Scalable Total Syntheses of *N*-Linked Tryptamine Dimers by Direct Indole-Aniline Coupling: Psychotrimine and Kapakahines B and F

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SUPPORTING INFORMATION

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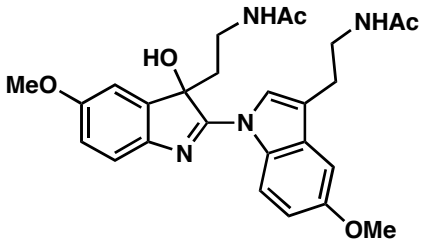
General Procedures. All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry acetonitrile (MeCN), dichloromethane (DCM), *N*-*N*-dimethylformamide (DMF), methanol (MeOH), tetrahydrofuran (THF), triethylamine, benzene and toluene were obtained by passing the previously degassed solvents through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254 or RP-18 F_{254s}) using UV light as the visualizing agent and an acidic solution of *p*-anisaldehyde, phosphomolybdic acid, cerric ammonium molybdate, Seebach's stain (PMA and CAM), ninhydrin, or potassium permanganate and heat as developing agents. E. Merck silica gel (60, particle size 0.043-0.063 mm) was used for flash column chromatography. J.T. Baker Bakerbond Octyl (C_8) 40 μm Prep LC Packing was used for reverse phase chromatography. NMR spectra were recorded on a Bruker DRX-600, Bruker DRX-500 or AV-400 spectrometer and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{1}H-NMR = 7.26, ^{13}C-NMR = 77.16, CD_3CN: ^{1}H-NMR = 1.94, ^{13}C-NMR = 118.26, DMSO-d_6: ^{13}C-NMR = 39.52, CD_3OD: ^{1}H-NMR = 3.31, ^{13}C-NMR = 49.00, CD_2Cl_2: ^{1}H-NMR = 5.32, ^{13}C-NMR = 54.00). The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, non = nonuplet, m = multiplet, br = broad, a = apparent. IR spectra were recorded on a Perkin-Elmer Spetrum BX spectrometer. High resolution mass spectra (HRMS) were recorded

on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 431 Polarimeter.

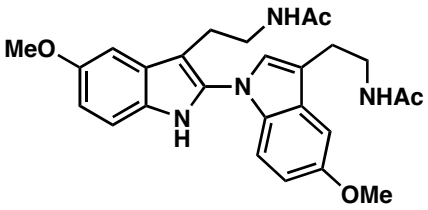
Note: Compounds **1**, **101**, **105**, **107** and **109** have been previously characterized, please see: Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886.

Compounds **102b**, **116**, **121**, **122**, **123**, **124** and **132** have been previously characterized, please see: Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 6360.



Melatonin dimer **29**: Melatonin (1.00 g, 4.31 mmol) and $Co(salen)_2$ (253 mg, 0.778 mmol, 0.18 equiv) were dissolved in DCM (200 mL, 0.02 M) under an atmosphere of oxygen. Oxygen was bubbled through the reaction intermittently for 24 hours. The reaction was quenched by washing with aqueous 1 M HCl (100 mL). The layers were separated and the organic layer was washed with aqueous 1 M NaOH (100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 1:2, DCM/acetone) to afford a white solid **29** (721 mg, 35%).

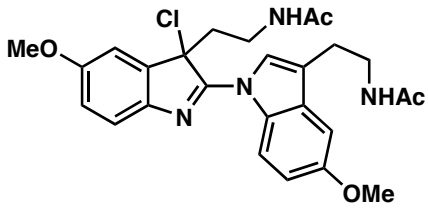
R_f = 0.15 (silica gel, 1:1 acetone/DCM); **M.p.**: 193-194 °C; **^{1}H-NMR** (400 MHz, CD_3OD) δ 8.62 (d, *J* = 9.0 Hz, 1 H), 8.06 (s, 1 H), 7.33 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 2.4 Hz, 1 H), 7.02 (d, *J* = 2.4 Hz, 1 H), 6.97 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.91 (dd, *J* = 8.4, 2.6 Hz, 1 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 3.61 – 3.42 (m, 2 H), 3.00 – 2.87 (m, 3 H), 2.68 – 2.60 (m, 1 H), 2.53 – 2.45 (m, 1 H), 2.40 – 2.34 (m, 1 H), 1.95 (s, 3 H), 1.42 (s, 3 H); **^{13}C-NMR** (150 MHz, CD_3OD) δ 173.4, 173.1, 169.2, 159.3, 157.7, 147.1, 140.5, 132.2, 132.2, 124.7, 120.7, 119.3, 118.5, 115.2, 113.7, 110.1, 102.4, 85.3, 56.2, 56.1, 40.6, 38.9, 36.0, 25.9, 22.7, 22.2; **IR** (film, cm^{-1}) 2923, 1629, 1562, 1473, 1260, 1163, 1054, 1033, 802, 734; **HRMS** (ESI^+) m/z Calc'd for $C_{26}H_{31}N_4O_5$ [M + H^+] 479.2289, found 479.2285.



Reduced melatonin dimer **30**: The hydroxyindolenine, **29**, (85.1 mg, 0.178 mmol) was dissolved in glacial acetic acid (3.6 ml, 0.05 M) and freshly activated zinc dust[1] (234 mg, 3.57 mmol, 20.0 equiv) was added. The vessel was flushed with nitrogen. After 1 hour at room temperature, the solution was diuluted with EtOAc (25 mL) and quenched with a saturated solution of $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was extracted additionally with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated to afford a yellow foam, **30** (78.9 mg, 96%).

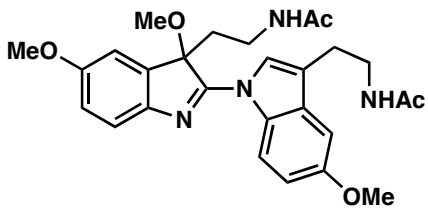
$\mathbf{R}_f$ = 0.18 (silica gel, 1:1 acetone/DCM); **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.24 (d, J = 8.8 Hz, 1 H), 7.18 – 7.13 (m, 4 H), 6.84 (d, J = 2.4 Hz, 1 H), 6.83 (d, J = 2.3 Hz, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.53 (t, J = 7.1 Hz, 2 H), 3.26 (t, J = 7.0 Hz, 2 H), 2.97 (t, J = 7.0 Hz, 2 H), 2.84 (t, J = 7.0 Hz, 2 H), 1.94 (3 H), 1.58 (s, 3 H); **^{13}C-NMR** (150 MHz, CD_3OD) δ 173.4, 173.1, 156.1, 155.5, 134.5, 132.6, 130.4, 130.0, 129.0, 128.5, 115.3, 113.6, 113.3, 113.0, 112.6, 106.8, 101.8, 101.7, 56.3, 41.2, 40.9, 26.0, 24.7, 22.7, 22.5; **IR** (film, cm^{-1}) 3286, 2925, 1632, 1564, 1476, 1454, 1436, 1365, 1258, 1217, 1175, 1113, 1055, 1033, 800, 736; **HRMS** (ESI^+) m/z Calc'd for $C_{26}H_{31}N_4O_4$ [M + H^+] 463.2345, found 463.2342.

[1] Commercial zinc dust was washed successively with 2% $HCl_{(aq)}$, water, 95% EtOH, and then Et_2O. The zinc dust was then dried under reduced pressure.



C3-chloroindolenine **31a**: The reduced melatonin dimer **30** (60.5 mg, 0.131 mmol) was suspended in DCM (8.0 mL, 0.02 M). The solution was cooled to 0 °C and solid NCS (18.3 mg, 0.137 mmol, 1.05 equiv) was added in a single portion. After 5 minutes, the reaction mixture was warmed to room temperature (23 °C) and became soluble. The solution was then concentrated. The crude material thus obtained was purified by flash column chromatography (0:1 to 1:1 acetone/DCM) to afford a yellow solid, **31a** (61.2 mg, 94%).

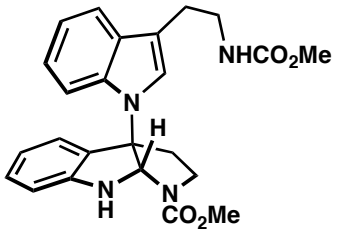
R_f = 0.21 (silica gel, 1:1 acetone/DCM); **M.p.**: 115 °C (decomp.); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 9.8 Hz, 1 H), 7.77 (s, 1 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.23 (at, *J* = 6.0 Hz, 1 H), 7.01 – 6.98 (m, 2 H), 6.96 (d, *J* = 2.3 Hz, 1 H), 6.92 (dd, *J* = 8.4, 2.6 Hz, 1 H); 5.42 (at, *J* = 5.8 Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.88 – 3.78 (m, 1 H), 3.41 – 3.17 (m, 3 H), 3.00 – 2.83 (m, 2 H), 2.56 – 2.50 (m, 1 H), 2.40 – 2.31 (m, 1 H), 2.02 (s, 3 H), 0.98 (s, 3 H) **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 171.3, 171.0, 164.7, 158.2, 156.6, 145.3, 137.2, 131.2, 130.9, 123.3, 120.5, 119.2, 118.1, 115.3, 113.5, 108.9, 101.4, 69.4, 56.0, 55.9, 39.6, 38.9, 36.9, 25.1, 23.1, 22.1; **IR** (film, cm^{-1}) 3681, 2923, 1734, 1653, 1561, 1475, 1261, 1166, 1055, 1033, 1014, 750; **HRMS** (ESI^+) m/z Calc'd for $C_{26}H_{30}ClN_4O_4$ [M + H^+] 497.1956, found 497.1939.



C3-methoxyindolenine **31b**: The chloroindolenine **31a** (8.8 mg, 0.018 mmol) was dissolved in MeOH (1.5 mL, 0.01 M) and K_2CO_3 (246 mg, 1.78 mmol, 100 equiv) was added. After 2 hours at room temperature (23 °C) the suspension was

concentrated, resuspended in DCM, and filtered through a cotton plug (repeated twice). After concentration the pure product a white solid was obtained (**31b**, 8.1 mg, 93%).

R_f = 0.14 (silica gel, 1:1 acetone/DCM); **M.p.**: 75-78 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 8.1, 1.4 Hz, 1 H), 7.79 (s, 1 H), 7.38 (d, *J* = 8.4 Hz, 1 H), 7.11 (at, *J* = 5.9 Hz, 1 H), 7.02 – 6.98 (m, 2 H), 6.93 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.87 (d, *J* = 2.5 Hz, 1 H), 5.39 (at, *J* = 5.9 Hz, 1 H), 3.90 – 3.88 (m, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.31 – 3.17 (m, 2 H), 3.06 (s, 3 H), 2.97 – 2.85 (m, 3 H), 2.33 – 2.15 (m, 2 H), 2.02 (s, 3 H), 0.95 (s, 3 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 171.0, 166.0, 157.9, 156.6, 147.0, 134.3, 130.9, 130.9, 123.2, 120.2, 119.1, 117.7, 114.8, 113.4, 109.3, 101.4, 91.0, 55.9 (2C), 53.0, 39.2, 37.4, 36.0, 25.1, 23.1, 22.2; **IR** (film, cm^{-1}) 3681, 3289, 2936, 1650, 1563, 1473, 1453, 1435, 1415, 1368, 1341, 1281, 1259, 1209, 1162, 1115, 1057, 1033, 801, 765, 735; **HRMS** (ESI^+) m/z Calc'd for $C_{27}H_{33}N_4O_5$ [M + H^+] 493.2451, found 493.2448.



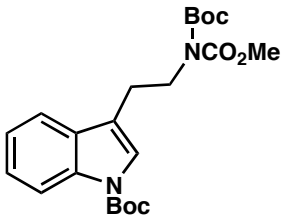
Tryptamine dimer **34**: The methyl carbamate of tryptamine, **33**,[2] (200.0 mg, 0.916 mmol was dissolved in MeCN (9.2 mL, 0.10 M) and cooled to –45°C. To this solution was added hydroxy(tosyloxy)iodobenzene[3] (359 mg, 0.915 mmol, 1.0 equiv) in five portions. After 3 hours, the reaction was diluted with EtOAc (10 mL)

[2] The methyl carbamate of tryptamine, **33**, was prepared by typical Schotten-Baumen conditions. It was recrystallized by dissolving in hot Et_2O, hexanes was added until the solution became opaque with a white precipitate and then reheated with addition of a minimal amount of Et_2O until dissolution. The solution was then cooled at 4°C (open to air), which after filtration afforded white flakes.

[3] [hydroxy(tosyloxy)iodo]benzene was prepared according to: Richter, H. W.; Koser, G. F.; Incarvito, C. D.; Rheingold, A. L. *Inorg. Chem.* **2007**, *46*, 5555. After heating the reaction mixture to reflux, the reaction mixture was allowed to cool to room temperature. After 1-2 days, the crystals were collected.

and quenched with a 1:1 mixture of saturated aqueous solution of $NaHCO_3$ and a saturated aqueous solution of $Na_2S_2O_3$ (30 mL). The layers were separated and the aqueous layer was extracted additionally with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (0:1 to 1:1 hexanes/EtOAc) to afford a yellow foam, **34** (0.6 mg, <1%).

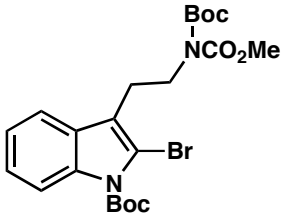
$\mathbf{R}_f$ = 0.18 (silica gel, 1:1 EtOAc/hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.58 (at, *J* = 7.0 Hz, 1 H), 7.39 – 7.33 (m, 1 H), 7.23-7.09 (m, 4 H), 6.96 (d, *J* = 8.5 Hz, 1 H), 6.85 – 6.81 (m, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 5.93 (s, 0.5 H), 5.88 (s, 0.5 H), 5.31 (s, 0.5 H), 4.90 (s, 0.5 H), 4.75 (brs, 1 H), 4.07 – 4.03 (m, 0.5 H), 3.95 – 3.91 (m, 0.5 H), 3.78 (s, 1.5 H), 3.73 (s, 1.5 H), 3.62 (s, 3 H), 3.51 – 3.38 (m, 2 H), 3.36 – 3.22 (m, 2 H), 2.90 – 2.87 (m, 2 H), 2.67 – 2.60 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 157.1, 155.5, 154.7, 149.3, 149.0, 135.2, 130.6, 129.7, 126.8, 124.8, 124.1, 124.1, 121.9, 119.6, 119.5, 119.5, 119.4, 119.3, 112.0, 111.9, 111.8, 110.5, 110.3, 79.4, 79.0, 75.7, 74.5, 52.9, 52.6, 52.0, 45.5, 45.3, 41.3, 35.7, 35.7, 28.1, 25.7; **IR** (film, cm^{-1}) 3344, 2953, 1696, 1610, 1528, 1453, 1384, 1309, 1256, 1233, 1200, 1117, 1050, 1033, 956, 890, 775, 743; **HRMS** (ESI^+) m/z Calc'd for $C_{24}H_{27}N_4O_4$ [M + H^+] 435.2032, found 435.2023.



Bis Boc tryptamine **SI-1**: The methyl carbamate of tryptamine **33** (50.0 mg, 0.229 mmol) and 4-dimethylaminopyridine (4.8 mg, 0.039 mmol, 0.2 equiv) were dissolved in DCM (1.5 mL, 0.2 M). Di-*tert*-butyl dicarbonate (120.0 mg, 0.550 mmol, 2.4 equiv) was added to the

reaction mixture, which was allowed to stir at room temperature for 2 hours. The reaction was concentrated. The crude material thus obtained was purified by flash column chromatography (0:1 to 1:10, EtOAc/hexanes) to afford a white foam, **SI-1** (90.2 mg, 94%).

R_f = 0.53 (silica gel, 3:1 hexanes/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.15 (brs, 1 H), 7.64 (d, *J* = 7.7 Hz, 1 H), 7.42 (s, 1 H), 7.33 (at, *J* = 7.2 Hz, 1 H), 7.27 (at, *J* = 7.8 Hz, 1 H), 3.97 (d, *J* = 7.8 Hz, 1 H), 3.93 (d, *J* = 7.2 Hz, 1 H), 3.84 (s, 3 H), 3.01 – 2.98 (m, 2 H), 1.68 (s, 9 H), 1.48 (s, 9 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 154.7, 151.9, 149.8, 135.6, 130.5, 124.5, 123.4, 122.6, 119.1, 117.4, 115.4, 83.6, 83.0, 53.8, 46.5, 28.3, 28.0, 24.8; **IR** (film, cm^{-1}) 2978, 1794, 1728, 1696, 1610, 1476, 1451, 1353, 1304, 1283, 1253, 1225, 1208, 1104, 1080, 1020, 965, 856, 767, 745; **HRMS** (ESI^+) m/z Calc'd for $C_{22}H_{30}N_2O_6Na$ [M + Na^+] 441.2002, found 441.2015.

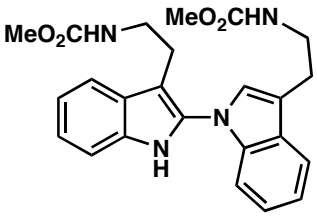


2-Bromo, bis-Boc tryptamine **37**: The bis-Boc compound **SI-1** (2.73 g, 6.52 mmol) was dissolved in DCM (65 mL, 0.1 M) and NBS[4] (1.19 g, 6.69 mmol, 1.0 equiv) was added. The reaction was allowed to stir at reflux for 1 hour at which point it was cooled to room temperature and quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (50 mL). The layers were separated and the aqueous layer was extracted additionally with DCM (3 × 50 mL). The combined organics were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography 1:0 to 4:1, hexanes/EtOAc) to afford a

[4] NBS was recrystallized according to Dauben, H. J.; McCoy, L. L. *J. Am. Chem. Soc.* **1959**, *81*, 4863.

white solid, **37** (2.92 g, 90%).

R_f = 0.33 (silica gel, 4:1 hexanes/EtOAc); **M.p.**: 78 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.2 Hz, 1 H), 7.58 (d, *J* = 7.2 Hz, 1 H), 7.29 – 7.20 (m, 2 H), 3.87 (d, *J* = 6.8 Hz, 1 H), 3.85 (d, *J* = 8.2 Hz, 1 H), 3.81 (s, 3 H), 3.04 (d, *J* = 7.9 Hz, 1 H), 3.02 (d, *J* = 7.1 Hz, 1 H), 1.68 (s, 9 H), 1.45 (s, 9 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 154.7, 151.6, 149.1, 136.5, 128.9, 124.6, 123.1, 120.0, 118.2, 115.4, 109.6, 84.9, 82.9, 53.8, 45.3, 28.3, 28.0, 25.0; **IR** (film, cm^{-1}) 2979, 1793, 1733, 1697, 1476, 1448, 1392, 1367, 1347, 1306, 1284, 1252, 1208, 1126, 1094, 1031, 965, 845, 821, 742, 703; **HRMS** (ESI^+) m/z Calc'd for $C_{22}H_{29}BrN_2O_6Na$ [M + Na^+] 519.1107, found 519.1110.



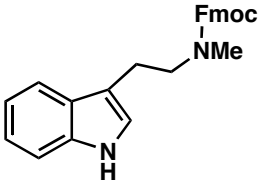
Methyl carbamate of tryptamine dimer **39**: The aryl bromide, **37**, (309 mg, 0.621 mmol), the methyl carbamate of tryptamine, **33** (542 mg, 2.48 mmol, 4.0 equiv), copper (I) iodide[5] (118 mg, 0.620 mmol, 1.0 equiv), K_3PO_4 (1.50 g, 7.07 mmol, 11.4 equiv), and racemic (±)-*trans*-*N*,*N*'-dimethyl-1,2-cyclohexanediamine (20 μL, 0.13 mmol, 0.20 equiv) were suspended in anhydrous 1,4-dioxane (3.0 mL, 0.2 M). The reaction mixture was sonicated with continuous argon bubbling and then heated at reflux (101 °C). After 24 hours the reaction mixture was cooled to room temperature, diluted with DCM (20 mL), filtered through celite and concentrated. The crude material thus obtained was partially purified by flash column chromatography (1:0 to 2:1, hexanes/EtOAc).

This material was then dissolved in DCM (2.0 mL) and TFA (0.5 mL, 4:1,

[5] Cuprous iodide was freshly purified according to Dieter, R. K.; Silks, L. A., Fishpaugh, J. R.; Kastner, M. E. *J. Am. Chem. Soc.* **1985**, *107*, 4679.

DCM/TFA) was added at room temperature (23 °C). After 1 hour the reaction mixture was diluted with toluene and concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 1:1, hexanes/EtOAc) to afford a white foam (54.4 mg, 21%).

R_f = 0.29 (silica gel, 1:1 EtOAc/hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.55 (s, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.61 (d, *J* = 7.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.30 – 7.14 (m, 5 H), 7.05 (s, 1 H), 5.32 (brs, 1 H), 4.70 (brs, 1 H), 3.61 (s, 3 H), 3.50 (add, *J* = 6.0, 6.0 Hz, 2 H), 3.39 (s, 3 H), 3.28 (add, *J* = 6.8, 6.3 Hz, 2 H), 2.96 (at, *J* = 6.4 Hz, 2 H), 2.86 (at, *J* = 7.7 Hz, 2 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 157.4, 157.0, 138.0, 133.7, 130.5, 128.3, 127.4, 126.7, 123.2, 123.1, 120.7, 120.4, 119.2, 114.9, 111.3, 110.8, 110.7, 106.7, 52.1, 52.0, 41.2, 41.1, 25.6, 24.2; **IR** (film, cm^{-1}) 3324, 2947, 1697, 1626, 1598, 1561, 1529, 1467, 1453, 1337, 1263, 1194, 1144, 1053, 1033, 1009, 745; **HRMS** (ESI^+) m/z Calc'd for $C_{24}H_{27}N_4O_4$ [M + H^+] 435.2032, found 435.2022.

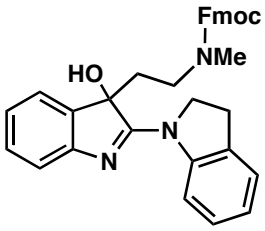


Fmoc methyl tryptamine **45**: The known methyl tryptamine[6] (600.0 mg, 3.44 mmol) was dissolved in DCM/saturated aqueous Na_2CO_3 (18:18 mL, 0.2 M) and FmocCl was added (892 mg, 3.45 mmol, 1.0 equiv). After 15 minutes at room temperature, the reaction mixture was acidified with 3 M HCl (40 mL), and the layers were separated. The aqueous layer was extracted additionally with DCM (3 × 20 mL). The combined organics were washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 3:1, hexanes/EtOAc) to afford white

[6] N_b-methyltryptamine was prepared according to Kametani, T.; Suzuki, T.; Ogasawara, K. *J. Chem. Soc.*, **1968**, *24*, 2965.

crystalline product, **45** (1.26 g, 92%).

R_f = 0.22 (silica gel, 2:1 hexanes/EtOAc); **M.p.**: 122-123 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 8.13 (s, 1 H), 7.81 – 7.55 (m, 5.5 H), 7.44 – 7.09 (m, 6.5 H), 7.02 (s, 0.5 H), 6.86 (s, 0.5 H), 4.47 – 4.41 (m, 2 H), 4.31 – 4.27 (m, 0.5 H), 4.14 – 4.09 (m, 0.5 H), 3.69 (at, *J* = 7.0 Hz, 1 H), 3.62 (at, *J* = 7.2 Hz, 1 H), 3.05 (at, *J* = 7.1 Hz, 1 H), 2.93 (s, 1.5 H), 2.92 (s, 1.5 H), 2.86 (at, *J* = 7.0 Hz, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 156.5, 156.4, 144.2, 141.4, 136.4, 127.7, 127.7, 127.6, 127.4, 127.1, 125.2, 125.0, 122.1, 122.1, 122.1, 120.1, 119.5, 119.5, 118.8, 118.7, 113.1, 113.0, 111.3, 67.4, 67.1, 50.1, 49.5, 47.5, 47.5, 35.1, 34.7, 24.0, 23.6; **IR** (film, cm^{-1}) 3314, 3050, 2936, 1679, 1619, 1478, 1449, 1428, 1404, 1357, 1338, 1297, 1264, 1244, 1199, 1136, 1120, 1101, 1070, 1033, 1009, 975, 937, 886, 809, 757, 701, 676**;** **HRMS** (ESI^+) m/z Calc'd for $C_{26}H_{25}N_2O_2$ [M + H^+] 397.1916, found 397.1906.

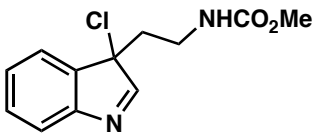


Indoline substituted tryptamine **47**: The Fmoc protected methyl tryptamine **45** (100.0 mg, 0.252 mmol) was dissolved in DCM (2.5 mL, 0.1 M) and triethylamine (35 μL, 0.251 mmol, 1.0 equiv) was added. The solution was cooled to 0 °C and a solution of NCS in DCM (37 mg, 0.277 mmol, 1.1 equiv; 1.2 mL, 0.2 M) was added dropwise. After 1.5 hours indoline[7] (40.0 μL, 0.36 mmol, 1.4 equiv) was added and the solution was allowed to warm to room temperature over 3 hours and stir at room temperature for an additional 9 hours. The reaction mixture was then exposed to an air atmosphere, quenched with aqueous 1 M HCl (30 mL), and the layers were separated. The aqueous

[7] Indoline was purified by distillation at reduced pressure with heating to afford a colorless oil.

layer was extracted additionally with DCM (3 × 20 mL). The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (10:1 to 2:1, hexanes/EtOAc) to afford a white foam (**47**, 78.8 mg, 59%).

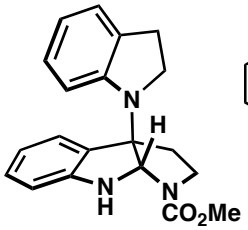
R_f = 0.06 (silica gel, 4:1 hexanes/EtOAc); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 8.44 – 8.39 (m, 1 H), 7.73 – 7.69 (m, 2 H), 7.51 – 7.25 (m, 5 H), 7.19 – 6.90 (m, 7 H), 6.77 – 6.66 (m, 1 H), 4.61 (brs, 0.5 H), 4.48 (brs, 0.5 H), 4.29 – 3.78 (m, 5 H), 3.12 – 2.16 (m, 6 H), 2.65 (s, 1.5 H), 2.62 (s, 1.5 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 170.5, 156.2, 156.1, 154.0, 153.7, 144.2, 144.1, 144.0, 141.4, 141.4, 141.3, 135.7, 135.7, 132.1, 130.1, 127.7, 127.3, 127.1, 125.1, 125.1, 125.0, 124.6, 124.5, 123.3, 122.5, 122.4, 121.4, 120.0, 117.5, 117.4, 117.2, 83.5, 83.3, 67.6, 67.3, 48.0, 47.3, 45.2, 44.2, 35.1, 33.8, 28.4, 28.2; **IR** (film, cm^{-1}) 3707, 3681, 3348, 2967, 2866, 2844, 1700, 1597, 1537, 1481, 1455, 1340, 1276, 1215, 1155, 1096, 1054, 1033, 1013, 872, 756, 740; **HRMS** (ESI^+) m/z Calc'd for $C_{34}H_{32}N_3O_3$ $[M + H^+]$ 530.2444, found 530.2432.

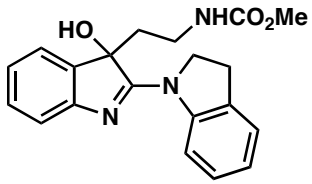


C3-chloroindolenine **50**: In a 5mm NMR tube, the methyl carbamate of tryptamine, **33**, (10.0 mg, 0.0458 mmol) was dissolved in CD_2Cl_2 (0.4 mL), triethylamine (9.6 μL, 0.069 mmol, 1.5 equiv) in a CD_2Cl_2 (50 μL) solution was added, and the solution was cooled to 0 °C. A CD_2Cl_2 solution of NCS (8.0 mg, 0.0599 mmol, 1.3 equiv; 0.2 mL, 0.3 M) was added (final concentration: 0.07 M). The reaction mixture was removed from the ice bath and vortexed while warming to room temperature. After 5 minutes at room temperature, the NMR data were collected and it was determined that the conversion was over 95%.

^{1}H-NMR (400 MHz, CD_2Cl_2) δ 8.00 (s, 1 H), 7.56 (d, *J* = 7.7 Hz, 1 H), 7.48 (d, *J* = 7.4 Hz, 1 H), 7.41 (at, *J* = 7.6 Hz, 1 H), 7.32 (at, *J* = 7.5 Hz, 1 H), 5.00 (brs, 1 H), 3.57 (s, 3 H), 3.15 – 3.12 (m, 2 H), 2.48 (m, 1 H), 2.38 – 2.28 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 172.2, 157.5, 153.9, 139.1, 131.1, 128.4, 123.6, 122.7, 72.4, 52.8, 38.3, 38.1.

Note: Attempted collection of high-resolution mass-spectrometry, IR and R_f of compound **50** was hampered by its instability. The ring-chain tautomer of **50**, the C3-chloro pyrroloindoline could be synthesized in its pure form in >95% conversion by treatment of **33** with *t*-butylhypochlorite (1.3 equiv) in DCM at 0 ºC.



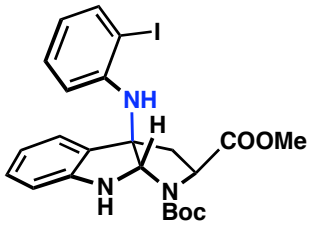


C3-substituted pyrroloindoline **49** and C2-substituted hydroxyindolenine **51**: The methyl carbamate of tryptamine, **33**, (200.0 mg, 0.916 mmol) was dissolved in DCM (9.2 mL, 0.1 M), triethylamine (153 μL, 1.10 mmol, 1.2 equiv) was added, and the solution was cooled to 0 °C. Solid NCS (134 mg, 1.00 mmol, 1.1 equiv) was added and the reaction mixture was allowed to warm to room temperature by removal from the ice bath. After the reaction mixture had warmed to room temperature (15 minutes), indoline (0.20 mL, 1.8 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 12 hours. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL) and the layers were separated. The aqueous layer was extracted additionally with DCM (3 × 20 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (10:1 to 2:1, hexanes/EtOAc) to afford a white foam **49** (55.6 mg, 18%)

and yellow foam **51** (144.9 mg, 45%).

C3-substituted pyrroloindoline **49**: $\mathbf{R_f}$ = 0.25 (silica gel, 3:1 hexanes/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 7.5 Hz, 1 H), 7.14 (at, *J* = 7.7 Hz, 1 H), 7.06 (at, *J* = 6.3 Hz, 1 H), 7.00 – 6.93 (m, 1 H), 6.77 – 6.54 (m, 4 H), 5.69 (s, 0.5 H), 5.65 (s, 0.5 H), 5.17 (brs, 0.5 H), 4.78 (brs, 0.5 H), 3.96 – 3.87 (m, 0.5 H), 3.83 – 3.74 (m, 0.5 H), 3.77 (s, 1.5 H), 3.73 (s, 1.5 H), 3.47 – 3.17 (m, 3 H), 3.02 – 2.80 (m, 3 H), 2.57 – 2.43 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 155.7, 154.9, 149.8, 149.6, 149.4, 132.0, 129.9, 129.9, 127.1, 124.9, 124.8, 119.4, 119.1, 118.6, 110.3, 110.2, 109.8, 109.7, 78.0, 77.0, 76.5, 75.3, 52.9, 52.6, 51.3, 51.2, 45.6, 45.5, 35.3, 35.2, 28.4, 28.3; **IR** (film, cm^{-1}) 3707, 3681, 3355, 2952, 2923, 2866, 2844, 1691, 1606, 1537, 1481, 1452, 1382, 1315, 1258, 1201, 1115, 1053, 1033, 1016, 953, 886, 743; **HRMS** (ESI^+) m/z Calc'd for $C_{20}H_{22}N_3O_2$ $[M + H^+]$ 336.1706, found 336.1699.

C2-substituted hydroxyindolenine **51**: $\mathbf{R_f}$ = 0.28 (silica gel, 1:1 EtOAc/hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.1 Hz, 1 H), 7.16 (at, *J* = 7.5 Hz, 1 H), 7.06 – 6.96 (m, 3 H), 6.91 (atd, *J* = 7.4, 0.9 Hz, 1 H), 6.88 (d, *J* = 7.2 Hz, 1 H), 6.68 (atd, *J* = 7.2, 1.3 Hz, 1 H), 4.66 (brs, 1 H), 4.43 (brs, 1 H), 4.08 (brs, 1 H), 3.37 (s, 3 H), 2.94 (at, *J* = 8.1 Hz, 2 H), 2.86 – 2.76 (m, 2 H), 2.46 – 2.34 (m, 1 H), 2.19 – 2.05 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 170.9, 156.9, 153.4, 143.7, 135.4, 132.0, 129.8, 127.2, 124.4, 123.3, 122.3, 121.8, 117.4, 117.0, 83.8, 51.9, 48.0, 36.7, 35.4, 28.2; **IR** (film, cm^{-1}) 3707, 3681, 3337, 2967, 2844, 2865, 1699, 1597, 1536, 1456, 1266, 1055, 1033, 1012, 754; **HRMS** (ESI^+) m/z Calc'd for $C_{20}H_{22}N_3O_3$ $[M + H^+]$ 352.1656, found 352.1656.

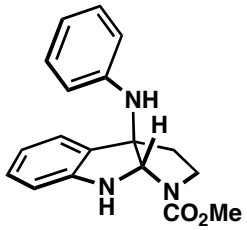


Tryptamine-aniline coupled product **53** (Table 1, Entry 21): Boc-Trp-OMe, **52**, (1.00 g, 3.14 mmol) and *o*-iodoaniline[8] (826 mg, 3.77 mmol, 1.2 equiv) were dissolved in dry MeCN/MeOH (31:2.3 mL) in a flame-dried flask. The solution was cooled to –45 °C with an acetone/$CO_{2(s)}$ bath. A solution of NIS (1.06 g, 4.71 mmol, 1.5 equiv) in MeCN (15.0 mL, 0.3 M NIS; 0.07 M final concentration) was added dropwise (10 minutes) to the reaction mixture. After 1 hour at that temperature, the red-colored reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (40 mL), diluted with EtOAc (20 mL) to give a light yellow organic phase, and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (0:1 to 1:3 EtOAc/hexanes) of the crude material afforded the pure product **53** (1.33 g, 79%) as a white foam and recovered starting material **52** (172 mg, 17%).

$[\alpha]^{20.0}$ -133.5 (*c* 1.0, $CHCl_3$); **R_f** = 0.29 (silica gel, 1:4 EtOAc/hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ 7.69 – 7.62 (m, 1 H), 7.19 – 7.08 (m, 2 H), 7.01 (at, *J* = 8.5 Hz, 1 H), 6.75 (at, *J* = 7.4 Hz, 1 H), 6.67 (d, *J* = 7.8 Hz, 1 H), 6.42 (at, *J* = 7.5 Hz, 1 H), 6.42 (d, *J* = 7.5 Hz, 0.7 H), 6.31 (d, *J* = 8.2 Hz, 0.3 H), 5.93 (s, 0.7 H), 5.81 (s, 0.3 H), 5.30 (bs, 0.7 H), 4.88 (bs, 0.3 H), 4.68 (s, 0.3 H), 4.59 (s, 0.7 H), 4.43 (dd, *J* = 4.2, 4.5 Hz, 0.3 H), 4.35 (t, *J* = 4.2, 4.5 Hz, 0.7 H), 3.84 – 3.81 (m, 3 H), 2.82 – 2.59 (m, 2 H), 1.53 (s, 2.8 H), 1.43 (s, 6.2 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ 173.0, 172.6, 154.1, 148.1, 147.7, 144.2, 144.2, 139.7, 139.6, 130.0, 129.4,

[8] Long, white needles were obtained by recrystallizing *o*-iodoaniline from refluxing hexanes (first hot filter through Celite).

129.2, 129.1, 123.0, 119.8, 119.7, 119.6, 119.5, 113.5, 113.2, 110.0, 109.9, 87.4, 81.6, 81.3, 78.7, 78.5, 77.4, 77.0, 72.7, 71.5, 58.7, 58.6, 53.1, 52.8, 43.2, 43.1, 28.7, 28.4; **IR** (film, cm^{-1}) 3385, 1751, 1696, 1586, 1507, 1457, 1388, 1367, 1314, 1205, 1163, 741; **HRMS** (ESI^+) m/z Calc'd for $C_{23}H_{27}IN_3O_4$ [M + H^+] 536.1046, found 536.1043.

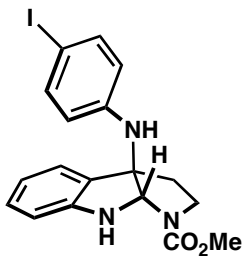


C3-substituted pyrroloindoline **62**: The methyl carbamate of tryptamine, **33**, (200.0 mg, 0.916 mmol) was dissolved in DCM (9.2 mL, 0.10 M), triethylamine (0.19 mL, 1.36 mmol, 1.5 equiv) was added, and the solution was cooled to 0 °C. Solid NCS (183.5 mg, 1.37 mmol, 1.5 equiv) was added and the reaction mixture was allowed to warm to room temperature by removal from the ice bath. After the reaction mixture had warmed to room temperature (15 minutes), aniline[9] (0.17 mL, 1.87 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 8 hours. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) and the layers were separated. The aqueous layer was extracted additionally with DCM (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 3:1, hexanes/EtOAc) to afford a white foam **62** (78.9 mg, 28%).

R_f = 0.52 (silica gel, 1:1 EtOAc/hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.21 – 7.06 (m, 4 H), 6.79 – 6.69 (m, 2 H), 6.54 (d, *J* = 7.8 Hz, 1 H) 6.51 (at, *J* = 7.9, 2 H), 5.75 (s, 0.5 H), 5.70 (s, 0.5 H), 5.18 (brs, 0.5 H), 4.83 (brs, 0.5 H), 4.07 (brs, 1 H), 3.89 – 3.81 (m, 0.5 H), 3.76 (s, 1.5 H), 3.73 (s, 1.5 H), 3.76 – 3.70 (m, 0.5 H),

[9] Aniline was purified by distillation at reduced pressure with heating to afford a colorless oil.

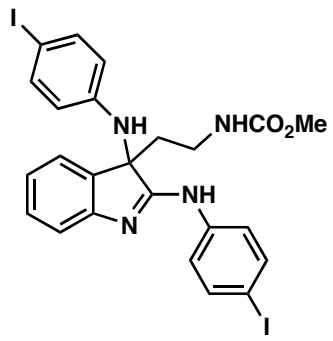
3.33 – 3.22 (m, 1 H), 2.72 – 2.56 (m, 1 H), 2.39 – 2.28 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 156.1, 155.4, 149.2, 148.9, 145.2, 145.1, 130.0, 130.0, 129.4, 129.3, 123.6, 123.5, 119.6, 119.4, 118.7, 118.5, 115.5, 115.2, 109.9, 109.7, 77.7, 72.4, 52.9, 52.7, 44.8, 44.6, 37.8, 37.7; **IR** (film, cm^{-1}) 3681, 3364, 2953, 2873, 2844, 1685, 1601, 1498, 1483, 1449, 1382, 1316, 1199, 1048, 1033, 746; **HRMS** (ESI^+) m/z Calc'd for $C_{18}H_{19}N_3O_2$ [M + H^+] 310.1556, found 310.1547.



C3-substituted pyrroloindoline **63**: The methyl carbamate of tryptamine, **33**, (200.0 mg, 0.916 mmol) and *p*-iodoaniline (301.1 mg, 1.37 mmol, 1.5 equiv) were dissolved in DCM (9.2 mL, 0.10 M), triethylamine (0.19 mL, 1.36 mmol, 1.5 equiv) was added, and the solution was cooled to –45 °C. Solid NCS (183.5 mg, 1.37 mmol, 1.5 equiv) was added and the reaction mixture was allowed to stir for 3 hours at that temperature. The reaction mixture was warmed to room temperature (23 °C), quenched with saturated aqueous $Na_2S_2O_3$ (15 mL), and the layers were separated. The aqueous layer was extracted additionally with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (100:1, DCM/MeOH) to afford a white foam **63** (106.3 mg, 27%) and recovered starting material, **33** (94.8 mg, 47%).

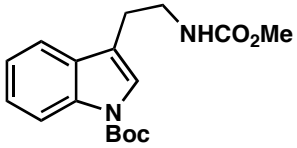
$\mathbf{R}_f$ = 0.07 (silica gel, 4:1 hexanes/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.37 – 7.30 (m, 2 H), 7.19 – 7.11 (m, 2 H), 6.81 – 6.72 (m, 1 H), 6.63 (d, *J* = 8.0, 1 H), 6.28 (at, *J* = 7.6 Hz, 2 H), 5.67 (s, 0.5 H), 5.62 (s, 0.5 H), 5.15 (brs, 0.5 H),

4.81 (brs, 0.5 H), 4.14 (brs, 0.5 H), 4.10 (brs, 0.5 H), 3.88 – 3.81 (m, 0.5 H), 3.76 (s, 1.5 H), 3.75 – 3.71 (m, 0.5 H), 3.73 (s, 1.5 H), 3.33 – 3.19 (m, 1 H), 2.63 – 2.47 (m, 1 H), 2.43 – 2.26 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 156.0, 155.3, 149.2, 148.9, 144.8, 138.0, 138.0, 130.2, 130.2, 129.2, 129.1, 123.6, 123.5, 119.8, 119.6, 117.5, 117.4, 117.2, 109.9, 109.8, 79.9, 79.7, 77.7, 73.4, 72.2, 53.1, 52.8, 44.8, 44.5, 38.2, 38.1; **IR** (film, cm^{-1}) 3681, 3363, 2952, 2868, 1688, 1610, 1589, 1485, 1452, 1384, 1320, 1201, 1053, 1033, 1015, 747; **HRMS** (ESI^+) m/z Calc'd for $C_{18}H_{19}IN_3O_2$ [M + H^+] 436.0516, found 436.0500



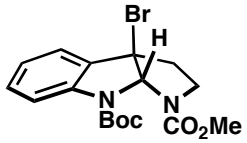
Double addition product **64**: The methyl carbamate of tryptamine, **33**, (200.0 mg, 0.916 mmol) and *p*-iodoaniline (301.1 mg, 1.37 mmol, 1.5 equiv) were dissolved in MeCN (9.2 mL, 0.10 M) and the solution was cooled to –45 °C. Solid NIS (308 mg, 1.37 mmol, 1.5 equiv) was added and the reaction mixture was allowed to stir for 3 hours at that temperature. The reaction mixture was warmed to room temperature (23 °C) and quenched with saturated aqueous $Na_2S_2O_3$ (10 mL), diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was extracted additionally with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (3:1 to 1:1, hexanes/EtOAc) to afford the double addition product **64** (197.3 mg, 33%), the mono addition product **63** (16.1 mg, 3%), and starting material **33** (104.9, 52%)

R_f = 0.22 (silica gel, 1:1 EtOAc/hexanes); **M.p.**: 208-210 °C; **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.64 (d, *J* = 8.0 Hz, 2 H), 7.52 (brs, 1 H), 7.32 – 7.09 (m, 6 H), 7.04 – 6.94 (m, 1 H), 6.15 – 6.04 (m, 2 H), 3.53 (s, 3 H), 2.92 (brs, 1 H), 2.75 (s, 1 H), 2.35 – 2.18 (m, 2 H); **^{13}C-NMR** (150 MHz, DMSO-d_6) δ 170.9, 156.4, 154.7, 145.7, 140.1, 137.2, 136.9, 134.4, 129.1, 122.6, 121.5, 121.4, 117.5, 116.1, 85.6, 78.6, 68.9, 51.2, 38.5, 34.9; **IR** (film, cm^{-1}) 1698, 1563, 1485, 1467, 1004, 812, 752; **HRMS** (ESI^+) m/z Calc'd for $C_{24}H_{23}I_2N_4O_2$ [M + H^+] 652.9905, found 652.9899.

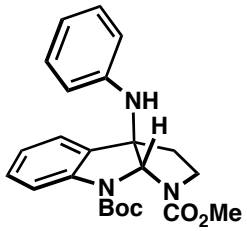


Mono Boc tryptamine **65**: The methyl carbamate of tryptamine **33** (50.0 mg, 0.229 mmol) and 4-dimethylaminopyridine (5.0 mg, 0.041 mmol, 0.2 equiv) were dissolved in DCM (1 mL, 0.2 M). Di-*tert*-butyl dicarbonate (55 mg, 0.25 mmol, 1.1 equiv) was added to the reaction mixture, which was allowed to stir at room temperature for 1 hour. The reaction was concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 10:1, hexanes/EtOAc) to afford a white solid, **65** (69.9 mg, 96%).

R_f = 0.30 (silica gel, 3:1 hexanes/EtOAc); **M.p.**: 96-98 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.0 Hz, 1 H), 7.54 (d, *J* = 7.6 Hz, 1 H), 7.41 (s, 1 H), 7.32 (at, *J* = 7.7 Hz, 1 H), 7.24 (at, *J* = 7.4 Hz, 1 H), 4.80 (brs, 1 H), 3.67 (s, 3 H), 3.52 (dd, *J* = 6.6, 6.2 Hz, 2 H), 2.91 (t, *J* = 6.7 Hz, 2 H), 1.67 (s, 9 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 157.1, 149.8, 135.7, 130.4, 124.6, 123.3, 122.6, 119.0, 117.6, 115.4, 83.7, 52.2, 40.7, 28.3, 25.7; **IR** (film, cm^{-1}) 3346, 2978, 1727, 1529, 1453, 1380, 1308, 1255, 1225, 1158, 1091, 1017, 856, 767, 747; **HRMS** (ESI^+) m/z Calc'd for $C_{17}H_{23}N_2O_4$ [M + H^+] 319.1658, found 319.1652.



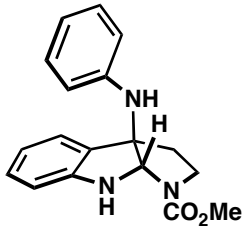
C3-bromopyrroloindoline **66**: The mono Boc protected tryptamine **65** (347 mg, 1.09 mmol) was dissolved in DCM (11 mL, 0.08 M). NBS (214 mg, 1.20 mmol, 1.4 equiv) was then added and the reaction mixture was allowed to stir at room temperature for 1 hour. The reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and the layers were separated. The aqueous layer was extracted additionally with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 9:1, hexanes/EtOAc) to afford a white foam **66**, (365 mg, 84%). $\mathbf{R}_f$ = 0.27 (silica gel, 4:1 hexanes/EtOAc); **M.p.**: 94-96 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.11 (at, *J* = 7.2 Hz, 1 H), 7.11 (at, *J* = 7.5 Hz, 1 H), 6.40 (s, 1 H), 3.83 – 3.75 (m, 1 H), 3.75 (s, 3 H), 2.92 – 2.71 (m, 3 H), 1.60 (s, 9 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 154.8, 152.2, 142.0, 132.4, 130.6, 124.3, 123.8, 117.5, 84.1, 82.2, 62.2, 52.8, 46.4, 41.1, 28.3; **IR** (film, cm^{-1}) 2980, 1708, 1604, 1478, 1445, 1389, 1367, 1151, 754; **HRMS** (ESI^+) m/z Calc'd for $C_{17}H_{21}BrN_2NaO_4$ [M + Na^+] 419.0582, found 419.0577.



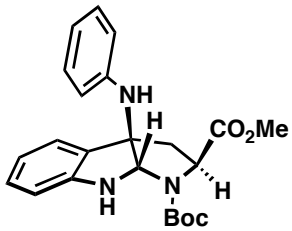
C3-substituted pyrroloindoline **67**: The bromide **66** (310.0 mg, 0.780 mmol), aniline (0.45 mL, 4.9 mmol, 6.3 equiv) and K_3PO_4 (320.0 mg, 1.51 mmol, 1.9 equiv) were suspended in DMSO (4.5 mL, 0.2 M) and heated to 100 °C for 24 hours. The reaction mixture was diluted with DCM (20 mL), filtered through celite, and concentrated. Water (100 mL) was added and the layers were separated. The aqueous layer was extracted

additionally with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 3:1, hexanes/EtOAc) to afford a yellow foam, **67** (39.1 mg, 12%).

R_f = 0.10 (silica gel, 4:1 hexanes/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 1 H), 7.34 – 7.26 (m, 2 H), 7.09 – 7.00 (m, 3 H), 6.73 (at, *J* = 7.3 Hz, 1 H), 6.40 – 6.34 (m, 3 H), 4.09 – 3.96 (m, 2 H), 3.74 (s, 3 H), 2.97 – 2.89 (m, 1 H), 2.47 – 2.37 (m, 1 H), 2.29 – 2.22 (m, 1 H), 1.52 (s, 9 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 155.5, 152.6, 144.9, 143.2, 132.1, 129.9, 129.3, 123.8, 123.5, 119.1, 116.3, 115.5, 81.9, 78.3, 72.1, 52.9, 44.4, 40.0, 28.4; **IR** (film, cm^{-1}) 3681, 3378, 2981, 2844, 1702, 1603, 1446, 1393, 1151, 1055, 1033, 1015, 750; **HRMS** (ESI^+) m/z Calc'd for $C_{23}H_{28}N_3O_4$ [M + H^+] 410.2080, found 410.2075.



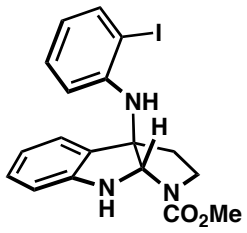
C3-substituted pyrroloindoline **62**: Compound **67** (12.7 mg, 0.031 mmol) was treated with TFA:DCM (60 μL:0.3 mL, 1:5) at 0 °C for 30 minutes. Toluene (2 mL) was added and the solution was concentrated at 0 °C to afford pure **62** (9.6 mg, quant.). For full characterization, see S-20.



Indole-aniline coupled product **69** (Table 2, Entry 2): Boc-Trp-OMe, **52** (50.0 mg, 0.157 mmol) was dissolved in DCM (1.6 mL, 0.10 M) and triethylamine (32.8 μL, 0.235 mmol, 1.5 equiv) was added. Solid NCS (25.2 mg, 0.189 mmol, 1.2

equiv) was added and the reaction mixture was stirred for 15 minutes at room temperature (23 °C). Aniline (28.6 μL, 0.314 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 9 hours. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and the layers were separated. The aqueous layer was extracted additionally with DCM (3 × 5 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 4:1, hexanes/EtOAc) to afford a yellow foam **69** (21.7 mg, 34%). **Note:** The d.r. of 5:1 was determined by the crude ^{1}H-NMR spectrum, the yield and data refer to the major diastereomer.

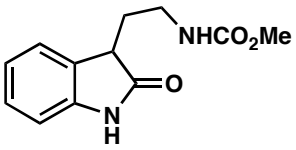
R_f = 0.23 (silica gel, 4:1 hexanes/EtOAc); **$[\alpha]^{20.0}$** -100.9 (*c* 0.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ 7.23 – 7.06 (m, 4 H), 6.82 – 6.65 (m, 3 H), 6.54 – 6.47 (m, 2 H), 5.92 (s, 0.67 H), 5.82 (s, 0.33 H), 5.26 (s, 0.67 H), 4.82 (s, 0.33 H), 4.42 – 4.34 (m, 0.67 H), 4.30 – 4.25 (m, 0.67 H), 4.20 (brs, 0.67), 3.80 (s, 3 H), 2.76 – 2.54 (m, 2 H), 1.51 (s, 3 H), 1.42 (s, 6 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ 173.9, 173.8, 154.3, 154.1, 148.1, 147.5, 146.5, 145.3, 145.1, 130.6, 130.5, 129.9, 129.8, 129.4, 129.3, 123.2, 119.7, 119.4, 118.8, 118.7, 118.6, 115.9, 115.8, 115.2, 110.3, 110.1, 81.6, 81.3, 78.5, 78.5, 72.8, 71.6, 58.8, 58.7, 52.8, 52.5, 41.9, 41.6, 28.6, 28.4; **IR** (film, cm^{-1}) 3681, 3380, 2973, 1744, 1693, 1602, 1498, 1390, 1163, 1054, 1033, 1013, 749; **HRMS** (ESI^+) m/z Calc'd for $C_{23}H_{28}N_3O_4$ [M + H^+] 410.2074, found 410.2073.



Pyrroloindoline **90**: The methyl carbamate of tryptamine, **33**, (20.0 mg, 0.0916 mmol) and *o*-iodophenylazide[10] (22.4 mg, 0.0914 mmol, 1.0 equiv) were dissolved in benzene (2.0 mL, 0.05 M). The solution was then degassed by sonication with continuous argon bubbling (15 minutes) and irradiated with a 400 W Hanovia lamp with a Pyrex filter (BioTage microwave vial) for 24 hours. The reaction mixture was concentrated and purified by flash column chromatography (1:0 to 4:1, hexanes/EtOAc) to afford a yellow film **90** (0.8 mg, 2%).

$\mathbf{R}_f$ = 0.13 (silica gel, 4:1 hexanes/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.65 (at, *J* = 7.0 Hz, 1 H), 7.17 – 7.13 (m, 2 H), 7.00 (at, *J* = 7.7 Hz, 1 H), 6.79 – 6.74 (m, 1 H), 6.65 (d, *J* = 7.7 Hz, 1 H), 6.46 – 6.36 (m, 2 H), 5.73 (s, 0.5 H), 5.66 (s, 0.5 H), 5.17 (brs, 0.5 H), 4.84 (brs, 0.5 H), 4.67 (brs, 0.5 H), 4.63 (brs, 0.5 H), 3.91 – 3.86 (m, 0.5 H), 3.80 – 3.74 (m, 0.5 H), 3.77 (s, 1.5 H), 3.74 (s, 1.5 H), 3.37 – 3.28 (m, 1 H), 2.65 – 2.55 (m, 1 H), 2.42 – 2.34 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 156.0, 155.2, 149.0, 148.8, 144.5, 139.5, 139.4, 130.0, 129.9, 129.3, 129.2, 129.0, 128.9, 123.5, 123.4, 119.9, 119.8, 119.5, 113.6, 113.3, 109.8, 109.6, 87.8, 87.6, 78.2, 73.8, 72.6, 52.9, 52.7, 44.6, 44.4, 39.2, 39.0; **IR** (film, cm^{-1}) 3681, 3386, 2952, 2872, 1690, 1449, 1380, 1315, 1199, 1050, 1033, 1005, 732; **HRMS** (ESI^+) m/z Calc'd for $C_{18}H_{19}IN_3O_2$ [M + H^+] 436.0516, found 436.0514.

[10] *o*-Iodophenylazide was prepared according to: Faucher, N.; Ambroise, Y.; Cintrat, J.-C.; Doris, E.; Pillon, F.; Rousseau, B. *J. Org. Chem.* **2002**, *67*, 932.



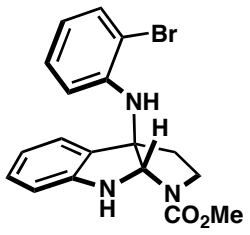
Oxindole **91**: The pyrroloindoline, **90**, (19.5 mg, 0.0448 mmol) was dissolved in DCM/TFA (1.0:0.1 mL, 0.04 M) and stirred at room temperature for 2 hours. At which point, toluene was added and the reaction mixture was concentrated. The crude material thus obtained was purified by flash column chromatography (3:1 to 2:1, hexanes/EtOAc) to afford the oxindole **91** (9.6 mg, 91%).

Alternative procedure to obtain oxindole **91:**

Oxindole **91**: The methyl carbamate of tryptamine, **33** (43.6 mg, 0.200 mmol) as a solution in glacial AcOH (1.8 mL) was added to a solution of DMSO (40 μL) and concentrated HCl (0.2 mL; final concentration: 0.1 M). After 45 minutes at room temperature (23 °C), the reaction was slowly poured into saturated aqueous Na_2CO_3 (30 mL), diluted with EtOAc (10 mL), and the layers were separated. The aqueous layer was extracted additionally with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (0:1 to 1:1, EtOAc/hexanes) to afford a white foam, **91** (37.2 mg, 79%).

$\mathbf{R}_f$ = 0.10 (silica gel, 1:1 EtOAc/hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.43 (brs, 1 H), 7.28 (d, *J* = Hz, 1 H), 7.21 (at, *J* = Hz, 1 H), 7.04 (at, *J* = Hz, 1 H), 6.90 (d, *J* = Hz, 1 H), 5.24 (brs, 1 H), 3.64 (s, 3 H), 3.52 – 350 (m, 1 H), 3.44 – 3.38 (m, 2 H), 2.21 – 2.20 (m, 1 H), 2.09 – 2.07 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 180.8, 157.3, 141.5, 129.3, 128.2, 124.2, 122.7, 110.1, 52.2, 44.0, 38.4, 30.6; **IR** (film, cm^{-1}) 3300, 1698, 1620, 1533, 1471, 1262, 1193, 1033, 752; **HRMS** (ESI^+) m/z Calc'd for $C_{12}H_{15}N_2O_3$ [M + H^+] 235.1077, found 235.1078.

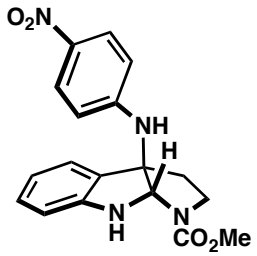
General Procedure for Tryptamine-Aniline Coupling: The tryptamine, (1 equiv) and aniline (1.2 equiv) were dissolved in dry MeCN/MeOH (13:1, 0.1 M) in a flame-dried flask. The solution was cooled to –45 °C with an acetone/$CO_{2(s)}$ bath. A solution of NIS (1.5 equiv) in MeCN (0.03 M NIS; final reaction concentration: 20:1 MeCN/MeOH, 0.07 M) was added dropwise in one portion to the reaction mixture. After 1 hour at that temperature, the reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (1 volume) and extracted with EtOAc (4 × 1 volume). The combined extracts were washed with brine (1 volume), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography was used for purification.



Tryptamine-aniline coupled product **96**: The general procedure was followed with the methyl carbamate of tryptamine (**33**, 22.0 mg, 0.10 mmol) to afford a white foam, **96** (26.6 mg, 68%) after flash column chromatography (10:1 to 3:1 hexanes/EtOAc).

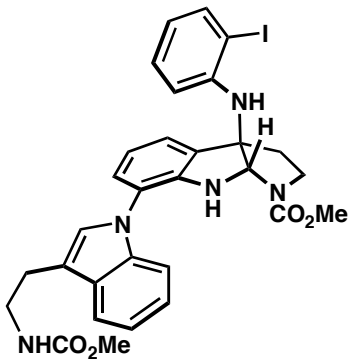
$\mathbf{R}_f$ = 0.13 (silica gel, 4:1 hexanes/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.41 (at, *J* = 7.4 Hz, 1 H), 7.19 – 7.12 (m, 2 H), 6.98 (t, *J* = 7.7 Hz, 1 H), 6.80 – 6.73 (m, 1 H), 6.65 (d, *J* = 7.7 Hz, 1 H), 6.55 (at, *J* = 7.6 Hz, 1 H), 6.48 – 6.40 (m, 1 H), 5.73 (s, 0.5 H), 5.66 (s, 0.5 H), 5.15 (s, 0.5 H), 4.89 – 4.71 (m, 1.5 H), 3.92 – 3.89 (m, 0.5 H), 3.80 – 3.72 (m, 3.5 H), 3.37 – 3.26 (m, 1 H), 2.67 – 2.53 (m, 1 H), 2.49 – 2.39 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 156.0, 155.2, 149.0, 148.8, 142.2, 132.8, 132.7, 130.0, 130.0, 129.1, 129.0, 128.3, 123.5, 123.4, 119.8, 119.8, 119.5, 119.0, 118.9, 114.3, 114.0, 111.4, 111.3, 109.8, 109.7, 78.2, 73.5, 72.3, 52.9, 52.7, 44.6, 44.4, 39.2, 38.9; **IR** (film, cm^{-1}) 3707, 3404, 2973, 1696, 1454, 1383, 1321, 1202, 1054,

1033, 1016, 744; **HRMS** (ESI$^+$) m/z Calc'd for $C_{18}H_{19}BrN_3O_2$ [M + H$^+$] 388.0655, found 388.0649.



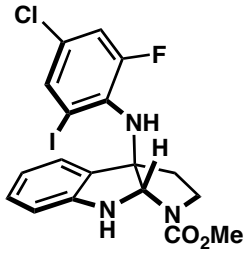
Tryptamine-aniline coupled product **97**: The general procedure was followed with the methyl carbamate of tryptamine (**33**, 100.0 mg, 0.458 mmol) to afford a yellow solid, **97** (120.2 mg, 74%), after flash column chromatography (20:1 to 10:1 DCM/acetone).

R$_f$ = 0.07 (silica gel, 3:1 hexanes/EtOAc); **M.p.**: 79-81 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.97 (d, *J* = 8.9 Hz, 2 H), 7.20 – 7.11 (m, 2 H), 6.79 – 6.75 (m, 1 H), 6.67 (d, *J* = 7.9 Hz, 1 H), 6.48 (d, *J* = 8.9 Hz, 1 H), 5.69 (s, 0.5 H), 5.65 (s, 0.5 H), 5.26 (s, 0.5 H), 5.06 (s, 0.5 H), 5.00 (s, 0.5 H), 4.93 (s, 0.5 H), 3.91 – 3.85 (m, 0.5 H), 3.83 – 3.73 (m, 0.5 H), 3.77 (s, 1.5 H), 3.74 (s, 1.5 H), 3.31 – 3.22 (m, 1 H), 2.66 – 2.38 (m, 2 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 155.9, 155.0, 150.8, 149.2, 148.9, 138.8, 130.5, 127.8, 127.7, 126.1, 123.4, 123.3, 119.9, 119.7, 113.3, 113.3, 109.9, 109.8, 77.9, 77.5, 73.3, 72.0, 53.0, 52.8, 44.6, 44.3, 38.7, 38.6; **IR** (film, cm^{-1}) 3707, 3681, 3357, 2981, 1685, 1594, 1453, 1302, 1281, 1110, 1053, 1033, 1015, 751, 736; **HRMS** (ESI$^+$) m/z Calc'd for $C_{18}H_{19}N_4O_4$ [M + H$^+$] 355.1401, found 355.1401.



Tryptamine-aniline coupled product **98**: The general procedure was followed with 37.3 mg (0.0858 mmol) of the tryptamine dimer, **106**, to afford a yellow foam **98** (13.6 mg, 24%) of the product after flash column chromatography (50:1 to 10:1 DCM/acetone).

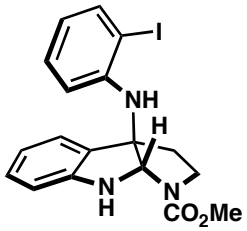
R_f = 0.34 (silica gel, 1:1 EtOAc/hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.72 – 7.64 (m, 2 H), 7.26 – 7.12 (m, 6 H), 7.10 – 7.03 (m, 1 H), 6.92 – 6.83 (m, 1 H), 6.52 – 6.42 (m, 2 H), 5.76 (s, 0.5 H), 5.63 (s, 0.5 H), 4.99 (s, 0.5 H), 4.99 – 4.85 (m, 1 H), 4.74 – 4.70 (m, 1.5 H), 3.99 – 3.90 (m, 0.5 H), 3.86 – 3.79 (m, 0.5 H), 3.69 (s, 1.5 H), 3.68 (s, 3 H), 3.62 (s, 1.5 H), 3.62 – 3.54 (m, 2 H), 3.44 – 3.39 (m, 1 H), 3.07 - 3.30 (m, 2 H), 2.70 – 2.60 (m, 1 H), 2.55 – 2.47 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 157.2, 157.2, 155.7, 155.0, 144.4, 144.4, 139.6, 139.5, 136.3, 136.2, 130.9, 130.9, 129.3, 129.3, 128.4, 127.6, 127.6, 125.9, 125.7, 122.8, 122.7, 122.5, 122.4, 121.5, 120.3, 120.2, 120.2, 120.1, 119.8, 119.4, 114.2, 114.2, 113.9, 113.6, 110.8, 110.7, 88.1, 88.0, 78.4, 77.6, 74.1, 73.0, 52.9, 52.8, 52.2, 44.7, 44.4, 41.4, 39.8, 39.2, 26.0; **IR** (film, cm^{-1}) 3386, 2951, 1698, 1494, 1454, 1383, 1318, 1199, 1056, 1033, 1006, 740; **HRMS** (ESI^+) m/z Calc'd for $C_{30}H_{31}IN_5O_4$ [M + H^+] 652.1421, found 652.1400.



Tryptamine-aniline coupled product **99**: The general procedure was followed with the methyl carbamate of tryptamine (**33**, 22.0 mg, 0.10 mmol) to afford a yellow foam, **99** (21.1 mg, 43%) after flash column chromatography (1:0 to 3:1 hexanes/EtOAc).

R_f = 0.32 (silica gel, 3:1 hexanes/EtOAc); **^{1}H-NMR** (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.52 (s, 1 H), 7.14 (at, *J* = 7.7 Hz, 1 H), 7.10 (d, *J* = 7.5 Hz, 1 H), 7.04 – 6.95 (m, 1 H), 6.74 (at, *J* = 7.5 Hz, 1 H), 6.66 – 6.62 (m, 1 H), 5.56 (s, 0.5 H), 5.55 (s, 0.5 H), 5.19 (s, 0.5 H), 4.78 (s, 0.5 H), 3.99 – 3.97 (m, 1 H), 3.86 – 3.77 (m, 0.5 H), 3.79 (s, 1.5 H), 3.74 – 3.66 (m, 0.5 H), 3.70 (s, 1.5 H), 3.17 – 3.05 (m, 1 H), 2.53 – 2.39 (m, 1 H), 2.37 – 2.26 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 155.7,

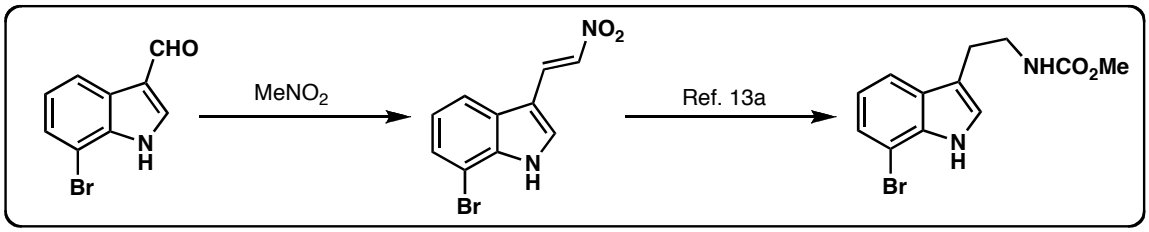
155.0, 153.6, 151.9, 149.8, 149.6, 134.1, 134.1, 133.6, 133.5, 130.2, 130.2, 129.5, 129.3, 127.7, 127.5, 123.9, 123.8, 119.5, 119.2, 117.7, 117.5, 110.3, 110.1, 95.7, 95.4, 81.1, 80.7, 75.7, 74.5, 52.8, 52.5, 45.4, 45.3, 36.1, 35.9; **IR** (film, cm^{-1}) 3707, 3364, 2923, 1694, 1453, 1387, 1054, 1032, 1013, 746; **HRMS** (ESI^+) m/z Calc'd for $C_{18}H_{17}ClFIN_3O_2$ $[M + H^+]$ 488.0033, found 488.0029.

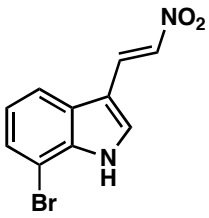


Tryptamine-aniline coupled product **90**: The general procedure was followed with the methyl carbamate of tryptamine (**33**, 50.0 mg, 0.229 mmol) to afford to product as a white foam, **90** (62.8 mg, 63%) after flash column chromatography (10:1 to 3:1 hexanes/EtOAc).

Note: For full characterization of **90**, see S-27.

Alternative procedure to obtain the methyl carbamate of 7-bromotryptamine (105):





Nitro compound **SI-2**:[11] 7-bromo-3-formyl-indole[12] (13.0 g, 58.0 mmol) and anhydrous NH_4OAc (19.1 g, 248 mmol, 4.3 equiv) were suspended in $MeNO_2$[13] (80 mL, 0.7 M). The suspension was heated to reflux for 45 minutes and then cooled to room temperature. The solution was concentrated under reduced pressure and water (100 mL) and EtOAc (100 mL) were added. The layers were separated and the aqueous layer was extracted additionally with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated to afford a yellow solid **SI-2** (14.7 g, 95%).

R_f = 0.37 (silica gel, 2:1 hexanes/EtOAc); **M.p.**: 207-208 °C; **^{1}H-NMR** (400 MHz, MeOD) δ 8.35 (d, *J* = 13.5 Hz, 1 H), 7.97 (s, 1 H), 7.90 (d, *J* = 13.5 Hz, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.18 (t, *J* = 7.8 Hz, 1 H); **^{13}C-NMR** (150 MHz, MeOD) δ 137.9, 135.9, 134.7, 133.7, 127.8, 127.2, 124.1, 120.6, 110.8, 106.6; **IR** (film, cm^{-1}) 3250, 1601, 1519, 1477, 1428, 1310, 1240, 1207, 1109, 1094, 1033, 976, 958, 803, 730, 721, 701; **HRMS** (ESI^+) m/z Calc'd for $C_{10}H_8BrN_2O_2$ [M + H^+] 266.9764, found 266.9761.

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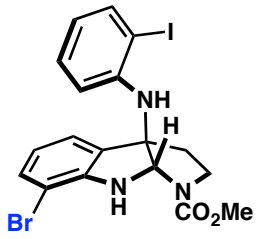
[11] The following procedure was modified from: Liu, J.-J.; Hino, T.; Tsuruoka, A.; Harada, N.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3487.

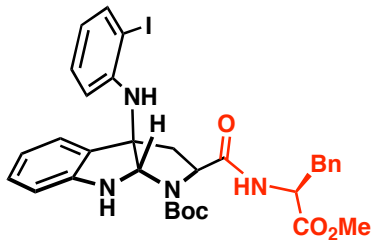
[12] 7-bromo-3-formyl-indole was prepared according to: Berthelot, A.; Piguel, S.; Le Dour, G.; Vidal, J. *J. Org. Chem.* **2003**, *68*, 9835.

[13] Nitromethane was purified by distillation over CaH_2.



Tryptamine-aniline coupled product **101**: **105** (117.4 mg, 0.395 mmol) and *o*-iodoaniline (98.6 mg, 0.450 mmol, 1.1 equiv) were dissolved in dry MeCN (4.0 mL, 0.1 *M*) under nitrogen in a flame-dried flask. Triethylamine (77 μL, 0.55 mmol, 1.4 equiv) was added and the solution was cooled to –45 °C with a MeCN/$CO_{2(s)}$ bath. A suspension of NIS (240 mg, 1.07 mmol, 2.7 equiv) in MeCN (2.4 mL) was added dropwise in three portions (every 20 minutes) to the reaction mixture. After an additional 20 minutes the reaction mixture was allowed to slowly warm to room temperature. Once the color of the reaction mixture was consistent, saturated aqueous $Na_2S_2O_3$ (10 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was then extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (1:0 to 4:1 hexanes/EtOAc) to provide a white foam of **101** (136 mg, 67%), along with recovered starting material, **105** (29.4 mg, 25%).

For full characterization of **101** and an alternative preparation see: Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886.

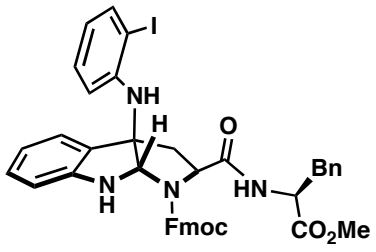


Boc-protected pyrroloindoline **102a**: Boc-Trp-Phe-OMe (150.0 mg, 0.322 mmol) was dissolved in acetonitrile (6 mL), and *o*-iodoaniline (84.7 mg, 0.386 mmol, 1.2 equiv) was added and the solution cooled to -45 °C. *N*-

Iodosuccinimide (122.4 mg, 0.544 mmol, 1.55 equiv) was dissolved in acetonitrile (1.5 mL) and was added to the cooled solution over one hour. The solution slowly darkened to a deep brown. Upon completion of the addition, the solution was allowed to warm to -35 °C over one hour and the reaction was quenched by pouring into a separatory funnel of saturated $Na_2S_2O_3$ (30 mL) with EtOAc (30 mL). The organic phase was then separated and the aqueous phase was extracted with EtOAc (4 X 15 mL). The solution was then dried with brine and $MgSO_4$ and then concentrated. The crude mixture was then purified by silica gel chromatography (3:2 Hexanes/Et_2O) to afford an off-white foam (172.1 mg, 78%).

$[\alpha]^{20.0}$ -143.3 (*c* 1.0, $CHCl_3$); **R_f** = 0.45 (silica gel, 3:2 Et_2O/Hexanes); **^{1}H-NMR** (600 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ 7.99 (d, *J* = 7.2 Hz, 1 H), 7.66 (at, *J* = 8.4 Hz, 1 H), 7.13 (aq, *J* = 7.8 Hz, 1 H), 7.05 (d, *J* = 7.2 Hz, 1 H), 7.02 (abrt, *J* = 6.6 Hz, 1 H), 6.97 – 6.91 (m, 4 H), 6.87 (d, *J* = 7.2 Hz, 0.67 H), 6.75 – 6.64 (m, 2.33 H), 6.37 (aq, *J* = 7.8 Hz, 1 H), 6.12 (d, *J* = 8.4 Hz, 0.33 H), 6.02 (d, *J* = 8.4 Hz, 0.67 H), 5.90 (d, *J* = 3.0 Hz, 0.33 H), 5.77 – 5.75 (m, 1.33 H), 5.39 (d, *J* = 3.0 Hz, 0.33 H), 5.19 (s, 0.33 H), 5.01 (q, *J* = 6.0 Hz, 0.33 H), 4.95 (q, *J* = 6.0 Hz, 0.67 H), 4.87 (d, *J* = 3.6 Hz, 0.67 H), 4.61 (d, *J* = 8.4 Hz, 0.67 H), 4.45 (d, *J* = 8.4 Hz, 0.33 H), 3.76 (s, 1 H), 3.74 (s, 2 H), 3.41 (dd, *J* = 14.4, 6.0 Hz, 0.67 H), 3.23 (d, *J* = 13.8 Hz, 0.67 H), 3.21 (dd, *J* = 13.8, 6.6 Hz, 0.33 H), 3.12 (dd, *J* = 13.8, 5.4 Hz, 0.33 H), 3.08 – 3.04 (m, 1 H), 2.46 (dd, *J* = 13.8, 8.4 Hz, 0.33 H), 2.26 (dd, *J* = 13.8, 8.4 Hz, 0.67 H), 1.47 (s, 6 H), 1.43 (s, 3 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ 171.7, 171.5, 171.2, 171.2, 155.9, 154.0, 147.0, 146.4, 144.7, 144.2, 139.9, 139.6, 135.7, 135.0, 129.4, 129.3, 129.2, 129.1, 128.7, 128.6, 128.5, 128.3, 128.0, 127.1, 126.6, 122.4, 119.5, 119.1, 119.0, 118.6, 113.0, 112.7, 109.6, 109.4,

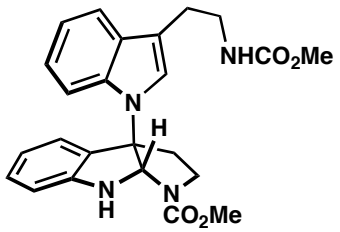
86.3, 86.1, 82.3, 82.1, 79.8, 79.3, 72.9, 71.5, 60.1, 59.7, 53.6, 52.9, 52.3, 43.4, 40.7, 38.1, 37.6, 28.4, 28.1; **IR** (film, cm^{-1}) 3707, 3681, 3352, 2973, 1744, 1685, 1513, 1367, 1316, 1054, 1032, 1009, 742; **HRMS** (ESI^+) m/z Calc'd for $C_{32}H_{36}IN_4O_5$ [$M+H^+$] 683.1725, found 683.1719.



Fmoc-protected pyrroloindoline **102c**: Fmoc-Trp-Phe-OMe (150.0 mg, 0.255 mmol) was dissolved in acetonitrile (6 mL), and *o*-iodoaniline (67.1 mg, 0.306 mmol, 1.2 equiv) was added and the solution cooled to –45 °C. *N*-Iodosuccinimide (88.9 mg, 0.395 mmol, 1.55 equiv) was dissolved in acetonitrile (1.5 mL) and was added to the cooled solution over one hour. The solution slowly darkened to a deep brown. Upon completion of the addition, the solution was allowed to warm to –35 °C over one hour and the reaction was quenched by pouring into a separatory funnel of saturated $Na_2S_2O_3$ (30 mL) with EtOAc (30 mL). The organic phase was then separated and the aqueous phase was extracted with EtOAc (4 × 15 mL). The solution was then dried with brine and $MgSO_4$ and then concentrated. The crude mixture was then purified by silica gel chromatography (1:1 Hexanes/Et_2O) to afford the off-white foam product **102c** (127.4 mg, 62%).

$[\alpha]_D^{20.0}$ -169.9 (*c* 1.0, $CHCl_3$); **R_f** = 0.26 (silica gel, 3:2 Et_2O/hexanes); **^{1}H-NMR** (600 MHz, $CDCl_3$, major rotamer) δ 7.92 (d, *J* = 7.8 Hz, 1 H), 7.84 (d, *J* = 7.8 Hz, 2 H), 7.70 (d, *J* = 7.2 Hz, 1 H), 7.66 (d, *J* = 7.8 H , 1 H), 7.61 (d, *J* = 7.8 Hz, 1 H), 7.60 (at, *J* = 7.8 Hz, 1 H), 7.49 (at, *J* = 7.8 Hz, 1 H), 7.44 (at, *J* = 7.8 Hz, 1 H), 7.34 (at, *J* = 7.2 Hz, 1 H), 7.13 (at, *J* = 7.8 Hz, 1 H), 6.95 (d, *J* = 7.2 Hz, 1 H), 6.92 (at, *J* = 7.2 Hz, 1 H), 6.89 (d, *J* =

7.2 Hz, 2 H), 6.66 (at, *J* = 7.2 Hz, 3 H), 6.58 (at, *J* = 7.2 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 1 H), 6.39 (at, *J* = 7.2 Hz, 1 H), 5.69 (d, *J* = 8.4 Hz, 1 H), 5.54 (s, 1H), 5.14 (d, *J* = 4.2 Hz, 1 H), 4.95 (td, *J* = 7.8, 5.4 Hz, 1 H), 4.90 (dd, *J* = 10.8, 4.2 Hz, 1 H), 4.55 (dd, *J* = 10.2, 4.2 Hz, 1 H), 4.41 (d, *J* = 8.4 Hz, 1 H), 4.32 (abrt, *J* = 4.2 Hz, 1 H), 3.77 (s, 3 H), 3.65 (d, *J* = 4.2 Hz, 1 H), 3.35 (dd, *J* = 13.8, 5.4 Hz, 1 H), 3.05 (d, *J* = 13.8 Hz, 1 H), 2.93 (dd, *J* = 13.8, 7.8 Hz, 1 H), 2.05 (dd, *J* = 14.4, 9.0 Hz, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, major rotamer) δ 171.7, 170.4, 156.2, 146.3, 144.6, 143.9, 143.7, 141.5, 141.2, 139.8, 135.6, 129.3, 129.1, 129.0, 128.2, 128.0, 127.7, 127.6, 126.3, 124.9, 124.4, 122.2, 120.0, 120.0, 119.1, 118.5, 112.5, 109.4, 86.4, 79.2, 72.3, 66.9, 59.5, 53.2, 52.4, 47.1, 40.5, 37.9; **IR** (film, cm^{-1}) 3707, 3681, 3327, 2981, 1741, 1689, 1511, 1424, 1315, 1180, 1054, 1032, 1007, 732, 699; **HRMS** (ESI^+) m/z Calc'd for $C_{42}H_{38}IN_4O_5$ [$M+H^+$] 805.1881, found 805.1877.

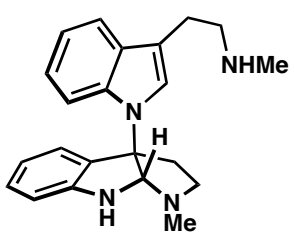


Methyl carbamate of tryptamine dimer **34**: The indole-aniline coupled product, **90** (58.9 mg, 0.135 mmol), the TMS alkyne, **103**[14] (80.9 mg, 0.406 mmol, 3.0 equiv), Cs_2CO_3 (88.1 mg, 0.270 mmol, 2.0 equiv), LiCl (5.74 mg, 0.135 mmol, 1.0 equiv) and $Pd(dppf)Cl_2$•DCM (22.1 mg, 0.0271 mmol, 0.20 equiv) were suspended in NMP (1.4 mL, 0.1 M). The reaction mixture was sonicated with continuous argon bubbling (15 minutes) and then heated to 100 °C for 1 hour. After cooling to room temperature, the reaction mixture was filtered through celite and diluted with EtOAc (15 mL). The crude mixture was then washed vigorously with aqueous 1 M HCl (40 mL) for

[14] Alkyne **103** was prepared previously, see Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 4525.

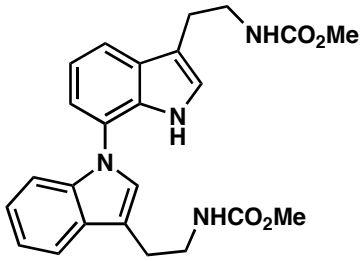
ca. 1 minute. The layers were separated and the aqueous layer was extracted additionally with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (0:1 to 1:1, hexanes/EtOAc) to afford the product, **34** (54.1 mg, 92%) and recovered alkyne **103** (51.6 mg).

Note: For full characterization of **34**, see S-10.



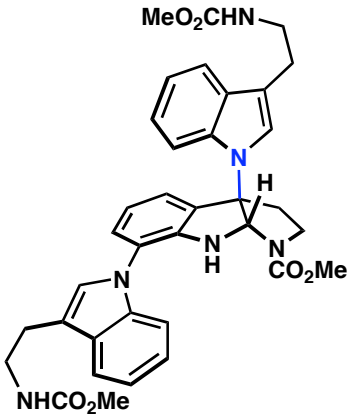
Methyl tryptamine dimer **104**: The methyl carbamate of tryptamine dimer **34** (224.4 mg, 0.516 mmol) was azeotroped with benzene and dissolved in anhydrous toluene (5.2 mL, 0.10 M). Under an inert atmosphere, an 80% solution of Red-Al, sodium bis(2-methoxyethoxy)aluminum hydride (3.5 M) in toluene (1.6 mL, 5.6 mmol, 11 equiv), was added dropwise. The reaction mixture was then heated to reflux for 30 minutes. After cooling to room temperature, the reaction was quenched by the dropwise addition of saturated aqueous Rochelle's salt, sodium potassium tartrate, (10 mL). The biphasic solution was vigorously stirred for 4 hours, diluted with DCM (10 mL), and the layers were separated. The aqueous layer was extracted additionally with DCM (3 × 20 mL). The combined organic layers were washed with brine (75 mL), dried over Na_2SO_4, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (1:5:100, NH_4OH/MeOH/$CHCl_3$) to provide a white foam **104** (154.1 mg, 86%).

R_f = 0.16 (silica gel, 1:10:90 NH_4OH/MeOH/$CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.57 (m, 1 H), 7.37 – 7.34 (m, 1 H), 7.20 (s, 1 H), 7.15 (td, *J* = 7.6, 1.5 Hz, 1 H), 7.08 – 7.04 (m, 3 H), 6.75 – 6.71 (m, 2 H), 5.20 (s, 1 H), 4.41 (brs, 1 H), 3.27 – 3.20 (m, 1 H), 3.03 – 3.01 (m, 1 H), 2.95 – 2.87 (m, 4 H), 2.73 – 2.67 (1 H), 2.49 (s, 3 H), 2.44 (s, 3 H), 2.46 – 2.39 (m, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 150.6, 136.1, 130.0, 129.9, 129.7, 125.0, 124.4, 121.6, 119.4, 119.2, 119.2, 112.2, 112.1, 109.9, 86.1, 76.6, 52.2, 51.7, 39.0, 36.4, 36.3, 25.7; **IR** (film, cm^{-1}) 3325, 2925, 2845, 1608, 1486, 1458, 1348, 1318, 2033, 1019, 742; **HRMS** (ESI^+) m/z Calc'd for $C_{22}H_{27}N_4$ [M + H^+] 347.2236, found 347.2228.



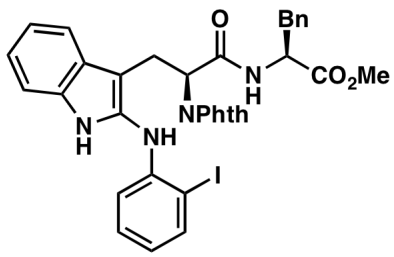
Methyl carbamate of tryptamine dimer **106**: The 7-bromotryptamine, **105** (68.5 mg, 0.231 mmol), methyl carbamate of tryptamine, **33** (150.9 mg, 0.691 mmol, 3.0 equiv), K_2CO_3 (223.0 mg, 1.61 mmol, 7.0 equiv), and CuI (13.2 mg, 0.0693 mmol, 0.30 equiv) was evacuated and backfilled with argon. The flask was evacuated and backfilled with argon one additional time. Under an argon atmosphere, 1,4-dioxane (1.0 mL, 0.23 M) was added followed by (±)-*trans*-*N*,*N*'-dimethyl-1,2-cyclohexanediamine (22 μL, 0.14 mmol, 0.60 equiv). Argon was bubbled through the reaction mixture while sonicating for 15 minutes. The suspension was heated at reflux for 20 hours, cooled to room temperature, diluted with DCM (5 mL), filtered through Celite and concentrated. The crude material was purified by flash column chromatography (20:1 to 10:1 DCM/acetone) to yield the dimeric product as a yellow foam **106** (45.3 mg, 45%).

R_f = 0.17 (silica gel, 1:1 EtOAc/hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 8.33 (brs, 1 H), 7.69 – 7.64 (m, 2 H), 7.29 – 7.20 (m, 6 H), 7.01 (s, 1 H), 4.90 (brs, 1 H), 4.83 (brs, 1 H), 3.66 (s, 3 H), 3.59 (s, 3 H), 3.57 – 3.47 (m, 4 H), 3.07 – 2.97 (m, 4 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 157.4, 157.2, 136.6, 131.9, 129.6, 128.6, 126.4, 124.0, 122.9, 122.7, 120.2, 119.9, 119.2, 119.1, 118.1, 114.1, 113.8, 110.9, 52.2 (2C), 41.5, 41.4, 26.0 (2C); **IR** (film, cm^{-1}) 3325, 2941, 1703, 1526, 1459, 1260, 1055, 1033, 1011, 742; **HRMS** (ESI^+) m/z Calc'd for $C_{24}H_{27}N_4O_4$ [M + H^+] 435.2032, found 435.2023.



Larock product **107**: A flask containing the aniline **98** (1.5 mg, 0.0023 mmol), alkyne **103** (3.2 mg, 0.016 mmol, 7 equiv), K_2CO_3 (1.12 mg, 0.0081 mmol, 3.5 equiv), LiCl (0.10 mg, 0.0023 mmol, 1.0 equiv), and $Pd(OAc)_2$ (0.17 mg, 0.75 μmol, 0.3 equiv) was evacuated and backfilled with argon. The flask was evacuated and backfilled with argon one additional time. DMF (230 μL, 0.01 M) was then added and the resulting suspension was sonicated with continuous argon bubbling for 15 minutes. After heating the suspension to 90 °C for 30 minutes, the reaction mixture was cooled to room temperature, diluted with DCM, and concentrated *in vacuo*. The residue was taken up in EtOAc (5 mL) and washed vigorously with aqueous 2 M HCl (5 mL) for approximately one minute. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash

column chromatography (1:0 to 1:2, hexanes/EtOAc) to afford the trimeric product, **107** (1 mg, 70%).

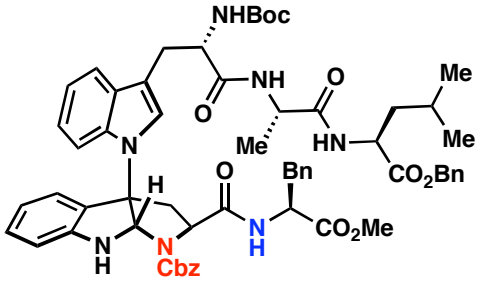


C-2 aniline **119**: Phth-Trp-Phe-OMe (50.0 mg, 0.101 mmol) was dissolved in acetonitrile (1.5 mL), and *o*-iodoaniline (26.5 mg, 0.121 mmol, 1.2 equiv) and triethylamine (16.9 μL, 0.121 mmol, 1.2 equiv) was added and the solution cooled to –45 °C. *N*-Chlorosuccinimide (27.0 mg, 0.202 mmol, 2.0 equiv) was dissolved in acetonitrile (1.0 mL) and was added to the cooled solution over 1 hour. The solution immediately darkened to a deep brown. Upon completion of the addition, the solution was allowed to warm to 4 °C over 1.5 hours and the reaction was concentrated. The crude mixture was then purified by silica gel chromatography (2:3 EtOAc/hexanes) to afford a yellow oil (17.9 mg, 25%).

$[\alpha]^{20.0}$ -43.1 (*c* 0.25, $CHCl_3$); $\mathbf{R}_f$ = 0.63 (silica gel, 1:1, EtOAc/hexanes); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.76 (brs, 1 H), 7.94 (dd, *J* = 5.4, 3.0 Hz, 2 H), 7.70 (dd, *J* = 8.4, 1.2 Hz, 1 H), 7.66 (dd, *J* = 5.4, 3.0 Hz, 2 H), 7.55 (d, *J* = 7.2 Hz, 1 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 7.13 (atd, *J* = 7.2, 1.2 Hz, 1 H), 7.09 (atd, *J* = 7.8, 1.2 Hz, 1 H), 7.02 – 6.94 (m, 4 H), 6.91 – 6.90 (m, 2 H), 6.55 (s, 1 H), 6.52 – 6.49 (m, 2 H), 6.29 (d, *J* = 7.2 Hz, 1 H), 5.20 (t, *J* = 7.2 Hz, 1 H), 4.88 (dt, *J* = 7.8, 6.0 Hz, 1 H), 3.69 (dd, *J* = 15.0, 7.8 Hz, 1 H), 3.68 (s, 3 H), 3.41 (dd, *J* = 14.4, 7.2 Hz, 1 H), 3.07 (dd, *J* = 13.8, 6.0 Hz, 1 H), 3.03 (dd, *J* = 13.8, 6.0 Hz, 1 H); **^{1}H-NMR** (600 MHz, CD_2Cl_2) δ 8.02 (brs, 1 H), 7.72 – 7.68 (m, 5 H), 7.52 (d, *J* = 7.8 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 1 H), 7.12 (at, *J* = 7.2 Hz, 1 H), 7.07 (at, *J* = 7.2 Hz, 1 H), 7.04 – 6.92 (m, 6 H), 6.54 (s, 1 H), 6.51 – 6.49 (m, 2 H), 6.29 (d, *J* = 7.2 Hz, 1

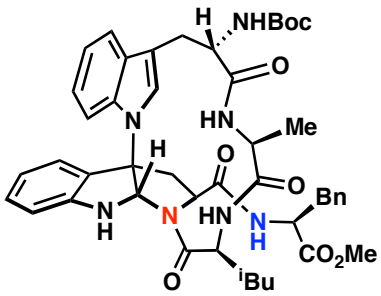
H), 5.12 (t, J = 7.8 Hz, 1 H), 4.82 (aq, J = 7.2, 6.0 Hz, 1 H), 3.67 (s, 3 H), 3.63 (dd, J = 15.0, 7.2 Hz, 1 H), 3.39 (dd, J = 15.0, 8.4 Hz, 1 H), 3.06 (dd, J = 13.8, 5.4 Hz, 1 H), 3.01 (dd, J = 13.8, 6.0 Hz, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 171.7, 168.2, 167.8, 145.4, 139.6, 135.6, 134.3, 133.9, 133.2, 131.7, 129.4, 129.2, 128.5, 127.4, 127.1, 123.6, 122.1, 121.4, 120.2, 118.2, 114.1, 110.7, 102.3, 85.6, 53.5, 53.3, 52.6, 37.8, 23.9; **^{13}C-NMR** (150 MHz, CD_2Cl_2) δ 172.0, 168.6, 168.1, 145.7, 139.9, 136.2, 134.8, 134.4, 133.7, 132.0, 129.8, 129.6, 128.8, 127.9, 127.4, 123.9, 122.3, 121.8, 120.3, 118.3, 114.3, 111.2, 102.1, 85.8, 53.9, 53.7, 52.9, 38.1, 24.0; **IR** (film, cm^{-1}) 3356, 2924, 1714, 1584, 1487, 1443, 1385, 1218, 1119, 1010; **HRMS** (ESI$^+$) m/z Calc'd for $C_{35}H_{30}IN_4O_5$ [M+H$^+$] 713.1255, found 713.1252.

Note: Purification of **119** required multiple silica gel columns and immediate characterization due to its instability. Not surprisingly, the compound was found to decompose when stored at -78 ºC.



Larock product **123**: A flask containing the aniline **102b** (1.00 g, 1.40 mmol), alkyne **116** (1.70 g, 2.83 mmol, 2.0 equiv), anhydrous Cs_2CO_3 (909 mg, 2.79 mmol, 2.0 equiv), anhydrous LiCl (59.2 mg, 1.40 mmol, 1.0 equiv), and Pd(dppf)Cl_2•DCM (228 mg, 0.279 mmol, 0.20 equiv) was evacuated and backfilled with argon. The flask was evacuated and backfilled with argon one additional time. DMF (10.0 mL, 1.4 M) was then added and the resulting suspension was sonicated briefly. Next, the reaction mixture was degassed by iterative freeze-pump-thaw cycles. After heating the suspension to 100 °C

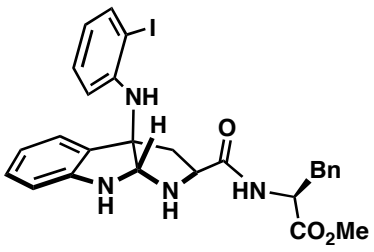
for 1.5 hours, the reaction mixture was cooled to room temperature, diluted with DCM (40 mL), filtered through Celite, and concentrated *in vacuo*. The residue was taken up in EtOAc (100 mL) and washed vigorously with aqueous 10 % HCl (100 mL) for approximately one minute. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (400 mL), brine (2 × 400 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (30:1 to 10:1, DCM/acetone) to afford the product, **123**, along with recovered alkyne **116** (0.70 g). The product was further purified by repetitive recrystallization from hot Et_2O:hexanes to afford a light tan powder (828 mg, 55%).



Undeisred macrocycle **124**: A flask containing anhydrous NaOAc (20.5 mg, 0.25 mmol, 6.4 equiv) and anhydrous LiCl (1.6 mg, 0.038 mmol, 0.96 equiv) was heated *in vacuo* with agitation at 170 °C for three hours. After cooling to room temperature and placing under an argon atmosphere, the pentapeptide, **127**, (42.3 mg, 0.039 mmol) and $Pd(OAc)_2$ (3.0 mg, 0.013 mmol, 0.34 equiv) were added. Next was added DMF (1.5 mL, 0.03 M) and the resulting suspension was sonicated with continuous argon bubbling for 15 minutes. Next, the reaction mixture was degassed via iterative freeze-pump-thaw cycles. After heating the suspension to 100 °C for 12 hours, the reaction mixture was cooled to room temperature, diluted with toluene (3 mL), filtered through Celite with EtOAc flushing, and concentrated. The residue was taken up in EtOAc (5 mL) and washed vigorously with aqueous HCl (2 M, 10 mL). The layers

were separated and the aqueous layer was extracted additionally with EtOAc (3 × 5 mL). The combined extracts were washed with saturated $NaHCO_3$ (15 mL), brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude material was purified by flash column chromatography (1:0 to 1:1, EtOAc:hexanes) to afford the product **124** (22.0 mg, 67%).

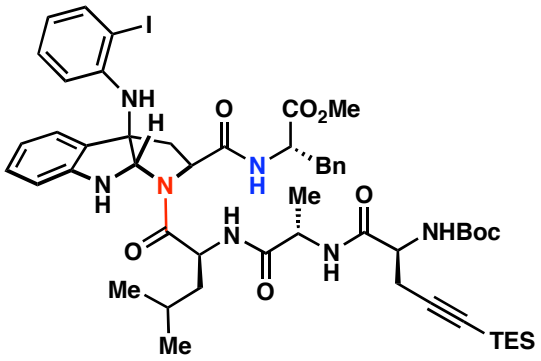
The following peptide coupling conditions afforded the undesired macrocycle **124** with greater than 20:1 selectivity. The crude material derived from hydrogenolysis (Pd/C (0.20 equiv), MeOH, H_2) of **123** (10.0 mg, 0.012 mmol), was dissolved in DMF (1.1 mL, 0.01 M). Next *N,N*-diisopropylethylamine (4.5 μL, 0.026 mmol, 2.2 equiv), 1-hydroxybenzotriazole, HOBt, (3.9 mg, 0.029 mmol, 2.5 equiv), and HATU (13.5 mg, 0.036 mmol, 3.0 equiv) were added. The reaction mixture was allowed to stir at room temperatue for 6 hours at which point the reaction mixture was quenched with aqueous HCl (1 M, 1 mL) and diluted with EtOAc (1 mL). The layers were separated and the aqueous layer was extracted additionally with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (2 × 5 mL), dried over $MgSO_4$, filtered and concentrated. The crude material thus obtained was purified by flash column chromatography (1:0 to 1:1, hexanes:EtOAc) to afford the product **124** (4.0 mg, 41%).



Pyrroloindoline **125**: Fmoc-protected pyrroloindoline (**102c**, 100.0 mg, 0.124 mmol) was dissolved in DCM (1.5 mL) and Et_2NH (0.5 mL) was added and the reaction monitored. After one hour, the reaction was complete and the crude mixture was loaded onto a silica gel plug. The fulvene was removed by

hexanes elution and the product flushed off with EtOAc/hexanes (1:1) and then MeOH/DCM (1:19) and concentrated to deliver the off-white foam product **125** (72.3 mg, quant.)

$[\alpha]^{20.0}$ -79.9 (*c* 1.0, $CHCl_3$); **R_f** = 0.39 (silica gel, 9:1, DCM/MeOH); **^{1}H-NMR** (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 1 H), 7.24 – 7.19 (m, 3 H), 7.12 – 7.07 (m, 4 H), 6.96 (at, *J* = 7.8 Hz, 1 H), 6.75 (at, *J* = 7.8 Hz, 1 H), 6.60 (d, *J* = 7.8 Hz, 1 H), 6.40 (at, *J* = 7.8 Hz, 1 H), 6.35 (d, *J* = 8.4 Hz, 1 H), 5.26 (s, 1 H), 4.92 (aq, *J* = 6.6 Hz, 1 H), 4.70 (s, 1 H), 4.63 (brs, 1 H), 3.73 (s, 3 H), 3.68 (dd, *J* = 10.2, 6.6 Hz, 1 H), 3.21 (dd, *J* = 13.8, 5.4 Hz, 1 H), 3.08 (dd, *J* = 13.8, 6.6 Hz, 1 H), 2.49 (dd, *J* = 12.0, 6.0 Hz, 1 H), 2.32 (dd, *J* = 12.6, 10.2 Hz, 1 H); **^{13}C-NMR** (150 MHz, $CDCl_3$) δ 172.3, 172.1, 149.6, 144.7, 139.4, 135.8, 130.0, 129.7, 129.3, 129.1, 128.7, 127.2, 123.8, 120.0, 119.3, 112.5, 109.7, 87.0, 79.8, 73.9, 59.3, 52.6, 52.5, 46.3, 38.0; **IR** (film, cm^{-1}) 3707, 3665, 3379, 2923, 1740, 1665, 1509, 1319, 1055, 1032, 1008, 744; **HRMS** (ESI^+) m/z Calc'd for $C_{27}H_{28}IN_4O_3$ [$M+H^+$] 583.1201, found 583.1203.



Pentapeptide **127**: Deprotected peptide (**126**, 40.0 mg, 0.069 mmol) was dissolved in DCM (6 mL) and triethylamine (19.1 μL, 0.137 mmol, 2.0 equiv.) was added. The alkyne (34.2 mg, 0.069 mmol, 1.0 equiv.) was then added in a solution of HATU (39.2 mg, 0.103 mmol, 1.5 equiv.) and HOBt•H_2O (13.7 mg, 0.089 mmol, 1.3 equiv.) and stirred for 8 hours. The crude mixture was concentrated and purified by silica gel chromatography (2:3 EtOAc/hexanes) to give the

desired product as a colorless oil (**127**, 15.9 mg, 22%) as well as recovered starting material (**125**, 9.8 mg, 25%).

$[\alpha]^{20.0}$ -114.2 (*c* 1.0, $CHCl_3$); **R_f** = 0.71 (silica gel, 3:2, EtOAc:hexanes); **^{1}H-NMR** (600 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ 7.62 – 7.60 (m, 1 H), 7.48 (brd, *J* = 7.2 Hz, 1 H), 7.31 (brs, 0.67 H), 7.25 – 7.20 (m, 1 H), 7.17 (at, *J* = 7.2 Hz, 1 H), 7.13 – 6.97 (m, 6 H), 6.93 (at, *J* = 7.2 Hz, 0.67 H), 6.86 (at, *J* = 7.8 Hz, 0.33 H), 6.80 (at, *J* = 7.2 Hz, 0.67 H), 6.77 – 6.73 (m, 1 H), 6.66 – 6.61 (m, 0.67 H), 6.37 (at, *J* = 7.2 Hz, 0.67 H), 6.34 (at, *J* = 6.6 Hz, 0.33 H), 6.12 (d, *J* = 4.2 Hz, 0.67 H), 6.03 (d, *J* = 6.0 Hz, 0.67 H), 5.96 (d, *J* = 8.4 Hz, 0.67 H), 5.69 (brs, 0.33 H), 5.46 (brs, 0.33 H), 5.31 (brs, 0.67 H), 5.19 (brs, 0.67 H), 5.10 (brs, 0.67 H), 4.99 (d, *J* = 9.6 Hz, 0.33 H), 4.96 (aq, *J* = 6.6 Hz, 0.33 H), 4.91-4.88 (m, 1 H), 4.79 (d, *J* = 8.4 Hz, 0.67 H), 4.68 – 4.52 (m, 2 H), 4.27 (brs, 0.33 H), 4.15 – 4.13 (m, 0.67 H), 3.72 (s, 1 H), 3.61 (s, 2 H), 3.22 – 3.16 (m, 1 H), 3.03 (brd, *J* = 14.4 Hz, 1 H), 2.99 (dd, *J* = 13.8, 6.6 Hz, 0.67 H), 2.82 (dd, *J* = 17.4, 5.4 Hz, 0.33 H), 2.74 – 2.60 (m, 2 H), 2.45 (brs, 1.33 H), 2.34 (dd, *J* = 13.8, 8.4 Hz, 0.67 H), 1.80 (brs, 2 H), 1.44 – 1.36 (m, 10 H), 1.25 (s, 2 H), 1.24 (s, 1 H), 1.08 (*J* = 4.8 Hz, 2 H), 1.02 (d, *J* = 4.8 Hz, 2 H), 0.97 (t, *J* = 7.8 Hz, 9 H), 0.84 (d, *J* = 6.6 Hz, 1 H), 0.79 (d, *J* = 6.6 Hz, 1 H), 0.56 (q, *J* = 7.8 Hz, 6 H); **^{13}C-NMR** (150 MHz, $CDCl_3$, 2:1 mixture of rotamers) δ 173.5, 173.3, 173.0, 172.8, 172.1, 171.8, 171.5, 170.9, 170.7, 170.4, 156.1, 155.8, 147.3, 147.2, 144.5, 144.2, 139.8, 139.6, 136.0, 135.3, 130.3, 129.7, 129.4, 129.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.4, 128.4, 127.5, 126.9, 122.8, 121.3, 119.5, 119.4, 118.9, 113.5, 112.6, 111.6, 110.0, 102.6, 87.0, 86.9, 86.2, 86.0, 80.7, 80.6, 79.9, 74.8, 71.1, 60.6, 59.8, 54.2, 53.7, 53.2, 52.6, 52.4, 50.7, 49.1, 48.9, 48.5, 46.2, 42.6, 40.2, 40.0, 38.1, 38.0, 34.0, 29.8, 28.4, 28.4, 25.7, 25.1, 24.8, 24.4, 23.6, 23.6, 23.5, 23.4, 23.3, 22.1, 21.5, 19.3, 17.3, 7.6,

4.4; **IR** (film, cm^{-1}) 3707, 3681, 3310, 2967, 1648, 1510, 1346, 1165, 1055, 1032, 1012, 741; **HRMS** (ESI^+) m/z Calc'd for $C_{52}H_{71}IN_7O_8Si$ [$M+H^+$] 1076.4172, found 1076.4146.

Complete Reference for Reference 5f:

Kung, A. L.; Zabludoff, S. D.; France, D. S.; Freedman, S. J.; Tanner, E. A.; Vieira, A.; Cornell-Kennon, S.; Lee, J.; Wang, B.; Wang, J.; Memmert, K.; Naegeli, H.-U.; Petersen, F.; Eck, M. J.; Bair, K. W.; Wood, A. W.; Livingston, D. M. *Cancer Cell*, **2004**, *6*, 33.