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# DUAL-ACTING AGENTS WITH $\alpha_1$-ADRENOCEPTOR ANTAGONISTIC AND STEROID 5$\alpha$-REDUCTASE INHIBITORY ACTIVITIES. SYNTHESIS AND EVALUATION OF ARYLPIPERAZINE DERIVATIVES

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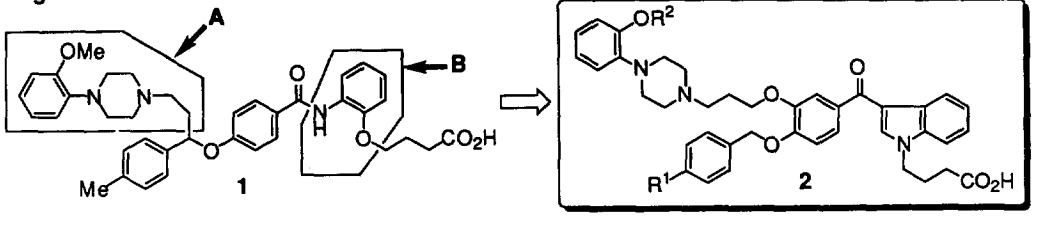
**Abstract:** A series of arylpiperazine derivatives were prepared and evaluated for their $\alpha_1$-adrenoceptor antagonistic activities and 5$\alpha$-reductase inhibitory activities. SAR study led to the identification of the potent dual-acting compound **2f**, which had a $pA_2$ value of 7.5 for $\alpha_1$-adrenoceptor antagonism and an $IC_{50}$ value of 1.5 nM for 5$\alpha$-reductase inhibition. 

Benign prostatic hyperplasia (BPH) is the most common disease in aging men[1]. This condition leads to a variety of urological symptoms including increased frequency of urination, poor urine stream, and hesitancy or delay in the start of urine flow[2]. To alleviate these symptoms, $\alpha_1$-adrenoceptor antagonists such as prazosin[3], terazosin[4], doxazosin[5] and tamsulosin[6] are now being used clinically to relax the smooth muscle of the prostate and urethra. However, since the hyperplastic growth of the prostate is believed to be largely dependent on the hormonal action of dihydrotestosterone (DHT)[7], which is produced by 5$\alpha$-reductase (5$\alpha$-R) from testosterone, 5$\alpha$-R inhibitor[8] is another choice for the treatment of BPH[9] to reduce the enlarged prostate. For this reason, there has been intense interest in developing 5$\alpha$-R inhibitors, and finasteride[10] is the first 5$\alpha$-R inhibitor that has been launched for clinical use in the US and Europe. Thus, a dual-acting agent which has both $\alpha_1$-adrenoceptor antagonistic action and 5$\alpha$-R inhibitory activity would provide an additional benefit in the treatment of the urinary tract disorder caused by BPH.

We recently reported that benzanilide derivative **1** proved to be a dual-acting agent with a $pA_2$ value of 7.8 for $\alpha_1$-adrenoceptor antagonism and an $IC_{50}$ value of 67 nM for 5$\alpha$-R inhibition[11]. However, its 5$\alpha$-R inhibitory activity needed to be improved to exert the both activities at the same dose level in vivo. It is well established that the lipophilic part and butanoic acid moiety are essential to 5$\alpha$-R inhibitory activity for nonsteroidal inhibitors in most cases. Considering these structural requirements for 5$\alpha$-R inhibition, we designed a compound in which the

**Figure 1**

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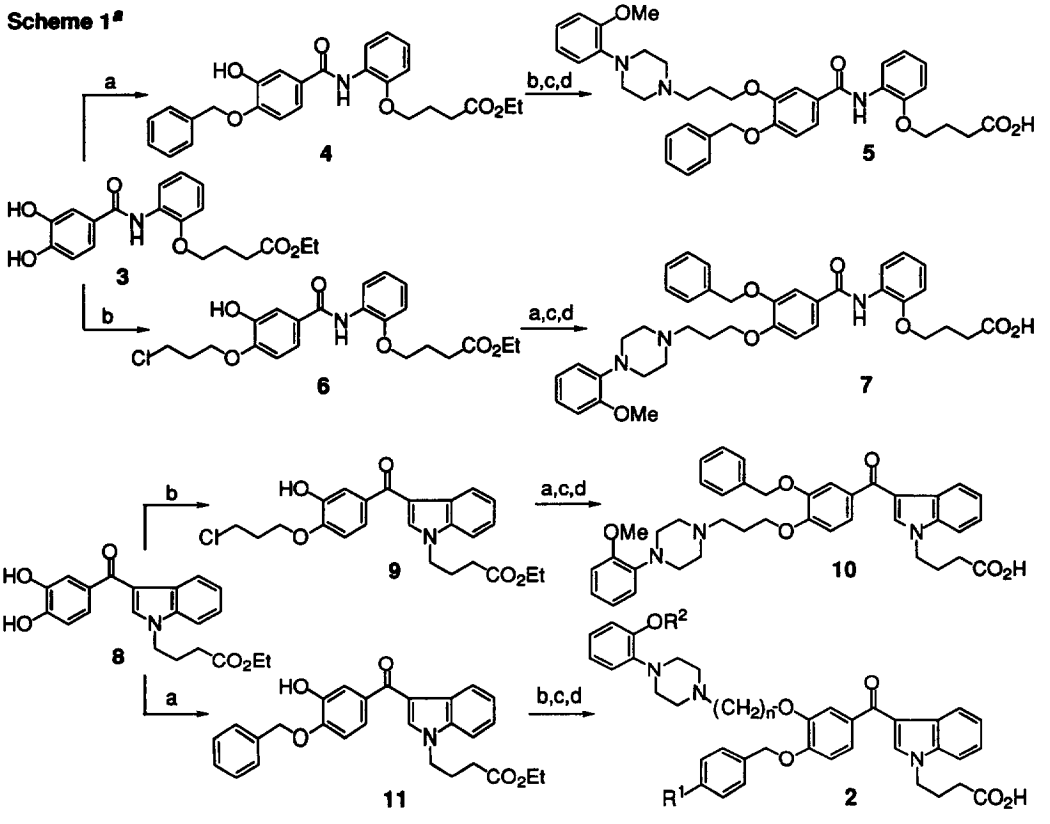
arylpiperazinylalkyl moiety (**A**), being dispensable for $\alpha_1$-adrenoceptor antagonistic action, was transferred from *p*- to *m*-position and the benzanilide moiety (**B**) was replaced by an acyl indole framework such as FK-143[12] (Figure 1). As a result, indole derivative **2** showed both $\alpha_1$-adrenoceptor antagonistic action as potent as **1** and more potent 5α-R inhibitory activity than **1**. In this report we describe the synthesis and structure–activity relationships of arylpiperazine derivatives.

## Chemistry

The synthesis of arylpiperazine derivatives is depicted in Scheme 1. Compounds **5** and **7** were prepared starting from catechol **3**[13]. In general, *O*-alkylation of catechol **3** was slightly more favorable at the *p*-hydroxy group of catechol than the *m*-hydroxy group in each reaction, and *O*-alkylated product at the *p*-hydroxy group was obtained in 40-50% yield after purification by column chromatography. Benzylation of catechol **3** using BnBr and $K_2CO_3$ in DMF at room temperature gave 4-benzyl ether **4**. *O*-Alkylation at the *m*-hydroxy group of **4** with Cl-$(CH_2)_n$-Br followed by the *N*-alkylation of 1-(2-methoxyphenyl)piperazine in the presence of KI and $K_2CO_3$ in DMF at 60 °C afforded the corresponding ester, which was subjected to alkaline hydrolysis to furnish compound **5**. Corresponding regioisomer **7** was also prepared using the same conditions by changing the order

**Scheme 1**[a]




[a] *reagents and conditions*: (a) $ArCH_2Br$, $K_2CO_3$, DMF, rt; (b) Cl-$(CH_2)_n$-Br, $K_2CO_3$, DMF, rt; (c) 1-(2-alkoxyphenyl)-piperazine, KI, $K_2CO_3$, DMF, 60 °C; (d) KOH, MeOH, $H_2O$, reflux.

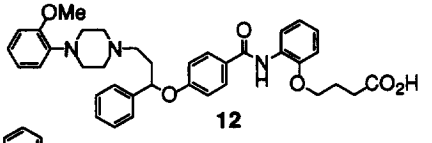
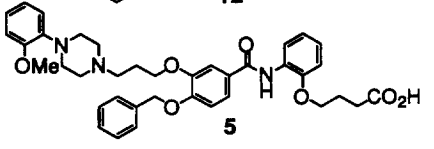
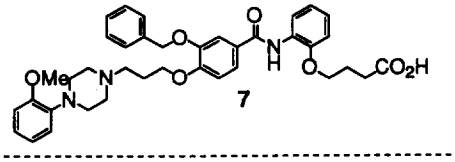
of the *O*-alkylation step. The synthesis of indole derivatives **2** and **10** was also carried out starting from catechol **8**[14] by the same conditions employed for the synthesis of **5** and **7**.

## Results and Discussion

A series of compounds were evaluated for their $\alpha_1$-adrenoceptor antagonism and 5α-R inhibition. $\alpha_1$-Adrenoceptor antagonism was expressed as $pA_2$ value calculated from phenylephrine-induced contraction of New Zealand rabbit prostate[15]. 5α-R inhibitory activity ($IC_{50}$) was determined using the prostate of male Sprague-Dawley rats.

First, the substituent at the C4 position on the benzoyl group in **1** was modified to furnish the compounds **5** and **7**, in which the arylpiperazine side chain and benzyl group were separated by using a catechol scaffold so that no asymmetric center consequently existed. As shown in Table 1, compound **5** enhanced both $\alpha_1$-adrenoceptor antagonism and 5α-R inhibition compared with compound **12**, while the corresponding isomer **7** reduced both activities. These results show that the position of the benzyloxy group is especially crucial for 5α-R inhibition, but the potency of 5α-R inhibition still needed to be improved.

**Table 1**

| compound | $\alpha_1$-antagonistic activity rabbit prostate, $pA_2$ | 5α-R inhibitory activity $IC_{50}$ (nM) |
|---|---|---|
|  **12** | 7.6 | 920 |
|  **5** | 8.0 | 490 |
|  **7** | 7.2 | 3500 |
| Urapidil[16] | 7.1 | — |
| ONO 3805[17] | — | 2.6 |

In an attempt to increase 5α-R inhibitory activity, the benzanilide moiety (**B**, Figure 1) was replaced with 3-acyl-1-alkylindole. As shown in Table 2, compound **2a** dramatically enhanced 5α-R inhibitory activity ($IC_{50}$ = 11 nM) without decreasing $\alpha_1$-adrenoceptor antagonistic activity compared with corresponding benzanilide derivative **5**, although regioisomer **10** diminished both activities. A similar trend in biological activities was observed in their regioisomers (**5** and **7**, **2a** and **10**) independent of **B** moiety.

Optimization of the length of the methylene chain (n) and substituents ($R^1$, $R^2$) were then examined (Table 3).

Results were similar to those with the benzanilide derivatives[11]. Introduction of the methyl group ($R^1$) at the *p*-position of the benzyl groups (compound **2b**) enhanced the 5α-R inhibitory activity while maintaining $\alpha_1$-adrenoceptor antagonistic activity, although the introduction of the ethyl group instead of the methyl group as the $R^1$ substituent (compound **2c**) caused a significant decrease in $\alpha_1$-adrenoceptor antagonistic action. Elongation or shortening of methylene length (compounds **2d** and **2e**) also led to the reduction of $\alpha_1$-adrenoceptor antagonistic action. The alkoxy group ($R^2O$) in the arylpiperazine moiety had a little effect on the activities; among the compounds bearing different alkoxy groups, ethoxy-substituted compound **2f** showed well-balanced activities with a $pA_2$ value of 7.5 for $\alpha_1$-adrenoceptor antagonism and an $IC_{50}$ value of 1.5 nM for 5α-R inhibition.

**Table 2**

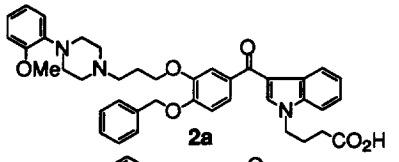
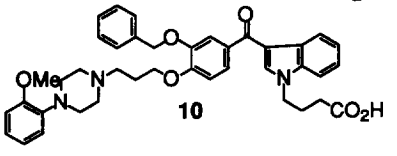
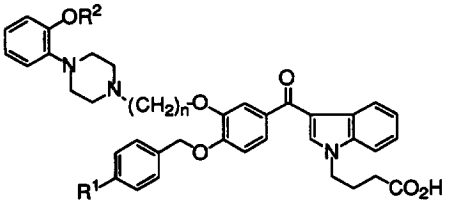
| compound | $\alpha_1$-antagonistic activity rabbit prostate, $pA_2$ | 5α-R inhibitory activity $IC_{50}$ (nM) |
|---|---|---|
|  **2a** | 7.8 | 11 |
|  **10** | 7.0 | 360 |

**Table 3**



| compound | $R^1$ | $R^2$ | n | $\alpha_1$-antagonistic activity rabbit prostate, $pA_2$ | 5α-R inhibitory activity $IC_{50}$ (nM) |
|---|---|---|---|---|---|
| **2a** | H | Me | 3 | 7.8 | 11 |
| **2b** | Me | Me | 3 | 7.7 | 3.5 |
| **2c** | Et | Me | 3 | 6.6 | 4.0 |
| **2d** | Me | Me | 2 | 6.8 | 4.8 |
| **2e** | Me | Me | 4 | 6.7 | 1.5 |
| **2f** | Me | Et | 3 | 7.5 | 1.5 |
| **2g** | Me | *n*-Pr | 3 | 6.8 | 3.0 |
| **2h** | Me | *i*-Pr | 3 | 6.8 | 2.9 |
| Urapidil[16] | | | | 7.1 | — |
| FK 143[12] | | | | — | 4.2 |

Selected compound **2f** was evaluated for its inhibitory effects on phenylephrine-induced increases in urethral pressure in anesthetized rabbits[18]. The results are shown in Figure 2. Inhibitory effects were observed at 2 min after intravenous administration. Compound **2f** inhibited increases in urethral pressure in a dose-dependent manner at a dose of 0.03 to 0.3 mg/kg.

Inhibition of prostatic 5α-R after oral administration of compound **2f** in rats[19] was also examined. As shown in Figure 3, compound **2f** inhibited prostatic 5α-R in a dose-dependent manner with an $ED_{50}$ value of 7.9 mg/kg.

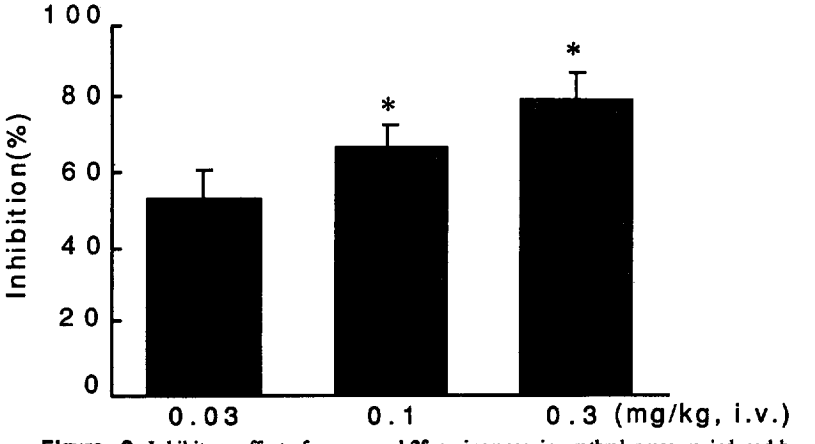



**Figure 2** Inhibitory effect of compound **2f** on increase in urethral pressure induced by phenylephrine in anesthetized rabbits. Compound **2f** was intravenously administered and the inhibitory effect was evaluated at 2 min after administration. *,P<0.05

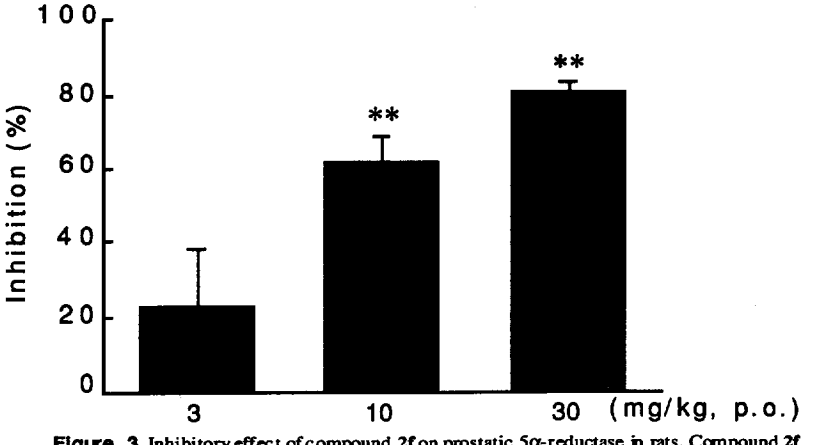



**Figure 3** Inhibitory effect of compound **2f** on prostatic 5α-reductase in rats. Compound **2f** was orally administered and the inhibitory effect was evaluated at 2 hr after administration. **,P<0.01

In summary, we demonstrated that the modification of the benzanilide moiety and arylpiperazinylalkyl moiety in compound **1** led to compound **2f** with significantly improved 5α-R inhibitory activity. Compound **2f** also showed both $\alpha_1$-adrenoceptor antagonistic and 5α-R inhibitory activities in vivo. Further investigation of this compound series will be reported in due course.

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**References and Notes:**

1. Geller, J. *J. Am. Geriatr. Soc.* **1991**, *39*, 1208.
2. Fukuya, S.; Kumamoto, Y.; Yokoyama, E.; Tsukamoto, T.; Izumi, T.; Abiko, Y. *J. Urol.* **1982**, *128*, 836.
3. Hedlund, H.; Anderson, K.-E.; Ek, A. *J. Urol.* **1983**, *130*, 275.
4. Lepor, H. *Prostate Suppl.* **1990**, *3*, 75.
5. Jankegt, R. A.; Chapple, C. *Eur. Urol.* **1983**, *24*, 319.
6. Kawabe, K.; Ueno, A.; Takimoto, Y.; Aso, Y.; Kato, H. *J. Urol.* **1990**, *144*, 908.
7. Wilbert, D. M.; Griffin, J. E.; Wilson, J. D. *J. Clin. Endocrinol. Metab.* **1983**, *56*, 113.
8. For reviews, see: (a) Frye, S. V. *Curr. Pharm. Des.* **1996**, *2*, 59. (b) Abell, A. D.; Henderson, B. R. *Curr. Med. Chem.* **1995**, *2*, 583. For recent studies of nonsteroidal inhibitors of 5α-reductase: (c) Kato, M.; Komoda, K.; Namera, A.; Sakai, Y.; Okada, S.; Yamada, A.; Yokoyama, K.; Migita, E.; Minobe, Y.; Tani, T. *Chem. Pharm. Bull.* **1997**, *45*, 1767. (d) Ishibashi, K.; Nakajima, K.; Sugioka, Y.; Sugiyama, M.; Hamada, T.; Horikoshi, H.; Nishi, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 561. (e) Sawada, K.; Hirai, H.; Golden, P.; Okada, S.; Sawada, Y.; Hashimoto, M.; Tanaka, H. *Chem. Pharm. Bull.* **1998**, *46*, 1683.
9. For a review, see: Kenny, B.; Ballard, S.; Blagg, J.; Fox, D. *J. Med. Chem.* **1997**, *40*, 1293.
10. Rasmusson, G. H.; Reynolds, G. F.; Steinberg, N. G.; Walton, E.; Patel, G. F.; Liang, T.; Cascieri, M. A.; Cheung, A. H.; Brooks, J. R.; Bermann, C. *J. Med. Chem.* **1986**, *29*, 2298.
11. Yoshida, K.; Horikoshi, Y.; Eta, M.; Chikazawa, J.; Ogishima, M.; Fukuda, Y.; Sato, H.; *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2967.
12. (a) FK-143, *Drugs Future* **1996**, *21*, 473. (b) Hirosumi, H.; Nakayama, O.; Fagan, T.; Sawada, K.; Chida, N.; Inami, M.; Takahashi, S.; Kojo, H.; Notsu, Y.; Okuhara, M. *J. Steroid Biochem. Molec. Biol.* **1995**, *52*, 357. (c) Hirosumi, H.; Nakayama, O.; Fagan, T.; Sawada, K.; Chida, N.; Inami, M.; Takahashi, S.; Kojo, H.; Notsu, Y.; Okuhara, M. *J. Steroid Biochem. Molec. Biol.* **1995**, *52*, 365.
13. Compound **3** was prepared as follows: (1) 3,4-dibenzyloxybezoyl chloride, ethyl 4-(2-aminophenoxy)-butyrate[20], $K_2CO_3$, AcOEt, $H_2O$; (2) $H_2$, 10% Pd/C, MeOH.
14. Maw, G. N.; Blagg, J.; Tuckwood, V.; Rawson, D. J. International Patent Application No. WO 95/23143, Aug. 31, 1995.
15. van Rossum, J. M. *Arch. Int. Pharmacodyn. Ther.* **1963**, *143*, 299.
16. Fujii, M.; Nagao, H.; Kurasaki, S.; Yajima, M. *Jpn. Pharmacol Ther.* **1992**, *20 (7)*, 91.
17. Nakai, H.; Terashima, H.; Arai, Y. EP 0 291 245, 1988; *Chem. Abstr.* **1988**, *110*, 212384t.
18. Testa, R.; Sironi, G.; Colombo, D.; Greto, L.; Leonardi, A. *Neurourol. Urodyn.* **1994**, *13*, 471.
19. Liang, T.; Cascieri, M. A.; Cheung, A. H.; Reynolds, G. F.; Rasmusson, G. H. *Endocrinology* **1985**, *117*, 571.
20. Nakai, H.; Terashima, H.; Arai, Y. EP 0291245, Nov. 17, 1988; *Chem. Abstr.* **1988**, *110*, 212384t.