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Design and Synthesis of Novel Aryloxyalkyl-arylpiperazine Derivatives as α_{1A}-Adrenoceptor Antagonists

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Abstract: A series of 1-[2-(substituted phenoxy)ethyl]-4-(2-methoxyphenyl)-piperazine derivatives have been synthesized. The radioligand receptor binding assay indicated that most of them bind with α_1-adrenoceptor specifically, and one of the compound possessed subtype A selectivity.

Keywords: α_1-Adrenoceptor, antagonist, aryloxyalkyl-arylpiperazine.

Benign prostatic hyperplasia (BPH) is the non-malignant enlargement of the prostate and clinically occurs predominantly in men aged over 60 years[1]. α_1-Adrenoceptor (α_1-AR) antagonists such as terazosin and doxazosin relax the smooth muscle in the prostate and lower urinary tract and are currently being used as treatment for BPH[2,3]. These clinical agents, while effective, have been associated with side effects such as orthostatic hypotension, dizziness, asthenia, and nasal congestion[4]. The side effect profile is presumably due to an inability of these antagonists to adequately discriminate between the α_1-AR in the vascular and lower urinary tracts.

Our group has long been studying aryloxyalkylamine derivatives due to its good bioactivity in blocking α_1-AR. The aryloxyalkylamine derivative **1** bearing (3,4-dimethoxyphenyl)ethyl side chain, has been identified as a moderate α_1-AR blocker and studied as antihypertensive agent in clinical trial[5]. Recently, pharmacology studies suggested that **1** and its conformation restrict derivative **2** can be used to treat BPH [6]. However, radioligand binding studies showed that **1** has no subtype selectivity[7] and the conformation restrict compound **2** only increase a little bit selectivity on α_{1A}-AR.

To improve the subtype A selectivity for the new aryloxyalkylamine derivatives, the (2-methoxyphenyl)piperazinyl moiety was introduced because its derivatives exhibited high affinity and selectivity on α_{1A}-AR and some of them have been chosen as candidate in clinical trial such as Rec15/2739[8] and RS-90978[9]. In this study, we report the preparation and *in vitro* α_1-AR affinity of a series of new aryloxyalkylamine derivatives which replace (3, 4-dimethoxyphenyl)ethylamine with (2-methoxyphenyl) piperazine (**6** and **7**).

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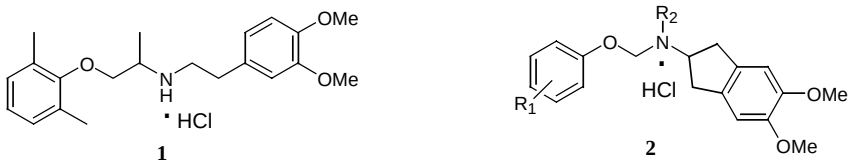
Figure 1 The structure of **1** and its conformation restricted derivative **2**



The substitution pattern in the phenyl ring of aryloxyalkylamine affects the potency of **1** analogues significantly on the basis of the known structure activity relationships (SAR). The 3D-QSAR of **1** and its analogues [10] suggests that little steric and modest negatively charged substitution in *ortho* or *para* position would be favorable to activity. Therefore, chloro, methyl and methoxy group were chosen with mono or double substitution in our initial studies considering the previous result of SAR. It is reported that the introducing chloro in 5-position of the phenyl ring in the (2-methoxyphenyl) piperazine could increase the affinity of α_{1A}-AR[11]. This urges us to design compounds **7** hoping that could improve subtype selectivity.

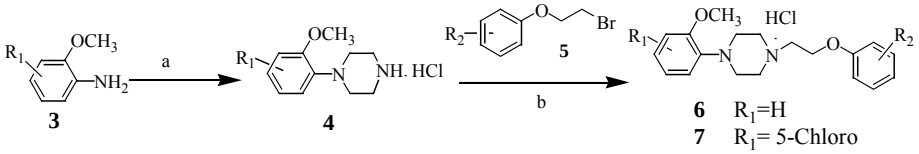
The target compounds **6** and **7** were prepared as outline in **Scheme 1**. The β-bromoethyl-phenyl ether **5** and corresponding arylpiperazine hydrochloride **4** were synthesized according to the method reported previously[12,13]. The arylpiperazine hydrochloride **4** was depronated with triethylamine and then reacted with **5** in dried acetonitrile refluxing overnight. After purifying with silica gel column, the target compounds **6** and **7** [14] were converted to their water-soluble hydrochloride salts for use.

Preliminary pharmacological screening carried out on all target compounds using function analysis of rat anococcyeus muscle[15] and then studied on radioligand binding. **Table 1** shows the biological data for all compounds and binding affinity estimates (pK_i)[16] refer to the inhibition of ^{125}I-BE2254 binding in rat cerebral cortex membranes. The data revealed that most of compounds bind α_1-AR specifically in radioligand binding assay.

It is interesting to note that substitution R_2 on the phenyl ring of aryloxyalkylamine still has profound impact on the α_1-AR antagonism activity. The affinities of the compounds (**6f, 6g**, **7f** and **7g**) with chloro group decreased obviously, which suggested that electron-withdrawing group maybe harmful to activity in blocking α_1-AR. But the earlier SAR of **1** and its analogues indicated that mono halogen (such as chloro and bromo) substitution of R_2 could remain potent[10]. On the other hand, the derivatives with electron- donating groups (methyl and methoxy) show improved affinity on α_1-AR, especially compound **6 h,** bearing a methoxy group at ortho position, is most potent among them.

As showed in **Table 1**, the (5-chloro-2-methoxy)phenyl piperazine derivatives **7a**-7**e** had the potency in the same order of magnitude as compared with **6a**-**6e**. In this series of compounds, the chloro substitution on the phenyl ring linked to piperazine is not able to enhance the affinity as we expected and seems to play minor and sometimes little negative effect on α_1-AR antagonism.

Scheme 1 Synthesis of 2-[(substituted phenoxy) ethyl]-4-(2-methoxyphenyl)-piperazine derivative



Reagent and conditions: (a) Bis-(2-chloroethyl)amine hydrochloride, *n*-BuOH, reflux, 20 h, 40-50% (b) (i) **5**, CH_3CN, Et_3N, reflux, 12 h; (ii) HCl(g) / EtOH, 50-76%

Table 1 The binding studies on target compounds inhibition of ^{125}I-BE2254 binding.

Compds	R_1	R_2	pK_i[a]
6a	H	2,6-dimethyl	6.27±0.13
6b	H	2-methyl	6.67±0.09
6c	H	3-methyl	6.35±0.24
6d	H	4-methyl	6.75±0.14
6e	H	2,3-dimethyl	6.60±0.31
6f	H	4-chloro	NA
6g	H	2,4-dichloro	NA
6h	H	2-methoxy	7.20±0.16
7a	5-chloro	2,6-dimethyl	6.24±0.14
7b	5-chloro	2-methyl	6.52±0.11
7c	5-chloro	3-methyl	6.72±0.27
7d	5-chloro	4-methyl	5.97±0.26
7e	5-chloro	2,3-dimethyl	5.91±0.29
7f	5-chloro	4-chloro	NA
7g	5-chloro	2,4-dichloro	NA
7h	5-chloro	2-methoxy	NA

[a]Values are means of three experiments, standard deviation is given in parentheses (NA = not active).

In another binding study, the competitive inhibition of ^{125}I-BE2254 binding to cloned α_1-adrenergic receptor subtypes was carried out on HEK 293 cell lines[17]. The results showed that compound **6h** has the selectivity to α_{1A} –AR and pK_i values for cloned α_{1A}, α_{1B} and α_{1D} –AR were 7.92±0.07, 6.24±0.30 and 7.28±0.07, respectively, which indicated that this compound exhibit more than 40-fold selectivity for α_{1A} over α_{1B} and 4-fold selectivity for α_{1A} over α_{1D}. It was also reported that the pK_i values of compound **1** for cloned α_{1A}, α_{1B} and α_{1D}-AR were 7.21±0.12, 6.88±0.04 and 7.26±0.06, respectively[7]. Therefore, compound **6h** showed a remarkable improvement of affinity and selectivity on α_{1A}-AR compared with compound **1**.

In conclusion, a series of novel arylpiperazine-aryloxyalkyl-containing compounds were designed, synthesized and evaluated for their biological properties. As the result, **6h** was characterized by its markable increase in α_{1A} –AR affinity and selectivity compared with the leading compoud **1**.

Acknowledgments

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References and Notes

1. S. A. Doggrell, *Drugs Fut.,* **2002**, *27*(10), 973.
2. J. L Pool, R. S. Kirby, *Int. Urol. Nephrol.,* **2001**, *33*(3), 407.
3. K. L. Copper, J. M. Mckiernan, S. A. Kaplan, *Drugs,* **1999**, *57*(1), 9.
4. R. R. Jr. Ruffolo, J. P. Hieble, *Eur. Urol.*, **1999**, *36*(Suppl 1), 17.
5. L. Xia, P. Z. Ni, J. Q. Qian, C.N. Patent 1,081,178, **1994**; *Chem. Abstr*., **1995**, *122*, 187121
6. L. Xia, P. Z. Ni, G. L. Yu, *et al.*, C.N. Patent 1,229,793, **1999**; *Chem. Abstr.,* **2000**, *133*, 135238.
7. Z. Z. Lu, Y. Y. Zhang, L. Xia, *et al.*, *Yaoxue Xuebao* (*Acta Pharm. Sin*., in Chinese), **2000**, *35*, 739.
8. R. Testa, L. Guarneri, M. Ibba, *et al.*, *Life Sci*., **1997**, *61*(22), 2177.
9. T. R. Elworthy, A. P. Ford, G. W. Bantle, *et al.*, *J. Med. Chem.,* **1997**, *40*(17), 2674.
10. H. Fang, J. F. Lu, L. Xia, *et al.*, *Chin. Sci. Bull*., **2001**, *46*(4), 303.
11. B. Kenny, S. Ballard, J. Blagg, *J. Med. Chem.,* **1997**, *40*(9), 1293.
12. L. H. Schwartzman, B. B. Corson, *J. Am. Chem. Soc.,* **1954**, *76*(2), 585.
13. P. T. Bysouth, R. W. Clarke, G.B. Patent 171,251, 1969; *Chem. Abstr.,* **1970**, *71*, 91527
14. For example, compound **7b**: Yield (76%) ^{1}H NMR ($CDCl_3$, 300MHz, δ ppm): 2.22 (s, 3H), 3.19 (m, 2H), 3.53-3.69 (m, 6H), 3.74 (m, 2H), 3.86 (s, 3H), 4.60 (m, 2H), 6.79-6.98 (m, 2H), 6.99-7.02 (m, 1H), 7.06-7.14 (m, 2H), 7.15-7.23 (m, 2H), 13.24 (br, 1H). IR (cm^{-1}): 3399, 1590, 1497, 1251. MS-ESI: 361 $(M+H)^+$. Anal. calcd. for $C_{20}H_{25}ClN_2O_2 \cdot HCl$: C, 60.46; H, 6.60; N, 7.05, Found: C, 60.42; H, 6.59; N, 7.04.
15. A. Gibson, D. Pollock, *Br. J. Pharmacol*., **1973**, *49*(3), 506.
16. The K_i values were calculated according to the equation $K_i=[IC_{50}]/(1+[radioligand]/K_d)$ Y. C. Cheng, W. H. Prusoff, *Biochem. Pharmacol*., **1973**, *22*(23), 3099.
17. C. Han, J. L. Li, K. P. Minneman, *Eur. J. Pharmacol*., **1990**, *190*(1-2), 97.

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