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Design, Synthesis and Pharmacological Evaluation of Novel 2-Arylsulfonyl Methyl-3-Piperazinyl Methyl Indole Derivatives as 5-HT$_6$ Receptor Ligands

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Abstract: A novel series of 2-arylsulfonylmethyl-3-piperazinylmethyl indole derivatives was designed as per the pharmacophoric requirement needed for 5-hydroxytryptamine$_6$ receptor (5-HT$_6$R) binding. Synthesis was achieved through the condensation reaction between indole-2-methanol and thiophenol derivatives to get intermediate 2 in moderate yields, which subsequently underwent mannich reaction followed by oxidation to yield the title series of compounds, which were confirmed by IR, NMR and MASS. All the compounds of the title series show moderate affinity towards human 5-HT$_6$R when tested at 100 nM concentration. One of the active compounds 4a shows procognition potential when tested in Morris water maze task. Synthesis, SAR and pharmacological profile of these derivatives were discussed in this paper.
Keywords: 5-HT$_6$R ligands; SAR; 2-Arylsulfonylmethyl-3-piperazinylmethyl indole; Synthesis.

Introduction

There are 15 different serotonin receptors that have been cloned and divided into 7 sub-classes 5-HT$_{1-7}$.[1] 5-hydroxytryptamine$_6$ receptor (5-HT$_6$R) is one of the most recently discovered member of 5-HT family and it shows about 30-40% homology to other human 5-HT receptors within the transmembrane region. 5-HT$_6$R belongs to the G-protein coupled receptor (GPCR) superfamily and is positively coupled to adenylyl cyclase.[2] 5-HT$_6$R are exclusively localized in the central nervous system (CNS) which elucidate its role in the treatment of various CNS disorders like Alzheimer's disease (AD), schizophrenia, depression, cognition, memory dysfunction [3-5] and also in the treatment of obesity and eating disorders.[6] Drugs like clozapine, loxapin, amoxipine and clomiprimine have high affinity for the 5-HT$_6$R .[7]

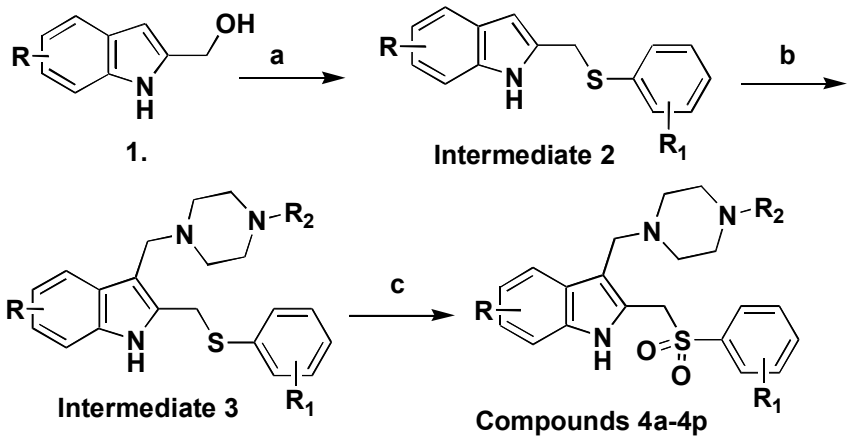
Enhancement of cognition and memory in Alzheimer's diseases is one of the potential therapeutic use of 5-HT$_6$R modulator ligands. The high levels of 5-HT$_6$R found in important structure of the forebrain, including the hippocampus and cortex, suggest a role of this receptor in memory and cognition as these areas are known to play a vital role in memory.[8] It's also proven by the studies that known 5-HT$_6$ antagonists

significantly increased glutamate and aspartate levels in the fontal cortex without elevating the levels of noradrenaline and dopamine.[9] This selective elevation of neurochemicals known to be involved in the memory and cognition, strongly suggests a role of 5-HT_6 ligands in cognition. [10 - 14]

Basic ionizable cyclic amines mainly piperazine motif and hydrogen bond acceptor sulfonamide or sulfone group with indole or other heterocyclic rings as a hydrophobic group are the necessary pharmacophoric requirement for the 5-HT_6R ligands . [3]

Keeping in mind the requirement needed for 5-HT_6R ligands, we have designed and synthesized a novel series of 2-arylsulfonylmethyl-3-piperazinylmethyl indole derivatives as 5-HT_6R ligand.

Figure 1. Synthetic Scheme for Compounds 4a-4p



Reagents : a. PTSA, ArSH,THF, Reflux **b.** 30% Formaldehyde, N-alkyl piperazine, RT
c. $CHCl_3$, MCPBA, PTSA, RT.

Table 1: Physicochemical Data for Compounds 4a-4p

Compound	Molecular Formula	Molecular Weight	Yield
4a	$C_{21}H_{25}N_3O_2S$	383	73.5 %
4b	$C_{21}H_{24}BrN_3O_2S$	461	75.8 %
4c	$C_{22}H_{26}BrN_3O_2S$	475	72.4%
4d	$C_{22}H_{26}BrN_3O_2S$	475	68.2 %
4e	$C_{22}H_{27}N_3O_3S$	413	73.1 %
4f	$C_{21}H_{24}ClN_3O_2S$	417	67.5 %
4g	$C_{22}H_{26}ClN_3O_2S$	431	72.2 %
4h	$C_{21}H_{23}ClFN_3O_2S$	435	65.2 %
4i	$C_{21}H_{24}BrN_3O_2S$	461	62.5 %
4j	$C_{22}H_{26}BrN_3O_2S$	475	70.2 %
4k	$C_{21}H_{23}BrClN_3O_2S$	495	68.1 %
4l	$C_{22}H_{26}BrN_3O_2S$	475	65.4 %
4m	$C_{21}H_{23}BrFN_3O_2S$	479	63.2 %
4n	$C_{22}H_{26}BrN_3O_3S$	491	63.8 %
4o	$C_{22}H_{27}N_3O_3S$	413	68.3 %
4p	$C_{23}H_{29}N_3O_3S$	427	69.2 %

The synthesis of compounds **4a-4p** was achieved as per Scheme given in **Figure 1**. The synthesis was achieved through the formation of respective substituted indole-2-caboxylic acid derivatives, which were purchased from local vendors or synthesized using the Reissert indole synthesis [15]. These acid derivatives were further reduced to **1** using Lithium aluminum hydride (LAH) in THF. The substituted indole-2-methanol derivatives (**1**) reacted with different thiophenols in presence of catalytic amount of p-TSA to give intermediate **2** in nearly 40-50% yield. Intermediates **2** were then conveniently treated with formaldehyde (30% aqueous solution) and N-alkyl piperazines under mannich reaction condition to obtain intermediate **3.** Mannich product, thus obtained, was oxidized using m-Chloroperbenzoic acid (m-CPBA) to get target **Compounds 4a-4p.**

The ESI-MS of all the compounds exhibited the $[M+H]^+$ as the parent ion, with the typical loss of $[M - 99 + H]^+$ fragment for N-methylpiperazine and $[M - 113 + H]^+$ fragment for N-ethylpiperazine. The ^{1}H-NMR spectra of all the compounds exhibited the prominent presence of N-methyl or N-ethylpiperazinyl protons with two pairs of methylene groups and the aromatic protons. All the spectral data was found to be satisfactory to confirm the structures.

All the synthesized compounds **4a-4p** were evaluated for their binding affinities at human 5-HT_6R at 100 nM concentration. The binding data is summarized in **Table 3**. Based on the results obtained, structure-activity relation ship (SAR) of these compounds is described in this paper.

Experimental

Melting points of synthesized compounds were determined using Electro Derman open capillary apparatus and are uncorrected. Infra red spectra were recorded on KBr disc and in solid state using Perkin-Elmer model 1600 FT-IR spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). Electrospray ionization mass spectra were recorded on a API 4000 triple quadrupole instrument (MDS-SCIEX, Concord, Ontario, Canada). ^{1}H-NMR spectra were obtained on a Bruker proton 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. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates. Chromatography refers to column chromatography performed using 60-120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions. All the reagents and chemicals used were of 'reagent grade'.

Pharmacological activity was performed using male Wistar rats, in accordance with the Institutional Animal Ethics Committee of Suven Life Sciences Ltd. Constituted as per the directions of the committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA) India.

General procedure for the synthesis of the 2-Arysulfonylmethyl-3-piperazinylmethyl indole derivatives 4a-4p

To a solution of substituted indol-2-yl methanol derivative (**1**, 0.045 mole) and substituted thiophenol (0.068 mole) in THF (60 mL) was added p-toluene sulfonic acid (0.0095 mole) in small portions and the mass was heated to reflux for 3-4 hours. After completion of the reaction (TLC), the mass was cooled to room temperature and 40 % lye solution (60 mL) was added to it. The product was extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine solution (1 x 100 mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure. The crude residue, so obtained was purified by flash chromatography over silica gel using 3 % ethyl acetate in n-hexane to obtain intermediate **2** in 40-50% yield, which was identified by IR, NMR and Mass spectral analyses.

N-alkyl piperazine (0.00206 mole), acetic acid and 30% aqueous formaldehyde solution (0.00206 mole) were charged in to a reaction flask and stirred on magnetic stirrer for 1 hour. Intermediate **2** (0.00188 mole) in 10 ml dioxane was added to reaction mass and stirred further 3 – 4 hours. After the completion of reaction (TLC), the reaction mixture was poured on to the chilled caustic solution (10 %) and the product was extracted with ethyl acetate (2 x 25 ml). The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The volatiles were removed under reduced pressure. The residue, thus obtained, was purified by flash chromatography over silica using ethyl acetate and 0.1% triethyl amine (TEA), to afford compound **3** in 70% yield, which was identified by IR, NMR and Mass Spectral analyses.

To a solution of **3** (3.5 mM) in chloroform (15 mL) was added p-toluene sulfonic acid (3.5 mM). The mass was stirred for 1 hour and m-Chloroperbenzoic acid (7 mM) was added in small portions. After completion of the reaction (TLC), the mass was diluted with 50 ml water, cooled to 10 °C, pH was adjusted to ~10 using lye solution and the product was extracted with chloroform (3 x 25 mL). The combined organic layer was washed with brine solution (2 x 15 ml) and solvent removed under reduced pressure to get residue, which was purified by fiash chromatography using ethyl acetate and 0.1% triethyl amine (TEA) to obtain the title **Compounds 4a-4p**, which were identified by IR, NMR and Mass Spectral analyses (**Table 2**).

Table 2 : Spectral Data for Compounds 4a-4p

2-(Benzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-1H-indole (4a).
Thick oil; IR (KBr, cm^{-1}): 1145, 1256, 1301, 1457, 3340; Mass (m/z): 384.2 $[M+H]^+$, ^{1}H-NMR (ppm): 2.07 – 2.40 (11H, m, N-CH_3 and piperazinyl), 3.08 (2H, s, -CH_2-N-), 4.80 (2H, s, -CH_2-SO_2-), 7.09 - 7.23 (1H, m, C-4), 7.24 - 7.37 (1H, m, C-7), 7.40 - 7.44 (3H, m, C-6, C-5, 4' H), 7.57 - 7.59 (2H, m, 3'-H and 5'-H), 7.63 - 7.65 (2H, m, 2'-H and 6'-H), 8.73 (1H, bs, NH).

2-(4-Bromobenzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-1H-indole (4b).
Thick oil; IR (KBr, cm^{-1}): 1149, 1260, 1313, 1456, 3377; Mass (m/z): 462.1, 464.4 $[M+H]^+$, ^{1}H-NMR (ppm): 2.03 (3H, s, N-CH_3), 2.08 - 2.41 (8H, m, piperazinyl) , 3.16 (2H, s, -CH_2-N-), 4.78 (2H, s, -CH_2-SO_2-), 7.11 - 7.13 (1H, m, C-4), 7.24 - 7.26 (1H, m, C-7), 7.38 - 7.40 (1H, m, C-6), 7.47 - 7.49 (2H, m, 3'-H and 5'-H), 7.55 - 7.57 (2H, m, 2'-H and 6'-H), 7.59 - 7.61 (1H, m, C-5), 8.72 (1H, bs, NH).

2-(4-Bromobenzenesulfonylmethyl)-3-(4-ethylpiperazin-1-ylmethyl)-1H-indole (4c).
M.R (^{o}C): 61- 63 ; IR (KBr, cm^{-1}): 1150, 1268, 1313, 1453, 3392; Mass (m/z): 476.2 478.1 $[M+H]^+$; ^{1}H-NMR (ppm): 1.04 - 1.08 (3H, t, N-CH_2CH_3), 2.11 - 2.46 (10H, m, N-CH_2 and piperazinyl), 3.17 (2H, s, -CH_2-N-), 4.78 (2H, s, -CH_2-SO_2-), 7.11 - 7.13 (1H, m, C-4), 7.22 - 7.24 (1H, m, C-7), 7.38 - 7.40 (1H, m, C-6), 7.47 - 7.49 (2H, m, 3'-H and 5'-H), 7.54 - 7.57 (2H, m, 2'-H and 6'-H), 7.59 - 7.61 (1H, m, C-5), 8.72 (1H, bs, NH).

2-(2-Bromobenzenesulfonylmethyl)-3-(4-ethylpiperazin-1-ylmethyl)-1H-indole (4d).
Thick oil; IR (KBr, cm^{-1}): 1160, 1261, 1311, 1447, 3377; Mass (m/z): 476.1, 478.3 $[M+H]^+$, ^{1}H-NMR (ppm): 1.05 - 1.08 (3H, t, N-CH_2CH_3), 2.35 - 2.41 (10H, m, N-CH_2 and piperazinyl), 3.30 (2H, s, -CH_2-N-), 4.59 (2H, s, -CH_2-SO_2-), 7.06 - 7.08 (1H, m, C-4), 7.18 - 7.26 (1H, m, C-7), 7.31 - 7.36 (3H, m, 3'-H, 4'-H and 5'-H), 7.41 (1H, m, C-5), 7.55 - 7.61 (2H, m, 2'-H and 6'-H), 8.90 (1H, bs, NH).

2-(4-methoxybenzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-1H-indole (4e).
Thick oil ; IR (KBr, cm^{-1}): 1150, 1268, 1313, 1453, 3392; Mass (m/z): 414.2 $[M+H]^+$; ^{1}H-NMR (ppm): 2.02 - 2.41 (11H, m, N-CH_3 and piperazinyl), 3.02 (2H, s,-CH_2-N-), 3.17 (2H, s, -CH_2-N-), 3.81 (3H, s, -OCH_3), 4.79 (2H, s, -CH_2-SO_2-), 6.85-6.88 (2H, m, 3'-H and 5'-H), 7.11 - 7.13 (1H, m, C-4), 7.22 - 7.24 (1H, m, C-7), 7.38 - 7.40 (1H, m, C-6), 7.54 - 7.57 (2H, m, 2'-H and 6'-H), 7.59 - 7.61 (1H, m, C-5), 8.72 (1H, bs, NH).

2-(Benzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-5-chloro-1H-indole (4f).
M.R (^{o}C): 170 -175; IR (KBr, cm^{-1}): 1141, 1257, 1353, 1446, 3478; Mass (m/z): 418.2, 420.5 $[M+H]^+$, ^{1}H-NMR (ppm): 2.02 - 2.41 (11H, m, N-CH_3 and piperazinyl), 3.02 (2H, s,-CH_2-N-), 4.75 (2H, s, -CH_2-SO_2-), 7.16 - 7.18 (1H, dd, J = 8.6, 1.98 Hz, C-6), 7.29 - 7.31 (1H, d, J = 8.6 Hz, C-7), 7.41 - 7.45 (2H, m, 3'-H and 5'-H), 7.55 - 7.56 (1H, d, J = 1.88 Hz, C-4), 7.61 – 7.64 (3H, m, 2'-H, 4'-H and 6'-H), 8.79 (1H, bs, NH).

2-(Benzenesulfonylmethyl)-3-(4-ethylpiperazin-1-ylmethyl)-5-chloro-1H-indole (4g).
M.R (^{o}C): 157-160 ; IR (KBr, cm^{-1}): 1137, 1248, 1342, 1448, 3359; Mass (m/z): 432.1 , 434.1 $[M+H]^+$, ^{1}H-NMR (ppm): 1.05 - 1.09 (3H, t, N-CH_2CH_3), 2.07 – 2.42 (10H, m, N-CH_2 and piperazinyl), 3.04 (2H, s, -CH_2-N-), 4.75 (2H, s, -CH_2-SO_2-), 7.16 - 7.18 (1H, dd, J = 8.64, 2.0 Hz, C-6), 7.29 - 7.31 (1H, d, J = 8.68 Hz, C-7), 7.42 -7.46 (2H, m, 3'-H and 5'-H), 7.55 - 7.55 (1H, d, J = 1.88, C-4), 7.61 – 7.64 (3H, m, 2'-H, 4'-H and 6'-H), 8.77 (1H, bs, NH).

2-(4-Fluorobenzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-5-chloro-1H-indole (4h).
Thick oil; IR (KBr, cm^{-1}): 1084, 1145, 1317, 1446, 2804, 3364; Mass (m/z): 436.2, 438.2 $[M+H]^+$, ^{1}H-NMR (ppm): 1.97 – 2.38 (11H, m, N-CH_3 and piperazinyl), 3.38 (2H, s, -CH_2-N-), 4.75 (2H, s, -CH_2-SO_2-), 7.09 - 7.13 (2H, m, C-6, 3'-H and 5'-H), 7.17 - 7.19 (1H, dd, J = 8.6, 2.0 Hz, C-6), 7.29 - 7.31 (1H, d, J = 8.6 Hz, C-7), 7.571 – 7.576 (1H, d, J = 1.88 Hz, C-4), 7.61 – 7.65 (2H, m, C-6, 2'-H and 6'-H), 8.81 (1H, bs, NH).

2-(Benzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-5-bromo-1H-indole (4i).
Thick oil; IR (KBr, cm^{-1}): 1167, 1283, 1346, 1451, 3367; Mass (m/z): 462.1, 464.2 $[M+H]^+$, ^{1}H-NMR (ppm): 1.97 – 2.42 (11H, m, N-CH_3 and piperazinyl), 3.01 (2H, s, -CH_2-N-), 4.76 (2H, s, -CH_2-SO_2-), 7.24 - 7.26 (1H, m, C-6), 7.27 - 7.32 (1H, m, C-7), 7.42 - 7.45 (2H, m, 3'-H and 5'-H), 7.59 - 7.63 (3H, m, 2'-H, 4'-H and 6'-H), 7.71 – 7.72 (1H, d, J = 1.6 Hz, C-4), 8.78 (1H, bs, NH).

2-(Benzenesulfonylmethyl)-3-(4-ethylpiperazin-1-ylmethyl)-5-bromo-1H-indole (4j).
M.R (^{o}C): 179-182 ; IR (KBr, cm^{-1}): 1167, 1247, 1305, 1448, 3361; Mass (m/z): 476.3, 478.1 $[M+H]^+$, ^{1}H-NMR (ppm): 1.03 - 1.07 (3H, t, N-CH_2CH_3), 2.00 – 2.39 (10H, m, N-CH_2 and piperazinyl), 3.01 (2H, s, -CH_2-N-), 4.77 (2H, s, -CH_2-SO_2-), 7.24 - 7.26 (1H, d, J = 8.4, C-7), 7.29 - 7.32 (1H, dd, J = 8.6, 1.8 Hz, C-6), 7.41 - 7.45 (2H, m, 3'-H and 5'-H), 7.59 - 7.63 (3H, m, 2'-H, 4'-H and 6'-H), 7.70 – 7.71 (1H, d, J = 1.6 Hz, C-4), 8.77 (1H, bs, NH).

2-(4-Chlorobenzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-5-bromo-1H-indole (4k).
Thick oil; IR (KBr, cm^{-1}): 1154, 1245, 1371, 1452, 3384; Mass (m/z): 496.3, 498.1 $[M+H]^+$, ^{1}H-NMR (ppm): 2.02 – 2.30 (11H, m, N-CH_3 and piperazinyl), 3.01(2H, s, -CH_2-N-), 4.75 (2H, s, -CH_2-SO_2-), 7.25 - 7.27 (1H, dd, J = 8.8, 1.6 Hz, C-6), 7.30 - 7.33 (1H, d, J = 8.4, C-7), 7.39 – 7.42 (2H, m, 3'-H and 5'-H), 7.54 - 7.56 (2H, m, 2'-H and 6'-H), 7.74 – 7.746 (1H, d, J = 2.0 Hz, C-4), 8.80 (1H, bs, NH).

2-(4-Methylbenzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-5-bromo-1H-indole (4l).
Thick oil; IR (KBr, cm^{-1}): 1164, 1246, 1343, 1445, 3373; Mass (m/z): 476.1 , 478.3 $[M+H]^+$, ^{1}H-NMR (ppm): 2.17 – 2.56 (11H, m, N-CH_3 and piperazinyl), 3.10 (2H, s, -CH_2-N-), 4.73 (2H, s, -CH_2-SO_2-), 7.22 - 7.27 (3H, m, C-6, 3'-H and 5'-H), 7.29 - 7.32 (1H, m, C-7), 7.50 - 7.52 (2H, m, 2'-H and 6'-H), 7.72 – 7.72 (1H, d, J = 1.6 Hz, C-4), 8.87 (1H, bs, NH).

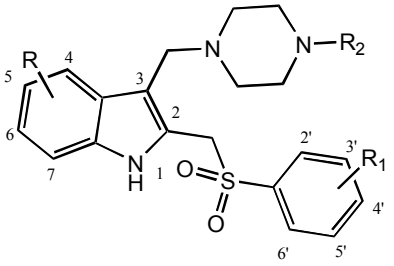
2-(4-Fluorobenzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-5-bromo-1H-indole (4m).
Thick oil; IR (KBr, cm^{-1}): 1028, 1154, 1371, 1452; Mass (m/z): 480.2, 482.5 $[M+H]^+$, ^{1}H-NMR (ppm): 2.17 – 2.56 (11H, m, N-CH_3 and piperazinyl), 3.10 (2H, s, -CH_2-N-), 4.73 (2H, s, -CH_2-SO_2-), 7.22 - 7.27 (3H, m, C-6, 3'-H and 5'-H), 7.29 - 7.32 (1H, m, C-7), 7.50 - 7.52 (2H, m, 2'-H and 6'-H), 7.723 – 7.727 (1H, d, J = 1.6 Hz, C-4), 8.87 (1H, bs, NH).

2-(4-methoxybenzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-5-bromo-1H-indole (4n).
Thick oil; IR (KBr, cm^{-1}): 1154, 1245, 1371, 1452, 3384; Mass (m/z): 492.1, 494.3 $[M+H]^+$, ^{1}H-NMR (ppm): 2.02 – 2.30 (11H, m, N-CH_3 and piperazinyl), 3.01(2H, s, -CH_2-N-), 3.78 (3H, s, -OCH_3), 4.75 (2H, s, -CH_2-SO_2-), 6.84 - 6.88 (2H, m, 3'-H and 5'-H), 7.25 - 7.27 (1H, dd, J = 8.8, 1.6 Hz, C-6), 7.30 - 7.33 (1H, d, J = 8.4, C-7), 7.54 - 7.56 (2H, m, 2'-H and 6'-H), 7.74 – 7.746 (1H, d, J = 2.0 Hz, C-4), 8.80 (1H, bs, NH).

2-(Benzenesulfonylmethyl)-3-(4-methylpiperazin-1-ylmethyl)-5-methoxy-1H-indole (4o).
Thick oil; IR (KBr, cm^{-1}): 1120, 1257, 1353, 1446, 3478; Mass (m/z): 414.3 $[M+H]^+$, ^{1}H-NMR (ppm): 2.02 - 2.41 (11H, m, N-CH_3 and piperazinyl), 3.02 (2H, s, -CH_2-N-), 3.79 (3H, s, -OCH_3), 4.75 (2H, s, -CH_2-SO_2-), 6.86 – 6.88 (1H, dd, J = 8.6, 1.98 Hz, C-6), 7.10 - 7.11 (1H, d, J = 1.88 Hz, C-4), 7.41 - 7.45 (2H, m, 3'-H and 5'-H), 7.53 - 7.55 (1H, d, J = 8.6 Hz, C-7), 7.61 – 7.64 (3H, m, 2'-H, 4'-H and 6'-H), 8.79 (1H, bs, NH).

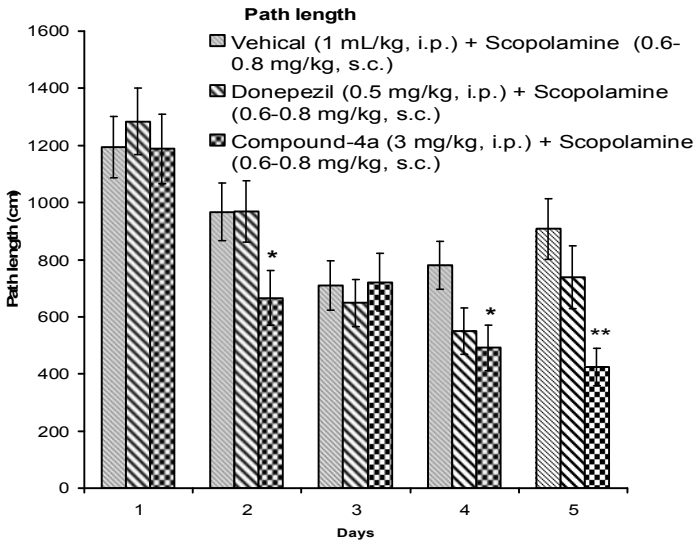
2-(Benzenesulfonylmethyl)-3-(4-ethylpiperazin-1-ylmethyl)-5-methoxy-1H-indole (4p).
Thick oil; IR (KBr, cm^{-1}): 1137, 1248, 1342, 1448, 3359; Mass (m/z): 428.1 $[M+H]^+$, ^{1}H-NMR (ppm): 1.05 - 1.09 (3H, t, N-CH_2CH_3), 2.07 – 2.42 (10H, m, N-CH_2 and piperazinyl), 3.04 (2H, s, -CH_2-N-), 3.81 (3H, s, -OCH_3), 4.75 (2H, s, -CH_2-SO_2-), 6.87 - 7.18 (1H, dd, J = 8.64, 2.0 Hz, C-6), 7.12 - 7.13 (1H, d, J = 1.98 Hz, C-4), 7.42 -7.46 (2H, m, 3'-H and 5'-H), 7.51 - 7.53 (1H, d, J = 8.6 Hz, C-7), 7.61 – 7.64 (3H, m, 2'-H, 4'-H and 6'-H), 8.77 (1H, bs).

Table 3 : 5-HT$_6$R binding data



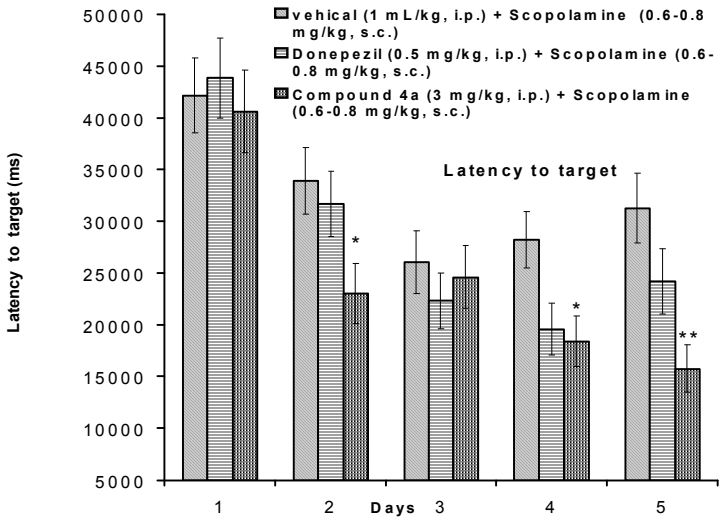
Compd. No.	R	R_1	R_2	Binding at 5-HT$_6$R % Inhibition at 100 nM
4a	H	H	Me	65.87
4b	H	4'-Br	Me	25.05
4c	H	4'-Br	Et	23.27
4d	H	2'-Br	Et	34.58
4e	H	4'-OMe	Me	39.22
4f	5-Cl	H	Me	39.58
4g	5-Cl	H	Et	22.58
4h	5-Cl	4'-F	Me	52.72
4i	5-Br	H	Me	50.53
4j	5-Br	H	Et	38.88
4k	5-Br	4'-Cl	Me	39.37
4l	5-Br	4'-Me	Me	34.81
4m	5-Br	4'-F	Me	37.79
4n	5-Br	4'-OMe	Me	43.27
4o	5-OMe	H	Me	38.28
4p	5-OMe	H	Et	20.22

Figure 2: Effect of acute treatment of compound 4a on path length in rats in Morris water maze test



Data represents Mean ± SEM of path length, *p< 0.05 ,**p< 0.01
(One Way ANOVA, Dunnett's post hoc analysis)

Figure 3: Effect of acute treatment of compound 4a on latency to target in rats in Morris water maze test.



Data represents Mean ± SEM of latency to target, *p< 0.05 ,**p< 0.01
(OneWay ANOVA, Dunnett's post hoc analysis)

Radioligand binding *in-vitro* assay for human 5-HT_6 receptor

Compounds were investigated by the reported procedure [16]. Briefly, receptor source and radioligand used were human recombinant expressed in HEK-293 cells and [^{3}H]LSD (60-80 Ci/mmol), respectively. The final ligand concentration was 1.5 nM and non-specific determinant was methiothepin mesylate (0.1 μM). The reference compound and positive control is methiothepin mesylate. Reactions were carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgCl_2$, 0.5 mM EDTA for 60 minutes at 37 °C. The reaction was terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters was determined and compared to control values in order to ascertain any interactions of test compound(s) with the cloned serotonin - 5-HT_6 binding site.

Morris water maze test

Wistar rats 10-12 weeks old were given 4 trials / day for 5 days; each trial was of 60 sec with an ITI of 600 sec. Each trial started with the rat placed facing the wall of the maze at one of the eight designated locations (0^o, 90^o, 180 ^{o}, 270^o) on 1st, 3rd and 5th day and (45^o, 135^o, 225^o, 315^o) on 2nd and 4th day. Compound was administered by gavages during the acquisition phase. Scopolamine was administered at a dose of 0.6 mg/kg on the first day and the dose of scopolamine was gradually increased at a rate of 0.05 mg/kg/day.

Results and Discussion

Binding affinities at the human 5-HT_6R at 100 nM concentration is given in **Table 3**. Among the synthesized derivatives, compound nos. **4a**, **4h** and **4i** show the highest binding affinity at human 5-HT_6R compared to the other compounds in the series with the inhibition values 65%, 50.5% and 52.7% respectively. The 5-halo, 5-alkoxy and unsubstituted indole derivatives seem to be tolerated and exhibited mild to moderate affinity, which can be further differentiated on the basis of their substitutions on the piperazine nucleus as well as on arylsulfonyl ring.

In unsubstitued indole (R=H) derivatives **4a-4d,** compound no. **4a** has shown the highest binding affinity towards 5-HT_6R, suggesting that unsubstitued arylsulfonyl ring (R_1= H) is preferred over the alkoxy and halo substituted arylsulfonyl ring. The mixed trend was observed in 5-halo substituted indole derivatives, where unsubstitued as well as substituted arylsulfonyl ring are well tolerated, as can be seen in compound no. **4h** and **4i**. The ortho substituted sulfonyl rings show marginal improvement in the binding affinity over para substituted one, as can be seen by comparing the compound no. **4c** with **4d**. In general the unsubstitued aryl sulfonyl ring was preferred over substituted aryl sulfonyl ring, the preferred order of substitution is H>F>OMe>Cl>Br.

Compounds no. **4o** and **4p** are the 5-methoxy derivatives, which show moderate affinity with 38% and 20% inhibition respectively. Replacement of methyl group on piperazine ring (R_2) with ethyl group,

shows decrease in binding affinity towards 5-HT_6R, suggesting that methyl group was preferred over ethyl group as can be seen by comparing compounds no. **4b**, **4f**, **4i** and **4o** with **4c**, **4g**, **4j** and **4p** respectively.

In-vivo activity

One of the active **Compound 4a** was further tested in Morris water maze model, which is one of the preferred animal model to test the cognitive potential. The test compound **4a** significantly reversed the scopolamine induced memory deficit at 3 mg/kg i.p. which is apparent from shorter path length (**figure 2**) and lesser target latency (**figure 3**). This result indicates that the Compound **4a** has the procognitive potential.

In summary, we successfully designed and synthesized a novel series of 2-arylsulfonylmethyl-3-piperazynylmethylindole derivatives in accordance with the pharmacophoric requirement needed for 5-HT_6R binding. As the synthesized series of compounds show the procognitive potential in Morris water maze task, it indicates that compounds can have the potential to be 5-HT_6R ligands and can be further developed for the cognitive dysfunctions.

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