Supporting Information

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

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Contents

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 **5h**,[2] tryptamine-derived urea **5i**,[3] unsaturated ketones **6c-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 (δ) are reported in ppm with the solvent resonance as the internal standard (e.g. DMSO δ 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

[1] M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797.
[2] R. J. Herr, J. L. Kuhler, H. Meckler, C. J. Opalka, *Synthesis* **2000**, *11*, 1569-1574.
[3] S. A. Rogers, D. C. Whitehead, T. Mullikin, C. Melander, *Org. Biomol. Chem.* **2010**, *8*, 3857–3859.
[4] L. A. Batory, C. E. McInnis, J. T. Njardarson, *J. Am. Chem. Soc.* **2006**, *128*, 16054–16055.
[5] R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84–86.

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

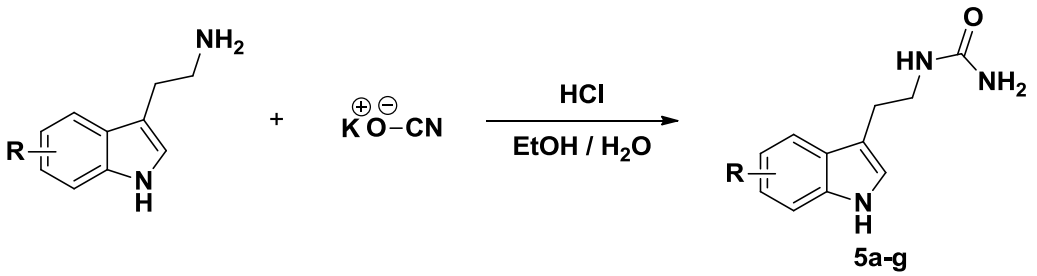
Optical rotations were recorded using a Perkin-Elmer 241 polarimeter; specific rotation (SR) ($[\alpha]_D^{23}$) are reported in 10^{-1} deg cm^2g^{-1}; concentrations (*c*) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm), temperatures (*T*) are given in degrees Celsius (°C).

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

2. Practical experimental

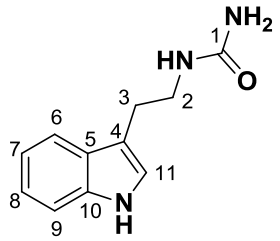
2.1 Synthesis of starting materials

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**.

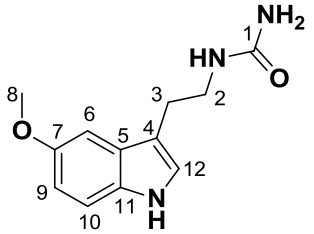
2.1.1.1 Synthesis and characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]urea 5a



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: CH_2Cl_2/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; **^{1}H NMR** (500 MHz, [D_6]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; NH_2 urea), 3.30 (q, *J*=7.5 Hz, 2H; H2), 2.81 (t, *J*=7.5 Hz, 2H; H3); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{11}H_{13}N_3NaO^+$) requires *m/z* 226.0951, found *m/z* 226.0956.

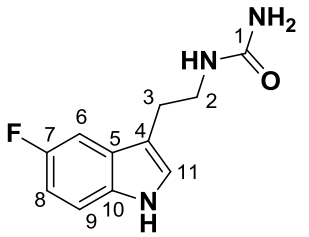
2.1.1.2 Synthesis and characterisation of 1-[2-(5-methoxy-*1H*-indol-3-yl)ethyl]urea 5b



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: CH_2Cl_2/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, [D_6]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; NH_2 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, [D_6]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]$^+$ ($C_{12}H_{15}N_3NaO_2^+$) 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

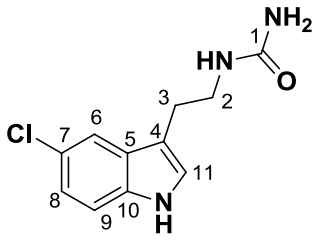


The title compound was synthesised according to general procedure **I**. 5-Fluorotryptamine (500 mg, 2.81 mmol) was reacted with KOCN (274 mg, 3.37 mmol) in ethanol (3.0 mL) and water (3.0 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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, [D_6]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 (td, *J*=9.0, 2.5 Hz, 1H; H9), 5.96 (br. s., 1H; NH urea), 5.44 (br. s., 2H; NH_2 urea), 3.23-3.19 (m, 2H; H2), 2.75 (t, *J*=7.0 Hz, 2H; H3); **^{13}C NMR** (125 MHz, [D_6]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 $[M+Na]^+$ ($C_{11}H_{12}FN_3NaO^+$) requires *m/z* 244.0857, found *m/z* 244.0862.

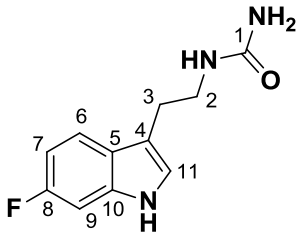
2.1.1.4 Synthesis and characterisation of 1-[2-(5-chloro-*1H*-indol-3-yl)ethyl]urea 5d



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: CH_2Cl_2/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; **^{1}H NMR** (500 MHz, $[D_6]$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; NH_2 urea), 3.26-3.22 (m, 2H; H2), 2.76 (t, *J*=7.5 Hz, 2H; H3); **^{13}C NMR** (125 MHz, $[D_6]$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 $[M+Na]^+$ ($C_{11}H_{12}ClN_3NaO^+$) requires *m/z* 260.0561, found *m/z* 260.0559.

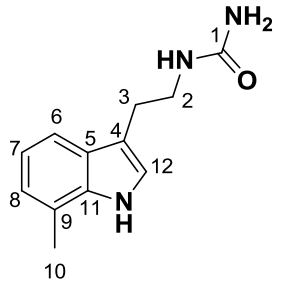
2.1.1.5 Synthesis and characterisation of 1-[2-(6-fluoro-*1H*-indol-3-yl)ethyl]urea 5e



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: CH_2Cl_2/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]$^+$ ($C_{11}H_{12}FN_3NaO^+$) requires *m/z* 244.0857, found *m/z* 244.0859.

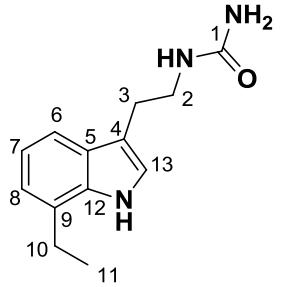
2.1.1.6 Synthesis and characterisation of 1-[2-(7-methyl-*1H*-indol-3-yl)ethyl]urea 5f



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_2Cl_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]$^+$ ($C_{12}H_{15}N_3NaO^+$) requires *m/z* 240.1107, found *m/z* 240.1110.

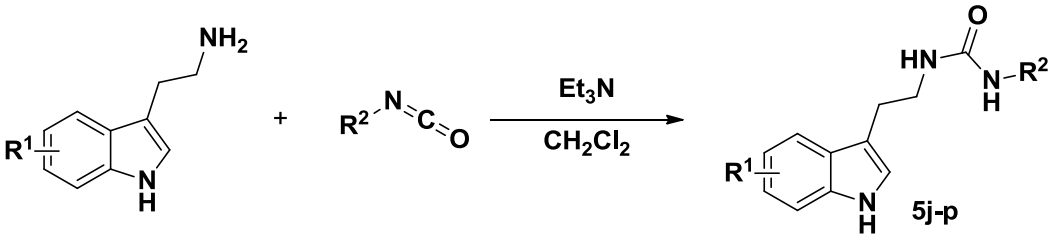
2.1.1.7 Synthesis and characterisation of 1-[2-(7-ethyl-*1H*-indol-3-yl)ethyl]urea 5g



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: CH_2Cl_2/MeOH 95/5) to afford product **5g** in 59% yield (0.730 g) as a brown powder.

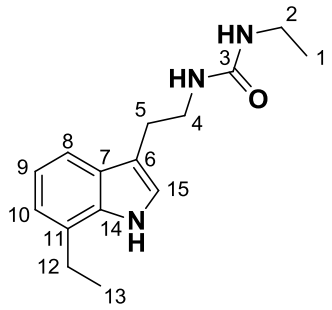
m.p. 164-166 °C; **IR** (neat) ν=3390, 3322, 3206, 2964, 1643, 1607, 1097, 1081, 799, 742; **^{1}H NMR** (400 MHz, [D_6]DMSO, 25 °C) δ=10.77 (br. s., 1H; NH indole), 7.36 (d, *J*=7.0 Hz, 1H; H6), 7.11 (d, *J*=2.0 Hz, 1H; H13), 6.93-6.85 (m, 2H; H7 and H8), 5.93 (br. s., 1H; NH urea), 5.42 (br. s., 2H; NH_2 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); **^{13}C NMR** (100 MHz, [D_6]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]$^+$ ($C_{13}H_{17}N_3NaO^+$) 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 CH_2Cl_2 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 CH_2Cl_2 and dried under vacuum to afford the desired ureas **5j-p**. The ureas were used in the next step without further purification.

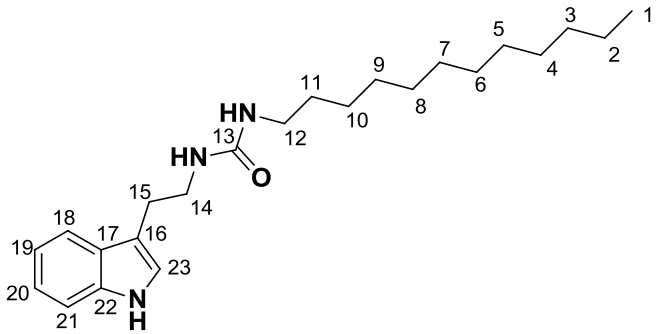
2.1.2.1 Synthesis and characterisation of 1-[2-(7-ethyl-*1H*-indol-3-yl)ethyl)-3-(ethyl]urea 5j



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_2Cl_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]$^+$ ($C_{15}H_{21}N_3NaO^+$) 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

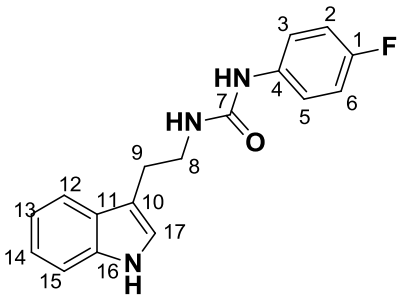


The title compound was synthesised according to general procedure **II**. Tryptamine (1.00 g, 6.24 mmol) was reacted with dodecylisocyanate (1.35 mL, 5.62 mmol) in CH_2Cl_2 (100 mL) for 14 hours. Product **5k** was isolated in 70% yield (1.62 g) as a white powder.

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), 28.9 (1C of C2-C10), 28.7 (1C of C2-C10), 28.6 (1C of C2-10), 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]$^+$ ($C_{23}H_{37}N_3NaO^+$) requires *m/z* 394.2829, found *m/z* 394.2832.

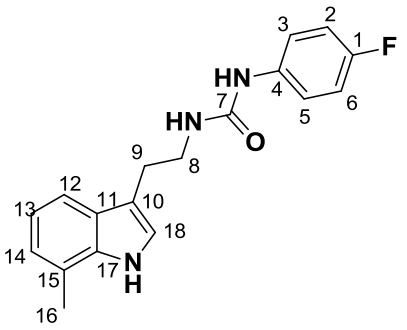
2.1.2.3 Synthesis and characterisation of 1-[2-(*1H*-indol-3-yl)ethyl)-3-(4-fluorophenyl]urea 5l



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_2Cl_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, 1623, 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]$^+$ ($C_{17}H_{16}FN_3NaO^+$) requires *m/z* 320.1170, found *m/z* 320.1166.

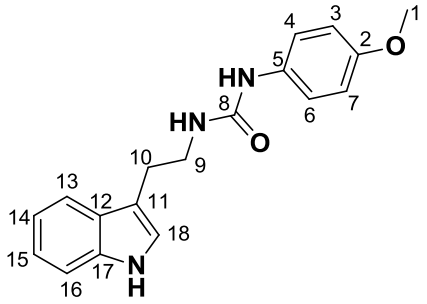
2.1.2.4 Synthesis and characterisation of 1-[2-(7-methyl-*1H*-indol-3-yl)ethyl)-3-(4-fluorophenyl]urea 5m



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 CH_2Cl_2 (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; **^{1}H NMR** (500 MHz, [D_6]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; H8), 2.86 (t, *J*=7.0 Hz, 2H; H9), 2.45 (s, 3H; H16); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{18}H_{18}FN_3NaO^+$) requires *m/z* 334.1326, found *m/z* 334.1326.

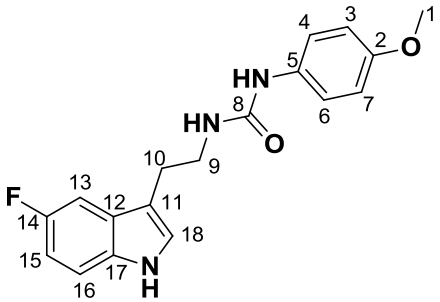
2.1.2.5 Synthesis and characterisation of 1-[2-(*1H*-indol-3-yl)ethyl)-3-(4-methoxyphenyl]urea 5n



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 CH_2Cl_2 (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; **^{1}H 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); **^{13}C 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]$^+$ ($C_{18}H_{19}N_3NaO_2^+$) requires *m/z* 332.1369, found *m/z* 332.1369.

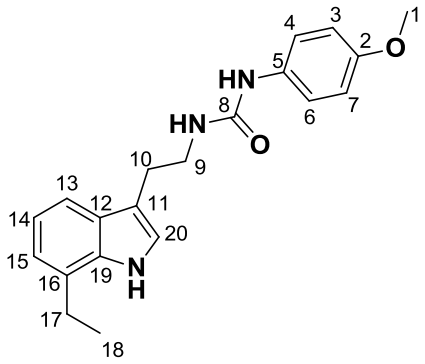
2.1.2.6 Synthesis and characterisation of 1-[2-(5-fluoro-*1H*-indol-3-yl)ethyl)-3-(4-methoxyphenyl]urea 5o



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_2Cl_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; **^{1}H 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); **^{13}C 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]$^+$ ($C_{18}H_{18}FN_3NaO_2^+$) requires *m/z* 350.1275, found *m/z* 350.1276.

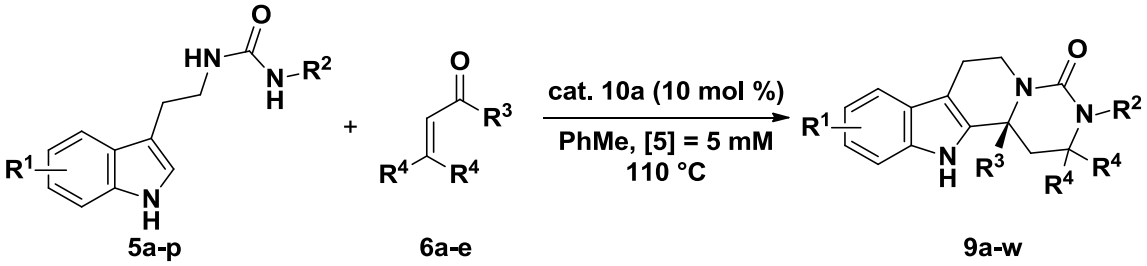
2.1.2.7 Synthesis and characterisation of 1-[2-(7-ethyl-*1H*-indol-3-yl)ethyl)-3-(4-methoxyphenyl]urea 5p



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 CH_2Cl_2 (50 mL) for 14 hours. Product **5p** was isolated in 45% yield (405 mg) as a pale brown powder.

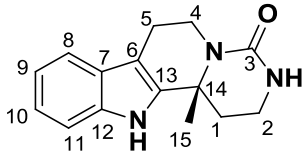
m.p. 160-162 °C; **IR** (neat) ν=3454, 3426, 3391, 2966, 2934, 1630, 1575, 1245, 1030, 832, 738; **^{1}H NMR** (500 MHz, [D_6]DMSO, 25 °C) δ=10.80 (br. s., 1H; NH indole), 8.27 (s, 1H; C5-NH urea), 7.40 (d, *J*=7.5 Hz, 1H; H13), 7.28 (d, *J*=9.0 Hz, 2H; H4 and H6), 7.15 (d, *J*=2.5 Hz, 1H; H20), 6.94-6.88 (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); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{20}H_{23}N_3NaO_2^+$) 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(12*H*)-one 9a

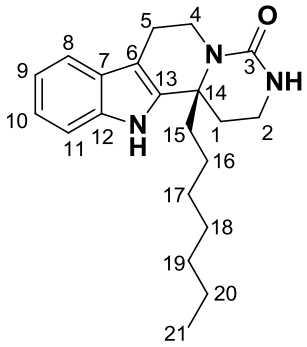


The title compound was synthesised according to general procedure **III**. Urea derivative **5a** (61 mg, 0.30 mmol) was reacted with methyl vinyl ketone **6a** (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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); $[\alpha]_D^{23}$=+50 (*c*=0.08, MeOH).

m.p. 178-180 °C; **IR** (neat) ν=3406, 3284, 3228, 1633, 1508, 743; **^{1}H NMR** (500 MHz, [D_6]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; H2), 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); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{15}H_{17}N_3NaO^+$) 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(12*H*)-one 9b

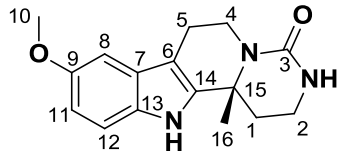


The title compound was synthesised according to general procedure **III**. Urea derivative **5a** (20 mg, 0.10 mmol) was reacted with heptyl vinyl ketone **6c** (77 mg, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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); $[\alpha]_D^{23}$=+40 (*c*=0.16, MeOH).

m.p. 112-114 °C; **IR** (neat) ν=3405, 3227, 2925, 2853, 1632, 1504, 1449, 740, 703; **^{1}H NMR** (500 MHz, [D_6]DMSO, 25 °C) δ=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_6]DMSO, 25 °C) δ=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]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{21}H_{29}N_3NaO^+$) requires *m/z* 362.2203, found *m/z* 362.2204.

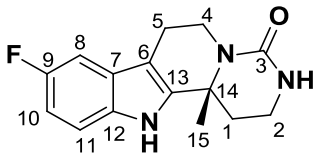
2.2.3 Synthesis and characterisation of (*R*)-9-methoxy-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9c



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: CH_2Cl_2/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, $t_{r\ (major)}$=27.9 min; $t_{r\ (minor)}$=43.8 min); $[\alpha]_D^{23}$=+71 (*c*=0.16, MeOH).
m.p. 140-142 °C; **IR** (neat) ν=3410, 3275, 2930, 1626, 1508, 1281, 1160, 800, 754; **^{1}H NMR** (500 MHz, [D_6]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); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{16}H_{19}N_3NaO_2^+$) 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(12*H*)-one 9d

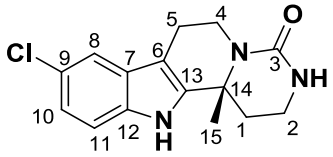


The title compound was synthesised according to general procedure **III**. Urea derivative **5c** (15 mg, 0.07 mmol) was reacted with methyl vinyl ketone **6a** (28 µL, 0.34 mmol) in PhMe (14 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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, $t_{r\ (major)}$=22.6 min; $t_{r\ (minor)}$=49.3 min); $[\alpha]_D^{23}$=+99 (*c*=0.09, MeOH).
m.p. 168-170 °C; **IR** (neat) ν=3401, 3283, 2926, 1630, 1509, 1449, 1158, 801, 754; **^{1}H NMR** (500 MHz, [D_6]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), 2.63-2.57 (m, 1H; H5'), 2.38-2.35 (m, 1H; H1'), 2.55-2.51 (m, 1H; H5), 1.75 (td, *J*=13.0, 5.5 Hz, 1H; H1); 1.53 (s, 3H; H15), **^{13}C NMR** (125 MHz, [D_6]DMSO, 25 °C) δ=156.8 (d, *J*=230 Hz, C9), 154.3 (C3), 141.5 (C13), 132.6 (C12), 126.5 (d, *J*=10 Hz, C7), 111.8 (d, *J*=10 Hz, C10), 108.7 (d, *J*=26 Hz, C11), 106.6 (C6), 102.8 (d, *J*=24 Hz, C8), 53.8 (C14), 35.8 (C4), 35.3 (C2), 33.7 (C1), 23.7 (C15), 21.2 (C5); **MS** *m/z* (ES+) 569 ([2M+Na]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{15}H_{16}FN_3NaO^+$) requires *m/z* 296.1170, found *m/z* 296.1175.

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(12*H*)-one 9e

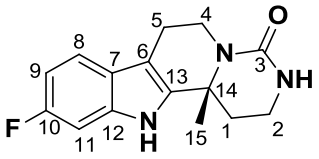


The title compound was synthesised according to general procedure **III**. Urea derivative **5d** (24 mg, 0.10 mmol) was reacted with methyl vinyl ketone **6a** (41 µL, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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); $[\alpha]_D^{23}$=+96 (*c*=0.09, MeOH).

m.p. 160-162 °C; **IR** (neat) ν=3305, 3188, 2917, 1632, 1507, 1433, 800, 759; **^{1}H NMR** (500 MHz, [D_6]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'); 3.20-3.10 (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), 2.38-2.35 (m, 1H; H1'), 1.75 (td, *J*=13.0, 5.5 Hz, 1H; H1), 1.53 (s, 3H; H15); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{15}H_{16}ClN_3NaO^+$) requires *m/z* 312.0874, found *m/z* 312.0869.

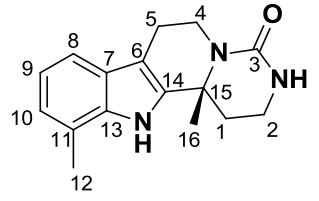
2.2.6 Synthesis and characterisation of (*R*)-10-fluoro-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9f



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: CH_2Cl_2/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); $[\alpha]_D^{23}$=+70 (*c*=0.13, MeOH).
IR (neat) ν=3275, 2966, 2924, 2854, 1629, 1505, 1472, 1378, 1282, 1259, 1114, 954; **^{1}H NMR** (500 MHz, [D_6]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); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{15}H_{16}FN_3NaO^+$) 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*]indol-4(12*H*)-one 9g

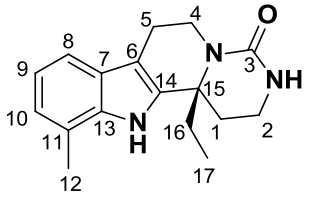


The title compound was synthesised according to general procedure **III**. Urea derivative **5f** (65 mg, 0.30 mmol) was reacted with methyl vinyl ketone **6a** (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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); $[\alpha]_D^{23}$=+133 (*c*=0.22, MeOH).

m.p. 170-172 °C; **IR** (neat) ν=3284, 3218, 2972, 1630, 1506, 1439, 1351, 1153, 778, 745; **^{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), 6.92-6.85 (m, 2H; H9 and H10), 6.43 (d, *J*=4.0 Hz, 1H; NH urea), 4.61 (dd, *J*=13.0, 4.0 Hz, 1H; H4'), 3.41-3.37 (m, 1H; H2'), 3.20-3.17 (m, 1H; H2), 2.92 (td, *J*=13.0, 4.0 Hz, 1H; H4), 2.66-2.54 (m, 3H; H1' and H5), 2.46 (s, 3H; H12), 1.74 (td, *J*=13.0, 5.5 Hz, 1H; H1), 1.57 (s, 3H; H16); **^{13}C NMR** (125 MHz, [D_6]DMSO, 25 °C) δ=154.3 (C3), 139.1 (C14), 135.4 (C13), 125.9 (C7), 120.2 (C11), 121.6 (C10), 118.7 (C9), 115.4 (C8), 106.6 (C6), 53.8 (C15), 35.8 (C4), 35.4 (C2), 33.6 (C1), 23.5 (C16), 21.4 (C5), 17.0 (C12); **MS** *m/z* (ES+) 561 ([2M+Na]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{16}H_{19}N_3NaO^+$) requires *m/z* 292.1420, found *m/z* 292.1419.

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

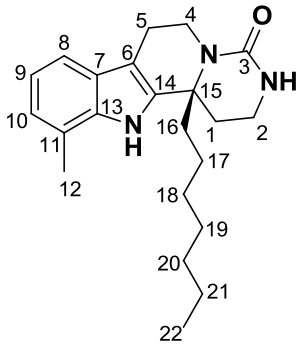


The title compound was synthesised according to general procedure **III**. Urea derivative **5f** (65 mg, 0.30 mmol) was reacted with ethyl vinyl ketone **6b** (0.15 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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).

m.p. 158-160 °C; **IR** (neat) ν=3412, 3283, 2967, 2936, 1632, 1505, 798, 741; **^{1}H NMR** (500 MHz, [D_6]DMSO, 25 °C) δ=10.46 (br. s., 1H; NH indole), 7.23 (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, 4.5 Hz, 1H; H4'), 3.32-3.21 (m, 1H; H2'), 3.13-3.06 (m, 1H; H2), 3.01 (td, *J*=13.0, 4.5 Hz, 1H; H4), 2.65-2.60 (m, 1H; H5'), 2.58-2.54 (m, 2H; H1' and H5), 2.47 (s, 3H; H12), 2.03 (q, *J*=7.5 Hz, 2H; H16), 1.78 (td, *J*=13.0, 5.5 Hz, 1H; H1), 0.88 (t, *J*=7.5 Hz, 3H; H17); **^{13}C NMR** (125 MHz, [D_6]DMSO, 25 °C) δ=155.0 (C3), 137.4 (C14), 135.5 (C13), 126.0 (C7), 121.6 (C10), 120.2 (C11), 118.6 (C9), 115.3 (C8), 107.8 (C6), 57.0 (C15), 37.2 (C4), 35.5 (C2), 32.6 (C1), 30.8 (C16), 21.0 (C5), 17.1 (C12), 9.7 (C17); **MS** *m/z* (ES+) 589 ([2M+Na]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{17}H_{21}N_3NaO^+$) requires *m/z* 306.1577, found *m/z* 306.1564.

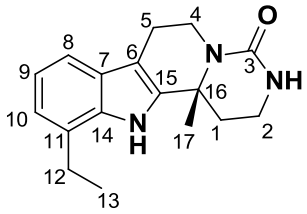
2.2.9 Synthesis and characterisation of (*R*)-11-methyl-12b-heptyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9i



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_2Cl_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 $[M+Na]^+$ ($C_{22}H_{31}N_3NaO^+$) requires *m/z* 376.2359, found *m/z* 376.2356.

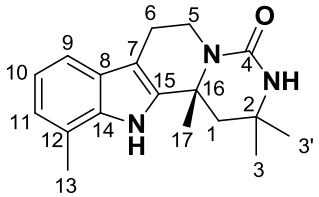
2.2.10 Synthesis and characterisation of (*R*)-11-ethyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9j



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: CH_2Cl_2/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, $t_{r\ (major)}$=27.6 min; $t_{r\ (minor)}$=38.8 min); $[\alpha]_D^{23}$=+98 (*c*=0.12, MeOH).
m.p. 288-290 °C (dec.); **IR** (neat) ν=3412, 3285, 2967, 2931, 1633, 1506, 1352, 1153, 794; **^{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), 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); **^{13}C NMR** (125 MHz, [D_6]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]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{17}H_{21}N_3NaO^+$) 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(12*H*)-one 9k

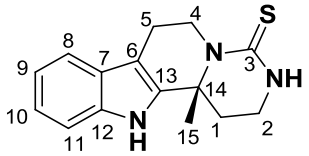


The title compound was synthesised according to general procedure **III**. Urea derivative **5f** (65 mg, 0.30 mmol) was reacted with mesityl oxide **6e** (0.17 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 95/5) 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, $t_{r\ (minor)}$=16.7 min; $t_{r\ (major)}$=18.6 min); $[\alpha]_D^{23}$=+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), 4.55 (dd, *J*=13.0, 5.0 Hz, 1H; H5'), 3.04 (ddd, *J*=13.0, 11.5, 5.0 Hz, 1H; H5), 2.65-2.55 (m, 2H; H6), 2.46 (s, 3H; H13), 2.34 (d, *J*=14.0, 1H; H1'), 2.23 (d, *J*=14.0, 1H; H1), 1.63 (s, 3H; H17), 1.26 (s, 3H; H3'), 0.92 (s, 3H; H3); **^{13}C 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]$^+$ ($C_{18}H_{23}N_3NaO^+$) 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(12*H*)-thione 9l

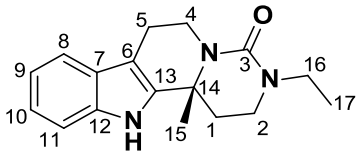


The title compound was synthesised according to general procedure **III**. Thiourea derivative **5h** (66 mg, 0.30 mmol) was reacted with methyl vinyl ketone **6a** (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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, ^3J(H,H)=4.5 Hz, 1H; NH urea), 7.43 (d, ^3J(H,H)=7.5 Hz, 1H; H8), 7.33 (d, ^3J(H,H)=8.0 Hz, 1H; H11), 7.08 (td, ^3J(H,H)=8.0, 1.5 Hz, 1H; H10), 6.99 (td, ^3J(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, ^3J(H,H)=13.0, 5.5 Hz, 1H; H1), 1.61 (s, 3H; H15); **^{13}C NMR** (125 MHz, [D_6]DMSO, 25 °C) δ=176.5 (C3), 138.0 (C13), 136.1 (C12), 126.90 (C7), 121.1 (C10), 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]$^+$ ($C_{15}H_{17}N_3NaS^+$) requires *m/z* 294.1035, found *m/z* 294.1030.

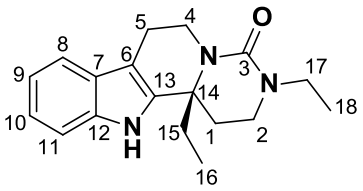
2.2.13 Synthesis and characterisation of (*R*)-3-ethyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9m



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: CH_2Cl_2/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, [D_6]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, [D_6]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]$^+$ ($C_{17}H_{21}N_3NaO^+$) requires *m/z* 306.1577, found *m/z* 306.1575.

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

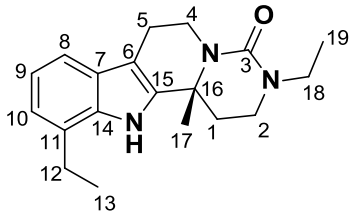


The title compound was synthesised according to general procedure **III**. Urea derivative **5i** (69 mg, 0.30 mmol) was reacted with ethyl vinyl ketone **6b** (0.15 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/Acetone 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, 1501, 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; H1'), 2.02-1.95 (m, 1H; H15'), 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; H16); **^{13}C 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]$^{+}$ ($C_{18}H_{23}N_3NaO^{+}$) 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(12*H*)-one 9o

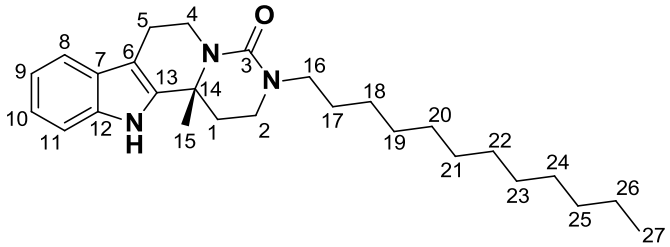


The title compound was synthesised according to general procedure **III**. Urea derivative **5j** (78 mg, 0.30 mmol) was reacted with methyl vinyl ketone **6a** (0.12 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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, 1503, 1455, 1355, 1277, 1176, 747; **^{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); **^{13}C 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]$^{+}$ ($C_{19}H_{25}N_3NaO^{+}$) requires *m/z* 334.1890, found *m/z* 334.1888.

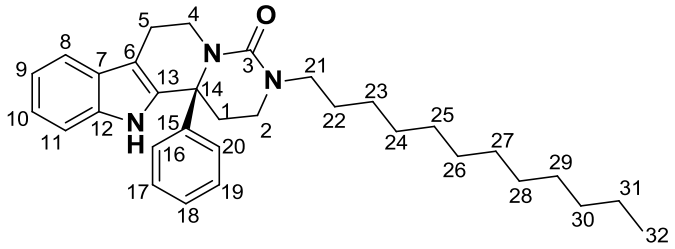
2.2.16 Synthesis and characterisation of (*R*)-3-dodecyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9p



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: CH_2Cl_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, $t_{r\ (major)}$=11.3 min; $t_{r\ (minor)}$=19.1 min); $[\alpha]_D^{23}$=+80 (*c*=0.56, MeOH).
IR (neat) ν=3231, 2923, 2852, 1602, 1502, 1453, 1352, 1297, 1275, 1173, 739; **^{1}H NMR** (500 MHz, [D_6]DMSO, 25 °C) δ=10.91 (br. s., 1H; NH indole), 7.39 (d, *J*=8.0 Hz, 1H; H8), 7.31 (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), 4.65 (dd, *J*=13.0, 4.5 Hz, 1H; H4'), 3.47 (td, *J*=13.0, 4.0 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 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 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 Hz, 3H; H27); **^{13}C NMR** (125 MHz, [D_6]DMSO, 25 °C) δ=154.0 (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 (1C of C18-C26), 29.0 (1C of C18-C26), 29.0 (1C of C18-C26), 29.1 (1C of C18-C26), 29.0 (1C of C18-C26), 28.8 (1C of C18-C26), 28.7 (1C of C18-C26), 27.1 (C17), 26.3 (1C of C18-C26), 23.5 (C15), 22.1 (1C of C18-C26), 21.3 (C5), 13.9 (C27); **MS** *m/z* (ES+) 869 ($[2M+Na]^+$, 100%); **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{27}H_{41}N_3NaO^+$) 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(12*H*)-one 9q

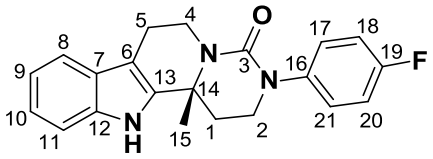


The title compound was synthesised according to general procedure **III**. Urea derivative **5k** (37 mg, 0.10 mmol) was reacted with phenyl vinyl ketone **6d** (66 µL, 0.50 mmol) in PhMe (20 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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); $[\alpha]_D^{23}$=−128 (*c*=0.50, MeOH).

m.p. 187-189 °C; **IR** (neat) ν=3257, 2922, 2852, 1603, 1496, 1453, 1354, 1272, 742, 701; **^{1}H NMR** (500 MHz, [D_6]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); **^{13}C NMR** (125 MHz, [D_6]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]$^-$ ($C_{32}H_{42}N_3O^-$) requires *m/z* 484.3333, found *m/z* 484.3332.

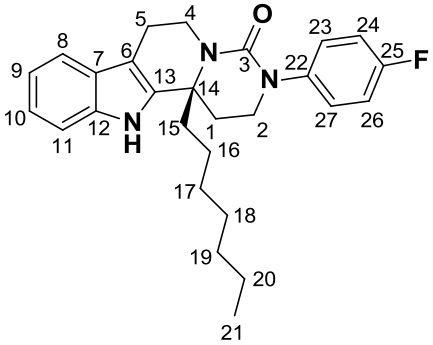
2.2.18 Synthesis and characterisation of (*R*)-3-(4-fluorophenyl)-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9r



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: CH_2Cl_2/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, $t_{r\ (major)}$=4.2 min; $t_{r\ (minor)}$=11.6 min); $[\alpha]_D^{23}$=+100 (*c*=0.05, MeOH).
The sample has been recrystallized 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; **^{1}H NMR** (500 MHz, [D_6]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*=7.5, 1.0 Hz, 1H; H10), 6.99 (td, *J*=7.5, 1.0 Hz, 1H; H9), 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); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{21}H_{20}FN_3NaO^+$) 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(12*H*)-one 9s

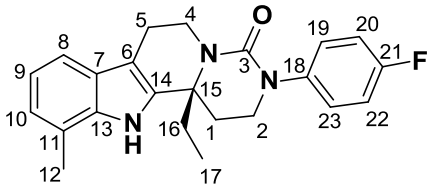


The title compound was synthesised according to general procedure **III**. Urea derivative **5l** (30 mg, 0.10 mmol) was reacted with heptyl vinyl ketone **6c** (77 mg, 0.5 mmol) in PhMe (20 mL) for

15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/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, $t_{r\ (major)}$=5.8 min; $t_{r\ (minor)}$=15.4 min); $[\alpha]_D^{23}$=+118 (*c*=0.31, MeOH).
m.p. 108-110 °C; **IR** (neat) ν=3270, 2924, 2853, 1616, 1596, 1509, 1448, 1215, 835, 743; **^{1}H NMR** (500 MHz, [D_6]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*=7.5, 1.5 Hz, 1H; H9), 4.70 (dd, *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); **^{13}C NMR** (125 MHz, [D_6]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]$^+$ ($C_{27}H_{32}FN_3NaO^+$) 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(12*H*)-one 9t

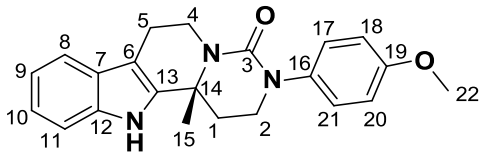


The title compound was synthesised according to general procedure **III**. Urea derivative **5m** (93 mg, 0.30 mmol) was reacted with ethyl vinyl ketone **6b** (0.15 mL, 1.5 mmol) in PhMe (60 mL) for 15 hours. The residue was purified by flash column chromatography on silica gel (solvent: CH_2Cl_2/MeOH 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, $t_{r\ (major)}$=7.0 min; $t_{r\ (minor)}$=12.1 min); $[\alpha]_D^{23}$=+122 (*c*=0.10, MeOH).
m.p. 191-193 °C; **IR** (neat) ν=3284, 3192, 2930, 1610, 1508, 1444, 1213, 832, 778, 746; **^{1}H NMR** (500 MHz, [D_6]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); **^{13}C NMR** (125 MHz, [D_6]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); 9.5 (C17); **MS** *m/z* (ES+) 777 ([2M+Na]$^+$, 100%); **HRMS** (ES+) exact mass calculated for [M+Na]$^+$ ($C_{23}H_{24}FN_3NaO^+$) requires *m/z* 400.1796, found *m/z* 400.1798.

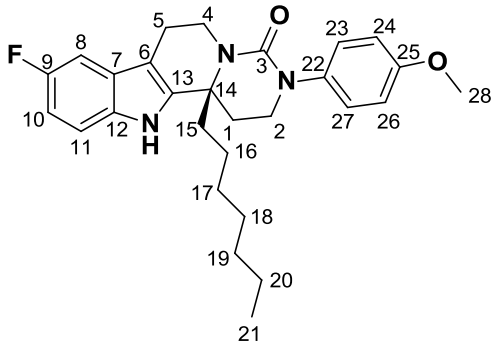
2.2.21 Synthesis and characterisation of (*R*)-3-(4-methoxyphenyl)-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9u



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: CH_2Cl_2/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); $[\alpha]_D^{23}$=+94(*c*=0.13, MeOH).
m.p. 122-124 °C; **IR** (neat) ν=3345, 3295, 2963, 2918, 1633, 1594, 1513, 1491, 751; **^{1}H 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); **^{13}C 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]$^+$ ($C_{22}H_{24}N_3O_2^+$) requires *m/z* 362.1863, found *m/z* 362.1860.

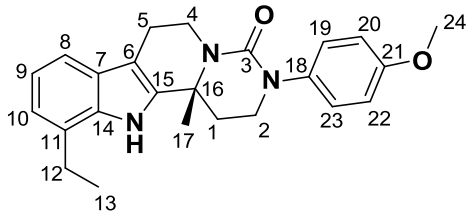
2.2.22 Synthesis and characterisation of (*R*)-3-(4-methoxyphenyl)-9-fluoro-12b-heptyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9v



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: CH_2Cl_2/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, $t_{r\ (major)}$=5.0 min; $t_{r\ (minor)}$=8.6 min); $[\alpha]_D^{23}$=+101 (*c*=0.21, MeOH).
IR (neat) ν=3247, 2928, 2856, 1602, 1512, 1445, 1170, 1034, 831, 797, 747; **^{1}H NMR** (500 MHz, [D_6]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); **^{13}C NMR** (125 MHz, [D_6]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 $[M+H]^+$ ($C_{28}H_{35}FN_3O_2^+$) requires *m/z* 464.2708, found *m/z* 464.2714.

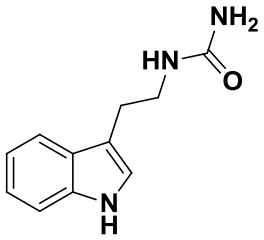
2.2.23 Synthesis and characterisation of (*R*)-3-(4-methoxyphenyl)-11-ethyl-12b-methyl-1,2,3,6,7,12b-hexahydropyrimido[1',6':1,2]pyrido[3,4-*b*]indol-4(12*H*)-one 9w



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: CH_2Cl_2/MeOH 95/5) to afford product **9w** in 74% yield (58 mg) as a brown powder.

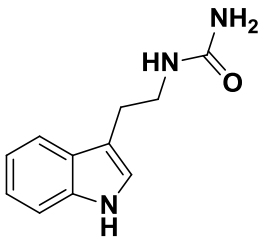
96% ee (Chiralcel AD 60:40 Hexane:Isopropanol, 1.0 mL/min, 220 nm, $t_{r\ (major)}$=4.3 min; $t_{r\ (minor)}$=7.0 min); $[\alpha]_D^{23}$=+106 (*c*=0.16, MeOH).
m.p. 121-123 °C; **IR** (neat) ν=3401, 3280, 2964, 2933, 1602, 1512, 1458, 1246, 1173, 1033, 830, 747; **^{1}H NMR** (500 MHz, [D_6]DMSO, 25 °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); **^{13}C NMR** (125 MHz, [D_6]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 $[M+H]^+$ ($C_{24}H_{28}N_3O_2^+$) requires *m/z* 390.2176, found *m/z* 390.2176.

3.1.1 ^{1}H NMR of compound 5a



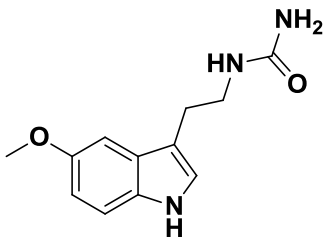
500 MHz, [D_6]DMSO

3.1.2 ^{13}C NMR of compound 5a



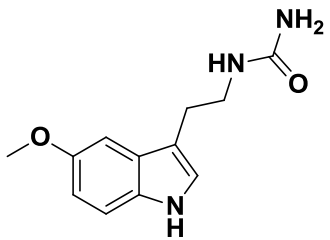
125 MHz, [D6]DMSO

3.2.1 ^{1}H NMR of compound 5b



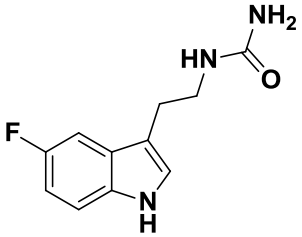
500 MHz, [D_6]DMSO

3.2.2 ^{13}C NMR of compound 5b



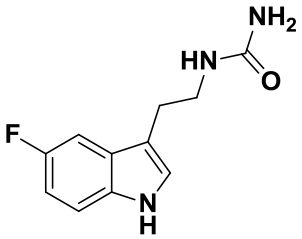
125 MHz, [D_6]DMSO

3.3.1 ^{1}H NMR of compound 5c



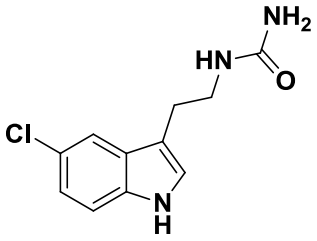
500 MHz, [D_6]DMSO

3.3.2 ^{13}C NMR of compound 5c



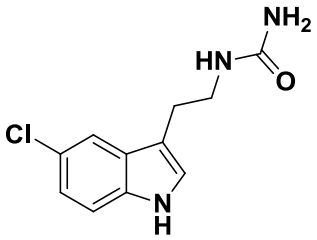
125 MHz, [D_6]DMSO

3.4.1 ^{1}H NMR of compound 5d



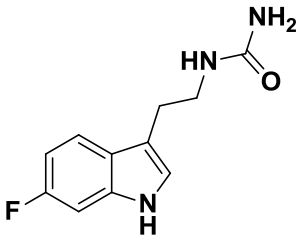
500 MHz, [D_6]DMSO

3.4.2 ^{13}C NMR of compound 5d



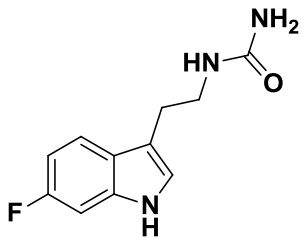
125 MHz, [D_6]DMSO

3.5.1 ^{1}H NMR of compound 5e



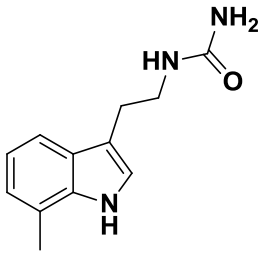
500 MHz, [D_6]DMSO

3.5.2 ^{13}C NMR of compound 5e



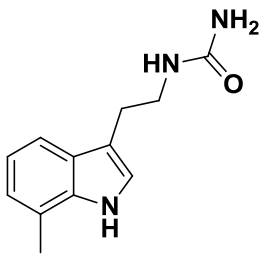
125 MHz, [D6]DMSO

3.6.1 ^{1}H NMR of compound 5f



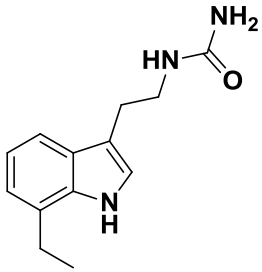
500 MHz, [D$_6$]DMSO

3.6.2 ^{13}C NMR of compound 5f



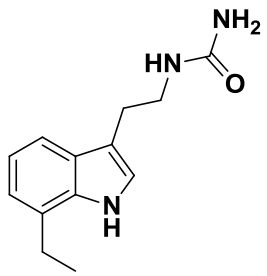
125 MHz, [D_6]DMSO

3.7.1 ^{1}H NMR of compound 5g



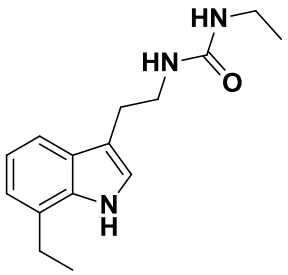
400 MHz, [D_6]DMSO

3.7.2 ^{13}C NMR of compound 5g



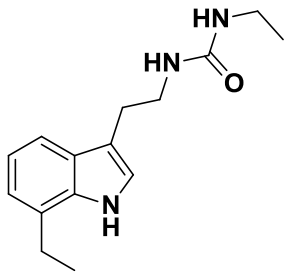
100 MHz, [D_6]DMSO

3.8.1 ^{1}H NMR of compound 5j



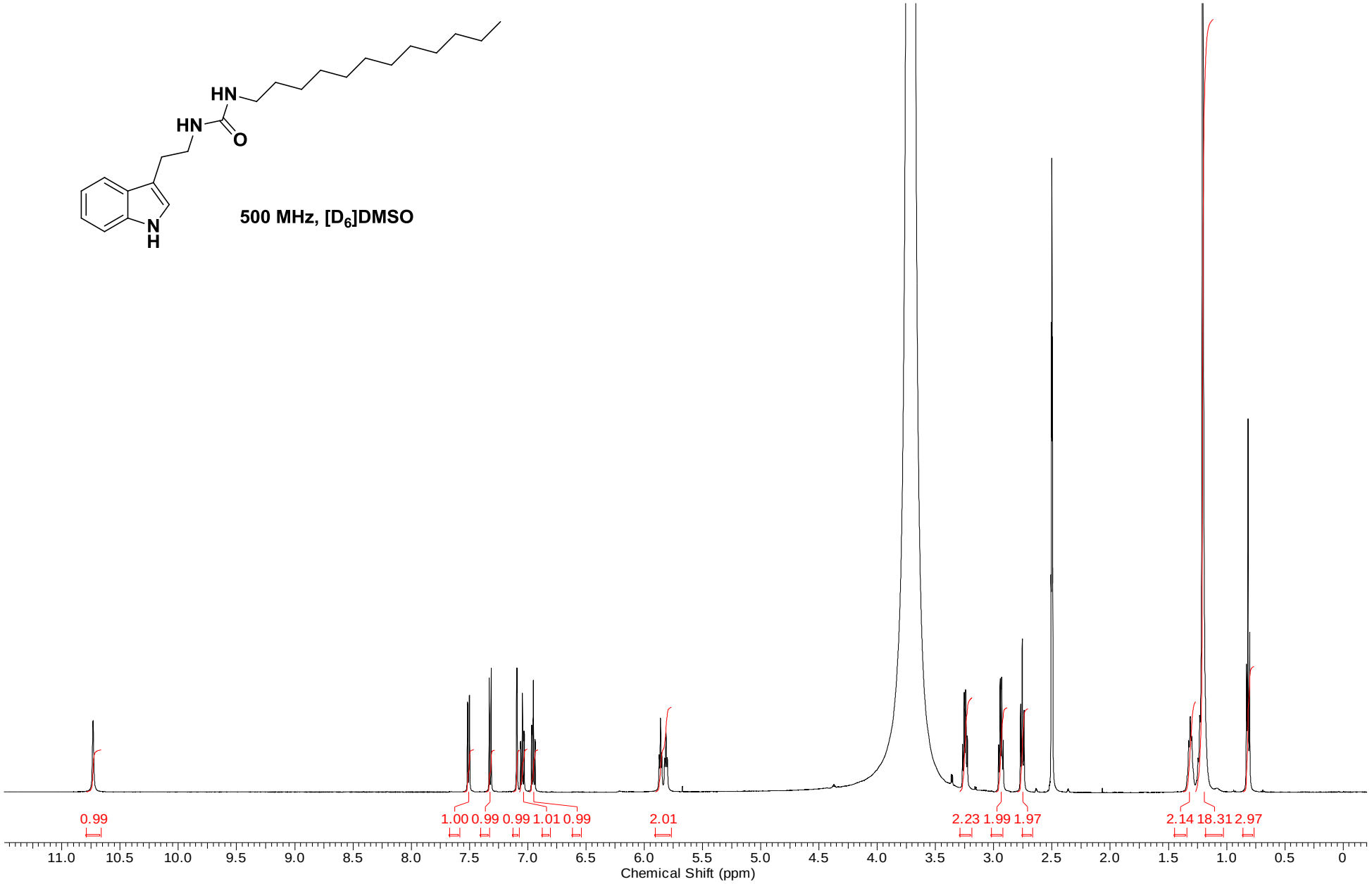
500 MHz, [D_6]DMSO

3.8.2 ^{13}C NMR of compound 5j

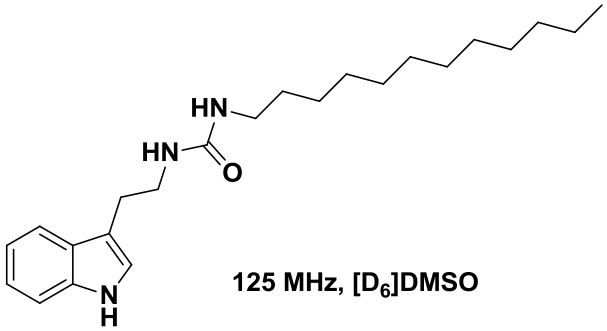


125 MHz, [D_6]DMSO

3.9.1 ^{1}H NMR of compound 5k

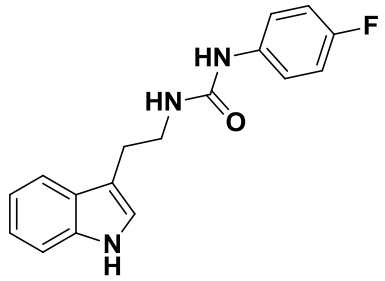


3.9.2 ^{13}C NMR of compound 5k



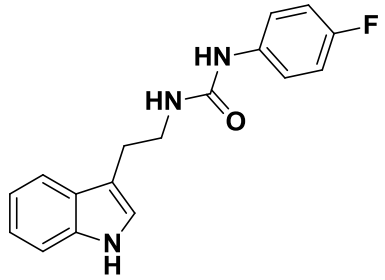
125 MHz, [D_6]DMSO

3.10.1 ^{1}H NMR of compound 5l



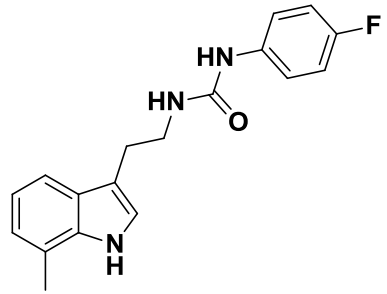
500 MHz, [D_6]DMSO

3.10.2 ^{13}C NMR of compound 5l



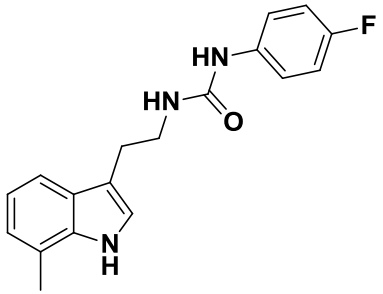
125 MHz, [D_6]DMSO

3.11.1 ^{1}H NMR of compound 5m



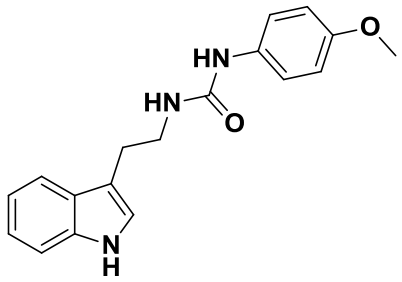
500 MHz, [D$_6$]DMSO

3.11.2 ^{13}C NMR of compound 5m



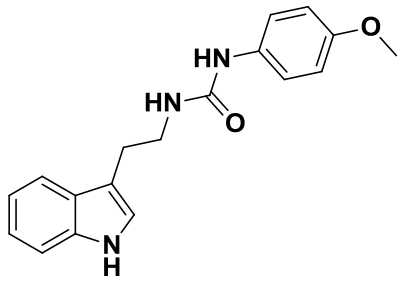
125 MHz, [D_6]DMSO

3.12.1 ^{1}H NMR of compound 5n



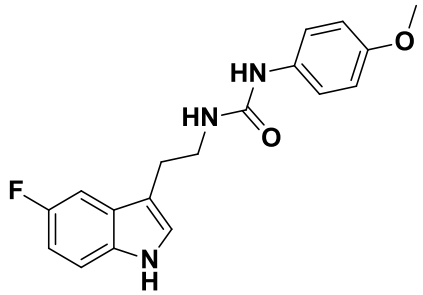
500 MHz, [D_6]DMSO

3.12.2 ^{13}C NMR of compound 5n



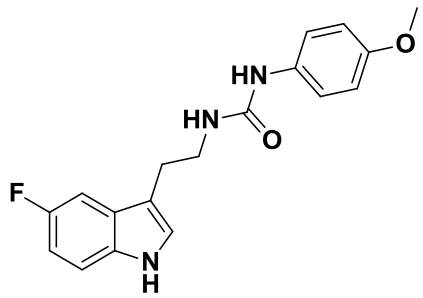
125 MHz, [D_6]DMSO

3.13.1 ^{1}H NMR of compound 5o



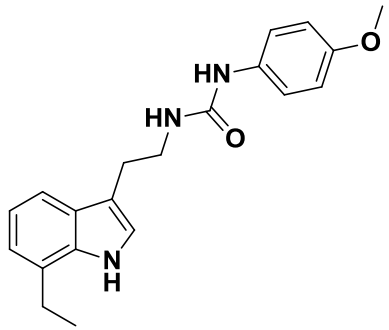
500 MHz, [D_6]DMSO

3.13.2 ^{13}C NMR of compound 5o



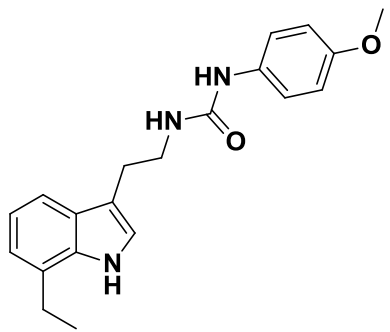
125 MHz, [D_6]DMSO

3.14.1 ^{1}H NMR of compound 5p



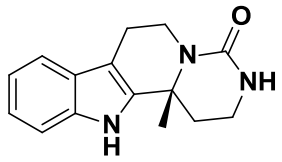
500 MHz, [D_6]DMSO

3.14.2 ^{13}C NMR of compound 5p



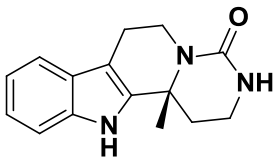
125 MHz, [D_6]DMSO

4.1.1 ^{1}H NMR of compound 9a



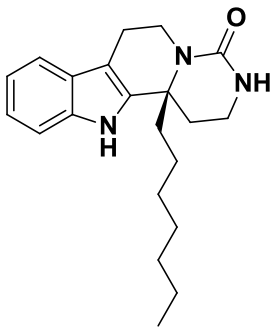
500 MHz, [D$_6$]DMSO

4.1.2 ^{13}C NMR of compound 9a



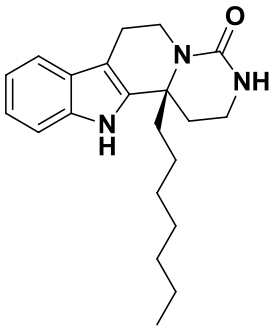
125 MHz, [D_6]DMSO

4.2.1 ^{1}H NMR of compound 9b



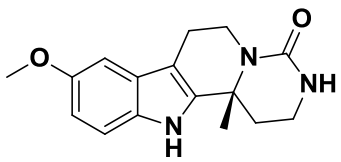
500 MHz, [D_6]DMSO

4.2.2 ^{13}C NMR of compound 9b



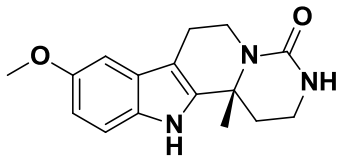
125 MHz, [D_6]DMSO

4.3.1 ^{1}H NMR of compound 9c



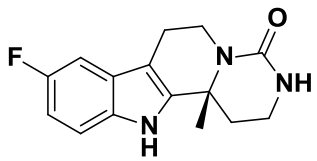
500 MHz, [D_6]DMSO

4.3.2 ^{13}C NMR of compound 9c



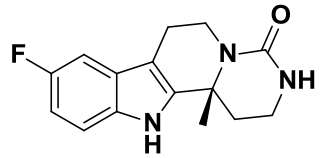
125 MHz, [D_6]DMSO

4.4.1 ^{1}H NMR of compound 9d



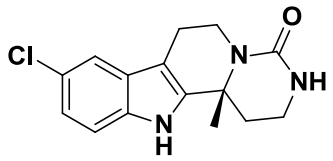
500 MHz, [D_6]DMSO

4.4.2 ^{13}C NMR of compound 9d



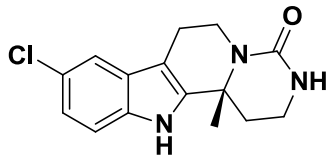
125 MHz, [D_6]DMSO

4.5.1 ^{1}H NMR of compound 9e



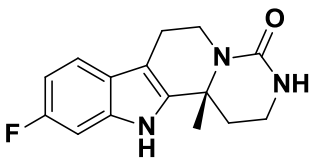
500 MHz, [D_6]DMSO

4.5.2 ^{13}C NMR of compound 9e



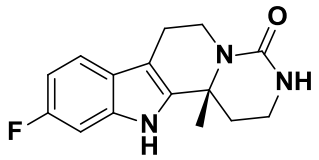
125 MHz, [D$_6$]DMSO

4.6.1 ^{1}H NMR of compound 9f



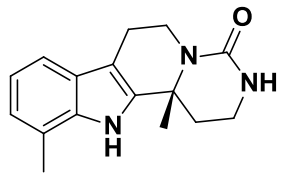
500 MHz, [D_6]DMSO

4.6.2 ^{13}C NMR of compound 9f



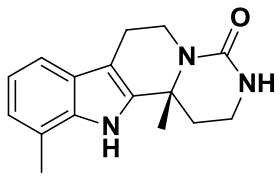
125 MHz, [D_6]DMSO

4.7.1 ^{1}H NMR of compound 9g



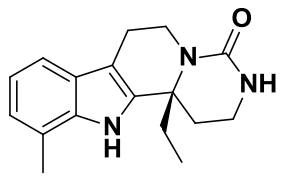
500 MHz, [D_6]DMSO

4.7.2 ^{13}C NMR of compound 9g



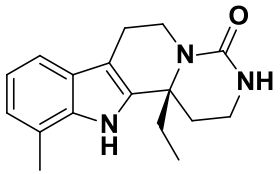
125 MHz, [D_6]DMSO

4.8.1 ^{1}H NMR of compound 9h



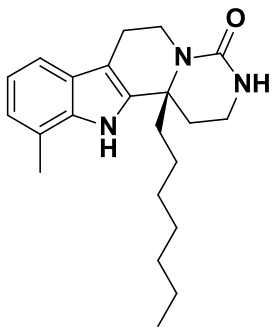
500 MHz, [D_6]DMSO

4.8.2 ^{13}C NMR of compound 9h



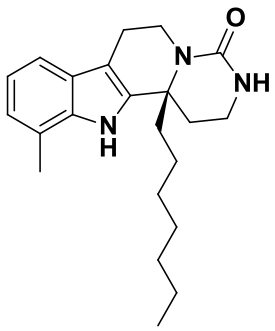
125 MHz, [D_6]DMSO

4.9.1 ^{1}H NMR of compound 9i



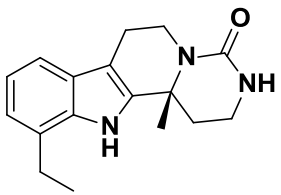
500 MHz, [D_6]DMSO

4.9.2 ^{13}C NMR of compound 9i



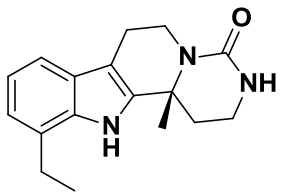
125 MHz, [D_6]DMSO

4.10.1 ^{1}H NMR of compound 9j



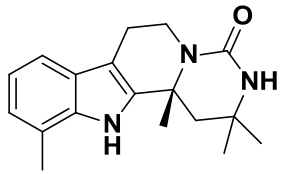
500 MHz, [D_6]DMSO

4.10.2 ^{13}C NMR of compound 9j



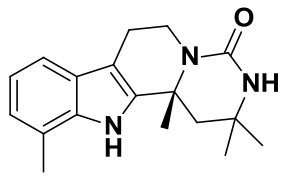
125 MHz, [D_6]DMSO

4.11.1 ^{1}H NMR of compound 9k



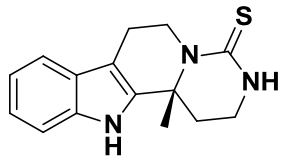
500 MHz, [D_6]DMSO

4.11.2 ^{13}C NMR of compound 9k



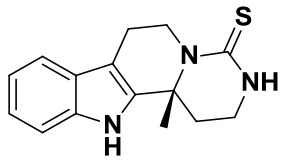
125 MHz, [D_6]DMSO

4.12.1 ^{1}H NMR of compound 9l



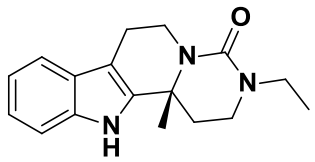
500 MHz, [D_6]DMSO

4.12.2 ^{13}C NMR of compound 9l



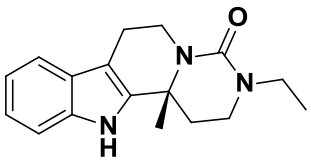
125 MHz, [D_6]DMSO

4.13.1 ^{1}H NMR of compound 9m



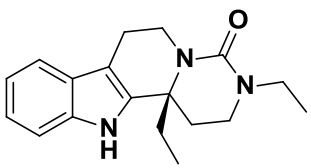
500 MHz, [D_6]DMSO

4.13.2 ^{13}C NMR of compound 9m



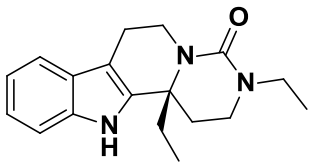
125 MHz, [D_6]DMSO

4.14.1 ^{1}H NMR of compound 9n



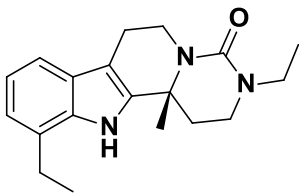
500 MHz, [D_6]DMSO

4.14.2 ^{13}C NMR of compound 9n



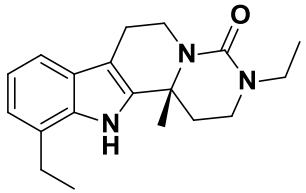
125 MHz, [D_6]DMSO

4.15.1 ^{1}H NMR of compound 9o



500 MHz, [D_6]DMSO

4.15.2 ^{13}C NMR of compound 9o

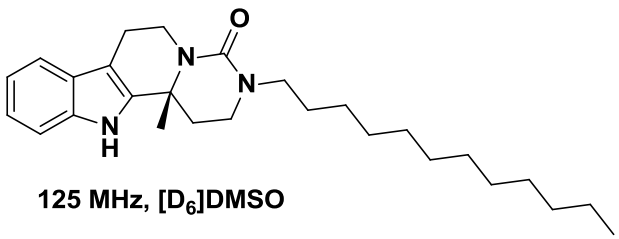


125 MHz, [D_6]DMSO

4.16.1 ^{1}H NMR of compound 9p

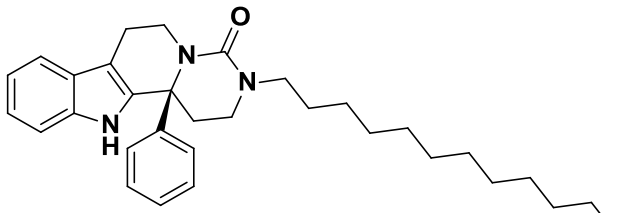
500 MHz, [D_6]DMSO

4.16.2 ^{13}C NMR of compound 9p



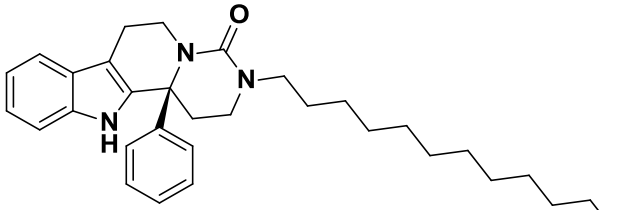
125 MHz, [D$_6$]DMSO

4.17.1 ^{1}H NMR of compound 9q



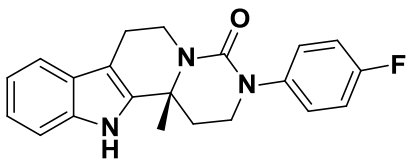
500 MHz, [D_6]DMSO

4.17.2 ^{13}C NMR of compound 9q



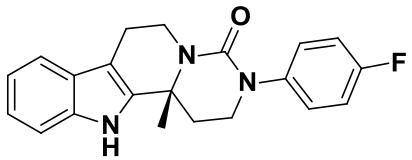
125 MHz, [D_6]DMSO

4.18.1 ^{1}H NMR of compound 9r



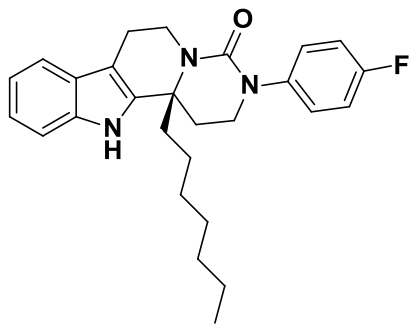
500 MHz, [D_6]DMSO

4.18.2 ^{13}C NMR of compound 9r



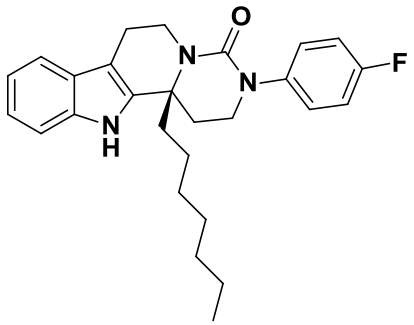
125 MHz, [D_6]DMSO

4.19.1 ^{1}H NMR of compound 9s



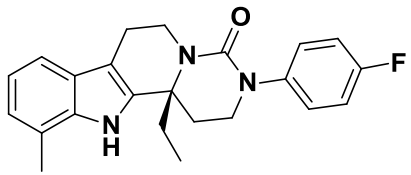
500 MHz, [D_6]DMSO

4.19.2 ^{13}C NMR of compound 9s



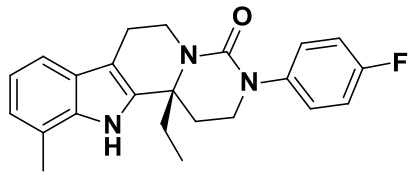
125 MHz, [D_6]DMSO

4.20.1 ^{1}H NMR of compound 9t



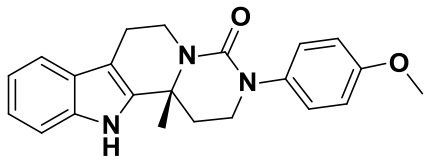
500 MHz, [D_6]DMSO

4.20.2 ^{13}C NMR of compound 9t



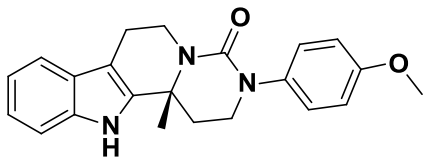
125 MHz, [D_6]DMSO

4.21.1 ^{1}H NMR of compound 9u



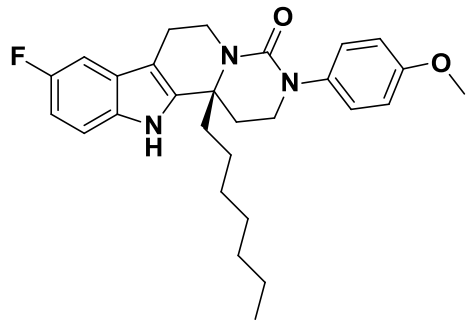
500 MHz, [D_6]DMSO

4.21.2 ^{13}C NMR of compound 9u



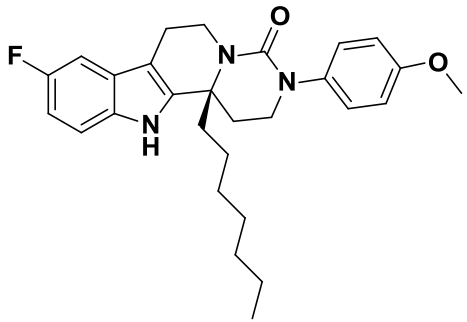
125 MHz, [D_6]DMSO

4.22.1 ^{1}H NMR of compound 9v



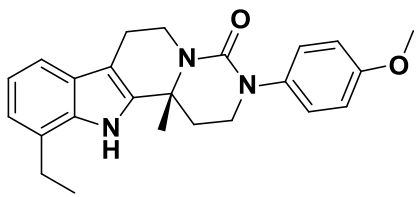
500 MHz, [D_6]DMSO

4.22.2 ^{13}C NMR of compound 9v



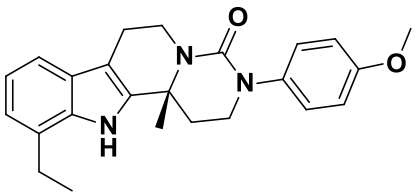
125 MHz, [D_6]DMSO

4.23.1 ^{1}H NMR of compound 9w



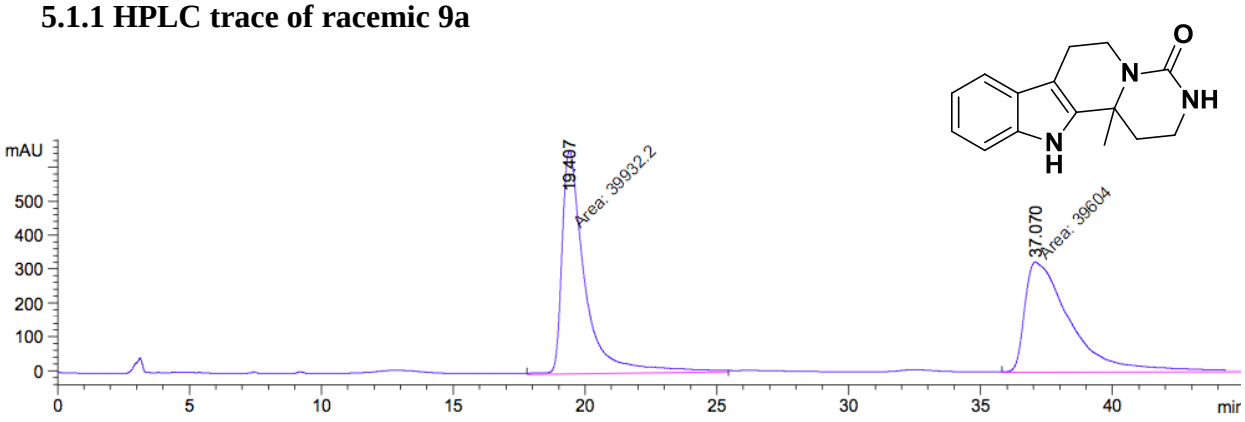
500 MHz, [D_6]DMSO

4.23.2 ^{13}C NMR of compound 9w



125 MHz, [D_6]DMSO

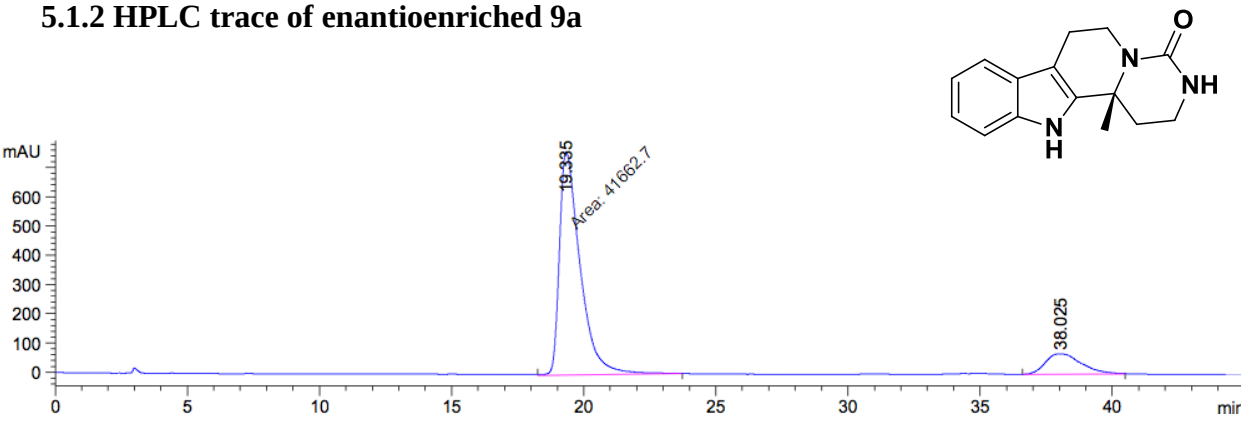
5.1.1 HPLC trace of racemic 9a



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.407	MM	1.0086	3.99322e4	659.87573	50.2063
2	37.070	MM	2.0265	3.96040e4	325.72067	49.7937
Totals :				7.95362e4	985.59641	

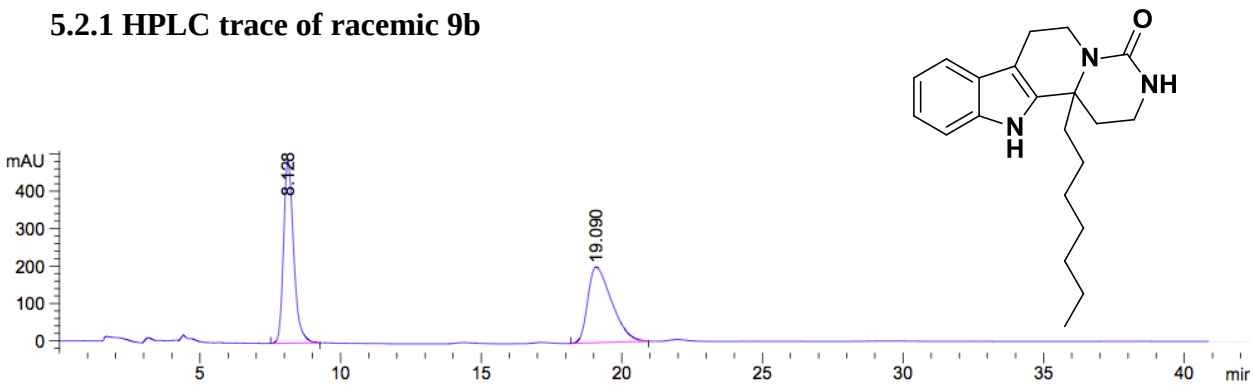
5.1.2 HPLC trace of enantioenriched 9a



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

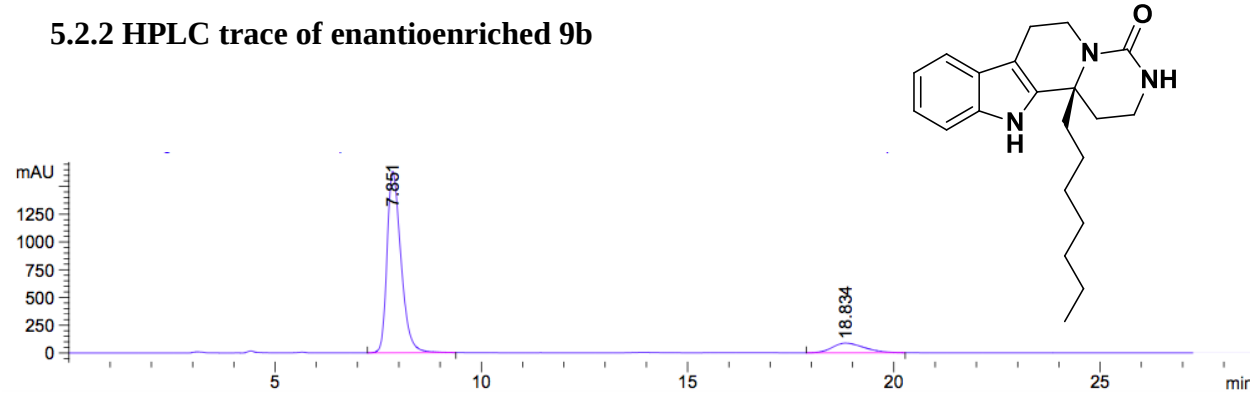
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.335	MM	0.9082	4.16627e4	764.53229	86.3892
2	38.025	BB	1.4435	6564.02441	69.52209	13.6108
Totals :				4.82268e4	834.05437	

5.2.1 HPLC trace of racemic 9b



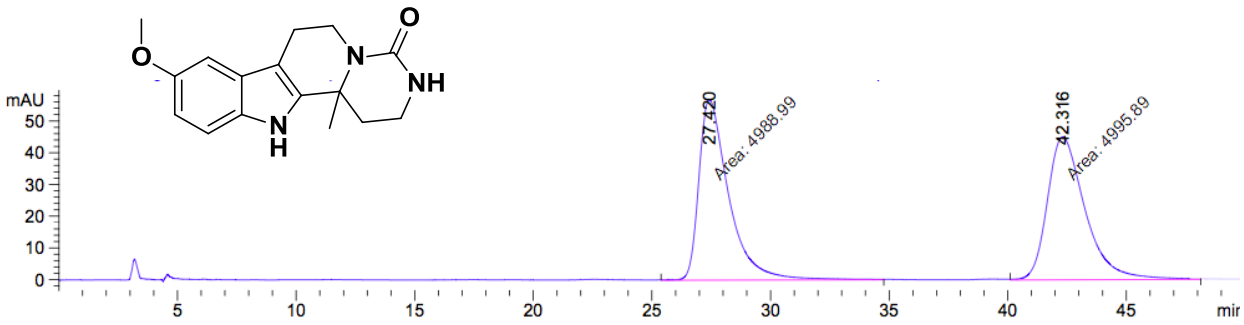
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.128	BB	0.3820	1.21420e4	488.52164	50.4201
2	19.090	BB	0.9003	1.19397e4	202.38368	49.5799
Totals :				2.40817e4	690.90532	

5.2.2 HPLC trace of enantioenriched 9b



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.851	BB	0.3594	3.82843e4	1633.63770	89.1371
2	18.834	BB	0.8287	4665.60693	86.58440	10.8629
Totals :				4.29499e4	1720.22209	

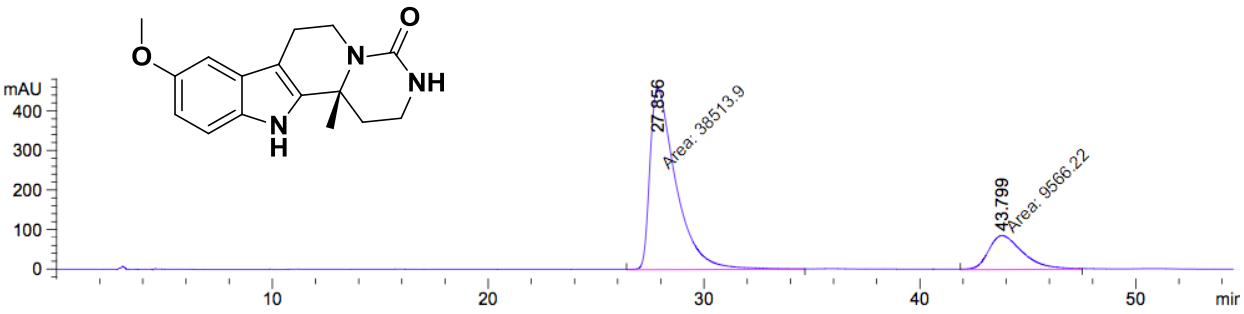
5.3.1 HPLC trace of racemic 9c



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.420	MM	1.4596	4988.99219	56.96652	49.9655
2	42.316	MM	1.8483	4995.88818	45.04830	50.0345
Totals :				9984.88037	102.01482	

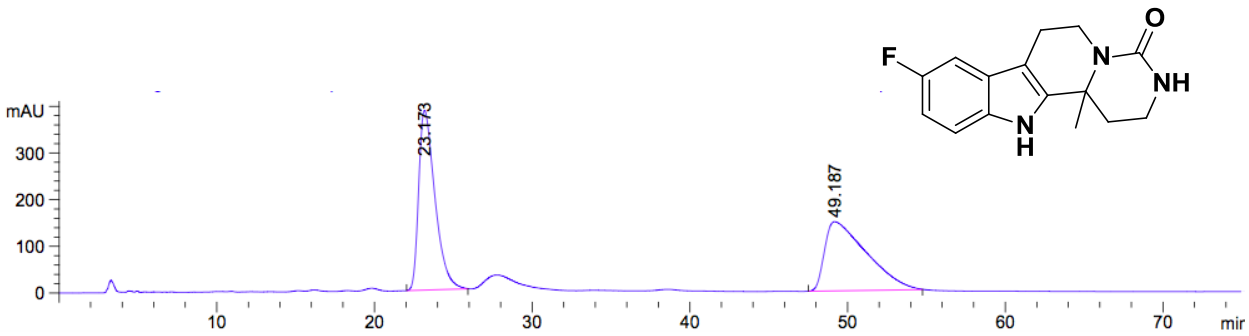
5.3.2 HPLC trace of enantioenriched 9c



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.856	MM	1.3996	3.85139e4	458.61905	80.1036
2	43.799	MM	1.8588	9566.22363	85.77356	19.8964
Totals :				4.80801e4	544.39261	

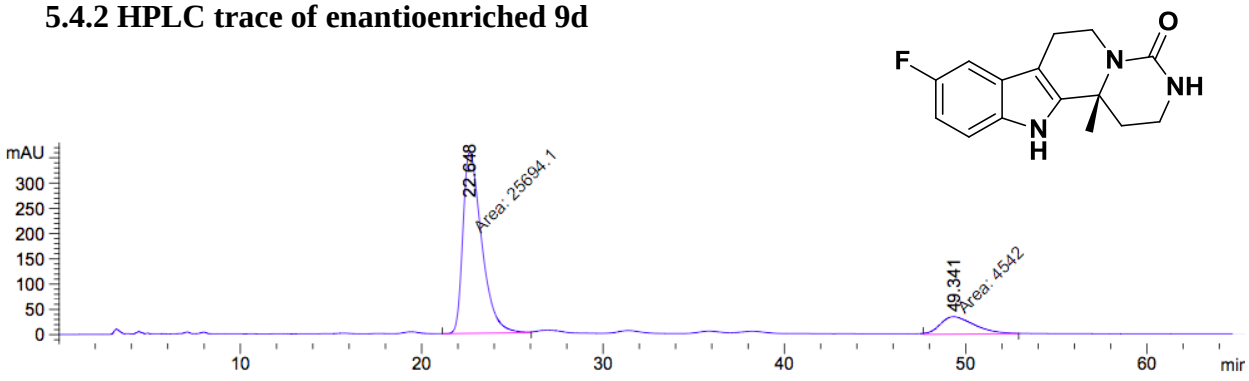
5.4.1 HPLC trace of racemic 9d



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.173	BB	1.0948	2.75907e4	384.66782	50.3224
2	49.187	BB	2.4675	2.72372e4	148.11012	49.6776
Totals :				5.48279e4	532.77794	

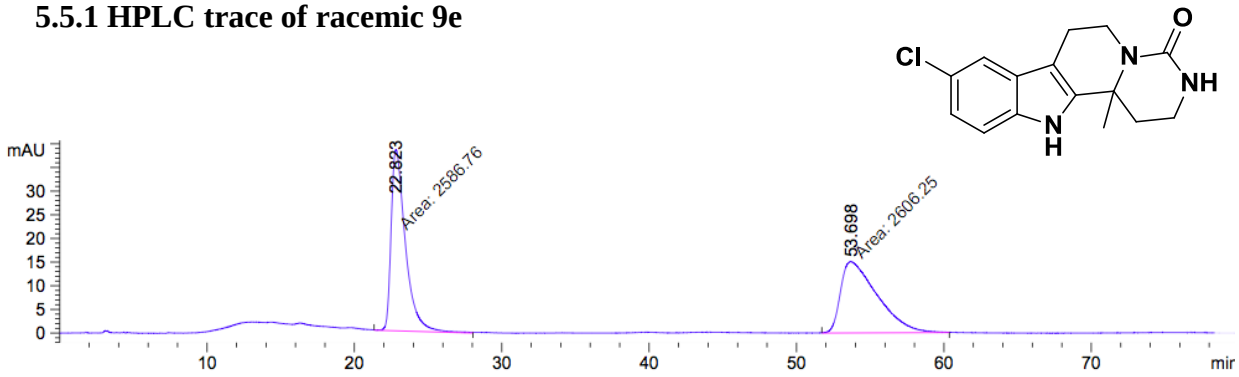
5.4.2 HPLC trace of enantioenriched 9d



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

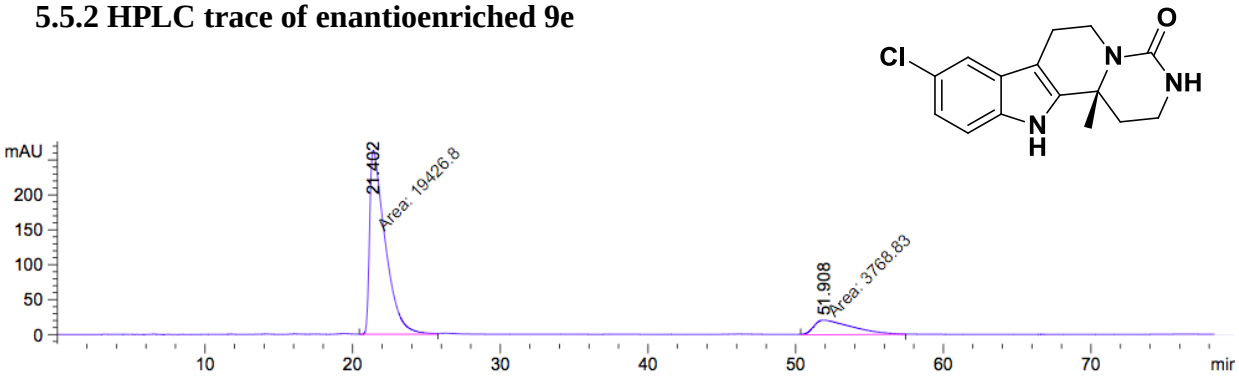
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.648	MM	1.1936	2.56941e4	358.76926	84.9782
2	49.341	MM	2.1947	4542.00195	34.49198	15.0218
Totals :				3.02361e4	393.26123	

5.5.1 HPLC trace of racemic 9e



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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	

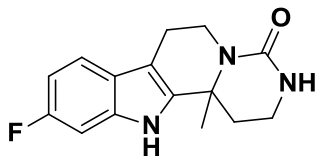
5.5.2 HPLC trace of enantioenriched 9e

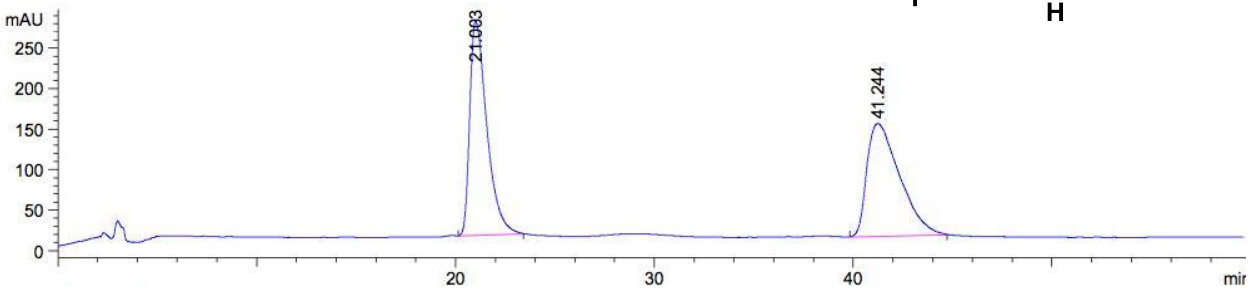


Signal 6: DAD1 F, Sig=300,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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

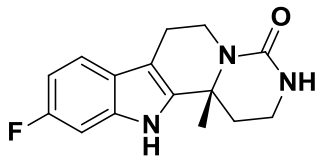


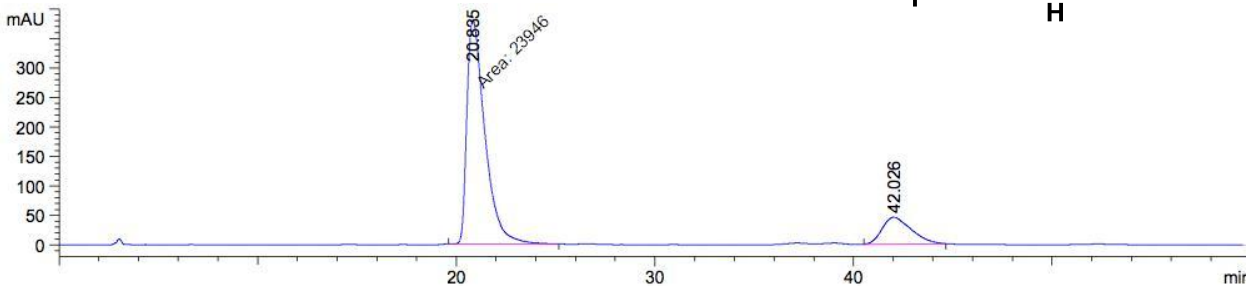


Signal 4: DAD1 D, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.003	BB	0.8935	1.58425e4	265.37149	49.8814
2	41.244	BB	1.5860	1.59178e4	139.10960	50.1186
Totals :				3.17603e4	404.48109	

5.6.2 HPLC trace of enantioenriched 9f

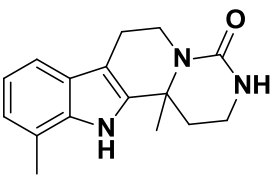


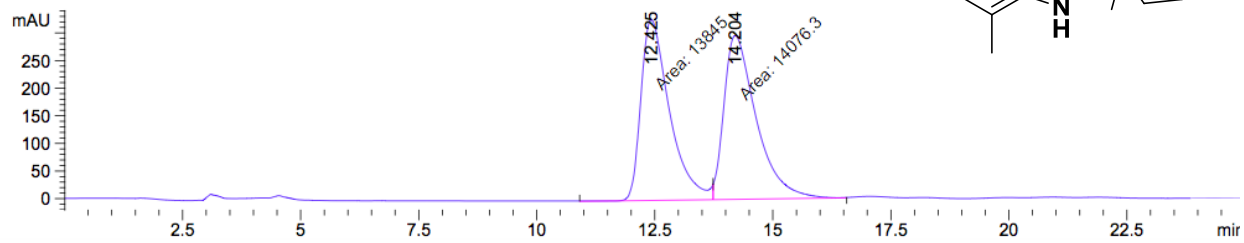


Signal 4: DAD1 D, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.835	MM	1.0511	2.39460e4	379.69293	83.7027
2	42.026	BB	1.3622	4662.39063	45.74164	16.2973
Totals :				2.86084e4	425.43457	

5.7.1 HPLC trace of racemic 9g

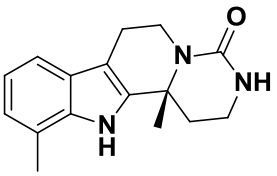


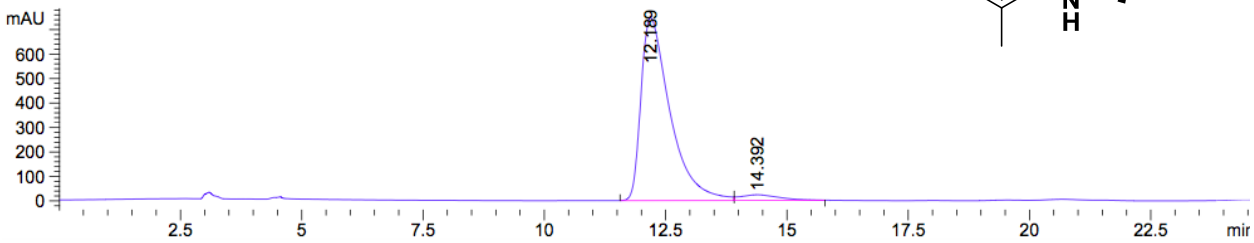


Signal 3: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
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

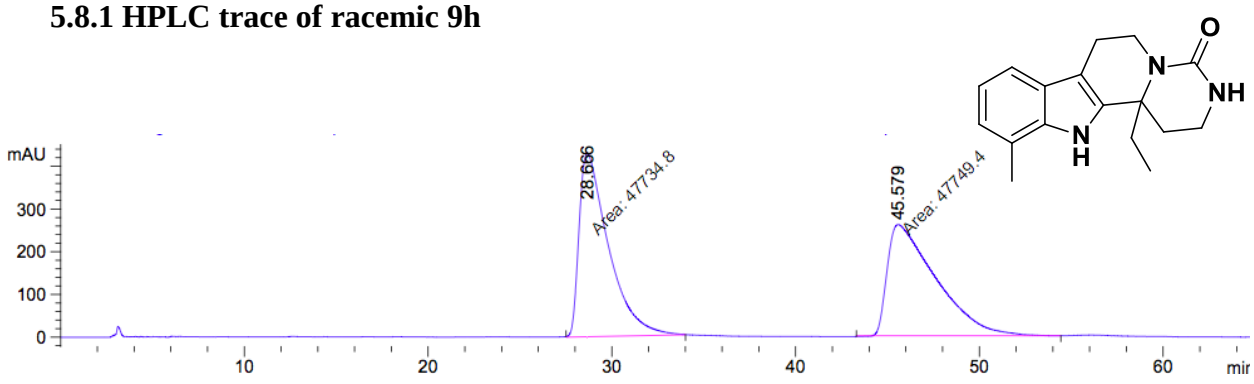




Signal 3: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.189	BB	0.6222	3.11330e4	747.04541	96.1247
2	14.392	BB	0.7902	1255.12329	22.80222	3.8753
Totals :				3.23881e4	769.84763	

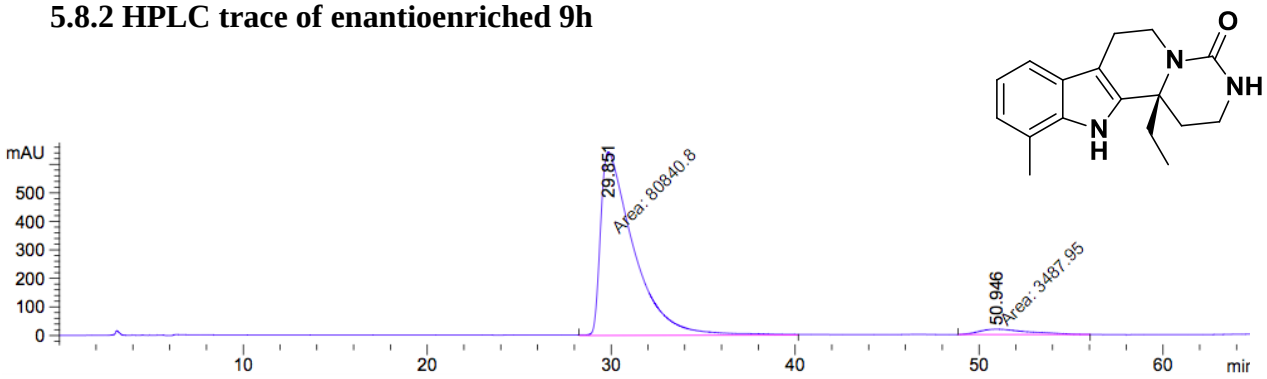
5.8.1 HPLC trace of racemic 9h



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.666	MM	1.8568	4.77348e4	428.45740	49.9924
2	45.579	MM	3.0576	4.77494e4	260.27856	50.0076
Totals :				9.54842e4	688.73596	

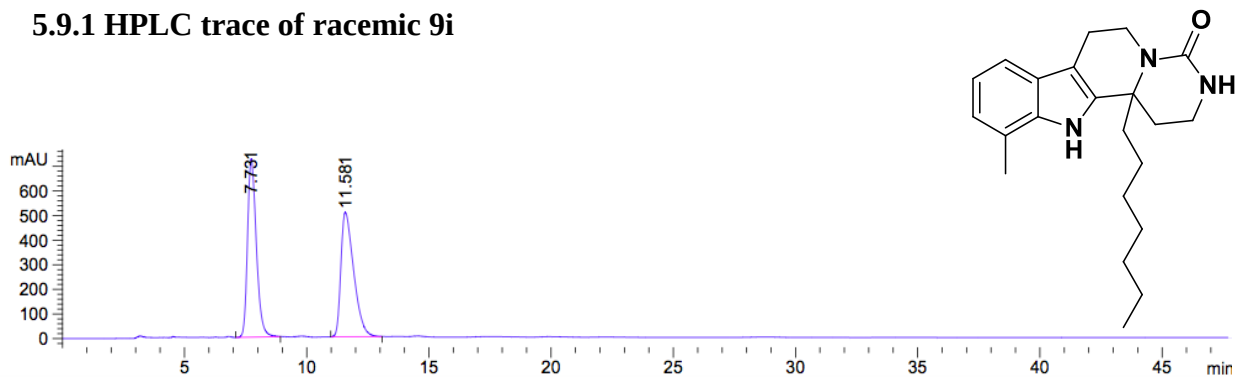
5.8.2 HPLC trace of enantioenriched 9h



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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	

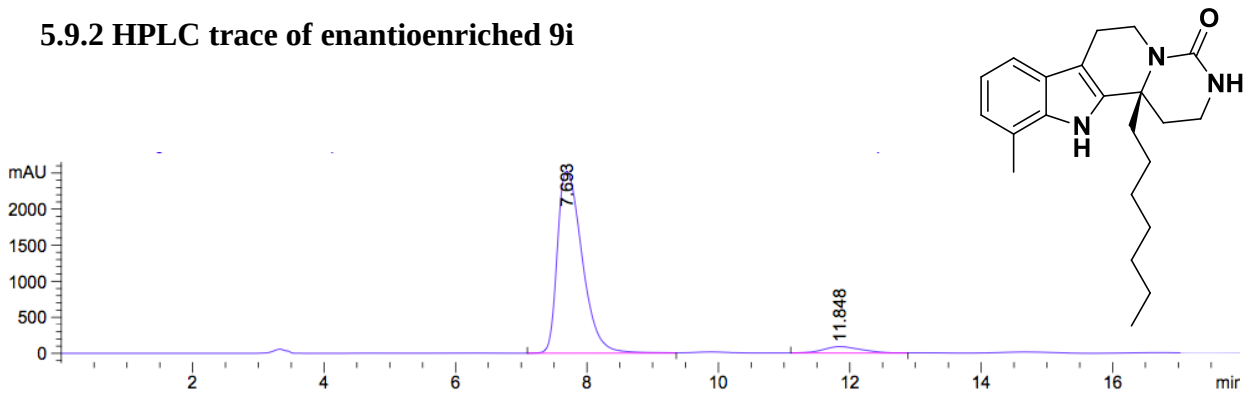
5.9.1 HPLC trace of racemic 9i



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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	

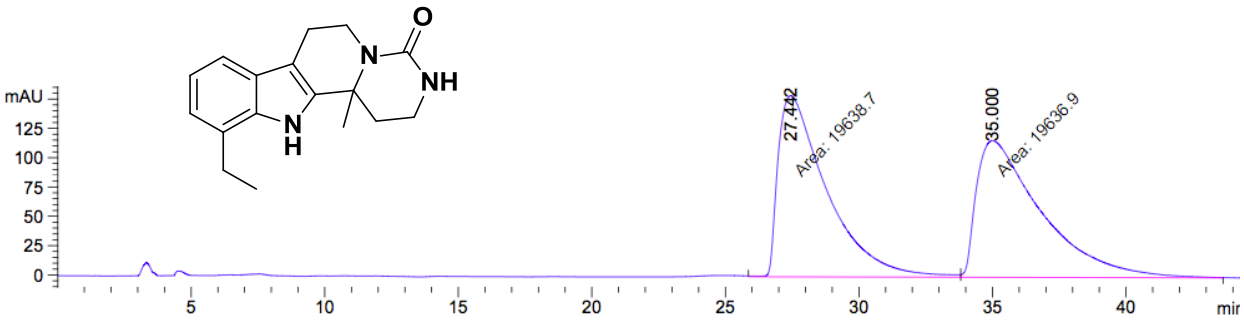
5.9.2 HPLC trace of enantioenriched 9i



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.693	BB	0.4075	6.59833e4	2519.54248	94.9799
2	11.848	BB	0.5960	3487.51880	88.07508	5.0201
Totals :				6.94708e4	2607.61756	

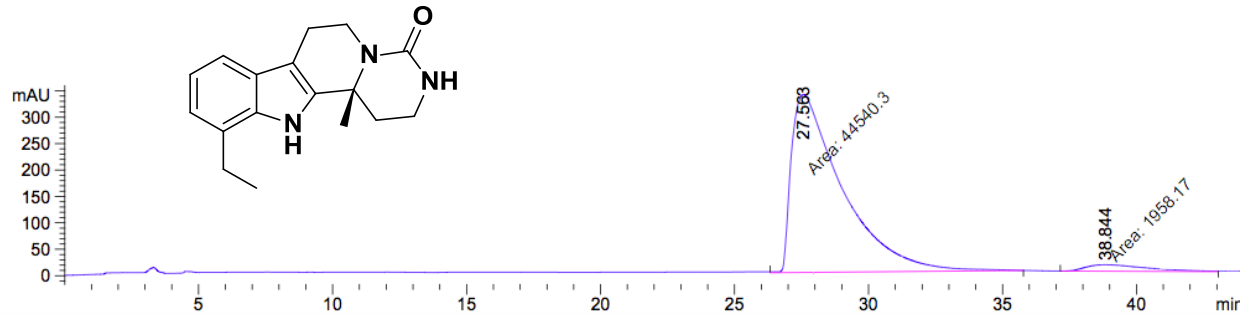
5.10.1 HPLC trace of racemic 9j



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.442	MF	2.1193	1.96387e4	154.44676	50.0023
2	35.000	FM	2.8073	1.96369e4	116.58168	49.9977
Totals :				3.92756e4	271.02844	

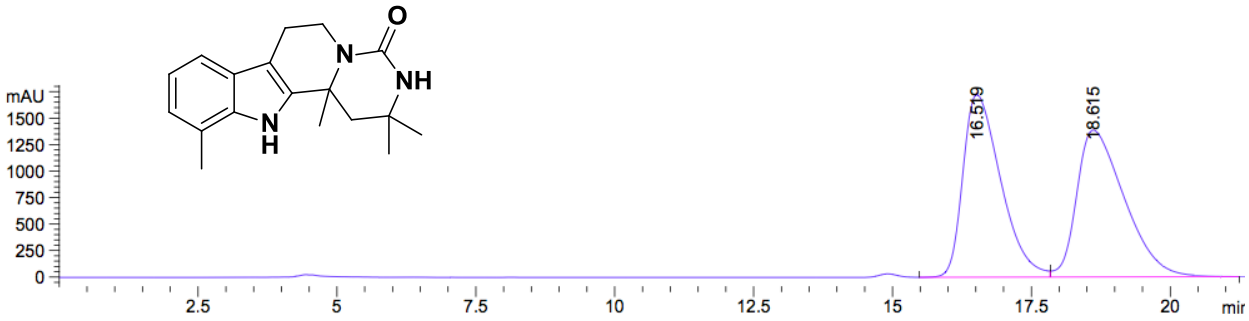
5.10.2 HPLC trace of enantioenriched 9j



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.563	MM	2.2048	4.45403e4	336.69745	95.7887
2	38.844	MM	2.6787	1958.16724	12.18364	4.2113
Totals :				4.64985e4	348.88109	

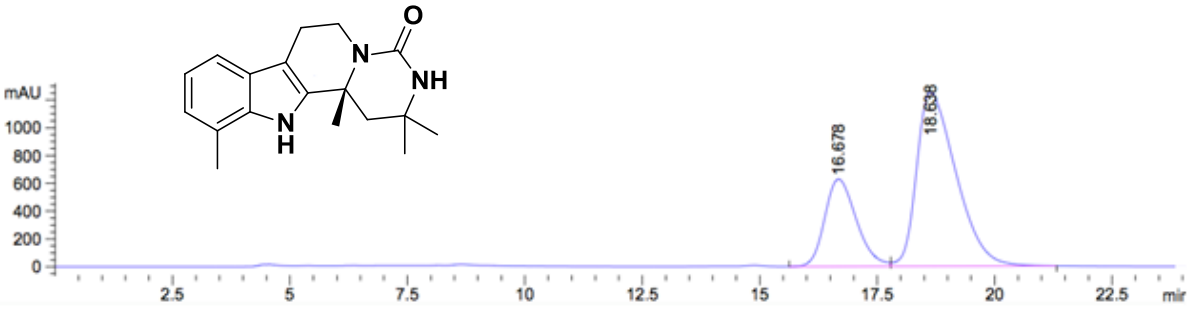
5.11.1 HPLC trace of racemic 9k



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.519	VV	0.7301	8.15249e4	1722.64880	49.6028
2	18.615	VB	0.9171	8.28304e4	1386.34863	50.3972
Totals :				1.64355e5	3108.99744	

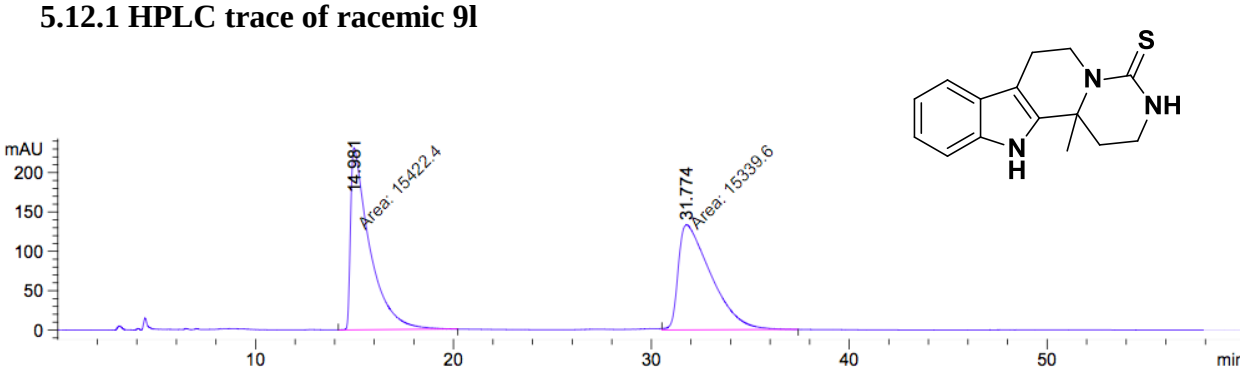
5.11.2 HPLC trace of enantioenriched 9k



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.678	BV	0.7231	2.93723e4	628.60034	28.6708
2	18.638	VB	0.8953	7.30743e4	1251.29919	71.3292
Totals :				1.02447e5	1879.89954	

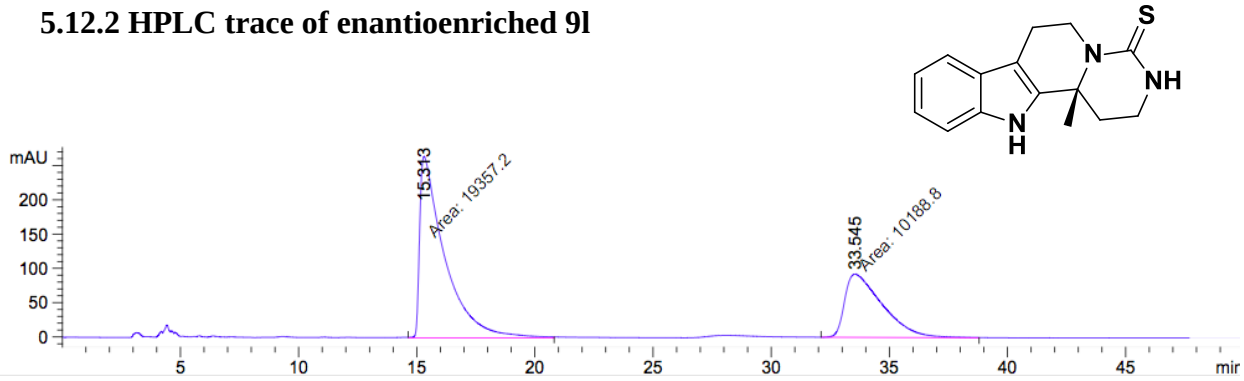
5.12.1 HPLC trace of racemic 9l



Signal 5: DAD1 E, Sig=240,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.981	MM	1.1128	1.54224e4	230.97691	50.1347
2	31.774	MM	1.9148	1.53396e4	133.51459	49.8653
Totals :				3.07620e4	364.49150	

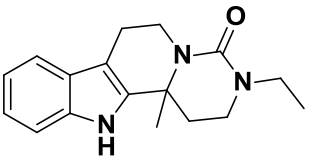
5.12.2 HPLC trace of enantioenriched 9l

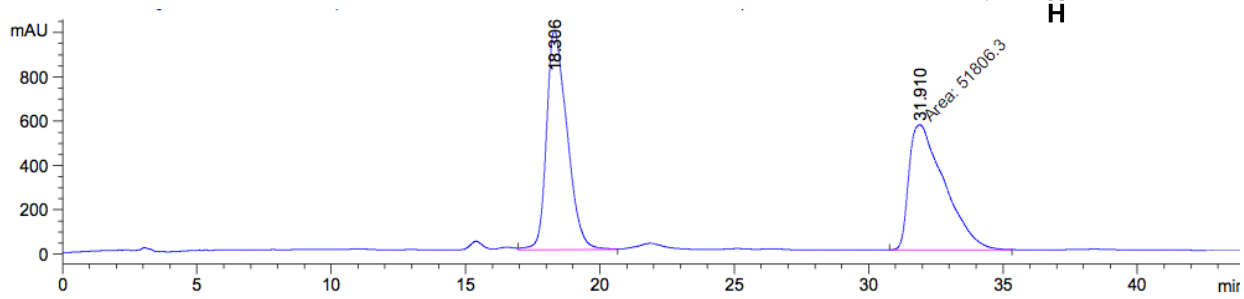


Signal 5: DAD1 E, Sig=240,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.313	MM	1.2197	1.93572e4	264.50677	65.5154
2	33.545	MM	1.8424	1.01888e4	92.16838	34.4846
Totals :				2.95459e4	356.67516	

5.13.1 HPLC trace of racemic 9m

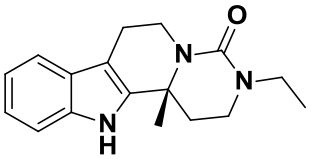


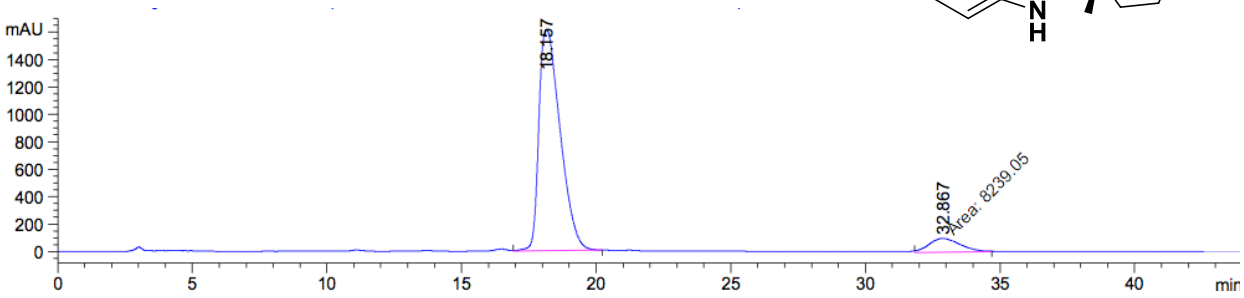


Signal 4: DAD1 D, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	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

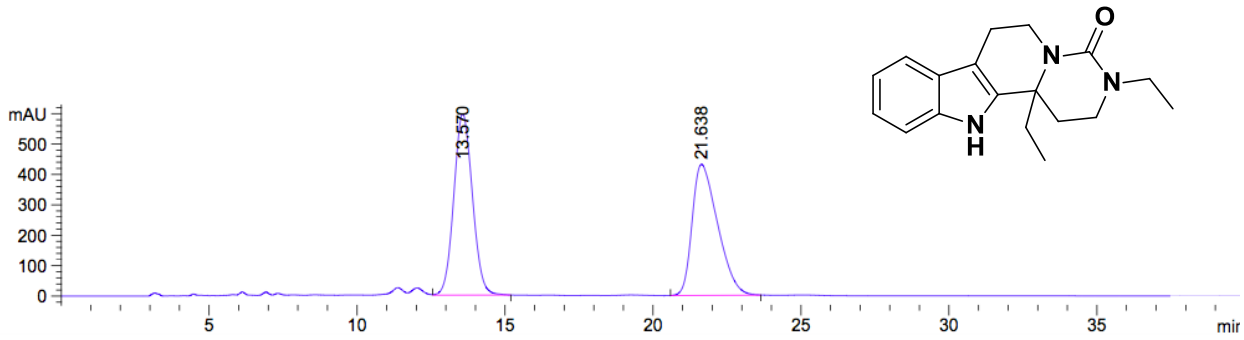




Signal 4: DAD1 D, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	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	

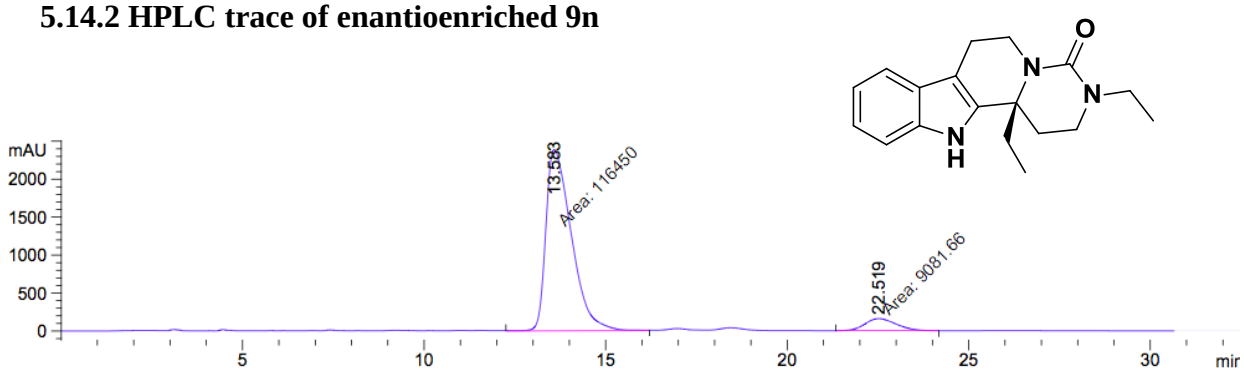
5.14.1 HPLC trace of racemic 9n



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

Peak #	RetTime [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	

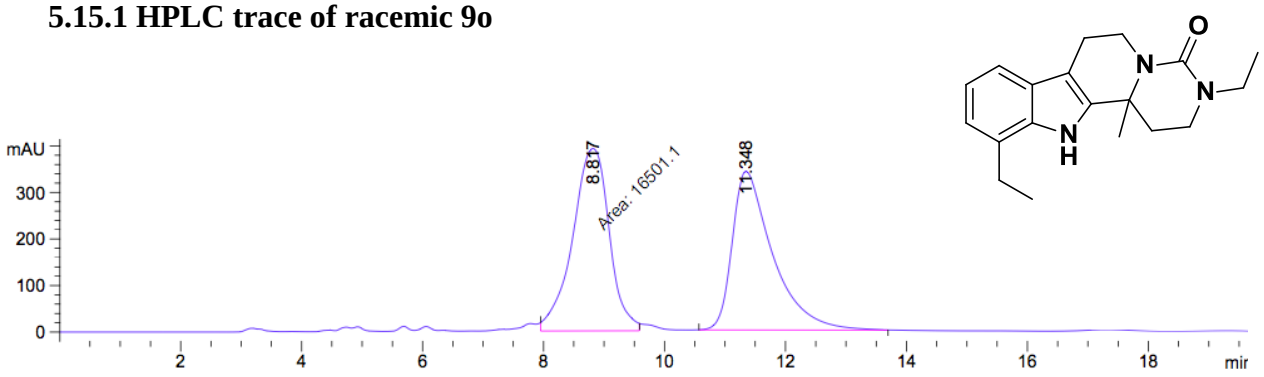
5.14.2 HPLC trace of enantioenriched 9n



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

Peak #	RetTime [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	

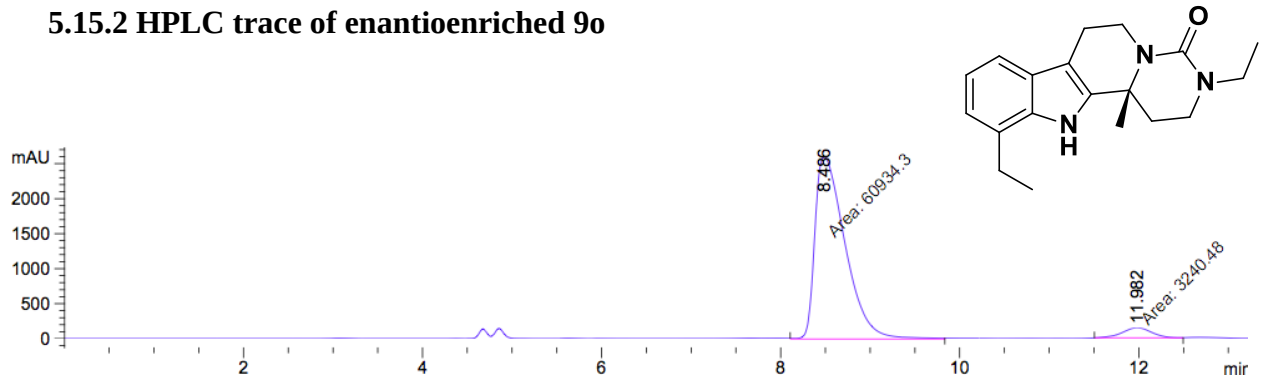
5.15.1 HPLC trace of racemic 9o



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.817	FM	0.7018	1.65011e4	391.85361	50.9273
2	11.348	BB	0.6821	1.59002e4	340.96487	49.0727
Totals :				3.24012e4	732.81848	

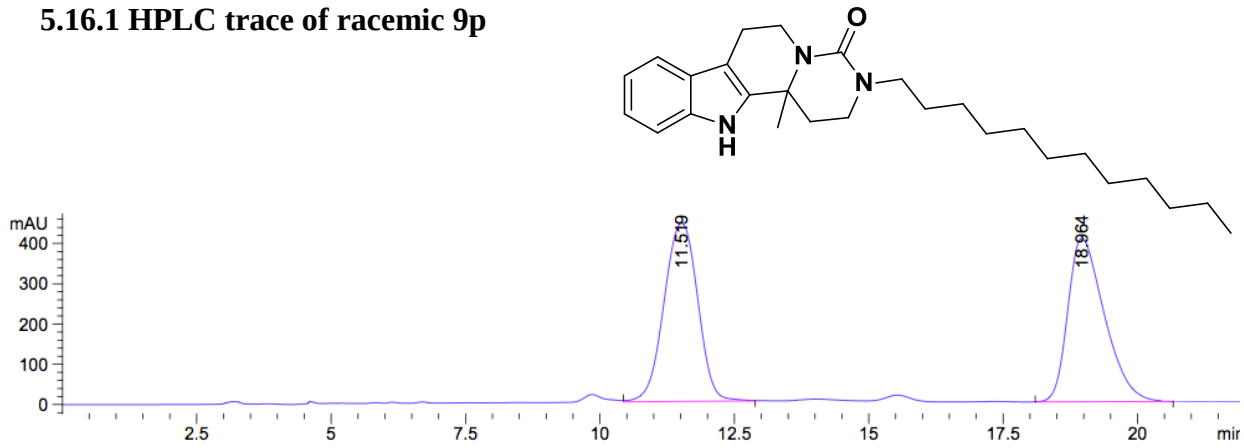
5.15.2 HPLC trace of enantioenriched 9o



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

Peak #	RetTime [min]	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	

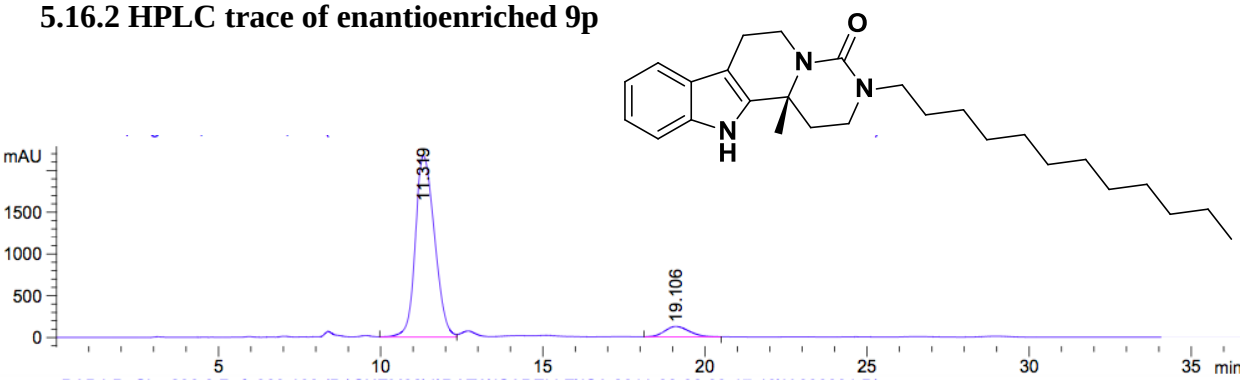
5.16.1 HPLC trace of racemic 9p



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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	

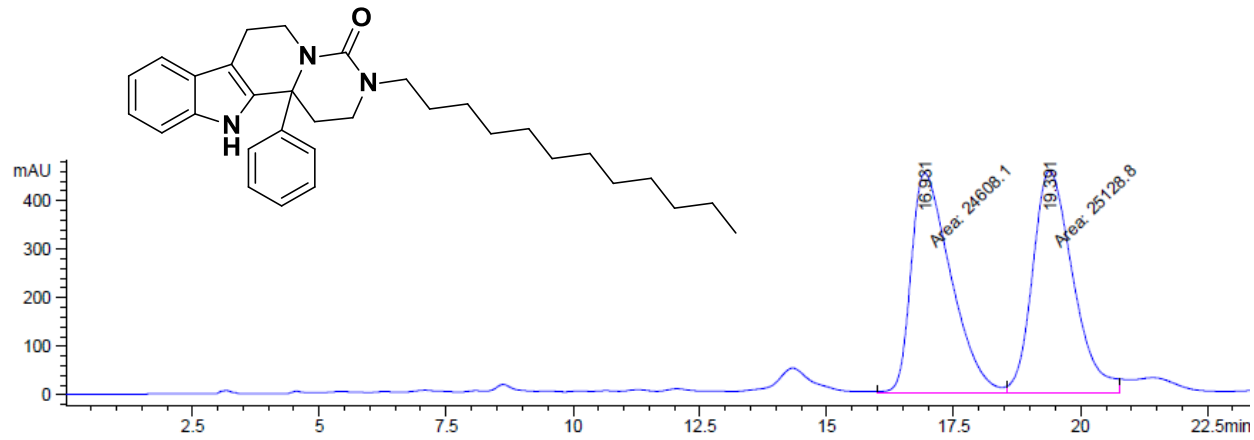
5.16.2 HPLC trace of enantioenriched 9p



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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	

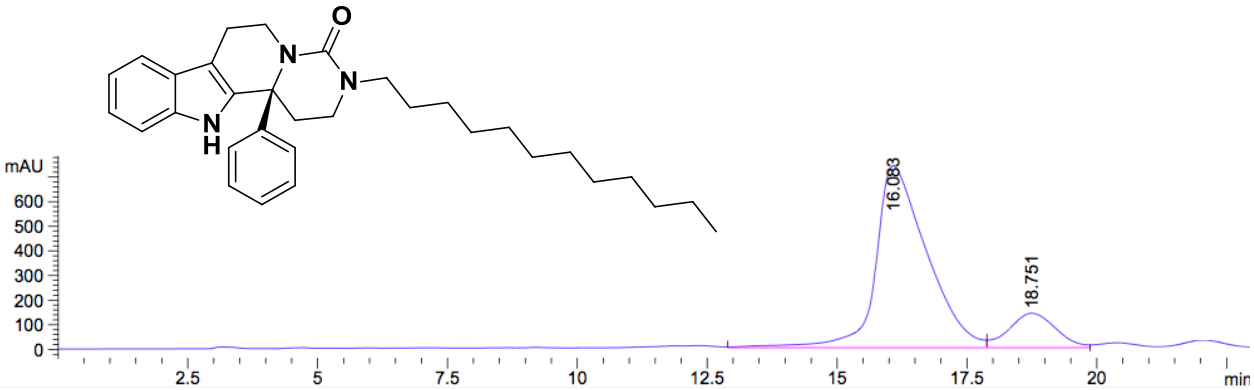
5.17.1 HPLC trace of racemic 9q



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.931	MM	0.9069	2.46081e4	452.25519	49.4765
2	19.391	MM	0.9167	2.51288e4	456.87338	50.5235
Totals :				4.97370e4	909.12857	

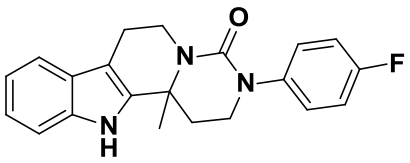
5.17.2 HPLC trace of enantioenriched 9q

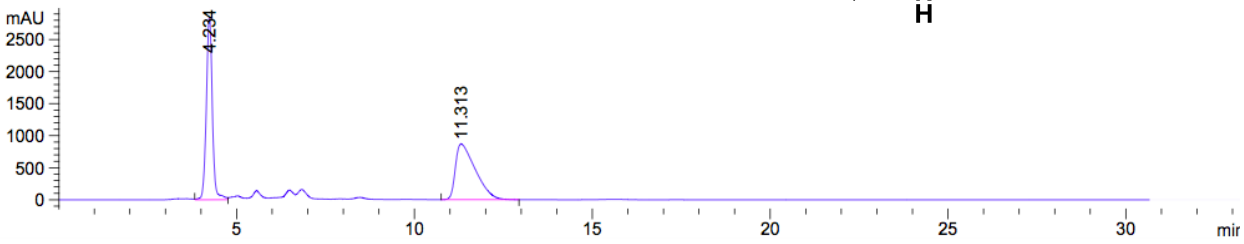


Signal 2: DAD1 B, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	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 :				5.94902e4	879.16621	

5.18.1 HPLC trace of racemic 9r

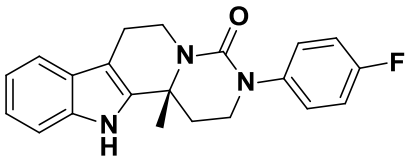


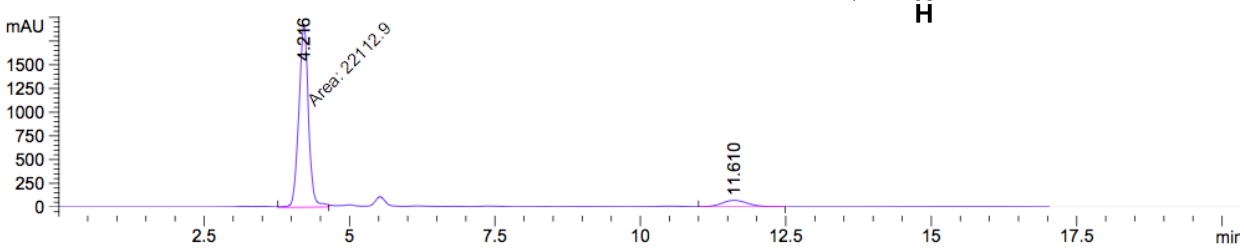


Signal 3: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	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	0.5883	3.37134e4	869.58191	50.1435
Totals :				6.72338e4	3714.83362	

5.18.2 HPLC trace of enantioenriched 9r

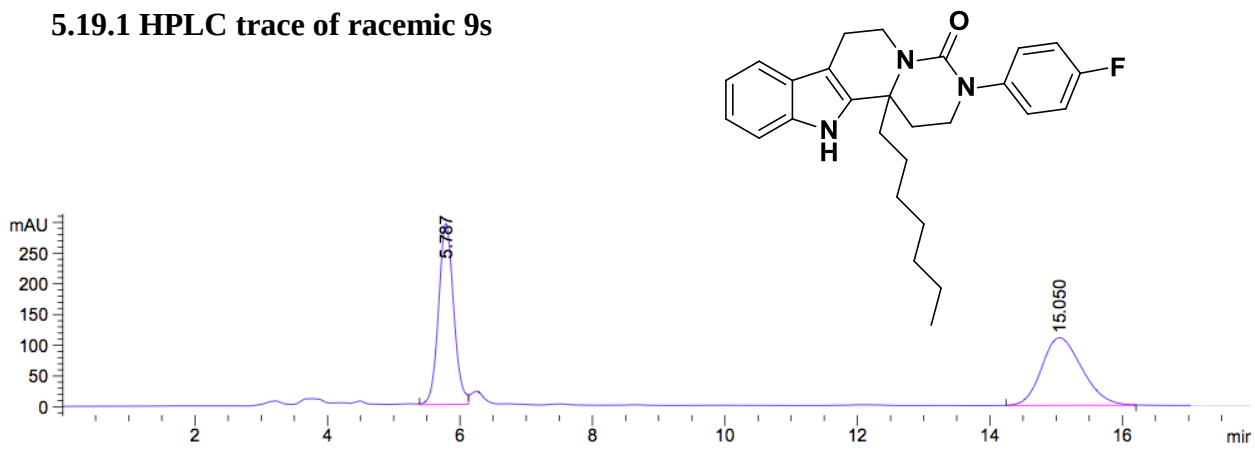




Signal 3: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	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 :				2.42171e4	1983.47108	

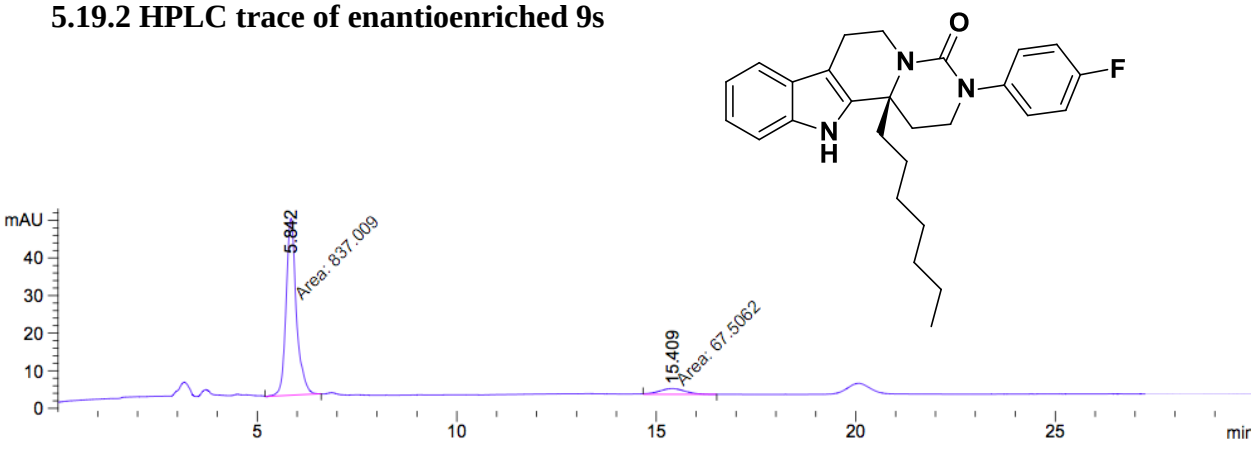
5.19.1 HPLC trace of racemic 9s



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.787	BV	0.2448	4665.55713	294.60724	50.1021
2	15.050	BB	0.6542	4646.53906	110.13287	49.8979
Totals :				9312.09619	404.74011	

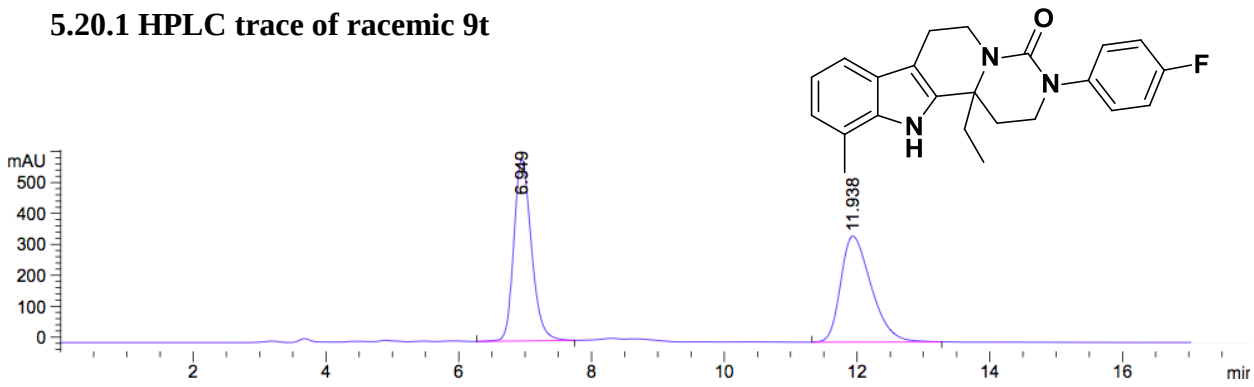
5.19.2 HPLC trace of enantioenriched 9s



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.842	MM	0.2959	837.00934	47.14312	92.5368
2	15.409	MM	0.7438	67.50617	1.51255	7.4632
Totals :				904.51551	48.65567	

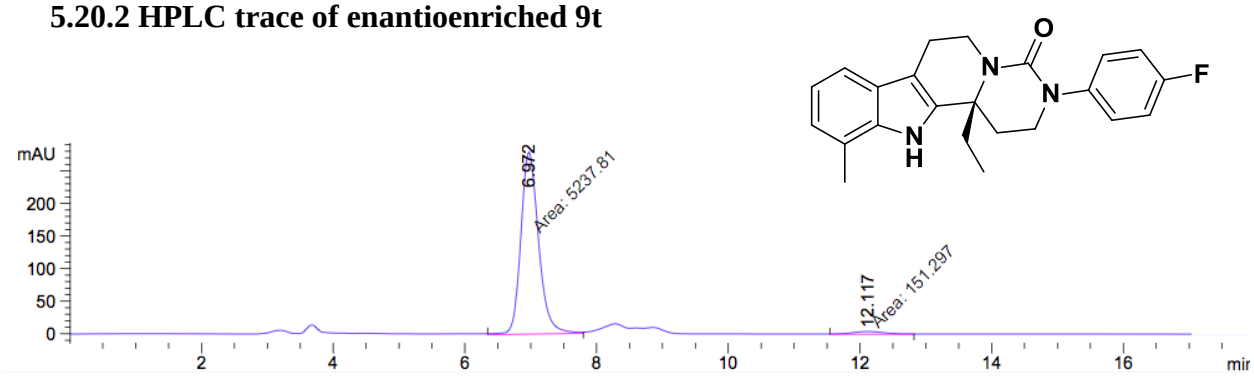
5.20.1 HPLC trace of racemic 9t



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.949	VB	0.2826	1.08061e4	587.42609	49.6517
2	11.938	BB	0.4931	1.09577e4	342.60583	50.3483
Totals :				2.17638e4	930.03192	

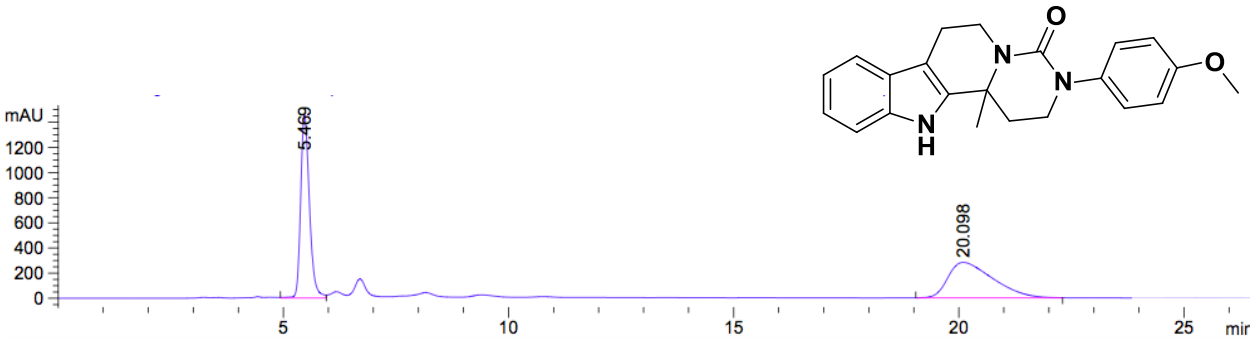
5.20.2 HPLC trace of enantioenriched 9t



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.972	MM	0.3129	5237.81445	278.97552	97.1925
2	12.117	MM	0.5935	151.29684	4.24903	2.8075
Totals :				5389.11130	283.22456	

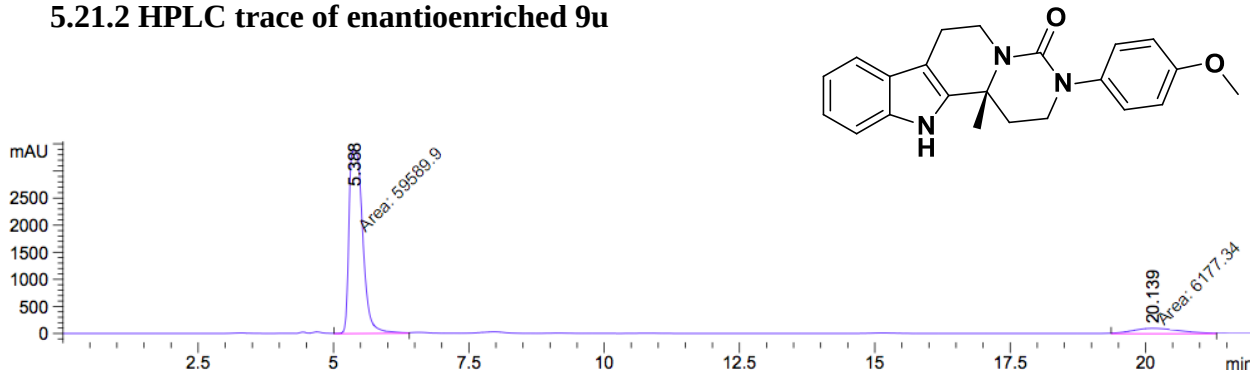
5.21.1 HPLC trace of racemic 9u



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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	

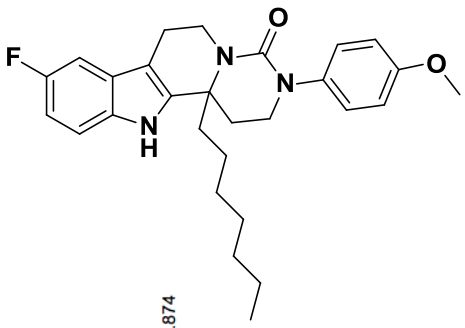
5.21.2 HPLC trace of enantioenriched 9u

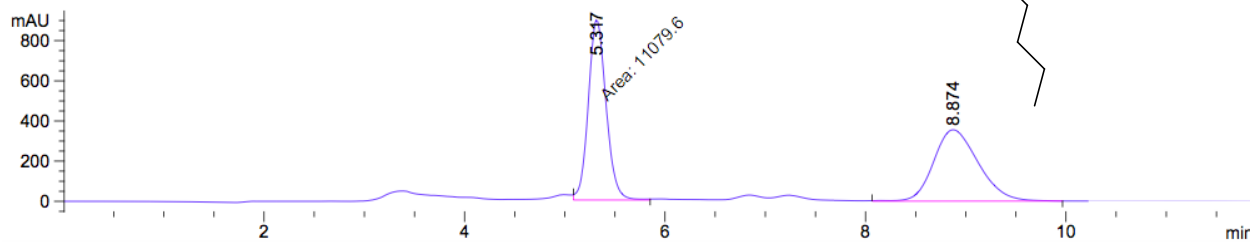


Signal 3: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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

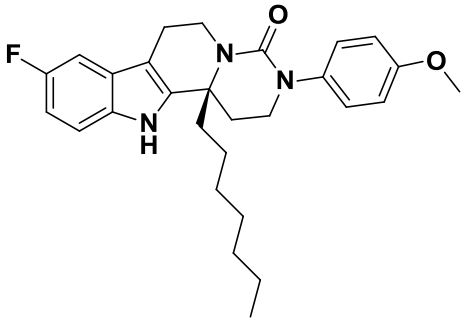


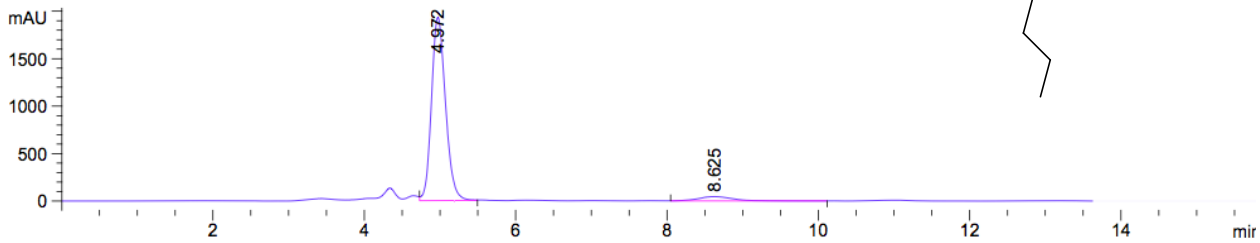


Signal 3: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.317	FM	0.2058	1.10796e4	897.13824	50.2426
2	8.874	BB	0.4785	1.09726e4	355.12552	49.7574
Totals :				2.20522e4	1252.26376	

5.22.2 HPLC trace of enantioenriched 9v

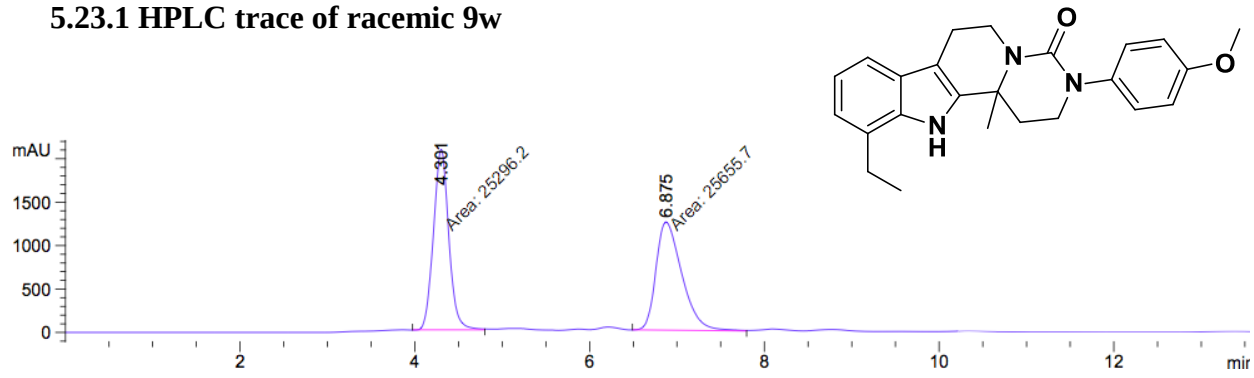




Signal 3: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.972	VB	0.1981	2.48334e4	1929.70862	94.6152
2	8.625	VB	0.4866	1413.32751	44.97867	5.3848
Totals :				2.62467e4	1974.68729	

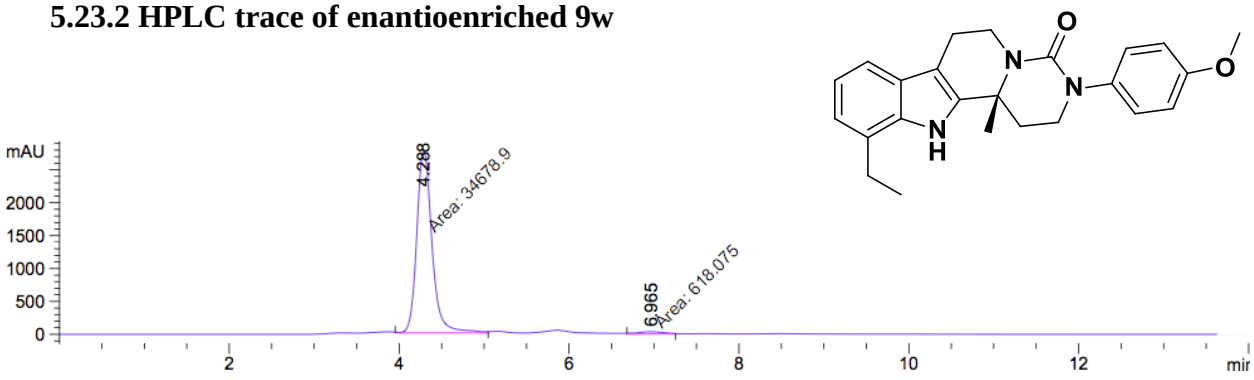
5.23.1 HPLC trace of racemic 9w



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

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	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	

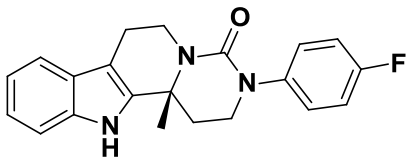
5.23.2 HPLC trace of enantioenriched 9w

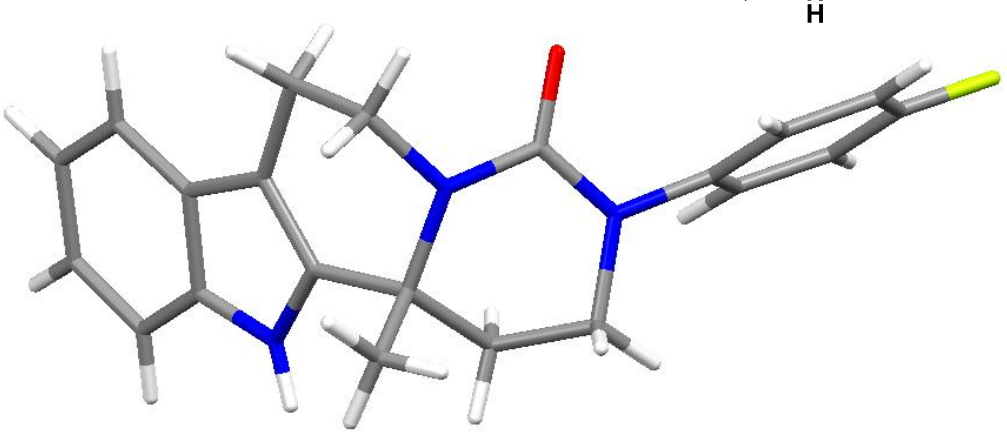


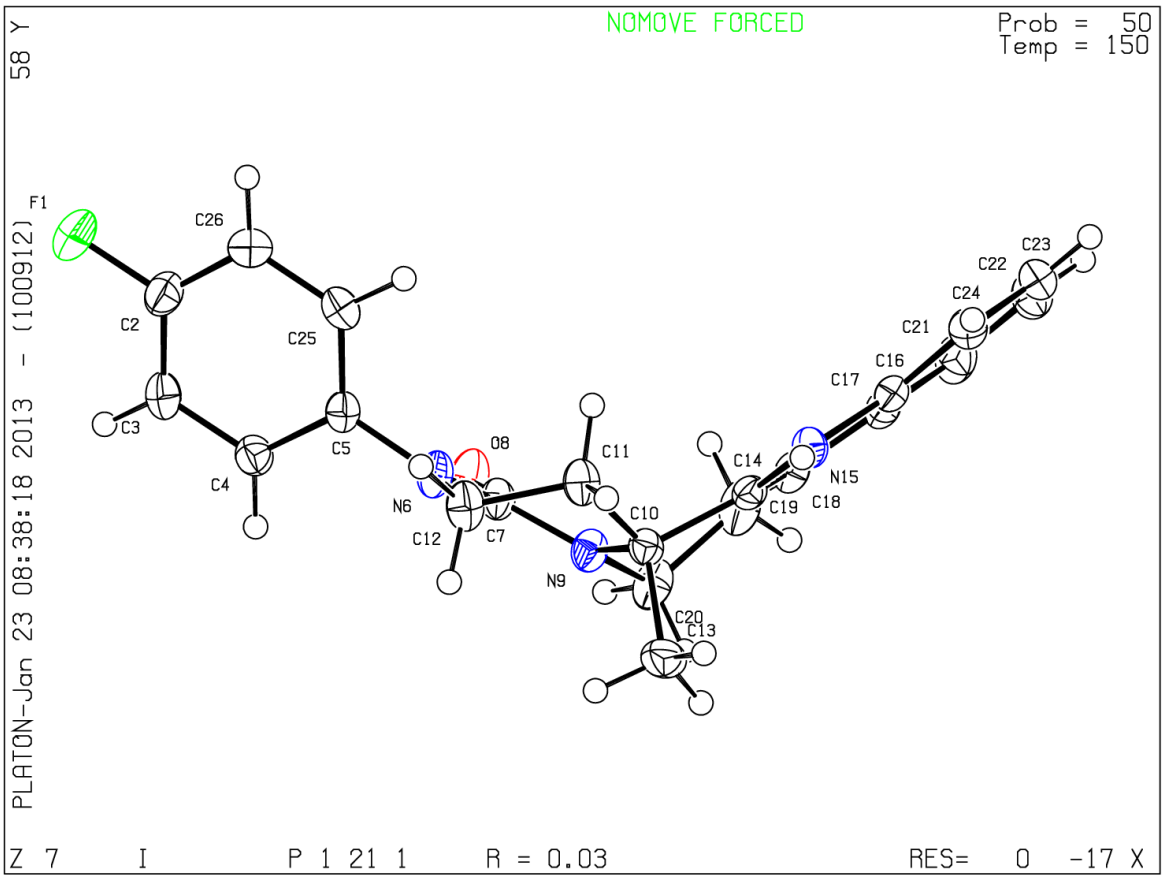
Signal 3: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.288	MM	0.2089	3.46789e4	2767.33862	98.2489
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







(9r)

Crystal data

$C_{21}H_{20}FN_3O$	$F(000)$ = 368
M_r = 349.41	D_x = 1.304 Mg m^{-3}
Monoclinic, $P2_1$	Melting point: not measured K
Hall symbol: P 2yb	Cu $K\alpha$ radiation, λ = 1.54180 Å
a = 7.1383 (1) Å	Cell parameters from 59434 reflections
b = 10.6018 (1) Å	θ = 4–77°
c = 12.0383 (1) Å	μ = 0.72 mm^{-1}
β = 102.3752 (6)°	T = 150 K
V = 889.88 (2) Å^3	Block, Clear_pale_colourless
Z = 2	0.20 × 0.15 × 0.08 mm

Data collection

Oxford Diffraction SuperNova diffractometer	3698 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	R_{int} = 0.020
ω scans	θ_{max} = 76.9°, θ_{min} = 3.8°
Absorption correction: Multi-scan CrysAlis, (Oxford Diffraction, 2002)	h = −9→8
T_{min} = 0.75, T_{max} = 0.94	k = −13→13
76919 measured reflections	l = −15→15
3711 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: Difference Fourier map
Least-squares matrix: Full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)]$ = 0.026	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.04P)^2 + 0.17P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$wR(F^2)$ = 0.067	$(\Delta/\sigma)_{max}$ = 0.0004
S = 0.97	$\Delta\rho_{max}$ = 0.14 e Å^{-3}
3711 reflections	$\Delta\rho_{min}$ = −0.14 e Å^{-3}
236 parameters	Absolute structure: Flack (1983), 1743 Friedel-pairs
1 restraint	Flack parameter: 0.06 (11)
Primary atom site location: Structure-invariant direct methods	

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)

	x	*y*	*z*	U_{iso}*/U_{eq}
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)	0.56999 (8)	0.0253
C10	0.55571 (14)	0.56518 (11)	0.57476 (9)	0.0218
C11	0.63833 (15)	0.66469 (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*

H251	0.3739	0.9162	0.7481	0.0371*
H41	0.0949	0.6206	0.8546	0.0315*
H31	−0.0490	0.7586	0.9615	0.0371*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
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)
O8	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)
C16	0.0343 (6)	0.0212 (5)	0.0224 (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)

Geometric parameters (Å, º)

F1—C2	1.3634 (13)	C13—H133	0.975
C2—C3	1.3738 (18)	C14—N15	1.3798 (13)
C2—C26	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)

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, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C11—H112···O8^{i}	0.96	2.49	3.3175 (18)	145
N15—H151···O8^{i}	0.86	1.97	2.8017 (18)	164

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