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(Phenylpiperazinyl)cyclohexylureas: Discovery 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—Benign prostatic hyperplasia/lower urinary tract symptoms (BPH/LUTS) can be effectively treated with α_1 adrenergic receptor antagonists. Unfortunately, currently marketed α_1 blockers produce CV-related side effects that are caused by the subtype non-selective nature of the drugs. To overcome this problem, it was postulated that an $\alpha_{1a/1d}$ subtype-selective antagonist would bring more benefit for the treatment of BPH/LUTS. As a continuation of our effort to develop selective $\alpha_{1a/1d}$ ligands, a series of (phenylpiperazinyl)cyclohexylureas was synthesized and evaluated for the ability to bind to three cloned human α_1-adrenergic receptor subtypes. Several *trans* isomers were shown to have equal affinity for both α_{1a}, and α_{1d} subtypes, with 14- to 47-fold selectivity versus the α_{1b} subtype and >15-fold selectivity versus dopamine D_2.

Because the proportion of older adults is steadily increasing and is predicted to grow in the 21st century, healthcare providers and the pharmaceutical industry have begun to pay greater attention to age-related diseases such as benign prostatic hyperplasia (BPH). BPH is a disease affecting the prostate, a walnut-sized male sex auxiliary gland located just below the bladder and surrounding the urethra. Excessive growth of the prostate with age will lead to BPH, which eventually causes obstruction of the bladder outlet and results in the manifestation of lower urinary tract symptoms (LUTS). These symptoms include increased frequency of urination, decreased urine stream, increased urgency and feeling of irritation, and sensation of incomplete bladder emptying.[1,2] Several methods for the treatment of BPH/LUTS are available. Besides surgical resection of the prostate (prostatectomy), drug intervention is a popular alternative. Pharmaceutical therapies for BPH/LUTS have been developed to treat the two pathological components in BPH, increased size and elevated muscle tone of prostate gland. In the first class of medicines are the 5-α-reductase inhibitors (e.g., finasteride and dutasteride), which work by reducing the size of the prostate. The second class is comprised of the α_1-adrenergic receptor antagonists (e.g., tamsulosin and terazosin), which work by relaxing prostate smooth muscle. One potential advantage of the α_1 blockers is that they can provide effective relief of symptoms in a very short period of time, compared with the typically slow onset of 5-α-reductase inhibitors. Unfortunately, the benefit of using α_1 blockers for treatment of BPH/LUTS is shadowed by the fact that all α_1 drugs currently on the market also produce potentially serious cardiovascular(CV)-associated side effects, specifically orthostatic hypotension.[3,4]

Molecular biology has classified the α_1-adrenergic receptor into α_{1a}, α_{1b}, and α_{1d} subtypes;[5–7] current

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α_1-blocking drugs have been shown to have approximately equal affinity for each subtype.[8] It is speculated that the orthostatic hypotension side effect of current α_1 blockers is caused by their lack of subtype selectivity. Among the α_1-adrenoceptor subtypes, α_{1a} was determined to play a major role in the control of human prostatic smooth muscle contraction, but the precise contribution of each subtype to adverse side effects has not yet been clearly defined.[8] Many α_{1a}-adrenoceptor subtype-selective antagonists have since been discovered, and they have demonstrated the ability to relax prostate muscle without causing CV side effects in animals.[9] Surprisingly, in subsequent human clinical trials, these α_{1a}-selective compounds were not proven to be effective in relieving LUTS, in sharp contrast to their subtype non-selective counterparts.[10] This finding strongly suggests that in addition to the α_{1a} subtype, other α_1 receptor subtypes may be implicated in BHP/LUTS. Recently, evidence has emerged indicating that the α_{1d} subtype is also involved in the mediation of LUTS.[11] Experimental data also suggest that the α_{1b} subtype may be associated with CV-related side effects.[12] These results, combined with the fact that tamsulosin (**1**, Fig. 1), a moderately $\alpha_{1a/1d}$-selective drug, is capable of treating both BPH and LUTS, led to the formation of new hypothesis that an antagonist with a balanced $\alpha_{1a/1d}$ selectivity profile will be efficacious yet will produce fewer side effects.[13] Unfortunately, convincing evidence for this hypothesis has been hindered by the fact that no α_1 antagonists with high α_{1a} and α_{1d} affinity and good selectivity versus α_{1b} are currently available.

We initiated a research program to validate this hypothesis by first discovering $\alpha_{1a/1d}$-selective compounds, then studying them in established animal models. Our primary goal was to design and synthesize potent and $\alpha_{1a/1d}$ subtype-selective antagonists with better selectivity profiles than marketed drug tamsulosin. In our previous papers, we reported the discovery of three new series of α_1 antagonists: (phenylpiperazinyl)cyclohexylphthalimides **2**,[14a] (phenylpiperazinyl)cyclohexylsulfonamides **3**,[14b] and (phenylpiperidinyl)cyclohexylsulfonamides **4**[14c] (Fig. 1). Many of these compounds exhibited equally high affinity for both α_{1a}- and α_{1d}-adrenoceptors, with very good selectivity against the α_{1b} subtype. As a part of this research, in this paper, we report the design and synthesis of (phenylpiperazinyl)cyclohexylureas **5** and evaluation of their binding affinities for cloned human α_{1a}, α_{1b}, and α_{1d}-adrenergic receptor subtypes and the dopamine D_2 receptor. As can be seen in the following results, some of these compounds show single-digit nanomolar affinities for α_{1a} and α_{1d} subtypes, with more than 10-fold selectivity versus the α_{1b} subtype. The data also reveal a configuration–activity-relationship unique to this urea series.

The (phenylpiperazinyl)cyclohexylureas were generally prepared by the sequence shown in Scheme 1. Readily available 1-(2-isopropoxyphenyl)piperazine was subjected to reductive alkylation with ^{t}Boc-protected 4-aminocyclohexanone to give a *cis*/*trans* mixture of substituted 1,4-diaminocyclohexane intermediates. Treatment with trifluoroacetic acid produced the free cyclohexylamine, which was acylated by various phenyl or benzyl isocyanates. Final chromatographic separation gave the individual *cis* and *trans* stereoisomers for all cases except the analogues prepared from 2-phenoxyphenylisocyanate (R = 2-PhO-C_6H_4), which were tested as the *cis*/*trans* mixture.[15]

The resulting series of analogues was prepared from the deprotected cyclohexylamines and phenyl or benzyl isocyanates to examine the effects of aromatic substitution on binding affinities for the three cloned human α_1-adrenoceptor subtypes and for the dopamine D_2 receptor.[16] The receptor binding results are summarized in Table 1, with binding data for tamsulosin (**1**) included for reference. We previously reported that the *cis* and *trans* isomers in the (phenylpiperazinyl)cyclohexylphthalimide (**2**)[14a] and (phenylpiperazinyl)cyclohexylsulfonamide (**3**)[14b] series exhibited substantial differences in binding affinity and selectivity

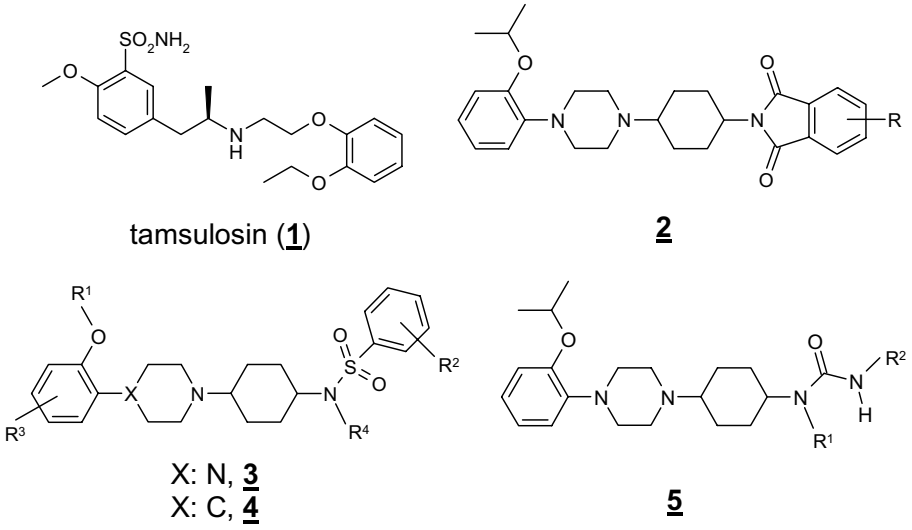
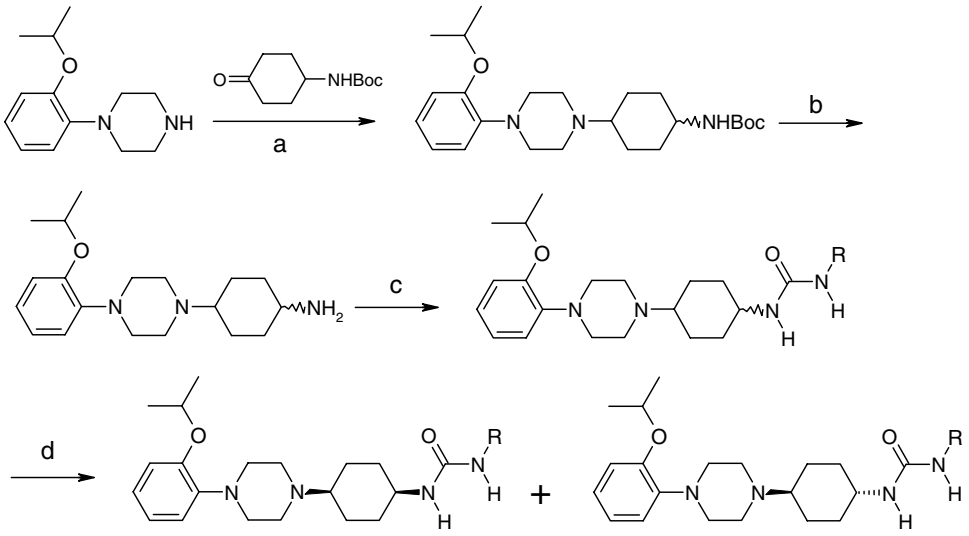


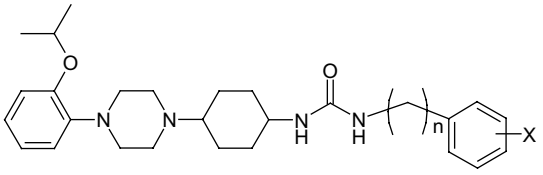
Figure 1. Structures of tamsulosin (**1**), (**2**), (**3**), (**4**), and (**5**).



Scheme 1. 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) $RNCO/CH_2Cl_2$, 50–85% yield; (d) SiO_2 column or prep TLC.

profile, with *cis* isomers generally having higher affinities and selectivities. However, in contrast to these previous findings, the trend in the phenylurea series is reversed, with the *trans* isomers (especially *trans*-**9**, **-12**, **-13**, **-14**, **-15**, **-16**, and **-17**) exhibiting higher α_1 binding affinities than their *cis* counterparts. This

Table 1. Binding profile of (phenylpiperazinyl)cyclohexylureas (K_i[a], nM)



Compound	Config.[16,17]	X	*n*	α_{1a}	α_{1b}	α_{1d}	D_2
1	—	Tamsulosin	—	0.19	2.0	0.2	—
6	Mixture	2-OPh	0	38	430	8.4	22
7	*cis*	2-Cl	0	48	373	46	878
	trans	2-Cl	0	11	39	3.0	33
8	*cis*	2-MeO	0	155	223	73	390
	trans	2-MeO	0	38	107	8.7	921
9	*cis*	3-Cl	0	22	277	29	108
	trans	3-Cl	0	5.1	71	1.5	84
10	*cis*	2,4-diMeO	0	110	475	92	288
	trans	2,4-diMeO	0	74	214	20	892
11	*cis*	2-MeO-5-Cl	0	101	207	64	99
	trans	2-MeO-5-Cl	0	34	81	2.7	1.2
12	*cis*	2,4-diF	0	14	475	26.5	35.5
	trans	2,4-diF	0	3.1	76	2.7	0.69
13	*cis*	2,5-diF	0	26	259	52	199
	trans	2,5-diF	0	1.7	36.4	1.2	0.46
14	*cis*	2,6-diF	0	52	299	92	22
	trans	2,6-diF	0	5.3	36	4.8	2.4
15	*cis*	3,4-diF	0	51	963	72	127
	trans	3,4-diF	0	3.6	60	1.6	54
16	*cis*	2,6-diCl	0	33	289	16	55
	trans	2,6-diCl	0	6.2	50	2.6	4.7
17	*cis*	2,4,6-triCl	0	51	483	25	103
	trans	2,4,6-triCl	0	6.5	112	3.7	6.5
18	*cis*	3-F	1	82	706	62	183
	trans	3-F	1	11	69	15	120

[a] K_i values for α_{1a}, α_{1b}, and α_{1d} were obtained by displacement of [^{125}I]-HEAT from recombinant human receptors. K_i values for D_2 were obtained by displacement of [^{125}I]-spiperone from recombinant human receptors.

opposite configuration–activity-relationship clearly indicates that phenylurea analogues occupy the antagonist binding sites in a very different manner than both phthalimides and sulfonamides. In general, the *trans* isomers bind with up to 4-fold higher affinity for α_{1d} than α_{1a}, and this trend appears to be independent of the substitution pattern on the phenyl ring. However, the presence of an electron donating methoxy substituent leads to relatively weaker affinity for both α_{1d} and α_{1a}, even in the favored *trans* series (**6**, *trans*-**8**, *trans*-**10**, and *trans*-**11**). Several phenylureas having fluorine or chlorine substituents show excellent, single-digit nanomolar α_{1a} and α_{1d} affinities with 14- to 47-fold selectivity versus the α_{1b} subtype (*trans*-**9**, *trans*-**12**, *trans*-**13**, *trans*-**15**, and *trans*-**17**). Compounds *trans*-**12**, *trans*-**13**, and *trans*-**17** in particular show equally high affinity for both α_{1a} and α_{1d} subtypes and are 5- to 34-fold selective versus α_{1b}; however, they also bind strongly to the D_2 receptor. Overall, the best two compounds in this series are *trans*-**9** and *trans*-**15**. They have roughly equal affinity for both α_{1a} and α_{1d} subtypes and are selective with α_{1a}/α_{1b} ratios of 14- and 17-fold, and α_{1d}/α_{1b} ratios of 30- and 47-fold, respectively. *Trans*-**9** and *trans*-**15** are not as potent as tamsulosin, but they have α_{1a}/α_{1b} selectivity similar to tamsulosin and substantially better α_{1d}/α_{1b} selectivity. *Trans*-**9** and **15** also show better selectivity versus the D_2 receptor (15- to 56-fold) than *trans*-**12**, *trans*-**13**, and *trans*-**17**. It was disappointing to discover that selectivity versus α_{1b} and D_2 receptors in the phenylurea series is not as good as our previously reported compounds, especially the sulfonamide analogues (**3** and **4**), which have selectivity ratios close to and sometimes better than 100-fold. Clearly, improvement of the selectivity profile of the phenylurea series should be a goal of future research.

In addition to the phenylureas, the related benzylurea analogues **18** were also prepared and tested. Like all of the phenylureas, *trans*-**18** is more potent than its *cis* counterpart. One encouraging observation is the much weaker D_2 affinity of *trans*-**18** than most *trans*-phenylureas. This may be a pharmacophore feature that can be explored in the future.

In conclusion, we have designed and synthesized a series of (phenylpiperazinyl)cyclohexylureas as an expansion of our efforts to develop $\alpha_{1a/1d}$-selective adrenergic receptor antagonists as new drugs for the treatment of BPH/LUTS. The binding affinities and selectivities of these compounds were evaluated in cloned human α_{1a}, α_{1b}, and α_{1d} adrenergic receptor subtypes and the dopamine D_2 receptor. The effect of aromatic substitution on affinity and selectivity was investigated. We discovered several compounds (*trans*-**9**, *trans*-**12**, *trans*-**13**, *trans*-**15**, and *trans*-**17**) that showed equally potent affinity for both α_{1a} and α_{1d} adrenoceptor subtypes. Two of these compounds (*trans*-**9** and *trans*-**15**) also had 14- to 47-fold selectivity versus the α_{1b} subtype and >15-fold selectivity versus D_2. Although from the perspective of $\alpha_{1a/1d}$ antagonism, urea analogues are not as selective as our previously developed sulfonamide analogues, their unique configuration–activity-relationship (i.e., *trans* isomers have higher affinity than *cis* isomers) opens the door to a new α_1 antagonist pharmacophore that warrants future research.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.11.068.

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15. Most *cis*/*trans* pairs of urea analogues were separable. Both *cis* and *trans* isomers give distinct yet consistent NMR patterns. The isomer having a higher R_f value by TLC was determined by 2D NMR to be the *cis* isomer. This result was confirmed by X-ray crystallography. See supplemental materials in Supporting Information section.
16. Many analogues in previously reported series showed affinity for the D_2 receptor. See Ref. 14.
17. NMR and MS data of representative compounds *cis*-**7**, *trans*-**7**, *cis*-**18**, and *trans*-**18**: *Cis*-**7**: NMR: δ ($CDCl_3$) 1.37 (d, J = 6 Hz, 6 H), 1.50–2.10 (m, 8 H), 2.20–2.38 (m, 1 H), 2.55–2.90 (m, 4 H), 3.00–3.30 (m, 4 H), 3.90–4.10 (m, 1 H), 4.50–4.75 (m, 1 H), 4.95–5.25 (m, 1 H), 6.70–7.10 (m, 6 H), 7.15–7.45 (m, 2 H), 8.15 (d, J = 6.9 Hz, 1 H); MS: 471/473 (M+1). *Trans*-**7**: NMR: δ ($CDCl_3$) 1.05–1.34 (m, 3 H), 1.38 (d, J = 6 Hz, 6 H), 1.41–2.25 (m, 5 H), 2.25–2.45 (m, 1 H), 2.60–2.85 (m, 4 H), 3.00–3.30 (m, 4 H), 3.50–3.80 (m, 1 H), 4.50–4.75 (m, 1 H), 4.75–5.20 (m, 1 H), 6.70–7.10 (m, 6 H), 7.15–7.50 (m, 2 H), 8.14 (d, J = 6.9 Hz, 1 H).; MS: 471/473 (M+1). *Cis*-**18**: NMR: δ ($CDCl_3$) 1.32 (d, J = 6.1 Hz, 6H), 1.61 (m, 4H), 1.7–1.8 (m, 4H), 2.30 (m, 1H), 2.70 (m, 4H), 3.11 (m, 4H), 3.82 (m, 1H), 4.33 (d, J = 6.2 Hz, 2H), 4.59 (m, 1H), 4.60 (bs, NH, 1H), 5.08 (bs, NH, 1H), 6.7–7.4 (m, 8H);MS: 469 (M+1). *Trans*-**18**: NMR: δ ($CDCl_3$) 1.10 (m, 2H), 1.33 (d, J = 6.0 Hz, 6H), 1.40 (m, 2H), 1.95 (bd, 2H), 2.10 (bd, 2H), 2.26 (m, 1H), 2.72 (m, 4H), 3.12 (m, 4H), 3.51 (m, 1H), 4.32 (bs, NH, 1H), 4.35 (d, J = 6.1 Hz, 2H), 4.60 (m, 1H), 4.80 (bs, NH, 1H), 6.7–7.4 (m, 8H); MS: 469 (M+1).