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Synthesis and biological activity of novel substituted N-(1-methylpiperidin-4-yl)-2-(arylsulfonyl)-1*H*-indol-4-yl-amines as 5-HT$_6$ receptor ligands

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ABSTRACT

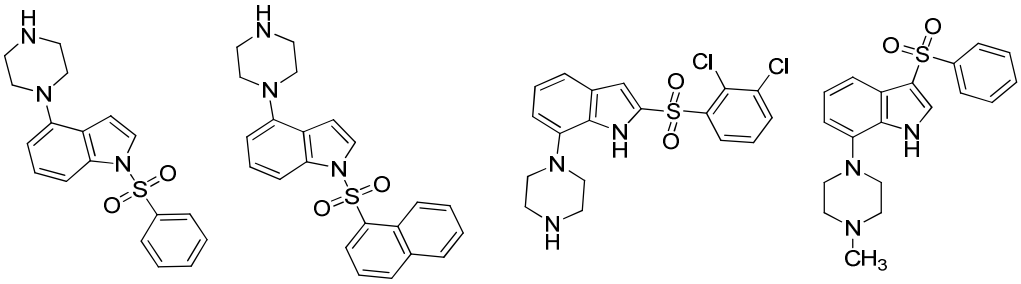
*A novel series of N-(1-methylpiperidin-4-yl)-2-(arylsulfonyl)-1H-indol-4-yl-amines was designed and synthesized as potential 5-HT$_6$ receptor ligands and tested for human 5-HT$_6$ receptor binding affinities. All the tested compounds showed moderate to high binding affinities towards 5-HT$_6$ receptor. The most potent compound **11b** was selected as a hit which can be further optimized to get the potential 5-HT$_6$ receptor ligands.*

Key words: GPCR, Serotonin**,** 5-HT$_6$ receptor, CNS, oxidation, reductive amination.

INTRODUCTION

5-HT$_6$ receptor, the family member of G-protein coupled receptors (GPCR) is present in brain regions that are associated with learning and memory [1, 2]. Blockade of their function increases acetylcholine and glutamate-mediated neurotransmission and enhances cognitive processes, which amply demonstrate the therapeutic usefulness of this receptor for CNS mediated disorders such as schizophrenia, AD and also in the obesity and eating disorders [3-12]. The unique pharmacology and nearly exclusive central nervous system (CNS) expression spurred significant interest in the functional role of the 5-HT$_6$ receptor. Research efforts in this area have led to the discovery of a number of potent and selective 5-HT$_6$ agonists and antagonists. The first selective 5-HT$_6$ ligands, Ro 04-6790 and Ro 63-0563 were reported by Roche [13, 14]. Shortly a series of piperazinylbenzenesulfonamides, including SB-271046 and SB-357134 were subsequently revealed by Smith Kline-Beecham [15, 16]. Cole showed that 4-piperazinyl- 1-sulfonylindoles (**Figure I**) as potential 5-HT$_6$ receptor antagonist [17, 18]. Researchers at Roche have claimed 3- as well as 2-sulfonylindole derivatives with a basic amine such as piperazine or piperidine at positions 4 through 7 on an indole as potent 5-HT$_6$ antagonists (**Figure I**) [19-21]. A number of

compounds have been advanced into development, undergoing Phase I and II clinical trials for cognitive impairment in Alzheimer's disease and schizophrenia. SAM-760, SB-742457 and SGS-518 are the phase II clinical candidates, where as Lu AE58054, PRX-07034, SYN-114 [22-25] and SUVN-502 are the phase I clinical candidates as of today [26-29].



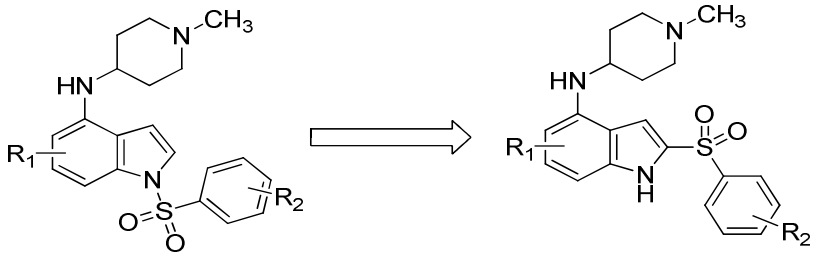
1 (*Ki* = 1 nM) **2** (K_i = 0.4 nM) **3** (K_i =0.2 nM) **4** (K_i = 0.5 nM)

Figure I

MATERIALS AND METHODS

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). Electronspray ionization mass spectra were recorded on a API 4000 triple quadrupole instrument (MDSSCIEX, Concord, Ontario, Canada). 1H-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 (d) and coupling constants are expressed in Hz. All the reagents and chemicals used were of 'reagent grade'.

Genesis of ligands: As part of project to develop 5-HT_6 receptor antagonists at Suven, we designed and synthesized N-(1-methylpiperidin-4-yl)-1-(arylsulfonyl)-1H-indol-4-yl-amine derivatives Compounds I [30], as potent, selective and orally bioavailable 5-HT_6 receptor antagonists. In continuation to our SAR studies around Compounds I and to establish the position of the arylsulfonyl group at indole with respect to 5-HT_6 receptor activity, we thought of evaluating Compounds II for the 5-HT_6 receptor binding (**Figure 2**). Where aryl sulfonyl group is moved from N-1 position of indole to C-2 position of indole. This manuscript describes the said modification.



Compounds I **Compounds II**

Figure 2: Genesis of ligands

General procedure for the synthesis of N-(1-methylpiperidin-4-yl)-2-(arylsulfonyl)-1H-indol-4-amine (11a-e).

a) Synthesis of 4-nitro-3-(arylthio)-1H-indole (7a-e):

To a stirred suspension of sodium hydride (0.75 gm, 18.75 mmole) in DMF (20 ml) was added a solution of 4-nitro indole (2 gm, 12.34 mmole) in DMF (10 ml) under nitrogen atmosphere at room temperature. After stirring 1 hr a solution diphenyl disulfide (2.96 gm, 13.58 mmole in 10 ml of DMF) was added at room temperature. The reaction mixture was stirred at room temperature for 20 hrs and was poured onto chilled water. It was then extracted with ethyl acetate (3x50 ml). The organic layers were combined, washed with brine, and dried over anhydrous sodium sulfate. After rotary evaporation, the resulting compound was further purified through coloumn chromatography to obtained 0.8 gm compound **7a**.

7a (R_2 = H): M.R (^oC): 142.0 – 146.7, IR (cm^{-1}): 3329, 3102, 2924, 1665, 1519; ^{1}H-NMR ($CDCl_3$): δ 7.07 – 7.20 (5H, m), 7.29 – 7.33 (1H, t), 7.61 (1H, d), 7.69 – 7.72 (1H, d), 7.73 – 7.75 (1H, m), 8.99 (1H, bs); Mass (m/z): 269 $(M-H)^-$.

7b (R_2 = 2'-Br): IR (cm^{-1}): 3339, 3102, 2924, 1666, 1519; ^{1}H-NMR (DMSO-d6): δ 6.46 – 6.48 (1H, dd, J = 1.54, 7.96 Hz), 6.94 – 6.98 (1H, dt, J = 1.55, 7.96 Hz), 7.06 – 7.11 (1H, dt, J = 1.33, 7.48 Hz), 7.34 – 7.38 (1H, t, J = 7.98 Hz), 7.51 – 7.54 (1H, dd, J = 1.26, 7.88 Hz), 7.72 – 7.74 (1H, dd, J = 0.78, 7.78 Hz), 7.88 – 7.92 (1H, dd, J = 0.76, 8.13 Hz), 8.07 (1H, s), 12.6 (1H, s); Mass (m/z): 346.9 $(M-H)^-$.

7c (R_2 = 2'-F): M.R (^oC): 142.9 – 145.4, IR (cm^{-1}): 3332, 3099, 2973, 1623, 1519; ^{1}H-NMR ($CDCl_3$): δ 6.88 – 6.91 (2H, m), 6.97 – 7.01 (1H, m), 7.05 – 7.09 (1H, m), 7.29 – 7.33 (1H, t, J = 8 Hz), 7.62 (1H, d = 2.73 Hz), 7.69 – 7.71 (1H, d, J = 8.14 Hz), 7.77 – 7.79 (1H, d, J = 7.81 Hz), 9.05 (1H, s); Mass (m/z): 287.2 $(M-H)^-$

7d (R_2 = 4'-CH_3): M.R (^oC): 142.9 – 145.4, IR (cm^{-1}): 3332, 3099, 2973, 1623, 1519; ^{1}H-NMR ($CDCl_3$): δ 2.25 (3H, s), 6.99 – 7.01 (2H, m), 7.05 – 7.07 (2H, m), 7.26 – 7.30 (1H, t, J = 7.98 Hz), 7.54 – 7.55 (1H, d, J = 2.65 Hz), 7.65 – 7.67 (1H, dd, J = 0.77, 8.18 Hz), 7.71 – 7.74 (1H, dd, J = 0.70, 7.78 Hz), 8.92 (1H, s); Mass (m/z): 283.1 $(M-H)^-$

7e (R_2 = 2'-CF_3): IR (cm^{-1}): 3334, 1623, 1519; ^{1}H-NMR ($CDCl_3$): δ 6.92 – 6.93 (1H, m), 7.12 – 7.22 (2H, m), 7.34 – 7.39 (1H, m), 7.61 – 7.63 (1H, m), 7.67 – 7.68 (1H, d, J = 2.74 Hz), 7.72 – 7.74 (1H, dd, J = 8.12 Hz), 7.81 – 7.83 (1H, dd, J = 7.76 Hz), 9.06 (1H, bs); Mass (m/z): 337.2 $(M-H)^-$

b) Synthesis of 4-nitro-2-(arylthio)-1H-indole (8a-e):

A mixture of intermediate **7a** (2.2 gm, 8.18 mmole) in 50 ml trifluroacetic acid was stirred at ambient temperature for 24 hrs, and then reaction mass was quenched with chilled water followed by extraction with ethyl acetate (3x50 ml). Combined all organic layers washed with saturated sodium bicarbonate solution, brine subsequently and dried over anhydrous sodium sulfate. Solvent was evaporated to obtain 0.750 gm of intermediate **8a**.

8a (R_2 = H): M.R (^oC): 138.4 – 143.2, IR (cm^{-1}): 3286, 3146, 2926, 1320, 1195; ^{1}H-NMR ($CDCl_3$): δ 7.27 – 7.29 (3H, m), 7.30 – 7.33 (3H, m), 7.49 (1H, s), 7.58 – 7.60 (1H, m), 8.12 – 8.15 (1H, m), 8.44 (1H, bs); Mass (m/z): 269 $(M-H)^-$.

8b (R_2 = 2'-Br): M.R (^oC): 197 – 199, IR (cm^{-1}): 3339, 3102, 2924, 1666, 1519; ^{1}H-NMR (DMSO-d6): δ 6.91 – 6.93 (1H, dd, J = 1.62, 7.88 Hz), 7.05 – 7.07 (1H, dt, J = 1.62, 7.83 Hz), 7.14 – 7.18 (1H, dt, J = 1.41, 7.55 Hz), 7.31 – 7.35 (1H, t, J = 7.98 Hz), 7.56 – 7.58 (1H, dd, J = 1.37, 7.91 Hz), 7.72 (1H, d, J = 0.78 Hz), 7.65 – 7.67 (1H, m), 8.15 – 8.17 (1H, m), 8.62 (1H, s); Mass (m/z): 346.9 $(M-H)^-$.

8c (R_2 = 2'-F): M.R (^oC): 181.7 – 184.7, IR (cm^{-1}): 3339, 3108, 2925, 1630, 1568; ^{1}H-NMR ($CDCl_3$): δ 7.07 – 7.15 (2H, m), 7.27 – 7.32 (3H, m), 7.50 (1H, d, J = 0.78 Hz), 7.61 – 7.64 (1H, m), 8.13 – 8.15 (1H, dd, J = 0.71, 8.04 Hz), 8.60 (1H, bs); Mass (m/z): 287.2 $(M-H)^-$

8d (R_2 = 4'-CH_3): M.R (^oC): 155.4 – 159.5, IR (cm^{-1}): 3328, 2928, 1623, 1568, 1467; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s), 7.15 – 7.17 (2H, m), 7.21 – 7.23 (1H, t, J = 9.06 Hz), 7.60 – 7.32 (2H, m), 7.39 (1H, d, J = 0.8 Hz), 7.53 – 7.56 (1H, m), 8.10 – 8.12 (1H, dd, J = 0.74, 8.06 Hz), 8.52 (1H, bs); Mass (m/z): 283.1 $(M-H)^-$

8e (R_2 = 2'-CF_3): M.R (^oC): 181.1 – 184.9, IR (cm^{-1}): 3340, 1594, 1518; ^{1}H-NMR ($CDCl_3$): δ 7.27 (1H, s), 7.31 – 7.41 (3H, m), 7.63 – 7.65 (2H, m), 7.70 – 7.72 (1H, dd, J = 7.30 Hz), 8.16 – 8.18 (1H, dd, J = 8.01 Hz), 8.55 (1H, bs); Mass (m/z): 337.3 $(M-H)^-$

c) Synthesis of 4-nitro-2-(arylsulfonyl)-1H-indole (9a-e):

To a stirred solution of intermediate **8a** (0.27 gm, 1 mmole) in chloroform (5 ml) at 15 – 20 ^oC was added 70-75% of m-chloro per benzoic acid (0.492 gm, 2 mmole) portion wise. The solution was stirred for 10 hrs at RT. Then the reaction mass was washed with saturated sodium bicarbonate solution and brine, and then dried over anhydrous sodium sulfate. Rotary evaporation of solvent resulted in 0.27 gm of intermediate **9a**.

9a (R_2 = H): M.R (^oC): 194.6 – 199.8, IR (cm^{-1}): 3266, 3155, 2922, 1571, 1519, 1329, 1152; ^{1}H-NMR (DMSO-d6): δ 7.51 – 7.55 (1H, t, J = 8.06 Hz), 7.62 (1H, d, J = 0.68 Hz), 7.64 – 7.68 (m, 2H), 7.71 – 7.75 (m, 1H), 7.92 – 7.94 (m, 1H), 8.05 – 8.08 (m, 2H), 8.15 – 8.18 (dd, 1H, J = 0.45, 7.82 Hz), 13.26 (1H, bs); Mass (m/z): 301.1 $(M-H)^-$.

9b (R_2 = 2'-Br): M.R (^oC): 242.3 – 245.2, IR (cm^{-1}): 3323, 3161, 2926, 1565, 1517, 1326, 1147; ^{1}H-NMR (DMSO-d6): δ 7.41 – 7.45 (m, 1H), 7.59 – 7.64 (m, 2H), 7.69 – 7.73 (m, 1H), 7.81 – 7.84 (m, 1H), 7.88 – 7.90 (m, 1H), 8.11 – 8.13 (m, 1H), 8.26 – 8.28 (m, 1H), 13.26 (1H, bs); Mass (m/z): 379 $(M-H)^-$.

9c (R_2 = 2'-F): M.R (^oC): 230.4 – 234.0, IR (cm^{-1}): 3328, 3153, 2926, 1596, 1516, 1331, 1158; ^{1}H-NMR (DMSO-d6): δ 7.42 – 7.45 (m, 1H), 7.50 – 7.54 (m, 2H), 7.64 (s, 1H), 7.78 – 7.83 (m, 1H), 7.93 – 7.95 (d, 1H, J = 8.27 Hz), 8.07 – 8.11 (m, 1H), 8.16 – 8.18 (d, 1H, J = 7.73 Hz), 13.26 (1H, bs); Mass (m/z): 319 $(M-H)^-$.

9d (R_2 = 4'-CH_3): M.R (^oC): 221.7 – 224.7, IR (cm^{-1}): 3264, 3154, 2961, 1519, 1331, 1148; ^{1}H-NMR (DMSO-d6): δ 2.36 (s, 3H), 7.42 – 7.45 (m, 2H), 7.49 – 7.56 (m, 1H), 7.56 (s, 1H), 7.61 – 7.64 (m, 1H), 7.85 – 7.87 (m, 2H), 8.13 – 8.15 (d, 1H, J = 7.66 Hz), 13.26 (1H, bs); Mass (m/z): 315.2 $(M-H)^-$.

9e (R_2 = 2'-CF_3): M.R (^oC): 259.7 – 263.6, IR (cm^{-1}): 3318, 3153, 1522, 1331, 1147; ^{1}H-NMR ($CDCl_3$): δ 7.41 – 7.45 (m, 1H), 7.52 (s, 1H), 7.76 – 7.84 (m, 2H), 7.89 – 7.93 (m, 2H), 8.14 – 8.16 (d, 1H, J = 7.85 Hz), 8.40 – 8.42 (m, 1H), 12.69 (1H, bs); Mass (m/z): 369.3 $(M-H)^-$.

d) Synthesis of 4-amino-2-(arylsulfonyl)-1H-indole (10a-e):

To a stirred solution of intermediate **9a** (3.02 gm, 10 mmole) in methanol (30 ml) was added 0.3 gm of 10% Pd-C at RT. Then the mass was treated with Hydrogen gas at atmospheric pressure for 3 hrs. Filtered the catalyst, evaporated the filtrate to obtain 2.44 gm of compound **10a**.

For halogens substituted compounds, nitro reduction was carried out using Fe/HCl or Ra-Ni/H_2.

10a (R_2 = H): M.R (^oC): 91.4 – 96.2, IR (cm^{-1}): 3376, 3103, 2922, 1583, 1508, 1307, 1135; ^{1}H-NMR ($CDCl_3$): δ 5.5 (bs, 2H), 6.22 – 6.24 (m, 1H), 6.58 – 6.63 (m, 1H), 6.96 – 7.00 (m, 1H), 7.38 (m, 1H), 7.59 – 7.68 (m, 3H), 7.93 – 7.96 (m, 2H), 8.63 (bs, 1H), Mass (m/z): 273.3 $(M+H)^+$.

10b (R_2 = 2'-Br): IR (cm^{-1}): 3376, 3103, 2922, 1583, 1508, 1307, 1135; ^{1}H-NMR (DMSO-d6): δ 5.88 (bs, 2H), 6.15 – 6.17 (d, 1H, J = 8.16 Hz), 6.99 – 7.01 (d, 1H, J = 8.15 Hz), 7.50 – 7.52 (m, 1H), 7.64 – 7.72 (m, 3H), 7.79 – 7.81 (m, 1H), 8.21 – 8.24 (dd, 1H, J = 1.48, 7.9 Hz), 12.13 (bs, 1H), Mass (m/z): 351.3 $(M+H)^+$.

10c (R_2 = 2'-F): M.R (^oC): 163.0 – 166.5, IR (cm^{-1}): 3399, 3331, 2922, 1621, 1592, 1580, 1329, 1150; ^{1}H-NMR (DMSO-d6): δ 5.67 (bs, 2H), 6.14 – 6.16 (d, 1H, J = 7.5 Hz), 6.54 – 6.56 (d, 1H, J = 8.23 Hz), 6.94 – 6.97 (t, 1H, J = 7.84 Hz), 7.37 – 7.46 (m, 2H), 7.48 (s, 1H), 7.71 – 7.77 (m, 1H), 7.95 – 7.99 (m, 1H), 11.93 (bs, 1H), Mass (m/z): 291.2 $(M+H)^+$.

10d (R_2 = 4'-CH3): IR (cm^{-1}): 3399, 3331, 2922, 1621, 1592, 1580, 1329, 1150; ^{1}H-NMR (CDCl3): δ 2.39 (s, 3H), 4.53 (bs, 2H), 6.39 – 6.41 (d, 1H, J = 7.5 Hz), 6.80 – 6.82 (d, 1H, J = 8.23 Hz), 7.11 – 7.15 (m, 2H), 7.28 – 7.30 (m, 2H), 7.84 – 7.87 (m, 2H), 8.82 (bs, 1H), Mass (m/z): 287.4 $(M+H)^+$.

10e (R_2 = 2'-CF_3): IR (cm^{-1}): 3328, 3019, 1586, 1308, 1155; ^{1}H-NMR (CDCl3): δ 4.12 (bs, 2H), 6.37 – 6.39 (d, 1H, J = 7.5 Hz), 6.86 – 6.88 (d, 1H, J = 8.32 Hz), 7.11 – 7.15 (t, 1H, J = 7.84 Hz), 7.18 (s, 1H), 7.66 – 7.72 (m, 2H), 7.82 – 7.86 (m, 1H), 8.22 – 8.24 (m, 1H), 11.93 (bs, 1H), Mass (m/z): 341 $(M+H)^+$.

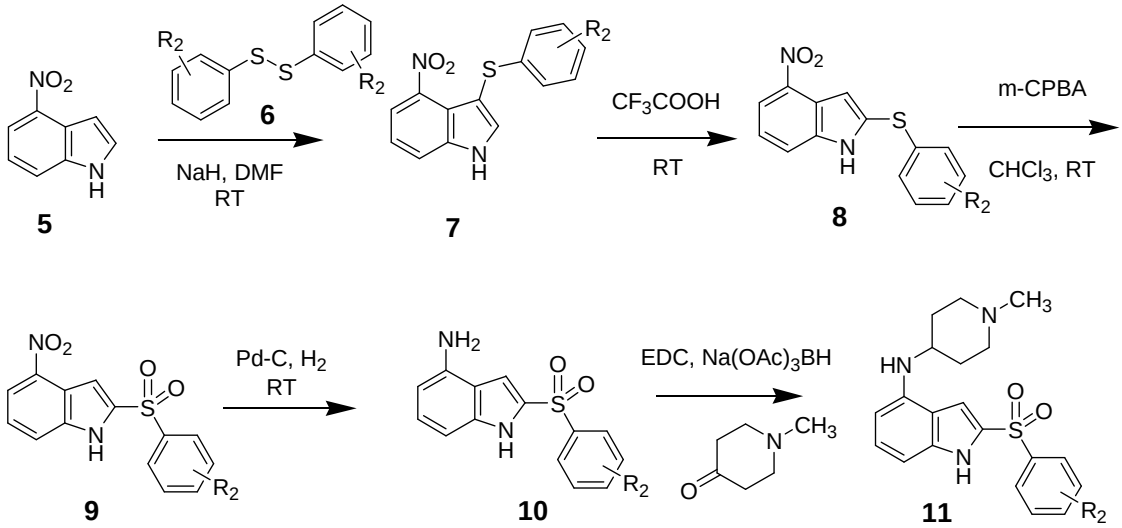
e) Synthesis of N-(1-methylpiperidin-4-yl)-2-(arylsulfonyl)-1H-indol-4-yl-amine (11a-e):

To a stirred solution of intermediate **10a** (0.272 gm, 1 mmole) in 1, 2-dichloroethane (5 ml) at RT was added N-methyl-4-piperidone (0.135 gm, 1.2 mmole). This reaction mixture was stirred for 1h at room temperature before being treated with sodium triacetoxy borohydride (0.318 gm, 1.5 mmole). Then it was stirred for 5 hr at RT, the reaction mass was quenched with chilled water basified with aq. NH_3. Layers separated, organic phase was washed with brine and then

dried over anhydrous sodium sulfate. After rotary evaporation, the resulting compound was further purified through coloumn chromatography to obtain 0.22 gm of **11a**.

11a (R_2 = H): M.R (^oC): 206.8 – 210.9, IR (cm^{-1}): 3409, 3346, 3327, 3127, 2922, 1586, 1515, 1307, 1148; ^{1}H-NMR ($CDCl_3$): δ 1.26 – 1.62 (m, 2H), 2.05 – 2.19 (m, 4H), 2.32 (s, 3H), 2.82 – 2.85 (m, 2H), 3.43 (m, 1H), 3.96 (d, 1H, J = 6.48 Hz), 6.25 – 6.27 (d, 1H, J = 7.76 Hz), 6.72 – 6.74 (d, 1H, J = 8.29 Hz), 7.15 – 7.19 (m, 2H), 7.47 – 7.49 (m, 2H), 7.53 – 7.57 (m, 1H), 7.96 – 7.99 (m, 2H), 8.89 (bs, 1H), Mass (m/z): 370.4 $(M+H)^+$.

Scheme 1



11b (R_2 = 2'- Br): M.R (^oC): 150 – 153.1, IR (cm^{-1}): 3398, 3289, 2934, 1588, 1508, 1320, 1149; ^{1}H-NMR (DMSO-d6): δ 1.27 – 1.53 (m, 2H), 1.84 – 2.02 (m, 4H), 2.32 (s, 3H), 2.75 – 2.78 (m, 2H), 3.32 (m, 1H), 5.87 – 5.89 (d, 1H, J = 7.72 Hz), 6.08 – 6.10 (d, 1H, J = 7.76 Hz), 6.56 – 6.58 (d, 1H, J = 8.29 Hz), 7.01 – 7.05 (t, 1H, J = 7.96 Hz), 7.56 – 7.58 (m, 1H), 7.63 – 7.67 (m, 2H), 7.81 – 7.83 (d, 1H, J = 7.64 Hz), 8.14 – 8.16 (m, 1H), 11.93 (bs, 1H), Mass (m/z): 448.4 $(M+H)^+$.
11c (R_2 = 2'-F): M.R (^oC): 210 – 212.2, IR (cm^{-1}): 3397, 3121, 2929, 1588, 1517, 1318, 1152; ^{1}H-NMR ($CDCl_3$): δ 1.44 – 1.53 (m, 2H), 1.89 – 2.02 (m, 4H), 2.17 (s, 3H), 2.75 – 2.78 (m, 2H), 3.26 (m, 1H), 5.91 – 5.93 (d, 1H, J = 7.8 Hz), 6.07 – 6.09 (d, 1H, J = 7.8 Hz), 6.56 – 6.58 (d, 1H, J = 8.2 Hz), 7.01 – 7.05 (t, 1H, J = 8 Hz), 7.38 – 7.49 (m, 2H), 7.64 (s, 1H), 7.74 – 7.75 (m, 1H), 7.96 – 8.0 (m, 1H), 11.97 (bs, 1H), Mass (m/z): 388.2 $(M+H)^+$.

11d (R_2 = 4'-CH3): M.R (^oC): 198.7 – 203.4, IR (cm^{-1}): 3571, 3384, 3129, 2946, 1589, 1514, 1372, 1146; ^{1}H-NMR (DMSO-d_6): δ 1.47 – 1.53 (m, 2H), 1.88 – 1.91 (m, 2H), 1.99 – 2.18 (m, 2H), 2.18 (s, 3H), 2.34 (s, 3H), 2.76 – 2.79 (m, 2H), 3.26 (m, 1H), 5.80 – 5.82 (d, 1H, J = 7.8 Hz), 6.06 – 6.08 (d, 1H, J = 7.8 Hz), 6.54 – 6.56 (d, 1H, J = 8.2 Hz), 6.98 – 7.02 (t, 1H, J = 8 Hz), 7.40 – 7.42 (m, 2H), 7.52 (s, 1H), 7.81 – 7.83 (d, 2H, J = 8.24 Hz), 1.96 (bs, 1H), Mass (m/z): 384.2 $(M+H)^+$.

11e (R_2 = 2'-CF3): IR (cm^{-1}): 3602, 3565, 3393, 3129, 2930, 1589, 1526, 1313, 1156; ^{1}H-NMR ($CDCl_3$): δ 1.45 – 1.53 (m, 2H), 1.89 – 1.93 (m, 2H), 1.99 – 2.05 (m, 2H), 2.18 (s, 3H), 2.77 –

2.80 (m, 2H), 3.32 (m, 1H), 5.93 – 5.95 (d, 1H, J = 7.6 Hz), 6.06 – 6.08 (d, 1H, J = 7.72 Hz), 6.57 – 6.59 (d, 1H, J = 8.16 Hz), 7.02 – 7.06 (t, 1H, J = 8 Hz), 7.62 (s, 1H), 7.86 – 7.95 (m, 2H), 8.0 – 8.01 (d, 1H, J = 7.4 Hz), 8.09 – 8.10 (d, 1H, J = 7.72 Hz), 12.03 (bs, 1H), Mass (m/z): 438.2 $(M+H)^+$.

RESULTS AND DISCUSSION

The critical intermediates 4-nitro indole (**5**) and substituted diphenyl disulfides (**6**) were prepared as per literature methods [31-32]. The synthesis of targeted compounds **11a-e** was carried out through intermediates **5** to **10a-c (Scheme-1)**. 4-Nitro indole was reacted with substituted diphenyl disulfides in presence of NaH as base in DMF solvent. The desired product was purified through column chromatography and was well characterized. The proton NMR showed desired signals at δ 7.07 – 7.20 (5H, m), 7.29 – 7.33 (1H, t), 7.61 (1H, d), 7.69 – 7.72 (1H, d), 7.73 – 7.75 (1H, m), 8.99 (1H, bs). Presence of Mass (m/z): 269 $(M-H)^-$ confirmed the formation of **4-nitro-3-(arylthio)-1H-indole (7a).**

The intermediate **7a** was treated with trifluoroacetic acid to obtain rearranged intermediate **8a.** The desired product was confirmed by spectral data like NMR and ESI-MS. In NMR absence of indole C-2 proton and presence of C-3 proton indicating the formation of **4-nitro-2-(arylthio)-1H-indole (8a).**

The intermediate **8a** was further oxidized with m-chloro per benzoic acid to obtain intermediate **8a**. The peaks at 1326, 1147 cm^{-1} in IR spectrum confirms the presence of sulfonyl group. This indicates that the formation of **4-nitro-2-(arylsulfonyl)-1H-indole (9a)**

The intermediate **9a** was reduced with hydrogen in presence of 10% Pd-C at atmospheric pressure, Peaks at 3376 cm^{-1}, 3295 cm^{-1} and the absence of the peak at 1520 cm^{-1} (nitro stretching) in IR spectrum confirms the formation of product. Desired NMR signals at δ 5.5 (bs, 2H), 6.22 – 6.24 (m, 1H), 6.58 – 6.63 (m, 1H), 6.96 – 7.00 (m, 1H), 7.38 (m, 1H), 7.59 – 7.68 (m, 3H), 7.93 – 7.96 (m, 2H), 8.63 (bs, 1H), Mass (m/z): 273.3 $(M+H)^+$ confirmed the formation of intermediate **4-amino-2-(arylsulfonyl)-1H-indole (10a).**

4-amino-2-(arylsulfonyl)-1H-indole (10a) was reacted with N-methyl-4-piperidone under reductive amination conditions to obtain compound **11a**. The NMR signals at δ 1.26 – 1.62 (m, 2H), 2.05 – 2.19 (m, 4H), 2.32 (s, 3H), 2.82 – 2.85 (m, 2H), 3.43 (m, 1H), 3.96 (d, 1H, J = 6.48 Hz), 6.25 – 6.27 (d, 1H, J = 7.76 Hz), 6.72 – 6.74 (d, 1H, J = 8.29 Hz), 7.15 – 7.19 (m, 2H), 7.47 – 7.49 (m, 2H), 7.53 – 7.57 (m, 1H), 7.96 – 7.99 (m, 2H), 8.89 (bs, 1H) and presence of Mass (m/z): 370.4 $(M+H)^+$, confirmed the formation of **N-(1-methylpiperidin-4-yl)-2-(arylsulfonyl)-1H-indol-4-yl-amine (11a).**

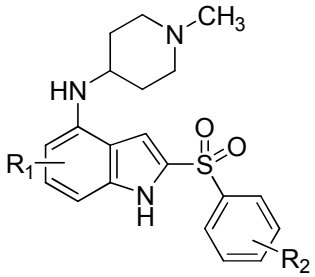
Radioligand binding assay for human 5-HT_6 Receptor:
Compounds were screened by the reported procedure [33]. Briefly, receptor source and radioligand used were human recombinant expressed in HEK-293 cells and [^{3}H] LSD (60-80 Ci/mmol) respectively. The final ligand concentration was 1.5 nmole and non-specific determinant was methiothepin mesylate (0.1 mmole). The reference compound and positive control was methiothepin mesylate. Reactions were carried out in 50 mmole TRIS-HCl (pH 7.4)

containing 10 mmole $MgCl_2$, 0.5 mmole 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. The binding study was carried out at Novascreen, USA [34].

Structure activity relationship (SAR): The well characterized N-(1-methylpiperidin-4-yl)-2-(arylsulfonyl)-1H-indol-4-yl-amines (**11a – 11e**) were tested for their *in vitro* affinity towards the human 5-HT_6 receptor, using radioligand binding assays. The percent inhibition was determined, and the results are depicted in **Table 1**. The most potent compounds **11b** and **11c** with percent inhibition 82.93 % and 58.18 % respectively indicated that moving the arylsulfonyl group from 1-postion to 2-postion of the indole, was well tolerated with respect to 5-HT_6 receptor affinity.

As compound **11b** was showing better affinity it was selected as a hit which can be further optimized to get the potential 5-HT6 receptor ligands.

Table1: 5-HT_6 receptor binding affinity [a]



Compound	R_1	R_2	% inhibition at 100 nM concentration
11a	H	H	54
11b	H	2'-Br	82.93
11c	H	2'-F	58.18
11d	H	4'-CH_3	31.53
11e	H	2'-CF_3	43.4

[a] 5-HT6 Receptor binding studies were carried out at Novascreen, USA.: Human recombinant / HEK293 cells; Radioligand: [^{3}H] LSD (60-80 Ci/mmoleol).

CONCLUSION

We have designed and synthesized a novel series of N-(1-methylpiperidin-4-yl)-2-(arylsulfonyl)-1H-indol-4-yl-amines as potential 5-HT_6 receptor ligands. From the results discussed above, it is evident that moving the arylsulfonyl group from 1-postion to 2-postion of the indole, as well tolerated with respect to 5-HT_6 receptor affinity.

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