Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Synthesis of Metergoline analogues and their evaluation as antiplasmodial agents

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Experimental Section

Metergoline and all other reagents were purchased from Sigma Aldrich. All target compounds and intermediates were characterised by ^{1}HNMR, ^{13}CNMR and MS. NMR spectra were recorded on a Bruker 400 spectrometer. The ^{1}H NMR data are reported as follows: chemical shift in parts per million (δ) downfield of tetramethylsilane (TMS), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd =doublets of doublets, dt = triplets of doublets and m = multiplet), coupling constant (Hz), and integrated value. The ^{13}C NMR spectra were measured with complete proton decoupling. MS was recorded on an AB SCIEX 4000 QTRAP® mass spectrophotometer. The purities were determined by Waters' HPLC using X-bridge C18 5µm column (4.6 x 150 mm); organic phase: 10 mM Ammonium acetate (pH 3.7) in HPLC grade methanol, aqueous phase: 10 mM Ammonium acetate (pH 3.7) in HPLC grade water; flow rate = 1.20 mL/min; detector: photodiode array (PDA). The purities of all compounds were found to be >95%. The optical rotation was recorded on Perkin Elmer 343 digital polarimeter at 20 ^{o}C. Melting points were obtained from a Reichert-Jung Thermovar hot-stage microscope apparatus and are uncorrected.

General synthetic procedure for compound 2

((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methanamine[1]

A suspension of metergoline **1** (1.0 g, 3.712 mmol) in methanol (30 ml) was taken in a 250 ml RBF and charged with 10% Pd/C (50% moisture). The reaction mixture was stirred at room temperature for 16h under a hydrogen balloon. Progress of the reaction was monitored

by TLC. After completion, reaction mixture was filtered through a bed of celite and the filtrate was evaporated under reduced pressure to afford 730mg (95%) of compound **2** as yellow viscous oil which then solidified on long standing in refrigerator.

Yellow powder; Yield: 95%; Mp 151–153 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.96 (1H, d, *J* =7.1 Hz), 6.75 (1H, d, *J* = 1.5 Hz), 3.78 (3H, s), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.16 (1H, dd, *J* = 7.6, 2.0 Hz), 3.07–2.95 (1H, m), 2.81–2.63 (4H, m), 2.52 (3H, s), 2.21-2.15 (1H, m), 2.10–1.92 (2H, m), 1.75 (2H, bs), 1.14 (1H, q, *J* = 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.57, 133.67, 126.66, 122.71, 122.38, 112.57, 110.94, 106.64, 67.67, 61.83, 46.59, 43.19, 40.57, 39.26, 32.61, 32.25, 27.00; ESI-MS (m/z): 270 $[M+H]^+$; HPLC purity: 99% (t_r = 4.75 min).

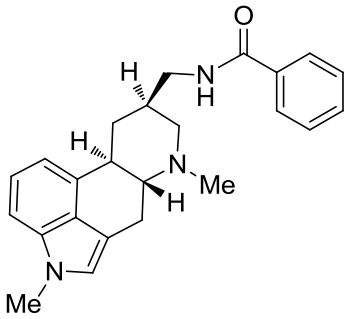
General Procedure A

Compound **2** (1.0 equiv.), carboxylic acid (1.2 equiv.) and 1-hydroxybenzotriazole (1.2 equiv.) were dissolved in DCM in a RBF. Diisopropylethylamine (3.0 equiv.) was then added dropwise at room temperature followed by addition of EDC.HCl (1.2 equiv.). Reaction mixture was stirred at room temperature for 24h. Progress of the reaction was monitored by TLC. After completion, reaction mixture was diluted with DCM and washed with water. Organic layer was separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Crude was purified by column chromatography on silica gel (60-120 mesh size; mobile phase: DCM-Methanol). All compounds were eluted in 3-7% methanol in DCM.

General Procedure B (for compound **13**, **14**, **28**, **33** and **35**)

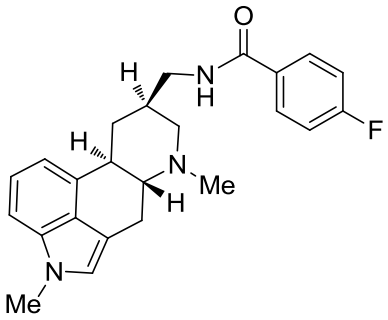
A solution of compound **2** (1.0 equiv.) and respective acid chloride (1.5 equiv.) in DCM was stirred at room temperature for 3h. Progress of the reaction was monitored by TLC. After completion, reaction mixture was diluted with DCM and washed with water. Organic layer after drying over anhydrous sodium sulphate was concentrated under reduced pressure. Crude was purified by column chromatography on silica gel (60-120 mesh size; mobile phase: DCM-Methanol). All compounds were eluted in 3-7% methanol in DCM.

Compound 3: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide[1]



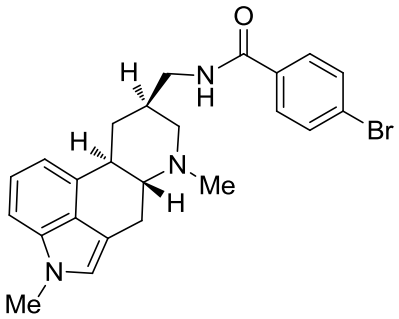
Off-white powder; Yield: 27%; Mp 205–207 °C; ^{1}H NMR (400 MHz, CDCl3): δ 7.86–7.80 (2H, m), 7.54–7.42 (3H, m), 7.22–7.14 (1H, m), 7.12 (1H, d, *J* = 8.2 Hz), 6.90 (1H, d, *J* = 7.1 Hz), 6.74 (1H, s), 6.44 (1H, bs), 3.76 (3H, s), 3.54–3.48 (2H, m), 3.41 (1H, dd, *J* = 14.7, 4.3 Hz), 3.26 (1H, d, *J* = 12.1 Hz), 3.15–3.06 (1H, m), 2.84–2.70 (2H, m), 2.54 (3H, s), 2.30 (1H, td, *J* = 10.8, 4.7 Hz), 2.14 (1H, t, *J* = 11.4 Hz), 1.34–1.19 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.77, 134.65, 132.75, 131.46, 128.61, 127.94, 126.98, 126.43, 122.78, 122.63, 112.63, 110.21, 106.98, 67.41, 61.27, 43.71, 42.92, 40.27, 36.34, 32.77, 32.04, 26.59; ESI-MS (m/z): 374 $[M+H]^+$; HPLC purity: 99% (t_r = 11.95 min).

Compound 4: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-fluorobenzamide



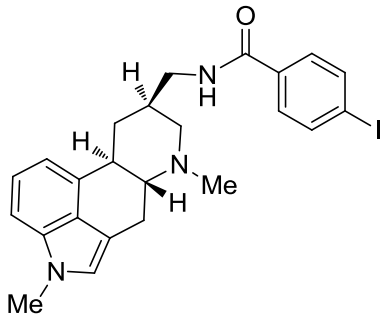
Off-white powder; Yield: 28%; Mp 212–214 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.77 (2H, m), 7.21–7.15 (1H, m), 7.12 (3H, t, *J* = 8.5 Hz), 6.89 (1H, d, *J* = 7.1 Hz), 6.73 (1H, d, *J* = 1.3 Hz), 6.23 (1H, bs), 3.75 (3H, s), 3.52–3.45 (2H, m), 3.39 (1H, dd, *J* = 14.7, 4.4 Hz), 3.13–3.06 (1H, m), 3.05–2.93 (1H, m), 2.77–2.63 (2H, m), 2.47 (3H, s), 2.31–2.20 (1H, m), 2.22–2.13 (1H, m), 2.06 (1H, t, *J* = 11.3 Hz), 1.30–1.18 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.69, 166.00, 134.47, 133.17, 130.92, 129.27, 129.18, 126.54, 122.74, 122.58, 115.78, 115.56 112.54, 110.66, 106.89, 67.44, 61.58, 43.91, 43.34, 40.60, 36.86, 32.76, 32.23, 27.00; ESI-MS (m/z): 392 $[M+H]^+$; HPLC purity: 99% (t_r = 12.33 min).

Compound 5: 4-Bromo-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide



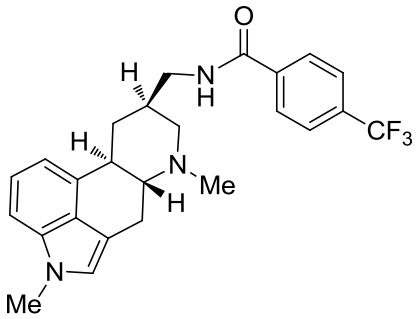
Off-white powder; Yield: 53%; Mp 213–215 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.3 Hz), 7.52 (2H, d, *J* = 8.3 Hz), 7.18–7.11 (2H, m), 7.09 (1H, d, *J* = 7.9 Hz), 6.83 (1H, d, *J* = 7.4 Hz), 6.71 (1H, s), 3.71 (3H, s), 3.67 (2H, q, *J* = 7.0 Hz), 3.56–3.43 (1H, m), 3.38 (2H, dd, *J* = 14.8, 4.3 Hz), 3.33–3.22 (1H, m), 3.06–2.92 (1H, m), 2.66 (3H, s, H-5), 2.63–2.52 (1H, m), 2.38–2.28 (1H, m), 1.20 (1H, dd, *J* = 13.4, 6.4 Hz), 0.86 (1H, d, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.03, 134.43, 133.12, 131.19, 131.12, 128.92, 126.19, 126.09, 124.98, 122.94, 112.89, 108.66, 107.42, 67.48, 60.62, 43.35, 42.06, 39.38, 35.12, 33.44, 32.83, 26.74; ESI-MS (m/z): 452 $[M+H]^+$; HPLC purity: 99% (t_r = 13.33 min).

Compound 6: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-iodobenzamide



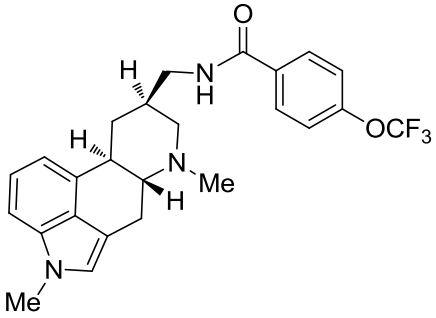
Off-white powder; Yield: 46%; Mp 227–229 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* = 7.5 Hz), 7.60 (2H, d, *J* = 8.4 Hz), 7.23–7.15 (1H, m), 7.12 (1H, d, *J* = 8.0 Hz), 6.89 (1H, d, *J* = 7.3 Hz), 6.75 (1H, s), 6.65 (1H, bs), 3.76 (3H, s), 3.52–3.33 (4H, m), 3.22–3.10 (1H, m), 2.93–2.81 (1H, m), 2.72 (1H, d, *J* = 13.5 Hz), 2.58 (3H, s), 2.49–2.34 (1H, m), 2.25–2.13 (1H, m), 1.37–1.24 (1H, m), 1.21 (1H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.99, 137.80, 137.18, 134.46, 133.93, 132.26, 128.70, 126.34, 122.83, 122.74 112.67, 109.76, 107.14 67.40, 61.06, 43.71, 42.64, 40.12, 35.89, 32.79, 31.87, 26.34; ESI-MS (m/z): 500 $[M+H]^+$; HPLC purity: 99% (t_r = 13.68 min).

Compound 7: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-(trifluoromethyl)benzamide



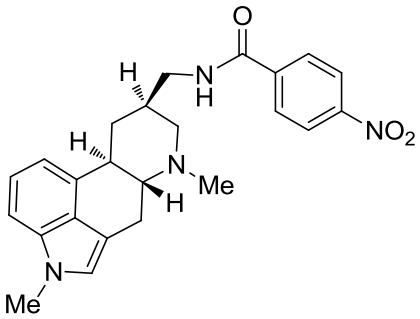
Off-white powder; Yield: 43%; Mp 228–230 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (2H, d, *J* = 8.1 Hz), 7.75 (2H, d, *J* = 8.7 Hz), 7.26–7.17 (1H, m), 7.15 (1H, d, *J* = 8.9 Hz), 6.92 (1H, d, *J* = 8.1 Hz), 6.76 (1H, d, *J* = 1.4 Hz), 6.36 (1H, bs), 3.79 (3H, s), 3.54 (2H, t, *J* = 6.4 Hz), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.13-3.05 (1H, m), 3.03 (1H, td, *J* = 12.2, 3.6 Hz), 2.74-2.65 (2H, m), 2.51 (3H, s), 2.37–2.26 (1H, m), 2.25–2.17 (1H, m), 2.10 (1H, t, *J* = 11.3 Hz), 1.28 (1H, q, *J* = 12.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.47, 137.99, 134.46, 133.07, 127.40, 126.51, 125.71, 125.68, 122.72, 122.59, 112.49, 110.59, 106.91, 67.41, 61.53, 43.99, 43.30, 40.56, 36.78, 32.74, 32.20, 26.97; ESI-MS (m/z): 442 $[M+H]^+$; HPLC purity: 99% (t_r = 13.54 min).

Compound 8: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-(trifluoromethoxy)benzamide



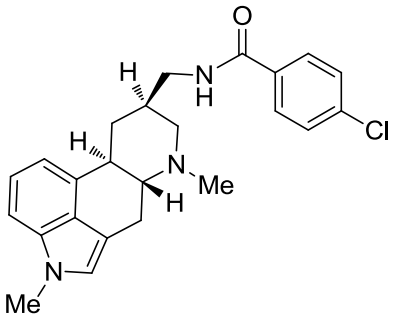
Brown powder; Yield: 23%; Mp 182–184 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (2H, d, *J* = 8.9 Hz), 7.29 (2H, d, *J* = 8.9 Hz), 7.21–7.15 (1H, m), 7.11 (1H, d, *J* = 8.2 Hz), 6.89 (1H, d, *J* = 6.2 Hz), 6.73 (1H, d, *J* = 1.4 Hz), 6.23 (1H, bs), 3.75 (3H, s), 3.49 (2H, t, *J* = 6.4 Hz), 3.39 (1H, dd, *J* = 14.6, 4.4 Hz), 3.13–3.07 (1H, m), 3.03–2.95 (1H, m), 2.77–2.65 (2H, m), 2.48 (3H, s), 2.27 (1H, dd, *J* = 12.0, 7.0 Hz), 2.23–2.14 (1H, m), 2.07 (1H, t, *J* = 11.3 Hz), 1.25 (1H, q, *J* = 12.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.40, 151.49, 134.45, 133.13, 128.77, 126.50, 122.64, 120.72, 112.50, 110.59, 106.89, 67.42, 61.53, 43.93, 43.29, 40.56, 36.80, 32.75, 32.19, 26.96; ESI-MS (m/z): 458 $[M+H]^+$; HPLC purity: 99% (t_r = 13.84 min).

Compound 9: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-nitrobenzamide



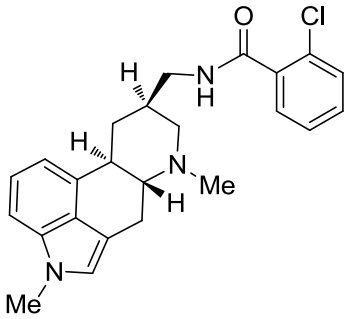
Orange powder; Yield: 37%; Mp 228–230 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (2H, d, *J* = 8.6 Hz), 7.95 (2H, d, *J* = 8.5 Hz), 7.17–7.11 (1H, m), 7.08 (1H, d, *J* = 8.1 Hz), 6.83 (1H, d, *J* = 7.2 Hz), 6.79 (1H, bs), 6.70 (1H, s), 3.72 (3H, s), 3.48 (2H, t, *J* = 6.2 Hz), 3.36 (1H, dd, *J* = 14.5, 4.4 Hz), 3.22 (1H, d, *J* = 11.0 Hz), 3.13–3.05 (1H, m), 2.83–2.67 (2H, m), 2.54 (3H, s), 2.45–2.37 (1H, m), 2.36–2.28 (1H, m), 2.18 (1H, t, *J* = 11.5 Hz), 1.30–1.18 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.81, 149.60, 140.02, 134.44, 132.11, 128.27, 126.28, 123.75, 122.79, 112.61, 109.65, 107.18 67.50, 61.22, 43.90, 42.82, 40.01, 36.17, 32.78, 31.93, 26.45; ESI-MS (m/z): 419 $[M+H]^+$; HPLC purity: 98% (t_r = 12.48 min).

Compound 10: 4-Chloro-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide[1]



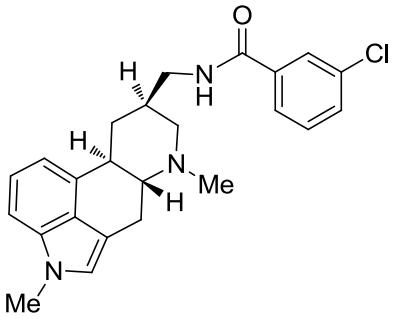
Off-white powder; Yield: 35%; Mp: 224–226 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (2H, d, *J* = 8.3 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 7.26 (1H, bs), 7.16–7.10 (1H, m), 7.07 (1H, d, *J* = 8.2 Hz), 6.83 (1H, d, *J* = 6.9 Hz), 6.69 (1H, s), 3.70 (3H, s), 3.41–3.30 (3H, m), 3.23 (1H, d, *J* = 10.4 Hz), 3.10–3.00 (1H, m), 2.82–2.72 (1H, m), 2.65 (1H, d, *J* = 12.6 Hz), 2.49 (3H, s), 2.27 (2H, td, *J* = 10.7, 4.2 Hz), 2.13–2.03 (1H, m), 1.27–1.13 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.71, 137.74, 134.46, 132.95, 132.51, 128.85, 128.48, 126.39, 122.80, 122.69 112.62, 110.01, 107.07 67.41, 61.20, 43.77, 42.83, 40.24, 36.17, 32.78, 31.97, 26.52; ESI-MS (m/z): 419 $[M+H]^+$; HPLC purity: 99% (t_r = 13.19 min); $[\alpha]_D^{20}$ -0.051^{o} (*c* 0.1, $CHCl_3$).

Compound 11: 2-Chloro-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide



White powder; Yield: 66%; Mp 180-182 ^{o}C; ^{1}H NMR (400 MHz, CDCl3): δ 7.74–7.72 (1H, m), 7.44–7.46 (1H, m), 7.42–7.35 (2H, m), 7.24-7.22 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.93 (1H, d, *J* = 7.1 Hz), 6.76 (1H, d, *J* = 1.3 Hz), 6.34 (1H, bs), 3.79 (3H, s), 3.54 (2H, t, *J* = 6.4 Hz), 3.42 (1H, dd, *J* = 14.6, 4.3 Hz), 3.20 (1H, d, *J* = 9.8 Hz), 3.06-3.01 (1H, m), 2.82-2.71 (2H, m), 2.53 (3H, s), 2.35-2.27 (1H, m), 2.25–2.19 (1H, m), 2.13 (1H, t, *J* = 11.3 Hz), 1.29 (1 H, q, *J* = 12.3 Hz); ^{13}C NMR (100 MHz, CDCl3): δ 166.61, 135.23, 134.46, 133.19, 131.31, 130.56, 130.33, 130.27, 127.17, 126.52, 122.76, 122.54, 112.56, 110.65, 106.85, 67.40, 61.54, 43.94, 43.32, 40.53, 36.65, 32.75, 32.19, 26.95; ESI-MS (m/z): 408 [M+H]+; HPLC purity: 99% (t_r = 12.89 min).

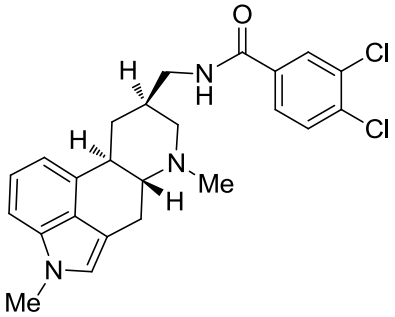
Compound 12: 3-Chloro-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide



White powder; Yield: 63%; Mp 183-185 ^{o}C; ^{1}H NMR (400 MHz, CDCl3): δ 7.82 (1H, t, *J* = 1.8 Hz), 7.68 (1H, d, *J* = 4.0 Hz), 7.51-7.47 (1H, m), 7.41 (1H, t, *J* = 7.8 Hz), 7.24-7.22 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.93 (1H, d, *J* = 7.0 Hz), 6.76 (1H, d, *J* = 1.2 Hz), 6.28 (1H, bs), 3.78 (3H, s), 3.52 (2H, t, *J* = 6.3 Hz), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.12 (1H, d, *J* = 9.9 Hz), 3.06–2.97 (1H, m), 2.80–2.67 (2H, m), 2.51 (3H, s), 2.31-2.23 (1H, m), 2.20-2.17 (1H, m), 2.09 (1H, t, *J* = 11.3 Hz), 1.33–1.22 (1H, m); ^{13}C NMR (100 MHz, CDCl3): δ 166.38, 136.54, 134.87, 134.46, 133.16, 131.51, 129.96, 127.33, 126.53, 124.95, 122.73, 122.55,

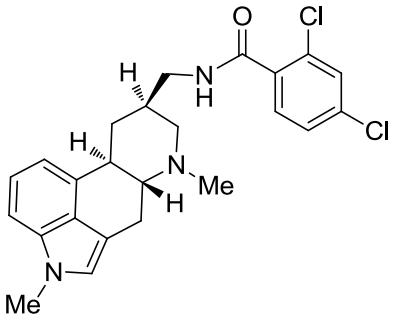
112.53, 110.67, 106.87, 67.41, 61.55, 43.95, 43.34, 40.60, 36.86, 32.75, 32.21, 27.00; ESI-MS (m/z): 408 [M+H]+; HPLC purity: 98% (t_r = 14.09 min).

Compound 13: 3,4-Dichloro-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide



Off-white powder; Yield: 53%; Mp 139-141 ^{o}C; ^{1}H NMR (400 MHz, MeOD): δ 8.06 (1H, dd, *J* = 4.1, 1.9 Hz), 7.82-7.76 (1H, m), 7.57 (1H, m), 7.20–7.13 (2H, m), 6.94–6.89 (2H, m), 3.78 (3H, s), 3.58–3.53 (1H, m), 3.53-3.42 (3H, m), 3.22–3.13 (1H, m), 2.91–2.79 (6H, m), 2.66 (1H, t, *J* = 12.1 Hz), 2.50–2.38 (1H, m), 1.37 (1H, dd, *J* = 25.2, 12.3 Hz); ^{13}C NMR (100 MHz, MeOD): δ 166.65, 130.97, 130.45, 130.37, 129.65, 129.20, 128.54, 126.72, 125.90, 123.00, 122.45, 112.42, 107.74, 107.11, 67.30, 59.81, 42.75, 40.85, 39.08, 35.16, 31.47, 30.87, 25.02; ESI-MS (m/z): 442 [M+H]+; HPLC purity: 97% (t_r = 14.16 min); $[\alpha]_D^{20}$ -0.055^{o} (*c* 0.1, $CHCl_3$).

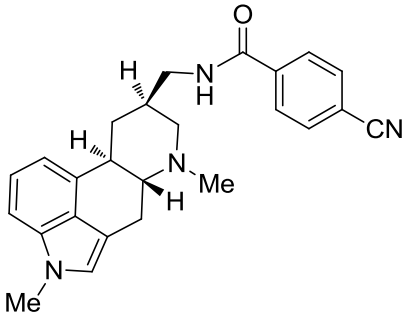
Compound 14: 2,4-Dichloro-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide



Off-white powder; Yield: 41%; Mp 160-162 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (1H, d, *J* = 8.3 Hz), 7.42 (1H, d, *J* = 1.9 Hz), 7.32 (1H, dd, *J* = 8.3, 2.0 Hz), 7.24-7.22 (1H, m), 7.17 (1H, d, *J* = 8.2 Hz), 6.93 (1H, bs), 6.91 (1H, d, *J* = 7.0 Hz), 6.79 (1H, d, *J* = 1.2 Hz), 3.79 (3H, s), 3.64–3.49 (4H, m), 3.46 (1H, dd, *J* = 14.5, 4.4 Hz), 3.22 (1H, dd, *J* = 16.3, 9.1 Hz), 2.86-2.72 (2H, m), 2.82 (3H, s), 2.61 (1H, t, *J* = 11.5 Hz), 1.40 (1H, q, *J* = 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.32, 136.83, 134.43, 133.42, 131.61, 130.99, 130.57, 130.07,

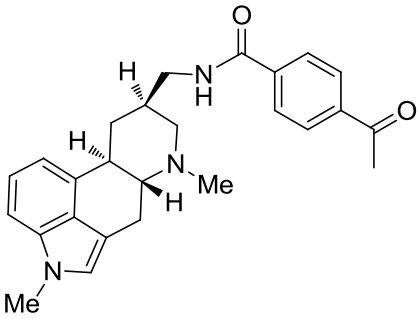
127.54, 125.97, 123.08, 122.96, 112.90, 108.07, 107.58, 67.66, 60.37, 42.99, 41.88, 38.71, 35.05, 32.86, 31.19, 25.34; ESI-MS (m/z): 442 [M+H]+; HPLC purity: 98% (t_r = 14.12 min).

Compound 15: 4-Cyano-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide



Brown powder; Yield: 52%; Mp 137-139 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (2H, d, *J* = 8.2 Hz), 7.66 (2H, d, *J* = 8.1 Hz), 7.30 (1H, bs), 7.18 – 7.13 (1H, m), 7.11 (1H, d, *J* = 8.2 Hz), 6.84 (1H, d, *J* = 6.6 Hz), 6.74 (1H, s), 3.73 (3H, s), 3.59 – 3.47 (3H, m), 3.47 – 3.36 (2H, m), 3.36 – 3.27 (1H, m), 3.02 (1H, dd, *J* = 13.7, 12.5 Hz), 2.69 (3H, s), 2.68 – 2.58 (1H, m), 2.43 – 2.33 (1H, m), 1.32 (1H, q, *J* = 11.9 Hz), 1.24 – 1.18 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ166.13, 138.09, 134.45, 132.33, 131.79, 130.90, 129.91, 128.01, 126.04, 123.04, 122.96, 112.84, 108.42, 107.57 67.57, 60.66, 43.48, 42.04, 39.42, 35.11, 32.87, 31.44, 25.67; ESI-MS (m/z): 399 [M+H]+; HPLC purity: 95% (t_r = 11.60 min); $[\alpha]_D^{20}$ -0.045^{o} (*c* 0.1, $CHCl_3$).

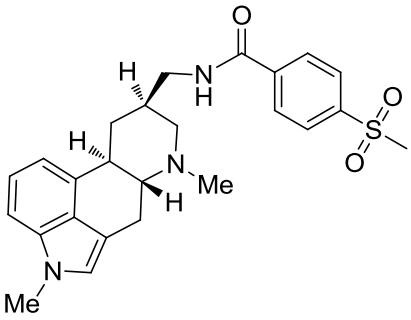
Compound 16: 4-Acetyl-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide



Light brown powder; Yield: 41%; Mp 198-200 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (2H, d, *J* = 8.2 Hz), 7.91 (2H, d, *J* = 8.3 Hz), 7.21–7.14 (1H, m), 7.11 (1H, d, *J* = 8.2 Hz), 6.88 (1H, d, *J* = 7.0 Hz), 6.73 (1H, s), 6.58 (1H, bs), 3.75 (3H, s), 3.48 (3H, q, *J* = 7.0 Hz), 3.39 (1H, dd, *J* = 14.7, 4.2 Hz), 3.21 (1H, d, *J* = 8.7 Hz), 3.11 – 3.01 (1H, m), 2.78 – 2.69 (1H, m), 2.62 (3H, s), 2.52 (3H, s), 2.40–2.32 (1H, m), 2.32–2.22 (1H, m), 2.12 (1H, t, *J* = 11.3 Hz), 1.37–1.13 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.40, 166.82, 139.23, 138.51,

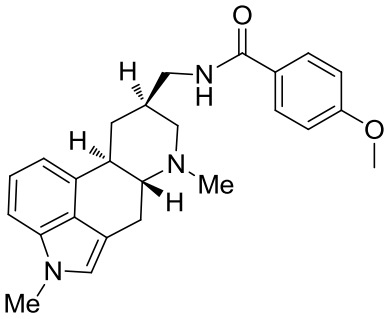
134.45, 132.67, 128.54, 127.34, 126.42, 122.76, 122.66, 112.58, 110.17, 107.02, 67.39, 65.82, 61.31, 43.86, 42.99, 40.32, 36.37, 32.76, 32.04, 26.76; ESI-MS (m/z): 416 [M+H]+; HPLC purity: 99% (t_r = 11.64 min).

Compound 17: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-(methylsulfonyl)benzamide



Light brown powder; Yield: 44%; Mp 209-211 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01–7.93 (4H, m), 7.21–7.15 (1H, m), 7.11 (1H, d, *J* = 8.2 Hz), 6.88 (1H, d, *J* = 7.1 Hz), 6.73 (1H, d, *J* = 1.2 Hz), 6.53 (1H, bs), 3.75 (3H, s), 3.54–3.46 (2H, m), 3.38 (1H, dd, *J* = 14.7, 4.3 Hz), 3.14–3.07 (1H, m), 3.05 (3H, s), 3.03–2.89 (1H, m), 2.77–2.64 (2H, m), 2.48 (3H, s), 2.33–2.21 (1H, m), 2.18 (1H, td, *J* = 10.4, 4.4 Hz), 2.06 (1H, t, *J* = 11.3 Hz), 1.35–1.17 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.14, 142.95, 139.79, 134.46, 133.05, 128.10, 127.75, 126.51, 122.71, 122.62, 112.49, 110.56, 106.93, 67.40, 61.51, 44.40, 44.10, 43.30, 40.55, 36.68, 32.76, 32.20, 26.96; ESI-MS (m/z): 452 [M+H]+; HPLC purity: 99% (t_r = 10.66 min).

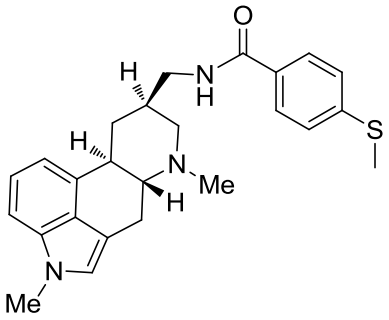
Compound 18: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-methoxybenzamide



Light brown powder; Yield: 41%; Mp 212-214 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (2H, d, *J* = 8.8 Hz), 7.21–7.15 (1H, m), 7.11 (1H, d, *J* = 8.2 Hz), 6.94 (2H, d, *J* = 8.8 Hz), 6.90 (1H, d, *J* = 7.1 Hz), 6.72 (1H, d, *J* = 1.3 Hz), 6.18 (1H, bs), 3.85 (3H, s), 3.75 (3H, s), 3.48 (2H, q, *J* = 7.0 Hz), 3.38 (1H, dd, *J* = 14.7, 4.3 Hz), 3.11-3.07 (1H, m), 3.03–2.95 (1H, m), 2.77–2.64 (2H, m), 2.47 (3H, s), 2.30–2.21 (1H, m), 2.21–2.14 (1H, m), 2.06 (1H, t, *J* = 11.3 Hz), 1.21 (1H, t, *J* = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.21, 162.21, 134.45,

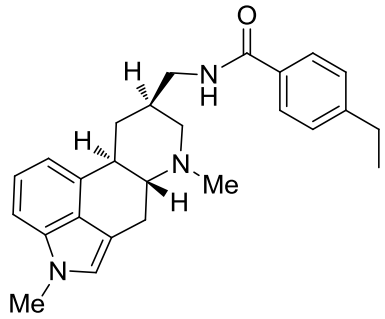
133.21, 128.67, 127.03, 126.52, 122.73, 122.53, 113.84, 112.56, 110.66, 106.83 67.43, 61.57, 55.41, 43.73, 43.29, 40.58, 36.89, 32.74, 32.21, 26.96; ESI-MS (m/z): 404 [M+H]+; HPLC purity: 99% (t_r = 12.13 min).

Compound 19: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-(methylthio)benzamide



Light brown powder; Yield: 31%; Mp 214-216 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 7.9 Hz), 7.24 (2H, d, *J* = 8.2 Hz), 7.18 – 7.11 (1H, m), 7.08 (1H, d, *J* = 7.8 Hz), 6.86 (1H, d, *J* = 6.5 Hz), 6.69 (1H, s), 6.34 (1H, bs), 3.71 (3H, s), 3.50–3.39 (2H, m), 3.36 (1H, dd, *J* = 14.7, 4.6 Hz), 3.18 (1H, d, *J* = 9.9 Hz), 3.09–2.98 (1H, m), 2.78–2.64 (2H, m), 2.48 (3H, s), 2.47 (3H, s), 2.34–2.20 (2H, m), 2.08 (1H, t, *J* = 11.5 Hz), 1.26–1.19 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.18, 143.40, 134.45, 132.81, 127.38, 126.44, 125.61, 125.12, 122.77, 122.62 112.61, 110.28, 106.96 67.42, 61.33, 43.71, 40.34, 36.44, 32.76, 32.06, 26.66, 15.14; ESI-MS (m/z): 420 [M+H]+; HPLC purity: 99% (t_r = 12.94 min).

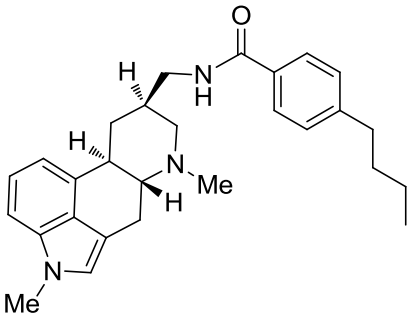
Compouns 20: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-ethylbenzamide



Light brown powder; Yield: 37%; Mp 192-194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (2H, d, *J* = 8.1 Hz), 7.21 (2H, d, *J* = 7.6 Hz), 7.17–7.10 (1H, m), 7.07 (1H, d, *J* = 8.1 Hz), 6.83 (1H, d, *J* = 7.0 Hz), 6.69 (1H, s), 6.61 (1H, bs), 3.70-3.59 (5H, m,), 3.54–3.29 (4H, m), 3.24 (1H, d, *J* = 10.9 Hz), 3.19–3.08 (1H, m), 2.90–2.77 (1H, m), 2.73–2.59 (3H, m), 2.54 (3H, s), 2.44–2.25 (2H, m), 2.20-2.15 (1H, m,), 1.21 (1H, q, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.83, 148.17, 134.43, 132.19, 131.86, 128.07 (2C), 127.50 (2C), 126.29, 122.81,

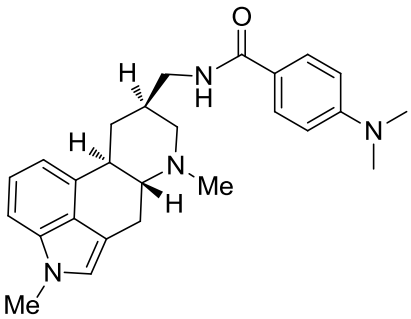
122.73, 112.73, 109.63, 107.10, 67.45, 61.06, 43.40, 42.59, 39.79, 36.07, 32.78, 31.80, 28.76, 26.25, 15.28; ESI-MS (m/z): 402 [M+H]+; HPLC purity: 98% (t_r = 13.39 min).

Compound 21: 4-butyl-N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)benzamide



Dark brown powder; Yield: 38%; Mp 171-173 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (2H, d, *J* = 8.0 Hz), 7.21 (2H, d, *J* = 7.8 Hz), 7.18–7.11 (1H, m), 7.07 (1H, d, *J* = 7.9 Hz), 6.86 (1H, d, *J* = 6.9 Hz), 6.69 (1H, s), 6.39–6.31 (1H, bs), 3.71 (3H, s), 3.52–3.40 (2H, m), 3.40–3.31 (1H, m), 3.18 (1H, dd, *J* = 10.6, 1.7 Hz), 3.11–3.00 (1H, m), 2.80–2.65 (2H, m), 2.65–2.59 (2H, m), 2.48 (3H, s), 2.24 (1H, td, *J* = 11.2, 4.6 Hz), 2.08 (1H, t, *J* = 11.4 Hz), 1.58-1.49 (2H, m), 1.36-1.29 (2H, m), 1.25-1.20 (2H, m), 0.90 (3H, t, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.74, 146.82, 134.45, 132.84, 132.01, 128.63, 126.98, 126.45, 122.77, 122.60 112.63, 110.29, 106.94 67.42, 61.30, 43.65, 42.96, 40.29, 36.43, 35.63, 35.52, 33.34, 32.06, 26.64, 22.29, 13.88; ESI-MS (m/z): 430 [M+H]+; HPLC purity: 99% (t_r = 14.69 min).

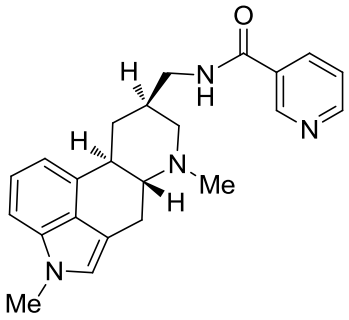
Compound 22: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)-4-(dimethylamino)benzamide



Off-white powder; Yield: 78%; Mp 258-260 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (2H, d, *J* = 8.7 Hz), 7.18–7.11 (1H, m), 7.07 (1H, d, *J* = 8.2 Hz), 6.86 (1H, d, *J* = 6.9 Hz), 6.68 (1H, s), 6.65 (2H, d, *J* = 8.6 Hz), 6.06 (1H, bs), 3.71 (3H, s), 3.47–3.40 (3H, m), 3.34 (1H, dd, *J* = 14.7, 4.4 Hz), 3.07 (1H, d, *J* = 10.6 Hz), 2.98 (6H, s), 2.73–2.61 (2H, m), 2.43 (3H, s), 2.25–2.17 (1H, m), 2.18–2.10 (1H, m), 2.07–1.98 (1H, m), 1.24–1.13 (1H, m); ^{13}C NMR (100

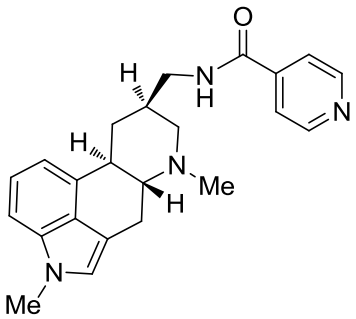
MHz, $CDCl_3$): δ 167.59, 152.52, 134.45, 133.29, 128.35 (2C), 126.53, 122.73, 122.49, 121.51 112.60, 111.18 (2C), 110.69, 106.79 67.45, 61.60, 43.57, 43.28, 40.58, 40.12, 36.97, 32.74, 32.22, 26.95, 15.26; ESI-MS (m/z): 417 [M+H]+; HPLC purity: 99% (t_r = 12.54 min).

Compound 23: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)nicotinamide[1]



Light-yellow powder; Yield: 45%; Mp 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (2H, d, *J* = 4.5 Hz), 7.68 (2H, dd, *J* = 4.5, 1.5 Hz), 7.24-7.20 (1H, m), 7.15 (1H, d, *J* = 8.2 Hz), 6.92 (1H, d, *J* = 7.0 Hz), 6.77 (1H, d, *J* = 1.4 Hz), 6.61 (1H, bs), 3.79 (3H, s), 3.56–3.51 (2H, m), 3.43 (1H, dd, *J* = 14.7, 4.4 Hz), 3.21 (1H, d, *J* = 9.8 Hz), 3.15-3.10 (1H, m), 2.85-2.75 (2H, m), 2.57 (3H, s), 2.51-2.47 (1H, m), 2.43-2.37 (1H, m), 2.36–2.30 (1H, m), 2.19 (1H, t, *J* = 11.4 Hz), 1.30 (1H, q, *J* = 12.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.85, 150.67, 141.59, 134.46, 132.49, 126.39, 122.78, 122.70, 120.90, 112.57, 110.04, 107.07, 67.48, 61.31, 43.80, 43.02, 40.21, 36.40, 32.78, 32.01, 26.66; ESI-MS (m/z): 375 [M+H]+; HPLC purity: 98% (t_r = 10.67 min).

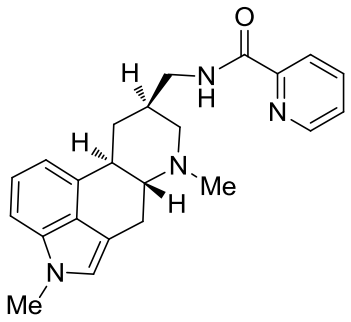
Compound 24: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)isonicotinamide[1]



Off-white powder; Yield: 23%; Mp 218-220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.09 (1H, s), 8.75 (1H, d, *J* = 3.5 Hz), 8.19 (1H, dt, *J* = 7.9, 1.9 Hz), 7.41 (1H, dd, *J* = 7.8, 4.9 Hz), 7.24–7.18 (1H, m), 7.15 (1H, d, *J* = 8.2 Hz), 6.92 (1H, d, *J* = 7.1 Hz), 6.80 (1H, bs), 6.77 (1H, d, *J* = 1.2 Hz), 3.78 (3H, s), 3.62–3.48 (2H, m), 3.43 (1H, dd, *J* = 14.6, 4.3 Hz), 3.27 (1H, d, *J* = 11.4 Hz), 3.16 (1H, m), 2.90–2.74 (2H, m), 2.60 (3H, s), 2.49-2.33 (2H, m), 2.24 (1H, t, *J* =

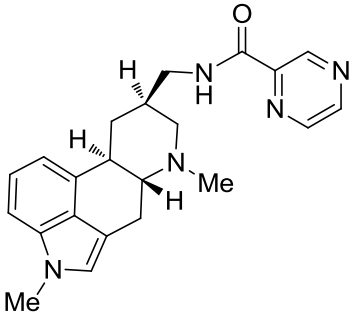
11.5 Hz), 1.31 (1H, q, *J* = 12.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.92, 152.24, 148.01, 135.18, 134.45, 132.36, 130.25, 126.35, 123.53, 122.81, 122.70, 112.65, 109.88, 107.08, 67.51, 61.27, 43.66, 42.88, 40.06, 36.30, 32.78, 31.96, 26.52; ESI-MS (m/z): 375 [M+H]+; HPLC purity: 98% (t_r = 10.70 min).

Compound 25: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)picolinamide[1]



Pale-yellow powder; Yield: 50%; Mp 168-170 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (1H, m), 8.26–8.24 (2H, m), 7.89 (1H, td, *J* = 7.7, 1.7 Hz), 7.46-7.39 (1H, m), 7.23-7.20 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.95 (1H, d, *J* = 7.4 Hz), 6.76 (1H, d, *J* = 1.4 Hz), 3.78 (3H, s), 3.55 (2H, t, *J* = 6.5 Hz), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.19 (1H, d, *J* = 9.8 Hz), 3.09 (1H, t, *J* = 8.8 Hz), 2.81-2.74 (2H, m), 2.54 (3H, s), 2.42-2.30 (1H, s), 2.29-2.23 (1H, m), 2.15 (1H, t, *J* = 11.3 Hz), 1.32 (2H, q, *J* = 12.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.51, 149.92, 148.10, 137.35, 134.45, 133.08, 126.49, 126.14, 122.75, 122.55, 122.28, 112.65, 110.50, 106.86, 67.44, 61.44, 43.18, 40.40, 36.59, 32.75, 32.10, 26.82; ESI-MS (m/z): 375 [M+H]+; HPLC purity: 98% (t_r = 11.51 min); $[\alpha]_D^{20}$ -0.053^{o} (*c* 0.1, $CHCl_3$).

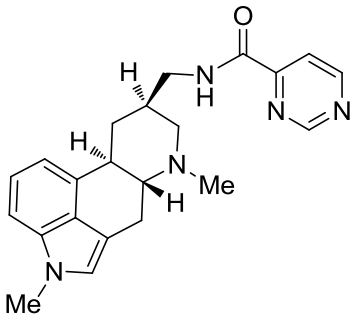
Compound 26: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)pyrazine-2-carboxamide



Off-white powder; Yield: 51%; Mp 202-204 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (1H, d, *J* = 1.4 Hz), 8.79 (1H, d, *J* = 2.4 Hz), 8.57 (1H, dd, *J* = 2.4, 1.5 Hz), 7.99 (1H, bs), 7.23-7.20 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.94 (1H, d, *J* = 7.1 Hz), 6.76 (1H, d, *J* = 1.2 Hz), 3.78 (3H, s), 3.58–3.55 (2H, m), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.17 (1H, d, *J* = 10.3 Hz), 3.10

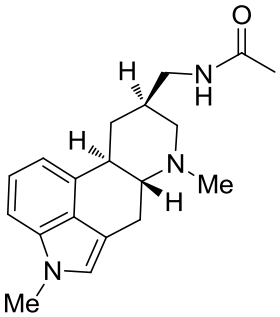
(1H, t, *J* = 8.9 Hz), 2.81-2.75 (2H, m), 2.54 (3H, s), 2.42-2.31 (1H, m), 2.29-2.25 (1H, m), 2.16 (1H, t, *J* = 11.3 Hz), 1.31 (1H, q, *J* = 12.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.19, 147.32, 144.53, 144.43, 142.52, 134.46, 132.90, 126.47, 122.74, 122.60, 112.58, 110.39, 106.94, 67.44, 61.35, 43.16, 40.36, 36.55, 32.76, 32.05, 26.80; ESI-MS (m/z): 376 [M+H]+; HPLC purity: 97% (t_r = 10.67 min); $[\alpha]_D^{20}$ -0.051^o (*c* 0.1, $CHCl_3$).

Compound 27: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)pyrimidine-4-carboxamide



Pale-yellow powder; Yield: 35%; Mp 168-170 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (1H, d, *J* = 1.3 Hz), 9.01 (1H, d, *J* = 5.0 Hz), 8.20 (1H, bs), 8.17 (1H, dd, *J* = 5.0, 1.4 Hz), 7.23–7.20 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.93 (1H, d, *J* = 7.0 Hz), 6.76 (1H, s), 3.78 (3H, s), 3.55 (2H, t, *J* = 6.5 Hz), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.17 (1H, d, *J* = 10.9 Hz), 3.09 (1H, t, *J* = 8.7 Hz), 2.81-2.74 (2H, m), 2.54 (3H, s), 2.43-2.31 (1H, m), 2.31–2.22 (1H, m), 2.15 (1H, t, *J* = 11.4 Hz), 1.31 (1H, q, *J* = 12.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.83, 159.29, 157.81, 156.19, 134.45, 132.90, 126.47, 122.74, 122.60, 118.59, 112.57, 110.41, 106.94, 67.42, 61.34, 43.35, 43.16, 40.36, 36.47, 32.76, 32.06, 26.81; ESI-MS (m/z): 376 [M+H]+; HPLC purity: 98% (t_r = 10.83 min).

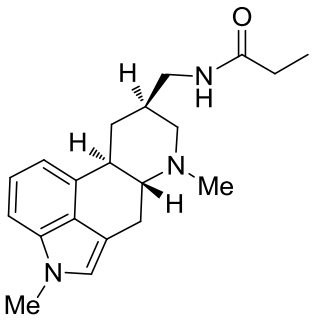
Compound 28: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)acetamide[1]



Off-white powder; Yield: 43%; Mp 191-193 ^{o}C; ^{1}H NMR (400 MHz, MeOD): δ 7.25-7.21 (1H, m), 7.14 (1H, d, *J* = 4.6 Hz), 6.89–6.87 (1H, m), 6.83 (1H, d, *J* = 1.4 Hz),), 3.75 (3H, s), 3.43 (1H, dd, *J* = 14.5, 4.4 Hz), 3.25–3.13 (3H, m), 2.98-2.92 (1H, m), 2.72–2.66 (2H, m),

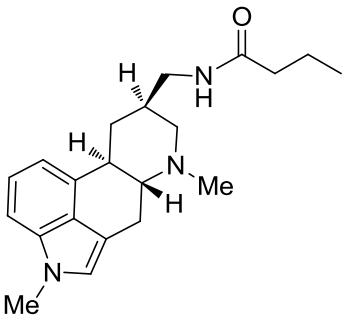
2.58 (3H, s), 2.33-2.27 (1H, m), 2.18–2.11 (2H, m), 2.02 (3H, s), 1.78–1.68 (2H, m), 1.14 (1H, q, *J* = 12.2 Hz); ^{13}C NMR (100 MHz, MeOD): δ 172.12, 134.61, 131.71, 126.21, 122.60, 122.28, 112.17, 109.05, 106.68, 67.39, 60.54, 42.65, 41.61, 39.67, 35.54, 31.47, 31.40, 25.76, 21.18.; ESI-MS (m/z): 312 [M+H]+; HPLC purity: 96% (t_r = 12.98 min).

Compound 29: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)propionamide[1]



Off-white powder; Yield: 67%; Mp 185-187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.91 (1H, d, *J* = 8.0 Hz), 6.76 (1H, d, *J* = 1.4 Hz), 5.70 (1H, bs), 3.78 (3H, s), 3.42 (1H, dd, *J* = 14.6, 4.3 Hz), 3.38–3.26 (2H, m), 3.16–3.06 (2H, m), 2.85-2.78 (1H, m), 2.70 (1H, d, *J* = 12.9 Hz), 2.56 (3H, s), 2.33–2.20 (4H, m), 2.12 (1H, t, *J* = 11.4 Hz), 1.27–1.16 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.98, 134.44, 132.70, 126.41, 122.77, 122.63, 112.60, 110.14, 106.98, 77.35, 77.03, 76.71, 67.48, 61.32, 43.07, 43.01, 40.17, 36.45, 32.76, 31.92, 29.81, 26.64, 9.98; ESI-MS (m/z): 326 [M+H]+; HPLC purity: 99% (t_r = 10.34 min).

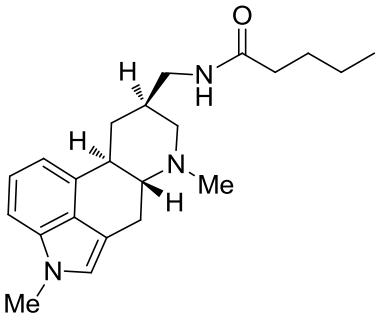
Compound 30: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)butyramide



Off-white powder; Yield: 71%; Mp 169-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.91 (1H, d, *J* = 7.0 Hz), 6.76 (1H, d, *J* = 1.4 Hz), 5.62 (1H, bs), 3.78 (3H, s), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.39–3.28 (2H, m), 3.15–3.05 (2H, m), 2.85–2.77 (1H, m), 2.70 (1H, dd, *J* = 12.8, 2.0 Hz), 2.56 (3H, s), 2.32–2.20 (4H, m), 2.11 (1H, t, *J* = 11.3 Hz), 1.78–1.68 (2H, m), 1.22 (1H, q, *J* = 12.2 Hz), 1.01 (3H, t, *J* = 7.4 Hz);

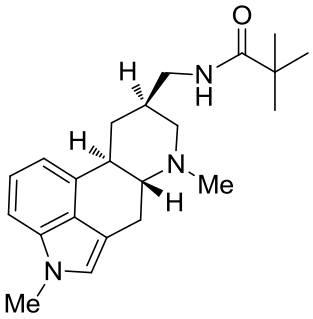
^{13}C NMR (100 MHz, $CDCl_3$): 173.13, 134.44, 132.78, 126.42, 122.76, 122.61, 112.58, 110.23, 106.95, 67.47, 61.35, 43.05, 40.22, 38.83, 36.50, 32.76, 31.95, 26.68, 19.25, 13.82; ESI-MS (m/z): 340 [M+H]+; HPLC purity: 97% (t_r = 11.16 min).

Compound 31: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)pentanamide



Off-white powder; Yield: 91%; Mp 166-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.92 (1H, d, *J* = 7.0 Hz), 6.76 (1H, s), 5.57 (1H, bs), 3.78 (3H, s), 3.41 (1H, dd, *J* = 14.6, 4.2 Hz), 3.32 (2H, t, *J* = 6.3 Hz), 3.09-2.98 (2H, m), 2.77-2.67 (2H, m), 2.52 (3H, s), 2.27-2.10 (4H, m), 2.04 (1H, t, *J* = 11.2 Hz), 1.72-1.64 (2H, m), 1.46-1.37 (2H, m), 1.20 (1H, q, *J* = 12.3 Hz), 0.97 (3H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.21, 134.45, 133.14, 126.50, 122.73, 122.55, 112.53, 110.58, 106.86, 67.43, 61.51, 43.27, 43.17, 40.49, 36.75, 36.67, 32.75, 32.08, 27.95, 26.92, 22.46, 13.80; ESI-MS (m/z): 354 [M+H]+; HPLC purity: 97% (t_r = 12.05 min).

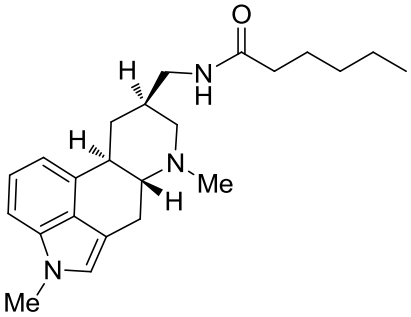
Compound 32: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)pivalamide



Yellow powder; Yield: 50%; Mp 102-104 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.91 (1H, d, *J* = 7.2 Hz), 6.76 (1H, d, *J* = 1.4 Hz), 5.80 (1H, bs), 3.78 (3H, s), 3.42 (H, dd, *J* = 14.7, 4.3 Hz), 3.32 (2H, t, *J* = 6.3 Hz), 3.11-3.03 (1H, m), 2.82–2.73 (1H, m), 2.68 (2H, dd, *J* = 12.8, 1.9 Hz), 2.54 (3H, s), 2.29-2.15 (2H, m), 2.08 (1H, t, *J* = 11.3 Hz), 1.26-1.21 (9H, m), 1.25–1.18 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.57, 134.45, 132.93, 126.45, 122.75, 122.58, 112.55, 110.36, 106.92, 67.44, 61.41, 43.13,

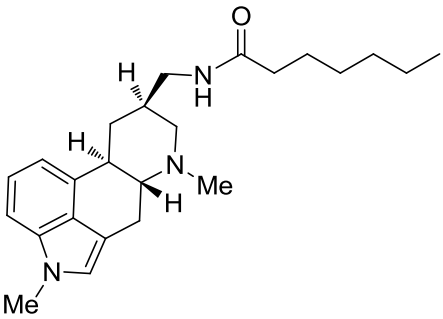
40.34, 38.83, 36.67, 32.75, 31.98, 27.70, 27.47, 26.76; ESI-MS (m/z): 354 [M+H]+; HPLC purity: >98% (t_r = 12.19 min).

Compound 33: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)hexanamide



White powder; Yield: 52%; Mp 133-135 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.19 (1H, m), 7.17 (1H, d, *J* = 8.2 Hz), 6.89 (1H, d, *J* = 6.9 Hz), 6.80 (1H, s), 6.24 (1H, bs), 3.79 (3H, s), 3.71-3.65 (1H, m), 3.56–3.33 (4H, m), 3.32-3.26 (1H, m), 2.95-2.87 (1H, m), 2.90 (3H, s), 2.76 (2H, d, *J* = 11.9 Hz), 2.65 (1H, t, *J* = 11.9 Hz), 2.29–2.23 (2H, m), 1.71–1.64 (2H, m), 1.39–1.29 (5H, m), 0.93 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.06, 134.41, 130.01, 125.84, 123.16, 122.98, 112.97, 107.70, 107.48, 67.84, 60.25, 42.14, 41.61, 38.24, 36.62, 34.80, 32.88, 31.52, 30.95, 25.39, 24.97, 22.41, 13.94.; ESI-MS (m/z): 368 [M+H]+; HPLC purity: 99% (t_r = 13.07 min).

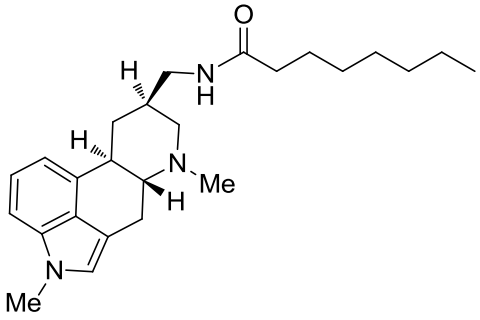
Compound 34: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)heptanamide



White powder; Yield: 49%; Mp 146-148 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.91 (1H, d, *J* = 7.1 Hz), 6.76 (1H, d, *J* = 1.3 Hz), 5.70 (1H, bs), 3.78 (3H, s), 3.42 (1H, dd, *J* = 14.6, 4.4 Hz), 3.38–3.27 (2H, m), 3.13-3.09 (2H, m), 2.89–2.80 (1H, m), 2.70 (1H, d, *J* = 12.9 Hz), 2.58 (3H, s), 2.37–2.29 (1H, m), 2.27–2.21 (3H, m), 2.14 (1H, t, *J* = 11.4 Hz), 1.72-1.65 (2H, m), 1.41–1.29 (6H, m), 1.22 (1H, q, *J* = 12.3 Hz), 0.92 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.39, 134.44, 132.56, 126.38, 122.77, 122.65, 112.62, 110.01, 107.01, 67.49, 61.25, 42.98, 42.91, 40.06, 36.91, 36.34,

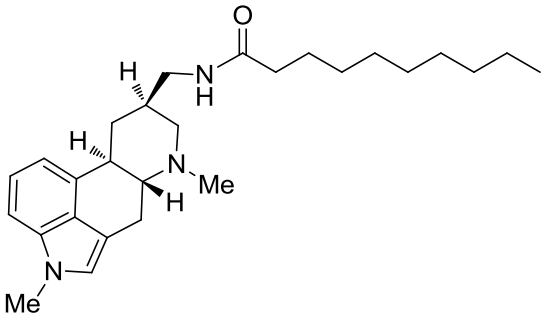
32.77, 31.87, 31.57, 29.03, 26.54, 25.81, 22.53, 14.03; ESI-MS (m/z): 382 [M+H]+; HPLC purity: 99% (t_r = 13.74 min).

Compound 35: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)octanamide



Off-white powder; Yield: 53%; Mp 141-143 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.91 (1H, d, *J* = 7.1 Hz), 6.75 (1H, d, *J* = 1.3 Hz), 5.63 (1H, bs), 3.78 (3H, s), 3.41 (1H, dd, *J* = 14.7, 4.3 Hz), 3.31 (2H, t, *J* = 6.3 Hz), 3.11–2.97 (2H, m), 2.79–2.65 (2H, m), 2.51 (3H, s), 2.26-2.22 (2H, m), 2.21–2.10 (2H, m), 2.04 (1H, t, *J* = 11.3 Hz), 1.74–1.64 (2H, m), 1.39–1.28 (8H, m), 1.20 (1H, q, *J* = 12.3 Hz), 0.91 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.26, 134.45, 133.11, 126.50, 122.73, 122.55, 112.55, 110.54, 106.86, 67.42, 61.48, 43.23, 43.16, 40.45, 36.96, 36.68, 32.74, 32.07, 31.73, 29.34, 29.06, 26.88, 25.89, 22.62, 14.05; ESI-MS (m/z): 396 [M+H]+; HPLC purity: 99% (t_r = 14.56 min); $[\alpha]_D^{20}$ -0.053^{o} (*c* 0.1, $CHCl_3$).

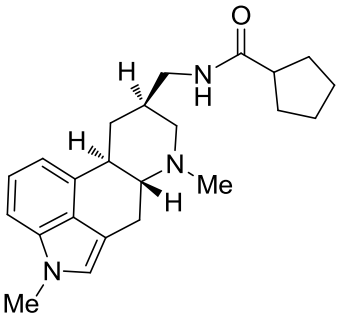
Compound 36: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)decanamide



Light-yellow powder; Yield: 64%; Mp 138-140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.92 (1H, d, *J* = 6.8 Hz), 6.76 (1H, s), 5.60 (1H, bs), 3.79 (3H, s), 3.42 (1H, dd, *J* = 14.5, 4.0 Hz), 3.37-3.29 (2H, m), 3.13-3.05 (2H, m), 2.83–2.76 (1H, m), 2.70 (1H, d, *J* = 13.4 Hz), 2.55 (3H, s), 2.30–2.19 (4H, m), 2.10 (1H, t, *J* = 11.2 Hz), 1.72-1.65 (2H, m), 1.42–1.17 (13H, m), 0.91 (3H, t, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.30, 134.45, 132.85, 126.44, 122.76, 122.60, 112.58, 110.29, 106.94, 67.47,

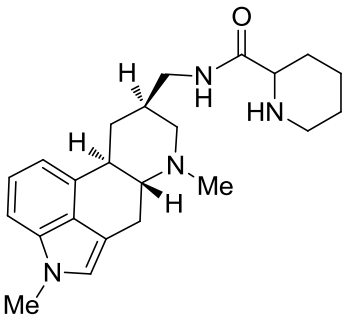
61.38, 43.08, 40.28, 36.96, 36.55, 32.76, 31.97, 31.87, 29.48, 29.39, 29.29, 26.73, 25.87, 22.66, 14.08; ESI-MS (m/z): 424 [M+H]+; HPLC purity: 99% (t_r = 15.80 min); $[\alpha]_D^{20}$ -0.049° (*c* 0.1, $CHCl_3$).

Compound 37: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)cyclopentanecarboxamide



Light-yellow powder; Yield: 63%; Mp 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 6.91 (1H, d, *J* = 7.1 Hz), 6.76 (1H, d, *J* = 1.4 Hz), 5.60 (1H, bs), 3.78 (3H, s), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.32 (2H, t, *J* = 6.3 Hz), 3.12–3.03 (2H, m), 2.81–2.75 (1H, m), 2.69 (1H, dd, *J* = 12.9, 2.0 Hz), 2.62–2.51 (1H, m), 2.54 (3H, s), 2.28–2.15 (2H, m), 2.08 (1H, t, *J* = 11.3 Hz), 1.97–1.73 (6H, m), 1.68–1.56 (2H, m), 1.22 (1H, q, *J* = 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.35, 134.44, 132.95, 126.46, 122.75, 122.58, 112.56, 110.37, 106.91, 67.46, 61.43, 46.05, 43.15, 43.10, 40.33, 36.67, 32.76, 31.99, 30.58, 30.53, 26.77, 25.93.; ESI-MS (m/z): 366 [M+H]+; HPLC purity: 97% (t_r = 12.28 min); $[\alpha]_D^{20}$ -0.055° (*c* 0.1, $CHCl_3$).

Compound 38: N-(((6aR,9S,10aR)-4,7-dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-fg]quinolin-9-yl)methyl)piperidine-2-carboxamide



Yellow powder; Yield: 41%; Mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.23–7.19 (1H, m), 7.14 (1H, d, *J* = 8.2 Hz), 7.11 (1H, bs), 6.92 (1H, d, *J* = 7.0 Hz), 6.75 (1H, s), 3.78 (3H, s), 3.42 (1H, dd, *J* = 14.7, 4.3 Hz), 3.38–3.23 (3H, m), 3.15–3.07 (2H, m), 3.04 (1H, t, *J* = 9.9 Hz), 2.79-2.61 (4H, m), 2.54 (3H, s), 2.28–2.15 (2H, m), 2.10-2.04 (2H, m), 1.85 (1H, s), 1.63 (1H, s), 1.56-1.41 (3H, m), 1.21 (1H, q, *J* = 12.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ

173.96, 134.44, 132.93, 126.45, 122.76, 122.58, 112.60, 110.38, 106.92, 67.44, 61.44, 60.36, 45.84, 43.17, 42.61, 40.40, 36.57, 32.76, 31.97, 30.06, 26.79, 25.84, 24.99; ESI-MS (m/z): 381 [M+H]+; HPLC purity: 98% (t_r = 8.45 min); $[\alpha]_D^{20}$ -0.051^o (*c* 0.1, $CHCl_3$).

In vitro Assays

Antiplasmodial assay

Title compounds were screened for *in vitro* antiplasmodial activity against a chloroquine sensitive (CQS) strain of *Plasmodium falciparum* (NF54). Continuous *in vitro* cultures of asexual erythrocyte stages of *P. falciparum* were maintained using a modified method of Trager and Jensen (1976)[2]. Quantitative assessment of antiplasmodial activity *in vitro* was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler (1993)[3]. The compounds were tested in triplicate on one occasion.

The test samples were prepared to a 20 mg/ml stock solution in 100% DMSO. Stock solutions were stored at -20ºC. Further dilutions were prepared in complete medium on the day of the experiment. Samples were tested as a suspension if not completely dissolved. Chloroquine (CQ) and artesunate were used as the reference drugs. Samples were initially screened at 1000 ng/ml. A full dose-response was performed to determine the concentration inhibiting 50% of parasite growth (IC50–value). Test samples were tested at a starting concentration of 100 µg/ml, which was then serially diluted 2-fold in complete medium to give 10 concentrations; with the lowest concentration being 0.2 µg/ml. The same dilution technique was used for all samples. References were tested at a starting concentration of 1000 ng/ml. The highest concentration of solvent to which the parasites were exposed to had no measurable effect on the parasite viability (data not shown).

Cytotoxicity assay

Title compounds were screened for *in vitro* cytotoxicity against a mammalian cell-line, Chinese Hamster Ovarian (CHO) using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT)-assay. The MTT-assay is used as a colorimetric assay for cellular growth and survival, and compares well with other available assays[4,5]. The tetrazolium salt MTT was used to measure all growth and chemosensitivity. Compounds were tested in triplicate on one occasion.

The same stock solutions prepared for antiplasmodial testing was used for cytotoxicity testing. Test compounds were stored at -20ºC until use. Dilutions were prepared on the day of the experiment. Emetine was used as the reference drug in all experiments. The initial concentration of emetine was 100 µg/ml, which was serially diluted in complete medium with 10-fold dilutions to give 6 concentrations, the lowest being 0.001 µg/ml. The

same dilution technique was applied to the all test samples. The highest concentration of solvent to which the cells were exposed to had no measurable effect on the cell viability (data not shown). The 50% inhibitory concentration (IC50) values were obtained from full dose-response curves, using a non-linear dose-response curve fitting analysis via GraphPad Prism v.4 software.

References:

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