Journal of Enzyme Inhibition and Medicinal Chemistry

ISSN: 1475-6366 (Print) 1475-6374 (Online) Journal homepage: http://www.tandfonline.com/loi/ienz20

# Synthesis and biological evaluation of novel $N_1$-phenylsulphonyl indole derivatives as potent and selective 5-$HT_6$R ligands for the treatment of cognitive disorders

**Ramakrishna V. S. Nirogi, Thrinath Reddy Bandyala, Pamuletinarasimha Reddy Gangadasari & Mukkanti Khagga**

**To cite this article:** Ramakrishna V. S. Nirogi, Thrinath Reddy Bandyala, Pamuletinarasimha Reddy Gangadasari & Mukkanti Khagga (2016): Synthesis and biological evaluation of novel $N_1$-phenylsulphonyl indole derivatives as potent and selective 5-$HT_6$R ligands for the treatment of cognitive disorders, Journal of Enzyme Inhibition and Medicinal Chemistry, DOI: 10.3109/14756366.2015.1103233

**To link to this article:** http://dx.doi.org/10.3109/14756366.2015.1103233

Published online: 03 Nov 2016.

Journal of Enzyme Inhibition and Medicinal Chemistry

http://informahealthcare.com/enz
ISSN: 1475-6366 (print), 1475-6374 (electronic)

J Enzyme Inhib Med Chem, Early Online: 1–15
 DOI: 10.3109/14756366.2015.1103233

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

# Synthesis and biological evaluation of novel $N_1$-phenylsulphonyl indole derivatives as potent and selective 5-$HT_6$R ligands for the treatment of cognitive disorders

Ramakrishna V. S. Nirogi[1], Thrinath Reddy Bandyala[1,2], Pamuletinarasimha Reddy Gangadasari[1], and Mukkanti Khagga[2]

[1]*Discovery Research, Suven Life Sciences Limited, Hyderabad, India and* [2]*Centre for Chemical Sciences and Technology, Institute of Science and Technology, Jawaharlal Nehru Technological University Hyderabad, Hyderabad, India*

**Abstract**

A series of 1-[3-(4-methyl piperazin-1-ylmethyl) phenylsulfonyl]-1*H*-indole and 1-[3-(4-ethyl piperazin-1-ylmethyl) phenylsulfonyl]-1*H*-indole derivatives were designed and synthesized as 5-$HT_6$ receptor (5-$HT_6$R) ligands. The lead compound 1-[4-methyl-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole dihydrochloride (**6b**), in this series, has shown potent *in vitro* binding affinity, selectivity, good pharmacokinetics (PK) profile and activity in the animal models of cognition.

**Keywords**

5-Hydroxytryptamine-6 receptor, animal models, central nervous system, cognition, novel object recognition test, structure–activity relationship

**History**

Received 15 May 2015
Revised 11 September 2015
Accepted 11 September 2015
Published online 28 October 2016

## Introduction

Alzheimer disease (AD), the most common cause of dementia in the elderly, is clinically characterized by progressive cognitive impairment associated with severe neuropsychiatric disturbances. These behavioral and psychological symptoms of dementia (BPSD) include hallucinations, delusions, aggressive behavior, over activity, anxiety and affective disturbances[1,2]. Current options for treating the cognitive symptoms associated with Alzheimer's are inadequate, giving urgency to the search for novel therapeutic strategies[3–5]. The 5-$HT_6$ receptor has been identified as a potential target for the treatment of cognitive deficits in Alzheimer's disease and schizophrenia.

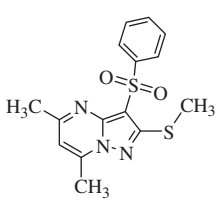
The serotonin-6 receptor (5-$HT_6$) is a *G*-protein-coupled receptor (GPCR) predominantly expressed in the central nervous system (CNS). In particular, it is widely reported to be located in brain regions associated with learning and memory such as the cerebral cortex, the hippocampus and the striatum[6]. It has been demonstrated that antagonism of the 5-$HT_6$ receptor modulates the release of a wide variety of neurotransmitters including elevation of extracellular levels of both glutamate and acetylcholine in brain regions such as the medial prefrontal cortex and the hippocampal formation[7,8]. This modulatory activity suggests potential utility for 5-$HT_6$ receptor antagonists in the treatment of cognitive impairments associated with Alzheimer's disease and schizophrenia.

Research efforts in this area have led to the discovery of a number of potent and selective 5-$HT_6$ receptor antagonists over the past decade, some of which have successfully undergone Phase-I clinical studies and some have been evaluated in clinical Phase-II studies for the treatment of AD[9]. As part of our own research program, we at Suven have designed and developed selective 5-$HT_6$ receptor competitive antagonist, SUVN-502 which has shown positive results in both preclinical and Phase-I study for cognitive impairment in schizophrenia and Alzheimer's disease[10]. Currently, several 5-$HT_6$R antagonists, for example SYN-120 (Biotie therapies)[11], SAM-760 (Pfizer)[12], AVN-211 (Figure 1, Avineuro Pharmaceuticals)[13], Lu AE58054 (Figure 1, Lundbeck)[14], SB-742457 (Figure 1, GlaxoSmithKline, Brentford, England, UK)[15] are the advanced stage clinical candidates for the treatment of different cognitive and mental disorders including Alzheimer's disease and schizophrenia.

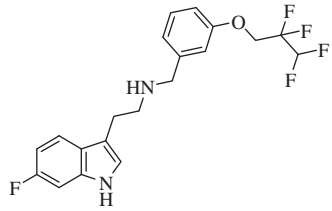
During this decade or so, there was a plenty of chemistry developed around different nuclei including the indole-based ones or even much simpler biphenyl sulfones and sulfonamides[16–33,34] (Figure 2). Suven has reported several series of 1-sulfonylindoles bearing the amino group at 3 or 4 or 5 position of the central core[31–33]. As part of our continuing research efforts in the 5-$HT_6$ area to identify potent and selective 5-$HT_6$ receptor ligands as potential treatments for cognitive dysfunction, we have attempted structural modification of earlier reported piperazinyl methyl-$N_1$-phenylsulfonyl indole derivatives[33]. We wished to determine whether introduction of piperazinyl methyl group on $N_1$-phenylsulfonyl moiety at C-3′ position would have a desired

Address for correspondence: Ramakrishna V. S. Nirogi, Discovery Research, Suven Life Sciences Limited, Serene Chambers, Road-5, Avenue-7, Banjara Hills, Hyderabad, 500 034, India. Tel: +91-40-23556038/23541142. Fax: +91-40-23541152. E-mail: nvsrk@suven.com

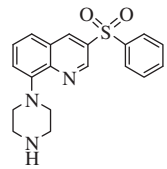
Figure 1. Structures of 5-$HT_6$R antagonists in clinical trials for Alzheimer's disease.



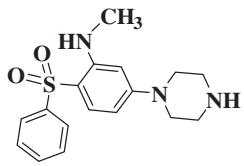
**AVN-211,** $K_i$ = 1.2 nM



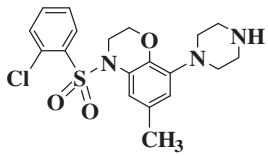
**Lu AE58054,** $K_i$ = 0.83 nM



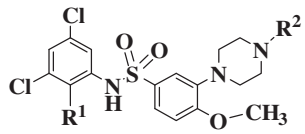
**SB-742457,** $K_i$ = 0.234 nM



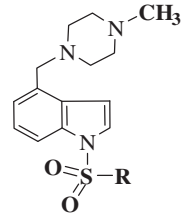
1: $K_i$ = 0.16 nM



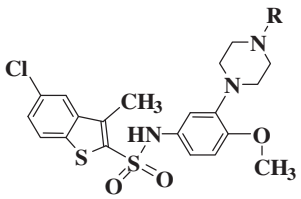
2: $K_i$ = 0.2 nM



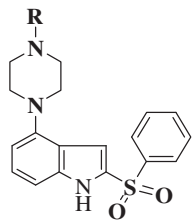
3: $R^1$ = H, $R^2$= $CH_3$, $K_i$ = 0.63 nM, $R^1$ = $OCH_3$, $R^2$ = H, **SB-399885,** $K_i$ = 0.8 nM



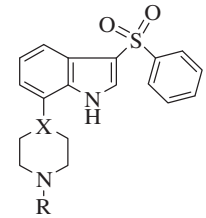
4: R = 2-Br-Ph, $K_i$ =1.4 nM



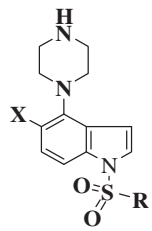
5: R = H, **SB-271046**, $K_i$ = 1.3 nM, R = $CH_3$, **SB-258510,** $K_i$ = 0.63 nM



6: R = H, $K_i$ = 0.2 nM, R = $CH_3$, $K_i$ = 0.2 nM



7: X = N, R = H, $K_i$ = 0.5 nM, X = N, R = $CH_3$, **RO-4368554,** $K_i$ = 0.5 nM, X = C, R = H, $K_i$ = 0.3 nM



8: X = Cl, R = Ph, $K_i$ = 1.0 nM, X = Cl, R = 3-Cl-Ph, **SB-699929,** $K_i$ = 0.3 nM,

Figure 2. Structures of known 5-$HT_6$ receptor ligands.

effect on the binding to 5-$HT_6$R and aimed to investigate the structure–activity relationship (SAR). Researchers have developed a pharmacophore model (Figure 3) for 5-$HT_6$ receptor antagonists, based on reported chemically diverse 5-$HT_6$ receptor antagonists[35–42,34]. In this pharmacophore model, four core features were taken into consideration which include the positive ionizable atom (PI, usually a secondary or tertiary amino group), a hydrogen bond acceptor group (HBA, usually a sulfone or sulfonamide group), a hydrophobic site (HYD) and $\pi$-electron donor aromatic or heterocyclic ring (AR). We have designed and synthesized a series of sulfonyl indoles bearing basic cyclic amines (i.e. $N_1$-$CH_3$ and $N_1$-$C_2H_5$ substituted piperazines) on phenyl ring at C-3′ position (Figure 4), this designed series of compounds has all the required pharmacophoric features for binding to 5-$HT_6$R, and hence, we expected these compounds to be potent 5-$HT_6$R ligands. Herein, we report a series of 1-[3–(4-methyl piperazin-1-ylmethyl) phenylsulfonyl]-1*H*-indole and 1-[3-(4-ethyl piperazin-1-ylmethyl) phenylsulfonyl]-1*H*-indole derivatives as potent and selective 5-$HT_6$R ligands (Compounds-6, Figure 4).

The selected compound 6b from this series was active in animal models of cognition. The synthesis, *in vitro* activity, selectivity, SAR, CYP liabilities in human liver microsomes, pharmacokinetics and pharmacological activities of this series of compounds are discussed in this paper.

Chemistry: The general synthetic strategy used for the preparation of 1-[3-(4-methyl piperazin-1-ylmethyl) phenylsulfonyl]-1*H*-indole and 1-[3-(4-ethyl piperazin-1-ylmethyl) phenylsulfonyl]-1*H*-indole derivatives (Compounds 6) was summarized in Scheme I.

Commercially available substituted 3-chlorosulfonyl benzoic acid 2 was reacted with substituted indoles 1 in the presence of sodium hydride as base at room temperature to obtain 3-(indole-1-sulfonyl) benzoic acid derivatives 3. The latter were treated with lithium aluminum hydride at 0 to 5 °C to obtain 1-(3-hydroxymethyl phenylsulfonyl)-1*H*-indole derivatives 4 in an overall yield of 33–55%.

The intermediates 4 were treated with manganese dioxide under reflux to afford 1-(3-formyl phenylsulfonyl)-1*H*-indole derivatives 5 in 75–85% yield. Finally, the aromatic aldehydes 5 were reacted with appropriate $N_1$-alkyl piperazines ($N_1$-$CH_3$ and $N_1$-$C_2H_5$) in the presence of sodium triacetoxy borohydride as reducing agent, to obtain the targeted compounds 6. The latter compounds were further treated with methanolic hydrochloric acid (16% w/v) to obtained the desired compounds as HCl salts (compounds 6) in 55–65% yield.

## 5-$HT_6$R-binding data (*in vitro*)

### Radioligand binding assay for human 5-$HT_6$ receptor

The *in vitro* 5-$HT_6$ receptor-binding assay was carried out on human recombinant receptor expressed in HEK293 cells; radioligand used was [$^3$H] LSD (60–80 Ci/mmol). Final ligand concentration was 1.5 nM, nonspecific determinant was

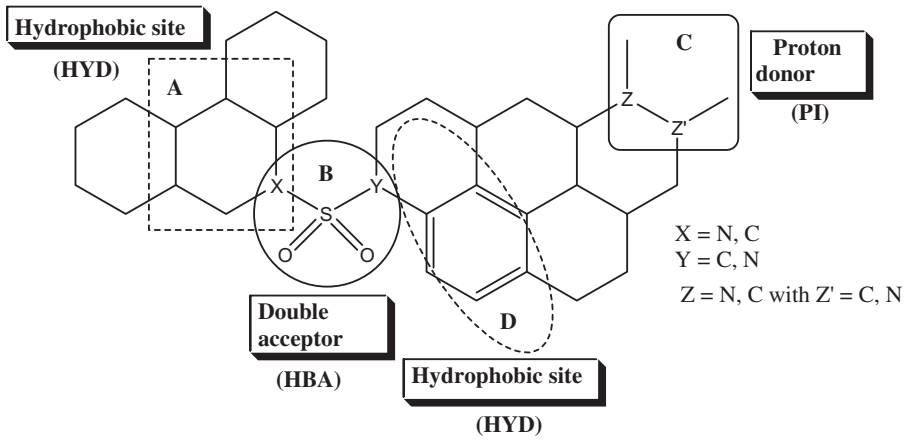
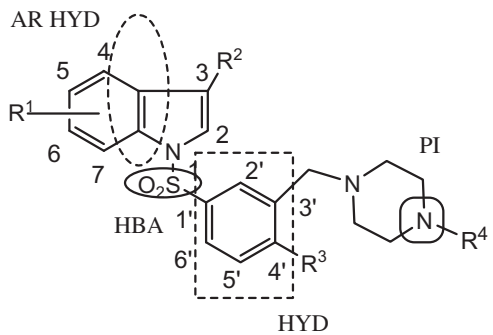



Figure 3. 5-$HT_6$ receptor pharmacophore model.




**Compounds-6**

Figure 4. General structure of designed 5-$HT_6$ receptor ligands.

methiothepin mesylate – [0.1 μM]; Methiothepin mesylate was used as reference compound and positive control. The radioligand binding study was carried out at NovaScreen, Hanover, MD.

## Materials and methods

### General considerations

Infrared spectra were recorded in KBr disc and in solid state using Perkin-Elmer model 1600 FT-IR spectrophotometer (Perkin-Elmer, Norwalk, CT). Electrospray ionization mass spectra were recorded on API 4000 triple quadrupole instrument (MDSSCIEX, 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 ($\delta$) and coupling constants are expressed in Hertz (Hz). Chromatography refers to column chromatography performed using 100–200 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions. All the reagents and chemicals used were of ''reagent grade''.

### Determination of % inhibition at 100 nM concentration, $k_i$ and $IC_{50}$ values for 5-$HT_6$ receptor

The *in vitro* 5-$HT_6$ receptor-binding assay was carried out on human recombinant expressed receptor in HEK293 cells; Radioligand used was [$^3$H]LSD (60–80 Ci/mmol). Final ligand concentration was 1.5 nM, nonspecific determinant was methiothepin mesylate – [0.1 μM]; methiothepin mesylate was used as reference compound and positive control. $K_i$ values were determined in duplicate and the average values are reported here. 5-$HT_6$ receptor-binding studies were carried out at NovaScreen Biosciences Corporation, (caliper life sciences), Hanover, MD, as per their standard protocol.

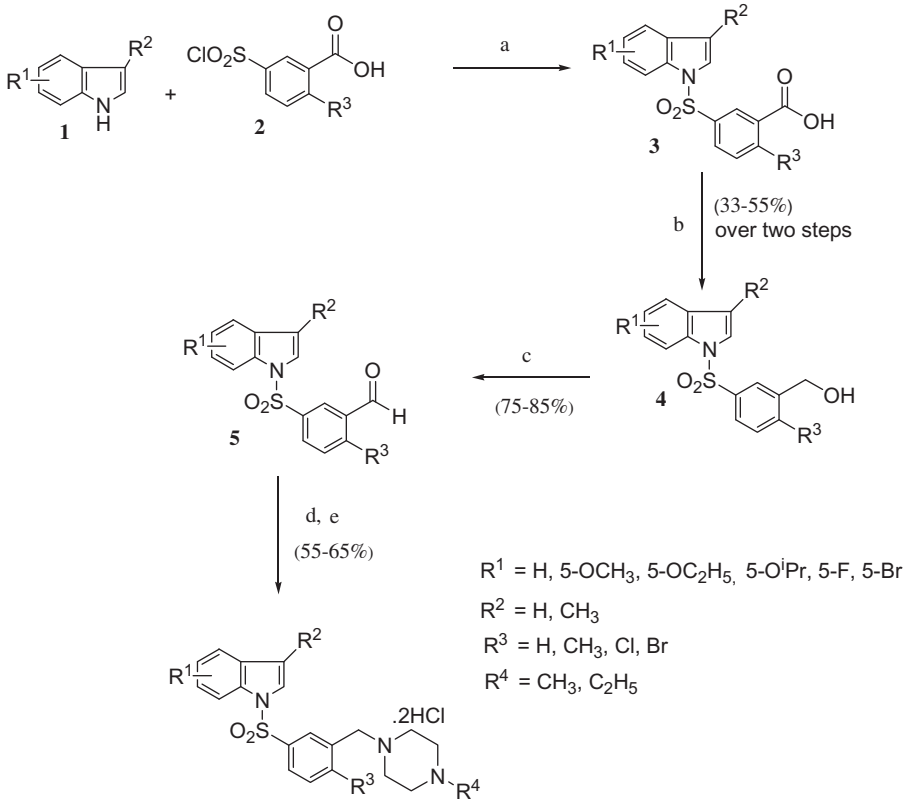
### Determination of $k_b$ and $IC_{50}$ values for 5-$HT_6$ receptor antagonists

A stable CHO cell line expressing recombinant human 5-$HT_6$ receptor and pCRE-Luc reporter system was used for cell-based assay. The assay offers a nonradioactive-based approach to determine potency of a compound to GPCRs. In this specific assay, the level of intracellular cyclic AMP which is modulated by the activation or inhibition of the receptor is measured. The recombinant cells harbor luciferase reporter gene under the control of cAMP response element. The above cells were plated in 96-well clear bottom white plates at a density of $5 \times 10^4$ cells/well using Hams F12 medium containing 10% fetal bovine serum (FBS) and incubated overnight at 37 °C and 5% $CO_2$ followed by serum starvation for 18–20 h. Increasing concentrations of test compounds were added along with 10 μM serotonin in OptiMEM to the cells. The incubation was continued at 37 °C in $CO_2$ incubator for 4 h. After 4 h, cells were lysed using lyses buffer and luciface assay buffer was added to each well and counts per second were recorded using luminescence counter. From CPS obtained, percentage inhibition was calculated for each well by normalizing CPS values obtained in the presence of the compounds to those with 10 μM 5-HT (0% inhibition) and with vehicle (100% inhibition). The percent inhibition was determined for all concentrations of the antagonists (0.1 nM–10 μM range, half-log increment) and plotted as a function of the antagonist concentration. The $K_b$ values were calculated with Prism (GraphPad Software Inc., La Jolla, CA) using built-in one site competition equation, by entering $EC_{50}$ values for 5-HT obtained in the same experiments (80–100 nM) and the 5-HT concentration 10 μM, as it was used in all the experiments.

### Rodent pharmacokinetic study

Male Wistar rats (225 ± 25 gm) were used as experimental animals. Three animals were housed in each cage. Two days prior to dosing day, male Wistar rats (225–250 gm) were anesthetized with isoflurane for the surgical placement of jugular vein catheter. Animals were fasted over night before oral dosing (p.o) and food pellets were allowed 2-h postdosing, whereas during intravenous dosing, food and water were provided as *ad libitum*. Three rats were dosed with compounds (10 mg/kg) orally and intravenously (10 mg/kg).

Scheme I. Reagents and conditions: (a) NaH, tetrahydrofuran, RT, 20–24 h; (b) $LiAlH_4$, 0–5 °C, 4–5 h; (c) $MnO_2$, Ethylene Dichloride, reflux, 3–4 h; (d) *N*-methyl (or) *N*-ethyl piperazine, Ethylene Dichloride, $Na(OAC)_3BH$, RT, 6–7 h; (e) Methanolic HCl (16% w/v), Diethylether, RT, 1 h.




**Compounds-6a to 6ac**

At each time point, blood was collected through jugular vein and immediately replenish with an equivalent volume of normal saline from freely moving rats. Collected blood was transferred into a labeled appendorf containing 10 µL of heparin as anticoagulant. Blood samples were collected at following time points: pre dose, 0.08 (only *i.v.*), 0.25-, 0.5-, 1-, 2-, 4-, 6-, 8- and 24-h postdose ($n = 3$). Blood was centrifuged at 4000 rpm for 10 min. Plasma was prepared and stored at −20 °C until analysis. The concentrations of the compounds were quantified in plasma by qualified LC-MS/MS method using suitable extraction technique. The compounds were quantified in the calibration range around 2–2000 ng/mL in plasma. Study samples were analyzed using calibration samples in the batch and quality control samples spread across the batch.

Pharmacokinetic parameters, $C_{max}$, $AUC_{0\text{-}t}$, $t_{1/2}$ and bioavailability, were calculated by noncompartmental model using standard noncompartmental model by using WinNonLin 5.0.1 version Software package (Pharsight corporation, Mountain view, CA).

### Rodent brain penetration study

Male Wistar rats (225 ± 25 gm) were used as experimental animals. Three animals were housed in each cage. Animals were given water and food *ad libitum* throughout the experiment and maintained on a 12-h light/dark cycle.

Brain penetration was determined at steady state in rat. One day prior to dosing day, male wistar rats (225 ± 25 gm) were anesthetized with halothane for the surgical placement of jugular and femoral vein catheters. After surgery, the rats were housed in individual rat infusion cage connected with infusion components and allowed free access to food and water.

The test compound was dissolved in water and administered at a constant infusion rate (5 mL/kg/h) upto 6 h at a target dose rate 1.0 mg free base/kg/h. Blood samples were removed during the latter part of the infusion to confirm steady-state blood concentrations, brian and blood was collected and estimated. The animals were sacrificed to collect the plasma and brain tissue and thenhomogenized using milli-Q water (20%). Plasma and brain was stored frozen at −20 °C until analysis. The concentrations of the test compound in plasma and brain were determined using LC-MS/MS method.

The test compound was quantified in plasma and brain homogenate by validated LC-MS/MS method using solid-phase extraction technique. The compound was quantified in the calibration range of 1–500 ng/mL in plasma and brain homogenate. Study samples were analyzed using calibration samples in the batch and quality control samples spread across the batch. Extent of brain-plasma ratio was calculated ($C_b/C_p$).

### Protocol for NORT

For object recognition test, male Wistar rats 10–12 weeks old were used. Arena was 50 × 50 × 50 cm. Open field was made up of acrylic. Twnety-four hours prior to testing, rats were habituated to individual test arenas for 20 min in the absence of any objects. Twnety-four hours after the habituation, during the familiarization phase (T1), rats were placed individually in the open field for 3 min, containing two identical objects (a1 and a2). T2 trial was carried out after 24 h after the T1 trial. Rats were allowed to explore the open field for 3 min in the presence of one familiar object (a3) and one novel object (b). Discriminative index was calculated.

## Experimental

### Experimental procedures and analytical characterization data of compounds 3a–3ab, 4a–4ab, 5a–5ab and 6a–6ac

General (representative) procedure for the synthesis of compound 6 g (Di HCl Salt)

*Preparation of 2-bromo-5-(indole-1-sulfonyl) benzoic acid (3 g).* A solution of indole (6.24 g, 53.33 mmol) in 25 mL

tetrahydrofuran (THF) was slowly added to a cooled (20 °C) suspension of sodium hydride (6.59 g, 164.74 mmol) in 20 mL of THF, over a period of 10 min maintaining the mass temperature at 25 °C under nitrogen atmosphere. The mass was further diluted with tetrahydrofuran (20 mL). The reaction mixture was further stirred for 1 h at the same temperature. Then, added a solution of 2-bromo-5-chlorosulfonyl benzoic acid (20.01 g, 66.81 mmol) in THF (30 mL) slowly over a period of 10 min. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was quenched onto 600 mL cold water. The reaction mass was acidified with concentrated hydrochloric acid to pH 2 and extracted the product with ethyl acetate (2 × 200 mL). The combined organic layer was washed with brine solution (2 × 50 mL), water (2 × 100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 17.81 g technical product. The material was used as such in the next step, with out further purification.

Melting range: 188.7–191.4 °C (dec); IR spectra ($cm^{-1}$): 1710, 1683, 1579, 1440, 1371, 1255, 1180, 1124, 744; ESIMS (*m/z*): 378.1, 380.0 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.6–6.61 (d, 1H, *J* = 3.88 Hz, Ar-**H**), 7.13–7.24 (m, 2H, Ar-**H**), 7.43–7.45 (m, 2H, Ar-**H**), 7.61–7.64 (m, 2H, Ar-**H**), 7.83–7.85 (d, 1H, *J* = 8.24, Ar-**H**), 8.23 (d, 1H, *J* = 2.04 Hz, Ar-**H**).

Similarly, compounds **3a**–**3ab** were prepared from respective starting materials **1** (commercially available substituted indoles) and **2** (commercially available substituted 3-chlorosulfonyl benzoic acids) by using the method described previously, for example **3 g** with some noncritical variations. The analytical data of compounds **3a**–**3ab** are presented below. The obtained technical product was used as such in the next step, with out further purification.

**3-(Indole-1-sulfonyl) benzoic acid (3a**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **H**): ESIMS (*m/z*): 300.1 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.69–6.70 (d, 1H, *J* = 3.08 Hz, Ar-**H**), 7.23–7.27 (m, 2H, Ar-**H**), 7.33–7.37 (m, 1H, Ar-**H**), 7.52–7.61 (m, 2H, Ar-**H**), 8.00–8.02 (m, 1H, Ar-**H**), 8.09–8.12 (m, 1H, Ar-**H**), 8.23–8.26 (m, 1H, Ar-**H**), 8.60 (d, 1H, *J* = 1.60 Hz, Ar-**H**).

**5-(Indole-1-sulfonyl)-2-methyl benzoic acid (3b**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **4′-CH$_3$**): Melting range (°C): 173.60–174.7 (Clear); IR ($cm^{-1}$): 3126, 2924, 1699, 1440, 1375, 1261, 1172, 1120; ESIMS (*m/z*): 314.4 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.62 (s, 3H, Ar-C**H$_3$**), 6.67–6.68 (d, 1H, *J* = 3.6 Hz, Ar-**H**), 7.21–7.25 (m, 1H, Ar-**H**), 7.30–7.34 (m, 2H, Ar-**H**), 7.51–7.53 (d, 1H, *J* = 7.8 Hz, Ar-**H**), 7.56–7.57 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.89–7.91 (dd, 1H, *J* = 8.16, 2.04 Hz, Ar-**H**), 7.98–8.00 (d, 1H, *J* = 8.32 Hz, Ar-**H**), 8.55–8.56 (d, 1H, *J* = 1.96 Hz, Ar-**H**).

**2-Chloro-5-(indole-1-sulfonyl) benzoic acid (3d**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **Cl**): Melting range (°C): 177.7–182.1 (dec); IR ($cm^{-1}$): 3138, 1695, 1442, 1375, 1259, 1178, 1124; ESIMS (*m/z*): 334.1, 336.1 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.71–6.72 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 7.24–7.28 (m, 1H, Ar-**H**), 7.33–7.37 (m, 1H, Ar-**H**), 7.54–7.56 (m, 3H, Ar-**H**), 7.90–7.93 (dd, 1H, *J* = 8.52, 2.40 Hz, Ar-**H**), 7.97–7.99 (d, 1H, *J* = 8.16 Hz, Ar-**H**), 8.50–8.51 (d, 1H, *J* = 2.36 Hz, Ar-**H**).

**3-(5-Methoxy indole-1-sulfonyl) benzoic acid (3 h**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **H**): ESIMS (*m/z*): 330.3 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 3.80 (s, 3H, Ar-OC**H$_3$**), 6.62–6.63 (d, 1H, *J* = 3.63 Hz, Ar-**H**), 6.93–6.94 (d, 1H, *J* = 2.50 Hz, Ar-**H**), 6.96–6.97 (m, 1H, Ar-**H**), 7.53–7.58 (m, 2H, Ar-**H**), 7.89–7.91 (d, 1H, *J* = 8.76 Hz, Ar-**H**), 8.05–8.08 (m, 1H, Ar-**H**), 8.22–8.25 (m, 1H, Ar-**H**), 8.56–8.57 (d, 1H, *J* = 1.72 Hz, Ar-**H**).

**3-(5-Ethoxy indole-1-sulfonyl) benzoic acid (3i**, $R^1$ = **5-OCH$_2$CH$_3$**, $R^2$ = **H**, $R^3$ = **H**): ESIMS (*m/z*): 344.3 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.38–1.42 (*t*, 3H, Ar-OCH$_2$C**H$_3$**), 3.98–4.04 (*q*, 2H, Ar-OC**H$_2$**CH$_3$), 6.60–6.61 (d, 1H, *J* = 3.60 Hz, Ar-**H**), 6.93–6.99 (m, 2H, Ar-**H**), 7.52–7.57 (m, 2H, Ar-**H**), 7.88–7.90 (d, 1H, *J* = 9.16 Hz, Ar-**H**), 8.05–8.09 (d, 1H, *J* = 7.88 Hz, Ar-**H**), 8.21–8.23 (d, 1H, *J* = 7.80 Hz, Ar-**H**), 8.56 (s, 1H, Ar-**H**).

**3-(5-Isopropoxy indole-1-sulfonyl) benzoic acid (3j**, $R^1$ = **5-OCH(CH$_3$)$_2$**, $R^2$ = **H**, $R^3$ = **H**): ESIMS (*m/z*): 358.2 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.31–1.32 (d, 6H, *J* = 6.04 Hz, Ar-OCH(C**H$_3$**)$_2$), 4.42–4.54 (sept, 1H, Ar-OC**H**(CH$_3$)$_2$), 6.60 (d, 1H, *J* = 3.56 Hz, Ar-**H**), 6.91–6.94 (dd, 1H, *J* = 8.96, 2.40 Hz, Ar-**H**), 6.97 (d, 1H, *J* = 2.36 Hz, Ar-**H**), 7.52–7.53 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.54–7.58 (m, 1H, Ar-**H**), 7.87–7.89 (d, 1H, *J* = 8.92 Hz, Ar-**H**), 8.06–8.09 (m, 1H, Ar-**H**), 8.23–8.25 (m, 1H, Ar-**H**), 8.58 (d, 1H, *J* = 1.61 Hz, Ar-**H**).

**3-(5-Fluoro indole-1-sulfonyl) benzoic acid (3k**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **H**): ESIMS (*m/z*): 318.1 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.65–6.66 (d, 1H, *J* = 3.08 Hz, Ar-**H**), 7.05–7.11 (m, 1H, Ar-**H**), 7.17–7.20 (dd, 1H, *J* = 8.64, 2.52 Hz, Ar-**H**), 7.59–7.62 (m, 2H, Ar-**H**), 7.94–7.98 (m, 1H, Ar-**H**), 8.07–8.09 (m, 1H, Ar-**H**), 8.25–8.27 (m, 1H, Ar-**H**), 8.57 (d, 1H, *J* = 1.64 Hz, Ar-**H**).

**5-(5-Methoxy indole-1-sulfonyl)-2-methyl benzoic acid, (3 l**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **CH$_3$**): Melting range (°C): 190.2–194.9 (dec); IR ($cm^{-1}$): 3151, 1728, 1440, 1369, 1219, 1145; ESIMS (*m/z*): 344.1 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.69 (s, 3H, Ar-C**H$_3$**), 3.81 (s, 3H, Ar-OC**H$_3$**), 6.60–6.61 (d, 1H, *J* = 3.08 Hz, Ar-**H**), 6.93 (d, 1H, *J* = 2.48 Hz, Ar-**H**), 6.95–6.97 (dd, 1H, *J* = 6.68, 2.20 Hz, Ar-**H**), 7.32–7.34 (d, 1H, *J* = 8.24, Ar-**H**), 7.52–7.53 (d, 1H, *J* = 3.60 Hz, Ar-**H**), 7.86–7.90 (m, 2H, Ar-**H**), 8.52–8.53 (d, 1H, *J* = 2.12 Hz, Ar-**H**).

**5-(5-Fluoro indole-1-sulfonyl)-2-methyl benzoic acid (3m**, $R^1$ = **5-F**, $R^2$ = **H**, $R^3$ = **CH$_3$**): Melting range (°C): 198.7–200.7 (dec); IR ($cm^{-1}$): 3500, 3111, 1693, 1452, 1369, 1267, 1128; ESIMS (*m/z*): 331.9 $[M-H]^-$; $^1$H-NMR (400 MHz, DMSO-$d_6$): **δ** 2.49 (s, 3H, Ar-C**H$_3$**), 6.83–6.84 (d, 1H, *J* = 3.24 Hz, Ar-**H**), 7.18–7.23 (m, 1H, Ar-**H**), 7.40–7.43 (dd, 1H, *J* = 9.08, 2.60 Hz, Ar-**H**), 7.51–7.53 (d, 1H, *J* = 8.24, Ar-**H**), 7.90–7.92 (m, 2H, Ar-**H**), 8.00–8.03 (dd, 1H, *J* = 8.16 & 2.24 Hz, Ar-**H**), 8.24–8.25 (d, 1H, *J* = 2.20 Hz, Ar-**H**), 13.46–13.49 (bs, 1H, Ar-COO**H**).

**2-Chloro-5-(5-fluoro indole-1-sulfonyl) benzoic acid (3o**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **Cl**): Melting range (°C): 189.6–191.5 (Clear); ESIMS (*m/z*): 352.5, 354.5 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.67–6.68 (d, 1H, *J* = 3.18 Hz, Ar-**H**), 7.06–7.11 (m, 1H, Ar-**H**), 7.18–7.20 (dd, 1H, *J* = 8.60, 2.52 Hz, Ar-**H**), 7.55–7.56 (d, 1H, *J* = 2.34 Hz, Ar-**H**), 7.58–7.60 (d, 1H, *J* = 8.48 Hz, Ar-**H**), 7.89–7.90 (dd, 1H, *J* = 8.50, 2.41 Hz, Ar-**H**), 7.91–7.94 (m, 1H, Ar-**H**), 8.48–8.49 (d, 1H, *J* = 2.36 Hz, Ar-**H**).

**2-Bromo-5-(5-fluoro indole-1-sulfonyl) benzoic acid (3q**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **Br**): Melting range (°C): 193.6–196.5 (Clear); IR ($cm^{-1}$): 3140, 2922, 1701, 1456, 1375, 1294, 1174, 1130; ESIMS (*m/z*): 397, 399 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.66 (d, 1H, *J* = 3.40 Hz, Ar-**H**), 6.66–7.09 (m, 1H, Ar-**H**), 7.17–7.20 (dd, 1H, *J* = 8.60, 2.52 Hz, Ar-**H**), 7.56–7.57 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.76–7.77 (m, 2H, Ar-**H**), 7.90–7.93 (dd, 1H, *J* = 9.12, 2.41 Hz, Ar-**H**), 8.40–8.41 (d, 1H, *J* = 1.32 Hz, Ar-**H**).

**2-Bromo-5-(5-bromo indole-1-sulfonyl) benzoic acid (3s**, $R^1$ = **Br**, $R^2$ = **H**, $R^3$ = **Br**):

ESIMS (*m/z*): 456.1, 458.2, 460.2 $[M-H]^-$.

**2-Chloro-5-(5-methoxy indole-1-sulfonyl) benzoic acid (3*t***, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **Cl**): Melting range (°C): 156.75–157.45 (Clear); IR ($cm^{-1}$): 3115, 1705, 1462, 1373, 1217, 1135; ESIMS (*m/z*): 364.2, 366.2 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 3.81 (s, 3H, Ar-OC**H$_3$**), 6.63–6.64 (d, 1H, *J* = 3.16 Hz, Ar-**H**), 6.94–6.98 (m, 2H, Ar-**H**), 7.49–7.54 (m, 2H, Ar-**H**), 7.86–7.89 (m, 2H, Ar-**H**), 8.47 (d, 1H, *J* = 2.40 Hz, Ar-**H**).

**2-Bromo-5-(5-methoxy indole-1-sulfonyl) benzoic acid (3v**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **Br)**: Melting range (°C): 177.50–177.80 (Clear); IR (cm$^{-1}$): 3130, 1714, 1467, 1373, 1222, 1147; ESIMS (*m/z*): 407.9, 409.8 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 3.81 (s, 3H, Ar-OC**H$_3$**), 6.63–6.64 (d, 1H, *J* = 3.12 Hz, Ar-**H**), 6.94–6.96 (dd, 1H, *J* = 8.88, 2.48 Hz, Ar-**H**), 6.97–6.98 (d, 1H, *J* = 2.2 Hz, Ar-**H**), 7.48–7.49 (d, 1H, *J* = 3.6 Hz, Ar-**H**), 7.74–7.79 (m, 2H, Ar-**H**), 7.85–7.87 (d, 1H, *J* = 8.84 Hz, Ar-**H**), 8.42 (d, 1H, *J* = 1.32 Hz, Ar-**H**).

**2-Chloro-5-(3-methyl indole-1-sulfonyl) benzoic acid (3x**, $R^1$ = **H**, $R^2$ = **CH$_3$**, $R^3$ = **Cl)**: Melting range (°C): 188.40–191.50 (Clear); IR (cm$^{-1}$): 2921, 1714, 1444, 1372, 1276, 1182, 1121; ESIMS (*m/z*): 348.0, 350.1 $[M-H]^-$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.25 (d, 3H, Ar-C**H$_3$**), 7.28–7.30 (m, 2H, Ar-**H**), 7.33–7.38 (m, 1H, Ar-**H**), 7.46–7.48 (d, 1H, *J* = 7.84 Hz, Ar-**H**), 7.51–7.53 (d, 1H, *J* = 8.52 Hz, Ar-**H**), 7.88–7.91 (dd, 1H, *J* = 8.48, 2.40 Hz, Ar-**H**), 7.97–7.99 (d, 1H, *J* = 8.20, Ar-**H**), 8.48–8.49 (d, 1H, *J* = 2.32 Hz, Ar-**H**).

**2-Bromo-5-(3-methyl indole-1-sulfonyl) benzoic acid (3z**, $R^1$ = **H**, $R^2$ = **CH$_3$**, $R^3$ = **Br)**: ESIMS (*m/z*): 392.2, 394.2 $[M-H]^-$.

**2-Chloro-5-(5-methoxy-3-methyl indole-1-sulfonyl) benzoic acid (3ab**, $R^1$ = **5-OCH$_3$**, $R^2$ = **CH$_3$**, $R^3$ = **Cl)**: ESIMS (*m/z*): 378.2, 380.2 $[M-H]^-$.

### Preparation of 1-[4-bromo-3-(hydroxymethyl) phenylsulfonyl]-1H-indole (4g)

A solution of 2-bromo-5-(indole-1-sulfonyl) benzoic acid (17.64 g, 46.42 mmol) in 30 mL tetrahydrofuran was slowly added to a cooled (0–5 °C) suspension of lithium aluminum hydride (2.3 g, 60.5 mmol) in 20 mL of THF. The reaction mass was stirred at 0–5 °C for 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled to −10 °C. Water (20 mL) was added slowly under nitrogen atmosphere. The reaction mass was diluted further with water (300 mL) and filtered through hyflow bed. The clear filtrate was extracted with ethyl acetate (4 × 100 mL). The combined organic layer was washed with brine solution (2 × 50 mL), water (2 × 50 mL) and dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residual mass was purified by column chromatography, the eluent system being ethyl acetate and hexane (2:8) to obtain 6.025 g of the title product, Yield: 33% (over 2 steps).

Melting range: 102.6–103.4 °C (dec); I.R (cm$^{-1}$): 3311, 1444, 1371, 1257, 1128, 879; ESIMS (*m/z*): 366 $[M+H]^+$, 368 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 4.69 (s, 2H, Ar-C**H$_2$**OH), 6.67–6.68 (dd, 1H, *J* = 3.64, 0.68 Hz, Ar-**H**), 7.23–7.25 (m, 1H, Ar-**H**), 7.32–7.33 (m, 1H, Ar-**H**), 7.55–7.64 (m, 4H, Ar-**H**), 7.97–7.99 (dd, 1H, *J* = 4.28, 0.8 Hz, Ar-**H**), 8.04–8.05 (d, 1H, Ar-**H**).

Similarly compounds **4a–4ab** were prepared from respective starting materials **3a–3ab** by using the method described earlier for the example **4 g** with some noncritical variations. The analytical data of compounds **4a–4ab** are presented below.

**[3-(Indole-1-sulfonyl)-phenyl]-methanol (4a**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **H)**: Yield: 55% (over 2 steps); ESIMS (*m/z*): 288.2 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.80 (bs, 1H, Ar-$CH_2$O**H**), 4.69 (s, 2H, Ar-C**H$_2$**OH), 6.66–6.67 (d, 1H, *J* = 3.60 Hz, Ar-**H**), 7.21–7.24 (m, 1H, Ar-**H**), 7.30–7.34 (m, 1H, Ar-**H**), 7.40–7.44 (m, 1H, Ar-**H**), 7.51–7.53 (m, 2H, Ar-**H**), 7.56–7.57 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.79–7.81 (d, 1H, *J* = 8.28 Hz, Ar-**H**), 7.88 (s, 1H, Ar-**H**), 7.78–8.00 (d, 1H, *J* = 8.32 Hz, Ar-**H**).

**1-[4-Methyl-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4b**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **CH$_3$)**: Yield: 48% (over 2 steps); Melting range (°C): 101.0–102.8 (Clear); IR (cm$^{-1}$): 3280, 1444, 1365, 1163, 1126; ESIMS (*m/z*): 302.7 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.72 (bs, 1H, Ar-$CH_2$O**H**), 2.27 (s, 3H, Ar-C**H$_3$**), 4.64–4.65 (d, 2H, Ar-C**H$_2$**OH), 6.64–6.65 (d, 1H, *J* = 3.6 Hz, Ar-**H**), 7.19–7.30 (m, 3H, Ar-**H**), 7.51–7.52 (d, 1H, *J* = 6.56 Hz, Ar-**H**), 7.57–7.58 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 7.92–7.93 (d, 1H, *J* = 1.92 Hz, Ar-**H**), 7.98 (d, 1H, *J* = 0.72 Hz, Ar-**H**), 8.05–8.07 (d, 1H, *J* = 0.68 Hz, Ar-**H**).

**1-[4-Chloro-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4d**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **Cl)**: Yield: 39% (over 2 steps); Melting range (°C): 104.5–107.4 °C (dec); IR (cm$^{-1}$): 3429, 1446, 1371, 1261, 1166, 1126; ESIMS (*m/z*): 322.1 $[M+H]^+$, 324.0 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.85 (bs, 1H, Ar-$CH_2$O**H**), 4.72 (s, 2H, Ar-C**H$_2$**OH), 6.67–6.68 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 7.21–7.25 (m, 1H, Ar-**H**), 7.32–7.37 (m, 1H, Ar-**H**), 7.39–7.41 (m, 1H, Ar-**H**), 7.52–7.56 (m, 2H, Ar-**H**), 7.72–7.74 (dd, 1H, *J* = 8.36, 2.28 Hz, Ar-**H**), 7.97–7.99 (d, 1H, *J* = 8.28 Hz, Ar-**H**), 8.06–8.07 (d, 1H, *J* = 2.0 Hz, Ar-**H**).

**5-Methoxy-1-[3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4 h**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **H)**: Yield: 48% (over 2 steps); ESIMS (*m/z*): 318.2 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.85–1.87 (bs, 1H, Ar-$CH_2$O**H**), 3.80 (s, 3H, Ar-OC**H$_3$**), 4.69 (s, 2H, Ar-C**H$_2$**OH), 6.58–6.59 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 6.91–6.93 (dd, 1H, *J* = 8.8, 2.52 Hz, Ar-**H**), 6.96 (d, 1H, *J* = 2.36 Hz, Ar-**H**), 7.38–7.42 (m, 1H, Ar-**H**), 7.51–7.52 (m, 2H, Ar-**H**), 7.75–7.77 (d, 1H, *J* = 7.84 Hz, Ar-**H**), 7.85–7.89 (m, 2H, Ar-**H**).

**5-Ethoxy-1-[3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4i**, $R^1$ = **5-OCH$_2$CH$_3$**, $R^2$ = **H**, $R^3$ = **H)**: Yield: 44% (over 2 steps); ESIMS (*m/z*): 332.3 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.80 (bs, 1H, Ar-$CH_2$O**H**), 1.38 – 1.42 (t, 3H, Ar-$OCH_2$C**H$_3$**), 3.98–4.04 (*q*, 2H, Ar-OC**H$_2$**$CH_3$), 4.69 (s, 2H, Ar-C**H$_2$**OH), 6.57–6.58 (d, 1H, *J* = 3.16 Hz, Ar-**H**), 6.90–6.95 (m, 2H, Ar-**H**), 7.40–7.42 (m, 1H, Ar-**H**), 7.50–7.52 (m, 2H, Ar-**H**), 7.75–7.77 (d, 1H, *J* = 7.84 Hz, Ar-**H**), 7.85–7.88 (m, 2H, Ar-**H**).

**5-Isopropoxy-1-[3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4j**, $R^1$ = **5-OCH(CH$_3$)$_2$**, $R^2$ = **H**, $R^3$ = **H)**: Yield: 43% (over 2 steps); ESIMS (*m/z*): 346.0 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.98 (bs, 1H, Ar-$CH_2$O**H**), 1.29–1.30 (d, 6H, *J* = 5.84 Hz, Ar-OCH(C**H$_3$**)$_2$), 4.46–4.52 (sept, 1H, Ar-OC**H**$(CH_3)_2$), 4.67 (s, 2H, Ar-C**H$_2$**OH), 6.55–6.56 (d, 1H, *J* = 3.0 Hz, Ar-**H**), 6.88–6.91 (dd, 1H, *J* = 9.0, 2.44 Hz, Ar-**H**), 6.95–6.96 (d, 1H, *J* = 2.40 Hz, Ar-**H**), 7.36–7.40 (m, 1H, Ar-**H**), 7.48–7.50 (m, 2H, Ar-**H**), 7.74–7.76 (d, 1H, *J* = 7.84 Hz, Ar-**H**), 7.84–7.86 (m, 2H, Ar-**H**).

**5-Fluoro-1-[3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4k**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **H)**: Yield: 51% (over 2 steps); ESIMS (*m/z*): 306.2 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.0 (bs, 1H, Ar-$CH_2$O**H**), 4.68 (s, 2H, Ar-C**H$_2$**OH), 6.61 (d, 1H, *J* = 3.08 Hz, Ar-**H**), 7.03–7.06 (m, 1H, Ar-**H**), 7.15–7.18 (m, 1H, Ar-**H**), 7.41–7.43 (m, 1H, Ar-**H**), 7.51–7.54 (m, 1H, Ar-**H**), 7.58–7.59 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.74–7.78 (m, 1H, Ar-**H**), 7.86 (s, 1H, Ar-**H**), 7.90–7.92 (m, 1H, Ar-**H**).

**5-Methoxy-1-[4-methyl-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4 l**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **CH$_3$)**: Yield: 47% (over 2 steps); Melting range (°C): 144.3–145.2 (Clear); IR (cm$^{-1}$): 3422, 1606, 1467, 1365, 1224, 1136; ESIMS (*m/z*): 331.7 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.75–1.78 (*t*, 1H, *J* = 5.75 Hz, Ar-$CH_2$O**H**), 2.27 (s, 3H, Ar-C**H$_3$**), 3.79 (s, 3H, Ar-OC**H$_3$**), 4.63–4.64 (d, 2H, *J* = 5.51 Hz, Ar-C**H$_2$**OH), 6.56–6.57 (d, 1H, *J* = 3.08 Hz, Ar-**H**), 6.90–6.92 (dd, 1H, *J* = 8.98, 2.50 Hz, Ar-**H**), 6.95 (d, 1H, *J* = 2.42 Hz, Ar-**H**), 7.18–7.20 (d, 1H, *J* = 8.02 Hz, Ar-**H**), 7.52–7.53 (d, 1H, *J* = 3.59 Hz, Ar-**H**), 7.66–7.68 (d, 1H, *J* = 8.0 Hz, Ar-**H**), 7.86–7.89 (m, 2H, Ar-**H**).

**5-Fluoro-1-[4-methyl-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4m**, $R^1$ = **5-F**, $R^2$ = **H**, $R^3$ = **CH$_3$)**: Yield: 45%

(over 2 steps); Melting range (°C): 129.0–131.1 (Clear); IR ($cm^{-1}$): 3441, 1593, 1462, 1371, 1215, 1136; ESIMS (*m/z*): 319.9 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.73 (bs, 1H, Ar-$CH_2OH$), 2.29 (s, 3H, Ar-$CH_3$), 4.66 (s, 2H, Ar-$CH_2OH$), 6.60–6.61 (d, 1H, *J* = 3.12 Hz, Ar-**H**), 7.03–7.06 (m, 1H, Ar-**H**), 7.15–7.18 (dd, 1H, *J* = 8.76, 2.52 Hz, Ar-**H**), 7.20–7.22 (d, 1H, *J* = 8.04 Hz, Ar-**H**), 7.60–7.61 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.67–7.70 (dd, 1H, *J* = 8.04, 2.12 Hz, Ar-**H**), 7.91–7.92 (m, 2H, Ar-**H**).

**5-Fluoro-1-[4-chloro-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4o**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **Cl**): Yield: 42% (over 2 steps); ESIMS (*m/z*): 340.2 $[M+H]^+$, 342.2 $[M+H]^{+2}$; IR ($cm^{-1}$): 3431, 1587, 1460, 1373, 1213, 1168, 1138; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.0 (bs, 1H, Ar-$CH_2OH$), 4.75 (s, 2H, Ar-$CH_2OH$), 6.63–6.64 (d, 1H, *J* = 3.08 Hz, Ar-**H**), 7.02–7.08 (m, 1H, Ar-**H**), 7.16–7.19 (dd, 1H, *J* = 8.68, 2.48 Hz, Ar-**H**), 7.39–7.41 (d, 1H, *J* = 8.04 Hz, Ar-**H**), 7.58–7.59 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.70–7.72 (dd, 1H, *J* = 8.4, 2.36 Hz, Ar-**H**), 7.91–7.95 (m, 1H, Ar-**H**), 8.05–8.06 (d, 1H, *J* = 2.36 Hz, Ar-**H**).

**5-Fluoro-1-[4-bromo-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4q**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **Br**): Yield: 39% (over 2 steps); Melting range (°C): 129.9–131.2 (Clear); ESIMS (*m/z*): 384 $[M+H]^+$, 386 $[M+H]^{+2}$; IR ($cm^{-1}$): 3431, 1585, 1462, 1369, 1215, 1168, 1136; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.0 (bs, 1H, Ar-$CH_2OH$), 4.71 (s, 2H, Ar-$CH_2OH$), 6.63–6.64 (d, 1H, *J* = 3.72 Hz, Ar-**H**), 7.05 (d, 1H, *J* = 2.40, Ar-**H**), 7.16–7.19 (dd, 1H, *J* = 8.68, 2.52 Hz, Ar-**H**), 7.58–7.62 (m, 3H, Ar-**H**), 7.91–7.94 (dd, 1H, *J* = 8.80, 2.42 Hz, Ar-**H**), 8.03 (d, 1H, *J* = 1.56 Hz, Ar-**H**).

**5-Bromo-1-[4-bromo-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4s**, $R^1$ = **Br**, $R^2$ = **H**, $R^3$ = **Br**): Yield: 41% (over 2 steps); 444.3 $[M+H]^+$, 446.2 $[M+H]^{+2}$, 448.2 $[M+H]^{+4}$.

**5-Methoxy-1-[4-chloro-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4t**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **Cl**): Yield: 43% (over 2 steps); ESIMS (*m/z*): 352.4 $[M+H]^+$, 354.5 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.11 (bs, 1H, Ar-$CH_2OH$), 3.80 (s, 3H, Ar-$OCH_3$), 4.72 (s, 2H, Ar-$CH_2OH$), 6.58–6.59 (d, 1H, *J* = 3.2 Hz, Ar-**H**), 6.91–6.96 (m, 2H, Ar-**H**), 7.36–7.38 (d, 1H, *J* = 8.0 Hz, Ar-**H**), 7.49–7.50 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 7.67–7.68 (dd, 1H, *J* = 8.36, 2.40 Hz, Ar-**H**), 7.85–7.87 (d, 1H, *J* = 8.96 Hz, Ar-**H**), 8.03–8.04 (d, 1H, *J* = 2.32 Hz, Ar-**H**).

**5-Methoxy-1-[4-bromo-3-(hydroxymethyl) phenylsulfonyl]-1*H*-indole (4v**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **Br**): Yield: 38% (over 2 steps); Melting range (°C): 112.7–114.0 (Clear); IR ($cm^{-1}$): 3348, 1612, 1471, 1375, 1224, 1141; ESIMS (*m/z*): 396.4 $[M+H]^+$, 398.6 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.99 (bs, 1H, Ar-$CH_2OH$), 3.80 (s, 3H, Ar-$OCH_3$), 4.68 (s, 2H, Ar-$CH_2OH$), 6.60–6.61 (d, 1H, *J* = 3.08 Hz, Ar-**H**), 6.91–6.94 (dd, 1H, *J* = 8.96, 2.52 Hz, Ar-**H**), 6.96–6.97 (d, 1H, *J* = 2.40 Hz, Ar-**H**), 7.50–7.51 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.56–7.61 (m, 2H, Ar-**H**), 7.86–7.88 (d, 1H, *J* = 9.0 Hz, Ar-**H**), 8.01 (d, 1H, *J* = 1.2 Hz, Ar-**H**).

**1-[4-Chloro-3-(hydroxymethyl) phenylsulfonyl]-3-methyl-1*H*-indole (4x**, $R^1$ = **H**, $R^2$ = **CH$_3$**, $R^3$ = **Cl**): Yield: 41% (over 2 steps); Melting range (°C): 106.6–109.3 (Clear); IR ($cm^{-1}$): 3546, 3339, 1567, 1447, 1372, 1273, 1196, 1117; ESIMS (*m/z*): 336.1 $[M+H]^+$, 338.6 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.97 (bs, 1H, Ar-$CH_2OH$), 2.24 (s, 3H, Ar-$CH_3$), 4.72 (s, 2H, Ar-$CH_2OH$), 7.23–7.27 (m, 1H, Ar-**H**), 7.29–7.30 (m, 1H, Ar-**H**), 7.32–7.34 (m, 1H, Ar-**H**), 7.35–7.38 (d, 1H, *J* = 8.40 Hz, Ar-**H**), 7.44–7.46 (d, 1H, *J* = 7.73 Hz, Ar-**H**), 7.69–7.72 (dd, 1H, *J* = 8.40, 2.38 Hz, Ar-**H**), 7.96–7.98 (d, 1H, *J* = 8.21 Hz, Ar-**H**), 8.05 (d, 1H, *J* = 2.3 Hz, Ar-**H**).

**1-[4-bromo-3-(hydroxymethyl) phenylsulfonyl]-3-methyl-1*H*-indole (4z**, $R^1$ = **H**, $R^2$ = **CH$_3$**, $R^3$ = **Br**): Yield: 38% (over 2 steps); Melting range (°C): 122.7–123.9 (Clear); I.R ($cm^{-1}$): 3541, 1148, 1373, 1166; ESIMS (*m/z*): 380.1 $[M+H]^+$, 382.1 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.98 (bs, 1H, Ar-$CH_2OH$), 2.24 (s, 3H, Ar-$CH_3$), 4.69 (s, 2H, Ar-$CH_2OH$), 7.27–7.30 (m, 2H, Ar-**H**), 7.31–7.33 (d, 1H, *J* = 7.16 Hz, Ar-**H**), 7.45–7.46 (d, 1H, *J* = 7.72 Hz, Ar-**H**), 7.55–7.57 (d, 1H, *J* = 8.36 Hz, Ar-**H**), 7.61–7.67 (d, 1H, *J* = 2.32 Hz, Ar-**H**), 7.96–7.99 (d, 1H, *J* = 8.24 Hz, Ar-**H**), 8.02–8.03 (d, 1H, *J* = 2.2 Hz, Ar-**H**).

**5-Methoxy-1-[4-Chloro-3-(hydroxymethyl) phenylsulfonyl]-3-methyl-1*H*-indole (4ab**, $R^1$ = **5-OCH$_3$**, $R^2$ = **CH$_3$**, $R^3$ = **Cl**): Yield: 43% (over 2 steps); Melting range (°C): 130.9–133.4 (Clear); I.R ($cm^{-1}$): 3293, 1611, 1453, 1366, 1228, 1133; ESIMS (*m/z*): 366.4 $[M+H]^+$, 368.6 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.07 (bs, 1H, Ar-$CH_2OH$), 2.19 (s, 3H, Ar-$CH_3$), 3.82 (s, 3H, Ar-$OCH_3$), 4.71 (s, 2H, Ar-$CH_2OH$), 6.85–6.86 (d, 1H, *J* = 2.44 Hz, Ar-**H**), 6.90–6.93 (dd, 1H, *J* = 8.92, 2.48 Hz, Ar-**H**), 7.24 (d, 1H, *J* = 1.2 Hz, Ar-**H**), 7.33–7.35 (d, 1H, *J* = 8.4 Hz, Ar-**H**), 7.64–7.67 (dd, 1H, *J* = 8.40, 2.40 Hz, Ar-**H**), 7.85–7.87 (d, 1H, *J* = 9.0 Hz, Ar-**H**), 8.01–8.02 (d, 1H, *J* = 2.32 Hz, Ar-**H**).

### Preparation of 1–(4-bromo-3-formyl phenylsulfonyl)-1H-indole (5g)

To a solution of 1-[4-bromo-3-(hydroxymethyl) phenyl sulfonyl]-1*H*-indole (4.73 g, 12.92 mmol) in ethylene dichloride (75 mL) was added manganese dioxide (8.92 g, 102.5 mmol). The reaction mass was heated to reflux temperature and maintained under reflux for 3 h, while monitoring the progress of the reaction by TLC. After completion of the reaction, the reaction mass was filtered through hyflow bed and the bed was washed with ethylene dichloride (2 × 10 mL). The clear filtrate was concentrated under reduced pressure to obtain the technical product. The technical material was triturated with of *n*-hexane (2 × 15 mL), decanted the solvent and dried under reduced pressure to obtain 3.42 g of the title product, Yield: 73%.

Melting range: 106.4–107.9 °C; I.R ($cm^{-1}$): 3074, 1691, 1571, 1440, 1371, 1253, 748; ESIMS (*m/z*): 364.0 $[M+H]^+$, 366 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.7–6.71 (d, 1H, *J* = 3.52 Hz, Ar-**H**), 7.23–7.28 (m, 1H, Ar-**H**), 7.33–7.38 (m, 1H, Ar-**H**), 7.52–7.54 (m, 2H, Ar-**H**), 7.71–7.73 (d, 1H, *J* = 8.4 Hz, Ar-**H**), 7.88–7.90 (dd, 1H, *J* = 8.44, 1.92 Hz, Ar-**H**), 7.96–7.98 (d, 1H, *J* = 8.28 Hz, Ar-**H**), 8.35–8.36 (d, 1H, *J* = 2.28 Hz, Ar-**H**), 10.27 (s, 1H, Ar-C**H**O).

Similarly, compounds **5a**–**5ab** were prepared from respective starting materials **4a**–**4ab** by using the method described previously for the example **5 g** with some noncritical variations. The analytical data of compounds **5a**–**5ab** are presented below.

**1-(3-Formyl phenylsulfonyl)-1*H*-indole (5a**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **H**): Yield: 82%; ESIMS (*m/z*): 286.1 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.69–6.70 (d, 1H, *J* = 3.04 Hz, Ar-**H**), 7.24–7.25 (m, 1H, Ar-**H**), 7.31–7.36 (m, 1H, Ar-**H**), 7.51–7.53 (d, 1H, *J* = 7.76 Hz, Ar-**H**), 7.56–7.57 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.60–7.63 (m, 1H, Ar-**H**), 7.99–8.03 (m, 2H, Ar-**H**), 8.09–8.12 (m, 1H, Ar-**H**), 8.35 (d, 1H, *J* = 1.6 Hz, Ar-**H**), 9.98 (s, 1H, Ar-C**H**O).

**1-(4-Methyl-3-formyl phenylsulfonyl)-1*H*-indole (5b**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **CH$_3$**): Yield: 85%; Melting range (°C): 88.3–89.3 (Clear); IR spectra ($cm^{-1}$): 1708, 1440, 1373, 1122; ESIMS (*m/z*): 300.1 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.65 (s, 3H, Ar-$CH_3$), 6.68–6.69 (d, 1H, *J* = 3.6 Hz, Ar-**H**), 7.21–7.25 (m, 1H, Ar-**H**), 7.31–7.35 (m, 2H, Ar-**H**), 7.52–7.54 (d, 1H, *J* = 7.68 Hz, Ar-**H**), 7.56–7.57 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.92–7.94 (dd, 1H, *J* = 8.12, 1.96 Hz, Ar-**H**), 7.98–8.01 (dd, 1H, *J* = 8.28, 0.68 Hz, Ar-**H**), 8.29 (d, 1H, *J* = 2.12 Hz, Ar-**H**), 10.21 (s, 1H, Ar-C**H**O).

**1-(4-Chloro-3-formyl phenylsulfonyl)-1*H*-indole (5d**, $R^1$ = **H**, $R^2$ = **H**, $R^3$ = **Cl**): Yield: 78%; Melting range (°C): 85.8–87.7 (Clear); IR ($cm^{-1}$): 1699, 1448, 1379, 1259, 1166;

ESIMS (*m/z*): 320.1 $[M+H]^+$, 322.3 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.70 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 7.23–7.27 (m, 1H, Ar-**H**), 7.32–7.34 (m, 1H, Ar-**H**), 7.51–7.54 (d, 3H, Ar-**H**), 7.96–7.99 (m, 2H, Ar-**H**), 8.38–8.39 (d, 1H, *J* = 2.4 Hz, Ar-**H**), 10.37 (s, 1H, Ar-C**H**O).

**5-Methoxy-1-(3-formyl phenylsulfonyl)-1*H*-indole (5 h**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **H**): Yield: 82%; ESIMS (*m/z*): 316.1 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 3.80 (s, 3H, Ar-OC**H$_3$**), 6.62–6.63 (d, 1H, *J* = 3.60 Hz, Ar-**H**), 6.93 (d, 1H, *J* = 2.57 Hz, Ar-**H**), 6.95–6.97 (m, 1H, Ar-**H**), 7.52–7.53 (d, 1H, *J* = 3.66 Hz, Ar-**H**), 7.60–7.64 (m, 1H, Ar-**H**), 7.88–7.91 (d, 1H, *J* = 8.88 Hz, Ar-**H**), 8.02–8.09 (m, 2H, Ar-**H**), 8.32–8.33 (d, 1H, *J* = 1.64 Hz, Ar-**H**), 9.99 (s, 1H, Ar-C**H**O).

**5-Ethoxy-1-(3-formyl phenylsulfonyl)-1*H*-indole (5i**, $R^1$ = **5-OCH$_2$CH$_3$**, $R^2$ = **H**, $R^3$ = **H**): Yield: 79%; ESIMS (*m/z*): 330.1 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.38–1.42 (*t*, 3H, Ar-OCH$_2$C**H$_3$**), 3.98–4.04 (*q*, 2H, Ar-OC**H$_2$**CH$_3$), 6.60–6.61 (d, 1H, *J* = 3.62 Hz, Ar-**H**), 6.92–6.93 (d, 1H, *J* = 2.47 Hz, Ar-**H**), 6.95–6.96 (m, 1H, Ar-**H**), 7.51–7.52 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 7.59–7.63 (m, 1H, Ar-**H**), 7.87–7.89 (d, 1H, *J* = 8.64 Hz, Ar-**H**), 8.02–8.08 (m, 2H, Ar-**H**), 8.32 (d, 1H, *J* = 1.68 Hz, Ar-**H**), 9.99 (s, 1H, Ar-C**H**O).

**5-Isopropoxy-1-(3-formyl phenylsulfonyl)-1*H*-indole (5j**, $R^1$ = **5-OCH(CH$_3$)$_2$**, $R^2$ = **H**, $R^3$ = **H**): Yield: 79%; ESIMS (*m/z*): 344.1 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.31–1.32 (d, 6H, *J* = 6.04 Hz, Ar-OCH(C**H$_3$**)$_2$), 4.47–4.53 (sept, 1H, Ar-OC**H**(CH$_3$)$_2$), 6.60 (d, 1H, *J* = 3.52 Hz, Ar-**H**), 6.91–6.93 (dd, 1H, *J* = 8.96, 2.40 Hz, Ar-**H**), 6.96–6.97 (d, 1H, *J* = 2.36 Hz, Ar-**H**), 7.51 (d, 1H, *J* = 3.60 Hz, Ar-**H**), 7.62–7.64 (m, 1H, Ar-**H**), 7.86–7.88 (d, 1H, *J* = 8.96 Hz, Ar-**H**), 8.02–8.09 (m, 2H, Ar-**H**), 8.33 (d, 1H, *J* = 1.6 Hz, Ar-**H**), 9.99 (s, 1H, Ar-C**H**O).

**5-Fluoro-1-(3-formyl phenylsulfonyl)-1*H*-indole (5k**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **H**): Yield: 81%; ESIMS (*m/z*): 304 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.66–6.67 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.06–7.09 (m, 1H, Ar-**H**), 7.17–7.19 (dd, 1H, *J* = 8.64, 2.52 Hz, Ar-**H**), 7.60–7.61 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 7.64–7.66 (m, 1H, Ar-**H**), 7.93–7.98 (m, 1H, Ar-**H**), 8.04–8.09 (m, 2H, Ar-**H**), 8.34 (d, 1H, *J* = 1.56 Hz, Ar-**H**), 10.0 (s, 1H, Ar-C**H**O).

**5-Methoxy-1-(4-methyl-3-formyl phenylsulfonyl)-1*H*-indole (5 l**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **CH$_3$**): Yield: 83%; Melting range (°C): 134.2–135.3 (Clear); IR ($cm^{-1}$): 3124, 1705, 1446, 1367, 1222, 1128; ESIMS (*m/z*): 330 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.60 (s, 3H, Ar-C**H$_3$**), 3.72 (s, 3H, Ar-OC**H$_3$**), 6.76–6.77 (d, 1H, *J* = 3.20 Hz, Ar-**H**), 6.92–6.95 (dd, 1H, *J* = 9.04, 2.56 Hz, Ar-**H**), 7.09 (d, 1H, *J* = 2.52 Hz, Ar-**H**), 7.52–7.54 (d, 1H, *J* = 8.20 Hz, Ar-**H**), 7.76–7.77 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 7.80–7.82 (d, 1H, *J* = 9.04 Hz, Ar-**H**), 8.03–8.06 (dd, 1H, *J* = 8.12, 2.24 Hz, Ar-**H**), 8.26–8.27 (d, 1H, *J* = 2.16 Hz, Ar-**H**), 10.19 (s, 1H, Ar-C**H**O).

**5-Fluoro-1-(4-methyl-3-formyl phenylsulfonyl)-1*H*-indole (5m**, $R^1$ = **5-F**, $R^2$ = **H**, $R^3$ = **CH$_3$**): Yield: 79%; Melting range (°C): 96.5–99.4 (Clear); IR ($cm^{-1}$): 3145, 1712, 1460, 1373, 1213, 1138; ESIMS (*m/z*): 318 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.67 (s, 3H, Ar-C**H$_3$**), 6.64–6.65 (d, 1H, *J* = 3.16 Hz, Ar-**H**), 7.03–7.09 (m, 1H, Ar-**H**), 7.16–7.19 (dd, 1H, *J* = 8.68, 2.52 Hz, Ar-**H**), 7.34–7.36 (d, 1H, *J* = 8.16 Hz, Ar-**H**), 7.60 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.89–7.94 (m, 2H, Ar-**H**), 8.26–8.27 (d, 1H, *J* = 2.12 Hz, Ar-**H**), 10.22 (s, 1H, Ar-C**H**O).

**5-Fluoro-1-(4-chloro-3-formyl phenylsulfonyl)-1*H*-indole (5o**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **Cl**): Yield: 78%; Melting range (°C): 92.5–94.4 (Clear); IR ($cm^{-1}$): 3136, 1699, 1579, 1452, 1377, 1207, 1163, 1132; ESIMS (*m/z*): 338.2 $[M+H]^+$, 340.4 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.66–6.67 (d, 1H, *J* = 3.20 Hz, Ar-**H**), 7.06–7.09 (m, 1H, Ar-**H**), 7.17–7.19 (dd, 1H, *J* = 8.60, 2.52 Hz, Ar-**H**), 7.53–7.55 (d, 1H, *J* = 8.52 Hz, Ar-**H**), 7.57–7.58 (d, 1H, *J* = 3.72 Hz, Ar-**H**), 7.90–7.94 (m, 1H, Ar-**H**), 7.95–7.97 (dd, 1H, 8.52, 2.44 Hz, Ar-**H**), 8.36–8.37 (d, 1H, *J* = 2.40 Hz, Ar-**H**), 10.39 (s, 1H, Ar-C**H**O).

**5-Fluoro-1-(4-bromo-3-formyl phenylsulfonyl)-1*H*-indole (5q**, $R^1$ = **F**, $R^2$ = **H**, $R^3$ = **Br**): Yield: 76%; Melting range (°C): 96.5–98.6 (Clear); IR ($cm^{-1}$): 3143, 1699, 1583, 1454, 1381, 1215, 1170, 1138; ESIMS (*m/z*): 382.2 $[M+H]^+$, 384.4 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 6.66–6.67 (d, 1H, *J* = 3.20 Hz, Ar-**H**), 7.07–7.10 (m, 1H, Ar-**H**), 7.18–7.20 (dd, 1H, *J* = 8.60, 2.50 Hz, Ar-**H**), 7.53–7.55 (d, 1H, *J* = 8.50 Hz, Ar-**H**), 7.57–7.58 (d, 1H, *J* = 3.72 Hz, Ar-**H**), 7.91–7.95 (m, 1H, Ar-**H**), 7.95–7.97 (dd, 1H, 8.50, 2.42 Hz, Ar-**H**), 8.36–8.37 (d, 1H, *J* = 2.40 Hz, Ar-**H**), 10.36 (s, 1H, Ar-C**H**O).

**5-Bromo-1-(4-bromo-3-formyl phenylsulfonyl)-1*H*-indole (5s**, $R^1$ = **Br**, $R^2$ = **H**, $R^3$ = **Br**): Yield: 74%; 442.3 $[M+H]^+$, 444.2 $[M+H]^{+2}$, 446.2 $[M+H]^{+4}$.

**5-Methoxy-1-(4-chloro-3-formyl phenylsulfonyl)-1*H*-indole (5t**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **Cl**): Yield: 80%; Melting range (°C): 141.6–142.5 (Clear); IR ($cm^{-1}$): 3116, 1701, 1462, 1375, 1224, 1136; ESIMS (*m/z*): 350.2 $[M+H]^+$, 352.3 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 3.80 (s, 3H, Ar-OC**H$_3$**), 6.62–6.63 (d, 1H, *J* = 3.62 Hz, Ar-**H**), 6.93–6.97 (m, 2H, Ar-**H**), 7.49–7.52 (m, 2H, Ar-**H**), 7.85–7.87 (d, 1H, *J* = 8.80 Hz, Ar-**H**), 7.93–7.96 (dd, 1H, *J* = 8.84, 2.48 Hz, Ar-**H**), 8.35 (d, 1H, *J* = 2.4 Hz, Ar-**H**), 10.38 (s, 1H, Ar-C**H**O).

**5-Methoxy-1-(4-bromo-3-formyl phenylsulfonyl)-1*H*-indole (5v**, $R^1$ = **5-OCH$_3$**, $R^2$ = **H**, $R^3$ = **Br**): Yield: 78%; Melting range (°C): 145.5–148.6 (Clear); IR ($cm^{-1}$): 1699, 1465, 1377, 1222, 1145; ESIMS (*m/z*): 394.2 $[M+H]^+$, 396.3 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 3.80 (s, 3H, Ar-OC**H$_3$**), 6.62 (d, 1H, *J* = 3.60 Hz, Ar-**H**), 6.93–6.96 (m, 2H, Ar-**H**), 7.49 (s, 1H, Ar-**H**), 7.70–7.72 (d, 1H, *J* = 8.32 Hz, Ar-**H**), 7.85–7.87 (m, 2H, Ar-**H**), 8.32 (s, 1H, Ar-**H**), 10.27 (s, 1H, Ar-C**H**O).

**1-[4-Chloro-3-formyl phenylsulfonyl]-3-methyl-1*H*-indole (5x**, $R^1$ = **H**, $R^2$ = **CH$_3$**, $R^3$ = **Cl**): Yield: 81%; Melting range (°C): 142.8–144.9 (Clear); IR ($cm^{-1}$): 2870, 1701, 1583 1447, 1371, 1166, 1115; ESIMS (*m/z*): 334.3 $[M+H]^+$, 336.5 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.24 (s, 3H, Ar-C**H$_3$**), 7.25–7.28 (m, 2H, Ar-**H**), 7.32–7.36 (m, 1H, Ar-**H**), 7.44–7.46 (d, 1H, *J* = 7.72 Hz, Ar-**H**), 7.49–7.51 (d, 1H, *J* = 8.48 Hz, Ar-**H**), 7.95–7.97 (m, 2H, Ar-**H**), 8.37 (d, 1H, *J* = 2.37 Hz, Ar-**H**), 10.37 (s, 1H, Ar-C**H**O).

**1-[4-Bromo-3-formyl phenylsulfonyl]-3-methyl-1*H*-indole (5z**, $R^1$ = **H**, $R^2$ = **CH$_3$**, $R^3$ = **Br**): Yield: 76%; Melting range (°C): 156.5–159.6 (Clear); IR ($cm^{-1}$): 1700, 1578, 1371, 1167; ESIMS (*m/z*): 378.2 $[M+H]^+$, 380.2 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.24 (s, 3H, Ar-C**H$_3$**), 7.26–7.28 (m, 2H, Ar-**H**), 7.32–7.36 (*t*, 1H, *J* = 7.44 Hz, Ar-**H**), 7.44–7.46 (d, 1H, *J* = 7.04 Hz, Ar-**H**), 7.69–7.71 (d, 1H, *J* = 8.36 Hz, Ar-**H**), 7.86–7.88 (d, 1H, *J* = 6.72 Hz, Ar-**H**), 7.95–7.97 (d, 1H, *J* = 8.2 Hz, Ar-**H**), 8.34 (d, 1H, *J* = 1.28 Hz, Ar-**H**), 10.27 (s, 1H, Ar-C**H**O).

**5-Methoxy-1-[4-Chloro-3-formyl phenylsulfonyl]-3-methyl-1*H*-indole (5ab**, $R^1$ = **5-OCH$_3$**, $R^2$ = **CH$_3$**, $R^3$ = **Cl**): Yield: 80%; ESIMS (*m/z*): 364.2 $[M+H]^+$, 366.3 $[M+H]^{+2}$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.19 (s, 3H, Ar-C**H$_3$**), 3.82 (s, 3H, Ar-OC**H$_3$**), 6.85–6.86 (d, 1H, *J* = 2.48 Hz, Ar-**H**), 6.92–6.95 (dd, 1H, *J* = 8.96, 2.52 Hz, Ar-**H**), 7.23 (d, 1H, *J* = 1.16 Hz, Ar-**H**), 7.48–7.50 (d, 1H, *J* = 8.48 Hz, Ar-**H**), 7.84–7.86 (d, 1H, *J* = 9.0 Hz, Ar-**H**), 7.91–7.93 (dd, 1H, *J* = 8.52, 2.40 Hz, Ar-**H**), 8.33–8.34 (d, 1H, *J* = 2.4 Hz, Ar-**H**), 10.37 (s, 1H, Ar-C**H**O).

### Preparation of 1-[4-bromo-3–(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole (6 g)

To a solution of 1–(4-bromo-3-formyl phenylsulfonyl)-1*H*-indole (1.004 g, 2.758 mmol) in 20 mL ethylene dichloride was

added *N*-ethyl piperazine (0.3757 g, 3.295 mmol). Reaction mass was stirred at 25 °C for 10 min. Sodium triacetoxy borohydride (0.8842 g, 4.171 mmol) was added over a period of 10 min. The reaction mass was stirred at 25 °C for 6 h while monitoring the progress of the reaction by TLC. After completion of the reaction, reaction mass was quenched onto 5% sodium bicarbonate solution (100 mL) and extracted the product with chloroform (3 × 50 mL). The combined organic layer was washed with brine solution (2 × 50 mL), water (2 × 50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The technical product was purified by column chromatography, eluent system being ethyl acetate and n-hexane (7:1) to obtain 0.9344 g of the title product.

Melting Range: 122.2–126.3 °C; ESIMS (*m/z*): 462 $[M+H]^+$; HRMS: $[M+H]^+$ $C_{21}H_{24}BrN_3O_2S$ calc. 462.0773, found. 462.0775.

Example 6 g (Di HCl salt): Preparation of 1-[4-bromo-3–(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole dihydrochloride.

To a clear solution of 1-[4-bromo-3–(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole (252.4 mg, 0.5463 mmol) in 15 mL diethyl ether under nitrogen atmosphere, a solution of methanolic hydrochloric acid (16% w/v, 0.32 mL, 1.402 mmol) was added in 5 min under stirring. The above reaction mass was further stirred at 25 °C, for a period of 1 h and concentrated under vacuum to obtain the above title product 262 mg, Yield: 65%, after 2 steps.

Melting range: 208.4–210.4 °C; IR spectra ($cm^{-1}$): 3429, 2935, 2245, 1440, 1172, 765; ESIMS (*m/z*): 462 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.20–1.24 (*t*, 3H, N-$CH_2C\mathbf{H_3}$), 2.83 (bs, 4H, Piperazine-**H**), 3.10–3.15 (*q*, 2H, N-$C\mathbf{H_2}CH_3$), 3.18 (bs, 4H, Piperazine-**H**), 3.91 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.75 (d, 1H, *J* = 3.70 Hz, Ar-**H**), 7.21 (m, 1H, Ar-**H**), 7.28–7.30 (m, 1H, Ar-**H**), 7.53–7.55 (d, 1H, *J* = 7.7 Hz, Ar-**H**), 7.58–7.59 (d, 1H, *J* = 3.72 Hz, Ar-**H**), 7.69 (m, 2H, Ar-**H**), 7.78 (d, 1H, *J* = 1.8 Hz, Ar-**H**), 7.9 (d, 1H, *J* = 8.2 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{24}BrN_3O_2S$ calc. 462.0773, found. 462.0775.

## Examples 6a–6ac

The compounds **6a–6ac** were prepared from respective starting materials by using the method described above for the example **6g** (Di HCl) with some noncritical variations. The analytical data of compounds **6a–6ac** are presented below. The compound **6a** was prepared from starting materials **5a** and *N*-methyl piperazine.

### *1-[3-(4-Methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole (**6a**)*

Yield: 63%; I.R ($cm^{-1}$): 2936, 1445, 1168, 823; ESI-MS (*m/z*): 370.3 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.29 (s, 3H, N-$C\mathbf{H_3}$), 2.36 (bs, 8H, Piperazine-**H**), 3.47 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.65–6.66 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.19–7.23 (m, 1H, Ar-**H**), 7.30 (m, 1H, Ar-**H**), 7.36–7.38 (m, 1H, Ar-**H**), 7.45–7.53 (m, 2H, Ar-**H**), 7.56–7.57 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.73–7.75 (m, 1H, Ar-**H**), 7.87 (m, 1H, Ar-**H**), 7.98–8.00 (d, 1H, *J* = 8.32 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{20}H_{23}N_3O_2S$ calc. 370.1511, found. 370.1514.

The compound **6b** was prepared from starting materials **5b** and *N*-methyl piperazine

### *1-[4-Methyl-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole dihydrochloride (**6b**)*

Yield: 65%, after 2 steps; Melting range: 180.4–183.0 °C; I.R ($cm^{-1}$): 3383, 2960, 1629, 1446, 1130, 948; ESIMS (*m/z*): 384.6 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.45 (s, 3H, Ar-$C\mathbf{H_3}$), 2.97 (s, 3H, N-$C\mathbf{H_3}$), 3.29–3.58 (bs, 8H, Piperazine-**H**), 4.25 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.72–6.73 (dd, 1H, *J* = 3.69, 0.39 Hz, Ar-**H**), 7.20–7.24 (m, 1H, Ar-**H**), 7.31–7.35 (m, 1H, Ar-**H**), 7.41–7.43 (d, 1H, *J* = 8.18 Hz, Ar-**H**), 7.52–7.54 (d, 1H, *J* = 7.8 Hz, Ar-**H**), 7.67–7.68 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.83–7.85 (dd, 1H, *J* = 8.14, 2.02 Hz, Ar-**H**), 8.02–8.04 (dd, 1H, *J* = 8.28, 0.52 Hz, Ar-**H**), 8.12 (d, 1H, *J* = 1.24 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{25}N_3O_2S$ calc. 384.1667, found. 384.1663.

The compound **6c** was prepared from starting materials **5b** and *N*-ethyl piperazine

### *1-[4-Methyl-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole dihydrochloride (**6c**)*

Yield: 62%, after 2 steps; Melting point: 250.13 °C; I.R ($cm^{-1}$): 3300, 2997, 1643, 1168, 752; ESIMS (*m/z*): 398.1 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.35–1.39 (*t*, 3H, N-$CH_2C\mathbf{H_3}$), 2.42 (s, 3H, Ar-$C\mathbf{H_3}$), 3.12–3.14 (bs, 6H, Piperazine-**H**), 3.23–3.29 (*q*, 2H, N-$C\mathbf{H_2}CH_3$), 3.6 (bs, 2H, Piperazine-**H**), 4.05 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.72–6.73 (dd, 1H, *J* = 3.12, 0.58 Hz, Ar-**H**), 7.20–7.24 (m, 1H, Ar-**H**), 7.30–7.34 (m, 1H, Ar-**H**), 7.38–7.40 (d, 1H, *J* = 8.17 Hz, Ar-**H**), 7.52–7.54 (d, 1H, *J* = 7.82 Hz, Ar-**H**), 7.65–7.66 (d, 1H, *J* = 3.69 Hz, Ar-**H**), 7.80–7.82 (dd, 1H, *J* = 8.11, 1.97 Hz, Ar-**H**), 8.0–8.02 (m, 2H, Ar-**H**); HRMS: $[M+H]^+$ $C_{22}H_{27}N_3O_2S$ calc. 398.1824, found. 398.1821.

The compound **6d** was prepared from starting materials **5d** and *N*-methyl piperazine.

### *1-[4-Chloro-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole dihydrochloride (**6d**)*

Yield: 59%, after 2 steps; Melting range: 210.6–213.90 °C; I.R ($cm^{-1}$): 3415, 2987, 1591, 1444, 1373, 1174, 736; ESIMS (*m/z*): 403.9 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.84 (s, 3H, N-$C\mathbf{H_3}$), 3.05 (bs, 4H, Piperazine-**H**), 3.28 (bs, 4H, Piperazine-**H**), 4.10 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.72–6.78 (d, 1H, *J* = 3.7 Hz, Ar-**H**), 7.18–7.22 (d, 1H, *J* = 7.4 Hz, Ar-**H**), 7.26–7.30 (d, 1H, *J* = 7.4 Hz, Ar-**H**), 7.49–7.51 (d, 2H, *J* = 8.4 Hz, Ar-**H**), 7.55–7.56 (d, 1H, *J* = 3.72 Hz, Ar-**H**), 7.82–7.84 (dd, 1H, *J* = 8.52, 2.32 Hz, Ar-**H**), 7.86–7.88 (dd, 2H, *J* = 7.92, 2.06 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{20}H_{22}ClN_3O_2S$ calc. 404.1121, found. 404.1117.

The compound **6e** was prepared from starting materials **5d** and *N*-ethyl piperazine.

### *1-[4-Chloro-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole dihydrochloride (**6e**)*

Yield: 62%, after 2 steps; Melting range: 196.0–197.1 °C; I.R ($cm^{-1}$): 3446, 2985, 2451, 1469, 1444, 1172, 740; ESIMS (*m/z*): 418.0 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.17–1.21 (*t*, 3H, N-$CH_2C\mathbf{H_3}$), 3.04 (bs, 8H, Piperazine-**H**), 3.10–3.15 (*q*, 2H, N-$C\mathbf{H_2}CH_3$), 4.10 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.69–6.70 (d, 1H, *J* = 3.61 Hz, Ar-**H**), 7.15–7.19 (d, 1H, *J* = 7.5 Hz, Ar-**H**), 7.23–7.27 (m, 1H, *J* = 7.3 Hz, Ar-**H**), 7.46–7.48 (d, 2H, *J* = 8.34 Hz, Ar-**H**), 7.52–7.53 (d, 1H, *J* = 3.71 Hz, Ar-**H**), 7.79–7.81 (dd, 1H, *J* = 8.5, 2.2 Hz, Ar-**H**), 7.84–7.86 (m, 2H, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{24}ClN_3O_2S$ calc. 418.1278, found. 418.1276.

The compound **6f** was prepared from starting materials **5 g** and *N*-methyl piperazine.

### *1-[4-Bromo-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole dihydrochloride (**6f**)*

Yield: 59%, after 2 steps; Melting range: 214.1–216.0 °C; I.R ($cm^{-1}$): 3429, 2372, 1440, 1170, 740; ESIMS (*m/z*): 447.9 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.26 (bs, 2H, Piperazine-**H**), 2.79 (s, 3H, N-$C\mathbf{H_3}$ & 2H, Piperazine-**H**), 3.09–3.11 (bs, 2H, Piperazine-**H**), 3.37–3.40 (bs, 2H, Piperazine-**H**), 3.7 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.86 (dd, 1H, *J* = 3.7, 0.57 Hz, Ar-**H**), 7.24–7.28 (m, 1H,

Ar-**H**), 7.33–7.37 (m, 1H, Ar-**H**), 7.59–7.61 (d, 1H, $J = 7.67$ Hz, Ar-**H**), 7.76–7.78 (dd, 1H, $J = 8.4$, 2.4 Hz, Ar-**H**), 7.80–7.81 (d, 1H, $J = 3.6$ Hz, Ar-**H**), 7.847.86 (d, 1H, $J = 8.44$ Hz, Ar-**H**), 7.93–7.95 (dd, 1H, $J = 8.0$, 0.35 Hz, Ar-**H**), 8.09 (bs, 1H, Ar-**H**); HRMS: $[M + H]^+$ $C_{20}H_{22}BrN_3O_2S$ calc. 448.0616, found. 448.0611.

The compound **6h** was prepared from starting materials **5 h** and *N*-methyl piperazine.

*5-Methoxy-1-[3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H-*indole (**6h**)*

Yield: 64%; I.R ($cm^{-1}$): 2936, 2790, 1615, 1465, 1224, 996; ESIMS (*m/z*): 400.3 $[M + H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.28 (s, 3H, N-C**H$_3$**), 2.35 (bs, 8H, Piperazine-**H**), 3.46 (s, 2H, Ar-C**H$_2$**-N), 3.80 (s, 3H, Ar-OC**H$_3$**), 6.57–6.58 (d, 1H, $J = 3.6$ Hz, Ar-**H**), 6.89–6.92 (dd, 1H, $J = 8.96$, 2.52 Hz, Ar-**H**), 6.95 (d, 1H, $J = 2.44$ Hz, Ar-**H**), 7.33–7.36 (m, 1H, Ar-**H**), 7.45–7.47 (m, 1H, Ar-**H**), 7.51–7.52 (d, 1H, $J = 3.6$ Hz, Ar-**H**), 7.69–7.71 (m, 1H, Ar-**H**), 7.83 (s, 1H, Ar-**H**), 7.86–7.89 (d, 1H, $J = 9.0$ Hz, Ar-**H**); HRMS: $[M + H]^+$ $C_{21}H_{25}N_3O_3S$ calc. 400.1617, found. 400.1619.

The compound **6i** was prepared from starting materials **5i** and *N*-methyl piperazine.

*5-Ethoxy-1-[3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H-*indole (**6i**)*

Yield: 62%; I.R ($cm^{-1}$): 3743, 2935, 1615, 1456, 1222, 900; ESIMS (*m/z*): 414.4 $[M + H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.38–1.42 (*t*, 3H, Ar-OCH$_2$C**H$_3$**), 2.28 (s, 3H, N-C**H$_3$**), 2.35 (bs, 8H, Piperazine-**H**), 3.48 (s, 2H, Ar-C**H$_2$**-N), 3.98–4.03 (*q*, 2H, Ar-OC**H$_2$**CH$_3$), 6.56–6.57 (d, 1H, $J = 3.60$ Hz, Ar-**H**), 6.89–6.92 (dd, 1H, $J = 8.96$, 2.45 Hz, Ar-**H**), 6.93–6.94 (d, 1H, $J = 2.38$ Hz, Ar-**H**), 7.32–7.36 (m, 1H, Ar-**H**), 7.44–7.46 (m, 1H, Ar-**H**), 7.50–7.51 (d, 1H, $J = 3.64$ Hz, Ar-**H**), 7.69–7.71 (m, 1H, Ar-**H**), 7.83 (s, 1H, Ar-**H**), 7.86–7.88 (d, 1H, $J = 8.98$ Hz, Ar-**H**); HRMS: $[M + H]^+$ $C_{22}H_{27}N_3O_3S$ calc. 414.1773, found. 414.1778.

The compound **6j** was prepared from starting materials **5j** and *N*-methyl piperazine.

*5-Isopropoxy-1-[3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H-*indole (**6j**)*

Yield: 63%; I.R ($cm^{-1}$): 2974, 1612, 1455, 1221, 923; ESIMS (*m/z*): 428.3 $[M + H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.31–1.32 (d, 6H, $J = 6.04$ Hz, Ar-OCH(C**H$_3$**)$_2$), 2.30 (s, 3H, N-C**H$_3$**), 2.46 (bs, 8H, Piperazine-**H**), 3.47 (s, 2H, Ar-C**H$_2$**-N), 4.47 (sept, 1H, Ar-OC**H**(CH$_3$)$_2$), 6.55–6.56 (d, 1H, $J = 3.56$ Hz, Ar-**H**), 6.87–6.90 (dd, 1H, $J = 8.96$, 2.44 Hz, Ar-**H**), 6.95–6.96 (d, 1H, $J = 2.44$ Hz, Ar-**H**), 7.33–7.37 (m, 1H, Ar-**H**), 7.45–7.47 (m, 1H, Ar-**H**), 7.50–7.51 (d, 1H, $J = 3.56$ Hz, Ar-**H**), 7.7–7.72 (m, 1H, Ar-**H**), 7.84–7.87 (m, 2H, Ar-**H**); HRMS: $[M + H]^+$ $C_{23}H_{29}N_3O_3S$ calc. 428.1930, found. 428.1936.

The compound **6k** was prepared from starting materials **5k** and *N*-methyl piperazine.

*5-Fluoro-1-[3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H-*indole (**6k**)*

Yield: 62%; I.R ($cm^{-1}$): 2937, 1590, 1460, 1216, 998; ESIMS (*m/z*): 388.3 $[M + H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.30 (s, 3H, N-C**H$_3$**), 2.36 (bs, 8H, Piperazine-**H**), 3.48 (s, 2H, Ar-C**H$_2$**-N), 6.61–6.62 (d, 1H, $J = 3.64$ Hz, Ar-**H**), 7.03 (m, 1H, Ar-**H**), 7.15–7.18 (m, 1H, Ar-**H**), 7.37–7.39 (m, 1H, Ar-**H**), 7.47 (m, 1H, Ar-**H**), 7.59–7.60 (d, 1H, $J = 3.64$ Hz, Ar-**H**), 7.71 (m, 1H, Ar-**H**), 7.84 (m, 1H, Ar-**H**), 7.92–7.94 (m, 1H, Ar-**H**); HRMS: $[M + H]^+$ $C_{20}H_{22}FN_3O_2S$ calc. 388.1417, found. 388.1421.

The compound **6l** was prepared from starting materials **5 l** and *N*-methyl piperazine.

*1-[4-Methyl-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-5-methoxy-1*H-*indole dihydrochloride (**6l**)*

Yield: 63%, after 2 steps; Melting range: 198.1–199.3 °C; I.R ($cm^{-1}$): 3427, 2974, 2372, 1616, 1465, 1224, 950; ESIMS (*m/z*): 414.3 $[M + H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.37 (s, 3H, Ar-C**H$_3$**), 2.78 (s, 3H, N-C**H$_3$**), 2.79–3.46 (bs, 8H, Piperazine-**H**), 3.73 (s, 3H, Ar-OC**H$_3$**), 3.83–3.90 (s, 2H, Ar-C**H$_2$**-N), 6.73–6.74 (d, 1H, $J = 3.6$ Hz, Ar-**H**), 6.91–6.93 (dd, 1H, $J = 9.01$, 2.5 Hz, Ar-**H**), 7.08 (d, 1H, $J = 2.46$ Hz, Ar-**H**), 7.39–7.41 (d, 1H, $J = 8.13$ Hz, Ar-**H**), 7.73–7.76 (m, 2H, Ar-**H**), 7.82–7.84 (d, 1H, $J = 9.02$ Hz, Ar-**H**), 8.11 (bs, 1H, Ar-**H**); HRMS: $[M + H]^+$ $C_{22}H_{27}N_3O_3S$ calc. 414.1773, found. 414.1775.

The compound **6m** was prepared from starting materials **5m** and *N*-methyl piperazine.

*1-[4-Methyl-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-5-fluoro-1*H-*indole dihydrochloride (**6m**)*

Yield: 57%, after 2 steps; Melting range: 220.3–223.4 °C; I.R ($cm^{-1}$): 3370, 2642, 1596, 1464, 1171, 949; ESIMS (*m/z*): 402.3 $[M + H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.45 (s, 3H, Ar-C**H$_3$**), 2.97 (s, 3H, N-C**H$_3$**), 3.29–3.62 (bs, 8H, Piperazine-**H**), 4.19 (s, 2H, Ar-C**H$_2$**-N), 6.72–6.73 (d, 1H, $J = 3.6$ Hz, Ar-**H**), 7.07–7.13 (m, 1H, Ar-**H**), 7.23–7.25 (dd, 1H, $J = 8.9$, 2.52 Hz, Ar-**H**), 7.41 7.43 (d, 1H, $J = 8.18$ Hz, Ar-**H**), 7.75–7.76 (d, 1H, $J = 3.67$ Hz, Ar-**H**), 7.82–7.89 (dd, 1H, $J = 8.14$, 1.96 Hz, Ar-**H**), 8.01–8.02 (m, 1H, Ar-**H**), 8.12 (bs, 1H, Ar-**H**); HRMS: $[M + H]^+$ $C_{21}H_{24}FN_3O_2S$ calc. 402.1573, found. 402.1569.

The compound **6n** was prepared from starting materials **5m** and *N*-ethyl piperazine.

*1-[4-Methyl-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-5-fluoro-1*H-*indole dihydrochloride (**6n**)*

Yield: 59%, after 2 steps; Melting range: 203.4–206.2 °C; I.R ($cm^{-1}$): 3425, 2458, 1594, 1443, 1171, 799; ESIMS (*m/z*): 416.3 $[M + H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.23–1.27 (*t*, 3H, N-CH$_2$C**H$_3$**), 2.38 (s, 3H, Ar-C**H$_3$**), 3.03–3.06 (bs, 8H, Piperazine-**H**), 3.35–3.37 (*q*, 2H, N-C**H$_2$**CH$_3$), 3.8 (s, 2H, Ar-C**H$_2$**-N), 6.81–6.82 (d, 1H, $J = 3.56$ Hz, Ar-**H**), 7.16–7.21 (dd, 1H, $J = 9.2$, 2.62 Hz, Ar-**H**), 7.397.41 (dd, 1H, $J = 9.16$, 2.58 Hz, Ar-**H**), 7.41–7.43 (d, 1H, $J = 7.86$ Hz, Ar-**H**), 7.79–7.81 (d, 1H, $J = 6.98$ Hz, Ar-**H**), 7.87–7.88 (d, 1H, $J = 3.66$ Hz, Ar-**H**), 7.94–7.98 (dd, 1H, $J = 9.02$, 4.42 Hz, Ar-**H**), 8.13 (bs, 1H, Ar-**H**); HRMS: $[M + H]^+$ $C_{22}H_{26}FN_3O_2S$ calc. 416.1730, found. 416.1727.

The compound **6o** was prepared from starting materials **5o** and *N*-methyl piperazine.

*1-[4-Chloro-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-5-fluoro-1*H-*indole dihydrochloride (**6o**)*

Yield: 58%, after 2 steps; Melting range: 220.2–221.3 °C; I.R ($cm^{-1}$): 3429, 2983, 1591, 1463, 1377, 1138, 950; ESIMS (*m/z*): 422.0 $[M + H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.84 (s, 3H, N-C**H$_3$**), 3.05 (bs, 4H, Piperazine-**H**), 3.34–3.36 (bs, 4H, Piperazine-**H**), 3.98 (s, 2H, Ar-C**H$_2$**-N), 6.60–6.61 (d, 1H, $J = 3.67$, Ar-**H**), 6.91–6.96 (dd, 1H, $J = 9.18$, 2.4 Hz, Ar-**H**), 7.04–7.07 (dd, 1H, $J = 8.99$, 2.41 Hz, Ar-**H**), 7.26–7.28 (d, 1H, $J = 8.52$ Hz, Ar-**H**), 7.53–7.54 (d, 1H, $J = 3.68$ Hz, Ar-**H**), 7.63–7.66 (dd, 1H, $J = 8.5$, 1.9 Hz, Ar-**H**), 7.72–7.75 (m, 1H, $J = 4.34$ Hz, Ar-**H**), 7.85–7.86 (d, 1H, $J = 2.18$ Hz, Ar-**H**); HRMS: $[M + H]^+$ $C_{20}H_{21}ClFN_3O_2S$ calc. 422.1027, found. 422.1023.

The compound **6p** was prepared from starting materials **5o** and *N*-ethyl piperazine.

*1-[4-Chloro-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-5-fluoro-1*H-*indole dihydrochloride (**6p**)*

Yield: 56%, after 2 steps; Melting range: 204.1–205.5 °C; I.R ($cm^{-1}$): 3414, 2976, 1622, 1458, 1139, 804; ESIMS (*m/z*): 436.0 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.20–1.23 (*t*, 3H, N-$CH_2C\mathbf{H_3}$), 3.04 (bs, 4H, Piperazine-**H**), 3.13–3.18 (*q*, 2H, N-$C\mathbf{H_2}CH_3$), 3.32–3.34 (bs, 4H, Piperazine-**H**), 4.05 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.65–6.66 (d, 1H, *J* = 3.67 Hz, Ar-**H**), 6.99–7.03 (m, 1H, Ar-**H**), 7.13–7.16 (dd, 1H, *J* = 9.0, 2.5 Hz, Ar-**H**), 7.41–7.43 (d, 1H, *J* = 8.55 Hz, Ar-**H**), 7.56–7.57 (d, 1H, *J* = 3.7 Hz, Ar-**H**), 7.74–7.76 (dd, 1H, *J* = 8.55, 2.26 Hz, Ar-**H**), 7.78–7.81 (dd, 1H, *J* = 9.0, 4.1 Hz, Ar-**H**), 7.86 (d, 1H, *J* = 2.3 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{23}ClFN_3O_2S$ calc. 436.1184, found. 436.1182.

The compound **6q** was prepared from starting materials **5q** and *N*-methyl piperazine.

*1-[4-Bromo-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-5-fluoro-1*H-*indole dihydrochloride (**6q**)*

Yield: 55%, after 2 steps; Melting range: 219.4–221.6 °C; I.R ($cm^{-1}$): 3435, 2924, 2366, 1633, 1452, 1134, 943; ESIMS (*m/z*): 465.7 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.83 (s, 3H, N-$C\mathbf{H_3}$), 2.93 (bs, 4H, Piperazine-**H**), 3.2–3.26 (bs, 4H, Piperazine-**H**), 3.96 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.70–6.71 (d, 1H, *J* = 3.6 Hz, Ar-**H**), 7.02–7.07 (m, 1H, Ar-**H**), 7.19–7.22 (dd, 1H, *J* = 9.02, 2.5 Hz, Ar-**H**), 7.6–7.62 (d, 1H, *J* = 3.72 Hz, Ar-**H**), 7.67–7.72 (bs, 2H, Ar-**H**), 7.8 (s, 1H, Ar-**H**), 7.82–7.86 (m, 1H, Ar-**H**); HRMS: $[M+H]^+$ $C_{20}H_{21}BrFN_3O_2S$ calc. 466.0522, found. 466.0519.

The compound **6r** was prepared from starting materials **5q** and *N*-ethyl piperazine.

*1-[4-Bromo-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-5-fluoro-1*H-*indole (**6r**)*

Yield: 58%; Melting range: 92.2–93.9 °C; IR ($cm^{-1}$): 2939, 1589, 1458, 1138, 808; ESIMS (*m/z*): 479.8 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.11 (*t*, 3H, N-$CH_2C\mathbf{H_3}$), 2.43–2.48 (bs, 8H, Piperazine-**H** & 2H, N-$C\mathbf{H_2}CH_3$), 3.51 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.62–6.63 (dd, 1H, *J* = 3.59, 0.44 Hz, Ar-**H**), 7.00–7.05 (m, 1H, Ar-**H**), 7.16–7.19 (dd, 1H, *J* = 8.66, 2.5 Hz, Ar-**H**), 7.5–7.6 (m, 3H, Ar-**H**), 7.917.95 (m, 1H, Ar-**H**), 7.97 (d, 1H, *J* = 1.94 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{23}BrFN_3O_2S$ calc. 480.0678, found. 480.0675.

The compound **6s** was prepared from starting materials **5s** and *N*-ethyl piperazine.

*1-[4-Bromo-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-5-bromo-1*H-*indole dihydrochloride (**6s**)*

Yield: 56%, after 2 steps; Melting range: 205.1–207.1 °C; I.R ($cm^{-1}$): 3435, 2346, 1439, 1172, 815; ESIMS (*m/z*): 540.2 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.07–1.22 (*t*, 3H, N-$CH_2C\mathbf{H_3}$), 2.59–2.89 (bs, 6H, Piperazine-**H**), 3.04–3.07 (*q*, 2H, N-$C\mathbf{H_2}CH_3$), 3.10–3.12 (bs, 2H, Piperazine-**H**), 3.34 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.50–6.51 (d, 1H, *J* = 3.39 Hz, Ar-**H**), 7.15 (m, 2H, Ar-**H**), 7.32 (m, 2H, Ar-**H**), 7.49 (dd, 1H, *J* = 9.24, 3.49 Hz, Ar-**H**), 7.61 (d, 1H, *J* = 8.74 Hz, Ar-**H**), 7.70 (bs, 1H, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{23}Br_2N_3O_2S$ calc. 539.9878, found. 539.9881.

The compound **6t** was prepared from starting materials **5t** and *N*-methyl piperazine.

*1-[4-Chloro-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-5-methoxy-1*H-*indole dihydrochloride (**6t**)*

Yield: 62%, after 2 steps; Melting range: 208.8–210.2 °C; I.R ($cm^{-1}$): 3446, 2981, 2372, 1585, 1465, 1222, 952; ESIMS (*m/z*): 434.1 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.82 (s, 3H, N-$C\mathbf{H_3}$), 3.05 (bs, 4H, Piperazine-**H**), 3.23–3.28 (bs, 4H, Piperazine-**H**), 3.60 (s, 3H, Ar-$OC\mathbf{H_3}$), 3.9 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.55–6.56 (d, 1H, *J* = 3.64 Hz, Ar-**H**), 6.67–6.79 (dd, 1H, *J* = 9.03, 2.44 Hz, Ar-**H**), 6.88–6.89 (d, 1H, *J* = 2.42 Hz, Ar-**H**), 7.20–7.22 (d, 1H, *J* = 8.53 Hz, Ar-**H**), 7.42–7.43 (d, 1H, *J* = 3.65 Hz, Ar-**H**), 7.58–7.61 (dd, 1H, *J* = 8.5, 2.1 Hz, Ar-**H**), 7.65–7.68 (d, 1H, *J* = 9.04 Hz, Ar-**H**), 7.79 (d, 1H, *J* = 2.21 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{24}ClN_3O_3S$ calc. 434.1227, found. 434.1225.

The compound **6u** was prepared from starting materials **5t** and *N*-ethyl piperazine.

*1-[4-Chloro-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-5-methoxy-1*H-*indole dihydrochloride (**6u**)*

Yield: 61%, after 2 steps; Melting range: 209.5–211.0 °C; I.R ($cm^{-1}$): 3448, 2983, 1585, 1465, 1222, 761; ESIMS (*m/z*): 448.0 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.19–1.23 (*t*, 3H, N-$CH_2C\mathbf{H_3}$), 2.97 (bs, 4H, Piperazine-**H**), 3.11–3.16 (*q*, 2H, N-$C\mathbf{H_2}CH_3$), 3.23 (bs, 4H, Piperazine-**H**), 3.67 (s, 3H, Ar-$OC\mathbf{H_3}$), 4.0 (s, 2H, Ar-$C\mathbf{H_2}$-N), 6.61–6.62 (d, 1H, *J* = 3.66 Hz, Ar-**H**), 6.83–6.86 (dd, 1H, *J* = 9.0, 2.5 Hz, Ar-**H**), 6.98 (d, 1H, *J* = 2.47 Hz, Ar-**H**), 7.39–7.41 (d, 1H, *J* = 8.54 Hz, Ar-**H**), 7.46–7.47 (d, 1H, *J* = 3.68 Hz, Ar-**H**), 7.71–7.74 (m, 2H, Ar-**H**), 7.80 (d, 1H, *J* = 2.2 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{22}H_{26}ClN_3O_3S$ calc. 448.1383, found. 448.1378.

The compound **6v** was prepared from starting materials **5v** and *N*-methyl piperazine.

*1-[4-Bromo-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-5-methoxy-1*H-*indole (**6v**)*

Yield: 63%; Melting range: 115.2–117 °C; I.R ($cm^{-1}$): 2929, 1606, 1371, 1217, 817; ESIMS (*m/z*): 477.9 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 2.33 (s, 3H, N-$C\mathbf{H_3}$), 2.35 (bs, 8H, Piperazine-**H**), 3.50 (s, 2H, Ar-$C\mathbf{H_2}$-N), 3.80 (s, 3H, Ar-$OC\mathbf{H_3}$), 6.58 (dd, 1H, *J* = 3.6, 0.48 Hz, Ar-**H**), 6.9 (dd, 1H, *J* = 8.97, 2.50 Hz, Ar-**H**), 6.95 (d, 1H, *J* = 2.43 Hz, Ar-**H**), 7.48 (d, 1H, *J* = 3.6 Hz, Ar-**H**), 7.56 (m, 2H, Ar-**H**), 7.85 (d, 1H, *J* = 8.9 Hz, Ar-**H**), 7.96 (d, 1H, *J* = 1.33 Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{24}BrN_3O_3S$ calc. 478.0722, found. 478.0715.

The compound **6w** was prepared from starting materials **5v** and *N*-ethyl piperazine.

*1-[4-Bromo-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-5-methoxy-1*H-*indole (**6w**)*

Yield: 59%; Melting range: 196.1–198.6 °C; I.R ($cm^{-1}$): 3444, 2430, 1614, 1438, 1224, 761; ESIMS (*m/z*): 491.9 $[M+H]^+$; $^1$H-NMR (400 MHz, $CDCl_3$): **δ** 1.22–1.27 (*t*, 3H, N-$CH_2C\mathbf{H_3}$), 2.65–2.66 (bs, 4H, Piperazine-**H**), 2.99–3.00 (bs, 2H, Piperazine-**H**), 3.12–3.14 (bs, 2H, Piperazine-**H**), 3.22–3.34 (*q*, 2H, N-$C\mathbf{H_2}CH_3$), 3.35–3.37 (s, 2H, Ar-$C\mathbf{H_2}$-N), 3.79 (s, 3H, Ar-$OC\mathbf{H_3}$), 6.67–6.79 (d, 1H, *J* = 3.69 Hz, Ar-**H**), 6.93–6.96 (dd, 1H, *J* = 9.01, 2.52 Hz, Ar-**H**), 7.10–7.11 (d, 1H, *J* = 2.4 Hz, Ar-**H**), 7.71–7.72 (dd, 1H, *J* = 8.45, 2.42 Hz, Ar-**H**), 7.75–7.76 (d, 1H, *J* = 3.65 Hz, Ar-**H**), 7.80–7.85 (m, 2H, Ar-**H**), 8.03 (bs, 1H, Ar-**H**); HRMS: $[M+H]^+$ $C_{22}H_{26}BrN_3O_3S$ calc. 491.0878, found. 491.0882.

The compound **6x** was prepared from starting materials **5x** and *N*-methyl piperazine.

*1-[4-Chloro-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-3-methyl-1*H-*indole dihydrochloride (**6x**)*

Yield: 61%, after 2 steps; Melting range: 216.9–218.7 °C; I.R ($cm^{-1}$): 3493, 2673, 1627, 1450, 1174, 962; ESIMS (*m/z*): 418.4 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.01 (s, 3H, Ar-$C\mathbf{H_3}$), 2.83 (s, 3H, N-$C\mathbf{H_3}$), 3.00 (bs, 4H, Piperazine-**H**), 3.2–3.35

(bs, 4H, Piperazine-**H**), 3.98 (s, 2H, Ar-C**H$_2$**-N), 7.12–7.14 (m, 1H, Ar-**H**), 7.15–7.31 (m, 4H, Ar-**H**), 7.62–7.63 (dd, 1H, $J = 8.54$, 1.96 Hz, Ar-**H**), 7.65–7.84 (m, 2H, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{24}ClN_3O_2S$ calc. 418.1278, found. 418.1275.

The compound **6y** was prepared from starting materials **5x** and *N*-ethyl piperazine.

*1-[4-Chloro-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-3-methyl-1*H*-indole dihydrochloride (**6y**)*

Yield: 63%, after 2 steps; Melting range: 218.9–220.5 °C; I.R ($cm^{-1}$): 3417, 2436, 1631, 1442, 1166, 966; ESIMS (*m/z*): 432.3 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.19–1.22 (*t*, 3H, N-$CH_2$C**H$_3$**), 2.00 (s, 3H, Ar-C**H$_3$**), 2.93 (bs, 4H, Piperazine-**H**) 3.11–3.16 (*q*, 2H, N-C**H$_2$**$CH_3$), 3.33–3.35 (bs, 4H, Piperazine-**H**), 4.01 (s, 2H, Ar-C**H$_2$-**N), 7.10–7.14 (m, 1H, Ar-**H**), 7.23–7.30 (m, 4H, Ar-**H**), 7.61 (dd, 1H, $J = 8.64$, 1.74 Hz, Ar-**H**), 7.82–7.84 (m, 2H, Ar-**H**); HRMS: $[M+H]^+$ $C_{22}H_{26}ClN_3O_2S$ calc. 432.1434, found. 432.1436.

The compound **6z** was prepared from starting materials **5z** and *N*-methyl piperazine.

*1-[4-Bromo-3-(4-methyl piperazin-1-ylmethyl) phenylsulfonyl]-3-methyl-1*H*-indole dihydrochloride (**6z**)*

Yield: 56%, after 2 steps; Melting range: 210.5–213 °C; I.R ($cm^{-1}$): 3429, 2370, 1631, 1174, 948; ESIMS (*m/z*): 462.2 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.97 (s, 3H, Ar-C**H$_3$**), 2.78 (s, 3H, N-C**H$_3$**), 2.79 (bs, 4H, Piperazine-**H**), 3.10–3.17 (bs, 4H, Piperazine-**H**), 3.72 (s, 2H, Ar-C**H$_2$-**N), 7.06–7.08 (m, 1H, Ar-**H**), 7.17–7.21 (m, 4H, Ar-**H**), 7.37 (m, 1H, Ar-**H**), 7.72 (bs, 1H, Ar-**H**), 7.79–7.82 (d, 1H, $J = 8.20$ Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{21}H_{24}BrN_3O_2S$ calc. 462.0773, found. 462.0778.

The compound **6aa** was prepared from starting materials **5z** and *N*-ethyl piperazine

*1-[4-Bromo-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-3-methyl-1*H*-indole dihydrochloride (**6aa**)*

Yield: 62%, after 2 steps; Melting range: 204.1–206.5 °C; I.R ($cm^{-1}$): 3439, 2434, 1566, 1442, 1174, 966; ESIMS (*m/z*): 476.2 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.16–1.19 (*t*, 3H, N-$CH_2$C**H$_3$**), 1.96 (s, 3H, Ar-C**H$_3$**), 2.77–2.94 (bs, 4H, Piperazine-**H**), 3.04 (*q*, 2H, N-C**H$_2$**$CH_3$), 3.08 (bs, 4H, Piperazine-**H**), 3.69 (s, 2H, Ar-C**H$_2$-**N), 7.04–7.20 (m, 4H, Ar-**H**), 7.22 (bs, 1H, Ar-**H**), 7.35–7.37 (d, 1H, $J = 8.2$ Hz, Ar-**H**), 7.72 (bs, 1H, Ar-**H**), 7.8–7.82 (d, 1H, $J = 8.16$ Hz, Ar-**H**); HRMS: $[M+H]^+$ $C_{22}H_{26}BrN_3O_2S$ calc. 476.0929, found. 476.0931.

The compound **6ab** was prepared from starting materials **5ab** and *N*-methyl piperazine.

*1-[4-Chloro-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-5-methoxy-3-methyl-1*H*-indole dihydrochloride (**6ab**)*

Yield: 61%, after 2 steps; Melting range: 213.3–214.2 °C; I.R ($cm^{-1}$): 3479, 2963, 2441, 1608, 1454, 1172, 883; ESIMS (*m/z*): 448.3 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 2.16 (s, 3H, Ar-C**H$_3$**), 2.77 (s, 3H, N-C**H$_3$**), 2.95–2.99 (bs, 6H, Piperazine-**H**), 3.45 (bs, 2H, Piperazine-**H**), 3.94 (s, 3H, Ar-OC**H$_3$**), 4.29 (s, 2H, Ar-C**H$_2$-**N), 6.92–6.96 (dd, 1H, $J = 8.96$, 2.52 Hz, Ar-**H**), 7.01 (d, 1H, $J = 2.44$ Hz, Ar-**H**), 7.54 (d, 1H, $J = 1.04$ Hz, Ar-**H**), 7.66–7.68 (d, 1H, $J = 8.52$ Hz, Ar-**H**), 7.79–7.83 (m, 2H, Ar-**H**), 8.22 (s, 1H, Ar-**H**); HRMS: $[M+H]^+$ $C_{22}H_{26}ClN_3O_3S$ calc. 448.1383, found. 448.1387.

The compound **6ac** was prepared from starting materials **5ab** and *N*-ethyl piperazine.

*1-[4-Chloro-3-(4-ethyl piperazin-1-yl methyl) phenylsulfonyl]-5-methoxy-3-methyl-1*H*-indole dihydrochloride (**6ac**)*

Yield: 59%, after 2 steps; Melting range: 217.5–220.8 °C; I.R ($cm^{-1}$): 3456, 2983, 1612, 1448, 1172, 962; ESIMS (*m/z*): 462.2 $[M+H]^+$; $^1$H-NMR (400 MHz, $D_2O$): **δ** 1.10–1.14 (*t*, 3H, N-$CH_2$C**H$_3$**), 1.91 (s, 3H, Ar-C**H$_3$**), 3.07–3.12 (bs, 10H, Piperazine-**H** & 2H, N-C**H$_2$**$CH_3$), 3.60 (s, 3H, Ar-OC**H$_3$**), 4.18 (s, 2H, Ar-C**H$_2$-**N), 6.74–6.8 (m, 2H, Ar-**H**), 7.11 (s, 1H, Ar-**H**), 7.37–7.39 (d, 1H, $J = 8.76$ Hz, Ar-**H**), 7.61–7.67 (m, 2H, Ar-**H**), 7.74 (s, 1H, Ar-**H**); HRMS: $[M+H]^+$ $C_{23}H_{28}ClN_3O_3S$ calc. 462.1540, found. 462.1543.

## Results and discussion

### Structure–activity relationship (SAR)

Several analogs of 1-[3–(4-methyl piperazin-1-ylmethyl) phenylsulfonyl]-1*H*-indoles and 1-[3–(4-ethyl piperazin-1-ylmethyl) phenylsulfonyl]-1*H*-indoles were synthesized and their radioligand binding affinities at the human 5-$HT_6$R at 100 nM concentration are given in Table 1.

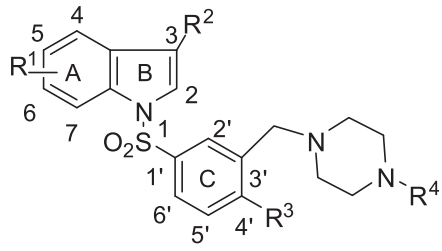
The binding data of these compounds at 100 nM concentration indicated that the compounds have high to moderate affinity to the 5-$HT_6$R. Among the compounds synthesized **6a**, **6b**, **6c**, **6d**, **6e**, **6x**, **6y**, **6z** and **6aa** have shown good binding affinity at human 5-$HT_6$R, when compared to other compounds in the series. Unsubstituted indole derivatives **6a**, **6b**, **6c and 6d** have shown higher 5-$HT_6$R-binding affinities than those of the corresponding 5-substituted compounds, suggesting that the substitution at 5th position of indole ring is not well tolerated. This can be seen by comparing the *in vitro* binding affinities of the compound **6a** with **6 h**, **6i**, **6j** and **6k**, compound **6b** with **6 l** and **6m**, compound **6c** with **6n** or compound **6d** with **6o** and **6t**. Compounds with electron donating and/or bulky groups (viz. $OCH_3$, $OC_2H_5$, $OCH(CH_3)_2$) at $C_5$ of indole showed moderate potency toward 5-$HT_6$R (compounds **6 h**, **6i** and **6j).** One-fourth of the activity was lost when electron-donating groups like methoxy group was introduced at $C_5$ of indole as can be seen by comparing the binding affinities of the compound **6a** with **6 h**, compound **6d** with **6t**, compound **6e** with **6u**, compound **6f** with **6v**, compound **6 g** with **6w**, compound **6x** with **6ab** or compound **6y** with **6ac**.

More or less a very similar trend was observed in the case of electron withdrawing and/or bulky halogen groups (viz. F, Br) as can be seen by comparing the binding affinities of the compound **6 g** with **6r** and **6s**. The $C_5$ halo substituted indole derivatives exhibited moderate affinity toward 5-$HT_6$R as can be seen from **6k–6s**. In terms of *in vitro* affinity, the preferred order of substitution on phenylsulfonyl ring at C-4′ position was found to be $CH_3$, H, Cl over Br as can be seen by comparing the binding affinities of the compounds **6b** with **6a**, **6d** and **6f**, compound **6k** with **6m**, **6o** and **6q**. In terms of activity, almost similar trend was observed in compounds with $N_1$-methyl or $N_1$-ethyl substitution on piperazine ring, as can be seen from comparing the binding affinities of the compound **6b** with **6c**, compound **6d** with **6e**, compound **6f** with **6 g**, compound **6t** with **6u**, compound **6v** with **6w**, compound **6x** with **6y** or compound **6z** with **6aa**.

Generally, replacement of the hydrogen atom at the indole-$C_3$ with the small methyl group is well tolerated and produced good *in vitro* potency, as can be seen by comparing affinities of the methyl-substituted derivatives **6x**, **6y**, **6z** and **6aa** with those of the corresponding $C_3$-unsubstituted compounds **6d**, **6e**, **6f** and **6g**.

The compounds showing >90% inhibition at 100 nM concentration at 5-$HT_6$R were further assessed for their $K_i$ (nM) values by performing complete dose response from 10 μM to 0.1 nM in semilogarithmic concentrations (Table 1).

Table 1. 5-$HT_6$R binding data† for compounds 6.




| Comp. No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | % Inhibition at 100 nM concentration* | $K_i$ (nM) |
|---|---|---|---|---|---|---|
| 6a | H | H | H | $CH_3$ | 92.41 | 7.50 ± 0.42 |
| 6b | H | H | $CH_3$ | $CH_3$ | 95.11 | 7.01 ± 0.26 |
| 6c | H | H | $CH_3$ | $C_2H_5$ | 95.48 | 3.96 ± 0.28 |
| 6d | H | H | Cl | $CH_3$ | 92.36 | 18.4 ± 0.84 |
| 6e | H | H | Cl | $C_2H_5$ | 92.06 | 15.6 ± 0.70 |
| 6f | H | H | Br | $CH_3$ | 88.79 | – |
| 6g | H | H | Br | $C_2H_5$ | 87.68 | – |
| 6h | 5-$OCH_3$ | H | H | $CH_3$ | 67.58 | – |
| 6i | 5-$OC_2H_5$ | H | H | $CH_3$ | 63.73 | – |
| 6j | 5-$O^iPr$ | H | H | $CH_3$ | 61.48 | – |
| 6k | 5-F | H | H | $CH_3$ | 79.20 | – |
| 6l | 5-$OCH_3$ | H | $CH_3$ | $CH_3$ | 62.18 | – |
| 6m | 5-F | H | $CH_3$ | $CH_3$ | 86.18 | – |
| 6n | 5-F | H | $CH_3$ | $C_2H_5$ | 78.54 | – |
| 6o | 5-F | H | Cl | $CH_3$ | 72.97 | – |
| 6p | 5-F | H | Cl | $C_2H_5$ | 64.82 | – |
| 6q | 5-F | H | Br | $CH_3$ | 70.45 | – |
| 6r | 5-F | H | Br | $C_2H_5$ | 62.52 | – |
| 6s | 5-Br | H | Br | $C_2H_5$ | 55.86 | – |
| 6t | 5-$OCH_3$ | H | Cl | $CH_3$ | 57.03 | – |
| 6u | 5-$OCH_3$ | H | Cl | $C_2H_5$ | 55.68 | – |
| 6v | 5-$OCH_3$ | H | Br | $CH_3$ | 54.21 | – |
| 6w | 5-$OCH_3$ | H | Br | $C_2H_5$ | 50.53 | – |
| 6x | H | $CH_3$ | Cl | $CH_3$ | 96.63 | 5.45 ± 0.28 |
| 6y | H | $CH_3$ | Cl | $C_2H_5$ | 92.91 | 7.85 ± 0.35 |
| 6z | H | $CH_3$ | Br | $CH_3$ | 93.23 | 9.11 ± 0.24 |
| 6aa | H | $CH_3$ | Br | $C_2H_5$ | 91.51 | 12.8 ± 0.63 |
| 6ab | 5-$OCH_3$ | $CH_3$ | Cl | $CH_3$ | 71.53 | – |
| 6ac | 5-$OCH_3$ | $CH_3$ | Cl | $C_2H_5$ | 68.10 | – |

*The data represent average of two determinations.
†5-$HT_6$ receptor-binding studies were carried out at NovaScreen Biosciences Corporation, (caliper life sciences), Hanover, MD, USA. Human recombinant/HEK293 cells; Radioligand: [$^3$H] LSD (60–80 Ci/mmol).
''–'' means not tested for **$K_i$ (nM)** determination.

The compound **6b** was also evaluated in 5-$HT_6$ reporter gene cell-based functional assay[43,44]. The tested compound **6b** has shown antagonistic activity by inhibiting the 5-HT-stimulated cAMP accumulation, with a $K_b$ value of 4.92 ± 0.13 nM and $IC_{50}$ value of 548.2 ± 3.6 nM.

Selected compounds that displayed satisfactory potency towards 5-$HT_6$R in *in vitro* binding assay were further profiled in selectivity assays, against a panel of related serotonin receptors like 5-$HT_{4b}$, 5-$HT_3$, 5-HT2A and 5-HT2C, histamine $H_1$, dopamine $D_2$, adrenergic $\alpha_{1B}$ and the transporters such as SERT, NET and DAT.

We were also pleased to find that the tested compounds (**6b, 6c** and **6x**) demonstrated <30% inhibition at maximum tested concentration of 10 μM, indicating that the tested compounds have very less activity toward these off targets and are highly selective toward 5$HT_6$ receptor (data not shown).

In drug discovery, a major challenge of CNS therapy is the blood–brain barrier (BBB). 5-$HT_6$ receptor antagonists should cross the blood brain barrier for treating cognitive dysfunction. This greatly limits the potential of a compound to become a successful CNS agent.

We have profiled the selected compounds (**6b**, **6c** and **6x)** for their PK parameters (Table 2). Brain and plasma levels were calculated in male Wistar rats after 6 h *i.v.* continuous infusion of compounds **6b**, **6c** and **6x** at 1 mg/kg/h dose. Among these compounds, **6b** has shown adequate brain to plasma ratio of 2.03 ± 0.42 (brain and plasma concentrations are 510 ± 145 ng/g, 286 ± 80 ng/mL), whereas compounds **6c** and **6x** were having lower to moderate brain to plasma ratio of 0.53 ± 0.13 (brain and plasma concentrations are 312 ± 82 ng/g, 59 ± 37 ng/mL) and 1.61 ± 0.39 (brain and plasma concentrations are 486 ± 250 ng/g, 293 ± 102 ng/mL), respectively. The pharmacokinetic profile of **6b**, **6c** and **6x** was assessed in male Wistar rats (Table 2). Following *i.v.* administration of 10 mg/kg, the compounds **6b**, **6c** and **6x** have shown good mean half-life of 2.69 ± 1.51 h, 6.25 ± 0.35 h and 5.84 ± 2.21 h, respectively. Following oral administration at 10 mg/kg, the compounds **6b** and **6c** have shown good plasma concentrations of 1375 ± 427 ng/mL,

Table 2. Pharmacokinetic profile of compounds **6b, 6c,** and **6x** in male wistar rats*.

| Compound | 6b | 6c | 6x |
|---|---|---|---|
| ***i.v.*** $(n=3)$ | | | |
| Dose (mg/kg) | 10 | 10 | 10 |
| $t_{1/2}$ (h) | $2.69 \pm 1.51$ | $6.25 \pm 0.35$ | $5.84 \pm 2.21$ |
| *Vz* (L/kg) | $3.6 \pm 1.2$ | $6.9 \pm 4.3$ | $7.5 \pm 1.0$ |
| Cl (mL/min/kg) | $34 \pm 12$ | $40 \pm 7$ | $52 \pm 7$ |
| ***p.o.*** $(n=3)$ | | | |
| Dose (mg/kg) | 10 | 10 | 10 |
| $t_{1/2}$ (h) | $7.85 \pm 2.62$ | $3.18 \pm 1.71$ | $1.73 \pm 0.56$ |
| $C_{max}$ (ng/mL) | $1375 \pm 427$ | $749 \pm 836$ | $106 \pm 1$ |
| $T_{max}$ (h) | $0.38 \pm 0.18$ | $0.50 \pm 0.43$ | $0.38 \pm 0.18$ |
| AUC (ng.h/mL) | $3194 \pm 1748$ | $1171 \pm 1046$ | $342 \pm 152$ |
| *F* (%) | $30 \pm 7$ | $14 \pm 10$ | $10 \pm 6$ |
| Brain (ng/g) | $570 \pm 145$ | $312 \pm 82$ | $486 \pm 250$ |
| Plasma (ng/mL) | $286 \pm 80$ | $592 \pm 37$ | $293 \pm 102$ |
| $C_b/C_p$ | $2.03 \pm 0.42$ | $0.53 \pm 0.13$ | $1.61 \pm 0.39$ |

*Fasted male wistar rats, vehicle used: water for injection for both oral and intravenous routes. Dosing volumes: 10 mL/kg *p.o.* and 2 mL/kg for *i.v.*; values are mean ± SD.

*i.v.* = intravenous, *p.o.* = per oral, $t_{1/2}$ = half-life, *Vz* = volume of distribution, Cl = clearance, $C_{max}$ = The peak plasma concentration of a drug after administration, $T_{max}$ = Time of maximum drug concentration, AUC = Area Under the Curve, *F* (%) = bioavailability, $C_b/C_p$ = brain to plasma ratio.

Table 3. Human CYP450[45] inhibitory data and microsomal metabolic stability for compound **6b***.

| | $IC_{50}$ (μM) | | % Metabolism in liver microsomes | |
|---|---|---|---|---|
| Compound | CYP 3A4 | CYP 2D6 | Human | Rat |
| **6b** | 6.9 | 4.3 | 94 | 100 |

*The cytochrome P450 inhibitory potential was determined using isoform-selective assays and heterologously expressed human CYP 2D6 and CYP 3A4. These values are the mean of duplicate determinations. Microsomal metabolic stability in wistar rat and human at 0.5 h, conc. 2.5 μM.

$749 \pm 836$ ng/mL, respectively, whereas compound **6x** has shown low plasma concentration of $106 \pm 1$ ng/mL.

The clearance was low ($34 \pm 12$ mL/min/kg) for compound **6b** as compared to those of **6c** and **6x**. The compounds **6b**, **6c** and **6x** have shown the volume of distributions (*Vz*, L/kg), that is, $3.6 \pm 1.2$, $6.9 \pm 4.3$ and $7.5 \pm 1.0$, respectively, at 10 mg/kg, *i.v.* dose.

The mean oral bioavailability for compound **6b** was better ($30 \pm 7\%$) as compared to that of **6c** ($14 \pm 10\%$) and **6x** ($10 \pm 6\%$). The moderate-to-low oral bioavailability of these compounds may be because of their poor metabolic stability in rat liver microsomes.

The *in vitro* metabolic stability of compound **6b** in rat and human liver microsomes was carried out for 30 minutes. Additional screening in *in vitro* ADME assays demonstrated that the compound **6b** has extensively metabolized (100% and 94%) in rat and human liver microsomes, respectively.

Based on above pharmacokinetic profile data, the compound **6b** was further evaluated for its CYP liabilities in human liver microsomes, the $IC_{50}$ values for compound **6b** was found to be 6.9 μM for CYP 3A4 enzymes and 4.3 μM for CYP 2D6 enzymes (Table 3).

Based on the overall pharmacokinetic and brain penetration data (Table 2), compound **6b** was selected for further profiling in pharmacological models of cognition. Object recognition is an attractive task for testing compounds for their potential against cognitive deficits in Alzheimer's disease and schizophrenia.

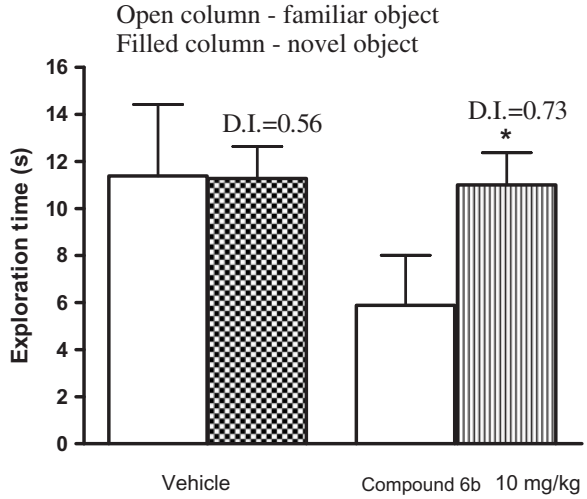



Figure 5. Novel object recognition test data for compound **6b** in rats. Compound 6b versus vehicle (paired t-test), $n = 9$–10/group, *p.o.*, dosing drug: 60 min prior to test (*p.o.*). Vehicle PEG 400 50% v/v; 1 mL/kg, *p.o.* $^*p < 0.05$ Student's *t*-test. D.I. = discriminative index.

Oral administration of compound **6b** (10 mg/kg) has significantly improved performance of rats in animal models of cognition like novel object recognition test[46] (NORT, Figure 5). Discriminative index of vehicle-treated group between familiar and novel object is 0.56, where as in compound **6b** treated group is 0.73 (Figure 5).

## Conclusion

We have identified a new series of 1-[3-(4-alkyl piperazin-1-ylmethyl)- phenylsulfonyl]-1*H*-indoles (**Compounds 6**) as potent, selective, orally available and brain penetrant 5-$HT_6$ receptor ligands. The lead compound, 1-[4-methyl-3-(4-methyl piperazin-1-yl methyl) phenylsulfonyl]-1*H*-indole dihydrochloride (**6b**) from this series has shown desired pharmacokinetic properties and is active in animal models of cognition such as NORT in preclinical trials. Based on its overall profile, the **compound 6b** was selected for further development.

## Acknowledgements

Mr. Venkateswarlu Jasti, CEO, Suven Life Sciences Ltd., Hyderabad, India is gratefully acknowledged.

## Declaration of interest

The study is supported by discovery analytical, DMPK, *In vitro*, *In vivo* departments.

## References

1. Cummings JL, Back C. The cholinergic hypothesis of neuropsychiatric symptoms in Alzheimer's disease. Am J Geriatr Psychiatry 1998;6:S64–78.
2. Garcia-Alloza M, Gil-Bea FJ, Diez-Ariza M, et al. Cholinergic-serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease. Neuropsychologia 2005;43:442–9.
3. Doody RS, Ferris SH, Salloway S, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurol 2009;72:1555–61.
4. Farlow MR, Cummings JL. Effective pharmacologic management of Alzheimer's disease. Am J Med 2007;120:388–97.
5. Van Marum RJ. Update on the use of memantine in Alzheimer's disease. Neuropsychiatr Dis Treat 2009;5:237–47.

6. Gerard C, Martres MP, Lefevre K, et al. Immunolocalization of serotonin 5-$HT_6$ receptor-like material in the rat central nervous system. Brain Res 1997;746:207–19.
7. Dawson LA, Nguyen HQ, Li P. The 5-$HT_6$ receptor antagonist SB-271046 selectively enhances excitatory neurotransmission in the rat frontal cortex and hippocampus. Neuropsychopharmacol 2001;25: 662–8.
8. Hirst WD, Stean TO, Rogers DC, et al. SB-399885 is a potent, selective 5-$HT_6$ receptor antagonist with cognitive enhancing properties in aged rat water maze and novel object recognition models. Eur J Pharmacol 2006;553:109–19.
9. Ramirez MJ, Lai MKP, Tordera RM, Francis PT. Serotonergic therapies for cognitive symptoms in Alzheimer's disease: rationale and current status. Drugs 2014;74:729–36.
10. Nirogi R, Kambhampati R, Shinde A, et al. Alzheimer's and dementia. International conference on Alzheimer's Disease, Vienna. 2009;5:250.
11. Biotie therapies. Available from: http://www.biotie.com/en/product_and_development/development_pipeline/syn120 [last accessed 1 May 2015].
12. Pfizer. Available from: http://www.pfizer.com/sites/default/files/productpipeline/pipeline_2013_0509.pdf/Neuroscience & pain [last accessed 1 May 2015].
13. Avineuro Pharmaceuticals. Available from: http://www.biocentury.com/products/avn-211 [last accessed 1 May 2015].
14. (a) Lundbeck. Available from: http://www.lundbeck.com/global [last accessed 1 May 2015]. (b) Jorn A, Benny B, Ben G, et al. Lu AE58054, a 5-$HT_6$ antagonist, reverses cognitive impairment induced by subchronic phencyclidine in a novel object recognition test in rats. Int J Neuropsychopharmacol 2010;13:1021–33.
15. GlaxoSmithKline. Available from: http://www.gsk.com/research/our-product-pipeline.html [last accessed 1 May 2015].
16. Ivachtchenko AV, Golovina ES, Kadieva MG, et al. Synthesis and structure−activity relationship (SAR) of (5,7-disubstituted 3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidin-2-yl)-methylamines as potent serotonin 5-HT6 receptor (5-HT6R) antagonists. J Med Chem 2011; 54:8161–73.
17. Ivachtchenko AV, Dmitriev DE, Golovina ES, et al. (3-Phenylsulfonylcycloalkano[e and d]pyrazolo[1,5-a]pyrimidin-2-yl)amines: potent and selective antagonists of the serotonin 5-HT6 receptor. J Med Chem 2010;53:5186–96.
18. Ivachtchenko AV, Golovina ES, Kadieva MG, et al. Antagonists of 5-HT6 receptors. Substituted 3-(phenylsulfonyl) pyrazolo[1,5-a]pyrido[3,4-e]pyrimidines and 3-(phenylsulfonyl) pyrazolo[1,5-a]pyrido[4,3-d]pyrimidines—Synthesis and 'structure–activity' relationship. Bioorg Med Chem Lett 2012;22:4273–80.
19. Ivachtchenko AV, Golovina ES, Kadieva MG, et al. Synthesis and SAR of 3-arylsulfonyl-pyrazolo[1,5-a]pyrimidines as potent serotonin 5-HT6 receptor antagonists. Bioorg Med Chem 2011;19: 1482–91.
20. Ivachtchenko AV, Golovina ES, Kadieva MG, et al. 2-Substituted 5,6-dimethyl-3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidines: new series of highly potent and specific serotonin 5-HT6 receptor antagonists. Eur J Med Chem 2011;46:1189–97.
21. (a) Glennon RA. Higher-end serotonin receptors: 5-HT(5), 5-HT(6), and 5-HT(7). J Med Chem 2003;4:2795–812. (b) Glennon RA, Lee M, Rangisetty JB, et al. 2-Substituted tryptamines: agents with selectivity for 5-HT(6) serotonin receptors. J Med Chem 2000;43:1011–18.
22. Liu KG, Robichaud AJ, Bernotas RC, et al. 5Piperazinyl-3-sulfonylindazoles as potent and selective 5-hydroxytryptamine-6 antagonists. J Med Chem 2010;53:7639–46.
23. Routledge C, Bromidge SM, Moss SF, et al. Characterization of SB-271046: a potent, selective and orally active 5-HT(6) receptor antagonist. Br J Pharmacol 2000;130:1606–12.
24. Bromidge SM, Brown AM, Clarke SE, et al. 5Chloro-N-(4-methoxy-3-piperazin-1-yl- phenyl)-3-methyl-2-benzothiophenesulfonamide (SB-271046): a potent, selective, and orally bioavailable 5-$HT_6$ receptor antagonist. J Med Chem 1999;42:202–5.
25. Johnson CN, Ahmed M, Miller ND. 5$HT_6$ receptor antagonists: prospects for the treatment of cognitive disorders including dementia. Curr Opin Drug Discov Devel 2008;11:642–54.
26. Cole DC, Lennox WJ, Stock JR, et al. Conformationally constrained $N_1$-arylsulfonyltryptamine derivatives as 5-$HT_6$ receptor antagonists. Bioorg Med Chem Lett 2005;15:4780–5.
27. Cole DC, Ellingboe JW, Lennox WJ, et al. N1-arylsulfonyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole derivatives are potent and selective 5-$HT_6$ receptor antagonists. Bioorg Med Chem Lett 2005;15:379–83.
28. (a) Cole DC, Lennox WJ, Lombardi S, et al. Discovery of 5-arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indole derivatives as potent, selective 5-$HT_6$ receptor agonists and antagonists. J Med Chem 2005;48(2):353–6. (b) Liu KG, Robichaud A. 5$HT_6$ antagonists as potential treatment for cognitive dysfunction. J Drug Dev Res 2009;70:145–68. (c) Beard CC, Clark RD, Fisher LM, et al. US Patent 0073700 A1; 2003.
29. Benhamú B, Martín-Fontecha M, Vázquez-Villa H, et al. Serotonin 5-$HT_6$ receptor antagonists for the treatment of cognitive deficiency in Alzheimer's disease. J Med Chem 2014;57:7160–81.
30. Nirogi R, Daulatabad A, Parandhama G, et al. Synthesis and pharmacological evaluation of aryl aminosulfonamide derivatives as potent 5-HT(6) receptor antagonists. Bioorg Med Chem Lett 2010; 20:4440–3.
31. Nirogi R, Dwarampudi A, Kambhampati R, et al. Rigidized 1-aryl sulfonyl tryptamines: synthesis and pharmacological evaluation as 5-HT6 receptor ligands. Bioorg Med Chem Lett 2011;21:4577–80.
32. Nirogi R, Deshpande A, Kambhampati R, et al. Indole-3-piperazinyl derivatives: novel chemical class of 5-$HT_6$ receptor antagonists. Bioorg Med Chem Lett 2011;21:346–9.
33. (a) Nirogi R, Kothmirkar P, Kambhampati R, et al. Novel and potent 5-piperazinyl methyl-$N_1$-aryl sulfonyl indolederivatives as 5-$HT_6$ receptor ligands. ACS Med Chem Lett 2010;1:340–4. (b) Nirogi R, Badange R, Kambhampati R, et al. Design, synthesis and pharmacological evaluation of 4-(piperazin-1-yl methyl)-$N_1$-arylsulfonyl indole derivatives as 5-$HT_6$ receptor ligands. Bioorg Med Chem Lett 2012;22:7431–5. (C) Ramakrishna VSN, Shirsath VS, Kambhampati RS, et al. Narylsulfonyl-3-substituted indoles having serotonin receptor affinity, process for their preparation and pharmaceutical composition containing them. WO 2004/048330 A1; 2004.
34. Ivachtchenko A, Golovina E, Kadieva M, et al. Synthesis of substituted diphenyl sulfones and their structure-activity relationship with the antagonism of 5-HT6 receptors. Bioorg Med Chem 2013; 21:4614–27.
35. Lopez-Rodriguez ML, Benhamu B, Fuente T, et al. A three-dimensional pharmacophore model for 5-hydroxytryptamine6 (5-$HT_6$) receptor antagonists. J Med Chem 2005;48:4216–19.
36. Bromidge SM. Potent and selective 5-$HT_6$ receptor antagonists. Spec Publ – R Soc Chem 2001;264:101–19.
37. Hirst WD, Minton JA, Bromidge SM, et al. Characterization of [(125)I]-SB-258585 binding to human recombinant and native 5-HT(6) receptors in rat, pig and human brain tissue. Br J Pharmacol 2000;130:1597–605.
38. Pullagurla MR, Westkaemper RB, Glennon RA. Possible differences in modes of agonist and antagonist binding at human 5-$HT_6$ receptors. Bioorg Med Chem Lett 2004;14:4569–73.
39. Dukat M, Mosier PD, Kolanos R, et al. Binding of serotonin and $N_1$-benzenesulfonyltryptamine-related analogs at human 5-$HT_6$ serotonin eceptors: receptor modeling studies. J Med Chem 2008;51: 603–11.
40. Sikazwe D, Bondarev ML, Dukat M, et al. Binding of sulfonyl-containing arylalkylamines at human 5-$HT_6$ serotonin receptors. J Med Chem 2006;49:5217–25.
41. Heal DJ, Smith SL, Fisas A, et al. Selective 5-$HT_6$ receptor ligands: progress in the development of a novel pharmacological approach to the treatment of obesity and related metabolic disorders. Pharmacol Ther 2008;17:207–31.
42. Ivachtchenko A, Dmitriev D, Golovina E, et al. Synthesis of cycloalkane-annelated 3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidines and their evaluation as 5-$HT_6$ receptor antagonists. Bioorg Med Chem Lett 2010;20:2133–6.
43. Kohen R, Fashingbauer LA, Heidmann DE, et al. Cloning of the mouse 5-$HT_6$ serotonin receptor and mutagenesis studies of the third cytoplasmic loop. Brain Res Mol Brain Res 2001;90:110–17.
44. Gonzalo R, Elisabeth S, Marta P, et al. Efficacy of selective 5-$HT_6$ receptor ligands determined by monitoring 5-$HT_6$ receptor-mediated cAMP signaling pathways. Br J Pharmacol 2006;148:1133–43.
45. Lewis DFV, Cytochromes P. Structure, function and mechanism. London: Taylor and Francis Publishing; 1996.
46. Ennaceur A, Neave N, Aggleton JP. The effects of neurotoxic lesions of the perirhinal cortex combined to fornix transection on object recognition memory in the rat. Behav Brain Res 1997;88:181–93.