Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Catalytic, asymmetric azidations at carbonyls: achiral and *meso*-anhydride desymmetrisation affords enantioenriched γ–lactams

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1. General

NMR spectral data were obtained from a Bruker DPX (400 MHz) or Bruker Avance II (600 MHz) using $CDCl_3$, DMSO-d_6 or D_2O with chemical shift data referenced relative to residual protic resonances of the deuterated solvent, (δ_H = 7.26, 2.50, and 4.79 ppm respectively). ^{13}C (100.9 or 150.9 MHz) spectra were recorded on the same instruments with total proton decoupling. Additional 2D spectral acquisitions (HSQC-ME, HMBC, TOCSY, NOESY/EXSY) were obtained in order to assist in the assignment of resonances where required. Conventional abbreviations for describing peak morphologies in NMR spectroscopic analysis are observed (*i.e.* s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets, etc.). All coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were obtained as neat solids or liquids unless otherwise stated on a Perkin-Elmer Spectrum100 FT-IR instrument fitted with an attenuated-total reflectance (ATR) accessory. Abbreviations used for descriptions of transmission band intensities are as follows: w, weak; m, medium; s, strong; vs, very strong; br., broad.

Thin-layer chromatography (TLC) analyses were performed using Merck-F_{254} silica gel plates and were visualised under ultraviolet (UV) irradiation, potassium permanganate, ninhydrin, ammonium molybdate or bromocresol green staining methods. Column and flash chromatography was performed using Sigma-Aldrich 60 Å, 230-400 mesh particle silica gel. Melting point data were recorded on a Griffin Melting Point Apparatus; readings were obtained in triplicate and are reported uncorrected. High-resolution mass spectrometry experiments were carried out in the Mass Spectrometry Unit, School of Chemistry, TCD.

Anhydrous $CHCl_3$ (amylene-stabilised) and HCl (as 2 M solution in Et_2O) were obtained from Sigma-Aldrich Ireland and transferred to reaction vessels using Schlenk techniques. Hünig's base on polystyrene (DIPEA@PS, Product ID: 38343) was purchased from Sigma-Aldrich Ireland and all other chemicals were of regent-grade, obtained from commercial suppliers and used without further purification unless otherwise noted.

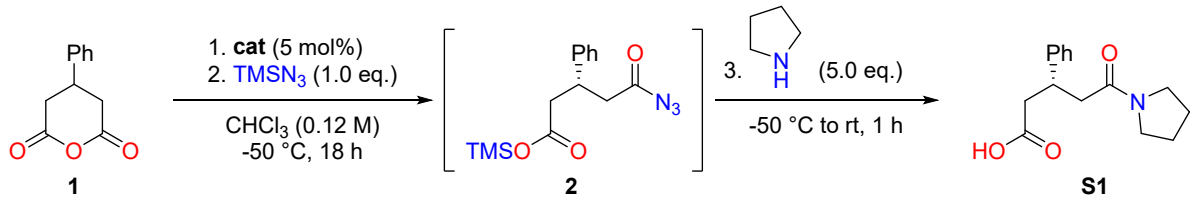
2. Experimental Procedures

2.1 Safety considerations

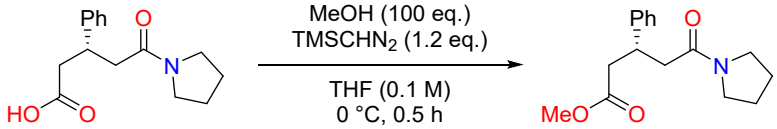
While we have not experienced any issues surrounding the use of $TMSN_3$ in these studies, it is imperative that the appropriate safety precautions are taken, especially when working on reaction scales > 1 mmol. In the following preparations, $TMSN_3$ has the potential to liberate toxic and explosive HN_3 on contact with H_2O or in acidic media. Any volatiles removed should be carried out in a well-ventilated fume hood and reactions performed with a blast shield in large-scale preparations. It is advised that all azide-containing waste should be quenched cautiously, and in an appropriate manner.[1]

2.2 General procedures

2.2.1 Gen A1: Preparation of enantioenriched pyrrolidinamides catalysed by *Cinchona* alkaloid sulfamides



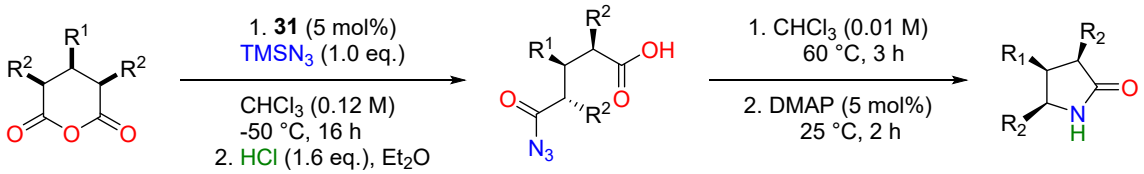
To a carousel tube under Ar atmosphere containing a magnetic stirrer bar, bifunctional catalyst (0.012 mmol, 0.05 eq.) and anhydride **1** (46.8 mg, 0.246 mmol), anhydrous $CHCl_3$ (2.00 mL, 0.12 M) was added *via* syringe and the resulting solution cooled to -50 °C and stirred for 20 minutes. $TMSN_3$ (32.4 µL, 0.246 mmol) was added *via* µsyringe and the resulting solution stirred at -50 °C for 18 h to form the silylated acyl azide intermediate **2**. Pyrrolidine (100 µL, 1.23 mmol, 5.0 eq.) was added dropwise *via* syringe down the side of the carousel tube and the resulting solution stirred for 45 mins at -50 °C. The solution was warmed to room temperature and partitioned between CH_2Cl_2 (15 mL) and $NaOH_{(aq.)}$ (15 mL, 1 M). The organic layer (which contained bifunctional catalyst, and could be recovered, unchanged) was removed and the aqueous layer carefully acidified to pH 1 with $HCl_{(aq.)}$ (5 mL, 1.5 M). ***Caution:*** HN_3 is generated in this step. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organics washed with H_2O (2 x 10 mL) and dried over anhydrous $MgSO_4$. The desiccant was filtered and solvent removed *in vacuo* to give the analytically-pure amido acid **S1** as a white powder.



S1 **3**

Amido acid **S1** (55 mg, 0.211 mmol) was placed in a 5 mL RBF charged with a magnetic stirrer bar and the flask placed under Ar atmosphere. Anhydrous THF (1.00 mL) was added and the resulting solution cooled to 0 °C. MeOH (100 µL), followed by $TMSCHN_2$ (150 µL, 0.300 mmol; 2 M solution in Et_2O) were added sequentially with stirring, and the resulting yellow solution warmed to room temperature over 30 mins. AcOH/MeOH (1:1) was added until gas evolution had ceased and the solution was concentrated *in vacuo* give the product as a colourless oil (57.8 mg, 99%). (EtOAc): R_f = 0.40. CSP-SFC: ACQUITY UPC^2 Trefoil CEL2 (2.5 µm, 3.0 mm x 150 mm); Mobile Phase: A = CO_2, B = EtOH/MeCN (1:1 *v/v*); temperature: 30 °C; inlet pressure: 1500 psi; flow rate = 1.2 mL/min; UV detection at 254 nm; RT: 3.69 min (major enantiomer) and 3.88 min (minor enantiomer). δ_H (600 MHz, $CDCl_3$): 7.29-7.32 (2H, m, H-3', H-5'), 7.26-7.28 (2H, m, H-2', H-6'), 7.21-7.23 (1H, m, H-4'), 3.76 (1H, app quin., H-3), 3.59 (3H, s, H-10), 3.40-3.42 (2H, m, H-6a, H-9a), 3.30-3.35 (1H, m, H-6b), 3.20-3.24 (1H, m, H-9b), 2.91 (1H, dd, *J* 15.5, 6.5, H-4a), 2.71 (1H, dd, *J* 15.5, 8.4, H-4b), 2.67 (1H, dd, *J* 15.0, 7.7, H-2a), 2.60, (1H, dd, *J* 15.0, 6.5, H-2b) and 1.76-1.90 (4H, m, H-7, H-8) ppm. δ_C (151 MHz, $CDCl_3$): 172.5 (C-5), 169.5 (C-1), 143.5 (C-1'), 128.6 (C-3', C-5'), 127.3 (C-2', C-6'), 126.8 (C-4'), 51.5 (C-10), 46.6, 45.6 (C-6, C-9) 41.0 (C-4), 40.0 (C-2), 38.3 (C-3), 26.0 and 24.3 (C-7, C-8) ppm. ν_{max} (neat)/ cm^{-1}: 2970 (s), 2876 (s), 1733 (C=O, ester), 1619 (C=O, amide), 1436 (s), 1372 (m), 1341 (m), 1254 (m), 1227 (m), 1191 (m), 1153 (m), 1084 (m), 1049 (s), 858 (w), 880 (w), 763 (s) and 702 (s) cm^{-1}. HRMS (ESI$^+$) *m/z*: Found: 276.1587 ([M + H]$^+$ $C_{16}H_{22}NO_3$; requires 276.1594).

2.2.2 Gen A2: Organocatalytic, enantioselective synthesis of chiral γ-lactams from prochiral anhydrides

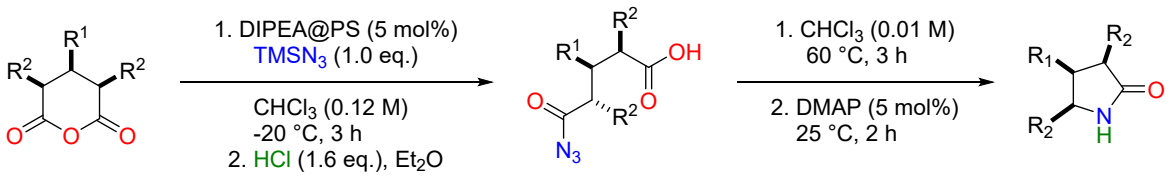


32 **33** **34**

To a 5 mL RBF containing a magnetic stirrer bar, sulfamide **31** (6.4 mg, 0.012 mmol) and achiral or *meso*-anhydride **32** (0.246 mmol) under Ar atmosphere, anhydrous $CHCl_3$ (2.00 mL, 0.12 M) was added *via* syringe before the solution was cooled to -50 °C for 30 mins. $TMSN_3$ (32.4 µL, 0.246 mmol) was then added in one portion and the resulting solution stirred at -50 °C for 16 h. HCl in Et_2O (200 µL, 0.400 mmol) was added in one portion and the resulting solution stirred for 15 mins at -50 °C. The solution was filtered, using anhydrous $CHCl_3$ (1 mL) to effect the transfer and volatiles removed expediently *in vacuo* (hi-vac) to give the analytically-pure acyl azide **33**. The solid was placed under Ar atmosphere and anhydrous $CHCl_3$ (25.0 mL, 0.01 M) added *via* syringe. The resulting solution was heated gently (vigorous gas evolution observed at *ca.* 40 °C) to 60 °C for 3 h under Ar atmosphere. The solution of isocyanate was then cooled to 25°C before DMAP (1.5 mg, 0.012 mmol) was added in one portion and the resulting solution stirred vigorously at 25 °C for 2 h. The solution was concentrated *in* vacuo and the residue purified by flash column chromatography to give the γ-lactam product.

2.2.3 Gen Rac: Preparation of racemic standards for UPC analysis

Prepared according to the methodology set out previously by the Connon group,[2] as below. Physical and spectral properties of the racemic lactams were identical to that of the enantioenriched forms.

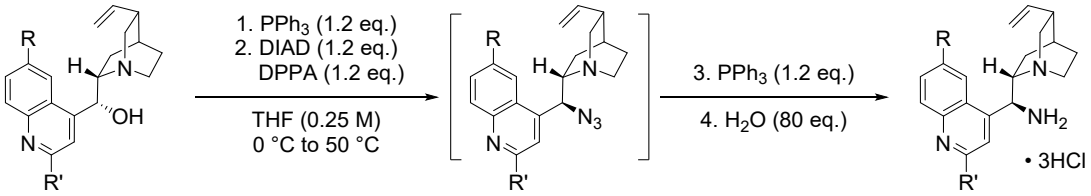


32 ***rac*-33** ***rac*-34**

To a 5 mL RBF containing a magnetic stirrer bar, DIPEA@PS (4 mg, 0.012 mmol) and achiral or *meso*-anhydride **32** (0.246 mmol) under Ar atmosphere, anhydrous $CHCl_3$ (2.00 mL, 0.12 M) was added *via* syringe before the solution was cooled to -20 °C for 10 mins. $TMSN_3$ (32.4 µL, 0.246 mmol) was then added in one portion and the resulting solution stirred at -20 °C for 1.5 h. HCl in Et_2O (200 µL, 0.400 mmol) was added in one portion and the resulting solution stirred for 15 mins at -20 °C. The solution was filtered, using anhydrous $CHCl_3$ (1 mL) to effect the transfer and volatiles removed expediently *in vacuo* (hi-vac) to give the analytically-pure acyl azide ***rac*-33**. The solid was placed under Ar atmosphere and anhydrous $CHCl_3$ (25.0 mL, 0.01 M) added *via* syringe. The resulting solution was heated gently (vigorous gas evolution observed at *ca.* 40 °C) to 60 °C for 3 h. The solution of isocyanate was then cooled to 25°C

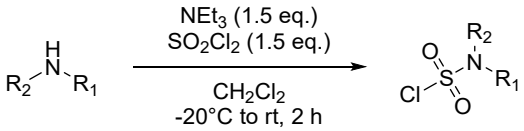
before DMAP (1.5 mg, 0.012 mmol) was added in one portion and the resulting solution stirred vigorously at 25 °C for 2 h. The solution was concentrated *in* vacuo and the residue purified by flash column chromatography to give the γ-lactam product.

2.2.4 Gen B: Preparation of 9-*epi*-9-Amino *Cinchona* alkaloids from native configuration alkaloids



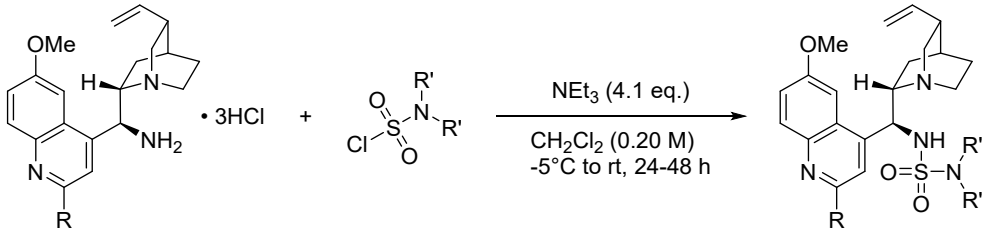
To an oven-dried 250 mL RBF containing a stirrer bar, *Cinchona* alkaloid derivative (18.50 mmol) and PPh_3 (5.82 g, 22.19 mmol) under Ar atmosphere, anhydrous THF (125 mL, 0.15 M) was added *via* syringe. The solution was cooled to 0 °C before DIAD (4.40 mL, 22.19 mmol) and DPPA (4.77 mL, 22.19 mmol), were added sequentially dropwise *via* syringe. The resulting yellow solution was warmed to room temperature and stirred at 20 °C for 24 h. The flask was fitted with a reflux condenser and the solution stirred at 50 °C for a further 2 h. PPh_3 (5.82 g, 22.19 mmol) was added portionwise with stirring and the solution heated at 50 °C for 2 h or until nitrogen evolution had ceased. H_2O (26.4 mL, 0.7 M) was added and the solution stirred at room temperature for 16 h. The resulting mixture was concentrated as far as possible *in vacuo* and the residue partitioned between 2 M HCl and CH_2Cl_2 (100 mL each). The aqueous phase was removed and the organic layer extracted with 2 M HCl (3 x 50 mL). The combined aqueous extracts were washed with CH_2Cl_2 (5 x 50 mL) and concentrated as far as possible. The viscous residue was stirred in EtOH and the resulting precipitate filtered and dried *in vacuo*. The precipitate can be purified by reprecipitation from boiling MeOH using EtOAc as antisolvent to give the alkaloid hydrochloride as a powder.

2.2.5 Gen C: Sulfamoyl chloride synthesis



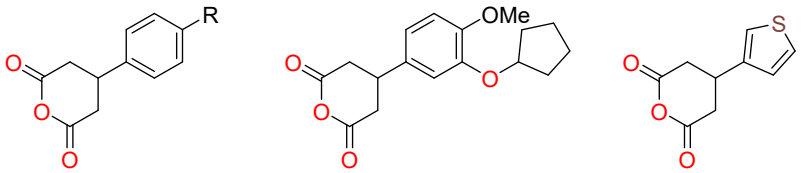
SO_2Cl_2 (1.5 eq.) in anhydrous CH_2Cl_2 (1.00 M) was cooled to -20 °C under Ar atmosphere before a solution of NEt_3 (1.5 eq.) and the appropriate secondary amine (1.0 eq.) in anhydrous CH_2Cl_2 (2 M with respect to amine) was added dropwise *via* syringe (>30 mins, exothermic). The resulting solution was stirred at -20 °C for 30 mins before warming to room temperature over 1.5 h. The resulting yellow mixture was slowly poured into ice-H_2O using CH_2Cl_2 to effect the transfer. The biphasic mixture was partitioned and the organic layer washed with H_2O and brine before being dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in the minimum CH_2Cl_2 and passed through a short plug of silica, eluted with CH_2Cl_2 to provide the analytically-pure sulfamoyl chloride product after drying *in vacuo*.

2.2.6 Gen D: *Cinchona* alkaloid sulfamide preparation from sulfamoyl chlorides



To a 25 mL RBF containing a magnetic stirrer bar and the appropriate alkaloid hydrochloride salt (1.00 mmol) was added anhydrous CH_2Cl_2 (5.00 mL, 0.20 M). To the resulting suspension, NEt_3 (4.20 mmol) was added dropwise at -5 °C and the resulting suspension stirred vigorously for 30 mins before sulfamoyl chloride (1.20 mmol) was added dropwise *via* syringe. The resulting solution was stirred at room temperature for 24-48 h until consumption of the sulfamoyl chloride was observed by TLC analysis. The solution was diluted with CH_2Cl_2 (25 mL) and washed sequentially with half-saturated $NaHCO_{3(aq.)}$, H_2O and brine (2 x 10 mL each). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil, purified by flash chromatography as appropriate (*vide infra*).

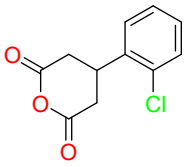
2.3 Preparation of cyclic anhydride substrates



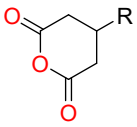
1 R = H
S2 R = Me
S3 X = Cl
S4 X = F

S5

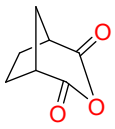
S6



S7



S8 R = OTBS
S9 R = Me
S10 R = *i*Pr
S11 R = *i*Bu

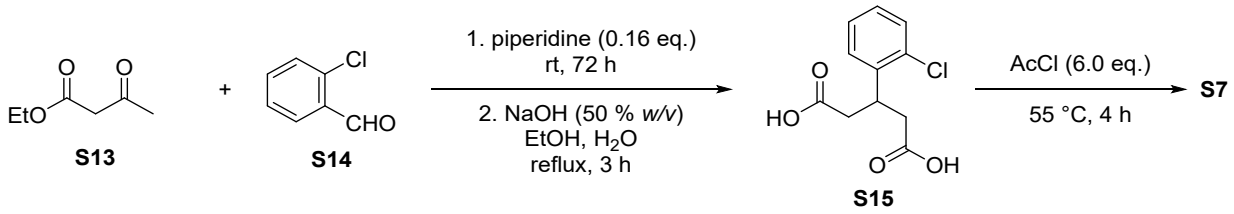


S12

Figure S1: Anhydride substrates examined in the study.

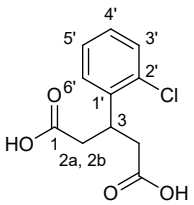
Anhydrides **1, S2-S6, S9-S12** were synthesised according to existing preparations.[2] Anhydride **S7** was prepared by a modified literature procedure, (*vide infra*) and anhydride **S8** was obtained from commercial suppliers and recrystallised to analytical purity from boiling hexanes prior to use in the lactamisation.

2.3.1 Preparation of 3-(2-chlorophenyl)glutaric anhydride



Scheme S1: Knoevenagel condensation of ethyl acetoacetate (**S13**) and 2-chlorobenzaldehyde (**S14**), hydrolysis-decarboxylation of the diester intermediate and cyclodehydration of the resulting diacid **S15** to the corresponding anhydride **S7**.

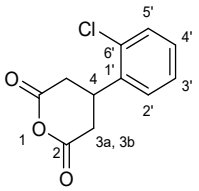
2.3.1.1 3-(2-Chlorophenyl)glutaric acid (**S15**)



To a stirred solution of **S13** (6.50 g, 50.00 mmol) and **S14** (3.52 g, 25.00 mmol) at 0 °C, piperidine (412 µL, 4.17 mmol) was added dropwise. The resulting solution was stirred at room temperature (22 °C) for 72 h. The yellow intractable reside was taken up in EtOH (25 mL) and added slowly to 50% $NaOH_{(aq)}$ (25 mL) and the solution stirred vigorously under reflux for 3 h. The solution was poured into ice cold water (20 mL) and the mixture acidified to pH 1 with HCl (conc.). The solution was extracted with EtOAc (3 x 50 mL) and the combined organic extracts washed with H_2O (2 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated *in vacuo*. After trituration of the resulting solid, in cold $CHCl_3$, the product was recovered as a white, crystalline powder (1.70 g, 28%), m.p. (from PE/CH_2Cl_2) 180-181°C (Lit.,[3] m.p. (from acetone) 152-154°C). Product spectroscopic data correlated well to that available in the literature,[4] and additional data are appended below. δ_H (400 MHz, DMSO-d_6): 12.16 (2H, br s, H-4), 7.39-7.44 (2H, m, H-3', H-6'), 7.30 (1H, app. dt, H-4'), 7.22 (1H, app. dt, H-5'), 3.93 (1H, quint, *J* 7.4, H-3) and 2.61 (4H, d, *J* 7.4, H-2) ppm. ν_{max} (neat, cm^{-1}): 2869 (m), 1708 (vs, C=O st.), 1441 (s), 1400 (m), 1294 (m), 1241 (w), 1050 (s), 1036 (s), 899 (m), 756 (s), 727 (s),

704 (s), 665 (m), 630 (m), 593 (m), 524 (w), 471 (m) and 453 (s) ppm. HRMS (ESI$^+$) *m/z*: Found: 241.0273 ([M - H]$^-$ $C_{11}H_{10}ClO_4$; requires: 241.0273).

2.3.1.2 3-(2-Chlorophenyl)glutaric anhydride (**S7**)

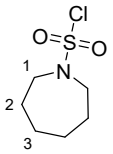


To an oven-dried 10 mL round-bottomed flask containing a magnetic stirrer bar and **S14** (725 mg, 2.99 mmol) under Ar atmosphere, AcCl was added (1.30 mL, 17.94 mmol) *via* syringe. The resulting suspension was heated at 55 °C for 3 h. After cooling the resulting brown solution to room temperature, the solution was concentrated as far as possible *in vacuo*. The resulting residue was partitioned between CH_2Cl_2 and half-saturated $NaHCO_3$ (10 mL each), the organic layer washed with distilled H_2O and brine (2 x 5 mL each) and dried over anhydrous $MgSO_4$ to give the analytically-pure product as an off-white crystalline powder after drying *in vacuo* (418 mg, 62%), m.p. 106-107 °C. δ_H (400 MHz, $CDCl_3$): 7.47 (1H, dd, *J* 7.6, 1.6, H-5'), 7.28-7.37 (2H, m, H-3', H-4'), 7.19 (1H, dd, *J* 7.4, 1.7, H-2'), 3.88-3.96 (1H, m, H-4), 3.17 (1H, dd, *J* 17.3, 4.6, H-3a) and 2.91 (1H, dd, *J* 17.3, 10.2, H-3b) ppm. δ_C (100 MHz, $CDCl_3$):165.6 (C-2), 136.3 (C-1'), 133.7 (C-6'), 130.6 (C-5'), 129.4 (C-4'), 127.9 (C-3'), 126.1 (C-2'), 35.6 (C-3), 30.9 (C-4) ppm. ν_{max} (neat, cm^{-1}): 2923 (m), 1805 and 1759 (vs, C=O st.), 1472 (m), 1425 (m), 1410 (m), 1350 (s), 1332 (s), 1250 (s), 1194 (s), 1132 (s), 1072 (m), 1020 (m)), 936 (s), 873 (s), 774 (vs), 731 (w), 700 (s), 677 (m), 620 (m), 572 (s) and 536 (s) cm^{-1}. HRMS (ESI$^+$) *m/z*: Found: 279.0403 ([M + MeOH + Na]$^+$ $C_{12}H_{13}ClNaO_4$; requires: 279.0395).

2.4 Catalyst preparation and characterisation data

2.4.1. Sulfamoyl chloride electrophiles

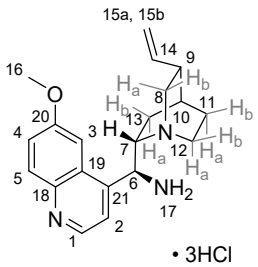
2.4.1.1 Azepane-1-sulfonyl chloride (**S16**)



Prepared according to **Gen C** using azepane (376 µL, 3.33 mmol) and purified by passing through a short plug of silica, eluting with CH_2Cl_2 to give the product as a colourless oil (394.4 mg, 60%). TLC (CH_2Cl_2, ninhydrin): R_f = 0.83. δ_H (400 MHz, $CDCl_3$): 3.46-3.53 (4H, m, H-1), 1.80-1.86 (4H, m, H-2) and 1.63-1.69 (4H, m, H-3) ppm. δ_C (101 MHz, $CDCl_3$): 50.1 (C-1), 27.5 (C-3) and 27.0 (C-2) ppm. ν_{max} (neat)/ cm^{-1}: 2932 (m), 2860 (m), 1462 (w), 1386 (S=O, s), 1367 (s), 1172 (s), 1144 (m), 1042 (m), 888 (m) and 693 (s) cm^{-1}.

2.4.2. Core modified 9-*epi*-alkaloid hydrochlorides

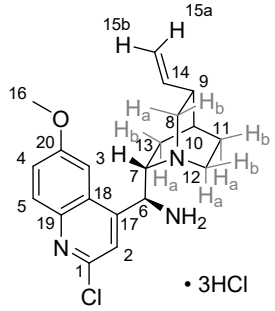
2.4.2.1 9-Amino-(9-deoxy)*epi*-quininium trihydrochloride (**S17**)



Prepared according to **Gen B** using anhydrous quinine (6.00 g, 18.50 mmol) to give the product as a light yellow powder after drying *in vacuo* (7.14 g, 89%), m.p. (from MeOH/EtOAc) 218 °C (decomp.), (Lit.,[5] m.p. 220-221 °C (decomp.)); $[\alpha]_D^{24}$ = +49.7 (*c* = 0.98 ,

H_2O). Product spectroscopic data correlated well to that in the literature.[5] δ_H (400 MHz, DMSO-d_6): 11.20 and 9.61 (3H, br s, 3HCl), 9.06 (1H, br s, H-1), 8.23-8.27 (2H, m, H-2, H-5), 7.94 (1H, d, *J* 2.1, H-3), 7.69 (1H, dd, *J* 9.2, 2.1, H-4), 5.93 (1H, d, *J* 9.1, H-6), 5.89-5.93 (1H, m, H-14), 5.29 (1H, app. d, H-15a), 5.17 (1H, app. d, H-15b), 4.71 (1H, app. q, H-7), 4.28-4.31 (2H, br s, H-17), 4.08-4.15 (1H, m, H-12a), 4.06 (3H, s, H-16), 3.72 (1H, dd, *J* 12.6, 10.7, H-8b), 3.34-3.42 (2H, m, H-12b, H-8a), 2.75 (1H, br s, H-9), 1.84-1.89 (3H, m, H-10, H-11a, H-11b), 1.48-1.56 (1H, m, H-13b) and 0.86-0.91 (1H, m, H-13a) ppm. δ_C (151 MHz, DMSO-d_6) : 159.6 (C-20), 145.7 (C-1), 141.8 (C-18), 140.6 (C-21), 138.7 (C-14), 128.8 (C-5), 125.0 (C-19, C-4), 121.7 (C-2), 117.1 (C-15), 103.3 (C-3), 59.2 (C-7), 57.0 (C-16), 52.4 (C-8), 48.2 (C-6), 42.2 (C-12), 36.3 (C-9), 26.0 (C-10), 24.0 (C-11) and 23.9 (C-13) ppm HRMS (ESI$^+$) *m/z*: Found: 324.2073 ([M + H]$^+$ $C_{20}H_{26}N_3O$; requires 324.2070).

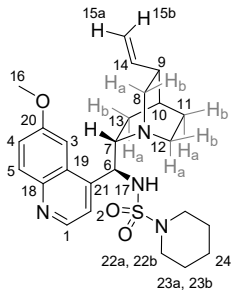
2.4.2.2 2'-Chloro-9-amino-(9-deoxy)-*epi*-quininium trihydrochloride (**S18**)



Prepared according to **Gen B** using C2'-chloroquinine[6] (1.39 g, 3.88 mmol) and precipitated after co-evaporation of residual H_2O with EtOH to give the product as a bright yellow powder (1.09 g, 80%), m.p. 198-204 °C (decomp.); $[\alpha]_D^{24}$ = +2.5 (*c* = 0.20 , H_2O). ^{1}H, ^{13}C NMR and EXSY spectroscopic analyses in DMSO-d_6 revealed rotameric species in the ratio 93:7 at 25°C. ^{13}C Resonances are clearly observable for the major rotamer only. Major rotamer: δ_H (400 MHz, DMSO-d_6): 11.12, 9.48 (3H, br s, NH), 8.15 (1H, s, H-2), 7.97 (1H, d, *J* 9.2, H-5), 7.83 (1H, d, *J* 1.9, H-3), 7.58 (1H, dd, *J* 9.2, 1.9, H-4), 5.87-5.96 (1H, m, H-14), 5.82 (1H, d, *J* 10.4, H-6), 5.26 (1H, d, *J* 17.3, H-15a), 5.16 (1H, d, *J* 10.5, H-15b), 4.61-4.68 (1H, app. q., H-7), 4.09-4.18 (1H, m, H-12a), 4.01 (3H, s, H-16), 3.70-3.76 (1H, m, H-8b), 3.28-3.38 (2H, m, H-8a, H-12b), 2.76 (1H, br s, H-9), 1.80-1.92 (3H, m, H-10, H-11a, H-11b), 1.57-1.63 (1H, m, H-13b) and 0.87 (1H, dd, *J* 13.3, 8.4, H-13a) ppm. δ_C (151 MHz, DMSO-d_6): 158.7 (C-20), 146.9 (C-1), 143.6 (C-19), 141.6 (C-17), 138.3 (C-14), 130.4 (C-5), 126.7 (C-18), 123.7 (C-3), 122.0 (C-2), 116.7 (C-15), 103.0 (C-4), 58.7 (C-7), 56.4 (C-16), 52.1 (C-8), 47.7 (C-6), 41.6 (C-12), 35.9 (C-9), 25.5 (C-10), 23.6 (C-11) and 23.4 (C-13) ppm. Minor rotamer: δ_H (400 MHz, DMSO-d_6): 11.12, 9.48 (3H, br s, NH), 8.11 (1H, s, H-2), 7.98 (1H, d, *J* 9.0, H-5), 7.54 (1H, dd, *J* 9.0, 2.0, H-4), 7.49 (1H, d, *J* 2.0, H-3), 5.77-5.86 (1H, m, H-14), 5.41 (1H, d, *J* 17.5, H-15a), 5.22-5.25 (1H, m, *J* 10.4, H-6), 5.16 (1H, d, *J* 10.5, H-15b), 4.96 (1H, app. q., H-7), 4.06 (3H, s, H-16), 3.93-3.95 (1H, m, H-12a), 3.70-3.76 (1H, m, H-8b), 3.28-3.38 (2H, m, H-8a, H-12b), 2.76 (1H, br s, H-9), 1.99 (1H, br s, H-10), 1.80-1.92 (2H, m, H-11a, H-11b), 1.21-1.29 (1H, m, H-13b) and 1.06-1.15 (1H, dd, *J* 13.3, 8.4, H-13a) ppm. ν_{max} (neat)/ cm^{-1}: 3478 (m, NH st.), 2560 (w), 1617 (s), 1510 (m), 1460 (m), 1395 (m), 1320 (w), 1279 (m), 1235 (s), 1140 (s), 1019 (m), 920 (s), 831 (s), 774 (s), 728 (w) and 681 (s) cm^{-1}. HRMS (APCI$^+$) *m/z*: Found: 358.1685 ([M + H]$^+$ $C_{20}H_{25}ClN_3O$; requires 358.1680).

2.4.3. *Cinchona* alkaloid-derived sulfamide organocatalysts

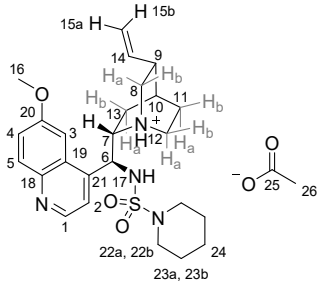
2.4.3.1 Quinine-derived piperidine sulfamide (**13**)



Prepared according to **Gen D** using **S17** (1.38 g, 3.19 mmol) and commercial piperidine-1-sulfonyl chloride (447 µL, 3.19 mmol) and the crude residue purified by flash chromatography (98:2 CH_2Cl_2/MeOH) to afford the product as a white, crystalline powder (460 mg, 30%), m.p. 51-52 °C. TLC (95:5 CH_2Cl_2/MeOH): R_f = 0.40; $[\alpha]_D^{22}$ +37.2 (*c* = 0.05, $CHCl_3$). ^{1}H, ^{13}C NMR and EXSY spectroscopic analyses revealed rotameric species in the ratio 68:32 in $CDCl_3$ at 25 °C. Major rotamer: δ_H (400 MHz, $CDCl_3$): 8.81 (1H, d, *J* 4.6, H-1),

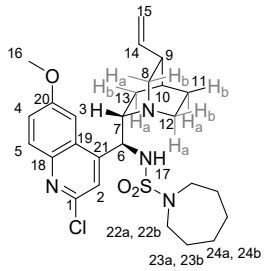
8.03 (1H, d, *J* 9.2, H-5), 7.56-7.59 (2H, m, H-2, H-3), 7.41 (1H, dd, *J* 9.2, 2.6, H-4), 5.90 (1H, br. s, H-17), 5.67-5.76 (1H, m, H-14), 5.10 (1H, d, *J* 10.8, H-6), 4.97-5.04 (2H, m, H-15a, H-15b), 4.00 (3H, s, H-16), 3.26-3.42 (2H, m, H-8b, H-12b), 3.09-3.19 (1H, m, H-7), 2.59-2.90 (6H, m, H-8a, H-12a, H-22a, H-22b), 2.31-2.40 (1H, m, H-9), 1.65-1.72 (3H, m, H-9, H-11a, H-11b), 1.39-1.45 (1H, m, H-13b), 1.00-1.06 (2H, m, H-4), 0.81-0.87 (1H, m, H-13a) and 0.70-0.76 (4H, m, H-23a, H-23b) ppm. δ_C (101 MHz, $CDCl_3$): 158.2 (C-20), 147.6 (C-1), 145.0 (C-18), 144.5 (C-21), 141.2 (C-14), 131.7 (C-5), 129.5 (C-19), 122.0 (C-4), 119.7 (C-2), 114.7 (C-15), 100.8 (C-3), 60.6 (C-7), 55.73 (C-16), 55.7 (C-8), 53.0 (C-6), 46.0 (C-22), 40.3 (C-12), 39.5 (C-9), 27.9 (C-11), 27.4 (C-10), 25.4 (C-13), 24.35 (C-23) and 23.1 (C-24) ppm. Minor rotamer: δ_H (400 MHz, $CDCl_3$): 8.68 (1H, d, *J* 4.3, H-1), 8.05 (1H, d, *J* 9.3, H-5), 7.84 (1H, d, *J* 2.7, H-3), 7.39 (1H, dd, *J* 9.3, 2.7, H-4), 7.27 (1H, d, *J* 4.3, H-2), 5.59-5.64 (1H, m, H-14), 4.90-4.98 (2H, m, H-15a, H-15b), 4.44 (1H, d, *J* 11.0, H-6), 3.95 (3H, s, H-16), 3.48-3.55 (1H, m, H-7), 3.18-3.42 (2H, m, H-8b, H-12b), 2.59-2.90 (6H, m, H-8a, H-12a, H-22a, H-22b), 2.31-2.40 (1H, m, H-9), 1.73-1.76 (1H, m, H-10), 1.60-1.64 (2H, m, H-11a, H-11b), 1.33-1.39 (1H, m, H-13b), 0.96-1.01 (2H, m, H-24) and 0.62-0.87 (5H, m, H-13a, H-23a, H-23b) ppm. δ_C (101 MHz, $CDCl_3$): 157.0 (C-20), 147.2 (C-1), 145.4 (C-18), 141.5 (C-21), 141.4 (C-14), 132.0 (C-5), 127.3 (C-19), 123.7 (C-2), 121.6 (C-4), 114.7 (C-15), 103.4 (C-3), 65.9 (C-7), 63.3 (C-6), 56.1 (C-16), 56.0 (C-8), 46.2 (C-22), 40.0 (C-12), 39.7 (C-9), 27.7 (C-11), 27.5 (C-10), 26.6 (C-13), 24.44 (C-23) and 23.1 (C-24) ppm.
NMR spectroscopic analysis of the solid in CD_3COOD identifies the title product as one species: δ_H (400 MHz, CD_3COOD): 8.97 (1H, d, *J* 5.0, H-1), 8.30 (1H, d, *J* 9.3, H-5), 8.04 (1H, d, *J* 5.0, H-2), 7.67 (1H, d, *J* 2.4, H-3), 7.63 (1H, dd, *J* 9.3, 2.4, H-4), 5.84 (1H, ddd, *J* 17.3, 10.2, 7.0, H-14), 5.45 (1H, d, *J* 11.4, H-6), 5.16-5.20 (1H, m, H-15b), 5.10-5.15 (1H, m, H-15a), 4.29-4.35 (1H, m, H-7), 4.00-4.08 (4H, m, H-12b, H-16), 3.91 (1H, dd, *J* 13.2, 10.5, H-8b), 3.55-3.64 (1H, m, H-12a), 3.22-3.27 (1H, m, H-8a), 2.84-2.89 (1H, m, H-9), 2.69-2.74 (2H, m, H-22a), 2.57-2.62 (2H, m, H-22b), 2.10-2.17 (2H, m, H-11), 1.97-2.00 (1H, m, H-10), 1.83-1.89 (1H, m, H-13b), 1.07-1.14 (1H, m, H-13a), 0.98-1.05 (2H, m, H-24), 0.64-0.74 (2H, m, H-23a) and 0.45-0.56 (2H, m, H-23b) ppm. ν_{max} (neat)/ cm^{-1}: 3214 (br. m, N-H st.), 2937 (s), 2859 (s), 1621 (s), 1591(m), 1508 (s), 1474 (m), 1452 (m), 1432 (m) 1356 (s, S=O), 1319 (s, S=O), 1302 (m), 1260 (m), 1240 (m), 1229 (s), 1155 (s), 1140 (s), 1102 (m), 1083 (m), 1053 (s), 1029 (s), 988 (s), 937 (s), 876 (m), 854 (s), 830 (m), 764 (w), 719 (m), 709 (m) and 670 (m) cm^{-1}. HRMS (APCI$^+$) *m/z*: Found: 471.2437 ([M + H]$^+$ $C_{25}H_{35}N_4O_3S$; requires 471.2424).

2.4.3.2 Piperidine sulfamide acetic acid complex (**13** • HOAc)



To a 2.5 mL RBF containing a solution of piperidine sulfamide **13** (75.1 mg, 0.160 mmol) in anhydrous $CHCl_3$ (160 µL, 1.0 M), AcOH (9.4 µL, 0.164 mmol) was added and the resulting solution heated to 40 °C for 1 h. The cooled yellow solution was concentrated *in vacuo* to provide the product as a white, crystalline solid (84.0 mg, 99%), m.p. 88-90 °C. $[\alpha]_D^{22}$ +18.6 (*c* = 0.05, $CHCl_3$). ^1H, ^{13}C NMR and EXSY spectroscopic analyses in $CDCl_3$ revealed rotameric species in the ratio 70:30 at 25 °C. Major Rotamer: δ_H (400 MHz, $CDCl_3$): 8.81 (1H, d, *J* 4.6, H-1), 8.05 (1H, d, *J* 9.3, H-5), 7.55-7.59 (2H, m, H-2, H-3), 7.41 (1H, dd, *J* 9.3, 2.6, H-4), 5.90 (1H, br. s, H-17), 5.67-5.76 (1H, m, H-14), 5.14 (1H, d, *J* 10.8, H-6), 4.97-5.04 (2H, m, H-15a, H-15b), 3.99 (3H, s, H-16), 3.45-3.51 (1H, m, H-12b), 3.36 (1H, dd, *J* 13.9, 10.3, H-8b), 3.14-3.21 (1H, m, H-7), 2.85-2.91 (1H, m, H-12a), 2.75-2.80 (1H, m, H-8a), 2.62-2.69 (4H, m, H-22a, H-22b), 2.40-2.44 (1H, m, H-9), 2.12 (3H, s, H-26), 1.71-1.77 (3H, m, H-10, H-11a, H-11b), 1.43-1.49 (1H, m, H-13b), 1.02-1.08 (2H, m, H-24), 0.83-0.89 (1H, m, H-13a) and 0.69-0.78 (4H, m, H-23a, H-23b) ppm. δ_C (100 MHz, $CDCl_3$): 175.2 (C-25), 158.4 (C-20), 147.8 (C-1), 145.0 (C-18), 144.5 (C-21), 140.2 (C-14), 131.8 (C-5), 129.4 (C-19), 122.2 (C-4), 119.9 (C-2), 115.5 (C-15), 101.0 (C-3), 60.2 (C-7), 55.85 (C-16), 55.2 (C-8), 53.0 (C-6), 46.2 (C-22), 40.4 (C-12), 38.9 (C-9), 27.9 (C-11), 27.5 (C-10), 27.3 (C-13), 23.3 (C-23), 23.1 (C-24) and 21.1 (C-26) ppm. Minor Rotamer: δ_H (400 MHz, $CDCl_3$): 8.70 (1H, d, *J* 4.3, H-1), 8.08 (1H, d, *J* 9.5, H-5), 7.86 (1H, d, *J* 2.5, H-3), 7.41 (1H, dd, *J* 9.5, 2.5, H-4), 7.30 (1H, d, *J* 4.3, H-2), 5.63-5.68 (1H, m, H-14), 6.98 (1H, d, *J* 17.3, H-15b), 4.92 (1H, d, *J* 10.4, H-15a), 4.46 (1H, d, *J* 10.9, H-6), 3.97 (3H, s, H-16), 3.50-3.54 (1H, m, H-7), 3.30 (1H, d, *J* 13.7, 10.2, H-8b), 3.15-3.50 (1H, m, H-12b), 2.70-2.82 (2H, m, H-8a, H-12a), 2.58-2.65 (4H, m, H-22a, H-22b), 2.33-2.66 (1H, m, H-9), 2.12 (3H, s, H-26), 1.73-1.76 (1H, m, H-10), 1.59-1.70 (2H, m, H-11a, H-11b), 1.33-1.39 (1H, m, H-13b), 0.96-1.01 (1H, m, H-13a) and 0.62-0.70 (4H, m, H-23a, H-23b) ppm. δ_C (101 MHz, $CDCl_3$): 175.2 (C-25), 158.4 (C-20), 147.2 (C-1), 145.4 (C-18), 141.7 (C-21), 141.2 (C-14), 132.0 (C-5), 127.1 (C-19), 123.9 (C-2), 121.8 (C-4), 115.0 (C-15), 103.4 (C-3), 63.3 (C-7), 56.2 (C-6), 56.0 (C-16), 55.9 (C-8), 46.4 (C-22), 40.0 (C-12), 39.7 (C-9), 27.6 (C-11), 27.5 (C-10), 26.7 (C-13), 24.6 (C-23), 23.2 (C-24) and 21.1 (C-26) ppm. ν_{max} (neat)/ cm^{-1}: 3587 (s, R_3N^+-H st.), 3360 (w, br, N-H st.), 3273 (w, br, N-H st.), 2941 (m, C-H st.), 1620 (m, OAc C-O st.), 1571 (s), 1507 (m), 1477 (m), 1455 (w), 1437 (m), 1407 (w), 1360 (w), 1315 (s, SO_2 st.), 1300 (s, SO_2 st.), 1262 (s), 1242 (m), 1220 (m), 1153 (m), 1138 (s), 1102 (m), 920 (m), 882 (s), 860 (s), 836 (m), 760 (m) and 720 (m) cm^{-1}. HRMS (APCI$^+$) *m/z*: Found: 471.2427 ([M - OAc]$^+$ $C_{25}H_{35}N_4O_3S$; requires 471.2424)

2.4.3.3 C2'-Chloroquinine azepane sulfamide (**31**)

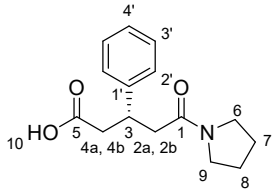


Prepared according to **Gen D** using **S18** (573 mg, 1.33 mmol) and sulfamoyl chloride **S16** (291.3 mg, 1.47 mmol), purified by flash chromatography (7:3 CH_2Cl_2/EtOAc) to give the title product as a white, crystalline powder (271 mg, 39%), m.p. 58-60 °C. TLC (98:2 CH_2Cl_2/MeOH): R_f = 0.44. $[\alpha]_D^{22}$ +2.1 (*c* = 0.13, $CHCl_3$). ^1H, ^{13}C NMR and EXSY spectroscopic analyses in $CDCl_3$ revealed rotameric species in the ratio 70:30 at 25 °C. Major Rotamer: δ_H (600 MHz, $CDCl_3$): 7.95 (1H, d, *J* 9.2, H-5), 7.56 (1H, s, H-2), 7.48 (1H, d, *J* 2.7, H-3), 7.42 (1H, dd, *J* 9.2, 2.7, H-4), 6.12 (1H, br. s, H-17), 5.68-5.74 (1H, m, H-14), 5.03 (1H, d, *J* 10.6, H-6),4.94-4.99 (2H, m, H-15), 3.98 (3H, s, H-16), 3.19-3.26 (2H, m, H-8b, H-12b), 2.75-2.83 (2H, m, H-7, H-12a), 2.55-2.72 (5H, m, H-8a, H-22a, H-22b), 2.28-2.33 (1H, m, H-9), 1.57-1.68 (3H, m, H-10, H-11a, H-11b), 1.37-1.41 (1H, m, H-13b), 1.27-1.38 (6H, m, H-23a, H-23b, H-24a, H-24b), 0.86-0.92 (1H, m, H-13a) ppm. δ_C (151 MHz, $CDCl_3$): 158.4 (C-20), 148.5 (C-21), 148.0 (C-1), 144.1 (C-18), 141.0 (C-14), 130.9 (C-5), 127.5 (C-19), 122.7 (C-4), 121.2 (C-2), 114.9 (C-15), 101.5 (C-3), 61.3 (C-7), 55.78 (C-8), 55.75 (C-16), 53.0 (C-6), 48.2 (C-22), 40.4 (C-12), 39.4 (C-9), 28.62 (C-23), 27.9 (C-11), 27.40 (C-10), 26.7 (C-24), 25.2 (C-13) ppm. Minor Rotamer: δ_H (600 MHz, $CDCl_3$): 7.96 (1H, d, *J* 9.2, H-5), 7.87 (1H, d, *J* 2.8, H-3), 7.40 (1H, dd, *J* 9.2, 2.8, H-5), 7.30 (1H, s, H-2), 6.29 (1H, br. s, H-17), 5.60-5.66 (1H, m, H-14), 4.89-4.95 (2H, m, H-15), 4.34 (1H, d, *J* 10.9, H-6), 3.93 (3H, s, H-16), 3.35-3.40 (1H, m, H-7), 3.19-3.25 (1H, m, H-8b), 3.05-3.12 (1H, m, H-12b), 2.72-2.76 (1H, m, H-12a), 2.55-2.72 (5H, m, H-8a, H-22a, H-22b), 2.28-2.33 (1H, m, H-9), 1.73-1.76 (1H, m, H-10), 1.58-1.61 (2H, m, H-11a, H-11b), 1.27-1.38 (7H, m, H-13b, H-23a, H-23b, H-24a, H-24b) and 0.94-0.99 (1H, m, H-13a) ppm. δ_C (151 MHz, $CDCl_3$): 157.3 (C-20), 147.5 (C-1), 145.1 (C-21), 144.7 (C-18), 141.0 (C-14), 131.0 (C-5), 125.9 (C-19), 124.0 (C-2), 122.5 (C-4), 114.8 (C-15), 104.0 (C-3), 62.6 (C-6), 56.0 (C-8), 55.7 (C-16), 48.3 (C-22), 40.0 (C-12), 39.6 (C-9), 28.57 (C-23), 27.6 (C-11), 27.43 (C-10), 26.64 (C-24), 26.54 (C-13) ppm. ν_{max} (neat)/ cm^{-1}: 3189 (w, br, N-H st.), 3073 (w, N-H st.), 2926 (m, C-H st.), 2862 (w), 1620 (s), 1581 (m), 1505 (s), 1455 (s), 1394 (m), 1234 (m), 1228 (m), 1143 (vs, br), 1101 (w), 1044 (w), 1030 (w), 987 (m), 941 (s), 880 (m), 828 (m), 768 (w), 692 (vs), 669 (m), 617 (w) and 576 (s) cm^{-1}. HRMS (APCI$^+$) *m/z*: Found: 519.2195 ([M + H]$^+$ $C_{26}H_{36}ClN_4O_3S$; requires 519.2192).

2.5 Synthesis and characterisation of desymmetrisation products (pyrrolidinamides and γ-lactams)

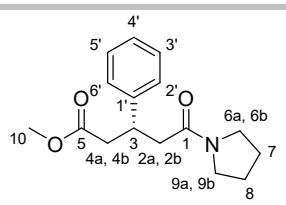
2.5.1 Pyrrolidinamide products

2.5.1.1 (*R*)-5-Oxo-3-phenyl-5-(pyrrolidin-1-yl)pentanoic acid (S1)



Prepared according to **Gen A1** using sulfamide **31** (6.4 mg, 0.012 mmol) to yield the title product as a white powder (55.3 mg, 86%), m.p. (from EtOAc) 108-109 °C. δ_H (600 MHz, $CDCl_3$): 7.28-7.32 (2H, m, H-3'), 7.21-7.25 (3H, m, H-2', H-4'), 3.70 (1H, app. quin, H-3), 3.35-3.44 (2H, m, H-9), 3.01-3.07 (2H, m, H-6), 2.95 (1H, ddd, *J* 14.8, 8.5, 2.4, H-4a), 2.77 (1H, ddd, *J* 14.4, 6.6, 2.3, H-2a), 2.73 (1H, ddd, *J* 14.8, 6.1, 2.6, H-4b), 2.66 (1H, ddd, *J* 14.4, 6.7, 2.1, H-2b) and 1.69-1.82 (4H, m, H-7, H-8) ppm. δ_C (151 MHz, $CDCl_3$): 174.9 (C-5), 170.8 (C-1), 143.2 (C-1'), 128.6 (C-3'), 127.2 (C-2'), 127.0 (C-4'), 46.9 (C-6), 45.9 (C-9), 40.6 (C-2), 40.1 (C-4), 38.8 (C-3), and 25.8, 24.3 (C-7 ,C-8) ppm. ν_{max} (neat)/ cm^{-1}: 2974 (m), 2868 (m), 1947 (br, w), 1698 (s, C=O), 1576 (s, amide I), 1481 (s), 1453 (s), 1367 (m), 1324 (s), 1267 (s), 1229 (s), 1191 (m), 1167 (m), 1113 (w), 1085 (m), 1067 (w), 1037 (w), 999 (m), 975 (m), 952 (m), 915 (m), 903 (m), 854 (m), 760 (s), 699 (s), 637 (m) and 576 (m) cm^{-1}. HRMS (APCI$^+$) *m/z*: Found: 262.1440 ([M + H]$^+$ $C_{15}H_{20}NO_3$; requires 262.1438).

2.5.1.2 (*R*)-Methyl 5-oxo-3-phenyl-5-(pyrrolidin-1-yl)pentanoate (**3**)

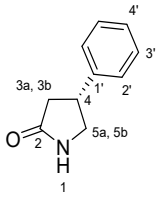


Amido acid **S1** (55.0 mg, 0.211 mmol) was placed in a 5 mL RBF charged with a magnetic stirrer bar and the flask placed under Ar atmosphere. Anhydrous THF (1 mL) was added and the resulting solution cooled to 0 °C. MeOH (100 µL), followed by $TMSCHN_2$ (0.237 mmol, 1.1 eq., 2 M in Et2O) were added sequentially with stirring, and the resulting solution warmed to room temperature over 30 mins. AcOH/MeOH (1:1) was added until gas evolution had ceased and the solution was concentrated *in vacuo* give the product as a colourless oil (57.8 mg, 99%). A sample of the oil was purified by preparative-TLC using EtOAc as mobile phase prior to CSP-SFC analysis. TLC (EtOAc): R_f = 0.40. CSP-SFC analysis: Step 3 was employed with UV detection at 254 nm; R_T: 3.88 min (major enantiomer) and 4.11 min (minor enantiomer). δ_H (600 MHz, $CDCl_3$): 7.29-7.32 (2H, m, H-3', H-5'), 7.26-7.28 (2H, m, H-2', H-6'), 7.21-7.23 (1H, m, H-4'), 3.76 (1H, app quin., H-3), 3.59 (3H, s, H-10), 3.40-3.42 (2H, m, H-6a, H-9a), 3.30-3.35 (1H, m, H-6b), 3.20-3.24 (1H, m, H-9b), 2.91 (1H, dd, *J* 15.5, 6.5, H-4a), 2.71 (1H, dd, *J* 15.5, 8.4, H-4b), 2.67 (1H, dd, *J* 15.0, 7.7, H-2a), 2.60, (1H, dd, *J* 15.0, 6.5, H-2b) and 1.76-1.90 (4H, m, H-7, H-8) ppm. δ_C (151 MHz, $CDCl_3$): 172.5 (C-5), 169.5 (C-1), 143.5 (C-1'), 128.6 (C-3', C-5'), 127.3 (C-2', C-6'), 126.8 (C-4'), 51.5 (C-10), 46.6, 45.6 (C-6, C-9) 41.0 (C-4), 40.0 (C-2), 38.3 (C-3), 26.0 and 24.3 (C-7, C-8) ppm. ν_{max} (neat)/ cm^{-1}: 2970 (s), 2876 (s), 1733 (C=O, ester), 1619 (C=O, amide), 1436 (s), 1372 (m), 1341 (m), 1254 (m), 1227 (m), 1191 (m), 1153 (m), 1084 (m), 1049 (s), 858 (w), 880 (w), 763 (s) and 702 (s) cm^{-1}. HRMS (ESI^+) *m/z*: Found: 276.1587 ([M + H]+ $C_{16}H_{22}NO_3$; requires 276.1594).

2.5.2 Enantioenriched γ-lactams

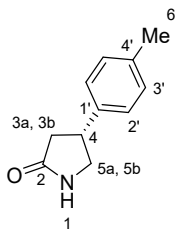
Note: Absolute stereochemistry of the lactam products were determined by comparison of the optical rotation data obtained for (*R*)-lactam **26** to previously-reported values (*vide infra*).

2.5.2.1 (*R*)-Phenibut lactam (**26**)



Prepared according to **Gen A2** using anhydride **1** (46.8 mg, 0.246 mmol) and purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to give the product as a white powder (35.7 mg, 90%, 69% *ee*), m.p. 75-76 °C (Lit.,[7] m.p. 73-75 °C). TLC (CH_2Cl_2/MeOH, 98:2): R_f = 0.42. A larger scale preparation using anhydride **1** (190.2 mg, 1.00 mmol) afforded the title product by the same method (148.3 mg, 92%, 70% *ee*) which was recrystallised from hot Hex/EtOAc to provide large, colourless plate crystals (100.6 mg, 62%, >99% *ee*) with $[\alpha]_D^{22}$ = -39.6 (c = 0.91, $CHCl_3$), (Lit.,[8] $[\alpha]_D^{25}$ = -39.4 (c = 0.90, $CHCl_3$) for 99% *ee* of the (*R*)-enantiomer). Spectroscopic data correlates well to that in the literature.[7] CSP-SFC analysis: Step 3 was employed with UV detection at 254 nm; R_T: 3.45 min (minor enantiomer) and 3.56 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 7.33-7.36 (2H, m, H-3'), 7.25-7.28 (3H, m, H-2', H-4'), 6.09 (1H, br s, H-4), 3.79 (1H, dd, *J* 9.4, 8.3, H-1a), 3.71 (1H, app. quin., H-2), 3.43 (1H, dd, *J* 9.4, 7.3, H-1b), 2.75 (1H, dd, *J* 17.0, 9.0, H-3a) and 2.52 (1H, dd, *J* 17.0, 8.9, H-3b) ppm. δ_C (100 MHz, $CDCl_3$): 177.7 (C-2), 142.1 (C-1'), 129.1(C-3'), 127.4 (C-4'), 126.9 (C-2'), 49.7 (C-5), 40.5 (C-4) and 38.1 (C-3) ppm. HRMS ($APCI^+$) *m/z*: Found: 162.0912 ($[M + H]^+$; $C_{10}H_{12}NO$ requires: 162.0913).

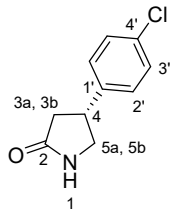
2.5.2.2 (*R*)-Tolibut lactam (**35**)



Prepared according to **Gen A2** using **S2** (50.2 mg, 0.246 mmol) and purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to give the product as a white powder (40.5 mg, 94%, 65% *ee*), m.p. 110-112 °C (Lit.,[9] m.p. 108-110 °C). TLC (EtOAc): R_f = 0.40. $[\alpha]_D^{22}$ = -9.6 (c = 0.15, $CHCl_3$), (Lit.,[9] $[\alpha]_D^{20}$ = -33.7 (c = 0.95, $CHCl_3$) for 99% *ee*). Spectroscopic data correlates well to that in the

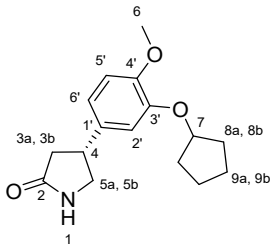
literature.[9] CSP-SFC analysis: Step 6 was employed with UV detection at 230 nm; R_T: 5.50 min (minor enantiomer) and 5.88 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 7.14 (4H, app. s, H-2', H-3'), 6.71 (1H, br. s, H-1), 3.77 (1H, dd, *J* 9.4, 8.3, H-5a), 3.61-3.70 (1H, m, H-4), 3.40 (1H, dd, *J* 9.4, 7.4, H-5b), 2.77 (1H, dd, *J* 16.9, 8.8, H-3a), 2.49 (1H, dd, *J* 16.9, 8.9) and 2.33 (3H, s, H-6) ppm. δ_C (100 MHz, $CDCl_3$): 177.9 (C-2), 139.0 (C-1'), 136.8 (C-4'), 129.5 (C-3'), 126.7 (C-2'), 49.8 (C-5), 40.0 (C-4), 38.2 (C-3) and 21.0 (C-6) ppm.

2.5.2.3 (*R*)-Baclofen lactam (**36**)



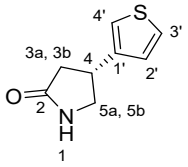
Prepared according to **GenA2** using **S3** (55.3 mg, 0.246 mmol) and purified by flash chromatography (EtOAc) to give the product as a white powder (46.2 mg, 96%, 64% *ee*), m.p. 110-112 °C (Lit.,[10] m.p. (from Hex/EtOAc) 108-110 °C). TLC (98:2 CH_2Cl_2/MeOH): R_f = 0.31. $[\alpha]_D^{22}$ = -16.5 (c = 0.15, $CHCl_3$), (Lit.,[7] $[\alpha]_D^{20}$ = -39.0 (c = 1.00, $CHCl_3$) for 99% *ee*). Product spectroscopic data correlated well to that in the literature.[7] CSP-SFC analysis: Step 4 was employed with UV detection at 254 nm; R_T: 3.47 min (major enantiomer) and 3.70 min (minor enantiomer). δ_H (600 MHz, $CDCl_3$): 7.30-7.32 (2H, m, H-3'), 7.17-7.20 (2H, app. d, H-2'), 6.14 (1H, br. s, H-1), 3.78 (1H, dd, *J* 9.5, 8.3, H-5a), 3.65-3.70 (1H, m, H-4), 3.38 (1H, dd, *J* 9.5, 7.1, H-5b), 2.74 (1H, dd, *J* 16.9, 9.0, H-3a) and 2.46 (1H, dd, *J* 16.9, 8.6, H-3b) ppm. δ_C (151 MHz, $CDCl_3$): 177.2 (C-2), 140.6 (C-1'), 133.0 (C-4'), 129.0 (C-3'), 128.1 (C-2'), 49.3 (C-5), 39.7 (C-4) and 37.7 (C-3) ppm.

2.5.2.4 (*R*)-Rolipram (**37**)



Prepared according to **Gen A2** using anhydride **S5** (74.9 mg, 0.246 mmol) and the crude residue purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to give the title product as an off-white crystalline powder (64.3 mg, 95%, 70% *ee*), m.p. 132-133°C (Lit.,[11] m.p. 131-133 °C). TLC (98:2 CH_2Cl_2/MeOH): R_f = 0.30. $[\alpha]_D^{22}$ = -12.1 (c = 0.15, MeOH), (Lit.,[7] $[\alpha]_D^{27}$ = -33.0 (c = 1.00, MeOH) for 99.3% ee). Product spectroscopic data correlated well to that in the literature.[12] CSP-SFC analysis: Step 3 was employed with UV detection at 254 nm; R_T: 4.01 min (minor enantiomer) and 4.22 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 6.83-6.84 (1H, m, H-5'), 6.76-6.79 (2H, m, H-2', H-6'), 6.06 (1H, br s, H-1), 4.74-4.79 (1H, m, H-7), 3.83 (3H, s, H-6), 3.75 (1H, dd, *J* 9.3, 8.2, H-5a), 3.38 (1H, dd, *J* 9.3, 7.4, H-5b), 2.71 (1H, dd, *J* 16.9, 8.8, H-3a), 2.47 (1H, dd, *J* 16.9, 8.9)1.78-1.97 (6H, m, H-8a, H-8b, H-9a) and 1.56-1.66 (2H, m, H-9b) ppm. δ_C (100 MHz, $CDCl_3$): 177.6 (C-2), 149.3 (C-4'), 148.0 (C-3'), 134.6 (C-1'), 118.9 (C-6'), 113.9 (C-2'), 112.3 (C-5'), 80.8 (C-7), 56.2 (C-6), 49.8 (C-5), 40.1 (C-4), 38.1 (C-3), 32.9 (C-8) and 24.1 (C-9) ppm.

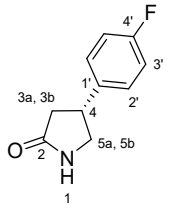
2.5.2.5 (*R*)-4-(Thiophen-3-yl)pyrrolidin-2-one (**38**)



Prepared according to **Gen A2** using anhydride **S6** (48.3 mg, 0.246 mmol) and the crude residue purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to give the title product as a white crystalline powder (37.4 mg, 91%, 65% *ee*), m.p. 86-88°C. TLC (98:2 CH_2Cl_2/MeOH): R_f = 0.28. $[\alpha]_D^{22}$ = -14.0 (c = 0.15, CHCl3). Product spectroscopic data correlated well to that in the literature.[12] CSP-SFC analysis: Step 3 was employed with UV detection at 254 nm; R_T: 3.35 min (major enantiomer) and 3.52 min (minor enantiomer). δ_H (400 MHz, $CDCl_3$): 7.32 (1H, dd, *J* 5.0, 2.9, H-3'), 7.02 (1H, dd, *J* 2.9, 1.3, H-2'), 6.99 (1H, dd, *J* 5.0, 1.3, H-4'), 6.58 (1H, br. s, H-1), 3.73-3.82 (2H, m, H-4, H-5a), 3.39-3.45 (1H, m, H-5b), 2.70-2.77 (1H, m, H-2a) and 2.44-2.54 (1H, m, H-2b) ppm.

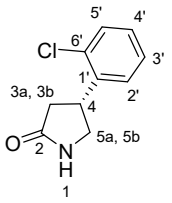
δ_C (100 MHz, $CDCl_3$): 177.8 (C-1), 142.7 (C-1'), 126.7 (C-3'), 126.2 (C-2'), 120.4 (C-4'), 49.2 (C-5), 37.9 (C-3) and 35.9 (C-4) ppm.

2.5.2.6 (*R*)-Fluoribut lactam (**39**)



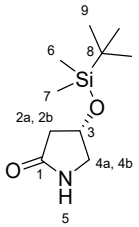
Prepared according to **Gen A2** using **S4** (51.2 mg, 0.246 mmol) and purified by flash column chromatography (4:1 EtOAc/CH_2Cl_2) to give the product as a white, crystalline powder (39.5 mg, 90%, 66% *ee*), m.p. 97-99 °C (Lit.,[13] m.p. 98-99 °C). TLC (1:1 EtOAc/CH_2Cl_2): R_f = 0.15. $[\alpha]_D^{22}$ = -7.8 (c = 0.15, MeOH), (Lit.,[14] $[\alpha]_D^{25}$ = -26.2 (c = 1.00, MeOH) for 96% *ee*). Product spectroscopic data correlated well to that in the literature.[13] CSP-SFC analysis: Step 1 was employed with UV detection at 254 nm; R_T: 3.01 min (major enantiomer) and 3.14 min (minor enantiomer). δ_H (400 MHz, $CDCl_3$): 7.18-7.23 (2H, m, H-3'), 6.99-7.05 (2H, m, H-2'), 6.70 (1H, br s, H-1), 3.77 (1H, dd, *J* 9.3, 8.3, H-5a), 6.62-3.71 (1H, m, H-4), 3.37 (1H, dd, *J* 9.3, 7.2, H-5b), 2.72 (1H, dd, *J* 16.9, 8.9, H-3a) and 2.44 (1H, dd, *J* 16.9, 8.7, H-3b) ppm. δ_F (376 MHz, $CDCl_3$): -115.53 (s) ppm. δ_C (100 MHz, $CDCl_3$): 177.8 (C-2), 162.0 (d, $^1J_{C\text{-}F}$ 245.5, C-4'), 138.0 (d, $^4J_{C\text{-}F}$ 3.1, C-1'), 128.4 (d, $^2J_{C\text{-}F}$ 8.0, C-3'), 115.8 (d, $^3J_{C\text{-}F}$ 21.2, C-2'), 49.8 (C-5), 39.8 (C-4) and 38.2 (C-3) ppm.

2.5.2.7 (*R*)-4-(2-Chlorophenyl)pyrrolidine-2-one (**40**)



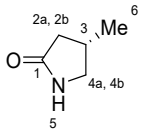
Prepared according to **Gen A2** using **S7** (55.3 mg, 0.246 mmol) and purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to give the product as a white, crystalline powder (45.2 mg, 94%, 65% *ee*), m.p. 112-114 °C (Lit.,[9] m.p. 112-115 °C). TLC (EtOAc): R_f = 0.49. $[\alpha]_D^{22}$ = -9.4 (c = 0.10, $CHCl_3$). Product spectroscopic data correlated well to that in the literature.[9] CSP-SFC analysis: Step 6 was employed with UV detection at 254 nm; R_T: 6.77 min (minor enantiomer) and 7.13 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 7.39 (1H, dd, *J* 7.8, 1.4, H-5'), 7.33 (1H, dd, *J* 7.7, 1.6, H-2'), 7.25-7.29 (1H, m, H-4'), 7.18-7.23 (1H, m, H-3'), 6.45 (1H, br. s, H-1), 4.12-4.20 (1H, m, H-4), 3.86 (1H, dd, *J* 9.7, 8.2, H-5a), 3.42 (1H, dd, *J* 9.7, 6.0, H-5b), 2.79 (1H, dd, *J* 17.0, 9.1, H-2a) and 2.53 (1H, dd, *J* 17.0, 7.3, H-2b) ppm. δ_C (101 MHz, $CDCl_3$): 177.5 (C-2), 139.3 (C-1'), 133.8 (C-6'), 130.0 (C-5'), 128.4 (C-4'), 127.4 (C-3'), 127.2 (C-2'), 48.3 (C-5), 36.68 (C-4) and 36.66 (C-3) ppm.

2.5.2.8 (*S*)-4-((*tert*-Butyldimethylsilyl)oxy)pyrrolidin-2-one (**41**)



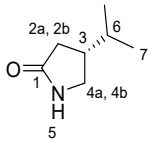
Prepared according to **Gen A2** using **S8** (60.0 mg, 0.246 mmol), to give a crude residue, which was purified by flash column chromatography (1:1 Hex/EtOAc) to give the title product as a white powder (42.4 mg, 80%, 56% *ee*), m.p. 78-80 °C (Lit.,[15] m.p. (from PE/EtOAc) 84-86 °C). TLC (1:1 Hex/EtOAc, Ninhydrin): R_f = 0.19. $[\alpha]_D^{22}$ = -2.4 (c = 0.15, $CHCl_3$), (Lit.,[16] $[\alpha]_D^{22}$ = -7.4 (c = 1.30, $CHCl_3$)). Product spectroscopic data correlates well to that in the literature.[15] CSP-SFC analysis: Step 3 was employed with UV detection at 212 nm; R_T: 2.61 min (minor enantiomer) and 2.73 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 5.98 (1H, br s, H-4), 4.53-4.58 (1H, m, H-3), 3.58 (1H, dd, *J* 10.0, 6.0, H-4a), 3.24 (1H, dd, *J* 10.0, 3.4, H-4b), 2.54 (1H, dd, *J* 17.0, 6.8, H-2a) and 2.26 (1H, dd, *J* 17.0, 4.2, H-2b) ppm. δ_C (100 MHz, $CDCl_3$): 176.2 (C-1), 68.0 (C-3), 51.6 (C-4), 40.5 (C-2), 25.8 (C-9), 18.0 (C-8), -4.7 (C-6) and -4.8 (C-7) ppm.

2.5.2.9 (*S*)-4-Methylpyrrolidin-2-one (**42**)



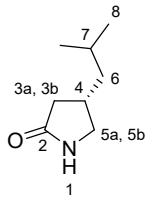
Prepared according to **Gen A2** using **S9** (31.5 mg, 0.246 mmol) and the crude residue purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to give the product as a white powder (22.2 mg, 91%, 70% *ee*), m.p. 54-55°C (Lit.,[17] m.p. (from Hex) 53-55 °C). TLC (95:5 CH_2Cl_2/MeOH, $KMnO_4$): R_f = 0.50. $[\alpha]_D^{22}$ = -4.0 (c = 0.10, $CHCl_3$), (Lit.,[18] $[\alpha]_D^{25}$ = -20.3 (c = 1.20, $CHCl_3$) for 99% *ee*). Product spectroscopic data correlated well to that in the literature.[19] CSP-SFC analysis: Step 5 was employed with UV detection at 212 nm; R_T: 5.26 min (minor enantiomer) and 5.43 min (major enantiomer). δ_H (400 MHz, $CDCl_3$): 6.25 (1H, br s, H-5), 3.53 (1H, dd, *J* 9.4, 7.6, H-4a), 2.99 (1H, dd, *J* 9.4, 6.1), 2.51-2.64 (1H, m, H-3), 2.48 (1H, dd, *J* 16.5, 8.5, H-2a), 1.97 (1H, dd, *J* 16.5, 7.1, H-2b) and 1.16 (3H, d, *J* 6.7, H-6) ppm. δ_C (100 MHz, $CDCl_3$): 178.6 (C-1), 49.6 (C-4), 38.5 (C-2), 29.6 (C-3) and 19.7 (C-6) ppm.

2.5.2.10 (*R*)-4-Isopropylpyrrolidin-2-one (**43**)



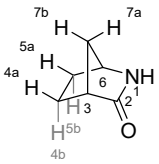
Prepared according to **Gen A2** using **S10** (38.4 mg, 0.246 mmol) and the crude residue purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to give the product as a white powder (29.0 mg, 92%, 70% *ee*), m.p. 90-92°C (Lit.,[20] m.p. 96-97 °C). TLC (97:3 CH_2Cl_2/MeOH, Ninhydrin): R_f = 0.25. $[\alpha]_D^{22}$ = +1.8 (c = 0.10, $CHCl_3$), (Lit.,[20] $[\alpha]_D^{25}$ = +16.9 (c = 1.05, $CHCl_3$) for 99% *ee*). Product spectroscopic data correlated well to that in the literature.[20] CSP-SFC analysis: Step 5 was employed with UV detection at 212 nm; R_T: 5.12 min (minor enantiomer) and 5.30 min (major enantiomer). δ_H (600 MHz, $CDCl_3$): 5.89 (1H br. s, H-5), 3.46 (1H, dd, *J* 9.3, 8.3, H-4a), 3.09 (1H, dd, *J* 9.2, 8.3, H-4b), 2.39 (1H, dd, *J* 16.7, 8.7, H-2a), 2.17-2.26 (1H, m, H-3), 2.07 (1H, dd, *J* 16.7, 9.6, H-2b), 1.56-1.64 (1H, m, H-6), 0.93 (3H, d, *J* 6.7, H-7) and 0.90 (3H, d, *J* 6.6, H-8) ppm. δ_C (151 MHz, $CDCl_3$): 178.3 (C-1), 46.2 (C-4), 42.3 (C-6), 35.2 (C-2), 32.5 (C-3), 20.6 (C-7) and 20.0 (C-8) ppm.

2.5.2.11 (*S*)-Pregabalin lactam (**44**)



Prepared according to **Gen A2** using **S11** (41.8 mg, 0.246 mmol) and purified by flash chromatography (Et_2O) to give the product as a colourless oil (32.6 mg, 94%, 64% *ee*). TLC (95:5 CH_2Cl_2/MeOH): R_f = 0.8. $[\alpha]_D^{22}$ = -0.81 (c = 0.16, $CHCl_3$), (Lit.,[21] $[\alpha]_D^{20}$ = -2.42 (c = 1.00, $CHCl_3$) for 99% *ee*). Product spectroscopic data correlated well to that in the literature.[21] CSP-SFC analysis: Step 6 was employed with UV detection at 212 nm; R_T: 1.88 min (minor enantiomer) and 2.00 min (major enantiomer). δ_H (600 MHz, $CDCl_3$): 6.28 (1H, br s, H-1), 3.47 (1H, dd, *J* 9.3, 7.9, H-5a), 2.98 (1H, dd, *J* 9.3, 7.1, H-5b), 2.53 (1H, app. sept., H-4), 2.40 (1H, dd, *J* 16.7, 8.6, H-3a), 1.97 (1H, dd, *J* 16.7, 8.5, H-3b), 1.52-1.61 (1H, m, H-7), 1.30-1.37 (2H, m, H-6) and 0.89 (6H, app. t, *J* 6.5, H-8a, H-8b) ppm. δ_C (151 MHz, $CDCl_3$): 178.5 (C-2), 48.3 (C-5), 43.9 (C-6), 37.1 (C-3), 33.0 (C-4), 26.2 (C-7), 22.7 (C-8a) and 22.5 (C-8b) ppm. HRMS (ESI^+) *m/z*: Found: 164.1047 ($[M + Na]^+$; $C_8H_{15}NNaO$ requires: 164.1046).

2.5.2.12 (1*S*, 4*R*)-2-Azabicyclo[2.2.1]heptan-3-one (**45**)



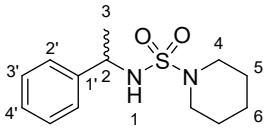
Prepared according to **Gen A2** using **S12** (34.5 mg, 0.246 mmol) to give a crude residue which was purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to give title compound as a white powder (21.8 mg, 80%, 72% *ee*), m.p. 79-81 °C (Lit.,[22] m.p. (from ^{i}PrOH) 78-81 °C. TLC (98:2 CH_2Cl_2/MeOH, Ninhydrin): R_f = 0.26. $[\alpha]_D^{22}$ = -48.6 (c = 0.15, $CHCl_3$), (Lit.,[23] $[\alpha]_D^{22}$ = -160.0 (c =

1.00, $CHCl_3$)). Product spectroscopic data correlated well to that in the literature.[22] CSP-SFC analysis: Step 2 was employed with UV detection at 212 nm; R_T: 2.67 min (major enantiomer) and 2.78 min (minor enantiomer). δ_H (400 MHz, $CDCl_3$): 6.02 (1H, br s, H-2), 3.86-3.89 (1H, m, H-3), 2.71-2.74 (1H, m, H-6), 1.77-1.93 (3H, m, H-4b, H-5a, H-7a), 1.54-1.66 (2H, m, H-4a, H-5b) and 1.41 (1H, dt, *J* 9.3, 1.4, H-7b) ppm. δ_C (100 MHz, $CDCl_3$): 181.2 (C-1), 55.4 (C-3), 45.1 (C-6), 41.3 (C-7), 30.2 (C-4) and 23.7 (C-5) ppm.

2.6 Compounds used in mechanistic studies

2.6.1 Racemic sulfamide hydrogen bond donor

2.6.1.1 *N*-(1-Phenylethyl)piperidine-1-sulfonamide (**S19**)



To an oven-dried 25 mL RBF containing a magnetic stirrer bar and piperidine-1-sulfonyl chloride (458 µL, 3.27 mmol), under inert (Ar) atmosphere, anhydrous CH_2Cl_2 (10 mL) was added by syringe and cooled to 0 °C. A solution of (±)-1-phenylethanamine (500 µL, 3.91 mmol) and NEt_3 (455 µL, 3.27 mmol) in CH_2Cl_2 (8 mL, 0.18 M) was added dropwise and the resulting solution warmed to room temperature and stirred for 24 h. NaOH (10 mL, 1 M) was added and the organic layer removed, washed successively with 1 M HCl and brine (2 x 10 mL each) and dried over Na_2SO_4. The mixture was filtered and the filtrate concentrated *in vacuo* to give a brown oil, which was purified by flash chromatography (EtOAc). Product containing fractions were combined and solvent removed *in vacuo* to give a pale yellow oil which crystallised upon standing. Trituration with hexanes afforded the product as a white, crystalline solid after filtration (650 mg, 74%), m.p. 54-56 °C (from EtOAc). TLC (10% MeOH in EtOAc): R_f = 0.8. δ_H (400 MHz, $CDCl_3$): 7.27-7.37 (5H, m, H-2',H-3', H-4'), 4.51 (1H, app. quin, H-2), 4.31 (1H, app. d, H-1), 3.00 (4H, app. t, H-4), 1.52 (3H, d, *J* 6.8, H-3) and 1.35-1.48 (6H, m, H-5, H-6) ppm. δ_C (100 MHz, $CDCl_3$): 143.3 (C-1'), 128.7 (C-3'), 127.6 (C-4'), 126.3 (C-2'), 53.8 (C-2), 46.6 (C-4), 25.1 (C-5), 24.0 (C-3) and 23.6 (C-6) ppm. ν_{max} (neat)/ cm^{-1}: 3262 (s, N-H st.), 2975 (m), 2932 (m), 2847 (m), 1455 (s), 1430 (m), 1320 (s, S=O), 1309 (s, S=O), 1143 (s), 1106 (s), 1086 (s), 1066 (s), 928 (s), 768 (s), and 712 (s) cm^{-1}. HRMS (ESI^+) *m/z*: Found: 291.1140 ($[M + Na]^+$ $C_{13}H_{20}N_2NaO_2S$; requires: 291.1138).

2.7 Computational methods

All calculations reported in the manuscript were carried out using standard DFT methods as implemented in Gaussian 16.[24] All initial explorations of minima and transition structures were performed at the wb97xd[25]/def2-TZVP[26] level of theory in a solvent model SMD (chloroform) at 298 K and 223 K in order to mimic experimental conditions. All structures were confirmed to be minima (no imaginary frequency).

The characteristics of the intermolecular interactions were analysed by means of the Atoms in Molecules (QTAIM) theory. [4] For this purpose we have located the most relevant bond critical points (BCP), and evaluated the electron density at each of them, by using the QTAIMAll program.[27] Coordinates and energetic paths for all SMD (chloroform) structures are included in this supporting information (Section 7).

3. Results and Discussion

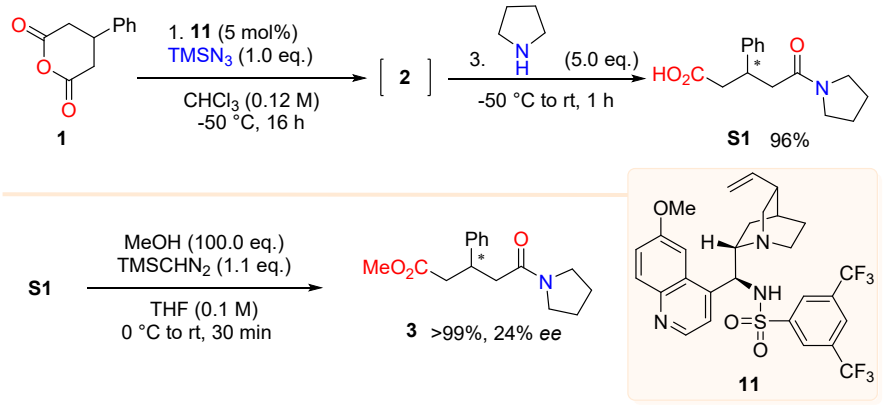
3.1. Development of suitable conditions for initial UPC analysis of enantioenriched pyrrolidinamides

3.1.1. Obviating reversibility of the reaction: Amidation with pyrrolidine

In order to evaluate the 'true' enantioselectivity of the desymmetrisation reaction facilitated by bifunctional catalysts, and mitigate against confounding factors that may alter the enantioselectivity on workup, the reversibility of the reaction upon warming observed here and in our previous work had to be first overcome. To this end, the ring opening of anhydride **1** with $TMSN_3$ in the presence of alkaloid sulfonamide **11** to provide the intermediate acyl azide **2** was examined. Alcoholysis of the silyl ester group was unsuccessful at low temperature, and it was decided that the most robust solution was to instead subject the acyl azide moiety of **2** to amidation with excess pyrrolidine. The addition of pyrrolidine was observed by NMR spectroscopy to displace azide fully at -50 °C within 1 h (Scheme S2).

The resulting amido acid **S1** was isolated by back-extraction in excellent yield and purity and subsequent methylation of the carboxylic acid moiety was affected by treatment of **S1** with $TMSCHN_2$ to yield scalemic esters **3** in quantitative yields. As the steps of

this protocol that proceed desymmetrisation were not expected to influence the enantioselectivity of the overall process, the amido esters **3** could be used as a proxy for the *ee* observed during desymmetrisation. Separation of the enantiomeric esters **3** was achieved by analytical CSP-SFC, demonstrating reproducibly that the acyl azide **2** was formed in 24% *ee* when the reaction was catalysed with sulfonamide **11**.

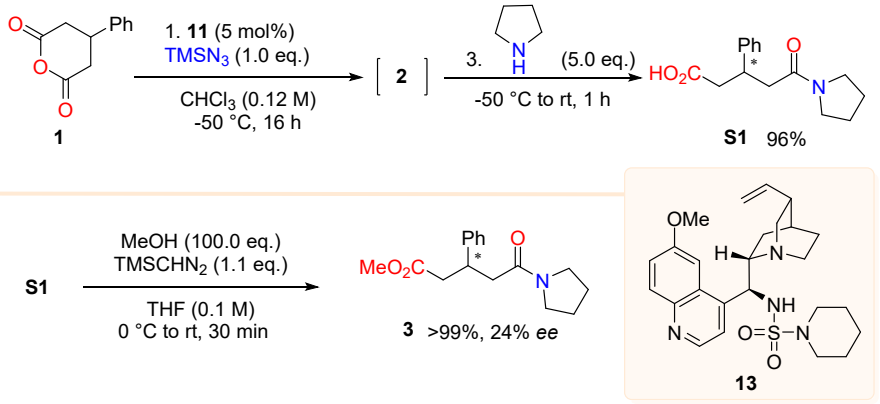


Scheme S2: Amidation of acyl azide intermediate **2** and methylation of the resulting amido acid **S1**.

3.1.2. Reaction optimisation: Solvent, temperature and concentration

Piperidine sulfamide **13** was examined in the desymmetrisation of anhydride **1** with $TMSN_3$ in order to determine the effect of solvent polarity, temperature and concentration on both conversion and enantioselectivity (Table S1). CH_2Cl_2 provided acyl azide **2** more efficiently than $CHCl_3$, but proved inferior with regards to enantioselectivity (entries 1 and 2). MeCN furnished almost racemic product (entry 3, 4% *ee*) and with poorer conversion to **2**. The use of ethereal solvents improved the conversion to acyl azide intermediate **2**, but proceeded with significantly diminished enantioselectivities (entry 4 and 5). Further decrease of the reaction temperature to -78°C in THF proffered a 9% increase in enantioselectivity, but did not outcompete selectivities observed in $CHCl_3$ at -50 °C. EtOAc was observed to be marginally more selective than all other solvent substitutions (entry 6, 40% *ee*) at the same temperature, but also failed to yield products with higher enantioselectivities than $CHCl_3$.

Table S1: Optimisation of reaction conditions for the enantioselective desymmetrisation of **167** with $TMSN_3$.



Entry	Solvent	Concentration (M)	T (°C)	t (h)	Yield **201** (%)[a]	*ee* **384** (%)[b]
1	$CHCl_3$	0.12	-50	16	89	55
2	CH_2Cl_2	0.12	-50	16	93	38
3	MeCN	0.12	-35	16	82	4
4	MTBE	0.12	-50	16	97	32
5[c]	THF	0.12	-50	16	97 (74)	36 (45)
6	EtOAc	0.12	-50	16	90	40
7	$CHCl_3$	0.50	-50	3	90	44
8[d]	$CHCl_3$	0.01	-50	48	90	35
9[e]	$CHCl_3$	0.12	-25	1.5	90	47
10[e]	$CHCl_3$	0.12	0	0.5	90	40
11[f]	$CHCl_3$	0.12	-50	16	98	55

[a] Yield determined by ^1H NMR spectroscopy relative to 4-iodoanisole as internal standard. [b] Determined by CSP-SFC. [c] Values in parentheses refer to results obtained when the reaction is performed at -78 °C. [d] Extended reaction time (3 h) allotted in the formation of **S1**. [e] Acyl azide **2** was cooled to -50 °C prior to the addition of pyrrolidine. [f] Reaction performed in the presence of BzOH (5 mol% loading).

The exact explanation for its superior performance as a solvent is unclear at this time, but based on a recent report examining the properties of liquid $CHCl_3$,[28] it is speculated that this observation can be attributed to the functional role of $CHCl_3$ as a non-nucleophilic polar, protic solvent which is anticipated to stabilise charged intermediates. $CHCl_3$ was subsequently chosen as the optimal reaction solvent for the transformation and examined at different concentrations and temperatures in an attempt to improve *ee* as far as possible.

Increasing the reaction concentration to 0.5 M resulted in shorter reaction times, but negatively impacted selectivity (entry 7, 44% *ee*). Interestingly, diluting the reaction to 0.01 M did not ameliorate enantioselectivity, but nonetheless provided the desymmetrisation product in comparable yields within 48 h (entry 8, 35% *ee*). Higher reaction temperatures reduced the overall reaction times, but resulted in lower observed enantioselectivities, as expected (entries 9 and 10). Lastly, the addition of BzOH (5 mol%) as a co-catalyst did not affect the rate of the reaction or enantioselectivity, but provided marginally enhanced conversions relative to the acid-free reaction with concurrent formation of 5 mol% TMSOBz in the initial stages of the reaction, implicating the required generation of aminium azide **13a** (see Figure 4).

3.2. Mechanistic investigation involving compartmentalisation of catalyst functionality

3.2.1. Racemic model of bifunctional catalysis by *Cinchona* alkaloid sulfamides

In an attempt to ascertain which components of bifunctional sulfamides (such as **13**) are involved in catalysis, a series of investigations involving 6-methoxyquinoline (**S23**), DABCO and a model racemic sulfamide **S19** were performed (Figure S1). This compartmentalised approach was chosen in order to test each component of the bifunctional sulfamides in isolation to gain mechanistic insight and inform rational catalyst design.

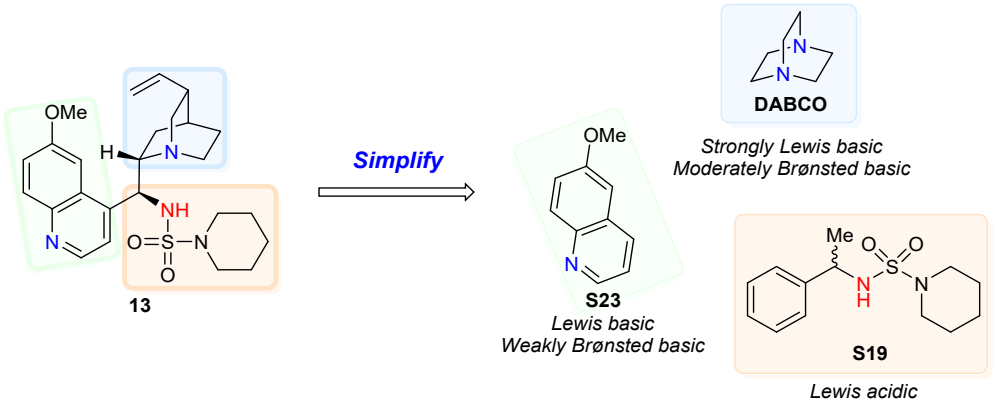
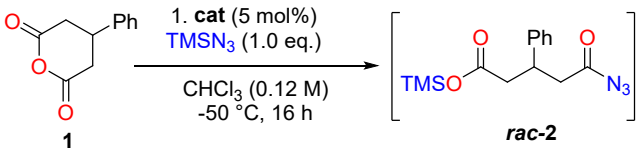


Figure S2: Modelling of the functional components of sulfamide **13** .

As both DABCO and quinoline **S23** were commercially available, after facile preparation of **S19** (Section 2.6.2.1) the components required to emulate catalysis of the desymmetrisation reaction between anhydride **1** and $TMSN_3$ were examined in a modular fashion (Table S2). Relative to chiral piperidine sulfamide **13**, which provided acyl azide **2** in 90% yield (entry 1), DABCO performed similarly well (entry 2, 86% yield). Quinoline **S23** catalysed the reaction to an even greater extent than stronger Brønsted bases after the allotted reaction time (97% yield, entry 3), but was a less efficient catalyst in the early stages of the reaction relative (44% conversion at 0.5 h) than either DABCO or chiral sulfamide **13**. Interestingly, the sulfamide hydrogen-bond donor **S19** did not catalyse the reaction in isolation, but did marginally enhance the efficiency of DABCO as a catalyst (88% yield, entry 5). From an enantioselectivity standpoint, although the difference in catalytic efficiencies observed between DABCO and quinoline **S23** was encouraging, it was conceivable that the quinoline moiety –situated far from stereochemical information in chiral sulfamide catalysts– could negatively impact *ee* by competing with catalysis at the quinuclidine centre.

Table S2: Mechanistic investigation of the organocatalytic desymmetrisation of anhydride **167** with $TMSN_3$.

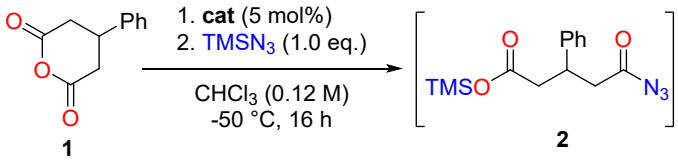


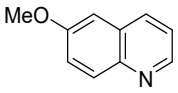
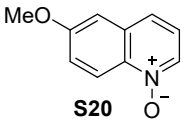
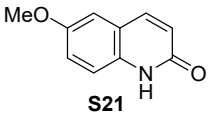
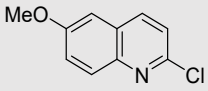
Entry	**cat.**	Conversion (t = 0.5 h, %)	Yield azide ***rac*-2**(%)[a]
1	**13**	80	90
2	DABCO	78	86
3	**S19**	44	97
4	**S20**	0	0
5	DABCO/**S20**	81	88

[a] Yield determined by ^{1}H NMR spectroscopy relative to 4-iodoanisole as internal standard.

Given this observation, it was anticipated that the attenuation of the Brønsted base activity at the quinoline nitrogen in the model system could be achieved through the installation of a deactivating group adjacent to the Brønsted base. If the catalytic activity of the quinoline in the model system could be suppressed by such a modification, then by translation of the same rationale to chiral systems, improvement of the observed selectivities on alkaloid-derived sulfamides (such as **13**) would be expected. In order to test this hypothesis, the quinoline derivatives **S20-S22** were first prepared from **S23** *via* known methods[29–31] and their ability to promote the reaction of **1** with $TMSN_3$ was evaluated under the standard reaction conditions (Table S3).

Table S3: Catalyst screen: 6-Methoxyquinoline derivatives.



Entry	cat.	$pK_{a(H)}$ (H_2O, 25 °C)	Yield azide **201** (%)[a]
1	 **S23**	5.0	97
2	 **S20**	3.8	9
3	 **S21**	14.5	<5
4	 **S22**	0.6[b]	0[c]

[a] Determined by ^{1}H NMR spectroscopy using 4-iodoanisole as internal standard. [b] pK_a calculated using Marvin (ChemAxon). [c] No further reaction observed at t = 96 h, or upon warming to 0 °C.

Relative to the unsubstituted quinoline **S23** (97% yield, entry 1), although species such as **S20** and **S21** are known to be powerful Lewis base catalysts of a variety of transformations involving organosilicon reagents, almost complete diminution of catalyst activity was observed (entry 2 and 3). Pleasingly, absence of catalytic activity accompanied the installation of a chlorine atom at the 2-position of the quinoline (0% yield, entry 4), illustrating that complete suppression of catalytic activity is possible in the model system under the proposed hypothesis.

With the above results in mind, translation of the same concept to chiral sulfamide catalysts was next approached. Following the preparation of C-2'-modified alkaloids **28-31** and their evaluation as promoters of enantioselective desymmetrisation of anhydride **1** with $TMSN_3$ (see Table 2), 2'-modified alkaloids were found to be superior to with regards to both conversion and enantioselectivity than quinine and cinchonidine-derived sulfamides (**13** and **27**, respectively) under the same conditions. Notably, no significant difference in enantioselectivity was observed between C2'-phenyl and C2'-chloro derivatives, illustrating that the enhanced selectivities are owing primarily to electronic deactivation of the quinoline nitrogen and cannot be readily attributed to additional steric interactions in the TS.

3.3. NMR spectroscopic- and DFT studies of *Cinchona* alkaloid sulfamides: general summary and catalytic cycle

As is the case in related studies involving sulfonamide-containing alkaloids,[33] sulfamide **13** was found to exist as a pair of two main rotamers in a 68:32 ratio in $CDCl_3$ at 25 °C; the presence of a strong intramolecular hydrogen bond between the quinuclidine nitrogen and the sulfamide donor conformationally 'locks' this portion of the molecule. The two forms, **13-I** and **13-II**, found to interconvert in solution by rotation about the C4'-C9 bond axis (highlighted in red, Figure S3), were investigated *via* NMR spectroscopy in $CDCl_3$.

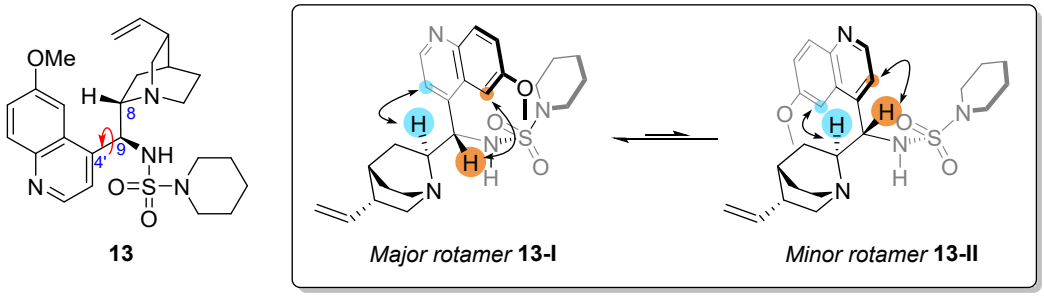


Figure S3: Major and minor rotamers of piperidine sulfamide **13**, as observed by ^{1}H NMR spectroscopic analysis in $CDCl_3$. Double-ended curly arrows denote NOE contacts.

In all substitution patterns examined in this study, *Cinchona* alkaloid-derived sulfamides such as **13** show a strong preference for an *anti*- relationship between H_8 and H_9, with strong dipolar coupling observed in both rotamers ($^3J_{(H8\text{-}H9)}$ = 10.7-11.9 Hz). The interconversion between states can be directly verified by a typical 2D NOESY experiment, or more recently by 1D-selective NOE experiments,[34] by the observation of cross-peaks between the two species in exchange (Figure S4).

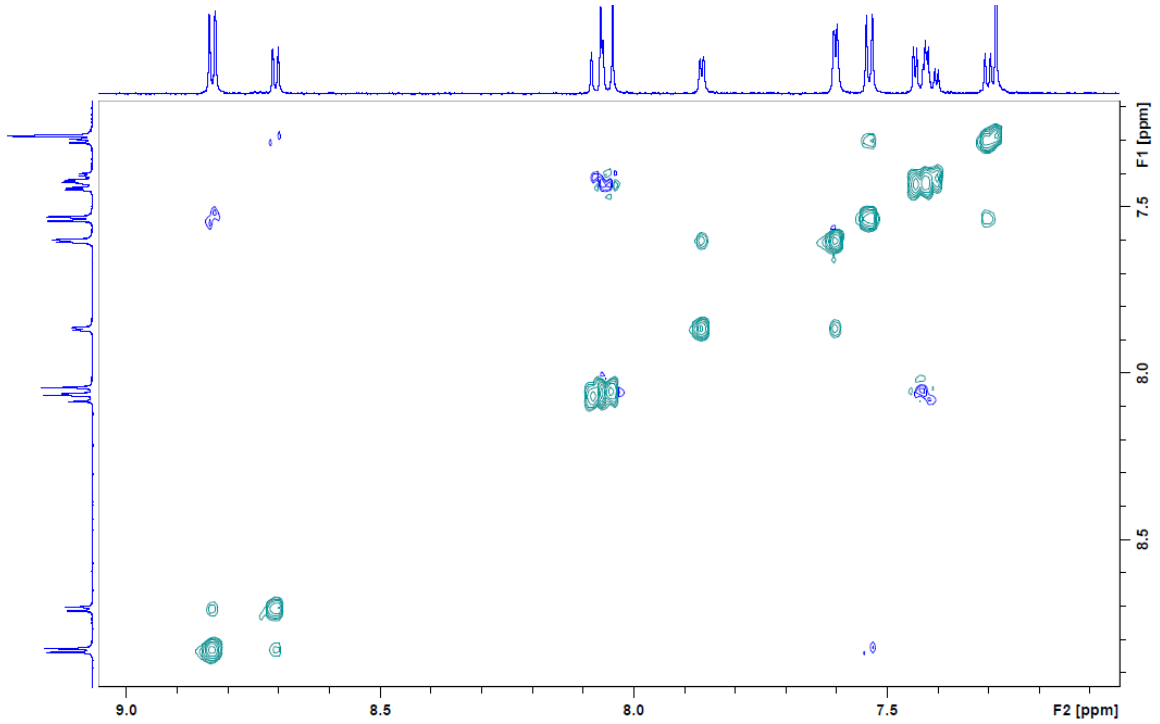


Figure S4: Extracted ^{1}H-^{1}H NOESY illustrating NOE correlations (blue) and EXSY cross-peaks (green) between rotameric species **13-I** and **13-II**.

No substantial differences in the population of each rotameric state were observed between **13** and other alkaloid sulfamides in $CDCl_3$. Furthermore, no meaningful correlation could be made between rotamer populations and enantioselectivity. Interestingly, disruption of the intramolecular hydrogen bond, which can be achieved by alkylation or acylation of the sulfamide HBD, results in the observation of conformer **13-II** only. By contrast, when observed in solution, protonation with an excess of organic acid (AcOH or BzOH) or substitution of $CDCl_3$ for more polar NMR solvents (CD_3OD or DMSO-d_6) favours conformation **13-I** while CD_3COOD favours **13-I** exclusively. Previous solution-phase studies have also found that the addition of polar, protic additives to native *Cinchona* alkaloids influenced conformation in $CDCl_3$.[35,36]

Following conformational analysis of sulfamide **13** at room temperature, we were intrigued by the possibility of determining the active conformation of the catalyst *in situ* in order to influence future catalyst design. Unfortunately, upon cooling a solution of sulfamide **13** in $CDCl_3$ to -20 °C, no significant change in the conformation or occupation of rotameric states of sulfamide **13** occurred (Figure S5), but the appearance of a broad singlet corresponding to the sulfamide NH could be observed at -20 °C with δ_H = 5.26 ppm.

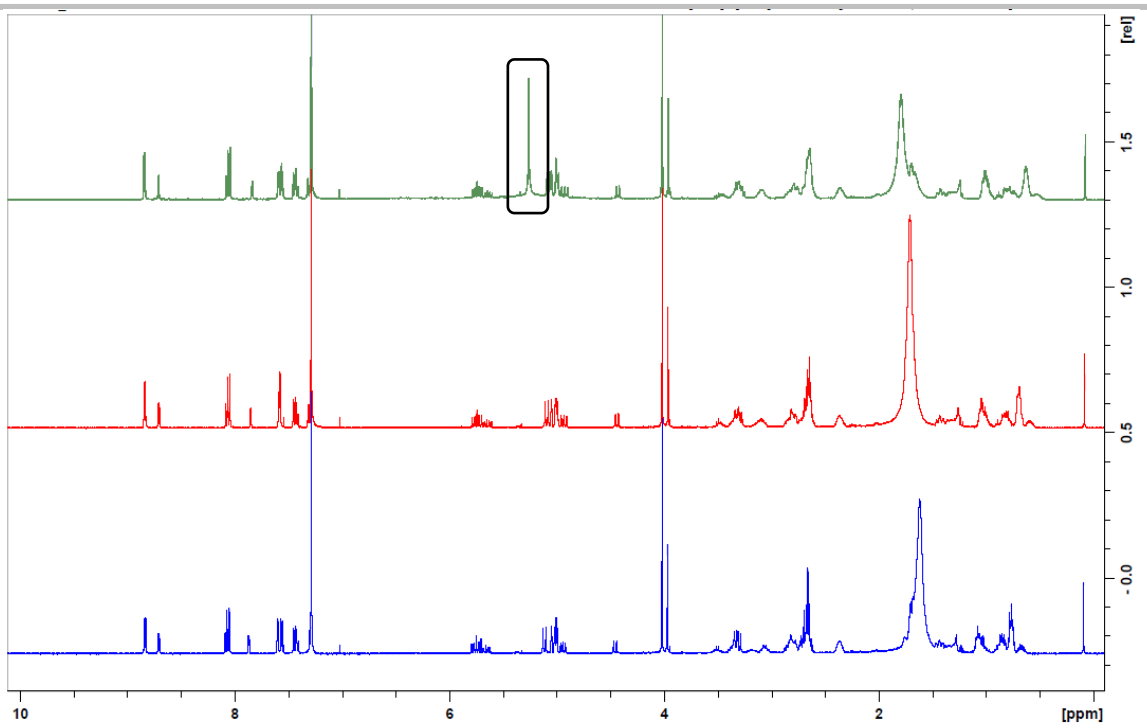


Figure S5: Variable-temperature ^{1}H NMR of catalyst **13** in $CDCl_3$ at 25 °C (bottom), 0 °C (middle) and -20 °C (top).

A DFT conformational analysis exploring the low-energy chemical space associated with **13** was performed in order to corroborate the above observations *in silico*. Two predominant conformers differing by the rotation of the C9-C4' bond were identified (Figure S6). The Boltzmann population ratio (66:34) predicted by the calculation in $CHCl_3$ is in good agreement with those obtained from ^{1}H NMR spectroscopic analysis. In addition, a repeat of the calculations at 223 K yielded a very similar population ratio of 61:39.

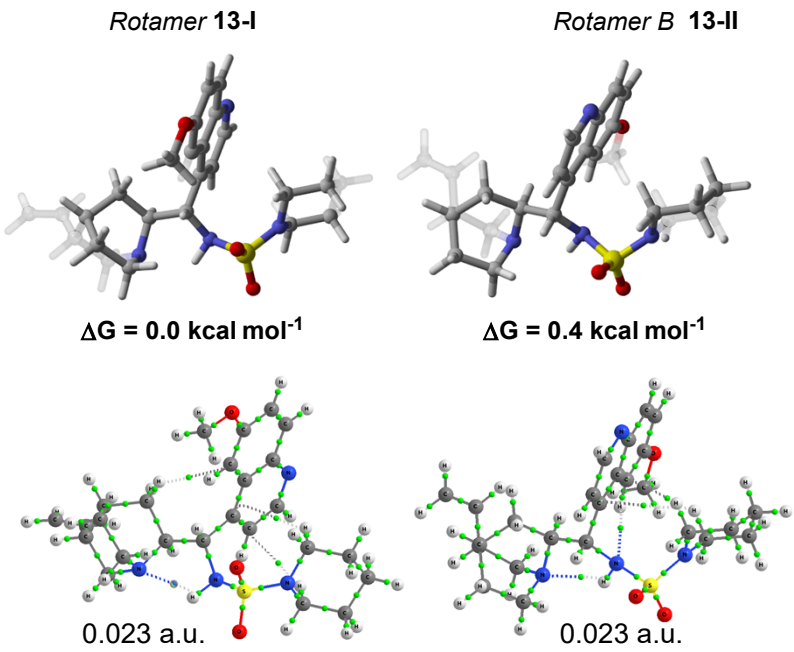


Figure S6. DFT calculations: structures, relative stabilities and QTAIM analysis of the major rotamers of catalyst **13**

A characterisation of the different intramolecular non-covalent interactions was also performed by means of the Quantum Theory of Atoms in Molecules (QTAIM) methodology (Figure S6). An intramolecular hydrogen-bond between the quinuclidine *N*-atom and the sulfamide unit is a discernible rigidifying feature of both conformations. The other interactions identified appear to be weak in nature.

It occurred to us that the true structure of the active catalytic species may be different from the free base sulfamide **13** when the catalyst is observed in the presence of the anhydride substrate and organosilyl reagent. Although no changes in catalyst resonances were observed in $CDCl_3$ in the presence of a stoichiometric amount of anhydride **1**, sulfamide **13** catalysed the rapid hydrolysis of $TMSN_3$ to HN_3 and silanol (TMSOH) in the presence of adventitious water at room temperature. This process was accompanied by concurrent dimerisation of TMSOH to TMS_2O. Notably, this behaviour was not observed when sulfamide **13** was substituted for bifunctional urea **9**, even upon addition of H_2O to the solution. This observation suggests that a catalyst functionality other than Brønsted base activity is important in this process. Silanol dimerisation has been noted previously in the context of aldehyde cyanosilylation with TMSCN when catalysed by disulfonimide Lewis acid catalysts.[37] Separately, the production of TMSOH and TMS_2O from $TMSN_3$ in the presence of a *Cinchona* alkaloid has also been noted by Aléman and co-workers.[38]

Although it could be postulated that one rotameric form of *Cinchona* alkaloid-derived sulfamides could be contributing negatively to stereoselection, variable temperature-NMR spectroscopy of piperidine sulfamide **13** revealed temperature-dependent convergence of rotamer populations. By performing the reaction in basified, anhydrous $CDCl_3$ as the reaction solvent, the reaction could be initiated under standard conditions at -50 °C by the addition of $TMSN_3$. Immediately, an aliquot of the resulting reaction mixture was removed and transferred to a pre-cooled Young's tube under inert atmosphere for NMR spectroscopic analysis at low temperature. Following this, we were surprised to observe a substantial shift in rotamer populations and catalyst ^{1}H NMR resonances favouring major rotamer **13-I** *in situ* (94:6 major/minor) relative to the free-base rotamer distribution (68:32 major/minor) at -20 °C (Figure S7) under otherwise identical conditions.

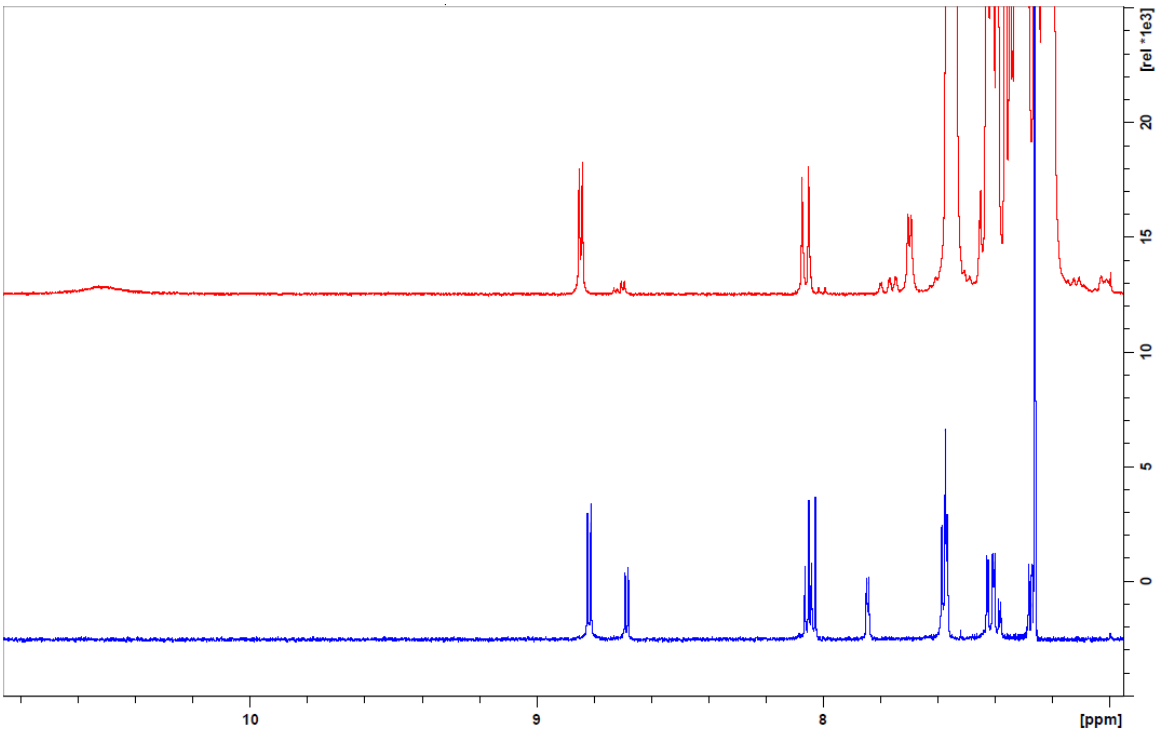


Figure S7: Extracted variable-temperature ^{1}H NMR spectra (aromatic region) of sulfamide catalyst **13** (blue) and species observed *in situ* (red) at -20 °C.

Although the isolated catalyst does not display this temperature-dependent behaviour as the free base form, the monoprotic acetate salt of **13** exhibited similar behaviour to that observed *in situ* (Figure S8). Attempts to isolate the analogous hydrogen azide salt by several methods were unsuccessful, though this can be adequately rationalised in the context of similar studies;[32] poor room temperature association has been observed in other amine complexes with HN_3, resulting in its dissociation on irreversible loss of $HN_{3(g)}$ by evaporation. Furthermore, **13 • HOAc** catalysed the desymmetrisation of anhydride **1** with $TMSN_3$ with the same observed enantioselectivity to that of the free base **13**. Given the similarities regarding the temperature-dependent behaviour (with respect to rotamer ratios and ^{1}H NMR spectroscopic chemical shifts) displayed by the species observed *in situ* and the isolated AcOH salt of **13** were found, the evidence suggests that the catalytically-active species in solution is the structurally-related HN_3 complex **13 • HN_3**.

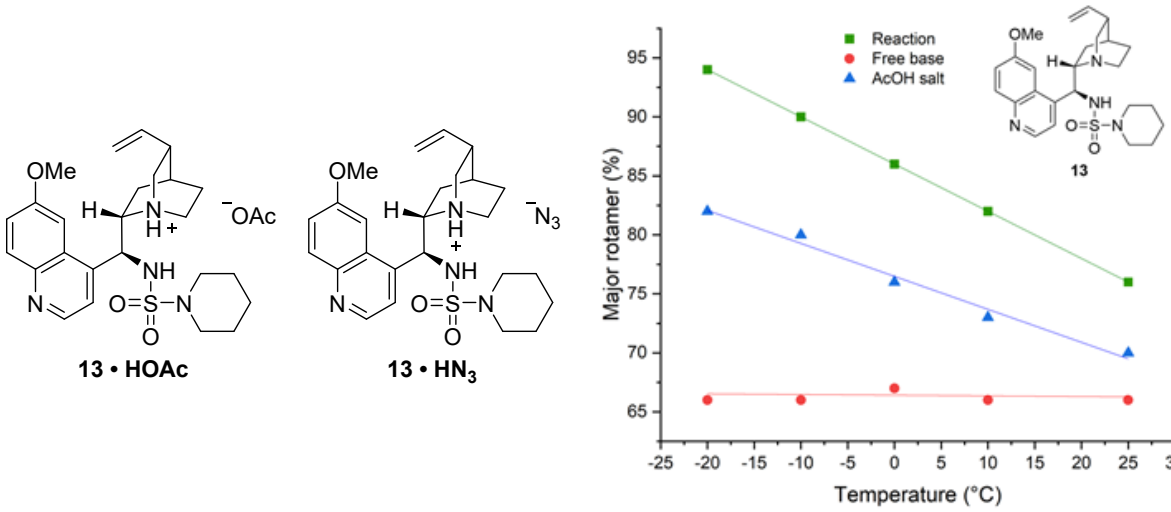
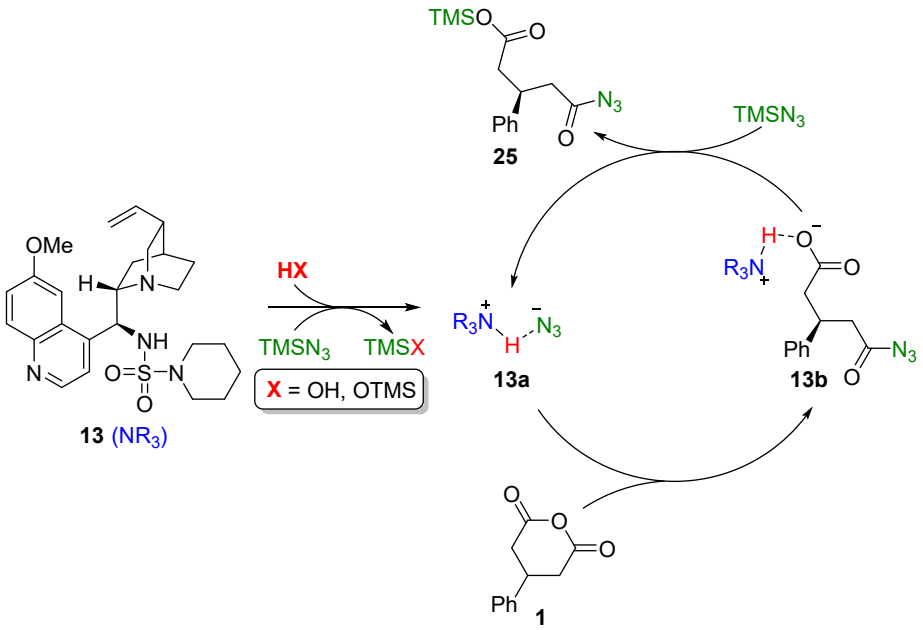


Figure S8: Acetic acid and HN_3 complexes of sulfamide **13** and the variation in the population of rotameric state **13-I** (%) with temperature (°C), as observed by variable-temperature ^1H NMR spectroscopy in $CDCl_3$.

Following the above, the following mechanistic rationale can be proposed: the free base form of the model sulfamide catalyst **13** is first converted to the active hydrazoate complex **13a** by trapping of adventitious HN_3, which is present in small amounts in commercial samples of $TMSN_3$ (Figure S5). This nucleophilic species then facilitates transfer of azide to the anhydride *via* a stereodetermining addition-elimination reaction at the prochiral carbonyl centre of **1**. The resulting carboxylate **13b** is then silylated by $TMSN_3$ to liberate the product **25** and regenerate the active catalyst **13a (Figure S9)**.



4. Figure S9. Proposed catalytic cycle for the desymmetrisation of cyclic anhydrides with equimolar $TMSN_3$ promoted by *Cinchona* alkaloid sulfamide organocatalysts.

References

[1] F. González-Bobes, N. Kopp, L. Li, J. Deerberg, P. Sharma, S. Leung, M. Davies, J. Bush, J. Hamm, M. Hrytsak, *Org. Proc. Res. Dev.* **2012**, *16*, 2051–2057.

[2] S. N. Smith, R. Craig, S. J. Connon, *Chem. Eur. J.* **2020**, *26*, 13378–13382.

[3] S. Pei, S. Xia, F. Yang, J. Chen, M. Wang, W. Sun, Z. Li, K. Yuan, J. Chen, *RSC Adv.* **2020**, *10*, 4446–4454.

[4] A. Leonardi, D. Barlocco, F. Montesano, G. Cignarella, G. Motta, R. Testa, E. Poggesi, M. Seeber, P. G. De Benedetti, F. Fanelli, *J. Med. Chem.* **2004**, *47*, 1900–1918.

[5] S. J. Shaw, D. A. Goff, L. A. Boralsky, M. Irving, R. Singh, *J. Org. Chem.* **2013**, *78*, 8892–8897.

[6] M. Litvajova, E. Sorrentino, B. Twamley, S. J. Connon, *Beilstein J. Org. Chem.* **2021**, *17*, 2287–2294.

[7] C. Shao, H. J. Yu, N. Y. Wu, P. Tian, R. Wang, C. G. Feng, G. Q. Lin, *Org. Lett.* **2011**, *13*, 788–791.

[8] J. P. Hilton-Proctor, O. Ilyichova, Z. Zheng, I. G. Jennings, R. W. Johnstone, J. Shortt, S. J. Mountford, M. J. Scanlon, P. E. Thompson, *Eur. J. Med. Chem.* **2020**, *191*, 112120.

[9] I. J. Montoya-Balbás, B. Valentín-Guevara, E. López-Mendoza, I. Linzaga-Elizalde, M. Ordoñez, P. Román-Bravo, *Molecules* **2015**, *20*, 22028–22043.

[10] T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125.

[11] P. L. Feldman, M. F. Brackeen, D. J. Cowan, B. E. Marron, F. J. Schoenen, J. A. Stafford, E. M. Suh, P. L. Domanico, D. Rose, M. A. Leesnitzer, E. S. Brawley, A. B. Strickland, M. W. Verghese, K. M. Connolly, R. Bateman-Fite, L. S. Noel, L. Sekut, S. A. Stimpson, *J. Med. Chem.* **1995**, *38*, 1505–1510.

[12] K. Hyodo, G. Hasegawa, H. Maki, K. Uchida, *Org. Lett.* **2019**, *21*, 2818–2822.

[13] A. S. Paraskar, A. Sudalai, *Tetrahedron* **2006**, *62*, 4907–4916.

[14] Q. Lang, G. Gu, Y. Cheng, Q. Yin, X. Zhang, *ACS Catal.* **2018**, *8*, 4824–4828.

[15] M. Yar, M. G. Unthank, E. M. McGarrigle, V. K. Aggarwal, *Chem. Asian J.* **2011**, *6*, 372–375.

[16] A. G. H. Wee, G. J. Fan, H. M. Bayirinoba, *J. Org. Chem.* **2009**, *74*, 8261–8271.

[17] R. M. Wiedhopf, E. R. Trumbull, J. R. Cole, *J. Pharm. Sci.* **1973**, *62*, 1206–1207.

[18] V. Rodríguez, M. Sánchez, L. Quintero, F. Sartillo-Piscil, *Tetrahedron* **2004**, *60*, 10809–10815.

[19] P. L. Wang, Y. Li, Y. Wu, C. Li, Q. Lan, X. S. Wang, *Org. Lett.* **2015**, *17*, 3698–3701.

[20] D. Enders, O. Niemier, *Heterocycles* **2005**, *66*, 385–403.

[21] J. Sietmann, M. Ong, C. Mück-Lichtenfeld, C. G. Daniliuc, J. M. Wiest, *Angew. Chem. Int. Ed.* **2021**, *60*, 9719–9723.

[22] Z. Galla, E. Forró, F. Fülöp, *Tetrahedron Asymmetry* **2016**, *27*, 729–731.

[23] M. L. Cardoso do Vale, J. E. Rodríguez-Borges, O. Caamaño, F. Fernández, X. García-Mera, *Tetrahedron* **2006**, *62*, 9475–9482.

[24] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. a. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. a. Petersson, H. Nakatsuji, X. Li, M. Caricato, a. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, a. F. Izmaylov, J. L. Sonnenberg, Williams, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. a. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. a. Keith, R. Kobayashi, J. Normand, K. Raghavachari, a. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, **2016**, Gaussian 16, Revision C.01, Gaussian, Inc., Wallin.

[25] J. Da Chai, M. Head-Gordon, *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615–6620.

[26] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.

[27] T. A. Keith in AIMAll, TK Gristmill Software (aim.tkgristmill.com), Vol. **2011**, TK Gristmill Software, (aim.tkgristmill.com)

[28] J. J. Shephard, A. K. Soper, S. K. Callear, S. Imberti, J. S. O. Evans, C. G. Salzmann, *Chem. Commun.* **2015**, *51*, 4770–4773.

[29] M. Puthanveedu, V. Polychronidou, A. P. Antonchick, *Org. Lett.* **2019**, *21*, 3407–3411.

[30] J. DeRuiter, A. N. Brubaker, W. L. Whitmer, J. L. Stein, *J. Med. Chem.* **1986**, *29*, 2024–2028.

[31] S. E. Wengryniuk, A. Weickgenannt, C. Reiher, N. A. Strotman, K. Chen, M. D. Eastgate, P. S. Baran, *Org. Lett.* **2013**, *15*, 792–795.

[32] J. Nelson, *Spectrochim. Acta Part A Mol. Spectrosc.* **1970**, *26*, 235–247

[33] K. Blise, M. W. Cvitkovic, N. J. Gibbs, S. F. Roberts, R. M. Whitaker, G. E. Hofmeister, D. Kohen, *J. Org. Chem.* **2017**, *82*, 1347–1355.

[34] D. X. Hu, P. Grice, S. V. Ley, *J. Org. Chem.* **2012**, *77*, 5198–5202.

[35] D. Ferri, T. Bürgi, A. Baiker, *J. Chem. Soc. Perkin Trans. 2* **1999**, 1305–1311.

[36] R. A. Olsen, D. Borchardt, L. Mink, A. Agarwal, L. J. Mueller, F. Zaera, *J. Am. Chem. Soc.* **2006**, *128*, 15594–15595.

[37] Z. Zhang, H. Y. Bae, J. Guin, C. Rabalakos, M. Van Gemmeren, M. Leutzsch, M. Klussmann, B. List, *Nat. Commun.* **2016**, *7*, 1–8.

[38] J. Humbrías-Martín, M. C. Pérez-Aguilar, R. Mas-Ballesté, A. Dentoni Litta, A. Lattanzi, G. Della Sala, J. A. Fernández-Salas, J. Alemán, *Adv. Synth. Catal.* **2019**, *361*, 4790–4796.

[39] Y. H. Joo, H. Gao, Y. Zhang, J. N. N. M. Shreeve, *Inorg. Chem.* **2010**, *49*, 3282–3288.

5. CSP-SFC analysis

5.1 Gradient tables and methods

Values obtained for enantiomeric excess were determined by integration of the chromatographic peaks obtained upon separation of the stereoisomers on a Waters' ACQUITY UPC² system using Trefoil AMY1, CEL1, CEL2 (2.5 µm, 3.0 x 150 mm) as chiral stationary phase. The standard method sets 'Steps 1 – 4' (below) were employed with the following parameters: Column temperature 30°C; inlet pressure 1500 bar; flow rate 1.20 mL/min, unless otherwise stated. Racemic samples of chiral products were prepared in order to screen adequate conditions for separation of stereoisomers prior to analysis of enantioenriched samples. Results were obtained in duplicate or triplicate, and % *ee* values are reported as an average of these runs.

Step 1.
Mobile phase: A = CO_2, B = EtOH/*i*PrOH/CH_3CN (1:1:1, *v*:*v*)
Chiral stationary phase: Trefoil AMY1 (2.5 µm, 3.0 x 150 mm)

Time (min)	% A	% B	Curve
0.00	97.0	3.0	Initial
4.50	40.0	60.0	6
6.00	40.0	60.0	6
8.00	97.0	3.0	6

Step 2.
Mobile phase: A = CO_2, B = MeOH/*i*PrOH (1:1, *v*:*v*)
Chiral stationary phase: Trefoil CEL1 (2.5 µm, 3.0 x 150 mm)

Time (min)	% A	% B	Curve
0.00	97.0	3.0	Initial
8.50	40.0	60.0	6
10.00	40.0	60.0	6
10.10	97.0	3.0	6

Step 3.
Mobile phase: A = CO_2, B = EtOH/MeCN (1:1, *v*:*v*)
Chiral stationary phase: Trefoil CEL2 (2.5 µm, 3.0 x 150 mm)

Time (min)	% A	% B	Curve
0.00	99.0	1.0	Initial
8.50	92.0	8.0	6
10.00	40.0	60.0	6
10.10	97.0	3.0	6

Step 4.
Mobile phase: A = CO_2, B = EtOH/*i*PrOH (1:1, *v*:*v*)
Chiral stationary phase: Trefoil AMY1 (2.5 µm, 3.0 x 150 mm)

Time (min)	% A	% B	Curve
0.00	99.0	1.0	Initial
4.50	40.0	60.0	6
8.10	40.0	60.0	6
8.20	97.0	3.0	6

Step 5.
Mobile phase: A = CO_2, B = MeOH/*i*PrOH (1:1, *v*:*v*)
Chiral stationary phase: Trefoil CEL1 (2.5 µm, 3.0 x 150 mm)

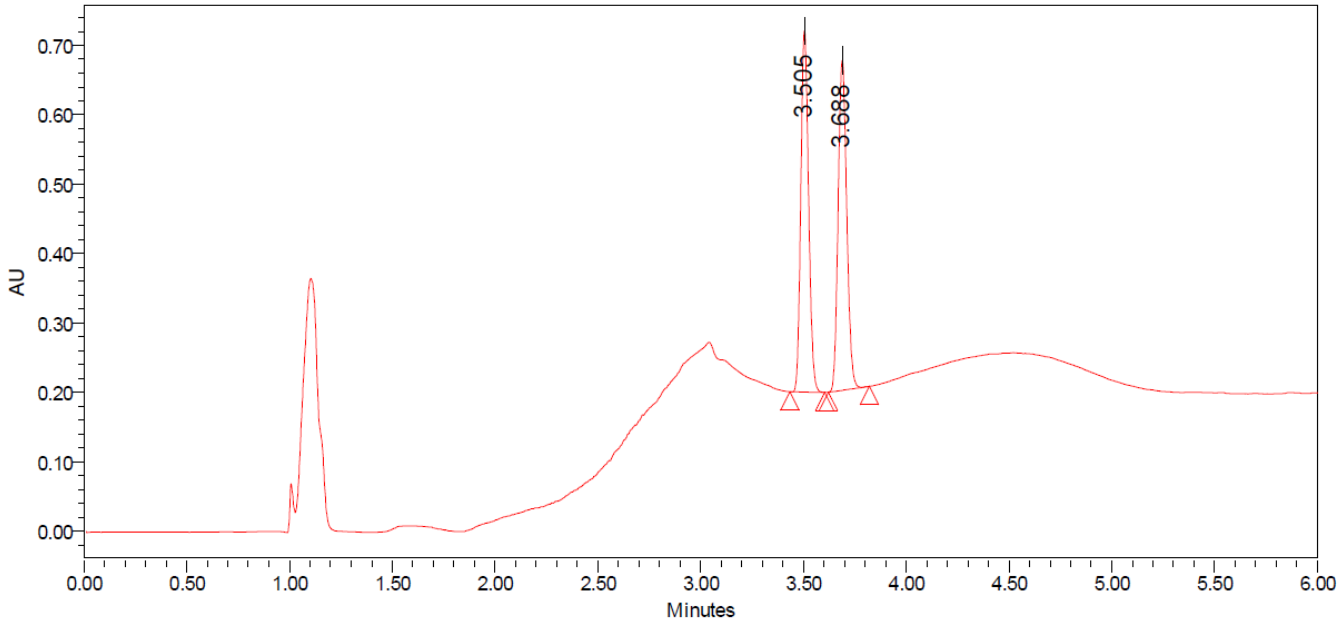
Time (min)	% A	% B	Curve
0.00	98.0	2.0	Initial
4.50	90.0	10.0	6
6.00	80.0	20.0	6
7.00	60.0	40.0	6

Step 6.
Mobile phase: A = CO_2, B = MeOH/iPrOH (1:1, v:v), isocratic (96:4 A/B)
Chiral stationary phase: Trefoil CEL1 (2.5 µm, 3.0 x 150 mm)
Flow rate: 2.00 mL/min
Column temperature: 35°C
Pressure: 2000 psi

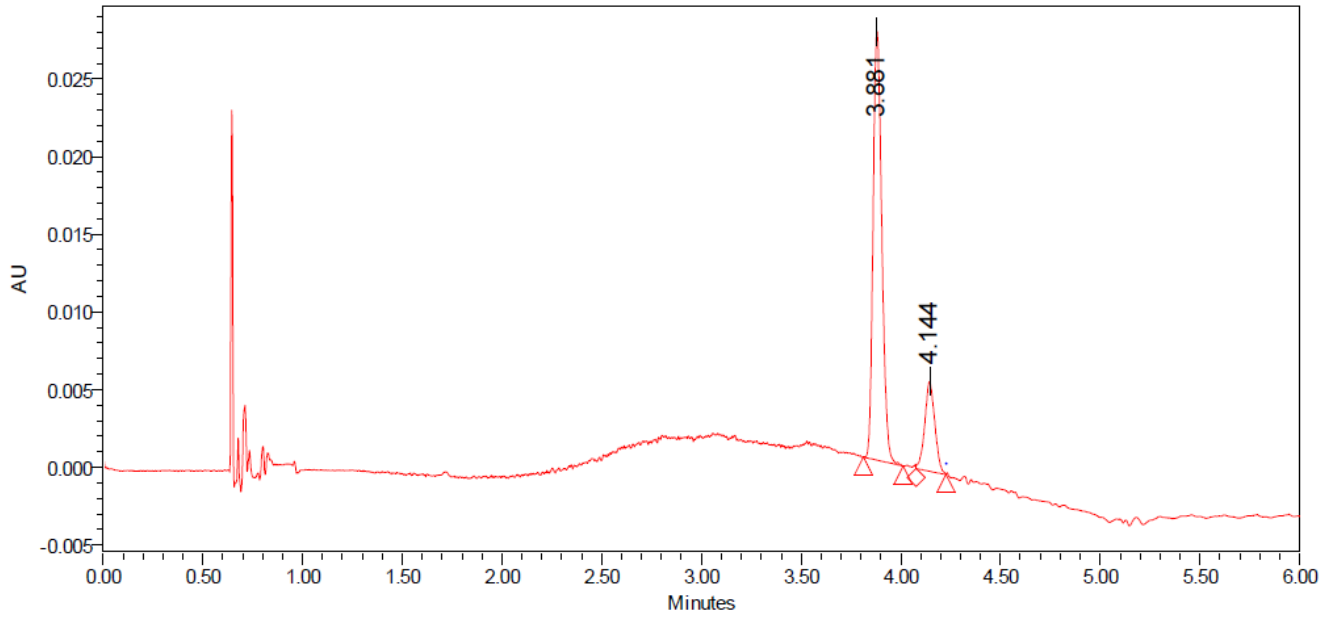
5.2 Chromatograms

Compound **3** (Step 3, 254 nm)

Racemic:



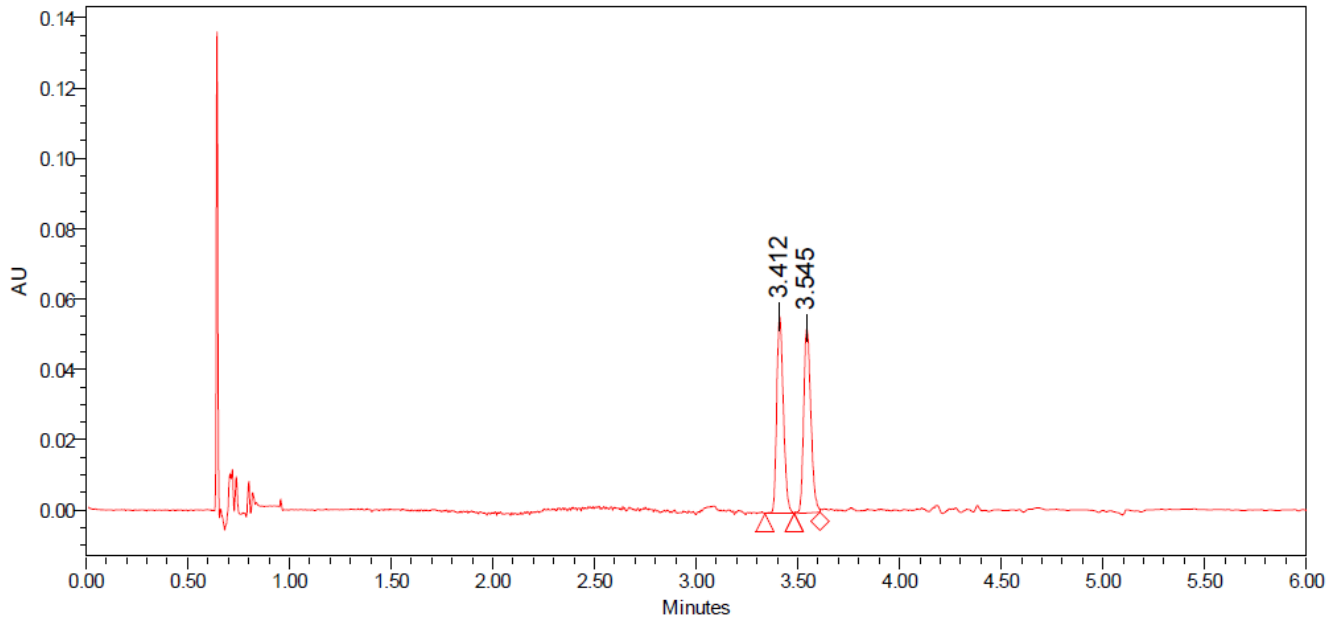
Enantioselective (58% *ee*):



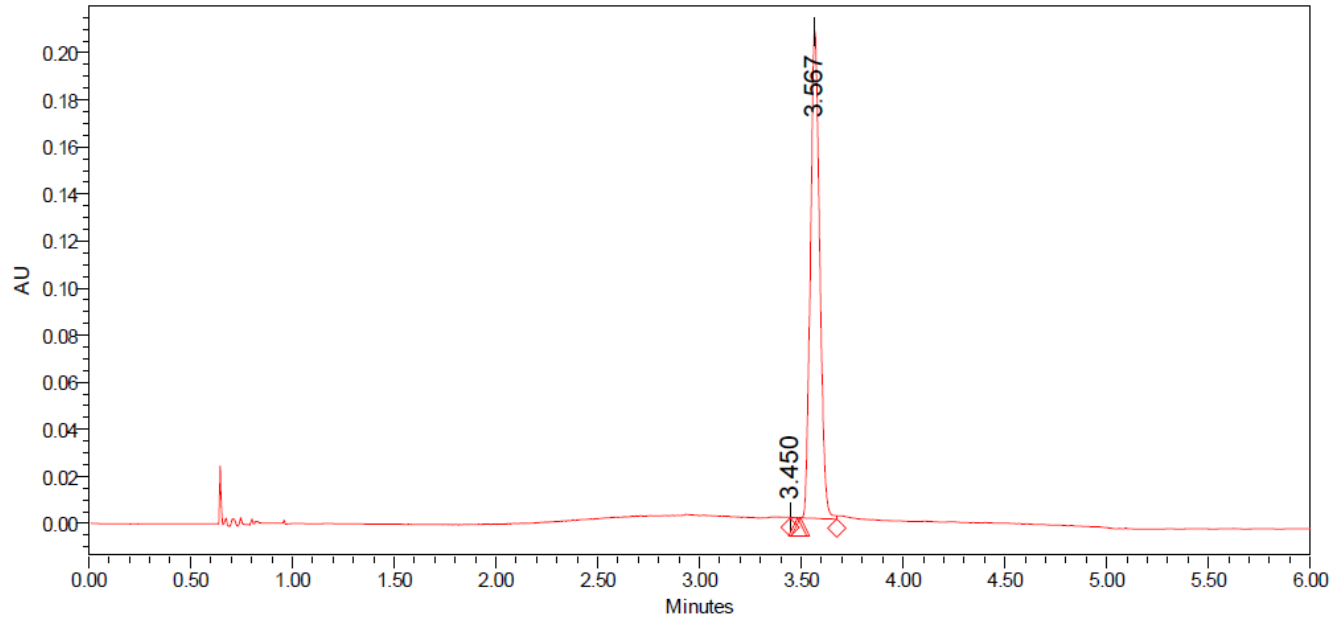
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	3.50	49.79	3.88	79.04
2	3.69	50.21	4.14	20.96
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **26** (Step 3, 254 nm)

Racemic:



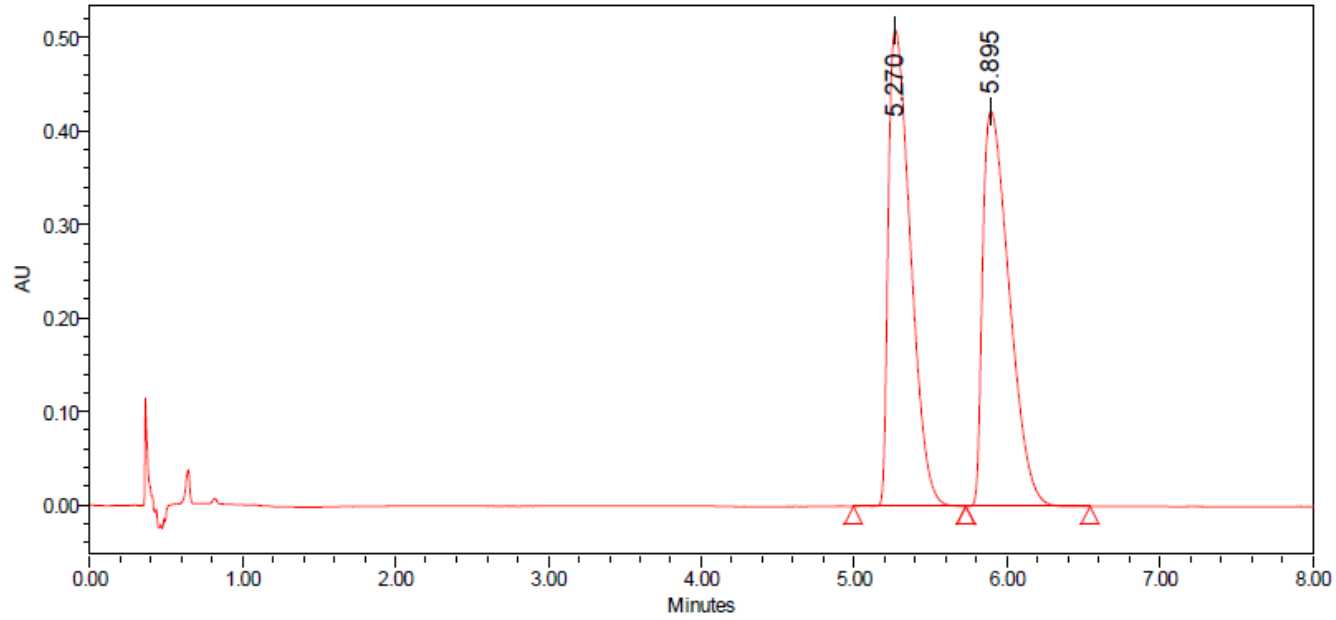
Enantioselective (recrystallised, >99% *ee*):



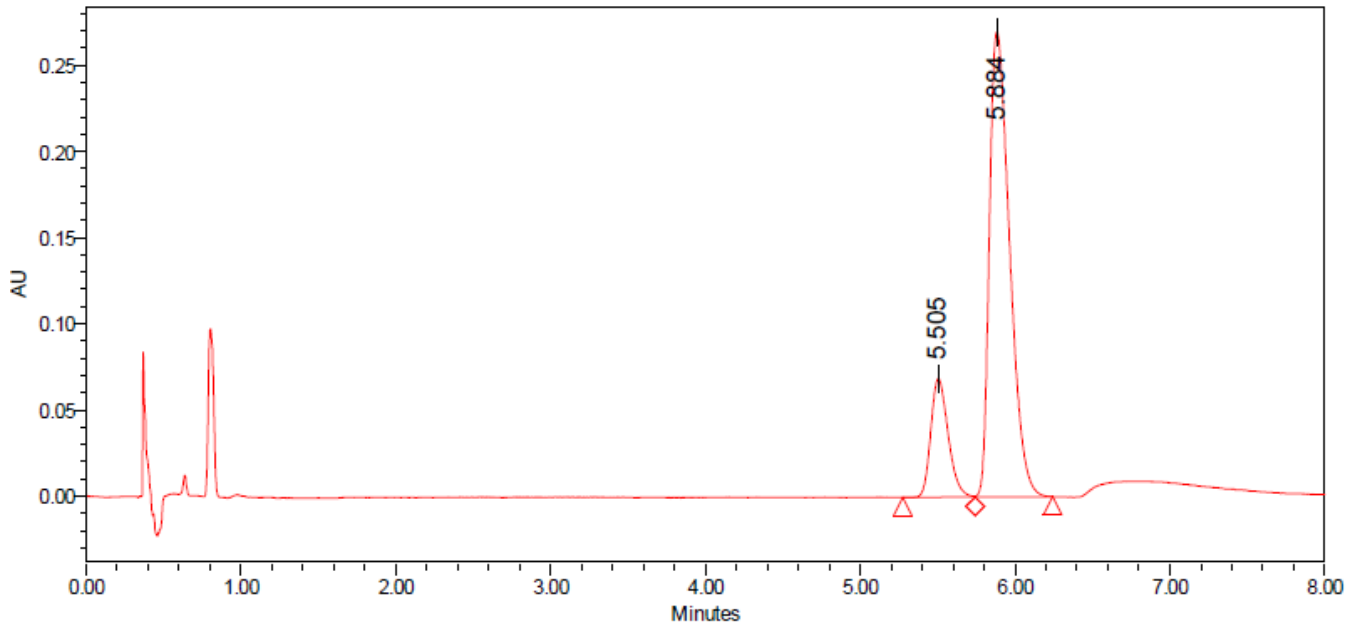
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	3.41	49.54	3.45	0.06
2	3.54	50.46	3.57	99.94
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **35** (Step 6, 230 nm)

Racemic:



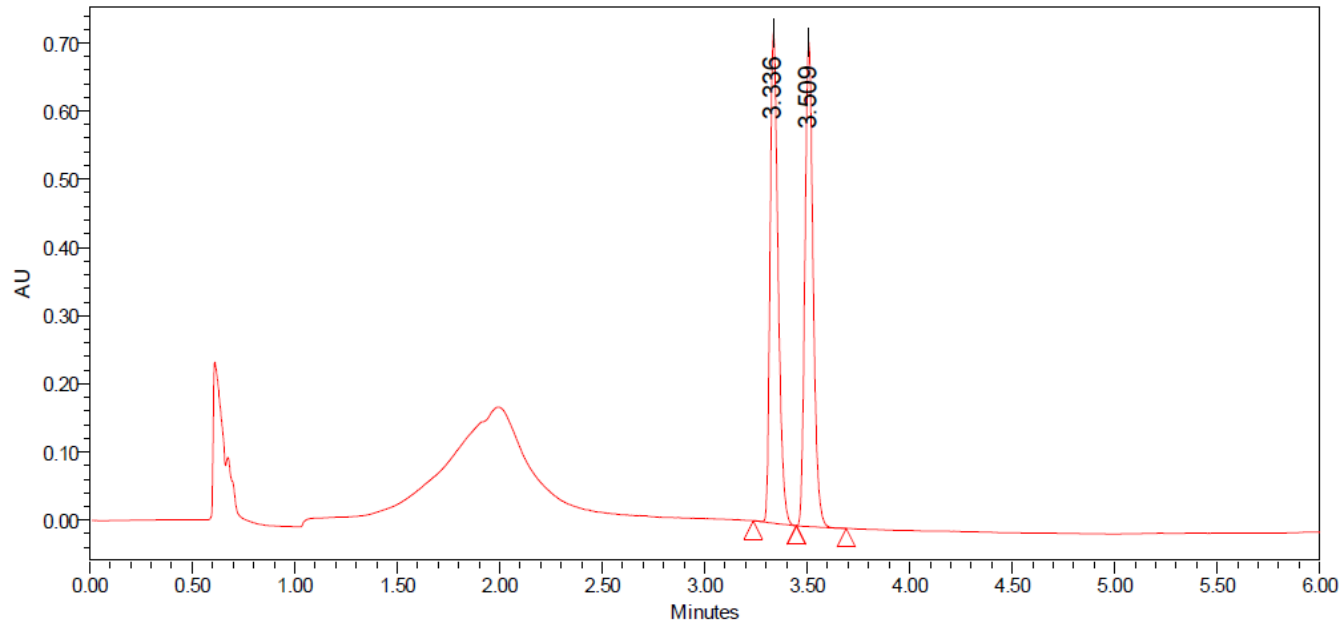
Enantioselective (65% *ee*):



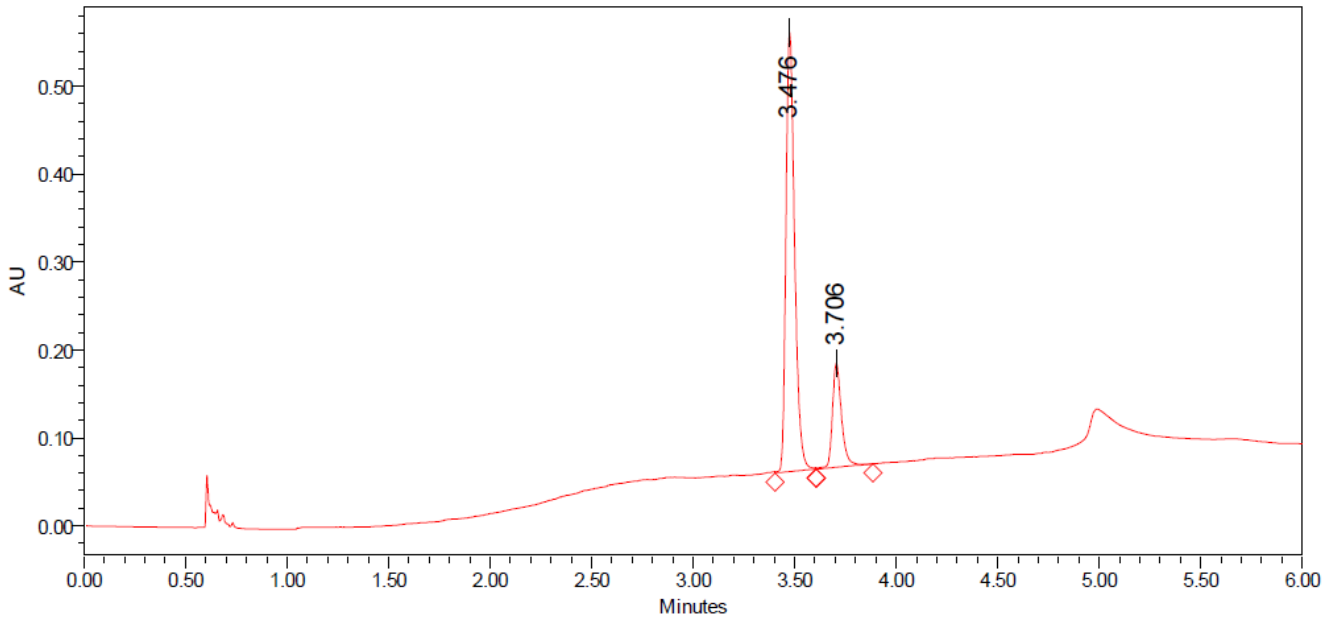
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	5.27	50.05	5.50	17.63
2	5.89	49.95	5.88	82.37
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **36** (Step 4, 254 nm)

Racemic:



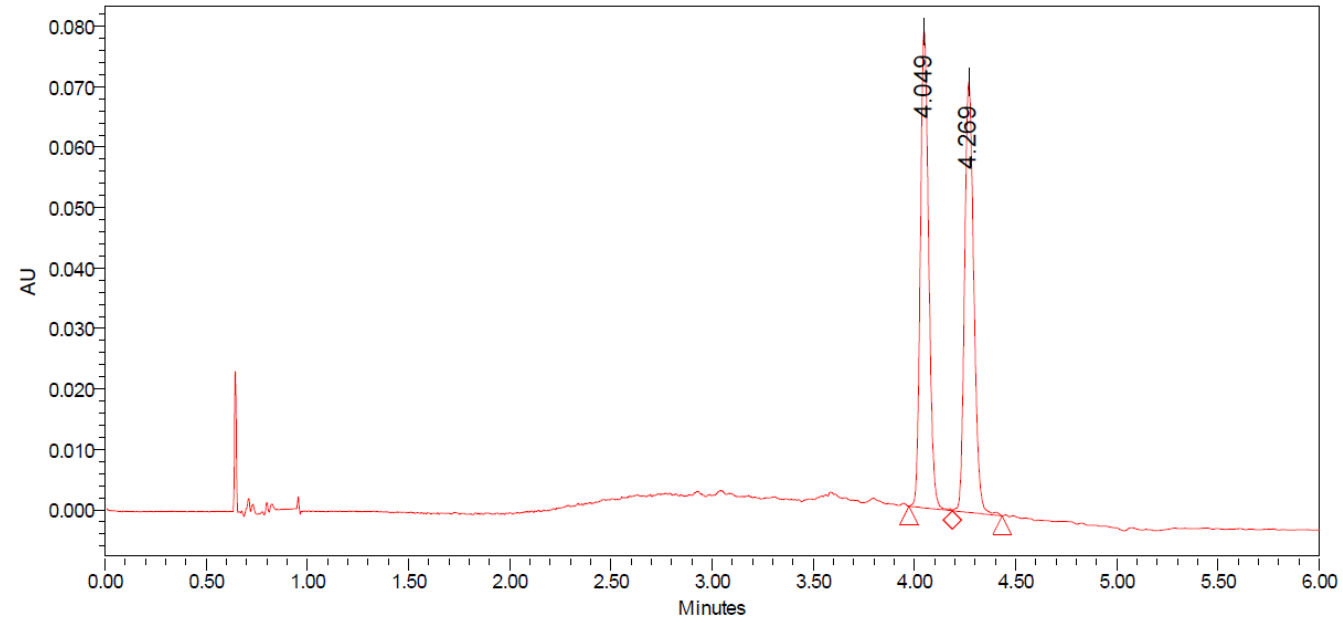
Enantioselective (64% *ee*):



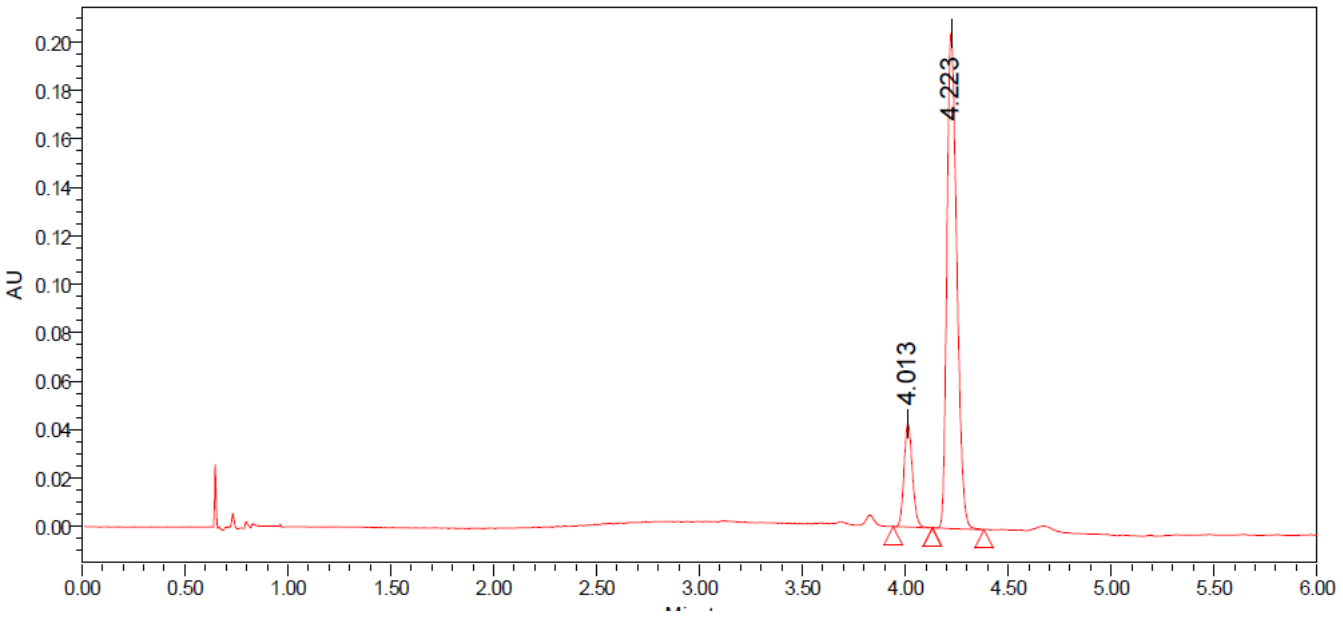
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	3.33	49.61	3.47	18.12
2	3.50	50.39	3.70	81.88
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **37** (Step 3, 230 nm)

Racemic:



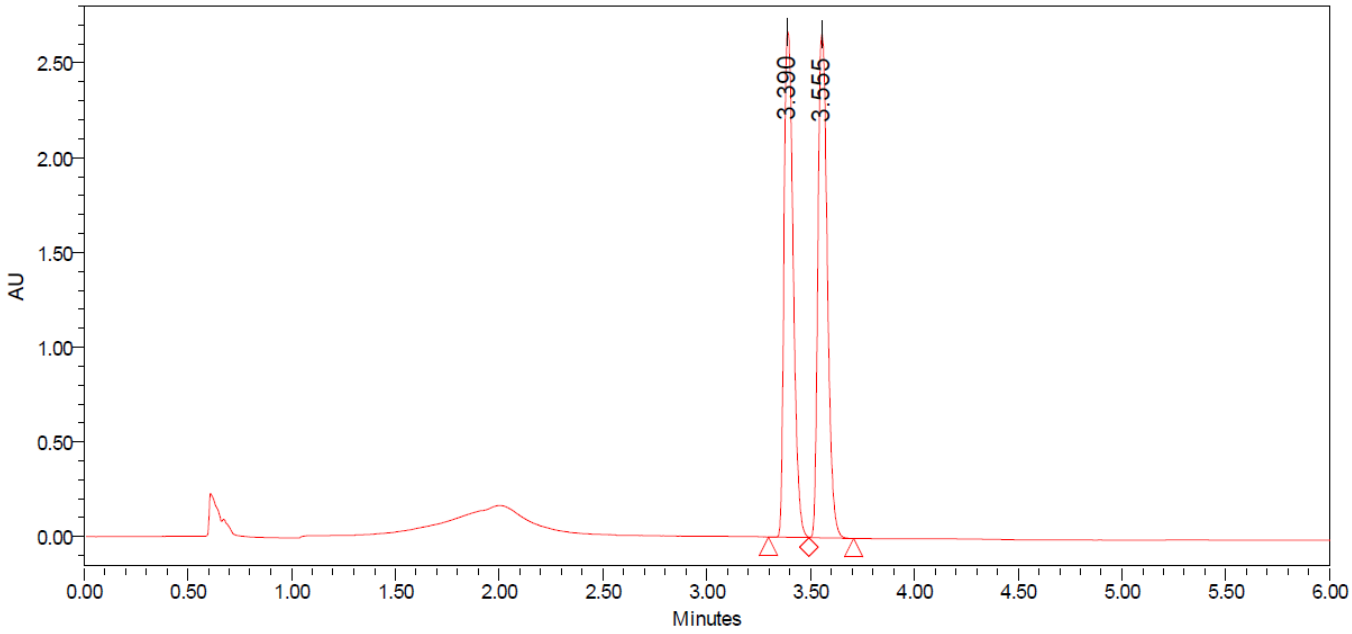
Enantioselective (70% *ee*):



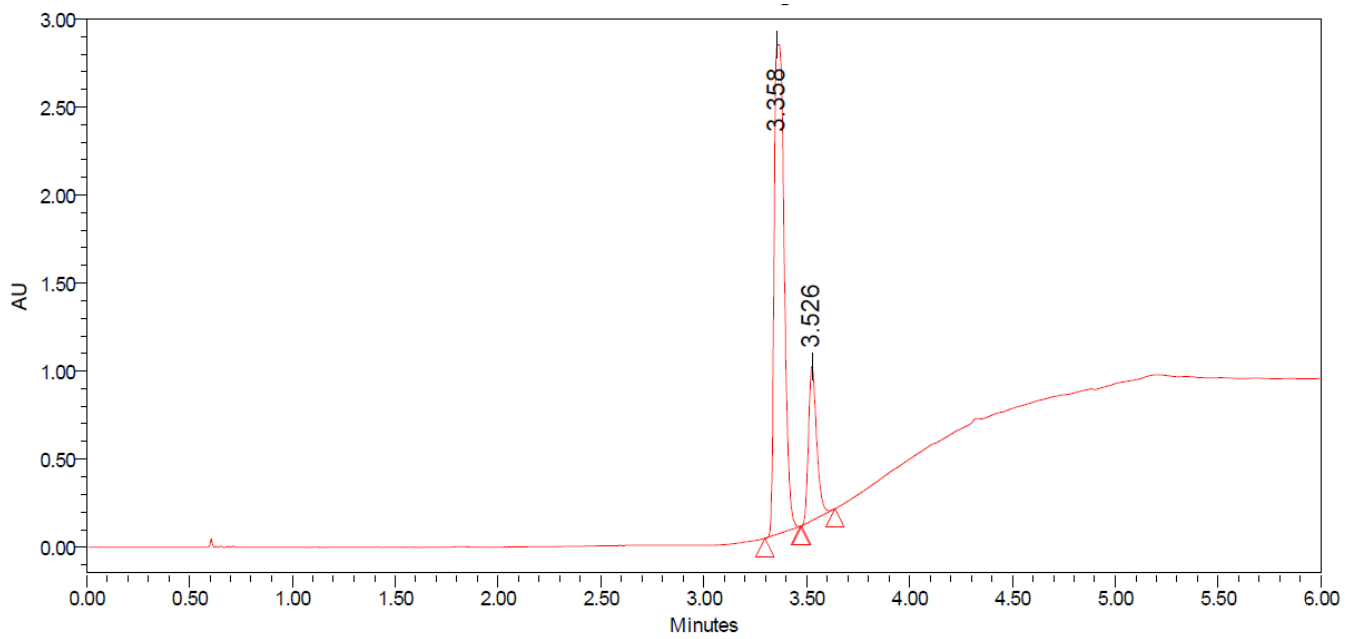
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	4.04	49.83	4.01	15.10
2	4.26	50.17	4.22	84.90
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **38** (Step 3, 254 nm)

Racemic:



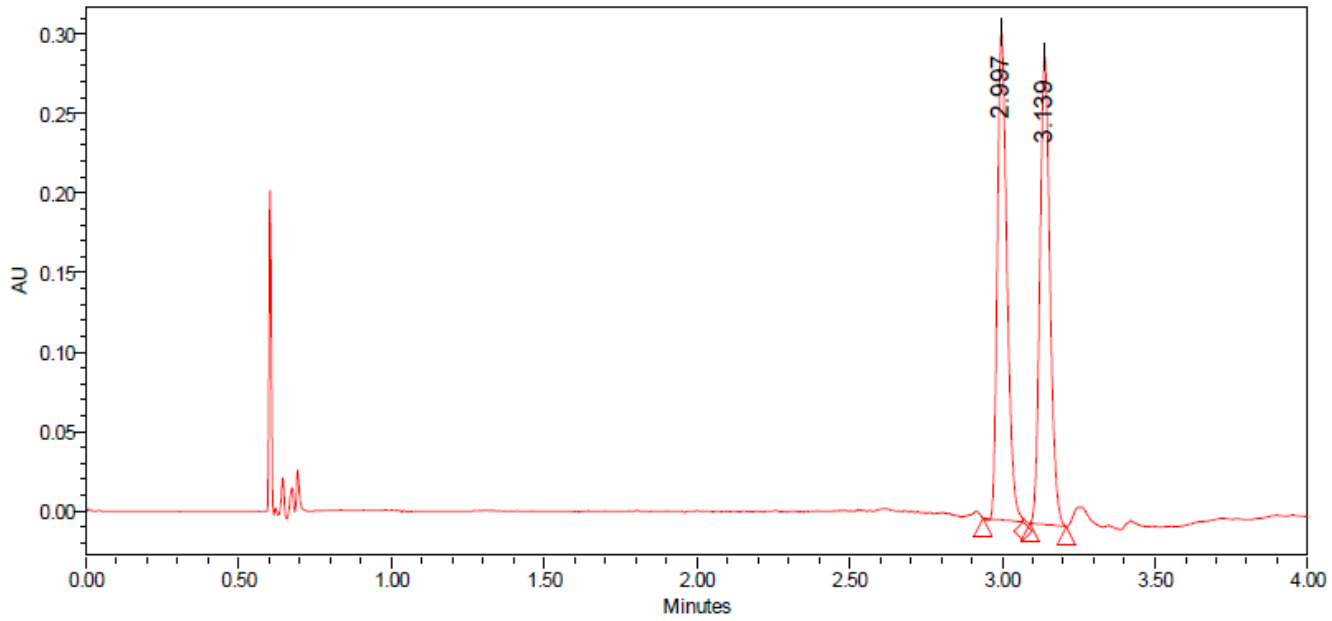
Enantioselective (65% *ee*):



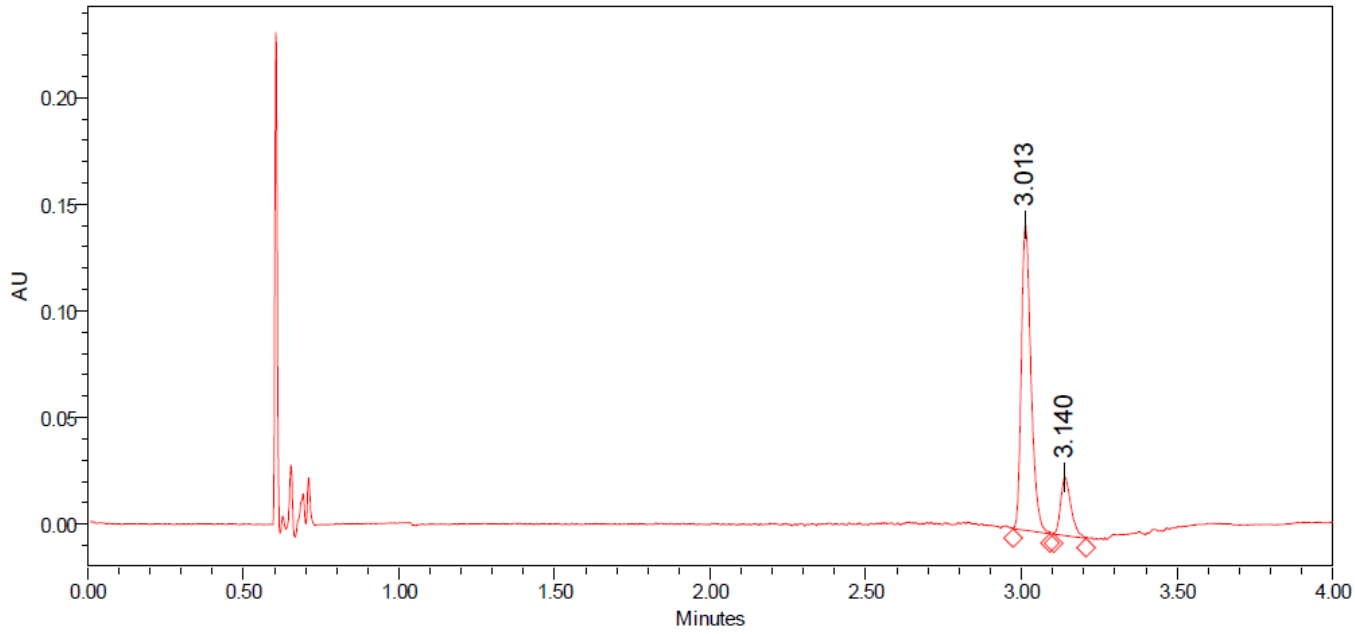
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	3.39	49.57	3.35	82.56
2	3.56	50.43	3.53	17.44
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **39** (Step 1, 254 nm)

Racemic:



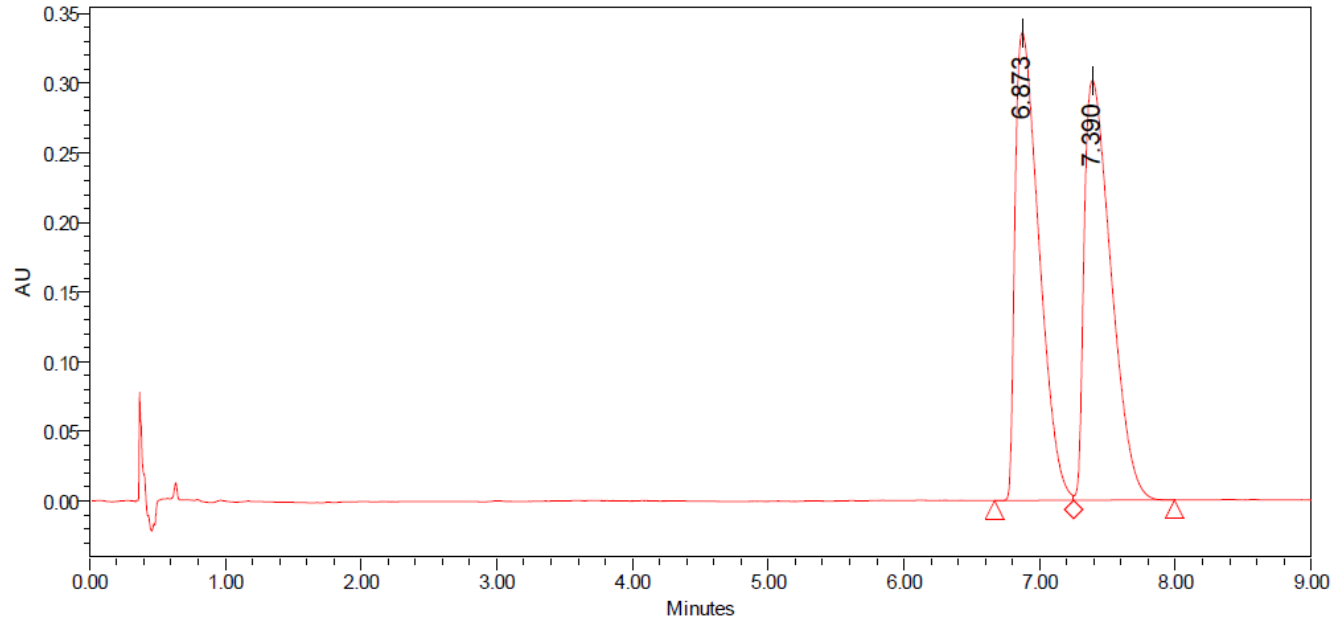
Enantioselective (66% *ee*):



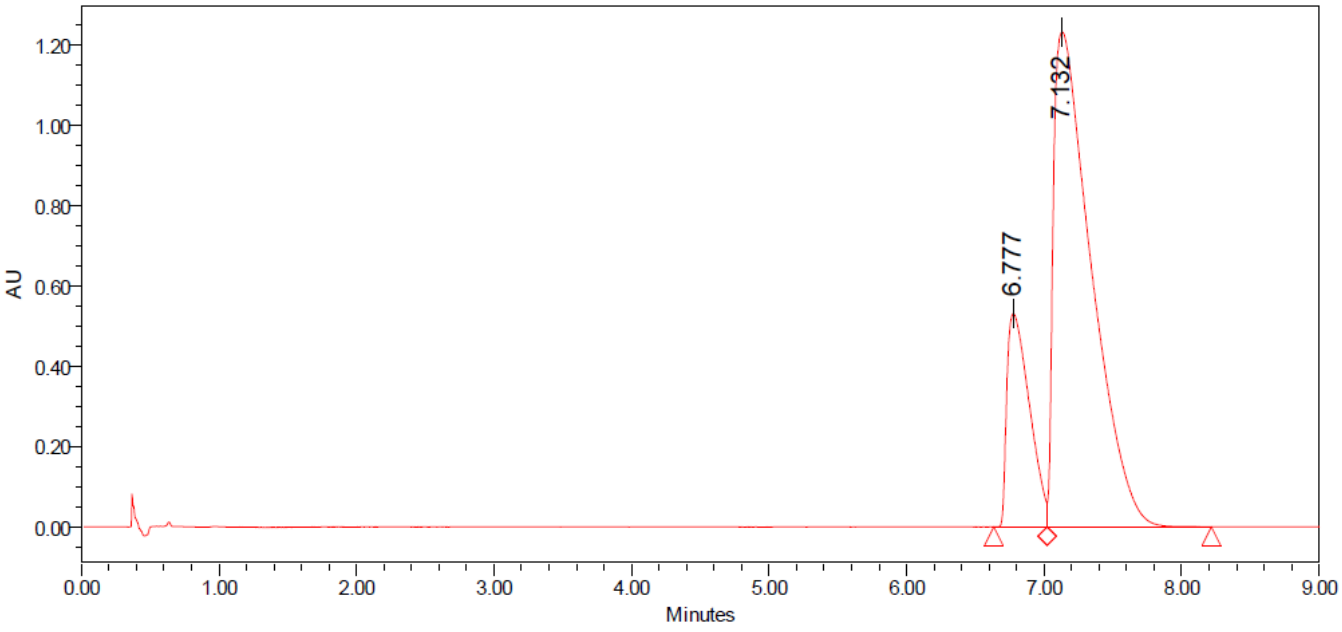
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	3.00	49.97	3.01	83.00
2	3.14	50.03	3.14	17.00
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **40** (Step 6, 254 nm)

Racemic:



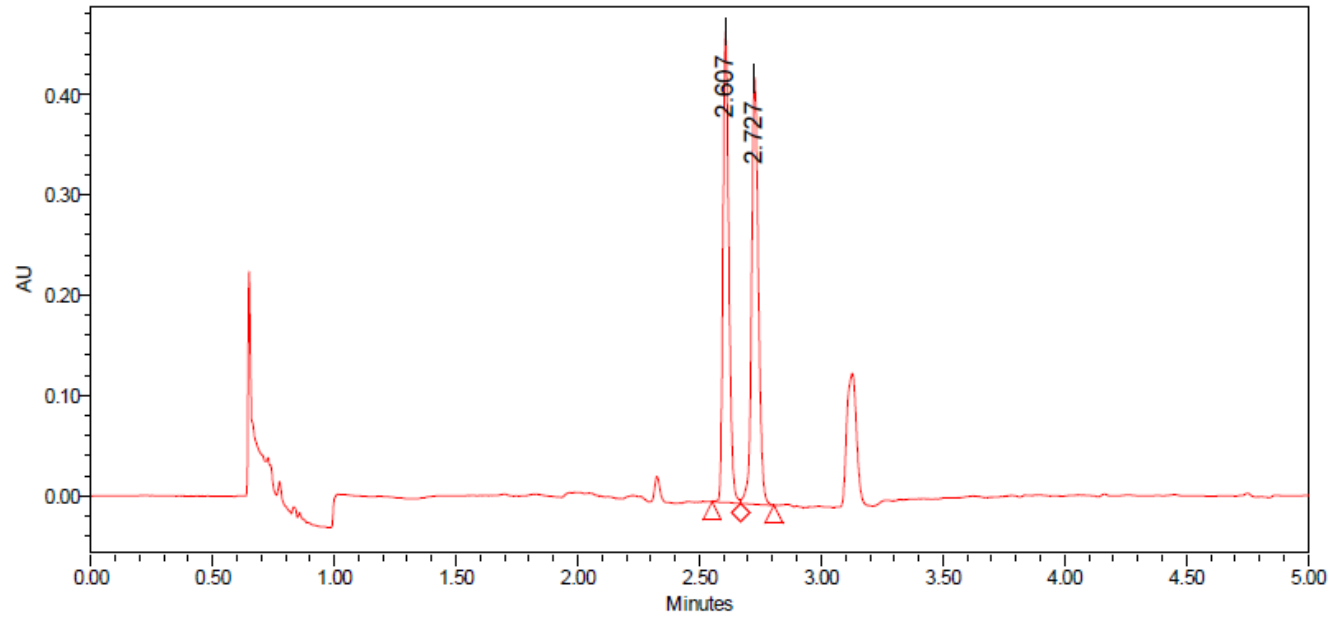
Enantioselective (65% *ee*):



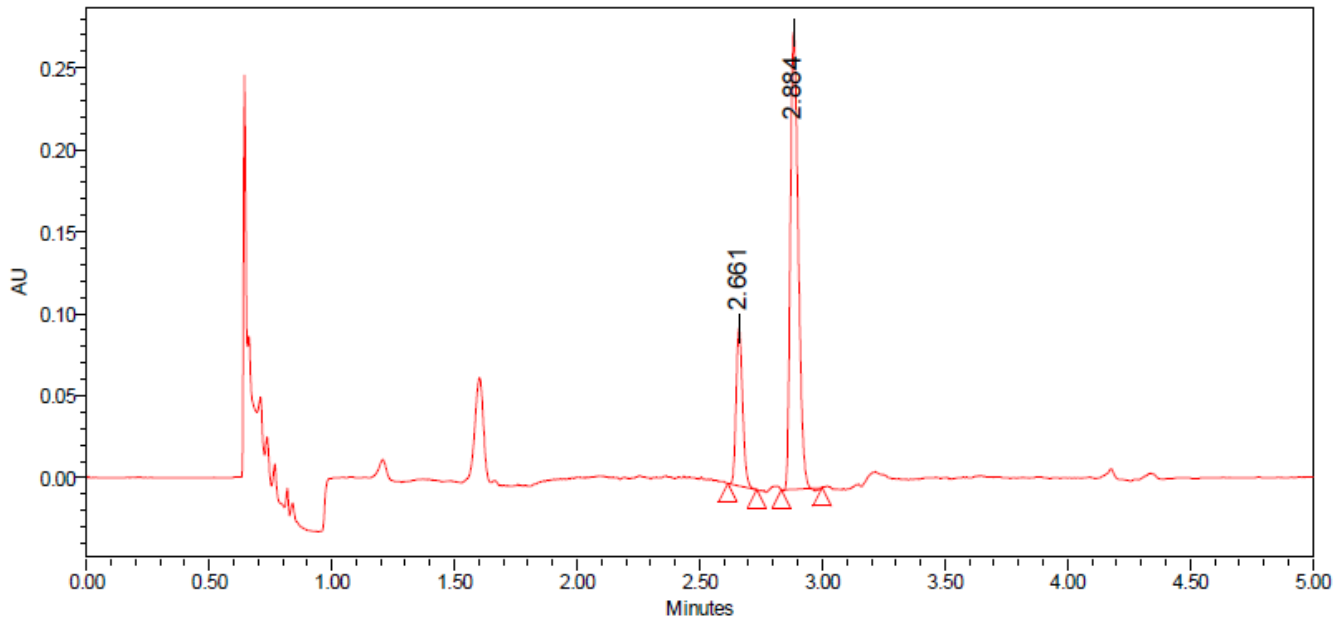
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	6.87	49.85	6.77	17.26
2	7.39	50.15	7.13	82.74
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **41** (Step 3, 212 nm)

Racemic:



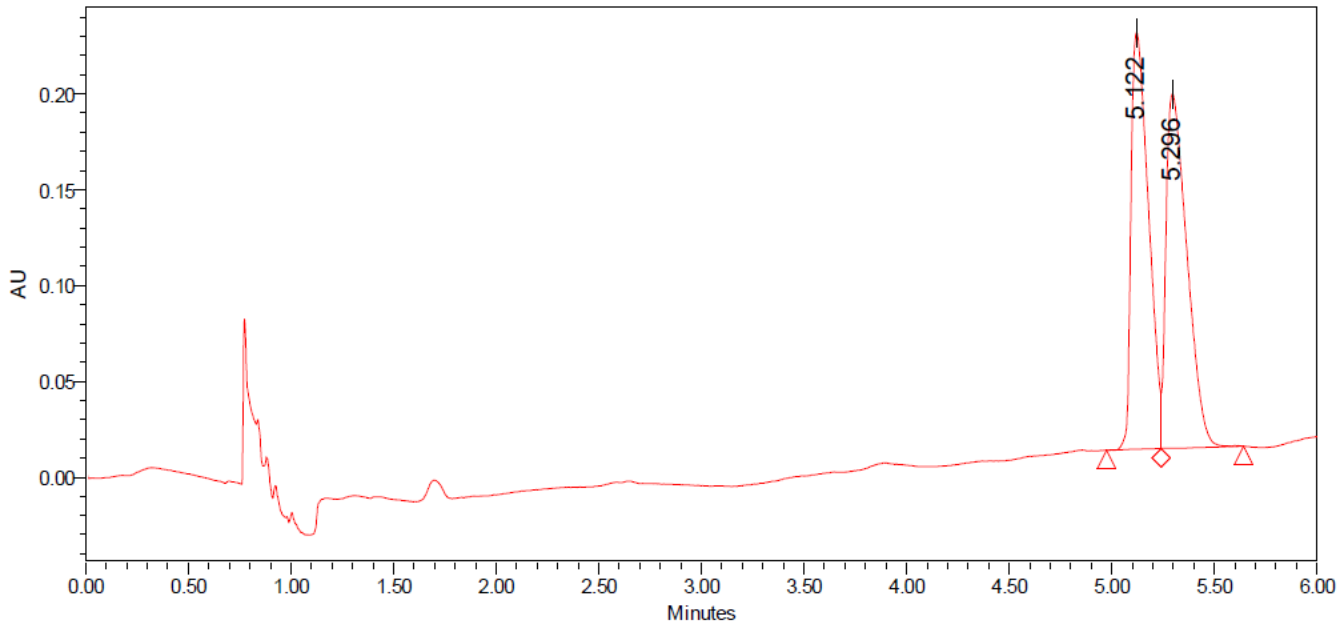
Enantioselective (56% *ee*):



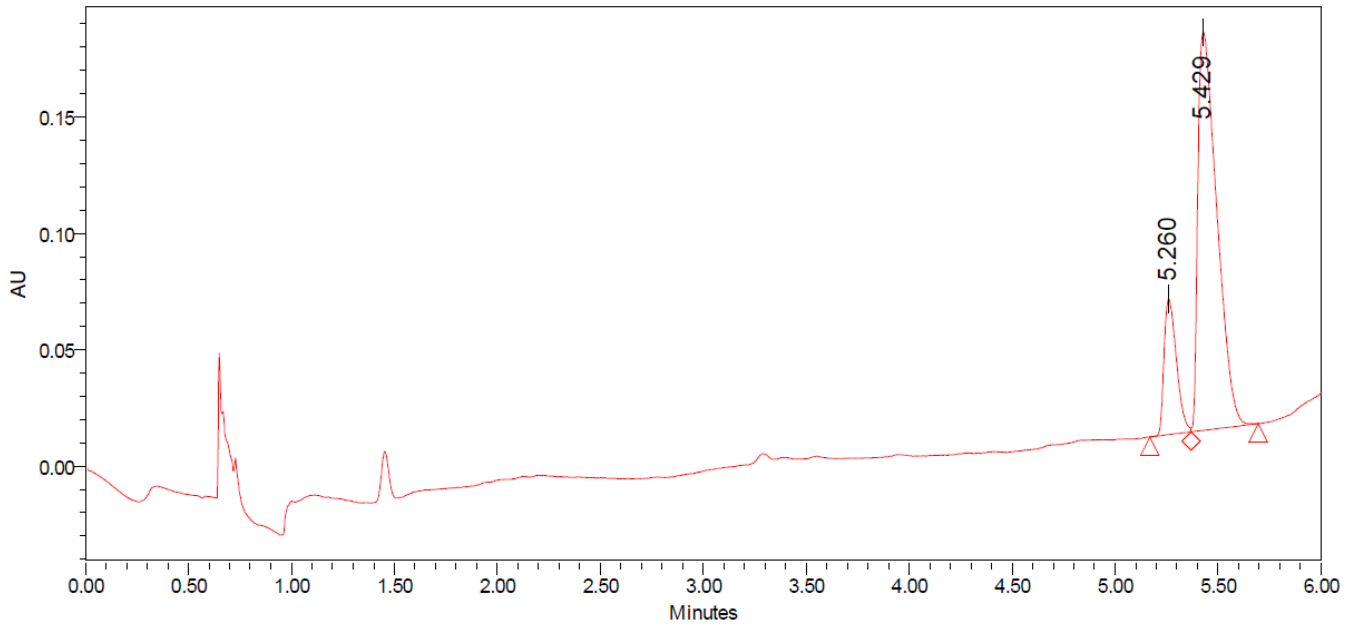
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	2.60	48.74	2.66	22.00
2	2.73	51.26	2.88	77.97
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **42** (Step 5, 212 nm)

Racemic:



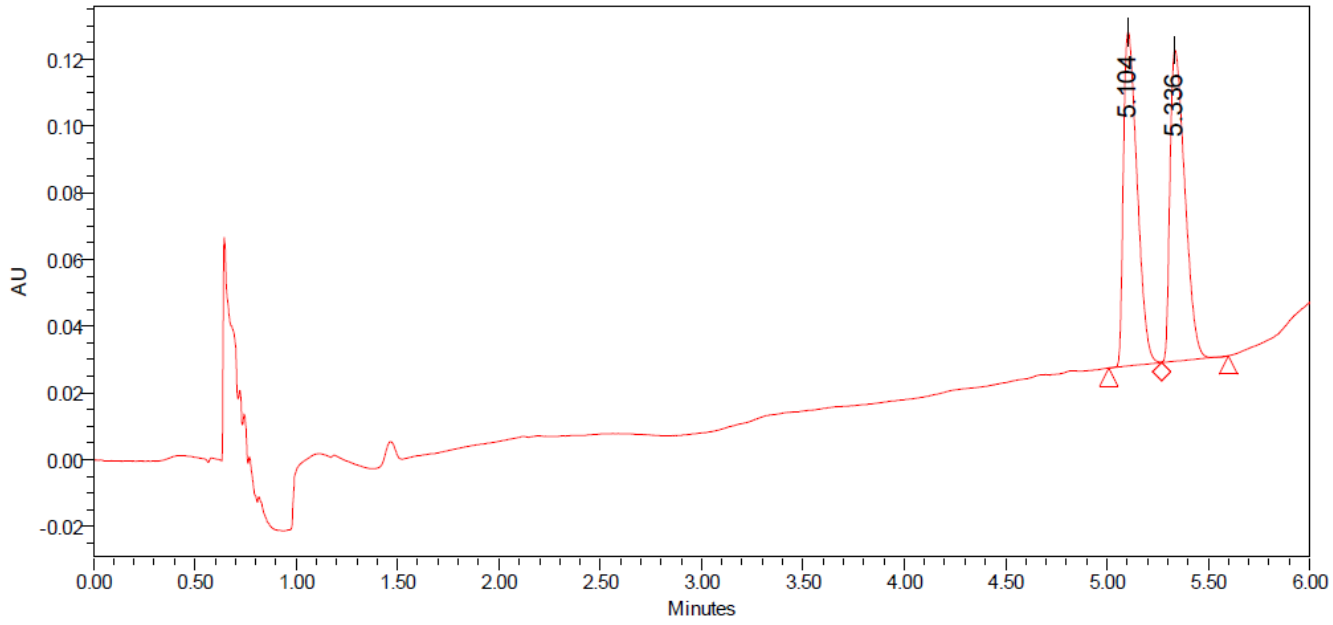
Enantioselective (70% *ee*):



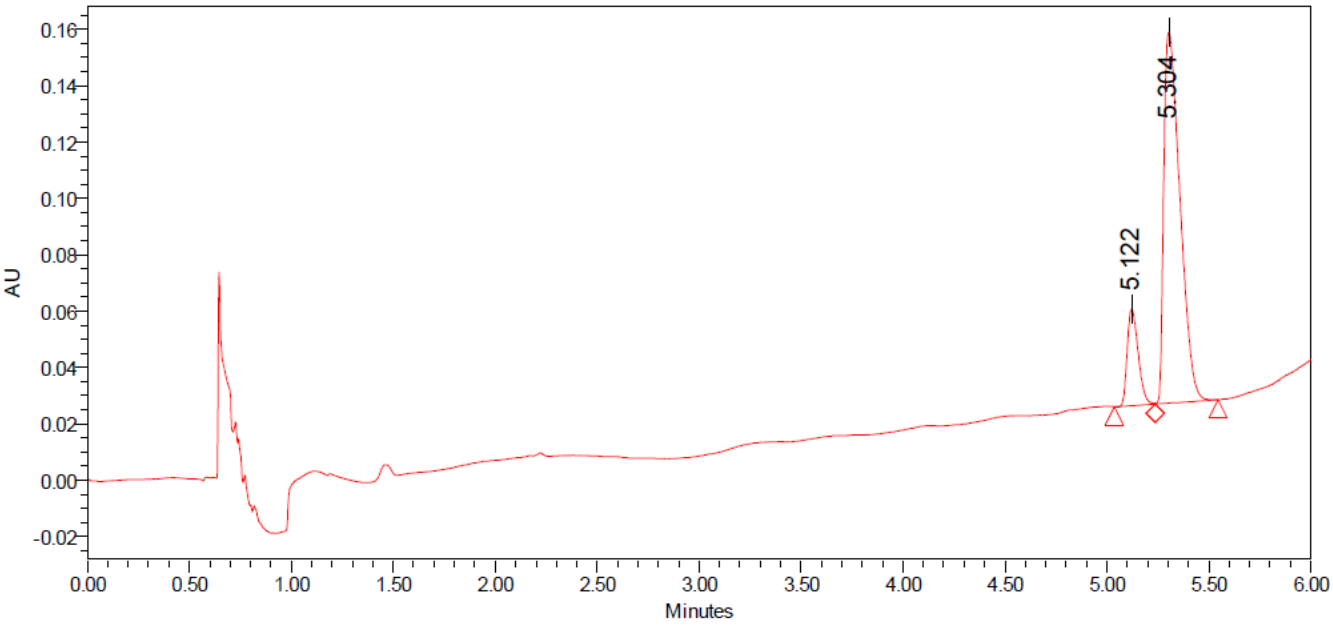
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	5.12	49.43	5.26	15.11
2	5.30	50.57	5.43	84.89
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **43** (Step 5, 212 nm)

Racemic:



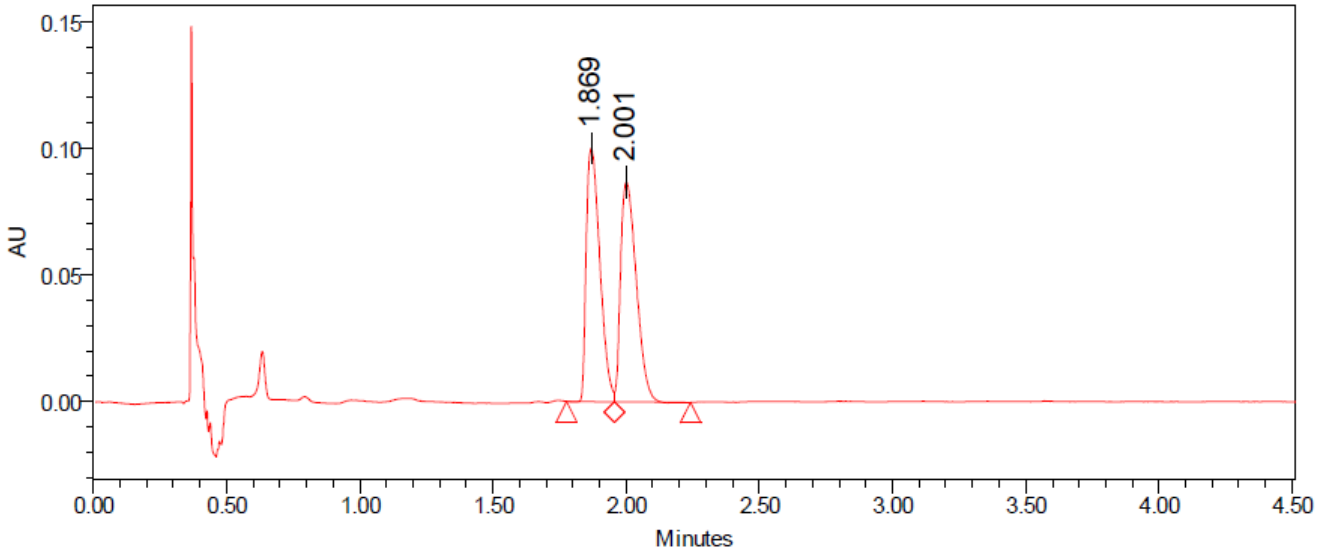
Enantioselective (70% *ee*):



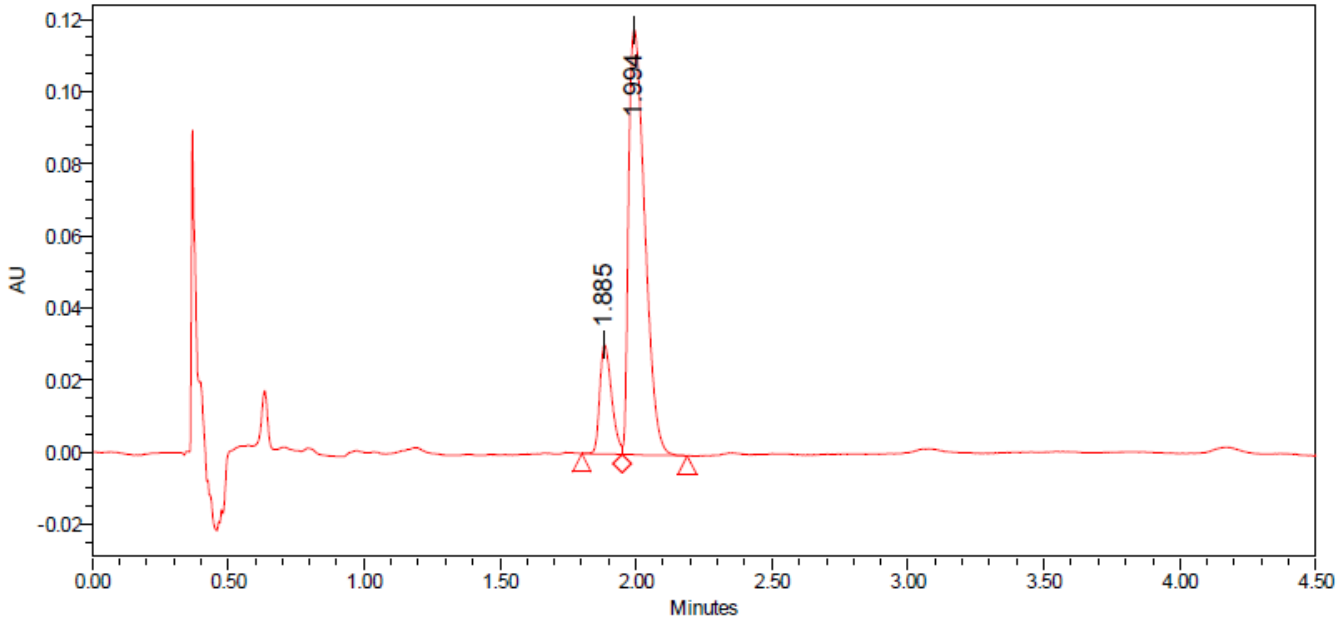
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	5.10	49.65	5.12	15.04
2	5.33	50.35	5.30	84.96
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **44** (Step 6, 212 nm)

Racemic:



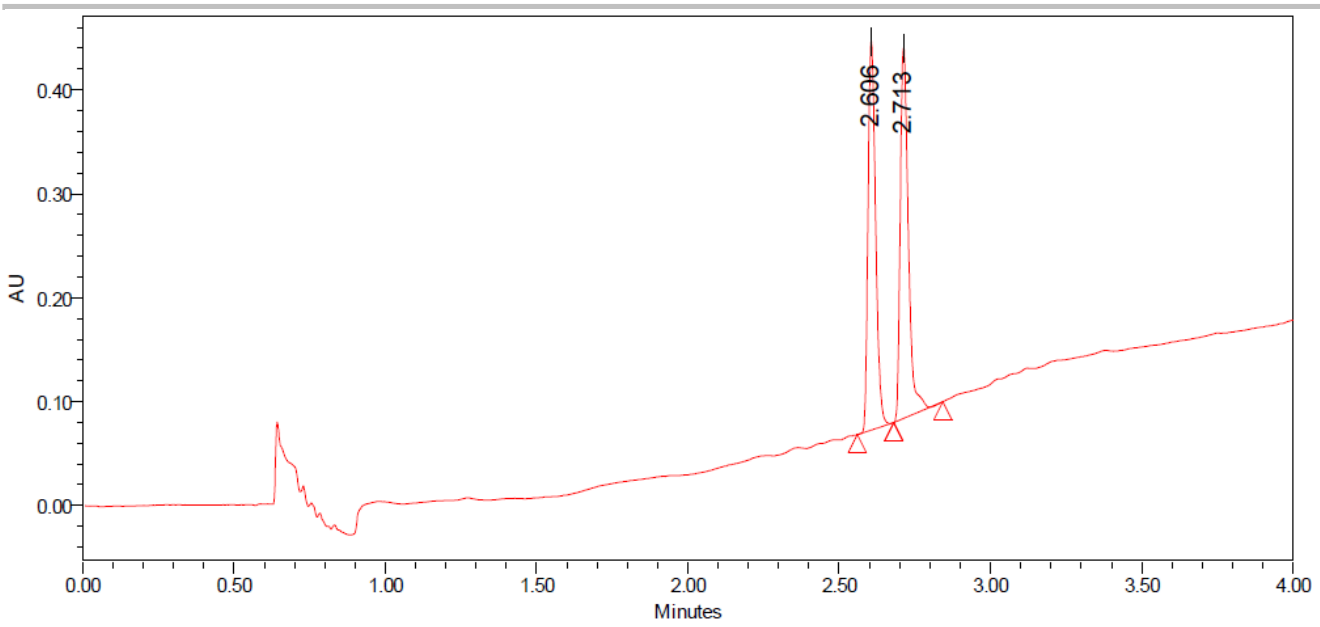
Enantioselective (64% *ee*):



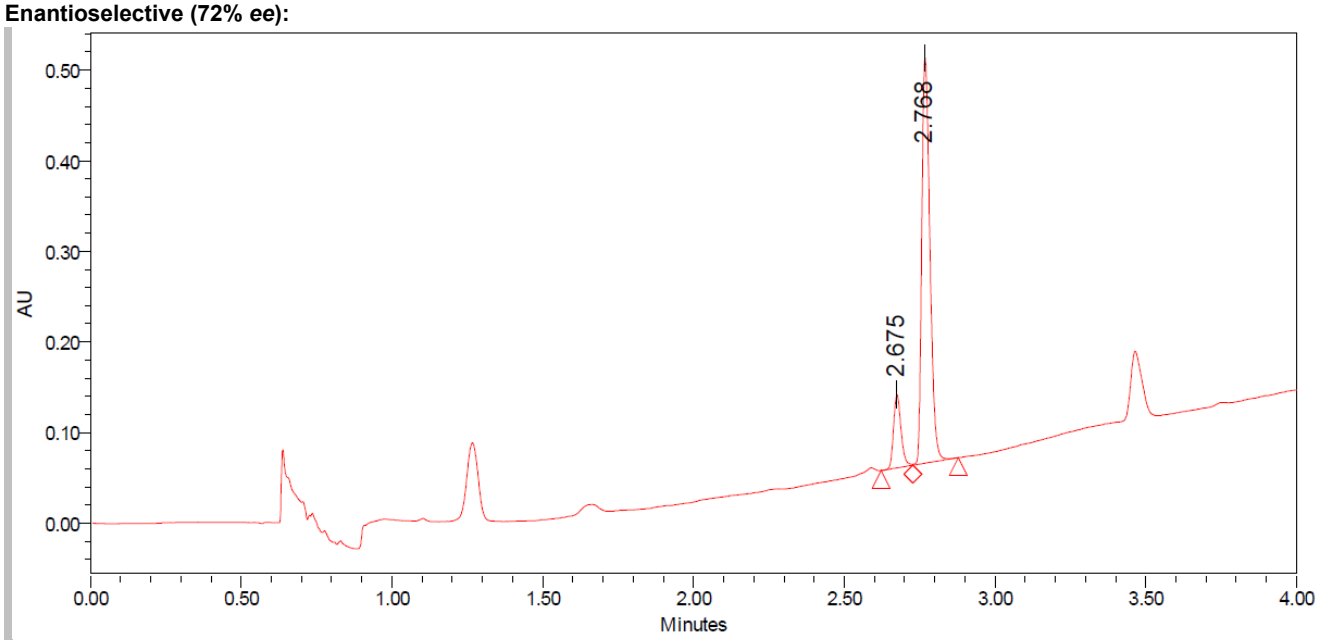
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	1.87	50.01	1.88	18.22
2	2.00	49.99	1.99	81.78
Total	(*Racemate*)	100	(*Enantioselective*)	100

Compound **45** (Step 2, 212 nm)

Racemic:



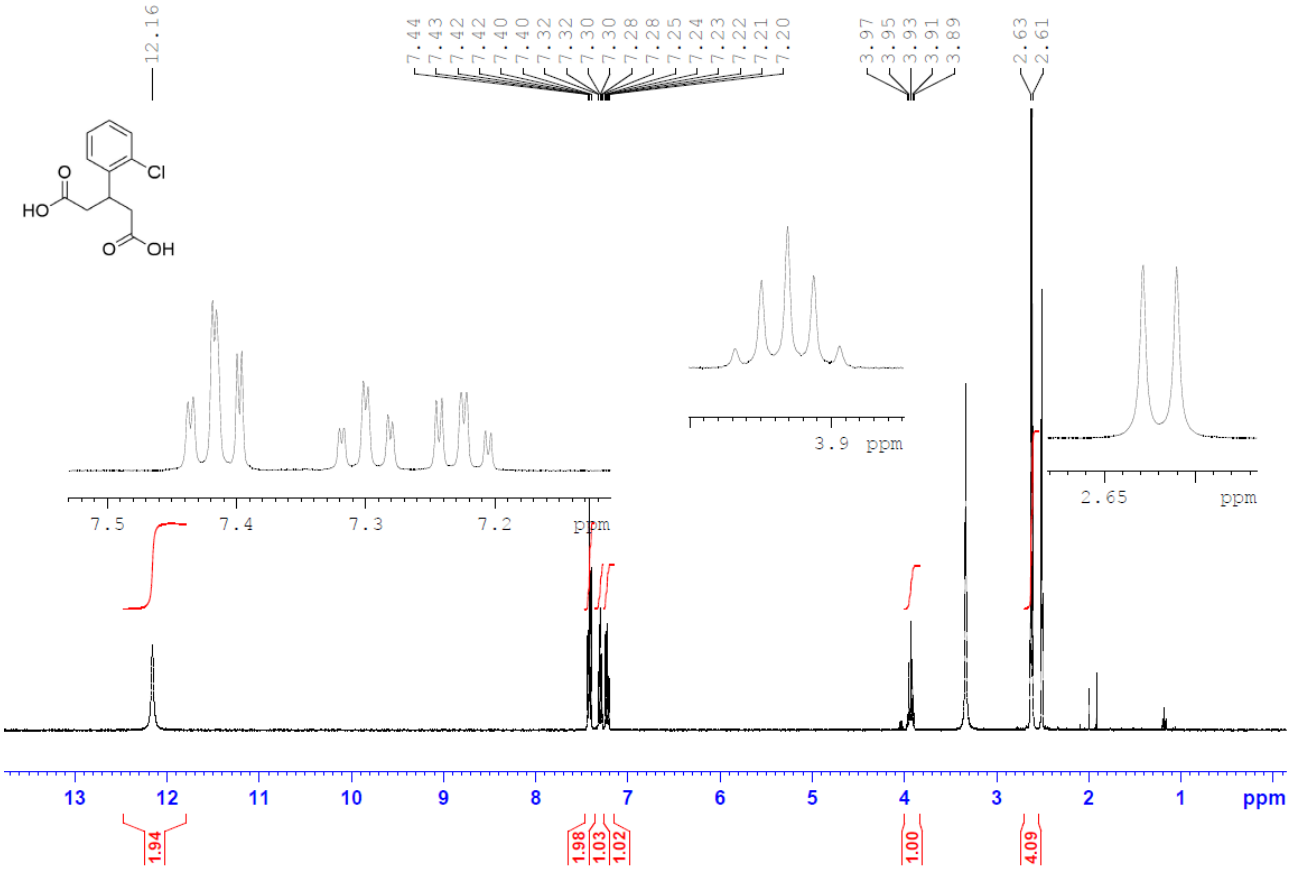
Enantioselective (72% *ee*):



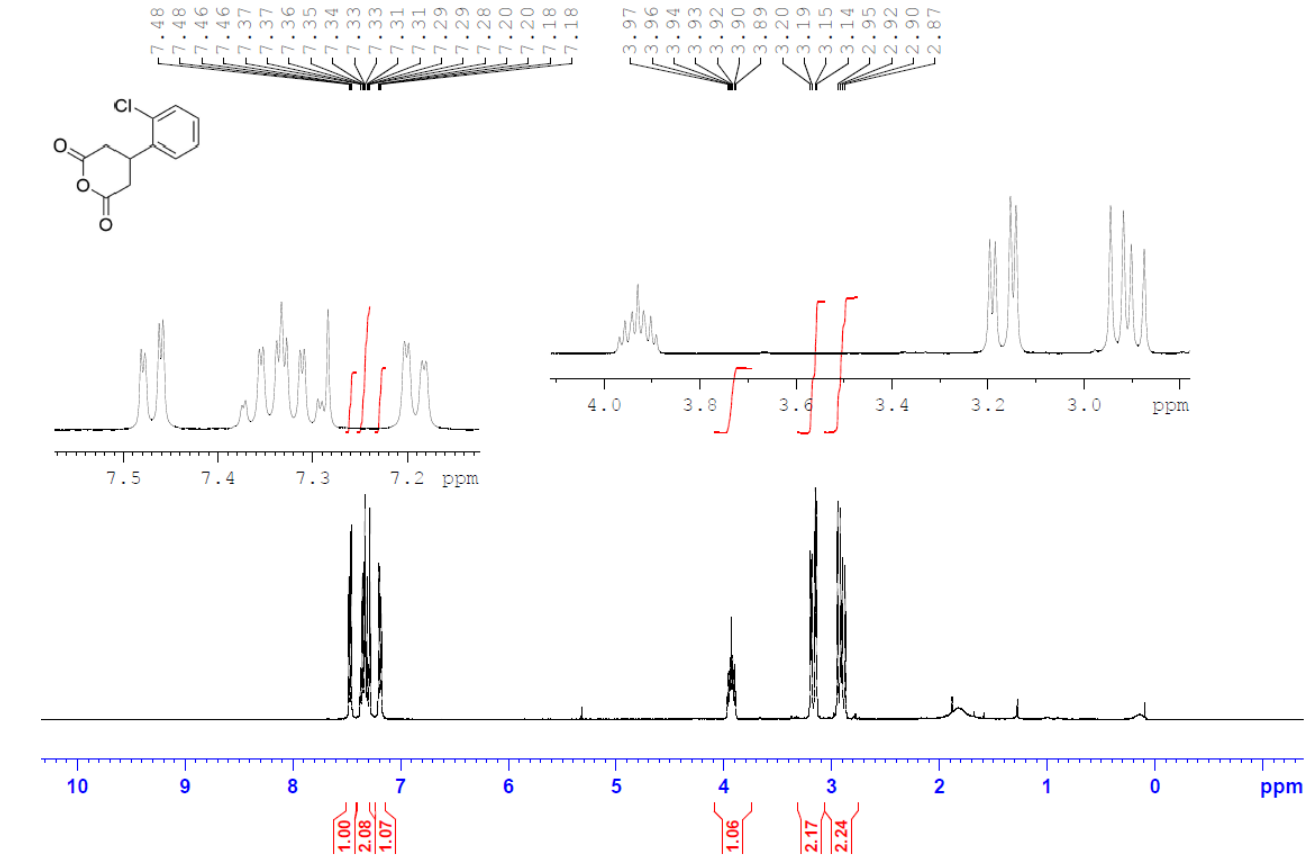
Entry	R_T (mins)	Area (%)	R_T (mins)	Area (%)
1	2.60	49.42	2.68	14.17
2	2.71	50.58	2.77	85.83
Total	(*Racemate*)	100	(*Enantioselective*)	100

7. NMR spectroscopic data

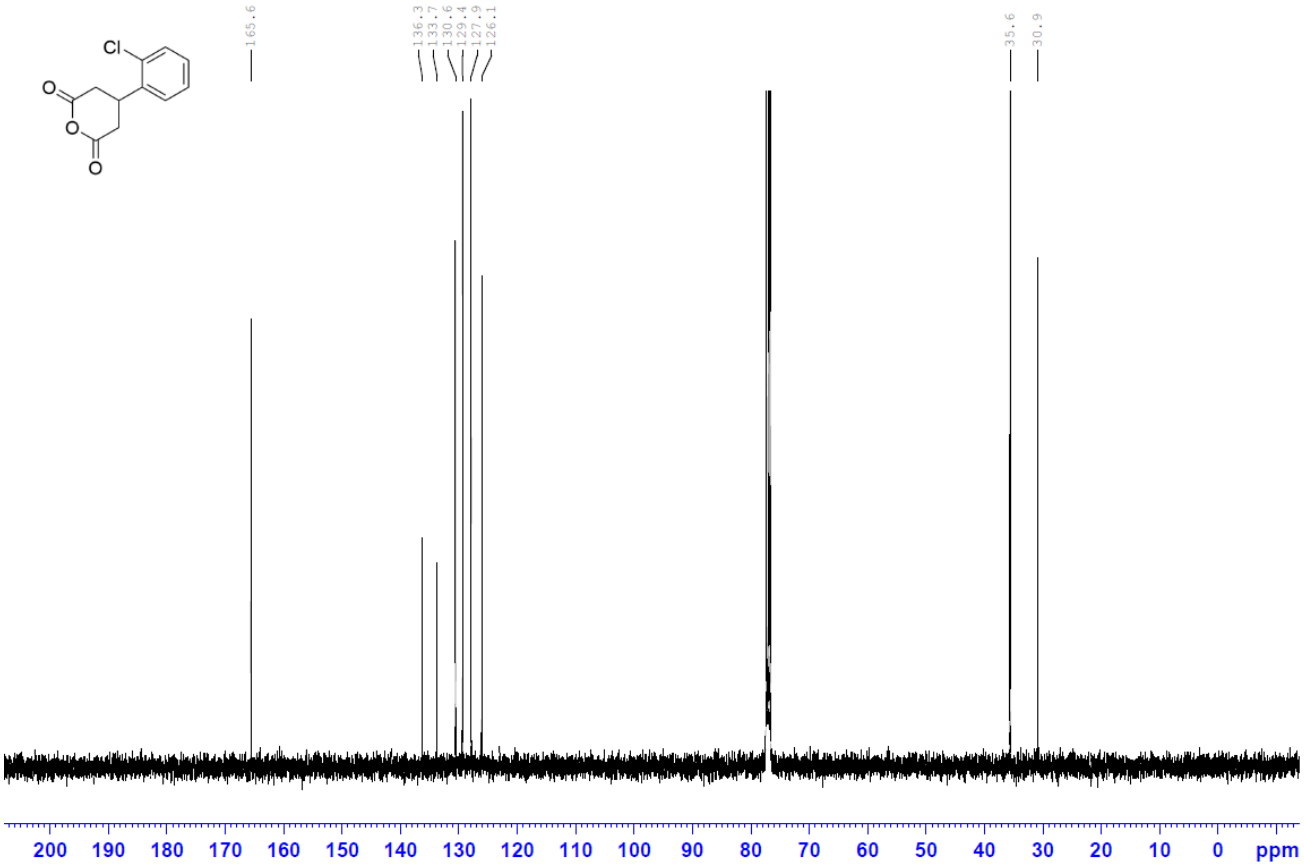
Compound **S15** (400MHz, DMSO-d_6)



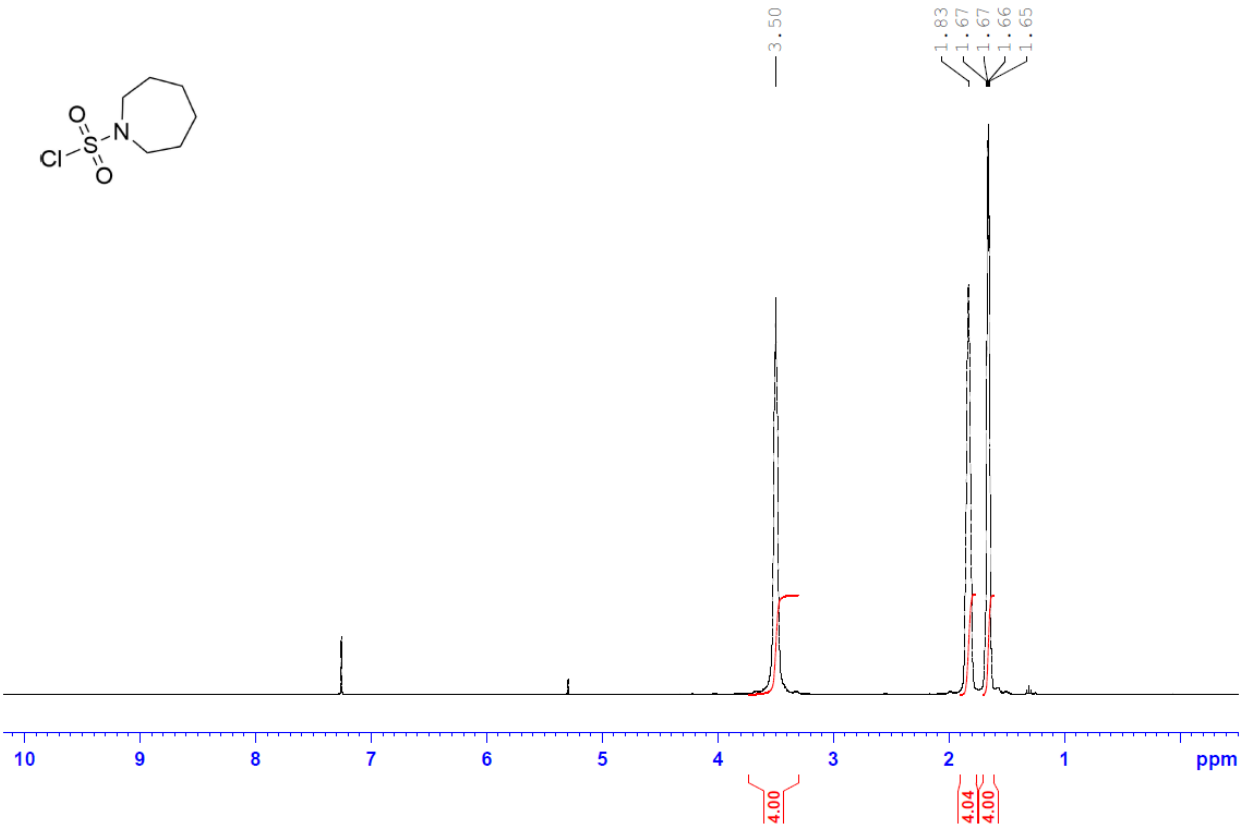
Compound **S7** ^{1}H NMR (400 MHz, $CDCl_3$)



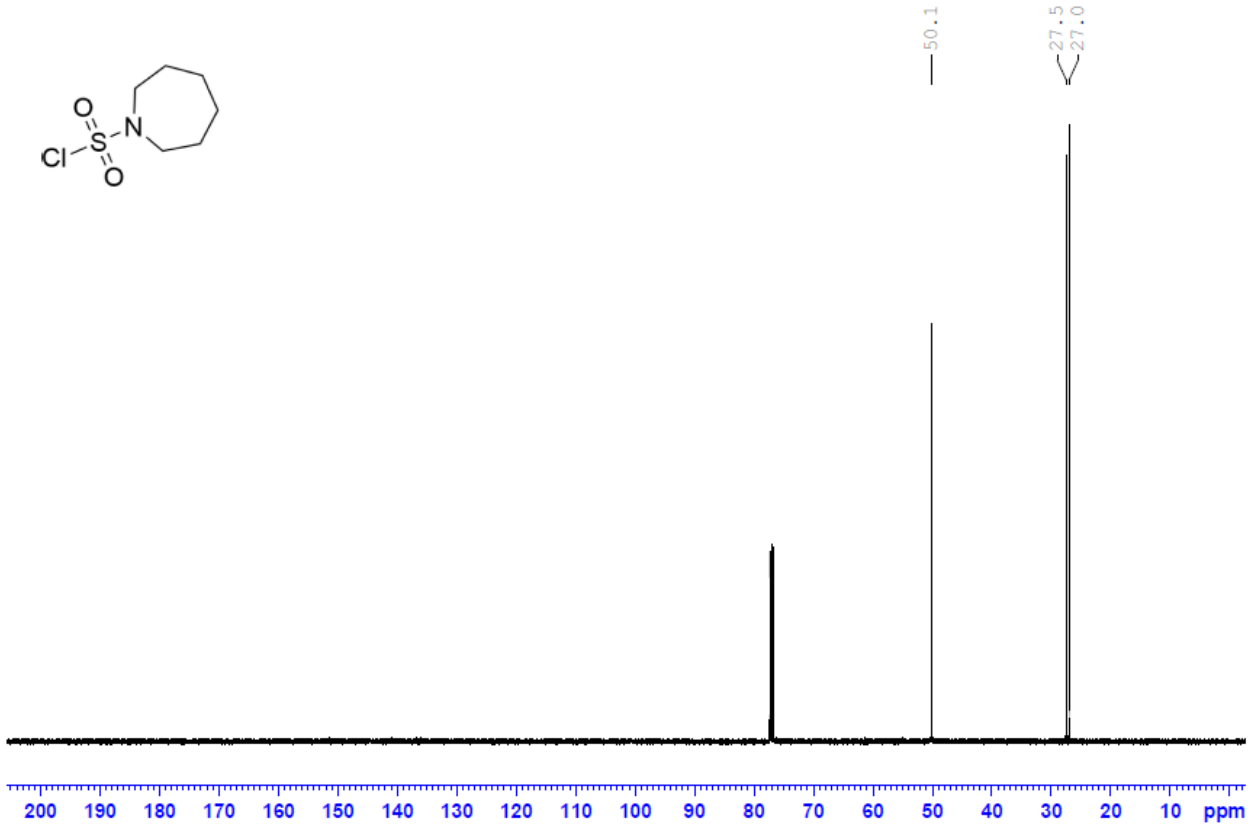
Compound **S7** ^{13}C NMR (101 MHz, $CDCl_3$)



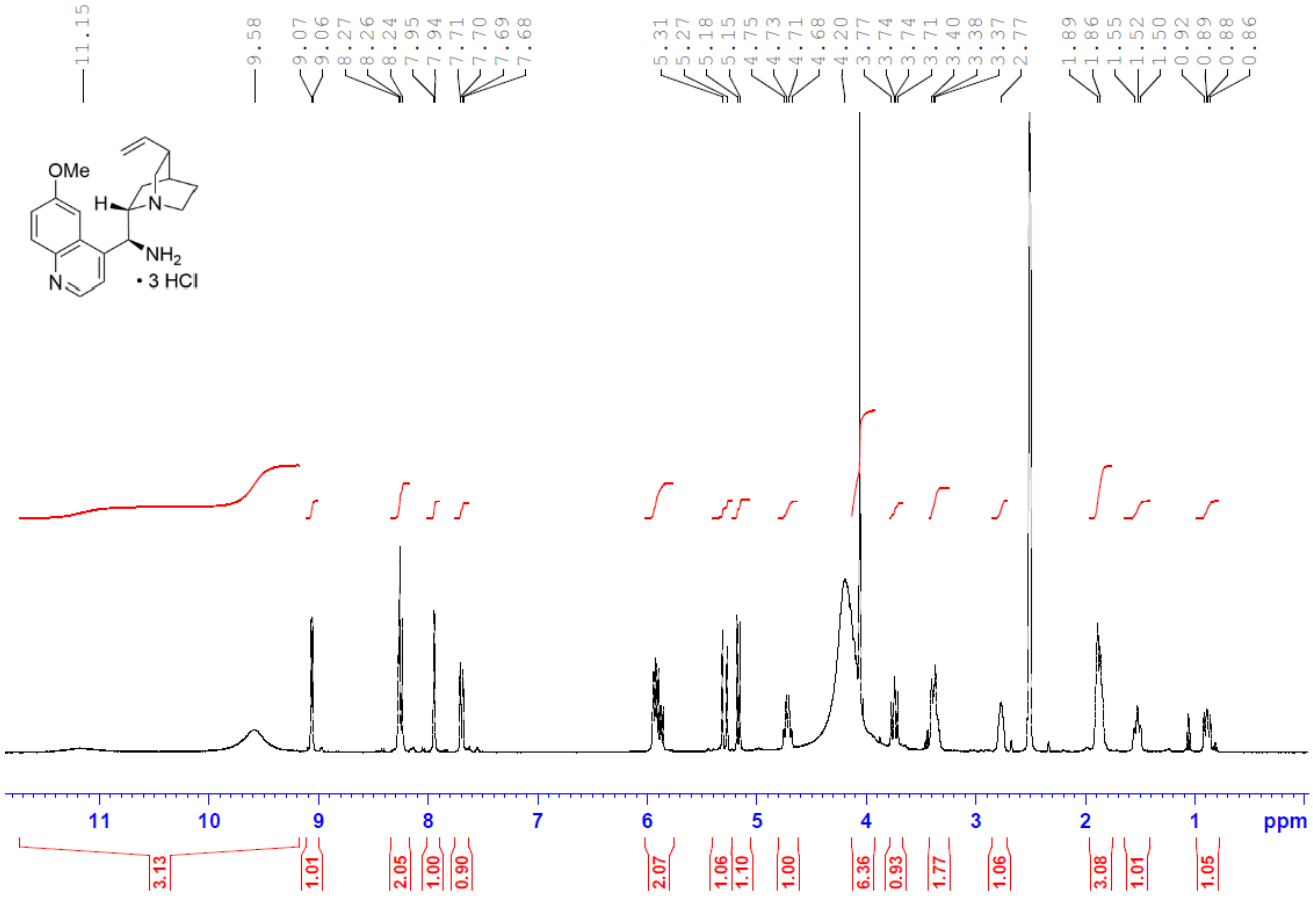
Compound **S16** ^{1}H NMR (400 MHz, $CDCl_3$)



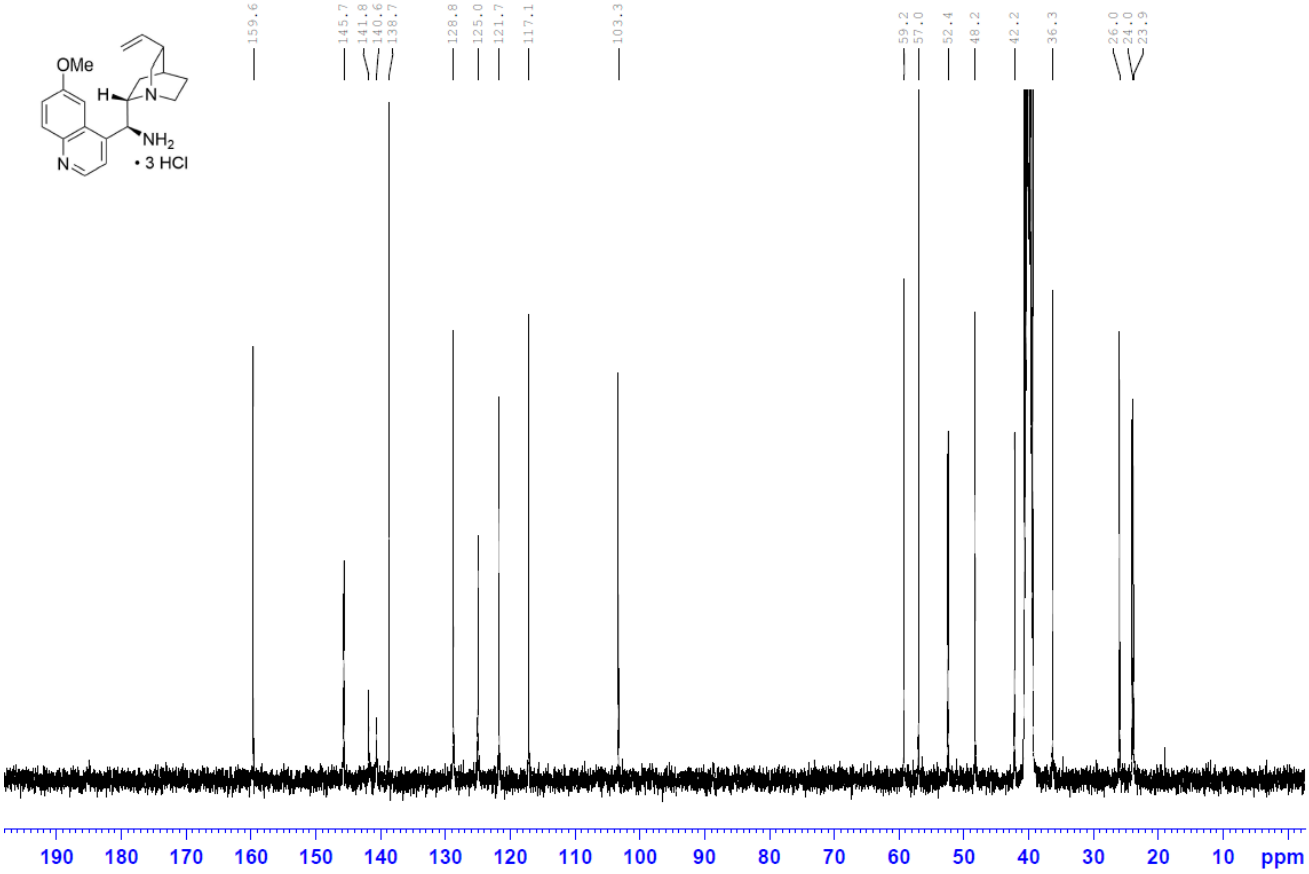
Compound **S16** ^{13}C NMR (101 MHz, $CDCl_3$)



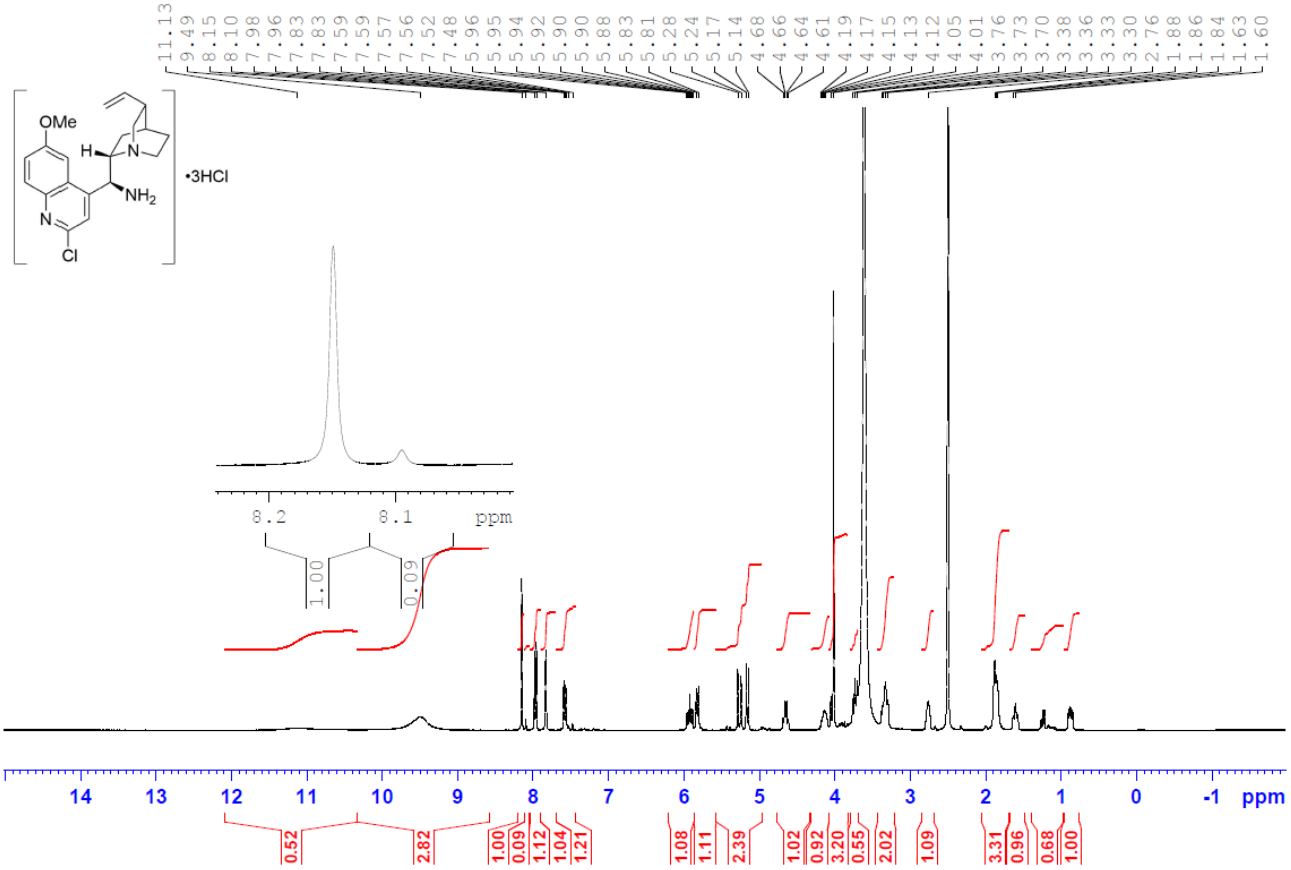
Compound **S17** ^{1}H NMR (400 MHz, DMSO-d_6)



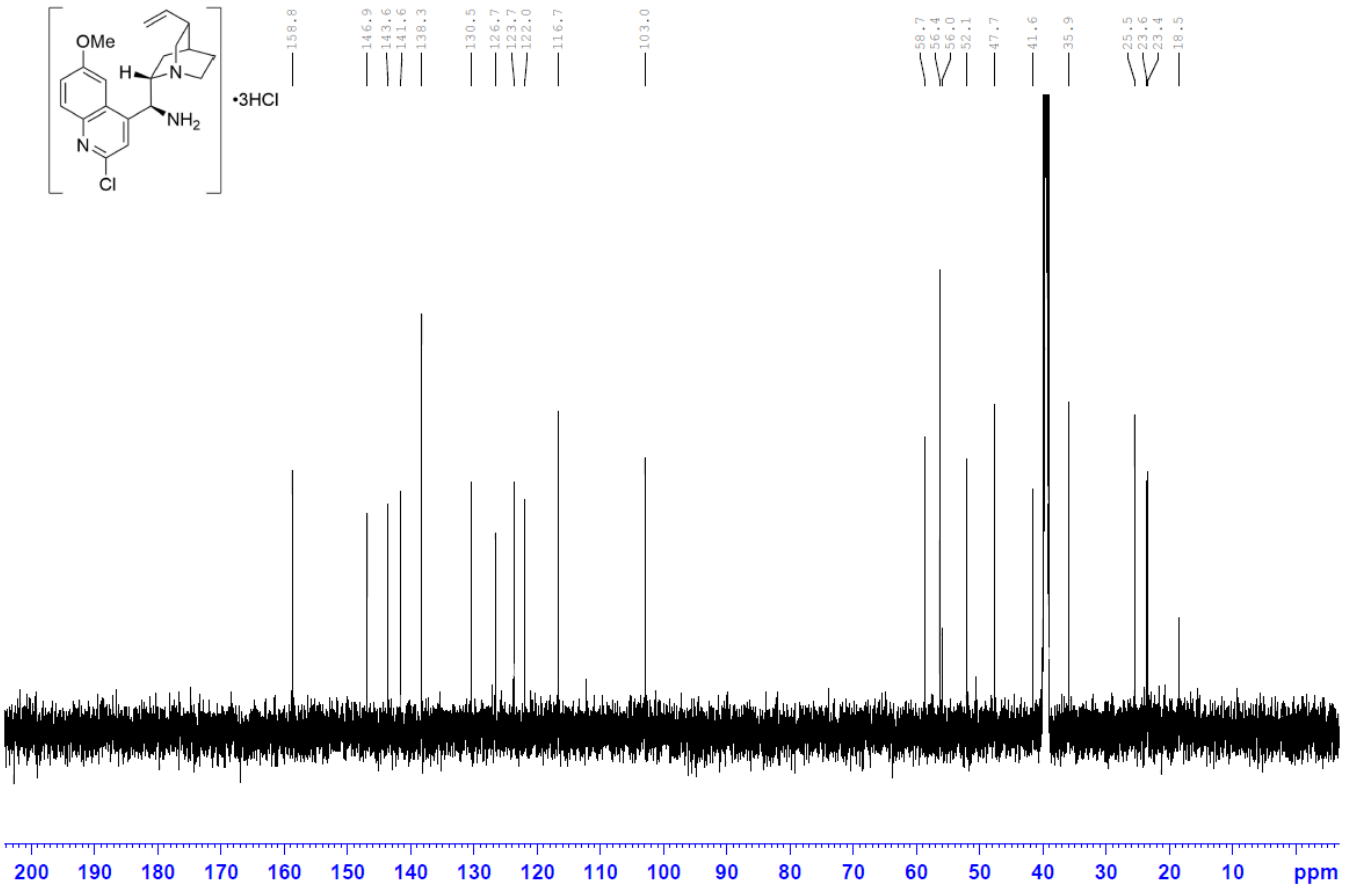
Compound **S17** ^{13}C NMR (101 MHz, DMSO-d_6)



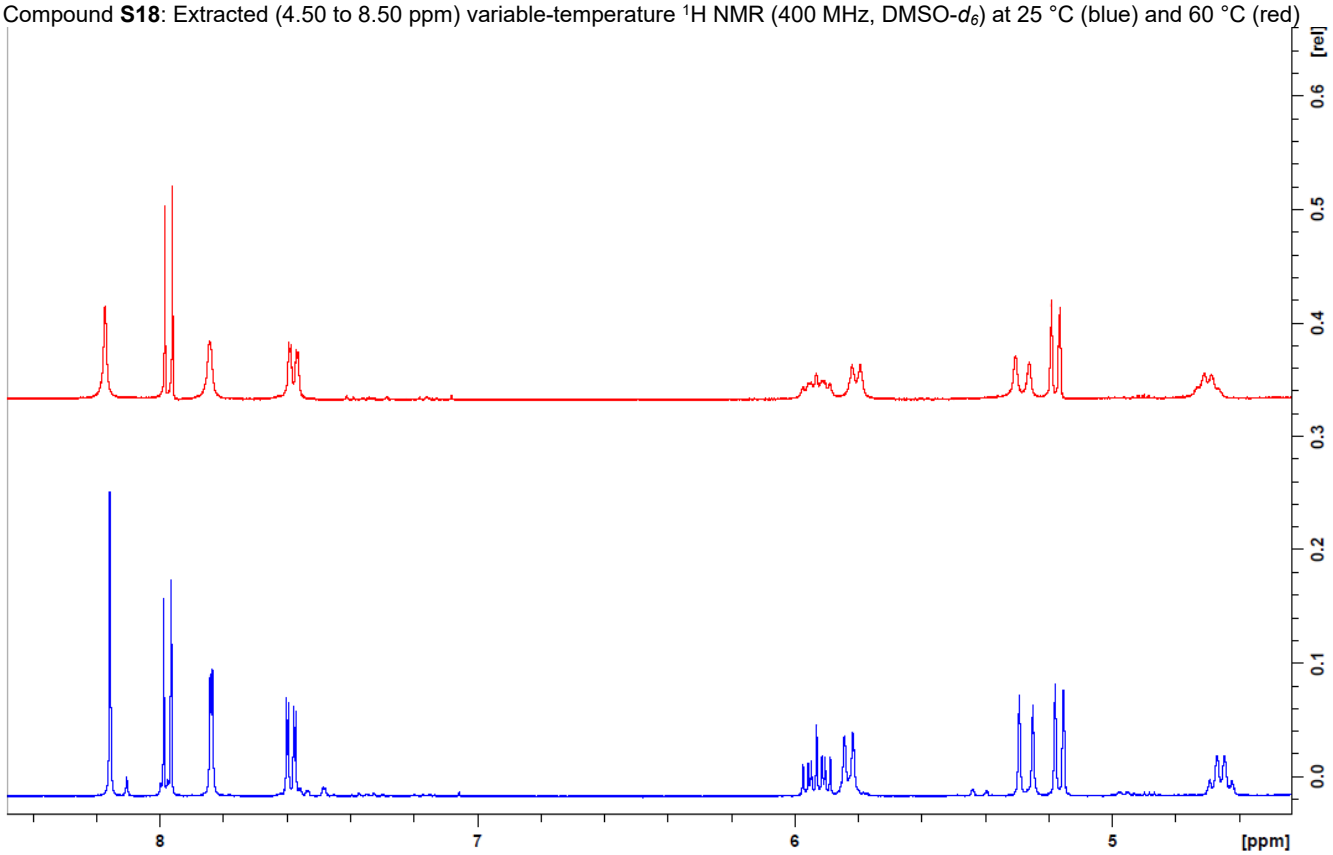
Compound **S18** ^{1}H NMR (400 MHz, DMSO-d_6)



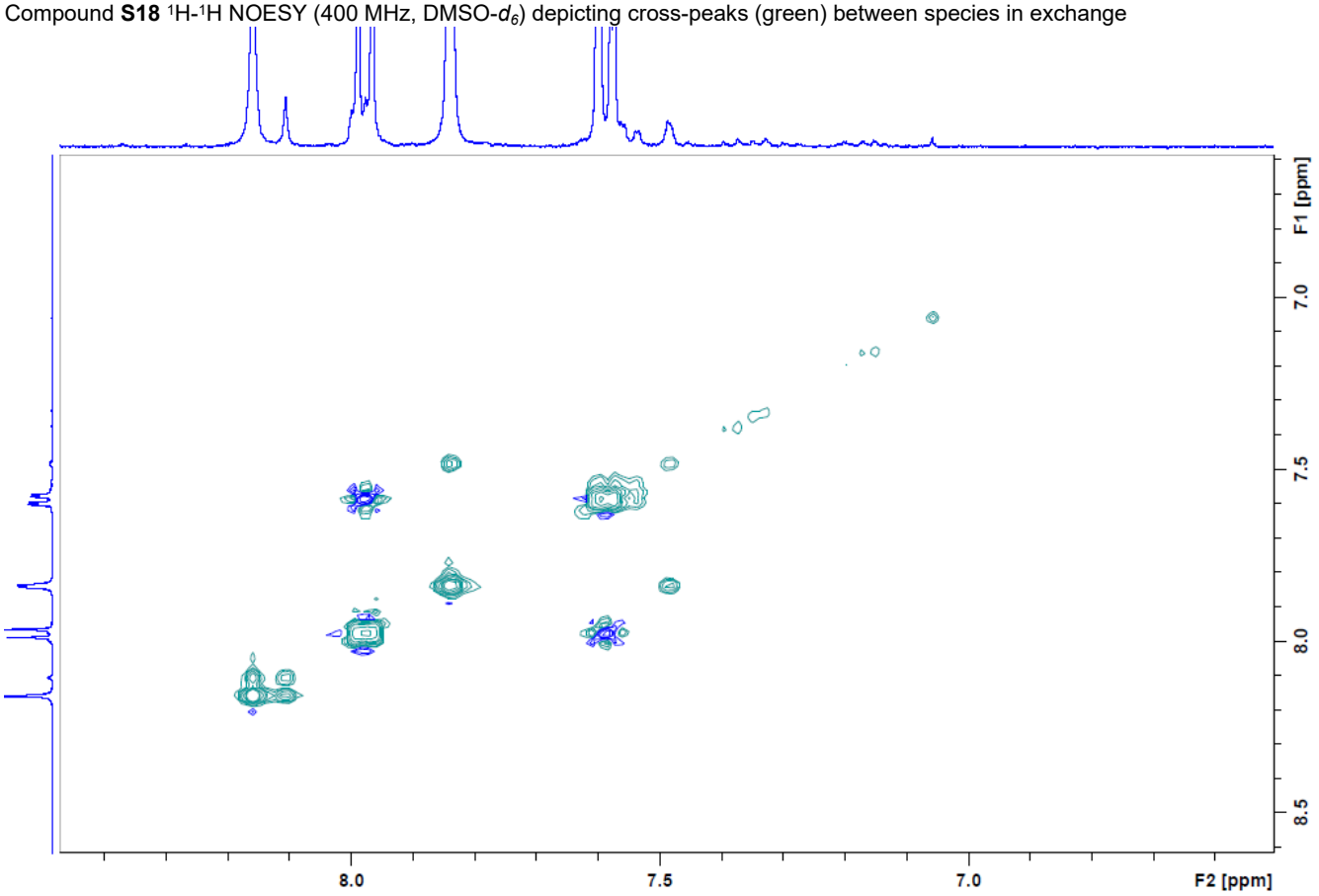
Compound **S18** ^{13}C NMR (101 MHz, DMSO-d_6)



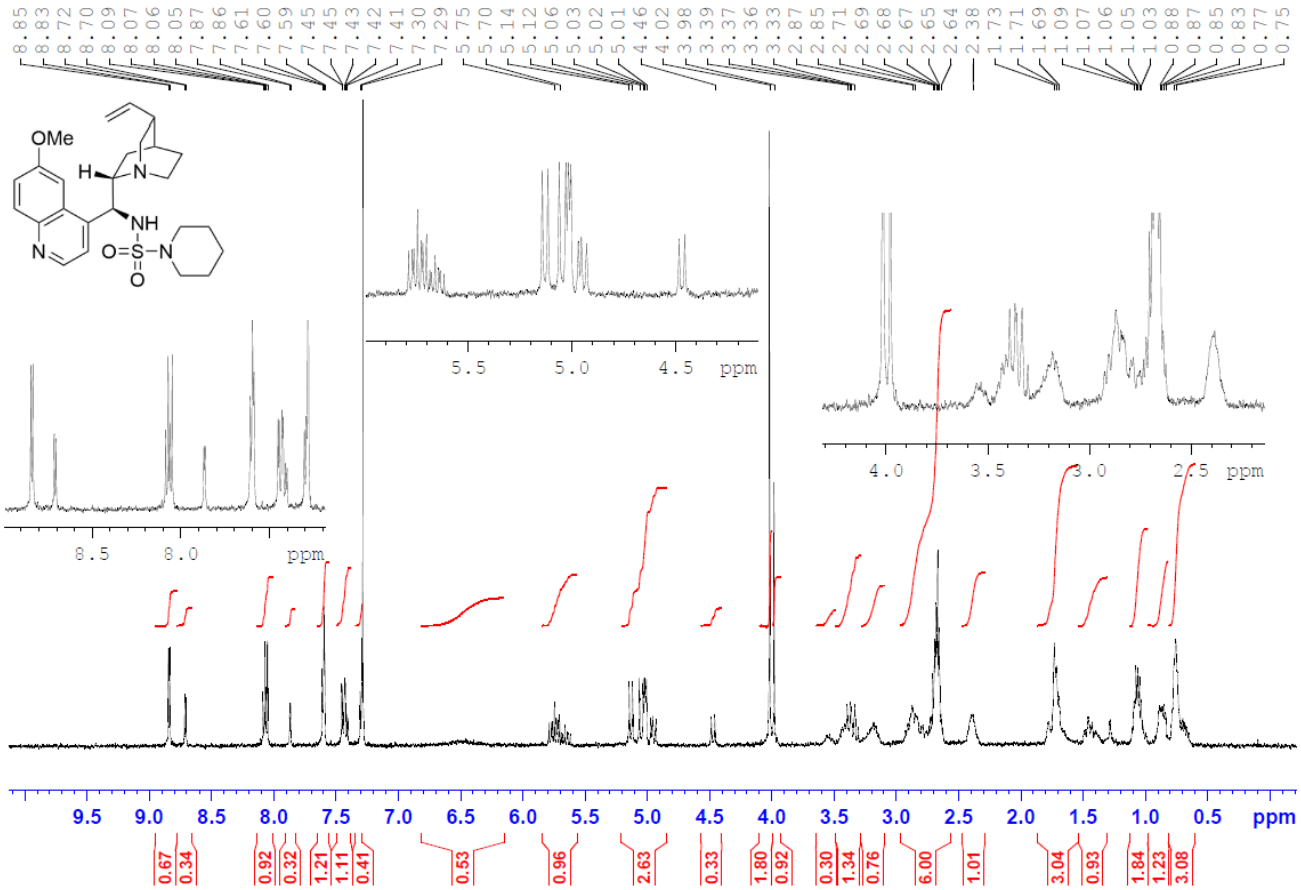
Compound **S18**: Extracted (4.50 to 8.50 ppm) variable-temperature ^{1}H NMR (400 MHz, DMSO-d_6) at 25 °C (blue) and 60 °C (red)



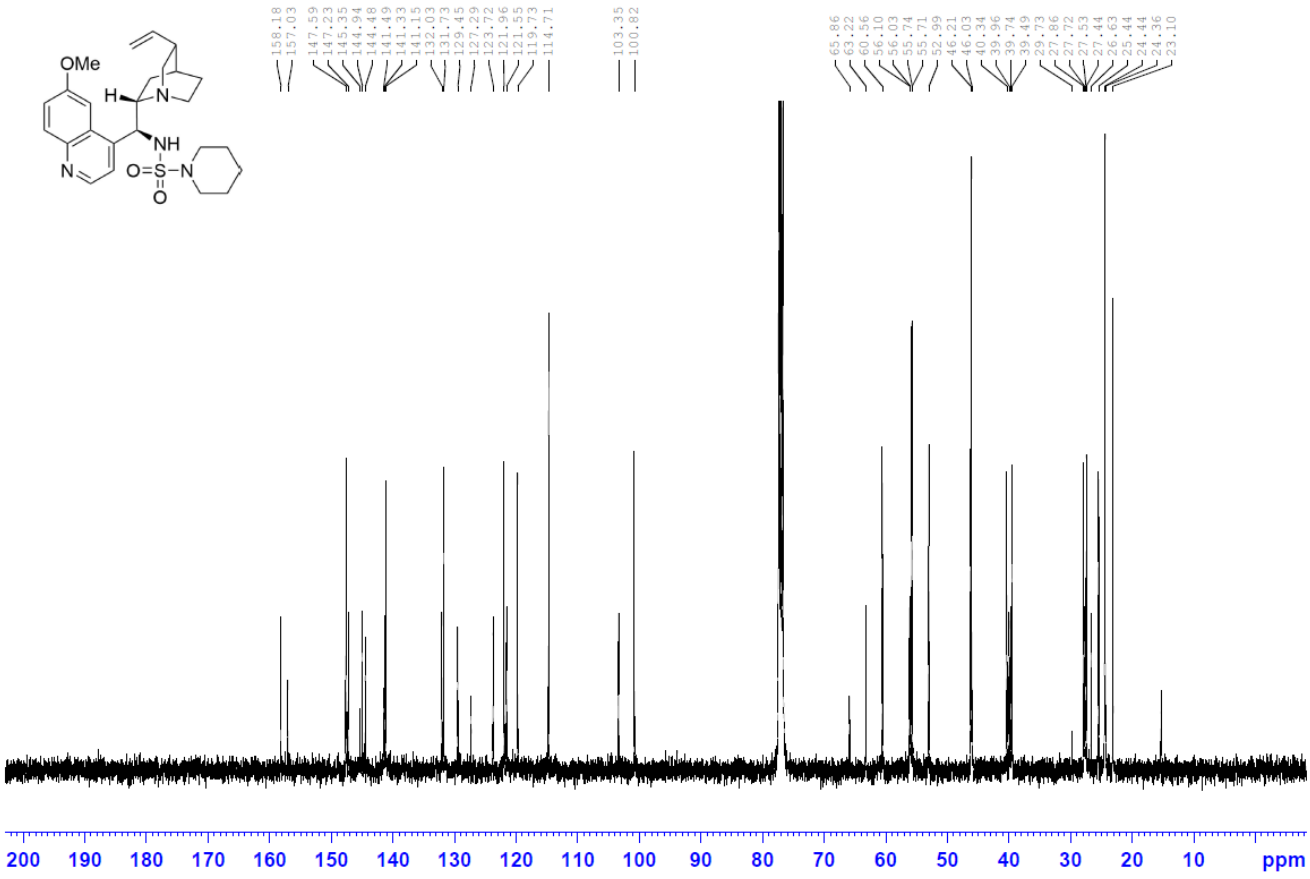
Compound **S18** ^{1}H-^{1}H NOESY (400 MHz, DMSO-d_6) depicting cross-peaks (green) between species in exchange



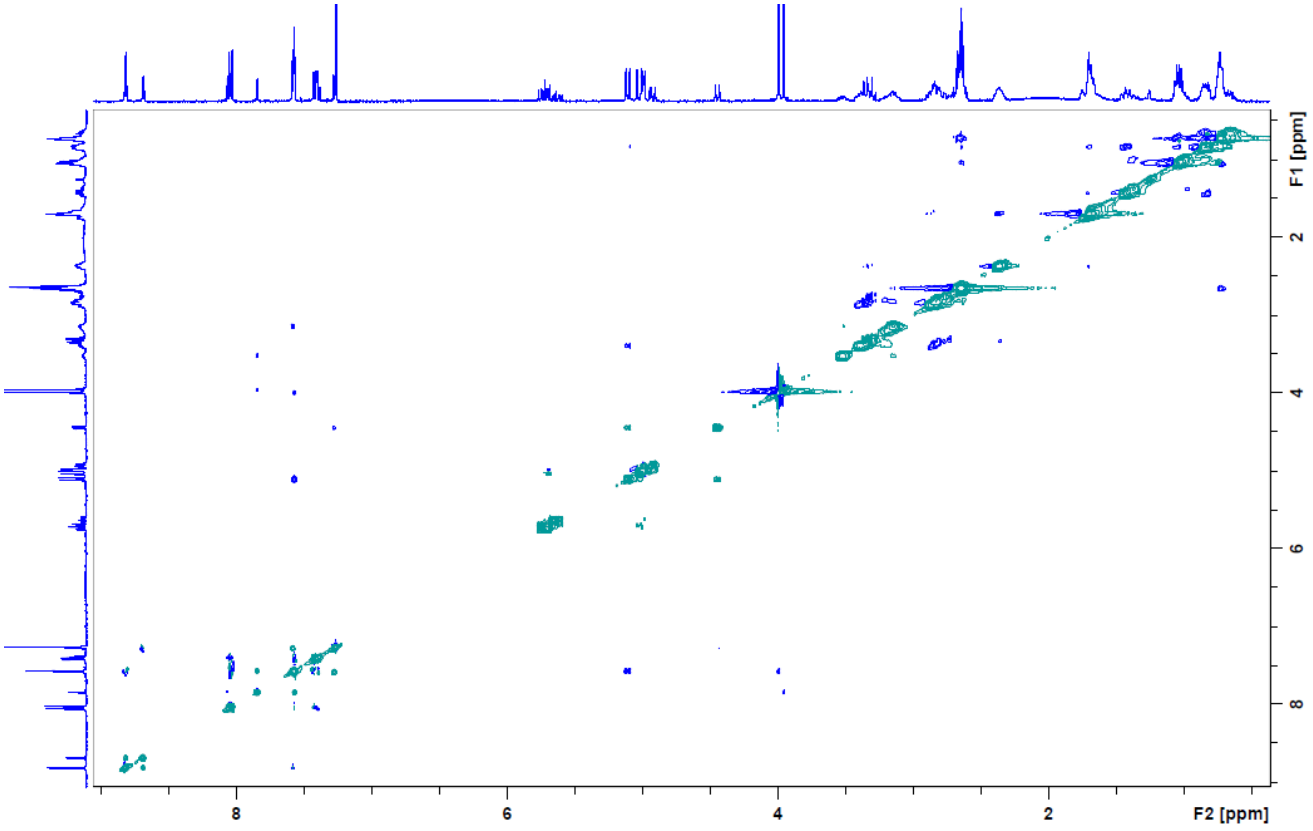
Piperidine sulfamide **13** ^{1}H NMR (400 MHz, $CDCl_3$)



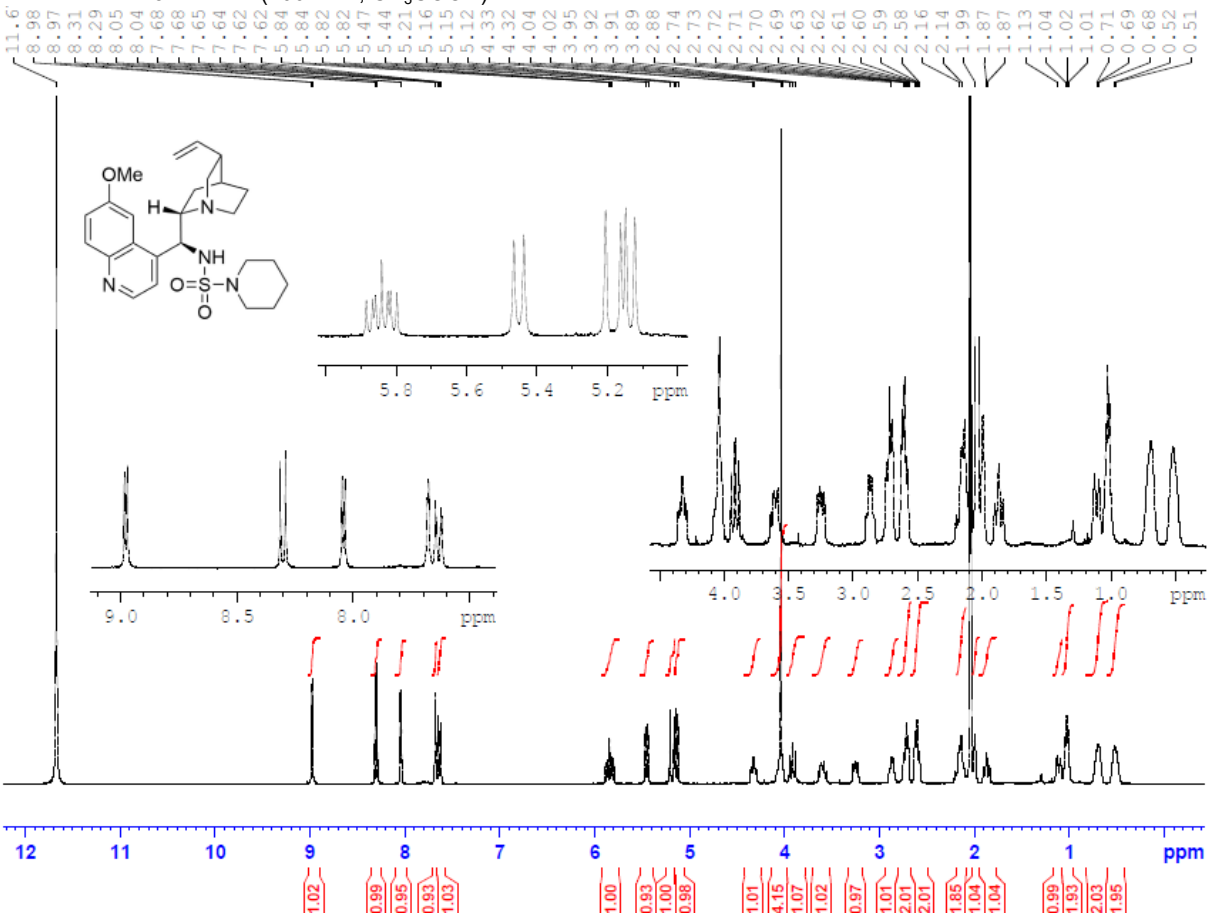
Piperidine sulfamide **13** ^{13}C NMR (101 MHz, $CDCl_3$)



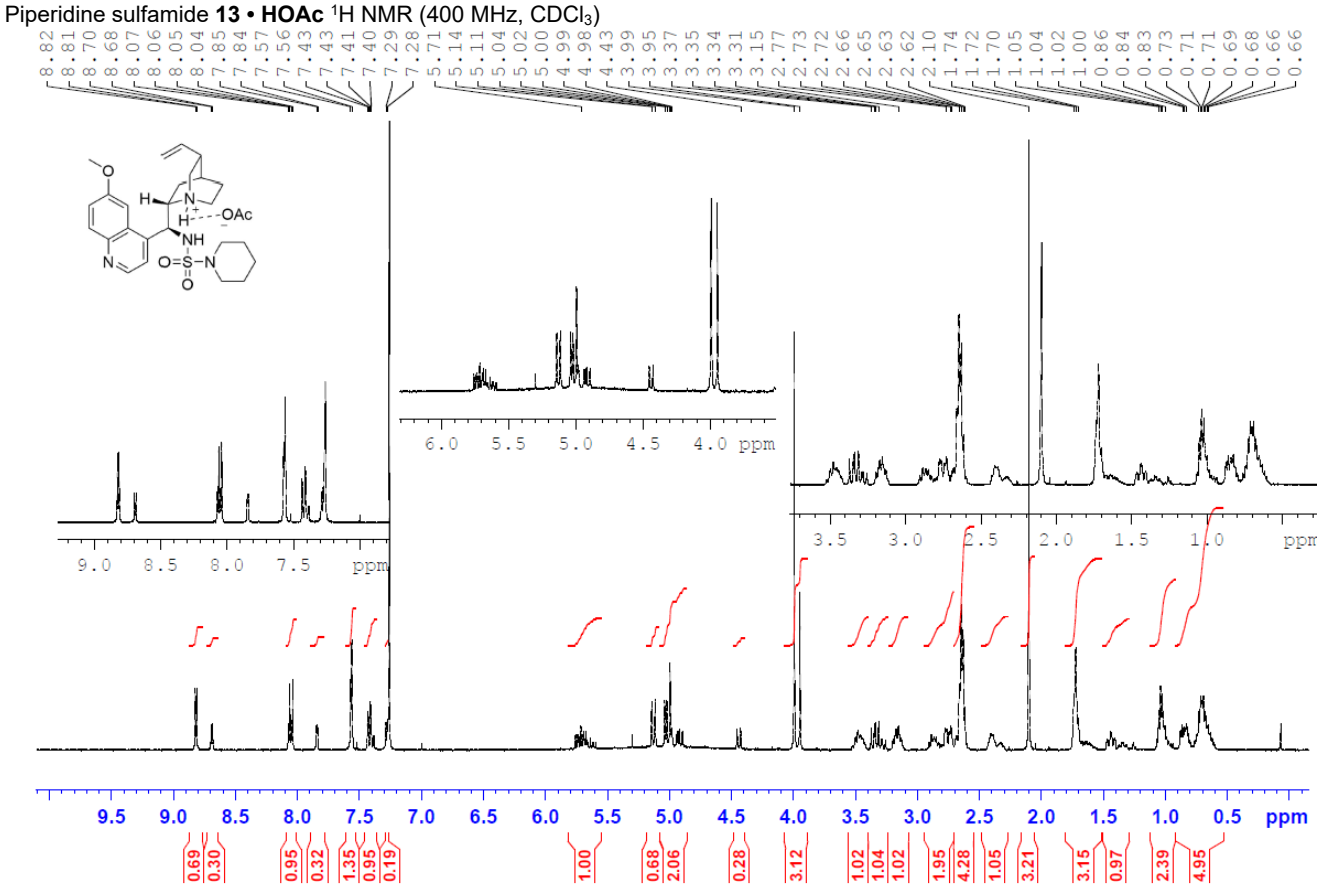
Piperidine sulfamide **13** ^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)



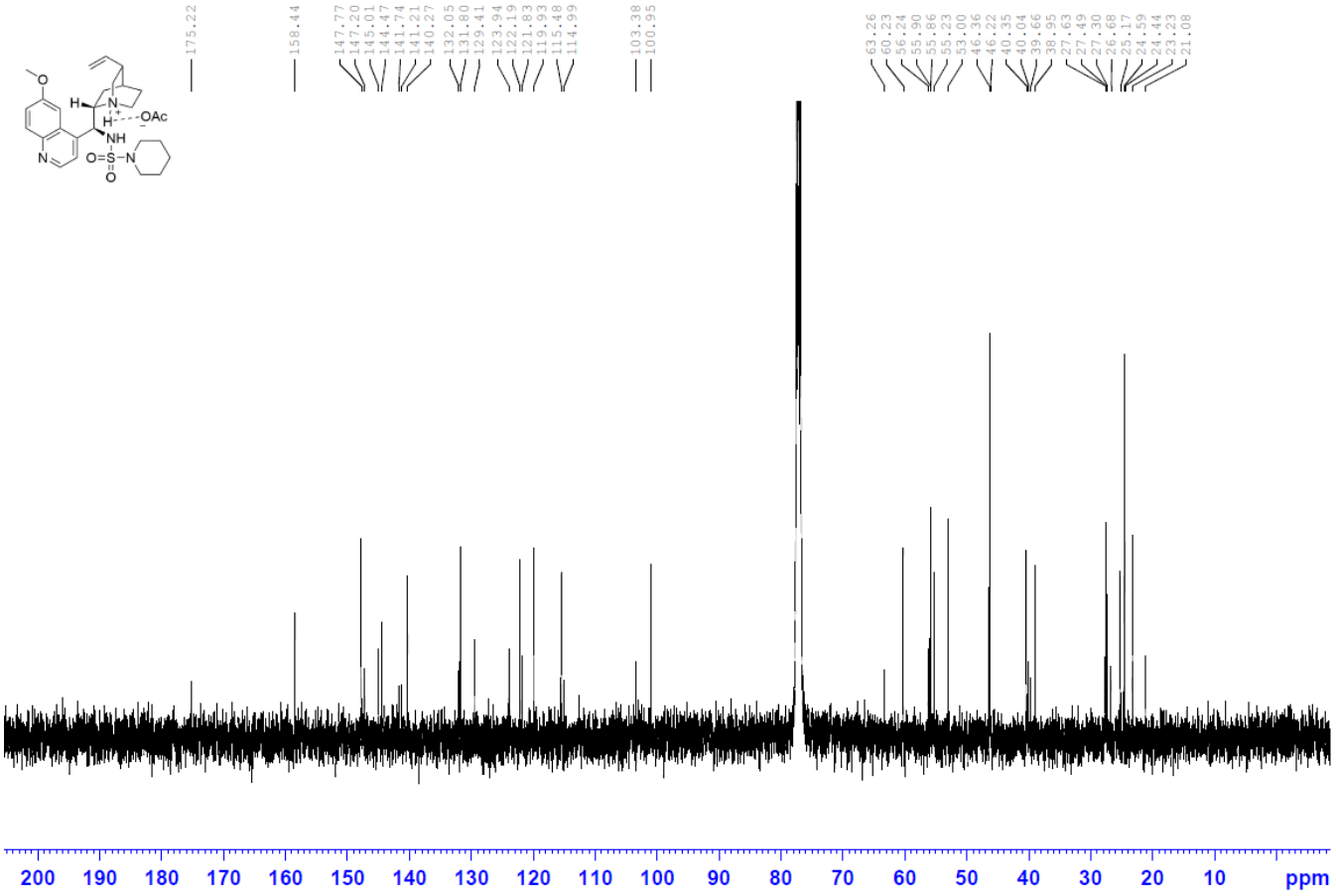
Piperidine sulfamide **13** ^{1}H NMR (400 MHz, CD_3COOD)



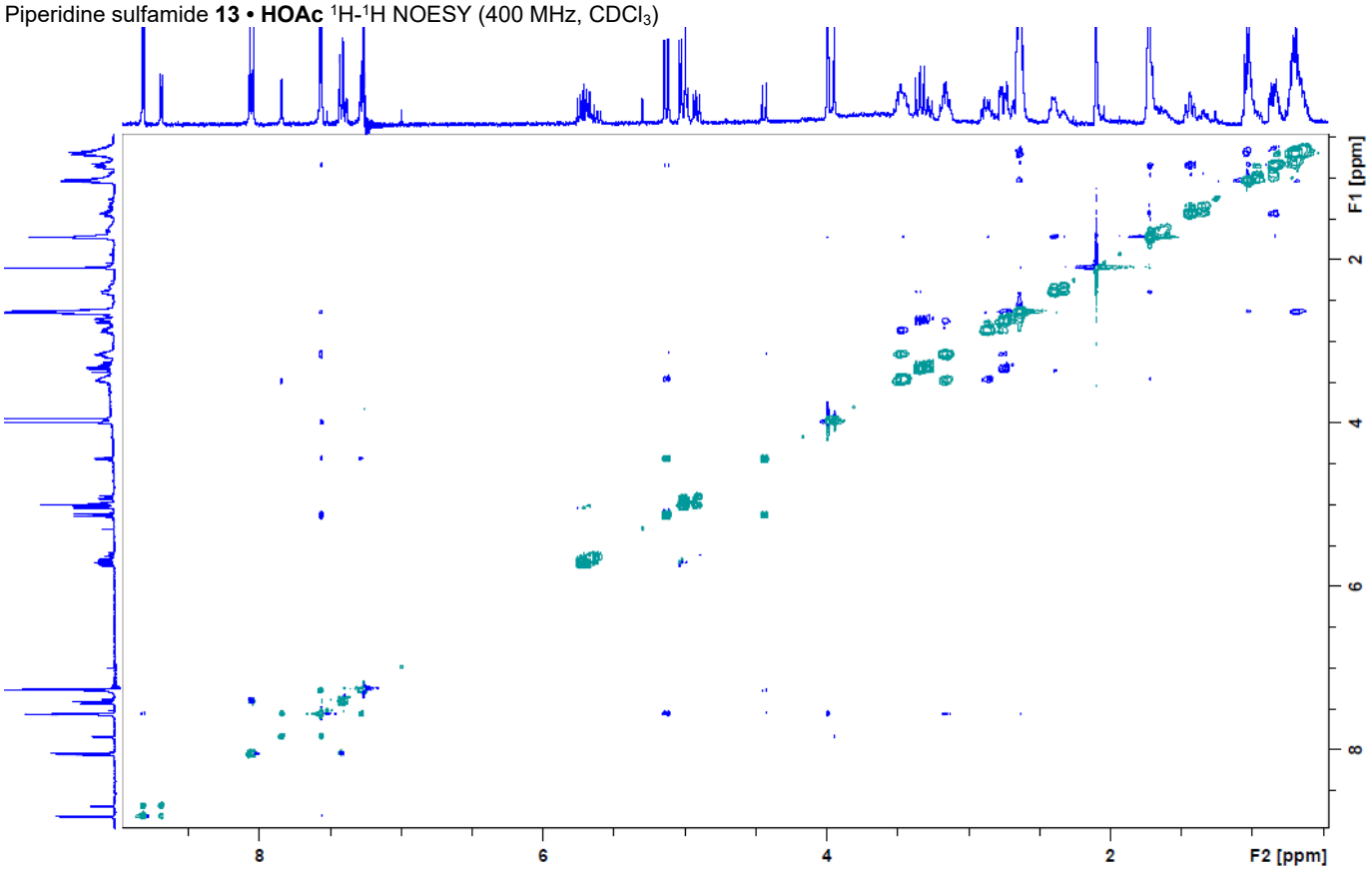
Piperidine sulfamide **13 • HOAc** ^{1}H NMR (400 MHz, $CDCl_3$)



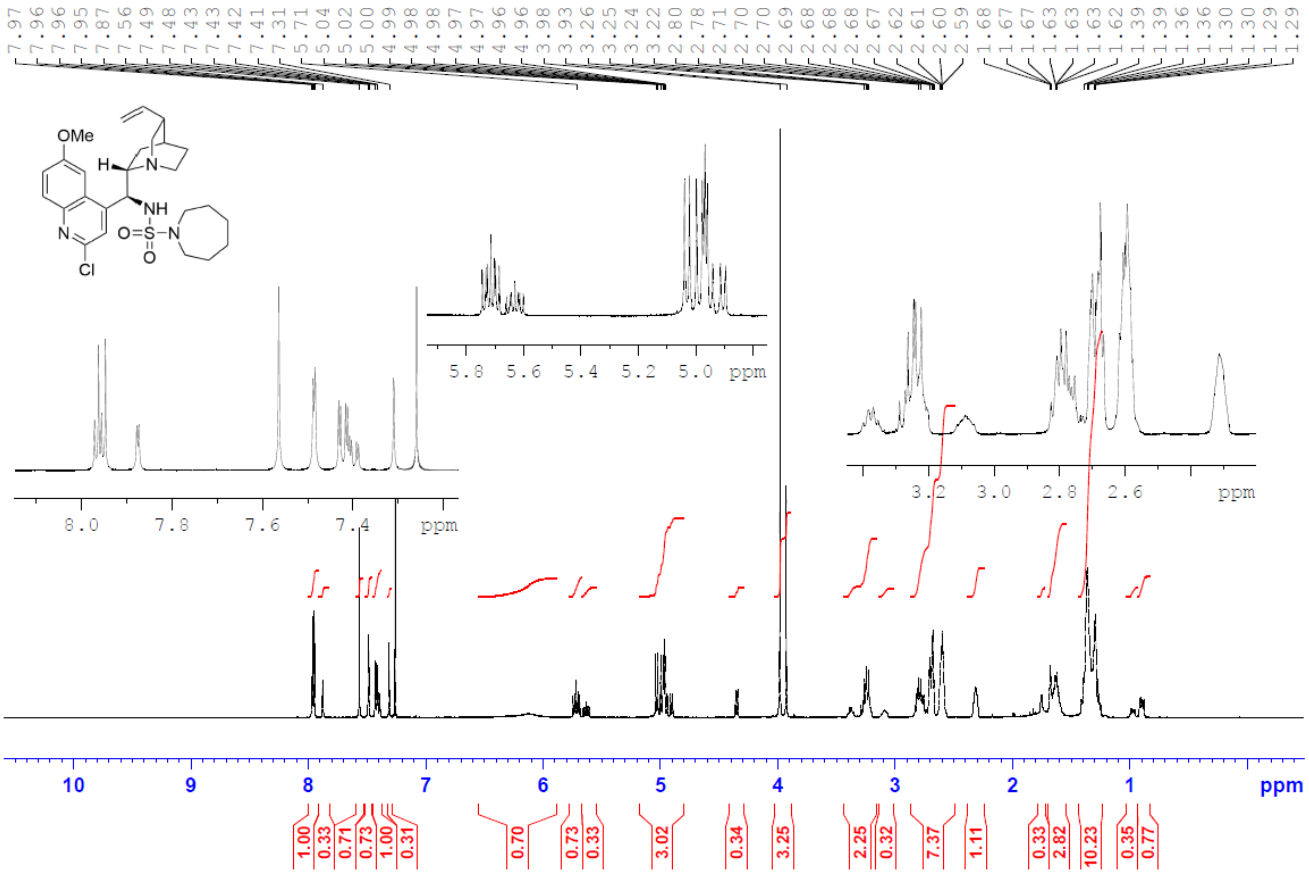
Piperidine sulfamide **13 • HOAc** ^{13}C NMR (101 MHz, $CDCl_3$)



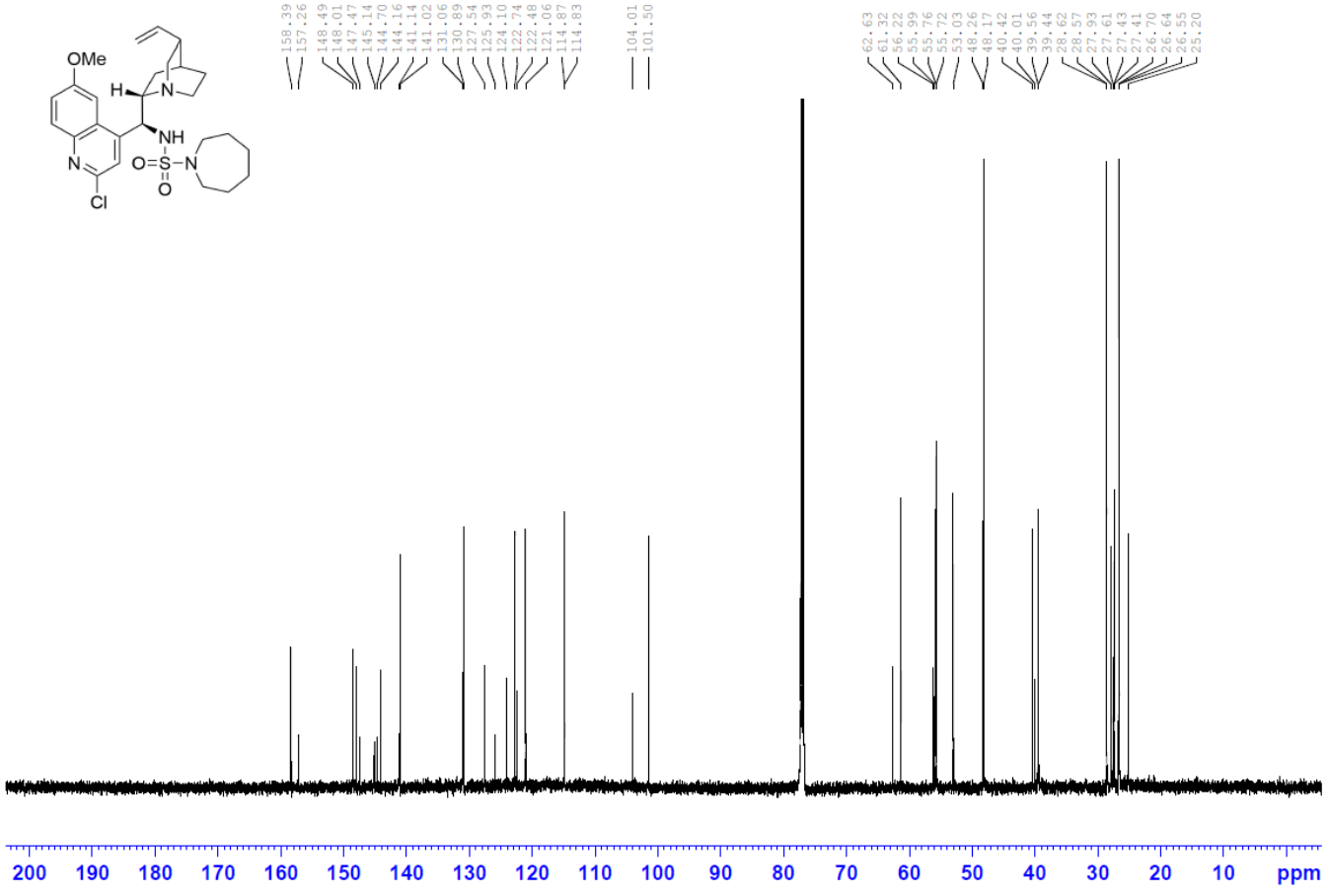
Piperidine sulfamide **13 • HOAc** ^{1}H-^{1}H NOESY (400 MHz, $CDCl_3$)



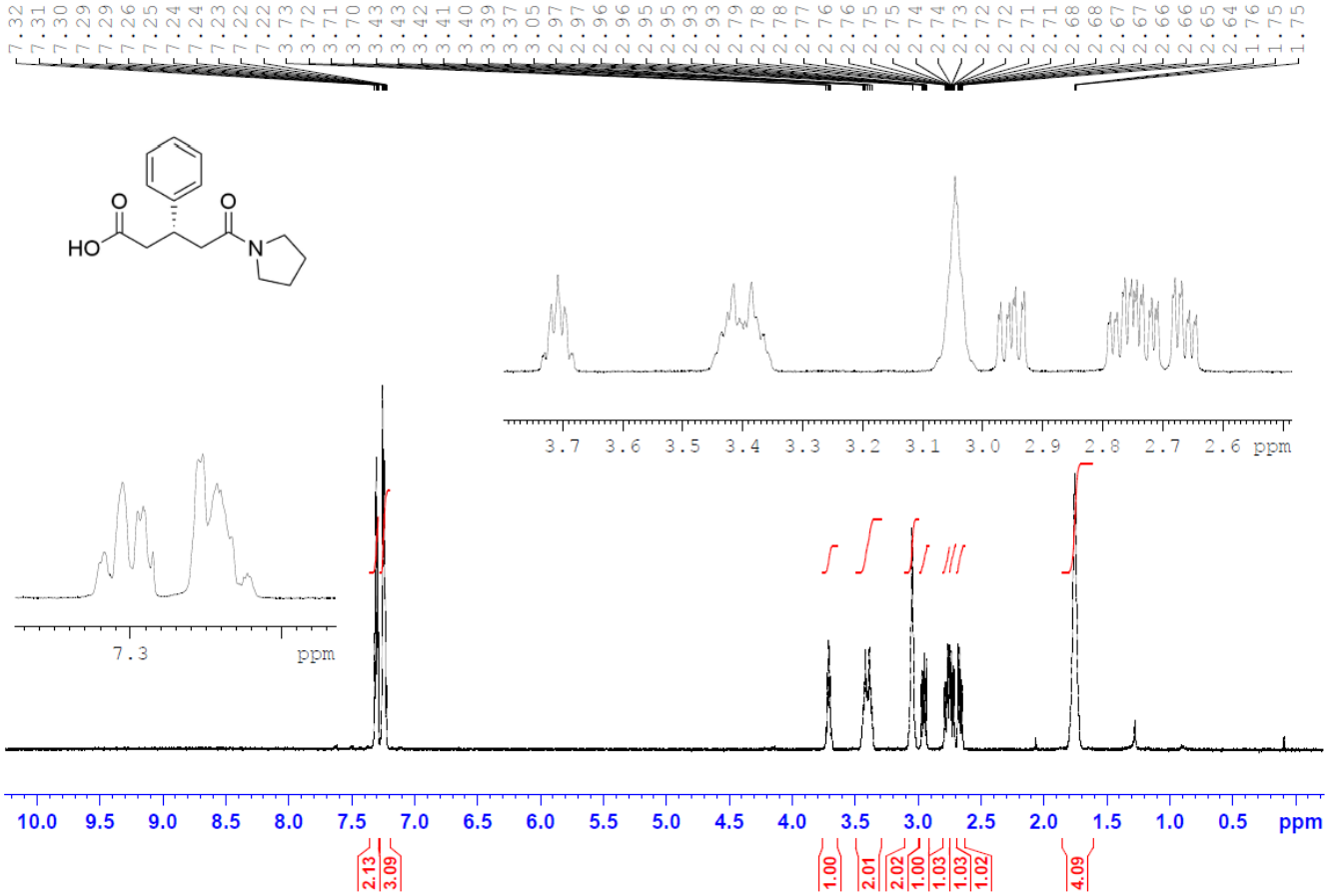
C2'-chloroazepane sulfamide **31** ^{1}H NMR (600 MHz, $CDCl_3$)



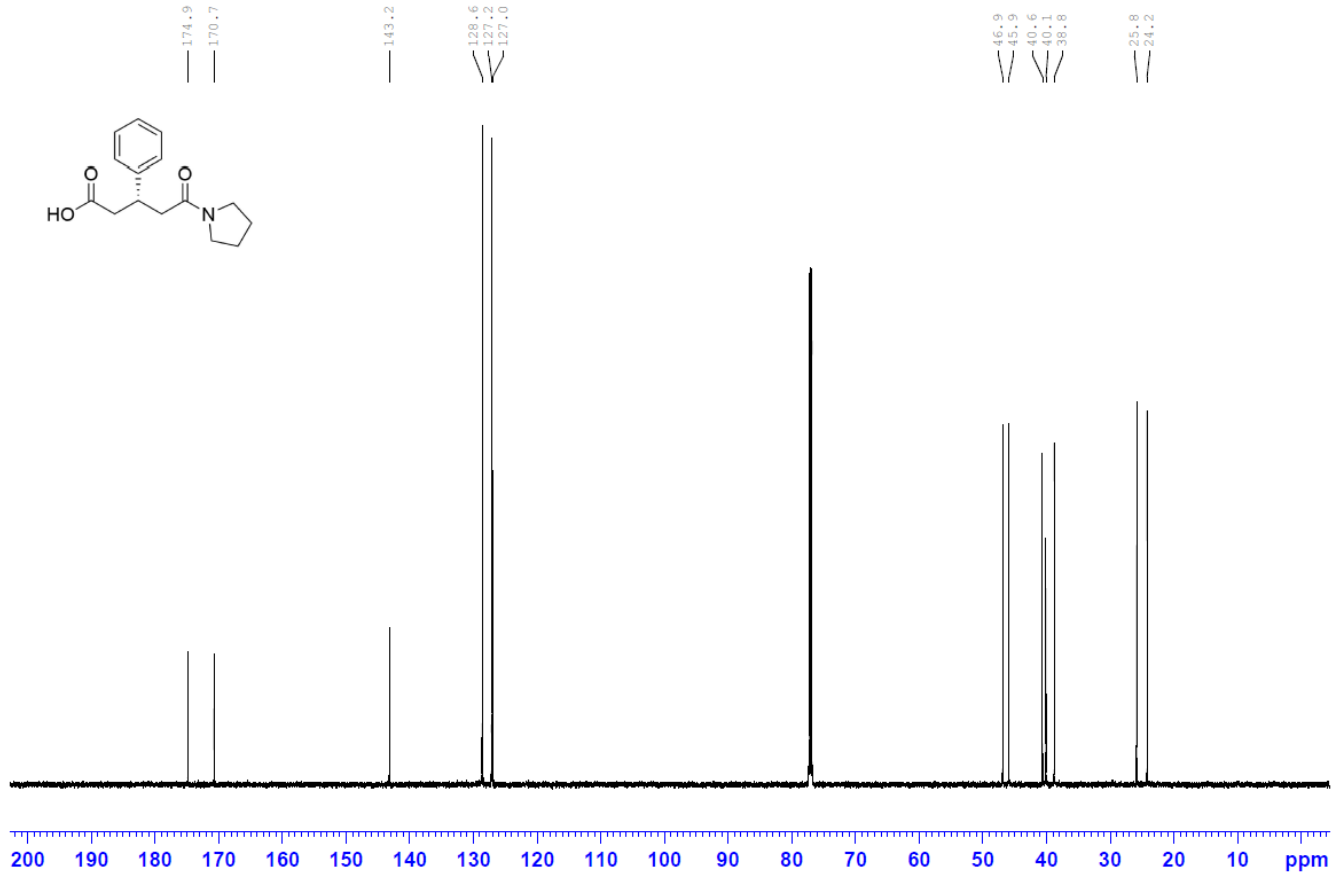
C2'-chloroazepane sulfamide **31** ^{13}C NMR (151 MHz, $CDCl_3$)



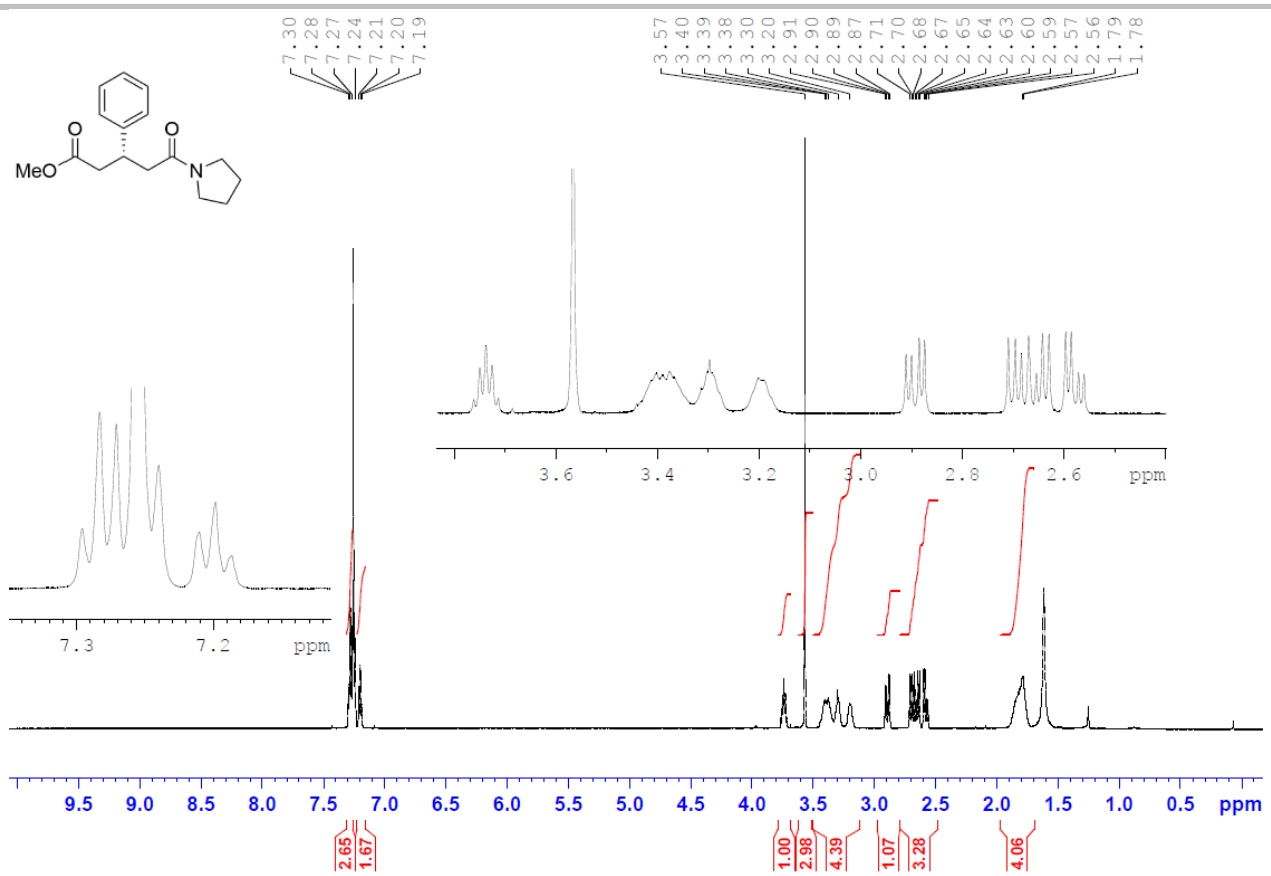
Compound **S1** ^{1}H NMR (600 MHz, $CDCl_3$)



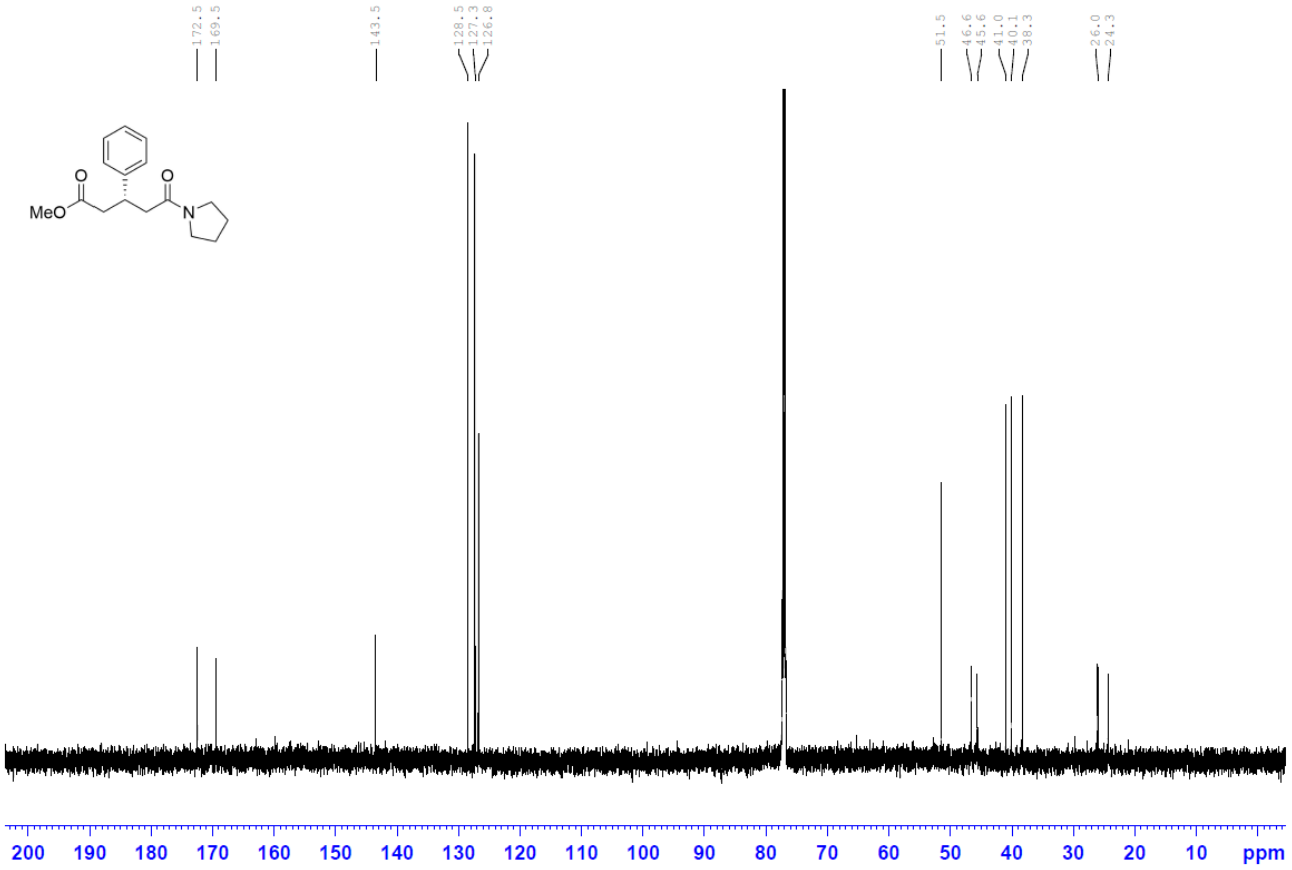
Compound **S1** ^{13}C NMR (151 MHz, $CDCl_3$)



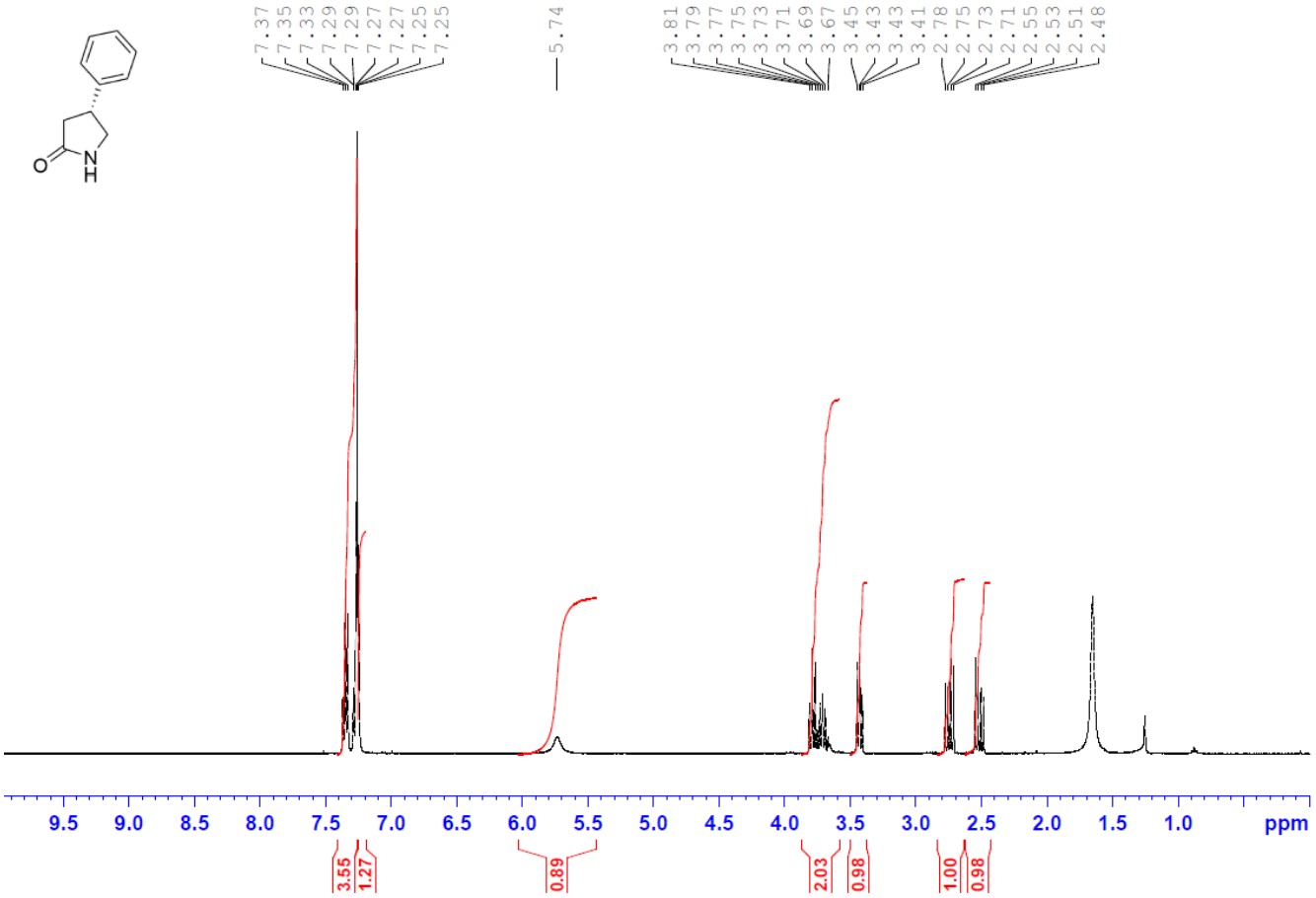
Compound **3** ^{1}H NMR (600 MHz, $CDCl_3$)



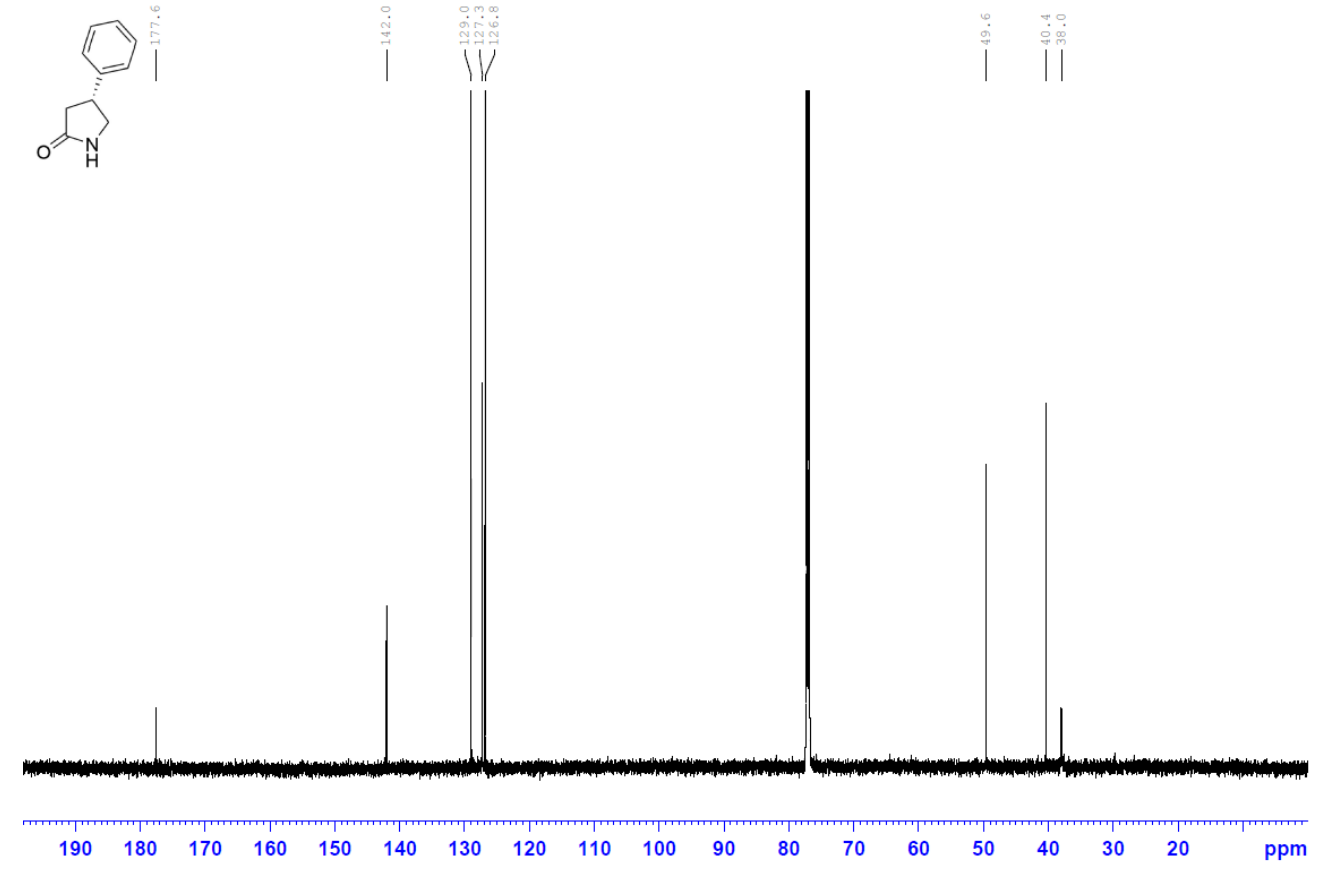
Compound **3** ^{13}C NMR (151 MHz, $CDCl_3$)



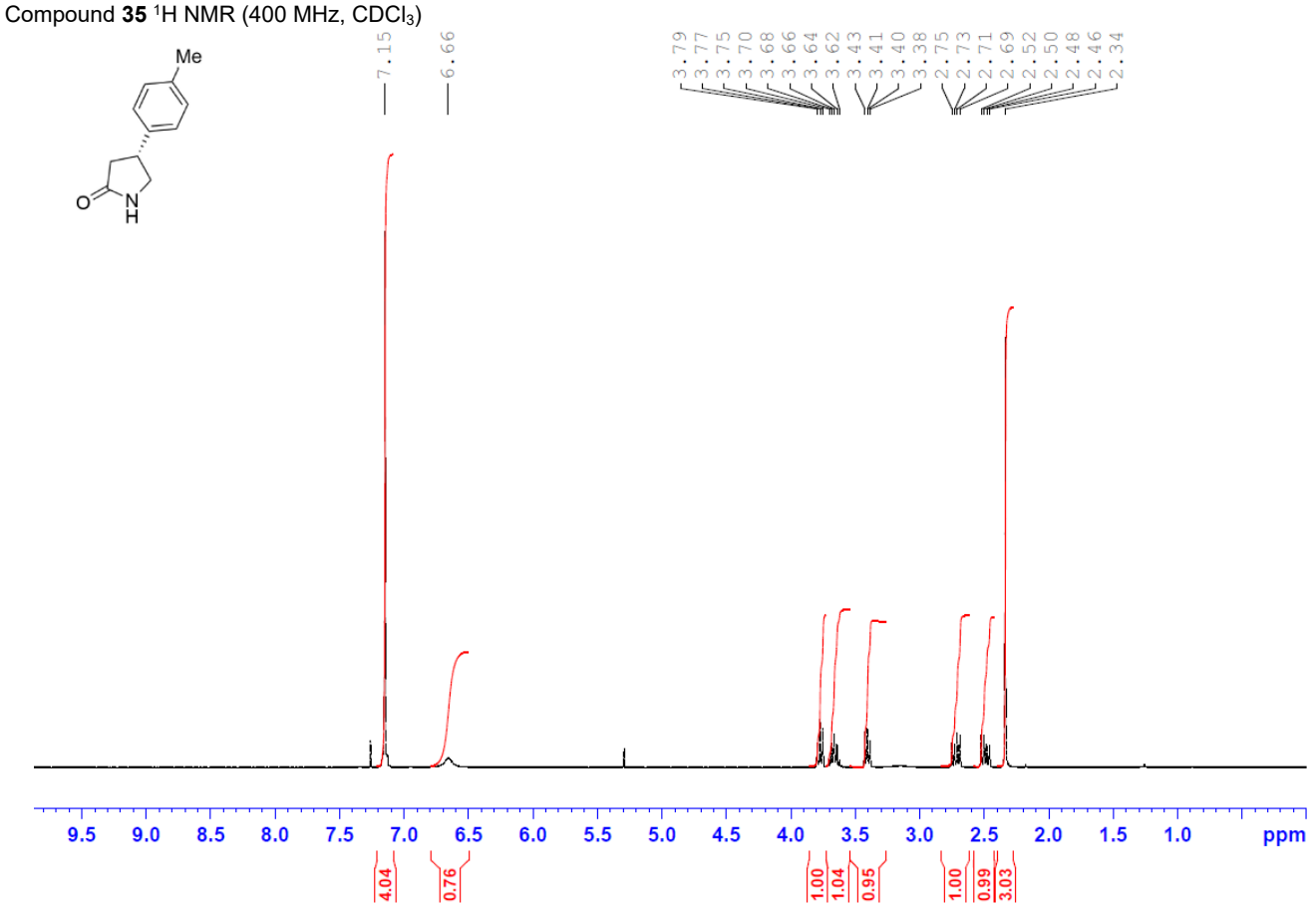
Compound **26** ^{1}H NMR (400 MHz, $CDCl_3$)



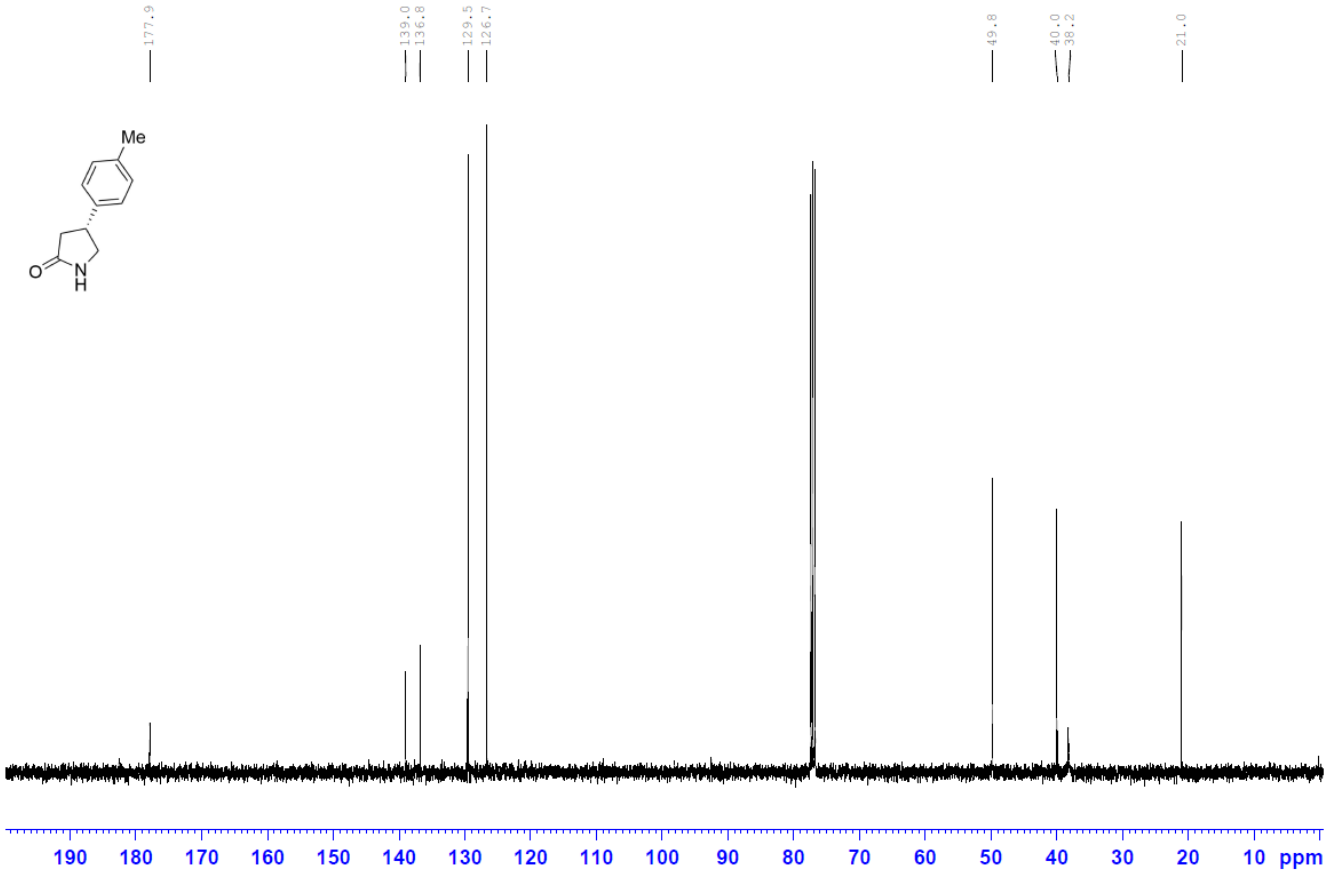
Compound **26** ^{13}C NMR (101 MHz, $CDCl_3$)



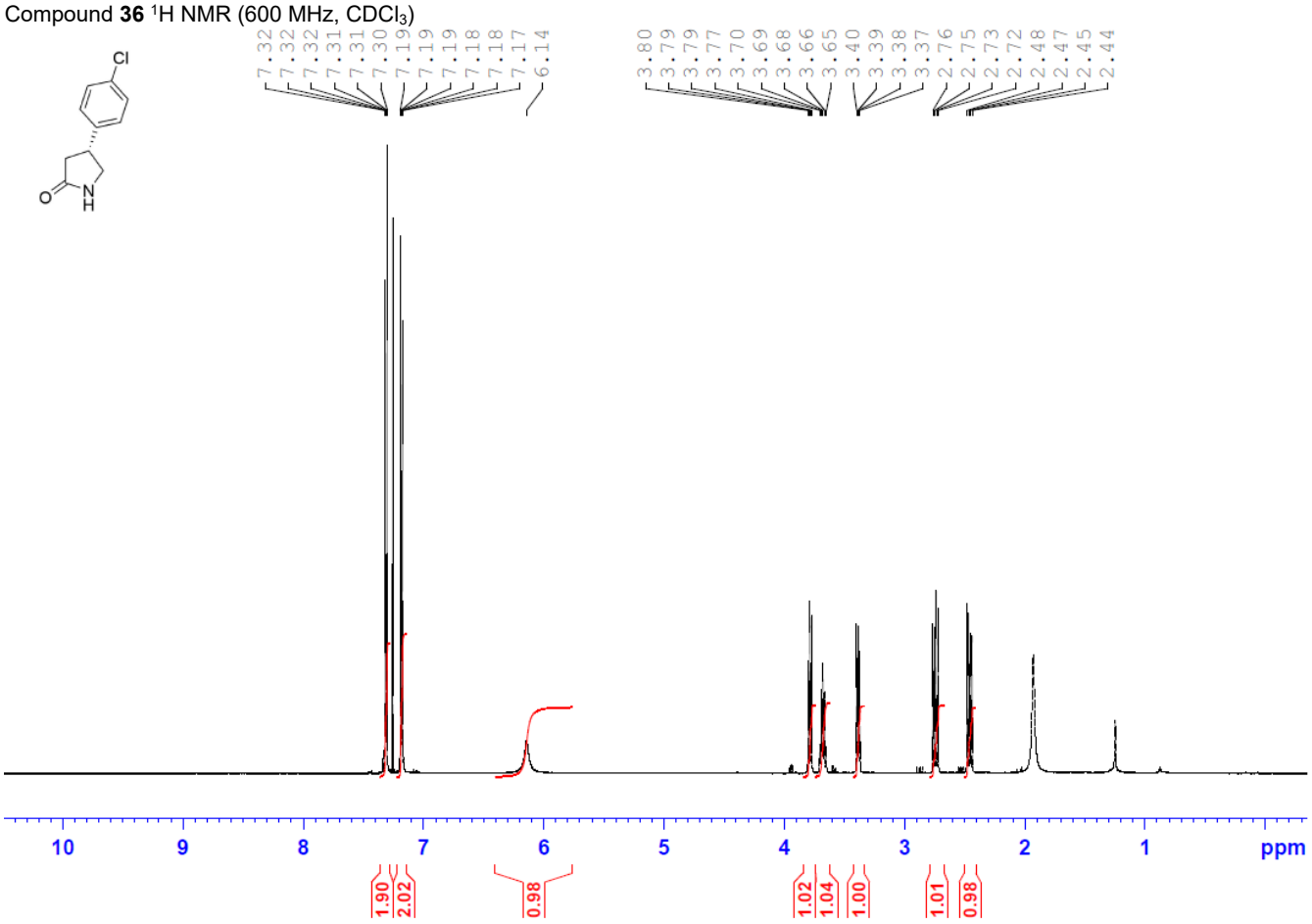
Compound **35** ^{1}H NMR (400 MHz, $CDCl_3$)



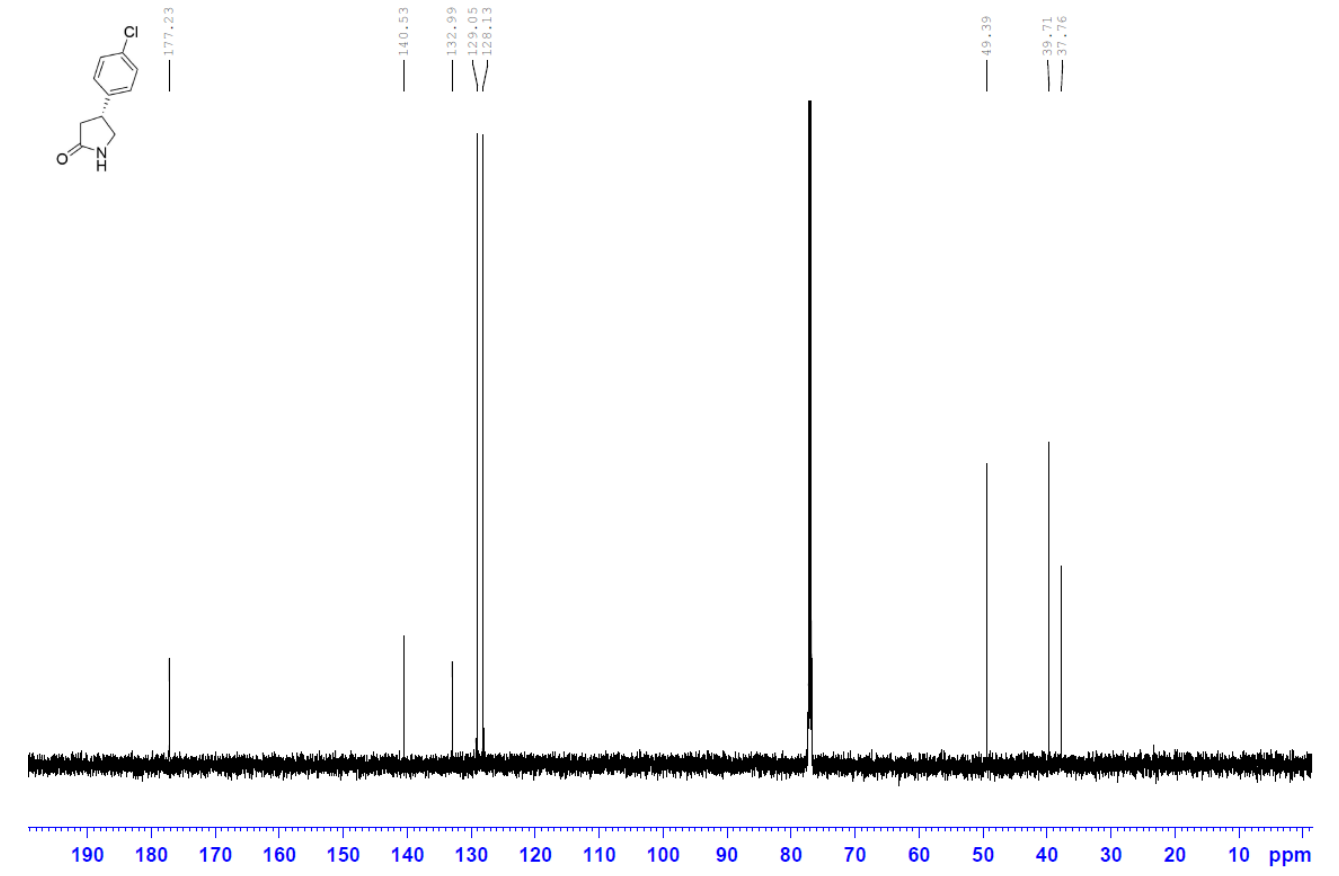
Compound **35** ^{13}C NMR (101 MHz, $CDCl_3$)



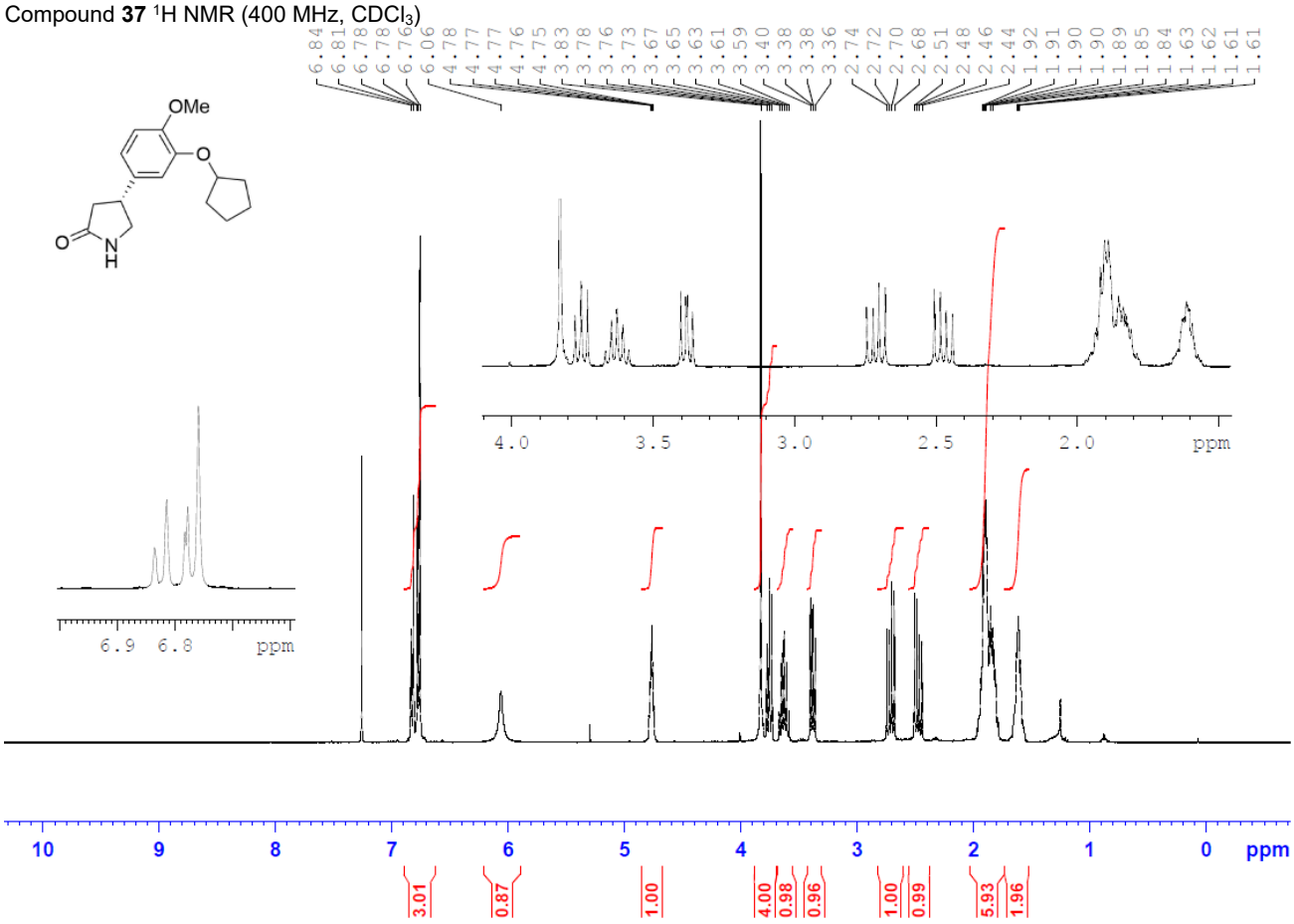
Compound **36** ^{1}H NMR (600 MHz, $CDCl_3$)



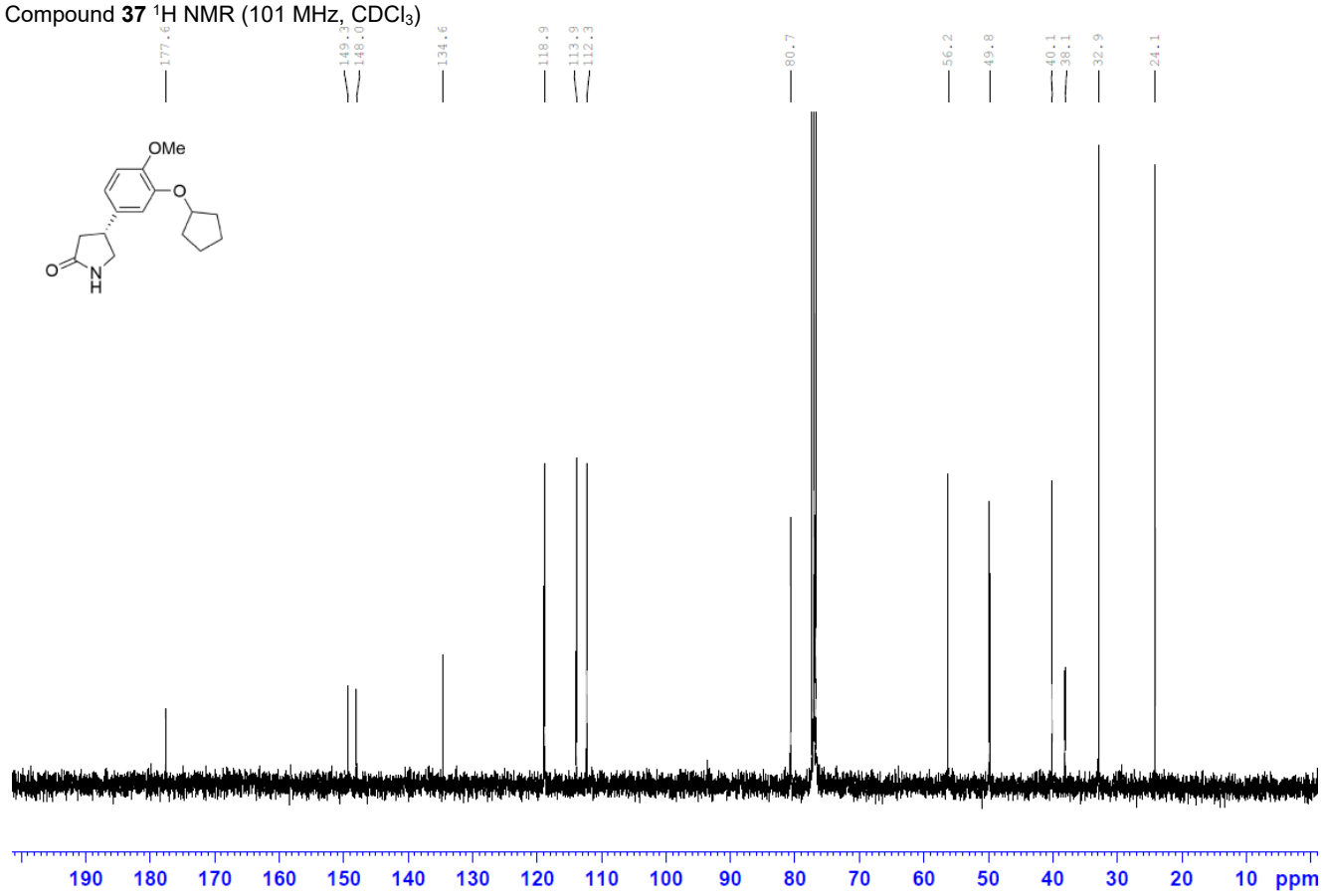
Compound **36** ^{13}C NMR (151 MHz, $CDCl_3$)



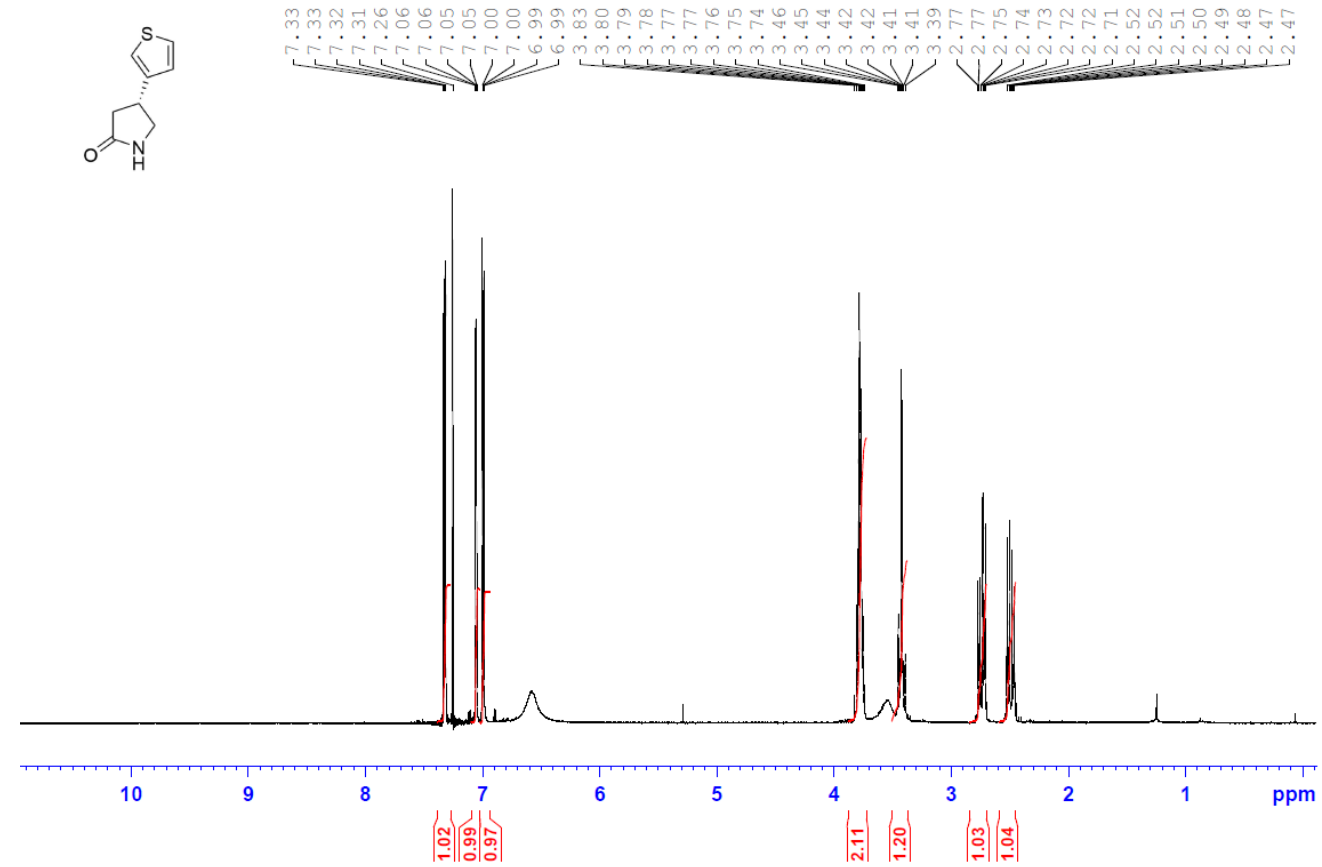
Compound **37** ^{1}H NMR (400 MHz, $CDCl_3$)



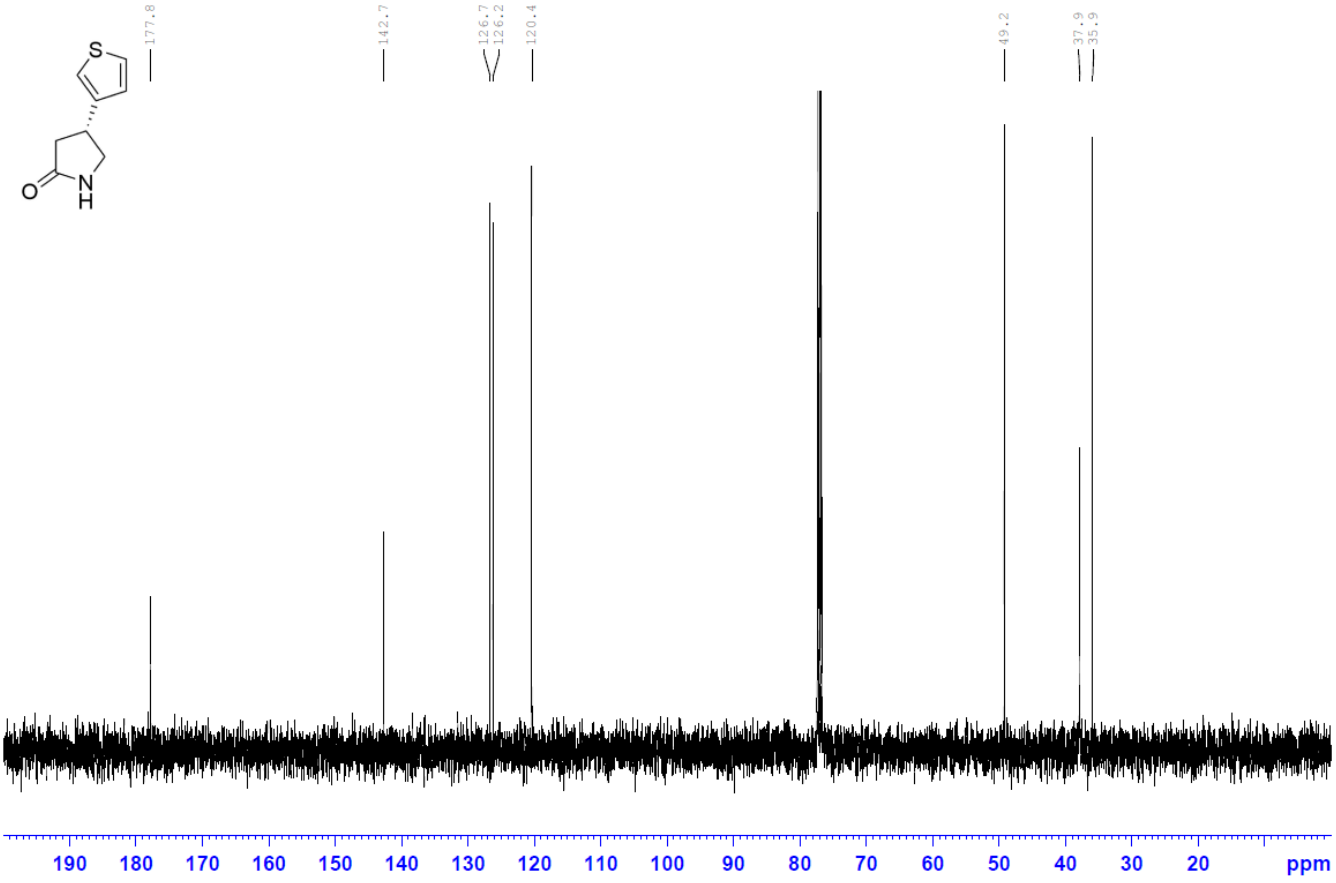
Compound **37** ^{1}H NMR (101 MHz, $CDCl_3$)



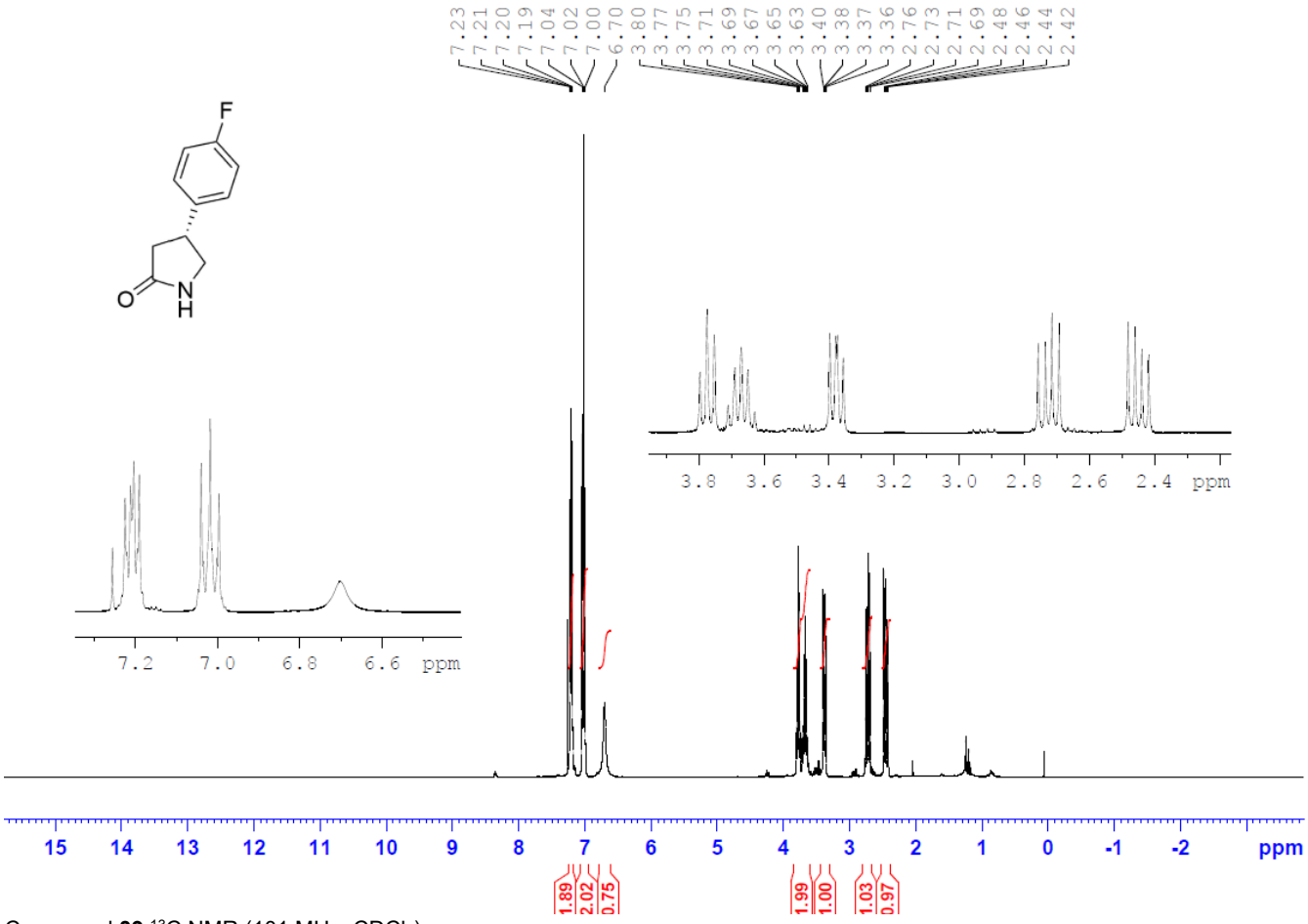
Compound **38** ^{1}H NMR (400 MHz, $CDCl_3$)



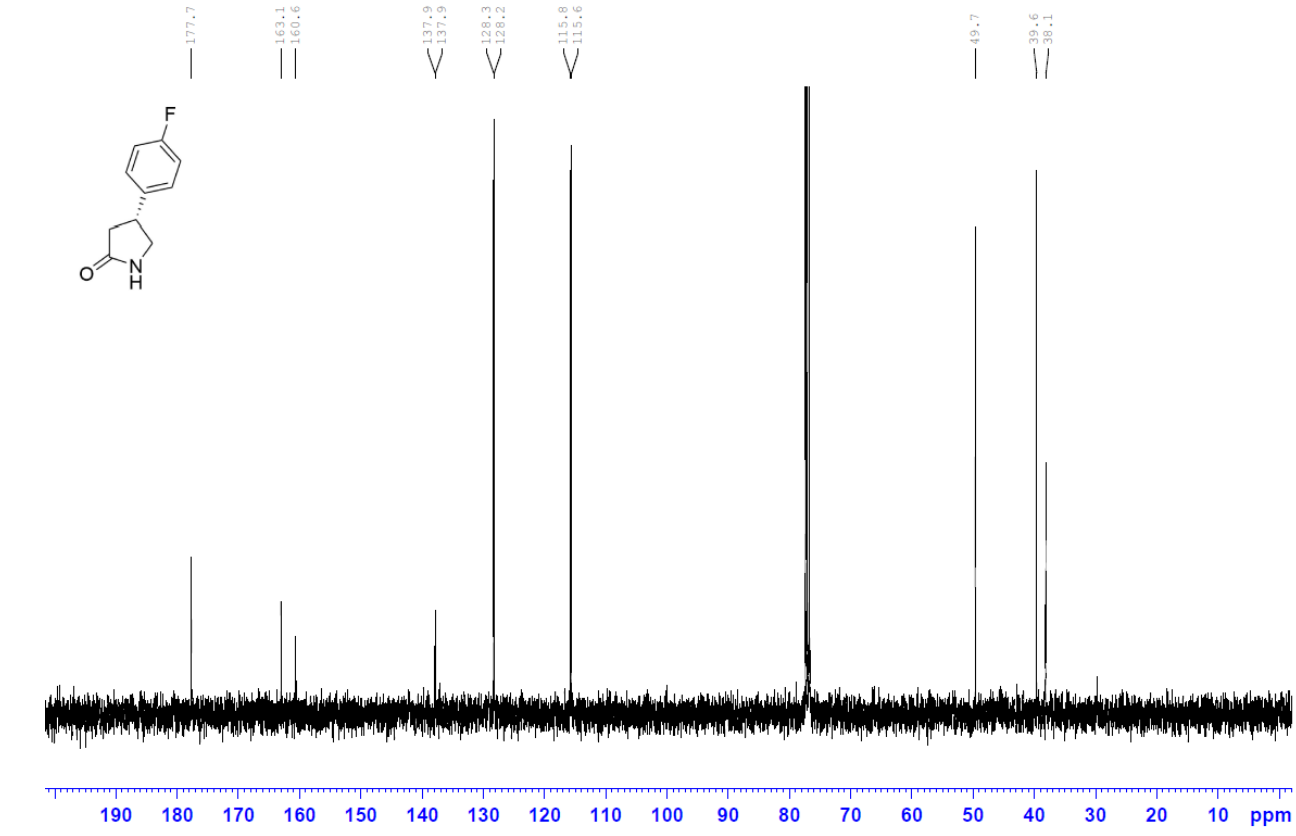
Compound **38** ^{1}H NMR (101 MHz, $CDCl_3$)



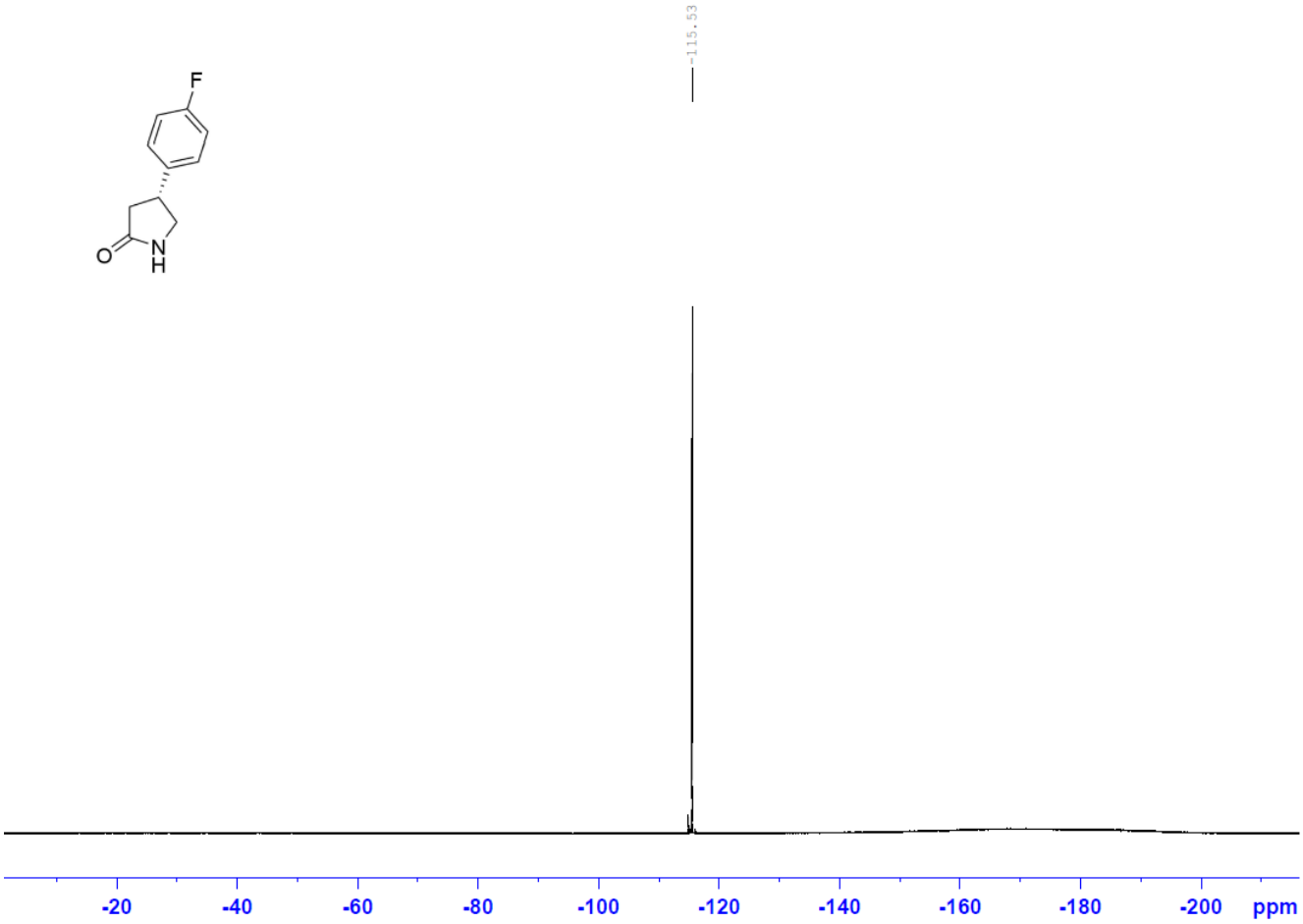
Compound **39** ^{1}H NMR (400 MHz, $CDCl_3$)



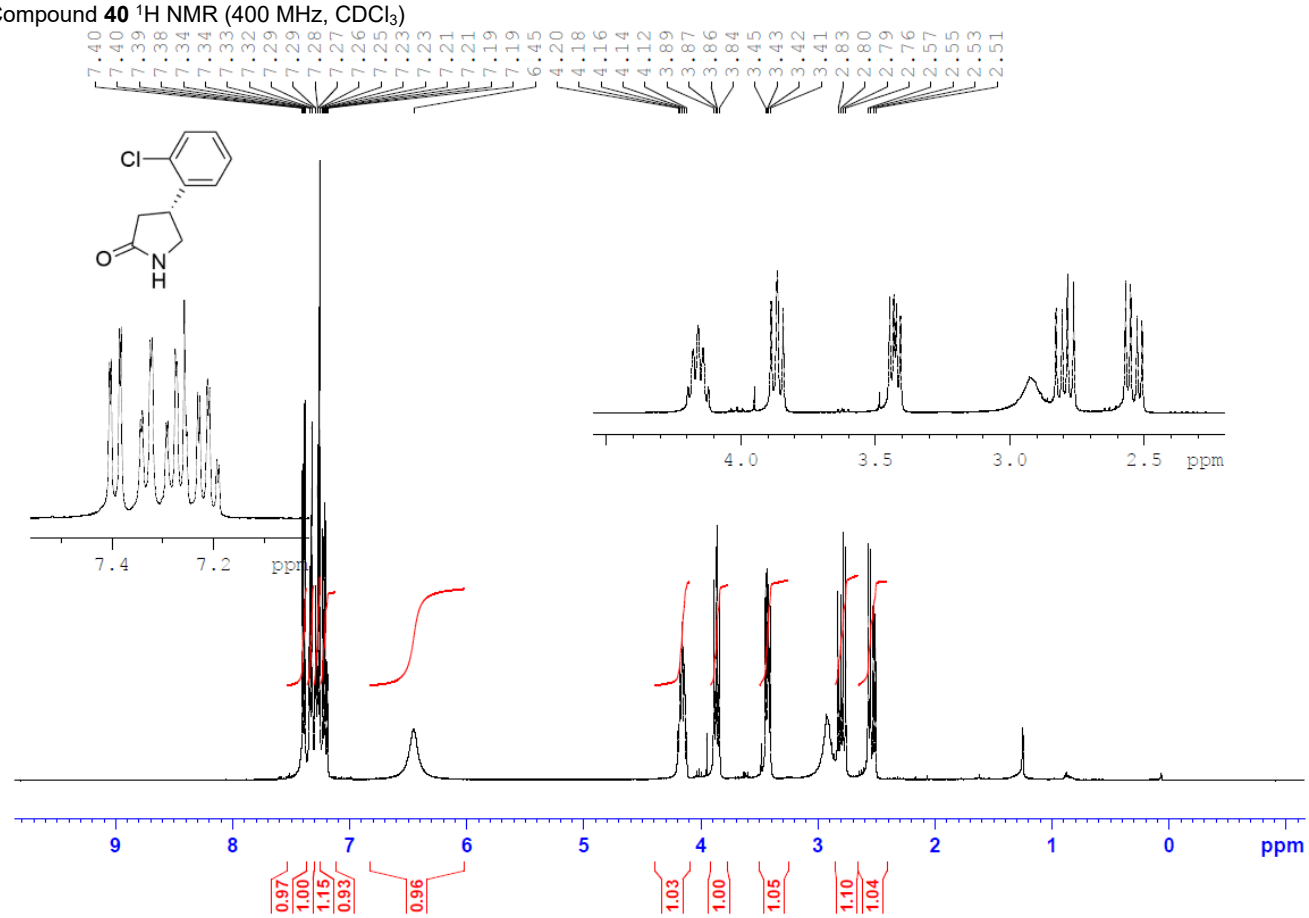
Compound **39** ^{13}C NMR (101 MHz, $CDCl_3$)



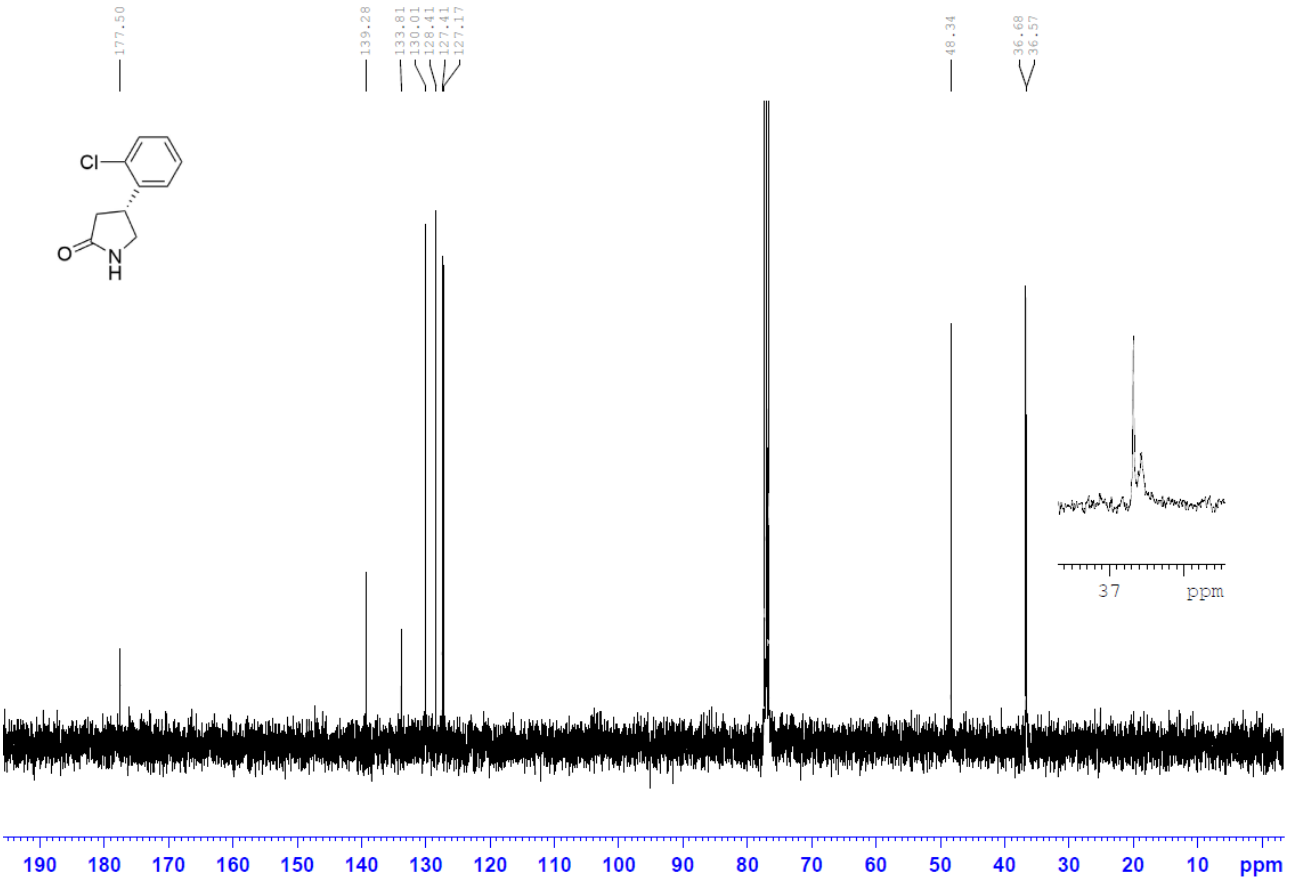
Compound **39** ^{19}F NMR (376 MHz, $CDCl_3$)



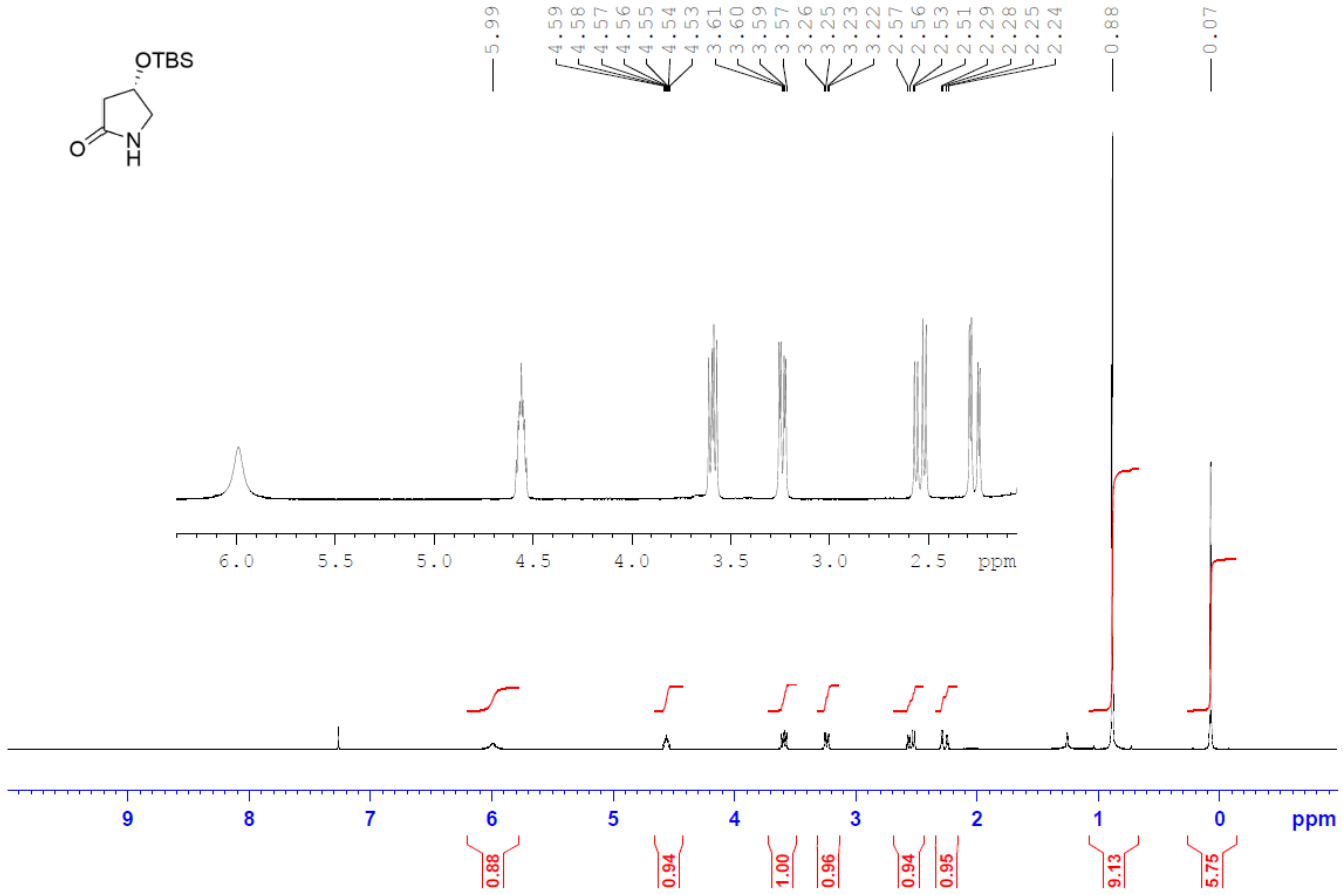
Compound **40** ^{1}H NMR (400 MHz, $CDCl_3$)



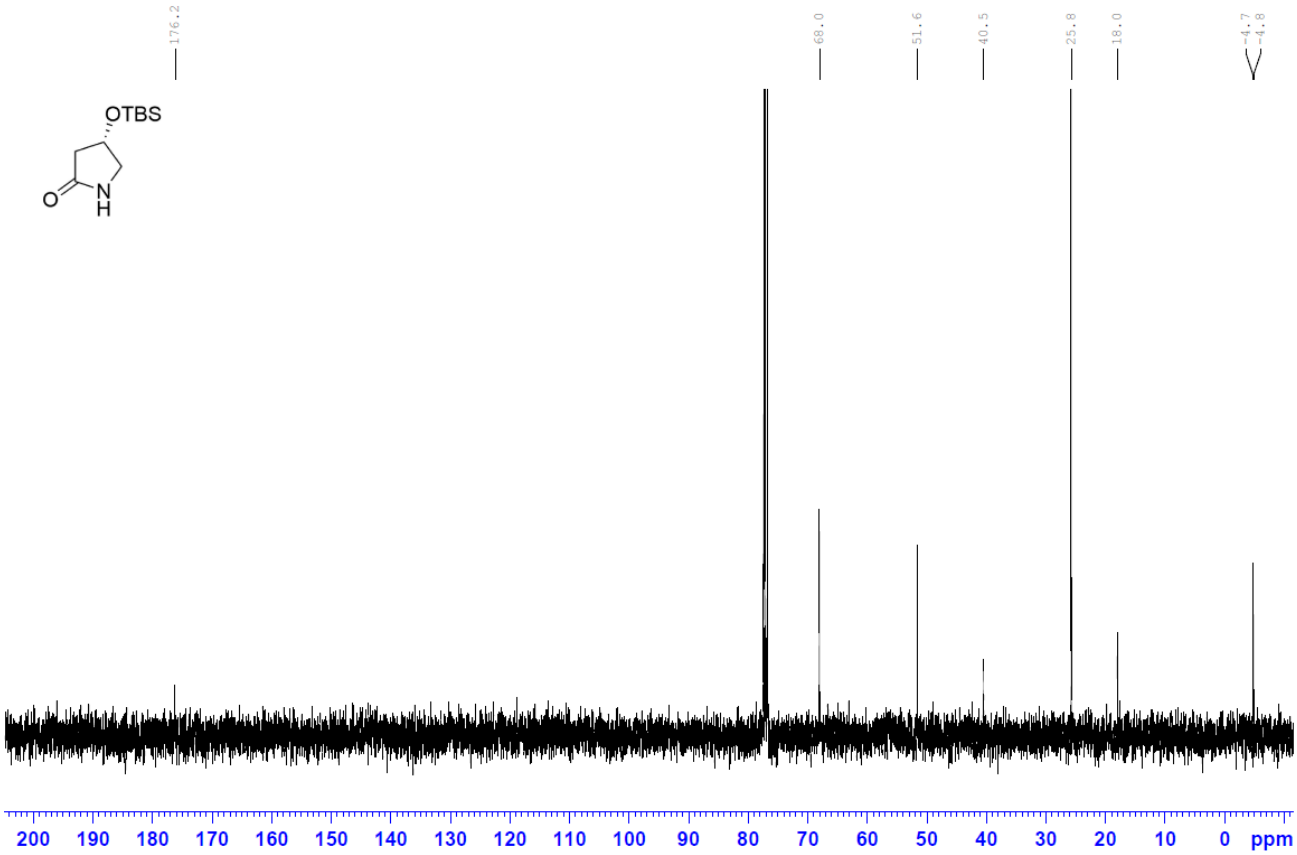
Compound **40** ^{13}C NMR (101 MHz, $CDCl_3$)



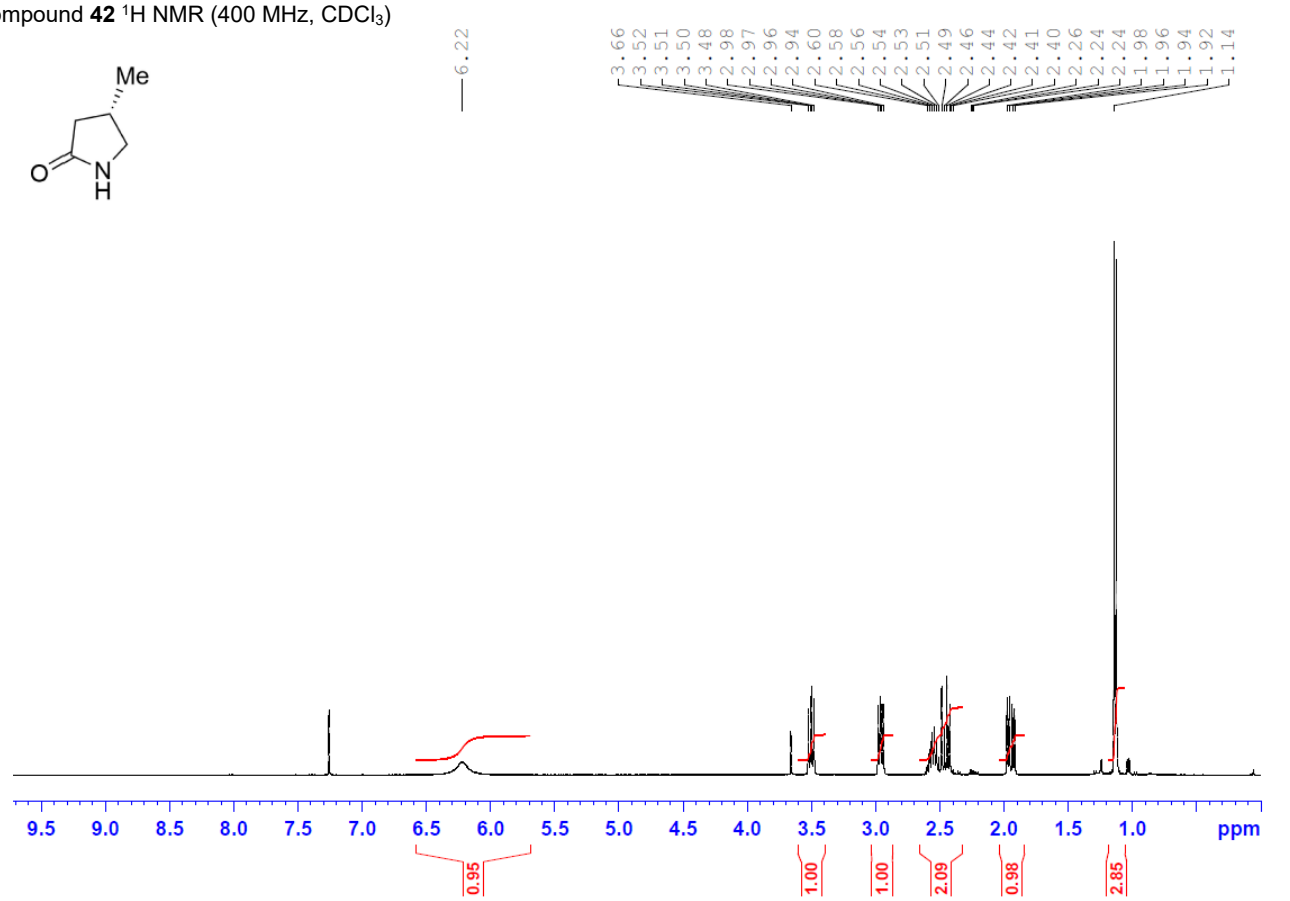
Compound **41** ^{1}H NMR (400 MHz, $CDCl_3$)



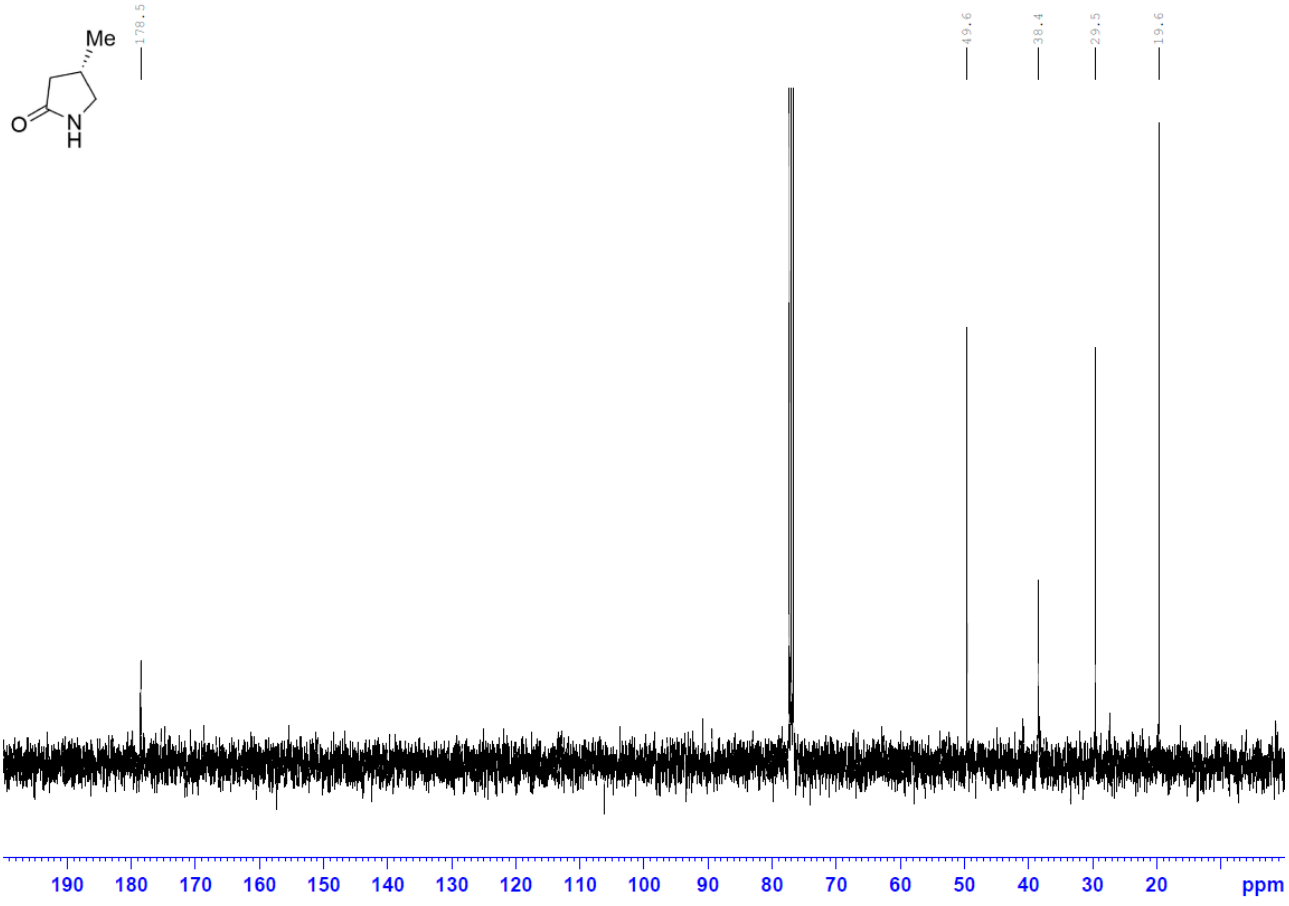
Compound **41** ^{13}C NMR (101 MHz, $CDCl_3$)



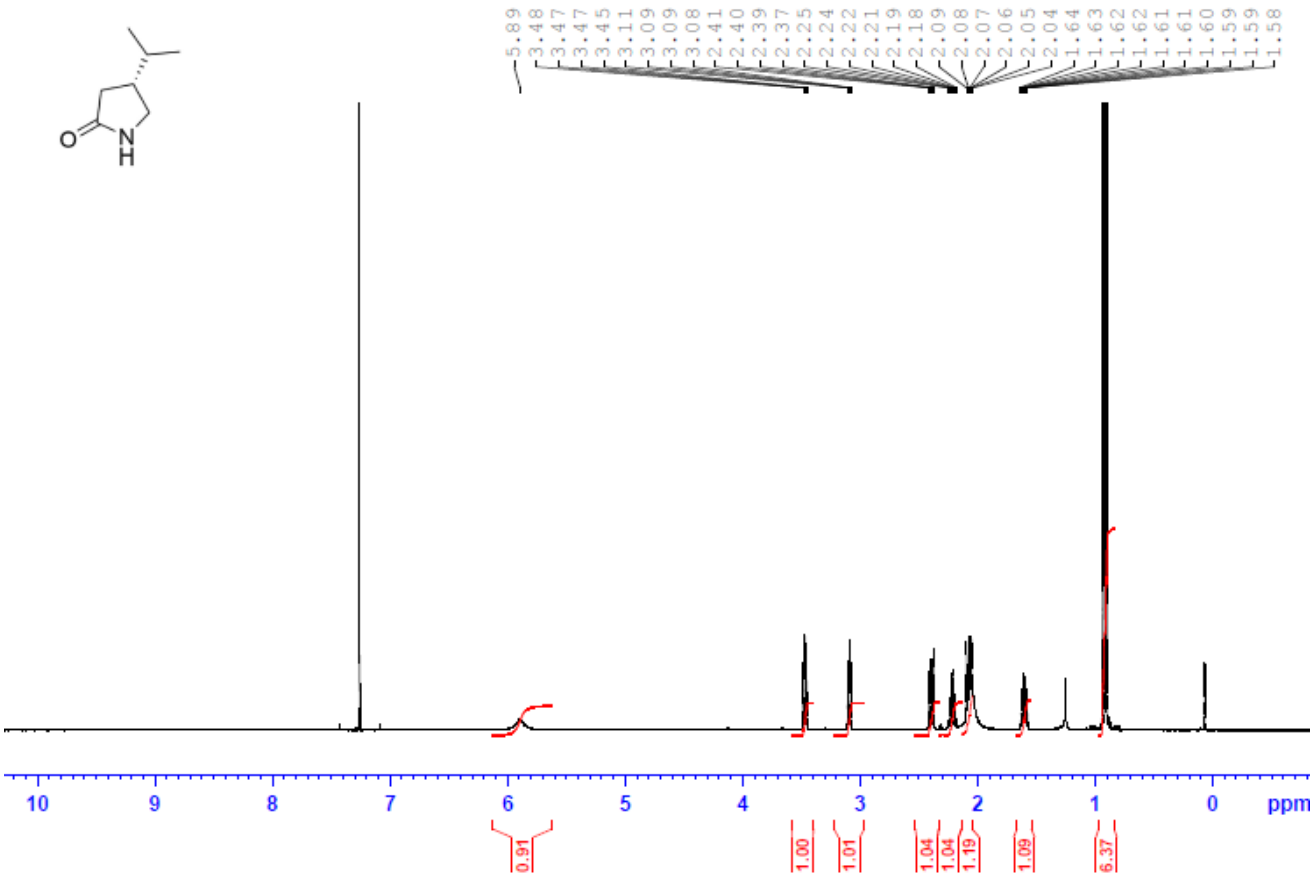
Compound **42** ^{1}H NMR (400 MHz, $CDCl_3$)



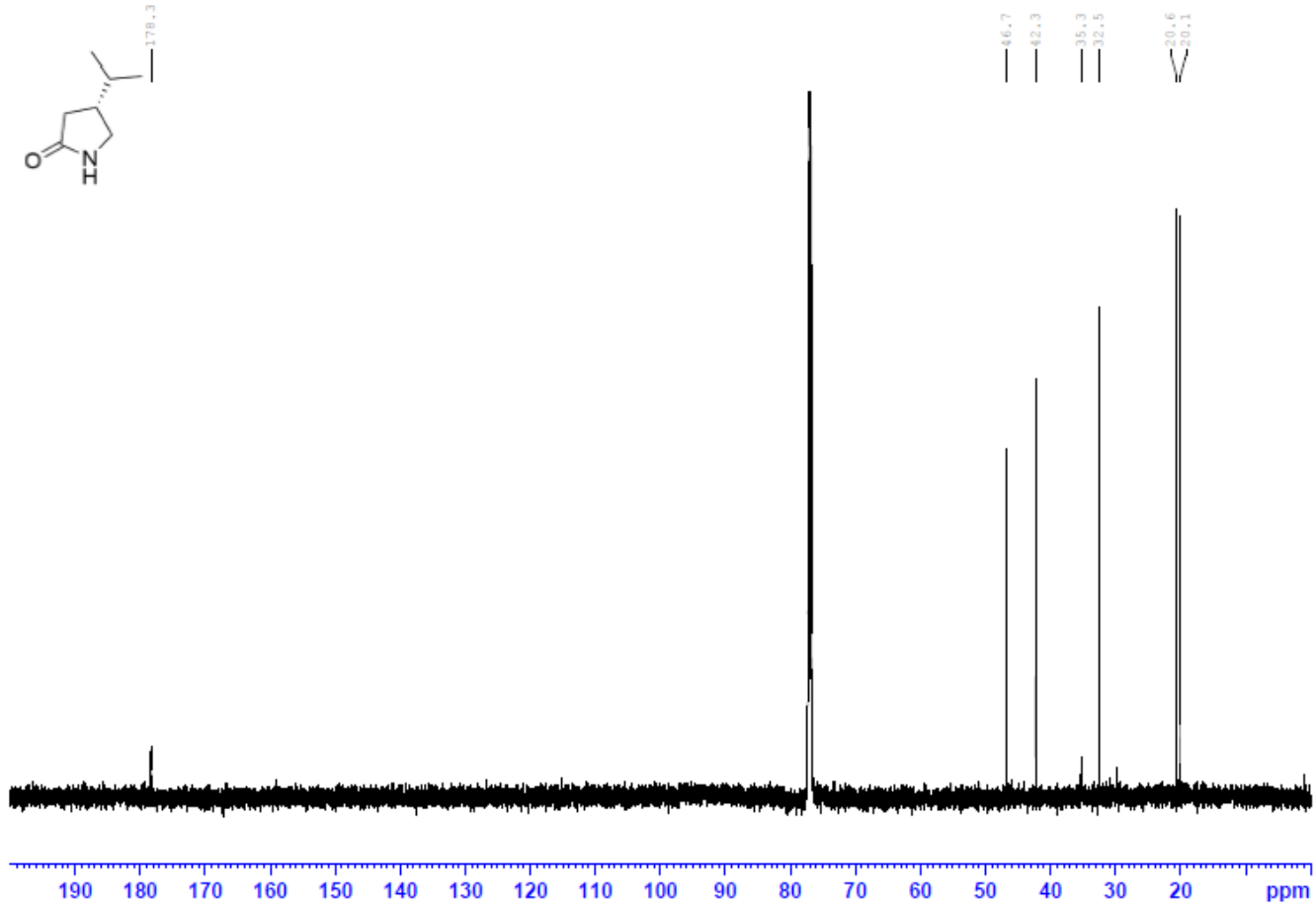
Compound **42** ^{13}C NMR (101 MHz, $CDCl_3$)



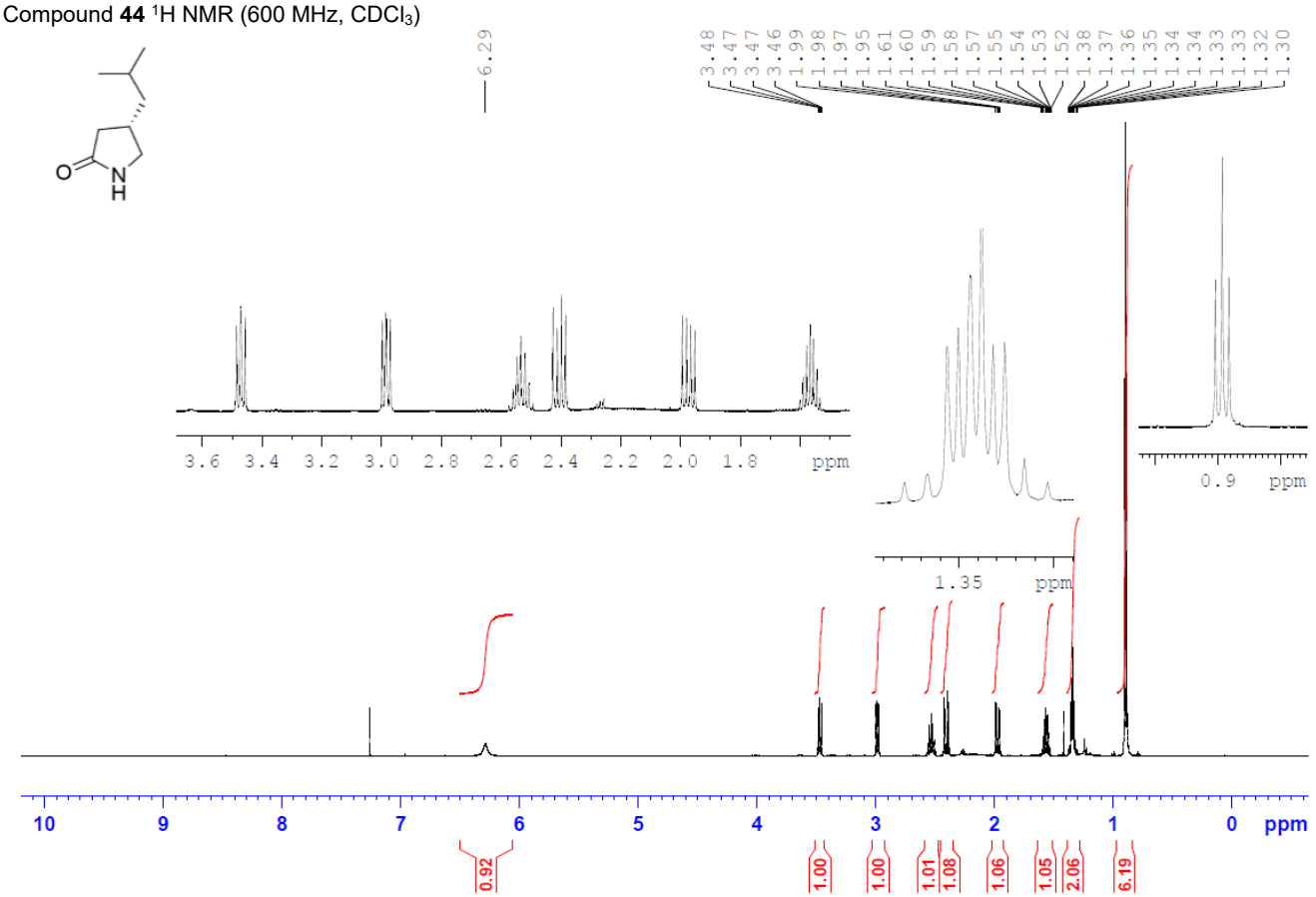
Compound **43** ^{1}H NMR (400 MHz, $CDCl_3$)



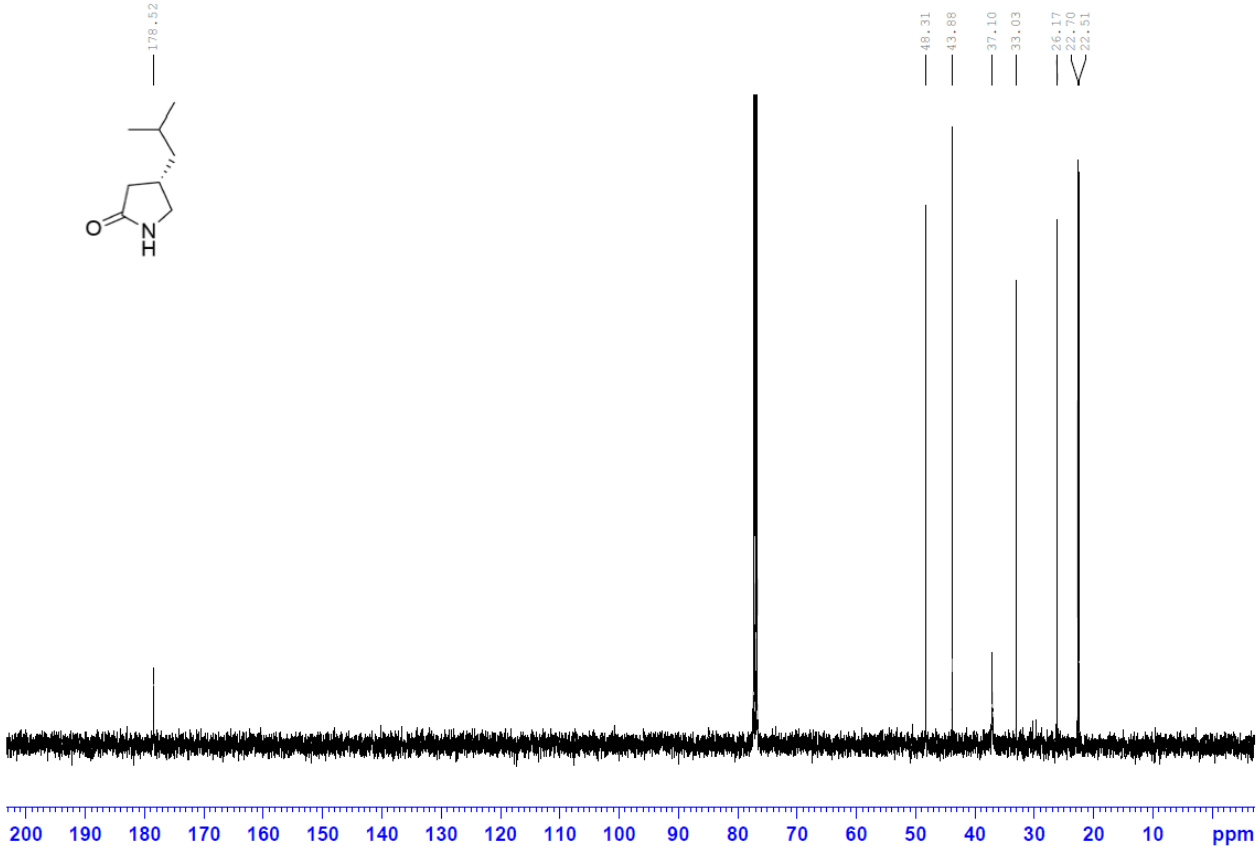
Compound **43** ^{13}C NMR (101 MHz, $CDCl_3$)



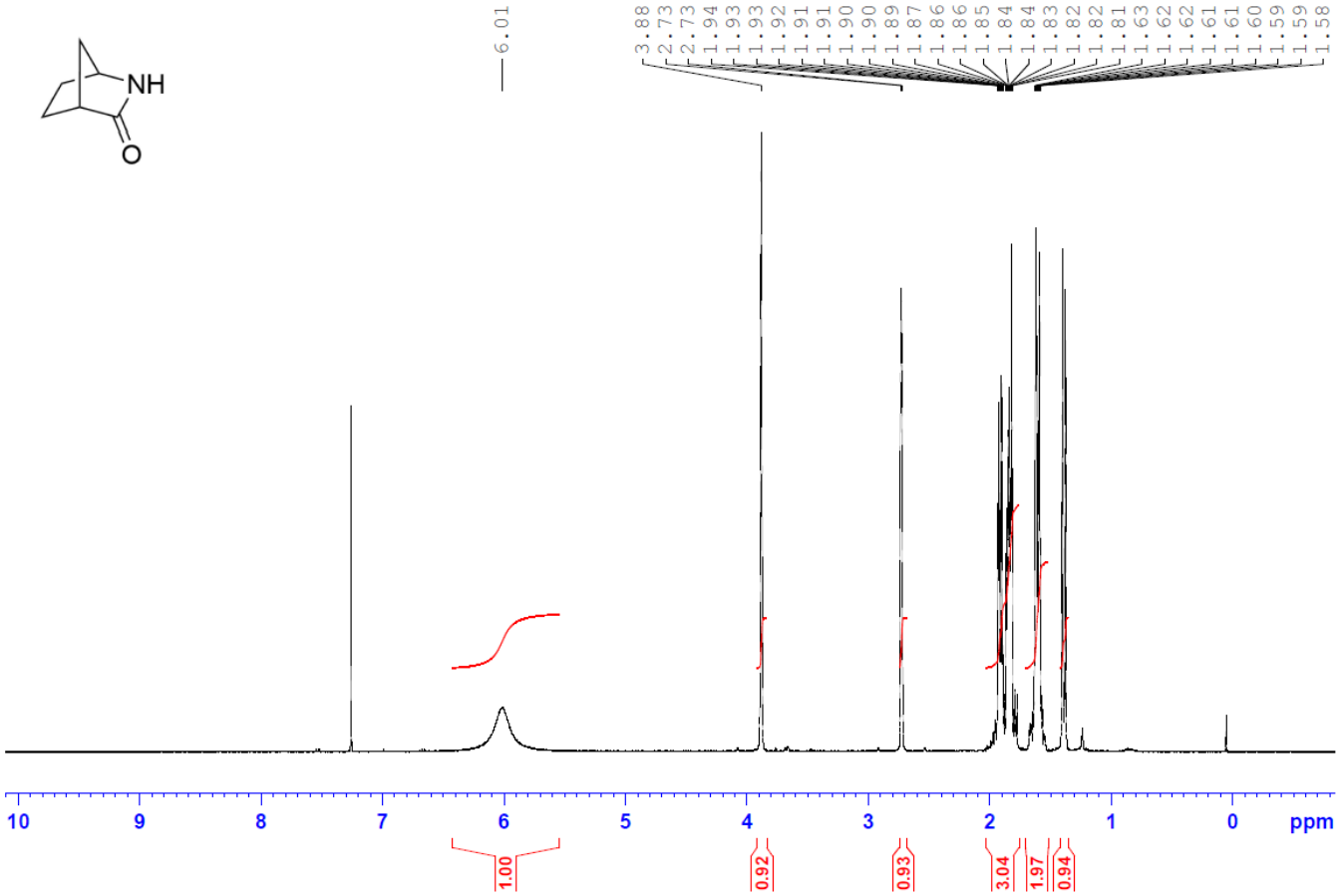
Compound **44** ^{1}H NMR (600 MHz, $CDCl_3$)



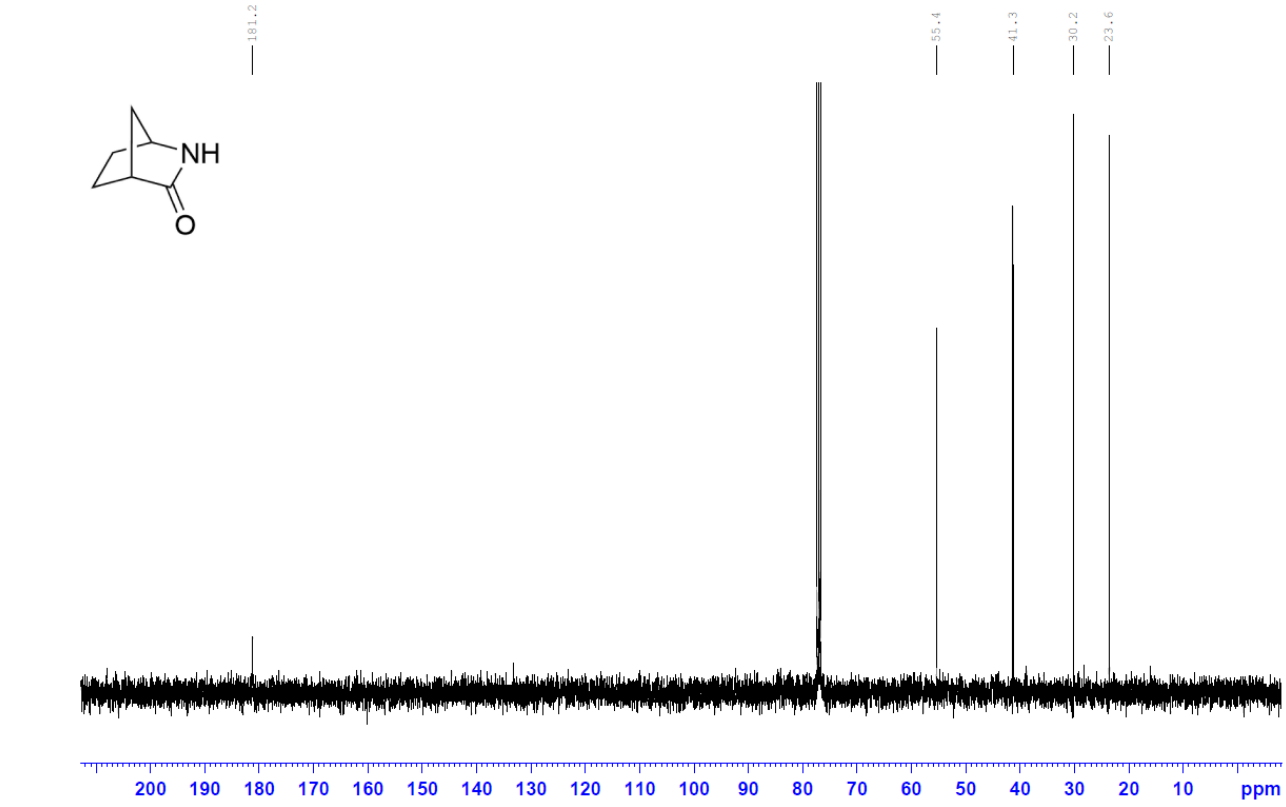
Compound **44** ^{13}C NMR (151 MHz, $CDCl_3$)



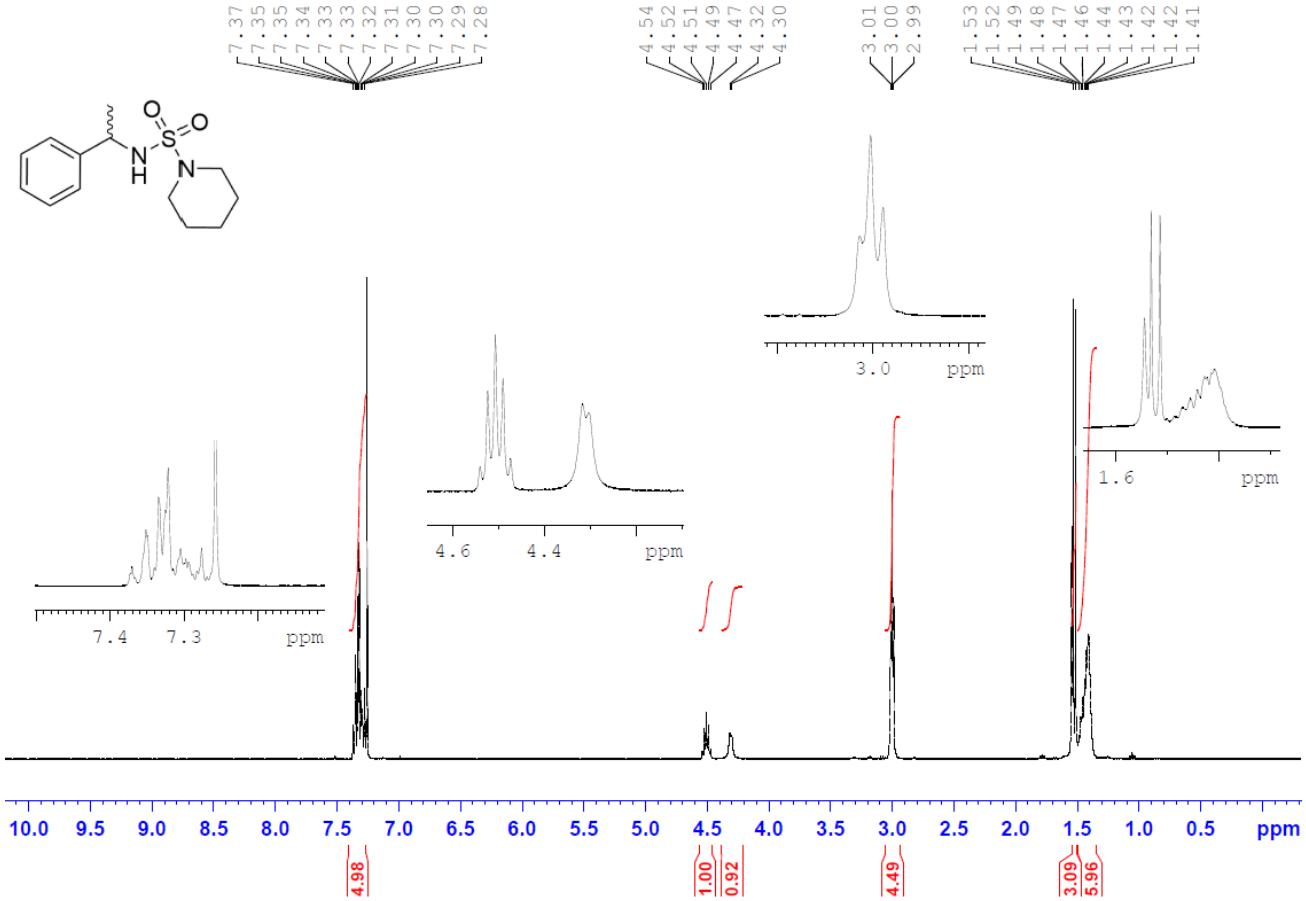
Compound **45** ^{1}H NMR (400 MHz, $CDCl_3$)



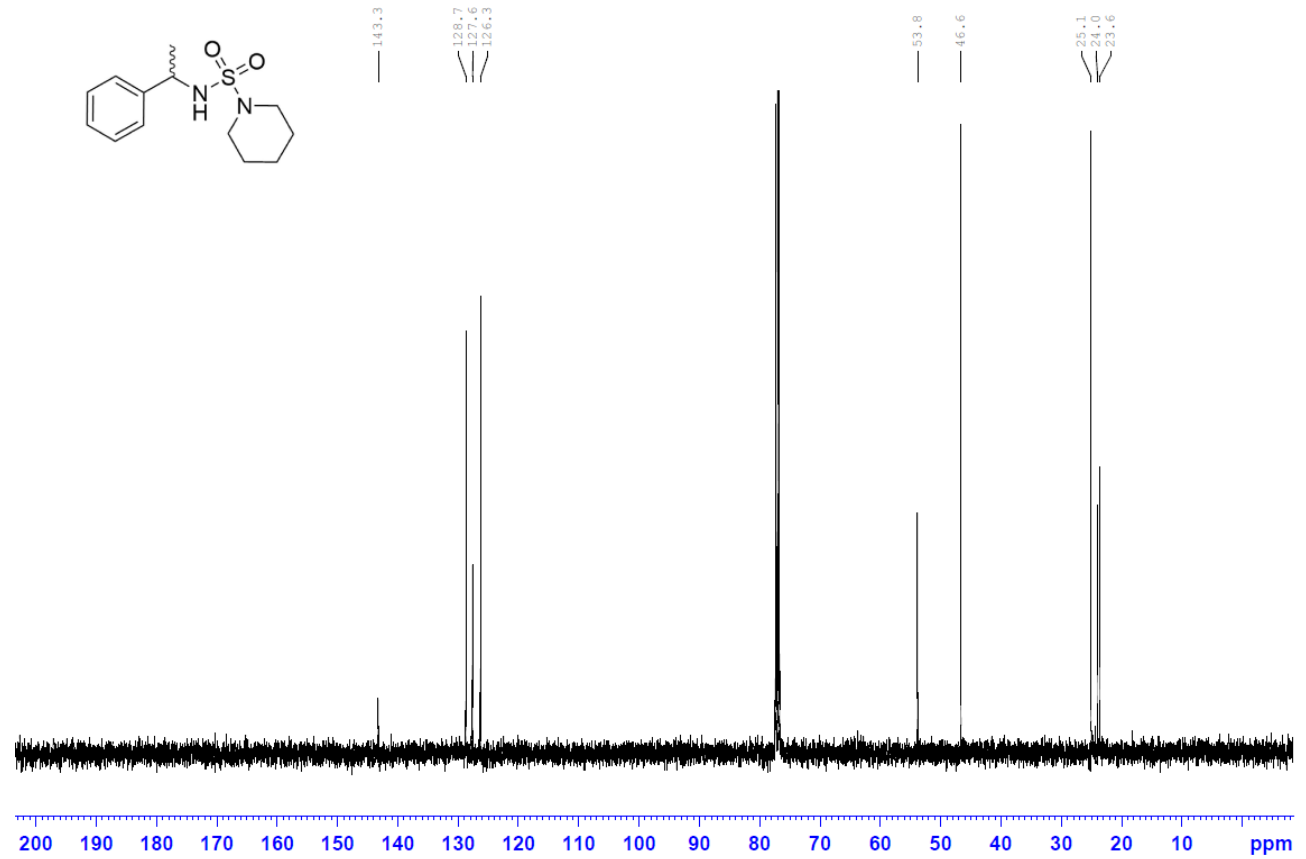
Compound **45** ^{13}C NMR (101 MHz, $CDCl_3$)



Compound **S19** ^{1}H NMR (400 MHz, $CDCl_3$)



Compound **S19** ^{13}C NMR (101 MHz, $CDCl_3$)



8. Coordinates

conformer_A (13-I)

0 1
N 0.0298542904 -1.8211473993 0.2226148701
H -0.7040956073 -2.4866977626 0.4603665868
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C 0.2121366048 0.3638842833 -0.9036682235
C 0.631302847 1.6912610634 -0.6185699645
C 0.5160195638 -0.1562569795 -2.1333096937
C 0.4055752534 2.341281502 0.6229171269
C 1.3379361228 2.3817961276 -1.6362066822
C 1.2218112873 0.6120912185 -3.0696705028
H 0.231470137 -1.1703672167 -2.3825340561
C 0.8571257556 3.6165821166 0.8308150802
H -0.1163862463 1.8226970925 1.4106638006
C 1.7848295493 3.7047029326 -1.3858090078
C 1.5532875648 4.3074965281 -0.1923580132
H 2.3194919537 4.2162424961 -2.1761638535
H 1.8945752568 5.3157586276 0.005790786
O 0.6960573715 4.3113228377 1.9746949628
N 1.6241546052 1.8367595063 -2.8430983128
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H 0.0065637374 4.4082878565 3.8599706981
H 0.5418095747 2.7820065447 3.374594182
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H -4.8027895588 -0.0402363742 2.3029896402
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C -4.8830605083 -0.7440636637 -0.3163911144
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H -4.4575480046 -2.7454753046 0.4751376594
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H -2.2457642546 1.4616819353 0.1467829548
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H -6.7118239935 -0.2784029688 -3.2530334901
H -7.3546181691 -0.5254917477 -1.5357833528
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O 1.3100535779 -3.4453179441 1.4918117823
C 3.2942463469 -0.3917116804 0.372191192
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C 4.8026815173 -0.5763912862 0.3004263217
H 3.0031771396 0.1316061099 1.278308162
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C 5.1906700138 -1.3988980045 -0.9244088522
H 5.1448957315 -1.0772193732 1.210610344
H 4.6514463859 -3.2773615704 -1.8614698876
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H 2.4192015818 -3.4639446908 -0.7458223793
H 4.771077492 -3.3500796885 -0.1037816708
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H 5.2731304687 0.4085067494 0.2673587406
H 2.9592852277 0.1974939478 -0.4889358579
N 2.642452391 -1.7015300944 0.349576529

conformer_B (13-II)

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C 0.1155071898 0.1925152798 1.3137720055
C 0.6196367366 1.4070311796 0.7658671108
C 0.3292180551 -0.0444355849 2.6443288359
C 0.4779021923 1.7787878693 -0.5956195462
C 1.3126494114 2.2766692576 1.6443961349
C 1.0253115457 0.8882778316 3.4307237188
H -0.0226937348 -0.9623683967 3.0982497777
C 0.9927541285 2.9630103193 -1.0499247477
H 0.0002729313 1.0967723549 -1.2777179652
C 1.8366436307 3.4926260497 1.1366932232
C 1.6810952601 3.8319708133 -0.1688648508
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H 2.0792244047 4.7590699498 -0.5616961745
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