SUPPLEMENTARY MATERIAL TO
Synthesis, cytotoxicity and computational study of novel protoberberine derivatives
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SPECTRAL DATA FOR SYNTHESISED COMPOUNDS
N-(2-Bromoallyl)pyridinium bromide (4). Compound 4 was synthesised from pyridine and 2,3-dibromopropene as a light brown amorphous solid (720 mg, 85 %). Its melting point was not determined due to the hygroscopic properties of the compound.
N-(2-Iodoallyl)isoquinolinium bromide (14a). Compound 14a was synthesised from isoquinoline and 3-bromo-2-iodoprop-1-ene as a light brown amorphous solid (1.13 g, 92 %). Its melting point was not determined due to the hygroscopic properties of the compound.
2-Iodoallyl-6,7-dimethoxy-2-isoquinolinium bromide (14b). Compound 14b was synthesised from 6,7-dimethoxyisoquinoline and 3-bromo-2-iodoprop-1-ene as a white amorphous solid, m.p. > 270 °C (1.10 g, 96 %).
4,9-Dihydro-2-(2-iodoallyl)-3H-pyrido[3,4-b]indolium bromide (22). Compound 22 was synthesised from 3,4-dihydro-β-carboline and 3-bromo-2-iodoprop-1-ene as a dark orange amorphous solid, (1.04 g, 80 %). Melting point was not determined due to hygroscopic properties of the compound.

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The products 7 and 8 were isolated after flash chromatography (SiO₂, 95:5 V/V, petroleum ether–diethyl ether) as a pale yellow oil, in ratio 1:1 (46 %). IR (ATR, ν / cm⁻¹): 2888, 1636, 1112, 961, 844; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 5.94–5.91 (m, 1H, H-3”), 5.84–5.76 (m, 2H, H-4, H-2”), 5.61 (dd, 1H, J = 4.4 and 1.6 Hz, H-3), 5.57 (brs, 1H, H-3’), 5.10 (d, 1H, J = 6.8 Hz, H-3”), 5.01 (brs, 1H, H-3’), 3.53 (d, 1H, J = 15.6 Hz, H-1”), 3.19 (d, 1H, J = 15.6 Hz, H-1’), 3.10–3.00 (m, 1H, H-2), 2.99–2.90 (m, 1H), 2.57–2.42 (m, 1H), 2.39–2.19 (m, 2H), 2.11–2.01 (m, 2H, H-5); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 135.6, 131.9, 129.2, 125.4, 117.6, 116.4 (=CH₂), 62.3 (CH₂CBr); 58.4 C(2), 46.3 C(6), 37.9 (CH₃CH=CH₂), 24.0 (C-5); MS (EI) m/z: 241.0, 200.0, 120.1, 80.1; HRMS (ESI): calculated for C₁₁H₁₇BrN [M+H]⁺ 242.05389, found 242.05474.

4-Allyl-1-(2-bromoallyl) piperidine (8)

IR (ATR, ν / cm⁻¹): 2909, 1629, 1445, 980, 909, 892; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 5.84–5.82 (m, 1H), 5.81–5.67 (m, 1H), 5.56 (s, 1H), 5.05–4.99 (m, 1H), 4.95 (s, 1H), 3.16 (s, 2H), 2.93–2.86 (m, 2H), 2.03–1.92 (m, 4H), 1.69–1.65 (m, 3H), 1.33–1.24 (m, 2H); ¹³C-NMR (75 MHz, CDCl₃, δ / ppm): 137.0, 131.1, 118.2, 115.7, 66.8, 53.5, 40.9, 35.6, 31.9; MS (EI) m/z: 244.1, 202.0, 164.1, 138.1, 120.1; HRMS (ESI): calculated for C₁₁H₁₅BrN [M+H]⁺ 244.06954, found 244.06931.
2,3,4,6,7,9a-Hexahydro-2,3-dimethylene-1H-quinolizine (9)

The product was isolated after flash chromatography (SiO₂, 9:1 V/V, petroleum ether–diethyl ether) as a pale yellow oil (30 mg, 26%). IR (ATR, ν / cm⁻¹): 2937, 2908, 2732, 1332, 1130, 891, 802; ¹H-NMR (500 MHz, CDCl₃ δ / ppm): 5.77–5.73 (m, 1H, H-9), 5.47 (dd, 1H, J = 10.0 and 1.5 Hz, H-8), 5.12 (t, 1H, J = 1.5 Hz, =CH₂), 5.08 (t, 1H, J = 2.0 Hz, =CH₂), 4.81 (t, 1H, J = 2.0 Hz, =CH₂), 4.75 (t, 1H, J = 2.5 Hz, =CH₂), 3.36 (d, 1H, J = 12.5 Hz, H-4), 2.91 (dt, 1H, J = 12.0 and 1.5 Hz, H-4), 2.88–2.85 (m, 1H, H-6), 2.67–2.64 (m, 1H, H-9a), 2.47–2.42 (m, 1H, H-7), 2.39 (dd, 1H, J = 10.5 and 3.5 Hz, H-6), 2.35 (dd, 1H, J = 13.5 and 3.5 Hz, H-1), 2.20–1.4 (m, 1H, H-1), 2.05–2.00 (m, 1H, H-7); ¹³C-NMR (125 MHz, CDCl₃ δ / ppm): 145.6 (C-2), 144.4 (C-3), 128.9 (C-8), 125.3 (C-9), 109.5 (C₁₋C=⁻C-3), 109.45 (C₂₋C=⁻C-2), 61.7 (C-4), 60.5 (C-9a), 51.1 (C-6), 40.2 (C-1), 26.0 (C-7); MS (EI) m/z: 160.1 [M-H]⁺, 146.1, 80.1, 67.1; HRMS (ESI): calculated for C₁₁H₁₆N [M+H]⁺ 162.12773, found 162.12773.

Dimethyl-4,6,7,10,11,11a-hexahydro-3H-pyrido[1,2-b]isoquinoline-8,9-dicarboxylate (10)

The product was isolated after flash chromatography (SiO₂, 9:1 V/V, diethyl ether–petroleum ether) as a creamy-white amorphous solid (38 mg, 72 %), m.p. 110–111 °C. IR (ATR, ν / cm⁻¹): 1712, 1273, 1071, 791, 757; ¹H-NMR (500 MHz, CDCl₃ δ / ppm): 5.78–5.75 (m, 1H, H-2), 5.51 (d, 1H, J = 10.0 Hz, H-1), 3.78 (s, 6H, COOCH₃), 3.10 (d, 1H, J = 20.0 Hz, H-11a), 2.95–2.82 (m, 7H, H-4, H-6, H-7, H-10), 2.43–2.40 (m, 2H, H-3, H-4), 2.05–2.03 (m, 2H, H-3, H-11), 1.94–1.90 (m, 1H, H-11); ¹³C-NMR (125 MHz, CDCl₃ δ / ppm): 168.3 (C=O), 168.1 (C=O), 132.8 (C-7), 131.8 (C-8), 128.7 (C-1), 124.9 (C-2), 123.2 (C-6a), 122.9 (C-10a), 57.5 (C-11a), 56.9 (C-6), 52.2 (COOCH₃), 50.6 (C-4), 36.1 (C-11), 32.2 (C-10), 30.3 (C-7), 25.9 (C-3); MS (ESI) m/z: 304.0, 272.0, 243.1,
134.1, 115.2; HRMS (ESI) calculated for C$_{17}$H$_{22}$NO$_4$ [M+H]$^+$ 304.15433, found 304.15410.

**Dimethyl 3,6,11,11a-tetrahydro-4H-pyrido[1,2-b]isoquinoline-8,9-dicarboxylate (11)**

The product was isolated after flash chromatography (SiO$_2$, 9:1 V/V, diethyl ether–petroleum ether) as a yellow oil (10 mg, 80%), which solidified upon standing, m.p. 75–78 °C. IR (ATR, ν / cm$^{-1}$): 1716, 1435, 1268, 1121, 776; $^1$H-NMR (500 MHz, CDCl$_3$ δ / ppm): 7.46 (s, 1H, H-10), 7.43 (s, 1H, H-7), 5.86–5.83 (m, 1H, H-2), 5.89 (d, 1H, J = 10.0 Hz, H-1), 3.98 (d, 1H, J = 15.5 Hz, H-6), 3.89 (s, 3H, COOCH$_3$), 3.88 (s, 3H, COOCH$_3$), 3.56 (d, 1H, J = 15.5 Hz, H-6), 3.04–3.01 (m, 1H, H-4), 2.99–2.96 (m, 1H, H-11a), 2.85 (d, 1H, J = 7.0 and 4.0 Hz, H-11), 2.78–2.72 (m, 1H, H-11), 2.52–2.47 (m, 2H, H-3, H-4), 2.10–2.06 (m, 1H, H-3); $^{13}$C-NMR (125 MHz, CDCl$_3$ δ / ppm): 168.1 (C=O), 167.9 (C=O), 138.5, 138.2, 129.9, 129.2, 129.2 (C-10), 128.3 (C-1), 127.0 (C-7), 125.5 (C-2), 57.6 (C-6), 57.0 (C-11a), 52.5 (2×CH$_3$), 50.8 (C-4), 35.7 (C-11), 25.8 (C-3) ppm; MS (ESI) m/z: 302.1, 271.1, 201.1, 155.1, 142.1; HRMS (ESI): calculated for C$_{17}$H$_{20}$NO$_4$ [M+H]$^+$ 302.13868, found 302.13883.

**Dimethyl 6-oxo-6H-pyrido[1,2-b]isoquinoline-8,9-dicarboxylate (12)**

The product was isolated after flash chromatography (SiO$_2$, 6:4 V/V, dichloromethane–diethyl ether) as orange needles (12 mg, 53%), m.p. 171–174 °C. IR (ATR, ν / cm$^{-1}$): 1715, 1668, 1634, 1616, 1119, 737; $^1$H-NMR (500 MHz, CDCl$_3$ δ / ppm): 9.11 (s, 1H, H-7), 8.88 (d, 1H, J = 7.6 Hz, H-4), 7.83 (s, 1H, H-10), 7.35 (d, 1H, J = 9.0 Hz, H-1), 7.14 (dd, 1H, J = 9.0 and 6.5 Hz, H-2), 6.85 (s, 1H, H-11), 6.75 (t, 1H, J = 6.5 Hz, H-3), 3.98 (s, 3H, COOCH$_3$), 3.96 (s, 3H, COOCH$_3$); $^{13}$C-NMR (125 MHz, CDCl$_3$ δ / ppm): 168.8 (C=O$_{ester}$), 166.4 (C=O$_{ester}$), 158.7 (C=O$_{lactam}$), 139.8 (10a), 137.9 (C-11a), 136.3 (C-9), 131.7 (C-8), 128.4 (C-2), 126.7 (C-4), 126.2 (C-10), 125.7 (C-1), 125.1 (C-8), 119.2 (C-6a), 119.1 (C-13) ppm.
113.1 (C-3), 100.3 (C-11), 52.9 (COOCH\textsubscript{3}), 52.6 (COOCH\textsubscript{3}); MS (ESI) \textit{m/z}: 312.1 ([M+H]\textsuperscript{+}), 280.1, 253.1, 222.1, 194.1, 166.1, 140.1; HRMS (ESI): calculated for C\textsubscript{17}H\textsubscript{14}NO\textsubscript{5} [M+H]\textsuperscript{+} 312.08665, found 312.08524.

1-Allyl-1,2,3,4-tetrahydro-2-(2-iodoallyl)isoquinoline (16a)

The product was isolated after flash chromatography (SiO\textsubscript{2}, 98:2 V/V, petroleum ether–diethyl ether) as a pale yellow oil (610 mg, 70\%).

IR (ATR, \textit{\nu} / cm\textsuperscript{-1}): 2907, 2803, 1637, 1615, 1498, 1427, 1123, 903, 742; \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3} \textit{\delta} / ppm): 7.26–7.03 (m, 4H, ArH), 6.36 (\textit{dd}, 1H, \textit{J} = 1.5 and 1.0 Hz, H-3"), 6.03–5.95 (m, 1H, H-2'), 5.86 (\textit{d}, 1H, \textit{J} = 1.0 Hz, H-3''), 5.04–4.99 (m, 2H, H-3", H-3'), 3.71 (\textit{dd}, 1H, \textit{J} = 7.5 and 5.5 Hz, H-1), 3.31 (\textit{d}, 2H, \textit{J} = 4.5 Hz, H-1'), 3.25–3.19 (m, 1H, H-3), 2.87–2.82 (m, 1H, H-4), 2.79–2.75 (m, 1H, H-3), 2.64 (\textit{dt}, 1H, \textit{J} = 16.5 and 4.5 Hz, H-4), 2.59–2.53 (m, 1H, H-1'), 2.47–2.42 (m, 1H, H-1'); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3} \textit{\delta} / ppm): 137.9, 136.7, 134.5, 128.9, 127.7, 126.3, 126.0, 115.9 (CH=C=CH\textsubscript{2}), 111.6 (IC=), 65.4 (CH\textsubscript{2}Cl=CH\textsubscript{2}), 61.1 (C-1), 43.3 (C-3), 40.7 (CH\textsubscript{2}CH=CH\textsubscript{2}), 25.2 (C-4); MS (EI) \textit{m/z}: 338.0, 298.0, 170.1, 130.1; HRMS (ESI): calculated for C\textsubscript{15}H\textsubscript{19}IN [M+H]\textsuperscript{+} 340.05567, found 340.05547.

1-Allyl-1,2,3,4-tetrahydro-2-(2-iodoallyl)-6,7-dimethoxyisoquinoline (16b)

The product was isolated after flash chromatography (SiO\textsubscript{2}, 9:1 V/V, petroleum ether–ethyl acetate) as a pale yellow oil (500 mg, 60\%).

IR (ATR, \textit{\nu} / cm\textsuperscript{-1}): 2932, 1511, 1225, 1105, 900; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3} \textit{\delta} / ppm): 7.38 (\textit{s}, 1H, ArH), 6.67 (\textit{s}, 1H, ArH), 6.51–6.48 (\textit{m}, 2H, H-3', H-3''), 5.81–5.84 (\textit{m}, 1H, H-2"), 5.21–5.16 (\textit{m}, 2H, H-3', H-3''), 4.43 (\textit{s}, 1H, H-1), 4.07–3.96 (\textit{m}, 2H), 3.87 (\textit{s}, 6H, OCH\textsubscript{3}), 3.90–3.80 (\textit{m}, 1H), 3.57–3.49 (\textit{m}, 2H), 3.12 (\textit{s}, 2H), 2.66 (\textit{s}, 1H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3} \textit{\delta} / ppm): 149.4, 148.0, 139.6, 131.9, 121.1, 120.7, 120.6, 111.1, 111.0, 61.7, 60.9, 43.5, 39.6, 21.9; MS (EI) \textit{m/z}: 399.1, 359.0, 321.1, 273.1; HRMS (ESI): calculated for C\textsubscript{17}H\textsubscript{23}INO\textsubscript{2} [M+H]\textsuperscript{+} 400.07680, found 400.07774.
**1,3,4,6,7,11b-Hexahydro-2,3-dimethylene-2H-pyrido[2,1-a]isoquinoline (17a)**

The product was isolated after flash chromatography (SiO$_2$, 8:2 $V/V$, petroleum ether–diethyl ether) as a pale yellow amorphous solid (210 mg, 70 %), m.p. 80–81 °C. IR (ATR, $\nu$/cm$^{-1}$): 2926, 2735, 1617, 1492, 1450, 1136, 1137, 732; $^1$H-NMR (500 MHz, CDCl$_3$ $\delta$/ppm): 7.21–7.10 (m, 4H, ArH), 5.16–5.15 (m, 2H, =CH$_2$), 4.87 (t, 1H, $J = 2.0$ Hz, =CH$_2$), 4.84 (brs, 1H, =CH$_2$), 3.49 (d, 1H, $J = 13.0$ Hz, H-4), 3.44 (d, 1H, $J = 10.5$ Hz, H-11b), 3.19–3.13 (m, 2H, H-4, H-7), 3.06–3.02 (m, 1H, H-6), 2.92 (dd, 1H, $J = 14.0$ and 3.0 Hz, H-1), 2.77 (dt, 1H, $J = 6.0$ and 3.0 Hz, H-7), 2.57 (td, 1H, $J = 4.0$ and 11.0 Hz, H-6), 2.40–2.34 (m, 1H, H-1); $^{13}$C-NMR (125 MHz, CDCl$_3$ $\delta$/ppm): 145.5, 144.1, 137.5, 134.4, 128.9, 126.2, 125.8, 125.3, 109.7 (CH$_2$), 109.4 (CH$_2$=), 62.3 (C-11b), 62.1 (C-4), 50.7 (C-6), 40.0 (C-1), 29.6 (C-7); MS (EI) $m/z$: 211.1, 196.1, 182.1, 130.0, 115.0; HRMS (ESI): calculated for C$_{15}$H$_{18}$N $[M+H]^+$ 212.14338, found 212.14299.

**1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-2,3-dimethylene-2H-pyrido[2,1-a]isoquinoline (17b)**

The product was isolated after flash chromatography (SiO$_2$, 65:35 $V/V$, petroleum ether–ethyl acetate) as a pale yellow amorphous solid (370 mg, 61 %), m.p. 65–67 °C. IR (ATR, $\nu$/cm$^{-1}$): 1510, 1257, 1227, 1130, 1021; $^1$H-NMR (500 MHz, CDCl$_3$ $\delta$/ppm): 6.67 (s, 1H, H-11), 6.59 (s, 1H, H-8), 5.16–5.15 (m, 2H, =CH$_2$), 4.87 (t, 1H, $J = 2.0$ Hz, =CH$_2$), 4.84 (s, 1H, =CH$_2$), 3.87 (s, 3H, OCH$_3$), 3.85 (s, 3H, OCH$_3$), 3.48 (d, 1H, $J = 13.0$ Hz, H-4), 3.36 (d, 1H, $J = 10.5$ Hz, H-11b), 3.16–3.00 (m, 3H, H-4, H-7, H-6), 2.86 (dd, 1H, $J = 13.5$ and 3.0 Hz, H-1), 2.67 (dt, 1H, $J = 15.5$ and 3.5 Hz, H-7), 2.55 (td, 1H, $J = 10.5$ and 4.0 Hz, H-6), 2.39–2.35 (m, 1H, H-1); $^{13}$C-NMR (125 MHz, CDCl$_3$ $\delta$/ppm): 147.5, 147.2, 145.4, 144.1, 129.4, 126.6, 111.4 (C-8), 109.7 (C-2’), 109.4 (C-3’), 108.5 (C-11), 62.0 (C-11b), 61.9 (C-4), 56.0 (OCH$_3$), 55.8 (OCH$_3$), 50.8 (C-6), 40.1 (C-1), 29.2 (C-7); MS (EI) $m/z$: 270.1, 256.1, 240.1, 190.0; HRMS (ESI): calculated for C$_{17}$H$_{22}$NO$_2$ $[M+H]^+$ 272.16451, found 272.16501.
**Dimethyl 5,8,9,12,13,13a-hexahydro-6H-isoquino[2,1-b]isoquinoline-10,11-dicarboxylate (18a)**

The product was isolated after flash chromatography (SiO₂, 95:5 V/V, diethyl ether–petroleum ether) as a pale yellow amorphous solid (70 mg, 90 %), m.p. 121–124 °C. IR (ATR, ν / cm⁻¹): 2950, 1716, 1433, 1267, 1196, 1068, 736; ¹H-NMR (500 MHz, CDCl₃ δ / ppm): 7.17–7.10 (m, 4H, ArH), 3.79 (s, 3H, COOCH₃), 3.78 (s, 3H, COOCH₃), 3.58 (dd, 1H, J₁=10.5 and 3.0 Hz, H-13b), 3.22 (brd, 1H, J₂=16.0 Hz, H-5), 3.17–3.14 (m, 1H, H-10), 3.09 (dd, 1H, J=11.0 and 4.0 Hz, H-6), 3.01–2.91 (m, 5H, H-8, H-9, H-12), 2.73 (brd, 1H, J=16.0 Hz, H-5), 2.59–2.49 (m, 2H, H-6, H-13), 2.22–2.16 (m, 1H, H-13); ¹³C-NMR (125 MHz, CDCl₃ δ / ppm): 168.3 (C=O ester); 168.1 (C=O ester), 137.6, 134.2, 132.8, 131.8, 128.8, 126.1, 125.9, 125.2, 123.2, 122.9, 59.2 (C-11b), 58.0 (C-8), 52.2 (2C, COOH₃), 50.8 (C-6), 36.7 (C-13), 32.2 (C-12), 30.1 (C-9), 29.3 (C-5); MS (ESI) m/z: 354.0, 322.0, 184.1, 132.0, 117.0; HRMS (ESI): calculated for C₂₁H₂₄NO₄ [M+H]+ 354.16998, found 354.16918.

**Methyl 5,8,9,12,13,13a-hexahydro-6H-isoquino[2,1-b]isoquinoline-11-carboxylate (18b').** Compounds 18b and 18b' were synthesised from 17a and methylpropiolate following the general procedure for the synthesis of cycloadducts by Diels–Alder reaction. Two products, separated by flash chromatography (SiO₂, 7:3 V/V, ethyl acetate–petroleum ether), were isolated in 1:1 ratio (30 mg, 72 % combined yield). Compound 18b' was isolated as yellow oil which solidified upon standing, m.p. 63–65 °C. IR (ATR, ν / cm⁻¹): 2948, 1717, 1434, 1255, 726; ¹H-NMR (500 MHz, CDCl₃ δ / ppm): 7.19–7.10 (m, 4H, ArH), 6.99–6.98 (m, 1H, H-10), 3.76 (s, 3H, COOCH₃), 3.59 (dd, 1H, J₁=11.0 and J₂=3.5 Hz, H-13a), 3.22–3.16 (m, 2H, H-8, H-5), 3.10 (ddd, 1H, J₁=11.0, 5.5 and 1.5 Hz, H-6), 3.00 (brd, 1H, J₂=15.0 Hz, H-8), 2.86–2.81 (m, 4H, H-12, H-9), 2.73 (brd, 1H, J₂=15.0 Hz, H-5), 2.59–2.54 (m, 2H, H-13, H-6), 2.24–2.19 (m, 1H, H-13); ¹³C-NMR (125 MHz, CDCl₃ δ / ppm): 167.3 (C=O), 137.8, 135.8 (C-10), 134.3, 128.8, 127.7, 126.1, 126.0, 125.3, 124.9, 122.5, 59.4 (C-13a), 58.4 (C-8), 51.6 (COOH₃), 50.9 (C-6), 37.2 (C-13), 29.9 (C-9), 29.8 (C-12), 29.4 (C-5); MS (ESI) m/z: 296.1, 264.1, 236.1, 220.1, 217.1, 144.1; HRMS (ESI): calculated for C₁₉H₂₂NO₂ [M+H]⁺ 296.16451, found 296.16488.
Methyl 5,8,9,12,13,13a-hexahydro-6H-isoquinolo[2,1-b]isoquinoline-10-carboxylate (18b). Compound was isolated as a yellow oil which solidified upon standing, m.p. 110–116 °C. IR (ATR, \( \nu / \text{cm}^{-1} \)): 2950, 1717, 1653, 1435, 1253, 724; \(^1\)H-NMR (500 MHz, CDCl\(_3\) \( \delta / \text{ppm} \)): 7.37–7.36 (m, 1H, ArH), 7.18–7.10 (m, 3H, ArH), 7.01–6.99 (m, 1H, H-11), 3.76 (s, 3H, COOCH\(_3\)), 3.58 (dd, 1H, \( J = 11.0 \) and 3.5 Hz, H-13a), 3.23 (d, 1H, \( J = 15.0 \) Hz, H-8), 3.21–3.15 (m, 1H, H-5), 3.09 (ddd, 1H, \( J = 11.0, 5.6 \) Hz and 2.0 Hz, H-6), 3.02 (brd, 1H, \( J = 16.5 \) Hz, H-8), 2.91–2.77 (m, 4H, H-9, H-12), 2.73 (brd, 1H, \( J = 16.5 \) Hz, H-5), 2.57 (td, 1H, \( J = 11.5 \) Hz and 3.5 Hz, H-6), 2.51 (brd, 1H, \( J = 16.5 \) Hz, H-13), 2.21–2.15 (m, 1H, H-13); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\) \( \delta / \text{ppm} \)): 167.3 (C=O), 137.9, 136.4, (C-11), 134.4, 128.8, 127.3, 126.0, 125.9, 125.2, 124.5, 122.9, 59.4 (C-13a), 58.7 (C-8), 51.6 (COOCH\(_3\)), 50.9 (C-6), 36.9 (C-13), 31.9 (C-12), 29.4 (C-5), 27.9 (C-9); MS (ESI) \( m/z \): 296.1; 184.1; 132.1; 117.1; HRMS (ESI): calculated for C\(_{19}\)H\(_{22}\)NO\(_2\) [M+H]\(^+\) 296.16451, found 296.16451.

Dimethyl 5,8,9,12,13,13a-hexahydro-2,3-dimethoxy-6H-isoquinolo[2,1-b]isoquinoline-10,11-dicarboxylate (18c). The product was isolated after flash chromatography (SiO\(_2\), 7:3 \( V/V \), ethyl acetate–petroleum ether) as a white amorphous solid (50 mg, 80 %), m.p. 170 °C. IR (ATR, \( \nu / \text{cm}^{-1} \)): 1711, 1517, 1280, 1256, 1070; \(^1\)H-NMR (500 MHz, CDCl\(_3\) \( \delta / \text{ppm} \)): 6.63 (s, 1H, H-4), 6.59 (s, 1H, H-5), 3.86 (s, 6H, COOCH\(_3\)), 3.79 (s, 6H, OCH\(_3\)), 3.52 (dd, \( J = 10.5 \) and 3.5 Hz, H-13a), 3.22 (d, 1H, \( J = 15.0 \) Hz, H-8), 3.11–2.95 (m, 7H, H-5, H-6, H-9, H-12, H-8), 2.65–2.61 (m, 1H, H-5), 2.58–2.52 (m, 1H, H-6), 2.46 (brd, 1H, \( J = 16.0 \) Hz, H-13), 2.21–2.15 (m, 1H, H-13); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\) \( \delta / \text{ppm} \)): 168.3 (C=O\(_{\text{ester}}\)), 168.2 (C=O\(_{\text{ester}}\)), 147.5, 147.4, 132.7, 132.0, 129.5, 126.5, 123.1, 122.9, 111.3, 108.3, 58.9 (C-13a), 58.0 (C-8), 56.0 (OCH\(_3\)), 55.8 (OCH\(_3\)), 52.2 (2C, COOCH\(_3\)), 51.0 (C-6), 36.9 (C-13), 32.3 (C-12), 30.2 (C-9), 28.9 (C-5); MS (EI) \( m/z \): 268.1, 210.1, 136.1; HRMS (ESI): calculated for C\(_{23}\)H\(_{28}\)NO\(_6\) [M+H]\(^+\) 414.19111, found 414.19005.

Dimethyl 5,8,13,13a-tetrahydro-6H-isoquinolo[2,1-b]isoquinoline-10,11-dicarboxylate (19a)

The product was isolated after flash chromatography (SiO\(_2\), 4:1 \( V/V \), diethyl ether–petroleum ether) as a yellow oil (15 mg, 63 %), which solidified upon
standing, m.p. 108−110 °C. IR (ATR, ν / cm−1): 3283, 2922, 1699, 1621, 1606, 1439, 1299, 1284, 1148, 1231, 737; 1H-NMR (500 MHz, CDCl3 δ / ppm): 7.53 (s, 1H, H-12), 7.48 (s, 1H, H-9), 7.25−7.14 (m, 4H, ArH), 4.08 (d, 1H, J = 15.5 Hz, H-8), 3.90 (s, 6H, COOCH3), 3.75 (d, 1H, J = 15.5 Hz, H-8), 3.70 (dd, 1H, J = 11.5 and 4.0 Hz, H-13a), 3.41 (dd, 1H, J = 16.5 and 4.0 Hz, H-13), 3.23−3.16 (m, 2H, H-5, H-6); 13C-NMR (125 MHz, CDCl3 δ / ppm): 168.1 (C=O), 167.9 (C=O), 138.4, 138.0, 137.1, 134.4, 130.0, 129.4, 128.9, 126.9, 126.4, 125.4, 59.3 (C-13a), 58.0 (C-8), 52.6 (2CH3), 50.9 (C-6), 36.5 (C-13), 29.4 (C-5); MS (ESI) m/z: 352.1, 130.1, 117.1, 103.1; HRMS (ESI) calculated for C21H22NO4 [M+H]+ 352.15433, found 352.15493.

**Methyl 5,8,13,13a-tetrahydro-6H-isoquino[2,1-b]isoquinoline-10-carboxylate (19b).** The product was isolated after flash chromatography (SiO2, 1:1 V/V, diethyl ether−petroleum ether) as yellow plates (10 mg, 72 %), m.p. 133−136 °C. IR (ATR, ν / cm−1): 2953, 2929, 1713, 1441, 1289, 1198, 745; 1H-NMR (500 MHz, CDCl3 δ / ppm): 7.82 (d, 1H, J = 8.0 Hz, H-11), 7.79 (s, 1H, H-9), 7.27−7.26 (m, 1H, ArH), 7.23–7.14 (m, 4H, ArH), 4.08 (d, 1H, J = 15.0 Hz, H-8), 3.90 (s, 3H, CH3), 3.75 (d, 1H, J = 15.5 Hz, H-8), 3.70 (dd, 1H, J = 11.0 and 3.5 Hz, H-13a), 3.42 (dd, 1H, J = 17.0 and 4.0 Hz, H-13), 2.80–2.76 (m, 1H, H-5), 2.69−2.64 (m, 1H, H-6); 13C-NMR (125 MHz, CDCl3 δ / ppm): 167.1 (C=O), 140.1, 137.4, 134.7, 134.4, 128.9, 128.8, 127.7, 127.5, 127.3, 126.2, 126.1, 125.4, 59.5 (C-13a), 58.3 (CH3), 51.9 (CH3), 51.1 (C-6), 36.8 (C-13), 29.4 (C-5); MS (EI) m/z: 293.1 [M+], 278.1, 232.0, 163.0, 130.1, 103.0; HRMS (ESI) calculated for C19H20NO2 [M+H]+ 294.14886, found 294.14906.

**Dimethyl 5,8,13,13a-tetrahydro-2,3-dimethoxy-6H-isoquino[2,1-b]isoquinoline-10,11-dicarboxylate (19c).** The product was isolated after flash chromatography (SiO2, 95:5 V/V, diethyl ether−petroleum ether) as yellow needles (12 mg, 78 %), m.p. 173−175 °C. IR (ATR, ν / cm−1): 1721, 1513, 1258, 1100, 728; 1H-NMR (500 MHz, CDCl3 δ / ppm): 7.55 (s, 1H, H-12), 7.47 (s, 1H, H-9), 6.1 (s, 1H, H-1), 6.23 (s, 1H, H-4), 4.08 (d, 1H, J = 15.5 Hz, H-8), 3.90 (s, 3H, COCH3), 3.89 (s, 6H, COCH3, OCH3), 3.87 (s, 3H, OCH3), 3.74 (d, 1H, J = 15.5 Hz, H-8), 3.63 (dd, 1H, J = 11.0 and 3.5 Hz, H-13a), 3.37 (dd, 1H, J = 16.5 and 3.5 Hz, H-13), 3.17−3.11 (m, 2H, H-5, H-6), 2.93 (dd, 1H, J = 16.5 and 11.0 Hz, H-13), 2.71−2.61 (m, 2H, H-6, H-5); 13C-NMR (125 MHz, CDCl3 δ / ppm): 168.1 (C=O), 168.0 (C=O), 147.7 (C-7), 147.5 (C-3), 138.3, 138.1, 129.9, 129.5, 129.4 (C-12), 128.9, 126.9 (C-9), 126.6, 111.4, 108.4, 59.0 (C-13a), 58.0 (C-8), 56.0 (OCH3), 55.8 (OCH3), 52.5 (2CH3, COCH3), 51.1 (C-6), 36.7 (C-13), 28.9 (C-5); MS (ESI) m/z: 412.1 [M+H]+; 380.1, 348.1, 322.1, 277.9, 250.1; HRMS (ESI): calculated for C23H26NO6 [M+H]+ 412.17642, found 412.17642.
**Dimethyl 5,6-dihydro-8-oxo-8H-isoquino[2,1-b]isoquinoline-10,11-dicarboxylate (20a)**

The product was isolated after flash chromatography (SiO₂, 4:1 V/V, diethyl ether–petroleum ether) as yellow needles (5 mg, 70%), m.p. 178–180 °C. This derivative gave specific azure colour with Dragendorff reagent. IR (ATR, ν / cm⁻¹): 1729, 1712, 1645, 1620, 1293, 1161, 772; ¹H-NMR (200 MHz, CDCl₃ δ / ppm): 8.88 (s, 1H), 7.84–7.78 (m, 3H), 7.42–7.27 (m, 2H), 7.00 (s, 1H), 4.37 (t, 2H, J = 6.0 Hz), 3.97 (s, 3H, COOCH₃), 3.94 (s, 3H, COOCH₃), 3.04 (t, 2H, J = 6.0 Hz, H-5); ¹³C-NMR (50 MHz, CDCl₃ δ / ppm): 168.5 (C=Oester), 166.6 (C=Oester), 161.3 (C=Olactam), 140.6, 138.7, 136.4, 135.7, 130.6, 130.2, 129.5, 128.7, 127.7, 127.3, 126.7, 125.4, 125.1, 101.8, 52.9, 52.7, 39.8, 28.3; MS (ESI) m/z: 364.1, 332.1, 317.1, 290.1, 230.1; HRMS (ESI): calculated for C₂₁H₁₈NO₅ [M+H]+ 364.11795, found 364.11783.

**Methyl 5,6-dihydro-8-oxo-8H-isoquino[2,1-b]isoquinoline-10-carboxylate (20b).** The product was isolated after flash chromatography (SiO₂, 7:3 V/V, diethyl ether–petroleum ether) as yellow rombs (8 mg, 45%), m.p. 202–204 °C. Compound gave specific purple-brown colour with Dragendorff reagent. IR (ATR, ν / cm⁻¹): 1703, 1651, 1614, 1600, 1288, 766; ¹H-NMR (500 MHz, CDCl₃ δ / ppm): 9.11 (d, 1H, J = 1.5 Hz, H-9), 8.24 (dd, 1H, J = 8.4 and 1.6 Hz, H-11), 7.86–7.84 (m, 1H, H-1), 7.62 (d, 1H, J = 8.2 Hz, H-12), 7.40–7.38 (m, 2H, H-2, H-3), 7.34–7.30 (m, 1H, H-4), 7.04 (s, 1H, H-13), 4.39 (t, 2H, J = 6.1 Hz, H-6), 3.97 (s, 3H, COOCH₃), 3.04 (t, 2H, J = 6.1 Hz, H-5); ¹³C-NMR (125 MHz, CDCl₃ δ / ppm): 166.6 (C=Oester), 161.9 (C=Olactam), 139.9, 139.8, 135.7, 132.5, 130.5, 129.9, 129.8, 128.1, 127.6, 126.4, 125.3, 102.2 (C-13), 52.2 (CH₃), 39.7 (C-6), 28.4 (C-5) ppm; MS (ESI) m/z: 306.0, 276.0, 247.1, 232.0, 176.1; 203.0; HRMS (ESI): calculated for C₁₉H₁₆NO₃ [M+H]+ 306.11247, found 306.11202.

**Dimethyl 5,6-dihydro-2,3-dimethoxy-8-oxo-8H-isoquino[2,1-b]isoquinoline-10,11-dicarboxylate (20c).** The product was isolated after flash chromatography (SiO₂, 1:1 V/V, diethyl ether–petroleum ether) as yellow needles (12 mg, 50%), m.p. 220–221 °C. Compound gave specific blue colour with Dragendorff reagent. IR (ATR, ν / cm⁻¹): 1709, 1563, 1514, 1241, 1046, 787; ¹H-NMR (500 MHz, CDCl₃ δ / ppm): 8.88 (s, 1H, H-9), 7.78 (s, 1H, H-12), 7.25 (s, 1H, H-1), 6.88 (s, 1H, H-13), 3.93 (s, 3H, COOCH₃), 3.86 (s, 3H, COOCH₃), 3.02 (t, 2H, J = 6.0 Hz, H-5).
1H, H-13), 6.76 (s, 1H, H-4), 4.36 (t, 2H, J = 6.0 Hz, H-6), 3.99 (s, 3H, OCH3),
3.96 (s, 3H, COOCH3), 3.95 (s, 3H, OCH3), 3.94 (s, 3H, COOCH3), 2.97 (t, 2H, J = 6.0 Hz, H-5); 13C-NMR (125 MHz, CDCl3): δ 168.5 (C=O ester), 166.6 (C=O ester), 161.4 (C=O lactam), 151.1 (C-2), 148.7 (C-3), 140.6, 138.9, 136.4, 130.6 (C-9), 129.3, 126.8, 126.4 (C-12), 124.6, 121.5, 110.5 (C-4), 108.1 (C-1), 100.4 (C-13), 56.3 (OCH3), 56.1 (OCH3), 52.9 (COOCH3), 52.6 (COOCH3), 39.9 (C-6),
27.8 (C-5); MS (EI) m/z: 355.1, 298.9, 281.1, 263.1, 207.0; HRMS (ESI): calculated for C23H22NO7 [M+H]+ 424.13908, found 424.13949.

1-Allyl-2,3,4,9-tetrahydro-2-(2-iodoallyl)-1H-pyrido[3,4-b]indole (23)

The product was isolated after flash chromatography (SiO2, 9:1 V/V, petroleum ether–diethyl ether) as a pale yellow oil (173 mg, 42 %). IR (ATR, ν / cm⁻¹): 3230, 3070, 2916, 1615, 1451, 741; 1H-NMR (200 MHz, CDCl3 δ / ppm): 7.76 (brs, 1H, N-H), 7.55–7.05 (m, 4H, ArH), 6.37 (d, 1H, J = 1.2 Hz, H-3”), 5.90–6.09 (m, 1H, H-2”), 5.89 (d, 1H, J = 1.0 Hz, H-3”), 5.16 (d, 2H, J = 12.0 Hz, H-3”), 3.74 (t, 1H, J = 6.6 Hz, H-1), 3.33 (s, 2H, H-1”), 3.25–3.00 (m, 1H), 2.86–2.45 (m, 4H); 13C-NMR (50 MHz, CDCl3 δ / ppm): 136.2, 135.7, 134.8, 127.0, 126.6, 121.6, 119.4, 118.1, 117.5, 111.8, 110.7, 108.1, 64.8, 56.7, 44.7, 39.4, 18.7; MS (EI) m/z: 378[M]+, 337 [M-allyl]+, 209.1, 169.1; HRMS (ESI) calculated for C17H20IN2 [M+H]+ 379.06657, found 379.06643.

1,2,3,4,6,7,12,12b-Octahydro-2,3-dimethylene-indolo[2,3-a]quinolizine (24)

The product was isolated after flash chromatography (SiO2, 7:3 V/V, petroleum ether–diethyl ether) as a pale yellow amorphous solid (126 mg, 50 %), m.p. 153–156 °C. IR (ATR, ν / cm⁻¹): 3418, 3049, 2949, 1643, 1314, 743; 1H-NMR
(500 MHz, CDCl$_3$ $\delta$ / ppm): 7.74 (brs, 1H, N-H), 7.48 (d, 1H, $J$ = 8.0 Hz, H-8), 7.31 (dt, 1H, $J$ = 8.0 and 0.5 Hz, H-11), 7.16–7.08 (m, 2H, H-9, H-10), 5.19–5.18 (m, 2H, =CH$_2$), 4.88 (s, 2H, =CH$_2$), 3.56 (d, 1H, $J$ = 12.5 Hz, H-4), 3.47–3.44 (m, 1H, H-12b), 3.18–3.13 (m, 2H, H-4, H-6), 3.07–2.99 (m, 1H, H-7), 2.79–2.74 (m, 2H; H-1, H-7), 2.66 (td, $J$ = 11.0 and 4.5 Hz, H-6), 2.50–2.44 (m, 1H, H-1); $^{13}$C-NMR (125 MHz, CDCl$_3$ $\delta$ / ppm): 144.4, 143.9, 136.1, 134.1, 127.2, 119.5, 118.2, 110.8 (C-11), 110.3 (C$_2$=CH$_2$), 110.1 (C$_3$=CH$_2$), 108.7 (C-7a), 61.4 (C-4), 59.2 (C-12b), 52.3 (C-6), 38.6 (C-1), 21.6 (C-7); MS (EI) $m$/z: 259.2 [M]$^+$, 235.1, 220.1, 206.1, 169.1; HRMS (ESI): calculated for C$_{17}$H$_{19}$N$_2$ [M+H]$^+$ 251.15428, found 251.15428.

11,12-Dicarbmethoxy-1,6,7,9,10,13,14,14a-octahydroindolo[2,3-a]benzo[e]-quinolizine (25)

The product was isolated after flash chromatography (SiO$_2$, 8:2 $V/V$, diethyl ether–petroleum ether) as a creamy-white amorphous solid (50 mg, 80 %), m.p. 161–163 °C. IR (ATR, $\nu$ / cm$^{-1}$): 2949, 1716, 1659, 1434, 1260, 1069, 738; $^1$H-NMR (500 MHz, CDCl$_3$ $\delta$ / ppm): 7.74 (s, 1H, ArH), 7.50 (d, 1H, $J$ = 8.0 Hz, ArH), 7.32 (d, 1H, $J$ = 8.0 Hz, ArH), 7.16 (t, 1H, $J$ = 7.2 Hz, ArH), 7.11 (t, 1H, $J$ = 7.0 Hz, ArH), 3.80 (s, 3H, COOCH$_3$), 3.79 (s, 3H, COOCH$_3$), 3.64–3.61 (m, 1H, H-3), 3.28 (brd, 1H, $J$ = 15.5 Hz, H-9), 3.20 (dd, 1H, $J$ = 11.5 and 4.5 Hz, H-7), 3.06–2.89 (m, 6H, H-6, H-9, H-10, H-13), 2.80–2.75 (m, 1H, H-6), 2.67 (td, 1H, $J$ = 11.0 and 4.0 Hz, H-7), 2.31–2.33 (m, 2H, H-14); $^{13}$C-NMR (125 MHz, CDCl$_3$ $\delta$ / ppm): 168.3 (C=O), 168.1 (C=O), 136.3, 134.1, 132.7, 131.9, 127.2, 123.7, 122.1, 121.6, 119.5, 118.3, 110.8, 108.7, 57.3 (C-9), 55.8 (C-14a), 52.3 (2C, COOCH$_3$), 51.9 (C-7), 34.9 (C-14), 32.3 (C-10), 30.3 (C-13), 21.5 (C-6); MS (ESI) $m$/z: 393.1, 171.1, 144.1, 117.1; HRMS (ESI): calculated for C$_{23}$H$_{23}$N$_2$O$_4$[M+H]$^+$ 393.18088, found 393.17969.

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11,12-dicarbomethoxy-1,6,7,9,14,14a-hexahydroindolo[2,3-a]benzo[e]quinolizine (26)

The product was isolated after flash chromatography (SiO₂, 9:1 V/V, diethyl ether–petroleum ether) as a pale yellow amorphous solid (17 mg, 72 %), m.p. 167–168 °C. IR (ATR, ν / cm⁻¹): 1720, 1434, 1271, 1125, 741; ¹H-NMR (500 MHz, CDCl₃ δ / ppm): 8.17 (s, 1H, N-H), 7.51 (d, 1H, J = 8.0 Hz, H-2), 7.45 (s, 2H, H-13, H-10), 7.10 (d, 1H, J = 8.0 Hz, H-5), 7.10 (d, 1H, J = 7.0 and 1.0 Hz, H-4), 7.10 (d, 1H, J = 7.0 and 1.0 Hz, H-3), 4.09 (d, 1H, J = 15.5 Hz, H-9), 3.91 (s, 3H, COOCH₃), 3.87 (s, 3H, COOCH₃), 3.70 (d, 1H, J = 15.5 Hz, H-9), 3.55–3.53 (m, 1H, H-14a), 3.27–3.24 (m, 1H, H-7), 2.94 (dd, 1H, J = 16.0 and 11.5 Hz, H-14), 2.08–2.06 (m, 1H, H-6), 2.71 (td, 1H, J = 11.5 and 3.5 Hz, H-7); ¹³C-NMR (125 MHz, CDCl₃ δ / ppm): 168.3 (C=O), 168.0 (C=O), 138.2, 137.3, 136.4, 133.6, 130.0, 129.4, 129.3, 127.1, 127.0, 121.7 (C-10), 119.5 (C-11), 118.2 (C-12), 110.9, 108.7, 57.3 (C-21), 55.8 (C-3), 52.7 (COOCH₃), 52.6 (COOCH₃), 52.2 (C-7), 34.6 (C-14), 21.4 (C-6); MS (ESI) m/z: 391.1, 374.1, 359.1, 144.1, 117.1; HRMS (ESI): calculated for C₂₃H₂₃N₂O₄ [M+H]+ 391.16523, found 391.16563.

11,12-dicarbomethoxy-1,6,7-trihydroindolo[2,3-a]benzo[e]quinolizine-9-on (27)

The product was isolated after flash chromatography (SiO₂, diethyl ether) as a yellow amorphous solid (5 mg, 45 %), m.p. 220–225 °C. Compound gave specific gray-blue colour with Dragendorff reagent. IR (ATR, ν / cm⁻¹): 3283, 2922, 1699, 1621, 1606, 1439, 1299, 1284, 1148, 1231, 737; ¹H-NMR (500 MHz, CDCl₃ δ / ppm): 8.77 (s, 1H, H-10), 8.74 (s, 1H, N-H ), 7.60 (d, 1H, J = 7.5 Hz, H-5), 7.56 (s, 1H, H-13), 7.45 (d, 1H, J = 8.0 Hz, H-2), 7.32 (t, 1H, J = 7.5 Hz, H-3), 7.18 (t, 1H, J = 7.5 Hz, H-4), 6.41 (s, 1H, H-14), 4.51 (t, 2H, J = 7.0 Hz,
H-7), 4.03 (s, 3H, COOCH$_3$), 3.63 (s, 3H, COOCH$_3$), 3.15 (t, 2H, $J = 7.0$ Hz, H-6); $^{13}$C NMR (125 MHz, CDCl$_3$ $\delta$ / ppm): 169.5 (C=O$_{ester}$), 165.9 (C=O$_{ester}$), 161.2 (C=O$_{lactam}$), 138.7, 138.4, 136.9, 134.9, 130.7, 127.4, 126.1, 125.9, 125.5, 125.0, 124.9, 120.7, 119.6, 115.6, 111.8, 97.7, 53.2 (COOCH$_3$), 52.2 (COOCH$_3$), 41.0 (C-7), 19.7 (C-6); MS (ESI) $m/z$: 403.1, 371.1, 355.1, 343.1, 283.1; HRMS (ESI): calculated for C$_{23}$H$_{19}$N$_2$O$_5$ [M+H]$^+$ 403.12885, found 403.12910.

**Compound 9**

COPIES OF SELECTED $^1$H- AND $^{13}$C-NMR SPECTRA
Compound 10
Compound II
Compound 17a
Compound 17b
Compound 18a
Compound 18b
Compound 18c
Compound 19a
Compound 19b
Compound 19c
Compound 20a
Compound 20b
Compound 20c
Compound 24
Compound 25
Compound 26