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Synthesis and biological testing of conformationally restricted serotonin analogues with bridgehead moieties

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General information

All reaction temperatures correspond to internal temperatures unless otherwise noted. Solvents for extraction and chromatography were technical grade and distilled from indicated drying agents: methylene chloride (P_2O_5); diethyl ether, THF (sodium, benzophenone), benzene, toluene (sodium), methanol (magnesium). Flash and column chromatography were performed on silica gel Acros (40–60 μm). Reaction control was carried out by thin-layer chromatography on “Silufol” plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer at 400 and 100 MHz, respectively, and are referenced to residual solvent signals. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), brs (broad singlet) d (doublet) brd (broad doublet), dd (doublet doublets), ddd (doublet doublets doublets), t (triplet), m (multiplet). Elemental analysis of synthesized compounds was performed on CNH analyzer “Carlo-Erba” ER-20. Infrared spectra (IR) were recorded on an UR-20 apparatus (thin layer in liquid paraffin) and reported in cm^{-1}. Melting points were measured in block with sealed capillaries and are uncorrected.

rac-**6,7,8,9,10,11-Hexahydro-5*H*-6,10-methanocycloocta[*b*]indol-9-amine (1)** obtained as described in ref. 1 was subjected to chromatography on silica gel (CH_2Cl_2/MeOH/NEt_3 100:1:0.5) affording isomers **1a** and **1b**.

rac-***Exo*-6,7,8,9,10,11-hexahydro-5*H*-6,10-methanocycloocta[*b*]indole-9-amine (1a)** (yellowish oil). <u>^{1}H NMR</u> (CD_3OD) δ 1.35 (m, 1H), 1.42–1.55 (m, 2H), 1.78 (m, 1H), 1.99 (m, 1H), 2.18–2.26 (m, 2H), 2.60 (d, 1H, *endo*-HC^{11}, J=16.5), 3.03–3.12 (m, 3H, HC^{6,9} and *exo*-HC^{11}), 6.94–7.04 (m, 2H, HC^{2,3}), 7.26 (d, 1H, J=7.9), 7.37 (d, 1H, J=7.6). <u>^{13}C NMR</u> (CD_3OD) δ 23.85, 24.51, 26.13, 26.37, 28.74, 33.74, 52.64, 107.65, 110.29, 116.29, 117.99, 119.96, 127.94, 136.00, 136.19. <u>IR</u> 3390, 3100–3450 cm^{-1}. Found (%): C, 79.47; H, 8.19; N, 12.60. Calc. for $C_{15}H_{18}N_2$ (%): C, 79.65; H, 7.96; N, 12.39.

rac-***Exo*-6,7,8,9,10,11-hexahydro-5*H*-6,10-methanocycloocta[*b*]indole-9-amine (1b)** (white solid, mp 190–192 °C). <u>^{1}H NMR</u> (CD_3OD) δ 1.03 (q, 1H, J=11.9, 6.3), 1.51 (m, 1H), 1.77–1.83 (m, 2H), 1.90 (dt, 1H, J=12.5, 2.7), 2.08 (m, 1H), 2.28 (m, 1H, HC^{10}), 2.75 (dd, 1H, *exo*-HC^{11}, J=16.8, 6.7), 2.88–2.95 (м, 2H, HC^{9}, *endo*-HC^{11}), 3.00 (m, 1H, HC^{6}), 6.94–7.03 (m, 2H, $HC^{2,3}$), 7.25 (d, 1H, J=7.8), 7.41 (d, 1H, J=7.6). ^{13}C NMR (CD_3OD) δ 19.37, 28.36, 28.63, 30.95, 32.92, 34.79, 53.99, 109.37, 111.13, 117.67, 118.26, 120.16, 127.39, 135.95, 137.72. IR (mineral oil) 3390, 3100–3450 cm^{-1}. Found (%): C, 79.51; H, 8.01; N, 12.45. Calc. for $C_{15}H_{18}N_2$ (%): C, 79.65; H, 7.96; N, 12.39.

rac-***Endo*****-6,7,8,9,10,11-hexahydro-5*****H*****-6,10-methanocycloocta[*****b*****]indole-9-aminium acetate.** To a solution of **1b** (50 mg) in dry Et_2O (3ml) was added 0.025 ml of glacial acetic acid. The precipitate was filtered washed with ether and dried in vacuum. Mp 204–207 °C. Found (%): C, 71.34; H, 7.76; N, 9.81. Calc. for $C_{17}H_{22}N_2O_2$ (%): C, 71.33; H, 7.69; N, 9.79.

rac-***Endo*****-9-amino-6,7,8,9,10,11-hexahydro-5*****H*****-6,10-methanocycloocta[*****b*****]indol-2-ol (3).** Boron tribromide (1.6 ml, 1.6 mmol, 1.0 M, solution in CH_2Cl_2) was added dropwise under nitrogen to a solution of **2**[2] (0.100 g, 0.39 mmol) in dry CH_2Cl_2 (10 ml) at -78 °C. The mixture was kept at -78 °C for 1 h and slowly warmed to room temperature. After being stirred for 4 h, the reaction solution was cooled to 0°C and treated with methanol (2 ml). The resulting solution was concentrated. The residue was dissolved in methanol (5 ml), and the solution was again concentrated. This procedure was repeated three times. The residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/aqueous NH_4OH 10:1:1) to afford **3** in 79% yield (0.075 g) as a white solid. Mp 294–296 °C (with decomposition).

^{1}H NMR (DMSO-d_6) δ 0.83 (q, 1H, J=12.5, 4.5), 1.33 (m, 1H), 1.57–1.75 (m, 3H), 1.89 (brd, 1H, J=12.1), 2.08 (dd, 1H, $HC^{6(10)}$, J=6.1, 3.3), 2.46 (dd, 1H, *exo*-HC^{11}, J=16.4, 6.8), 2.80–2.92 (m, 3H), 6.47 (dd, 1H, HC^{3}, J=8.6, 2.4), 6.67 (d, 1H, HC^{1}, J=2.4), 7.00 (d, 1H, HC^{4}, J=8.6), 8.48 (brs, 1H, NH), 10.16 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ 19.42, 28.43, 28.63, 31.03, 32.94, 34.78, 54.03, 102.23, 108.60, 109.90, 111.29, 128.05, 130.38, 138.31, 150.42. IR 3400, 3315, 3275, 3000–2300 cm^{-1}. Found (%): C, 74.38; H, 7.44; N, 11.57. Calc. for $C_{15}H_{18}ON_2$ (%): C, 74.10; H 7.64; N, 11.31.

rac-***Endo*****-2-hydroxy-6,7,8,9,10,11-hexahydro-5*****H*****-6,10-methanocycloocta[*****b*****]indol-9-aminium acetate.** To a solution of **3** (60 mg) in dry Et_2O (5ml) was added glacial acetic acid 0.01 ml. The precipitate was filtered, washed with ether and dried in vacuum. Mp 290–295 °C (with decomposition). ^{1}H NMR (CD_3OD) δ 1.35 (m, 1H), 1.68 (m, 1H), 1.87 (m, 2H), 1.91 (s, 3H, CH_3), 1.98 (brd, 1H, J=12.9), 2.15 (brd, 1H, J=12.9), 2.54 (brs, 1H, $HC^{6(10)}$), 2.79 (d, 1H, *endo*-HC^{11}, J=16.9), 2.89 (dd, 1H, *exo*-HC^{11}, J=16.9, 6.1), 3.07 (brs, 1H, $HC^{6(10)}$), 3.40 (dt, 1H, HC^{9}, J=12.4, 4.3), 6.62 (dd, 1H, HC^{3}, J=8.6, 2.0), 6.84 (d, 1H, HC^{1}, J=2.0), 7.10 (d, 1H, HC^{4}, J=8.6). Found (%): C, 67.55; H, 7.28; N, 9.27. Calc. for $C_{17}H_{22}N_2O_3$ (%): C, 67.44; H 7.28; N, 9.29.

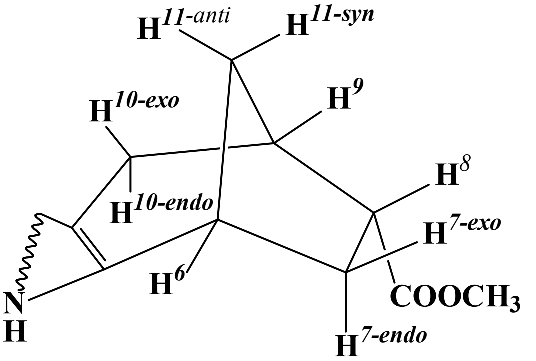
rac-***Exo*-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indol-8-amine (5a)** was obtained as described in ref. 3.

rac-***Exo*-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indol-8-aminium acetate.** To a solution of **5a** (90 mg) in dry Et_2O (6 ml) was added 0.05 ml of glacial acetic acid. The precipitate was filtered, washed with ether and dried in vacuum. Mp 174–176 °C. Found (%): C, 70.46; H 7.41; N, 10.24. Calc. for $C_{16}H_{20}N_2O_2$ (%): C, 70.59; H, 7.35; N, 10.29.

rac-***Endo*-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indol-8-amine (5b).** The isocyanate **9** (0.2 g, 0.84 mmol) was heated at 45–50 °C with aqueous 20% HCl solution (5 ml) for 3 h. The mixture was stirred at room temperature overnight, diluted with water (10 ml). The resulting mixture was extracted with diethyl ether (2×5 ml). Aqueous phase was made alkaline with Na_2CO_3 and then extracted with diethyl ether (3×5 ml). The combined organic layers were washed with brine, dried over K_2CO_3 and evaporated under vacuum. The resulted residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH/ NEt_3 100:1:1) affording **5b** in 56% yield (0.098 g).

^{1}H NMR ($CDCl_3$) δ 1.42 (dt, 1H, *endo*-HC^7, J=12.9, 3.3), 1.62 (brs, 2H, NH_2), 1.95 (dt, 1H, *anti*-HC^{11}, J=11.2, 4.9), 2.09 (d, 1H, *syn*-HC^{11}, J=11.2), 2.43 (ddd, 1H, *exo*-HC^7, J=12.9, 10.6, 5.9), 2.67 (m, 1H, $HC^{6(9)}$), 2.85 (dd, 1H, *exo*-HC^{10}, J=16.0, 4.3), 2.90–2.96 (m, 2H), 3.66 (ddd, 1H, $\underline{H}$-C-NH_2, J=10.6, 7.0, 3.3), 7.05–7.12 (m, 2H, $HC^{2,3}$), 7.28 (d, 1H, HC^1, J=7.6), 7.45 (d, 1H, HC^4, J=7.6), 7.97 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 22.65, 34.23, 37.06, 39.03, 45.21, 53.94, 105.04, 110.81, 117.83, 119.34, 120.69, 127.69, 135.42, 142.89. IR (mineral oil) 3400, 3360, 3290, 3150–3400 cm^{-1}. Found (%): C, 79.25; H, 7.55; N, 13.20. Calc. for $C_{14}H_{16}N_2$ (%): C, 79.21; H 7.70; N, 13.08.

rac-***Endo*-[Methyl 5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indole-8-carboxylate] (7).** To a suspension of phenyl hydrazine hydrochloride 0.19 g (1.315 mmol) in 2 ml of glacial acetic acid was added a solution of *endo*-methyl 2-oxobicyclo[3.2.1]octane-6-carboxylate **6**[2] 0.2 g (1.099 mmol) in 1 ml of glacial acetic acid at 90–100 °C. The reaction mixture was stirred at this temperature for 40 min. The reaction mixture was poured into cold water (10 ml) and extracted with diethyl ether. The organic layer was washed very carefully with sodium bicarbonate and saturated sodium chloride. After drying over Na_2SO_4 it was evaporated to dryness affording dark-yellow oil. The residue was purified by chromatography on silica gel (CH_2Cl_2/benzene 1:4) to afford **7** in 65% yield (0.183 g) as yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.01 (dt, 1H, *syn*-HC^{11}, J=11.0, 4.5), 2.10 (d, 1H, *anti*-HC^{11}, J=11.0), 2.16 (ddd, 1H, *exo*-HC^7, J=12.4, 11.5, 5.9), 2.43 (ddd, 1H, *endo*-HC^7, J=12.4, 4.3, 2.2), 2.60 (d, 1H, *endo*-HC^{10}, J=16.2), 2.95 (dd, 1H, *exo*-HC^{10}, J=16.2, 4.6), 3.08–3.13 (m, 2H, $HC^{6,9}$), 3.27 (ddd, 1H, $\underline{H}$-C-$COOCH_3$, J=11.5, 7.1, 4.3), 3.61 (s, 3H, OCH_3), 7.05–7.13 (m, 2H, $HC^{2,3}$), 7.28 (d, 1H, HC^1, J=7.3), 7.39 (d, 1H, HC^4, J=7.3), 7.72 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 25.70, 34.84, 36.53, 38.16 (2C), 47.03, 51.46, 104.89, 110.74, 117.75, 119.20, 120.59, 127.88, 135.47, 141.13, 174.34. IR (mineral oil) 3400, 1730 cm^{-1}. Found (%): C, 75.29; H, 6.67; N, 5.49. Calc. for $C_{16}H_{17}O_2N$ (%): C, 75.18; H 6.79; N, 5.31.



$^3J_{6,7\text{-}exo}$ 5.9	$^3J_{8,9}$ 4.3
$^3J_{6,11\text{-}anti}$ 4.5	$^3J_{9,10\text{-}exo}$ 4.6
$^3J_{7\text{-}exo,8}$ 11.5	$^3J_{9,11\text{-}anti}$ 4.5
$^3J_{7\text{-}endo,8}$ 7.1	$^2J_{10\text{-}exo,10\text{-}endo}$ 16.2
$^2J_{7\text{-}exo,7\text{-}endo}$ 12.4	$^2J_{11\text{-}syn,11\text{-}anti}$ 11.0

Coupling constants (J, Hz) of hydrogens in the bridgehead moiety of 7 (indol fragment is not shown).

***rac-Endo*-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indole-8-carboxylic acid (8).** To a solution of the ester **7** (0.5 g, 1.96 mmol) in THF (5 ml) was added aqueous 10% HCl (10 ml). The resulted mixture was refluxed for 4 h. The reaction solution was cooled, extracted with diethyl ether (3×5 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 100:1) to afford **8** in 72% yield (0.34 g) as buff solid. Mp 110–113 °C.

^{1}H NMR ($CDCl_3$) δ 2.06 (m, 1H, *anti*-HC^{11}), 2.10 (d, 1H, *syn*-HC^{11}, J=11.1), 2.17 (m, 1H, *exo*-HC^7), 2.38 (ddd, 1H, *endo*-HC^7, J=12.8, 4.3, 2.2), 2.80 (d, 1H, *endo*-HC^{10}, J=16.5), 2.97 (dd, 1H, *exo*-HC^{10}, J=16.5, 4.3), 3.07–3.13 (m, 2H, HC^{6,9}), 3.30 (ddd, 1H, H-C-COOH, J=11.4, 7.1, 4.3), 7.07–7.17 (m, 2H, HC^{2,3}), 7.29 (d, 1H, HC^1, J=7.6) 7.41 (d, 1H, HC^4, J=7.6), 7.69 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 25.49, 34.77, 36.35, 38.24, 39.13, 46.89, 104.88, 110.78, 117.89, 119.23, 120.66, 127.87, 135.42, 141.05, 182.83. IR (mineral oil) 3400, 2500–3300, 1715 cm^{-1}. Found (%): C, 74.69; H, 6.22; N, 5.81. Calc. for $C_{15}H_{15}O_2N$ (%): C, 74.60; H 6.38; N, 5.70.

***Endo*-isocyanato-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indole (9).** To a solution of the carboxylic acid **8** (0.3 g, 1.24 mmol) in THF (10 ml) was added triethylamine (0.24 ml, 1.74 mmol) and ClCOOEt (0.15 ml, 1.61 mmol) at -10 °C and the mixture was stirred at -10 °C for 30 min. Then a solution of NaN_3 (0.10 g, 1.61 mmol) in H_2O (0.5 ml) was added to the mixture at -10 °C. The mixture was stirred at this temperature for 1 h. The reaction mixture was quenched by addition of H_2O (3 ml) and toluene (10 ml). The organic layer was separated, washed with brine and dried over the resulting mixture was extracted with ethyl ether (3×10 ml), washed with brine, dried over $MgSO_4$ for 12 h. The resulted solution in toluene was refluxed for

1 h and evaporated in vacuum to afford **9** in 91% yield as yellow oil. Isocyanate **9** was used without further purification.

^{1}H NMR (CDCl$_3$) δ 2.06 (m, 1H, *anti*-HC^{11}), 2.10 (d, 1H, *syn*-HC^{11}, J=11.0), 2.21–2.29 (m, 2H, HC^7), 2.83 (d, 1H, *endo*-HC^{10}, J=16.5), 2.92 (dd, 1H, *exo*-HC^{10}, J=16.5, 4.3), 3.07–3.13 (m, 2H, HC^{6,9}), 4.05 (m, 1H, H-C-NCO), 7.07-7.17 (m, 2H, HC^{2,3}), 7.30 (d, 1H, HC^1, J=7.6) 7.41 (d, 1H, HC^4, J=7.6), 7.72 (brs, 1H, NH). ^{13}C NMR (CDCl$_3$) δ 29.00, 34.10, 35.47, 44.35, 47.55, 59.46, 104.28, 111.00, 117.45, 119.00, 120.52, 124.46, 128.98, 135.61, 140.82. IR (mineral oil) 3400, 2290 cm^{-1}.

***rac*-*Exo*-amino-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indol-2-ol (11).** Boron tribromide (1.6 ml, 1.6 mmol, 1.0 M solution in CH$_2$Cl$_2$) was added dropwise under nitrogen to a solution of **10**[3] (0.100 g, 0.41 mmol) in dry CH$_2$Cl$_2$ (10 ml) at -78 °C. The mixture was kept at -78 °C for 1 h and slowly warmed to room temperature. After being stirred for 4 h, the reaction solution was cooled to 0 °C and treated with methanol (2 ml). The resulting solution was concentrated. The residue was dissolved in methanol (5 ml), and the solution was again concentrated. This procedure was repeated three times. The residue was purified by chromatography on silica gel (CHCl$_3$/MeOH/aqueous NH$_4$OH 10:1:1) to afford **11** in 67% yield (0.063 g) as white solid. Mp 218–220 °C.

^{1}H NMR (DMSO-d$_6$) δ 1.50 (dt, 1H, *exo*-HC^7, J=12.1, 5.3), 1.66 (d, 1H, *syn*-HC^{11}, J=10.4), 2.08 (dt, 1H, *anti*-H^{11}, J=10.4, 4.6), 2.19 (dd, 1H, *endo*-HC^7, J=12.1, 7.6), 2.23 (brs, 1H, HC^9), 2.44 (d, 1H, *endo*-HC^{10}, J=15.2), 2.75 (dd, 1H, *exo*-H^{10}, J=15.2, 4.3), 3.05 (brs, 1H, HC^6), 3.09 (dd, 1H, HC^8, J=7.6, 5.3), 6.47 (dd, 1H, HC^3, J=8.6, 2.3), 6.57 (d, 1H, HC^1, J=2.3), 6.99 (d, 1H, HC^4, J=8.6), 10.28 (s, 1H, OH). ^{13}C NMR (DMSO-d$_6$) δ 29.53, 33.70, 35.80, 44.25, 46.99, 57.63, 101.98, 102.56, 109.81, 111.51, 128.63, 130.22, 143.16, 150.69. IR 3384, 3340, 3276, 3000–2400 cm^{-1}. Found (%): C, 73.68; H, 7.02; N, 12.28. Calc. for C$_{14}$H$_{16}$N$_2$O (%): C, 73.34; H 6.98; N, 12.22.

***rac*-*Exo*-2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indol-8-aminium acetate.** To a solution of **11** (63 mg) in dry Et$_2$O (5ml) was added glacial acetic acid (0.03 ml). The precipitate was filtered off, washed with diethyl ether and dried in vacuum. ^{1}H NMR (CD$_3$OD) δ 1.88 (m, 1H), 1.93 (s, CH$_3$), 2.00 (d, 1H, *syn*-HC^{11}, J=10.9), 2.21 (m, 1H), 2.53 (m, 1H), 2.63–2.72 (m, 2H), 3.01 (dd, 1H, *exo*-HC^{10}, J=15.4, 4.3), 3.27 (brs, 1H), 3.43 (m, 1H, HC^8), 6.59 (dd, 1H, HC^3, J=8.3, 2.0), 6.71 (d, 1H, HC^1, J=2.0), 7.08 (d, 1H, HC^4, J=8.3). Found (%): C, 66.67; H, 6.94; N, 9.72. Calc. for C$_{16}$H$_{20}$N$_2$O$_3$ (%): C, 66.47; H 6.99; N, 9.53.

***rac*-*Exo*-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indole-8-carboxamide (13).** The mixture of **12**[3] (0.15 g, 0.62 mmol) and 1,1'-carbonyldiimidazole (CDI) in dry THF (7 ml) was stirred for 3 h under nitrogen, then anhydrous ammonia gas was flown into the solution for 1

h. The solvent was evaporated in vacuum and the residue was dissolved in 10 ml of ethyl acetate. The resulting solution was treated with water (3×3 ml), with brine (3ml), dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 40:1) to afford **13** in 73% yield (0.11 g) as white solid. Mp 175–177 °C.

^{1}H NMR (DMSO-d$_6$) δ 1.74 (d, 1H, HC^{11}, J=10.9), 1.92 (dt, 1H, HC^{11}, J=10.9, 4.6), 2.44 (t, 1H, HC^8, J=7.8), 1.99–2.09 (m, 2H), 2.57 (d, 1H, *endo*-HC^{10}, J=15.1), 2.65 (brs, 1H, HC$^{6(9)}$), 2.86 (dd, 1H, *exo*-H^{10}, J=15.1, 4.2), 3.14 (brs, 1H, HC$^{6(9)}$), 6.71 (brs, 1H, NH_2), 6.98–6.89 (m, 2H), 7.24 (d, 1H, J=7.8), 7.27 (d,1H, J=7.8), 7.29 (brs, 1H, NH_2), 10.70 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 31.17, 35.74, 36.20, 39.52, 41.19, 48.45, 103.95, 111.04, 117.32, 118.71, 120.10, 127.81, 135.65, 141.65, 179.37. IR (mineral oil) 3390, 3190, 1650 cm^{-1}. Found (%): C, 74.80; H, 6.57; N, 11.48. Calc. for $C_{15}H_{16}N_2O$ (%): C, 75.00; H, 6.67; N, 11.67.

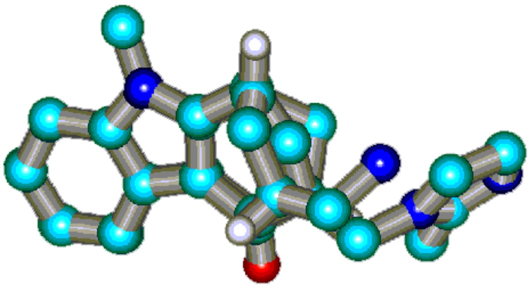
rac-**[*Exo*-(5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indol-8-ylmethyl]amine (14).** To a suspension of 0.032 g (0.84 mmol) $LiAlH_4$ in 3 ml of dry THF was added 0.1 g (0.42 mmol) of amide **13**. The resulted mixture was refluxed for 3 h. Then 0.2 ml of 2N NaOH and 0.2 ml of water added and the mixture was refluxed for 30 min. The precipitate was filtered off, treated with warm THF, refluxed in 3 ml THF for 1 h and the precipitate was filtered off again. The organic fractions were combined and evaporated under vacuum. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH/NEt_3 100:2:1) to afford **14** in 64% yield (0.06 g).

^{1}H NMR ($CDCl_3$) δ 1.38 (brs, 2H, NH_2), 1.51 (ddd, 1H, *exo*-HC^7, J=11.9, 6.4, 5.3), 1.81–1.92 (m, 3H, HC^{8,11}), 2.17 (ddd, 1H, *endo*-HC^7, J=11.9, 8.1, 1.8), 2.44 (brs, 1H, HC^9), 2.59 (dd, 1H, *endo*-HC^{10}, J=15.2, 2.0), 2.65 (dd, 1H, C<u>H</u>$_2$NH$_2$, J=12.4, 7.1), 2.73 (dd, 1H, C<u>H</u>$_2$NH$_2$, J=12.4, 7.8), 3.02 (dd, 1H, *exo*-HC^{10}, J=15.2, 4.3), 3.09 (brs, 1H, HC^6), 7.06–7.13 (m, 2H, HC^{2,3}), 7.30 (d, 1H, HC^1 or HC^4, J=7.3), 7.43 (d, 1H, HC^1 or HC^4, J=7.3), 7.82 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 31.30, 34.95, 35.74, 37.81, 41.41, 47.44, 48.24, 105.45, 110.68, 117.70, 119.28, 120.58, 128.11, 135.34, 141.42. IR (mineral oil) 3390, 3100–3450 cm^{-1}. Found (%): C, 79.54; H, 8.01; N, 12.32. Calc. for $C_{15}H_{18}N_2$ (%): C, 79.65; H, 7.96; N, 12.39.

rac-**[*Exo*-(5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indol-8-ylmethyl]aminium acetate.** To a solution of **14** (50 mg) in dry Et_2O (3ml) was added glacial acetic acid (0.02 ml). The precipitate was filtered off, washed with diethyl ether and dried in vacuum. Mp 120–122 °C.

^{1}H NMR (CD_3OD) δ 1.63 (ddd, 1H, *exo*-HC^7, J=12.1, 6.9, 5.2), 1.92 (s, 3H, CH_3), 1.96 (m, 2H), 2.10 (m, 1H), 2.27 (dd, 1H, *endo*-HC^7, J=12.1, 8.6), 2.52 (brs, 1H, HC^9), 2.63 (dd, 1H, *endo*-HC^{10}, J=15.2, 2.0), 2.90 (dd, 1H, C<u>H</u>$_2$NH$_2$, J=12.5, 7.1), 2.99–3.05 (m, 2H), 3.21 (brs, 1H, H^6), 6.93–7.02 (m, 2H, HC^{2,3}), 7.25 (d, 1H, HC$^{1(4)}$, J=7.9), 7.31 (d, 1H, H$^{4(1)}$, J=7.8). Found (%): C, 71.08; H, 7.60; N, 9.52. Calc. for $C_{17}H_{22}N_2O_2$ (%): C, 71.33; H, 7.69; N, 9.79.

Overlay of the (6*S*,8*S*,9*R*)-isomer of compound **14** and active *R*-isomer of ondansetron (nitrogen atoms are shown in dark blue, most of hydrogen atoms are omitted for clarity):



rac-**N-[*Exo*-5,6,7,8,9,10-hexahydro-6,9-methanocyclohepta[*b*]indol-8-yl]urea (16).** Anhydrous ammonia gas was flown into the solution of **15**[3] 0.060 g (0.252 mmol) in 10 ml of dry Et_2O for 20 min. The solvent was evaporated in vacuum to afford 0.0635 g (99%) of **15** as pale yellow solid. Mp 181–183 °C.

<u>^{1}H NMR</u> (CD_3OD) δ 1.69 (dt, 1H, *exo*-HC^7, J=12.7, 5.7), 1.90 (brd, 1H, *syn*-H^{11}, J=11.0), 2.06 (m, 1H), 2.44–2.49 (m, 2H), 2.79 (dd, 1H, *endo*-H^{10}, J=15.3, 2.0), 2.94 (dd, 1H, *exo*-H^{10}, J=15.3, 4.5), 3.19 (brs, 1H, HC^6), 3.86 (t, 1H, HC^8, J=6.5), 6.92–7.02 (m, 2H, $HC^{2,3}$), 7.24 (d, 1H, $HC^{1(4)}$, J=7.8), 7.32 (d, 1H, $HC^{4(1)}$, J=7.8). <u>^{13}C NMR</u> (DMSO-d_6) δ 29.59, 34.51, 35.09, 42.93, 45.02, 55.73, 103.58, 111.35, 117.53, 118.69, 120.11, 127.92, 135.87, 141.93, 158.79. <u>IR</u> (mineral oil) 3400, 3200, 3140, 3100–3500, 1660 cm^{-1}. Found (%): C, 70.48; H, 6.81; N, 16.40. Calc. for $C_{15}H_{17}N_3O$ (%): C, 70.59; H, 6.67; N, 16.47.

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