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# Direct Amidation of Unprotected α-Amino Acids using $B(OCH_2CF_3)_3$.

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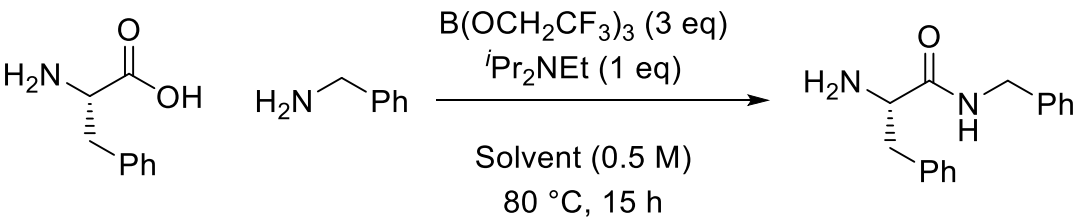
# Supplementary Information

## 1. Solvent screen for direct amidation of phenylalanine




| Entry | Solvent | Yield (%)[a] |
|---|---|---|
| 1 | MeCN | 61 |
| 2 | PhME | 39 |
| 3 | EtOAc | 33 |
| 4 | 2-MeTHF | 43 |
| 5 | Dimethyl carbonate | 51 |
| 6 | TBME | 39 |
| 7 | CPME | 65 |
| 8 | CPME[b] | 69 |
| 9 | CPME[c] | 89 |

[a]NMR yield measured using naphthalene as an internal standard; [b]100 °C; [c]125 °C

## 2. General methods

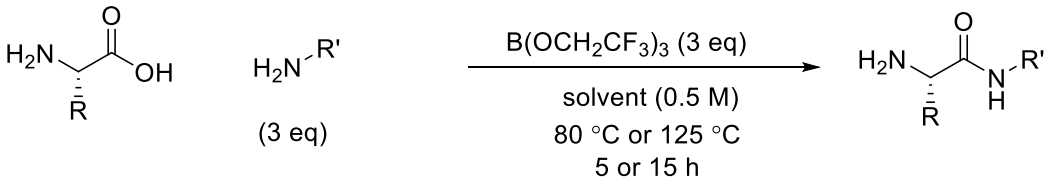
All reagents and solvents were purchased and used as supplied unless otherwise stated. All reactions were carried out at atmospheric pressure with stirring and under air atmosphere unless otherwise indicated. All resins were pre-washed with EtOAc, $Et_2O$ and $CH_2Cl_2$ and dried *in vacuo* prior to use. *In vacuo* is used to describe evaporation of solvent by Büchi rotary evaporator between 17 ºC and 70 ºC at a pressure of ~ 10 mmHg. All reactions were monitored by TLC or $^1$H NMR. TLC plates used were pre-coated with silica gel 60 F254 on aluminium (Merck KGaA). The spotted TLCs were visualised by UV light (254 nm or 365 nm) or chemically stained ($KMnO_4$). Column chromatography purification was performed using silica gel (Merck silica gel, 40-60 μm). $[\alpha]_D$ values are given in $10^{-1}$ deg cm$^2$ g$^{-1}$, concentration (*c*) in g per 100 mL. $^1$H NMR and $^{13}$C NMR spectra were recorded at 300, 400, 500 MHz or 600 MHz (for $^1$H) and 75, 100, 125 MHz or 150 MHz (for $^{13}$C) on a Bruker AMX300, AMX400, AMX500 or AMX600 at ambient temperature, unless otherwise indicated. Deuterated solvents for NMR detection used were $CDCl_3$, MeOD or DMSO-*d6* as stated in the spectrum. Peaks are assigned as singlet (s), doublet (d), triplet (t) or multiplet (m). All shifts are reported in parts per million (ppm) and compared against residual solvent signals: $CDCl_3$ ($\delta$ = 7.26 ppm, s), DMSO ($\delta$ = 2.56 ppm, qn) or MeOD ($\delta$ = 4.87, s and 3.31, qn) as the internal standard. Coupling constants (*J*) are quoted in Hertz (Hz) to one decimal place. Mass spectrometry was performed on VG70 SE (EI, CI, ES- modes). Infra-red spectra were obtained using a Perkin-Elmer Spectrum 100 FTIR Spectrometer operating in ATR mode, all frequencies given in reciprocal centimetres (cm$^{-1}$). Melting points were measured with a Gallenkamp heating block and are uncorrected.

**Preparation of Tris(2,2,2-trifluoroethyl)borate**

100 g scale: A suspension of $B_2O_3$ (100.0 g, 1.44 mol) in 2,2,2-trifluoroethanol (210 mL, 2.88 mol) was stirred at 80 °C for 24 h. The reaction mixture was allowed to cool and then filtered to remove excess boric anhydride. The filtrate was purified by distillation to give $B(OCH_2CF_3)_3$ as a clear liquid (108 g, 0.19 mol, 44%); bp 125-129 °C; $\nu_{max}$ (film/cm$^{-1}$) 3168, 1440, 1380; $\delta_H$ (600 MHz, $CDCl_3$) 4.23 (q, *J* = 8.6 Hz, 6H); $\delta_C$ (150 MHz , $CDCl_3$) 61.8 (q, *J* = 36.3 Hz), 123.3 (q, *J* = 278.4 Hz); LRMS (EI) 309 ([M]$^+$, 100); Data in agreement with the literature.[1]

## 3. General procedures

**Direct amidation of unprotected amino acids with propylamine and different amines**



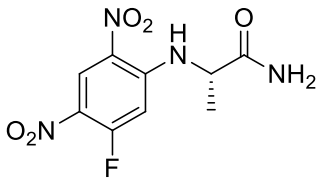

**Method A:** All reactions were performed on 0.5 or 1.0 mmol scale. An unprotected amino acid (1 eq) and amine (3 eq) were stirred at 80 °C or 125 °C in CPME (0.5 M, unless stated otherwise) with $B(OCH_2CF_3)_3$ (3 eq) for 5 or 15 h. Upon completion, the mixture was diluted with EtOAc or $CH_2Cl_2$ (3 mL) and water (0.5 mL). Amberlite IRA-743 and Amberlyst A-26(OH) were added and stirred for 30 min. The mixture was dried over $MgSO_4$ and then filtered. The solids were washed with EtOAc (3 × 20 mL) and the product concentrated *in vacuo* to give the amino amide. Amides derived from non-volatile amines were purified either by trituration ($Et_2O$) or column chromatography as stated below.

**Method B:** A solution of $B(OCH_2CF_3)_3$ (3.0 mmol, 3.0 eq) in CPME (1 mL, unless stated otherwise) was added dropwise to a mixture of an unprotected amino acid (1.0 mmol, 1.0 eq) and propylamine (3.0 mmol, 3.0 eq) in CPME (1 mL) over 1 h at 80 °C or 125 °C. The resulting mixture was stirred for 5 or 15 h. Upon completion, the mixture was diluted with EtOAc or $CH_2Cl_2$ (3 mL) and water (0.5 mL). Amberlite IRA-743 and Amberlyst A-26(OH) were added and stirred for 30 min. The mixture was dried over $MgSO_4$ and then filtered. The solids were washed with EtOAc (3 × 20 mL) and the product concentrated *in vacuo.* The volatile propylamine was removed *in vacuo* by the addition of $CHCl_3$ to get the clean product. Amides with different amines were purified either by trituration ($Et_2O$) or column chromatography as stated.

## 4. General methods for er determination

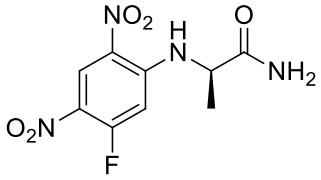
### Synthesis of both enantiomers of Marfey's reagent

***(S)*-2-((5-Fluoro-2,4-dinitrophenyl)amino)propanamide "L-Marfey"**



L-Alaninamide (473 mg, 3.80 mmol) was dissolved in 1 M NaOH (3.9 mL) and the resulting mixture was dissolved in acetone (60 mL). $MgSO_4$ (10 g) was added and the resulting mixture was stirred for 3 h at room temperature. $MgSO_4$ was then filtered off. 1,5-Difluoro-2,4-dinitrobenzene (FFDNB) (668 mg, 3.27 mmol) was dissolved in acetone (15 mL). L-Alaninamide solution was then added dropwise to FFDNB and the solution was stirred for 0.5 h. Water (80 mL) was added and the crystals formed were filtered and washed with acetone/water mixture (3 × 15 mL). The product was obtained as bright yellow crystals (563 mg, 63%, er 100%); mp 223-224 °C [Lit.[2] 222-223 °C]; $\nu_{max}$ (solid/$cm^{-1}$) 3439, 3339, 1670, 1632, 1580; $[\alpha]_D^{25}$ +54.0 (*c* 0.99, Acetone); $\delta_H$ (600 MHz, DMSO-$d_6$) 1.44 (d, *J* = 6.8 Hz, 3H, $CH_3$), 4.39 (p, *J* = 6.8 Hz, 1H, CH), 6.96 (d, *J* = 14.3 Hz, 1H, CFCH), 7.52 (s, 1H, CON*H*H), 7.75 (s, 1H, CONH*H*), 8.90 (d, *J* = 8.1 Hz, 1H, $C(NO_2)CH$), 9.11 (d, *J* = 6.7 Hz, 1H, N*H*); $\delta_C$ (150 MHz, DMSO-$d_6$) 18.4, 51.6, 102.2 (d, $J_{CF}$ = 27.1 Hz), 125.1 (d, $J_{CF}$ = 9.6 Hz), 127.4 (d, $J_{CF}$ = 15.4 Hz), 127.5, 147.6 (d, $J_{CF}$ = 14.1 Hz), 159.1 (d, $J_{CF}$ = 266.7 Hz, C-F), 172.4; LRMS (ES−): 270 ($[M-H]^-$, 100); HRMS: Found (ES−): $[M-H]^-$ 270.4001 $C_9H_7N_4O_5F$, requires 270.0411. Data in agreement with the literature.[2]

***(R)*-2-((5-Fluoro-2,4-dinitrophenyl)amino)propanamide "D-Marfey"**



D-Alaninamide (472 mg, 3.79 mmol) was dissolved in 1 M NaOH (3.9 mL) and the resulting mixture was dissolved in acetone (60 mL). $MgSO_4$ (10 g) was added and the resulting mixture was stirred for 3 h at room temperature. $MgSO_4$ was then filtered off. 1,5-Difluoro-2,4-dinitrobenzene (FFDNB) (668 mg, 3.27 mmol) was dissolved in acetone (15 mL). D-Alaninamide solution was then added dropwise to FFDNB and the solution was stirred for 0.5

h. Water (80 mL) was added and the crystals formed were filtered and washed with acetone/water mixture (3 × 15 mL). The product was obtained as bright yellow crystals (596 mg, 67%, er 100%): mp 223-224 °C [Lit.[2] 222-223 °C]; $\nu_{max}$ (solid/cm$^{-1}$) 3442, 3338, 3190, 1670, 1631, 1579; $[\alpha]_D^{25}$ −60.0 (*c* 0.69, Acetone); $\delta_H$ (600 MHz, DMSO-*d*$_6$) 1.44 (d, *J* = 6.8 Hz, 3H, $CH_3$), 4.39 (p, *J* = 6.8 Hz, 1H, CH), 6.96 (d, *J* = 14.3 Hz, 1H, CFCH), 7.52 (s, 1H, CON*H*H), 7.75 (s, 1H, CONH*H*), 8.90 (d, *J* = 8.1 Hz, 1H, C($NO_2$)CH), 9.11 (d, *J* = 6.7 Hz, 1H, N*H*); $\delta_C$ (150 MHz, DMSO-$d_6$) 18.4, 51.6, 102.2 (d, $J_{CF}$ = 27.1 Hz), 125.1 (d, $J_{CF}$ = 9.6 Hz), 127.4 (d, $J_{CF}$ = 15.4 Hz), 127.5, 147.6 (d, $J_{CF}$ = 14.1 Hz), 159.1 (d, $J_{CF}$ = 266.7 Hz, C-F), 172.4; LRMS (ES−): 270 ([M−H]$^-$, 100); HRMS: Found (ES−): [M−H]$^-$ 270.3989 $C_9H_7N_4O_5F$, requires 270.0411. Data in agreement with the literature.[2]

**Chiral aldehyde method [3]:** Two NMR samples of an amino amide with slight excess (1.2 eq) of chiral aldehyde *(S)*-2-((tert-butyldimethylsilyl)oxy)propanal (***(S)*-**aldehyde) and *(R)*-2-((tert-butyldimethylsilyl)oxy)propanal (***(R)*-**aldehyde) were prepared in MeOD and $^{13}$C NMR was measured to determined enantiomeric ratio of the amide product. This method was applied to amides **5a**, **5b** and **5i**.

**Marfey's reagent method [2]:** 1 eq of chiral amide was mixed with 1.5 eq of L- and D-Marfey's reagent and 1.0 eq of $Et_3N$ in DMSO-*d6*. The mixture was heated at 40 °C for 1 h before $^1$H NMR spectrum was collected. This method was applied to amides **5d-f**, **5h**, **5m**, **5y**, **6a-d**, **6f**, **6h, 6k, 6m-n.**

**Chiral shift agent method [4]:** 1 eq of amide and its racemic equivalent were mixed with 1.2 eq of *(R)*-(−)-1-(9-Anthryl)-2,2,2-trifluoroethanol in $CDCl_3$ and the er was determined by $^1$H NMR. This method was applied to amides **5n** and **6i.**

**Chiral HPLC:** Chiral HPLC was used to determine the enantiopurity of amides **5j** and **7**; the amino amide **5j** was protected with $Boc_2O$ prior to analysis.

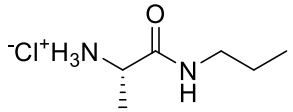
Chiralcel OD-1 was used for **5j** (n-Hex/i-PrOH; 9/1; v/v; 0.5 ml/min; 218 nm; $R_t$(S) = 23.58 min.

Chiralcel OD-H was used for **7** (n-Hex/PrOH; 80/20, 0.5 ml/min; 220 nm; $R_t$(R) = 7.86 min.

## 5. Spectroscopic Data

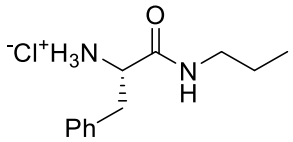
**Amidation of natural amino acids**

### *(S)*-2-Amino-*N*-propylpropanamide hydrochloride 5a.HCl



Prepared according to method A, at 80 °C for 15 h in MeCN to give a colourless oil which was further stirred with 2 M HCl in MeOH and concentrated *in vacuo* to yield a white solid (60 mg, 71%, er 93:7, determined using aldehyde method); mp 197-198 °C; $[\alpha]_D^{20}$ +4.4 (*c* 0.38, MeOH); $\nu_{max}$ (solid/cm$^{-1}$) 3330 (N-H), 2850 (C-H), 1650 (C=O); $\delta_H$ (600 MHz, DMSO-$d_6$) 0.86 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 1.34 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CH), 1.43 (sx, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_3$), 3.01-3.12 (m, 2H, C*H*$_2$NH), 3.79 (br quint, *J* = 6.0 Hz, 1H, C*H*), 8.21 (br s, 3H, NH$_3^+$Cl$^-$), 8.49 (br t, *J* = 5.5 Hz, 1H, NH); $\delta_C$ (150 MHz, DMSO-$d_6$) 11.4, 17.3, 22.2, 40.4, 48.2, 169.3; HRMS: Found (CI): $[M\text{-}Cl]^+$ 131.118930 $C_6H_{15}N_2O$, requires 131.11844.

### *(S)*-2-Amino-3-phenyl-*N*-propylpropanamide hydrochloride 5b.HCl

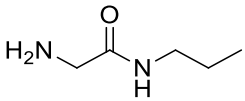


Prepared according to method A, at 80 °C for 15 h to give a colourless oil which was further stirred with 2 M HCl in MeOH and concentrated *in vacuo* to yield an off-white solid (118 mg, 90%, er 94:6, determined using aldehyde method); mp 150-151 °C [Lit.[5] 155 °C]; $[\alpha]_D^{25}$ +21.7 (*c* 0.62, MeOH) [Lit.[5] $[\alpha]_D^{25}$ +62.9 (*c* 0.62, MeOH)]; $\nu_{max}$ (solid/cm$^{-1}$) 3342 (N-H), 2876 (C-H), 1656 (C=O); $\delta_H$ (600 MHz, DMSO-$d_6$) 0.73 (t, *J* = 7.5 Hz, 3H, CH$_3$), 1.23-1.36 (m, 2H, C*H*$_2$CH$_3$), 2.86-2.92 (m, 1H, C*H*HPh), 2.99-3.09 (3H, m, CH*H*Ph and NHC*H*$_2$), 3.97 (br s, 1H, C*H*CH$_2$), 7.22-7.27 (m, 3H, ArH), 7.28-7.33 (m, 2H, ArH), 8.40 (br s, 3H, NH$_3^+$Cl$^-$), 8.55 (br t, *J* = 5.5 Hz, 1H, N*H*CH$_2$); $\delta_C$ (150 MHz, DMSO-$d_6$) 11.4, 22.0, 37.0, 40.4, 53.5, 127.1, 128.4, 129.5, 135.1, 167.5; HRMS: Found (CI): $[M\text{-}Cl]^+$ 207.149184 $C_{12}H_{19}N_2O$, requires 207.14974

Scale up procedure:

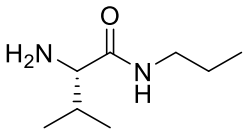
**(*S*)-2-amino-3-phenyl-N-propylpropanamide (*S*)-5b:** Prepared according to method B, at 80 °C for 15 h to yield a pale yellow oil (1.19 g, 95%, er 94:6, determined using Marfey's reagent); $[\alpha]_D^{25}$+24.0 (*c* 1.0, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3294, 2960, 2930, 2872, 1637, 1533, 1439; $\delta_H$ (600 MHz, $CDCl_3$) 0.90 (t, *J*= 7.4 Hz, 3 H, C*H*$_3$), 1.48 (br s, 2 H, N*H*$_2$), 1.51 (sx, *J*= 7.3 Hz, 2H, C*H*$_2$CH$_3$), 2.69 (dd, *J*= 13.7, 9.3 Hz, 1 H, CH*H*Ph), 3.22 (m, 2 H, NHC*H*$_2$), 3.28 (dd, *J*= 13.7, 4.1 Hz, 1 H, CH*H*Ph), 3.59 (dd, 9.3, 4.1 Hz, 1H, C*H*); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 22.9, 40.9, 41.2, 56.6, 126.9, 128.8, 129.4, 138.1, 174.3. LRMS: (ES+): 207.3 ([M+H]$^+$, 100).

**2-Amino-*N*-propylacetamide 5c**



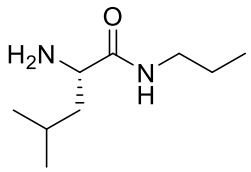

Prepared according to method A, at 80 °C for 15 h to give a yellow oil (41 mg, 71%); $\nu_{max}$ (film/cm$^{-1}$) 3297 (N-H), 2961 (C-H), 2873, 1643 (C=O); $\delta_H$ (300 MHz, $CDCl_3$) 0.93 (t, *J* = 7.4 Hz, 3H, $CH_3$), 1.53 (m, 2H, $CH_3CH_2$), 1.62, 3.24 (m, 2H, CONHC*H*$_2$), 3.30 (s, 2H, $COCH_2$); $\delta_C$ (75 MHz, $CDCl_3$) 11.5, 23.0, 40.8, 44.9, 172.8; LRMS: (ES+): 117 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 117.1025 $C_5H_{13}N_2O$, requires 117.1028.

***(S)*-2-Amino-3-methyl-*N*-propylbutanamide 5d**




Prepared according to method B, at 110 °C for 5 h to yield a colourless oil (131 mg, 83%, er 91:9, determined using Marfey's reagent); $[\alpha]_D^{25}$ −3.8 (*c* 1.0, MeOH); $\nu_{max}$ (solid/cm$^{-1}$) 3311 (N-H), 2900 (C-H), 1645 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.73 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH), 0.84 (t, *J* = 7.4 Hz, 3H, C*H*$_3$CH$_2$), 0.90 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH), 1.35 (br s, 2H, N*H*$_2$), 1.44 (sx, *J* = 7.4 Hz, 2H, C*H*$_2$CH$_3$), 2.16-2.23 (m, C*H*(CH$_3$)$_2$), 3.06-3.20 (m, 3H, C*H*NH$_2$ and C*H*$_2$NH), 7.31 (br s, 1H, NH); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 16.1, 19.8, 23.0, 30.9, 40.7, 60.2, 174.4; HRMS: Found (CI): [M+H]$^+$ 157.149348 $C_8H_{19}N_2O$, requires 159.14974.

**(*S*)-2-Amino-4-methyl-*N*-propylpentanamide 5e**

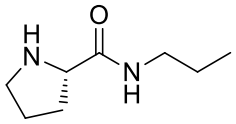


Prepared according to method A, at 80 °C for 15 h to give a colourless oil (63 mg, 73%, er >99:1, determined using Marfey's reagent); $[\alpha]_D^{20}$ +5.2 (*c* 2.0, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3325 (N-H), 2849 (C-H), 1661 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.83-0.87 (m, 6H, C*H*$_3$CH$_2$ and C*H*$_3$CH), 0.89 (d, *J* = 6.4 Hz, 3H C*H*$_3$CH), 1.24-1.29 (m, 1H, C*H*(CH$_3$)$_2$), 1.33-1.49 (m, 4H, NH$_2$ and C*H*$_2$CH$_3$), 1.58-1.70 (m, 2H, C*H*$_2$CH), 3.30 (dd, *J* = 9.8, 3.8 Hz, 1H, C*H*NH$_2$), 3.13 (app. q, *J* = 6.6 Hz, 2H, NHC*H*$_2$), 7.30 (br s, 1H, NH); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 21.4, 22.9, 23.5, 24.9, 40.7, 44.2, 53.6, 175.7; HRMS: Found (CI): $[M+H]^+$ 173.165643 $C_9H_{21}N_2O$, requires 173.16539.

Scale up procedure:

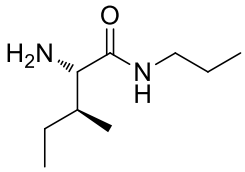
Prepared according to method A, at 80 °C for 15 h to yield a colourless oil (1.49 g, 87%, er >99:1, determined using Marfey's reagent); $[\alpha]_D^{25}$ +5.2 (*c* 2.0, MeOH); Spectroscopic data identical to **5e*.***

***(S)-N*-Propylpyrrolidine-2-carboxamide 5f**



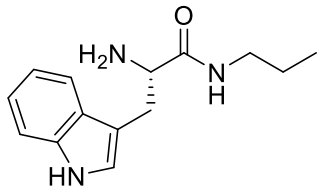
Prepared according to method A, at 80 °C for 15 h to give a colourless oil (142 mg, 91%, er > 99:1, determined using Marfey's reagent); $[\alpha]_D^{25}$ −63.2 (*c* 1.0, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3325 (N-H), 2899 (C-H), 1660 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.84 (t, *J* = 7.4 Hz, 3H, $CH_3$), 1.40-1.49 (m, 2H, C*H*$_2$CH$_3$), 1.57-1.67 (m, 2H, CHCH$_2$C*H*$_2$), 1.82 (app sx, *J* = 6.4 Hz, 1H, CHC*H*H), 2.00-2.29 (m, 2H, NH and CHCH*H*), 2.81 (dt, *J* = 10.2, 6.3 Hz, 1H, C*H*HNH), 2.93 (dt, *J* = 10.2, 6.8 Hz, 1H, CH*H*NH) 3.06-3.16 (m, 2H, CONHC*H*$_2$), 3.64 (dd, *J* = 9.2, 5.3 Hz, 1H, CH), 7.60 (br s, 1H, CONH); $\delta_C$ (150 MHz, $CDCl_3$) 11.4, 23.0, 26.3, 30.9, 40.6, 47.3, 60.6, 175.2; HRMS: Found (CI): $[M+H]^+$ 157.134661 $C_8H_{17}N_2O$, requires 157.13409.

***(2S,3S)*-2-Amino-3-methyl-*N*-propylpentanamide 5g**



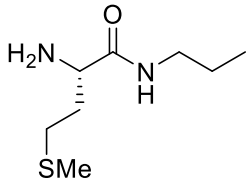
Prepared according to method A, at 125 °C for 15 h to give a yellow oil (155 mg, 90%, dr 75:25) or according to method B, at 125 °C for 5 h to give a yellow oil (131 mg, 76%, dr 83:17); $[\alpha]_D^{20}$ +3.41 (*c* 1.2, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3325 (N-H), 2899 (C-H), 1660 (C=O); $\delta_H$ (600 MHz, $CDCl_3$, both diastereoisomers reported, where possible major (*) and minor (†) peaks are denoted) 0.72† (d, *J* = 6.9 Hz, 0.51H, C*H*$_3$CH), 0.84* (t, *J* = 7.4 Hz, 2.51H, C*H*$_3$CH$_2$CH$_2$NH), 0.87* (t, *J* = 7.4 Hz, 3.41H), 0.91* (d, *J* = 7.0 Hz, 2.51H, C*H*$_3$CH),1.04* (m, 0.83H, CH$_3$CH$_2$C*H*), 1.27-1.20† (m, 0.34H, CH$_2$), 1.38-1.28 (m, 2.62H), 1.52-1.44 (m, 2.07H), 1.96- 1.89 (m, 0.83H), 2.03 (m, 0.17H), 3.24-3.08 (m, 2.70H), 3.29† (d, *J* = 3.2 Hz, 0.17H, COC*H*), 7.30* (br s, 0.83H, NH), 7.41† (br s, 0.17H, NH); $\delta_C$ (150 MHz, DMSO-*d6*) 11.4, 11.5, 11.6, 11.8, 13.6, 15.9, 22.5, 22.5, 23.8, 26.1, 37.9, 38.5, 40.1, 57.7, 59.4, 174.5; LRMS: (CI): 173 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 173.16480 $C_9H_{21}N_2O$, requires 173.16484.

**(*S*)-2-Amino-3-(1H-indol-3-yl)-*N*-propylpropanamide 5h**



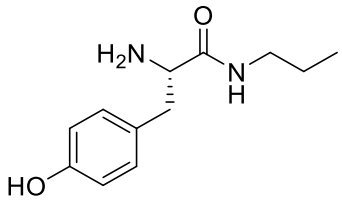
Prepared according to method B, at 80 °C for 5 h to yield a brown oil (203 mg, 83%, er 92:8, determined using Marfey's reagent); Product can be further purified by column chromatography (EtOAc:MeOH gradient from 0 to 10 % MeOH) to give a brown oil (193 mg, 79%); $[\alpha]_D^{25}$ +11.2 (*c* 0.95, MeOH, 25 °C); $\nu_{max}$ (film/cm$^{-1}$) 3261 (N-H), 2960, 2927, 2872, 1641 (C=O), 1522; $\delta_H$ (600 MHz, $CDCl_3$) 0.87 (t, *J* = 7.4 Hz, 3H, $CH_3$), 1.48 (s, *J* = 7.2 Hz, 2H, C*H*$_2$CH$_3$), 2.89 (dd, *J* = 14.5, 9.0 Hz, 1H, ArCH*H*), 3.21 (m, 2H, NHC*H*$_2$), 3.37 (dd, *J* = 14.5, 4.1 Hz, 1H, ArC*H*H), 3.69 (dd, *J* = 9.0, 4.2 Hz, 1H, COC*H*), 7.02 (d, *J* = 2.0 Hz, 1H, ArH), 7.09 (m, 1H, ArH), 7.18 (m, 1H, ArH), 7.32 (t, *J* = 5.4 Hz, 1H, CON*H*), 7.36 (d, *J* = 8.1 Hz, 1H, ArH), 7.64 (d, *J* = 7.9 Hz, 1H, ArH), 8.72 (s, 1H, NH); $\delta_C$ (150 MHz, $CDCl_3$) 175.1, 136.6, 127.6, 123.4, 123.4, 122.2, 119.5, 119.0, 111.5, 55.8, 40.9, 31.0, 22.9, 11.5; LRMS: (ES+): 246 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 246.1606 $C_{14}H_{20}N_3O$, requires 246.1606.

***(S)*-2-Amino-4-(methylthio)-*N*-propylbutanamide 5i**



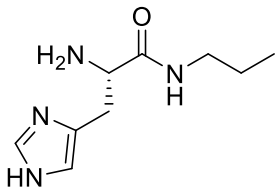

Prepared according to method A, at 80 °C for 15 h to give a colourless oil (77 mg, 81%, er 96:4, determined using aldehyde method); $[\alpha]_D^{20}$ +6.0 (*c* 0.92 MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3349 (N-H), 2901 (C-H), 1648 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.83 (t, *J* = 7.4 Hz, 3H, $CH_3$), 1.44 (sx, *J* = 7.3 Hz, 2H, C*H*$_2$CH$_3$), 1.49 (br s, 2H, $NH_2$), 1.63-1.70 (m, 1H, C*H*HCH), 2.01 (s, 3H, $SCH_3$), 2.01-2.08 (m, 1H, CH*H*CH), 2.51 (t, *J* = 7.4 Hz, 2H, C*H*$_2$S), 3.11 (q, *J* = 6.9 Hz, 2H, NHC*H*$_2$), 3.38 (dd, *J* = 8.1, 4.7 Hz, 1H, CH), 7.27 (br s, 1H, NH); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 15.4, 22.9, 30.7, 34.3, 40.8, 54.4, 174.6; Found (CI): $[M+H]^+$ 191.121334 $C_8H_{19}N_2SO$, requires 191.12181.

***(S)*-2-Amino-3-(4-hydroxyphenyl)-*N*-propylpropanamide 5j**



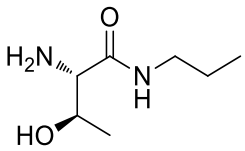

Prepared according to method A, at 80 °C for 15 h to give a yellow oil (60 mg, 27%, er 85:15, determined using chiral HPLC); $[\alpha]_D^{25}$ +4.3 (*c* 0.63, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3291, 2961, 2929, 1641, 1512; $\delta_H$ (600 MHz, $CDCl_3$) 0.86 (t, *J* = 7.4 Hz, 3H, $CH_3$), 1.48 (m, 2H, C*H*$_2$CH$_3$), 2.61 (dd, *J* = 13.8, 8.9 Hz, 1H, ArCH*H*), 3.09 (dd, *J* = 13.8, 4.4 Hz, 1H, ArC*H*H), 3.18 (m, 2H, NHC*H*$_2$), 3.54 (dd, *J* = 8.9, 4.4 Hz, 1H, COC*H*), 6.79 (d, *J* = 8.4 Hz, 2H, 2 × ArH), 6.98 (d, *J* = 8.4 Hz, 2H, 2 × ArH), 7.34 (t, *J* = 5.8 Hz, 1H, NH); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 22.8, 40.3, 41.1, 56.6, 115.9, 128.4, 130.4, 155.9, 175.1; LRMS (ES+) 223 ([M+H]$^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 223.1443 $C_{12}H_{19}N_2O_2$, requires 223.1447.

**(*S*)-2-Amino-3-(1H-imidazol-4-yl)-*N*-propylpropanamide 5k**



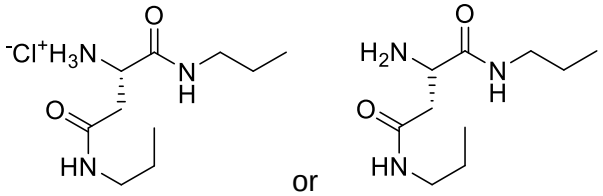
Prepared according to method B, at 125 °C for 15 h to yield a brown oil (147 mg, 37%); Product can be further purified by column chromatography ($CH_2Cl_2$:MeOH 80:20 with 1% $Et_3N$) to give a brown oil (90 mg, 23%); $[\alpha]_D^{20}$ +5.5 (*c* 0.23, MeOH); $\nu_{max}$ (film/$cm^{-1}$) 3203 (N-H), 3096, 2963, 2928, 1641 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.87 (t, *J* = 7.4 Hz, 3H, $CH_3$); 1.49-1.42 (m, 2H, $CH_3CH_2$), 2.95 (dd, *J* = 14.6, 7.2 Hz, 1H, ArC*H*H), 3.03 (dd, *J* = 14.7, 4.3 Hz, 1H, ArCH*H*), 3.18 (app. q, 2H, $CH_3CH_2CH_2$), 3.61 (dd, *J* = 7.2, 4.5 Hz, 1H, COCH), 6.84 (s, 1H, NHC*H*), 7.54 (s, 1H, NCH), 7.54 (br s, 1H, CONH); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 22.9, 29.8, 32.0, 41.0, 55.2, 120.0, 132.4, 135.3, 174.8; LRMS (CI) 197 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 197.13959 $C_9H_{17}N_4O$, requires 197.13969.

***(2S,3R)*-2-Amino-3-hydroxy-*N*-propylbutanamide 5l**



Prepared according to method A, at 80 °C for 15 h in MeCN to give a yellow solid (43 mg, 54%, dr >99:1); mp 75-77 °C; $[\alpha]_D^{20}$ −11.9 (*c* 0.82, MeOH); $\nu_{max}$ (solid/$cm^{-1}$) 3323 (N-H), 3278, 2962, 1646 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.94 (t, *J* = 7.4 Hz, 3H, $CH_2CH_3$), 1.20 (d, *J* = 6.5 Hz, 3H, $CH_3CHOH$), 1.55 (m, 2H, $CH_2CH_3$), 1.77 (br s, 1H, OH), 3.31-3.18 (m, 3H, $CONHCH_2$ and C*H*OH), 4.28 (m, 1H, COC*H*), 7.44 (s, 1H, NH); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 18.8, 23.0, 40.9, 59.5, 68.2, 173.7; LRMS (ES+) 161 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 161.1290 $C_7H_{17}N_2O_2$, requires 161.1290.

***(S)*-2-Amino-*N*$^1$,*N*$^4$-dipropylsuccinamide hydrochloride 5m.HCl or *(S)*-2-Amino-*N*$^1$,*N*$^4$-dipropylsuccinamide 5m**

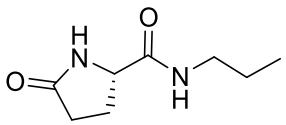



Prepared according to method A, at 80 °C for 15 h to give a colourless oil which was further stirred with 2 M HCl in MeOH and concentrated *in vacuo* to yield a white solid (89 mg, 68%, er 81:19, determined using Marfey's reagent) or prepared according to method B, at 80 °C for 15 h and further purified by column chromatography ($CH_2Cl_2$:MeOH 9:1) to give a white solid (152 mg, 71%, er 89:11, determined using Marfey's reagent);

***(S)*-2-Amino-*N*$^1$,*N*$^4$-dipropylsuccinamide hydrochloride 5m.HCl**: mp 165-167 °C; $[\alpha]_D^{20}$ +8.3 (*c* 0.23, MeOH); $\nu_{max}$ (solid/cm$^{-1}$) 3342 (N-H), 3280 (N-H), 2960, 2930, 2873 (C-H), 1660 (C=O), 1646 (C=O); $\delta_H$ (600 MHz, DMSO-$d_6$) 0.84 (td, $J$ = 7.4, 1.9 Hz, 6H, 2 × $CH_3$), 1.41 (septet, $J$ = 6.9 Hz, 4H, 2 × C$H_2$CH$_3$), 2.63 (dd, $J$ = 16.1, 7.5 Hz , 1H, CHC*H*H), 2.68 (dd, $J$ = 16.1, 5.5 Hz, 1H, CHCH*H*), 2.96-3.13 (m, 4H, 2 × $CH_2$), 4.01 (br s, 1H, CH), 8.22 (br s, 3H, $NH_3^+Cl^-$), 8.30 (br t, $J$ = 5.5 Hz, 1H, NH), 8.46 (br t, $J$ = 5.5 Hz, 1H, NH); $\delta_C$ (150 MHz, DMSO-$d_6$) 11.4, 11.5, 22.1, 22.2, 35.9, 40.4, 40.5, 49.5, 167.7, 168.2; HRMS: Found (CI): $[M\text{-}Cl]^+$ 216.170142 $C_{10}H_{22}N_3O_2$, requires 216.17120.

***(S)*-2-Amino-*N*$^1$,*N*$^4$-dipropylsuccinamide 5m**: mp 130-131 °C; $[\alpha]_D^{20}$ −17.4 (*c* 1.0, MeOH); $\nu_{max}$ (solid/cm$^{-1}$) 3278 (N-H), 2960, 2932, 2872 (C-H), 1633 (C=O), 1546 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.86 (2 × t, $J$ = 7.4, 6H, 2 × $CH_3$), 1.46 (2 × sx, $J$ = 7.4 Hz, 4H, 2 × C$H_2$CH$_3$), 2.21 (s, 2H, $NH_2$), 2.45 (dd, $J$ = 14.6, 8.0 Hz, 1H, CHC*H*H'), 2.61 (dd, $J$ = 14.6, 4.3 Hz, 1H, CHCH*H'*), 3.18 – 3.09 (m, 4H, 2 × C$H_2$CH$_2$CH$_3$), 3.63 (dd, $J$ = 8.0, 4.3 Hz, 1H, $NH_2$C*H*), 6.95 (s, 1H), 7.64 (s, 1H); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 11.5, 22.8, 22.8, 40.8, 41.1, 41.2, 52.8, 171.3, 174.2; LRMS: (ES+): 216 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 216.1713 $C_{10}H_{22}N_3O_2$, requires 216.1712.

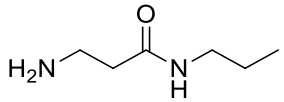
**(*S*)-5-Oxo-N-propylpyrrolidine-2-carboxamide 5n**



Prepared according to method A, at 80 °C for 15 h to yield a white solid (161 mg, 94%, er > 99:1, determined using chiral shift reagent); mp 107-109 °C; $[\alpha]_D^{20}$ −11.3 (*c* 0.25, MeOH); $\nu_{max}$ (solid/cm$^{-1}$) 3289 (N-H), 3090, 2961, 2931, 1695 (C=O), 1652 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.87 (t, *J* = 7.4 Hz, 3H, $CH_3$), 1.48 (sx, *J* = 7.3 Hz, 2H, $CH_3CH_2$), 2.18-2.09 (m, 1H, $CHHCH_2CH$), 2.22-2.28 (m, 1H, $CHHCH_2CH$), 2.34 (m, 1H, $CH_2CHHCH$), 2.45 (m, 1H, $CH_2CHHCH$), 3.17 (m, 2H, $CH_3CH_2CH_2$), 4.12 (dd, *J* = 9.0, 4.7 Hz, 1H, CH), 7.01 (t, *J* = 5.1 Hz, 1H, $CONHCH_2$), 7.64 (s, 1H, CONHCH); $\delta_C$ (150 MHz, $CDCl_3$) 11.5; 22.8, 26.1, 29.5, 41.4, 57.3, 172.2, 179.7; HRMS: LRMS (CI) 188 ($[M+H+CH_4]^+$, 100), 171 ($[M+H]^+$, 30); HRMS: Found (CI): $[M+H]^+$ 171.11281 $C_8H_{15}N_2O_2$, requires 171.11280.

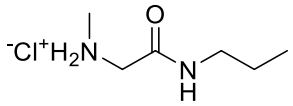
**<u>Amidation of non-proteinogenic amino acids</u>**

**3-Amino-*N*-propylpropanamide 5u**



Prepared according to method A, at 80 °C for 15 h in MeCN to yield an off-white solid (88 mg, 68%); mp 122-125 °C; $\nu_{max}$ (solid/cm$^{-1}$) 3295 (N-H), 2959, 2931, 2872, 1643 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.92 (m, 3H, $CH_3$), 1.51(m, 2H, $CH_3CH_2$), 3.00 (m, 2H), 2.31 (m, 2H), 3.21 (m, 2H, $COCH_2$), 6.97 (s, 1H, NH); $\delta_C$ (151 MHz, $CDCl_3$) 11.6, 23.0, 38.4, 38.7, 41.1, 172.6; LRMS (ES+): 131 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 131.1183 $C_6H_{15}N_2O$, requires 131.1179.

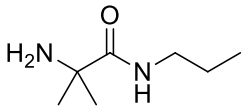
**2-(Methylamino)-*N*-propylacetamide hydrochloride 5v.HCl**



Prepared according to method A, at 80 °C for 15 h to give a colourless oil which was further stirred with 2 M HCl in MeOH to yield a white solid (72 mg, 84%); mp 128-129 °C; $\nu_{max}$ (solid/cm$^{-1}$) 3340 (N-H), 2901 (C-H), 1659 (C=O); $\delta_H$ (600 MHz, DMSO-$d_6$) 0.86 (t, *J* = 7.3 Hz,

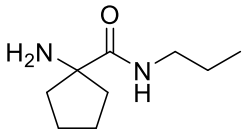
3H, C*H*$_3$CH$_2$), 1.43 (sx, *J* = 7.3 Hz, 2H, CH$_2$CH$_3$), 2.52 (s, 3H, C*H*$_3$NH$_2^+$Cl$^-$), 3.07 (m, 2H, CH$_2$CH$_2$CH$_3$), 3.65 (s, 2H, CH$_2$NH), 8.56 (br s, 1H, NH), 8.99 (br s, 2H, NH$_2^+$Cl$^-$); $\delta_C$ (150 MHz, DMSO-$d_6$) 11.4, 222, 32.6, 40.4, 48.9, 164.8; HRMS: Found (CI): [M-Cl]$^+$ 131.117931 $C_6H_{15}N_2O$, requires 131.11844.

**2-Amino-2-methyl-*N*-propylpropanamide 5w**



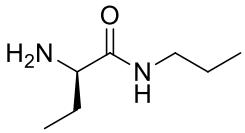
Prepared according to method A, at 125 °C for 15 h to yield a pale yellow oil (99 mg, 70%); $\nu_{max}$ (film/cm$^{-1}$) 3350 (br, N-H), 2964, 2930, 2873, 1642 (C=O), 1524, 1461; $\delta_H$ (500 MHz, $CDCl_3$) 0.83-0.96 (m, 3H, CH$_2$C*H*$_3$), 1.33 (s, 6H, (C*H*$_3$)$_2$), 1.46-1.53 (m, 4H, N*H*$_2$ and C*H*$_2$CH$_3$), 3.13-3.25 (m, 2H, NHC*H*$_2$), 7.61 (br s, 1H); $\delta_C$ (150 MHz, $CDCl_3$) 11.4, 22.9, 29.4, 40.9, 54.9, 177.5; LRMS (ES+) 145.1 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 145.1339, $C_8H_{19}N_2O$, requires 145.1341.

**1-Amino-*N*-propylcyclopentanecarboxamide 5x**



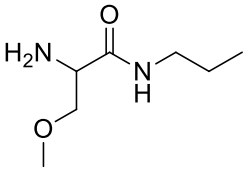
Prepared according to method A, at 125 °C for 15 h to yield a yellow oil (98 mg, 58%); $\nu_{max}$ (film/cm$^{-1}$) 3300 (N-H), 2957 (C-H), 2871 (C-H), 1651 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 0.93 (t, *J* = 7.4 Hz, 3H, CH$_3$), 1.47-1.42 (m, 2H, CH$_2$C*H*HC*H*HCH$_2$), 1.54 (app. sx, *J* = 7.3 Hz, 2H, C*H*$_2$CH$_3$), 1.80-1.73 (m, 2H, CH$_2$C*H*HC*H*HCH$_2$), 1.85 (td, *J* = 6.8, 3.4 Hz, 2H, C*H*H CH$_2$ CH$_2$C*H*H), 2.26-2.23 (m, 2H, C*H*H CH$_2$ CH$_2$C*H*H), 3.22 (app q, *J* = 6.7 Hz, 2H, NHC*H*$_2$), 7.80 (s, 1H, NH); $\delta_C$ (150 MHz, $CDCl_3$) 11.5, 23.0, 24.5, 40.6, 41.1, 65.2, 177.3; LRMS (CI) 171 ([M+H]$^+$, 100); HRMS: Found (CI): [M+H]$^+$ 171.1491 $C_9H_{19}N_2O$, requires 171.1492.

**(*R*)-2-Amino-*N*-propylbutanamide 5y**



Prepared according to method B, at 80 °C for 5 h to yield a pale yellow oil (120 mg, 83%, er 94:6, determined using Marfey's reagent); $[\alpha]_D^{20}$ −9.6 (*c* 1.0, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3297 (br, N-H), 2964, 2934, 2876, 1645 (C=O), 1527, 1459; $\delta_H$ (600 MHz, $CDCl_3$) 0.89 (t, *J* = 7.4 Hz, 3H, $CH_2CH_3$), 0.93 (t, *J* = 7.4 Hz, 3H, $CH_2CH_3$), 1.43-1.63 (m, 5H, $NH_2$ and $CH_3CHHCHNH_2$, $CH_3CH_2CH_2$), 1.81-1.85 (m, 1 H, $CH_3CHHCHNH_2$), 3.16-3.21 (m, 2 H, $CH_3CH_2CH_2$) 3.26 (m, 1 H, $NH_2CH$) 7.27 (br s, 1 H, N*H*); $\delta_C$ (150 MHz, $CDCl_3$) 10.1, 11.5, 23.0, 28.2, 40.8, 56.5, 174.9; LRMS (ES+) 145 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 145.1346 $C_7H_{17}N_2O$, requires 145.1341.

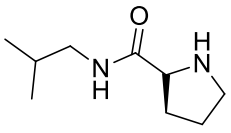
**(±)-2-Amino-3-methoxy-*N*-propylpropanamide 5z**



Prepared according to method B, at 80 °C for 3 h to yield a colourless oil (133 mg, 83%); $\nu_{max}$ (film/cm$^{-1}$) 3305 (br, N-H), 3098, 2963, 2931, 2875, 2649, 1530; $\delta_H$ (600 MHz, $CDCl_3$) 0.86 (t, *J* = 7.4 Hz, 3H, $CH_2CH_3$), 1.47 (app sx, *J* = 7.3 Hz, 2H, $CH_2CH_3$), 1.76 (br s, 2H, $NH_2$), 3.14 (m, 2H, $NHCH_2$), 3.31 (s, 3H, $OCH_3$), 3.48-3.57 (m, 3H, $CHCH_2$), 7.42 (br s, 1H, N*H*); $\delta_C$ (150 MHz, $CDCl_3$) 11.4, 22.9, 40.8, 54.9, 58.9, 74.7, 172.7; LRMS (ES+) 161 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 161.1282 $C_7H_{16}N_2O_2$, requires 161.1285.

**Amine scope**

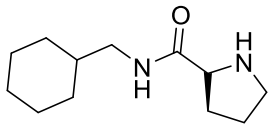
***(S)*-*N*-Isobutylpyrrolidine-2-carboxamide 6a**



Prepared according to method A, at 80 °C for 15 h and further purified by column chromatography ($CH_2Cl_2$:MeOH gradient from 100:0 to 10:1) to yield a colourless oil (114 mg, 67%, er 99:1, determined using Marfey's reagent); $[\alpha]_D^{25}$ −57.0 (*c* 0.8, MeOH); $\nu_{max}$ (film/cm$^{-1}$)

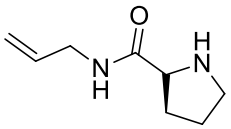
3302 (br, NH), 3069, 2957, 2869, 1652 (C=O), 1525, 1466; $\delta_H$ (600 MHz, $CDCl_3$) 0.87-0.90 (m, 6 H, ($CH_3$)$_2$), 1.66-1.76 (m, 3H, $CH_2CH_2CH$, $CH(CH_3)_2$), 1.89-1.92 (m, 1H, $CH_2CHHCH$), 2.10-2.14 (m, 1H, $CH_2CHHCH$), 2.26 (br s, 1H, $CH_2NHCH$), 2.87-2.90 (m, 1H, $CHHNHCH$), 2.99-3.07 (m, 2H, $CH_3CHCH_2$), 3.05-3.08 (m, 1H, $CHHNHCH$), 3.71-3.74 (m, 1H, $CHCON$), 7.70 (br s, 1H, $CONH$); $\delta_C$ (150 MHz, $CDCl_3$) 20.2, 26.3, 28.7, 30.9, 46.3, 47.4, 60.7, 175.0; LRMS (ES+) 171 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 171.1495 $C_9H_{19}N_2O$, requires 171.1497.

***(S)-N*-(Cyclohexylmethyl)pyrrolidine-2-carboxamide 6b**



Prepared according to method A, at 80 °C for 15 h and further purified by column chromatography ($CH_2Cl_2$:MeOH gradient from 100:0 to 10:1) to yield a colourless oil (154 mg, 73%, er 99:1, determined using Marfey's reagent); $[\alpha]_D^{25}$ −33.5 (*c* 1.0, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3306 (br, NH), 2920, 2850, 1650 (C=O), 1524, 1447; $\delta_H$ (600 MHz, $CDCl_3$) 0.87-0.90 (m, 2H, $CyCH_2$), 1.11-1.24 (m, 3H, $CyCH_2$), 1.66-1.76 (m, 3H, $CyCH_2$), 1.66-1.76 (m, 7H, $CyCH_2$ and $CH_2CH_2CH$, $CH(CH_2)_2$), 1.87-1.91 (m, 1H, $CH_2CHHCH$), 2.08-2.14 (m, 2H, $CH_2NHCH$ and $CH_2CHHCH$), 2.85-2.90 (m, 1H, $CHHNHCH$), 2.97-3.09 (m, 3H, $CHHNHCH$ and $CONCH_2$), 3.69-3.72 (m, 1H, $NHCHCO$), 7.66 (br s, 1H, $NH$); $\delta_C$ (150 MHz, $CDCl_3$) 25.9, 26.3, 26.5, 30.9, 30.9, 38.1, 45.2, 47.4, 60.8, 175.1; LRMS (ES+) 211 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 211.1806 $C_{12}H_{23}N_2O$, requires 211.1810.

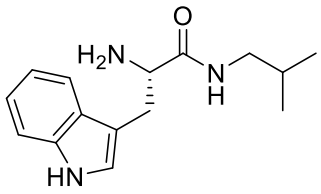
***(S)-N*-Allylpyrrolidine-2-carboxamide 6c**



Prepared according to method A, at 80 °C for 15 h and further purified by column chromatography ($CH_2Cl_2$:MeOH:$Et_3N$ gradient from 100:0:1 to 100:10:1) to yield a pale brown oil (122 mg, 89%, er 99:1, determined using Marfey's reagent); $[\alpha]_D^{25}$ −72.3 (*c* 0.8, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3305 (br, NH), 3078, 2966, 2871, 1639 (C=O), 1518, 1419, 1338; $\delta_H$ (600 MHz, $CDCl_3$) 1.64-1.77 (m, 2H, $CHCH_2CH_2CH$), 1.85-1.94 (m, 1H, $CH_2CHHCH$), 2.07-2.16 (m, 3H, $CH_2CHHCH$, and $NH_2$), 2.89 (td, *J* = 10.2, 6.3 Hz, 1H, $CH_2CHHNH$), 3.00 (td, *J* = 10.2, 6.8

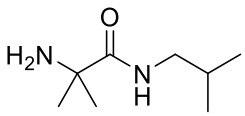
Hz, 1H, CH*H*NH), 3.74 (dd, *J* = 9.2, 5.3 Hz, 1H, NHC*H*), 3.78-3.90 (m, 2H, $CH_2$=CHC$H_2$), 5.09 (d, *J* = 10.3 Hz, 1H, CH*H*=CH), 5.13 (d, *J* = 17.1 Hz, 1H, CH*H*=CH), 5.82 (dtt, *J* = 17.1, 10.4, 5.4 Hz, 1H, $CH_2$=C*H*), 7.74 (br s, 1H, N*H*); $\delta_C$ (150 MHz, $CDCl_3$) 26.3, 30.9, 41.3, 47.4, 60.7, 115.8, 134.6, 175.2; LRMS (ES+) 155 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 155.1182, $C_8H_{20}N_2O$, requires 155.1184.

***(S)*-2-Amino-3-(1H-indol-3-yl)-*N*-isobutylpropanamide 6d**



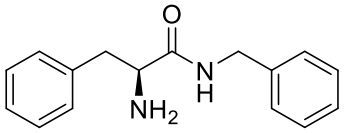

Prepared according to method B, at 80 °C for 5 h to yield a dark brown oil (201 mg, 78%, er 93:7, determined using Marfey's reagent); Product can be further purified by column chromatography (EtOAc:MeOH gradient from 0 to 10 % MeOH) to give a brown oil (192 mg, 74%); $[\alpha]_D^{20}$ +6.9 (*c* 1.3, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3270 (br), 2956, 2925, 2870, 1644 (C=O), 1528, 1435; $\delta_H$ (600 MHz, $CDCl_3$) 0.88 (d, *J* = 6.7 Hz, 6H, (C$H_3$)$_2$), 1.75 (m, 1H, $CH_2$C*H*), 2.90 (dd, *J* = 15.0, 9.0 Hz, 1H, CC$H_2$), 3.09 (m, 2H, C$H_2$CH(C$H_3$)$_2$), 3.40 (dd, *J* = 14.8, 4.2 Hz, 1H, CC$H_2$), 3.73 (dd, *J* = 9.1, 4.2 Hz, 1H, C*H*$NH_2$), 7.07 (d, *J* = 2.3 Hz, 1H, ArH), 7.12 (dd, *J* =7.9, 7.0 Hz, 1H, ArH), 7.20 (dd, *J* = 8.1, 7.1 Hz, 1H, ArH), 7.38 (m, 2H, ArH and CON*H*), 7.68 (d, *J* = 7.9 Hz, 1H, ArH), 8.44 (br s, 1H, Ar-NH); $\delta_C$ (150 MHz, $CDCl_3$) 20.2, 28.6, 31.0, 46.5, 55.8, 111.4, 111.9, 119.1, 119.7, 122.3, 123.2, 127.6, 136.6, 174.9; LRMS (ES+) 260 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 260.1761 $C_{15}H_{22}N_3O$, requires 260.1763.

**2-Amino-*N*-isobutyl-2-methylpropanamide 6e**



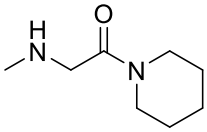

Prepared according to method A, at 125 °C for 15 h to yield a pale brown oil (129 mg, 82%); $\nu_{max}$ (film/cm$^{-1}$) 3350 (br, NH), 2959, 2928, 2871, 1643 (C=O), 1521, 1467; $\delta_H$ (600 MHz, $CDCl_3$) 0.86 (d, *J* = 6.6, 3H, CH(C$H_3$)$_2$), 0.88 (d, *J* = 6.8, 3H, CH(C$H_3$)$_2$), 1.26-1.36 (s, 6H, C(C$H_3$)$_2$), 1.53 (br s, 2H, N$H_2$), 1.66-1.79 (m, 1H, C*H*(C$H_3$)$_2$), 2.96-3.07 (m, 2H, C$H_2$), 7.69 (br s, 1H, N*H*); $\delta_C$ (150 MHz, $CDCl_3$) 20.2, 28.6, 29.4, 46.6, 54.9, 177.5; LRMS (ES+) 159.2 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 159.1494 $C_8H_{19}N_2O$, requires 159.1497.

**(*S*)-2-Amino-*N*-benzyl-3-phenylpropanamide 6f**



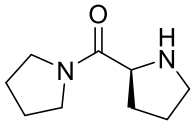
Prepared according to method B, at 80 °C for 3 h and further purified by column chromatography ($CH_2Cl_2$:MeOH gradient from 100:0 to 100:10) to yield a white solid (184 mg, 72%, er 94:6, determined using Marfey's reagent); mp 68-69 °C [lit.[6] 67-71 °C]; $[\alpha]_D^{25}$ +9.8 (*c* 1.2, MeOH); $\nu_{max}$ (solid/$cm^{-1}$) 3314 (br), 3062, 3028, 2981, 2926, 1733, 1651 (C=O), 1603; $\delta_H$ (600 MHz, $CDCl_3$) 1.37 (br s, 2H, N*H*$_2$), 2.77 (dd, *J* = 13.8, 9.2, Hz 1H, PhCH*H*), 3.31 (dd, *J* = 13.7, 4.1 Hz, 1H, PhC*H*H), 3.67 (dd, *J* = 9.1, 4.1 Hz, 1H, C*H*CO), 4.43 (dd, *J* = 14.8, 5.8, 1H, CHC*H*$_2$), 4.47 (dd, *J* = 14.8, 6.0, 1H, CHC*H*$_2$), 7.20-7.37 (m, 10H, Ar*H*), 7.59 (br s, 1H, N*H*); $\delta_C$ (150 MHz, $CDCl_3$) 41.2, 43.3, 56.6, 126.9, 127.5, 127.9, 128.8, 128.8, 129.5, 138.0, 138.5, 174.2; LRMS (ES+) 255 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 255.1500 $C_8H_{20}N_2O$, requires 255.1497. Data in agreement with the literature.[6]

**2-(Methylamino)-1-(piperidin-1-yl)ethan-1-one 6g**



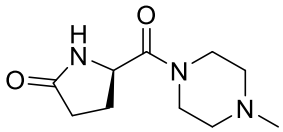
Prepared according to method A, at 125 °C for 15 h. Product was further purified by column chromatography ($CH_2Cl_2$:MeOH gradient from 100:0 to 10:1) to yield a pale brown oil (123 mg, 79%); $\nu_{max}$ (film/$cm^{-1}$) 3401 (br, NH), 2932, 2854, 1629 (C=O), 1468; $\delta_H$ (600 MHz, $CDCl_3$) 1.54-1.57 (m, 4H, 2 × $NCH_2CH$*H*, $NCH_2CH_2CH_2$), 1.63-1.66 (m, 2 H, 2 × $NCH_2CH$*H*), 2.27 (br s, 1H, N*H*), 2.44 (s, 3H, C*H*$_3$), 3.31 (t, *J* = 5.5 Hz, 2H, NC*H*$_2$), 3.38 (s, 2H, NHC*H*$_2$), 3.56 (t, *J* = 5.5 Hz, 2H, NC*H*$_2$); $\delta_C$ (150 MHz, $CDCl_3$) 24.6, 25.6, 26.5, 36.7, 43.1, 45.6, 52.2, 169.1; HRMS: Found (ES+): $[M+H]^+$ 157.1331 $C_8H_{17}N_2O$, requires 157.1335.

***(S)*-1-Prolylpyrrolidine 6h**



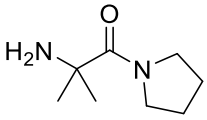
Prepared according to method B at 125 °C for 15 h to give a dark brown oil (145 mg, 86%, er 96:4, determined using Marfey's reagent); $[\alpha]_D^{25}$ −72.3 (*c* 1.0 MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3405 (br, N-H)), 2968, 2875, 1625 (C=O), 1596, 1453; $\delta_H$ (500 MHz, $CDCl_3$) 1.54-1.67 (m, 2H, $CHCH_2CH_2$), 1.68-1.72 (m, 1H, CHC*H*H), 1.77 (q, 2H *J* = 6.8 Hz, $CH_2CHHCHHCH_2$), 1.87 (q, 2H, *J* = 6.8 Hz, $CH_2CHHCHHCH_2$), 1.98-2.03 (m, 1H, CHC*H*H), 2.71-2.76 (m, 1H, C*H*HNH), 3.06-3.11 (m, 2H, C*H*HN*H)*, 3.27-3.45 (m, 4H, 2 × $NCH_2$), 3.68 (t, *J* = 7.4 Hz, 1H, C*H*); $\delta_C$ (125 MHz, $CDCl_3$) 24.1, 26.1, 26.5, 30.4, 45.9, 46.0, 47.7, 59.6, 172.60; LRMS (EI+) 168.1, 126.09 ($[M+H]^+$, 50, 100); HRMS: Found (ES+): $[M+H]^+$ 168.12568, $C_9H_{16}N_2O$, requires 168.12571.

**(*R*)-5-(4-Methylpiperazine-1-carbonyl)pyrrolidin-2-one 6i**



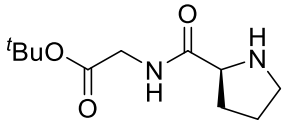
Prepared according to method B, at 125 °C for 15 h. During the resin workup, Amberlyst 15 was also used, and the corresponding crude was further purified by column chromatography ($CH_2Cl_2$:MeOH gradient from 95:5 to 10:1) to yield a clear oil (130 mg, 62%, er 97:3, determined using chiral shift method); $[\alpha]_D^{25}$ +23.5 (*c* 1.0, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3244 (br, NH), 2939, 2798, 1683 (C=O), 1657 (C=O), 1457; $\delta_H$ (600 MHz, $CDCl_3$), 2.08-2.10 (m, 1H, C*H*HCON), 2.28 (s, 3H, $CH_3$), 2.30-2.44 (m, 7H, CH*H*CON, $CHCH_2$, $CH_3N(CH_2)_2$), 3.44-3.46 (m, 2H, $CH_2NCO$), 3.60-3.63 (m, 2H, $CH_2NCO$), 4.46 (dd, *J* = 8.2, 5.4 Hz, 1H, C*H*), 6.79 (br s, 1H, N*H*); $\delta_C$ (150 MHz, $CDCl_3$) 25.4, 29.6, 42.2, 44.9, 46.0, 54.1, 54.6, 54.9, 169.9, 178.3; LRMS: (ES+): 212.1 ($[M+H]^+$, 20), 423.3 ($[2M+H]^+$, 100); LRMS: (ES+): 212.2 ($[M+H]^+$, 20), 423.3 ($[2M+H]^+$, 50), 634.4 ($[3M+H]^+$,100); HRMS: Found (ES+): $[M+H]^+$ 212.1401 $C_{10}H_{17}N_3O_2$, requires 212.1399.

**2-Amino-2-methyl-1-(pyrrolidin-1-yl)propan-1-one 6j**



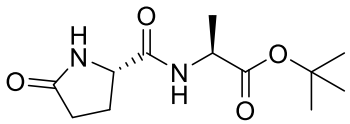
Prepared according to method B, at 125 °C for 15 h and further purified by column chromatography ($CH_2Cl_2$:MeOH gradient from 100:0 to 10:1) to yield a colourless oil (78 mg, 51%); $\nu_{max}$ (film/cm$^{-1}$) 3405 (br, NH), 2966, 2923, 1648 (C=O), 1596; $\delta_H$ (600 MHz, $CDCl_3$) 1.40 (s, 6H, $(CH_3)_2$), 1.82 (br s, 2H, $NCH_2CH_2$), 1.93 (br s, 2H, $NCH_2CH_2$), 1.99 (br s, 2H, $NH_2$), 3.51 (br s, 2H, $NCH_2$), 3.68 (br s, 2H, $NCH_2$); $\delta_C$ (150 MHz, $CDCl_3$) 23.3 (br), 27.8, 48.3, 55.4, 175.6; LRMS: (ES+): 157.3 ([M+H]$^+$,100); HRMS: Found (ES+): [M+H]$^+$ 157.1337 $C_8H_{17}N_2O$, requires 157.1335.

***tert*-Butyl (S)-prolylglycinate 6k**



Prepared according to method B at 125 °C for 15 h to give a brown oil (168 mg, 74%, er 94:6, determined using Marfey's reagent); $[\alpha]_D^{20}$ −35.9 (*c* 1.0 MeOH); $\nu_{max}$ (solid/cm$^{-1}$) 3309 (br,NH)), 2975, 2874, 1738 (C=O), 1650 (C=O), 1524, 1454; $\delta_H$ (600 MHz, $CDCl_3$) 1.45 (s, 9H, $^t$Bu), 1.69-1.76 (m, 2H, $CHCH_2CH_2$),1.89-1.94 (m, 1H, CHC*H*H), 2.12-2.16 (m, 1H, CHC*H*H), 2.42 (br s, 1H, CHN*H*), 2.95 (dt, *J* = 10.3, 6.3 Hz, 1H, C*H*HNH), 3.02 (dt, *J* = 10.3, 6.8 Hz, 1H, C*H*HNH), 3.79 (dd, *J* = 9.2, 5.3 Hz, 1H, C*H)*, 3.91 (m, 2H, $CH_2$COO), 8.08 (br s, 1H, CONH); $\delta_C$ (150 MHz, $CDCl_3$) 26.2, 28.2, 30.8, 41.6, 47.4, 60.5, 82.1, 169.3, 175.4; LRMS (EI+) 228.10, 155.08 ([M+H]$^+$, 10, 100); HRMS: Found (ES+): [M+H]$^+$ 228.1467, $C_{11}H_{20}N_2O_3$, requires 228.1468.

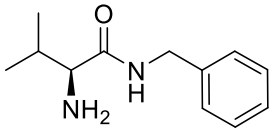
**tert-Butyl ((*S*)-5-oxopyrrolidine-2-carbonyl)-L-alaninate 6l**



Prepared according to method B, at 125 °C for 15 h and further purified by column chromatography ($CH_2Cl_2$:MeOH gradient from 100:0 to 10:1) to yield a colourless oil (212 mg, 83%, dr > 99:1) ; $[\alpha]_D^{20}$ −69.5 (*c* 1.0, MeOH); $\nu_{max}$ (film/cm$^{-1}$) 3274 (br, NH), 2979, 1730 (C=O), 1665 (C=O), 1584 (C=O); $\delta_H$ (600 MHz, $CDCl_3$) 1.36 (d, *J* = 7.15 Hz, 3 H, $CHCH_3$), 1.44 (s, 9 H, $(CH_3)_3$), 2.17-2.22 (m, 1H, CHC*H*H), 2.29-2.34 (m, 1 H, COC*H*H), 2.42-2.47 (m, 1 H,

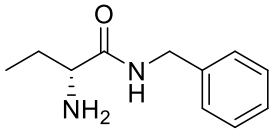
COCH*H*), 2.50-2.53 (m, 1H, CHC*H*H), 4.19 (dd, *J* = 9.0, 5.2 Hz, 1H, C*H*$CH_2$), 4.47 (app q. *J* = 7.4 Hz, 1H, C*H*$CH_3$), 7.23 (br d, *J* = 7.5 Hz, 1H, CON*H*), 7.28 (br s, 1H, CON*H*); $\delta_C$ (150 MHz, $CDCl_3$) 18.3, 25.9, 28.1, 29.5, 48.6, 57.4, 82.4, 172.1, 172.6, 179.7; HRMS: Found (ES+): $[M+H]^+$ 257.1495 $C_{12}H_{21}N_2O_4$, requires 257.1496.

***(S)*-2-Amino-*N*-benzyl-3-methylbutanamide 6m**




Prepared according to method B, at 125 °C for 5 h and further purified by column chromatography (Toluene:MeOH 10:1) to yield a white solid (169 mg, 82%, er 95:5, determined using Marfey's reagent); mp 110-112 °C [lit.[7] 115.1-116.0 °C]; $[\alpha]_D^{25}$ +32.4 (*c* 1.0, MeOH); [Lit.[7] $[\alpha]_D^{25}$ +37.4 (*c* 1.0, MeOH)]; $\nu_{max}$ (solid/$cm^{-1}$) 3286 (br, NH)), 2955, 2925, 2870, 1640 (C=O), 1540, 1494, 1426, 1345; $\delta_H$ (600 MHz, $CDCl_3$) 0.84 (d, *J* = 6.9 Hz, 3H, C$H_3$), 1.01 (d, *J* = 7.0 Hz, 3H, C$H_3$), 1.41 (br s, 2H, N$H_2$), 2.37 (m, 1H, C*H*$CH_3$), 3.29 (d, *J* = 3.3 Hz, 1H, C*H*$NH_2$), 4.43 (dd, *J* = 14.7, 6.0 Hz, 1H, CONHCH*H*), 4.48 (dd, *J* = 14.7, 6.0 Hz, 1H, CONHCH*H*), 7.26-7.30 (m, 3H, ArH), 7.31-7.36 (m, 2H, ArH), 7.65 (br s, 1H, N*H*); $\delta_C$ (150 MHz, $CDCl_3$) 16.1, 19.9, 30.9, 43.2, 60.3, 127.5, 127.9, 128.7, 138.7, 174.4; LRMS (ES+) 207.2 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 207.1499 $C_{12}H_{19}N_2O$, requires 207.1497. Data in agreement with the literature.[7]

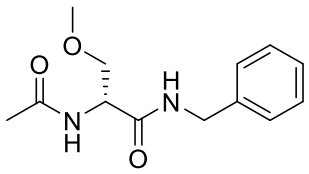
***(R)*-2-Amino-*N*-benzylbutanamide 6n**




Prepared according to method B, at 80 °C for 5 h and further purified by column chromatography (Toluene: MeOH 100:10) to yield a yellow oil (217 mg, 57%, er 94:6, determined using Marfey's reagent); $[\alpha]_D^{20}$ −2.7 (*c* 1.0, MeOH); $\nu_{max}$ (film/$cm^{-1}$) 3291 (br, NH), 3063, 2964, 2875, 1646 (C=O), 1523, 1538; $\delta_H$ (600 MHz, $CDCl_3$) 0.89-1.02 (t, *J* = 8.0 Hz, 3H, $CH_2CH_3$), 1.43-1.63 (m, 2H, 1H, N$H_2$, $CH_3CH_2$), 1.83-1.96 (m, 1H, $CH_3CH_2$), 3.28-3.38 (m, 1H, C*H*$NH_2$) 4.38-4.48 (m, 2H, NHC$H_2$) 7.20-7.38 (m, 5H, ArH), 7.65 (br s, 1H, N*H*); $\delta_C$ (150 MHz, $CDCl_3$) 10.2, 28.2, 43.2, 56.5, 127.5, 127.8, 128.8, 138.7, 175.1; LRMS (ES+) 193 ($[M+H]^+$, 100); HRMS: Found (ES+): $[M+H]^+$ 193.1343 $C_{11}H_{17}N_2O$, requires 193.1341. Data in agreement with the literature.[8]

**Synthesis of Lacosamide (anti-epileptic)**

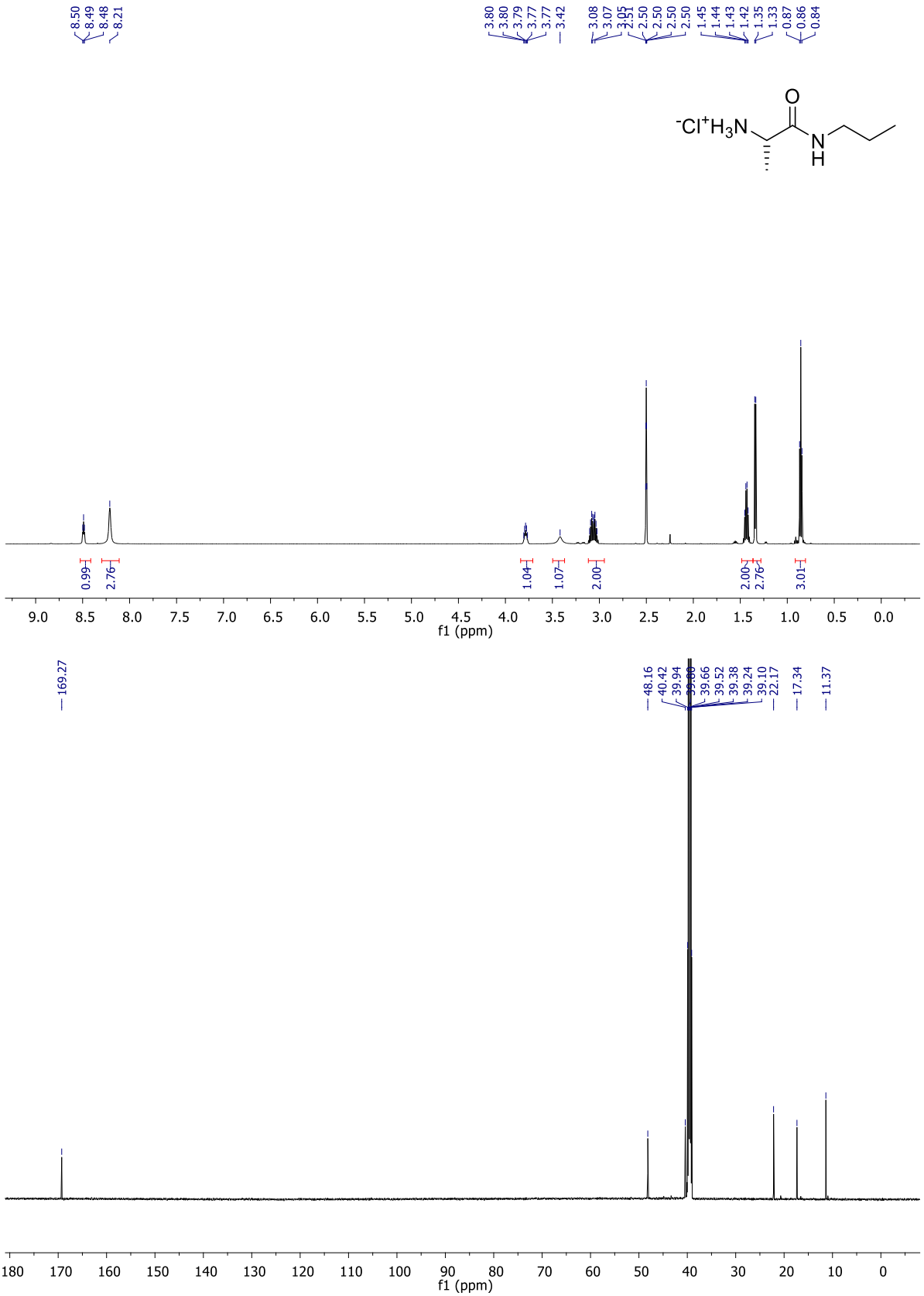
**(*R*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide (Lacosamide) 7**



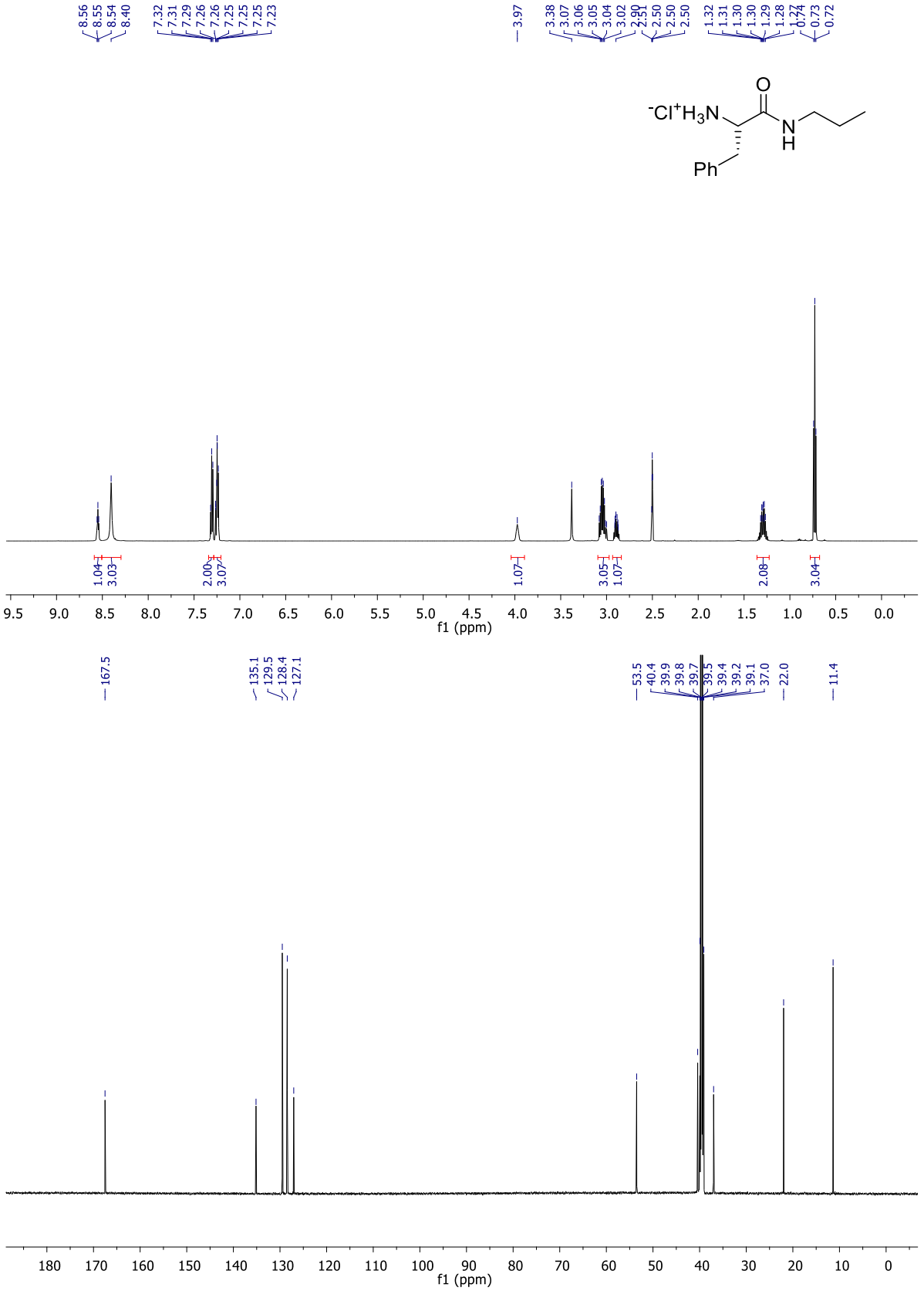
A solution of $B(OCH_2CF_3)_3$ (3.0 mmol, 3.0 equiv.) in CPME (1 mL) was added dropwise to a mixture of *O*-methyl-D-serine (119 mg, 1.0 mmol) and benzylamine (0.327 mL, 3.0 mmol) in CPME (1 mL) over 1 h at 125 °C. The resulting mixture was stirred for 3 h at 125 °C. Upon completion, the mixture was diluted with EtOAc (3 mL) and water (0.5 mL). Amberlite IRA-743 and Amberlyst A-26(OH) were added and stirred for 30 min. The mixture was dried over $MgSO_4$ and then filtered. The solids were washed with EtOAc (3 × 20 mL) and the product concentrated *in vacuo.* The crude product was purified by column chromatography ($CH_2Cl_2$:MeOH 95:5) to give a colourless oil which was directly reacted with acetic anhydride (0.21 mL, 2.2 mmol, 2 equiv.) and a catalytic amount of DMAP (12 mg, 0.05 equiv.) in $CH_2Cl_2$ (5 mL) under inert atmosphere at room temperature. After 2 h of stirring, the reaction mixture was concentrated *in vacuo* to give a yellow solid, which was further purified by column chromatography ($CH_2Cl_2$:MeOH 98:2) and recrystallised from hot EtOAc to give Lacosamide as a white solid (311 mg, 62% er 94:6, determined using chiral HPLC); mp 135-136 °C [lit.[9] 140 °C]; $[\alpha]_D^{25}$ +12.1 (*c* 1.0, MeOH) [lit.[9] $[\alpha]_D^{25}$ +16.2 (*c* 1.0, MeOH)]; $\nu_{max}$ (solid/$cm^{-1}$) 3284 (br, NH), 3067, 2921, 2888, 2873, 2806, 1631 (C=O), 1539; $\delta_H$ (600 MHz, $CDCl_3$) 2.01 (s, 3H, C*H*$_3$CO), 3.36 (s, 3H, C*H*$_3$O), 3.44 (dd, *J* = 9.2, 7.4 Hz, 1H, C*H*$_2$), 3.78 (dd, *J* = 9.2, 4.1 Hz, 1H, C*H*$_2$), 4.46 (d, *J* = 5.6 Hz, 2H, CONC*H*$_2$), 4.56 (dd, *J* = 7.4, 4.1 Hz, 1H, C*H*); $\delta_C$ (150 MHz, $CDCl_3$) 23.3, 43.7, 52.5, 59.2, 71.9, 127.6, 127.6, 128.8, 138.0, 170.1, 170.5; LRMS (ES+) 251 ([M+H]$^+$, 100); HRMS: Found (ES+): [M+H]$^+$ 251.1393 $C_{13}H_{18}N_2O_3$, requires 251.1390. Data in agreement with the literature.[9]

## 6. $^{1}H$ and $^{13}C$ NMR spectra

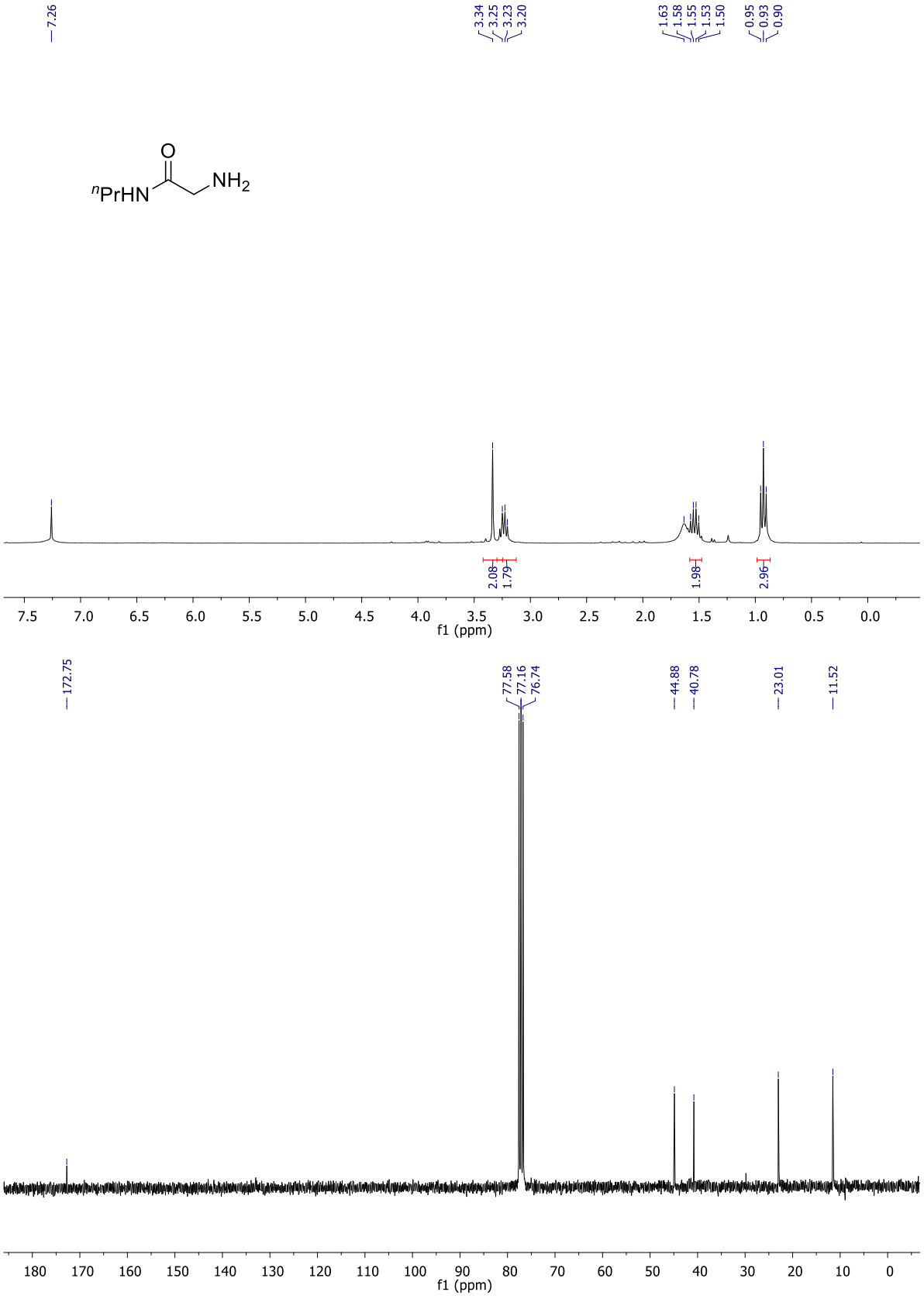
### (*S*)-2-Amino-*N*-propylpropanamide hydrochloride 5a.HCl



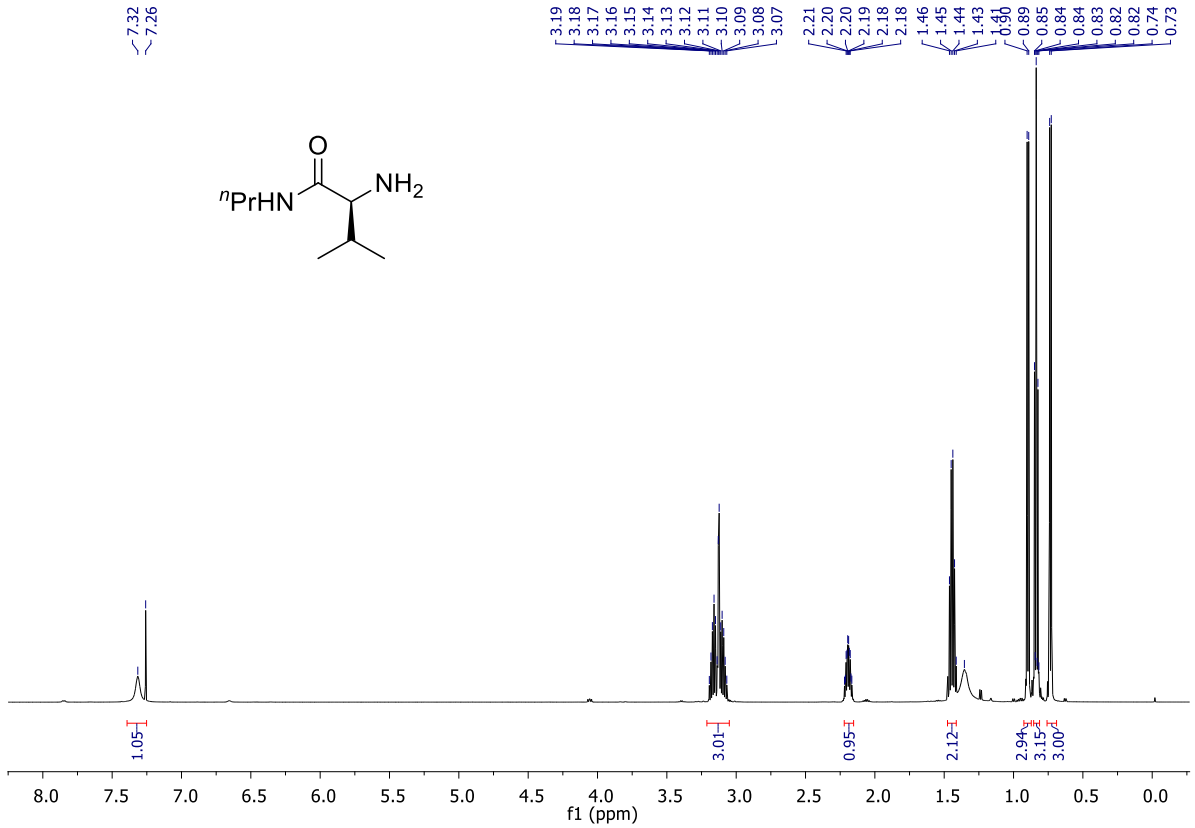
**(*S*)-2-Amino-3-phenyl-*N*-propylpropanamide hydrochloride 5b.HCl**

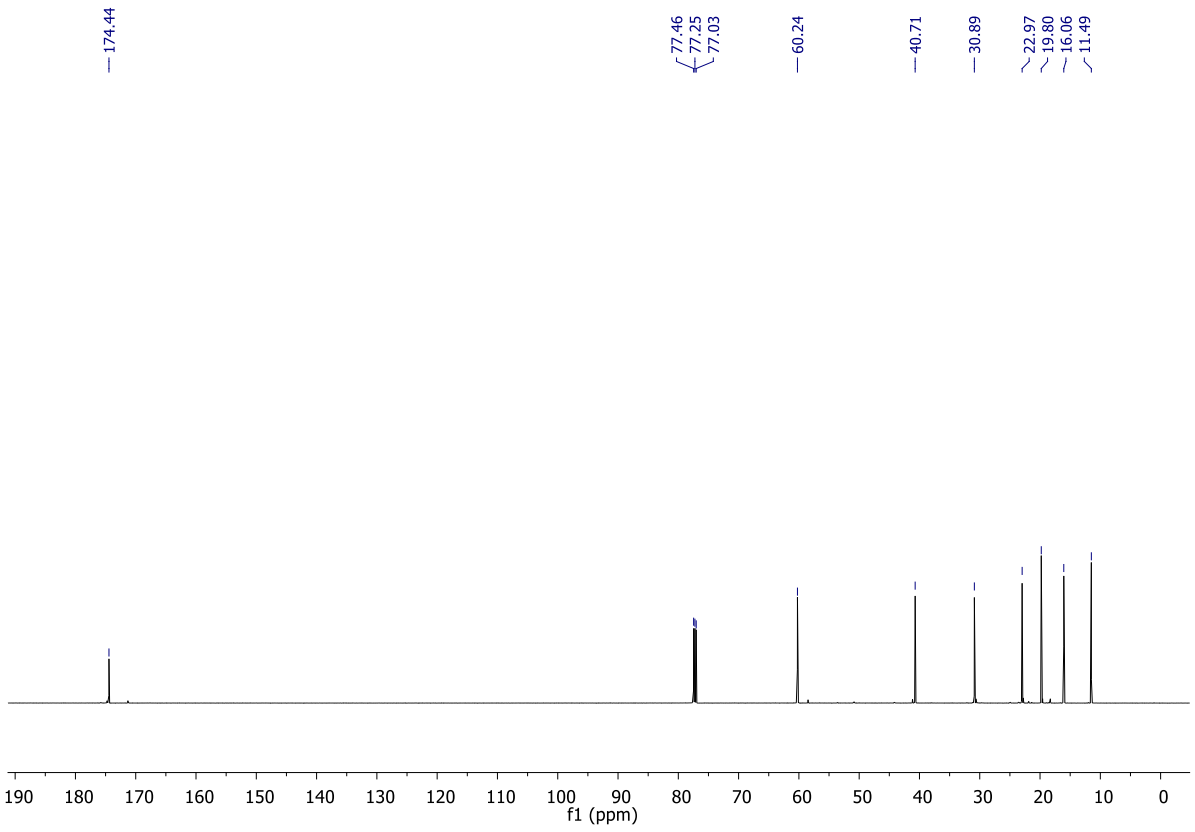


## 2-Amino-*N*-propylacetamide 5c

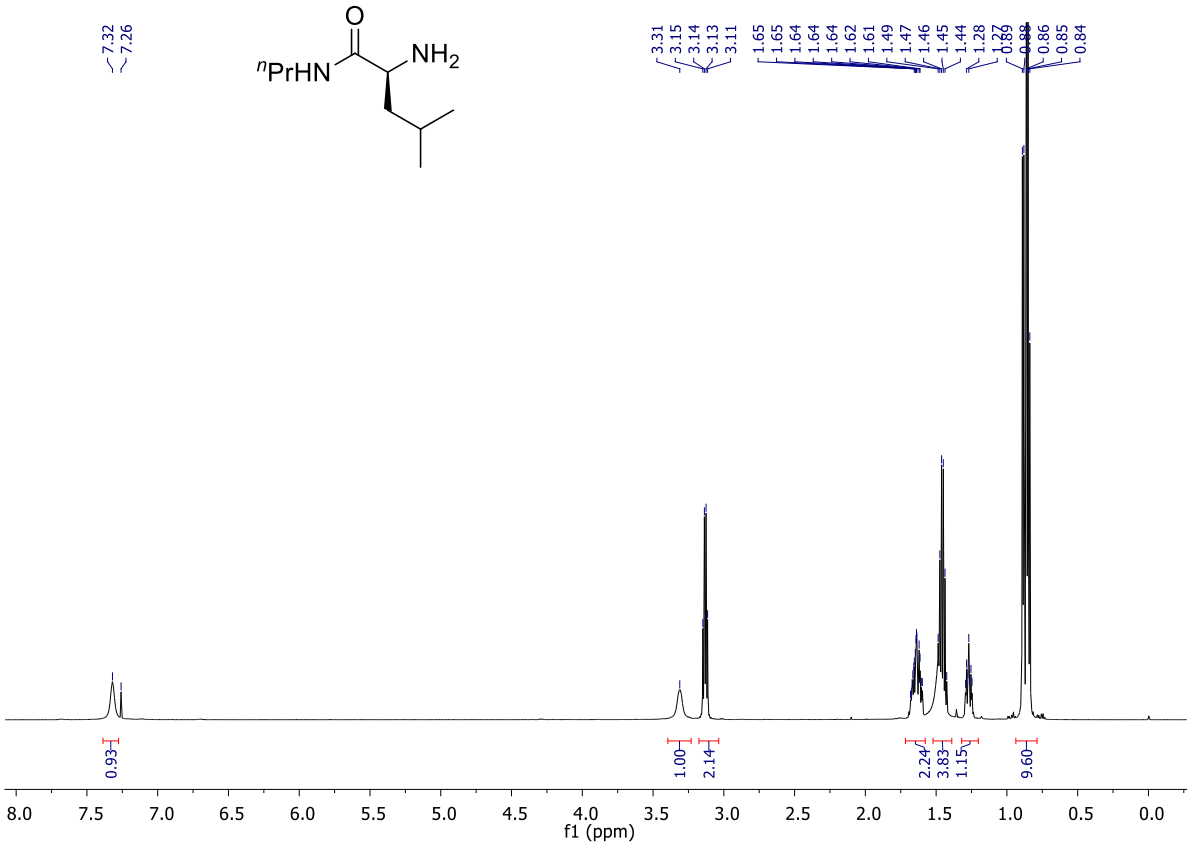


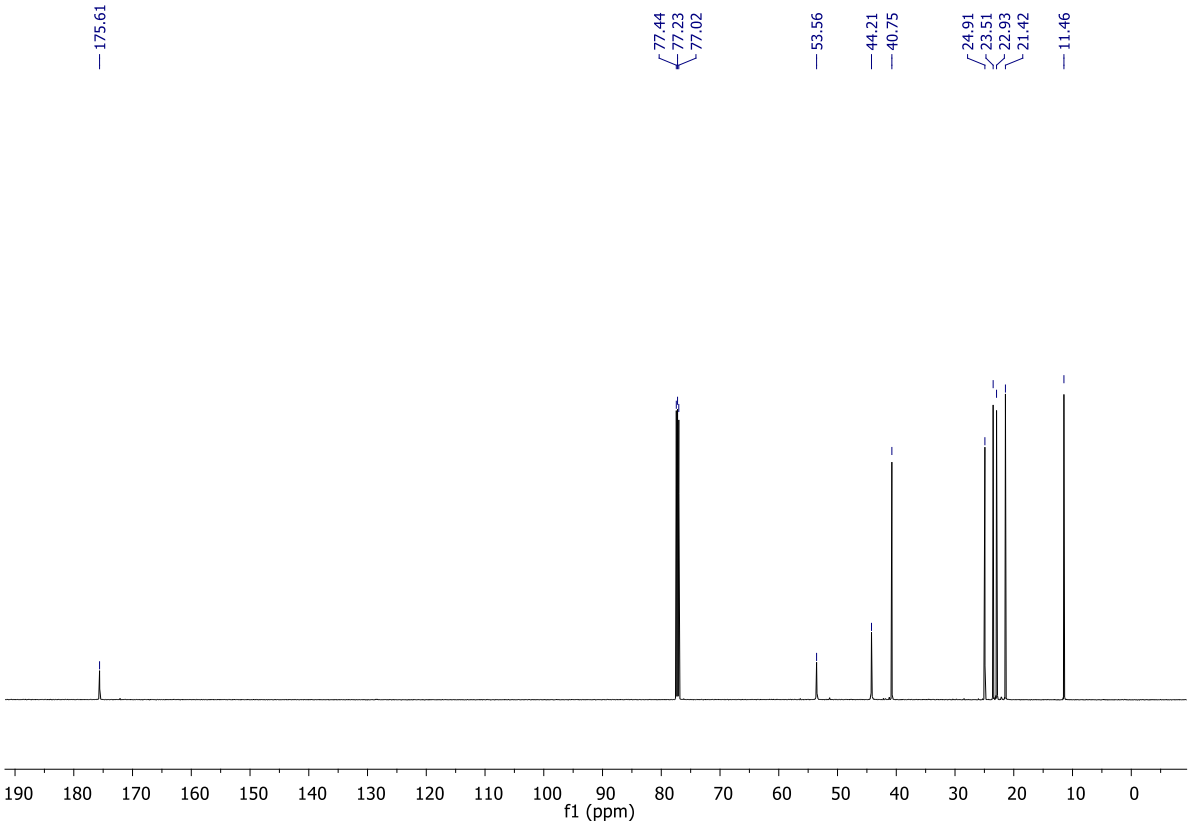
**(*S*)-2-Amino-3-methyl-*N*-propylbutanamide 5d**



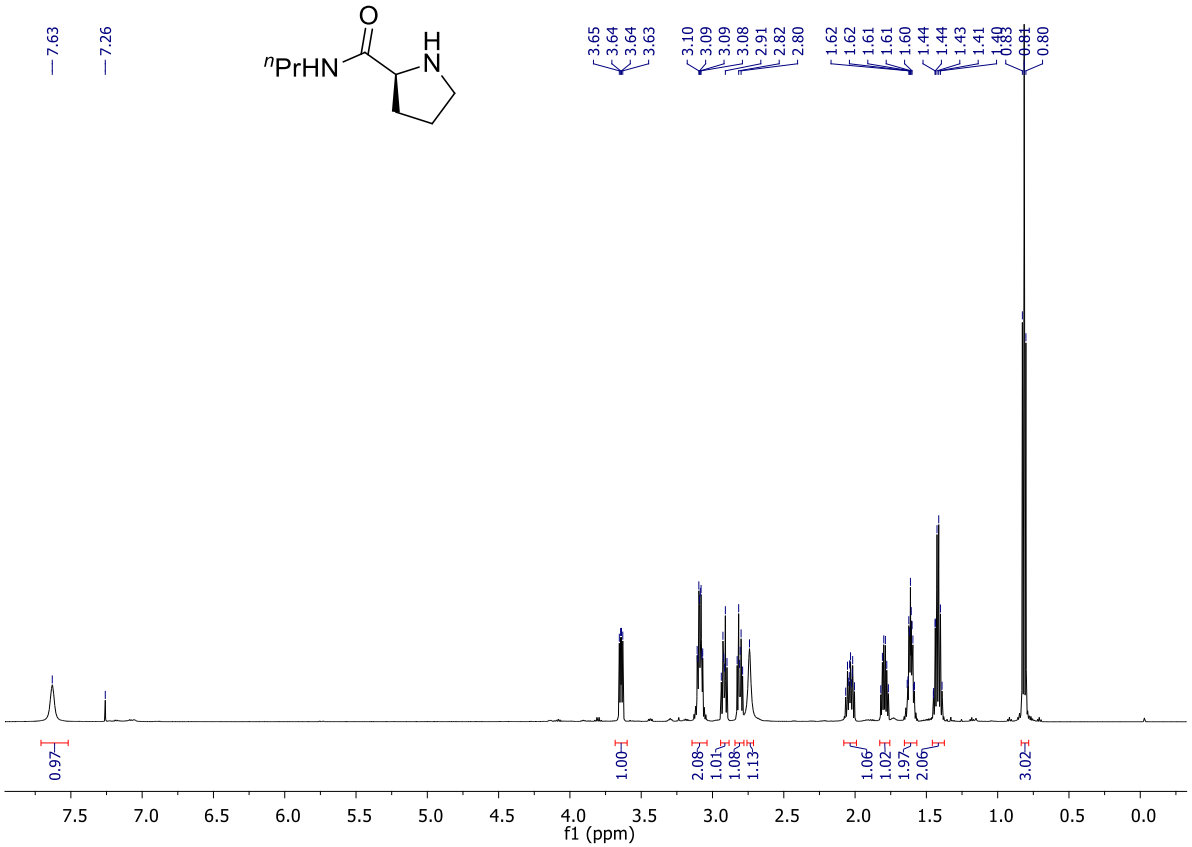



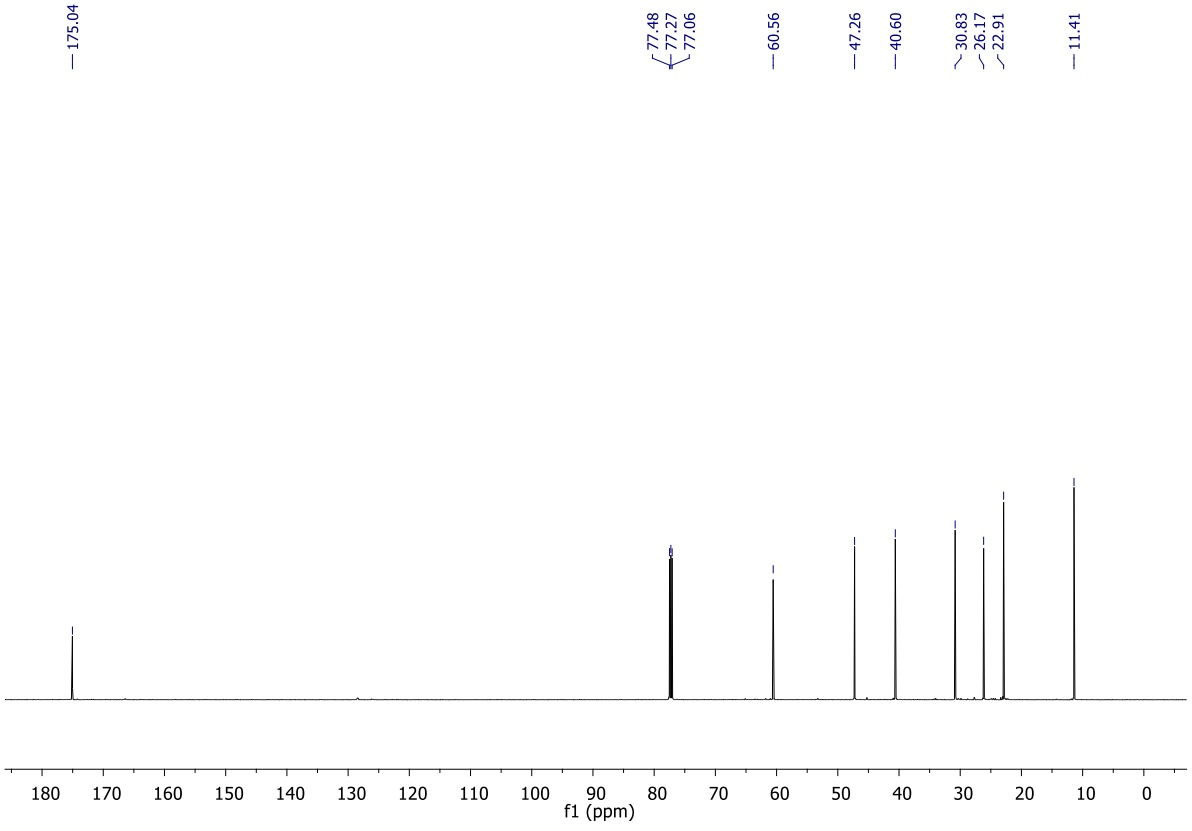
**(*S*)-2-Amino-4-methyl-*N*-propylpentanamide 5e**



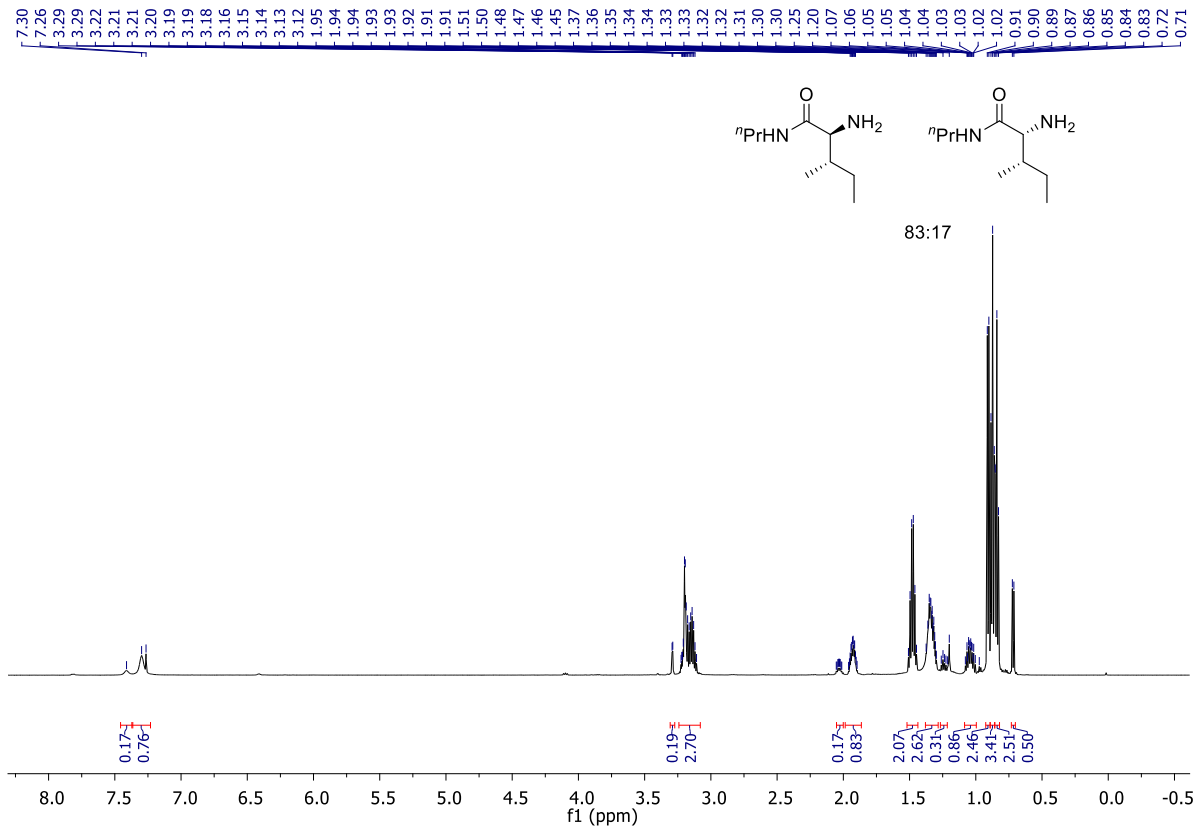



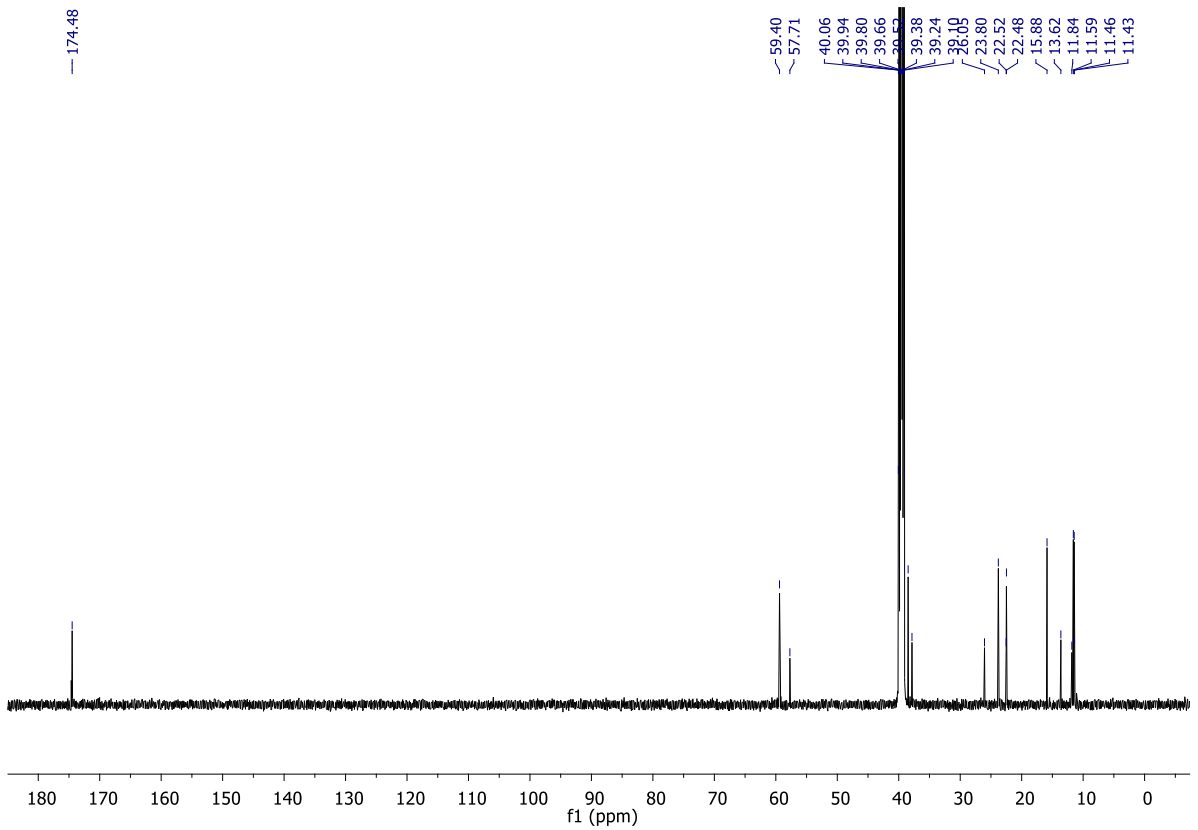
## (*S*)-*N*-Propylpyrrolidine-2-carboxamide 5f



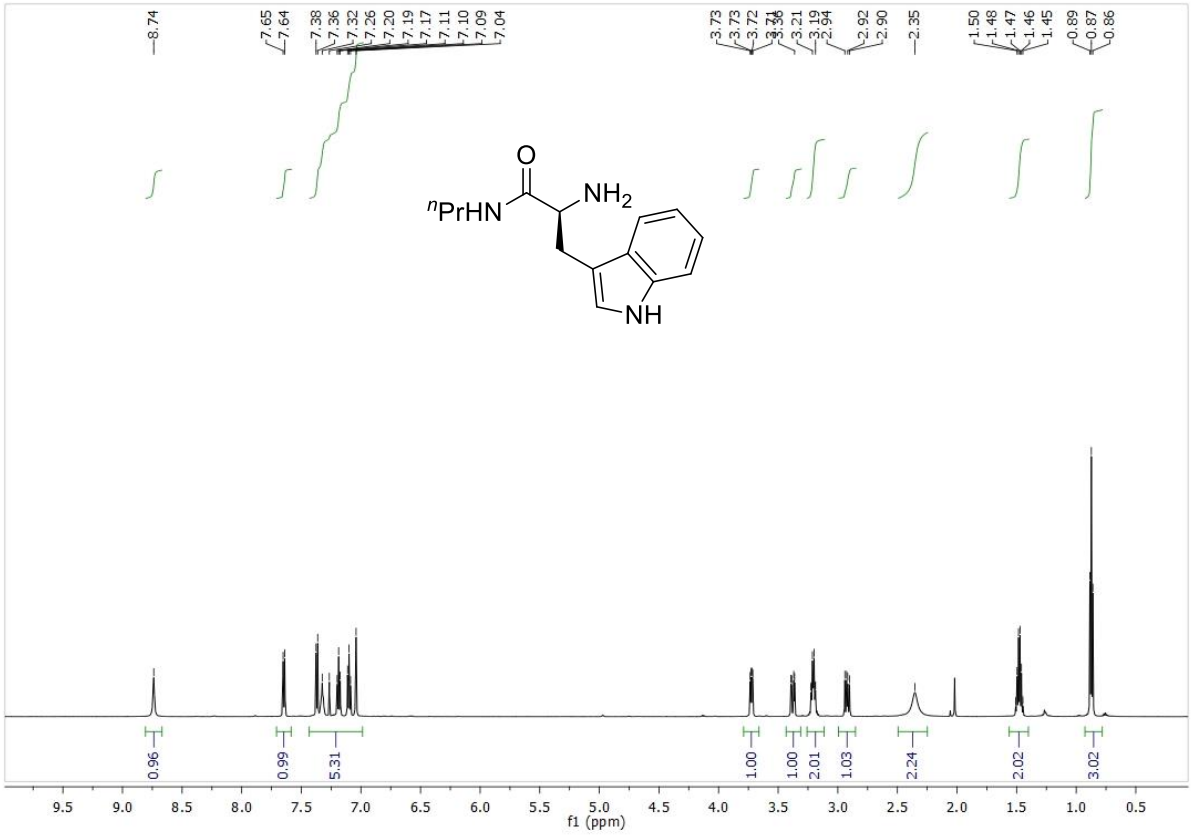



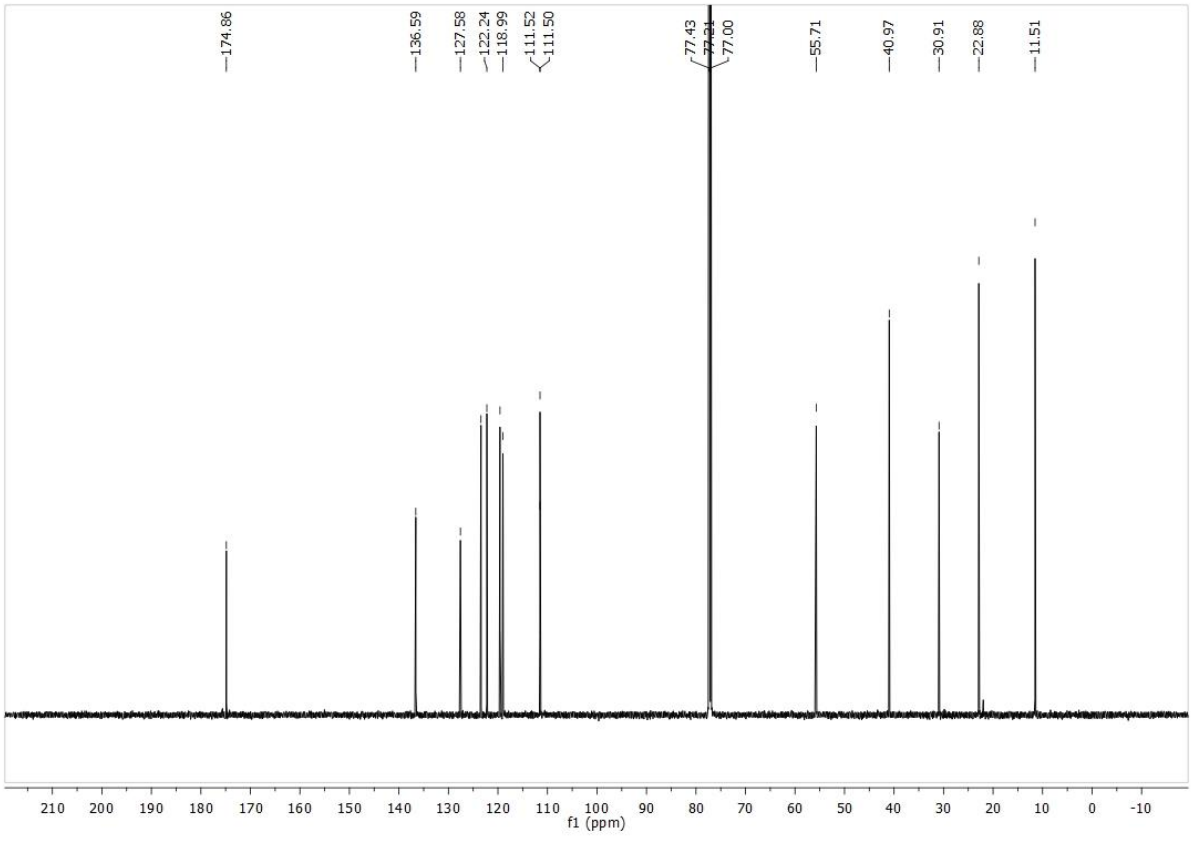
## (*2S,3S*)-2-Amino-3-methyl-*N*-propylpentanamide 5g



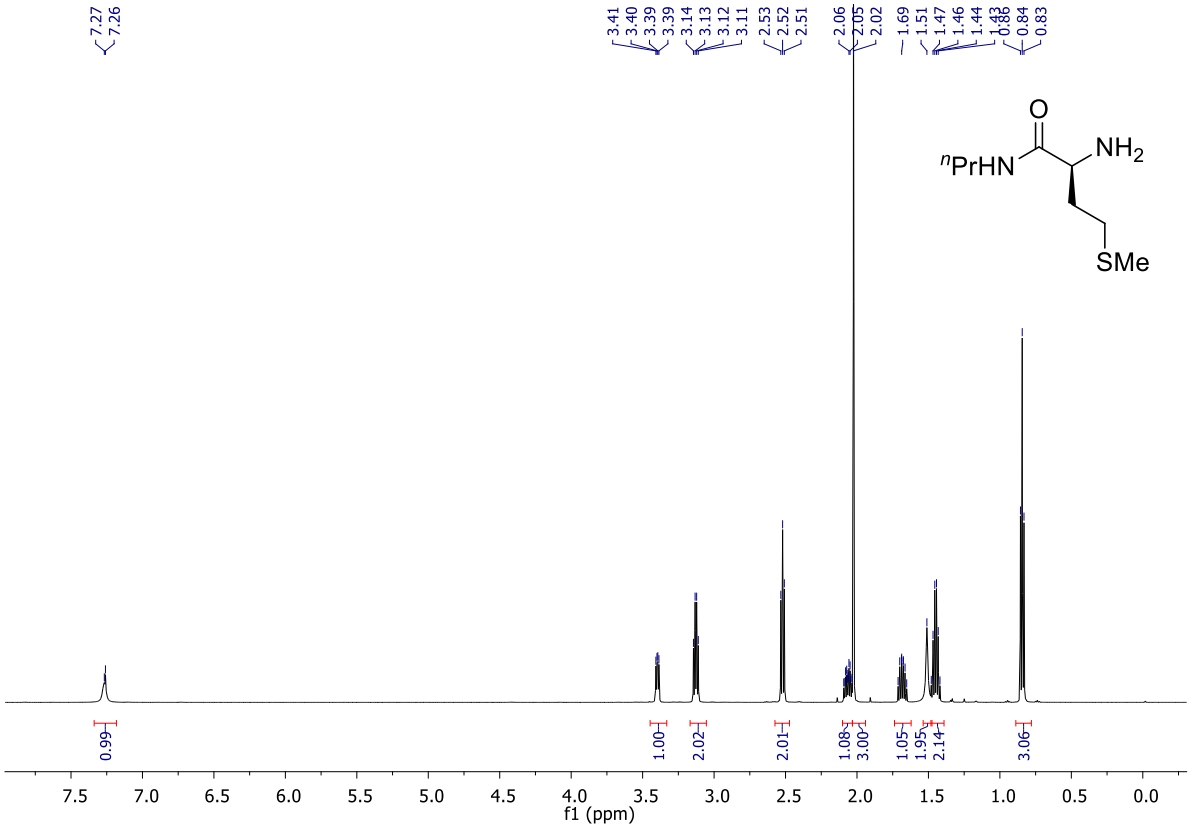



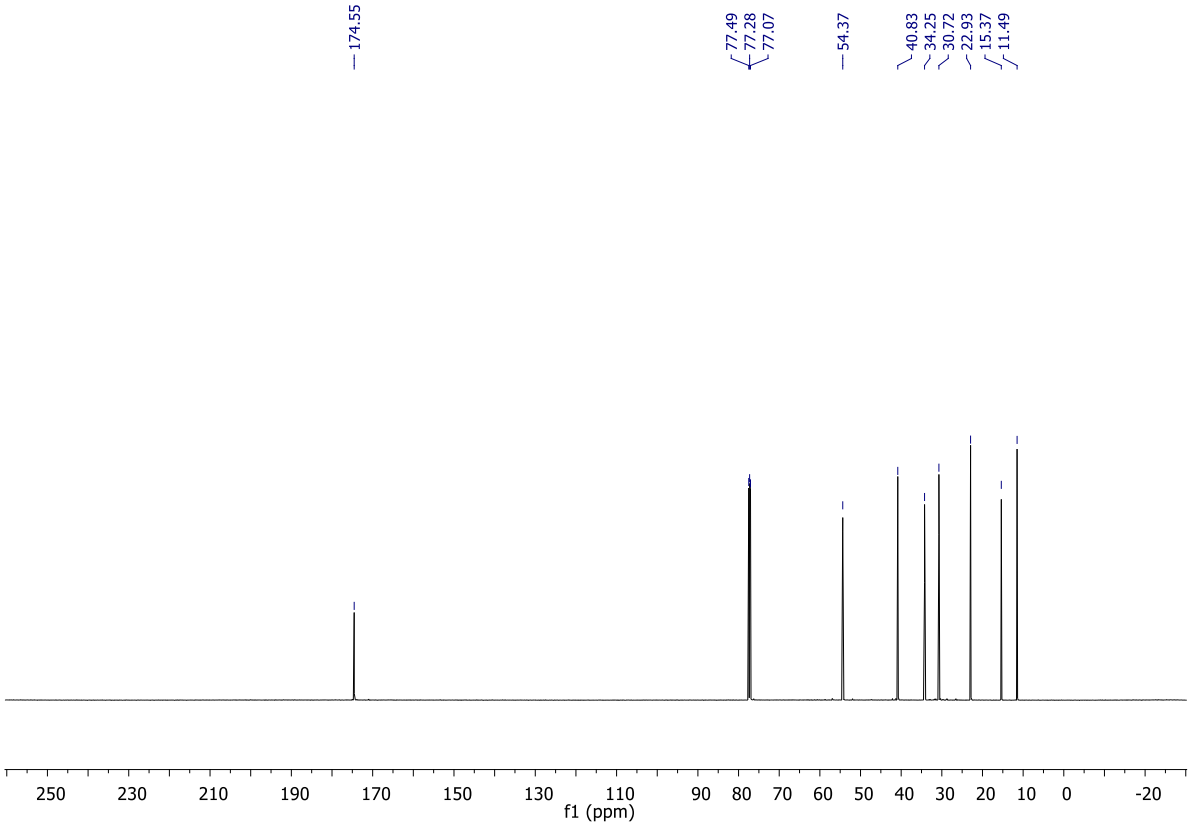
**(*S*)-2-Amino-3-(1H-indol-3-yl)-*N*-propylpropanamide 5h**



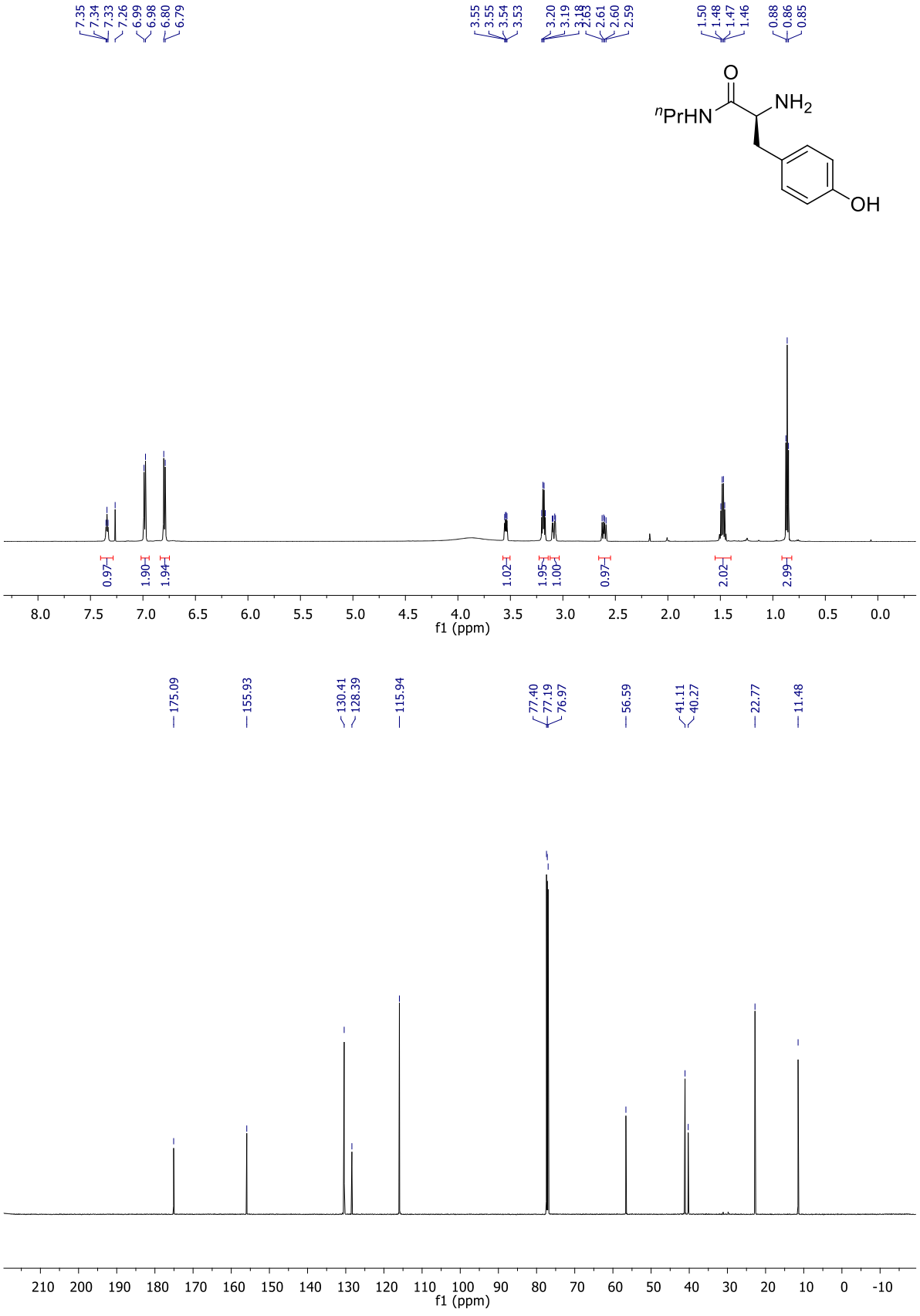



**(*S*)-2-Amino-4-(methylthio)-*N*-propylbutanamide 5i**

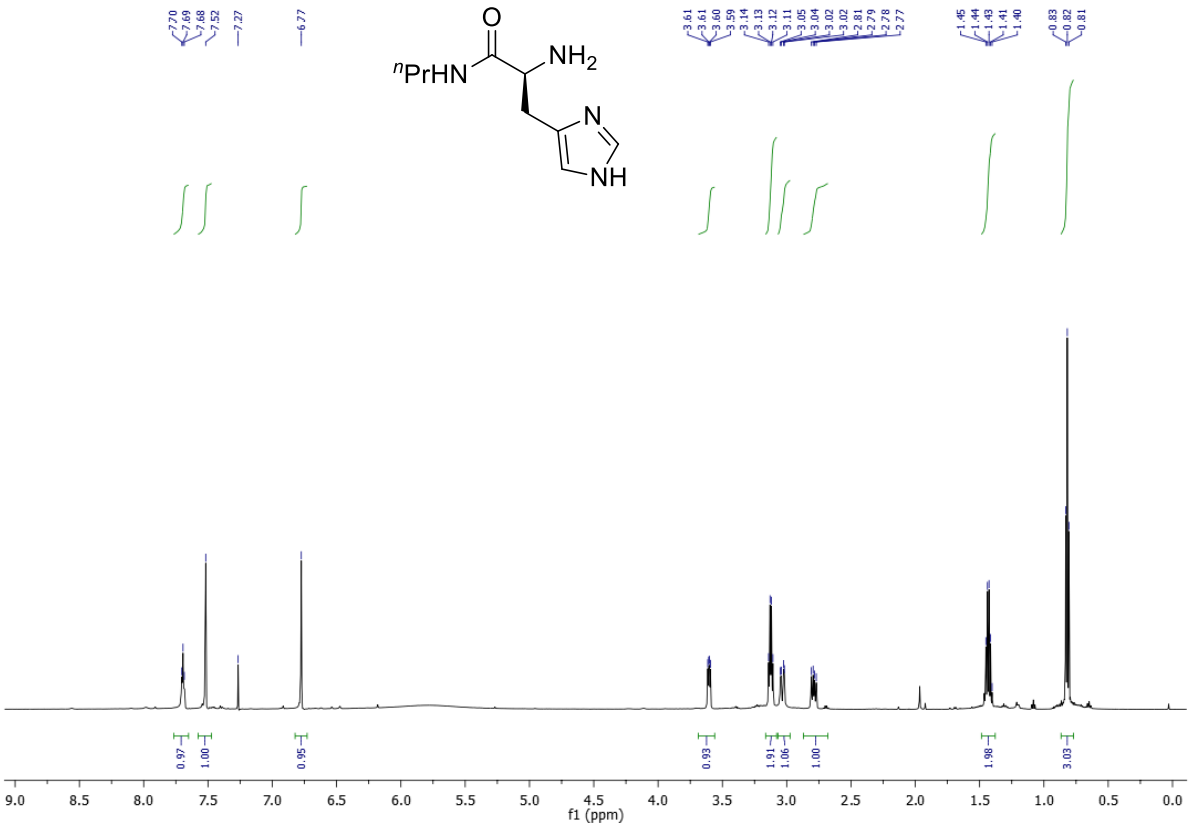


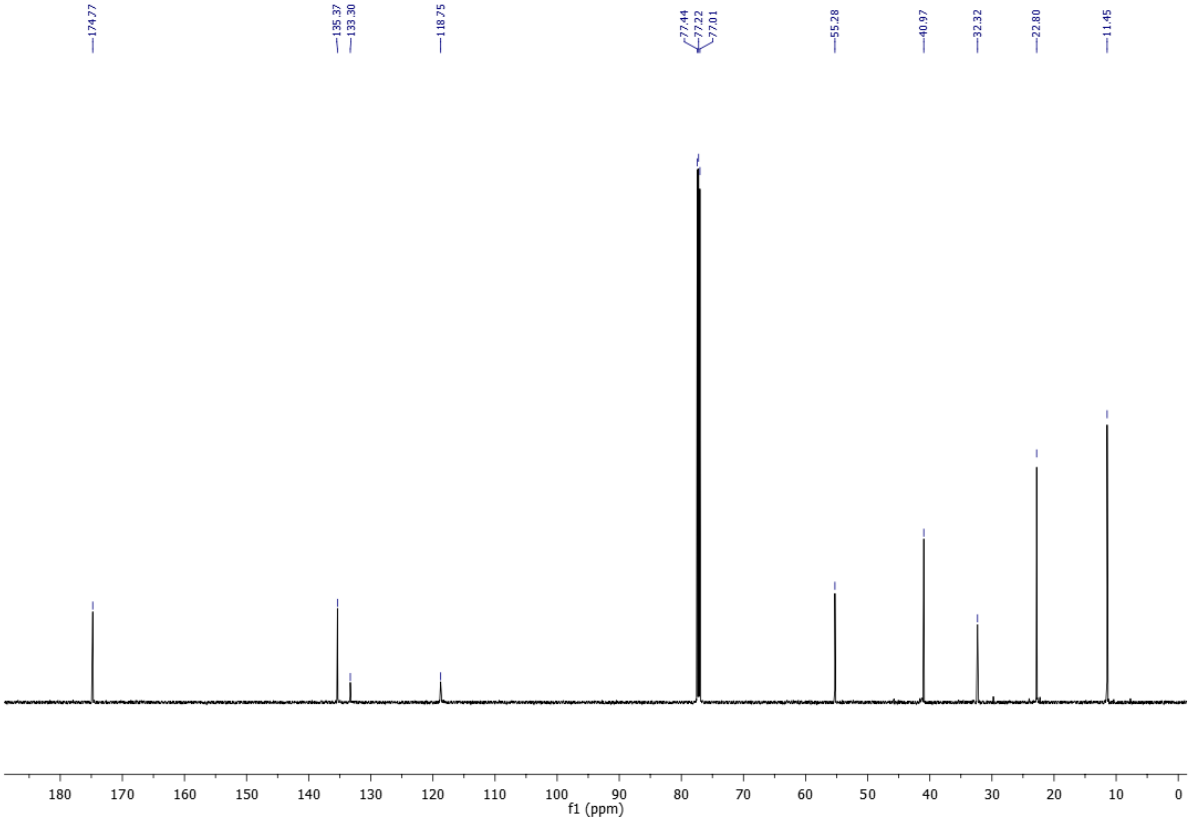



**(*S*)-2-Amino-3-(4-hydroxyphenyl)-*N*-propylpropanamide 5j**

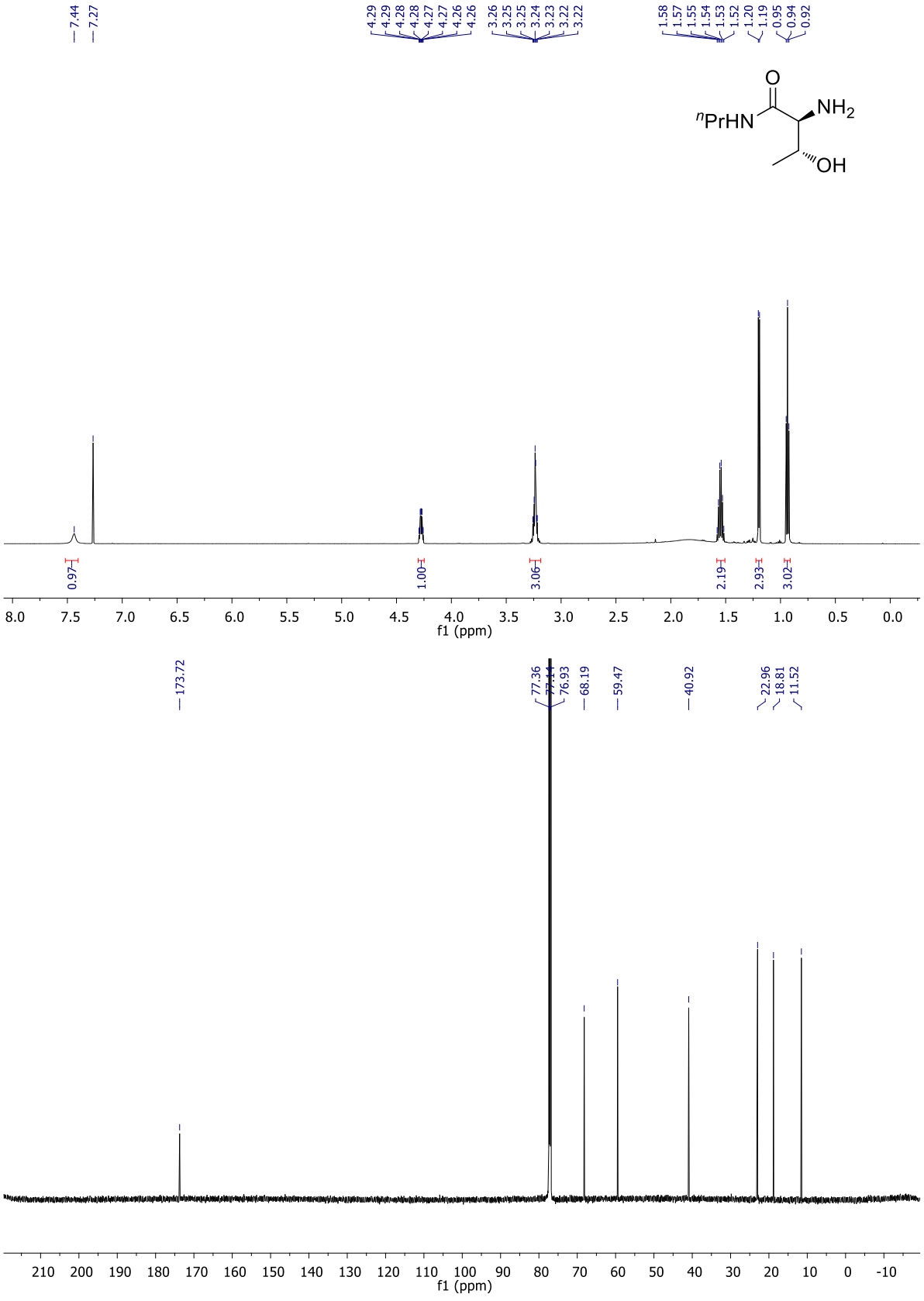


## *(S)*-2-Amino-3-(1H-imidazol-4-yl)-N-propylpropanamide 5k

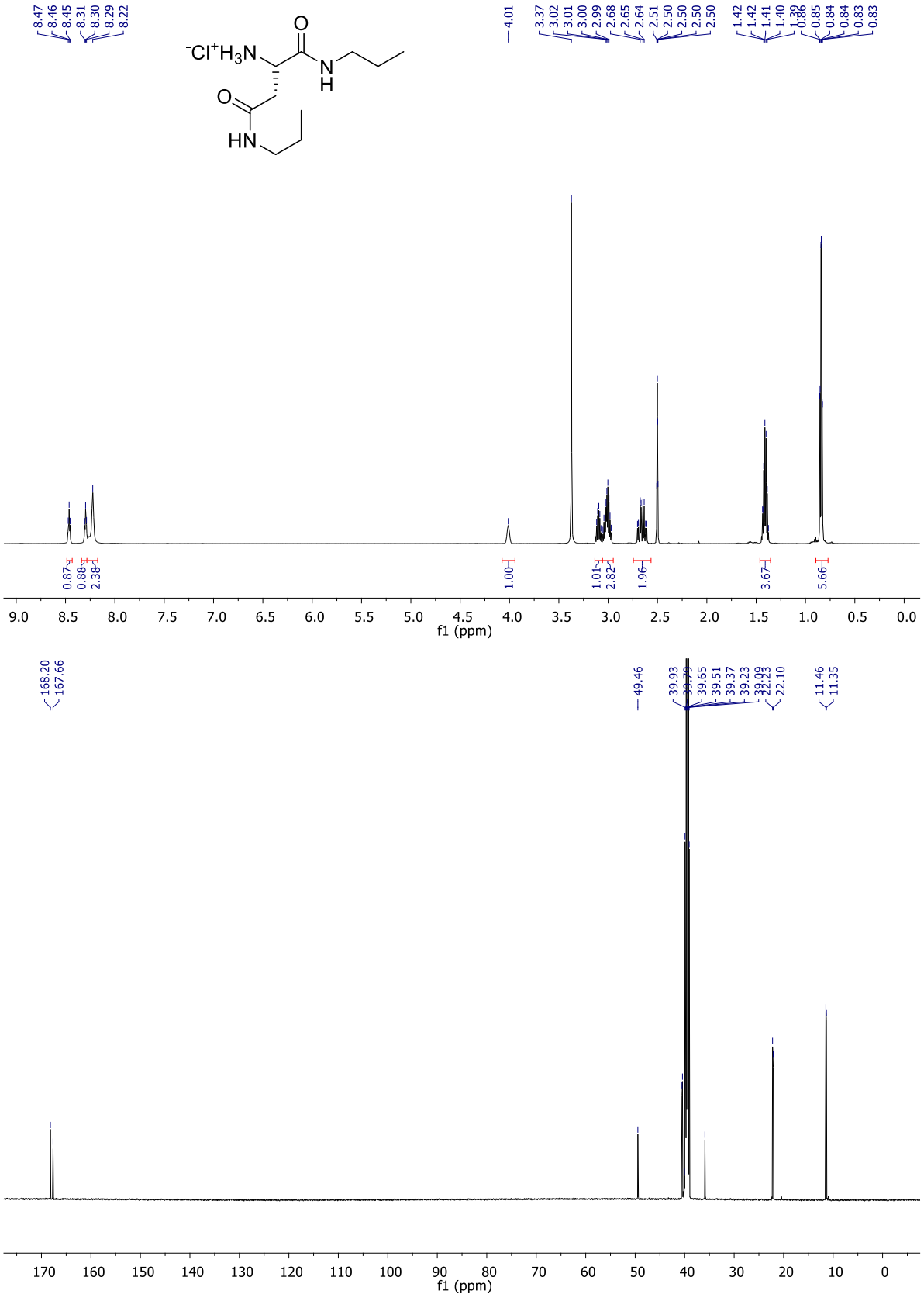


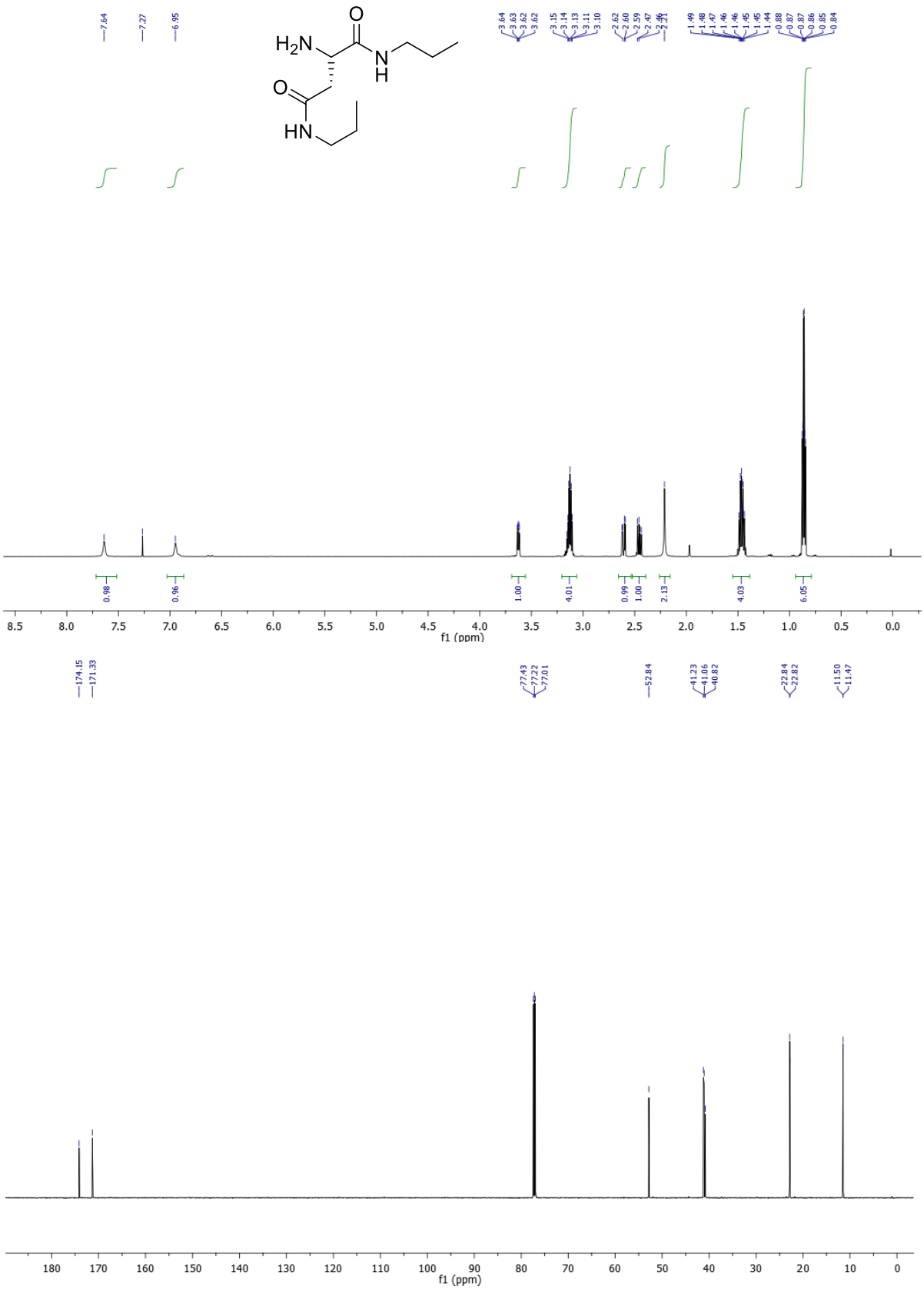
**(*2S,3R*)-2-Amino-3-hydroxy-*N*-propylbutanamide 5l**



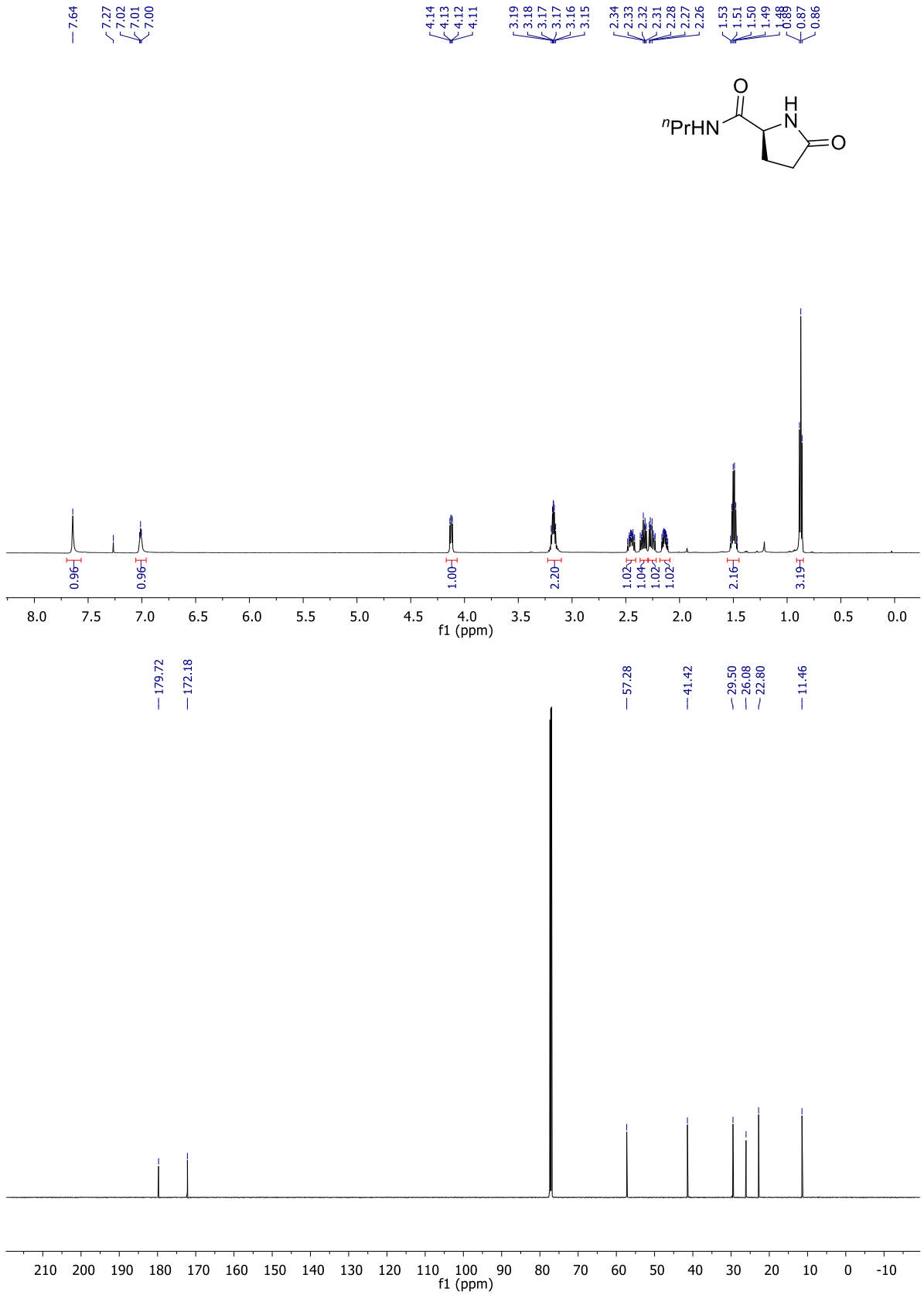
**(*S*)-2-Amino-*N*$^1$,*N*$^4$-dipropylsuccinamide hydrochloride 5m.HCl**



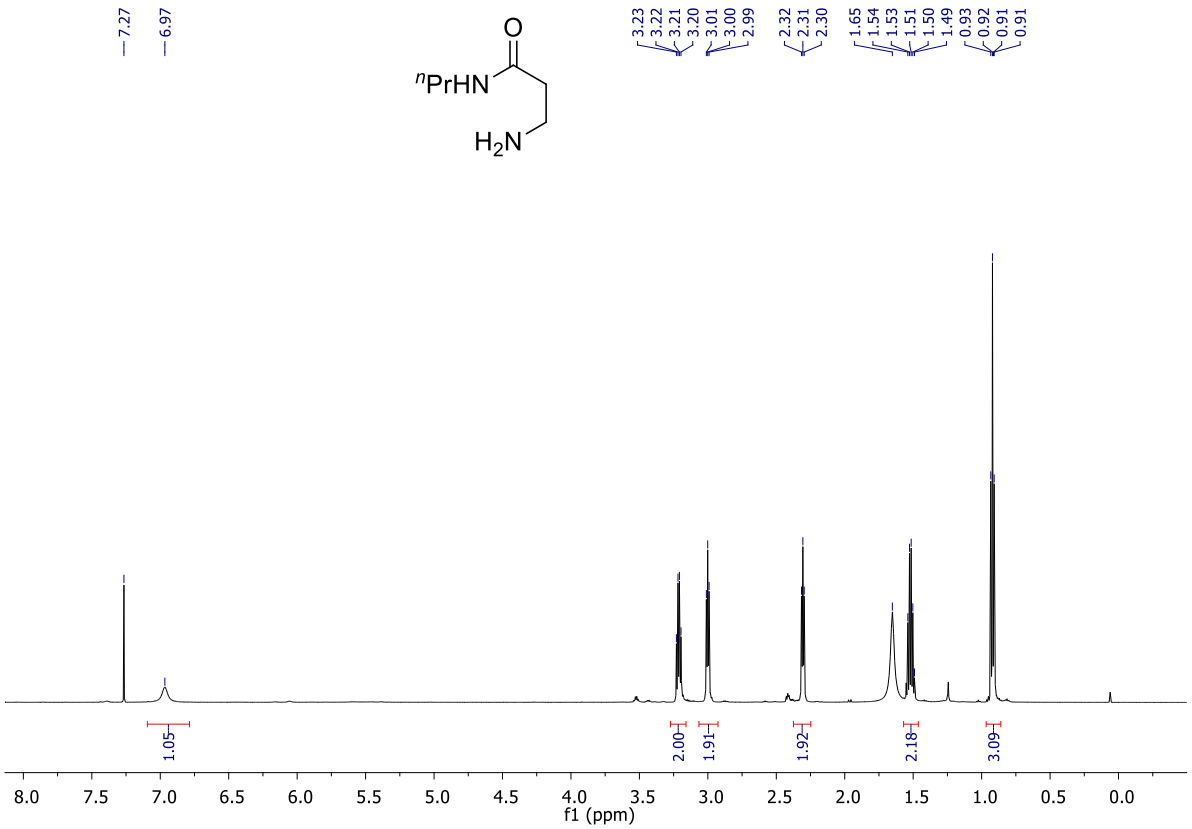
## *(S)*-2-Amino-$N^1$,$N^4$-dipropylsuccinamide 5m

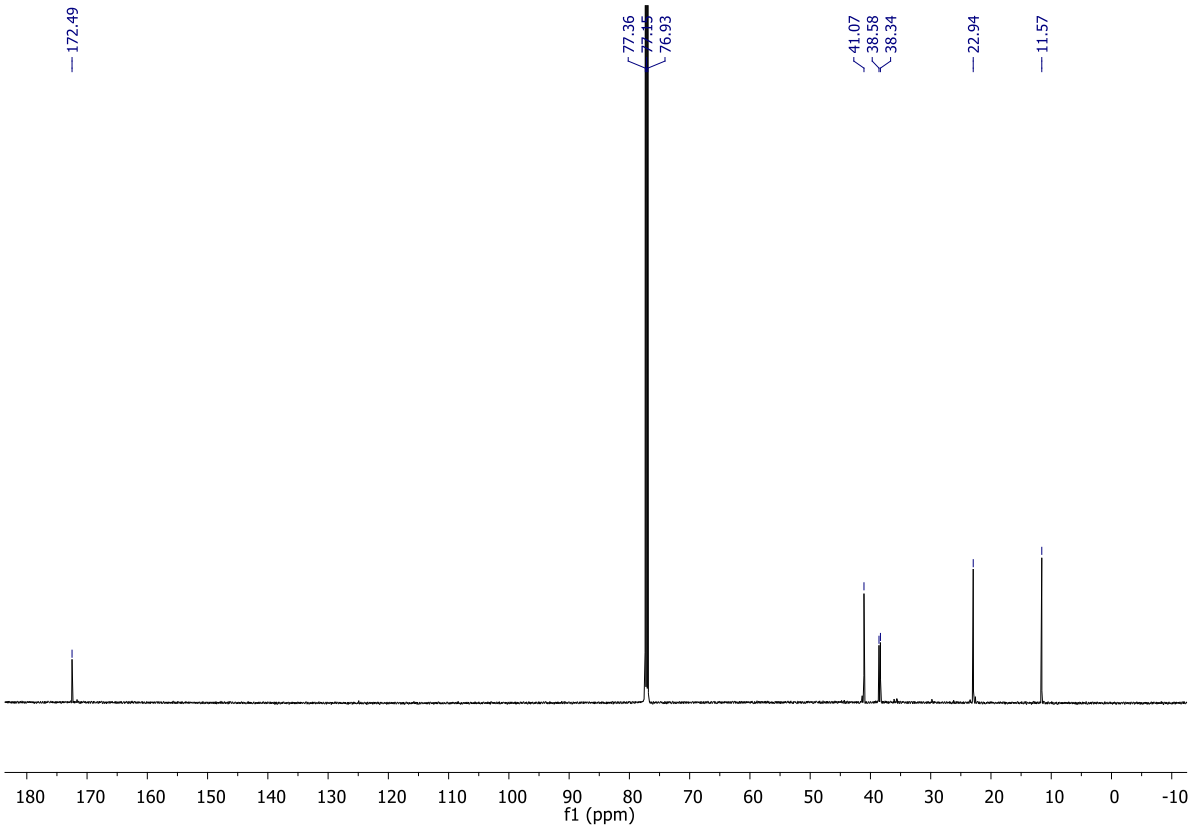


## (*S*)-5-Oxo-N-propylpyrrolidine-2-carboxamide 5n

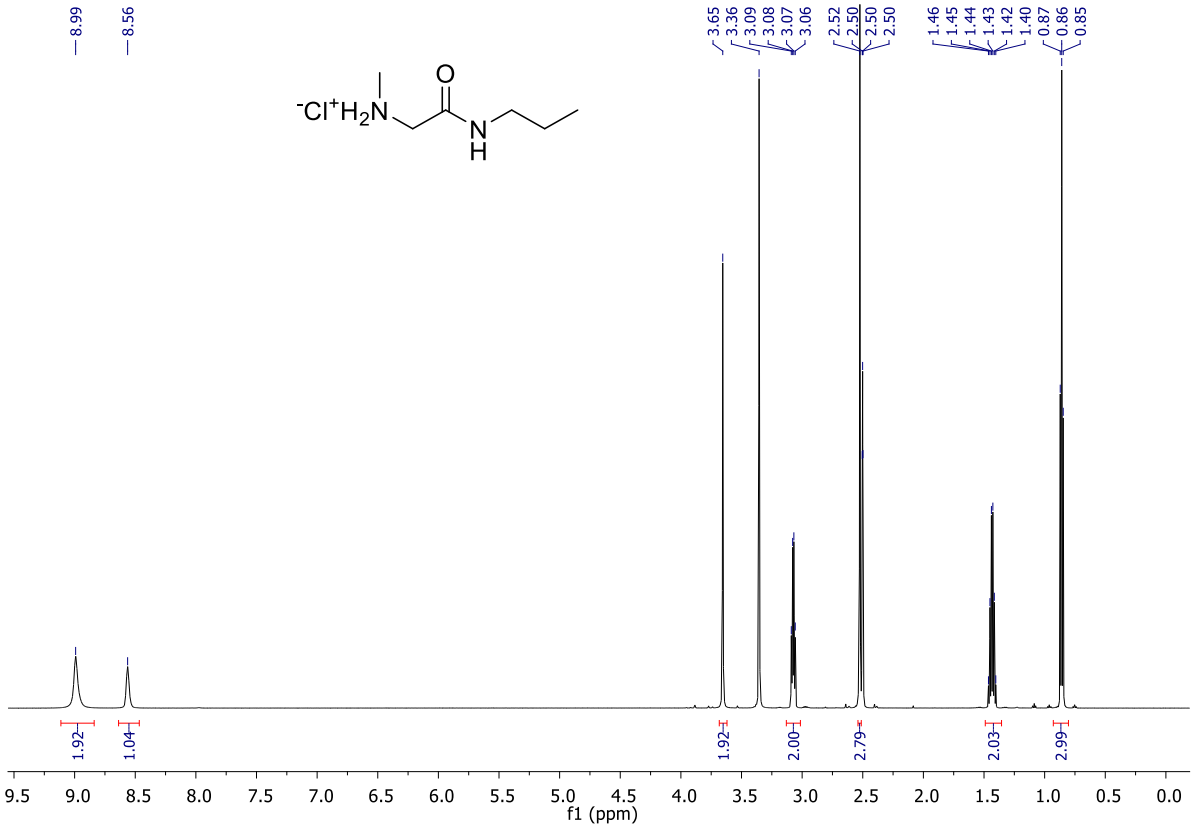


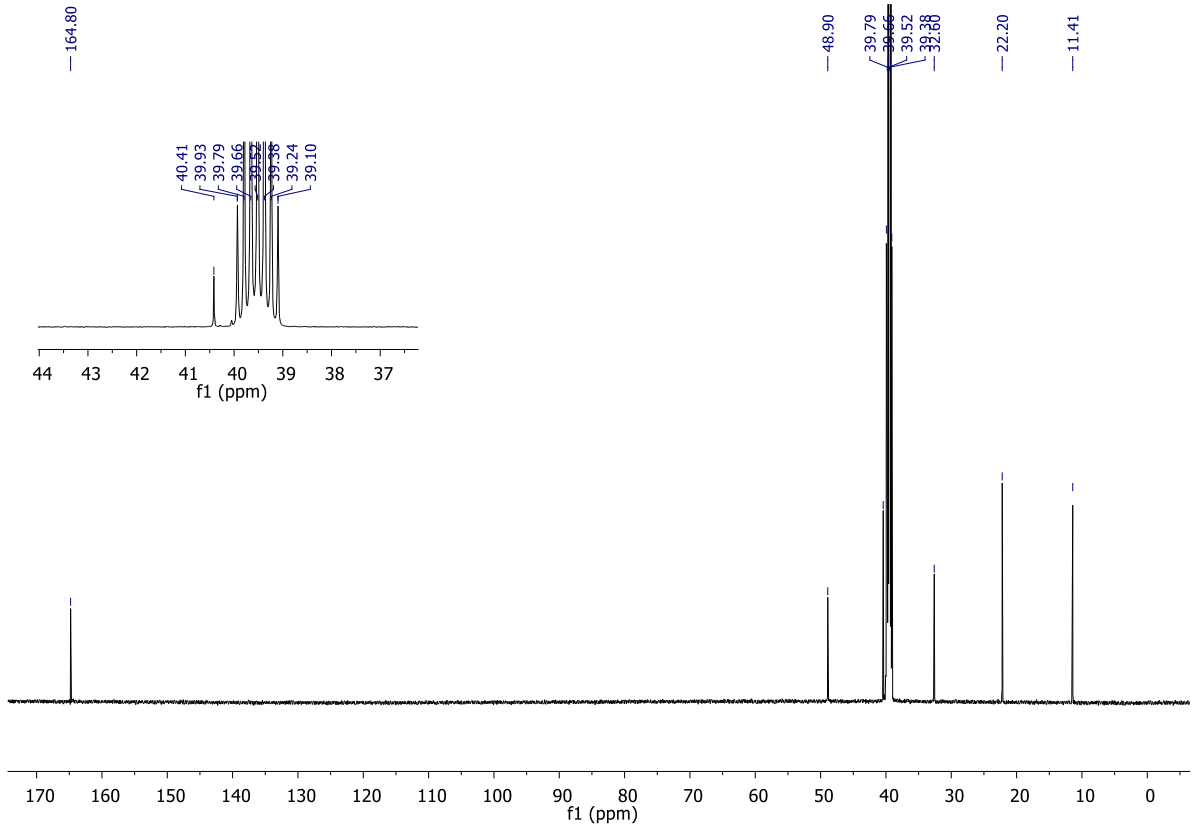
## 3-Amino-*N*-propylpropanamide 5u



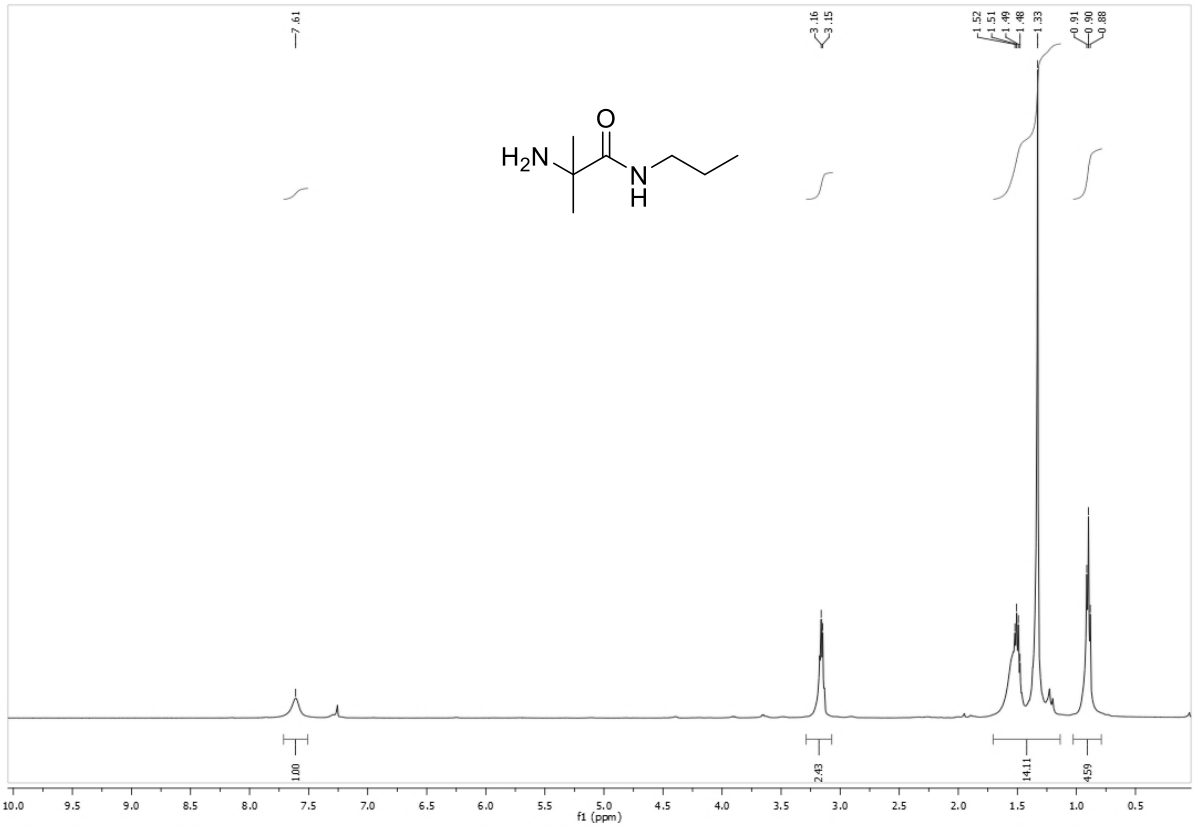



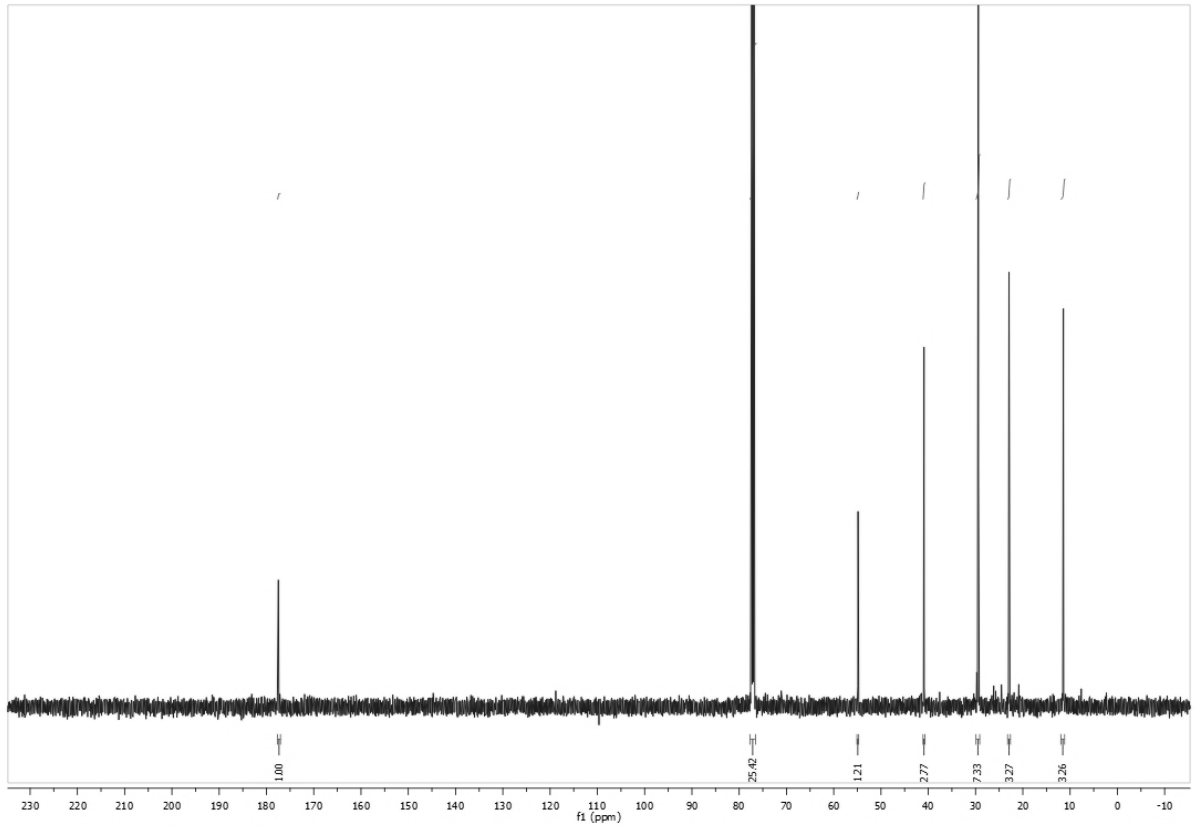
## 2-(Methylamino)-*N*-propylacetamide hydrochloride 5v.HCl



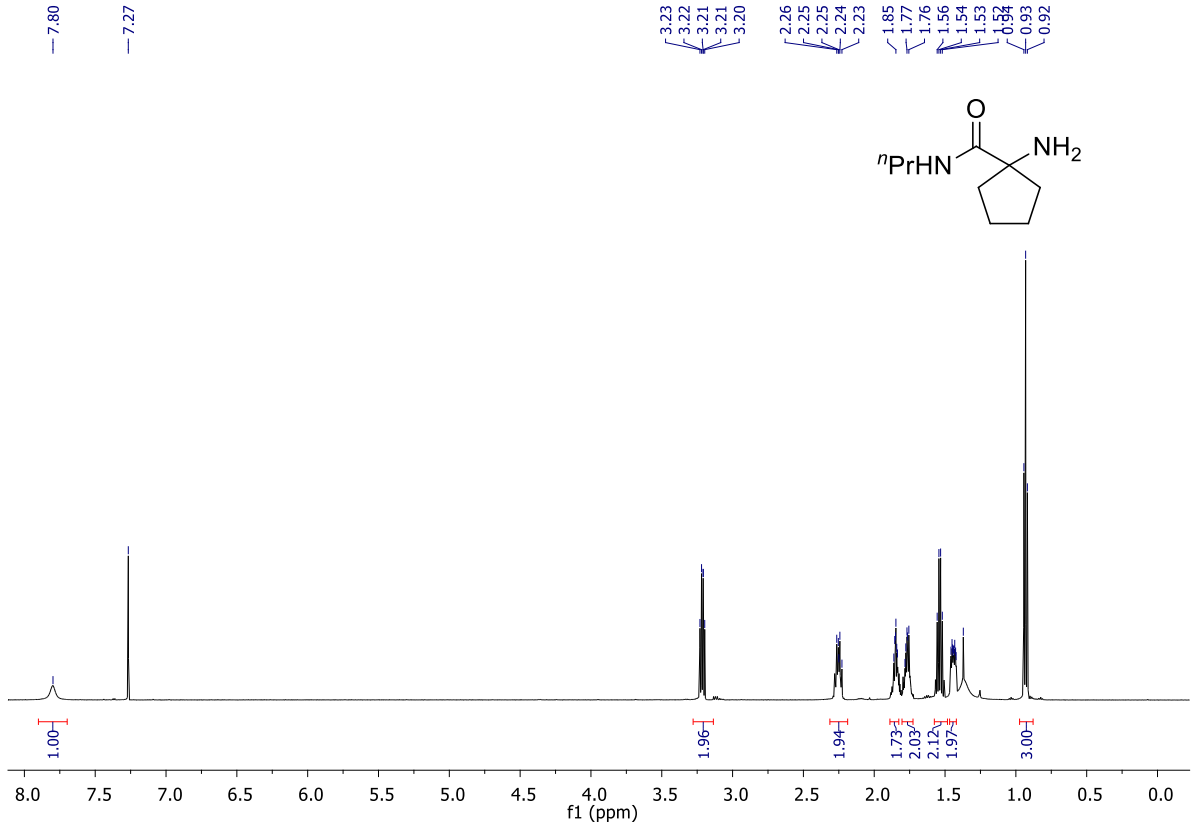



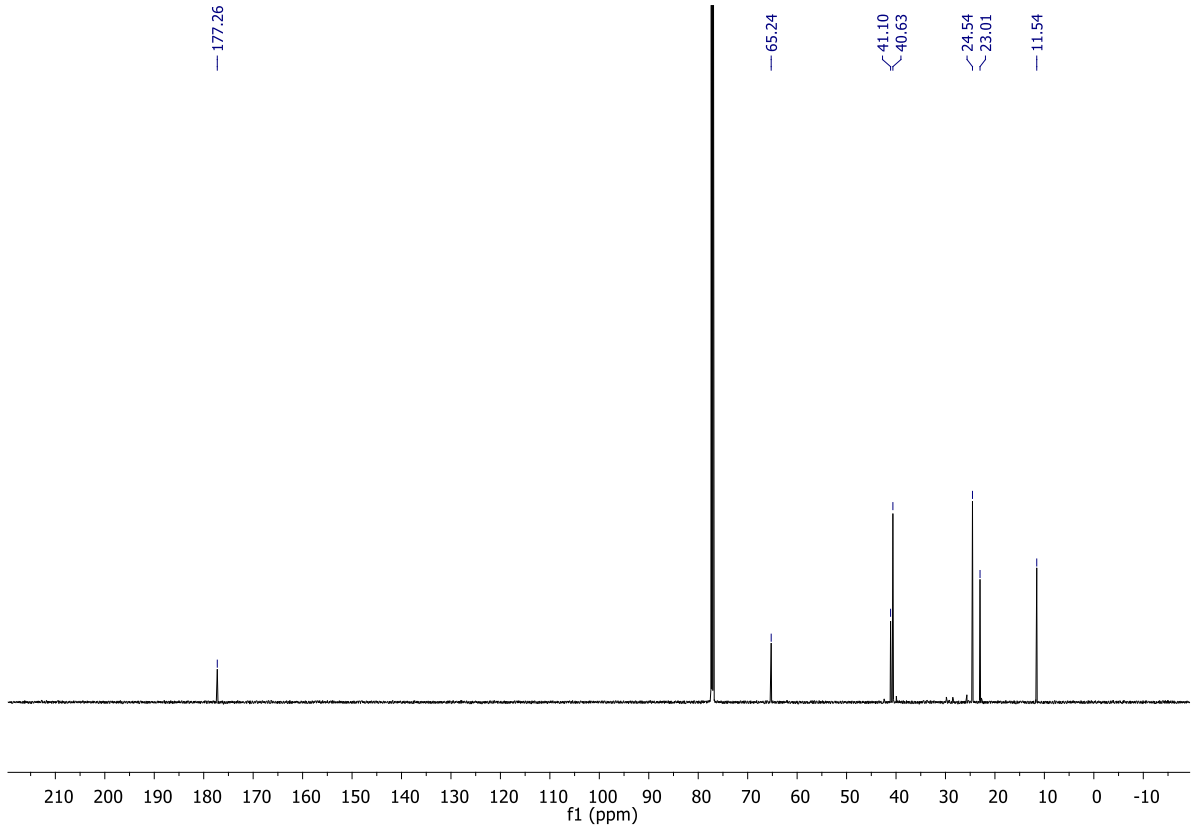
## 2-Amino-2-methyl-N-propylpropanamide 5w



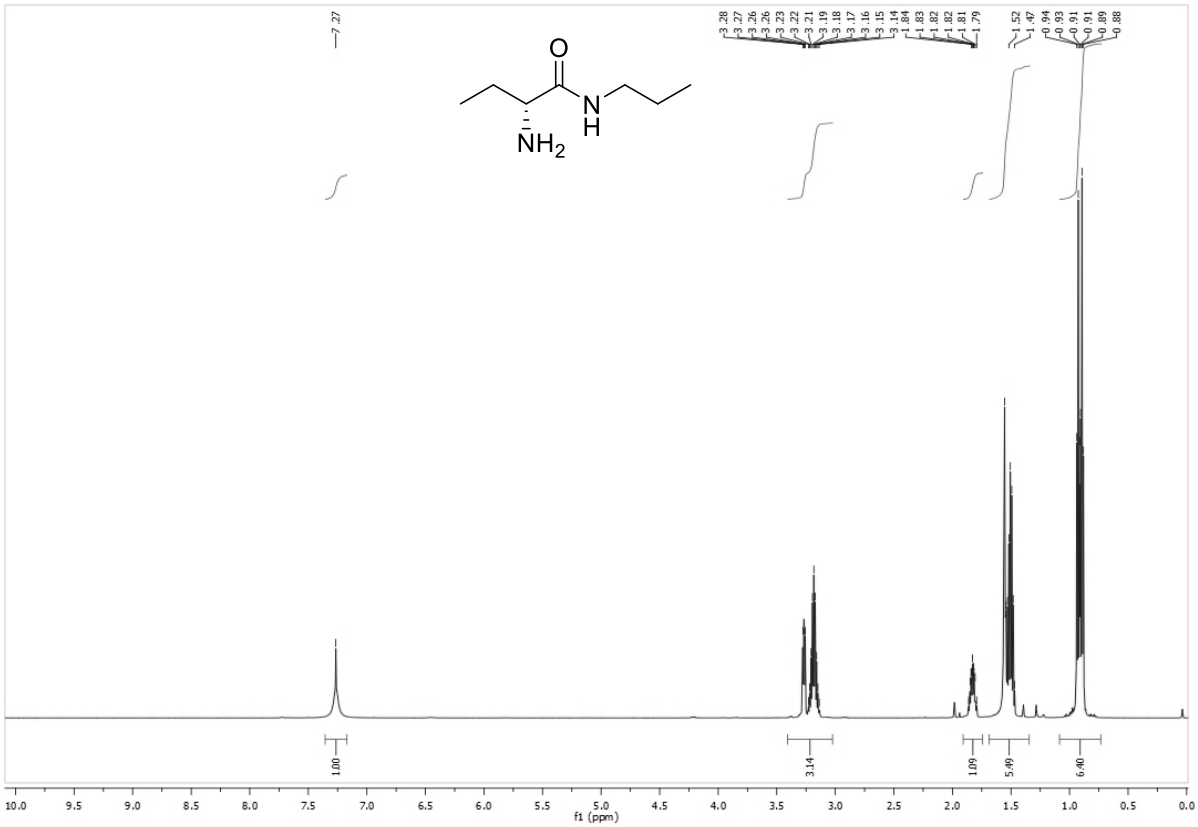



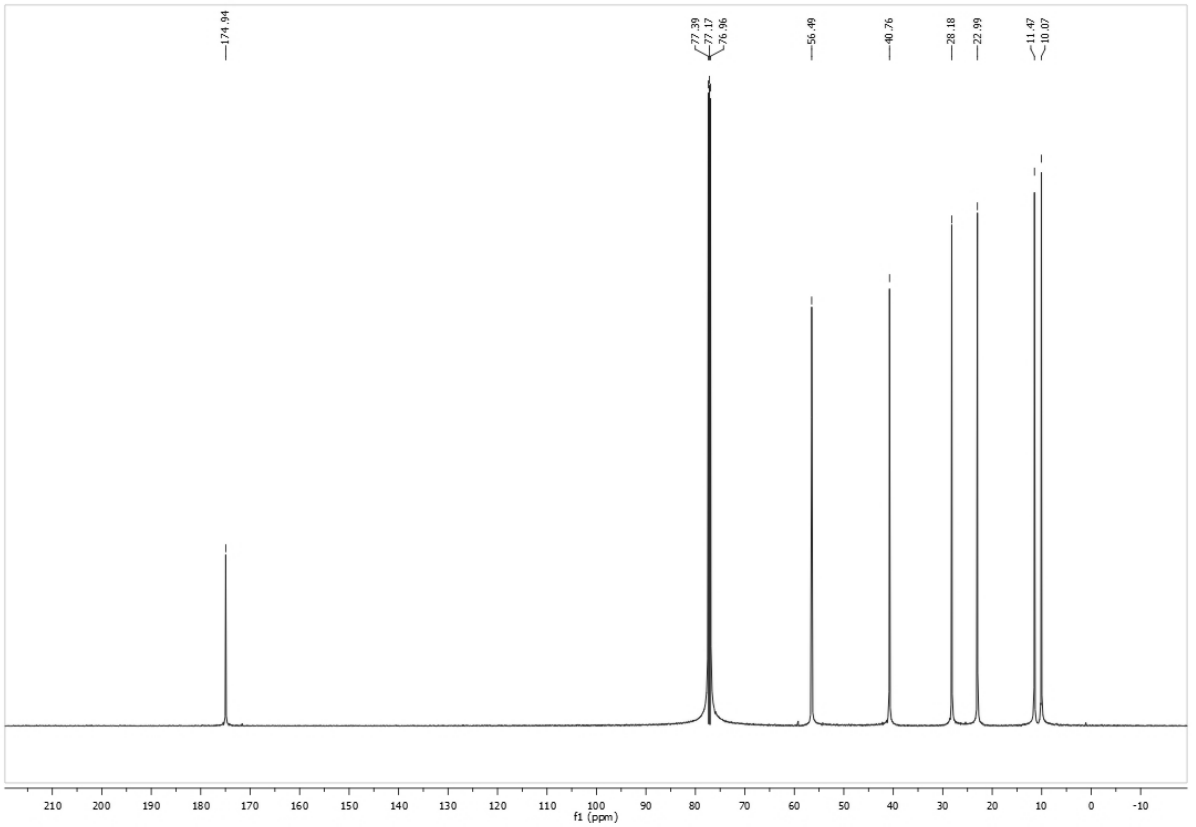
## 1-Amino-*N*-propylcyclopentanecarboxamide 5x



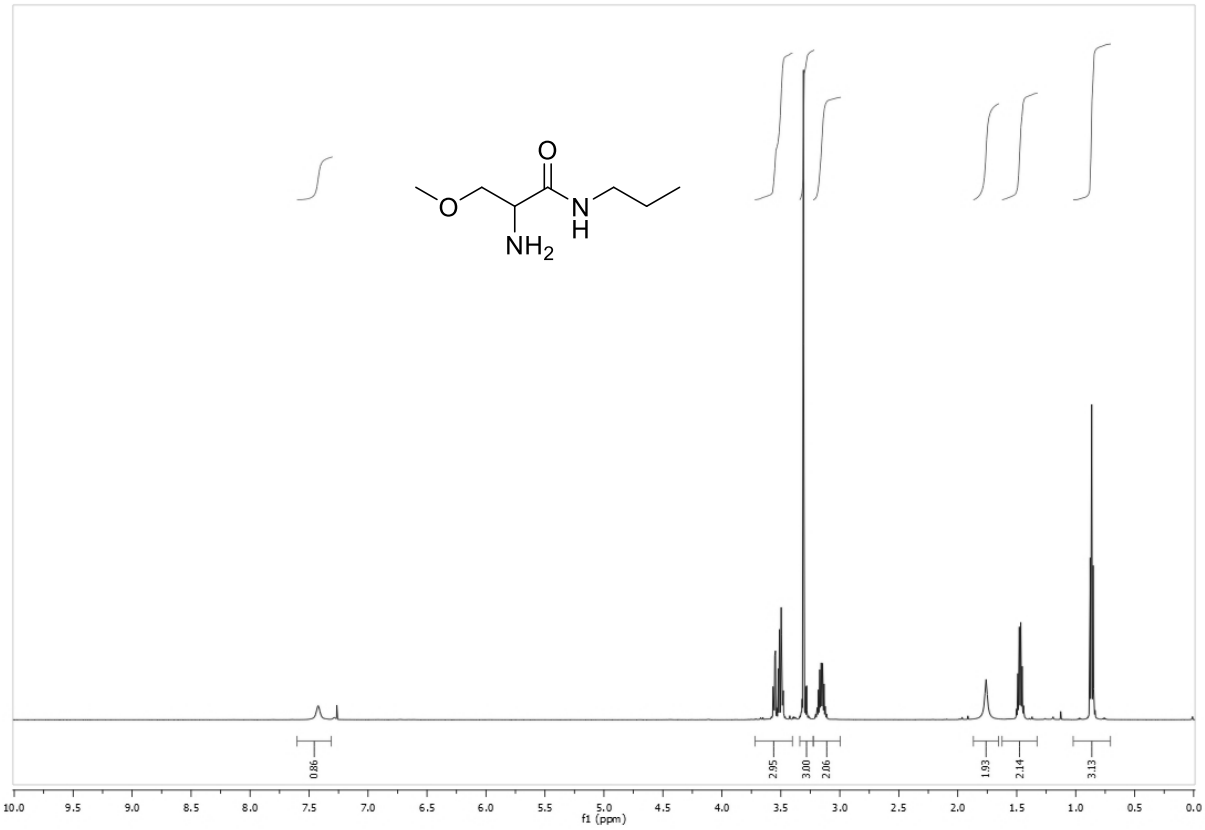



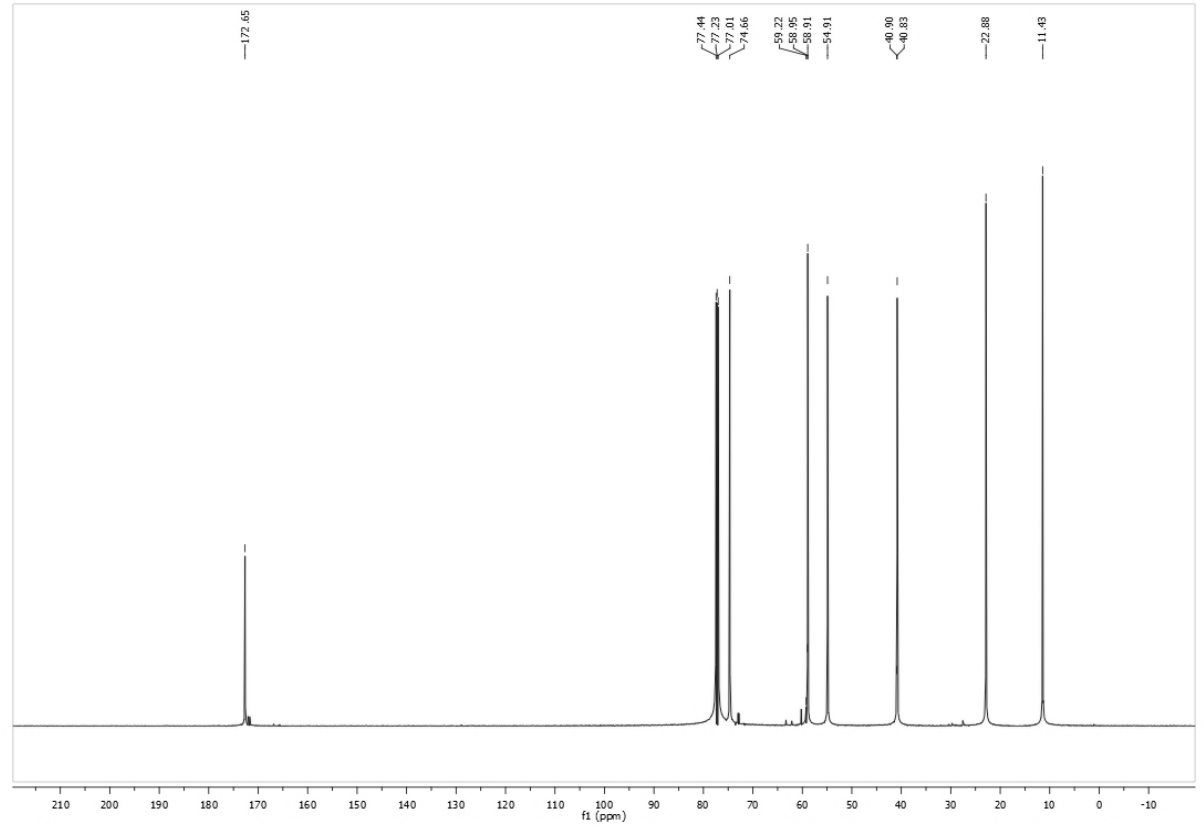
***(R)*-2-Amino-N-propylbutanamide 5y**



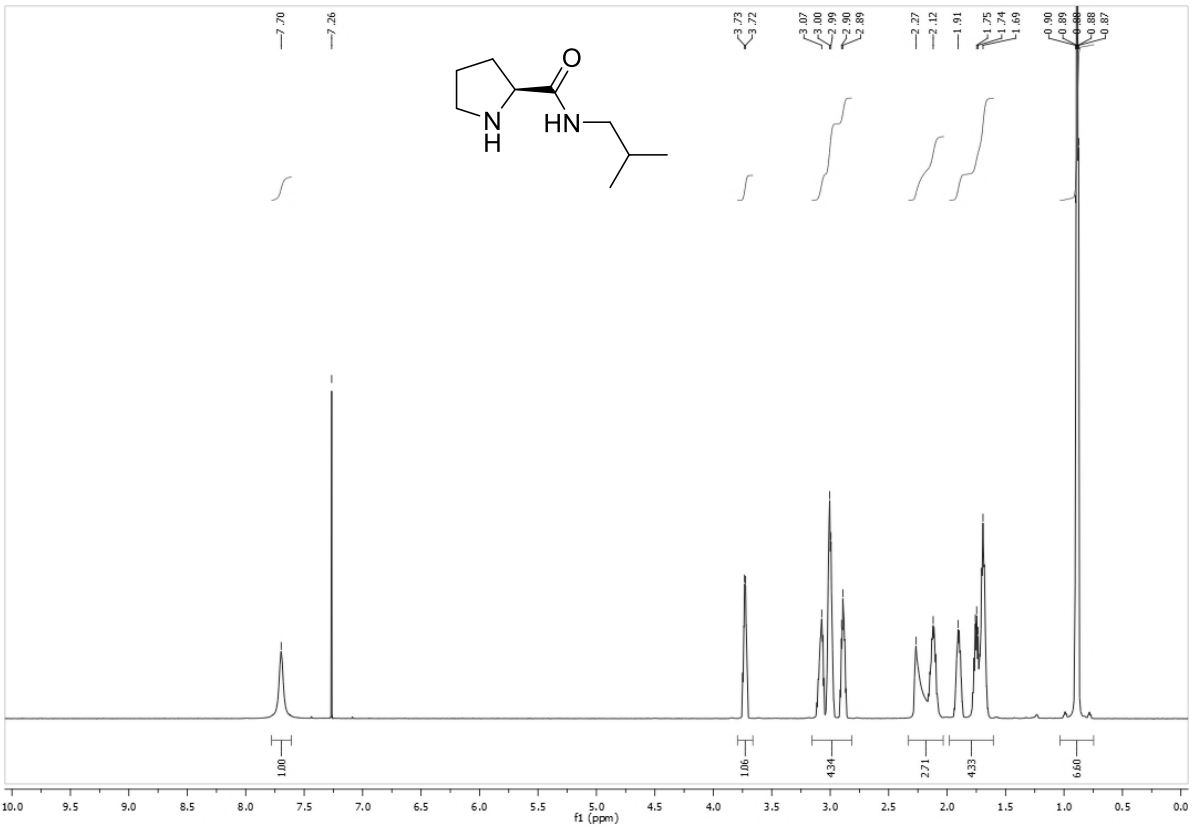



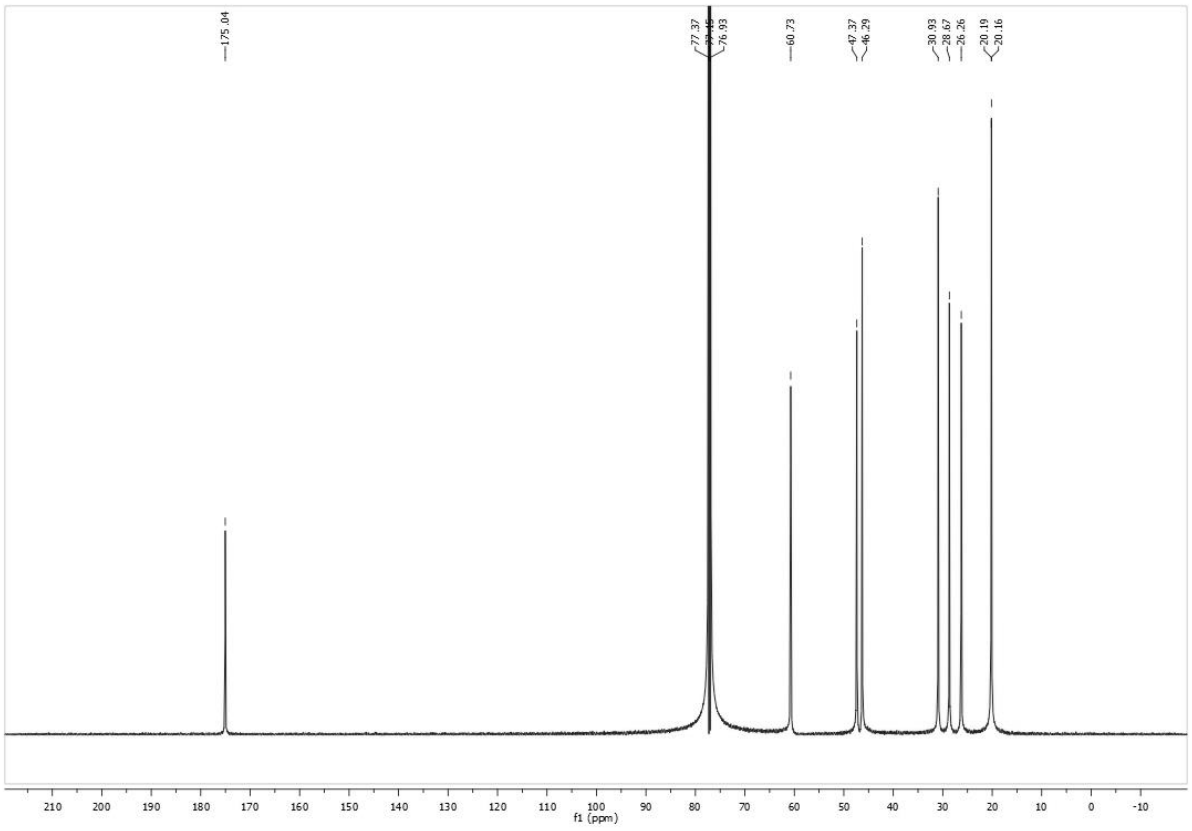
**(±)-2-Amino-3-methoxy-*N*-propylpropanamide 5z**



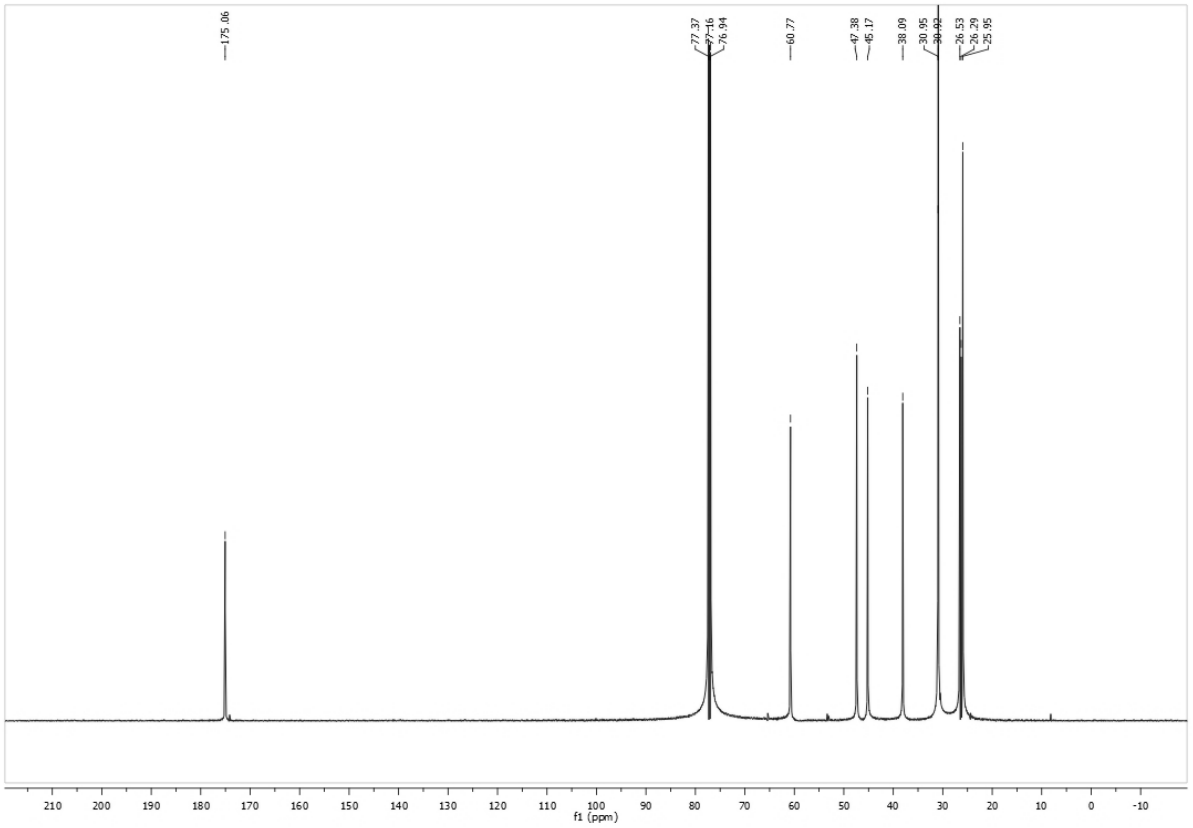



## *(S)-N*-Isobutylpyrrolidine-2-carboxamide 6a

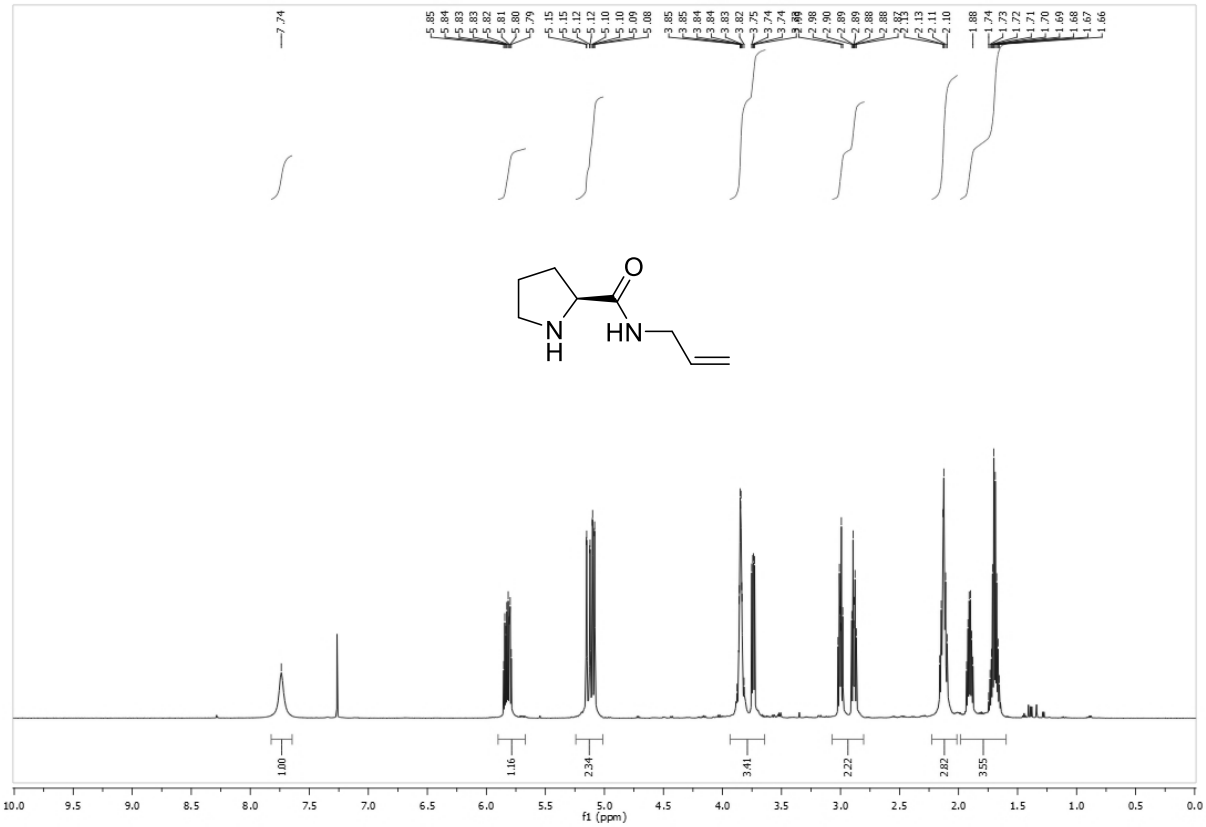


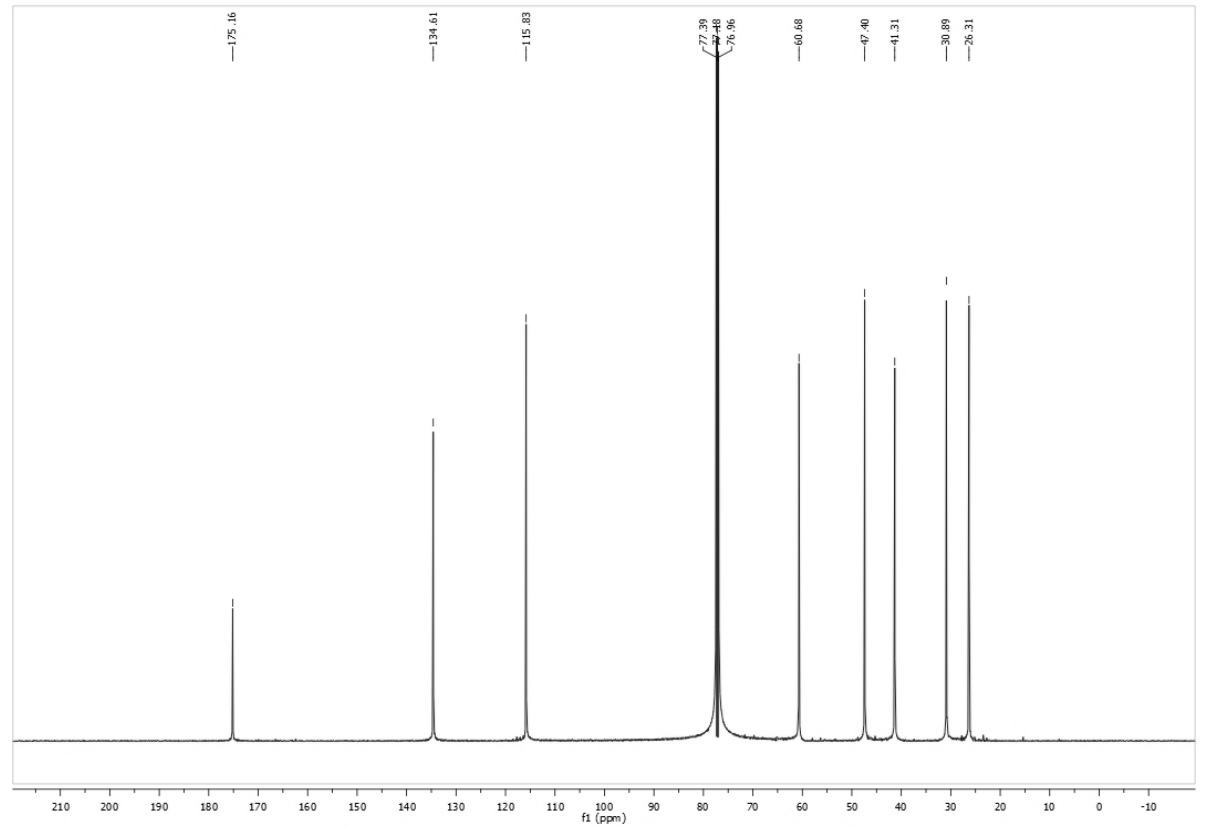



***(S)-N*-(Cyclohexylmethyl)pyrrolidine-2-carboxamide 6b**

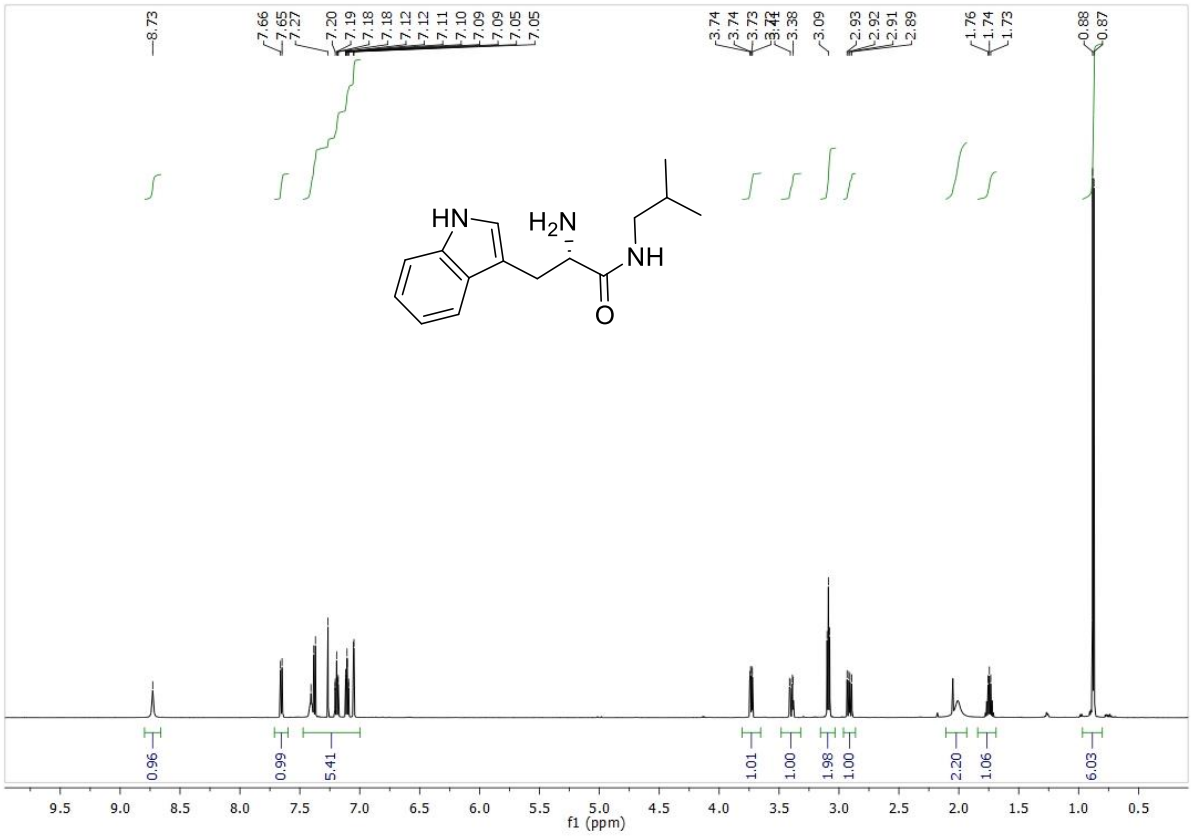



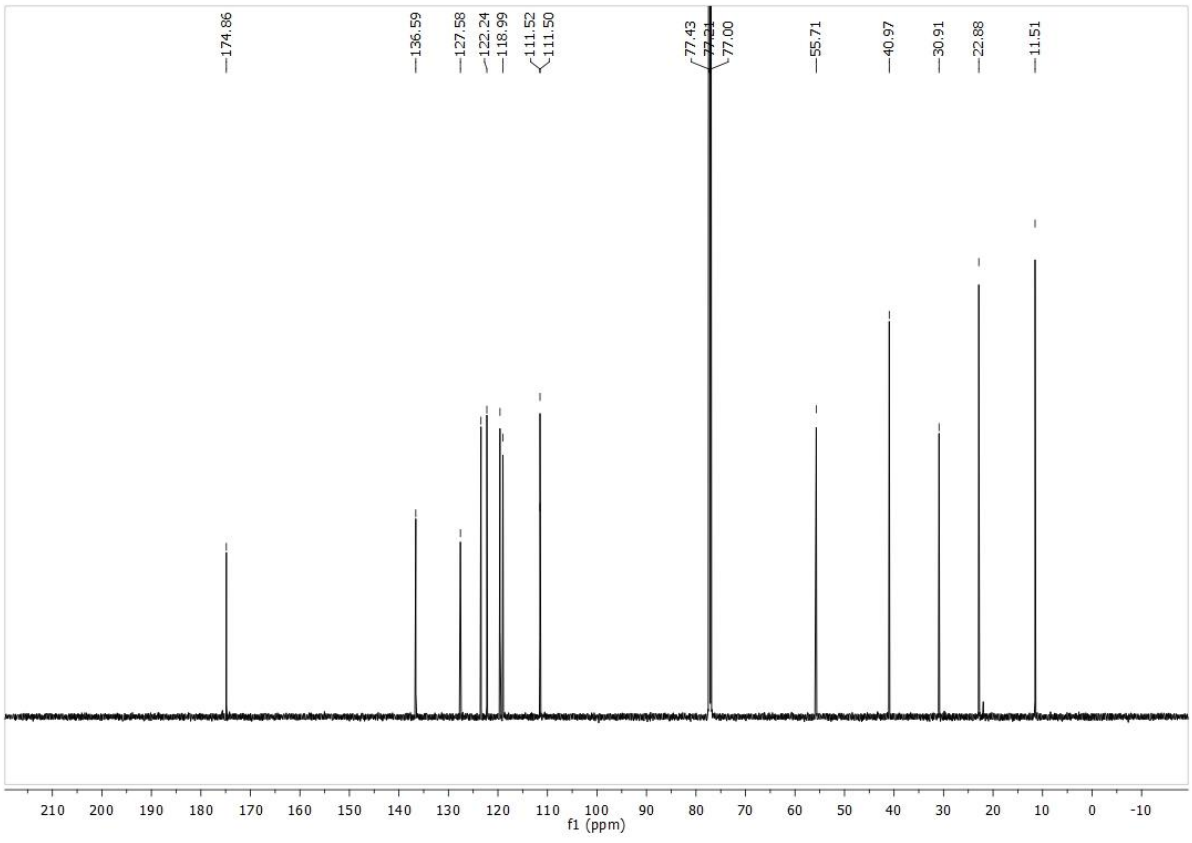
## *(S)-N*-Allylpyrrolidine-2-carboxamide 6c



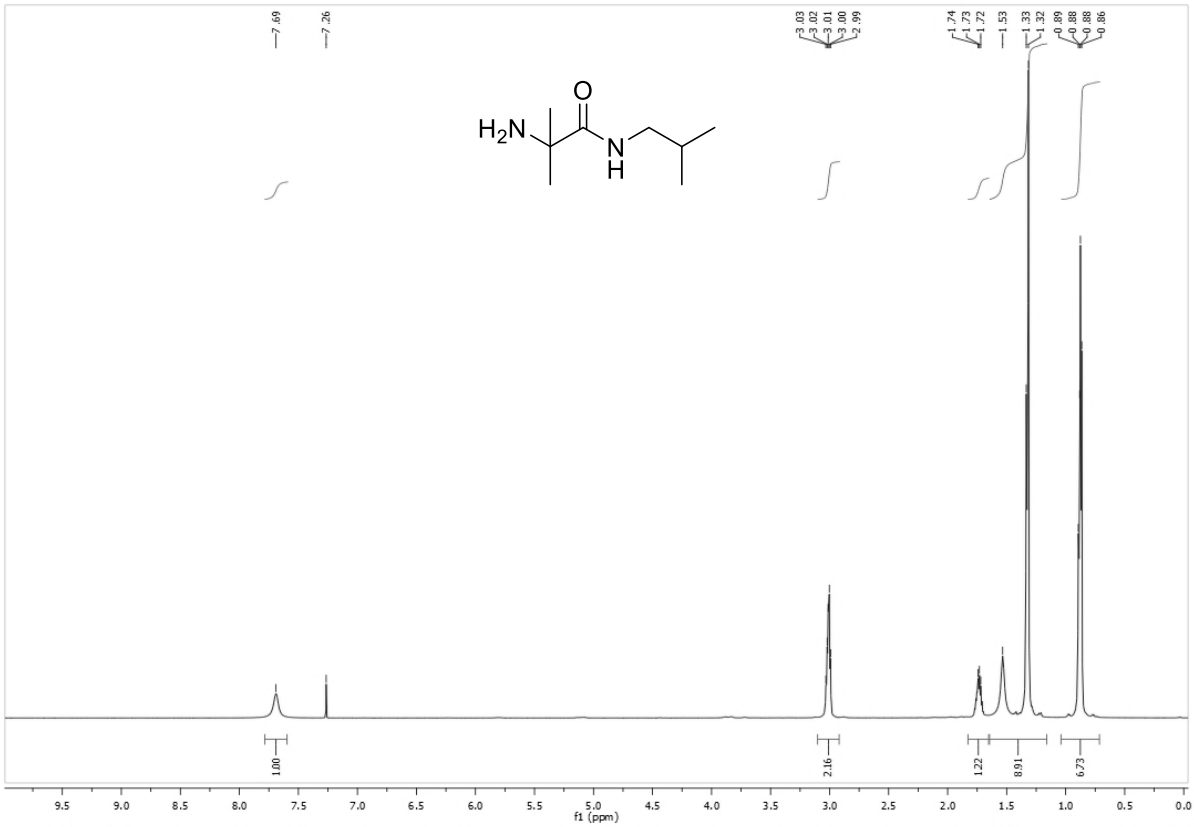



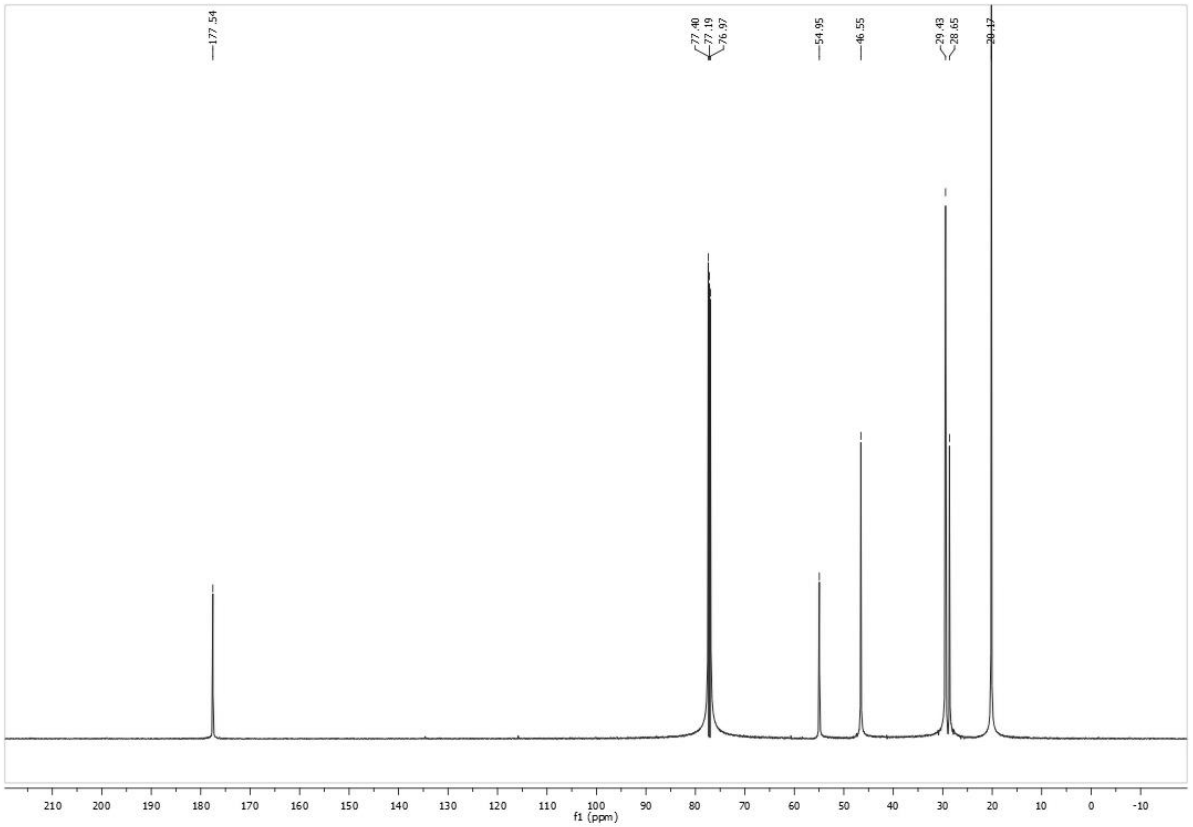
## *(S)*-2-Amino-3-(1H-indol-3-yl)-*N*-isobutylpropanamide 6d



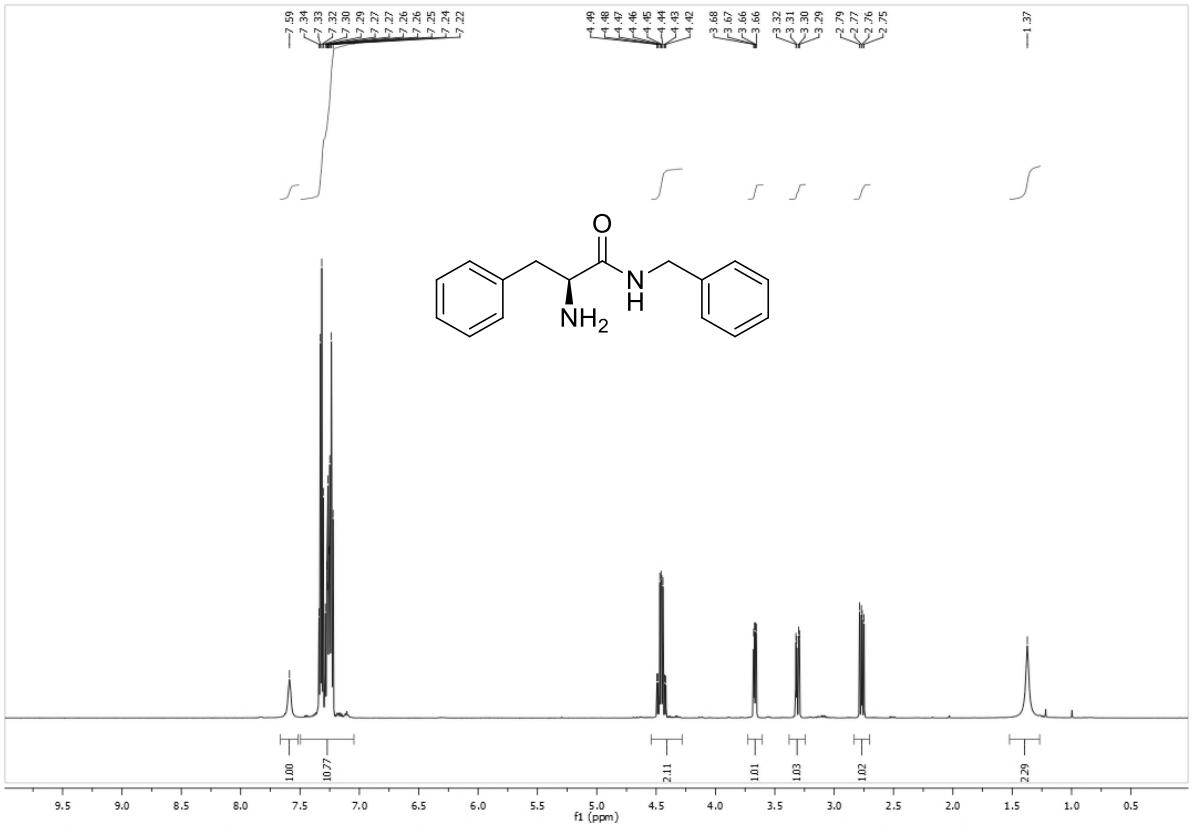



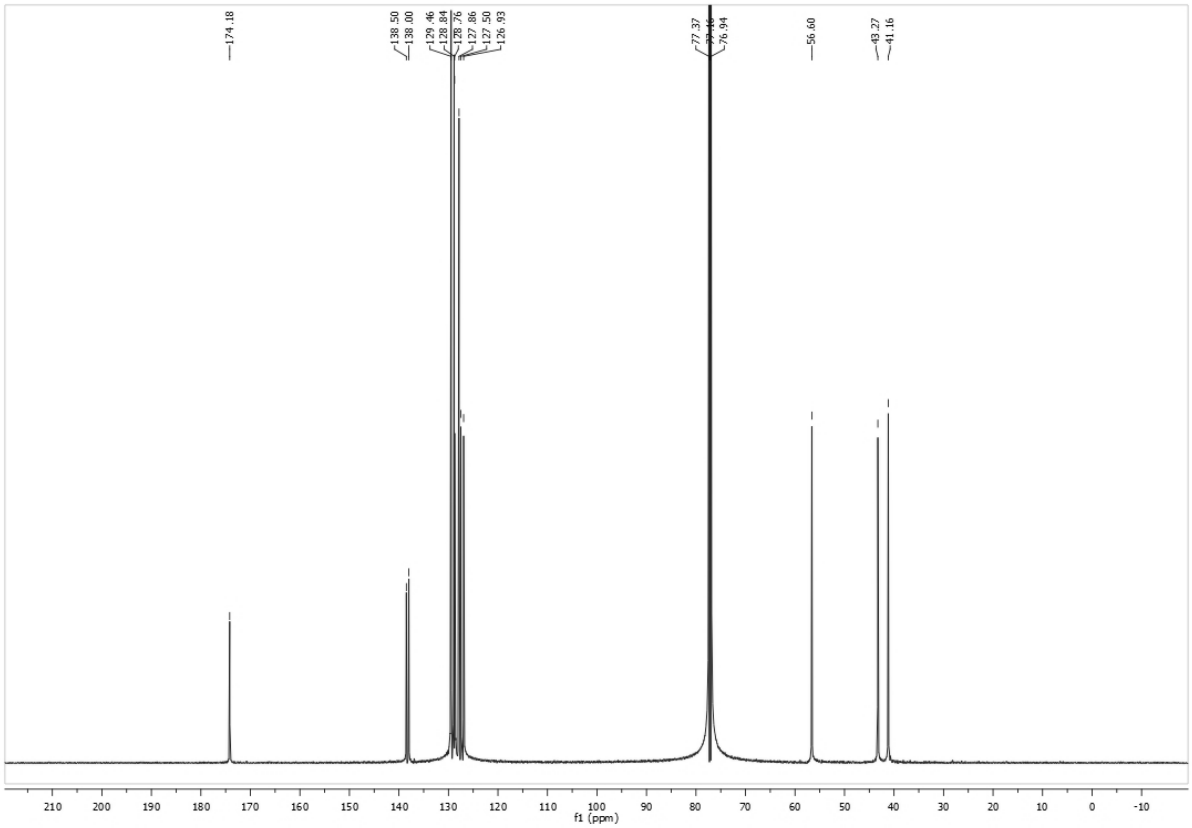
## 2-Amino-*N*-isobutyl-2-methylpropanamide 6e



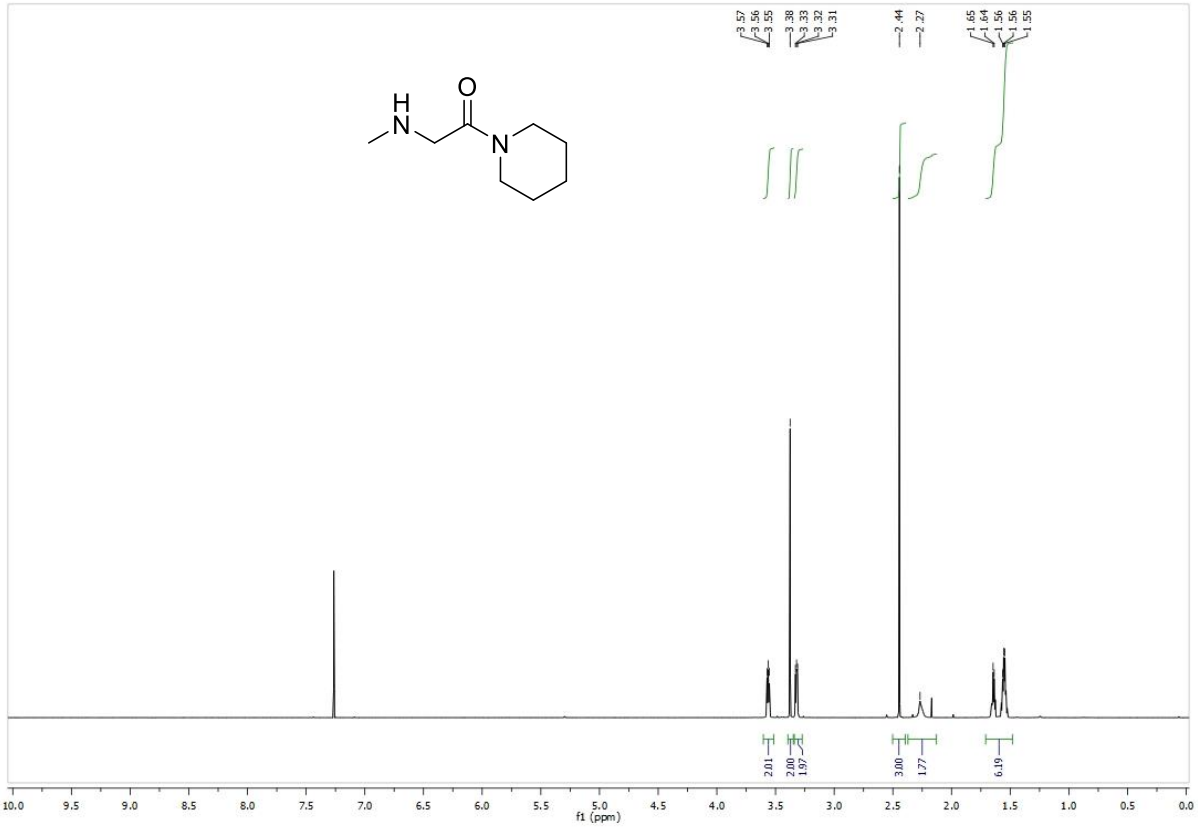



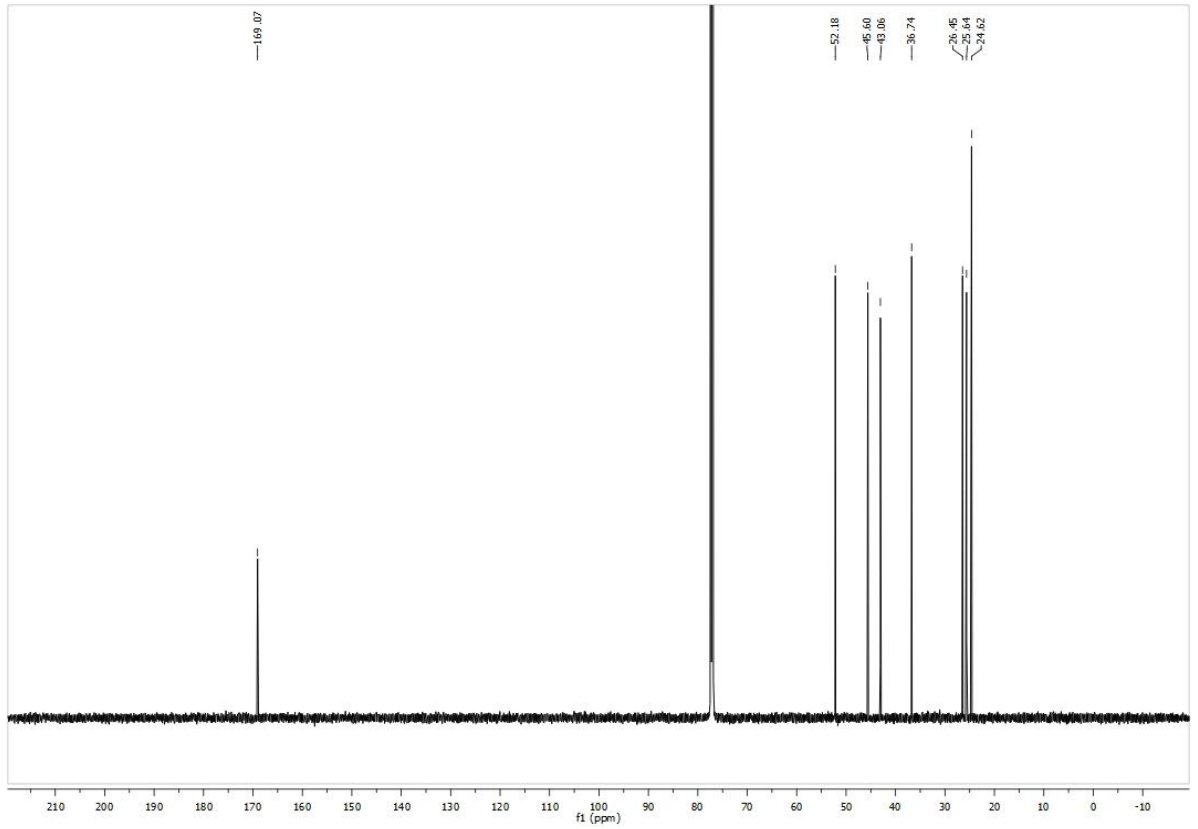
## *(S)*-2-Amino-*N*-benzyl-3-phenylpropanamide 6f



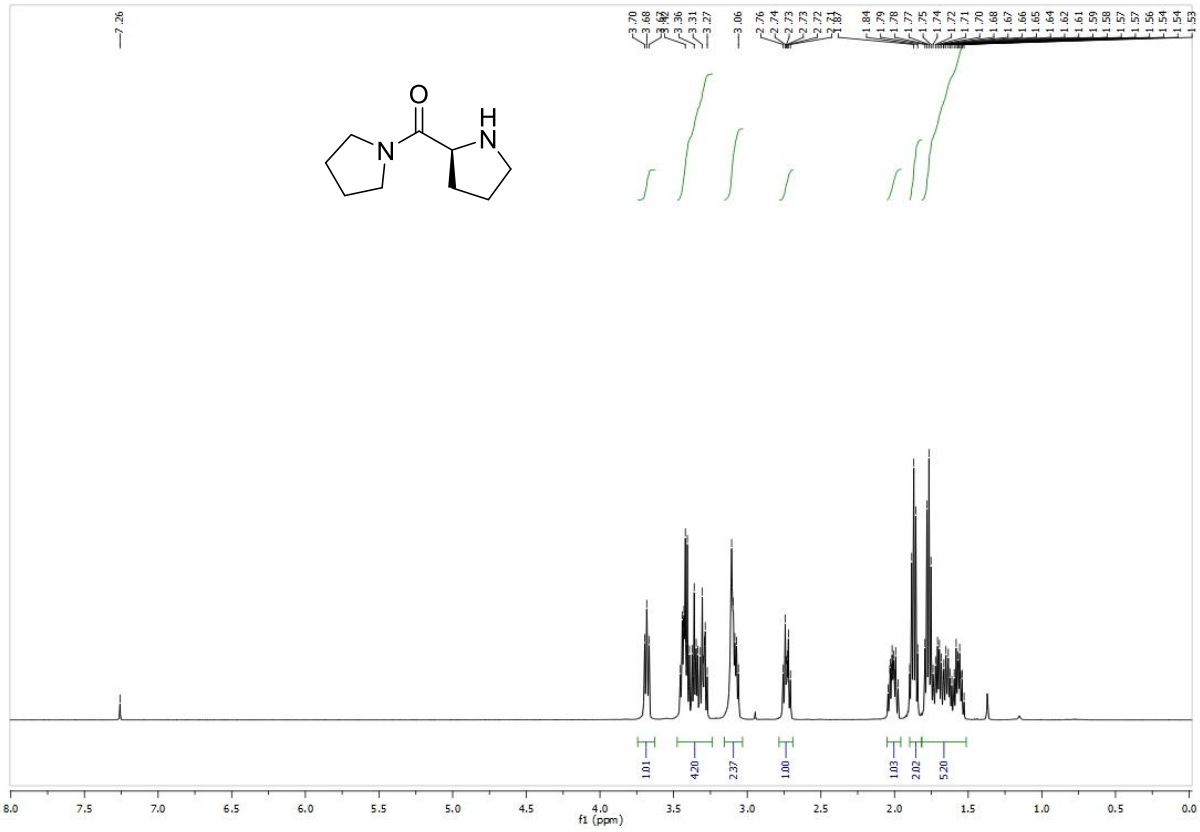



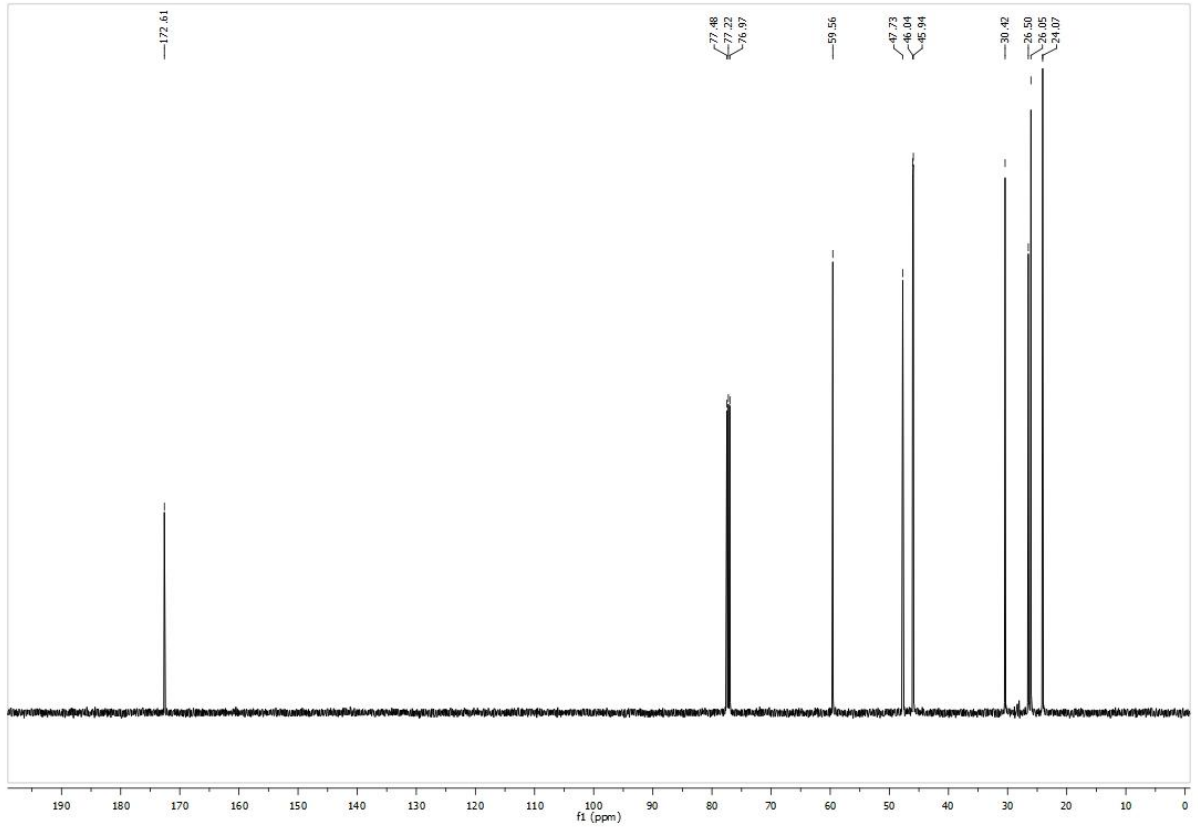
## 2-(methylamino)-1-(piperidin-1-yl)ethan-1-one 6g



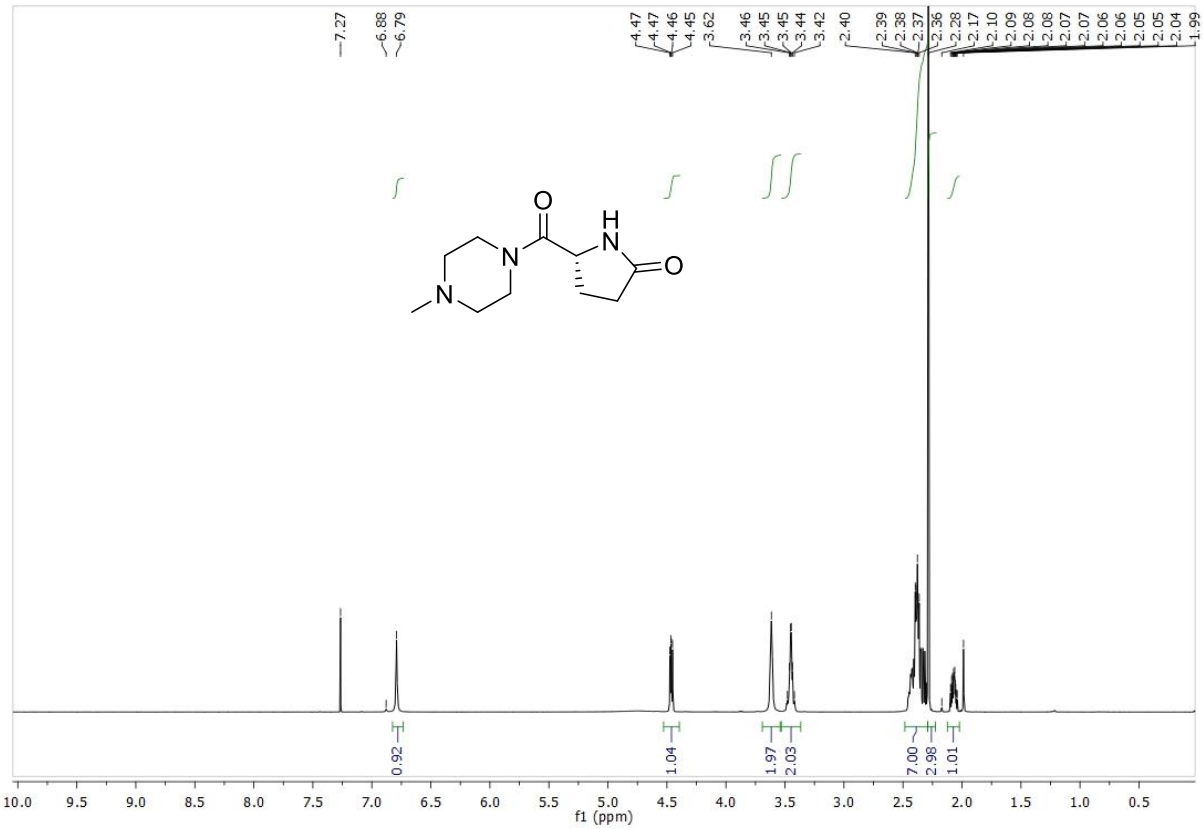



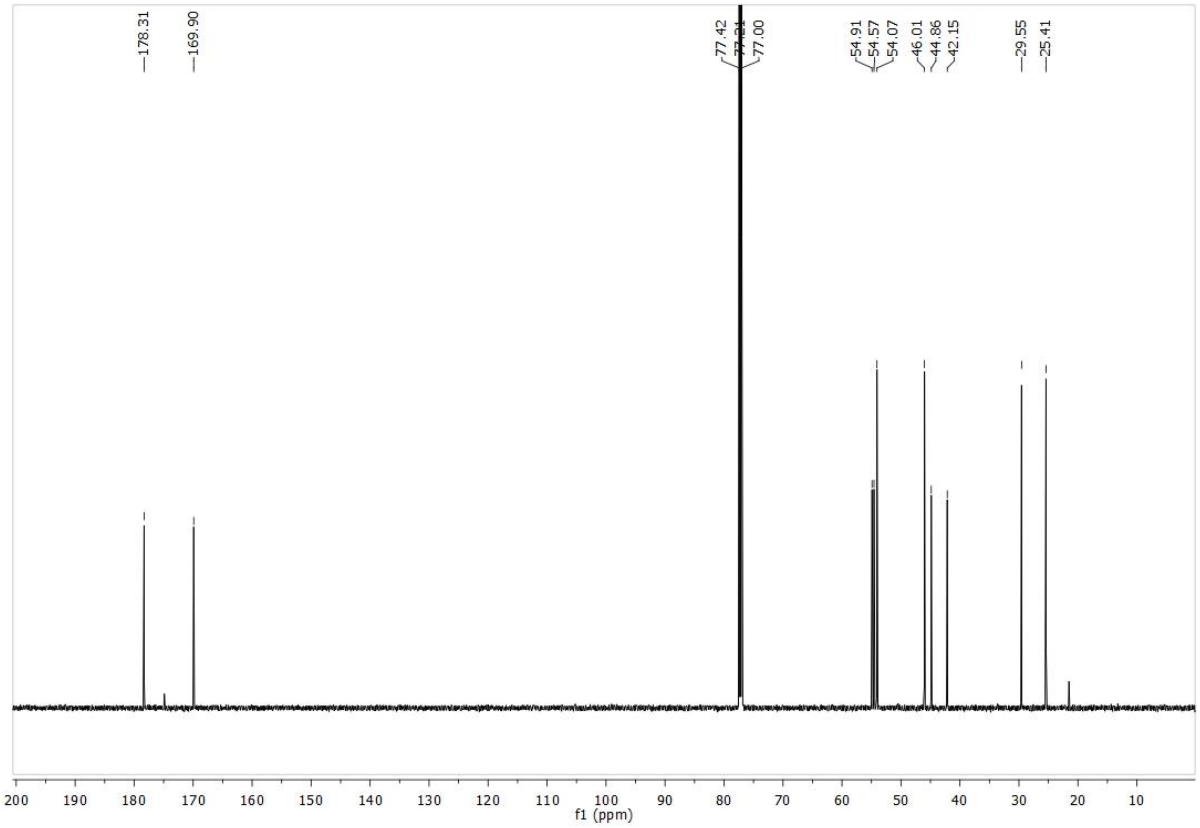
## *(S)*-1-Prolylpyrrolidine 6h



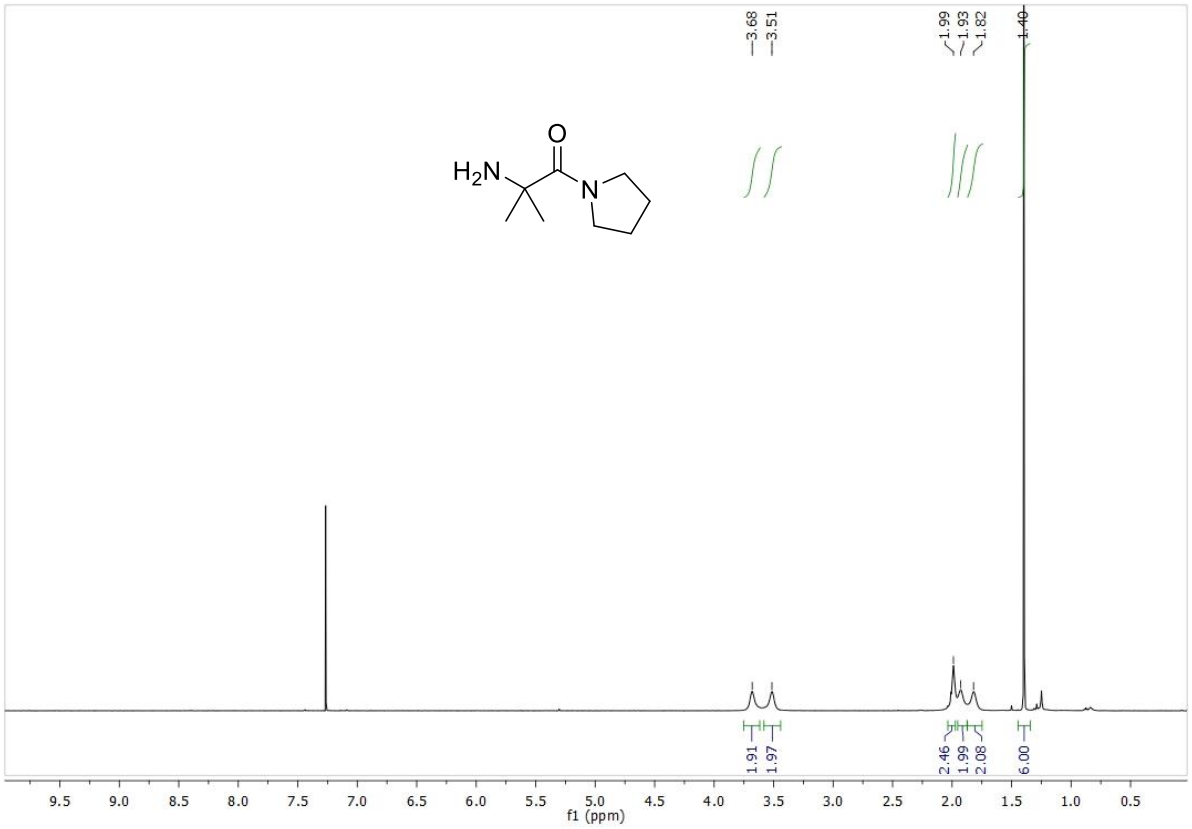



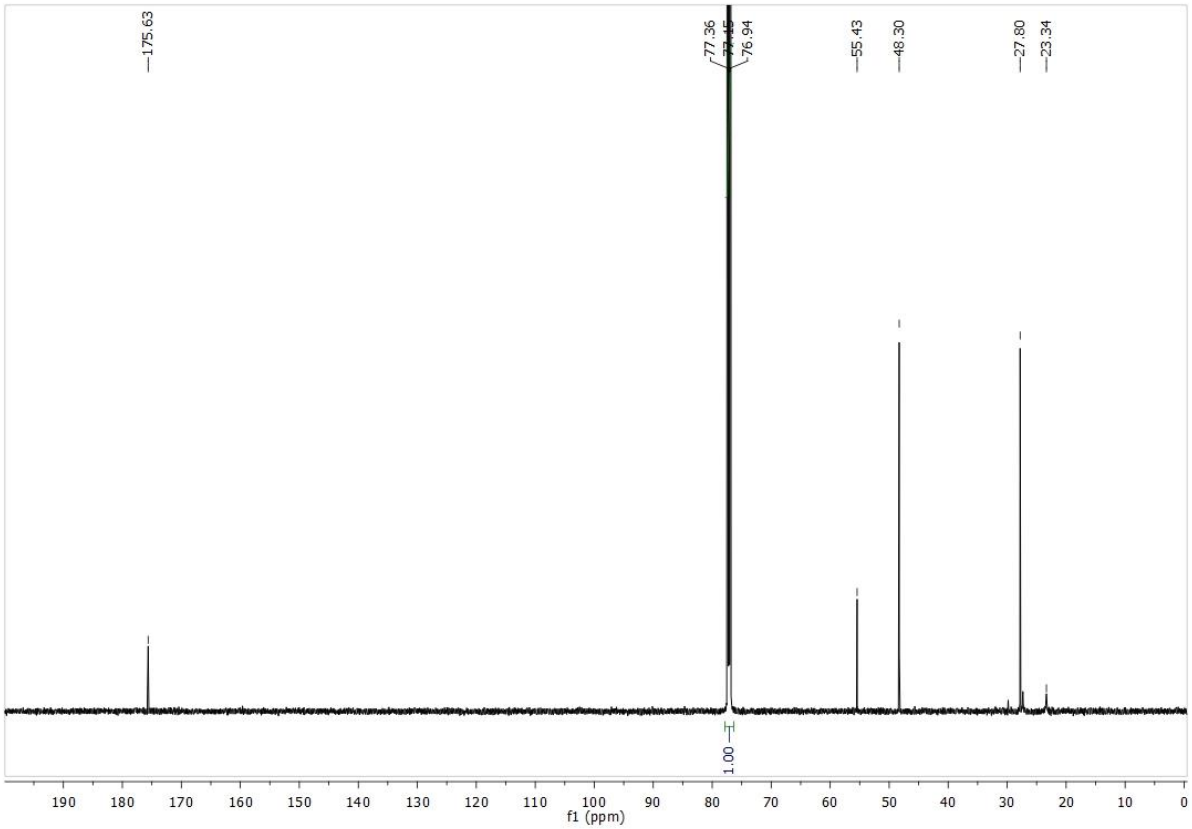
**(*R*)-5-(4-Methylpiperazine-1-carbonyl)pyrrolidin-2-one 6i**



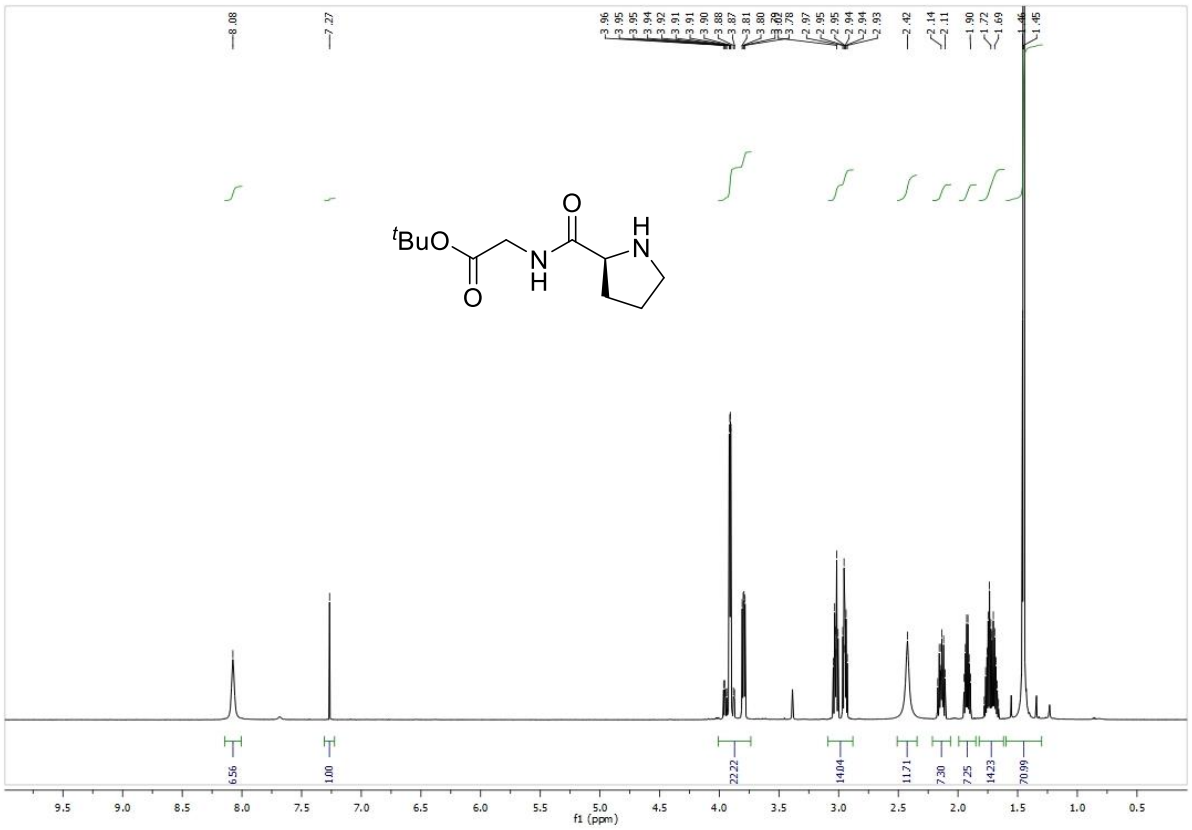



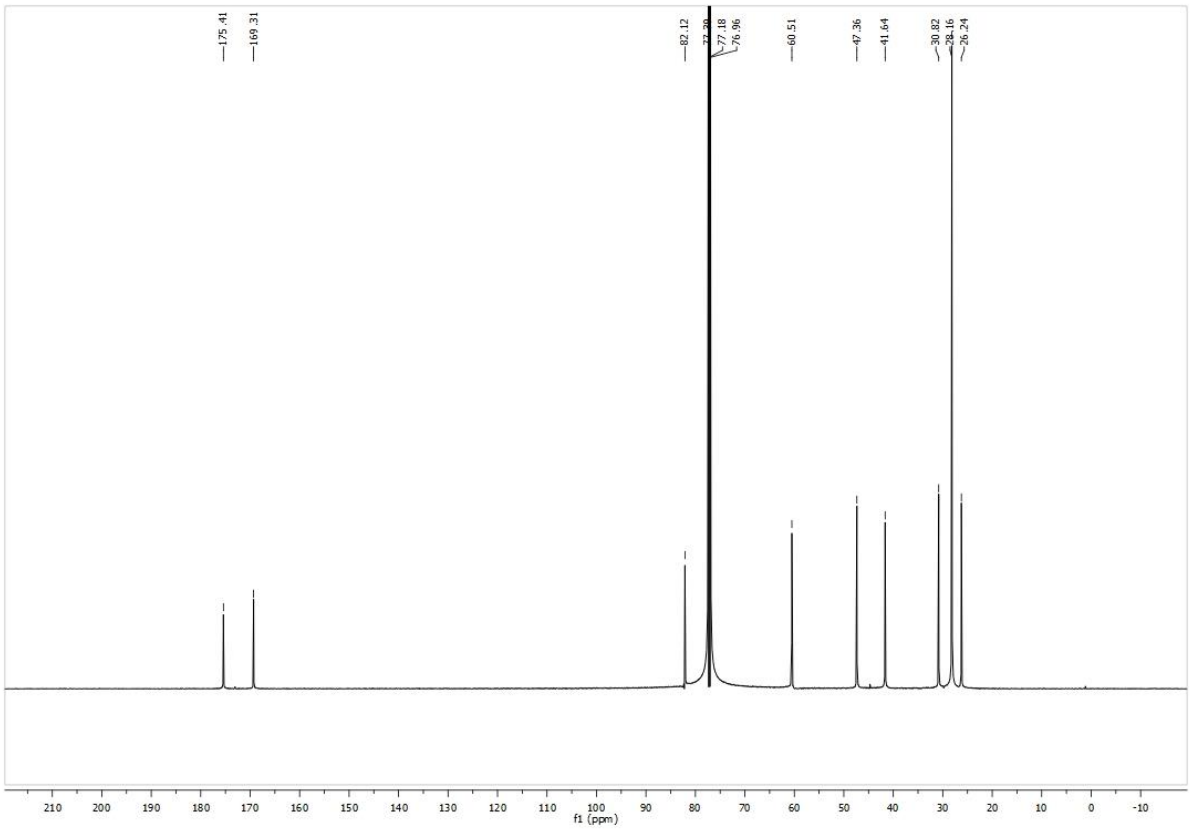
**2-Amino-2-methyl-1-(pyrrolidin-1-yl)propan-1-one 6j**



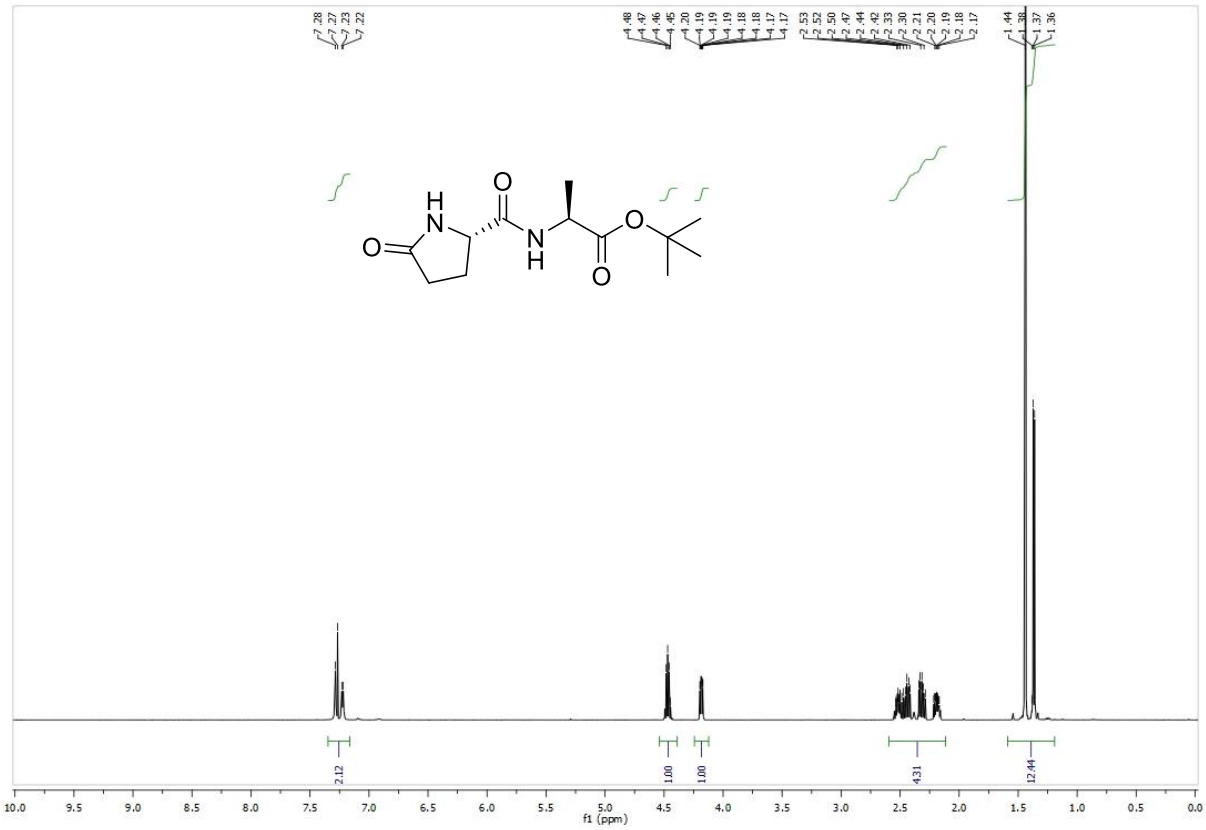



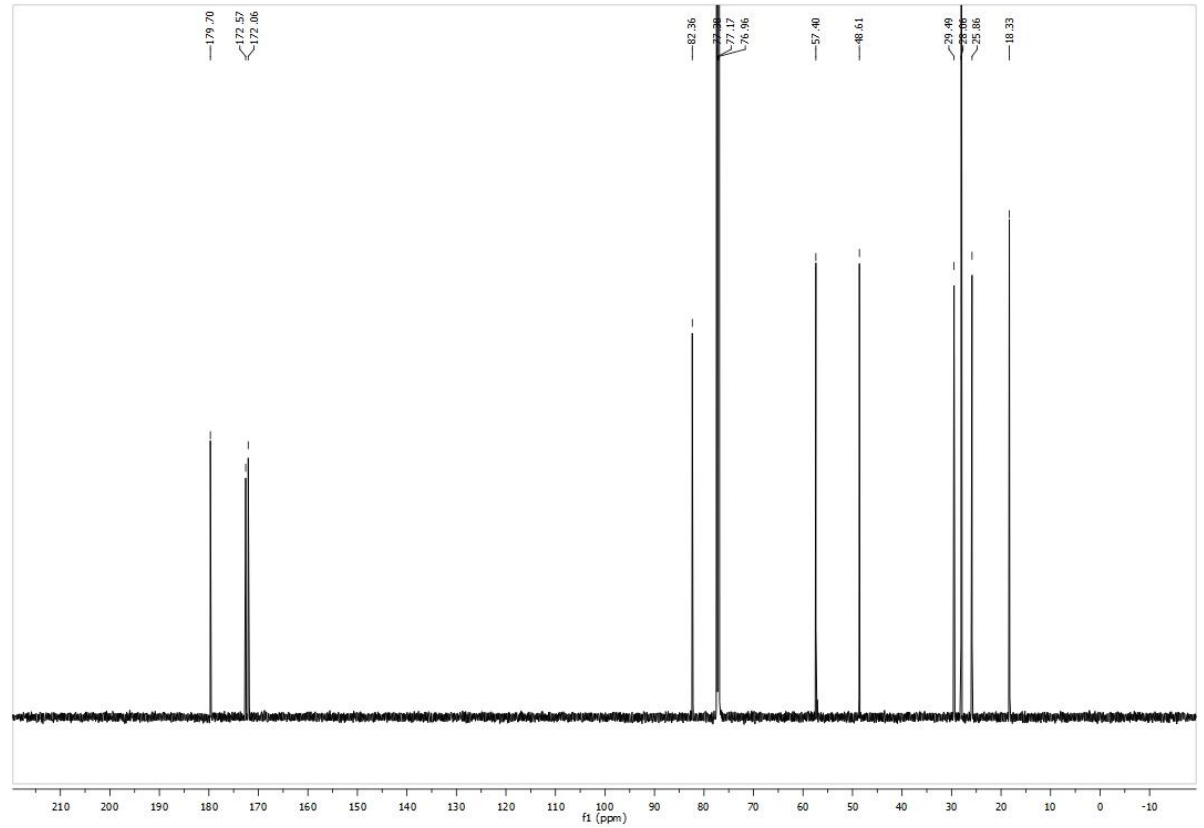
***tert*-Butyl (*S*)-prolylglycinate 6k**



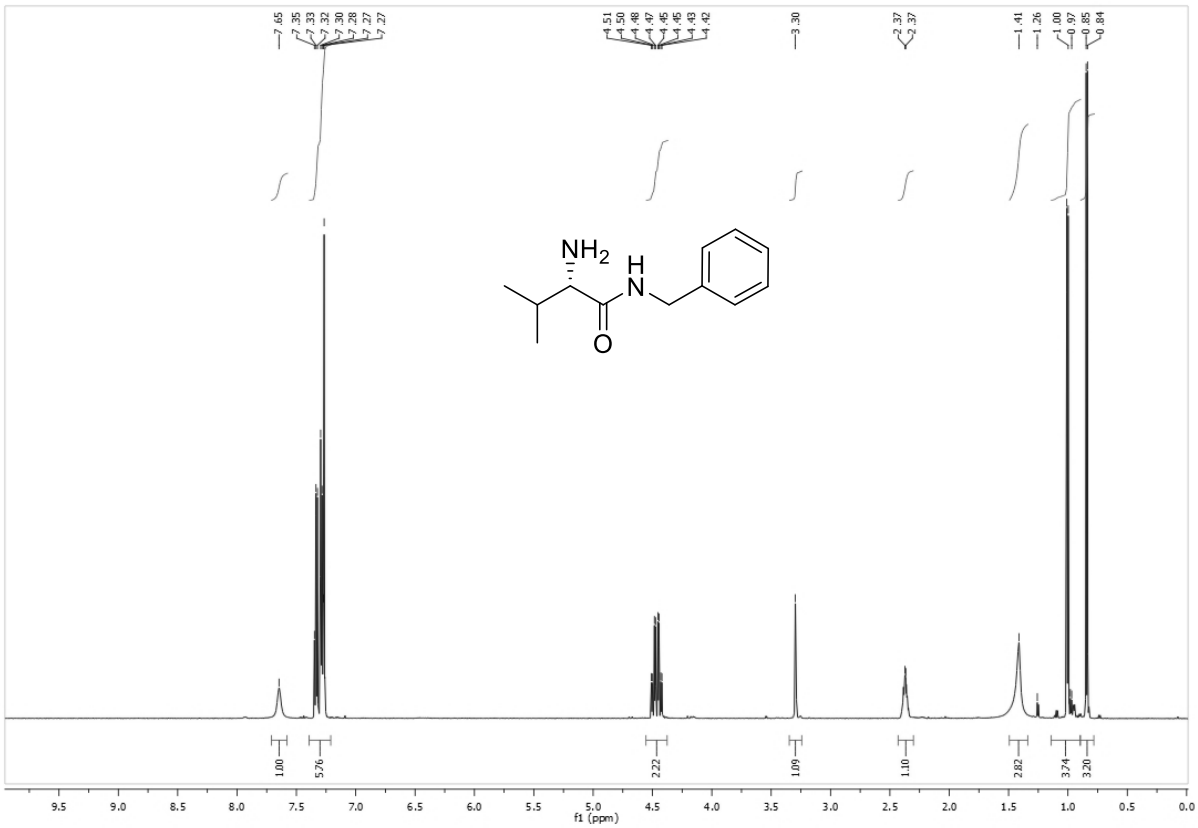



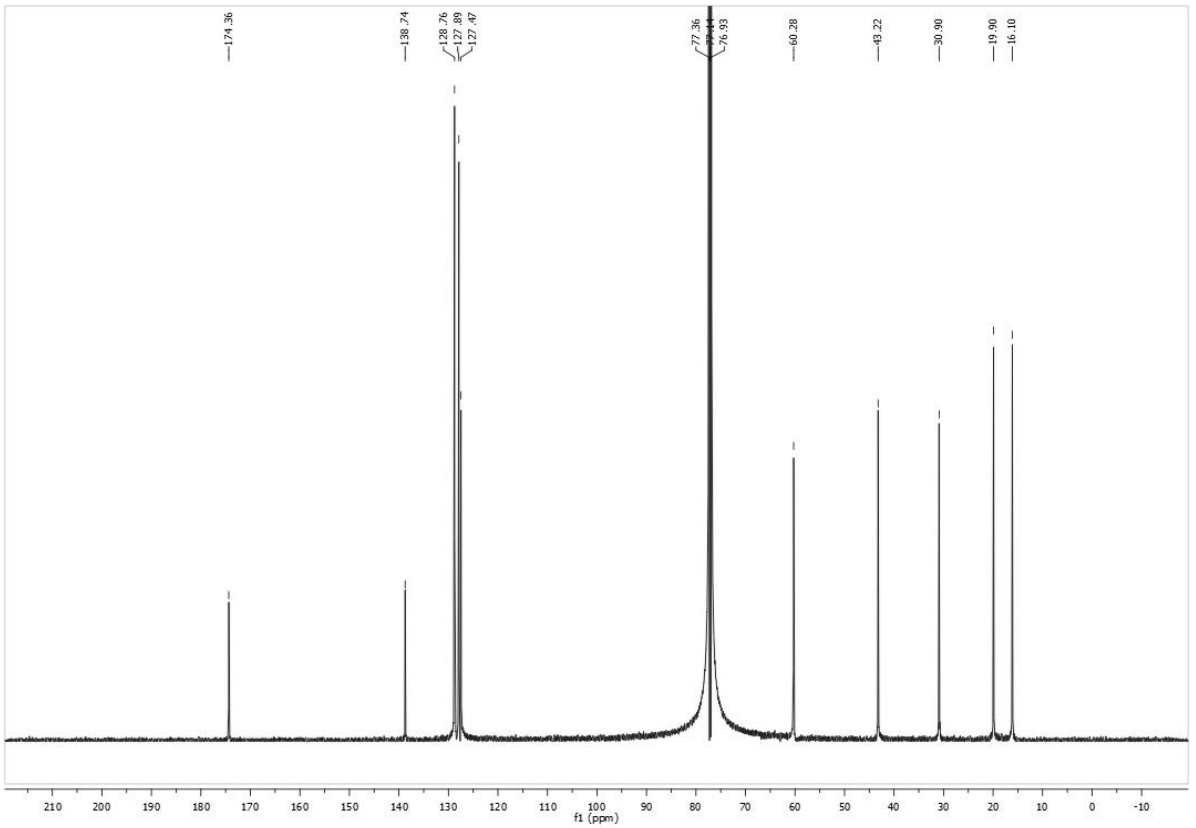
**tert-Butyl ((*S*)-5-oxopyrrolidine-2-carbonyl)-L-alaninate 6l**



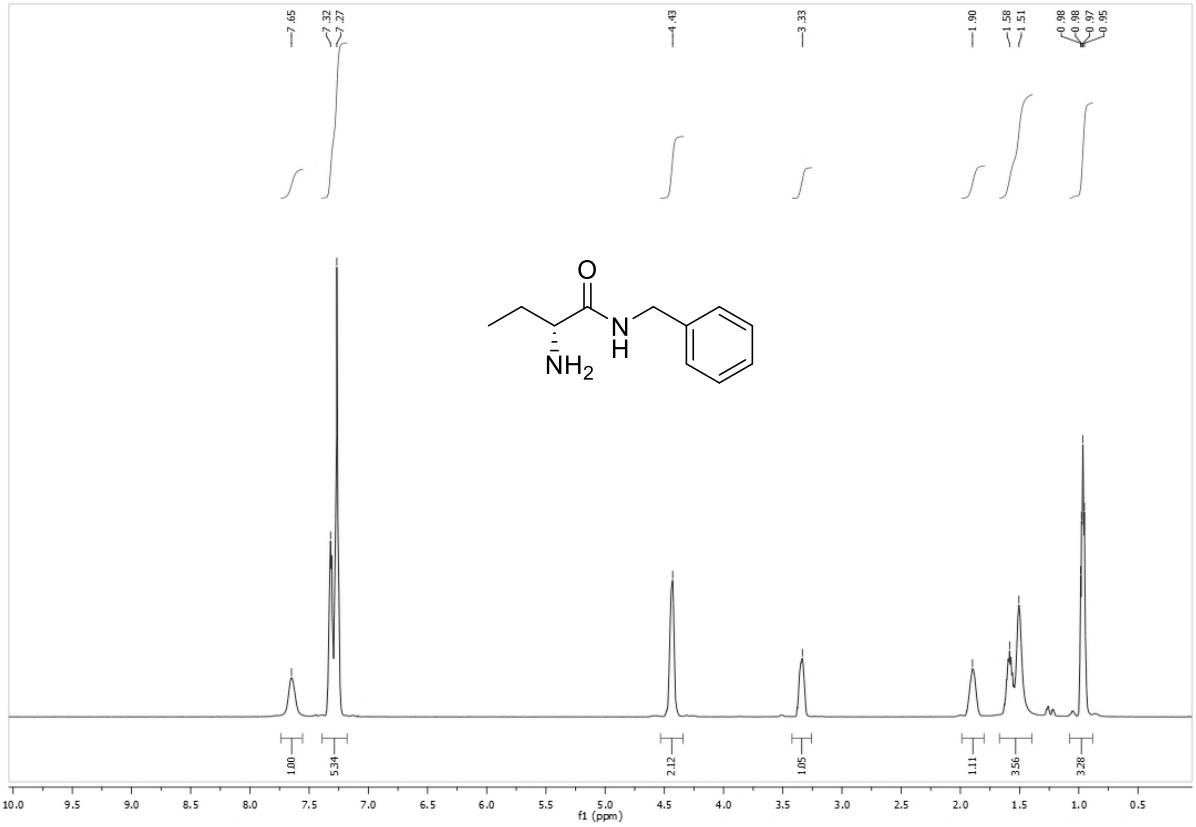



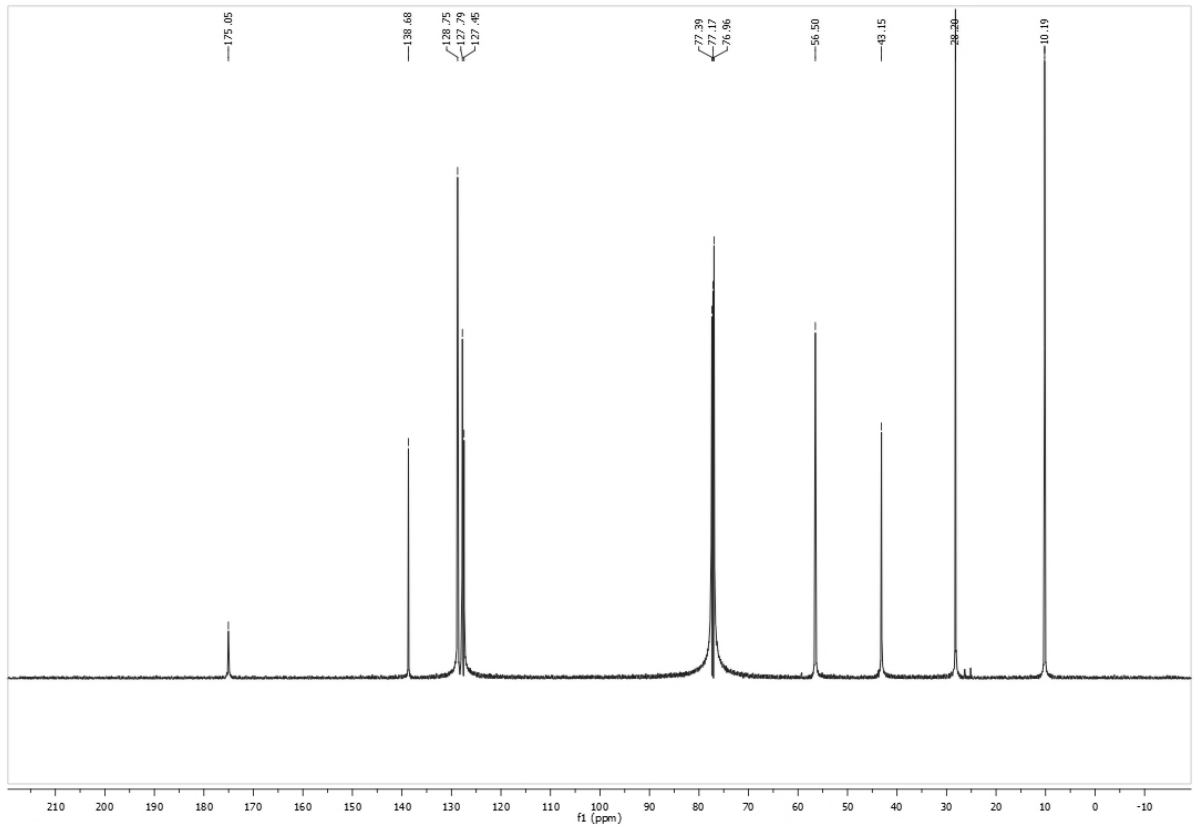
## *(S)*-2-Amino-*N*-benzyl-3-methylbutanamide 6m



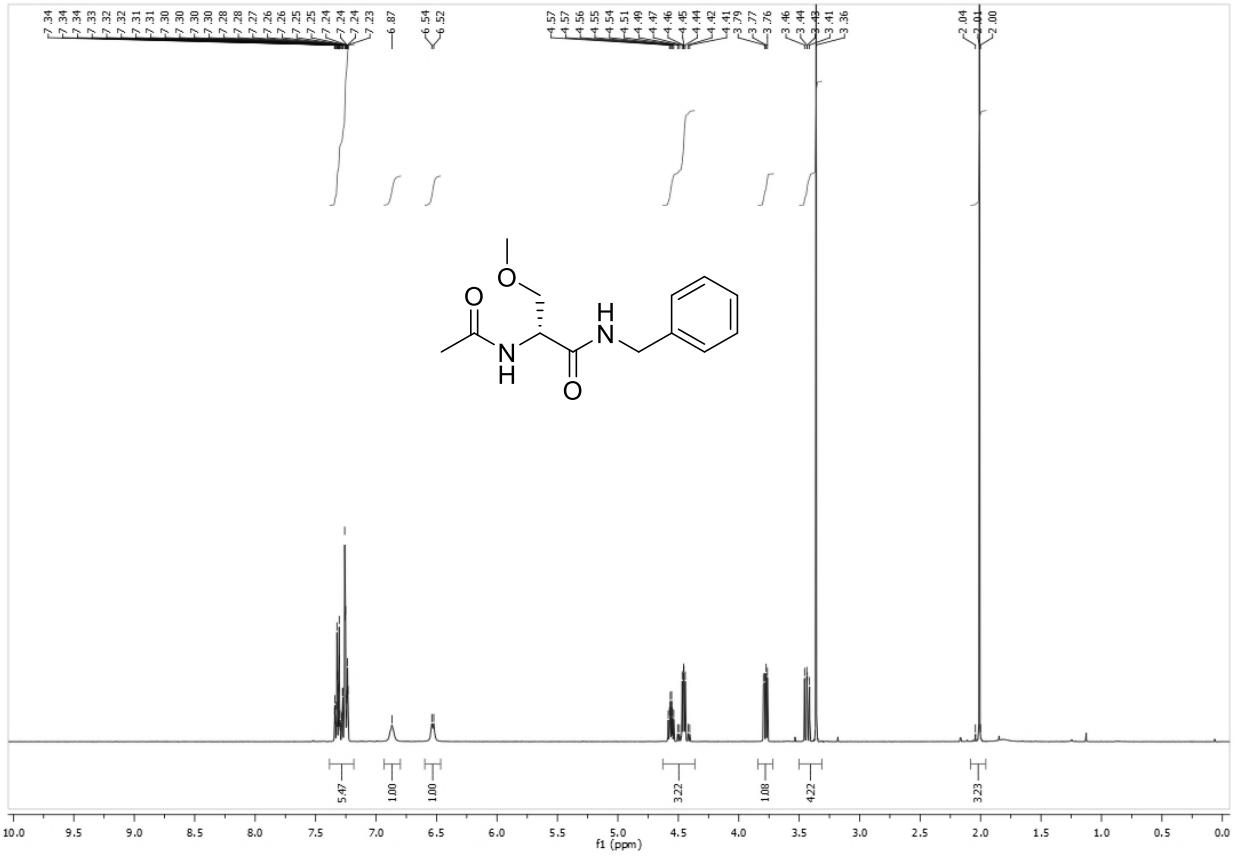



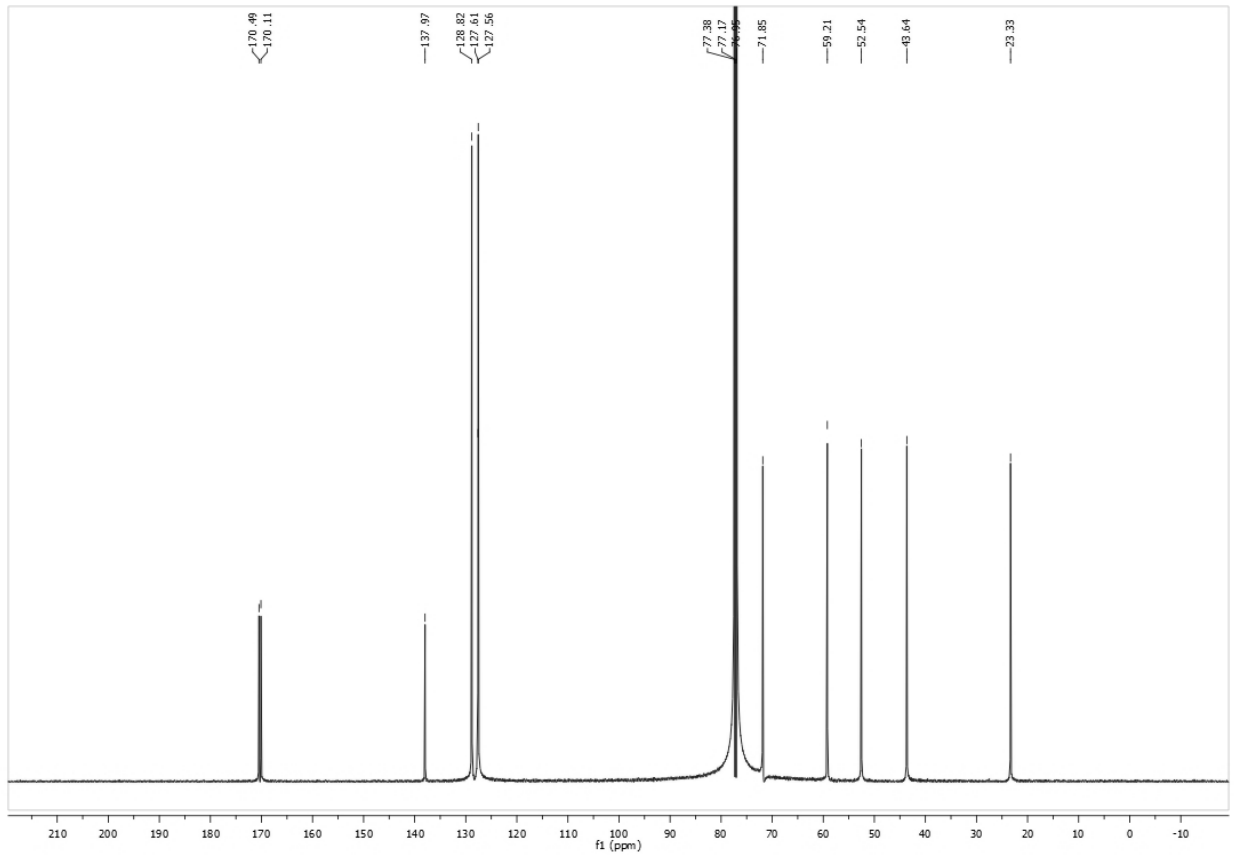
## *(R)*-2-Amino-*N*-benzylbutanamide 6n



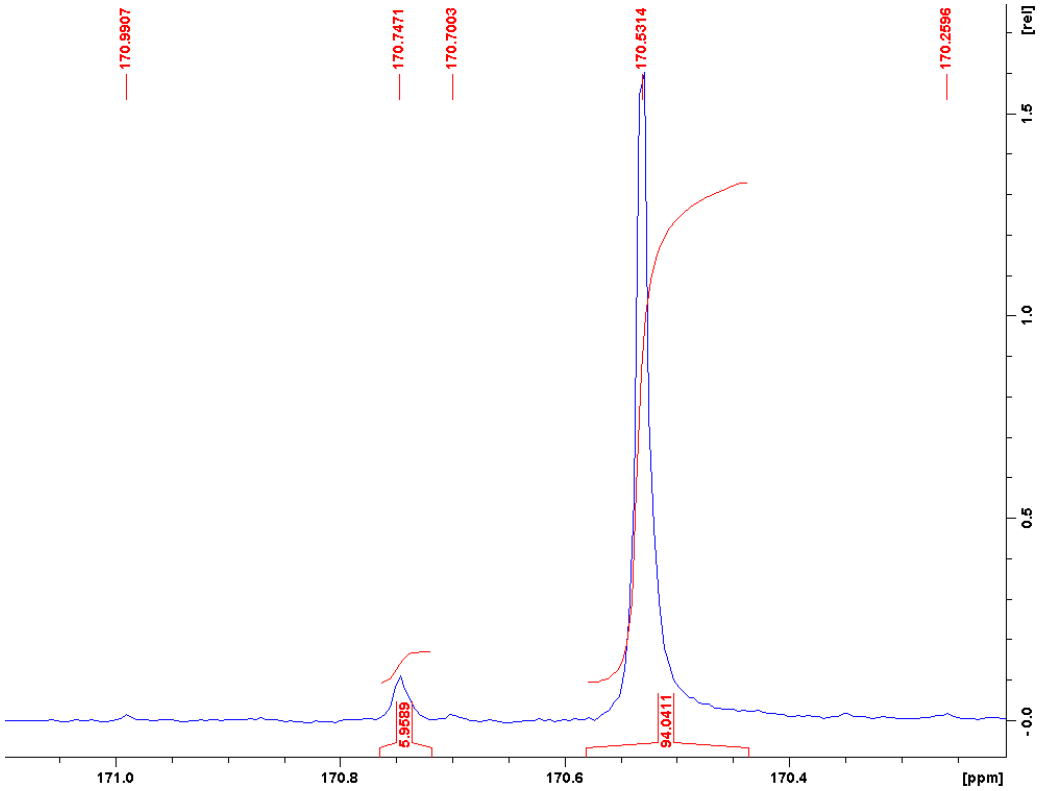
**(*R*)-2-Acetamido-*N*-benzyl-3-methoxypropanamide (Lacosamide) 7**



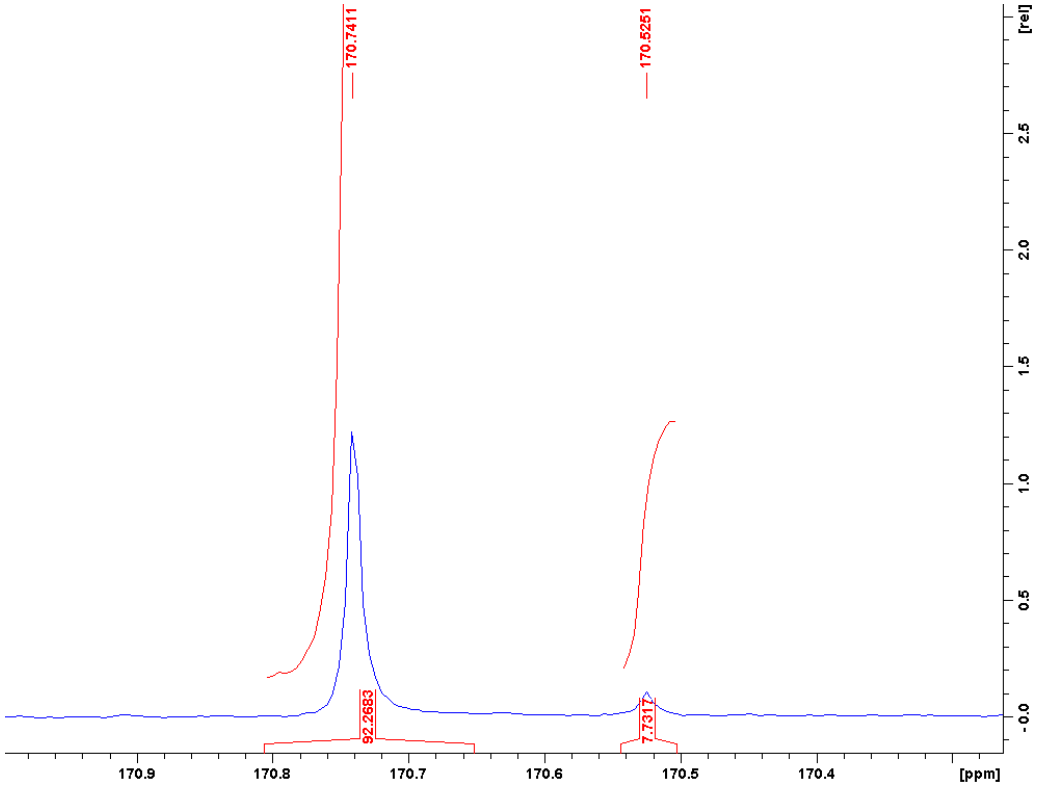



## 7. $^{1}$H NMR spectra and HPLC traces used for enantiopurity measurements

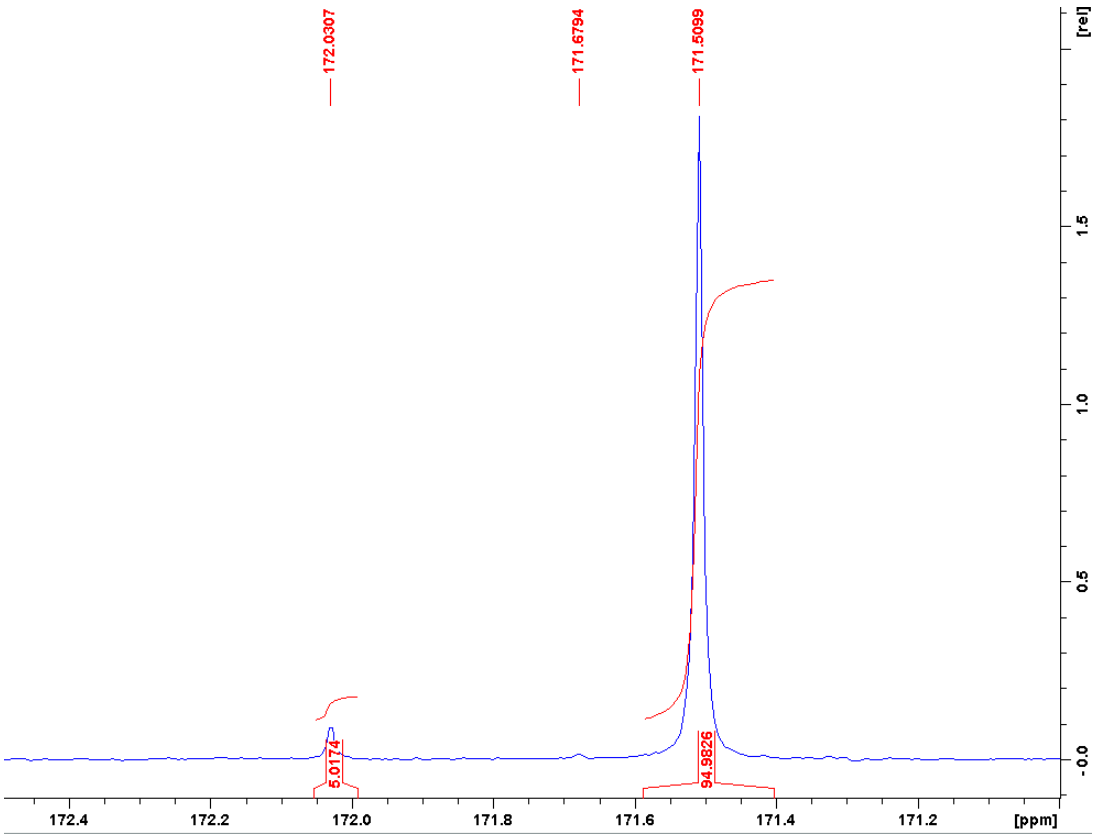
**(*S*)-2-Amino-*N*-propylpropanamide 5a.HCl – (*R*)-aldehyde**



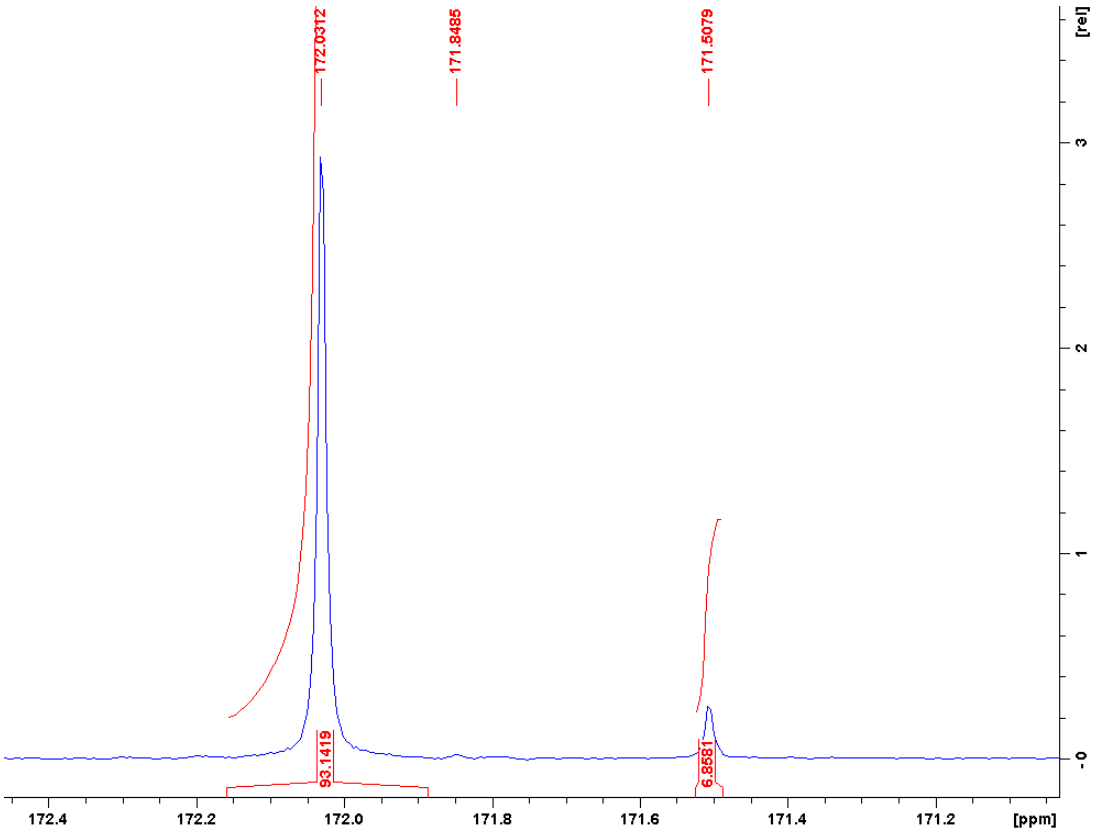

**(*S*)-2-Amino-*N*-propylpropanamide 5a.HCl – (*S*)-aldehyde**



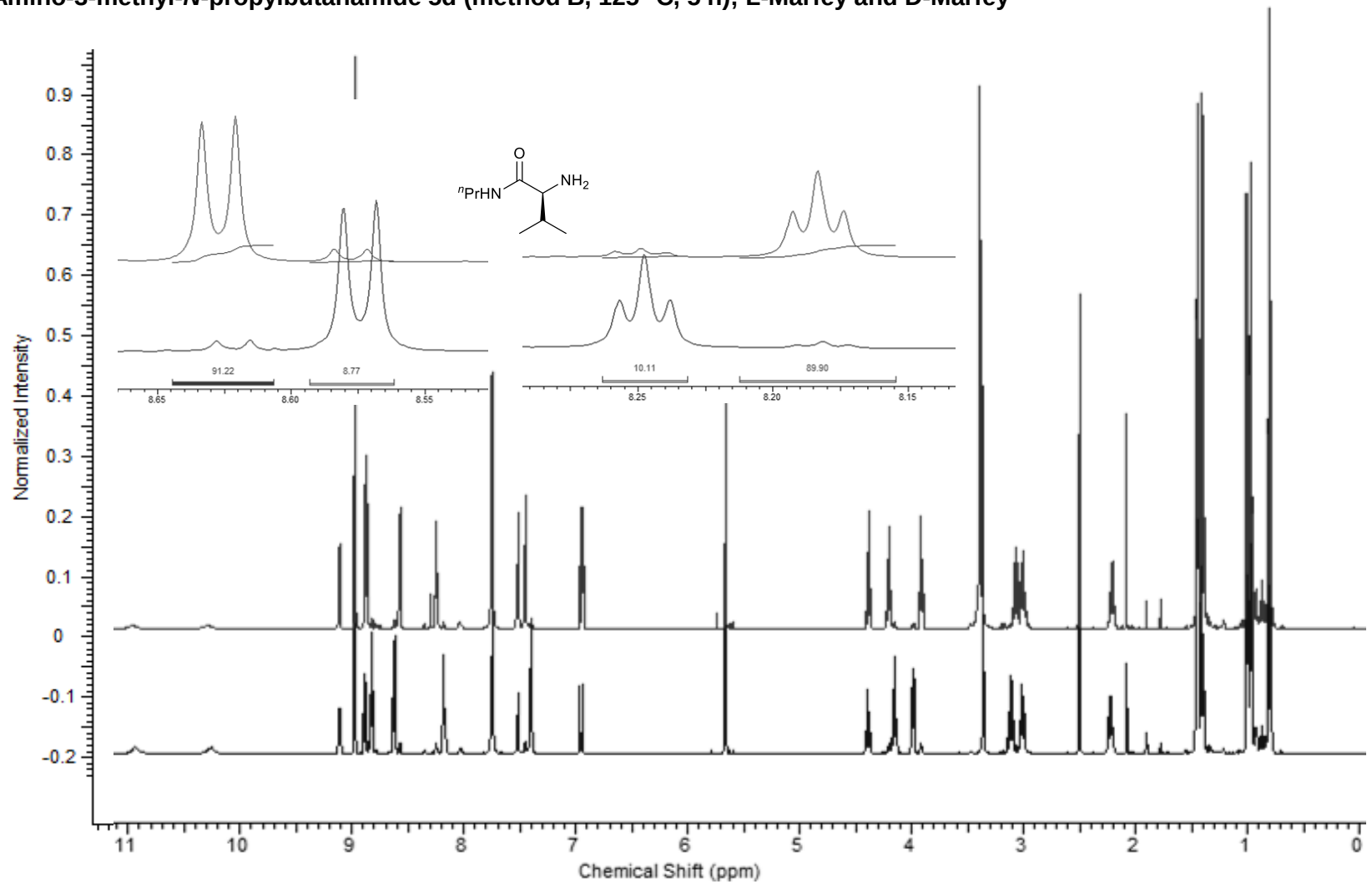
**(*S*)-2-Amino-3-phenyl-*N*-propylpropanamide 5b.HCl – (*R*)-aldehyde**



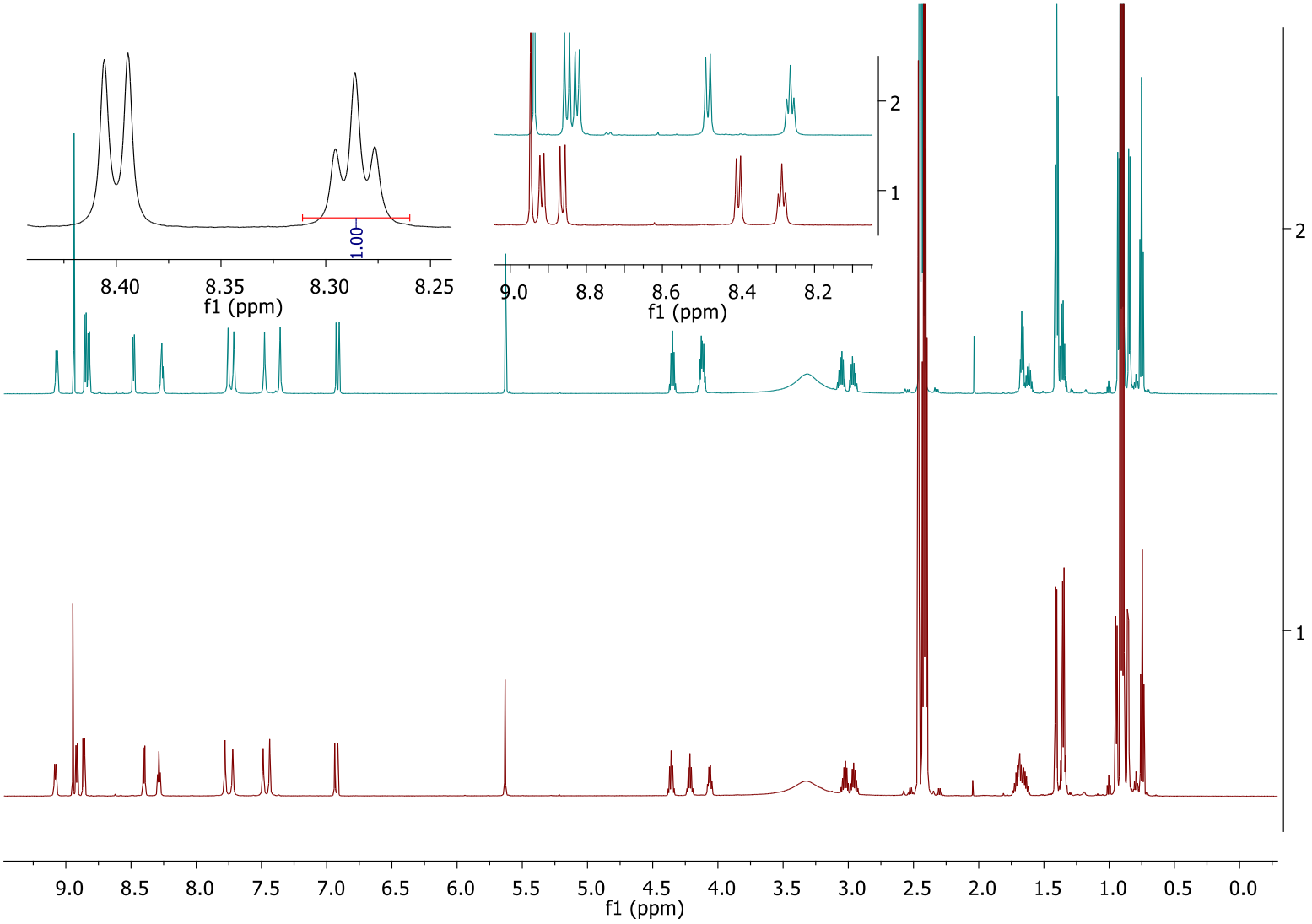

**(*S*)-2-Amino-3-phenyl-*N*-propylpropanamide 5b.HCl – (*S*)-aldehyde**



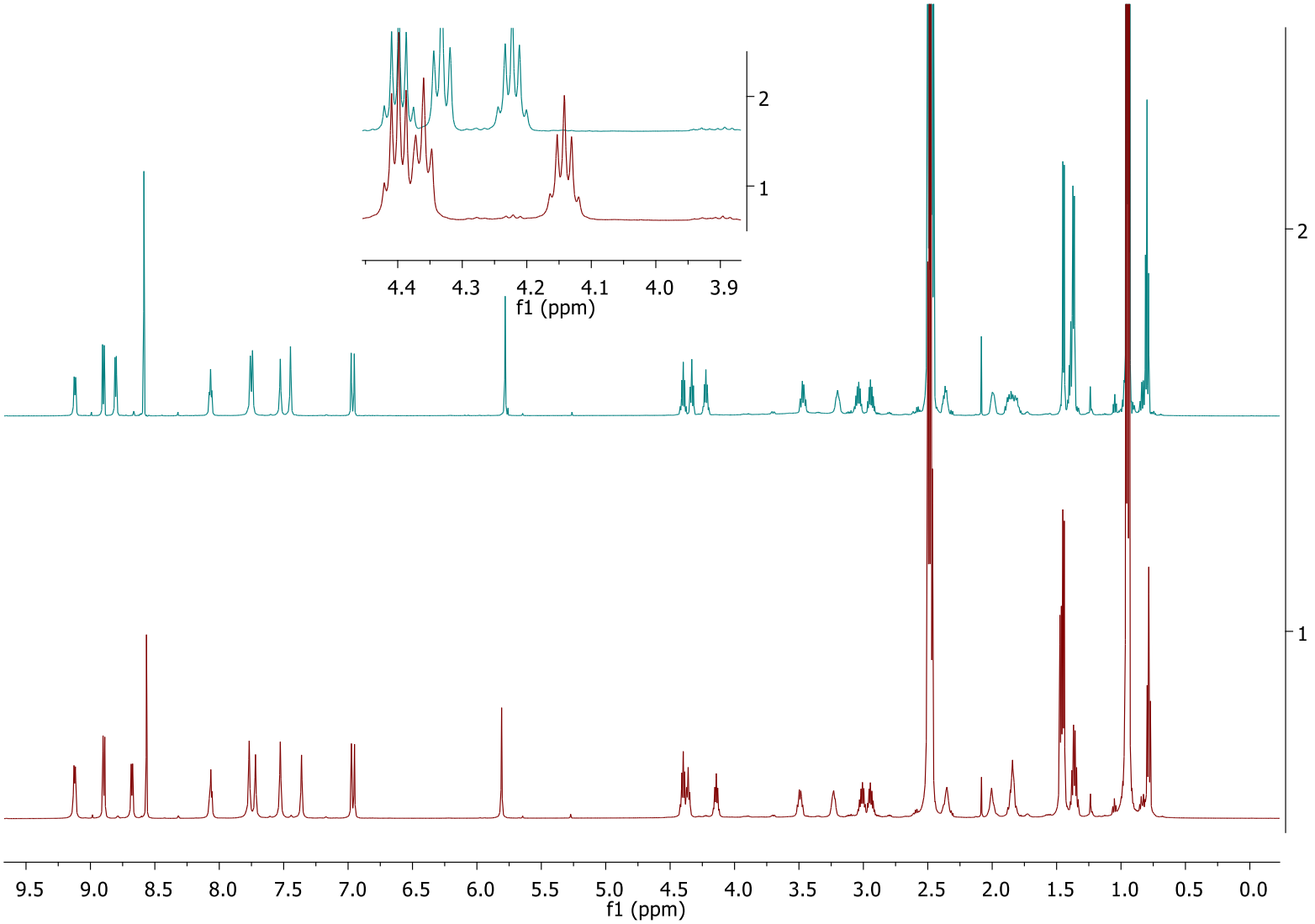
**(*S*)-2-Amino-3-methyl-*N*-propylbutanamide 5d (method B, 125 °C, 5 h); L-Marfey and D-Marfey**



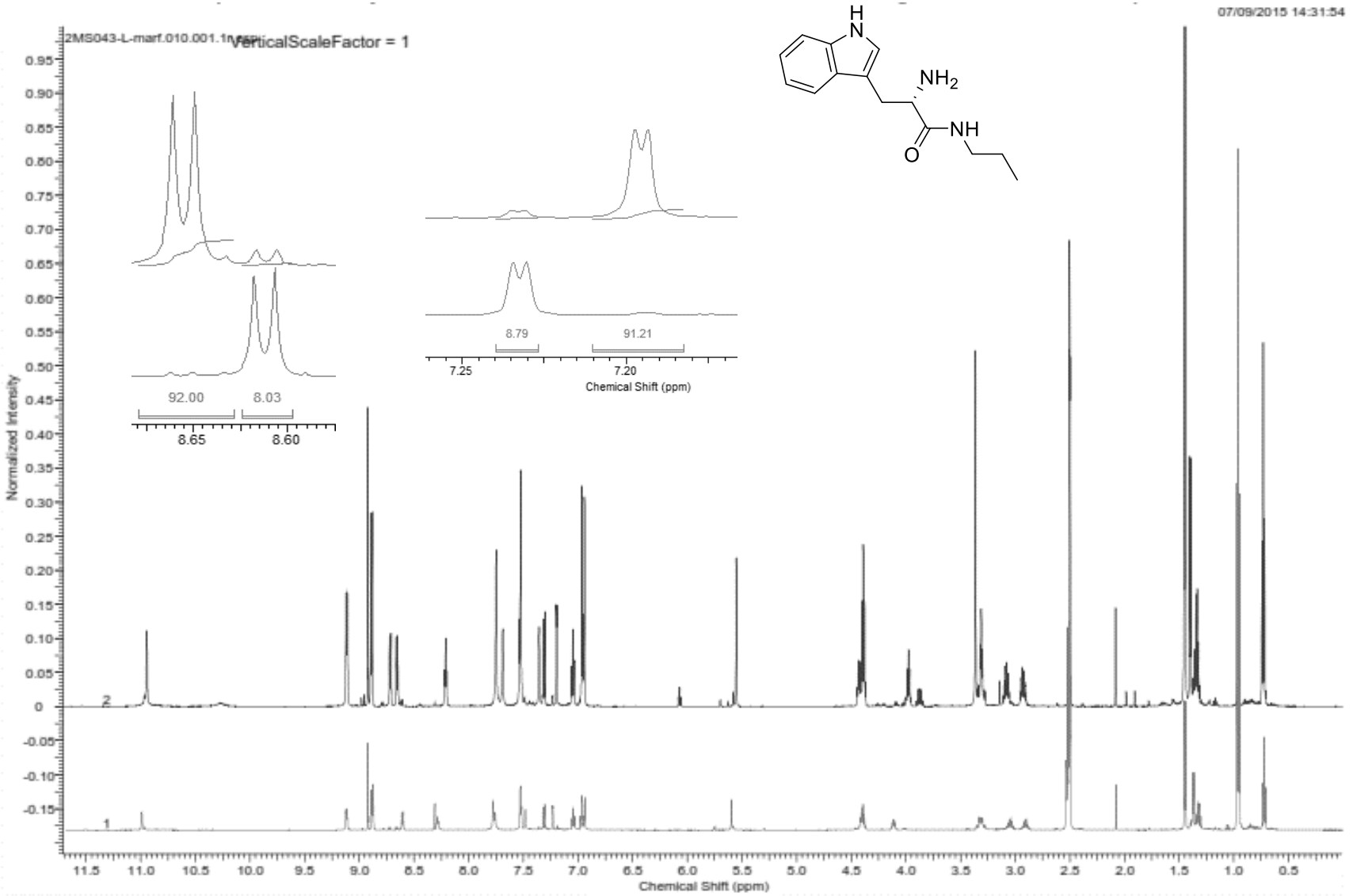
**(*S*)-2-Amino-4-methyl-*N*-propylpentanamide 5e; L-Marfey and D-Marfey**



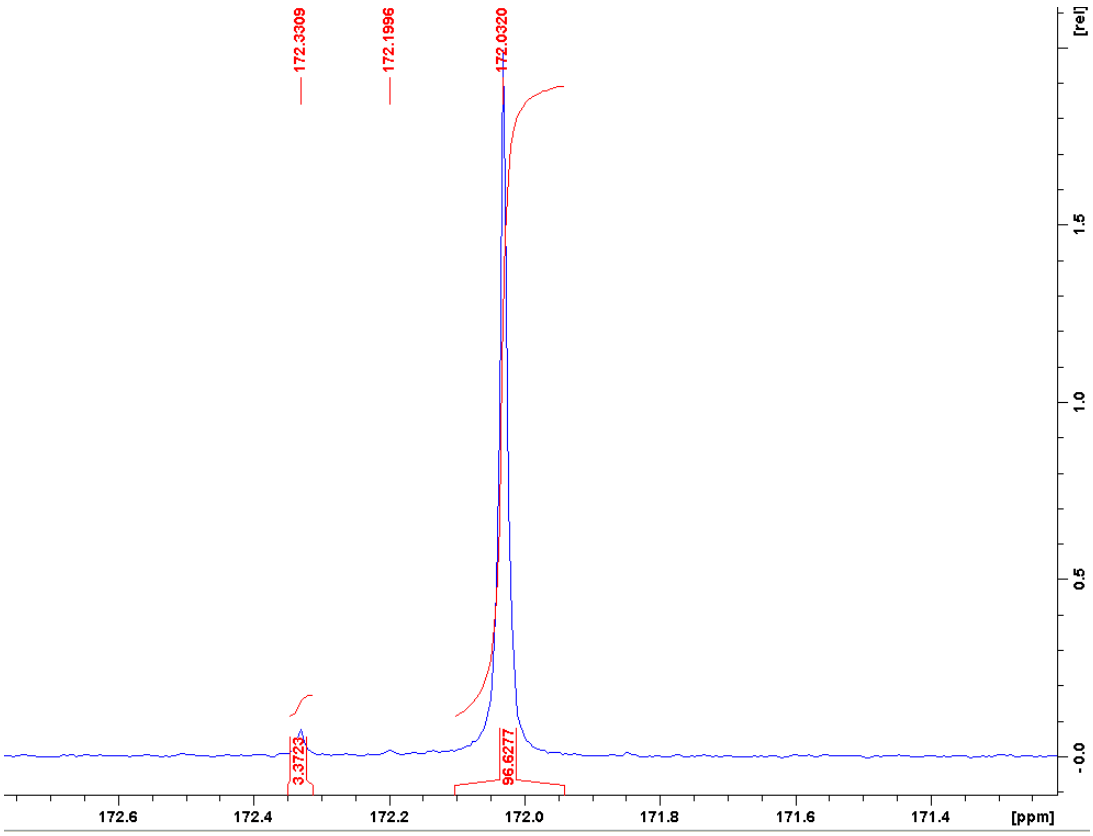
**(*S*)-*N*-Propylpyrrolidine-2-carboxamide 5f; L-Marfey and D-Marfey**



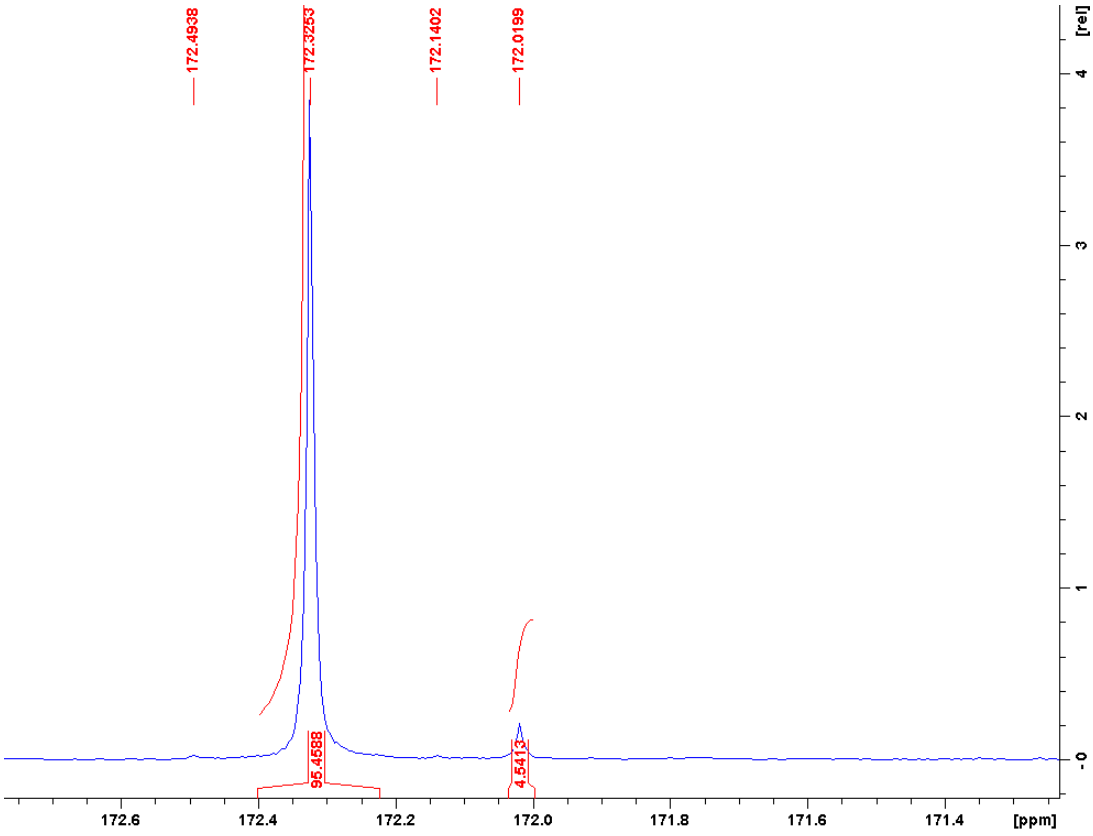
**(*S*)-2-Amino-3-(1H-indol-3-yl)-*N*-propylpropanamide 5h (Method B, at 80 °C for 5 h); L-Marfey and D-Marfey**



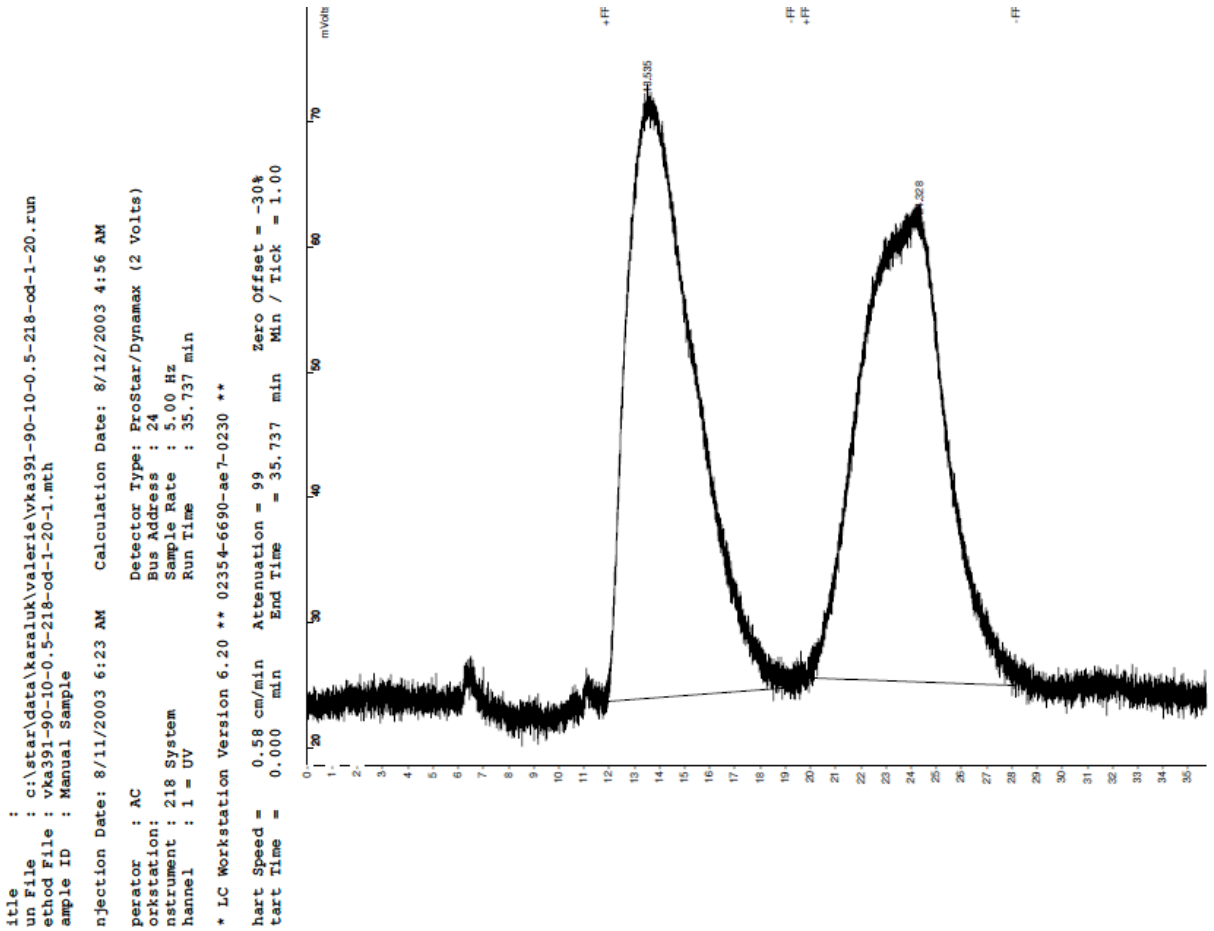
**(*S*)-2-Amino-4-(methylthio)-*N*-propylbutanamide 5i – (*R*)-aldehyde**




**(*S*)-2-Amino-4-(methylthio)-*N*-propylbutanamide 5i – (*S*)-aldehyde**



## *(R,S)*-2-Amino-3-(4-hydroxyphenyl)-*N*-propylpropanamide rac-5j

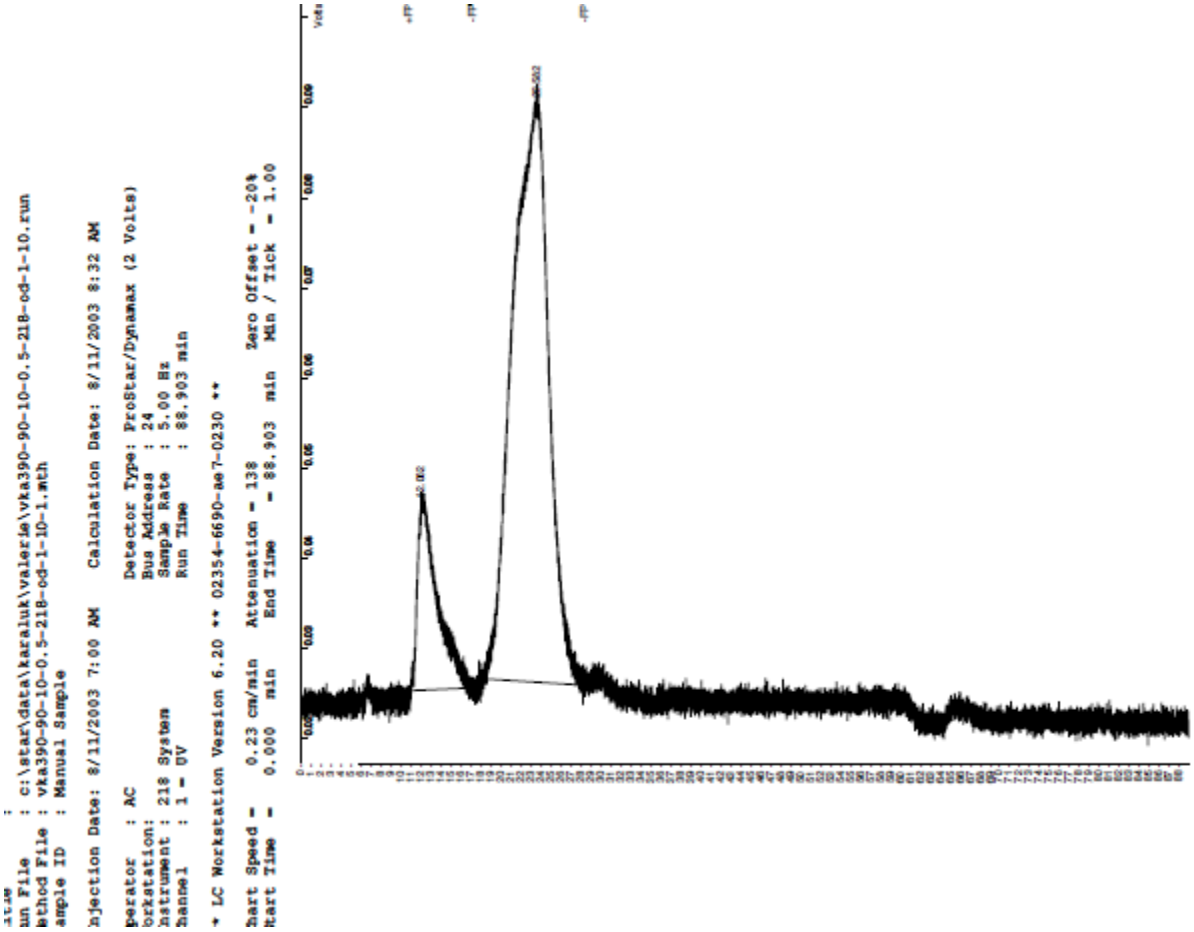



```
Print Date: Tue Aug 12 04:56:28 2003            Page 1 of 1

Title        :
Run File     : c:\star\data\karaluk\valerie\vka391-90-10-0.5-218-od-1-20.run
Method File  : vka391-90-10-0.5-218-od-1-20-1.mth
Sample ID    : Manual Sample

Injection Date: 8/11/2003 6:23 AM    Calculation Date: 8/12/2003 4:56 AM

Operator    : AC                     Detector Type: ProStar/Dynamax (2 Volts)
Workstation:                         Bus Address  : 24
Instrument : 218 System              Sample Rate  : 5.00 Hz
Channel     : 1 - UV                 Run Time     : 35.737 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

| Peak No. | Peak Name | Result () | Ret. Time (min) | Time Offset (min) | Area (counts) | Sep. Code | Width 1/2 (sec) | Status Codes |
|---|---|---|---|---|---|---|---|---|
| 1 | | 50.0583 | 13.535 | 0.000 | 8942808 | BB | 179.0 | |
| 2 | | 49.9417 | 24.328 | 0.000 | 8921987 | BB | 218.2 | |
| | Totals: | 100.0000 | | 0.000 | 17864795 | | | |

```
Total Unidentified Counts :   17864796 counts

Detected Peaks: 2            Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 24311 microVolts          LSB:     1 microVolts

Noise (used): 3675 microVolts - monitored before this run

Manual injection

********************************************************************************
```

## *(S)*-2-Amino-3-(4-hydroxyphenyl)-*N*-propylpropanamide 5j




Print Date: Tue Aug 12 04:55:18 2003 Page 1 of 1

Title :
Run File : c:\star\data\karaluk\valerie\vka390-90-10-0.5-218-od-1-10.run
Method File : vka390-90-10-0.5-218-od-1-10-1.mth
Sample ID : Manual Sample

Injection Date: 8/11/2003 7:00 AM Calculation Date: 8/11/2003 8:32 AM

Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 = UV Run Time : 88.903 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

| Peak No. | Peak Name | Result () | Ret. Time (min) | Time Offset (min) | Area (counts) | Sep. Code | Width 1/2 (sec) | Status Codes |
|---|---|---|---|---|---|---|---|---|
| 1 | | 15.2839 | 12.062 | 0.000 | 2943300 | BB | 105.3 | |
| 2 | | 84.7161 | 23.582 | 0.000 | 16314168 | BB | 239.3 | |
| | Totals: | 100.0000 | | 0.000 | 19257468 | | | |

Total Unidentified Counts : 19257468 counts

Detected Peaks: 2 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

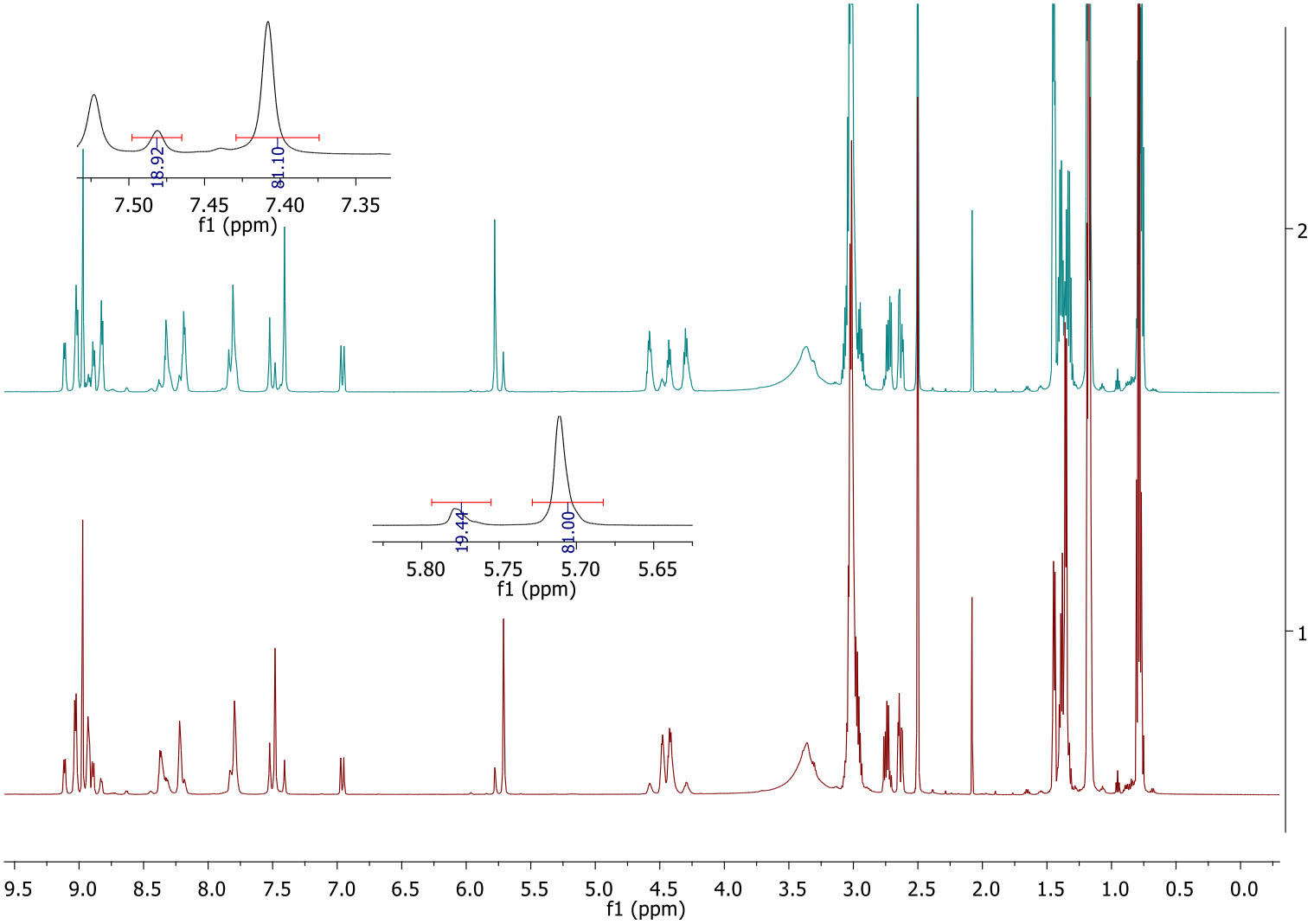
Baseline Offset: 24836 microVolts LSB: 1 microVolts

Noise (used): 4138 microVolts - monitored before this run

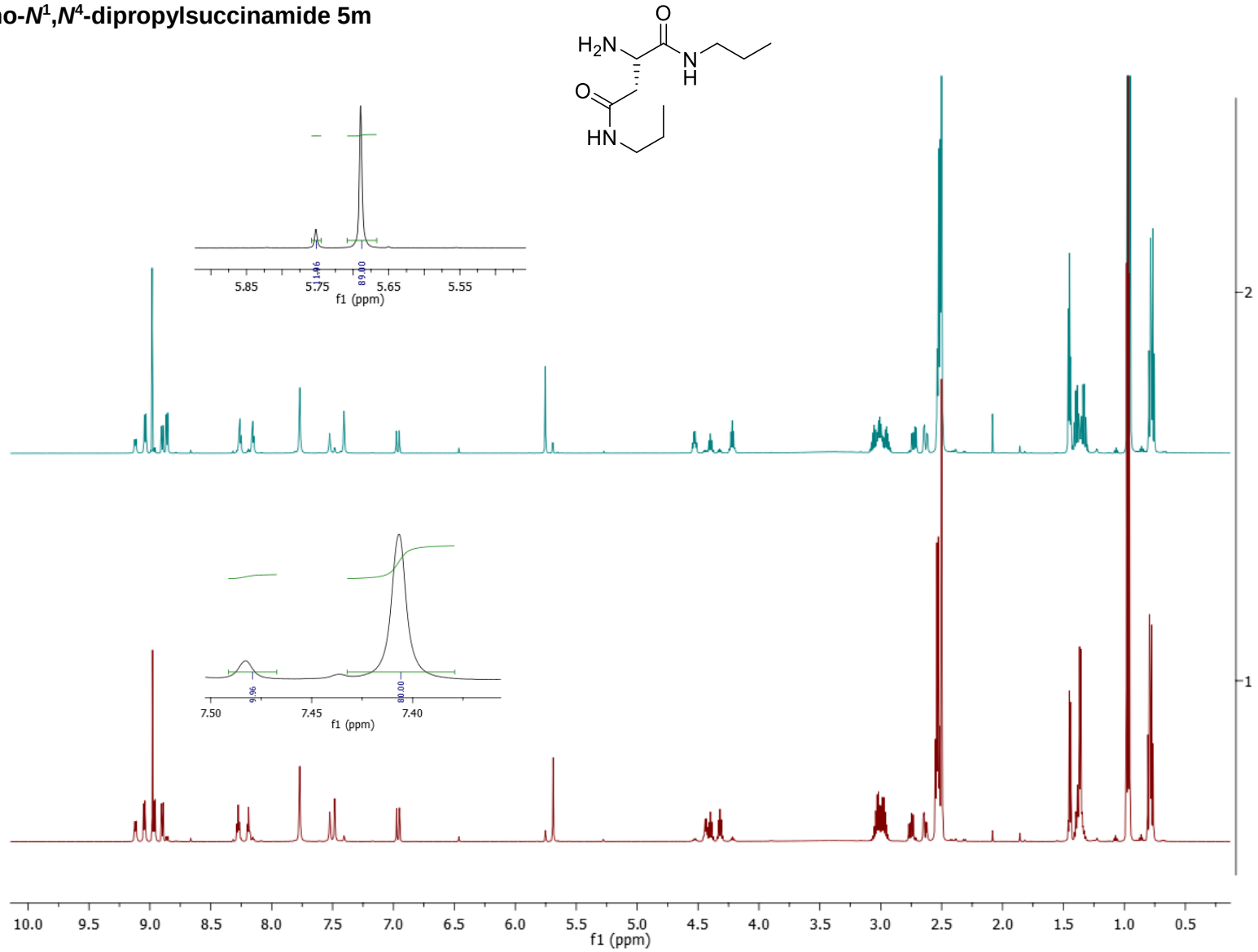
Manual injection

**********

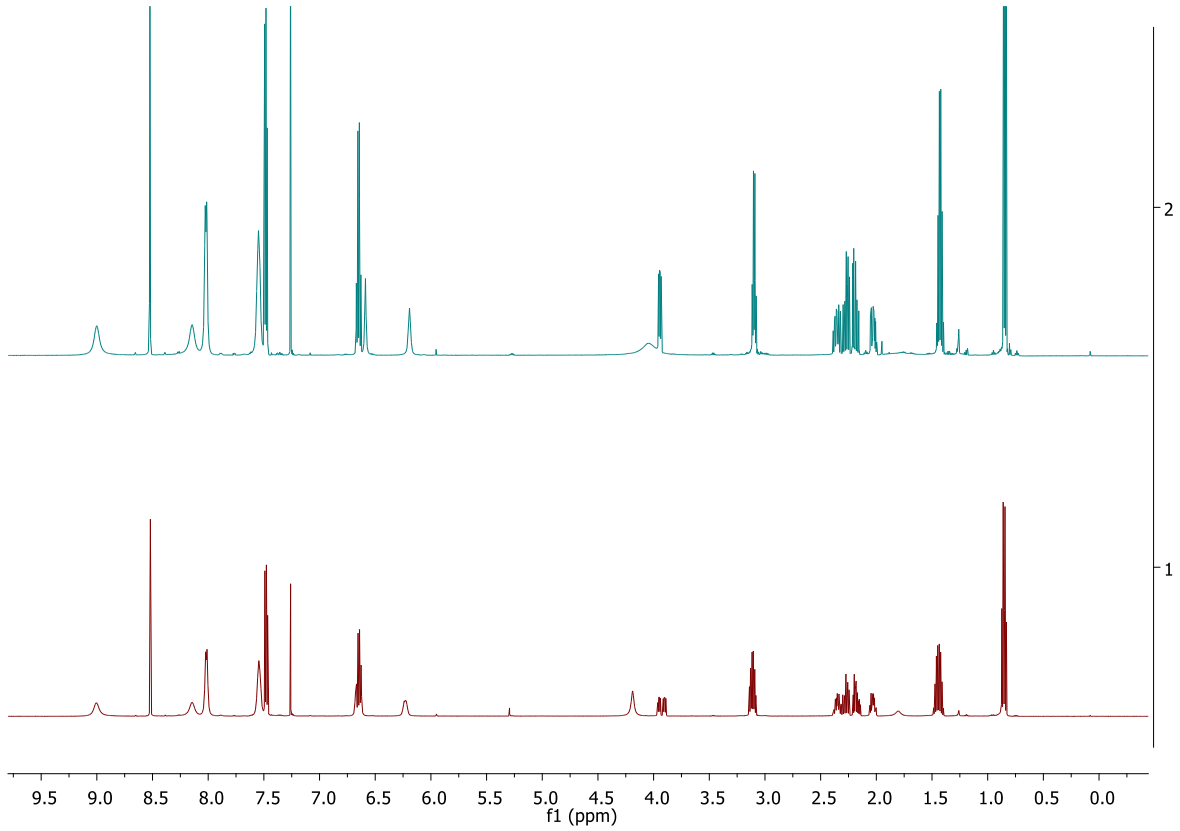
**(*S*)-2-Amino-*N*$^1$,*N*$^4$-dipropylsuccinamide hydrochloride 5m; L-Mardey and D-Marfey**

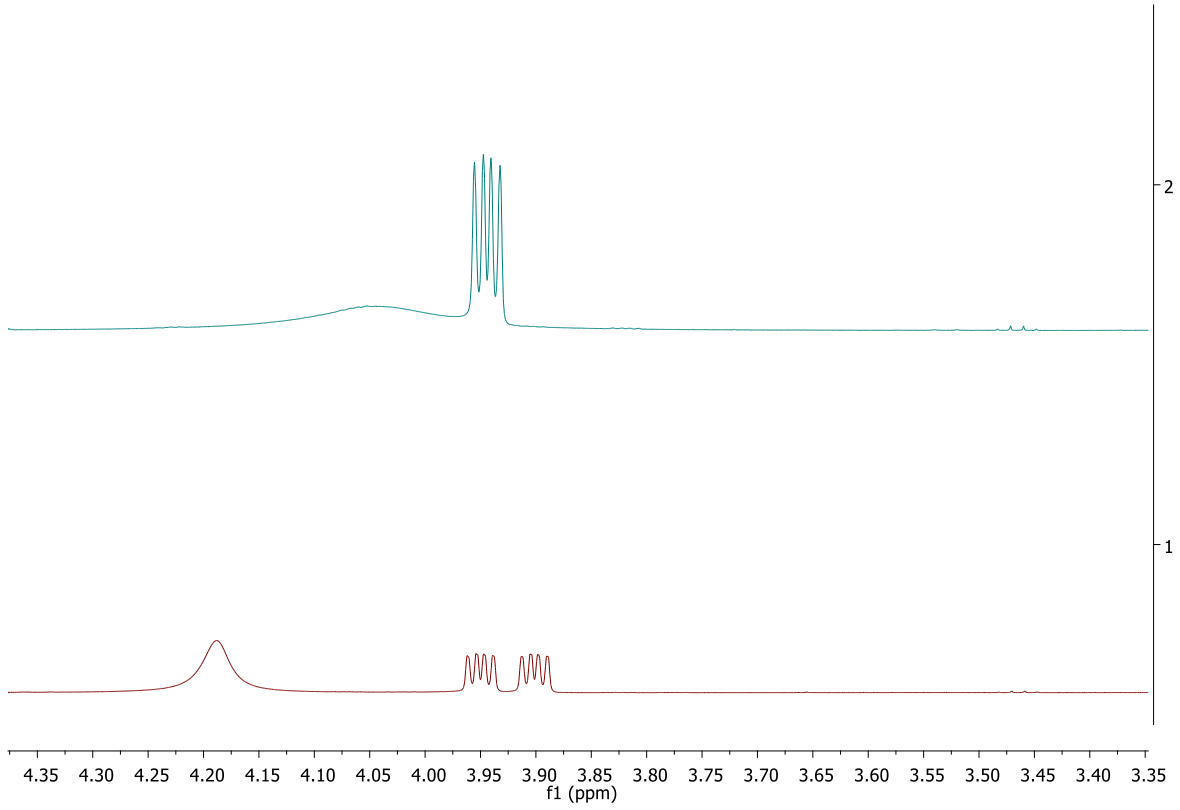


***(S)*-2-Amino-*N*$^1$,*N*$^4$-dipropylsuccinamide 5m**

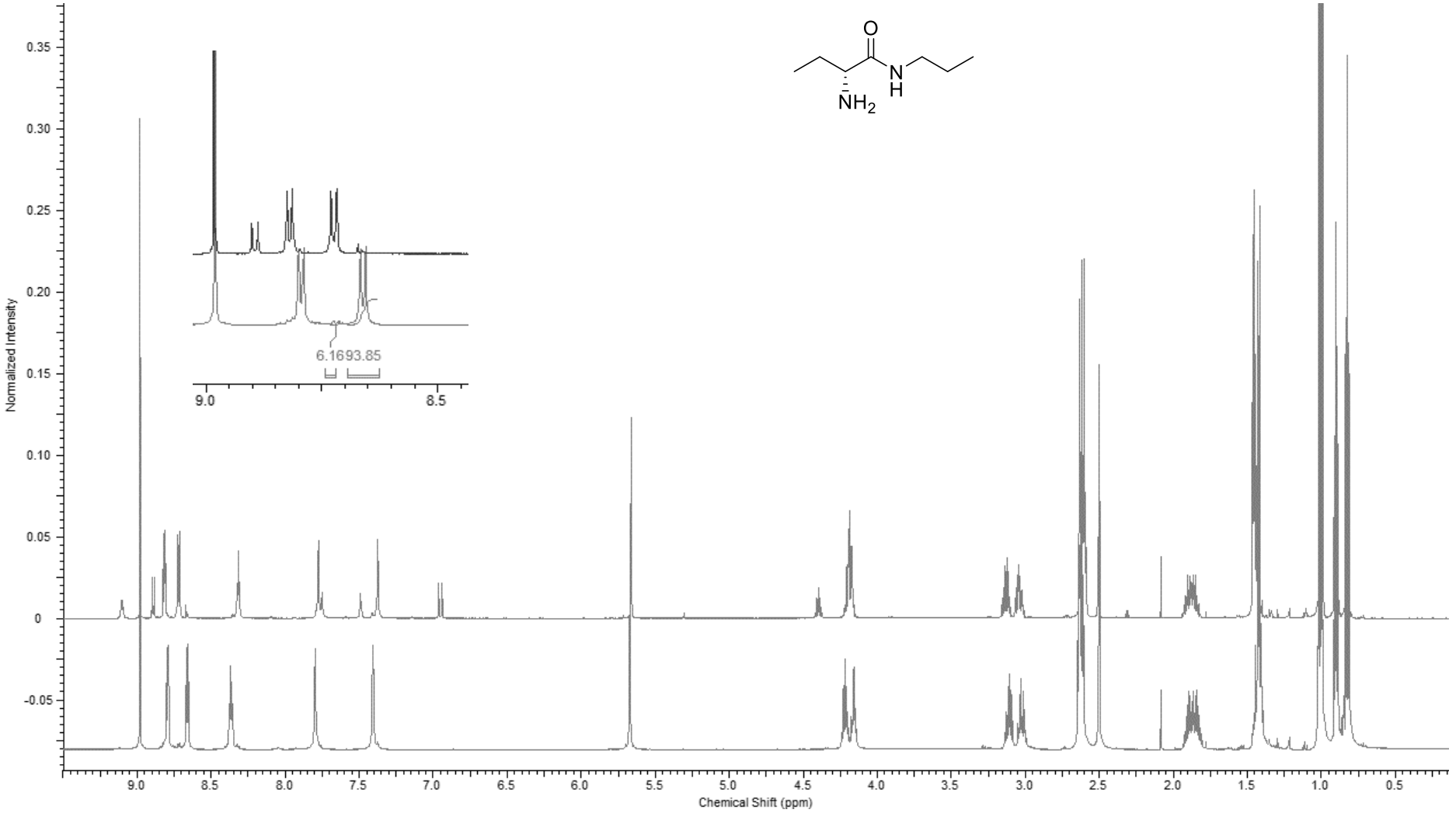


**(*S*)-5-Oxo-*N*-propylpyrrolidine-2-carboxamide 5n; Chiral shift agent**

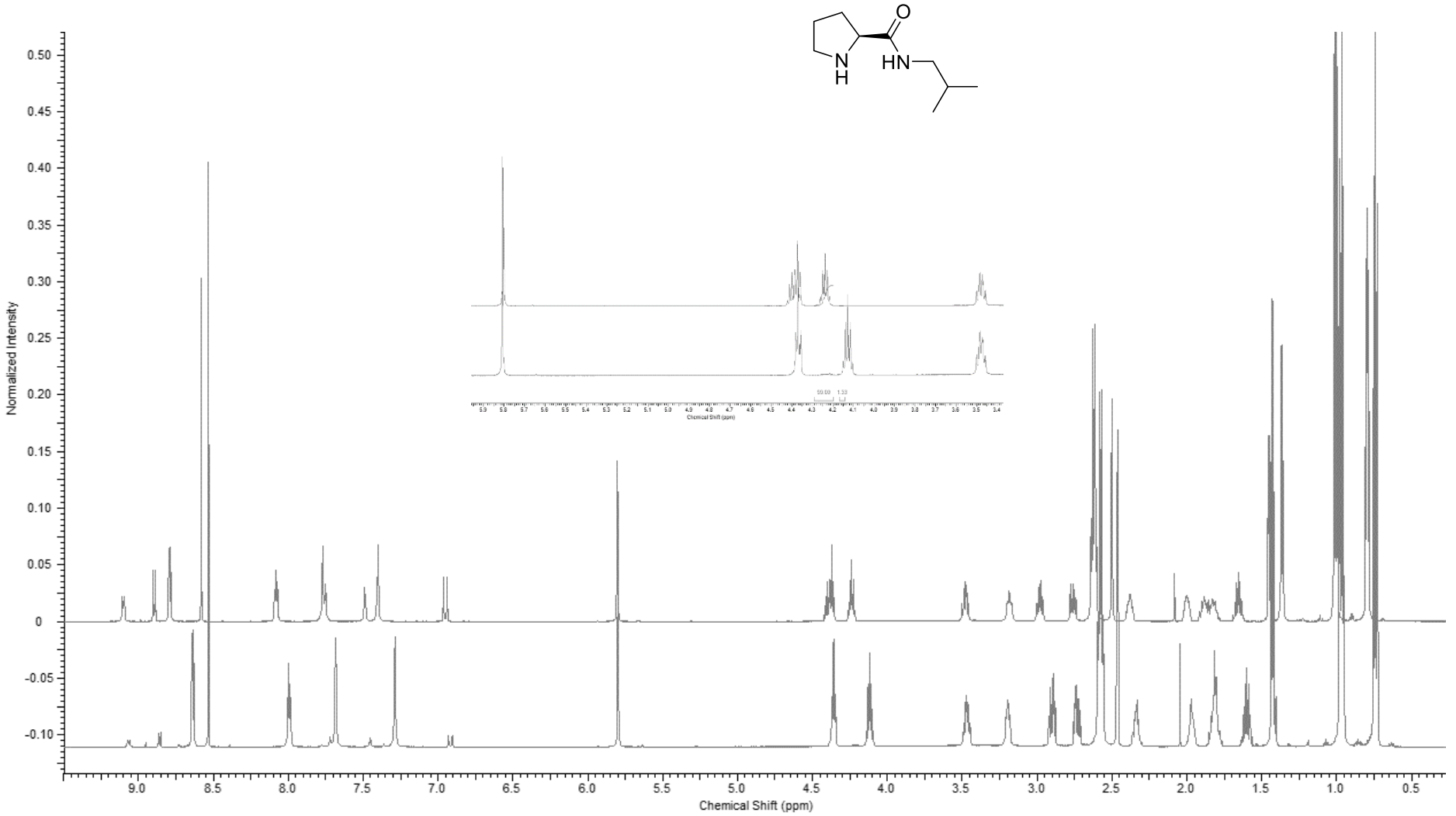


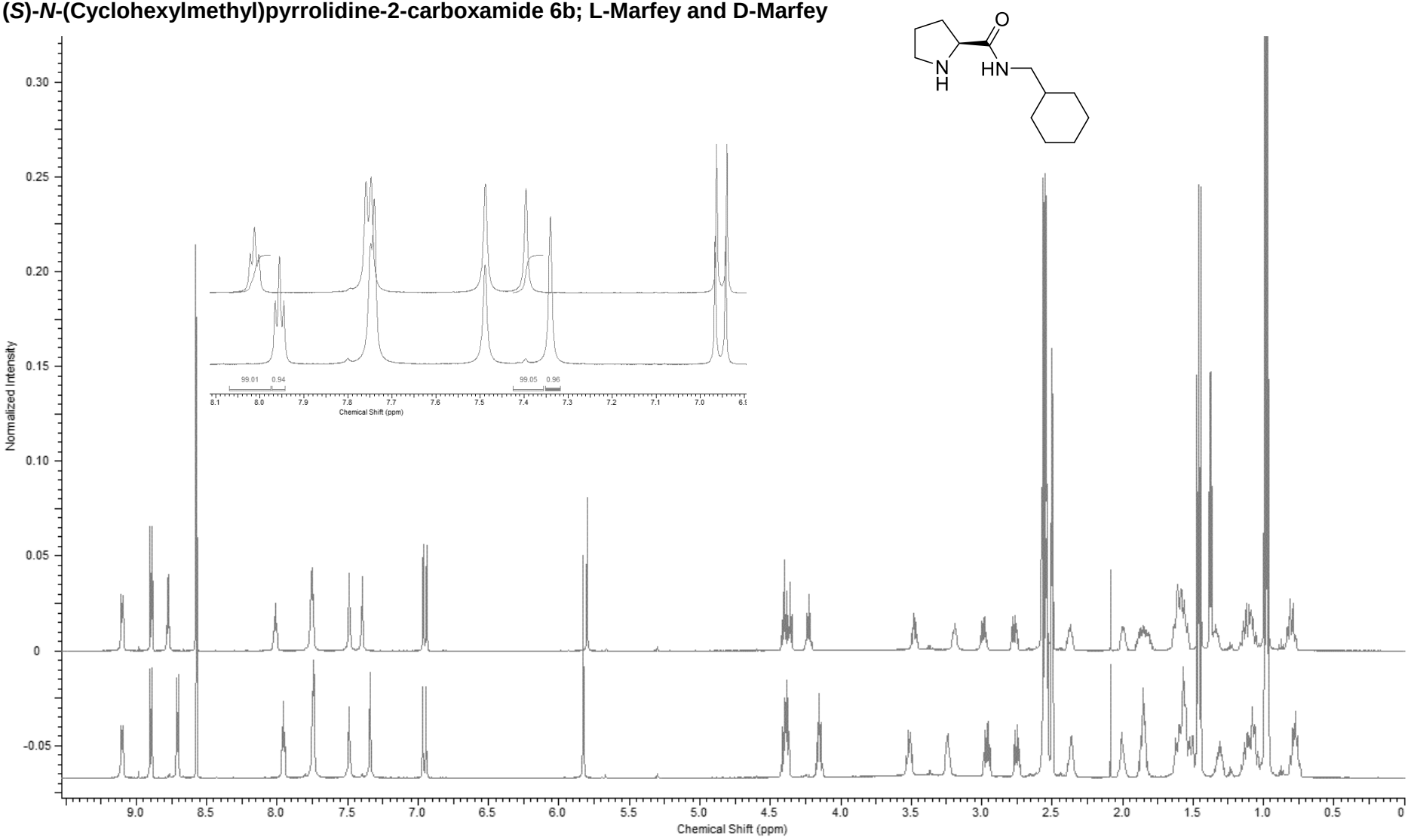
**(*R*)-2-Amino-*N*-propylbutanamide 5y; L-Marfey and D-Marfey**



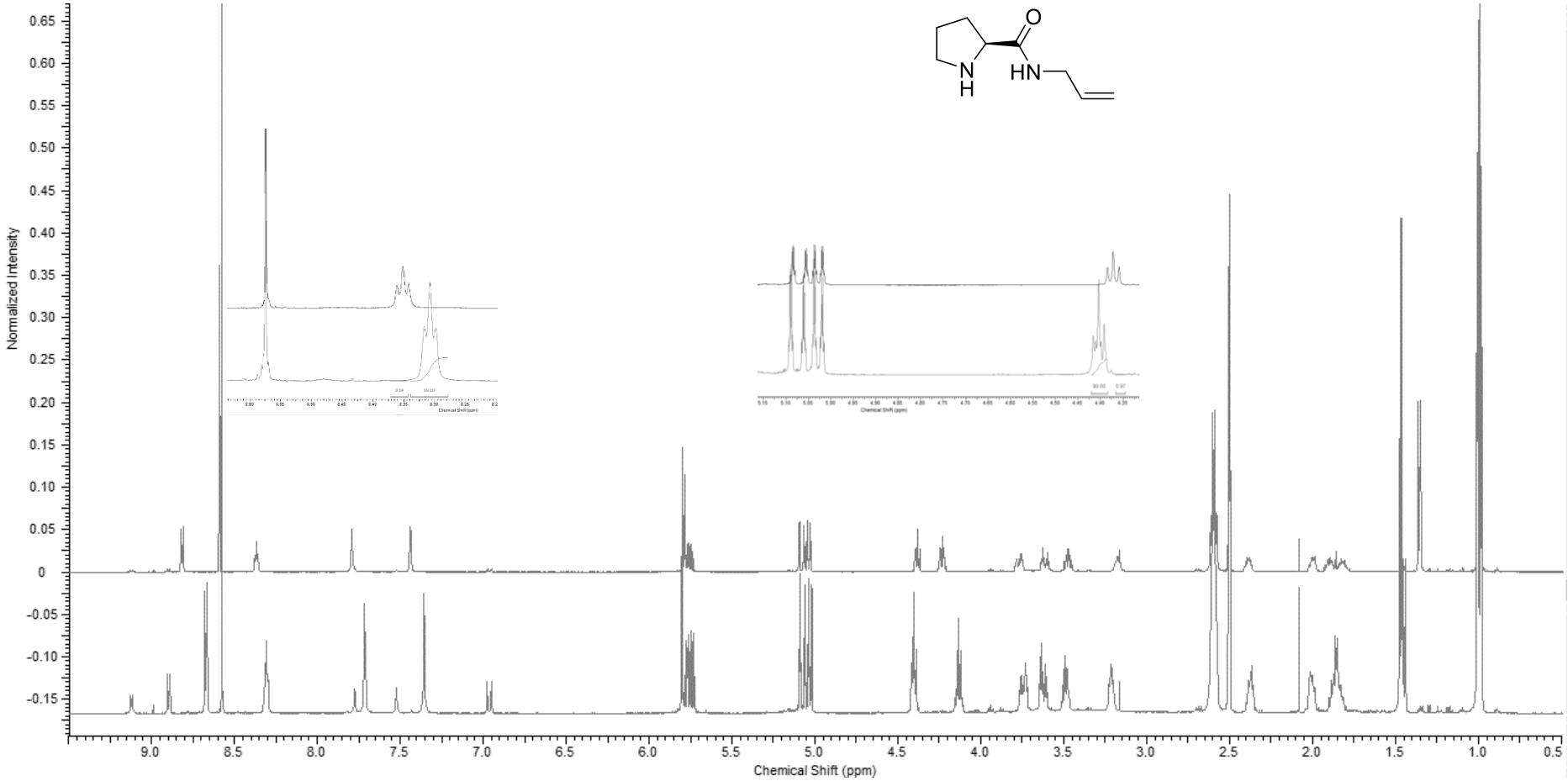
**(*S*)-*N*-Isobutylpyrrolidine-2-carboxamide 6a; L-Marfey and D-Marfey**



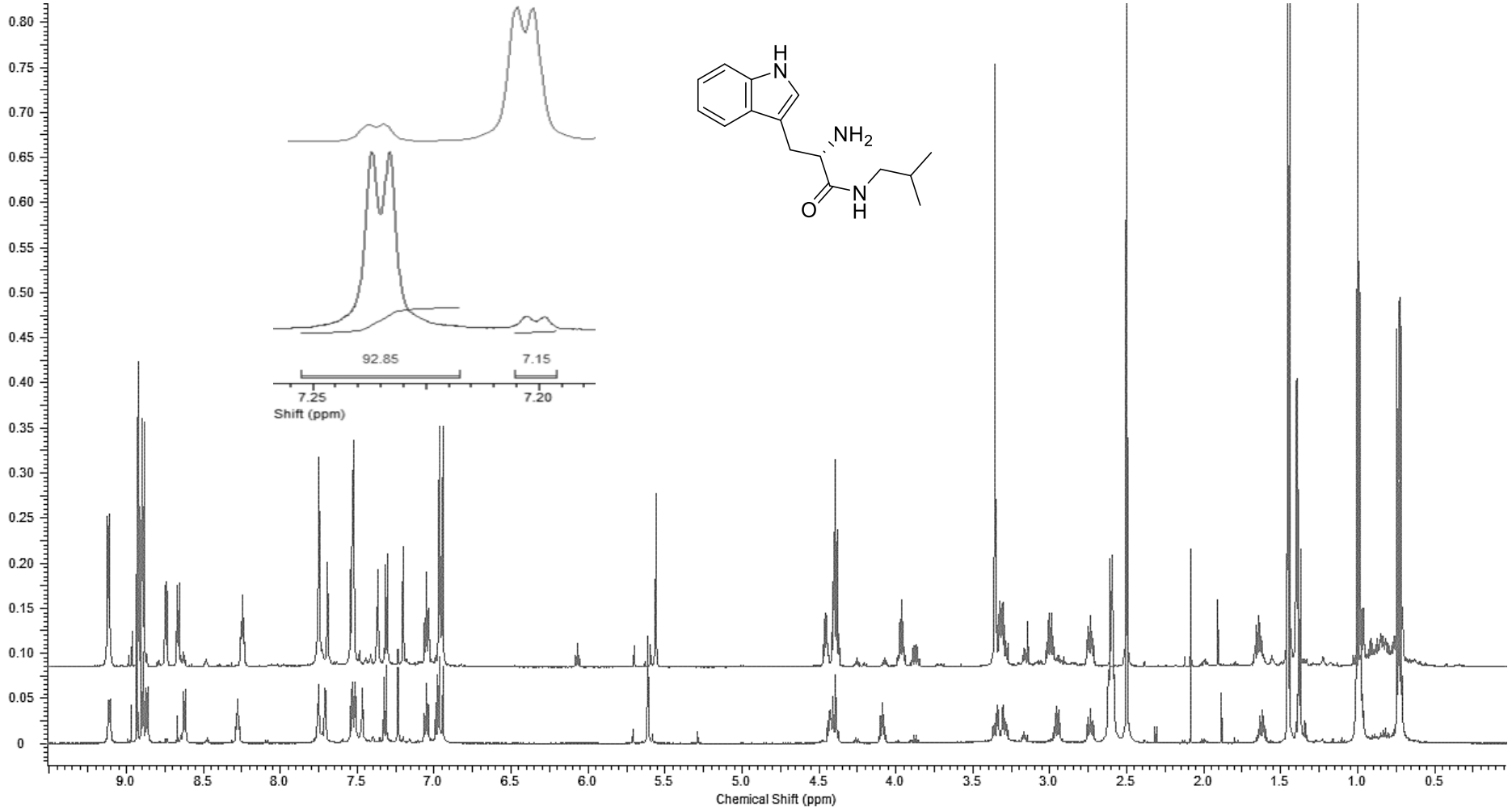
**(*S*)-*N*-(Cyclohexylmethyl)pyrrolidine-2-carboxamide 6b; L-Marfey and D-Marfey**



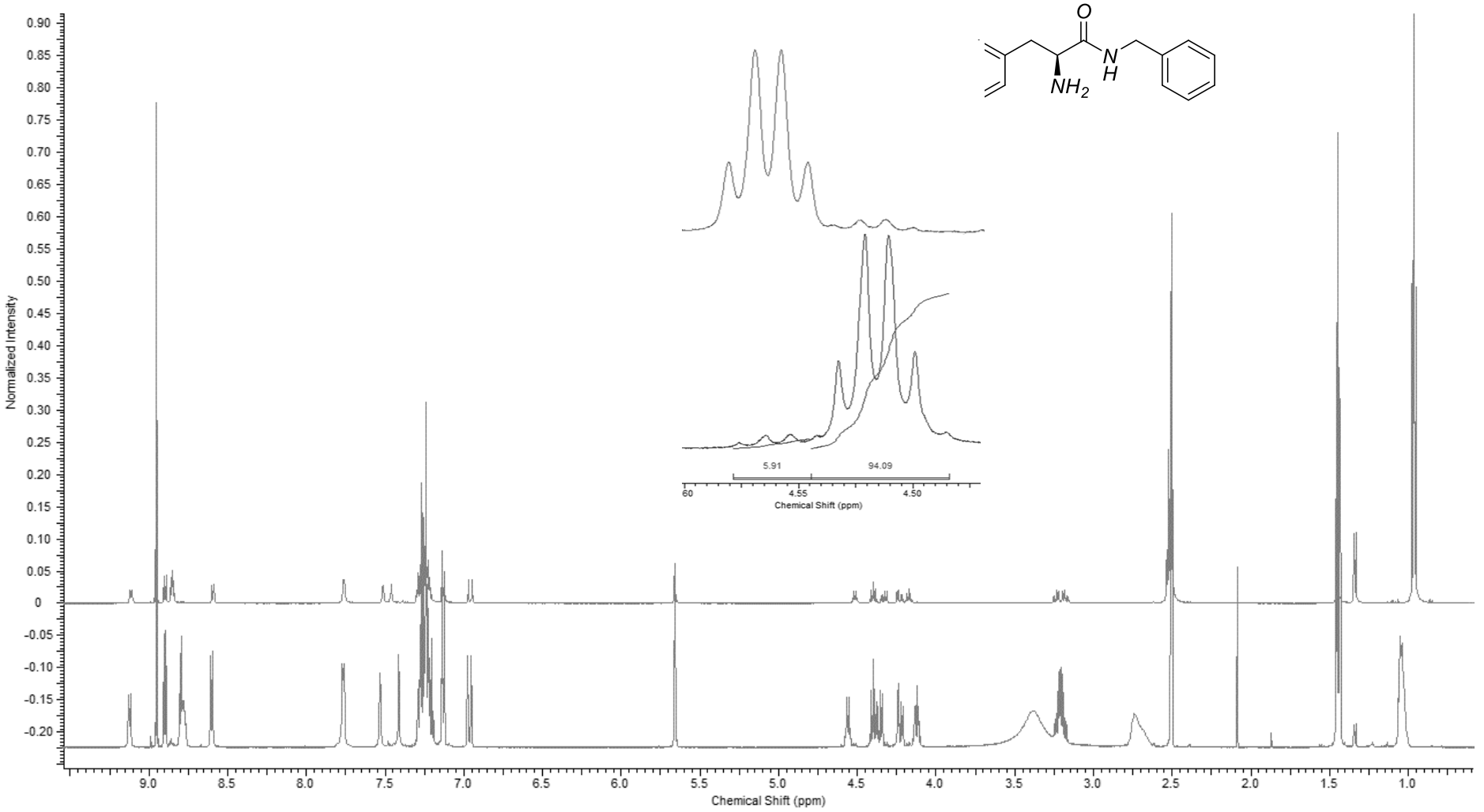
**(*S*)-*N*-Allylpyrrolidine-2-carboxamide 6c; L-Marfey and D-Marfey**



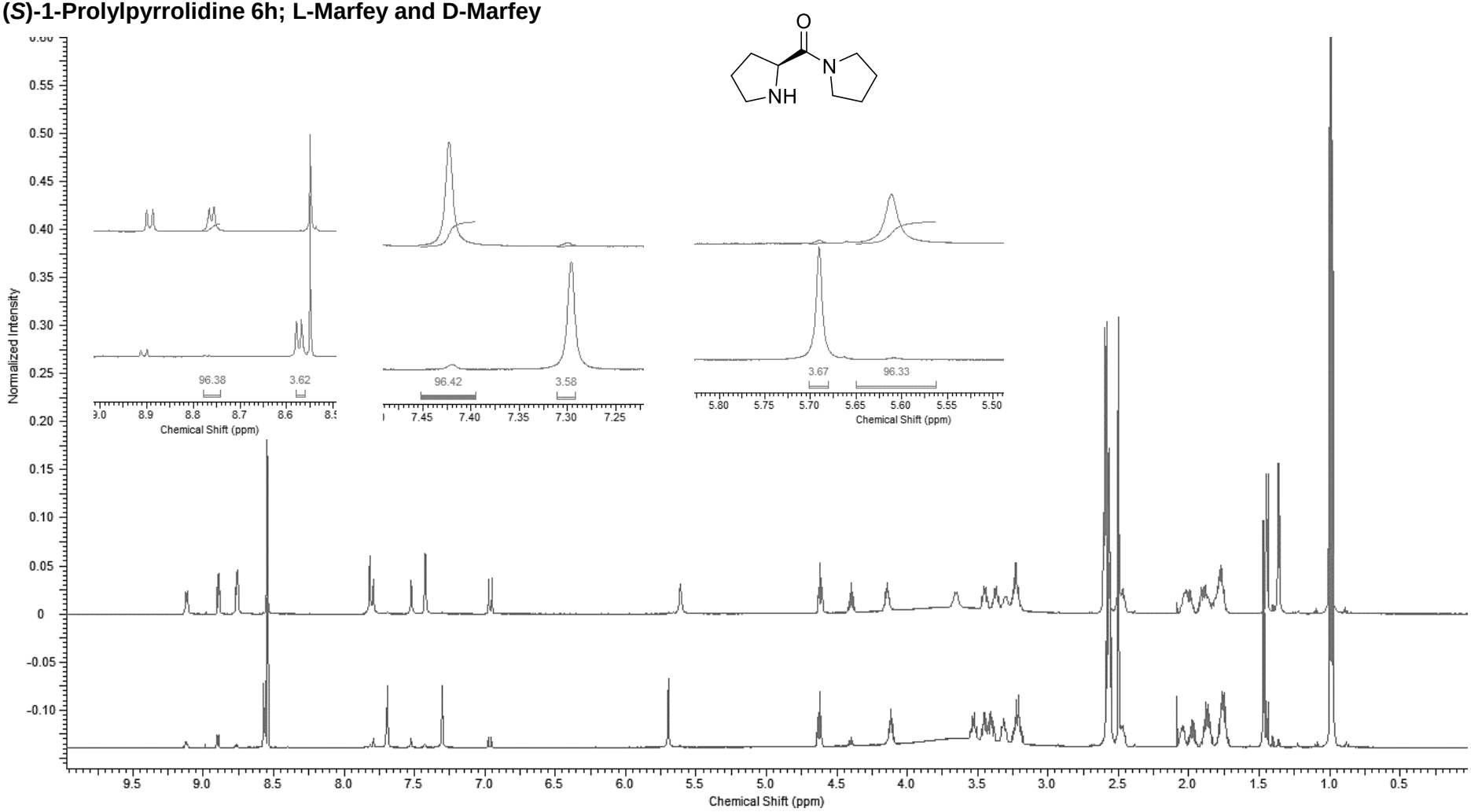
**(*S*)-2-Amino-3-(1H-indol-3-yl)-*N*-isobutylpropanamide 6d; L-Marfey and D-Marfey**



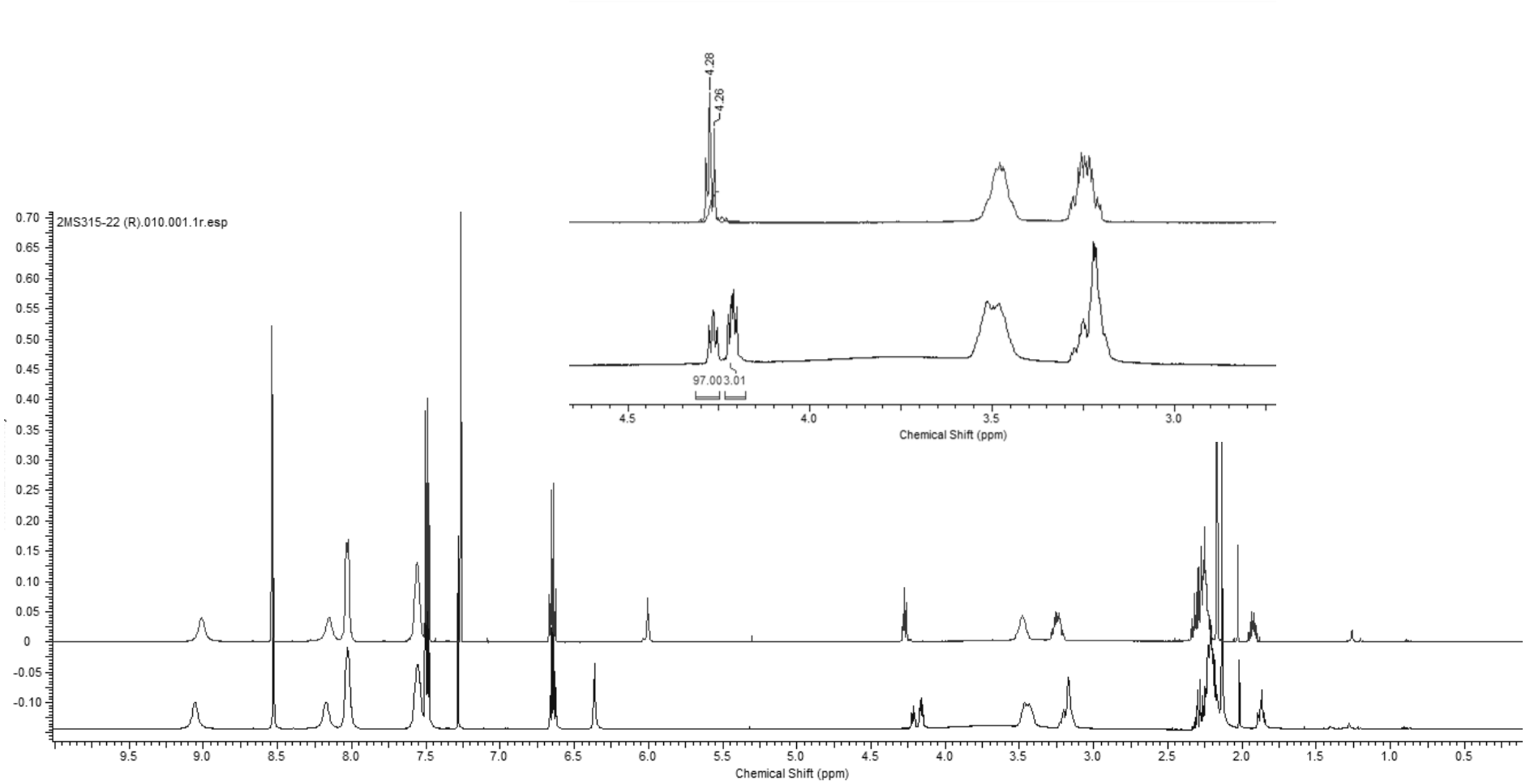
***(S)*-2-Amino-*N*-benzyl-3-phenylpropanamide 6f; L-Marfey and D-Marfey**



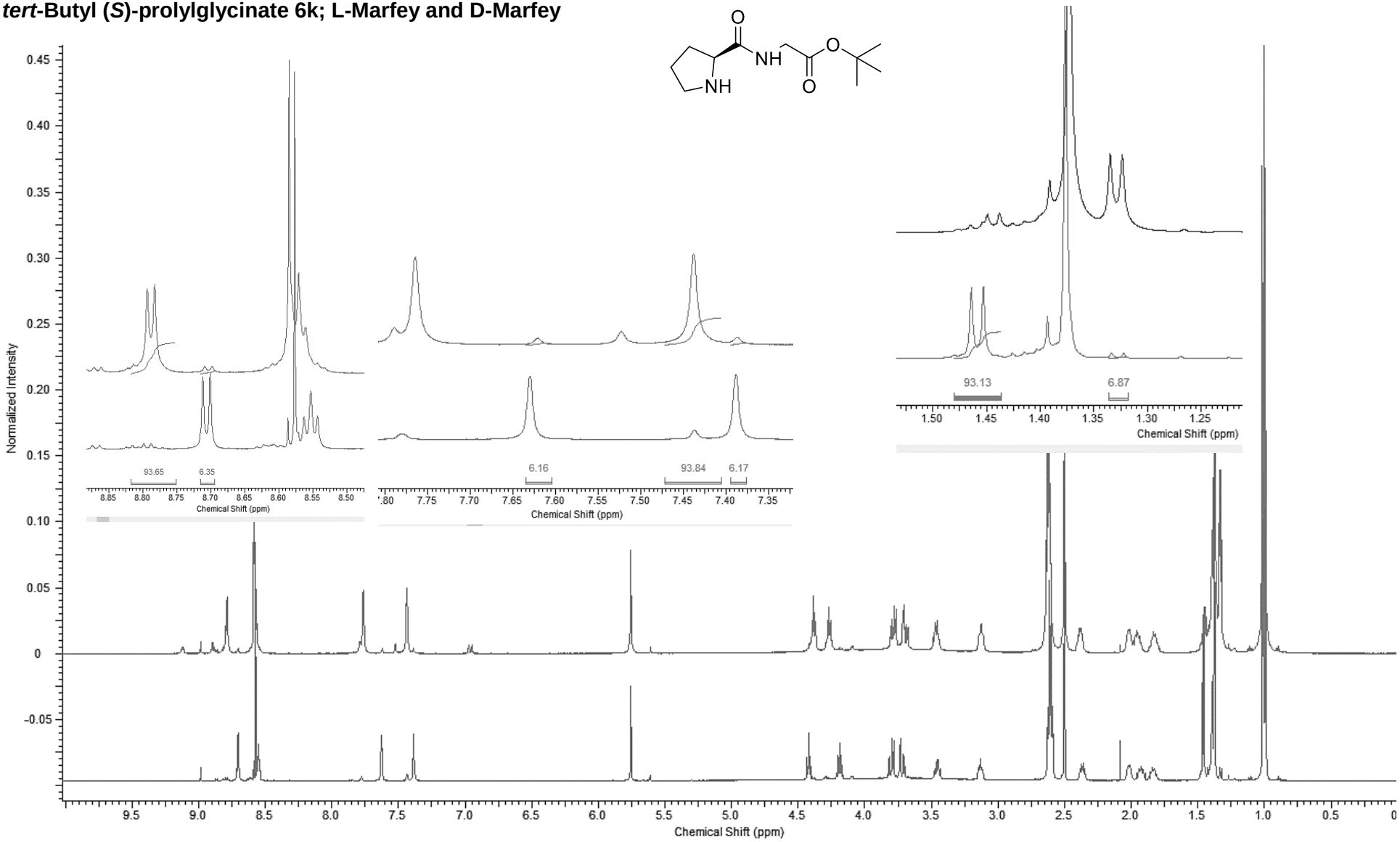
**(*S*)-1-Prolylpyrrolidine 6h; L-Marfey and D-Marfey**



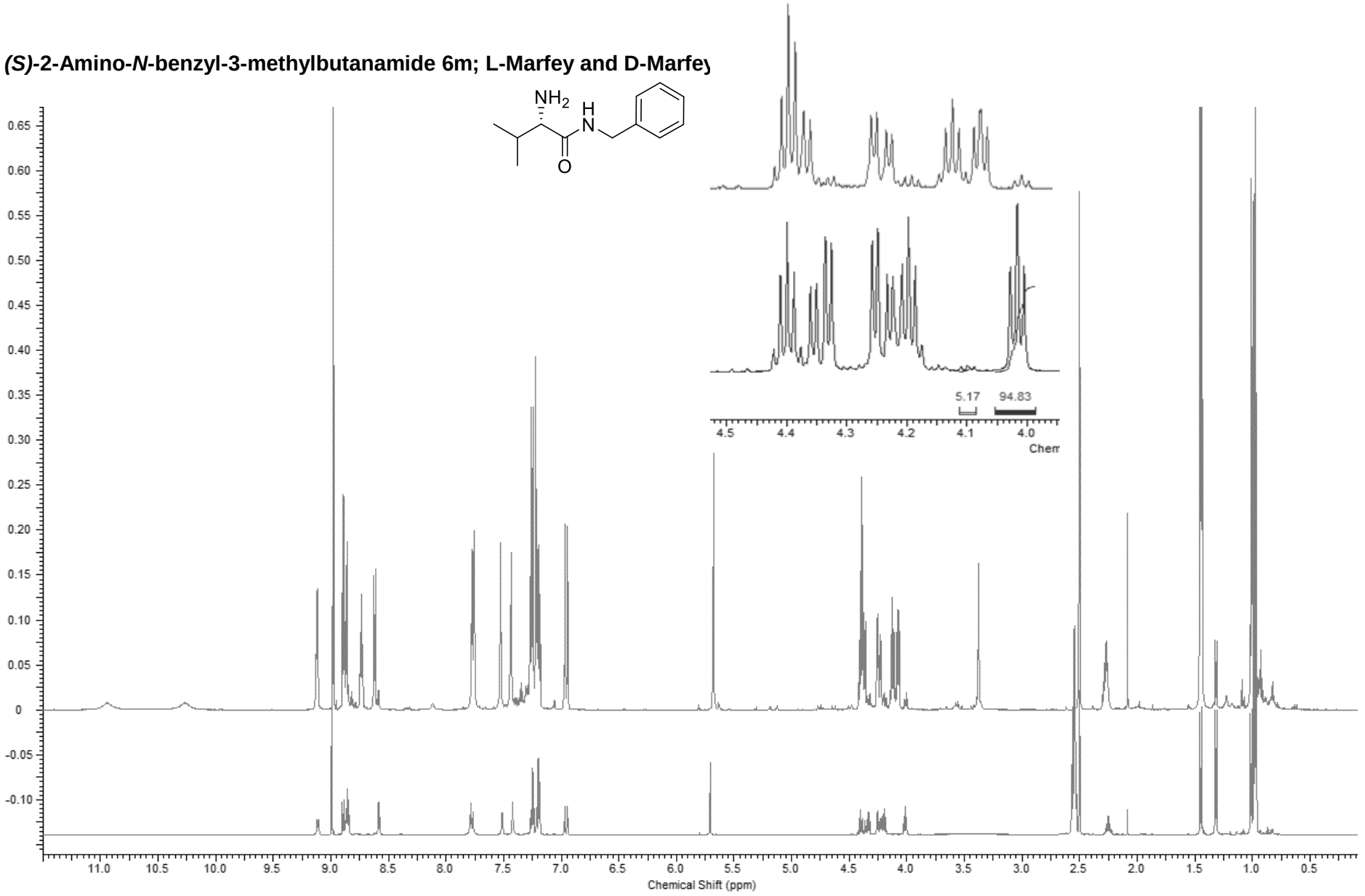
**(*R*)-5-(4-Methylpiperazine-1-carbonyl)pyrrolidin-2-one 6i; Chiral shift agent**



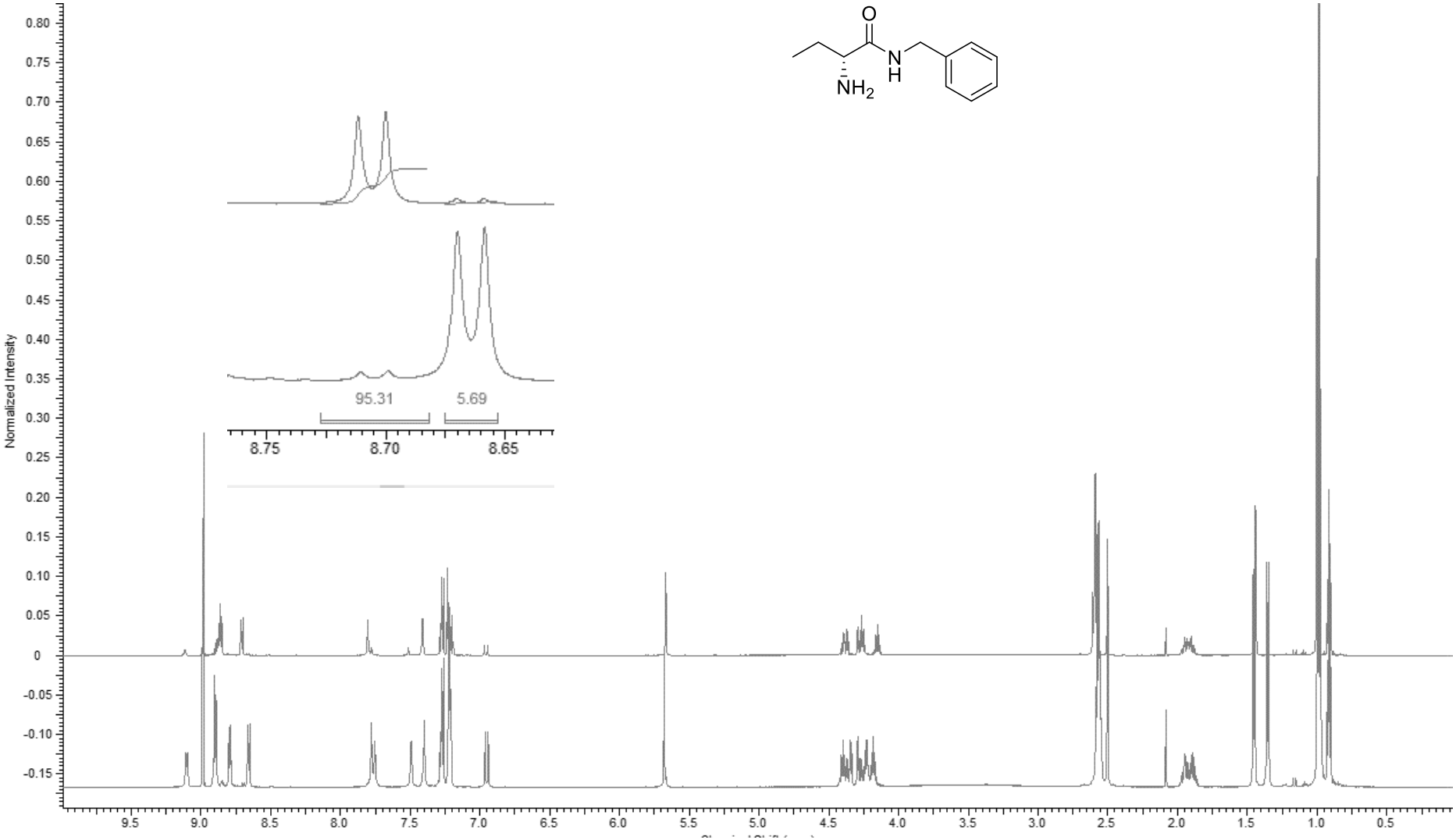
***tert*-Butyl (*S*)-prolylglycinate 6k; L-Marfey and D-Marfey**



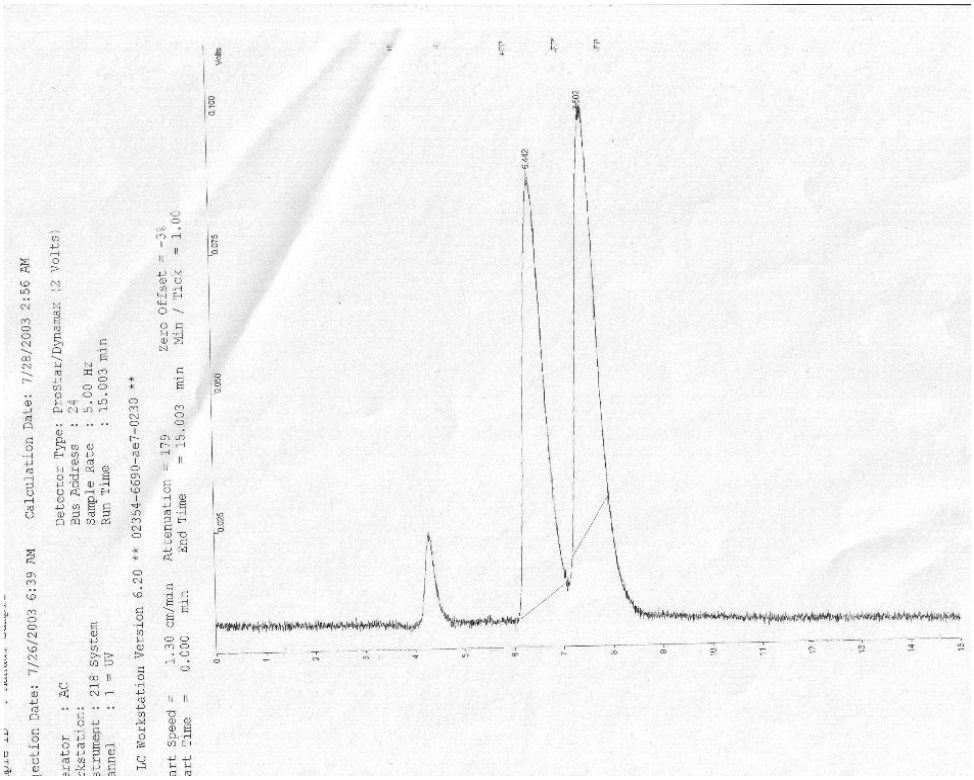
**(*S*)-2-Amino-*N*-benzyl-3-methylbutanamide 6m; L-Marfey and D-Marfey**

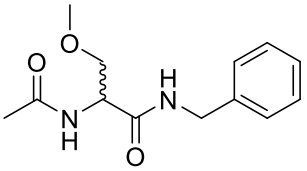


***(R)*-2-Amino-*N*-benzylbutanamide 6n; L-Marfey and D-Marfey**

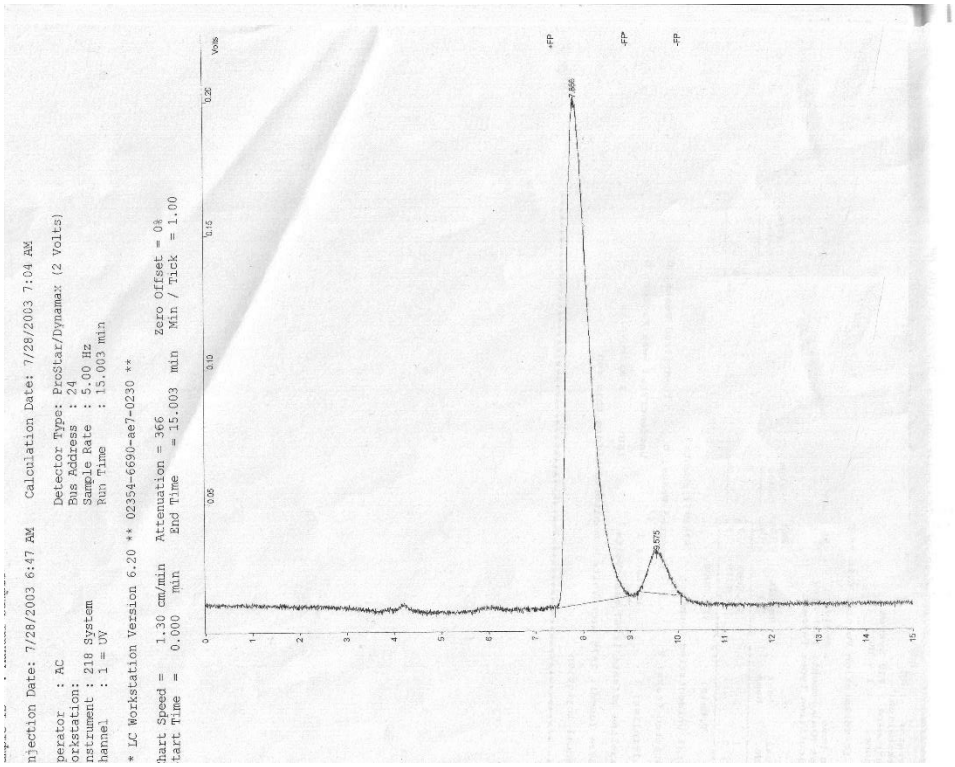


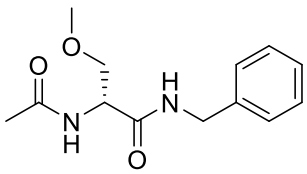
**(±)-2-acetamido-N-benzyl-3-methoxypropanamide (Lacosamide) rac-7**



**(*R*)-2-acetamido-N-benzyl-3-methoxypropanamide (Lacosamide) 7**



Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

| Peak No. | Peak Name | Result () | Ret. Time (min) | Time Offset (min) | Area (counts) | Sep. Code | Width 1/2 (sec) | Status Codes |
|---|---|---|---|---|---|---|---|---|
| 1 | | 93.5681 | 7.855 | 0.000 | 6320411 | BB | 31.1 | |
| 2 | | 6.4319 | 9.575 | 0.000 | 434466 | BB | 24.0 | |
| | Totals: | 100.0000 | | 0.000 | 6754877 | | | |

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