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Synthesis of indole derivatives fused with bicyclo[3.2.1]octane framework

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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: petroleum ether (P_2O_5); ethyl acetate (K_2CO_3); 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. If otherwise was not stated ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz correspondingly. Spectra are referenced to residual chloroform (d 7.26 ppm ^{1}H; d 77.0 ppm ^{13}C). Chemical shifts are given in ppm (d); multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet). Electron impact mass spectra were obtained with typical voltage of 70 eV. Elemental analysis of synthesised compounds was performed on CNH analyser "Carlo-Erba" ER-20. Infrared spectra (IR) were registered on 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.

Exo-Methyl 2-oxobicyclo[3.2.1]octane-6-carboxylate (**4**) was synthesized as described earlier.[1] B.p. 120-123°C/4 torr. ^{1}H NMR (δ): 3.58 c (3H, CH_3), 2.76 (1H, dd, J=5.87, 9.20 Hz, $\underline{H}CCOOCH_3$), 2.64 (1H, t, J=5.87 Hz), 2.52 (1H, dd, J=3.33, 7.24 Hz), 2.28-2.08 (3H, m), 1.99-1.87 (2H, m), 1.84-1.77 (1H, m), 1.70-1.60 (2H, m).

General procedure for Fischer indolization:

To a solution of phenyl hydrazine hydrochloride (1.1-1.2 mmol) in 2 ml of glacial acetic acid was added a solution of *exo*-methyl 2-oxobicyclo[3.2.1]octane-6-carboxylate (1 mmol) in 1 ml of glacial acetic acid at 90-100°C. The reaction mixture was stirred at this temperature for 30-40 min, after which 3-4 ml of water was added. The precipitate was filtered, washed with water and dried in a vacuum at 80°C.

exo-Methyl (indolo[2,3-b])bicyclo[3.2.1]oct-2-ene-6-carboxylate (**5**) was isolated as ivory crystals after recrystallization from petroleum ether-benzene in 74% yield. M.p. 136.5-139.1ºC. Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.29; H 6.67; N, 5.49. Found: C, 75.43; H, 6.83; N, 5.91. ^{1}H NMR (δ): 1.96 (1H, d, ^{2}J=11.12 Hz, H^8), 2.11-2.03 (1H, m), 2.32-2.17 (2H, m), 2.69 (1H, d, ^{2}J=15.41 Hz, $H^{4\text{-endo}}$), 2.73 (1H, m, H^6), 2.96 (1H, m, H^5), 3.05 (1H, dd, ^{3}J=4.30, ^{2}J=15.41 Hz, $H^{4\text{-exo}}$), 3.19 (1H, m, H^1), 3.72 (3H, s, OCH_3), 7.17-7.06 (2H, m, $H^{5',6'}$), 7.31 (1H, d, J=7.33 Hz, $H^{4'}$), 7.43 (1H, d, ^{3}J=7.33 Hz, $H^{7'}$), 7.75 (1H, br, NH). ^{13}C NMR (δ): 30.96, 35.76, 35.97, 39.13, 40.60), 47.80 (cage); 51.82 (CH_3); 104.92, 110.76, 117.76, 119.47, 120.91, 127.93, 135.40, 140.61 (indole); 177.38 (C=O). IR (mineral oil): 3400, 1730 cm^{-1}.

exo-Methyl (5´-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene-6-carboxylate (**7**) was isolated as light yellowish crystals after recrystallization from petroleum ether-benzene in 52% yield. M.p. 149-152ºC. Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.58; H, 6.67; N, 4.91. Found: C, 71.50; H, 6.65; N, 5.10. ^{1}H NMR (δ): 1.96 (1H, d, ^{2}J=10.86 Hz, H^8), 2.11-2.03 (1H, m), 2.33-2.17 (2H, m), 2.66 (1H, d, ^{2}J=15.16 Hz, $H^{4\text{-endo}}$), 2.74 (1H, t, ^{3}J=7.84 Hz, H^6), 2.96 (1H, m, H^5), 3.01 (1H, dd, ^{3}J=4.29, ^{2}J=15.16 Hz, $H^{4\text{-exo}}$), 3.16 (1H, dd, ^{3}J=4.04, ^{3}J=4.30 Hz, H^1), 3.71 (3H, s, CH_3), 3.86 (3H, s, CH_3), 6.78 (1H, dd, ^{4}J=2.27, ^{3}J=8.84 Hz, $H^{6'}$), 6.88 (1H, d, ^{4}J=2.27 Hz, $H^{4'}$), 7.20 (1H, d, ^{3}J=8.84 Hz, $H^{7'}$), 7.63 (1H, br, NH). ^{13}C NMR (δ): 30.99, 35.86, 35.96, 39.12, 40.58, 47.81 (cage); 51.83 (COO<u>C</u>H$_3$); 56.00 (C–O<u>C</u>H$_3$); 100.22, 104.76, 110.57, 111.40, 128.35, 130.50, 141.64 (indole); 154.15 (<u>C</u>–OCH$_3$); 177.42 (C=O). IR (mineral oil): 3400, 1730 cm^{-1}. MS (EI) m/e (relative intensity): 286 (100) $[M+H]^+$, 198 (71), 186 (37), 154 (23), 128 (13), 77 (16), 55 (25).

General procedure for ester hydrolysis:

A mixture of the ester (1 mmol) and aqueous 2M NaOH (5 ml) in methanol (5 ml) was stirred at room temperature until complete dissolving (4-6 h). The solution was concentrated by evaporation under reduced pressure, diluted with water (20 ml) and washed with ethyl ether (3x10 ml). The aqueous layer was adjusted to pH 5 with HCl and then extracted with ethyl ether (3x10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under vacuum.

exo-(Indolo[2,3-b])bicyclo[3.2.1]oct-2-ene-6-carboxylic acid (**6a**) was isolated as ivory crystals in 92%. M.p. 185.6-187.3ºC. Anal. Calcd. for $C_{15}H_{15}O_2N$: C, 74.69; H, 6.22; N, 5.81. Found: C, 74.86; H, 6.22; N, 5.98. ^{1}H NMR (δ): 1.99 (1H, d, ^{2}J=11.12 Hz, H^8), 2.12-2.04 (1H, m), 2.39-2.21 (1H, m), 2.38-2.30 (1H, m), 2.81-2.68 (2H, m, $H^{6,4\text{-endo}}$), 3.10-3.01 (2H, m), 3.21 (1H, t, ^{3}J=4.04 Hz, H^1), 7.17-7.07 (2H, m, $H^{5',6'}$), 7.32 (1H, d, ^{3}J=7.58 Hz, $H^{4'}$), 7.43 (1H, d, ^{3}J= 7.58 Hz, $H^{7'}$), 7.75 (1H, br, NH). ^{13}C NMR (δ): 30.99, 35.59, 35.91, 39.00, 40.64, 47.92 (cage);

103.87, 110.99, 117.38, 118.71, 120.14, 127.78, 135.61, 141.41 (indole), 179.77 (C=O). IR (mineral oil): 3400 (NH), 1710 (C=O) cm^{-1}.

exo-(5´-Methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene-6-carboxylic acid (**8a**) was isolated as ivory crystals in 94%. M.p. 155-160ºC. Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 70.85; H, 6.27; N, 5.17. Found: C, 70.69; H 6.35; N, 5.23. ^{1}H NMR (δ): 1.98 (1H, d, ^{2}J=11.10 Hz, H^8), 2.11-2.04 (1H, m), 2.39-2.19 (2H, m), 2.67 (1H, dd, ^{3}J=3.29, ^{2}J=16.43 Hz, $H^{4\text{-exo}}$), 2.78 (1H, t, J=7.83 Hz, H^6), 3.07-2.99 (2H, m), 3.18 (1H, t, ^{3}J=4.30 Hz, H^1), 3.86 (3H, s, CH_3), 6.78 (1H, dd, ^{4}J=2.52, ^{3}J=8.84 Hz, $H^{6'}$), 6.88 (1H, d, ^{4}J=2.52 Hz, $H^{4'}$), 7.18 (1H, d, ^{3}J=8.84 Hz, $H^{7'}$), 7.63 (1H, br, NH). ^{13}C NMR (δ): 31.07, 35.62, 35.92, 38.97, 40.68, 47.95 (cage); 55.82 (C–O<u>C</u>H$_3$); 99.74, 103.51, 109.73, 111.67, 128.09, 130.80, 142.45 (indole); 153.52 (<u>C</u>–OCH$_3$); 178.62 (C=O). IR (mineral oil): 3400 (NH), 1710 (C=O) cm^{-1}.

General procedure for Curtius rearrangement:

To a solution of the carboxylic acid (1 mmol), triethylamine (1.4 mmol) in THF (6 ml) was added ClCOOEt (1.4 mmol) and the mixture was stirred at -10°C for 30 min. Then a solution of NaN_3 (1.3 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. Then the reaction was quenched by addition of H_2O and the resulting mixture was extracted with ethyl ether (3x10 ml), washed with brine, dried over Na_2SO_4 and evaporated in vacuum. A solution of the residue in toluene (5 ml) was stirred at 100°C for 1 h and evaporated in vacuum.

exo-6-Isocyanato(indolo[2,3-b])bicyclo[3.2.1]oct-2-ene-6 (**6b**) was isolated by flash chromatography (1:7, EtOAc/petroleum ether) in 63% yield. M.p. 140.0-143.9ºC. Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.63; H 5.88; N, 11.76. Found: C, 75.69; H, 6.08; N, 11.62. ^{1}H NMR (δ): 1.96 (1H, ddd, ^{3}J=4.54, ^{3}J=6.06, ^{2}J=12.63 Hz, $H^{7\text{-exo}}$), 2.01 (1H, d, ^{2}J=12.13 Hz, H^8), 2.20 (1H, m, H^8), 2.59 (1H, dd, ^{3}J=7.83, ^{2}J=12.63 Hz, $H^{7\text{-endo}}$), 2.77-2.69 (2H, m, $H^{4\text{-endo},5}$), 3.03 (1H, dd, ^{3}J=4.80, ^{2}J=15.92 Hz, $H^{4\text{-exo}}$), 3.21 (1H, dd, ^{3}J=4.05, ^{3}J=4.54 Hz, H^1), 3.85 (1H, dd, ^{3}J=6.06, ^{3}J=7.83 Hz, H^6), 7.17-7.07 (2H, m, $H^{5',6'}$), 7.30 (1H, d, ^{3}J=7.59 Hz, $H^{4'}$), 7.42 (1H, d, ^{3}J=7.58 Hz, $H^{7'}$), 7.72 (1H, br, NH). ^{13}C NMR (δ): 28.99, 34.17, 35.65, 44.35, 47.55, 59.49 (cage); 104.28, 110.84, 117.80, 119.64, 121.14, 122.02, 127.63, 135.47, 140.36 (indole + N<u>C</u>O). IR (mineral oil): 3400 (NH), 2290 (N=C=O) cm^{-1}.

exo-6-Isocyanato(5´-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene (**8b**) was isolated by flash chromatography (1:7, EtOAc/petroleum ether) in 67% yield. M.p. 140-144°C. Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.54; H, 6.05; N, 10.23. ^{1}H NMR (δ): (1H, dt, ^{3}J=5.56, ^{2}J=12.89 Hz, $H^{7\text{-exo}}$), 2.00 (1H, d, ^{2}J=11.37 Hz, H^8), 2.24-2.16 (1H, m, H^8), 2.59 (1H, ddd, ^{4}J=1.77, ^{3}J=7.83, ^{2}J=12.89 Hz, H^7), 2.69 (1H, d, ^{2}J=15.41 Hz, $H^{4\text{-endo}}$), 2.72 (1H, t, ^{3}J=4.55 Hz, H^5), 2.99 (1H, dd, ^{3}J=4.55, ^{2}J=15.41 Hz, $H^{4\text{-exo}}$), 3.18 (1H, t, ^{3}J=4.54 Hz, H^1), 3.86-

3.84 (4H, m, H^6, CH_3), 6.79 (1H, dd, ^4J=2.53, ^3J=8.59 Hz, $H^{6'}$), 6.88 (1H, d, ^4J=2.27 Hz, $H^{4'}$), 7.18 (1H, d, ^3J=8.58 Hz, $H^{7'}$), 7.62 (1H, br, NH). ^{13}C NMR (δ): 29.03, 34.14, 35.70, 44.35, 47.52, 56.01 (cage); 59.50 (OCH_3); 100.17, 104.00, 110.74, 111.59, 128.03, 128.29, 130.54, 141.43 (indole + NCO); 154.15 (C–OCH_3). IR (mineral oil): 3350 (NH), 2290 (N=C=O)cm^{-1}.

General procedure for preparation of amines from isocyanates:

The isocyanate (1 mmol) was heated at 60°C with 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 ethyl ether (3x5 ml). Aqueous phase was made alkaline with Na2CO3 and then extracted with ethyl ether (3x10 ml). The combined organic layers were washed with brine, dried over K_2CO_3 and evaporated under vacuum.

exo-6-Amino(indolo[2,3-b])bicyclo[3.2.1]oct-2-ene-6 (**6c**) was isolated as white crystals in 56%. M.p. 201-202ºC. Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.24; H, 7.55; N, 13.21. Found: C, 79.55; H, 7.63; N, 13.15. ^1H NMR (δ): 2.24 (2H, br, NH_2), 1.56 (1H, ddd, ^3J=5.06, ^3J=5.81, ^2J=12.52 Hz, $H^{7\text{-exo}}$), 1.91 (1H, d, ^2J=11.11 Hz, H^8), 2.17 (1H, ddd, ^3J=4.05, ^3J=5.81, ^2J=11.11 Hz, H^8), 2.34 (1H, ddd, ^4J=1.76, ^3J=4.55, ^2J=5.81 Hz, H^5), 2.45 (1H, ddd, ^4J=2.28, ^3J=7.33, ^2J=12.52 Hz, $H^{7\text{-endo}}$), 2.68 (1H, dd, ^4J=1.76, ^2J=15.41 Hz, $H^{4\text{-endo}}$), 3.03 (1H, dd, ^3J=4.55, ^2J=15.41 Hz, $H^{4\text{-exo}}$), 3.14 (1H, dd, ^3J=4.05, ^3J=5.06 Hz, H^1), 3.33 (1H, dd, ^3J=5.81, ^3J=7.33 Hz, H^6), 7.13–7.05 (2H, m, $H^{5',6'}$), 7.30 (1H, d, ^3J=7.58 Hz, $H^{4'}$), 7.42 (1H, d, ^3J=7.58 Hz, $H^{7'}$), 7.72 (1H, br, NH). ^{13}C NMR (δ): 29.32, 33.77, 36.22, 45.14, 47.70 (cage); 57.66 (C–NH_2); 104.85, 110.72, 117.68, 119.33, 120.64, 127.93, 135.39, 141.56 (indole). IR (mineral oil): 3400 (NH), 3350, 3290 cm^{-1}.

exo-6-Amino(5-methoxyindolo[2,3-b])bicyclo[3.2.1]oct-2-ene-6 (**8c**) was isolated as white crystals in 54%. M.p. 120-122°C. Anal. Calcd. for $C_{15}H_{18}ON_2$: C, 74.38; H, 7.44; N, 11.57. Found: C, 74.08; H, 7.41; N, 11.52. ^1H NMR (δ): 1.53 (3H, m, $H^{7\text{-exo}}$, NH_2), 1.90 (1H, d, ^2J=11.19 Hz, H^8), 2.19-2.11 (1H, m, H^8), 2.33 (1H, t, ^3J=4.61 Hz, H^5), 2.45 (1H, ddd, ^4J=2.20, ^3J=6.36, ^2J=12.72 Hz, $H^{7\text{-endo}}$), 2.63 (1H, d, ^4J=1.75, ^2J=15.35 Hz, $H^{4\text{-endo}}$), 2.95 (1H, dd, ^3J=4.61, ^2J=15.35 Hz, $H^{4\text{-exo}}$), 3.11 (1H, t, ^3J=4.60 Hz, H^1), 3.32 (1H, t, ^3J=6.36 Hz, H^6), 3.86 (3H, s, CH_3), 6.76 (1H, dd, ^4J=2.27, ^3J=8.58 Hz, $H^{6'}$), 6.88 (1H, d, ^4J=2.27 Hz, $H^{4'}$), 7.17 (1H, d, ^3J=8.58 Hz, $H^{7'}$), 7.62 (1H, br, NH). ^{13}C NMR (δ): 29.34, 33.73, 36.31, 45.12, 47.68 (cage); 56.00 (OCH_3); 57.66 (C–NH_2); 100.16, 104.73, 110.29, 111.32, 128.32, 130.46, 142.59 (indole); 154.06 (C–OCH_3).

General procedure for acylation:

The amine (1 mmol) was dissolved in acetic anhydride (1 ml) and the solution was stirred for 20 h. Water (4 ml) was added to the solution and this mixture was stirred for 30 min. Solid

sodium bicarbonate was added until the solution had a pH 6-7. The mixture was extracted with CH_2Cl_2, the combined organic layers were dried over Na_2SO_4 and evaporated under vacuum.

exo-6-Acetylamino-(indolo[2,3-b])-bicyclo[3.2.1]oct-2-ene (**2**) was isolated by column chromatography (1:50, methanol/CH_2Cl_2) in 69% yield. M.p. 213-216ºC. Anal. Calcd. for $C_{16}H_{18}ON_2$: C, 75.59; H, 7.09; N, 11.02. Found: C, 75.49, H, 7.05, N, 10.96. ^{1}H NMR (δ): 1.66-1.56 (1H, m), 2.03-1.95 (5H, m), 2.59-2.49 (2H, m), 2.89 (1H, dd, ^{4}J=1.77, ^{2}J=15.66 Hz, $H^{4\text{-endo}}$), 2.98 (1H, dd, ^{3}J=4.55, ^{2}J=15.66 Hz, $H^{4\text{-exo}}$), 3.15 (1H, m, H^1), 4.10 (1H, m, H^6), 5.57 (1H, d, ^{3}J=5.81 Hz, NHCO), 7.13-7.05 (2H, m, $H^{5',6'}$), 7.30 (1H, d, ^{3}J=7.35 Hz, $H^{4'}$), 7.43 (1H, d, ^{3}J=7.35 Hz, $H^{7'}$), 7.74 (1H, br, NH). ^{13}C NMR (δ): 22.70, 30.47, 33.32, 36.78, 39.76, 41.84, 48.20 (cage + CH_3); 107.33, 113.92, 120.55, 120.97, 122.33, 132.26, 136.19, 140.82 (indole); 168.93 (C=O). IR (mineral oil): 3400 (NH indole), 3280 (NH), 1602 (C=O) cm^{-1}.

exo-6-Acetylamino-(5'-methoxyindolo[2,3-b])-bicyclo[3.2.1]oct-2-ene (**3**) was isolated by column chromatography (1:50, methanol/CH_2Cl_2) in 70% yield. M.p. 202-205ºC. Anal. Calcd. for $C_{17}H_{20}O_2N_2$: C, 71.83; H, 7.04; N, 9.86. Found: 71.88, H, 7.20, N, 9.88. ^{1}H NMR (δ): 1.59 (1H, m), 2.05-1.90 (5H, m), 2.55-2.45 (2H, m), 2.85 (1H, dd, ^{2}J=15.41 Hz, $H^{4\text{-endo}}$), 2.95 (1H, m, $H^{4\text{-exo}}$), 3.12 (1H, br, H^1), 3.86 (3H, s, CH_3), 4.10 (1H, m, H^6), 5.62 (1H, br, NH), 6.77 (1H, dd, ^{4}J=2.53, ^{3}J=8.59 Hz, $H^{6'}$), 6.89 (1H, d, ^{4}J=2.27 Гц, $H^{4'}$), 7.17 (1H, d, ^{3}J=8.58 Hz, $H^{7'}$), 7.67 (1H, br, NH). ^{13}C NMR (δ): 23.43, 29.36, 34.65, 35.45, 42.56, 45.00, 55.55, 56.00 (cage + CH_3 + OCH_3); 100.22, 104.91, 110.51, 111.39, 128.27, 130.54, 141.23 (indole); 154.00 (C–OCH_3); 169.61 (C=O). IR (mineral oil): 3400 (NH indole), 3280 (NH), 1600 (C=O) cm^{-1}.

[1]a) E. P. Butkus, A. I. Zilinskas, N. S. Zefirov and P. P. Kadziauskas, *Zh. Org. Khim.*, 1986, **22**, 871 (in Russian).

b) E. Butkus, U. Berg, A. Stoncius and A. Zilinskas, *Mendeleev Commun.*, 1995, **5**, 96.