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Aminocyclohexylsulfonamides: Discovery of metabolically stable $\alpha_{1a/1d}$-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, but these drugs also produce side effects that are related to their subtype non-selective nature. To overcome this limitation, it was hypothesized that an $\alpha_{1a/1d}$ subtype-selective antagonist would be efficacious while keeping side effects to a minimum. To discover $\alpha_{1a/1d}$-selective antagonists and improve metabolic stability of our previously reported compounds, we have designed and synthesized a series of (phenylpiperazinyl)- or (phenylpiperidinyl)-cyclohexylsulfonamides. By incorporating the information obtained from metabolism studies, we were able to discover several compounds that are both $\alpha_{1a/1d}$ adrenoceptor subtype selective and show increased stability toward human liver microsomal metabolism. The selectivity profile of these compounds provides great improvement over the commercial drug tamsulosin, hence may pave the way to the development of new and efficacious therapeutic agents with reduced side effects.

The prostate is a male sex auxiliary gland located just below the bladder and surrounding the urethra. Excessive growth of the prostate with age results in benign prostatic hyperplasia (BPH), which causes obstruction of the bladder outlet and 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 components in BPH, namely the increased size and elevated muscle tone of the prostate gland, drug therapy for BPH/LUTS has been classified into two categories. Drugs in the first category, 5-α-reductase inhibitors (e.g., finasteride and dutasteride), work by reducing the size of the prostate; drugs in the second category, α_1-adrenergic receptor antagonists (e.g., tamsulosin and terazosin), work by relaxing prostate muscle. The α_1 blockers have an advantage over 5-α-reductase inhibitors because they can provide effective relief of symptoms in very short period of time. Unfortunately, all α_1 drugs currently on the market also produce cardiovascular related side effects such as orthostatic hypotension.[3,4]

Three α_1-adrenergic receptor subtypes have been discovered to date. They are termed α_{1a}, α_{1b}, and α_{1d},[5–7] and current α_1 drugs are known to bind to all of them indiscriminately or with low selectivity.[8] It is speculated that orthostatic hypotension caused by present α_1 blockers is a result of their subtype non-selective nature. In the early 1990s, the α_{1a}-adrenoceptor subtype was determined to play a dominant role in controlling prostatic muscle contraction.[8] Although many α_{1a}-adrenoceptor

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subtype-selective antagonists have been discovered,[9a–c] the failure of these compounds in clinical trials indicates that other α_1-receptor subtypes might be implicated in the BHP/LUTS.[10] Recent studies have provided evidence that the α_{1d} subtype is involved in the mediation of LUTS.[11a–c] In addition, 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 new hypothesis that an antagonist with balanced $\alpha_{1a/1d}$ selectivity profile will be efficacious yet produce less severe side effects.[13a–e] So far, validation of this hypothesis has been hampered by the fact that no α_1 compound with high selectivity for $\alpha_{1a/1d}$ versus α_{1b} is currently available.

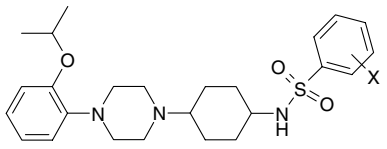
We initiated a research program to validate this hypothesis by first identifying a $\alpha_{1a/1d}$-selective compound, then studying it in established animal models. Our primary goal was to design and synthesize potent and $\alpha_{1a/1d}$ subtype-selective antagonists with superior selectivity profiles compared to the marketed drug tamsulosin. In our previous papers,[14] we described the discovery of series of *cis*-(phenylpiperazinyl)-cyclohexylsulfonamides (**2**, Fig. 1) and *cis*-(phenylpiperidinyl)-cyclohexylsulfonamides (**3**, Fig. 1). These compounds proved to have equal affinity for both α_{1a} and α_{1d} subtypes, with good selectivity against the α_{1b} subtype. Encouraged by these results, our effort was shifted to evaluate the pharmacokinetic properties of these compounds. We first investigated the metabolic stability of piperazine analogues (**4**). Six analogues were chosen for evaluation in a human liver microsomal (HLM) metabolism assay. Half-lives were determined and are listed in Table 1. It was disappointing to discover that these compounds have short in vitro metabolic half-lives, typically less than 5 min, that strongly indicates that these compounds would not survive first pass metabolism.

To avoid the low bioavailability predicted by these results, we needed to establish the metabolic pathway of these compounds to identify potential weak points on the molecule and modify the structure accordingly. This would serve as a good foundation for the further development of metabolically stable analogues. To accomplish this, compound **8** was chosen as a substrate in an in vitro metabolism study. After incubation with HLM for up to 60 min at 37 °C in the presence of NADPH and HPLC/MS analysis, three major metabolites, which included de-alkylation/hydroxylation product **A**, double hydroxylation product **B**, and sulfonamide cleavage product **C**, were identified. Judging by their structure and relative abundance, the metabolic pathway of **8** could be constructed (Scheme 1). It was discovered that the principal degradation steps for compound **8** were de-alkylation of the alkoxy group and hydroxylation on the aromatic rings, although cleavage of the sulfonamide group also played a relatively minor role.

The study of metabolic fate of **8** provided valuable information for the further development of metabolically stable analogues. The metabolic pathways of **8** clearly suggested three possible modifications of the core structure to increase its resistance to metabolism. These modifications are: (1) changing the alkoxy group to block Path A; (2) reducing electron density of the alkoxylated aromatic ring attached to the piperazine to retard Path B; and (3) increasing steric bulk of the sulfonamide group to slow down Path C (Fig. 2). More specifically, we believed cyclizing the isopropoxy group or introducing fluorine atoms on the alkoxy group might be effective ways to block de-alkylation. To retard hydroxylation of the alkoxy-phenyl ring, we decided to replace the piperazine ring with a piperidine ring. We also tried to incorporate alkyl groups on the sulfonamide nitrogen atom to increase steric hindrance and reduce metabolic cleavage. A set of compounds were designed and synthesized according to these three approaches.

The (phenylpiperazinyl)- or (phenylpiperidinyl)-cyclohexylsulfonamides were generally prepared by the following sequence (Scheme 2).[14] A suitably substituted phenylpiperazine or phenylpiperidine was subjected to the reductive alkylation with ^{t}Boc protected 4-aminocyclohexanone to give a *cis*/*trans* mixture of diaminocyclo-

Table 1. Half-lives of **5**–**10** in HLM experiments ($T_{1/2}$, min)



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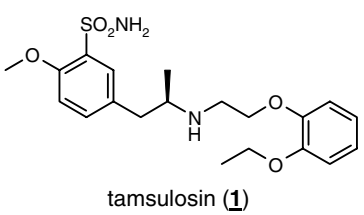
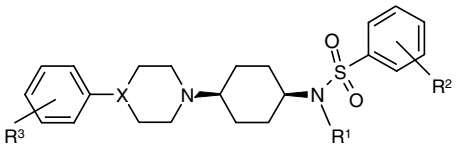
Compound	Configuration	X	$T_{1/2}$
5	*cis*	4-SO_2Me	2.5
6	*cis*	3,4-diOMe	4.9
7	*cis*	2-MeO-5-Me	<2.0
8	*cis*	2-MeO-5-F	<2.0
9	*cis*	2-MeO-5-Cl	<2.0
10	*cis*	2,4-diCl	3.5

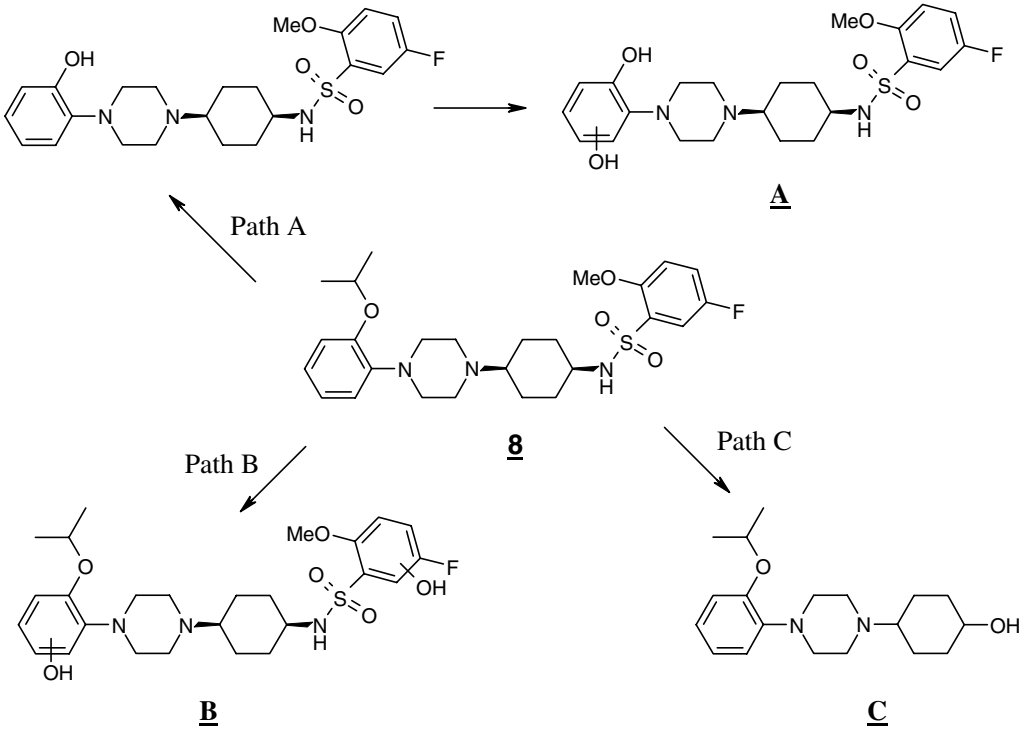


tamsulosin (**1**)



2 X = N
3 X = C

Figure 1. Structure of tamsulosin, **2** and **3**.



Scheme 1. Major metabolic pathways of compound **8**.

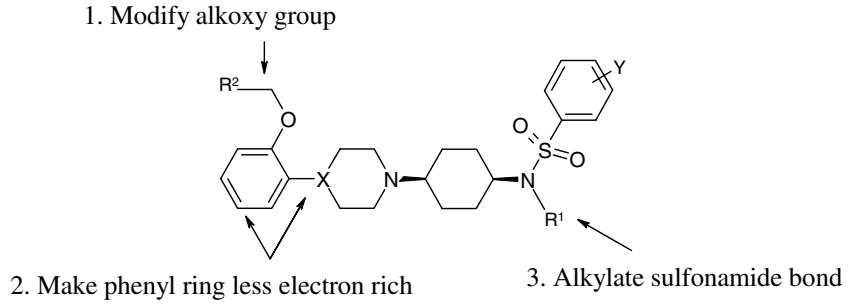
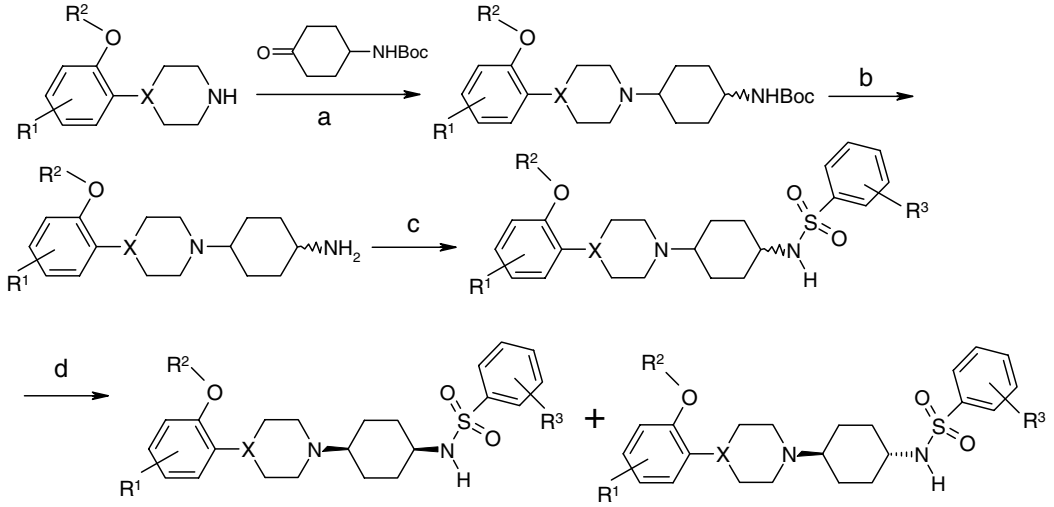
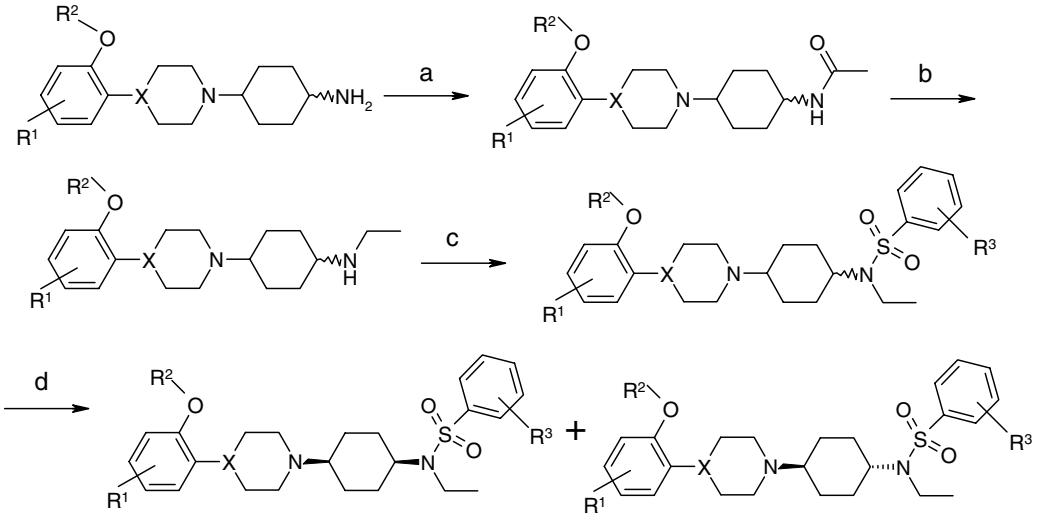


Figure 2. Three modifications of structure to enhance metabolic stability.



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



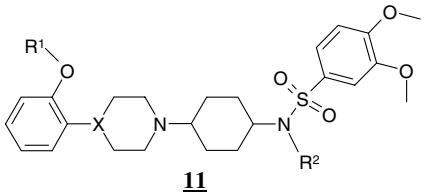
Scheme 3. Reagents and conditions: (a) CH_3COCl, Et_3N, CH_2Cl_2, rt, 8 h, 85% yield; (b) $LiAlH_4$/THF, reflux, 2 h, 90% yield; (c) arylsulfonyl chloride/CH_2Cl_2/Na_2CO_3 (aq), rt, 8 h, 63% yield; (d) SiO_2 column or prep TLC.

hexane intermediates. Treatment with TFA produced the free amine, which was acylated by various sulfonyl chlorides. Final chromatographic separation gave the desired isomers.[15]

For *N*-alkylated analogues, the following synthetic procedure was used (Scheme 3). The cyclohexylamine was first acylated with acetyl chloride followed by LAH reduction to give the *N*-ethylamine, which was allowed to react with a sulfonyl chloride to yield the *cis*/*trans* mixture of sulfonamides. Chromatographic separation gave the desired isomers.[16]

A series of (phenylpiperazinyl)-cyclohexylsulfonamides and (phenylpiperidinyl)-cyclohexylsulfonamides (**11**) were synthesized and tested for binding to cloned human α_{1a}, α_{1b}, and α_{1d} adrenergic receptors and the dopamine D_2 receptor. Results for several typical examples are summarized in Table 2. To assess metabolic stability, these compounds were tested in HLMs; their half-lives are also listed in Table 2. Data for the unmodified reference compound, (phenylpiperazinyl)-cyclohexylsulfonamide *cis*-**6**, are included for comparison. Based on our previous experience, 3,4-dimethoxy was chosen as the optimum substitution on the phenyl ring attached to

Table 2. Binding profile (K_i, nM) and metabolic half-lives (min) of **6**–**18**



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Compound	Configuration	X	R_2	R_1	K_i (nM)				HLM
					α_{1a}	α_{1b}	α_{1d}	D_2	$T_{1/2}$
6	*cis*	N	H	$(CH_3)_2CH$	2.0	106	0.68	136	4.9
	trans	N	H	$(CH_3)_2CH$	23	126	24	62	
12	*cis*	N	Et	$(CH_3)_2CH$	15	326	22	113	
	trans	N	Et	$(CH_3)_2CH$	23	109	6.7	2.7	
13	*cis*	C	H	$(CH_3)_2CH$	1.8	151	1.7	165	12
	trans	C	H	$(CH_3)_2CH$	28	148	40	55	
14	*cis*	C	H	Cyclopropyl	0.91	141	2.0	144	18
	trans	C	H	Cyclopropyl	11	133	34	133	
15	*cis*	C	H	CH_2FCH_2	11	354	8.8	330	20
	trans	C	H	CH_2FCH_2	69	4403	49	284	
16	*cis*	C	H	CHF_2CH_2	12	278	8.6	228	21
	trans	C	H	CHF_2CH_2	31	681	86	88	
17	*cis*	N	H	CF_3CH_2	1.2	86	0.35	192	35
	trans	N	H	CF_3CH_2	54	39	8.3	114	
18	*cis*	C	H	CF_3CH_2	1.8	123	2.2	112	56
	trans	C	H	CF_3CH_2	21	368	23	83	

the sulfonamide. We found that, as in our previously reported sulfonamide compounds,[14] the *cis* isomers of this series also have better selectivity profiles than their *trans* counterparts. In addition, they also have lower affinities for the D_2 receptor. Compound *cis*-**12**, an *N*-ethylated analogue that was originally designed to slow down the cleavage of sulfonamide bond (Path C), shows much reduced affinity for α_{1a} and α_{1d}. Since this may indicate the importance of an N–H hydrogen bond interaction with the receptor, the *N*-alkylation approach was not pursued further. As for the activity of N–H compounds, except for the slight loss of α_{1a} and α_{1d} affinities for fluorinated analogues *cis*-**15** and **16**, compounds *cis*-**13**, **14**, **17**, and **18** all show equal affinity for both α_{1a} and α_{1d} subtypes and excellent selectivity profiles. Their α_{1a}/α_{1b} and α_{1d}/α_{1b} ratios range from about 60-fold to more than 200-fold. These selectivity ratios are much improved over commercial drug tamsulosin (**1**), which are about 10-fold (K_i values for tamsulosin, **1**, in the $\alpha_{1a,}$ α_{1b}, and α_{1d} binding assays were 0.19, 2.0, and 0.2 nM, respectively).

Perhaps the most striking differences among these analogues are their half-lives against HLM metabolism. Our reference compound *cis*-**6**, a 2-*i*-propoxyphenylpiperazine analogue, has a short (<5 min) half-life. Replacement of piperazine with piperidine, which reduces electron density on the phenyl ring (Fig. 2, modification 2), results in the still short yet noticeably improved half-life of 12 min (*cis*-**13** vs *cis*-**6**). Cyclization of *i*-propyl group into a cyclopropyl group (*cis*-**14**) extends the half-life of the analogue even further (Fig. 2, modification 1). When fluorine atoms were introduced to the alkoxy side chain to block de-alkylation (Path A), we were encouraged by the results. Monofluoroethoxy or difluoroethoxy substitution was able to effectively increase half-life several fold (*cis*-**15** and **16** vs *cis*-**6**). When the trifluoroethoxy group was introduced, the half-life of the piperazine analogue (*cis*-**17**) reached a satisfactory level (35 min for *cis*-**17** vs 4.9 min for *cis*-**6**). Finally when the 2-trifluoroethoxyphenylpiperidine analogue *cis*-**18** was prepared and tested, the half-life neared the 1-h mark. By systematically altering the structure to block metabolic pathways, we were able to produce compounds such as *cis*-**17** and **18** that not only had excellent α_{1a} and α_{1d} affinity and selectivity versus α_{1b}, but also showed favorable metabolic stability.

In conclusion, to discover a $\alpha_{1a/1d}$-selective adrenoceptor antagonist as a new drug for the treatment of BPH/LUTS and improve metabolic stability of our previously discovered compounds, we carried out an in vitro metabolism study of compound **8**. Identification of the structure of metabolites helped us to establish the major metabolic pathways. A series of (phenylpiperazinyl)- or (phenylpiperidinyl)-cyclohexylsulfonamides were designed and synthesized by incorporating the information obtained from metabolism studies. Through systematic introduction of structural features that blocked metabolic pathways, we were able to discover compounds *cis*-**17** and *cis*-**18** that are both selective ligands for the α_{1a} and α_{1d} adrenoceptor subtypes and are stable against HLM metabolism. The selectivity profile exhibited by these compounds provides great improvement over the commercial drug tamsulosin, and hence paves the way toward development of new, efficacious therapeutic agents with fewer side effects.

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15. The isomers with higher R_f values in TLC are the *cis* isomers. The isomers with lower R_f values are the *trans* isomers. This assignment is based on the NMR pattern of

similar (piperazinyl)-cyclohexylsulfonamide compounds with known *cis* or *trans* configurations.

16. NMR and MS data of representative compounds. *cis*-**12** NMR: δ ($CDCl_3$) 1.28 (t, J = 8.2 Hz, 3H), 1.3–1.5 (m, 4H), 1.34 (d, J = 8.1 Hz, 6H), 1.81 (m, 2H), 2.06 (br d, 2H), 2.15 (br s, 1H), 2.60 (br s, 4H), 3.10 (br s, 4H), 3.28 (q, J = 8.2 Hz, 2H), 3.74 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 4.58 (m, 1H), 6.8–7.6 (m, 7H) MS: 546 (M+1). *trans*-**12** NMR: δ ($CDCl_3$) 1.24 (t, J = 8.0 Hz, 3H), 1.3–1.6 (m, 4H), 1.34 (d, J = 8.1 Hz, 6H), 1.85 (br d, 2H), 1.98 (br d, 2H), 2.27 (m, 1H), 2.73 (m, 4H), 3.13 (br s, 4H), 3.24 (q, J = 8.0 Hz, 2H), 3.62 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 4.60 (m, 1H), 6.8–7.6 (m, 7H) MS: 546 (M+1). *cis*-**13** 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). *trans*-**13** 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). *cis*-**14** NMR: δ ($CDCl_3$) 0.75 (m, 4H), 1.22 (m, 2H), 1.3–1.8 (m, 10H), 2.32 (m, 3H), 2.85 (m, 1H), 3.05 (br d, 2H), 3.40 (m, 1H), 3.72 (m, 1H), 3.94 (s, 3H), 3.96 (s, 3H), 5.20 (d, J = 7.5 Hz, NH, 1H), 6.8–7.6 (m, 7H) MS: 515 (M+1). *trans*-**14** NMR: δ ($CDCl_3$) 0.76 (m, 4H), 1.2–1.5 (m, 4H), 1.58 (m, 2H), 1.70 (m, 2H), 1.8–2.0 (m, 4H), 2.23 (m, 3H), 2.80 (m, 1H), 2.90 (br d, 2H), 3.02 (m, 1H), 3.72 (m, 1H), 3.92 (s, 3H), 3.96 (s, 3H), 4.50 (d, J = 7.6 Hz, NH, 1H), 6.8–7.6 (m, 7H) MS: 515 (M+1). *cis*-**17** NMR: δ ($CDCl_3$) 1.4–1.8 (m, 8H), 2.26 (m, 1H), 2.77 (br s, 4H), 3.10 (br s, 4H), 3.42 (m, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 4.41 (q, J = 14 Hz, 2H), 4.62 (d, J = 7.2 Hz, NH, 1H), 6.8–7.6 (m, 7H) MS: 558 (M+1). *trans*-**17** NMR: δ ($CDCl_3$) 1.1–1.4 (m, 4H), 1.93 (m, 4H), 2.22 (m, 1H), 2.68 (m, 4H), 3.05 (br s, 4H), 3.14 (m, 1H), 3.94 (s, 3H), 3.96 (s, 3H), 4.38 (q, J = 15 Hz, 2H), 4.85 (d, J = 7.2 Hz, NH, 1H), 6.8–7.6 (m, 7H) MS: 558 (M+1). *cis*-**18** 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). *trans*-**18** 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).