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Design, synthesis and biological screening of N_1-arylsulfonyl (*1H*-indole-2-yl)-1-(piperazinyl) methanone derivatives as 5-HT_6 receptor ligands: Part I

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ABSTRACT

The usefulness of 5-HT_6 antagonists in the treatment of cognitive disorders and more recently in obesity and feeding disorders is well documented. Keeping in mind the minimum pharmacophoric requirement needed for the 5-HT_6 receptor binding, a new series of N_1-arylsulfonyl (1H-indole-2-yl)-1-(piperazinyl) methanone derivatives were designed, synthesized and tested for their in-vitro affinity towards the 5-HT_6 receptor.

Key words: N_1-arylsulfonyl (*1H*-indole-2-yl)-1-(piperazinyl) methanone derivatives, serotonin, 5-HT_6 receptor, *in-vitro* affinity.

INTRODUCTION

At least 15 distinct human serotonin (5-HT) receptors have been cloned which are divided into seven main classes (5-HT_{1-7}). 5-HT_6 receptor belongs to G-protein receptor and is positively coupled to adenylate cyclase [1]. The intriguing distribution in the brain, together with its high affinity for a wide range of drugs used in the psychiatry, has stimulated significant research interest [2]. There has been increasing interest in the role of 5-HT_6 receptors in higher cognitive processes [2-3] such as memory and Alzheimer's disease. However, the newer literature [4] strongly indicates the possible role of 5-HT_6 antagonists in the obesity and feeding disorders.

Chemically diverse compounds like N-aryl Piperazines, aryl sulfonamides and N-arylsulfonyl substituted indoles have been reported as 5-HT_6 receptors ligands [2]. Selective 5-HT_6 antagonists from Roche (Ro 04-6790 and Ro 63-0563) and Smithkline Beecham (SB-357134 and SB-742757) have been reported and provide evidence supporting a role for 5-HT_6 receptor antagonists in cholinergic and glutaminergic neurotransmission [5-6]. MS-245 and PMDT [7] have also been reported as ligands for 5-HT_6 receptors.

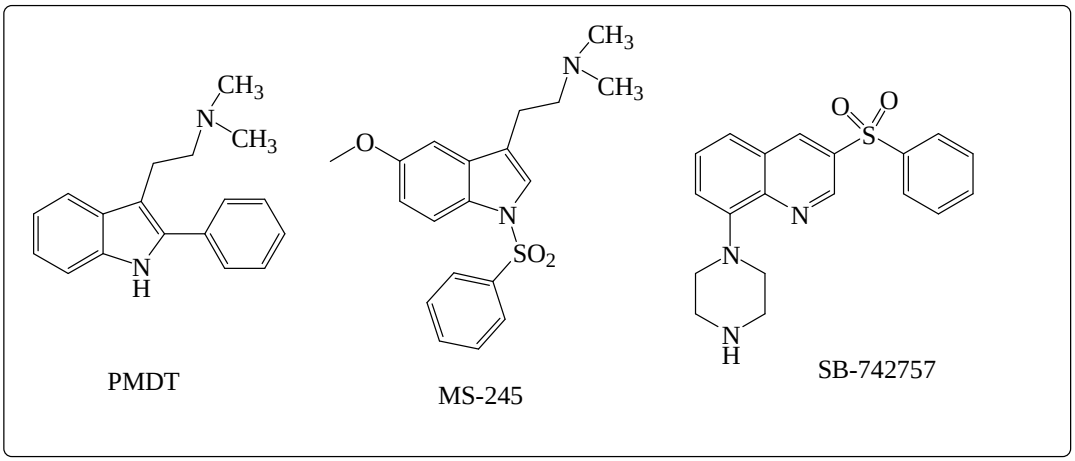


Fig. 1: Reported 5-HT$_6$ receptor ligands

Basic ionizable cyclic amines mainly piperazine motif and hydrogen bond acceptor sulfonamide or sulfone group with indole or other heterocyclic rings as a hydrophobic group are the necessary pharmacophoric requirement for the 5-HT$_6$R ligands.

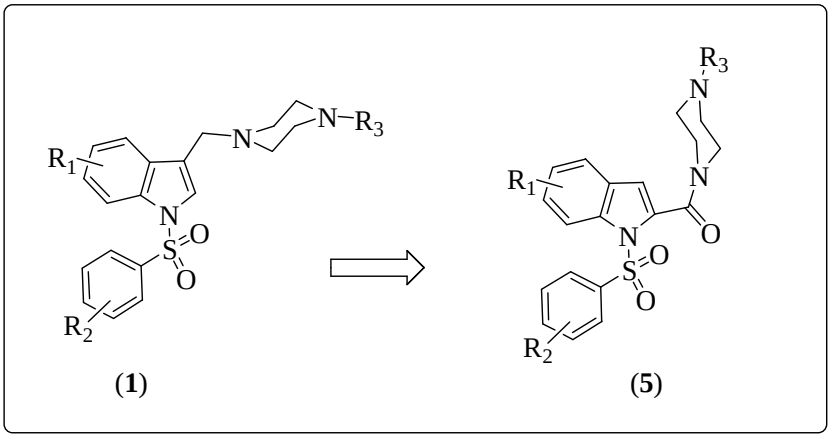


Fig. 2: Genesis of ligand

Earlier, we at Suven have reported N_1-arylsulfonyl-3-piperazinyl methyl indole derivatives **(1)** as potent and selective 5-HT$_6$ receptor ligands [8]. In continuation to that effort and to explore the SAR around those derivatives, we developed a new series of N_1-arylsulfonyl (*1H*-indole-2-yl)-1-(piperazinyl) methanone derivatives. Design, synthesis and biological evaluation of these new derivatives is described 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 derivatives (4)

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 ^{o}C 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.

***(5-Methoxy-1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (4a, 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-Ethoxy-1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (4b, R^1 = 5-OC_2H_5)*:** IR (cm^{-1}): 3260 (indole –NH stretching), 1591 (amidic carbonyl stretching), 1520, 1140; ^{1}H-NMR ($CDCl_3$): δ 1.42 - 1.45 (3H, t, -CH_3), 2.35 (3H, s, N-CH_3), 2.48 - 2.52 (4H, t, piperazinyl), 3.95 (4H, bs, piperazinyl), 4.03 - 4.08 (2H, quart, -OCH_2), 6.68 - 6.69 (1H, d, J = 2.56 Hz), 6.93 - 6.96 (1H, dd, J = 2.42 and 8.84 Hz), 7.04 - 7.046 (1H, d, J = 2.26 Hz), 7.30 - 7.32 (1H, d, J = 8.85 Hz), 9.26 (1H, bs, -NH); Mass (m/z): 288.4 $(M+H)^+$.

***(5-Methyl-1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (4c, R^1 = 5-CH_3)*:** IR (cm^{-1}): 3245 (indole –NH stretching), 1594 (amidic carbonyl stretching), 1522, 1141; ^{1}H-NMR ($CDCl_3$): δ 2.32 (3H, s, N-CH_3), 2.34 (3H, s, -CH_3), 2.46 - 2.51 (4H, t, piperazinyl -), 3.96 (4H, bs, piperazinyl -), 6.68 - 6.69 (1H, d, J = 1.44 Hz), 7.08 - 7.11 (1H, dd, J = 1.32, 8.4 Hz), 7.30 - 7.32 (1H, d, J = 8.36 Hz), 7.40 - 7.402 (1H, d, J = 1.32 Hz), 9.58 (1H, bs, -NH); Mass (m/z): 258.1 $(M+H)^+$.

***(5-Thiomethyl-1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (4d, R^1 = 5-SCH_3)*:** IR (cm^{-1}): 3265 (indole –NH stretching), 1593 (amidic carbonyl stretching), 1528, 1141; ^{1}H-NMR ($CDCl_3$): 2.35 (3H, s, N-CH_3), 2.50 - 2.52 (7H, m, piperazinyl and -S-Me), 3.95 (4H, bs, piperazinyl), 6.70 - 6.71 (1H, d, J = 1.44 Hz), 7.27 - 7.30 (1H, dd, J = 1.76 and 8.52 Hz), 7.35 - 7.37 (1H, d, J = 8.68 Hz), 7.61 (1H, d, J = 0.72 Hz), 9.29 (1H, bs, -NH); Mass (m/z): 290.4 $(M+H)^+$.

***(5-Isopropyl-1H-indol-2-yl)-(4-methylpiperazin-1-yl) methanone (4e, R^1 = 5-iPr)*:** IR (cm^{-1}): 3249 (indole –NH stretching), 1593 (amidic carbonyl stretching), 1522, 1135; ^{1}H-NMR ($CDCl_3$): 1.29 - 1.30 (6H, t, -isopropyl, J = 6.87 Hz), 2.34 (3H, s, N-CH_3), 2.48 - 2.50 (4H, t, piperazinyl), 2.96 - 3.03 (1H, sept., -isopropyl), 3.94 (4H, bs, piperazinyl), 6.725 - 6.728 (1H, d, J = 1.29 Hz), 7.17 - 7.20 (1H, dd, J = 1.60 and 8.48 Hz), 7.34 - 7.36 (1H, d, J = 8.49 Hz), 7.47 – 7.475 (1H, d, J = 1.21 Hz), 9.12 (1H, bs, -NH); Mass (m/z): 286.1 $(M+H)^+$.

2.3 General procedure for (1-Arylsulfonyl-*1H*-indol-2-yl)-(4-methylpiperazin-1-yl)-methanone derivatives (5)

To a stirred solution of sodium hydride (0.9 mmole, 50 % suspension in mineral oil) in 10 mL THF was added a solution of **4** (0.75 mmole) dissolved in 3 mL of THF under nitrogen atmosphere at 25 - 30 ^{o}C. The mass was further stirred for 45 min. A solution of substituted benzenesulfonyl chloride (1.05 mmole) in 3 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 by 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 25 mL) and dried over anhydrous magnesium sulfate. The organic volatiles were removed under vacuum to obtain the title compound. The product was purified by flash chromatography using 1% TEA in ethyl acetate.

***4'-Fluorophenyl sulfonyl-5-methoxy indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5a, R^1 = 5-OCH_3, R^2 = 4'-F)*:** MR (^{o}C): 77 - 87.4; IR (KBr, cm^{-1}): 2939, 2796, 1639 (amidic carbonyl stretching), 1431, 1375 (SO_2 stretching), 1163 (SO_2 stretching), 1088; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, N-CH_3), 2.46 - 2.55 (4H, bs, piperazinyl), 3.45 (2H, bs, piperazinyl), 3.80 (3H, s, -OCH_3), 3.86 (2H, bs, piperazinyl), 6.62 (1H, s), 6.93 - 6.97 (2H, m), 7.07 - 7.12 (2H, m), 7.87 - 7.89 (1H, d, J = 8.8 Hz), 8.11 - 8.14 (2H, m); Mass (m/z): 432.5 $[M+H]^+$.

5-Methoxy indole phenylsulfonyl -2yl-(4-methylpiperazinyl-1-yl)methanone (5b, R^1 = 5-OCH_3, R^2 = H) **:** Oily mass; IR (KBr, cm^{-1}): 2963, 1634 (amidic carbonyl stretching), 1444, 1372 (SO_2 stretching), 1177 (SO_2 stretching), 1091; ^{1}H-NMR ($CDCl_3$): δ 2.36 (3H, s, N-CH_3), 2.49 - 2.57 (4H, bs, piperazinyl), 3.47 (2H, bs, piperazinyl), 3.84 (3H, s, -OCH_3), 3.83 (2H, bs, piperazinyl), 6.16 (1H, s), 6.93 - 6.96 (2H, m), 7.41 - 7.75 (3H, m), 7.88 - 7.91 (1H, d, J = 8.84 Hz), 8.07 - 8.09 (2H, m); Mass (m/z): 414.0 $[M+H]^+$.

3'Trifuloromethyl phenylsulfonyl-5-methoxy indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5c, R^1 = O5-OCH_3, R^2 = 3'-CF_3) **:** Oily mass; IR (KBr, cm^{-1}): 2940, 2802, 1628 (amidic carbonyl stretching), 1450, 1378 (SO_2 stretching), 1142 (SO_2 stretching), 1055; ^{1}H-NMR ($CDCl_3$): δ 2.36 (3H, s, N-CH_3), 2.48 - 2.58 (4H, bs, piperazinyl), 3.47 (2H, bs, piperazinyl), 3.80 (3H, s, -OCH_3), 3.87 (2H, bs, piperazinyl), 6.63 (1H, s), 6.94 - 6.99 (2H, m), 7.58 - 7.62 (1H, t, J = 7.92 Hz), 7.76 - 7.78 (1H, d, J = 7.84 Hz), 7.88 - 7.90 (1H, d, J = 9.12 Hz), 8.33 - 8.39 (2H, m); Mass (m/z): 482.1 $[M+H]^+$.

4'-Bromophenylsulfonyl-5-methoxy indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5d, R^1 = 5-OCH_3, R^2 = 4'-Br)**:** Oily mass; IR (KBr, cm^{-1}): 2939, 1639 (amidic carbonyl stretching), 1453, 1376 (SO_2 stretching), 1164 (SO_2 stretching), 1088; ^{1}H-NMR ($CDCl_3$): δ 2.34 (3H, s, N-CH_3), 2.45 - 2.54 (4H, bs, piperazinyl), 3.44 (2H, bs, piperazinyl), 3.80 (3H, s, -OCH_3), 3.85 (2H, bs, piperazinyl), 6.63 (1H, s), 6.94 - 6.99 (2H, m), 7.58 - 7.62 (1H, t, J = 7.92 Hz), 7.76 - 7.78 (1H, d, J = 7.84 Hz), 7.88 - 7.90 (1H, d, J = 9.12 Hz), 8.33 - 8.39 (2H, m); Mass (m/z): 492.3, 494.3 $[M+H]^+$.

4'-Isopropylphenylsulfonyl-5-methoxy indole-2yl-(4-methylpiperazinyl-1- yl) methanone (5e, R^1 = 5-OCH_3, R^2 = 4'-iPr)**:** MR (^{o}C): 77.4 - 87.5; IR (KBr, cm^{-1}): 2962, 1642 (amidic carbonyl stretching), 1453, 1371 (SO_2 stretching), 1165 (SO_2 stretching), 1055; ^{1}H-NMR ($CDCl_3$): δ 1.16 - 1.18 (6H, d, J = 6.93 Hz), 2.34 (3H, s, N-CH_3), 2.43 - 2.53 (4H, bs, piperazinyl), 2.86 - 2.89 (1H, sept, -isopropyl) 3.45 (2H, bs, piperazinyl), 3.80 (3H, s, -OCH_3), 3.87 (2H, bs, piperazinyl), 6.59 (1H, s), 6.93 - 6.97 (2H, m), 7.26 - 7.28 (2H, m), 7.91- 7.93 (1H, d, J = 8.80 Hz), 7.98 - 8.00 (2H, m), 8.33 - 8.39 (2H, m); Mass (m/z): 456.4 $[M+H]^+$.

4'-Methoxyphenylsulfonyl-5-methoxy indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5f, R^1 = 5-OCH_3, R^2 = 4'-OMe)**:** Oily mass; IR (KBr, cm^{-1}): 2940, 1641 (amidic carbonyl stretching), 1454, 1371 (SO_2 stretching), 1164 (SO_2 stretching), 1055; ^{1}H-NMR ($CDCl_3$): δ 2.34 (3H, s, N-CH_3), 2.51 - 2.55 (4H, bs, piperazinyl), 3.44 (2H, bs, piperazinyl), 3.77 (3H, s, -OCH_3), 3.85 (3H, s, -OCH_3), 3.86 (2H, bs, piperazinyl), 6.59 (1H, s), 6.85 - 6.96 (4H, m), 7.89 - 7.91 (1H, d, J = 8.78 Hz), 7.99 - 8.02 (2H, m); Mass (m/z): 444.5 $[M+H]^+$.

5-Methyl indole phenyl sulfonyl -2yl-(4-methylpiperazinyl-1-yl)methanone (5g, R^1 = 5-CH_3, R^2 = H)**:** Oily mass; IR (KBr, cm^{-1}): 2938, 1641 (amidic carbonyl stretching), 1448, 1371 (SO_2 stretching), 1179 (SO_2 stretching), 1090; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, N-CH_3), 2.38 (3H, s, -CH_3), 2.41 - 2.56 (4H, bs, piperazinyl), 3.46 (2H, bs, piperazinyl), 3.87 (2H, bs, piperazinyl), 6.61 (1H, s), 7.14 - 7.16 (1H, dd, J = 1.32, 8.68 Hz), 7.26 - 7.28 (1H, d, J = 8.72 Hz), 7.41 - 7.45 (2H, m), 7.49 - 7.51 (1H, m), 7.87 - 7.89 (1H, d, J = 8.68 Hz), 8.09 - 8.12 (1H, m); Mass (m/z): 398.5 $[M+H]^+$.

4'-Bromoyphenylsulfonyl-5-methyl indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5h, R^1 = 5- CH_3, R^2 = 4' -Br)**:** MR (^{o}C): 76.8 - 79.7; IR (KBr, cm^{-1}): 2938, 2796, 1640 (amidic carbonyl stretching), 1439, 1375 (SO_2 stretching), 1182 (SO_2 stretching), 1089; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, N-CH_3), 2.39 (3H, s, -CH_3), 2.44 - 2.55 (4H, bs, piperazinyl), 3.44 (2H, bs, piperazinyl), 3.86 (2H, bs, piperazinyl), 6.61 (1H, s), 7.15 - 7.18 (1H, dd, J = 1.44, 8.64 Hz), 7.26 - 7.29 (1H, m), 7.55 - 7.58 (2H, dd, J = 1.84, 6.8 Hz), 7.84 - 7.87 (1H, d, J = 8.56 Hz), 7.95 - 7.98 (1H, m); Mass (m/z): 475.9, 478 $[M+H]^+$.

3'-Trifluoromethylphenylsulfonyl-5-methyl indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5i, R^1 = 5- CH_3, R^2 = 3' - CF_3) **:** Oily mass; IR (KBr, cm^{-1}): 2920, 2798, 1640 (amidic carbonyl stretching), 1438, 1380 (SO_2 stretching), 1326, 1180 (SO_2 stretching), 1138; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, N-CH_3), 2.39 (3H, s, -CH_3), 2.46 - 2.57 (4H, bs, piperazinyl), 3.47 (2H, bs, piperazinyl), 3.87 (2H, bs, piperazinyl), 6.62 (1H, s), 7.17 - 7.20 (1H, dd, J = 1.4, 8.56 Hz), 7.26 - 7.30 (1H, m), 7.58 - 7.62 (1H, t, J = 7.88 Hz), 7.76 - 7.78 (1H, d, J = 8.54 Hz), 7.85 - 7.87(1H, d, J = 8.56 Hz), 8.36 - 8.41 (2H, m); Mass (m/z): 466.3 $[M+H]^+$.

***4'-Fluorophenylsulfonyl-5-methyl indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5j, R^1 = 5- CH_3, R^2 = 4'-F)*:** Oily mass; IR (KBr, cm^{-1}): 2921, 1641 (amidic carbonyl stretching), 1440, 1376 (SO_2 stretching), 1182 (SO_2 stretching), 1089; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, N-CH_3), 2.39 (3H, s, -CH_3), 2.45 - 2.55 (4H, bs, piperazinyl), 3.45 (2H, bs, piperazinyl), 3.86 (2H, bs, piperazinyl), 6.61 (1H, s), 7.04 - 7.17 (3H, m), 7.29 (1H, d, J = 0.64 Hz), 7.85 - 7.87 (1H, d, J = 8.52 Hz), 8.13 - 8.16 (2H, m); Mass (m/z): 416.5 $[M+H]^+$.

***4'-Fluorophenylsulfonyl-5-thiomethyl indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5k, R^1 = 5-SCH_3, R^2 = 4'- F)*:** Oily mass; IR (KBr, cm^{-1}): 2963, 1641 (amidic carbonyl stretching), 1436, 1377 (SO_2 stretching), 1261, 1177 (SO_2 stretching), 1088; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, N-CH_3), 2.49 (3H, s, SCH_3), 2.51 - 2.55 (4H, bs, piperazinyl), 3.27 - 3.29 (2H, bs, piperazinyl), 3.45 - 3.49 (2H, bs, piperazinyl-), 6.61 (1H, s), 7.10 - 7.14 (2H, m), 7.26 - 7.29 (1H, m), 7.39(1H, d, J = 1.68 Hz), 8.14 - 8.17 (1H, d, J = 1.68 Hz); Mass (m/z): 448.2 $[M+H]^+$.

***5- Thiomethylphenylsulfonyl indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5l, R^1 = 5-SCH_3, R^2 = H)*:** Oily mass; IR (KBr, cm^{-1}): 2963, 2797, 1641 (amidic carbonyl stretching), 1437, 1374 (SO_2 stretching), 1261, 1173 (SO_2 stretching), 1091; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, N-CH_3), 2.48 (3H, s, SCH_3), 2.52 - 2.56 (4H, bs, piperazinyl), 3.46 - 3.49 (2H, bs, piperazinyl), 3.87 (2H, bs, piperazinyl), 6.60 (1H, s), 7.26 - 7.38 (2H, m), 7.43 - 7.54 (3H, m), 7.90 - 7.93 (1H, d, J = 8.76 Hz), 8.10 - 8.12 (2H, m); Mass (m/z): 430.1 $[M+H]^+$.

***3'-Trifluoromethylphenylsulfonyl-5- thiomethyl indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5m, R^1 = 5-SCH_3, R^2 = 3'- CF_3)* :** Oily mass; IR (KBr, cm^{-1}): 2963, 1632 (amidic carbonyl stretching), 1436, 1378 (SO_2 stretching), 1262, 1173 (SO_2 stretching), 1052; ^{1}H-NMR ($CDCl_3$): δ 2.35 (3H, s, N-CH_3), 2.49 (3H, s, SCH_3), 2.52 - 2.57 (4H, bs, piperazinyl), 3.47 (2H, bs, piperazinyl), 3.87 (2H, bs, piperazinyl), 6.62 (1H, s), 7.28 - 7.31 (1H, dd, J = 1.84, 8.8 Hz), 7.39(1H, d, J = 1.72 Hz), 7.60 - 7.64 (1H, t, J = 7.92 Hz), 7.79 - 7.81 (1H, d, J = 7.84 Hz), 7.89 - 7.91 (1H, d, J = 8.8 Hz), 8.36 - 8.42 (2H, m); Mass (m/z): 498.2 $[M+H]^+$.

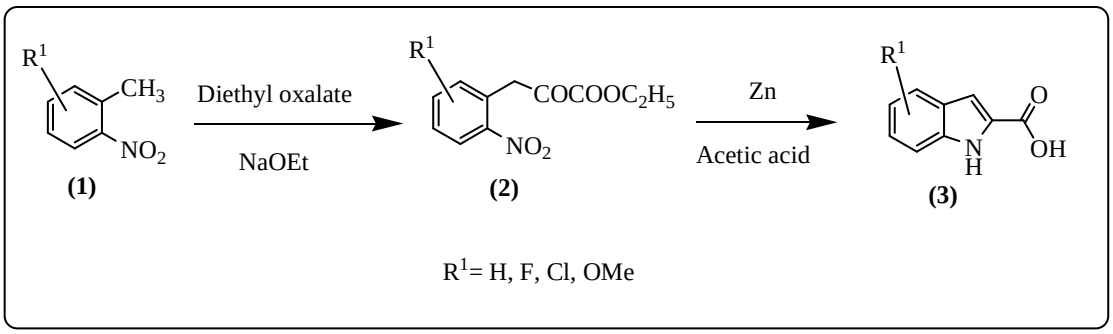
***3'-Trifluoromethylphenylsulfonyl-5-isopropyl indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5n, R^1 = 5-iPr, R^2 = 3'- CF_3)* :** Oily mass; IR (KBr, cm^{-1}): 2961, 1644 (amidic carbonyl stretching), 1435, 1380 (SO_2 stretching), 1264, 1172 (SO_2 stretching), 1073; ^{1}H-NMR ($CDCl_3$): δ 1.24 - 1.25 (6H, d, J = 4.28 Hz), 2.35 (3H, s, N-CH_3), 2.45 (2H, bs, piperazinyl), 2.54 - 2.56 (2H, t, piperazinyl), 2.93 - 3.00 (1H, sept, isopropyl), 3.48 (2H, bs, piperazinyl), 3.87 (2H, bs, piperazinyl), 6.64 (1H, s), 7.24 - 7.26 (1H, m), 7.35(1H, d, J = 1.36 Hz), 7.59 - 7.63 (1H, t, J = 7.92 Hz), 7.77 - 7.79 (1H, d, J = 7.84 Hz), 7.88 - 7.90 (1H, d, J = 8.8 Hz), 8.39 - 8.44 (2H, m); Mass (m/z): 493.9 $[M+H]^+$.

***4'-Fluorophenylsulfonyl-5-isopropyl indole-2yl-(4-methylpiperazinyl-1-yl)methanone (5o, R^1 = 5-iPr, R^2 = 4'- F)*:** Oily mass; IR (KBr, cm^{-1}): 2960, 1642 (amidic carbonyl stretching), 1445, 1377 (SO_2 stretching), 1264, 1188 (SO_2 stretching), 1089; ^{1}H-NMR ($CDCl_3$): δ 1.24 - 1.25 (6H, d, J = 4.28 Hz), 2.34 (3H, s, N-CH_3), 2.45 (2H, bs, piperazinyl), 2.51 - 2.55 (2H, t, piperazinyl), 2.92 – 2.99 (1H, sept, isopropyl), 3.46 (2H, bs, piperazinyl), 3.86 (2H, bs, piperazinyl), 6.62 (1H, s), 7.09 - 7.13 (1H, dd, J = 2.12, 8.52 Hz), 7.21 - 7.24 (1H, m), 7.34 - 7.35 (1H, t, J = 1.52 Hz), 7.87 - 7.90 (1H, d, J = 8.64 Hz), 8.16 - 8.20 (2H, m); Mass (m/z): 444.5 $[M+H]^+$.

***5-Ethoxy indole phenylsulfonyl -2yl-(4-methylpiperazinyl-1-yl)methanone (5p, R^1 = 5-OC_2H_5, R^2 = H)*:** Oily mass; IR (KBr, cm^{-1}): 2971, 2802, 1636 (amidic carbonyl stretching), 1453, 1364 (SO_2 stretching), 1177 (SO_2 stretching), 1090; ^{1}H-NMR ($CDCl_3$): δ 1.38 - 1.41 (3H, t, J = 7 Hz), 2.35 (3H, s, N-CH_3), 2.47 - 2.55 (4H, bs, piperazinyl), 3.46 (2H, bs, piperazinyl), 3.87 (2H, bs, piperazinyl), 3.97 - 4.03 (2H, quat, J = 6.96 Hz), 6.60 (1H, s), 6.91 - 6.95 (2H, m), 7.41 - 7.75 (3H, m), 7.88 - 7.91 (1H, d, J = 8.96 Hz), 8.07 - 8.09 (2H, m); Mass (m/z): 428.1 $[M+H]^+$.

RESULTS AND DISCUSSION

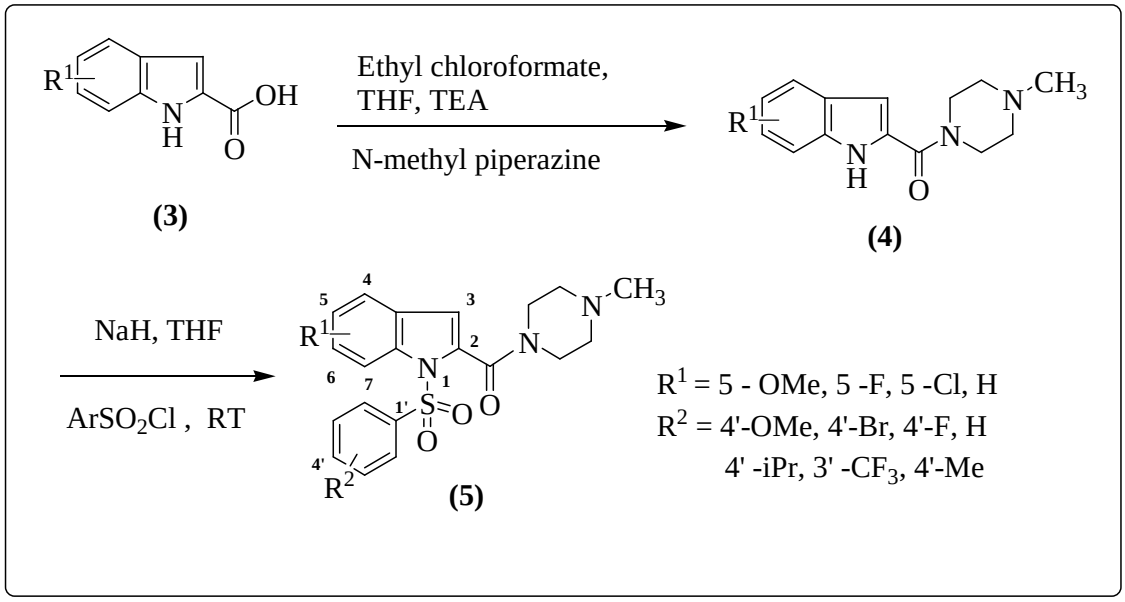
Various substituted indoles-2-carboxyate derivatives were synthesized using the Reissert indole synthesis [9-10] as per the scheme given below.



Scheme - 1

The substituted o-nitro toluene derivatives **(1)** were reacted with diethyl oxalate to give o-nitro phenylpyruvate derivatives **(2)** as a condensation product. In presence of Zn in acetic acid, the intermediate **2** gave various substituted indole-2-carboxylic acid derivatives **(3)** as the reductive cyclization product.

The general synthetic strategy used for the preparation of title **Compounds 5a-p** has been summarized in **Scheme 2**.



Scheme -2

Substituted indole 2-carboxylic acids **(3)** were reacted with ethyl chloro formate followed by N-methyl piperazine to obtain amide derivatives **(4)**. The structure of amide derivatives was confirmed by the spectral data. In IR spectrum, amide derivatives showed sharp peak in the range of 3258 - 3264 cm^{-1} due to indole NH stretching and peak at 1599 - 1610 cm^{-1} due to amidic carbonyl stretching. The mass spectra exhibited the $[M+H]^+$ peak as parent ion and $[M-100]^+$ peak due to loss of N-methyl piperazine group. 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.

These amide derivatives were further reacted with appropriate arylsulfonyl chloride in presence of base to obtain the targeted compounds **5a-p.** 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 [11] 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 - [1 µM]; Reference Compound was Methiothepin mesylate, Positive Control was Methiothepin mesylate.

The synthesized derivatives were further tested for their % inhibition at 1 µM concentration as per the protocol given above. To our surprise all the derivatives have shown less than 10 % inhibition towards 5-HT_6 receptor, indicating that these compounds either have very mild or no affinity for 5-HT_6 receptor.

CONCLUSION

In summary, the new series of N_1-arylsulfonyl(*1H*-indole-2-yl)-1-(piperazinyl) methanone derivatives were designed and synthesized to identify and map the pharmacophoric requirement needed for 5-HT_6 receptor binding. As the synthesized series of compounds have shown very mild affinity towards the 5-HT_6 receptor, indicating that amide functionality with one ionisable basic center at second position of indole nucleus is not advantageous for 5-HT_6 receptor binding. Further effort to improve upon the affinity by making both the piperazinyl nitrogen basic in nature is the subject matter of our subsequent communication.

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