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Synthesis and biological activity of N_1-substituted-3-aminoalkoxy indoles as potential 5-HT_6 receptor ligands

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ABSTRACT

A novel series of N_1-substituted-3-aminoalkoxy indoles was designed and synthesized as potential 5-HT_6 receptor ligands and tested for human 5-HT_6 receptor binding affinities. All the tested compounds showed moderate to high binding affinities towards 5-HT_6 receptor. The most potent compound ***6j*** *(h5-HT_6 receptor Ki being 10.2 nM) was selected for further studies.*

Keywords: Serotonin, 5-HT_6 receptor, N_1-substituted-3-aminoalkoxy indoles, CNS targets.

INTRODUCTION

Serotonin (5-Hydroxy tryptamine, 5-HT) was first discovered in the late 1940s and the continued interest by scientific community led to identification of seven families of 5-HT receptors till date. Presently, many serotoninergic agents are reported which act through 5-HT_{1-4} receptors and are marketed worldwide *viz.* sumatriptan, buspirone, ondansetron and risperidone. But, till date there are no therapeutic drugs reported which acts through 5-HT_{5-7} receptors. In the last two decades, the 5-HT_6 receptor population identified by molecular cloning in rat, human and mouse [1-4] has shown most progress in the identification of potent and selective 5-HT_6 receptor ligands. Several molecules like **SB-742457**, **SUVN-502**, **PRX-07034, AVN-211, SAM-531** and **Lu-AE58054** have entered clinical trials [5-9]. As part of our continuous contribution in CNS targets and designing the molecules having 5-HT_6 receptor affinity, we have synthesized a novel series of N_1-substituted-3-aminoalkoxy indoles as 5-HT_6 receptor ligands. In this paper, we have disclosed the details of design and synthesis of this novel series along with its human radioligand 5-HT_6 receptor *in-vitro* binding data.

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, USA). 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 400MHz. 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. All the reagents and chemicals used were of 'reagent grade'.

Design of ligands: Glennon *et. al.* first discovered the potential use of sulfonamide motif in the indole type structures for binding and antagonism of 5-HT$_6$ receptors. His efforts have led to the discovery of most potent 5-HT$_6$ receptor antagonist **MS-245 (I)** [10, 11]. Soon after the disclosure of **MS-245**, various efforts were made by different research groups to modify the tryptamine side chain and replacing indole with different heterocyclic rings [12-16].

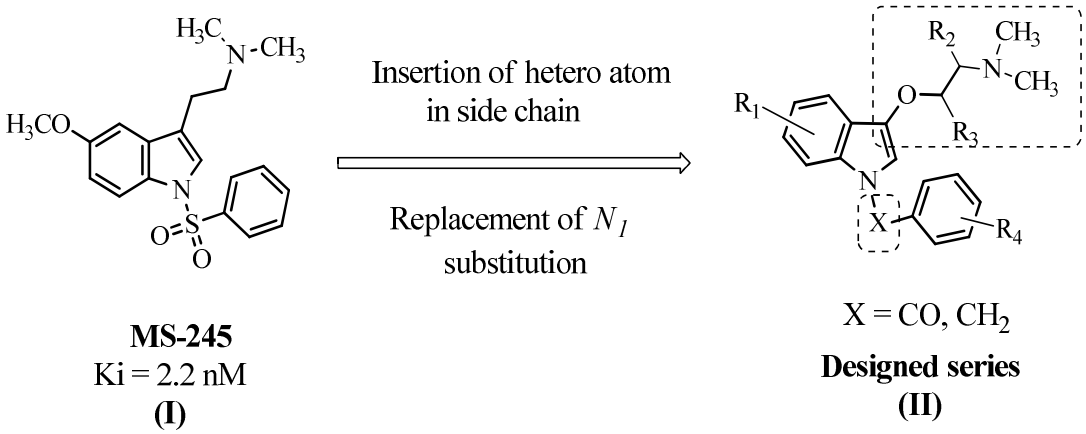


Figure 1: Design of ligands.

Our efforts in the area of CNS and especially designing the molecules with desired 5-HT$_6$ receptor affinity, has generated a novel series of N_1-substituted-3-aminoalkoxy indoles as 5-HT$_6$ receptor ligands (**II**, Figure: 1). In this effort, we have explored the effect of replacement of tryptamine side chain with 3-aminoalkoxy side chain at C-3 of indole, with simultaneous modification at N_1 of indole. The N_1 protection was replaced with substituted / unsubstituted benzyl and benzoyl functionalities. All the compounds **(Table-1)** were tested in *in-vitro* radioligand binding assay. The result of these efforts is the subject matter of this article.

General procedure for the synthesis of (3a-j):

Potassium carbonate (2 mmole) was added to a solution of **1a-f** (1 mmole) in tetrahydrofuran (8 volumes) and stirred at 25 – 30 ^{0}C for 90 min. In a separate flask, the corresponding intermediate **2a-c** (3 mmole) was taken in toluene (30 ml) and stirred with 20% sodium hydroxide solution (10 volumes). The toluene layer was separated and transferred to the above mass under stirring. The reaction mass was heated at reflux (90 – 95 ^{0}C) for 4-6 hr. The reaction mass was then cooled to 25 – 30 ^{0}C and filtered the inorganic solids at suction and washed with appropriate volumes of ethyl

acetate. The filtrate was concentrated under reduced pressure to obtain products as dark brown colored oily mass. The residues, thus obtained, were used as such in next step without purifications (based on TLC and ESI-MS analysis).

6-Chloro-3-(2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3a; R_1=6-Cl; R_2=R_3=H): ^{1}H-NMR ($CDCl_3$/TMS, 400 MHz): 2.37 (s, 6H, N(C**H**$_3$)$_2$), 2.66 (s, 3H, COC**H**$_3$), 2.77 – 2.81 (t, 2H, Me_2NC**H**$_2$), 4.43 – 4.46 (t, 2H, OC**H**$_2$), 7.20 – 7.22 (d, 1H, J = 8.20 Hz, aromatic), 7.36 – 7.39 (dd, 1H, J = 8.79, 1.54 Hz, aromatic), 7.93 (s, 1H, aromatic), 8.73 (d, 1H, aromatic). ESI-MS: 281.1 (M+1), Yield = 60 % (purified).

5-Chloro-3-(2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3b; R_1=5-Cl, R_2=R_3=H): ESI-MS: 281.2 (M+1), Yield = 100 % (Technical).

3-(2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3c; R_1=R_2=R_3=H): ESI-MS: 247.3 (M+1), Yield = 95 % (Technical).

3-(1-methyl-2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3d; R_1=R_2=H, R_3=Me): ESI-MS: 261.2 (M+1), Yield = 100 % (Technical).

5-Methoxy-3-(2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3e; R_1=5-OMe, R_2=R_3=H): ESI-MS: 277.2 (M+1), Yield = 100 % (Technical).

5-Bromo-3-(2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3f; R_1=5-Br, R_2=R_3=H): ESI-MS: 325, 327 (M+1), Yield = 90 % (Technical).

5-Chloro-3-(2-methyl-2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3g; R_1=5-Br, R_2=Me, R_3=H): ESI-MS: 295.3 (M+1), Yield = 100 % (Technical).

5-Bromo-3-(1-methyl-2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3h; R_1=5-Br, R_2=H, R_3=Me): ESI-MS: 339, 341.1 (M+1), Yield = 90 % (Technical).

5-Ethoxy-3-(2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3i; R_1=5-OEt, R_2=R_3=H): ESI-MS: 291.3 (M+1), Yield = 90 % (Technical).

3-(2-Methyl-2-dimethylaminoethoxy)-1-acetyl-*1H*-indole (3j; R_1=H, R_2=Me, R_3=H): ESI-MS: 261.3 (M+1), Yield = 100 % (Technical).

General procedure for the synthesis of (4a-j):

A solution of **3a-j** (1 mmole) in methanol (5 volumes) was added to a solution of sodium hydroxide (2 mmole) in water (5 volumes) under strring. The reaction mass was heated at 60 – 65 ^oC for 2 hr. After completion of the reaction (TLC), cooled the reaction mass to 25 – 30 ^oC and distilled off solvent under reduced pressure. Added water to the mass and extracted the product into appropriate volumes of ethyl acetate. The combined ethyl acetate layers were washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain products as oily mass. The residue, thus obtained, was purified by flash chromatography over silica gel using 1% triethylamine (TEA) in ethyl acetate to obtain the desired intermediates **4a-j**.

6-Chloro-3-(2-dimethylaminoethoxy)-*1H*-indole (4a; R_1=6-Cl; R_2=R_3=H): IR (KBr, cm^{-1}): 3430 (-NH); ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H), 2.76 – 2.78 (t, 2H), 4.07 – 4.10 (t, 2H), 6.70 – 6.71 (d, 1H, J = 2.3 Hz), 6.94 – 6.96 (dd, 1H, J = 1.64, 8.46 Hz), 7.28 (d, 1H, J = 1.51 Hz), 7.50 – 7.52 (d, 1H, J = 8.45 Hz), 9.48 (s, 1H); (M+1): 239.3; HPLC purity = 97.44%, Yield: 60 %.

5-Chloro-3-(2-dimethylaminoethoxy)-*1H*-indole (4b; R_1=5-Cl, R_2=R_3=H): m.p: 103.7–108.9 ^{o}C; IR (KBr, cm^{-1}): 3153 (-NH), 1459; ^{1}H-NMR ($CDCl_3$/TMS): 2.37 (s, 6H), 2.76 – 2.79 (t, 2H), 4.08 – 4.11 (t, 2H), 6.72 – 7.62 (m, 5H, Ar & -NH); (M+1): 239.1; HPLC purity: 93.32 %; Yield = 65 %

3-(2-dimethylaminoethoxy)-*1H*-indole (4c; R_1=H, R_2=R_3=H): (M+1): 205; IR (KBr, cm^{-1}): 2970, 3431 (-NH); Yield = 45 %

3-(1-methyl-2-dimethylaminoethoxy)-*1H*-indole (4d; R_1=R_2=H, R_3=Me): IR (KBr, cm^{-1}): 3133; ^{1}H-NMR ($CDCl_3$/TMS): 1.34 – 1.35 (d, 3H), 2.34 (s, 6H), 2.47 – 2.53 (m, 1H), 2.69 – 2.74 (m, 1H), 4.28 – 4.36 (m, 1H), 6.78 – 7.65 (m, 6H; Ar & NH); (M+1): 219.5; HPLC purity: 95.40 %; Yield = 50 %.

5-Methoxy-3-(2-dimethylaminoethoxy)-*1H*-indole (4e; R_1=5-OMe, R_2=R_3=H): IR (KBr, cm^{-1}): 1239, 3119 (-NH); ^{1}H-NMR ($CDCl_3$/TMS): 2.37 (s, 6H), 2.78 – 2.81 (t, 2H), 3.84 (s, 3H), 4.09 – 4.12 (t, 2H), 6.69 – 7.17 (m, 4H), 7.48 (s, 1H, -NH); (M+1): 235.2; HPLC purity: 95.47 %.

5-Bromo-3-(2-dimethylaminoethoxy)-*1H*-indole (4f; R_1=5-Br, R_2=R_3=H): IR (KBr, cm^{-1}): 3154 (-NH), 1459; ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H), 2.70 – 2.73 (t, 2H), 4.09 – 4.12 (t, 2H), 6.70 – 7.73 (m, 5H, Ar & -NH); (M+1): 283.2, 285.2; Yield = 50 %.

5-Chloro-3-(2-methyl-2-dimethylaminoethoxy)-*1H*-indole (4g; R_1=5-Br, R_2=Me, R_3=H): IR (KBr, cm^{-1}): 3129 (-NH); ^{1}H-NMR ($CDCl_3$/TMS): 1.32 – 1.34 (d, 3H), 2.33 (s, 6H), 2.43 – 2.50 (m, 1H), 2.66 – 2.71 (m, 1H), 4.23 – 4.31 (m, 1H), 6.79 – 7.61 (m, 5H, Ar & NH); (M+1): 297, 299; Yield = 70 %.

5-Bromo-3-(1-methyl-2-dimethylaminoethoxy)-*1H*-indole (4h; R_1=5-Br, R_2=H, R_3=Me): IR (KBr, cm^{-1}): 3130 (-NH); ^{1}H-NMR ($CDCl_3$/TMS): 1.14 – 1.16 (d, 3H), 2.32 (s, 6H), 2.98 – 3.03 (m, 1H), 3.80 – 3.84 (m, 1H), 4.02 – 4.09 (m, 1H), 6.71 – 7.54 (m, 5H, Ar & -NH); (M+1): 297.1, 299.1; Yield = 60 %.

5-Ethoxy-3-(2-dimethylaminoethoxy)-*1H*-indole (4i; R_1=5-OEt, R_2=R_3=H): IR (KBr, cm^{-1}): 3191 (-NH); ^{1}H-NMR ($CDCl_3$/TMS): 1.40 – 1.43 (t, 3H), 2.36 (s, 6H), 2.76 – 2.79 (t, 2H), 4.02 – 4.07 (q, 2H), 4.08 – 4.11 (t, 2H), 6.68 – 7.25 (m, 4H), 7.51 (s, 1H, NH); HPLC purity: 95.69 %; Yield = 30 %.

3-(2-Methyl-2-dimethylaminoethoxy)-*1H*-indole (4j; R_1=H, R_2=Me, R_3=H): IR (KBr, cm^{-1}): 3141 (-NH); (M+1): 219.4; ^{1}H-NMR ($CDCl_3$/TMS): 1.32 – 1.34 (d, 3H), 2.37 (s, 6H), 3.02 – 3.06 (m, 1H), 3.87 – 3.90 (m, 1H), 4.09 – 4.13 (m, 1H), 6.70 – 7.67 (m, 6H, Ar & -NH); HPLC purity: 94.18 %; Yield = 45 %.

General procedure for the synthesis of (6a-s): Sodium hydride (50% on mineral oil, 1.5 mmole) was added to a solution of **4a-j** (1 mmole) in N,N-dimethyl formamide (10 volumes) and stirred the reaction mass at 25 – 30 ^{o}C for 1 hr, under nitrogen atmosphere. A solution of corresponding intermediate **5a-d** (1 mmole) in N, N-dimethyl formamide (1 volume) was added to the reaction mass over 1 min and stirred the reaction mass at 25 – 30 ^{o}C for 1 hr. After completion of the raction (TLC), added water and extracted the product with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain product, which was purified by flash column chromatography using 0.5 % triethylamine in ethyl acetate to obtain final compounds **6a-s**. (**Note:** The substituted intermediate 5a-d were commercially procured).

6-Chloro-(1-benzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6a; R_1=6-Cl, R_2=R_3=H, R_4=H, X=CO): IR (cm^{-1}): 1681 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.34 (s, 6H), 2.73 – 2.79 (t, 2H), 3.99 – 4.04 (t, 2H), 6.69 – 8.37 (m, 9H); HPLC purity: 98.91 %; Yield = 80 %

6-Chloro-1-(2'-Bromobenzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6b; R_1=6-Cl, R_2=R_3=H, R_4=2'-Br, X=CO): IR (cm^{-1}): 1671 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.32 (s, 6H), 2.71 – 2.76 (t, 2H), 3.97 (t, 2H), 6.2 (s, 1H), 7.26 – 7.72 (m, 6H), 8.52 (s, 1H); (M+1): 421.1, 423.1; HPLC purity: 97.76 %; Yield = 75 %

5-Chloro-1-(benzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6c; R_1=5-Cl, R_2=R_3=R_4=H, X=CO): IR (cm^{-1}): 877, 1682 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.32 (s, 6H), 2.74 – 2.77 (t, 2H), 4.00 – 4.03 (t, 2H), 6.77 (s, 1H), 7.31 – 7.33 (dd, 1H, J = 2.0 & 8.0 Hz), 7.51 – 7.54 (m, 2H), 7.58 – 7.62 (m, 2H), 7.69 – 7.72 (m, 2H), 8.20 – 8.22 (d, 1H, J = 8.7 Hz); (M+1): 343.3; HPLC purity: 99.37 %; Yield = 80 %.

1-(2'-Bromobenzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6d; R_1=R_2=R_3=H, R_4=2'-Br, X=CO): IR spectra (cm^{-1}): 1680 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H), 2.77 – 2.83 (t, 2H), 4.11 – 4.16 (t, 2H), 7.13 (s, 1H), 7.13 – 7.42 (m, 4H), 7.59 – 7.84 (4H, m); (M+1): 387, 389; Yield = 65 %.

1-(2'-Bromobenzoyl)-3-(1-methyl-2-dimethylaminoethoxy)-*1H*-indole (6e; R_1=R_2=H, R_3=Me, R_4=2'-Br, X=CO): IR (cm^{-1}): 1679 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 1.15 – 1.17 (d, 3H), 2.36 (s, 6H), 3.11 – 3.13 (m, 1H), 3.85 – 3.87 (m, 1H), 4.11 – 4.15 (m, 1H), 7.13 (s, 1H), 7.25 – 7.29 (m, 2H), 7.35 – 7.40 (m, 2H), 7.69 – 7.77 (m, 4H); (M+1): 401, 403; Yield = 70 %.

1-(Benzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6f; R_1=R_2=R_3=R_4=H, =CO): IR (cm^{-1}): 1678 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.34 (s, 6H), 2.74 – 2.80 (t, 2H), 4.01 – 4.07 (t, 2H), 6.72 (s, 1H), 7.26 – 7.74 (m, 1H), 8.23 – 8.27 (s, 1H); (M+1): 309.4; HPLC purity: 99.47 %; Yield = 65 %

5-Methoxy-1-(2'-Bromobenzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6g; R_1=5-OMe, R_2=R_3=H, R_4=2'-Br, X=CO): IR (cm^{-1}): 1678 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.33 (s, 6H), 2.73 – 2.79 (bs, 2H), 3.87 (s, 3H), 4.09 – 4.13 (bs, 2H), 6.17 – 8.50 (m, 8H); HPLC purity: 95.38 %; Yield = 50 %

5-Bromo-1-(2'-Bromobenzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6h; R_1=5-Br, R_2=R_3=H, R_4=2'-Br, X=CO): IR spectra (cm^{-1}): 1686 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.35 (6H, s), 2.75 – 2.78 (2H, t), 4.00 – 4.02 (2H, t), 6.15 (1H, bs), 7.20 – 7.80 (6H, m), 8.45 (1H, bs); (M+1): 465.1, 466.1, 467.2; Yield = 60 %

5-Bromo-1-(2'-Bromobenzoyl)-3-(2-methyl-2-dimethylaminoethoxy)-*1H*-indole (6i; R_1=5-Br, R_2=Me, R_3=H, R_4=2'-Br, X=CO): IR (cm^{-1}): 1686 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 1.36 –1.38 (d, 3H), 2.31 (s, 6H), 2.45 – 2.49 (m, 1H), 2.67 – 2.72 (m, 1H), 4.33 – 4.37 (m, 1H), 7.17 – 7.21 (m, 2H), 7.37 – 7.42 (m, 2H), 7.56 – 7.567 (d, 1H, J = 2.04 Hz), 7.64 – 7.67 (m, 2H), 7.88 – 7.90 (dd, 1H, J = 7.60 Hz); (M+1): 471.3, 473.2; Yield = 60 %.

5-Bromo-1-(benzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6j; R_1=5-Br, R_2=R_3=R_4=H, X=CO): IR (cm^{-1}): 1686 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H), 2.77 – 2.80 (t, 2H), 4.02 – 4.05 (t, 2H), 6.72 (s, 1H), 7.45 – 7.47 (dd, 1H, J = 8.8 Hz), 7.50 – 7.71 (m, 5H), 7.78 (d, 1H, J = 1.90 Hz), 8.15 – 8.17 (d, 1H, J = 8.76 Hz); (M+H): 387.3, 389.3; HPLC purity: 95.20 %; Yield = 65 %.

5-Ethoxy-1-(benzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6k; R_1=5-OEt, R_2=R_3=R_4=H, X=CO): IR (cm^{-1}): 1458, 1671; ^{1}H-NMR ($CDCl_3$/TMS): 1.4 – 1.27 (t, 3H), 2.34 (s, 6H), 2.75 – 2.78 (t, 2H), 4.01 – 4.03 (t, 2H), 4.07 – 4.12 (q, 2H), 6.68 – 8.18 (m, 9H); (M+1): 353.4; HPLC purity: 92.47 %; Yield = 80 %

1-(2'-Bromobenzyl)-3-(1-Methyl-2-dimethylaminoethoxy)-*1H*-indole (6l; R_1=R_2=H, R_3=Me, R_4=2'-Br, X=CH_2): IR (cm^{-1}): 1330, 1565; ^{1}H-NMR ($CDCl_3$/TMS): 1.15 – 1.16 (d, 3H), 2.38 (s, 6H), 3.05 – 3.08 (m, 1H), 3.89 – 3.93 (m, 1H), 4.09 – 4.13 (m, 1H), 5.30 (s, 2H), 7.10 (s, 1H), 7.25 – 7.31 (m, 2H), 7.34 – 7.39 (m, 2H), 7.66 – 7.83 (m, 4H); (M+1): 401, 403; Yield = 80 %.

1-(2'-Bromobenzyl)-3-(2-Methyl-2-dimethylaminoethoxy)-*1H*-indole (6m; R_1=H, R_2=Me, R_3=H, R_4=2'-Br, X=CH_2): IR (cm^{-1}): 745, 1329, 1563; ^{1}H-NMR ($CDCl_3$/TMS): 1.19 (d, 3H), 2.39 (s, 6H), 3.02 – 3.07 (m, 1H), 3.86 – 3.89 (m, 1H), 4.07 – 4.11 (m, 1H), 5.28 (s, 2H), 6.51 – 6.62 (m, 3H), 7.07 – 7.12 (m, 3H), 7.16 – 7.25 (m, 2H), 7.57 – 7.59 (m, 1H), 7.68 – 7.70 (d, 1H); (M+1): 387.4, 389.4; HPLC purity: 97.05 %.

1-(2'-Bromobenzyl)-3-(1-Methyl-2-dimethylaminoethoxy)-*1H*-indole (6n; R_1=R_2=H, R_3=Me, R_4=2'-Br, X=CH_2): IR (cm^{-1}): 745, 1329, 1563; ^{1}H-NMR ($CDCl_3$/TMS): 1.19 (d, 3H), 2.39 (s, 6H), 3.02 – 3.07 (m, 1H), 3.86 – 3.89 (m, 1H), 4.07 – 4.11 (m, 1H), 5.28 (s, 2H), 6.51 – 6.62 (m, 3H), 7.07 – 7.12 (m, 3H), 7.16 – 7.25 (m, 2H), 7.57 – 7.59 (m, 1H), 7.68 – 7.70 (d, 1H); (M+1): 387.4, 389.4; HPLC purity: 97.05 %.

5-Chloro-1-(2'-Bromobenzyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6o; R_1=5-Cl, R_2=R_3=H, R_4=2'-Br, X=CH_2): IR (cm^{-1}): 1286, 1473, 1560; ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H), 2.76 – 2.78 (t, 2H), 4.07 – 4.09 (t, 2H), 5.25 (s, 2H), 6.49 – 6.51 (m, 1H), 6.65 (s, 1H), 7.06 – 7.14 (m, 4H), 7.57 – 7.59 (m, 1H0, 7.65 – 7.66 (d, 1H, J = 1.6 Hz); (M+1): 409.4, 411.4; HPLC purity: 98.06 %; Yield = 50 %

5-Methoxy-1-(2'-Bromobenzyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6p; R_1=5-OMe, R_2=R_3 =H, R_4=2'-Br, X=CH_2): IR (cm^{-1}): 1235, 1494; ^{1}H-NMR ($CDCl_3$/TMS): 2.37 (s, 6H), 2.77 – 2.80 (t, 2H), 3.85 (s, 3H), 4.08 – 4.13 (t, 2H), 5.24 (s, 2H), 6.49 – 7.58 (m, 8H); (M+1): 403, 405.4; HPLC purity: 96.09 %; Yield = 75 %.

5-Bromo-1-(2'-Bromobenzyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6q; R_1=5-Br, R_2=R_3=H, R_4=2'-Br, X=CH_2): IR spectra (cm^{-1}): 1285, 1468, 1559, 1571, 2941; ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H), 2.69 – 2.79 (t, 2H), 4.05 – 4.13 (t, 2H), 5.24 (s, 2H), 6.47 – 6.62 (m, 2H), 7.00 – 7.26 (m, 4H), 7.54 – 7.62 (m, 1H), 7.81 – 7.82 (d, 1H); (M+1): 452.1, 453.1, 455.1; Yield = 70 %

5-Bromo-1-(2'-Bromobenzyl)-3-(1-methyl-2-dimethylaminoethoxy)-*1H*-indole (6r; R_1=5-Br, R_2=H, R_3=Me, R_4=2'-Br, X=CH_2): IR spectra (cm^{-1}): 1026, 1262, 1466, 1569, 2963; ^{1}H-NMR ($CDCl_3$/TMS): 1.32 – 1.34 (d, 3H), 2.36 (s, 6H), 2.51 – 2.55 (m, 1H), 2.70 – 2.75 (m, 1H), 4.31 – 4.33 (m, 1H), 5.26 (s, 2H), 6.48 – 6.51 (m, 1H), 6.71 (s, 1H), 7.02 – 7.04 (d, 1H, J = 8.72 Hz), 7.11 – 7.14 (dd, 2H, J = 2.72 Hz), 7.21 – 7.24 (dd, 1H, J = 1.84 Hz and 8.76 Hz), 7.57 – 7.59 (m, 1H), 7.79 – 7.80 (d, 1H, J = 1.76Hz); (M+1): 466, 468; Yield = 60 %.

6-Chloro-1-(2'-Bromobenzyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6s; R_1=6-Cl, R_2=R_3=H, R_4=2'-Br, X=CH_2): IR (cm^{-1}): 1324, 1467; ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H), 2.74 – 2.80 (t, 2H), 4.02 – 4.08 (t, 2H), 5.22 (s, 2H), 6.49 – 6.54 (m, 1H), 6.59 (s, 1H), 7.00 – 7.05 (dd, 1H), 7.11 – 7.16 (m, 3H), 7.57 – 7.61 (m, 2H); HPLC purity: 98.20 %; Yield = 65 %.

RESULTS AND DISCUSSION

The required starting material i.e. substituted 1-acetyl indoxyls **1** were synthesized from differently substituted anthranilic acids or substituted 2-halo benzoic acids using literature reported methods [17, 18]. These various substituted 1-acetyl indoxyls **1** were reacted with dimethylaminoethyl chlorides **2** to obtain 1-acetyl-3-aminoaloxy indoles **3**. These were further deacetylated with sodium hydroxide base to obtain the intermediate 3-aminoaloxy-*1H*-indoles **4**. Reaction of these with substituted benzyl bromides and benzoyl chlorides **5** resulted in targeted compounds substituted-1-(2'-Bromobenzoyl)-3-(substituted-2-dimethyl amino ethoxy)-*1H*-indole and substituted-1-(2'-Bromobenzyl)-3-(substituted-2-dimethyl amino ethoxy)-*1H*-indole.

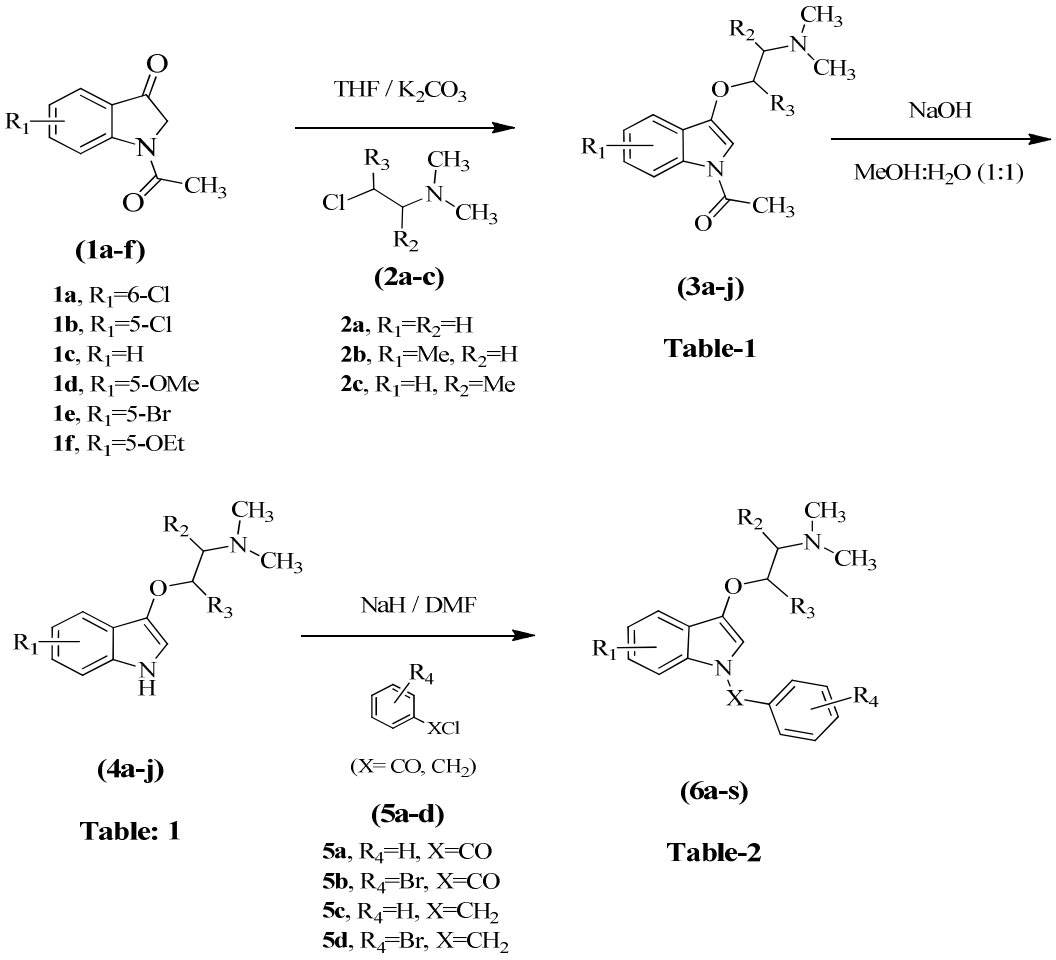
Synthesis of compounds with α-methyl and β-methyl substituents in the side chain was obtained following essentially the same route, using appropriately substituted dimethylamino ethyl chlorides, that were procured commercially.

6-Chloro-3-(2-dimethylamino-ethoxy)-1-acetyl-*1H*-indole **3a** was prepared by reaction of corresponding 6-Chloro-1-acetyl indoxyl with 2-chloro-N,N-dimethylethanamine hydrochloride in presence of potassium carbonate as base, under reflux condition. There was presence of desired peaks at δ 2.37 (s, 6H, -N(C**H**$_3$)$_2$), 2.66 (s, 3H, COC**H**$_3$), 2.77 – 2.81 (t, 2H, Me$_2$NC**H**$_2$), 4.43 – 4.46 (t, 2H, OC**H**$_2$), 7.20 – 7.22 (d, 1H, J = 8.20 Hz, aromatic), 7.36 – 7.39 (dd, 1H, J = 8.79, 1.54 Hz, aromatic), 7.93 (s, 1H, aromatic) and 8.73 (d, 1H, aromatic) in ^{1}H-NMR ($CDCl_3$/TMS, 400 MHz) spectrum. The ESI-MS analysis was consistent with (M+1) peak at 281.3 amu. These data confirmed the formation of **3a**.

The intermediate **3a** was hydrolyzed with sodium hydroxide in water: methanol (1:1) at 60 – 65 ^{o}C. The product 6-chloro-3-(2-dimethylaminoethoxy)-*1H*-indole **4a** showed peaks at 3430 cm^{-1} (NH stretching) in IR spectrum. The proton NMR ($CDCl_3$/TMS, 400 MHz) showed desired peaks at δ 2.36 (s, 6H, $N(CH_3)_2$), 2.76 – 2.78 (t, 2H, Me_2NCH_2), 4.07 – 4.10 (t, 2H, OCH_2), 7.20 – 7.22 (d, 1H, d, J = 2.32 Hz, aromatic), 6.94 – 6.96 (dd, 1H, J = 1.67, 8.47 Hz, aromatic), 7.28 (d, 1H, aromatic), 7.50 – 7.52 (d, 1H, J = 8.45 Hz; aromatic) and 9.48 (s, 1H, N**H**). The ESI-MS analysis was consistent with (M+1) peak at 239 amu. These data confirmed the formation of **4a**.

Intermediate **4a** was reacted with commercially available 2'-Bromo benzoyl chloride in strong base like sodium hydride and DMF as a solvent. The desired product was purified by column chromatography and characterized. There was presence of C=O stretching peak at 1671 cm^{-1}. The proton NMR ($CDCl_3$/TMS, 400 MHz) showed signals at δ 2.32 (s, 6H), 2.71 – 2.76 (t, 2H), 3.97 (t, 2H), 6.2 (s, 1H), 7.26 – 7.72 (m, 6H, aromatic), 8.52 (s, 1H, aromatic). Further, presence of (M+1) peak at 421.1 and 423.1 amu in ESI-MS confirmed the formation of desired compound. 6-chloro-1-(2'-Bromobenzoyl)-3-(2-dimethyl amino ethoxy)-*1H*-indole **6a**.

Scheme-1



(1a-f)

1a, R_1=6-Cl
1b, R_1=5-Cl
1c, R_1=H
1d, R_1=5-OMe
1e, R_1=5-Br
1f, R_1=5-OEt

(2a-c)

2a, R_1=R_2=H
2b, R_1=Me, R_2=H
2c, R_1=H, R_2=Me

(3a-j)

Table-1

(4a-j)

Table: 1

(5a-d)

5a, R_4=H, X=CO
5b, R_4=Br, X=CO
5c, R_4=H, X=CH_2
5d, R_4=Br, X=CH_2

(6a-s)

Table-2

Table-1: Synthesis of intermediates 3a-j and 4a-j

Intermediates	R_1	R_2	R_3
3a, 4a	6-Cl	H	H
3b, 4b	5-Cl	H	H
3c, 4c	H	H	H
3d, 4d	H	H	Me
3e, 4e	5-OMe	H	H
3f, 4f	5-Br	H	H
3g, 4g	5-Br	Me	H
3h, 4h	5-Br	H	Me
3i, 4i	5-OEt	H	H
3j, 4j	H	Me	H

Using similar conditions another targeted compound e.g. **6p** was prepared by reacting corresponding intermediate **3e** with commercially available 2'-Bromo benzyl chloride **5d** in presence of strong base like sodium hydride and DMF as solvent. The product was fully characterized with spectral data. Thus the proton NMR ($CDCl_3$/TMS, 400 MHz) showed peaks at δ 2.37 (s, 6H, N(C**H**$_3$)$_2$), 2.77 – 2.80 (t, 2H, C**H**$_2$-N), 3.85 (s, 3H, OC**H**$_3$), 4.08 – 4.13 (t, 2H, OC**H**$_2$), 5.24 (s, 2H, C**H**$_2$-benzylic), 6.49 – 7.58 (m, 8H, aromatic). The (M+1) peaks were observed at 403 and 405.4 amu in ESI-MS analysis, confirming the formation of desired compound 5-methoxy-1-(2'-Bromobenzyl)-3-(2-dimethyl amino ethoxy)-*1H*-indole, **6 (i.e. 6p)**.

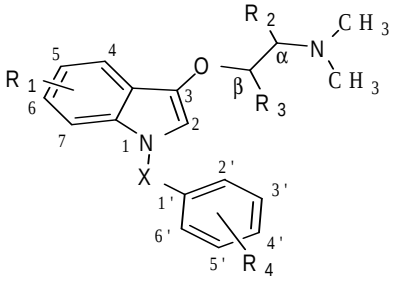
Radioligand Binding Data *(In-Vitro)*

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

Compounds were investigated by the reported procedure [19]. 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 minutes at 37 °C. The reaction was terminated by rapid vacuum filtration onto glass fiber filters. Radioactivity trapped onto the filters was determined and compared to control values in order to ascertain any interactions of test compound (s) with the cloned serotonin - 5-HT$_6$ binding site. The binding study was carried out at Novascreen, USA.

Structure activity relationship (SAR): All the compounds were tested in radioligand binding assay at Novascreen, USA. The most potent compounds **6g** and **6j** with Ki 18.4 and 10.2 nM respectively, indicated that these modifications are tolerated. The substitutions like halo and alkoxy are well tolerated at C-5 of indole. Benzoyl derivatives were found much tolerated as compared with benzyl derivatives. The smaller alkyls like methyl are tolerated at α and β positions in the side chain.

Table. 2 5-HT$_6$R binding affinities[a]



Comp.	R_1	R_2	R_3	R_4	X	5-HT$_6$ Ki, nM	%Inhibition at 1μM
6a	6-Cl	H	H	H	CO	-	41.91
6b	6-Cl	H	H	2'-Br	CO	-	52.00
6c	5-Cl	H	H	H	CO	38.1	-
6d	H	H	H	2'-Br	CO	-	98.37
6e	H	H	Me	2'-Br	CO	160	-
6f	H	H	H	H	CO	-	73.43
6g	5-OMe	H	H	2'-Br	CO	18.4	-
6h	5-Br	H	H	2'-Br	CO	-	97.71
6i	5-Br	Me	H	2'-Br	CO		84.00
6j	5-Br	H	H	H	CO	10.2	-
6k	5-OEt	H	H	H	CO	-	72.20
6l	H	H	Me	2'-Br	CH_2	22.5	-
6m	H	Me	H	2'-Br	CH_2	91.9	-
6n	H	H	Me	2'-Br	CH_2	>500	-
6o	5-Cl	H	H	2'-Br	CH_2	64.0	-
6p	5-OMe	H	H	2'-Br	CH_2	-	95.64
6q	5-Br	H	H	2'-Br	CH_2	-	96.26
6r	5-Br	H	Me	2'-Br	CH_2	-	61.48
6s	6-Cl	H	H	2'-Br	CH_2	-	77.48

[a]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 Ki value reported was an average of the assay conducted in duplicate.*

CONCLUSION

We have designed and synthesized a novel series of N_1-substituted-3-aminoalkoxy indoles as 5-HT_6 receptor ligands. These synthesized compounds were modification of standard 5-HT_6 receptor antagonist **MS-245**. The tryptamine side chain was replaced with substituted aminoalkoxy side chain with simultaneous replacement of indole N_1 protection (SO_2 group was replaced with CO and CH_2 groups). The initial finding revealed that all these modifications are well tolerated and does retain the 5-HT_6 receptor binding affinity. The active compounds **6g** and **6j** (h5-HT_6 receptor Ki = 18.4 and 10.2 nM respectively) from the presented series were selected for evaluating pharmacokinetic and pharmacological studies and investigations are under progress.

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