antagonistic activities and the biological data ($pA_2$) are summarized in Table 1. The result showed that three compounds, **2**, **3**, and **13**, displayed high $\alpha_1$-AR antagonistic $pA_2$ of 8.56, 8.56, and 9.12, respectively. All three compounds have similar or better $\alpha_1$-AR antagonistic activities compared with those of prazosin, which is a classical agent used in clinic for the treatment of BPH.

On the basis of these preliminary findings, an extensive SAR study of these aryl-piperazines was initiated using a novel 3D-QSAR technique, Self-Organizing Molecular Field Analysis (SOMFA).[7,8] The structures of these compounds were built and optimized by

**Table 1.** Chemical and biological data for phenyl-piperazines

| Compound | Ar | R | $pA_2$ |
|---|---|---|---|
| **1** | 4-Pyridine | 2,4-Dimethyl | 7.07 |
| **2** | 2-Furan | 5-Chloro-2-methoxy | 8.56 |
| **3** | 2-Furan | 3-Methoxy | 8.56 |
| **4** | 2-Furan | 4-Methoxy | 7.85 |
| **5** | 2-Oxo-2*H*-chromene | 2-Methoxy | 7.71 |
| **6** | 2-Oxo-2*H*-chromene | 5-Chloro-2-methoxy | 7.31 |
| **7** | 2-Oxo-2*H*-chromene | 4-Methoxy | 7.74 |
| **8** | 3-Pyridine | 4-Methyl | 6.53 |
| **9** | 4-Pyridine | 4-Methyl | 6.50 |
| **10** | 2-Furan | 4-Methyl | 6.47 |
| **11** | 2-Benzofuran | 4-Methyl | 6.92 |
| **12** | 3-Pyridine | 2,4-Dimethyl | 5.94 |
| **13** | 2-Furan | 2-Methoxy | 9.12 |
| **14** | 2-Furan | 2,4-Dimethyl | 7.72 |
| **15** | 2-Benzofuran | 2,4-Dimethyl | 7.36 |
| **16** | 3-Pyridine | 4-Methoxy | 5.79 |
| **17** | 4-Pyridine | 4-Methoxy | 5.95 |
| **18** | 3-Pyridine | 2-Methoxy | 7.87 |
| **19** | 4-Pyridine | 2-Methoxy | 7.91 |
| **20** | 3-Pyridine | 5-Chloro-2-methoxy | 5.56 |
| **21** | 4-Pyridine | 5-Chloro-2-methoxy | 7.18 |
| **22** | 2-Benzofuran | 5-Chloro-2-methoxy | 5.63 |
| Prazosin | | | 8.82 |

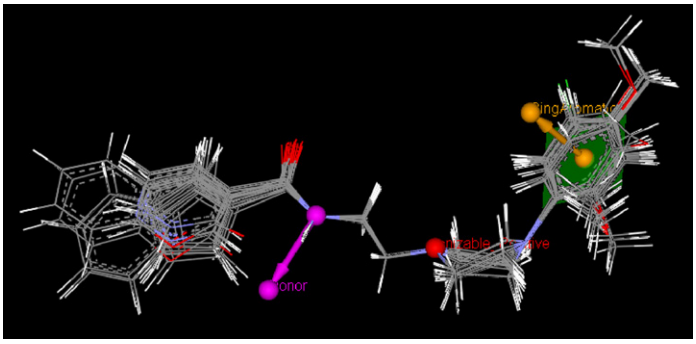


**Figure 2.** Superposition of all 22 compounds.

molecular mechanics methodology with CVFF force field using InsightII program.[9] The optimized structures were assigned with Gasteiger–Marsili charges and performed RMS overlapping to fit with the compound **13**, which has the best biological activity, as a reference, according to three-point pharmacophore. The final overlaid geometries, as represented in Figure 2, were processed with the SOMFA program to develop the 3D-QSAR model.

In this SOMFA study, shape and electrostatic potential were generated. To integrate the predictive power of these two properties into one final model, their individual predictions were combined using a weighted average of the shape and electrostatic potential based QSAR or a mixing coefficient ($c_1$). With the highest value of $r^2$, the SOMFA models were then derived by the partial least-squares (PLS) regression with cross-validation. From statistical analysis of the SOMFA model, good cross-validated correlation coefficient $q^2$ value (0.708), moderate noncross-validated correlation coefficient $r^2$ value (0.743), $F$ test value $F(57.67)$, and standard error of estimate $SE$ value (0.52) were obtained, indicating a good conventional statistical correlation. The SOMFA results indicated that the value of mixing coefficient $c_1$ is 0.9, which means that the contribution of shape field and electrostatic field to QSAR equation is 90% and 10%, respectively. Table 2 summarizes the actual and estimated p$A_2$ of 22 compounds that were synthesized.

**Table 2.** Actual and estimated activities p$A_2$ for compound **1**–**22** by SOMFA analysis[a]

| Compound | Actual p$A_2$ | Estimated p$A_2$ | Error |
|---|---|---|---|
| **1** | 7.07 | 6.39 | 0.68 |
| **2** | 8.56 | 8.24 | 0.32 |
| **3** | 8.56 | 8.30 | 0.26 |
| **4** | 7.85 | 6.79 | 1.06 |
| **5** | 7.71 | 8.00 | −0.29 |
| **6** | 7.31 | 7.79 | −0.48 |
| **7** | 7.74 | 6.39 | 1.35 |
| **8** | 6.53 | 6.71 | −0.18 |
| **9** | 6.50 | 6.50 | 0.00 |
| **10** | 6.47 | 6.99 | −0.52 |
| **11** | 6.92 | 6.85 | 0.07 |
| **12** | 5.94 | 6.54 | −0.60 |
| **13** | 9.12 | 8.42 | 0.70 |
| **14** | 7.72 | 7.34 | 0.38 |
| **15** | 7.36 | 6.90 | 0.46 |
| **16** | 5.79 | 6.13 | −0.34 |
| **17** | 5.95 | 6.23 | −0.28 |
| **18** | 7.87 | 7.33 | 0.54 |
| **19** | 7.91 | 7.60 | 0.31 |
| **20** | 5.56 | 5.12 | 0.44 |
| **21** | 7.18 | 7.30 | −0.12 |
| **22** | 5.63 | 5.38 | 0.25 |

[a] Error = Actual p$A_2$ − Estimated p$A_2$.

**Figure 3.** The shape master grid with compound **13**.

The SOMFA shape master grid for the analysis is shown in Figure 3. In this figure, we found a high density of red points around the 2- and 5-positions at the phenyl ring, which indicates a favorable steric interaction; simultaneously we found high density of blue points around the 3- and 4-positions at the phenyl ring, and around the Ar substituent, which means an unfavorable shape interaction.

In conclusion, in the current work we successfully designed a series of potent aryl-piperazine $\alpha_1$-AR antagonists based on a three-point pharmacophore. The study of the 3D-QSAR for this series of aryl-piperazines may provide some useful information for further design of more aryl-piperazine derivatives as potent and selective $\alpha_1$-adrenoceptor antagonists.

## Acknowledgments

We gratefully acknowledge Dr. Ting Wang (European Molecular Biology Laboratory, Germany) for the use

of 3DFS program. This work was supported by the National High-Tech Research and Development Plan (Grant No. 2002AA2Z3118).

## References and notes

1. Thorpe, A.; Neal, D. *Lancet* **2003**, *361*, 1359.
2. Chess-Williams, R. *Expert Opin. Pharmacother.* **2002**, *3*, 167.
3. Pool, J. L.; Kirby, R. S. *Int. Urol. Nephrol.* **2001**, *33*, 407.
4. Fang, H.; Lu, J. F.; Xia, L. *J. Chin. Pharm. Sci.* **2003**, *12*, 188.
5. Wang, T.; Zhou, J. H. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 71.
6. For example, compound **2**: Yield (48%). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ (ppm): 3.19–3.21(m, *N*–$CH_2$, 2H), 3.33 (m, *N*–$CH_2$, 2H), 3.50–3.65 (m, 3× *N*–$CH_2$, 6H), 3.86 (s, $ArOCH_3$, 3H), 3.98 (m, CONH–C**H**$_2$, 2H), 6.49 (m, Ar–H, 1H), 6.80–6.96 (m, Ar–H, 1H), 7.03 (m, Ar–H, 1H), 7.04–7.07 (m, Ar–H, 1H), 7.29–7.31 (m, Ar–H, 1H), 7.55 (m, Ar–H, 1H), 8.51 (s, NHCO, 1H), 12.55 (br, $N^+H$, 1H). IR ($cm^{-1}$): 3437, 3248, 1667, 1498. EI-MS: 363 ($M^+$), 239 (base peak), 154, 95. HR-MS: Calcd mass, 363.1350, Meas. mass, 363.1344.
7. Robinson, D. D.; Winn, P. J.; Lyne, P. D.; Richards, W. G. *J. Med. Chem.* **1999**, *42*, 573.
8. Li, M. Y.; Du, L. P.; Wu, B.; Xia, L. *Bioorg. Med. Chem.* **2003**, *11*, 3945.
9. InsightII molecular modeling package, Version 2000. Accelrys Inc., San Diego, CA.