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RESEARCH ARTICLE

Synthesis and structure–activity relationship of novel conformationally restricted analogues of serotonin as 5-HT$_6$ receptor ligands

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Abstract

5-Hydroxytryptamine 6 receptors (5-HT$_6$R) are being perceived as the possible target for treatment of cognitive disorders as well as obesity. The present article deals with the design, synthesis, *in vitro* binding and structure–activity relationship of a novel series of tetracyclic tryptamines with the rigidized *N*-arylsulphonyl, *N*-arylcarbonyl and *N*-benzyl substituents as 5-HT$_6$ receptor ligands. The chiral sulphonyl derivatives **15a** and **17a** showed high affinity at 5-HT$_6$R with the K_i of 23.4 and 20.5 nM, respectively. The lead compound from the series **15a** has acceptable ADME properties, adequate brain penetration and is active in animal models of cognition like Novel Object Recognition Task (NORT) and water maze.

Keywords: Heck reaction, cognition, NORT, serotonin, 5-HT$_6$

Introduction

5-Hydroxytryptamine 6 receptor (5-HT$_6$R), a member of GPCR family, plays an important role in cognition and memory formation, due to its exclusive localization in the brain regions associated with learning and memory[1–3]. Blockage of 5-HT$_6$R enhances the cognitive process through cholinergic and glutamatergic neurotransmission, which demonstrates the therapeutic usefulness of this receptor in the central nervous system (CNS)-mediated disorders such as schizophrenia and Alzheimer's disease (AD)[4–10].

Up to date, a lot of research work has been done in identifying different 5-HT$_6$R agonists and antagonists, out of which a few of them are currently in the different stages of clinical development. SAM-531[11], SB-742457[12,13] and LY-483518 (SGS-518)[14,15] are the phase II clinical candidates, whereas Lu AE58054[16], PRX-07034, SYN-114[8] and SUVN-502[17] are the phase I clinical candidates as of today.

Tryptamine derivatives are reported as 5-HT$_6$ receptor ligands[18] as they have the structural resemblance with the 5-hydroxytryptamine (5-HT). *N*-Phenylsulphonyl-5-methoxy-*N*,*N*-dimethyltryptamine (MS-245) (Figure 1) is a 5-HT$_6$R antagonist reported by Glennon et al. in early 2000[18]. Russell et al.[19] have reported conformational constraint of the basic amine of the tryptamine on the adjacent phenyl ring with flexible *N*-arylsulphonyl motif leading to a compound with good binding affinity of 7.2 nM towards the 5-HT$_6$ receptor (Figure 1, **36**). Mooradian et al.[20] has published the 5-HT$_6$R binding activity for some carbazole derivatives, which are in fact the conformationally restricted tryptamines. Several other research groups attempted modifications of *N*,*N*-dimethylamino ethyl side chain at C3 of

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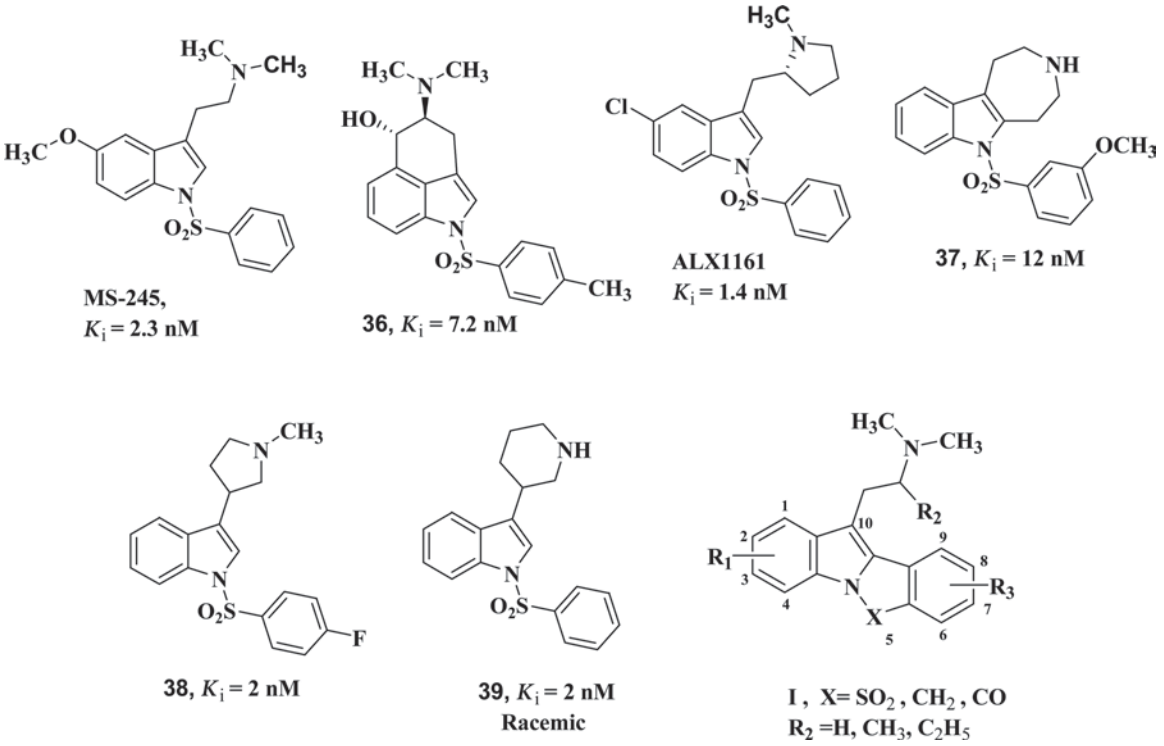


Figure 1. Structures of I and reported 5-HT_6 ligands.

indole of MS-245. Pyrrolidine derivatives (Figure 1, ALX1161) have been reported by Abate et al.[21] as potent 5-HT_6 ligands. Most studied compound from these modifications ALX1161 has shown excellent affinity and selectivity.[22,23] This compound was shown to possess excellent brain exposure (brain/plasma 23.4, i.p.) and reasonable oral bioavailability in rats (%F = 17). Liu et al.[24] reported the novel class of azepinoindoles by rigidifying the amino side chain to C2 position of indole (Figure 1, **37**) to overcome the selectivity issue of 1-sulphonyl tryptamine over its 5-HT subtypes. Subsequently, additional classes where the pyrrolidine and piperidine rings are directly attached to C3 of indole (Figure 1, **38** and **39**) were also reported by Cole et al.[25]

Interestingly, though a lot of work has already been published on the effect of changes made in the nature of side chain of tryptamines with respect to activity, to the best of our knowledge there are almost no studies reported so far to understand the relative necessity or required orientation of *N*-arylsulphonyl moiety with respect to activity. Hence, in our efforts for identifying the novel 5-HT_6R ligands, we thought of constraining the MS-245 compound by tethering the arylsulphonyl groups to C2 of indole, which will result in tetracyclic compounds **I** (Figure 1). The proposed tetracyclic derivatives of tryptamines, compounds **I**, include all the components of MS-245 like arylsulphonyl substitution and side chain at C3 of indole. Since the compounds **I** bear all the necessary pharmacophoric functionalities like a basic amine, the aromatic rings in a triangular arrangement as well as the sulphonamide linkage[7], it was expected to bind to 5-HT_6 receptors. Once the desired activity is achieved in the series, it was further aimed to see the effect of replacing the sulphonyl moiety of the tetracyclic compounds with a methylene or a carbonyl group and study the effect of the change on the binding to 5-HT_6 receptors.

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 a API 4000 triple quadruple instrument (MDS-SCIEX, Concord, Ontario, Canada). ^{1}H-NMR spectra were obtained on a Bruker proton NMR spectrometer (Fallanden, Switzerland) at 400 MHz. Deuterated reagents were used as solvents and were commercially procured. Tetramethylsilane (TMS) was used as an internal standard. Chemical shift values are expressed in parts per million (δ) and coupling constants are expressed in Hz. Chromatography refers to column chromatography performed using 60–120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions. All the reagents and chemicals used were of 'reagent grade'. Various substituted indoles were synthesized in-house with the help of reported procedures and were characterized thoroughly before using. Substituted benzenesulphonyl chlorides were synthesized in-house from the substituted benzene by chlorosulphonation or from the corresponding amines using the diazo

intermediates. Substituted benzyl chlorides were either commercially obtained or synthesized in-house from the substituted toluene by *N*-chlorosuccinimide reaction. Similarly, substituted benzoyl chlorides were synthesized in-house from the corresponding benzoic acids using thionyl chloride.

Synthesis

General procedure for the synthesis of derivatives 6–20

1-(2′-Bromophenylsulphonyl)-*N*,*N*-dimethyltryptamine derivative (0.286 mmol) was taken in a 100-mL three-necked round-bottomed flask, along with *N*,*N*-dimethylacetamide (10 mL), potassium acetate (0.343 mmol, 33.6 mg) and tetrakis (triphenyl phosphine) palladium(0), (0.0143 mmol, 16.5 mg). The reaction mixture was maintained under nitrogen atmosphere at 125–130°C with stirring for 5 h. After the completion of reaction (TLC), excess of dimethylacetamide was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatography using methanol:ethyl acetate (2:8) as an eluent. The compounds **6**–**20** were characterized by the spectral data.

2-Methoxy-10-[(2-N,N-dimethylamino-2-methyl)ethyl] benzo[d]isothiazolo[3,2-a]indol-S,S-dioxide (15). Yield: 68.5%; Mp 202.4–205.3°C; IR (cm^{-1}): 2933, 1461, 1438, 1323, 1174, 582; Mass (*m*/*z*): 371.2 (M+H)$^+$; ^{1}H-NMR ($CDCl_3$): δ 1.00–1.02 (3H, d, *J* = 6.44 Hz, CH$\underline{CH_3}$), 2.44 (6H, s, N($\underline{CH_3}$)$_2$), 2.81–2.87 (1H, dd, *J* = 13.44 Hz, $\underline{CH_2}$CH(CH_3)NMe_2), 2.93–3.10 (1H, m, $\underline{CH}$(CH_3)NMe_2), 3.18–3.23 (1H, dd, *J* = 13.44, 3.20 Hz, $\underline{CH_2}$CH(CH_3)NMe_2), 3.87 (3H, s, $\underline{OCH_3}$), 6.99–7.02 (2H, m), 7.45–7.59 (1H, m), 7.58–7.62 (1H, m), 7.64–7.69 (1H, m), 7.79–7.85 (2H, m), ^{13}C-NMR ($CDCl_3$): δ 14.12, 28.23, 40.78, 55.75, 60.02, 103.59, 112.50, 114.78, 116.05, 122.26, 122.66, 127.34, 128.22, 128.44, 130.21, 133.91, 134.76, 138.11, 156.28; HRMS: [M+H]$^+$ $C_{20}H_{22}N_2O_3S$ calc. 371.1429, found. 371.1422.

General procedure for the synthesis of derivatives 21–30

1-(2′-Bromobenzyl)-*N*,*N*-dimethyltryptamine derivative (0.286 mmol) was taken in a 100-mL, three-necked round-bottomed flask, along with *N*,*N*-dimethylacetamide (10 mL), potassium acetate (0.343 mmol, 33.6 mg) and tetrakis (triphenyl phosphine) palladium(0), (0.0143 mmol, 16.5 mg). The reaction mixture was maintained under nitrogen atmosphere at 125–130°C with stirring for 5 h. After the completion of reaction (TLC), excess of dimethylacetamide was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatography using methanol:ethyl acetate (2:8) as an eluent. The compounds **21**–**30** were characterized by the spectral data.

2-Fluoro-10-(2-N,N-dimethylaminoethyl)isoindolo[2,1-a] indole (24). Light brown syrupy mass. Yield: 66.2%; IR (cm^{-1}): 2952, 2458, 1483, 1189, 791, 720; Mass (*m*/*z*): 295.3 (M+H)$^+$; ^{1}H-NMR ($CDCl_3$): δ 2.86 (6H, s, N($\underline{CH_3}$)$_2$), 3.21–3.25 (2H, m, $\underline{CH_2}CH_2NMe_2$), 3.34–3.44 (2H, m, $CH_2\underline{CH_2}NMe_2$), 5.18 (2H, s, C5-$\underline{CH_2}$), 6.98–7.04 (1H, dt, *J* = 9.23, 2.52 Hz), 7.36–7.42 (1H, dt), 7.43–7.49 (2H, m), 7.53–7.56 (1H, dd, *J* = 10.2, 2.44 Hz), 7.60–7.62 (1H, d, *J* = 7.44 Hz), 8.04–8.06 (1H, d, *J* = 7.52 Hz); ^{13}C-NMR (DMSO-d_6): δ 19.41, 41.67, 48.52, 56.26, 100.44, 100.49, 104.27, 104.50, 109.38, 109.64, 110.85, 110.95, 121.48, 124.00, 127.4, 128.11, 130.09, 131.65, 131.70, 131.80, 142.22, 142.27, 155.95, 158.25; HRMS: [M+H]$^+$ $C_{19}H_{19}FN_2$ calc. 295.1610, found. 295.1610.

General procedure for the synthesis of derivatives 31–35

1-(2′-Bromobenzoyl)-*N*,*N*-dimethyltryptamine derivative (0.286 mmol) was taken in a 100-mL, three-necked round-bottomed flask, along with *N*,*N*-dimethylacetamide (10 mL), potassium acetate (0.343 mmol, 33.6 mg) and tetrakis (triphenylphosphine) palladium(0), (0.0143 mmol, 16.5 mg). The reaction mixture was maintained under nitrogen atmosphere at 125–130°C with stirring for 5 h. After the completion of reaction (TLC), excess of dimethylacetamide was distilled off under reduced pressure. The residue obtained was purified by silica gel column chromatography using methanol:ethyl acetate (2:8) as an eluent. The compounds **31**–**35** were characterized by the following spectral data.

2-Phenyl-10-(2-N,N-dimethylaminoethyl)isoindolo[2,1-a] indol-5-one (31). Yield; 56.1 %; Mp 148–151°C; IR (cm^{-1}): 2939, 1716, 1606, 1458, 1361, 885, 758; Mass (m/z): 367.3 (M+H)$^+$; ^{1}H-NMR ($CDCl_3$): δ 2.39 (6H, s, N($\underline{CH_3}$)$_2$), 3.07–3.11 (2H, m, $\underline{CH_2}CH_2NMe_2$), 3.65–3.70 (2H, m, $CH_2\underline{CH_2}NMe_2$), 7.32–7.39 (2H, m), 7.44–7.48 (2H, m), 7.52–7.55 (2H, m), 7.57–7.64 (4H, m), 7.77–7.80 (1H, dd), 7.91–7.93 (1H, d, *J* = 7.84 Hz); ^{13}C-NMR (DMSO-d_6): δ 27.33, 50.18, 63.86, 117.91, 123.93, 124.31, 126.94, 130.21, 130.68, 131.91, 132.32, 133.93, 134.02, 137.34, 138.02, 139.18, 139.50, 139.99, 140.54, 141.32, 145.41, 166.52; HRMS: [M+H]$^+$ $C_{25}H_{22}N_2O$ calc 367.1810, found. 367.1801.

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

Compounds were investigated by the reported procedure. In brief, 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 SYMBOL 109\f "Symbol"M). The reference compound and positive control is methiothepin mesylate.

Reactions were carried out in 50 mM Tris–HCl (pH 7.4) containing 10 mM $MgCl_2$, 0.5 mM EDTA for 60 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 with control values in order to ascertain any interactions of test compound(s) with the cloned serotonin–5-HT$_6$-binding site.

Novel Object Recognition Task

The lead compound **15a** was tested in Novel Object Recognition Task (NORT)[26] using the detailed protocol given in the Supporting information.

Results and discussion

Chemistry

The general synthetic strategy used for the title compounds **6**–**35** has been summarized in Scheme 1. Various substituted tryptamines **1** were either obtained commercially or synthesized using various literature methods[27]. Treatment of substituted tryptamines **1**, with the desired substituted 2-bromoarylsulphonyl/carbonyl/alkyl chlorides in presence of appropriate base and the polar aprotic solvents yielded the intermediates, *N*-arylsulphonyl/carbonyl/alkyl tryptamines **2**, which were isolated and fully characterized. The *N*-(2′-bromo)arylsulphonyl/carbonyl/alkyl tryptamines **2** were cyclized using various palladium catalysts and well-known literature procedures of Heck reaction[28–30], to get the desired compounds **6**–**35**.

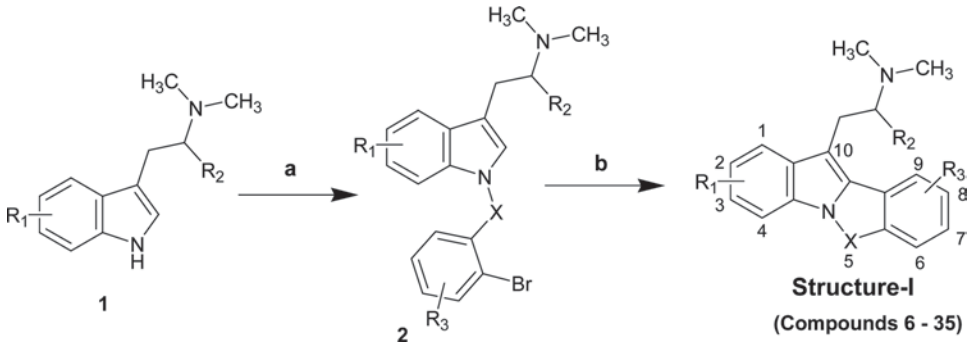
Synthesis of α-substituted/unsubstituted tryptamines was achieved by the route depicted in Scheme 2. The various substituted indoles were converted to their 3-formyl derivatives **3**, by the known literature methods. These substituted 3-formyl indoles were then condensed with nitro alkane under alkaline conditions. The adducts **4** were reduced using lithium aluminium hydride to the corresponding α-substituted/unsubstituted tryptamines **5**, which were further dimethylated using well-known reductive formylation procedures involving formaldehyde and sodium cyanoborohydride, to the substituted tryptamines, **1**.

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

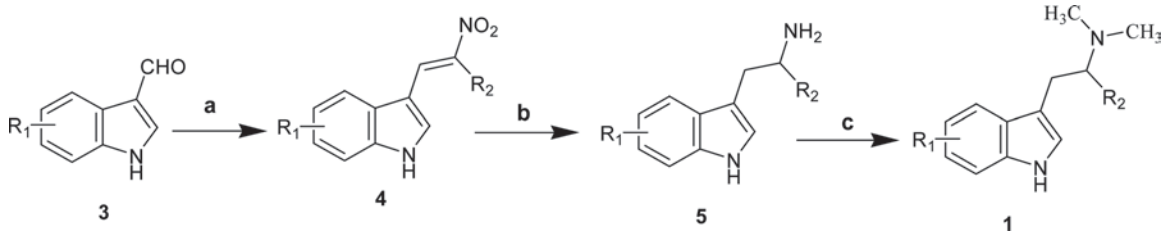
Structure–activity relationship

All the synthesized compounds **6**–**20** ($X=SO_2$), **21**–**30** ($X=CH_2$) and **31**–**35** ($X=CO$) were evaluated for their binding affinity towards 5-HT_6 receptor using the radioligand-binding assay. The inhibitory constant, K_i values were summarized in Table 1.

All the sulphonamide compounds **6**–**19** show high to moderate affinity towards the receptor with the exception of the compound 20 (K_i = >1000 nM). The lower alkoxy racemate analogues 15 (R_1 = 2-OCH_3, $R_2=CH_3$, K_i = 11.6 nM) and 17 (R_1 = 2-OC_2H_5, $R_2=CH_3$, K_i = 11.1 nM) show high affinity towards the receptor. The other analogues with no substitution at R_2 position (R_2 = H) resulted in 3–8-fold decrease in binding affinities compared with those of substituted ones ($R_2=CH_3$ or C_2H_5) as can be seen by comparing the K_i values of compounds 6 (R_2 = H, K_i = 246 nM) and 14 (R_2 = H, K_i = 96 nM) with compounds 11 ($R_2=CH_3$, K_i = 87 nM) and 15 (R_2 = CH3, K_i = 11.6 nM), respectively.

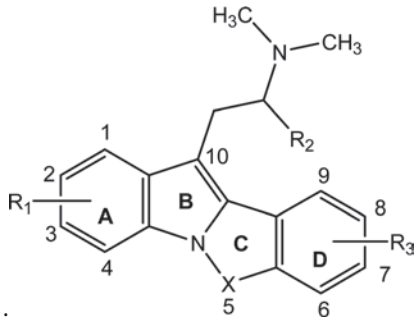


Scheme 1. Reagents and conditions: (a) base, DMF at 10°C, followed by Ar-X-Cl, 3–4 h, (b) tetrakis triphenylphosphine palladium ($Pd(P(Ph)_3)_4$), CH_3COOK, DMA, 120–130°C, 3–4 h.



Scheme 2. Reagents and conditions: (a) nitro alkane, piperidine, acetic acid, benzene, reflux, 5–6 h, (b) $LiAlH_4$, THF, reflux, 1–2 h, (c) CH_3OH, HCHO, $NaBH_3CN$, pH 6.5 with CH_3COOH, reflux, 2 h.

Table 1. K_i values for compounds **6**–**35** on 5-HT$_6$ (h) receptors.



Compound No.	X	R_1	R_2	R_3	K_i (nM)
6	-SO_2-	-H	-H	-H	246
7	-SO_2-	2-F	-H	-H	267
8	-SO_2-	2-F	-CH_3	-H	116[a]
9	-SO_2-	2-CH_3	-H	8-OCH_3	269
10	-SO_2-	4-Cl	-H	-H	126
11	-SO_2-	-H	-CH_3	-H	87.6[a]
12	-SO_2-	2-Ph	-H	-H	26.8
13	-SO_2-	2-Br	-CH_3	-H	54.1[a]
14	-SO_2-	2-OCH_3	-H	-H	96
15	-SO_2-	2-OCH_3	-CH_3	-H	11.6[a]
16	-SO_2-	2-OCH_3	-C_2H_5	-H	28.3[a]
17	-SO_2-	2-OC_2H_5	-CH_3	-H	11.1[a]
18	-SO_2-	2-OBn	-CH_3	-H	100[a]
19	-SO_2-	2-*O*-iPr	-CH_3	-H	239[a]
20	-SO2-	2-OCH_2cyHex	-CH_3	-H	>1000[a]
21	-CH_2-	2-*O*-iPr	-CH_3	-H	73.2[a]
22	-CH_2-	2-OCH_3	-H	-H	86.7
23	-CH_2-	2-OCH_3	-CH_3	-H	279[a]
24	-CH_2-	2-F	-H	-H	24.3
25	-CH_2-	2-Cl	-H	-H	80.7
26	-CH_2-	1-Cl, 4-CH_3	-H	-H	104
27	-CH_2-	2,4-di-F	-H	-H	153
28	-CH_2-	3,4-Benzo	-H	-H	92.6
29	-CH_2-	2-SCH_3	-H	-H	49.7
30	-CH_2-	2-F	-H	7-Cl	37.6
31	-CO-	2-Ph	-H	-H	84.6
32	-CO-	-H	CH_3	-H	296[a]
33	-CO-	2-Cl	-H	-H	393
34	-CO-	-H	-H	-H	135
35	-CO-	2-OCH_3	-CH_3	-H	197.0[a]

K_i values were calculated from the % binding at eight concentrations (n=2), experimental protocol is described in Methods section.
[a]The K_i values indicate that these are the results of racemic compounds.

Apart from the alkoxy substitution at second position (R_1) in sulphonamide analogues, the other substituents like halogens (2-F, 2-Br, 4-Cl), lower alkyl groups (2-CH_3) and 2-phenyl groups are well-tolerated for 5-HT$_6$ receptor binding as can be seen from the K_i values. The higher alkoxy analogues like 2-*O*-iPr (compound **19**, K_i = 239 nM), 2-OBn (compound **18**, K_i = 100 nM), 2-OCH_2cyHex (compound **20**, K_i = >1000 nM) show decrease in binding affinity as compared with its lower alkoxy 2-OCH_3 (compound **15**, K_i = 11.6 nM) and 2-OC_2H_5 (compound **17**, K_i = 11.1 nM) analogues, indicating that lower alkoxy groups are more suitable at this position. Replacement of methyl group at R2 position by ethyl group resulted in 2–3-fold decrease in binding affinity as can been seen by comparing the K_i values of compound **15** (K_i = 11.6 nM) with **16** (K_i = 28.3 nM).

The other synthesized benzyl analogues **21**–**30** and benzoyl analogues **31**–**35** show the reverse trend, where substitution at R_2 position with alkyl groups lead to decrease in binding affinities as compared with their

unsubstituted analogues as can be seen by comparing the K_i values of compound **22** (R_2 = H, K_i = 86 nM) and **34** (R_2 = H, K_i = 135 nM) with **23** (R_2 = CH_3, K_i = 279 nM) and **32** (R_2 = CH_3, K_i = 296 nM), respectively.

Among the benzyl analogues (X = CH_2), compounds **24** with fluoro substitution at second position in ring A shows the highest affinity with K_i value 24.3 nM, whereas its chloro analogue (compound **25**, K_i = 80.7 nM) shows nearly 3-fold decrease in binding affinity. The insertion of additional fluoro group (ring A) in compound **24** resulted in 6-fold decrease in binding affinity (compound **27**, K_i = 153 nM), whereas insertion of chloro at seventh position in ring D in compound **24** resulted in marginal decrease in affinity towards receptor (compound **30**, K_i = 37.6 nM).

Based on the K_i results, the most potent sulphonamides, 2-methoxy **15** and 2-ethoxy **17** analogues with α-methyl substitution in the side chain were resolved and tested for their specific rotation and binding affinities at 5-HT_6R. The specific rotation and K_i values are summarized in Table 2. In both of the cases, laevo isomers are more active than dextro isomers, indicating that the specific orientation of the dimethylamino substitution in the side chain is important as far as the 5-HT_6 receptor binding is concerned.

Compounds **15a** and **17a** were further evaluated for the CYP liability and metabolic stability studies. The compounds strongly inhibited CYP2D6 human enzyme with IC_{50}'s of 0.49 and 1.2 μM for **15a** and **17a**, respectively. Inhibition of the more abundant CYP3A4 appears to be not an issue with this series with IC_{50}'s estimated to be above 35 μM for both **15a** and **17a**. Compound **17a** is extensively metabolized (92.1% and 57.9%) compared with compound **15a** (73.8% and 41.8%) in rat and human, respectively.

The compound **15a** was tested for its functional agonism/antagonism. The functional agonism/antagonism assay was conducted at MDS Pharma Services. The assay measured changes in cAMP level in a recombinant CHO cell line in agonist and antagonist mode. The compound did not exhibit any agonist activity but showed full antagonism of 5-HT_6-induced cAMP accumulation. In fact, the compound reduced basal cAMP level indicating a inverse agonist activity.

To estimate the oral bioavailability in rats, pharmacokinetic studies were performed on compound **15a** and the results are given in Table 3.

In order to assess the brain-penetrating ability of compound **15a**, it was dosed at 3 mg/kg, i.p. to male Wistar rats and sacrificed at 30 min post dose and brain and plasma exposure were measured using LC-MS/MS. The brain exposure of compound **15a** was 772 ng/g, which is equivalent to 2.08 μM with a Cb/Cp of 6.24, indicating that the compound has high brain penetration.

Compound **15a** was further evaluated for its cognitive potential in NORT paradigm and Morris water maze. Compound **15a** has shown improvement in cognitive performance at 1 mg/kg oral dose in NORT model (Figure 2). Most of the memory-enhancing compounds show an inverted U-shaped dose response. This could be one of the reasons why the compound showed positive effect only at the lowest tested doses. In Morris water maze model, it has significantly reversed the scopolamine-induced memory deficit at 1 and 3 mg/kg, p.o. dose, which was apparent from lesser target latency (Figure 3).

Table 2. The comparative *in vitro* data of racemic and resolved compounds **15** and **17**.

Compound No.	Compound identification	Specific rotation $[\alpha]_D$ at 25°C (C = 0.5% in $CHCl_3$)	K_i (5-HT_6) nM
15	Racemic	—	11.6
15a	Laevo isomer	(–) 9.4°	23.4
15b	Dextro isomer	(+) 9.1°	141
17	Racemic		11.1
17a	Laevo isomer	(–) 5.6°	20.8
17b	Dextro isomer	(+) 5.3°	120

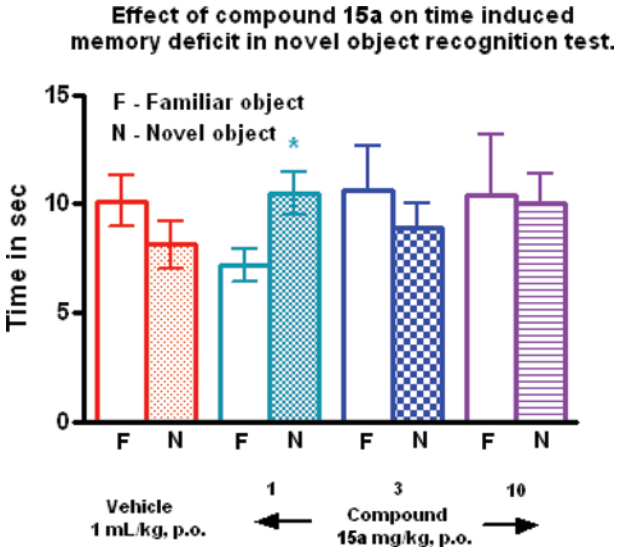


Figure 2. Novel Object Recognition Task. *p < 0.05 (Student's 't' test)

Table 3. Pharmacokinetic profile of compound **15a**.

Compound **15a**								
Route	n	Dose (mg/kg)	C_{max} (ng/mL)	AUC_t (ng h/mL)	$t_{1/2}$ (h)	V_z (mL/kg)	Cl (mL/h/kg)	%F
Oral	3	3	51 ± 71	106 ± 137	2.44 ± 1.37	339,516	140,737	16.6
i.v.	3	3	855 ± 457	633 ± 198	1.6 ± 0.5	11,107	5049	

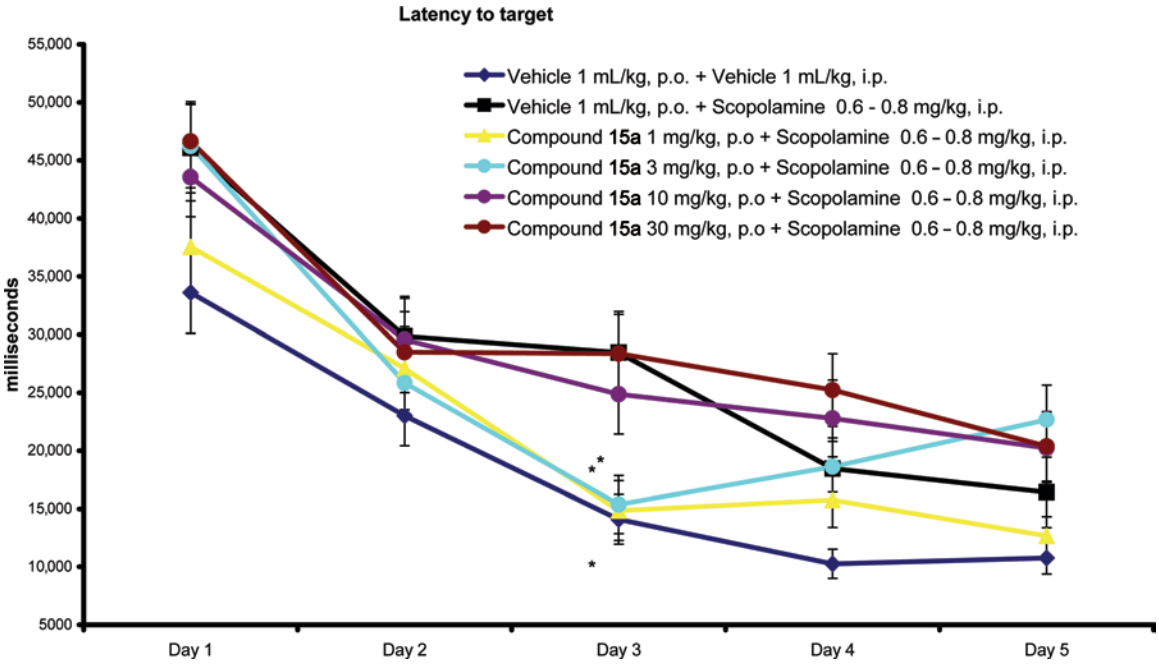


Figure 3. Effect of compound **15a** in Morris water maze (acute dosing). *$p < 0.05$ (one way ANNOVA followed by Dunnett's 't' test).

Conclusions

From the results as discussed above, it is evident that the rigidized derivatives of *N*-arylsulphonyl tryptamines have slightly reduced affinity than the corresponding flexible derivatives. The major finding of the study, however, was the role of alkyl substitution at α-position of the amino alkyl side chain. The presence of smaller alkyl groups in the tryptamine side chain results in increased affinity to the 5-HT$_6$R, as is evident from the K_i values of compounds **15** and **17**. Also, the lead compound from the series was found to have excellent brain penetration, an important requirement for CNS drugs.

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Declaration of interest

The authors report no declarations of interest.

Supporting information

Analytical data of rest of the compounds, protocols for Morris water maze test, NORT and CYP inhibition assay were given in the Supporting information.

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