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Synthesis of novel (1-substituted benzenesulfonyl-1*H*-indol-5-yl)-(4-substituted piperazin-1-yl)-methanone derivatives as 5-HT$_6$R ligands

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ABSTRACT

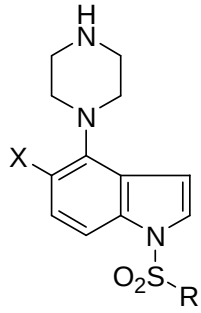
(1H-Indol-5-yl)-(4-substituted piperazin-1-yl)-methanone derivatives, 6a and 6b were synthesized following the method given in Scheme - 1. Intermediates 6a & 6b were further reacted with substituted benzene sulfonyl chlorides to obtain the targeted compounds, (1-substituted benzenesulfonyl-1H-indol-5-yl)-(4-substitutedpiperazin-1-yl)-methanone derivatives 7a-m (Scheme - 2). All the synthesized compounds 7a-m were well characterized with spectral data and checked the in-vitro binding affinity towards 5-HT$_6$ receptors. These compounds have shown mild to moderate potency towards serotonin 5-HT$_6$ receptors and are considered as initial hits to do further modifications.

Keywords: 5-HT$_6$ receptor, Serotonin**,** In-vitro analysis, Leimgruber reaction, Amide coupling, Sulfonylation.

INTRODUCTION

Though 5-hydroxytryptamine (5-HT) research is almost a decade old [1 - 3] still it represents one of the most attractive areas in medicinal chemistry [4]. Fourteen serotonin receptor (5-HTR) subtypes have been identified so far that are classified into seven families (5-HT$_{1-7}$) [5, 6] based on amino acid sequences, pharmacology and intracellular mechanisms. With the exception of the ionotropic 5-HT$_3$ receptor, all of the 5-HT subtypes are G protein-coupled receptors (GPCRs) [7 - 10]. To date many serotoninergic agents acting at 5-HT$_{1-4}$ receptors are clinically used [11] for the treatment of certain central nervous system (CNS) illnesses. One of the most recent additions to the family of serotonin receptors is the human 5-HT$_6$ receptor (h5-HT$_6$R), which was cloned in 1996 [12, 13] as a gene codifying a polypeptide chain of 440 amino acids [13,14] that is

positively coupled to the adenylate cyclase [15 - 17] cascade via the Gs protein. The high affinity of several antipsychotic and antidepressant agents [13, 18, 19] boosted the first studies exploring the 5-HT_6 receptor potential for the treatment of schizophrenia and bipolar affective disorder. Thus, 5-HT_6 receptor research has focused on the development of agents with potential application for the treatment of CNS pathologies related to, for example, cognition, obesity and convulsive disorders [20 - 22]. Cole showed that 4-piperazinyl- 1-sulfonylindoles (**I**) (see **Fig: 1**) were potent 5-HT_6R antagonists, which further demonstrated the promiscuous nature of the receptor site [23, 24]. This was supported by additional 4-piperazinyl- 1-sulfonylindole 5-HT_6 antagonists independently discovered by researchers at GlaxoSmithKline (**II** and **III**) (see **Fig: 1**) [25, 26], Roche (**IV**) (see **Fig: 1**) [23], and Biovitrum [27, 28]. In addition to excellent affinity, **III** (SB-699929) was also shown to have high selectivity (>100-fold against a range of 50 receptors), good BBB exposure (brain/plasma = 3), and a suitable PK profile (oral F = 49% and CL = 44 mL/min/kg in rats). Above reported compounds have 1-sulfonyl-*1H*-indole and piparazinyl moiety. So based on the above pharmacophore model, we prepared a series of (1-substituted benzenesulfonyl-1H-indol-5-yl)-(4-substituted piperazin-1-yl)-methanone derivatives and checked their *in-vitro* activity towards human 5-HT_6 receptors. These compounds have shown moderate binding potency towards the 5-HT_6 receptors.



I : X = H, R = Ph, Ki = 1.0 nM

II : X = H, R = 5-chloro-3-methylbenzothiophen-2-yl, Ki = 0.3 nM

III : X = Cl, R = 3-Cl-Ph, SB-699929, Ki = 0.3 nM

IV : X = H, R = 1-Naph, Ki = 0.4 nM

Fig: 1

MATERIALS AND METHODS

Methodology and instrumentation: All the reagents used in the present work were of AR / LR grade. All the solvents used for carrying out chromatographic experiments and spectroscopic experiments were of HPLC grade and spectroscopic grade respectively. Both ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 400 MHz on a Bruker NMR spectrometer instrument (Fallanden, Switzerland). Deuterated reagents were used as solvents and were commercially procured. TMS was used as internal reference standard. Chemical shift values are expressed in parts per million (δ) values and coupling constants are expressed in Hz. All mass spectra were recorded using electrospray ionization (ESI) technique on an API 2000, ABS triple quadrupole instrument

(MDS-SCIEX, Concord, Ontario, Canada). Infrared spectra were recorded on KBr disc and in solid state using IR Pristage 2 instrument of Shimadzu make. Column chromatography was performed using 60-120 mesh silica gel and executed under nitrogen pressure (flash 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 obtained from Merck & Co, Germany.

Preparation of Methyl 3-Methyl-4-nitro-benzoate (2).
3-methyl-4-nitro benzoic acid **1** (12.0 g 66.2 mmole) was dissolved in methanol (50 mL) and added 0.5 mL of sulfuric acid. The reaction mass was heated at reflux temperature for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mass was concentrated under vacuum. The residual mass was diluted with ice water (100 mL), basified with saturated sodium bicarbonate solution and extracted with ethyl acetate (4 x 50 mL). Combined organic layer was washed with brine solution (2 x 30 mL), dried over anhydrous sodium sulfate and the organic layer was concentrated under vacuum to obtain 12.5 g of intermediate **2** (Yield 96 %).

2: Purity (HPLC): 99.79 %, M.R (^{o}C): 80 - 81; IR spectra (cm^{-1}): 3043, 2958, 1731 (C=O), 1519 (NO_2 stretching), 1430, 1388, 1343, 1196, 1118, 978, 835, 731, 497; ^{1}H-NMR (ppm): δ 2.63 (s, 3H, Ar-CH_3), 3.97 (s, 3H, OCH_3), 7.96 - 8.03 (m, 3H, ArH).

Preparation of Methyl 3-(2-dimethylamino-vinyl)-4-nitro-benzoate (3).
Methyl 3-methyl-4-nitrobenzoate **2** (12.0 g 61.5 mmole) was added to N, N-dimethyl formamide dimethylacetal (DMFDMA) (50 mL) and the resulting reaction mass was heated at a mass temperature of 100 - 110 ^{o}C for 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was diluted with ice water (100 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layer was washed with brine solution (2 x 30 mL), dried over anhydrous sodium sulfate and the organic layer was concentrated under vacuum to obtain 14.0 g of intermediate **3 (**Yield 91%).

3: IR spectra (cm^{-1}): 3085, 2954, 1720 (C=O), 1624, 1600, 1562, 1499, 1332, 1305, 1263, 1097, 935, 746; ^{1}H-NMR (ppm): δ 2.94 - 2.95 (s, 6H, N $(CH_3)_2$), 3.95 (s, 3H, OCH_3), 5.76 - 5.80 (d, 1H, styrene 1H), 7.07 - 7.11 (d, 1H, styrene 1H), 7.53 - 7.56 (dd, 1H, ArH), 7.82 - 7.84 (d, 1H, J = 8.0 Hz, ArH), 8.14 (s, 1H, ArH).

Preparation of Methyl *1H*-Indole-5-carboxylate (4).
The intermediate **3** (14.0 g, 56.0 mmole) was dissolved in a mixture of methanol (100 mL) and tetrahydrofuran (100 mL) and placed in an autoclave. Pd/C (10 %, 1.4 g) was added to the autoclave and applied 4 - 5 Kg hydrogen pressure. The autoclave was heated at 50 ^{o}C temperature for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mass was filtered through hyflow bed and the cake was washed with methanol (2 x 20 mL). The clear filtrate was concentrated under vacuum to obtain 8.8 g of the compound **4** (Yield 89.7%).

4: Purity (HPLC): 99.79 %, M.R (^{o}C): 124 - 125; IR spectra (cm^{-1}): 3318, 2949, 1696, 1610, 1437, 1349, 1329, 1272, 1198, 986, 756, 683; ^{1}H-NMR (ppm): δ 3.94 (s, 3H, OCH_3), 6.67 (s,

1H, ArH), 7.27 - 7.30 (d, 1H, ArH), 7.41 - 7.43 (d, 1H, J = 8.0 Hz, ArH), 7.91 - 7.94 (d, 1H, ArH), 8.38 (bs, 1H, NH), 8.43 (s, 1H, ArH).

Preparation of *1H*-Indole-5-carboxylic acid (5).

The intermediate **4** (16.0 g, 91.4 mmole) was dissolved in absolute ethanol (80 mL) and 10% sodium hydroxide solution (80 mL) taken in a 250 mL 4-necked round bottom flask . Reaction mixture was stirred at room temperature and monitored by TLC. After completion of reaction ethanol was distilled off under under vacuum and the residual mass was diluted with ice water (100 mL) and extracted with diethyl ether (2 x 50 mL). Aqueous layer was cooled to 10 ^{o}C and acidified with hydrochloric acid solution and the product was extracted with ethylacetate (4 x 100 mL). Combined organic layer was washed with brine solution (2 x 25 mL), dried over anhydrous sodium sulfate and concentrated under vacuum to obtain the intermediate **5** (13.16 g) the yield being 90 %.

5: Purity (HPLC): 98.79 %, M.R (^{o}C): 207 - 209; IR spectra (cm^{-1}): 3357, 1664, 1610, 1580, 1438, 1356, 1333, 1311, 1248, 1135, 894, 751, 666, 548; ^{1}H-NMR (ppm): δ 6.56 (s, 1H, ArH), 7.42 - 7.44 (m, 2H, ArH), 7.69 - 7.71 (m, 1H, ArH), 8.23 (s, 1H, ArH), 11.4 (bs, 1H, NH), 12.3 (bs, 1H, COOH); Mass (m/z): 160.2 (M-1).

Preparation of (*1H*-Indol-5-yl)-(4-substituted-piperazin-1-yl)-methanone 6a & 6b.

The intermediate **5** (10 g, 62.5 mmole) was dissolved in tetrahydrofuran (100 mL) and taken in a flask. Added triethylamine (9.0 mL, 64.69 mmole), cooled to 10 ^{o}C and added ethylchloroformate (7.0 g, 64.5 mmole) through dropping funnel in 30 min. Reaction mass was stirred at room temperature for 20 h while monitoring the progress of the reaction by TLC. After completion of reaction substituted piperazine (64 mmole) was added to the reaction mass and stirred further at room temperature for 1 h, while monitoring TLC for the completion of reaction. The reaction mass was then diluted with ethylacetate (100 mL) and the product was extracted into aqueous layer with chilled 50 % hydrochloric acid solution (50 mL). Aqueous layer was separated, cooled to 10 ^{o}C, basified with 10 % sodium hydroxide solution and the product was extracted with ethylacetate (4 x 100 mL). Combined organic layer was washed with brine solution (50 mL) and dried over anhydrous sodium sulfate. Organic layer was concentrated under vacuum to obtain the intermediate **6 (a, b**) in 70 - 75 % yield.

(*1H*-Indol-5-yl)-(4-methyl-piperazin-1-yl)-methanone (6a, R = CH_3).

Yield: 70 %, IR (cm^{-1}): 3422, 2941, 2803, 1606, 1436, 1297, 1000, 750; ^{1}H-NMR ($CDCl_3$): δ 2.34 (s, 3H, N-CH_3), 2.38 - 2.50 (bs, 4H, piperazine) 3.71 (bs, 4H, piperazine), 6.57 - 6.58 (d, 1H, J = 4.0 Hz, ArH), 7.24 - 7.27 (m, 2H, ArH), 7.37 - 7.39 (d, 1H, J = 8 Hz, ArH), 7.72 (s, 1H, ArH), 8.44 - 8.52 (bs, 1H, NH); Mass (m/z): 244.4 (M+1).

(4-Ethyl-piperazin-1-yl)-(*1H*-indol-5-yl)-methanone (6b, R = C_2H_5).

Yield: 75 %, ^{1}H-NMR ($CDCl_3$): δ 1.06 - 1.12 (t, 3H, CH_2CH_3), 2.43 - 2.48 (m, 6H, 2H, CH_2CH_3, 4H - piperazine), 3.66 (bs, 4H, piperazine), 6.55 - 6.56 (d, 1H, J = 4.0 Hz, ArH), 7.21 - 7.24 (m, 2H, ArH), 7.31 - 7.33 (m, 1H, ArH), 7.71 (s, 1H, ArH), 8.79 (bs, 1H, NH); Mass (m/z): 258.5 (M+1).

Alternatively compounds **6a** and **6b** also can be prepared by the method described by us in our earlier publication [29].

General procedure for preparation of (1-substituted benzenesulfonyl-*1H*-indol-5-yl)-(4-substitutedpiperazin-1-yl)-methanone 7 (a-m).

A solution of **6 (a, b)** (10 mmole) dissolved in 15 mL tetrahydrofuran, was slowly added to a 250 mL flask, containing a suspension of potassium hydride (30% w /w) (2.0 g, 15 mmole) in 50 mL tetrahydrofuran under nitrogen atmosphere, while maintaining the temperature below 10 ^{o}C. The reaction mixture was stirred for a period of 1 h at 25 ^{o}C. To this well stirred solution, substituted benzenesulfonyl chloride (12.46 mmoles) was added slowly, while maintaining the temperature below 10 ^{o}C. The reaction mixture was further stirred for a period of 2 h while monitoring the progress of the reaction by TLC. After completion of the reaction, the reaction mixture was poured on to 100 g of ice-water mixture under stirring and the resulting mass was extracted with ethyl acetate (5 x 50 mL). The combined ethyl acetate extracts were then washed with water (40 mL), brine (30 mL) and dried over anhydrous sodium sulfate and the organic volatiles were removed under reduced pressure. The residual thick syrupy mass was purified over silica gel column with ethyl acetate containing triethylamine (8 to 10 %) as eluent to obtain the pure compound **7 (a-m)** in 60 - 80 % yield.

(4-Methyl-piperazin-1-yl)-[1-(3-trifluoromethyl-benzenesulfonyl)-*1H*-indol-5-yl]-methanone (7a, R = CH_3, R_1 = 3-CF_3).

Purity (HPLC): 98.21 %, Yield: 70 %, Syrupy mass, IR spectra (cm^{-1}): 2940, 2795, 1632, 1435, 1382, 1326, 1295, 1179, 1133, 1071, 792, 693; ^{1}H-NMR (ppm): δ 2.32 (s, 3H, N-$\underline{CH_3}$), 2.39 - 2.49 (bs, 4H, piperazine), 3.39 - 3.81 (bs, 4H, piperazine), 6.73 - 6.74 (d, 1H, J = 4.0 Hz, ArH), 7.38 - 7.40 (m, 1H, ArH), 7.59 - 7.64 (m, 3H, ArH), 7.81 - 7.83 (m, 1H, ArH), 8.0 - 8.36 (m, 2H, ArH), 8.51 (s, 1H, ArH); Mass (m/z): 452.2 (M+1).

(1-Benzenesulfonyl-*1H*-indol-5-yl)-(4-methyl-piperazin-1-yl)-methanone (7b, R = CH_3, R_1 = H).

Purity (HPLC): 99.52 %, Yield: 80 %, Syrupy mass, IR spectra (cm^{-1}): 3435, 2939, 2794, 1630, 1437, 1375, 1295, 1175, 1131, 1001, 793, 685, 579; ^{1}H-NMR (ppm): δ 2.31 (s, 3H, N-$\underline{CH_3}$), 2.34 - 2.48 (bs, 4H, piperazine), 3.46 - 3.79 (bs, 4H, piperazine), 6.68 - 6.69 (d, 1H, J = 4.0 Hz, ArH), 7.34 - 7.37 (m, 1H, ArH), 7.45 - 7.47 (m, 2H, ArH), 7.55 - 7.62 (m, 3H, ArH), 7.85 - 7.87 (m, 2H, ArH), 8.0 - 8.02 (m, 1H, ArH); Mass (m/z): 384.2 (M+1).

[1-(4-Isopropylbenzenesulfonyl)-*1H*-indol-5-yl]-(4-methylpiperazin-1-yl)-methanone (7c, R = CH_3, R_1 = 4 - iPr).

Purity (HPLC): 98.47 %, Yield: 75 %, Syrupy mass, IR spectra (cm^{-1}): 3435, 2964, 2794, 1633, 1425, 1375, 1295, 1174, 1132, 1001, 788, 667, 586; ^{1}H-NMR (ppm): δ 1.20 - 1.25 (d, 6H, CH($\underline{CH_3}$)$_2$), 2.32 (s, 3H, N-$\underline{CH_3}$), 2.36 - 2.48 (bs, 4H, piperazine), 2.80 - 2.92 (sept, 1H, $\underline{CH}$(CH_3)$_2$), 3.46 - 3.80 (bs, 4H, piperazine), 6.67 - 6.68 (d, 1H, J = 4.0 Hz, ArH), 7.27 - 7.34 (m, 2H, ArH), 7.36 - 7.364 (m, 1H, ArH), 7.587 - 7.588 (m, 1H, ArH), 7.62 - 7.63 (m, 1H, ArH), 7.76 - 7.78 (m, 2H, ArH), 8.0 - 8.02 (m, 1H, ArH); Mass (m/z): 426.3 (M+1).

(4-Methyl-piperazin-1-yl)-[1-(toluene-4-sulfonyl)-*1H*-indol-5-yl]-methanone (7d, R = CH_3, R_1 = CH_3).

Purity (HPLC): 99.74 %, Yield: 68 %, Syrupy mass, IR spectra (cm^{-1}): 2963, 2794, 1632, 1437, 1373, 1294, 1260, 1173, 1131, 1022, 794, 674, 580; ^{1}H-NMR (ppm): δ 2.32 (s, 3H, N-$\underline{CH_3}$), 2.35

(s, 3H, Ar-$\underline{CH_3}$), 2.42 - 2.51 (bs, 4H, piperazine), 3.46 - 3.80 (bs, 4H, piperazine), 6.67 - 6.68 (d, 1H, J = 4.0 Hz, ArH), 7.21 - 7.24 (m, 2H, ArH), 7.33 - 7.36 (m, 1H, ArH), 7.581 - 7.584 (m, 1H, ArH), 7.611 - 7.621 (m, 1H, ArH), 7.73 - 7.75 (m, 2H, ArH), 7.99 - 8.021 (m, 1H, ArH); Mass (m/z): 398.3 (M+1).

[1-(4-Bromo-benzenesulfonyl)-*1H*-indol-5-yl]-(4-methyl-piperazin-1-yl)-methanone (7e, R = CH_3, R_1 = Br).
Purity (HPLC): 95.40 %, Yield: 65 %, MR (^oC): 139 - 145; IR spectra (cm^{-1}): 3135, 2937, 2795, 1630, 1570, 1450, 1376, 1295, 1275, 1179, 1131, 1010, 741, 614, 580; ^{1}H-NMR (ppm): δ 2.32 (s, 3H, N-$\underline{CH_3}$), 2.37 - 2.48 (bs, 4H, piperazine), 3.46 - 3.79 (bs, 4H, piperazine), 6.70 - 6.71 (d, 1H, J = 4.0 Hz, ArH), 7.36 - 7.38 (m, 1H, ArH), 7.57 - 7.60 (m, 4H, ArH), 7.70 - 7.72 (m, 2H, ArH), 7.97 - 8.0 (m, 1H, ArH); Mass (m/z): 462.3 (M+1).

(4-Methyl-piperazin-1-yl)-[1-(2, 4, 5-trichloro-benzenesulfonyl)-*1H*-indol-5-yl]-methanone (7f, R = CH_3, R_1 = 2, 4, 5-Cl).
Purity (HPLC): 99.10 %, Yield: 66 %, MR (^oC): 183 - 185; IR spectra (cm^{-1}): 3435, 3093, 2929, 2799, 1633, 1570, 1438, 1379, 1295, 1271, 1179, 1122, 1000, 873, 744, 688, 562; ^{1}H-NMR (ppm): δ 2.32 (s, 3H, N-$\underline{CH_3}$), 2.37 - 2.48 (bs, 4H, piperazine), 3.46 - 3.80 (bs, 4H, piperazine), 6.70 – 6.71 (d, 1H, J = 4.0 Hz, ArH), 7.32 - 7.35 (m, 1H, ArH), 7.54 (s, 1H, ArH), 7.64 - 7.73 (m, 3H, ArH), 8.33 (s, 1H, ArH); Mass (m/z): 486.2 (M+1).

[1-(4-Methoxy-benzenesulfonyl)-*1H*-indol-5-yl]-(4-methyl-piperazin-1-yl)-methanone (7g, R = CH_3, R_1 = 4 – OCH_3).
Purity (HPLC): 97.51 %, Yield: 61 %, Syrupy mass, IR spectra (cm^{-1}): 3435, 3109, 2940, 2794, 1631, 1595, 1498, 1372, 1295, 1266, 1161, 1131, 1001, 833, 792, 678, 580; ^{1}H-NMR (ppm): δ 2.32 (s, 3H, N-$\underline{CH_3}$), 2.36 - 2.48 (bs, 4H, piperazine), 3.46 - 3.80 (bs, 4H, piperazine), 3.82 (s, 3H, O$\underline{CH_3}$), 6.66 - 6.67 (d, 1H, J = 4.0 Hz, ArH), 6.87 - 6.89 (m, 2H, ArH), 7.33 - 7.356 (m, 1H, ArH), 7.58 - 7.61 (m, 2H, ArH), 7.79 - 7.81 (m, 2H, ArH), 7.99 - 8.01 (s, 1H, ArH); Mass (m/z): 414.4 (M+1).

[1-(4-Fluoro-benzenesulfonyl)-*1H*-indol-5-yl]-(4-methyl-piperazin-1-yl)-methanone (7h, R = CH_3, R_1 = 4 – F).
Purity (HPLC): 97.17 %, Yield: 73%, MR (^oC): 143 - 153; IR spectra (cm^{-1}): 3108, 2945, 2796, 1628, 1589, 1494, 1436, 1372, 1296, 1238, 1161, 1131, 994, 844, 780, 734, 679, 539; ^{1}H-NMR (ppm): δ 2.32 (s, 3H, N-$\underline{CH_3}$), 2.35 - 2.36 (bs, 4H, piperazine), 3.47 - 3.79 (bs, 4H, piperazine), 6.69 - 6.70 (d, 1H, J = 4.0 Hz, ArH), 7.10 - 7.14 (m, 2H, ArH), 7.36 - 7.38 (m, 1H, ArH), 7.59 - 7.60 (m, 2H, ArH), 7.87 - 7.90 (m, 2H, ArH), 7.99 - 8.01 (s, 1H, ArH); Mass (m/z): 402.4 (M+1).

(4-Ethyl-piperazin-1-yl)-[1-(4-fluoro-benzenesulfonyl)-*1H*-indol-5-yl]-methanone (7i, R = C_2H_5, R_1 = 4 – F).
Purity (HPLC): 99.28 %, Yield: 66 %, Syrupy mass, IR spectra (cm^{-1}): 3459, 3105, 2973, 2814, 1628, 1591, 1494, 1438, 1377, 1292, 1242, 1158, 1130, 1016, 836, 751, 679, 539; ^{1}H-NMR (ppm): δ 1.08 - 1.12 (t, 3H, $CH_2\underline{CH_3}$), 2.45 - 2.54 (bs, 4H, piperazine, q, 2H, $\underline{CH_2}CH_3$), 3.48 - 3.82 (bs, 4H, piperazine), 6.69 - 6.70 (d, 1H, J = 4.0 Hz, ArH), 7.10 - 7.14 (m, 2H, ArH), 7.36 - 7.38 (m, 1H, ArH), 7.59 - 7.60 (m, 2H, ArH), 7.87 - 7.90 (m, 2H, ArH), 7.99 - 8.01 (s, 1H, ArH); Mass (m/z): 416.5 (M+1).

[1-(4-Bromo-benzenesulfonyl)-*1H*-indol-5-yl]-(4-ethyl-piperazin-1-yl)-methanone (7j, R = C_2H_5, R_1 = 4 – Br).
Purity (HPLC): 96.03 %, Yield: 63 %, Syrupy mass, ^{1}H-NMR (ppm): δ 1.08 - 1.11 (t, 3H, $CH_2\underline{CH_3}$), 2.43 - 2.52 (bs, 4H, piperazine, q, 2H, $\underline{CH_2}CH_3$), 3.48 - 3.85 (bs, 4H, piperazine), 6.70 - 6.71 (d, 1H, J = 4.0 Hz, ArH), 7.36 - 7.38 (m, 1H, ArH), 7.57 - 7.60 (m, 4H, ArH), 7.70 - 7.72 (m, 2H, ArH), 7.97 - 7.99 (s, 1H, ArH); Mass (m/z): 476.2 (M+1).

(4-Ethyl-piperazin-1-yl)-[1-(4-isopropyl-benzenesulfonyl)-*1H*-indol-5-yl]-methanone (7k, R = C_2H_5, R_1 = 4 – iPr).
Purity (HPLC): 98.24 %, Yield: 74 %, Syrupy mass, ^{1}H-NMR (ppm): δ 1.07 - 1.11 (t, 3H, $CH_2\underline{CH_3}$), 1.18 - 1.20 (d, 6H, $CH(\underline{CH_3})_2$), 2.38 - 2.52 (bs, 4H, piperazine, q, 2H, $\underline{CH_2}CH_3$), 2.88 - 2.92 (sept, 1H, $\underline{CH}(CH_3)_2$), 3.48 - 3.83 (bs, 4H, piperazine), 6.67 - 6.68 (d, 1H, J = 4.0 Hz, ArH), 7.27 - 7.29(m, 2H, ArH), 7.34 - 7.36 (m, 1H, ArH), 7.58 - 7.62 (m, 2H, ArH), 7.76 - 7.78 (m, 2H, ArH), 8.0 - 8.02 (s, 1H, ArH); Mass (m/z): 440.3 (M+1).

(4-Ethyl-piperazin-1-yl)-[1-(toluene-4-sulfonyl)-*1H*-indol-5-yl]-methanone (7l, R = C_2H_5, R_1 = 4 – CH_3).
Yield: 76 %, Syrupy mass, IR spectra (cm^{-1}): 3452, 2974, 2814, 1631, 1531, 1438, 1373, 1291, 1173, 1131, 1016, 786, 752, 675, 540;^{1}H-NMR (ppm): δ 1.10 - 1.14 (t, 3H, $CH_2\underline{CH_3}$), 2.35 (s, 3H, ArH-CH_3), 2.50 - 2.60 (bs, 4H, piperazine, q, 2H, $\underline{CH_2}CH_3$), 3.48 - 3.83 (bs, 4H, piperazine), 6.67 - 6.68 (d, 1H, J = 4.0 Hz, ArH), 7.22 - 7.27 (m, 2H, ArH), 7.33 - 7.36 (m, 1H, ArH), 7.58 - 7.62 (m, 2H, ArH), 7.73 - 7.76 (m, 2H, ArH), 7.99 - 8.01 (s, 1H, ArH).

(4-Ethyl-piperazin-1-yl)-[1-(3-trifluoromethyl-benzenesulfonyl)-*1H*-indol-5-yl]-methanone (7m, R = C_2H_5, R_1 = 3 - CF_3).
Purity (HPLC): 98.62 %, Yield: 64 %, Syrupy mass, IR spectra (cm^{-1}): 3452, 2975, 2816, 1627, 1534, 1438, 1381, 1326, 1291, 1179, 1134, 1016, 822, 752, 693, 570; ^{1}H-NMR (ppm): δ 1.09 - 1.13 (t, 3H, $CH_2\underline{CH_3}$), 2.47 - 2.58 (bs, 4H, piperazine, q, 2H, $\underline{CH_2}CH_3$), 3.48 - 3.83 (bs, 4H, piperazine), 6.73 - 6.74 (d, 1H, J = 4.0 Hz, ArH), 7.38 - 7.40 (m, 1H, ArH), 7.59 - 7.63 (m, 3H, ArH), 7.81 - 7.83 (m, 1H, ArH), 8.0 - 8.02 (m, 2H, ArH), 8.15 (s, 1H, ArH).

RESULTS AND DISCUSSION

The starting material **1** was reacted with methanol in presence of sulfuric acid to obtain the ester intermediate **2 (Scheme 1).** The peaks at 1731 cm^{-1} for ester carbonyl and 1519 cm^{-1} for nitro group stretching in IR spectrum confirmed the formation of the ester compound. The chemical shift values at 2.63 (s, 3H, Ar$\underline{CH_3}$), 3.97 (s, 3H, O$\underline{CH_3}$), 7.96 - 8.03 (m, 3H, ArH) in ^{1}H-NMR spectrum confirm the structure of the product.

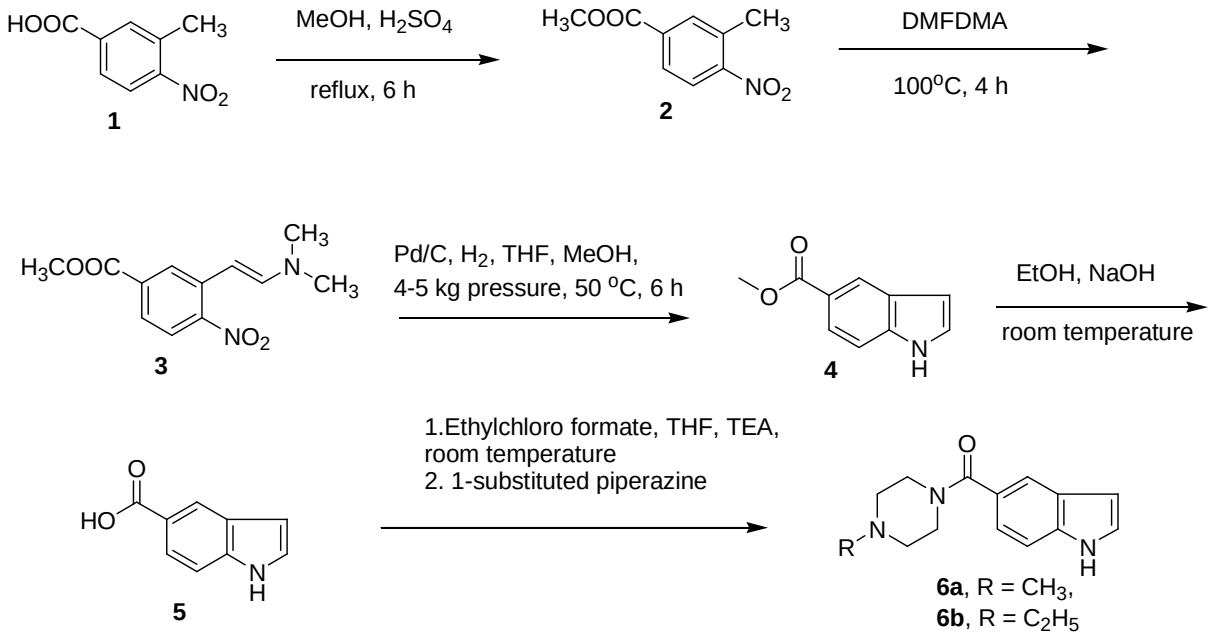
The intermediate **2** was reacted with DMFDMA to obtain the intermediate styrene derivative **3 (Scheme 1).** The peak at 1720 cm^{-1} in IR spectrum confirms the presence of ester carbonyl. The chemical shift values at δ 2.94 - 2.95 (s, 6H, N $\underline{(CH_3)_2}$), 3.95 (s, 3H, O$\underline{CH_3}$), 5.76 - 5.80 (d, 1H, styrene 1$\underline{H}$), 7.07 - 7.11 (d, 1H, styrene 1$\underline{H}$), 7.53 - 7.56 (m, 1H, ArH), 7.82 - 7.84 (d, 1H, J = 8.0 Hz, ArH), 8.14 (s, 1H, ArH) in ^{1}H-NMR spectrum confirms the structure of the intermediate **3**.

The intermediate styrene derivative **3** was cyclized under reductive cyclization conditions, using hydrogen gas (5 Kg pressure) in presence of 10% Pd/C catalyst in an autoclave to obtain the

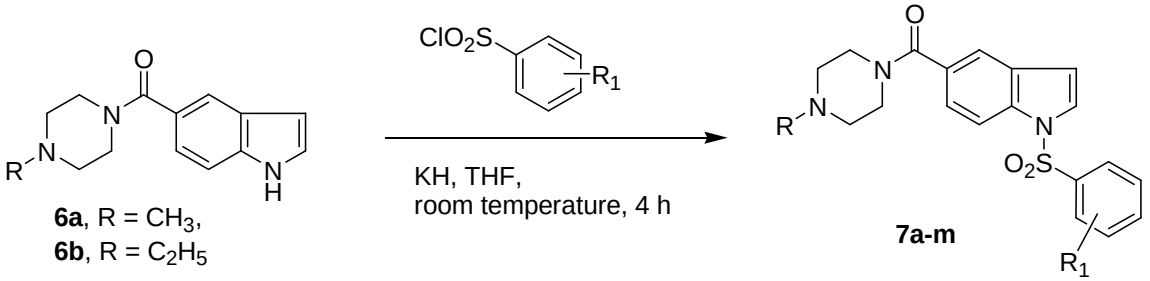
intermediate **4.** IR spectrum showed the ester carbonyl peak at 1696 cm^{-1} and indole NH peak at 3318 cm^{-1}. The chemical shift values at 3.94 (s, 3H, O$\underline{CH_3}$), 6.67 (s, 1H, ArH), 7.27 - 7.30 (d, 1H, ArH), 7.41 - 7.43 (d, 1H, J = 8.0 Hz, ArH), 7.91 - 7.94 (d, 1H, ArH), 8.38 (bs, 1H, N$\underline{H}$), 8.43 (s, 1H, ArH) in ^{1}H-NMR spectrum confirmed the structure of the intermediate **4**.

The intermediate **4** was hydrolyzed under basic condition to obtain the intermediate **5**. IR spectrum showed the acid carbonyl peak at 1664 cm^{-1} and indole NH peak at 3357 cm^{-1}. The chemical shift values at 6.56 (s, 1H, ArH), 7.42 - 7.44 (m, 2H, ArH), 7.69 - 7.71 (m, 1H, ArH), 8.23 - (s, 1H, ArH), 11.4 (bs, 1H, N$\underline{H}$), 12.3 (bs, 1H, COO$\underline{H}$) in ^{1}H-NMR spectrum confirmed the structure of the intermediate **5**.

The intermediate **5** was reacted with ethylchloroformate to form an anhydride derivative which was in-situ reacted with N-methyl piperazine to obtain the intermediate **6a**. In IR spectrum amide peak was observed at 1606 cm^{-1} and NH peak was observed at 3422 cm^{-1}. The chemical shift values in ^{1}H-NMR spectrum at δ 2.34 (s, 3H, N-$\underline{CH_3}$), 2.39 - 2.50 (bs, 4H, piperazine), 3.70 (bs, 4H, piperazine), 6.55 - 6.56 (d, 1H, J = 4.0 Hz, ArH), 7.21 - 7.27 (m, 2H, ArH), 7.31 - 7.33 (d, 1H, J = 8 Hz, ArH), 7.72 (s, 1H, ArH), 8.90 (bs, 1H, N$\underline{H}$) confirmed the structure of the product. The [M+1] peak at 244.3 amu in mass spectrum confirmed the molecular weight of the intermediate.



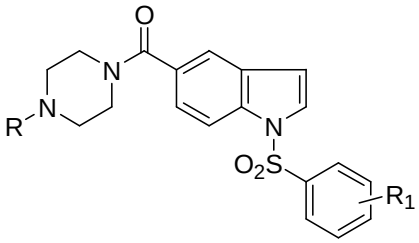
Scheme – 1



Scheme - 2

The intermediate **6a** was then reacted with 3-trifluoromethyl benzene sulfonylchloride to obtain the compound **7a** (**Scheme 2**). In IR spectra (cm^{-1}): carbonyl group was present at 1632 cm^{-1}. The chemical shift values at δ 2.32 (s, 3H, N-$\underline{CH_3}$), 2.39 - 2.49 (bs, 4H, piperazine), 3.39 - 3.81 (bs, 4H, piperazine), 6.73 - 6.74 (d, 1H, J = 4.0 Hz, ArH), 7.38 - 7.40 (m, 1H, ArH), 7.59 - 7.64 (m, 3H, ArH), 7.81 - 7.83 (m, 1H, ArH), 8.0 - 8.36 (m, 2H, ArH), 8.51 (s, 1H, ArH) in ^{1}H-NMR spectrum confirmed the structure of the compound **7a.** The [M+1] peak at 452.2 amu in mass spectrum confirmed the molecular weight of the compound.

Table – I: 5-HT_6 receptor binding data



Compound	R	R_1	5-HT_6R % Inhibition (h) at 1µM concentration*
7a	CH_3	3 – CF_3	50.02
7b	CH_3	H	42.75
7c	CH_3	4 – iPr	47.18
7d	CH_3	4 – CH_3	55.13
7e	CH_3	4 – Br	58.36
7f	CH_3	2, 3, 5 - tri Cl	61.25
7g	CH_3	4 – OCH_3	45.91
7h	CH_3	4-F	52.41
7i	C_2H_5	4 – F	51.00
7j	C_2H_5	4 – Br	60.05
7k	C_2H_5	4 – iPr	45.85
7l	C_2H_5	4 – CH_3	53.11
7m	C_2H_5	3 – CF_3	43.98

******* *the data represents average of two determinations.*

CONCLUSION

In conclusion, we have prepared and characterized a series of (1-substituted benzenesulfonyl-1H-indol-5-yl)-(4-substitutedpiperazin-1-yl)-methanone derivatives **7a-m** and tested for their in-*vitro* activity towards 5-HT_6 receptors. These derivatives were found to be moderately potent towards

5-HT_6 receptors (% inhibition at human 5-HT_6R are given in the Table - I). Further efforts are ongoing to modify the structure / substituents so that we can improve upon the *in-vitro* potency of the series.

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