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Synthesis and activity of conformationally rigidized N_1-substituted-3-amino alkoxy indoles using intramolecular Heck reaction

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ABSTRACT

A novel series of conformationally rigidized N_1-substituted-3-aminoalkoxy indoles (tetracyclic derivatives) were designed and synthesized using intramolecular Heck cyclization in presence of tetrakis triphenyl phosphine palladium (0) catalyst. The compounds were characterized with spectral data and were tested for human 5-HT_6 receptor binding affinities. All the compounds showed moderate binding affinities towards human 5-HT_6 receptor.

Keywords: 5-HT_6 receptor, binding affinities, CNS research, Alzheimer's disease.

INTRODUCTION

The 5-HT_6 receptor (5-HT_6R) is cloned member of the serotonin receptor family, which comprises currently a total of 14 distinct receptors with a variety of different functions and diverse localization patterns. It is positively coupled to adenylate cyclase and rather unique in its structure, exhibiting only 30-40% sequence homology versus all the other serotonin receptor subtypes. High levels of 5-HT_6R were found in the olfactory tubercle, striatum, frontal cortex and hippocampus with almost no localization in the periphery [1-7]. This makes 5-HT_6R a promising target in the area of CNS research.

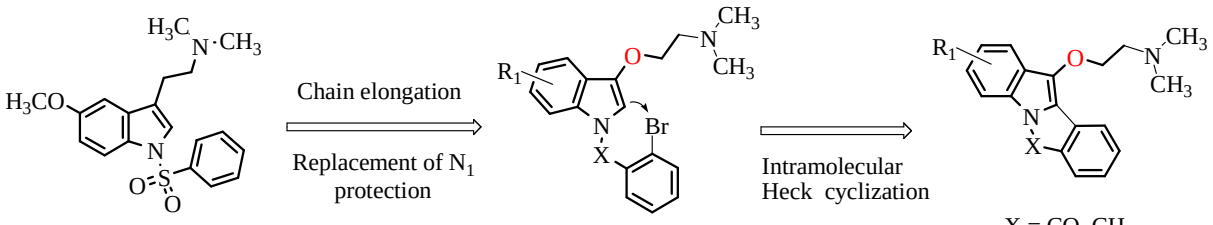
Ligands for the 5-HT_6R may be useful in the treatment of CNS disorders such as schizophrenia, depression, Alzheimer's disease (AD) [8–12] and metabolic disorders like obesity. Up to date, there have been various 5-HT_6R antagonists developed, among which few compounds have entered into clinical trials like **SB-742457** and **SUVN-502** for cognition, **PRX-07034** for obesity

and **LY-483518 (SGS-518)** for schizophrenia are in advanced stages of clinical studies. The clinical study data for all these compounds are reported in literature [13-16].

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). Electronspray 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 **MS-245 (I)** [17, 18] as most potent 5-HT$_6$ receptor antagonist. Based upon this lead structure, earlier we have designed and synthesized a novel series of *N$_1$*-substituted-3-aminoalkoxy indole as potential 5-HT$_6$ receptor ligand **II** [19]. Based upon our earlier reported conformationally rigidized compounds [20-23], we have designed a novel series of conformationally rigidized *N$_1$*-substituted-3-aminoalkoxy indoles **III** (tetracyclic derivatives) (Figure-1). The **compounds-II** were intramolecularly cyclized through C-2 position of indole using Heck reaction [24-26] to obtain the targeted **compounds-III**.



MS-245
Ki = 2.2 nM
(I)

Earlier series
(II)

Designed series
(III)

Figure 1: Design of ligands.

General procedure for the synthesis of 2a-c:
The intermediate **1a-c** (1 mmole) was added to a stirring mixture of potassium carbonate (2 mmole) and dry acetonitrile (8-10 volumes). Heated the reaction mass at 75-80 ^{o}C for 40-45 min. Cooled the mass to 40 ^{o}C and added 1-bromo-2-chloro ethane (2.5 mmole) and further heated to 75-80 ^{o}C and stirred for 5 hr. After completion of the reaction (based on TLC observations), cooled the mass to RT and slowly quenched over appropriate quantities of crushed ice. The mass was extracted into excess volumes of ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain technical product, which was purified by flash column chromatography using ethyl acetate and n-Hexane (1:1) as an eluent to obtain pure intermediates **2a-c**.

5-Chloro-3-(2-chloroethoxy)-1-acetyl-*1H*-indole (2a; R_1=5-Cl).
Yield: 60 %; Melting range: 124.3 – 126.5 ^oC; IR (KBr, cm^{-1}): 1694 (C=O); ^{1}H-NMR (DMSO-d_6): 2.57 (s, 3H, COC**H**$_3$), 4.01 – 4.03 (t, 2H, C**H**$_2$Cl), 4.34 – 4.36 (t, 2H, C**H**$_2$O), 7.37 – 7.51 (m, 2H, Ar-H), 7.56 (s, 1H, Ar-H), 8.30 – 8.32 (d, 1H, Ar-H); MS: 273.3 (M+1).

6-Chloro-3-(2-chloroethoxy)-1-acetyl-*1H*-indole (2b; R_1=6-Cl).
Yield: 65 %; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1698 (C=O); ^{1}H-NMR (DMSO-d_6): 2.55 (s, 3H, COC**H**$_3$), 4.00 – 4.03 (t, 2H, C**H**$_2$Cl), 4.33 – 4.36 (t, 2H, C**H**$_2$O), 7.49 – 7.55 (m, 2H, Ar-H), 7.64 – 7.65 (m, 1H, Ar-H), 8.25 – 8.27 (d, 1H, Ar-H); MS: 273.2 (M+1).

5-Methoxy-3-(2-chloroethoxy)-1-acetyl-*1H*-indole (2c; R_1=5-OMe).
Yield: 60 %; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1704 (C=O); ^{1}H-NMR (DMSO-d_6): 2.57 (s, 3H, -COC**H**$_3$), 3.83 (s, 3H, -OC**H**$_3$), 3.99 – 4.02 (t, 2H, C**H**$_2$Cl), 4.31 – 4.33 (t, 2H, C**H**$_2$O), 7.02 – 7.35 (m, 2H, Ar-H), 7.46 (s, 1H, Ar-H), 8.15 – 8.17 (d, 1H, Ar-H); MS: 268.3 (M+1).

General procedure for the synthesis of 3a-c:
A solution of **2a-c** (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 (based upon TLC observations), cooled the reaction mass to 25 – 30 ^oC and distilled off solvent under reduced pressure. Added water (10 volumes) 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 masses. The product was purified by flash column chromatography over silica gel using ethyl acetate and n-Hexane (1:1) to obtain the desired intermediates **3a-c**.

5-Chloro-3-(2-chloroethoxy)-*1H*-indole (3a; R_1=5-Cl).
Yield: 60 %; Syrupy mass; IR (KBr, cm^{-1}): 1466, 3440 (-NH); ^{1}H-NMR (DMSO-d_6): 3.92 – 3.95 (t, 2H, C**H**$_2$Cl), 4.20 – 4.23 (t, 2H, C**H**$_2$O), 7.04 – 7.10 (m, 2H, Ar-H), 7.7.29 – 7.39 (d, 1H, Ar-H), 7.44 (d, 1H, Ar-H), 10.8 (s, 1H, -NH); MS: 228.2, 230.2 (M-1).

6-Chloro-3-(2-chloroethoxy)-*1H*-indole (3b; R_1=6-Cl).
Yield: 70 %; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1275, 1463, 3435; ^{1}H-NMR (DMSO-d_6): 3.92 – 3.95 (t, 2H, C**H**$_2$Cl), 4.20 – 4.23 (t, 2H, C**H**$_2$O), 7.08 (d, 1H, Ar-H), 7.14 – 7.16 (dd, 1H, Ar-H), 7.25 – 7.27 (d, 1H, Ar-H), 7.58 (d, 1H, Ar-H), 10.75 (s, 1H, -NH); MS: 228.2, 230.1 (M-1).

5-Methoxy-3-(2-chloroethoxy)-*1H*-indole (3c; R_1=5-OMe).
Yield: 75 %; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 3440 (CO); ^{1}H-NMR (DMSO-d_6): 3.81 (s, 3H, -OC**H**$_3$), 3.98 – 4.01 (t, 2H, C**H**$_2$Cl), 4.22 – 4.25 (t, 2H, C**H**$_2$O), 7.10 – 7.35 (m, 2H, Ar-H), 7.42 – 7.59 (m, 3H, Ar-H), 10.8 (s, 1H, -NH); MS: 224 (M-1).

General procedure for the synthesis of 4a-c:
Added a solution of **3a-c** (1 mmole) in N,N-dimethyl formamide (4 volumes) to a stirring solution of potassium carbonate (4 mmoles), N,N-dimethyl formamide (4 volumes) and N,N-dimethylamine hydrochloride (2.5 mmoles). Heated the reaction mass to 100 - 110 ^oC and stirred for 6 hr. After completion of the reaction (TLC observations), cooled the reaction mass to 25 –

30 ^{o}C Added water (10 volumes) 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, which were purified by flash column chromatography over silica gel using 1% triethylamine : ethyl acetate : Hexane to obtain the pure intermediates **4a-c**.

5-Chloro-3-(2-dimethylaminoethoxy)-*1H*-indole (4a; R_1=5-Cl).
Yield: 50%; Melting range:103 – 108.2 ^{o}C; IR (KBr, cm^{-1}): 3153 (-NH), 1459; ^{1}H-NMR ($CDCl_3$/TMS): 2.37 (s, 6H, NMe_2), 2.76 – 2.79 (t, 2H, NC**H**$_2$), 4.08 – 4.11 (t, 2H, OC**H**$_2$), 6.72 – 7.62 (m, 5H, Ar-H & NH); MS: 239.1 (M+1); HPLC purity: 99 %;

6-Chloro-3-(2-dimethylaminoethoxy)-*1H*-indole (4b; R_1=6-Cl).
Yield: 55%; Syrupy mass; IR (KBr, cm^{-1}): 3430 (-NH); ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H, NMe_2), 2.76 – 2.78 (t, 2H, NC**H**$_2$), 4.07 – 4.10 (t, 2H, OC**H**$_2$), 6.70 – 6.71 (d, 1H, J = 2.3 Hz, Ar-H), 6.94 – 6.96 (dd, 1H, J = 1.64, 8.46 Hz, Ar-H), 7.28 (d, 1H, J = 1.51 Hz, Ar-H), 7.50 – 7.52 (d, 1H, J = 8.45 Hz, Ar-H), 9.48 (s, 1H, Ar-H); MS: 239.3 (M+1); HPLC purity = 98.02 %.

5-Methoxy-3-(2-dimethylaminoethoxy)-*1H*-indole (4c; R_1=5-OMe).
Yield: 65 %; Syrupy mass; IR (KBr, cm^{-1}): 1239, 3119 (-NH); ^{1}H-NMR ($CDCl_3$/TMS): 2.37 (s, 6H, NMe_2), 2.78 – 2.81 (t, 2H, NC**H**$_2$), 3.84 (s, 3H, OC**H**$_3$), 4.09 – 4.12 (t, 2H, OC**H**$_2$), 6.69 – 7.17 (m, 4H, Ar-H), 7.48 (s, 1H, -NH); MS: 235.2 (M+1); HPLC purity: 95.47 %.

General procedure for the synthesis of 6a-f:
Sodium hydride (50% on mineral oil, 1.5 mmole) was added to a solution of **4a-c** (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** & **5b** (1 mmole) in N, N-dimethyl formamide (1 volume) was added to the reaction mass over 5-10 min and stirred the reaction mass at 25 – 30 ^{o}C for 1 hr. After completion of the raction (TLC observations), added water (10 volumes) and extracted the product with appropriate volumes of 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 compounds **6a-f**.

(Note: The substituted intermediate **5a-b** were commercially procured from Aldrich).

5-Chloro-1-(2'-bromobenzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6a; R_1=5-Cl, X=CO).
Yield: 65%; Syrupy mass; IR spectra ($CHCl_3$, cm^{-1}): 1687 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H, NMe_2), 2.75 – 2.79 (t, 2H, NC**H**$_2$), 4.00 – 4.03 (t, 2H, OCH_2), 6.10 (s, 1H, Ar-H), 7.30 – 7.80 (m, 6H, Ar-H), 8.49 (s, 1H, Ar-H); MS: 421.2, 423.2 (M+1).

6-Chloro-1-(2'-bromobenzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6b; R_1=6-Cl, X=CO).
Yield: 75%; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1671 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.31 (s, 6H, NMe_2), 2.71 – 2.77 (t, 2H, NCH_2), 3.98 (t, 2H, OCH_2), 6.22 (s, 1H, Ar-H), 7.25 – 7.77 (m, 6H, Ar-H), 8.55 (s, 1H, Ar-H); MS: 421.1, 423.1 (M+1); HPLC purity: 99 %.

5-Methoxy-1-(2'-bromobenzoyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6c; R_1=5-OMe, X=CO):
Yield: 50%; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1678 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.33 (s, 6H, NMe_2), 2.73 – 2.79 (bs, 2H, NC**H**$_2$), 3.87 (s, 3H, OC**H**$_3$), 4.09 – 4.13 (bs, 2H, OC**H**$_2$), 6.17 – 8.50 (m, 8H, Ar-H); MS: 417.1, 419.1 (M+1); HPLC purity: 95.38 %.

5-Chloro-1-(2'-bromobenzyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6d; R_1=5-Cl, X=CH_2).
Yield: 50%; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1286, 1473, 1560; ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H, NMe_2), 2.76 – 2.78 (t, 2H, C**H**$_2$N), 4.07 – 4.09 (t, 2H, OC**H**$_2$), 5.25 (s, 2H, N_1-benzylic), 6.49 – 6.51 (m, 1H, Ar-H), 6.65 (s, 1H, Ar-H), 7.06 – 7.14 (m, 4H, Ar-H), 7.57 – 7.59 (m, 1H, Ar-H), 7.65 – 7.66 (d, 1H, J = 1.6 Hz, Ar-H); MS: 409.4, 411.4 (M+1); HPLC purity: 98.06 %.

6-Chloro-1-(2'-bromobenzyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6e; R_1=6-Cl, X=CH_2).
Yield: 65%; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1324, 1467; ^{1}H-NMR ($CDCl_3$/TMS): 2.36 (s, 6H, NMe_2), 2.74 – 2.80 (t, 2H, NC**H**$_2$), 4.02 – 4.08 (t, 2H, OC**H**$_2$), 5.22 (s, 2H, N_1-benzylic), 6.49 – 6.54 (m, 1H, Ar-H), 6.59 (s, 1H, Ar-H), 7.00 – 7.05 (dd, 1H, Ar-H), 7.11 – 7.16 (m, 3H, Ar-H), 7.57 – 7.61 (m, 2H, Ar-H); HPLC purity: 98.20 %.

5-Methoxy-1-(2'-bromobenzyl)-3-(2-dimethylaminoethoxy)-*1H*-indole (6f; R_1=5-OMe, X=CH_2).
Yield: 75%; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1235, 1494; ^{1}H-NMR ($CDCl_3$/TMS): 2.37 (s, 6H, NMe_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, N_1-benzylic), 6.49 – 7.58 (m, 8H, Ar-H); MS: 403, 405.4 (M+1); HPLC purity: 96.09 %.

General procedure for the synthesis of targeted compounds 7a-f:
Dry potassium acetate (2 mmoles) and tetrakis triphenyl phosphine palladium (0) catalyst (0.05 mmole) was added to a stirred solution of intermediate **6a-f** (1 mmole) and N,N-dimethyl acetamide (DMA, 5 volumes) under nitrogen atmosphere. The reaction mass was heated to 115 – 120 ^{o}C and stirred for 3 hr. After completion (TLC) of reaction, mass was cooled to 25 – 30 ^{o}C. Added water and extracted the product into appropriate volumes of ethyl acetate. The combined organic layers were concentrated under reduced pressure to obtain gummy masses. These were purified by flash chromatography over silica gel using 1 % methanol in chloroform to obtain the pure products **7a-f**.

2-Chloro-10-(2-N,N-dimethylamino ethoxy)-4b-aza indeno [2,1-a]indene-5-one (7a, R_1=2-Cl, X=CO).
Yield: 30%; Thick syrupy mass; IR (KBr, cm^{-1}): 1686 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.35 (s, 6H, Me_2N-), 2.75 – 2.78 (t, 2H, NC**H**$_2$), 4.01 – 4.03 (2H, t; -OC**H**$_2$), 7.20 – 7.80 (m, 6H, Ar-H), 8.45 (s, 1H, Ar-H); MS: 341.4 (M+1); HPLC purity: 97.4 %.

3-Chloro-10-(2-N,N-dimethylamino ethoxy)-4b-aza indeno [2,1-a]indene-5-one (7b, R_1=3-Cl, X=CO):
Yield: 40%; Thick syrupy mass; IR ($CHCl_3$, cm^{-1}): 1678 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.24 (s, 6H, Me_2N), 2.66 – 2.69 (t, 2H, C**H**$_2$N), 4.40 – 4.43 (t, 2H, -OC**H**$_2$), 7.36 – 7.38 (dd, 1H, J = 1.61, 8.22 Hz; Ar-H), 7.61 – 7.65 (m, 1H, Ar-H), 7.69 (d, 1H, J = 1.51 Hz, Ar-H), 7.85 – 7.89 (m, 2H, Ar-H), 8.01 – 8.02 (d, 1H, Ar-H), 8.16 – 8.18 (d, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$,

400MHz): 45.83, 57.87, 68.93, 106.30, 116.84, 117, 121, 126.6, 128.7, 131, 133, 134, 143, 162; MS: 341.1 (M+1).

2-Methoxy-10-(2-N,N-dimethylamino ethoxy)-4b-aza indeno [2,1-a]indene-5-one (7c, R_1=2-OMe, X=CO).
Yield: 25%; Thick syrupy mass; IR (KBr, cm^{-1}): 1678 (C=O); ^{1}H-NMR ($CDCl_3$/TMS): 2.24 (s, 6H, Me_2N), 2.64 – 2.67 (t, 2H, C**H**$_2$NMe_2), 3.83 (s, 3H, OC**H**$_3$), 4.37 – 4.40 (t, 2H, -OC**H**$_2$), 7.03 – 7.06 (dd, 1H, J = 1.80, 8.10 Hz, Ar-H), 7.26 – 7.27 (d, 1H, J = 2.0 Hz, Ar-H), 7.52 – 7.61 (m, 2H, Ar-H), 7.82 – 7.86 (m, 1H, Ar-H), 8.00 – 8.02 (d, 1H, Ar-H), 8.11 – 8.12 (d, 1H, Ar-H); MS: 337.5 (M+1).

2-((2-Chloro-6H-isoindolo[2,1-a]indol-11-yl)oxy)-N,N-dimethylethanamine (7d; R_1=2-Cl, X=CH_2):
Yield: 35%; Syrupy mass: IR ($CHCl_3$, cm^{-1}): 1216, 1473, 3019; ^{1}H-NMR ($CDCl_3$/TMS): 2.22 (s, 6H, N**Me**$_2$), 2.65 – 2.68 (t, 2H, C**H**$_2$N), 4.01 – 4.04 (t, 2H, C**H**$_2$O), 5.22 (2H, s, N_1-benzylic), 6.49 – 6.52 (m, 1H, Ar-H), 7.11 – 7.14 (m, 1H, Ar-H), 7.20 – 7.24 (m, 2H, Ar-H), 7.35 – 7.37 (d, 1H, J = 8.80 Hz, Ar-H), 7.47 (d, 1H, J = 1.91 Hz, Ar-H), 7.64 – 7.66 (d, 1H, J = 1.28 Hz, Ar-H); MS: 327.2 (M+1); HPLC purity: 91 %.

2-((3-Chloro-6H-isoindolo[2,1-a]indol-11-yl)oxy)-N,N-dimethylethanamine (7e, R_1=3-Cl, X=CH_2).
Yield: 25%; Syrupy mass; IR (KBr, cm^{-1}): 1320, 1469; ^{1}H-NMR ($CDCl_3$/TMS): 2.22 (s, 6H, NMe_2), 2.64 – 2.67 (t, 2H, NC**H**$_2$), 4.00 – 4.03 (t, 2H, OC**H**$_2$), 5.36 (s, 2H, N_1-benzylic), 6.51 (d, 1H), 6.97 – 7.06 (m, 1H, Ar-H), 7.22 – 7.25 (m, 2H, Ar-H), 7.47 – 7.50 (m, 2H, Ar-H), 7.67 (m, 1H, Ar-H); MS: 327.5 (M+1); HPLC purity: 94.86 %;

2-((2-Methoxy-6H-isoindolo[2,1-a]indol-11-yl)oxy)-N,N-dimethylethanamine (7f, R_1=5-OMe, X=CH_2).
Yield: 30%; Syrupy mass; IR ($CHCl_3$, cm^{-1}): 1235, 1494; ^{1}H-NMR ($CDCl_3$/TMS): 2.37 (s, 6H, NMe_2), 2.77 – 2.80 (t, 2H, NC**H**$_2$), 3.85 (s, 3H, OC**H**$_3$), 4.08 – 4.13 (t, 2H, OC**H**$_2$), 5.24 (s, 2H, N_1-benzylic), 6.49 – 6.52 (m, 1H, Ar-H), 6.81 – 6.84 (dd, 1H, J = 2.48, 8.88 Hz, Ar-H), 7.04 – 7.06 (d, 1H, J = 8.96 Hz; Ar-H), 7.10 – 7.12 (m, 2H, Ar-H), 7.56 – 7.58 (m, 1H, Ar-H); MS: 323.5.

RESULTS AND DISCUSSION

The required starting material substituted 1-acetylindoxyls **1a-c** were synthesized from reported methods [27, 28]. The synthesis of targeted compounds **7a-c** was carried out through intermediates **2a-c** to **6a-c (scheme-1)**. The intermediates **6a-c** were earlier tested for affinity towards 5-HT_6 receptor. To understand the role of structural regidizations in those molecules, we have further designed and synthesized a novel series of tetracyclic compounds. We have made an attempt to form C-C bond using palladium catalyzed intramolecular Heck reaction between C-2 of indole and the carbon ortho to benzoyl or benzyl group on the benzene ring **(scheme-1)**. The compounds were tested for *in-vitro* radioligand binding assay and results are discussed.

Intermediate **1a** was reacted with commercially available 1-bromo-2-chloro ethane in presence of potassium carbonate and acetonitrile as a solvent. The desired product was purified by flash column chromatography and well characterized. There was presence of C=O stretching peak at 1694 cm^{-1}. The PMR (400 MHz/DMSO-d_6) showed the expected signals at δ 2.57 (s, 3H, N_1-COC**H**$_3$), 4.01 – 4.03 (t, 2H, -C**H**$_2$Cl), 4.34 – 4.36 (t, 2H, -C**H**$_2$O), 7.37 – 7.51 (m, 2H, Ar-H), 7.56 (s, 1H, Ar-H), 8.30 – 8.32 (d, 1H, Ar-H). Further, presence of (M+1) peak at 273.3 amu in ESI-MS confirmed the formation of desired intermediate 5-Chloro-3-(2-chloroethoxy)-1-acetyl-*1H*-indole **(2a; R_1=5-Cl)**.

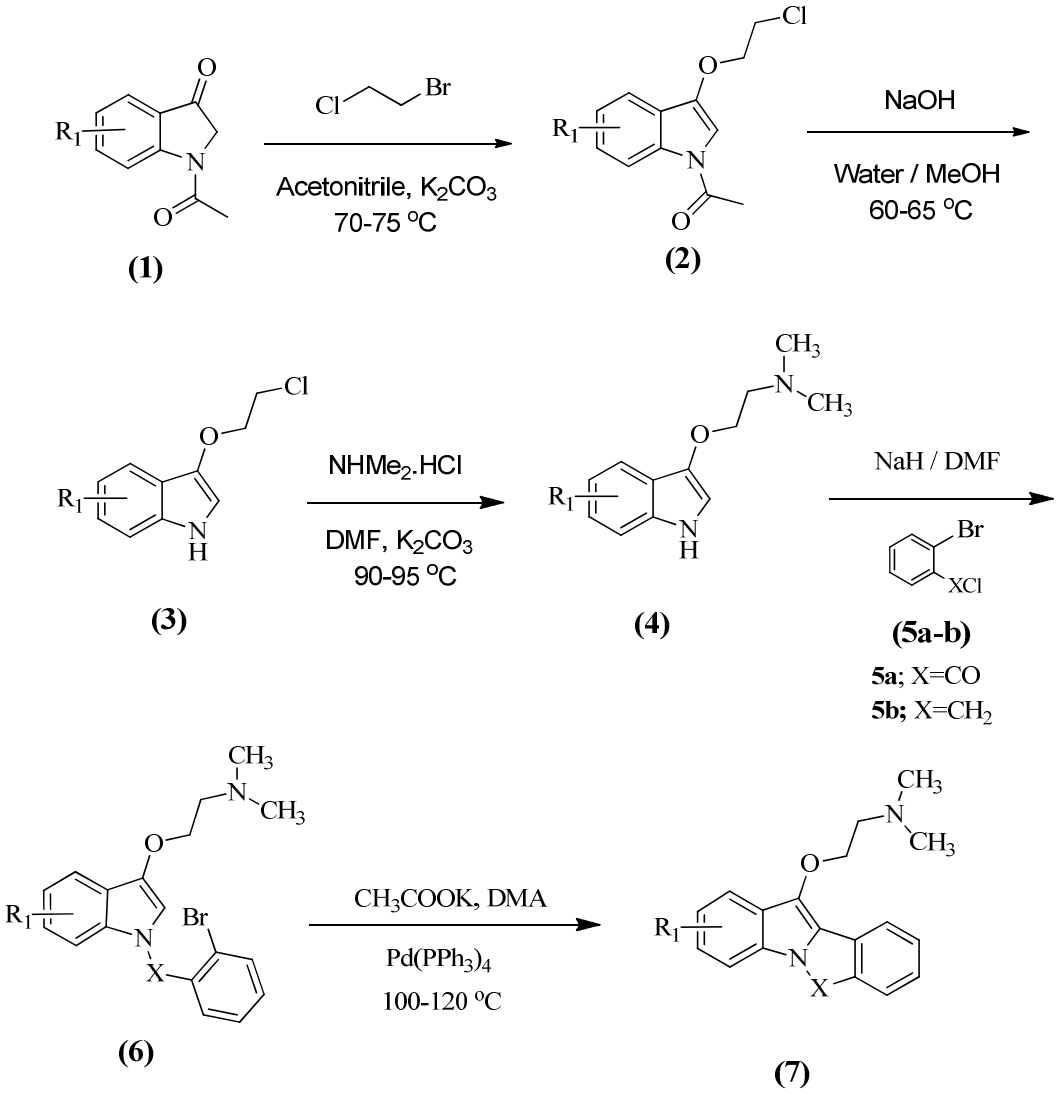
Intermediate **2a** was reacted with sodium hydroxide in presence of water and methanol under heating conditions. The isolated product was purified by flash column chromatography and characterized. There C=O stretching peak was disappeared and new –NH stretching peak was observed at 3440 cm^{-1}. The PMR (400 MHz/DMSO-d_6) showed the expected signals at δ 3.92 – 3.95 (t, 2H, C**H**$_2$Cl), 4.20 – 4.23 (t, 2H, C**H**$_2$O), 7.04 – 7.10 (m, 2H, Ar-H), 7.7.29 – 7.39 (d, 1H, Ar-H), 7.44 (d, 1H, Ar-H), 10.8 (s, 1H, -NH). Further, presence of (M-1) peak at 228.2 amu in ESI-MS confirmed the formation of desired intermediate 5-Chloro-3-(2-chloroethoxy)-*1H*-indole **(3a; R_1=5-Cl).**

Intermediate **3a** was further reacted with N,N-dimethylamine hydrochloride (Me_2NH.HCl) in presence of potassium carbonate as base and N,N-dimethyl formamide (DMF) as a solvent. The reaction was generally carried out at higher temperatures. The isolated product was purified by flash column chromatography and characterized. There was presence of –NH peak at 3153 cm^{-1} in IR spectrum. The PMR (400 MHz/DMSO-d_6) showed the expected signals at δ 2.37 (s, 6H, NMe_2), 2.76 – 2.79 (t, 2H, C**H**$_2$$NMe_2$), 4.08 – 4.11 (t, 2H, C**H**$_2$O), 6.72 – 7.62 (m, 5H, Ar-H and N**H**); further, presence of (M+1) at 239.1 in ESI-MS spectrum confirmed the formation of desired intermediate **5-Chloro-3-(2-dimethylaminoethoxy)-*1H*-indole (4a; R_1=5-Cl).**

Intermediate **4a** was reacted with commercially available 2'-bromo benzoyl chloride **5a** in presence of 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 frequency at 1687 cm^{-1}. The proton NMR (400 MHz/DMSO-d_6) showed signals at δ 2.36 (s, 6H, NMe_2), 2.75 – 2.79 (t, 2H, NC**H**$_2$), 4.00 – 4.03 (t, 2H, OC**H**$_2$), 6.10 (s, 1H, Ar-H), 7.30 – 7.80 (m, 6H, Ar-H), 8.49 (s, 1H, Ar-H). Further, presence of characteristic (M+1) peak at 421.2 and 423.2 amu (due to bromine isotopes) in ESI-MS confirmed the formation of desired product 5-chloro-1-(2'-bromobenzoyl)-3-(2-dimethyl amino ethoxy)-*1H*-indole **6a, (R_1=5-Cl)**.

Using similar conditions another intermediate **6d** was prepared by reacting corresponding intermediate **4a** with commercially available 2'-bromobenzyl chloride **5b** in presence of strong base like sodium hydride and DMF as solvent. The product was isolated and fully characterized. The PMR (TMS/$CDCl_3$, 400 MHz) analysis showed peaks at δ 2.36 (s, 6H, -NMe_2), 2.76 – 2.78 (t, 2H, C**H**$_2$$NMe_2$), 4.07 – 4.09 (t, 2H, -C**H**$_2$O), 5.25 (s, 2H, N_1-benzylic), 6.49 – 6.51 (m, 1H, Ar-H), 6.65 (s, 1H, Ar-H), 7.06 – 7.14 (m, 4H, Ar-H), 7.57 – 7.59 (m, 1H, Ar-H), 7.65 – 7.66 (d, 1H, J = 1.6 Hz, Ar-H). Further, the (M+1) peaks were observed at 403 and 405.4 amu in ESI-MS analysis, confirming the formation of desired product 5-Chloro-1-(2'-bromobenzyl)-3-(2-dimethyl amino ethoxy)-*1H*-indole **(6d; R_1=5-Cl, X=CH_2)**.

Scheme-1



(1) **(2)** **(3)** **(4)** **(5a-b)**

5a; X=CO

5b; X=CH_2

(6) **(7)**

Compound **6a (R_1=5-Cl, X=CO)** was cyclized in presence of catalytic amount of tetrakis triphenyl phosphino palladium (0) i.e. $Pd(PPh_3)_4(0)$ and potassium acetate base **(scheme-1)**. The reaction was generally carried out in high boiling solvents like N, N-dimethyl acetamide (DMA). The product was purified by flash column chromatography and identified as 2-chloro-10-(2-N,N-dimethylamino ethoxy)-4b-aza indeno [2,1-a]indene-5-one **7a (R_1=5-Cl, X=CO)**. There was presence of -CO stretching peak at 1686 **in** IR (KBr, cm^{-1}) spectrum. The PMR ($TMS/CDCl_3$, 400 MHz) analysis showed peaks at 2.35 (s, 6H, $-NMe_2$), 2.75 – 2.78 (t, 2H, $-NMe_2C\mathbf{H}_2$), 4.01 – 4.03 (2H, t; $-OC\mathbf{H}_2$), 7.20 – 7.80 (m, 6H, Ar-H), 8.45 (s, 1H, Ar-H). Further the mass analysis showed the (M+1) at 341.4, confirming the formatin of desired compound.

Smilarly, compound **6d (R_1=5-Cl, X=CH_2)** was cyclized in presence of catalytic amount of tetrakis triphenyl phosphino palladium (0) and potassium acetate base **(scheme-1)**. The product was purified by flash column chromatography and identified as 2-((2-Chloro-6H-isoindolo[2,1-a]indol-11-yl)oxy)-N,N-dimethylethanamine **7d (R_1=5-Cl, X=CH_2)**. The PMR ($TMS/CDCl_3$,

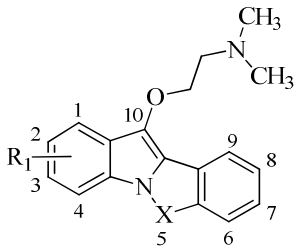
400 MHz) analysis showed peaks at 2.22 (s, 6H, N**Me**$_2$), 2.65 – 2.68 (t, 2H, C**H**$_2$-N), 4.01 – 4.04 (t, 2H, C**H**$_2$-O), 5.22 (2H, s, *N*$_1$-benzylic), 6.49 – 6.52 (m, 1H, Ar-H), 7.11 – 7.14 (m, 1H, Ar-H), 7.20 – 7.24 (m, 2H,m, Ar-H), 7.35 – 7.37 (d, 1H, J = 8.80 Hz, Ar-H), 7.47 (d, 1H, J = 1.91 Hz, Ar-H), 7.64 – 7.66 (d, 1H, J = 1.28 Hz, Ar-H). Further the mass analysis showed the (M+1) at 327.2, confirming the formatin of desired compound.

5-HT$_6$R BINDING DATA *(IN-VITRO)*

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

Compounds were investigated by the reported procedure [29]. 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. [30].

Table-1: 5-HT$_6$ receptor binding affinities[a]



Comp.	R_1	X	%Inhibition at 1µM
7a	2-Cl	CO	68.21
7b	3-Cl	CO	60.66
7c	2-OMe	CO	45.25
7d	2-Cl	CH_2	49.39
7e	3-Cl	CH_2	55.09
7f	2-OMe	CH_2	35.89

[a]5-HT$_6$ Receptor binding studies were carried out at Novascreen, USA.: Human recombinant / HEK293 cells; Radioligand: [^{3}H] LSD (60-80 Ci/mmol).

CONCLUSION

We have designed and synthesized a novel series of conformationally rigidized *N*$_1$-substituted-3-aminoalkoxy indoles. These compounds were synthesized using intramoleular Heck reaction in

presence of tetrakis triphenyl phosphine palladium (0) catalyst. All the compounds were tested for 5-HT_6R binding affinities and were found to be moderately active towards 5-HT_6R. Further structural modifications to achieve the optimum 5-HT_6R binding affinities are under progress.

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