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Synthesis and biological screening of 2-(4-methylpiperazin-1-yl methyl)-1-(arylsulfonyl)-*1H*-indole derivatives as 5-HT$_6$ receptor ligands: Part II

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ABSTRACT

As a part of our ongoing research to develop novel and selective 5-HT$_6$ receptor antagonists, a new series of 2-(4-methylpiperazin-1-yl methyl)-1-(arylsulfonyl)-1H-indole derivatives were designed to study the effect of two ionisable basic centers on the 5-HT$_6$ receptor binding affinity. The *synthesis and their in-vitro affinity towards the 5-HT$_6$ receptor is the subject matter of this communication.*

Key words: 2-(4-methylpiperazin-1-yl methyl)-1-(arylsulfonyl)-*1H*-indole derivatives, serotonin, 5-HT$_6$ receptor, i*n-vitro* affinity.

INTRODUCTION

5-Hydroxytryptamine6 receptor (5-HT$_6$R), the family member of G-protein coupled receptors (GPCR) [1] and is present in various regions of the brain associated with learning and memory [2, 3]. Blockade of the receptor increases acetylcholine and glutamate-mediated neurotransmission and enhances the cognitive processes, which amply demonstrate the therapeutic usefulness of this receptor for CNS mediated disorders such as schizophrenia and Alzheimer's disease [4].

In our earlier communication, we reported the evaluation of N$_1$-arylsulfonyl (*1H*-indole-2-yl)-1-(piperazinyl) methanone derivatives **(1)**. These derivatives contain the piperazinyl motif in which one of the nitrogen is amide functionality, while the terminal nitrogen as an ionizable basic center.

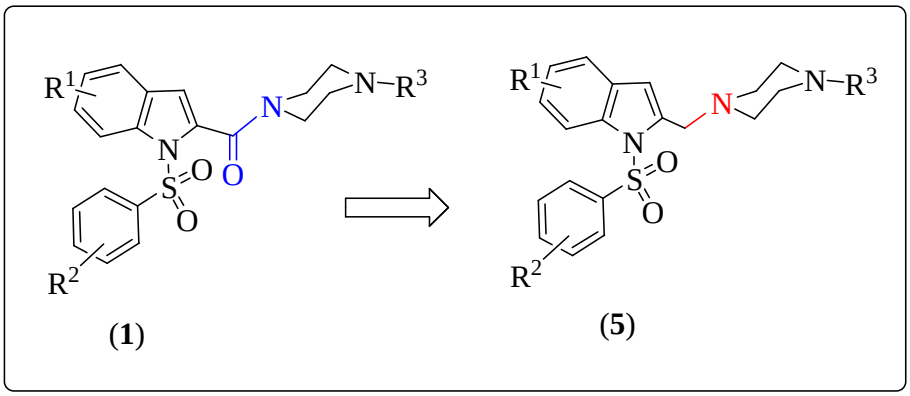


Figure 1: Genesis of ligand

Unfortunately derivatives **1** showed very mild affinity towards the 5-HT_6 receptor may be because of the amidic nature of one of the nitorgen. In continuation to that effort, we designed the new series of 2-(4-methylpiperazin-1-yl methyl)-1-(arylsulfonyl)-*1H*-indole derivatives by keeping both of the piperazinyl nitrogens basic in nature. Thus, the main aim of the present study is to find out the effect of two ionizable basic centers on the binding affinity towards the 5-HT_6 receptor. Synthesis and *in-vitro* affinity of these molecules is discussed in this paper.

MATERIALS ANDS METHODS

2.1 Chemistry

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'.

2.2 General procedure for ((*1H*-indol-2-yl)-(4-methyl-piperazin-1-yl)-methanone derivative (3)

To a stirred solution of substituted indole-2-caboxylic acid (0.0078 mol) and TEA (0.0093 mol) in THF (25 ml) was added ethyl chloroformate (0.0094 mol) and stirred the mass at 25 - 30 ^oC for 2 hr. Then, N-methyl piperazine (0.0094 mol) was added to the reaction mass and stirred the mass till completion of the reaction on TLC (4 hr). The organic volatiles were evaporated under reduced pressure and residual mass was dissolved in 100 ml of ethyl acetate. The organic layer was separated, washed with water (2 x 25 ml), brine solution (1 x 25 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure to obtain the crude mass, which was purified by column chromatography using 2 % TEA in ethyl acetate to obtain the title compound in 55 - 65 % yield.

(5-methoxy-1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (3a, R^1 = 5-OCH_3):IR (cm^{-1}): 3264 (indole -NH stretching), 1602 (amidic carbonyl stretching), 1520, 1140; ^{1}H-NMR ($CDCl_3$): δ 2.34 (3H, s, -CH_3), 2.48 - 2.51 (4H, t, piperazinyl), 3.84 (3H, s, -OCH_3), 3.94 (4H, bs, piperazinyl), 6.70 - 6.705 (1H, d, J = 1.52 Hz), 6.94 - 6.97 (1H, dd, J = 2.36 and 8.84 Hz), 7.33 - 7.36 (1H, d, J = 8.72 Hz), 7.60 - 7.61 (1H, d, J = 2 Hz), 9.15 (1H, bs, -NH); Mass (m/z): 274.4 $(M+H)^+$.

(5-Chloro-1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (3b, R^1 = 5-Cl): Oily mass; IR (cm^{-1}): 3263 (indole –NH stretching), 1596 (amidic carbonyl stretching), 1523, 1441, 1257, 1147; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, -CH_3), 2.49 - 2.52 (4H, t, piperazinyl), 3.94 (4H, bs, piperazinyl), 6.70 - 6.71 (1H, d, J = 1.56 Hz), 7.21 - 7.26 (1H, dd, J = 1.92 and 8.72 Hz), 7.33 - 7.36 (1H, d, J = 8.72 Hz), 7.60 - 7.61 (1H, d, J = 2 Hz), 9.34 (1H, bs, -NH); Mass (m/z): 278.1 $(M+H)^+$.

(5-Fluoro-1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (3c, R^1 = 5-F):Oily mass; IR (cm^{-1}): 3264 (indole – NH stretching), 1602 (amidic carbonyl stretching), 1531, 1409, 1146; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, -CH_3), 2.49 - 2.52 (4H, t, piperazinyl), 3.96 (4H, bs, piperazinyl), 6.73 - 6.735 (1H, d, J = 1.67 Hz), 7.00 - 7.05 (1H, m), 7.25 - 7.28 (1H, m), 7.35 - 7.37(1H, m), 9.66 (1H, bs, -NH); Mass (m/z): 262.2 $(M+H)^+$.

(1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (3d, R^1 = H):IR (cm^{-1}): 3253 (indole -NH stretching), 1594 (amidic carbonyl stretching), 1529, 1133; ^{1}H-NMR ($CDCl_3$): 2.34 (3H, s, N-CH_3), 2.48 - 2.52 (4H, t, piperazinyl), 3.96 (4H, bs, piperazinyl), 6.68 - 6.69 (1H, d, J = 2.56 Hz), 7.01 - 7.10 (2H, m), 7.40 - 7.55 (2H, m), 9.21 (1H, bs, -NH); Mass (m/z): 244.3 $(M+H)^+$.

2.2 General procedure for 2-(4-methylpiperazin-1-ylmethyl)-*1H*-indole derivatives (4)

To a stirred solution LAH (0.3g, 8.05 mmol) in THF (10 ml) was added intermediate **3a** (R^1 = 5-OMe, 1.1g, 0.027 mol) in THF (10 ml) under N_2 atm. The reaction mass was heat to reflux for 2 hr. After completion of reaction on TLC, the mass was cooled to 0 ^{O}C and quenched by careful addition of 10 ml ice cold water. The mass was filtered through hyflow bed and washed with ethyl acetate. Collective organic layer was dried over Na_2SO_4 and the organic volatiles were evaporated under reduced pressure to obtain a crude mass, which was further purified by column chromatography using 3% TEA in ethyl acetate.

5-methoxy-2-(4-methylpiperazin-1-yl) methyl-1H-indole (4a, R^1 = 5- OCH_3): Oily mass; IR (cm^{-1}): 3037 (indole NH stretching), 2950, 2819, 1449, 1215; ^{1}H-NMR (CDCl3): δ 2.29 (3H, s, N-CH_3), 2.45 - 2.49 (8H, bs, piperazinyl) 3.63 (2H, s, -CH_2), 3.83 (3H, s, -OCH_3), 6.282 - 6.285 (1H, d, J = 1.16 Hz), 6.79 - 7.81 (1H, dd, J = 2.4 and 8.76 Hz), 7.017 - 7.023 (1H, d, J = 2.44 Hz), 7.02 - 7.22 (1H, d, J = 8.76 Hz), 8.40 (1H, bs); Mass (m/z): 260.3 $(M+H)^+$.

5-Chloro-2-(4-methylpiperazin-1-yl) methyl-1H-indole (4b, R^1 = 5- Cl): Oily mass; IR (cm^{-1}): 3114 (indole NH stretching), 2838, 1480, 1280; ^{1}H-NMR (CDCl3): δ 2.29 (3H, s, N-CH_3), 2.35 - 2.51 (8H, bs, piperazinyl) 3.64 (2H, s, -CH_2), 6.29 (1H, d, J = 1.16 Hz), 7.07 - 7.10 (1H, d, J = 2.28 Hz), 7.21 - 7.24 (1H, m), 7.49 - 7.50 (1H, d, J = 1.88 Hz), 8.57 (1H, bs); Mass (m/z): 264.2, 266 $(M+H)^+$.

5-Fluoro-2-(4-methylpiperazin-1-yl)methyl-1H-indole (4c, R^1 = 5- F): Oily mass; IR (cm^{-1}): 3109 (indole NH stretching), 1451, 1290, 1155, 789; ^{1}H-NMR ($CDCl_3$): δ 2.29 (3H, s, N-CH_3), 2.32 - 2.50 (8H, bs, piperazinyl) 3.64 (2H, s, -CH_2), 6.314 - 6.317 (1H, d, J = 1.16Hz), 6.86 - 7.91 (1H, m), 7.16 - 7.24 (2H, m), 8.63 (1H, bs); Mass (m/z): 248.3 $(M+H)^+$.

2-(4-methylpiperazin-1-yl) methyl-1H-indole (4d, R^1 = H): Oily mass; IR (cm^{-1}): 3122 (indole NH stretching), 1457, 1275; ^{1}H-NMR ($CDCl_3$): δ 2.29 (3H, s, N-CH_3), 2.34 - 2.45 (8H, bs, piperazinyl) 3.62 (2H, s, -CH_2), 7.17 - 7.29 (4H, m), 8.59 (1H, bs); Mass (m/z): 230.2 $(M+H)^+$.

2.3 General procedure for 1-Arylsulfonyl-2-(4-methylpiperazin-1-yl methyl)-*1H*-indole derivatives (5a-l)

To a stirred solution of sodium hydride (40 mg, 1.003 mmol) in 5 mL THF was added a solution of **4a** (R^1 = 5-OCH_3, 0.2 g, 0.772 mmol) dissolved in 5 mL of THF under nitrogen atmosphere at RT. The mass was further stirred for 45 min. A solution of 4-bromo benzenesulfonyl chloride (0.295g, 1.15 mmol) in 5 ml THF was added to the above reaction mass and the mass was further stirred for 2 hr at 25 - 30 ^{o}C. The progress of the reaction was monitored on TLC. After completion of the reaction, the mass was quenched on to water (25 mL) and the product was extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with brine solution (1 x 100 mL) and dried over anhydrous magnesium sulfate. The organic volatiles were removed under vacuum to obtain the crude compound. The crude product was purified by flash chromatography using 2% TEA in ethyl acetate.

5-methoxy-1-(4'-bromobenzenesulfonyl)-2-(4-methylpiperazine-1-yl)methyl-1H-indole (5a, R^1 = 5- OCH_3, R^2 = 4'- Br): Oily mass; IR (KBr, cm^{-1}): 2941, 2792, 1476, 1370 (SO_2 stretching), 1169 (SO_2 stretching), 1057; ^{1}H-NMR ($CDCl_3$): δ 2.30 (3H, s, N-CH_3), 2.35 - 2.59 (8H, bs, piperazinyl), 3.81 (3H, s, -OCH_3), 3.82 (2H, s, benzylic), 6.48 (1H, s), 7.42 - 7.45 (1H, dd, J= 8.2, 1.84 Hz), 7.65 - 7.66 (1H, d, J = 1.76 Hz), 6.88 – 6.91 (2H, m), 7.51 - 7.55 (2H, m), 7.93 - 7.96 (3H, m); Mass (m/z): 478.1, 480.1 $[M+H]^+$.

5-Methoxy -1-(4'-Bromo benzenesulfonyl) -2- (4-methylpiperazine-1-yl)methyl-1H-indole (5b, R^1 = 5-OCH_3, R^2 = 4'- iPr): Oily mass; IR (KBr, cm^{-1}): 2962, 2798, 1474, 1366 (SO_2 stretching), 1207, 1168 (SO_2 stretching), 1056;

^{1}H-NMR ($CDCl_3$): δ 1.19 - 1.20 (6H, d, J = 3.36 Hz) 2.27 (3H, s, N-CH_3), 2.57 (8H, bs, piperazinyl), 2.88 - 2.90 (1H, sept, isopropyl) 3.82 (3H, s, -OCH_3), 3.84 (2H, s, benzylic), 6.47 (1H, s), 6.88 - 6.95 (2H, m), 7.22 - 7.26 (2H, m), 7.88 - 6.91 (2H, dd, J = 1.64, 8.52 Hz), 8.02 - 8.04 (1H, d, J = 8.36 Hz); Mass (m/z): 442.3 $[M+H]^+$.

5-Methoxy -1-(benzenesulfonyl) -2- (4-methylpiperazine-1-yl)methyl-1H-indole (5c, R^1 = 5-OCH_3, R^2 = H): Oily mass; IR (KBr, cm^{-1}): 2937, 2795, 1474, 1367 (SO_2 stretching), 1207, 1168 (SO_2 stretching), 1057; ^{1}H-NMR ($CDCl_3$): δ 2.26 (3H, s, N-CH_3), 2.55 (8H, bs, piperazinyl), 3.81 (3H, s, -OCH_3), 3.84 (2H, s, benzylic), 6.48 (1H, s), 6.87 - 6.91 (2H, m), 7.38 - 7.42 (2H, m), 7.49 - 6.51 (1H, dd, J = 7.44 Hz), 7.98 - 8.47 (3H, m); Mass (m/z): 400.1 $[M+H]^+$.

5-Methoxy-1-(3'-trifluorobenzenesulfonyl)-2-(4-methylpiperazine-1-yl)methyl-1H-indole (5d, R^1 = 5-OCH_3, R^2 = 3'- CF_3): MR (^{o}C): 99.5 - 101.5; IR (KBr, cm^{-1}): 2942, 2798, 1476, 1375 (SO_2 stretching), 1210, 1172 (SO_2 stretching), 1072; ^{1}H-NMR ($CDCl_3$): δ 2.23 (3H, s, N-CH_3), 2.54 (8H, bs, piperazinyl), 3.82 (5H, s, -OCH_3 and benzylic), 6.50 (1H, s), 6.90 - 6.93 (2H, m), 7.53 - 7.57 (1H, t, J = 7.88 Hz), 7.77 - 7.79 (1H, d, J = 7.84 Hz), 7.95 - 8.97 (1H, d, J = 8.76 Hz); Mass (m/z): 467.9 $[M+H]^+$.

5-Methoxy-1-(4'-methoxybenzenesulfonyl)-2-(4-methylpiperazine-1-yl)methyl-1H-indole (5e, R^1 = 5-OCH_3, R^2 = 4'- OCH_3): MR (^{o}C): 99.5 - 101.5; IR (KBr, cm^{-1}): 2936, 2795, 1498, 1366 (SO_2 stretching), 1263, 1163 (SO_2 stretching), 1092; ^{1}H-NMR ($CDCl_3$): δ 2.29 (3H, s, N-CH_3), 2.41 - 2. 59 (8H, bs, piperazinyl), 3.82 (6H, s, -OCH_3), 3.84 (2H, s, benzylic), 6.46 (1H, s), 6.82 - 6.90 (4H, m), 7.97 - 7.98 (1H, d, J = 8.84 Hz), 8.00 - 8.03 (2H, m); Mass (m/z): 430.1 $[M+H]^+$.

5-Fluoro-1-(benzenesulfonyl) -2- (4-methylpiperazine-1-yl)methyl-1H-indole (5f, R^1 = 5-F, R^2 = H): Oily mass; IR (KBr, cm^{-1}): 2933, 2795, 1466, 1366 (SO_2 stretching), 1174 (SO_2 stretching), 1091; ^{1}H-NMR ($CDCl_3$): δ 2.26 (3H, s, N-CH_3), 2.30 - 2. 56 (8H, bs, piperazinyl), 3.86 (2H, s, benzylic), 6.52 (1H, s), 6.98 - 7.03 (1H, m), 7.09 - 7.12 (1H, dd , J = 2.56, 8.48 Hz), 7.41 - 7.45 (2H, t), 7.52 - 7.54 (1H, t, J= 7.48 Hz), 8.02 - 8.06 (2H, m); Mass (m/z): 388.1 $[M+H]^+$.

5-Fluoro-1-(4'-fluoro benzenesulfonyl) -2- (4-methylpiperazine-1-yl)methyl-1H-indole (5g, R^1 = 5-F, R^2 = 4'-F): Oily mass; IR (KBr, cm^{-1}): 2931, 2794, 1466, 1371 (SO_2 stretching), 1178 (SO_2 stretching), 1089; ^{1}H-NMR ($CDCl_3$): δ 2.28 (3H, s, N-CH_3), 2.33 - 2. 59 (8H, bs, piperazinyl), 3.85 (2H, s, benzylic), 6.51 (1H, s), 6.99 - 7.03 (1H, m), 7.08 - 7.12 (3H, m), 7.98 - 8.01 (1H, m), 8. 16 - 8.19 (1H, m); Mass (m/z): 406.3 $[M+H]^+$.

5-Chloro-1-(4'-Bromo benzenesulfonyl) -2- (4-methylpiperazine-1-yl)methyl-1H-indole (5h, R^1 = 5-Cl, R^2 = 4'-CH_3): Oily mass; IR (KBr, cm^{-1}): 2941, 2789, 1449, 1372 (SO_2 stretching), 1173 (SO_2 stretching), 1056; ^{1}H-NMR ($CDCl_3$): δ 2.28 (3H, s, N-CH_3), 2.36 (3H, s, -CH_3), 2.42 - 2. 58 (8H, bs, piperazinyl), 3.86 (2H, s, benzylic), 6.48 (1H, s), 6.99 - 7.03 (1H, m), 7.20 - 7.23 (3H, m), 7.41 - 7.41 (1H, d, J= 2.02 Hz), 7.91 - 7.94 (1H, d, J = 8.32 Hz), 8.00 - 8.02 (1H, d, J = 8.84 Hz); Mass (m/z): 418.3, 420.1 $[M+H]^+$.

1-(benzenesulfonyl) -2- (4-methylpiperazine-1-yl)methyl-1H-indole (5i, R^1 = H, R^2 = H): Oily mass; IR (KBr, cm^{-1}): 2941, 2794, 1454, 1364 (SO_2 stretching), 1242, 1176 (SO_2 stretching), 1154, 1058; ^{1}H-NMR ($CDCl_3$): δ 2.25 (3H, s, N-CH_3), 2.31 - 2.56 (8H, bs, piperazinyl), 3.87 (2H, s, benzylic), 6.55 (1H, s), 7.20 - 7.53 (6H, m), 8.08 - 8.12 (3H, m); Mass (m/z): 370.1 $(M+H)^+$.

1-(4'-Fluorobenzenesulfonyl) -2- (4-methylpiperazine-1-yl) methyl-1H-indole (5j, R^1 = H, R^2 = 4' -F): Oily mass; IR (KBr, cm^{-1}): 2941, 2790, 1451, 1378 (SO_2 stretching), 1240, 1181 (SO_2 stretching), 1162, 1059; ^{1}H-NMR ($CDCl_3$): δ 2.31 (3H, s, N-CH_3), 2.41 - 2.62 (8H, bs, piperazinyl), 3.87 (2H, s, benzylic), 6.54 (1H, s), 7.04 - 7.32 (4H, m), 7.45 - 7.49 (1H, m), 8.03 - 8.19 (1H, dd), 8.20 - 8.23 (2H, m); Mass (m/z): 388.1 $(M+H)^+$.

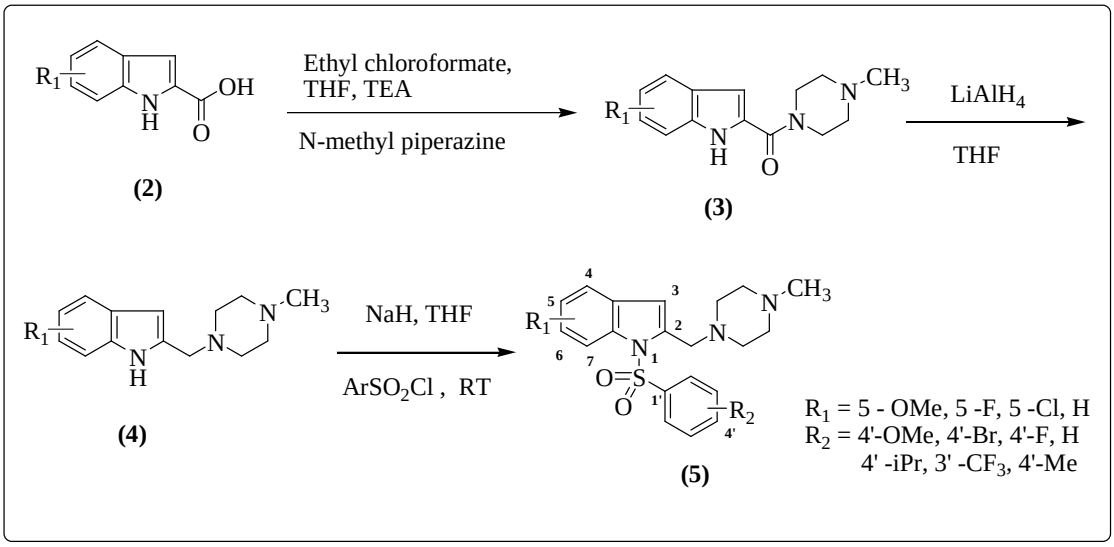
1-(4'-isopropylbenzenesulfonyl)-2-(4-methylpiperazine-1-yl) methyl-1H-indole (5k, R^1 = H, R^2 = 4' - iPr): Oily mass; IR (KBr, cm^{-1}): 2931, 2799, 1454, 1388 (SO_2 stretching), 1240, 1178 (SO_2 stretching), 1158, 1056; ^{1}H-NMR ($CDCl_3$): δ 1.18 - 1.22 (6H, d), 2.26 (3H, s, N-CH_3), 2.31 - 2.55 (8H, bs, piperazinyl), 2.90 (1H, sept), 3.87 (2H, s, benzylic), 7.20 (1H, s), 7.21 - 7.28 (4H, m), 7.44 - 7.54 (1H, m), 7.96 - 7.99 (2H, m), 8.00 - 8.13 (1H, m); Mass (m/z): 412.3 $(M+H)^+$.

***1-(4'-Methoxybenzenesulfonyl) -2- (4-methylpiperazine-1-yl) methyl-1H-indole (5l, R^1 = H, R^2 = 4' - OCH_3)*:** Oily mass; IR (KBr, cm^{-1}): 2940, 2794, 1454, 1364 (SO_2 stretching), 1242, 1176 (SO_2 stretching), 1153, 1090; ^{1}H-NMR ($CDCl_3$): δ 2.28 (3H, s, N-CH_3), 2.35 - 2.59 (8H, bs, piperazinyl), 3.80 (3H, s, OCH_3) 3.88 (2H, s, benzylic), 6.53 (1H, s), 6.83 - 6.87 (2H, dd), 7.19 - 7.27 (2H, m), 7.43 - 7.47 (1H, m), 8.06 - 8.12 (3H, m); Mass (m/z): 400 $(M+H)^+$.

RESULTS AND DISCUSSION

The general synthetic strategy used for the preparation of title **Compounds 5a-l** has been summarized in **Scheme 1**.

Various substituted indole 2-carboxylic acids **(1)** were synthesized as per the reported procedures. These indole 2-carboxylic acid derivatives on treatment with ethyl chloroformate followed by N-methyl piperazine gave amide derivatives **(3)**. The structure was confirmed by the spectral data. In IR spectrum, amide derivatives **(3)** showed peak at 1599 - 1610 cm^{-1} due to amidic carbonyl stretching. The mass spectra exhibited the $[M+H]^+$ peak as parent ion. The NMR spectrum ($CDCl_3$) showed presence of N-methyl protons [-CH_3] at δ 2.32 - 2.34 range along with two sets of 4 piperazinyl protons at δ 2.48 and δ 3.94.



Scheme -1

These amide derivatives further reduced to 2-piperazinylmethyl indoles derivatives **(4)** in presence of lithium aluminium hydride. The structure of 2-Piperazinylmethyl indoles derivatives was confirmed by the absence of amidic carbonyl frequency at 1599 - 1610 cm^{-1} in IR. The ^{1}H-NMR ($CDCl_3$) spectrum showed broad peak for 8 piperazinyl protons as broad singlet at δ 2.45 - 2.5 (8H, br, piperazinyl) and the presence of two benzylic methylene protons at δ 3.63 (2H, s, -CH_2). The $(M+H)^+$ molecular ion peak in the mass confirms the structure.

The 2-piperazinylmethyl indoles derivatives were further reacted with appropriate arylsulfonyl chloride in presence of base to obtain the targeted compounds **5a-l.** The presence of peaks at 1370 cm^{-1} and 1169 cm^{-1} due to -SO_2 stretching frequencies in IR spectrum confirms the sulfonamide formation.

5-HT_6 Receptor binding studies:

The *in-vitro* 5-HT_6 receptor binding assay [5] was carried out on Human recombinant receptor expressed in HEK-293 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.

Table -1: 5-HT$_6$ receptor binding data

Compound No.	R^1	R^2	% Inhibition at 1 µM
5a	5-OMe	4'-Br	18.9 %
5b	5-OMe	4'-iPr	36.6 %
5c	5-OMe	H	24.2 %
5d	5-OMe	3'-CF_3	40.8 %
5e	5-OMe	4'-OMe	30.9 %
5f	5-F	H	18.2 %
5g	5-F	4'-F	26.4 %
5h	Cl	4'-CH_3	28.2 %
5i	H	H	22.5 %
5j	H	4'-F	54.1 %
5k	H	4'-iPr	22.3 %
5l	H	4'-OMe	17.3 %

All the synthesized compounds were screened for their % inhibition at the human 5-HT$_6$ receptor at 1µM concentration. All derivatives have shown mild to moderate affinity towards the 5-HT$_6$ receptor. Compounds **5j** and **5d** showed the highest inhibition of 54.1 % and 40.8 % respectively. By comparing the *in-vitro* data of both the present and parent series, we came to the conclusion that 2-piperazinylmethyl-N-aryl sulfonamide indole derivatives **(5)** with two basic centers are advantageous over the parent series of compounds **(1)** for 5-HT$_6$ receptor binding.

CONCLUSION

In summary, we successfully designed and synthesized a new series of 2-(4-methylpiperazin-1-yl methyl)-1-(arylsulfonyl)-*1H*-indole derivatives by keeping both piperazinyl nitrogens basic in nature. Impressed with the *in-vitro* results, we came to the conclusion that the series having the potential to be 5-HT$_6$ receptor ligands and the efforts should require to improve upon the potency of these molecules. Keeping that in mind, we focused our attention towards improvement in the potency and is the subject matter of our subsequent communication.

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