Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.


# Supporting Information

# Economic kilogram-scale synthesis of the antiepileptic drug brivaracetam utilizing porcine pancreatic lipase

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## General Experimental

## Experimental

**General Methods**: All commercial reagents were used without further purification. Specific rotation was recorded on Anton Paar MCP 5300 polarimeter. Metling points were recorded on Buchi M-565. HPLC was recorded on Waters Alliance 2695 apparatus. Chiral HPLC chromatographic conditions of **3** were as follows: column: Daicel Chiralpak AD-H, (250 x 4.6) mm, 5µm; mobile phase: n-hexane: isopropanol: trifluoroacetic acid (80 : 20 : 0.02, V/V/V); diluent: n-hexane: isopropanol: trifluoroacetic acid (80 : 20 : 0.02, V/V/V); flow rate: 1.0 mL/min; detection wavelength: 210 nm. Chiral HPLC chromatographic conditions of **1** were as follows: column: Daicel Chiralpak AD-H, (250 x 4.6) mm, 5µm; mobile phase: n-hexane: isopropanol: diethylamine (85 : 15 : 0.02, V/V/V); diluent: hexane: isopropanol: (80 : 20, V/V); flow rate: 1.0 mL/min; detection wavelength: 215 nm. High resolution mass spectra (HRMS) were obtained on a Waters Xevo G2-S QTof (LC-HRMS) instrument using electrospray spray ionization in positive mode. $^{1}H$ and $^{13}C$ NMR spectra were recorded at room temperature (~20 °C), using tetramethylsilane (TMS) as an internal standard on a Bruker Avance II 400 MHz NMR spectrometer. $^{1}H–^{1}H$ and $^{1}H–^{13}C$ correlations were used to confirm the NMR peak assignments. Chemical shifts are expressed in parts per million (ppm) and coupling constants (J) in hertz (Hz).

**Dimethyl 2-(cyanomethyl)-2-propylmalonate** (**5**): A 2000 mL bottom flask equipped with refrigerant and mechanical agitation was charged with dimethyl propyl malonate **4** (300 g, 1.72 mol), THF (600 mL) and potassium carbonate (276 g, 2 mol) and cooled to -10 $^{o}$C, to this solution was added bromoacetonitrile (227.3 g, 1.9 mol) dropwise by syringe for 1 h, the resulting mixture was warmed slowly to 10°C and stirred for 3 h. Then, the reaction was quenched with saturated aqueous $NH_4Cl$ (300 mL), THF was removed under reduced pressure and $CH_2Cl_2$ (1200 mL), water (300 mL) were added, The extracted organic layer was washed twice with saturated aqueous $NH_4Cl$ (600 mLx2) and concentrated under reduced pressure to afford cyno diester **5** (349 g, 95%) as a colorless oil. $^{1}H$ NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 6H), 2.96 (s, 2H), 2.06 (m, 2H),

1.25 (q, *J* = 7.2Hz, 2H), 0.98 ppm (t, *J* = 7.2Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.3, 116.3, 55.5, 53.3, 35.0, 21.9, 17.6, 14.0 ppm; HRMS (ESI): m/z: calcd for $C_{10}H_{16}NO_4$ $[M+H]^+$: 214.1074; found: 214.1068.

**Methyl 2-(cyanomethyl)pentanoate** (**6**)：A 1000 mL bottom flask equipped with mechanical agitation was charged with nitrile **5** (130 g, 0.61 mol), LiBr (53 g, 0.61 mol), DMF (650 mL) and water (22.0 g, 1.22 mol), the resulting mixture was heated to 130 °C and stirred for 4 h. Then, the mixture was cooled to 20 °C and saturated saturated aqueous $NH_4Cl$ (260 mL) was added. The aqueous layer was extracted with toluene (400 mL), the organic layer was washed with water (390 mLx2), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford the cyano ester **6** (86.7 g, 92%) as a colorless oil. $^1$H NMR (400 MHz, d$^6$-Acetone): δ = 3.70 (s, 3 H), 2.82 (m, 2 H), 2.73 (m, 2 H), 1.70-1.62 (m, 2 H), 1.36 (m, 2 H), 0.92 ppm (t, *J* = 7.2 Hz, 3 h); $^{13}$C NMR (100 MHz, d$^6$-Acetone): δ = 174.1, 118.9, 52.3, 41.9, 34.2, 20.4, 14.1 ppm; HRMS (ESI): m/z: calcd for $C_8H_{14}NO_2$ $[M+H]^+$ : 156.1019; found: 154.1023.

**(R)-2-(Cyanomethyl)pentanoic acid** (**7**): A 2000 mL bottom flask equipped with refrigerant and mechanical agitation was charged with tris (hydroxymethyl) aminomethane (2.7 g, 22 mmol ) and water (720 mL). pH was adjusted to 8.0 with 1 N HCl, then, cyano ester **6** (90 g, 0.58mol), porcine pancreatic lipase (45 g), and THF (90 mL) was added to the mixture at 30 °C, pH of the reaction mxitue was uninterruptedly monitored and auto adjusted by an online precision pH meter for 18 h using 1 N NaOH. Celite (45.0 g) was added and the resulting mixture was stirred for 1 h, after filtration, the aqueous phase was extracted with ethyl acetate (450 mLx3) and the combined organic layer was concentrated under reduced pressure to afford (S)-2-(cyanomethyl)pentanoate. After pH was adjusted to 2 with 1 N $H_2SO_4$ at 0 °C, the resulting water layer was extracted with ethyl acetate (450 mLx2), the combined organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford chiral acid **7** (38.4 g, 47%) as a colorless oil. [α]25 D = +21.6 (c = 1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.86-2.79 (m, 3 H), 2.74-2.67 (m, 1 H), 2.63-2.54 (m, 1 H), 1.85-1.78 (m, 1H), 1.72-1.65 (m, 1 H), 1.49-1.38 (m, 2 H), 0.95 ppm (t, *J* =

7.2Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 178.2, 117.6, 70.5, 41.1, 33.1, 19.7, 18.9, 13.7 ppm; HRMS (ESI): m/z: calcd for $C_7H_{10}NO_2$ $[M+H]^+$: 140.0717; found: 140.0722.

**Racemization of unhydrolyzed Methyl (S)-2-(cyanomethyl)pentanoate** : A 500 mL round-bottomed flask was charged with recycled methyl (S)-2-(cyanomethyl)pentanoate from the work-up organic layer of **7** (44 g, 0.28 mol), 1, 8-Diazabicyclo[5.4.0]undec-7-ene (12.7 g, 84 mmol) and DMF (100 mL), the racemization mixture was stirred at 130 °C for 5h. Then, DMF was removed under reduced pressure. Water (500 mL) was added and the aqueous layer was extracted with ethyl acetate (320 mLx2). The combined organic layer was washed with saturated NaCl (320mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give racemic ester **6** (43 g, 98%), [α]25 D = 0 (c = 1.0, MeOH), which could be reused for enzymatic hydrolysis without further purification.

**Methyl (R)-2-(cyanomethyl)pentanoate** (**3**): A 250 mL round-bottomed flask was charged with chiral acid **7** (32 g, 0.23 mol), 30% aq. HCl (5.8 g, 58 mmol) and methanol (128 mL), the mixture was heated to 40 °C and stirred for 20 h. Then, methanol was removed under reduced pressure. The aqueous layer was extracted with dichloromethane (400 mLx2). The combined organic layer was washed with saturated NaCl (320 mL), saturated $NaHCO_3$ (320 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give chiral ester **3** (33.1 g, 93%) as a colorless oil, which was used directly in the next step. HRMS (ESI): m/z: calcd for $C_8H_{14}NO_2$ $[M+H]^+$: 156.1019; found: 154.1016.

**(R)-3-(Hydroxymethyl)hexanenitrile** (**8**): A 500 mL round-bottomed flask was charged with chiral ester **3** (32.5 g, 0.21 mol) and THF (325 mL). Sodium borohydride (15.9 g, 0.42 mol) was added to the mixture in potion under 20 °C. After warmed to 40 °C, methanol (46.9 g, 1.46 mol) was added dropwise and the resulting mixture was stirred for 6 h. Then, the reaction, mixture was cooled to 0 °C, pH was adjusted to 7.5 by 1 N HCl, and the resulting mixture was extracted with ethyl acetate (320 mLx2). The combined organic layer was washed with saturated NaCl (320 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give cyno alcohol **8**

(22.5 g, 84%) as a colorless oil, which was used directly in the next step. [α]25 D = +13.6 (c = 1.0, MeOH), HRMS (ESI): m/z: calcd for $C_7H_{14}NO$ $[M+H]^+$: 128.1070; found: 128.1075.

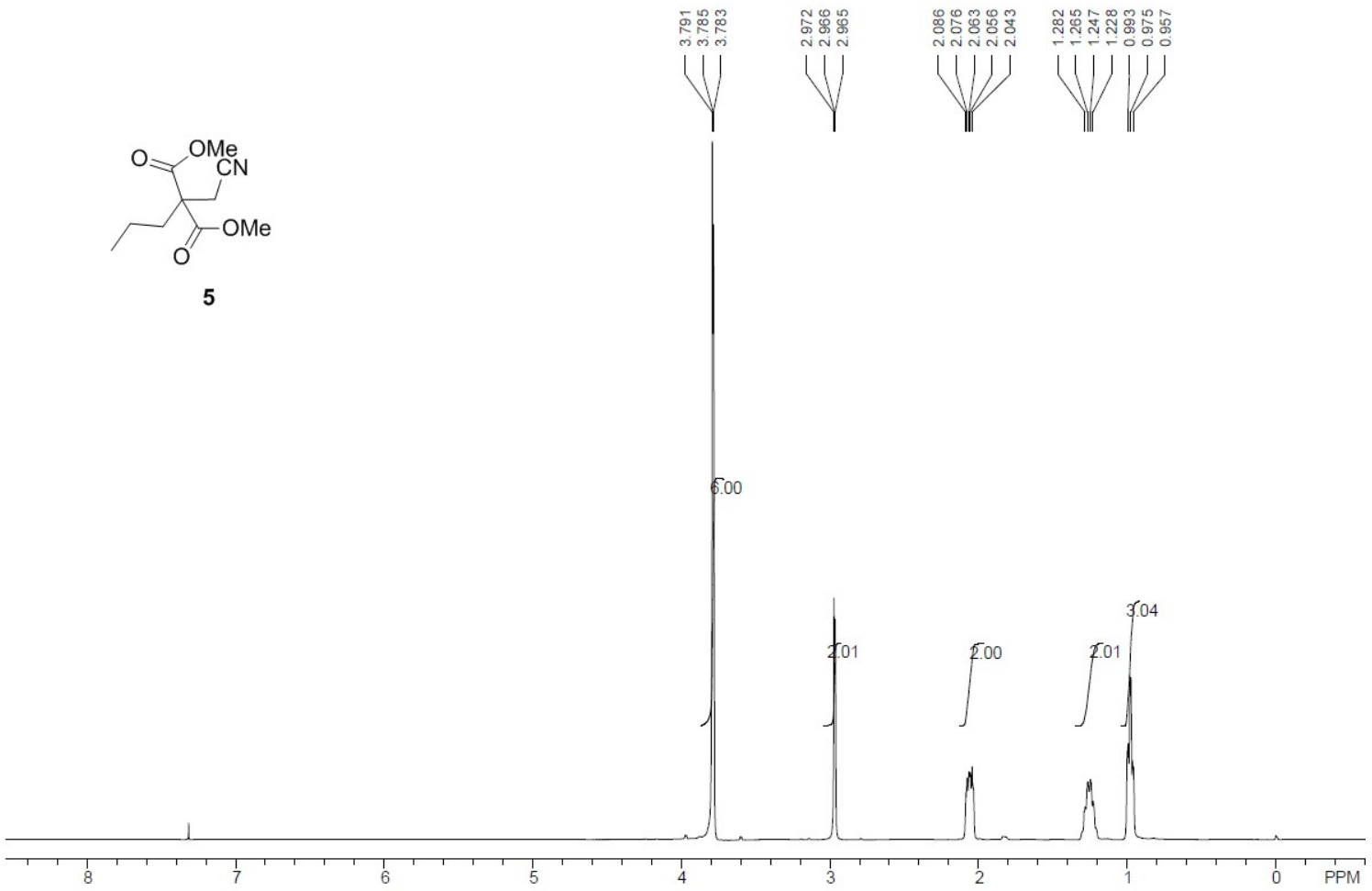
**(R)-2-(Cyanomethyl)pentyl 4-methylbenzenesulfonate** (**9**): A 500 mL round-bottomed flask was charged with cyno alcohol **8** (16 g, 0.12 mol), triethylamine (38.2 g, 0.38 mol) and methylene chloride (160 mL) and cooled to 0 °C. TsCl (33.6 g, 0.18 mol) was added to the resulting mixture dropwise, the mixture was warmed to 25 °C and stirred for 16 h. Then, the mixture was washed with saturated $NaHCO_3$ (200 mL), saturated NaCl (200 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford tosylate **9** (33.6 g, 95%) as a colorless oil. [α]25 D: = +17.3 (c = 1.0g, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.79 (m, 2 H), 7.36 (m, 2 H), 4.07 (m, 1 H), 3.92 (m, 1 H), 2.43 (s, 3 H), 2.39 (m, 2 H), 2.12 (m, 1 H), 1.38 (m, 2 H), 1.29 (m, 2 H), 0.88 ppm (m, 3 H); $^{13}$C NMR (100Hz, $CDCl_3$): δ = 145.2, 132.4, 130.0, 127.9, 117.4, 70.5, 35.0, 31.8, 21.6, 19.6, 19.2, 13.8 ppm; HRMS (ESI): m/z: calcd for $C_{14}H_{20}NO_3S$ $[M+H]^+$ : 282.1158; found: 282.1165.

**(S)-2-(((R)-2-(Cyanomethyl)pentyl)amino)butanamide** (**2**): A 500 mL round-bottomed flask was charged with tosylate **9** (10.4 g, 37 mmol), tetrbutylammonium iodide (6.8 g, 18.5 mmol), $Na_2CO_3$ (8.7 g, 82 mmol), (S)-2-aminobutyamide (6.6 g, 65 mmol) and acetonitrile (85 mL), the resulting mixture was heated to 80 °C and stirred for 5 h. Then, the reaction mixture was cooled to 20 °C, water (100 mL) and ethyl acetate (100 mL) were added, the extracted organic layer was washed with saturated NaCl (200 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford cyno amide **2** (6.9 g, 88%) as a colorless oil. [α]25 D = -16.7 (c＝1.0, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.73 (s ,1H), 6.42 (s ,1H), 2.88 (m, 1H), 2.62 (m, 1H), 2.51-2.32 (m, 3H), 1.75 (m, 1H), 1.62-1.51(m, 2H), 1.34-1.21(m, 5H), 0.89-0.82 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 177.5, 118.7, 64.1, 51.1, 35.5, 33.5, 26.2, 19.9, 19.6, 9.9, 7.5 ppm; HRMS (ESI): m/z: calcd for $C_{11}H_{22}N_3O$ $[M+H]^+$: 212.1757; found: 212.1752.

**(S)-2-((R)-2-Oxo-4-propylpyrrolidin-1-yl)butanoic acid** (**10**): A 500 mL round-bottomed flask was charged with butanamide **2** (11.6 g, 55 mmol), 30% aq. HCl (87

mL) and methanol (116 mL). The resulting mixture was heated to 50 °C and stirred for 18 h. Then, pH of the mixture was adjusted to 12 under 0 °C, the residue was extracted with ethyl acetate (100 mLx3), Then the organic layer was washed with saturated NaCl (200 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure, the residue was purified by silica gel column chromatography (EtOAc/hexane 1:3) to afford brivaracetam acid **10** (9.3 g, 80%) as a colorless oil. [α]25 D= -26.1 (c = 1.0, $CDCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): δ = 11.22 (br, 1 H), 4.59 (m, 1 H), 3.36 (m, 1 H), 3.14 (t, *J* = 8.3 Hz, 1 H), 2.52 (m, 1 H), 2.28 (m, 1 H), 2.12 (m, 1 H), 2.03 (m, 1 H),1.64 (m, 1 H), 1.39 (m, 2 H), 1.28 (m, 2 H), 0.87 (t, 3 H), 0.85 ppm (t, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 175.9, 173.0, 54.3, 48.4, 36.6, 35.4, 31.1, 20.9, 19.6, 13.0, 9.8 ppm; HRMS (ESI): m/z: calcd for $C_{11}H_{20}NO_3$ $[M+H]^+$ : 214.1438; found: 214.1445.

**Brivaracetam** (**1**): A 1000 mL round-bottomed flask was charged with brivaracetam acid **10** (20 g, 94 mmol), triethylamine (26.0 g, 259 mmol) and methylene chloride (200 mL) and cooled to 0 °C, pivaloyl chloride (18.1 g, 150 mmol) was added dropwise in 2 h, then, ammonia gas was bubbled to the reaction mixture for 10 h. After the reaction was completed, the mixture was washed with water (400 mL), saturated NaCl (400 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The residue was recrystallized with isopropyl acetate and cyclohexane (1:3,v/v) to obtain brivaracetam **1** (19 g, 95%) as a white crystal. purity (HPLC): 99.9%, 99.8% de.; mp: 75 °C; [α]25 D: = -60.2 (c = 1.0, MeOH); $^1$H NMR (400 $MH_Z$, $CDCl_3$): δ = 6.71 (s, 1 H), 6.14 (s, 1 H), 4.51 (dd, *J* = 9.0, 6.4 Hz, 1 H), 3.61 (dd, *J* = 9.6, 8.0 Hz, 1 H), 3.00 (dd, *J* = 9.7, 6.7 Hz, 1 H), 2.53 (dd, *J* = 14.8, 8.5 Hz, 1 H), 2.39 (m, 1 H), 2.12 (dd, *J* = 16.5, 7.8 Hz, 1 H), 2.03 (m, 1 H), 1.70 (m, 1 H), 1.44-1.24 (m, 4 H), 0.94 (m, 3 H), 0.90 ppm (m, 3 h); $^{13}$C NMR (100MHz, $CDCl_3$): δ = 175.3, 172.7, 55.7, 49.4, 37.7, 37.0, 31.6, 21.1, 20.4, 13.7, 10.2 ppm; HRMS (ESI): m/z: calcd for $C_{11}H_{21}N_2O_2$ $[M+H]^+$ : 213.1598; found: 213.1594.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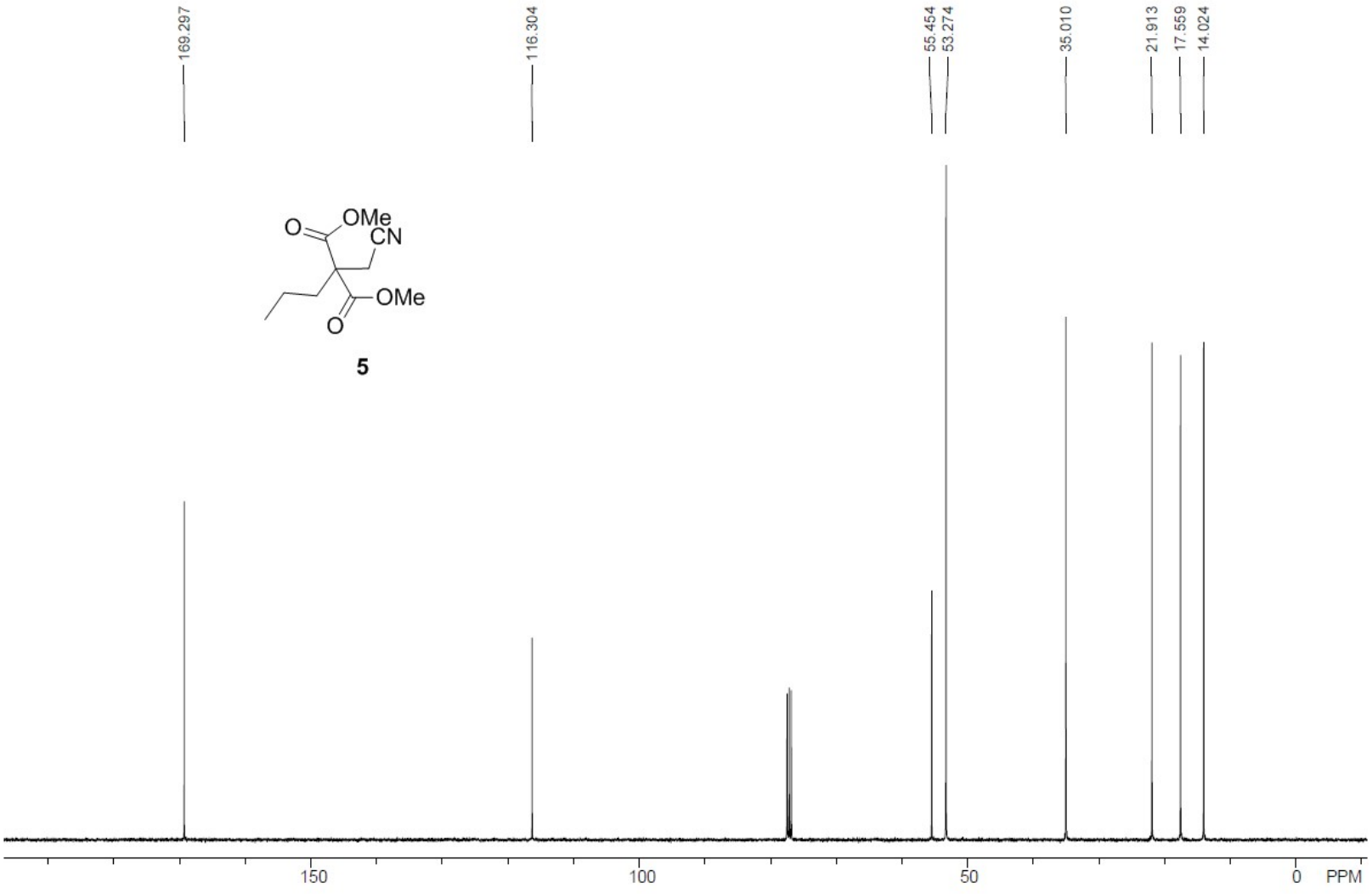
**5**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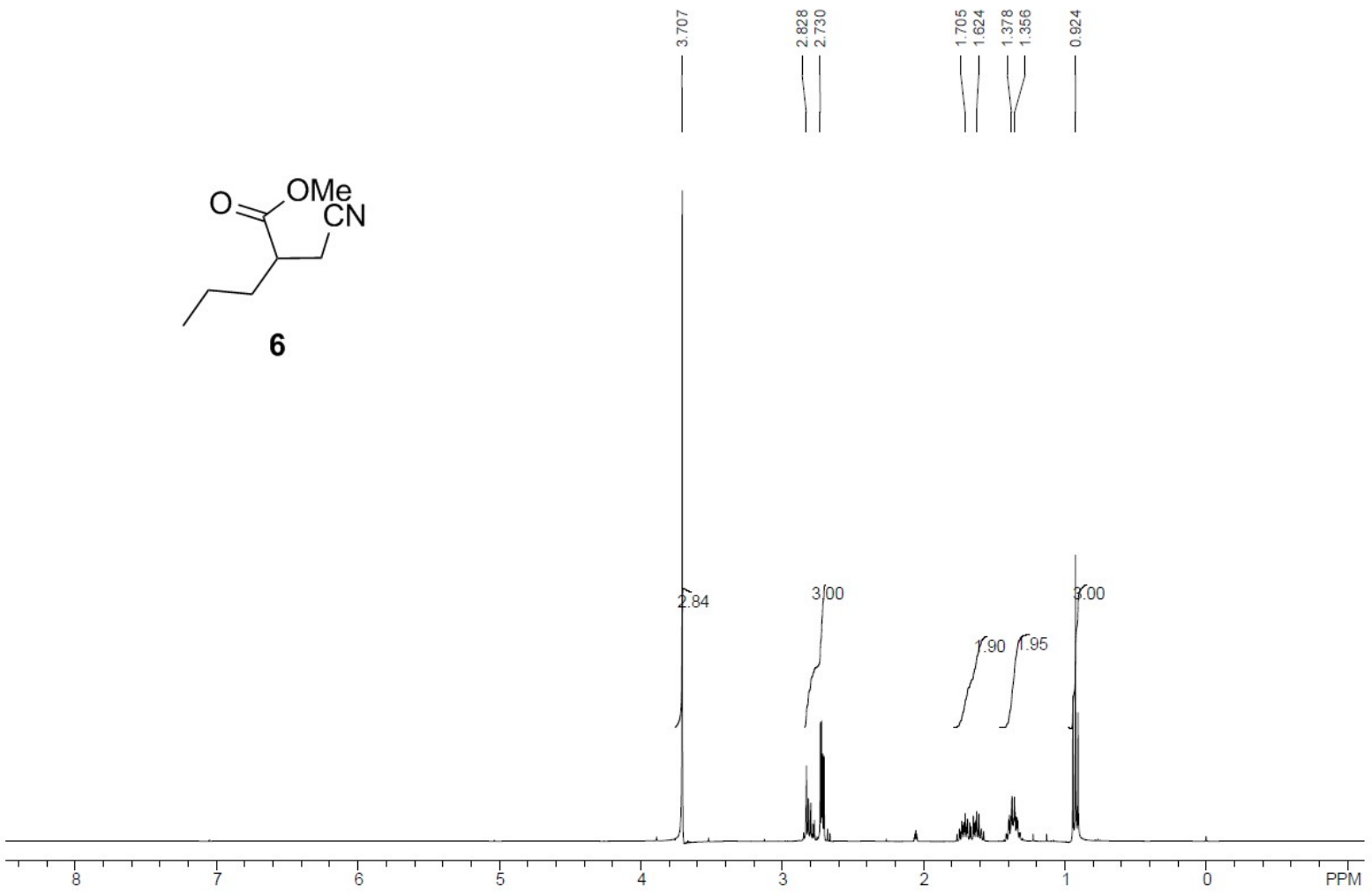
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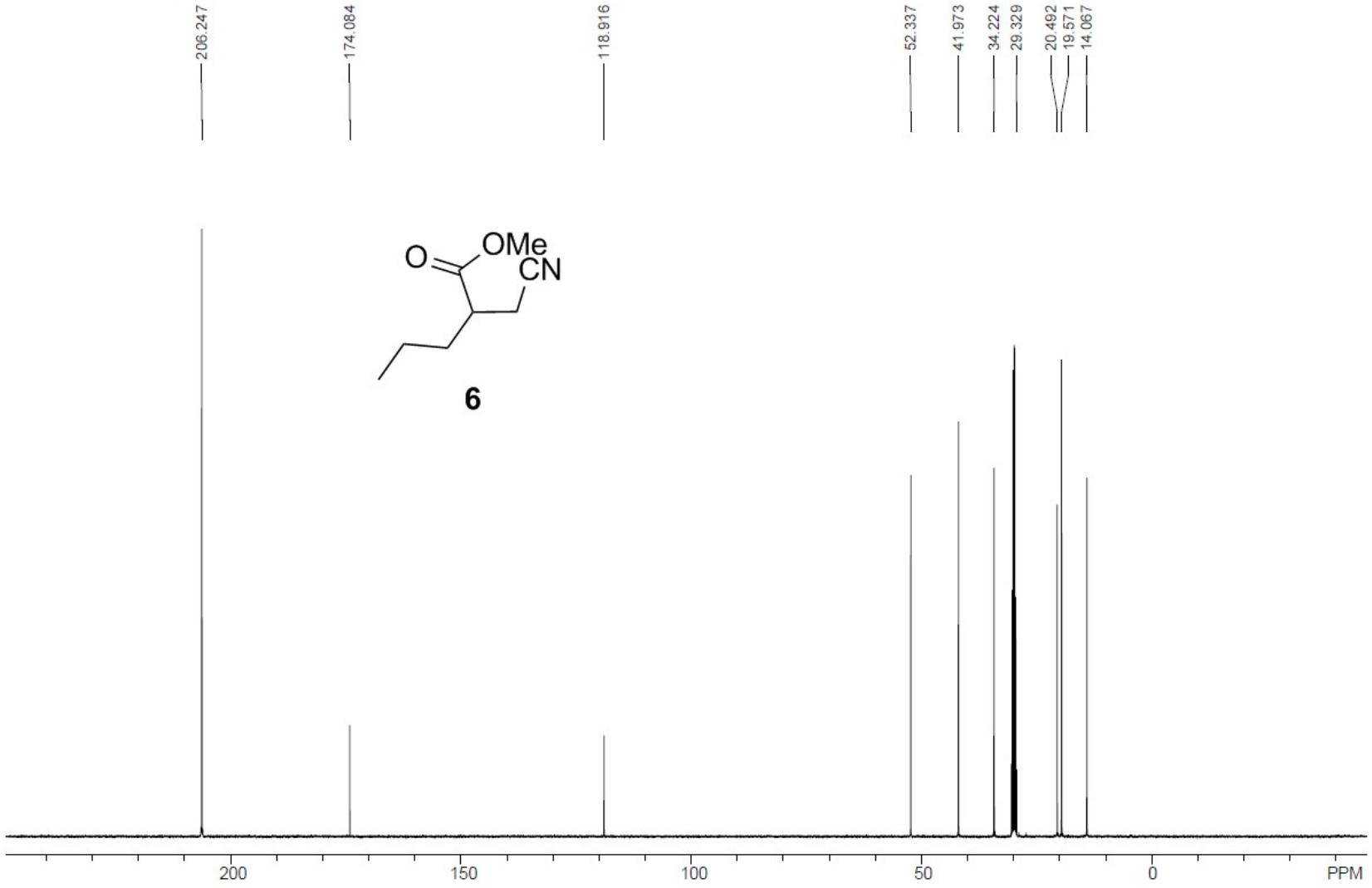
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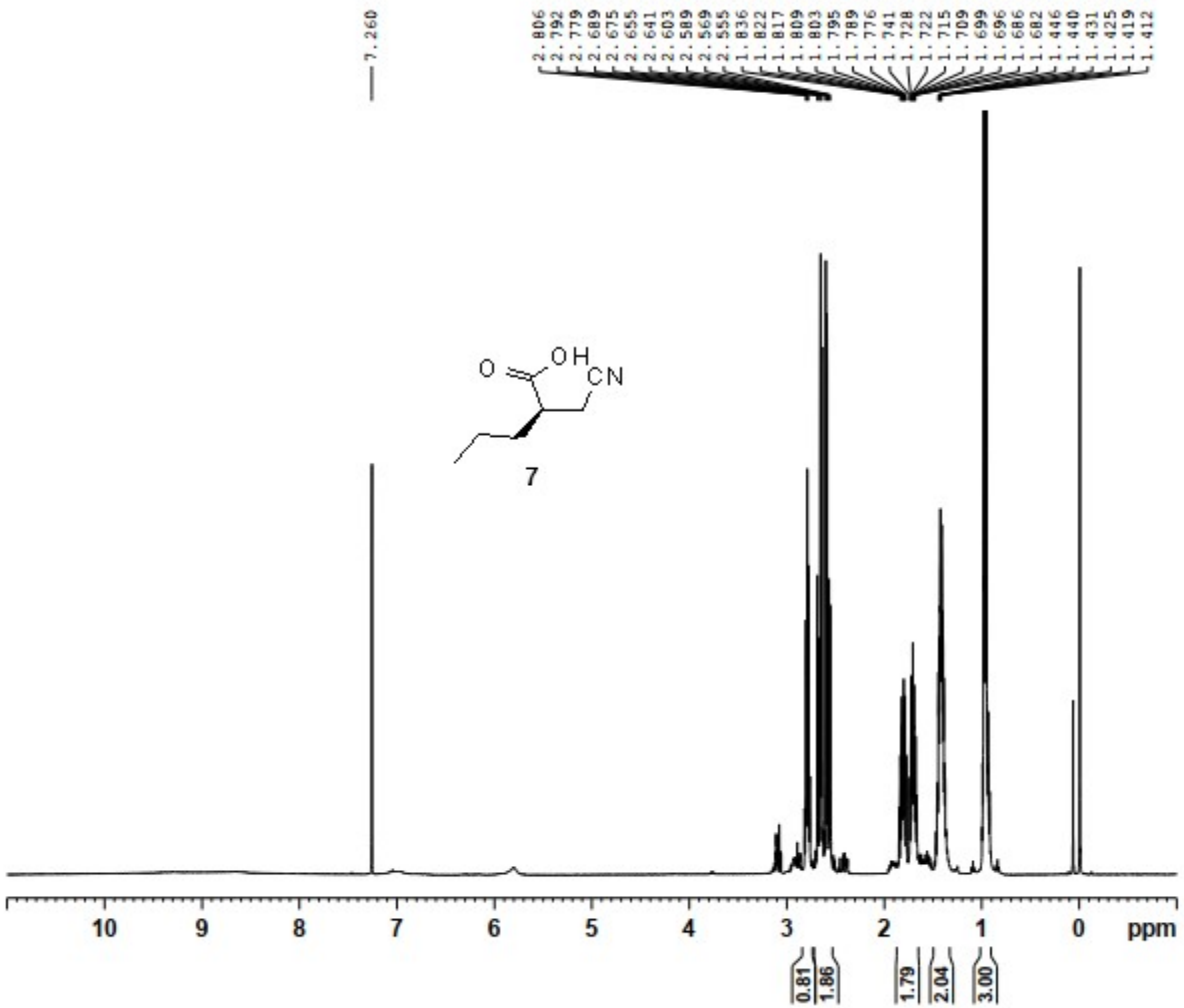
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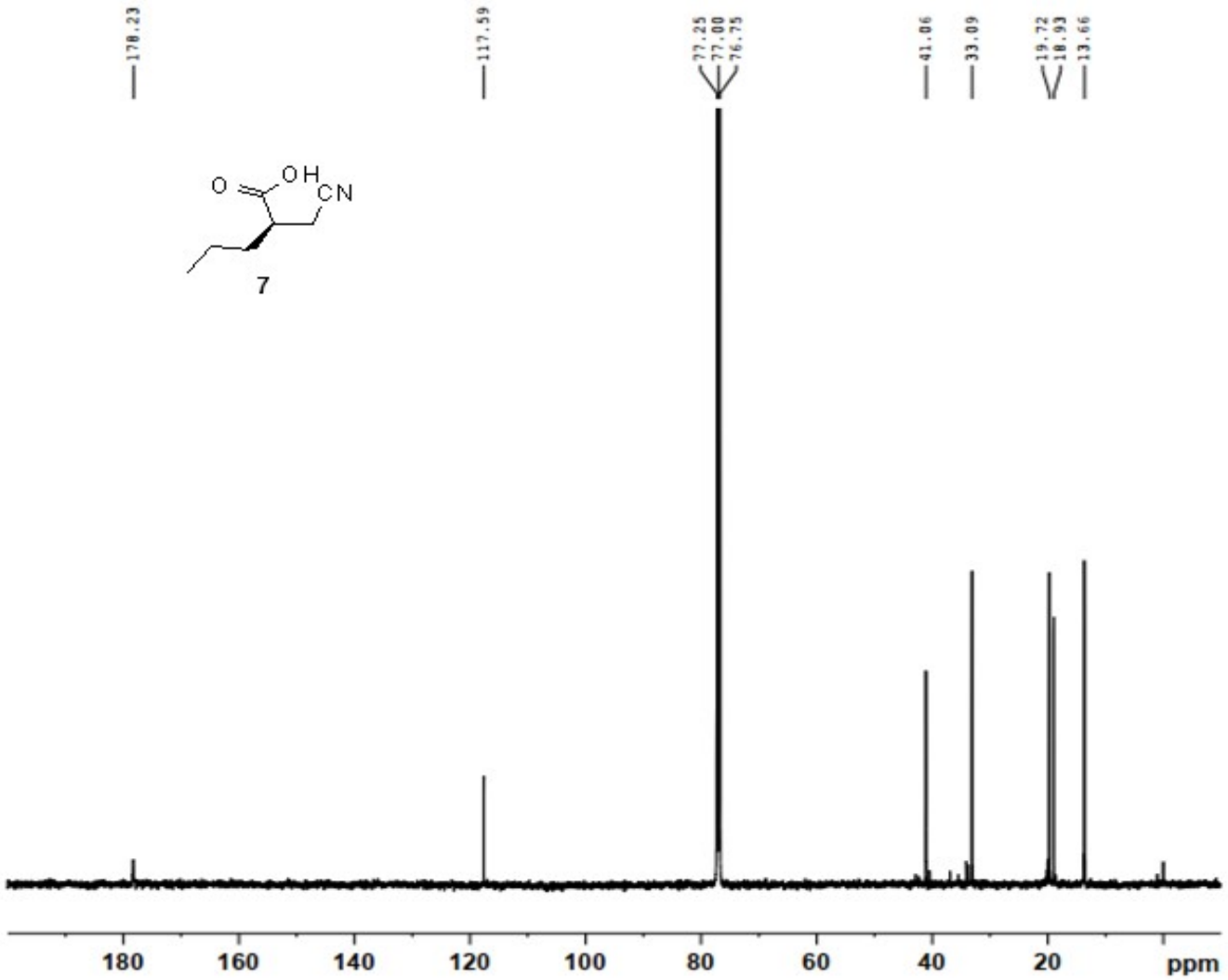
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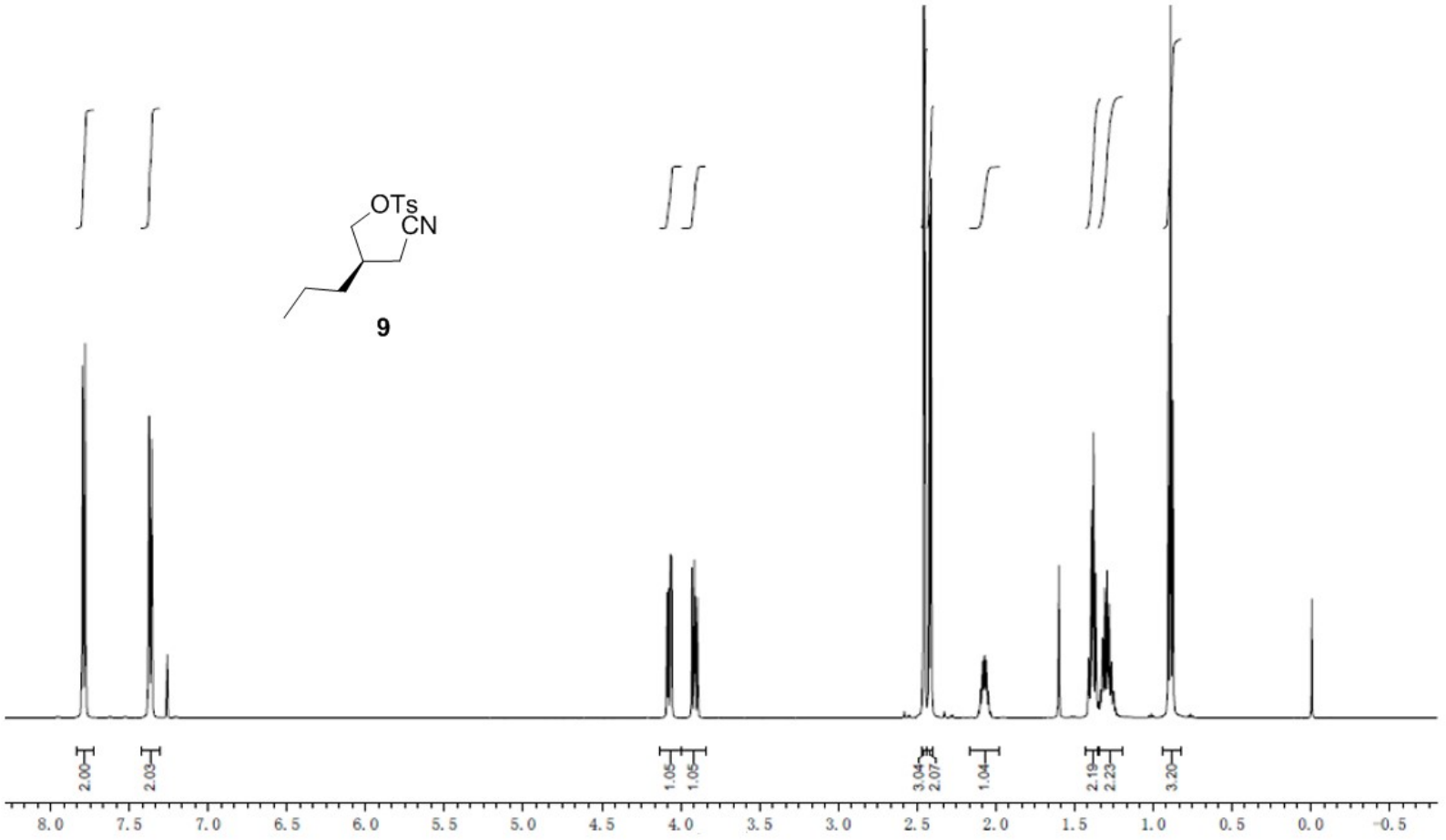
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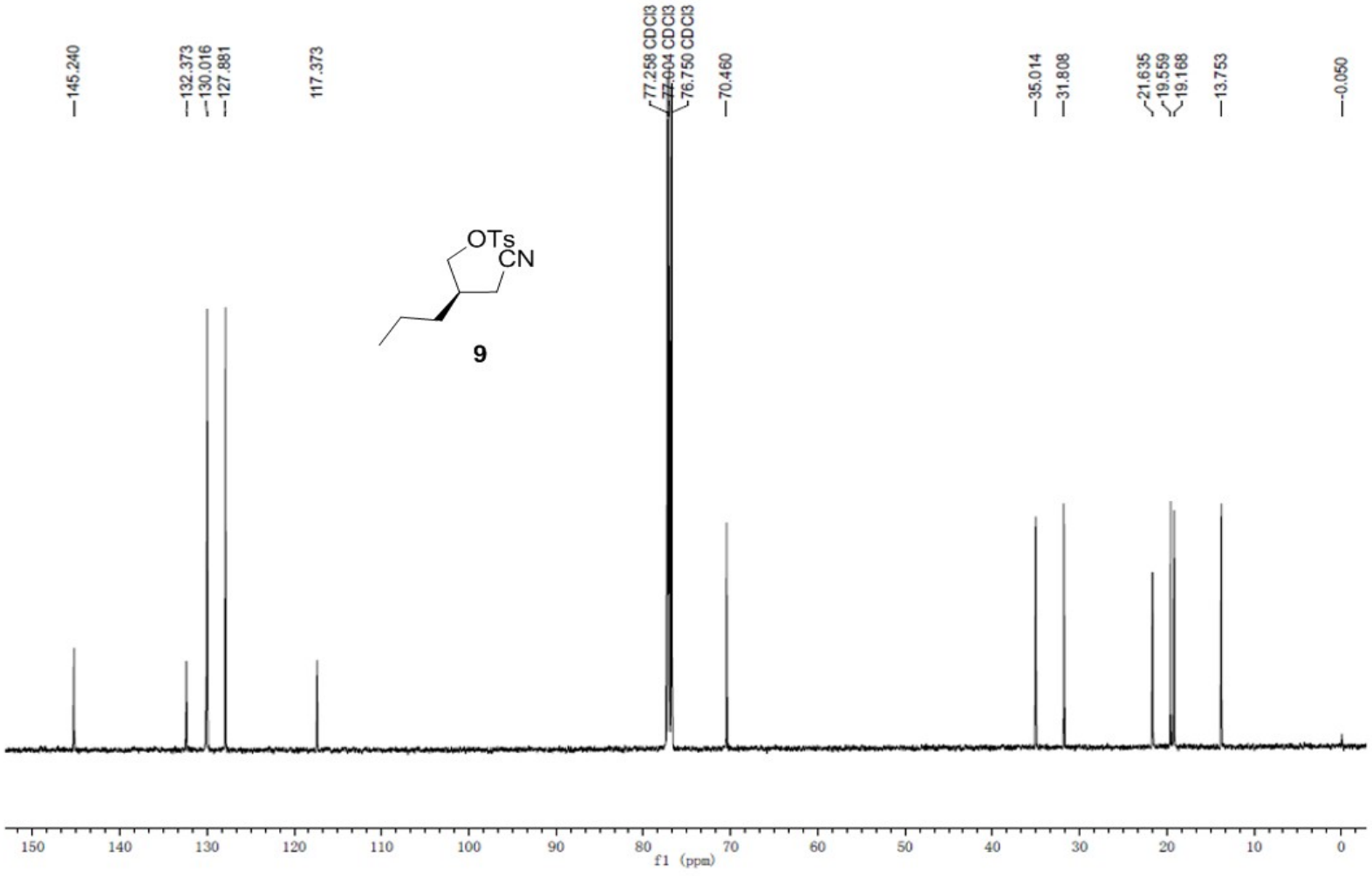
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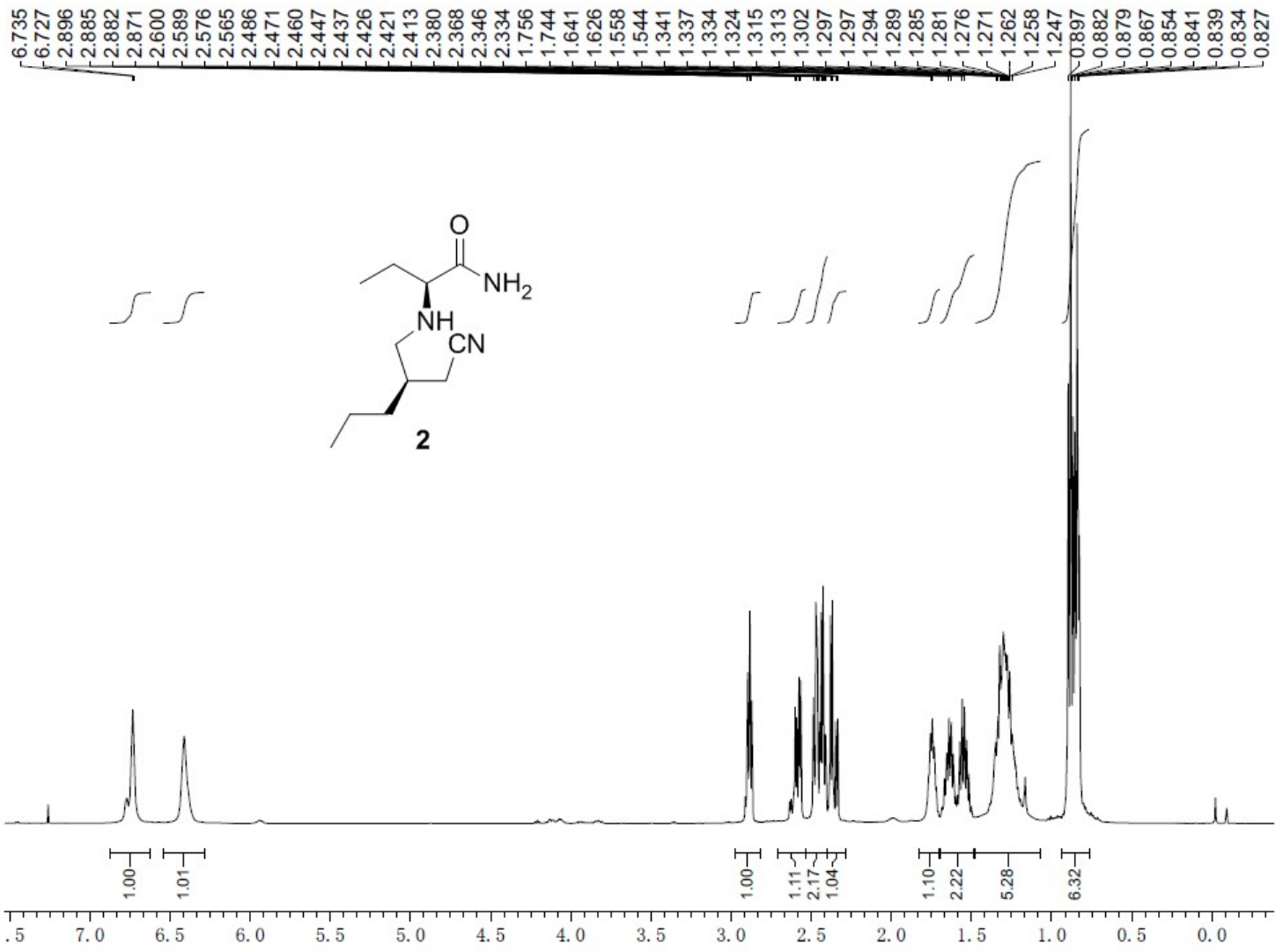
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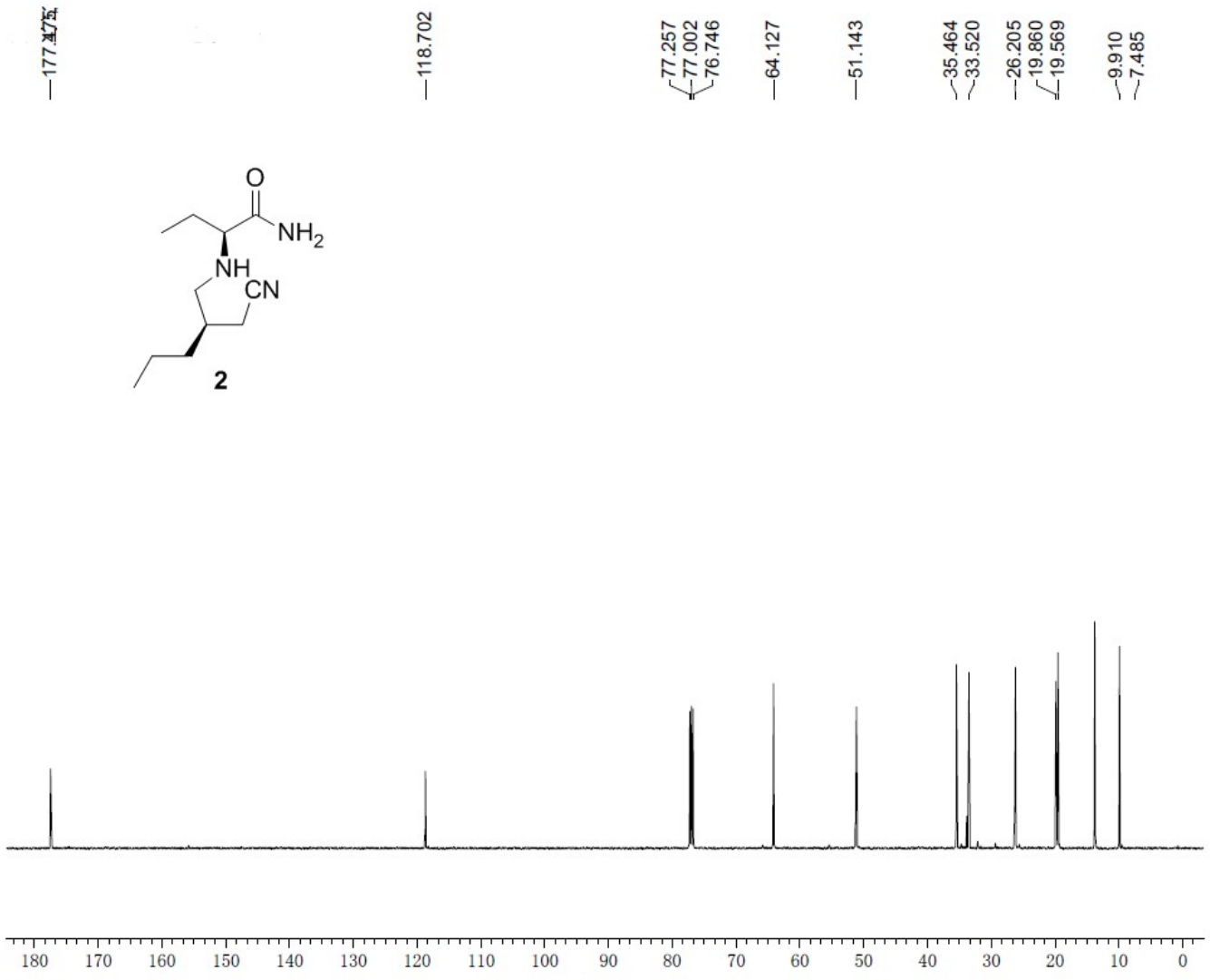
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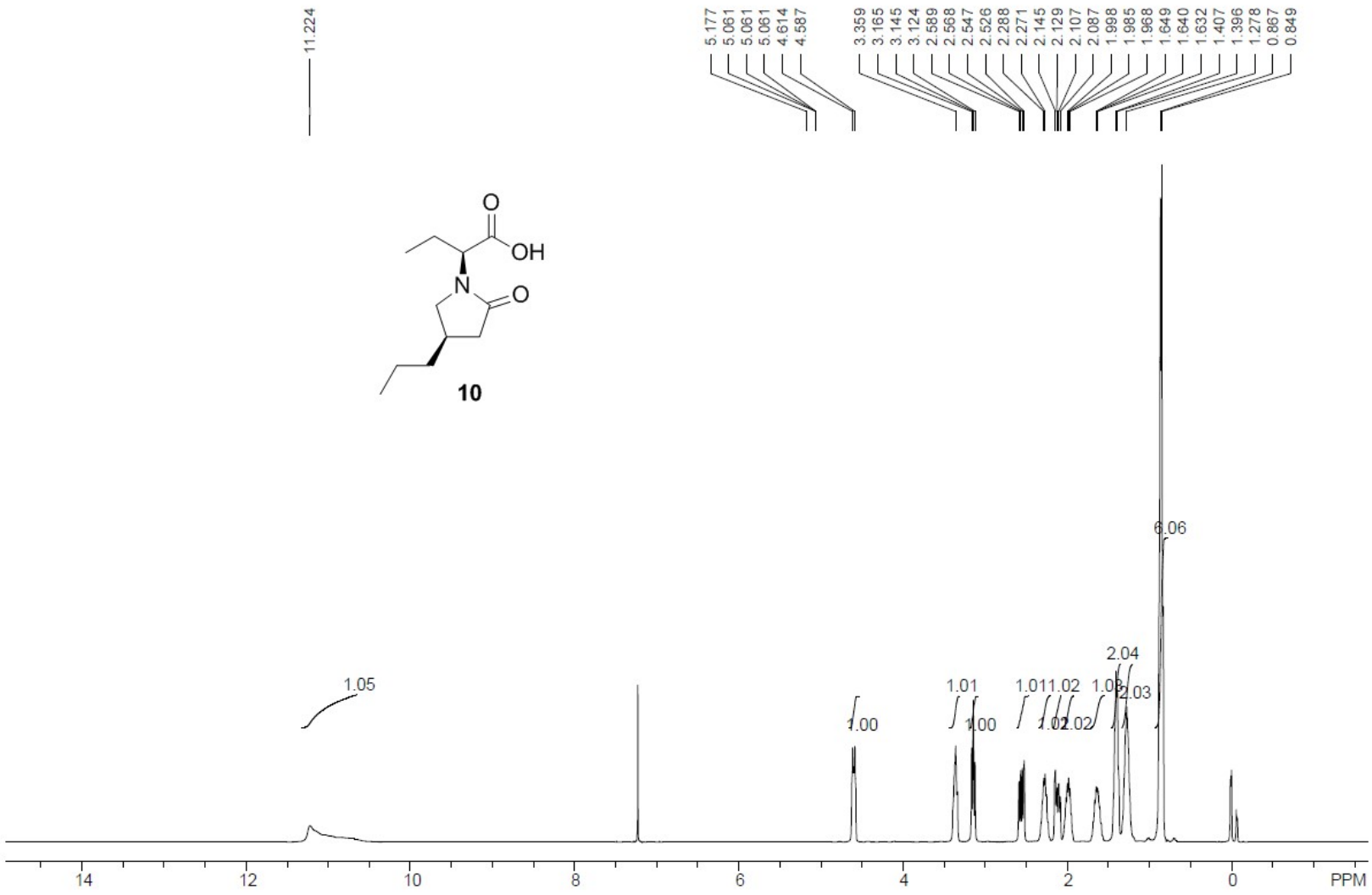
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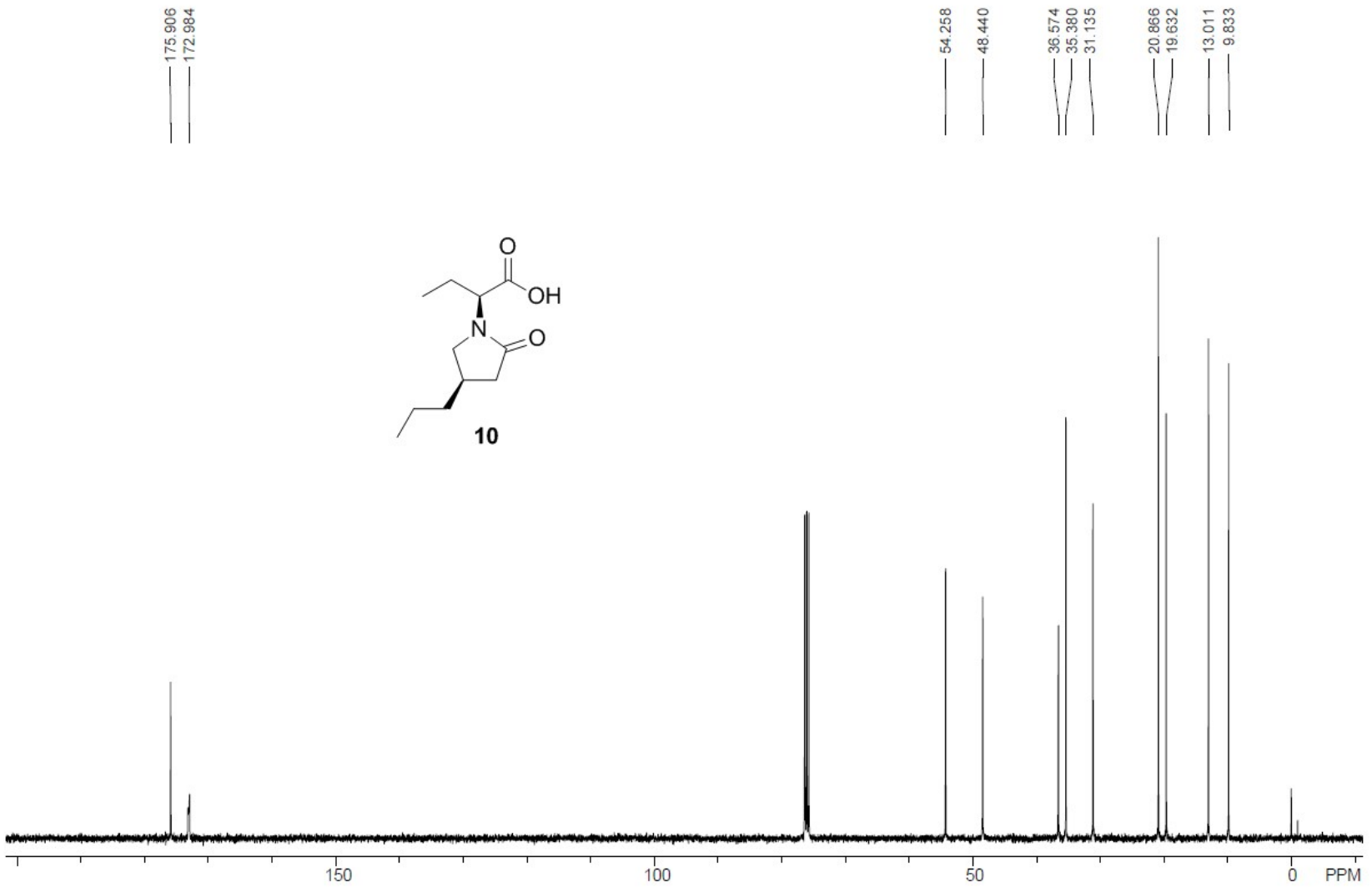
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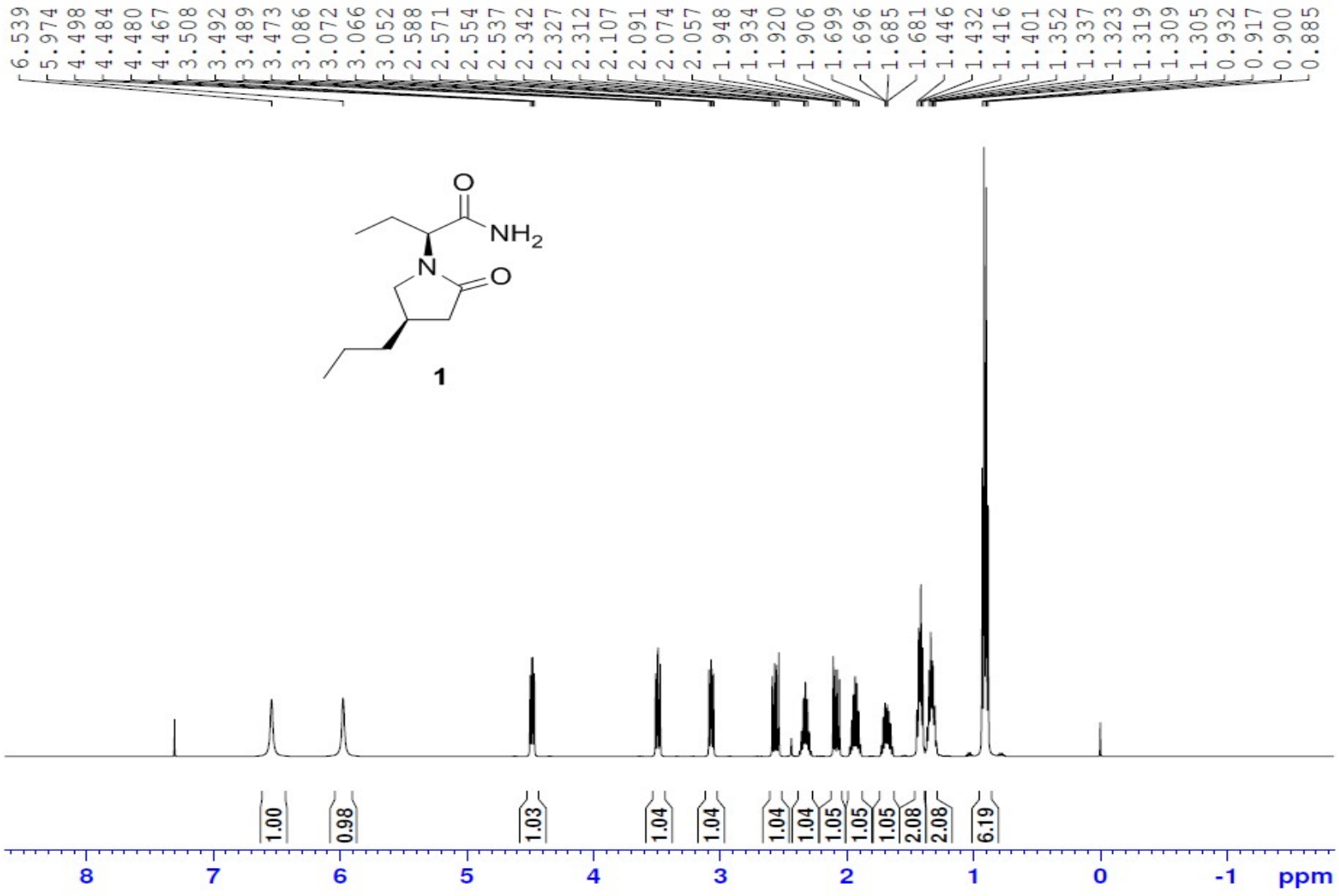
PPM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3.066
3.052
2.588
2.571
2.554
2.537
2.342
2.327
2.312
2.107
2.091
2.074
2.057
1.948
1.934
1.920
1.906
1.699
1.696
1.685
1.681
1.446
1.432
1.416
1.401
1.352
1.337
1.323
1.319
1.309
1.305
0.932
0.917
0.900
0.885
O
NH2
N
O
1
1.00
0.98
1.03
1.04
1.04
1.04
1.04
1.05
1.05
1.05
2.08
2.08
6.19
8
7
6
5
4
3
2
1
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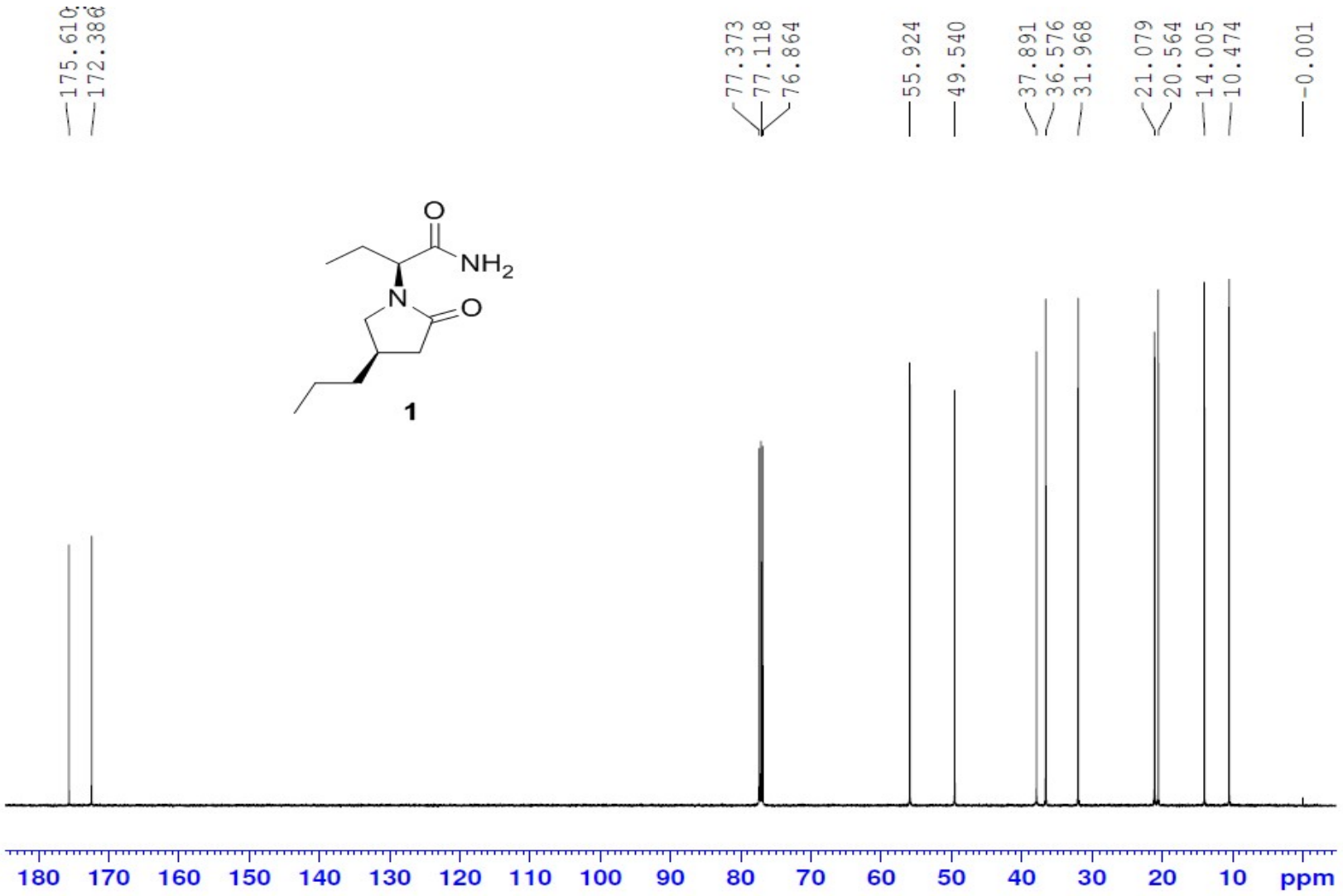
-1
ppm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172.386
77.373
77.118
76.864
55.924
49.540
37.891
36.576
31.968
21.079
20.564
14.005
10.474
0.001
O
NH2
N
O
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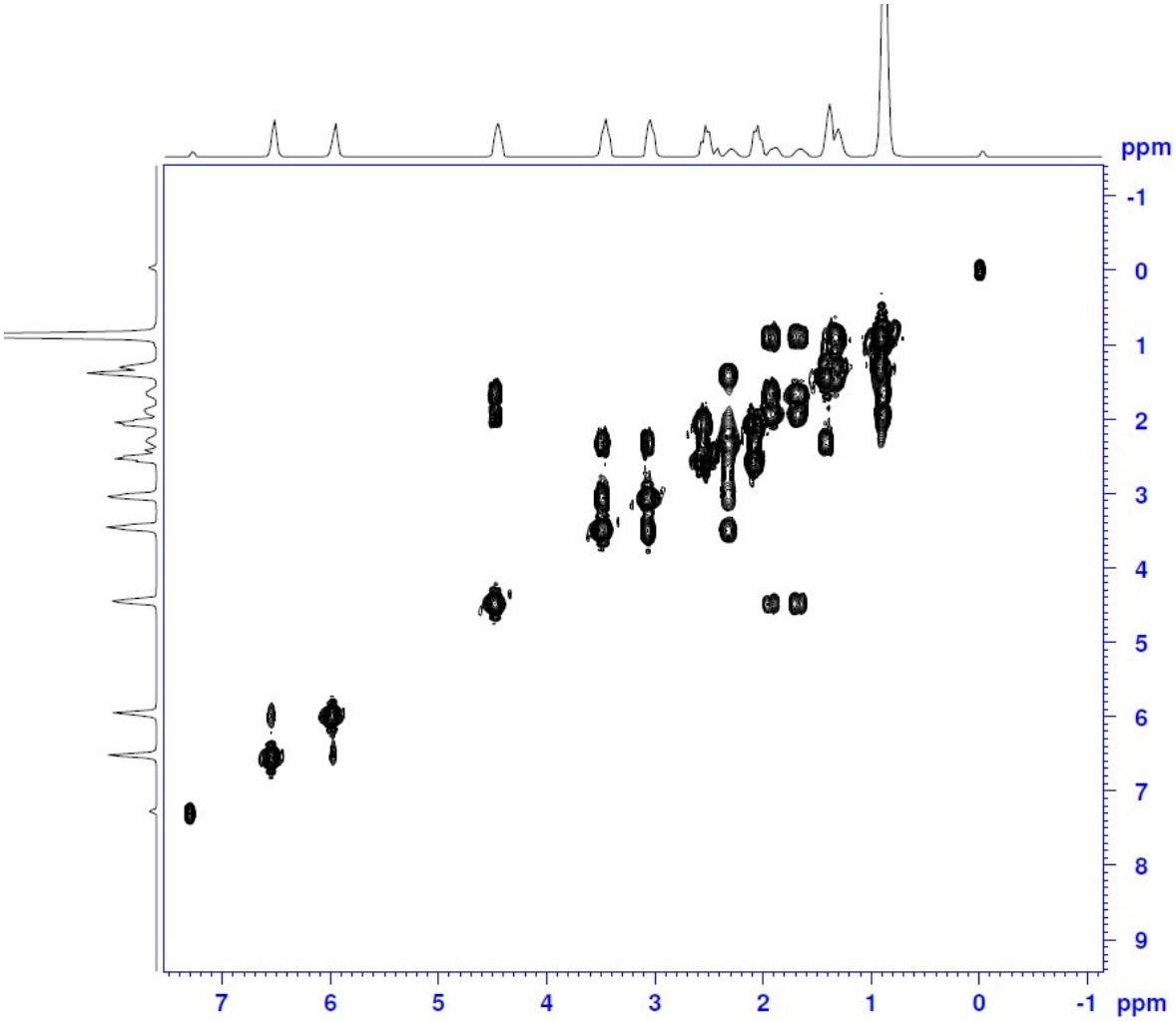
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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2
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4
5
6
7
8
9
7
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5
4
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2
1
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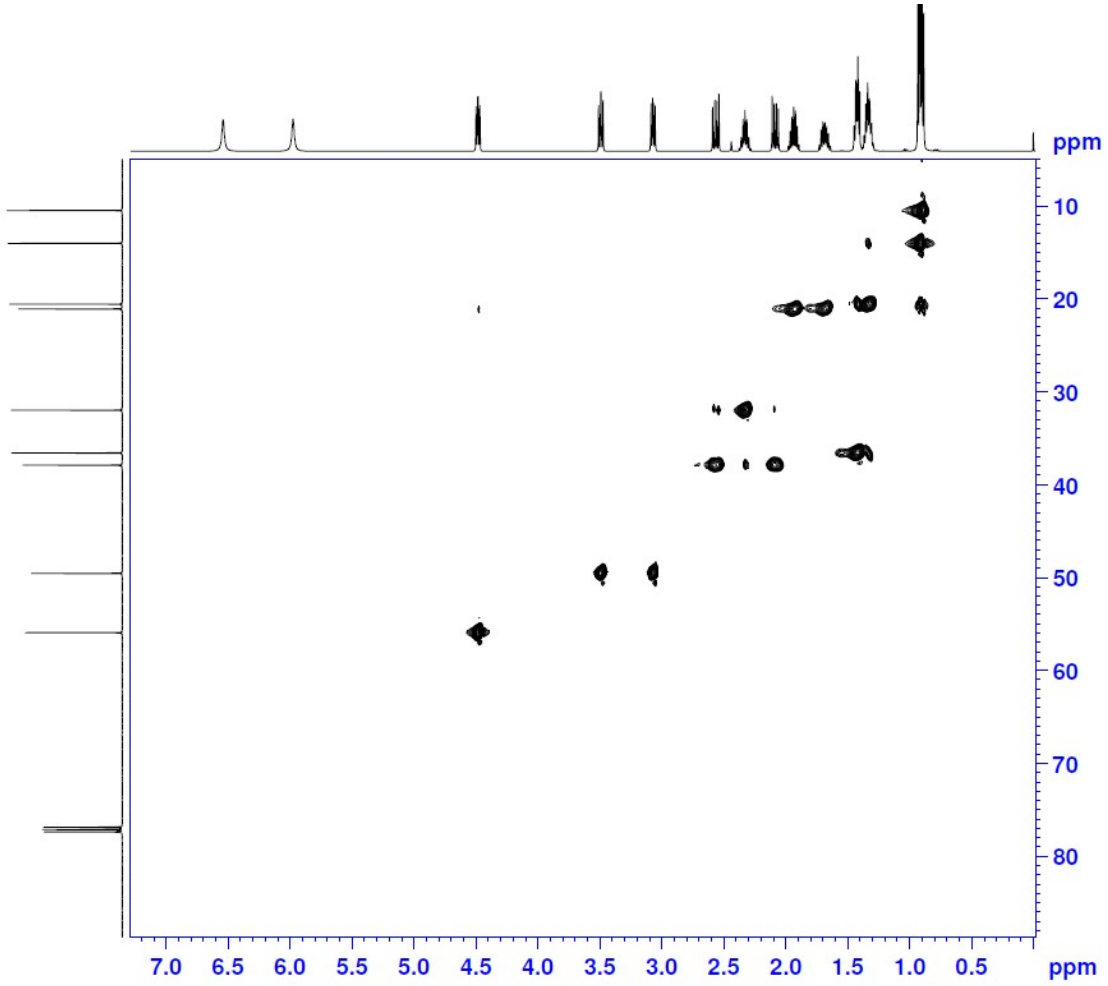
ppm


ppm
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40
50
60
70
80
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6.5
6.0
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5.0
4.5
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3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm