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Novel and Potent 5-Piperazinyl Methyl-N_1-aryl Sulfonyl Indole Derivatives as 5-HT_6 Receptor Ligands

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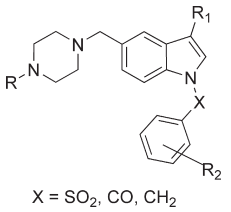
ABSTRACT The exclusive distribution of 5-HT_6 receptors in the brain regions associated with learning and memory makes it an ideal target for cognitive disorders. A novel series of 5-piperazinyl methyl-N_1-aryl sulfonyl indoles were designed and synthesized as 5-HT_6R ligands. Most of the synthesized compounds are potent when tested by in vitro radioligand binding assay. The lead compound from the series does not have the CYP liabilities and is active in an animal model of cognition.

KEYWORDS 5-Piperazinyl methyl-N_1-aryl sulfonyl indole, 5-HT_6R, NORT, SAR, Morris water mazes, PK profile



The 5-HT_6 receptors (5-HT_6R) are perceived by the scientific community as possible targets for the treatment of cognitive disorders as well as obesity.[1−3] Many pharmaceutical companies like Roche,[4,5] GlaxoSmith-Kline,[6] Eli Lilly, Predix, Dr. Esteves lab, Wyeth, etc. have patents covering diverse structures (Figure 1). Several 5-HT_6R antagonists (SB-742457,[7,8] SAM-531, and Lu AE58054) have already entered[9−15] phase II clinical trials for the enhancement of cognitive function; PRX-07034[16] is projected for both obesity and cognition. Over a period of 5 years, we at Suven have designed and developed a number of structurally diverse, potent, and selective 5-HT_6R antagonists through classical medicinal chemistry and scaffold hopping approaches. Our own internally developed compound SUVN-502 has completed phase I clinical trials for cognitive impairment in schizophrenia and Alzheimer's disease.[17]

A general survey of the literature reveals that the reported 5-HT_6R ligands[18] have some major common features that are apparent as the basic minimum pharmacophore, the basic nitrogen, which could be the primary binding site at the receptor aspartate residue, and two other aromatic sites, which may be involved in the secondary binding (π-staking) interactions with the receptor. In an effort to identify and map the pharmacophoric requirements for the 5-HT_6R ligands, several diverse classes of compounds were taken up for synthesis and evaluation. N_1-aryl sulfonyl tryptamine is one of the major classes of compounds reported as 5-HT_6R ligands.[19−22]

Interestingly, although a lot of work has already been published on the effect of changes made in the nature of the side chain of tryptamines,[18] the alkyl piperazinyl or other cyclic amino side chains were not much studied and evaluated on the indole nucleus. Hence, we initiated research in this direction and reported our initial findings on N_1-aryl sulfonyl indole-3-piperzinylmethyl series.[23] The compounds from this series (compounds I) are potent, safe, brain penetrant, highly selective, and orally bioavailable 5-HT_6R antagonists. To further explore the structure−activity relationship (SAR) scope, the CH_2 piperazinyl moiety in compounds I was moved from the C3 of indole to the C5 of indole. The details of the chemistry, SAR, and pharmacological data presented over here are the subject matter of this paper.

The synthesis of final compounds was carried out as shown in Schemes 1−3. 4-Nitro-3-methyl benzoic acid **1** was treated with thionylchloride and substituted piperazines to obtain the amide **2**. The latter compound, when treated with DMFDMA and pyrrolidine,[24,25] gave the styrene derivative **3**. The styrene derivative **3** underwent reductive cyclization, when treated with hydrazine hydrate and Raney Ni, to obtain **4**. The intermediate **4** was subsequently reduced to 5-piperazinyl methyl indoles **5** with lithium aluminum hydride. The intermediate **5** was then treated with various substituted benzene sulfonylchlorides to obtain the title compounds **6** (Scheme 1).

The following strategy was adopted to prepare compounds **11** and **12** (Scheme 2). Indole 5-carboxaldehyde **7**[24,25] was treated with NCS to obtain the 3-chloro indole derivatives **8**. The intermediate **8** was further reacted with

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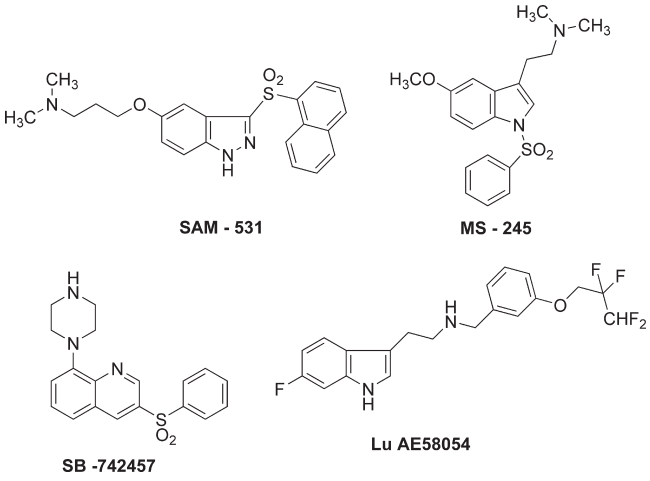


Figure 1. Reported 5-HT_6R ligands.

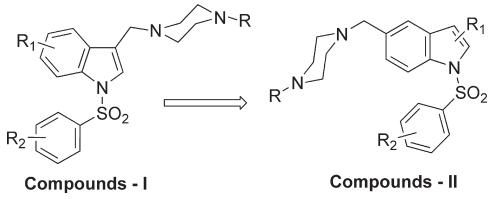
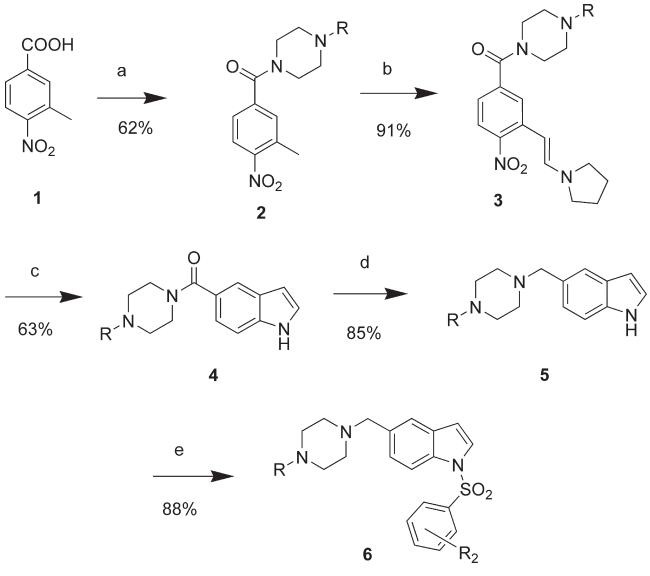


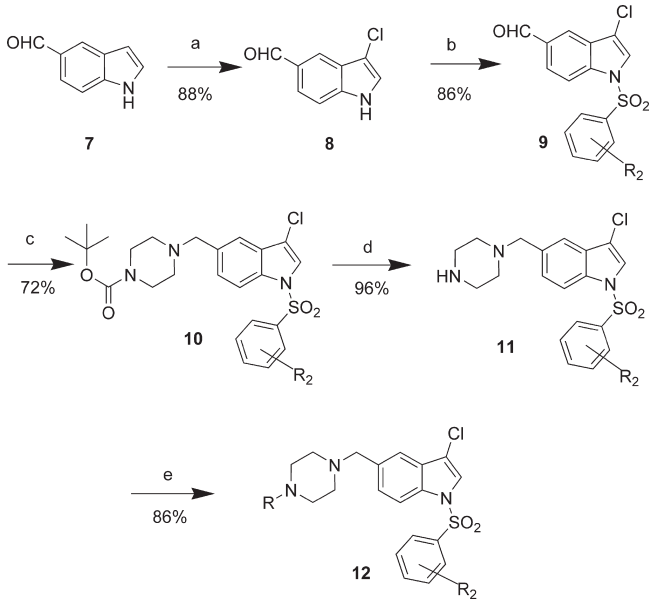
Figure 2. Design of 5-piperazinyl methyl-N_1-aryl sulfonyl indoles.

Scheme 1. Synthesis of 5-Piperazinyl Methyl-N_1-aryl Sulfonyl Indoles **6**[a]



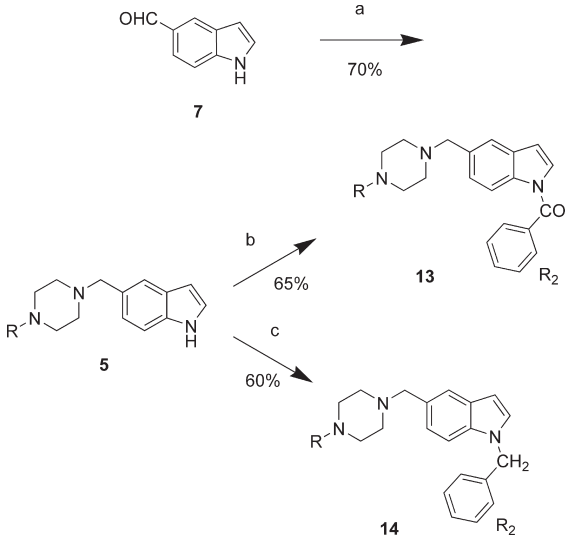
[a] Reagents and conditions: (a) Thionylchloride, substituted piperazines, THF, DMF, 10 °C to room temperature, 4 h. (b) DMFDMA, DMF, pyrrolidine, 100−110 °C, 6 h. (c) Hydrazine hydrate, Raney Ni, THF, MeOH, 70 °C, 5 h. (d) LAH, THF, 70 °C, 6 h. (e) THF, KH, various substituted benzenesulfonylchlorides, room temperature, 3 h.

Scheme 2. Synthesis of 3-Chloro-5-piperazinyl Methyl-N_1-aryl Sulfonyl Indoles **12**[a]



[a] Reagents and conditions: (a) NCS, 1,4-dioxane, room temperature, 4 h. (b) THF, KH, various substituted benzenesulfonyl chlorides, room temperature, 4 h. (c) *N*-Boc-substituted piperazines, sodium triacetoxy borohydride, EDC, room temperature, 8 h. (d) TFA, DCM, room temperature, 2 h. (e) DMF, K_2CO_3, R−X (R = CH_3 or C_2H_5, and X = I), room temperature, 4 h.

Scheme 3. Synthesis of 5-Piperazinyl Methyl-N_1-aryl Carbonyl and Benzyl Indoles **13**[a] and **14**[a]



[a] Reagents and conditions: (a) Substituted piperazines, sodium triacetoxy borohydride, EDC, room temperature, 8 h. (b) THF, KH, various substituted benzoyl chlorides, room temperature, 4 h. (c) THF, KH, various substituted benzyl chlorides, room temperature, 4 h.

various substituted benzenesulfonyl chlorides to obtain the sulfonyl derivatives **9**. The sulfonyl derivatives **9** when treated with *N*-Boc piperazines under reductive amination conditions gave the 5-piperazinyl methyl indole derivatives **10**. Intermediate **10** was deprotected with trifluoro acetic acid to obtain compound **11**. Compound **11** was alkylated

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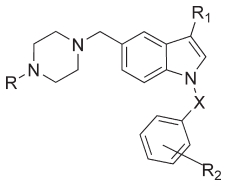
Table 1. 5-HT_6 Receptor Binding Data of Compounds II[a]



sr. no.	R	R_1	X	R_2	5-HT_6 K_i (nM)
6a	Et	H	SO_2	2-Br	2.56
6b	Et	H	SO_2	2,3-di-Cl	5.52
6c	Et	H	SO_2	3-CF_3	5.72
6d	Et	H	SO_2	4-iPr	5.81
6e	Et	H	SO_2	4-Me	11.0
6f	Et	H	SO_2	4-F	3.21
6g	Et	H	SO_2	2,4-di-F	12.4
6h	Et	H	SO_2	4-Cl	28.20
6i	Me	H	SO_2	H	3.83
6j	Me	H	SO_2	4-F	14.6
6k	Me	H	SO_2	4-iPr	17.9
6l	Me	H	SO_2	2-Cl, 5-CF_3	11.3
6m	Me	H	SO_2	2-Br	8.30
6n	Me	H	SO_2	2,3-di-Cl	18.00
6o	Me	H	SO_2	4-Cl	3.02
6p	Me	H	SO_2	3-CF_3	3.15
6q	H	H	SO_2	2-Br	7.77
6r	H	H	SO_2	H	2.52
6s	H	H	SO_2	4-iPr	14.9
11a	H	Cl	SO_2	4-F	2.58
11b	H	Cl	SO_2	2,4-di-F	5.57
12a	Me	Cl	SO_2	2-Cl,5-CF_3	4.16
12b	Me	Cl	SO_2	4-Cl	9.33
12c	Me	Cl	SO_2	4-F	2.97
12d	Me	Cl	SO_2	2,4-di-F	3.36
13	Me	H	CO	H	> 1000
14	Et	H	CH_2	H	> 1000

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors stably expressed in HEK293 cells. K_i values were determined in triplicate.

with alkyl halide to yield the targeted *N*-alkylpiperazinyl derivatives **12**. Intermediate **7** was treated with substituted piperazines under reductive amination conditions to obtain the 5-piperazinyl methyl indole derivatives **5**. Intermediate **5** was further treated with various benzoyl chlorides to obtain compound **13**. Similarly, **5** was treated with various benzyl chlorides to obtain compound **14** (Scheme 3).

The in vitro 5-HT_6R binding assay of all final compounds was carried out on human recombinant receptor expressed in HEK293 cells: The radioligand used was [^{3}H] LSD (60−80 Ci/mmol). The final ligand concentration was 1.5 nM, and the nonspecific determinant was methiothepin mesylate (0.1 μM). The reference compound was methiothepin mesylate, and the positive control was methiothepin mesylate.

Among the compounds synthesized (Table 1), compound **6a**, which is a 2-bromo benzenesulfonyl indole derivative, was found to have potent affinity with the K_i of 2.56 nM in the binding assay. SAR data indicate that the electron-withdrawing groups like halo at the *ortho* or *para* position (**6a**,**f**,**o**, **11a**, and **12c**) and electron-donating groups like alkyl groups (**6d**) at the *para* position on sulfonyl aromatic ring were found to be the most preferred substitutions in terms of in vitro affinity. The halo substitution at the C3 position of the indole ring was well-tolerated and proved to have greater affinity as can be seen from the K_i values of compounds **12a** and **12c** as compared to those of **6l** and **6j**, respectively. Replacement of terminal alkyl substitution R on piperazine with H maintains the binding affinity toward 5-HT_6R, indicating that secondary amine seems to be well-tolerated at this position as can be seen from the K_i values of compounds **6a**, **12c**, and **12d** as compared to compounds **6q**, **11a**, and **11b**, respectively. The sulfonyl linker at N_1 of indole seems to be very critical for activity. The replacement of linker with carbonyl (**13**) or methylene group (**14**) gave compounds that have a low binding affinity toward 5-HT_6R.

Some of the selected potent compounds were evaluated for their cytochrome P450 inhibitory potential and metabolic stability (Tables 2 and 3, respectively). Low to moderate levels of inhibition were seen at several of the major human P450 enzymes with the highest level of inhibition seen against CYP3A4,[26] which was 32.89% inhibition at a 10 μM

Table 2. Human Cytochrome P450 Inhibitory Potential of Selected Compounds[a]

	% inhibition											
	CYP1A2 (h)		CYP2A6 (h)		CYP2C19 (h)		CYP2C9*1 (h)		CYP2D6 (h)		CYP3A4 (h)	
sr. no.	3 μM	10 μM	3 μM	10 μM	3 μM	10 μM	3 μM	10 μM	3 μM	10 μM	3 μM	10 μM
6a	3.64	17.9	−0.39	10.81	22.76	43.59	7.47	15.95	48.33	76.23	−3.67	32.89
6d	14.52	18.16	−1.26	21.89	23.85	51.11	7.12	46.27	10.45	35.68	30.52	68.07
6f	13.65	8.34	−7.74	10.17	6.75	4.7	−14.26	19.55	10.29	45.98	18.62	34.24
6i	14.44	17.34	−2.24	4.81	9.91	31.19	−8.69	18.23	11.97	31.21	8.24	5.47
11b	14.5	14.57	−3.62	6.37	31.85	72.92	−12.62	27.75	1.46	17.71	26.35	44.97
12c	3.4	26.92	14.1	19.8	10.11	21.49	6.42	9.13	6.42	15.23	2.6	39.03

[a] The cytochrome P450 inhibitory potential was determined using isoform-selective assays and heterologously expressed human CYP1A2, CYP2A6, CYP2C9*1, CYP2C19, CYP2D6 and CYP3A4. These values are means of duplicate determinations.

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concentration for the lead compound **6a**. These results showed that the compounds from this series would likely have a lower potential for drug−drug interactions. Compounds **6a**,**f**,**o**,**p** and **12c** were, however, extensively metabolized in rat and human liver microsomes (Table 3).

Two of the compounds, **6a** and **12c**, were examined further for selectivity against serotonergic and Muscarinic receptors (Table 4). Both compounds have shown excellent selectivity over the 5-HT_7, 5-HT_4, and M_1 receptors.

The lead compound **6a**, which has shown excellent binding affinity and selectivity, was selected for pharmacokinetic profiling. The pharmacokinetic profile of compound **6a** was assessed in male Wistar rats (Table 5). The dose of 10 mg/kg was rapidly absorbed in rats with an oral half-life of 6.04 ± 2.54 h and had low oral bioavailability. The observed oral C_{max} value was 13 ± 4.0 ng/mL. The clearance (128367 ± 48173 mL/h/kg) was found to be very high. Extensive rat metabolism coupled with high clearance could be the reason of low bioavailability (4.2 ± 0.7) of the lead compound. In a steady-state brain penetration study in male Wistar rat, the Cb/Cp for **6a** was found to be 19.3 ± 5.9.

Compound **6a** was further profiled in animal models of cognition like novel object recognition test (NORT) and Morris water maze.[27,28] Oral administration of compound **6a** has shown improvement in the performance of rats (Figure 3) in NORT and significantly reversed scopolamine-induced special memory deficit (Figure 4) in Morris water maze test, indicating cognitive improvement potential of compound **6a**.

In conclusion, our SAR exploration of N_1-aryl sulfonyl 5-methyl piperazinyl indole leads to the finding that moving the *N*-methyl piperazinyl moiety from C3 to C5 of indole maintains the in vitro affinity of these novel compounds. Two of these potent compounds (i.e., **6a** and **12c**) have excellent selectivity over other tested receptors. The lead compound **6a** is active in NORT and Morris water maze, indicating the cognitive potential of the compound.

Table 3. Percent Surrogate Metabolism for Compounds[a]

	surrogate % metabolism	
compound	human	Wistar rat
6a	83	100
6f	57	100
6o	59	98
6p	69	98
12c	87	100

[a] Microsomal metabolic stability in Wistar rat and human at 0.5 h; concentration, 2.5 μM.

Table 4. Selectivity Data of Compounds **6a** and **12c**

	IC_{50} (nM)		
compound	5-HT_4	5-HT_7	M_1
6a	> 10000	> 10000	1425 (kb)
12c	> 10000	> 10000	> 10000

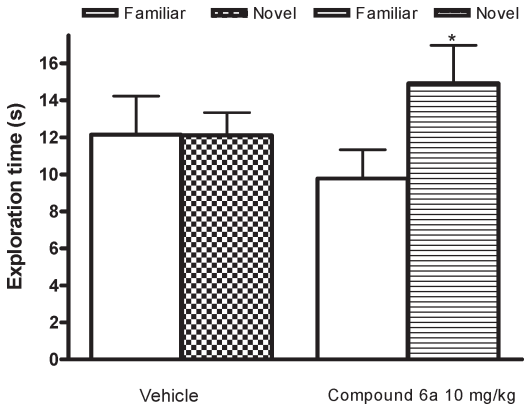

Figure 3. Novel object recognition test in adult rat. *$p < 0.05$ vs vehicle (paired *t* test), $n = 9-12$/group.

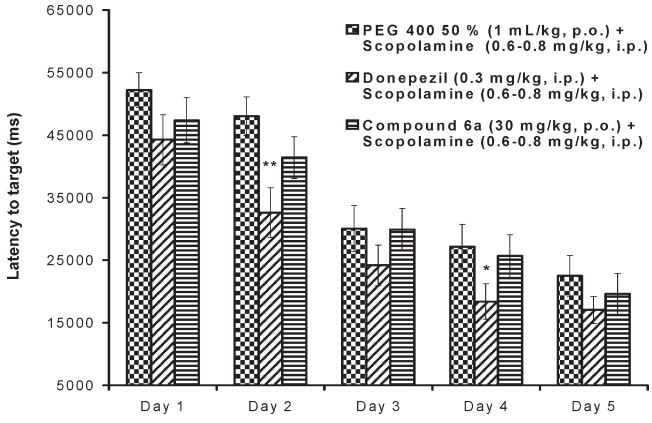

Figure 4. Morris water maze. Data represent means ± SEMs of latency to target; **$p < 0.01$ (one-way ANOVA, Dunnett's posthoc analysis), $n = 10$.

Table 5. Pharmacokinetic Profile of Compound **6a** in Male Wistar Rats[a]

			compound **6a**					
route	*n*	dose (mg/kg)	C_{max} (ng/mL)	AUC_t (ng h/mL)	$t_{1/2}$ (h)	V_z (mL/kg)	Cl (mL/h/kg)	*F* (%)
oral	3	10	13 ± 4.0	59 ± 17	6.04 ± 2.54	1035145 ± 240694	128367 ± 48173	4.2 ± 0.7
iv	3	10	716 ± 69	1382 ± 156	2.10 ± 0.18	21801 ± 3646	7186 ± 764	

[a] Fasted male Wistar rats. Vehicle used: water for injection for both oral and intravenous routes. Dosing volumes: 10 mL/kg for oral and 2 mL/kg for iv.

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SUPPORTING INFORMATION AVAILABLE

Representative experimental procedures, NMR, MS, and HPLC data for all new test compounds (**6a**−**s**, **11a**,**b**, **12a**−**d**, **13**, and **14**). This material is available free of charge via the Internet at http://pubs.acs.org.

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ABBREVIATIONS

5-HT, 5-hydroxy tryptamine; 5-HT$_6$R, 5-hydroxy tryptamine 6 receptor; NORT, novel object recognition test; SAR, structure−activity relationship.

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