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RESEARCH ARTICLE

Design, synthesis and pharmacological evaluation of conformationally restricted N-arylsulfonyl-3-aminoalkoxy indoles as a potential 5-HT$_6$ receptor ligands

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Abstract

A series of novel conformationally restricted N$_1$-arylsulfonyl-3-aminoalkoxy indoles were designed and synthesized as 5-HT$_6$ receptor (5-HT$_6$R) ligands. Many of the synthesized compounds have moderate *in vitro*-binding affinities at 5-HT$_6$R. The lead compound **8b** (% inhibition = 97.2 at 1 μM) from this series has good pharmacokinetic profile in male Wister rats and is active in animal model of cognition like Morris water maze. The details of chemistry, SAR, pharmacokinetics and pharmacological data constitute the subject matter of this report.

Keywords: 5-HT$_6$ receptor ligands, SAR, conformationally restricted, Morris water maze

Introduction

5-HT$_6$R was first identified by molecular cloning in the rat[1,2], then in man[3] and subsequently in mouse[4]. These receptors are predominantly expressed in the central nervous system, including the olfactory tubercle, nucleus accumbens, striatum, hippocampus and cerebral cortex, with a notably higher level of expression in the striatum of both rat and human brains. Due to the high presence of 5-HT$_6$R in brain, the 5-HT$_6$R active ligands play an important role in CNS disorders such as schizophrenia, dementia, Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders. Various structurally diverse small molecules containing the basic nitrogen (for primary binding) and the two other aromatic sites (for secondary binding) have been known to bind selectively at 5-HT$_6$R[5–8]. In the past decade various molecules like SB-742457, SUVN-502, PRX-07034, SAM-531, SAM-315, LY-483518 and Lu AE58054 were reported as 5-HT$_6$R ligands with positive clinical data[9–13].

Among these reported 5-HT$_6$R ligands, a few were reported with conformationally constrained features. There are reports by Glennon *et al.* with fused tryptamine side chain in six member ring (fused cyclohexyl type) that makes it conformationally restricted,[14] viz., tetrahydrocarbazole derivatives (Compound **1** in Figure 1). Although there was change in their spatial orientations, the compounds were active towards 5-HT$_6$R. Similarly, GSK and Wyeth (Compound **4** and **5** in Figure 1) also reported potent 5-HT$_6$R ligands with fused indole scaffold[15,16]; their focus also was mainly on side chain and indole template. Although there was substantial amount of work reported with constrained or fused tryptamines, not much work was reported around conformationally restricted sulfonamides. Recently, we at Suven reported constrained pyrrolidinyl indoles[17] and indole sulfonamides[18,19], as 5-HT$_6$R ligands (Structures **2** and **3** in Figure 1). These series of compounds have good affinity towards 5-HT$_6$R with selectivity over other known GPCRs. The compounds were active in *in vivo* models of cognition like Morris water maze and NORT. These compounds have acceptable pharmacokinetic profile for further development. Based on this knowledge and observations, we have designed and synthesized a series of 3-aminoalkoxy indole derivatives with

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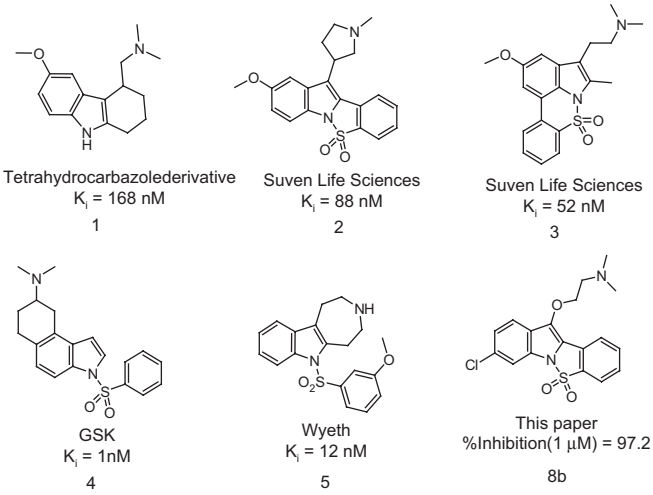
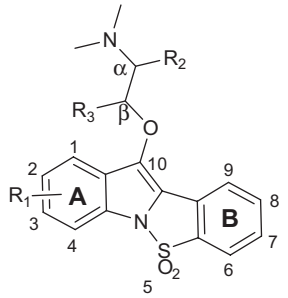


Figure 1. Chemical structures of compounds that bind to 5-HT_6R.

Table 1. 5-HT_6R binding affinities.



Compound	R_1	R_2	R_3	5-HT_6 Ki, nM	% Inhibition at 1 μM
8a	2-H	H	H	—	82.3
8b	3-Cl	H	H	—	97.2
8c	2-Cl	H	H	464	—
8d	2-OMe	H	H	127	—
8e	2-OiPr	H	H	—	67.35
8f	2-OMe	Me	H	—	68.26
8g	3-F	H	Me	—	74.13
8h	2-Cl	Me	H	—	48.15
8i	2-Cl	H	Me	—	61.07
8j	2-H	Me	H	—	74.28
8k	2-OEt	H	H	—	61.67
8l	2-H	H	Me	—	60.18
8m	3-F	Me	H	—	46.68
8n	2-OMe	H	Me	—	86.38
8o	1-F	H	H	>500	—

5-HT receptor binding studies carried out at Novascreen, USA.: Human recombinant/HEK293 cells; Radioligand: [^{3}H] LSD (60–80 Ci/mmol). Final ligand concentration: 1.5 nM, non-specific determinant: Methiothepin mesylate: [0.1 M]; reference compound: Methiothepin mesylate, positive control: Methiothepin mesylate.

Note: The α- and β-methyl derivatives were tested as racemic mixture. The percent inhibition at 1 μM was an average of the assay conducted in duplicate. The K_i value reported was an average of the assay conducted in duplicate.

constrained sulfonamide ring (Compound **8b** in Figure 1). The lead compound, **8b** was evaluated for pharmacokinetic parameters, % surrogate metabolism, human CYP3A4 and 2D6 liabilities. Further, the compound **8b** was tested in animal model of cognition, viz., Morris water maze. The results of these studies are discussed in this communication.

Results and discussion

Structure activity relationship

As a part of our SAR studies compounds **8a–8o** were synthesized and evaluated for their binding affinities at human 5-HT_6 receptor at 1 μM concentration and a few of them for K_i values (Table 1). Among these compounds,

the derivatives **8a**, **8b**, **8g**, **8j** and **8n** were found to have highest binding affinities with percent inhibition, at 1 μM concentration, being 82.3%, 97.2%, 74.13%, 74.28% and 86.38%, respectively.

Substitutions tried on **ring A** were mostly 2-alkoxy and 2-halo. The compound **8d**, with 2-methoxy substitution, was active with K_i of 127 nM, while the compound **8c**, with 2-chloro substitution has a K_i of 464 nM. This shows that 2-chloro substitution was detrimental for the activity.

Based on our SAR efforts in different tryptamine type of compounds[20], modification was carried out in N,N-dimethylaminoethoxy side chain at C-3 of indole with the insertion of methyl at **α** or **β** positions with respect to terminal nitrogen. Among the various derivatives prepared with this modified side chain, the most active derivative **8n** (86.38% inhibition) has 2-methoxy substitution with methyl at **β** position in side chain. Its analogue with methyl substitution at **α** position with respect to the tertiary nitrogen (**8f**) has less binding affinity (68.26% inhibition) towards 5-HT$_6$R. The compound **8a**, without any substitution in the side chain, has 82.3% inhibition, while the **α**-methyl analogue **8j** has slightly reduced potency, with 74.28% inhibition. The derivative **8m** with 3-fluoro substitution on **ring A** and **α**-methyl group in the side chain was least active with 46.68% inhibition at 5-HT$_6$R. Its analogue **8g**, with **β**-methyl group in the side chain was found to have better binding affinity (74.13% inhibition), indicating that the position of methyl group in the side chain has an important role to play regarding a favourable conformation for binding at 5-HT$_6$R.

Furthermore, some of the selected compounds were profiled for their selectivity against a few receptors including 5-HT receptor subtypes like 5-HT$_4$, 5-HT$_7$ and Muscarinic M$_1$. Compounds were found to have IC_{50} > 10,000 nM for these panel of CNS receptors (Table 2).

The compound **8b** was tested in cell-based assay for 5-HT$_4$ receptor binding along with the standard, GR113808 (IC_{50} = <0.1 nM). The compound **8b** has no affinity ($IC_{50} \geq 10{,}000$ nM) towards this receptor (see Figure 2).

Similarly, the compound **8b** was tested in cell-based assays for 5-HT$_7$ receptor and Muscarinic M$_1$ receptor binding, the standards being Clozapine (IC_{50} = 1 nM) and Atropine (IC_{50} = 1 nM), respectively (see Figures 3 and 4).

Table 2. Selectivity profile of compounds on other receptors.

Compound	5-HT$_7$	M$_1$	5-HT$_4$
		IC_{50} nM	
8a	>10,000	>10,000	>10,000
8b	>10,000	>10,000	>10,000

Compounds were tested for IC_{50} value in non-radioactive cell-based assay.

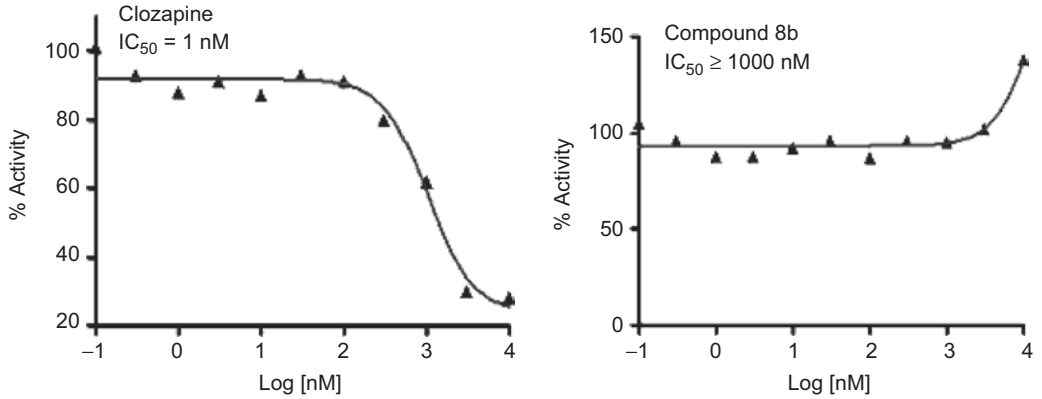


Figure 2. Evaluation of compound **8b** for 5-HT$_7$ receptor binding in cell-based assay.

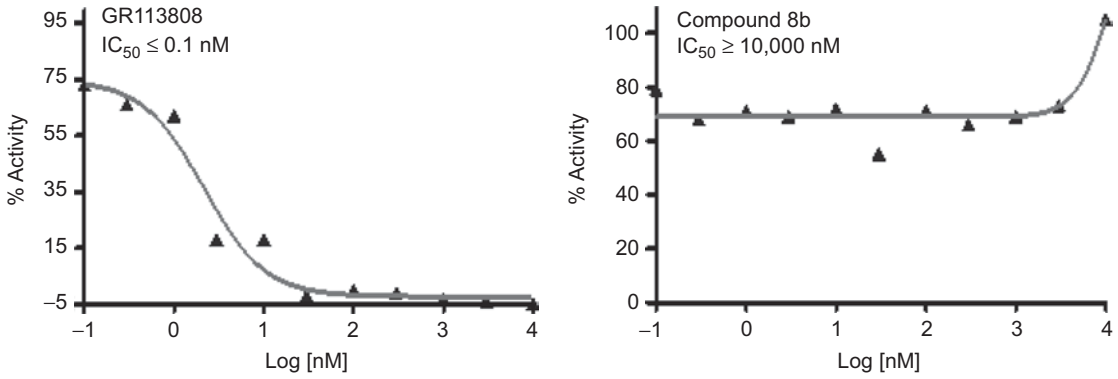


Figure 3. Evaluation of compound **8b** for 5-HT$_4$ receptor binding in cell-based assay.

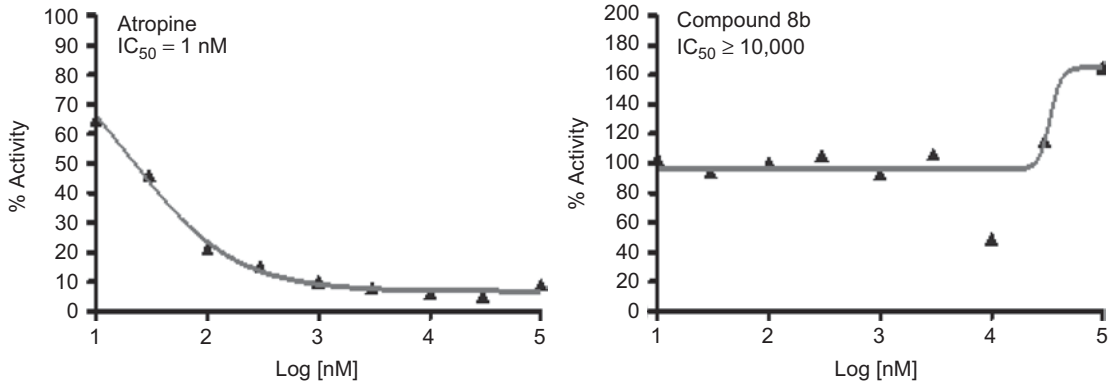


Figure 4. Evaluation of compound **8b** for M_1 receptor binding in cell-based assay.

As can be seen the compound was inactive towards these receptors.

Before testing the analogs in rodent behavioral assays *in vivo*, the Pharmacokinetic and ADME surrogate properties were determined in rat, the species ultimately used for behavioral models.

The active compounds, **8a** and **8b** from this series, were tested for their human cytochrome P450 inhibitory potential. The selected compound, **8b** was found to have an IC_{50} value of 5.06 μM and 37.05 μM for CYP2D6 and CYP3A4 respectively, while the compound **8a** was having IC_{50} values 7.65 μM and >45 μM for CYP2D6 and CYP3A4 respectively. Further, the compounds **8a** and **8b** were evaluated for their surrogate % metabolism in rat and human liver microsomes. The compound **8b** has high metabolism (95.59%) in human liver microsomes, while it has relatively lower metabolism in rat liver microsomes (77.54%). This is in contrast to the metabolism shown by compound **8a**. The compound **8a** has low metabolism in human liver microsomes (50.98%), whereas it has high metabolism in rat liver microsomes (100%) (Table 3)

The most potent 5-HT_6R ligand, **8b** from this series was further evaluated for its pharmacokinetic profile in male Wister rats (Table 4). The compound has high volume of distribution (17.5 l/kg) with high systemic clearance (8.2 ± 2.8 l/h/kg). The dose of 10 mg/kg was rapidly absorbed in rats and it had an elimination half life ($t_{1/2}$) of 1.49 ± 0.26 h, when it was administered orally. The bioavailability (%F) was found to be 35 ± 5% and the observed C_{max} value was 0.31 ± 0.05 μg/ml.

Since brain penetration was an important requirement for agents targeting CNS disorders, the steady state brain penetration study for compound **8b** was carried out in male Wister rats ($n = 4$). 5 ml/h/kg constant infusion in 50% PEG was carried out over a period of 6 h. The steady state brain and plasma ratio (Cb/Cp) in male Wister rats was 9.04 ± 1.86, confirming high brain penetration for this compound.

The compound **8b** was further evaluated for its efficacy in animal model of cognition like Morris water maze test[21].

Table 3. Human cytochrome P450 inhibitory data and % surrogate metabolism for compounds **8a** and **8b**.

	IC_{50} (μM)		Surrogate % metabolism	
Compound	2D6	3A4	Human	Wister rat
8a	7.65	>45	50.98	100
8b	5.06	37.05	95.59	77.54

The cytochrome P450 inhibitory potential was determined using isoform-selective assays and heterologously expressed human CYP2D6 and CYP3A4. These values are the mean of duplicate determinations. Microsomal metabolic stability in Wistar rat and human at 0.5 h, Con. 2.5 μM.

Table 4. Pharmacokinetic profile of compound **8b** in male Wister rats.

	Compound **8b**	
Dose mg/kg	10	10
Route	Oral	i.v.
n	3	3
C_{max} (μg/ml)	0.31 ± 0.05	1.65 ± 0.13
T_{max} (h)	0.67	0.08
AUC_t (μg·h/ml)	1.2 ± 0.13	3.4 ± 0.27
AUC_{inf} (μg·h/ml)	1.2 ± 0.14	3.4 ± 0.27
$t_{1/2}$ (h)	1.49 ± 0.26	1.59 ± 0.28
CL (L/h/kg)	8.2	2.8
V_z (L/kg)	17.5	6.6
MRT_{last}	3.46	1.81
Cb/Cp (mg/kg/h)	9.04 ± 1.87	
F (%)	35 ± 5	

Fasted male Wistar rats, vehicle used: water for injection for both oral and i.v. routes.
Dosing volumes: 10 ml/kg for oral and 2 ml/kg for i.v.

Morris water maze test

The following protocol was followed for the experiment.

Protocol: Wister rats 10–12 weeks old were given 4 trials/day for 5 days; each trial was of 60 s with an ITI of 600 s. Each trial started with the rat placed facing the wall of the maze at one of the eight designated locations (0°, 90°, 180°, 270°) on 1st, 3rd and 5th day and (45°, 135°, 225°, 315°) on 2nd and 4th day. Compound **8b** was administered by gavages during the acquisition phase. Scopolamine was administered at a dose of

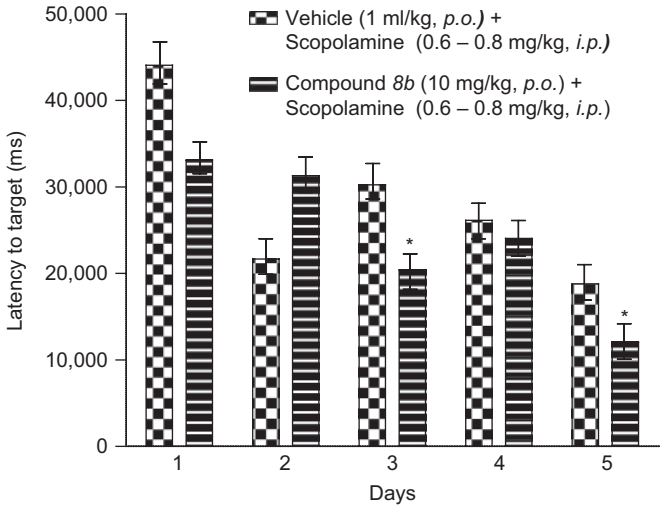


Figure 5. Latency to target in Morris water maze task. Data represents mean ± SEM of latency to target recorded as time taken to locate the hidden platform in water. Compound **8b** at 10 mg/kg p.o. reversed scopolamine-induced deficit and significant difference from scopolamine-treated group is indicated with asterisk (unpaired *t*-test; *$p < 0.05$).

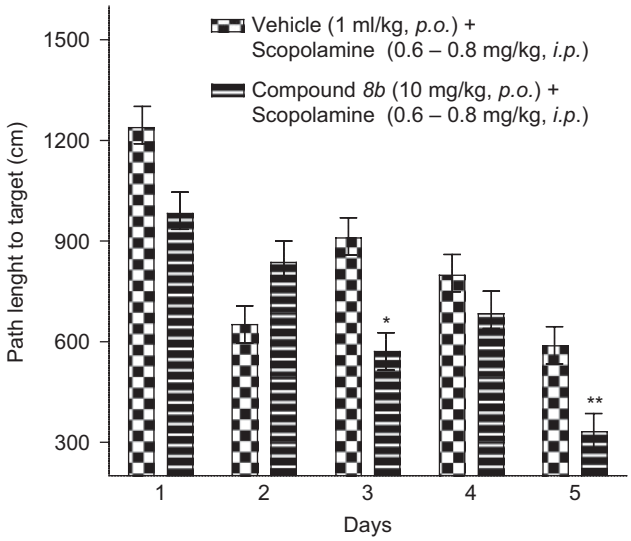


Figure 6. Path length to target in Morris water maze task. Data represents mean ± SEM of path length recorded as path taken to locate the hidden platform in water. Compound **8b** at 10 mg/kg p.o. reversed scopolamine-induced deficit and significant difference from scopolamine-treated group is indicated with asterisk (unpaired *t*-test *$p < 0.05$; **$p < 0.01$).

0.6 mg/kg on the first day and the dose of scopolamine was gradually increased at a rate of 0.05 mg/kg/day. Compound **8b** was administered 30 min before the administration of scopolamine. Compound **8b** significantly reversed the spatial memory deficit induced by scopolamine in the Morris water maze trial indicating cognitive improvement potential of the compound (Figures 5 and 6).

Materials and Methods

Infra red spectra were recorded on 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 a 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 (d) and coupling constants are expressed in Hz. Chromatography refers to column chromatography performed using 60–120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions. All the reagents and chemicals used were of 'reagent grade'. Substituted benzene sulfonyl chlorides were synthesized in-house from the substituted benzene by chlorosulfonation or from the corresponding amines via the diazo intermediates.

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

Compounds were investigated by the reported procedure[22,23]. Briefly, receptor source and radioligand used were human recombinant expressed in HEK-293 cells and [^{3}H] LSD (60–80 Ci/mmol), respectively. The final ligand concentration was 1.5 nM and non-specific determinant was methiothepin mesylate (0.1 µM). The reference compound and positive control was methiothepin mesylate. Reactions were carried out in 50 mM TRIS-HCl (pH 7.4) containing 10 mM $MgCl_2$, 0.5 mM EDTA for 60 min at 37 °C. The reaction was terminated by rapid vacuum filtration onto glass fibre filters. Radioactivity trapped onto the filters was determined and compared to control values in order to ascertain any interactions of test compound(s) with the cloned serotonin-5-HT$_6$ binding site.

Determination of IC_{50} values for 5-HT_4 receptor binding, using cell-based functional assay

Recombinant CHO cells were established by transfecting an expression vector encoding human 5-HT_{4a} gene and CRE-Luc reporter system. Isolated colonies were screened with 1000 nM 5-HT for the induction of luciferase reporter gene. The clone demonstrating highest 5-HT induced reporter gene was used in the evaluation of the known and novel compounds. Increasing concentrations of the compound were incubated with or without 1000 nM 5-HT for antagonist or agonist mode, respectively, for 5 h in 96 well plate. After incubation, cells were harvested, lysed and reporter gene activity was determined. The data was analyzed using Prism GraphPad software.

Determination of IC_{50} values for 5-HT_7 receptor binding, using cell-based functional assay

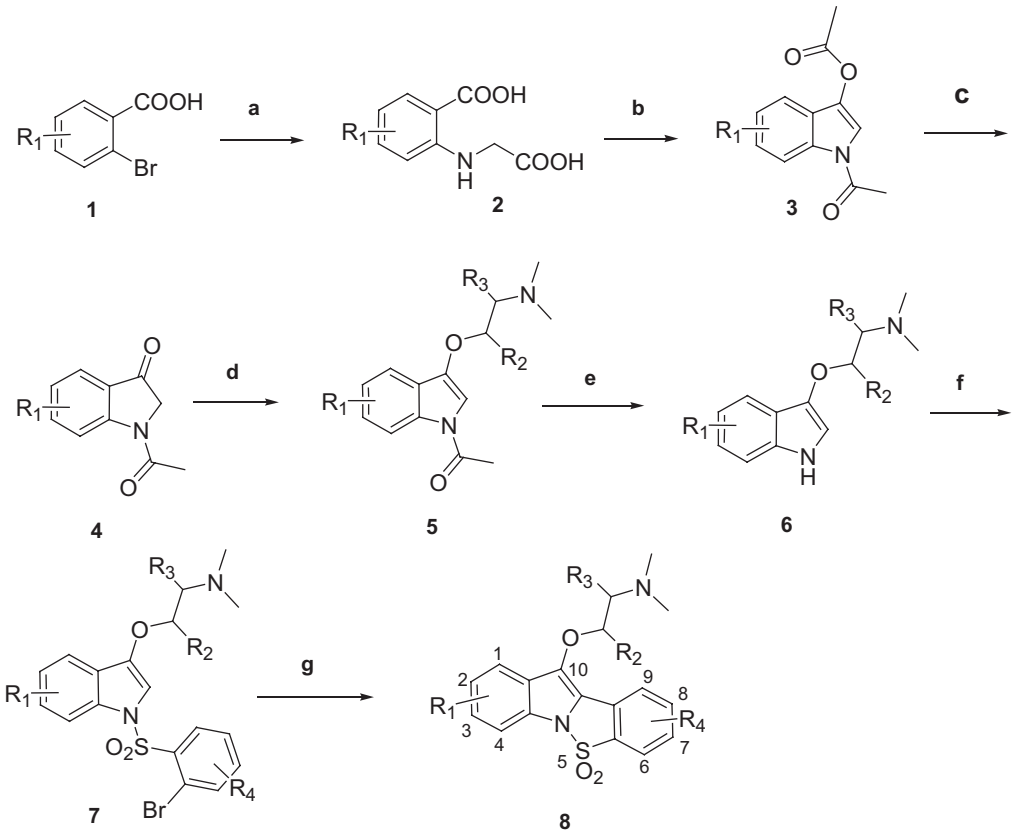
CHO cells were transfected with an expression vector encoding rat 5-HT_7 gene and CRE-Luc reporter system. Colonies were isolated and screened with 1000 nM 5-HT for the induction of luciferase reporter gene. The clone demonstrating highest 5-HT induced reporter gene was used in the evaluation of the known and novel compounds. Increasing concentrations of the compound were incubated with or without 1000 nM 5-HT for antagonist or agonist mode respectively for 5 h in 96 well plate. After incubation, cells were harvested, lysed and reporter gene activity was measured. The data was analyzed using Prism GraphPad software.

Determination of IC_{50} values for acetylcholine receptor M_1 binding, using cell-based functional assay

Muscarinic acetylcholine receptor M1 was cloned into an expression vector and transfected in CHO cells along with CRE-Luc reporter system. Isolated colonies were screened with 10,000 nM acetylcholine. Clones exhibiting highest acetylcholine dependent reporter gene induction were utilized in the evaluation of known and novel compounds. Increasing concentrations of the compound were incubated with or without 10,000 nM acetylcholine for antagonist or agonist mode, respectively, for 5 h in 96 well plate. After incubation, cells were harvested, lysed and reporter gene activity was determined. The data was analyzed using Prism GraphPad software.

Synthesis

The general synthetic strategy followed for the preparation of the title compounds was summarized in Scheme 1. Various substituted indoxyls were synthesized using literature methods[24,25]. More often, the indoxyls were synthesized starting from the appropriately substituted 2-bromobenzoic acids. The substituted 2-bromobenzoic acids were treated with Glycine to obtain the diacids (2). These diacids were then



Scheme 1. **Reagents:** (**a**) Glycine, water, NaOH; (**b**) DMF, NaOAc, Ac_2O; (**c**) Na_2SO_3, MeOH/water; (**d**) THF, K_2CO_3, $Me_2NCH_2CH_2Cl$, reflux; (**e**) NaOH, MeOH, reflux; (**f**) 2-Bromobenzenesulfonyl chloride, THF, KOH powder; (**g**) DMA, CH_3COOK, $P(PPh_3)_4Pd$, 120°C.

subjected to cyclization in presence of acetic anhydride and N,N-dimethylformamide at higher temperature (120 °C) followed by, *in situ*, decarboxylation to obtain the corresponding 1-acetyl-3-acetyloxy indoles (3). The compounds (3) were deacetylated under mild conditions using sodium sulfite and methanol/water (1:1) at room temperature to obtain indoxyls (4), which were used after purification for further synthesis.

Various alternative methods were used for the etherification of indoxyls; the best system was found to be the one involving dimethylaminoethyl chloride in tetrahydrofuran in presence of potassium carbonate. Further, for the derivatization of N_1 of indole, potassium hydroxide powder and tetrahydrofuran was found to be the best condition for sulfonylation. The N_1 sulfonylated compound was further treated with dry potassium acetate and tetrakis triphenyl phosphino palladium (0) catalyst in N,N-dimethyl acetamide (DMA) solvent to obtain the desired compounds **8a–8r**.

Synthesis of compounds with α-methyl and β-methyl substituents in the side chain were obtained following essentially the same route, using appropriately substituted dimethylamino ethyl chlorides, that were procured commercially.

Experimental

General (representative) procedure for the synthesis of compound 8d

Potassium carbonate (872 mmol) was added to a solution of 1-acetyl-6-chloro indoxyl (**4**) (436.3 mmol) in tetrahydrofuran (950 ml) and stirred at 25–30°C for 90 min. The free base of (2-Chloroethyl)dimethylamine hydrochloride (1308 mmol) was liberated and extracted into toluene by stirring over 350 ml toluene and a solution of sodium hydroxide (1308 mmol) in water (250 ml). The organic layer containing the free base was then separated and transferred to the above reaction mixture. The reaction mass was heated to reflux at 90–95°C and maintained for 4 h. After completion of the reaction (TLC), the reaction mass was cooled to 25–30°C and filtered the solid at suction and washed with ethyl acetate (250 ml × 3). The filtrate was collected and concentrated under reduced pressure to obtain oily product. The residue, thus obtained, was purified by flash chromatography over silica gel using 1% triethylamine (TEA) in ethyl acetate to get intermediate **5**.

The intermediate **5** (61.5 mmol) dissolved in methanol (100 ml) and was added to a solution of sodium hydroxide (123 mmol) in water (100 ml), heated to 60–65°C and maintained for 2 h. After completion of the reaction (TLC), the mass was cooled to 25–30°C and distilled off methanol and water mixture to obtain oily mass. Water (1000 ml) was added to the residual mass and extracted the product with ethyl acetate (3 × 100 ml). The separated ethyl acetate layers were combined, washed with brine solution (100 ml), dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain a thick oily mass. The residue, thus obtained, was purified by flash chromatography over silica gel using 1% TEA in ethyl acetate to get intermediate **6**, which was identified by IR, NMR and mass spectral analysis.

Potassium hydroxide powder (60.35 mmol) was added to a solution of intermediate **6** (30.1 mmol) in tetrahydrofuran (150 ml) and stirred the reaction mass for 1 h at 25–30 °C under nitrogen atmosphere. 2-Bromobenzenesulfonyl chloride (45.2 mmol) dissolved in tetrahydrofuran (100 ml) was added to the reaction mass drop wise over a period of 15 min. The reaction mass was stirred at 25–30 °C for 60 min. After completion (TLC) of the reaction, the solvent was distilled off completely under reduced pressure to get oil. Water (250 ml) was added to the residual mass and extracted the product with dichloromethane (2 × 200 ml). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residual mass, so obtained, was purified by flash chromatography over silica gel using 1% TEA in ethyl acetate to get intermediate **7**, which was identified by IR, NMR and mass spectral analyses.

Dry potassium acetate (2.006 mmol) was added to a solution of intermediate **7** (1.18 mol) in DMA followed by tetrakis triphenyl phosphine palladium (0) catalyst (0.059 mmol) under nitrogen atmosphere. The reaction mass was heated to 110–120 °C and stirred for 1 h. After completion of the reaction (TLC), the reaction mass was cooled to 25–30 °C. Water (50 ml) was added and extracted product into ethyl acetate (100 ml × 3). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulphate and concentrated under reduced pressure to obtain oily product. The residue, thus obtained, was purified by flash chromatography over silica gel using 1% methanol in chloroform to get compound **8d**, which was identified by IR, NMR and mass spectral analysis.

*10-(2-N,N-Dimethylaminoethoxy)-5-Thia-4b-azaindeno [2,1-a]indene-5,5-Dioxide (**8a**).* Thick oil; IR (KBr, cm^{-1}): 1179, 1334, 1441, 1620, 2944; mass (*m/z*): 343.2 [M + H]$^+$; ^{1}H-NMR (ppm): 2.37 (6H, s, N(*CH*$_3$)$_2$), 2.75–2.78 (2H, t, *CH*$_2$-N(CH$_3$)$_2$), 4.38–4.41 (2H, t, *CH*$_2$O), 7.24–7.26 (1H, m, *C2-H*), 7.38–7.46 (2H, m, *C3-H* and *C7-H*), 7.66–7.69 (3H, m, *C1-H*, *C4-H* and *C8-H*), 7.79–7.81 (1H, d, J = 7.84 Hz, *C9-H*), 7.93–7.94 (1H, d, J = 7.84 Hz, *C6-H*); HRMS: [M + H]$^+$ $C_{18}H_{19}N_2O_3S$ calc. 343.1116, found. 343.1112.

*3-Chloro-10-(2-N,N-Dimethylaminoethoxy)-5-Thia-4-b-aza indeno [2,1-a]indene-5,5-Dioxide (**8b**).* M.R (°C): 104.5–109.8; IR (KBr, cm^{-1}): 1175, 1310, 1397, 1630, 2789, 3620; mass (*m/z*): 377.1 [M + H]$^+$; ^{1}H-NMR (ppm): 2.36 (6H, s, N(*CH*$_3$)$_2$), 2.74–2.77 (2H, t, CH$_2$-N(*CH*$_3$)$_2$), 4.35–4.38 (2H, t, *CH*$_2$O); 7.20–7.23 (1H, dd, J = 8.50, 1.77 Hz, *C2-H*), 7.46–7.48 (1H, m, *C8-H*), 7.57–7.60 (1H, d, J = 8.47 Hz, *C1-H*), 7.67–7.69 (2H, m, *C4-H* and *C7-H*), 7.79–7.81 (1H, d, J = 7.88 Hz, *C6-H*), 7.92–7.94 (1H, d, J = 7.83 Hz, *C9-H*); HRMS: [M + H]$^+$ $C_{18}H_{18}ClN_2O_3S$ calc. 377.0726, found. 377.0730.

*2-Chloro-10-(2-N,N-Dimethylaminoethoxy)-5-Thia-4-b-aza indeno [2,1-a]indene-5,5-Dioxide (**8c**).* Thick oil; IR (KBr, cm^{-1}): 1174, 1317, 1433, 1621, 3430; mass (*m/z*): 377.1 $[M + H]^+$; ^{1}H-NMR (ppm): 2.38 (6H, s, N(CH_3)$_2$), 2.75–2.78 (2H, t, CH_2-N(CH_3)$_2$), 4.34–4.37 (2H, t, CH_2O); 7.32–7.35 (1H, dd, J = 8.65, 1.86 Hz, *C3-H*), 7.48–7.50 (1H, m, *C8-H*), 7.58–7.60 (1H, d, J = 8.77 Hz, *C4-H*), 7.65–7.68 (2H, m, *C1-H* and *C7-H*), 7.80–7.82 (1H, d, J = 7.86 Hz, *C6-H*), 7.94–7.96 (1H, d, J = 7.84 Hz, *C9-H*); HRMS: $[M + H]^+$ $C_{18}H_{18}ClN_2O_3S$ calc. 377.0726, found. 377.0732.

*2-Methoxy-10-(2-N,N-Dimethylaminoethoxy)-5-Thia-4b-azaindeno[2,1-a]indene-5,5-Dioxide (**8d**).* Thick oil; IR (KBr, cm^{-1}): 1155, 1170, 1324, 1442, 1614, 3436; mass (*m/z*): 373.1 $[M + H]^+$; ^{1}H-NMR (ppm): 2.37 (6H, s, N(CH_3)$_2$), 2.74–2.77 (2H, t, CH_2-N(CH_3)$_2$), 3.85 (3H, s, OCH_3), 4.33–4.36 (2H, t, CH_2O); 6.98–7.01 (1H, dd, J = 8.8, 2.0 Hz, *C3-H*), 7.10–7.11 (1H, d, J = 2.36 Hz, *C1-H*), 7.44–7.45 (1H, m, *C7-H*), 7.55–7.57 (1H, d, J = 8.88 Hz, *C4-H*), 7.63–7.67 (1H, m, *C8-H*), 7.78–7.80 (1H, d, J = 7.8 Hz, *C6-H*), 7.90–7.92 (1H, d, J = 7.8 Hz, *C9-H*); HRMS: $[M + H]^+$ $C_{19}H_{21}N_2O_4S$ calc. 373.1222, found. 373.1218.

*2-Isopropoxy-10-(2-N,N-Dimethylaminoethoxy)-5-Thia-4b-azaindeno[2,1-a]indene-5,5-Dioxide (**8e**).* M.R (°C): 70.4–74.1; IR (KBr, cm^{-1}): 1177, 1333, 1461, 1686, 2975, 3461; mass (*m/z*): 401.4 $[M + H]^+$; ^{1}H-NMR (ppm): 1.35–1.37 (6H, d, (CH_3)$_2$CH-), 2.37 (6H, s, N(CH_3)$_2$), 2.74–2.77 (2H, t, CH_2-N(CH_3)$_2$), 4.33–4.36 (2H, t, CH_2O); 4.53–4.59 (1H, septet, CH(CH_3)$_2$), 6.97–7.00 (1H, dd, J = 8.87. 2.42 Hz, *C3-H*), 7.12 (1H, d, J = 2.29 Hz, *C1-H*), 7.43–7.45 (1H, m, *C8-H*), 7.54–7.56 (1H, d, J = 8.82 Hz, *C4-H*), 7.64 (1H, m, *C7-H*), 7.77–7.79 (1H, d, *C6-H*), 7.90–7.92 (1H, d, *C9-H*); HRMS: $[M + H]^+$ $C_{21}H_{25}N_2O_4S$ calc. 401.1535, found. 401.1530.

*(±) 2-Methoxy-10-(2-N,N-Dimethylamino-2-methylethoxy)-5-Thia-4b-azaindeno[2,1-a]indene-5,5-Dioxide (**8f**).* M.R (°C): 77.6–80.1; IR (KBr, cm^{-1}): 1175, 1324, 1437, 1626, 2962, 3431; mass (*m/z*): 387.3 $[M + H]^+$; ^{1}H-NMR (ppm): 1.15–1.17 (3H, d, CH_3-CH-), 2.37 (6H, s, N(CH_3)$_2$), 3.01–3.09 (1H, m, CH-CH_3), 3.87 (3H, s, OCH_3), 4.09–4.11 (1H, dd, CH_2-CH), 4.30–4.34 (1H, dd, O-CH_2), 6.98–7.01 (1H, dd, J = 8.8, 2.36 Hz, *C3-H*), 7.09–7.10 (1H, d, J = 2.36 Hz, *C1-H*), 7.43–7.45 (1H, m, *C8-H*), 7.55–7.58 (1H, d, J = 8.80 Hz, *C4-H*), 7.63–7.65 (1H, m, *C7-H*), 7.78–7.80 (1H, d, J = 7.8 Hz, *C6-H*), 7.88–7.90 (1H, d, J = 7.76 Hz, *C9-H*); HRMS: $[M + H]^+$ $C_{20}H_{23}N_2O_4S$ calc. 387.1378, found. 387.1375.

*(±) 3-Fluoro-10-(2-N,N-Dimethylamino-1-methylethoxy)-5-Thia-4b-aza indeno [2,1-a]indene-5,5-Dioxide (**8g**).* M.R (°C): 82.6–85.5; IR (KBr, cm^{-1}): 1184, 1337, 1617, 2721, 3434; mass (*m/z*): 375.2 $[M + H]^+$; ^{1}H-NMR (ppm): 1.33–1.35 (3H, d, J = 5.4 Hz, CH_3-CH), 2.37 (6H, s, N(CH_3)$_2$), 2.49–2.54 (1H, m, CH_2-N(CH_3)$_2$), 2.75–2.80 (1H, m, CH_2-N(CH_3)$_2$), 4.55–4.60 (1H, m, J = 5.4 Hz, CH-CH_3), 6.99–7.0 (1H, m, J = 2.2 Hz, *C2-H*), 7.39–7.40 (1H, dd, *C4-H*), 7.44–7.46 (1H, m, *C7-H*), 7.61–7.66 (2H, m, *C1-H* and *C8-H*), 7.79–7.81 (1H, d, J = 7.8 Hz, *C9-H*), 7.93–7.95 (1H, d, J = 7.8 Hz, *C6-H*); HRMS: $[M + H]^+$ $C_{19}H_{20}FN_2O_3S$ calc. 375.1178, found. 375.1175.

*(±) 2-Chloro-10-(2-N,N-Dimethylamino-2-methylethoxy)-5-Thia-4b-aza indeno [2,1-a]indene-5,5-Dioxide (**8h**).* Thick oil; IR (KBr, cm^{-1}): 1172, 1331, 1317, 1437, 1620, 3435; mass (*m/z*): 391.3 $[M + H]^+$; ^{1}H-NMR (ppm): 1.15–1.16 (3H, d, J = 5.4 Hz, CH_3-CH), 2.37 (6H, s, N(CH_3)$_2$), 3.01–3.11 (1H, m, CH-N(CH_3)$_2$), 4.10–4.11 (1H, m, O-CH_2), 4.29–4.34 (1H, m, O-CH_2), 7.32–7.35 (1H, dd, J = 8.60, 1.88 Hz, *C3-H*), 7.48–7.49 (1H, m, *C7-H*), 7.58–7.60 (1H, d, J = 8.70 Hz, *C4-H*), 7.64–7.65 (1H, d, J = 1.68 Hz, *C1-H*), 7.66–7.68 (1H, m, *C8-H*), 7.80–7.82 (1H, d, J = 7.80 Hz, *C6-H*), 7.91–7.93 (1H, d, J = 7.8 Hz, *C9-H*); HRMS: $[M + H]^+$ $C_{19}H_{20}ClN_2O_3S$ calc. 391.0883, found. 391.0886.

*(±) 2-Chloro-10-(2-N,N-Dimethylamino-1-methylethoxy)-5-Thia-4b-aza indeno [2,1-a]indene-5,5-Dioxide (**8i**).* M.R (°C): 88.6–92.0; IR (KBr, cm^{-1}): 1177, 1346, 1443, 1598, 2931, 3436; mass (*m/z*): 391.2 $[M + H]^+$; ^{1}H-NMR (ppm): 1.34–1.35 (3H, d, J = 6.24 Hz, CH_3-CH), 2.37 (6H, s, N(CH_3)$_2$), 2.49–2.53 (1H, m, CH_2-N(CH_3)$_2$), 2.76–2.81 (1H, m, CH_2-N(CH_3)$_2$), 4.52–4.57 (1H, m, J = 6.24 Hz, CH-CH_3), 7.32–7.34 (1H, dd, J = 8.56, 1.92 Hz, *C3-H*), 7.47–7.49 (1H, m, *C7-H*), 7.58–7.60 (1H, d, J = 8.64 Hz, *C4-H*), 7.67–7.68 (2H, m, *C1-H* and *C8-H*), 7.80–7.82 (1H, d, J = 7.88 Hz, *C6-H*), 7.98–7.99 (1H, d, J = 7.84 Hz, *C9-H*); HRMS: $[M + H]^+$ $C_{19}H_{20}ClN_2O_3S$ calc. 391.0883, found. 391.0887.

*(±) 10-(2-N,N-Dimethylamino-2-methylethoxy)-5-Thia-4b-aza indeno [2,1-a]indene-5,5-Dioxide (**8j**).* M.R (°C): 60.1–63.3; IR (KBr, cm^{-1}): 1180, 1335, 1441, 1619, 2967; mass (*m/z*): 357.1 $[M + H]^+$; ^{1}H-NMR (ppm): 1.15–1.17 (3H, d, CH_3CH), 2.37 (6H, s, N(CH_3)$_2$), 3.01–3.09 (1H, m, CH-CH_3), 4.09–4.11 (1H, dd, O-CH_2), 4.30–4.34 (1H, dd, O-CH_2), 7.32–7.34 (1H, dd, J = 8.56, 1.92 Hz, *C3-H*), 7.24–7.26 (1H, m, *C2-H*), 7.38–7.46 (2H, m, *C6-H* and *C7-H*), 7.66–7.69 (3H, m, *C1-H*, *C4-H* and *C8-H*), 7.79–7.81 (1H, d, J = 7.84 Hz, *C9-H*); HRMS: $[M + H]^+$ $C_{19}H_{21}N_2O_3S$ calc. 357.1273, found. 357.1270.

*2-Ethoxy-10-(2-N,N-Dimethylaminoethoxy)-5-Thia-4-b-aza indeno [2,1-a]indene-5,5-Dioxide (**8k**).* M.R (°C): 101.2–103.8; IR (KBr, cm^{-1}): 1175, 1234, 1315, 1441, 1622, 3615; mass (*m/z*): 387.5 $[M + H]^+$; ^{1}H-NMR (ppm): 1.40–1.46 (3H, t, CH_3CH_2O), 2.37 (6H, s, N(CH_3)$_2$), 2.74–2.77 (2H, t, CH_2-N(CH_3)$_2$), 4.05–4.10 (2H, q, CH_2O), 4.33–4.36 (2H, t, CH_2O), 6.98–7.01 (1H, dd, J = 8.92, 2.44 Hz, *C3-H*), 7.09–7.10 (1H, d, J = 2.32 Hz, *C1-H*), 7.43–7.45 (1H, m, *C7-H*), 7.54–7.57 (1H, d, J = 8.80 Hz, *C4-H*), 7.62–7.64 (1H, m, *C6-H*), 7.77–7.79 (1H, d, J = 7.88 Hz, *C8-H*), 7.90–7.92 (1H, d, J = 7.84 Hz, *C9-H*); HRMS: $[M + H]^+$ $C_{20}H_{23}N_2O_4S$ calc. 387.1378, found. 387.1375.

*(±) 10-(2-N,N-Dimethylamino-1-methylethoxy)-5-Thia-4b-aza indeno [2,1-a]indene-5,5-Dioxide (**8l**).* Thick oil; IR (KBr, cm^{-1}): 1180, 1335, 1441, 1614, 2940; mass (*m/z*): 357.2 $[M + H]^+$; ^{1}H-NMR (ppm): 1.34–1.36 (3H, d, J = 6.20 Hz, CH_3-CH), 2.37 (6H, s, N(CH_3)$_2$), 2.51–2.55 (1H, m, CH_2-N(CH_3)$_2$), 2.76–2.81 (1H, m, CH_2-N(CH_3)$_2$), 4.61–4.65 (1H, m, J = 6.20 Hz, CH-CH_3), 7.24–7.26 (1H, m, *C2-H*), 7.35–7.46 (2H, m, *C3-H* and *C7-H*), 7.63–7.69 (3H, m, *C1-H*, *C4-H* and *C8-H*), 7.79–7.81 (1H, d, J = 7.84 Hz, *C9-H*), 7.95–7.97 (1H, d, J = 7.84 Hz, *C6-H*); HRMS: $[M + H]^+$ $C_{19}H_{21}N_2O_3S$ calc. 357.1273, found. 357.1278.

(±) 3-Fluoro-10-(2-N,N-Dimethylamino-2-methylethoxy)-5-Thia-4b-aza indeno [2,1-a]indene-5,5-

*Dioxide (**8m**).* M.R (°C): 108.9–111.9; IR (KBr, cm^{-1}): 1154, 1184, 1336, 1618, 2778, 2968; mass (*m/z*): 375.2 [M + H]$^+$; ^{1}H-NMR (ppm): 1.15–1.17 (3H, d, CH_3CH), 2.37 (6H, s, N(CH_3)$_2$), 3.04–3.09 (1H, m, *CH*-CH_3), 4.12–4.16 (1H, dd, CH_2-CH), 4.32–4.36 (1H, dd, CH_2-CH), 6.99–7.0 (1H, m, J = 2.2 Hz, *C3-H*), 7.39–7.40 (1H, dd, *C4-H*), 7.44–7.46 (1H, m, *C7-H*), 7.59–7.68 (2H, m, *C1-H* and *C8-H*), 7.79–7.81 (1H, d, J = 7.8 Hz, *C9-H*), 7.87–7.89 (1H, d, J = 7.8 Hz, *C6-H*); HRMS: [M + H]$^+$ $C_{19}H_{20}FN_2O_3S$ calc. 375.1178, found. 375.1175.

*(±) 2-Methoxy-10-(2-N,N-Dimethylamino-1-methylethoxy)-5-Thia-4b-aza indeno [2,1-a]indene-5-,5-Dioxide (**8n**).* Thick oil; IR (KBr, cm^{-1}): 1180, 1335, 1441, 1614, 2940; mass (*m/z*): 387.2 [M + H]$^+$; ^{1}H-NMR (ppm): 1.34–1.36 (3H, d, J = 6.20 Hz, CH_3-CH), 2.37 (6H, s, N(CH_3)$_2$), 2.51–2.55 (1H, m, CH_2-N(CH_3)$_2$), 2.76–2.81 (1H, m, CH_2-N(CH_3)$_2$), 3.85 (3H, s, OCH_3), 4.61–4.65 (1H, m, J = 6.20 Hz, *CH*-CH_3), 6.98–7.01 (1H, dd, J = 8.8, 2.0 Hz, *C3-H*), 7.10–7.11 (1H, d, J = 2.36 Hz, *C1-H*), 7.44–7.45 (1H, m, *C7-H*), 7.55–7.57 (1H, d, J = 8.88 Hz, *C4-H*), 7.63–7.67 (1H, m, *C8-H*), 7.78–7.80 (1H, d, J = 7.8 Hz, *C6-H*), 7.90–7.92 (1H, d, J = 7.8 Hz, *C9-H*); HRMS: [M + H]$^+$ $C_{20}H_{23}N_2O_4S$ calc. 387.1378, found. 387.1375.

*1-Fluoro-10-(2-N,N-Dimethylaminoethoxy)-5-Thia-4-b-aza indeno [2,1-a]indene-5,5-Dioxide (**8o**).* Thick oil; IR (KBr, cm^{-1}): 1179, 1334, 1441, 1620, 2944; mass (*m/z*): 361.1 [M + H]$^+$; ^{1}H-NMR (ppm): 2.37 (6H, s, N(CH_3)$_2$), 2.75–2.78 (2H, t, CH_2-N(CH_3)$_2$), 4.38–4.41 (2H, t, CH_2O), 6.72–6.73 (1H, m, *C2-H*), 7.1–7.21 (2H, m, *C3-H* and *C4-H*), 7.31–7.33 (1H, m, *C8-H*), 7.55–7.57 (1H, d, J = 8.88 Hz, *C7-H*), 7.78–7.80 (1H, d, J = 7.8 Hz, *C6-H*), 7.90–7.92 (1H, d, J = 7.8 Hz, *C9-H*); HRMS: [M + H]$^+$ $C_{18}H_{18}FN_2O_3S$ calc. 361.1022, found. 361.1017.

Conclusion

The results indicate that these analogues were having moderate activity profile towards 5-HT$_6$R. The most potent compound **8b** from this series was active in animal model of cognition like Morris water maze, having good oral bioavailability (%F = 35) and brain penetration. Further SAR modification to improve the binding affinities, metabolic stability and to make these compounds adequately brain penetrant, is under progress.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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