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Design, synthesis and biological activity of novel substituted 2-Aryl sulfonyl methyl tryptamines as potential 5-HT$_6$ Receptor ligands

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ABSTRACT

*The future of 5-HT$_6$R ligands as potential therapeutic drugs seems quite exciting. There is an increasing research interest in the role of 5-HT$_6$ receptors in higher cognitive processes such as memory, obesity and eating disorder. Selective agents are required for the proposed therapeutic application. A series of novel compounds **6a-t** based on substituted 2-Arylsulfonylmethyl tryptamines as potential 5-HT$_6$ receptor ligands is reported. Design, Synthesis, in-vitro binding data and structure-activity relationship have been discussed. Compound **6i** was found to be the most potent, which can be further optimized to get the potential 5-HT$_6$ receptor ligands.*

Keywords: CNS, GPCR, Serotonin, 5-HT$_6$R ligands, Oxidation, Reduction, *In-vitro* binding, SAR.

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that mediates a wide range of physiological functions [1-3] by interacting with seven serotoninergic receptor families (5-HT$_{1-7}$) subdivided into 14 subpopulations [4]. The human 5-hydroxytryptamine6 (5-HT$_6$) receptor is one of the most recently discovered serotonin receptor families 5-HT$_1$ – 5-HT$_7$ [5]. It is a G-protein coupled receptor (GPCR) [6] positively coupled to adenylate cyclase. They are almost exclusively expressed in the central nervous system (CNS), mainly in the olfactory tubercle, striatum, nucleus accumbens and hippocampus [7-10]. This exclusive location makes it a promising and novel target receptor for CNS drug development with minimal peripheral side effects [11]. There has been an increasing research interest in the role of 5-HT$_6$ receptors in the treatment of CNS-mediated diseases such as Alzheimer's disease (cognitive function), Schizophrenia, anxiety, depression, epilepsy, drug abuse, obesity and appetite control. During the past few years, chemically diverse ligands with potent affinity and high selectivity have been reported for 5-HT$_6$ receptors [12], indole nucleus being the most extensively studied one. Glennon et al. have published various substituted tryptamines as 5-HT$_6$ receptor ligands, which include the N-Arylsulfonyl tryptamines [13], eg. MS-245 and 2-Methyl tryptamines eg. MMDT, 2-Phenyl tryptamines [14], eg. PMDT. Researchers at Roche have claimed 3-as well as 2-sulfonylindole derivatives with a basic amine such as piperazine or piperidine at positions 4 or 7 on an indole as potent 5-HT$_6$ antagonists [15-17]. Suven recently published a series of N-(1-methylpiperidin-4-yl)-2-(arylsulfonyl)-1H-indol-4-yl-amines as potential 5-HT$_6$ receptor ligands[18].

Several molecules like SB-742457[19], PRX-07034, AVN-211, Lu-AE58054 [20], SAM-760 [21] and SYN-114 [22] have entered clinical trials, Our own internally developed 5-HT_6R antagonist compound SUVN-502 has completed phase-I trials [23]. There are large numbers of other publications as well, which amply demonstrate the usefulness of these compounds. All these published compounds have some major common features, which are apparent as the basic minimum pharmacophore. A basic nitrogen (positive ionizable atom, **PI**), which could be a primary binding site at the receptor aspartate residue, a hydrogen bond acceptor group (**HBA**), a hydrophobic site (**HYD**) and an aromatic ring hydrophobic site (**AR**) which may be involved in the essential or secondary binding (through π staking) interactions with the receptor. Interestingly, lot of work has already been published on the effect of variations in the nature of side-chain of tryptamines on their affinity. Though, most of the designed or identified ligands clearly have at least two aromatic rings [24], there are almost no efforts made to understand the required relative orientation between these two aromatic rings with respect to the tryptamine side chain. Thus, we have synthesized and tested 2-arylsulfonyl methyl tryptamine derivatives (**compounds 6**) as selective 5-HT_6 receptor ligands, in our attempt to check the effect of the relative orientation of the aromatic rings.

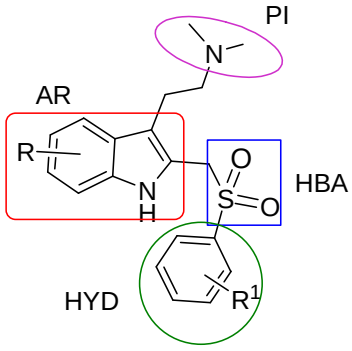


Figure I - Compounds 6

MATERIALS AND METHODS

All the solvents used for carrying out chromatographic experiments and spectroscopic experiments were of HPLC grade and spectroscopic grade respectively. Infra red spectra were recorded on KBr disc and in solid state using Perkin-Elmer model 1600 FTIR spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). Electrospray ionization mass spectra were recorded on a API 4000 triple quadrupole instrument (MDSSCIEX, Concord, Ontario, Canada). ^{1}H-NMR spectra were obtained on a Bruker proton NMR spectrometer (Fallanden, Switzerland) at 400MHz. 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 (□) and coupling constants are expressed in Hz. All the reagents and chemicals used were of 'reagent grade'. Room temperature refers to 25 - 30 ^{0}C, all the organic extracts were dried over anhydrous sodium sulphate, after work up. Column chromatography was performed using 100-200 mesh silica gel and executed under nitrogen pressure (flash column chromatography) conditions, using LR grade solvents as eluents. Melting points were taken on a Branstead Melting point apparatus (Model - 9300) in open capillary tubes and are uncorrected. TLC checking was done using pre-coated silica gel sheets 60 F_{254} obtained from Merck & Co, Germany.

Design of Ligands: N-Arylsulfonyl tryptamine, viz **MS-245** (K_i = 2.3 nM) is a known 5-HT_6 receptor ligand with high affinity. We planned to study the effect of arylsulfonyl moiety by moving it to C_2 of indole nucleus with an additional methylene spacer and by keeping the necessary pharmacophoric elements, supported by pharmacophore models established recently [24]. Our preliminary molecular modeling studies with the proposed compounds indicated that the movement of arylsulfonyl attachment from N_1 of tryptamine to C_2 of tryptamine with a methylene spacer maintains the desired pharmacophoric arrangement required for 5-HT_6 receptor ligands. Accordingly, we have designed **Compounds 6** where arylsulfonyl moiety was moved to C_2 of indole nucleus from N_1 with an additional spacer methylene (**Figure II**). Overlapping experiments of **Compound 6t** and **MS-245** (**Figure III**) using CS ChemOffice software have shown that the desired pharmacophoric arrangement required for 5-HT_6 receptor ligands was still maintained in the proposed molecules. The preliminary molecular modeling studies were carried out using CS ChemOffice software [25].

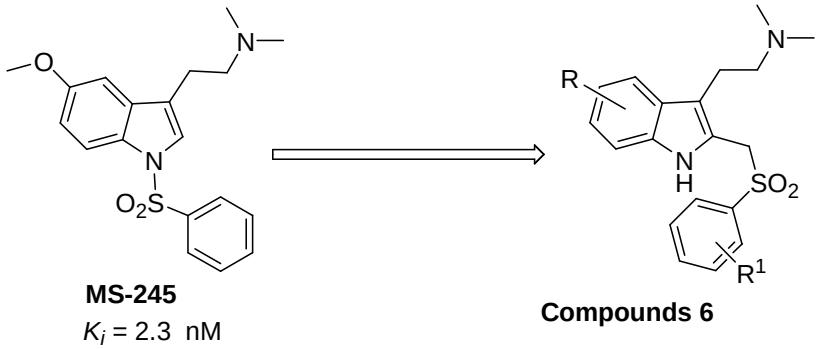


Figure II - Design of Ligands

The 5-methoxy derivative of **compounds 6** (i.e. **6t**) was energy minimized and compared with the corresponding conformations of **MS-245**. We observed that there were two different low energy conformers to the derivatives **6**, with the penalty of about 10 KJ/mole. The conformation which corresponds to the lower energy (**Figure III**) indicated better overlap.

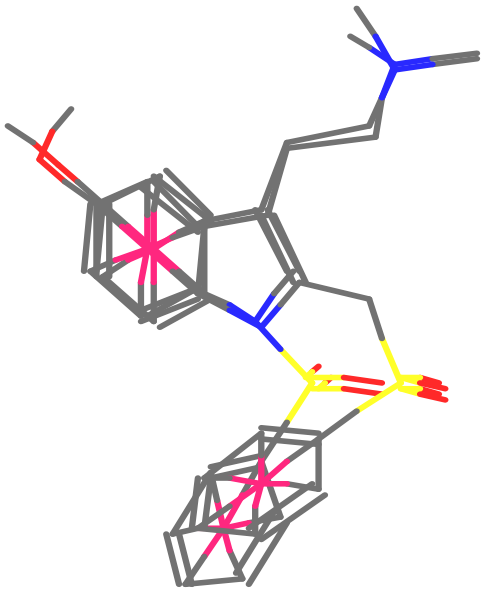


Figure III - Overlap of MS 245 and Compound 6t

Molecular Modeling The compounds were energy minimized using CS Chem 3D Pro from CambridgeSoft [23]. Molecular dynamics was performed using MM2 with the step interval of 2 fs, frame interval of 10 fs and heating/cooling rate of 1.0 Kcal/atom/ps. The minimum energy conformers of the compounds were used for overlapping.

EXPERIMENTAL SECTION

(5-Fluoro-1*H*-indol-2-yl) methanol (2, R=5-F): A solution of 5-Fluoro-1*H*-indole-2-carboxylic acid ethyl ester (**1, R=5-F)** (18.6 g, 89.8 mmole) in 130 mL of tetrahydrofuran (THF) was added to a suspension of lithium aluminium hydride (3.41 g, 89.8 mmole) in 50 mL of THF at RT under nitrogen blanket, then heated to reflux temperature and the reaction was monitored by TLC. Reaction was completed in 3hr. Reaction mixture was cooled to 0 ^{o}C, then ethyl acetate (EtOAc, 200 mL) and water (100 mL) were added sequentially and filtered through hyflow bed. The bed was washed with EtOAc (50 mL) and the organic and aqueous layers were separated. Aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with water (2 x 100 mL), dried over anhydrous sodium sulphate, filtered and solvent was removed under reduced pressure to obtain **2 (R=5-F)** (13.34 g, yield: 90 %) which was sufficiently pure for next step. Mass: 166 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$): 2.46 - 2.56 (bs, 1H, CH_2O**H**),

3.78 (s, 2H, C**H**$_2$OH), 7.11 - 7.15 (m, 2H, Ar-**H**), 7.50 (s, 1H, Ar-**H**), 7.82 - 7.88 (m, 1H, Ar-**H**), 8.1 (bs, 1H, N**H**). Similarly other alcohols were prepared from respective starting materials**.**

5-Fluoro-2-phenylsulfanylmethyl-1*H*-indole (3a, R=5-F, R^1=H): To a solution of **2 (R=5-F)** (7.5 g, 45 mmole) and thiophenol (7.49 g, 68 mmole) in THF (60 mL) was added p-toluene sulphonic acid monohydrate (1.81 g, 9.5 mmole) in small portions and stirred under reflux for 3 hr. After completion of the reaction, the reaction mass was cooled to 10 ^{o}C then added 40 % lye solution (60 mL) and the product was extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with water (2 x 100 mL) dried over anhydrous sodium sulphate, filtered and solvent was removed under reduced pressure. The crude mass was purified by column chromatography (3 % EtOAc in n-hexane) to obtain **3a (R=5-F, R^1=H)** (4.7 g) yield: 40 %; Mass: 258.4 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$): 4.24 (s, 2H, C**H**$_2$S), 6.29 (s, 1H, Ar-**H**), 6.86 - 6.92 (m, 1H, Ar-**H**), 7.13 - 7.32 (m, 7H, Ar-**H**), 8.21 (bs, 1H, N**H**). Similarly compounds **3b-t** were prepared from respective starting materials.

2-(5-Fluoro-2-phenylsulfanylmethyl-1*H*-indol-3-yl)-N,N-dimethyl-2-oxo acetamide (4a, R=5-F, R^1=H): To a solution of **3a** (2.9 g, 11.2 mmole) in diethyl ether (30 mL) at 10 °C was added oxalyl chloride (1.57 g, 12.4 mmole) drop-wise and the mass was stirred for 1hr at RT. The reaction mass was cooled again to 10 °C and dimethyl amine aqueous solution (36 %, 10 mL, 60 mmole) was added drop-wise. The reaction mixture was stirred for 2 hr at RT. The reaction mixture was concentrated under vacuum and the residual mass was poured on to crushed ice. The solid obtained was filtered and dried under vacuum at 55 °C for 3 hr to obtain **4a** (3.33 g) yield: 83 %; Mass: 357.3 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$): 2.94 (s, 3H, amide-N-C**H**$_3$), 3.11 (s, 3H, amide-N-C**H**$_3$), 4.53 (s, 2H, C**H**$_2$S), 6.93 - 6.97 (dd, 1H, J = 9.0 & 2.47 Hz, Ar-**H**) 7.16 - 7.30 (m, 6H, Ar-**H**), 7.50 - 7.52 (d, 1H, J = 9.24 Hz, Ar-**H**), 9.57 (bs, 1H, N**H**). Similarly compounds **4b-t** were prepared from respective starting materials **3b-t.**

[2-(5-Fluoro-2-phenylsulfanylmethyl-1*H*-indol-3-yl) ethyl] dimethylamine (5a, R=5-F, R^1=H): LAH (1.76 g, 46.3 mmole) was taken in anhydrous THF (60 mL) under nitrogen and **4a** (3.3 g, 9.26 mmole) was added portion-wise. The reaction mixture was refluxed for 6 hr. The mass was cooled to 10 °C. Ice-cold water (10 mL) and EtOAc (50 mL) was added, stirred well, filtered the solids through hyflow and washed the solids with 100 mL of ethyl acetate. Organic layer was separated and washed with water (2 x 30 mL), dried, filtered and solvent was removed under reduced pressure. The residue was purified by column chromatography (20 % EtOAc in n-hexane) to obtain **5a (**1.91g) yield: 62 %; Mass: 329.4 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$): 2.28 (s, 6H, NMe_2), 2.29 - 2.32 (m, 2H, C**H**$_2$-CH_2-NMe_2), 2.68 - 2.73 (m, 2H, C**H**$_2$-NMe_2), 4.19 (s, 2H, C**H**$_2$S), 6.88 - 6.89 (d, 1H, J = 2.4 Hz, Ar-**H**), 7.11 - 7.15 (m, 1H, Ar-**H**), 7.16 - 7.20 (q, 1H, J = 4.44 Hz, Ar-**H**), 7.21 - 7.30 (m, 5H, Ar-**H**), 8.13 (bs, 1H, N**H**). Similarly compounds **5b-t** were prepared from respective starting materials **4b-t.**

[2-(2-Benzenesulfonylmethyl-5-fluoro-1*H*-indol-3-yl) ethyl] dimethylamine hydrochloride (6a, R=5-F, R^1=H): To a solution of **5a** (1.15 g, 3.5 mmole) in chloroform (15 mL) was added p-toluene sulfonic acid monohydrate (0.66 g, 3.5 mmole). The mass was stirred for 1 hr and m-chloroperbenzoic acid (2.42 gm, 7.0 mmole) was added in small portions at RT. After completion of the reaction (2.5 hr) the mass was cooled to 10 °C, pH was adjusted to ~10 with aqueous ammonia 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 was removed under reduced pressure to obtain crude product which was purified by flash column chromatography using neutral silicagel (100-200 mesh), eluting solvent system being EtOAc, to yield free base. The latter was converted to hydrochloride salt using isopropanol saturated with hydrochloride gas (15 %) for 1hr to obtain 349 mg of the product **6a**. HPLC purity: 99.30 %; Yield: 25 %; Melting range (°C): 253.2 - 253.8 (dec); IR spectra (cm^{-1}): 3152, 2921, 2608, 1630, 1307, 1155, 735, 688; Mass: 361.3 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6): 2.74 - 2.75 (d, 6H, J = 5.04 Hz, NMe_2), 2.83 - 2.86 (m, 2H, C**H**$_2$-CH_2-NMe_2), 2.90 - 2.97 (m, 2H, C**H**$_2$-NMe_2), 4.91 (s, 2H, C**H**$_2$$SO_2$), 6.953 - 6.958 (d, 1H, J = 2.12 Hz, Ar-**H**), 7.33 - 7.38 (d, 1H, J = 4.38 Hz, Ar-**H**), 7.41 - 7.44 (dd, 1H, J = 8.88 & 2.08 Hz, Ar-**H**), 7.60 - 7.64 (m, 2H, Ar-**H**), 7.73 - 7.80 (m, 3H, Ar-**H**), 10.38 (bs, 1H, N**H**), 11.20 (s, 1H, **H**Cl). Similarly compounds **6b-t** were prepared from respective starting materials **5b-t.**

[2-(2-Benzenesulfonylmethyl-5-chloro-1*H*-indol-3-yl) ethyl] dimethylamine hydrochloride (6b, R=5-Cl, R^1=H): HPLC purity: 97.56 %; Yield: 33 %; Melting range (°C): 250.5 - 252.2 (dec); IR spectra (cm^{-1}): 3160, 2930, 2589, 1581, 1300, 1150, 605; Mass: 377.3 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6): 2.74 - 2.76 (d, 6H, J = 4.76 Hz, NMe_2), 2.82 - 2.86 (m, 2H, C**H**$_2$-CH_2-NMe_2), 2.90 - 2.95 (m, 2H, C**H**$_2$-NMe_2), 4.91 (s, 2H, C**H**$_2$$SO_2$), 7.0 - 7.11 (dd,

1H, J = 8.72 & 2.08 Hz, Ar-**H**), 7.37 - 7.39 (d, 1H, J = 8.6 Hz, Ar-**H**), 7.59 - 7.64 (m, 2H, Ar-**H**), 7.68 - 7.69 (d, 1H, J = 1.88 Hz, Ar-**H**), 7.73 - 7.79 (m, 3H, Ar-**H**), 10.27 (bs, 1H, N**H**), 11.31 (s, 1H, **H**Cl).

{2-[2-(4-Chloro benzenesulfonylmethyl)-5-Chloro-1*H*-indol-3-yl] ethyl} dimethylamine hydrochloride (6c, R=5-Cl, R^1=4'-Cl): HPLC purity: 99.40 %; Yield: 28 %; Melting range (°C): 263.0 - 263.5 (dec.); IR spectra (cm^{-1}): 3139, 2948, 2599, 1580, 1313, 1155, 763; Mass: 411.2 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6): 2.77 - 2.77 (d, 6H, J = 3.64 Hz, NMe_2), 2.87 - 2.91 (m, 2H, C**H$_2$**-CH_2-NMe_2), 2.99 – 3.0 (m, 2H, C**H$_2$**-NMe_2), 4.96 (s, 2H, C**H$_2$**SO_2), 7.09 - 7.12 (dd, 1H, J = 8.64 & 1.96 Hz, Ar-**H**), 7.36 - 7.39 (d, 1H, J = 8.68 Hz, Ar-**H**), 7.69 - 7.80 (m, 5H, Ar-**H**), 10.27 (bs, 1H, N**H**), 11.29 (s, 1H, **H**Cl).

{2-[2-(4-Chloro benzenesulfonylmethyl)-5-bromo-1*H*-indol-3-yl] ethyl} dimethylamine hydrochloride (6d, R=5-Br, R^1=4'-Cl): HPLC purity: 98.47 %; Yield: 32 %; Melting range (°C): 262.7 - 263.3 (dec.); IR spectra (cm^{-1}): 3126, 2918, 2593, 2471, 1581, 1313, 1154, 762; Mass: 455.0 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6): 2.78 - 2.79 (d, 6H, J = 4.92 Hz, NMe_2), 2.87 - 2.93 (m, 2H, C**H$_2$**-CH_2-NMe_2), 2.98 - 3.04 (m, 2H, C**H$_2$**-NMe_2), 4.98 (s, 2H, C**H$_2$**SO_2), 7.22 - 7.24 (dd, 1H, J = 8.64 & 1.84 Hz, Ar-**H**), 7.34 - 7.36 (d, 1H, J = 8.64 Hz, Ar-**H**), 7.70 - 7.74 (m, 2H, Ar-**H**), 7.77 - 7.81 (m, 2H, Ar-**H**), 7.85 -7.86 (d, 1H, J = 1.72 Hz, Ar-**H**), 10.27 (bs, 1H, N**H**), 11.32 (s, 1H, **H**Cl).

{2-[2-(4-Fluoro benzenesulfonyl methyl)-1*H*-indol-3-yl] ethyl} dimethylamine (6e, R=H, R^1=4'-F): HPLC purity: 96.71 %; Yield: 27 %; IR spectra (cm^{-1}): 3390, 2917, 2710, 1590, 1315, 1147, 753, 655; Mass: 361.3 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$): 2.58 (s, 6H, NMe_2), 2.63 - 2.68 (m, 2H, C**H$_2$**-CH_2-NMe_2), 2.83 - 2.87 (m, 2H, C**H$_2$**-NMe_2), 4.67 (s, 2H, C**H$_2$**SO_2), 7.11 - 7.17 (m, 3H, Ar-**H**), 7.23 - 7.25 (m, 1H, Ar-**H**), 7.38 - 7.40 (d, 1H, J = 7.84 Hz**,** Ar-**H**), 7.45 - 7.47 (d, 1H, J = 7.88 Hz, Ar-**H**), 7.79 - 7.82 (m, 2H, Ar-**H**), 8.74 (bs, 1H, N**H**).

[2-(2-Benzenesulfonylmethyl-1*H*-indol-3-yl) ethyl] dimethylamine hydrochloride (6f, R=H, R^1=H): HPLC purity: 99.22 %; Yield: 43 %; Melting range (°C): 243.5 - 244.6 (dec); IR spectra (cm^{-1}): 3226, 2959, 2621, 1619, 1301, 1147; Mass: 343.3 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6): 2.73-2.75 (d, 6H, J = 4.76 Hz, NMe_2), 2.85 - 3.0 (m, 4H, C**H$_2$**-C**H$_2$**-NMe_2), 4.90 (s, 2H, C**H$_2$**SO_2), 6.97 - 7.01 (m, 1H, Ar-**H**), 7.08 - 7.12 (m, 1H, Ar-**H**), 7.34 - 7.36 (d, 1H, J = 7.84 Hz, Ar-**H**), 7.59 - 7.63 (m, 3H, Ar-**H**), 7.73 - 7.77 (m, 1H, Ar-**H**), 7.79 - 7.81 (d, 2H, J = 8.08 Hz, Ar-**H**), 10.6 (bs, 1H, N**H**), 11.09 (s, 1H, **H**Cl).

{2-[2-(4-Chloro benzenesulfonylmethyl)-5-fluoro-1*H*-indol-3-yl] ethyl} dimethylamine hydrochloride (6g, R=5-F, R^1=4'-Cl): HPLC purity: 97.40 %; Yield: 25 %; Melting range (°C): 254.7 - 255.1 (dec); IR spectra (cm^{-1}): 3192, 2957, 2917, 2612, 1582, 1311, 1155; Mass: 395.2 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6): 2.77 - 2.78 (d, 6H, J=4.8 Hz, NMe_2), 2.89 - 2.91 (m, 2H, C**H$_2$**-CH_2-NMe_2), 2.98 - 3.02 (m, 2H, C**H$_2$**-NMe_2), 4.95 (s, 2H, C**H$_2$**SO_2), 6.93 - 6.99 (d, 1H, Ar-**H**), 7.35 - 7.37 (d, 1H, J = 4.56 Hz, Ar-**H**), 7.42 - 7.45 (dd, 1H, J = 8.96 & 2.44 Hz, Ar-**H**), 7.69 - 7.73 (m, 2H, Ar-**H**), 7.77 - 7.80 (m, 2H, Ar-**H**), 10.27 (bs, 1H, N**H**), 11.17 (s, 1H, **H**Cl).

[2-(2-Benzenesulfonylmethyl)-5,7-difluoro-1*H*-indol-3-yl ethyl] dimethylamine (6h, R=5,7-Di-F, R^1=H): HPLC purity: 99.60 %; Yield: 65 %; Melting range (°C): 215.2 - 216.1; IR spectra (cm^{-1}): 3336, 2984, 2929, 2727, 1585, 1344, 1151, 715, 687; Mass: 379.2 $[M+H]^+$; ^{1}H-NMR (CDCl3**):** 1.71 - 1.97 (m, 2H, C**H$_2$**-CH_2-NMe_2), 2.16 (s, 6H, NMe_2), 2.33 - 2.39 (m, 2H, C**H$_2$**-NMe_2), 4.51 (s, 2H, C**H$_2$**SO_2), 6.76 - 6.80 (m, 1H, Ar-**H**), 6.89 - 6.92 (dd, 1H, J = 8.88 & 2.04 Hz**,** Ar-**H**), 7.44 - 7.48 (m, 2H, Ar-**H**), 7.61 - 7.66 (m, 3H, Ar-**H**), 8.77 (bs, 1H, N**H**).

[2-(2-Benzenesulfonylmethyl)-4-chloro-7-methyl-1*H*-indol-3-yl ethyl] dimethylamine hydrochloride (6i, R=4-Cl, 7-CH_3, R^1=H): HPLC purity: 99.32 %; Yield: 26 %; Melting range (°C): 262.7 - 263.0 (dec); IR spectra (cm^{-1}): 3157, 2939, 2577, 1616, 1300, 1152, 731; Mass: 391.2 $[M+H]^+$; ^{1}H-NMR (DMSO-d_6): 2.35 (s, 3H, Ar-C**H$_3$**), 2.78 (s, 6H, NMe_2), 3.09 - 3.13 (m, 4H, C**H$_2$**-C**H$_2$**-NMe_2), 4.90 (s, 2H, C**H$_2$**SO_2), 6.87 - 6.89 (d, 1H, J = 7.72 Hz, Ar-**H**), 6.93 - 6.95 (d, 1H, J = 7.68 Hz, Ar-**H**), 7.62 - 7.66 (t, 2H, J = 7.88 Hz, Ar-**H**), 7.76 - 7.80 (t, 1H, J = 7.52 Hz, Ar-**H**), 7.84 - 7.86 (d, 2H, J = 8.28 Hz, Ar-**H**), 10.34 (bs, 1H, N**H**), 11.35 (s, 1H, **H**Cl).

{2-[2-(4-Methoxy benzenesulfonylmethyl)-5-chloro-1*H*-indol-3-yl] ethyl} dimethylamine (6j, R=5-Cl, R^1=4'-OCH_3): HPLC purity: 98.38 %; Yield: 33 %; Melting range (°C): 191.5 - 193.6 (dec); IR spectra (cm^{-1}): 3344, 2927, 1595, 1294, 1134, 800; Mass: 407.4, 409.6 $[M+H]^+$; ^{1}H-NMR (CDCl3**):** 1.89 – 1.93 (m, 2H, C**H$_2$**-CH_2-NMe_2), 2.17 (s, 6H, NMe_2), 2.36 - 2.42 (m, 2H, C**H$_2$**-NMe_2), 3.82 (s, 3H, O**CH$_3$**), 4.48 (s, 2H, C**H$_2$**SO_2), 6.85 – 7.0

(m, 2H, Ar-**H**), 7.15 – 7.18 (dd, 1H, J = 8.64 & 2.0 Hz, Ar-**H**), 7.28 – 7.3 (d, 1H, J = 8.64 Hz, Ar-**H**), 7.41 - 7.42 (d, 1H, J = 1.84 Hz, Ar-**H**), 7.49 - 7.51 (m, 2H, Ar-**H**), 8.78 (bs, 1H, N**H**).

{2-[2-(2-Bromo benzenesulfonylmethyl)-5-methoxy-1*H*-indol-3-yl] ethyl} dimethylamine (6k, R=5-OCH$_3$, R^1=2'-Br): HPLC purity: 99.30 %; Yield: 31 %; IR spectra (cm^{-1}): 3361, 1625, 1301, 1149, 772; Mass: 451.0 [M+H]$^+$; ^{1}H-NMR (CDCl$_3$): 2.20 - 2.24 (m, 2H, C**H$_2$**-CH$_2$-NMe$_2$), 2.30 (s, 6H, NMe$_2$), 2.64 - 2.69 (m, 2H, C**H$_2$**-NMe$_2$), 3.81 (s, 3H, OC**H$_3$**), 4.88 (s, 2H, C**H$_2$**SO$_2$), 6.85 - 6.87 (dd, 1H, J = 8.76 & 2.36 Hz, Ar-**H**), 6.9 - 6.906 (d, 1H, J = 2.2 Hz, Ar-**H**), 7.22 - 7.24 (d, 1H, J = 8.76 Hz, Ar-**H**), 7.33 - 7.38 (m, 1H, Ar-**H**), 7.4 - 7.46 (m, 1H, Ar-**H**), 7.76 - 7.79 (d, 1H, J = 7.84 Hz, Ar-**H**), 7.87 - 7.89 (d, 1H, J = 7.84 Hz, Ar-**H**), 8.44 (bs, 1H, N**H**).

{**2-[2-(4-Chloro benzenesulfonylmethyl)-1*H*-indol-3-yl] ethyl} dimethylamine hydrochloride (6l, R=H, R^1=4'-Cl):** HPLC purity: 96.27 %; Yield: 27 %; Melting range (°C): 216.5 - 217 (dec); IR spectra (cm^{-1}): 3444, 3153, 2961, 2602, 1581,1474, 1313, 1155, 763, 713, 615; Mass: 377.3 [M+H]$^+$; ^{1}H-NMR (DMSO-d_6): 2.78 – 2.80 (d, 6H, J = 4.8 Hz, NMe$_2$), 2.93 - 2.95 (m, 2H, C**H$_2$**-CH$_2$-NMe$_2$), 3.01 – 3.05 (m, 2H, C**H$_2$**-NMe$_2$), 4.95 (s, 2H, C**H$_2$**SO$_2$), 7.00 - 7.04 (m, 1H, Ar-**H**), 7.10 - 7.14 (m, 1H, Ar-**H**) 7.36 - 7.38 (d, 1H, J = 8.08 Hz, Ar-**H**), 7.61- 7.63 (d, 1H, J = 7.92 Hz, Ar-**H**), 7.71 - 7.73 (m, 2H, Ar-**H**), 7.78 - 7.81 (m, 2H, Ar-**H**), 10.30 (bs, 1H, N**H**), 11.08 (s, 1H, **H**Cl).

[2-(2-Benzenesulfonylmethyl)-5-bromo-1*H*-indol-3-yl ethyl] dimethylamine hydrochloride (6m, R=5-Br, R^1=H): HPLC purity: 96.58 %; Yield: 28 %; Melting range (°C): 248.1 - 250.1 (dec); IR spectra (cm^{-1}): 3153, 2931, 2579, 1582, 1369, 1298, 1150, 1085, 601; Mass: 421.2, 423.2 [M+H]$^+$; ^{1}H-NMR (DMSO-d_6): 2.73 - 2.75 (d, 6H, J = 4.88 Hz, NMe$_2$), 2.82 - 2.88 (m, 2H, C**H$_2$**-CH$_2$-NMe$_2$), 2.90 - 2.97 (m, 2H, C**H$_2$**-NMe$_2$), 4.92 (s, 2H, CH$_2$SO$_2$), 7.20 - 7.22 (dd, 1H, J = 8.64 & 1.8 Hz, Ar-**H**), 7.32 - 7.34 (d, 1H, J = 8.64 Hz, Ar-**H**), 7.59 - 7.63 (m, 2H, Ar-**H**), 7.73 - 7.82 (m, 4H, Ar-**H**), 10.43 (bs, 1H, N**H**), 11.33 (s, 1H, **H**Cl).

{2-[2-(4-Methoxy benzenesulfonylmethyl)-1*H*-indol-3-yl] ethyl} dimethylamine (6n, R=H, R^1=4'-OCH$_3$): HPLC purity: 96.53 %; Yield: 31 %; Melting range (°C): 167.59 - 169.61 (dec); IR spectra (cm^{-1}): 3352, 2929, 1595, 1291, 1247, 1135, 704, 660; Mass: 373.3 [M+H]$^+$; ^{1}H-NMR (CDCl$_3$): 1.90 – 1.97 (m, 2H, C**H$_2$**-CH$_2$-NMe$_2$), 2.17 (s, 6H, NMe$_2$), 2.20 - 2.49 (m, 2H, C**H$_2$**-NMe$_2$), 3.80 (s, 3H, OC**H$_3$**), 4.49 (s, 2H, C**H$_2$**SO$_2$), 6.83 – 6.88 (m, 2H, Ar-**H**), 7.08 – 7.12 (t, 1H, J = 7.8 Hz, Ar-**H**), 7.21 – 7.25 (t, 1H, J = 7.72 Hz, Ar-**H**), 7.38 - 7.40 (d, 1H, J = 8.2 Hz, Ar-**H**), 7.46 - 7.48 (d, 1H, J = 8.0 Hz, Ar-**H**), 7.50 - 7.53 (m, 2H, Ar-**H**), 8.68 (bs, 1H, N**H**).

{2-[2-(4-Methoxy benzenesulfonylmethyl)-5-fluoro-1H-indol-3-yl] ethyl} dimethylamine (6o, R=5-F, R1=4'-OCH$_3$): HPLC purity: 98.62 %; Yield: 35 %; Melting range (°C): 197.1 – 198.5 (dec); IR spectra (cm^{-1}): 3343, 2929, 1591, 1252, 1137, 799; Mass: 391.5 [M+H]$^+$; ^{1}H-NMR (CDCl$_3$): 1.92 – 1.96 (m, 2H, C**H$_2$**-CH$_2$-NMe$_2$), 2.18 (s, 6H, NMe$_2$), 2.41 - 2.43 (m, 2H, C**H$_2$**-NMe$_2$), 3.82 (s, 3H, OC**H$_3$**), 4.48 (s, 2H, C**H$_2$**SO$_2$), 6.85 – 6.9 (m, 2H, Ar-**H**), 6.95 – 7.00 (dd, 1H, J = 9.0 & 2.4 Hz, Ar-**H**), 7.08 – 7.13 (dd, 1H, J = 9.45 & 2.28 Hz, Ar-**H**), 7.27 - 7.32 (d, 1H, J = 4.4 Hz, Ar-**H**), 7.5 - 7.55 (m, 2H, Ar-**H**), 8.70 (bs, 1H, N**H**).

{2-[2-(4-Chloro benzenesulfonylmethyl)-5-methoxy-1*H*-indol-3-yl] ethyl} dimethylamine (6p, R=5-OCH$_3$, R^1=4'-Cl): HPLC purity: 95.97 %; Yield: 35 %; IR spectra (cm^{-1}): 3429, 1578, 1316, 1264, 1090, 1029, 806; Mass: 407.5, 409.5 [M+H]$^+$; ^{1}H-NMR (CDCl$_3$): 2.39 - 2.46 (m, 2H, C**H$_2$**-CH$_2$-NMe$_2$), 2.47 (s, 6H, NMe$_2$), 2.71 - 2.75 (m, 2H, C**H$_2$**-NMe$_2$), 3.86(s, 3H, OC**H$_3$**), 4.61 (s, 2H, C**H$_2$**SO$_2$), 6.89 - 6.91 (m, 2H, Ar-**H**), 7.26 - 7.29 (m, 1H, Ar-**H**), 7.42 - 7.45 (m, 2H, Ar-**H**), 7.66 - 7.68 (m, 2H, Ar-**H**), 8.57 (bs, 1H, N**H**).

{2-[2-(4-Chloro benzenesulfonylmethyl)-4-chloro-7-methyl-1*H*-indol-3-yl] ethyl} dimethylamine (6q, R=4-Cl, 7-CH$_3$, R^1=4'-Cl): HPLC purity: 98.33 %; Yield: 39 %; Melting range (°C): 185.6 – 186.0 (dec); IR spectra (cm^{-1}): 3355, 2961, 2923, 1578, 1466, 1310, 1147, 1088, 768; Mass: 425.1, 427.1, 429.0 [M+H]$^+$; ^{1}H-NMR (CDCl$_3$): 2.33 (s, 6H, NMe$_2$), 2.47 (s, 3H, Ar-C**H$_3$**), 2.83 – 2.87 (m, 4H, C**H$_2$**-C**H$_2$**-NMe$_2$), 4.62 (s, 2H, C**H$_2$**SO$_2$), 6.91 - 6.93 (d, 1H, J = 7.48 Hz, Ar-**H**), 6.98 – 7.00 (d, 1H, J = 7.72 Hz, Ar-**H**), 7.43 - 7.47 (m, 2H, Ar-**H**), 7.65 - 7.68 (m, 2H, Ar-**H**), 8.71 (bs, 1H, N**H**).

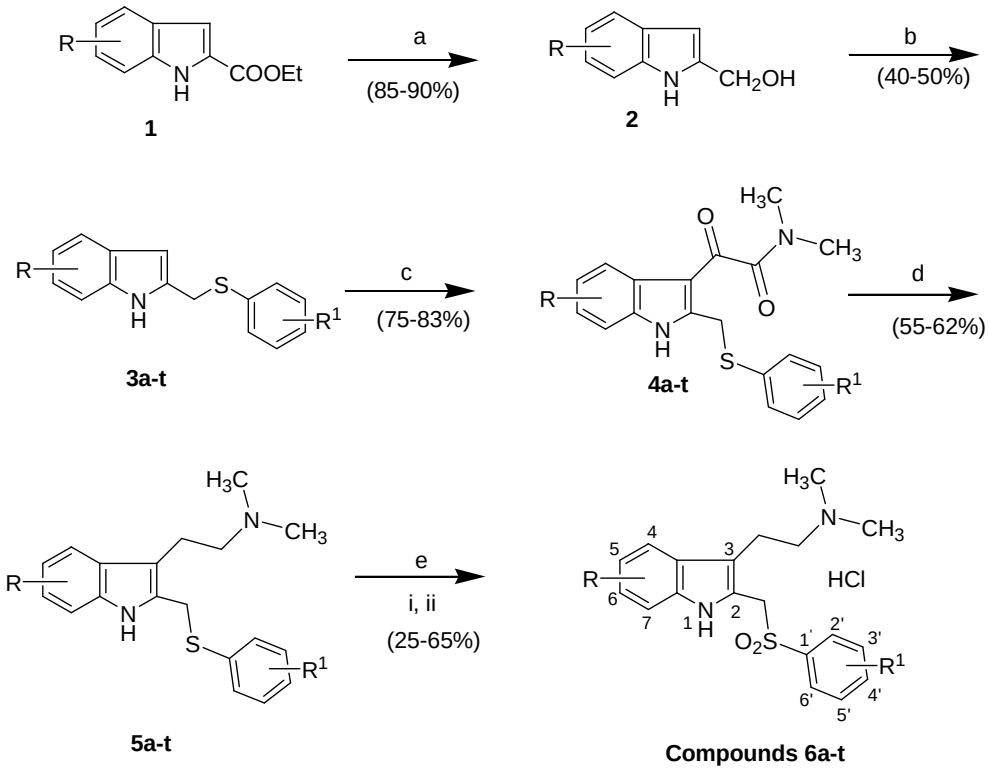
{2-[2-(4-Chloro benzenesulfonylmethyl)- 5,7-di fluoro-1*H*-indol-3-yl] ethyl} dimethylamine (6r, R=5,7-Di F, R^1=4'-Cl): HPLC purity: 97.07 %; Yield: 36 %; IR spectra (cm^{-1}): 3434, 2924, 1591, 1473, 1326, 1151, 1085, 763; Mass: 413.3, 415.2, [M+H]$^+$; ^{1}H-NMR (CDCl$_3$): 2.0 – 2.07 (m, 2H, C**H$_2$**-CH$_2$-NMe$_2$), 2.23 (s, 6H, NMe$_2$), 2.44 – 2.50 (m, 2H, C**H$_2$**-NMe$_2$), 4.54 (s, 2H, C**H$_2$**SO$_2$), 6.74 - 6.82 (dd, 1H, J = 9.12 & 1.48 Hz, Ar-**H**), 6.91 – 6.95 (dd,

1H, J = 8.84 & 2.08 Hz, Ar-**H**), 7.42 - 7.45 (m, 2H, Ar-**H**), 7.58 - 7.61 (m, 2H, Ar-**H**), 8.85 (bs, 1H, N**H**).

{2-[2-(4-Methyl benzenesulfonylmethyl)-1*H*-indol-3-yl] ethyl} dimethylamine (6s, R=H, R^1=4'-CH_3): HPLC purity: 95.29 %; Yield: 37 %**;** IR spectra (cm^{-1}): 3372, 2925, 2761, 1671, 1459, 1288, 1248, 1138, 1083, 713, 657; Mass: 357.3 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$): 2.16 (s, 6H, NMe_2), 2.35 - 2.39 (m, 2H, C**H**$_2$-CH_2-NMe_2), 2.40 - 2.47 (m, 2H, C**H**$_2$-NMe_2), 2.43 (s, 3H, Ar-C**H**$_3$), 4.50 (s, 2H, C**H**$_2SO_2$), 7.08 - 7.12 (m, 1H, Ar-**H**), 7.19 - 7.28 (m, 3H, Ar-**H**), 7.38 - 7.40 (d, 1H, J = 8.04 Hz, Ar-**H**), 7.46 - 7.49 (m, 3H, Ar-**H**), 8.80 (bs, 1H, N**H**).

[2-(2-Benzenesulfonylmethyl)-5-methoxy-1*H*-indol-3-yl ethyl] dimethylamine (6t, R=5-OCH_3, R^1=H): HPLC purity: 98.90 %; Yield: 33 %; IR spectra (cm^{-1}): 3361, 1625, 1301, 1149, 772; Mass: 373.3 $[M+H]^+$; ^{1}H-NMR ($CDCl_3$): 2.20 - 2.24 (m, 2H, C**H**$_2$-CH_2-NMe_2), 2.30 (s, 6H, NMe_2), 2.64 - 2.69 (m, 2H, C**H**$_2$-NMe_2), 3.81 (s, 3H, OC**H**$_3$), 4.88 (s, 2H, C**H**$_2SO_2$), 6.85 - 6.87 (dd, 1H, J = 8.76 & 2.36 Hz, Ar-**H**), 6.9 - 6.906 (d, 1H, J = 2.2 Hz, Ar-**H**), 7.22 - 7.24 (d, 1H, J = 8.76 Hz, Ar-**H**), 7.33 - 7.38 (m, 1H, Ar-**H**), 7.73 - 7.82 (m, 4H, Ar-**H**), 8.79 (bs, 1H, N**H**).

Scheme- I



a = (R=5-F, R^1=H)	h = (R=5,7-Di-F, R^1=H)	o = (R=5-F, R^1=4'-OCH_3)
b = (R=5-Cl, R^1=H)	i = (R=4-Cl,7-CH_3, R^1=H)	p = (R=5-OCH_3, R^1=4'-Cl)
c = (R=5-Cl, R^1=4'-Cl)	j = (R=5-Cl, R^1=4'-OCH_3)	q = (R=4-Cl,7-CH_3, R^1=4'-Cl)
d = (R=5-Br, R^1=4'-Cl)	k = (R=5-OCH_3, R^1=2'-Br)	r = (R=5,7-Di-F, R^1=4'-Cl)
e = (R=H, R^1=4'-F)	l = (R=H, R^1=4'-Cl)	s = (R=H, R^1=4'-CH_3)
f = (R=H, R^1=H)	m = (R=5-Br, R^1=H)	t = (R=5-OCH_3, R^1=H)
g = (R=5-F, R^1=4'-Cl)	n = (R=H, R^1=4'-OCH_3)	

Reagents and conditions: *a) $LiAlH_4$, THF, reflux 3 hr; b) ArSH, THF, p-TSA reflux 3 hr; c) Oxalyl chloride, diethyl ether, RT 1 hr then dimethyl amine aqueous solution (36 %), RT, 2 hr; d) $LiAlH_4$, THF, reflux 6 hr; e) i) m-CPBA, $CHCl_3$, p-TSA, RT 2.5 hr. ii) IPA.HCl (15 %) 1 hr.*

RESULTS AND DISCUSSION

The general synthetic strategy used for the preparation of title **Compounds 6** has been summarized in **Scheme I**. Substituted indole-2-carboxylate esters were synthesized by reported procedure [26]. Ethyl ester of appropriately substituted indole-2-acid was reduced to corresponding alcohol using Lithium Aluminum Hydride (LAH) in 85-90 % yield. IR spectrum showed absence of ester peak at 1730 cm^{-1} and presence of -OH at 3450 cm^{-1}, confirmed the formation of indole-2-methanol. The appropriate alcohol was reacted with substituted thiol in presence of p-TSA to obtain the corresponding substituted 2-phenylthiomethyl indole derivatives [27] **3a-t** in 40-50 % yield, ^{1}H-NMR showed peak at 4.24 for SC**H$_2$** and the $[M+H]^+$ peak at 258.4 amu in mass spectrum confirmed the molecular weight of the intermediate **3a**. This compound upon treatment with oxalyl chloride followed by N, N-dimethylamine aqueous solution (36 %) gave **4a-t** in 75-83 % yield. ^{1}H-NMR of **4a** showed peaks at 2.94 and 3.11 for amidic protons in $N(CH_3)_2$, 4.53 for –SC**H$_2$** and the $[M+H]^+$ peak at 357.3 amu in mass spectrum confirmed the molecular weight of the intermediate **4a**. These amides **4a-t** were then reduced using LAH in THF solvent under reflux to obtain the corresponding substituted 2-phenylthiomethyl tryptamine derivatives **5a-t** in 55-62 % yield. ^{1}H-NMR of **5a** showed peaks at 2.29-2.32 for C**H$_2$**-CH_2-NMe_2, 2.68-2.73 for C**H$_2$**-NMe_2, 2.28 for NMe_2 and 4.19 for C**H$_2$**S and the $[M+H]^+$ peak at 329.4 amu in mass spectrum confirmed the molecular weight of the intermediate **5a**. These derivatives **5a-t** were oxidized and the crude product purified by flash column chromatography to obtain compounds **6** as free bases. The latter were converted to HCl salt to obtain the targeted compounds **6** in 25–65 % yield. ^{1}H-NMR of **6a** showed peak at 4.91 for C**H$_2$**SO_2 and the $[M+H]^+$ peak at 361.3 amu in mass spectrum confirmed the molecular weight of **6a**. In IR spectrum peaks at 1307 cm^{-1} and 1155 cm^{-1} confirmed the presence of sulfone group. The most optimum oxidizing conditions were found to be treatment with m-CPBA in chloroform at RT (25 ^{0}C). p-TSA was used in the reaction to prevent the N-oxide formation. The structures of all the compounds (**6a-t**) were fully characterized using spectral data.

5-HT$_6$R BINDING DATA (*IN-VITRO)*

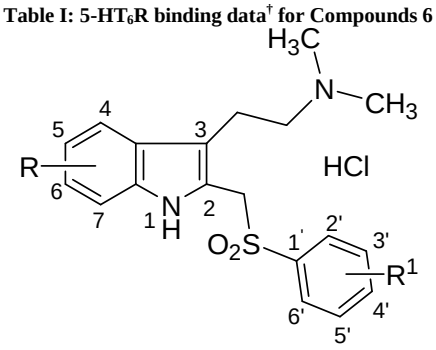
Radioligand binding assay for human 5-HT$_6$ receptor:

The *in-vitro* 5-HT$_6$ receptor binding assay was carried out on Human recombinant expressed receptor 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 μM]; Reference Compound was Methiothepin mesylate, Positive Control was Methiothepin mesylate. The radioligand binding study was carried out at NovaScreen, USA. [28].

Structure-activity relationship (SAR):

Radioligand binding affinities at the human 5-HT$_6$R at 100 nM concentration is given in **Table I**. The binding data of these compounds at 100 nM concentration indicated that the compounds have drastically reduced affinity to the 5-HT$_6$R compared to that of **MS-245** (*Ki* =2.3 nM). As can be seen from **Table I,** Compounds **6d**, **6i** and **6j** show good binding affinity at human 5-HT$_6$R when compared to other compounds in the series with the percent inhibition values 43.75 %, 54.55 % and 43.84 % respectively. The halo substituted indole derivatives seem to be tolerated, as they exhibited mild to moderate affinity towards 5-HT$_6$R. Unsubstituted indole derivatives have low binding affinity towards 5-HT$_6$R, as can be seen by comparing compounds **6b**, **6c**, **6d**, **6i** and **6j** with **6e** and **6f,** suggesting the need for halo substituted indole derivatives to show binding affinity. In general the unsubstituted aryl sulfonyl ring was preferred over substituted aryl sulfonyl ring, as can be seen by comparing compounds **6b** and **6i** with **6c**, The preferred order of substitution on arylsulfonyl ring was H > OCH_3 > Cl > Br > F. The compound **6i** was identified as most potent from the synthesized compounds which can be further optimized to get the potential 5-HT$_6$ receptor ligands.

Table I: 5-HT$_6$R binding data† for Compounds 6



S.No.	R	R^1	Salt	% Inhibition at 100nM concentration*
6a	5-F	H	HCl	11.46
6b	5-Cl	H	HCl	40.49
6c	5-Cl	4'-Cl	HCl	28.87
6d	5-Br	4'-Cl	HCl	43.75
6e	H	4'-F	-	10.23
6f	H	H	HCl	20.16
6g	5-F	4'-Cl	HCl	14.85
6h	5, 7-Di- F	H	-	20.04
6i	4-Cl, 7-CH_3	H	HCl	54.55
6j	5-Cl	4'-OCH_3	-	43.84
6k	5-OCH_3	2'-Br	-	18.1
6l	H	4'-Cl	HCl	-
6m	5-Br	H	HCl	-
6n	H	4'-OCH_3	-	-
6o	5-F	4'-OCH_3	-	-
6p	5-OCH_3	4'-Cl	-	-
6q	4-Cl, 7-CH_3	4'-Cl	-	-
6r	5, 7-Di- F	4'-Cl	-	-
6s	H	4'-CH_3	-	-
6t	5-OCH_3	H	-	29.45

*The data represents average of two determinations. †5-HT$_6$ Receptor binding studies were carried out at NovaScreen Biosciences Corporation, (caliper life sciences), Hanover, Maryland, U.S.A. Human recombinant / HEK293 cells; Radioligand: [^{3}H] LSD (60-80 Ci/mmol).

CONCLUSION

The shifting of aryl sulfonyl moiety from N_1 to C_2 of tryptamine with a methylene spacer led to drastic reduction of affinity. It could be due to the unfavorable orientations of sulfonyl aromatic ring with respect to the side-chain amino function or the presence of free NH at N_1. Further investigations to probe other possible reasons are going on as part of our continuing 5-HT$_6$ receptor research programme.

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