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Synthesis of Benzanilide Derivatives as Dual Acting Agents with α_1-Adrenoceptor Antagonistic Action and Steroid 5-α Reductase Inhibitory Activity

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Abstract:

Synthesis of benzanilide derivatives which have dual α_1-adrenoceptor antagonistic action and steroid 5α-reductase inhibitory activity and their structure-activity relationships is described.

Keywords: antagonist; enzyme inhibitor; hormones; substituent effects.

Introduction: Benign prostatic hyperplasia (BPH) is a common disease in aging men,[1] and a substantial percentage of men with BPH develop a bladder outlet obstruction.[2] The obstruction caused by BPH is thought to be attributable to two main components, i. e., a static component related to enlarged prostatic tissue mass and a dynamic component involving excessive contraction of prostate and urethra.[3]

Since it has been reported that the administration of α_1-adrenoceptor antagonists alleviate these symptoms,[4] prazosin,[5] terazosin,[6] doxazosin,[7] and tamsulosin[8] are clinically used for their treatment at the present time. Another approach has been sought to reduce the static component of obstruction due to the enlarged prostate.[9] Since dihydrotestosterone has been established as a dominant factor of prostatic growth, research on inhibitors of steroid 5α-reductase (5α-R), an enzyme which converts testosterone to the more potent dihydrotestosterone, has been carried out.[10] This approach led to the identification and subsequent development of finasteride,[11] which is currently the only 5α-R inhibitor approved for BPH treatment.

From this standpoint, we speculated that a dual-acting agent which has both α_1-adrenoceptor antagonistic action and steroid 5α-R inhibitory activity would be an effective therapeutic agent for urethral obstruction caused by BPH. The benzanilide skeleton of the structure of **1** (Fig. 1), which was identified as an α_1- adrenoceptor antagonist in our basic studies[12] (pA_2=7.1), seems to

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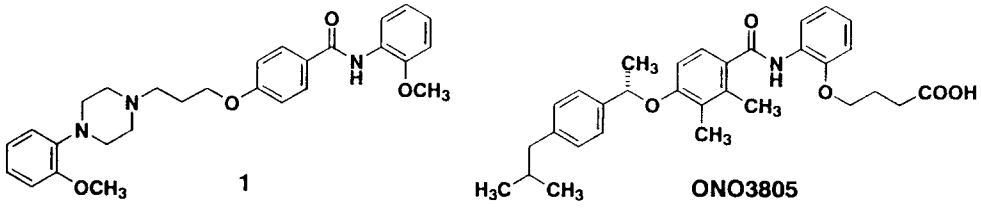
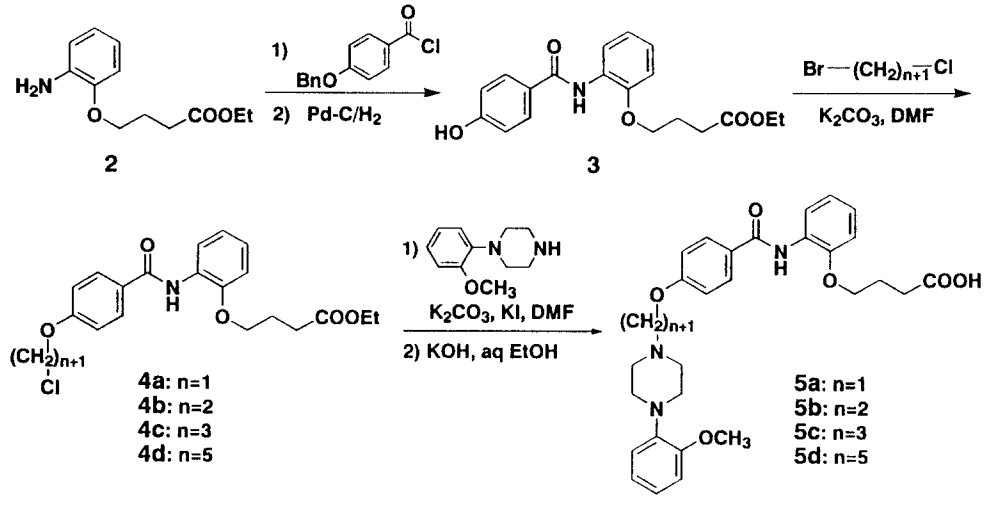
Figure 1



be very close to that of ONO3805,[13] which has been reported as a non-steroidal 5α-R inhibitor. We synthesized the compound **5b** by replacing the methoxy group of **1** with a 4-carboxypropyl group. Compound **5b** retained α_1-antagonistic activity (pA_2=7.0), and it also possessed 5α-R inhibitory activity (IC_{50} =41 μM). Based on these results, we considered compound **5b** a leading candidate compound for the above-mentioned use. In this paper, we report the synthesis and biological properties of benzanilide derivatives which have dual α_1-adrenoceptor antagonistic activity and 5α-R inhibitory activity.

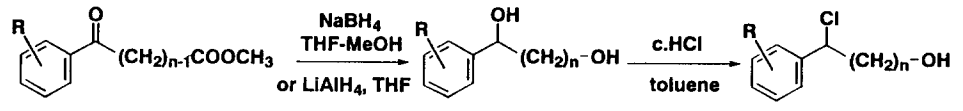
Synthesis: The phenolic benzanilide **3**, synthesized from **2**[13] according to the reported procedure was alkylated by 1-bromo-ω-chloroalkane to afford **4a~d** in good yield. Alkylation of 1-(2-methoxyphenyl)piperazine with **4a~d** followed by alkaline hydrolysis gave the desired compounds **5a~d** (Scheme 1).

Scheme 1



Aryl substituted chlorohydrins **8a~i** were prepared from the oxo esters **6a~i** depicted in Scheme 2. Methyl-3-oxo-3-arylpropionates **6a~g** were reduced by $NaBH_4$ in THF-methanol to give the corresponding diols **7a~g**. These diols were treated with 2.5~3.0 mol eq concentrated HCl in toluene under vigorous stirring at 0°C to give the corresponding chlorohydrins **8a~g**. Lithium aluminum hydride reduction of **6h** and **6i** in THF at 0°C gave diols **7h** and **7i** in 66%

Scheme 2

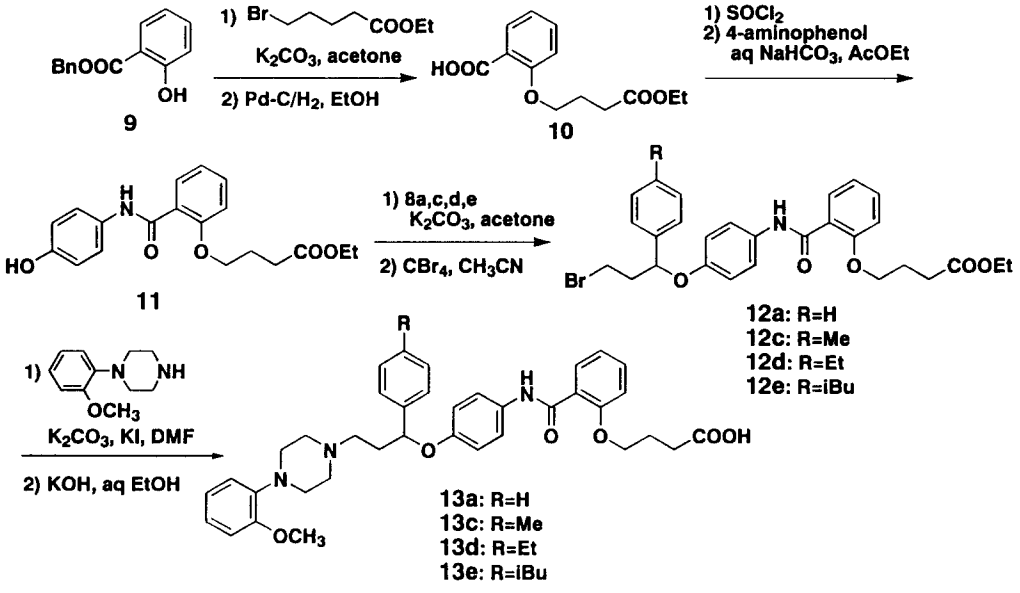


6a: n=2, R=H **6b**: n=2, R=3-Me **6c**: n=2, R=4-Me **6d**: n=2, R=4-Et **6e**: n=2, R=4-iBu **6f**: n=2, R=4-MeO **6g**: n=2, R=4-Br **6h**: n=3, R=H **6i**: n=4, R=H

7a: n=2, R=H **7b**: n=2, R=3-Me **7c**: n=2, R=4-Me **7d**: n=2, R=4-Et **7e**: n=2, R=4-iBu **7f**: n=2, R=4-MeO **7g**: n=2, R=4-Br **7h**: n=3, R=H **7i**: n=4, R=H

and 60% yields, respectively. Diols **7h** and **7i** were reacted with concentrated HCl according to the same procedure as that described in the synthesis of **8a~g** to give **8h** and **8i** accompanied by small amounts of the corresponding dichlorides, which were easily purified by column chromatography.

Scheme 3

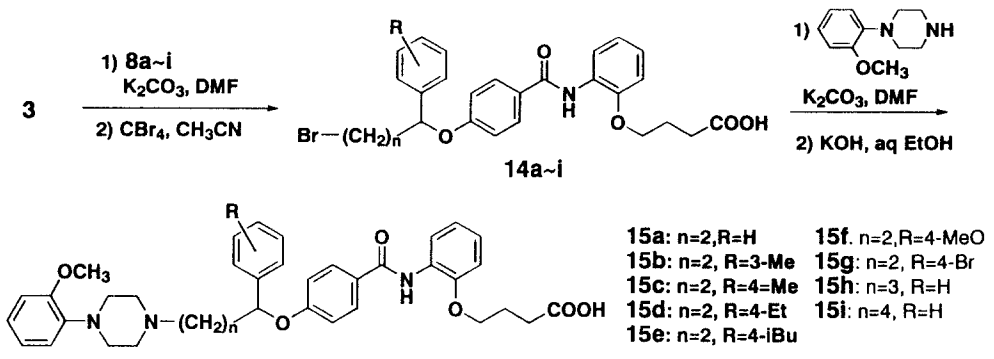


12a: R=H **12c**: R=Me **12d**: R=Et **12e**: R=iBu

13a: R=H **13c**: R=Me **13d**: R=Et **13e**: R=iBu

Compounds **13a~d** were synthesized from benzyl salicylate (**9**) (Scheme 3). Alkylation of **9** with ethyl 4-bromobutyrate, followed by hydrogenolysis of benzyl ester gave **10** in 84% yield. The acid chloride prepared from **10** was reacted with 4-aminophenol under Schotten-Baumann conditions to give anilide **11** in 89% yield. After alkylation of **11** with **8a**, **8c**, **8d**, and **8e** in DMF, the products were converted to the corresponding bromides **12a**, **12c**, **12d**, and **12e** with carbon tetrabromide in acetonitrile. Alkylation of **12a**, **12c**, **12d**, and **12e** with 1-(2-methoxyphenyl)-piperazine in the presence of KI, followed by alkaline hydrolysis gave **13a**, **13c**, **13d**, and **13e**, respectively.

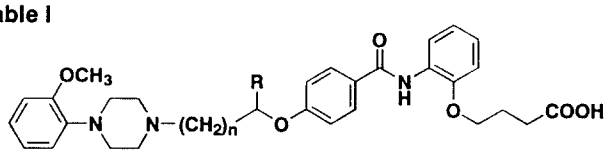
Scheme 4



Compounds **15a~i** were synthesized from **3** under the same conditions as described for the synthesis of **13a**, **13c**, **13d**, and **13e** (Scheme 4).

Biological results and discussion: The compounds were evaluated for their α_1-adrenoceptor antagonism to phenylephrine-induced contractions of New Zealand White rabbit prostate,[14] and their 5α-R inhibitory activities were evaluated by measuring the rate of conversion of testosterone to dihydrotestosterone on Sprague-Dawley rat prostatic 5α-R. The obtained biological data (pA_2 and IC_{50}) are summarized in Tables I~III.

Table I

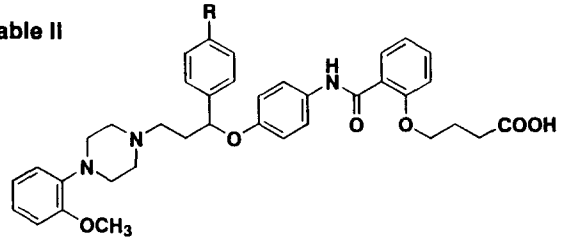


Compound	n	R	α_1 Antagonistic Activity (pA_2)	5α-R Inhibitory Activity IC_{50}(μM)
5a	1	H	6.6	29
5b	2	H	7.0	41
15a	2	Ph	7.6	1.0
5c	3	H	7.1	43
15h	3	Ph	6.5	0.75
15i	4	Ph	6.6	0.91
5d	5	H	7.0	9.5
ONO3805				0.0026

First, the relationship between the number of methylene groups (n) of **5a~5d** and biological activities was investigated. Significant differences in activities were not observed among these compounds; however, α_1-antagonistic activity of **5a** was obviously reduced and 5α-R inhibitory activity of **5d** (n=5) was slightly more potent than that of the other compounds. The introduction of a phenyl group (**15a**) markedly increased both α_1- antagonistic activity and

5α-R inhibitory activity compared with **5b**. Further optimization of the length of the methylene chain in the series of phenyl substituted compounds (**15h** and **15i**) was studied. The most potent α_1-antagonistic activity was observed with **15a**, with the potency decreasing as the length of methylene chain increased. A significant difference in 5α-R inhibitory activity was not detected, however.

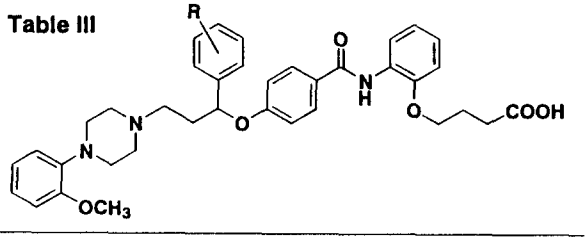
Table II



Compound	R	α_1 Antagonistic Activity (pA_2)	5α-R Inhibitory Activity IC_{50}(μM)
13a	H	7.1	0.73
13c	Me	7.1	0.44
13d	Et	6.7	0.13
13e	iBu	5.2	0.096

In another series of benzanilides, **13a** showed slightly less potent α_1-antagonistic activity and almost equal 5α-R inhibitory activity compared with **15a**. We found that as for the alkyl substituent at the 4-position of the phenyl group, α_1-antagonistic activity decreases, and 5α-R inhibitory activity increases when the alkyl substituents become larger, as shown in Table II.

Table III



Compound	R	α_1 Antagonistic Activity (pA_2)	5α-R Inhibitory Activity IC_{50}(μM)
15a	H	7.6	1.0
15b	3-Me	6.6	0.36
15c	4-Me	7.8	0.067
15d	4-Et	7.4	0.070
15e	4-i-Bu	5.7	0.039
15f	4-MeO	6.7	0.17
15g	4-Br	7.0	0.21

In the investigation of the substituent effects on the phenyl group of **15a**, the introduction of a methyl group at the 3-position (**15b**) resulted in a slight enhancement of 5α-R inhibitory activity, and a 10-fold decrease in α_1-antagonistic activity. In contrast the 4-methyl isomer **15c**

showed significant enhancements of both activities compared with **15b**. The introduction of a large alkyl group at the 4-position caused an increase in 5α-R inhibitory activity; however, α_1-antagonistic activity markedly reduced (**15c**, **15d**, **15e**). Other substituents **15f** and **15g** had no affect on enhancing the activities.

In conclusion, we synthesized a new class of benzanilide derivatives which as expected have both α_1-antagonistic activity and 5α-R inhibitory activity. The compound **15c** is particularly potent in both respects. Further investigations of the optimal requirements for these activities will be reported in future publications.

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