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Conformationally constrained N_1-arylsulfonyltryptamine derivatives as 5-HT$_6$ receptor antagonists

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Abstract—Several series of conformationally constrained N_1-arylsulfonyltryptamine derivatives were prepared and tested for 5-HT$_6$ receptor binding affinity and ability to modulate cAMP production in a cyclase assay. The 3-piperidin-3-yl-, 3-(1-methylpyrrolidin-2-ylmethyl)-, and 3-pyrrolidin-3-yl-1*H*-indole arrays (**8**–**13**) appear to be able to adopt a conformation that allows high affinity 5-HT$_6$ receptor binding, while the β-carboline array **14** binds with a significantly weaker (10- to 100-fold) affinity. N_1-Benzenesulfonyl-3-piperidin-3-yl-1*H*-indole **9a** is a high affinity full agonist with EC$_{50}$ = 24 nM. Several of the N_1-arylsulfonyl-3-(1-methylpyrrolidin-2-ylmethyl)-1*H*-indole derivatives behave as very potent antagonists ((*S*)-**11r**, (*S*)-**11t**; IC$_{50}$ = 0.8, 1.0 nM).

The human 5-HT$_6$ receptor was cloned in 1996 and consists of a 440 amino acid residue, seven-transmembrane protein, with <40% protein sequence homology with the other 5-HT receptors.[1] The 5-HT$_6$ receptor is positively coupled to adenylyl cyclase,[2] and located almost exclusively in the central nervous system, with highest density in the cerebral cortex, nucleus accumbens, caudate-putamen, and hippocampus, and moderate densities in the thalamus and substantia nigra.[3] A wide range of antipsychotic agents and antidepressants have high affinity for the 5-HT$_6$ receptor,[4] stimulating considerable effort to understand its role in treatment of CNS disorders, including schizophrenia, depression, and impaired learning and memory.[5–10]

Among the first 5-HT$_6$ receptor antagonists was a series of bismethylaminopyrimidinyl- and bismethylaminopyridinyl-sulfonamides, Ro-04-6790 (**1**) and Ro-63-0563 (**2**) (Fig. 1).[11] Subsequently, a series of piperazinyl-benzenesulfonamide antagonists SB-271046 (**3**)[12] and SB-357134 (**4**),[13] with improved affinity and physical properties, were reported. N_1-arylsulfonyltryptamines, such as MS-245 (**5**; K_i = 2.3 nM), have also been shown to

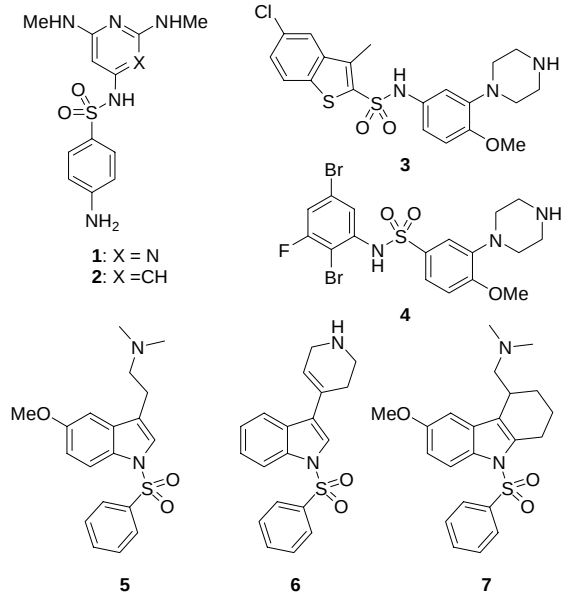

Figure 1. Structures of 5-HT$_6$ receptor ligands.

Keywords: N_1-Arylsulfonyltryptamine; 5-HT6; Serotonin; Receptor; Antagonist.
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bind to the 5-HT_6 receptor with high affinity,[14,15] as have the conformationally constrained N_1-arylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (**6**; K_i = 2 nM)[16,17] and the (9-arylsulfonyl-2,3,4,9-tetrahydro-1*H*-carbazol-4-yl)-methylamine (**7**; K_i = 1.5 nM).[18]

In this report, we present the results of a study into the structural–activity relationships of a series of conformationally constrained N_1-arylsulfonyltryptamine derivatives. The effect of indole substitution on 5-HT_6 receptor binding affinity of N_1-arylsulfonyltryptamine derivatives has been studied and, in general, substitution on the 4-, 5-, 6-, or 7-positions does not increase the affinity, relative to the unsubstituted indole[14,16]. Thus, the focus of this work is on the conformationally constrained aminoethyl portion and the N_1-arylsulfonyl substituents.

Seven arrays, represented by the generic structures **8**–**14** (Fig. 2), were prepared. Array **8** was prepared, as shown in Scheme 1, by coupling indole with 1-benzyl-3-piperdinone hydrate in refluxing isopropylalcohol (IPA) with excess 1 N KOH to give 3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole **15**.[19] Removal of the benzyl group was carried out by a modified version of a procedure by Olofson et al.[20] in which the benzylamine was stirred at room temperature with α-chloroethyl chloroformate (ACE-Cl) in dichloroethane (DCE) to give the α-chloroethyl carbamate, which was cleaved to the free amine by refluxing in MeOH. Subsequent protection gives the *N*-Boc core **16**, which was coupled with a set of sulfonyl chlorides in THF with potassium *tert*-butoxide. Finally, the Boc group was removed by stirring with 2 N HCl in dioxane. The compounds were purified by reverse-phase semi-preparative HPLC.[21]

Coupling of indole with 1-Boc-3-piperdinone leads to the formation of the enamine isomer **17**, due to the electron with-drawing nature of the *N*-substituent.[22] Hydrogenation gives the reduced *N*-Boc-3-piperidin-3-yl-1*H*-indole **18**. Array **9** was then prepared, as described above for array **8**.

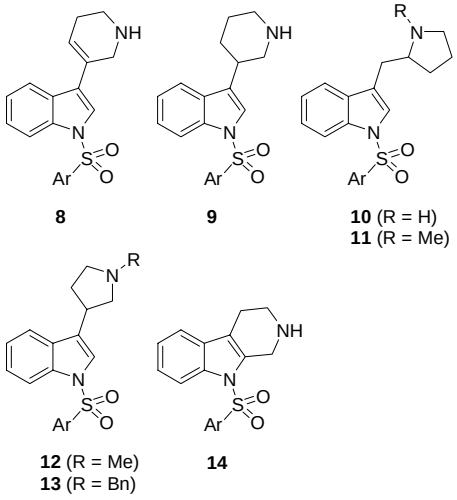
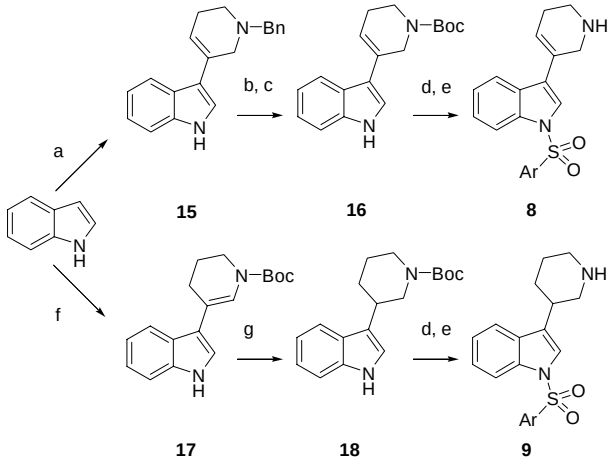


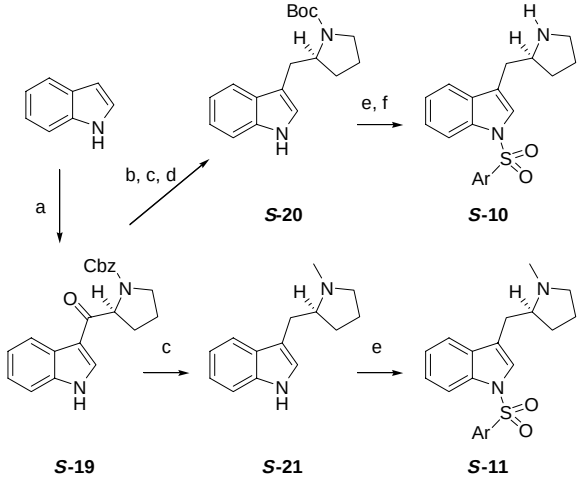
Figure 2. Conformationally constrained N_1-arylsulfonyltryptamine arrays.



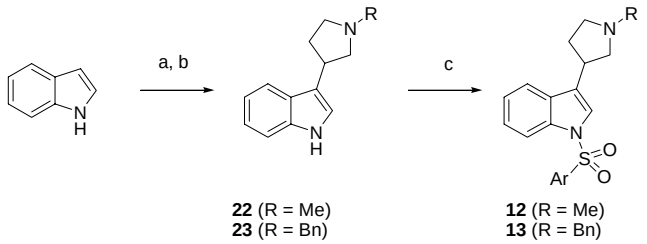
Scheme 1. Reagents and conditions: (a) 1-benzyl-3-piperidone, KOH, IPA, Δ; (b) (i) ACE-Cl, DCE, rt; (ii) MeOH, Δ; (c) $(Boc)_2O$, K_2CO_3, acetone, water, rt; (d) $ArSO_2Cl$, *t*-BuOK, THF, rt; (e) 2 N HCl, dioxane, rt; (f) 1-Boc-3-piperidone, KOH, IPA, Δ; (g) H_2, Pd/C MeOH, rt.

The reaction of the magnesium salt of indole with either (*S*)- or (*R*)-*N*-Cbz-proline acid chloride in toluene afforded the 3-ketoindole **19** (Scheme 2: (*S*)-enantiomer shown).[23] Removal of the Cbz group was effected by hydrogenation over palladium on carbon with formic acid in methanol. The keto group was reduced with $LiAlH_4$ in refluxing THF and the pyrrolidine protected as the *N*-Boc derivative **20**. Array **10** was prepared, as described above for array **8**. Reduction of **19** with $LiAlH_4$ in refluxing THF afforded the 3-(1-methyl-pyrrolidin-2-ylmethyl)-1*H*-indole **21**, which was converted to array **11** by sulfonylation.

The synthesis of the N_1-arylsulfonyl-3-(1-alkyl-pyrrolidin-3-yl)-1*H*-indole arrays **12**–**13** was carried out by coupling indole with *N*-methyl- and *N*-benzylmaleimide in refluxing acetic acid, followed by reduction with $LiAlH_4$ to give the 3-(1-methyl- and 3-(1-benzylpyrrolidin-3-yl)-1*H*-indole cores **22**–**23** (Scheme 3)[23] that were sulfonylated.



Scheme 2. Reagents and conditions: (a) (*S*)-*N*-Cbz-Pro-Cl, EtMgBr, DCM, 0 °C; (b) HCO_2H, Pd/C, MeOH, rt; (c) $LiAlH_4$, THF, Δ; (d) $(Boc)_2O$, K_2CO_3, acetone, water, rt; (e) $ArSO_2Cl$, *t*-BuOK, THF, rt.



Scheme 3. Reagents and conditions: (a) *N*-methyl- or *N*-benzylmaleimide, AcOH, Δ; (b) $LiAlH_4$, THF, Δ; (c) $ArSO_2Cl$, *t*-BuOK, THF, rt.

The 9-arylsulfonyl-2,3,4,9-tetrahydro-1*H*-β-carboline array **14** was prepared by Boc protection of the β-carboline, followed by sulfonylation and deprotection, as described for array **8**.

All the conformationally constrained N_1-arylsulfonyltryptamine derivatives were assayed for their ability to displace [^{3}H]-LSD from cloned human 5-HT_6 receptors stably expressed in HeLa cells.[16] N_1-Benzenesulfonyl-3-(1,2,5,6-tetrahydropyridin-3-yl)- 1*H*-indole **8a** had excellent affinity (K_i = 4.6 nM) for the 5-HT_6 receptor. Mono- and dihalo, alkyl and alkoxy substituted arylsulfonamides (**8b**–**8q**; K_i = 8.5–48 nM) all had slightly reduced affinity, as did the heteroaryl sulfonamides (**8t**–**8w**; K_i = 8–58 nM) (Table 1).

The racemic N_1-arylsulfonyl-3-piperidin-3-yl-1*H*-indole series **9** showed similar SAR trends with the unsubstituted benzenesulfonamide having high affinity (**9a**; K_i = 2 nM) and the substituted benzenesulfonamides and heteroarylsulfamides having equal or slightly lower binding affinity (**9f**–**9x**; K_i = 2–44 nM). The enantiomers of **9a** were separated[24] and showed a 3-fold difference in binding affinity (*K*i = 1 nM vs. 3 nM).

In general, the (*S*)-N_1-arylsulfonyl-3-pyrrolidin-2-ylmethyl-1*H*-indole series **10** had lower 5-HT_6 receptor affinity (**10a**–**10x**; K_i = 20–283 nM), with the exception of 4-aminophenylsulfonamide (**10m**; K_i = 7 nM). Increased binding affinity for 4-aminophenylsulfonamide tryptamines has been previously reported.[25] The corresponding (*R*)-N_1-arylsulfonyl-3-pyrrolidin-2-ylmethyl-1*H*-indoles were not prepared. Both (*R*)- and (*S*)-enantiomers of N_1-arylsulfonyl-3-(1-methyl-pyrrolidin-2-ylmethyl)-1*H*-indole series **11** had high affinity (**11a**–**11x**; K_i = 3–19 nM). The unsubstituted phenyl-, 3-, and 4-halophenyl-, 4-aminophenyl-, and 5-halothiophenesulfonyl derivatives had the highest affinity. Interestingly, even the large 5-chloro-3-methylbenzothiophene analog retains high affinity (**11x**; K_i = 11 nM).

All members of the racemic N_1-arylsulfonyl-3-(1-methyl-pyrrolidin-3-yl)-1*H*-indole array **12** had excellent 5-HT_6 receptor affinity (**12c**–**12r**; K_i = 1–5 nM). Surprisingly, members of the N_1-arylsulfonyl-3-(1-benzyl-pyrrolidin-3-yl)-1*H*-indole array **13** also had high affinity (**13k**–**13y**; K_i = 1–9 nM), in spite of a large *N*-benzyl substituent. This was in contrast to the N_1-arylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole series where the larger *N*-Bn derivatives had significantly weaker affinity than the corresponding *N*-Me analogs.[16]

The 9-arylsulfonyl-2,3,4,9-tetrahydro-1*H*-β-carbolines (**14a**–**14m**; K_i = 41–252 nM) had weaker 5-HT_6 receptor affinity.

Each of the compounds **5**–**9**, **11**–**12**, and **14** was expanded to a set of roughly 200 molecule conformations (OMEGA software, OpenEye Scientific), generating 2400 total molecule conformations that were aligned (ROCS software, OpenEye Scientific) with each other. An overlap score was assigned to each alignment based on the molecule shape and pharmacophore orientation. These alignments were analyzed to find out the conformation that had the largest average overlap with the remaining conformations. This conformation was defined as the reference conformation. A consensus of those conformations, which match that of the reference conformation, was obtained and is shown in Figure 3.

With the N_1-phenylsulfonylindole groups aligned, the basic amine of compounds **5**–**9** and **11**–**12** can adopt a similar position. This is in contrast to **14** that cannot adopt a conformation where the basic amine overlays with the basic amine of the other molecules.

Glennon has shown that in the N_1-arylsulfonylskatole series absence of a basic amine results only in a 3-fold loss in affinity, relative to the tryptamine with the 4-aminophenylsulfonyl group.[25] However, we show here that compound **14m** (K_i = 116 nM), which has this 4-aminophenylsulfonyl group and where the basic amine is restricted to a position that does not overlap with the basic amines of the other cores, is about 100-fold less potent than the corresponding N_1-(4-aminophenylsulfonyl)-3-(1-methyl-pyrrolidin-3-yl)-1*H*-indole **12m** (K_i = 1 nM).

High affinity compounds were assayed for their ability to modulate cAMP production in a cyclase assay (Table 1).[16] None of the N_1-arylsulfonyl-3-(1,2,5,6-tetrahydropyridin-3-yl)-1*H*-indole derivatives **8** showed any antagonist activity; however, several compounds of the series did show a modest ability to stimulate cAMP production indication agonist activity. Several racemic N_1-arylsulfonyl-3-piperidin-3-yl-1*H*-indole analogs had agonist activity. Of particular interest is **9a** that stimulated cAMP production with an EC_{50} value of 24 nM and behaved as a full agonist, and although the enantiomers had only 3-fold difference in affinity (K_i = 1 nM vs. 3 nM) all the agonist activity could be attributed to one enantiomer, while the diastomer failed to show any functional activity. The N_1-(4-methoxybenzene)sulfonyl-3-piperidin-3-yl-1*H*-indole **9l** (IC_{50} = 7 nM) behaved as a partial antagonist.

Several of the N_1-arylsulfonyl-3-(1-methylpyrrolidin-2-ylmethyl)-1*H*-indole derivatives were very potent antagonists in the cAMP stimulation assay, in particular, (***S***)**-11r** and (***S***)**-11t** were full antagonists with IC_{50} values of approximately 1 nM. Members of the N_1-arylsulfonyl-3-(1-methyl- and N_1-arylsulfonyl-3-(1-benzyl-

Table 1. 5-HT_6 binding affinity and functional activity of constrained N_1-arylsulfonyltryptamines

Compound	Ar-SO_2	K_i (nM)[a]	cAMP assay IC_{50} (nM)[b]	I_{max} (%)	cAMP assay EC_{50} (nM)[c]	E_{max} (%)
8a	Ph	4.6 ± 0.4			159.0 ± 8.5	41.0 ± 1.4
8b	2-F-Ph	9.2 ± 0.5			51.0 ± 0.7	52.0 ± 0.0
8c	2-Cl-Ph	13.0 ± 1.8				
8d	2-CF_3-Ph	21.7 ± 0.9				
8e	3-F-Ph	8.5 ± 1.3			269.5 ± 15.9	51.5 ± 0.4
8f	3-Cl-Ph	14.0 ± 0.6				
8g	3-CF_3-Ph	44.7 ± 2.1				
8h	4-F-Ph	10.5 ± 1.1			344.5 ± 11.0	62.0 ± 0.7
8i	4-Cl-Ph	22.0 ± 0.9				
8l	4-MeO-Ph	16.0 ± 0.6				
8n	2,4-diF-Ph	13.0 ± 1.4				
8o	2,3-diCl-Ph	20.0 ± 2.9				
8p	3,4-diF-Ph	26.0 ± 1.5				
8q	3,4-diCl-Ph	48.0 ± 2.9				
8t	5-Cl-thienyl	22.7 ± 2.7				
8v	diMe-oxazole	58.0 ± 2.4				
8w	5-Cl-1,3-diMe-pyrazole	8.0 ± 0.2			89.5 ± 8.8	50.0 ± 0.0
9a (racemic)	Ph	2.0 ± 0.1			24.0 ± 3.5	100.0 ± 0.0
9a (enantiomer 1)	Ph	3.0 ± 0.1	0.0	0.0	0.0	0.0
9a (enantiomer 2)	Ph	1.0 ± 0.1			36.0 ± 6.4	100.0 ± 0.0
9f	3-Cl-Ph	2.0 ± 0.1				
9j	4-CF_3-Ph	10.0 ± 0.3				
9l	4-MeO-Ph	10.0 ± 1.0	7.3 ± 1.0	65.5 ± 1.1		
9p	3,4-diF-Ph	7.0 ± 1.0			66.0 ± 5.0	60.5 ± 0.4
9s	thienyl	9.8 ± 2.6				
9t	5-Cl-thienyl	3.0 ± 0.3			58.5 ± 0.4	93.0 ± 1.4
9x	5-Cl-3-Me-benzothiophene	44.0 ± 3.0				
(***S***)-**10a**	Ph	27.7 ± 7.6				
(***S***)-**10c**	2-Br-Ph	43.0 ± 7.0				
(***S***)-**10f**	3-Cl-Ph	22.0 ± 2.0				
(***S***)-**10i**	4-Cl-Ph	49.0 ± 4.0				
(***S***)-**10j**	4-I-Ph	34.0 ± 4.0				
(***S***)-**10k**	4-Me-Ph	33.0 ± 5.0				
(***S***)-**10l**	4-MeO-Ph	40.0 ± 5.0				
(***S***)-**10m**	4-NH_2-Ph	7.0 ± 1.0	7.6 ± 0.3	79.2 ± 0.1		
(***S***)-**10q**	3,4-diCl-Ph	49.0 ± 3.0				
(***S***)-**10r**	3,4-diMeO-Ph	23.0 ± 3.0				
(***S***)-**10t**	5-Cl-thienyl	25.0 ± 3.0				
(***S***)-**10u**	5-Br-thienyl	20.0 ± 1.0				
(***S***)-**10x**	5-Cl-3-Me-benzothiophene	283.7 ± 4.5				
(***R***)-**11a**	Ph	8.0 ± 1.0	0.6 ± 0.1	75.0 ± 0.7		
(***R***)-**11u**	5-Br-thienyl	4.0 ± 0.2			102.8 ± 18.5	76.5 ± 0.4
(***S***)-**11a**	Ph	5.0 ± 1.0	81.4 ± 0.4	87.0 ± 1.4		
(***S***)-**11c**	2-Br-Ph	7.0 ± 1.0	76.5 ± 10.2	87.5 ± 1.0		
(***S***)-**11f**	3-Cl-Ph	4.0 ± 0.3	96.2 ± 2.3	77.0 ± 0.0		
(***S***)-**11i**	4-Cl-Ph	7.0 ± 0.4	8.2 ± 1.7	86.0 ± 0.0		
(***S***)-**11j**	4-I-Ph	3.0 ± 0.2	49.5 ± 13.8	99.5 ± 0.4		
(***S***)-**11k**	4-Me-Ph	5.0 ± 1.0	56.3 ± 14.4	78.5 ± 0.4		
(***S***)-**11l**	4-MeO-Ph	19.3 ± 6.3				
(***S***)-**11m**	4-NH_2-Ph	3.0 ± 0.1	24.5 ± 1.1	100.0 ± 0.0		
(***S***)-**11q**	3,4-diCl-Ph	12.0 ± 3.0	7.3 ± 0.6	86.5 ± 0.3		
(***S***)-**11r**	3,4-diMeO-Ph	8.0 ± 0.2	0.8 ± 0.2	100.0 ± 0.0		
(***S***)-**11t**	5-Cl-thienyl	4.0 ± 0.1	1.0 ± 0.0	99.0 ± 0.0		
(***S***)-**11u**	5-Br-thienyl	3.0 ± 0.1	112.0 ± 12.7	96.0 ± 1.4		
(***S***)-**11x**	5-Cl-3-Me-benzothiophene	11.0 ± 2.0	11.0 ± 0.0	87.5 ± 1.1		
12c	2-Br-Ph	1.0 ± 0.1	53.3 ± 12.2	98.5 ± 1.1		
12h	4-F-Ph	2.0 ± 0.1	52.5 ± 5.3	83.5 ± 1.8		
12i	4-Cl-Ph	1.0 ± 0.2	85.5 ± 11.7	86.5 ± 1.1		
12j	4-I-Ph	1.0 ± 0.2	43.6 ± 5.3	93.5 ± 0.4		
12m	4-NH_2-Ph	1.0 ± 0.2	15.5 ± 2.5	89.5 ± 1.8		
12q	3,4-diCl-Ph	3.0 ± 0.4	107.1 ± 18.3	100.0 ± 0.0		
12r	3,4-diMeO-Ph	5.0 ± 1.0	93.7 ± 0.3	100.0 ± 0.0		
13c	2-Br-Ph	14.0 ± 1.0	21.0 ± 5.6	62.0 ± 1.0		
13k	4-Me-Ph	8.0 ± 1.0	123.0 ± 2.1	72.0 ± 1.4		
13m	4-NH_2-Ph	1.0 ± 0.2	25.0 ± 0.7	97.0 ± 2.1		
13q	3,4-diCl-Ph	15.0 ± 0.3	61.0 ± 9.2	63.0 ± 1.4		

(*continued on next page*)

Table 1 (*continued*)

Compound	Ar-SO_2	K_i (nM)[a]	cAMP assay IC_{50} (nM)[b]	I_{max} (%)	cAMP assay EC_{50} (nM)[c]	E_{max} (%)
13u	5-Br-thienyl	9.0 ± 1.0	110.0 ± 5.7	69.0 ± 0.7		
13y	4-Me-2-NH_2-thiazole	3.0 ± 0.1	110.0 ± 7.1	97.0 ± 1.4		
14a	Ph	252.7 ± 63.8				
14f	3-Cl-Ph	41.7 ± 10.7				
14k	4-Me-Ph	271.3 ± 37.3				
14m	4-NH_2-Ph	116.0 ± 5.5				

[a] Displacement of [^{3}H]-LSD binding to cloned h5-HT_6 receptors stably expressed in HeLa cells. Mean of three determinations.[16]
[b] Inhibition of cAMP production in HeLa cells stably transfected with human 5-HT_6 receptors. Mean of three determinations.
[c] Agonism of cAMP production in HeLa cells stably transfected with human 5-HT_6 receptors. Mean of three determinations.

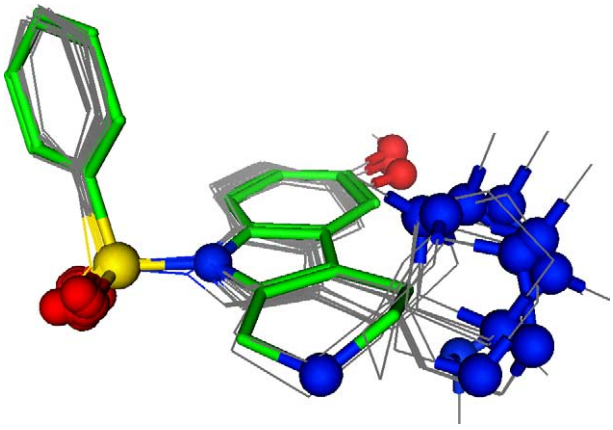


Figure 3. Alignment of conformationally constrained N_1-arylsulfonyltryptamine derivatives **5**, **6**, **7** (*R* and *S*), **8**, **9** (*R* and *S*), **11** and **12** (*R* and *S*), and **14** (Ar = Ph). Compound **14** is shown in green, while others are shown in grey.

pyrrolidin-3-yl)-1*H*-indole array **12**–**13** functioned as antagonists with modest IC_{50} values (15–100 nM).

In summary, several arrays of conformationally constrained N_1-arylsulfonyltryptamines were prepared and tested for 5-HT_6 receptor binding and functional assessment. Similar SAR, as has been reported for the N_1-arylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole derivatives, was observed with various substituted phenyl-, heteroaryl-, and fused arylsulfonyl groups being tolerated.[16]

The 3-piperidin-3-yl, 3-pyrrolidin-2-ylmethyl, and 3-pyrrolidin-3-yl constrained aminoethyl groups (**8**–**13**) appear to be able to adopt a conformation that allows high affinity 5-HT_6 receptor binding, while the β-carboline **14** binds with a significantly weaker (10- to 100-fold) affinity.

N_1-Benzenesulfonyl-3-piperidin-3-yl-1*H*-indole **9a** is a high affinity full agonist with an EC_{50} of 24 nM. Several of the N_1-arylsulfonyl-3-(1-methylpyrrolidin-3-ylmethyl)-1*H*-indole derivatives behave as very potent antagonists ((***S***)-**11r**, (***S***)-**11t**; IC_{50} = 0.8, 1.0 nM).

Acknowledgment

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