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(Arylpiperazinyl)cyclohexylsufonamides: 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 by α_1-adrenergic receptor antagonists. Unfortunately, all currently marketed α_1 blockers produced CV related side effects that are caused by the subtype non-selective nature of the drugs. To overcome this problem, it was postulated that a $\alpha_{1a/1d}$ subtype selective antagonist would bring more benefit for the treatment of BPH/LUTS. In developing selective $\alpha_{1a/1d}$ ligands, (arylpiperazinyl)cyclohexylsulfonamides were synthesized and their binding profiles against three cloned human α_1-adrenergic receptor subtypes were evaluated. Many compounds show equal affinity for both α_{1a} and α_{1d} subtypes with good selectivity against the α_{1b} subtype. They also overcome the problem of dopamine receptor affinity that previous analogues had exhibited.

The increasing elderly population within society has caused healthcare givers and the pharmaceutical industry to spend more effort on age related diseases such as Benign Prostatic Hyperplasia (BPH). The prostate is a male sex auxiliary gland situated just below the bladder and surrounding the urethra. Excessive growth of the prostate with age will result in BPH, which causes 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.[1,2] As a urological disorder, BPH/LUTS is not a life-threatening disease, but it has adverse impacts on the patient's life style.

Several methods for the treatment of BPH/LUTS may be chosen, depending on the severity of the disease. In addition to surgery (prostatectomy), drug interventions are also available. Since there are two pathological components in BPH, namely the increased size and elevated muscle tone of prostate gland, medication for BPH/LUTS has been classified into two categories. The first category, 5-α-reductase inhibitors (finasteride and dutasteride), work by reducing the size of prostate; another category, α_1-adrenergic receptor antagonists (tamsulosin and terazosin), work by relaxing prostate smooth muscle. Unlike 5-α-reductase inhibitors that take considerable time to show results, the α_1 blockers can provide effective relief of symptoms in very short period of time. Unfortunately, the advantage of using α_1 blockers for treatment of BPH/LUTS is limited by the fact that all α_1 drugs currently on the market also produce significant side effects, specifically, the cardiovascular-associated orthostatic hypotension.[3,4]

Keywords: BPH/LUTS; α_1-Adrenergic receptors; $\alpha_{1a/1d}$ Subtype selective antagonist; (Arylpiperazinyl)cyclohexylsulfonamides.
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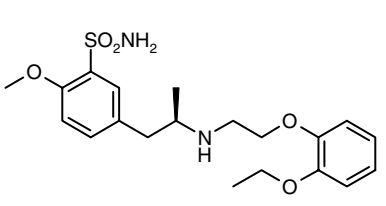
Since late 1980s, molecular biology studies have identified three α_1-adrenergic receptor subtypes, classified as α_{1a}, α_{1b}, and α_{1d}.[5–7] Current α_1 blocking drugs are known to bind to all of them relatively indiscriminately.[8] It is speculated that orthostatic hypotension is caused by the subtype non-selective nature of present α_1 blockers.[8] Further studies also revealed that among three α_1 subtypes, the α_{1a}-adrenoceptor subtype plays a dominant role in controlling human prostatic smooth muscle contraction,[8] but the exact contribution of each subtype to the orthostatic hypotension is not yet clearly determined. Many α_{1a}-adrenoceptor subtype selective antagonists have since been discovered, and they have demonstrated the ability to relax prostate muscle in animals without producing cardiovascular side effects.[9a–c] Surprisingly, in subsequent clinical trials, these α_{1a} selective compounds have not 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 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] There are also experimental data suggesting that α_{1b} subtype may be associated with CV related side effects.[12] On the other hand, tamsulosin (**1**), a moderately $\alpha_{1a/1d}$ selective drug is capable of treating both BPH and LUTS. These results led to the formation of new hypothesis that, rather than non-selective or pure α_{1a} selective drug, an antagonist with balanced $\alpha_{1a/1d}$ selectivity profile will 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 unsuccessful, due to the fact that no α_1 antagonist with high selectivity for the $\alpha_{1a/1d}$ subtypes is currently available.

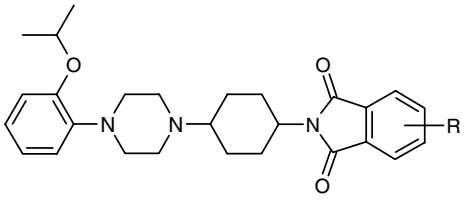
We initiated a research program to validate this hypothesis by first discovering $\alpha_{1a/1d}$ selective compounds, then studying them in established animal models. Our primary goal was to design and synthesize potent and $\alpha_{1a/1d}$ subtype selective antagonists, with superior selectivity profile compared to marketed drug tamsulosin. In our previous papers,[14] we reported the discovery of a series of (phenylpiperazinyl)cyclohexylphthalimides (**2**). These compounds showed equal affinity for both α_{1a} and α_{1d} subtypes, with good selectivity against the α_{1b} subtype. Unfortunately, they also interacted with the dopamine D_2 receptor.[15] In this paper, we report our efforts to overcome this problem through the design and synthesis of a series of (arylpiperazinyl)cyclohexylsulfonamides (**3**), and the evaluation of their subtype selectivities for cloned human α_{1a}-, α_{1b}-, and α_{1d}-adrenergic receptors. As will be shown, compounds not only possess excellent $\alpha_{1a/1d}$ affinity and selectivity, but also show much reduced dopamine activity (Fig. 1).

The (phenylpiperazinyl)cyclohexylsulfonamides (X = CH) were prepared by the following general sequence (Scheme 1). The appropriately substituted phenylpiperazine was subjected to reductive amination with ^{t}Boc protected 4-aminocyclohexanone to give a *cis*/*trans* mixture of diaminocyclohexane intermediates. Treatment with TFA produced the corresponding free amine, which was sulfonylated by various sulfonyl chlorides. Final chromatographic separation gave the individual isomer.[16,18] The related (pyridine-2-ylpiperazinyl)cyclohexylsulfonamides (X = N) were prepared by the same synthetic route starting from substituted (pyridine-2-yl)piperazines.[17]

We first investigated analogues with mono-substituted sulfonamide aryl ring (**4**). In addition to binding affinity for the α_1-adrenoceptor subtypes, each analogue's dopamine D_2 affinity was evaluated. For this series, we observed striking differences in affinity and selectivity profiles between cis and trans isomers (e.g., *cis*-**5** vs *trans*-**5**, *cis*-**9** vs *trans*-**9**, and *cis*-**13** vs *trans*-**13**). Generally speaking, trans isomers had relatively weaker affinity toward the α_{1d} subtype. This made cis-isomers more desirable compounds since they had $\alpha_{1a/1d}$ selectivity profiles closer to the desired 1:1 ratio. Although it is difficult to outline any SAR from such limited number of compounds, several analogues with electron



tamsulosin (**1**)



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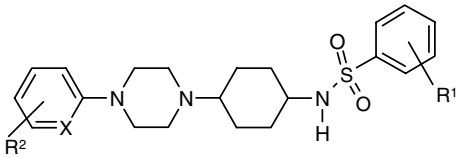

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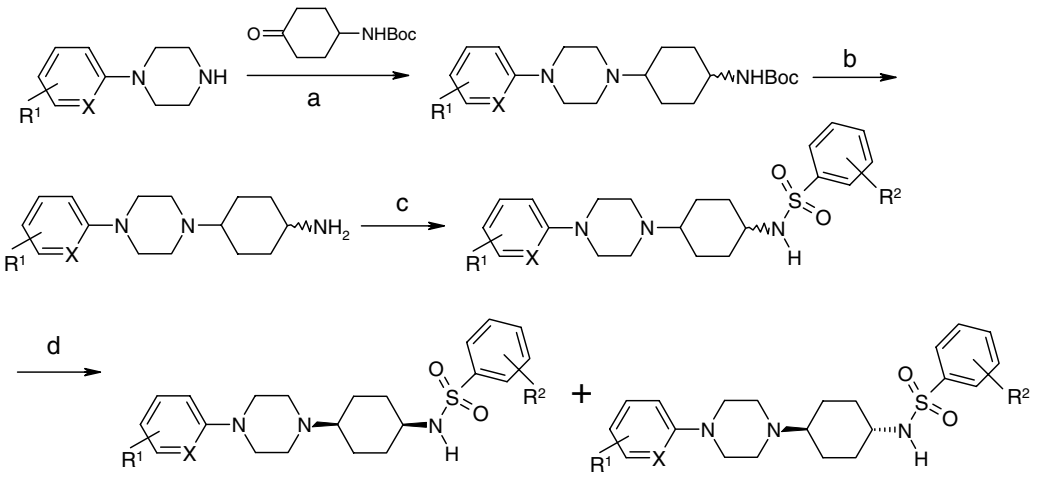
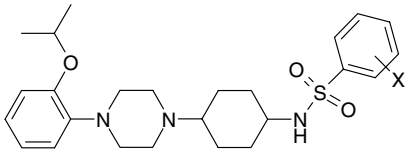
Figure 1. The structure of tamsulosin, compound **2** and **3**.



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) sulfonyl chloride/CH_2Cl_2/Na_2CO_3 (aq), rt, 8 h, 60–90% yield; (d) SiO_2 column or prep. TLC.

Table 1. Binding profiles of analogues with mono-substituted sulfonamide aryl ring **4** (K_i, nM)



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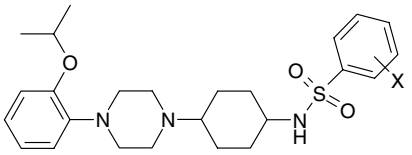
Compound	Configuration	X	α_{1a}	α_{1b}	α_{1d}	D_2
1			0.19	2.0	0.2	
5	*Cis*[16]	H	13.7	111	5.2	191
	Trans[16]	H	2.7	487	55	34
6	*Cis*	2-CN	9.6	217	6.3	55
	Trans	2-CN	0.77	31	3.2	2.4
7	*Cis*	2-F	5.6	103	2.4	149
	Trans	2-F	0.88	385	30	31
8	*Cis*	2-NO_2	6.3	201	2.5	51
	Trans	2-NO_2	1.0	236	27	86
9	*Cis*	3-F	3.5	108	3.3	74
	Trans	3-F	0.73	545	24.5	64
10	*Cis*	3-CF_3	14	222	1.4	118
	Trans	3-CF_3	20	334	35	39
11	*Cis*	4-F	5.6	150	4.8	69
	Trans	4-F	1.3	301	36	27
12	*Cis*	4-SO_2Me	4.8	195	3.4	122
	Trans	4-SO_2Me	7.5	392	22	14
13	*Cis*	4-OCF_3	17	174	2.1	430
	Trans	4-OCF_3	100	1254	111	58

withdrawing groups showed equal affinity for α_{1a} and α_{1d} subtypes, with good selectivity against the α_{1b} subtype (**6**, **8**, **9**, and **12**). Their α_{1a}/α_{1b} ratios ranged from 23- to 40-fold, and their α_{1d}/α_{1b} ratios ranged from 33- to 80-fold. This represents an improvement over the 10-fold α_{1a}/α_{1b} ratio shown by commercial drug tamsulosin (**1**). Perhaps the most encouraging trend we observed was that many (phenylpiperazinyl)cyclohexylsulfonamides had much reduced dopamine affinities, which were difficult to remove from our previously investigated $\alpha_{1a/1d}$ selective antagonists[15] (Table 1).

We next concentrated our efforts on analogues with di-substituted sulfonamide aryl ring (**4**). The binding study results are summarized in Table 2. Once again, cis isomers exhibit more favorable $\alpha_{1a/1d}$ selectivity ratios (i.e., closer to the desired 1:1 ratio) than trans isomers, although again no apparent relationship between substitution pattern and affinity was observed. However, compared with the mono-substituted series, di-substituted analogues showed an even better selectivity profile, especially compounds **14**, **18**, and **23**. Their α_{1a}/α_{1b} ratios ranged from 70-fold to more than 300-fold, and their

Table 2. Binding profiles of analogues with di-substituted sulfonamide aryl ring **4** (K_i, nM)



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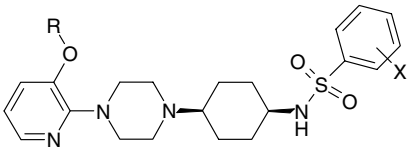
Compound	Configuration	X	α_{1a}	α_{1b}	α_{1d}	D_2
14	*Cis*	3,4-diOMe	1.6	109	1.0	94
	Trans	3,4-diOMe	23	126	24	62
15	*Cis*	2,5-diOMe	8.7	153	5.1	81
	Trans	2,5-diOMe	17	424	56	62
16	*Cis*	2-MeO-5-Me	18	162	7	110
	Trans	2-MeO-5-Me	0.9	218	31	50
17	*Cis*	2-MeO-5-F	6.0	162	5.0	173
	Trans	2-MeO-5-F	11	714	66	139
18	*Cis*	2-MeO-5-Cl	1.0	78	0.75	101
	Trans	2-MeO-5-Cl	3.8	250	11	78
19	*Cis*	2-MeO-5-Br	1.6	42	0.8	37
	Trans	2-MeO-5-Br	10	131	38	36
20	*Cis*	2-MeO-5-CF_3	36	473	14	194
	Trans	2-MeO-5-CF_3	25	258	15	1.9
21	*Cis*	2-MeO-5-NO_2	4.3	85	2.2	45
	Trans	2-MeO-5-NO_2	1.0	173	22	18
22	*Cis*	3-Cl-4-Me	11	167	11	60
	Trans	3-Cl-4-Me	1.5	193	16	52
23	*Cis*	2,4-diCl	4.5	177	0.64	42
	Trans	2,4-diCl	1.6	596	8.6	76
24	*Cis*	3-Cl-2-F	12	120	6.2	198
	Trans	3-Cl-2-F	0.56	348	24	271
25	*Cis*	4-Cl-2-F	11	101	1.5	130
	Trans	4-Cl-2-F	3.0	243	19	42

α_{1d}/α_{1b} ratios ranged from 60- to 270-fold. 3,4-dimethoxy substituted compound *cis*-**14** and 2-methoxy-5-chloro substituted compound *cis*-**18** also showed very good selectivity against the D_2 receptor. These compounds are the α_{1a}/α_{1d} selective antagonist that met our initial goal. Their structural features lay a solid foundation for the further development of new BPH/LUTS drugs.

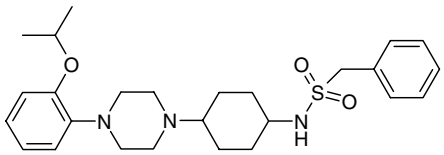
To increase water solubility of (phenylpiperazinyl)cyclohexylsulfonamides and potentially gain favorable PK properties, we decided to incorporate a pyridine group into the scaffold. Several analogues were designed following the best substitution patterns in sulfonamide portion. In this series, only the cis isomers were prepared and are reported in Table 3. Judging from these binding data, it was very clear that in most cases, replacement of the phenyl ring with pyridinyl has a detrimental effect on binding affinity; even the best analogue in this series, **27** is much weaker than its phenyl counterpart **18**. It is possible that under physiological conditions, this part of receptor

Table 3. Binding profiles of pyridine containing analogues **26**–**31** (K_i, nM)



Compound	R	X	α_{1a}	α_{1b}	α_{1d}	D_2
26	*i*-Pr	3,4-diOMe	61	112	19	810
27	*i*-Pr	2-MeO-5-Cl	11	399	12	259
28	*i*-Pr	2-F-5-Cl	45	1855	15	356
29	*c*-PrCH_2	3,4-diOMe	189	364	64	123
30	*c*-PrCH_2	2-MeO-5-Cl	19	601	48	588
31	*c*-PrCH_2	2-F-5-Cl	36	952	44	425

Table 4. Binding profiles of compounds **32**–**35** (K_i nM)



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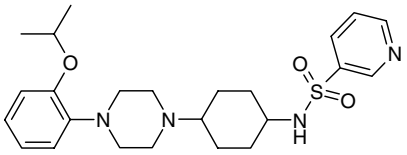

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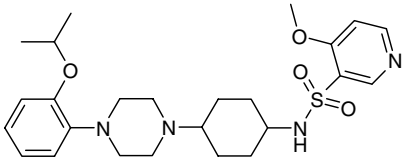

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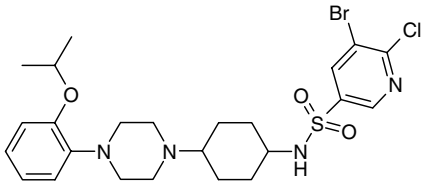

35

Compound	Configuration	α_{1a}	α_{1b}	α_{1d}	D_2
32	*Cis*	1.2	82	3.6	24
	Trans	3.9	200	12	71
33	*Cis*	5.0	400	46	15
	Trans	5.8	192	5.5	55
34	*Cis*	4.9	169	9.4	92
	Trans	13.4	268	76	43
35	*Cis*	14.4	125	0.14	61
	Trans	3.5	279	14.6	80

does not favor a positively charged aromatic ring. We speculated that the iso-propoxy group could be a metabolic weak point for these molecules, and therefore we decided to replace it with cyclopropylmethoxy group. The binding data show that compounds with a cyclopropylmethoxy group are slightly inferior to their iso-propoxy counterparts, perhaps due to a strict size or electronic requirement in this part of the α_{1a} and α_{1d} binding pockets.

Finally, we prepared and tested several related compounds, including benzylsulfonamide **32** and pyridylsulfonamides **33**, **34**, and **35** (Table 4). Extending phenylsulfonamide **5** by one carbon unit gave benzylsulfonamide **32,** which had better affinity and selectivity than phenylsulfonamide **5**. Unfortunately, this change also gave the compound higher dopamine affinity. To increase the compound's water solubility, we replaced the sulfonamide phenyl ring in **5** with a pyridine. The resulting unsubstituted compound *cis*-**33** lost substantial α_{1d} affinity. Interestingly, the trans isomer of **33** is a better $\alpha_{1a/1d}$ antagonist than cis isomer, a very rare phenomenon. Addition of a methoxy group to **33** gave **34**, which improved the affinity (*cis*-**34** vs *cis*-**33**), but still was inferior to our benchmark compounds *cis*-**14** and -**18**. Introduction of chloro and bromo groups to the pyridine gave **35**, which resulted in loss of affinity in the α_{1a} subtype.

In conclusion, to discover an $\alpha_{1a/1d}$ selective antagonist as a new drug for the treatment of BPH/LUTS, we have designed and synthesized a series of (arylpiperazinyl)cyclohexylsulfonamides. Binding affinity and selectivity for these compounds were evaluated in cloned human α_{1a}-, α_{1b}-, and α_{1d}-adrenergic receptor subtypes. The effect of aromatic substitution on their affinity and selectivity was investigated. We discovered several compounds (*cis*-**8**, -**9**, -**12**, -**14**, -**18**, and -**23**) that showed equally high affinity for both α_{1a}- and α_{1d}-adrenoceptor subtypes, with good selectivity against the α_{1b} subtypes. Among these compounds, *cis*-**14** and -**18** also had respectable selectivity over the dopamine D_2 receptor in addition to their excellent $\alpha_{1a/1d}$ selectivity. This selectivity profile is a great improvement over the commercial drug tamsulosin, and we believe this discovery has enriched our knowledge about α_1 blockers and will eventually lead to the development of $\alpha_{1a/1d}$ selective drug for the treatment of BPH/LUTS. Future work will be concentrating on improvement of PK properties and progress will be reported in due course.

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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.2007.04.008.

References and notes

1. Shapiro, E.; Lepor, H. *Urol. Clin. North Am.* **1995**, *22*, 285.
2. Berry, S. J.; Coffey, D. S.; Walsh, P. C.; Ewing, L. L. *J. Urol.* **1984**, *132*, 474.
3. Lepor, H.; Meretyk, S.; Knapp-Maloney, G. *J. Urol.* **1992**, *147*, 1554.
4. Caine, M. *J. Urol.* **1986**, *136*, 1.
5. Bruno, J. F.; Whittaker, J.; Song, J.; Berelowitz, M. *Biochem. Biophys. Res. Commun.* **1991**, *179*, 1485.
6. Ramarao, C. S.; Kincade Denker, J. M.; Perez, D. M.; Galvin, R. J.; Riek, R. P.; Graham, R. M. *J. Biol. Chem.* **1992**, *267*, 21936.
7. Hirasawa, A.; Horie, K.; Tanaka, T.; Takagaki, K.; Murai, M.; Yano, J.; Tsujimoto, G. *Biochem. Biophys. Res. Commun.* **1993**, *195*, 902.
8. Forray, C.; Bard, J. A.; Wetzel, J.; Chiu, G.; Shapiro, E.; Tang, R.; LePor, H.; Hartig, P. R.; Weinshank, R. L.; Branchek, T. A.; Gluchowski, C. *Mol. Pharmacol.* **1994**, *45*, 703.
9. (a) Wetzel, J. M.; Miao, S. W.; Forray, C.; Borden, L. A.; Branchek, T. A.; Gluchowski, C. *J. Med. Chem.* **1995**, *38*, 1579; (b) Wong, W. C.; Chiu, G.; Wetzel, J. M., et al. *J. Med. Chem.* **1998**, *41*, 2643; (c) Lagu, B.; Tian, D.; Chiu, G.; Nagarathram, D.; Fang, J.; Shen, Q.; Forray, C.; Ransom, R. W.; Chang, R. S. L.; Vyas, K. P.; Zhang, K.; Gluchowski, C. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 175.
10. Blue, D. R., Jr.; Grino, P. B.; Jung, D. T.; et al. In *Proceedings of the Fifth International Consultation on BPH*; June 25, **2000** [abstract].
11. (a) Ilampel, C.; Dolber, P. C.; Smith, M. P., et al. *J. Urol.* **2002**, *167*, 1513; (b) Gu, B.; Reiter, J. P.; Schwinn, D. A., et al. *J. Urol.* **2004**, *172*, 758; (c) Smith, M. S.; Scharnbra, U. M.; Wilson, K. H.; Page, S. O.; Schwinn, D. A. *Brain. Res. Mol. Brain Res.* **1999**, *63*, 254.
12. Cavalli, A.; Lattion, A. L.; Hummler, E., et al. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 11589.
13. (a) Schwinn, D. A.; Price, D. T.; Narayan, P. *Mayo Clin. Proc.* **2004**, *79*(11), 1423; (b) Roehrborn, C. G.; Schwinn, D. *J. Urol.* **2004**, *171*, 1029; (c) Sarma, P. K. S.; Tiwari, A.; Pal, A. *Expert Opin. Ther. Pat.* **2005**, *15*(10), 1333; (d) Daniels, D. V.; Gever, J. R.; Jasper, J. R.; Kava, M. S., et al. *Eur. J. Pharmacol.* **1999**, *370*, 337; (e) Lowe, F. C. *Clin. Ther.* **2004**, *26*, 1701.
14. Li, S.; Chiu, G.; Pulito, V. L.; Liu, J.; Connolly, P. J.; Middleton, S. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*(6), 1646.
15. Unpublished results.
16. The isomer with the higher R_f value by TLC is the cis isomer. The isomer with lower R_f value is the trans isomer. This has been determined by 2-D NMR and confirmed by X-ray structure determination.
17. Genin, M. J.; Poel, T. J.; Yagi, Y.; Biles, C.; Althaus, I.; Keiser, B. J., et al. *J. Med. Chem.* **1996**, *39*, 5267.
18. NMR and MS data of representative compounds. *Cis*-**5** NMR: δ ($CDCl_3$) 1.32 (d, J = 6.0 Hz, 6H), 1.47 (m, 2H), 1.55 (m, 2H), 1.68 (m, 4H), 2.22 (m, 1H), 2.65 (m, 4H), 3.08 (br s, 4H), 3.45 (m, 1H), 4.56 (m, 1H), 4.92 (d, J = 6.5 Hz, NH, 1H), 6.8–8.0 (m, 9H). MS: 458 (M+1). *Trans*-**5** NMR: δ ($CDCl_3$) 1.22 (m, 4H), 1.33 (d, J = 6.1 Hz, 6H), 1.90 (m, 4H), 2.23 (m, 1H), 2.67 (m, 4H), 3.08 (br s, 5H), 4.57 (m, 1H), 4.65 (d, J = 7.0 Hz, NH, 1H), 6.8–8.0 (m, 9H). MS: 458 (M+1). *Cis*-**14** NMR: δ ($CDCl_3$) 1.32 (d, J = 6.1 Hz, 6H), 1.4–1.8 (m, 8H), 2.21 (m, 1H), 2.63 (br s, 4H), 3.06 (br s, 4H), 3.39 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 4.60 (m, 1H), 4.82 (d, J = 6.5 Hz, NH, 1H), 6.8–7.6 (m, 7H). MS: 558 (M^+). *Trans*-**14** NMR: δ ($CDCl_3$) 1.24 (m, 4H), 1.34 (d, J = 6.2 Hz, 6H), 1.92 (m, 4H), 2.22 (m, 1H), 2.68 (m, 4H), 3.05 (br s, 5H), 3.92 (s, 3H), 3.94 (s, 3H), 4.62 (m, 1H), 4.75 (d, J = 6.5 Hz, NH, 1H), 6.8–7.6 (m, 7H). MS: 558 (M+1). *Cis*-**17** NMR: δ ($CDCl_3$) 1.33 (d, J = 6.2 Hz, 6H), 1.45 (m, 2H), 1.60 (m, 2H), 1.71 (m, 4H), 2.27 (m, 1H), 2.71 (br s, 4H), 3.14 (br s, 4H), 3.39 (m, 1H), 3.98 (s, 3H), 4.62 (m, 1H), 5.05 (d, J = 7.0 Hz, NH, 1H), 6.8–7.8 (m, 7H). MS: 506 (M+1). *Trans*-**17** NMR: δ ($CDCl_3$) 1.24 (m, 4H), 1.35 (d, J = 6.1 Hz, 6H), 1.94 (m, 4H), 2.27 (m, 1H), 2.70 (m, 4H), 3.10 (br s, 5H), 3.98 (s, 3H), 4.57 (m, 1H), 4.82 (d, J = 6.5 Hz, NH, 1H), 6.8–7.8 (m, 7H). MS: 506 (M+1). *Cis*-**18** NMR: δ ($CDCl_3$) 1.32 (d, J = 6.1 Hz, 6H), 1.47 (m, 2H), 1.59 (m, 2H), 1.71 (m, 4H), 2.22 (m, 1H), 2.68 (m, 4H), 3.09 (br s, 4H), 3.40 (m, 1H), 3.95 (s, 3H), 4.57 (m, 1H), 4.83 (d, J = 6.9 Hz, NH, 1H), 6.8–8.0 (m, 7H). MS: 522 (M+1). *Trans*-**18** NMR: δ ($CDCl_3$) 1.23 (m, 4H), 1.34 (d, J = 6.0 Hz, 6H), 1.89 (m, 4H), 2.23 (m, 1H), 2.68 (m, 4H), 3.05 (br s, 5H), 3.96 (s, 3H), 4.58 (m, 1H), 4.80 (d, J = 7.0 Hz, NH, 1H), 6.8–8.0 (m, 7H). MS: 522 (M+1). *Cis*-**32** NMR: δ ($CDCl_3$) 1.33 (d, J = 6.0 Hz, 6H), 1.55 (m, 4H), 1.64 (m, 2H), 1.78 (m, 2H), 2.22 (m, 1H), 2.66 (m, 4H), 3.08 (br s, 4H), 3.41 (m, 1H), 4.20 (d, J = 7.1 Hz, NH, 1H), 4.22 (s, 2H), 4.58 (m, 1H), 6.8–7.5 (m, 9H). MS: 472 (M+1). *Trans*-**32** NMR: δ ($CDCl_3$) 1.20 (m, 4H), 1.33 (d, J = 6.1 Hz, 6H), 1.95 (bd, 2H), 2.05 (bd, 2H), 2.23 (m, 1H), 2.70 (m, 4H), 3.03 (m, 1H), 3.10 (br s, 4H), 3.95 (d, J = 7.1 Hz, NH, 1H), 4.23 (s, 2H), 4.56 (m, 1H), 6.8–7.5 (m, 9H). MS: 472 (M+1).