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Design, synthesis and preliminary screening of novel 3-(2-*N*,*N*-dimethylaminoethylthio) indole derivatives as potential 5-HT$_6$ receptor ligands

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Abstract

The synthesis and potential 5-hydroxytryptamine$_6$ receptor (5-HT$_6$R) antagonist activity of a novel series of *N*-arylsulfonyl-3-(2-*N*,*N*-dimethylaminoethylthio) indoles has been reported. The molecular modeling, synthesis and *in-vitro* radioligand binding data of this series are discussed. The present article describes 37 derivatives of the title series. It was observed that the increased side-chain length with the insertion of a sulfur atom did not lead to the loss of binding affinity of these compounds, although the affinities were reduced. The compounds exhibited moderate affinity and selectivity to human 5-HT$_6$ receptors.

Keywords: *5-HT$_6$ receptor ligands, molecular modeling, SAR,* N-*aryl sulfonyl indoles, synthesis*

Introduction

Although the 5-hydroxytryptamine$_6$ receptor (5-HT$_6$R) is one of the most recently discovered member of the 5-HT and in general GPCR family, it has been subject to substantial research involving the molecular biology, biology and the medicinal chemistry. [1] The numerous possible applications that can be targeted through 5-HT$_6$R are now becoming apparent. 5-HT$_6$R, which is positively coupled to adenylate cyclase[2] is almost exclusively expressed in the central nervous system (CNS) [1,3]. This exclusive location of these receptors makes them the ideal target receptors for CNS drug development, since they are least likely to possess the peripheral side-effects. Most of the diseases involving 5-HT$_6$R are related to the CNS and therefore constitute a very important therapeutic class of compounds. The drugs acting on serotonergic systems are implicated in various psychotherapeutic conditions including manic syndromes, Schizophrenia, Alzheimer's disease, etc [2–4]. 5-HT$_6$ receptor has been implicated in the psychotic disorders, [5–8] affective disorders, [5,9,10] anxiety, [11–13] epilepsy [14] and potentially the regulation of food consumption. [15–18] However, the most compelling evidence suggests the role of these receptors is in normal as well as impaired cognitive function and dementia [17,19–21]. A recently published study has demonstrated the use of the partial agonist E-6837 in the treatment of obesity and eating disorders [19].

Various substituted tryptamines has been reported as the 5-HT$_6$R ligands [22]. Work at Roche and Glaxo Smithkline Beecham has resulted in identifying chemically diverse compounds that bind to 5-HT$_6$R i.e. Ro-04-6790, Ro-63-0563, SB-271046, SB-399885 and SB-357134 etc [3,22,23] Most of the earlier known compounds contain a dialkylaminoalkyl side-chain as an essential part of the pharmacophore. The tryptamine nucleus has been exhaustively explored for the development of ligands to serotonin receptors. However, the major class of compounds dominating the developmental pipelines today is aryl piperazines. Piperazine is

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used as a critical part of the pharmacophore. A basic amino functionality required for binding at the aspartate residue of the transmembrane domain III (TM-3) receptor is thus the terminal nitrogen of a diamine - piperazine. However, unlike the trend in the development of ligands for other GPCRs there has been no report of replacing the *N*,*N*-dimethylaminoethyl chain with the *N*,*N*-dimethylaminoethylthio- or *N*,*N*-dimethylaminoethoxy side-chains. Recently there has been an attempt to define the 3-dimentional pharmacophoric model for the requirements of the 5-HT$_6$ receptor antagonists [2].

We have reported a series of novel 3-substituted piperazinylmethyl indoles [24] and 3-(substituted) aminoalkoxy indole derivatives as potent 5-HT$_6$R antagonists [25]. The latter series of compounds exhibited potent antagonistic binding at the 5-HT$_6$R with the lead molecules having Ki in the range of 1–5 nM.

In continuation to our SAR studies to establish the role of the "oxygen" atom in the side chain with respect to activity we considered replacing it with an isosteric "sulfur" atom. Hence the major aim of the present study was to undertake the synthesis of *N*-arylsulfonyl-3-dimethylaminoethylthio-indole derivatives to explore the feasibility of an aminoalkylthio side-chain at C3 of indole as against the aminoalkoxy and aminoalkyl side-chains on the affinity at serotonin receptors.

Materials and methods

General considerations

Infra red spectra were recorded in 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. 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'. Various substituted indoles were synthesized in-house with the help of reported procedures[26] and were characterized thoroughly before using. Substituted benzene sulfonyl chlorides were synthesized in-house from the substituted benzene by chlorosulfonation or from the corresponding amines using the diazo intermediates.

Synthesis

*General procedure for the synthesis of the 1-((substituted) benzenesulfonyl)-3-dimethylaminoethylthio-1*H*-indoles, Compound I (7–32)*. The (*S*)-(Un(substituted)-3-indolyl)isothiourea hydroiodide salt (**2**, 0.0267 mol) was dissolved in alkaline solution (1.2 g NaOH in 20 mL ethanol). To the above reaction mixture, alcoholic solution of dimethylaminoethylchloride (0.0361 mol) previously neutralised with 1.5 g NaOH in 20 mL of ethanol was added. Additional alkali solution (1 g NaOH in 15 mL ethanol) was added and the reaction mass was refluxed for 35–40 min. After completion of the reaction (TLC), the reaction mixture was cooled and the solvent was distilled under reduced pressure. The residue was diluted with 100 mL of water and extracted with ethyl acetate (EtOAc) (3 × 50 mL). The combined organic layer was washed with brine solution, dried over sodium sulphate and concentrated under reduced pressure. The residue so obtained was purified by flash chromatography over silica gel using 1% triethylamine (TEA) in EtOAc to get intermediate **3**, which was identified by IR, NMR and mass spectral analyses.

To the ice cooled suspension of potassium hydride (0.0012 mol, washed with hexane before use), in tetrahydrofuran (THF) was added a solution of **3** (0.0008 mol) in THF over 15 min. Then the mixture was warmed to 25–30 °C and maintained for 2 h. To this mixture, a solution of appropriate benzenesulfonyl chloride in THF (0.0012 mol) was added slowly. After completion of the reaction (TLC), excess of THF was distilled off and the residue was diluted with ice water and extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with cold water (2 × 25 mL), dried over sodium sulfate and evaporated under reduced pressure at below 50 °C. The crude residue was purified by silica gel column chromatography using 30% methanol in EtOAc to obtain the title compounds I, which was identified by IR, NMR and mass spectral analyses.

*1-(2-Bromobenzenesulfonyl)-3-dimethylaminoethylthio-1*H*-indole (7)*. Brown coloured syrupy mass; IR (KBr, cm^{-1}): 2939, 1634, 1445, 1372, 1263, 1177, 741, 586; Mass (m/z): 439.2, 441.2 [M + H]$^+$; ^{1}H-NMR (ppm): 2.24 (6H, s, -N(CH$_3$)$_2$), 2.52–2.55 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.89–2.92 (2H, m, -SCH$_2$-), 7.26–7.30 (2H, m, C-4 and 4′-H), 7.4–7.52 (2H, m, C-5 and C-6), 7.64–7.68 (3H, m, 3′-H, 5′-H, 6′-H), 7.85 (1H, s, C-2), 8.18–8.20 (1H, dd, J = 7.9, 1.7 Hz, C-7); HRMS: [M + H]$^+$C$_{18}$H$_{20}$BrN$_2$O$_2$S$_2$ calc. 439.0194, found. 439.0189.

*1-(4-Fluorobenzenesulfonyl)-3-dimethylaminoethylthio-1*H*-indole (8)*. Light brown coloured sticky mass; IR (KBr, cm^{-1}): 2941, 1591, 1493, 1375, 1240, 1180, 837, 577; Mass (m/z): 379.3 [M + H]$^+$; ^{1}H-NMR (ppm): 2.23 (6H, s, -N(CH$_3$)$_2$), 2.47–2.51 (2H,

m, -C*H*$_2$N(CH$_3$)$_2$), 2.87–2.91 (2H, m, -SCH$_2$-), 7.09–7.13 (2H, m, 3′, 5′-H), 7.3–7.37 (2H, m, C-5 and C-6 indole), 7.56 (1H, s, C-2 indole), 7.6–7.64 (1H, d, J = 7.3, 0.6 Hz, C-4 indole), 7.88–7.92 (2H, m, 2′, 6′-H), 7.96–7.98 (1H, d, J = 8.2 Hz, C-7 indole); HRMS: [M + H]$^+$C$_{18}$H$_{20}$FN$_2$O$_2$S$_2$ calc. 379.0994, found. 379.0991.

*{2-[1-(2-Bromobenzenesulfonyl)-1*H*-indole-3-sulphinyl]ethyl}dimethylamine (9)*. Light brown coloured syrupy mass; IR (KBr, cm^{-1}): 2926, 1573, 1446, 1376, 1265, 1181, 741, 586; Mass (m/z): 455.1, 457.1 [M + H]$^+$; ^{1}H-NMR (ppm): 2.29 (6H, s, -N(CH$_3$)$_2$), 2.58–2.64 (1H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.84–2.87 (1H, m, C*H*$_2$N(CH$_3$)$_2$), 3.2–3.25 (1H, m, -SCH$_2$-), 3.35–3.4 (1H, m, -SCH$_2$-), 7.31–7.33 (2H, m, 4′-H, 5′-H), 7.47–7.56 (2H, m, C-5, C-6 indole), 7.68–7.70 (2H, m, C-4 indole, 3′-H), 7.83–7.88 (1H, m, 6′-H), 8.2 (1H, s, C-2 indole), 8.3–8.32 (1H, dd, J = 8.0, 1.6 Hz, C-7 indole); HRMS: [M + H]$^+$C$_{18}$H$_{20}$BrN$_2$O$_3$S$_2$ calc. 455.0093, found. 455.0085.

*1-(3-Trifluoromethylbenzenesulfonyl)-3-dimethylaminoethylthio-1*H*-indole (10)*. Light brown coloured crystalline product; M.R (°C): 53.6–56.0; IR (KBr, cm^{-1}): 2943, 1609, 1443, 1380, 1326, 1178, 728, 595; Mass (m/z): 429.1 [M + H]$^+$; ^{1}H-NMR (ppm): 2.2 (6H, s, -N(CH$_3$)$_2$), 2.48–2.52 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.88–2.95 (2H, m, -SCH$_2$-), 7.32–7.39 (2H, m, C-5, C-6), 7.56 (1H, s, C-2), 7.6–7.64 (2H, m, 4′-H, 5′-H), 7.79–7.82 (1H, bd, J = 8.2 Hz, C-4), 7.98–8.0 (1H, d, J = 8.0 Hz, C-7), 8.03–8.05 (1H, d, 6′-H), 8.16 (1H, bs, 2′-H); HRMS: [M + H]$^+$C$_{19}$H$_{20}$F$_3$N$_2$O$_2$S$_2$ calc. 429.0896, found. 429.0889.

*1-(Benzenesulfonyl)-3-dimethylaminoethylthio-1*H*-indole (11)*. Brown coloured syrupy mass; IR (KBr, cm^{-1}): 2938, 1604, 1446, 1372, 1265, 1175, 730, 594; Mass (m/z): 361.3 [M + H]$^+$; ^{1}H-NMR (ppm): 2.22 (6H, s, -N(CH$_3$)$_2$), 2.47–2.51 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.87–2.90 (2H, m, -SCH$_2$-), 7.27–7.7 (5H, m, 3′-H, 4′-H, 5′-H, C-5, C-6), 7.60 (1H, s, C-2), 7.62–7.64 (1H, d, J = 8.16 Hz, C-4), 7.87–7.89 (2H, m, 2′-H, 6′-H), 7.9–8.0 (1H, bd, J = 8.2 Hz, C-7); HRMS: [M + H]$^+$C$_{18}$H$_{21}$N$_2$O$_2$S$_2$ calc. 361.1093, found. 361.1088.

*1-(4-Methylbenzenesulfonyl)-3-dimethylaminoethylthio-1*H*-indole (12)*. Pale yellow coloured syrupy mass; IR (KBr, cm^{-1}): 2930, 1597, 1444, 1371, 1265, 1174, 711, 587; Mass (m/z): 375.3 [M + H]$^+$; ^{1}H-NMR (ppm): 2.22 (6H, s, -N(CH$_3$)$_2$), 2.34 (3H, s, 4′-CH$_3$), 2.46–2.50 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.85–2.89 (2H, m, -SCH$_2$-), 7.21–7.36 (4H, m, 3′-H, 5′-H, C-5, C-6), 7.6 (1H, s, C-2), 7.61–7.63 (1H, d, J = 7.6 Hz, C-4), 7.75–7.77 (2H, m, 2′-H, 6′-H), 7.97–7.99 (1H, bd, J = 8.3 Hz, C-7); HRMS: [M + H]$^+$C$_{19}$H$_{23}$N$_2$O$_2$S$_2$ calc. 375.1189, found. 375.1184.

*1-(4-Isopropylbenzenesulfonyl)-3-dimethylaminoethylthio-5-bromo-1*H*-indole (13)*. Brown coloured syrupy mass; IR (KBr, cm^{-1}): 2963, 1595, 1439, 1375, 1284, 1172, 776, 591; Mass (m/z): 481.1, 483.1 [M + H]$^+$; ^{1}H-NMR (ppm): 1.18–1.20 (6H, d, isopropyl), 2.22 (6H, s, -N(CH$_3$)$_2$), 2.45–2.48 (2H, t, J = 7.0 Hz, -C*H*$_2$N(CH$_3$)$_2$), 2.83–2.85 (2H, t, J = 7.0 Hz, -SCH$_2$-), 2.87–2.92 (1H, m, CH of isopropyl), 7.28–7.30 (2H, m, 3′-H, 5′-H), 7.43–7.46 (1H, dd, J = 8.8, 1.9 Hz, C-6), 7.61 (1H, s, C-2), 7.76–7.77 (3H, m, 2′-H, 6′-H, C-4), 7.86–7.88 (1H, d, J = 8.8 Hz, C-7); HRMS: [M + H]$^+$C$_{21}$H$_{26}$BrN$_2$O$_2$S$_2$ calc. 481.0591, found. 481.0590.

*1-(2-Bromobenzenesulfonyl)-3-dimethylaminoethylthio-5-bromo-1*H*-indole (14)*. Dark brown sticky mass; IR (KBr, cm^{-1}): 2941, 1571, 1442, 1376, 1285, 1176, 756, 592; Mass (m/z): 517.1, 519.1, [M + H]$^+$; ^{1}H-NMR (ppm): 2.24 (6H, s, -N(CH$_3$)$_2$), 2.49–2.53 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.86–2.89 (2H, m, -SCH$_2$-), 7.34–7.37 (1H, dd, J = 8.8, 1.9 Hz, C-6), 7.42-7.46 (1H, dt, J = 7.8, 1.7 Hz, 5′-H), 7.50–7.54 (2H, m, C-7 and 4′-H), 7.67–7.69 (1H, dd, J = 7.9, 1.2 Hz, 3′-H), 7.82–7.83 (1H, d, J = 1.8 Hz, C-4), 7.84 (1H, s, C-2), 8.19–8.21 (1H, dd, J = 8.0, 1.7 Hz, 6′-H); HRMS: [M + H]$^+$C$_{18}$H$_{19}$Br$_2$N$_2$O$_2$S$_2$ calc. 516.9288, found. 516.9283.

*1-(4-Fluorobenzenesulfonyl)-3-dimethylaminoethylthio-5-bromo-1*H*-indole (15)*. Light brown coloured syrupy mass; IR (KBr, cm^{-1}): 2941, 1590, 1377, 1241, 1179, 777, 584; Mass (m/z): 457 [M + H]$^+$; ^{1}H-NMR (ppm): 2.23 (6H, s, -C*H*$_2$N(CH$_3$)$_2$), 2.45-2.49 (2H, m, -NCH$_2$), 2.84–2.88 (2H, m, -SCH$_2$-), 7.11–7.15 (2H, m, 3′-H, 5′-H), 7.44–7.47 (1H, dd, J = 8.8, 1.9 Hz, C-6), 7.57 (1H, s, C-2), 7.77–7.78 (1H, d, J = 8.8 Hz, C-4), 7.83–7.85 (1H, d, J = 8.8 Hz, C-7), 7.86–7.9 (2H, m, 2′-H, 6′-H); HRMS: [M + H]$^+$C$_{18}$H$_{19}$BrFN$_2$O$_2$S$_2$ calc. 457.0095, found. 457.0098.

*1-(3-Trifluoromethylbenzenesulfonyl)-3-dimethylaminoethylthio-5-bromo-1*H*-indole (16)*. Light yellow coloured powder; M.R (°C): 77.8–82.7; IR (KBr, cm^{-1}): 2942, 1569, 1441, 1383, 1283, 1177, 752, 692, 594; Mass (m/z): 507.2, 509.2 [M + H]$^+$; ^{1}H-NMR (ppm): 2.23 (6H, s, -N(CH$_3$)$_2$), 2.47–2.50 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.86–2.90 (2H, m, -SCH$_2$-), 7.47–7.50 (1H, dd, J = 8.8, 1.9 Hz, C-6), 7.58 (1H, s, C-2), 7.60–7.64 (1H, t, J = 7.9, 5′-H), 7.78 (1H, d, J = 1.8 Hz, C-4), 7.82–7.87 (2H, m, 4′-H, 6′-H), 8.01–8.03 (1H, d, J = 8.0 Hz, C-7), 8.14 (1H, bs, 2′-H); HRMS: [M + H]$^+$C$_{19}$H$_{19}$BrF$_3$N$_2$O$_2$S$_2$ calc. 507.0023, found. 507.0032.

*1-(2-Bromobenzenesulfonyl)-3-dimethylaminoethylthio-5-chloro-1*H*-indole (17)*. Cream coloured powder; M.R (°C): 71.9–73.5; IR (KBr, cm^{-1}): 2940, 1573, 1443, 1376, 1285, 1176, 762, 592; Mass (m/z): 473,

475 $[M + H]^+$; ^{1}H-NMR (ppm): 2.24 (6H, s, -N(CH_3)$_2$), 2.49–2.52 (2H, m, -CH_2N(CH_3)$_2$), 2.86–2.89 (2H, m, -SCH_2-), 7.21–7.23 (1H, dd, J = 8.8, 2.1 Hz, C-6), 7.42–7.46 (1H, dt, J = 7.8, 1.7 Hz, 5′-H), 7.50–7.54 (1H, dt, J = 7.6, 1.3 Hz, 4′-H), 7.56–7.58 (1H, d, J = 8.8 Hz, C-7), 7.66 (1H, d, J = 2.0 Hz, C-4), 7.67–7.69 (1H, dd, J = 7.9, 1.3 Hz, 3′-H), 7.85 (1H, s, C-2), 8.18–8.21 (1H, dd, J = 7.9, 1.7 Hz, 6′-H); HRMS: $[M + H]^+C_{18}H_{19}BrClN_2O_2S_2$ calc. 472.9792, found. 472.9786.

*1-(4-Isopropylbenzenesulfonyl)-3-dimethylaminoethylthio-5-chloro-1*H*-indole (18)*. Light yellow coloured sticky mass; IR (KBr, cm^{-1}): 2963, 1596, 1442, 1375, 1385, 1173, 794, 592; Mass (m/z): 437.3 $[M + H]^+$; ^{1}H-NMR (ppm): 1.18–1.20 (6H, d, J = 6.94 Hz, -CH(CH_3)$_2$), 2.23 (6H, s, -N(CH_3)$_2$), 2.46–2.50 (2H, m, -CH_2N(CH_3)$_2$), 2.84–2.87 (2H, m, -SCH_2-), 2.89–2.92 (1H, m, -CH(CH_3)$_2$), 7.28–7.32 (3H, m, 3′-H, 5′-H, C-6), 7.60–7.61 (1H, d, J = 2.0 Hz, C-4), 7.63 (1H, s, C-2), 7.76–7.78 (2H, m, 2′-H, 6′-H), 7.91–7.93 (1H, d, J = 8.8 Hz, C-7); HRMS: $[M + H]^+C_{21}H_{26}ClN_2O_2S_2$ calc. 437.1098, found. 437.1095.

*1-(3-Trifluoromethylbenzenesulfonyl)-3-dimethylaminoethylthio-5-chloro-1*H*-indole (19)*. Light brown coloured solid; M.R (°C): 82.3–83.9; IR (KBr, cm^{-1}): 2942, 1573, 1443, 1383, 13268, 1177, 792, 595; Mass (m/z): 463.1 $[M + H]^+$; ^{1}H-NMR (ppm): 2.2 (6H, s, -N(CH_3)$_2$), 2.47–2.51 (2H, m, -CH_2N(CH_3)$_2$), 2.87–2.9 (2H, m, -SCH_2-), 7.33–7.36 (1H, dd, J = 8.8, 2.0 Hz, C-6), 7.59–7.64 (3H, m, C-2, C-4, 5′-H), 7.82-7.84 (1H, d, J = 7.8 Hz, 4′-H), 7.90–7.92 (1H, d, J = 8.8 Hz, C-7), 8.01–8.03 (1H, d, J = 8.0 Hz, 6′-H), 8.14 (1H, s, 2′-H); HRMS: $[M + H]^+C_{19}H_{19}ClF_3N_2O_2S_2$ calc. 463.0588, found. 463.0582.

*1-(4-Methoxybenzenesulfonyl)-3-dimethylaminoethylthio-5-fluoro-1*H*-indole (20)*. Brown coloured syrupy mass; IR (KBr, cm^{-1}): 2962, 1594, 1463, 1372, 1164, 589; Mass (m/z): 409.4 $[M + H]^+$; ^{1}H-NMR (ppm): 2.23 (6H, s, -N(CH_3)$_2$), 2.47–2.51 (2H, m, -CH_2N(CH_3)$_2$), 2.83–2.87 (2H, m, -SCH_2-), 3.81 (3H, s), 6.88–6.90 (2H, m, 3′-H, 5′-H), 7.04–7.10 (1H, dt, J = 8.0, 2.6 Hz, C-6), 7.27–7.29 (1H, dd, J = 8.6, 2.5 Hz, C-4), 7.64 (1H, s, C-2), 7.79–7.81 (2H, m, 2′-H, 6′-H), 7.90–7.94 (1H, m, C-7); HRMS: $[M + H]^+C_{19}H_{22}FN_2O_3S_2$ calc. 409.1087, found. 409.1081.

*1-(4-Isopropylbenzenesulfonyl)-3-dimethylaminoethylthio-5-fluoro-1*H*-indole (21)*. Brown coloured syrupy mass; IR (KBr, cm^{-1}): 2963, 1463, 1375, 1173, 856, 594; Mass (m/z): 421.3 $[M + H]^+$; ^{1}H-NMR (ppm): 1.17–1.20 (6H, d, -CH(CH_3)$_2$), 2.22 (6H, s, -N(CH_3)$_2$), 2.45–2.49 (2H, m, -CH_2N(CH_3)$_2$), 2.83–2.87 (2H, m, -SCH_2-), 2.88–2.92 (1H, m, -CH(CH_3)$_2$), 7.06–7.11 (1H, dt, J = 9.0, 2.6 Hz, C-6), 7.25–7.31 (3H, m, 3′-H, 5′-H, C-4), 7.65 (1H, s, C-2), 7.75–7.80 (2H, m, 2′-H, 6′-H), 7.92–7.96 (1H, m, C-7); HRMS: $[M + H]^+C_{21}H_{26}FN_2O_2S_2$ calc. 421.1387, found. 421.1386.

*1-(4-Bromobenzenesulfonyl)-3-dimethylaminoethylthio-5-fluoro-1*H*-indole (22)*. Off white sticky mass; IR (KBr, cm^{-1}): 2946, 1463, 1375, 1159, 857, 576; Mass (m/z): 457.3 $[M + H]^+$; 459.3 $(M + H)^+$; ^{1}H-NMR (ppm): 2.23 (6H, s, -N(CH_3)$_2$), 2.46–2.50 (2H, m, -CH_2N(CH_3)$_2$), 2.85–2.88 (2H, m, -SCH_2-), 7.07–7.12 (1H, dt, 8.6, 2.6 Hz, C-6), 7.27–7.30 (1H, dd, J = 8.4, 2.6 Hz, C-4), 7.58–7.62 (3H, m, 3′-H, 5′-H, C-2), 7.69–7.73 (2H, m, 2′-H, 6′-H), 7.89–7.93 (1H, m, C-7); HRMS: $[M + H]^+C_{18}H_{19}BrFN_2O_2S_2$ calc. 457.0095, found. 457.0093.

*1-(2-Bromobenzenesulfonyl)-3-dimethylaminoethylthio-5-fluoro-1*H*-indole (23)*. Light brown sticky mass; IR (KBr, cm^{-1}): 2925, 1463, 1160, 857, 788, 595; Mass (m/z): 457.2 $(M + H)^+$, 459.2 $[M + H]^+$; ^{1}H-NMR (ppm): 2.24 (6H, s, -N(CH_3)$_2$), 2.49–2.53 (2H, m, -CH_2N(CH_3)$_2$), 2.85–2.89 (2H, m, -SCH_2-), 6.97–7.02 (1H, dt, J = 9.0, 2.6 Hz, C-6), 7.33–7.36 (1H, dd, J = 8.5, 2.5 Hz, C-4), 7.41–7.45 (1H, dt, J = 7.7, 1.7 Hz, 4′-H), 7.49–7.54 (1H, dt, J = 7.8, 1.2 Hz, 5′-H), 7.58–7.62 (1H, dd, J = 9.0, 4.2 Hz, C-7), 7.67–7.69 (1H, dd, J = 7.8, 1.0 Hz, 3′-H), 7.89 (1H, s, C-2), 8.17–8.19 (1H, dd, J = 8.0–1.6 Hz, 6′-H); HRMS: $[M + H]^+C_{18}H_{19}BrFN_2O_2S_2$ calc. 457.0094, found. 457.0089.

*1-(4-Fluorobenzenesulfonyl)-3-dimethylaminoethylthio-5-fluoro-1*H*-indole (24)*. Dark brown sticky mass; IR (KBr, cm^{-1}): 2961, 1590, 1463, 1378, 1293, 1180, 1159, 857, 683, 589; Mass (m/z): 397.2, $[M + H]^+$, ^{1}H-NMR (ppm): 2.23 (6H, s, -N(CH_3)$_2$), 2.47–2.51 (2H, m, -CH_2N(CH_3)$_2$), 2.85-2.88 (2H, m, -SCH_2-), 7.07–7.17 (3H, m, 3′-H, 5′-H, C-6), 7.27–7.31 (1H, dd, J = 8.5, 4.2 Hz, C-4), 7.61 (1H, s, C-2), 7.87–7.95 (3H, m, 2′-H, 6′-H, C-7); HRMS: $[M + H]^+C_{18}H_{19}F_2N_2O_2S_2$ calc. 397.0884, found. 397.0881.

*1-(2-Bromobenzenesulfonyl)-3-dimethylaminoethylthio-5-methoxy-1*H*-indole (25)*. Cream coloured crystalline powder; M.R (°C): 89.4–91.7; IR (KBr, cm^{-1}): 2940, 1610, 1469, 1372, 1212, 1166, 851, 597; Mass (m/z): 469.2, 471.2 $[M + H]^+$, ^{1}H-NMR (ppm): 2.24 (6H, s, -N(CH_3)$_2$), 2.51–2.55 (2H, m, -CH_2N(CH_3)$_2$), 2.87–2.91 (2H, m, -SCH_2-), 3.84 (3H, s, OCH_3), 6.86–6.88 (1H, dd, J = 9.0, 2.5 Hz, C-6), 7.1–7.11 (1H, d, J = 2.5 Hz, C-4), 7.4–7.48 (1H, dt, J = 7.6 Hz, 1.7 Hz, 4′-H), 7.46–7.50 (1H, dt, J = 7.7, 1.33 Hz, 5′-H), 7.53–7.55 (1H, d, J = 8.9 Hz, C-7), 7.65–7.67 (1H, dd, J = 7.9, 1.3 Hz, 3′-H), 7.8 (1H, s, C-2), 8.11–8.13 (1H, dd, J = 7.9, 1.7 Hz, 6′-H); HRMS: $[M + H]^+C_{19}H_{22}BrN_2O_3S_2$ calc. 469.0255, found. 469.0260.

*1-(4-Fluorobenzenesulfonyl)-3-dimethylaminoethylthio-5-methoxy-1*H-*indole (26)*. Light brown coloured crystalline powder; M.R (°C): 103.1–107.6; IR (KBr, cm^{-1}): 2962, 1585, 1443, 1375, 1303, 1183, 854, 586; Mass (m/z): 409 $[M + H]^+$, ^{1}H-NMR (ppm): 2.22 (6H, s, -N(CH_3)$_2$), 2.46–2.50 (2H, m, -CH_2N(CH_3)$_2$), 2.85–2.89 (2H, m, -SCH_2-), 3.83 (3H, s, OCH_3), 6.95–6.98 (1H, dd, J = 9.0, 2.0 Hz, C-6), 7.04–7.049 (1H, d, J = 2.5 Hz, C-4), 7.08–7.12 (2H, m, 3′-H, 5′-H), 7.52 (1H, s, C-2), 7.85–7.88 (3H, m, 2′-H, 6′-H, C-7); HRMS: $[M + H]^+C_{19}H_{22}FN_2O_3S_2$ calc. 409.1079, found. 409.1083.

*1-(Benzenesulfonyl)-3-dimethylaminoethylthio-5-methoxy-1*H-*indole (27)*. Light tan coloured powdery mass; M.R (°C): 89.4–90.9; IR (KBr, cm^{-1}): 2941, 1610, 1470, 1371, 1213, 1165, 851, 603; Mass (m/z): 391.4 $[M + H]^+$, ^{1}H-NMR (ppm): 2.22 (6H, s, -N(CH_3)$_2$), 2.46–2.49 (2H, m, -CH_2N(CH_3)$_2$), 2.84–2.88 (2H, m, -SCH_2-), 3.83 (3H, s, OCH_3), 6.94–6.97 (1H, dd, J = 9.0, 2.5 Hz, C-6), 7.04 (1H, d, J = 2.5 Hz, C-4), 7.41–7.45 (2H, m, 3′-H, 5′-H), 7.52–7.54 (1H, m, 4′-H), 7.56 (1H, s, C-2), 7.83–7.86 (2H, m, 2′-H, 6′-H), 7.87–7.89 (1H, d, J = 9.0 Hz, C-7); HRMS: $[M + H]^+C_{19}H_{23}N_2O_3S_2$ calc. 391.1150, found. 391.1147.

*1-(4-Bromobenzenesulfonyl)-3-dimethylaminoethylthio-5-methoxy-1*H-*indole (28)*. Dark brown crystalline powder; M.R (°C): 90.4–94.5; IR (KBr, cm^{-1}): 2938, 1609, 1477, 1373, 1210, 1165, 854, 619; Mass (m/z): 469.2, 471.2 $[M + H]^+$, ^{1}H-NMR (ppm): 2.23 (6H, s, -N(CH_3)$_2$), 2.46–2.5 (2H, m, -CH_2N(CH_3)$_2$), 2.85–2.89 (2H, m, -SCH_2-), 3.83 (3H, s, OCH_3), 6.95–6.98 (1H, dd, J = 9.0, 2.52 Hz, C-6), 7.03–7.04 (1H, d, J = 2.5 Hz, C-4), 7.5 (1H, s, C-2), 7.55–7.57 (2H, m, 3′-H, 5′-H), 7.68–7.7 (2H, m, 2′-H, 6′-H), 7.84–7.86 (1H, d, J = 9.2 Hz, C-7); HRMS: $[M + H]^+C_{19}H_{22}BrN_2O_3S_2$ calc. 469.0255, found. 469.0259.

*1-(4-Isopropylbenzenesulfonyl)-3-dimethylaminoethylthio-5-methoxy-1*H-*indole (29)*. Cream coloured powdery mass; M.R (°C): 78.0–80.6; IR (KBr, cm^{-1}): 2963, 1610, 1469, 1372, 1213, 1166, 851, 597; Mass (m/z): 433.3 $[M + H]^+$, ^{1}H-NMR (ppm): 1.17–1.19 (6H, d, J = 7.0 Hz, -CH(CH_3)$_2$), 2.22 (6H, s, -N(CH_3)$_2$), 2.46–2.49 (2H, m, -CH_2N(CH_3)$_2$), 2.84–2.92 (3H, m, -SCH_2- and -C*H*-(CH_3)$_2$), 3.83 (3H, s, OCH_3), 6.94–6.97 (1H, dd, J = 9.0, 2.5 Hz, C-6), 7.04–7.05 (1H, d, J = 2.5 Hz, C-4), 7.25–7.28 (2H, m, 3′-H, 5′-H), 7.57 (1H, s, C-2), 7.75–7.78 (2H, m, 2′-H, 6′-H), 7.88–7.90 (1H, d, J = 9.0 Hz, C-7); HRMS: $[M + H]^+C_{22}H_{29}N_2O_3S_2$ calc. 433.1578, found. 433.1581.

{*2-[5-Methoxy-1-(2-bromobenzenesulfonyl)-1*H-*indole-3-sulphinyl]ethyl*} *dimethylamine (30)*. Dark brown syrupy mass; IR (KBr, cm^{-1}): 2973, 1652, 1470, 1375, 1175, 1029, 769, 598; Mass (m/z): 485.2, 487.2 $[M + H]^+$, ^{1}H-NMR (ppm): 2.29 (6H, s, -N(CH_3)$_2$), 2.59–2.6 (1H, m, -CH_2N(CH_3)$_2$), 2.82–2.85 (1H, m, NCH_2), 3.19–3.22 (1H, m, -SCH_2-), 3.38–3.43 (1H, m, SCH_2), 3.82 (3H, s, OCH_3), 6.92–6.94 (1H, dd, J = 9.2, 2.5 Hz, C-6), 7.3–7.31 (1H, d, J = 2.4 Hz, C-4), 7.43–7.49 (1H, dt, 7.7, 1.6 Hz, 5′-H), 7.52–7.59 (2H, m, 4′-H and C-7), 7.68–7.72 (1H, dd, J = 7.9, 1.1 Hz, 3′-H), 8.14 (1H, s, C-2), 8.24–8.26 (1H, dd, J = 8.0, 1.6 Hz, 6′-H); HRMS: $[M + H]^+C_{19}H_{22}BrN_2O_4S_2$ calc. 485.0186, found. 485.0189.

*1-(4-Methoxybenzenesulfonyl)-3-dimethylaminoethylthio-5-methoxy-1*H-*indole (31)*. Brown coloured syrupy mass; IR (KBr, cm^{-1}): 2942, 1594, 1469, 1370, 1213, 1164, 680, 595; Mass (m/z): 421.2 $[M + H]^+$, ^{1}H-NMR (ppm): 2.22 (6H, s, -N(CH_3)$_2$), 2.45–2.49 (2H, m, -CH_2N(CH_3)$_2$), 2.83–2.87 (2H, m, -SCH_2-), 3.79 (3H, s, OCH_3 at C-6), 3.83 (3H, s, 4′-OCH_3), 6.85–6.88 (2H, m, 3′-H, 5′-H), 6.93–6.96 (1H, dd, J = 9.0, 2.5 Hz, C-6), 7.04 (1H, d, J = 2.5 Hz, C-4), 7.55 (1H, s, C-2), 7.76–7.79 (2H, m, 2′-H, 6′-H), 7.85–7.88 (1H, d, J = 9.0 Hz, C-7); HRMS: $[M + H]^+C_{20}H_{25}N_2O_4S_2$ calc. 421.1283, found. 421.1279.

*1-(4-Methylbenzenesulfonyl)-3-dimethylaminoethylthio-5-methoxy-1*H-*indole (32)*. Tan coloured crystalline powder; M.R (°C): 78.0–80.6; IR (KBr, cm^{-1}): 2941, 1610, 1470, 1371, 1213, 1165, 851, 677, 596; Mass (m/z): 405.3 $[M + H]^+$, ^{1}H-NMR (ppm): 2.22 (6H, s, -N(CH_3)$_2$), 2.33 (3H, s, 4′-CH_3), 2.45–2.49 (2H, m, -CH_2N(CH_3)$_2$), 2.83–2.87 (2H, m, -SCH_2-), 3.83 (3H, s, OCH_3), 6.93–6.96 (1H, dd, J = 9.0, 2.5 Hz, C-6), 7.03–7.04 (1H, d, J = 2.5 Hz, C-4), 7.2–7.22 (2H, d, J = 8.1 Hz, 3′-H, 5′-H), 7.55 (1H, s, C-2), 7.71–7.73 (2H, d, J = 8.4 Hz, 2′-H, 6′-H), 7.85–7.88 (1H, d, J = 9.0 Hz, C-7); HRMS: $[M + H]^+C_{20}H_{25}N_2O_3S_2$ calc. 405.1299, found. 405.1292.

*General procedure for the synthesis of the 1-((substituted) benzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-1*H-*indoles, Compound II (33–43)*. *N,N*-Dimethyl aminoethylthio acetone (0.007 mol) was added to aqueous sulfuric acid (30 mL, 10% w/v) followed by (un)substituted phenyl hydrazine (0.0084 mol) at room temperature. The reaction mixture was refluxed for 5–6 h. After completion of the reaction (TLC), the mixture was cooled to room temperature, basified to pH 10–11 using aqueous NaOH solution (20% w/v) and extracted with EtOAc (3 × 100 mL). Organic phase was separated, washed with brine solution and dried over anhydrous sodium sulfate. The residual mass obtained after solvent removal (under vacuum) was purified by flash chromatography to obtain intermediate **6**, which was identified by IR, NMR and mass spectral analyses. Compound II was

prepared following the general procedure described under Compound 1.

*1-(4-Fluorobenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-1*H*-indole (33)*. Dark brown coloured syrupy mass; IR (KBr, cm^{-1}): 1591, 1372, 1232, 1180, 719, 574; Mass (m/z): 393.3 [M + H]$^+$, ^{1}H-NMR: 2.15 (6H, s, -N(CH$_3$)$_2$), 2.318–2.36 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.7-2.72 (2H, m, -SCH$_2$-), 2.74 (3H, s, CH$_3$ at C-2) 7.0–7.1 (2H, m, 3′-H, 5′-H), 7.3–7.33 (2H, m, C-5 and C-6), 7.62–7.63 (1H, m, C-4), 7.78–7.81 (2H, m, 2′-H, 6′-H), 8.17–8.18 (1H, m, C-7); HRMS: [M + H]$^+$C$_{19}$H$_{22}$FN$_2$O$_2$S$_2$ calc. 393.1076, found. 393.1079.

*1-(4-Bromobenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-1*H*-indole (34)*. Dark brown coloured syrupy mass; IR (KBr, cm^{-1}): 2969, 1574, 1373 1183, 747, 602, 571; Mass (m/z): 453.2, 455.2 [M + H]$^+$, ^{1}H-NMR (ppm): 2.15 (6H, s, -N(CH$_3$)$_2$), 2.32–2.35 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.7–2.73 (2H, m, -SCH$_2$-), 2.74 (3H, s, CH$_3$ at C-2), 7.3–7.33 (2H, m, C-5 and C-6), 7.54–7.56 (2H, m, 3′-H, 5′-H), 7.61–7.64 (3H, m, 2′-H, 6′-H, C-4), 8.15–8.18 (1H, m, C-7); HRMS: [M + H]$^+$C$_{19}$H$_{22}$BrN$_2$O$_2$S$_2$ calc. 453.0291, found. 453.0287.

*1-(4-Methylbenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-1*H*-indole (35)*. Light brown coloured sticky mass; IR (KBr, cm^{-1}): 2963, 2927, 1598, 1450, 1371, 1175, 659, 574; Mass (m/z): 389.5 [M + H]$^+$, ^{1}H-NMR (ppm): 2.14 (6H, s, -N(CH$_3$)$_2$), 2.31–2.35 (5H, m, CH$_3$ on C-2, -C*H*$_2$N(CH$_3$)$_2$), 2.69–2.73 (2H, m, -SCH$_2$-), 2.74 (3H, s, 4′-CH$_3$), 7.19–7.21 (2H, m, 3′-H, 5′-H), 7.28–7.31 (2H, m, C-5, C-6), 7.61–7.67 (3H, m, 2′-H, 6′-H, C-4), 8.19–8.21 (1H, m, C-7); HRMS: [M + H]$^+$C$_{20}$H$_{25}$N$_2$O$_2$S$_2$ calc. 389.1387, found. 389.1383.

*1-(4-Isopropylbenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-1*H*-indole (36)*. Brown coloured syrupy mass; IR (KBr, cm^{-1}): 2964, 1596, 1450, 1371, 1177, 583; Mass (m/z): 417.5 [M + H]$^+$, ^{1}H-NMR (ppm): 1.18–1.20 (6H, d, J = 6.88 Hz, -CH(C*H*$_3$)$_2$), 2.13 (6H, s, -N(CH$_3$)$_2$), 2.31–2.35 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.7–2.73 (2H, m, -SCH$_2$-), 2.75 (3H, s, CH$_3$ at C-2), 2.87–2.91 (1H, h, J = 7.0 Hz, -C*H*(CH$_3$)$_2$), 7.25–7.32 (4H, m, 3′-H, 5′-H, C-5, C-6), 7.62–7.63 (1H, m, C-4), 7.69–7.71 (2H, m, 2′-H, 6′-H), 8.21–8.23 (1H, m, C-7); HRMS: [M + H]$^+$C$_{22}$H$_{29}$N$_2$O$_2$S$_2$ calc. 417.1692, found. 417.1693.

*1-(4-Bromobenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-5-fluoro-1*H*-indole (37)*. Cream coloured crystalline powder; M.R (°C): 68.0–71.4; IR (KBr, cm^{-1}): 2935, 1590, 1469, 1377, 1154, 745, 562; Mass (m/z): 471.4, 473.4 [M + H]$^+$, ^{1}H-NMR (ppm): 2.15 (6H, s, -N(CH$_3$)$_2$), 2.31–2.35 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.69–2.7 (2H, m, -SCH$_2$-), 2.72 (3H, s, CH$_3$ at C-2), 7.0–7.06 (1H, dt, J = 9.0, 1.7 Hz, C-6), 7.27–7.3 (1H, dd, J = 8.4, 2.6 Hz, C-4), 7.56–7.61 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 8.1–8.13 (1H, m, C-7); HRMS: [M + H]$^+$C$_{19}$H$_{21}$BrFN$_2$O$_2$S$_2$ calc. 471.0193, found. 471.0188.

*1-(4-Isopropylbenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-5-fluoro-1*H*-indole (38)*. Light yellow coloured sticky mass; IR (KBr, cm^{-1}): 2965, 1594, 1468, 1372, 1176, 788, 589, 573; Mass (m/z): 435.4 [M + H]$^+$, ^{1}H-NMR (ppm): 1.19–1.2 (6H, d, J = 6.92 Hz, -CH(C*H*$_3$)$_2$), 2.14 (6H, s, -N(CH$_3$)$_2$), 2.30–2.34 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.67–2.71 (2H, m, -SCH$_2$-), 2.73 (3H, s, CH$_3$ at C-2), 2.87–2.94 (1H, sep, J = 6.9 Hz, -C*H*(CH$_3$)$_2$), 7.0–7.05 (1H, dt, J = 9.0, 2.6 Hz, C-6), 7.26–7.3 (3H, m, 3′-H, 5′-H, C-4), 7.66–7.68 (2H, m, 2′-H, 6′-H), 8.14–8.18 (1H, m, C-7); HRMS: [M + H]$^+$C$_{22}$H$_{28}$FN$_2$O$_2$S$_2$ calc. 435.1596, found. 435.1591.

*1-(4-Bromobenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-5-methoxy-1*H*-indole (39)*. Pale green sticky mass; IR (KBr, cm^{-1}): 2928, 1609, 1373, 1166, 794, 563; Mass (m/z): 483 (M + H)$^+$, 485 [M + H]$^+$, ^{1}H-NMR (ppm): 2.15 (6H, s, -N(CH$_3$)$_2$), 2.3–2.32 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.68–2.72 (5H, m, -SCH$_2$- and CH$_3$ at C-2), 3.86 (3H, s, OCH$_3$), 6.9–6.93 (1H, dd, J = 9.1, 2.6 Hz, C-6), 7.07 (1H, d, J = 2. 6 Hz, C-4), 7.53–7.6 (4H, m, 2′-H, 3′-H, 5′-H, 6′-H), 8.04–8.06 (1H, d, J = 9.0 Hz, C-7); HRMS: [M + H]$^+$C$_{20}$H$_{24}$BrN$_2$O$_3$S$_2$ calc. 483.0389, found. 483.0391.

*1-(4-Fluorobenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-5–methoxy-1*H*-indole (40)*. Tan coloured powder; M.R (°C): 73.7–75.5; IR (KBr, cm^{-1}): 2935, 2773, 1591, 1474, 1372, 1181, 684, 567; Mass (m/z): 423.3 [M + H]$^+$, ^{1}H-NMR (ppm): 2.15 (6H, s, -N(CH$_3$)$_2$), 2.31–2.34 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.68–2.70 (2H, m, -SCH$_2$-), 2.71 (3H, s, CH$_3$ at C-2), 3.86 (3H, s, OCH$_3$), 6.9–6.93 (1H, dd, J = 9.1, 2.6 Hz, C-6), 7.06–7.1 (3H, m, C-4, 3′-H, 5′-H), 7.74–7.78 (2H, m, 2′-H, 6′-H), 8.05–8.07 (1H, d, J = 9.0 Hz, C-7); HRMS: [M + H]$^+$C$_{20}$H$_{24}$FN$_2$O$_3$S$_2$ calc. 423.1193, found. 423.1197.

*1-(4-Isopropylbenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-5-methoxy-1*H*-indole (41)*. Dark brown sticky mass; IR (KBr, cm^{-1}): 2963, 1609, 1474, 1370, 1167, 788, 674, 575; Mass (m/z): 447.5 [M + H]$^+$, ^{1}H-NMR (ppm): 1.18 (6H, d, J = 6.9, -CH(C*H*$_3$)$_2$), 2.13 (6H, s, -N(CH$_3$)$_2$), 2.30–2.34 (2H, m, -C*H*$_2$N(CH$_3$)$_2$), 2.68–2.71 (2H, m, -SCH$_2$-), 2.72 (3H, s, CH$_3$), 2.87–2.91 (1H, m, -C*H*(CH$_3$)$_2$), 3.86 (3H, s, OCH$_3$), 6.9–6.93 (1H, dd, J = 9.0, 2.64 Hz, C-6), 7.07–7.08 (1H, d, J = 2. 6 Hz, C-4), 7.24–7.26 (2H, m, 3′-H, 5′-H), 7.65–7.67 (2H, m, 2′-H, 6′-H), 8.09–8.11 (1H, d, J = 9.0 Hz, C-7); HRMS: [M + H]$^+$C$_{23}$H$_{31}$N$_2$O$_3$S$_2$ calc. 447.1791, found. 447.1789.

1-(4-Methylbenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-5-methoxy-1H-indole (42). Tan coloured powder; M.R (°C): 70.4–74.7; IR (KBr, cm^{-1}): 2933, 1609, 1474, 1369, 1167, 680, 567; Mass (m/z): 419.4 $[M + H]^+$, ^{1}H-NMR (ppm): 2.16 (6H, s, -N(CH_3)$_2$), 2.34 (3H, s, CH_3 at C-2), 2.35–2.37 (2H, m, -CH_2N(CH_3)$_2$), 2.69–2.73, (5H, m, 4′- CH_3 and -SCH_2-), 3.86 (3H, s, OCH_3), 6.89–6.92 (1H, dd, J = 9.0, 2.6 Hz, C-6), 7.06 (1H, d, J = 2.6 Hz, C-4), 7.18–7.2 (2H, d, J = 8.1 Hz, 3′-H, 5′-H), 7.61–7.64 (2H, m, 2′-H, 6′-H), 8.07–8.09 (1H, d, J = 9.0 Hz, C-7); HRMS: $[M + H]^+C_{21}H_{27}N_2O_3S_2$ calc. 419.1463, found. 419.1449.

1-(2-Bromobenzenesulfonyl)-2-methyl-3-dimethylaminoethylthio-5-methylthio-1H-indole (43). Pale yellow coloured crystalline powder; M.R (°C): 76.2–78.9; IR (KBr, cm^{-1}): 2923, 1572, 1448, 1369, 1235, 1177, 764, 582; Mass (m/z): 499.3, 501.3 $[M + H]^+$, ^{1}H-NMR (ppm): 2.22 (6H, s, -N(CH_3)$_2$), 2.44–2.48 (2H, m, -CH_2N(CH_3)$_2$), 2.54 (3H, s, CH_3), 2.62 (3H, s, SCH_3), 2.76–2.80 (2H, m, -SCH_2-), 7.15–7.18 (1H, dd, J = 8.8, 2.0 Hz, C-6), 7.43–7.47 (2H, m, 4′-H, 5′-H), 7.56 (1H, d, J = 1.9 Hz, C-4), 7.67–7.69 (1H, dd, J = 7.5, 1.4 Hz, 3′-H), 7.78–7.82 (1H, d, J = 8.8 Hz, C-7), 7.88–7.91 (1H, dd, J = 7. 8, 1.9 Hz, 6′-H); HRMS: $[M + H]^+C_{20}H_{24}BrN_2O_2S_3$ calc. 499.0183, found. 499.0181.

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

Compounds were investigated by the reported procedure.[4] 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 nM and non-specific determinant was methiothepin mesylate (0.1 μM). The reference compound and positive control is methiothepin mesylate.

Reactions were carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgCl_2$, 0.5 mM 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.

Results and discussion

Molecular modeling

The *N*-Arylsulfonyl tryptamines, *viz*: MS-245 (Figure 1) are known to be ligands to 5-HT$_6$R with high affinity and they bind as antagonists. [22] We have in past studied the effects of rigidizing the aromatic rings on the affinity and functionality of these receptors. [27] As part of continuing effort to identify the useful

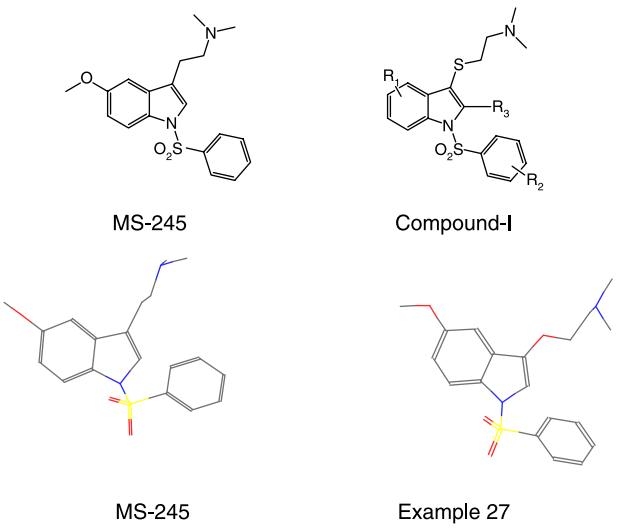


Figure 1. Chemical structures and energy minimized conformations of MS-245 and Example 27.

ligands at 5-HT$_6$R, various studies have been reported with the rigidized side-chain in terms of the 5 or 6 membered rings. [28] The aim of present study was to investigate the role of side-chain flexibility and elongation on the binding affinity of these compounds.

When the corresponding compounds MS-245 and Compound I (Example 27, Figure 1) were independently energy minimized and subjected to superimposition, both the molecules showed significant conformational similarity with the r.m.s.d. of 0.13. However, the most important aspect that needs to be highlighted is the spatial orientation of the terminal tertiary nitrogen with respect to both the aromatic rings (triangular pharmacophore) was similar, in spite of an extra sulfur atom in the side-chain. Also evident from Figure 1, is that the aromatic Ring B in case of MS-245 fall in the same domain as that of Example 27 with respect to the basic amino function and the aromatic Ring A (indole). This study was therefore aimed at investigating the effect of inducing the flexibility in the side-chain on the affinity of tryptamines at 5-HT$_6$R.

The minimum energy conformations of MS-245 and Example 27 were generated using the AM1 method in CS Chem Office software (Cambridge Soft Corporation, MA, USA). Molecular dynamics was performed with the step interval of 2.0 fs and frame intervals of 10 fs up to 1000 °Kelvin and heating/cooling rate of 1 Kcal/atom/ps. The minimum energy conformations of both the molecules were then used for the comparisons. The conformational similarity between these molecules was studied by overlapping the molecules (Figure 2). The overlapping procedure used three point selections, which also happen to be the pharmacophorically important points like the terminal tertiary nitrogen, the centroids of the aromatic rings etc. The overlap was performed with

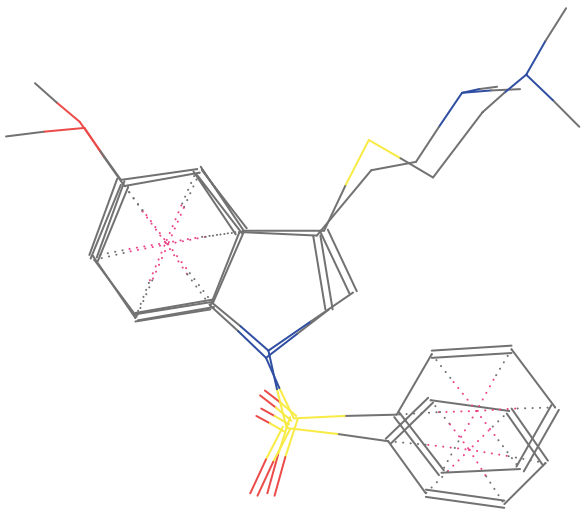


Figure 2. Superimposed 3D structures of MS-245 and Example 27.

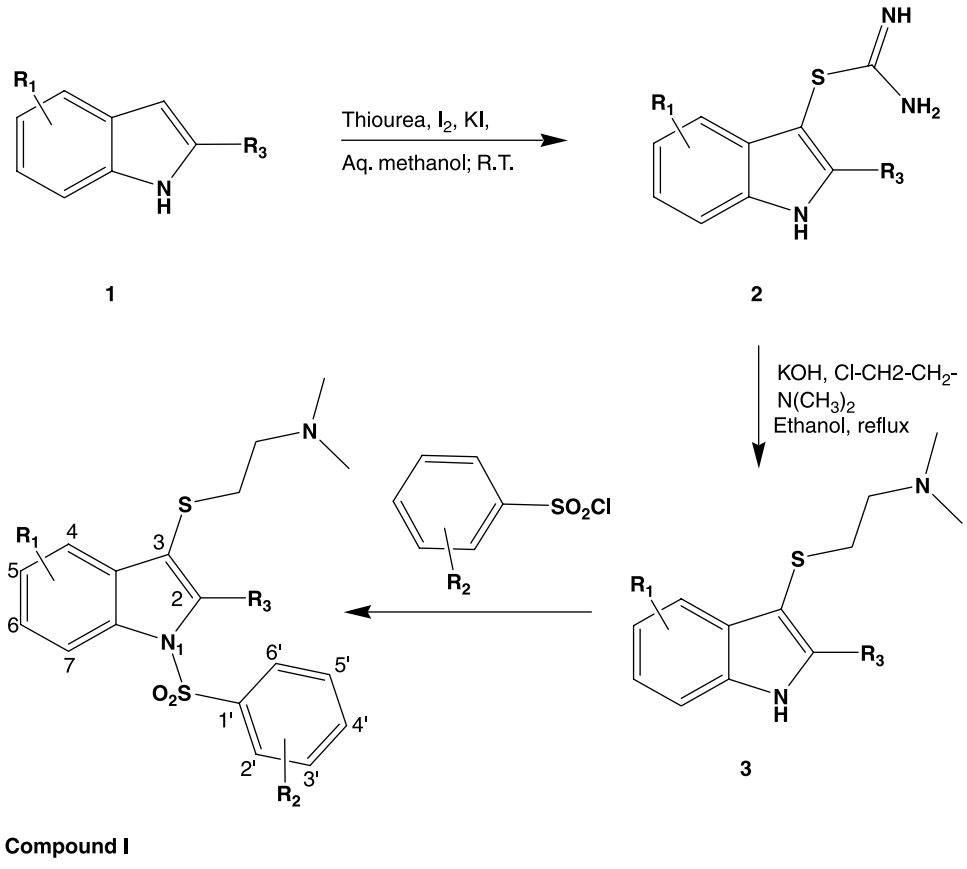
the minimum RMS error of 0.1 and the minimum RMS gradient of 0.01.

Chemistry

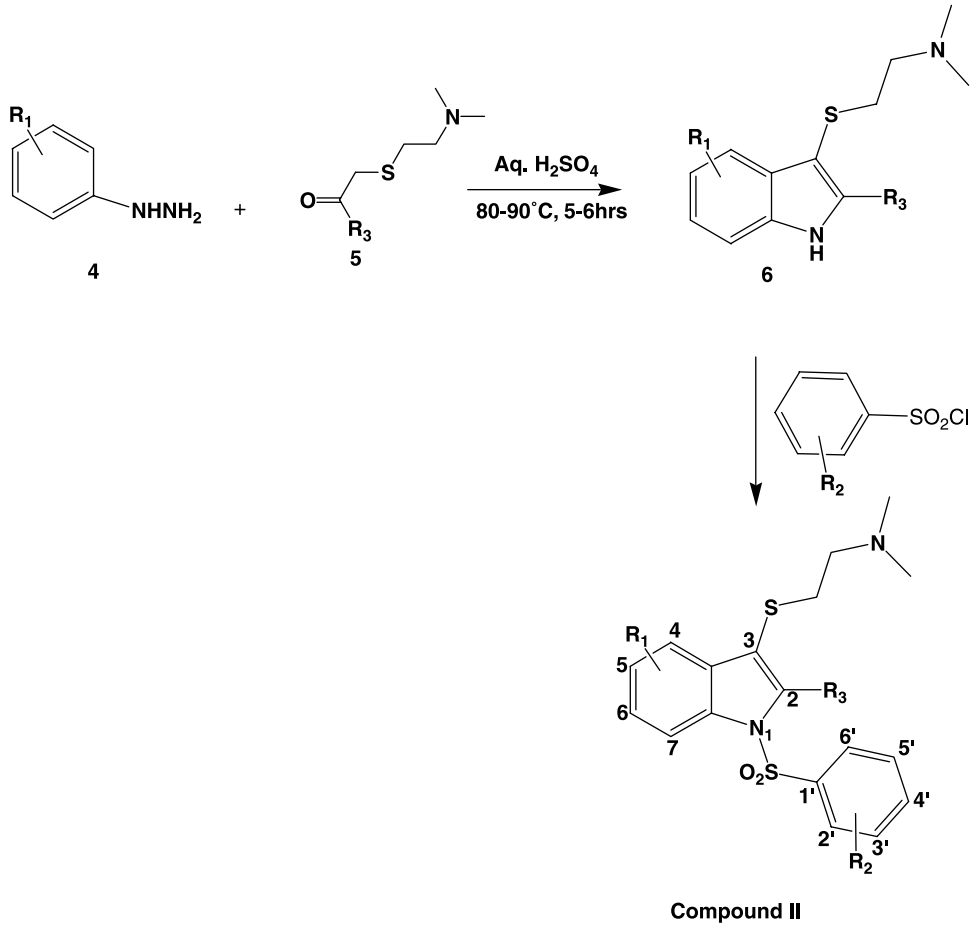
The synthesis of compound I was achieved through the formation of respective substituted indolyl thiuronium salts, **2** (Scheme 1). Using the method of Harris, [26] various substituted indoles were treated under oxidizing conditions in presence of iodine and potassium iodide with thiourea. The iodine was rapidly consumed and the work up yielded the crystalline thiuronium salts of indole in high yields.

It is known that the treatment of these thiuronium salts with the aqueous alkali leads to the formation of 3-indolyl thiols, which are also isolable; however, they are known to undergo rapid oxidation to the corresponding substituted di-indolyl disulfides. Therefore, it was decided to liberate the indolyl thiol *in-situ* and use it directly as a nucleophile in the next reaction with the 2-*N*,*N*-dimethylaminoethyl chloride. This reaction in ethanol and KOH yielded the 3-(2-*N*,*N*-dimethylaminoethyl)thioindoles, **3**. Intermediates **3** were then conveniently treated with the various sulfonyl chlorides in presence of various bases and solvents, gave compound I.

Compounds II in-turn were synthesized by using the Fischer indole synthesis strategy (Scheme 2). Reaction of chloroacetone with 2-*N*,*N*-dimethylaminoethanethiol yielded the *N*,*N*-dimethylaminoethylthio acetone, **5**. Reaction of this ketone, **5** with the corresponding phenyl hydrazines, **4** under acidic conditions yielded the respective 2–Methyl-3-(2-*N*,*N*-dimethylaminoethyl)thioindoles, **6**. Treatment of intermediates **6** with the various aryl sulphonyl chlorides yielded compound II.



Scheme 1. Synthesis of compound I



Scheme 2. Synthesis of compound II

The ESI-MS of all the compounds exhibited the $[M + H]^+$ as the parent ion, with the typical loss of dimethylaminoethyl fragment to give rise to $[M\text{-}72 + H]^+$ ion. ^{1}H-NMR spectra of all the compounds exhibited the prominent presence of dimethylaminoethyl side-chain protons along with the aromatic protons. All the other spectral data was found to be satisfactory to confirm their structures.

Structure Activity Relationship

Compound I and II were evaluated for their binding at the human 5-HT$_6$R at 100 nM concentrations. Some of the compounds were also evaluated for their Ki at human 5-HT$_6$R (Table I).

As can be noted from Table I, most of the 2-methyl substituted indole derivatives had very weak binding at the receptor at 100 nM concentrations. Due to the very low binding affinity (Ki $= 0.15\,\mu$M to $1\,\mu$M), it could not be concluded as to which substitutions are playing important role in binding. Further, the best compound was derivative **42** with the Ki of $0.153\,\mu$M and the corresponding % binding at 100 nM concentration was only 22%. Eventually, this percent specific binding at 100 nM concentrations was used for scoring and comparison of the molecules within this series.

Our preliminary molecular modeling study suggested the synthesis of corresponding 2-unsubstituted derivatives. The subsequent study on 2-unsubstituted derivatives with the similar substitution pattern yielded the compounds with better affinity. The 5-unsubstituted derivatives were found to have the least affinity to the receptor whereas the 5-methoxy derivatives were found to possess the maximum affinity within the class. The 5-halo substituents also seem to be tolerated and exhibited the moderate affinity, which can be further classified on the basis of their substituents on the arylsulfonyl ring.

The ortho bromo substituted derivatives were the best amongst all the different 5-substituted derivatives, namely, derivative **7, 14, 17, 23** and **25** showed maximum affinity in the 5-H, 5-bromo, 5-chloro, 5-fluoro and 5-methoxy classes respectively (Table I). This indicates a specific stereoelectronic role of 2-bromo substituents on the binding pattern of these molecules. Interestingly, equally good binding was also exhibited by 4-bromo substituted derivatives in the arylsulfonyl ring, viz; derivative **22** and **28**.

Table I. 5-HT$_6$ receptor binding data.

Compd. No	Binding at 5-HT$_6$ receptor	
	% Binding at 100 nM	Ki (μM)
7	34.44	–
8	28.13	–
9⋆	7.89	–
10	30.60	–
11	30.43	–
12	42.63	–
13	22.95	–
14	48.94	–
15	42.33	–
16	–	–
17	54.96	–
18	12.64	–
19	–	–
20	13.15	–
21	–	–
22	43.33	–
23	56.32	–
24	16.37	–
25	57.19	–
26	28.11	–
27	40.67	–
28	50.55	–
29	38.48	–
30⋆	–	–
31	–	–
32	47.54	–
33	9.05	>1
34	10.55	0.25
35	12.19	0.23
36	2.49	>1
37	–	>1
38	2.56	>1
39	14.15	0.67
40	6.46	0.44
41	–	0.42
42	21.61	0.15
43	11.50	–

⋆ Compound no. **9** and **30** are the oxides at the side-chain sulfur.

Since the possible metabolite of these compounds could be the corresponding S-oxide, the representative derivatives were converted deliberately to their S-oxides. The derivatives **9** and **30**, however, showed drastically reduced affinity as compared to the corresponding thioether derivatives, **7** and **25**, probably because the S-oxidation forces the side-chain amino group to the totally undesired orientation with respect to the two aromatic rings in the molecule. This could also be the reason of lesser affinity of the 2-methyl derivatives, where, the substitution at C2 of indole may lead to the conformational difference in the orientation of the side-chain, although to a lesser degree.

Conclusions

The binding affinities of derivatives with dimethylaminoalkylthio and dimethylaminoalkoxy side-chains were 50 to 100 fold less than the corresponding tryptamines. It was generally observed that the introduction of the spacer 'S' atom on the side-chain was not advantageous for the binding of these analogues to 5-HT$_6$R. However, it is interesting to note that the corresponding ether derivatives, which were reported from our laboratories, have much higher binding affinities in the range of 5 to 10 nM.[25] The present compounds I with (substituted) aminoalkylthio indoles differ from the earlier reported 3-(substituted) aminoalkoxy indoles only in the replacement of 'O' with 'S'. Conventionally, it is viewed as the classic 'bioisosteric' replacement, which should lead to the compounds with almost equivalent binding affinities. The results of the present study however reveal that these two derivatives do not have similar, but about 100 fold different binding affinities.

The drastic difference in the binding affinities of these derivatives indicates the pivotal role of spacer heteroatom in defining the orientation of the side-chain in the binding conformation of these derivatives. The slight difference in the orientation leads to the vast difference in binding affinities. Although we attempted to investigate the finer differences in the energy-minimized conformations of these isosters, the energy-minimized conformations do not reveal the major differences. The apparent orientation difference in the position of terminal nitrogen may be actually minor given the allowed flexibility of aminoethyl moiety.

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References

[1] Woolley ML, Marsden CA, Fone KC. 5-HT$_6$ receptors. Curr Drug Targets - CNS and Neurol Disord 2004;3:59–79.

[2] Sebben M, Ansanay H, Bockaert J, Dumuis A. 5-HT$_6$-receptors positively coupled to adenylyl cyclase in striatal neurones in culture. Neuroreport 1994;5:2553–2557.

[3] Holenz J, Pauwels PJ, Diaz JL, Merce R, Codony X, Buschmann H. Medicinal chemistry strategies to 5-HT$_6$ receptor ligands as potential cognitive enhancers and antiobesity agents. Drug Disc Today 2006;11:283–299.

[4] Monsma FJ, Jr, Shen Y, Ward RP, Hamblin MW, Sibley DR. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. Mol Pharmacol 1993; 43:320–327.

[5] Roth BL, Craigo SC, Choudhary MS, Uluer A, Monsma FJ, Jr, Shen Y, Meltzer HY, Siblev DR. Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. J Pharmacol Exp Ther 1994;268:1403–1410.

[6] Tsai SJ, Chiu HJ, Wang YC, Hong CJ. Association study of serotonin-6 receptor variant (C267T) with schizophrenia and aggressive behavior. Neurosci Lett 1999;271:135–137.

[7] Yu YW, Tsai SJ, Lin CH, Hsu CP, Yang KH, Hong CJ. Serotonin-6 receptor variant (C267T) and clinical response to clozapine. Neuroreport 1999;10:1231–1233.

[8] Pouzet B, Didriksen M, Arnt J. Effects of the 5-HT(6) receptor antagonist, SB-271046, in animal models for schizophrenia. Pharmacol Biochem Behav 2002;71:635–643.
[9] Yau JL, Noble J, Widdowson J, Seckl JR. Impact of adrenalectomy on 5-HT6 and 5-HT7 receptor gene expression in the rat hippocampus. Brain Res Mol Brain Res 1997;45: 182–186.
[10] Vogt IR, Shomron AD, Neidt H, Erdmann J, Cichon S, Schulze TG, Muller DJ, Maier W, Albus M, Borrmann HM, Knapp M, Rietschel M, Propping P, Nothen MM. Investigation of the human serotonin 6 [5-HT6] receptor gene in bipolar affective disorder and schizophrenia. Amer J Med Gen 2000;96:217–221.
[11] Yoshioka M, Matsumoto M, Togashi H, Mori K, Saito H. Central distribution and function of 5-HT6 receptor subtype in the rat brain. Life Sci 1998;62:1473–1477.
[12] Unsworth CD, Molinoff PB. Characterization of a 5-hydroxytryptamine receptor in mouse neuroblastoma N18TG2 cells. J Pharmacol Exp Ther 1994;269:246–255.
[13] Otano A, Frechilla D, Cobreros A, Cruz OLM, Insausti A, Insausti R, Hamon M, Del RJ. Anxiogenic-like effects and reduced stereological counting of immunolabelled 5-hydroxytryptamine6 receptors in rat nucleus accumbens by antisense oligonucleotides. Neurosci 1999;92:1001–1009.
[14] Routledge C, Bromidge SM, Moss SF, Price GW, Hirst W, Newman H, Riley G, Gager T, Stean T, Upton N, Clarke SE, Brown AM, Middlemiss DN. Characterization of SB-271046: A potent, selective and orally active 5-HT(6) receptor antagonist. Br J Pharmacol 2000;130:1606–1612.
[15] Svartengren J. The serotonin 5-HT6 receptor antagonist BVT-5182 reduces body weight of high fat diet-induced mice. Int J Obes 2003;27(Suppl. 1. Abst T1):1–094.
[16] Bentley JC, Bourson A, Boess FG, Fone KC, Marsden CA, Petit N, Sleight AJ. Investigation of stretching behaviour induced by the selective 5-HT6 receptor antagonist, Ro 04-6790, in rats. Br J Pharmacol 1999;126:1537–1542.
[17] Woolley ML, Bentley JC, Sleight AJ, Marsden CA, Fone KC. A role for 5-ht6 receptors in retention of spatial learning in the morris water maze. Neuropharmacol 2001;41:210–219.
[18] Riemer C, Borroni E, Levet TB, Martin JR, Poli S, Porter RH, Bos M. Influence of the 5-HT6 receptor on acetylcholine release in the cortex: Pharmacological characterization of 4-(2-bromo-6-pyrrolidin-1-ylpyridine-4-sulfonyl)phenylamine, a potent and selective 5-HT6 receptor antagonist. J Med Chem 2003;46:1273–1276.
[19] Fisas A, Codony X, Romero G, Dordal A, Giraldo J, Merce R, Holenz J, Heal D, Buschmann H, Pauwels PJ. Chronic 5-HT_6 receptor modulation by E-6837 induces hypophagia and sustained weight loss in diet-induced obese rats. Brit J Pharmacol 2006;148:973–983.
[20] Tsai SJ, Chiu HJ, Wang YC, Hong CJ. Association study of serotonin-6 receptor variant (C267T) with schizophrenia and aggressive behavior. Neurosci Lett 1999;271:135–137.
[21] Rogers DC, Hagan JJ. 5-HT6 receptor antagonists enhance retention of a water maze task in the rat. Psychopharmacol (Berl) 2001;158:114–119.
[22] Glennon RA. Higher-end serotonin receptors: 5-HT(5), 5-HT(6), and 5-HT(7). J Med Chem. 2003;46:2795–2812.
[23] Perez GG, Meneses A. Oral administration of the 5-HT6 receptor antagonists SB-357134 and SB-399885 improves memory formation in an autoshaping learning task. Pharmacol Biochem Behav 2005;81:673–682.
[24] Shirsath VS, Deshpande AD, Dwarampudi AR, Bhatta VR, Bhosale SB, Kota S, Kandikere VN, Kambhampati RS, Nirogi RVS. Novel substituted piperazines: New chemical class of selective 5-HT_6 receptor antagonists Poster No. 142 (Abstract No. 142 (Abstract No. 938409), 231st Annual ACS Meeting, Atlanta 2006.
[25] Nirogi RVS, Daulatabad AV, Daulatabad SA, Bhosale SB, Gaddiraju NV, Kandikere VN, Kambhampati RS, Shirsath VS. 3-(Amino) alkoxy indoles: Potent and selective 5-HT_6 receptor antagonists Poster No. 140 (Abstract No. 938426), 231st Annual ACS Meeting, Atlanta 2006.
[26] Harris RLN. A convenient synthesis of 3-indolthiol and derivatives. Tetrahedron Lett 1969;51:4465–4466.
[27] Jasti V, Nirogi RVS, Kambhampati RS, Battula SR, Arava VR, Vadlamudi RVSV. Novel tetracyclic arylsulfonyl indoles having serotonin receptor affinity useful as therapeutic agents, process for their preparation and pharmaceutical compositions containing them. WO 2004/000849 :A2.
[28] Nirogi RVS, Kambhampati RS, Shirsath VS, Jasti V. Benzothiazino indoles. WO 2005/005439 2005; A1.