-SUPPLEMENTARY MATERIALS-

Concise Approach to γ-(Het)aryl- and γ-Alkenyl-γ-Aminobutyric Acids. Synthesis of vigabatrin

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General Information

The structures of synthesised compounds were elucidated with the aid of 1D NMR (^{1}H, ^{13}C) and 2D NMR (NOESY, HSQC ^{1}H-^{13}C) spectroscopy. NMR spectra were acquired on Bruker Avance 600, Bruker Avance 500, and Agilent 400-MR spectrometers at room temperature; the chemical shifts δ were measured in ppm with respect to solvent (^{1}H: $CDCl_3$, δ = 7.26 ppm; CD_3OD, δ = 3.35 ppm; DMSO-d_6, δ = 2.50 ppm; D_2O, δ = 4.79 ppm; ^{13}C: $CDCl_3$, δ = 77.0 ppm; CD_3OD, δ = 49.9 ppm; DMSO-d_6, δ = 39.5 ppm). Splitting patterns are designated as s, singlet; d, doublet; dd, double doublet; m, multiplet; br., broad. Coupling constants (*J*) are in Hertz. IR spectra were recorded on Thermo Nicolet IR spectrometer with Fourier transform IR 200. Registration of spectra was carried out at a resolution of 4 cm^{-1}, the number of scans 20. Samples were placed on the working surface of the internal reflection (ATR) element from ZnSe with the angle of incidence of 45°. High resolution and accurate mass measurements were carried out using a BrukermicrOTOF-Q^{TM} ESI-TOF (Electrospray Ionisation/Time of Flight). Elemental analyses were performed with Fisons EA-1108 CHNS elemental analyser instrument. Melting points (mp) were measured on Electrothermal 9100 capillary melting point apparatus. Analytical thin layer chromatography (TLC) was carried out with silica gel plates (silica gel 60, F_{254}, supported on aluminium); visualisation was done by a UV lamp (365 nm). Column chromatography was performed on Macherey-Nagel silica gel (230–400 mesh). Enantiomeric purity of the optically active compound **2a** was determined by chiral HPLC with a Hitachi LaChrome Elite-2000 chromatograph using a Daicel Chiralpac AD-H column (0.46 × 25 cm) at room temperature. The column was eluted with n-hexane/i-PrOH = 80:20 at a flow rate of 1 mL/min, and peak detection was accomplished using a UV detector at 219 nm. Chiral HPLC analysis for (*R*)-**3a** was performed with an Agilent 1200 chromatograph. The separation was accomplished in isocratic mode using a Diasphere-110-Chirasel-E column: Nautilus-R, BioChemMack S&T (Russia), 5.0 μm, 4.0×250 mm. The column was eluted with methanol/0.1 M aq. solution of $NaH_2PO_4 \cdot 2H_2O$ = 20/80 at a flow rate of 0.8 mL/min, and peak detection was accomplished using a UV detector at 220 nm at 25 °C. All reactions were carried out using freshly distilled and dry solvents. Cyclopropanes **1** were prepared by Knoevenagel/Corey-Chaykovsky reactions sequence from the corresponding aldehydes.[S1,S2] Commercial reagents employed in the synthesis were analytical grade, obtained from Aldrich or Alfa Aesar.

Synthesis and analytical data for 2-oxopyrrolidine-3-carboxamides 2

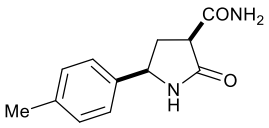
General Procedure 1

To cyclopropane (1 equiv.) in a glass vial with a screw cap was added approx. 6 M methanolic solution of NH_3 (10 equiv.) so that the volume of the solution does not exceed 1/3 of the vial volume. The vial was tightly closed, the reaction vessel was immediately immersed in an oil bath preheated to 130 °C and vigorously stirred for 9–18 h until TLC control showed the complete consumption of the starting material. The reaction mixture was then cooled to room temperature until crystallization occurred. If the powder did not crystallise, MeOH was evaporated by 1/3 and the wall of the vial was rubbed with a spatula. Then the mixture was filtered and rinsed with a minimum amount of cold MeOH/Et_2O (2:1) mixture. The resulting solid was dried under a vacuum diaphragm pump for 1 h to give pure 2-oxopyrrolidine-3-carboxamide **2**.

General Procedure 2

To cyclopropane (1 equiv.) in a glass vial amine solution (10 equiv.) in methanol was added in one portion so that the volume of the solution does not exceed 1/3 of the vial volume. The vial was tightly closed and the reaction vessel was immediately placed in an oil bath preheated to 130 °C and vigorously stirred for 9 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The residue was then purified using silica gel column chromatography.

(3*RS*,5*SR*)-2-Oxo-5-(*p*-tolyl)pyrrolidine-3-carboxamide (**2a**) was obtained from dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate **1a** (350 mg, 1.4 mmol) and NH_3 (6 M solution in MeOH, 2.4 mL, 14 mmol) according to the *General Procedure 1* but extra portion of NH_3 (6 M solution in MeOH, 2.4 mL, 14 mmol) was added after 9 h and the reaction proceeded for another 9 h. White solid (246 mg, 80%), mp 184–185 °C (NMR was registered immediately after the sample preparation).



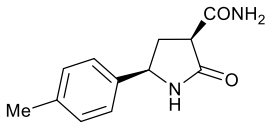
^{1}H NMR (CD_3OD, 600 MHz): δ = 7.26 (d, ^3J = 7.9 Hz, 2H, Ar), 7.16 (d, ^3J = 7.9 Hz, 2H, Ar), 4.69–4.66 (m, 1H, CH), 3.55–3.52 (m, 1H, CH), 2.71–2.68 (m, 1H, CH_2), 2.32 (s, 3H, CH_3), 2.24–2.23 (m, 1H, CH_2). Signals of NH-groups were not observed.

^{13}C NMR (CD_3OD, 150 MHz): δ = 177.5 (CO), 174.8 (CO), 141.2 (C), 139.7 (C), 131.3 (2×CH), 128.2 (2×CH), 58.4 (CH), 36.7 (CH), 36.6 (CH_2), 22.0 (CH_3).

IR (KBr): 3385, 3186, 3026, 2920, 2864, 1668, 1614, 1515, 1456, 1428, 1375, 1306, 1281, 1273, 1221, 1184, 1113, 1090, 1043, 1021, 1011 cm^{-1}.

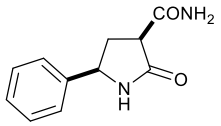
HRMS ESI-TOF: m/z = 219.1135 $[M+H]^+$ (219.1128 calcd for $C_{12}H_{15}N_2O_2^+$).

(3*S*,5*R*)-2-Oxo-5-(*p*-tolyl)pyrrolidine-3-carboxamide ((3*S*,5*R*)-***2a***) was obtained from dimethyl



(*S*)-2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate (*S*)-**1a**[S3] (150 mg, 0.6 mmol) and NH_3 (6 M solution in MeOH, 1 mL, 6 mmol) according to the *General Procedure 1* but extra portion of NH_3 (6 M solution in MeOH, 1 mL, 6 mmol) was added after 9 h and the reaction proceeded for another 9 h. White solid (92 mg, 70%), m.p. 184–185 °C, $[\alpha]_D^{21}$ +17.1 (c 0.105 in MeOH). NMR spectra coincide with those for *rac*-**2a**.

(3*RS*,5*SR*)-2-Oxo-5-phenylpyrrolidine-3-carboxamide (**2b**) was obtained from dimethyl 2-



phenylcyclopropane-1,1-dicarboxylate **1b** (300 mg, 1.3 mmol) and NH_3 (6 M methanolic solution, 2.2 mL, 13.2 mmol) according to the *General Procedure 1* as a mixture of two diastereomers with *dr* 90:10 [(3*RS*,5*SR*)-**2b**:(3*RS*,5*RS*)-**2b**, **A**:**B**]. White solid (186 mg, 71%), m.p. 191–192 °C. NMR spectra of the major isomer are given.

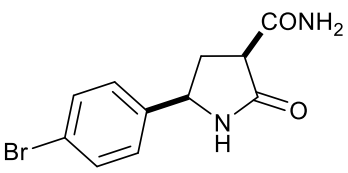
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.34 (br.s, 1H, NH), 7.53 (br.s, 1H, NH), 7.39–7.25 (m, 5H, Ar), 7.16 (br.s, 1H, NH), 4.60 (dd, ^3J = 8.9 Hz, ^3J = 7.1 Hz, 1H, CH), 3.34 (dd, ^3J = 10.5 Hz, ^3J = 8.9 Hz, 1H, CH), 2.60–2.51 (m, 1H, CH_2), 2.11–2.00 (m, 1H, CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 174.1 (CO), 170.7 (CO), 143.2 (C), 128.6 (2×CH), 127.5 (CH), 126.2 (2×CH), 55.2 (CH), 48.4 (CH), 34.1 (CH_2).

IR (KBr): 3416, 3367, 3258, 3183, 3066, 3035, 2957, 2912, 2859, 2799, 1694, 1629, 1497, 1456, 1432, 1397, 1364, 1330, 1304, 1285, 1268, 1221, 1204, 1150, 1094, 1077, 1031 cm^{-1}.

HRMS ESI-TOF: *m/z* = 205.0981 $[M+H]^+$ (205.0972 calcd for $C_{11}H_{13}N_2O_2^+$).

(3*RS*,5*SR*)-5-(4-Bromophenyl)-2-oxopyrrolidine-3-carboxamide (**2c**) was obtained from



dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate **1c** (737 mg, 2.4 mmol) and NH_3 (6 M solution in MeOH, 4 mL, 24 mmol) according to the *General Procedure 1*; white solid (470 mg (71%), m.p. 202–203 °C. NMR spectra, recorded 1 h after the

sample preparation, showed the presence of *ca*. 10% of the second diastereomer. NMR spectra of the major isomer are given.

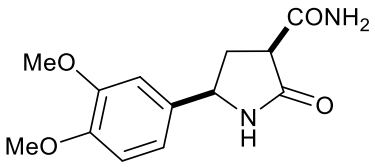
^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.35 (br.s, 1H, NH), 7.57 (d, ^3J = 8.4 Hz, 2H, Ar), 7.51 (br.s, 1H, NH), 7.30 (d, ^3J = 8.4 Hz, 2H, Ar), 7.14 (1H, NH), 4.61 (dd, ^3J = 8.4 Hz, ^3J = 7.3 Hz, 1H, CH), 3.34 (dd, ^3J = 10.6 Hz, ^3J = 8.7 Hz, 1H, CH), 2.58 (ddd, ^2J = 12.4 Hz, ^3J = 8.7 Hz, ^3J = 7.3 Hz, 1H, CH_2), 2.02 (ddd, ^2J = 12.4 Hz, ^3J = 10.6 Hz, ^3J = 8.4 Hz, 1H, CH_2).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 174.0 (CO), 170.4 (CO), 142.6 (C), 131.3 (2×CH), 128.3 (2×CH), 120.3 (C), 54.4 (CH), 48.2 (CH), 33.7 (CH_2).

IR (KBr): 3451, 3328, 3196, 3080, 2991, 2955, 2898, 1696, 1604, 1488, 1451, 1412, 1364, 1337, 1300, 1277, 1205, 1187, 1090, 1070, 1009 cm^{-1}.

HRMS ESI-TOF: m/z = 283.0067 $[M+H]^+$ (283.0077 calcd for $C_{11}H_{12}{}^{79}BrN_2O_2^+$).

(3*RS*,5*SR*)-5-(3,4-Dimethoxyphenyl)-2-oxopyrrolidine-3-carboxamide (**2d**) was obtained from



dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate **1d** (300 mg, 1.0 mmol) and NH_3 (6 M methanolic solution, 2 mL, 12 mmol) according to the *General Procedure 1*. White solid (213 mg, 79%), m.p. 209–210 °C.

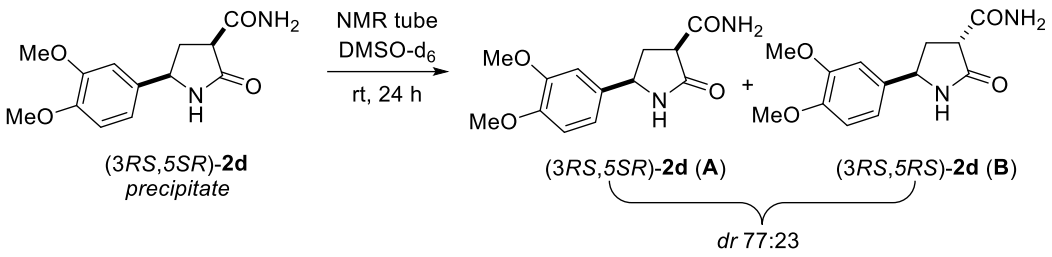
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.27 (br.s, 1H, NH), 7.50 (br.s, 1H, NH), 7.13 (br.s, 1H, NH), 6.95 (d, ^4J = 1.9 Hz, 1H, Ar), 6.91 (d, ^3J = 8.4 Hz, 1H, Ar), 6.84 (dd, ^3J = 8.4 Hz, ^4J = 1.9 Hz, 1H, Ar), 4.54 (dd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, 1H, CH), 3.74 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 3.35–3.29 (m, 1H, CH), 2.55–2.49 (m, 1H, CH_2), 2.09–2.01 (m, 1H, CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 173.9 (CO), 170.7 (CO), 148.8 (C), 148.2 (C), 135.5 (C), 118.2 (CH), 111.8 (CH), 109.9 (CH), 55.6 (CH_3O), 55.5 (CH_3O), 54.9 (CH), 48.3 (CH), 34.0 (CH_2).

IR (KBr): 3385, 3206, 2996, 2949, 2914, 2846, 1682, 1524, 1457, 1384, 1293, 1260, 1181, 1114, 1029, 851, 817 cm^{-1}.

HRMS ESI-TOF: *m/z* = 265.1185 $[M+H]^+$ (265.1183 calcd for $C_{13}H_{17}N_2O_4^+$).

When spectra of **2d** were recorded 24 hours after preparation of the solution of **2d** in DMSO-d_6, they demonstrated the formation of an equilibrium mixture of diastereomers (3*RS*,5*SR*)-**2d**:(3*RS*,5*RS*)-**2d** in a ratio of 77:23. This process is well known for the related CH acids and occurs *via* facile enolisation of $CH(CONH_2)CONH$-fragment.

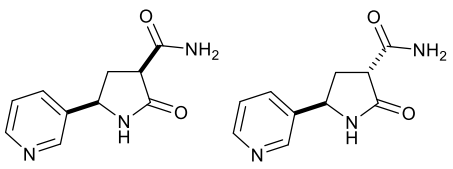


^{1}H NMR (DMSO-d$_6$, 400 MHz, after 24 h): δ = 8.30 (br.s, 1H, NH, **B**), 8.29 (br.s, 1H, NH, **A**), 7.52 (br.s, 1H, NH, **A**), 7.47 (br.s, 1H, NH, **B**), 7.15 (br.s, 1H+1H, NH, **A**, **B**), 6.96 (d, ^4J = 1.9 Hz, 1H, Ar, **A**), 6.91 (d, ^3J = 8.4 Hz, 1H+1H, Ar, **A**, **B**), 6.88 (d, ^4J = 1.9 Hz, 1H, Ar, **B**), 6.83 (dd, ^3J = 8.4 Hz, ^4J = 1.9 Hz, 1H, Ar, **A**), 6.79 (dd, ^3J = 8.4 Hz, ^4J = 1.9, 1H, Ar, **B**), 4.68 (dd, ^3J = 7.8 Hz, ^3J = 5.3 Hz, 1H, CH, **B**), 4.54 (dd, ^3J = 8.5 Hz, ^3J = 7.0 Hz, 1H, CH, **A**), 3.75 (s, 3H, CH$_3$O, **B**), 3.74 (s, 3H, CH$_3$O, **A**), 3.73 (s, 3H, CH$_3$O, **A**), 3.72 (s, 3H, CH$_3$O, **B**), 3.37–3.25 (m, 1H+1H, CH, **A**, **B**), 2.69–2.61 (m, 1H, CH$_2$, **B**), 2.57–2.49 (m, 1H, CH$_2$, **A**), 2.10–2.00 (m, 1H, CH$_2$, **A**), 1.99–1.90 (m, 1H, CH$_2$, **B**).

^{13}C NMR (DMSO-d$_6$, 100 MHz, after 24 h): δ = 174.2 (CO, **B**), 174.0 (CO, **A**), 171.1 (CO, **B**), 170.8 (CO, **A**), 148.9 (C, **B**), 148.8 (C, **A**), 148.2 (C, **A**), 148.1 (C, **B**), 136.0 (C, **B**), 135.5 (C, **A**), 118.2 (CH, **A**), 117.6 (CH, **B**), 111.8 (CH, **B**), 111.7 (CH, **A**), 109.9 (CH, **A**), 109.7 (CH, **B**), 55.6 (2×CH$_3$O, **A**), 55.49 (CH$_3$O, **B**), 55.47 (CH$_3$O, **B**), 55.4 (CH, **B**), 54.9 (CH, **A**), 48.4 (CH, **A**), 47.6 (CH, **B**), 34.3 (CH$_2$, **B**), 34.0 (CH$_2$, **A**).

Scale-up (6.8 mmol): **2d** was obtained from dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate **1d** (2.0 g, 6.8 mmol) and NH$_3$ (6 M methanolic solution, 11.3 mL, 68 mmol) according to the *General Procedure 1*. White solid (1.3 g, 72%), m.p. 209–210 °C.

(3*RS*,5*SR*)- ***and*** **(3*RS*,5*RS*)-2-Oxo-5-(pyridin-3-yl)pyrrolidine-3-carboxamide** (**2e**) was obtained from dimethyl 2-(pyridin-3-yl)cyclopropane-1,1-dicarboxylate **1e** (115 mg, 0.49 mmol), NH$_3$ (6 M solution in MeOH, 0.82 mL, 4.9 mmol) according to the *General Procedure 2*, reaction time 8.5 h. Product was isolated by silica gel column chromatography as a mixture of diastereomers, (3*RS*,5*SR*)-**2e**:(3*RS*,5*RS*)-**2e**, **A**:**B** with *dr* = 60:40. Yellowish oil (72 mg, 72%); R$_f$ = 0.23 (CHCl$_3$:methanol; 5:1).



^{1}H NMR (CD$_3$OD, 400 MHz): δ = 8.58–8.53 (m, 1H+1H, Ar, **A**, **B**), 8.51–8.47 (m, 1H+1H, Ar, **A**, **B**), 7.96–7.92 (m, 1H, Ar, **A**), 7.87–7.82 (m, 1H, Ar, **B**), 7.50–7.44 (m, 1H+1H, Ar, **A**, **B**), 4.97 (dd, ^3J = 8.2 Hz, ^3J = 5.9 Hz, 1H, CH, **B**), 4.85–4.79 (m, 1H, CH, **A**), 3.63–3.52 (m, 1H+1H, CH, **A**, **B**, exchange for deuterium atoms), 2.98–2.89 (m, 1H, CH$_2$, **B**), 2.80 (dd, ^2J = 12.9 Hz, ^3J = 7.3 Hz, 1H,

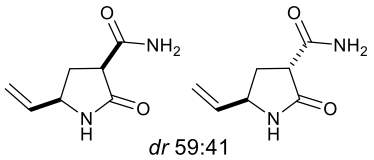
CH_2, **A**), 2.27 (dd, ^2J = 12.9 Hz, ^3J = 8.2 Hz, 1H, CH_2, **A**), 2.22–2.13 (m, 1H, CH_2, **B**). Signals of NH-groups were not observed.

^{13}C NMR (CD_3OD, 100 MHz): δ = 175.1 (CO, **B**), 174.9 (CO, **A**), 172.0 (CO, **B**), 171.9 (CO, **A**), 147.9 (CH, **A**), 147.8 (CH, **B**), 146.8 (CH, **A**), 146.4 (CH, **B**), 138.7 (C, **B**), 138.3 (C, **A**), 134.5 (CH, **A**), 134.1 (CH, **B**), 123.8 (CH+CH, **A**, **B**), 77.7 (CH+CH, **A**, **B**), 54.0 (CH, **B**), 53.4 (CH, **A**), 33.28 (CH_2, **B**), 33.25 (CH_2, **A**).

IR (film): 3373, 2956, 2929, 2396, 2351, 1959, 1935, 1709, 1662, 1610, 1569, 1552, 1534, 1466, 1435, 1382, 1273, 1192, 1140, 1092, 1047, 1028, 1006 cm^{-1}.

HRMS ESI-TOF: *m/z* = 206.0920 $[M+H]^+$ (206.0924 calcd for $C_{10}H_{12}N_3O_2^+$).

(3*RS*,5*SR*)- *and* (3*RS*,5*RS*)-2-Oxo-5-vinylpyrrolidine-3-carboxamide (**2f**) was obtained from



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dimethyl 2-vinylcyclopropane-1,1-dicarboxylate **1f** (500 mg, 2.7 mmol), NH_3 (6 M solution in MeOH, 4.5 mL, 27 mmol) according to the *General Procedure 1*. Product was isolated as a mixture of diastereomers (3*RS*,5*SR*)-**2f**:(3*RS*,5*RS*)-**2f**, **A**:**B** with *dr* = 59:41 Yield: 290 mg (69%); white solid, mp 199–200 °C (lit. 215 °C[S4]; 192–194 °C[S5]).

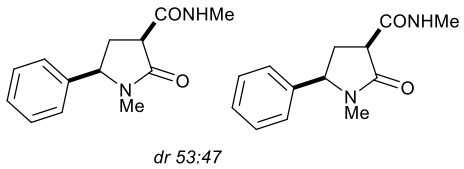
^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.20–8.07 (br.s, 1H+1H, NH, **A**, **B**), 7.53–7.43 (br.s, 1H+1H, NH, **A**, **B**), 7.12–7.04 (br.s, 1H+1H, NH, **A**, **B**), 5.85–5.70 (m, 1H+1H, =CH, **A**, **B**), 5.19 (d, ^3J = 17.1 Hz, 1H, $=CH_2$, **A**), 5.15 (d, ^3J = 17.1 Hz, 1H, $=CH_2$, **B**), 5.05 (d, ^3J = 10.2 Hz, 1H+1H, $=CH_2$, **A**, **B**), 4.10–4.06 (m, 1H, CH, **B**), 4.01–3.95 (m, 1H, CH, **A**), 3.20 (dd, ^3J = 9.7 Hz, ^3J = 8.9 Hz, 1H, CH, **A**), 3.14 (dd, ^3J = 9.3 Hz, ^3J = 7.0 Hz, 1H, CH, **B**), 2.42 (ddd, ^2J = 12.8 Hz, ^3J = 8.0 Hz, ^3J = 7.0 Hz, 1H, CH_2, **B**), 2.30 (ddd, ^2J = 12.7 Hz, ^3J = 8.9 Hz, ^3J = 7.3 Hz, 1H, CH_2, **A**), 1.92 (ddd, ^2J = 12.7 Hz, ^3J = 9.7 Hz, ^3J = 8.2 Hz, 1H, CH_2, **A**), 1.83 (ddd, ^2J = 12.8 Hz, ^3J = 9.3 Hz, ^3J = 4.5 Hz, 1H, CH_2, **B**).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 173.8 (CO, **B**), 173.7 (CO, **A**), 170.8 (CO, **B**), 170.4 (CO, **A**), 139.9 (=CH, **B**), 139.7 (=CH, **A**), 115.3 ($=CH_2$, **A**), 114.5 ($=CH_2$, **B**), 54.2 (CH, **A**), 54.1 (CH, **B**), 47.8 (CH, **A**), 46.8 (CH, **B**), 30.75 (CH_2, **A**), 30.72 (CH_2, **B**).

IR (KBr): 3402, 3201, 3086, 2902, 2777, 1680, 1618, 1460, 1425, 1371, 1319, 1271, 933 cm^{-1}.

HRMS ESI-TOF: *m/z* = 155.0812 $[M+H]^+$ (155.0815 calcd for $C_7H_{11}N_2O_2^+$).

(3*RS*,5*SR*)- ***and*** **(3*RS*,5*RS*)-*N*,1-Dimethyl-2-oxo-5-phenylpyrrolidine-3-carboxamide** (**2g**) was



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obtained from dimethyl 2- phenylcyclopropane-1,1-dicarboxylate **1b** (364 mg, 1.56 mmol), methylamine (9.81 M solution in MeOH, 1.6 mL, 15.6 mmol) according to the *General Procedure 2*. The ratio of diastereomers (*dr* = 53:47, (3*RS*,5*SR*)-**2g**:(3*RS*,5*RS*)-**2g**, **A**:**B**) was determined from the ^{1}H NMR spectra of the crude reaction mixture. Yield: 299 mg (83%). First fraction (**B** prevails) – beige paste, second fraction (**A** prevails) – white solid, mp 119–120 °C, R_f(**A**) = 0.40; R_f(**B**) = 0.52 (ethyl acetate:methanol; 10:1).

For (3*RS*,5*SR*)-**2g**–enriched fraction:

^{1}H NMR ($CDCl_3$, 600 MHz) for (3*RS*,5*SR*)-**2g**: δ = 7.72 (br.s, 1H, NH), 7.35–7.30 (m, 3H, Ar), 7.20–7.15 (m, 2H, Ar), 4.39 (dd, ^{3}J = 8.9 Hz, ^{3}J = 7.3 Hz, 1H, CH), 3.33 (dd, ^{3}J = 11.0 Hz, ^{3}J = 8.8 Hz, 1H, CH), 2.82 (d, ^{3}J = 4.7 Hz, 3H, CH_3NH), 2.72–2.68 (m, 1H, CH_2), 2.58 (s, 3H, CH_3N), 2.36–2.31 (m, 1H, CH_2).

^{13}C NMR ($CDCl_3$, 150 MHz) for (3*RS*,5*SR*)-**2g**: δ = 172.6 (CO), 168.3 (CO), 139.5 (C, Ar), 128.8 (2×CH, Ar), 128.3 (CH, Ar), 126.8 (2×CH, Ar), 62.5 (*C*HPh), 46.5 (CH), 30.9 (CH_2), 28.4 (CH_3N), 26.0 (CH_3NH).

IR (KBr) 3285, 3099, 2973, 2936, 2882, 1662, 1570, 1480, 1460, 1396, 1374, 1284, 1269, 1246, 1159, 1110 cm^{-1}.

HRMS ESI-TOF: *m/z* = 233.1287 $[M+H]^+$ (233.1285 calcd for $C_{13}H_{17}N_2O_2^+$).

For (3*RS*,5*RS*)-**2g**–enriched fraction:

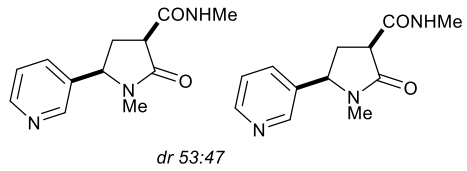
^{1}H NMR ($CDCl_3$, 600 MHz) for (3*RS*,5*RS*)-**2g**: δ = 7.45 (br.s, 1H, NH), 7.29–7.26 (m, 3H, Ar), 7.13–7.10 (m, 2H, Ar), 4.55 (dd, ^{3}J = 8.7 Hz, ^{3}J = 4.8 Hz, 1H, CH), 3.41 (dd, ^{3}J = 10.0 Hz, ^{3}J = 7.0 Hz, 1H, CH), 2.95 (ddd, ^{2}J = 13.5 Hz, ^{3}J = 8.7 Hz, ^{3}J = 7.0 Hz, 1H, CH_2), 2.80 (d, ^{3}J = 5.1 Hz, 3H, CH_3NH), 2.65 (s, 3H, CH_3N), 2.08 (ddd, ^{2}J = 13.5 Hz, ^{3}J = 10.0 Hz, ^{3}J = 4.8 Hz, 1H, CH_2).

^{13}C NMR ($CDCl_3$, 150 MHz) for (3*RS*,5*RS*)-**2g**: δ = 172.6 (CON), 168.1 (CON), 140.2 (C, Ar), 129.0 (2×CH, Ar), 128.0 (CH, Ar), 126.0 (2×CH, Ar), 62.7 (*C*HPh), 46.1 (CH), 30.7 (CH_2), 28.5 (CH_3N), 26.1 (CH_3NH).

IR (Nujol, cm^{-1}): 3480, 3319, 2945, 1684, 1668, 1553, 1456, 1400, 1362, 1282, 1260, 1110 cm^{-1}.

HRMS ESI-TOF: *m/z* = 233.1288 $[M+H]^+$ (233.1285 calcd for $C_{13}H_{17}N_2O_2^+$).

(3*RS*,5*SR*)- *and* (3*RS*,5*RS*)-*N*,1-Dimethyl-2-oxo-5-(pyridin-3-yl)pyrrolidine-3-carboxamide (**2h**)



dr 53:47

was obtained from dimethyl 2-(pyridin-3-yl)cyclopropane-1,1-dicarboxylate **1e** (300 mg, 1.3 mmol), methylamine (9.81 M solution in MeOH, 1.3 mL, 13 mmol) according to the *General Procedure 2*. Product was isolated by silica gel column chromatography as a mixture of diastereomers (3*RS*,5*SR*)-**2h**:(3*RS*,5*RS*)-**2h**, **A**:**B** with *dr* = 53:47.

Yield 166 mg (56%), colorless oil. R_f(**A**) = 0.56; R_f(**B**) = 0.51 ($CHCl_3$:methanol; 8:1).

^{1}H NMR ($CDCl_3$, 400 MHz) for (3*RS*,5*SR*)-**2h**: δ = 7.59 (br.s, 1H, NH), 7.56–7.52 (m, 1H, Ar), 7.45–7.41 (m, 1H, Ar), 7.29–7.27 (m, 1H, Ar), 7.26–7.24 (m, 1H, Ar), 4.43 (dd, ^3J = 8.0 Hz, ^3J = 7.8 Hz, 1H, CH), 3.34 (dd, ^3J = 10.0 Hz, ^3J = 9.1 Hz, 1H, CH), 2.78 (d, ^3J = 4.9 Hz, 3H, CH_3NH), 2.69 (ddd, ^2J = 13.9 Hz, ^3J = 10.0 Hz, ^3J = 8.0 Hz, 1H, CH_2), 2.56 (s, 3H, CH_3N), 2.33 (ddd, ^2J = 13.9 Hz, ^3J = 9.1 Hz, ^3J = 7.8 Hz, 1H, CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) for (3*RS*,5*SR*)-**2h**: δ = 172.5 (CO), 167.9 (CO), 149.9 (CH), 148.7 (CH), 135.2 (C), 134.2 (CH), 124.0 (CH), 60.0 (CH), 46.6 (CH), 30.3 (CH_2), 28.5 (CH_3N), 26.2 (CH_3N).

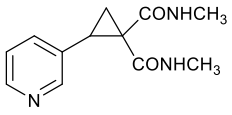
^{1}H NMR ($CDCl_3$, 400 MHz) for (3*RS*,5*RS*)-**2h**: δ = 8.54–8.50 (m, 2H, Ar), 8.45–8.40 (m, 2H, Ar), 7.40 (br.s, 1H, NH), 4.58 (dd, ^3J = 8.6 Hz, ^3J = 5.0 Hz, 1H, CH), 3.40 (dd, ^3J = 9.9 Hz, ^3J = 6.6 Hz, 1H, CH), 2.97 (ddd, ^2J = 13.9 Hz, ^3J = 8.6 Hz, ^3J = 6.6 Hz, 1H, CH_2), 2.76 (d, ^3J = 4.8 Hz, 3H, CH_3NH), 2.62 (s, 3H, CH_3N), 2.03 (ddd, ^2J = 13.9 Hz, ^3J = 9.9 Hz, ^3J = 5.0 Hz, 1H, CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) for (3*RS*,5*RS*)-**2h**: δ = 172.5 (CO), 167.7 (CO), 149.7 (CH), 148.1 (CH), 138.6 (CH), 135.7 (C), 123.8 (CH), 60.5 (CH), 46.1 (CH), 30.5 (CH_2), 28.4 (CH_3N), 26.1 (CH_3N).

IR (film): 3508, 3302, 3089, 2945, 2807, 2404, 2236, 1940, 1701, 1687, 1659, 1643, 1576, 1561, 1546, 1478, 1435, 1426, 1399, 1364, 1321, 1306, 1259, 1161, 1109, 1043, 1027 cm^{-1}.

HRMS ESI-TOF: *m/z* = 234.1244 $[M+H]^+$ (234.1237 calcd for $C_{12}H_{16}N_3O_2^+$).

***N,N'*-Dimethyl-2-(pyridin-3-yl)cyclopropane-1,1-dicarboxamide** (**4a**) was obtained as a side



product in the reaction of dimethyl 2-(pyridin-3-yl)cyclopropane-1,1-dicarboxylate **1e** (300 mg, 1.3 mmol) with methylamine (9.81 M solution in MeOH, 1.3 mL, 13 mmol) according to the *General Procedure 2*. Compound **4a** was isolated using silica gel column chromatography. White foam (87 mg, 29%), m.p. 188–189 °C, R_f = 0.42 ($CHCl_3$:methanol; 8:1).

^{1}H NMR ($CDCl_3$+CD_3OD, 400 MHz): δ = 8.27–8.23 (m, 2H, Ar), 7.44 (dd, ^{3}J = 8.0 Hz, ^{4}J = 1.8 Hz, 1H, Ar), 7.11 (dd, ^{3}J = 8.0 Hz, ^{3}J = 4.9 Hz, 1H, Ar), 4.00 (br.s, 2H, NH), 2.69 (s, 3H, CH_3), 2.59 (dd, ^{3}J = 8.8 Hz, ^{3}J = 7.6 Hz, 1H, CH), 2.34 (s, 3H, CH_3), 1.94–1.85 (m, 2H, CH_2).

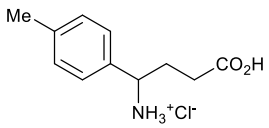
^{13}C NMR ($CDCl_3$+CD_3OD, 100 MHz): δ = 169.6 (CO), 167.8 (CO), 148.8 (CH), 147.3 (CH), 136.4 (CH), 131.8 (C), 123.1 (CH), 37.8 (C), 29.2 (CH), 26.3 (CH_3), 25.7 (CH_3), 14.3 (CH_2).

IR (KBr): 3435, 3309, 3213, 3046, 3000, 2947, 2897, 2463, 2357, 2308, 1658, 1638, 1580, 1543, 1479, 1445, 1403, 1351, 1291, 1244, 1225, 1187, 1149, 1134, 1108, 1073, 1034 cm^{-1}.

HRMS ESI-TOF: *m/z* = 234.1240 $[M+H]^+$ (234.1237 calcd for $C_{12}H_{16}N_3O_2^+$).

Synthesis and analytical data for γ-aryl-γ-aminobutyric acid derivatives 3

4-Amino-4-(*p*-tolyl)butyric acid hydrochloride (**3a·HCl**)



Hydrochloric acid (6 M aq. solution, 4.8 mL, 28 mmol) was added to 2-oxo-5-(*p*-tolyl)pyrrolidine-3-carboxamide **2a** (305 mg, 1.4 mmol); the resulting solution was refluxed for 6 h. Then the reaction mixture was washed with ethyl acetate (2 × 5 mL) and concentrated to dryness. The residue was dissolved in 1 mL of water and flushed through a small pad of silica using EtOAc/*i*-PrOH/H_2O (3:3:1) as eluent. Light yellow solid (295 mg, 92%), m.p. 202–204 °C.

^{1}H NMR (CD_3OD, 600 MHz): δ = 7.33–7.29 (m, 4H, Ar), 4.32 (dd, ^3J = 9.9 Hz, ^3J = 5.9 Hz, 1H, CH), 2.37 (s, 3H, CH_3), 2.34–2.30 (m, 1H, CH_2), 2.24–2.15 (m, 3H, CH_2). Signals of CO_2H and NH_3-groups were not observed.

^{13}C NMR (CD_3OD, 100 MHz): δ = 176.6 (CO_2H), 141.5 (C), 135.3 (C), 131.9 (2×CH), 129.4 (2×CH), 56.7 (CH), 31.9 (CH_2), 31.4 (CH_2), 22.2 (CH_3).

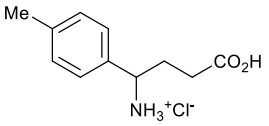
IR (KBr): 3112, 3015, 2918, 1731, 1599, 1492, 1444, 1401, 1273, 1214, 1168, 1124, 1088, 1054, 1020 cm^{-1}.

HRMS ESI-TOF: *m/z* = 194.1184 $[M]^+$ (194.1176 calcd for $C_{11}H_{16}NO_2^+$).

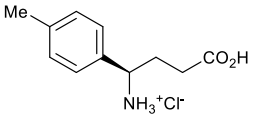
General Procedure 3

To cyclopropane (1 equiv.) in a glass vial with a screw cap was added *ca*. 6 M methanolic solution of NH_3 (10 equiv.) so that the volume of the solution does not exceed 1/3 of the vial volume. The vial was tightly closed, the reaction vessel was immediately immersed in an oil bath preheated to 130 °C and vigorously stirred for 9 h. The reaction mixture was then cooled to room temperature, and MeOH was evaporated. The resulting solid was dried under a vacuum diaphragm pump for 1 h and transferred to a round bottom flask. HCl (6 M aq. solution, 20 equiv.) was then added, and the mixture was refluxed for 6–8 h. The acid solution was removed under reduced pressure. The residue was purified by repeated addition of benzene and subsequent evaporation on a rotary evaporator while heating the bath above 70 °C (method **A**) or by column chromatography on silica gel, eluent: EtOAc/*i*-PrOH/H_2O, 3:3:1 (method **B**).

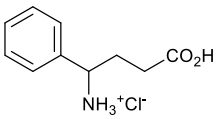
4-Amino-4-(*p*-tolyl)butyric acid hydrochloride (**3a·HCl**) was synthesised from dimethyl 2-(*p*-tolyl)cyclopropane dicarboxylate **1a** (350 mg, 1.4 mmol) and NH_3 (6 M methanolic solution, 2.4 mL, 14.0 mmol) according to the *General Procedure 3*, using heating under reflux with HCl (6 M aq. solution, 4.8 mL, 28 mmol) for 6 h and purification by method **A**. Light yellow solid (295 mg, 91%), m.p. 202–204 °C. NMR spectra coincide with those for sample obtained from **2a**.



(*R*)-4-Amino-4-(*p*-tolyl)butyric acid hydrochloride ((*R*)-**3a·HCl**) was synthesised from dimethyl (*S*)-2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate (*S*)-**1a**[S3] (105 mg, 0.42 mmol) and NH_3 (6 M solution in MeOH, 705 µL, 4.2 mmol) according to the *General Procedure 3*, using heating under reflux with HCl (6 M aq. solution, 1.4 mL, 8.4 mmol) for 6 h and purification by method **A**. Light yellow solid (85 mg, 88%), m.p. 202–204 °C. NMR spectra coincide with those for racemic **3a·HCl**.



4-Amino-4-phenylbutyric acid hydrochloride (**3b·HCl**) was synthesised from dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1b** (613 mg, 2.6 mmol), NH_3 (6 M methanolic solution, 4 mL, 24.0 mmol) and HCl (6 M aq. solution, 4.2 mL, 25 mmol) according to the *General Procedure 3* (purification by method **A**). Yellowish solid (480 mg, 85%). NMR data are consistent with the reported ones.[S6-S9]

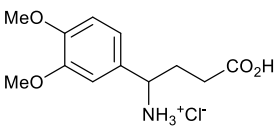


^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.80 (br.s, 3H, NH_3), 7.54–7.49 (m, 2H, Ar), 7.43–7.34 (m, 3H, Ar), 4.21 (br.s, 1H, CH), 2.31–2.11 (m, 2H, CH_2), 2.09–1.95 (m, 2H, CH_2). Signal of CO_2H-group was not observed.

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 173.4 (CO_2H), 137.4 (C), 128.8 (CH), 128.6 (2×CH), 127.6 (2×CH), 53.8 (CH), 30.0 (CH_2), 29.6 (CH_2).

HRMS ESI-TOF: *m/z* = 180.1025 $[M]^+$ (180.1019 calcd for $C_{10}H_{14}NO_2^+$).

4-Amino-4-(3,4-dimethoxyphenyl)butyric acid hydrochloride (**3c·HCl**)



To dimethyl 2-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate **1d** (197 mg, 0.67 mmol) in a glass vial with screw cap was added *ca*. 6 M methanolic solution of NH_3 (1.1 mL, 6.7 mmol) so that the volume of the solution does not exceed 1/3 of the vial volume. The vial was tightly closed, the reaction vessel was immediately immersed in an oil bath preheated to 130 °C and vigorously stirred for 9

h. The reaction mixture was then cooled to room temperature, and volatiles were evaporated. The residue was dried under a vacuum diaphragm pump for 1 h and transferred to a round bottom flask. Hydrochloric acid (3 M solution, 5.6 mL, 16.6 mmol) was added; the resulting solution was refluxed for 4 h, cooled to room temperature, washed with ethyl acetate (2 × 5 mL) and concentrated to dryness. The residue was dissolved in 1 mL of water and flushed through a plug of silica using EtOAc/*i*-PrOH/H_2O (3:3:1) as eluent. Yellow solid (172 mg, 93%), dec. p. 215 °C.

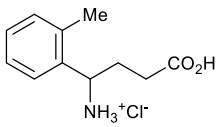
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.30 (s, 1H, Ar), 6.96 (s, 2H, Ar), 4.15–4.12 (m, 1H, CH), 3.77 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 2.23–2.11 (m, 2H, CH_2), 2.05–1.99 (m, 2H, CH_2). Signals of CO_2 and NH_3 groups were not observed.

^{13}C NMR (DMSO-d_6, 150 MHz): δ = 173.4 (CO_2H), 148.9 (2×C), 129.5 (C), 120.1 (CH), 111.5 (CH), 111.1 (CH), 55.7 (CH_3O), 55.5 (CH_3O), 53.7 (CH), 30.1 (CH_2), 29.5 (CH_2).

IR (KBr): 3115, 2993, 2933, 2908, 2836, 2600, 1727, 1607, 1595, 1517, 1467, 1445, 1403, 1386, 1337, 1264, 1243, 1211, 1191, 1165, 1142, 1096, 1023 cm^{-1}.

HRMS ESI-TOF: *m/z* = 240.1236 $[M]^+$ (240.1230 calcd for $C_{12}H_{18}NO_4^+$).

4-Amino-4-(*o*-tolyl)butyric acid hydrochloride (**3d·HCl**) was synthesised from dimethyl 2-(*o*-tolyl)cyclopropane-1,1-dicarboxylate **1g** (425 mg, 1.7 mmol), NH_3 (6 M methanolic solution, 3 mL, 18.0 mmol) and HCl (6 M aq. solution, 4.0 mL, 24 mmol) according to the *General Procedure 3* (purification by method **A**). White solid (288 mg, 89%), m.p. 228–229 °C.



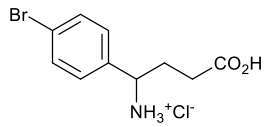
^{1}H NMR (CD_3OD, 400 MHz): δ = 7.53–7.49 (m, 1H, Ar), 7.38–7.26 (m, 3H, Ar), 4.74 (dd, ^3J = 8.9 Hz, ^3J = 5.8 Hz, 1H, CH), 2.42 (s, 3H, CH_3), 2.40–2.32 (m, 1H, CH), 2.32–2.17 (m, 3H, CH_2). Signals of CO_2H and NH_3-groups were not observed.

^{13}C NMR (CD_3OD, 100 MHz): δ = 174.0 (CO_2H), 136.2 (C), 134.2 (C), 130.5 (CH), 128.4 (CH), 126.5 (CH), 124.8 (CH), 49.3 (CH), 28.9 (CH_2), 28.8 (CH_2), 17.7 (CH_3).

IR (KBr): 3390, 2960, 2776, 2509, 2343, 2202, 2155, 1712, 1606, 1584, 1496, 1415, 1402, 1358, 1301, 1193, 1180, 1163, 1061, 1027 cm^{-1}.

HRMS ESI-TOF: *m/z* = 194.1182 $[M]^+$ (194.1176 calcd for $C_{11}H_{16}NO_2^+$).

4-Amino-4-(4-bromophenyl)butyric acid hydrochloride (**3e·HCl**) was synthesised from dimethyl



2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate **1c** (737 mg, 2.4 mmol), NH_3 (6 M methanolic solution, 4 mL, 24.0 mmol) and HCl (6 M aq. solution, 5.5 mL, 33 mmol) according to the *General Procedure 3* (purification by method **A**). Yellowish solid (582 mg, 84%), m.p. 219–220 °C.

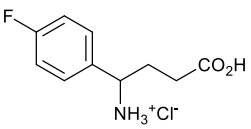
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.67–7.58 (m, 2H, Ar), 7.44–7.36 (m, 2H, Ar), 4.21 (dd, ^3J = 7.9 Hz, ^3J = 5.9 Hz, 1H, CH), 2.25–2.07 (m, 2H, CH_2), 2.05–1.90 (m, 2H, CH_2). Signals of CO_2H and NH_3-groups were not observed.

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 174.0 (CO_2H), 137.4 (C), 131.6 (2×CH), 129.9 (2×CH), 121.7 (C), 53.3 (CH), 30.8 (CH_2), 29.9 (CH_2).

IR (KBr): 3491, 2996, 2962, 2631, 2606, 2250, 2194, 1734, 1595, 1490, 1378, 1223, 1151, 1093, 1075, 1012 cm^{-1}.

Anal. calcd. for $C_{10}H_{13}BrClNO_2$: C, 40.77; H, 4.45; N, 4.76. Found: C, 40.87; H, 4.39; N, 4.63.

***4*-Amino-4-(4-fluorophenyl)butyric acid hydrochloride** (**3f·HCl**) was synthesized from dimethyl



2-(4-fluorophenyl)cyclopropane-1,1-dicarboxylate **1h** (500 mg, 2.0 mmol), NH_3 (6 M methanolic solution, 3.7 mL, 22 mmol) and HCl (6 M aq. solution, 3.5 mL, 21 mmol) according to the *General Procedure 3* (purification by method **A**). Yellowish solid (385 mg, 83%), m.p. 201–202 °C.

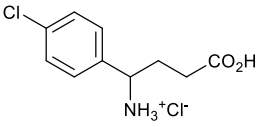
^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.94–6.83 (br.s, $\Delta\nu_{1/2}$ = 363 Hz, 4H, NH_3+CO_2H), 7.65–7.52 (m, 2H, Ar), 7.29–7.18 (m, 2H, Ar), 4.28–4.21 (m, 1H, CH), 2.29–2.18 (m, 1H, CH_2), 2.18–2.09 (m, 1H, CH_2), 2.06–1.93 (m, 2H, CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 173.7 (CO_2H), 162.1 (d, $^1J_{CF}$ = 245 Hz, C), 133.9 (C), 130.0 (d, $^3J_{CF}$ = 8 Hz, 2×CH), 115.6 (d, $^2J_{CF}$ = 22 Hz, 2×CH), 53.2 (CH), 30.4 (CH_2), 29.8 (CH_2).

IR (KBr): 3369, 3119, 3043, 3019, 2967, 2634, 2029, 1713, 1607, 1516, 1408, 1307, 1232, 1165, 1095, 1016 cm^{-1}.

HRMS ESI-TOF: *m/z* = 198.0924 $[M]^+$ (198.0925 calcd for $C_{10}H_{13}FNO_2^+$).

4-Amino-4-(4-chlorophenyl)butyric acid hydrochloride (**3g·HCl**) was synthesised from dimethyl



2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate **1i** (507 mg, 1.9 mmol), NH_3 (6 M methanolic solution, 3 mL, 18.0 mmol) and HCl (6 M aq. (purification by method **A**). White solid (382 mg, 81%), m.p. 206–207 °C.

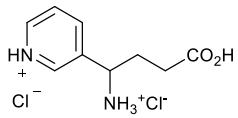
^{1}H NMR (CD_3OD, 500 MHz): δ = 7.62–7.31 (m, 4H, Ar), 4.41 (dd, ^3J = 9.3 Hz, ^3J = 5.6 Hz, 1H, CH), 2.45–2.34 (m, 1H, CH_2), 2.32–2.16 (m, 3H, CH_2).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 174.8 (CO_2H), 134.9 (2×C), 129.2 (2×CH), 129.0 (2×CH), 54.1 (CH), 29.9 (CH_2), 29.1 (CH_2).

IR (KBr): 3034, 2819, 2290, 1735, 1601, 1492, 1417, 1384, 1364, 1210, 1149, 1098, 1029, 1017 cm^{-1}.

HRMS ESI-TOF: *m/z* = 214.0632 $[M]^+$ (214.0629 calcd for $C_{10}H_{13}{}^{35}ClNO_2^+$).

4-Amino-4-(pyridin-3-yl)butyric acid dihydrochloride (3h·2HCl)



To cyclopropane **1e** (172 mg, 0.73 mmol) in a glass vial with a screw cap was added *ca*. 6 M methanolic solution of NH_3 (10 equiv., 1.2 mL, 7.3 mmol) so that the volume of the solution does not exceed 1/3 of the vial volume. The vial was tightly closed, the reaction vessel was immediately immersed in an oil bath preheated to 130 °C and vigorously stirred for 9 h. The reaction mixture was then cooled to room temperature, and MeOH was evaporated. The resulting solid was dried under a vacuum diaphragm pump for 1 h and transferred to a round bottom flask.

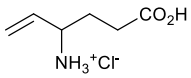
Hydrochloric acid (6 M solution, 1.2 mL, 7.2 mmol) was added to pyrrolidone **2e** (150 mg, 0.73 mmol); the resulting solution was refluxed for 6 h. Then the reaction mixture was evaporated to dryness and 1 M solution of NaOH (3.1 mL, 3.1 mmol) was added to the residue. The obtained mixture was stirred at 75 °C for 3 h and air was passed through it until all the ammonia had evaporated (the color of wet indicator paper stopped changing in the absence of the ammonia at the outlet of the flask). 0.5 M solution of hydrochloric acid was added to pH 3. The reaction mixture was concentrated to dryness. The residue was dissolved in 1 mL of water and flushed through a small pad of silica using EtOAc/*i*-PrOH/H_2O (3:3:1) as eluent. Yellowish solid (112 mg, 71%), dec. p. 190 °C.

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 9.21 (br.s, 3H, NH_3), 9.08 (s, 1H, Ar), 8.88 (d, ^3J = 5.4 Hz, 1H, Ar), 8.73 (d, ^3J = 8.0 Hz, 1H, Ar), 8.02 (dd, ^3J = 8.0 Hz, ^3J = 5.4 Hz, 1H, Ar), 4.57 (br.s, 1H, CH), 2.35–2.25 (m, 2H, CH_2), 2.21–2.10 (m, 2H, CH_2). Signal of CO_2H-group was not observed.

^{13}C NMR (DMSO-d_6, 150 MHz): δ = 173.6 (CO_2H), 143.8 (CH), 147.7 (CH), 143.4 (CH), 136.8 (C), 127.1 (CH), 51.4 (CH), 30.2 (CH_2), 29.1 (CH_2).

HRMS ESI-TOF: *m/z* = 181.0981 $[M]^+$ (181.0972 calcd for $C_9H_{13}N_2O_2^+$).

4-Aminohex-5-enoic acid hydrochloride (**3i·HCl**) was synthesised from dimethyl 2-vinylycloprop

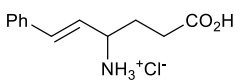


ane-1,1-dicarboxylate **1f** (500 mg, 2.7 mmol), NH_3 (6 M methanolic solution, 4.5 mL, 27.0 mmol) and HCl (6 M aq. solution, 4.5 mL, 27.0 mmol) according to the *General Procedure 3* (purification by method **B**). Yellowish solid (255 mg, 57%), m.p. 208–209 °C (lit. 207–209 °C[S10]). NMR spectra are consistent with the reported ones.[S10-S12]

^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.48 (br.s, 3H, NH_3), 5.75 (ddd, ^3J = 17.6 Hz, ^3J = 10.0 Hz, ^3J = 7.7 Hz, 1H, CH=), 5.33–5.24 (m, 2H, CH_2=), 3.60 (br.s, 1H, CH), 2.29–2.19 (m, 2H, CH_2), 1.99–1.88 (m, 1H, CH_2), 1.79–1.68 (m, 1H, CH_2). Signal of CO_2H-group was not observed.

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 173.6 (CO_2H), 134.3 (=CH), 120.0 (=CH_2), 52.4 (CH), 29.6 (CH_2), 27.5 (CH_2).

(*E*)-4-Amino-6-phenylhex-5-enoic acid hydrochloride (**3j·HCl**) was synthesised from dimethyl 2-styrylcyclopropane-1,1-dicarboxylate **1j** (340 mg, 1.3 mmol), NH_3 (6 M methanolic solution, 2 mL, 12.0 mmol) and HCl (6 M aq. solution, 2.4 ml, 14.4 mmol) according to the *General Procedure 3* (purification by method **B**). Yellowish solid (111 mg, 47%).



^{1}H NMR (DMSO-d_6, 400 MHz): δ = 12.24 (br.s, 1H, CO_2H), 8.61 (br.s, 3H, NH_3), 7.43–7.39 (m, 2H, Ar), 7.37–7.31 (m, 2H, Ar), 7.30–7.25 (m, 1H, Ar), 6.69 (d, ^3J = 15.9 Hz, 1H, Ph-CH=), 6.20 (dd, ^3J = 15.9 Hz, ^3J = 8.4 Hz, 1H, =CH-), 3.84–3.77 (m, 1H, CH), 2.34–2.25 (m, 2H, CH_2), 2.11–2.02 (m, 1H, CH_2), 1.93–1.82 (m, 1H, CH_2).

^{13}C NMR (DMSO-d_6, 100 MHz): δ = 173.6 (CO_2H), 135.6 (C), 134.1(CH), 128.8 (2×CH), 128.3 (CH), 126.6 (2×CH), 125.5 (CH), 52.3 (CH), 29.8 (CH_2), 27.9 (CH_2).

IR (KBr): 3466, 3434, 3152, 3046, 1730, 1723, 1635, 1623, 1512, 1495, 1448, 1405, 1174, 1125, 1074, 1043 cm^{-1}.

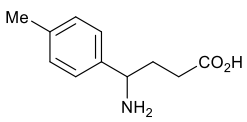
HRMS ESI-TOF: *m/z* = 204.1036 $[M-H]^-$ (204.1030 calcd for $C_{12}H_{14}NO_2^-$).

General Procedure 4

To 2 M solution of amino acid hydrochloride (1 equiv.) in deionised water 2 M aqueous solution of NaOH (1 equiv.) was added. The resulting mixture was stirred at room temperature for 5 minutes until precipitate formed. Precipitate was filtered on a porous glass filter and washed

once with ice water. Obtained amino acid was dried under vacuo and used without any further purification.

4-Amino-4-(*p*-tolyl)butyric acid (**3a**) was synthesised from hydrochloride **3a·HCl** (80 mg, 0.35 mmol) and NaOH (2 M aq. solution, 175 µL, 0.35 mmol) according to the *General Procedure 4*. White solid (60 mg, 90%), m.p. 158–160 °C.



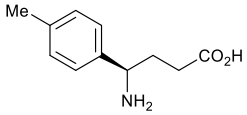
^{1}H NMR (D_2O:CD_3OD 10:1, 400 MHz): δ = 7.22 (s, 4H, Ar), 4.22–4.19 (m, 1H, CH), 2.25 (s, 3H, CH_3), 2.18–1.98 (m, 4H, 2×CH_2). Signals of CO_2H and NH_3-groups were not observed.

^{13}C NMR (D_2O:CD_3OD 10:1, 100 MHz): δ = 181.5 (CO_2H), 140.5 (C), 133.6 (C), 130.6 (2×CH), 128.0 (2×CH), 55.8 (CH), 34.2 (CH_2), 30.9 (CH_2), 21.1 (CH_3).

IR (KBr): 3127, 3025, 2947, 2921, 2859, 2661, 1652, 1622, 1537, 1519, 1446, 1398, 1386, 1376, 1317, 1258, 1212, 1187, 1141, 1113, 1079, 1036, 1022 cm^{-1}.

HRMS ESI-TOF: *m/z* = 194.1184 $[M+H]^+$ (194.1176 calcd for $C_{11}H_{16}NO_2^+$).

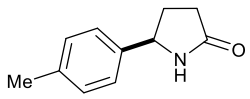
(*R*)-4-Amino-4-(*p*-tolyl)butyric acid ((*R*)-**3a**) was synthesised from hydrochloride (*R*)-**3a·HCl** (47 mg, 0.20 mmol) and NaOH (2 M aq. solution, 100 µL, 0.20 mmol) according to the *General Procedure 4*. White solid (28 mg, 70%), m.p. 158–160 °C, $[\alpha]_D^{20}$ = −12.0 (c 0.41 in MeOH). NMR spectra coincide with those for racemic **3a**.



General Procedure 5 for derivatization of 4-amino-4-(*p*-tolyl)butyric acid 5a to pyrrolidin-2-one 5a

To a suspension of amino acid (1 equiv.) in toluene (0.0 3M) aluminium oxide (5 parts in weight) and water (8 parts in volume) were added. The resulted mixture was refluxed for 5 hours, using Dean-Stark trap to collect water. The reaction mixture was then cooled to room temperature, filtered and the solid was repeatedly washed with methanol. Combined organic fraction was evaporated under vacuo and used without any further purification and flushed through a plug of silica using EtOAc/petroleum ether (from 1:10 to 1:2) as eluent.

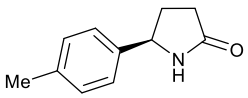
5-(p-Tolyl)pyrrolidin-2-one (5a) was synthesized from 4-amino-4-(p-tolyl)butyric acid **3a** (8 mg, 0.04 mmol), toluene (1.2 mL), H_2O (64 µL) and Al_2O_3 (40 mg) according to the *General Procedure 5*. (83%, 6 mg). NMR data are consistent with the reported ones [S13].



^{1}H NMR (CD_3OD, 600 MHz): δ 7.20–7.17 (m, 4H, Ar), 4.76–4.74 (m, 1H, CH), 2.59–2.53 (m, 1H, CH_2), 2.44–2.41 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 1.95–1.88 (m, 1H, CH_2).

^{13}C NMR (CD_3OD, 151 MHz): δ 181.7 (CO), 141.7 (C), 139.0 (C), 130.9 (2×CH), 127.2 (2×CH), 60.1 (CH), 32.7 (CH_2), 32.0 (CH_2), 21.6 (CH_3).

(R)-5-(p-Tolyl)pyrrolidin-2-one ((R)-5a) was synthesized from (*R*)-4-amino-4-(p-tolyl)butyric acid (***R*)-3a** (35 mg, 0.2 mmol), toluene (6 mL), H_2O (280 µL) and Al_2O_3 (175 mg) according to the *General Procedure 5*. (85%, 27 mg). NMR data are consistent with the reported ones [S13].



^{1}H NMR (CD_3OD, 600 MHz): δ 7.20–7.17 (m, 4H, Ar), 4.76–4.74 (m, 1H, CH), 2.59–2.53 (m, 1H, CH_2), 2.44–2.41 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 1.95–1.88 (m, 1H, CH_2).

^{13}C NMR (CD_3OD, 151 MHz): δ 181.7 (CO), 141.7 (C), 139.0 (C), 130.9 (2×CH), 127.2 (2×CH), 60.1 (CH), 32.7 (CH_2), 32.0 (CH_2), 21.6 (CH_3).

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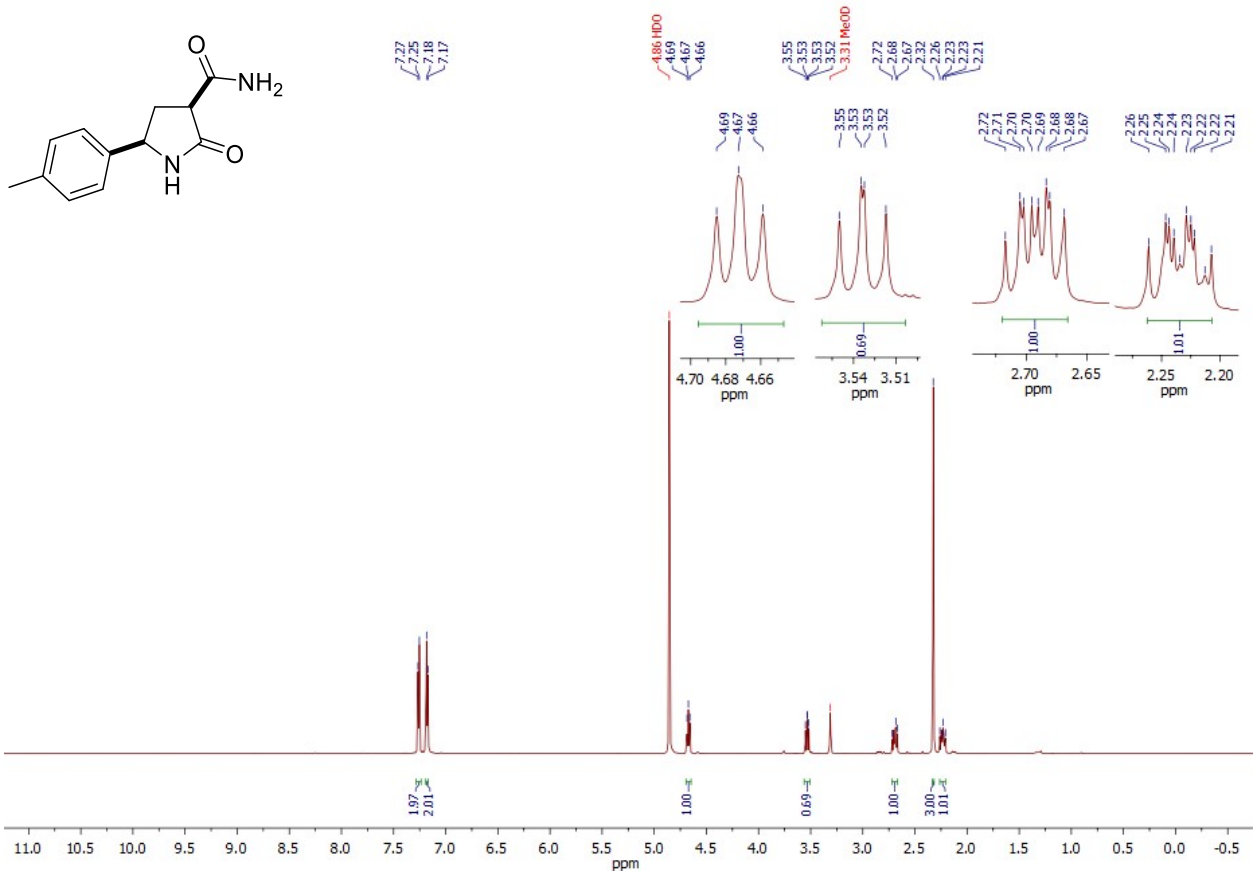
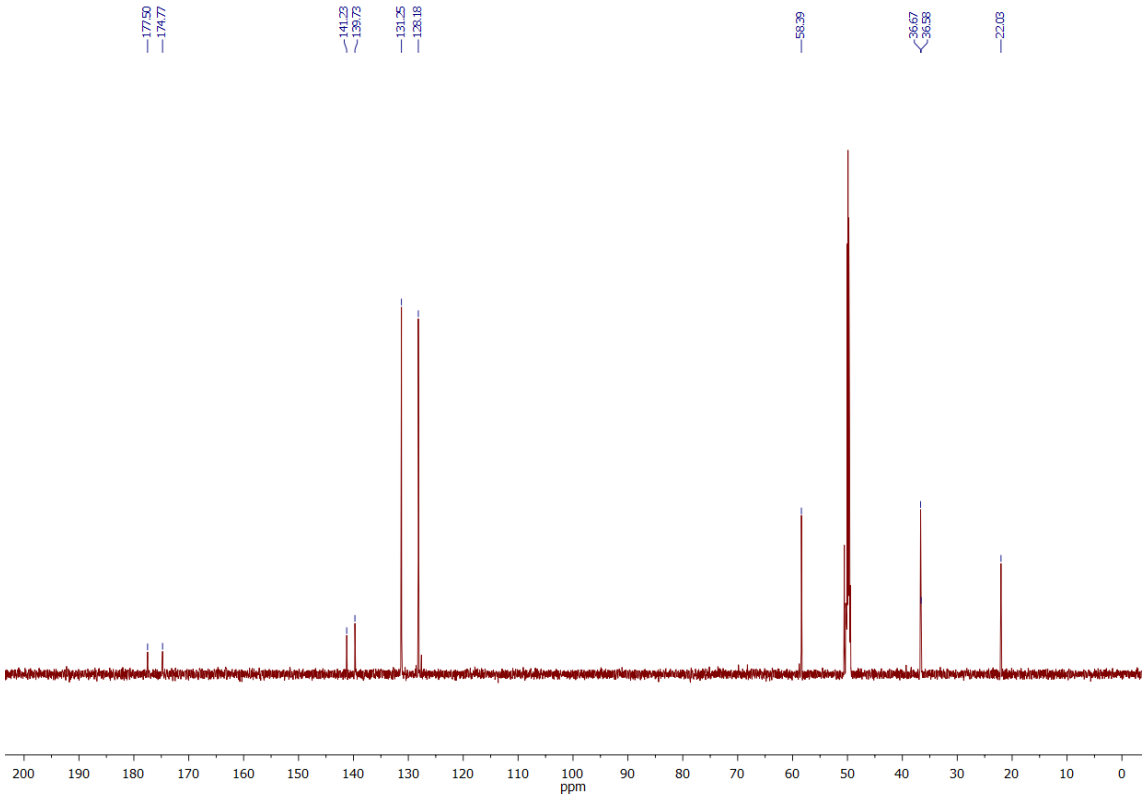
Copies of NMR spectra

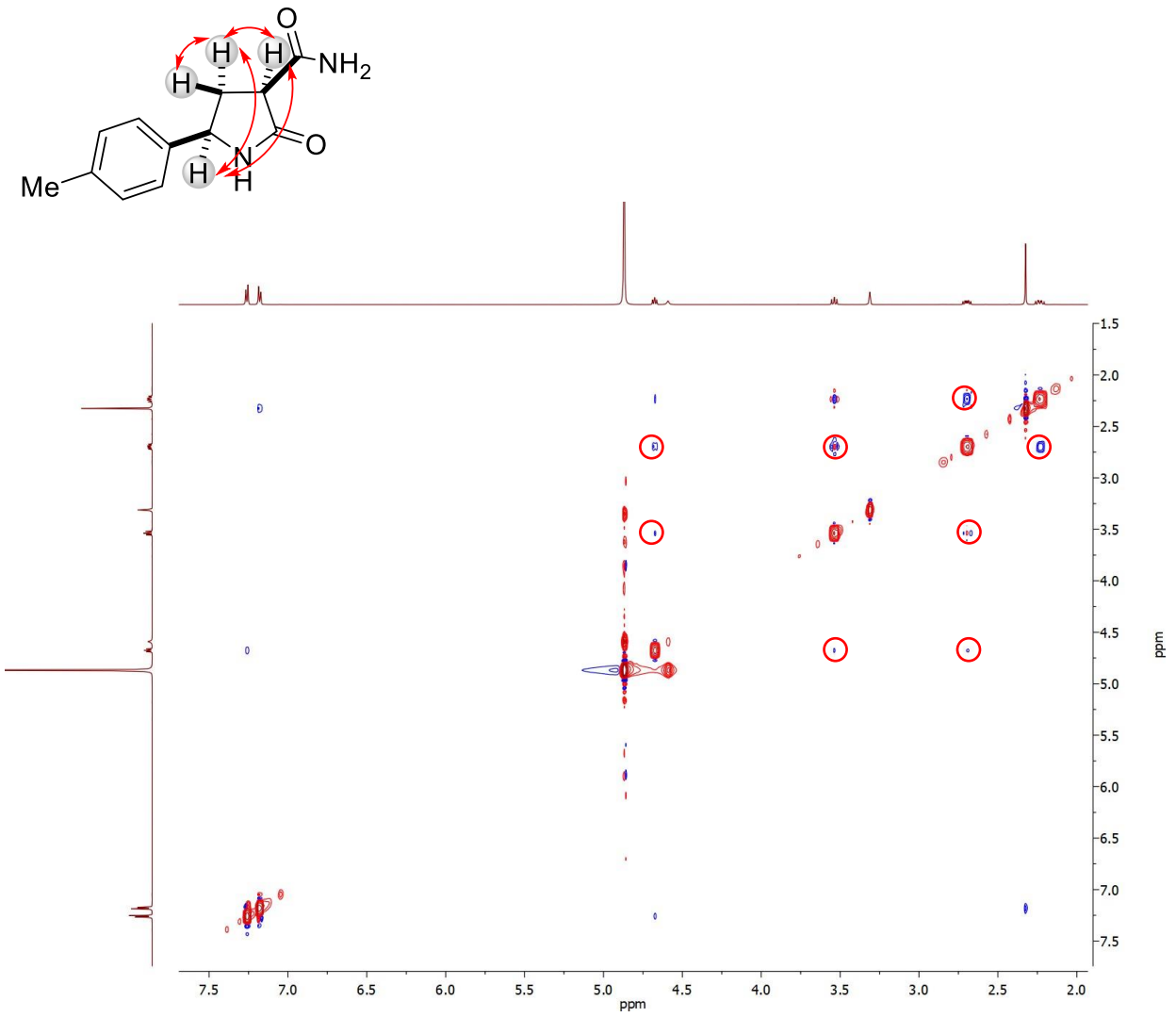
^{1}H NMR (CD_3OD, 600 MHz) of **2a**



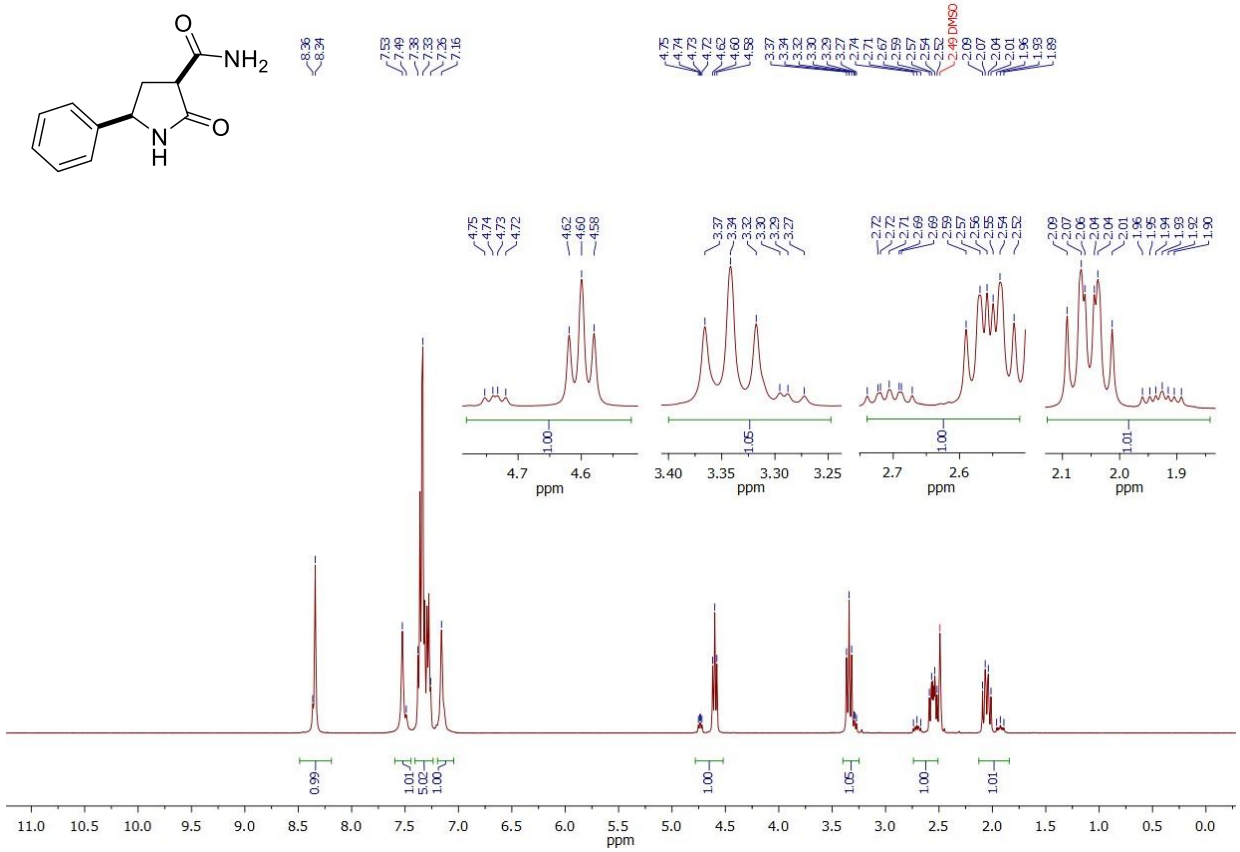
^{13}C NMR (CD_3OD, 151 MHz) of **2a**



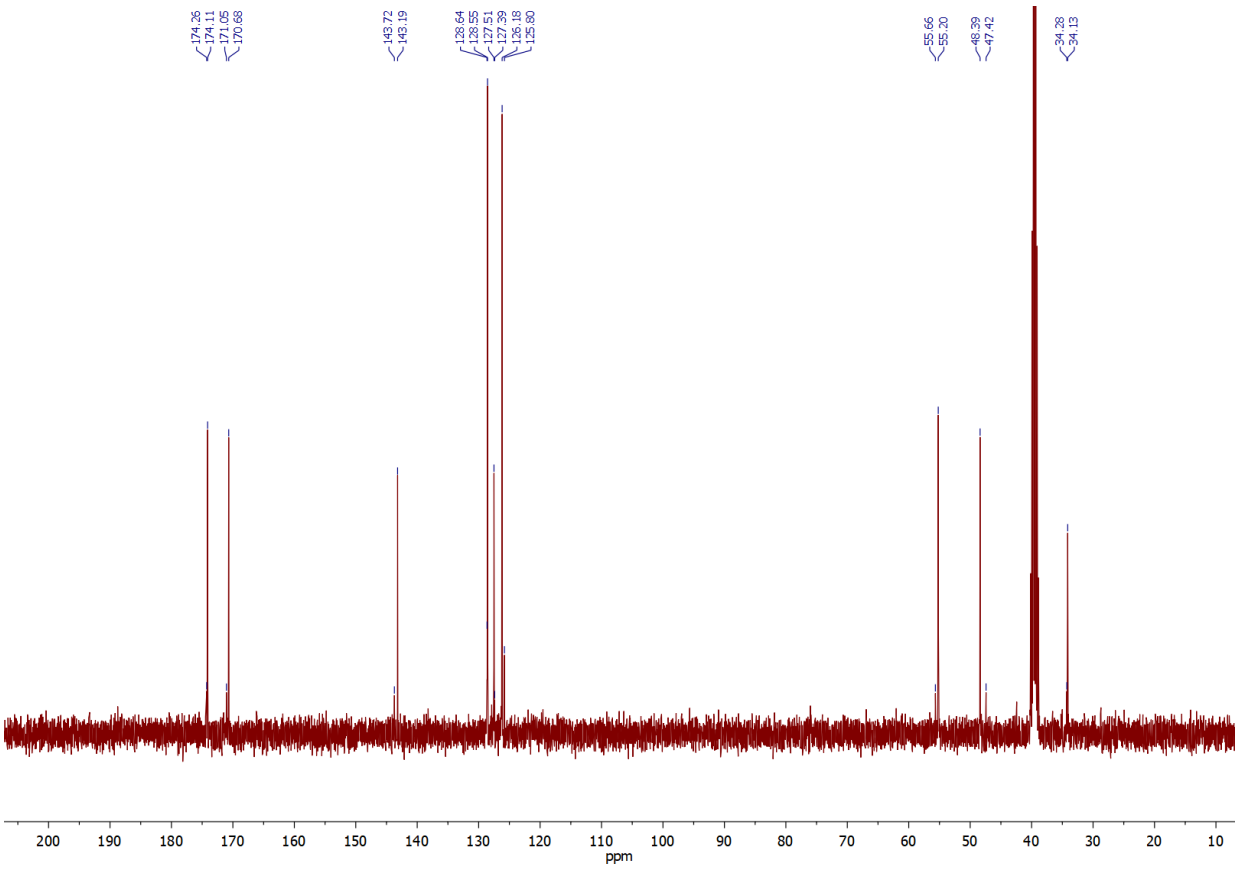
NOESY (CD_3OD) of **2a**



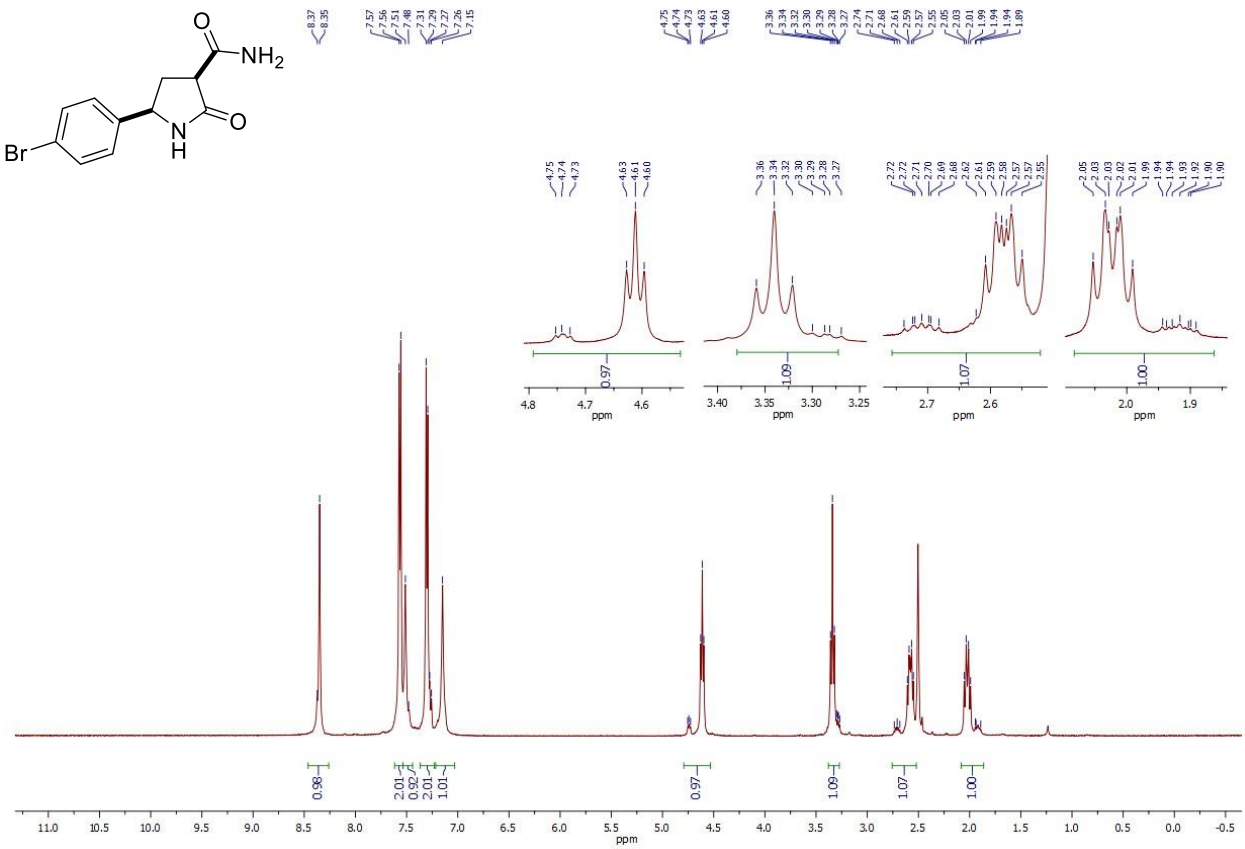
^{1}H NMR (DMSO-d$_6$, 400 MHz) of **2b** (*dr* 90:10)



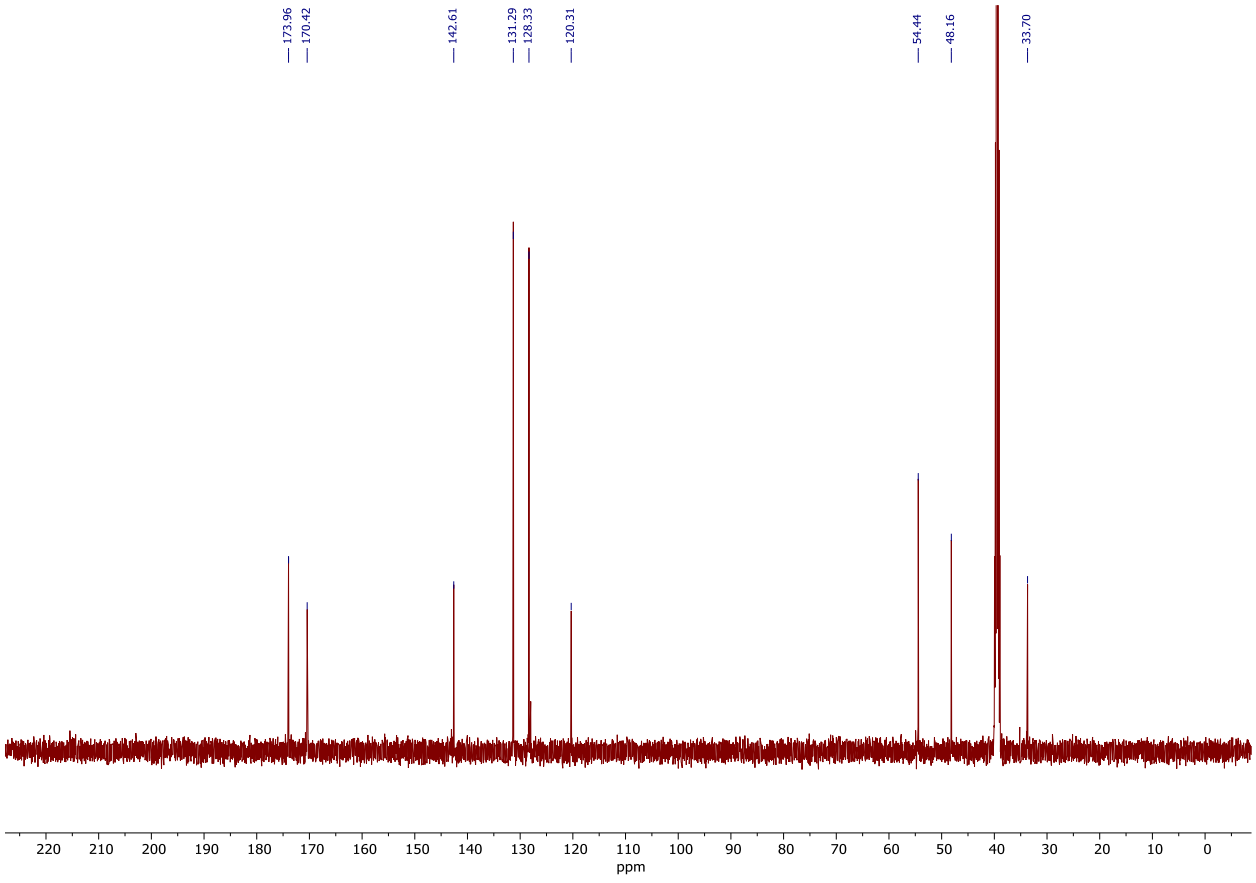
^{13}C NMR (DMSO-d$_6$, 100 MHz) of **2b** (*dr* 90:10)



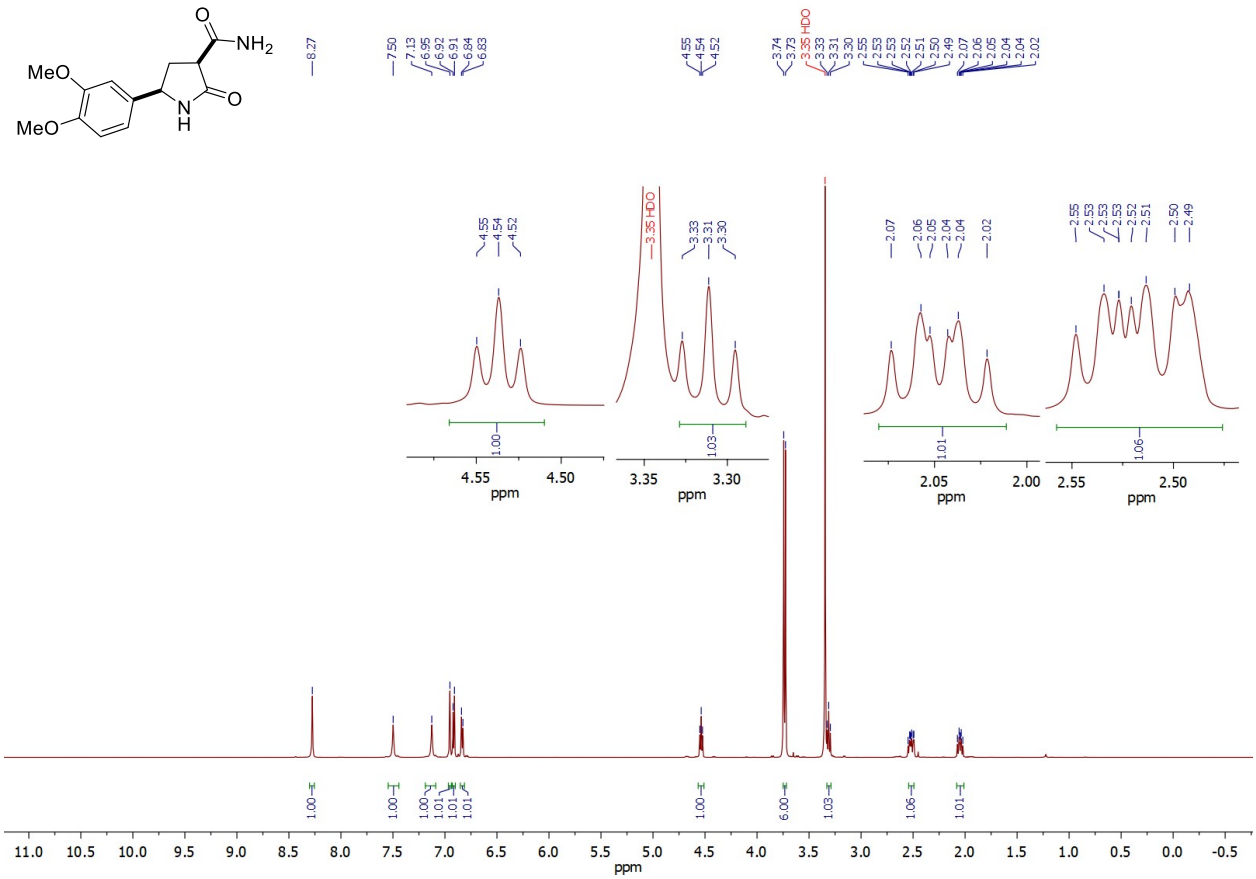
^{1}H NMR (DMSO-d$_6$, 500 MHz) of **2c** (*dr* 90:10)



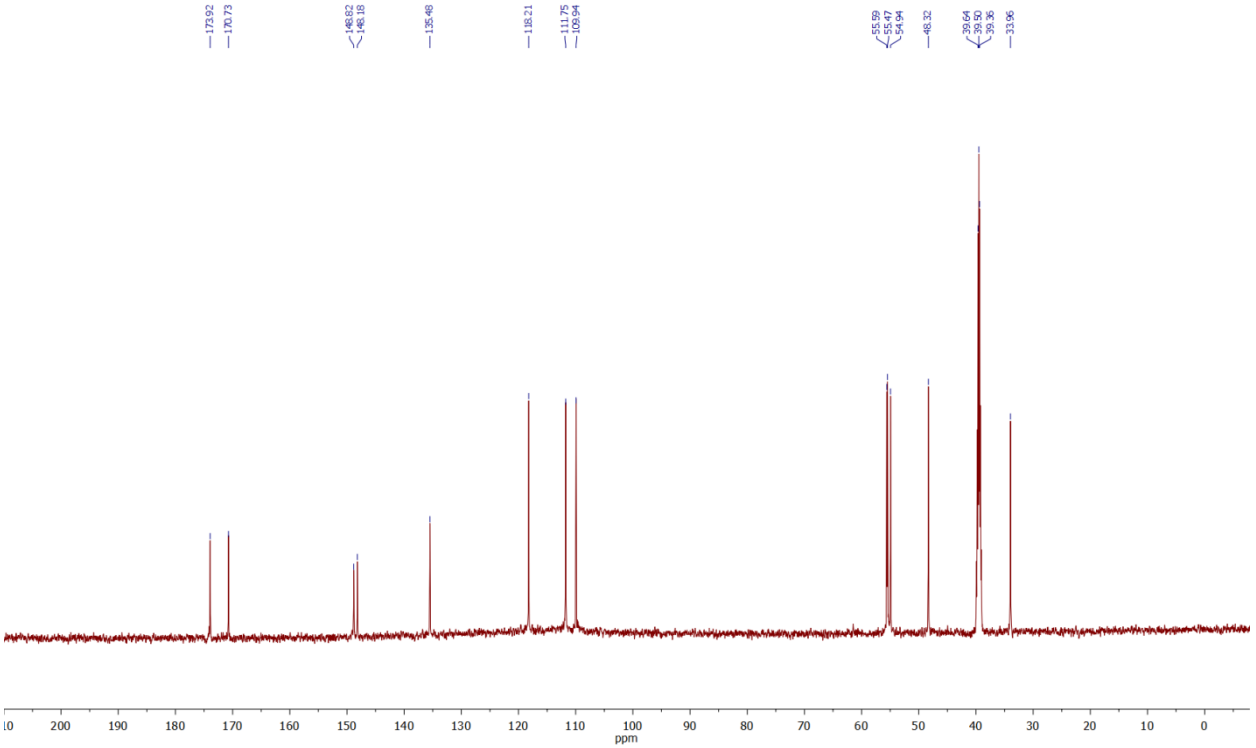
^{13}C NMR (DMSO d$_6$, 125 MHz) of **2c** (*dr* 90:10)



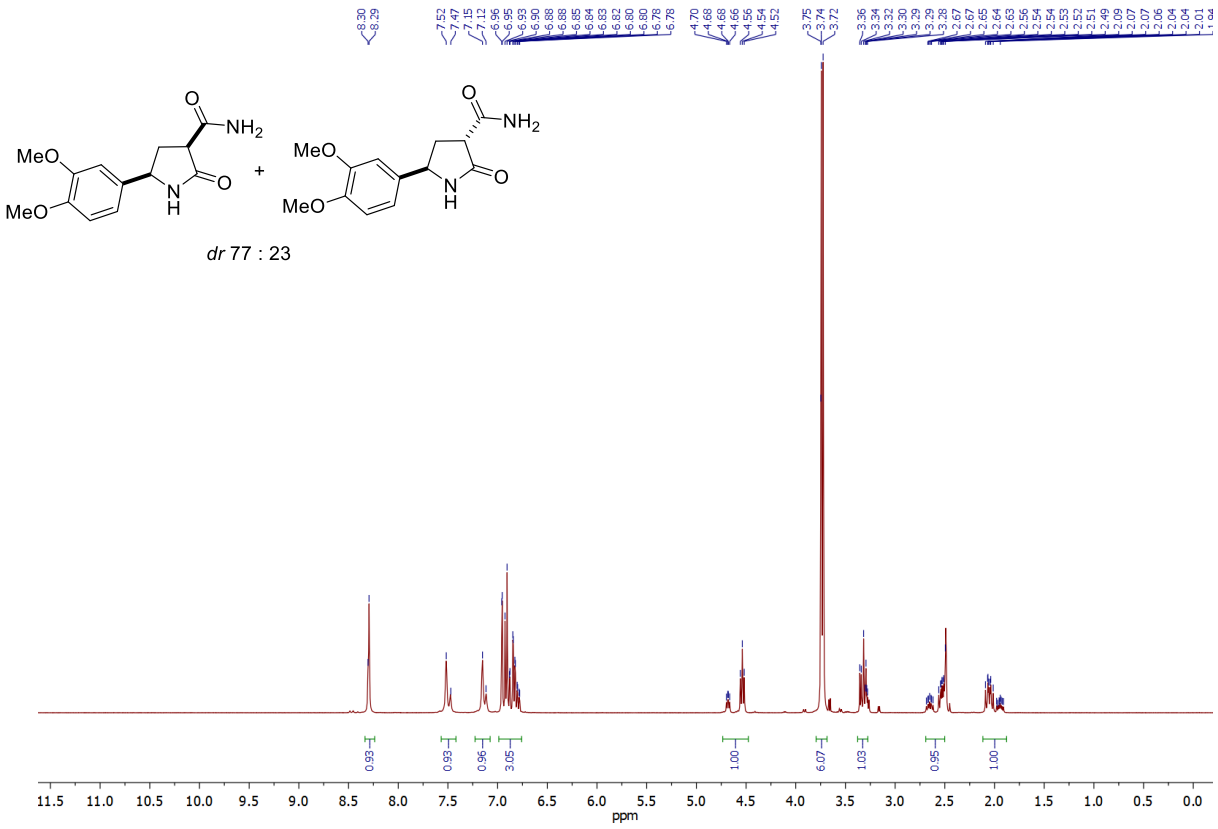
^{1}H NMR (DMSO-d_6, 600 MHz) of **2d**, freshly prepared solution



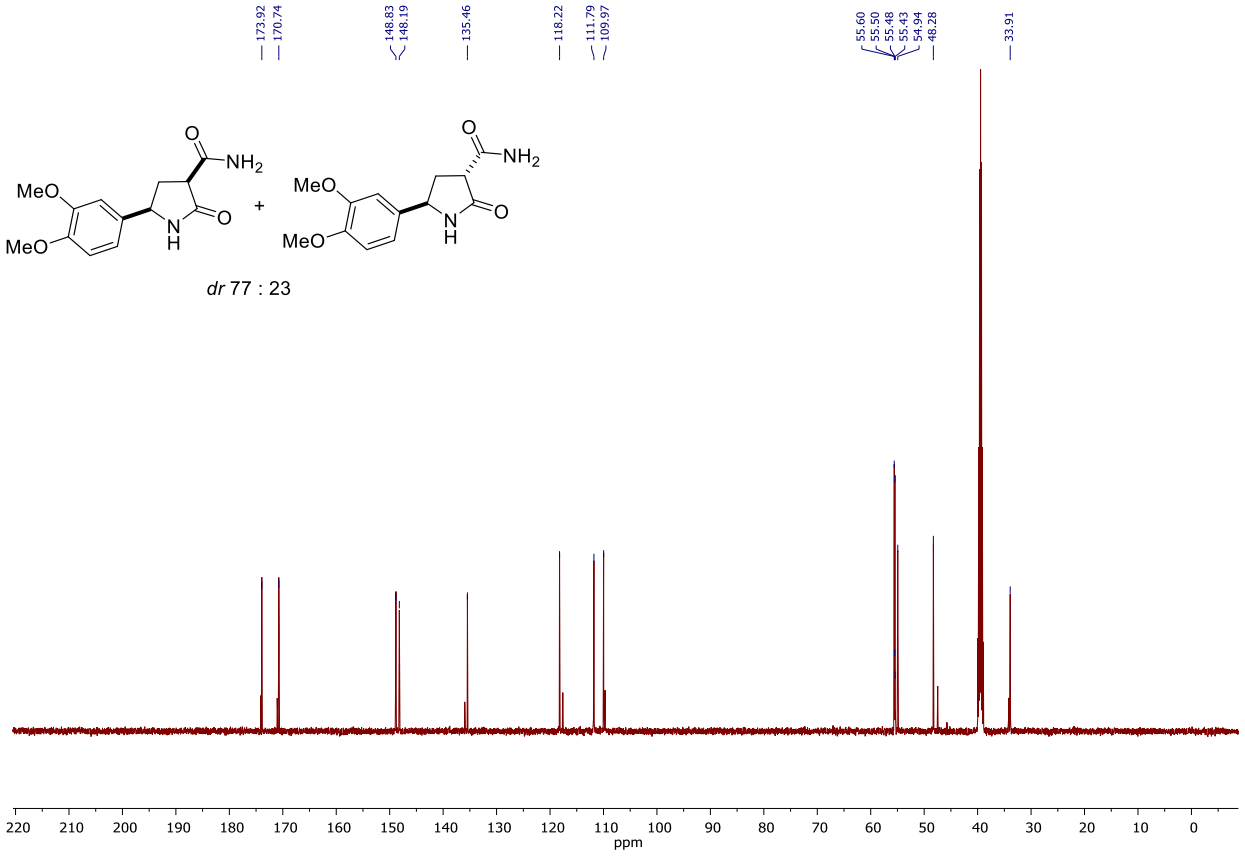
^{13}C NMR (DMSO-d_6, 150 MHz) of **2d**, freshly prepared solution



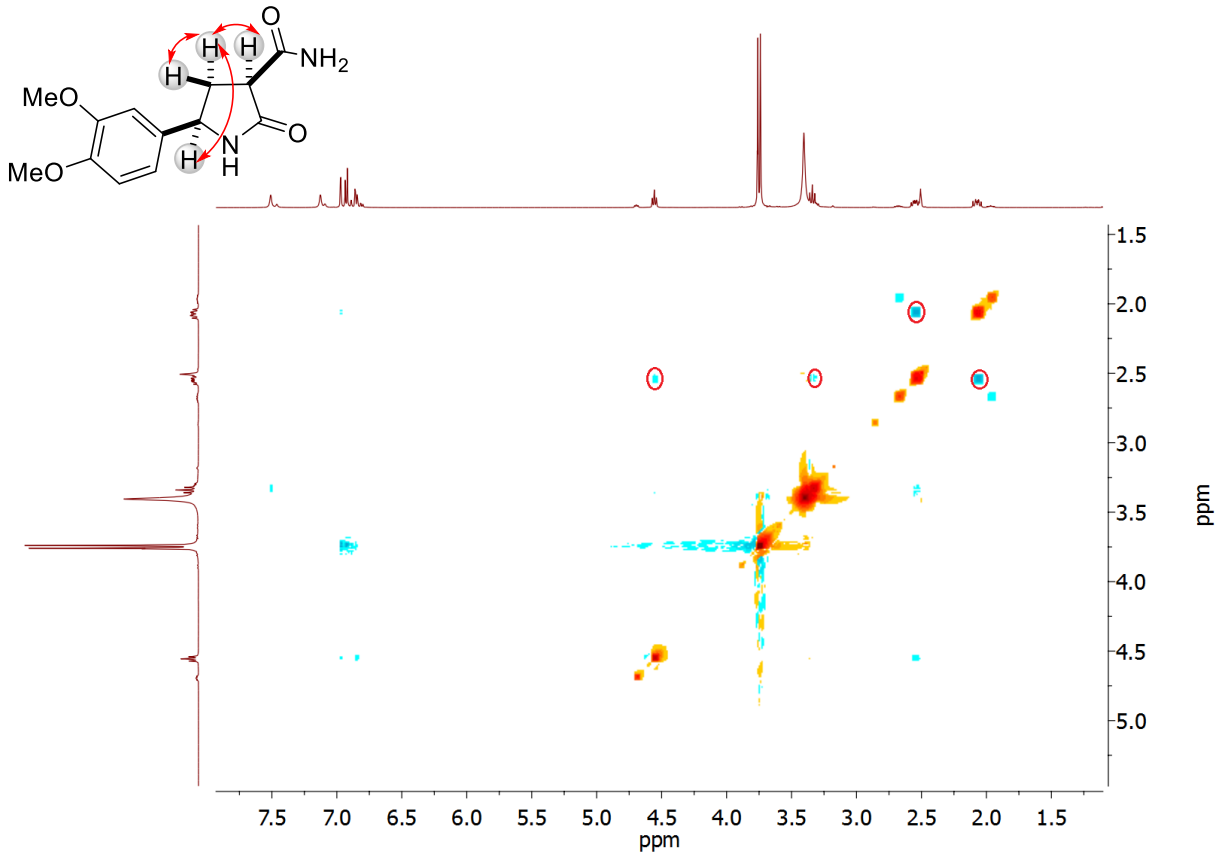
^{1}H NMR (DMSO-d$_6$, 400 MHz) of **2d**, after 24 h (*dr* 77:23)



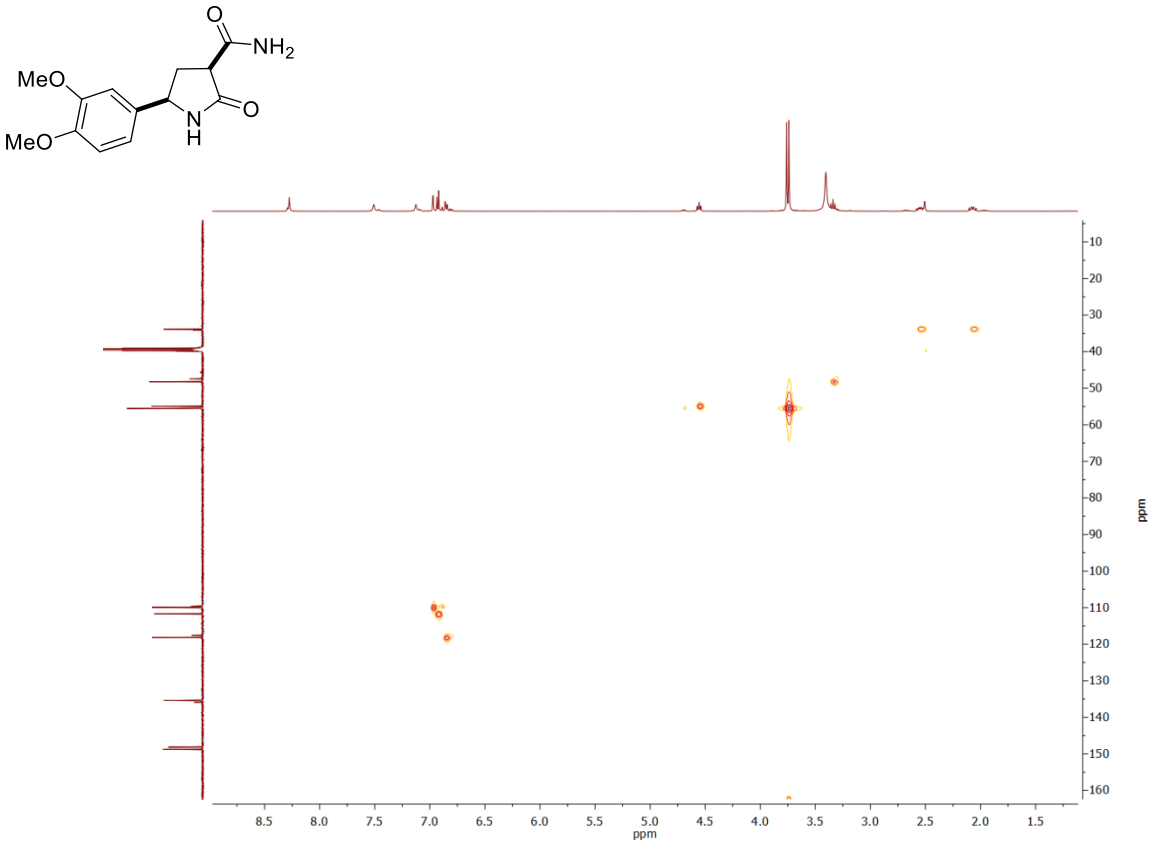
^{13}C NMR (DMSO-d$_6$, 100 MHz) of **2d**, after 24 h (*dr* 77:23)



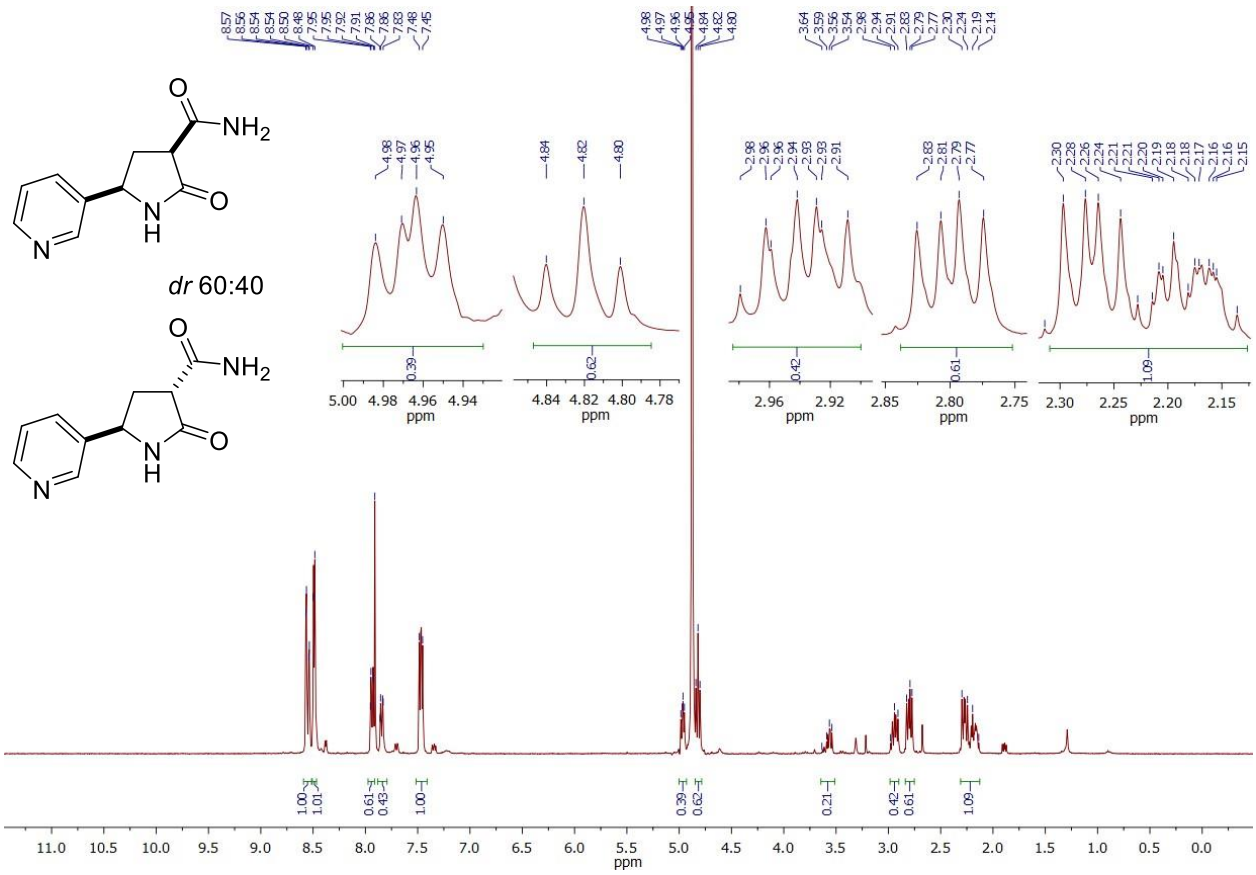
NOESY (DMSO-d_6) of **2d**



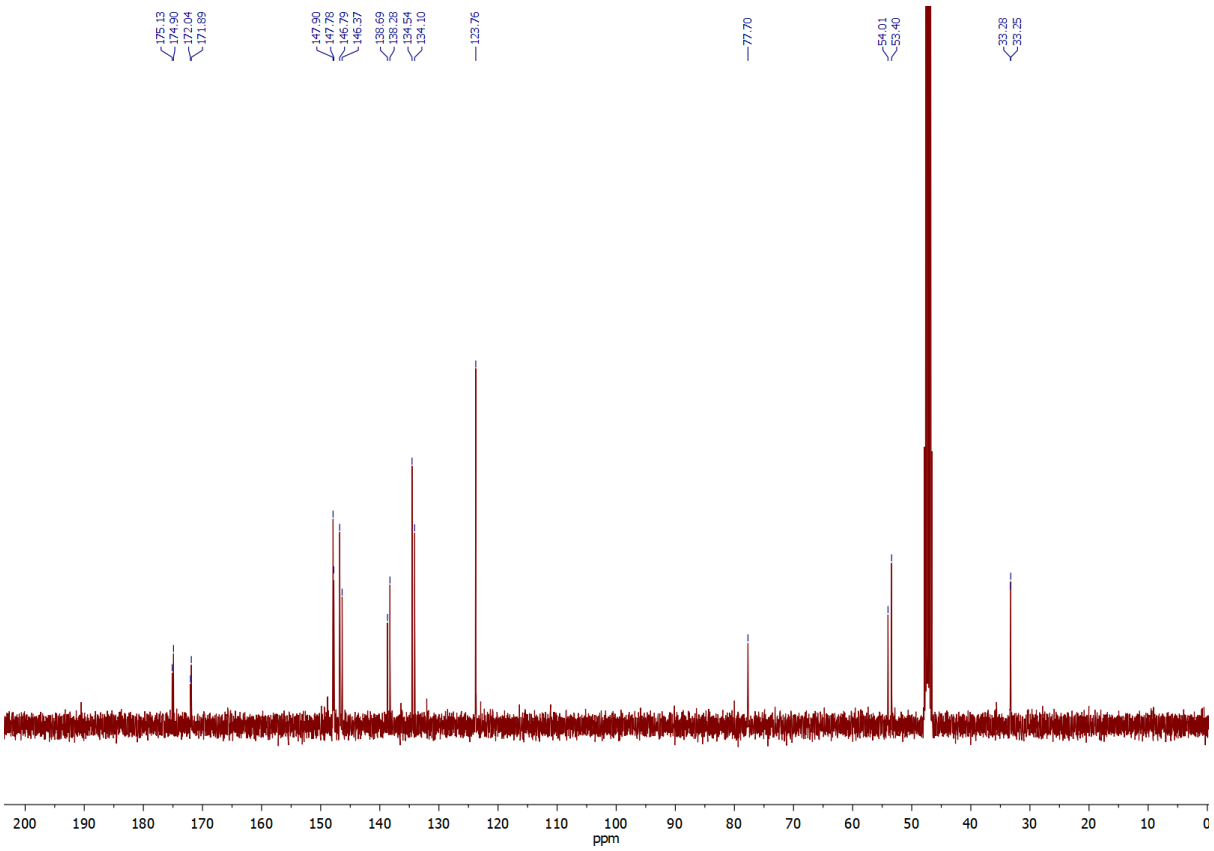
HSQC ^{1}H-^{13}C (DMSO-d_6) of **2d**



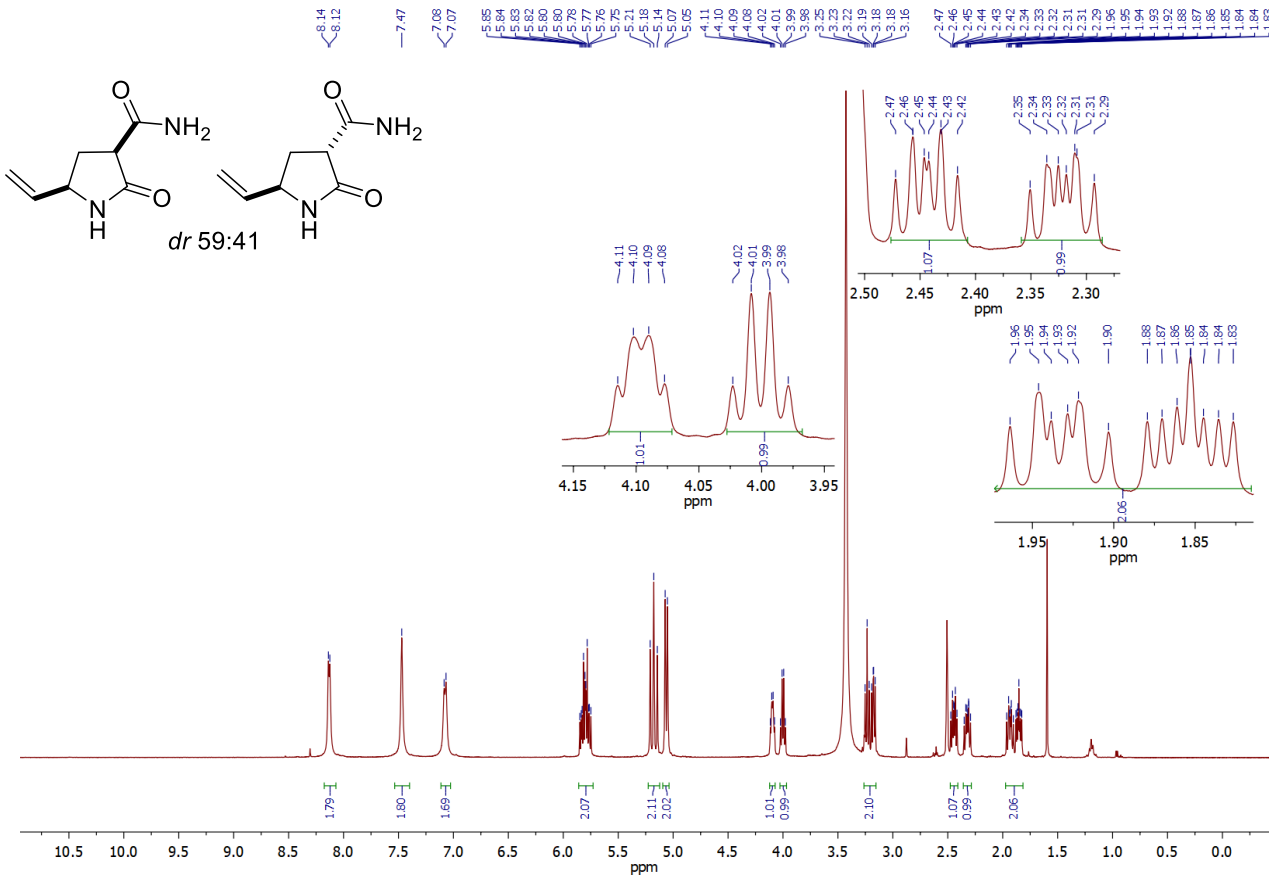
^{1}H NMR (CD_3OD, 400 MHz) of **2e** (*dr* 60:40)



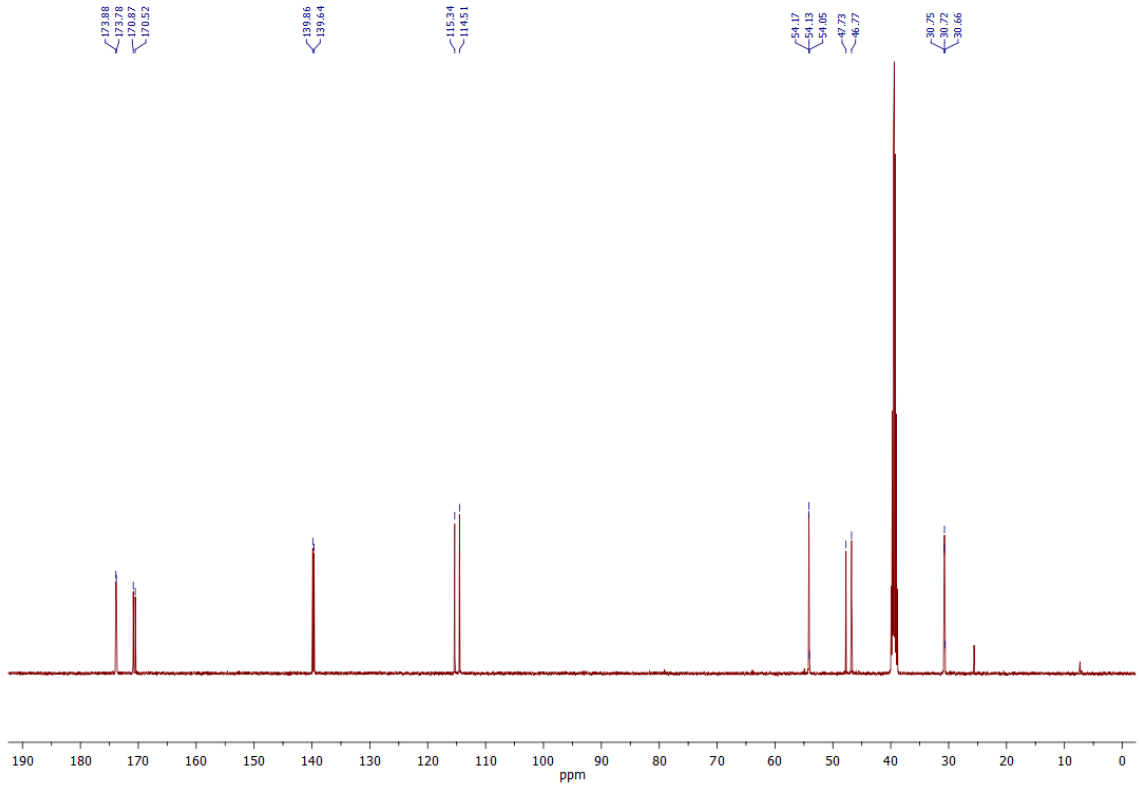
^{13}C NMR (CD_3OD, 100 MHz) of **2e** (*dr* 60:40)



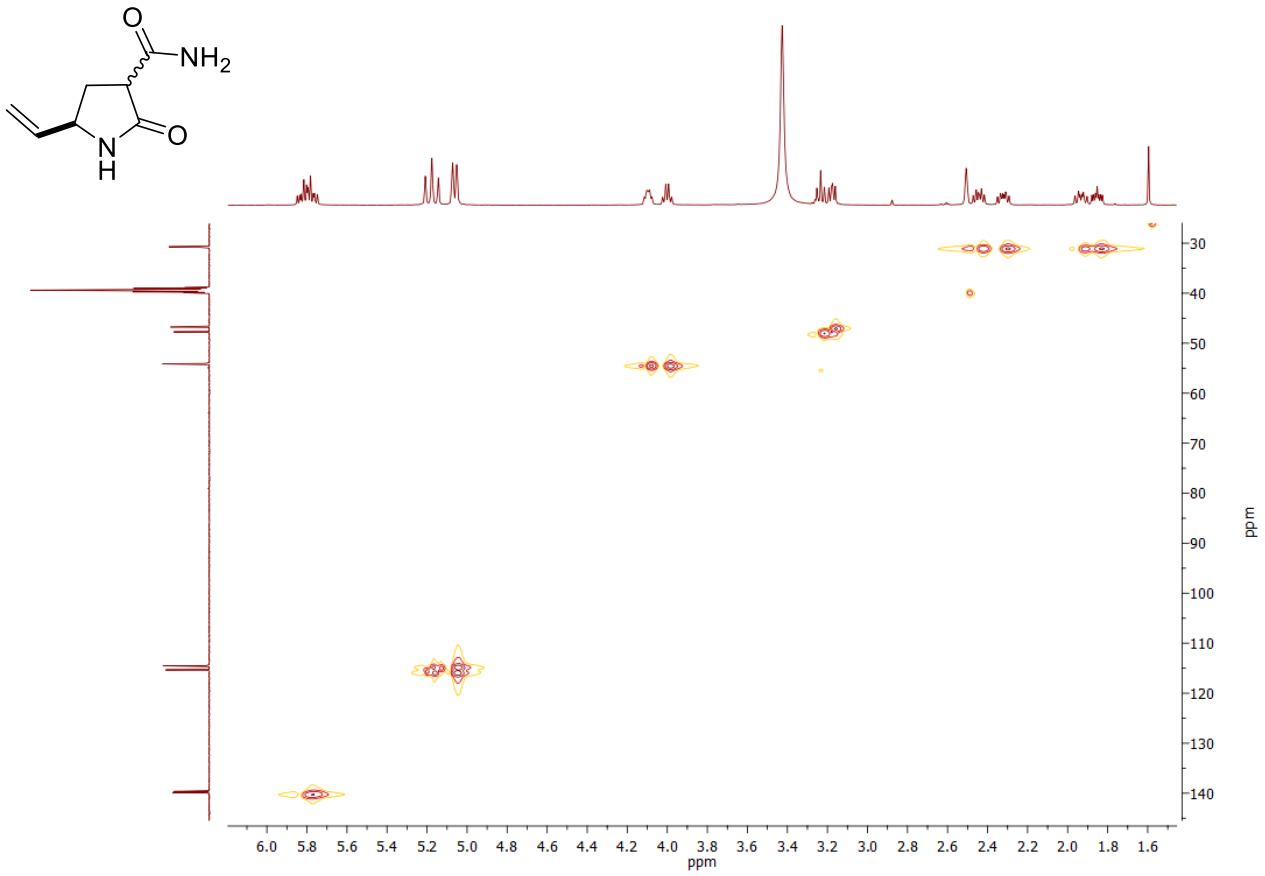
^{1}H NMR (DMSO-d$_6$, 500 MHz) of **2f**



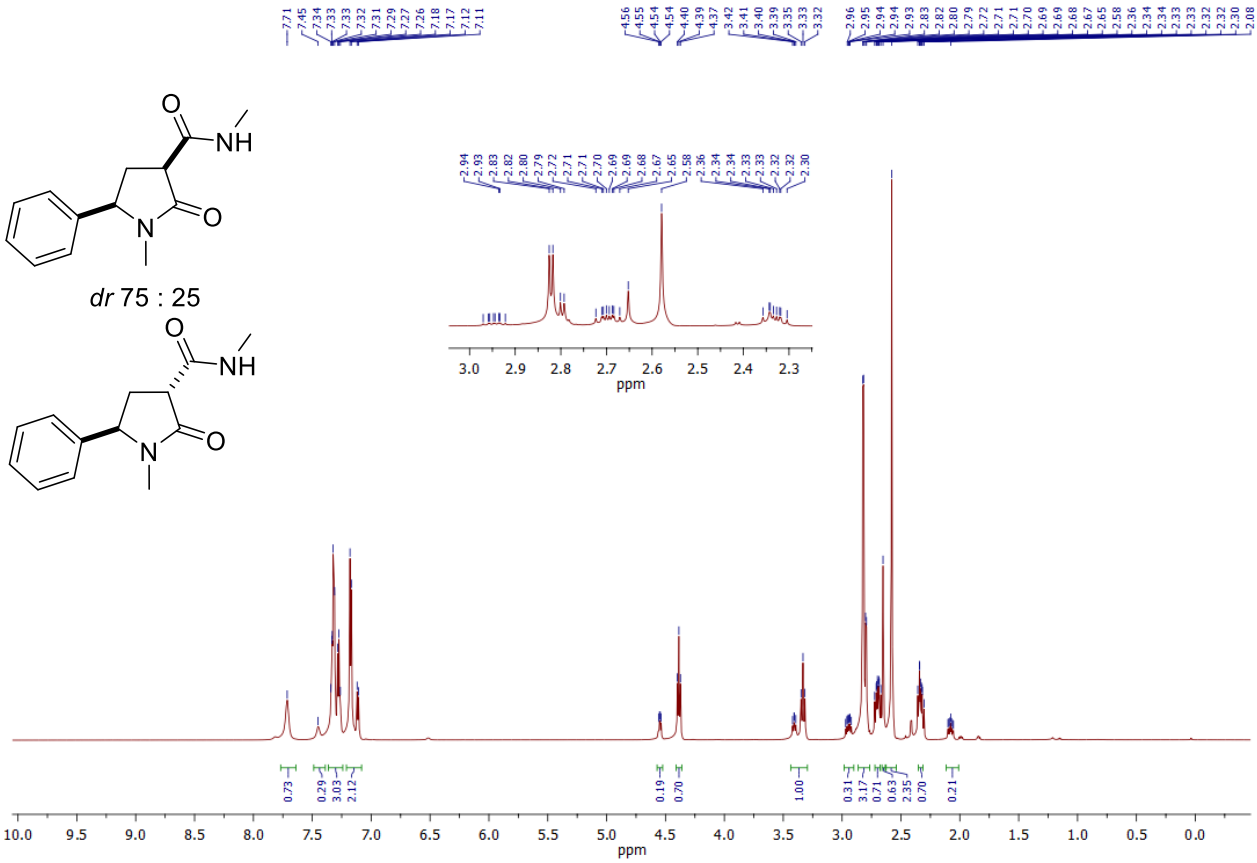
^{13}C NMR (DMSO-d$_6$, 125 MHz) (*dr* 59:41)



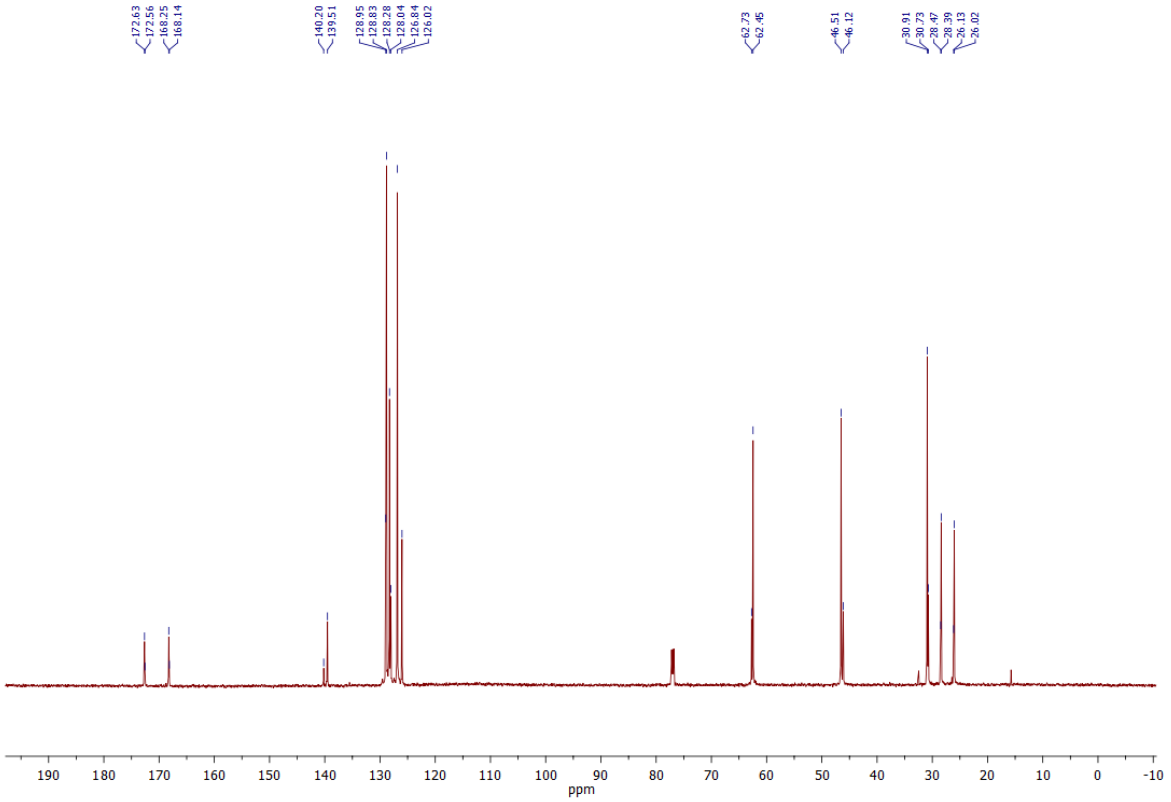
HSQC ^{1}H-^{13}C (DMSO-d_6) of **2f**



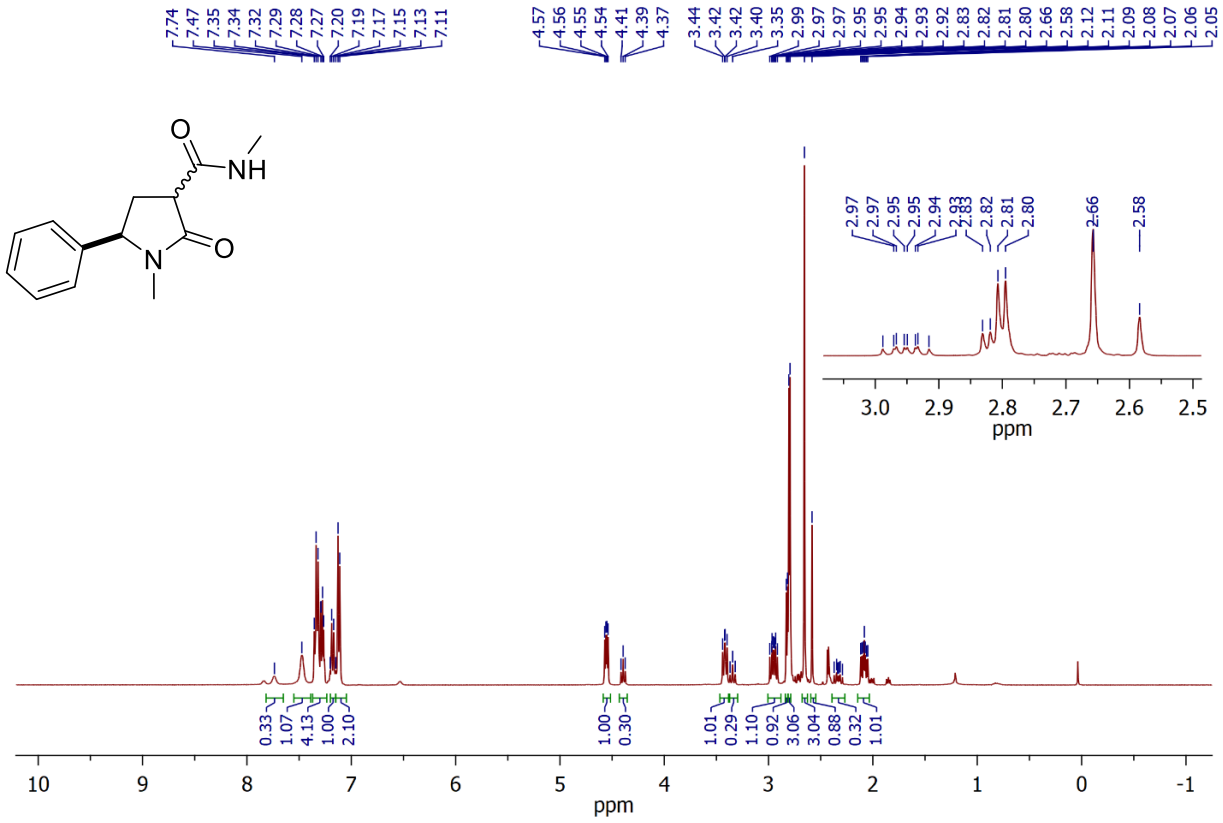
^{1}H NMR ($CDCl_3$, 600 MHz) of **2g** (isomer **A** prevails, *dr* 75:25)



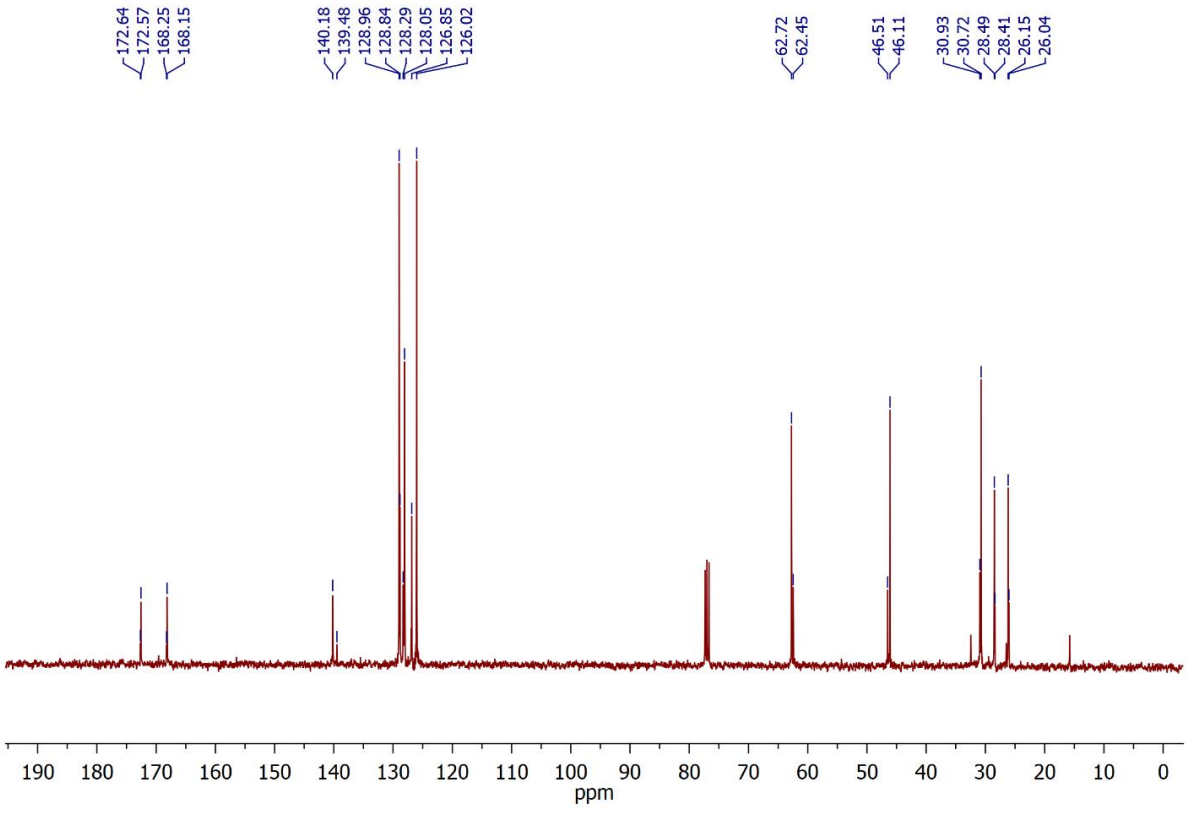
^{13}C NMR ($CDCl_3$, 150 MHz) of **2g** (isomer **A** prevails, *dr* 75:25)



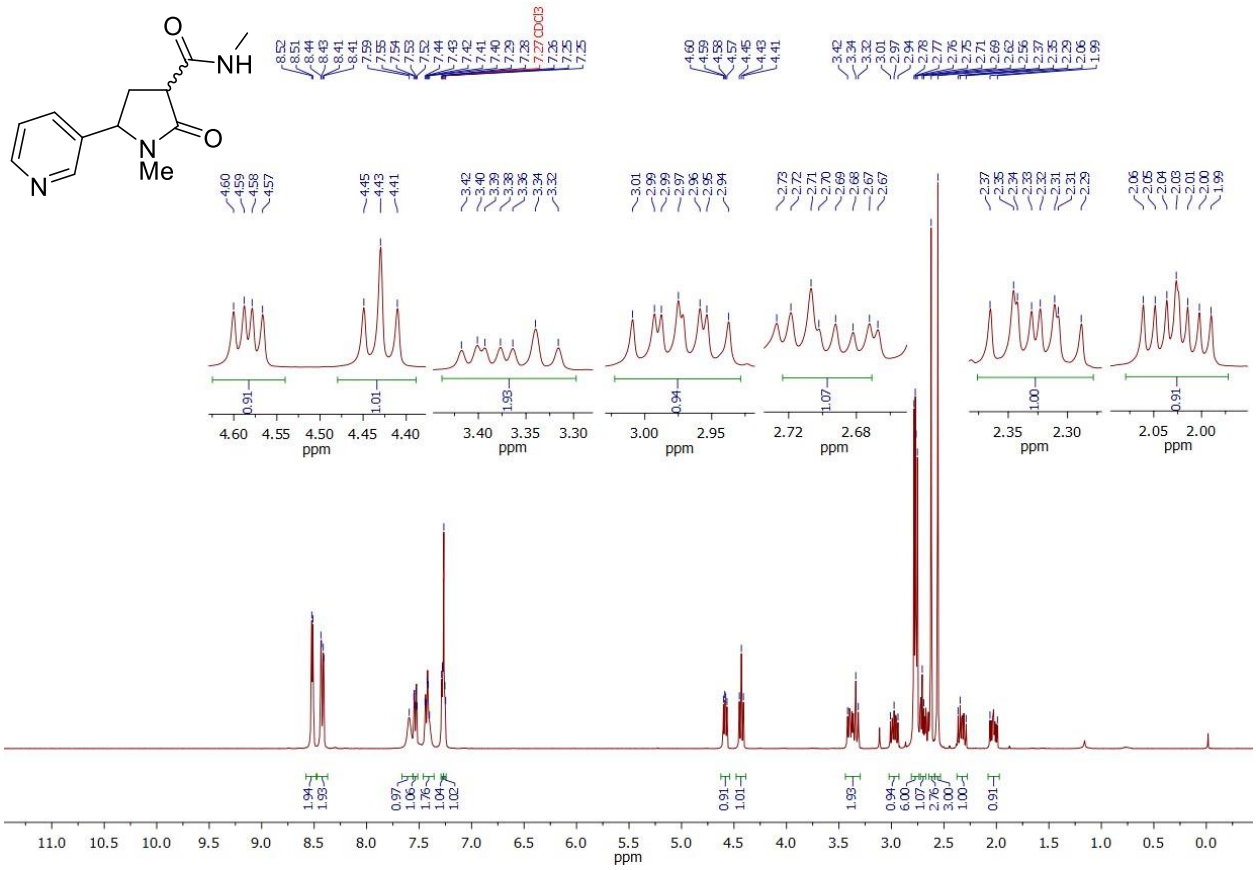
^{1}H NMR ($CDCl_3$, 600 MHz) of **2g** (isomer **B** prevails, *dr* 23:77, purity ≥ 93%)



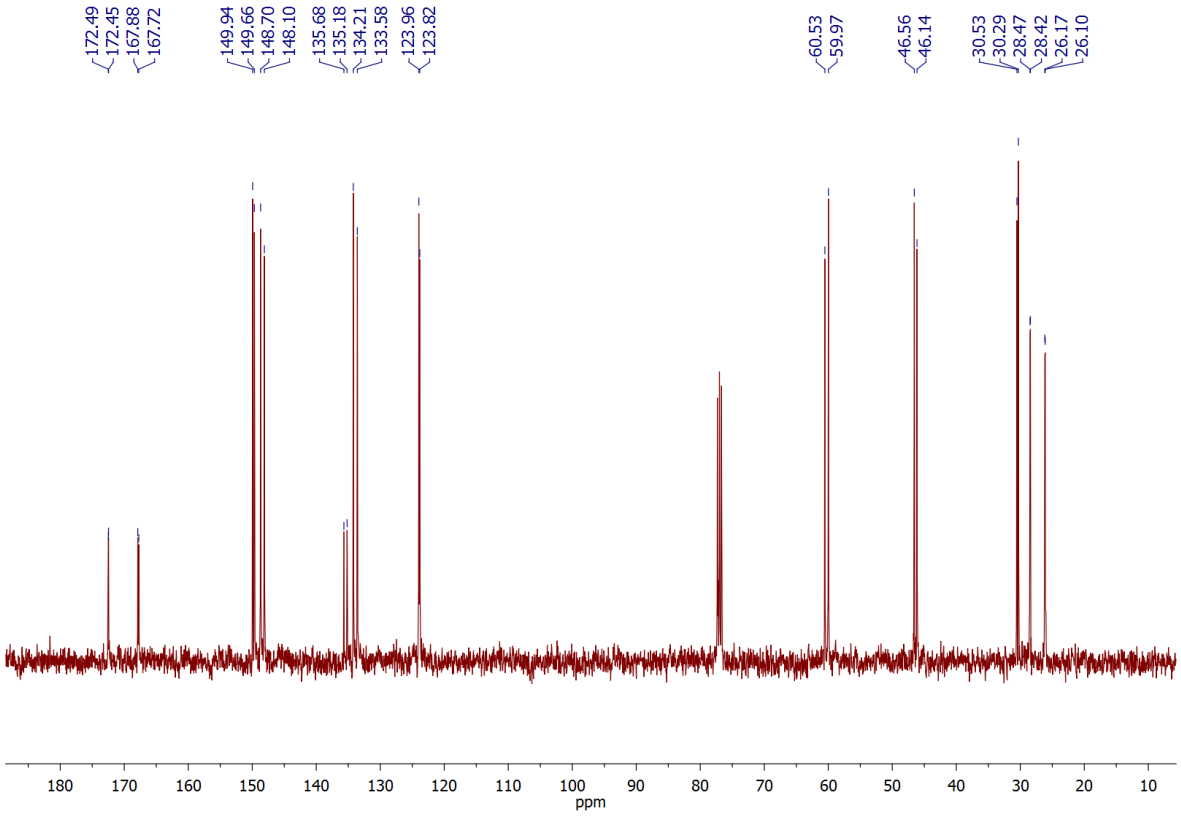
^{13}C NMR ($CDCl_3$, 150 MHz) of **2g** (isomer **B** prevails, *dr* 23:77, purity ≥ 93%)



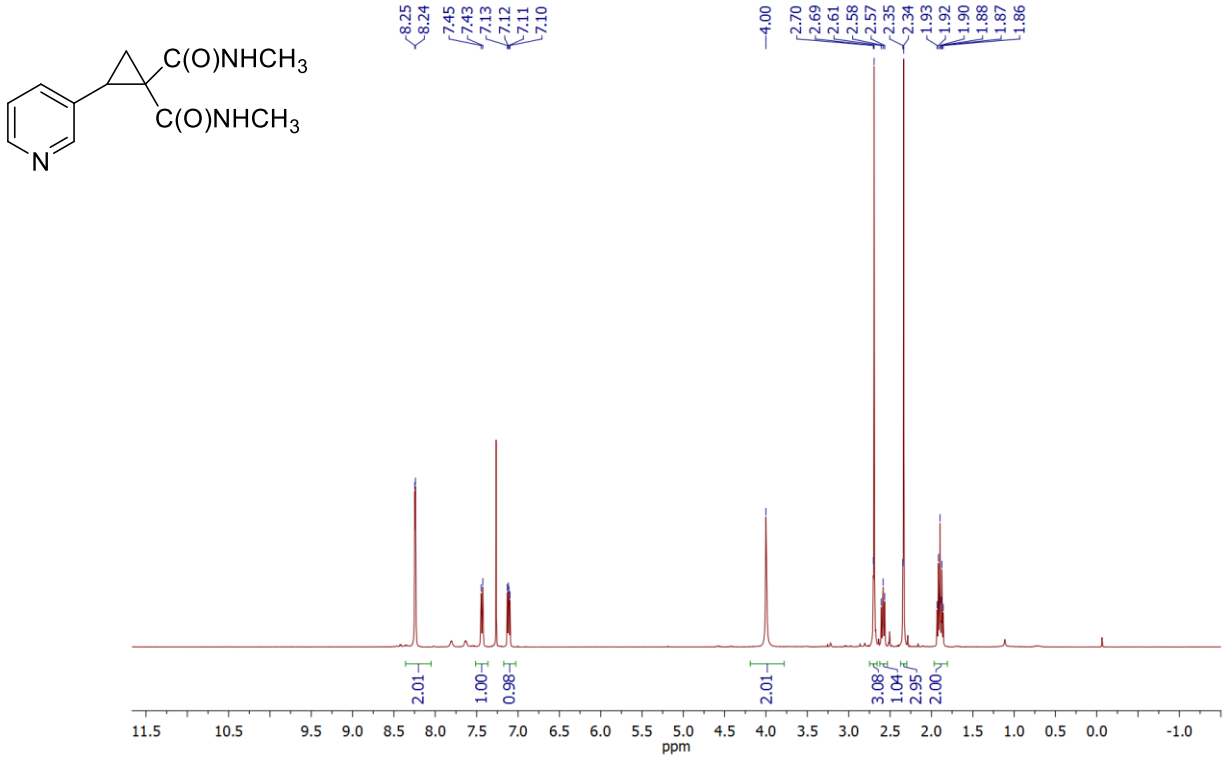
^{1}H NMR ($CDCl_3$, 400 MHz) of **2h** (*dr* 53:47)



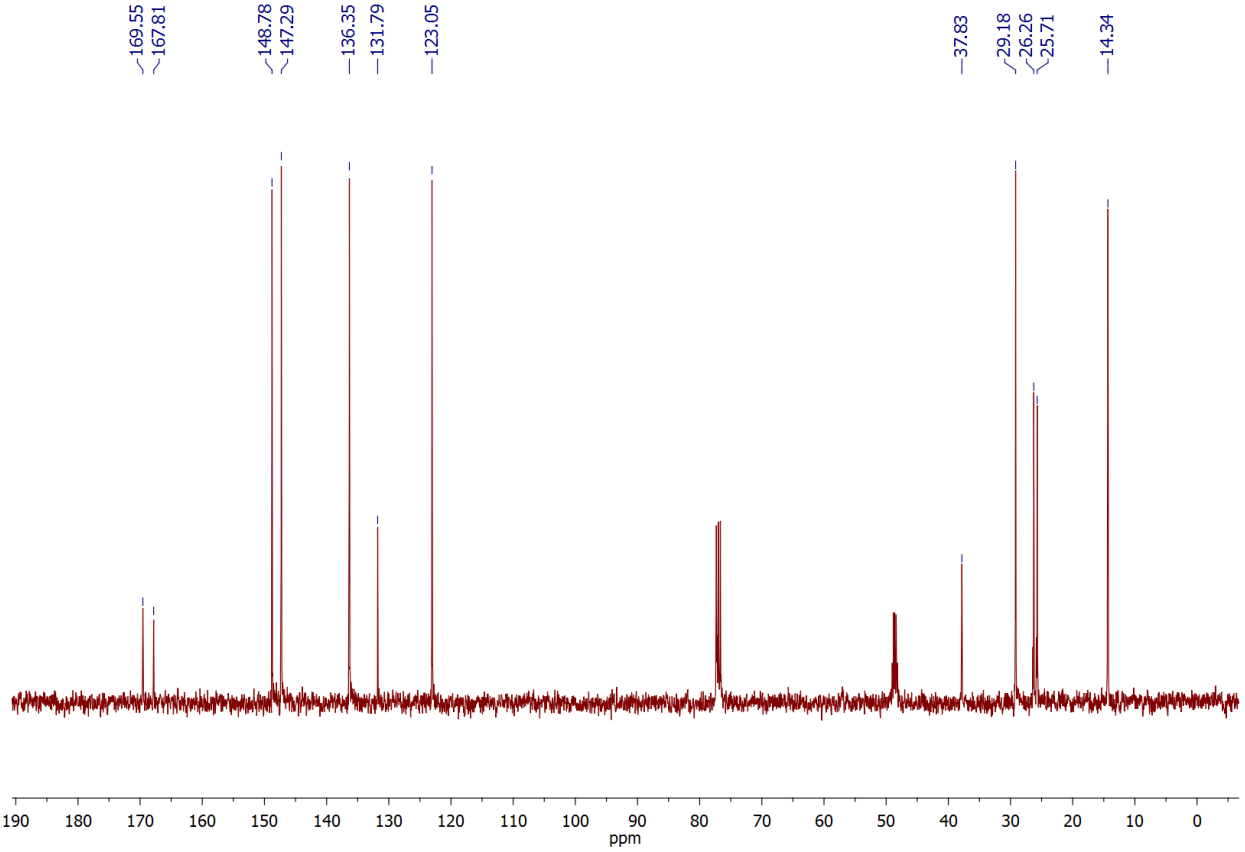
^{13}C NMR ($CDCl_3$, 100 MHz) of **2h** (*dr* 53:47)



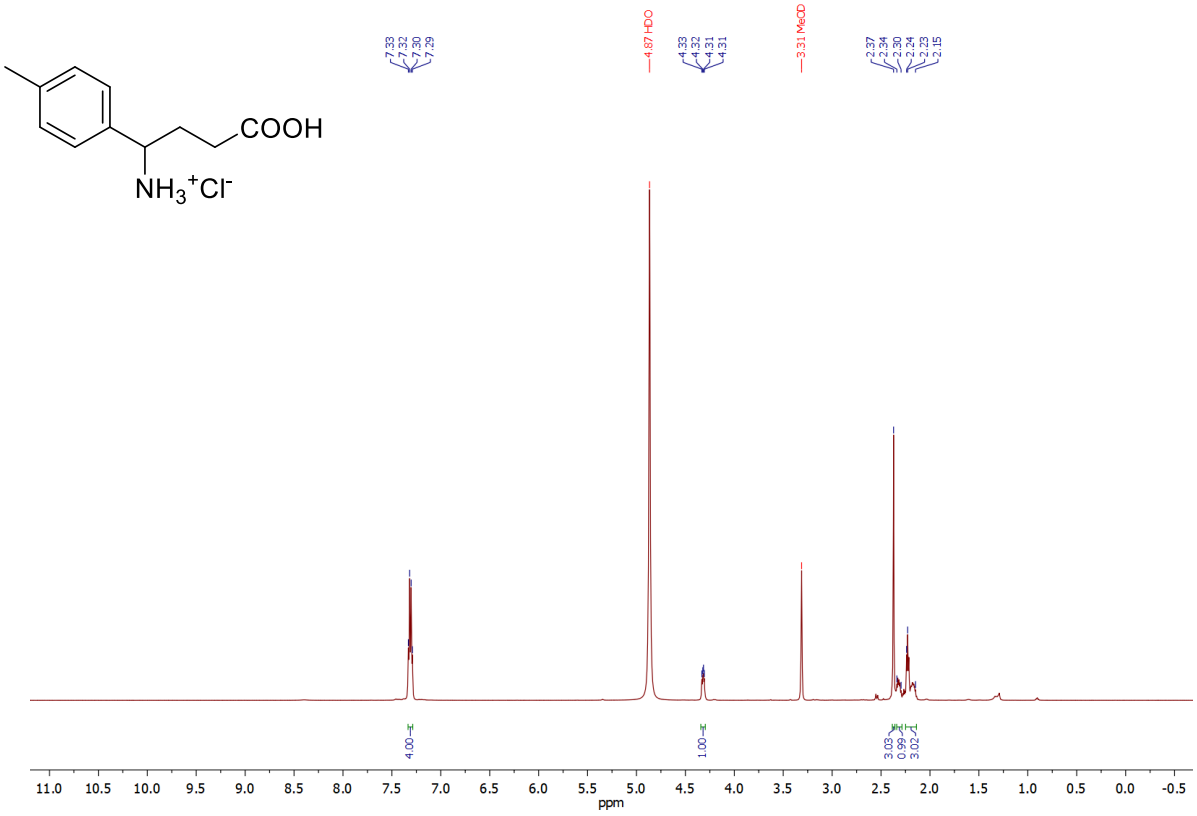
^{1}H NMR ($CDCl_3$ + CD_3OD, 400 MHz) of **4a**



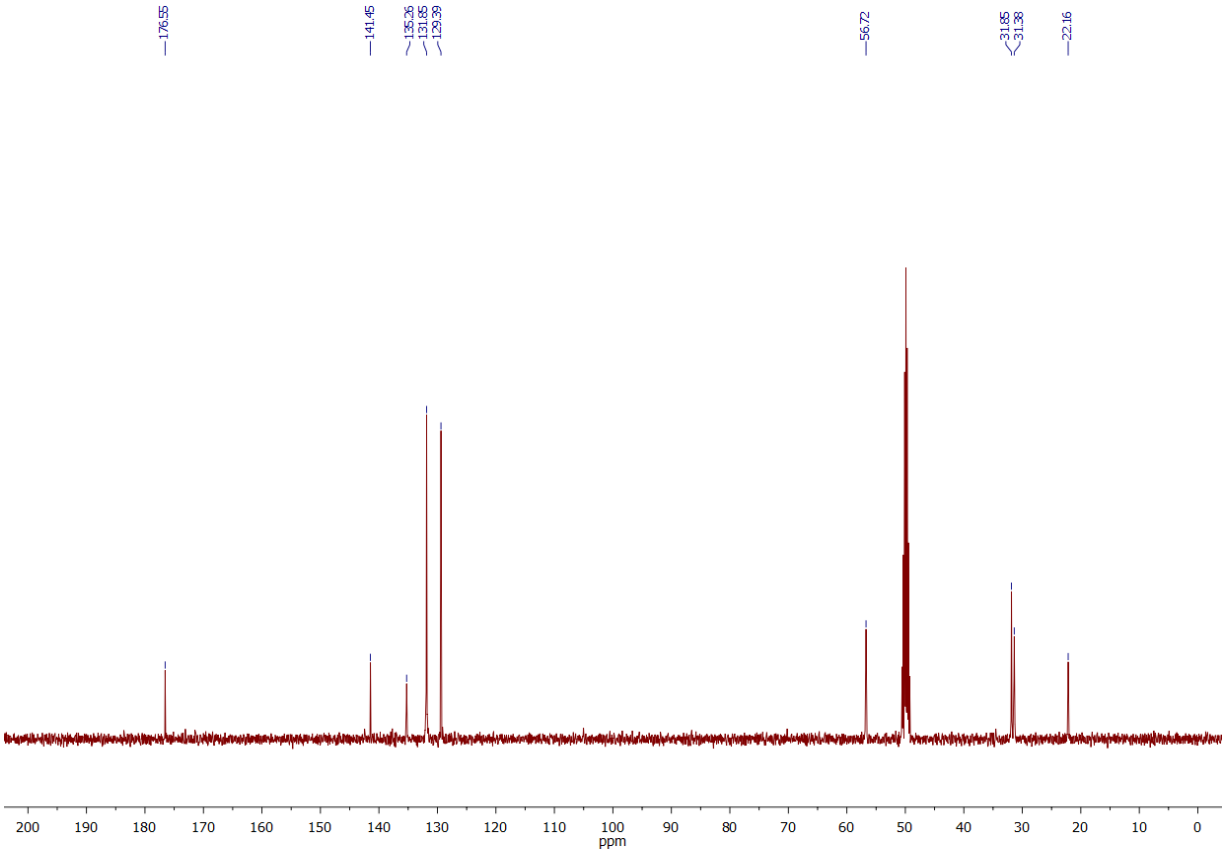
^{13}C NMR ($CDCl_3$ + CD_3OD, 100 MHz) of **4a**



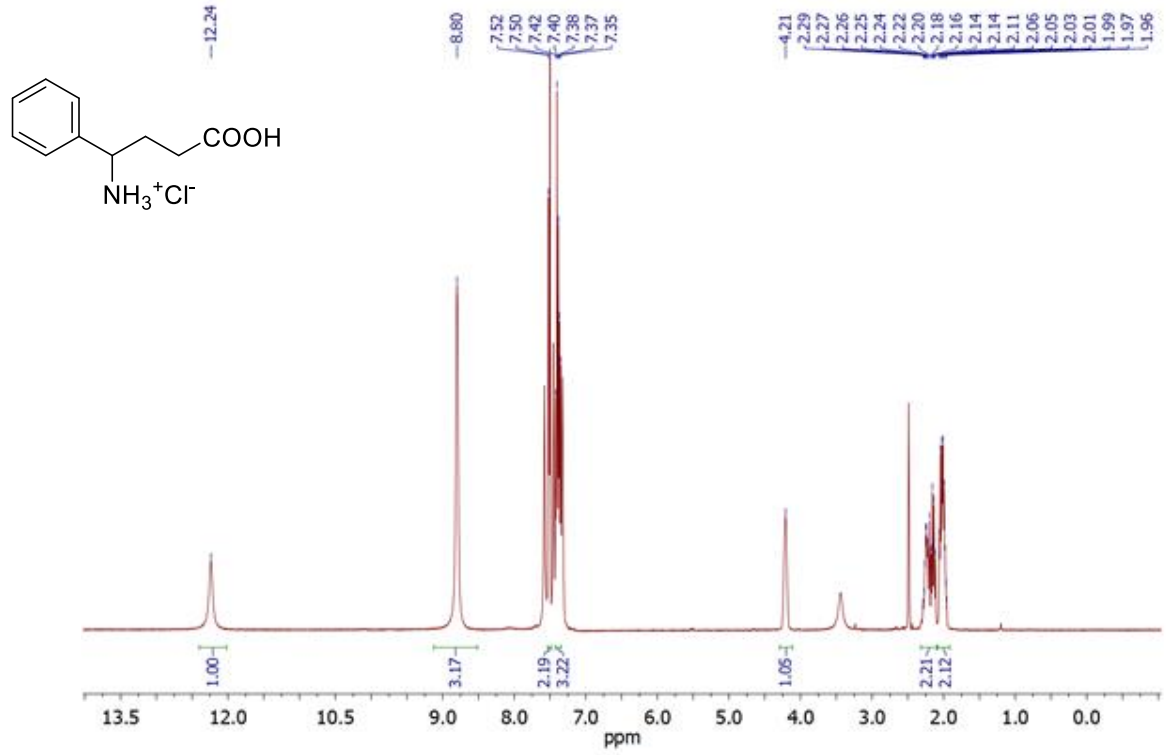
^{1}H NMR (CD_3OD, 600 MHz) of **3a·HCl**



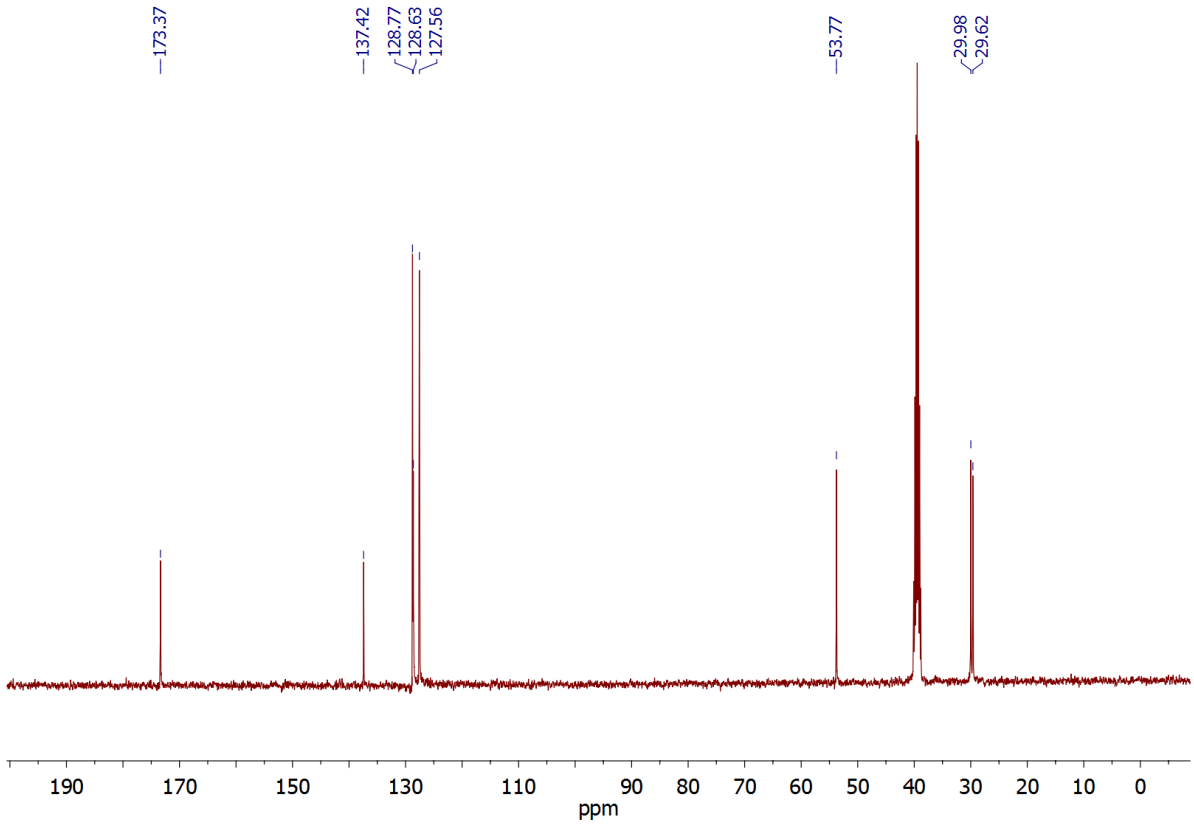
^{13}C NMR (CD_3OD, 100 MHz) of **3a·HCl**



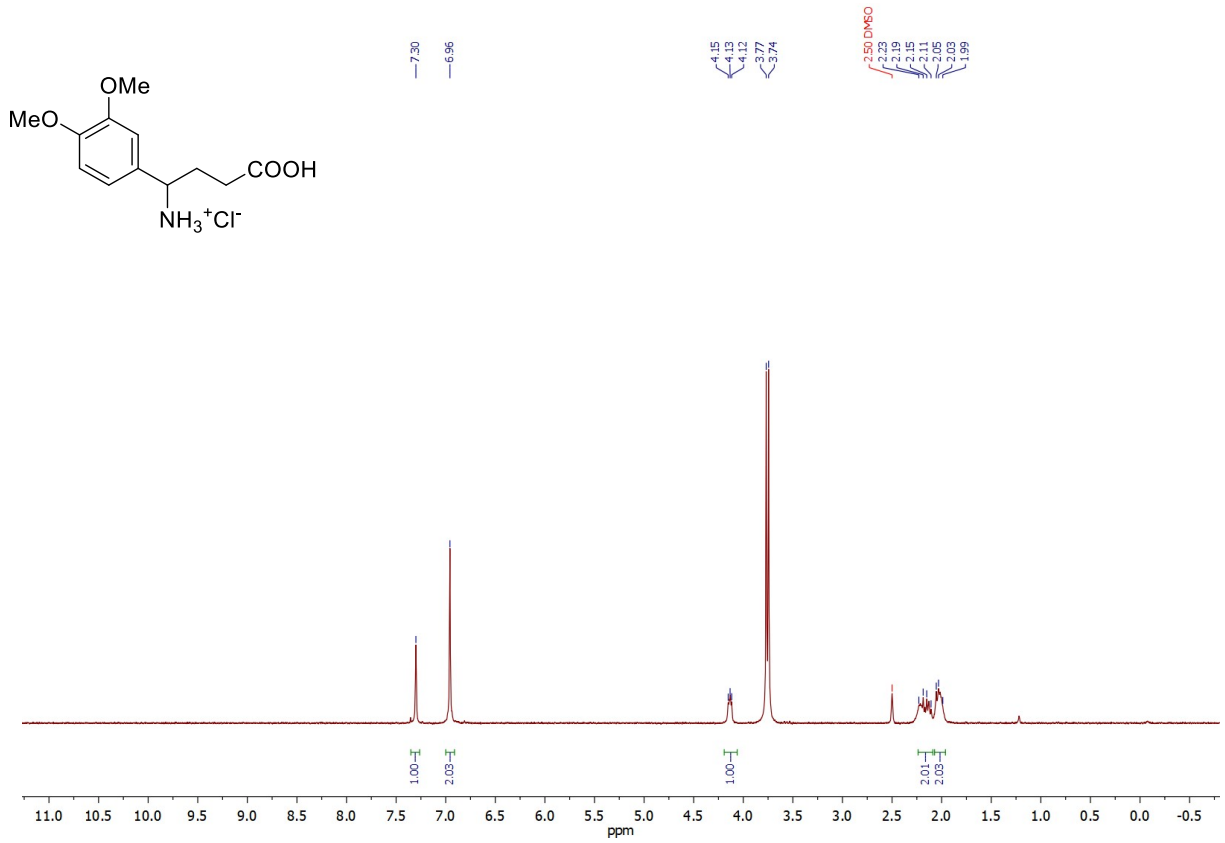
^{1}H NMR (DMSO-d_6, 400 MHz) of **3b·HCl**



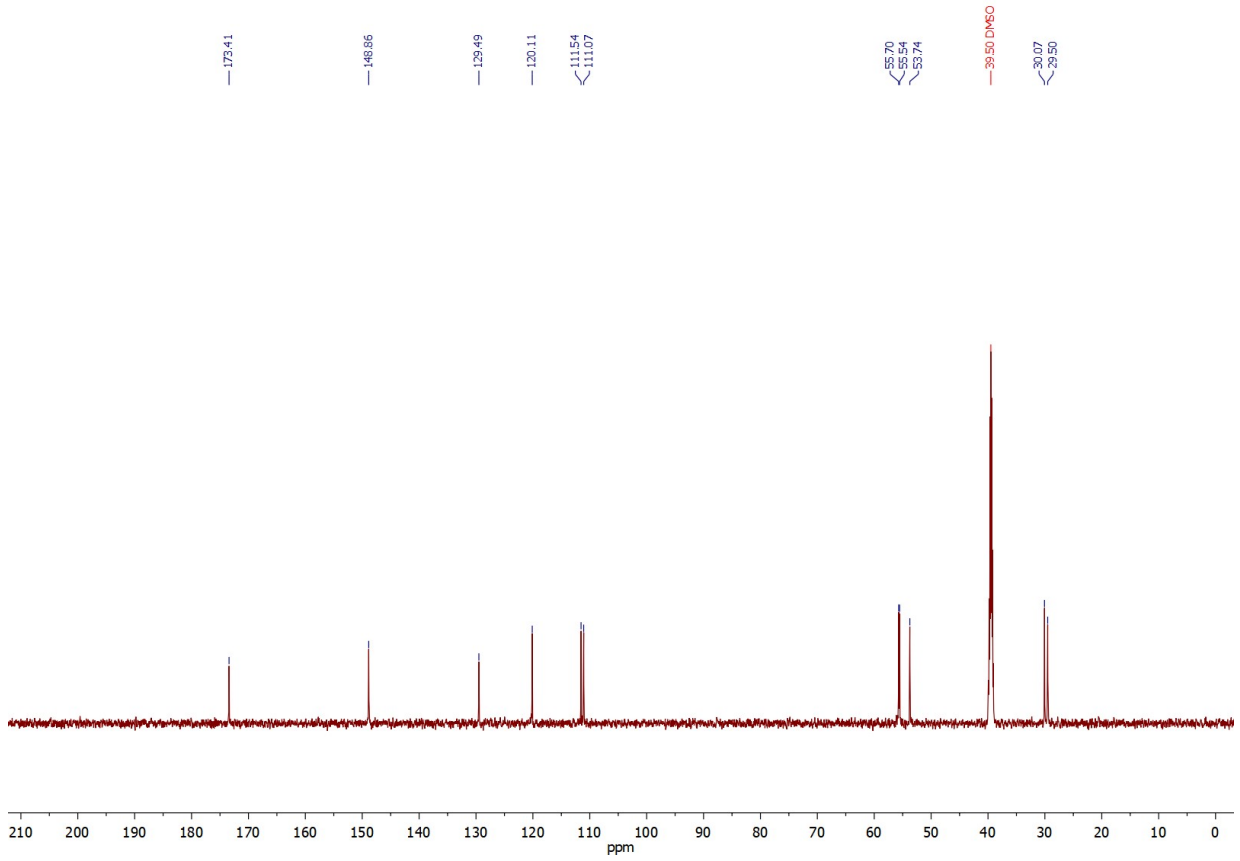
^{13}C NMR (DMSO-d_6, 100 MHz) of **3b·HCl**



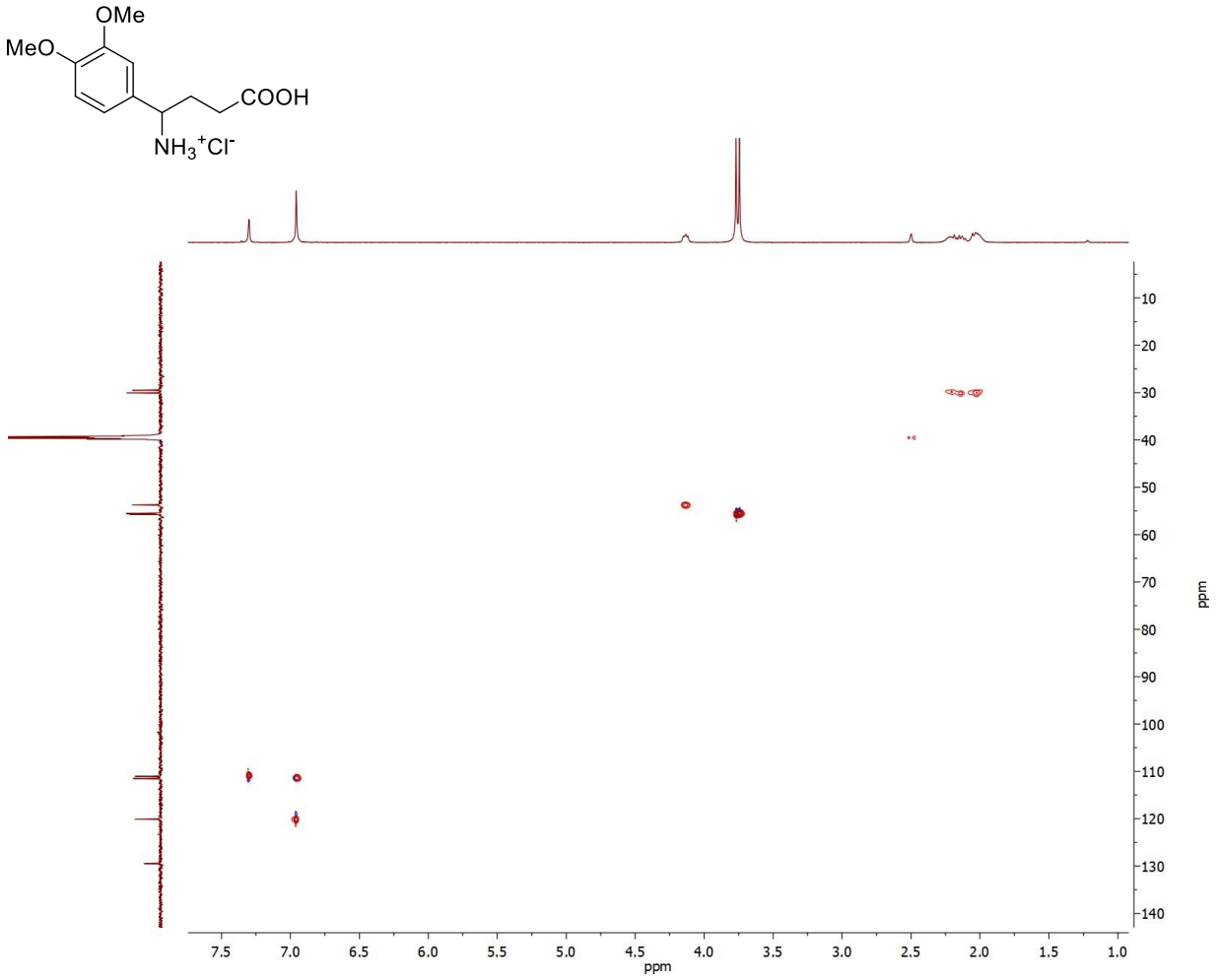
^{1}H NMR (DMSO-d_6, 400 MHz) of **3c·HCl**



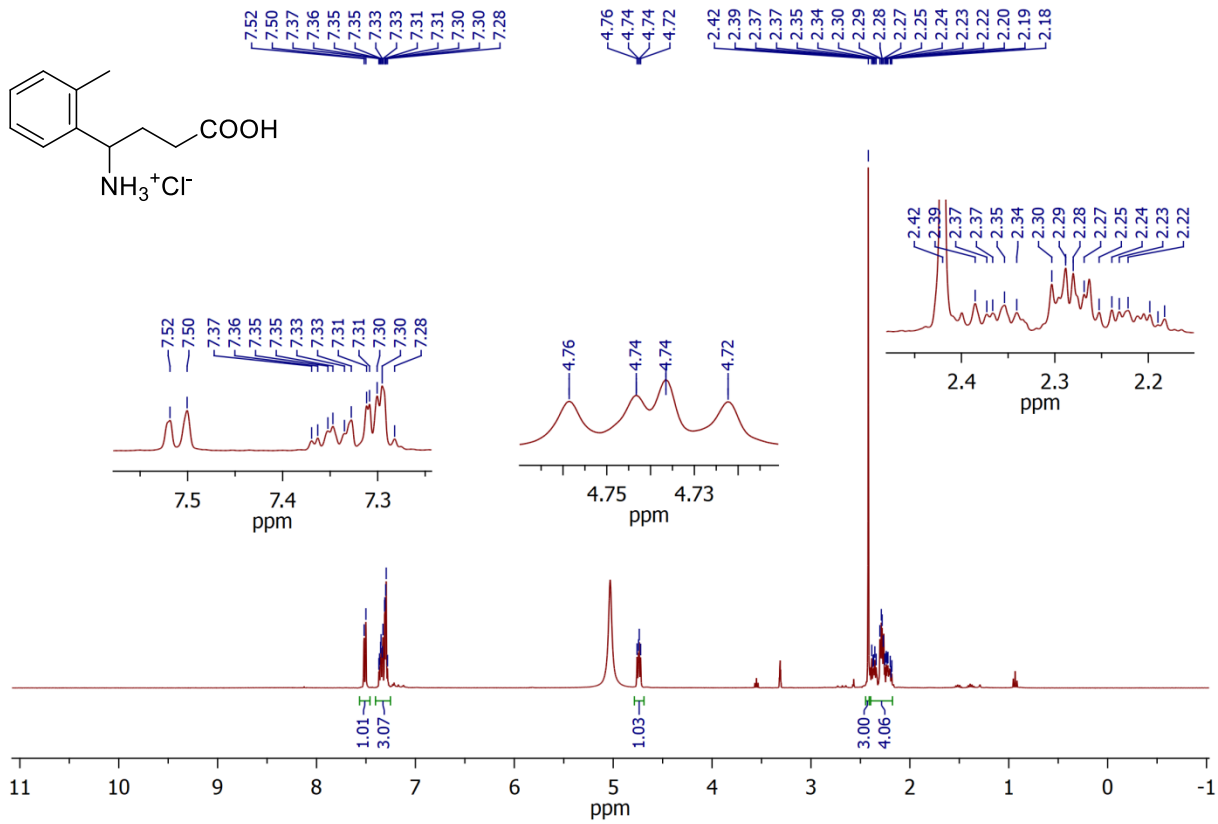
^{13}C NMR (DMSO-d_6, 150 MHz) of **3c·HCl**



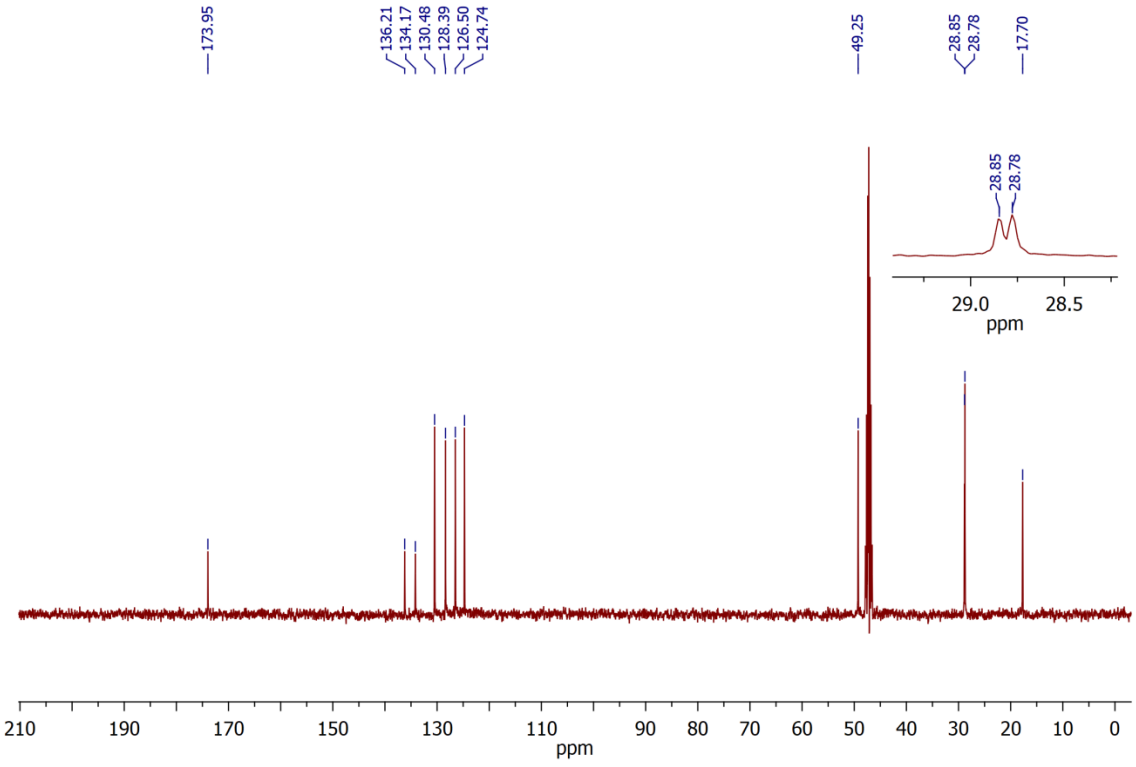
HSQC ^{1}H-^{13}C (DMSO-d_6) of **3c·HCl**



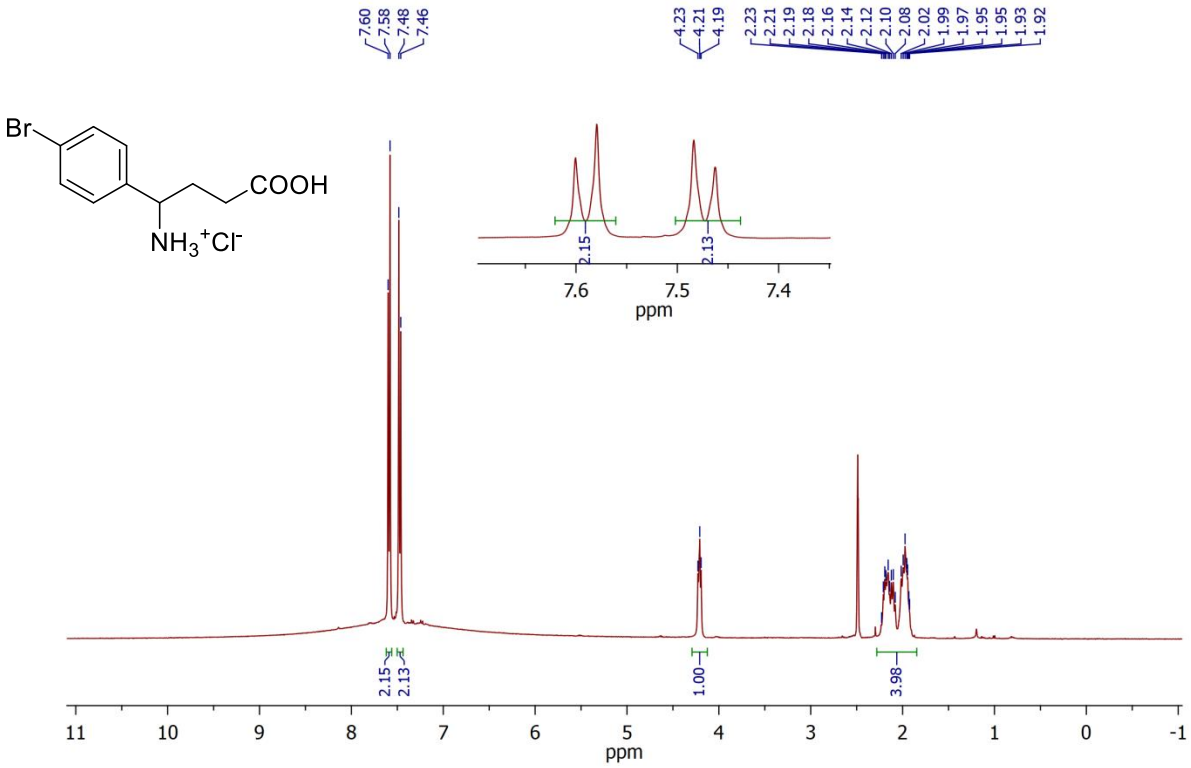
^{1}H NMR (CD_3OD, 400 MHz) of **3d·HCl**



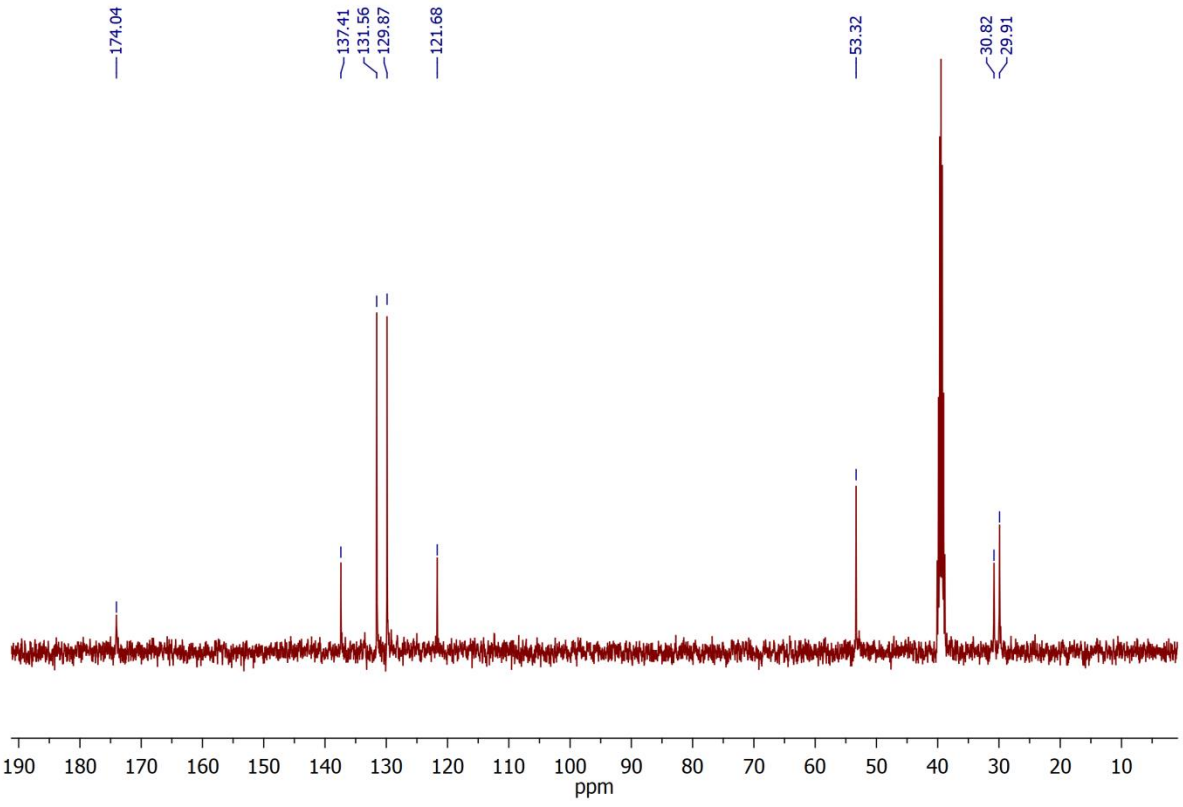
^{13}C NMR (CD_3OD, 100 MHz) of **3d·HCl**



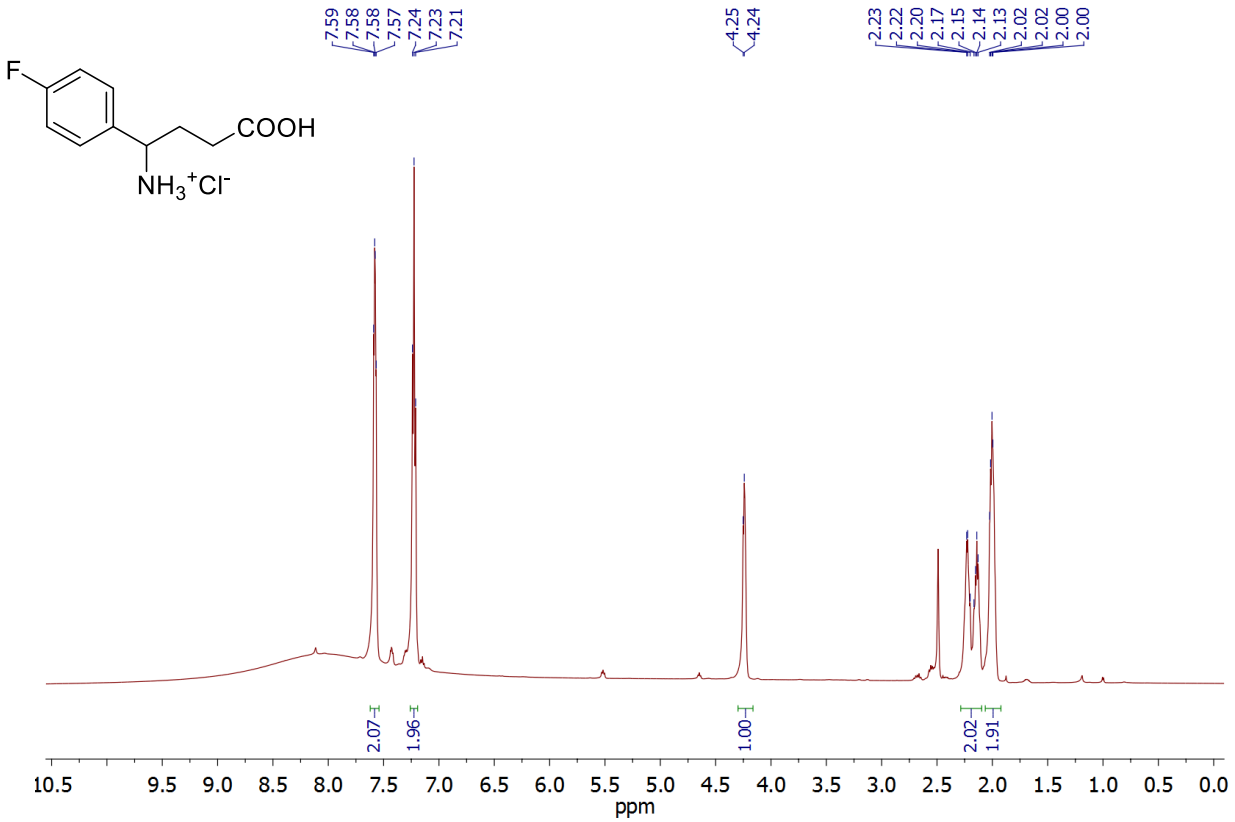
^{1}H NMR (DMSO-d_6, 400 MHz) of **3e·HCl**



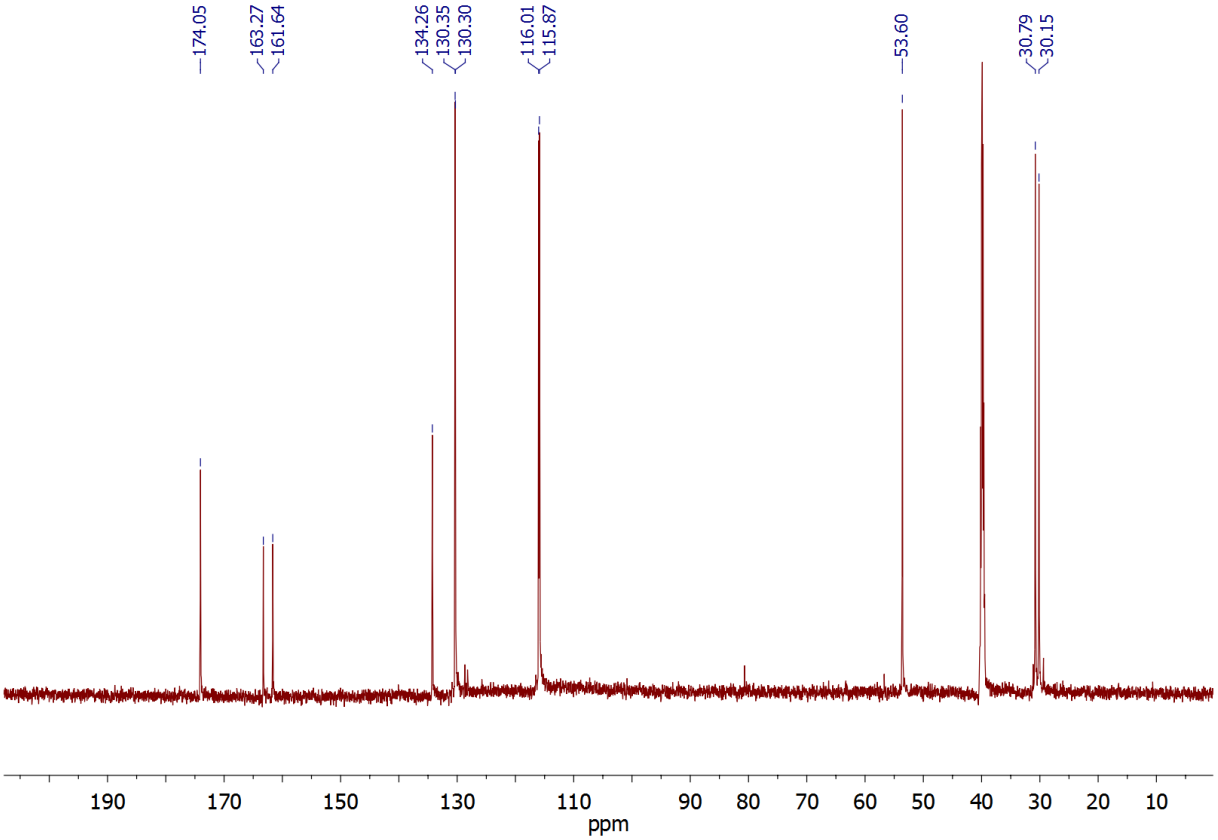
^{13}C NMR (DMSO-d_6, 100 MHz) of **3e·HCl**



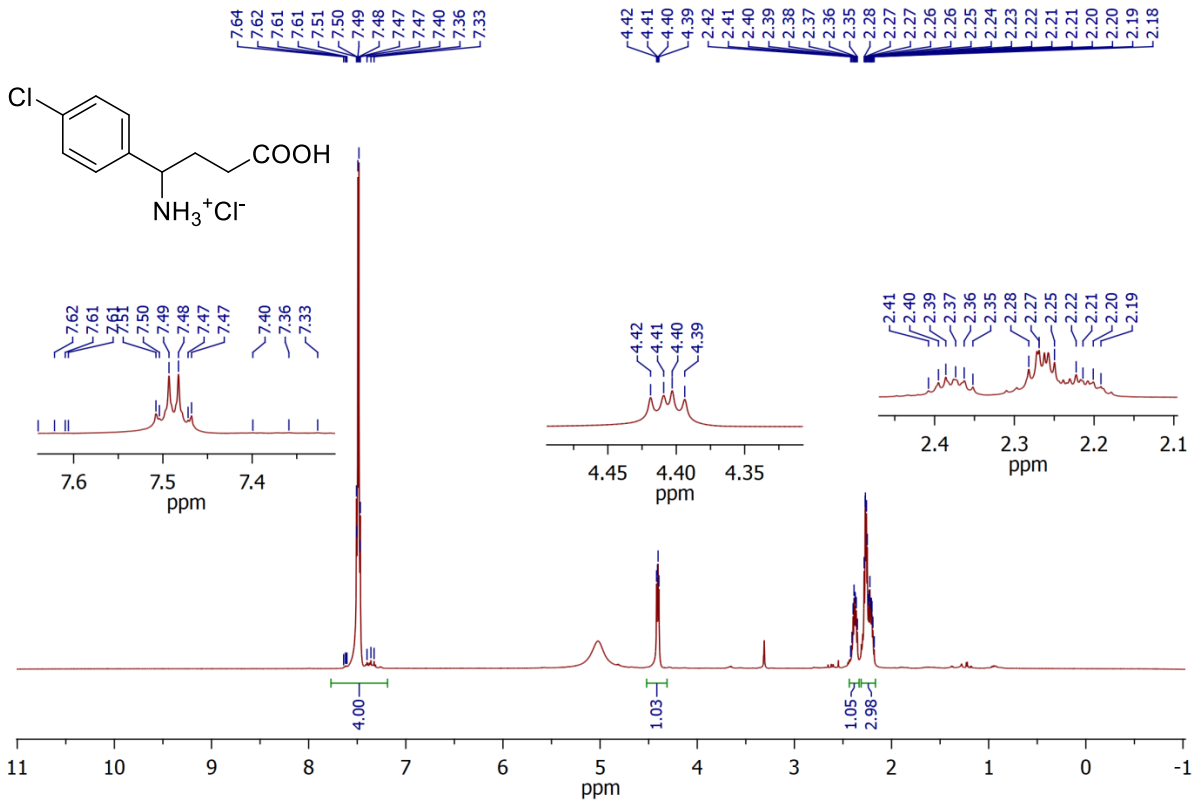
^{1}H NMR (DMSO-d_6, 400 MHz) of **3f·HCl**



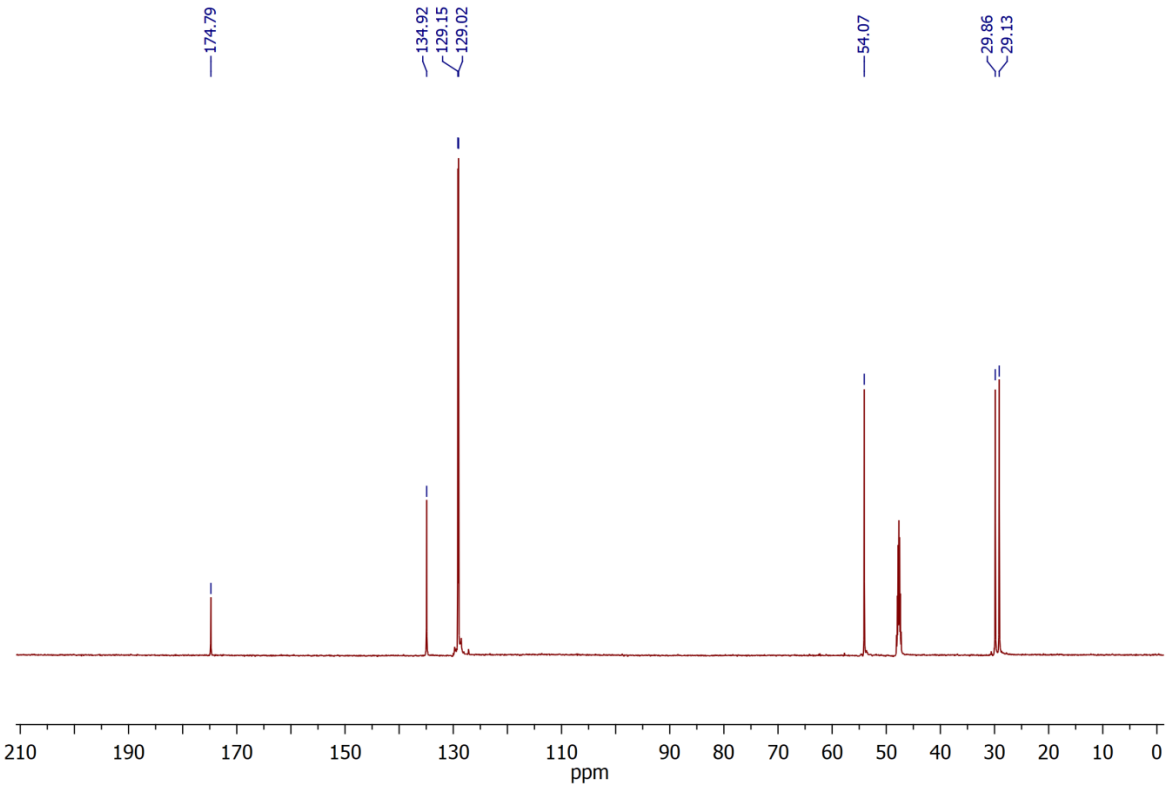
^{13}C NMR (DMSO-d_6, 100 MHz) of **3f·HCl**



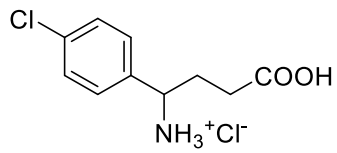
^{1}H NMR (CD_3OD, 600 MHz) of **3g·HCl**

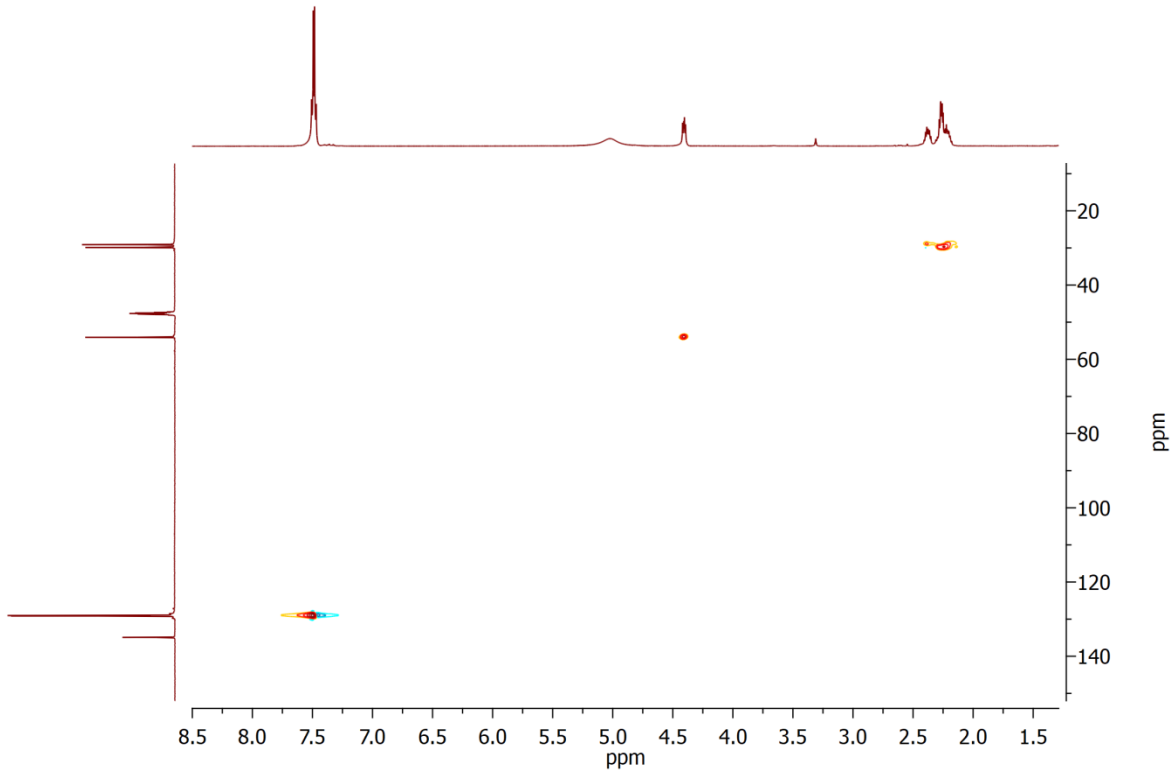


^{13}C NMR (CD_3OD, 150 MHz) of **3g·HCl**

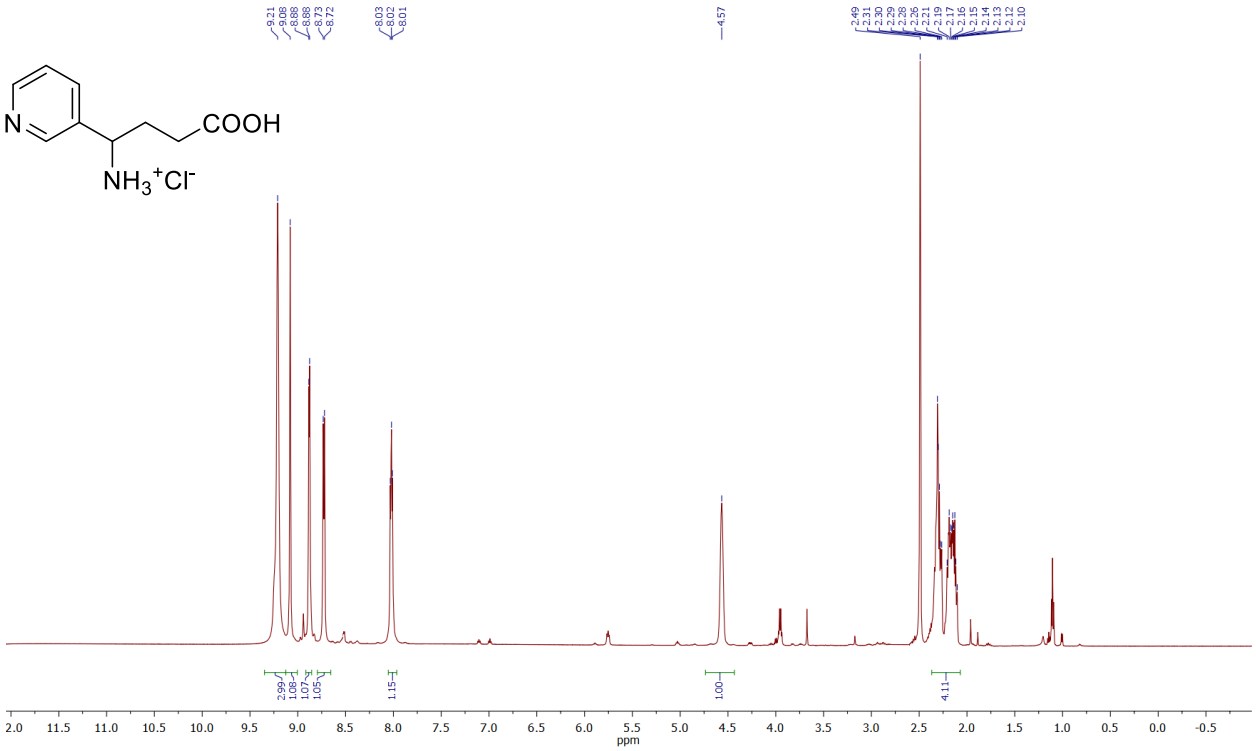


HSQC ^{1}H-^{13}C (CD_3OD) of **3g·HCl**

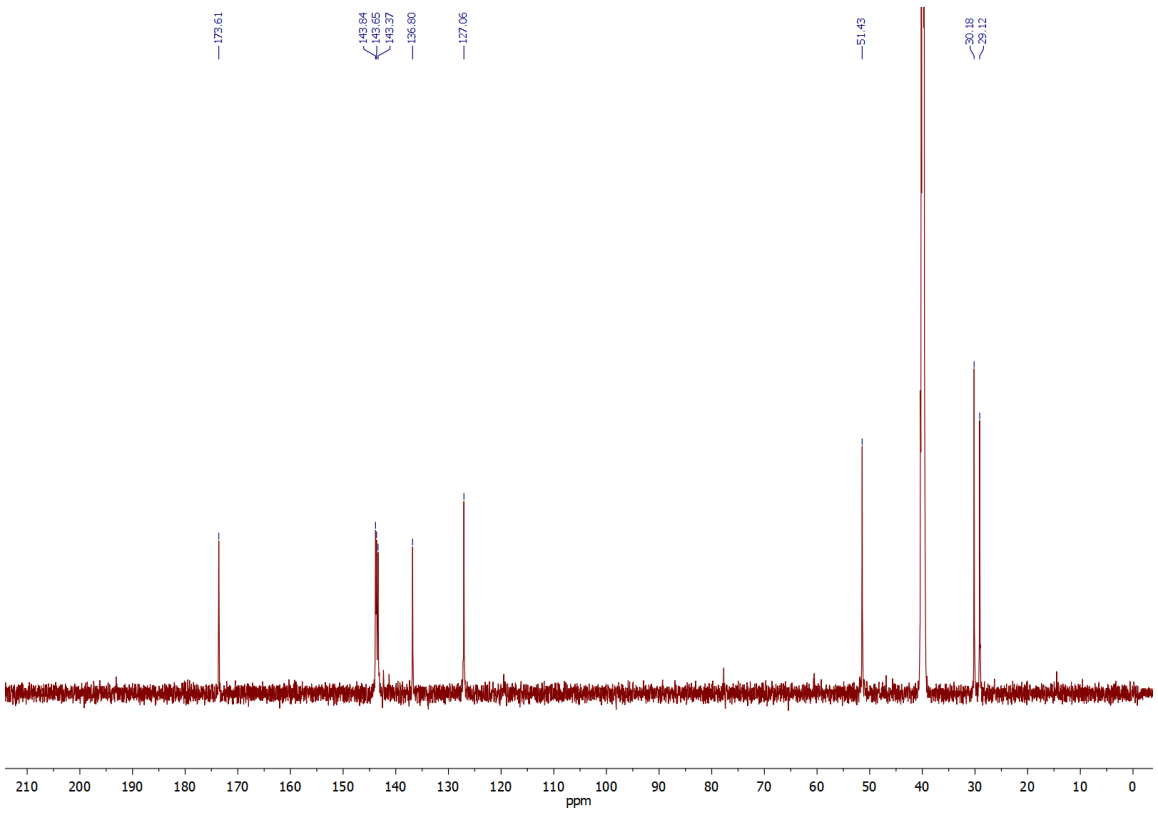




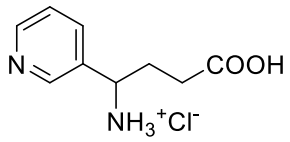
^{1}H NMR (DMSO-d_6, 600 MHz) of **3h·HCl**

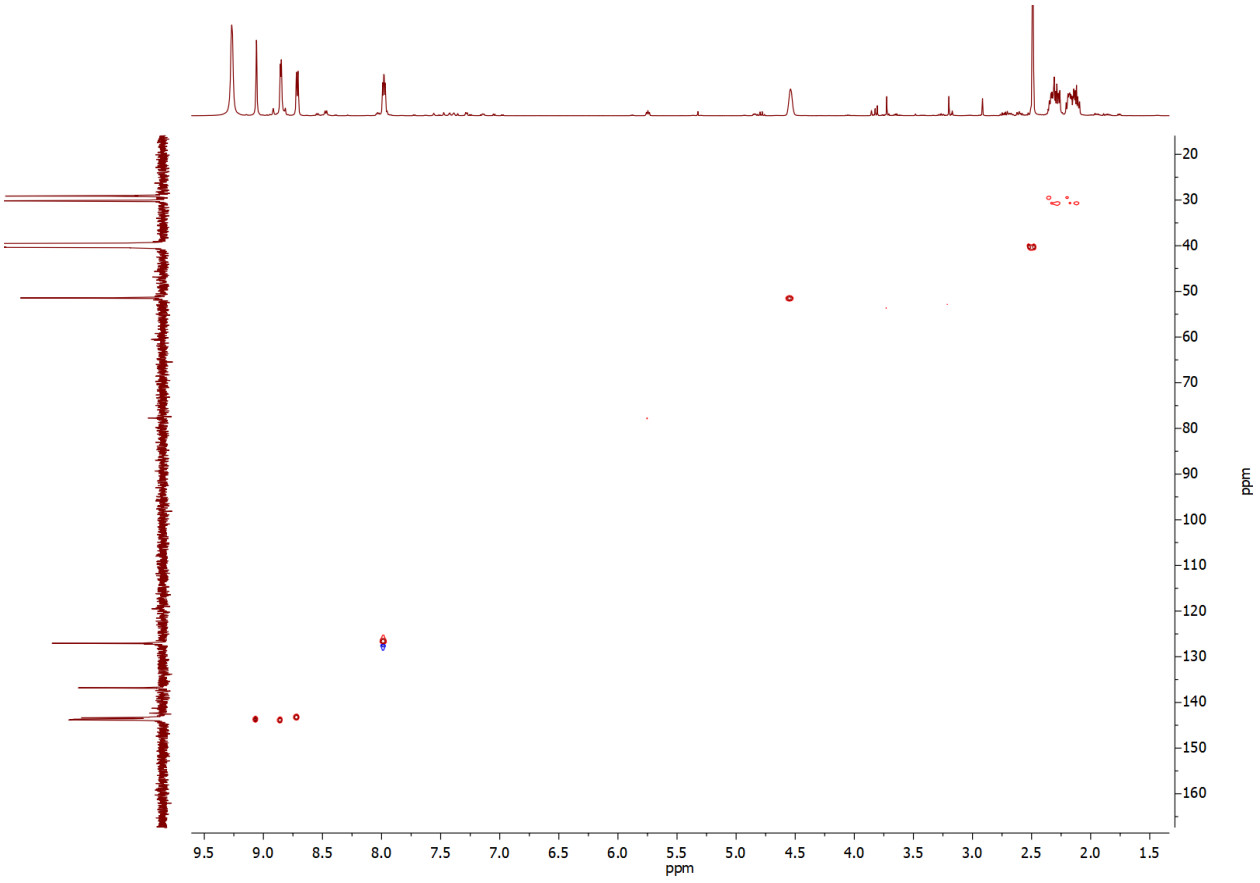


^{13}C NMR (DMSO-d_6, 150 MHz) of **3h·HCl**

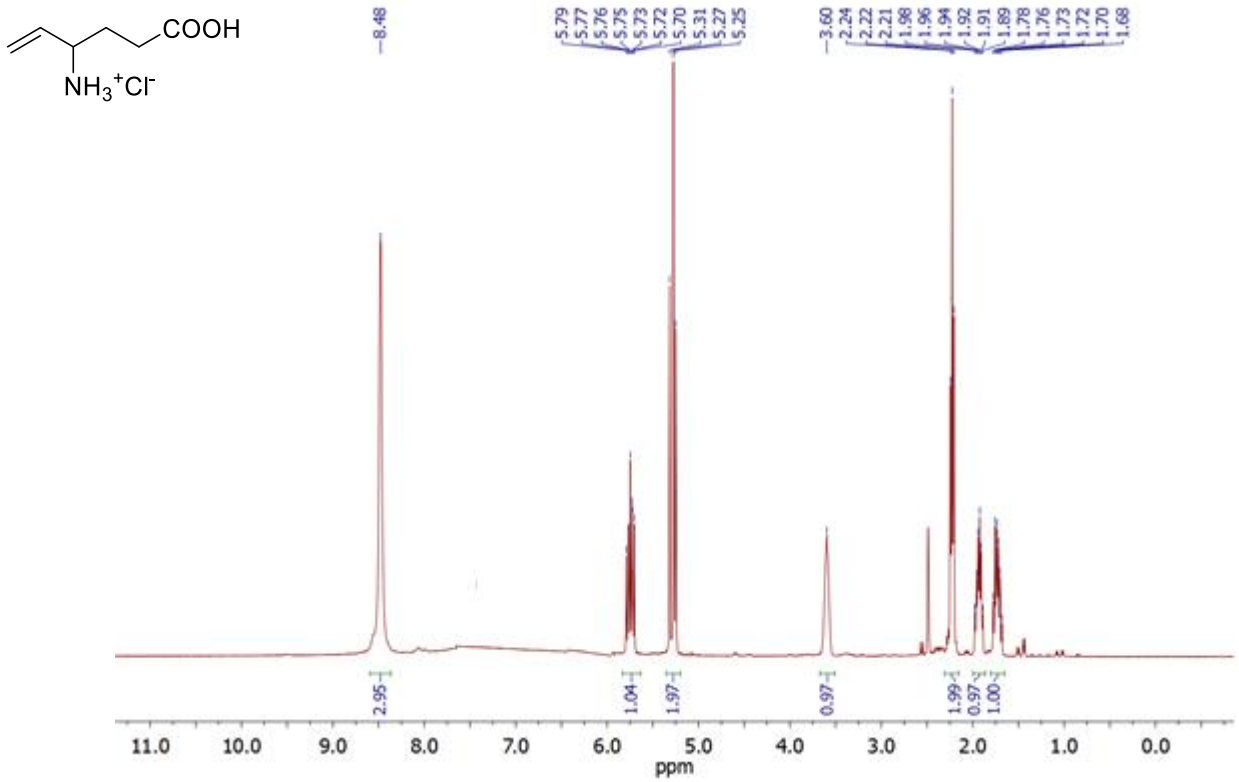


HSQC ^{1}H-^{13}C (DMSO-d_6) of **3h·HCl**

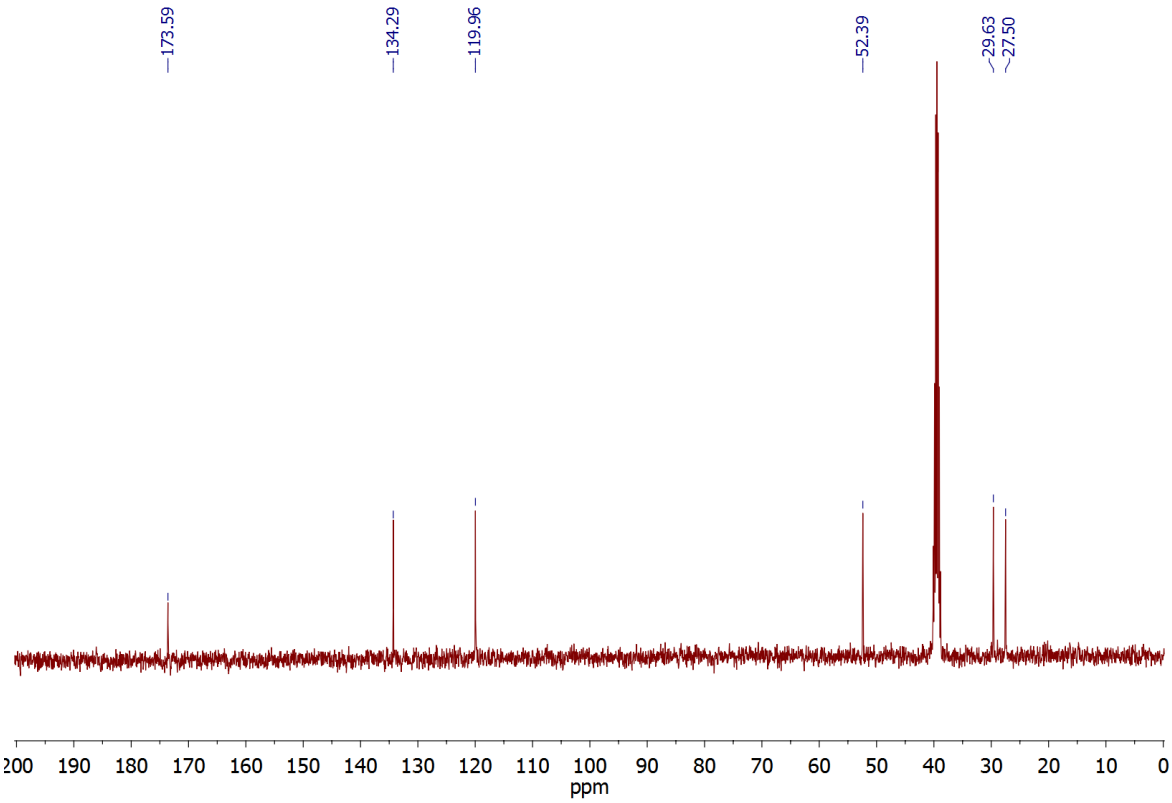




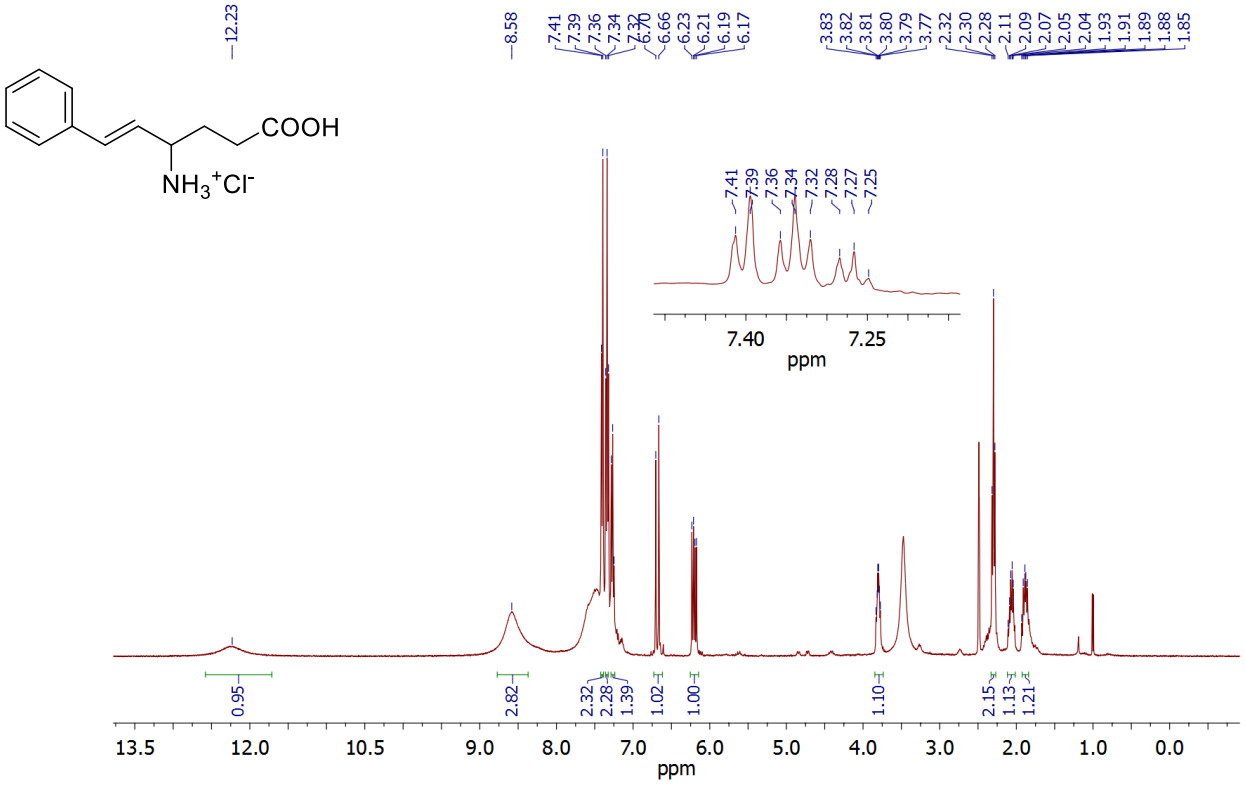
^{1}H NMR (DMSO-d_6, 400 MHz) of **3i·HCl**



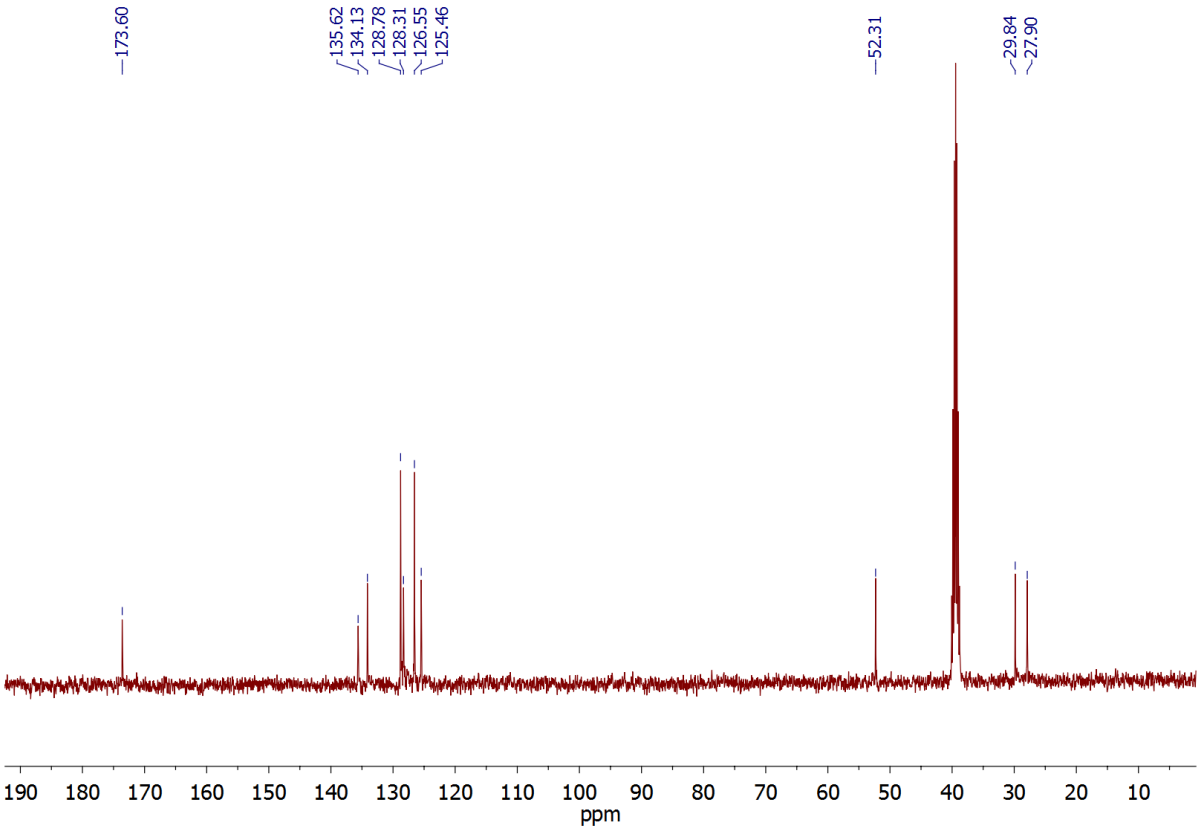
^{13}C NMR (DMSO-d_6, 100 MHz) of **3i·HCl**



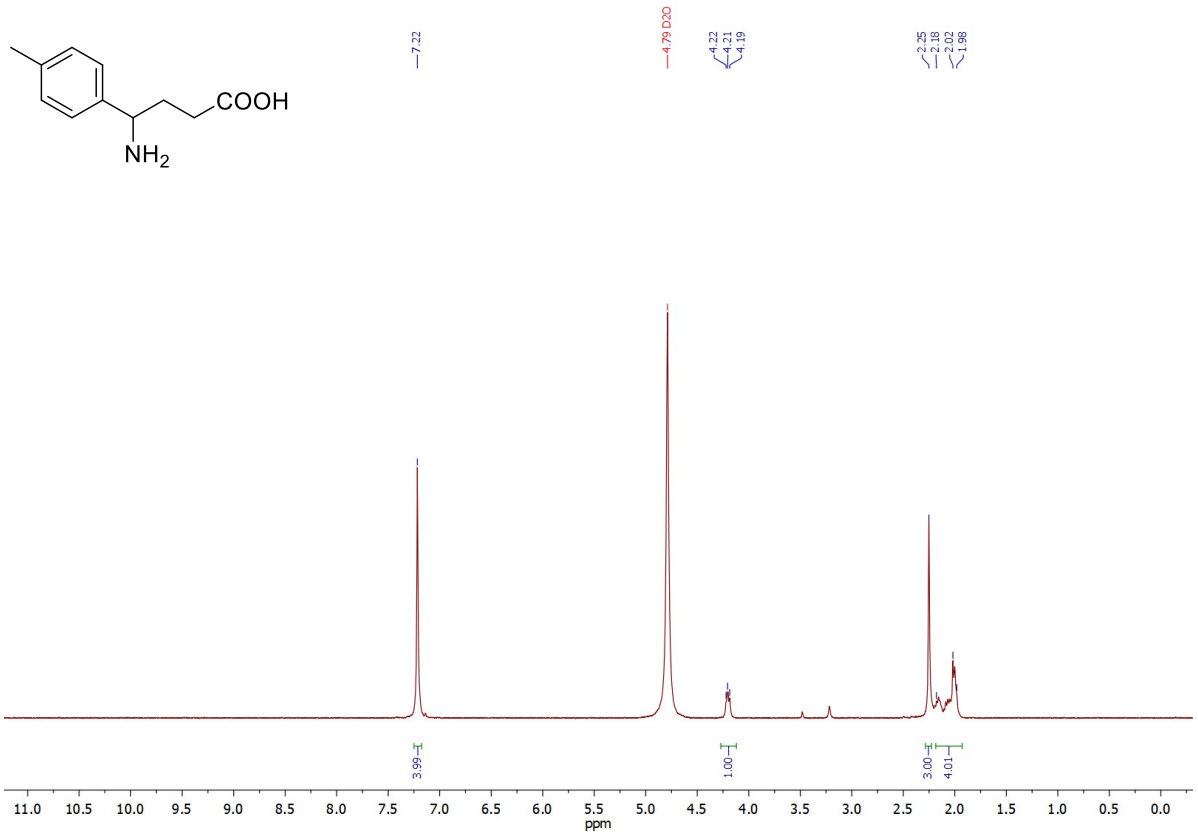
^{1}H NMR (DMSO-d_6, 400 MHz) of **3j·HCl**



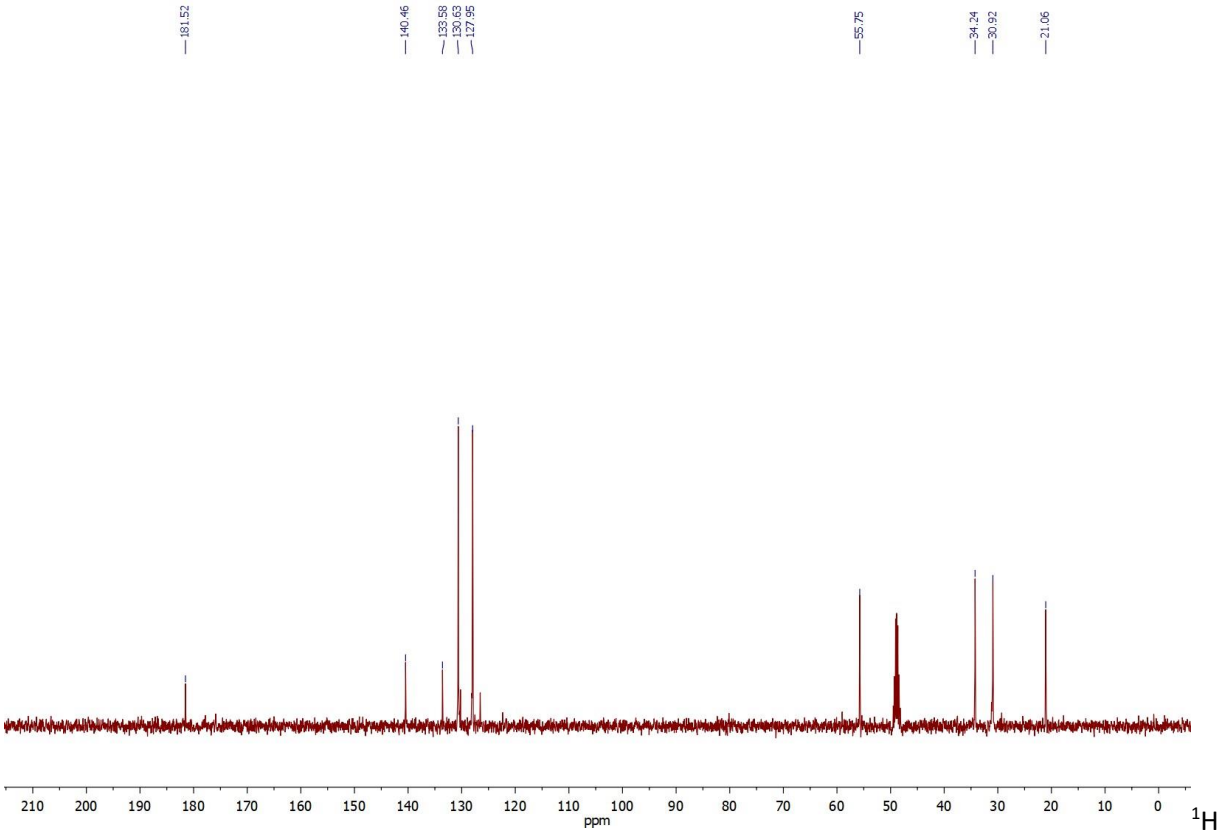
^{13}C NMR (DMSO-d_6, 100 MHz) of **3j·HCl**



^{1}H NMR (D_2O:CD_3OD, 400 MHz) of **3a**

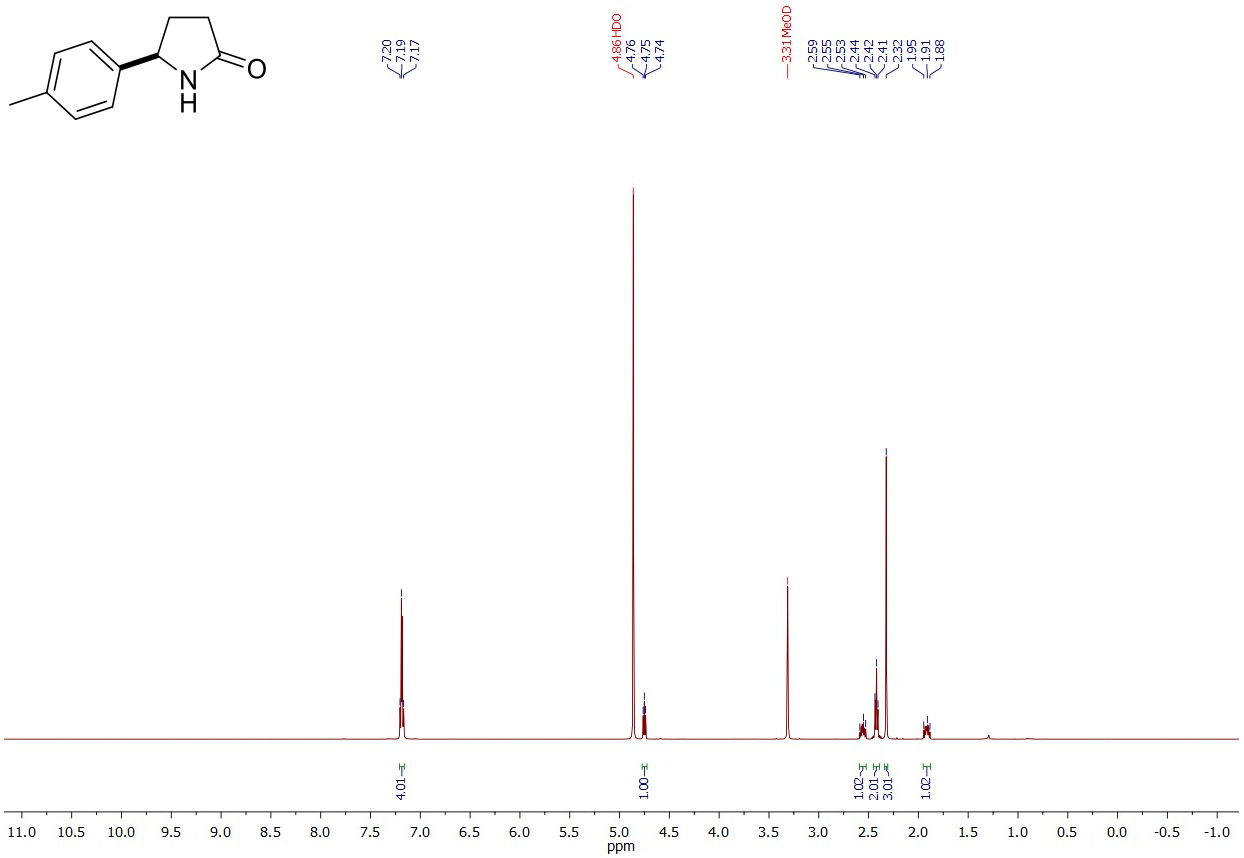


^{13}C NMR (D_2O:CD_3OD, 100 MHz) of **3a**

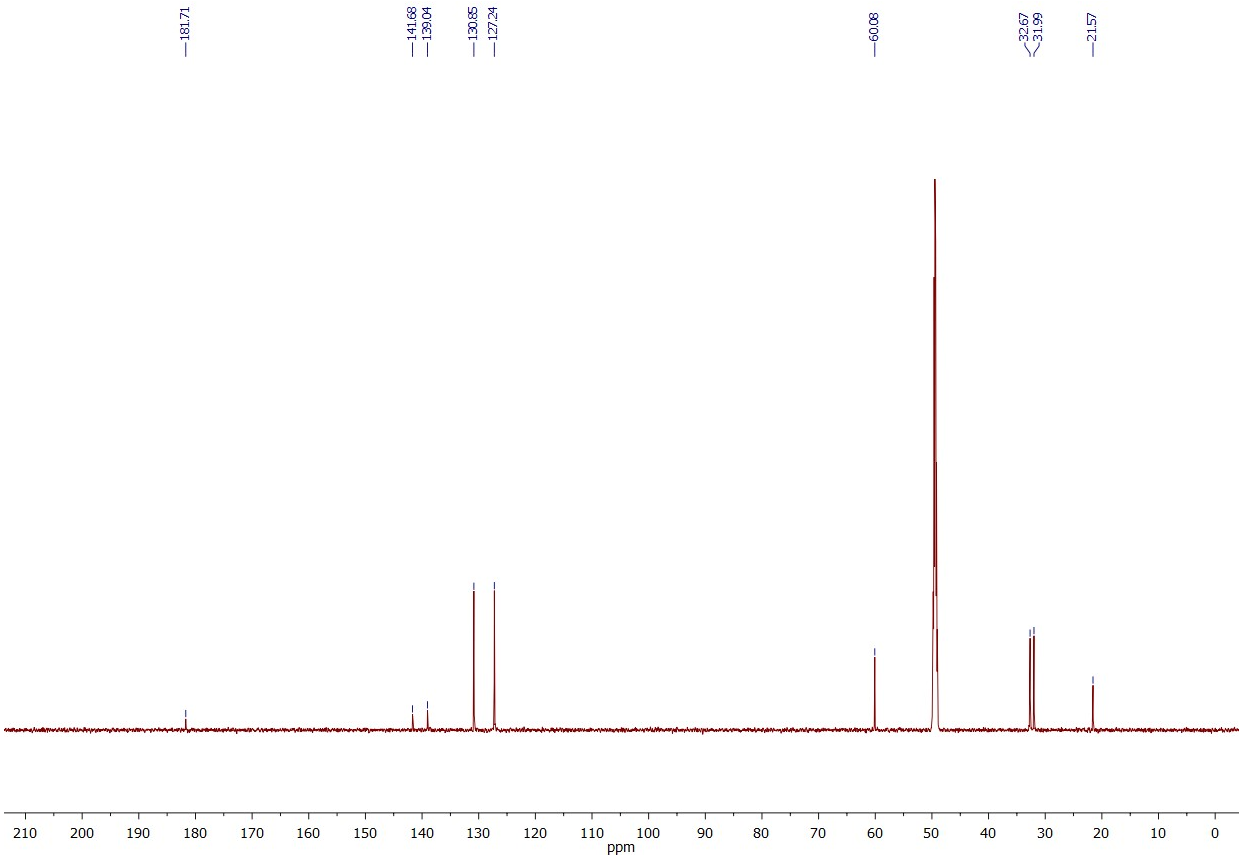


^{1}H

NMR (CD_3OD, 600 MHz) of **5a**

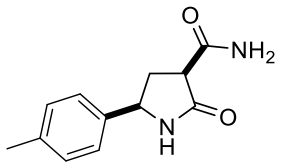


^{13}C NMR (CD_3OD, 151 MHz) of **5a**

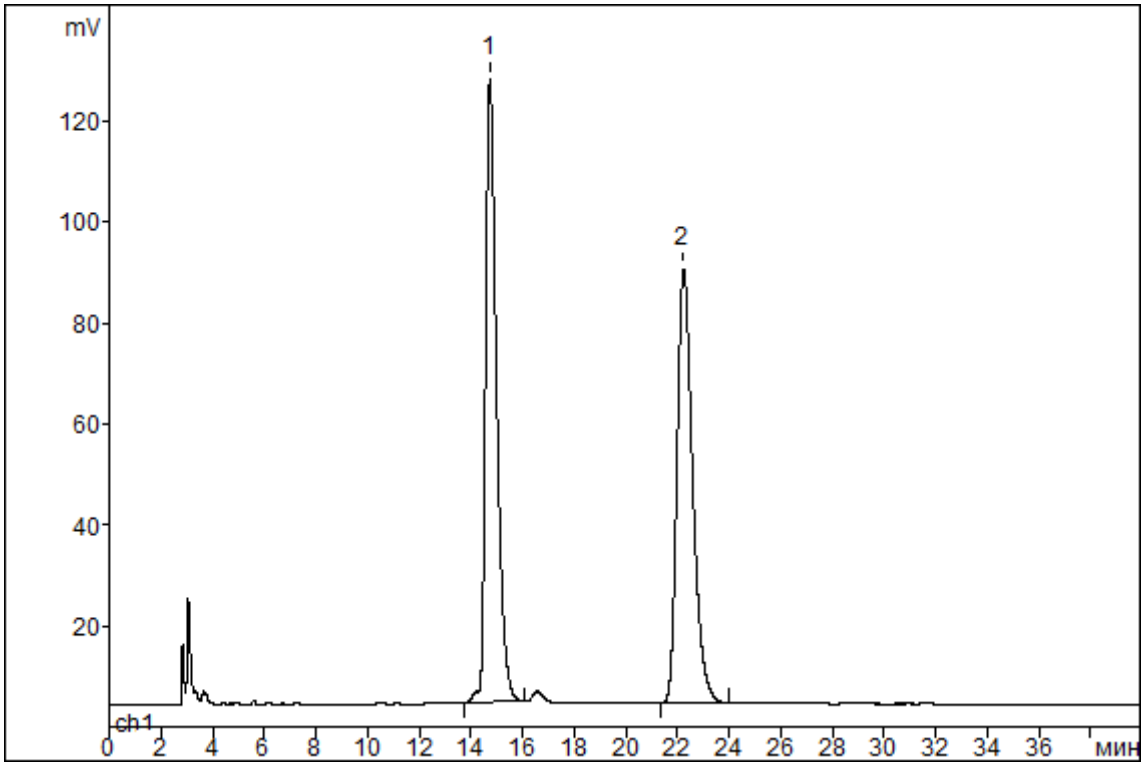


HPLC reports for (3*RS*,5*SR*)-2a and (3*S*,5*R*)-2a (freshly prepared solutions)

(3*RS*,5*SR*)-**2a** (freshly prepared solution)



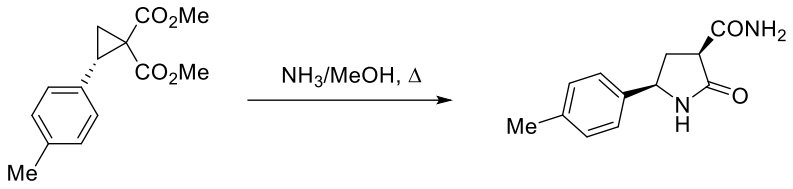
2a



RESULTS

No	Retention min	Area mV*sec	Area %	Name
1	14.73	3666.993	50.38	
2	22.24	3611.016	49.62	
2	40.00	7278.009	100.00	

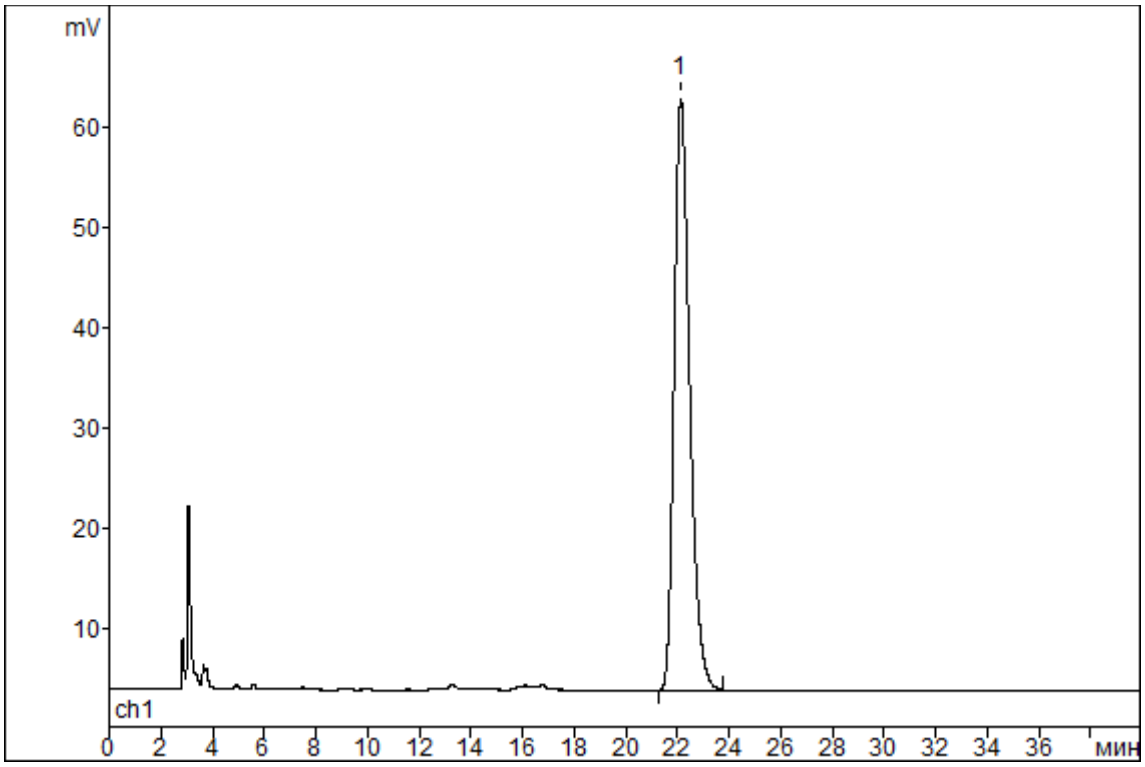
(3*S*,5*R*)-**2a** (freshly prepared solution)



(2*S*)-**1a** (*ee* >99%)

(3*S*,5*R*)-**2a**, 70% (*ee* >99%)

precipitate

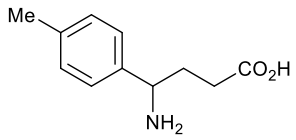


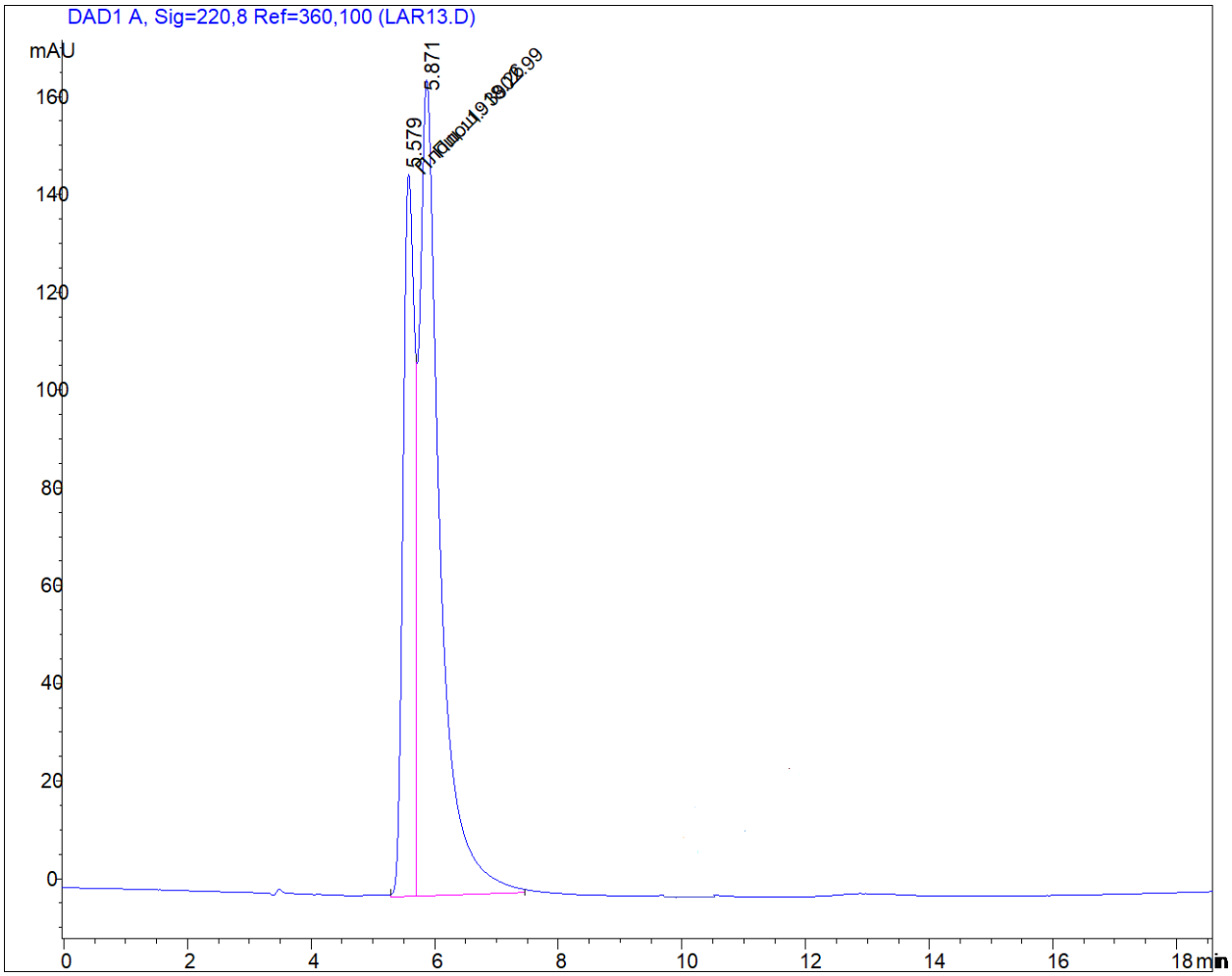
RESULTS

No	Retention min	Area mV*sec	Area %	Name
1	22.13	2470.072	100.00	
1	40.00	2470.072	100.00	

HPLC reports for racemic 3a and for (*R*)-3a

Racemic 3a

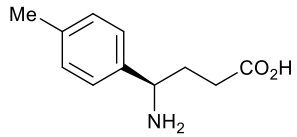


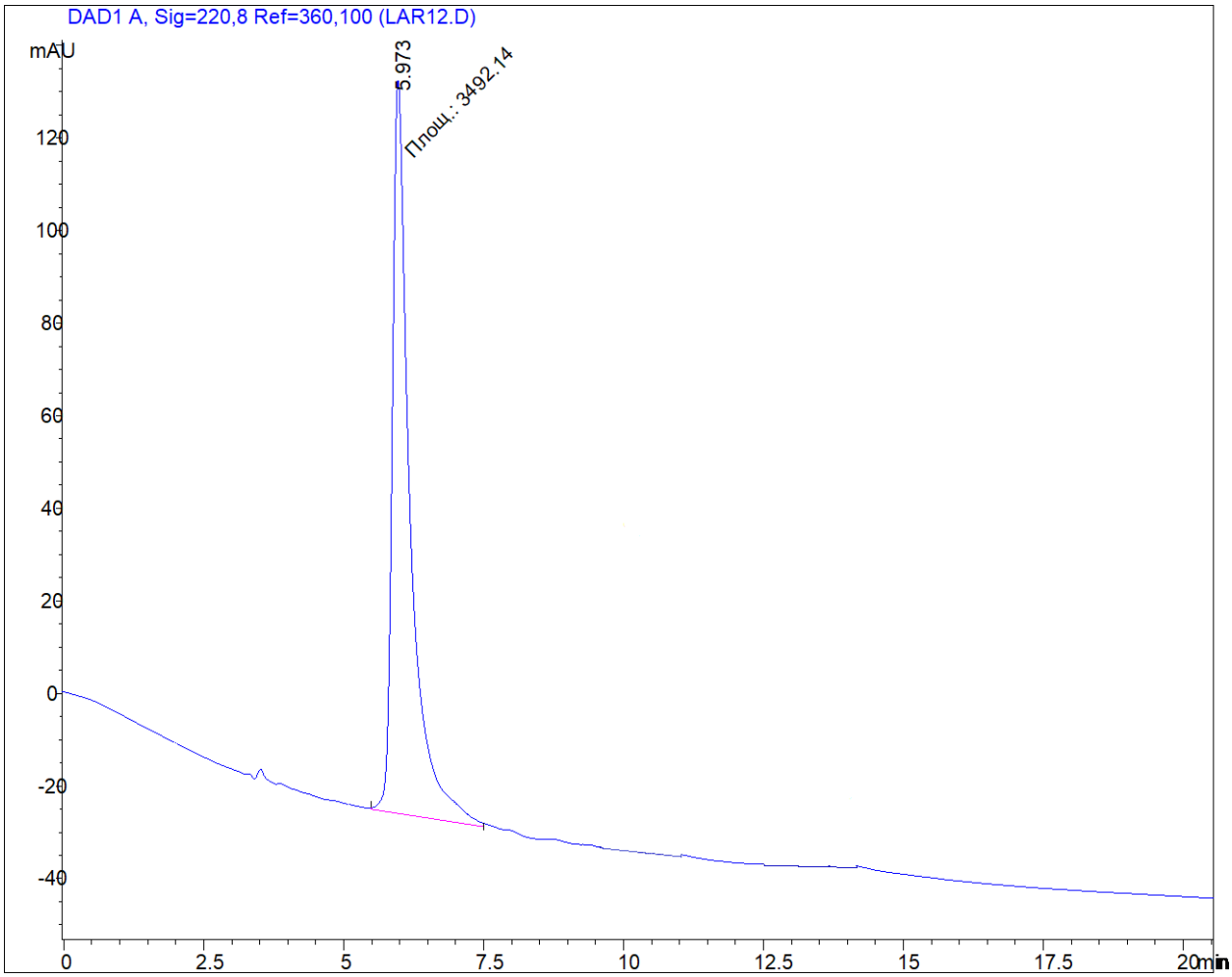


RESULTS

No	Retention min	Area mV*sec	Area %	Name
1	5.579	1918.3	33.0	
2	5.871	3903.0	67.0	
2	18.50	5821.3	100.00	

(*R*)-**3a**

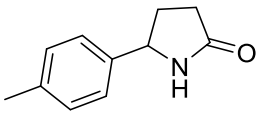


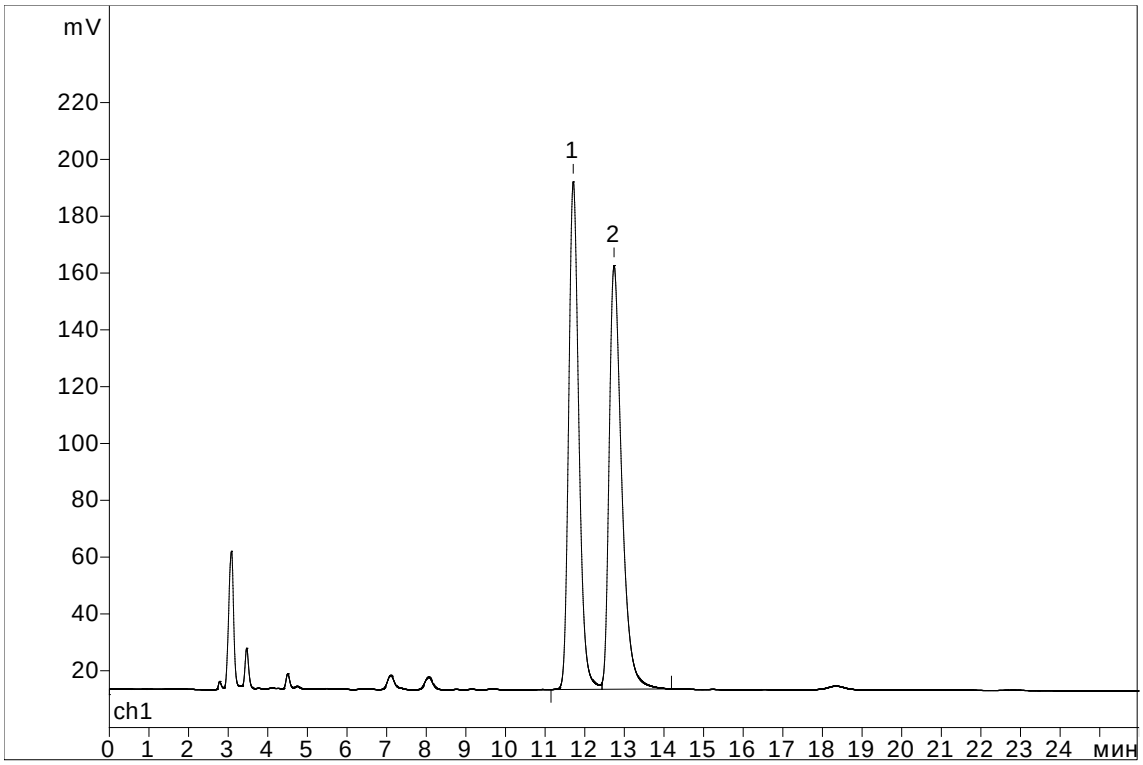


RESULTS

No	Retention min	Area mV*sec	Area %	Name
1	5.973	3492.14	100.00	
1	20.00	3492.14	100.00	

HPLC report for racemic 5a

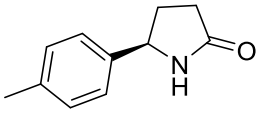


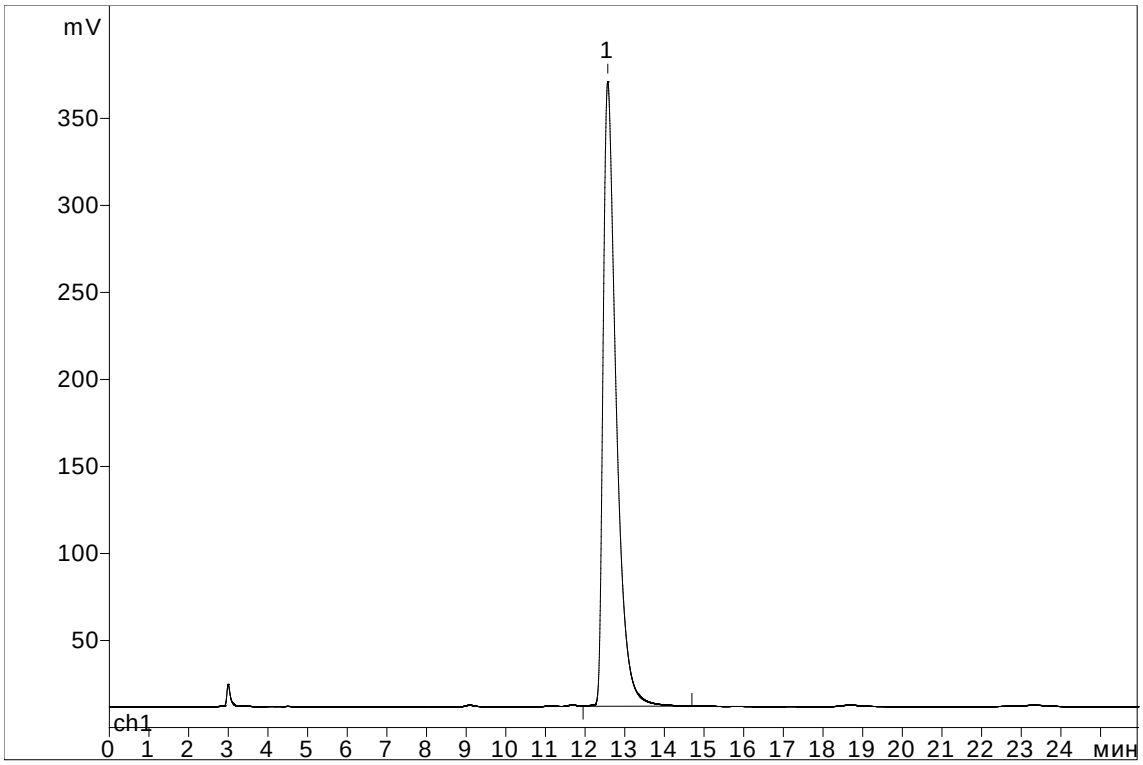


RESULTS

No	Retention min	Area mV* sec	Area %	Name
1	11.71	3201.266	49.44	
2	12.74	3273.576	50.56	
2	40.00	6474.842	100.00	

HPLC report for (*R*)-**5a**





RESULTS

No	Retention min	Area mV* sec	Area %	Name
1	12.57	8244.432	100.00	
1	26.00	8244.432	100.00	