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SUPPORTING INFORMATION

Supporting Information
for DOI: 10.1055/s-0032-1316911

Thieme

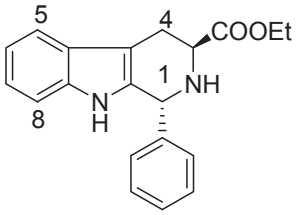
Supporting information: synthesis of functionalized diketopiperazines as cyclotryprostatin and tryprostatin analogues

General methods. ^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were run with a Jeol JNM-EX 270 NMR spectrometer. Peak assignments were performed with the aid of the DEPT technique, 2D-COSY spectra and HETCOR spectra. IR assignments were obtained from a Perkin Elmer Spectrum One spectrophotometer. Mass spectra were measured with an Agilent 1100 Series mass spectrometer (detector VL, 70 eV, ES 4000 V). Melting points were measured with a Buchi B-540 apparatus. Flash chromatography was carried out on a glass column with ACROS silica gel (particle size 0.035-0.07 mm, pore diameter ca. 6 nm). All solvents and reagents were obtained from commercial suppliers and were used without further purification.

1. General procedure for the synthesis of compounds 6a-c and 7a-c

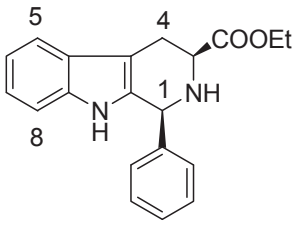
A solution of *L*-trytophan ethyl ester **4** (2.9 g, 11.74 mmol) and benzaldehyde **5a** (1.25 g, 11.74 mmol) in benzene (50 ml) was refluxed for 48 h. Then, the solvent was evaporated to give a crude product, which was extracted three times with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by means of column chromatography on silicagel (hexane/EtOAc, 4/6) gave *trans*- isomers **6a** (1.1 g, 30%) and *cis*-isomer **7a** (2.3 g, 61%).

***trans*-Ethyl-1-phenyl-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 6a**



Yield (30%), white powder**,** mp: 151-151.5°C, $[\alpha]_D^{15}$ = -3.4° (c = 0.59, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 1.33 (3H, t, *J* = 7.3 Hz, Me), 3.02 (1H, ddd, *J* = 2.0, 11.2, 15.2 Hz, H-4a), 3.2 (1H, ddd, *J* = 1.7, 15.2, 4.3 Hz, H-4b), 3.9 (1H, dd, *J* = 11.2, 4.3 Hz, H-3), 4.22-4.31 (2H, m, OCH_2), 5.23 (1H, dd *J* = 1,7, 2.0 Hz, H-1), 7.10-7.25 (3H, m, 3x =CH), 7.34-7.39 (5H, m, 5x =CH), 7.43 (1H, br. s, H-9), 7.55 (1H, dd, *J* = 7.9, 2.0 Hz, H-5). ^{13}C NMR-68 MHz ($CDCl_3$): δ 14.23 (Me), 25.68 (C-4), 56.94 (C-3), 58.69 (C-1), 61.20 (OCH_2), 108.97 (C_{quat}), 110.89 (C-8), 118.22 (C-5), 119.59 (C-6), 121.90 (C-7), 127.13 (C_{quat}), 128.57 (=CH), 128.62 (2x =CH), 128.95 (2x =CH), 134.73 (C_{quat}), 136.14 (C_{quat}), 140.77 (C_{quat}), 172.76 (C=O). IR (KBr) ν 3387 (NH), 1720 (C=O), 1625, 1490, 1470, 1455, 1368, 1324, 1267, 1226, 1144, 1034, cm^{-1}. MS *m/z* (%). 221 ($M+H^+$, 100), 221 (30), 220 (50).

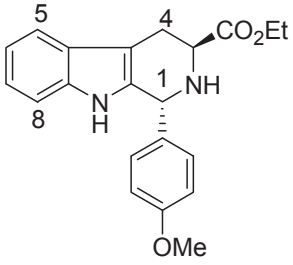
***cis*-Ethyl-1-phenyl-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 7a**



Yield (61%), white powder**,** mp: 167.5-168 °C, $[\alpha]_D^{15}$ = -4.1° (c = 0.48, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 1.26 (3H, t, *J* = 6.9 Hz, Me), 3.10 (1H, ddd, *J* = 1.8, 7.0, 15.5 Hz, H-4a), 3.28 (1H, ddd, *J* = 1.0, 15.5, 5.3 Hz, H-4b), 3.94 (1H, dd, *J* = 7.0, 5.3 Hz, H-3), 4.11-4.23 (2H, m, OCH_2), 5.40 (1H, br. s ,H-1), 7.10-7.16 (2H, m, H-6, H-7), 7.18-7.36 (6H, m, 5x =CH, H-8), 7.57 (1H, d, *J* = 8.9 Hz, H-5), 7.63 (1H, br. s, H-9). ^{13}C NMR-68 MHz ($CDCl_3$): δ 14.19 (Me), 24.69 (C-4), 52.49 (C-3), 54.97 (C-1), 61.04 (OCH_2), 108.53 (C_{quat}), 110.87 (C-8), 118.25 (C-5), 119.48 (C-6), 121.92 (C-7), 127.02 (C_{quat}), 128.08 (=CH), 128.41 (2x =CH), 128.75 (2x =CH),

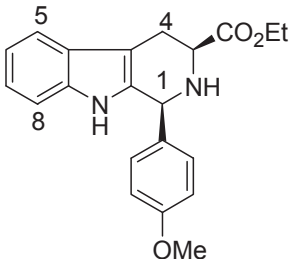
133.20 (C_{quat}), 136.15 (C_{quat}), 142.04 (C_{quat}), 173.67 (C=O). IR (KBr) ν 3400 (NH), 1737 (C=O), 1625, 1455, 1335, 1214, 1124 cm^{-1}. MS *m/z* (%). 221 ($M+H^+$, 100), 221 (20), 220 (50).

***trans*-Ethyl-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 6b**



Yield (28%), white powder**,** mp : 140.5-141°C, $[\alpha]_D^{15}$ = -1.9° (c = 0.52, CH_2Cl_2). ^1H NMR-300 MHz ($CDCl_3$): δ 1.32 (3H, t, *J* = 7.2 Hz, Me), 2.03 (1H, br. s, NH), 2.97 (1H, ddd, *J* = 2.5, 11.3, 15.1 Hz, H-4a), 3.20 (1H, ddd, *J* = 1.9, 15.1, 4.4 Hz, H-4b), 3.79 (3H, s, OMe), 3.92 (1H, dd, *J* = 11.3, 4.4, H-3), 4.20-4.30 (2H, m, OCH_2), 5.17 (1H, dd, *J* = 1,9, 2.5 Hz, H-1), 6.87 (2H, d, *J* = 8.8 Hz, H-3′, H-5′), 7.07-7.21 (3H, m, 3x =CH), 6.27 (2H, d, *J* = 8.8 Hz, H-2′, H-6′), 7.52 (1H, br. s, H-9), 7.54 (1H, d, *J* = 8.8 Hz, H-5). ^{13}C NMR-75 MHz ($CDCl_3$): δ 14.19 (Me), 25.66 (C-4), 55.30 (OMe), 56.93 (C-3), 57.97 (C-1), 61.19 (OCH_2), 108.81 (C_{quat}), 110.87 (C-8), 114.22 (C-3′, C-5′), 118.16 (C-5), 119.50 (C-6), 121.80 (C-7), 127.12 (C_{quat}), 129.77 (C-2′, C-6′), 132.77 (C_{quat}), 135.01 (C_{quat}), 136.06 (C_{quat}), 159.72 (C_{quat}), 172.80 (C=O). IR (KBr) ν 3305 (NH), 1721 (C=O), 1609, 1511, 1454, 1303, 1263, 1248, 1210, 1121, 1037, cm^{-1}. MS *m/z* (%). 351 ($M+H^+$, 100), 349 (30), 250 (30), 236(10).

***cis*-Ethyl-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 7b**

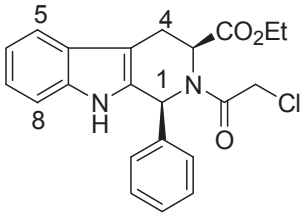


Yield (56%), white powder**,** mp: 194.5-196 °C, $[\alpha]_D^{15}$ = -6.4° (c = 0.465, CH_2Cl_2). ^1H NMR-300 MHz ($CDCl_3$): δ 1.25 (3H, t, *J* = 7.2 Hz, Me), 2.47 (1H, br. s, NH), 3.09 (1H, ddd, *J* = 1.7, 7.2, 15.3 Hz, H-4a), 3.24 (1H, ddd, *J* = 1.1, 15.3, 5.5 Hz, H-4b), 3.78 (3H, s, OMe), 3.91 (1H, dd, *J* = 7.2, 5.5 Hz, H-3), 4.10-4.24 (2H, m, OCH_2), 5.34 (1H, br. s, H-1), 6.83 (2H, d, *J* = 8.8 Hz, H-3′, H-5′), 7.08-7.23 (5H, m, overlap, 3x =CH, H-2′, H-6′), 7.54 (1H, db, *J* = 8.8 Hz, H-5), 7.67 (1H, br. s, H-9). ^{13}C NMR-68 MHz ($CDCl_3$): δ 14.16 (Me), 24.67 (C-4), 52.36 (C-3), 54.27 (C-1), 55.27 (OMe), 60.97 (OCH_2), 108.37 (C_{quat}), 110.83 (C-8), 113.98 (C-3′, C-5′), 118.17 (C-5), 119.39 (C-6), 121.80 (C-7), 127.00 (C_{quat}), 129.51 (C-2′, C-6′), 133.57 (C_{quat}), 134.16 (C_{quat}), 136.10 (C_{quat}), 159.35 (C_{quat}), 173.67 (C=O). IR (KBr) ν 3312 (NH), 1730 (C=O), 1606, 1509, 1453, 1332, 1302, 1248, 1223, 1178, 1126, 1033 cm^{-1}. MS *m/z* (%). 351 ($M+H^+$, 100), 250 (30), 236 (10).

2. Synthesis of compounds 8a-c and 9a-c.

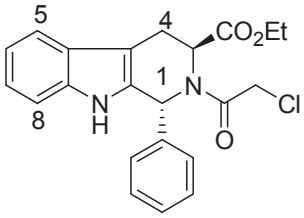
To a solution of the *cis*-isomer **6a** (800 mg, 2.5 mmol) in a saturated solution of $NaHCO_3$ (20ml) and EtOAc (20ml) was added chloroacetyl chloride (333mg, 3 mmol). The reaction mixture was stirred at 0°C for 30 min. Afterwards, the solvent was evaporated and the residue extracted with CH_2Cl_2. The combined organic phases were washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by means of column chromatography on silicagel (hexane/EtOAc, 6/4) gave compound **9a** in 91% (900 mg). Compounds **8a** and **8b** gave significant peak-broadening so that no reliable ^1H and ^{13}C-NMR spectra could be collected.

***cis*-Ethyl-2-(2-chloroacetyl)-1-phenyl-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 9a**



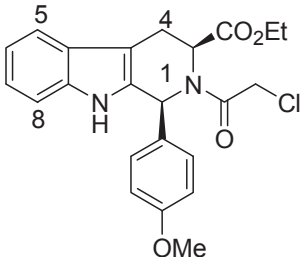
Yield (91%), white powder, mp: 156.5-158 °C, $[\alpha]_D^{15}$ = -2.12° (c = 0.47, CH_2Cl_2). ^{1}H NMR-300 MHz ($CDCl_3$): δ 0.62-0.90 (3H, m, C<u>H</u>$_3$CH$_2$), 2.98-3.12 (1H, m, C<u>H</u>$_A$H$_B$O), 3.17 (1H, dd and m, J = 6.9 Hz, 15.7 Hz, C<u>H</u>$_A$H$_B$-4 and CH$_A$<u>H</u>$_B$O), 3.67-3.75 (1H, m, CH$_A$<u>H</u>$_B$-4), 4.21 (1H, d, *J* = 12.4 Hz, C<u>H</u>$_A$H$_B$Cl), 4.35 (1H, d, *J* = 12.4 Hz, CH$_A$<u>H</u>$_B$Cl), 4.91 (1H, d, *J* = 4.4 Hz, CH-3), 6.95 (1H, s, CH-1), 7.13-7.36 (6H, m, 6xCH$_{Ar}$), 7.60 (1H, d, J = 9.9 Hz, CH$_{Ar}$), 7.80 (1H, br. s, NH). ^{13}C NMR-68 MHz ($CDCl_3$): δ 13.55 (<u>C</u>H$_3$CH$_2$), 21.58 (CH$_2$-4), 42.24 (CH$_2$Cl), 52.32 (CH-1), 53.74 (CH-3), 61.77 (CH$_2$O), 107.83 (C$_{quat}$), 111.13 (2xCH$_{Ar}$), 118.70 (2xCH$_{Ar}$), 119.92 (CH$_{Ar}$), 122.64 (CH$_{Ar}$), 126.46 (C$_{quat}$), 128.35 (CH$_{Ar}$), 128.35 (CH$_{Ar}$), 129.65 (CH$_{Ar}$), 136.52 (C$_{quat}$), 139.06 (C$_{quat}$), 167.15 (C=O), 169.64 (C=O). IR (KBr) ν 3367, 3315 (NH), 1741, 1728 (C=O), 1658 (C=O), 1626, 1492, 1455, 1425, 1319, 1262, 1238, 1206. cm^{-1}. MS *m/z* (%). 397/399 (M+H$^+$, 100), 351 (30).

***trans*-Ethyl-2-(2-chloroacetyl)-1-phenyl-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 8a**



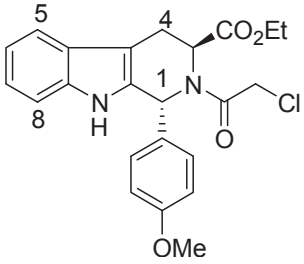
Yield (96%), white powder, mp: 216.5-218 °C, $[\alpha]_D^{15}$ = -38.4° (c = 0.65, CH_2Cl_2). ^{13}C NMR-68 MHz ($CDCl_3$): δ 13.54 (Me), 21.60 (C-4), 42.21 (C-2'), 52.35 (C-3), 53.77 (C-1), 61.75 (OCH$_2$), 107.88 (C$_{quat}$), 111.12 (C-8), 118.70 (C-5), 119.94 (C-6), 122.66 (C-7), 126.47 (C$_{quat}$), 128.44 (C-2′, C-6′), 129.64 (C-3′, C-5′, C$_{quat}$), 136.52 (C$_{quat}$), 139.06 (C$_{quat}$), 167.16 (C=O), 169.62 (C=O). IR (KBr) ν 3391 (NH), 1714, 1667 (C=O), 1609, 1511, 1452, 1387, 1367, 1242, 1029. cm^{-1}. MS *m/z* (%). 397/399 (M+H$^+$, 100), 351 (25).

***cis*-Ethyl-2-(2-chloroacetyl)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 9b**



Yield (88%), white powder, mp: 205.5-206 °C, $[\alpha]_D^{15}$ = -2.7° (c = 0.37, CH_2Cl_2). ^{1}H NMR-300 MHz ($CDCl_3$): δ 0.79 (3H, t, *J* = 6.4 Hz, CH$_3$CH$_2$), 3.14 (2H, dd, *J* = 7,0 Hz, 15.6 Hz), 3.63-3.77 (6H, s+m, CH$_2$O and OCH$_3$), 4.19 (1H, d, *J* = 12.1 Hz, C<u>H</u>$_A$H$_B$Cl), 4.34 (1H, d, *J* = 12.1 Hz, CH$_A$<u>H</u>$_B$Cl), 4.86 (1H, d, *J* = 5.0 Hz, CH-3), 6.70 (2H, d, J = 8.3 Hz, 2xCH$_{Ar}$), 6.84 (1H, s, CH-1), 7.11-7.27 (5H, m, 5xCH$_{Ar}$), 7.58 (1H, d, J = 7.2 Hz, CH$_{Ar}$), 8.07 (1H, br. s, NH). ^{13}C NMR-68 MHz ($CDCl_3$): δ 13.60 (<u>C</u>H$_3$CH$_2$), 21.57 (CH$_2$-4), 42.35 (CH$_2$Cl), 51.86 (CH-1), 53.65 (CH-3), 61.83 (CH$_2$O), 107.51 (C$_{quat}$), 111.19 (2xCH$_{Ar}$), 113.50 (CH$_{Ar}$), 118.64 (2xCH$_{Ar}$), 119.79 (CH$_{Ar}$), 122.52 (CH$_{Ar}$), 126.47 (C$_{quat}$), 130.00 (C$_{quat}$), 130.98 (C$_{quat}$), 131.39 (C$_{quat}$), 136.54 (C$_{quat}$), 159.45 (C$_{quat}$-OMe), 167.12 (C=O), 169.76 (C=O). IR (KBr) ν 3369 (NH), 1736, 1656 (C=O), 1609, 1510, 1453, 1422, 1304, 1249, 1176 cm^{-1}. MS *m/z* (%). 427/429 (M+H$^+$, 80), 348 (30), 347 (100), 319 (32).

***trans*-Ethyl-2-(2-chloroacetyl)-1-(4-methoxyphenyl)-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 8b**

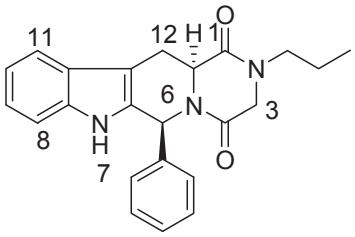


Yield (98%), white powder, mp: 174-176 °C, $[\alpha]_D^{15}$ = -25.4° (c = 0.59, CH_2Cl_2). IR (KBr) ν 3369 (NH), 1732, 1639 (C=O), 1609, 1509, 1440, 1342, 1253, 1174, 1045 cm^{-1}**.** MS *m/z* (%). 427/429 ($M+H^+$, 100), 321 (10), 319 (30).

3. General procedure for the synthesis of compounds 10 and 11

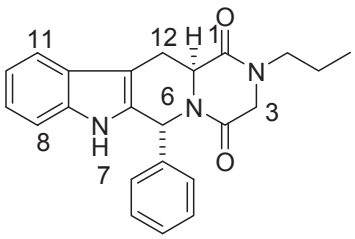
A mixture of **9a** (100 mg, 0.25 mmol) and propylamine (64 mg, 1.25 mmol) in dry EtOH (10 ml) was stirred for 24 h at room temperature. Then, the mixture was poured in water and extracted with EtOAc for three times. The combined organic phases were washed, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by means of column chromatography on silicagel (hexane/EtOAc, 1/1) gave pure compound **11a** (88 mg, 94%).

***cis*-6-Phenyl-2-propyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 11a**



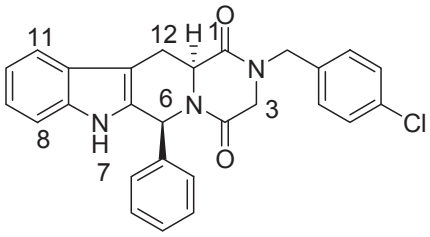
Yield 94%. White powder, mp : 254-255.5 °C, $[\alpha]_D^{15}$ = -35° (c = 0.4, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 0.92 (3H, t, *J* = 7.3 Hz, Me), 1.53-1.67 (2H, m, H-2´), 3.19-3.34 (2H, m, overlap, H-12a, H-1a´), 3.48-3.61 (1H, m, H-1´b), 3.75 (1H, dd, *J* = 17.2, 4.6 Hz, H-12b), 3.89 (1H, d, *J* = 17.5 Hz, H-3a), 4.06 (1H, d, *J* = 17.5 Hz, H-3b), 4.31 (1H, dd, *J* = 10.2, 3.3 Hz, H-13), 6.26 (1H, br. s, H-6), 7.13-7.32 (8H, m, 5x =CH, H-8, H-9, H-10), 7.59 (1H, dd, *J* = 8.9, 3.0 Hz, H-11), 8.01 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 11.14 (Me), 20.20 (C-2´), 23.55 (C-12), 47.89 (C-1´), 50.26 (C-3), 56.17 (C-13), 56.73 (C-6), 108.54 (C_{quat}), 111.21 (C-8), 118.59 (C-11), 120.03 (C-10), 122.41 (C-9), 126.18 (C_{quat}), 126.93 (2x =CH), 127.80 (=CH), 128.71 (2x =CH), 132.81 (C_{quat}), 136.51 (C_{quat}), 141.38 (C_{quat}), 166.39 (C=O), 167.17 (C=O). IR (KBr) ν 3317 (NH), 2955, 1671 (C=O), 1656 (C=O), 1623, 1426, 1310, 1271, 1226, 1209, 1155 cm^{-1}. MS *m/z* (%). 374 ($M+H^+$, 100).

***trans*-6-Phenyl-2-propyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 10b**



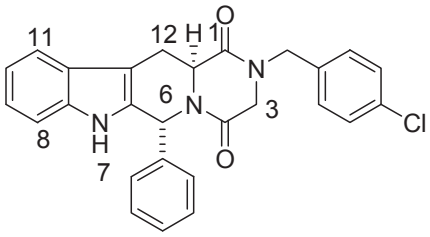
Yield 90%. White powder, mp : 192-193.5 °C, $[\alpha]_D^{15}$ = -240° (c = 0.5, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 0.91 (3H, t, *J* = 7.3 Hz, Me), 1.49-1.63 (2H, m, H-2´), 2.90 (1H, ddd, dd, *J* = 1.1, 11.6, 15.2 Hz, H-12a), 3.02-3.12 (1H, m, H-1´a), 3.47-3.54 (2H, m, overlap, H-1´b, H-12b), 3.84 (1H, d, *J* = 17.8 Hz, H-3a), 4.40 (1H, d, *J* = 17.8 Hz, H-3b), 4.24 (1H, dd, *J* = 11.6, 4.0 Hz, H-13), 7.02 (1H, br. s, H-6), 7.08-7.28 (8H, m, 5x =CH, H-8, H-9, H-10), 7.51 (1H, dd, *J* = 8.9, 2.9 Hz, H-11), 8.58 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 11.02 (Me), 19.59 (C-2´), 27.60 (C-12), 47.48 (C-1´), 49.24 (C-3), 51.99 (C-6), 52.13 (C-13), 108.68 (C_{quat}), 111.09 (C-8), 118.26 (C-11), 119.80 (C-10), 122.43 (C-9), 126.15 (C_{quat}), 128.61 (2x =CH), 128.72 (3x =CH), 129.62 (C_{quat}), 136.30 (C_{quat}), 138.22 (C_{quat}), 161.59 (C=O), 165.14 (C=O). IR (KBr) ν 3219 (NH), 2929, 1662 (C=O), 1653 (C=O), 1620, 1495, 1455, 1335, 1262, 1164 cm^{-1}. MS *m/z* (%). 374 ($M+H^+$, 100), 149 (20), 102 (20).

***cis*-2-(4-Chlorobenzyl)-6-phenyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 11d**



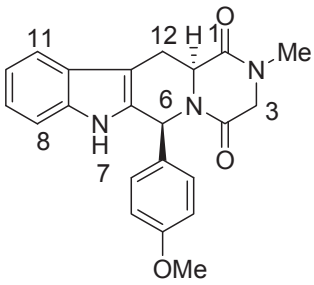
Yield 91%. White powder, mp: 190-192 °C, $[\alpha]_D^{15}$ = -14.7° (c = 0.475, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$, acetone-d_6): δ 3.27 (1H, dd, *J* = 11.2, 15.9 Hz, H-12a), 3.78 (1H, dd, *J* = 15.9, 3.6 Hz, H-12b), 3.79 (1H, d, *J* = 15.8 Hz, H-1a´), 3.89 (1H, d, *J* = 15.8 Hz, H-1´b), 4.29 (1H, dd, *J* = 11.2, 3.6 Hz, H-13), 4.37 (1H, d, *J* = 14.9 Hz, H-3a), 4.81 (1H, d, *J* = 14.9 Hz, H-3b), 6.24 (1H, br. s, H-6), 7.11-7.30 (12H, m, 12x =CH), 7.60 (1H, dd, *J* = 8.9, 3.0 Hz, H-11), 8.09 (1H, br. s, H-7), ^{13}C NMR-68 MHz ($CDCl_3$, acetone-d_6): δ 23.63 (C-12), 49.07 (C-1´), 49.92 (C-3), 56.26 (C-13), 56.57 (C-6), 105.96 (C_{quat}), 111.43 (C-8), 118.38 (C-11), 119.76 (C-10), 122.14 (C-9), 126.18 (C_{quat}), 126.97 (2x =CH), 127.63 (=CH), 128.59 (2x =CH), 129.13(2x =CH), 129.77 (2x =CH, C_{quat}), 133.28 (C_{quat}), 134.14 (C_{quat}), 136.74 (C_{quat}), 141.79 (C_{quat}), 166.77 (C=O), 167.02 (C=O). IR (KBr) ν 3233 (NH), 2911, 1691 (C=O), 1670 (C=O), 1643, 1597, 1492, 1451, 1411, 1322, 1309, 1217, 1091, 1013 cm^{-1}. MS *m/z* (%). 456/458 ($M+H^+$, 100), 304 (10), 149 (10), 102 (70).

***trans*-2-(4-Chlorobenzyl)-6-phenyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 10c**



Yield 81%. White powder, mp: 268-270 °C, $[\alpha]_D^{15}$ = -131.6° (c = 0.575, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 2.93 (1H, ddd, *J* = 1.0, 12.0, 15.5 Hz, H-12a), 3.56 (1H, dd, *J* = 15.5, 4.3 Hz, H-12b), 3.83 (1H, d, *J* = 16.5 Hz, H-1a´), 3.93 (1H, d, *J* = 16.5 Hz, H-1´b), 4.27 (1H, d, *J* = 14.5 Hz, H-3a), 4.36 (1H, dd, *J* = 11.9, 4.3 Hz, H-13), 4.76 (1H, d, *J* = 14.5 Hz, H-3b), 7.00 (1H, br. s, H-6), 7.11-7.33 (11H, m, 11x =CH), 7.53 (1H, db, *J* = 8.2, 3.0 Hz, H-11), 8.16 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 27.73 (C-12), 48.70 (C-1´), 48.79 (C-3), 52.02 (C-13), 52.54 (C-6), 108.62 (C_{quat}), 111.14 (C-8), 118.33 (C-11), 119.96 (C-10), 122.59 (C-9), 126.18 (C_{quat}), 128.68 (2x =CH), 128.80 (2x =CH), 129.14 (2x =CH), 129.60 (=CH), 129.81 (2x =CH, C_{quat}), 133.39 (C_{quat}), 134.16 (C_{quat}), 136.31 (C_{quat}), 138.17 (C_{quat}), 161.59 (C=O), 165.42 (C=O). IR (KBr) ν 3376 (NH), 2926, 1675 (C=O), 1648 (C=O), 1583, 1491, 1461, 1328, 1154, 1091, 1014, 907 cm^{-1}. MS *m/z* (%). 456/458 ($M+H^+$, 100), 304 (10), 149 (10), 102 (70).

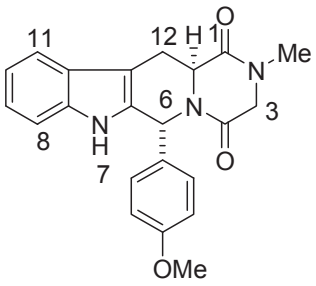
***cis*-6-(4-Methoxyphenyl)-2-methyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 11e**



Yield 95%. White powder, mp: 250-250.5 °C, $[\alpha]_D^{15}$ = -4.9° (c = 0.41, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 3.00 (3H, s, Me), 3.22 (1H, ddd, *J* = 1.1, 11.6, 16.1 Hz, H-12a), 3.69 (3H, s, OMe), 3.77 (1H, dd, *J* = 16.1, 4.7 Hz, H-12b), 3.87 (1H, d, *J* = 17.6 Hz, H-3a), 4.05 (1H, d, *J* = 17.6 Hz, H-3b), 4.26 (1H, dd, *J* = 11.6, 4.7 Hz, H-13), 6.20 (1H, br. s, H-6), 6.74 (2H, dd, *J* = 8.8, 3.0 Hz, H-3´, H-5´), 7.20-7.28 (5H, m, overlap, H-2´, H-6´, H-8, H-9, H-10), 7.61 (1H, db, *J* = 9.1 Hz, H-11), 8.15 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 23.17 (C-12), 33.60 (Me), 52.09 (C-3), 55.22 (OMe), 56.20 (C-13, C-6), 106.48

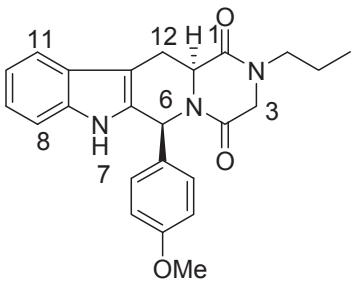
(C_{quat}), 111.24 (C-8), 113.93 (C-3′, C-5′), 118.55 (C-11), 120.08 (C-10), 122.39 (C-9), 126.16 (C_{quat}), 128.69 (C-2′, C-6′), 133.12 (C_{quat}), 133.34 (C_{quat}), 136.53 (C_{quat}), 159.03 (C_{quat}), 166.53 (C=O), 166.79 (C=O). IR (KBr) ν 3233 (NH), 2930, 1672 (C=O), 1651 (C=O), 1604, 1509, 1324, 1247, 1170, 1031 cm^{-1}. MS *m/z* (%). 376 ($M+H^+$, 50), 269 (50), 268 (100).

***trans*-6-(4-Methoxyphenyl)-2-methyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 10d**



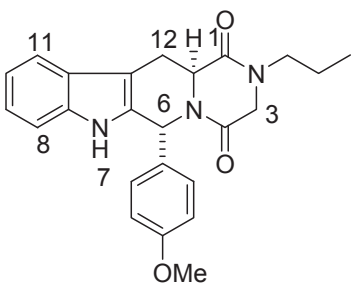
Yield 86%. White powder, mp: 258-259 °C, $[\alpha]_D^{15}$ = -9.2° (c = 0.435, CH_2Cl_2). ^1H NMR-270 MHz ($CDCl_3$): δ 2.93 (1H, dd, *J* = 11.9, 15.2 Hz, H-12a), 2.94 (3H, s, Me), 3.53 (1H, dd, *J* = 15.2, 4.3 Hz, H-12b), 3.73 (3H, s, OMe), 3.91 (1H, d, *J* = 17.5 Hz, H-3a), 4.08 (1H, d, *J* = 17.5 Hz, H-3b), 4.30 (1H, dd, *J* = 11.9, 4.3 Hz, H-13), 6.77 (2H, d, *J* = 8.9 Hz, H-3′, H-5′), 6.98 (1H, br. s, H-6), 7.16 (2H, d, *J* = 8.9 Hz, H-2′, H-6′), 7.12-7.19 (2H, m, H-9, H-10), 7.30 (1H, dd, *J* = 8.2, 1.3 Hz, H-8), 7.52 (1H, db, *J* = 8.2 Hz, H-11), 8.32 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 27.60 (C-12), 33.30 (Me), 51.39 (C-3), 51.59 (C-6), 52.36 C-13), 55.29 (OMe), 108.82 (C_{quat}), 111.12 (C-8), 114.14 (C-3′, C-5′), 118.31 (C-11), 119.93 (C-10), 122.55 (C-9), 126.27 (C_{quat}), 129.99 (C-2′, C-6′, C_{quat}), 130.49 (C_{quat}), 136.37 (C_{quat}), 159.89 (C_{quat}), 161.49 (C=O), 165.48 (C=O). IR (KBr) ν 3300 (NH), 2955, 1676 (C=O), 1650 (C=O), 1608, 1509, 1452, 1408,1320, 1170, 1032 cm^{-1}. MS *m/z* (%). 376 ($M+H^+$, 100), 269 (15), 268 (98), 240 (10), 203 (15), 189 (10).

***cis*-6-(4-Methoxyphenyl)-2-propyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 11f**



Yield 89%. White powder, mp: 182.0 °C decomp. ^1H NMR-270 MHz ($CDCl_3$): δ 0.91 (3H, t, *J* = 7.3 Hz, Me), 1.51-1.65 (2H, m, H-2′), 3.16-3.30 (2H, m, overlap, H-1′a, H-12a), 3.48-3.59 (1H, m, H-1′b), 3.67 (3H, s, OMe), 3.73 (1H, dd, *J* = 16.2, 5.0 Hz, H-12b), 3.86 (1H, d, *J* = 17.2 Hz, H-3a), 4.04 (1H, d, *J* = 17.2 Hz, H-3b), 4.25 (1H, dd, *J* = 11.6, 5.0 Hz, H-13), 6.20 (1H, br. s, H-6), 6.72 (2H, dd, *J* = 8.6, 3.0 Hz, H-3′, H-5′), 7.10-7.25 (5H, m, overlap, H-2′, H-6′, H-8, H-9, H-10), 7.58 (1H, db, *J* = 8.9, H-11), 8.28 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 11.09 (Me), 20.16 (C-2′), 23.39 (C-12), 47.82 (C-1′), 50.26 (C-3), 55.13 (OMe), 55.92 (C-13), 56.15 (C-6), 106.34 (C_{quat}), 111.19 (C-8), 113.89 (C-3′, C-5′), 118.45 (C-11), 119.89 (C-10), 122.23 (C-9), 126.13 (C_{quat}), 128.45 (C-2′, C-6′), 133.14 (C_{quat}), 133.35 (C_{quat}), 136.44 (C_{quat}), 158.94 (C_{quat}), 166.39 (C=O), 167.17 (C=O). MS *m/z* (%). 376 ($M+H^+$, 52), 269 (54), 268 (100).

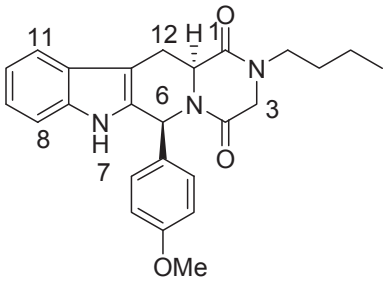
***trans*-6-(4-Methoxyphenyl)-2-propyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 10e**



Yield 93%. White powder, mp: 174.5°C decomp. ^1H NMR-270 MHz ($CDCl_3$): δ 0.92 (3H, t, *J* = 7.3 Hz, Me), 1.50-1.64 (2H, m, H-2′), 2.89 (1H, ddd, *J* = 2.3, 11.9, 15.5 Hz, H-12a), 3.09-3.16 (1H, m, H-1′a), 3.44-3.66 (2H, m, overlap, H-12b, H-

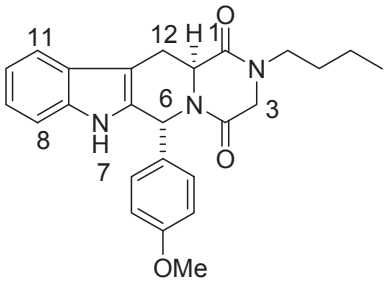
1´b), 3.71 (3H, s, OMe), 3.83 (1H, d, *J* = 17.5 Hz, H-3a), 4.05 (1H, d, *J* = 17.48 Hz, H-3b), 4.27 (1H, dd, *J* = 11.9, 4.0 Hz, H-13), 6.73 (2H, d, *J* = 8.6 Hz, H-3´, H-5´), 6.94 (1H, br. s, H-6), 7.09-7.20 (4H, m, overlap, H-2´, H-6´, H-9, H-10), 7.28 (1H, db, *J* = 7.9 Hz, H-8), 7.52 (1H, db, *J* = 8.6 Hz, H-11), 8.53 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 11.03 (Me), 19.61 (C-2´), 27.60 (C-12), 47.48 (C-1´), 49.29 (C-3), 51.50 (C-6), 52.38 (C-13), 55.20 (OMe), 108.61 (C_{quat}), 111.09 (C-8), 114.00 (C-3´, C-5´), 118.24 (C-11), 119.77 (C-10), 122.39 (C-9), 126.20 (C_{quat}), 129.94 (C-2´, C-6´), 130.04 (C_{quat}), 130.44 (C_{quat}), 136.28 (C_{quat}), 159.69 (C_{quat}), 161.78 (C=O), 165.19 (C=O). MS *m/z* (%) 390 ($M+H^+$, 30), 387 (30), 386 (100), 250 (25), 222 (10).

***cis*-6-(4-Methoxyphenyl)-2-butyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 11g**



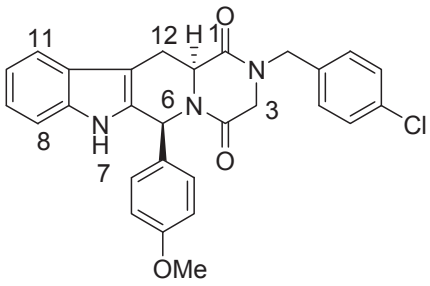
Yield 90. White powder, mp: 176-177 °C, $[\alpha]_D^{15}$ = -39.5° (c = 0.405, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 0.93 (3H, t, *J* = 7.3 Hz, Me), 1.28-1.38 (2H, m, H-3´), 1.48-1.59 (2H, m, H-2´), 3.16-3.34 (2H, m, overlap, H-1´a, H-12a), 3.52-3.63 (1H, m, H-1´b), 3.68 (3H, s, OMe), 3.70 (1H, dd, overlap, H-12b), 3.87 (1H, d, *J* = 17.5 Hz, H-3a), 4.00 (1H, d, *J* = 17.5 Hz, H-3b), 4.26 (1H, dd, *J* = 11.2, 4.0 Hz, H-13), 6.21 (1H, br. s, H-6), 6.73 (2H, d, *J* = 8.6 Hz, H-3´´, H-5´´), 7.13-7.25 (5H, m, overlap, H-2´´, H-6´´, H-8, H-9, H-10), 7.58 (1H, db, *J* = 7.9 Hz, H-11), 8.14 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 13.00 (Me), 19.93 (C-3´), 23.45 (C-12), 28.95 (C-2´), 46.07 (C-1´), 50.28 (C-3), 55.17 (OMe), 55.99 (C-13), 56.21 (C-6), 106.47 (C_{quat}), 111.21 (C-8), 113.94 (C-3´, C-5´), 118.49 (C-11), 119.96 (C-10), 122.30 (C-9), 126.16 (C_{quat}), 128.50 (C-2´, C-6´), 133.14 (C_{quat}), 133.37 (C_{quat}), 136.48 (C_{quat}), 159.01 (C_{quat}), 166.34 (C=O), 167.19 (C=O). IR (KBr) ν 3247 (NH), 2955, 1671 (C=O), 1656 (C=O), 1623, 1511, 1425, 1320, 1249, 1174, 1029 cm^{-1}. MS *m/z* (%). 418 ($M+H^+$, 50), 311 (20), 310 (100).

***trans*-6-(4-Methoxyphenyl)-2-butpyl-2,3,6,7,12,12a-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 10f**



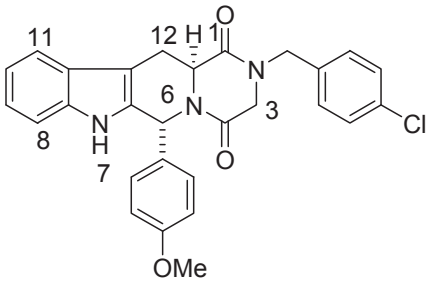
Yield 93%. White powder, mp: 209-209.5 °C, $[\alpha]_D^{15}$ = -94.7° (c = 0.54, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 0.94 (3H, t, *J* = 7.3 Hz, Me), 1.25-1.36 (2H, m, H-3´), 1.39-1.58 (2H, m, H-2´), 2.90 (1H, dd, *J* = 15.2, 11.9 Hz, H-12a), 3.11-3.21 (1H, m, H-1´a), 3.48-3.59 (2H, m, overlap, H-12b, H-1´b), 3.72 (3H, s, OMe), 3.88 (1H, dd, *J* = 17.8 Hz, H-3a), 4.06 (1H, d, *J* = 17.8 Hz, H-3b), 4.27 (1H, dd, *J* = 11.9, 4.0 Hz, H-13), 6.74 (2H, d, *J* = 8.6 Hz, H-3´´, H-5´´), 6.95 (1H, br. s, H-6), 7.10-7.26 (4H, m, overlap, H-2´´, H-6´´, H-9, H-10), 7.29 (1H, db, *J* = 8.3 Hz, H-8), 7.51 (1H, db, *J* = 8.2 Hz, H-11), 8.44 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 13.69 (Me), 19.87 (C-3´), 27.60 (C-12), 28.41 (C-2´) , 45.57 (C-1´), 49.31 (C-3), 51.52 (C-6), 52.40 (C-13), 55.24 (OMe), 108.68 (C_{quat}), 111.09 (C-8), 114.02 (C-3´´, C-5´´), 118.26 (C-11), 119.80 (C-10), 122.43 (C-9), 126.21 (C_{quat}), 129.97 (C-2´´, C-6´´), 130.04 (C_{quat}), 130.42 (C_{quat}), 136.28 (C_{quat}), 159.73 (C_{quat}), 161.78 (C=O), 165.10 (C=O). IR (KBr) ν 3316 (NH), 2954, 1666 (C=O), 1660 (C=O), 1622, 1584, 1513, 1452, 1308, 1253, 1175, 1160, 1034 cm^{-1}. MS *m/z* (%). 418 ($M+H^+$, 100), 391 (10), 347 (30), 311 (10), 310 (30).

***cis*-2-(4-Chlorobenzyl)-6-(4-methoxyphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 11i**



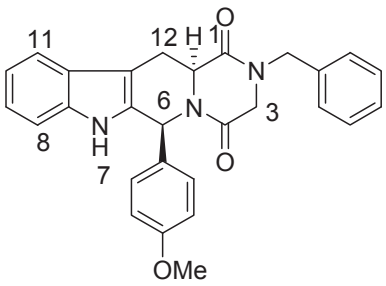
Yield 91%. White powder, mp : 194-196 °C. decomp, $[\alpha]_D^{15}$ = -25° (c = 0.36, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 3.28 (1H, ddd, d, *J* = 1.0, 11.5, 15.8 Hz, H-12a), 3.73 (3H, s, OMe), 3.80 (1H, dd, *J* = 5.0, 15.5 Hz, H-12b), 3.83 (1H, d, *J* = 17.5 Hz, H-1´a), 3.94 (1H, d, *J* = 17.5 Hz, H-1´b), 4.36 (1H, dd, *J* = 5.0, 11.5 Hz, H-13), 4.37 (1H, d, *J* = 14.9 Hz, H-3a), 4.84 (1H, d, *J* = 14.9 Hz, H-3b), 6.21 (1H, br. s, H-6), 6.76 (2H, d, *J* = 8.9 Hz, H-3´´, H-5´´), 7.15-7.32 (8H, m, 8x =CH), 7.62 (1H, db, *J* = 9.2 Hz, H-11), 7.83 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 23.59 (C-12), 49.13 (C-1´), 49.85 (C-3), 55.20 (C-13), 56.05 (OMe), 56.24 (C-6), 106.45 (C_{quat}), 111.23 (C-8), 113.98 (C-3´, C-5´), 118.51 (C-11), 119.57 (C_{quat}), 120.07 (C-10), 122.44 (C-9), 126.16 (C_{quat}), 128.55 (C-2´, C-6´), 129.14 (2x =CH), 129.70 (2x=CH), 133.04 (C_{quat}), 133.22 (C_{quat}), 133.78 (C_{quat}), 136.50 (C_{quat}), 159.10 (C_{quat}), 166.67(C=O), 166.73 (C=O). IR (KBr) ν 3333 (NH), 2928, 1686 (C=O), 1642 (C=O), 1623, 1510, 1491, 1438, 1409, 1307, 1251, 1091 cm^{-1}. MS *m/z* (%). 486 ($M+H^+$, 90), 378 (70), 264 (30), 230 (30), 125 (100).

***trans*-2-(4-Chlorobenzyl)-6-(4-methoxyphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 10h**



Yield 92%. White powder, mp: 277-279 °C, $[\alpha]_D^{15}$ = -64.8° (c = 0.46, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 2.94 (1H, dd, d, *J* = 11.9, 14.2 Hz, H-12a), 3.60 (1H, dd, *J* = 4.3, 14.2 Hz, H-12b), 3.75 (3H, s, OMe), 3.84 (1H, d, *J* = 17.5 Hz, H-1´a), 3.95 (1H, d, *J* = 17.5 Hz, H-1´b), 4.32 (1H, d, *J* = 14.5 Hz, H-3a), 4.37 (1H, dd, *J* = 4.3, 11.9 Hz, H-13), 4.75 (1H, d, *J* = 14.5 Hz, H-3b), 6.78 (2H, d, *J* = 8.6 Hz, H-3´´, H-5´´), 6.95 (1H, br. s, H-6), 7.14-7.34 (9H, m, 9x =CH), 7.54 (1H, db, *J* = 7.9 Hz, H-11), 8.08 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 27.78 (C-12), 48.72 (C-1´), 48.84 (C-3), 51.55 (C-6), 52.43 (C-13), 55.31 (OMe), 108.73 (C_{quat}), 111.12 (C-8), 114.14 (C-3´, C-5´), 118.34 (C-11), 120.02 (C-10), 122.64 (C-9), 126.22 (C_{quat}), 129.18 (C-2´, C-6´), 129.88 (2x=CH), 129.97 (C_{quat}), 130.06 (2x=CH), 130.26 (C_{quat}), 133.44 (C_{quat}), 134.19 (C_{quat}), 136.26 (C_{quat}), 159.91 (C_{quat}), 161.45 (C=O), 165.46 (C=O). IR (KBr) ν 3323 (NH), 2927, 1686 (C=O), 1652 (C=O), 1624, 1611, 1512, 1467, 1330, 1255, 1176, 1185, 1092, 1033 cm^{-1}. MS *m/z* (%). 486/488 ($M+H^+$, 100), 391 (50), 380 (25), 378 (40), 279 (25), 238 (20), 149 (350).

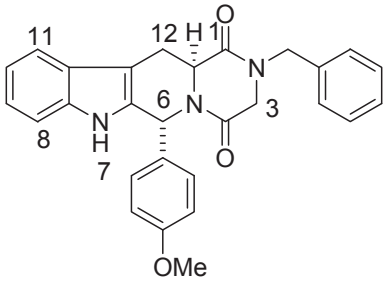
***cis*-2-Benzyl-6-(4-methoxyphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 11h**



Yield 89%. White powder, mp: 190-191 °C, $[\alpha]_D^{15}$ = -32.6° (c = 0.46, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 3.28 (1H, dd, d, *J* = 10.9, 15.2, H-12a), 3.70

(3H, s, OMe), 3.82 (1H, dd, *J* = 4.6, 15.2 Hz, H-12b), 3.84 (1H, d, *J* = 17.5 Hz, H-1´a), 3.93 (1H, d, *J* = 17.5 Hz, H-1´b), 4.34 (1H, dd, *J* = 4.6, 10.9 Hz, H-13), 4.38 (1H, d, *J* = 14.5 Hz, H-3a), 4.90 (1H, d, *J* = 14.5 Hz, H-3b), 6.20 (1H, br. s, H-6), 6.74 (2H, d, *J* = 8.6 Hz, H-3´´, H-5´´), 7.14-7.35 (10H, m, 10x =CH), 7.61 (1H, db, *J* = 8.9 Hz, H-11), 7.93 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 23.65 (C-12), 49.74 (C-1´), 49.79 (C-3), 55.20 (C-13), 56.05 (OMe), 56.28 (C-6), 106.54 (C_{quat}), 111.21 (C-8), 113.98 (C-3´´, C-5´´), 118.53 (C-11), 120.05 (C-10), 122.41 (C-9), 126.20 (C_{quat}), 128.12 (=CH), 128.33 (2x =CH), 128.52 (2x=CH), 128.97 (2x=CH), 133.10 (C_{quat}), 133.33 (C_{quat}), 135.20 (C_{quat}), 136.49 (C_{quat}), 159.06 (C_{quat}), 166.57 (C=O), 166.95 (C=O). IR (KBr) ν 3323 (NH), 2928, 1686 (C=O), 1641 (C=O), 1609, 1509, 1495, 1438, 1415, 1363, 1322, 1306, 1277, 1218, 1174, 1030 cm^{-1}. MS *m/z* (%). 452 (M+H$^+$, 100), 445 (15), 320 (15), 319 (15), 212 (9), 196 (45).

***trans*-2-Benzyl-6-(4-methoxyphenyl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione 10g**

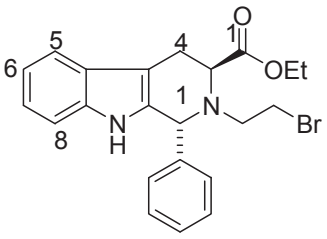


Yield 85%. White powder, mp: 230°C decomp, $[\alpha]_D^{15}$ = -53.3° (c = 0.45, CH_2Cl_2). ^{1}H NMR-270 MHz ($CDCl_3$): δ 2.94 (1H, dd, d, *J* = 11.6, 15.5 Hz, H-12a), 3.56 (1H, dd, *J* = 5.0, 15.5 Hz, H-12b), 3.72 (3H, s, OMe), 3.83 (1H, d, *J* = 17.8 Hz, H-1´a), 3.92 (1H, d, *J* = 17.8 Hz, H-1´b), 4.29 (1H, d, *J* = 14.5 Hz, H-3a), 4.36 (1H, dd, *J* = 4.0, 11.6 Hz, H-13), 4.82 (1H, d, *J* = 14.5 Hz, H-3b), 6.75 (2H, d, *J* = 8.6 Hz, H-3´´, H-5´´), 6.92 (1H, br. s, H-6), 7.24-7.30 (4H, m, 4x =CH), 7.31-7.54 (6H, m, 6x =CH), 7.53 (1H, db, *J* = 8.2 Hz, H-11), 8.27 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 27.87 (C-12), 48.86 (C-1´), 49.34 (C-3), 51.57 (C-6), 52.52 (C-13), 55.34 (OMe), 108.86 (C_{quat}), 111.14 (C-8), 114.17 (C-3´´, C-5´´), 118.38 (C-11), 120.02 (C-10), 122.62 (C-9), 126.29 (C_{quat}), 128.24 (=CH), 128.53 (C-2´´, C-6´´), 129.02 (2x=CH, C_{quat}), 130.10 (2x=CH), 130.36 (C_{quat}), 133.91 (C_{quat}), 136.31 (C_{quat}), 159.92 (C_{quat}), 161.68 (C=O), 165.42 (C=O). IR (KBr) ν 3323 (NH), 2927, 1686 (C=O), 1652 (C=O), 1624, 1611, 1512, 1467, 1330, 1255, 1176, 1185, 1092, 1033 cm^{-1}. MS *m/z* (%). 486 (M+H$^+$, 100), 391 (50), 380 (25), 378 (40), 279 (25), 238 (20), 194 (100).

4. Synthesis of *trans*-ethyl-2-(2-bromoethyl)-1-phenyl-2,3,4,9-tetrahydro-*1H*-β-carboline-3-carboxylate 12

A mixture of **6a** (800 mg, 2.5 mmol), 1,2-dibromoethane (5.52 g, 60.4 mmol) and K_2CO_3 (380 mg, 2.75 mmol) was stirred at reflux for 24 h. Then, the mixture was poured in water and extracted with EtOAc for three times. The combined organic phases were washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by means of column chromatography on silicagel (hexane/EtOAc) gave pure **12** in 48% yield.

***trans*-Ethyl-2-(2-bromoethyl)-1-phenyl-2,3,4,9-tetrahydro-1H-β-carboline-3-carboxylate 12**



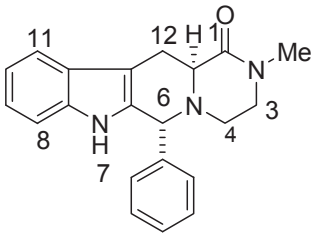
Yield 45%. Yellow oil. ^{1}H NMR-300 MHz ($CDCl_3$): δ 1.19 (3H, t, *J* = 7.2 Hz, Me), 3.00 (1H, dd, *J* = 3.58, 9.1 Hz, H-4a), 3.10-3.22 (3H, m, overlap, H-4b, H-1´), 3.29-

3.35 (2H, m, H-2´), 4.01-4.17 (3H, m, overlap, H-3, OC<u>H</u>$_2$), 5.42 (1H, s, H-6), 7.05-7.16 (3H, m, 3x =CH), 7.24-7.39 (5H, m, 5x =CH), 7.51 (1H, db, *J* = 8.8, H-5). ^{13}C NMR-68 MHz ($CDCl_3$): δ 14.21 (Me), 24.94 (C-2´), 31.42 (C-4), 54.70 (C-1´), 59.51 (C-3), 60.61 (OC<u>H</u>$_2$), 61.62 (C-1), 106.14 (C_{quat}), 110.81 (C-8), 118.22 (C-5), 119.36 (C-6), 121.70 (C-7), 126.88 (C_{quat}), 128.37 (=CH), 128.78 (2x =CH), 129.01 (2x =CH), 134.86 (C_{quat}), 136.48 (C_{quat}), 141.82 (C_{quat}), 173.18 (C=O). IR (KBr) ν 3396 (NH), 2927, 2854, 1731 (C=O), 1603, 1493, 1463, 1455, 1268, 1186, 1113, 1028 cm^{-1}. MS *m/z* (%) 443/445 (M+H$^+$, 10), 426/428 (10), 426/428 (30), 363/365(10), 348 (27), 347 (100), 220 (32).

5. General procedure for the synthesis of compounds 13

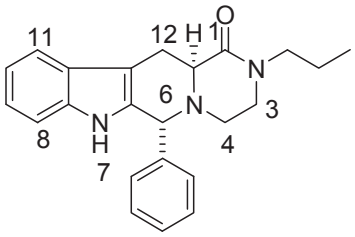
A mixture of **12** (100 mg, 0.25 mmol) and the appropriate amine (1.25 mmol) in dry EtOH (10 ml) was stirred for 24 h at room temperature. Then, the solvent was evaporated and the residue extracted with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by means of column chromatography on silicagel (hexane/EtOAc) gave pure **13**.

***trans*-2-Methyl-6-phenyl-3,4,6,7,12,12a-hexahydro-*2H*-pyrazino[1',2':1,6]pyrido[3,4-*b*]indol-1-one 13a**



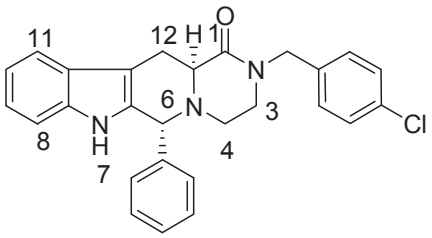
Yield 94%. White powder, mp: 253.4-255.8 ^{o}C ^{1}H NMR-300 MHz ($CDCl_3$): δ 2.48 (1H, ddd, *J* = 3.99, 9.20, 12.11 Hz, H-3a), 2.93 (3H, s, Me), 2.95 (1H, dd, *J* = 11.01, 15.93 Hz, H-12a), 3.05 (1H, dt, *J* = 12.11, 3.99 Hz, H-3b), 3.20 (1H, dt, *J* = 11.55, 3.99 Hz, H-4a), 3.48 (1H, dd, *J* = 15.93, 4.68 Hz, H-12b), 3.58 (1H, ddd, *J* = 11.55, 3.99, 9.20 Hz, H-4b), 3.70 (1H, dd *J* = 11.01, 4.68 Hz, H-13), 5.11 (1H, s, H-6), 7.08-7.20 (4H, m, 4x =CH), 7.22-7.33 (4H, m, 4x =CH), 7.58 (1H, db, *J* = 8.81, H-11), 7.78 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 24.87 (C-12), 34.39 (Me), 46.70 (C-3), 48.41 (C-4), 54.66 (C-13), 63.13 (C-6), 109.21 (C_{quat}), 110.84 (C-8), 118.59 (C-11), 119.58 (C-10), 122.04 (C-9), 126.89 (C_{quat}), 128.37 (3x =CH), 129.52 (2x =CH), 131.93 (C_{quat}), 136.39 (C_{quat}), 137.21 (C_{quat}), 169.93 (C=O). IR (KBr) ν 3219 (NH), 2924, 2853, 1632 (C=O), 1493, 1454, 1333, 1164, 1074 cm^{-1}. MS *m/z* (%). 332 (M+H$^+$, 80), 328 (10), 221 (10), 220 (100).

***trans*-6-Phenyl-2-propyl-3,4,6,7,12,12a-hexahydro-*2H*-pyrazino[1',2':1,6]pyrido[3,4-*b*]indol-1-one 13b**



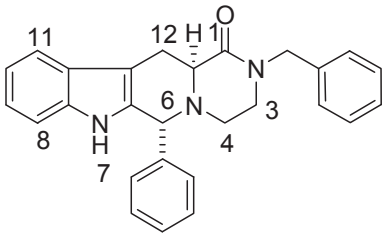
Yield 90%. White powder, mp : 215.5-216.5 ^{o}C. ^{1}H NMR-300 MHz ($CDCl_3$): δ 0.88 (3H, m, Me), 1.46-1.60 (2H, m, H-2´), 2.42 (1H, ddd, *J* = 3.9, 9.9, 11.9 Hz, H-3a), 2.92 (1H, dd, *J* = 11.3, 16.0 Hz, H-12a), 3.04 (1H, dt, *J* = 11.9, 4.0 Hz, H-3b), 3.13-3.20 (2H, m, overlap, H-1´a, H-4a), 3.42-3.60 (3H, m, overlap, H-1´b, H-4b, H-12b), 3.70 (1H, dd *J* = 11.0, 4.7 Hz, H-13), 5.12 (1H, s, H-6), 7.08-7.15 (4H, m, 4x =CH), 7.17-7.30 (4H, m, 4x =CH), 7.57 (1H, db, *J* = 8.8 Hz, H-11), 7.74 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 11.22 (Me), 20.17 (C-2´), 25.44 (C-12), 46.34 (C-1´), 46.93 (C-3), 48.44 (C-4), 54.76 (C-13), 63.15 (C-6), 109.39 (C_{quat}), 110.83 (C-8), 118.59 (C-11), 119.55 (C-10), 121.99 (C-9), 126.91 (C_{quat}), 128.34 (3x =CH), 129.59 (2x =CH), 132.02 (C_{quat}), 136.39 (C_{quat}), 136.92 (C_{quat}), 169.58 (C=O). IR (KBr) ν 3218 (NH), 2937, 2872, 1623 (C=O), 1496, 1455, 1332, 1336, 1265, 1227, 1164 cm^{-1}. MS *m/z* (%). 360 (M+H$^+$, 100), 356 (30), 357 (30), 221 (10), 220 (98).

***trans*-2-(4-Chlorobenzyl)-6-phenyl-3,4,6,7,12,12a-hexahydro-*2H*-pyrazino[1',2':1,6]pyrido[3,4-*b*]indol-1-one 13d**



Yield 92%. White powder, mp: 98-99 °C. ^{1}H NMR-300 MHz ($CDCl_3$): δ 2.41 (1H, ddd, *J* = 3.9, 9.9, 11.6 Hz, H-3a), 2.95-3.15 (3H, m, overlap, H-3b, H-4a, H-12a), 3.46 (1H, ddd, *J* = 11.3, 11.0, 3. 9 Hz, H-4b), 3.57 (1H, dd, *J* = 16.0, 5.0 Hz, H-12b), 3.78 (1H, dd, *J* = 11.0, 5.0, H-13), 4.54 (2H, t, *J* = 16.8 Hz, H-1´), 5.13 (1H, s, H-6), 7.09-7.33 (12H, m, 12x =CH), 7.61 (1H, db, *J* = 8.8 Hz, H-11), 7.65 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 25.37 (C-12), 45.82 (C-4), 46.90 (C-3), 49.35 (C-1´), 54.95 (C-13), 63.13 (C-6), 109.23 (C_{quat}), 110.86 (C-8), 118.62 (C-11), 119.68 (C-10), 122.13 (C-9), 126.86 (C_{quat}), 128.43 (2x =CH), 128.84 (2x =CH), 129.47 (3x =CH), 129.56 (2x =CH), 131.93 (C_{quat}), 133.40 (C_{quat}), 135.17 (C_{quat}), 136.39 (C_{quat}), 136.91 (C_{quat}), 169.99 (C=O). IR (KBr) ν 3401 (NH), 2914, 2853, 1658 (C=O), 1597, 1492, 1467, 1452, 1324, 1159 cm^{-1}. MS *m/z* (%). 442/444 ($M+H^+$, 100), 438/440 (70), 220 (88).

***trans*-2-Benzyl-6-phenyl-3,4,6,7,12,12a-hexahydro-*2H*-pyrazino[1',2':1,6]pyrido[3,4-*b*]indol-1-one 13c**

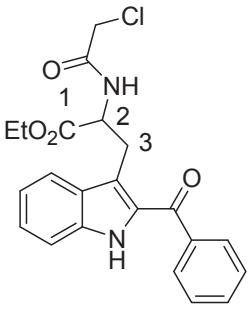


Yield 93%. White powder, mp: 109-110 °C. ^{1}H NMR-300 MHz ($CDCl_3$): δ 2.37 (1H, ddd, *J* = 3.9, 9.6, 11.6 Hz, H-3a), 2.97 (1H, dd, *J* = 4.2, 11.6 Hz, H-3b), 3.01-3.17 (2H, m, overlap, H-12a, H-4a), 3.43 (1H, ddd, *J* = 15.1, 4.2, 10.0 Hz, H-4b), 3.58 (1H, dd, *J* = 16.0, 5.0 Hz, H-12b), 3.76 (1H, dd, *J* = 11.0, 5.0 Hz, H-13), 4.51 (1H, d, *J* = 14.6 Hz, H-1´a), 4.59 (1H, d, *J* = 14.6 Hz, H-1´d), 5.07 (1H, s, H-6), 7.05-7.38 (13H, m, 13x =CH), 7.58 (1H, db, *J* = 8.8 Hz, H-11), 7.89 (1H, br. s, H-7). ^{13}C NMR-68 MHz ($CDCl_3$): δ 25.37 (C-12), 45.74 (C-4), 46.87 (C-3), 49.89 (C-1´), 54.93 (C-13), 63.10 (C-6), 109.12 (C_{quat}), 110.89 (C-8), 118.56 (C-11), 119.56 (C-10), 122.01 (C-9), 126.89 (C_{quat}), 127.50 (=CH), 128.05 (2x =CH), 128.36 (3x =CH), 128.66 (2x =CH), 129.55 (2x =CH), 132.05 (C_{quat}), 136.44 (C_{quat}), 136.59 (C_{quat}), 137.09 (C_{quat}), 169.96 (C=O). IR (KBr) ν 3400 (NH), 2916, 2853, 1633 (C=O), 1597, 1493, 1467, 1454, 1328, 1258, 1146, 1074cm^{-1}. MS *m/z* (%) 408 ($M+H^+$, 100), 404 (40), 221 (12), 420 (80), 412 (27), 178 (17).

6. General procedures for the synthesis of compounds 18

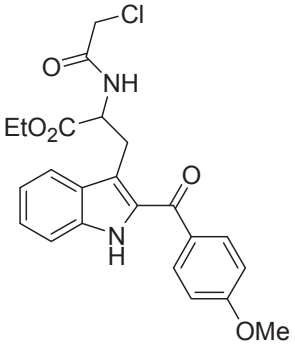
9b (500 mg, 0.226 mmol) and NBS (65 mg, 1.13 mmol) in a mixture of THF (10ml), CH_3COOH (10ml) and H_2O (10ml) were stirred at 0 °C for 15 min and subsequently at room temperature for 3 h. Then, the mixture was poured in water and extracted tree times with EtOAc. The combined organic phases were washed with aqueous Na_2CO_3, dried ($MgSO_4$) and evaporated *in vacuo*. Purification by means of column chromatography on silicagel (hexane/EtOAc, 4/6) gave pure **18b** (460 mg, 88%).

Ethyl-3-(2-benzoyl-1*H*-indol-3-yl)-2-(2-chloroacetylamino)-propionate 18a



Yield 84%. White powder, mp. 158°C. ^{1}H NMR-300 MHz ($CDCl_3$): δ 1.24 (3H, t, J = 7.2 Hz, C$\underline{H}_3$CH$_2$), 3.54-3.62 (2H, m, CH$_2$-3), 3.83 (1H, d, J_{AB} = 15.4 Hz, C$\underline{H}_A$H$_B$Cl), 3.96 (1H, d, J_{AB} = 15.4 Hz, CH$_A\underline{H}_B$Cl), 4.05-4.22 (2H, m, C$\underline{H}_2$CH$_3$), 4.75 (1H, td, J = 6.1, 7.2 Hz, CH-2), 7.22 (1H, sextet, J = 4.4 Hz, CH$_{Ar}$), 7.39 (2H, d, J = 3.9 Hz, 2xCH$_{Ar}$), 7.53-7.58 (2H, m, 2xCH$_{Ar}$), 7.63-7.67 (1H, m, CH$_{Ar}$), 7.77-7.84 (3H, m, 3xCH$_{Ar}$), 8.15 (1H, br. d, J = 6.6 Hz, NH), 8.51 (1H, br. s, NH). ^{13}C NMR-75 MHz ($CDCl_3$): δ 14.12 (C$\underline{H}_3$CH$_2$), 26.70 (CH$_2$-3), 42.27 (CH$_2$Cl), 54.76 (CH-2), 61.71 (C$\underline{H}_2$CH$_3$), 112.55 (CH$_{Ar}$), 119.91 (C$_{quat}$), 120.72 (CH$_{Ar}$), 121.25 (CH$_{Ar}$), 126.78 (CH$_{Ar}$), 127.73 (C$_{quat}$), 128.93 (2xCH$_{Ar}$), 129.39 (2xCH$_{Ar}$), 131.94 (C$_{quat}$), 132.84 (CH$_{Ar}$), 136.51 (C$_{quat}$), 138.29 (C$_{quat}$), 166.66 (HN-C=O), 171.27 (EtO-C=O), 188.68 (Ph-C=O). IR (ATR) ν 3264 (NH), 1752 (C=O), 1649 (C=O), 1632 (C=O), 1535, 1446, 1269, 1179 cm^{-1}. MS *m/z* (%) 413 (M+H$^+$, 100), 415 (32).

Ethyl-3-(2-(4-methoxybenzoyl)-1*H*-indol-3-yl)-2-(2-chloroacetylamino)-propionate 18b

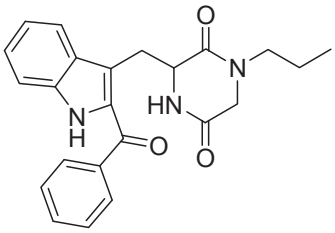


Yield 88%. White powder, mp. 175.5°C. ^{1}H NMR-300 MHz ($CDCl_3$): δ 1.25 (3H, td, J = 7.4, 1.7 Hz, C$\underline{H}_3$CH$_2$), 3.51-3.60 (2H, m, CH-3), 3.84 (1H, d, J_{AB} = 14.8 Hz, C$\underline{H}_A$H$_B$Cl), 3.92 (3H, s, OCH$_3$), 3.97 (1H, d, J_{AB} = 14.8 Hz, CH$_A\underline{H}_B$Cl), 4.04-4.21 (2H, m, C$\underline{H}_2$CH$_3$), 4.73 (1H, q, J = 6.6 Hz, CH-2), 7.01-7.04 (2H, m, 2xCH$_{Ar}$), 7.19-7.25 (1H, m, CH$_{Ar}$), 7.38-7.40 (2H, m, 2xCH$_{Ar}$), 7.76-7.86 (3H, m, 3xCH$_{Ar}$), 8.38 (1H, br. d, J = 5.5 Hz, NH), 8.49 (1H, br. s, NH). ^{13}C NMR-75 MHz ($CDCl_3$): δ 14.07 (C$\underline{H}_3$CH$_2$), 26.50 (CH$_2$-3), 42.26 (CH$_2$Cl), 54.91 (CH-2), 55.66 (OCH$_3$), 61.74 (C$\underline{H}_2$CH$_3$), 112.60 (CH$_{Ar}$), 114.14 (2xCH$_{Ar}$), 119.01 (C$_{quat}$), 120.46 (CH$_{Ar}$), 121.07 (CH$_{Ar}$), 126.38 (CH$_{Ar}$), 127.59 (C$_{quat}$), 130.67 (C$_{quat}$), 132.05 (2xCH$_{Ar}$), 132.40 (C$_{quat}$), 136.41 (CH$_{Ar}$), 163.58 (C$_{quat}$-OMe), 166.86 (HN-C=O), 171.39 (EtO-C=O), 187.36 (Ph-C=O). IR (ATR) ν 3253 (NH), 2982, 1732 (C=O), 1650 (C=O), 1626, 1597, 1531, 1509, 1252, 1170, 1024 cm^{-1}. MS *m/z* (%) 443 (M+H$^+$, 100), 445 (40).

7. General procedure for the synthesis of 3-(2-aroyl-*1H*-indol-3-ylmethyl)- piperazine-2,5-diones 19

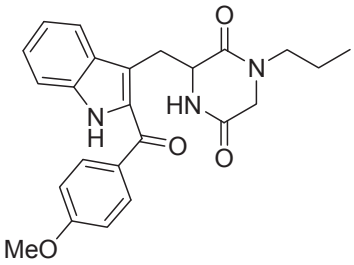
A mixture of **18b** (100 mg, 0.226 mmol) and propylamine (65 mg, 1.25 mmol) in dry EtOH (10ml) was stirred for 24h at room temperature. Then, the mixture was poured in water and extracted with EtOAc for three times. The combined organic phases were washed, dried ($MgSO_4$) and evaporated *in vacuo.* Purification by means of column chromatography on silicagel (EtOAc/MeOH, 9/1) gave pure **19b** (76 mg, 80%).

3-(2-Benzoyl-*1H*-indol-3-ylmethyl)-1-propylpiperazine-2,5-dione 19a



Yield 80%. Pale white powder, mp. 221°C decomp. ^{1}H NMR-300 MHz ($CDCl_3$): δ 0.84 (3H, t, *J* = 7.3 Hz, C<u>H</u>$_3$CH$_2$), 1.42-1.51 (2H, m, C<u>H</u>$_2$CH$_3$), 3.15-3.37 (4H, m, NCH_2 and CH_2-1'), 3.56-3.70 (2H, m, CH_2-6), 4.15-4.22 (1H, br. s, CH-3), 7.14 (1H, d, J = 16.0 Hz, NH), 7.21-7.28 (1H, m, CH_{Ar}), 7.33-7.39 (2H, m, 2xCH_{Ar}), 7.43-7.55 (4H, m, 4xCH_{Ar}), 7.61-7.65 (1H, m, CH_{Ar}), 7.82 (1H, m, *J* = 7.7 Hz, CH_{Ar}), 10.62 (1H, br. d, *J* = 28.1 Hz, NH). ^{13}C NMR-75 MHz ($CDCl_3$): δ 11.11 (<u>C</u>H$_3$CH$_2$), 19.80 (CH$_3$<u>C</u>H$_2$), 29.68 (CH-1'), 47.91 (NCH_2), 49.14 (CH_2-6), 56.71 (CH-3), 112.84 (CH_{Ar}), 118.50 (C_{quat}), 121.13 (CH_{Ar}), 121.24 (CH_{Ar}), 126.90 (CH_{Ar}), 127.39 (C_{quat}), 128.58 (2xCH_{Ar}), 129.31 (2xCH_{Ar}), 132.26 (CH_{Ar}), 132.84 (C_{quat}), 137.36 (C_{quat}), 137.41 (C_{quat}), 138.69 (C_{quat}), 165.81 (HN-C=O), 166.26 (HN-C=O), 189.06 (Ph-C=O). IR (ATR) ν 3254 (NH), 2932, 1738 (C=O), 1677 (C=O), 1664 (C=O), 1598, 1524, 1434, 1252, 1170 cm^{-1}. MS *m/z* (%) 390 (M+H$^+$, 100).

3-[2-(4-Methoxybenzoyl)-*1H*-indol-3-ylmethyl]-1-propylpiperazine-2,5-dione 19b



Yield 80%. Pale white powder, mp. 210.5°C. ^{1}H NMR-300 MHz ($CDCl_3$): δ 0.82-0.89 (3H, m, C<u>H</u>$_3$CH$_2$), 1.38-1.48 (2H, m, C<u>H</u>$_2$CH$_3$), 3.03-3.64 (6H, m, NCH_2, CH_2-1' and CH_2-6), 4.06-4.18 (1H, br. s, CH-3), 6.745-6.78 (2H, m, CH_{Ar}), 6.95 (1H, br. s, NH), 7.18-7.48 (4H, m, 4xCH_{Ar}), 7.43-7.55 (4H, m, 4xCH_{Ar}), 7.58 (1H, d, J = 7.7 Hz, CH_{Ar}), 7.75 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 10.23 (1H, br. s, NH). ^{13}C NMR-75 MHz ($CDCl_3$): δ 11.05 (<u>C</u>H$_3$CH$_2$), 19.77 (CH$_3$<u>C</u>H$_2$), 28.82 (CH-1'), 47.68 (NCH_2), 49.16 (CH_2-6), 55.59 (OCH_3), 56.29 (CH-3), 112.90 (CH_{Ar}), 113.73 (2xCH_{Ar}), 117.65 (C_{quat}), 120.91 (CH_{Ar}), 121.13 (CH_{Ar}), 126.28 (CH_{Ar}), 127.36 (C_{quat}), 130.90 (C_{quat}), 131.90 (2xCH_{Ar}), 133.06 (C_{quat}), 136.99 (C_{quat}), 163.12 (C_{quat}-OMe), 166.02 (HN-C=O), 166.29 (HN-C=O), 187.53 (Ph-C=O). IR (ATR) ν 3396 (NH), 3257 (NH), 1683 (C=O), 1651 (C=O), 1627 (C=O), 1606, 1463, 1423, 1316, 1253, 1031 cm^{-1}. MS *m/z* (%) 420 (M+H$^+$, 100).