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Novel Thiophene Derivatives for the Treatment of Benign Prostatic Hyperplasia

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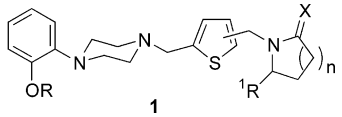
Abstract—The syntheses and biological activities of a novel series of 2,4- and 2,5-disubstituted thiophenes are reported. These analogues have shown excellent affinity and selectivity against α_1-adrenoreceptor subtypes.

Benign prostatic hyperplasia is the most common clinical disorder observed in men above age 60. The condition causes a variety of urological symptoms, including poor urine flow from the bladder, increased frequency in urination, nocturia and hesitancy or delay in starting the urine flow. There are two components to BPH. The static component is characterized by a nonmalignant enlargement of prostatic tissue; resulting in obstruction of urethra.[1] The dynamic component, regulated by α_1-adrenergic receptors (α_1-ARs), is due to the increased smooth muscle tone in the bladder neck and prostate.

α_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] α_1-ARs are involved in the regulation of cardiovascular and central nervous systems (CNS).[3] The three native α_1-AR subtypes (α_{1a}, α_{1b} and α_{1d}) have been cloned from a number of species, including human.[4] It is believed that the use of a selective α_{1a}-AR antagonist would be valuable for the treatment of BPH.[1,5]

Several non-subtype selective α_1-AR antagonists of the quinazoline class (i.e., prazosin, tetrazosin and doxazosin) have been approved for the treatment of BPH. These agents cause relaxation of the prostate smooth muscle and other urinary tract tissues by blocking the adrenergic receptors.[6] These compounds exhibit various side effects, due in part to their nonselective binding with other α_1-AR subtypes.[7] Tamsulosin, a non-quinazoline, also suffers from side effects, despite its modest α_{1a}-AR selectivity.[8] Substantial efforts at designing α_{1a}-AR antagonists have been shown.[9] Herein, we will describe a new series of potent and selective α_{1a}-AR antagonists.



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Initial effort in screening our corporate chemical library against α_1-ARs in a radioligand binding assay had led to the discovery of **13a**. We quickly established that 1-(2-alkoxyaryl)piperazine moiety was necessary for its potency and selectivity. At that point, we decided to modify the alkoxy group, thiophene substitutions and/or the lactam ring according to the general formula **1**.

In order to evaluate the effects of differing amide groups on α_{1a}-selectivity, we initially explored the analogues prepared in Scheme 1. Aldehyde **4** smoothly underwent reductive amination[9] with piperazine **3** affording thiophene **6**. The latter was converted to the aldehyde **8** upon metal halogen exchange with ^{t}BuLi and subsequent quenching with DMF. The aldehyde **8** was reduced to the alcohol **10**. When **10** was treated with excess $SOCl_2$, salt **12** was obtained as white foam after removal of the volatile materials. Salt **12** reacted with lactam anions to furnish *N*-alkylated products (**13b–d**).

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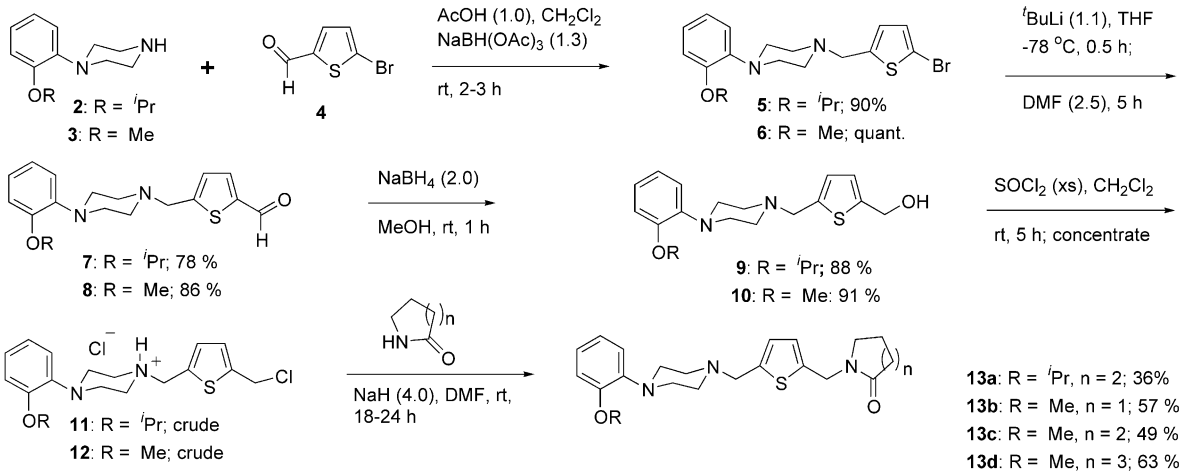
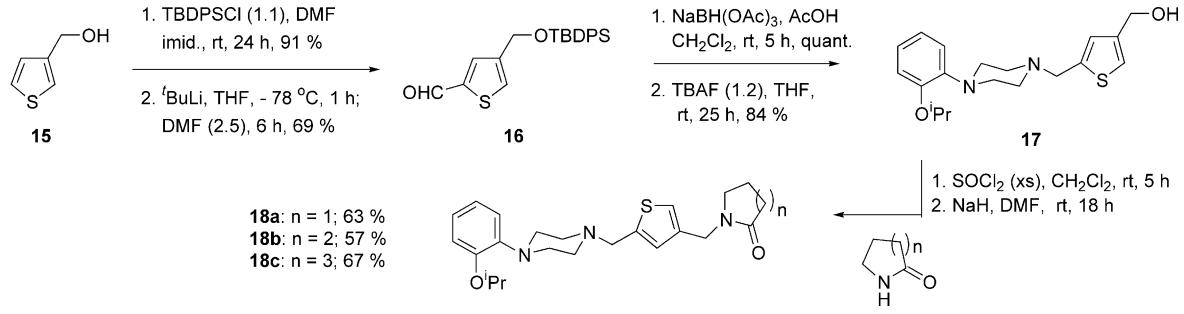


Scheme 1. Synthesis of 2,5-disubstituted thiophene tethered lactams.

Figure 1. 2,5-Disubstituted analogues differing in substitution at the 5-position.



Scheme 2. Synthesis of 2,4-disubstituted thiophene tethered lactams.

Having demonstrated the alcohol **10** as a key intermediate for the coupling with lactams, the isopropoxy analogue **13a**[10] was prepared in the same fashion, starting from the same aldehyde (**4**) as shown in Scheme 1.

The reductive amination[11] of aldehyde **8** was carried out with 2°-amines in the presence of $NaBH(OAc)_3$ to give 3°-amines, **14a** and **14 b** (Fig. 1), in good yields.

3-Thiophenemethanol (**15**) was protected with *tert*-butyl diphenylsilyl chloride, the latter was formylated under strong basic conditions (^{t}BuLi; DMF). The ^{1}HNMR data[12] of the crude material showed the presence of a single regiomer and was assigned as **16**.[13] Reductive amination of the aldehyde **16** with piperazine **2**, followed by deprotection of the silyl group with TBAF furnished alcohol **17**. The alcohol **17** then was converted to the chloro-derivative and alkylated with various lactams to afford compounds **18a–c** (Scheme 2).[12,14]

The binding data[15] was measured using [^{125}I]-HEAT [(±)-(β-(([^{125}I]3-iodo-4-hydroxyphenyl)ethyl)amino-methyl)-tetralone] radioligand binding assay, in which the binding affinity of the compounds to COS cell membranes, expressing the human adrenergic receptor subtypes (α_{1a}-AR, α_{1b}-AR, and α_{1d}-AR), were evaluated.[9d,16]

The 2-methoxyphenyl substituted compounds (**13b–d**) were not as potent as the lead **13a** (Table 1). Also, the potency of the analogues **13b–d** remained in the same order while the size of the lactam ring varied from five to seven. In this series of compounds, almost no selectivity was observed between α_{1a} and α_{1d}. Though, the selectivity between the subtypes α_{1a} and α_{1b} was good (>125-fold). From Table 1, it is clear that the affinity of the derivatives **6–10**, lacking the lactam portion, against the α_{1a} subtype was poor (>128 nM). When the lactam portion in **13b** was replaced with a pyrrolidinyl group (**14a**), potency remained more or less the same. However, upon modification of the 2-piperidinone (viz., **13c**) to a piperidinyl moiety (**14b**) potency dropped dramatically by 30-fold. Thus, a carbonyl group may be required for potency as well as selectivity.

Table 1. Binding affinities[a] to the human α_1-Ars

Compd	K_i (nM)			K_i ratio	
	α_{1a}	α_{1b}	α_{1d}	α_{1b}/α_{1a}	α_{1d}/α_{1a}
6	128	757	92	6	0.7
8	578	1878	262	3.2	0.4
10	202	1063	138	5.3	0.7
13a	0.3	413	18	1251	54
13b	40	>5000	23	>125	0.6
13c	14	>5000	12	>357	0.9
13d	18	>5000	13	>278	0.7
14a	12	592	15	49	1.3
14b	419	2569	130	6.1	0.3
17	331	>5000	339	>15	1
18a	0.2	259	25	1523	147
18b	0.5	384	92	768	184
18c	1.8	615	47	342	26

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

Since the lead compound **13a**, having an isopropyl substituent, was more potent than the corresponding methoxy analogues (**13b–d**), we decided to conduct additional SAR studies holding the isopropyl constant.

The affinity of the 2,4-disubstituted thiophenes (**18a–c**) was in the sub-nanomolar range. In the same vein, selectivity against α_{1d} increased to around 150-fold (**18a** and **18b**); better than that of **13a**. It should be noted that, by changing the substitution pattern from a 2,5-disubstituted thiophene (*para*-bioisoster) to its 2,4-derivative (*meta*-), the affinity was retained and selectivity was enhanced. Compounds **18a–c**, are highly potent against α_{1a}-AR and very selective against the other subtypes, α_{1b}-AR and α_{1d}-AR.

In summary, a convenient synthesis of 2,4-disubstitued thiophenes from a 3-substituted thiophene and general route for the introduction of lactam moieties at the 4- and 5-thiophenemethyl center were illustrated. The SAR studies of these series have shown the importance of the isopropyl group and the need for a carbonyl group in the thiophene substituent and led to the discovery of a family of very potent and selective α_{1a}-AR inhibitors.

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12. **General procedure A**: ^{t}BuLi (1.7 M; 7.9 mL, 13.4 mmol) was added to a solution of **6** (4.1 g, 11.2 mmol) in THF at −78 °C. After 1 h, DMF (2.0 mL, 25.8 mmol) was added and stirred for another 6 h. It was allowed to warm to 0 °C, and satd NH_4Cl was added, followed by extraction with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The material was flushed through a short silica gel plug eluting with EtOAc, affording the aldehyde **8** in 86% yield.

General procedure B: $SOCl_2$ (3.0 mL, excess) was added to the alcohol **10** (0.182 g, 0.57 mmol) in CH_2Cl_2 (5.0 mL) at rt. After 6 h, the volatile materials were removed in a rotary evaporator and dried in vacuo to obtain the chloro derivative as foam. In a separate flask, 2-pyrrolidinone (0.098 g, 1.16 mmol) was added slowly to a suspension of NaH (0.055 g, 2.3 mmol) in DMF (1 mL). After 0.5 h, a solution (1.0 mL, DMF) of the above chloro derivative was injected slowly. Stirred for 18 h, then satd NH_4Cl was added and extracted with EtOAc. The combined extracts were washed with water, brine, then dried (Na_2SO_4), and concentrated. Silica gel chromatography (10–25% EtOAc/hexanes) afforded product **13b** in 57% yield.
13. After completion of this work, there appeared a paper on the synthesis of similar compounds on solid support. Li, Z.; Ganesan, A. *Synlett* **1998**, 405.
14. ^{1}H NMR [(300 MHz, $CDCl_3$), (ppm)] and mass spectral data of selected compounds: Compound **8**: 9.85 (s, 1H), 7.64 (d, $J=3.7$ Hz, 1H), 7.06 (d, $J=3.7$ Hz, 1H), 6.84–7.01 (m, 4H), 3.85 (s, 3H), 3.81 (s, 2H), 3.11 (br s, 4H), 2.73 (t, $J=4.5$ Hz, 4H). MS (ES): m/z 317 $[M+H]^+$. Compound **13b**: 6.77–7.00 (m, 6H), 4.57 (s, 2H), 3.85 (s, 3H), 3.74 (s, 2H), 3.37 (t, $J=7.0$ Hz, 2H), 3.10 (br s, 4H), 2.69 (br s, 4H), 2.42 (t, $J=8.1$ Hz, 2H), 2.01 (quintet, $J=7.5$ Hz, 2H). MS (ES): m/z 386 $[M+H]^+$. Compound **14a**: 6.78–7.02 (m, 4H), 6.76 (d, $J=3.4$ Hz, 1H), 6.74 (d, $J=3.4$ Hz, 1H), 4.03 (d, $J=14.0$ Hz, 1H), 3.86 (d, $J=14.0$ Hz, 1H), 3.85 (s, 3H), 3.74 (s, 2H), 3.70 (s, 3H), 3.33 (dd, $J=5.8$ Hz, 8.7 Hz, 1H), 3.10 (m, 5H), 2.70 (br s,

4H), 2.55 (dd, $J=6.5$ Hz, 8.0 Hz, 1H), 1.61–2.18 (m, 4H). MS (ES): m/z 430 $[M+H]^+$. Compound **16**: 9.87 (s, 1H), 7.67 (dd, $J=1.4$ Hz, 6.0 Hz, 4H), 7.61 (d, $J=0.8$ Hz, 1H) 7.55 (br s, 1H), 7.36–7.44 (m, 6H), 4.74 (s, 2H), 1.09 (s, 9H). MS (ES): m/z 381 $[M+H]^+$. Compound **18a**: 7.02 (br s, 1H), 6.84–6.91 (m, 4H), 6.84 (br s, 1H), 4.59 (septet, $J=6.0$ Hz, 1H), 4.39 (s, 2H), 3.72 (s, 2H), 3.31 (t, $J=7.0$ Hz, 2H), 3.12 (br s, 4H), 2.65 (br s, 4H), 2.43 (t, $J=8.0$ Hz, 2H), 2.00 (quintet, $J=7.5$ Hz, 2H), 1.34 (d, $J=6.0$ Hz, 6H). MS (ES): m/z 414 $[M+H]^+$.

15. The K_i values were calculated according to the equation $K_i=[IC_{50}]/(1+[\text{radioligand}]/K_d)$ Cheng, Y.-C.; Prusofff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.

16. Antagonist activity of the lead compound (**13a**) was assessed by the inhibition of (±)-norepinephrine-induced contractions in isolated rat prostate (predominantly express α_{1a}) and aorta tissues (predominantly express α_{1d}). Either rat aorta or rat prostate tissue are bathed in buffer or buffer plus test compound. The effects of increasing concentrations of norepinphrine upon tissue tension are measured. The pA_2 value is the negative log of the molar concentration of the test compound that would produce a 2-fold shift in the concentration–response curve of the agonist (NE). For compound **13c**, the pA_2 values for prostate and aorta are 8.311 and 6.898, respectively.