Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Enhancing the Usefulness of Cross Dehydrogenative Coupling Reactions with a Removable Protecting Group

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1. General experimental details

All commercially available reagents and solvents were purchased and used as received from Sigma-Aldrich or Alfa-Aesar. Drying of glassware at 115 °C overnight and activation of molecular sieves in a microwave was performed when anhydrous conditions were required. Dichloromethane was distilled over calcium hydride. Reflux reactions were performed with a paraffin oil bath. Flash column chromatography was performed with Grace Silica Gel 60 (40 – 63 μm, 230 – 400 mesh), with solvent ratios as specified. All novel compounds listed below are italicised. Spectroscopic data for single enantiomers were identical to those for the racemate.

Melting points were obtained on an Optimelt Automated Melting Point System and reported in degrees Celsius. Optical rotation was recorded on a Perkin Elmer 341 polarimeter with Na lamp (589 nm). Enantioselective normal phase high-performance liquid chromatography was performed on a Waters 500 analytical HPLC pump (Chiralcel OD-H column, 0.5 mL flowrate, 0.5μL injection volume, specified solvent ratios) with a Waters 2487 dual wavelength absorbance detector (set at 254 nm and 270 nm) and a Waters 410 differential refractometer.

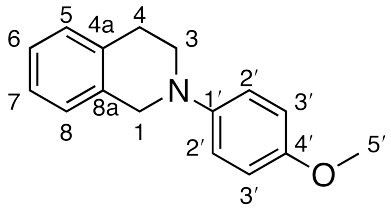
^{1}H and ^{13}C nuclear magnetic resonance spectroscopy was conducted on either a Bruker Avance III 500 at a frequency of 500.13 MHz and 125 MHz or a Bruker Avance III 400 at a frequency of 400.13 MHz and 100 MHz, with deuterated solvents ($CDCl_3$ or MeOD) used without further purification. Signals are reported in the order chemical shift (ppm downfield with respect to the solvent residual), integration, multiplicity, coupling constants *J* (in Hertz) and assignments.

Low-resolution mass spectrometry was performed on a Finnigan LCQ mass spectrometer, with either electrospray ionisation (ESI) mode or atmospheric-pressure chemical ionisation (APCI) under positive mode. High-resonance mass spectrometry was performed on a Bruker 7T Fourier Transform Ion Cyclotron Resonance mass spectrometer, with either electrospray ionisation (ESI) mode or atmospheric-pressure chemical ionisation (APCI) under positive mode.

Infrared spectroscopy was performed on a Bruker Alpha FT-IR spectrometer under transmission mode, with absorbances reported as wave numbers.

2. Experimental procedures and characterisation data

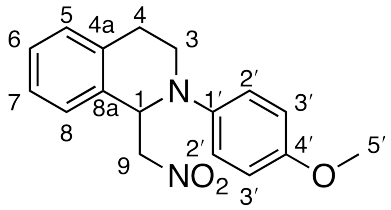
2-(4′-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 4[1]



To a degassed mixture of 1,2,3,4-tetrahydroisoquinoline (3.00 g, 22.6 mmol, 1.5 eq), ethylene glycol (2.80 g, 2.52 mL, 30.0 mmol, 2.0 eq) and isopropanol (15 mL) were added 4-iodoanisole (3.52 g, 15.0 mmol, 1.0 eq), potassium phosphate tribasic (9.56 g, 30.0 mmol, 2.0 eq) and copper(I) iodide (0.429 g, 1.50 mmol, 0.1 eq) and the resultant suspension was stirred at 80 °C for 24 h. The reaction mixture was diluted with diethyl ether (50 mL) and filtered through a pad of Celite. The solution was diluted with water (100 mL) and extracted into diethyl ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The majority of the product was isolated through recrystallisation from hexane:ethyl acetate (10:1) to give the product as a white solid. The mother liquor from the recrystallisation was purifed by flash column chromatography (hexanes:ethyl acetate 10:1) to give the product as a white solid (combined yield 2.75 g, 76%).

m.p. 93 – 94 °C (no lit m.p.). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.99 (2H, t, *J* 5.7, H^4), 3.45 (2H, t, *J* 5.7, H^3), 3.78 (3H, s, $H^{5'}$), 4.30 (2H, s, H^1), 6.85 – 6.87 (2H, m, $H^{2'}$), 6.97 – 6.99 (2H, m, $H^{3'}$), 7.11 – 7.25 (4H, m, H^5 – H^8). **IR** ($CHCl_3$) ν_{max}/cm^{-1} 1504, 1466. **m/z** (ESI) 238.3 ($[M-H]^+$, 100%). **HRMS** (ESI) 240.13838 (MH^+); calcd. for $C_{16}H_{18}NO$ (MH^+) 240.13829. Spectroscopic data match those in the literature.[2]

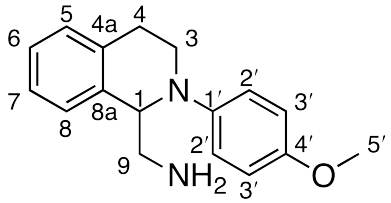
1-(Nitromethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 9b



To 2,3-dichloro-5,6-cyano-1,4-benzoquinone (1.18g, 5.18 mmol, 1.1 eq) in nitromethane (50 mL) was added 2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1.13 g, 4.71 mmol, 1.0 eq) and the reaction mixture stirred at rt for 30 min. *N*,*N*-Diisopropylethylamine (0.911 g, 1.23 mL, 7.06 mmol, 1.5 eq) was added and the reaction mixture stirred at rt for a further minute. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution (200 mL) and extracted into ethyl acetate (3 × 100 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution (3 × 200 mL), concentrated under reduced pressure and the residue purified by flash column chromatography (5:1 hexanes:ethyl acetate) to give the product as a yellow oil (1.40 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (1H, dt, *J* 16.5, 4.0, H^4), 3.02 (1H, ddd, *J* 16.5, 9.5, 6.5, H^4), 3.52 – 3.61 (2H, m, H^3), 3.75 (3H, s, $H^{5\prime}$), 4.56 (1H, dd, *J* 12.0, 6.0, H^9), 4.83 (1H, dd, *J* 12.0, 8.5, H^9), 5.39 (1H, dd, *J* 8.5, 6.0, H^1), 6.81 – 6.83 (2H, m, $H^{2\prime}$), 6.90 – 6.92 (2H, m, $H^{3\prime}$), 7.14 – 7.26 (4H, m, H^5 – H^8). **IR** ($CHCl_3$) ν_{max}/cm^{-1} 1558, 1497, 1465, 1380, 1034. **m/z** (ESI) 238.2 ($[M\text{-}CH_2NO_2]^+$, 100%). Spectroscopic data match those in the literature.[3]

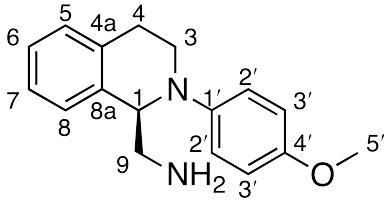
***1-(Aminomethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline 10a*[4]**



To 1-(nitromethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.768 g, 2.58 mmol, 1.0 eq) in 100 mL MeOH:NH_3 (9:1) was added Raney nickel (0.3 mL slurry, approximately 0.250 g) and the reaction mixture stirred under H_2 (100 psi) for 4 h at rt. The reaction mixture was filtered through Celite and the volatiles removed under reduced pressure. The residue was diluted with water (50 mL) and extracted into dichloromethane (50 mL). The aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (95:4.5:0.5 dichloromethane:methanol:ammonia) to give the product as a brown oil (0.594 g, 87%).

^{1}H NMR (400 MHz, MeOD): δ 2.59 (1H, dt, *J* 16.4, 4.0, H^4), 2.80 – 2.88 (1H, m, H^4), 2.91 (1H, dd, *J* 13.2, 4.8, H^9), 3.01 (1H, dd, *J* 13.2, 9.2, H^9), 3.52 – 3.56 (2H, m, H^3), 3.71 (3H, s, $H^{5'}$), 4.50 (1H, dd, *J* 9.2, 4.8, H^1), 6.77 – 6.81 (2H, m), 6.93 – 6.99 (2H, m), 7.02 – 7.18 (4H, m). **^{13}C NMR** (100 MHz, MeOD): δ 26.3 (C^4), 44.9 (C^3), 46.7 (C^9), 56.0 (C^{10}), 62.4 (C^1), 115.6 ($C^{2'}$), 121.0 ($C^{3'}$), 127.2 (C^6), 127.8 (C^7), 128.3 (C^8), 130.1 (C^5), 136.8 (C^{4a}), 137.1 (C^{8a}), 146.1 ($C^{1'}$), 155.4 ($C^{4'}$). **IR** ($CHCl_3$) ν_{max}/cm^{-1} 2401, 1506, 1261, 1095. **m/z** (ESI) 269.0 (MH^+, 90%), 252.1 ($[M\text{-}NH_2]^+$, 63%), 238.1 ($[M\text{-}CH_2NH_2]^+$, 100%). **HRMS** (ESI) 269.16464 (MH^+); calcd. for $C_{17}H_{21}N_2O$ (MH^+) 269.16484.

1-(R)-(Aminomethyl)-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, (R)-10a

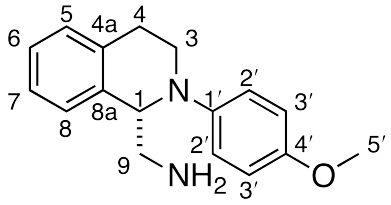


To 1-(aminomethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1.02 g, 3.80 mmol, 1.0 eq) in isopropanol:water (5:1, 38 mL, ~0.1 M) was added (+)-dibenzoyl-D-tartaric acid (1.87 g as crystallised with 2*i*PrOH, 3.80 mmol, 1.0 eq) and the solution was heated gently until complete dissolution was observed. The reaction was left at rt (12 – 18 °C) for 24 h. The crystals obtained were filtered, washed with isopropanol and recrystallised twice from the minimum amount of isopropanol water (9:1). The resultant crystals were dissolved in ethyl acetate (50 mL) and saturated sodium hydrogen carbonate solution (50 mL). The aqueous phase was extracted into ethyl acetate (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give the amine (0.174 g, 34% wrt single enantiomer) as a brown oil.

Spectroscopic data (^{1}H NMR) match those of the racemate.

$[\alpha]_D^{20}$ = +97.4 (*c* 5.0, $CHCl_3$). Analysis of the sample by enantioselective HPLC indicated enantiopurity of 97%. Absolute stereochemistry assigned retrospectively from enantioselective HPLC data of praziquantel synthesised from this compound.

1-(S)-(Aminomethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, (S)-10a

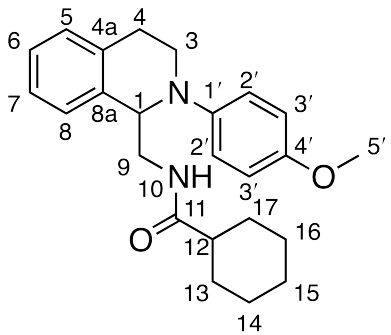


To 1-(aminomethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.741 g, 2.76 mmol, 1.0 eq) in isopropanol:water (5:1, 28 mL, ~0.1 M) was added (-)-dibenzoyl-L-tartaric acid (1.36 g as crystallised with 2*i*PrOH, 2.76 mmol, 1.0 eq) and the solution heated gently until complete dissolution was observed. The reaction was left to sit at rt (12 – 18 °C) for 24 h. The crystals obtained were isolated, washed with isopropanol and recrystallised twice from minimum isopropanol water (9:1). The resultant crystals were dissolved in ethyl acetate (50 mL) and saturated sodium hydrogen carbonate solution (50 mL). The aqueous phase was extracted into ethyl acetate (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give the amine (0.102 g, 27% wrt single enantiomer) as a brown oil.

Spectroscopic data (^{1}H NMR) match those of the racemate.

$[\alpha]_D^{20}$ = -62.4 (*c* 5.0, $CHCl_3$). Analysis of the sample by enantioselective HPLC indicated enantiopurity of 95%. Absolute stereochemistry assigned retrospectively from enantioselective HPLC data of praziquantel synthesised from this compound.

1-(N-Cyclohexylcarboxamido methyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 13a

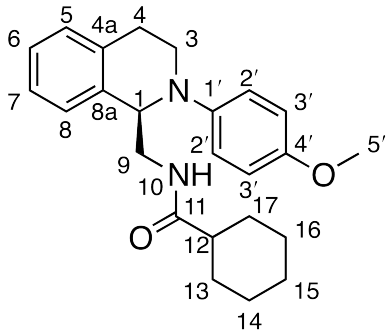


To 1-(aminomethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.274 g, 1.02 mmol, 1.0 eq) in dichloromethane over ice, was added triethylamine (0.207 g, 0.283 mL,

2.04 mmol, 2.0 eq) and 4-(*N*,*N*-dimethylamino)pyridine (0.006 g, 0.05 mmol, 0.05 eq). Cyclohexanecarbonyl chloride (0.194 g, 0.176 mL, 1.33 mmol, 1.3 eq) was added dropwise and the reaction mixture stirred over ice. The reaction was monitored by TLC (90:9:1 dichloromethane:methanol:ammonia) until starting material was observed to disappear (approximately 4 h), after which the reaction mixture was diluted with water (50 mL) and extracted into dichloromethane (3 × 50 mL). The organic phases were combined, dried ($MgSO_4$), concentrated and purified by flash column chromatography (3:1 hexane:ethyl acetate) to give the product (0.353 g, 98%) as a white solid.

mp 135 – 136 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.15 – 1.42 (5H, m), 1.63 – 1.81 (5H, m), 1.99 (1H, td, *J* 11.4, 3.6, H^{12}), 2.67 (1H, ddd, *J* 16.2, 8.4, 4.2, H^4), 2.94 (1H, ddd, *J* 16.2, 15.6, 7.8, H^4), 3.42 (1H, ddd, *J* 13.8, 9.3, 4.2, H^9), 3.50 – 3.53 (2H, m, H^3), 3.65 – 3.69 (1H, m, H^9), 3.74 (3H, s, $H^{5'}$), 4.66 (1H, dd, *J* 9.0, 9.0, H^1), 5.89 (1H, br s, NH), 6.80 – 6.82 (2H, m, $H^{3'}$), 6.93 – 6.95 (2H, m, $H^{2'}$), 7.16 – 7.22 (4H, m, H^5 – H^8). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.8, 25.9, 26.2 (C^4), 29.6, 29.7, 43.4 (C^3), 43.7 (C^9), 45.5 (C^{12}), 55.7 (C^{16}), 59.6 (C^1), 114.8 ($C^{3'}$), 118.5 ($C^{2'}$), 126.2 (C^6 – C^8), 127.0 (C^6 – C^8), 127.6 (C^6 – C^8), 128.9 (C^5), 135.3 (C^{4a} or C^{8a}), 135.7 (C^{4a} or C^{8a}), 144.6 ($C^{1'}$), 153.5 ($C^{4'}$), 176.2 (C^{11}). **IR** ν_{max}/cm^{-1} 3290, 3053, 2929, 2853, 1644, 1510, 1244, 1037. **m/z** (APCI) 379.2 (MH^+, 100%). **HRMS** (APCI) 379.23820 (MH^+); calcd. for $C_{24}H_{31}N_2O_2$ (MH^+) 379.23801.

1-(*R*)-(*N*-Cyclohexylcarboxamido methyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, (*R*)-13a

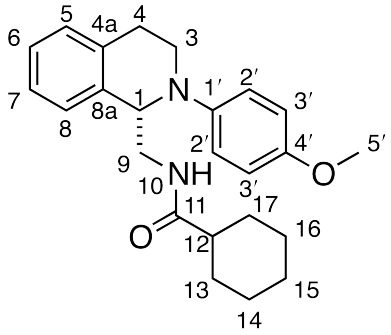


Synthesised from 1-(*R*)-(aminomethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline according to the procedure for the racemate in a yield of 98%.

Spectroscopic data (^{1}H NMR) match those of the racemate.

$[\alpha]_D^{20}$ = +35.0 (c 5.0, $CHCl_3$). Analysis of the sample by enantioselective HPLC indicated enantiopurity of 95%. Absolute stereochemistry assigned retrospectively from enantioselective HPLC data of praziquantel synthesised from this compound.

1-(*S*)-(*N*-Cyclohexylcarboxamido methyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, (*S*)-13a

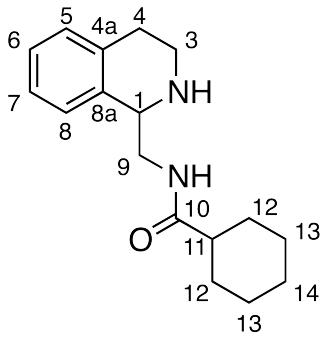


Synthesised from 1-(*S*)-(aminomethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline according to the procedure for the racemate in a yield of 86%.

Spectroscopic data (^{1}H NMR) match those of the racemate.

$[\alpha]_D^{20}$ = -55.2 (*c* 5.0, $CHCl_3$). Analysis of the sample by enantioselective HPLC indicated enantiopurity of 95%. Absolute stereochemistry assigned retrospectively from enantioselective HPLC data of praziquantel synthesised from this compound.

1-(*N*-Cyclohexylcarboxamido methyl)-1,2,3,4-tetrahydroisoquinoline, 14a[5]

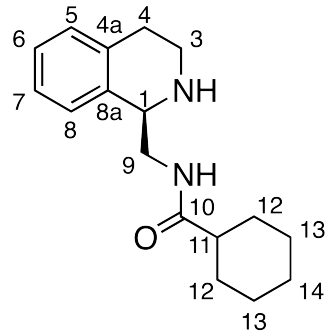


To 1-(*N*-cyclohexylcarboxamido methyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.100 g, 0260 mmol, 1.0 eq) in acetonitrile:water (1:1, 5 mL) at 0

°C was added ceric ammonium nitrate (0.425 g, 0.790 mmol, 3.0 eq) in acetonitrile:water (1:1, 5 mL) and the reaction stirred at 0 °C for 5 min. The reaction mixture was diluted with water (20 mL) and ethyl acetate (20 mL). The aqueous phase was extracted with ethyl acetate (2 × 20 mL), diluted with saturated sodium hydrogen carbonate solution (20 mL) and further extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by flash column chromatography (95:4.5:0.5 dichloromethane:methanol:ammonia) to give the product (0.51 g, 81%) as a brown oil.

^{1}H NMR (500 MHz, MeOD): δ 1.19 – 1.43 (6H, m, H^{12} – H^{14}), 1.67 – 1.79 (4H, m, H^{12} – H^{14}), 2.18 (1H, tt, *J* 12.0, 3.5, H^{11}), 2.76 – 2.86 (2H, m), 2.91 – 2.96 (1H, m), 3.18 – 3.23 (1H, m), 3.49 (1H, dd, *J* 14.0, 8.5, H^9), 3.55 (1H, dd, *J* 14.0, 4.0, H^9), 4.08 (1H, dd, *J* 8.5, 4.0, H^1), 7.09 – 7.20 (4H, m, H^5 – H^8). **^{13}C NMR** (125 MHz, MeOD): 26.8 (C^{12}), 26.9 (C^{13}), 29.9 (C^3), 30.7 (C^{11}), 40.5 (C^4), 44.8 (C^9), 46.5 (C^{14}), 56.6 (C^1), 127.0 (C^6 or C^7), 127.7 (C^6 or C^7), 127.8 (C^8), 130.6 (C^5), 136.4 (C^{4a} or C^{8a}), 136.6 (C^{4a} or C^{8a}), 178.3 (C^{10}). **m/z** (ESI+) 273.3 (MH^+, 100%). Spectroscopic data match those in the literature.[6]

1-(*R*)-(*N*-Cyclohexylcarboxamido methyl)-1,2,3,4-tetrahydroisoquinoline, (*R*)-14a[5]

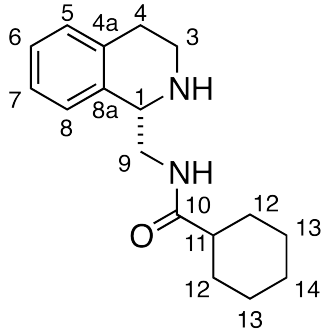


Synthesised from 1-(*R*)-(*N*-cyclohexylcarboxamido methyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline according to the procedure for the racemate in a yield of 80%

Spectroscopic data (^{1}H NMR) match those in the literature.

$[\alpha]_D^{20}$ = -18.6 (*c* 5.0, $CHCl_3$). Analysis of the sample by enantioselective HPLC indicated enantiopurity of 97%. Absolute stereochemistry assigned retrospectively from enantioselective HPLC data of praziquantel synthesised from this compound.

1-(*S*)-(*N*-Cyclohexylcarboxamido methyl)-1,2,3,4-tetrahydroisoquinoline, (*S*)-14a[5]

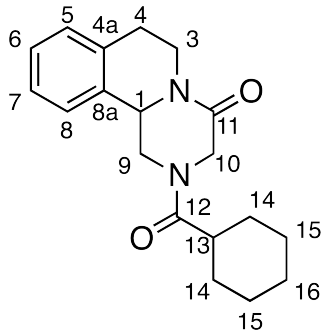


Synthesised from 1-(*S*)-(*N*-cyclohexlcarboxamido methyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline according to the procedure for the racemate in a yield of 46%.

Spectroscopic data (^{1}H NMR) match those of the racemate.

$[\alpha]_D^{20}$ = +11.6 (*c* 5.0, $CHCl_3$). Analysis of the sample by enantioselective HPLC indicated enantiopurity of 95%. Absolute stereochemistry assigned retrospectively from enantioselective HPLC data of praziquantel synthesised from this compound.

2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-a]isoquinolino-4-one, *rac*-praziquantel, 6a[6]

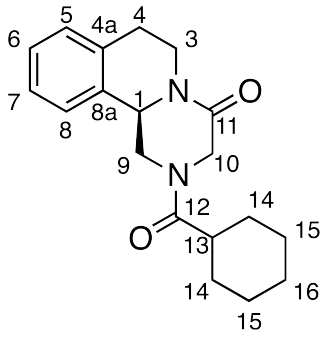


To 1-(*N*-cyclohexylcarbonylamido methyl)-1,2,3,4-tetrahydroisoquinoline (0.036 g, 0.13 mmol, 1.0 eq) in dichloromethane (0.330 mL), was added sodium hydroxide (50%, 0.063 mL, 0.79 mmol, 6.0 eq) and chloroacetyl chloride (0.16 g, 0.012 mL, 0.15 mmol, 1.1 eq)

and the reaction mixture stirred at rt for 30 min. Benzyltriethylammonium chloride (0.003 g, 0.013 mmol, 0.1 eq) was added and the reaction mixture stirred at reflux for 2 h. The reaction mixture was diluted with water (5 mL) and dichloromethane (5 mL), and the aqueous phase extracted with dichloromethane (2 × 5 mL). The combined organic phases were washed successively with water (2 × 10 mL), 5% hydrochloric acid (10 mL), water (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the compound (0.032 g, 78%) as a white foam.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 – 1.28 (3H, m, H^{14} – H^{16}), 1.50 – 1.60 (2H, m, H^{14} – H^{16}), 1.72 – 1.81 (5H, m, H^{14} – H^{16}), 2.43 – 2.49 (1H, m, H^{13}), 2.76 – 2.83 (2H, m, one of H^4 and one of H^9), 2.87 – 2.97 (2H, m, one of H^3 and one of H^4), 4.07 (1H, d, *J* 17.3, H^{10}), 4.46 (1H, d, *J* 17.4, H^{10}), 4.78 – 4.80 (2H, m, H^1 and H^3), 5.15 (1H, d, *J* 13.0, H^9), 7.16 – 7.18 (1H, m, H^5 – H^8), 7.22 – 7.27 (3H, m, H^5- H^8). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 25.9 (C^{14} – C^{16}), 28.9 (C^4), 29.1 (C^{14} – C^{16}), 29.4 (C^{14} – C^{16}), 39.2 (C^3), 40.9 (C^{13}), 45.3 (C^9), 49.2 (C^{10}), 55.1 (C^1), 125.6 (C^5 – C^8), 127.1 (C^5 – C^8), 127.6 (C^5 – C^8), 129.4 (C^5 – C^8), 132.9 (C^{8a}), 134.9 (C^{4a}), 164.6 (C^{11}), 174.9 (C^{12}). **IR** ν_{max}/(cm^{-1}) 2929, 2852, 1649, 1448, 1421. **m/z** (ESI+) 335.4 ($[M+Na]^+$, 100%). Spectroscopic data match those in the literature.[7]

(11b*R*)-2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-a]isoquinolino-4-one, (*R*)-praziquantel, (*R*)-6a[6]

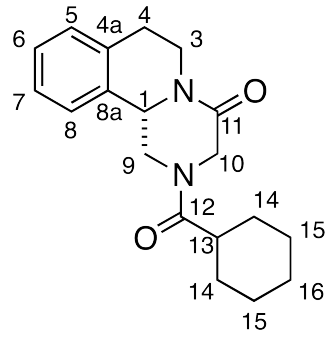


Synthesised from 1-(*R*)-(*N*-cyclohexylcarboxamido methyl)-1,2,3,4-tetrahydroisoquinoline according to the procedure for the racemate in a yield of 18%

Spectroscopic data (^{1}H NMR) match those of the racemate.

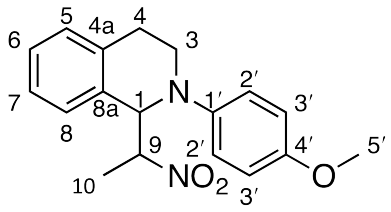
$[\alpha]_D^{23}$ = -132.0 (*c* 1.0, $CHCl_3$). lit.[6] $[\alpha]_D^{23}$ = -135.0 (*c* 1.0, $CHCl_3$). Analysis of the sample by enantioselective HPLC indicated enantiopurity of 97%. Absolute stereochemistry assigned through comparison of data from enantioselective HPLC of the synthesised compound and known samples.

(11b*S*)-2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-a]isoquinolino-4-one, (*S*)-praziquantel, (*S*)-6a[6]



Synthesised from 1-(*S*)-(*N*-cyclohexylcarboxamido methyl)-1,2,3,4-tetrahydroisoquinoline according to the procedure for the racemate in a yield of 78%. $[\alpha]_D^{23}$ = +128.0 (*c* 1.0, $CHCl_3$). Analysis of the sample by enantioselective HPLC indicated enantiopurity of 95%. Absolute stereochemistry assigned through comparison of data from enantioselective HPLC of the synthesised compound and known samples.

1-(Nitroethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 9b

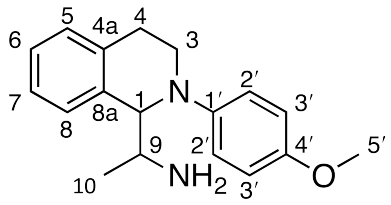


To DDQ (3.19 g, 13.1 mmol, 1.1 eq) in nitroethane (100 mL) was added 2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3.05 g, 12.8 mmol, 1.0 eq) and the reaction mixture stirred at rt for 30 min. *N*,*N*-Diisopropylethylamine (2.47 g, 3.34 mL,

19.1 mmol, 1.5 eq) was added and the reaction mixture stirred for a further minute. The reaction mixture was diluted with saturated sodium hydrogen carbonate solution (200 mL) and extracted into ethyl acetate (3 × 200 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution (3 × 200 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purifed by flash column chromatography (5:1 hexane:ethyl acetate) to give the product as a yellow oil (3.96 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 ($3H^{maj}$, d, *J* 6.4, H^{10}), 1.67 ($3H^{min}$, d, *J* 6.4, H^{10}), 2.75 – 2.85 (1H, m, H^4), 2.94 – 3.00 (1H, m, H^4), 3.45 – 3.56 ($1H^{maj}$ and $2H^{min}$, m, H^3), 3.73 ($3H^{maj}$, s, $H^{5'}$), 3.75 ($3H^{min}$, s, $H^{5'}$), 3.78 – 3.81 ($1H^{maj}$, m, H^3), 4.82 – 4.90 ($1H^{min}$, m, H^9), 4.96 – 5.07 ($2H^{maj}$ and $1H^{min}$, m, H^{1maj} and H^{1min} and H^{9maj}), 6.78 – 6.83 (2H, m, $H^{3'}$), 6.91 – 6.93 (2H, m, $H^{2'}$), 7.02 ($1H^{min}$, d, *J* 7.6, H^8), 7.10 ($1H^{maj}$, d, *J* 7.6, H^8), 7.14 – 7.26 ($3H^{maj}$ and $3H^{min}$, m, $H^{5\text{-}7maj}$ and $H^{5\text{-}7min}$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.7 (C^{10maj}), 17.2 (C^{10min}), 26.2 (C^{4maj}), 26.4 (C^{4min}), 44.2 (C^{3maj}), 45.2 (C^{3min}), 55.7 ($C^{5'}$), 62.4 (C^{1min}), 63.6 (C^{1maj}), 85.9 (C^{9maj}), 88.9 (C^{9min}), 114.7 ($C^{3'maj}$), 114.8 ($C^{3'min}$), 118.4 ($C^{2'min}$), 119.1 ($C^{2'maj}$), 126.2 (C^{6maj} or C^{7maj}), 126.6 (C^{6min} or C^{7min}), 127.3 (C^{8min}), 128.1 (C^{6min} or C^{7min}), 128.2 (C^{6maj} or C^{7maj}), 128.5 (C^{8maj}), 129.1 (C^{5min}), 129.4 (C^{5maj}), 132.2 ($C^{8a\text{-}maj}$), 133.8 ($C^{8a\text{-}min}$), 135.1 ($C^{4a\text{-}min}$), 136.0 ($C^{4a\text{-}maj}$), 143.7 ($C^{1'\text{-}maj}$), 144.0 ($C^{1'\text{-}min}$), 153.7 ($C^{4'\text{-}min}$), 154.0 ($C^{4'\text{-}maj}$). **m/z** (APCI) 238.1 ($[M\text{-}CH_3CHNO_2]^+$, 100%), 312.9 (MH^+, 20%). **IR** ν_{max}/cm^{-1} 2935, 2835, 1549, 1509, 1454, 1246, 1035, 826, 753. Spectroscopic data match those in the literature.[2]

1-(Aminoethyl)-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 10b

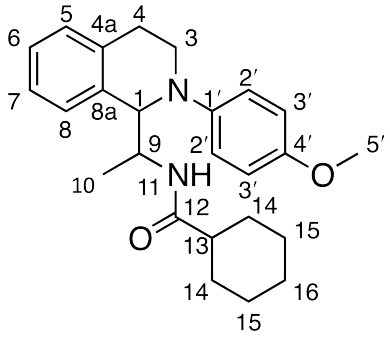


To 1-(nitroethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (1.00 g, 3.21 mmol, 1.0 eq) in methanol:ammonia (9:1, 100 mL) was added Raney nickel (0.3 mL slurry) and the reaction mixture stirred at rt under hydrogen (100 psi) for two h. The volatiles were removed under reduced pressure and the reaction mixture diluted with water (50 mL) and extracted into dichloromethane (3 × 50 mL). The combined organic

phases were dried ($MgSO_4$), concentrated under reduced pressure and purified by flash column chromatography (95:4.5:0.5 dichloromethane:methanol:ammonia) to give the product as a brown solid (0.086 g, 10%). The product was found to be unstable in solution and was not fully characterised by NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (3H, d, *J* 6.4, H^{10}), 2.79 (1H, dt, *J* 16.5, 5.6), 2.93 (1H, ddd, *J* 16.5, 8.7, 6.0), 3.21 (1H, dt, *J* 14.8, 6.0), 3.46 – 3.52 (1H, m), 3.73 (3H, s, $H^{5'}$), 3.73 – 3.80 (1H, m), 4.14 (1H, d, *J* 8.4), 6.78 – 6.80 (2H, m), 6.91 – 6.93 (2H, m), 7.09 – 7.11 (1H, m), 7.14 – 7.19 (3H, m). **m/z** (APCI+) 266.1 (100%, $[M\text{-}NH_2]^+$), 282.9 (25%, MH^+). **IR** ν_{max}/cm^{-1} 3424 (br), 2959, 1739, 1509, 1365, 1229. **HRMS** (ESI+) 283.18027 (MH^+) calcd. for 283.18049 ($C_{18}H_{22}N_2O^+$, MH^+).

1-(N-Cyclohexylcarbonylamido ethyl)-2-(4'-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 13b

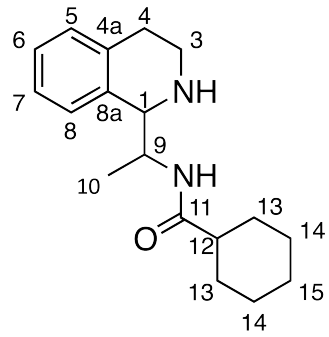


To 1-(aminoethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.085 g, 0.30 mmol, 1.0 eq), 4-(*N*,*N*-dimethylamino)pyridine (0.011 g, 0.09 mmol, 0.3 eq) and triethylamine (0.046 g, 0.063 mL, 0.45 mmol, 1.5 eq) in dichloromethane (20 mL) at 0 °C, was added cyclohexanecarbonyl chloride (0.048 g, 0.044 mL, 0.33 mmol, 1.1 eq) and the reaction mixture stirred at 0 °C for two h. The reaction mixture was diluted with water (20 mL) and extracted into dichloromethane (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by flash column chromatography (3:1 hexane:ethyl acetate) to give the product as a white solid (0.115 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 ($3H^{min}$, d, *J* 7.2, H^{10}), 1.14 ($3H^{maj}$, d, *J* 6.4, H^{10}), 1.19 – 1.35 (5H, m, $H^{14\text{-}16}$), 1.65 – 1.75 (5H, m, $H^{14\text{-}16}$), 1.96 (1H, tt, *J* 11.6, 3.2, H^{13}), 2.71

($1H^{min}$, dt, *J* 1.4, 4.0, H^4), 2.89 ($1H^{maj}$, dt, *J* 15.6, 5.2, H^4), 2.96 – 2.97 ($1H^{min}$, m, H^4), 3.08 – 3.16 ($1H^{maj}$, m, H^4), 3.20 – 3.27 ($1H^{maj}$, m, H^3), 3.48 – 3.55 ($2H^{min}$, m, H^3), 3.63 – 3.68 ($1H^{maj}$, m, H^3), 3.75 (3H, s, $H^{5'}$), 4.28 – 4.37 ($1H^{maj}$, m, H^9), 4.48 – 4.55 ($1H^{min}$, m, H^9), 4.56 ($1H^{maj}$, d, *J* 7.6, H^1), 4.75 ($1H^{min}$, d, *J* 4.0, H^1), 5.49 ($1H^{maj}$, d, *J* 7.2, H^{11}), 5.81 ($1H^{min}$, d, *J* 8.4, H^{11}), 6.80 – 6.82 ($2H^{min}$, m, $H^{3'}$), 6.85 – 6.87 ($2H^{maj}$, m, $H^{3'}$), 6.94 – 6.99 ($2H^{maj}$ and $2H^{min}$, m, $H^{2'\text{-}maj}$ and $H^{2'\text{-}min}$), 7.10 – 7.12 ($1H^{maj}$, m, H^8), 7.15 – 7.23 ($3H^{maj}$ and $3H^{min}$, m, $H^{5\text{-}7maj}$ and $H^{5\text{-}7min}$), 7.30 ($1H^{min}$, d, *J* 6.8, H^8). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.3 (C^{10min}), 17.8 (C^{10maj}), 26.7 (C^{4min}), 27.7 (C^{4maj}), 26.0 ($C^{14\text{-}16}$), 28.9 ($C^{14\text{-}16}$), 29.5 ($C^{14\text{-}16}$), 29.6 ($C^{14\text{-}16}$), 29.7 ($C^{14\text{-}16}$), 29.9 ($C^{14\text{-}16}$), 44.7 (C^{3maj}), 45.5 (C^{13min}), 45.6 (C^{13maj}), 46.7 (C^{3min}), 49.1 (C^{9maj}), 50.5 (C^{9min}), 55.8 ($C^{5'}$), 62.6 ($C^{1'}$), 114.7 ($C^{3'\text{-}min}$), 114.9 ($C^{3'\text{-}maj}$), 115.5 ($C^{2'\text{-}maj}$), 120.1 ($C^{2'\text{-}min}$), 125.8 (C^{5maj}), 126.3 ($C^{5\text{-}7min}$), 126.7 ($C^{5\text{-}7min}$), 127.3 (C^{8maj}), 127.6 (C^{8min}), 128.5 (2 signals, C^{6maj} and C^{7maj}), 129.0 ($C^{5\text{-}7min}$). **m/z** (APCI+) 266.1 (100%, $(M\text{-}[NHCOC_6H_{11}])^+$), 393.1 (75%, MH^+). **IR** ν_{max}/cm^{-1} 3300, 2925, 1641, 1511, 1451, 1245, 1217, 1039. **HRMS** (ESI+) found 415.23565 (MNa^+) calcd. for 415.23560 ($C_{25}H_{32}N_2O_2Na^+$, MNa^+).

1-(N-Cyclohexylcarbonylamido ethyl)-1,2,3,4-tetrahydroisoquinoline, 14b

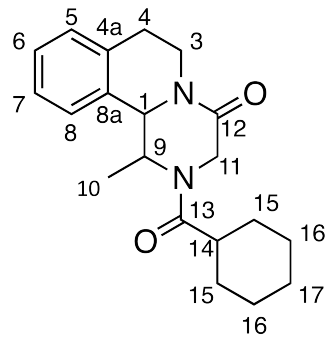


To 1-(*N*-cyclohexylcarbonylamido ethyl)-2-(4′-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (0.115 g, 0.29 mmol, 1.0 eq) in acetonitrile:water (1:1, 5 mL) at 0 °C was added ceric ammonium nitrate (0.482 g, 0.88 mmol, 3.0 eq) in 5 mL acetonitrile:water (1:1, 5 mL). The reaction mixture was stirred at 0 °C for 5 min. The reaction mixture was diluted with water (10 mL) and extracted into ethyl acetate (2 × 20 mL). The aqueous phase was diluted with saturated sodium hydrogen carbonate solution (20 mL) and further extracted into ethyl acetate (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by flash column chromatography (95:4.5:0.5 dichloromethane:methanol:ammonia) to give

the product as a brown oil (0.041 g, 49%). The product was found to be unstable in solution and was not completely characterised.

m/z (APCI+) 160.1 (100%, (M-[$NHCOC_6H_{11}$])$^+$), 287.1 (77%, MH^+). **IR** ν_{max}/cm^{-1} 3285 (br), 2926, 1854, 1640, 1509, 1450, 1256, 1210, 1126. **HRMS** (ESI+) found 287.21185 (MH^+) calcd. for 287.21179 ($C_{18}H_{26}N_2O^+$, MH^+).

***1-Methyl-2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolino-4-one, 6b*[6]**



To 1-(*N*-cyclohexylcarbonylamido ethyl)-1,2,3,4-tetrahydroisoquinoline (0.040 g, 0.14 mmol, 1.0 eq) in sodium hydroxide solution (50%, 0.7 mL) and dichloromethane (2 mL) was added chloroacetyl chloride (0.017 g, 0.012 mL, 0.15 mmol, 1.1 eq) and the reaction mixture stirred at rt for 45 min. Benzyltriethylammonium chloride (0.003 g, 0.014 mmol, 0.1 eq) was added and the reaction mixture stirred at reflux for 2 h. The reaction mixture was diluted with water (10 mL) and extracted into dichloromethane (2 ×10 mL). The aqueous phase was diluted with hydrochloric acid solution (5%, 10 mL) and further extracted into dichloromethane (2 × 10 mL). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure and the residue purified by flash column chromatography (3:1 ethyl acetate:hexane) to give the product as white solid (0.028 g, 61%).

m.p. 173 – 175 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.33 – 1.38 (2H, m, H^{15}), 1.43 (3H, d, *J* 7.0, H^{10}), 1.45 – 1.48 (2H, m, H^{15}), 1.64 – 1.70 (4H, m, H^{16}), 1.75 – 1.78 (2H, m, H^{17}), 2.27 – 2.32 (1H, m, H^{14}), 2.84 (1H, dt, *J* 16.1, 5.7, H^4), 3.07 – 3.13 (1H, m, H^4), 3.21 – 3.26 (1H, m, H^3), 4.01 (1H, d, *J* 17.5, H^{11}), 4.21 (1H, d, *J* 17.5, H^{11}), 4.37 (1H, s, H^1), 4.50 (1H, dt, *J* 12.4, 6.1, H^3), 5.55 (1H, apparent d, *J* 5.5, H^9), 7.14 – 7.15 (1H, m, H^5),

7.13 – 7.24 (2H, m, H^6 and H^7), 7.32 – 7.33 (1H, m, H^8). **^{13}C NMR** (125 MHz, $CDCl_3$): δ (125 MHz, $CDCl_3$): δ 16.5 (C^{10}), 25.8 (3 signals, C^{15}, C^{16} and C^{17}), 27.9 (C^4), 28.8 (C^{16} or C^{17}), 29.2 (C^{16} or C^{17}), 41.0 (C^{13}), 42.0 (C^3), 43.1 (C^9), 45.5 (C^{11}), 60.3 (C^1), 123.6 (C^8), 126.9 (C^6 or C^7), 128.8 (C^6 or C^7), 129.0 (C^5), 135.6 (C^{8a}), 135.7 (C^{4a}), 164.9 (C^{12}), 174.8 (C^{13}). **IR** ν_{max}/cm^{-1} 2923, 2856, 1740, 1648, 1421, 1364, 1217. **HRMS** (ESI+) found 349.18874 (MNa^+) calcd. for 349.18865 ($C_{20}H_{26}N_2O_2Na^+$, MNa^+).

3. Selected NMR spectra

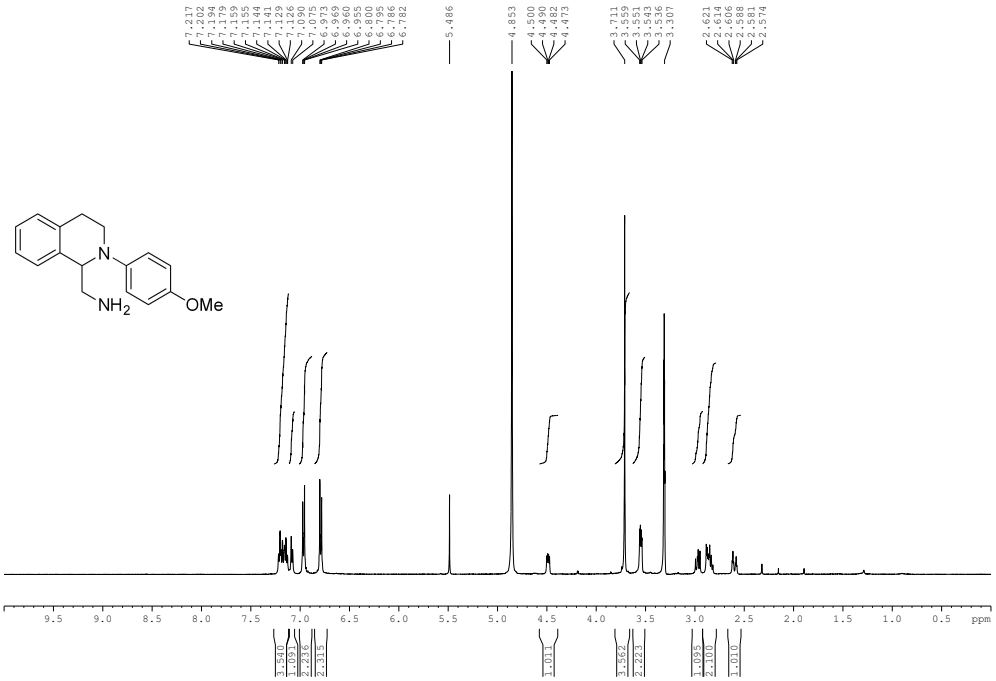


Figure S1. ^{1}H NMR spectrum (400 MHz) of **10a** in MeOD.

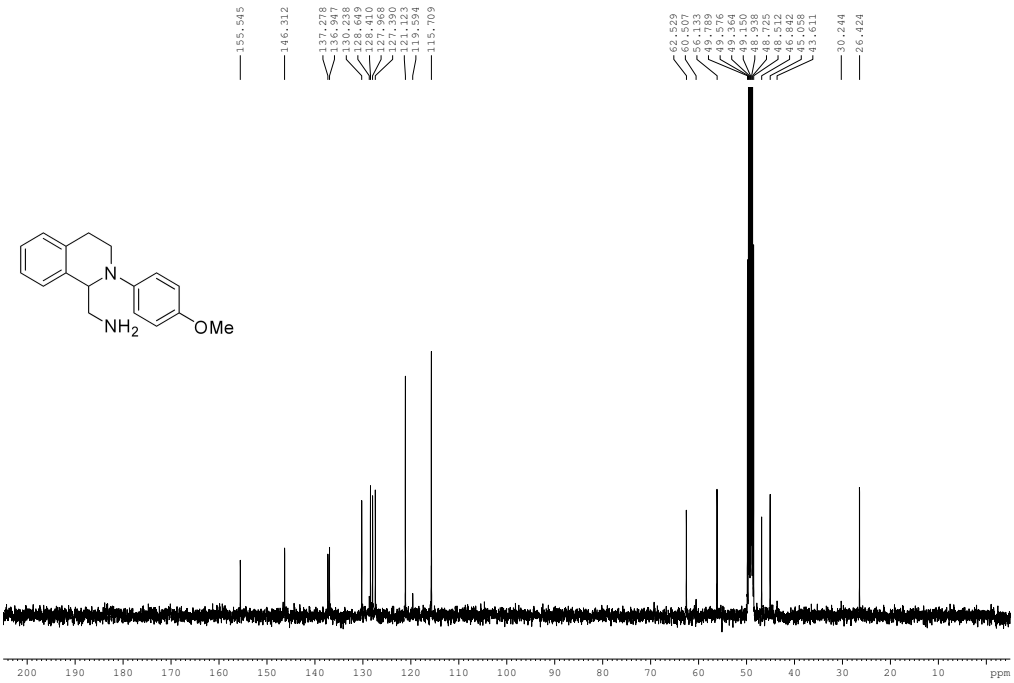


Figure S2. ^{13}C NMR spectrum (100 MHz) of 1**0a** in MeOD.

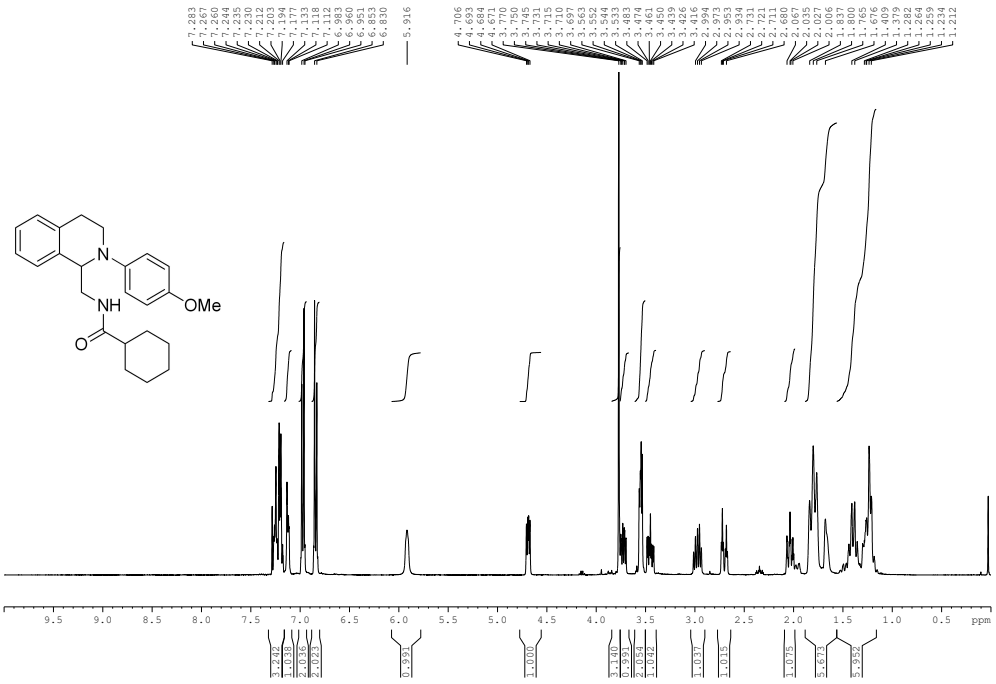


Figure S3. ^{1}H NMR spectrum (400 MHz) of **13a** in $CDCl_3$.

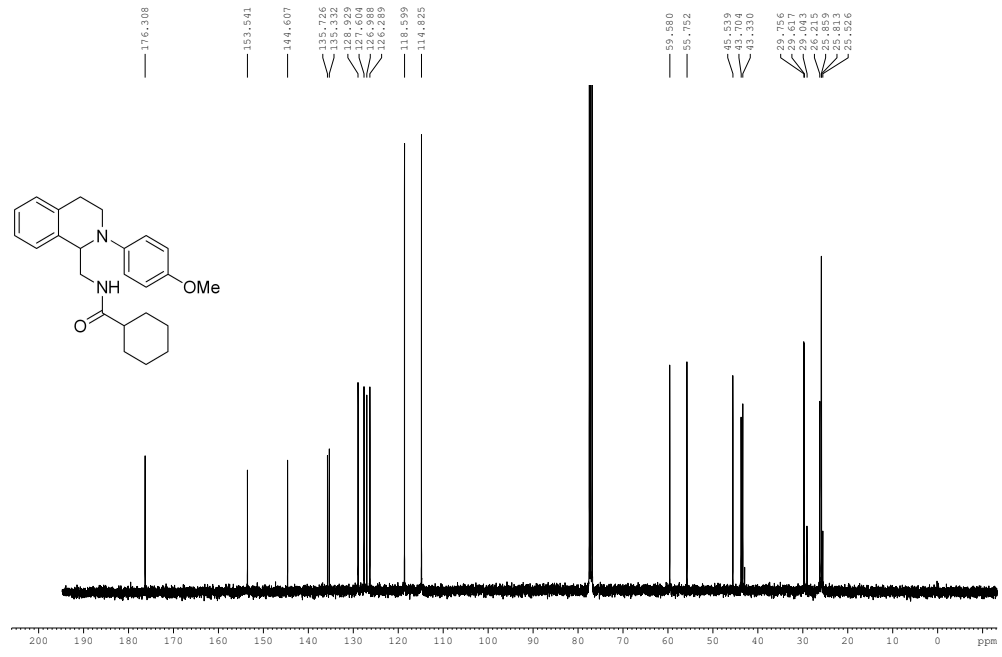


Figure S4. ^{13}C NMR spectrum (100 MHz) of **13a** in $CDCl_3$.

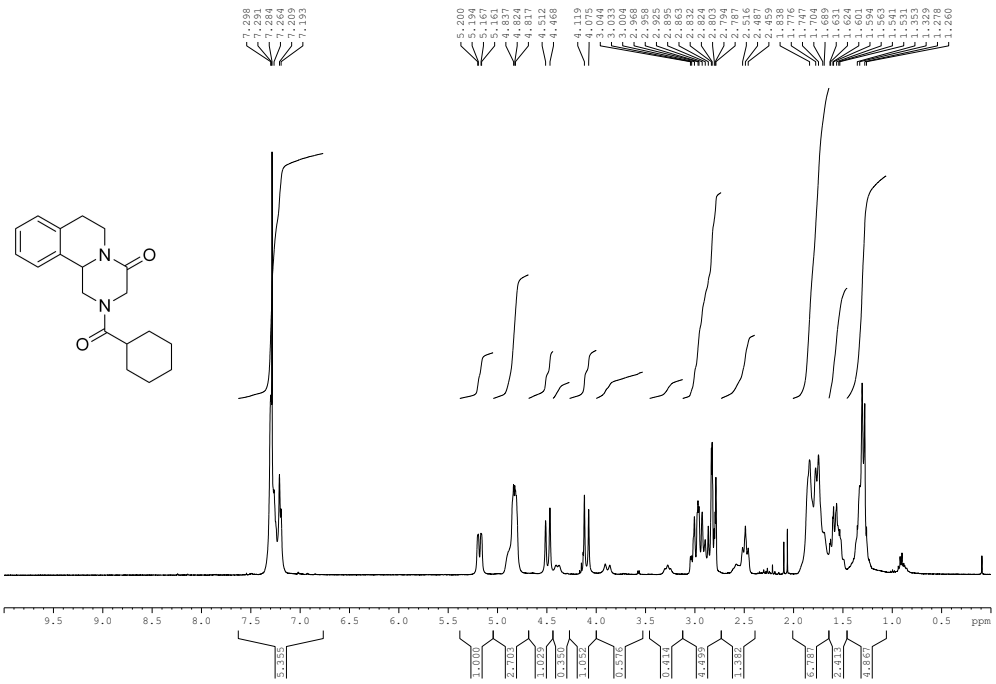


Figure S5. ^{1}H NMR spectrum (400 MHz) of **6a** in $CDCl_3$.

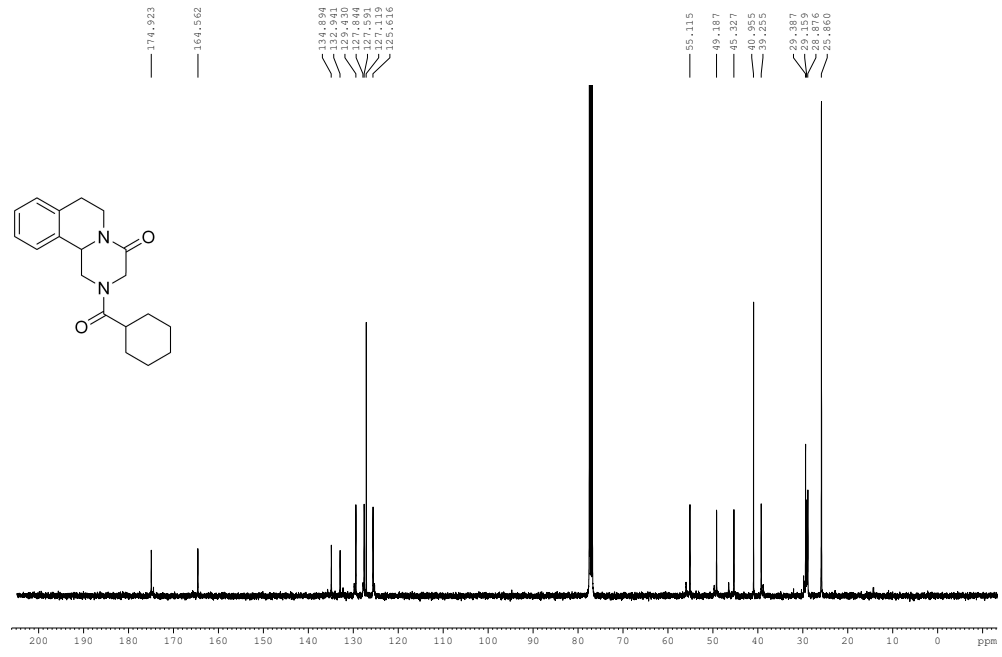


Figure S6. ^{13}C NMR spectrum (100 MHz) of **6a** in $CDCl_3$.

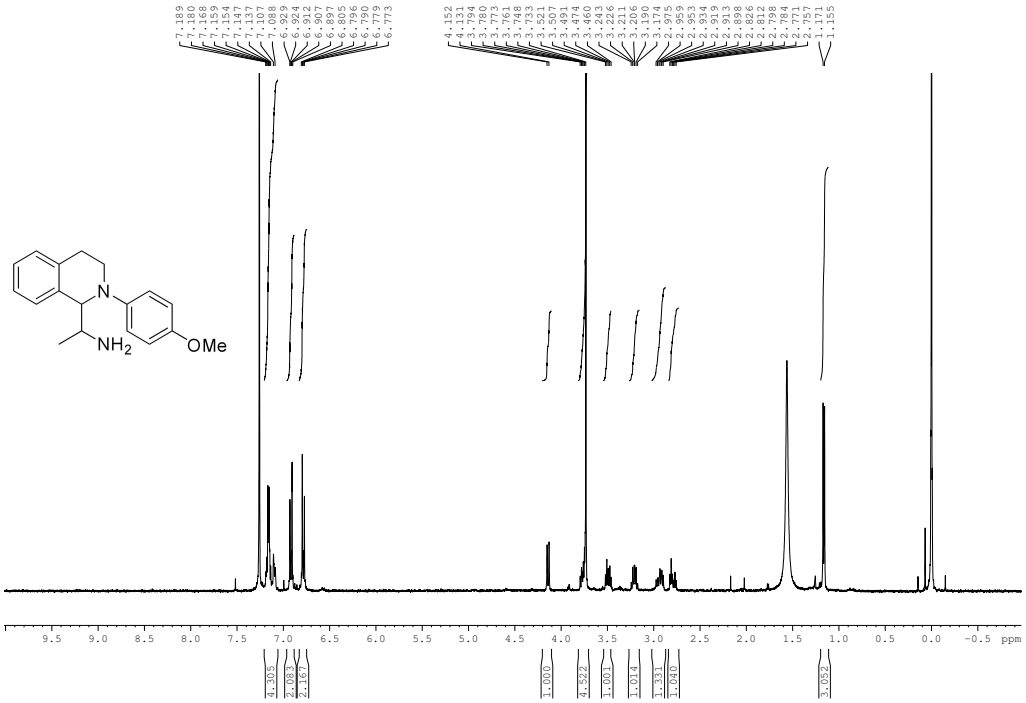


Figure S7. ^{1}H NMR spectrum (400 MHz) of **10b** in $CDCl_3$.

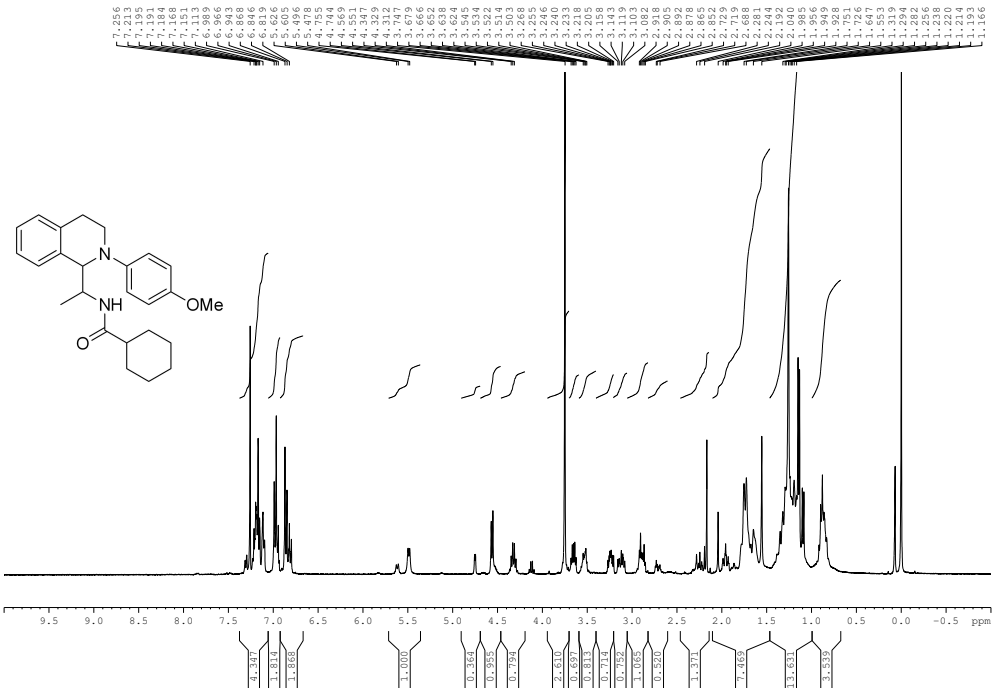


Figure S8. ^{1}H NMR spectrum (400 MHz) of **13b** in $CDCl_3$.

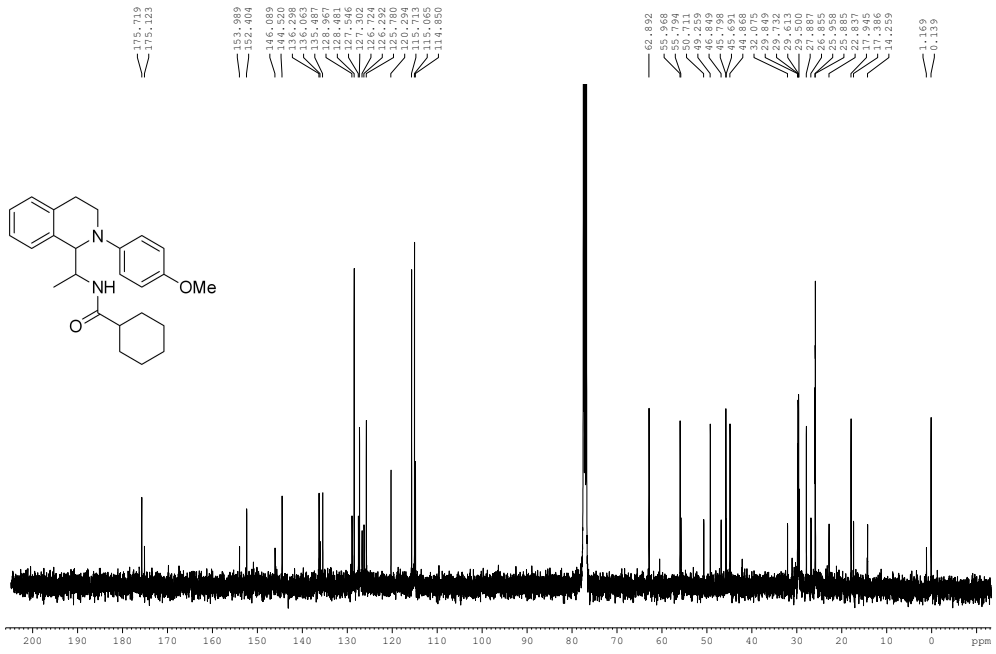


Figure S9. ^{13}C NMR spectrum (100 MHz) of **13b** in $CDCl_3$.

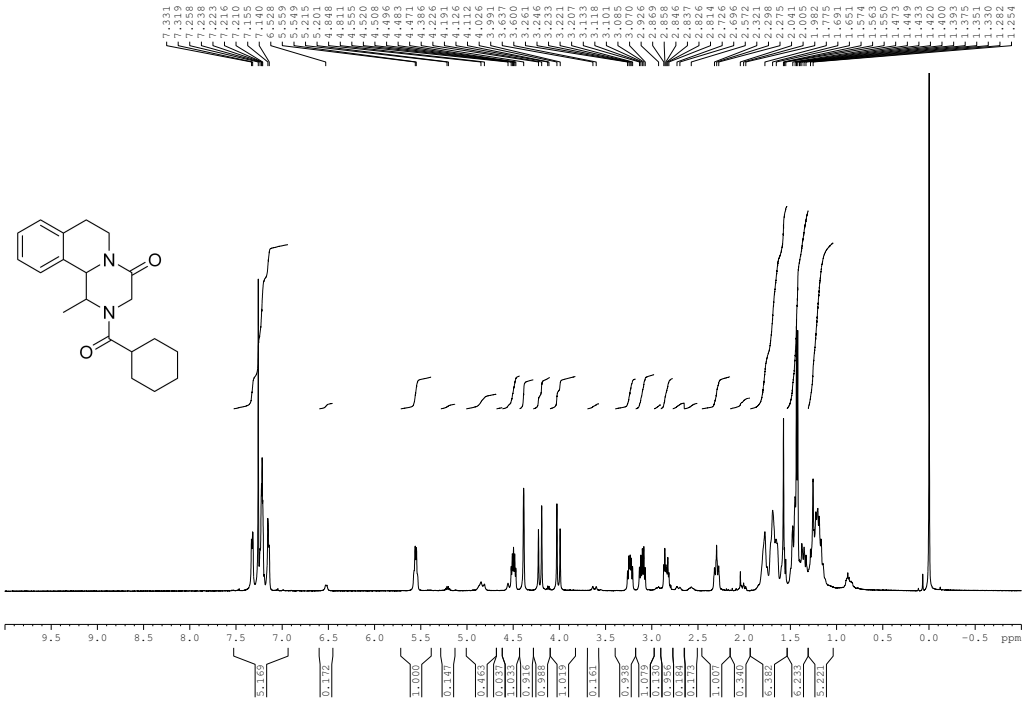


Figure S10. ^{1}H NMR spectrum (500 MHz) of **6b** in $CDCl_3$.

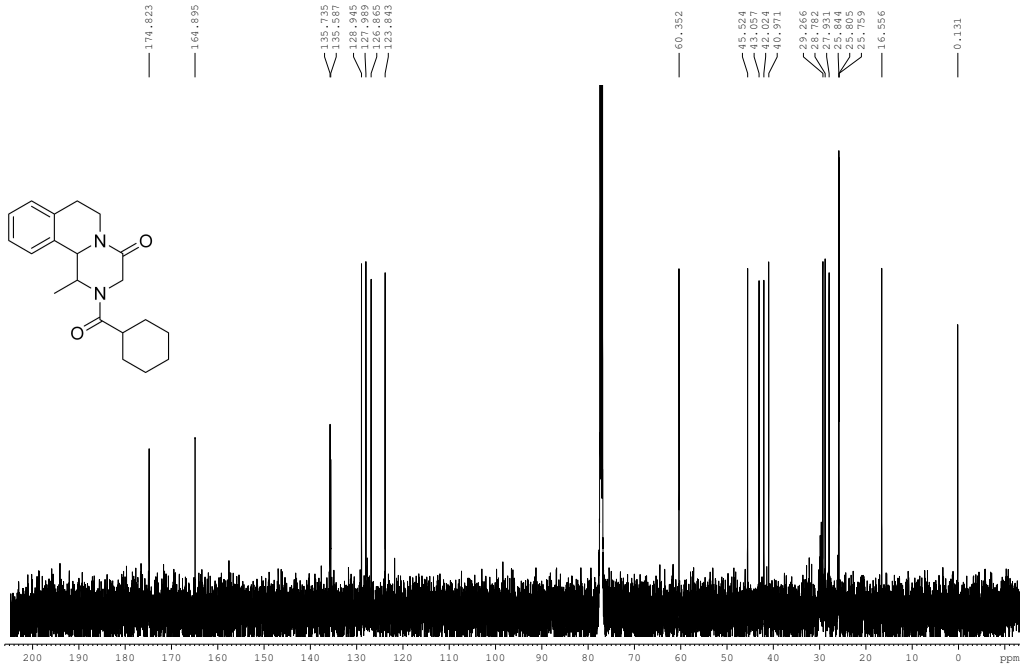


Figure S11. ^{13}C NMR spectrum (125 MHz) of **6b** in $CDCl_3$.

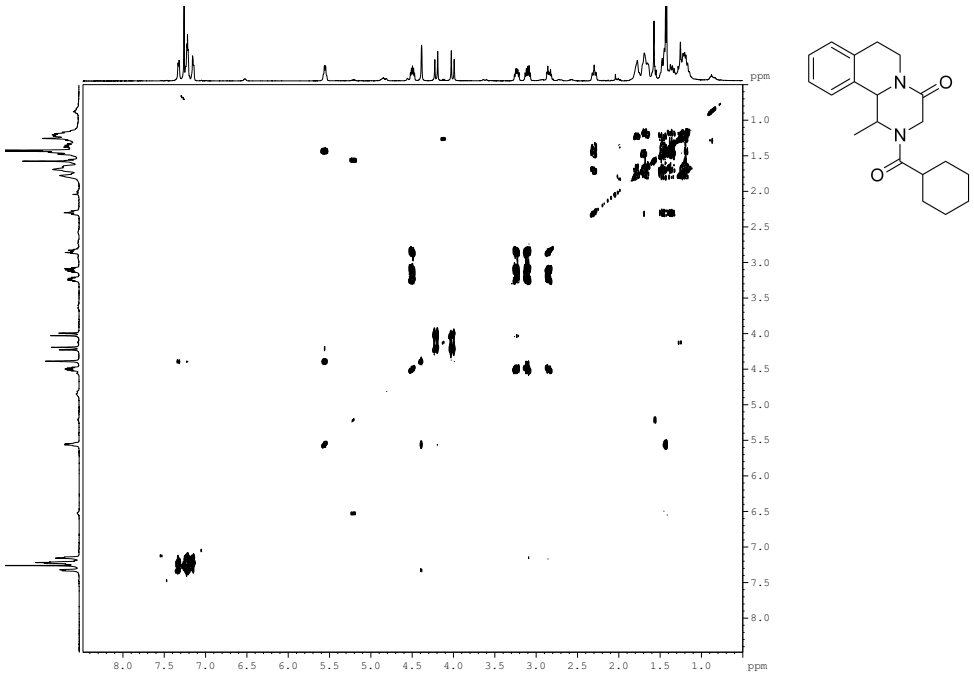


Figure S12. ^{1}H-^{1}H COSY of **6b** in $CDCl_3$.

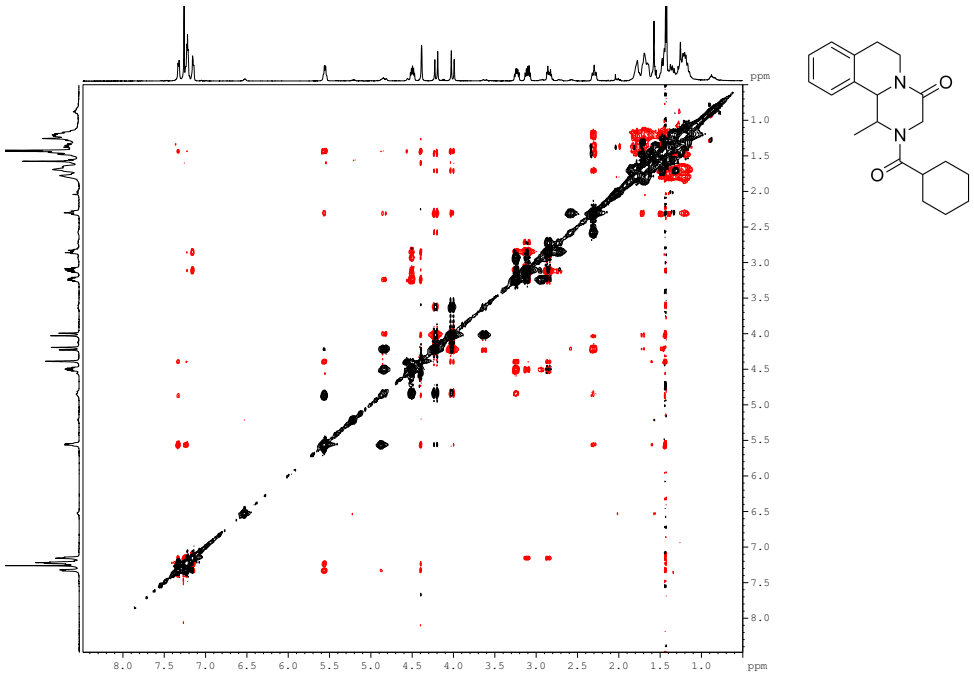


Figure S13. ^{1}H-^{1}H NOESY of **6b** in $CDCl_3$.

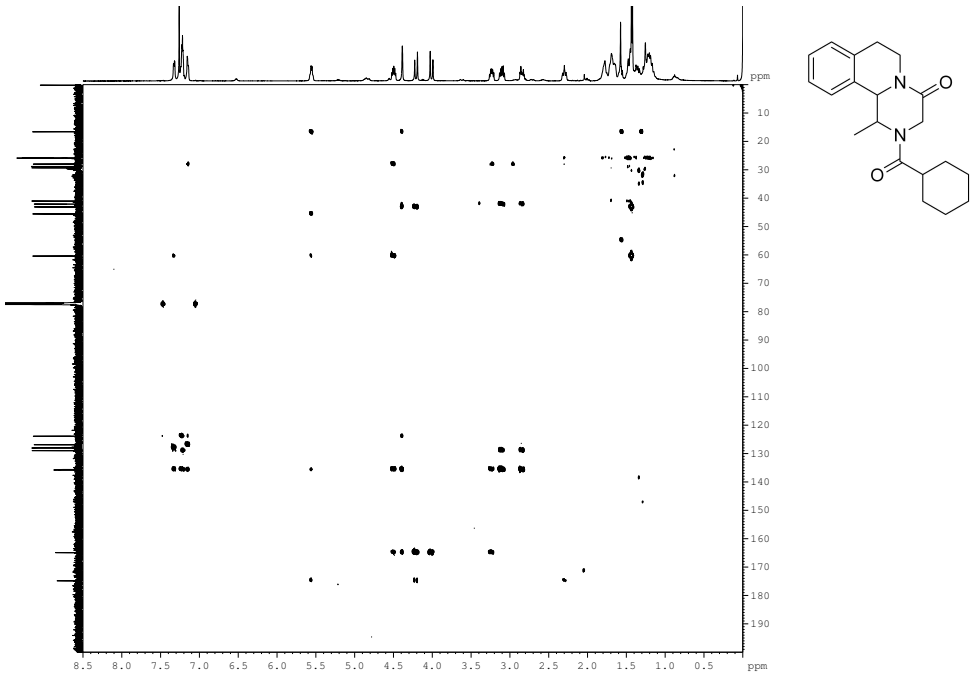


Figure S14. ^{1}H-^{13}C HMBC of **6b** in $CDCl_3$.

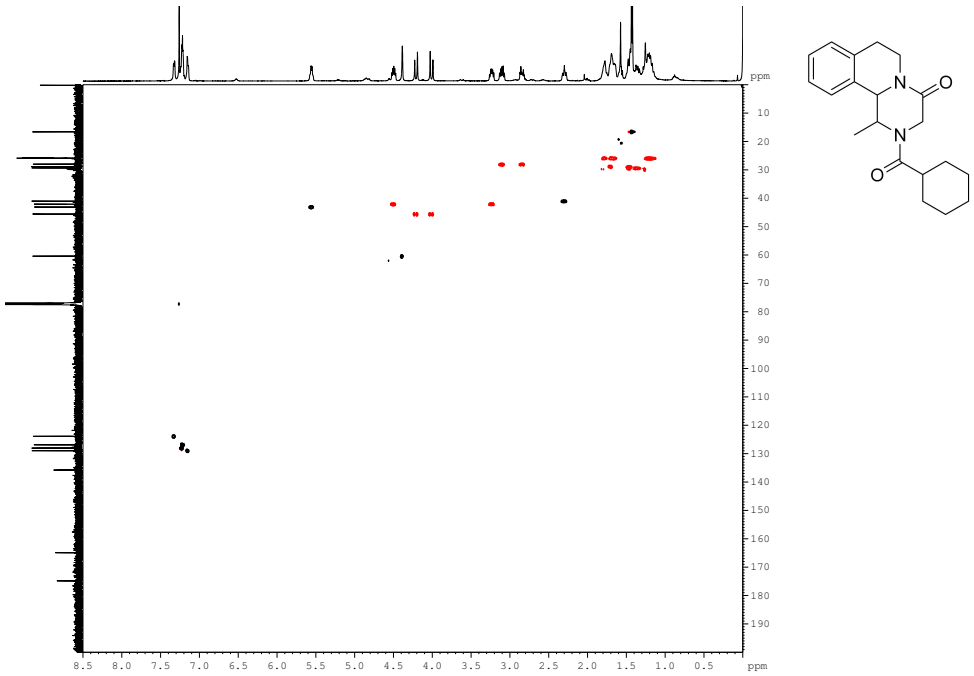
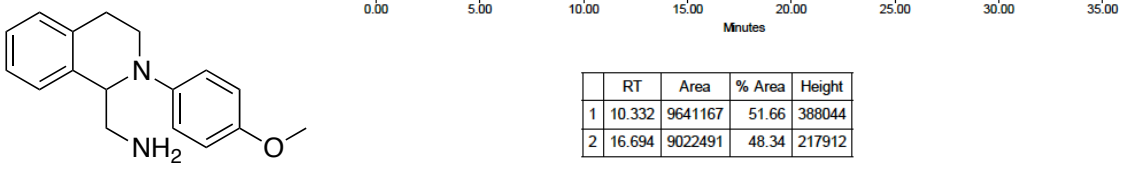


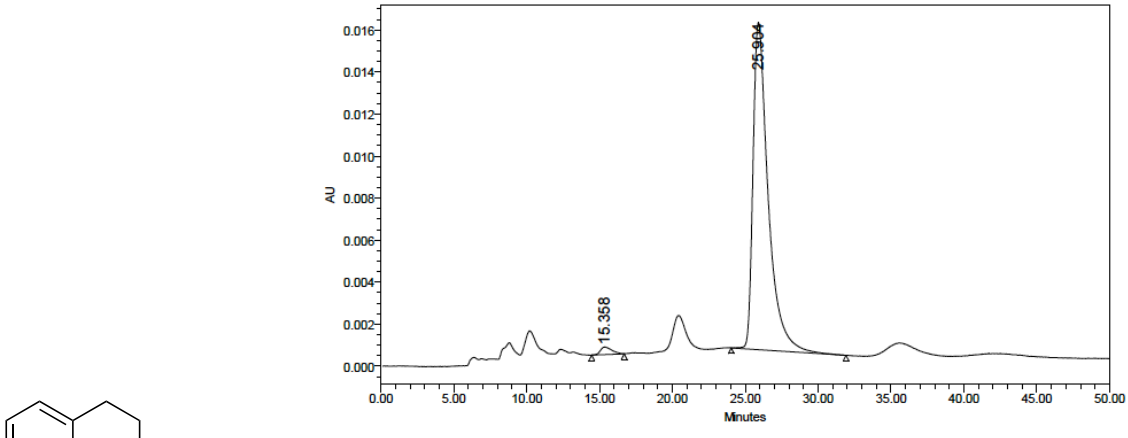
Figure S15. ^{1}H-^{13}C HSQC of **6b** in $CDCl_3$.

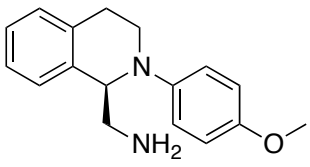
4. Enantioselective HPLC traces



	RT	Area	% Area	Height
1	10.332	9641167	51.66	388044
2	16.694	9022491	48.34	217912

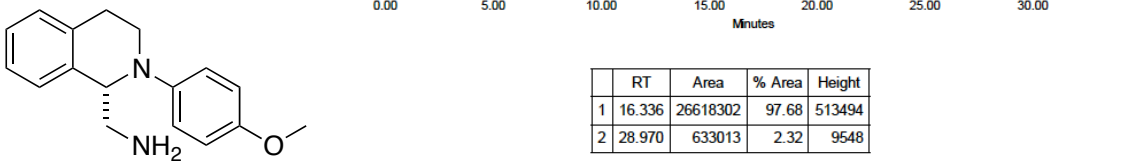
Figure S16. Enantioselective HPLC trace of **10a** (40:60:0.1 *i*PrOH:hexanes:Et_3N), monitoring at 254 nm.





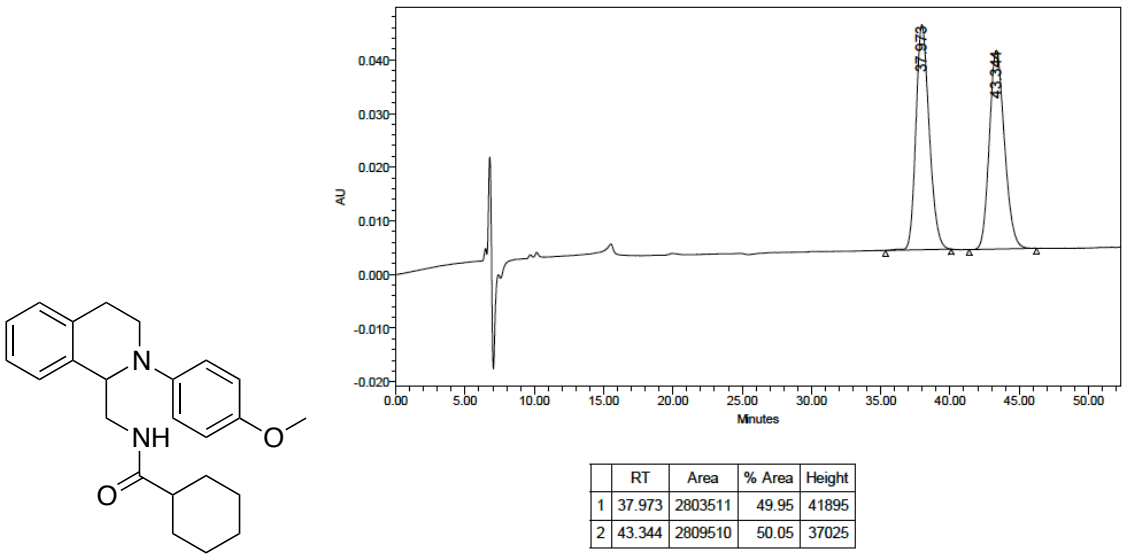
	RT	Area	% Area	Height
1	15.358	19627	1.71	364
2	25.904	1126503	98.29	15564

Figure S17. Enantioselective HPLC trace of **(*R*)-10a** (40:60:0.1 *i*PrOH:hexanes:Et_3N), monitoring at 254 nm.



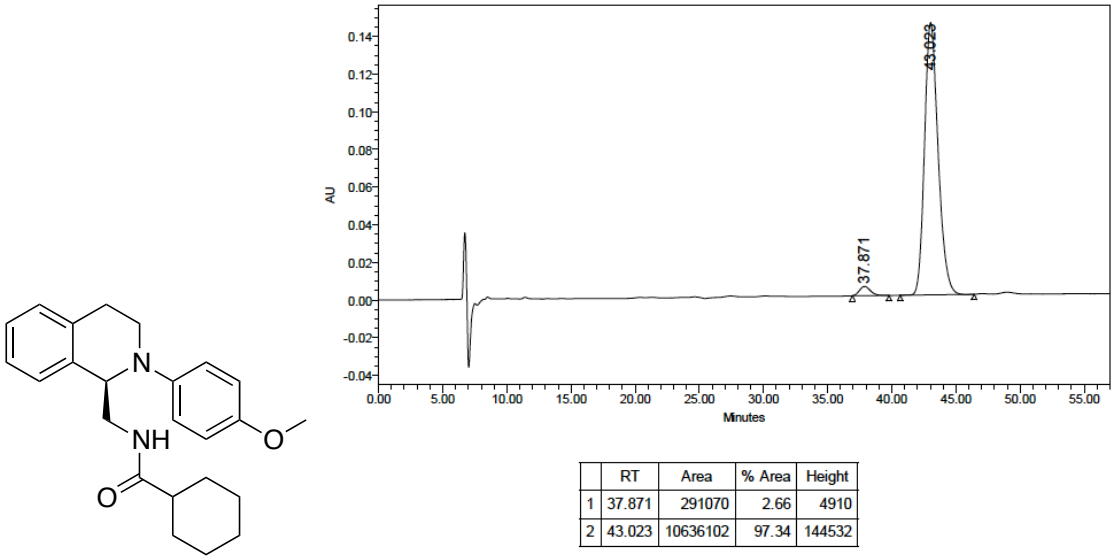
	RT	Area	% Area	Height
1	16.336	26618302	97.68	513494
2	28.970	633013	2.32	9548

Figure S18. Enantioselective HPLC trace of **(*S*)-10a** (40:60:0.1 *i*PrOH:hexanes:Et_3N), monitoring at 254 nm.



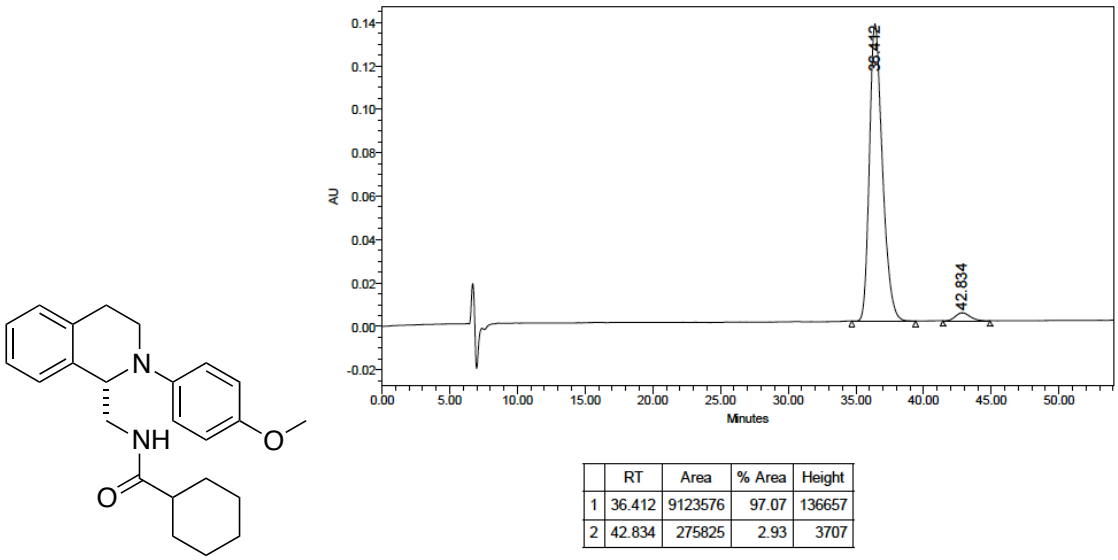
	RT	Area	% Area	Height
1	37.973	2803511	49.95	41895
2	43.344	2809510	50.05	37025

Figure S19. Enantioselective HPLC trace of **13a** (5:95:0.1 EtOH:hexanes:Et_3N), monitoring at 254 nm.



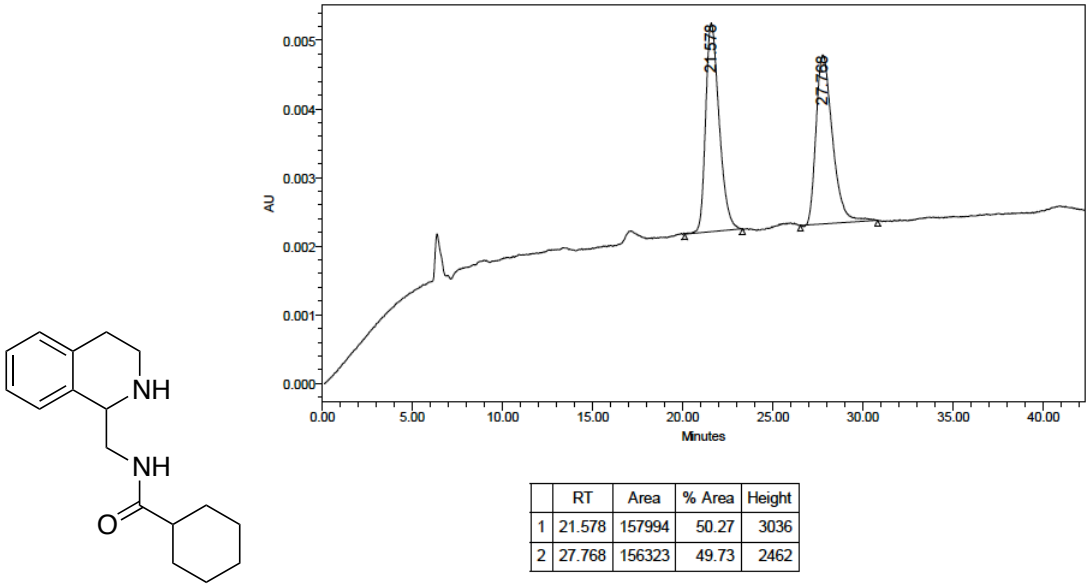
	RT	Area	% Area	Height
1	37.871	291070	2.66	4910
2	43.023	10636102	97.34	144532

Figure S20. Enantioselective HPLC trace of **(*R*)-13a** (5:95:0.1 EtOH:hexanes:Et_3N), monitoring at 254 nm.



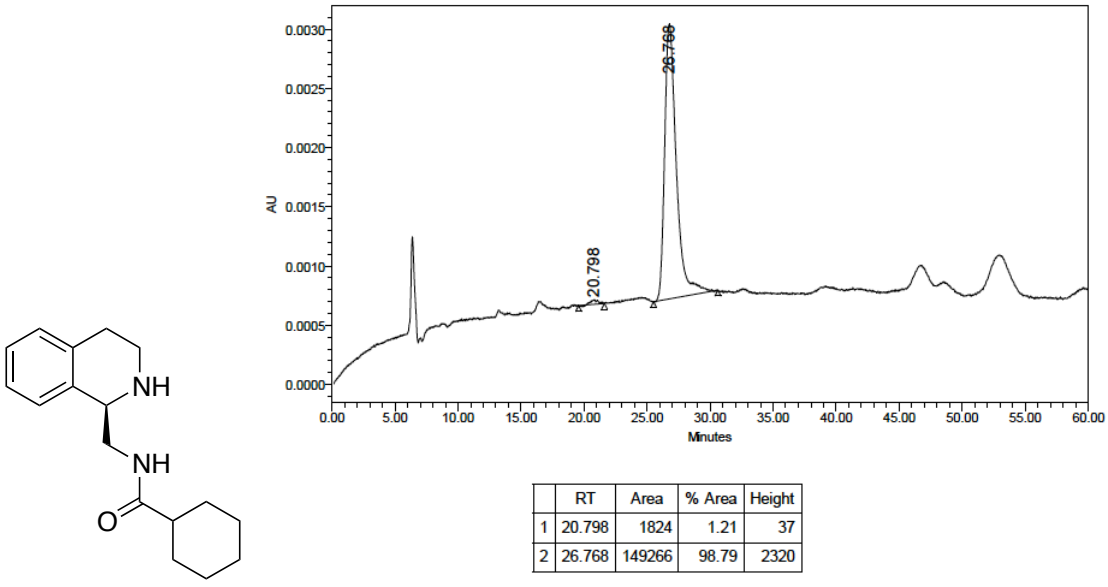
	RT	Area	% Area	Height
1	36.412	9123576	97.07	136657
2	42.834	275825	2.93	3707

Figure S21. Enantioselective HPLC trace of **(*S*)-13a** (5:95:0.1 EtOH:hexanes:Et_3N), monitoring at 254 nm.



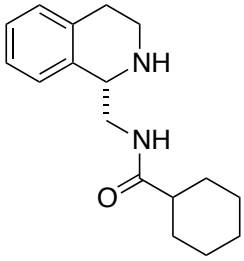
	RT	Area	% Area	Height
1	21.578	157994	50.27	3036
2	27.768	156323	49.73	2462

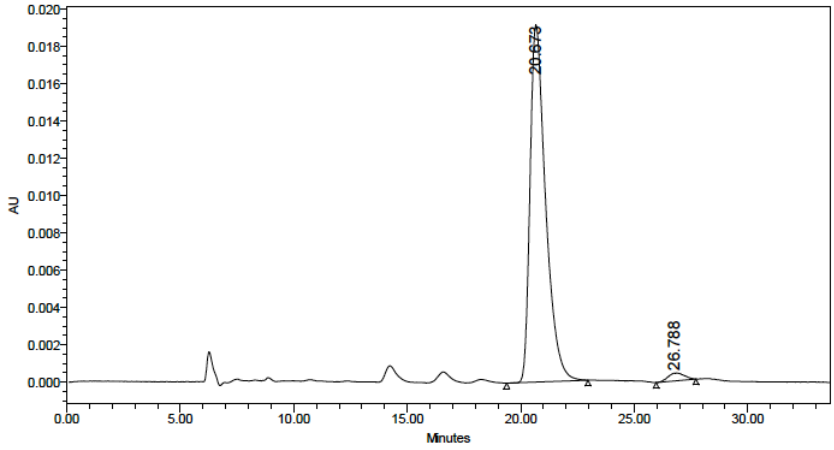
Figure S22. Enantioselective HPLC trace of **14a** (10:90:0.1 EtOH:hexanes:Et_3N), monitoring at 254 nm.



	RT	Area	% Area	Height
1	20.798	1824	1.21	37
2	26.768	149266	98.79	2320

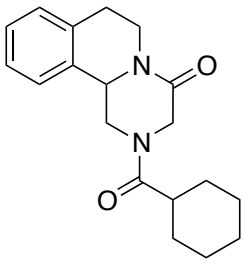
Figure S23. Enantioselective HPLC trace of **(*R*)-14a** (10:90:0.1 EtOH:hexanes:Et_3N), monitoring at 254 nm.

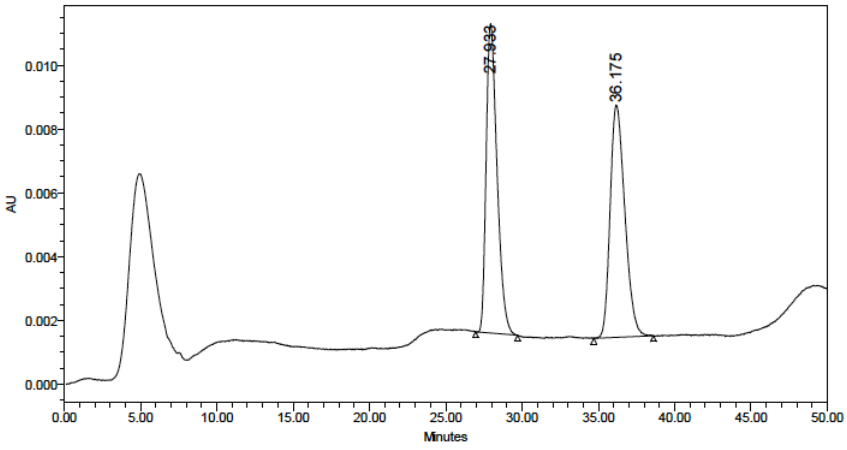




	RT	Area	% Area	Height
1	20.673	912015	97.76	19134
2	26.788	20897	2.24	421

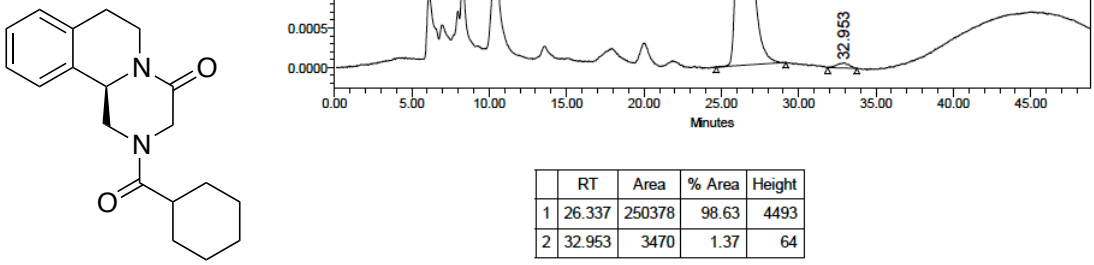
Figure S24. Enantioselective HPLC trace of **(*S*)-14a** (10:90:0.1 EtOH:hexanes:Et_3N), monitoring at 254 nm.





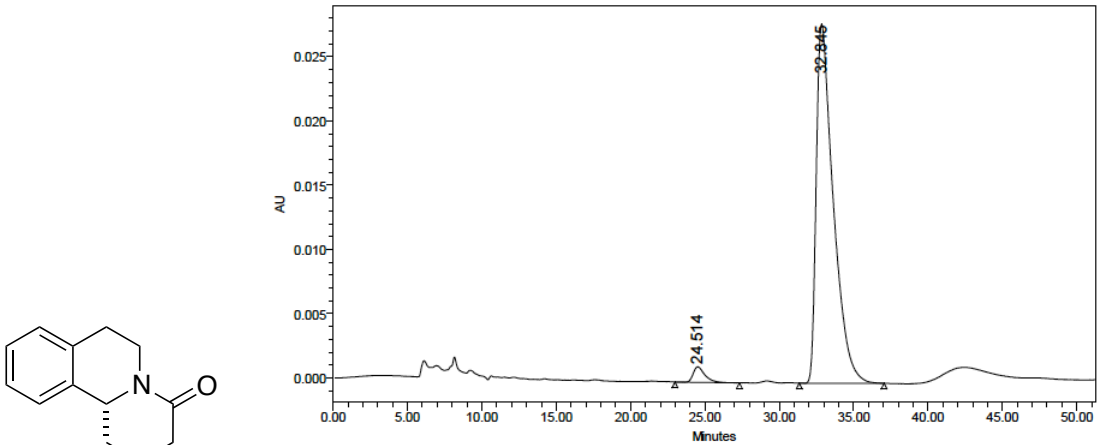
	RT	Area	% Area	Height
1	27.933	479094	49.58	9683
2	36.175	487121	50.42	7275

Figure S25. Enantioselective HPLC trace of **6a** (15:85:0.1 EtOH:hexanes:Et_3N), monitoring at 270 nm.



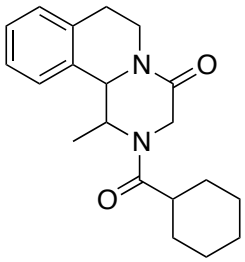
	RT	Area	% Area	Height
1	26.337	250378	98.63	4493
2	32.953	3470	1.37	64

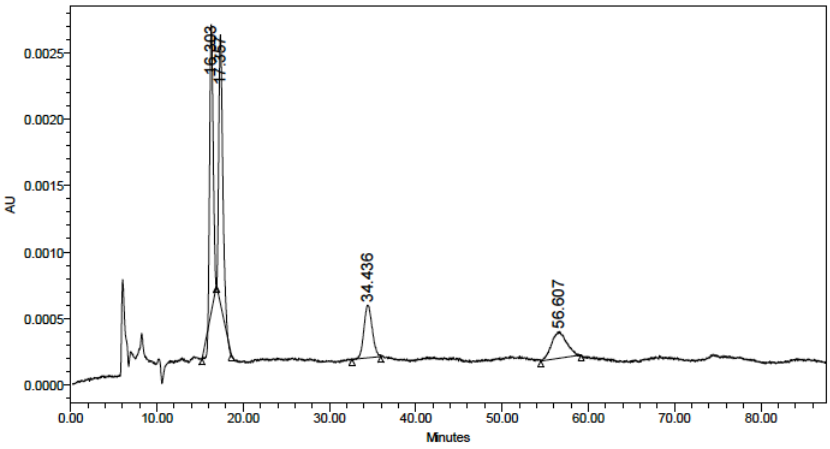
Figure S26. Enantioselective HPLC trace of (*R*)-**6a** (15:85:0.1 EtOH:hexanes:Et_3N), monitoring at 270 nm.



	RT	Area	% Area	Height
1	24.514	66770	2.92	1224
2	32.845	2222132	97.08	27923

Figure S27. Enantioselective HPLC trace of (*S*)-**6a** (15:85:0.1 EtOH:hexanes:Et_3N), monitoring at 270 nm.





	RT	Area	% Area	Height
1	16.303	63871	35.46	2161
2	17.357	65599	36.42	2025
3	34.436	26440	14.68	396
4	56.607	24209	13.44	201

Figure S28. Enantioselective HPLC trace of **6b** (15:85:0.1 EtOH:hexanes:Et_3N), monitoring at 270 nm.

5. Design of Experiment procedures

Design of experiments (DoE) is a statistical approach to modeling a response as a function of a number of factors, in order to discover the conditions for an optimal output of the experiment. The Box-Behnken design requires three levels of each of the factors to be defined, and allows an estimate of optimum factor values that is most efficient when they lie within the space defined by the ranges chosen in the design. In the present system it was decided that this could be fulfilled after ballpark conditions were first found through initial, single experiments. Equimolar amounts of amine **8** and (+)-dibenzoyl-D-tartaric acid[8] were used and concentrations giving sufficient (but not complete) crystallization were found. This allowed values for each level to be defined as given in Table S1.

Factors	**Time /h**	**Temp /^{o}C**	**Solvent ratio**	**Conc /M**
Code	**A**	**B**	**C**	**D**
-1	6	0	1	0.05
0	15	12.5	3.5	0.1
1	24	25	6	0.2

Table S1. Factor levels and their codes used in the experimental design.

The design was generated in Matlab (Version R2011a, The Mathworks, USA) and consists of 27 experiments at designated values of each of the factors (Table S2). The center point was performed in triplicate to estimate repeatability of the measurements. The response was the yield of recovered amine or the enantiomeric excess. According to the experimental design, individual experiments (0.75 mmol amine and tartaric acid, with concentration being varied through varying the volume of solvent) were conducted in parallel, with start times staggered.

Run	A	B	C	D
1	-1	-1	0	0
2	-1	1	0	0
3	1	-1	0	0
4	1	1	0	0
5	0	0	-1	-1
6	0	0	-1	1
7	0	0	1	-1
8	0	0	1	1
9	-1	0	0	-1
10	-1	0	0	1
11	1	0	0	-1
12	1	0	0	1
13	0	-1	-1	0
14	0	-1	1	0
15	0	1	-1	0
16	0	1	1	0
17	-1	0	-1	0
18	-1	0	1	0
19	1	0	-1	0
20	1	0	1	0
21	0	-1	0	-1
22	0	-1	0	1
23	0	1	0	-1
24	0	1	0	1
25	0	0	0	0
26	0	0	0	0
27	0	0	0	0

Table S2. Coded factor levels for the experiments in a Box-Behnken design for four factors. The center point is repeated in triplicate. See Table S1 for factors and experimental level values.

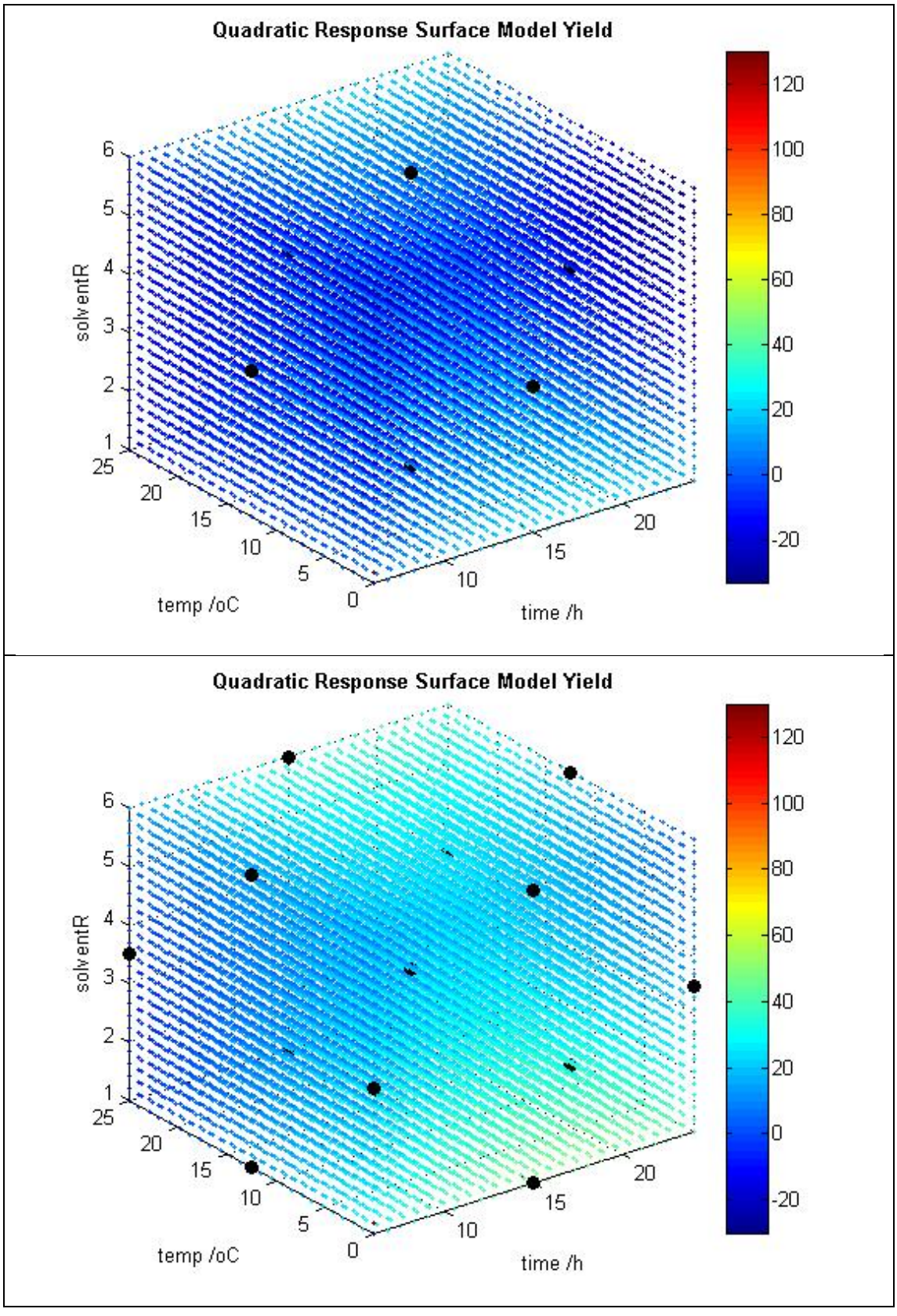
After the allotted time (factor A), any solvent was decanted from the reaction mixture and washed once with 5 mL isopropanol. The resultant crystals were left in the vials used for the experiment and dried *in vacuo*. The free amine was liberated by dissolving the crystals in saturated sodium hydrogen carbonate solution (20 mL) and extracting into ethyl acetate (20 mL). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure and dried *in vacuo*, with the mass recorded and a yield calculated. Analysis of the liberated amine was performed by enantioselective HPLC (Chiralcel OD-H column, 0.5 mL flow rate, 0.5 mL injection volume, 60:40:0.1 hexanes:isopropanol:triethylamine) to give the enantiomeric excess.

The statistical model fitted to the responses is a full quadratic including interaction terms.

$$Y = \beta_0 + \beta_1 a + \beta_2 b + \beta_3 c + \beta_4 d + \beta_5 ab + \beta_6 ac + \beta_7 ad + \beta_8 bc + \beta_9 bd + \beta_{10} cd + \beta_{11} a^2 + \beta_{12} b^2 + \beta_{13} c^2 + \beta_{14} d^2 \quad \text{(S1)}$$

where Y is the response variable, a, b, c, and d are levels of the factors A, B, C, and D respectively, and b_0 … b_{14} are coefficients of the model.

Once the model is obtained it is possible to find values of the factor levels that maximize the response variable.
Figure S29 shows the yield as a heat map in the three dimensional space of the time, temperature and solvent ratio, at the three values of concentration of resolving agent.



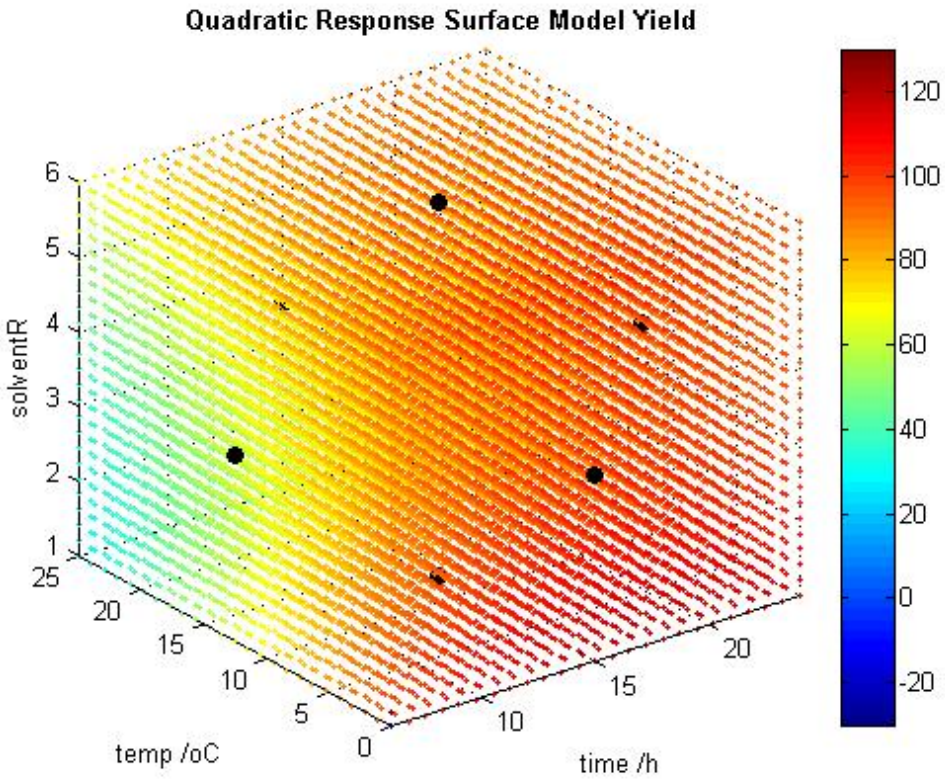
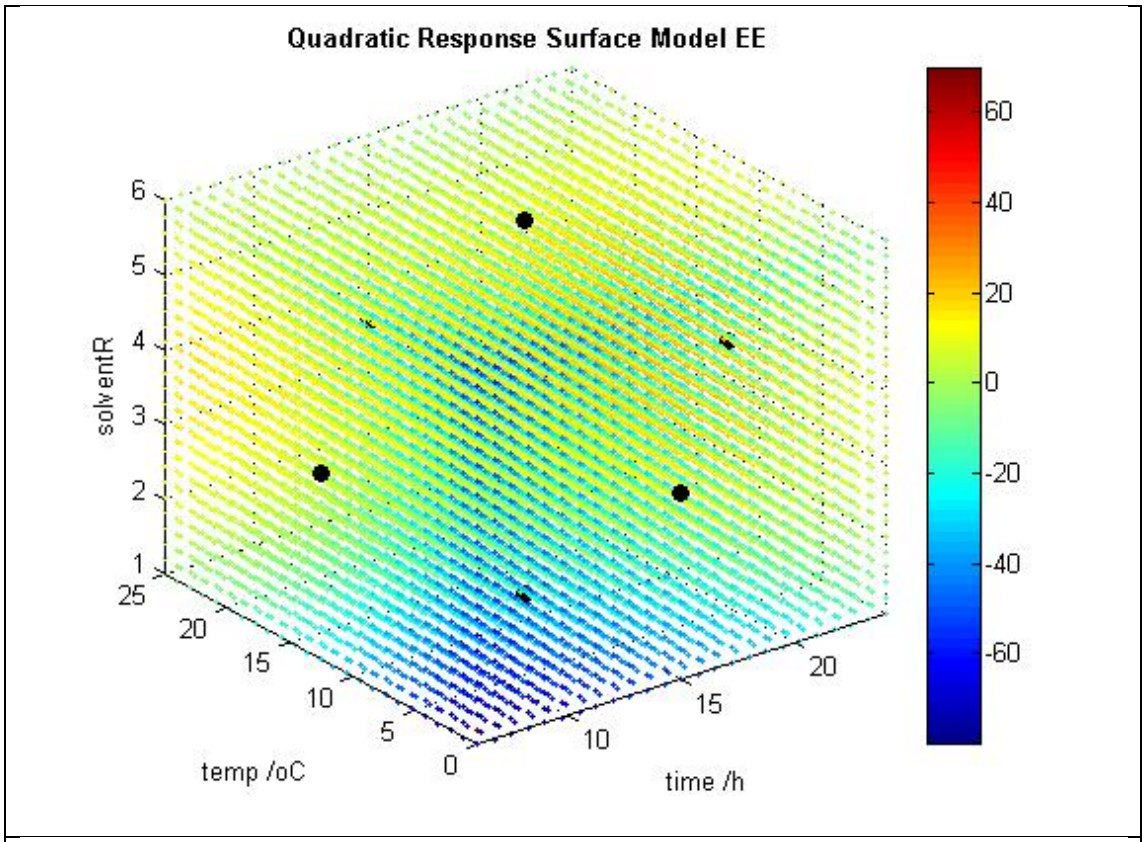
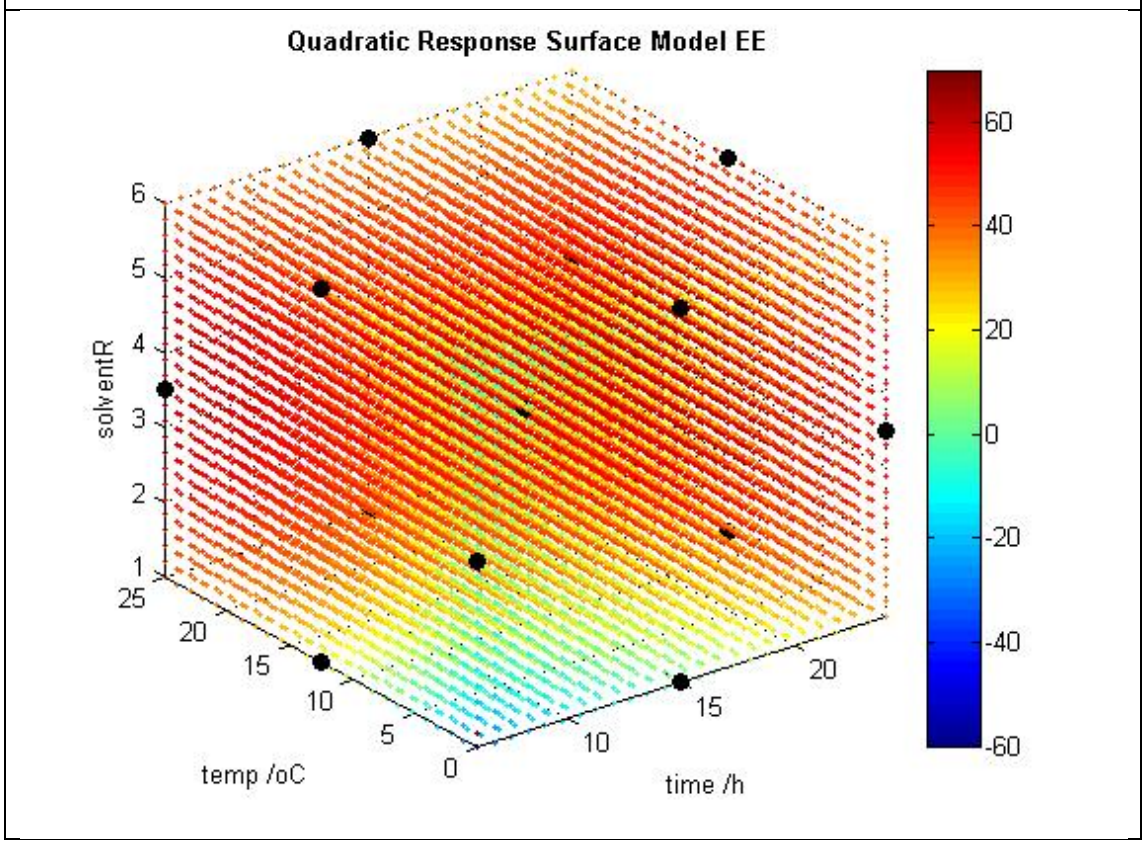


Figure S29. Yield of product as a function of duration of experiment, temperature, and solvent ratio, at three concentrations: top: 0.05 M, middle: 0.1 M and bottom: 0.2 M. The color scale represents yield as a % of recovered amine, and the filled circles are the design points

The interpretation of the figures is that increasing the concentration increases the yield, and at the highest concentration (0.2 M), the yield is greatest at the lowest temperature, lowest solvent ratio, and a middle time. The model shows significant interactions among the factors. At higher temperatures a greater solvent ratio is favored, while the optimum is at low temperature and low solvent ratio.
Figure S30 is a similar series of graphs for the enantiomeric excess.





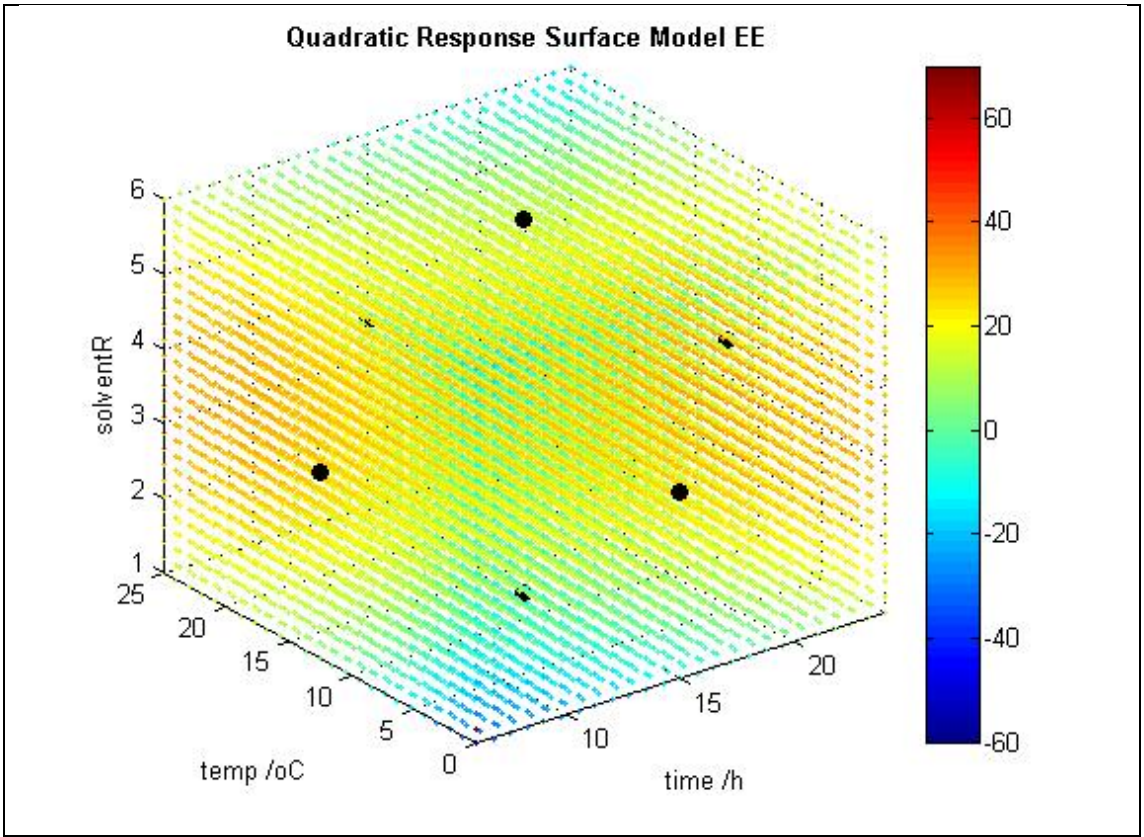


Figure S30. Enantiomeric excess of product as a function of duration of experiment, temperature, and solvent ratio, at three concentrations: top: 0.05 M, middle: 0.1 M and bottom: 0.2 M. The color scale represents enantiomeric excess of the amine as a percentage and the filled circles are the design points

Maximal values of *ee* are found in the middle range of concentration, with greater times and temperatures favored, with little effect of solvent ratio.

Though yield and *ee* were not found to be very compatible in terms of temperature and solvent ratio. While further optimization was possible, the best combination was taken (described in main paper) with enantioenrichment being provided by recrystallization.

6. Biological evaluation

Determination of antischistosomal activity on adult *Schistosoma mansoni*

Adult schistosomes were collected from the hepatic portal system and mesenteric veins of female NMRI mice (n=5, obtained from Harlan Laboratories (Horst, the Netherlands)), seven weeks post subcutaneous infection with ~ 100 cercarcia following standard procedures.[9] The animal work was approved by the local veterinary agency (permit 2070). Schistosomes were cultured in RPMI 1640 medium (supplemented with 5% inactivated foetal calf serum (iFCS) and 100 U/mL penicillin and 100 µg/mL streptomycin (Invitrogen, Carlsbad, USA)) at 37 °C in an atmosphere of 5% CO_2 until usage.

The test compound was tested in triplicate at various concentrations ranging from 0.31-25.0 µg/mL (25.0, 8.33, 2.78, 0.93 and 0.31 µg/mL) using a DMSO stock solution (conc. 10 mg/mL) and repeated once. The stock solution was diluted in supplemented RPMI1640 medium within 24 flat bottom well plates (BD Falcon, USA) to obtain a final concentration of 25 µg/mL. The lower concentrations were obtained by using a threefold dilution series. Three worms of both sexes were placed into each well containing 2 mL drug and medium. Wells with the highest concentration of DMSO in medium served as controls. After an incubation time of 72 h phenotypes of schistosomes were monitored using the motility scale described by Ramirez *et al*, and an inverse microscope (Carl Zeiss, Germany, magnification 80x).[10] The IC_{50} value was calculated using CompuSyn software (Version 3.0.1, 2007; ComboSyn, Inc) as described before.[11]

7. References

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