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(Phenylpiperidinyl)cyclohexylsulfonamides: Development of $\alpha_{1a/1d}$-selective adrenergic receptor antagonists for the treatment of benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS)

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Abstract—Although α_1 adrenergic receptor blockers can be very effective for the treatment of benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS), their usage is limited by CV-related side-effects that are caused by the subtype non-selective nature of the current drugs. To overcome this problem, it was hypothesized that a $\alpha_{1a/1d}$ subtype selective antagonist would bring more benefit for the therapy of BPH/LUTS. In developing such selective $\alpha_{1a/1d}$ ligands, a series of (phenylpiperidinyl)cyclohexylsulfonamides has been synthesized and evaluated for binding to three cloned human α_1-adrenergic receptor subtypes. Many compounds showed equal affinity for both α_{1a} and α_{1d} subtypes with good selectivity versus the α_{1b} subtype.

The prostate is a walnut-sized auxiliary sexual gland that is situated just below the bladder and surrounds the urethra. Overgrowth of the prostate with age will cause benign prostatic hyperplasia (BPH), which results in obstruction of the bladder outlet and eventually leads to lower urinary tract symptoms (LUTS). These symptoms include increased urinary frequency, decreased urine stream, increased urgency and feeling of irritation, and sensation of incomplete bladder emptying.[1,2a,b] Since there are two pathological components in BPH, namely the increased size and elevated muscle tone of the prostate gland, medication therapy for BPH/LUTS has been classified into two categories. The first category, 5-α-reductase inhibitors (finasteride and dutasteride), works by reduction of the size of prostate; another category, α_1-adrenergic receptor antagonists (tamsulosin and terazosin), works by relaxation of prostate smooth muscle. The α_1 blockers have an advantage over 5-α-reductase inhibitors in that they can provide effective relief of symptoms in a short period of time. Unfortunately, the usage of α_1 blockers for the treatment of BPH/LUTS is also limited by the fact that all α_1 drugs currently on the market produce side-effects. The most prominent of these is the cardiovascular associated orthostatic hypotension.[3,4]

In the late 1980s, molecular biology studies identified three α_1-adrenergic receptor subtypes, classified as α_{1a}, α_{1b}, and α_{1d}.[5–7] The current α_1 drugs are known to bind to all of them indiscriminately or with low selectivity.[8] This characteristic is speculated to be associated with side-effects. Further studies also revealed that the α_{1a}-adrenoceptor subtype plays a dominant role in controlling human prostatic smooth muscle contraction,[8] but the exact contribution of each of three α_1 subtypes to the side-effect of orthostatic hypotension has not yet been clearly determined. Many α_{1a}-adrenoceptor subtype selective antagonists have since been discovered, and they

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have demonstrated the ability to relax prostate muscle without producing cardiovascular side effects.[9a–d] Surprisingly, in subsequent clinical trials, these α_{1a} selective compounds have not been proven to be effective in relieving LUTS, especially the symptom of irritation. This is in sharp contrast to their subtype non-selective counterparts[10] and strongly suggests that in addition to the α_{1a} subtype, other α_1 receptor subtype(s) may be implicated in the BHP/LUTS.

For the past several years, many studies have provided evidence indicating that the α_{1d} subtype is involved in the mediation of LUTS.[11a–c] Experimental data suggest that the α_{1b} subtype may be associated with CV-related side-effects.[12] These results, combined with the fact that a moderately $\alpha_{1a/1d}$ selective drug, tamsulosin (**1**) (Fig. 1), is capable of treating both BPH and LUTS, led to the formation of new hypothesis. Rather than targeting a non-selective or pure α_{1a} selective drug, an antagonist with a balanced $\alpha_{1a/1d}$ selectivity profile should be efficacious yet produce less side effects, hence rendering optimum benefit for BPH/LUTS patients.[13a–e] Unfortunately, providing convincing proof for this hypothesis has been hampered by the fact that no α_1-blocking compound with high $\alpha_{1a/1d}$ selectivity is currently available.

We initiated a research program to validate this hypothesis by first identifying a $\alpha_{1a/1d}$ selective compound, then studying it in established animal models. Our primary goal was to design and synthesize potent and $\alpha_{1a/1d}$ subtype selective antagonist with a selectivity profile superior to marketed drug tamsulosin (**1**) (Fig. 1). In our previous paper,[14] we reported the discovery of a series of (phenylpiperazinyl)cyclohexylsulfonamides (**2**). These compounds showed equal affinity for both the α_{1a} and α_{1d} subtypes, with good selectivity against the α_{1b} subtype. These compounds also had much reduced dopamine affinity compared with some of our previously developed compounds.[15] As a logical extension of the piperazine scaffold, in this paper we want to report the design and synthesis of a series of (phenylpiperidinyl)cyclohexylsulfonamides (**3**) (Fig. 1), and the evaluation of their subtype selectivity in cloned human α_{1a}, α_{1b}, and α_{1d} adrenergic receptors. These piperidine compounds not only increase structural diversity, but also may provide better metabolic stability than the piperazine analogues.

The (phenylpiperidinyl)cyclohexylsulfonamides were generally prepared by the following sequence (Schemes 1 and 2). A bromophenol was first O-alkylated, followed by halogen–metal exchange using *n*-butyl lithium. The resulting aryllithium reagent was then reacted with *N*-Boc-protected piperidinone to give the substituted 4-phenyl-4-hydroxypiperidine. Dehydration using methanesulfonyl chloride and triethylamine was followed by hydrogenation to remove the C–C double bond. Final

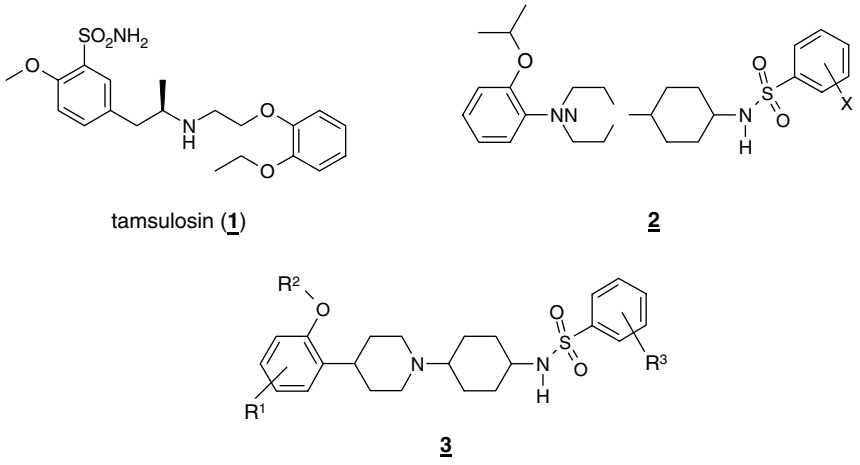
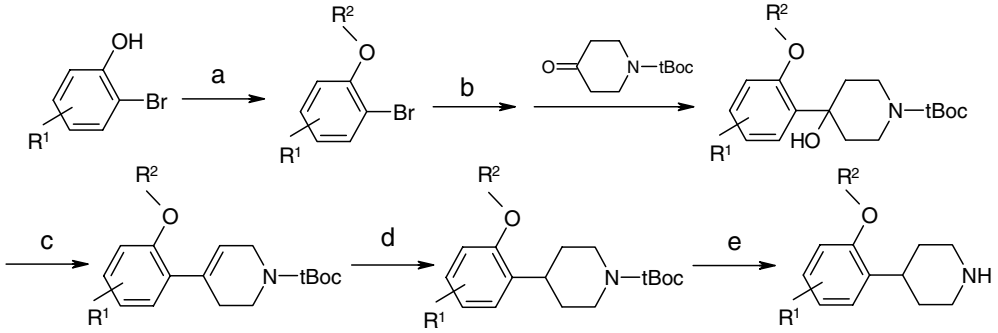
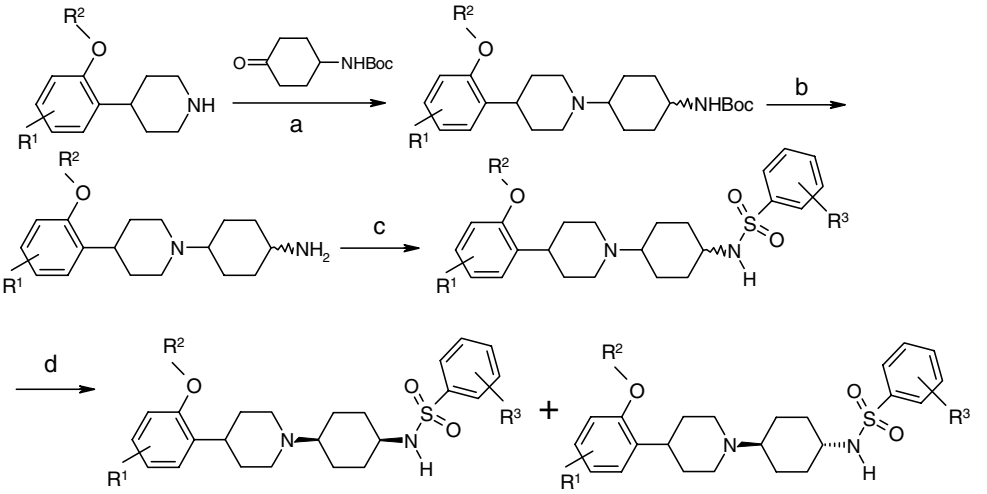


Figure 1. The structures of tamsulosin, compounds **2** and **3**.



Scheme 1. Reagents and conditions: (a) R^2–X, NaH, DMF, rt, 8 h, 50–85% yield; (b) *n*-BuLi/THF, −78 °C, 1 h; 35–60% yield in two steps; (c) MsCl/CH_2Cl_2/Et_3N, −78 °C, 12 h, 50% yield; (d) H_2 (45 psi)-Pd/C, rt, 8 h, 80% yield; (e) TFA/CH_2Cl_2, 0 °C, 3 h, 100% yield.



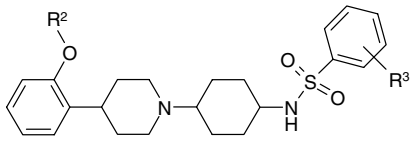
Scheme 2. Reagents and conditions: (a) $Na(AcO)_3BH$, HOAc, CH_2Cl_2, rt, 8 h, 40–65% yield; (b) CF_3CO_2H/CH_2Cl_2, rt, 2 h, 90–100% yield; (c) sulfonyl chloride/CH_2Cl_2/Na_2CO_3 (aq), rt, 8 h, 60–90% yield; (d) SiO_2 column or preparative TLC.

treatment with TFA yielded the free piperidine product (Scheme 1).

To complete the synthesis, ^{t}Boc-protected 4-aminocyclohexanone was subjected to reductive amination with the substituted phenylpiperidine to give a cis/trans mixture of diaminocyclohexane intermediates. Treatment with TFA produced the free amine, which was reacted with various sulfonyl chlorides. Final chromatographic separation gave the desired isomeric products[16] (Scheme 2).

We first investigated (alkoxyphenylpiperidinyl)cyclohexylsulfonamides (**4**). A series of analogues were prepared and evaluated; the results are summarized in Table 1 (K_i values for tamsulosin, **1**, in the α_{1a}, α_{1b}, and α_{1d} binding assays were 0.19, 2.0, and 0.2 nM, respectively.). In addition to binding affinity for the α_1-adrenoceptor subtypes, each analogue's dopamine D_2 affinity was also evaluated. For the choice of R^2 substitutions, we followed the SAR from our earlier piperazine series.[14] Considering the possible metabolic vulnerability of the 2-propoxy group, it was replaced with a cyclopropoxy group in some analogues. Just as in the piperazine series, we observed noticeable differences in binding affinities and selectivity profiles between cis and trans isomers (e.g., *cis*-**5** vs *trans*-**5**, *cis*-**7** vs. *trans*-**7**). Generally speaking, cis isomers were the more desirable compounds since they had better $\alpha_{1a/1d}$ selectivity profiles. However, the cyclopropoxy group did not appear to offer substantial advantage over 2-propoxy substitution in terms of α_1 binding affinity. As for the R^3 group, 3, 4-diMeO seemed to give consistently better results. It was discovered that several analogues showed equal affinity for α_{1a} and α_{1d} subtypes, with good selectivity against α_{1b} subtype (*cis*-**5**, **6**, and **7**). Their α_{1a}/α_{1b} ratios ranged from 65- to 155-fold, and their α_{1d}/α_{1b} ratios ranged from 64- to 187-fold. This represented a substantial improvement over the 10-fold

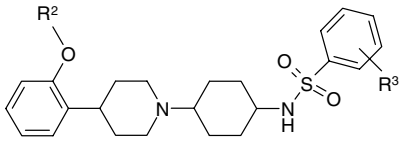
Table 1. Binding profiles of (alkoxyphenylpiperidinyl)cyclohexylsulfonamides **4** (K_i, nM)



4

Compound	Configuration	R^2	R^3	α_{1a}	α_{1b}	α_{1d}	D_2
5	*cis*[17]	2-Propyl	3,4-DiMeO	2.2	144	0.77	144
	trans[17]			28	148	40	55
6	*cis*	2-Propyl	3,4-DiF	3.0	470	7.3	79
	trans			1.4	1385	87	79
7	*cis*	Cyclopropyl	3,4-DiMeO	0.91	141	2.0	144
	trans			11	133	34	133
8	*cis*	Cyclopropyl	2-MeO-5-Cl	1.3	82	2.6	129
	trans			4.5	305	47	154
9	*cis*	Cyclopropyl	2-F-5-Cl	1.8	107	2.1	187
	trans			3.8	337	32	159
10	*cis*	Cyclopropyl	3,4-(OCH_2O)	16	275	13	66
	trans			14	340	57	71

Table 2. Binding profiles of (fluoroalkoxyphenylpiperidinyl)cyclohexylsulfonamides **4** (K_i, nM)



4

Compound	Configuration	R^2	R^3	α_{1a}	α_{1b}	α_{1d}	D_2
11	*cis*	CH_2CF_3	3,4-DiMeO	1.8	123	2.2	111
	trans			21	368	23	83
12	*cis*	CH_2CF_3	3,4-(OCH_2CH_2O)	4.0	92	3.0	57
	trans			2.2	91	26	23
13	*cis*	CH_2CF_3	2-MeO-5-Cl	6.2	216	1.6	69
	trans			10	703	36	82
14	*cis*	CH_2CF_3	2-F-5-Cl	5.9	181	0.98	78
	trans			4.8	787	44	37
15	*cis*	CH_2CF_3	3-$OCHF_2$	7.0	261	5.9	85
	trans			12	355	70	129
16	*cis*	CH_2CF_3	4-$OCHF_2$	5.4	76	2.7	154
	trans			38	302	86	104
17	*cis*	CH_2CH_2F	3,4-DiMeO	8.5	401	5.5	201
	trans			69	4403	49	284
18	*cis*	CH_2CHF_2	3,4-DiMeO	12	300	4.1	276
	trans			31	681	86	88

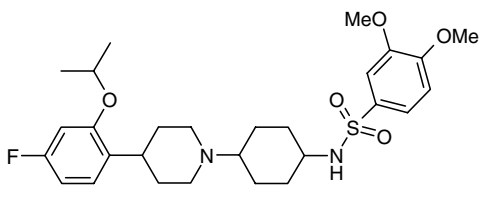
ratios shown by the commercial drug tamsulosin (**1**). It was also observed that many (phenylpiperidinyl)cyclohexylsulfonamides had much reduced dopamine affinities.

To strengthen the alkoxy group against possible metabolism, we decided to incorporate fluorine into the alkyl side-chain. Several fluoroethoxy-substituted compounds were synthesized and their binding study results are summarized in Table 2. We quickly discovered that within the mono-, di-, and trifluoro-substitutions, only trifluoroethoxy gave optimal results in terms of affinity and selectivity (*cis*-**11** vs. *cis*-**17** and *cis*-**18**). Once again, the R^3 group followed the same trend as in Table 1 and cis isomers were more desirable than trans isomers. Compounds *cis*-**11**, *cis*-**13**, and *cis*-**14** had single-digit nanomolar affinity for both α_{1a} and α_{1d} subtypes and with reasonably good selectivity. Their α_{1a}/α_{1b} ratios ranged from 30- to 68-fold, and α_{1d}/α_{1b} ratios ranged from 56- to 184-fold. Many compounds also displayed good selectivity against the D_2 receptor.

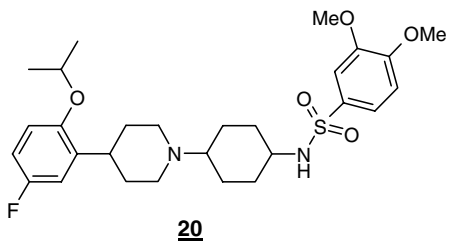
Finally, we prepared and tested several compounds with fluorinated aromatic rings, including 4-fluoro (**19**) and 5-fluoro (**20**) analogues (Table 3). In addition to the established trend that the cis isomers had higher binding affinities than the trans isomers, it was also observed that fluoro substitution at the 4-position was detrimental to α_{1a} and α_{1d} affinity (*cis*-**19** vs. *cis*-**20**). This might indicate electronic restriction at this position. In contrast, fluoro-substitution at the 5-position had little detrimental effect on affinity and selectivity; *cis*-**20** had a similar profile to *cis*-**5**.

In conclusion, to identify $\alpha_{1a/1d}$ selective antagonists as new drugs for the treatment of BPH/LUTS, we have designed and synthesized a series of (phenylpiperidinyl)cyclohexylsulfonamides. These compounds were

Table 3. Binding profiles of compounds **19**and **20** (K_i, nM)



19



20

Compound	Configuration	α_{1a}	α_{1b}	α_{1d}	D_2
19	*cis*	16	690	12	106
	trans	23	639	60	104
20	*cis*	3.3	299	1.6	178
	trans	43	1487	53	94

evaluated for their ability to bind to cloned human α_{1a}, α_{1b}, and α_{1d} adrenergic receptor subtypes as well as the dopamine D_2 receptor. The effect of aromatic substitution and fluorination of the alkoxy side-chain and phenyl ring on binding affinity and selectivity has been investigated. We discovered several compounds (*cis*-**5**, **6**, **7**, **11**, and **20**) that showed equal affinity for both α_{1a} and α_{1d} adrenoceptor subtypes, with very good selectivity over the α_{1b} subtype. This selectivity profile provides a great improvement over the commercial drug tamsulosin. Future work will further explore the issue of metabolic stability, and progress will be reported in due course.

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15. Unpublished results.
16. The isomers with higher R_f values in TLC are the cis isomers. The isomers with lower R_f values are the trans isomers. The assignment is based on the NMR pattern of similar (piperazinyl)cyclohexylsulfonamide compound with known cis or trans configuration.
17. NMR and MS data of representative compounds.
Compound *cis*-**5** NMR: δ ($CDCl_3$) 1.33 (d, J = 6.0 Hz, 6H), 1.4–1.9 (m, 12H), 2.22 (m, 3H), 2.8–3.1 (m, 3H), 3.44 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 4.52 (m, 1H), 5.08 (d, J = 7.5 Hz, NH, 1H), 6.8–7.6 (m, 7H) MS: 517 (M+1).
Compound *trans*-**5** NMR: δ ($CDCl_3$) 1.25 (m, 4H), 1.34 (d, J = 6.0 Hz, 6H), 1.65 (m, 2H), 1.8–2.1 (m, 6H), 2.30 (m, 3H), 2.95 (m, 3H), 3.08 (m, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 4.52 (m, 1H), 4.90 (d, J = 7.3 Hz, NH, 1H), 6.8–7.6 (m, 7H). MS: 517 (M+1).
Compound *cis*-**6** NMR: δ ($CDCl_3$) 1.32 (d, J = 5.8 Hz, 6H), 1.53 (m, 4H), 1.6–1.8 (m, 6H), 1.82 (br d, 2H), 2.20 (m, 3H), 2.91 (m, 1H), 3.00 (br d, 2H), 3.45 (m, 1H), 4.52 (m, 1H), 4.90 (br s, NH, 1H), 6.8–7.8 (m, 7H) MS: 493 (M+1).
Compound *trans*-**6** NMR: δ ($CDCl_3$) 1.22 (m, 4H), 1.35 (d, J = 6.1 Hz, 6H), 1.64 (m, 2H), 1.80 (bd, 2H), 1.92 (br t, 4H), 2.28 (m, 3H), 2.93 (m, 3H), 3.10 (m, 1H), 4.50 (m, 1H), 4.60 (br s, NH, 1H), 6.8–7.8 (m, 7H). MS: 493 (M+1).
Compound *cis*-**11** NMR: δ ($CDCl_3$) 1.4–1.8 (m, 10H), 1.84 (br d, 2H), 2.25 (m, 3H), 2.90 (m, 3H), 3.42 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 4.35 (q, J = 15 Hz, 2H), 5.20 (d, J = 7.8 Hz, NH, 1H), 6.7–7.6 (m, 7H) MS: 557 (M+1).
Compound *trans*-**11** NMR: δ ($CDCl_3$) 1.1–1.4 (m, 4H), 1.65 (m 2H), 1.8–2.0 (m, 6H), 2.30 (m, 3H), 2.93 (m, 3H), 3.04 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 4.33 (q, J = 14.8 Hz, 2H), 4.80 (d, J = 8.1 Hz, NH, 1H), 6.7–7.5 (m, 7H) MS: 557 (M+1).
Compound *cis*-**18** NMR: δ ($CDCl_3$) 1.4–1.6 (m, 4H), 1.6–1.8 (m, 6H), 1.82 (br d, 2H), 2.25 (m, 3H), 2.88 (m, 1H), 2.95 (br d, 1H), 3.40 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 4.16 (dt, J_1 = 13 Hz, J_2 = 3.0 Hz, 2H), 5.02 (d, J = 7.8 Hz, NH, 1H), 6.10 (tt, J_1 = 38 Hz, J_2 = 2.0 Hz, 1H), 6.8–7.6 (m, 7H) MS: 539 (M+1).
Compound *trans*-**18** NMR: δ ($CDCl_3$) 1.1–1.4 (m, 4H), 1.66 (m, 2H), 1.80 (br d, 2H), 1.90 (br d, 2H), 2.27 (m, 3H), 2.93 (m, 3H), 3.05 (m, 1H), 3.94 (s, 3H), 3.96 (s, 3H), 4.15 (dt, J_1 = 13.5 Hz, J_2 = 3.1 Hz, 2H), 4.60 (d, J = 7.8 Hz, NH, 1H), 6.10 (tt, J_1 = 38 Hz, J_2 = 2.0 Hz, 1H), 6.7–7.6 (m, 7H) MS: 539 (M+1).
Compound *cis*-**20** NMR: δ ($CDCl_3$) 1.36 (d,J = 6.0Hz, 6H), 1.4–2.0 (m, 12H), 2.33 (m, 3H), 2.91 (m, 1H), 3.10 (br d, 1H), 3.40 (m, 2H), 3.45 (m, 1H), 3.96 (s, 3H), 3.98 (s, 3H), 4.52 (m, 1H), 5.20 (d, J = 7.5 Hz, NH, 1H), 6.8–7.6 (m, 6H) MS: 535 (M+1).
Compound *trans*-**20** NMR: δ ($CDCl_3$) 1.26 (m, 4H), 1.35 (d, J = 6.1 Hz, 6H), 1.64 (m, 2H), 1.8–2.0 (m, 6H), 2.32 (m, 3H), 2.90 (m, 3H), 3.04 (m, 1H), 3.94 (s, 3H), 3.98 (s, 3H), 4.52 (m, 1H), 4.70 (d, J = 7.8 Hz, NH, 1H), 6.7–7.6 (m, 6H) MS: 535 (M+1).