



Synthesis and Structure Activity Relationship of Rigidized Indolyl Pyrrolidine Derivatives as 5-HT₆ Receptor Ligands

RAMAKRISHNA NIROGI^{1,*}, ADIREDDY DWARAMPUDI^{1,2}, VENUGOPALARAO BHATTA¹, LAXMAN KOTA¹ and P.K. DUBEY²

¹Discovery Research, Suven Life Sciences Ltd., Serene Chambers, Road-5, Avenue-7, Banjara Hills, Hyderabad-500 034, India

²Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad-500 085, India

*Corresponding author: Fax: +91 40 23541152; Tel: +91 40 23556038/23541142; E-mail: nvsrk@suven.com

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A novel series of rigidized indolyl pyrrolidine derivatives have been designed by constraining the tryptamine nitrogen through α and β carbons. All the synthesized derivatives have shown moderate affinities at 5-HT₆R when tested in *in vitro* binding assay. Synthesis, structure activity relationship (SAR), pharmacokinetic profile and *in vivo* efficacy of a selected compound is the subject matter of this communication.

Key Words: 5-HT₆R, Structure activity relationship, Pharmacokinetic, Brain penetration, Water maze, Cognition.

INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) plays an important role in the modulation of neuropsychiatric disorders and exerts its actions *via* fourteen classes of receptors, which are involved in controlling an array of physiological functions and promoting pathophysiological conditions in states of excess or deficiency. 5-HT₆R was identified in 1990 in rat and it has become a promising target for the treatment of neuropsychological disorders like anxiety, depression, schizophrenia, epilepsy, obesity, abnormal feeding behaviour and cognitive dysfunctions¹⁻⁷.

Scientists from industries and academia evinced enormous interest in the development of newer ligands for 5-HT₆ receptors, which have the capability to address debilitating CNS related disorders, hitherto a highly unmet clinical field. There are large number of other publications as well as patents in the past two decades disclosing variety of scaffolds for 5-HT₆R ligands including N-phenylsulfonyl tryptamine (MS-245)⁸ and 2-phenyltryptamine (PMDT)⁹, which demonstrate the potential of 5-HT₆R ligands. A number of 5-HT₆ receptor antagonists like SB-742457¹⁰, LuAE58054¹¹, SUVN-502¹² and SAM-760¹³ have entered clinical development.

In our recent publication¹⁴ we have disclosed the effects of rigidization of phenyl sulfonyl ring in MS-245 through C-2 of indole (Fig. 1). This series of compounds **1** have shown moderate binding affinities towards the 5-HT₆R and were found to be selective ligands towards 5-HT₆R. In continuation to this effort, we thought of constraining the tryptamine terminal nitrogen by its incorporation into a five membered pyrrolidine

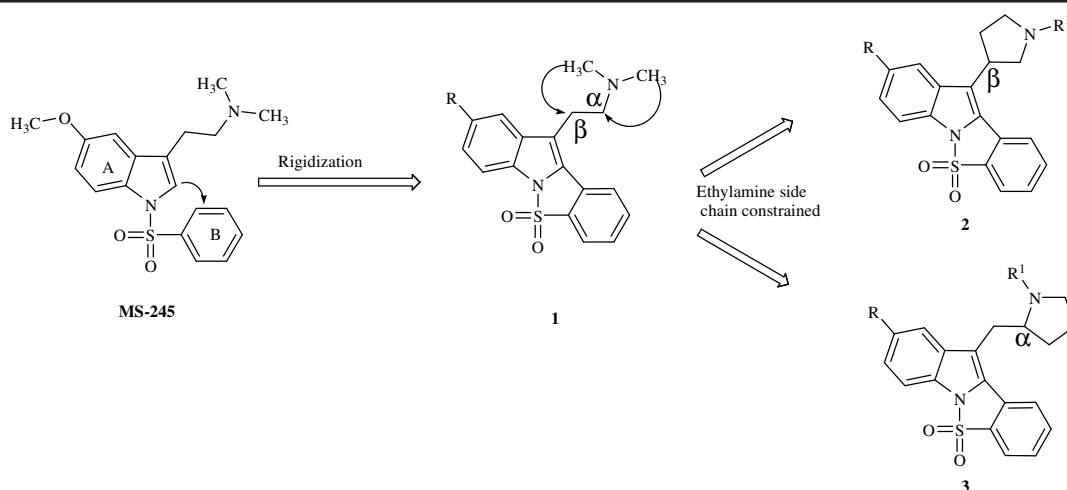
ring through α and β carbons. The results of these efforts are the subject matter of this paper.

EXPERIMENTAL

Infrared spectra were recorded on KBr disc and in the solid state using Perkin-Elmer model 1600 FT-IR spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). Electron spray ionization mass spectra were recorded on a API 4000 triple quadrupole instrument (MDS-SCIEX, Concord, Ontario, Canada). ¹H 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 internal standard. Chemical shift values were expressed in parts per million (δ) and coupling constants were expressed in Hertz (Hz). Column chromatography was performed using 60-120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions. All the reagents and solvents used were of reagent grade. Various substituted indoles were synthesized in-house using literature reported procedures¹⁵ and analytically characterized them thoroughly using spectral data. 2-Bromobenzenesulfonyl chloride was synthesized in-house from 2-bromoaniline *via* diazonium salt intermediate¹⁶.

3-(1*H*-Indol-3-yl)-1-methyl pyrrolidine-2,5-dione (**5a**):

A mixture of indole (**4a**, 2 g, 17.09 mmol) and maleic acid (2 g, 17.24 mmol) were heated to 50 °C and stirred until the mass solidified. The mixture was allowed to stand for 0.5 h and then diluted with a solution of potassium hydroxide (28.76 g, 51.27 mmol) in 50 mL of water. The reaction mass was heated to 80 °C and stirred for 0.5 h. The mass was cooled to room

Fig. 1. Genesis of ligands **2** and **3**

temperature and washed with diethyl ether. The aqueous phase was acidified using hydrochloric acid and the resulting solids were filtered, washed with water and dried. 3-Indolylsuccinic acid (2.6 g, 11.15 mmol), thus obtained, was reacted with 1,3-dimethyl urea (3 g, 34.09 mmol) at 180 °C and stirred for 1 h. The hot mixture was diluted with water, cooled to room temperature and the resulting solids were filtered and further purified by flash chromatography (silica gel, EtOAc/hexanes, 2/3) to obtain **5a** (1.7 g, 68 %), which was confirmed by IR, NMR and mass spectral analyses. Similarly compounds **5b-5h** were synthesized.

5a: M.R (°C): 173.5-175.0; IR (KBr, $\nu_{\max}$, cm^{-1}): 3334, 1769, 1677, 745; mass (m/z): 229 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 2.75-2.81 (1H, m), 2.91 (3H, s, N- CH_3), 3.15-3.25 (1H, m), 4.33-4.37 (1H, m), 7.10-7.27 (2H, m), 7.45-7.47 (1H, m), 8.02-8.07 (2H, m), 8.77 (1H, bs).

3-(1-Methyl pyrrolidin-3-yl)-1H-indole (6a): To a stirred suspension of lithium aluminum hydride (0.85 g, 22.27 mmol) in tetrahydrofuran (15 mL) was added a solution of compound **5a** (1.7 g, 7.42 mmol) in tetrahydrofuran (20 mL) and the resulting slurry was stirred for 4 h at reflux temperature. After the completion of reaction, the reaction mixture was cooled to 10 °C, poured on to chilled water (20 mL) and stirred for 0.5 h. The slurry, thus obtained, was filtered through celite pad and washed with ethyl acetate. The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 $\times$ 20 mL). The combined organic layer was washed with brine solution (15 mL) and dried over sodium sulfate. Organic volatiles were removed under reduced pressure. The residual mass, thus obtained, was purified by flash chromatography (silica gel, EtOAc/TEA, 99/1) to afford compound **6a** (0.52 g, 70 %), which was confirmed by IR, NMR and mass spectral analyses. Similarly compounds **6b-6h** were synthesized.

6a: M.R (°C): 85.3-89.6; IR (KBr, $\nu_{\max}$, cm^{-1}): 3409, 2940, 1452, 737; mass (m/z): 201 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.94-1.98 (1H, m), 2.37-2.40 (1H, m), 2.42 (3H, s), 2.52-2.57 (1H, m), 2.60-2.65 (1H, m), 2.82-2.86 (1H, m), 3.10-3.15 (1H, m), 3.56-3.61 (1H, m), 7.10-7.13 (1H, m), 7.21-7.25 (1H, m), 7.39-7.41 (1H, m), 7.68-7.72 (1H, d, $J = 8.04$ Hz), 7.77-7.78 (1H, d, $J = 7.84$ Hz), 8.32 (1H, bs).

1-(2-Bromo benzenesulfonyl)-3-(1-methyl pyrrolidin-3-yl)-1H-indole (7a): 2-Bromobenzenesulfonyl chloride (0.76

g, 2.98 mmol) solution in dimethylformamide (5 mL) was added to a stirred solution of compound **6a** (0.5 g, 2.48 mmol) and sodium hydride (60 %, 0.18 g, 3.73 mmol) in dimethyl formamide (20 mL) under nitrogen at room temperature. The reaction mass was stirred for 3 h at room temperature. After the completion of reaction, the reaction mixture was quenched with 25 mL ice-cold water and the product was extracted with ethyl acetate (3 $\times$ 15 mL). The combined organic phase was washed sequentially with water and brine, dried over anhydrous sodium sulphate and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, EtOAc/TEA, 99/1) to afford the title compound **7a** (0.83 g, 80 %), which was confirmed by IR, NMR and mass analyses. Similarly compounds **7b-7h** were synthesized.

7a: M.R (°C): 86.2-88.0; IR (KBr, $\nu_{\max}$, cm^{-1}): 2777, 1369, 1178, 593; Mass (m/z): 419 [$M + 1$], 421 [$M + 3$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.96-1.98 (1H, m), 2.36-2.40 (1H, m), 2.43 (3H, s), 2.54-2.61 (2H, m), 2.83-2.87 (1H, m), 3.10-3.15 (1H, m), 3.59-3.61 (1H, m), 7.22-7.24 (2H, m), 7.35-7.40 (1H, m), 7.43-7.48 (1H, m), 7.57-7.62 (2H, m), 7.65-7.69 (2H, m), 8.02-8.04 (1H, dd, $J = 8.72$ and 2.16 Hz).

10-(1-Methyl pyrrolidin-3-yl)-5-thia-4b-aza-indeno-[2,1-a]indene-5,5-dioxide (2a): A solution of compound **7a** (0.5 g, 1.19 mmol), potassium acetate (0.23 g, 2.38 mmol) and *tetrakis*(triphenyl phosphine) palladium(0) (0.068 g, 0.059 mmole) in *N,N*-dimethyl acetamide (10 mL) was stirred for 5 h at 125-130 °C under nitrogen atmosphere. After the completion of reaction, the resulting solution was partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The residual mass, thus obtained, was purified by flash chromatography (silica gel, EtOAc/TEA, 99.5/0.5) to give **2a** (0.31 g, 78 %), which was confirmed by IR, NMR and mass spectral analyses. Similarly compounds **2b-2h** were synthesized.

2a: M.R (°C): 167.8-173.1; IR (KBr, $\nu_{\max}$, cm^{-1}): 2940, 1325, 1181, 583; Mass (m/z): 339 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 2.20-2.25 (1H, m), 2.33-2.37 (1H, m), 2.50 (3H, s), 2.83-2.97 (4H, m), 4.02-4.07 (1H, m), 7.24-7.25 (1H, m), 7.35-7.40 (1H, m), 7.48-7.51 (1H, m), 7.64-

7.68 (1H, m), 7.70-7.72 (1H, d, $J = 7.72$ Hz), 7.83-7.85 (1H, d, $J = 8.12$ Hz), 7.87-7.89 (1H, d, $J = 8.12$ Hz), 8.05-8.07 (1H, d, $J = 8.00$ Hz).

2b: M.R (°C): 97.7-106.8; IR (KBr, $\nu_{\max}$ cm^{-1}): 2924, 1334, 1180, 582; Mass (m/z): 353 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.14-1.17 (3H, t, $J = 7.24$ Hz), 2.17-2.24 (1H, m), 2.33-2.37 (1H, m), 2.59-2.75 (3H, m), 2.91-3.03 (3H, m), 4.04-4.07 (1H, m), 7.23-7.29 (1H, m), 7.36-7.40 (1H, m), 7.46-7.50 (1H, m), 7.65-7.70 (1H, m), 7.71-7.73 (1H, d, $J = 8.12$ Hz), 7.83-7.86 (2H, m), 8.12-8.13 (1H, d, $J = 7.92$ Hz).

2c: M.R (°C): 132.3-143.5; IR (KBr, $\nu_{\max}$ cm^{-1}): 2796, 1325, 1165, 580; Mass (m/z): 369 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 2.16-2.21 (1H, m), 2.32-2.35 (1H, m), 2.48 (3H, s), 2.75-2.77 (1H, m), 2.82-2.87 (1H, m), 2.93-2.97 (2H, m), 3.86 (3H, s), 3.97-4.01 (1H, m), 6.98-7.01 (1H, dd, $J = 8.80$ and 2.48 Hz), 7.44-7.48 (2H, m), 7.58-7.61 (1H, d, $J = 8.80$ Hz), 7.63-7.67 (1H, m), 7.81-7.83 (1H, d, $J = 7.80$ Hz), 8.01-8.03 (1H, d, $J = 7.96$ Hz).

2d: M.R (°C): 98.8-108.8; IR (KBr, $\nu_{\max}$ cm^{-1}): 2967, 1332, 1178, 580; Mass (m/z): 383 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.12-1.16 (3H, t, $J = 7.32$ Hz), 2.16-2.21 (1H, m), 2.35-2.37 (1H, m), 2.61-3.02 (6H, m), 3.87 (3H, s), 4.03-4.05 (1H, m), 6.99-7.01 (1H, dd, $J = 8.84$ & 2.44 Hz), 7.44-7.48 (2H, m), 7.59-7.61 (1H, d, $J = 8.84$ Hz), 7.63-7.66 (1H, m), 7.81-7.83 (1H, d, $J = 7.80$ Hz), 8.06-8.08 (1H, d, $J = 7.92$ Hz).

2e: M.R (°C): 115.9-118.9; IR (KBr, $\nu_{\max}$ cm^{-1}): 2922, 1329, 1175, 559; mass (m/z): 383 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.42-1.47 (3H, t, $J = 6.96$ Hz), 2.18-2.22 (1H, m), 2.32-2.43 (1H, m), 2.49 (3H, s), 2.77-2.79 (1H, m), 2.86-2.88 (1H, m), 2.92-2.95 (2H, m), 3.94-3.99 (1H, m), 4.06-4.11 (2H, q, $J = 6.96$ Hz), 6.98-7.01 (1H, dd, $J = 8.80$ and 2.42 Hz), 7.44-7.48 (2H, m), 7.57-7.60 (1H, d, $J = 8.80$ Hz), 7.62-7.66 (1H, m), 7.80-7.82 (1H, d, $J = 7.84$ Hz), 8.01-8.03 (1H, d, $J = 7.92$ Hz).

2f: M.R (°C): 110-115.1; IR (KBr, $\nu_{\max}$ cm^{-1}): 2966, 1328, 1179, 559; mass (m/z): 397 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.17-1.21 (3H, t, $J = 7.20$ Hz), 1.44-1.47 (3H, t, $J = 6.96$ Hz), 2.18-2.23 (1H, m), 2.32-2.38 (1H, m), 2.59-2.68 (2H, m), 2.74-2.80 (1H, m), 2.88-2.90 (1H, m), 2.95-2.99 (2H, m), 3.98-4.00 (1H, m), 4.06-4.11 (2H, q, $J = 6.96$ Hz), 6.98-6.99 (1H, dd, $J = 8.80$ & 2.36 Hz), 7.44-7.48 (2H, m), 7.57-7.60 (1H, d, $J = 8.80$ Hz), 7.62-7.64 (1H, m), 7.80-7.82 (1H, d, $J = 7.80$ Hz), 8.05-8.07 (1H, d, $J = 7.92$ Hz).

2g: M.R (°C): 141.8-145.7; IR (KBr, $\nu_{\max}$ cm^{-1}): 2972, 1325, 1180, 586; mass (m/z): 397 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.36-1.38 (6H, d, $J = 6.40$ Hz), 2.17-2.20 (1H, m), 2.33 (1H, m), 2.48 (3H, s), 2.74-2.76 (1H, m), 2.81-2.83 (1H, m), 2.90-2.94 (2H, m), 3.95-3.97 (1H, m), 4.53-4.56 (1H, m), 6.97-6.99 (1H, dd, $J = 8.80$ and 2.40 Hz), 7.46-7.49 (2H, m), 7.57-7.59 (1H, d, $J = 8.80$ Hz), 7.62-7.64 (1H, m), 7.81-7.82 (1H, d, $J = 7.80$ Hz), 8.00-8.01 (1H, d, $J = 7.96$ Hz).

2h: IR (KBr, $\nu_{\max}$ cm^{-1}): 2970, 1335, 1182, 580; mass (m/z): 411 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.19-1.25 (3H, t, $J = 7.24$ Hz), 1.37-1.39 (6H, d, $J = 6.42$ Hz), 2.19-2.25 (1H, m), 2.32-2.39 (1H, m), 2.59-2.76 (3H, m), 2.84-2.86 (1H, m), 2.92-2.95 (2H, m), 4.01-4.06 (1H, m), 4.45-4.48 (1H, m), 6.98-7.00 (1H, dd, $J = 8.84$ & 2.48 Hz), 7.44-

7.48 (2H, m), 7.55-7.59 (1H, d, $J = 8.84$ Hz), 7.63-7.65 (1H, m), 7.80-7.81 (1H, d, $J = 7.82$ Hz), 7.99-8.00 (1H, d, $J = 7.90$ Hz).

3-Bromo-1-(tert-butyl dimethyl silanyl)-1H-indole (8a): To a cooled solution of indole (**4a**, 2 g, 17.09 mmol) in tetrahydrofuran (20 mL) at -78°C was added a solution of *n*-butyllithium (32 mL, 1.6 M solution in hexane, 51.28 mmol) dropwise *via* cannula under nitrogen atmosphere. The reaction mass was warmed to -10°C , stirred for 0.5 h and again cooled to -50°C . Then a solution of *tert*-butyl dimethyl silyl chloride (7.7 g, 51.28 mmol) in tetrahydrofuran (30 mL) was added dropwise to this mixture. The temperature was raised to 0°C and stirred for 3 h at the same temperature. The reaction mixture was cooled to -78°C , freshly crystallized *N*-bromosuccinimide (6.06 g, 34.18 mmol) was added *via* a solid-addition funnel and the resulting mixture was stirred for 2 h at -78°C and then allowed warm to room temperature. After completion of the reaction, the mass was poured into a mixture of hexane (100 mL) and pyridine (1 mL). The resulting suspension was filtered through a celite pad, the filtrate was concentrated under reduced pressure. The crude residue was then purified by flash chromatography (silica gel, 100 % hexane) to obtain **8a** (3.4 g, 68 %) as a colourless solid, which was confirmed by IR, NMR and mass analyses. Similarly compounds **8b-8d** were synthesized.

8a: M.R (°C): 73.2-74.1; IR (KBr, $\nu_{\max}$ cm^{-1}): 2931, 1445, 1287, 739; Mass (m/z): 310.2 [$M + 1$], 312.2 [$M + 3$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 0.60 (6H, s), 0.91 (9H, s), 7.16-7.23 (3H, m), 7.47-7.50 (1H, m), 7.55-7.58 (1H, m).

(1H-Indol-3-yl)-(1-methyl pyrrolidin-2-yl)methanone (9a): To a stirred solution of compound **8a** (1 g, 3.41 mmol) in tetrahydrofuran (15 mL) cooled to -78°C was added a solution of *n*-butyllithium (6.4 mL, 1.6 M solution in hexane, 10.23 mmol) dropwise *via* cannula under nitrogen atmosphere. The resulting solution was stirred for 15 min at -78°C , then added a solution of 1-methyl pyrrolidine-2-carboxylate (0.65 g, 5.10 mmol) in tetrahydrofuran (10 mL). Reaction mass was stirred for 12 h at room temperature. After completion of the reaction, the reaction mass was quenched in saturated ammonium chloride solution and the compound was extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulphate and solvent removed under reduced pressure. The residual mass, thus obtained, was purified by flash chromatography (silica gel, EtOAc/TEA, 99/1) to afford the compound **9a** (0.46 g, 60 %), which was confirmed by IR, NMR and mass analyses. Similarly compounds **9b-9d** were synthesized.

9a: IR (KBr, $\nu_{\max}$ cm^{-1}): 3314, 1769, 1277, 735; mass (m/z): 229.3 [$M + 1$]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.85-1.90 (1H, m), 1.99-2.04 (2H, m), 2.25-2.28 (1H, m), 2.35-2.38 (1H, m), 2.40 (3H, s, N-CH₃), 3.22-3.26 (1H, m), 3.43-3.47 (1H, m), 7.27-7.32 (2H, m), 7.42-7.44 (1H, m), 8.37-8.38 (1H, m), 8.47-8.49 (1H, m), 8.84 (1H, bs).

3-(1-Methyl pyrrolidin-2-ylmethyl)-1H-indole (10a): To a stirred suspension of lithium aluminum hydride (0.11 g, 2.96 mmol) in tetrahydrofuran (10 mL) was added a solution of compound **9a** (0.45 g, 1.97 mmol) in tetrahydrofuran (10 mL) and the resulting slurry was heated at reflux for 4 h. After the completion of reaction, the reaction mixture was cooled to

10 °C, poured on to chilled water (20 mL) and stirred for 0.5 h. The slurry, thus obtained, was filtered through celite pad and washed with ethyl acetate (15 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 × 15 mL). The combined organic layer was washed with brine solution (15 mL) and dried over anhydrous sodium sulfate. Organic volatiles were removed under reduced pressure. The residual mass, thus obtained, was purified by flash chromatography (silica gel, EtOAc/TEA, 99/1) to afford compound **10a** (0.35 g, 83 %), which was confirmed by IR, NMR and mass analyses. Similarly compounds **10b-10d** were synthesized.

10a: IR (KBr, $\nu_{\max}$, cm^{-1}): 3399, 2920, 1472, 717; mass (m/z): 215.2 [M + 1]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.58-1.61 (2H, m), 1.77-1.80 (2H, m), 2.21-2.23 (1H, m), 2.46-2.50 (4H, m), 2.58-2.64 (1H, m), 3.13-3.22 (2H, m), 7.02-7.03 (1H, m), 7.11-7.14 (1H, m), 7.17-7.21 (1H, m), 7.35-7.37 (1H, m), 7.60-7.62 (1H, d, $J = 7.84$ Hz), 8.00 (1H, bs).

1-(2-Bromo benzenesulfonyl)-3-(1-methyl pyrrolidin-2-ylmethyl)-1H-indole (11a): 2-Bromobenzenesulfonyl chloride (0.50 g, 1.96 mmol) in dimethylformamide (5 mL) was added to a stirred solution of compound **10a** (0.35 g, 1.63 mmol) and sodium hydride (50 %, 0.098 g, 2.45 mmol) in dimethylformamide (15 mL) under nitrogen atmosphere at room temperature and the reaction mass was stirred for 3 h at room temperature. After the completion of reaction, the reaction mixture was quenched with 15 mL ice-cold water and the product was extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed sequentially with water and brine, dried over anhydrous sodium sulphate and concentrated *in vacuo*. The resultant residue was purified by flash chromatography (silica gel, EtOAc/TEA, 99/1) to afford the title compound **11a** (0.56 g, 80 %), which was confirmed by IR, NMR and mass analyses. Similarly compounds **11b-11d** were synthesized.

11a: M.R (°C): 86.2-88.0; IR (KBr, $\nu_{\max}$, cm^{-1}): 2765, 1369, 1178, 596; mass (m/z): 433 [M + 1], 435 [M + 3]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.54-1.58 (2H, m), 1.64-1.68 (2H, m), 2.22-2.24 (1H, m), 2.48-2.53 (4H, m), 2.56-2.59 (1H, m), 3.10-3.14 (2H, m), 7.21-7.25 (2H, m), 7.36-7.41 (1H, m), 7.45-7.49 (1H, m), 7.52-7.57 (1H, m), 7.58 (1H, s), 7.65-7.77 (2H, m), 8.04-8.07 (1H, dd, $J = 7.88$ and 1.68 Hz).

10-(1-Methyl pyrrolidin-2-ylmethyl)-5-thia-4b-aza indeno[2,1-a]indene-5,5-dioxide (3a): A solution of compound **11a** (0.55 g, 1.27 mmol), potassium acetate (0.25 g, 2.55 mmol) and *tetrakis*(triphenyl phosphine) palladium(0) (0.073 g, 0.063 mmol) in *N,N*-dimethyl acetamide (10 mL) was stirred for 5 h at 125-130 °C under nitrogen atmosphere. After the completion of reaction, the resulting solution was partitioned between water and ethyl acetate. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The residual mass, thus obtained was purified by flash chromatography (silica gel, EtOAc/TEA, 99.5/0.5) to give **3a** (0.35 g, 80 %), which was confirmed by IR, NMR and mass analyses. Similarly compounds **3b-3d** were synthesized.

3a: M.R (°C): 200.6-201.9; IR (KBr, $\nu_{\max}$, cm^{-1}): 2788, 1332, 1177, 547; mass (m/z): 353 [M + 1]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.60-1.80 (4H, m), 2.25-2.27 (1H, m), 2.54-2.62 (4H, m), 2.87-2.93 (1H, m), 3.14-3.20 (1H, m), 3.32-3.35 (1H, m), 7.25-7.28 (1H, m), 7.36-7.38 (1H, m), 7.48-7.50 (1H, m), 7.59-7.61 (1H, d, $J = 8.00$ Hz), 7.64-7.68 (1H, m), 7.69-7.71 (1H, d, $J = 8.00$ Hz), 7.83-7.85 (1H, d, $J = 7.82$ Hz), 7.88-7.90 (1H, d, $J = 7.84$ Hz).

3b: M.R (°C): 190.7-195.1; IR (KBr, $\nu_{\max}$, cm^{-1}): 2769, 1322, 1174, 582; mass (m/z): 383 [M + 1]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.62-1.65 (2H, m), 1.78-1.80 (2H, m), 2.27-2.29 (1H, m), 2.55-2.63 (4H, m), 2.86-2.90 (1H, m), 3.14-3.19 (1H, m), 3.28-3.32 (1H, m), 3.86 (3H, s), 6.99-7.01 (1H, dd, $J = 8.84$ and 2.00 Hz), 7.02-7.05 (1H, m), 7.45-7.49 (1H, m), 7.58-7.60 (1H, d, $J = 8.84$ Hz), 7.63-7.66 (1H, m), 7.81-7.83 (1H, d, $J = 7.83$ Hz), 7.81-7.88 (1H, d, $J = 7.84$ Hz).

3c: M.R (°C): 113.0-120.0; IR (KBr, $\nu_{\max}$, cm^{-1}): 2774, 1334, 1174, 584; mass (m/z): 397 [M + 1]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.43-1.46 (3H, t, $J = 6.96$ Hz), 1.60-1.64 (2H, m), 1.77-1.81 (2H, m), 2.26-2.28 (1H, m), 2.54-2.61 (4H, m), 2.84-2.90 (1H, m), 3.13-3.18 (1H, m), 3.27-3.31 (1H, m), 4.05-4.10 (2H, q, $J = 6.96$ Hz), 6.98-7.01 (1H, dd, $J = 8.71$ and 2.20 Hz), 7.02-7.05 (1H, m), 7.44-7.48 (1H, m), 7.57-7.59 (1H, d, $J = 8.71$ Hz), 7.62-7.66 (1H, m), 7.81-7.83 (1H, d, $J = 7.82$ Hz), 7.85-7.87 (1H, d, $J = 7.86$ Hz).

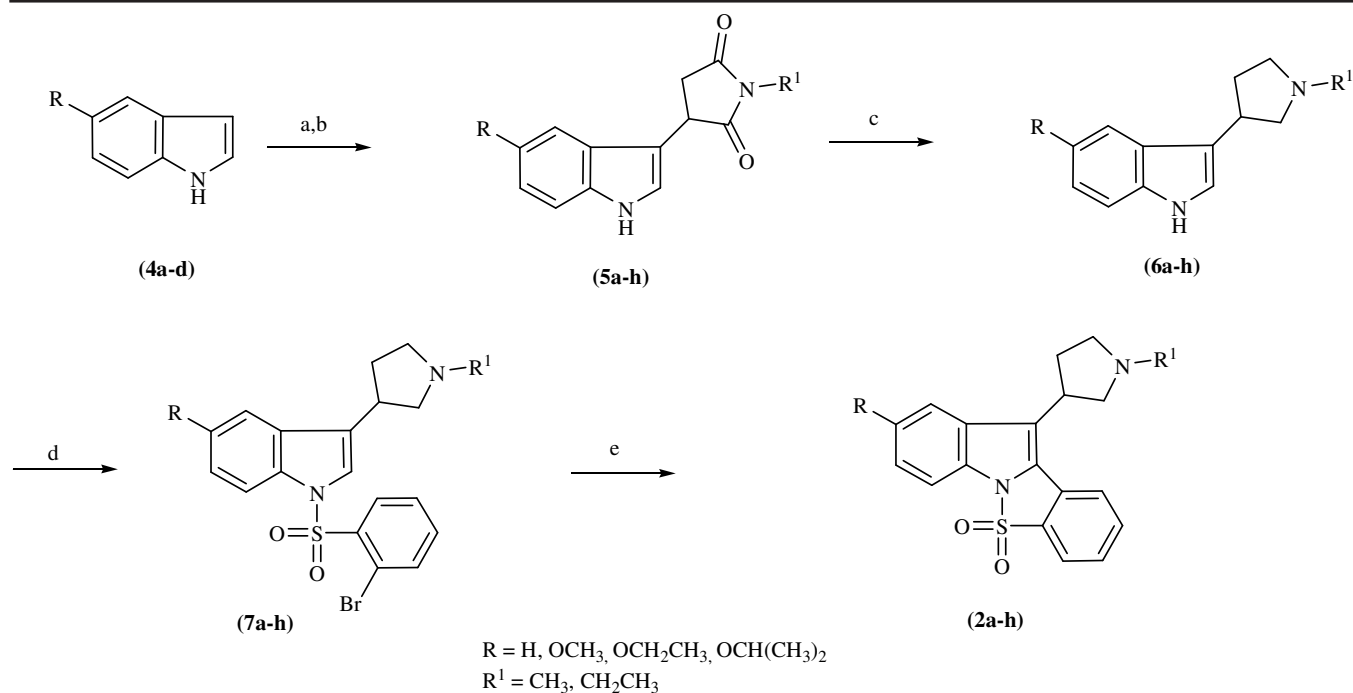
3d: M.R (°C): 123.6-125.1; IR (KBr, $\nu_{\max}$, cm^{-1}): 2777, 1326, 1174, 580; mass (m/z): 411 [M + 1]; ^1H NMR (400 MHz) (CDCl_3) δ (ppm): 1.35-1.37 (6H, d, $J = 6.40$ Hz), 1.60-1.64 (2H, m), 1.77-1.81 (2H, m), 2.26-2.28 (1H, m), 2.55-2.62 (4H, m), 2.84-2.90 (1H, m), 3.12-3.18 (1H, m), 3.26-3.31 (1H, m), 4.53-4.56 (1H, m), 6.98-7.00 (1H, dd, $J = 8.80$ and 2.0 Hz), 7.01-7.04 (1H, m), 7.44-7.48 (1H, m), 7.56-7.58 (1H, d, $J = 8.80$ Hz), 7.62-7.66 (1H, m), 7.80-7.87 (1H, d, $J = 7.80$ Hz), 7.85-7.87 (1H, d, $J = 7.80$ Hz).

RESULTS AND DISCUSSION

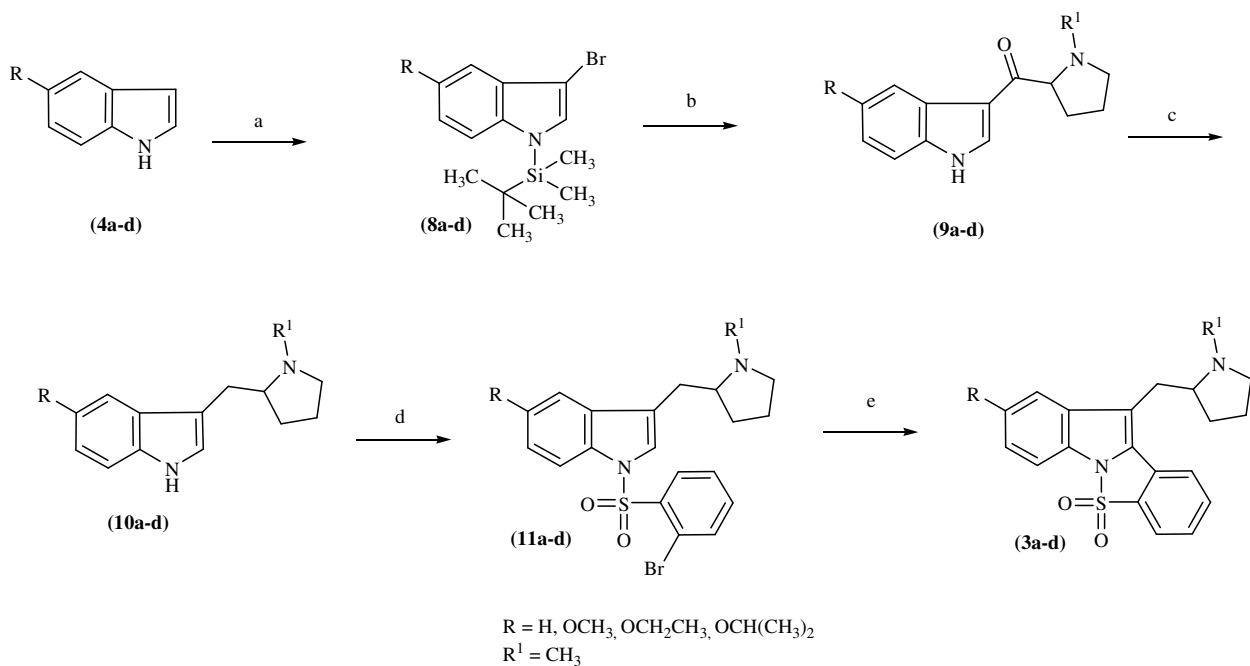
The target compounds were synthesized according to the representative **Schemes I and II**.

Indole-3-substituted pyrrolidine diones (**5a-5h**) were synthesized by reacting equimolar amounts of indole and maleic acid at 50 °C. The resulting indole-3-succinic acid derivatives were further reacted with dialkyl ureas at 180 °C. The diones, thus obtained, were reduced using lithium aluminum hydride to the corresponding pyrrolidine compounds (**6a-6h**). The intermediates (**6a-6h**) were reacted with 2-bromobenzene-sulfonyl chloride in the presence of a base to obtain the intermediates (**7a-7h**), which were further subjected to Heck cyclization reaction to obtain the desired series of compounds (**2a-2h**).

N-Silylated-3-bromo indole derivatives (**8a-8d**) were synthesized by protection of indoles with substituted silyl chlorides in the presence of *n*-butyllithium, followed by bromination at C-3 of indole position using *N*-bromo succinimide. The intermediates **8a-8d** were reacted with *N*-methyl proline esters in the presence of *n*-butyl lithium resulting in indole-3-methanone derivatives (**9a-9d**). These methanone derivatives were reduced by using lithium aluminum hydride to obtain



Scheme-I: (a) Maleic acid, 50 °C, 1h; (b) 1,3-Dialkylurea, 180-190 °C, 1h, 68 %; (c) LAH, THF, reflux, 4 h, 70 %; (d) 2-Bromo benzenesulfonyl chloride, NaH, DMF, RT, 3 h, 80 %; (e) CH_3COOK , $\text{Pd(PPh}_3)_4$, DMA, 130 °C, 5 h, 78 %



Scheme-II: (a) $n\text{-BuLi}$, $\text{tert-butyl dimethyl silyl chloride}$, NBS, THF, -78 °C, 6 h, 68 %; (b) $n\text{-BuLi}$, 1-alkyl pyrrolidine-2-carboxylic acid methyl ester, THF, -78 °C, 12 h, 60 %; (c) LAH, THF, reflux, 4 h, 83 %; (d) 2-Bromo benzenesulfonyl chloride, NaH, DMF, RT, 3 h, 80 %; (e) CH_3COOK , $\text{Pd(PPh}_3)_4$, DMA, 130 °C, 5 h, 80 %

corresponding amines (10a-10d). The intermediates (10a-10d) were reacted with 2-bromo benzenesulfonyl chloride in the presence of base to afford the intermediates (11a-11d), which were further subjected to the familiar Heck reaction to obtain the target compounds (3a-3d). All the intermediates and final compounds were fully characterized by IR, NMR and mass spectral data.

Structure activity relationship (SAR): Analytically well characterized 10-(1-methyl pyrrolidin-3-yl)-5-thia-4b-aza-indeno[2,1-a]indene-5,5-dioxide (2a-2h) and 10-(1-methyl

pyrrolidin-2-ylmethyl)-5-thia-4b-aza-indeno[2,1-a]indene-5,5-dioxide (3a-3d) derivatives were tested for their 5-HT₆R *in vitro* binding affinity at 100 nM concentration. All the compounds were tested as racemates and the results are given in Table-1. As part of our structure activity relationship studies, initially we rigidized the tryptamine side chain into the pyrrolidine ring through β carbon *i.e.*, 10-(1-methyl pyrrolidin-3-yl)-5-thia-4b-aza-indeno[2,1-a]indene-5,5-dioxide (unsubstituted indole 2a) and the % inhibition at 100 nM concentration was found to be 54.65 percent. Later, we introduced

TABLE-2
 PHARMACOKINETIC PROFILE OF COMPOUND **2c**^a

Route	n	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (h)	AUC _t (ng h/mL)	t _{1/2} (h)	F (%)
Oral	3	10	107 ± 49	1.3 ± 0.6	946 ± 563	7.48 ± 0.85	34
i.v.	3	10	1476 ± 455	0.08 ± 0.0	2769 ± 307	4.13 ± 0.31	

^aFasted 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.

the substitution on phenyl ring of indole with electron donating groups like methoxy (**2c**, 95.52 %), ethoxy (**2e**, 58.54 %), isopropoxy (**2g**, 53 %) at second position (**R**) and these were found to have moderate affinities at 5-HT₆R and it appears that there is a slight preference for lower alkoxy (methoxy) substitution. Replacement of methyl with ethyl on the amine had little effect on 5-HT₆R binding affinities as can be seen by comparing **2c** (95.52 %) with **2d** (66.63 %) and **2e** (58.54 %) with **2f** (41.97 %). Based on these results, we evaluated the effect of rigidization of the tryptamine side chain into the pyrrolidine ring through α carbon. This change resulted in compounds with less potency compared to their respective counterparts as can be seen by comparing **2c** (95.52 %) vs **3b** (63.42 %) and **2e** (58.54 %) vs **3c** (52.36 %)). The overall result indicates that rigidization through α and β carbons are tolerated for 5-HT₆R binding. Among all the synthesized compounds, **2c** (95.52 %) has shown highest percent of inhibition at 5-HT₆R, when tested at 100 nM concentration, indicating that rigidization of the tryptamine side chain into the pyrrolidine ring through β carbon was more favorable than rigidization through α carbon.

 TABLE-1
 5-HT₆R BINDING AFFINITIES OF
 COMPOUND **2** AND **3** DERIVATIVES^a

Compound	R	R ¹	Inhibition % at 100 nM
2a	H	CH ₃	54.65
2b	H	C ₂ H ₅	43.76
2c	OCH ₃	CH ₃	95.52
2d	OCH ₃	C ₂ H ₅	66.63
2e	OC ₂ H ₅	CH ₃	58.54
2f	OC ₂ H ₅	C ₂ H ₅	41.97
2g	OCH(CH ₃) ₂	CH ₃	53.00
2h	OCH(CH ₃) ₂	C ₂ H ₅	31.93
3a	H	CH ₃	58.61
3b	OCH ₃	CH ₃	63.42
3c	OC ₂ H ₅	CH ₃	52.36
3d	OCH(CH ₃) ₂	CH ₃	49.07

^aAll compounds were characterized and purity was assessed using ¹H NMR, MS and HPLC. 5-HT₆R Receptor binding studies were carried out at Novascreeen, USA. using Human recombinanat/HEK293 cells; Radioligand: [³H] LSD (60-80 Ci/mmol).

The most active compound **2c** was further evaluated for its pharmacokinetic profile in male Wister rats and the results are given in Table-2. Compound **2c** displayed good oral exposure with AUC 946 ± 563 ng h/mL and longer i.v. half-life (t_{1/2} = 7.48 ± 0.85 h) and oral bioavailability of 34 %. The brain and plasma levels of compound **2c** were calculated in male Wister rats and it has shown high brain to plasma ratio of 13.8 ± 2.6.

Compound **2c** was further evaluated for its cognitive retention in behavioural assay model like Morris water maze. It has significantly reversed the scopolamine induced memory

deficit at 10 mg/kg p.o. dose in Morris water maze model, which was apparent from lesser target latency (Fig. 2).

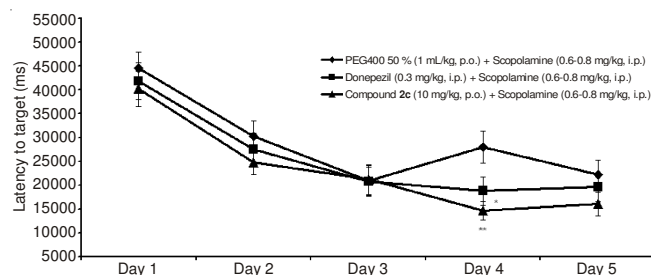


Fig. 2. Morris water maze test data for compound **2c** in rats. Data represents Mean ± SEM of latency to target, ***p* < 0.01, **p* < 0.05, (one way ANOVA, Dunnett's post hoc analysis)

Conclusion

In summary, a novel series of compounds **2** and **3** were designed by constraining the tryptamine side chain into a pyrrolidine ring through α and β carbons and were found to have moderate affinities at 5-HT₆R. The most active compound **2c** has shown the acceptable pharmacokinetic profile along with the cognition potential at 10 mg/kg (Watermaze). The overall results indicated that these compounds have the potential to be 5-HT₆R ligands. Hence further efforts for their chiral separation and detailed profiling are under progress and constitute subject matter of our next publication.

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