Supporting Information

Enantioselective Michael Addition/Iminium Ion Cyclization Cascades of Tryptamine-Derived Ureas

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1. General experimental

All non-aqueous reactions were conducted using oven-dried glassware and were magnetically stirred unless otherwise stated. Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise stated.

1.1 Solvents and reagents

Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure. Reagents used were obtained from commercial suppliers or purified according to standard procedures. Triethylamine was distilled from calcium hydride under a positive pressure of dry nitrogen and stored over potassium hydroxide. Tryptamines,\(^1\) tryptamine-derived thiourea \(^5\)h,\(^2\) tryptamine-derived urea \(^5\)i,\(^3\) unsaturated ketones \(^6\)c-\(^d\)\(^4\) and catalysts \(^10\)\(^5\) were prepared according to reported procedures. Petroleum ether (PE) refers to distilled light petroleum of fraction 30 - 40 °C. Anhydrous dichloromethane and toluene were dried by filtration through activated alumina (powder ∼150 mesH; pore size 58Å, basic) columns. Deuterated solvents were used as supplied.

1.2 Chromatography

Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates and visualised by fluorescence quenching under UV light. In addition, TLC plates were stained with \(p\)-anisaldehyde. Chromatographic purification was performed on VWR 60 silica gel 40-63 µm using technical grade solvents that were used as supplied.

1.3 Melting points

Melting points were obtained on a Leica Galen III Hot-stage melting point apparatus and microscope and are uncorrected.

1.4 NMR spectra

NMR spectra were recorded on a Bruker Spectrospin spectrometer operating at 400 MHz or 500 MHz (\(^1\)H acquisitions) and 100 MHz or 125 MHz (\(^13\)C acquisitions). Chemical shifts (\(\delta\)) are reported in ppm with the solvent resonance as the internal standard (e.g. DMSO \(\delta\) 2.50 ppm for \(^1\)H and 39.52 ppm for \(^13\)C). Coupling constants (\(J\)) are reported in hertz (Hz). Data are reported as follows: \(s\) = singlet, \(d\) = doublet, \(t\) = triplet, \(q\) = quartet, \(dd\) = doublet of doublets, \(ddd\) = doublet of doublets of doublets, \(dt\) = doublet of triplets, \(td\) = triplet of doublets, \(m\) = multiplet, \(br\). \(s\). = broad signal, coupling constants in Hz, integration, assignment. Two-dimensional

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spectroscopy (COSY, HSQC and HMBC) was used to assist in the assignment. The data are not reported.

1.5 Mass spectra
Low-resolution mass spectra (ESI) were recorded on a Waters LCT Premier XE Micromass mass spectrometer. High-resolution mass spectra (ESI) were recorded on Bruker Daltonics MicroTOF mass spectrometer. High-resolution mass spectra (EI) were recorded on a Bruker FT-ICR Apex III mass spectrometer.

1.6 Infrared spectra
Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film on a sodium chloride plate. Only selected maximum absorbances are reported.

1.7 Determination of enantiomeric excesses
Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on Agilent Technologies 1200 Series or 1260 Infinity Series systems (column and solvent conditions are given for each compound).

1.8 Optical rotations
Optical rotations were recorded using a Perkin-Elmer 241 polarimeter; specific rotation (SR) ([α]D23) are reported in 10⁻¹ deg cm²g⁻¹; concentrations (c) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm), temperatures (T) are given in degrees Celsius (°C).

All atom numbering used in this section is arbitrary and does not follow any particular convention.
2. Practical experimental

2.1 Synthesis of starting materials

2.1.1 General procedure I for the preparation of tryptamine-derived ureas 5a-g

Concentrated HCl (37% in water, 1.2 eq.) was added to tryptamine (1.0 eq.) at 0 °C and the mixture was dissolved in refluxing ethanol (1.05 mL/mmol). The solution was cooled to room temperature and added to a solution of KOCN (1.2 eq.) dissolved in distilled water (1.05 mL/mmol). The resulting mixture was stirred at room temperature for the indicated time. The reaction mixture was then concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to afford the desired ureas 5a-g.

2.1.1.1 Synthesis and characterisation of 1-[2-(1H-indol-3-yl)ethyl]urea 5a

The title compound was synthesised according to general procedure I. Tryptamine (10.0 g, 62.4 mmol) was reacted with KOCN (6.08 g, 74.9 mmol) in ethanol (65 mL) and water (65 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 5a in 55% yield (7.03 g) as a white powder.

m.p. 140-142 °C; IR (neat) ν=3413, 3376, 3344, 3146, 1637, 1552, 1455, 1348, 1088, 747, 737; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.83 (br. s., 1H; NH indole), 7.55 (d, J=7.5 Hz, 1H; H₆), 7.36 (d, J=7.5 Hz, 1H; H₉), 7.15 (d, J=2.5 Hz, 1H; H₁₁), 7.08 (td, J=7.5, 1.0 Hz, 1H; H₈), 6.99 (td, J=7.5, 1.0 Hz, 1H; H₇), 6.01-5.98 (m, 1H; NH urea), 5.49 (br. s., 2H; NH₂ urea), 3.30 (q, J=7.5 Hz, 2H; H₂), 2.81 (t, J=7.5 Hz, 2H; H₃); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=158.8 (C₁), 136.3 (C₁₀), 127.3 (C₅), 122.6 (C₁₁), 120.9 (C₈), 118.4 (C₇), 118.2 (C₆), 112.0 (C₄), 111.4 (C₉), 39.6 (C₂), 26.1 (C₃); MS m/z (ES⁺) 226 ([M+Na⁺], 100%); HRMS (ES⁺) exact mass calculated for [M+Na⁺]⁺ (C₁₁H₁₃N₃NaO⁺) requires m/z 226.0951, found m/z 226.0956.
2.1.1.2 Synthesis and characterisation of 1-[2-(5-methoxy-1H-indol-3-yl)ethyl]urea 5b

The title compound was synthesised according to general procedure I. 5-Methoxytryptamine (500 mg, 2.63 mmol) was reacted with KOCN (256 mg, 3.16 mmol) in ethanol (2.8 mL) and water (2.8 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 5b in 52% yield (307 mg) as a brown powder.

m.p. 141-143 °C; IR (neat) ν=3489, 3385, 3184, 1655, 1608, 1491, 1455, 1215, 800, 702; \(^1\)H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.65 (br. s., 1H; NH indole); 7.23 (d, J=8.5 Hz, 1H; H10), 7.10 (d, J=1.5 Hz, 1H; H12), 7.04 (d, J=2.0 Hz, 1H; H6), 6.72 (dd, J=8.5, 2.0 Hz, 1H; H9), 5.96 (br. s., 1H; NH urea), 5.45 (br. s., 2H; NH₂ urea), 3.76 (s, 3H; H8), 3.28-3.25 (m, 2H; H2), 2.76 (t, J=7.0 Hz, 2H; H3); \(^13\)C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=158.7 (C1), 152.9 (C7), 131.4 (C11), 127.6 (C5), 123.3 (C12), 111.9 (C10), 111.8 (C4), 111.0 (C9), 100.2 (C6), 55.3 (C8), 39.5 (C2), 26.1 (C3); MS m/z (ES+) 489 ([2M+Na]⁺, 100%); HRMS (ES+) exact mass calculated for [M+Na]⁺ (C₁₂H₁₅N₃NaO₂) requires m/z 256.1056, found m/z 256.1058.

2.1.1.3 Synthesis and characterisation of 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]urea 5c

The title compound was synthesised according to general procedure I. 5-Fluorotryptamine (500 mg, 2.81 mmol) was reacted with KOCN (274 mg, 3.37 mmol) in ethanol (3.0 mL) and water (3.0 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 5c in 53% yield (330 mg) as a brown powder.

m.p. 159-161 °C; IR (neat) ν=3501, 3343, 3305, 1694, 1634, 1580, 1118, 935, 774; \(^1\)H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.92 (br. s., 1H; NH indole); 7.33 (dd, J=9.0, 4.5 Hz, 1H; H8), 7.30 (dd, J=10.0, 2.5 Hz, 1H; H6), 7.22 (d, J=2.0 Hz, 1H; H11), 6.91 (t, J=9.0 Hz, 2H; H9), 5.96 (br. s., 1H; NH urea), 5.44 (br. s., 2H; NH₂ urea), 3.23-3.19 (m, 2H; H2), 2.75 (t, J=7.0 Hz, 2H; H3); \(^13\)C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=158.7 (C1), 156.1 (d, J=229 Hz, C7),
132.9 (C5), 127.5 (d, J=10 Hz, C10), 124.8 (C11), 112.4 (d, J=5 Hz, C4), 112.2 (d, J=10 Hz, C8), 108.9 (d, J=25 Hz, C9), 103.0 (d, J=25 Hz, C6), 48.6 (C2), 26.0 (C3); MS m/z (ES+) 465 ([2M+Na]+, 100%); HRMS (ES+) exact mass calculated for [M+Na]+ (C11H12FN3NaO+) requires m/z 244.0857, found m/z 244.0862.

2.1.1.4 Synthesis and characterisation of 1-[2-(5-chloro-1H-indol-3-yl)ethyl]urea 5d

The title compound was synthesised according to general procedure I. 5-Chlorotryptamine (500 mg, 2.16 mmol) was reacted with KOCN (211 mg, 2.59 mmol) in ethanol (2.3 mL) and water (2.3 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH2Cl2/MeOH 95/5) to afford product 5d in 49% yield (252 mg) as a pale yellow powder.

m.p. 169-171 °C; IR (neat) ν=3481, 3440, 3345, 1646, 1553, 1333, 1100, 796, 662; 1H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=11.06 (br. s., 1H; NH indole), 7.59 (d, J=2.0 Hz, 1H; H6), 7.36 (d, J=8.5 Hz, 1H; H9), 7.23 (s, 1H; H11), 7.06 (dd, J=8.5, 2.0 Hz, 1H; H8), 5.97 (br. s., 1H; NH urea), 5.49 (br. s., 2H; NH₂ urea), 3.26-3.22 (m, 2H; H2); 13C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=158.7 (C1), 134.6 (C10), 128.4 (C5), 124.6 (C11), 122.9 (C7), 120.8 (C8), 117.7 (C6), 112.8 (C9), 112.1 (C4), 39.5 (C2), 25.9 (C3); MS m/z (ES+) 497 ([2M+Na]+, 100%); HRMS (ES+) exact mass calculated for [M+Na]+ (C11H12ClN3NaO+) requires m/z 260.0561, found m/z 260.0559.

2.1.1.5 Synthesis and characterisation of 1-[2-(6-fluoro-1H-indol-3-yl)ethyl]urea 5e

The title compound was synthesised according to general procedure I. 6-Fluorotryptamine (400 mg, 2.25 mmol) was reacted with KOCN (218 mg, 2.69 mmol) in ethanol (2.4 mL) and water (2.4 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH2Cl2/MeOH 95/5) to afford product 5e in 52% yield (260 mg) as a brown powder.
**m.p.** 161-163 °C; **IR** (neat) ν=3500, 3359, 3334, 1638, 1577, 1566, 1134, 1097, 800; $^1$H NMR (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.89 (br. s., 1H; NH indole), 7.53 (dd, $J$=8.5, 5.5 Hz, 1H; H6), 7.14 (d, $J$=2.5 Hz, 1H; H11), 7.10 (dd, $J$=10.0, 2.0 Hz, 1H; H9), 6.83 (td, $J$=8.5, 2.5 Hz, 1H; H7), 5.93 (br. s., 1H; NH urea), 5.42 (br. s., 2H; NH$_2$ urea), 3.28-3.21 (m, 2H; H2), 2.75 (t, $J$=7.0 Hz, 2H; H3); $^{13}$C NMR (125 MHz, [D$_6$]DMSO, 25 °C) δ=158.79 (d, $J$=231 Hz, C8), 158.7 (C1), 136.0 (d, $J$=10 Hz, C4), 124.1 (C5), 123.2 (C11), 119.3 (d, $J$=10 Hz, C6), 112.3 (C10), 106.6 (d, $J$=25 Hz, C7), 97.2 (d, $J$=25 Hz, C9), 39.5 (C2), 26.0 (C3); **MS** m/z (ES+) 465 ([2M+Na]$^+$, 100%); HRMS (ES+) exact mass calculated for [M+Na]$^+$ (C$_{11}$H$_{12}$FN$_3$NaO$^+$) requires m/z 244.0857, found m/z 244.0859.

**2.1.1.6 Synthesis and characterisation of 1-[2-(7-methyl-1H-indol-3-yl)ethyl]urea 5f**

![Chemical structure](image)

The title compound was synthesised according to general procedure I. 7-Methyltryptamine (1.00 g, 5.74 mmol) was reacted with KOCN (561 mg, 6.91 mmol) in ethanol (6.0 mL) and water (6.0 mL) for 60 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH$_2$Cl$_2$/MeOH 95/5) to afford product 5f in 55% yield (0.690 g) as a white powder.

**m.p.** 144-146 °C; **IR** (neat) ν=3402, 3392, 3322, 3201, 1643, 1607, 1516, 777, 743; $^1$H NMR (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.78 (br. s., 1H; NH indole), 7.38 (d, $J$=7.5 Hz, 1H; H6), 7.14 (d, $J$=2.5 Hz, 1H; H12), 6.92-6.87 (m, 2H; H7 and H8), 5.96 (t, $J$=5.5 Hz, 1H; NH urea), 5.46 (br. s., 2H; NH$_2$ urea), 3.31-3.27 (m, 2H; H2), 2.79 (t, $J$=7.0 Hz, 2H; H3), 2.45 (s, 3H; H10); $^{13}$C NMR (125 MHz, [D$_6$]DMSO, 25 °C) δ=158.8 (C1), 135.8 (C11), 126.9 (C5), 122.3 (C12), 121.4 (C8), 120.4 (C9), 118.4 (C7), 116.0 (C6), 112.4 (C4), 39.6 (C2), 26.2 (C3), 16.8 (C10); **MS** m/z (ES+) 457 ([2M+Na]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ (C$_{12}$H$_{15}$N$_3$NaO$^+$) requires m/z 240.1107, found m/z 240.1110.
2.1.1.7 Synthesis and characterisation of 1-[2-(7-ethyl-1H-indol-3-yl)ethyl]urea 5g

The title compound was synthesised according to general procedure I. 7-Ethyltryptamine (1.00 g, 5.31 mmol) was reacted with KOCN (517 mg, 6.37 mmol) in ethanol (5.6 mL) and water (5.6 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 5g in 59% yield (0.730 g) as a brown powder.

m.p. 164-166 °C; IR (neat) ν=3390, 3322, 3206, 2964, 1643, 1607, 1097, 1081, 799, 742; ¹H NMR (400 MHz, [D₆]DMSO, 25 °C) δ=10.77 (br. s., 1H; NH indole), 7.36 (d, J=7.0 Hz, 1H; H6), 7.11 (d, J=2.0 Hz, 1H; H13), 6.93-6.85 (m, 2H; H7 and H8), 5.93 (br. s., 1H; NH urea), 5.42 (br. s., 2H; NH₂ urea), 3.30-3.24 (m, 2H; H2), 2.86-2.81 (m, 2H; H10), 2.89-2.75 (m, 2H; H3), 1.25 (t, J=7.5 Hz, 3H; H11); ¹³C NMR (100 MHz, [D₆]DMSO, 25 °C) δ=159.6 (C1), 135.8 (C12), 128.0 (C9), 127.6 (C5), 123.1 (C13), 120.5 (C8), 119.4 (C7), 116.9 (C6), 113.3 (C4), 39.5 (C2), 27.1 (C3), 24.6 (C10), 15.3 (C11); MS m/z (ES+) 485 ([2M+Na]⁺, 100%); HRMS (ES+) exact mass calculated for [M+Na]⁺ (C₁₃H₁₇N₃NaO⁺) requires m/z 254.1264, found m/z 254.1265.

2.1.2 General procedure II for the preparation of tryptamine-derived ureas 5j-p

Tryptamine (1.0 eq.) was dissolved in CH₂Cl₂ at room temperature. Triethylamine (2.0 eq.) was added and the reaction mixture was cooled to 0 °C. Isocyanate (0.90 eq.) was then added dropwise and the reaction mixture was allowed to slowly warm to room temperature over the indicated time. The resulting precipitate was filtered off washing with CH₂Cl₂ and dried under vacuum to afford the desired ureas 5j-p. The ureas were used in the next step without further purification.
2.1.2.1 Synthesis and characterisation of 1-[2-(7-ethyl-1H-indol-3-yl)ethyl]-3-(ethyl)urea 5j

The title compound was synthesised according to general procedure II. 7-Ethyltryptamine (500 mg, 2.66 mmol) was reacted with ethylisocyanate (0.190 mL, 2.39 mmol) in CH$_2$Cl$_2$ (50 mL) for 14 hours. Product 5j was isolated in 99% yield (623 mg) as a brown powder.

**m.p.** 142-144 °C; **IR** (neat) ν=3317, 3063, 2971, 2874, 1571, 1450, 1256, 738, 657; **$^1$H NMR** (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.76 (br. s., 1H; NH indole), 7.36 (d, $J$=7.5 Hz, 1H; H8), 7.10 (d, $J$=2.0 Hz, 1H; H15), 6.93-6.88 (m, 2H; H9 and H10), 5.83-5.78 (m, 1H; NH urea), 5.75-5.71 (m, 1H; NH urea), 3.31-3.23 (m, 2H; H4), 3.04-2.99 (m, 2H; H2), 2.83 (q, $J$=7.5 Hz, 2H; H12), 2.77 (t, $J$=7.5 Hz, 2H; H5), 1.25 (t, $J$=7.5 Hz, 3H; H13), 0.98 (t, $J$=7.0 Hz, 3H; H1); **$^{13}$C NMR** (125 MHz, [D$_6$]DMSO, 25 °C) δ=158.0 (C3), 134.9 (C14), 127.1 (C11), 126.7 (C7), 122.2 (C15), 119.6 (C10), 118.5 (C9), 116.0 (C8), 112.4 (C6), 39.5 (C4), 34.0 (C2), 26.2 (C5), 23.7 (C12), 15.7 (C1), 14.4 (C13); **MS** $m/z$ (ES$^+$) 541 ([2M+Na]$^+$, 100%); **HRMS** (ES$^+$) exact mass calculated for [M+Na]$^+$ (C$_{15}$H$_{21}$N$_3$NaO$^+$) requires $m/z$ 282.1577, found $m/z$ 282.1585.

2.1.2.2 Synthesis and characterisation of 1-[2-(1H-indol-3-yl)ethyl]-3-(dodecyl)urea 5k

The title compound was synthesised according to general procedure II. Tryptamine (1.00 g, 6.24 mmol) was reacted with dodecylisocyanate (1.35 mL, 5.62 mmol) in CH$_2$Cl$_2$ (100 mL) for 14 hours. Product 5k was isolated in 70% yield (1.62 g) as a white powder.

**m.p.** 110-112 °C; **IR** (neat) ν=3431, 3353, 3322, 2920, 2848, 1618, 1583, 735; **$^1$H NMR** (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.74 (br. s., 1H; NH indole), 7.52 (d, $J$=7.5 Hz, 1H; H18), 7.33 (d, $J$=7.5 Hz, 1H; H21), 7.10 (d, $J$=2.0 Hz, 1H; H23), 7.06 (td, $J$=7.5, 1.0 Hz, 1H; H20), 6.96 (td,
$J$=7.5, 1.0 Hz, 1H; H19), 5.87 (t, $J$=5.5 Hz, 1H; NH urea), 5.82 (t, $J$=5.5 Hz, 1H; NH urea), 3.28-3.24 (m, 2H; H14), 2.97-2.93 (m, 2 H; H12), 2.77 (t, $J$=7.0 Hz, 2H; H15), 1.35-1.30 (m, 2H; H11), 1.28-1.14 (m, 18H; H2-H10), 0.83 (t, $J$=7.0 Hz, 3H; H1);

$^{13}$C NMR (125 MHz, [D$_6$]DMSO, 25 °C) δ= 158.4 (C13), 136.2 (C22), 127.2 (C17), 122.6 (C23), 120.9 (C20), 118.3 (C19), 118.2 (C18), 112.0 (C16), 111.3 (C21), 40.2 (C14), 39.2 (C12), 31.2 (1C of C2-C10), 29.9 (C11), 29.0 (1C, C2-C10), 29.0 (1C of C2-C10), 28.9 (1C of C2-C10), 28.7 (1C of C2-C10), 28.6 (1C of C2-C10), 28.6 (1C of C2-C10), 26.3 (1C of C2-C10), 26.0 (C15), 22.0 (1C of C2-C10), 13.9 (C1);

MS m/z (ES+) 743 ([2M+H]$^+$, 100%); HRMS (ES+) exact mass calculated for [M+Na]$^+$ (C$_{23}$H$_{37}$N$_3$NaO$^+$) requires m/z 394.2829, found m/z 394.2832.

2.1.2.3 Synthesis and characterisation of 1-[2-(1H-indol-3-yl)ethyl]-3-(4-fluorophenyl)urea 5l

The title compound was synthesised according to general procedure II. Tryptamine (1.00 g, 6.24 mmol) was reacted with 4-fluorophenylisocyanate (0.640 mL, 5.62 mmol) in CH$_2$Cl$_2$ (100 mL) for 14 hours. Product 5l was isolated in 99% yield (1.67 g) as a white powder.

m.p. 172-174 °C; IR (neat) ν=3368, 3292, 2918, 2877, 1556, 1505, 1219, 838, 738; $^1$H NMR (500 MHz, [D$_6$]DMSO, 25 °C) δ= 10.84 (br. s., 1H; NH indole), 8.52 (s, 1H; C4-NH urea), 7.58 (d, $J$=8.0 Hz, 1H; H12), 7.41-7.38 (m, 2H; H3 and H5), 7.35 (d, $J$=8.0 Hz, 1H; H15), 7.18 (d, $J$=2.0 Hz, 1H; H17), 7.09-7.03 (m, 3H; H2, H6 and H14), 6.98 (td, $J$=8.0, 1.5 Hz, 1H; H13), 6.11 (t, $J$=5.5 Hz, 1H; C8-NH urea), 3.42-3.36 (m, 2H; H8), 2.86 (t, $J$=7.5 Hz, 2H; H9); $^{13}$C NMR (125 MHz, [D$_6$]DMSO, 25 °C) δ= 156.8 (d, $J$=236 Hz, C1), 155.3 (C7), 136.9 (C4), 136.3 (C16), 127.2 (C11), 122.7 (C17), 120.9 (C14), 119.2 (d, $J$=8 Hz, C3 and C5), 118.3 (C13), 118.2 (C12), 115.1 (d, $J$=21 Hz, C2 and C6), 111.7 (C10), 111.4 (C15), 39.5 (C8), 25.8 (C9); MS m/z (ES+) 617 ([2M+Na]$^+$, 100%); HRMS (ES+) exact mass calculated for [M+Na]$^+$ (C$_{17}$H$_{16}$FN$_3$NaO$^+$) requires m/z 320.1170, found m/z 320.1166.
2.1.2.4 Synthesis and characterisation of 1-[2-(7-methyl-1H-indol-3-yl)ethyl)-3-(4-fluorophenyl)urea 5m

The title compound was synthesised according to general procedure II. 7-Methyltryptamine (500 mg, 2.87 mmol) was reacted with 4-fluorophenylisocyanate (0.290 mL, 2.58 mmol) in CH₂Cl₂ (50 mL) for 14 hours. Product 5m was isolated in 53% yield (476 mg) as a white powder.

**m.p.** 164-166 °C; **IR** (neat) ν=3414, 3322, 1630, 1570, 1506, 1215, 832, 748; **¹H NMR** (500 MHz, [D₆]DMSO, 25 °C) δ=10.81 (br. s., 1H; NH indole), 8.52 (s, 1H; C4-NH urea), 7.42-7.38 (m, 3H; H3, H5 and H12), 7.17 (d, J=2.0 Hz, 1H; H18), 7.07-7.04 (m, 2H; H2 and H6), 6.87-6.92 (m, 2H; H13 and H14), 6.10 (t, J=5.5 Hz, 1H; C8-NH urea), 3.46-3.39 (m, 2H; C9), 2.86 (t, J=7.0 Hz, 2H; H9), 2.45 (s, 3H; H16); **¹³C NMR** (125 MHz, [D₆]DMSO, 25 °C) δ=156.8 (d, J=240 Hz, C1), 155.2 (C7), 137.0 (C4), 135.8 (C17), 126.9 (C11), 122.5 (C18), 121.4 (C14), 120.4 (C15), 119.1 (d, J=8 Hz, C3 and C5), 118.5 (C13), 116.0 (C12), 115.1 (d, J=21 Hz, C2 and C6), 112.2 (C10), 39.5 (C8), 26.0 (C9), 16.8 (C16); **MS** m/z (ES⁺) 645 ([2M+Na]⁺, 100%); **HRMS** (ES⁺) exact mass calculated for [M+Na]⁺ (C₁₈H₁₈F₃N₃O⁺) requires m/z 334.1326, found m/z 334.1326.

2.1.2.5 Synthesis and characterisation of 1-[2-(1H-indol-3-yl)ethyl)-3-(4-methoxyphenyl)urea 5n

The title compound was synthesised according to general procedure II. Tryptamine (1.00 g, 6.24 mmol) was reacted with 4-methoxyphenylisocyanate (0.730 mL, 5.62 mmol) in CH₂Cl₂ (100 mL) for 14 hours. Product 5n was isolated in 99% yield (1.88 g) as a white powder.
**m.p.** 165-167 °C; **IR** (neat) ν=3370, 3288, 1624, 1556, 1506, 1244, 834, 745; **1H NMR** (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.84 (br. s., 1H; NH indole), 8.28 (s, 1H; C5-NH urea), 7.58 (d, J=7.5 Hz, 1H; H13), 7.36 (d, J=8.0 Hz, 1H; H16), 7.29 (dd, J=8.0, 1.5 Hz, 2H; H4 and H6), 7.18 (d, J=2.0 Hz, 1H; H18), 7.08 (td, J=7.5, 1.5 Hz, 1H; H15), 6.99 (td, J=8.0, 1.5 Hz, 1H; H14), 6.82 (dd, J=8.0, 1.5 Hz, 2H; H3 and H7), 6.03 (t, J=5.5 Hz, 1H; C9-NH urea), 3.71 (s, 3H; H1), 3.40-3.38 (m, 2H; H9), 2.86 (t, J=7.5 Hz, 2H; H10); **13C NMR** (125 MHz, [D$_6$]DMSO, 25 °C) δ=155.5 (C8), 153.9 (C2), 136.3 (C17), 133.7 (C5), 127.2 (C12), 122.7 (C18), 120.9 (C15), 119.4 (C4 and C6), 118.2 (C14), 118.2 (C13), 113.9 (C3 and C7), 111.8 (C11), 111.4 (C16), 55.1 (C1), 39.5 (C9), 25.9 (C10); **MS** m/z (ES+) 310 ([M+H]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ requires m/z 332.1369, found m/z 332.1369.

2.1.2.6 Synthesis and characterisation of 1-[2-(5-fluoro-1H-indol-3-yl)ethyl]-3-(4-methoxyphenyl]urea 5o

The title compound was synthesised according to general procedure II. 5-Fluorotryptamine (747 mg, 4.19 mmol) was reacted with 4-methoxyphenylisocyanate (0.490 mL, 3.77 mmol) in CH$_2$Cl$_2$ (75 mL) for 14 hours. Product 5o was isolated in 44% yield (605 mg) as a brown powder.

**m.p.** 179-181 °C; **IR** (neat) ν=3369, 3278, 2917, 1622, 1553, 1505, 1200, 1108, 834, 803; **1H NMR** (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.95 (br. s., 1H; NH indole), 8.28 (s, 1H; C5-NH urea), 7.37-7.31 (m, 2H; H13 and H15), 7.29-7.26 (m, 3H; H4, H6 and H18), 6.92 (td, J=9.0, 2.5 Hz, 1H; H16), 6.81 (d, J=9.0 Hz, 2H; H3 and H7), 6.02 (t, J=5.5 Hz, 1H; C9-NH urea), 3.70 (s, 3H; H1), 3.40-3.36 (m, 2H; H9), 2.82 (t, J=7.0 Hz, 2H; H10); **13C NMR** (125 MHz, [D$_6$]DMSO, 25 °C) δ=156.6 (d, J=231 Hz, C14), 155.4 (C8), 153.9 (C2), 133.7 (C5), 132.9 (C17), 127.5 (d, J=10 Hz, C12), 124.9 (C18), 119.4 (C4 and C6), 113.9 (C3 and C7), 112.2 (d, J=25 Hz, C15), 112.2 (C11), 109.1 (d, J=25 Hz, C16), 103.1 (d, J=21 Hz, C13), 55.1 (C1), 39.5 (C9), 25.8 (C10); **MS** m/z (ES+) 655 ([2M+H]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ requires m/z 350.1275, found m/z 350.1276.
2.1.2.7 Synthesis and characterisation of 1-[2-(7-ethyl-1H-indol-3-yl)ethyl]-3-(4-methoxyphenyl)urea 5p

The title compound was synthesised according to general procedure II. 7-Ethyltryptamine (500 mg, 2.66 mmol) was reacted with 4-methoxyphenylisocyanate (0.310 mL, 2.39 mmol) in CH₂Cl₂ (50 mL) for 14 hours. Product 5p was isolated in 45% yield (405 mg) as a pale brown powder.

m.p. 160-162 °C; IR (neat) ν=3454, 3426, 3391, 2966, 2934, 1630, 1575, 1245, 1030, 832, 738; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.80 (br. s., 1H; NH indole), 8.27 (s, 1H; C5-NH urea), 7.40 (d, J=7.5 Hz, 1H; H13), 7.28 (d, J=9.0 Hz, 2H; H4 and H6), 7.15 (d, J=2.5 Hz, 1H; H20), 6.94-6.88 (m, 2H; H14 and H15), 6.81 (d, J=9.0 Hz, 2H; H3 and H7), 6.01 (t, J=5.5 Hz, 1H; C8-NH urea), 3.42-3.36 (m, 2H; H9), 3.69 (s, 3H; H1), 2.82-2.86 (m, 4H; H10 and H17), 1.26 (t, J=7.5 Hz, 3H; H18); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=155.5 (C8), 153.9 (C2), 135.0 (C19), 133.7 (C5), 127.1 (C16), 126.8 (C12), 122.4 (C20), 119.6 (C15), 119.4 (C4 and C6), 118.6 (C14), 116.0 (C13), 113.9 (C3 and C7), 112.2 (C11), 55.1 (C1), 39.5 (C9), 26.0 (C10), 23.7 (C17), 14.4 (C18); MS m/z (ES+) 697 ([2M+Na]⁺, 100%); HRMS (ES+) exact mass calculated for [M+Na]⁺ (C₂₀H₂₃N₃NaO₂⁺) requires m/z 360.1682, found m/z 360.1681.
2.2 General procedure III for the enantioselective synthesis of products 9

(Thio)urea derivative 5 (1.0 eq.) was suspended in dry PhMe (200 mL/mmol) and enone 6 (5.0 eq.) was added in one portion at room temperature, immediately followed by the addition of catalyst 10a (0.10 eq.) in one portion. The resulting suspension was heated at 110 °C for the indicated time. The solvent was removed in vacuo and the residue was purified by flash column chromatography on silica gel to afford the desired cyclised products 9a-w. [Racemic samples were synthesised in an analogous manner to general procedure III, replacing catalyst 10a with p-TsOH (0.10 eq.).]

2.2.1 Synthesis and characterisation of (R)-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9a

The title compound was synthesised according to general procedure III. Urea derivative 5a (61 mg, 0.30 mmol) was reacted with methyl vinyl ketone 6a (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9a in 76% yield (58 mg) as a white powder.

73% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, t_r (major)=19.3 min; t_r (minor)=38.0 min; [α]_D²³⁺=+50 (c=0.08, MeOH).

m.p. 178-180 °C; IR (neat) ν=3406, 3284, 3228, 1633, 1508, 743; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.92 (br. s., 1H; NH indole), 7.40 (d, J=8.0 Hz, 1H; H8), 7.32 (d, J=8.0 Hz, 1H; H11), 7.06 (td, J=8.0, 1.0 Hz, 1H; H10), 6.97 (td, J=8.0, 1.0 Hz, 1H; H9), 6.45 (d, J=4.0 Hz, 1H; NH urea), 4.62 (dd, J=13.0, 4.5 Hz, 1H; H4’), 3.35-3.30 (m, 1H; H2’), 3.21-3.14 (m, 1H; H1’), 2.93 (td, J=13.0, 4.5 Hz, 1H; H4), 2.66-2.60 (m, 1H; H5’), 2.59-2.53 (m, 1H; H5), 2.40-2.37 (m, 1H; H1’), 1.75 (td, J=13.0, 5.5 Hz, 1H; H1), 1.54 (s, 3H; H15); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=154.3 (C3), 139.3 (C13), 135.9 (C12), 126.3 (C7), 120.9 (C10), 118.5 (C9), 117.9 (C8), 111.0 (C11), 106.1 (C6), 53.7 (C14), 35.9 (C4), 35.4 (C2), 33.8 (C1), 23.7 (C15), 21.3 (C5); MS m/z (ES+) 533 ([2M+Na]⁺, 100%); HRMS (ES+) exact mass calculated for [M+Na]⁺ (C₁₅H₁₇N₃NaO⁺) requires m/z 278.1264, found m/z 278.1267.
2.2.2 Synthesis and characterisation of \((R)\)-12b-heptyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-b]indol-4(12H)-one 9b

The title compound was synthesised according to general procedure III. Urea derivative 5a (20 mg, 0.10 mmol) was reacted with heptyl vinyl ketone 6c (77 mg, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH2Cl2/MeOH 95/5) to afford product 9b in 59% yield (20 mg) as a white powder.

78% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1 mL/min, 220 nm, \(t_r\) (major)=7.9 min; \(t_r\) (minor)=18.8 min); [\(\alpha\)]\textsubscript{D}\textsuperscript{23} =+40 (c=0.16, MeOH).

m.p. 112-114 °C; IR (neat) \(\nu=3405, 3227, 2925, 2853, 1632, 1504, 1449, 740, 703\); \(^1\)H NMR (500 MHz, [D\textsubscript{6}]DMSO, 25 °C) \(\delta=10.85\) (br. s., 1H; NH indole), 7.34-7.30 (m, 2H; H8 and H11), 7.06 (t, \(J=7.5\) Hz, 1H; H10), 6.97 (td, \(J=7.5, 1.0\) Hz, 1H; H9), 6.42 (d, \(J=3.5\) Hz, 1H; NH urea), 4.67 (dd, \(J=13.0, 5.0\) Hz, 1H; H4’), 3.27 (td, \(J=12.0, 4.5\) Hz, 1H; H2’), 3.12-3.08 (m, 1H; H2), 3.00 (td, \(J=13.0, 5.0\) Hz, 1H; H4), 2.67-2.63 (m, 1H; H5’), 2.58-2.53 (m, 1H; H5), 2.40-2.36 (m, 1H; H1’), 2.02-1.95 (m, 1H; H15’), 1.88-1.83 (m, 1H; H15), 1.74 (td, \(J=12.5, 5.5\) Hz, 1H; H1), 1.39-1.33 (m, 1H; H16’), 1.28-1.15 (m, 9H; H16-H20), 0.82 (t, \(J=7.0\) Hz, 3H; H21); \(^{13}\)C NMR (125 MHz, [D\textsubscript{6}]DMSO, 25 °C) \(\delta=154.7\) (C3), 137.8 (C13), 135.0 (C12), 126.2 (C7), 120.8 (C10), 118.4 (C9), 117.8 (C8), 111.1 (C11), 107.0 (C6), 56.5 (C14), 38.0 (C15), 37.0 (C4), 35.5 (C2), 32.8 (C1), 31.2 (1C of C17-C20), 29.7 (1C of C17-C20), 28.8 (1C of C17-C20), 24.6 (C16), 22.0 (1C of C17-C20), 21.0 (C5), 13.9 (C21); MS \(m/z\) (ES+) 701 ([2M+Na]\textsuperscript{+}, 100%); HRMS (ES+) exact mass calculated for [M+Na]\textsuperscript{+} (C\textsubscript{21}H\textsubscript{29}N\textsubscript{3}NaO\textsuperscript{+}) requires \(m/z\) 362.2203, found \(m/z\) 362.2204.
2.2.3 Synthesis and characterisation of (R)-9-methoxy-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9c

The title compound was synthesised according to general procedure III. Urea derivative 5b (47 mg, 0.20 mmol) was reacted with methyl vinyl ketone 6a (81 µL, 1.0 mmol) in PhMe (40 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9c in 77% yield (44 mg) as a white powder.

60% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, tᵣ (major)=27.9 min; tᵣ (minor)=43.8 min; [α]D²³=+71 (c=0.16, MeOH).
m.p. 140-142 °C; IR (neat) ν=3410, 3275, 2930, 1626, 1508, 1160, 800, 754; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.74 (br. s., 1H; NH indole), 7.19 (d, J=8.5 Hz, 1H; H12), 6.90 (d, J=2.5 Hz, 1H; H8), 6.70 (dd, J=8.5, 2.5 Hz, 1H; H11), 6.44 (d, J=3.5 Hz, 1H; NH urea), 4.61 (dd, J=13.0, 4.5 Hz, 1H; H4'), 3.75 (s, 3H; H10), 3.33-3.29 (m, 1H; H2'), 3.18-3.12 (m, 1H; H2), 2.91 (td, J=13.0, 4.5 Hz, 1H; H4), 2.61-2.53 (m, 2H; H5), 2.37-2.34 (m, 1H; H1'), 1.75 (td, J=13.0, 5.0 Hz, 1H; H1), 1.52 (s, 3H; H16); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=154.3 (C3), 153.1 (C9), 140.0 (C14), 131.0 (C13), 126.6 (C7), 111.6 (C12), 110.7 (C11), 106.0 (C6), 100.1 (C8), 55.4 (C10), 53.7 (C15), 35.9 (C4), 21.4 (C5), 35.4 (C2), 33.8 (C1), 23.7 (C16); MS m/z (ES⁺) 593 ([2M+Na]+, 100%); HRMS (ES⁺) exact mass calculated for [M+Na]⁺ (C₁₆H₁₉N₃NaO₂⁺) requires m/z 308.1369, found m/z 308.1370.

2.2.4 Synthesis and characterisation of (R)-9-fluoro-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9d

The title compound was synthesised according to general procedure III. Urea derivative 5c (15 mg, 0.07 mmol) was reacted with methyl vinyl ketone 6a (28 µL, 0.34 mmol) in PhMe (14 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9d in 75% yield (14 mg) as a yellow powder.

70% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, tᵣ (major)=22.6 min; tᵣ (minor)=49.3 min; [α]D²³=+99 (c=0.09, MeOH).
m.p. 168-170 °C; IR (neat) ν=3401, 3283, 2926, 1630, 1509, 1449, 1158, 801, 754; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=11.04 (br. s., 1H; NH indole), 7.29 (dd, J=9.0, 4.5 Hz, 1H;
H10), 7.09 (dd, J=9.5, 2.0 Hz, 1H; H8), 6.89 (td, J=9.0, 2.5 Hz, 1H; H11), 6.46 (d, J=4.0 Hz, 1H; NH urea), 4.61 (dd, J=13.0, 4.5 Hz, 1H; H4'), 3.20-3.10 (m, 1H; H2), 3.36-3.31 (m, 1H; H2'), 2.92 (td, J=13.0, 4.5 Hz, 1H; H4), 2.67-2.58 (m, 1H; H5'), 2.57-2.53 (m, 1H; H5), 1.75 (td, J=13.0, 5.5 Hz, 1H; H1); 1.53 (s, 3H; H15), 13C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=156.8 (d, J=230 Hz, C9), 154.3 (C3), 141.5 (C13), 134.4 (C12), 127.4 (C7), 123.1 (C9), 120.7 (C10), 117.3 (C8), 112.5 (C11), 106.3 (C6), 53.7 (C14), 35.8 (C4), 35.3 (C2), 33.6 (C1), 23.6 (C15), 21.1 (C5); MS m/z (ES+) 288 ([M-H]+' 100%), HRMS (ES+) exact mass calculated for [M+Na]⁺ (C₁₅H₁₆ClN₂NaO⁺) requires m/z 312.0874, found m/z 312.0869.

2.2.5 Synthesis and characterisation of (R)-9-chloro-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-b]indol-4(12H)-one 9e

The title compound was synthesised according to general procedure III. Urea derivative 5d (24 mg, 0.10 mmol) was reacted with methyl vinyl ketone 6a (41 µL, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9e in 77% yield (23 mg) as a pale brown powder.

68% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 300 nm, t_r (major)=21.4 min; t_r (minor)=51.9 min); [α]_D²³+96 (c=0.09, MeOH).

m.p. 160-162 °C; IR (neat) ν=3305, 3188, 2917, 1632, 1507, 1433, 800, 759; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=11.16 (br. s., 1H; NH indole), 7.44 (d, J=2.0 Hz, 1H; H8), 7.32 (d, J=8.5 Hz, 1H; H11), 7.06 (dd, J=8.5, 2.0 Hz, 1H; H10), 6.47 (br. s., 1H; NH urea), 4.61 (dd, J=13.0, 4.5 Hz, 1H; H4'), 3.32-3.37 (m, 1H; H2'); 2.91 (td, J=13.0, 4.5 Hz, 1H; H4), 2.67-2.58 (m, 1H; H5'), 2.57-2.53 (m, 1H; H5), 1.75 (td, J=13.0, 5.5 Hz, 1H; H1)), 1.53 (s, 3H; H15); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=154.2 (C3), 141.2 (C13), 134.4 (C12), 127.4 (C7), 123.1 (C9), 120.7 (C10), 117.3 (C8), 112.5 (C11), 106.3 (C6), 53.7 (C14), 35.8 (C4), 35.3 (C2), 33.6 (C1), 23.6 (C15), 21.1 (C5); MS m/z (ES-) 288 ([M-H]' 100%), HRMS (ES+) exact mass calculated for [M+Na]⁺ (C₁₅H₁₆ClN₂NaO⁺) requires m/z 312.0874, found m/z 312.0869.
2.2.6 Synthesis and characterisation of (R)-10-fluoro-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]pyrido[3,4-b]indol-4(12H)-one 9f

The title compound was synthesised according to general procedure III. Urea derivative 5e (20 mg, 0.09 mmol) was reacted with methyl vinyl ketone 6a (37 µL, 0.45 mmol) in PhMe (18 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9f in 73% yield (20 mg) as a yellow oil.

67% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, t_r (major)=20.8 min; t_r (minor)=42.0 min; [α]_D^{23} =+70 (c=0.13, MeOH).

IR (neat) ν=3275, 2966, 2924, 2854, 1629, 1505, 1472, 1378, 1282, 1259, 1114, 954; ^1H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=11.06 (br. s., 1H; NH indole). 7.39 (dd, J=8.5, 5.5 Hz, 1H; H8), 7.09 (dd, J=10.0, 2.0 Hz, 1H; H11), 6.83 (ddd, J=10.0, 8.5, 2.0 Hz, 1H; H9), 6.45 (d, J=4.0 Hz, 1H; NH urea), 4.61 (dd, J=12.5, 4.0 Hz, 1H; H4'), 3.19-3.11 (m, 1H; H2'), 3.38-3.31 (m, 1H; H2'), 2.91 (td, J=12.5, 4.0 Hz, 1H; H4), 2.66-2.59 (m, 1H; H5'), 2.57-2.53 (m, 1H; H5), 2.38-2.35 (m, 1H; H1'), 1.74 (td, J=13.0, 5.5 Hz, 1H; H1), 1.52 (s, 3H; H15); ^13C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=158.7 (d, J=233 Hz, C10), 154.3 (C3), 139.9 (C13), 135.8 (d, J=10 Hz, C12), 123.1 (C7), 118.9 (d, J=10 Hz, C8), 106.7 (d, J=25 Hz, C9), 106.4 (C6), 97.2 (d, J=25 Hz, C11), 53.7 (C14), 35.8 (C4), 35.3 (C2), 33.7 (C1), 23.6 (C15), 21.2 (C5); MS m/z (ES+) 547 ([2M+H]^+, 100%); HRMS (ES+) exact mass calculated for [M+Na]^+ (C₁₅H₁₆FN₃NaO^+)) requires m/z 296.1170, found m/z 296.1164.

2.2.7 Synthesis and characterisation of (R)-11,12b-dimethyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]pyrido[3,4-b]indol-4(12H)-one 9g

The title compound was synthesised according to general procedure III. Urea derivative 5f (65 mg, 0.30 mmol) was reacted with methyl vinyl ketone 6a (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9g in 78% yield (63 mg) as a white powder.

92% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, t_r (major)=12.2 min; t_r (minor)=14.4 min; [α]_D^{23} =+133 (c=0.22, MeOH).
2.2.8 Synthesis and characterisation of \((R)-12b\text{-ethyl-11-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-b]indol-4(12\text{H})\text{-one 9h}}

The title compound was synthesised according to general procedure III. Urea derivative 5f (65 mg, 0.30 mmol) was reacted with ethyl vinyl ketone 6b (0.15 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH\text{2}Cl\text{2}/MeOH 95/5) to afford product 9h in 74% yield (63 mg) as a brown powder.

92% ee (Chiralcel AD 95:5 Hexane:Isopropanol, 1.0 mL/min, 220 nm, \(t_r\) (major)=29.9 min; \(t_r\) (minor)=50.9 min; \([\alpha]_D^{23}=+103\) (c=0.13, MeOH).
2.2.9 Synthesis and characterisation of (R)-11-methyl-12b-heptyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9i

The title compound was synthesised according to general procedure III. Urea derivative 5f (22 mg, 0.10 mmol) was reacted with heptyl vinyl ketone 6c (77 mg, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH$_2$Cl$_2$/MeOH 95/5) to afford product 9i in 54% yield (19 mg) as a yellow powder.

90% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, $t_r$ (major)=7.7 min; $t_r$ (minor)=11.8 min); [$\alpha$]$_D^{23}$ =+42 ($c$=0.25, MeOH).

m.p. 187-189 °C; IR (neat) ν=3309, 3286, 3195, 2921, 2853, 1633, 1513, 1449, 1026, 746, 700; $^1$H NMR (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.47 (br. s., 1H; NH indole), 7.31 (d, $J$=7.5 Hz, 1H; H8), 6.90-6.85 (m, 2H; H9 and H10), 6.41 (d, $J$=3.0 Hz, 1H; NH urea), 4.68 (dd, $J$=13.0, 5.0 Hz, 1H; H4'), 3.33-3.25 (m, 1H; H2'), 3.12-3.10 (m, 1H; H2), 2.97 (td, $J$=13.0, 5.0 Hz, 1H; H4), 2.66-2.60 (m, 1H; H5'), 2.56-2.51 (m, 1H; H5), 2.50-2.48 (m, 1H; H1'), 2.47 (s, 3H; H12), 2.00-1.94 (m, 2H; H16), 1.78 (td, $J$=13.0, 5.5 Hz, 1H; H1), 1.40-1.33 (m, 1H; H17'), 1.25-1.19 (m, 9H; H17-H21), 0.82 (t, $J$=7.0 Hz, 3H; H22); $^{13}$C NMR (125 MHz, [D$_6$]DMSO, 25 °C) δ=154.9 (C3), 137.7 (C14), 135.5 (C13), 125.9 (C7), 121.6 (C10), 120.2 (C11), 118.6 (C9), 115.3 (C8), 107.6 (C6), 56.7 (C15), 38.1 (C16), 37.2 (C4), 35.5 (C2), 33.1 (C1), 31.2 (1C of C18-C21), 29.6 (1C of C18-C21), 28.5 (1C of C18-C21), 24.6 (C17), 22.0 (1C of C18-C21), 21.0 (C5), 17.1 (C12), 13.9 (C22); MS $m/z$ (ES+) 354 ([M+H]$^+$, 100%); HRMS (ES+) exact mass calculated for [M+Na]$^+$ (C$_{22}$H$_{31}$N$_3$NaO$^+$) requires $m/z$ 376.2359, found $m/z$ 376.2356.
2.2.10 Synthesis and characterisation of (R)-11-ethyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1′,6′:1,2]pyrido[3,4-b]indol-4(12H)-one 9j

The title compound was synthesised according to general procedure III. Urea derivative 5g (23 mg, 0.10 mmol) was reacted with methyl vinyl ketone 6a (41 µL, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9j in 71% yield (20 mg) as a pale brown powder.

92% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, t<sub>r (major)</sub>=27.6 min; t<sub>r (minor)</sub>=38.8 min); [α]<sub>D</sub><sup>23</sup>=+98 (c=0.12, MeOH).

m.p. 288-290 °C (dec.); IR (neat) ν=3412, 3285, 2967, 2931, 1633, 1506, 1352, 1153, 794; <sup>1</sup>H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.57 (br. s., 1H; NH indole), 7.22 (d, J=7.5 Hz, 1H; H8), 6.93-6.88 (m, 2H; H9 and H10), 6.43 (d, J=4.0 Hz, 1H; NH urea), 4.61 (dd, J=13.0, 4.5 Hz, 1H; H4'), 3.38-3.22 (m, 1H; H2'), 3.21-3.12 (m, 1H; H2), 2.92 (td, J=13.0, 4.5 Hz, 1H; H4), 2.86 (q, J=7.5 Hz, 2H; H12), 2.60-2.55 (m, 3H; H1' and H5), 1.73 (td, J=13.0, 5.5 Hz, 1H; H1), 1.57 (s, 3H; H17), 1.27 (t, J=7.5 Hz, 3H; H13); <sup>13</sup>C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=154.3 (C3), 139.0 (C15), 134.6 (C14), 126.6 (C11), 126.1 (C7), 119.7 (C10), 118.8 (C9), 115.5 (C8), 106.6 (C6), 53.8 (C16), 35.8 (C4), 35.4 (C2), 33.6 (C1), 23.7 (C17), 23.4 (C12), 21.4 (C5), 14.5 (C13); MS m/z (ES+) 567 ([2M+H]<sup>+</sup>), 100%; HRMS (ES+) exact mass calculated for [M+Na]<sup>+</sup> (C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>NaO<sup>+</sup>) requires m/z 306.1577, found m/z 306.1577.

2.2.11 Synthesis and characterisation of (R)-2,2,11,12b-tetramethyl-1,2,3,6,7,12b-hexahydropyrimido[1′,6′:1,2]pyrido[3,4-b]indol-4(12H)-one 9k

The title compound was synthesised according to general procedure III. Urea derivative 5f (65 mg, 0.30 mmol) was reacted with mesityl oxide 6e (0.17 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9k in 78% yield (70 mg) as an off-white powder.

43% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 0.7 mL/min, 220 nm, t<sub>r (minor)</sub>=16.7 min; t<sub>r (major)</sub>=18.6 min); [α]<sub>D</sub><sup>23</sup>=+91 (c=0.09, MeOH).
m.p. 288-290 °C (dec.); IR (neat) ν=3261, 3193, 2962, 2928, 1608, 1484, 1421, 1185, 778, 744; \(^1\)H NMR (500 MHz, [D\(_6\)]DMSO, 25 °C) δ=10.57 (s, 1H; NH indole), 7.20 (d, \(J=7.5\) Hz, 1H; H9), 6.94-6.79 (m, 2H; H10 and H11), 6.46 (s, 1H; NH urea), 2.65-2.55 (m, 2H; H6), 2.46 (s, 3H; H13), 2.34 (d, \(J=14.0\) Hz, 1H; H1'), 2.23 (d, \(J=14.0\) Hz, 1H; H1), 1.63 (s, 3H; H17), 1.26 (s, 3H; H3'), 0.92 (s, 3H; H3);

13C NMR (125 MHz, [D\(_6\)]DMSO, 25 °C) δ=155.3 (C4), 139.6 (C15), 135.2 (C14), 126.1 (C8), 121.5 (C11), 120.2 (C12), 118.6 (C10), 115.3 (C9), 106.1 (C7), 54.1 (C16), 48.3 (C2), 45.8 (C1), 36.4 (C5), 30.6 (C3'), 30.5 (C3), 27.1 (C17), 20.9 (C6), 17.0 (C13); MS m/z (ES+) 595 ([2M+H]+, 100%); HRMS (ES+) exact mass calculated for [M+Na]+ (C\(_{18}\)H\(_{23}\)N\(_3\)NaO\(_7\)+) requires m/z 320.1733, found m/z 320.1724.

### 2.2.12 Synthesis and characterisation of (R)-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-b]indol-4(12H)-thione 9l

The title compound was synthesised according to general procedure III. Thiourea derivative 5h (66 mg, 0.30 mmol) was reacted with methyl vinyl ketone 6a (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH\(_2\)Cl\(_2\)/MeOH 95/5) to afford product 9l in 72% yield (59 mg) as a white powder.

31% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 240 nm, \(t_r\) (major)=15.3 min; \(t_r\) (minor)=33.5 min); [\(\alpha\)]\(_{D}^{23}\)=+38 (c=0.40, MeOH).

m.p. 153-155 °C; IR (neat) ν=3403, 3236, 2975, 2933, 1521, 1493, 1328, 1176, 748; \(^1\)H NMR (500 MHz, [D\(_6\)]DMSO, 25 °C) δ=10.98 (br. s., 1H; NH indole), 8.26 (d, \(J(H,H)=4.5\) Hz, 1H; NH urea), 7.43 (d, \(J(H,H)=7.5\) Hz, 1H; H8), 7.33 (d, \(J(H,H)=8.0\) Hz, 1H; H11), 7.08 (td, \(J(H,H)=8.0, 1.5\) Hz, 1H; H10), 6.99 (td, \(J(H,H)=7.5, 1.5\) Hz, 1H; H9), 5.66-5.61 (m, 1H; H4'), 3.34-3.26 (m, 2H; H2' and H4), 3.23-3.11 (m, 1H; H2), 2.69-2.65 (m, 2H; H5), 2.53-2.49 (m, 1H; H1'), 1.77 (td, \(J(H,H)=13.0, 5.5\) Hz, 1H; H1), 1.61 (s, 3H; H15); 13C NMR (125 MHz, [D\(_6\)]DMSO, 25 °C) δ=176.5 (C3), 138.0 (C13), 136.1 (C12), 126.9 (C7), 124.8 (C15), 120.8 (C14), 118.6 (C9), 118.0 (C8), 111.1 (C11), 106.4 (C6), 55.3 (C14), 43.6 (C4), 36.2 (C2), 33.0 (C1), 24.0 (C15), 20.8 (C5); MS m/z (ES+) 565 ([2M+Na]+, 100%); HRMS (ES+) exact mass calculated for [M+Na]+ (C\(_{15}\)H\(_{17}\)N\(_3\)NaO\(_7\)+) requires m/z 294.1035, found m/z 294.1030.
2.2.13 Synthesis and characterisation of \((R)-3\text{-ethyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido}[1',6':1,2]pyrido[3,4-b]indol-4(12H)-one\) 9m

The title compound was synthesised according to general procedure III. Urea derivative 5i (69 mg, 0.30 mmol) was reacted with methyl vinyl ketone 6a (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/Acetone 95/5) to afford product 9m in 73% yield (62 mg) as a yellow powder.

83% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, \(t_r\) (major)=18.2 min; \(t_r\) (minor)=32.9 min); \([\alpha]_D^{23}=+110\) (c=0.12, MeOH).

m.p. 263-265 °C (dec.); IR (neat) ν=3406, 3233, 3195, 2972, 2928, 1604, 1403, 1453, 1352, 1297, 1279, 741; \(^1\)H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.92 (br. s., 1H; NH indole), 7.40 (d, \(J=8.0\) Hz, 1H; H8), 7.31 (d, \(J=8.0\) Hz, 1H; H11), 7.06 (td, \(J=8.0, 1.5\) Hz, 1H; H10), 6.97 (td, \(J=8.0, 1.5\) Hz, 1H; H9), 4.64 (dd, \(J=13.0, 4.5\) Hz, 1H; H4’), 3.48 (td, \(J=12.5\) Hz, 1H; H2’), 3.41-3.35 (m, 1H; H16’), 3.27-3.15 (m, 2H; H16 and H2), 2.93 (td, \(J=13.0, 4.5\) Hz, 1H; H4), 2.64-2.59 (m, 2H; H5), 2.49-2.45 (m, 1H; H1’), 1.83 (td, \(J=12.5, 5.5\) Hz, 1H; H1), 1.52 (s, 3H; H15), 0.71 (t, \(J=7.0\) Hz, 3H; H17); \(^{13}\)C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=153.8 (C3), 139.3 (C13), 136.0 (C12), 126.2 (C7), 120.9 (C10), 118.5 (C9), 117.9 (C8), 111.0 (C11), 106.2 (C6), 53.8 (C14), 42.2 (C16), 41.3 (C2), 36.6 (C4), 33.7 (C1), 23.4 (C15), 21.3 (C5), 12.6 (C17); MS m/z (ES⁺) 589 ([2M+Na]⁺, 100%); HRMS (ES⁺) exact mass calculated for [M+Na]⁺ (C₁₇H₂₁N₃NaO⁺) requires m/z 306.1577, found m/z 306.1575.

2.2.14 Synthesis and characterisation of \((R)-3,12b\text{-diethyl-1,2,3,6,7,12b-hexahydropyrimido}[1',6':1,2]pyrido[3,4-b]indol-4(12H)-one\) 9n

The title compound was synthesised according to general procedure III. Urea derivative 5i (69 mg, 0.30 mmol) was reacted with ethyl vinyl ketone 6b (0.15 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/Acetone 95/5) to afford product 9n in 73% yield (65 mg) as a pale yellow powder.

86% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, \(t_r\) (major)=13.6 min; \(t_r\) (minor)=22.5 min); \([\alpha]_D^{23}=+144\) (c=0.07, MeOH).
m.p. 188-190 °C; IR (neat) ν=3234, 2971, 2933, 1604, 1452, 1348, 741; $^1$H NMR (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.85 (br. s., 1H; NH indole), 7.41 (d, $J$=8.0 Hz, 1H; H8), 7.33 (d, $J$=8.0 Hz, 1H; H11), 7.06 (td, $J$=8.0, 1.5 Hz, 1H; H10), 6.97 (td, $J$=8.0, 1.5 Hz, 1H; H9), 4.70 (dd, $J$=13.0, 4.5 Hz, 1H; H4'), 3.43-3.35 (m, 1H; H2'), 3.41-3.29 (m, 1H; H17'), 3.26-3.20 (m, 1H; H17), 3.19-3.11 (m, 1H; H2'), 3.04 (td, $J$=13.0, 4.5 Hz, 1H; H4'), 2.67-2.63 (m, 1H; H5'), 2.60-2.52 (m, 1H; H5), 2.47-2.42 (m, 1H; H17'), 2.02-1.95 (m, 1H; H17'), 1.94-1.90 (m, 1H; H15), 1.86 (td, $J$=13.0, 4.0 Hz, 1H; H1), 1.02 (t, $J$=7.5 Hz, 3H; H18), 0.89 (t, $J$=7.5 Hz, 3H; H19); 13C NMR (125 MHz, [D$_6$]DMSO, 25 °C) δ=154.2 (C3), 137.6 (C13), 136.1 (C12), 126.2 (C7), 120.9 (C10), 118.4 (C9), 117.8 (C8), 111.1 (C11), 107.2 (C6), 56.9 (C14), 42.2 (C17), 40.5 (C2), 37.6 (C4), 32.2 (C1), 30.5 (C15), 21.0 (C5), 12.5 (C18), 9.5 (C16); MS m/z (ES+) 617 ([2M+Na]$^+$, 100%); HRMS (ES+) exact mass calculated for [M+Na]$^+$ (C$_{18}$H$_{23}$N$_3$NaO$^+$) requires m/z 320.1733, found m/z 320.1731.

2.2.15 Synthesis and characterisation of (R)-3,11-diethyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-b]indol-4(12H)-one 9o

The title compound was synthesised according to general procedure III. Urea derivative 5j (78 mg, 0.30 mmol) was reacted with methyl vinyl ketone 6a (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH$_2$Cl$_2$/MeOH 95/5) to afford product 9o in 76% yield (71 mg) as a red oil. 90% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, $t_r$ (major)=8.5 min; $t_r$ (minor)=12.0 min); [$\alpha$]$^D_{23}$=+109 ($c$=0.78, MeOH).

IR (neat) ν=3262, 2967, 2931, 2872, 1604, 1455, 1355, 1277, 1176, 741; $^1$H NMR (500 MHz, [D$_6$]DMSO, 25 °C) δ=10.57 (br. s., 1H; NH indole), 7.22 (d, $J$=7.5 Hz, 1H; H8), 6.93-6.88 (m, 2H; H9 and H10), 4.65 (dd, $J$=13.0, 5.0 Hz, 1H; H4'), 3.49 (td, $J$=12.0, 4.5 Hz, 1H; H2'), 3.45-3.38 (m, 1H; H18'), 3.25-3.18 (m, 2H; H2 and H18), 2.93 (td, $J$=13.0, 5.0 Hz, 1H; H4'), 2.86 (q, $J$=7.5 Hz, 2H; H12), 2.63-2.53 (m, 3H, H1' and H5), 1.82 (td, $J$=13.0, 5.5 Hz, 1H; H1), 1.55 (s, 3H; H17), 1.27 (t, $J$=7.5 Hz, 3H; H13), 1.04 (t, $J$=7.5 Hz, 3H; H19); 13C NMR (125 MHz, [D$_6$]DMSO, 25 °C) δ=153.8 (C3), 139.0 (C15), 134.6 (C14), 126.6 (C11), 126.0 (C7), 119.7 (C10), 118.8 (C9), 115.5 (C8), 106.7 (C6), 56.9 (C16), 42.2 (C18), 40.4 (C2), 36.5 (C4), 33.5 (C1), 23.7 (C12), 23.12 (C17), 21.4 (C5), 14.5 (C13), 12.6 (C19); MS m/z (ES+) 645 ([2M+Na]$^+$, 100%); HRMS (ES+) exact mass calculated for [M+Na]$^+$ (C$_{19}$H$_{25}$N$_3$NaO$^+$) requires m/z 334.1890, found m/z 334.1888.
2.2.16 Synthesis and characterisation of \((R)-3\text{-dodecyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-b]indol-4(12H)-one} \text{9p}\)

The title compound was synthesised according to general procedure III. Urea derivative \(5k\) (0.11 g, 0.30 mmol) was reacted with methyl vinyl ketone \(6a\) (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CHCl\(_2\)/MeOH 95/5) to afford product \(9p\) in 75% yield (95 mg) as an orange oil.

87% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, \(t_\text{r (major)}\)=11.3 min; \(t_\text{r (minor)}\)=19.1 min); \([\alpha]_D^{23} = +80\) (c=0.56, MeOH).

\(\text{IR (neat)} v=3231, 2923, 2852, 1602, 1502, 1453, 1352, 1297, 1275, 1173, 739; \text{\(1H NMR (500 MHz, [D_6]DMSO, 25 ^\circ\text{C}\)} \delta=10.91 \text{ (br. s., 1H; NH indole), 7.39 (d, \(J=8.0\text{ Hz, 1H; H8}), 7.31 (d, \(J=8.0\text{ Hz, 1H; H11}), 7.06 (td, \(J=8.0, 1.0\text{ Hz, 1H; H10}), 6.97 (td, \(J=8.0, 1.0\text{ Hz, 1H; H9}), 4.65 (dd, \(J=13.0, 4.5\text{ Hz, 1H; H4'}\)), 3.47 (td, \(J=13.0, 4.0\text{ Hz, 1H; H2'}\)), 3.41-3.36 (m, 1H; H16'), 3.24-3.19 (m, 1H; H2), 3.15-3.07 (m, 1H; H16), 2.94 (td, \(J=13.0, 4.5\text{ Hz, 1H; H4'}\)), 2.65-2.60 (m, 1H; H5'), 2.58-2.54 (m, 1H; H5), 2.46-2.39 (m, 1H; H1'), 1.83 (td, \(J=13.0, 5.5\text{ Hz, 1H; H1'}\)), 1.52 (s, 3H; H15), 1.49-1.42 (m, 2H; H17), 1.29-1.20 (m, 18H; H18-H26), 0.86 (t, \(J=7.5\text{ Hz, 3H; H27}); \text{\(13C NMR (125 MHz, [D_6]DMSO, 25 ^\circ\text{C}\)} \delta=154.0 \text{ (C3), 139.3 (C13), 136.0 (C12), 126.2 (C7), 120.9 (C10), 118.4 (C9), 117.9 (C8), 111.0 (C11), 106.2 (C6), 53.8 (C14), 47.5 (C16), 41.0 (C2), 36.7 (C4), 33.7 (C1), 31.3 (C1 of C18-C26), 29.0 (C1 of C18-C26), 29.0 (C1 of C18-C26), 29.1 (C1 of C18-C26), 29.0 (C1 of C18-C26), 28.8 (C1 of C18-C26), 28.7 (C1 of C18-C26), 28.1 (C17), 26.3 (C1 of C18-C26), 23.5 (C15), 22.1 (C1 of C18-C26), 21.3 (C5), 13.9 (C27); \text{MS m/z (ES+)} 869 ([2M+Na]^+, 100%); \text{HRMS (ES+)} \text{exact mass calculated for [M+Na]^+ (C}_{27}\text{H}_{41}\text{N}_3\text{NaO}^+\text{ requires m/z 446.3142, found m/z 446.3139.}
2.2.17 Synthesis and characterisation of (S)-3-dodecyl-12b-phenyl-1,2,3,6,7,12b-
hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9q

The title compound was synthesised according to general procedure III. Urea derivative 5k (37 mg, 0.10 mmol) was reacted with phenyl vinyl ketone 6d (66 µL, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9q in 64% yield (31 mg) as a brown powder.

71% ee (Chiralcel AD 90:10 Hexane:Isopropanol, 1.0 mL/min, 220 nm, t_r (major)=16.1 min; t_r (minor)=18.8 min; [α]_D^23 = -128 (c=0.50, MeOH).

m.p. 187-189 °C; IR (neat) ν=3257, 2922, 2852, 1603, 1496, 1453, 1354, 1272, 742, 701; ^1H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=11.35 (br. s., 1H; NH indole), 7.45-7.37 (m, 6H; H8, H11, H16, H17, H19 and H20), 7.34-7.28 (m, 1H; H18), 7.11 (td, J=7.5, 1.0 Hz, 1H; H10), 6.99 (td, J=7.5, 1.0 Hz, 1H; H9), 4.74 (dd, J=13.0, 5.0 Hz, 1H; H4’), 3.45-3.39 (m, 1H; H2’), 3.17-3.01 (m, 2H; H2 and H21’), 2.99-2.89 (m, 1H; H21), 2.82 (td, J=13.0, 5.0 Hz, 1H; H4), 2.74-2.66 (m, 2H; H1’ and H5’), 2.62-2.58 (m, 1H; H5), 2.30 (td, J=13.0, 5.0 Hz, 1H; H1), 1.43-1.35 (m, 2H; H22), 1.25-1.07 (m, 18H; H23-H31), 0.86 (t, J=7.5 Hz, 3H; H32); ^13C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=155.0 (C3), 143.4 (C15), 136.3 (C13 or C12), 136.2 (C12 or C13), 128.5 (C17 and C19), 127.2 (C18), 126.3 (C7), 125.7 (C16 and C20), 121.3 (C10), 118.7 (C9), 118.1 (C8), 111.2 (C11), 107.9 (C6), 61.3 (C14), 47.4 (C21), 41.1 (C2), 38.5 (C4), 35.4 (C1), 31.3 (C31 or C30), 29.1 (1C of C23-C29), 29.0 (1C of C23-C29), 28.9 (1C of C23-C29), 28.8 (1C of C23-C29), 28.7 (1C of C23-C29), 28.6 (1C of C23-C29), 27.0 (C22), 26.1 (1C of C23-C29), 22.1 (C30 or C31), 20.9 (C5), 14.0 (C32); MS m/z (ES+) 508 ([M+Na]+, 100%); HRMS (ES−) exact mass calculated for [M−H]− (C₃₂H₄₂N₆O³⁻) requires m/z 484.3333, found m/z 484.3332.
2.2.18 Synthesis and characterisation of (R)-3-(4-fluorophenyl)-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9r

The title compound was synthesised according to general procedure III. Urea derivative 5l (90 mg, 0.30 mmol) was reacted with methyl vinyl ketone 6a (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9r in 74% yield (78 mg) as a white powder.

83% ee (Chiralcel AD 60:40 Hexane:Isopropanol, 1.0 mL/min, 240 nm, tᵣ (major)=4.2 min; tᵣ (minor)=11.6 min; [α]D²³⁺=+100 (c=0.05, MeOH).
The sample has been recrystallised from MeOH to give crystals suitable for X-Ray (99% ee).
m.p. 190-191 °C; IR (neat) ν=3401, 3273, 2932, 1622, 1509, 1454, 1214, 835, 745; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.99 (br. s., 1H; NH indole), 7.43 (d, J=7.5 Hz, 1H; H8), 7.36-7.32 (m, 3H; H11, H17 and H21), 7.17-7.14 (m, 2H; H18, H20), 7.09 (td, J=13.0, 5.0 Hz, 1H; H4’), 4.67 (dd, J=13.0, 5.0 Hz, 1H; H4’), 3.94 (td, J=12.0, 4.0 Hz, 1H; H2’), 3.55 (dd, J=12.0, 4.0 Hz, 1H; H2’), 3.06 (td, J=13.0, 5.0 Hz, 1H; H4), 2.72-2.61 (m, 2H; H5), 2.57-2.54 (m, 1H; H1’), 2.08 (td, J=12.0, 5.5 Hz, 1H; H1), 1.68 (s, 3H; H15); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=159.3 (d, J=240 Hz, C19), 153.4 (C3), 140.8 (C16), 139.1 (C13), 136.0 (C12), 128.0 (d, J=9 Hz, C17 and C21), 126.2 (C7), 121.0 (C10), 118.5 (C9), 118.0 (C8), 114.9 (d, J=23 Hz, C18 and C20), 111.1 (C11), 106.2 (C6), 54.5 (C14), 44.3 (C2), 37.0 (C4), 34.0 (C1), 24.3 (C15), 21.2 (C5); MS m/z (ES⁺) 721 ([2M+Na]⁺, 100%); HRMS (ES⁺) exact mass calculated for [M+Na]⁺ (C₂₁H₂₀FN₃NaO⁺) requires m/z 372.1483, found m/z 372.1488.

2.2.19 Synthesis and characterisation of (R)-3-(4-fluorophenyl)- 12b-heptyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9s

The title compound was synthesised according to general procedure III. Urea derivative 5l (30 mg, 0.10 mmol) was reacted with heptyl vinyl ketone 6c (77 mg, 0.5 mmol) in PhMe (20 mL) for...
15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9s in 55% yield (24 mg) as a white powder.

85% ee (Chiralcel AD 80:20 Hexane:Isopropanol, 1.0 mL/min, 220 nm, tᵣ (major)=5.8 min; tᵣ (minor)=15.4 min); [α]²³⁺+=118 (c=0.31, MeOH).

m.p. 108-110 °C; IR (neat) ν=3270, 2924, 2853, 1616, 1596, 1509, 1448, 1215, 835, 743; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.92 (br. s., 1H; NH indole), 7.43 (d, J=7.5 Hz, 1H; H8), 7.37-7.30 (m, 3H; H11, H23 and H27), 7.19-7.13 (m, 2H; H24 and H26), 7.08 (td, J=7.5, 1.5 Hz, 1H; H10), 6.99 (td, J=13.5, 4.5 Hz, 1H; H4’), 3.78 (td, J=11.5, 4.0 Hz, 1H; H2), 3.56-3.51 (m, 1H; H2), 3.13 (td, J=13.5, 4.5 Hz, 1H; H4), 2.72-2.60 (m, 2H; H5), 2.59-2.51 (m, 1H; H1’), 2.12-2.06 (m, 2H; H1 and H15’), 2.03-1.98 (m, 1H; H15), 1.49-1.46 (m, 1H; H16’), 1.41-1.38 (m, 1H; H16), 1.27-1.18 (m, 8H; H17-H20), 0.84 (t, J=7.0 Hz, 3H; H21); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=159.3 (d, J=240 Hz, C25), 153.9 (C3), 140.8 (C22), 137.7 (C13), 136.1 (C12), 127.8 (d, J=10 Hz, C23 and C27), 126.2 (C7), 121.0 (C10), 118.5 (C9), 117.9 (C8), 114.9 (d, J=21 Hz, C24 and C26), 111.1 (C11), 107.1 (C6), 57.3 (C14), 44.4 (C2), 38.4 (C15), 37.8 (C4), 32.9 (C1), 31.2 (1C of C17-C20), 29.5 (1C of C17-C20), 28.6 (1C of C17-C20), 24.5 (C16), 22.0 (1C of C17-C20), 20.9 (C5), 13.9 (C21); MS m/z (ES+) 434 ([M+H]+, 100%); HRMS (ES+) exact mass calculated for [M+Na]+ (C₂₇H₃₂FN₃NaO⁺) requires m/z 456.2422, found m/z 456.2416.

2.2.20 Synthesis and characterisation of (R)-3-(4-fluorophenyl)-11-methyl-12b-ethyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9t

The title compound was synthesised according to general procedure III. Urea derivative 5m (93 mg, 0.30 mmol) was reacted with ethyl vinyl ketone 6b (0.15 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9t in 75% yield (85 mg) as a white powder.

94% ee (Chiralcel AD 80:20 Hexane:Isopropanol, 1.0 mL/min, 220 nm, tᵣ (major)=7.0 min; tᵣ (minor)=12.1 min); [α]²³⁺+=122 (c=0.10, MeOH).

m.p. 191-193 °C; IR (neat) ν=3284, 3192, 2930, 1610, 1508, 1444, 1213, 832, 778, 746; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.55 (br. s., 1H; NH indole), 7.35-7.30 (m, 2H; H19 and H23), 7.25 (d, J=7.5 Hz, 1H; H8), 7.18-7.13 (m, 2H; H20 and H22), 6.93-6.87 (m, 2H; H9 and H10), 4.70 (dd, J=13.0, 4.5 Hz, 1H; H4’), 3.77 (td, J=11.0, 4.5 Hz, 1H; H2’), 3.56-3.51 (m, 1H; H2), 3.14 (td, J=13.0, 4.5 Hz, 1H; H4), 2.69-2.61 (m, 3H; H1’ and H5), 2.48 (s, 3H; H12), 2.18-2.10 (m, 3H; H1 and H16), 0.96 (t, J=7.5 Hz, 3H; H17); ¹³C NMR (125 MHz, [D₆]DMSO,
25 °C) δ=159.2 (d, J=239 Hz, C21), 154.2 (C3), 140.8 (C18), 137.4 (C14), 135.5 (C13), 127.8 (d, J=9 Hz, C19 and C23), 126.0 (C7), 121.8 (C10), 120.3 (C11), 118.7 (C9), 115.4 (C8), 114.9 (d, J=21 Hz, C20 and C22), 107.8 (C6), 57.8 (C15), 44.5 (C2), 38.0 (C4), 32.6 (C1), 31.2 (C16), 20.9 (C5), 17.1 (C12); MS m/z (ES+) 777 ([2M+Na]^+, 100%);
HRMS (ES+) exact mass calculated for [M+Na]^+ (C23H24FN3NaO^+^) requires m/z 400.1796, found m/z 400.1798.

2.2.21 Synthesis and characterisation of (R)-3-(4-methoxyphenyl)-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9u

The title compound was synthesised according to general procedure III. Urea derivative 5n (93 mg, 0.30 mmol) was reacted with methyl vinyl ketone 6a (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH2Cl2/MeOH 95/5) to afford product 9u in 76% yield (82 mg) as a white powder.

81% ee (Chiralcel AD 60:40 Hexane:Isopropanol, 1.0 mL/min, 220 nm, t_r (major)=5.4 min; t_r (minor)=20.1 min); [α]_D^23 =+94(c=0.13, MeOH).

m.p. 122-124 °C; IR (neat) ν=3345, 3295, 2963, 2918, 1633, 1594, 1513, 1491, 751; ^1H NMR (500 MHz, [D_6]DMSO, 25 °C) δ=10.98 (br. s., 1H; NH indole), 7.43 (d, J=7.5 Hz, 1H; H8), 7.34 (d, J=7.5 Hz, 1H; H11), 7.21 (d, J=9.0 Hz, 2H; H17 and H21), 7.08 (td, J=7.5, 1.0 Hz, 1H; H10), 6.99 (td, J=7.5, 1.0 Hz, 1H; H9), 6.89 (d, J=9.0 Hz, 2H; H18 and H20), 4.67 (dd, J=13.0, 5.0 Hz, 1H; H4'), 3.89 (td, J=12.0, 4.0 Hz, 1H; H2'), 3.71 (s, 3H; H22), 3.54-3.48 (m, 1H, H2), 3.04 (td, J=13.0, 5.0 Hz, 1H; H4), 2.68-2.62 (m, 2H; H5), 2.56-2.53 (m, 1H; H1'), 2.06 (td, J=13.0, 5.0 Hz, 1H; H1), 1.67 (s, 3H; H15); ^13C NMR (125 MHz, [D_6]DMSO, 25 °C) δ=156.62 (C19), 153.60 (C3), 139.20 (C16), 137.56 (C13), 136.00 (C12), 127.48 (C17 and C21), 126.22 (C7), 120.97 (C10), 118.52 (C9), 117.95 (C8), 113.59 (C18 and C20), 111.07 (C11), 106.23 (C6), 55.21 (C22), 54.37 (C14), 44.66 (C2), 36.93 (C4), 34.11 (C1), 24.15 (C15), 21.21 (C5); MS m/z (ES+) 745 ([2M+Na]^+, 100%); HRMS (ES+) exact mass calculated for [M+H]^+ (C22H24N3O2^+^) requires m/z 362.1863, found m/z 362.1860.
2.2.22 Synthesis and characterisation of (R)-3-(4-methoxyphenyl)-9-fluoro-12b-heptyl-1,2,3,6,7,12b-hexahydropyrimido[1′,6′:1,2]pyrido[3,4-b]indol-4(12H)-one 9v

The title compound was synthesised according to general procedure III. Urea derivative 5o (33 mg, 0.10 mmol) was reacted with heptyl vinyl ketone 6c (77 mg, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9v in 60% yield (28 mg) as a yellow oil.

89% ee (Chiralcel AD 60:40 Hexane:Isopropanol, 1.0 mL/min, 240 nm, tᵣ (major)=5.0 min; tᵣ (minor)=8.6 min; [α]D²³=+101 (c=0.21, MeOH).

IR (neat) ν=3247, 2928, 2856, 1602, 1512, 1445, 1170, 1034, 797, 747; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=11.02 (br. s., 1H; NH indole), 7.33 (dd, J=9.0, 4.0 Hz, 1H; H10), 7.22-7.15 (m, 3H; H8, H23 and H27), 6.94-6.86 (m, 3H; H11, H24 and H26), 4.68 (dd, J=13.0, 5.0 Hz, 1H; H4'), 3.75 (s, 3H; H28), 3.73-3.69 (m, 1H; H2'), 3.54-3.44 (m, 1H; H2), 3.10 (td, J=13.0, 5.0 Hz, 1H; H4), 2.73-2.57 (m, 3H; H1' and H5), 2.15-2.02 (m, 2H; H1 and H15'), 2.01-1.96 (m, 1H; H15), 1.42-1.39 (m, 1H; H16'), 1.30-1.20 (m, 9H; H16-H20), 0.84 (t, J=7.5 Hz, 3H; H21); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=156.8 (d, J=229 Hz, C9), 156.6 (C25), 154.1 (C3), 139.9 (C13), 137.5 (C22), 132.7 (C12), 127.3 (C23 and C27), 126.4 (d, J=10 Hz, C7), 113.6 (C24 and C26), 112.0 (d, J=10 Hz, C10), 108.8 (d, J=24 Hz, C11), 107.5 (C6), 102.8 (d, J=24 Hz, C8), 57.2 (C14), 55.2 (C28), 44.7 (C2), 38.3 (C15), 37.7 (C4), 32.9 (C1), 31.2 (1C of C17-C20), 29.5 (1C of C17-C20), 28.6 (1C of C17-C20), 24.5 (C16), 22.1 (1C of C17-C20), 20.9 (C5), 13.9 (C21); MS m/z (ES+) 464 ([M+H]+, 100%); HRMS (ES+) exact mass calculated for [M+H]+ (C₂₈H₃₅FN₃O₂⁺) requires m/z 464.2708, found m/z 464.2714.
2.2.23 Synthesis and characterisation of (R)-3-(4-methoxyphenyl)-11-ethyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1’,6’:1,2]pyrido[3,4-b]indol-4(12H)-one 9w

The title compound was synthesised according to general procedure III. Urea derivative 5p (68 mg, 0.20 mmol) was reacted with methyl vinyl ketone 6a (81 µL, 1.0 mmol) in PhMe (40 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH₂Cl₂/MeOH 95/5) to afford product 9w in 74% yield (58 mg) as a brown powder.

96% ee (Chiralcel AD 60:40 Hexane:Isopropanol, 1.0 mL/min, 220 nm, tₘₐᵢₐᵢᵢ = 4.3 min; tᵣ (minor) = 7.0 min); [α]D²³ = +106 (c=0.16, MeOH).

m.p. 121-123 °C; IR (neat) ν=3401, 3280, 2964, 2933, 1602, 1512, 1458, 1246, 1173, 1033, 830, 747; ¹H NMR (500 MHz, [D₆]DMSO, 25 °C) δ=10.63 (br. s., 1H; NH indole), 7.26-7.19 (m, 3H; H8, H19 and H23), 6.96-6.86 (m, 4H; H9, H10, H20 and H22), 4.65 (dd, J=13.0, 5.5 Hz, 1H; H4’), 3.89 (td, J=12.0, 4.0 Hz, 1H; H2’), 3.55-3.50 (m, 1H; H2), 3.75 (s, 3H; H24), 3.03 (td, J=13.0, 5.5 Hz, 1H; H4), 2.87 (q, J=7.5 Hz, 2H; H12), 2.66-2.61 (m, 2H; H5), 2.73-2.67 (m, 1H; H1’), 1.28 (t, J=7.5 Hz, 3H; H13), 2.04 (td, J=13.0, 5.0 Hz, 1H; H1), 1.70 (s, 3H; H17); ¹³C NMR (125 MHz, [D₆]DMSO, 25 °C) δ=156.6 (C21), 153.6 (C3), 138.9 (C15), 137.6 (C18), 134.7 (C14), 127.5 (C19 and C23), 126.6 (C11), 126.0 (C7), 119.8 (C10), 118.9 (C9), 115.5 (C8), 113.6 (C20 and C22), 106.7 (C6), 55.2 (C24), 54.5 (C16), 44.7 (C2), 36.9 (C4), 34.0 (C1), 23.9 (C17 or C12), 23.7 (C12 or C17), 21.3 (C5), 14.5 (C13); MS m/z (ES+) 390 ([M+H]⁺, 100%); HRMS (ES+) exact mass calculated for [M+H]⁺ (C₂₄H₂₈N₃O₂⁺) requires m/z 390.2176, found m/z 390.2176.
3.1.1 $^1$H NMR of compound 5a

Chemical Shift (ppm)
3.1.2 $^{13}$C NMR of compound 5a

![Chemical Structure](image)

$125\text{ MHz, [D$_6$]DMSO}$
3.2.1 $^1$H NMR of compound 5b

500 MHz, [D$_6$]DMSO
3.2.2 $^{13}$C NMR of compound 5b

Chemical Shift (ppm)

125 MHz, [D$_6$]DMSO
3.3.1 $^1$H NMR of compound 5c

500 MHz, [D$_6$]DMSO
3.3.2 $^{13}$C NMR of compound 5c

125 MHz, [D$_6$]DMSO
3.4.1 $^1$H NMR of compound 5d

\[
\begin{align*}
\text{Chemical Shift (ppm)}
\end{align*}
\]

500 MHz, [D$_6$]DMSO
3.4.2 $^{13}$C NMR of compound 5d

Chemical Shift (ppm)
3.5.1 $^1$H NMR of compound 5e

500 MHz, [D$_6$]DMSO
3.5.2 $^{13}$C NMR of compound 5e

\[
\text{Chemical Shift (ppm)}
\]

\[
\begin{align*}
125 \text{ MHz, [D}_6\text{]DMSO} \\
\end{align*}
\]
3.6.1 $^1$H NMR of compound 5f

500 MHz, [D$_6$]DMSO
3.6.2 $^{13}\text{C}$ NMR of compound 5f

[Chemical structure image]

125 MHz, [D$_6$]DMSO
3.7.1 $^1$H NMR of compound 5g

![Chemical structure of compound 5g]

$400$ MHz, [D$_6$]DMSO
3.7.2 $^{13}$C NMR of compound 5g

![Chemical structure and NMR spectrum](image-url)

**Chemical Shift (ppm)**

- 176
- 168
- 160
- 152
- 144
- 136
- 128
- 120
- 112
- 104
- 96
- 88
- 80
- 72
- 64
- 56
- 48
- 40
- 32
- 24
- 16
- 8
- 0

100 MHz, [D$_6$]DMSO
3.8.1 $^1$H NMR of compound 5j

500 MHz, [D$_6$]DMSO
3.8.2 $^{13}$C NMR of compound 5j

$^{125}$MHz, [D$_6$]DMSO

Chemical Shift (ppm)
3.9.1 $^1$H NMR of compound 5k

500 MHz, [D$_6$]DMSO
3.9.2 $^{13}$C NMR of compound 5k
3.10.1 $^1$H NMR of compound 5l

500 MHz, [D$_6$]DMSO
3.10.2 $^{13}$C NMR of compound 5l

Chemical Shift (ppm)

125 MHz, [D$_6$]DMSO
3.11.1 $^1$H NMR of compound 5m
3.11.2 $^{13}$C NMR of compound 5m

$^{13}$C NMR spectrum of compound 5m.

Diagram of compound 5m.

125 MHz, $[D_6]$DMSO
3.12.1 $^1$H NMR of compound 5n

500 MHz, [D$_6$]DMSO
3.12.2 $^{13}$C NMR of compound 5n

125 MHz, [D$_6$]DMSO
3.13.1 $^1$H NMR of compound 5o

![Chemical Structure](image)

500 MHz, [D$_8$]DMSO

[journal image]
3.13.2 $^{13}$C NMR of compound 5o

$^{13}$C NMR spectrum of compound 5o in $[D_6]$DMSO at 125 MHz.

Chemical Shift (ppm)
3.14.1 $^1$H NMR of compound 5p

500 MHz, [D$_6$]DMSO

Chemical Shift (ppm)

0.90 0.87 1.00 1.86 0.96 2.13 0.96 1.86 1.00 0.87 0.90 3.31 4.09 1.91 3.15 1.32 0.89 1.32 0.89
3.14.2 $^{13}$C NMR of compound 5p
4.1.1 $^1$H NMR of compound 9a

500 MHz, [D$_6$]DMSO
4.1.2 $^{13}$C NMR of compound 9a

125 MHz, [D$_6$]DMSO
4.2.1 $^1H$ NMR of compound 9b

500 MHz, $[D_6]$DMSO
4.2.2 $^{13}$C NMR of compound 9b

125 MHz, [D$_6$]DMSO
4.3.1 $^1$H NMR of compound 9c

$500$ MHz, [D$_6$]DMSO
4.3.2 $^{13}$C NMR of compound 9c
4.4.1 $^1$H NMR of compound 9d

500 MHz, [D$_6$]DMSO
4.4.2 $^{13}$C NMR of compound 9d

$^{13}$C NMR spectrum of compound 9d in [D$_6$]DMSO at 125 MHz.
4.5.1 $^1$H NMR of compound 9e

500 MHz, [D$_6$]DMSO
4.5.2 $^{13}$C NMR of compound 9e

Chemical Shift (ppm)
4.6.1 $^1$H NMR of compound 9f

500 MHz, [D$_6$]DMSO
4.6.2 $^{13}$C NMR of compound 9f

125 MHz, [D$_6$]DMSO
4.7.1 $^1$H NMR of compound 9g

500 MHz, [D$_6$]DMSO
4.7.2 $^{13}$C NMR of compound 9g

125 MHz, [D$_5$]DMSO
4.8.1 $^1$H NMR of compound 9h

500 MHz, [D$_6$]DMSO
4.8.2 $^{13}$C NMR of compound 9h

125 MHz, [D$_6$]DMSO
4.9.1 $^1$H NMR of compound 9i
4.9.2 $^{13}$C NMR of compound 9i

![Chemical Structure of Compound 9i](image)

125 MHz, [D$_6$]DMSO
4.10.1 $^1$H NMR of compound 9j

500 MHz, [D$_6$]DMSO
4.10.2 $^{13}$C NMR of compound 9j

125 MHz, [D$_6$]DMSO
4.11.1 $^1$H NMR of compound 9k

500 MHz, [D$_6$]DMSO
4.11.2 $^{13}$C NMR of compound 9k

125 MHz, [D$_6$]DMSO
4.12.1 $^1$H NMR of compound 9l

500 MHz, [D$_6$]DMSO

Chemical Shift (ppm): 3.06, 1.20, 2.03, 2.90, 1.02, 1.07, 1.05, 0.98, 1.03, 0.98, 0.99, 2.90, 2.03, 1.20, 3.06
4.12.2 $^{13}$C NMR of compound 9l

125 MHz, [D$_6$]DMSO
4.13.1 $^1$H NMR of compound 9m

500 MHz, [D$_6$]DMSO
4.13.2 $^{13}$C NMR of compound 9m

$^{13}$C NMR of compound 9m

125 MHz, [D$_6$]DMSO
4.14.1 $^1$H NMR of compound 9n

500 MHz, [D$_6$]DMSO
4.14.2 $^{13}$C NMR of compound 9n

125 MHz, [D$_6$]DMSO
4.15 $^1$H NMR of compound 9o

500 MHz, [D$_6$]DMSO
4.15.2 $^{13}$C NMR of compound 9o

$^{125}$ MHz, [D$_6$]DMSO
4.16.1 $^1$H NMR of compound 9p

$^1$H NMR of compound 9p

500 MHz, [D$_6$]DMSO
4.16.2 $^{13}$C NMR of compound 9p

125 MHz, [D$_6$]DMSO
4.17.1 $^1$H NMR of compound 9q

500 MHz, [D$_6$]DMSO
4.17.2 $^{13}$C NMR of compound 9q

125 MHz, [D$_6$]DMSO
4.18 $^1H$ NMR of compound 9r

500 MHz, [D$_6$]DMSO
4.18.2 $^{13}$C NMR of compound 9r

$^{125}$ MHz, [D$_6$]DMSO
4.19.1 $^1$H NMR of compound 9s

500 MHz, [D$_6$]DMSO
4.19.2 $^{13}$C NMR of compound 9s

125 MHz, [D$_6$]DMSO
4.20.1 $^1$H NMR of compound 9t

$^1$H NMR of compound 9t

$500 \text{ MHz, } [D_6]\text{DMSO}$
4.20.2 $^{13}$C NMR of compound 9t

125 MHz, [D$_6$]DMSO
4.21.1 $^1$H NMR of compound 9u

$500 \text{ MHz, } [D_6]\text{DMSO}$
4.21.2 $^{13}$C NMR of compound 9u

![Chemical Structure](image)

125 MHz, [D$_6$]DMSO
4.22.1 $^1$H NMR of compound 9v

500 MHz, [D$_6$]DMSO
4.22.2 $^{13}$C NMR of compound 9v

![Chemical structure](image)

125 MHz, [D$_6$]DMSO
4.23.1 $^1$H NMR of compound 9w

500 MHz, [D$_6$]DMSO
4.23.2 $^{13}$C NMR of compound 9w

125 MHz, [D$_6$]DMSO
5.1.1 HPLC trace of racemic 9a

5.1.2 HPLC trace of enantioenriched 9a
5.2.1 HPLC trace of racemic 9b

| Peak RetTime Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|-------------------|-------------|--------------|--------------|--------|
| 1                 | 8.128 BB    | 0.3820       | 1.21420e4    | 488.52164 | 50.4201 |
| 2                 | 19.090 BB   | 0.9003       | 1.19397e4    | 202.38368 | 49.5799 |

Totals: 2.40817e4 690.90532

5.2.2 HPLC trace of enantioenriched 9b

| Peak RetTime Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|-------------------|-------------|--------------|--------------|--------|
| 1                 | 7.851 BB    | 0.3594       | 3.82643e4    | 1633.63770 | 89.1371 |
| 2                 | 18.834 BB   | 0.8287       | 4665.60693   | 86.58440  | 10.8629 |

Totals: 4.29499e4 1720.22209
5.3.1 HPLC trace of racemic 9c

Signal 3: DAD1 C, Sig=220, 8 Ref=360,100

| Peak | RetTime | Type | Width | Area  | Height | Area % |
|------|---------|------|-------|-------|--------|--------|
| 1    | 27.420  | MM   | 1.459 | 4988.99219 | 56.96652 | 49.9655 |
| 2    | 42.316  | MM   | 1.848 | 4995.88818 | 45.04830 | 50.0345 |

Totals: 9984.88037 102.01482

5.3.2 HPLC trace of enantioenriched 9c

Signal 4: DAD1 D, Sig=220,16 Ref=400,100

| Peak | RetTime | Type | Width | Area  | Height | Area % |
|------|---------|------|-------|-------|--------|--------|
| 1    | 27.856  | MM   | 1.399 | 3.85139e+4 | 458.61905 | 80.1036 |
| 2    | 43.799  | MM   | 1.858 | 9566.22363 | 85.77356 | 19.8964 |

Totals: 4.80801e+4 544.39261
5.4.1 HPLC trace of racemic 9d

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak RetTime | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area [%] |
|--------------|------|-------------|--------------|--------------|----------|
| 1            | BB   | 23.173      | 1.0948       | 2.75907e4    | 384.66782| 50.3224  |
| 2            | BB   | 49.187      | 2.4675       | 2.72372e4    | 148.11012| 49.6776  |

Totals: 5.48279e4 532.77794

5.4.2 HPLC trace of enantioenriched 9d

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak RetTime | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area [%] |
|--------------|------|-------------|--------------|--------------|----------|
| 1            | MM   | 22.648      | 1.1936       | 2.56941e4    | 358.76926| 84.9782  |
| 2            | MM   | 49.341      | 2.1947       | 4542.00195   | 34.49198 | 15.0218  |

Totals: 3.02361e4 393.26123
### 5.5.1 HPLC trace of racemic 9e

![HPLC trace of racemic 9e](image1)

| Peak | RetTime | Type | Width | Area      | Height | Area         |
|------|---------|------|-------|-----------|--------|--------------|
| 1    | 22.823  | MM   | 1.1244| 2586.76172| 38.34214| 49.8124      |
| 2    | 53.698  | MM   | 2.8856| 2606.24707| 15.05342| 50.1876      |

Totals: 5193.00879 53.39557

### 5.5.2 HPLC trace of enantioenriched 9e

![HPLC trace of enantioenriched 9e](image2)

Signal 6: DAD1 F, Sig=300,8 Ref=360,100

| Peak | RetTime | Type | Width | Area      | Height | Area         |
|------|---------|------|-------|-----------|--------|--------------|
| 1    | 21.402  | MM   | 1.2289| 1.94268e4 | 263.47858| 83.7520      |
| 2    | 51.908  | MM   | 3.0132| 3768.82812| 20.84603| 16.2480      |

Totals: 2.31956e4 284.32461
5.6.1 HPLC trace of racemic 9f

5.6.2 HPLC trace of enantioenriched 9f
5.7.1 HPLC trace of racemic 9g

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area   | Height | Area 100% | Area 150% |
|------|---------|------|-------|--------|--------|-----------|-----------|
| 1    | 12.425  | MF   | 0.7049| 1.38450e4 | 327.35123 | 49.5858   |
| 2    | 14.204  | FM   | 0.7906| 1.40763e4 | 296.74359 | 50.4142   |

Totals : 2.79213e4 624.09482

5.7.2 HPLC trace of enantioenriched 9g

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area   | Height | Area 100% | Area 150% |
|------|---------|------|-------|--------|--------|-----------|-----------|
| 1    | 12.189  | BB   | 0.6222| 3.11330e4 | 747.04541 | 96.1247   |
| 2    | 14.392  | BB   | 0.7902| 1255.12329| 22.60222 | 3.8753    |

Totals : 3.23881e4 769.84763
5.8.1 HPLC trace of racemic 9h

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area  | Height | Area % |
|------|---------|------|-------|-------|--------|--------|
| 1    | 28.666  | MM   | 1.856 | 4.77348e4 | 428.45740 | 49.9924 |
| 2    | 45.579  | MM   | 3.0576| 4.77494e4 | 260.27856 | 30.0076 |

Totals: 9.54842e4 688.73596

5.8.2 HPLC trace of enantioenriched 9h

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area  | Height | Area % |
|------|---------|------|-------|-------|--------|--------|
| 1    | 29.851  | MM   | 2.0953| 8.08408e4 | 643.03217 | 95.8639 |
| 2    | 50.946  | MM   | 3.1174| 3487.94824 | 18.64770  | 4.1361  |

Totals: 8.43287e4 661.67986
5.9.1 HPLC trace of racemic 9i

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area     | Height  | Area     | %       |
|------|---------|------|-------|----------|---------|----------|---------|
| 1    | 7.731   | VB   | 0.3864| 1.81636e4| 724.63928| 49.7133  |
| 2    | 11.581  | BB   | 0.5562| 1.83731e4| 505.28064| 50.2867  |

Totals: 3.65367e4 1229.91992

5.9.2 HPLC trace of enantioenriched 9i

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area     | Height  | Area     | %       |
|------|---------|------|-------|----------|---------|----------|---------|
| 1    | 7.693   | BB   | 0.4075| 6.59833e4| 2519.54248| 94.9799  |
| 2    | 11.848  | BB   | 0.5960| 3407.51880| 88.07508  | 5.0201   |

Totals: 6.94708e4 2607.61756
5.10.1 HPLC trace of racemic 9j

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area  | Height | Area % |
|------|---------|------|-------|-------|--------|--------|
| 1    | 27.442  | MF   | 2.1193| 1.96387 | 154.44676 | 50.0023 |
| 2    | 35.000  | EM   | 2.8073| 1.96369 | 116.58168 | 49.9977 |

Totals: 3.92756e4  271.02844

5.10.2 HPLC trace of enantioenriched 9j

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area  | Height | Area % |
|------|---------|------|-------|-------|--------|--------|
| 1    | 27.553  | MM   | 2.2048| 4.45403e4 | 336.69745 | 95.7887 |
| 2    | 38.844  | MM   | 2.6787| 1.958.16724 | 12.18364 | 4.2113 |

Totals: 4.64985e4  348.88109
5.11.1 HPLC trace of racemic 9k

![HPLC trace of racemic 9k](image)

Signal 2: DAD1 B, Sig=220,8 Ref=360,100

| Peak RetTime Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|-------------------|-------------|--------------|--------------|--------|
| 1                 | 16.519 VV   | 8.15249e4    | 1722.64880   | 49.6028|
| 2                 | 18.615 VB   | 8.28304e4    | 1386.34863   | 50.3972|

Totals: 1.64355e5 3108.99744

5.11.2 HPLC trace of enantioenriched 9k

![HPLC trace of enantioenriched 9k](image)

Signal 2: DAD1 B, Sig=220,8 Ref=360,100

| Peak RetTime Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|-------------------|-------------|--------------|--------------|--------|
| 1                 | 16.678 BV   | 2.93723e4    | 628.60034    | 28.6708|
| 2                 | 18.638 VB   | 7.30743e4    | 1251.29919   | 71.3292|

Totals: 1.02447e5 1879.89954
5.12.1 HPLC trace of racemic 9l

5.12.2 HPLC trace of enantioenriched 9l
5.13.1 HPLC trace of racemic 9m

![HPLC trace of racemic 9m](image1)

Signal 4: DAD1 D, Sig=220,16 Ref=360,100

| Peak RetTime Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|-------------------|-------------|--------------|--------------|--------|
| #                 |             |              |              |        |
| 1                 | 18.306 VB   | 0.7677       | 5.26164e4    | 990.61047 | 50.3879 |
| 2                 | 31.910 MM   | 1.5287       | 5.18063e4    | 564.81622 | 49.6121 |

Totals: 1.04423e5 1555.42670

5.13.2 HPLC trace of enantioenriched 9m

![HPLC trace of enantioenriched 9m](image2)

Signal 4: DAD1 D, Sig=220,16 Ref=360,100

| Peak RetTime Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|-------------------|-------------|--------------|--------------|--------|
| #                 |             |              |              |        |
| 1                 | 18.157 VB   | 0.8547       | 8.84266e4    | 1615.15283 | 91.4768 |
| 2                 | 32.867 MM   | 1.3423       | 8239.05469   | 102.30173 | 8.5232 |

Totals: 9.66657e4 1717.45456
5.14.1 HPLC trace of racemic 9n

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | Ret Time [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|------|----------------|------|-------------|--------------|--------------|--------|
| 1    | 13.570         | VB   | 0.6803      | 2.60506e4    | 595.58911    | 50.2209|
| 2    | 21.638         | BB   | 0.9189      | 2.58214e4    | 431.04242    | 49.7791|

Totals: 5.18720e4 1026.63153

5.14.2 HPLC trace of enantioenriched 9n

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | Ret Time [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|------|----------------|------|-------------|--------------|--------------|--------|
| 1    | 13.583         | MM   | 0.8133      | 1.16450e5    | 2386.23022   | 92.7655|
| 2    | 22.519         | MM   | 0.9697      | 9081.65625   | 156.08818    | 7.2345 |

Totals: 1.25532e5 2542.31841
5.15.1 HPLC trace of racemic 9o

![HPLC trace of racemic 9o]

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area [%] |
|------|---------|------|-------------|--------------|--------------|----------|
| 1    | 8.817   | FM   | 0.7018      | 1.65011e4    | 391.85361    | 50.9273  |
| 2    | 11.348   | HH   | 0.6821      | 1.59002e4    | 340.96487    | 49.0727  |

Totals: 3.24012e4 732.81848

5.15.2 HPLC trace of enantioenriched 9o

![HPLC trace of enantioenriched 9o]

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area [%] |
|------|---------|------|-------------|--------------|--------------|----------|
| 1    | 8.486   | MM   | 0.3900      | 6.09343e4    | 2604.19678   | 94.9505  |
| 2    | 11.982   | MM   | 0.3750      | 3240.48462   | 144.01950    | 5.0495   |

Totals: 6.41747e4 2748.21628
5.16.1 HPLC trace of racemic 9p

![HPLC trace of racemic 9p]

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area    | Height | Area % |
|------|---------|------|-------|---------|--------|--------|
| 1    | 11.519  | VB   | 0.6965| 1.93258e4 | 443.37531 | 50.1671 |
| 2    | 18.964  | BB   | 0.7236| 1.91970e4 | 406.00046 | 49.8329 |

Totals: 3.85229e4 849.37576

5.16.2 HPLC trace of enantioenriched 9p

![HPLC trace of enantioenriched 9p]

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area    | Height | Area % |
|------|---------|------|-------|---------|--------|--------|
| 1    | 11.319  | VV   | 0.6470| 8.95164e4 | 2171.06934 | 93.2987  |
| 2    | 19.106  | BB   | 0.8106| 6429.60840 | 123.25988 | 6.7013   |

Totals: 9.59460e4 2294.32922
5.17.1 HPLC trace of racemic 9q

![HPLC trace of racemic 9q](image)

**Signal 3: DAD1 C, Sig=220,8 Ref=360,100**

| Peak | Ret Time [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area [%] |
|------|----------------|------|-------------|----------------|--------------|----------|
| 1    | 16.931         | MM   | 0.9069      | 2.46081e4      | 452.25519    | 49.4765  |
| 2    | 19.381         | MM   | 0.9167      | 2.51288e4      | 456.87338    | 50.5235  |

**Totals:**

| Area [mAU*sec] | 4.97370e4 |
|----------------|-----------|
| Area [%]       | 908.12557 |

5.17.2 HPLC trace of enantioenriched 9q

![HPLC trace of enantioenriched 9q](image)

**Signal 2: DAD1 B, Sig=220,8 Ref=360,100**

| Peak | Ret Time [min] | Type | Width [min] | Area [mAU*sec] | Height [mAU] | Area [%] |
|------|----------------|------|-------------|----------------|--------------|----------|
| 1    | 16.083         | VV   | 0.9892      | 5.07680e4      | 739.23029    | 85.3385  |
| 2    | 18.751         | VV   | 0.9612      | 8722.18164     | 139.93593    | 14.6615  |

**Totals:**

| Area [mAU*sec] | 5.94902e4 |
|----------------|-----------|
| Area [%]       | 879.16621 |
5.18.1 HPLC trace of racemic 9r

![HPLC trace of racemic 9r](image)

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak RetTime | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------------|------|-------------|--------------|--------------|-------|
| 1            | 4.234 VV | 0.1774     | 3.35204e4   | 2845.25171   | 49.8565 |
| 2            | 11.313 BB | 0.9883     | 3.37134e4   | 869.59191    | 50.1435 |

Totals: 6.72338e4 3714.83362

5.18.2 HPLC trace of enantioenriched 9r

![HPLC trace of enantioenriched 9r](image)

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak RetTime | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|--------------|------|-------------|--------------|--------------|-------|
| 1            | 4.216 MF | 0.1924     | 2.21129e4   | 1915.04517   | 91.3112 |
| 2            | 11.610 VB | 0.4788     | 2104.17700  | 68.42592     | 8.6888  |

Totals: 2.4217e4 1983.47108
5.19.1 HPLC trace of racemic 9s

Signal 2: DAD1 B, Sig=220,16 Ref=360,100

| Peak RetTime | Type | Width | Area   | Height | Area   | %    |
|--------------|------|-------|--------|--------|--------|------|
| 1            | 5.787 BV | 0.2448 | 4665.55713 | 294.60724 | 56.1021 |
| 2            | 15.050 BB | 0.6542 | 4646.53906 | 110.13287 | 49.8979 |

Totals: 9312.09619 404.74011

5.19.2 HPLC trace of enantioenriched 9s

Signal 2: DAD1 B, Sig=220,8 Ref=360,100

| Peak RetTime | Type | Width | Area   | Height | Area   | %    |
|--------------|------|-------|--------|--------|--------|------|
| 1            | 5.842 NM | 0.2959 | 837.00934 | 47.14312 | 92.5368 |
| 2            | 15.409 NM | 0.7438 | 67.50617 | 1.51255 | 7.4632 |

Totals: 904.51551 48.65567
5.20.1 HPLC trace of racemic 9t

Signal 2: DAD1 B, Sig=220,16 Ref=360,100

| Peak | RetTime | Type | Width | Area | Height | Area % |
|------|---------|------|-------|------|--------|--------|
| 1    | 6.949   | VB   | 0.282 | 587.42609 | 49.6517 |
| 2    | 11.938  | BB   | 0.4931| 342.60583 | 50.3483 |

Totals: 2.17638e4 930.03192

5.20.2 HPLC trace of enantioenriched 9t

Signal 2: DAD1 B, Sig=220,16 Ref=360,100

| Peak | RetTime | Type | Width | Area | Height | Area % |
|------|---------|------|-------|------|--------|--------|
| 1    | 6.972   | MM   | 0.3129| 5237.81445 | 97.1925 |
| 2    | 12.117  | MM   | 0.5935| 151.29684  | 2.8075 |

Totals: 5389.11130 283.22456
5.21.1 HPLC trace of racemic 9u

![HPLC trace of racemic 9u]

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area | Height | Area |
|------|---------|------|-------|------|--------|------|
| 1    | 5.469   | VV   | 0.2079 | 1.97446e4 | 1458.60791 | 50.3041 |
| 2    | 20.098  | BB   | 1.0570 | 1.95059e4 | 281.99466 | 49.6959 |

Totals: 
3.92505e4 1740.60257

5.21.2 HPLC trace of enantioenriched 9u

![HPLC trace of enantioenriched 9u]

Signal 3: DAD1 C, Sig=220,8 Ref=360,100

| Peak | RetTime | Type | Width | Area | Height | Area |
|------|---------|------|-------|------|--------|------|
| 1    | 5.388   | MM   | 0.2943 | 5.95899e4 | 3374.79736 | 90.6073 |
| 2    | 20.139  | MM   | 1.0297 | 6177.33545 | 99.98903 | 9.3927 |

Totals: 
6.57673e4 3474.78639
5.22.1 HPLC trace of racemic 9v

5.22.2 HPLC trace of enantioenriched 9v
5.23.1 HPLC trace of racemic 9w

Signal 3: DAD1 C, Sig=220.8 Ref=360,100

| Peak | RetTime | Type | Width | Area  | Height | Area  | %     |
|------|---------|------|-------|-------|--------|-------|-------|
| 1    | 4.301   | MM   | 0.2031| 2.52962e4| 2076.03149| 49.6473|       |
| 2    | 6.875   | MM   | 0.3434| 2.56557e4| 1245.01917| 50.3527|       |

Totals: 5.09519e4 3321.05066

5.23.2 HPLC trace of enantioenriched 9w

Signal 3: DAD1 C, Sig=220.8 Ref=360,100

| Peak | RetTime | Type | Width | Area  | Height | Area  | %     |
|------|---------|------|-------|-------|--------|-------|-------|
| 1    | 4.288   | MM   | 0.2089| 3.46789e4| 2767.33862| 96.2489|       |
| 2    | 6.965   | MM   | 0.3215| 618.07465| 32.04358| 1.7511|       |

Totals: 3.52970e4 2799.38220
6. Single crystal X-ray diffraction data for compound 9r
Crystal data

$\text{C}_{21}\text{H}_{20}\text{FN}_3\text{O}$

$M_r = 349.41$

Monoclinic, $P2_1$

Hall symbol: $P 2yb$

$\alpha = 7.1383 (1) \text{ Å}$

$\beta = 10.6018 (1) \text{ Å}$

$\gamma = 12.0383 (1) \text{ Å}$

$\beta = 102.3752 (6) ^\circ$

$V = 889.88 (2) \text{ Å}^3$

$Z = 2$

$F(000) = 368$

$D_x = 1.304 \text{ Mg m}^{-3}$

Melting point: not measured K

Cu $K\alpha$ radiation, $\lambda = 1.54180$ Å

Cell parameters from 59434 reflections

$\theta = 4^\circ - 77^\circ$

$\mu = 0.72$ mm$^{-1}$

$T = 150$ K

Block, Clear pale colourless

$0.20 \times 0.15 \times 0.08$ mm

Data collection

Oxford Diffraction SuperNova diffractometer

Graphite monochromator

$\omega$ scans

Absorption correction: Multi-scan

CrysAlis, (Oxford Diffraction, 2002)

$T_{\text{min}} = 0.75$, $T_{\text{max}} = 0.94$

76919 measured reflections

3711 independent reflections

Refinement

Refinement on $F^2$

Least-squares matrix: Full

$R[F^2 > 2\sigma(F^2)] = 0.026$

$wR(F^2) = 0.067$

$S = 0.97$

3711 reflections

236 parameters

1 restraint

Primary atom site location: Structure-invariant direct methods

Hydrogen site location: Difference Fourier map

H-atom parameters constrained

Method = Modified Sheldrick

$P = (\max(F_o^2,0) + 2F_c^2)/3$

$(\Delta/\sigma)_{\text{max}} = 0.0004$

$\Delta_{\text{pmax}} = 0.14 \text{ e Å}^{-3}$

$\Delta_{\text{pmin}} = -0.14 \text{ e Å}^{-3}$

Absolute structure: Flack (1983), 1743 Friedel-pairs

Flack parameter: 0.06 (11)

Special details

**Refinement.** The Flack $x$ parameter [Flack, 1983; Flack & Bernardinelli (2000)] refined to 0.05 (12), reducing to -0.001 (8) on the application of Bijvoet difference restraints [Thompson & Watkin, 2010]. Analysis of the Bijvoet differences [Hooft et al., 2008] gave a Hooft $y$ parameter of -0.03 (3), $G$ of 1.06 (6), and a probability that the structure was the correct hand of >99.99% given that the structure is enantiopure or a racemic twin using the Bayesian method.
### Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

| Atom | x       | y       | z       | Uiso/ueq |
|------|---------|---------|---------|----------|
| F1   | -0.00358 (14) | 0.99563 (10) | 0.98412 (8) | 0.0521 |
| C2   | 0.08003 (19) | 0.91592 (13) | 0.92023 (10) | 0.0338 |
| C3   | 0.03623 (17) | 0.78974 (13) | 0.92022 (10) | 0.0307 |
| C4   | 0.12329 (16) | 0.70895 (12) | 0.85599 (9) | 0.0265 |
| C5   | 0.24939 (15) | 0.75645 (12) | 0.79293 (9) | 0.0234 |
| N6   | 0.34433 (12) | 0.67285 (11) | 0.72988 (8) | 0.0266 |
| C7   | 0.24483 (14) | 0.61977 (12) | 0.63222 (9) | 0.0245 |
| O8   | 0.06797 (10) | 0.63142 (11) | 0.60392 (7) | 0.0354 |
| N9   | 0.34627 (13) | 0.55022 (10) | 0.57476 (9) | 0.0218 |
| C10  | 0.55571 (14) | 0.56518 (11) | 0.66405 (9) | 0.0263 |
| C11  | 0.63833 (15) | 0.64699 (13) | 0.66405 (9) | 0.0263 |
| C12  | 0.55036 (14) | 0.65099 (13) | 0.76740 (9) | 0.0295 |
| H122 | 0.5690 | 0.5654 | 0.8010 | 0.0358* |
| H121 | 0.6061 | 0.7131 | 0.8290 | 0.0358* |
| H111 | 0.6023 | 0.7505 | 0.6305 | 0.0308* |
| H112 | 0.7748 | 0.6552 | 0.6829 | 0.0315* |
| C13  | 0.66062 (18) | 0.43964 (12) | 0.60394 (11) | 0.0347 |
| H131 | 0.7933 | 0.4519 | 0.6016 | 0.0510* |
| H132 | 0.6064 | 0.3733 | 0.5510 | 0.0514* |
| H133 | 0.6515 | 0.4144 | 0.6805 | 0.0517* |
| C14  | 0.57102 (14) | 0.61045 (11) | 0.45813 (8) | 0.0212 |
| N15  | 0.73261 (13) | 0.66928 (10) | 0.43752 (7) | 0.0239 |
| C16  | 0.69180 (16) | 0.71246 (11) | 0.32716 (9) | 0.0254 |
| C17  | 0.50181 (16) | 0.67627 (12) | 0.27700 (9) | 0.0273 |
| C18  | 0.42830 (14) | 0.61120 (12) | 0.36264 (9) | 0.0251 |
| C19  | 0.23178 (16) | 0.55907 (15) | 0.36077 (10) | 0.0356 |
| C20  | 0.23698 (17) | 0.48506 (13) | 0.46907 (10) | 0.0329 |
| H201 | 0.1072 | 0.4720 | 0.4813 | 0.0390* |
| H202 | 0.3000 | 0.4056 | 0.4636 | 0.0387* |
| H192 | 0.1893 | 0.5047 | 0.2969 | 0.0433* |
| H191 | 0.1373 | 0.6304 | 0.3556 | 0.0438* |
| C21  | 0.4220 (2) | 0.71176 (14) | 0.16416 (10) | 0.0375 |
| C22  | 0.5310 (2) | 0.78393 (14) | 0.10684 (11) | 0.0435 |
| C23  | 0.7175 (2) | 0.82134 (13) | 0.15866 (12) | 0.0414 |
| C24  | 0.8014 (2) | 0.78619 (12) | 0.26938 (11) | 0.0329 |
| H241 | 0.9257 | 0.8092 | 0.3035 | 0.0375* |
| H231 | 0.7898 | 0.8695 | 0.1190 | 0.0488* |
| H221 | 0.4770 | 0.8096 | 0.0284 | 0.0521* |
| H211 | 0.2899 | 0.6869 | 0.1277 | 0.0455* |
| H151 | 0.8427 | 0.6708 | 0.4829 | 0.0304* |
| C25  | 0.28774 (18) | 0.88460 (13) | 0.79390 (10) | 0.0307 |
| C26  | 0.20334 (19) | 0.96629 (13) | 0.85882 (10) | 0.0349 |
| H261 | 0.2290 | 1.0539 | 0.8611 | 0.0430* |
Geometric parameters (Å, °)

|       | F1—C2   | 1.3634 (13) | C13—H133      | 0.975   |
|-------|---------|-------------|---------------|---------|
| C2—C3| 1.3738 (18) | C14—N15     | 1.3798 (13)   |         |
| C2—C6| 1.3730 (18) | C14—C18     | 1.3628 (14)   |         |
| C3—C4| 1.3869 (16) | N15—C16     | 1.3761 (14)   |         |
| C3—H31| 0.925     | N15—H151    | 0.856         |         |
| C4—C5| 1.3903 (15) | C16—C17     | 1.4143 (16)   |         |
| C4—H41| 0.958     | C16—C24     | 1.3931 (16)   |         |
| C5—N6| 1.4288 (14) | C17—C18     | 1.4304 (15)   |         |
| C5—C25| 1.3855 (17) | C17—C21     | 1.4070 (16)   |         |
| N6—C7| 1.3585 (14) | C18—C19     | 1.5035 (15)   |         |

Atomic displacement parameters (Å²)

|       | U¹¹ | U¹² | U¹³ | U¹² | U¹³ | U¹³ |
|-------|-----|-----|-----|-----|-----|-----|
| F1    | 0.0684 (6) | 0.0416 (4) | 0.0565 (5) | 0.0120 (4) | 0.0357 (4) | −0.0078 (4) |
| C2    | 0.0395 (6) | 0.0338 (6) | 0.0304 (6) | 0.0095 (5) | 0.0125 (5) | −0.0018 (5) |
| C3    | 0.0290 (6) | 0.0386 (6) | 0.0272 (5) | 0.0000 (5) | 0.0124 (4) | −0.0001 (4) |
| C4    | 0.0272 (5) | 0.0276 (5) | 0.0255 (5) | −0.0021 (4) | 0.0075 (4) | 0.0002 (4) |
| C5    | 0.0211 (5) | 0.0291 (5) | 0.0200 (5) | 0.0014 (4) | 0.0045 (4) | −0.0007 (4) |
| N6    | 0.0186 (4) | 0.0368 (5) | 0.0248 (4) | 0.0014 (4) | 0.0058 (3) | −0.0041 (4) |
| C7    | 0.0211 (4) | 0.0288 (5) | 0.0250 (5) | −0.0027 (4) | 0.0081 (4) | −0.0016 (4) |
| C8    | 0.0184 (4) | 0.0559 (5) | 0.0319 (4) | −0.0008 (4) | 0.0052 (3) | −0.0121 (4) |
| N9    | 0.0203 (4) | 0.0284 (5) | 0.0290 (4) | −0.0048 (3) | 0.0094 (3) | −0.0052 (4) |
| C10   | 0.0184 (5) | 0.0237 (5) | 0.0244 (5) | 0.0001 (4) | 0.0074 (4) | 0.0015 (4) |
| C11   | 0.0185 (4) | 0.0362 (5) | 0.0244 (5) | −0.0024 (4) | 0.0055 (4) | −0.0017 (4) |
| C12   | 0.0199 (5) | 0.0443 (7) | 0.0240 (5) | 0.0030 (4) | 0.0042 (4) | 0.0009 (5) |
| C13   | 0.0356 (6) | 0.0293 (6) | 0.0421 (6) | 0.0087 (5) | 0.0149 (5) | 0.0101 (5) |
| C14   | 0.0206 (4) | 0.0194 (4) | 0.0247 (5) | 0.0021 (4) | 0.0076 (4) | −0.0008 (4) |
| N15   | 0.0221 (4) | 0.0277 (4) | 0.0224 (4) | −0.0021 (3) | 0.0060 (3) | −0.0007 (4) |
| N16   | 0.0343 (6) | 0.0212 (5) | 0.0222 (5) | 0.0027 (4) | 0.0098 (4) | −0.0023 (4) |
| C17   | 0.0307 (5) | 0.0285 (5) | 0.0229 (5) | 0.0085 (4) | 0.0060 (4) | −0.0025 (4) |
| C18   | 0.0225 (5) | 0.0290 (5) | 0.0240 (5) | 0.0028 (4) | 0.0052 (4) | −0.0047 (4) |
| C19   | 0.0234 (5) | 0.0512 (7) | 0.0316 (6) | −0.0045 (5) | 0.0042 (4) | −0.0137 (6) |
| C20   | 0.0268 (5) | 0.0365 (6) | 0.0384 (6) | −0.0107 (5) | 0.0135 (5) | −0.0156 (5) |
| C21   | 0.0429 (7) | 0.0448 (7) | 0.0233 (5) | 0.0136 (6) | 0.0038 (5) | −0.0002 (5) |
| C22   | 0.0631 (9) | 0.0436 (8) | 0.0250 (6) | 0.0160 (6) | 0.0121 (6) | 0.0064 (5) |
| C23   | 0.0690 (9) | 0.0284 (6) | 0.0342 (6) | 0.0037 (6) | 0.0277 (6) | 0.0050 (5) |
| C24   | 0.0444 (7) | 0.0264 (5) | 0.0322 (6) | −0.0043 (5) | 0.0175 (5) | −0.0027 (4) |
| C25   | 0.0339 (6) | 0.0319 (6) | 0.0288 (6) | −0.0026 (5) | 0.0126 (4) | 0.0045 (5) |
| C26   | 0.0441 (7) | 0.0263 (6) | 0.0360 (6) | 0.0033 (5) | 0.0124 (5) | 0.0028 (5) |
| Bond                  | Distance (Å) | Bond                  | Angle (°) |
|-----------------------|--------------|-----------------------|-----------|
| N6—C12                | 1.4615 (13)  | C19—C20               | 1.5152 (19)|
| C7—O8                 | 1.2413 (13)  | C19—H192              | 0.956     |
| C7—N9                 | 1.3644 (14)  | C19—H191              | 1.006     |
| N9—C10                | 1.4923 (12)  | C20—H201              | 0.978     |
| N9—C20                | 1.4682 (14)  | C20—H202              | 0.964     |
| C10—C11               | 1.5311 (15)  | C21—C22               | 1.377 (2) |
| C10—C13               | 1.5307 (15)  | C21—H211              | 0.987     |
| C10—C14               | 1.5098 (14)  | C22—C23               | 1.401 (2) |
| C11—C12               | 1.5160 (14)  | C22—H221              | 0.980     |
| C11—H111              | 1.006        | C23—C24               | 1.3900 (19)|
| C11—H112              | 0.957        | C23—H231              | 0.928     |
| C12—H122              | 0.990        | C24—H241              | 0.927     |
| C12—H121              | 1.008        | C25—C26               | 1.3877 (17)|
| C13—H131              | 0.962        | C25—H251              | 0.969     |
| C13—H132              | 0.972        | C26—H261              | 0.946     |
| F1—C2—C3              | 118.46 (11)  | C10—C14—N15           | 122.74 (9)|
| F1—C2—C26             | 118.12 (12)  | C10—C14—C18           | 126.60 (9)|
| C3—C2—C26             | 123.42 (11)  | N15—C14—C18           | 110.38 (9)|
| C2—C3—C4              | 118.18 (11)  | C14—N15—C16           | 108.17 (9)|
| C2—C3—H31             | 121.6        | C14—N15—H151          | 125.6     |
| C4—C3—H31             | 120.3        | C16—N15—H151          | 125.8     |
| C3—C4—C5              | 120.04 (10)  | N15—C16—C17           | 107.89 (9)|
| C3—C4—H41             | 119.7        | N15—C16—C24           | 130.05 (11)|
| C5—C4—H41             | 120.3        | C17—C16—C24           | 121.94 (11)|
| C4—C5—N6              | 120.11 (10)  | C16—C17—C18           | 106.83 (9)|
| C4—C5—C25             | 120.03 (10)  | C16—C17—C21           | 119.49 (11)|
| N6—C5—C25             | 119.83 (10)  | C18—C17—C21           | 133.61 (11)|
| C5—N6—C7              | 119.81 (9)   | C17—C18—C14           | 106.70 (9)|
| C5—N6—C12             | 119.65 (9)   | C17—C18—C19           | 130.67 (10)|
| C7—N6—C12             | 120.44 (9)   | C14—C18—C19           | 122.47 (10)|
| N6—C7—O8              | 120.57 (10)  | C18—C19—C20           | 109.07 (10)|
| N6—C7—N9              | 117.29 (9)   | C18—C19—H192          | 111.5     |
| O8—C7—N9              | 122.10 (10)  | C20—C19—H192          | 109.0     |
| C7—N9—C10             | 124.52 (9)   | C18—C19—H191          | 109.6     |
| C7—N9—C20             | 117.27 (9)   | C20—C19—H191          | 109.6     |
| C10—N9—C20            | 115.60 (8)   | H192—C19—H191         | 108.1     |
| N9—C10—C11            | 109.41 (8)   | C19—C20—N9            | 112.27 (10)|
| N9—C10—C13            | 110.69 (9)   | C19—C20—H201          | 110.7     |
| C11—C10—C13           | 110.01 (9)   | N9—C20—H201           | 107.1     |
| N9—C10—C14            | 105.64 (8)   | C19—C20—H202          | 108.6     |
| C11—C10—C14           | 109.88 (9)   | N9—C20—H202           | 107.1     |
| C13—C10—C14           | 111.12 (9)   | H201—C20—H202         | 111.0     |
| C10—C11—C12           | 110.19 (9)   | C17—C21—C22           | 118.50 (13)|
| C10—C11—H111          | 108.3        | C17—C21—H211          | 120.5     |
| C12—C11—H111          | 107.5        | C22—C21—H211          | 120.9     |
| C10—C11—H112          | 108.3        | C21—C22—C23           | 121.26 (12)|
C12—C11—H112  112.0  C21—C22—H221  119.4
H111—C11—H112  110.5  C23—C22—H221  119.4
C11—C12—N6  107.31 (8)  C22—C23—C24  121.64 (12)
C11—C12—H122  112.4  C22—C23—H231  120.5
N6—C12—H122  108.0  C24—C23—H231  117.9
C11—C12—H121  112.0  C16—C24—C23  117.14 (13)
N6—C12—H121  109.7  C16—C24—H241  120.8
H122—C12—H121  107.4  C23—C24—H241  122.0
C10—C13—H131  108.2  C5—C25—C26  120.52 (11)
C10—C13—H132  111.9  C5—C25—H251  118.8
H131—C13—H132  109.5  C26—C25—H251  120.6
C10—C13—H133  109.1  C25—C26—C2  117.79 (12)
H131—C13—H133  109.3  C25—C26—H261  121.6
H132—C13—H133  108.9  C2—C26—H261  120.6

Hydrogen-bond geometry (Å, °)

| D—H···A          | D—H | H···A  | D···A     | D—H···A |
|------------------|-----|-------|-----------|---------|
| C11—H112···O8i   | 0.96| 2.49  | 3.3175 (18)| 145     |
| N15—H151···O8i   | 0.86| 1.97  | 2.8017 (18)| 164     |

Symmetry code: (i) x+1, y, z.