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[3-[(1-Methylpiperidin-4-yl) methyl] arylsulfonyl]-1*H*-indoles: Synthesis, SAR and biological evaluation as a novel class of 5-HT$_6$ Receptor Antagonists

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Abstract. In continuation to our efforts to develop better treatment options for cognitive decline, we have been focussing on 5-HT$_6$ receptor (5-HT$_6$R) antagonists, which are known to be involved in improving cognitive function in numerous animal models. In this paper, we report a novel series of [3-[(1-Methylpiperidin-4-yl) methyl] arylsulfonyl]-1*H*-indole derivatives as potent and selective 5-HT$_6$R antagonists. The lead compound from this series shows potent *in vitro* binding affinity, functional antagonistic activity at 5-HT$_6$R, good pharmacokinetic profile, excellent selectivity and no Cytochrome P450 liabilities.

Keywords. [3-[(1-Methylpiperidin-4-yl) methyl] arylsulfonyl]-1*H*-indoles; 5-HT$_6$R antagonists; cognitive impairment; structure activity relationship; cross selectivity; pharmacokinetic profile.

1. Introduction

Cognitive decline is a defining symptom of many severe neurological disorders, viz., Alzheimer's disease (AD), Schizophrenia, Parkinson's disease (PD), etc.[1] The current options to treat cognitive symptoms associated with neurological disorders mentioned above include drugs like Donepezil[2] and Memantine.[3] These drugs have limited efficacy and poor tolerability.[4] This poses a great need for the discovery of new drugs for the treatment of cognition through a novel mechanism of action, and thus 5-hydroxytryptamine-6-receptor (5-HT$_6$R) has attracted a lot of attention in the recent past. 5-HT$_6$R belongs to serotonin super family and they are exclusively located in those regions in the brain that are associated with learning and memory.[5] Studies have found that known 5-HT$_6$R antagonists have selectively increased glutamate and acetylcholine levels in brain, a phenomenon associated with learning and memory.[6] The exclusive Central Nervous System (CNS) location and high affinity of several psychiatric drugs towards this receptor suggests that antagonism of 5-HT$_6$R could potentially provide effective treatment towards cognitive dysfunction associated with AD.[7]

SB-742457, **A**[8] and Lu AE58054, **B**[9] are the two advanced stage 5-HT$_6$R antagonists that have completed phase II clinical trials. Modification in the side chain of *N*-arylsulfonyl tryptamine, for e.g., MS-245, **C**,[10] a known 5-HT$_6$R antagonist has led to the discovery of structurally diverse compounds as depicted by structures **D**[11] (reported by our research group) and **E**[12] which are potent 5-HT$_6$R antagonists. In general, these compounds are characterized by having the cyclic amine moiety on indole nucleus. We were interested in evaluating the effect of migrating the cyclic amine moiety from indole central core to arylsulfonyl group on indole, as the latter type of compounds are not reported in the literature. Thus we have designed a new series, i.e., **Compounds I**, which align with pharmacophoric model of 5-HT$_6$R[13] and we expect them to be potent 5-HT$_6$R ligands. In this paper, we report synthesis and *in vitro* preliminary biological data of **Compounds I** (figure 1).

2. Experimental

2.1 *General information*

All the reagents and chemicals used were of 'reagent grade.' Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates, and spots

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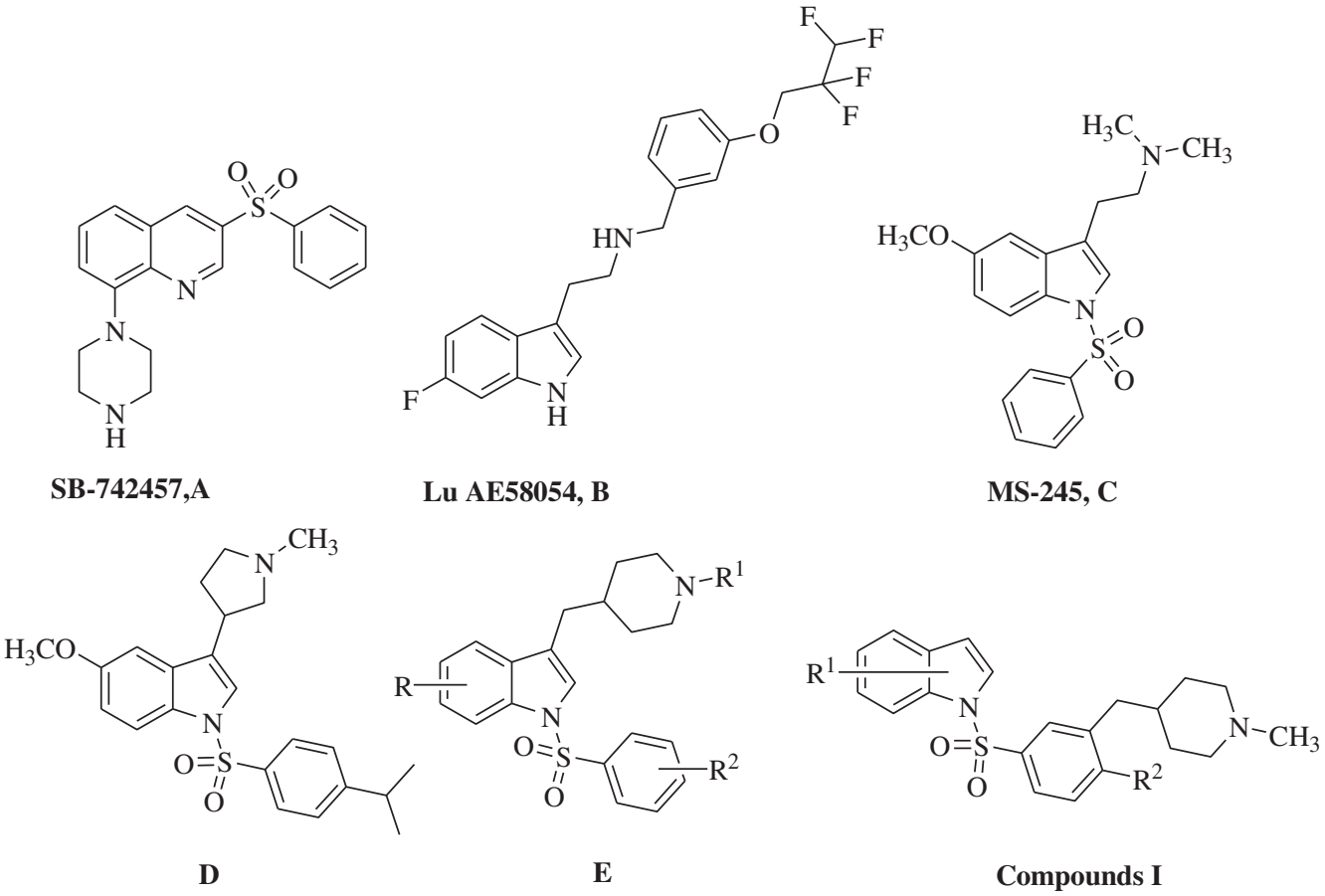


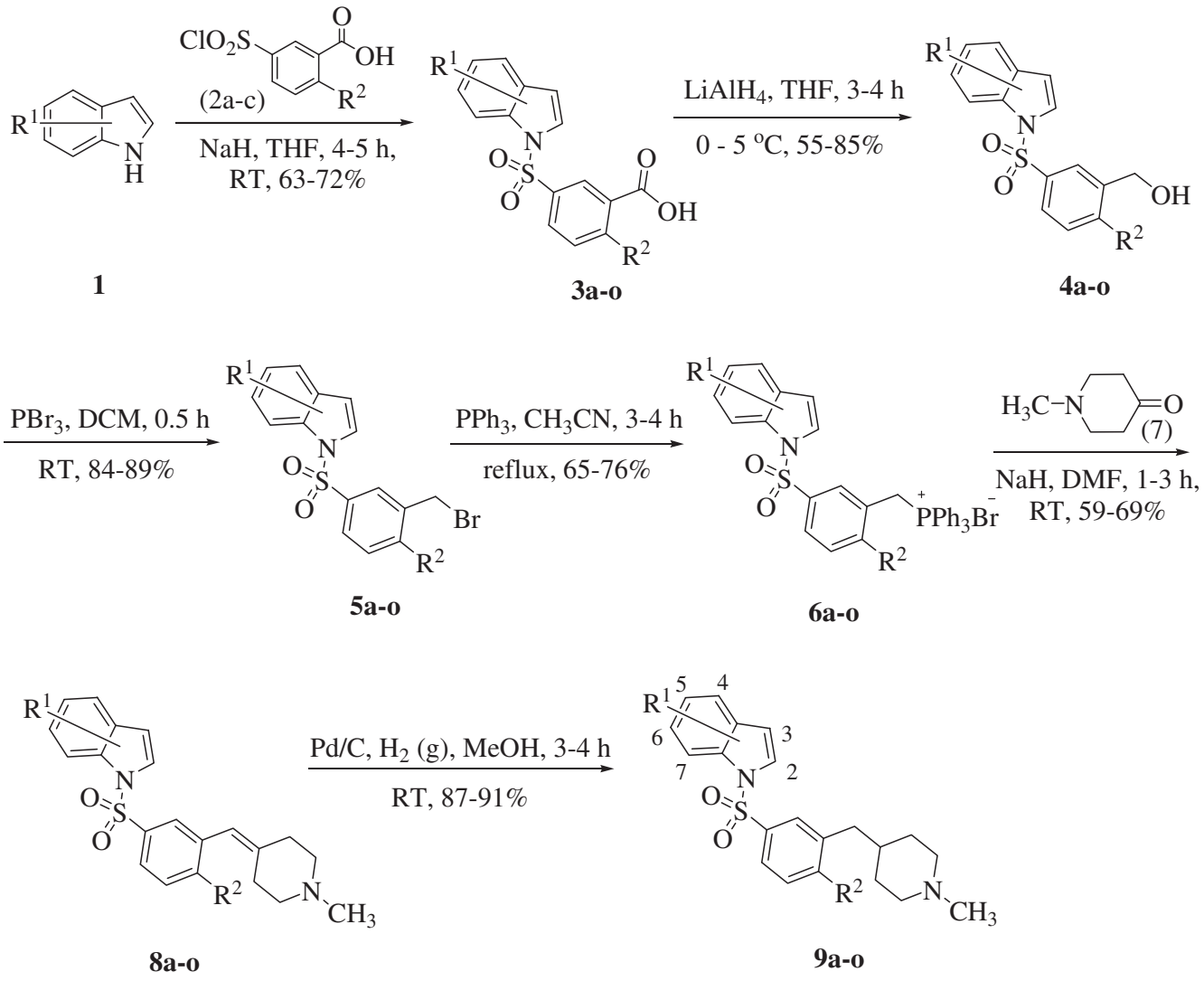
Figure 1. Reported 5-HT_6R antagonists.

were visualized in UV light (254 nm) and/or iodine. Purification of compounds was accomplished by column chromatography performed using 60–120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions. Purity of the final compounds (>95%) was established using Agilent 1100 high-performance liquid chromatography (HPLC) system. All the mentioned yields refer to isolated pure products. Infrared spectra were recorded on KBr disk and in solid state using Perkin-Elmer model 1600 FT-IR spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). ^{1}H NMR spectra were obtained on a Bruker NMR spectrometer (Fallanden, Switzerland) at 400 MHz. Deuterated reagents were used as solvents and were commercially procured. Tetramethylsilane (TMS) was used as an internal standard, chemical shift values are expressed in parts per million (δ) and coupling constants are expressed in Hz. Electrospray ionization mass spectra were recorded on a API 4000 triple quadrupole instrument (MDS-SCIEX, Concord, Ontario, Canada).

Indole derivatives were either commercially procured or synthesized as per literature methods.[14] Substituted benzoic acids were reacted with chlorosulfonic acid to afford substituted 3-carboxybenzenesulfonyl chlorides **2a–c**. Synthesis of targeted compounds **9a–o** was achieved as depicted in scheme 1. Substituted indoles **1** were reacted with substituted sulfonyl chlorides **2a–c** in presence of sodium hydride to obtain intermediates **3a–o**. The carboxylic acid group of intermediates **3a–o** was reduced with lithium aluminium hydride in THF to obtain benzyl alcohol derivatives **4a–o**. Reaction of **4a–o** with phosphorus tribromide gave the benzyl bromide derivatives **5a–o**. The intermediates **5a–o** on reaction with triphenyl phosphine gave the phosphonium salts **6a–o,** which on further reaction with 1-methylpiperidone under Wittig reaction conditions gave the alkene intermediates **8a–o**. The Pd/C catalyzed hydrogenation of intermediates **8a–o** afforded the targeted compounds **9a–o**.

2.2 *Synthesis of arylsulfonyl chlorides: General procedure for the preparation of 3- Chlorosulfonylbenzoic acid (2a, $R^2 = H$)*

Benzoic acid (5 g, 40.9 mmol) was added in portions to chlorosulfonic acid (14.3 g, 122.9 mmol) under stirring at 5–10°C and then stirred at 110°C for 2 h. The reaction mixture was cooled to room temperature, poured on to



Scheme 1. Synthesis of [3-[(1-Methylpiperidin-4-yl) methyl] arylsulfonyl]-1*H*-indoles **9a-o**.

crushed ice (~100 g) under stirring during which solids precipitated. These solids were filtered, extracted with ethyl acetate (150 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain the title compound as solid mass (5.4 g, 60% yield). IR (cm^{-1}): 3410 (broad, due to –OH stretching vibrations of –COOH group) and ~1313 and 1182 (sharp, strong, due to asymmetric and symmetric stretching vibrations of $–SO_2$ group respectively). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.78 (1H, t, J = 1.60 Hz), 8.48 (1H, d, J = 8.0 Hz), 8.28–8.31 (1H, dd, J = 8.0, 1.6 Hz), 7.80 (1H, t, J = 8.0 Hz). ESI mass: m/e 219.1 $(M - H)^+$.

2.3 *General procedure for the preparation of 3-Methyl-1-(3-carboxybenzenesulfonyl)-1H-indole (3m, R^1 =3-CH_3, R^2 = H)*

A solution of 3-methyl-1*H*-indole (1 g, 7.6 mmol) in dry THF was added to a stirred suspension of NaH (0.91 g, 22.9 mmol, 60% oil suspension) at 25–30°C under stirring and maintained for 30 min. Then a solution of 3-chlorosulfonyl benzoic acid (1.85 g, 8.39 mmol) in dry THF was added to the above mixture at room temperature and stirred for 4 h. The reaction mixture was then poured on to water (50 mL), acidified with dil. HCl and extracted with ethyl acetate (50 mL × 3). The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resultant crude compound was chromatographed (SiO_2, 30:70 EtOAc-hexanes as eluent) to afford title compound as solid mass (1.51 g, 63% yield). IR (cm^{-1}): 3411 (–OH stretching vibrations of –COOH group), 1679 (stretching vibrations of –C=O functional group of carboxylic acid), 1374 and 1154 (asymmetric and symmetric stretching vibrations of $–SO_2$ group respectively). ^{1}H NMR (400 MHz, DMSO-d_6)δ: 8.35 (1H, s), 8.15 (2H, t, J = 7.42 Hz), 7.93 (1H, d, J = 8.27 Hz), 7.68 (1H, t, J = 7.88 Hz), 7.62 (1H, s), 7.53

(1H, d, $J = 7.74$ Hz), 7.37 (1H, t, $J = 7.49$ Hz), 7.27 (1H, t, $J = 7.54$ Hz), 2.20 (3H, s). ESI mass: m/e 313.9 $(M - H)^+$.

2.4 *General procedure for the preparation of 3-Methyl-1-(3-hydroxymethyl benzenesulfonyl)-1H-indole (4m, R^1 =3-CH_3, $R^2 = H$)*

A solution of **3m** (1.5 g, 4.76 mmol) in dry THF (25 mL) was added to a stirred suspension of lithium aluminium hydride (0.54 g, 14.3 mmol) below 0°C and further stirred for 3 h at this temperature. After completion of the reaction (TLC), ice cold water (5 mL) was added slowly to the reaction mixture to decompose excess of LAH. The resultant mixture was filtered and the residue was washed with ethyl acetate (25 mL × 2). The filtrate was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant crude compound was chromatographed (SiO_2, 25:75 EtOAc-hexanes as eluent) to afford title compound as syrupy mass (1.2 g, 84% yield). IR (cm^{-1}): 3199 ($ArCH_2O$-H stretching vibration), 1371 and 1166 (asymmetric and symmetric stretching vibrations of $–SO_2$ group respectively). ^{1}H NMR (400 MHz, $CDCl_3$)δ: 7.98 (1H, d, $J =$ 8.27 Hz), 7.86 (1H, bs), 7.77 (1H, d, $J = 7.87$ Hz), 7.50 (1H, d, $J = 7.63$ Hz), 7.45 (1H, d, $J = 7.57$ Hz), 7.39 (1H, t, $J = 7.79$ Hz), 7.29–7.33 (2H, m), 7.23 (1H, d, $J = 7.16$ Hz), 4.68 (2H, d, $J = 5.4$ Hz), 2.24 (3H, s). ESI mass: m/e 302.2 $(M + H)^+$.

2.5 *General procedure for the preparation of 3-Methyl-1-(3-bromomethylbenzenesulfonyl)-1H-indole (5m, R^1 =3-CH_3, $R^2 = H$)*

Phosphorus tribromide (0.16 mL, 1.66 mmol) was added to a stirred solution of **4m** (1 g, 3.32 mmol) in DCM (20 mL) at 5–10°C and then stirred below 10°C for further 0.5 h. After completion of the reaction (TLC), the reaction mixture was poured on to cold water (25 mL). The organic layer was separated, washed with saturated $NaHCO_3$ solution (10 mL), brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain title compound as oily mass (1.02 g, 85% yield). This was used as such for further reaction.

2.6 *General procedure for the preparation of [3-(3-Methyl-1H-indole-1-sulfonyl) benzyl]-triphenyl phosphonium bromide (6m, R^1 =3-CH_3, $R^2 = H$)*

Triphenyl phosphine (0.72 g, 2.74 mmol) was added to a stirred solution of **5m** (1 g, 2.74 mmol) in acetonitrile (25 mL) at room temperature. The reaction mixture was then refluxed for 4 h and then concentrated to obtain a crude compound. The crude compound was triturated with ethyl acetate (25 mL) and resultant white solids were filtered and dried under vacuum to obtain title compound (1.15 g, 67% yield). ^{1}H NMR (400 MHz, DMSO-d_6)δ: 7.88 (2H, t, $J = 7.44$ Hz), 7.81 (2H, d, $J = 7.89$ Hz), 7.55–7.67 (15H, m), 7.40 (1H, t, $J =$ 7.87 Hz), 7.18 – 7.29 (4H, m), 5.25 (2H, d, $J = 15.78$ Hz), 2.18 (3H, s).

2.7 *General procedure for the preparation of 3-Methyl-1-[3-(1-methylpiperidin-4-ylidene methyl) benzenesulfonyl]-1H-indole (8m, R^1 =3-CH_3, $R^2 = H$)*

Sodium hydride (0.096 g, 2.39 mmol, 60% oil suspension) was added to a stirred solution of **6m** (1g, 1.59 mmol) at room temperature, then heated to 55°C and maintained for 1 h. 1-Methyl-4-piperidone (0.22 g, 1.91 mmol) was added to the above mixture at room temperature followed by stirring at 60°C for 3 h. The reaction mixture was then cooled to room temperature, poured on to water (50 mL), extracted with ethyl acetate (50 mL x 4). The organic extracts were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resultant crude compound was chromatographed (SiO_2, 2:98 ammonical MeOH:EtOAc as eluent) to afford title compound as syrupy mass (0.41 g, 68% yield). IR (cm^{-1}): ∼3021 (asymmetric stretching vibrations of -C=C- functional group), ∼1328 and 1153 (asymmetric and symmetric stretching vibrations of $–SO_2$ group respectively). ^{1}H NMR (400 MHz, DMSO-d_6)δ: 7.99 (1H, d, $J = 8.23$ Hz), 7.66–7.69 (1H, m), 7.62–7.62 (1H, s), 7.46 (1H, d, $J = 7.94$ Hz), 7.33–7.37 (2H, m), 7.28–7.31 (2H, m), 7.23–7.24 (1H, m), 6.20 (1H, s), 2.49 (2H, t, $J = 5.36$ Hz), 2.39 (2H, t, $J = 5.60$ Hz), 2.31 (3H, s), 2.27–2.30 (4H, m), 2.24 (3H, s). ESI mass: m/e 381.3 $(M + H)^+$.

2.8 *General procedure for the preparation of 3-Methyl-1-[3-(1-methylpiperidin-4-yl methyl) benzenesulfonyl]-1H-indole (9m, R^1 =3-CH_3, $R^2 = H$)*

A stirred mixture of **8m** (0.4 g, 1.05 mmol) and Pd/C in methanol was stirred for 4 h under H_2 (g) bubbling. Then the reaction mixture was filtered and concentrated under reduced pressure. The resultant crude mass was chromatographed (SiO_2, 2:98 ammonical MeOH:EtOAc as eluent) to afford title compound as solid mass (0.36 g, 90% yield). IR (cm^{-1}): 2930 (due to sp^3 C-H stretching vibrations), 1365 and 1171

(asymmetric and symmetric stretching vibrations of –SO_2 group respectively). ^{1}H NMR (400 MHz, $CDCl_3$)δ: 7.97 (1H, d, J = 8.24 Hz), 7.61–7.66 (2H, m), 7.44 (1H, d, J = 7.56 Hz), 7.26–7.32 (3H, m), 7.21–7.25 (2H, m), 2.75–2.78 (2H, m), 2.51 (2H, d, J = 6.68 Hz), 2.24 (6H, s), 1.76–1.81 (2H, m), 1.26–1.43 (3H, m), 1.19–1.24 (2H, m);^{13}C NMR (100 MHz, $CDCl_3$)δ: 141.9, 137.8, 135.2, 134.2, 131.7, 128.8, 126.8, 124.4, 124.0, 123.0, 122.9, 119.2, 118.7, 113.6, 55.5, 46.1, 42.5, 36.9, 31.7, 9.5. ESI mass: m/e 383.5 $(M + H)^+$.

3. Results and Discussion

3.1 *5-HT$_6$R receptor binding assay*

The *in vitro* 5-HT$_6$R binding assay of all targeted compounds, that is, **Compounds I(9a–o)** was carried out on human recombinant receptor expressed in HEK293 cells: Radioligand used was [^{3}H]-LSD (60–80 Ci/mmol). Final ligand concentration was 1.5 nM, Non-specific determinant was methiothepin mesylate—[0.1 μ M]; reference compound was methiothepin mesylate, positive control was methiothepin mesylate.

3.2 *Structure activity relationship (SAR)*

Most of the synthesized compounds have shown potent affinity towards 5-HT$_6$R by displacing the radioligand [^{3}H]-LSD when tested at 100 nM concentration (table 1). By using unsubstituted indole, we initially synthesized 1-[3-[(1-methyl piperidin-4-yl) methyl] benzenesulfonyl]-1*H*-indole, that is, compound **9a**. This compound displayed a potent affinity with an inhibition of 97.49% towards 5-HT$_6$R. We then introduced selective substitutions like methyl and methoxy at R^2 position of **Compounds I** and synthesized **9b** and **9c** respectively. These compounds were also found to have potent affinity towards 5-HT$_6$R with an inhibition of 98.65% and 92.14% respectively. Encouraged with these results and also to better understand the SAR of the series, we inserted various substitutions at R^1 of indole and R^2 was fixed as H, methyl or methoxy and obtained the compounds (**9d–9o**). Compounds **9d–9h** were achieved by introducing –OCH_3 group at 4th and 5th position of indole and substitutions at R^2 position was kept constant as discussed above. Among these, compounds **9d** bearing a methoxy group 5th position of indole core and **9h** bearing a methoxy group at 4th position of indole core have displayed an inhibition of 81.15% and 61.62% respectively towards 5-HT$_6$R. The inhibitory potential of these compounds were lower when compared to unsubstituted parent compounds **9a–9c**. A similar trend of reduction in affinity was observed for **9e** (R^1 = 5–OCH_3, R^2 = -CH_3, 50.54%), **9f** (R^1 = 5–OCH_3, R^2 = -OCH_3, 83.49%) and **9g** (R^1 = 4–OCH_3, R^2 = -CH_3, 75.68%), indicating that the introduction of electron donating groups on indole core could have diminishing effect on binding affinity towards 5-HT$_6$R. The other substitutions evaluated include fluoro group at 5th and 6th positions (**9i–9l**) and methyl group at 3rd position (**9m–9o**) of indole. Among fluoro substituted derivatives, compound **9i** where R^1 =

Table 1. SAR data of **Compounds I**[a].

Compound	R^1	R^2	% inhibition at h 5-HT$_6$R at 100 nM concentration[a, b]	cAMP functional assay for 5-HT$_6$R[c]		
				K_b *(nM)*	IC_{50} *(nM)*	I_{max}
9a	H	H	97.49	2.78	5.75	100%
9b	H	–OCH_3	98.65	0.8	11.80	99%
9c	H	–CH_3	92.14			
9d	5-OCH_3	H	81.15			
9e	5-OCH_3	–CH_3	56.54			
9f	5-OCH_3	–OCH_3	83.49			
9g	4-OCH_3	–CH_3	75.68			
9h	4-OCH_3	H	61.62			
9i	5-F	H	82.35	2.6	6.12	98%
9j	5-F	–CH_3	75.68			
9k	6-F	H	96.53			
9l	6-F	–CH_3	90.31			
9m	3-CH_3	H	101	0.4	6.50	100%
9n	3-CH_3	–CH_3	99.69	1.5	4.96	99%
9o	3-CH_3	–OCH_3	100.54	0.9	12.80	99%

[a]Displacement of [^{3}H]-LSD binding to cloned human 5-HT$_6$ receptors stably expressed in HEK293 cells. % binding towards 5-HT$_6$R values were determined in duplicate and the average values are reported here.
[b]The binding assays were carried out at Novascreen Biosciences Corporation, USA as per their standard protocol.
[c]K_b values were determined using non-radioactive cell based assay. IC_{50} and I_{max} values are the mean of two experiments.

5–F, R^2 = H and **9j** where R^1 = 5–F, R^2 = -CH_3 have displayed an inhibition of 82.35% and 75.68% respectively towards 5-HT_6R. The other compounds of the series, that is, **9k** (96.53%) and **9l** (90.31%) with R^1 = 6–F displayed better affinity towards 5-HT_6R compared **9i** and **9j** respectively. In general, compounds bearing electron withdrawing substitution on indole core have displayed better affinity towards 5-HT_6R compared to electron donating groups, with the exception of 3-methyl substituted indole derivatives. Among all the synthesized derivatives, compounds **9m** (R^1 = 3–CH_3, R^2 = H, 101%),**9n** (R^1 = 3–CH_3, R^2 = -CH_3, 99.69%) and **9o** (R^1 = 3–CH_3, R^2 = -OCH_3, 100.54%) were the most potent. From the above SAR, it could be observed that compounds bearing a methyl substitution at 3rd position of indole nucleus are more preferable compared to compounds having substitutions at other positions of indole nucleus. In general, a series of **Compounds I**, was identified as a novel structural motif having potent 5-HT_6R binding affinity.

After achieving the compounds with potent affinity, our next aim was to investigate the antagonistic potential of the synthesized analogues of **Compounds I** towards 5-HT_6R. For this purpose, few of the select compounds from the series were further evaluated for their functional activity at 5-HT_6R using non radioactive CHO based cell assay.[15] A similar SAR trend was observed from the tested compounds as they showed full antagonistic activity by inhibiting the 5-HT stimulated cAMP accumulation as can be seen from the IC_{50} and I_{max} values (table 1).

A number of compounds which displayed excellent potency in both radioligand binding and cell based functional assay were further profiled for selectivity on a panel of closely related 5-HT receptors, histamine H_1 and H_3, dopamine D_2 and D_3, adrenergic α_{1B}, and the transporters like SERT, DAT and NET. Most of the compounds displayed 50–100 fold selectivity over all the receptors tested (data not shown) indicating limited side-effects due to unforeseen add-on therapies.

3.3 *Microsomal metabolic stability and pharmacokinetic study*

The potent compounds of the series, that is, **9m**, **9n** and **9o** were further evaluated for Cytochrome P450 liabilities, microsomal metabolic stability studies (table 2) and pharmacokinetic profile (table 3). Compounds **9m** and **9n** were moderately metabolized in human (45%) and (51%) respectively whereas compound **9o** was extensively metabolized (85%). These compounds were extensively metabolized in rat liver microsomes. Further evaluation of these compounds towards most common cytochrome P450 (CYPs) enzymes (2D6, 3A4) showed low (IC_{50} >10 μM towards CYP 2D6) to moderate inhibition (IC_{50} >2.5 μM towards CYP 3A4) indicating that the compounds from this series may have lower potential for drug–drug interaction in human, through the major metabolic enzymes in the liver.

Table 2. Microsomal metabolic stability and Cytochrome P450 data of selected compounds[a].

	IC_{50} (μ M)		Surrogate % metabolism in liver microsomes	
Compound	CYP 2D6	CYP 3A4	human	Wistar rat
9m	26.13	7.65	45	81
9n	23.81	5.49	51	93
9o	31.81	2.56	85	98

[a]The Cytochrome P450 inhibitory potential was determined using isoform selective assays using human liver microsomes. These values are the mean of duplicate determinations. Microsomal metabolic stability was performed at 30 min incubations in Wistar rat and Human (2.5 μM).

Pharmacokinetic studies of select compounds were assessed in male wistar rats. Compound **9m** at an oral dose of 10 mg/kg was rapidly absorbed in rats with a good *iv* half-life of 3.24 ± 1.82 h with an adequate oral bioavailability of 14 ± 6%. It had displayed C_{max} = 153 ± 41 ng/mL occurred at T_{max} 0.83 ± 0.29 h. The oral exposure for this compound was found to be 390 ± 61 ng h/mL. It had a clearance of 61 ± 15 mL/min/kg with a volume of distribution of 19 ± 14 L/kg for *iv* dose. The C_{max} of compounds **9n** and **9o** were found

Table 3. Pharmacokinetic profile of selected compounds in male wistar rats.[a]

Compound	**9m**	**9n**	**9o**
	Intravenous		
dose (mg/kg)	10	10	10
$t_{1/2}$(h)	3.24 1.82	3.06 ± 1.21	1.70 ± 0.22
Vz (L/kg)	19.7 ± 14	22.6 ± 7.8	10.9 ± 3.24
CL (mL/min/kg)	61 ± 26	90 ± 24	73 ± 19
	Oral		
dose (mg/kg)	10	10	10
C_{max} (ng/mL)	153 ± 41	72 ± 24	93 ± 29
T_{max} (h)	0.83 ± 0.29	0.83 ± 0.29	0.85 ± 0.27
AUC_t (ng h/mL)	390 ± 61	251 ± 52	285 ± 61
F (%)	14 ± 6	13 ± 4	12 ± 2
C_b/C_p^b	2.05 ± 0.12	1.78 ± 0.53	0.42 ± 0.07

[a]Fasted male Wistar rats, water was used as a vehicle for dose formulation preparation; 10 mL/kg for oral and 2 mL/kg for intravenous was used as dosing volume. Values are mean ± SD; N = 3 animals/route.
[b]Discrete brain penetration was performed in rats at 10 mg/kg at 1 h after oral administration.

to be 72 ± 24 ng/mL and 93 ± 29 ng/mL respectively. The oral bioavailability of compounds **9n** and **9o** were found to be 13 ± 4 and 12 ± 2 respectively. The high metabolism of these compounds in rats could be possible reason for high clearance. The compounds **9m** and **9n** have demonstrated an adequate brain penetration (C_b/C_p) of 2.05 ± 0.12 and 1.78 ± 0.53 respectively. This selective partitioning of compounds into the brain would be one of important requirements for achieving *in vivo* activity against neuropsychiatric disorders.

4. Conclusion

We have identified a novel series of **Compounds I**, that is, [3-[(1-Methylpiperidin-4-yl) methyl] arylsulfonyl]-1*H*-indole derivatives, obtained by migrating cyclic amine moiety from indole core to arylsulfonyl group on indole. This novel series of compounds reported here have potent *in vitro* binding affinities. Few of the selected compounds have displayed adequate brain penetration, acceptable selectivity and good overall Pharmacokinetic properties. Based on the above findings, the novel series of **Compounds I,** in general, was selected for further optimization and development in animal models for detailed efficacy studies.

Supplementary Information

The electronic supporting information can be seen at www.ias.ac.in/chemsci.

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