Chapter 6: Experimental

General Experimental Techniques

For reactions requiring anhydrous conditions, glassware was dried in an oven at 100 °C and reactions were carried out under a nitrogen or argon atmosphere. Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C were achieved using an ice-bath. All compounds were named using ACD IUPAC name predictor.

Solvents and Reagents

Commercial reagents were used as purchased without any further purification unless otherwise stated. Chiral Brønsted acids (**BPA-1A** to **BPA-1B, BPA-1C** and **BPA-1D**) were synthesised by Dr Michael Muratore and Dr Lie Shi following standard literature procedure.[1] Bulk solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Anhydrous toluene, tetrahydrofuran and dichloromethane were obtained by filtration through activated alumina (powder ~150 mesh, pore size 58Å, basic, Sigma-Aldrich) columns. Dichloroethane and acetonitrile were distilled over calcium hydride. Petroleum ether (PE) refers to distilled light petroleum with boiling points in the range of 40 °C – 60 °C. Tryptamine derivatives 2-(1*H*-indol-3-yl)ethanamine, 2-(5-methyl-1*H*-indol-3-yl)ethanamine and 2-(5-methoxy-1*H*-indol-3-yl)ethanamine were used as provided from commercial suppliers. Known tryptamine derivatives were made following literature methods.[2] 5-cyano-tryptamine, 4-chloro-tryptamine and 7-bromo-tryptamine were synthesised as described.

Chromatography

All reactions were monitored by thin-layer chromatography (TLC) where appropriate using Merck Kiesel gel 60 F_{254} (230-400 mesh) silica plates which were visualised by UV-light (250 nm) or by staining using aqueous potassium permanganate solutions or vanillin,

sulphuric acid in ethanol where appropriate. Column chromatography was carried out using Merck Kieselgel 60 silica gel (230-400 mesh). Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on a Hewlett-Packard 1050 Series system or Agilent 1200 Series system (column and solvent conditions are given with the compound).

Spectroscopy and Characterisation

All ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were collected on either a Bruker DPX400 (400 MHz ^{1}H, 100 MHz ^{13}C), Bruker DQX400 (400 MHz ^{1}H, 100 MHz ^{13}C) or Bruker AVC500 (500 MHz ^{1}H, 125 MHz ^{13}C) and in the deuterated solvent stated. Chemical shift values (δ) are reported relative to tetramethylsilane (δ = 0 ppm) using the solvent residual as an internal reference. ^{1}HNMR peak splitting (multiplicity) and coupling constants are quoted as seen in the spectra and are not compared to theoretically expected multiplicity. Assignments were aided by COSY and HSQC experiments.

Low resolution mass spectrometric (*m/z*) data was acquired by electrospray ionisation (ESI) on an LCT Premier instrument.. High resolution mass spectra (accurate mass) were recorded on a Bruker Micromass GCT spectrometer.

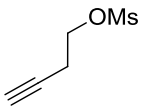
Infrared spectra (ν_{max}) were recorded (wavenumber cm^{-1}) from a thin film on a PIKE diamond ATR module. Only selected maximum absorbances are reported.

Optical rotations were recorded using an Optical Activity AA-1000 polarimeter or a Perkin-Elmer 241 polarimeter; specific rotation (SR) ($[\alpha]_D^T$) are reported in 10^{-1} $deg.cm^2.g^{-1}$; 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).

Melting points were measured on a Leica Galen III microscope apparatus, samples were measured mounted on a cover glass window.

6.1 Chapter 1: Experimental

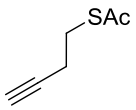
Preparation and characterisation of but-3-yn-1-yl methanesulfonate (39).[3]



To a stirred solution of 3-butyn-1-ol (15. ml, 231 mmol) and triethylamine (41 ml, 551 mmol) in CH_2Cl_2 (140 ml) at 0°C was added a solution of methanesulphonyl chloride (23 ml, 137 mmol) in CH_2Cl_2 (30 ml). The reaction mixture was stirred overnight, diluted with 2M HCl solution (45 ml) and extracted with CH_2Cl_2 (3 x 75 ml). The combined extracts were washed with 1M HCl solution, saturated sodium hydrogen carbonate solution, brine and dried over ($MgSO_4$), filtered and concentrated in *vacuo* to give the product **39** (31 g, 91%) as a pale yellow oil that required no further purification. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 4.23 (t, *J* = 6.6, 2H, $SOCH_2$), 3.00 (s, 3H, CH_3), 2.59 (td, *J* = 6.6, 2.5, 2H, $SOCH_2CH_2$), 2.06 (t, *J* = 2.5, 1H, CH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 78.6 ($HC{\equiv}CCH_2$), 71.0 ($SOCH_2$), 67.1 ($C{\equiv}CH$), 37.7 (CH_3), 19.7 ($C{\equiv}CCH_2$); ***m/z*** (EI/FI) 148 ($[M-H]^-$, 100%).

Data was in accordance with that reported in the literature.[3]

Preparation and characterisation of S-but-3-yn-1-yl ethanethioate (40)[3]

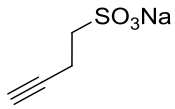


To a stirred solution of but-3-yn-1-yl methanesulfonate **39** (5.0 g, 34 mmol) in acetonitrile (100 ml) was added potassium carbonate (7.0 g, 50 mmol) and thioacetic acid (7.2 g, 101 mmol). The reaction mixture was stirred for 2 days, diluted with water (100 ml) and extracted with ethyl acetate (3 x 100 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated in *vacuo* to give the crude product. The residue was purified by flash column

chromatography (silica gel) to give thioester **40** (8.70 g, 54%) as a clear oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 3.04 (t, *J* = 7.0, 2H, SCH_2), 2.49 (td, *J* = 7.0, 2.5, 2H, SCH_2CH_2), 2.35 (s, 3H, CH_3), 2.03 (t, *J* = 2.5, 1H, CH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 195.0 (CO), 82.0 (HC≡C), 69.6 (C≡CH), 30.5 (CH_3), 28.1 (SCH_2), 19.4 (SCH_2CH_2); ***m/z*** (EI/FI) 128 ($[M\text{-}H]^-$, 100%).

Data was in accordance with that reported in the literature.[3]

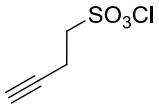
Preparation and characterisation of sodium but-3-yne-1-sulfonate (41)[3]



To a stirred solution of **40** (5.00 g, 39 mmol) in acetic acid (65 ml) at 60 °C was added dropwise 30% hydrogen peroxide solution in water (25 ml, 196 mmol). The reaction mixture was stirred for 1 h, cooled to rt then to 0 °C and $Na_2SO_{3(aq)}$ (1.5M) was added slowly until the solution no longer turned potassium iodide paper blue. The solution was then concentrated in *vacuo* to give the sulfonate ester **41** as a mixture of salts (assumed 99% yield) as an white solid. **^{1}H NMR** (D_2O, 400 MHz) δ_H 2.98 (t, *J* = 7.5, 2H, SCH_2), 2.53 (td, *J* = 7.5, 2.5, 2H, SCH_2CH_2), 2.27 (t, *J* = 2.5, 1H, CH); **^{13}C NMR** (D_2O, 100 MHz) δ_C 82.6 (HC≡C), 70.6 (C≡CH), 49.7 (SCH_2), 14.5 (SCH_2CH_2); ***m/z*** (ES-) 133 ($[M-H]^-$, 100%).

Data was in accordance with that reported in the literature.[3]

Preparation and characterisation of but-3-yne-1-sulfonyl chloride (42)[3]

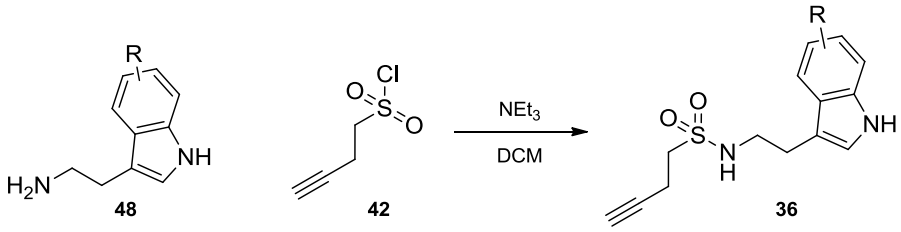


To a suspension of but-3-yne-1-sulfonic acid sodium salt **41** (2.3 g, 15 mmol) in CH_2Cl_2 (16 ml) DMF (2.4 ml, 31 mmol) and thionyl chloride (7.9 ml) were added. The reaction mixture was refluxed for 3 hours, cooled to rt, filtered and passed through a pad of silica eluting with CH_2Cl_2. The solution was concentrated in *vacuo* purification by FCC to afford **42** as a pale

yellow oil. **FT-IR** ν_{max} 3297 (C≡C-H), 1371 ($S=O_{(as)}$), 1169 ($S=O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 250MHz) δ_H 3.91 (t, *J* = 7.5, 2H, SCH_2), 3.00 (td, *J* = 7.5, 2.5, 2H, SCH_2CH_2), 2.23 (t, *J* = 2.5, 1H, CH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 14.9 (SCH_2CH_2), 62.9 (SCH_2), 72.0 (C≡CH), 77.3 ($HC{\equiv}CCH_2$).

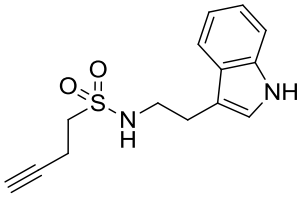
Data was in accordance with that reported in the literature.[3]

General procedure A for preparation of 36



To a stirred solution of sulfonylchloride **42** (1.1 eq) in dichloromethane (5 ml/mmol of tryptamine) under argon at -78 °C was added the desired tryptamine derivative **48** (1 eq) and triethyamine (1.1 eq) in dichloromethane (7 ml/mmol of tryptamine). The mixture was stirred at -78 °C for 5 to 10 mins then concentrated *in vacuo* (in a room temperature water bath) to give the crude product. The residue was purified by flash column chromatography (CH_2Cl_2:Et_2O, 1:0 to 8:2) to give the desired sulfonamide derivative **36**.

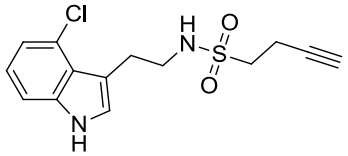
Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36a)



The title compound **36a** was synthesised according to general procedure **A** to give **36a** as an off white solid (90% yield). Recrystallization from ethanol gives thin white crystalline plates.

m.p. 122.4-122.5 °C; **FT-IR** ν_{max} 3419 (N–H), 3409 (N–H), 1306 ($S{=}O_{(as)}$), 1126 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.10 (bs, 1H, ArNH), 7.60 (d, *J* = 8.0, 1H, ArCH), 7.39 (d, *J* = 8.0, 1H, ArCH), 7.23 (t, *J* = 8.0, 1H, ArCH), 7.16 (t, *J* = 8.0, 1H, ArCH), 7.1 (d, *J* = 2.5, 1H, ArCH), 4.34 (t, *J* = 6.0, 1H, CH_2NH), 3.46 (q, *J* = 6.0, 2H, $ArCH_2CH_2$), 3.11 (t, *J* = 7.0, 2H, SCH_2), 3.07 (t, *J* = 6.5, 2H, $ArCH_2$), 2.59 (td, *J* = 7.0, 3.0, 2H, SCH_2CH_2), 1.65 (t, *J* = 3.0, 1H, C≡CH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ: 136.4 (ArC_{quat}), 126.9 (ArC_{quat}), 122.8 (ArCH), 122.5 (ArCH), 119.7 (ArCH), 118.6 (ArCH), 111.7 (ArC_{quat}), 111.4 (ArCH), 79.8 (HC≡C), 70.5 (C≡CH), 49.9 (SCH_2), 43.3 ($NHCH_2$), 26.2 ($ArCH_2$), 14.1 ($HCCCH_2$); ***m/z*** (ES+) 299 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}N_2NaO_2S^+$) requires *m/z* 299.0825, found *m/z* 299.0822.

Preparation and characterisation of N-[2-(4-chloro-1H-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36b)

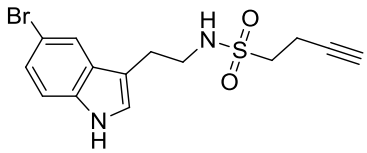


The title compound **36b** was synthesised according to general procedure **A** to give **36b** as an off white solid (80% yield). Recrystallization from ethanol gives thin white crystalline plates.

m.p. 84-85 °C; **FT-IR** ν_{max} 3381 (N–H), 3280 (N–H), 1312 ($S{=}O_{(as)}$), 1129 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.21 (br s, 1H ArNH), 7.29 (dd, *J* = 5.5, 3.0, 1H, ArCH), 7.03 (d, *J* = 2.0, 1H, ArCH), 7.06-7.12 (m, 2H, ArCH), 4.33 (t, 1H, SNH), 3.51 (q, *J* = 6.5, 2H, NCH_2), 3.27 (t, *J* = 6.5, 2H, $ArCH_2$), 3.14 (t, *J* = 7.0, 2H, SCH_2), 2.63 (td, *J* = 7.0, 3.0, 2H, SCH_2CH_2), 1.69 (t, *J* = 3.0, 1H, C≡CH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 138.0 (ArC_{quat}), 126.0 (ArC_{quat}), 124.6 (ArCH), 123.8 (ArC_{quat}), 122.9 (ArCH), 120.7 (ArCH), 112.0 (ArC_{quat}), 110.2 (ArCH), 79.8 (HC≡C), 70.5 (C≡CH), 49.8 (SCH_2), 44.6 (NCH_2), 27.1 ($ArCH_2$), 14.1 (SCH_2CH_2); **m/z** (ES+) 333 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for

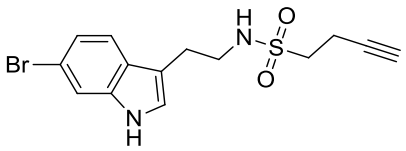
$[M+Na]^+$ ($C_{14}H_{15}ClN_2O_2SNa^+$) requires *m/z* 333.0435 & 335.0406 found 333.0431 & 335.0401.

Preparation and characterisation of *N*-[2-(5-bromo-1*H*-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36c)



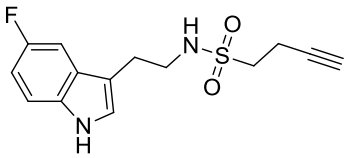
The title compound **36c** was synthesised according to general procedure **A** to give **36c** as a brown solid (25% yield). Recrystallization from ethanol gives an off white solid. **m.p.** 68-70 °C; **FT-IR** ν_{max} 3415-3394 (N–H and ArN–H), 1305 ($S{=}O_{(as)}$), 1132 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 8.12 (bs, 1H, ArNH), 7.71 (d, *J* = 1.5, 1H, ArCH) 7.31 (dd, *J* = 8.5, 2.0, 1H, ArCH), 7.27 (d, *J* = 8.5, 1H, ArCH), 7.13 (d, *J* = 2.0, 1H, ArCH), 4.29 (t, *J* = 6.0, 1H, SNH), 3.45 (q, *J* = 6.5, 2H, NCH_2), 3.15 (t, *J* = 7.0, 2H, SCH_2), 3.03 (t, *J* = 6.5, 2H, NCH_2CH_2), 2.63 (td, *J* = 7.0, 2.5, 2H, SCH_2CH_2), 1.75 (t, *J* = 3.0, 1H, C≡CH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 135.0 (ArCBr), 128.7 (ArC_{quat}), 125.4 (ArCH), 123.9 (ArCH), 121.2 (ArCH), 113.0 (ArC_{quat}), 112.8 (ArCH), 111.5 (ArC_{quat}), 79.8 (HC≡C), 70.5 (HC≡C), 50.0 (SCH_2), 43.1 ($SNCH_2$), 26.1 (NCH_2CH_2), 14.1 (SCH_2CH_2); ***m/z*** (ES+) 377 ($[M+Na]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}BrN_2O_2SNa^+$) requires *m/z* 376.9930 & 378.9909, found *m/z* 376.9925 & 378.9904.

Preparation and charactarisation of *N*-[2-(6-bromo-1H-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36d)



The title compound **36d** was synthesised according to general procedure **A** to give **36d** as an off white solid (73 % yield). Recrystallization from ethanol gives an off white solid. **m.p.** 110-112 °C; **FT-IR** ν_{max} 3416 (N–H), 3290 (ArN–H), 1301 ($S{=}O_{(as)}$), 1127 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H; 8.10 (br s, 1H, ArNH), 7.55 (s, 1H, ArCH), 7.45 (d, *J* = 8.5, 1H, ArCH), 7.25 (d, *J* = 8.5, 1H, ArCH), 7.09 (s, 1H, ArCH), 4.31 (t, *J* = 6.5, 1H, SNH), 3.44 (q, *J* = 6.5, 2H, NCH_2), 3.12 (t, *J* = 7.0, 2H, SCH_2), 3.04 (t, *J* = 6.5, 2H, $ArCH_2$), 2.61 (td, *J* = 7.0, 2.5, 2H, SCH_2CH_2), 1.73 (t, *J* = 2.5, 1H, C≡CH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C; 137.2 (ArC_{quat}), 125.9 (ArC_{quat}), 123.3 (ArCH), 123.0 (ArCH), 119.8 (ArCH), 116.0 (ArCBr), 114.4 (ArCH), 112.0 (ArC_{quat}), 79.8 (HC≡C), 70.5 (C≡CH), 50.0 (SCH_2), 43.3 (NCH_2), 26.1 ($ArCH_2$), 14.1 ($HCCCH_2$); **m/z** (ES+) 377 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}BrN_2O_2SNa^+$) requires *m/z* 376.9930 & 378.9909, found *m/z* 376.9926 & 378.9905.

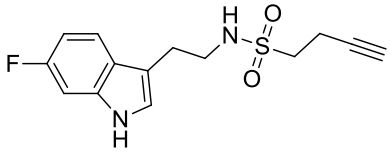
Preparation and characterisation of *N*-[2-(5-fluoro-1H-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36e)



The title compound 36**e** was synthesised according to general procedure **A** to give **36e** as an off white solid (57% yield). Recrystallization from ethanol gives thin white crystalline plates. **m.p.** 99-101 °C; **FT-IR** ν_{max} 3419 (N–H), 3294 (ArN–H), 1300 ($S{=}O_{(as)}$), 1126 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H; 8.17 (br s, 1H, ArNH), 7.30 (dd, *J* = 9.0, 4.0, 1H, ArCH), 7.22 (dd, *J* = 9.5, 2.0, 1H, ArCH), 7.14 (d, *J* = 2.0, 1H, ArCH), 6.97 (td, *J* = 9.0, 2.5, 1H, ArCH), 4.40 (t, *J* = 6.0, 1H, SNH), 3.43 (q, *J* = 6.5, 2H, $NHCH_2$), 3.12 (t, *J* = 7.0, 2H, SCH_2), 3.01 (t, *J* = 6.5, 2H, $ArCH_2$), 2.61 (td, *J* = 7.0, 3.0, 2H, SCH_2CH_2), 1.73 (t, *J* = 2.5, 1H, C≡CH) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C; 157.8 (d, ArCF, *J* 236 Hz), 132.9 (ArC_{quat}), 127.3 (d, ArC_{quat}, *J*

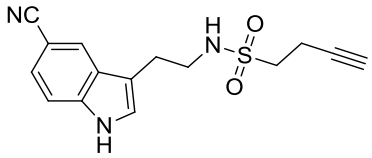
10 Hz), 124.6 (ArCH), 112.1 (d, ArCH, *J* 10 Hz), 111.8 (d, ArC_{quat}, *J* 4.8 Hz), 110.8 (d, ArCH, *J* 26 Hz), 103.5 (d, ArCH, *J* 24 Hz), 79.8 (HC≡C), 70.5 (C≡CH), 49.9 (SCH_2), 43.1 ($SNCH_2$), 26.2 ($ArCH_2$), 14.1 (SCH_2CH_2); **^{19}F NMR** ($CDCl_3$, 376 MHz), -124.0 (ArF); **m/z** (ES+) 317 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}FN_2O_2SNa^+$) requires *m/z* 317.0730, found *m/z* 317.0724.

Preparation and characterisation of *N*-[2-(6-fluoro-1*H*-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36f)



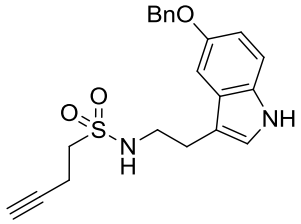
The title compound **36f** was synthesised according to general procedure **A** to give **36f** as an off white solid (46% yield). Recrystallization from ethanol gives thin white crystalline plates. **m.p.** 98-99 °C; **FT-IR** ν_{max} 3419 (N–H), 3307 (ArN–H), 1301 ($S=O_{(as)}$), 1127 ($S=O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H; 8.15 (br s, 1H, ArNH), 7.49 (dd, *J* = 9.0, 5.0, 1H, ArCH), 7.07 (m, 2H, ArCH), 6.92 (td, *J* = 9.0, 2.0, 1H, ArCH), 4.39 (t, *J* = 6.0, 1H, SNH), 3.44 (q, *J* = 6.5, 2H, NCH_2), 3.11 (t, *J* = 7.0, 2H, SCH_2), 3.03 (t, *J* = 6.5, 2H, $ArCH_2$), 2.60 (td, *J* = 7.0, 2.5, 2H, SCH_2CH_2), 1.74 (t, *J* = 3.0, 1H, C≡CH) **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C; 160.1 (d, ArCF, *J* 239 Hz), 136.3 (d, ArC_{quat}, *J* 12 Hz), 123.6 (ArC_{quat}), 123.0 (d, ArCH, *J* 3 Hz)), 119.3 (d, ArCH, *J* 10 Hz) 111.8 (ArC_{quat}), 108.5 (d, ArCH, *J* 24 Hz), 97.7 (d, ArCH, *J* 26 Hz) 79.8 (HC≡C), 70.5 (C≡CH), 49.9 (SCH_2), 43.3 (NCH_2), 26.2 ($ArCH_2$), 14.1 (SCH_2CH_2); **^{19}F NMR** ($CDCl_3$, 376 MHz), -120.4 (ArF); **m/z** (ES+) 317 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}FN_2O_2SNa^+$) requires *m/z* 317.0730, found *m/z* 317.0727.

Preparation and characterisation of *N*-[2-(5-cyano-1*H*-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36g)



The title compound **36g** was synthesised according to general procedure **A** to give **36g** as an off white solid (42% yield). Recrystallization from ethanol gives thin white crystalline plates. **m.p.** 135-136 °C; **FT-IR** ν_{max} 3339 (N–H), 3294 (ArN–H), 2225 (C≡N), 1318 (S=$O_{(as)}$), 1136 (S=$O_{(sy)}$); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 11.46 (br s, 1H, ArNH), 8.09 (s, 1H, ArCH), 7.51 (d, *J* = 8.0, 1H, ArCH), 7.44 - 7.39 (m, 2H, ArCH), 7.26 (t, *J* = 6.0, 1H, SNH), 3.23 (td, *J* = 7.0, 6.0, 2H, NCH_2), 3.15 (t, *J* = 7.5, 2H, SCH_2), 2.93 (t, *J* = 3.0, 1H, C≡CH), 2.90 (t, *J* = 7.0, 2H, $ArCH_2$), 2.50* (m, *J* 7.5, 3.0, 2H, HC≡CCH_2); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 138.7 (ArC_{quat}), 127.9 (ArC_{quat}), 126.7 (ArCH), 125.1 (ArCH), 124.5 (ArCH), 121.8 (ArCN), 113.5 (ArCH), 113.5 (ArC_{quat}), 101.2 (ArC_{quat}), 82.0 (HC≡C), 73.4 (C≡CH), 50.2 (SCH_2), 43.9 (NCH_2), 26.4 ($ArCH_2$), 14.2 (SCH_2CH_2); **m/z** (ES+) 324 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{15}N_3O_2SNa^+$) requires *m/z* 324.0777, found *m/z* 324.0770.

Preparation and characterisation of *N*-(2-(5-(benzyloxy)-1H-indol-3-yl)ethyl)but-3-yne-1-sulfonamide (36h)

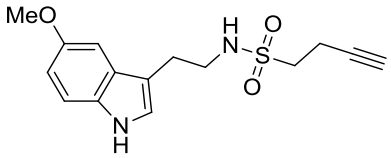


36h was synthesised according to general procedure **A** as an off white solid (35% yield). Recrystallization from ethanol gives a white solid. **m.p.** 88-90 °C; **FT-IR** ν_{max} 3417 3415-3394 (SN-H and ArN-H), 3292 (C≡C-H),1304 (S=$O_{(as)}$), 1130 (S=$O_{(sy)}$); **^{1}H NMR** δ_H ($CDCl_3$,

* Signal hidden under DMSO peak, confirmed by HSQC and COSY.

500 MHz) 7.99 (bs, 1H, ArNH), 7.49 (d, *J* = 7.5, 2H, PhCH), 7.4 (t, *J* = 7.5, 2H, PhCH), 7.33 (t, *J* = 7.5, 1H, PhCH), 7.28 (d, *J* = 9.0, 1H, ArCH), 7.11 (d, *J* = 2.0, 1H, ArCH), 7.07 (d, *J* = 2.0, 1H, ArCH), 6.97 (dd, *J* = 9.0, 2.0, 1H, ArCH), 5.13 (s, 2H, OCH_2Ph), 4.33 (t, *J* = 6.0, 1H, SNH), 3.42 (app q, *J* = 6.5, 2H, $SNCH_2$), 3.10 (t, *J* = 7.5, 2H, SCH_2), 3.02 (t, *J* = 6.5, 2H, $SNCH_2CH_2$), 2.59 (td, *J* = 7.5 , 2.5, 2H, SCH_2CH_2), 1.68 (t, *J* = 2.5, 1H, C≡CH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 153.3 (ArCOBn), 137.5 (ArC quat), 131.7 (ArCH), 128.5 (2 x PhCH), 127.8 (PhCH), 127.6 (2 x PhCH), 127.4 (ArC quat), 123.5 (ArCH), 113.3 (ArCH), 112.1 (ArCH), 111.4 (ArC quat), 102.2 (ArCH), 79.7 (HC≡C), 71.0 (PhCO), 70.5 (C≡CH) 49.9 (SCH_2), 43.2 ($SNCH_2$), 26.2 (NCH_2CH_2), 14.1 (SCH_2CH_2); ***m/z*** (ES+) 405 ($[M+Na]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{22}N_2O_3SNa^+$) requires *m/z* 405.1243, found *m/z* 405.1236.

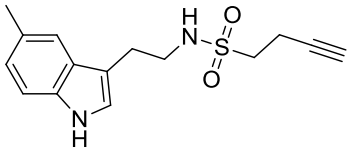
Preparation and charactarisation of *N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36i)



The title compound **36i** was synthesised according to general procedure **A** to give **36i** as an off white solid (81% yield). Recrystallization from ethanol gives an off white solid. **m.p.** 70-72 °C; **FT-IR** ν_{max} 3405 (SN–H), 3282 (ArN–H), 1317 ($S=O_{(as)}$), 1134 ($S=O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.04 (br s, 1H, ArNH), 7.27 (d, *J* = 8.5, 1H, ArCH), 7.05 (d, *J* = 1.5, 1H, ArCH), 7.03 (d, *J* = 2.5, 1H, ArCH), 6.89 (dd, *J* = 8.5, 2.5, 1H, ArCH), 4.42 (t, *J* = 6.5, 1H, SNH), 3.88 (s, 3H, OCH_3), 3.44 (q, *J* = 6.5, 2H, NCH_2), 3.11 (t, *J* = 7.0, 2H, SCH_2), 3.02 (t, *J* = 6.5, 2H, $ArCH_2$), 2.59 (td, *J* = 7.0, 2H, SCH_2CH_2), 1.72 (t, *J* = 3.0, 1H, C≡CH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 154.2 (ArCOMe), 131.5 (ArC_{quat}), 127.4 (ArC_{quat}), 123.5 (ArCH), 112.6 (ArCH), 112.2 (ArCH), 111.4 (ArC_{quat}), 100.5 (ArCH), 79.8 (HC≡C), 70.5

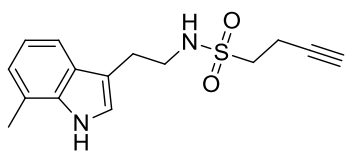
(C≡CH), 56.0 (OCH_3), 49.9 (SCH_2), 43.3 (NCH_2), 26.2 ($ArCH_2$), 14.1 (SCH_2CH_2); **m/z** (ES+) 329 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_3SNa^+$) requires *m/z* 329.0930, found *m/z* 329.0921.

Preparation and characterisation of *N*-[2-(5-methyl-1H-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36j)



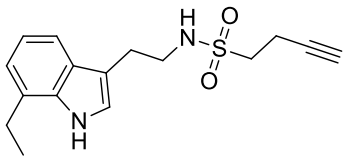
The title compound **36j** was synthesised according to general procedure **A** to give **36j** as an off white solid (72% yield). Recrystallization from ethanol gives an off white solid. **m.p.** 112-114 °C; **FT-IR** ν_{max} 3412 (N–H), 3300 (ArN–H), 1307 ($S=O_{(as)}$), 1127 ($S=O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 7.99 (br s, 1H, ArNH), 7.37 (s, 1H, ArCH), 7.28 (d, *J* = 7.0, 1H, ArCH), 7.06 (d, *J* = 1.5, 1H, ArCH), 7.05 (dd, *J* = 7.0, 1.5, 1H, ArCH), 4.32 (t, *J* = 6.5, 1H, SNH), 3.45 (q, *J* = 6.5, 2H, NCH_2), 3.11 (t, *J* = 7.5, 2H, SCH_2), 3.04 (t, *J* = 6.5, 2H, $ArCH_2$), 2.59 (td, *J* = 7.0, 2.5, 2H, SCH_2CH_2), 2.47 (s, 3H, $ArCH_3$), 1.64 (t, *J* = 2.5, 1H, C≡CH); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 134.8 (ArC_{quat}), 129.0 (ArCMe), 127.2 (ArC_{quat}), 124.0 (ArCH), 122.9 (ArCH), 118.2 (ArCH), 111.1 (ArCH), 111.0 (ArC_{quat}), 79.8 (HC≡C), 70.5 (C≡CH), 49.9 (SCH_2), 43.3 (NCH_2), 26.2 ($ArCH_2$), 21.5 ($ArCH_3$), 14.1 ($HCCCH_2$); **m/z** (ES+) 313 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2NaO_2S^+$) requires *m/z* 313.0981, found 313.0973.

Preparation and characterisation of *N*-[2-(7-methyl-1*H*-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36k)



The title compound **36k** was synthesised according to general procedure **A** to give **36k** as an off white solid (95% yield). Recrystallization from ethanol gives an off white solid. **m.p.** 113-117 °C; **FT-IR** ν_{max} 3400 (N–H), 3291 (ArN–H), 1303 ($S{=}O_{(as)}$), 1127 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.05 (br s, 1H, ArNH), 7.45 (d, *J* = 7.5, 1H, ArCH), 7.10 (d, *J* = 2.0, 1H, ArCH), 7.08 (t, *J* = 7.5, 1H, ArCH), 7.03 (d, *J* = 7.5, 1H, ArCH), 4.36 (t, *J* = 6.0, 1H, SNH), 3.46 (q, *J* = 6.0, 2H, NCH_2), 3.09 (t, *J* = 7.0, 2H, SCH_2), 3.06 (t, *J* = 6.0, 2H, $ArCH_2$), 2.57 (td, *J* = 7.0, 3.0, 2H, SCH_2CH_2), 2.50 (s, 3H, $ArCH_3$), 1.68 (t, *J* = 3.0, 1H, C≡CH); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 136.1 (ArC_{quat}), 126.5 (ArC_{quat}), 122.9 (ArCH), 122.5 (ArCH), 120.6 ($ArCCH_3$), 119.9 (ArCH), 116.3 (ArCH), 112.1 (ArC_{quat}), 79.8 (HC≡C), 70.5 (C≡CH), 49.9 (SCH_2), 43.3 (NCH_2), 26.3 ($ArCH_2$), 16.6 ($ArCH_3$), 14.1 (SCH_2CH_2); ***m/z*** (ES+) 313 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_2SNa^+$) requires *m/z* 313.0981, found *m/z* 313.0977.

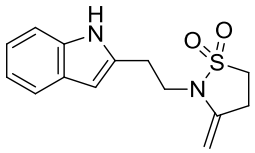
Preparation and characterisation of *N*-[2-(7-ethyl-1H-indol-3-yl)ethyl]but-3-yne-1-sulfonamide (36l)



The title compound **36l** was synthesised according to general procedure **A** to give **36l** as an off white solid (25% yield). Recrystallization from ethanol gives thin white crystalline plates. **m.p.** 109-112 °C; **FT-IR** ν_{max} 3404 (N–H), 3297 (ArN–H), 1312 ($S{=}O_{(as)}$), 1129 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 8.04 (br s, 1H, ArNH), 7.45 (d, *J* = 7.5, 1H, ArCH), 7.11 (d, *J* = 3.0, 1H, ArCH), 7.11 (t, *J* = 7.5, 1H, ArCH), 7.07 (d, *J* = 7.5, 1H, ArCH), 4.31 (t, *J* = 6.5, 1H, SNH), 3.46 (q, *J* = 6.5, 2H, NCH_2), 3.11 (t, *J* = 7.5, 2H, SCH_2), 3.07 (t, *J* = 6.5, 2H, NCH_2CH_2), 2.87 (q, *J* = 7.5, 2H, $ArCH_2CH_3$), 2.59 (td, *J* = 7.5, 3.0, 2H, SCH_2CH_2), 1.65 (t, *J* = 3.0, 1H, C≡CH), 1.37 (t, *J* = 7.5, 3H, $ArCH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 135.3

(ArC_{quat}), 126.8 (ArC_{quat}), 126.7 (ArC_{quat}), 122.4 (ArCH), 121.0 (ArCH), 120.1 (ArCH), 116.3 (ArCH), 112.1 (ArC_{quat}), 79.7 (HC≡C), 70.4 (C≡CH), 49.9 (SCH_2), 43.3 (NCH_2), 26.3 (NCH_2CH_2), 24.0 ($ArCH_2CH_3$), 14.1 (SCH_2CH_2), 13.8 ($ArCH_2CH_3$); **m/z** (ES-) 303 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}N_2O_2SNa^+$) requires *m/z* 327.1138 , found *m/z* 327.1134.

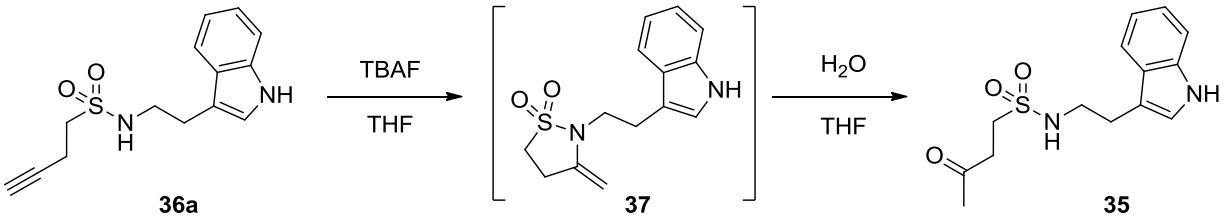
Preparation and characterisation of 2-(2-(1*H*-indol-2-yl)ethyl)-3-methyleneisothiazolidine 1,1-dioxide (37)



To a stirred solution of alkyne **36a** (500 mg, 1.81 mmol) in dry THF (20 ml) a solution of TBAF (9.1 ml, 1M THF) was added under nitrogen and heated to reflux for 13 h. The reaction was monitored by ^1H NMR ($CDCl_3$ passed through a short pad of K_2CO_3 prior to use). Upon completion, the reaction mixture was passed rapidly through a pad of silica eluting with EtOAc. Concentration of the filtrate gave a pale brown solid **37** which was carried through crude due to its instability (60% crude yield). **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 8.08 (br s, 1H, ArNH), 7.66 (d, *J* = 8.0, 1H, ArCH), 7.38 (d, *J* = 8.0, 1H, ArCH), 7.22 (td, *J* = 7.0, 1.5, 1H, ArCH), 7.15 (td, *J* = 7.5, 1.0, 1H ArCH), 7.09 (d, *J* = 2.0, 1H, ArCH), 4.17 (d, *J* = 2.0, 1H, NC=CH_aH_b), 4.10 (d, *J* = 2.0, 1H, NC=CH_aH_b), 3.71 (t, *J* = 8.0, 2H, SCH_2), 3.23 (t, *J* = 7.5, 2H, $SNCH_2$), 3.17 (t, *J* = 8.0, 2H, SCH_2CH_2), 3.04 (t, *J* = 7.5, 2H, $ArCH_2$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 139.4 (NC=CH_2), 136.2 (ArC quat), 127.3 (ArC quat), 122.2 (ArCH), 120.1 (ArCH), 119.5 (ArCH), 118.6 (ArCH), 112.5 (ArC quat), 111.2 (ArCH), 83.0 (NC=CH_2), 46.1 ($SNCH_2$), 41.7 (SCH_2), 25.5 ($ArCH_2$); 23.2 (SCH_2CH_2); **Conformation by chemical transformation:** Treatment of compound **37** with water yields ketone **35**.

Conformation by chemical transformation: Treatment of **37** with chiral Brønsted acid in toluene give tetracycle **38a**.

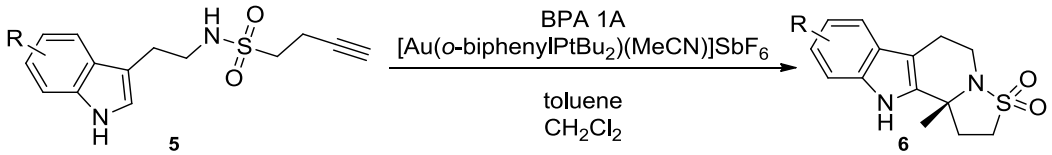
Preparation and characterisation of *N*-[2-(1H-indole-3-yl)ethyl]-3-oxobutane-1-sulfonamide (35)



36a **37** **35**

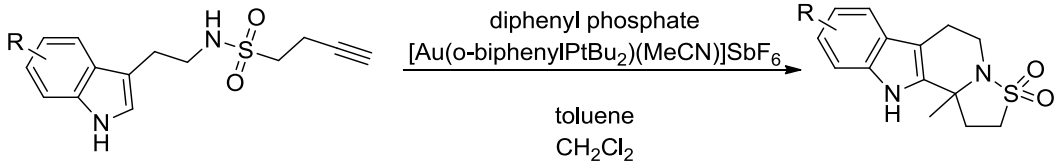
To a stirred solution of sulfonamide **36a** (500 mg, 1.81 mmol) in dry THF (20 ml), a solution of TBAF (9.1 ml, 1M in THF) was added under nitrogen and heated to reflux for 13 hours. The reaction was monitored by ^{1}H NMR ($CDCl_3$ passed through a short pad of K_2CO_3 prior to use). Upon completion, water (20 ml) was added and the solution was stirred for 1 h. The aqueous layer was separated and the organic layer was washed with water 5 times. Purification by flash column chromatography (silica) afforded **35** (230 mg, 25%). **m.p.** 108-109 °C; **FT-IR** ν_{max} 3346 (ArN–H, broad), 3252 (SN–H) 1707 (C=O) 1313 ($S=O_{(as)}$), 1138 ($S=O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 8.12 (br s, 1H, ArNH), 7.60 (d, *J* = 7.5, 1H, ArCH), 7.39 (d, *J* = 8.0, 1H, ArCH), 7.23 (t, *J* = 7.5, 1H, ArCH), 7.15 (t, *J* = 8.0, 1H, ArCH), 7.09 (s, 1H, ArCH), 4.26 (br s, 1H, SNH), 3.45 (q, *J* = 6.0, 2H, $SNCH_2$), 3.19 (t, *J* = 7.5, 2H, SCH_2), 3.05 (t, *J* = 6.0, 2H, $ArCH_2$), 2.77 (t, *J* = 7.0, 2H, SCH_2CH_2), 2.11 (s, 3H, $COCH_3$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 204.5 (CO) 136.5 (ArC quat), 127.0 (ArC quat), 122.8 (ArCH), 122.5 (ArCH), 119.8 (ArCH), 118.6 (ArCH), 111.7 ($ArCCH_2$), 111.5 (ArCH), 46.7 (SCH_2), 43.3 ($SNCH_2$), 37.3 (SCH_2CH_2), 29.9 ($COCH_3$), 26.2 ($ArCH_2$); ***m/z*** (ES+) 317 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}N_2NaO_3S^+$) requires *m/z* 317.0930, found *m/z* 317.0927.

General procedure B for preparation of 38



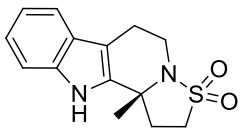
To a solution of the desired sulfonamide **36** (1 eq) and **BPA-1A** (0.1 eq) in toluene (14 ml per 0.1 mmol of sulfonamide) at 60 °C in a foil covered flask was added [Au(o-biphenylPtBu$_2$)(MeCN)]SbF$_6$ (**E**) (0.005 eq) in dichloromethane (0.67 ml per 1 mmol of sulfonamide). The reaction was allowed to stir at 60 °C for 1 to 12 hours. Upon completion the mixture was concentrated *in vacuo* and purified by flash column chromatography (CH_2Cl_2:MTBE ($CH_3OC(CH_3)_{3)}$) 1:0 to 9:1).

General procedure C for preparation of racemic 38



To a solution of the desired sulfonamide **36** (1 eq) and diphenylphosphate (0.1 eq) in toluene (14 ml per 0.1 mmol of sulfonamide **36**) at 60 °C in a foil covered flask was added [Au(o-biphenylPtBu$_2$)(MeCN)]SbF$_6$ (**E**) (0.05 eq) in dichloromethane (0.67 ml per 1 mmol of sulfonamide). The reaction was allowed to stir at 60 °C for 1 to 12 hours. Upon completion the mixture is concentrated *in vacuo* and purified by flash column chromatography (CH_2Cl_2:MTBE ($CH_3OC(CH_3)_3$), 1:0 to 9:1).

Preparation and characterisation of (*R*)-11b-methyl-1,2,5,6,11,11b-hexahydroisothiazolo[2',3':1,2]pyrido[3,4-b]indole 3,3-dioxide (38a)

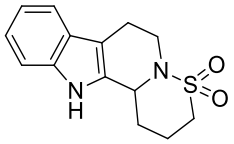


The title compound **38a** was synthesised according to general procedure **B** providing **38a** as a white solid (84% yield, 88% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 6.0 min, minor t_R = 15.4 min); $[\alpha]_D^{21}$ = +113.8 (*c* 0.16, 1:1 MeOH:CH_2Cl_2).

Racemic-38a was synthesised according to general procedure **C** as an off white solid.

m.p. 279-283 °C; **FT-IR** ν_{max} 3397 (N–H), 1289 ($S{=}O_{(as)}$), 1145 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 7.78 (br s, 1H, ArNH), 7.50 (d, *J* = 8.0, 1H, ArCH), 7.35 (d, *J* = 8.0, 1H, ArCH), 7.22 (ddd, *J* = 8.0, 7.0, 1.0, 1H, ArCH) 7.15 (ddd, *J* = 8.0, 7.0, 1.0, 1H, ArCH), 4.05 (dd, *J* = 14.5, 5.0, 1H, $SNCH_aH_b$), 3.33 (ddd, *J* = 15.0, 12.0, 4.5, 1H, $SNCH_aH_b$), 3.19 (m, 2H, $ArCH_aH_b$, SCH_aH_b), 2.90 (ddd, *J* = 12.0, 11.0, 7.0, 1H, SCH_aH_b), 2.65 (m, 3H, $ArCH_aH_b$, $SCH_2CH_aH_b$), 1.73 (s, 3H, CCH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 135.9 (ArC_{quat}), 133.9 (ArC_{quat}), 126.8 (ArC_{quat}), 122.8 (ArCH), 120.1 (ArCH), 118.7 (ArCH), 111.9 (ArCH), 109.7 (ArC_{quat}), 59.1 ($NCCH_2$), 46.0 ($NSCH_2$), 38.1 ($SNCH_2$), 33.6 ($NSCH_2CH_2$), 28.2 (CCH_3), 19.9 ($ArCH_2$); (ES+) 299 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}N_2O_2SNa^+$) requires *m/z* 299.0825, found *m/z* 299.0821.

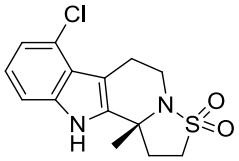
Preparation and characterisation of 2,3,6,7,12,12b-hexahydro-1*H*-[1,2]thiazino[2',3':1,2]pyrido[3,4-b]indole 4,4-dioxide (43a)



The title compound **43a** was isolated along side **36a** according to general procedure **B** providing a white solid (8% yield). **m.p.** 261-265 °C (decomposition); **FT-IR** ν_{max} 3412 (N–H), 1323 ($S{=}O_{(as)}$), 1149 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 7.73 (br s, 1H, ArNH), 7.51 (d, *J* = 8.0, 1H, ArCH), 7.34 (d, *J* = 8.0, 1H, ArCH), 7.21 (t, *J* = 8.0, 1H, ArCH), 7.14 (t, *J* = 8.0, 1H, ArCH), 4.97 (d, *J* = 11.0, 1H, $NCHCH_2$), 3.68 (m, 1H, $SNCH_aH_b$), 3.60 (m, 1H,

$SNCH_aH_b$), 3.21 (dt, *J* = 13.5, 3.5, 1H, $NSCH_aCH_b$), 3.02 (td, *J* = 13.5, 4.0, 1H, $NSCH_aH_b$), 2.95 (m, 1H, $ArCH_aH_b$), 2.89 (dt, *J* = 15.5, 4.5, 1H, $ArCH_aH_b$), 2.44 (qt, *J* = 14.0, 3.5, 1H, $NSCH_2CH_aH_b$), 2.24 (dt, *J* = 14.0, 3.5, 1H, $NSCH_2CH_aH_b$), 2.05 (dq, *J* = 14.5, 3.0, 1H, $NSCH_2CH_2CH_aH_b$), 1.84 (m, 1H, $NSCH_2CH_2CH_aH_b$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 136.2 (ArC_{quat}), 132.0 (ArC_{quat}), 126.5 (ArC_{quat}), 122.4 (ArCH), 120.0 (ArCH), 118.4 (ArCH), 110.9 (ArCH), 108.7 (ArC_{quat}), 55.5 ($NCCH_2$), 46.8 ($NSCH_2$), 39.8 ($SNCH_2$), 27.8 ($NSCH_2CH_2CH_2$), 22.8 ($NSCH_2CH_2$), 21.4 ($ArCH_2$); ***m/z*** (ES+) 299 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}N_2O_2SNa^+$) requires *m/z* 299.0825, found *m/z* 299.0819.

Preparation and characterisation of (*R*)-7-chloro-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-*b*]indole 3,3-dioxide (38b)



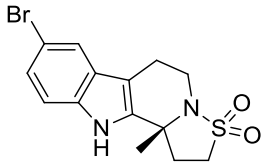
The title compound 38**b** was synthesised according to general procedure **B** providing a white solid (77% yield, 95% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 5.8 min, minor t_R = 8.1 min); $[\alpha]_D^{25}$ = +94.3 (*c* 0.21, 1:1 MeOH:CH_2Cl_2).

Racemic-38b was synthesised according to general procedure **C** as an off white solid,

m.p. 208 °C (decomposition); **FT-IR** ν_{max} 3321 (N–H), 1303 ($S=O_{(as)}$), 1136 ($S=O_{(sy)}$); **^{1}H NMR** (CD_3OD, 500 MHz) δ_H 7.25 (dd, *J* = 8.0, 1.0, 1H, ArCH), 7.03 (t, *J* = 8.0, 1H, ArCH), 6.96 (d, *J* = 7.5, 1H, ArCH), 3.92 (dd, *J* = 15.0, 5.5, 1H, NCH_aH_b), 3.37 (ddd, *J* = 15.0, 12.0, 4.5, 1H, NCH_aH_b), 3.32-3.23 (m, 2H, $NCH_2CH_aH_b$, SCH_aH_b), 3.09 (ddd, *J* = 15.5, 4.0, 1.0, 1H, $NCH_2CH_aH_b$), 2.92 (ddd, *J* = 12.5, 10.0, 7.0, 1H, SCH_aH_b), 2.77 (ddd, *J* = 13.5, 7.0, 5.5,

1H, $SCH_2CH_aH_b$), 2.60 (ddd, *J* = 13.5, 10.0, 6.5, 1H, $SCH_2CH_aH_b$), 1.72 (s, 3H, $NCCH_3$); **^{13}C NMR** (CD_3OD, 125 MHz) δ_C 139.1 (ArC_{quat}), 137.4 (ArCCl), 126.9 (ArC_{quat}), 125.2 (ArC_{quat}), 123.4 (ArCH), 120.6 (ArCH), 111.0 (ArCH), 108.8 (ArC_{quat}), 60.6 ($NCCH_3$), 47.0 (SCH_2), 38.7 (NCH_2), 34.3 (SCH_2CH_2), 28.0 (NCH_2CH_2), 23.0 ($NCCH_3$); **m/z** (ES+) 333 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}ClN_2O_2SNa^+$) requires *m/z* 333.0435 & 335.0406, found *m/z* 333.0435 & 335.0405.

Preparation and characterisation of (*R*)-8-bromo-11b-methyl-1,2,5,6,11,11b-hexahydroisothiazolo[2',3':1,2]pyrido[3,4-b]indole 3,3-dioxide (38c)



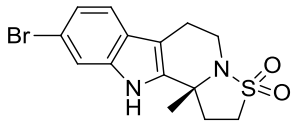
The title compound **38c** was synthesised according to general procedure **B** as a white solid (82% yield, 90% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 10.0 min, minor t_R = 27.2 min); $[\alpha]_D^{21}$ = +101.6 (*c* 0.25, 1:1 MeOH:CH_2Cl_2).

Racemic-38c was synthesised according to general procedure **C** as an off white solid.

m.p. 266 °C (decomposition); **FT-IR** ν_{max} 3410 (N–H), 1301 ($S{=}O_{(as)}$), 1143 ($S{=}O_{(sy)}$); **^{1}H NMR** (d_6-acetone, 500 MHz) δ_H 10.42 (br s, 1H, ArNH), 7.63 (d, *J* = 2.0, 1H, ArCH), 7.31 (d, *J* = 8.5, 1H, ArCH), 7.23 (dd, *J* = 8.5, 2.0, 1H, ArCH), 3.91 (dd, *J* = 15.0, 6.0, 1H, SCH_aH_b), 3.37 (ddd, *J* = 15.0, 12.5, 5.0, 1H, SCH_aH_b), 3.28 (dt, *J* = 12.5, 6.0, 1H, NCH_aH_b), 3.05 (ddd, *J* = 15.5, 12.5, 6.0, 1H, $SCH_2CH_aH_b$), 2.95-2.80 (m, 2H, NCH_aH_b, $ArCH_aH_b$), 2.65-2.60 (m, 2H, $ArCH_aH_b$, $SCH_2CH_aH_b$), 1.72 (s, 3H, CH_3); **^{13}C NMR** (d_6-acetone, 125 MHz) δ_C 138.2 (ArCBr), 136.0 (ArC_{quat}), 129.6 (ArC_{quat}), 125.2 (ArCH), 121.6 (ArCH), 113.8 (ArCH), 112.7 (ArC_{quat}), 108.6 (ArC_{quat}), 59.8 ($NCCH_2$), 46.7 (NCH_2), 38.1 (SCH_2), 34.0 ($ArCH_2$), 28.0 (CH_3), 20.5 (SCH_2CH_2); ***m/z*** (ES−) 355 ($[M-H]^-$, 100%), **HRMS** (ES+) exact

mass calculated for $[M+Na]^+$ ($C_{14}H_{15}BrN_2O_2SNa^+$) requires *m/z* 376.9930 & 378.9909, found *m/z* 376.9922 & 378.9900.

Preparation and characterisation of (*R*)-9-bromo-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-*b*]indole 3,3-dioxide (38d)



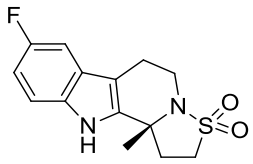
The title compound **38d** was synthesised according to general procedure **B** providing a white solid (81% yield, 91% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 8.3 min, minor t_R = 32.0 min); $[\alpha]_D^{25}$ = +148.2 (*c* 0.23, 1:1 MeOH:CH_2Cl_2).

Racemic-38d was synthesised according to general procedure **C** as an off white solid.

m.p. 228 °C (decomposition); **FT-IR** ν_{max} 3369 (N–H), 1295 ($S{=}O_{(as)}$), 1135 ($S{=}O_{(sy)}$); **^{1}H NMR** (CD_3OD, 500 MHz) δ_H 7.48 (d, *J* = 1.5, 1H, ArCH), 7.34 (d, *J* = 8.5, 1H, ArCH), 7.14 (dd, *J* = 8.5, 1.5, 1H, ArCH), 3.94 (dd, *J* = 15.0, 6.0, 1H, NCH_aH_b), 3.38 (ddd, *J* = 15.0, 12.0, 4.5, 1H, NCH_aH_b), 3.34-3.27* (m, 1H, SCH_aH_b), 3.05 (ddd, *J* = 15.5, 12.0, 6.0, 1H, $NCH_2CH_aH_b$), 2.92 (ddd, *J* = 12.5, 10.0, 7.0, 1H, SCH_aH_b), 2.76 (ddd, *J* = 13.5, 7.0, 5.5, 1H, $SCH_2CH_aH_b$), 2.63-2.56 (m, 2H, $NCH_2CH_aH_b$, $SCH_2CH_aH_b$, 1.70 (s, 3H, CH_3); **^{13}C NMR** (CD_3OD, 125 MHz) δ_C 138.6 (ArC_{quat}), 137.1 (ArC_{quat}), 127.0 (ArC_{quat}), 123.3 (ArCH), 120.5 (ArCH), 116.1 (ArCBr), 114.9 (ArCH), 109.1 (ArC_{quat}), 60.7 ($NCCH_3$), 47.0 (SCH_2), 38.6 (NCH_2), 34.2 (SCH_2CH_2), 27.9 ($NCCH_3$), 20.8 (NCH_2CH_2); **m/z** (ES+) 377 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}BrN_2O_2SNa^+$) requires *m/z* 376.9930 & 378.9909, found *m/z* 376.9928 & 378.9906.

* signal hidden under methanol peak, confirmed by HSQC and COSY

Preparation and characterisation of (*R*)-8-fluoro-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-*b*]indole 3,3-dioxide (38e)

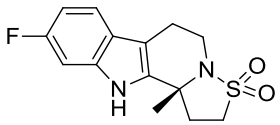


The title compound **38e** was synthesised according to general procedure **B** providing a white solid (85% yield, 93% e.e.).Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 8.5 min, minor t_R = 26.9 min); $[\alpha]_D^{25}$ = +164.3 (*c* 0.21, 1:1 MeOH:CH_2Cl_2).

Racemic-38e was synthesised according to general procedure **C** as an off white solid.

m.p. 205 °C (decomposition); **FT-IR** ν_{max} (N–H), 1299 ($S{=}O_{(as)}$), 1135 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 7.74 (br s, 1H, ArNH), 7.25 (dd, *J* = 9.0, 4.5, 1H, ArCH), 7.31 (dd, *J* = 9.0, 2.5, 1H, ArCH), 6.95 (td, *J* = 9.0, 2.5, 1H, ArCH), 4.05 (dd, *J* = 14.5, 5.5, 1H, NCH_aH_b), 3.32 (ddd, *J* = 14.5, 12.0, 4.5, 1H, NCH_aH_b), 3.23 (ddd, *J* = 12.0, 6.5, 5.0, 1H, SCH_aH_b), 3.13 (ddd, *J* = 15.5, 12.0, 5.5, 1H, $NCH_2CH_aH_b$), 2.91 (ddd, *J* = 12.0, 10.5, 7.0, 1H, SCH_aH_b), 2.68 (ddd, *J* = 13.0, 7.5, 4.5, 1H, $SCH_2CH_aH_b$), 2.65-2.54 (m, 2H, $SCH_2CH_aH_b$, $NCH_2CH_aH_b$), 1.72 (s, 3H, $NCCH_3$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 157.7 (d, ArCF, *J* 237.5 Hz), 135.8 (ArC_{quat}), 132.3 (ArC_{quat}), 127.3 (d, ArCH, *J* 9.5 Hz), 111.5 (d, ArCH, *J* 9.5 Hz), 111.0 (d, ArCH, *J* 26.7 Hz), 109.8 (d, ArC_{quat}, *J* 5.0 Hz), 103.9 (d, ArCH, *J* 24.0 Hz), 59.0 ($NCCH_3$), 45.9 (SCH_2), 37.9 (NCH_2), 33.5 (SCH_2CH_2), 28.1 ($NCCH_3$), 19.9 (NCH_2CH_2); **^{19}F NMR** ($CDCl_3$, 376 MHz), -123.7 (ArF); **m/z** (ES+) 317 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}FN_2O_2SNa^+$) requires *m/z* 317.0730, found *m/z* 317.0724.

Preparation and characterisation of (*R*)-9-fluoro-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-*b*]indole 3,3-dioxide (38f)

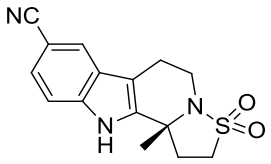


The title compound **38f** was synthesised according to general procedure B providing a white solid (85% yield, 83% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 7.4 min, minor t_R = 25.1 min); $[\alpha]_D^{25}$ = + 138.1 (*c* 0.24, 1:1 MeOH:CH_2Cl_2).

Racemic-38f was synthesised according to general procedure **C** as an off white solid: Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 7.2 min, minor t_R = 24.2 min);

m.p. 220 °C (decomposition); **FT-IR** ν_{max} 3318 (N–H), 1280 ($S{=}O_{(as)}$), 1122 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 7.80 (br s, 1H, ArNH), 7.39 (dd, *J* = 8.5, 5.0, 1H, ArCH), 7.03 (dd, *J* = 9.5, 2.0, 1H, ArCH), 6.90 (ddd, *J* = 9.5, 8.5, 2.0, 1H, ArCH), 4.04 (dd, *J* = 14.5, 5.5, 1H, NCH_aH_b), 3.32 (ddd, *J* = 14.5, 12.0, 4.5, 1H, NCH_aH_b), 3.23 (ddd, *J* = 12.0, 6.0, 4.5, 1H, SCH_aH_b), 3.14 (ddd, *J* = 15.5, 12.0, 6.0, 1H, $NCH_2CH_aH_b$), 2.91 (ddd, *J* = 12.0, 10.5, 7.0, 1H, SCH_aH_b), 2.68 (ddd, *J* = 13.0, 7.0, 5.0, 1H, $SCH_2CH_aH_b$), 2.64-2.57 (m, 2H, $SCH_2CH_aH_b$, $NCH_2CH_aH_b$), 1.72 (s, 3H, $NCCH_3$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 160.2 (d, ArCF, *J* 237.0 Hz), 135.9 (d, ArC_{quat}, *J* 12.5 Hz), 134.1 (d, ArC_{quat}, *J* 4.0 Hz), 123.4 (ArC_{quat}), 119.4 (d, ArCH, *J* 10.5 Hz), 109.7 (ArC_{quat}), 108.7 (d, ArCH, *J* 25.0 Hz), 97.6 (d, ArCH, *J* 26.5 Hz), 59.0 ($NCCH_3$), 45.9 (SCH_2), 37.9 (NCH_2), 33.4 (SCH_2CH_2), 28.1 ($NCCH_3$), 19.8 (NCH_2CH_2); **^{19}F NMR** ($CDCl_3$, 376 MHz), -119.6 (ArF); **m/z** (ES+) 317 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{15}FN_2O_2SNa^+$) requires *m/z* 317.0730, found *m/z* 317.0728.

Preparation and characterisation of (*R*)-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-b]indole-8-carbonitrile 3,3-dioxide (38g)



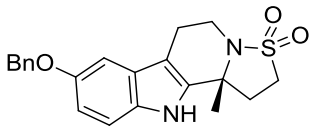
The title compound **38g** was synthesised according to general procedure **B** providing a white solid (60% yield, 96% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 13.1 min, minor t_R = 53.6 min); $[\alpha]_D^{25}$ = +95.9 (*c* 0.16, 1:1 MeOH:CH_2Cl_2).

Racemic-38g was synthesised according to general procedure **C** as an off white solid.

m.p. 210 °C (decomposition); **FT-IR** ν_{max} 3316 (N–H), 2219 (C≡N), 1302 ($S{=}O_{(as)}$), 1134 ($S{=}O_{(sy)}$); **^{1}H NMR** (CD_3OD, 500 MHz) δ_H 7.90 (s, 1H, ArCH), 7.46 (d, 1H, ArCH, *J* = 8.5), 7.43 (dd, *J* = 8.5, 1.5, 1H, ArCH), 3.97 (dd, *J* = 15.0, 5.5, 1H, NCH_aH_b), 3.41 (ddd, *J* = 15.0, 11.5, 4.5, 1H, NCH_aH_b), 3.35-3.30* (m, 1H, SCH_aH_b), 3.09 (ddd, *J* = 15.5, 12.0, 6.0, 1H, $NCH_2CH_aH_b$), 2.94 (ddd, *J* = 12.5, 9.5, 7.0, 1H, SCH_aH_b), 2.78 (ddd, *J* = 13.0, 7.0, 5.5, 1H, $SCH_2CH_aH_b$), 2.71-2.59 (m, 2H, $SCH_2CH_aH_b$, $NCH_2CH_aH_b$), 1.72 (s, 3H, $NCCH_3$); **^{13}C NMR** (CD_3OD, 125 MHz) δ_C 139.7 (ArC_{quat}), 139.2 (ArC_{quat}), 128.0 (ArC_{quat}), 125.9 (ArCH), 124.9 (ArCH), 121.8 (ArCCN), 113.2 (ArCH), 110.0 (ArCN), 102.8 (ArC_{quat}), 60.5 ($NCCH_3$), 47.0 (SCH_2), 38.4 (NCH_2), 34.1 (SCH_2CH_2), 27.8 ($NCCH_3$), 20.7 (NCH_2CH_2); **m/z** (ES+) 324 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{15}N_3O_2SNa^+$) requires *m/z* 324.0777, found *m/z* 324.0775.

Preparation and characterisation of (*R*)-8-(benzyloxy)-11b-methyl-1,2,5,6,11,11b-hexahydroisothiazolo[2',3':1,2]pyrido[3,4-b]indole 3,3-dioxide (38h)

* Signal hidden under methanol peak, confirmed by HSQC and COSY.



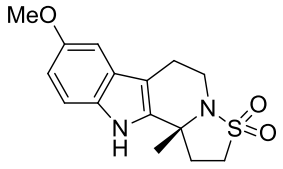
38h was synthesised according to general procedure **B** as a colourless oil (96% yield, 10 : 1 ratio, of 22c : 23c) . Purification by FCC (CH_2Cl_2 : MTBE, 97.5 : 2.5 to 90 : 10) gives a white solid (87 % yield, 73% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 11.8 min, minor t_R = 14.4 min); $[\alpha]_D^{20}$ = +77.5 (*c* 0.20, 1:1 MeOH : CH_2Cl_2)

Rac-38h was synthesised according to general procedure **C** as an off white solid: Chiralcel

AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 11.8 min, minor t_R = 21.6 min);

FT-IR ν_{max} 3358 (NH), 1301 ($S=O_{(as)}$), 1135 ($S=O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 7.69 (br s, 1H, ArNH), 7.48 (d, *J* = 7.5, 2H, ArCH), 7.40 (t, *J* = 7.5, 2H, PhCH), 7.33 (t, *J* = 7.5, 1H, PhCH), 7.24 (d, *J* = 9.0, 1H, ArCH), 7.02 (d, *J* = 2.0, 1H, ArCH), 6.94 (dd, *J* = 9.0, 2.5, 1H, ArCH), 5.11 (s, 2H, $ArOCH_2$), 4.04 (dd, *J* = 14.5, 5.5, 1H, $SNCH_aH_b$), 3.32 (ddd, *J* = 14.5, 11.5, 5.0, 1H, $SNCH_aH_b$), 3.16 (m, 2H, $ArCH_aH_b$, SCH_aH_b), 2.90 (td, *J* = 11.5, 7.0, 1H, SCH_aH_b), 2.63 (m, 3H, $ArCH_aH_b$, $SCH_2CH_aH_b$), 1.71 (s, 3H, $C(C)_3CH_3$) ; **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 152.2 (ArCO), 137.8 (ArC quat), 136.7 (ArC quat), 131.0 (ArC quat), 128.3 (2 x PhCH), 127.6 (PhCH), 127.5 (PhCH), 126.6 (ArC quat), 111.9 (ArCH), 111.8 (ArCH), 106.2 (ArC quat), 101.9 (ArCH), 69.8 ($ArOCH_2$), 58.7 (SNC quat), 45.6 (NCH_2), 36.8 (SCH_2), 32.9 ($ArCH_2$), 27.4 (CCH_3), 19.7 (SCH_2CH_2); ***m/z*** (ES+) 405 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{22}N_2NaO_3S^+$) requires *m/z* 405.1243, found *m/z* 405.1238.

Preparation and characterisation of (*R*)-8-methoxy-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-b]indole 3,3-dioxide (38i)

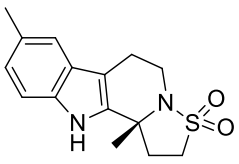


The title compound **38i** was synthesised according to general procedure **B** providing a white solid (75% yield, 80% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 8.2 min, minor t_R = 14.3 min); $[\alpha]_D^{25}$= 93.2 (*c* 0.734, 1:1 MeOH:CH_2Cl_2).

Racemic-38i was synthesised according to general procedure **C** as an off white solid.

m.p. 210-220 °C (decomposition); **FT-IR** ν_{max} 3365 (N–H), 2506 (ArOC–H), 1298 ($S{=}O_{(as)}$), 1137 ($S{=}O_{(sy)}$); **^{1}H NMR** (CD_3OD, 500 MHz) δ_H 7.21 (d, *J* = 9.0, 1H, ArCH), 6.92 (d, *J* = 2.5, 1H, ArCH), 6.77 (dd, *J* = 9.0, 2.5, 1H, ArCH), 3.93 (dd, *J* = 14.5, 5.5, 1H, NCH_aH_b), 3.82 (s, 3H, OCH_3), 3.38 (ddd, *J* = 14.5, 12.0, 4.5, 1H, NCH_aH_b), 3.28 (dt, *J* = 12.0, 6.0, 1H, SCH_aH_b), 3.05 (ddd, *J* = 15.5, 12.0, 6.0, 1H, $NCH_2CH_aH_b$), 2.90 (ddd, *J* = 12.5, 10.0, 7.0, 1H, SCH_aH_b), 2.77 (ddd, *J* = 13.0, 7.0, 5.0, 1H, $SCH_2CH_aH_b$), 2.58 (m, 2H, $SCH_2CH_aCH_b$, $NCH_2CH_aH_b$), 1.70 (s, 3H, $NCCH_3$); **^{13}C NMR** (CD_3OD, 125 MHz) δ_C 155.3 (ArCO), 136.8 (ArC_{quat}), 133.0 (ArC_{quat}), 128.3 (ArC_{quat}), 112.9 (ArCH), 112.7 (ArCH), 108.6 (ArC_{quat}), 101.2 (ArCH), 61.0 ($NCCH_3$), 56.3 (OCH_3), 47.1 (SCH_2), 38.8 (NCH_2), 34.3 (SCH_2CH_2), 28.1 ($NCCH_3$), 21.0 (NCH_2CH_2); **m/z** (ES-) 305 ([M-H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_3SNa^+$) requires *m/z* 329.0930, found *m/z* 329.0917.

Preparation and characterisation of (*R*)-8,11b-dimethyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-*b*]indole 3,3-dioxide (38j)

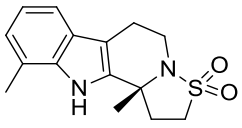


The title compound **38j** was synthesised according to general procedure **B** providing a white solid (84% yield, 87% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 6.7 min, minor t_R = 14.0 min); $[\alpha]_D^{25}$ = 101.3 (*c* 0.20, 1:1 MeOH:CH_2Cl_2).

Racemic-38j was synthesised according to general procedure **C** as an off white solid.

m.p. 220 °C (decomposition); **FT-IR** ν_{max} 3390 (N–H), 1300 ($S{=}O_{(as)}$), 1141 ($S{=}O_{(sy)}$); **^{1}H NMR** (CD_3OD, 500 MHz) δ_H 7.21 (br s, 1H, ArCH), 7.20 (d, *J* = 8.0, 1H, ArCH), 6.95 (dd, *J* = 8.0, 1.5, 1H, ArCH), 3.93 (dd, *J* = 14.5, 5.5, 1H, NCH_aH_b), 3.42-3.35 (m, 1H, NCH_aH_b), 3.35-3.26 (m, 1H, SCH_aH_b), 3.05 (ddd, *J* = 15.5, 12.0, 6.0, 1H, $NCH_2CH_aH_b$), 2.91 (ddd, *J* = 12.0, 10.0, 7.0, 1H, SCH_aH_b), 2.78 (ddd, *J* = 13.5, 7.0, 5.0, 1H, $SCH_2CH_aH_b$), 2.62-2.54 (m, 2H, $SCH_2CH_aH_b$, $NCH_2CH_aH_b$), 2.41 (s, 3H, $ArCH_3$), 1.70 (s, 3H, $NCCH_3$); **^{13}C NMR** (CD_3OD, 125 MHz) δ_C 136.2 (ArC_{quat}), 136.1 (ArC_{quat}), 129.2 (ArC_{quat}), 128.3 (ArC_{quat}), 124.4 (ArCH), 118.7 (ArCH), 111.7 (ArCH), 108.3 (ArC_{quat}), 61.0 ($NCCH_3$), 47.1 (SCH_2), 38.8 (NCH_2), 34.3 (SCH_2CH_2), 28.1 ($NCCH_3$), 21.6 ($ArCH_3$), 20.9 (NCH_2CH_2); **m/z** (ES+) 313 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_2SNa^+$) requires *m/z* 313.0981, found *m/z* 313.0973.

Preparation and characterisation of (*R*)-10,11b-dimethyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-b]indole 3,3-dioxide (38k)

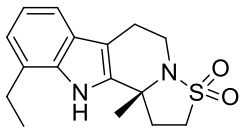


The title compound **38k** was synthesised according to general procedure **B** providing a white solid (85% yield, 92% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 5.0 min, minor t_R = 6.1 min); $[\alpha]_D^{25}$ = +182.1 (*c* 0.25, 1:1 MeOH:CH_2Cl_2).

Racemic-38k was synthesised according to general procedure **C** as an off white solid.

m.p. 195 °C (decomposition); **FT-IR** ν_{max} 3338 (N-H), 1296 ($S{=}O_{(as)}$), 1125 ($S{=}O_{(sy)}$); **^{1}H NMR** (CD_3OD, 500 MHz) δ_H 7.25 (dd, *J* = 7.0, 2.0, 1H, ArCH), 6.94 (t, *J* = 7.0, 1H, ArCH), 6.91 (d, *J* = 7.0, 1H, ArCH), 3.93 (dd, *J* = 15.0, 5.5, 1H, NCH_aH_b), 3.38 (ddd, *J* = 15.0, 12.0, 4.5, 1H, NCH_aH_b), 3.28 (m, 1H, SCH_aH_b), 3.07 (ddd, *J* = 15.5, 12.0, 6.0, 1H, $NCH_2CH_aH_b$), 2.94-2.83 (m, 2H, SCH_aH_b, $SCH_2CH_aH_b$), 2.65-2.56 (m, 2H, $NCH_2CH_aH_b$, $SCH_2CH_aH_b$), 2.50 (s, 3H, $ArCH_3$), 1.74 (s, 3H, $NCCH_3$); **^{13}C NMR** (CD_3OD, 125 MHz) δ_C 137.2 (ArC_{quat}), 135.9 (ArC_{quat}), 127.7 (ArC_{quat}), 123.6 (ArCH), 121.6 (ArC_{quat}), 120.4 (ArCH), 116.7 (ArCH), 109.2 (ArC_{quat}), 61.1 ($NCCH_3$), 47.1 (SCH_2), 38.7 (NCH_2), 34.2 (SCH_2CH_2), 28.0 ($NCCH_3$), 21.1 (NCH_2CH_2), 17.1 ($ArCH_3$); **m/z** (ES+) 313 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{15}H_{18}N_2O_2SNa^+$) requires *m/z* 313.0981, found *m/z* 313.0974.

Preparation and characterisation of (*R*)-10-ethyl-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-b]indole 3,3-dioxide (38l)

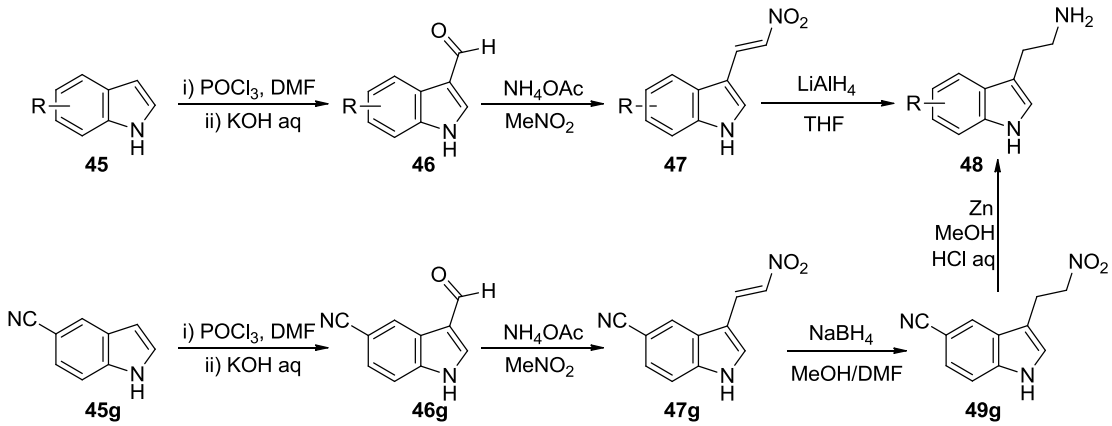


The title compound **38l** was synthesised according to general procedure **B** providing a white solid (83% yield, 95% e.e.).Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220 nm, major t_R = 7.9 min, minor t_R = 10.2 min); $[\alpha]_D^{25}$= +204.4 (*c* 0.09, 1:1 MeOH:CH_2Cl_2).

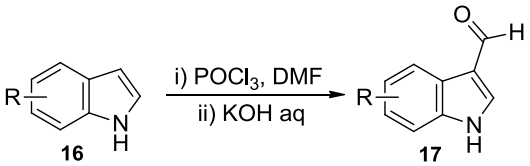
Racemic-38l was synthesised according to general procedure **C** as an off white solid: Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 8.0 min, minor t_R = 10.3 min);

m.p. 190 °C (decomposition); **FT-IR** ν_{max} 3341 (N–H), 1296 ($S{=}O_{(as)}$), 1124 ($S{=}O_{(sy)}$); **^{1}H NMR** (CD_3OD, 500 MHz) δ_H 7.25 (dd, *J* = 7.0, 2.5, 1H, ArCH), 6.99-6.94 (m, 2H, ArCH), 3.93 (dd, *J* = 15.0, 5.5, 1H, NCH_aH_b), 3.39 (ddd, *J* = 15.0, 12.0, 4.5, 1H, NCH_aH_b), 3.29 (dd, *J* = 11.5, 7.0, 5.0, 1H, SCH_aH_b), 3.07 (ddd, *J* = 15.5, 12.0, 6.0, 1H, $NCH_2CH_aH_b$), 2.95-2.83 (m, 4H, $ArCH_2CH_3$, $SCH_2CH_aH_b$, SCH_aH_b), 2.65-2.57 (m, 2H, $SCH_2CH_aH_b$, $NCH_2CH_aCH_b$), 1.74 (s, 3H, $NCCH_3$), 1.34 (t, *J* = 7.5, 3H, $ArCH_2CH_3$); **^{13}C NMR** (CD_3OD, 125 MHz) δ_C 136.4 (ArC_{quat}), 135.8 (ArC_{quat}), 128.1 (ArC_{quat}), 127.9 (ArC_{quat}), 121.7 (ArCH), 120.5 (ArCH), 116.7 (ArCH), 109.2 (ArC_{quat}), 61.1 ($NCCH_3$), 47.1 (SCH_2), 38.7 (NCH_2), 34.2 (SCH_2CH_2), 28.0 ($NCCH_3$), 25.1 ($ArCH_2CH_3$), 21.1 (NCH_2CH_2), 14.9 ($ArCH_2CH_3$); **m/z** (ES+) 327 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{20}N_2O_2SNa^+$) requires *m/z* 327.1138, found *m/z* 327.1135.

Preparation and characterisation of tryptamine derivatives

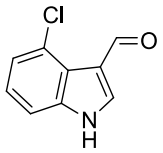


General procedure D for the preparation of indole carbaldehydes (46)



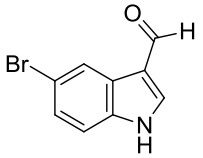
Phosphorus oxychloride (2.5 eq) was added dropwise to dry dimethyl formamide (5 ml per 1 ml of $POCl_3$) with ice-bath cooling under nitrogen. The mixture was stirred for 5 minutes before the chosen indole (1 equivalent) was added in dimethyl formamide (10 ml per 1 g of indole). The mixture was then allowed to warm to room temperature and stirred for 3 hours. The reaction became a thick suspension that required vigorous stirring. Potassium hydroxide solution (3.8 M, 10 eq) was added v*ia* dropping funnel and the mixture was heated at reflux for 14-16h. The solution was cooled to room temperature before adding a saturated sodium hydrogen carbonate solution and ethyl acetate until the mixture became clear and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over sodium sulphate, filtered and concentrated *in vacuo* to furnish the desired aldehyde **46** that required no further purification.

Preparation and characterisation of 4-chloro-1*H*-indole-3-carbaldehyde (46b)



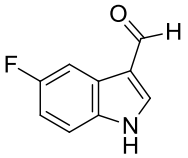
The title compound **46b** was synthesised according to general procedure **D** in 85% yield as a light brown solid. **m.p.** 147-148 °C; **FT-IR** ν_{max} 1636 (C=O); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 12.57 (br s, 1H, ArNH), 10.49 (s, 1H, CHO), 8.30 (s, 1H, ArCH), 7.52 (d, *J* = 8.0, 1H, ArCH), 7.30 (d, *J* = 8.0, 1H, ArCH), 7.23 (t, *J* = 8.0, 1H, ArCH); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 185.6 (C=O), 139.1 (ArC_{quat}), 134.9 (ArCH), 125.4 (ArC_{quat}), 124.4 (ArCH), 123.8 (ArC_{quat}), 123.4 (ArCH), 118.7 (ArC_{quat}), 112.8 (ArCH); ***m/z*** (ES−) 178 ($[M-H]^-$, 100%), **HRMS** (ES-) exact mass calculated for $[M-H]^-$ ($C_9H_5ClNO^-$) requires *m/z* 178.0065 & 180.0036 found *m/z* 178.0065 & 180.0033.

Preparation and characterisation of 5-bromo-1*H*-indole-3-carbaldehyde (46c)



The title compound was synthesised according to general procedure **D** in 100% yield as a colourless powder. **m.p.** 187-191 ºC; **FT-IR** ν_{max}(NaCl) 1651 cm^{-1} (C=O); **^{1}H NMR** (d_4-MeOD, 400 MHz) δ_H 9.87 (s, 1H, CHO), 8.29 (s, 1H, ArCH), 8.12 (s, 1H, ArCH), 7.37 (m, 2H, 2 × ArCH); **^{13}C NMR** (d_4-MeOD, 100 MHz) δ_C 187.3 (C=O), 140.3 (ArCH), 137.5 (ArC_{quat}), 127.9 (ArCH), 127.4 (ArC_{quat}), 125.0 (ArCH), 119.5 (ArC_{quat}), 116.9 (ArC_{quat}), 114.8 (ArCH); ***m/z*** (ES+) 224, 226 ($[M+H]^+$, 40%), 246, 248 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_7BrNO^+$) requires ***m/z*** 223.9706, found ***m/z*** 223.9712.

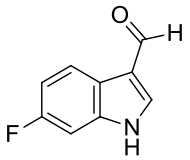
Preparation and characterisation of 5-fluoro-1*H*-indole-3-carbaldehyde (46e)[4]



The title compound was synthesised according to general procedure **D** in 98% yield as a colourless powder. **m.p.** 143-146 ºC (lit.[4] 170-171 °C); **FT-IR** ν_{max}(NaCl) 1648 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 12.26 (s, 1H, NH), 9.93 (s, 1H, CHO), 8.36 (s, 1H, ArH), 7.76 (dd, J = 9.0, 2.5, 1H, ArH), 7.54 (dd, J = 9.0, 4.5, 1H, ArH), 7.13 (dt, J = 9.0, 2.5, 1H, ArH); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 185.0 (C=O), 158.6 (d, $J_{C,F}$ 235 Hz, ArC_{quat}), 139.7 (ArCH), 133.6 (ArC_{quat}), 124.6 (d, $J_{C,F}$ 15.0 Hz, ArC_{quat}), 118.0 (d, $J_{C,F}$ 5.0 Hz, ArC_{quat}), 113.7 (d, $J_{C,F}$ 10.0 Hz, ArCH), 111.5 (d, $J_{C,F}$ 26.5 Hz, ArCH), 105.6 (d, $J_{C,F}$ 25.0 Hz, ArCH);

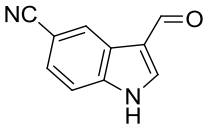
m/z (ES−) 162 ([M−H]$^-$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_9H_7FNO^+$) requires ***m/z*** 164.0506, found ***m/z*** 164.0510.

Preparation and characterisation of 6-fluoro-1*H*-indole-3-carbaldehyde (48f)[5]



The title compound was synthesised according to general procedure **D** in 96% yield as a colourless powder. Analytical data in agreement with the literature.[5] **m.p.** 165-168 ºC (lit.[5] 178-179 °C); **FT-IR** ν_{max}(NaCl) 1647 cm^{-1} (C=O); **^{1}H NMR** (d_6-DMSO, 500 MHz) δ_H 12.20 (s, 1H, NH), 9.92 (s, 1H, CHO), 8.31 (s, 1H, ArH), 8.08 (dd, *J* = 9.5, 5.5, 1H, ArH), 7.32 (dd, *J* = 5.5, 2.5, 1H, ArH), 7.09 (td, *J* = 9.5, 2.5, 1H, ArH); **^{13}C NMR** (d_6-DMSO, 125 MHz) δ_C 184.9 (C=O), 159.5 (d, $J_{C,F}$ 235 Hz, ArC_{quat}), 139.2 (ArCH), 137.1 (d, $J_{C,F}$ 12.0 Hz, ArC_{quat}), 121.9 (d, $J_{C,F}$ 22.5 Hz, ArCH), 120.7 (ArC_{quat}), 118.0 (ArC_{quat}), 110.4 (d, $J_{C,F}$ 25.5 Hz, ArCH), 98.7 (d, $J_{C,F}$ 25.0 Hz, ArCH); ***m/z*** (ES+) 164 ([M+H]$^+$, 100%), **HRMS** (ES+) exact mass calculated for [M+H]$^+$ ($C_9H_7FNO^+$) requires ***m/z*** 164.0506, found ***m/z*** 164.0506.

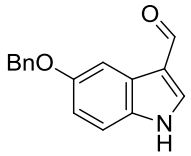
Preparation and characterisation of 3-formyl-1*H*-indole-5-carbonitrile (46g)



The title compound **46g** was synthesised according to general procedure **D** in 97% yield as an off white solid. **m.p.** 230-233 °C; **FT-IR** ν_{max} 3207 (N–H), 2221 (C≡N), 1648 (C=O); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 12.54 (br s, 1H, ArNH), 9.99 (s, 1H, ArCHO), 8.49 (s, 1H, ArCH), 8.45 (d, *J* = 2.0, 1H, ArCH), 7.69 (d, *J* = 8.5, 1H, ArCH), 7.62 (dd, *J* = 8.5, 2.0, 1H, ArCH); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 186.2 (C=O), 141.1 (ArCH), 139.7 (ArC_{quat}), 127.2 (ArCH), 126.6 (ArCH) 124.8 (ArC_{quat}), 120.8 (ArC_{quat}), 118.9 (ArCN), 114.8 (ArCH),

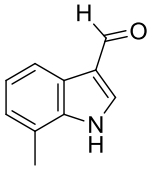
105.2 (ArC_{quat}); ***m/z*** (ES−) 169 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_6N_2NaO^+$) requires *m/z* 193.0372, found 193.0368.

Preparation and characterisation of 5-(benzyloxy)-1*H*-indole-3-carbaldehyde (48h)



The title compound was synthesised according to general procedure **D** 50 % yield as an off-white solid. **m.p.** 219-222 °C; **FT-IR** ν_{max} 1615 (C=O); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 12.08 (br s, 1H, ArNH), 9.90 (s, 1H, ArCHO), 8.21 (s, 1H, ArH), 7.70 (d, *J* = 2.5, 1H, ArH), 7.48 (d, *J* = 7.0, 2H, PhCH), 7.43 (d, *J* = 9.0, 1H, ArH), 7.39 (t, *J* = 7.0, 2H, PhCH), 7.32 (t, *J* = 7.0, 1H, PhCH), 6.97 (dd, *J* = 8.5, 2.5, 1H, ArH), 5.13 (s, 2H, $ArOCH_2$); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 185.6 (C=O), 155.5 (ArCO), 139.4, 138.3 (ArCH), 132.9, 129.2 (2 x PhCH), 128.5 (PhCH), 128.5 (2 x PhCH), 125.8 (ArC_{quat}), 118.9 (ArC_{quat}), 114.7 (ArCH), 114.1 (ArCH), 105.0 (ArCH), 70.5 ($ArOCH_2$); ***m/z*** (ES−) 250 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{13}NNaO_2^+$) requires *m/z* 274.0838, found *m/z* 274.0836.

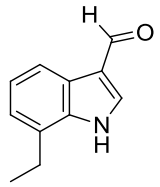
Preparation and characterisation of 7-methyl-1*H*-indole-3-carbaldehyde (46k)[6]



The title compound was prepared according to general procedure **D**, on a 30 mmol scale and isolated after chromatography eluting with dichloromethane/acetone 9:1 to 3:1 as a pale brown solid (82% yield, 3.91 g). Analytical data in agreement with the literature.[6] **m.p.** 209-211 ºC; **FT-IR** ν_{max} (NaCl) 3243 cm^{-1} (N-H), 3243 cm^{-1} (C=O), 1649 cm^{-1} (C=O); **^{1}H NMR** (d_6-acetone, 400 MHz) δ_H 11.18 (br s, 1H, ArNH), 10.03 (s, 1H, C(O)H), 8.16 (d, *J* = 3.0, 1H,

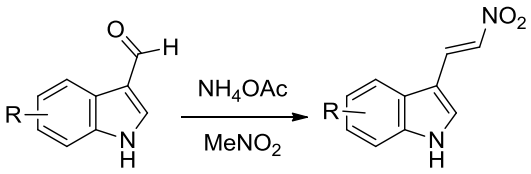
ArH), 8.07 (d, *J* = 7.5, 1H, ArH), 7.16 (t, *J* = 7.5, 1H, ArH), 7.09 (d, *J* = 7.5, 1H, Ar-H), 2.54 (s, 3H, CH_3); **^{13}C NMR** (d_6-acetone, 100 MHz) δ_C 185.4 (C=O), 137.6 (ArCH), 125.2 (ArC_{quat}), 125.1 (ArCH), 123.3 (ArCH), 122.4 (ArC_{quat}), 120.5 (ArC_{quat}), 119.8 (ArCH), 16.8 (CH_3); ***m/z*** (ES−) 158 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{10}NO^+$) requires ***m/z*** 160.0757, found ***m/z*** 160.0758.

Preparation of 7-ethyl-1*H*-indole3-carbaldehyde (46l)



The title compound was prepared according to general procedure **D**, on a 17.2 mmol scale and used without further purification in the next reaction (3.50 g, 84% yield crude).

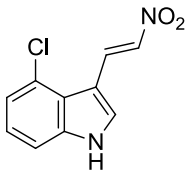
General procedure E for the synthesis of nitro-olefins 47



A mixture of the corresponding aldehyde **46** (1 eq), and ammonium acetate (dried under reduced pressure until the crystals became free flowing) (3 eq) in nitromethane (20 ml per 1 g of aldehyde) were heated at reflux under nitrogen for 1 hour (behind a blast shield). The reaction mixture was then allowed to cool to room temperature. **Two purification methods: 1)** The solvent was removed *in vacuo* and the residue washed with water and filtered. The filtration cake was pre-absorbed onto silica gel and purified by flash column chromatography (PE:ethyl acetate, 2:1) to furnish the desired nitro-olefin. **2)** The reaction was allowed to cool to room temperature and left to crystaillize for 14-16 h. The solid was filtered, washed with

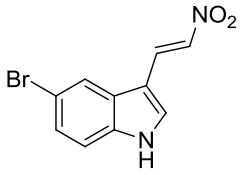
water and dried over phosphourous pentoxide in a vacuum dessicator affording the desired nitro-olefin **47**.

Preparation and characterisation of (*E*)-4-chloro-3-(2-nitrovinyl)-1*H*-indole (47b)



The title compound **47b** was synthesised according to general procedure **E** in 98% yield as a orange solid. **m.p.** 158-160 °C (decomposition); **FT-IR** ν_{max} 3258 (N–H), 1605 (C=C), 1491 ($NO_{2\ (asy)}$), 1293 ($NO_{2(sy)}$); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 12.57 (br s, 1H, ArNH), 8.92 (d, *J* = 13.5, 1H, O_2NCH=CH), 8.53 (s, 1H, ArCH), 8.12 (d, *J* = 13.5, 1H, O_2NCH=CH), 7.50 (dd, *J* = 7.6, 1.5, 1H, ArCH), 7.23 (m, 2H, ArCH); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 139.2 (ArC_{quat}), 134.4 (O_2NCHCH), 133.4 (O_2NCHCH), 132.6 (ArCH), 125.4 (ArC_{quat}), 124.5 (ArCH), 123.6 (ArC_{quat}), 123.5 (ArCH), 113.1 (ArCH), 107.8 (ArC_{quat}); ***m/z*** (ES−) 221 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_7ClN_2NaO_2^+$) requires ***m/z*** 245.0088 & 247.0059 found ***m/z*** 245.0084 & 247.0056.

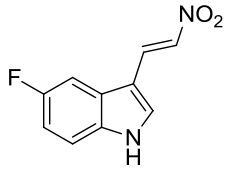
Preparation and characterisation of 5-bromo-3-((*E*)-2-nitrovinyl)-1*H*-indole (47c)[7]



The title compound was synthesised from **46c** according to general procedure **E** in 93% yield as an orange amorphous solid. The analytical data were in agreement with the literature.[7] **m.p.** 178-181 ºC (dec.) (lit.[143a] 192-193 ºC); **FT-IR** ν_{max}(NaCl) 1613 cm^{-1} (C=C), 1298 cm^{-1} (NO_2), 1227 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 500 MHz) δ_H 11.40 (br s, 1H, NH), 8.35 (d, *J* = 13.5, 1H, alkene-H), 8.20 (d, *J* = 2.0, 1H, ArCH), 8.18 (s, 1H, ArCH), 7.98 (d, *J* = 13.5, 1H,

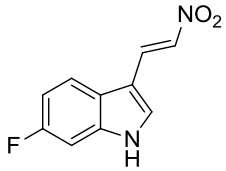
alkene-H), 7.54 (d, *J* = 8.5, 1H, ArCH), 7.42 (dd, *J* = 8.5, 2.0, 1H, ArCH); **^{13}C NMR** (d_6-acetone, 125 MHz) δ_C 137.6 (ArC_{quat}), 136.3 (ArCH), 133.8 (alkene-C), 133.6 (alkene-C), 127.7 (ArC_{quat}), 127.2 (ArCH), 123.7 (ArCH), 115.8 (ArC_{quat}), 115.3 (ArCH), 109.1 (ArCquat.); ***m/z*** (ES−) 265, 267 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{10}H_6BrN_2O_2^-$) requires ***m/z*** 266.9598, found ***m/z*** 266.9598.

Preparation and characterisation of 5-fluoro-3-((*E*)-2-nitrovinyl)-1*H*-indole (47e)[7]



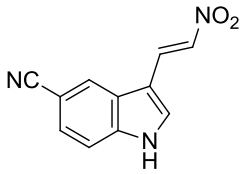
The title compound was synthesised from **46e** according to general procedure **E** in 98% yield as an orange solid. Analytical data in agreement with previous report.[7] **m.p.** 158-160 ºC (dec.); **FT-IR** ν_{max}(NaCl) 1613 cm^{-1} (C=C), 1304 cm^{-1} (NO_2), 1256 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 500 MHz) δ_H 11.22 (br s, 1H, ArNH), 8.23 (d, *J* = 13.5, 1H, alkene-H), 8.09 (s, 1H, ArCH), 7.79 (d, *J* = 13.5, 1H, alkene-H), 7.62 (dd, *J* = 6.0, 2.5, 1H, ArH), 7.47 (dd, *J* = 9.0, 4.5, 1H, ArCH), 6.98 (td, *J* = 9.0, 2.5, 1H, ArCH); **^{13}C NMR** (d_6-acetone, 125 MHz) δ_C 160.0 (d, $J_{C,F}$ 237 Hz, ArC_{quat}), 136.9 (ArCH), 135.4 (ArC_{quat}), 134.2 (alkene-C), 133.1 (alkene-C), 126.5 (ArC_{quat}), 114.7 (d, $J_{C,F}$ 9.5 Hz, ArCH), 112.4 (d, $J_{C,F}$ 26.0 Hz, ArCH), 109.6 (ArC_{quat}), 106.6 (d, $J_{C,F}$ 24.5 Hz, ArCH); ***m/z*** (ES−) 205 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{10}H_6FN_2O_2^-$) requires ***m/z*** 205.0419, found ***m/z*** 205.0418.

Preparation and characterisation of 6-fluoro-3-((*E*)-2-nitrovinyl)-1*H*-indole (47f)



The title compound was synthesised from **46f** according to general procedure E in 66% yield as a red powder. **m.p.** 170-172 ºC (dec.); **FT-IR** ν_{max}(NaCl) 1616 cm^{-1} (C=C), 1320 cm^{-1} (NO_2), 1229 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 500 MHz) δ_H 11.32 (br s, 1H, ArNH), 8.35 (d, *J* = 13.5, 1H, alkene-H), 8.16 (s, 1H, ArCH), 7.97 (dd, *J* = 9.5, 5.0, 1H, ArCH), 7.91 (d, *J* = 13.5, 1H, alkene-H), 7.33 (dd, *J* = 9.0, 2.0, 1H, ArCH), 7.09 (td, *J* = 9.5, 2.0, 1H, ArCH),; **^{13}C NMR** (d_6-acetone, 500 MHz) δ_C 161.2 ($J_{C,F}$ 237 Hz, ArC_{quat}), 139.2 (ArC_{quat}), 139.1 (ArC_{quat}), 136.3 (ArCH), 134.2 (alkene-C), 133.2 (alkene-C), 122.4 ($J_{C,F}$ 10.0 Hz, ArCH), 110.9 ($J_{C,F}$ 24.5 Hz, ArCH), 109.7 (ArC_{quat}), 99.9 ($J_{C,F}$ 26.0 Hz, ArCH); ***m/z*** (ES−) 205 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{10}H_6FN_2O_2^-$) requires ***m/z*** 205.0419, found ***m/z*** 205.0419.

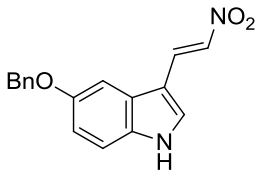
Preparation and characterisation of (*E*)-3-(2-nitrovinyl)-1*H*-indole-5-carbonitrile 47g



The title compound **47g** was synthesised according to general procedure **E** in 98% yield as a yellow solid. **m.p.** 142 °C (decomposition); **FT-IR** 2222 (C≡N), 1621 (C=C), 1528 ($NO_{2(asy)}$), 1340 ($NO_{2(sy)}$); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 12.6 (br s, 1H, ArNH), 8.66 (s, 1H, ArCH), 8.40 (d, *J* = 13.5, 1H, O_2NCHCH), 8.38 (s, 1H, ArCH), 8.22 (d, *J* = 13.5, 1H, O_2NCHCH), 7.67 (d, *J* = 8.5, 1H, ArCH), 7.61 (d, *J* = 8.5, 1H, ArCH); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 140.2 (ArC_{quat}), 138.3 (ArCH), 134.0 ($O_2NCH=CH$) 134.0 (ArC_{quat}), 127.0 ($O_2NCH=CH$), 126.9 (ArCH), 125.3 (ArCH), 120.9 (ArCN), 114.8 (ArCH), 109.5 (ArC_{quat}),

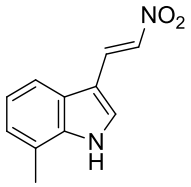
104.8 (ArC_{quat}); ***m/z*** (ES−) 212 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_7N_3NaO_2^+$) requires ***m/z*** 236.0430, found ***m/z*** 236.0430.

Preparation and characterisation of (*E*)-5-(benzyloxy)-3-(2-nitrovinyl)-1*H*-indole (47h)



The title compound was synthesised from **46h** according to general procedure **E** in 88% yield as a red solid. **m.p.** 180-182 °C; **FT-IR** ν_{max} 1601 (C=C), 1457 ($NO_{2(asy)}$), 1240 ($NO_{2(sy)}$); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H d_6-DMSO, 400 MHz) δ_H 12.14 (br s, 1H, ArNH), 8.40 (d, *J* = 13.5, 1H, O_2NCH=CH), 8.19 (s, 1H, ArCH), 8.04 (d, *J* = 13.5, 1H, O_2NCH=CH), 7.51 (m, 3H), 7.41 (m, 3H), 7.33 (t, *J* = 7.1, 1H, PhCH), 6.97 (d, *J* = 8.5, 1H, ArCH), 5.22 (s, 2H, $ArOCH_2$); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 155.5 (ArCO), 138.4 (ArC_{quat}), 137.3 (O_2NCH=CH), 135.7 (ArCH), 133.4 (ArC_{quat}), 131.7 (O_2NCH=CH), 129.3 (2 x PhCH), 128.6 (2 xPhCH), 128.6 (PhCH), 126.3 (ArC quat), 114.6 (ArCH), 114.4 (ArCH), 109.1 (ArC quat), 105.0 (ArCH), 70.8 ($ArOCH_2$); ***m/z*** (ES−) 293 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{17}H_{13}N_2O_3^-$) requires ***m/z*** 293.0932 & 294.0965, found ***m/z*** 293.0927 & 294.0957.

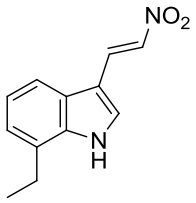
Preparation and characterisation of 7-methyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole (47k)



The title compound was synthesised according to general procedure **E** on a 25 mmol scale and was obtained as an orange solid after purification by column chromatography on short-path silica gel column eluting with dichloromethane (4.85 g, 98%). **m.p.** 226-230 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3263 cm^{-1} (N-H), 1611 cm^{-1} (C=C), 1587 cm^{-1} (C=C), 1522 cm^{-1} (NO_2),

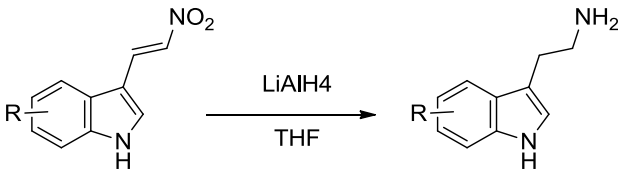
1301 cm^{-1} (NO_2); **^{1}H NMR** (d_6-acetone, 400 MHz) δ_H 11.24 (br s, 1H, ArNH), 8.36 (d, *J* = 13.5, 1H, NO_2C=CH), 8.11 (d, *J* = 3.0, 1H, ArCH), 7.89 (d, *J* = 13.5, 1H, NO_2CH=C), 7.76 (d, *J* = 8.0, 1H, ArCH), 7.20 (t, *J* = 7.5, 1H, ArCH), 7.11 (d, *J* = 7.0, 1H, ArCH), 2.54 (s, 3H, CH_3); **^{13}C NMR** (d_6-acetone, 100 MHz) δ_C 138.3 (ArC_{quat}), 135.3 (ArCH), 134.8 ($CHCHNO_2$), 132.7 ($CHCHNO_2$), 125.6 (ArC_{quat}), 125.1 (ArCH), 123.1 (ArCH), 123.0 (ArC_{quat}), 118.9 (ArCH), 110.0 (ArC_{quat}), 16.8 (CH_3); ***m/z*** (ES+) 225 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{10}N_2O_2Na^+$) requires ***m/z*** 225.0634, found ***m/z*** 225.0636.

Preparation and characterisation of 7-ethyl-3-[(*E*)-2-nitrovinyl]-1*H*-indole (47l)



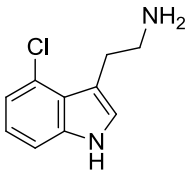
The title compound was synthesised according to general procedure **E** on a 10 mmol scale (theoretical) and was obtained as an orange solid after purification by column chromatography on short-path silica gel column eluting with dichloromethane (2.50 g, 60% over 2 steps). **m.p.** 203-206 ºC; **FT-IR** ν_{max}(NaCl) 3333 cm^{-1} (N-H), 1615 cm^{-1} (C=C), 1553 cm^{-1} (C=C), 1523 cm^{-1} (NO_2), 1302 cm^{-1} (NO_2); **^{1}H NMR** (d_4-MeOD, 500 MHz) δ_H 8.37 (d, *J* = 13.0, 1H, NO_2C=CH), 7.89 (s, 1H, H-1), 7.86 (d, *J* = 13.0, 1H, NO_2CH=C), 7.63 (d, *J* = 8.0, 1H, ArCH), 7.21 (t, *J* = 7.5, 1H, ArCH), 7.11 (d, *J* = 7.5, 1H, ArCH), 2.91 (q, *J* = 7.5, 2H, CH_2CH_3), 1.32 (t, *J* = 7.5, 3H, CH_3); **^{13}C NMR** (d_4-MeOD, 125 MHz) δ_C 138.0 (ArC_{quat}), 135.8 (ArCH), 135.8 ($CHCHNO_2$), 132.4 ($CHCHNO_2$), 129.8 (ArC_{quat}), 126.2 (ArC_{quat}), 123.5 (ArCH), 123.5 (ArCH), 118.9 (ArCH), 110.4 (ArC_{quat}), 25.0 (CH_2CH_3), 14.9 (CH_2CH_3); ***m/z*** (ES+) 239 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{12}N_2O_2Na^+$) requires ***m/z*** 239.0791, found ***m/z*** 239.0788.

General procedure F for the synthesis of tryptamines 48



A solution nitro olefin **47** (1 equivalent) in tetrahydrofuran (10 ml per 1 mmol of nitro olefin) was added to a stirred slurry of lithium aluminium hydride powder (6 equivalents) in tetrahydrofuran (equal mass to volume, e.g. 1 g ($LiAlH_4$):1ml (tetrahydrofuran)) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 36 hours. The reaction was cooled to 0 °C and was quenched by dropwise addition of water until effervescence ceased. The mixture was then filtered and the solid washed with ethylacetate, the filtrate was concentrated *in vacuo* to furnish the desired tryptamine **48** which was purified by flash column chromatography or acidic extraction from CH_2Cl_2 solution followed by addition of solid KOH until the pH measures 14 (by universal indicator paper) and extracted with CH_2Cl_2 dried over $NaSO_4$ and concentrated.

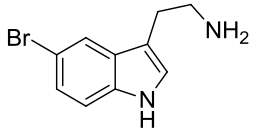
Preparation and characterisation of 2-(4-chloro-1*H*-indol-3-yl)ethanamine (48b)



The title compound was synthesised from **47b** according to general procedure **F** and purified by flash column chromatography (DCM ramping to DCM : MeOH : NEt_3, 85 : 10 : 5) in 57% yield as a orange solid. **m.p.** 83-93 °C; **FT-IR** ν_{max} 3351 (NH_2), 3294 (ArN–H); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 9.02 (br s, 1H, ArNH), 7.22 (dd, *J* = 6.5, 2.5, 1H, ArCH), 7.08-7.02 (m, 2H, ArCH), 6.99 (s, 1H, ArCH), 3.13 (t, *J* = 6.5, 2H, NCH_2), 3.06 (t, *J* = 6.5, 2H, $ArCH_2$) 1.72 (br s, 2H, NH_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 138.1 (ArC_{quat}), 126.3 (ArC_{quat}), 124.1 (ArC_{quat}), 123.9 (ArCH), 122.3 (ArCH), 120.3 (ArCH), 113.7 (ArC_{quat}), 110.0 (ArCH), 43.5

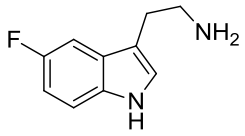
(NCH_2), 30.4 ($ArCH_2$); ***m/z*** (ES+) 195 ($[M+H]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}ClN_2^+$) requires ***m/z*** 195.0684 & 197.0654 found ***m/z*** 195.0681 & 197.0656.

Preparation and characterisation of 2-(5-bromo-1*H*-indol-3-yl)ethanamine (48c)[8]



The title compound was synthesised from **47c** according to general procedure **F** in 90% yield as a brown oil. The analytical data were in agreement with the literature.[8] **FT-IR**ν_{max}(NaCl) 3140 cm^{-1} (N-H, broad); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.83 (br s, 1H, ArNH), 7.77 (d, *J* = 1.5, 1H, ArCH), 7.24-7.32 (m, 2H, ArCH), 7.05 (s, 1H, ArCH), 3.06 (t, *J* = 6.5, 2H, $ArCH_2CH_2NH_2$), 2.90 (t, *J* = 6.5, 2H, $ArCH_2CH_2NH_2$), 1.76 (br s, 2H, NH_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 135.1 (ArC_{quat}), 129.3 (ArC_{quat}), 124.7 (ArCH), 123.5 (ArCH), 121.4 (ArCH), 113.2 (ArC_{quat}), 112.7 (ArCH), 112.5 (ArC_{quat}), 42.1 ($ArCH_2CH_2NH_2$), 29.1 ($ArCH_2CH_2NH_2$); ***m/z*** (ES−) 237, 239 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}BrN_2^+$) requires ***m/z*** 239.0178 & 241.0158, found ***m/z*** 239.0178 & 241.0158.

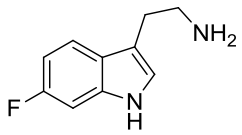
Preparation and characterisation of 2-(5-fluoro-1*H*-indol-3-yl)ethanamine (48e)[8]



The title compound was synthesised from **47e** according to general procedure **F** in 76% yield as a brown oil. Analytical data in agreement with previous reports.[8] **FT-IR** ν_{max}(NaCl) 3176 cm^{-1} (N-H, broad); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.94 (br s, 1H, NH), 7.22-7.26 (m, 2H, 2 × ArCH), 7.04 (s, 1H, ArCH), 6.93 (td, *J* = 9.0, 2.5, 1H, ArCH), 3.03 (t, *J* = 6.5, 2H,

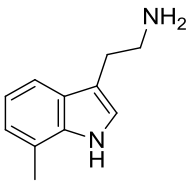
$ArCH_2CH_2NH_2$), 2.87 (t, J = 6.5, 2H, $ArCH_2CH_2NH_2$), 1.53 (br s, 2H, NH_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 157.6 (d, $J_{C,F}$ 233 Hz, ArC_{quat}), 133.0 (ArC_{quat}), 127.7 (d, $J_{C,F}$ 9.5 Hz, ArC_{quat}), 124.0 (ArCH), 113.5 (d, $J_{C,F}$ 5.0 Hz, ArCquat.), 111.8 (d, $J_{C,F}$ 9.5 Hz, ArCH), 110.2 (d, $J_{C,F}$ 26.0 Hz, ArCH), 103.6 (d, $J_{C,F}$ 23.0 Hz, ArCH), 42.1 ($ArCH_2CH_2NH_2$), 29.3 ($ArCH_2CH_2NH_2$); ***m/z*** (ES−) 177 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}FN_2^+$) requires ***m/z*** 179.0979, found ***m/z*** 179.0974.

Preparation and characterisation of 2-(6-fluoro-1*H*-indol-3-yl)ethanamine (48f)



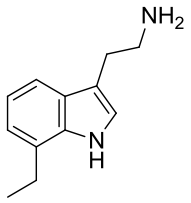
The title compound was synthesised from **47f** according to general procedure **F** in 90% yield as an off-white solid. **m.p.** 75-77 ºC; **FT-IR** ν_{max}(NaCl) 3195 cm^{-1} (N-H, broad); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 8.61 (br s, 1H, ArNH), 7.51 (dd, J = 9.5, 5.5, 1H, ArH), 7.03 (dd, J = 9.5, 2.0, 1H, ArH), 6.99 (s, 1H, ArH), 3.04 (t, J = 6.5, 2H, $ArCH_2CH_2NH_2$), 6.89 (td, J = 9.5, 2.0, 1H, ArCH), 2.89 (t, J = 6.5, 2H, $ArCH_2CH_2NH_2$), 1.42 (br s, 2H, NH_2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 159.9 (d, $J_{C,F}$ 236 Hz, ArCquat.), 136.3 (ArCquat.), 124.1 (ArCquat.), 122.3 (ArCH), 119.5 (d, $J_{C,F}$ 10.0 Hz, ArCH), 113.7 (ArCquat.), 107.9 (d, $J_{C,F}$ 24.5 Hz, ArCH), 97.4 (d, $J_{C,F}$ 26.0 Hz, ArCH), 42.3 ($ArCH_2CH_2NH_2$), 29.4 ($ArCH_2CH_2NH_2$); ***m/z*** (ES−) 177 ($[M-H]^-$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}FN_2^+$) requires ***m/z*** 179.0979, found ***m/z*** 179.0979.

Preparation and characterisation of 2-(7-methyl-1*H*-indol-3-yl)ethanamine (48k)



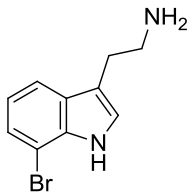
The title compound was synthesised according to general procedure **F** on a 24 mmol scale and was isolated as a brown gum that was used without further purification (4.40 g, 99%). **FT-IR** ν_{max}(NaCl) 3338 cm^{-1} (N-H), 3286 cm^{-1} (N-H), 1588 cm^{-1} (C=C), 741 cm^{-1}; **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 10.84 (br s, 1H, ArNH), 7.35 (br s, 1H, ArH), 7.13 (br s, 1H, ArH), 6.84 (br s, 2H, Ar-H), 2.88 (br s, 4H, CH_2CH_2N), 2.44 (s, 3H, CH_3); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 135.9 (ArC_{quat}), 126.9 (ArC_{quat}), 122.6 (ArCH), 121.4 (ArCH), 120.5 (ArC_{quat}), 118.4 (ArCH), 116.0 (ArCH), 112.3 (ArC_{quat}), 41.8 (CH_2NH_2), 27.7 ($CH_2CH_2NH_2$), 16.8 (CH_3); ***m/z*** (ES−) 173 ($[M-H]^-$, 100%), **HRMS** (ES−) exact mass calculated for $[M-H]^-$ ($C_{11}H_{13}N_2^-$) requires ***m/z*** 173.1084, found ***m/z*** 173.1077.

Preparation and characterisation of 2-(7-ethyl-1*H*-indol-3-yl)ethanamine (48l)



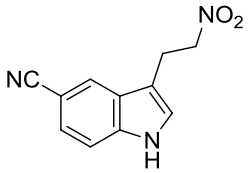
The title compound was synthesised according to general procedure **F** on a 11.6 mmol scale and was isolated as a pale brown solid that was used without further purification (2.20 g, 99%). **m.p.** 203-205 ºC (dec.); **FT-IR** ν_{max}(NaCl) 3398 cm^{-1} (N-H), 3282 cm^{-1} (N-H), 1586 cm^{-1} (C=C), 1473 cm^{-1} (CH_2), 743 cm^{-1} (ArC-H OOP); **^{1}H NMR** (d_6-DMSO, 400 MHz) δ_H 11.05 (br s, 1H, ArNH), 7.42 (d, *J* = 7.5, 1H, ArH), 7.24 (d, *J* = 2.5, 1H, ArH), 6.88-6.98 (m, 2H, ArH), 3.07 (app. s, 4H, CH_2CH_2N), 2.86 (q, *J* = 7.5, 2H, CH_2CH_3), 1.26 (t, *J* = 7.5, 3H, CH_2CH_3); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 135.1 (ArC_{quat}), 127.1 (ArC_{quat}), 126.8 (ArC_{quat}), 123.1 ((ArCH)), 118.9 (ArCH), 118.8 (ArCH), 115.9 (ArCH), 110.1 (ArC_{quat}), 39.3 ($CH_2CH_2NH_2$), 23.8 ($CH_2CH_2NH_2$), 23.3 (CH_2CH_3), 14.5 (CH_2CH_3); ***m/z*** (ES−) 223 ($[M+Cl]^-$, 35%), **HRMS** (ES−) exact mass calculated for $[M+Cl]^-$ ($C_{12}H_{16}N_2Cl^-$) requires ***m/z*** 223.1007, found ***m/z*** 223.1001.

Preparation and characterisation of 2-(7-bromo-1*H*-indol-3-yl)ethanamine (48m)



The title compound **48m** was synthesised according to general procedure **F** from known nitro-olefin[9] after acid base extraction isolated as a orange solid (50% yield). **m.p.** 89-99 °C; **FT-IR** ν_{max} 3556 (NH_2), 3293 (ArN–H); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.67 (br s, 1H, ArNH), 7.55 (d, *J* = 8.0, 1H, ArCH), 7.35 (d, *J* = 8.0, 1H, ArCH), 7.07 (s, 1H, ArCH), 7.00 (t, *J* = 8.0, 1H, ArCH), 3.04 (t, *J* = 6.5, 2H, NCH_2), 2.90 (t, *J* = 6.5, 2H, $ArCH_2$), 1.58 (br s, 2H, NH_2); **^{13}C NMR** (d_6-DMSO, 100 MHz) δ_C 135.1 (ArC_{quat}), 128.8 (ArC_{quat}), 124.3 (ArCH), 122.7 (ArCH), 120.4 (ArCH), 118.1 (ArCH), 114.9 (ArC_{quat}), 104.8 (ArCBr), 42.3 (NCH_2), 29.5 ($ArCH_2$); ***m/z*** (ES+) 239 ($[M+H]^+$, 100 %), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{12}BrN_2^+$) requires ***m/z*** 239.0187 & 241.0158 found ***m/z*** 239.0178 & 241.0157.

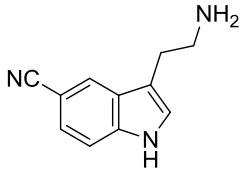
Preparation and characterisation of 3-(2-nitroethyl)-1*H*-indole-5-carbonitrile (49g)[10]



Sodium borohydride (25.8 mmol, 11 eq) was added portionwise to a solution of nitro-olefin **47g** (2.35 mmol, 1 eq) in dimethyl formamide (20 ml) and methanol (20 ml). The reaction mixture was stirred at room temperature until the reaction reached completion (complete consumption of starting material by TLC analysis). Hydrochloric acid solution (2M) was added until the pH of the solution reached pH 7. The mixture was extracted with dichloromethane (3 × 30 ml) and the organic layer was washed with brine and dried over sodium sulfate filtered and concentrated *in vacuo*. Purification by column chromatography afforded the title compound **49g** as a off white solid (70 % yield). **m.p.** 134-136 °C; **FT-IR**

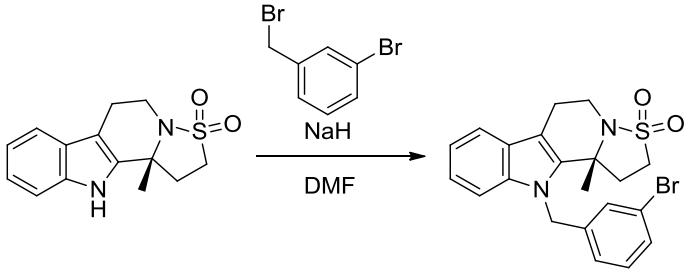
ν_{max} 3290 (ArN–H), 2222 (C≡N),1539 ($NO_{2\ (asy)}$), 1369 ($NO_{2(sy)}$); **^{1}H NMR** (CD_3OD, 400 MHz) δ_H 8.05 (s, 1H, ArCH), 7.49 (d, *J* = 8.5, 1H, ArCH), 7.40 (d, *J* = 8.5, 1H, ArCH), 7.30 (s, 1H, ArCH), 4.79-4.71 (m, 2H, NO_2CH_2), 3.50-3.45 (m, 2H, $ArCH_2$); **^{13}C NMR** (CD_3OD, 100 MHz) δ_C 138.8 (ArC_{quat}), 127.1 (ArC_{quat}), 125.9 (ArCH), 124.4 (ArCH), 124.1 (ArCH), 120.8 (ArCN), 112.6 (ArCH), 111.1 (ArC_{quat}), 101.7 (ArC_{quat}), 75.8 (O_2NCH_2), 23.0 ($ArCH_2$) ; ***m/z*** (ES+) 238 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_9N_3NaO_2^+$) requires ***m/z*** 238.0587 & 239.0620 found ***m/z*** 238.0589 & 239.0627.

Preparation and characterisation of 3-(2-aminoethyl)-1*H*-indole-5-carbonitrile (48g)



A solution of nitroalkane **49g** (1.53 mmol, 10 eq) in methanol (45 ml) was added to a mixture of zinc (35 mmol, 23 eq) in hydrochloric acid solution (2M, 45 ml) and heated to reflux over 2 hours. The reaction was cooled to room temperature and filtered. Sodium hydroxide (1M) was added the filtrate until the solution reached pH 11. The solution was extracted with a dichloromethane : methanol (95 : 5) solution and dried over $NaSO_4$. Concentration afforded the title compound **48g** as a light brown solid (88% yield). **m.p.** 114-125 °C; **FT-IR** ν_{max} br 3224 (ArN–H, NH_2), 2216 (C≡N); **^{1}H NMR** (CD_3OD, 400 MHz) δ_H 8.03 (br s, 1H, ArCH), 7.47 (d, *J* = 8.5, 1H, ArCH), 7.38 (d, *J* = 8.5, 1H, ArCH), 7.28 (br s, 1H, ArCH), 2.95 (br s, 4H, NCH_2, $ArCH_2$); **^{13}C NMR** (CD_3OD, 100 MHz) δ_C 139.0 (ArC_{quat}), 127.9 (ArC_{quat}), 125.3 (ArCH), 124.3 (ArCH), 124.1 (ArCH), 121.0 (ArCCN), 113.7 (ArC_{quat}), 112.5 (ArCH), 101.2 (ArCCN), 42.0 (NCH_2), 27.8 ($ArCH_2$); ***m/z*** (ES−) 186 ($[M+H]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{12}N_3^+$) requires ***m/z*** 186.1026 & 187.1059 found ***m/z*** 186.1032 & 187.0944.

11-(3-bromobenzyl)-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-b]indole 3,3-dioxide (50)

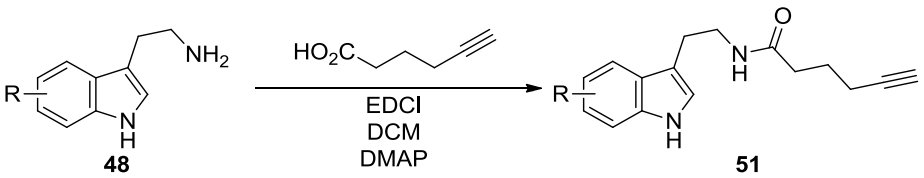


38a (0.12 mmol, 1 eq) was dissolved in DMF (1 ml/0.12 mmol of **38a**) under argon and added to a dried flask containing sodium hydride (1.6 mmol, 1.3 eq) in an ice bath. The mixture was stirred at 0°C for 10 mins and then allowed to warm to room temperature stirring for a further 10 mins. 3-bromobenzylbromide (0.37 mmol, 3 eq) was added to the mixture in one portion and allowed to stir at room temperature for 3 h. The reaction was diluted with water (5 ml/0.12 mmol of **38a**) and extracted with ethyl acetate (3 x 5 ml/0.12 mmol of **38a**). The combined organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Purification by FCC to gave **50** as a white solid (68% yield). Recrystallization from ether by slow evaporation gave crystals of high enough quality for single crystal x-ray diffraction (<99% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 12.0 min, minor t_R = 18.1 min). **m.p.** 195-196 °C; **FT-IR** ν_{max} 1291 ($S{=}O_{(as)}$), 1134 ($S{=}O_{(sy)}$); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 7.55 (m, 1H, ArCH), 7.39 (d, *J* = 8.0, 1H, PhCH), 7.20-7.15 (m, *J* = 8.0, 3H, 2 × ArCH, PhCH), 7.12 (t, *J* = 8.0, 1H, ArCH), 7.03 (m, 1H, ArCH), 6.62 (d, 1H, PhCH), 5.43 (d, *J* = 18.0, 1H, NCH_aH_bPh), 5.38 (d, *J* = 18.0, 1H, NCH_aH_bPh), 4.08 (dd, *J* = 14.5, 5.5, 1H, $NCH_aCH_bCH_2$), 3.34 (ddd, *J* = 14.5, 12.5, 4.5, 1H, $NCH_aH_bCH_2$), 3.27-3.15 (m, 2H, SCH_aH_b, $ArCH_aH_b$), 3.01 (dt, *J* = 6.0, 12.5, 7.0, 1H, SCH_aH_b), 2.78 (dd, *J* = 15.5, 4.0, 1H, $ArCH_aH_b$), 2.64 (m, 1H, $SCH_2CH_aH_b$), 2.56 (m, 1H, $SCH_2CH_aH_b$), 1.67 (s, 3H, $NCCH_3$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 139.5 (ArC_{quat}) 136.9 (ArC_{quat}), 135.3 (ArC_{quat}), 130.8 (PhCH), 130.6 (PhCH), 128.5 (PhCH), 126.6 (ArC_{quat}), 123.9 (PhCH), 123.2 (PhCBr), 123.0 (ArCH),

120.2 (ArCH), 118.9 (ArCH), 109.7 (ArCH), 109.6 (ArC_{quat}), 59.6 ($NCCH_3$), 47.3 (NCH_2Ph), 45.4 (SCH_2), 36.4 (NCH_2), 32.7 (SCH_2CH_2), 27.6 ($NCCH_3$), 20.9 ($ArCH_2$); **HRMS** (TOF MS FI+) exact mass calculated for $[M]^+$ ($C_{21}H_{21}BrN_2O_2S^+$) requires *m/z* 444.0507 and 446.0488, found *m/z* 444.0519 and446.0502

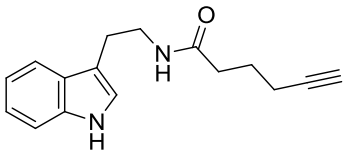
Methodology extention for amide derivitives

General procedure G for the preparation of 51



Hexynoic acid (1 eq) was added in one portion to a suspension of (1.5 eq) and DMAP (0.04 eq) in dichloromethane (3 ml/mmol of hexynoic acid) under argon and the mixture was stirred for 5 mins. A solution of tryptamine **48** (1.4 eq) in dichloromethane (7 ml/mmol of hexynoic acid) was added to the solution. The reaction mixture was stirred at rt for 12 h. Upon completion hydrochloric acid solution (1M, 10 ml) was added. The layers were separated and the aqueous was extracted with dichloromethane (2 × 20 ml). The combined organics were washed with brine, dried over sodium sulfate and concentrated *in vacuo.* The residue was purified by flash column chromatography (CH_2Cl_2:Et_2O, 1:0 to 7:3).

Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]hex-5-ynamide (51a)

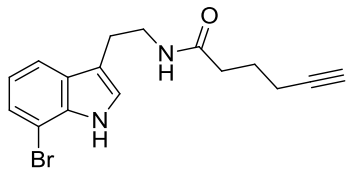


The title compound **51a** was synthesis according to general procedure **G** as a white solid (86% yield) and re-crystallized from ethanol.

m.p. 89-91 °C; **FT-IR** ν_{max} 3403 (N–H), 3286 (ArN–H), 1641 (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.29 (br s, 1H, ArNH), 7.62 (d, *J* = 8.0, 1H, ArCH), 7.39 (d, *J* = 8.0, 1H, ArCH),

7.23 (t, *J* = 7.5, 1H, ArCH), 7.14 (t, *J* = 7.5, 1H, ArCH), 7.04 (d, *J* = 2.0, 1H, ArCH), 5.63 (br s, 1H, OCNH), 3.62 (q, *J* = 6.5, 2H, NCH_2), 2.99 (t, *J* = 6.5, 2H, NCH_2CH_2), 2.25 (t, *J* = 7.5, 2H, $OCCH_2$), 2.22 (td, *J* = 7.5, 2.5, 2H, $HC{\equiv}CCH_2$), 1.94 (t, *J* = 2.5, 1H, C≡CH), 1.84 (quin, *J* = 7.5, 2H, $OCCH_2CH_2$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 172.2 (CO), 136.4 (ArC_{quat}), 127.3 (ArC_{quat}), 122.2 (ArCH), 122.1 (ArCH), 119.5 (ArCH), 118.7 (ArCH), 112.9 (ArC_{quat}), 111.3 (ArCH), 83.6 (HC≡C), 69.2 (C≡CH), 39.7 (NCH_2), 35.1 ($OCCH_2$), 25.3 (NCH_2CH_2), 24.2 ($OCCH_2CH_2$), 17.8 ($HC{\equiv}CCH_2$); ***m/z*** (ES+) 277 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}N_2NaO^+$) requires *m/z* 277.1311, found *m/z* 277.1316.

Preparation and characterisation of *N*-[2-(7-bromo-1*H*-indol-3-yl)ethyl]hex-5-ynamide (51m)

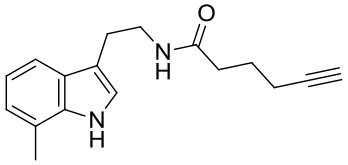


The title compound **51m** was synthesis according to general procedure **G** as a brown solid (65% yield) trituration (Et_2O and re-crystallized from ethanol.)

m.p. 87-89 °C; **FT-IR** ν_{max} 3400 (N–H), 3300 (ArN–H), 1636 (C=O); **^{1}H NMR** (DMSO-d_6, 400 MHz) δ_H 11.05 (br s, 1H, ArNH), 7.93 (t, *J* = 6.5, 1H, OCNH), 7.55 (d, *J* = 7.5, 1H, ArCH), 7.28 (d, *J* = 7.5, 1H, ArCH), 7.21 (d, *J* = 2.0, 1H, ArCH), 6.94 (t, *J* = 7.5, 1H, ArCH), 3.32 (q, *J* = 6.5, 2H, NCH_2), 2.80 (t, *J* = 7.5, 2H, $OCCH_2$), 2.78 (t, *J* = 2.5, 1H, C≡CH), 2.18-2.10 (m, 4H, $ArCH_2$, $HC{\equiv}CCH_2$), 1.65 (quin, *J* = 7.5, 2H, $OCCH_2CH_2$);**^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 172.2 (CO), 135.3 (ArC_{quat}), 129.9 (ArC_{quat}), 124.9 (ArCH), 124.3 (ArCH), 120.6 (ArCH), 118.8 (ArCH), 114.3 (ArC_{quat}), 105.1 (ArCBr), 85.0 (HC≡C), 72.3 (C≡CH), 41-39.7 (signal hidden under DMSO peak, confirmed by HSQC and COSY) (NCH_2) 35.1 ($ArCH_2$), 26.0 ($OCCH_2$) 25.1 ($OCCH_2CH_2$), 18.3 ($HC{\equiv}CCH_2$); ***m/z*** (ES+) 355 ($[M+Na]^+$,

100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{17}N_2BrNaO^+$) requires *m/z* 355.0416 & 357.0397, found *m/z* 355.0404 & 357.0385.

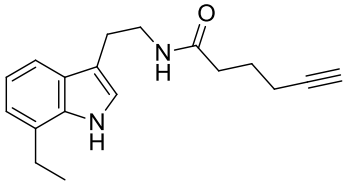
Preparation and Characterisation of *N*-[2-(7-methyl-1*H*-indol-3-yl)ethyl]hex-5-ynamide (51k)



The title compound **51k** was synthesis according to general procedure **G** as a white solid (56% yield) and re-crystallized from ethanol.

m.p. 76-77 °C; **FT-IR** ν_{max} 3402 (ArNH), 3288 (NH), 1648 (C=O); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ_H 8.00 (br s, 1H, ArNH), 7.47 (d, *J* = 7.5, 1H, ArCH), 7.07 (t, *J* = 7.5, 1H, ArCH), 7.07 (d, *J* = 2.5, 1H, ArCH), 7.03 (d, *J* = 7.5, 1H, ArCH), 5.55 (br s, 1H, OCNH), 3.62 (q, *J* = 6.5, 2H, NCH_2), 2.98 (t, *J* = 6.5, 2H, NCH_2CH_2), 2.50 (s, 3H, $ArCH_3$), 2.25 (t, *J* = 7.5, 2H, $OCCH_2$), 2.23 (td, *J* = 7.5, 2.5, 2H, $HC{\equiv}CCH_2$), 1.93 (t, *J* = 2.5, 1H, C≡CH), 1.84 (quin, *J* = 7.5, 2H, $OCCH_2CH_2$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ_C 172.0 (CO), 136.0 (ArC_{quat}), 126.8 (ArC_{quat}), 122.8 (ArCH), 121.7 (ArCH), 120.4 (ArC_{quat}), 119.8 (ArCH), 116.4 (ArCH), 113.6 (ArC_{quat}), 83.6 (HC≡C), 69.1 (HC≡C), 39.7 (NCH_2), 35.1 ($OCCH_2$), 25.5 (NCH_2CH_2), 24.1 ($OCCH_2CH_2$), 17.8 ($HC{\equiv}CCH_2$), 16.6 ($ArCH_3$); ***m/z*** (ES+) 291 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2NaO^+$) requires *m/z* 291.1468 & 292.1501, found *m/z* 291.1470 & 292.1503.

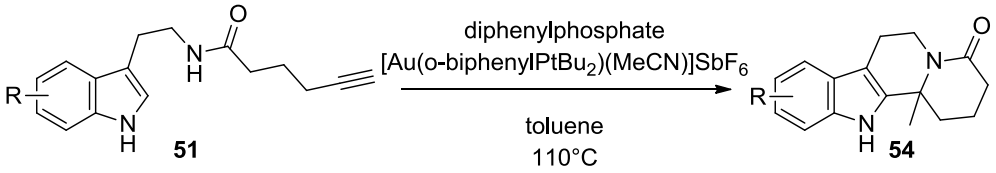
Preparation and Characterisation of -[2-(7-ethyl-1*H*-indol-3-yl)ethyl]hex-5-ynamide (51l)



The title compound **51l** was synthesis according to general procedure **G** as a yellow oil (45% yield).

FT-IR ν_{max} 3404 (NH), 3289 (ArN–H), 1649 (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.17 (br s, 1H, ArNH), 7.48 (d, *J* = 7.5, 1H, ArCH), 7.11 (t, *J* = 7.5, 1H, ArCH), 7.07 (d, *J* = 7.5, 1H, ArCH), 7.05 (d, *J* = 2.0, 1H, ArCH), 5.61 (br s, 1H, OCNH), 3.62 (q, 2H, NCH_2, *J* = 6.5), 2.98 (t, *J* = 6.5, 2H, NCH_2CH_2), 2.88 (q, *J* = 7.5, 2H, $ArCH_2CH_3$), 2.25 (t, *J* = 7.5, 2H, $OCCH_2$), 2.23 (td, *J* = 7.5, 2.5, 2H, $HC{\equiv}CCH_2$) 1.94 (t, *J* = 2.5, 1H, C≡CH), 1.84 (quint, *J* = 7.0, 2H, $OCCH_2CH_2$), 1.38 (t, *J* = 7.5, 3H, $ArCH_2CH_3$) ; **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 172.2 (CO), 135.3 (ArC_{quat}), 127.1 (ArC_{quat}), 126.7 (ArC_{quat}), 121.7 (ArCH), 120.8 (ArCH), 119.8 (ArCH), 116.5 (ArCH), 113.4 (ArC_{quat}), 83.6 (HC≡C), 69.1 (C≡CH), 39.7 (NCH_2), 35.1 ($OCCH_2$), 25.5 ($NCCH_2CH_2$), 24.2 ($OCCH_2CH_2$), 24.0 ($ArCH_2CH_3$), 17.8 ($HC{\equiv}CCH_2$), 13.8 ($ArCH_2CH_3$); ***m/z*** (ES+) 305 ($[M+H]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2NaO^+$) requires *m/z* 305.1624, found *m/z* 305.1624.

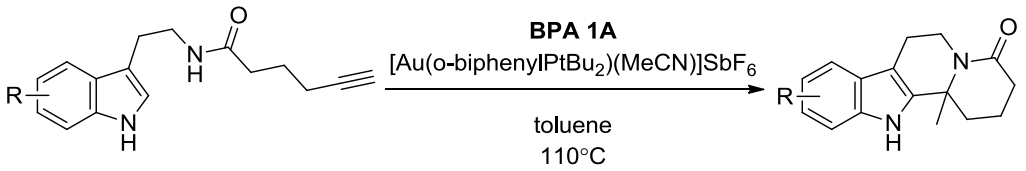
General procedure H for the racemic preparation of cyclic amides 54



To a foil covered flask $[Au(o\text{-}biphenylPtBu_2)(MeCN)]SbF_6$ (**E**) (0.05 eq), diphenylphosphate (0.1 eq) and desired amide derivative (**51**) (1 eq) were added and placed under nitrogen atmosphere. Toluene (14 ml/1 mmol of **51**) was added in one portion and the reaction was

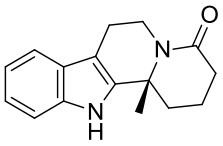
heated to 110 °C and left for 48 to 72 hours. The solvent was removed *in vacuo* and purified by flash column chromatography (CH_2Cl_2 : Et_2O, 1 : 0 to 7 : 3).

General procedure I for the enantioselective preparation of cyclic amides 51



To a foil covered flask [Au(o-biphenylPtBu$_2$)(MeCN)]SbF$_6$ (**E**) (0.01 eq) was added in dichloromethane (1 ml/ 0.15 mmol of **9**), the dichloromethane was subsequently removed *via* stream of nitrogen. **BPA 1A** (0.1 eq) and desired amide derivative (**51**) (0.15 mmol, 1 eq) was added and placed under nitrogen atmosphere. Toluene (21 ml) was added in one portion and the reaction was heated to 110 °C typically for 20 to 72 h until TLC shows consumption of starting material. The solvent was removed *in vacuo* and purified by flash column chromatography (DCM : Et_2O, 1 : 0 to 7 : 3).

Preparation and characterisation of (*R*)-12b-methyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (54a)

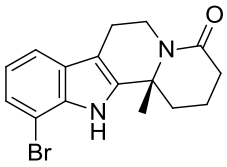


The title compound **54a** was synthesis according to general procedure **I** as a white solid (86% yield, 66% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 5.1 min, minor t_R = 11.8 min); $[\alpha]_D^{25}$ = +157.7 (*c* 0.26, CH_2Cl_2).

Racemic-54a was synthesised according to general procedure **H** as a white solid.

m.p. 180 °C (decomposition); **FT-IR** ν_{max} 3254 (N–H), 1606 (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.38 (br s, 1H, ArNH), 7.51 (d, *J* = 7.5, 1H, ArCH), 7.34 (d, *J* = 7.5, 1H, ArCH), 7.19 (t, *J* = 7.5, 1H, ArCH), 7.13 (t, *J* = 7.5, 1H, ArCH), 5.13 (dd, *J* = 12.5, 5.0, 1H, NCH_aH_b), 3.04 (td, *J* = 12.5, 4.5, 1H, NCH_aH_b), 2.85 (ddd, *J* = 15.5, 11.5, 5.0, 1H, $NCH_2CH_aH_b$), 2.76 (dd, *J* = 15.5, 5.0, 1H, $NCH_2CH_aH_b$), 2.61 (dd, *J* = 17.0, 5.0, 1H, $OCCH_aH_b$), 2.44 (ddd, *J* = 18.0, 10.5, 7.0, 1H, $OCCH_aH_b$), 2.32 (m, 1H, $OCCH_2CH_2CH_aH_b$), 2.09-1.84 (m, 3H, $OCCH_2CH_2CH_aH_b$, $OCCH_2CH_aH_b$), 1.70 (s, 3H, $NCCH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 169.3 (CO), 138.5 (ArC_{quat}), 136.1 (ArC_{quat}), 126.7 (ArC_{quat}), 122.0 (ArCH), 119.7 (ArCH), 118.4 (ArCH), 110.9 (ArCH), 108.0 (ArC_{quat}), 56.7 ($NCCH_3$), 36.5 (NCH_2), 35.5 ($OCCH_2CH_2CH_2$), 32.1 ($OCCH_2$), 26.0 (CCH_3), 21.3 (NCH_2CH_2), 16.8 ($OCCH_2CH_2$); ***m/z*** (ES+) 277 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{18}N_2NaO^+$) requires *m/z* 277.1311, found *m/z* 277.1306.

Preparation and Characterisation of (*R*)-11-bromo-12b-methyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (54m)

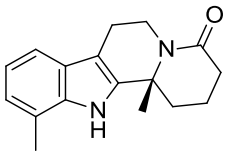


The title compound **54m** was synthesis according to general procedure **I** as a white solid (99% yield, 93% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 5.1 min, minor t_R = 6.6 min); $[\alpha]_D^{25}$ = +164.0 (*c* 0.15, CH_2Cl_2)

Racemic-54m was synthesised according to general procedure **H** as a white solid: Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 5.1 min, minor t_R = 6.7 min);

m.p. 130-137 °C; **FT-IR** ν_{max} 3190 (N–H), 1606 (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.09 (br s, 1H, ArNH), 7.44 (d, *J* = 8.0, 1H, ArCH), 7.33 (d, *J* = 8.0, 1H, ArCH), 7.01 (t, *J* = 8.0, 1H, ArCH), 5.12 (dd, *J* = 13.0, 4.5, 1H, NCH_aH_b), 3.01 (td, *J* = 12.5, 4.5, 1H, NCH_aH_b), 2.83 (ddd, *J* = 15.5, 12.0, 5.0, 1H, $NCH_2CH_aH_b$), 2.71 (dd, *J* = 15.0, 4.0, 1H, $NH_2CH_aH_b$), 2.60 (br d, *J* = 17.0, 1H, $OCCH_aH_b$), 2.50-2.33 (m, 2H, $OCCH_aH_b$, $OCCH_2CH_2CH_aH_b$), 2.10-1.85 (m, 3H, $OCCH_2CH_2CH_aH_b$, $OCCH_2CH_aH_b$), 1.71 (s, 3H, $NCCH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 169.2 (CO), 139.2 (ArC_{quat}), 134.7 (ArC_{quat}), 128.0 (ArC_{quat}), 124.5 (ArCH), 121.0 (ArCH), 117.7 (ArCH), 109.6 (ArC_{quat}), 104.5 (ArC_{quat}), 56.7 ($NCCH_3$), 36.2 (NCH_2), 35.5 ($OCCH_2CH_2CH_2$), 32.1 (NCH_2CH_2), 26.0 ($NCCH_3$), 21.4 ($OCCH_2$), 16.7 ($OCCH_2CH_2$); ***m/z*** (ES+) 355 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{17}BrN_2NaO^+$) requires *m/z* 355.0416 & 357.0397, found *m/z* 355.0409 & 357.0392.

Preparation and Characterisation of (*R*)-11,12b-dimethyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (54k)



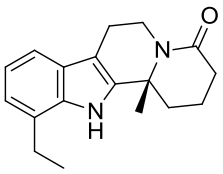
The title compound **54k** was synthesis according to general procedure **I** as white solid (90% yield, 90% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 4.4 min, minor t_R = 5.4 min); $[\alpha]_D^{25}$ = +167.6 (*c* 0.34, CH_2Cl_2).

Racemic-54k was synthesised according to general procedure **H** as a white solid.

m.p. 140-145 °C (decomposition); **FT-IR** ν_{max} 3265 (N–H), 1605 (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.05 (br s, 1H, ArNH), 7.36 (d, *J* = 7.5, 1H, ArCH), 7.06 (t, *J* = 7.5, 1H, ArCH), 7.00 (d, *J* = 7.5, 1H, ArCH), 5.12 (dd, *J* = 12.5, 4.5, 1H, NCH_aH_b), 3.03 (td, *J* = 12.5, 4.5,

1H, NCH_aH_b), 2.84 (ddd, *J* = 15, 11.5, 4.5, 1H, $NCH_2CH_aH_b$), 2.74 (dd, *J* = 15.0, 4.5, 1H, $NCH_2CH_aH_b$), 2.60 (br d, *J* = 17.5, 1H, $OCCH_aH_b$), 2.51 (s, 3H, $ArCH_3$), 2.49-2.34 (m, 2H, $OCCH_aH_b$, $OCCH_2CH_2CH_aH_b$), 2.09-1.86 (m, 3H, $OCCH_2CH_2CH_aH_b$, $OCCH_2CH_aH_b$), 1.71 (s, 3H, $NCCH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 169.2 (CO), 138.2 (ArC_{quat}), 135.6 (ArC_{quat}), 126.3 (ArC_{quat}), 122.8 (ArCH), 120.2 (ArC_{quat}), 120.0 (ArCH), 116.1 (ArCH), 108.7 (ArC_{quat}), 56.8 ($NCCH_3$), 36.4 (NCH_2), 35.6 ($OCCH_2CH_2CH_2$), 32.1 ($OCCH_2$), 26.0 ($NCCH_3$), 21.3 (NCH_2CH_2), 16.79 ($ArCH_3$), 16.78 ($OCCH_2CH_2$); ***m/z*** (ES+) 291 ($[M+H]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{20}N_2NaO^+$) requires *m/z* 291.1468, found *m/z* 291.1467.

Preparation and Characterisation of (*R*)-11-ethyl-12b-methyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one (54l)



The title compound **54l** was synthesis according to general procedure **I** white solid (60% yield, 86% e.e.). Chiralcel AD, 80:20 Hexane/IPA, 1ml/min, 220, major t_R = 4.1 min, minor t_R = 4.9 min); $[\alpha]_D^{25}$ = +120.6 (*c* 0.34, CH_2Cl_2)

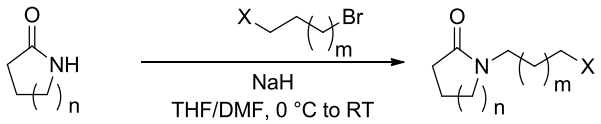
Racemic-54l was synthesised according to general procedure **H** as a white solid.

m.p. 127-129 °C; **FT-IR** ν_{max} 3277 (N–H), 1605 (C=O); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ_H 8.00 (br s, 1H, ArNH), 7.37 (d, *J* = 7.5, 1H, ArCH), 7.10 (t, *J* = 7.5, 1H, ArCH), 7.05 (d, *J* = 7.5, 1H, ArCH), 5.12 (dd, *J* = 13.0, 4.5, 1H, NCH_aH_b), 3.03 (td, *J* = 12.5, 4.5, 1H, NCH_aH_b), 2.88 (q, *J* = 7.5, 2H, $ArCH_2CH_3$), 2.84 (td, *J* = 12.0, 5.0, 1H, $NCH_2CH_aH_b$), 2.74 (dd, *J* = 15.0, 4.0, 1H, $NCH_2CH_aH_b$), 2.60 (br d, *J* = 17.0, 1H, $OCCH_aH_b$), 2.49-2.31 (m, 2H,

$OCCH_aH_b$, $OCCH_2CH_2CH_aH_b$), 2.08-1.85 (m, 3H, $OCCH_2CH_2CH_aH_b$, $OCCH_2CH_aH_b$), 1.71 (s, 3H, $NCCH_3$), 1.38 (t, J = 7.5, 3H, $ArCH_2CH_3$); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ_C 169.2 (CO), 138.1 (ArC_{quat}), 134.8 (ArC_{quat}), 126.5 (ArC_{quat}), 126.4 (ArC_{quat}), 120.7 (ArCH), 120.1 (ArCH), 116.2 (ArCH), 108.7 (ArC_{quat}), 56.7 ($NCCH_3$), 36.4 (NCH_2), 35.6 ($OCH_2CH_2CH_2$), 32.1 ($OCCH_2$), 26.0 ($NCCH_3$), 24.0 ($ArCH_2CH_3$), 21.3 (NCH_2CH_2), 16.8 ($OCCH_2CH_2$), 13.9 ($ArCH_2CH_3$); ***m/z*** (ES+) 305 ($[M+Na]^+$, 100%), **HRMS** (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{22}N_2NaO^+$) requires *m/z* 305.1624, found *m/z* 305.1626.

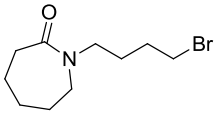
5.2 Chapter 2: Experimental

General procedure J for the synthesis of *N*-alkylated lactams 103



According to literature procedure,[11] to a suspension of NaH (60% dispersion in mineral oil, 1.5 eq.) in a mixture of THF:DMF (5:1, 0.09 M) was added the corresponding lactam (1.0 eq.) at 0 °C and stirred for 1 h. the corresponding bromoalkane (2.5 - 5.0 eq.) was then added to the mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred 18 h. Upon completion the reaction was quenched with water. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by FCC to yield the title compound **103**.

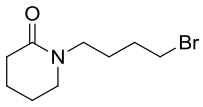
Preparation and characterisation of 1-(4-bromobutyl)azepan-2-one (103a)



Prepared according to general procedure **J** using ε-caprolactam (5.00 g, 44.0 mmol) and 1,4-dibromobutane (220 mmol). Purification by FCC yielded *N*-alkyl lactam **103a** (8.20 g, 75%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1634 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.38 (t, *J* = 6.5, 2H, C$\underline{H_2}$Br), 3.33 (t, *J* = 7.0, 2H, C$\underline{H_2}$CH$_2$CH$_2$CH$_2$Br), 3.24 - 3.30 (m, 2H, C(O)CH$_2$CH$_2$CH$_2$CH$_2$C$\underline{H_2}$), 2.40 - 2.50 (m, 2H, C(O)C$\underline{H_2}$), 1.79 ("quin", *J* = 7.0, 2H, C$\underline{H_2}$CH$_2$Br), 1.53 - 1.71 (m, 8H, C$\underline{H_2}$CH$_2$CH$_2$Br, C(O)CH$_2$C$\underline{H_2}$, C(O)CH$_2$CH$_2$C$\underline{H_2}$, C(O)CH$_2$CH$_2$CH$_2$C$\underline{H_2}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.7 (C$\underline{O}$), 49.4

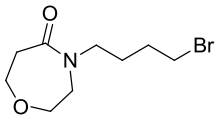
(C(O)$CH_2CH_2CH_2CH_2\underline{C}H_2$), 46.9 ($\underline{C}H_2CH_2CH_2CH_2Br$), 37.2 (C(O)$\underline{C}H_2$), 33.7 ($\underline{C}H_2Br$), 29.9 ($\underline{C}H_2CH_2Br$), 29.8, 28.6, 26.5, 23.4; ***m/z*** (ESI^+) 270 ($[M+Na]^+$), **HRMS** (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{18}BrNNaO^+$) requires *m/z* 270.0464 and 272.0444, found *m/z* 270.0469 and 272.0450.

Preparation and characterisation of 1-(4-bromobutyl)piperidin-2-one (103c)



Prepared according to general procedure **J** using δ-valerolactam (5.00 g, 50.4 mmol) and 1,4-dibromobutane (220 mmol). Purification by FCC yielded *N*-alkyl lactam **103c** (7.07 g, 60%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1631 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.30 - 3.43 (m, 4H, $C\underline{H}_2Br$, $C\underline{H}_2(CH_2)_3Br$), 3.22 (t, *J* = 5.5, 2H, C(O)$(CH_2)_3C\underline{H}_2$), 2.38 (t, *J* = 6.0, 2H, C(O)$C\underline{H}_2$), 1.61 - 1.92 (m, 8H, $C\underline{H}_2CH_2Br$, $C\underline{H}_2(CH_2)_2Br$, C(O)$CH_2C\underline{H}_2$, C(O)$(CH_2)_2C\underline{H}_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.6 ($\underline{C}O$), 47.6 (C(O)$(CH_2)_3\underline{C}H_2$), 45.7 ($\underline{C}H_2Br$, $\underline{C}H_2(CH_2)_3Br$), 33.4, 32.1 (C(O)$\underline{C}H_2$), 29.7, 25.4, 23.1, 21.2; ***m/z*** (ESI^+) 234 $[M+H]^+$; **HRMS** (ES^+) exact mass calculated for $[M+Na]^+$ ($C_9H_{16}BrNNaO^+$) requires *m/z* 256.0307 and 258.0287, found *m/z* 256.0306 and 258.0288.

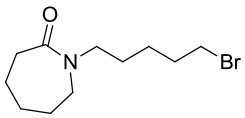
Preparation and characterisation of 4-(4-bromobutyl)-1,4-oxazepan-5-one (103e)



Prepared according to general procedure **J** using 1,4-oxazepan-5-one (0.900 g, 7.8 mmol) and 1,4-dibromobutane (220 mmol). Purification by FCC yielded *N*-alkyl lactam **103e** (1.68 g, 86%) as a clear colourless oil. **IR** ν_{max}(film)/cm^{-1} 1640 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.74 – 3.81 (m, 4H, (C(O)$CH_2C\underline{H}_2OC\underline{H}_2$), 3.41 – 3.50 (m, 6H, (O)$NC\underline{H}_2CH_2O$, $BrC\underline{H}_2$, and $Br(CH_2)_3C\underline{H}_2$), 2.74 – 2.78 (m, 2H, NC(O)$C\underline{H}_2$), 1.83 – 1.92 (m, 2H), 1.63 – 1.73 (m,

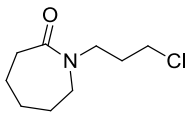
2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.3 (<u>C</u>O), 70.6, 65.5, 51.6, 47.4, 41.2 (C(O)<u>C</u>H_2), 33.5 (<u>C</u>H_2Br), 29.7, 26.4; ***m/z*** (ESI^+) 250 ($[M+H]^+$, ^{79}Br); **HRMS** (ES^+) exact mass calculated for $[M+Na]^+$ ($C_9H_{16}BrNNaO_2^+$) requires *m/z* 272.0257 and 274.0236, found *m/z* 272.0260 and 274.0240.

Preparation and characterisation of 1-(5-bromopentyl)azepan-2-one (103g)



Prepared according to general procedure **J** using ε-caprolactam (1.00 g, 8.85 mmol) and 1,5-dibromopentane (220 mmol). Purification by FCC yielded *N*-alkyl lactam **103g** (1.69 g, 73%) as a pale yellow oil. **IR** ν_{max}(film)/cm^{-1} 1636 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 3.37 (t, *J* = 7.0, 2H, C<u>H</u>$_2$Br), 3.33 (t, *J* = 7.5, 2H, C<u>H</u>$_2$$(CH_2)_4$Br), 3.28 - 3.31 (m, 2H, C(O)$(CH_2)_4$C<u>H</u>$_2$), 2.45 - 2.49 (m, 2H, C(O)C<u>H</u>$_2$), 1.85 ("quin", *J* = 7.0, 2H, C<u>H</u>$_2$$CH_2$Br), 1.56 - 1.73 (m, 6H, C(O)CH_2C<u>H</u>$_2$, C(O)$(CH_2)_2$C<u>H</u>$_2$, C(O)$(CH_2)_3$C<u>H</u>$_2$), 1.45 - 1.54 (m, 2H, C<u>H</u>$_2$$(CH_2)_3$Br), 1.36 - 1.44 (m, 2H, C<u>H</u>$_2$$(CH_2)_2$Br); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.5 (<u>C</u>O), 49.5 (C(O)$(CH_2)_4$<u>C</u>H_2), 47.8 (<u>C</u>$H_2$$(CH_2)_4$Br), 37.2 (C(O)<u>C</u>$H_2$), 33.7 (<u>C</u>$H_2$Br), 32.4 (<u>C</u>$H_2$$CH_2$Br), 29.9, 28.6, 27.2 (<u>C</u>$H_2$$(CH_2)_3$Br), 25.3 (<u>C</u>$H_2$$(CH_2)_2$Br), 23.4; ***m/z*** ($ESI^+$) 262 ($[M+H]^+$); **HRMS** ($ES^+$) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{20}BrNNaO^+$) requires *m/z* 284.0620 and 286.0600, found *m/z* 284.0621 and 286.0604.

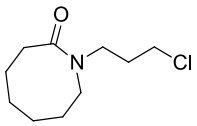
Preparation and characterisation of 1-(3-chloropropyl)azepan-2-one (103h)



Prepared according to general procedure **J** using azepan-2-one (2.3 g, 20 mmol) and 1-bromo-3-chloropropane (4.9 ml, 50 mmol). Purification by FCC yielded *N*-alkyl lactam **103h** (2.59 g, 69%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 1625(C=O); **^{1}H NMR** (400 MHz,

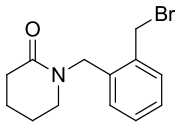
$CDCl_3$) δ_H 3.56 (t, 2H, *J* = 7.0, $ClCH_2CH_2C\underline{H_2}$), 3.50 (t , *J* = 7.0, 2H, $ClC\underline{H_2}$), 3.36 – 3.41 (m, 2H, $NC\underline{H_2}CH_2CH_2CH_2$), 2.50 – 2.55 (m, 2H, $C(O)C\underline{H_2}$), 2.01 ("quin", *J* = 7.0, 2H, $ClCH_2C\underline{H_2}$), 1.59 – 1.78 (m, 6H, $C(O)CH_2C\underline{H_2}C\underline{H_2}C\underline{H_2}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 176.1 ($\underline{C}(O)$), 50.3 ($N\underline{C}H_2CH_2CH_2CH_2$), 46.4 ($ClCH_2CH_2\underline{C}H_2$), 42.6 ($Cl\underline{C}H_2$), 37.3 ($C(O)\underline{C}H_2$), 31.2 ($ClCH_2C\underline{H_2}$), 30.0, 28.7, 23.4; ***m/z*** (ESI^+) 190 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_9H_{17}ClNO^+$) requires *m/z* 190.09932 and 19.09637, found *m/z* 190.09921 and 192.09620.

Preparation and characterisation of 1-(3-chloropropyl)azocan-2-one (103i)



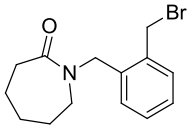
Prepared according to general procedure **J** using azocan-2-one (0.88 g, 6.9 mmol) and 1-bromo-3-chloropropane (1.7 ml, 17 mmol). Purification by FCC yielded *N*-alkyl lactam **103i** (0.98 g, 70%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 1626 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.58 (t, 2H, *J* = 6.5, $ClC\underline{H_2}$), 3.48 - 3.53 (m, 2H, $NC\underline{H_2}CH_2CH_2CH_2$), 3.44 (t, *J* = 6.5, 2H, $ClCH_2CH_2C\underline{H_2}$), 2.46 – 2.53 (m, 2H, $C(O)C\underline{H_2}$), 2.07 (quin, *J* = 6.5, 2H, $ClCH_2C\underline{H_2}$), 1.76 – 1.86 (m, 2H, $C(O)CH_2C\underline{H_2}$), 1.63 – 1.73 (m, 2H, $NCH_2C\underline{H_2}CH_2CH_2$), 1.44 - 1.60 (m, 4H, $NCH_2CH_2C\underline{H_2}C\underline{H_2}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.2 ($\underline{C}(O)$), 47.7 ($N\underline{C}H_2CH_2CH_2CH_2$), 43.3 ($ClCH_2CH_2\underline{C}H_2$), 42.9 ($Cl\underline{C}H_2$), 34.0 ($C(O)\underline{C}H_2$), 30.9 ($ClCH_2\underline{C}H_2$), 29.3 ($NCH_2\underline{C}H_2CH_2CH_2$), 28.7 ($C(O)CH_2\underline{C}H_2$), 26.3 ($NCH_2CH_2CH_2\underline{C}H_2$), 24.3 ($NCH_2CH_2\underline{C}H_2CH_2$); ***m/z*** ($ESI^+$) 204 ($[M+H]^+$); **HRMS** ($ES^+$) exact mass calculated for $[M+H]^+$ ($C_{10}H_{19}ONCl^+$) requires *m/z* 204.11497 and 206.11202, found *m/z* 204.11486 and 206.11187.

Preparation and characterisation of 1-[2-(bromomethyl)benzyl]piperidin-2-one (103j)



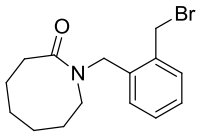
Prepared according to general procedure **J** using piperidin-2-one (3.00 g, 30 mmol) and 1,2-bis(bromomethyl)benzene (27.0 g, 105 mmol). Purification by FCC yielded *N*-alkyl lactam **103j** (2.79 g, 33%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 1627 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 – 7.32 (m, 1H, ArH), 7.19 – 7.24 (m, 2H, ArH), 7.10 – 7.12 (m, 1H, ArH), 4.70 (s, 2H, NCH_2Ar), 4.52 (s, 2H, BrCH_2), 3.10 (t, *J* = 6.0, 2H, NCH_2), 2.47 (t, *J* = 6.0, 2H, C(O)CH_2), 1.70 – 1.79 (m, 4H, C(O)CH_2CH_2CH_2,); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.0 (CO), 136.7 (ArC_{quat}), 135.3 (ArC_{quat}), 131.3 (ArCH), 129.7 (ArCH), 129.0 (ArCH), 128.3 (ArCH), 47.4 (NCH_2Ar), 47.2 (NCH_2CH_2), 32.3 (C(O)CH_2), 31.5 (BrCH_2), 23.0, 21.2; ***m/z*** (ESI$^+$) 304 ([M+Na]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_{13}H_{16}BrNNaO^+$) requires *m/z* 304.0307 and 306.0287, found *m/z* 304.0308 and 306.0289.

Preparation and characterisation of 1-[2-(bromomethyl)benzyl]azepan-2-one (103k)



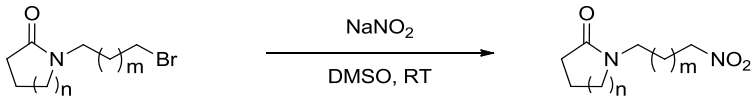
Prepared according to general procedure **J** using azepan-2-one (2.00 g, 17.6 mmol) and 1,2-bis(bromomethyl)benzene (11.5g, 44 mmol). Purification by FCC yielded *N*-alkyl lactam **103k** (2.62 g, 51%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 1633 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 – 7.40 (m, 1H), 7.28 – 7.33 (m, 2H), 7.20 – 7.23 (m, 1H), 4.76 (s, 2H, NCH_2Ar), 4.60 (s, 2H, ArCH_2Br), 3.29 – 3.34 (m, 2H, NCH_2CH_2), 2.66 – 2.71 (m, 2H, COCH_2), 1.72 – 1.79 (m, 4H), 1.56 – 1.63 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 176.1 (CO), 136.4, 136.0, 131.2, 129.6, 129.0, 128.1, 48.4 (NCH_2CH_2), 47.8 (NCH_2Ar), 37.1 (COCH_2), 31.5 (ArCH_2Br), 30.0, 27.8, 23.4; ***m/z*** (ESI$^+$) 296 ([M+H]$^+$, ^{79}Br), 297 ([M+H]$^+$, ^{81}Br); **HRMS** (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_{14}H_{18}BrNNaO^+$) requires *m/z* 318.0464 and 320.0444, found *m/z* 318.0462 and 320.0443.

Preparation and characterisation of 1-[2-(bromomethyl)benzyl]azocan-2-one (103l)



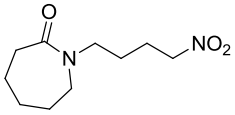
Prepared according to general procedure **J** using azocan-2-one (1.93 g, 15.2 mmol) and 1,2-bis(bromomethyl)benzene (9.9 g, 38 mmol). Purification by FCC yielded *N*-alkyl lactam **103l** (2.02 g, 43%) as a colourless oil. **IR** ν_{max}(film)/cm^{-1} 1627 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35 – 7.37 (m, 1H), 7.27 – 7.30 (m, 2H), 7.19 – 7.22 (m, 1H), 4.76 (s, 2H, NC$\underline{H_2}$Ar), 4.56 (s, 2H, BrC$\underline{H_2}$), 3.38 – 3.43 (m, 2H, NC$\underline{H_2}CH_2$), 2.65 – 2.70 (m, 2H, C(O)C$\underline{H_2}$), 1.86 – 1.92 (m, 2H), 1.65 - 1.71 (m, 2H), 1.50 – 1.62 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.8 (C=O), 136.3, 135.5, 131.2, 129.4, 129.1, 128.2, 45.4 (N$\underline{C}H_2$Ar), 44.2 (N$\underline{C}H_2CH_2$), 33.7 (C(O)$\underline{C}H_2$), 31.5 (Br$\underline{C}H_2$), 28.9, 28.3, 26.3, 24.3; ***m/z*** (ESI$^+$) 306 ([M+H]$^+$, ^{79}Br), 308 ([M+H]$^+$, ^{81}Br), **HRMS** (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_{15}H_{20}BrNNaO^+$) requires *m/z* 332.0620 and 334.0601, found *m/z* 332.0624 and 334.0605.

General procedure K for the synthesis of nitrated *N*-alkylated lactams 100



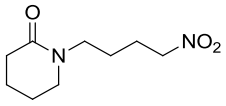
To a stirred solution of **103** (1.0 eq.) in DMSO (0.5 M) under an inert atmosphere was added solid $NaNO_2$ (2.0 eq.). The resulting mixture was stirred for 3 h (or until the reaction was complete by TLC analysis) at room temperature then quenched with water. The organic phase was separated and the aqueous layer was extracted (EtOAc). The combined organic extracts were washed (brine), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by FCC to yield the corresponding nitrated lactams **100**.

Preparation and characterisation of 1-(4-Nitrobutyl)azepan-2-one (100a)



Prepared according to general procedure **K** using **103a** (5.00 g, 20.2 mmol). Purification by FCC yielded nitrated lactam **100a** (2.61 g, 60%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1633 (C=O), 1548 (NO_2), 1377 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.42 (t, *J* = 6.5, 2H, $C\underline{H_2}NO_2$), 3.39 (t, *J* = 7.0, 2H, $C\underline{H_2}(CH_2)_3NO_2$), 3.27 - 3.34 (m, 2H, $C(O)(CH_2)_4C\underline{H_2}$), 2.45 - 2.52 (m, 2H, $C(O)C\underline{H_2}$), 1.91 - 2.03 (m, 2H, $C\underline{H_2}CH_2NO_2$), 1.52 - 1.76 (m, 8H, $C\underline{H_2}(CH_2)_2NO_2$, $C(O)CH_2C\underline{H_2}$, $C(O)(CH_2)_2C\underline{H_2}$, $C(O)(CH_2)_3C\underline{H_2}$),; **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 176.0 ($\underline{C}O$), 75.1 ($\underline{C}H_2NO_2$), 49.5 ($C(O)(CH_2)_4\underline{C}H_2$), 46.7 ($\underline{C}H_2(CH_2)_3NO_2$), 37.2 ($C(O)\underline{C}H_2$), 29.9, 28.6, 24.7, 24.5 ($\underline{C}H_2CH_2NO_2$), 23.4; ***m/z*** (ESI$^+$) 215 $[M+H]^+$; **HRMS** (ES$^+$) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{18}N_2NaO_3^+$) requires *m/z* 237.1210, found *m/z* 237.1214.

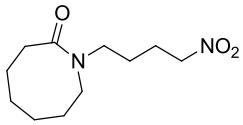
Preparation and characterisation of 1-(4-Nitrobutyl)piperidin-2-one (100c)



Prepared according to general procedure **K** using **103c** (2.00 g, 8.55 mmol). Purification by FCC yielded nitrated lactam **100c** (0.62 g, 36%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1624 (C=O), 1546 (NO_2), 1353 (NO_2); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 4.45 (t, *J* = 7.0, 2H, $C\underline{H_2}NO_2$), 3.43 (t, *J* = 7.0, 2H, $C\underline{H_2}(CH_2)_3NO_2$), 3.26 (t, *J* = 5.5, 2H, $C(O)(CH_2)_3C\underline{H_2}$), 2.38 (t, *J* = 6.5, 2H, $C(O)C\underline{H_2}$), 1.95 - 2.06 (m, 2H, $C\underline{H_2}CH_2NO_2$), 1.74 - 1.86 (m, 4H, $C(O)CH_2C\underline{H_2}$, $C(O)(CH_2)_2C\underline{H_2}$), 1.65 ("dt", *J* = 14.5, 7.5, 2H, $C\underline{H_2}(CH_2)_2NO_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.0 ($\underline{C}O$), 75.1 ($\underline{C}H_2NO_2$), 47.8 ($C(O)(CH_2)_3\underline{C}H_2$), 45.7 ($\underline{C}H_2(CH_2)_3NO_2$), 32.3 ($C(O)\underline{C}H_2$), 24.5 ($\underline{C}H_2CH_2NO_2$), 23.7 ($\underline{C}H_2(CH_2)_2NO_2$), 23.2, 21.3;

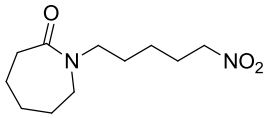
m/z (ESI$^+$) 201 [M+H]$^+$; **HRMS** (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_9H_{16}N_2NaO_3^+$) requires *m/z* 223.1053, found *m/z* 223.1060.

Preparation and characterisation of 1-(4-Nitrobutyl)azocan-2-one (100d)



Prepared according to general procedure **K** using **103d** (1.31 g, 5.00 mmol). Purification by FCC yielded nitrated lactam **100d** (0.63 g, 55%) as a yellow. **IR** ν_{max}(film)/cm^{-1} 1622 (C=O), 1546 (NO_2), 1380 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.42 (t, *J* = 7.0, 2H, C$\underline{H_2}$NO$_2$), 3.39 - 3.48 (m, 2H, C(O)(CH$_2$)$_5$C$\underline{H_2}$), 3.34 (t, *J* = 7.0, 2H, C$\underline{H_2}$(CH$_2$)$_3$NO$_2$), 2.41 - 2.51 (m, 2H, C(O)C$\underline{H_2}$), 1.93 - 2.05 (m, 2H, C$\underline{H_2}$CH$_2$NO$_2$), 1.71 - 1.83 (m, 2H, C(O)CH$_2$C$\underline{H_2}$), 1.57 - 1.69 (m, 4H, C(O)(CH$_2$)$_4$C$\underline{H_2}$, C$\underline{H_2}$(CH$_2$)$_2$NO$_2$), 1.41 - 1.56 (m, 4H, C(O)(CH$_2$)$_2$C$\underline{H_2}$, C(O)(CH$_2$)$_3$C$\underline{H_2}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.1 (C$\underline{O}$), 75.2 (C$\underline{H_2}$NO$_2$), 46.9 (C(O)(CH$_2$)$_5$C$\underline{H_2}$), 43.9 (C$\underline{H_2}$(CH$_2$)$_3$NO$_2$), 33.9 (C(O)C$\underline{H_2}$), 29.2, 28.7, 26.2, 24.7, 24.5, 24.3; ***m/z*** (ESI$^+$) 229 [M+H]$^+$; **HRMS** (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_{11}H_{20}N_2NaO_3^+$) requires *m/z* 251.1366, found *m/z* 251.1365.

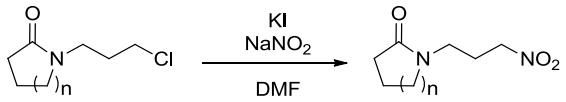
Preparation and characterisation of 1-(5-Nitropentyl)azepan-2-one (100g)



Prepared according to general procedure **K** using **103g** (1.64 g, 6.26 mmol). Purification by FCC yielded nitrated lactam **100g** (0.86 g, 60%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1634 (C=O), 1547 (NO_2), 1372 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.39 (t, *J* = 7.0, 2H, C$\underline{H_2}$NO$_2$), 3.38 (t, *J* = 7.5, 2H, C$\underline{H_2}$(CH$_2$)$_4$NO$_2$), 3.31 - 3.35 (m, 2H, C(O)(CH$_2$)$_4$C$\underline{H_2}$), 2.48 - 2.56 (m, 2H, C(O)C$\underline{H_2}$), 2.00 - 2.11 (m, 2H, C$\underline{H_2}$CH$_2$NO$_2$), 1.52 - 1.81 (m, 8H, C(O)CH$_2$C$\underline{H_2}$, C(O)(CH$_2$)$_2$C$\underline{H_2}$, C(O)(CH$_2$)$_3$C$\underline{H_2}$, C$\underline{H_2}$(CH$_2$)$_3$NO$_2$), 1.34 - 1.45 (m, 2H, C$\underline{H_2}$(CH$_2$)$_2$NO$_2$); **^{13}C**

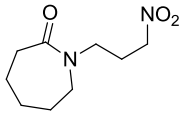
NMR (100 MHz, $CDCl_3$) δ_C 175.6 (<u>C</u>O), 75.3 (<u>C</u>H_2NO_2), 49.4 (C(O)$(CH_2)_4$<u>C</u>H_2), 47.4 (<u>C</u>$H_2(CH_2)_4NO_2$), 37.1 (C(O)<u>C</u>H_2), 29.8, 28.5, 27.1 (<u>C</u>$H_2(CH_2)_3NO_2$), 26.8 (<u>C</u>$H_2CH_2NO_2$), 23.3, 23.3; ***m/z*** (ESI^+) 229 $[M+H]^+$; **HRMS** (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{20}N_2NaO_3^+$) requires *m/z* 251.1366, found *m/z* 251.1365.

General procedure L for the synthesis of nitrated *N*-alkylated lactams 100h and 100i



To a stirred solution of **103h-103i** (1.0 eq.) in DMSO (1.2 M) under an inert atmosphere was added solid $NaNO_2$ (2.4 eq.) and KI (0.05 eq). The resulting mixture was stirred at room temperature until the reaction was complete. The reaction was then quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by FCC to yield the corresponding nitrated lactams **100h-100i.**

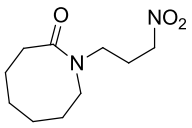
Preparation and characterisation of 1-(3-nitropropyl)azepan-2-one (100h)



Prepared according to general procedure **L** using **103h** (1.6 g, 8.5 mmol). Purification by FCC yielded nitrated lactam **100h** (0.35 g, 21%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1635 (C=O), 1549 (NO_2), 1369 (NO_2); **^{1}H NMR** (400 MHz, C_6D_6) δ_H 3.81 (t, *J* = 7.0, 2H, NO_2C<u>H</u>$_2$), 3.00 (t, *J* = 7.0, 2H, C(O)NC<u>H</u>$_2CH_2CH_2NO_2$), 2.51 – 2.53 (m, 2H, NC<u>H</u>$_2CH_2CH_2CH_2$), 2.19 – 2.22 (m, 2H, C(O)C<u>H</u>$_2$), 1.65 ("quin", 2H, *J* = 7.0, NO_2CH_2C<u>H</u>$_2$), 1.23 – 1.29 (m, 2H, C(O)CH_2C<u>H</u>$_2$), 1.14 – 1.20 (m, 2H, C(O)CH_2CH_2C<u>H</u>$_2$), 0.98 – 1.04 (m, 2H, NCH_2C<u>H</u>$_2CH_2CH_2$); **^{13}C NMR** (400 MHz, C_6D_6) δ_C 175.4 (<u>C</u>(O)), 73.5 (NO_2<u>C</u>H_2), 49.5 (C(O)N<u>C</u>$H_2CH_2CH_2CH_2$), 45.4 ($NO_2CH_2CH_2$<u>C</u>H_2), 37.4 (C(O)<u>C</u>H_2), 30.2

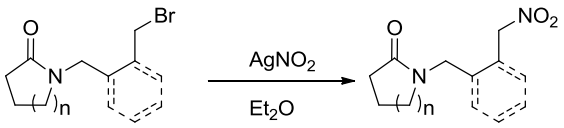
(C(O)$CH_2CH_2\underline{C}H_2$), 29.2 ($NCH_2\underline{C}H_2CH_2CH_2$), 26.6 ($NO_2CH_2\underline{C}H_2$), 23.9 (C(O)$CH_2\underline{C}H_2$); ***m/z*** ($ESI^+$) 201 ($[M+H]^+$); **HRMS** ($ES^+$) exact mass calculated for $[M+Na]^+$ ($C_9H_{16}N_2NaO_3^+$) requires *m/z* 223.1053 and 224.1086 found *m/z* 223.1062 and 224.1091.

Preparation and characterisation of 1-(3-nitropropyl)azocan-2-one (100i)



Prepared according to general procedure **L** using **103i** (1.0 g, 4.9 mmol). Purification by FCC yielded nitrated lactam **100i** (0.35 g, 33%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1626 (C=O), 1547 (NO_2), 1377 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.45 (t, 2H, *J* = 7.0, $NO_2C\underline{H}_2$), 3.48 (t, 2H, *J* = 5.9, C(O)$NC\underline{H}_2CH_2CH_2CH_2$), 3.42 (t, 2H, *J* = 6.5, $NO_2CH_2CH_2C\underline{H}_2$), 2.46 – 2.53 (m, 2H, C(O)$C\underline{H}_2$), 2.25-2.34 (m, 2H, $NO_2CH_2C\underline{H}_2$), 1.76 - 1.85 (m, 2H, C(O)$CH_2C\underline{H}_2$), 1.63 - 1.71 (m, 2H, C(O)$NCH_2C\underline{H}_2CH_2CH_2$), 1.44 - 1.59 (m, 4H, C(O)$CH_2CH_2C\underline{H}_2C\underline{H}_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.6 ($\underline{C}$(O)) 73.5 ($NO_2\underline{C}H_2$), 47.5 ($N\underline{C}H_2CH_2CH_2CH_2$), 42.5 ($NO_2CH_2CH_2\underline{C}H_2$), 33.9 (C(O)$\underline{C}H_2$), 29.2 ($NCH_2\underline{C}H_2CH_2CH_2$), 28.7 (C(O)$CH_2\underline{C}H_2$), 26.2, 25.9 ($NO_2CH_2\underline{C}H_2$), 24.2; ***m/z*** ($ESI^+$) 215.13902 ($[M+H]^+$); **HRMS** ($ES^+$) exact mass calculated for $[M+H]^+$ ($C_{10}H_{19}O_3N_2^+$) requires *m/z* 215.13902 and 216.14237, found *m/z* 215.13888 and 216.14224.

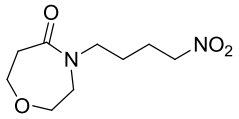
General procedure M for the synthesis of nitrated N-alkylated lactams 100e and 100k



To a stirred solution of **103** (1.0 eq.) in diethylether (1.9M) with the exclusion of light (in a foil covered flask) under an inert atmosphere was added $AgNO_2$ (4.0 eq.). The resulting

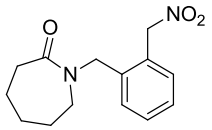
mixture was stirred for 5 days at room temperature. The mixture was then filtered, washing the filter cake with diethylether. The filtrate was concentrated *in vacuo* and purified by FCC to yield the corresponding nitrated lactams **100**.

Preparation and characterisation of 4-(4-nitrobutyl)-1,4-oxazepan-5-one (100e)



Prepared according to general procedure **M** using **103e** (1.5 g, 6.0 mmol). Purification by FCC yielded nitrated lactam **100e** (0.55 g, 42%) as a clear colourless oil. **IR** ν_{max}(film)/cm^{-1} 1640 (C=O), 1548 (NO_2), 1372 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.44 – 4.49 (t, *J* = 7.0, 2H, C$\underline{H_2}$$NO_2$), 3.78 – 3.81 (m, 2H), 3.73 – 3.78 (m, 2H), 3.44 – 3.48 (m, 4H, OCH_2C$\underline{H_2}$N, C$\underline{H_2}$$(CH_2)_3NO_2$), 2.75 – 2.79 (m, 2H C$\underline{H_2}$C(O)), 1.98 – 2.07 (m, 2H), 1.57 - 1.67 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.5 (C=O), 75.0 ($\underline{C}H_2NO_2$), 70.5, 65.5, 51.6, 47.3, 41.2 (C(O)$\underline{C}H_2$), 24.7, 24.4; ***m/z*** (ESI$^+$) 217 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+Na]$^+$ ($C_9H_{16}N_2NaO_4^+$) requires *m/z* 239.1002, found *m/z* 239.1012.

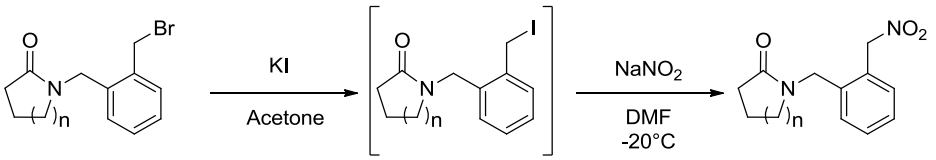
Preparation and characterisation of 1-[2-(nitromethyl)benzyl]azepan-2-one (100k)



Prepared according to general procedure **M** using **103k** (2.00 g, 6.27 mmol). Purification by FCC yielded nitrated lactam **100k** (0.43 g, 24%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1620 (C=O), 1551 (NO_2), 1370 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37-7.46 (m, 3H), 7.31 – 7.34 (m, 1H), 5.68 (s, 2H, ArC$\underline{H_2}$$NO_2$), 4.72 (s, 2H, NC$\underline{H_2}$Ar), 3.23 – 3.27 (m, 2H, NC$\underline{H_2}$$CH_2$), 2.56 – 2.61 (m, 2H, C(O)C$\underline{H_2}$), 1.67 - 1.76 (m, 4H), 1.52 - 1.59 (m, 2H); **^{13}C**

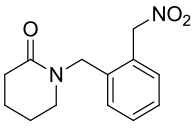
NMR (100 MHz, $CDCl_3$) δ_C 176.0 (<u>C</u>O), 137.7 (Ar<u>C</u>$_{quat}$), 132.4 (Ar<u>C</u>$_{quat}$), 130.6 (Ar<u>C</u>H), 130.3 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 128.5 (Ar<u>C</u>H), 76.7 (NO_2<u>C</u>H_2), 48.4 (N<u>C</u>H_2CH_2), 48.1 (N<u>C</u>H_2Ar), 36.8 (CO<u>C</u>H_2), 29.8, 27.6, 23.2; ***m/z*** (ESI^+) 263 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{18}N_2NaO_3^+$) requires *m/z* 285.1210, found *m/z* 285.1210.

General procedure N for the synthesis of nitrated N-alkylated lactams 100j and 100l



To a stirred solution of **103** (1.0 eq.) in acetone (1.2 M) under an inert atmosphere was added sodium iodide (2.0 eq.). The resulting mixture was stirred for 24 h at room temperature with the exclusion of light (in an aluminium foil covered flask). The mixture was concentrated *in vacuo* then dissolved in diethyl ether and washed with water. The organic layer was concentrated to afford the crude iodide, which was used without purification. The iodide was dissolved in DMF (0.25 M) under nitrogen. Sodium nitrite (3 eq) was added and the reaction was cooled to – 20 °C and stirred until the reaction was complete by ^{1}HNMR analysis. The reaction was diluted with EtOAc, washed with brine and dried over Na_2SO_4. The organic layer was concentrated *in vacuo* and purified by FCC to yield the corresponding nitrated lactams **100j** and **100l**.

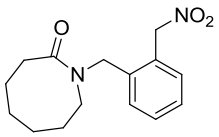
Preparation and characterisation of 1-[2-(nitromethyl)benzyl]piperidin-2-one (100j)



Prepared according to general procedure **N** using **103j** (1.77 g, 6.27 mmol) crude iodide was obtained in (1.9 g, 92%). The iodide (1 g, 3 mmol) was used according to procedure E.

Purification by FCC (Et_2O) yielded nitrated lactam **100j** (0.2 g, 27%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1616 (C=O), 1548 (NO_2), 1374 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29 – 7.38 (m, 3H), 7.22 – 7.25 (m, 1H), 5.59 (s, 2H, NO_2CH_2), 4.67 (s, 2H, NCH_2Ar), 3.04 (t, 2H, NCH_2CH_2), 2.35 (t, *J* = 6.0, 2H, $C(O)CH_2$), 1.63 – 1.72 (m, 4H, $C(O)CH_2CH_2$, $C(O)CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.8 (CO) 137.2 (ArC_{quat}), 132.6 (ArC_{quat}), 130.7 (ArCH), 130.2 (ArCH), 129.0 (ArCH), 128.6 (ArCH), 76.7 (NO_2CH_2), 47.9 (NCH_2Ar), 47.2 (NCH_2CH_2), 32.2 ($C(O)CH_2$), 22.8, 21.1; ***m/z*** (ESI^+) 249 ($[M+H]^+$) **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{17}O_3N_2^+$) requires *m/z* 249.12337 and 250.12672, found *m/z* 249.12327 and 250.12656.

Preparation and characterisation of 1-[2-(nitromethyl)benzyl]azocan-2-one (100l)

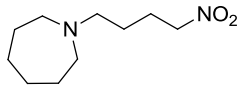


Prepared according to general procedure **N** using **103l** (2.0 g, 6.5 mmol). Purification by FCC (Et_2O) yielded nitrated lactam **100l** (0.36 g, 20%) as a white solid. (**m.p.** = 90-95 °C). **IR** ν_{max}(film)/cm^{-1} 1626 (C=O), 1542 (NO_2), 1363 (NO_2); **^{1}H NMR** (500 MHz, C_6D_6) δ_H 7.01 (td, *J* = 7.5, 1.0, 1H, ArH), 6.95 (td, *J* = 7.5, 1.0, 1H, ArH), 6.91 (br d, *J* = 7.5, 1H, ArH), 6.86 (br d, *J* = 7.5, 1H, ArH), 5.16 (s, 2H, NO_2CH_2Ar), 4.49 (br s, 2H, $C(O)NCH_2Ar$), 2.76 – 2.81 (m, 2H, NCH_2CH_2), 2.29 – 2.35 (m, 2H, $C(O)CH_2CH_2$), 1.54 – 1.61 (m, 2H, $C(O)CHCH_2$), 1.03 - 1.18 (m, 6H, $NCH_2CH_2CH_2CH_2$); **^{13}C NMR** (125 MHz, C_6D_6) δ_C 174.7 (C(O)), 138.7 (ArC_{quat}), 133.3 (ArC_{quat}), 130.8 (ArCH), 130.1 (ArCH), 129.9 (ArCH), 128.0–128.8 (ArCH)[*], 76.7 (NO_2CH_2Ar), 44.7 ($C(O)NCH_2Ar$), 44.6 (NCH_2CH_2), 33.9 ($C(O)CH_2CH_2$), 29.3 $C(O)CH_2CH_2$), 28.3, 26.6, 24.6; ***m/z*** (ESI^+) 277 ($[M+H]^+$); **HRMS**

[*] Hidden under C_6H_6 peak, assigned with the help of HSQC

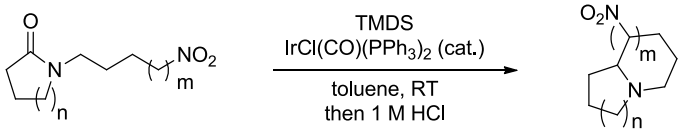
(ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}O_3N_2^+$) requires *m/z* 277.15467 and 278.15802, found *m/z* 277.15442 and 278.15787.

Characterisation of 1-(4-Nitrobutyl)azepane (104a)



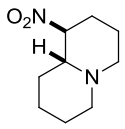
IR ν_{max}(film)/cm^{-1} 1548 (NO_2), 1378 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 1.49 - 1.67 (m, 10H, $C\underline{H}_2(CH_2)_2NO_2$, 2 × $NCH_2C\underline{H}_2$, 2 × $N(CH_2)_2C\underline{H}_2$), 2.06 ("quin", *J* = 7.5, 2H, $C\underline{H}_2CH_2NO_2$), 2.51 (t, *J* = 7.0, 2H, $C\underline{H}_2(CH_2)_3NO_2$), 2.57 - 2.63 (m, 4H, 2 × $NC\underline{H}_2$), 4.43 (t, *J* = 7.0, 2H, $C\underline{H}_2NO_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 24.2, 25.4, 26.9, 28.1 (4 × $\underline{C}H_2$), 55.4 ($N\underline{C}H_2$), 57.0 ($\underline{C}H_2(CH_2)_3NO_2$), 75.6 ($\underline{C}H_2NO_2$); ***m/z*** ($ESI^+$) 201 (100%, $[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{21}N_2O_2$) requires *m/z* 201.1598, found *m/z* 201.1599.

General procedure O for the synthesis of nitrated bicycles 101.



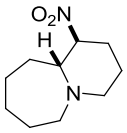
To a stirred solution of **100** (1.0 eq.) in toluene (0.01 M) under an inert atmosphere at room temperature was added TMDS (2.0 eq.) and $IrCl(CO)(PPh_3)_2$ (0.005 eq.). The resulting solution was stirred until complete conversion of the starting material (TLC) then quenched with 1 M HCl (12 mL/mmol **100**). The aqueous layer was separated and the organic layer was extracted (1 M HCl, 3 × 12 mL/mmol **100**). The combined aqueous extracts were washed (Et_2O, 3 × 6 mL/mmol **100**) and basified to pH 10 (K_2CO_3). The aqueous layer was then extracted (Et_2O, 3 × 6 mL/mmol **100**), the organic phases combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by FCC to yield the title compound **101.**

Preparation and characterisation of (*R,*S**)-1-nitrooctahydro-2H-quinolizine (100c)[12]**



Prepared according to general procedure **O** using **100c** (0.0630 g, 0.315 mmol). Purification by FCC to yield the title compound **101c** (0.026 g, 45%, d.r. >98:2) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1543 (NO_2), 1371 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.30 (ddd, *J* = 12.0, 9.5, 4.0, 1H, C$\underline{H}$NO$_2$), 2.88 ("d", *J* = 11.5, 1H, NCH$_c$C$\underline{H}_d$), 2.79 ("d", *J* = 12.0, 1H, NC$\underline{H}_c$CH$_d$), 2.22 - 2.32 (m, 2H, CH$_a\underline{H}_b$CHNO$_2$, C$\underline{H}$CHNO$_2$), 2.08 - 2.20 (m, 2H, NC$\underline{H}_a$CH$_b$, NCH$_a\underline{H}_b$), 1.95 ("qd", *J* = 12.5, 4.5, 1H, C$\underline{H}_a$H$_b$CHNO$_2$), 1.48 - 1.86 (m, 6H), 1.18 - 1.37 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 89.4 (C$\underline{H}$NO$_2$), 64.0 (C$\underline{H}$CHNO$_2$), 56.1 (N$\underline{C}$H$_2$), 55.3 (N$\underline{C}$H$_2$), 30.5 (C$\underline{H}_2$CHNO$_2$), 28.8, 25.3, 23.5, 23.0; ***m/z*** (ESI$^+$) 185 ([M+H]$^+$). All data in agreement with that previously reported in the literature.[12]

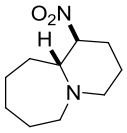
Preparation and characterisation of (*R,*S**)-1-nitrodecahydropyrido[1,2-*a*]azepine (101a)**



Prepared according to general procedure **O** using **100a** (0.100 g, 0.467 mmol). Purification by FCC to yield the title compound **101a** (0.074 g, 80%, d.r. 88:12) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1543 (NO_2), 1375 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H – major diastereomer: 4.36 (ddd, *J* = 11.5, 9.5, 4.0, 1H, C$\underline{H}$NO$_2$), 2.62 - 2.87 (m, 4H, NCH$_a\underline{H}_b$, NC$\underline{H}_c\underline{H}_d$, C$\underline{H}$CHNO$_2$), 2.57 (td, *J* = 12.0, 3.5, 1H, NC$\underline{H}_a$H$_b$), 2.19 - 2.29 (m, 1H, CH$_a\underline{H}_b$CHNO$_2$), 1.94 (qd, *J* = 12.5, 5.0, 1H, C$\underline{H}_a$H$_b$CHNO$_2$), 1.44 - 1.75 (m, 10H),; minor diastereomer observable: 4.51 - 4.63 (m, 1H), 3.26 - 3.36 (m, 1H), 2.88 - 2.96 (m, 1H), 2.46 - 2.52 (m, 1H), 2.00 - 2.09 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C – major diastereomer:

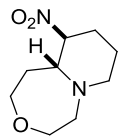
88.0 (<u>C</u>HNO$_2$) 65.2 (<u>C</u>HCHNO$_2$), 55.7 (N<u>C</u>H$_2$), 54.8 (N<u>C</u>H$_2$), 30.5, 29.7, 28.6, 28.2, 23.8, 23.4; minor diastereomer observable: 85.6 (<u>C</u>HNO$_2$), 62.7 (<u>C</u>HCHNO$_2$), 56.5 (N<u>C</u>H$_2$), 48.3 (N<u>C</u>H$_2$), 27.6, 25.9, 25.3, 25.2, 24.1, 23.2; ***m/z*** (ESI$^+$) 199 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{10}H_{19}N_2O_2^+$) requires *m/z* 199.1441, found *m/z* 199.1437.

Large scale preparation and characterisation of (*R,*S**)-1-nitrodecahydropyrido[1,2-*a*]azepine (101a)**



Prepared according to general procedure **O** using **100a** (2.00 g, 9.35 mmol). Purification of crude mixture (d.r. 88:12) by FCC to yield the title compound **101a** (1.31 g, 71%, single diastereomer, the minor diastereomer decomposed during FCC). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.35 (ddd, *J* = 11.5, 9.5, 4.0, 1H, C<u>H</u>NO$_2$), 2.62 - 2.88 (m, 4H, NCH$_a$<u>H$_b$</u>, N<u>C</u>H$_c$<u>H$_b$</u>, C<u>H</u>CHNO$_2$), 2.56 (“td”, *J* = 12.0, 3.0, 1H, N<u>C</u>H$_a$H$_b$), 2.17 - 2.29 (m, 1H, CH$_a$<u>H$_b$</u>CHNO$_2$), 1.93 (“qd”, *J* = 12.5, 5.0, 1H, C<u>H$_a$</u>H$_b$CHNO$_2$), 1.43 - 1.76 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 88.0 (<u>C</u>HNO$_2$), 65.1 (<u>C</u>HCHNO$_2$), 55.7 (N<u>C</u>H$_2$), 54.7 (N<u>C</u>H$_2$), 30.5, 29.7, 28.6, 28.2, 23.8, 23.4.

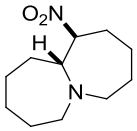
Preparation and characterisation of (*R,*S**)-10-nitrooctahydro-2*H*-pyrido[1,2-*d*][1,4]oxazepine (101e)**



Prepared according to general procedure **O** using **100e** (0.095 g, 0.44 mmol). Purification by FCC to yield the title compound **101e** (0.045 mg, 51%, d.r. 91:9) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1540 (NO$_2$), 1374 (NO$_2$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H – major diastereomer: 4.35 (ddd, *J* = 11.5, 9.5, 4.5, 1H, NO$_2$C<u>H</u>), 3.80 – 3.86 (m, 1H,

OC$\underline{H}_a$$H_b$$CH_2$CH), 3.68 – 3.76 (m, 3H, OC$H_a\underline{H}_b$$CH_2CH, OC\underline{H}_a\underline{H}_b$$CH_2$N), 2.79 – 2.95 (m, 4H, NC$\underline{H}_a$$H_b$$CH_2CH_2$, NC$\underline{H}CHNO_2$, NC$\underline{H}_a\underline{H}_b$$CH_2$O), 2.53 ("td", *J* = 12.0, 3.0, 1H, NC$H_a\underline{H}_b$$CH_2CH_2$), 2.23 - 2.29 (m, 1H, NO_2CHC$\underline{H}_a$$H_b$), 1.89 – 2.00 (m, 1H, NO_2CHC$H_a\underline{H}_b$), 1.80 – 1.86 (m, 2H, O$CH_2C\underline{H}_2$CH), 1.72 - 1.79 (m, 1H, NO_2CH$CH_2C\underline{H}_a$$H_b$), 1.59 - 1.70 (m, 1H, NO_2CH$CH_2CH_a\underline{H}_b$); minor diastereomer observable: 4.59 – 4.64 (m, 1H, $NO_2C\underline{H}$), 3.45 – 3.52 (m, 1H), 3.03 – 3.10 (m, 1H), 1.42 – 1.49 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C – major diastereomer: 87.9 ($NO_2\underline{C}$H), 69.2 (O$\underline{C}H_2CH_2$CH), 65.5 (O$\underline{C}H_2CH_2$N), 63.7 (N$\underline{C}$HCHNO_2), 57.8 (N$\underline{C}H_2CH_2$O), 55.3 (N$\underline{C}H_2CH_2CH_2$), 32.7 (O$CH_2\underline{C}H_2$CH), 29.9 NO_2CH$\underline{C}H_2$), 23.2 N$CH_2\underline{C}H_2CH_2$); minor diastereomer observable: 84.9 ($NO_2\underline{C}$H), 67.6, 66.3, 61.0, 56.6, 27.7, 23.6; ***m/z*** (ESI$^+$) 201 ([M+H]$^+$); **HRMS** (ESI$^+$) exact mass calculated for [M+H]$^+$ ($C_9H_{17}N_2O_3^+$) requires *m/z* 201.1234, found *m/z* 201.1233.

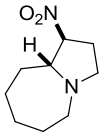
Preparation and characterisation of (*R,*S**)-1-nitrodecahydro-1*H*-azepino[1,2-*a*]azepine (101f)**



Prepared according to general procedure **O** using **100f** (0.100 g, 0.439 mmol). Purification by FCC to yield the title compound **101f** (0.061 g , 65%, d.r. 86:14) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1539 (NO_2), 1358 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.35 ("dt", *J* = 9.5, 6.0, 1H, C$\underline{H}NO_2$), 3.17 - 3.31 (m, 1H, C$\underline{H}$CHNO_2), 2.71 - 2.99 (m, 4H, 2 × N$C\underline{H}_2$), 1.13 - 2.18 (m, 14H); minor diastereomer observable: 4.57 (ddd, *J* = 8.5, 5.5, 3.5, 1H, C$\underline{H}NO_2$), 3.11 ("dt", *J* = 12.0, 3.5, 1H, C$\underline{H}$CHNO_2), 2.71 - 2.99 (m, N$C\underline{H}_2$), 2.24 - 2.38 (m, 1H), 1.13 - 2.18 (m, 13H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C – major diastereomer: 92.5 ($\underline{C}HNO_2$), 65.9

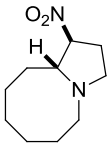
(CHCHNO$_2$), 54.6 (NCH$_2$), 50.8 (NCH$_2$), 33.0, 31.7, 29.5, 29.2, 28.3, 26.4, 22.6; minor diastereomer observable: 91.7 (CHNO$_2$), 65.8 (CHCHNO$_2$), 56.3 (NCH$_2$), 52.6 (NCH$_2$), 31.7, 31.0, 30.8, 28.9, 26.9, 22.7; ***m/z*** (ESI$^+$) 213 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{11}H_{21}N_2O_2^+$) requires *m/z* 213.1598, found *m/z* 213.1604.

Preparation and characterisation of (*R,*S**)-1-nitrooctahydro-1*H*-pyrrolo[1,2-*a*]azepine (101h)**



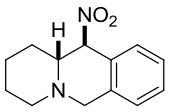
Prepared according to general procedure **O** using **100h** (0.81 g, 0.40 mmol). Purification by FCC to yield the title compound **101h** (0.049 g, 61%, d.r. 55:45) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1546 (NO$_2$), 1376 (NO$_2$); **^{1}H NMR** (400 MHz, $CDCl_3$) – major diastereomer: δ_H 4.58 (ddd, *J* = 8.5, 5.5, 3.0, 1H, NO$_2$CH), 3.01 – 3.14 (m, 2H, NCH$_a$H$_b$CH$_2$CHNO$_2$, NCH$_a$H$_b$CH$_2$CH$_2$), 2.90 (ddd, *J* = 10.5, 5.5, 3.0, 1H, NCHCHNO$_2$), 2.78 (ddd, *J* = 10.5, 9.5, 7.0, 1H, NCH$_a$H$_b$CH$_2$CHNO$_2$), 2.22 - 2.44 (m, 3H, NCH$_2$CH$_a$H$_b$CHNO$_2$, NCH$_a$H$_b$CH$_2$CH$_2$), 2.06 - 2.14 (m, 1H, NCH(C)CH$_a$H$_b$), 1.51 - 1.80 (m, 7H); minor diastereomer observable: 5.00 ("td", *J* = 8.0, 4.5, 1H), 3.29 ("td", *J* = 8.5, 2.5, 1H), 2.65 (ddd, *J* = 10.0, 7.5, 2.5, 1H), 2.57 ("ddt", *J* = 13.5, 9.0, 4.5, 1H), 1.29 – 1.39 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) major diastereomer: δ_C 92.0 (NO$_2$CH), 70.8 (NCHCHNO$_2$), 55.7 (NCH$_2$CH$_2$CHNO$_2$), 54.8 (NCH$_2$CH$_2$CH$_2$), 34.1 (NCH(C)CH$_2$), 29.5 (NO$_2$CHCH$_2$CH$_2$N), 28.2, 25.7, 25.4; minor diastereomer observable: 90.2, 67.0, 54.9, 54.3, 28.8, 28.3, 26.9, 26.2, 24.3***m/z*** (ESI$^+$) 185 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_9H_{17}N_2O_2^+$) requires *m/z* 185.12845, found *m/z* 185.12844.

Preparation and characterisation of (*R,*S**)-1-nitrodecahydropyrrolo[1,2-*a*]azocine (101i)**



Prepared according to general procedure **O** using **100i** (0.084 g, 0.39 mmol). Purification by FCC to yield the title compound **101i** (0.048 g, 62%, d.r. 67:33)* as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1545 (NO_2), 1373 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H – major diastereomer: 4.57 (ddd, *J* = 8.0, 4.5, 2.5, 1H, NO_2CH), 3.14 (m, 2H, $CH_aH_bCH_2CHNO_2$, $NCHCHNO_2$), 2.87 ("dt", *J* = 13.5, 6.5, 1H, $CH_aH_bCH_2CHNO_2$), 2.80 (ddd, *J* = 11.0, 9.0, 7.0, 1H, $NCH_aH_bCH_2CH_2$), 2.55 ("dt", *J* = 13.0, 5.0, 1H, $NCH_aH_bCH_2CH_2$), 2.30 - 2.37 (m, 1H, $CH_aH_bCHNO_2$), 2.16 – 2.27 (m, 1H, $CH_aH_bCHNO_2$), 1.44 - 1.85 (m, 10H); minor diastereomer observable: 4.92 – 5.00 (m, 1H, NO_2CH), 3.23 – 3.34 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C – major diastereomer: 91.8 ($CHNO_2$), 68.2 ($NCHCHNO_2$), 55.5 ($NCH_2CH_2CH_2$), 54.8 ($NCH_2CH_2CHNO_2$), 33.6, 29.3 ($NCH_2CH_2CHNO_2$), 27.6, 26.8, 25.8, 22.7; minor diastereomer observable: 89.2 (NO_2CH), 65.3 ($NCHCHNO_2$), 54.3, 28.1, 27.8, 26.9, 25.5, 23.4; ***m/z*** (ESI^+) 199 ([M+H]); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{19}N_2O_2^+$) requires *m/z* 199.14410, found *m/z* 199.14400.

Preparation and characterisation of (*R,*S**)-11-nitro-1,3,4,6,11,11a-hexahydro-2*H*-pyrido[1,2-*b*]isoquinoline (101j)**

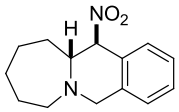


Prepared according to general procedure **O** using **100j** (0.84 g, 0.34 mmol). Purification by FCC to yield the title compound **101j** (0.062 g, 79%, d.r. >98:2) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1544 (NO_2), 1351 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.30 (t, *J* = 7.5, 1H, ArH), 7.24 (t, *J* = 7.5, 1H, ArH), 7.19 (d, *J* = 7.5, 1H, ArH), 7.13 (d, *J* = 7.5, 1H, ArH),

* d.r. represented in the spectra provided in the section below shows a higher d.r.. However, this may be due to the minor diastereomer decomposing in the NMR tube.

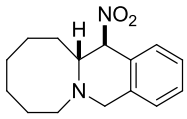
5.65 (d, *J* = 9.0, 1H, $NO_2C\underline{H}$), 3.81 (d, *J* = 15.5, 1H, $NC\underline{H_a}H_bAr$), 3.62 (d, *J* = 15.5, 1H, $NCH_a\underline{H_b}Ar$), 3.05 – 3.10 (m, 1H, $NC\underline{H_a}H_bCH_2CH_2$), 2.88 – 2.93 (m, 1H, $NC\underline{H}CHNO_2$), 2.30 (t, *J* = 11.5, 1H, $NCH_a\underline{H_b}CH_2CH_2$), 1.95 – 2.02 (m, 1H, $NCH(C)C\underline{H_a}H_b$), 1.80 - 1.88 (m, 1H, $NCH_2CH_2C\underline{H_a}H_b$), 1.58 - 1.78 (m, 2H, $NCH_2C\underline{H_a}\underline{H_b}$), 1.49 - 1.58 (m, 1H, $NCH(C)CH_a\underline{H_b}$), 1.32 - 1.43 (m, 1H, $NCH_2CH_2CH_a\underline{H_b}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 135.1 ($Ar\underline{C}_{quat}$), 129.0 ($Ar\underline{C}H$), 127.8 ($Ar\underline{C}_{quat}$), 127.3 ($Ar\underline{C}H$), 126.4 ($Ar\underline{C}H$), 126.0 ($Ar\underline{C}H$), 91.6 ($NO_2\underline{C}H$), 62.0 ($N\underline{C}H(C)$), 57.6 ($N\underline{C}H_2Ar$), 55.6 ($N\underline{C}H_2CH_2CH_2$), 30.6 ($NCH(C)\underline{C}H_2$), 25.1 ($NCH_2\underline{C}H_2$), 23.1 ($NCH_2CH_2\underline{C}H_2$); ***m/z*** ($ESI^+$) 233 ($[M+H]^+$), **HRMS** ($ES^+$) exact mass calculated for $[M+Na]^+$ ($C_{13}H_{16}N_2NaO_2^+$) requires *m/z* 255.1104, found *m/z* 255.1104.

Preparation and characterisation of (*R*,S**)-12-nitro-5,7,8,9,10,11,11a,12-octahydroazepino[1,2-*b*]isoquinoline (101k)



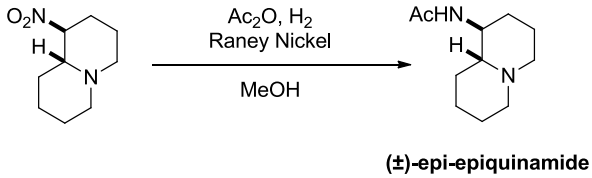
Prepared according to general procedure **O** using **100k** (0.115 g, 0.440 mmol). Purification by FCC to yield the title compound **101k** (0.087 g, 81%, d.r. >98:2) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1547 (NO_2), 1360 (NO_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.11 – 7.30 (m, 3H, Ar$\underline{H}$), 7.06 (d, *J* = 7.5, 1H, Ar$\underline{H}$), 5.50 (d, *J* = 7.0, 1H, $NO_2C\underline{H}$), 3.92 (d, *J* = 15.5, 1H, $NCH_a\underline{H_b}Ar$), 3.84 (d, *J* = 15.5, 1H, $NC\underline{H_a}H_bAr$), 3.44 – 3.51 (m, 1H, $NC\underline{H}CHNO_2$), 2.80 – 2.95 (m, 2H, $NC\underline{H_2}CH_2$), 1.45 - 1.77 (m, 8H);**^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 136.7 ($Ar\underline{C}_{quat}$), 128.9 ($Ar\underline{C}H$), 128.1 ($Ar\underline{C}_{quat}$), 128.1 ($Ar\underline{C}H$), 126.9 ($Ar\underline{C}H$), 126.5 ($Ar\underline{C}H$), 89.9 ($NO_2\underline{C}H$), 63.0 ($NO_2CH\underline{C}H$), 55.1 ($N\underline{C}H_2$), 54.9 ($N\underline{C}H_2$), 29.4, 28.3, 28.1, 25.0; ***m/z*** (ESI^+) 247 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{19}N_2O_2^+$) requires *m/z* 247.1441, found *m/z* 247.1443.

Preparation and characterisation of (R*,S*)-13-nitro-7,8,9,10,11,12,12a,13-octahydro-5*H*-azocino[1,2-*b*]isoquinoline (101l)



Prepared according to general procedure **O** using **100l** (0.100 g, 0.36 mmol). Purification by FCC to yield the title compound **101l** (0.049 g, 52%, d.r. >96:4) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1544 (NO_2), 1363 (NO_2); **^{1}H NMR** (500 MHz, C_6D_6) δ_H 6.98 – 7.03 (m, 2H, ArH), 6.92 (t, *J* = 7.5, 1H, Ar<u>H</u>), 6.74 (d, *J* = 7.5, 1H, Ar<u>H</u>), 5.19 (d, *J* = 6.5, 1H, NO_2C<u>H</u>), 3.71 (ddd, *J* = 9.5, 6.5, 3.5, 1H, NC<u>H</u>CH_2Ar), 3.66 (d, *J* = 16.0, 1H, NCHC<u>H$_a$</u>H_bAr), 3.44 (d, *J* = 16.0, 1H, NCHCH_a<u>H$_b$</u>Ar), 2.36 – 2.50 (m, 2H, NC<u>H$_2$</u>CH_2), 1.16 - 1.59 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 136.4 (Ar<u>C$_{quat}$</u>), 129.1 (Ar<u>C</u>H), 128.7 (Ar<u>C</u>H), 128.2 (Ar<u>C$_{quat}$</u>), 126.8 (Ar<u>C</u>H), 126.6 (Ar<u>C</u>H), 89.1 (NO_2<u>C</u>H), 61.0 (NC<u>H</u>$CHNO_2$), 53.2 (N<u>C</u>H_2Ar), 51.7 (N<u>C</u>H_2CH_2), 28.9, 27.2, 27.1, 26.7, 26.6; ***m/z*** (ESI$^+$) 261 ([M+H]$^+$); **HRMS** (ESI$^+$) exact mass calculated for [M+H]$^+$ ($C_{15}H_{21}N_2O_2^+$) requires *m/z* 261.15975, found *m/z* 261.15953.

Preparation and characterisation of *N*-(octahydro-2*H*-quinolizin-1-yl)acetamide ((±)-*epi*-epiquinamide)

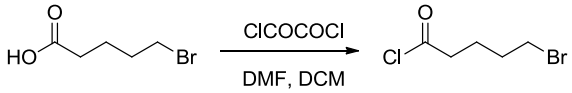


To **101c** (90 mg, 0.49 mmol) dissolved in methanol (5 ml) was added acetic anhydride (230 µl, 2.45 mmol) followed by an Raney 2400 nickel slurry in water (420 µl) under nitrogen. The atmosphere was then exchanged for hydrogen (purging 3 times) and the reaction was stirred for 40 h. The reaction atmosphere was changed back to nitrogen the reaction mixture was filtered through celite, washing with methanol. Concentration of the filtrate *in vacuo* afforded crude (±)-*epi*-epiquinamide, which was purified by FCC (20-50% MeOH in EtOAc) giving the title compound (±)-*epi*-epiquinamide (72 mg, 75%, d.r. >98:2) as a white solid (m.p. 172-

174 °C), literature m.p. 170-175 ºC.[12] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.13 (br. s., 1H, N<u>H</u>Ac), 3.64 - 3.84 (m, 1H, C<u>H</u>NHAc), 2.87 (d, *J* = 11.5, 1H, NC<u>H$_c$</u>H$_d$), 2.78 (d, *J* = 11.0, 1H, NC<u>H$_a$</u>H$_b$), 1.94 - 2.06 (m, 6H), 1.47 - 1.88 (m, 7H), 1.06 - 1.35 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.4 (<u>C</u>O), 67.3 (N<u>C</u>H), 56.4 (N<u>C</u>H$_2$), 55.7 (N<u>C</u>H$_2$), 51.0 (<u>C</u>HNHAc), 32.0, 29.0, 25.5, 24.3, 23.9, 23.4 (Ac); ***m/z*** (ESI$^+$) 197 ([M+H]$^+$); Data in agreement with that reported previously in the literature.[12]

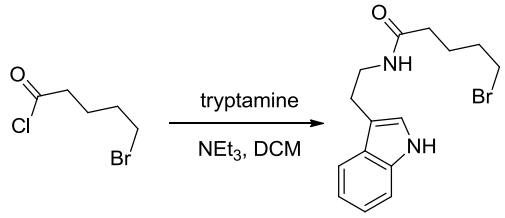
5.3 Chapter 3: Thesis Experimental

Preparation and characterisation of 5-bromopentanoyl chloride



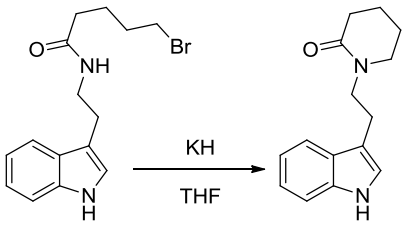
To a solution of 5-bromopentanoic acid (1 eq.) in dichloromethane (5ml/mmol of acid) at 0 °C was added oxalylchloride (5eq) and DMF (1 eq.). The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated *in vacuo* and used without purification in the next step.

Preparation and characterisation of 5-bromo-*N*-[2-(1*H*-indol-3-yl)ethyl]pentanamide (124c)



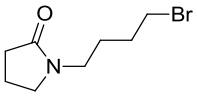
To a solution of 5-bromopentanoyl chloride (1 eq) in dichloromethane (1 ml/mmol of chloride) at 0 °C was slowly added a mixture of tryptamine (1 eq) and triethylamine (2 eq) in dichlorormethane (5 ml/mmol) and stirred for 1h at 0 °C the reaction was allowed to warm to room temperature and stirred for a further hour. The reaction was diluted with DCM and washed with HCl (1M), saturated $NaHCO_3$ and brine. The organics were concentrated *in vacuo,* passed though a plug of silica affording used without purification in the next step.

Preparation and characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]piperidin-2-one (123c)



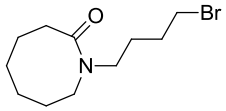
Potassium hydride (30% in mineral oil, 3.5 eq) was washed 3 times with hexane under nitrogen and suspended in THF. The mixture was heated to 60 °C and indole bromide **124c** (1eq) was added in THF via syringe pump over 30 mins and stirred for a further 30 mins at 60 °C. The reaction was cooled to 0 °C with an ice bath. HCl (4M) was added to neutralise the reaction. The mixture was subsequently extracted with DCM, washed with brine, dried over $NaSO_4$ and concentrated *in vacuo.* Purification by FCC yielded **123c** (25% over 3 steps) as an off white solid. **m.p.** 151 - 153 °C; **IR** ν_{max}(film)/cm^{-1} 1612 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.42 (br s, 1H, NH), 7.67 (d, *J* = 8.0, 1H, ArH), 7.37 (d, *J* = 8.0, 1H, ArH), 7.19 (t, *J* = 7.5, 1H, ArH), 7.13 (t, *J* = 7.5, 1H, ArH), 7.04 (d, *J* = 2, 1H, ArH), 3.67 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 3.17 (t, *J* = 6.0, 2H, $NC(O)(CH_2)_3CH_2$), 3.05 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 2.41 (t, *J* = 6.5, 2H, $NC(O)CH_2$), 1.65 – 1.77 (m, 4H, $NC(O)CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.8 (NC(O)), 136.2 (ArC_{quat}), 127.5 (ArC_{quat}), 122.0 (ArCH), 121.8 (ArCH), 119.2 (ArCH), 118.7 (ArCH), 113.1 (ArC_{quat}), 111.2 (ArCH), 48.6 ($NC(O)(CH_2)_3CH_2$), 48.4 (NCH_2CH_2Ar), 32.4 ($NC(O)CH_2$), 23.2, 23.0, 21.2; ***m/z*** (ESI^+) 243 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}ON_2^+$) requires *m/z* 243.14919, found *m/z* 243.14882.

Preparation and characterisation of 5,5-Br (1-(4-bromobutyl)pyrrolidin-2-one) (103b)



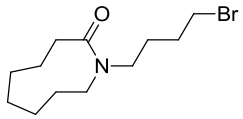
Prepared according to general procedure **J** yielded **103b** (65%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1663 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.42 (t, *J* = 6.5, 2H, CH_2Br), 3.37 (t, *J* = 7.0, 2H, $C(O)CH_2CH_2CH_2$), 3.29 (t, *J* = 7.0, 2H, $CH_2(CH_2)_3Br$), 2.38 (t, *J* = 8.0, 2H, $C(O)CH_2$), 1.97 - 2.05 (m, 2H, $C(O)CH_2CH_2$), 1.79 - 1.86 (m, 2H, CH_2CH_2Br), 1.63 - 1.71 (m, 2H, $CH_2(CH_2)_2Br$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.1 (C(O)), 47.0 ($C(O)(CH_2)_2CH_2$), 41.4 ($CH_2(CH_2)_3Br$), 33.2 (CH_2Br), 30.9 ($C(O)CH_2$), 29.6 (CH_2CH_2Br), 25.6 ($CH_2(CH_2)_2Br$), 17.8 ($C(O)CH_2CH_2$); ***m/z*** (ESI$^+$) 220 ($[M+H]^+$); **HRMS** (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_8H_{15}BrNO$) requires *m/z* 220.03315 and 222.03111, found *m/z* 220.03304 and 222.03095.

Preparation and characterisation of (1-(4-bromobutyl)azocan-2-one) (103d)



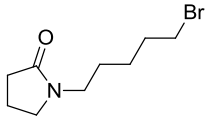
Prepared according to general procedure **J** yielded **103d** (83%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1624 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.40 – 3.49 (m, 4H, CH_2Br, $C(O)(CH_2)_5CH_2$), 3.34 (m, 2H, $Br(CH_2)_3CH_2$), 2.48 – 2.53 (m, 2H, $C(O)CH_2$), 1.76 – 1.90 (m, 4H, $BrCH_2CH_2$, $C(O)CH_2CH_2$), 1.63 – 1.74 (m, 4H, $C(O)(CH_2)_4CH_2$, $CH_2(CH_2)_2Br$), 1.43 – 1.57 (m, 4H, $C(O)(CH_2)_2CH_2$, $C(O)(CH_2)_3CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.0 (C(O)), 47.0 ($C(O)(CH_2)_5CH_2$), 44.2 ($Br(CH_2)_3CH_2$), 33.7 ($C(O)CH_2$), 33.4 (CH_2Br), 30.0 (CH_2CH_2Br), 29.3 ($C(O)(CH_2)_4CH_2$), 28.6 ($C(O)CH_2CH_2$), 26.3 ($CH_2(CH_2)_2Br$), 26.2 ($C(O)(CH_2)_2CH_2$), 24.3 ($C(O)(CH_2)_3CH_2$); ***m/z*** (ESI$^+$) 262 ($[M+H]^+$); **HRMS** (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}BrNO^+$) requires *m/z* 262.08010 and 264.07806, found *m/z* 262.07987 and 264.07774.

Preparation and characterisation of (1-(4-bromobutyl)azonan-2-one) (103m)



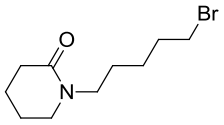
Prepared according to general procedure **J** yielded **103m** (73%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1624 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.45 – 3.50 (m, 2H, $C(O)(CH_2)_6CH_2$), 3.42 (t, *J* = 6.5, 2H, $BrCH_2$), 3.33 (t, *J* = 7.0, 2H, $CH_2(CH_2)_3Br$), 2.48 – 2.53 (m, 2H, $C(O)CH_2$), 1.75 – 1.89 (m, 4H, CH_2CH_2Br, $C(O)CH_2CH_2$), 1.62 – 1.74 (m, 4H, CH_2CH_2Br, $C(O)(CH_2)_5CH_2$), 1.43 – 1.59 (m, 6H, $C(O)(CH_2)_2CH_2$, $C(O)(CH_2)_3CH_2$, $C(O)(CH_2)_4CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.3 (C(O)), 48.2 ($C(O)(CH_2)_6CH_2$), 44.0 ($Br(CH_2)_3CH_2$), 34.6 ($C(O)CH_2$), 33.4 (CH_2Br), 30.0 (CH_2CH_2Br), 28.2, 26.7 ($C(O)(CH_2)_5CH_2$), 25.8 ($Br(CH_2)_2CH_2$), 25.4, 24.6 ($C(O)CH_2CH_2$), 22.0; ***m/z*** (ESI$^+$) 276 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{12}H_{23}BrNO^+$) requires *m/z* 276.09575 and 278.09371, found *m/z* 276.09514 and 278.09300.

Preparation and characterisation of (1-(5-bromopentyl)pyrrolidin-2-one) (103f)



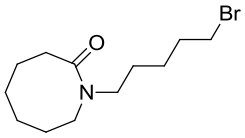
Prepared according to general procedure **J** yielded **103f** (65%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1672 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.36 – 3.43 (m, 4H, CH_2Br and $C(O)(CH_2)_2CH_2$), 3.30 (t, *J* = 7.0, 2H, $CH_2(CH_2)_4Br$), 2.40 (t, *J* = 8.0, 2H, $C(O)CH_2$), 1.99 - 2.07 (m, 2H, $C(O)CH_2CH_2$), 1.86 - 1.93 (m, 2H, CH_2CH_2Br), 1.53 - 1.60 (m, 2H, $CH_2(CH_2)_3Br$) 1.41 – 1.50 (m, 2H, $CH_2(CH_2)_2Br$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.9 (C(O)), 47.1 ($C(O)(CH_2)_2CH_2$), 42.2 ($CH_2(CH_2)_3Br$), 33.5 (CH_2Br), 32.2 ($BrCH_2CH_2$), 31.0 ($C(O)CH_2$), 26.4 ($CH_2(CH_2)_3Br$), 25.3 ($CH_2(CH_2)_2Br$), 17.9 ($C(O)CH_2CH_2$); ***m/z*** (ESI$^+$) 234 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_9H_{17}BrNO^+$) requires *m/z* 234.04880, found *m/z* 234.04870.

Preparation and characterisation of (1-(5-bromopentyl)piperidin-2-one) (103n)



Prepared according to general procedure **J** yielded **103n** (72%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1622 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.39 (t, *J* = 7.0 2H, CH_2Br), 3.34 (t, *J* = 7.5, 2H, $Br(CH_2)_4CH_2$) 3.25 (t, *J* = 5.5, 2H, $C(O)(CH_2)_3CH_2$), 2.36 (t, *J* = 6.0, 2H, $C(O)CH_2$),1.87 (quin, *J* = 7.0, 2H, $BrCH_2CH_2$), 1.73 – 1.82 (m, 4H, $C(O)CH_2CH_2$, $C(O)(CH_2)_2CH_2$), 1.51 - 1.60 (m, 2H, $CH_2(CH_2)_3Br$) 1.39 – 1.47 (m, 2H, $CH_2(CH_2)_2Br$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.7 (C(O)), 47.8 ($C(O)(CH_2)_3CH_2$), 46.8 ($Br(CH_2)_4CH_2$), 33.6 (CH_2Br), 32.3, 32.2 , 26.0 ($CH_2(CH_2)_3Br$), 25.3 ($CH_2(CH_2)_2Br$), 23.2, 21.2; ***m/z*** (ESI$^+$) 248 ($[M+H]^+$); **HRMS** (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{10}H_{19}BrNO$) requires *m/z* 248.06445 and 250.06241, found *m/z* 248.06416 and 250.06201.

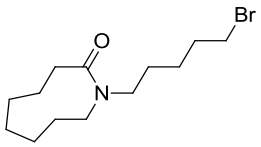
Preparation and characterisation of (1-(5-bromopentyl)azocan-2-one) (103o)



Prepared according to general procedure **J** yielded **103o** (72%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1625 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.42 – 3.46 (m, 2H, $C(O)(CH_2)_5CH_2$), 3.48 (t, *J* = 7.0, 2H, $BrCH_2$), 3.29 (t, *J* = 7.5, 2H, $CH_2(CH_2)_4Br$), 2.47 – 2.51 (m, 2H, $C(O)CH_2$), 1.86 (m, 2H, CH_2CH_2Br), 1.75 – 1.81 (m, 2H, $C(O)CH_2CH_2$), 1.38 – 1.66 (m, 10H, $CH_2(CH_2)_2Br$, $CH_2(CH_2)_3Br$, $C(O)(CH_2)_2CH_2$, $C(O)(CH_2)_3CH_2$, $C(O)(CH_2)_4CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.9 (C(O)), 47.2 ($C(O)(CH_2)_5CH_2$), 45.2 ($Br(CH_2)_4CH_2$), 33.7 ($C(O)CH_2$), 33.6 (CH_2Br), 32.3 (CH_2CH_2Br), 29.3 ($C(O)(CH_2)_4CH_2$), 28.6 ($C(O)CH_2CH_2$), 26.8 ($CH_2(CH_2)_3Br$), 26.1, 25.5, 24.3; ***m/z*** (ESI$^+$) 276

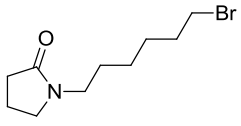
([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{12}H_{23}BrNO^+$) requires *m/z* 276.09575 and 278.09371, found *m/z* 276.09524 and 278.09309.

Preparation and characterisation of (1-(5-bromopentyl)azonan-2-one) (103p)



Prepared according to general procedure **J** yielded **103p** (75%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1627 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.47 – 3.51 (m, 2H, $C(O)(CH_2)_6CH_2$), 3.41 (t, *J* = 7.0, 2H, $BrCH_2$), 3.30 (t, *J* = 7.5, 2H, $CH_2(CH_2)_4Br$), 2.48 – 2.53 (m, 2H, $C(O)CH_2$), 1.89 (quin, *J* = 7.0, 2H, CH_2CH_2Br), 1.77 – 1.84 (m, 2H, $C(O)CH_2CH_2$), 1.41 – 1.69 (m, 12H, $Br(CH_2)_2CH_2$, $Br(CH_2)_3CH_2$, $C(O)(CH_2)_2CH_2$, $C(O)(CH_2)_3CH_2$, $C(O)(CH_2)_4CH_2$, $C(O)(CH_2)_5CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.2 (C(O)), 48.4 ($C(O)(CH_2)_6CH_2$), 45.0 ($Br(CH_2)_4CH_2$), 34.7 ($C(O)CH_2$), 33.7 (CH_2Br), 32.4 (CH_2CH_2Br), 28.3, 26.9, 26.5, 25.6, 25.6, 24.7 ($C(O)CH_2CH_2$), 22.1; ***m/z*** (ESI$^+$) 290 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{13}H_{25}BrNO^+$) requires *m/z* 290.11140 and 292.10936, found *m/z* 290.11103 and 292.10888.

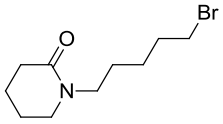
Preparation and characterisation of (1-(6-bromohexyl)pyrrolidin-2-one) (103q)



Prepared according to general procedure **J** yielded **103q** (63%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1676 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.33 – 3.41 (m, 4H, CH_2Br, $C(O)(CH_2)_2CH_2$), 3.25 (t, *J* = 7.5, 2H, $CH_2(CH_2)_5Br$), 2.37 (t, *J* = 8.0, 2H, $C(O)CH_2$), 2.00 (m, 2H, $C(O)CH_2CH_2$), 1.84 (quin, *J* = 7.0, 2H, CH_2CH_2Br), 1.40 - 1.56 (m, 4H, $CH_2(CH_2)_4Br$, $CH_2(CH_2)_2Br$) 1.26 – 1.34 (m, 2H, $CH_2(CH_2)_3Br$); **^{13}C NMR** (100 MHz,

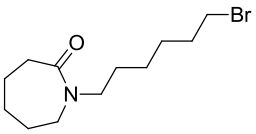
$CDCl_3$) δ_C 174.8 (C(O)), 47.0 ($C(O)(CH_2)_2CH_2$), 42.3 ($CH_2(CH_2)_3Br$), 33.7 (CH_2Br), 32.6 ($BrCH_2CH_2$), 31.0 ($C(O)CH_2$), 27.7 ($CH_2(CH_2)_2Br$), 27.0 ($CH_2(CH_2)_4Br$), 25.9 ($CH_2(CH_2)_3Br$), 17.9 ($C(O)CH_2CH_2$; ***m/z*** (ESI^+) 248 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{19}BrNO^+$) requires *m/z* 248.06445 and 250.06241, found *m/z* 248.06432 and 250.06214.

Preparation and characterisation of (1-(6-bromohexyl)piperidin-2-one) (103r)



Prepared according to general procedure **J** yielded **103r** (71%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1632 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.39 (t, *J* = 7.0, 2H, CH_2Br), 3.34 (t, *J* = 7.5, 2H, $Br(CH_2)_5CH_2$) 3.26 (t, *J* = 5.5, 2H, $C(O)(CH_2)_3CH_2$), 2.36 (t, *J* = 6.0, 2H, $C(O)CH_2$), 1.74 – 1.88 (m, 6H, $BrCH_2CH_2$, $C(O)CH_2CH_2$, $C(O)(CH_2)_2CH_2$), 1.54 (quin, *J* = 7.5, 2H, $CH_2(CH_2)_4Br$) 1.46 (m, 2H, $CH_2(CH_2)_2Br$), 1.28 – 1.36 (m, 2H, $CH_2(CH_2)_3Br$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.6 (C(O)), 47.8 ($C(O)(CH_2)_3CH_2$), 47.0 ($Br(CH_2)_5CH_2$), 33.8 (CH_2Br), 32.6 (CH_2CH_2Br), 32.2 ($C(O)CH_2$) , 27.9 ($CH_2(CH_2)_2Br$), 26.8 ($CH_2(CH_2)_4Br$), 26.0 ($CH_2(CH_2)_3Br$), 23.2, 21.3; ***m/z*** (ESI^+) 262 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}BrNO$) requires *m/z* 262.08010 and 264.07806, found *m/z* 262.07980 and 264.07763.

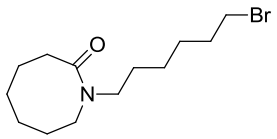
Preparation and characterisation of (1-(6-bromohexyl)azepan-2-one) (103s)



Prepared according to general procedure **J** yielded **103s** (72%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1636 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.30 – 3.41 (m, 6H, CH_2Br,

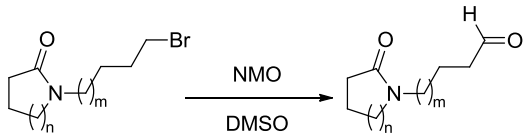
$Br(CH_2)_3CH_2$, $C(O)(CH_2)_4CH_2$), 2.48 – 2.52 (m, 2H, $C(O)CH_2$), 1.84 (m, 2H, $BrCH_2CH_2$), 1.58 – 1.75 (m, 6H, $C(O)CH_2CH_2$, $C(O)(CH_2)_2CH_2$, $C(O)(CH_2)_3CH_2$), 1.40 – 1.54 (m, 4H, $CH_2(CH_2)_2Br$, $CH_2(CH_2)_4Br$), 1.26 – 1.34 (m, 2H, $CH_2(CH_2)_3Br$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.6 (C(O)), 49.5 ($C(O)(CH_2)_4CH_2$), 48.0 ($Br(CH_2)_4CH_2$), 37.2 ($C(O)CH_2$), 33.8 (CH_2Br), 32.6 (CH_2CH_2Br), 29.9, 28.7, 27.9 ($CH_2(CH_2)_2Br$), 27.9 ($CH_2(CH_2)_4Br$), 26.0 ($CH_2(CH_2)_3Br$), 23.4; ***m/z*** (ESI^+) 276 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{23}BrNO^+$) requires *m/z* 276.09575 and 278.09371, found *m/z* 276.09546 and 278.09334.

Preparation and characterisation of (1-(6-bromohexyl)azocan-2-one) (103t)



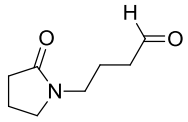
Prepared according to general procedure **J** yielded **103t** (73%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1627 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.43 – 3.47 (m, 2H, $C(O)(CH_2)_5CH_2$), 3.39 (t, *J* = 7.0, 2H, $BrCH_2$), 3.29 (t, *J* = 7.5, 2H, $CH_2(CH_2)_5Br$), 2.47 – 2.52 (m, 2H, $C(O)CH_2$), 1.76 – 1.88 (m, 4H, CH_2CH_2Br and $C(O)CH_2CH_2$), 1.64 (quin, *J* = 6.0, 2H, $C(O)(CH_2)_4CH_2$), 1.42 – 1.60 and 1.27 – 1.35 (m, 8H and m, 2H, $CH_2(CH_2)_2Br$, $CH_2(CH_2)_3Br$, $C(O)(CH_2)_4CH_2$, $C(O)(CH_2)_2CH_2$, $C(O)(CH_2)_3CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.8 (C(O)), 47.0 ($C(O)(CH_2)_5CH_2$), 45.3 ($Br(CH_2)_5CH_2$), 33.8 ($C(O)CH_2$), 33.8 (CH_2Br), 32.6 (CH_2CH_2Br), 29.3 ($C(O)(CH_2)_4CH_2$), 28.7 ($C(O)CH_2CH_2$), 27.8, 27.6, 26.2, 26.2, 24.3; ***m/z*** (ESI^+) 290 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{25}BrNO^+$) requires *m/z* 290.11140 and 292.10936, found *m/z* 290.11112 and 292.10895.

General procedure P for the synthesis of aldehyde tethered lactams 128



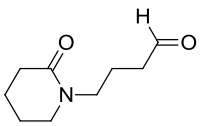
To a solution of bromo-lactam **103** (1 eq) in DMSO (1 ml/mmol of **103**) was added NMO (4 eq) and stirred overnight. The reaction was diluted with dichloromethane and washed with brine. The organics were concentrated *in vacuo* and purified by FCC to afford the desired aldehyde **128**.

Preparation and characterisation of (4-(2-oxopyrrolidin-1-yl)butanal) (128b)[13]



Prepared according to general procedure **P** yielded **128b** (41%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1656 (NC=O), 1719 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.74 (s, 1H, C(O)H), 3.32 – 3.40 (m, 2H, NCH_2), 3.22 – 3.29 (m, 2H, NCH_2), 2.42 – 2.50 (m, 2H, $C(O)CH_2$), 2.30 – 2.39 (m, 2H, $C(O)CH_2$), 1.91 – 2.05 (m, 2H, $NCH_2CH_2CH_2C(O)H$), 1.77 – 1.86 (m, 2H, $NC(O)CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.3 ($CH_2C(O)$), 174.9 (NC(O)), 47.0 (NCH_2), 41.7 (NCH_2), 41.0 ($H(O)CH_2$), 30.8 ($NC(O)CH_2$), 19.6, 17.8; ***m/z*** (ESI$^+$) 156 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_8H_{14}O_2N^+$) requires *m/z* 156.10191, found *m/z* 156.10184. Data matches literature.[13]

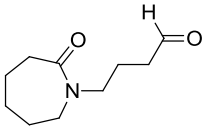
Preparation and characterisation of (4-(2-oxopiperidin-1-yl)butanal) (128c)[14]



Prepared according to general procedure **P** yielded **128c** (50%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1610 (NC=O), 1719 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.77 (s, 1H,

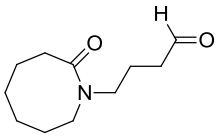
CHO), 3.35 – 3.45 (m, 2H, NCH_2), 3.21 – 3.35 (m, 2H, NCH_2), 2.44 – 2.55 (m, 2H, $C(O)CH_2$), 2.27 – 2.41 (m, 2H, $C(O)CH_2$), 1.70 – 1.92 (m, 6H, $HC(O)CH_2CH_2$, $NC(O)CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.7 (CHO), 169.8 (NC(O)), 47.8 (NCH_2), 46.2 (NCH_2), 41.2 ($C(O)CH_2$), 32.3 ($C(O)CH_2$), 23.2, 21.3 , 19.5; ***m/z*** (ESI^+) 170 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_9H_{16}O_2N^+$) requires *m/z* 170.11756, found *m/z* 170.11747. Data matches literature.[14]

Preparation and characterisation of (4-(2-oxoazepan-1-yl)butanal) (128a)



Prepared according to general procedure **P** yielded **128a** (65%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1601 (NC=O), 1720 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (s, 1H, CHO), 3.30 – 3.43 (m, 4H, $NCH_2(CH_2)_2CHO$, $NC(O)(CH_2)_4CH_2$), 2.24 – 2.52 (m, 2H, CH_2CHO), 2.31 (t, *J* = 7.0, 2H, $NC(O)CH_2$), 1.77 – 1.86 (m, 2H, CH_2CH_2CHO), 1.57 – 1.74 (m, 6H, $NC(O)CH_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.7 (CHO), 175.7 (NC(O)), 49.7 ($NC(O)(CH_2)_4CH_2$), 47.5 ($CH_2(CH_2)_2CHO$), 36.9 (CH_2CHO), 31.4 ($NC(O)CH_2$), 29.8, 28.4, 23.2, 23.2 (CH_2CH_2CHO); ***m/z*** (ESI^+) 184 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{18}O_2N^+$) requires *m/z* 184.13321, found *m/z* 184.13304.

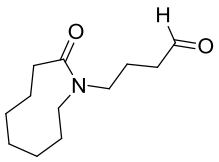
Preparation and characterisation of (4-(2-oxoazocan-1-yl)butanal) (128d)



Prepared according to general procedure **P** yielded **128d** (53%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1615 (NC=O), 1719 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.76 (s, 1H,

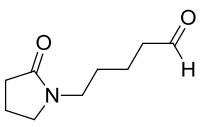
CHO), 3.42 – 3.47 (m, 2H, NC(O)$(CH_2)_5CH_2$), 3.33 (t, *J* = 7.0, 2H, $NCH_2(CH_2)_2CHO$) 2.45 – 2.51 (m, 4H, $NC(O)CH_2$, CH_2CHO), 1.88 (m, 2H, CH_2CH_2CHO), 1.75 – 1.81 (m, 2H, $NC(O)CH_2CH_2$), 1.60 – 1.67 (m, 2H, NC(O)$(CH_2)_4CH_2$) 1.42 – 1.57 (m, 4H, NC(O)$(CH_2)_2CH_2$, NC(O)$(CH_2)_3CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.8 (CHO), 175.1 (NC(O)), 47.1 (NC(O)$(CH_2)_5CH_2$), 44.4 ($NCH_2(CH_2)_2CHO$), 41.3 (CH_2CHO), 33.8 ($NC(O)CH_2$), 29.2 (NC(O)$(CH_2)_4CH_2$), 28.6 ($NC(O)CH_2CH_2$), 26.2, 24.3, 20.3; ***m/z*** (ESI^+) 198 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{20}O_2N^+$) requires *m/z* 198.14886, found *m/z* 198.14855.

Preparation and characterisation of (4-(2-oxoazonan-1-yl)butanal) (128m)



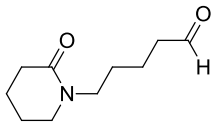
Prepared according to general procedure **P** yielded **128m** (63%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1594 (NC=O), 1721 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (s, 1H, CHO), 3.41 – 3.54 (m, 2H, NCH_2), 3.29 – 3.40 (m, 2H, NCH_2) 2.41 – 2.56 (m, 4H, $NC(O)CH_2$, CH_2CHO), 1.87 (quin, *J* = 7.0, 2H, $HC(O)CH_2CH_2$), 1.72 – 1.82 (m, 2H), 1.59 – 1.69 (m, 2H), 1.39 – 1.58 (m, 6H, $CH_2(CH_2)_2CHO$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.8 (CHO), 175.9 (NC(O)), 48.5 (NCH_2), 44.3 (NCH_2), 41.2 (CH_2CHO), 34.4 ($NC(O)CH_2$), 28.2, 26.7, 25.4, 25.3, 24.6, 22.0; ***m/z*** (ESI^+) 212 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{22}O_2N^+$) requires *m/z* 212.16451, found *m/z* 212.16445.

Preparation and characterisation of (5-(2-oxopyrrolidin-1-yl)pentanal) (128f)[13]



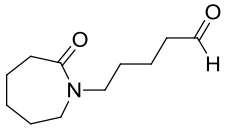
Prepared according to general procedure **P** yielded **128f** (53%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1663 (NC=O), 1719 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.76 (s, 1H, CHO), 3.38 (t, *J* = 7.0, 2H, NC(O)$(CH_2)_2CH_2$), 3.30 (t, *J* = 7.0, 2H, $NCH_2(CH_2)_3$CHO), 2.47 – 2.52 (m, 2H, CH_2CHO), 2.36 – 2.42 (m, 2H, NC(O)CH_2), 1.98 – 2.06 (m, 2H, NC(O)CH_2CH_2), 1.52 – 1.67 (m, 4H, $CH_2CH_2CH_2$CHO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.0 (CHO), 175.1 (NC(O)), 47.0 (NC(O)$(CH_2)_2CH_2$), 43.2 (CH_2CHO), 41.9 ($NCH_2(CH_2)_3$CHO), 31.0 (NC(O)CH_2), 26.6, 19.1, 17.9 (NC(O)CH_2CH_2); ***m/z*** (ESI$^+$) 170 ([M+H]. Data is in accordance with that in the literature.[13]

Preparation and characterisation of (5-(2-oxopiperidin-1-yl)pentanal) (128n)



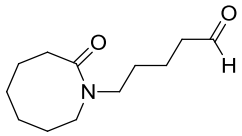
Prepared according to general procedure **P** yielded **128n** (55%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1616 (NC=O), 1719 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.76 (s, 1H, CHO), 3.37 (t, *J* = 7.0, 2H, $NCH_2(CH_2)_3$CHO), 3.23 – 3.28 (m, 2H, NC(O)$(CH_2)_3CH_2$), 2.49 (t, *J* = 6.5, 2H, CH_2CHO), 2.34 – 2.39 (m, 2H, NC(O)CH_2), 1.73 – 1.83 (m, 4H, NC(O)$CH_2CH_2CH_2$), 1.53 – 1.66 (m, 4H, $CH_2CH_2CH_2$CHO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.2 (CHO), 169.7 (NC(O)), 47.8 (NC(O)$(CH_2)_3CH_2$), 46.5 ($NCH_2(CH_2)_3$CHO), 43.4 (CH_2CHO), 32.2 (NC(O)CH_2), 26.4, 23.2, 21.3, 19.2; ***m/z*** (ESI$^+$) 184 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{10}H_{18}O_2N^+$) requires *m/z* 184.13321, found *m/z* 184.13308.

Preparation and characterisation of (5-(2-oxoazepan-1-yl)pentanal) (128g)



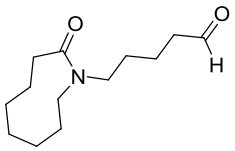
Prepared according to general procedure **P** yielded **128g** (62%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1624 (NC=O), 1720 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (s, 1H, CHO), 3.37 (t, *J* = 7.0, 2H, $NCH_2(CH_2)_3CHO$), 3.29 - 3.34 (m, 2H, $NC(O)(CH_2)_4CH_2$), 2.46 – 2.53 (m, 4H, CH_2CHO, $NC(O)CH_2$), 1.49 – 1.75 (m, 10H, CH_2CH_2CHO, $CH_2(CH_2)_2CHO$, $NC(O)(CH_2)_3CH_2$, $NC(O)(CH_2)_2CH_2$, $NC(O)CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.2 (CHO), 175.8 (NC(O)), 49.5 ($NC(O)(CH_2)_4CH_2$), 47.6 ($NCH_2(CH_2)_3CHO$), 43.4 (CH_2CHO), 37.2 ($NC(O)CH_2$), 29.9, 28.6, 27.4, 23.4, 19.2; ***m/z*** (ESI$^+$) 198 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{11}H_{20}O_2N^+$) requires *m/z* 198.14886, found *m/z* 198.14868.

Preparation and characterisation of (5-(2-oxoazocan-1-yl)pentanal) (128o)



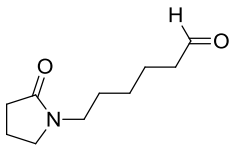
Prepared according to general procedure **P** yielded **128o** (69%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1613 (NC=O), 1720 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (s, 1H, CHO), 3.42 – 3.47 (m, 2H, $NC(O)(CH_2)_5CH_2$), 3.31 (t, *J* = 7.0, 2H, $NCH_2(CH_2)_3CHO$) 2.45 – 2.51 (m, 4H, $NC(O)CH_2$, CH_2CHO), 1.75 – 1.81 (m, 2H, $NC(O)CH_2CH_2$), 1.43 – 1.67 (m, 10H, $NC(O)(CH_2)_2CH_2$,$NC(O)(CH_2)_3CH_2$, $NC(O)(CH_2)_4CH_2$, $CH_2(CH_2)_2CHO$, CH_2CH_2CHO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.4 (CHO), 174.9 (NC(O)), 47.0 ($NC(O)(CH_2)_5CH_2$), 44.7 ($NCH_2(CH_2)_3CHO$), 43.5 (CH_2CHO), 33.9 ($NC(O)CH_2$), 29.3 ($NC(O)(CH_2)_4CH_2$), 28.6 ($NC(O)CH_2CH_2$), 27.2, 26.2 ($NC(O)(CH_2)_2CH_2$), 24.3, 19.4 ($NC(O)(CH_2)_3CH_2$); ***m/z*** (ESI$^+$) 212 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{12}H_{22}O_2N^+$) requires *m/z* 212.16451, found *m/z* 212.16427.

Preparation and characterisation of (5-(2-oxoazonan-1-yl)pentanal) (128p)



Prepared according to general procedure **P** yielded **128p** (52%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1626 (NC=O), 1720 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (s, 1H, CHO), 3.44 – 3.49 (m, 2H, NC(O)$(CH_2)_6CH_2$), 3.28 – 3.34 (m, 2H, $NCH_2(CH_2)_3$CHO) 2.46 – 2.51 (m, 4H, NC(O)CH_2 and CH_2CHO), 1.75 – 1.83 (m, 2H, NC(O)CH_2CH_2), 1.43 – 1.68 (m, 12H, NC(O)$(CH_2)_5CH_2$ NC(O)$(CH_2)_4CH_2$, NC(O)$(CH_2)_3CH_2$ NC(O)$(CH_2)_2CH_2$, CH_2CH_2CHO and $CH_2(CH_2)_2$CHO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.4 (CHO), 175.2 (NC(O)), 48.3 (NC(O)$(CH_2)_6CH_2$), 44.5 ($NCH_2(CH_2)_3$CHO), 43.5 (CH_2CHO), 34.8 (NC(O)CH_2), 28.4, 26.8, 26.7, 25.5, 24.7 (NC(O)CH_2CH_2), 22.0, 19.4; ***m/z*** (ESI$^+$) 226 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{13}H_{24}O_2N^+$) requires *m/z* 226.18016, found *m/z* 226.17995.

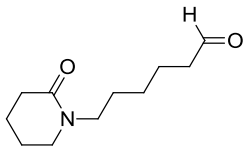
Preparation and characterisation of (6-(2-oxopyrrolidin-1-yl)hexanal) (128q)



Prepared according to general procedure **P** yielded **128q** (41%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1660 (NC=O), 1719 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (s, 1H, CHO), 3.36 (t, *J* = 7.0, 2H, NC(O)$(CH_2)_2CH_2$), 3.26 (t, *J* = 7.5, 2H, $NCH_2(CH_2)_4$CHO), 2.43 (td, *J* = 7.5, 1.5, 2H, CH_2CHO), 2.37 (t, *J* = 8.0, 2H, NC(O)CH_2), 1.96 – 2.04 (m, 2H, NC(O)CH_2CH_2), 1.65 (quin, *J* = 7.5, 2H, CH_2CH_2CHO), 1.53 (quin, *J* = 7.5, 2H, NC(O)CH_2), 1.27 – 1.36 (m, 2H, CH_2CH_2CHO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.3 (CHO), 174.9 (NC(O)), 47.1 (NC(O)$(CH_2)_2CH_2$), 43.7 (CH_2CHO), 42.2 ($NCH_2(CH_2)_4$CHO), 31.0 (NC(O)CH_2), 27.0 ($CH_2(CH_2)_3$CHO), 26.3 ($CH_2(CH_2)_2$CHO), 21.6 (CH_2CH_2CHO), 17.9

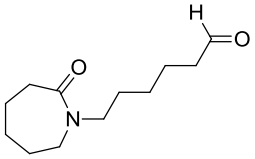
(NC(O)CH_2CH_2); ***m/z*** (ESI^+) 184 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{18}O_2N^+$) requires *m/z* 184.13321, found *m/z* 184.13318.

Preparation and characterisation of (6-(2-oxopiperidin-1-yl)hexanal) (128r)



Prepared according to general procedure **P** yielded **128r** (60%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1619 (NC=O), 1720 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.74 (s, 1H, CHO), 3.33 (t, *J* = 7.5, 2H, $NCH_2(CH_2)_4CHO$), 3.24 (t, *J* = 5.5, 2H, $NC(O)(CH_2)_3CH_2$), 2.42 (td, *J* = 7.5, 1.5, 2H, CH_2CHO), 2.35 (t, *J* = 6.0, 2H, $NC(O)CH_2$), 1.72 – 1.82 (m, 4H, $NC(O)CH_2CH_2CH_2$), 1.65 (quin, *J* = 7.5, 2H, CH_2CH_2CHO), 1.55 (quin, *J* = 7.5, 2H, $CH_2(CH_2)_3CHO$), 1.28 – 1.35 (m, 2H, CH_2CH_2CHO); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.5 (CHO), 169.5 (NC(O)), 47.8 ($NC(O)(CH_2)_3CH_2$), 46.8 ($NCH_2(CH_2)_4CHO$), 43.7 (CH_2CHO), 32.3 ($NC(O)CH_2$), 26.7 ($CH_2(CH_2)_3CHO$), 26.3 ($CH_2(CH_2)_2CHO$), 23.2, 21.7 (CH_2CH_2CHO), 21.3; ***m/z*** (ESI^+) 198 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{20}O_2N^+$) requires *m/z* 198.14886, found *m/z* 198.14865.

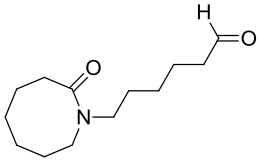
Preparation and characterisation of (6-(2-oxoazepan-1-yl)hexanal) (128s)



Prepared according to general procedure **P** yielded **128s** (62%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1621 (NC=O), 1720 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.74 (s, 1H, CHO), 3.29 – 3.37 (m, 4H, $NCH_2(CH_2)_4CHO$, $NC(O)(CH_2)_4CH_2$), 2.47 – 2.52 (m, 2H, $NC(O)CH_2$), 2.42 (td, *J* = 7.5, 1.5, 2H, CH_2CHO), 1.58 – 1.74 (m, 8H, CH_2CH_2CHO,

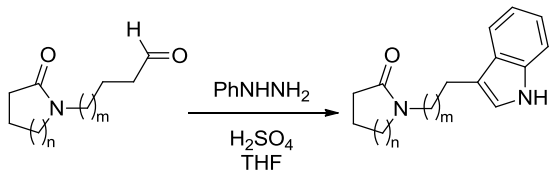
$NC(O)(CH_2)_3CH_2$, $NC(O)(CH_2)_2CH_2$, $NC(O)CH_2CH_2$), 1.51 (quin, *J* = 7.5, 2H, $CH_2(CH_2)_3CHO$), 1.27 – 1.37 (m, 2H, $CH_2(CH_2)_2CHO$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.5 (CHO), 175.7 (NC(O)), 49.5 ($NC(O)(CH_2)_4CH_2$), 47.9 ($NCH_2(CH_2)_4CHO$), 43.7 (CH_2CHO), 37.2 ($NC(O)CH_2$), 29.9, 28.6, 27.8, 26.3, 23.4, 21.8; ***m/z*** (ESI^+) 212 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{22}O_2N^+$) requires *m/z* 212.16451, found *m/z* 212.16415.

Preparation and characterisation of (6-(2-oxoazocan-1-yl)hexanal) (128t)



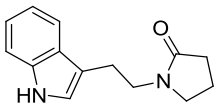
Prepared according to general procedure **P** yielded **128t** (77%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1625 (NC=O), 1721 (HC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.75 (s, 1H, CHO), 3.42 – 3.46 (m, 2H, $NC(O)(CH_2)_5CH_2$), 3.29 (t, *J* = 7.0, 2H, $NCH_2(CH_2)_4CHO$), 2.41 – 2.50 (m, 4H, $NC(O)CH_2$, CH_2CHO), 1.75 – 1.81 (m, 2H, $NC(O)CH_2CH_2$), 1.60 – 1.69 (m, 4H, $NC(O)(CH_2)_4CH_2$, CH_2CH_2CHO), 1.43 – 1.59 (m, 6H, $CH_2(CH_2)_3CHO$, $NC(O)(CH_2)_2CH_2$, $NC(O)(CH_2)_3CH_2$), 1.28 – 1.36 (m, 2H, $CH_2(CH_2)_2CHO$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.6 (CHO), 174.7 (NC(O)), 47.0 ($NC(O)(CH_2)_5CH_2$), 45.0 ($NCH_2(CH_2)_4CHO$), 43.7 (CH_2CHO), 33.9 ($NC(O)CH_2$), 29.3 ($NC(O)(CH_2)_4CH_2$), 28.7 ($NC(O)CH_2CH_2$), 27.5, 26.5, 26.2, 24.3, 21.7 (CH_2CH_2CHO); ***m/z*** (ESI^+) 226 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{24}O_2N^+$) requires *m/z* 226.18016, found *m/z* 226.17995.

General Proceedure Q for Fischer indole synthesis



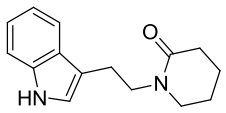
To a stirred mixture of aldehyde **128** (1 eq) and phenylhydrazine (4 eq) was added a mixture of sulphuric acid and THF (1:25 ratio) (2.5 ml/mmol of aldehyde) and heated at reflux for 3 h. The reaction mixture was allowed to cool to room temperature, diluted with DCM and washed with HCl (1M), the aqueous layer was extracted with DCM and the combined organics were concentrated *in vacuo* and purified by FCC affording indole **123**.

Preparation and characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]pyrrolidin-2-one (123b)



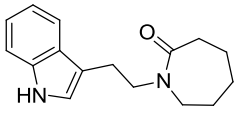
Prepared according to general procedure **Q** yielded **123b** (60%) as a pale brown solid. **m.p.** 135–137 °C; **IR** ν_{max}(film)/cm^{-1} 1656 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.59 (br s, 1H, NH), 7.62 (d, *J* = 8.0, 1H, ArH), 7.37 (d, *J* = 8.0, 1H, ArH), 7.20 (t, *J* = 7.5, 1H, ArH), 7.13 (t, *J* = 7.5, 1H, ArH), 7.04 (d, *J* = 2.0, 1H, ArH), 3.65 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 3.32 (t, *J* = 7.0, 2H, $NC(O)(CH_2)_2CH_2$), 3.02 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 2.39 (t, *J* = 8.0, 2H, $NC(O)CH_2$), 1.90 – 1.97 (m, 2H, $NC(O)CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.0 (NC(O)), 136.2 (ArC_{quat}), 127.3 (ArC_{quat}), 121.9 (ArCH), 121.8 (ArCH), 119.1 (ArCH), 118.4 (ArCH), 112.5 (ArC_{quat}), 111.2 (ArCH), 47.5 ($NC(O)(CH_2)_2CH_2$), 42.9 (NCH_2CH_2Ar), 31.1 ($NC(O)CH_2$), 23.2 (NCH_2CH_2Ar), 17.9 ($NC(O)CH_2CH_2$); ***m/z*** (ESI^+) 229 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}ON_2^+$) requires *m/z* 229.13354, found *m/z* 229.13331.

Preparation and characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]piperidin-2-one (123c)



Prepared according to general procedure Q yielded **123c** (58%) as a pale brown solid. **m.p.** 151–153 °C; **IR** ν_{max}(film)/cm^{-1} 1612 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.42 (br s, 1H, NH), 7.67 (d, *J* = 8.0, 1H, ArH), 7.37 (d, *J* = 8.0, 1H, ArH), 7.19 (t, *J* = 7.5, 1H, ArH), 7.13 (t, *J* = 7.5, 1H, ArH), 7.04 (d, *J* = 2.0, 1H, ArH), 3.67 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 3.17 (t, *J* = 6.0, 2H, $NC(O)(CH_2)_3CH_2$), 3.05 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 2.41 (t, *J* = 6.5, 2H, $NC(O)CH_2$), 1.65 – 1.77 (m, 4H, $NC(O)CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.8 (NC(O)), 136.2 (ArC_{quat}), 127.5 (ArC_{quat}), 122.0 (ArCH), 121.8 (ArCH), 119.2 (ArCH), 118.7 (ArCH), 113.1 (ArC_{quat}), 111.2 (ArCH), 48.6 ($NC(O)(CH_2)_3CH_2$), 48.4 (NCH_2CH_2Ar), 32.4 ($NC(O)CH_2$), 23.2, 23.0, 21.2; ***m/z*** (ESI^+) 243 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}ON_2^+$) requires *m/z* 243.14919, found *m/z* 243.14882.

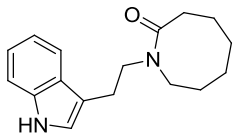
Preparation and characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]azepan-2-one (123a)



Prepared according to general procedure **Q** yielded **123a** (57%) as a pale brown solid. **m.p.** 153 – 156 °C; **IR** ν_{max}(film)/cm^{-1} 1618 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.48 (br s, 1H, NH), 7.67 (d, *J* = 8.0, 1H, ArH), 7.37 (d, *J* = 8.0, 1H, ArH), 7.19 (t, *J* = 7.5, 1H, ArH), 7.13 (t, *J* = 7.5, 1H, ArH), 7.03 (d, *J* = 2.0, 1H, ArH), 3.72 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 3.27 – 3.33 (m, 2H, $NC(O)(CH_2)_4CH_2$), 3.02 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 2.52 – 2.60 (m, 2H, $NC(O)CH_2$), 1.63 – 1.73 (m, 4H, $NC(O)CH_2CH_2CH_2CH_2$), 1.52 – 1.61 (m, 2H, $NC(O)(CH_2)_3CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.8 (NC(O)), 136.3 (ArC_{quat}), 127.5 (ArC_{quat}), 122.1 (ArCH), 121.8 (ArCH), 119.1 (ArCH), 118.6 (ArCH), 113.0 (ArC_{quat}), 111.2 (ArCH), 50.3 ($NC(O)(CH_2)_4CH_2$), 49.3 (NCH_2CH_2Ar), 37.4 ($NC(O)CH_2$), 29.9, 28.5

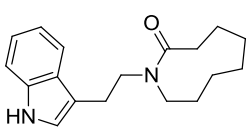
($NC(O)CH_2CH_2CH_2CH_2$), 24.0, 23.4; ***m/z*** (ESI^+) 257 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}ON_2^+$) requires *m/z* 257.16484, found *m/z* 257.16442.

Preparation and characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]azocan-2-one (123d)



Prepared according to general procedure **Q** yielded **123d** (67%) as a pale brown solid. **m.p.** 197–199 °C; **IR** ν_{max}(film)/cm^{-1} 1610 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.36 (br s, 1H, NH), 7.70 (d, *J* = 8.0, 1H, ArH), 7.37 (d, *J* = 8.0, 1H, ArH), 7.19 (t, *J* = 7.5, 1H, ArH), 7.12 (t, *J* = 7.5, 1H, ArH), 7.04 (d, *J* = 2.0, 1H, ArH), 3.64 (t, *J* = 7.5, 2H, $NCH_2(CH_2)_3Ar$), 3.41 (t, *J* = 5.5, 2H, $NC(O)(CH_2)_5CH_2$), 3.06 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 2.51 – 2.57 (m, 2H, $NC(O)CH_2$), 1.80 – 1.88 (m, 2H, $NC(O)CH_2CH_2$), 1.61 – 1.66 (m, 2H, $NC(O)(CH_2)_4CH_2$), 1.45 – 1.59 (m, 4H, $NC(O)(CH_2)_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.8 (NC(O)), 136.3 (ArC_{quat}), 127.5 (ArC_{quat}), 122.0 (ArCH), 121.8 (ArCH), 119.2 (ArCH), 118.8 (ArCH), 113.4 (ArC_{quat}), 111.1 (ArCH), 47.7 ($NC(O)(CH_2)_5CH_2$), 46.6 (NCH_2CH_2Ar), 34.1 ($NC(O)CH_2$), 29.4 ($NC(O)(CH_2)_4CH_2$), 28.7 ($NC(O)CH_2CH_2$), 26.2, 24.4, 23.8 (NCH_2CH_2Ar); ***m/z*** (ESI^+) 271 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}ON_2^+$) requires *m/z* 271.18049, found *m/z* 271.17997.

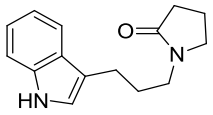
Preparation and characterisation of 1-[2-(1*H*-indol-3-yl)ethyl]azonan-2-one (123m)



Prepared according to general procedure **Q** yielded **123m** (67%) as a pale brown solid. **m.p.** 169 – 171 °C; **IR** ν_{max}(film)/cm^{-1} 1608 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.63 (br s, 1H, NH), 7.69 (d, *J* = 8.0, 1H, ArH), 7.36 (d, *J* = 8.0, 1H, ArH), 7.18 (t, *J* = 7.5, 1H, ArH),

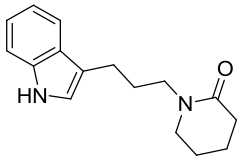
7.12 (t, *J* = 7.5, 1H, ArH), 7.01 (d, *J* = 2.0, 1H, ArH), 3.64 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 3.39 – 3.47 (m, 2H, $NC(O)(CH_2)_6CH_2$), 3.07 (t, *J* = 7.5, 2H, NCH_2CH_2Ar), 2.51 – 2.59 (m, 2H, $NC(O)CH_2$), 1.80 – 1.89 (m, 2H, $NC(O)CH_2CH_2$), 1.45 – 1.69 (m, 8H, $NC(O)CH_2CH_2CH_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.2 (NC(O)), 136.3 (ArC_{quat}), 127.4 (ArC_{quat}), 122.0 (ArCH), 121.7 (ArCH), 119.1 (ArCH), 118.7 (ArCH), 113.1 (ArC_{quat}), 111.2 (ArCH), 48.9 ($NC(O)(CH_2)_6CH_2$), 46.5 (NCH_2CH_2Ar), 34.8 ($NC(O)CH_2$), 28.2, 26.9, 25.5, 24.7 ($NC(O)CH_2CH_2$), 23.3 (NCH_2CH_2Ar), 22.1; ***m/z*** (ESI^+) 285 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}ON_2^+$) requires *m/z* 285.19614, found *m/z* 285.19565.

Preparation and characterisation of 1-[3-(1*H*-indol-3-yl)propyl]pyrrolidin-2-one (123f)



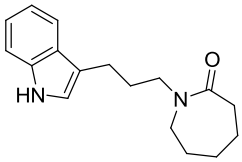
Prepared according to general procedure **Q** yielded **123f** (75%) as a pale brown solid. **m.p.** 103 – 104 °C; **IR** ν_{max}(film)/cm^{-1} 1658 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.46 (br s, 1H, NH), 7.59 (d, *J* = 8.0, 1H, ArH), 7.36 (d, *J* = 8.0, 1H, ArH), 7.19 (t, *J* = 7.5, 1H, ArH), 7.12 (t, *J* = 7.5, 1H, ArH), 7.01 (d, *J* = 2.0, 1H, ArH), 3.33 – 3.42 (m, 4H, $NCH_2(CH_2)_2Ar$, $NC(O)(CH_2)_2CH_2$), 2.78 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 2.40 (t, *J* = 8.0, 2H, $NC(O)CH_2$), 1.90 – 2.03 (m, 4H, $NCH_2CH_2CH_2Ar$, $NC(O)CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.0 (NC(O)), 136.3 (ArC_{quat}), 127.2 (ArC_{quat}), 121.6 (ArCH), 121.6 (ArCH), 118.9 (ArCH), 118.6 (ArCH), 115.1 (ArC_{quat}), 111.2 (ArCH), 47.0 ($NC(O)(CH_2)_2CH_2$), 42.3 ($NCH_2CH_2CH_2Ar$), 31.1 ($NC(O)CH_2$), 27.5 ($NCH_2CH_2CH_2Ar$), 22.4 ($NCH_2CH_2CH_2Ar$), 17.8 ($NC(O)CH_2CH_2$); ***m/z*** (ESI^+) 243 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{19}ON_2^+$) requires *m/z* 243.14919, found *m/z* 243.14897.

Preparation and characterisation of 1-[3-(1*H*-indol-3-yl)propyl]piperidin-2-one (123n)



Prepared according to general procedure **Q** yielded **123n** (38%) as a pale brown solid. **m.p.** 125 – 126 °C; **IR** ν_{max}(film)/cm^{-1} 1613 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.34 (br s, 1H, NH), 7.60 (d, *J* = 8.0, 1H, ArH), 7.36 (d, *J* = 8.0, 1H, ArH), 7.18 (t, *J* = 7.5, 1H, ArH), 7.11 (t, *J* = 7.5, 1H, ArH), 7.03 (d, *J* = 2, 1H, ArH), 3.49 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 3.22 – 3.28 (m, 2H, $NC(O)(CH_2)_3CH_2$), 2.79 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 2.37 – 2.42 (m, 2H, $NC(O)CH_2$), 1.99 (quin, 2H, $NCH_2CH_2CH_2Ar$), 1.74 -1.79 (m, 4H, $NC(O)CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.7 (NC(O)), 136.4 (ArC_{quat}), 127.4 (ArC_{quat}), 121.7 (ArCH), 121.4 (ArCH), 119.0 (ArCH), 118.7 (ArCH), 115.6 (ArC_{quat}), 111.1 (ArCH), 47.8 ($NC(O)(CH_2)_3CH_2$), 47.1 ($NCH_2CH_2CH_2Ar$), 32.4 ($NC(O)CH_2$), 27.2 ($NCH_2CH_2CH_2Ar$), 23.2, 22.5 ($NCH_2CH_2CH_2Ar$), 21.3; ***m/z*** (ESI^+) 257 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}ON_2^+$) requires *m/z* 257.16484, found *m/z* 257.16438.

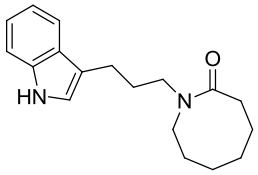
Preparation and characterisation of 1-[3-(1*H*-indol-3-yl)propyl]azepan-2-one (123g)



Prepared according to general procedure **Q** yielded **123g** (51%) as a pale brown solid. **m.p.** 127 – 129 °C; **IR** ν_{max}(film)/cm^{-1} 1623 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.30 (br s, 1H, NH), 7.60 (d, *J* = 8.0, 1H, ArH), 7.36 (d, *J* = 8.0, 1H, ArH), 7.19 (t, *J* = 7.5, 1H, ArH), 7.11 (t, *J* = 7.5, 1H, ArH), 7.04 (d, *J* = 2.0, 1H, ArH), 3.50 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 3.30 – 3.35 (m, 2H, $NC(O)(CH_2)_4CH_2$), 2.78 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 2.52 – 2.58

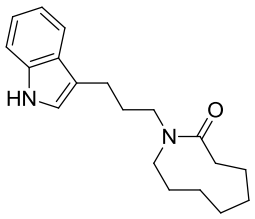
(m, 2H, $NC(O)CH_2$), 1.98 (quin, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 1.59 – 1.76 (m, 6H, $NC(O)CH_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.7 (NC(O)), 136.4 (ArC_{quat}), 127.4 (ArC_{quat}), 121.7 (ArCH), 121.5 (ArCH), 119.0 (ArCH), 118.7 (ArCH), 115.6 (ArC_{quat}), 111.1 (ArCH), 49.6 ($NC(O)(CH_2)_4CH_2$), 48.2 ($NCH_2CH_2CH_2Ar$), 37.4 ($NC(O)CH_2$), 30.0, 28.7, 28.4 ($NCH_2CH_2CH_2Ar$), 23.4, 22.5; ***m/z*** (ESI^+) 271 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}ON_2^+$) requires *m/z* 271.18049, found *m/z* 271.17994.

Preparation and characterisation of 1-[3-(1*H*-indol-3-yl)propyl]azocan-2-one (123o)



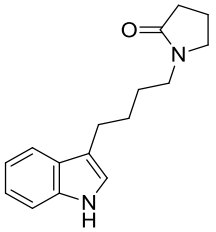
Prepared according to general procedure **Q** yielded **123o** (37%) as a pale brown solid. **m.p.** 101 – 102 °C; **IR** ν_{max}(film)/cm^{-1} 1611 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.44 (br s, 1H, NH), 7.60 (d, *J* = 8.0, 1H, ArH), 7.36 (d, *J* = 8.0, 1H, ArH), 7.18 (t, *J* = 7.5, 1H, ArH), 7.10 (t, *J* = 7.5, 1H, ArH), 7.04 (d, *J* = 2.0, 1H, ArH), 3.42 – 3.48 (m, 4H, $NCH_2CH_2CH_2Ar$, $NC(O)(CH_2)_5CH_2$), 2.79 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 2.50 – 2.55 (m, 2H, $NC(O)CH_2$), 2.01 (quin, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 1.79 – 1.86 (m, 2H, $NC(O)CH_2CH_2$), 1.44 – 1.66 (m, 6H, $NC(O)CH_2CH_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.8 (NC(O)), 136.4 (ArC_{quat}), 127.4 (ArC_{quat}), 121.6 (ArCH), 121.5 (ArCH), 118.9 (ArCH), 118.7 (ArCH), 115.5 (ArC_{quat}), 111.1 (ArCH), 47.1 ($NC(O)(CH_2)_5CH_2$), 45.4 ($NCH_2CH_2CH_2Ar$), 34.0 ($NC(O)CH_2$), 29.4 ($NC(O)(CH_2)_4CH_2$), 28.7 ($NC(O)CH_2CH_2$), 28.0 ($NCH_2CH_2CH_2Ar$) 26.2 ($NC(O)CH_2CH_2CH_2$), 24.3 ($NC(O)CH_2CH_2CH_2CH_2$), 22.6 ($NCH_2CH_2CH_2Ar$); ***m/z*** (ESI^+) 285 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}ON_2^+$) requires *m/z* 285.19614, found *m/z* 285.19565.

Preparation and characterisation of 1-[3-(1*H*-indol-3-yl)propyl]azonan-2-one (123p)



Prepared according to general procedure **Q** yielded **123p** (65%) as a pale brown solid. **m.p.** 169 – 171 °C; **IR** ν_{max}(film)/cm^{-1} 1609 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.46 (br s, 1H, NH), 7.69 (d, *J* = 8.0, 1H, ArH), 7.36 (d, *J* = 8.0, 1H, ArH), 7.18 (t, *J* = 7.5, 1H, ArH), 7.11 (t, *J* = 7.5, 1H, ArH), 7.04 (d, *J* = 2.0, 1H, ArH), 3.41 – 3.51 (m, 4H, $NCH_2CH_2CH_2Ar$, $NC(O)(CH_2)_6CH_2$), 2.79 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 2.51 – 2.56 (m, 2H, $NC(O)CH_2$), 2.02 (quin, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 1.80 – 1.87 (m, 2H, $NC(O)CH_2CH_2$), 1.45 – 1.67 (m, 8H, $NC(O)CH_2CH_2CH_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.2 (NC(O)), 136.4 (ArC_{quat}), 127.4 (ArC_{quat}), 121.6 (ArCH), 121.5 (ArCH), 118.9 (ArCH), 118.6 (ArCH), 115.5 (ArC_{quat}), 111.1 (ArCH), 48.4 ($NC(O)(CH_2)_6CH_2$), 45.2 ($NCH_2CH_2CH_2Ar$), 34.8 ($NC(O)CH_2$), 28.3, 27.5 ($NCH_2CH_2CH_2Ar$), 26.9, 25.5, 24.8 ($NC(O)CH_2CH_2$), 22.6 ($NCH_2CH_2CH_2Ar$), 22.1; ***m/z*** (ESI^+) 299 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}ON_2^+$) requires *m/z* 299.21179, found *m/z* 299.21118.

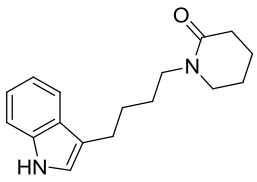
Preparation and characterisation of 1-[4-(1*H*-indol-3-yl)butyl]pyrrolidin-2-one (123q)



Prepared according to general procedure **Q** yielded **123q** (65%) as a pale brown solid. **m.p.** 78 – 79 °C; **IR** ν_{max}(film)/cm^{-1} 1660 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.36 (br s, 1H, NH), 7.60 (d, *J* = 8.0, 1H, ArH), 7.36 (d, *J* = 8.0, 1H, ArH), 7.19 (t, *J* = 7.5, 1H, ArH), 7.11 (t, *J* = 7.5, 1H, ArH), 6.96 (d, *J* = 2.0, 1H, ArH), 3.29 – 3.34 (m, 4H, $NCH_2(CH_2)_3Ar$,

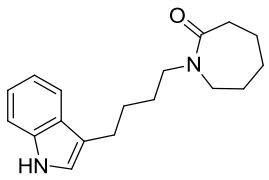
NC(O)$(CH_2)_2CH_2$), 2.79 (t, *J* = 7.5, 2H, N$(CH_2)_3CH_2$Ar), 2.39 (t, *J* = 8.0, 2H, NC(O)CH_2), 1.93 – 2.01 (m, 2H, NC(O)CH_2CH_2), 1.67 – 1.76 (m, 2H, CH_2CH_2Ar), 1.57 – 1.65 (m, 2H, $CH_2CH_2CH_2$Ar); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.9 (NC(O)), 136.3 (ArC_{quat}), 127.4 (ArC_{quat}), 121.6 (ArCH), 121.4 (ArCH), 118.9 (ArCH), 118.7 (ArCH), 115.9 (ArC_{quat}), 111.1 (ArCH), 47.0 (NC(O)$(CH_2)_2CH_2$), 42.3 ($NCH_2CH_2CH_2CH_2$Ar), 31.1 (NC(O)CH_2), 27.2, 26.9, 24.6 ($NCH_2CH_2CH_2CH_2$Ar), 17.8 (NC(O)CH_2CH_2); ***m/z*** (ESI$^+$) 257 ($[M+H]^+$); **HRMS** (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}ON_2^+$) requires *m/z* 257.16484, found *m/z* 257.16438.

Preparation and characterisation of 1-[4-(1*H*-indol-3-yl)butyl]piperidin-2-one (123r)



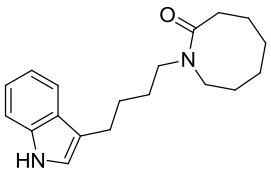
Prepared according to general procedure **Q** yielded **123r** (53%) as a pale brown solid. **m.p.** 147 – 150 °C; **IR** ν_{max}(film)/cm^{-1} 1613 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.41 (br s, 1H, NH), 7.60 (d, *J* = 8.0, 1H, ArH), 7.35 (d, *J* = 8.0, 1H, ArH), 7.18 (t, *J* = 7.5, 1H, ArH), 7.11 (t, *J* = 7.5, 1H, ArH), 6.96 (d, *J* = 2.0, 1H, ArH), 3.41 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2CH_2$Ar), 3.20 – 3.24 (m, 2H, NC(O)$(CH_2)_3CH_2$), 2.79 (t, *J* = 7.0, 2H, $NCH_2CH_2CH_2CH_2$Ar), 2.36 – 2.42 (m, 2H, NC(O)CH_2), 1.61 – 1.80 (m, 8H, $NCH_2CH_2CH_2CH_2$Ar, C(O)$CH_2CH_2CH_2CH_2$,); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.6 (NC(O)), 136.4 (ArC_{quat}), 127.4 (ArC_{quat}), 121.6 (ArCH), 121.4 (ArCH), 118.8 (ArCH), 118.8 (ArCH), 116.1 (ArC_{quat}), 111.1 (ArCH), 47.7 (NC(O)$(CH_2)_3CH_2$), 46.9 ($NCH_2CH_2CH_2CH_2$Ar), 32.3 (NC(O)CH_2), 27.3, 26.8, 24.8 ($NCH_2CH_2CH_2CH_2$Ar), 23.2, 21.3; ***m/z*** (ESI$^+$) 271 ($[M+H]^+$); **HRMS** (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}ON_2^+$) requires *m/z* 271.18049, found *m/z* 271.17997.

Preparation and characterisation of 1-[4-(1*H*-indol-3-yl)butyl]azepan-2-one (123s)



Prepared according to general procedure **Q** yielded **123s** (59%) as a pale brown solid. **m.p.** 95 – 96 °C; **IR** ν_{max}(film)/cm^{-1} 1623 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.30 (br s, 1H, NH), 7.60 (d, *J* = 8.0, 1H, ArH), 7.35 (d, *J* = 8.0, 1H, ArH), 7.18 (t, *J* = 7.5, 1H, ArH), 7.11 (t, *J* = 7.5, 1H, ArH), 6.96 (d, *J* = 2.0, 1H, ArH), 3.42 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2CH_2Ar$), 3.26 – 3.31 (m, 2H, $NC(O)(CH_2)_4CH_2$), 2.79 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2CH_2Ar$), 2.50 – 2.55 (m, 2H, $NC(O)CH_2$), 1.54 – 1.77 (m, 10H, $NCH_2CH_2CH_2CH_2Ar$, $NC(O)CH_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.6 (NC(O)), 136.4 (ArC_{quat}), 127.5 (ArC_{quat}), 121.6 (ArCH), 121.4 (ArCH), 118.9 (ArCH), 118.8 (ArCH), 116.2 (ArC_{quat}), 111.1 (ArCH), 49.5 ($NC(O)(CH_2)_4CH_2$), 48.0 ($NCH_2CH_2CH_2CH_2Ar$), 37.3 ($NC(O)CH_2$), 29.9, 28.6, 27.9, 27.4, 24.8 ($NCH_2CH_2CH_2CH_2Ar$), 23.4; ***m/z*** (ESI^+) 285 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}ON_2^+$) requires *m/z* 285.19614, found *m/z* 285.19561.

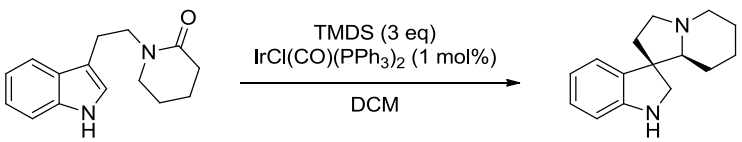
Preparation and characterisation of 1-[4-(1*H*-indol-3-yl)butyl]azocan-2-one (123t)



Prepared according to general procedure **Q** yielded **123t** (65%) as a pale brown solid. **m.p.** 108 – 113 °C; **IR** ν_{max}(film)/cm^{-1} 1612 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.34 (br s, 1H, NH), 7.60 (d, *J* = 8.0, 1H, ArH), 7.35 (d, *J* = 8.0, 1H, ArH), 7.17 (t, *J* = 7.5, 1H, ArH), 7.10 (t, *J* = 7.5, 1H, ArH), 6.97 (d, *J* = 2.0, 1H, ArH), 3.32 – 3.46 (m, 4H,

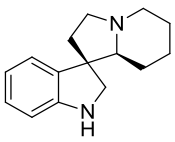
$NCH_2CH_2CH_2CH_2Ar$, $NC(O)(CH_2)_5CH_2$), 2.79 (t, *J* = 7.0, 2H, $NCH_2CH_2CH_2CH_2Ar$), 2.47 – 2.53 (m, 2H, $NC(O)CH_2$), 1.44 – 1.85 (m, 12H, $NCH_2CH_2CH_2CH_2Ar$, $NC(O)CH_2CH_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 174.7 (NC(O)), 136.4 (ArC_{quat}), 127.5 (ArC_{quat}), 121.6 (ArCH), 121.4 (ArCH), 118.8 (ArCH), 118.8 (ArCH), 116.2 (ArC_{quat}), 111.1 (ArCH), 46.9 ($NC(O)(CH_2)_5CH_2$), 45.1 ($NCH_2CH_2CH_2CH_2Ar$), 34.0 ($NC(O)CH_2$), 29.3, 28.7 ($NC(O)CH_2CH_2$), 27.6 ($NCH_2CH_2CH_2CH_2Ar$), 27.6, 26.2, 24.8 ($NCH_2CH_2CH_2CH_2Ar$), 24.4; ***m/z*** (ESI^+) 299 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{27}ON_2^+$) requires *m/z* 299.21179, found *m/z* 299.21124.

General procedure R to spirocyclic indoline 125



To a solution of indole **123** (1 eq) and TMDS (3 eq) in DCM (24 ml/mmol of **123**) was added Vaska's complex (1 mol%). The reaction was allowed to stir for 30 minutes and monitored by TLC. Upon completion the reaction was concentrated *in vacuo* and purified by FCC to afford the desired spirocyclic indoline 125.

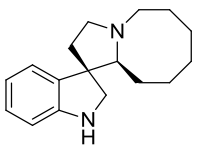
Preparation and characterisation of (1'*S**,8a'*S**)-3',5',6',7',8',8a'-hexahydro-2'H-spiro[indoline-3,1'-indolizine] (125c)



Prepared according to general procedure **R** yielded **125c** (0.105 g, 92%, d.r. >98:2) as yellow oil. **IR** ν_{max}(film)/cm^{-1} 2931 (NH); **^{1}H NMR** (700 MHz, $CDCl_3$) δ_H major diastereomer: 7.09 (dd, *J* = 7.5, 1.0, 1H, ArH), 7.05 (td, *J* = 7.5, 1.0, 1H, ArH), 6.76 (td, *J* = 7.5, 1.0, 1H, ArH),

6.64 (d, *J* = 7.5, 1H, ArH), 3.84 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.23 (m, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.14 – 3.21 (m, 2H, $CH_aH_bNCH_cH_d$), 2.24 – 2.33 (m, 2H, $ArNCH_2CCH_aH_bCH_aH_bNCH_2$), 1.99 (m, 1H, $ArNCH_2CCH_2CH_2NCH_cH_d$), 1.89 – 1.95 (m, 1H, $ArNCH_2CCH_aH_bCH_2N$), 1.83 (d, *J* = 10.5, 1H, $NCHC_2$), 1.77 (br d, *J* = 13.5, 1H, $NCH_2CH_2CH_aH_bCH_2$), 1.63 (br d, *J* = 13.5, 1H, $NCH_2CH_aH_bCH_2CH_2$), 1.53 – 1.59 (m, 1H, $NCH_2CH_aH_bCH_2CH_2$), 1.50 (br d, *J* = 13.0, 1H, $NCH_2CH_2CH_2CH_aH_b$), 1.36 – 1.42 (m, 1H, $NCH_2CH_2CH_2CH_aH_b$), 1.11 ("qt", *J* = 13.0, 4.0, 1H, $NCH_2CH_2CH_aH_bCH_2$); Observable minor diastereomer: ^{1}H NMR (500 MHz, CD_2Cl_2) δ_H 7.21 – 7.25 (m, 1H, ArH), 6.96 – 7.00 (m, 1H, ArH), 6.66 – 6.70 (m, 1H, ArH), 6.56 – 6.59 (m, 1H, ArH), 3.46 – 3.52 (m, 2H, $ArNCH_aH_b$), 1.80 – 1.85 (m, 1H, $NCH(C)_2$), 0.84 – 0.95 (m,1H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ_C major diastereomer: 151.7 (ArC_{quat}), 134.2 (ArC_{quat}), 127.8 (ArCH), 122.8 (ArCH), 118.7 (ArCH), 109.5 (ArCH), 74.8 ($NCHC_2$), 57.6 ($ArNCH_2$), 54.2 ($NCH_2CH_2CH_2CH_2$), 54.0 ($ArNCH_2CCH_2CH_2N$), 53.9 (NCH_2C_{quat}), 37.8 ($ArNCH_2CCH_2CH_2N$), 25.3 ($NCH_2CH_2CH_2CH_2$), 25.2 ($NCH_2CH_2CH_2CH_2$), 24.2 ($NCH_2CH_2CH_2CH_2$); Observable minor diastereomer ^{13}C NMR (125 MHz, CD_2Cl_2) δ_C 152.0, 127.7, 125.7, 118.8, 109.5, 74.4, 59.5, 54.3, 39.0, 25.8, 24.7; ***m/z*** (ESI^+) 229 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}N_2^+$) requires *m/z* 229.16993, found *m/z* 229.16963.

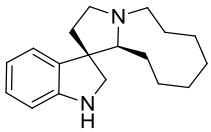
Preparation and characterisation of (1'*S,10a'*S**)-3',5',6',7',8',9',10',10a'-octahydro-2'H-spiro[indoline-3,1'-pyrrolo[1,2-a]azocine] (125d)**



Prepared according to general procedure **R** yielded **125d** (0.053 g, 41%, d.r. 59:41) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2920 (NH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H major

diastereomer: 7.04 – 7.09 (m, 2H, ArH), 6.75 (t, *J* = 7.0, 1H, ArH), 6.65 (d, *J* = 7.5, 1H, ArH), 3.84 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.20 – 3.32 (m, 2H, $ArNCH_aH_b$, $NCH_aH_bCH_2CH_2$), 3.08 – 3.18 (m, 1H, $NCH_aH_bCH_2CH_2$), 2.68 – 2.80 (m, 3H, $ArNCH_2CCH_2CH_aH_b$, $NCHC_2$), 2.11 (ddd, *J* = 13.0, 8.5, 4.5, 1H, $ArNCH_2CCH_aH_b$), 1.93 – 2.03 (m, 1H, $ArNCH_2CCH_aH_b$), 1.47 – 1.82 (m, 9H), 1.33 – 1.42 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C **major diastereomer:** 151.3 (ArC_{quat}), 134.5 (ArC_{quat}*), 127.9 (ArCH), 123.1 (ArCH), 118.6 (ArCH), 109.6 (ArCH), 72.8 ($NCHC_2$), 56.7 ($ArNCH_2CCH_2$), 56.5 ($ArNCH_2$), 54.8 ($ArNCH_2CCH_2CH_2N$), 54.4 ($NCH_2CH_2CH_2$), 38.1 ($ArNCH_2CCH_2CH_2N$), 27.6, 26.4, 26.1, 25.8, 25.1; ***m/z*** (ESI^+) 257 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}N_2^+$) requires *m/z* 257.20123, found *m/z* 257.20079.

Preparation and characterisation of (1'*S,11a'*S**)-2',3',5',6',7',8',9',10',11',11a'-decahydrospiro[indoline-3,1'-pyrrolo[1,2-a]azonine] (125m)**

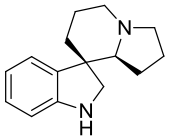


Prepared according to general procedure **R** yielded **125m** (0.097 g, 72%, d.r. 72:28) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2920 (NH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H major diastereomer: 6.95 (td, *J* = 7.5, 1.0, 1H, ArH), 6.89 (d, *J* = 7.5, 1H, ArH), 6.64 (td, *J* = 7.5, 1.0, 1H, ArH), 6.55 (d, *J* = 7.5, 1H, ArH), 3.65 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.12 – 3.23 (m, 2H, $CH_aH_bNCH_cH_d$, $ArNCH_aH_b$), 2.88 – 3.01 (m, 3H, $NCHC_2$, $CH_aH_bNCH_cH_d$), 2.62 (q, 1H, $CH_aH_bNCH_cH_d$), 1.85 – 1.96 (m, 2H, $ArNCH_2CCH_2CH_aH_bNCH_cH_d$), 1.26 – 1.76 (m, 12H); observable minor diastereomer: 6.78 (t, *J* = 7.5, ArCH), 6.71 (d, *J* = 8.0, ArCH), 3.27 – 3.42 (m, 2H, $ArNCH_aH_b$), 2.49 – 2.59 (m, 1H), 2.34 – 2.45 (m, 1H), 2.00 – 2.14 (m, 1H) ; **^{13}C**

* Broad peak in the baseline of the spectrum.

NMR (100 MHz, $CDCl_3$) δ_C major diastereomer: 150.8 (ArC_{quat}), (cannot see the second ArC_{quat}), 127.7 (ArCH), 122.8 (ArCH), 118.7 (ArCH), 109.6 (ArCH), 71.9 ($NCHC_2$), 56.5 ($ArNCH_2$), 55.7 ($ArNCH_2C_{quat}$), 54.4 ($CH_aH_bNCH_cH_d$), 52.4 ($CH_aH_bNCH_cH_d$), 38.7 ($ArNCH_2CCH_2CH_aH_bNCH_cH_d$), 28.6 (broad 2 x CH_2)*, 26.7, 25.9, 24.4, 23.6; observable minor diastereomer: 152.0, 125.4, 118.3, 109.6, 61.6, 58.7, 56.4, 53.5, 33.6, 29.1, 27.8, 27.2, 25.1; ***m/z*** (ESI^+) 271 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{27}N_2^+$) requires *m/z* 271.21688, found *m/z* 271.21630.

Preparation and characterisation of (3*S**,8a'*S**)-2',3',5',6',7',8a'-hexahydro-1'H-spiro[indoline-3,8'-indolizine] (125f)

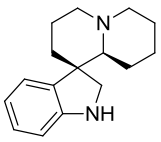


Prepared according to general procedure **R** yielded **125f** (0.062 g, 54%, d.r. 58:42) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2931 (NH); **^{1}H NMR** (400 MHz, d_6-benzene) δ_H major diastereomer: 7.07 (td, *J* = 7.5, 1.5, 1H, ArH), 6.97 (dd, *J* = 7.5, 1.0, 1H, ArH), 6.78 (td, *J* = 7.5, 1, 1H, ArH), 6.44 (d, *J* = 7.5, 1H, ArH), 3.75 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.05 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 2.89 – 2.98 (m, 2H, $CH_aH_bNCH_cH_d$), 1.89 – 1.97 (m, 2H, $NCHC_2$, $CH_aH_bNCH_cH_d$), 1.81 – 1.87 (m, 1H, $CH_aH_bNCH_cH_d$), 1.65 – 1.76 (m, 2H), 1.49 – 1.60 (m, 3H), 1.27 – 1.43 (m, 3H); observable minor diastereomer: 7.95 (d, *J* = 7.5, ArCH), 6.50 (d, *J* = 7.5, ArCH), 2.80 (d, *J* = 8.5, $ArNCH_aH_b$), 1.99 – 2.07 (m, 1H), 1.15 (td, *J* = 12.5, 4.0, 1H); **^{13}C NMR** (100 MHz, d_6-benzene) δ_C 152.5 (ArC_{quat}), 135.0 (ArC_{quat}), 128.0 – 128.9 (ArCH), 123.1 (ArCH), 118.5 (ArCH), 109.7 (ArCH), 72.1 ($NCHC_2$), 55.4 ($CH_aH_bNCH_cH_d$), 53.7 ($CH_aH_bNCH_cH_d$), 53.6 ($ArNCH_2$), 48.9 ($ArNCH_2C_{quat}$), 38.0, 25.8, 23.5, 21.2; observable

* Seen by correlation with a proton signal in HSQC.

minor diastereomer: 153.1, 133.0, 118.5, 109.9, 70.1, 59.5, 55.6, 53.8, 48.7, 37.6, 27.0, 22.8, 21.4; ***m/z*** (ESI^+) 229 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}N_2^+$) requires *m/z* 229.16993, found *m/z* 229.16941.

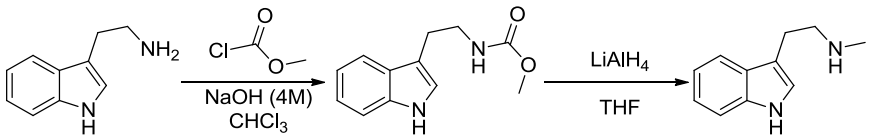
Preparation and characterisation of (1'*S,9a'*S**)-2',3',4',6',7',8',9',9a'-octahydrospiro[indoline-3,1'-quinolizine] (125n)**



Prepared according to general procedure **R** yielded **125n** (0.067 g, 55%, d.r. 72:28) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2931 (NH); **^{1}H NMR** (500 MHz, d_6-benzene) δ_H major diastereomer: 7.04 (t, *J* = 7.5, 1H, ArH), 6.97 (d, *J* = 7.5, 1H, ArH), 6.71 (t, *J* = 7.5, 1H, ArH), 6.59 (d, *J* = 7.5, 1H, ArH), 3.9 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.35 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 2.87 – 2.98 (m, 2H, $CH_aH_bNCH_cH_d$), 2.02 – 2.20 (m, 2H, $CH_aH_bNCH_cH_d$), 1.90 – 1.99 (m, 1H, $NCHC_2$), 1.55 – 1.88 (m, 7H), 1.28 – 1.40 (m, 1H), 1.15 – 1.22 (m, 1H). 1.04 – 1.15 (m, 1H); observable minor diastereomer: 7.63 – 7.73 (m, 1H, ArCH), 7.02 – 7.08 (m, 1H, ArCH), 6.69 – 6.75 (m, 1H, ArCH), 6.59 – 6.63 (m, 1H, ArCH), 3.50 – 3.59 (m, 1H, $ArNCH_aH_b$), 3.12 – 3.16 (m, 1H, $ArNCH_aH_b$), 2.85 -3.00 (m, 2H), 1.77 – 2.18 (m, 5H), 1.61 – 1.71 (m, 2H), 1.40 – 1.57 (m, 4H), 1.15 – 1.30 (m, 1H), 0.93 – 1.04 (m, 1H); **^{13}C NMR** (100 MHz, d_6-benzene) δ_C 151.6 (ArC_{quat}), (unseen ArC_{quat}), 127.9 (ArCH), 122.7 (ArCH), 118.2 (ArCH), 109.2 (ArCH), 70.2 ($NCHC_2$), 57.4 (CH_2NCH_2), 57.0 (CH_2NCH_2), 53.8 ($ArNCH_2$), 49.4 ($ArNCH_2C_{quat}$), 38.2 ($ArNCH_2CCH_2$), 29.7, 25.7, 24.6, 22.0; observable minor diastereomer: 151.8 (ArC_{quat}), 127.5 (ArCH), 127.3 (ArCH), 117.9 (ArCH), 109.3 (ArCH), 58.8 ($ArNCH_2$), 57.7 ($ArNCH_2C_{quat}$), 48.8 (NCH_2CH_2), 24.9, 21.6; ***m/z*** (ESI^+) 243 ($[M+H]^+$);

HRMS (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires *m/z* 243.18558, found *m/z* 243.18523.

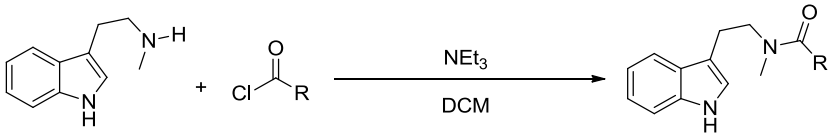
Synthesis of 2-(1*H*-indol-3-yl)-*N*-methylethanamine (131)



An aqueous solution of sodium hydroxide (1 eq, 4M) was added to a mixture of tryptamine (1 eq) and methyl-chloroformate (1 eq) in chloroform (2.5 ml/mmol of amine) and stirred vigorously at r.t. for 3 h. The reaction mixture was washed with water and the aqueous layer extracted with DCM. The organics were combined, washed with brine, dried over Na_2SO_4, concentrated *in vacuo* and used without further purification in the next step.

Crude carbamate (1 eq) was dissolved in THF (2ml/ mmol of carbamate) and was cooled to 0 °C under nitrogen. $LiAlH_4$ (3 eq) was then added portionwise to control the exothermic reaction. The mixture was heated to reflux for 1 h, then cooled to 0 °C and quenched with a mixture of aqueous NaOH solution (15%) and THF to loosen the gel formation. The quenched mixture was filtered through Celite, dried with $MgSO_4$, filtered and concentrated to afford the title compound, which was used without purification.

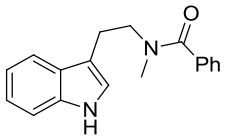
General procedure S towards acyclic examples 130



2-(1*H*-indol-3-yl)-*N*-methylethanamine (1 eq) and triethylamine (1.2 eq) in DCM (7 ml/mmol of amine) was added to a solution of chloride (1.05 eq) in DCM (3ml/mmol of amine) at 0 °C

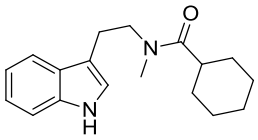
and allowed to warm to room temperature. The reaction mixture was concentrated and purified by FCC to afford the pure amide **130**.

Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylbenzamide (130a)



Prepared according to general procedure **S** yielded **130a** (0.36 g, 44%) as a light brown solid. **m.p.** 197–198 °C; **IR** ν_{max}(film)/cm^{-1} 3175 (N–H), 1607 (NC=O); **^{1}H NMR** (500 MHz, d_6-DMSO, 90°C) δ_H 10.58 (br s, 1H, ArNH), 7.20 – 7.55 (m, 7H, ArCH), 7.02 – 7.13 (m, 2H, ArCH), 6.89 – 6.98 (m, 1H, ArCH), 3.53 – 3.71 (m, 2H, NCH_2CH_2), 2.91 – 3.13 (m, 5H, NCH_2CH_2, NCH_3); **^{13}C NMR** (125 MHz, d_6-DMSO) δ_C mixture of rotamers: 171.1 (NC(O)), 170.2 (NC(O)), 137.3 (ArC_{quat}), 136.6 (ArC_{quat}), 136.5 (ArC_{quat}), 129.6, 129.6, 129.4, 129.2, 128.6, 128.5, 127.7, 127.3, 127.1, 126.6, 123.4, 123.2, 121.3, 118.7, 118.6, 118.2, 111.8, 111.7, 110.8, 51.8, 48.1, 37.7, 32.7, 24.2, 22.9; ***m/z*** (ESI$^+$) 279 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{18}H_{19}ON_2^+$) requires *m/z* 279.14919, found *m/z* 279.14871.

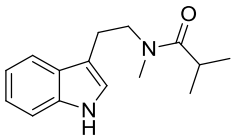
Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylcyclohexanecarboxamide (130b)



Prepared according to general procedure **S** yielded **130b** (0.26 g, 46%) as a light brown solid. **m.p.** 86–88 °C; **IR** ν_{max}(film)/cm^{-1} 3187 (N–H), 1616 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H mixture of rotamers: 8.53 (br s, $1H_{major}$, ArNH), 8.37 (br s, $1H_{minor}$, ArNH) 7.69 (d, *J* = 8.0,

$1H_{minor}$, ArCH), 7.61 (d, *J* = 8.0, $1H_{major}$, ArCH), 7.34 – 7.42 (m, 1H, ArCH), 7.09 – 7.25 (m, 2H, ArH)), 7.02 (d, *J* = 2.5, $1H_{minor}$, ArH), 6.95 (d, *J* = 2.5, $1H_{major}$, ArH), 3.60 – 3.72 (m, 2H, NCH_2CH_2), 2.94 – 3.06 (m, 5H, CH_3, NCH_2CH_2), 2.42 – 2.52 (m, $1H_{minor}$, NC(O)CH), 2.01 – 2.10 (m, $1H_{major}$, NC(O)CH), 1.22 – 1.85 (m, 10H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C mixture of rotamers: 176.9 (NC(O)), 176.0 (NC(O)), 136.4, 136.2, 127.5, 127.0, 122.6, 122.1, 122.0, 121.8, 119.5, 119.2, 118.8, 118.0, 113.1, 111.7, 111.5, 111.1, 49.9 (NCH_2CH_2), 48.9 (NCH_2CH_2), 40.9 (CH_3NCH), 40.2 (CH_3NCH), 35.8 (CH_3), 33.5 (CH_3), 29.3, 29.1, 28.9, 25.9, 25.6, 25.4, 24.5 (NCH_2CH_2), 23.1 (NCH_2CH_2); ***m/z*** (ESI^+) 285 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{25}ON_2^+$) requires *m/z* 285.19614, found *m/z* 285.19562.

Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-*N*,2-dimethylpropanamide (130c)

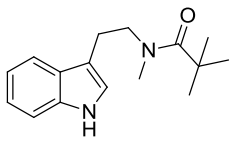


Prepared according to general procedure **S** yielded **130c** (0.26 g, 53%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 3257 (N–H), 1615 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H mixture of rotamers (ratio 1:1, a:b[*]): 8.45 (br s, 1Ha, ArNH), 8.32 (br s, 1Hb, ArNH), 7.70 (d, *J* = 8.0, 1Ha, ArCH), 7.58 (d, *J* = 8.0, 1Hb, ArCH), 7.34 – 7.42 (m, 1Hab, ArCH), 7.10 – 7.25 (m, 2Hab, ArCH), 7.03 (d, *J* = 2.0, 1Ha, ArCH), 6.98 (d, *J* = 2.0, 1Hb, ArCH), 3.70 (t, *J* = 7.5, 2Ha, NCH_2CH_2Ar), 3.64 (t, *J* = 7.0, 2Hb, NCH_2CH_2Ar), 2.96 – 3.07 (m, 5Hab, NCH_2CH_2Ar, NCH_3), 2.75 – 2.85 (m, 1Ha, $C(O)CH(CH_3)_2$), 2.54 – 2.63 (m, 1Hb, $C(O)CH(CH_3)_2$), 1.15 (d, *J* = 6.5, 6Ha, CCH_3), 0.96 (d, *J* = 6.5, 6Hb, CCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C mixture

[*] Due to the 1:1 ratio of each rotamer the assignment is not split into major and minor but into *a* and *b* for each signal. However, *a* and *b* do not necessarily represent the same rotamer, instead, *a* shall always be the highest chemical shift signal for each rotameric signal and *b* shall be the lower chemical shift signal.

of rotamers (ratio 1:1, a:b*): 177.6 (C(O)a), 176.9 (C(O)b), 136.3 (ArC_{quat}a), 136.2 (ArC_{quat}b), 127.5 (ArC_{quat}a), 127.0 (ArC_{quat}b), 122.3 (ArCHa), 122.1 (ArCHb), 122.0 (ArCHa), 121.8 (ArCHb), 119.5 (ArCHa), 119.2 (ArCHb), 118.8 (ArCHa), 118.1 (ArCHb), 113.1 (ArC_{quat}a), 111.9 (ArC_{quat}b), 111.4 (ArCHa), 111.1 (ArCHb), 50.3 (NCH_2CH_2Ara), 49.0 (NCH_2CH_2Arb), 35.8 (NCH_2CH_2Ara), 33.7 (NCH_2CH_2Arb), 30.4 (C(O)CHa), 29.9 (C(O)CHb), 24.7 (NCH_3a), 23.1 (NCH_3b), 19.5 (CCH_3a), 19.2 (CCH_3b); ***m/z*** (ESI^+) 245 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{21}ON_2^+$) requires *m/z* 245.16484, found *m/z* 245.16466.

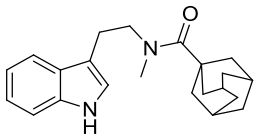
Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-*N*,2,2-trimethylpropanamide (130d)



Prepared according to general procedure **S** yielded **130d** (0.35 g, 48%) as a light brown solid **m.p.** 132–134 °C; **IR** ν_{max}(film)/cm^{-1} 3269 (N–H), 1614 (NC=O); **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 10.84 (br s, 1H, ArNH), 7.60 (d, *J* = 8.0, 1H, ArCH), 7.34 (d, *J* = 8.0, 1H, ArCH), 7.15 (d, *J* = 2.0, 1H, ArCH), 7.05 – 7.10 (m, 1H, ArCH), 6.96 – 7.01 (m, 1H, ArCH), 3.51 – 3.58 (m, 2H, NCH_2CH_2), 3.01 (s, 3H, NCH_3), 2.86 – 2.92 (m, 2H, NCH_2CH_2), 1.20 (s, 9H, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C* 175.8 (NC(O)), (missing ArC_{quat}), 136.2 (ArC_{quat}), 127.2 (ArC_{quat}), 122.7 (ArCH), 121.0 (ArCH), 118.3 (ArCH), 118.3 (ArCH), 111.4 (ArCH), 50.6 (NCH_2CH_2), 38.2 (NCH_3), 36.3 ($NC(O)C_{quat}$), 28.1 ($C(CH_3)_3$), 23.0 (NCH_2CH_2); ***m/z*** (ESI^+) 259 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}ON_2^+$) requires *m/z* 259.18049 and 260.18384, found *m/z* 259.18008 and 260.18350.

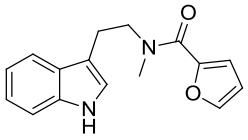
Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methyltricyclo[3.3.1.1^{3,7}]decane-1-carboxamide (130e)

* One of the aryl quaternary carbon signals could not be seen by ^{13}C NMR.



Prepared according to general procedure **S** yielded **130e** (0.43 g, 63%) as a light brown solid. **m.p.** 150–160 °C; **IR** ν_{max}(film)/cm^{-1} 3218 (N–H), 1601 (NC=O); **^{1}H NMR** (400 MHz, d_6-DMSO) δ_H 10.84 (br s, 1H, ArNH), 7.58 (d, *J* = 8.0, 1H, ArCH), 7.34 (d, *J* = 8.0, 1H, ArCH), 7.14 (d, *J* = 2.0, 1H, ArCH), 7.03 – 7.09 (m, 1H, ArCH), 6.95 – 7.01 (m, 1H, ArCH), 3.52 – 3.62 (m, 2H, NCH_2CH_2), 3.03 (s, 3H, NCH_3), 2.85 – 2.91 (m, 2H, NCH_2CH_2), 1.88 – 2.00 (m, 9H, $NC(O)CCH_2CH$), 1.62 – 1.70 (m, 6H, $NC(O)CCH_2CHCH_2$); **^{13}C NMR** (100 MHz, d_6-DMSO) δ_C 175.1 (NC(O)), 136.2 (ArC_{quat}), 127.2 (ArC_{quat}), 122.7 (ArCH), 121.0 (ArCH), 118.3 (ArCH), 118.3 (ArCH), 111.4 (ArCH), 111.4 (ArC_{quat}), 50.8 (NCH_2CH_2), 38.4 (3 x $NC(O)CCH_2$), 36.5 ($NC(O)C_{quat}$) 36.1 (3 x $NC(O)CCH_2CHCH_2$), 35.9 (NCH_3) 28.0 (3 x $NC(O)CCH_2CH$), 23.2 (NCH_2CH_2); ***m/z*** (ESI^+) 337 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{29}ON_2^+$) requires *m/z* 337.22744, found *m/z* 337.22691.

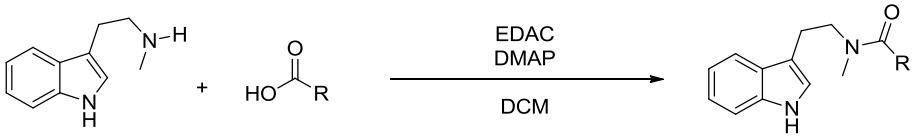
Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylfuran-2-carboxamide (130f)



Prepared according to general procedure **S** yielded **130f** (0.35 g, 57%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 3262 (N–H), 1606 (NC=O); **^{1}H NMR** (500 MHz, d_6-DMSO, 90°C) δ_H 10.57 (br s, 1H, ArNH), 7.72 (d, *J* = 1.0, 1H, ArCH), 7.54 (d, *J* = 8.0, 1H, ArCH), 7.35 (d, *J* = 8.0, 1H, ArCH), 7.12 (d, *J* = 2.0, 1H, ArCH), 7.05 – 7.09 (m, 1H, ArCH), 6.96 – 7.01 (m, 1H, ArCH) 6.89 (d, *J* = 3.0, 1H, ArCH), 6.55 (dd, *J* = 3.5, 1.5, 1H, ArCH), 3.74 – 3.80 (m, 2H, NCH_2CH_2), 3.11 (s, 3H, NCH_3), 2.99 – 3.05 (m, 2H, NCH_2CH_2); **^{13}C NMR** (125 MHz, d_6-

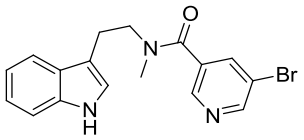
DMSO, 90°C) δ_C 163.1 (NC(O)), 144.4 (ArCH), 138.4 (ArC_{quat}), 136.2 (ArC_{quat}), 129.4 (ArC_{quat}), 127.1 (ArC_{quat}), 122.9 (ArCH), 121.0 (ArCH), 118.3 (ArCH), 118.2 (ArCH), 114.8 (ArCH), 111.4 (ArCH), 111.1 (ArCH), 51.4 and 49.3 (two rotamers of NCH_2CH_2), 37.6 and 33.8 (two rotamers of NCH_3), 23.9 and 22.8 (two rotamers of NCH_2CH_2); ***m/z*** (ESI^+) 269 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{17}O_2N_2^+$) requires *m/z* 269.12845, found *m/z* 269.12798.

General procedure T towards acyclic examples



To a solution of 2-(1H-indol-3-yl)-N-methylethanamine (1 eq) and carboxylic acid (1.3 eq) in DCM (5ml/mmol of amine) was added EDAC (1.5 eq) and DMAP (0.1 eq). The reaction was stirred at room temperature until the reaction reached completion. The reaction mixture was diluted with DCM and washed with HCl (1M), brine, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by FCC to afford pure amide **130**.

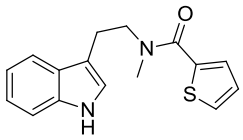
Preparation and characterisation of 5-bromo-*N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylpyridine-3-carboxamide (130g)



Prepared according to general procedure **T** yielded **130g** (0.99 g, 96%) as a light brown solid. **m.p.** 148-149 °C;. **IR** ν_{max}(film)/cm^{-1} 3235 (N–H), 1612 (NC=O); **^{1}H NMR** (500 MHz, d_6-DMSO) δ_H mixture of rotamers: 10.82 – 10.88 (m, 1H, ArNH), 8.77 (d, *J* = 1.5, $1H_{minor}$, ArH), 8.58 (d, *J* = 2.0, $1H_{major}$, ArH), 8.54 (s, $1H_{minor}$, ArH), 8.25 (d, $1H_{major}$, ArH), 8.04 (s,

$1H_{minor}$, ArH), 7.63 (d, *J* = 8.0, $1H_{minor}$, ArH), 7.48 (s, $1H_{major}$, ArH), 7.36 (d, *J* = 8.0, $1H_{minor}$, ArH), 7.32 (d, *J* = 8.0, $1H_{major}$, ArH), 7.25 (s, $1H_{minor}$, ArH), 6.98 – 7.11 (m, $2H_{minor}$, $3H_{major}$, ArH), 6.80 – 6.85 (m, $1H_{major}$, ArH), 3.72 (t, *J* = 7.5, $2H_{minor}$, NCH_2CH_2), 3.47 (t, *J* = 7.0, $2H_{major}$, NCH_2CH_2), 3.08 (s, $3H_{major}$, NCH_3), 3.03 (t, *J* = 7.5, $2H_{minor}$, NCH_2CH_2), 2.86 – 2.93 (m, $3H_{minor}$ and $2H_{major}$, NCH_3, NCH_2CH_2); **^{13}C NMR** (125 MHz, d_6-DMSO) δ_C mixture of rotamers: 166.6 ($NC(O)_{major}$), 166.0 ($NC(O)_{minor}$), 150.9, 150.3, 145.9, 145.2, 136.9, 136.3, 136.2, 136.0, 134.2, 133.9, 127.3, 126.7, 123.3, 123.0, 121.0, 120.0, 119.8, 118.3, 118.2, 117.5, 111.5, 111.4, 111.2, 110.2, 51.5 (NCH_2CH_{2major}), 48.0 (NCH_2CH_{2minor}), 37.3 (CH_{3minor}), 32.5 (CH_{3major}), 23.4 (NCH_2CH_{2major}), 22.4 (NCH_2CH_{2minor}); ***m/z*** (ESI^+) 258 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{17}ON_3Br^+$) requires *m/z* 358.05495, found *m/z* 358.05467.

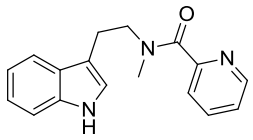
Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylthiophene-2-carboxamide (130h)



Prepared according to general procedure **T** yielded **130h** (0.53 g, 65%) as a light brown solid. **m.p.** 125-126 °C; **IR** ν_{max}(film)/cm^{-1} 3215 (N–H), 1600 (NC=O); **^{1}H NMR** (500 MHz, d_6-DMSO, 90°C) δ_H 10.58 (br s, 1H, ArNH), 7.56 (d, *J* = 4.4, 1H, ArCH), 7.51 (d, *J* = 7.5, 1H, ArCH), 7.32 – 7.38 (m, 2H, ArCH), 7.12 (br s, 1H, ArCH), 7.04 – 7.10 (m, 2H, ArCH), 6.95 – 7.01 (m, 1H, ArCH), 3.76 (t, 2H, NCH_2CH_2), 3.12 (s, 3H, NCH_3), 3.00 – 3.07 (m, 2H, NCH_2CH_2); **^{13}C NMR** (125 MHz, d_6-DMSO, 90°C) δ_C 162.8 (NC(O)), 137.8 (ArC_{quat}), 136.0 (ArC_{quat}), 128.3 (ArCH), 128.1 (ArCH), 126.8 (ArC_{quat}), 126.4 (ArCH), 122.3 (ArCH), 120.5 (ArCH), 117.8 (ArCH), 117.6 (ArCH), 110.9 (ArCH), 110.8 (ArC_{quat}), 49.9 (NCH_2CH_2), 35.3

(NCH_3), 23.0 (NCH_2CH_2); ***m/z*** (ESI^+) 285 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{17}ON_2S^+$) requires *m/z* 285.10561, found *m/z* 285.10508.

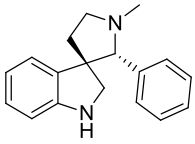
Preparation and characterisation of *N*-[2-(1*H*-indol-3-yl)ethyl]-*N*-methylpyridine-2-carboxamide (130i)



Prepared according to general procedure **T** yielded **130i** (0.58 g, 72%) as a light brown solid. **m.p.** 122-124 °C; **IR** ν_{max}(film)/cm^{-1} 3260 (N–H), 1624 (NC=O); **^{1}H NMR** (500 MHz, d_6-DMSO) δ_H mixture of rotamers: 10.85 (s, $1H_{minor}$, ArNH), 10.79 (s, $1H_{major}$, ArNH), 8.59 (d, *J* = 4.5, $1H_{minor}$, ArCH) 8.51 – 8.55 (m, $1H_{major}$, ArCH), 7.91 (td, *J* = 7.5, 1.5, $1H_{minor}$, ArCH), 7.63 – 7.69 (m, 1H, ArCH), 7.53 (d, *J* = 8.0, $1H_{minor}$, ArCH), 7.46 (ddd, *J* = 7.5, 4.5, 1, $1H_{minor}$, ArCH), 7.33 – 7.38 (m, 1H, ArCH), 7.29 (d, *J* = 8.0, $1H_{major}$, ArCH), 7.23 (d, *J* = 2.0, $1H_{minor}$, ArCH), 7.11 (d, *J* = 8.0, $1H_{major}$, ArCH), 7.05 – 7.09 (m, 1H, ArCH), 6.98 – 7.04 (m, $2H_{major}$, $1H_{minor}$, ArCH), 6.80 – 6.85 (m, $1H_{major}$, ArCH), 3.70 – 3.75 (m, $2H_{minor}$, NCH_2CH_2), 3.48 – 3.55 (m, $2H_{major}$, NCH_2CH_2), 3.07 (s, $3H_{major}$, NCH_3), 3.00 – 3.05 (m, $2H_{minor}$, NCH_2CH_2), 2.90 – 2.97 (m, $3H_{minor}$ and $2H_{major}$, NCH_3, NCH_2CH_2); **^{13}C NMR** (125 MHz, d_6-DMSO) δ_C[*] mixture of rotamers: 168.8 ($NC(O)_{major}$), 168.2 ($NC(O)_{minor}$), 155.1, 155.0, 148.6, 148.3, 137.6, 137.2, 136.6, 136.5, 127.6, 127.3, 124.7, 124.4, 123.4, 123.2, 123.1, 122.9, 121.4, 121.2, 118.7, 118.5, 118.1, 111.8, 111.7, 111.0, 51.3 (NCH_2CH_{2major}), 48.4 (NCH_2CH_{2minor}), 37.1 (CH_{3minor}), 33.1 (CH_{3major}), 24.3 (NCH_2CH_{2major}), 22.9 (NCH_2CH_{2minor}); ***m/z*** (ESI^+) 280 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{18}ON_3^+$) requires *m/z* 280.14444, found *m/z* 280.14401.

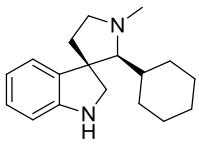
[*] Two of the aryl carbon signals could not be seen by ^{13}C NMR.

Preparation and characterisation of (2'*R,3*S**)-1'-methyl-2'-phenylspiro[indoline-3,3'-pyrrolidine] (133a)**



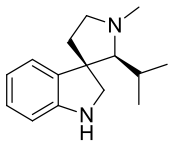
Prepared according to general procedure **R** yielded **133a** (0.119 g, 92%, d.r. 57:43) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2950 (N–H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H **major diastereomer:** 7.30 (d, *J* = 7.5, 1.0, 1H, ArCH), 7.21 – 7.25 (m, 1H, ArH), 7.03 – 7.14 (m, 4H, ArH), 6.82 – 6.91 (m, 1H, ArCH), 6.61 (td, *J* = 7.5, 1.0, 1H, ArCH), 6.37 (d, *J* = 8.0, 1H, ArCH), 3.74 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.58 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.30 – 3.48 (m, 2H, $NCH_aH_bCH_2$, NCHAr), 2.49 – 2.63 (m, 1H, $NCH_aH_bCH_2$), 2.31 – 2.44 (m, 1H, $NCH_2CH_aH_b$), 2.25 (s, 3H, NCH_3), 2.04 – 2.17 (m, 1H, $NCH_2CH_aH_b$); **minor diastereomer:** 7.21 – 7.25 (m, 2H, ArH), 7.03 – 7.14 (m, 5H, ArH), 6.82 – 6.91 (m, 1H, ArH), 6.51 (d, *J* = 7.5, 1H, ArH), 3.30 – 3.48 (m, 3H, $ArNCH_aH_b$, $NCH_aH_bCH_2$, NCHAr), 3.13 (d, *J* = 10.0, 1H, $ArNCH_aH_b$), 2.49 – 2.63 (m, 1H, $NCH_aH_bCH_2$), 2.31 – 2.44 (m, 1H, $NCH_2CH_aH_b$), 2.30 (s, 3H, NCH_3), 2.04 – 2.17 (m, 1H, $NCH_2CH_aH_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C **mixture of diastereomer:** 151.4 (ArC_{quat}), 150.8 (ArC_{quat}), 138.9 (ArC_{quat}), 138.4 (ArC_{quat}), 135.4 (ArC_{quat}), 134.1 (ArC_{quat}), 128.4 (ArCH), 128.0 (ArCH), 127.8 (ArCH), 127.7 (ArCH), 127.3 (ArCH), 127.1 (ArCH), 127.0 (ArCH), 126.8 ($ArCH_{major}$), 125.6 (ArCH), 122.9 ($ArCH_{major}$), 118.9 ($ArCH_{minor}$), 118.3 ($ArCH_{major}$), 110.3 ($ArCH_{minor}$), 109.3 ($ArCH_{major}$) 81.6 ($NCHPh_{major}$), 80.7 ($NCHPh_{minor}$), 59.7 ($ArNCH_{2major}$), 57.2 ($ArNCH_{2minor}$), 57.2 ($ArNCH_2C_{quatmajor}$), 56.7 ($ArNCH_2C_{quatminor}$), 55.2 (NCH_2CH_{2minor}), 54.7 (NCH_2CH_{2major}), 41.1 (NCH_{3major}), 41.0 (NCH_{3minor}), 39.2 (NCH_2CH_{2minor}), 37.9 (NCH_2CH_{2major}); ***m/z*** (ESI$^+$) 265 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{18}H_{21}N_2^+$) requires *m/z* 265.16993 and 266.17328, found *m/z* 265.16954 and 266.17284.

Preparation and characterisation of (2'*S,3*S**)-2'-cyclohexyl-1'-methyl-1,2-dihydrospiro[indole-3,3'-pyrrolidine] (133b)**



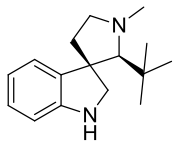
Prepared according to general procedure **R** yielded **133b** (0.115 g, 85%, d.r. 67:33) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2956 (NH); **^{1}H NMR** (700 MHz, $CDCl_3$) δ_H major diastereomer: 7.01 – 7.09 (m, 2H, ArH), 6.71 – 6.77 (m, 1H, ArH), 6.64 (d, *J* = 8.0, 1H, ArH), 3.83 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.64 (br s, 1H, NH), 3.32 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.23 (dt, *J* = 10.0, 6.5, 1H, $NCH_aH_bCH_2$), 2.53 – 2.62 (m, 5H, $NCH_aH_bCH_2$, CH_3, $NCHCHC_2$), 1.92 – 2.05 (m, 2H, $NCH_2CH_aH_b$), 1.74 (d, *J* = 7.5, 2H), 1.58 – 1.68 (m, 3H, $NCHCHC_2$), 1.43 – 1.56 (m, 1H), 1.04 – 1.29 (m, 5H); observable minor diastereomer: 7.21 (d, *J* = 7.5, ArCH), 3.47 (d, *J* = 7.6, $ArNCH_aH_b$), 3.40 (m, $ArNCH_aH_b$), 2.37 – 2.46 (m, 1H), 2.20 – 2.29 (m, 1H), 0.78 – 0.95 (m, 2H); **^{13}C NMR** (175 MHz, $CDCl_3$) δ_C major diastereomer: 150.4 (ArC_{quat}), 136.0 (ArC_{quat}), 127.6 (ArCH), 122.6 (ArCH), 118.6 (ArCH), 109.6 (ArCH), 78.4 ($NCHC_2$), 56.4 ($ArNCH_2C_{quat}$) 56.1 ($ArNCH_2$), 55.2 (NCH_2CH_2), 44.4 (CH_3), 40.2 (NCH_2CH_2), 39.7 ($NCHCH(CH_2)_2$), 32.2, 30.1, 27.0, 26.6, 26.4; observable minor diastereomer: 151.7, 127.7, 124.9, 118.5, 109.5, 79.5, 62.4, 55.6, 45.2, 40.9, 38.8, 32.6, 29.8, 26.7, 26.5; ***m/z*** (ESI$^+$) 271 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{18}H_{27}N_2^+$) requires *m/z* 271.21688, found *m/z* 271.21625.

Preparation and characterisation of (2'*S,3*S**)-1'-methyl-2'-(propan-2-yl)-1,2-dihydrospiro[indole-3,3'-pyrrolidine] (133c)**



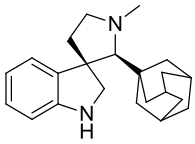
Prepared according to general procedure **R** yielded **133c** (0.106 g, 92%, d.r. 76:24) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2958 (N–H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H **major diastereomer:** 7.02 – 7.09 (m, 2H, ArH), 6.75 (t, *J* = 7.5, 1H, ArH), 6.64 (d, *J* = 8.0, 1H, ArH), 3.86 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.31 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.21 (dt, *J* = 10.0, 6.0, 1H, $NCH_aH_bCH_2$), 2.51 – 2.60 (m, 4H, $NCH_aH_bCH_2$, NCH_3), 2.47 – 2.51 (m, 1H, $NCHCH(CH_3)_2$), 1.92 – 2.04 (m, 3H, $NCH_2CH_aH_b$, $CH(CH_3)_2$), 0.99 (d, *J* = 7.0, 3H, CCH_3), 0.91 (d, *J* = 7.0, 3H, CCH_3); **minor diastereomer:** 7.25 – 7.30 (m, 1H, ArH) 7.03 – 7.08 (m, 1H, ArCH), 6.71 – 6.77 (m, 1H, ArH), 6.65 (d, *J* = 8.0, 1H, ArH), 3.53 (d, *J* = 9.0, 1H, $ArNCH_aH_b$), 3.36 – 3.47 (m, 2H, $ArNCH_aH_b$, $CH_3NCH_aH_b$), 2.47 – 2.60 (m, 4H, NCH_3, $NCH_aH_bCH_2$), 2.24 – 2.38 (m, 2H, $NCHCH(CH_3)_2$, $NCH_2CH_aH_b$), 1.76 – 1.96 (m, 2H, $NCH_2CH_aH_b$, $CH(CH_3)_2$), 0.95 – 1.00 (m, 3H, CCH_3), 0.63 (d, *J* = 7.0, 3H, CCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C **major diastereomer:** 150.6 (ArC_{quat}), 136.2 (ArC_{quat}), 127.6 (ArCH), 122.8 (ArCH), 118.6 (ArCH), 109.5 (ArCH), 78.8 ($NCHCH(CH_3)_2$), 56.4 ($ArNCH_2$), 56.0 ($ArNCH_2C_{quat}$), 55.1 (NCH_2CH_2), 43.9 (NCH_3), 40.2 (NCH_2CH_2), 28.7 ($NCHCH(CH_3)_2$), 22.1 (CCH_3), 19.1 (CCH_3); **observable minor diastereomer:** 151.6 (ArC_{quat}), 136.2 (ArC_{quat}), 127.9 (ArCH), 125.2 (ArCH), 118.7 (ArCH), 109.6 (ArCH), 80.4 ($CH_3NCHCH(CH_2)_3$), 61.8 ($ArNCH_2$), 55.5 (NCH_2CH_2), 44.8 (NCH_3), 38.7 (NCH_2CH_2), 21.9 (CCH_3), 21.0 (CCH_3); ***m/z*** (ESI$^+$) 231 ($[M+H]^+$); **HRMS** (ES$^+$) exact mass calculated for $[M+H]^+$ ($C_{15}H_{23}N_2^+$) requires *m/z* 231.18558, found *m/z* 231.18513.

Preparation and characterisation of (2'*S,3*S**)-2'-*tert*-butyl-1'-methyl-1,2-dihydrospiro[indole-3,3'-pyrrolidine] (133d)**



Prepared according to general procedure **R** yielded **133d** (0.074 g, 61%, d.r. >98:2) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2950 (N–H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H **major diastereomer:** 7.02 – 7.07 (m, 2H, ArCH), 6.76 (td, *J* = 7.5, 1.0, 1H, ArCH), 6.65 (dd, *J* = 8.0, 1.0, 1H, ArCH), 4.07 (d, *J* = 9.0, 1H, $ArNCH_aH_b$), 3.32 (d, *J* = 9.0, 1H, $ArNCH_aH_b$), 3.16 – 3.27 (m, 1H, $NCH_aH_bCH_2$), 2.65 – 2.79 (m, 5H, $NCH_aH_bCH_2$, CH_3NCHC_{quat}), 2.02 – 2.11 (m, 1H, $NCH_2CH_aH_b$), 1.84 – 1.94 (m, 1H, $NCH_2CH_aH_b$), 1.01 (s, 9H, $C(CH_3)_3$; **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C **major diastereomer:** 150.0 (ArC_{quat}), 137.2 (ArC_{quat}), 127.4 (ArCH), 122.6 (ArCH), 118.6 (ArCH), 109.7 (ArCH), 81.3 (NCC_{quat}), 57.5 ($ArNCH_2C_{quat}$), 56.0 ($ArNCH_2$), 54.8 (NCH_2CH_2), 46.3 (NCH_3), 39.5 (NCH_2CH_2), 36.2 ($NCHC(CH_3)_3$), 28.8 ($C(CH_3)_3$); ***m/z*** (ESI^+) 245 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{25}N_2^+$) requires *m/z* 245.20123, found *m/z* 245.20084.

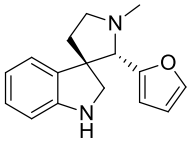
Preparation and characterisation of (2'*S,3*S**)-1'-methyl-2'-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,2-dihydrospiro[indole-3,3'-pyrrolidine] (133e)**



Prepared according to general procedure **R** yielded **133e** (0.108 g, 67%, d.r. >98:2) as a white solid. **m.p.** 102-107 °C; **IR** ν_{max}(film)/cm^{-1} 2901 (N–H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H **major diastereomer:** 7.00 – 7.07 (m, 2H, ArCH), 6.74 (t, *J* = 7.5, 1H, ArCH), 6.65 (d, *J* = 7.5, 1H, ArCH), 4.21 (d, *J* = 9.0, 1H, $ArNCH_aH_b$), 3.20 – 3.32 (m, 2H, $ArNCH_aH_b$, $NCH_aH_bCH_2$), 2.67 – 2.81 (m, 5H, $NCH_aH_bCH_2$, NCH_3, $NCHC_{quat}$), 2.09 (dt, *J* = 12.5, 5.0, 1H, $NCH_2CH_aH_b$), 1.93 (br s, 3H), 1.80 – 1.89 (m, 1H, $NCH_2CH_aH_b$), 1.59 – 1.80 (m, 12H);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C **major diastereomer:** 149.8 (ArC_{quat}), 136.0 (ArC_{quat}), 127.5 (ArCH), 122.0 (ArCH), 118.6 (ArCH), 109.8 (ArCH), 81.9 (CH_3NCHC_{quat}), 57.3 ($ArNCH_2C_{quat}$), 55.7 ($ArNCH_2$), 55.0 (NCH_2CH_2), 47.0 (NCH_3), 39.8, 38.8 (NCH_2CH_2), 38.4 ($NCHC_{quat}$), 36.7, 28.3; ***m/z*** (ESI^+) 323 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{31}N_2^+$) requires *m/z* 323.24818, found *m/z* 323.24684.

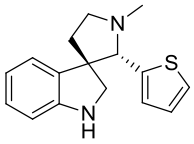
Preparation and characterisation of (2'*S**,3*S**)-2'-(furan-2-yl)-1'-methyl-1,2-dihydrospiro[indole-3,3'-pyrrolidine] (133f)



Prepared according to general procedure **R** yielded **133f** (0.120 g, 95%, d.r. 58:42) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2957 (N–H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H **major diastereomer:** 7.19 – 7.25 (m, 1H, ArCH), 6.91 – 6.99 (m, 2H, ArH), 6.53 – 6.64 (m, 2H, ArH), 6.17 (dd, *J* = 3.0, 2.0, 1H, ArH), 5.92 (d, *J* = 3.0, 1H, ArH), 3.70 (d, *J* = 9.0, 1H, $ArNCH_aH_b$), 3.49 – 3.59 (m, 2H, $ArNCH_aH_b$, CH_3NCH), 3.24 – 3.34 (m, 1H, $CH_3NCH_aH_b$), 2.57 – 2.67 (m, 1H, $CH_3NCH_aH_b$), 2.15 – 2.45 (m, 4H, CH_3, $NCH_2CH_aH_b$), 2.05 – 2.13 (m, 1H, $NCH_2CH_aCH_b$); **minor diastereomer:** 7.37 (d, *J* = 1.0, 1H, ArH) 7.19 – 7.25 (m, 1H, ArCH), 7.06 (td, 7.5, 1H, ArH), 6.81 (t, *J* = 7.5, 1H, ArH), 6.53 – 6.64 (m, 1H, ArH), 6.30 (dd, *J* = 3.0, 2.0, 1H, ArH), 6.07 (d, *J* = 3.0, 1H, ArH), 3.49 – 3.59 (m, 2H, $ArNCH_aH_b$, CH_3NCH), 3.24 – 3.34 (m, 2H, $ArNCH_aH_b$, $CH_3NCH_aH_b$), 2.57 – 2.67 (m, 1H, $CH_3NCH_aH_b$), 2.15 – 2.45 (m, 5H, CH_3, $NCH_2CH_aH_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C **major diastereomer:** 153.7 (ArC_{quat}), 151.0 (ArC_{quat}), 141.3 (ArCH), 133.2 (ArC_{quat}), 127.5 (ArCH), 124.7 (ArCH), 118.6 (ArCH), 109.9 (ArCH), 109.4 (ArCH), 107.9 (ArCH), 73.7 (CH_3NCHAr), 60.8 ($ArNCH_2$), 56.6 ($ArNCH_2C_{quat}$), 54.3 (NCH_2CH_2), 40.8 (CH_3), 38.1 (NCH_2CH_2); **minor diastereomer:** 152.8 (ArC_{quat}), 150.9 (ArC_{quat}), 142.1 (ArCH), 135.3

(ArC_{quat}), 127.8 (ArCH), 122.7 (ArCH), 118.9 (ArCH), 110.0 (ArCH), 109.9 (ArCH), 108.3 (ArCH), 74.1 (CH_3NCHAr), 58.0 ($ArNCH_2$), 56.2 ($ArNCH_2C_{quat}$), 54.8 (NCH_2CH_2), 40.8 (CH_3), 39.2 (NCH_2CH_2); ***m/z*** (ESI^+) 255 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}ON_2^+$) requires *m/z* 255.14919, found *m/z* 255.14889.

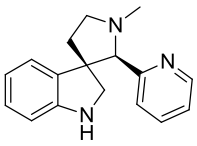
Preparation and characterisation of (2'*S,3*S**)-1'-methyl-2'-(thiophen-2-yl)-1,2-dihydrospiro[indole-3,3'-pyrrolidine] (133h)**



Prepared according to general procedure **R** yielded **133h** (0.130 g, 96%, d.r. 57:43) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2941 (N–H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H **major diastereomer:** 7.16 (dd, *J* = 7.5, 1.0, 1H, ArCH), 7.05 – 7.10 (m, 1H, ArH), 6.99 (td, *J* = 7.5, 1.0, 1H, ArH), 6.79 – 6.82 (m, 1H, ArH), 6.74 (dd, *J* = 3.5, 1.0, 1H, ArH), 6.69 (td, *J* = 7.5, 1.0, 1H, ArCH), 6.49 (d, *J* = 7.5, 1H, ArCH), 3.64 – 3.69 (m, 2H, $ArNCH_aH_b$, CH_3NCHAr), 3.56 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.42 (ddd, *J* = 9.5, 8.5, 3.5, 1H, $NCH_aH_bCH_2$), 2.55 (td, *J* = 9.0, 8.1, 1H, $NCH_aH_bCH_2$), 2.30 – 2.45 (m, 4H, $NCH_2CH_aCH_b$, CH_3), 2.04 – 2.19 (m, 1H, $NCH_2CH_aCH_b$); **minor diastereomer:** 7.24 (dd, *J* = 7.5, 1.0, 1H, ArH), 7.21 (dd, *J* = 5.0, 1.0, 1H, ArH), 7.05 – 7.10 (m, 1H, ArH), 6.90 (dd, *J* = 5.0, 3.5, 1H, ArH), 6.83 – 6.86 (m, 1H, ArH), 6.64 (d, *J* = 3.5, 1H, ArH), 6.57 (d, *J* = 7.5, 1H, ArH), 3.73 (s, 1H, CH_3NCHAr), 3.62 – 3.67 (m, 1H, $ArNCH_aH_b$), 3.36 (ddd, *J* = 9.5, 8.5, 3.5, 1H, $NCH_aH_bCH_2$), 3.19 (d, *J* = 10.0, 1H, $ArNCH_aH_b$), 2.59 – 2.67 (m, 1H, $NCH_aH_bCH_2$), 2.30 – 2.45 (m, 4H, $NCH_2CH_aCH_b$, CH_3), 2.04 – 2.19 (m, 1H, $NCH_2CH_aCH_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C **major diastereomer:** 151.2 (ArC_{quat}), 143.4 (ArC_{quat}), 133.6 (ArC_{quat}), 127.8 (ArCH), 125.7 (ArCH), 125.7 (ArCH), 125.0 (ArCH), 124.8 (ArCH), 118.5 (ArCH), 109.3 (ArCH), 76.6 (CH_3NCHAr), 59.2 ($ArNCH_2$), 57.1 ($ArNCH_2C_{quat}$), 54.2 (NCH_2CH_2), 41.2 (CH_3), 37.5

(NCH_2CH_2); **minor diastereomer:** 151.4 (ArC_{quat}), 142.9 (ArC_{quat}), 134.6 (ArC_{quat}), 128.0 (ArCH), 126.4 (ArCH), 125.6 (ArCH), 124.2 (ArCH), 122.8 (ArCH), 118.8 (ArCH), 110.1 (ArCH), 76.3 (CH_3NCHAr), 57.2 ($ArNCH_2$), 56.9 ($ArNCH_2C_{quat}$), 54.8 (NCH_2CH_2), 41.4 (CH_3), 38.7 (NCH_2CH_2); ***m/z*** (ESI^+) 271 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{19}N_2S^+$) requires *m/z* 271.12635, found *m/z* 271.12590.

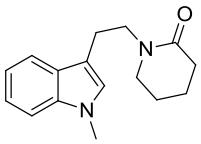
Preparation and characterisation of (2'*R,3*S**)-1'-methyl-2'-(pyridin-2-yl)-1,2-dihydrospiro[indole-3,3'-pyrrolidine] (133i)**



Prepared according to general procedure **R** yielded **133i** (0.121 g, 91%, d.r. >98:2) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 2941 (N–H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.36 – 8.39 (m,1H, ArCH), 7.36 (td, *J* = 7.5, 2.0, 1H, ArCH), 7.10 (d, *J* = 8.0, 1H, ArH), 6.95 – 7.03 (m, 2H, ArH), 6.84 (td, *J* = 7.5, 1.5, 1H, ArH), 6.55 (td, *J* = 7.5, 1.0, 1H, ArCH), 6.37 (d, *J* = 8.0, 1H, ArCH), 3.96 (d, *J* = 9.5, 1H, $ArNCH_aH_b$), 3.54 – 3.59 (m, 2H, $ArNCH_aH_b$, NCHAr), 3.44 (td, *J* = 8.5, 3.0, 1H, $NCH_aH_bCH_2$), 2.59 ("q", *J* = 9.0, 1H, $NCH_aH_bCH_2$), 2.28 – 2.42 (m, 4H, $NCH_2CH_aCH_b$, CH_3), 2.12 (ddd, *J* = 12.5, 9.0, 3.0, 1H, $NCH_2CH_aCH_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C[*] 150.8 (ArC_{quat}), 148.3 (ArCH), 135.1 (ArCH), 127.4 (ArCH), 125.2 (ArCH), 122.6 (ArCH), 121.8 (ArCH), 118.3 (ArCH), 109.5 (ArCH), 82.3 (NCHAr), 59.6 ($ArNCH_2$), 57.3 ($ArNCH_2C_{quat}$), 54.8 (NCH_2CH_2), 41.1 (CH_3), 38.2 (NCH_2CH_2); ***m/z*** (ESI^+) 266 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{20}N_3^+$) requires *m/z* 266.16517, found *m/z* 266.16491.

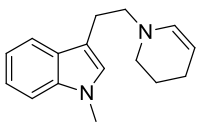
Preparation and characterisation of 1-[2-(1-methyl-1*H*-indol-3-yl)ethyl]piperidin-2-one (146)

[*] Two of the aryl quaternary carbon signals could not be seen by ^{13}C NMR.



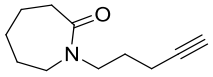
A solution of **123** (0.33 mmol, 1 equiv.) in DMF (2ml) was added slowly to a cooled flask (0 °C) of sodium hydride (0.44 mmol, 1.3 equiv.) under argon and was stirred for 10 mins at 0 °C then 20 mins at room temperature. Methyl iodide (0.54 mmol, 1.6 equiv.) was added and the reaction was stirred for 3h. The reaction mixture was quenched with a $(5\%)_{aq}$ LiCl solution and extracted with EtOAc. The combined organics were washed with brine and dried over Na_2SO_4 concentrated and purified by FCC to yielded **146** (0.056 g, 66%) as a yellow solid. **m.p.** 115-118 °C **IR** ν_{max}(film)/cm^{-1} 1618 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.67 (d, *J* = 8.0, 1H, ArH), 7.30 (d, *J* = 8.0, 1H, ArH), 7.23 (td, *J* = 7.5, 1.0, 1H, ArH), 7.10 – 7.15 (m, 1H, ArH), 6.91 (s, 1H, ArH), 3.74 (s, 3H, NCH_3), 3.61 – 3.67 (m, 2H, NCH_2CH_2Ar), 3.19 (t, *J* = 5.5, 2H, $NCH_2CH_2CH_2$), 3.01 – 3.06 (m, 2H, NCH_2CH_2Ar), 2.41 (t, *J* = 6.5, 2H, $C(O)CH_2$), 1.65 – 1.78 (m, 4H, $NCH_2CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.5 (NC(O)), 136.8 (ArC_{quat}), 127.8 (ArC_{quat}), 126.6 (ArCH), 121.4 (ArCH), 118.8 (ArCH), 118.6 (ArCH), 111.8 (ArC_{quat}), 109.1 (ArCH), 48.5 (NCH_2CH_2Ar), 48.5 ($NCH_2CH_2CH_2$), 32.5 ($ArNCH_3$), 32.3 ($NC(O)CH_2$), 23.1, 22.8, 21.2; ***m/z*** (ESI^+) 257 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}ON_2^+$) requires *m/z* 257.16484, found *m/z* 257.16419.

Preparation and characterisation of 1-[2-(1-methyl-1*H*-indol-3-yl)ethyl]piperidin-2-one (148)



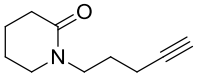
An NMR spectrum was taken of a solution of **146** (0.05 mmol, 1 equiv.), TMDS (0.15 mmol, 3 equiv.) and mesitylene (0.05 mmol, 1 equiv.) in CD_2Cl_2 (0.6 ml). The solution was then added Vaska's complex (0.001 mmol, 0.02 equiv.) in a vial before returning the solution to the NMR tube. The ^{1}H NMR spectrum was then recorded giving **148** (89% NMR yield). **^{1}H NMR** (400 MHz, CD_2Cl_2) δ_H 7.56 – 7.60 (m, 1H, ArH), 7.28 – 7.32 (m, 1H, ArH), 7.17 – 7.22 (m, 1H, ArH), 7.05 – 7.11 (m, 1H, ArH), 6.90 (s, 1H, ArH), 5.92 – 5.96 (m, 1H, NCH=CH), 4.32 – 4.37 (m, 1H, NCH=CH), 3.74 (s, 3H, NCH_3), 3.03 – 3.12 (m, 4H, CH_2NCH_2), 2.89 – 2.95 (m, 2H, $ArCH_2$), 1.95 – 2.05 (m, 2H), 1.84 – 1.92 (m, 2H); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ_C* 136.5, 127.2, 121.9, 119.3, 119.1, 113.0, 109.7, 96.3, 56.8, 47.6, 33.0, 26.8, 23.6, 21.9.

Preparation and characterisation of 1-(pent-4-yn-1-yl)azepan-2-one (154a)



Prepared according to general procedure **J** yielded **154a** (1.4 g, 65%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1628 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.43 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2CCH$), 3.31 – 3.37 (m, 2H, $NCH_2CH_2CH_2CH_2$), 2.45 – 2.53 (m, 2H, $NC(O)CH_2$), 2.20 (td, *J* = 7.0, 2.5, 2H, CH_2CCH), 1.95 (t, *J* = 2.5, 1H, CCH), 1.59 – 1.79 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 175.7 (NC(O)), 83.6 (CH_2CCH), 68.6 (CCH), 49.9 ($NCH_2CH_2CH_2CH_2$), 47.5 ($NCH_2CH_2CH_2CCH$), 37.2 ($C(O)CH_2$), 29.9, 28.9, 27.0, 23.4, 16.0 (CH_2CCH); ***m/z*** (ESI^+) 180 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{18}ON^+$) requires *m/z* 180.13829, found *m/z* 180.13809.

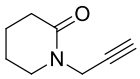
Preparation and characterisation of 1-(pent-4-yn-1-yl)piperidin-2-one (154b)



* Missing two out of the 10 possible aromatic or alkene carbon signals.

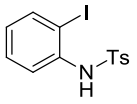
Prepared according to general procedure **J** yielded **154b** (1.1 g, 30%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1619 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.41 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2CC$), 3.25 – 3.31 (m, 2H, $NCH_2CH_2CH_2CH_2$), 2.34 (t, *J* = 6.0, 2H, $C(O)CH_2$), 2.15 – 2.24 (m, 2H, $HCCCH_2$), 1.94 (t, *J* = 2.5, 1H, CCH), 1.70 – 1.83 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.7 (NC(O)), 83.6 (CCH), 68.6 (CCH), 48.2 ($NCH_2CH_2CH_2CH_2$), 46.3 ($NCH_2CH_2CH_2CCH$), 32.2 ($C(O)CH_2$), 25.9, 23.2, 21.3, 16.0 (CH_2CCH); ***m/z*** (ESI$^+$) 166 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{10}H_{16}ON^+$) requires *m/z* 166.12264, found *m/z* 166.12245.

Preparation and characterisation of 1-(prop-2-yn-1-yl)piperidin-2-one (154c)



Prepared according to general procedure **J** yielded **154c** (2.0 g, 70%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1627 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 4.22 (d, *J* = 2.5, 2H, CH_2CCH), 3.39 (t, *J* = 6.0, 2H, NCH_2CH_2), 2.38 (t, *J* = 6.5, 2H, $C(O)CH_2$), 2.18 (t, *J* = 2.5, 1H, CCH), 1.75 – 1.89 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.4 (NC(O)), 78.7 (CH_2CCH), 71.6 (CH_2CCH), 47.1 (NCH_2CCH), 35.5 (NCH_2CH_2), 32.3 ($C(O)CH_2$), 23.0, 21.3; ***m/z*** (ESI$^+$) 138 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_8H_{12}ON^+$) requires *m/z* 138.09134, found *m/z* 138.09104.

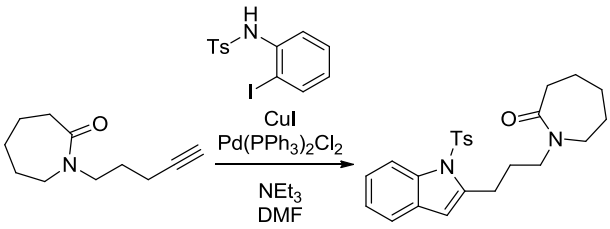
Preparation and characterisation of *N*-(2-iodophenyl)-4-methylbenzenesulfonamide (155)[15]



2-Iodoaniline (5.0 g, 23 mmol) was dissolved in pyridine (40 ml) under nitrogen. TsCl (4.6 g, 24 mmol) was added in one portion to the reaction mixture and the reaction was stirred for

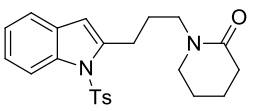
1.5 h at room temperature. The reaction was concentrated *in vacuo* and purified by FCC affording **155** (8.5 g, 99%) as an off white solid. **IR** ν_{max}(film)/cm^{-1} 3301 (N–H), 1335, 1159 (NS=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.62 – 7.68 (m, 4H, ArH), 7.28 – 7.34 (m, 1H, ArH), 7.20 – 7.24 (d, *J* = 8.0, 1H, ArH), 6.79 – 6.86 (m, 2H, ArH), 2.39 (s, 3H, ArCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 144.2 , 139.1, 137.5, 135.9, 129.6, 129.5, 127.4, 126.8, 122.4 , 92.3 (ArCI), 21.6 (CH_3); Data is in accordance with literature.[15]

General procedure U for Larock indole formation 156



A solution of **155** (1 eq), triethylamine (2 eq), CuI (0.25 eq) and $Pd(PPh_3)_2Cl_2$ (0.07 eq) in DMF (1.5 ml/ mmol **155**) was stirred for 30 mins under argon. Alkyne **154** (1.1 eq) was added in one portion and the reaction was stirred at 60 °C and monitored by TLC analysis. Upon completion the reaction mixture was concentrated *in vacuo*, suspended in DCM amd washed with NaOH (4M), brine, dried over $MgSO_4$ concentrated and purified by FCC to afford **156**.

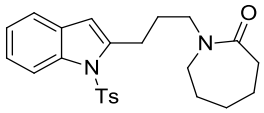
Preparation and Characterisation of 1-(3-(1H-indol-3-yl)propyl)piperidin-2-one (156b)



Prepared according to general procedure **U** yielded **156b** (0.9 g, 76%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1632 (NC=O), 1365, 1173 (NS=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.15 (d, *J* = 8.0, 1H, ArCH), 7.59 (d, *J* = 8.0, 2H, ArCH), 7.40 d, *J* = 7.5, 1H, ArCH), 7.15 – 7.26 (m, 4H, ArH), 6.46 (s, 1H, ArCH), 3.49 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 3.29 – 3.35 (m, 2H,

$NCH_2CH_2CH_2CH_2$), 3.01 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 2.36 – 2.42 (m, 2H, $C(O)CH_2$), 2.33 (s, 3H, CH_3), 2.03 (quin, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 1.74 – 1.86 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C* 169.8 (NC(O)), 144.7 (ArC_{quat}), 141.4 (ArC_{quat}), 137.2 (ArC_{quat}), 136.0 (ArC_{quat}), 129.8 (ArCH), 126.2 (ArCH), 123.9 (ArCH), 123.6 (ArCH), 120.2 (ArCH), 114.8 (ArCH), 109.4 (ArCH), 47.9 ($NCH_2CH_2CH_2CH_2$), 46.7 ($NCH_2CH_2CH_2Ar$), 32.4 ($C(O)CH_2$), 26.7 ($NCH_2CH_2CH_2Ar$), 26.7 ($NCH_2CH_2CH_2Ar$), 23.3, 21.5 (CH_3), 21.4; ***m/z*** (ESI^+) 433 ($[M+Na]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{26}O_3N_2NaS^+$) requires *m/z* 433.15563, found *m/z* 433.15459.

Preparation and Characterisation of 1-(3-(1-tosyl-1H-indol-3-yl)propyl)azepan-2-one (156a)

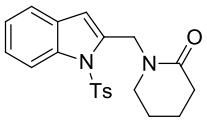


Prepared according to general procedure **U** yielded **156a** (0.9 g, 77%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1635 (NC=O), 1366, 1173 (NS=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.15 (d, *J* = 8.0, 1H, ArCH), 7.60 (d, *J* = 8.0, 2H, ArCH), 7.41 (d, *J* = 7.5, 1H, ArCH), 7.15 – 7.26 (m, 4H, ArH), 6.46 (s, 1H, ArCH), 3.49 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 3.35 – 3.40 (m, 2H, $NCH_2CH_2CH_2CH_2$), 3.00 (t, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 2.51 – 2.57 (m, 2H, $C(O)CH_2$), 2.33 (s, 3H, CH_3), 1.99 (quin, *J* = 7.5, 2H, $NCH_2CH_2CH_2Ar$), 1.62 – 1.80 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C† 175.8 (NC(O)), 144.7 (ArC_{quat}), 141.4 (ArC_{quat}), 137.2 (ArC_{quat}), 136.0 (ArC_{quat}), 129.8 (ArCH), 126.2 (ArCH), 123.9 (ArCH), 123.5 (ArCH), 120.2 (ArCH), 114.8 (ArCH), 109.3 (ArCH), 49.7 ($NCH_2CH_2CH_2CH_2$), 47.8 ($NCH_2CH_2CH_2Ar$), 37.3 ($C(O)CH_2$), 30.0, 28.7, 27.7 ($NCH_2CH_2CH_2Ar$), 26.6 ($NCH_2CH_2CH_2Ar$), 23.4, 21.5 (CH_3); ***m/z*** (ESI^+)

* One of the aryl quaternary carbon signals could not be seen by ^{13}C NMR.
† One of the aryl quaternary carbon signals could not be seen by ^{13}C NMR.

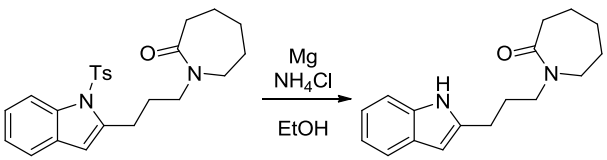
425 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{24}H_{29}O_3N_2S^+$) requires *m/z* 425.18934, found *m/z* 425.18834.

Preparation and characterisation of 1-((1-tosyl-1H-indol-3-yl)methyl)piperidin-2-one (156c)



Prepared according to general procedure **U** yielded **156c** (0.77 g, 67%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 1632 (NC=O), 1368, 1173 (NS=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.13 (d, *J* = 8.0, 1H, ArCH), 7.74 (d, *J* = 8.0, 2H, ArCH), 7.41 (d, *J* = 7.5, 1H, ArCH), 7.17 – 7.31 (m, 4H, ArH), 6.40 (s, 1H, ArCH), 5.04 (s, 2H, NCH_2Ar), 3.44 (br s, 2H, NCH_2CH_2), 2.52 (br s, 2H, $C(O)CH_2$), 2.33 (s, 3H, CH_3), 1.90 (br s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.0 (NC(O)), 144.9 (ArC_{quat}), 137.3 (ArC_{quat}), 136.9 (ArC_{quat}), 135.3 (ArC_{quat}), 129.9 (ArCH), 129.5 (ArC_{quat}), 126.4 (ArCH), 124.2 (ArCH), 123.7 (ArCH), 120.5 (ArCH), 114.6 (ArCH), 108.9 (ArCH), 48.4 (NCH_2CH_2), 45.5 (NCH_2Ar), 32.3 ($C(O)CH_2$), 23.4, 21.5, 21.4; ***m/z*** (ESI$^+$) 383 ([M+H]$^+$); **HRMS** (ES$^+$) exact mass calculated for [M+H]$^+$ ($C_{21}H_{23}O_3N_2S^+$) requires *m/z* 383.14239, found *m/z* 383.14176.

General procedure V towards 157

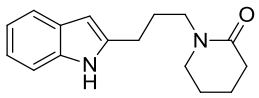


156a 77% **157a** 76%

To a stirred solution of **156** (1 eq) in EtOH (7 ml/ mmol **156**) was added magnesium turnings (5 eq) and ammonium chloride (2.2 eq). The reaction was monitored by TLC analysis and upon completion the reaction mixture was filtered, diluted with EtOAc and washed with

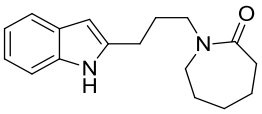
saturated ammonium chloride, brine, dried over Na_2SO_4, concentrated *in vacuo* and purified by FCC to afford **157**.

Preparation and characterisation 1-[3-(1*H*-indol-2-yl)propyl]piperidin-2-one (157b)



Prepared according to general procedure **V** yielded **157b** (0.40 g, 90%) as a light brown solid **m.p.** 125–126 °C; **IR** ν_{max}(film)/cm^{-1} 1640 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.15 (br s, 1H, ArNH), 7.54 (d, *J* = 8.0, 1H, ArCH), 7.41 (d, *J* = 8.0, 1H, ArCH), 7.12 (td, *J* = 7.5, 1.0, 1H, ArCH), 7.03 – 7.08 (m, 1H, ArCH), 6.23 (s, 1H, ArCH), 3.54 (t, *J* = 6.5, 2H, $NCH_2CH_2CH_2Ar$), 3.26 – 3.32 (m, 2H, $NCH_2CH_2CH_2CH_2$), 2.70 – 2.76 (m, 2H, $ArCH_2$), 2.46 – 2.52 (m, 2H, $NC(O)CH_2$), 1.80 – 1.95 (m, 6H, $ArCH_2CH_2$, $NC(O)CH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 170.8 (NC(O)), 139.5 (ArC_{quat}), 136.0 (ArC_{quat}), 128.6 (ArC_{quat}), 120.5 (ArCH), 119.4 (ArCH), 119.0 (ArCH), 110.9 (ArCH), 99.0 (ArCH), 47.5 ($NCH_2CH_2CH_2Ar$), 45.7 ($NCH_2CH_2CH_2CH_2$), 32.2 ($NC(O)CH_2$), 27.2 ($NCH_2CH_2CH_2Ar$), 24.2 ($ArCH_2$), 23.1, 21.2; ***m/z*** (ESI^+) 257 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{21}ON_2^+$) requires *m/z* 257.16484, found *m/z* 257.16446.

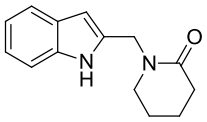
Preparation and characterisation of 1 1-(3-(1H-indol-3-yl)propyl)azepan-2-one (157a)



Prepared according to general procedure **V** yielded **157a** (0.20 g, 70%) as a light brown solid **m.p.** 94–96 °C;. **IR** ν_{max}(film)/cm^{-1} 3246 (N–H), 1624 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.15 (br s, 1H, ArNH), 7.54 (d, *J* = 7.5, 1H, ArCH), 7.41 (d, *J* = 8.0, 1H, ArCH), 7.02 – 7.14 (m, 1H, ArH), 6.22 (s, 1H, ArCH), 6.39 (s, 1H, ArCH), 3.53 (t, *J* = 6.0, 2H,

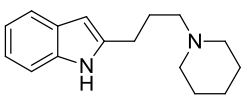
$NCH_2CH_2CH_2Ar$), 3.34 – 3.41 (m, 2H, $NCH_2CH_2CH_2CH_2$), 2.70 – 2.77 (m, 2H, $NCH_2CH_2CH_2Ar$), 2.60 – 2.67 (m, 2H, $C(O)CH_2$), 1.87 (quin, *J* = 6.0, 2H, $NCH_2CH_2CH_2Ar$), 1.64 – 1.82 (m, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 177.0 (NC(O)), 139.6 (ArC_{quat}), 136.1 (ArC_{quat}), 128.7 (ArC_{quat}), 120.6 (ArCH), 119.4 (ArCH), 119.1 (ArCH), 111.0 (ArCH), 99.0 (ArCH), 49.3 ($NCH_2CH_2CH_2CH_2$), 46.8 ($NCH_2CH_2CH_2Ar$), 37.3 ($C(O)CH_2$), 29.9, 28.4, 28.3 ($NCH_2CH_2CH_2Ar$), 24.1 ($NCH_2CH_2CH_2Ar$), 23.4; ***m/z*** (ESI^+) 271 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}ON_2^+$) requires *m/z* 271.18049, found *m/z* 271.18006.

Preparation and characterisation of 1-((1H-indol-3-yl)methyl)piperidin-2-one (157c)



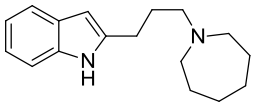
Prepared according to general procedure **V** yielded **157c** (0.23 g, 65%) as a light brown solid **m.p.** 140–145 °C; **IR** ν_{max}(film)/cm^{-1} 3244 (N–H), 1622 (NC=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.21 (br s, 1H, ArNH), 7.58 (d, *J* = 8.0, 1H, ArCH), 7.35 (d, *J* = 8.0, 1H, ArCH), 7.18 (t, *J* = 7.5, 1H, ArH), 7.09 (m, 1H, ArCH), 6.39 (s, 1H, ArCH), 4.57 (s, 2H, NCH_2Ar), 3.37 (br s, 2H, $NCH_2CH_2CH_2CH_2$), 2.44 (br s, 2H, $C(O)CH_2$), 1.77 (br s, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 171.3 (NC(O)), 136.5 (ArC_{quat}), 135.0 (ArC_{quat}), 127.5 (ArC_{quat}), 121.9 (ArCH), 120.2 (ArCH), 119.5 (ArCH), 111.1 (ArCH), 101.5 (ArCH), 47.9 ($NCH_2CH_2CH_2CH_2$), 45.1 (NCH_2Ar), 32.3 ($C(O)CH_2$), 23.0, 21.0; ***m/z*** (ESI^+) 251 ($[M+Na]^+$); **HRMS** (ES^+) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{16}ON_2Na^+$) requires *m/z* 251.11548, found *m/z* 251.11504.

Preparation and characterisation of 2-[3-(piperidin-1-yl)propyl]-1*H*-indole (159b)



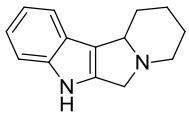
Prepared according to general procedure **R** yielded **159b** (0.030 g, 50%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 3401 (N-H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.41 (br s, 1H, ArNH), 7.58 (d, *J* = 8.0, 1H, ArCH), 7.31 – 7.49 (m, 1H, ArCH), 7.09 – 7.28 (m, 1H, ArCH), 6.82 – 7.08 (m, 1H, ArCH), 6.07 (br s, 1H, ArCH), 2.64 –2.89 (m, 2H, $ArCH_2$), 2.19 – 2.54 (m, 6H, $NCH_2CH_2CH_2Ar$, $N(CH_2CH_2)_2$), 1.31 – 1.90 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 139.7 (ArC_{quat}), 136.2 (ArC_{quat}), 128.9 (ArC_{quat}), 120.5 (ArC_{quat}), 119.6 (ArCH), 119.1 (ArCH), 110.5 (ArCH), 99.0 (ArCH), 59.2 ($NCH_2CH_2CH_2Ar$), 54.5 ($N(CH_2CH_2)_2$), 27.3 ($NCH_2CH_2CH_2Ar$), 25.6, 25.2, 24.1; ***m/z*** (ESI^+) 243 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}N_2^+$) requires *m/z* 243.18558, found *m/z* 243.18527.

Preparation and characterisation of 2-[3-(azepan-1-yl)propyl]-1*H*-indole (159a)



Prepared according to general procedure **R** yielded **159a** (0.028 g, 44%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 3401 (N-H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.27 (br s, 1H, ArNH), 7.55 (d, *J* = 7.5, 1H, ArCH), 7.33 (d, *J* = 7.5, 1H, ArCH), 7.03 – 7.16 (m, 2H, ArCH), 6.23 (s, 1H, ArCH), 2.91 (t, *J* = 6.5, 2H, $ArCH_2$), 2.69 – 2.75 (m, 4H, $N(CH_2CH_2CH_2)_2$), 2.60 (t, *J* = 6.5, 2H, $NCH_2CH_2CH_2Ar$), 1.90 (quin, *J* = 6.5, 2H, $NCH_2CH_2CH_2Ar$), 1.69 – 1.83 (m, 8H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 139.9 (ArC_{quat}), 136.1 (ArC_{quat}), 129.0 (ArC_{quat}), 120.5 (ArC_{quat}), 119.6 (ArCH), 119.1 (ArCH), 110.5 (ArCH), 98.9 (ArCH), 58.3 ($NCH_2CH_2CH_2Ar$), 55.8 ($N(CH_2CH_2CH_2)_2$), 27.6 ($N(CH_2CH_2CH_2)_2$), 27.0 ($NCH_2CH_2CH_2Ar$), 26.9 ($N(CH_2CH_2CH_2)_2$), 26.4 ($NCH_2CH_2CH_2Ar$); ***m/z*** (ESI^+) 257 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}N_2^+$) requires *m/z* 257.20123, found *m/z* 257.20069.

Preparation and characterisation of 6,8,9,10,11,11a-hexahydro-5*H*-indolizino[2,1-*b*]indole (158c)

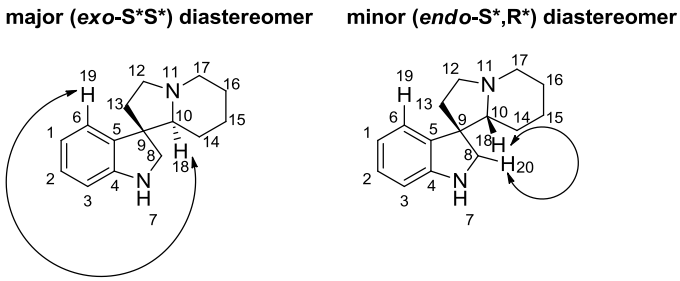


Prepared according to general procedure **R** yielded **158c** (0.042 g, 79%) as a yellow oil. **IR** ν_{max}(film)/cm^{-1} 3229 (N–H); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.58 – 7.62 (m, 1H, ArCH), 7.35 – 7.39 (m, 1H, ArCH), 7.07 – 7.17 (m, 2H, ArCH), 6.25 (s, 1H, NH), 4.37 – 4.43 (m, 1H, NCHAr), 4.18 (d, *J* = 13.0, 1H, NCH_aH_bAr), 3.72 (d, *J* = 13.0, 1H, NCH_aH_bAr), 3.12 (dt, *J* = 11.5, 4.0, 1H), 2.75 (ddd, *J* = 11.5, 9.5, 4.5, 1H), 2.57 – 2.66 (m, 1H), 1.90 – 2.02 (m, 2H), 1.53 – 1.82 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 140.5 (ArC_{quat}), 132.8 (ArC_{quat}), 131.9 (ArC_{quat}), 120.8 (ArCH), 120.5 (ArCH), 119.2 (ArCH), 109.4 (ArCH), 92.8 (ArCH), 76.5 (NCHAr), 51.1 (NCH_2), 49.9 (NCH_2), 29.2, 24.6, 22.1; ***m/z*** (ESI^+) 213 ($[M+H]^+$); **HRMS** (ES^+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{17}N_2^+$) requires *m/z* 213.13863, found *m/z* 213.13872.

6. Appendicies

Appendix A: NOE and NOESY data for Spiro-indoline 125c

Figures A.1 shows the NOE study of **125c** (in $CDCl_3$) spectrum **A** shows the ^{1}HNMR of **125c**. Spectrum **B** shows irradiation of 19_{minor}, No significant NOE interaction can be seen. Spectrum **C** shows the irradiation of 19_{major} which shows a good NOE interaction with H_{major}. Spectra **D** and **F** shows the irradiation of 8_{major} which shows no NOE interaction with 18_{major}. Spectrum **E** shows the irradiation of 8_{minor} this shows a small NOE interaction with 18_{minor}. Spectrum **G** shows the irradiation of 18_{major} which shows an NOE interaction with 19_{major}. Spectrum **H** shows the irradiation of 18_{minor} which shows a good NOE interaction with 8_{minor}. Further NOE studies with a solvent swap to CD_2Cl_2 can be seen in Figure **A.2** in this spectrum 18_{minor} can clearly be seen (Spectrum **I**). Spectrum **K** shows the irradiation of 8_{minor}, this time a clear NOE interaction with 18_{minor} can be seen. When 18_{minor} is irradiated (Spectrum **M**) again a clear NOE interaction can be seen with 8_{minor}. A NOESY experiment also shows the same NOE interactions (Figure A.3). This information implies the major diastereomer is the (*exo*-S*,S*) diastereomer for compound 125c.



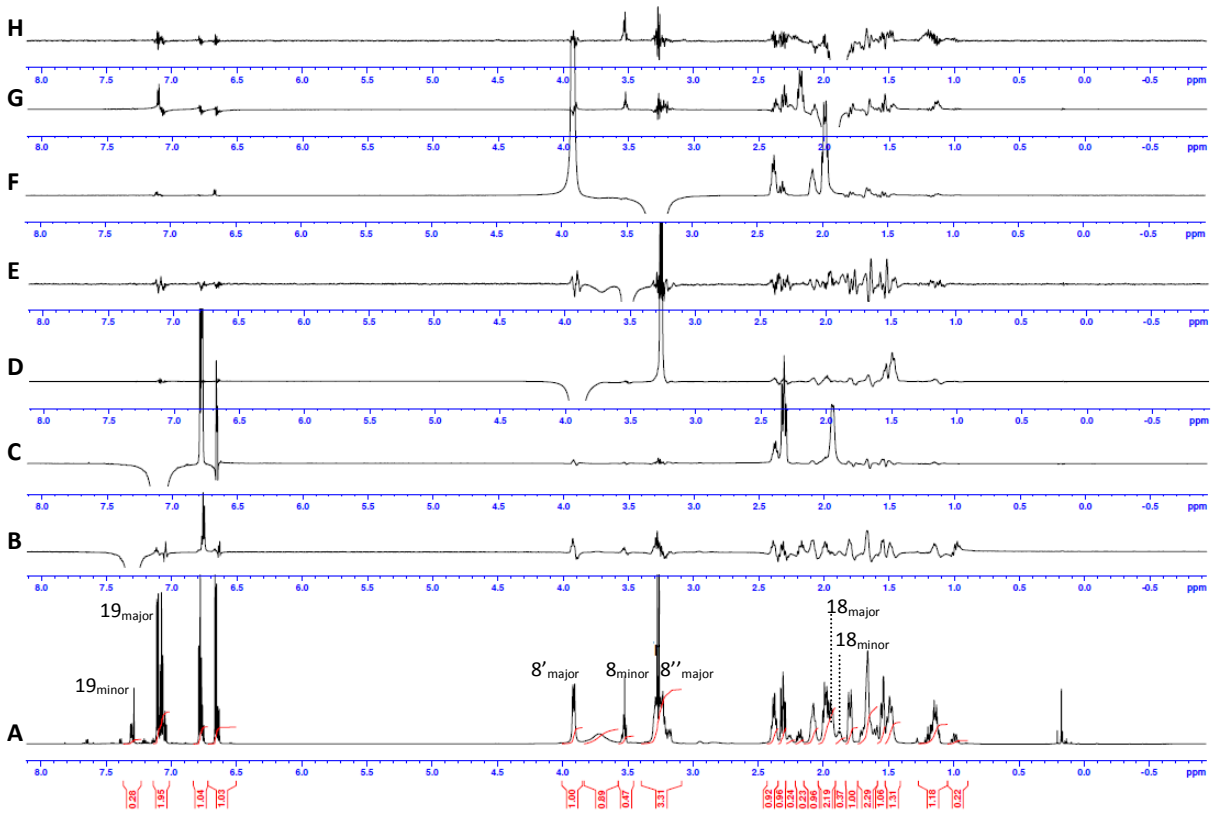


Figure A.1. NOE data for data for Spiro-indoline **125c** in $CDCl_3$

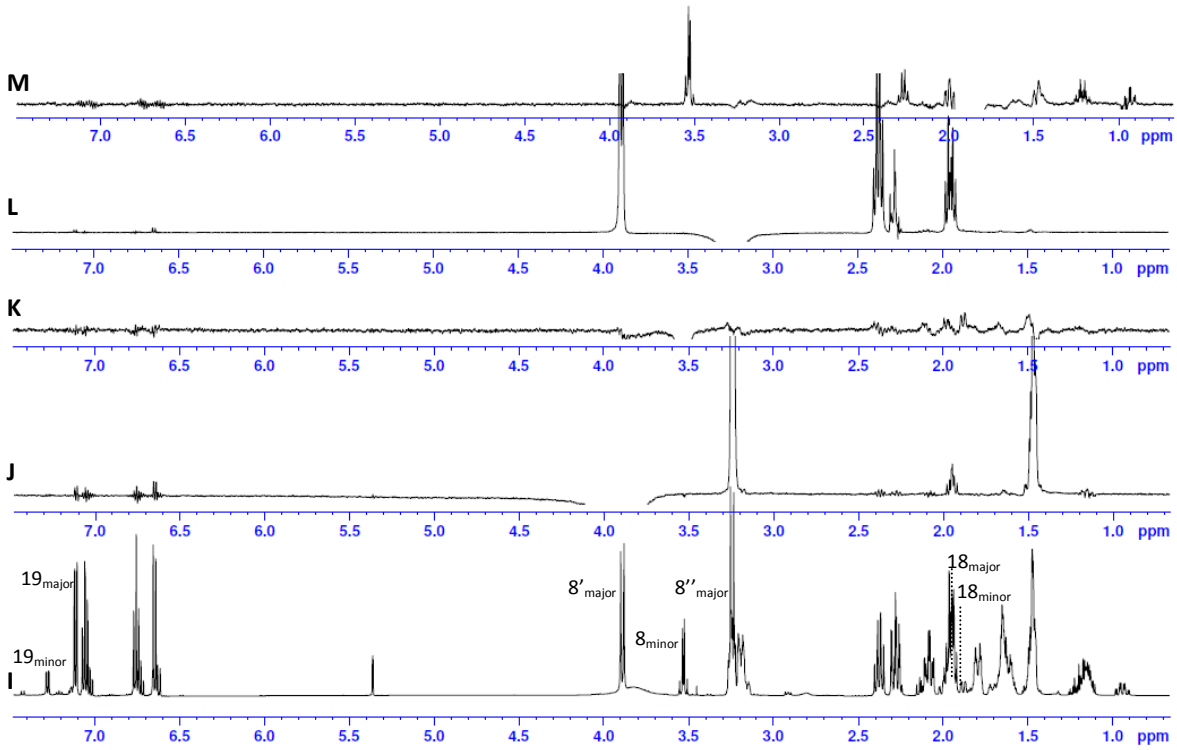


Figure A.1. NOE data for data for Spiro-indoline **125c** in CD_2Cl_2

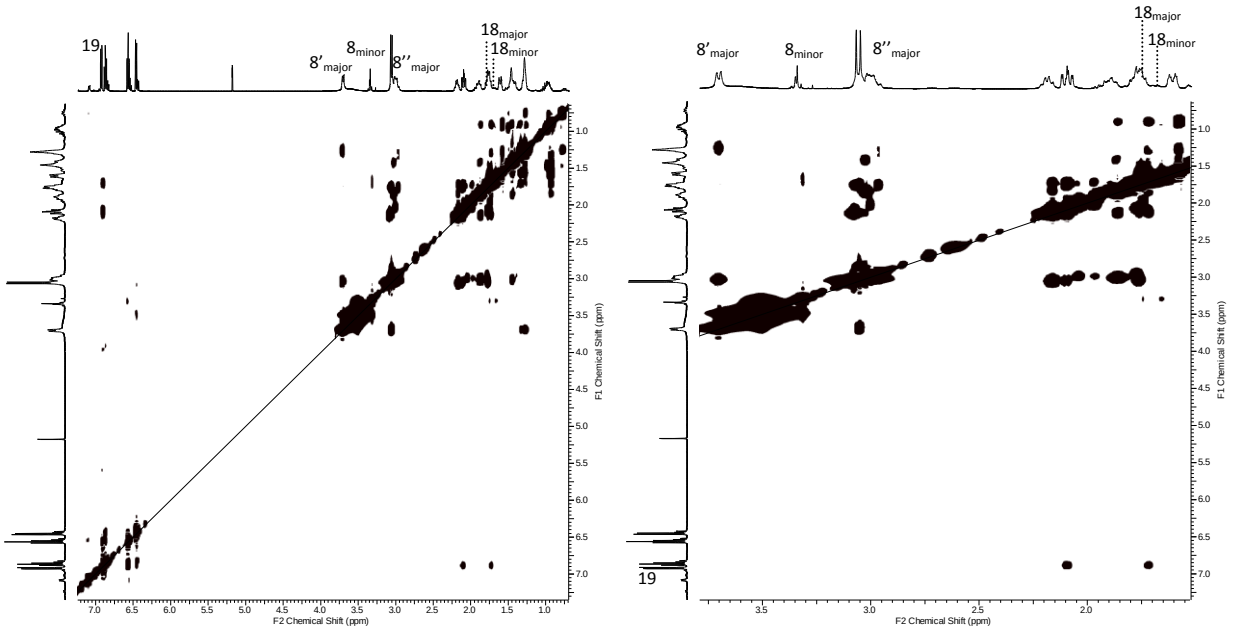
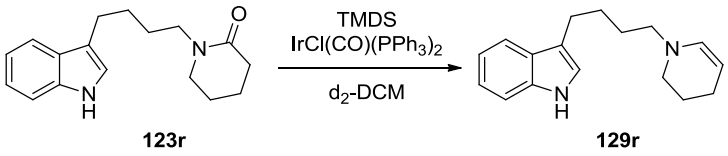
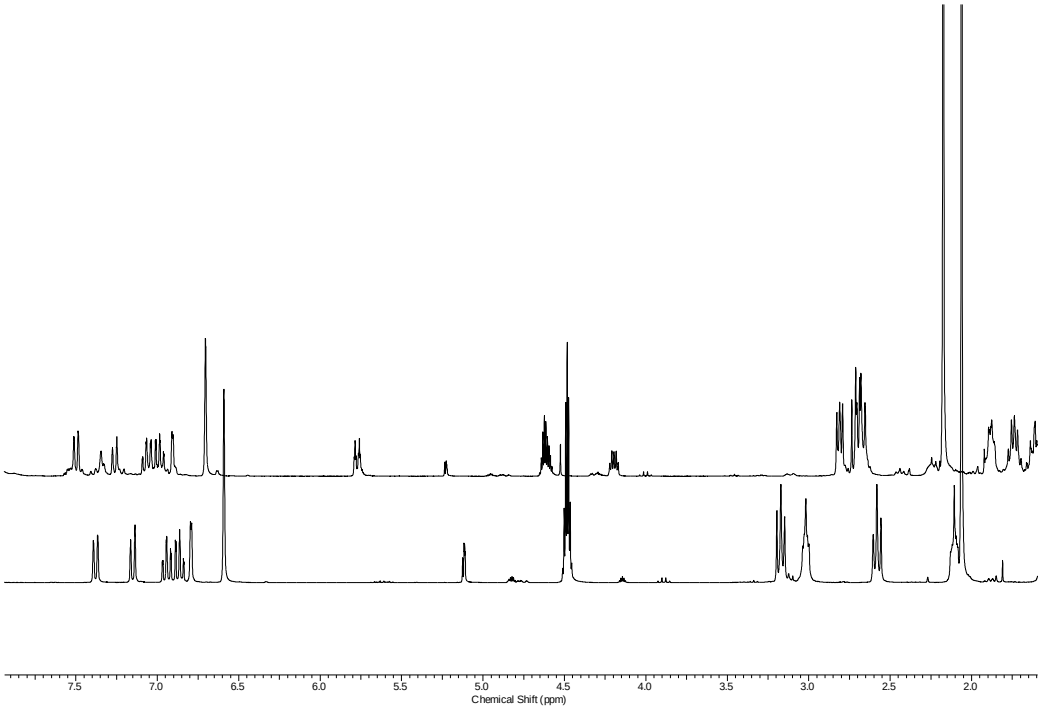


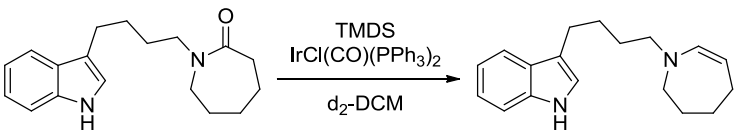
Figure A.3. NOESY data for data for Spiro-indoline **125c** in $CDCl_3$

Appendix B: HNMR reaction of 123r, 123s and 123t

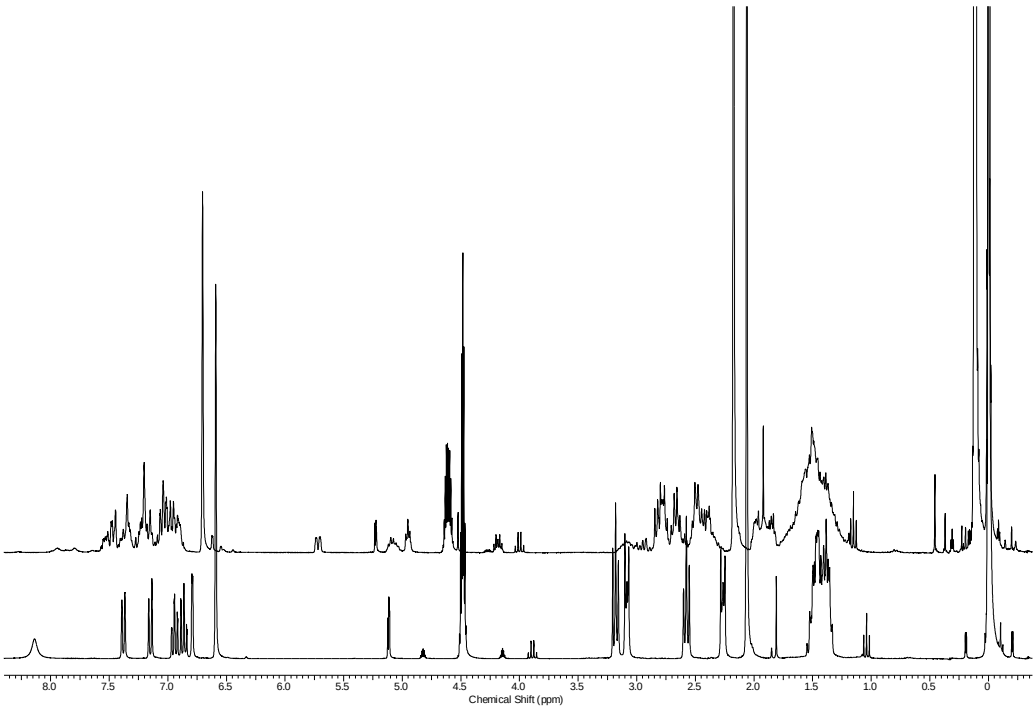


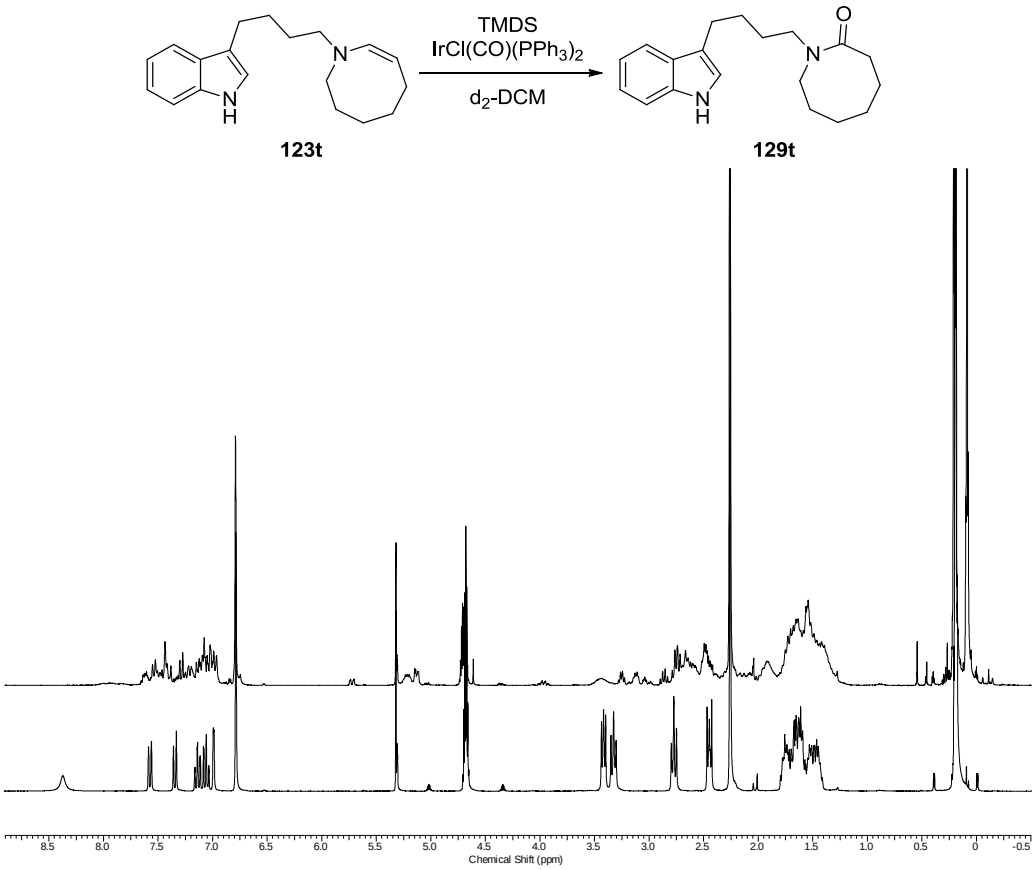
123r **129r**





123s **129s**





The above spectra show complete conversion of 123r to the proposed enamine **129r**. For examples 123s and 123t as well as the proposed enamine 129r and 129t respectively there are also two further alkene signals, which may be due to some form of alkene rearrangement.

Appendix C: NOESY data for 133c

Figures A.4 show the NOESY NMR study of $133c_{major}$, including the full NOESY spectrum and a zoomed in spectrum of for clarity. An NOE interaction of proton 10 with the aromatic proton 6 can be seen. It also shows no NOE interaction between proton 10 and either proton at position 8. This information implies the major diastereomer is the (*exo*-S*,S*) diastereomer for compound **133c**.

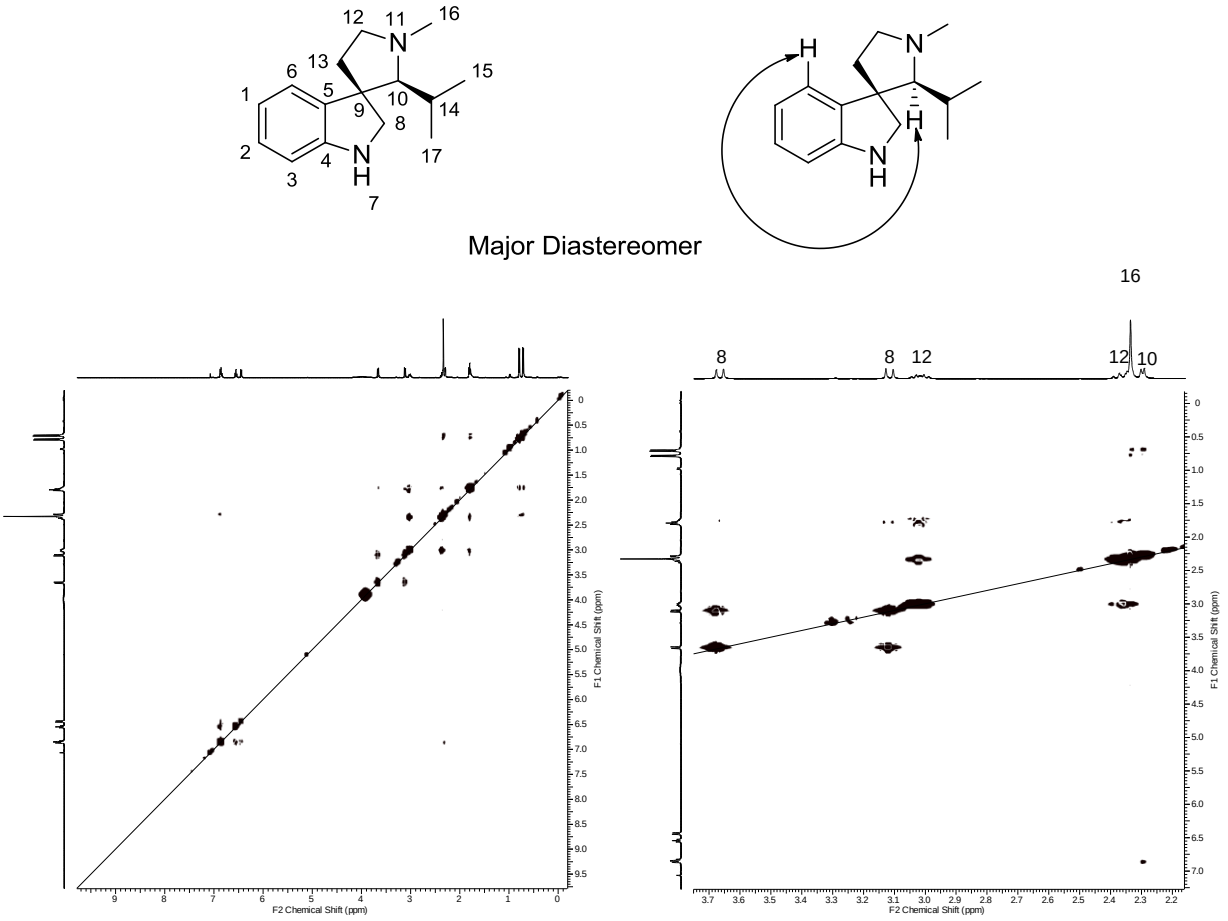


Figure A.4. NOESY experiment on **133c**$_{major}$ in $CDCl_3$

Investigating the NOESY of the minor diastereomer agrees with this assignment (Figure A.5). NOESY spectrum shows the NOE interaction of proton 10 with one of the proton signals for position 8. It also shows no NOE interaction of proton 10 with the aromatic proton 6.

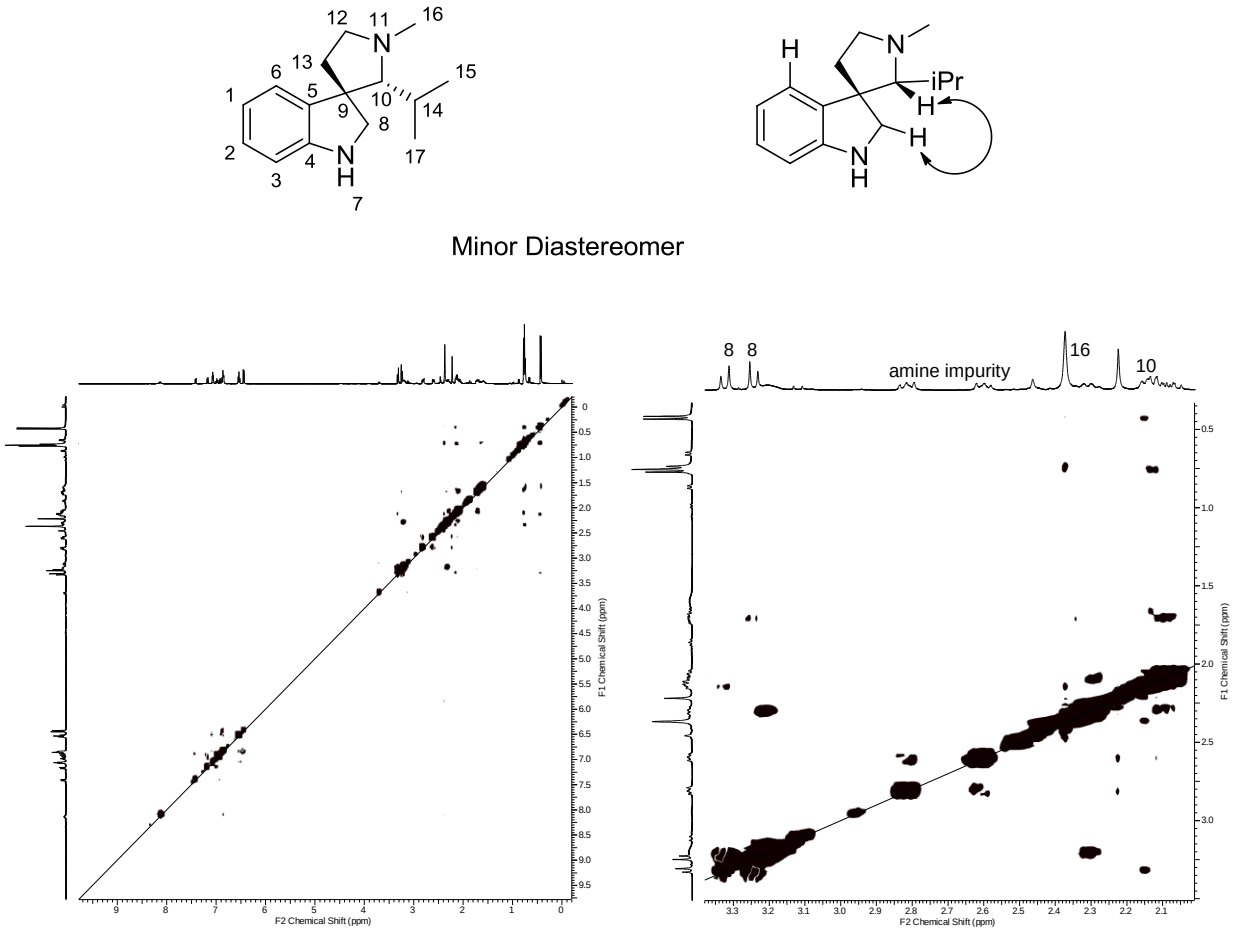


Figure A.5. NOESY experiment on **133**c_{minor} in $CDCl_3$

Appendix D: NOESY data for 133d

Figures A.6 shows the NOESY NMR study of **133d**$_{major}$, including the full NOESY spectrum and a zoomed in spectrum of for clarity. An NOE interaction of proton 10 with the aromatic proton 6 can be seen the NOESY. It also shows no NOE interaction between proton 10 and either proton at position 8. This information implies the major diastereomer is the (*exo*-S*,S*) diastereomer for compound 133d.

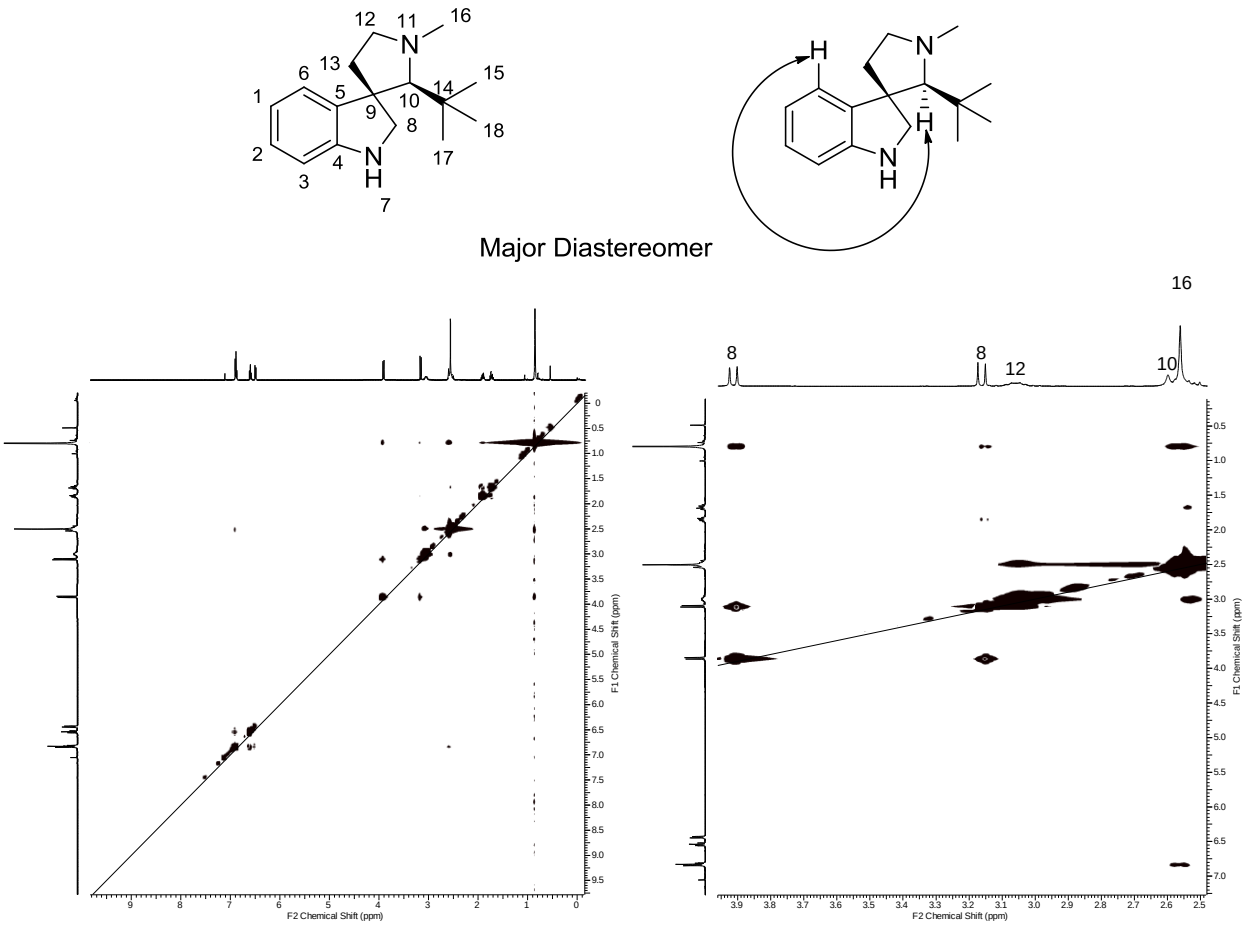


Figure A.6. NOESY experiment on 133d in $CDCl_3$

Appendix E: NOESY data for 133a

Figure A.7 shows the NOESY NMR study of **133a**$_{\text{major and minor}}$, including the full NOESY spectrum and a zoomed in spectrum of for clarity. An NOE interaction of proton 10_{major} with the proton at position 8_{major} can be seen the NOESY. It also shows no NOE interaction between proton 10_{major} and an aromatic proton, however this aromatic proton probably originates from the phenyl ring instead of the indoline proton 6 This information implies the major diastereomer is the (*endo*-S*,S*) diastereomer for compound **133a**.

Inspecting the minor signals shows that proton 10_{minor} doesn't an NOE interaction with either proton at position 8. This implies that the minor diastereomer is the (*exo*-S*,R*) diastereomer.

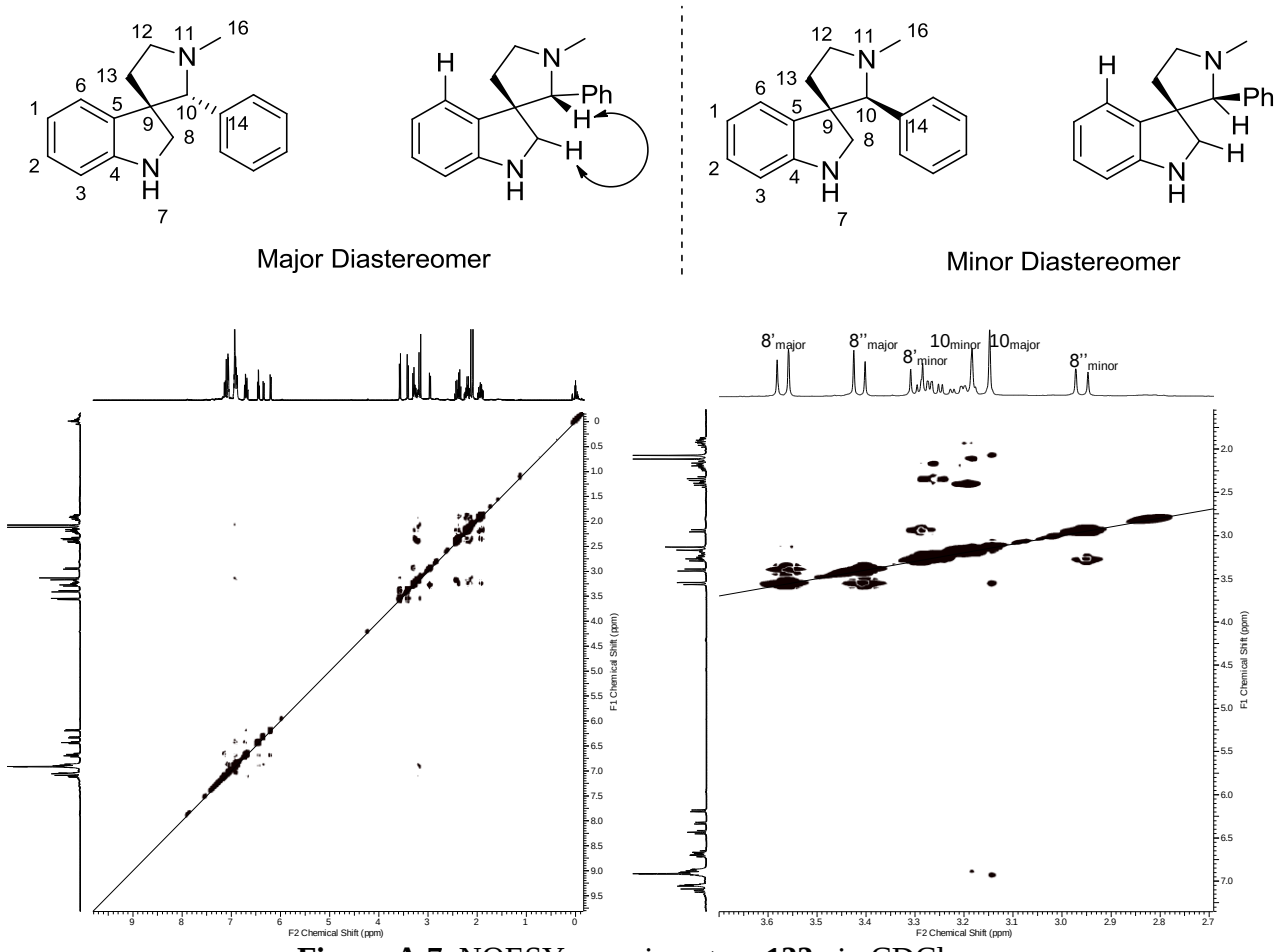


Figure A.7. NOESY experiment on **133a** in $CDCl_3$

Appendix F: NOESY data for **133i**

Figures A.8 show the NOESY NMR study of **133i**$_{major}$ including the full NOESY spectrum and a zoomed in spectrum of for clarity. An NOE interaction of proton 10 with the aromatic proton 6 can be seen in the NOESY. It also shows no NOE interaction between proton 10 and either proton at position 8. This information implies the major diastereomer is the (S*,S*) diastereomer for compound **133i**.

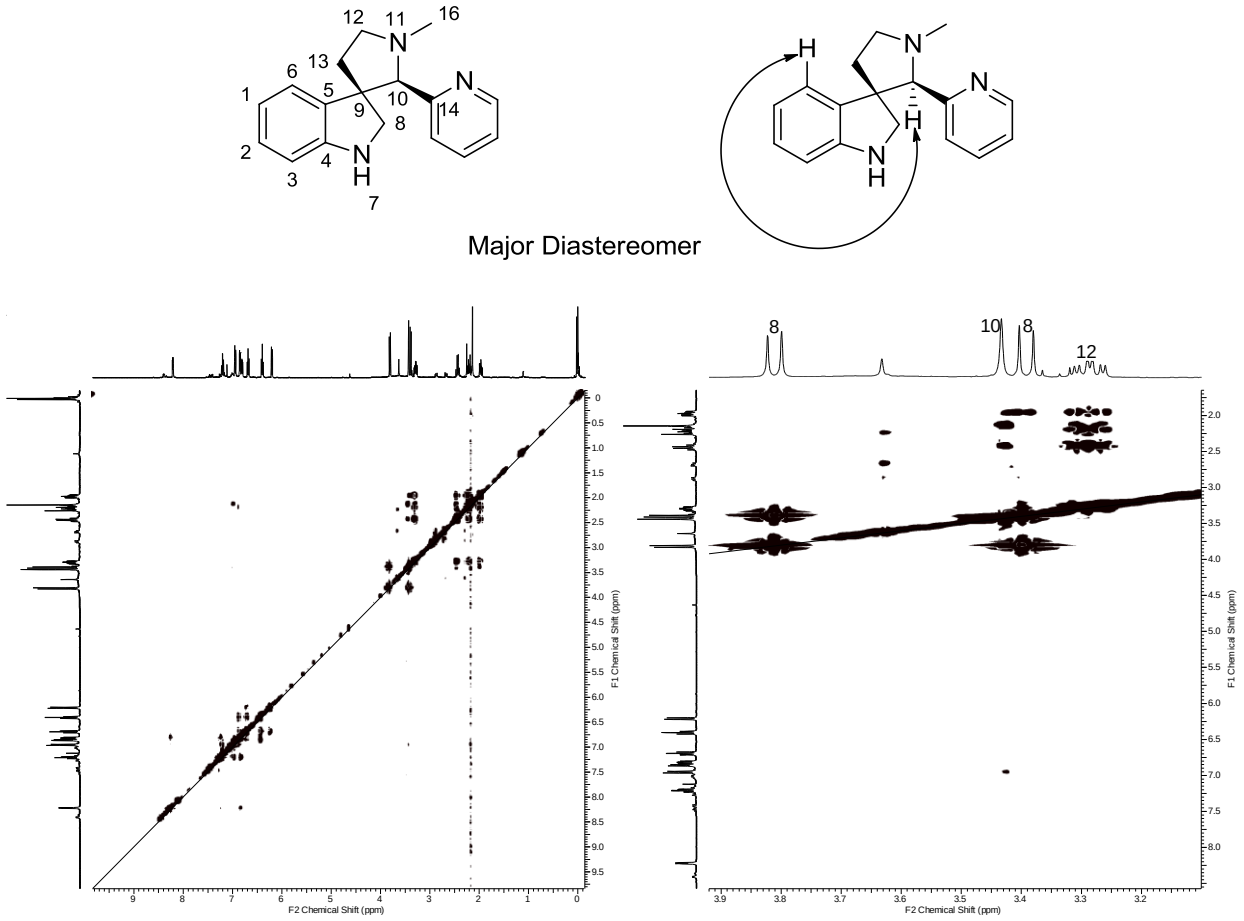
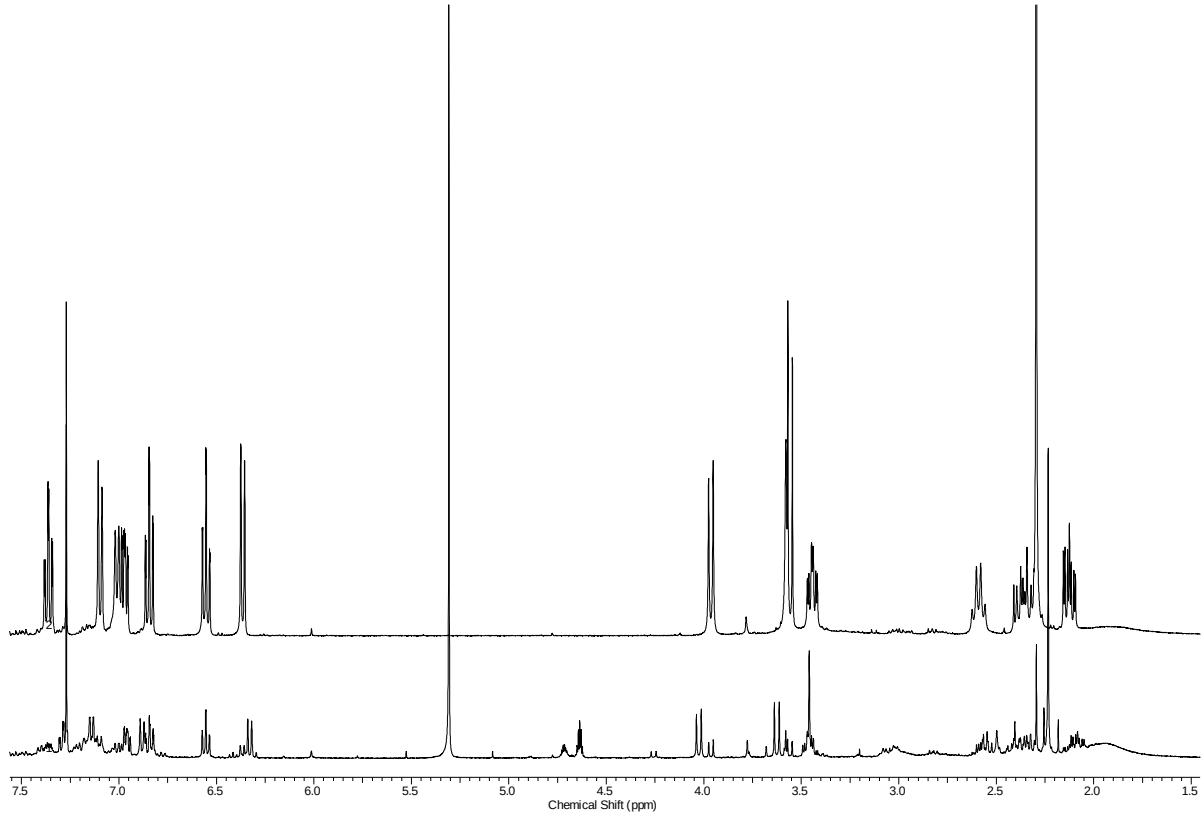
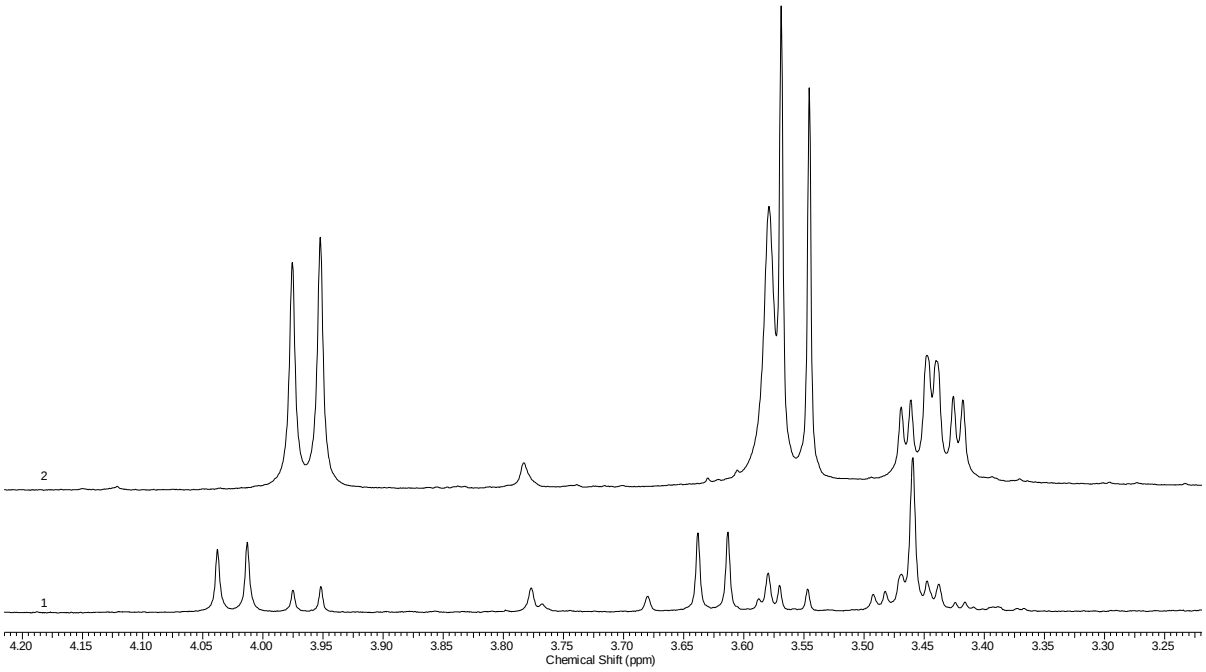


Figure A.8. NOESY experiment on **133i** in $CDCl_3$

Appendix G: comparison of crude ^{1}H NMR and purified ^{1}H NMR for 133i

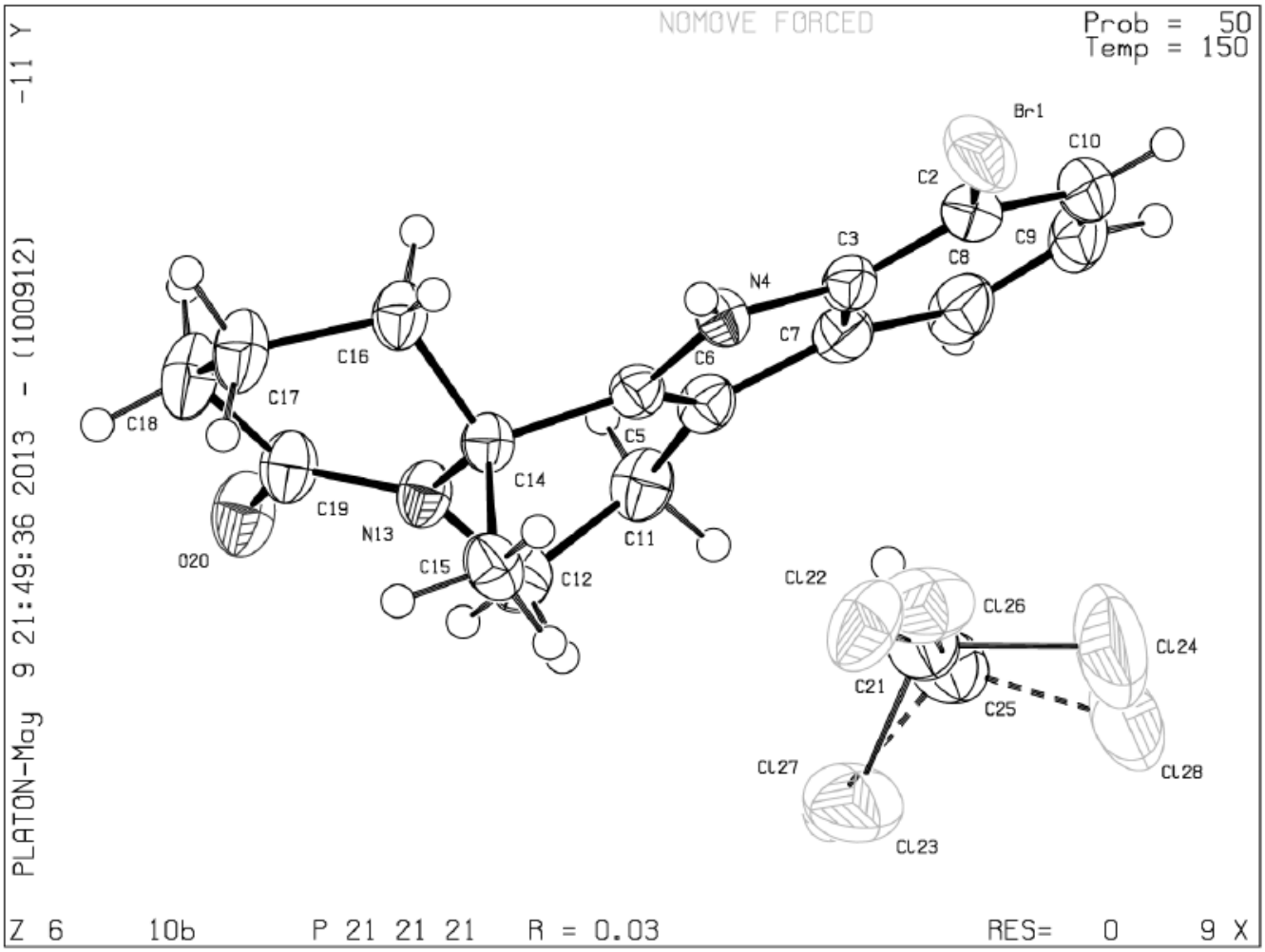




Appendix H: X-ray data[16]

X-ray data for compound 10b

11-bromo-12b-methyl-2,3,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-4(1*H*)-one



(10b)

Crystal data

$C_{16}H_{17}BrN_2O\cdot CHCl_3$	D_x = 1.567 Mg m^{-3}
M_r = 452.60	Melting point: not measured K
Orthorhombic, $P2_12_12_1$	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hall symbol: P 2ac 2ab	Cell parameters from 83413 reflections
a = 11.0236 (2) Å	θ = 5–27°
b = 12.9544 (2) Å	μ = 2.57 mm^{-1}
c = 13.4366 (2) Å	T = 150 K
V = 1918.80 (5) Å^3	Block, Clear_pale_colourless
Z = 4	0.62 × 0.38 × 0.30 mm
F(000) = 912	

Data collection

Nonius KappaCCD diffractometer	4092 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.087$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.2°$
Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -14 \rightarrow 14$
$T_{min} = 0.17$, $T_{max} = 0.46$	$k = -16 \rightarrow 16$
56832 measured reflections	$l = -17 \rightarrow 17$
4361 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: Difference Fourier map
Least-squares matrix: Full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.034$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = $1.0/[A_0*T_0(x) + A_1*T_1(x) \cdots + A_{n-1}]*T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 69.2 115. 71.6 31.4 7.79
$wR(F^2) = 0.083$	$(\Delta/\sigma)_{max} = 0.002$
$S = 1.00$	$\Delta\rho_{max} = 0.42$ e Å^{-3}
4361 reflections	$\Delta\rho_{min} = -0.44$ e Å^{-3}
255 parameters	Absolute structure: Flack (1983), 1893 Friedel-pairs
162 restraints	Flack parameter: −0.007 (8)
Primary atom site location: Other	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
Br1	0.65201 (3)	0.67046 (3)	1.08633 (3)	0.0538	
C2	0.6812 (2)	0.65084 (19)	0.9491 (2)	0.0375	
C3	0.5948 (2)	0.60131 (18)	0.89063 (19)	0.0304	
N4	0.48228 (17)	0.56306 (15)	0.91457 (17)	0.0289	
C5	0.4336 (2)	0.51801 (19)	0.82999 (17)	0.0269	
C6	0.5127 (2)	0.52769 (19)	0.75153 (19)	0.0299	
C7	0.6164 (2)	0.58180 (19)	0.78843 (19)	0.0321	
C8	0.7263 (2)	0.6159 (2)	0.7450 (2)	0.0424	

C9	0.8085 (3)	0.6668 (3)	0.8039 (3)	0.0480	
C10	0.7884 (2)	0.6833 (2)	0.9055 (3)	0.0454	
C11	0.4861 (3)	0.4819 (2)	0.65142 (19)	0.0377	
C12	0.3845 (3)	0.4028 (2)	0.66363 (19)	0.0366	
N13	0.28353 (19)	0.44722 (18)	0.72179 (15)	0.0318	
C14	0.3093 (2)	0.47060 (19)	0.82822 (17)	0.0274	
C15	0.3064 (3)	0.3708 (2)	0.88971 (19)	0.0361	
C16	0.2171 (2)	0.5493 (2)	0.8680 (2)	0.0348	
C17	0.0883 (3)	0.5161 (3)	0.8449 (2)	0.0433	
C18	0.0731 (3)	0.5135 (3)	0.7325 (2)	0.0475	
C19	0.1766 (2)	0.4651 (2)	0.6760 (2)	0.0360	
O20	0.16200 (19)	0.44316 (18)	0.58674 (15)	0.0457	
C21	0.6761 (2)	0.3428 (2)	0.9014 (2)	0.0530	0.739 (8)
Cl22	0.5983 (2)	0.3334 (2)	1.01359 (14)	0.0620	0.739 (8)
Cl23	0.6434 (4)	0.2372 (4)	0.8252 (3)	0.0789	0.739 (8)
Cl24	0.83178 (19)	0.3520 (3)	0.9223 (3)	0.1103	0.739 (8)
C25	0.7068 (7)	0.3351 (4)	0.8686 (6)	0.0653	0.261 (8)
Cl26	0.6526 (11)	0.3566 (4)	0.9885 (5)	0.0775	0.261 (8)
Cl27	0.6276 (5)	0.2345 (8)	0.8120 (6)	0.0449	0.261 (8)
Cl28	0.8619 (7)	0.3086 (6)	0.8709 (8)	0.0923	0.261 (8)
H81	0.7411	0.6060	0.6779	0.0511*	
H91	0.8809	0.6888	0.7744	0.0580*	
H101	0.8460	0.7155	0.9432	0.0539*	
H111	0.5574	0.4481	0.6240	0.0450*	
H112	0.4596	0.5355	0.6043	0.0454*	
H121	0.4164	0.3434	0.7000	0.0432*	
H122	0.3531	0.3786	0.6004	0.0436*	
H151	0.2278	0.3397	0.8850	0.0533*	
H152	0.3263	0.3876	0.9579	0.0534*	
H153	0.3649	0.3239	0.8652	0.0533*	
H161	0.2277	0.5547	0.9386	0.0418*	
H162	0.2337	0.6164	0.8380	0.0419*	
H171	0.0313	0.5647	0.8702	0.0517*	
H172	0.0713	0.4491	0.8731	0.0517*	
H181	0.0687	0.5825	0.7066	0.0583*	
H182	0.0010	0.4749	0.7145	0.0575*	
H211	0.6492	0.4053	0.8682	0.0639*	0.739 (8)
H251	0.6951	0.3976	0.8291	0.0778*	0.261 (8)
H41	0.4494	0.5652	0.9709	0.0352*	

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br1	0.05236 (17)	0.05674 (18)	0.05220 (17)	−0.01281 (15)	−0.00665 (15)	−0.01813 (14)
C2	0.0338 (13)	0.0294 (12)	0.0493 (14)	−0.0009 (9)	−0.0014 (10)	−0.0007 (10)
C3	0.0248 (10)	0.0280 (11)	0.0384 (13)	0.0008 (8)	0.0029 (9)	0.0030 (9)
N4	0.0265 (9)	0.0308 (9)	0.0296 (9)	−0.0035 (7)	0.0008 (8)	0.0000 (8)
C5	0.0273 (11)	0.0266 (10)	0.0268 (11)	0.0007 (9)	0.0003 (9)	0.0009 (8)
C6	0.0280 (11)	0.0317 (11)	0.0300 (11)	0.0023 (9)	0.0047 (9)	0.0034 (9)
C7	0.0298 (12)	0.0283 (11)	0.0383 (12)	0.0008 (9)	0.0069 (9)	0.0066 (9)
C8	0.0327 (13)	0.0425 (15)	0.0519 (16)	0.0041 (11)	0.0126 (12)	0.0144 (13)
C9	0.0264 (12)	0.0435 (14)	0.074 (2)	−0.0011 (12)	0.0071 (12)	0.0162 (15)
C10	0.0295 (12)	0.0356 (13)	0.0710 (19)	−0.0050 (10)	−0.0010 (14)	0.0032 (15)
C11	0.0330 (13)	0.0502 (15)	0.0299 (12)	0.0037 (11)	0.0059 (10)	−0.0006 (11)
C12	0.0365 (13)	0.0437 (14)	0.0297 (11)	0.0059 (10)	−0.0013 (10)	−0.0064 (10)
N13	0.0276 (10)	0.0424 (11)	0.0256 (9)	0.0032 (8)	−0.0018 (8)	−0.0006 (8)
C14	0.0255 (11)	0.0329 (11)	0.0239 (10)	−0.0003 (9)	−0.0005 (8)	0.0000 (8)
C15	0.0358 (12)	0.0379 (12)	0.0345 (13)	−0.0085 (10)	−0.0042 (10)	0.0052 (10)
C16	0.0262 (12)	0.0447 (14)	0.0335 (12)	0.0011 (10)	0.0023 (10)	−0.0025 (11)
C17	0.0260 (13)	0.067 (2)	0.0373 (14)	0.0027 (12)	0.0013 (10)	−0.0036 (13)
C18	0.0296 (13)	0.073 (2)	0.0398 (14)	0.0070 (13)	−0.0048 (11)	−0.0062 (14)
C19	0.0314 (13)	0.0475 (14)	0.0291 (12)	0.0015 (10)	−0.0041 (10)	0.0027 (10)
O20	0.0391 (10)	0.0690 (12)	0.0290 (8)	0.0048 (9)	−0.0072 (9)	−0.0025 (9)
C21	0.0506 (19)	0.0427 (18)	0.066 (2)	−0.0010 (16)	−0.0121 (18)	0.0043 (17)
Cl22	0.0550 (10)	0.0807 (10)	0.0502 (7)	0.0210 (8)	−0.0150 (6)	−0.0013 (8)
Cl23	0.089 (2)	0.0648 (14)	0.0833 (17)	−0.0014 (16)	0.0082 (15)	−0.0288 (13)
Cl24	0.0523 (9)	0.127 (2)	0.151 (3)	−0.0348 (11)	−0.0107 (13)	0.022 (2)
C25	0.071 (4)	0.050 (4)	0.075 (4)	−0.001 (3)	−0.030 (4)	−0.005 (3)
Cl26	0.111 (5)	0.059 (2)	0.063 (3)	0.019 (3)	−0.030 (3)	−0.0177 (19)
Cl27	0.0318 (19)	0.047 (3)	0.056 (3)	0.0025 (14)	−0.0096 (16)	−0.0139 (19)
Cl28	0.065 (3)	0.081 (3)	0.131 (5)	−0.026 (2)	−0.034 (3)	0.014 (3)

Geometric parameters (Å, º)

Br1—C2	1.889 (3)	N13—C19	1.349 (3)
C2—C3	1.391 (4)	C14—C15	1.534 (3)
C2—C10	1.384 (4)	C14—C16	1.536 (3)
C3—N4	1.374 (3)	C15—H151	0.958
C3—C7	1.416 (4)	C15—H152	0.967
N4—C5	1.385 (3)	C15—H153	0.945
N4—H41	0.840	C16—C17	1.516 (4)
C5—C6	1.374 (3)	C16—H161	0.957
C5—C14	1.502 (3)	C16—H162	0.977

C6—C7	1.429 (4)	C17—C18	1.520 (4)
C6—C11	1.499 (4)	C17—H171	0.952
C7—C8	1.415 (4)	C17—H172	0.966
C8—C9	1.371 (5)	C18—C19	1.507 (4)
C8—H81	0.926	C18—H181	0.961
C9—C10	1.399 (5)	C18—H182	0.969
C9—H91	0.936	C19—O20	1.244 (3)
C10—H101	0.914	C21—Cl22	1.738 (3)
C11—C12	1.527 (4)	C21—Cl23	1.746 (3)
C11—H111	0.972	C21—Cl24	1.743 (3)
C11—H112	0.984	C21—H211	0.972
C12—N13	1.477 (3)	C25—Cl26	1.740 (5)
C12—H121	0.976	C25—Cl27	1.743 (5)
C12—H122	0.968	C25—Cl28	1.744 (5)
N13—C14	1.489 (3)	C25—H251	0.976
Br1—C2—C3	119.8 (2)	N13—C14—C15	110.0 (2)
Br1—C2—C10	121.2 (2)	C5—C14—C16	109.1 (2)
C3—C2—C10	119.0 (3)	N13—C14—C16	110.1 (2)
C2—C3—N4	130.7 (2)	C15—C14—C16	111.0 (2)
C2—C3—C7	121.0 (2)	C14—C15—H151	109.7
N4—C3—C7	108.3 (2)	C14—C15—H152	108.4
C3—N4—C5	108.0 (2)	H151—C15—H152	111.2
C3—N4—H41	126.0	C14—C15—H153	109.9
C5—N4—H41	125.9	H151—C15—H153	108.9
N4—C5—C6	110.2 (2)	H152—C15—H153	108.7
N4—C5—C14	122.6 (2)	C14—C16—C17	111.1 (2)
C6—C5—C14	127.2 (2)	C14—C16—H161	108.2
C5—C6—C7	106.6 (2)	C17—C16—H161	109.8
C5—C6—C11	121.9 (2)	C14—C16—H162	108.8
C7—C6—C11	131.5 (2)	C17—C16—H162	110.1
C6—C7—C3	106.8 (2)	H161—C16—H162	108.7
C6—C7—C8	134.0 (3)	C16—C17—C18	108.3 (2)
C3—C7—C8	119.2 (3)	C16—C17—H171	110.9
C7—C8—C9	118.5 (3)	C18—C17—H171	107.3
C7—C8—H81	120.6	C16—C17—H172	110.8
C9—C8—H81	120.8	C18—C17—H172	110.4
C8—C9—C10	122.1 (3)	H171—C17—H172	109.0
C8—C9—H91	117.7	C17—C18—C19	115.2 (2)
C10—C9—H91	120.1	C17—C18—H181	110.1
C9—C10—C2	120.1 (3)	C19—C18—H181	104.1
C9—C10—H101	120.0	C17—C18—H182	110.5

C2—C10—H101	119.8	C19—C18—H182	106.4
C6—C11—C12	108.2 (2)	H181—C18—H182	110.4
C6—C11—H111	111.1	C18—C19—N13	120.3 (2)
C12—C11—H111	109.4	C18—C19—O20	118.8 (2)
C6—C11—H112	110.9	N13—C19—O20	120.9 (3)
C12—C11—H112	109.0	Cl22—C21—Cl23	110.61 (6)
H111—C11—H112	108.2	Cl22—C21—Cl24	110.54 (6)
C11—C12—N13	110.4 (2)	Cl23—C21—Cl24	110.61 (6)
C11—C12—H121	108.5	Cl22—C21—H211	107.9
N13—C12—H121	108.3	Cl23—C21—H211	108.7
C11—C12—H122	112.6	Cl24—C21—H211	108.5
N13—C12—H122	108.7	Cl26—C25—Cl27	110.58 (6)
H121—C12—H122	108.3	Cl26—C25—Cl28	110.60 (6)
C12—N13—C14	116.3 (2)	Cl27—C25—Cl28	110.59 (6)
C12—N13—C19	119.0 (2)	Cl26—C25—H251	108.9
C14—N13—C19	124.7 (2)	Cl27—C25—H251	108.4
C5—C14—N13	105.81 (19)	Cl28—C25—H251	107.6
C5—C14—C15	110.8 (2)		

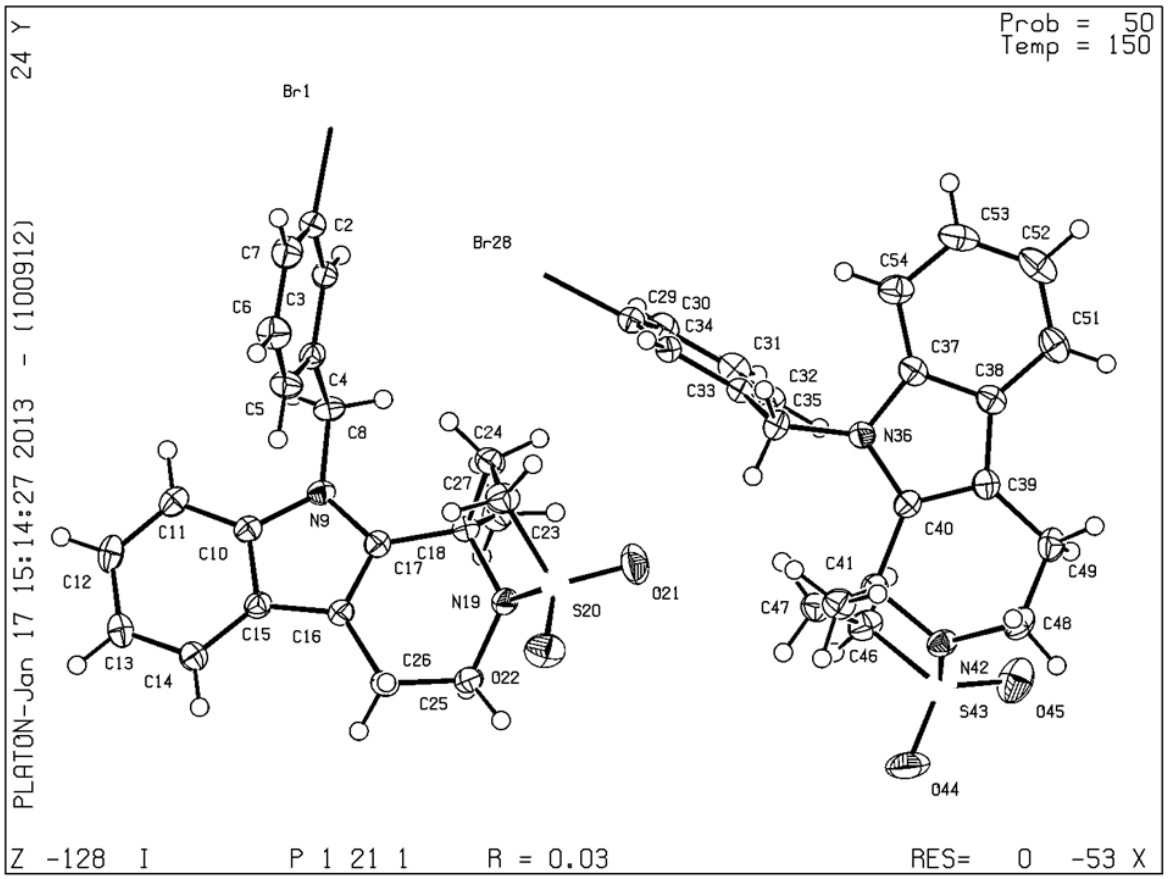
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C16—H161···O20^{i}	0.96	2.33	3.229 (4)	155 (1)
C21—H211···C7	0.97	2.55	3.511 (4)	170 (1)
C25—H211···C7	1.11	2.55	3.517 (4)	145 (1)
C25—H251···C7	0.98	2.60	3.517 (4)	157 (1)
N4—H41···O20^{i}	0.84	1.99	2.809 (4)	166 (1)

Symmetry code: (i) −*x*+1/2, −*y*+1, *z*+1/2.

1.1. X-Ray data for compound 15a

11-(3-bromobenzyl)-11b-methyl-1,2,5,6,11,11b-hexahydro[1,2]thiazolo[2',3':1,2]pyrido[3,4-b]indole 3,3-dioxide



(15a)

Crystal data

$C_{21}H_{21}BrN_2O_2S$	$F(000)$ = 912
M_r = 445.38	D_x = 1.541 Mg m^{-3}
Monoclinic, $P2_1$	Melting point: not measured K
Hall symbol: P 2yb	Mo $K\alpha$ radiation, λ = 0.71073 Å
a = 10.4507 (1) Å	Cell parameters from 4512 reflections
b = 16.2752 (2) Å	θ = 5–27°
c = 11.5043 (1) Å	μ = 2.27 mm^{-1}
β = 101.0903 (5)°	T = 150 K
V = 1920.19 (3) Å^3	Block, Clear_pale_colourless
Z = 4	0.50 × 0.30 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer	7894 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	R_{int} = 0.063
ω scans	θ_{max} = 27.5°, θ_{min} = 5.1°

Absorption correction: Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -13 \rightarrow 13$
$T_{min} = 0.54$, $T_{max} = 0.71$	$k = -21 \rightarrow 19$
35947 measured reflections	$l = -14 \rightarrow 14$
8412 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: Difference Fourier map
Least-squares matrix: Full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.029$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.03P)^2 + 1.16P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$wR(F^2) = 0.064$	$(\Delta/\sigma)_{max} = 0.001$
$S = 0.99$	$\Delta\rho_{max} = 1.11$ e Å^{-3}
8412 reflections	$\Delta\rho_{min} = -0.93$ e Å^{-3}
488 parameters	Absolute structure: Flack (1983), 3898 Friedel-pairs
1 restraint	Flack parameter: 0.010 (4)
Primary atom site location: Structure-invariant direct methods	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	1.41297 (2)	0.38134 (3)	0.34172 (2)	0.0285
C2	1.3005 (2)	0.46900 (15)	0.2792 (2)	0.0226
C3	1.1759 (2)	0.45052 (14)	0.2192 (2)	0.0208
C4	1.0911 (2)	0.51396 (14)	0.1758 (2)	0.0205
C5	1.1330 (2)	0.59512 (15)	0.1918 (2)	0.0256
C6	1.2588 (3)	0.61223 (16)	0.2519 (2)	0.0295
C7	1.3438 (2)	0.54976 (17)	0.2968 (2)	0.0287
C8	0.9538 (2)	0.49079 (14)	0.1142 (2)	0.0228
N9	0.86899 (18)	0.56083 (12)	0.08136 (17)	0.0205
C10	0.8749 (2)	0.60797 (14)	−0.0176 (2)	0.0206
C11	0.9386 (2)	0.59243 (16)	−0.1112 (2)	0.0245
C12	0.9203 (3)	0.64855 (17)	−0.2034 (2)	0.0276
C13	0.8431 (2)	0.71881 (16)	−0.2021 (2)	0.0263
C14	0.7847 (2)	0.73585 (15)	−0.1068 (2)	0.0247
C15	0.8018 (2)	0.68067 (14)	−0.0121 (2)	0.0211
C16	0.7523 (2)	0.67577 (14)	0.0958 (2)	0.0209

C17	0.7947 (2)	0.60349 (14)	0.1504 (2)	0.0201
C18	0.7553 (2)	0.56948 (14)	0.2609 (2)	0.0213
N19	0.66573 (19)	0.63045 (12)	0.30024 (17)	0.0222
S20	0.72133 (6)	0.66744 (5)	0.43267 (5)	0.0261
O21	0.6787 (2)	0.61696 (14)	0.51981 (17)	0.0420
O22	0.6911 (2)	0.75361 (12)	0.43494 (18)	0.0378
C23	0.8865 (3)	0.64467 (16)	0.4315 (2)	0.0296
C24	0.8725 (3)	0.56237 (15)	0.3669 (2)	0.0263
C25	0.5806 (2)	0.68198 (16)	0.2122 (2)	0.0268
C26	0.6594 (2)	0.73246 (16)	0.1396 (2)	0.0266
C27	0.6827 (3)	0.48793 (16)	0.2380 (3)	0.0307
Br28	0.97901 (3)	0.32754 (3)	0.39862 (3)	0.0391
C29	0.8383 (2)	0.32493 (17)	0.4816 (2)	0.0267
C30	0.7437 (3)	0.26470 (16)	0.4539 (2)	0.0289
C31	0.6397 (3)	0.26565 (16)	0.5129 (2)	0.0274
C32	0.6313 (2)	0.32589 (16)	0.5970 (2)	0.0230
C33	0.7276 (2)	0.38529 (16)	0.62490 (18)	0.0207
C34	0.8335 (2)	0.38422 (16)	0.56645 (19)	0.0224
C35	0.7227 (2)	0.45407 (15)	0.7126 (2)	0.0227
N36	0.64904 (19)	0.43309 (12)	0.80417 (17)	0.0219
C37	0.6932 (2)	0.37513 (16)	0.89065 (19)	0.0228
C38	0.6024 (2)	0.36932 (15)	0.9660 (2)	0.0233
C39	0.4999 (2)	0.42615 (15)	0.9219 (2)	0.0229
C40	0.5304 (2)	0.46350 (14)	0.8242 (2)	0.0210
C41	0.4522 (2)	0.53135 (14)	0.7525 (2)	0.0216
N42	0.32641 (19)	0.53898 (13)	0.79549 (18)	0.0241
S43	0.20060 (6)	0.50210 (5)	0.70227 (6)	0.0298
O44	0.1293 (2)	0.56807 (15)	0.63536 (19)	0.0477
O45	0.1262 (2)	0.44851 (15)	0.76296 (19)	0.0450
C46	0.2931 (2)	0.45221 (17)	0.6100 (2)	0.0296
C47	0.4093 (2)	0.50934 (15)	0.6192 (2)	0.0253
C48	0.3300 (3)	0.53143 (17)	0.9239 (2)	0.0290
C49	0.3814 (2)	0.44762 (16)	0.9713 (2)	0.0271
C50	0.5235 (3)	0.61384 (15)	0.7699 (2)	0.0287
C51	0.6273 (3)	0.31427 (16)	1.0623 (2)	0.0300
C52	0.7391 (3)	0.26805 (17)	1.0798 (2)	0.0363
C53	0.8298 (3)	0.27482 (17)	1.0041 (2)	0.0339
C54	0.8077 (2)	0.32787 (17)	0.9083 (2)	0.0299
H31	1.1491	0.3960	0.2068	0.0270*
H51	1.0756	0.6379	0.1623	0.0299*
H61	1.2857	0.6670	0.2623	0.0363*

H71	1.4282	0.5614	0.3364	0.0342*
H81	0.9166	0.4571	0.1684	0.0282*
H82	0.9589	0.4601	0.0431	0.0281*
H111	0.9921	0.5464	−0.1109	0.0302*
H121	0.9601	0.6385	−0.2681	0.0355*
H131	0.8301	0.7549	−0.2672	0.0273*
H141	0.7350	0.7834	−0.1051	0.0321*
H231	0.9229	0.6857	0.3847	0.0360*
H232	0.9390	0.6411	0.5113	0.0359*
H241	0.8532	0.5197	0.4199	0.0333*
H242	0.9514	0.5494	0.3388	0.0331*
H251	0.5302	0.7191	0.2529	0.0329*
H252	0.5226	0.6463	0.1588	0.0332*
H262	0.7075	0.7748	0.1883	0.0328*
H261	0.6021	0.7573	0.0731	0.0329*
H272	0.6491	0.4727	0.3074	0.0469*
H271	0.6120	0.4938	0.1716	0.0470*
H273	0.7424	0.4459	0.2212	0.0471*
H301	0.7504	0.2247	0.3964	0.0338*
H311	0.5751	0.2252	0.4965	0.0308*
H321	0.5599	0.3262	0.6348	0.0293*
H341	0.9011	0.4224	0.5859	0.0268*
H351	0.6820	0.5011	0.6698	0.0308*
H352	0.8113	0.4677	0.7496	0.0309*
H462	0.2456	0.4477	0.5289	0.0352*
H461	0.3205	0.3981	0.6406	0.0348*
H472	0.3853	0.5577	0.5718	0.0322*
H471	0.4803	0.4814	0.5922	0.0319*
H481	0.2415	0.5390	0.9379	0.0329*
H482	0.3877	0.5736	0.9652	0.0330*
H491	0.4041	0.4489	1.0576	0.0331*
H492	0.3152	0.4064	0.9474	0.0330*
H501	0.4693	0.6565	0.7280	0.0460*
H502	0.5448	0.6273	0.8528	0.0461*
H503	0.6027	0.6101	0.7397	0.0461*
H511	0.5675	0.3105	1.1133	0.0423*
H521	0.7544	0.2303	1.1425	0.0472*
H531	0.9059	0.2427	1.0187	0.0368*
H541	0.8669	0.3322	0.8573	0.0380*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br1	0.02460 (11)	0.03028 (12)	0.02933 (12)	0.00474 (10)	0.00169 (9)	0.00640 (11)
C2	0.0225 (11)	0.0244 (11)	0.0212 (11)	0.0034 (9)	0.0049 (9)	0.0025 (9)
C3	0.0221 (11)	0.0198 (11)	0.0216 (11)	0.0010 (9)	0.0071 (9)	0.0010 (9)
C4	0.0211 (11)	0.0217 (12)	0.0193 (11)	0.0015 (9)	0.0053 (9)	−0.0025 (9)
C5	0.0250 (12)	0.0211 (12)	0.0296 (13)	0.0010 (10)	0.0022 (10)	0.0006 (10)
C6	0.0307 (13)	0.0213 (12)	0.0357 (14)	−0.0051 (10)	0.0047 (11)	−0.0021 (10)
C7	0.0239 (12)	0.0358 (14)	0.0255 (12)	−0.0033 (11)	0.0029 (10)	−0.0023 (11)
C8	0.0211 (11)	0.0190 (11)	0.0275 (12)	0.0031 (9)	0.0028 (9)	−0.0028 (9)
N9	0.0204 (9)	0.0188 (9)	0.0222 (10)	0.0031 (8)	0.0039 (8)	−0.0018 (8)
C10	0.0181 (10)	0.0222 (11)	0.0208 (11)	−0.0010 (9)	0.0019 (8)	−0.0024 (9)
C11	0.0217 (11)	0.0272 (12)	0.0252 (12)	−0.0006 (10)	0.0062 (9)	−0.0054 (10)
C12	0.0286 (13)	0.0353 (14)	0.0207 (12)	−0.0091 (10)	0.0097 (10)	−0.0070 (10)
C13	0.0293 (13)	0.0282 (13)	0.0221 (12)	−0.0063 (11)	0.0063 (10)	0.0017 (10)
C14	0.0261 (12)	0.0227 (11)	0.0256 (12)	−0.0009 (10)	0.0059 (10)	0.0021 (10)
C15	0.0206 (11)	0.0223 (11)	0.0204 (11)	0.0013 (9)	0.0040 (9)	−0.0022 (9)
C16	0.0207 (11)	0.0223 (11)	0.0204 (11)	0.0025 (9)	0.0056 (9)	−0.0001 (9)
C17	0.0197 (11)	0.0213 (11)	0.0191 (11)	−0.0005 (9)	0.0033 (9)	−0.0020 (9)
C18	0.0211 (11)	0.0206 (11)	0.0224 (11)	0.0025 (9)	0.0051 (9)	0.0006 (9)
N19	0.0223 (10)	0.0258 (10)	0.0189 (9)	0.0033 (8)	0.0052 (8)	−0.0012 (8)
S20	0.0333 (3)	0.0253 (3)	0.0204 (3)	0.0026 (3)	0.0068 (2)	−0.0016 (2)
O21	0.0581 (13)	0.0468 (12)	0.0250 (10)	0.0043 (10)	0.0174 (9)	0.0065 (9)
O22	0.0465 (12)	0.0251 (10)	0.0408 (11)	0.0051 (9)	0.0060 (9)	−0.0097 (8)
C23	0.0278 (13)	0.0338 (14)	0.0250 (13)	0.0028 (11)	−0.0009 (10)	−0.0035 (10)
C24	0.0294 (13)	0.0262 (12)	0.0224 (12)	0.0048 (10)	0.0031 (10)	0.0026 (10)
C25	0.0240 (12)	0.0345 (14)	0.0225 (12)	0.0092 (10)	0.0055 (9)	0.0019 (10)
C26	0.0300 (13)	0.0259 (12)	0.0251 (12)	0.0092 (10)	0.0083 (10)	0.0045 (10)
C27	0.0299 (13)	0.0255 (13)	0.0386 (15)	−0.0049 (10)	0.0113 (11)	−0.0017 (11)
Br28	0.04223 (16)	0.04041 (15)	0.04193 (16)	0.01248 (13)	0.02604 (12)	0.00676 (13)
C29	0.0299 (12)	0.0266 (11)	0.0256 (12)	0.0087 (11)	0.0104 (9)	0.0067 (10)
C30	0.0406 (15)	0.0255 (12)	0.0206 (12)	0.0056 (11)	0.0056 (10)	−0.0031 (10)
C31	0.0311 (13)	0.0233 (12)	0.0257 (12)	−0.0036	0.0004 (10)	−0.0011

				(10)		(10)
C32	0.0221 (11)	0.0242 (11)	0.0229 (11)	0.0000 (10)	0.0045 (9)	0.0030 (10)
C33	0.0203 (10)	0.0216 (10)	0.0198 (10)	0.0025 (10)	0.0032 (8)	0.0033 (10)
C34	0.0206 (10)	0.0237 (11)	0.0235 (10)	0.0018 (10)	0.0061 (8)	0.0046 (10)
C35	0.0211 (11)	0.0245 (12)	0.0238 (12)	−0.0027 (9)	0.0076 (9)	−0.0021 (9)
N36	0.0241 (10)	0.0210 (10)	0.0210 (10)	0.0024 (8)	0.0056 (8)	0.0009 (8)
C37	0.0288 (11)	0.0205 (11)	0.0176 (10)	−0.0001 (11)	0.0012 (8)	−0.0038 (9)
C38	0.0268 (11)	0.0230 (12)	0.0185 (10)	−0.0006 (10)	−0.0001 (9)	−0.0027 (9)
C39	0.0251 (12)	0.0239 (12)	0.0193 (11)	−0.0024 (9)	0.0036 (9)	−0.0024 (9)
C40	0.0204 (11)	0.0214 (11)	0.0213 (11)	−0.0007 (9)	0.0044 (9)	−0.0035 (9)
C41	0.0252 (12)	0.0207 (11)	0.0193 (11)	0.0018 (9)	0.0056 (9)	−0.0021 (9)
N42	0.0234 (10)	0.0258 (10)	0.0230 (10)	0.0036 (8)	0.0044 (8)	−0.0047 (8)
S43	0.0215 (3)	0.0392 (4)	0.0274 (3)	0.0046 (3)	0.0012 (2)	−0.0061 (3)
O44	0.0384 (11)	0.0639 (15)	0.0374 (11)	0.0288 (11)	−0.0014 (9)	−0.0022 (10)
O45	0.0324 (10)	0.0618 (14)	0.0418 (11)	−0.0150 (10)	0.0094 (9)	−0.0119 (10)
C46	0.0263 (13)	0.0342 (14)	0.0270 (13)	0.0038 (11)	0.0021 (10)	−0.0089 (11)
C47	0.0301 (13)	0.0265 (12)	0.0185 (11)	0.0045 (10)	0.0032 (9)	−0.0013 (9)
C48	0.0285 (13)	0.0356 (14)	0.0242 (12)	0.0016 (11)	0.0082 (10)	−0.0088 (10)
C49	0.0254 (12)	0.0358 (14)	0.0208 (12)	−0.0038 (11)	0.0063 (9)	−0.0017 (10)
C50	0.0325 (13)	0.0211 (12)	0.0326 (13)	0.0005 (10)	0.0068 (11)	−0.0024 (10)
C51	0.0403 (14)	0.0284 (13)	0.0198 (11)	−0.0037 (11)	0.0022 (10)	−0.0004 (10)
C52	0.0541 (18)	0.0255 (13)	0.0247 (13)	0.0014 (12)	−0.0037 (12)	0.0015 (10)
C53	0.0378 (15)	0.0278 (13)	0.0309 (14)	0.0115 (11)	−0.0060 (11)	−0.0032 (11)
C54	0.0316 (13)	0.0286 (12)	0.0275 (12)	0.0061 (11)	0.0007 (10)	−0.0062 (11)

Geometric parameters (Å, º)

Br1—C2	1.900 (2)	Br28—C29	1.901 (2)
C2—C3	1.385 (3)	C29—C30	1.386 (4)
C2—C7	1.392 (4)	C29—C34	1.381 (4)
C3—C4	1.389 (3)	C30—C31	1.387 (4)
C3—H31	0.933	C30—H301	0.940

C4—C5	1.393 (3)	C31—C32	1.392 (4)
C4—C8	1.521 (3)	C31—H311	0.936
C5—C6	1.390 (4)	C32—C33	1.388 (3)
C5—H51	0.938	C32—H321	0.934
C6—C7	1.383 (4)	C33—C34	1.401 (3)
C6—H61	0.936	C33—C35	1.514 (3)
C7—H71	0.931	C34—H341	0.935
C8—N9	1.449 (3)	C35—N36	1.460 (3)
C8—H81	0.967	C35—H351	0.963
C8—H82	0.969	C35—H352	0.968
N9—C10	1.384 (3)	N36—C37	1.384 (3)
N9—C17	1.397 (3)	N36—C40	1.395 (3)
C10—C11	1.394 (3)	C37—C38	1.406 (3)
C10—C15	1.416 (3)	C37—C54	1.404 (3)
C11—C12	1.384 (4)	C38—C39	1.432 (3)
C11—H111	0.934	C38—C51	1.410 (3)
C12—C13	1.401 (4)	C39—C40	1.368 (3)
C12—H121	0.935	C39—C49	1.500 (3)
C13—C14	1.382 (4)	C40—C41	1.519 (3)
C13—H131	0.941	C41—N42	1.497 (3)
C14—C15	1.396 (3)	C41—C47	1.554 (3)
C14—H141	0.934	C41—C50	1.529 (3)
C15—C16	1.437 (3)	N42—S43	1.642 (2)
C16—C17	1.367 (3)	N42—C48	1.475 (3)
C16—C26	1.495 (3)	S43—O44	1.442 (2)
C17—C18	1.515 (3)	S43—O45	1.436 (2)
C18—N19	1.493 (3)	S43—C46	1.765 (3)
C18—C24	1.557 (3)	C46—C47	1.517 (4)
C18—C27	1.526 (3)	C46—H462	0.972
N19—S20	1.637 (2)	C46—H461	0.971
N19—C25	1.475 (3)	C47—H472	0.963
S20—O21	1.432 (2)	C47—H471	0.971
S20—O22	1.4389 (19)	C48—C49	1.528 (4)
S20—C23	1.768 (3)	C48—H481	0.977
C23—C24	1.525 (4)	C48—H482	0.975
C23—H231	0.980	C49—H491	0.976
C23—H232	0.976	C49—H492	0.965
C24—H241	0.971	C50—H501	0.964
C24—H242	0.966	C50—H502	0.962
C25—C26	1.522 (3)	C50—H503	0.960
C25—H251	0.978	C51—C52	1.372 (4)

C25—H252	0.969	C51—H511	0.938
C26—H262	0.966	C52—C53	1.409 (4)
C26—H261	0.964	C52—H521	0.938
C27—H272	0.964	C53—C54	1.384 (4)
C27—H271	0.960	C53—H531	0.940
C27—H273	0.970	C54—H541	0.933
Br1—C2—C3	118.66 (18)	Br28—C29—C30	119.17 (19)
Br1—C2—C7	119.59 (18)	Br28—C29—C34	118.45 (19)
C3—C2—C7	121.7 (2)	C30—C29—C34	122.4 (2)
C2—C3—C4	119.4 (2)	C29—C30—C31	118.1 (2)
C2—C3—H31	120.6	C29—C30—H301	120.3
C4—C3—H31	120.0	C31—C30—H301	121.6
C3—C4—C5	119.7 (2)	C30—C31—C32	120.5 (2)
C3—C4—C8	117.6 (2)	C30—C31—H311	119.7
C5—C4—C8	122.8 (2)	C32—C31—H311	119.8
C4—C5—C6	119.9 (2)	C31—C32—C33	120.8 (2)
C4—C5—H51	119.5	C31—C32—H321	119.4
C6—C5—H51	120.6	C33—C32—H321	119.8
C5—C6—C7	121.1 (2)	C32—C33—C34	119.0 (2)
C5—C6—H61	119.1	C32—C33—C35	123.6 (2)
C7—C6—H61	119.8	C34—C33—C35	117.4 (2)
C2—C7—C6	118.2 (2)	C33—C34—C29	119.2 (2)
C2—C7—H71	121.0	C33—C34—H341	120.5
C6—C7—H71	120.8	C29—C34—H341	120.3
C4—C8—N9	113.68 (19)	C33—C35—N36	113.44 (19)
C4—C8—H81	107.5	C33—C35—H351	108.4
N9—C8—H81	108.3	N36—C35—H351	108.2
C4—C8—H82	108.7	C33—C35—H352	108.1
N9—C8—H82	108.4	N36—C35—H352	109.2
H81—C8—H82	110.3	H351—C35—H352	109.5
C8—N9—C10	121.95 (19)	C35—N36—C37	121.92 (19)
C8—N9—C17	128.4 (2)	C35—N36—C40	130.2 (2)
C10—N9—C17	108.04 (18)	C37—N36—C40	107.90 (19)
N9—C10—C11	129.7 (2)	N36—C37—C38	108.5 (2)
N9—C10—C15	108.5 (2)	N36—C37—C54	129.4 (2)
C11—C10—C15	121.9 (2)	C38—C37—C54	122.1 (2)
C10—C11—C12	117.1 (2)	C37—C38—C39	106.6 (2)
C10—C11—H111	121.1	C37—C38—C51	118.8 (2)
C12—C11—H111	121.8	C39—C38—C51	134.6 (2)
C11—C12—C13	121.7 (2)	C38—C39—C40	107.6 (2)
C11—C12—H121	118.5	C38—C39—C49	129.2 (2)

C13—C12—H121	119.8	C40—C39—C49	123.2 (2)
C12—C13—C14	121.0 (2)	N36—C40—C39	109.4 (2)
C12—C13—H131	119.8	N36—C40—C41	124.8 (2)
C14—C13—H131	119.2	C39—C40—C41	125.7 (2)
C13—C14—C15	118.7 (2)	C40—C41—N42	107.20 (18)
C13—C14—H141	121.0	C40—C41—C47	113.02 (19)
C15—C14—H141	120.4	N42—C41—C47	103.86 (18)
C10—C15—C14	119.5 (2)	C40—C41—C50	111.70 (19)
C10—C15—C16	106.2 (2)	N42—C41—C50	108.67 (19)
C14—C15—C16	134.1 (2)	C47—C41—C50	111.9 (2)
C15—C16—C17	107.8 (2)	C41—N42—S43	113.44 (15)
C15—C16—C26	128.5 (2)	C41—N42—C48	117.98 (19)
C17—C16—C26	123.4 (2)	S43—N42—C48	119.11 (17)
N9—C17—C16	109.5 (2)	N42—S43—O44	110.06 (13)
N9—C17—C18	124.5 (2)	N42—S43—O45	110.16 (12)
C16—C17—C18	125.7 (2)	O44—S43—O45	116.07 (14)
C17—C18—N19	107.40 (18)	N42—S43—C46	95.66 (11)
C17—C18—C24	112.60 (19)	O44—S43—C46	107.95 (13)
N19—C18—C24	104.89 (19)	O45—S43—C46	115.04 (14)
C17—C18—C27	112.3 (2)	S43—C46—C47	101.51 (17)
N19—C18—C27	108.10 (19)	S43—C46—H462	112.0
C24—C18—C27	111.1 (2)	C47—C46—H462	111.6
C18—N19—S20	113.29 (15)	S43—C46—H461	110.9
C18—N19—C25	120.05 (18)	C47—C46—H461	110.7
S20—N19—C25	119.29 (16)	H462—C46—H461	109.9
N19—S20—O21	109.75 (12)	C41—C47—C46	106.6 (2)
N19—S20—O22	109.60 (11)	C41—C47—H472	111.4
O21—S20—O22	116.58 (13)	C46—C47—H472	110.1
N19—S20—C23	95.05 (11)	C41—C47—H471	109.3
O21—S20—C23	108.72 (13)	C46—C47—H471	109.9
O22—S20—C23	115.00 (13)	H472—C47—H471	109.4
S20—C23—C24	100.68 (17)	N42—C48—C49	111.8 (2)
S20—C23—H231	110.1	N42—C48—H481	108.2
C24—C23—H231	110.0	C49—C48—H481	109.4
S20—C23—H232	112.2	N42—C48—H482	108.9
C24—C23—H232	113.0	C49—C48—H482	108.2
H231—C23—H232	110.5	H481—C48—H482	110.3
C23—C24—C18	107.68 (19)	C48—C49—C39	109.4 (2)
C23—C24—H241	109.5	C48—C49—H491	110.1
C18—C24—H241	108.6	C39—C49—H491	109.5
C23—C24—H242	110.3	C48—C49—H492	109.6

C18—C24—H242	110.4	C39—C49—H492	109.2
H241—C24—H242	110.3	H491—C49—H492	109.0
N19—C25—C26	111.43 (19)	C41—C50—H501	110.0
N19—C25—H251	109.4	C41—C50—H502	110.1
C26—C25—H251	109.1	H501—C50—H502	109.5
N19—C25—H252	108.4	C41—C50—H503	109.2
C26—C25—H252	108.3	H501—C50—H503	109.2
H251—C25—H252	110.2	H502—C50—H503	108.8
C25—C26—C16	107.9 (2)	C38—C51—C52	119.1 (2)
C25—C26—H262	110.1	C38—C51—H511	119.2
C16—C26—H262	109.7	C52—C51—H511	121.7
C25—C26—H261	110.0	C51—C52—C53	121.5 (2)
C16—C26—H261	109.6	C51—C52—H521	119.1
H262—C26—H261	109.6	C53—C52—H521	119.4
C18—C27—H272	109.2	C52—C53—C54	120.8 (2)
C18—C27—H271	109.4	C52—C53—H531	119.5
H272—C27—H271	109.7	C54—C53—H531	119.7
C18—C27—H273	109.3	C37—C54—C53	117.6 (2)
H272—C27—H273	109.5	C37—C54—H541	121.1
H271—C27—H273	109.8	C53—C54—H541	121.2

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C12—H121···O44^{i}	0.94	2.54	3.390 (4)	152
C23—H232···O44^{ii}	0.98	2.51	3.347 (4)	143
C35—H351···O21	0.96	2.55	3.430 (4)	152
C46—H461···O22^{iii}	0.97	2.50	3.282 (4)	137

Symmetry codes: (i) *x*+1, *y*, *z*−1; (ii) *x*+1, *y*, *z*; (iii) −*x*+1, *y*−1/2, −*z*+1.

For both compounds, data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997). Program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007) for (10b); *SIR92* (Altomare *et al.*, 1994) for (15a). For both compounds, program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Chapter 8: Experimental References

[1] a) P. Wipf, J. K. Jung. *J. Org. Chem.* **2000**, 65, 6319-6337 b) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan. *J. Am. Chem. Soc.* **2006**, 128, 84; K. Maruoka, T. Itoh, Y. Araki, T. Shirasaka, H. Yamamoto. *Bull. Chem. Soc. Jpn.* **1988**, 61, 2975.

[2] a) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon. *J. Am. Chem. Soc.* **2009**, *131*, 31, 10796; b) F. Hadjaz, S. Besret, S. Yous, S. Dilly, N. Lebegue, P. Chavatte, P. Berthelot, P. Carato, F. Martin-Nizard, P. Duriez. *European Journal of Medicinal Chemistry*, **2011** , 46, 6, 2575.

[3] Cheung, F. K.; Hayes, A. M.; Morris, D, J.; Wills, M. *Org. Biomol. Chem.* **2007**, *5*, 1093.

[4] Kalir, A.; Szara, S. *J. Med. Chem.* **1963**, *6*, 716.

[5] Pedras, M. S.; Ahiahonu, P. W. K. *Bioorg. Med. Chem.* **2002**, *10*, 3307.

[6] Sako, K.; Aoyama, H.; Sato, S.; Hashimoto, Y.; Baba, M. *Bioorg. Med. Chem.* **2008**, *16*, 3780.

[7] Mor, M.; Rivara, S.; Silva, C.; Bordi, F.; Plazzi, P. V. *J. Med. Chem.* **1998**, *41*, 3831.

[8] a) Nicolaou, K. C.; Krasovskiy, A.; Trépanier, V. É.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.*, **2008**, *47*, 4217; b) Guo, W.; Wong, T. C. *Mag. Res. Chem.* **1986**, *24*, 75.

[9] Newhouse, T.; Lewis, C.A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 7119.

[10] Somel, M.; Wakida, M.; Ohta, T. *Chem. Pharm. Bull.* **1988**, *34*, 1162.

[11] Ikeda, T.; Kawamura, M.; Murase, N.; Nukui, S., Shishido, Y.; Kawai, M.; Okumura, Y. Patent: US2001/46993 A1, **2001.**

[12] Fitch, R. W.; Sturgeon, G. D.; Patel, S. R.; Spande, T. F.; Garraffo, H. M.; Daly, J. W.; Blaauw, R. H. *J. Nat. Prod.* **2009,** *72*, 243.

[13] Bélanger, G.; Larouche-Gauthier, R.; Ménard, F.; Miguel Nantel, M.; Francis Barabé, F. *Org. Lett.*, **2005**, *7*, 4431.

[14] Dado, G. P.; Samuel H. Gellman, S. H. *J. Am. Chem. Soc.*, **1994**, *116*, 1054.

[15] Zenner, J. M.; Larock, R. C. *J. Org. Chem.* **1999**, *64*, 7312.

[16] Single crystal X-ray diffraction data were collected using a Nonius Kappa CCD diffractometer and data were reduced using Denzo-SMN.[12] The structures were solved with SIR92/SuperFlip[13] and refined with CRYSTALS.[14] The Flack x parameter[15] refined to -0.007(8) and 0.010(4) for **10b** and **15a** respectively. For further information, see ESI (CIF); full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC XXXXX-X, respectively. Copies of

these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] Otwinowski, Z.; Minor, W. *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.* Carter, C. W, Sweet, R. M, Eds.; Academic Press. **1997**, 276,

[13] a) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M.; *J. Appl. Cryst.* **1994**, 27, 435; b) Palatinus, L.; Chapuis, G. *J. Appl. Cryst.* **2007**, 40, 786.

[14] a) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Cryst.* **2003**, 36, 1487; b) Cooper, R. I.; Thompson, A. L.; Watkin, D. J.; *J. Appl. Cryst.* **2010**, 43, 1100.

[15] a) Flack, H. D. *Acta Cryst.* **1983**, A39, 876; b) Thompson, A. L.; Watkin, D. J. *J. Appl. Cryst.* **2011**, 44, 1017.