Supporting Information for:

Equilibrium Acidities of Proline Derived Organocatalysts in DMSO

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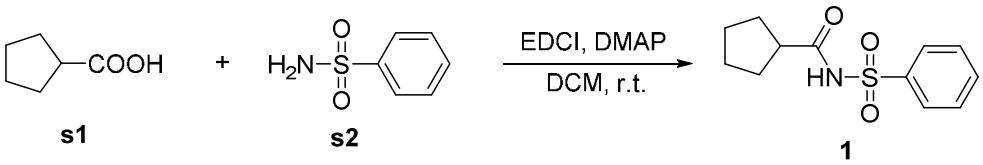
EXPERIMENTAL SECTION

General Information: All commercial reagents were used as received, unless otherwise stated. ^{1}H and ^{13}C NMR were recorded on a Bruker AV400 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad. All first-order splitting patterns that could not be easily interpreted are designated as multiplet (m). Mass spectra were obtained using Matrix-Assisted Laser Desorption/ Ionization (MALDI) mass spectrometer.

Synthesis: Indicators 9-CN-FH, 9-$PhSO_2$-FH, 2-Br-9-PhS-FH, 9-(p-BrPhS)-FH, 9-iPrS-FH, 9-Ph-FH were synthesized and characterized by known methods.[1] Carbazole and Fluorene were commercially available and purification was carried out according to literature.[1a, 2] Proline Tetrazole (**13**),[3] Prolinsulfonamide (**2**-**7**),[4] N-aryl Proline Amide (**8**-**11**),[5] (S)-4-methyl-N-(pyrrolidinyl-2-methyl)benzenesulfonamide (**14**)[6] were synthesized according to published literature procedures. Proline Amide,

N-Boc L-Proline were commercially available and were carefully recrystallized and dried prior to use.

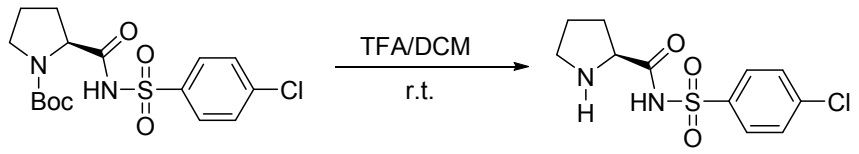
Preparation of N-(phenylsulfonyl)cyclopentanecarboxamide 1:



s1 **s2** **1**

To a solution of **s1** (20 mmol) in DCM (100ml) were added sulfonamide **s2** (25 mmol), EDCI(25mmol), and DMAP(5 mmol). The reaction mixture was stirred at room temperature for 48h. The solution was concentrated in vacuo and then 100ml 1M HCl was added. The mixture was extracted with 80ml EtOAc twice and the combined organic layer was dried over Na_2SO_4. The crude product was purified by flash column chromatography with PE/EA=5:1. The obtained product was recrystallized twice from EtOH prior to use. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.18 – 7.99 (m, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 2.67 – 2.55 (m, 1H), 1.90 – 1.47 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.97, 138.72, 134.09, 129.15, 128.41, 45.60, 29.70, 25.99. HRMS (MALDI$^+$): calcd for [$C_{12}H_{15}NO_3S$+Na^+] 276.0670, found: 276.0672. *Anal*. Calcd, for: $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.76; H, 5.95; N, 5.55.

Preparation of N-4-chlorobenzenesulfonyl-L-proline amide 5



s5 **5**

A solution of **s5** in 1:1 mixture of TFA and DCM was stirred at room temperature for 4h. Then the solution was concentrated in vacuo and saturated $NaHCO_3$ was added dropwise at 0°C until no bubbles was produced. The solution was extracted with DCM/MeOH (10:1) mixture and dried over Na_2SO_4. Compound **5** was obtained as white solid after twice recrystallization in MeOH. ^{1}H NMR (400 MHz, DMSO) δ 8.51 (s, 1H), 7.81 – 7.74 (m, 1H), 7.51 – 7.44 (m, 1H), 3.91 – 3.75 (m, 1H), 3.19 – 2.98 (m, 1H), 2.18 – 2.04 (m, 1H), 1.88 – 1.62 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 171.66, 144.08, 135.01, 128.92, 127.86, 61.90, 45.29, 29.06, 23.35. HRMS (MALDI$^+$): calcd for [$C_{11}H_{13}ClN_2O_3S$+Na^+] 311.0233, found: 311.0230. *Anal*. Calcd, for: $C_{11}H_{13}ClN_2O_3S$: C, 45.76; H, 4.54; N, 9.70. Found: C, 45.79; H, 4.57; N, 9.65.

Measurement

All manipulations were carried out under dry argon according to literature.[1a] Weights of indicators and acids were recorded to ± 0.01 mg . Others were recorded to ±0.0001 g, and absorbance was measured with a UV/vis spectrophotometer. Preparation of DMSO and dimsyl follow the instructions of literature.[1a] **Homo-Hydrogen Bonding calibration** was performed according to literature.[7]

Table S1. pK_a values of proline and its analogue**s**

Acid	pK_{a_app} [a]	pK_{a_cal} [b]	lgK_{hb} [c]	Indicator [d]
15 L-Proline	13.32 ± 0.04	13.35 ± 0.04	2.56 ± 0.17	2-Br-9-PhS-FH
16 N-Boc L-Proline	11.55 ± 0.01	11.56 ± 0.01	2.17 ± 0.15	9-PhSO_2-FH
17 Pipecolinic Acid	13.31 ± 0.11	13.40 ± 0.10	3.48 ± 0.12	2-Br-9-PhS-FH

[a] Apparent pK_a values. [b] Calibrated pK_a values using methods developed by Bordwell[7] . [c] K_{hb} (L^{-1} mol^{-1}), Homo-Hydrogen-Bonding constants. [d] FH, fluorine.

Selected titration spectrums:

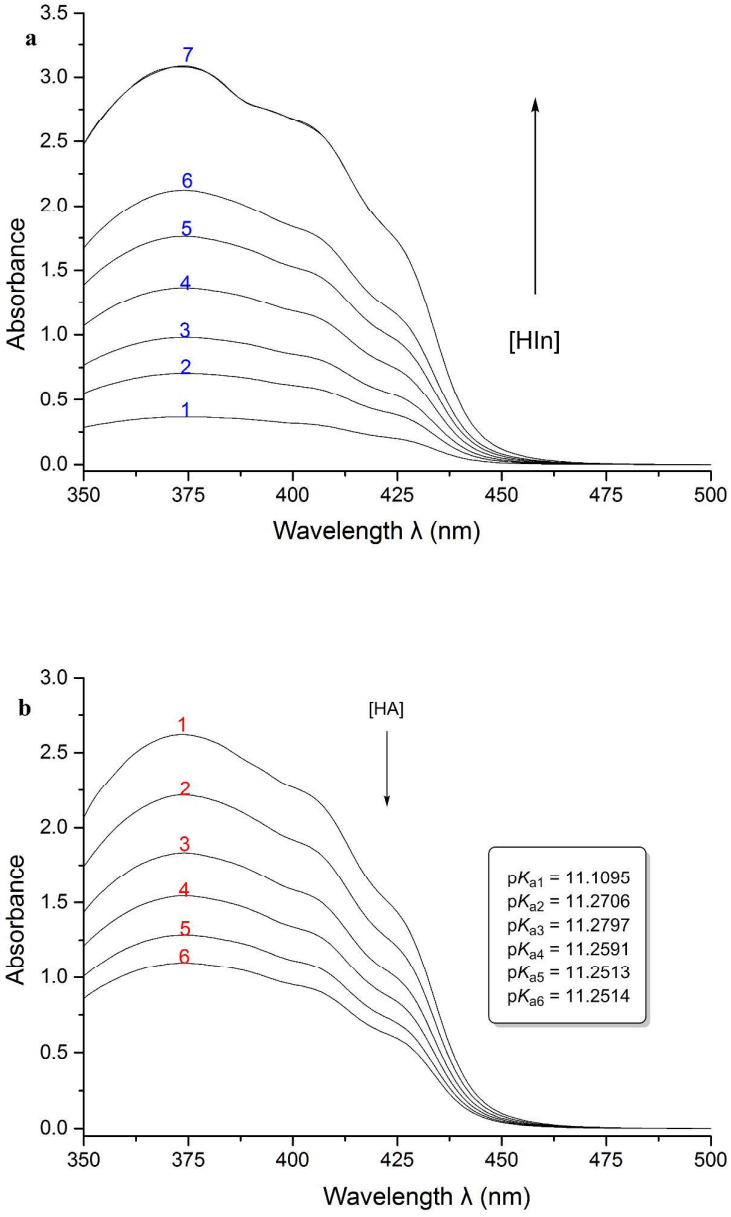


Figure S-1 (a) Absorption spectra of the incicator anion derived from 9-PhSO$_2$FH for various added amount of 9-PhSO$_2$FH during the **First** titration. (b) Absorption spectra of the indicator anion for various added amount of Proline Tetrazole (1) during the **First** titration

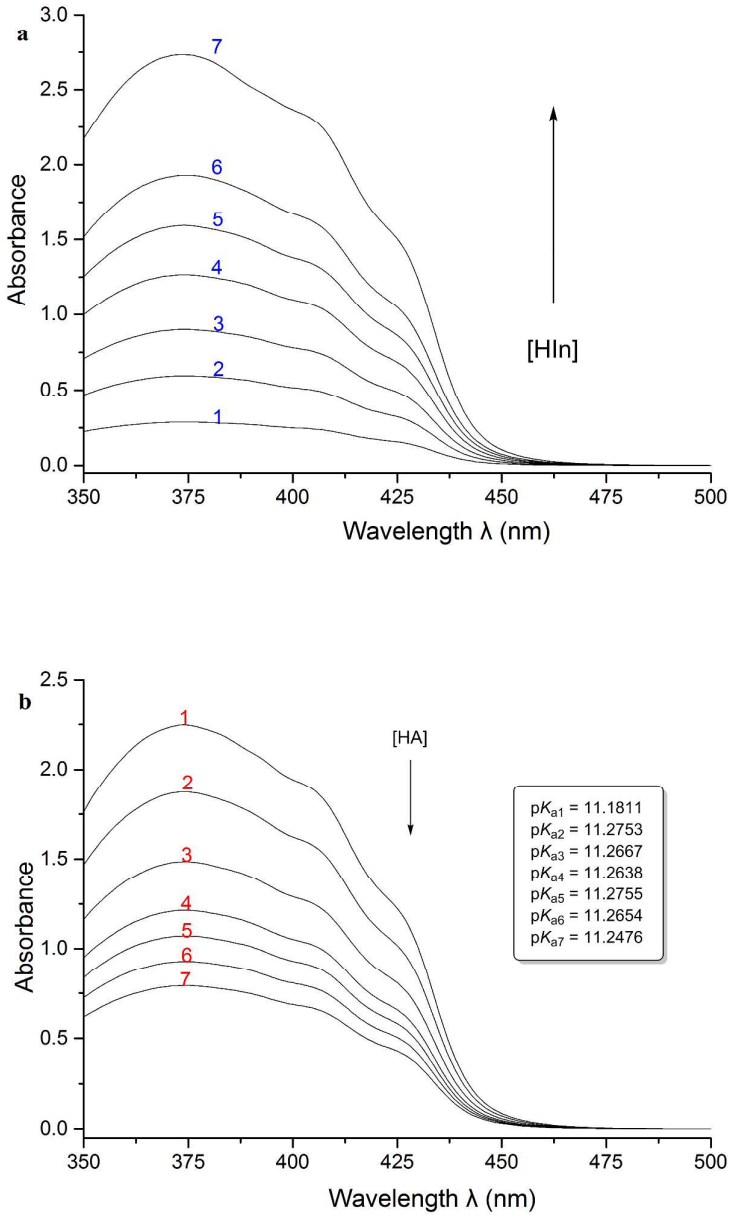


Figure S-2 (a) Absorption spectra of the incicator anion derived from 9-PhSO_2FH for various added amount of 9-PhSO_2FH during the **Second** titration. (b) Absorption spectra of the indicator anion for various added amount of Proline Tetrazole (1) during the **Second** titration

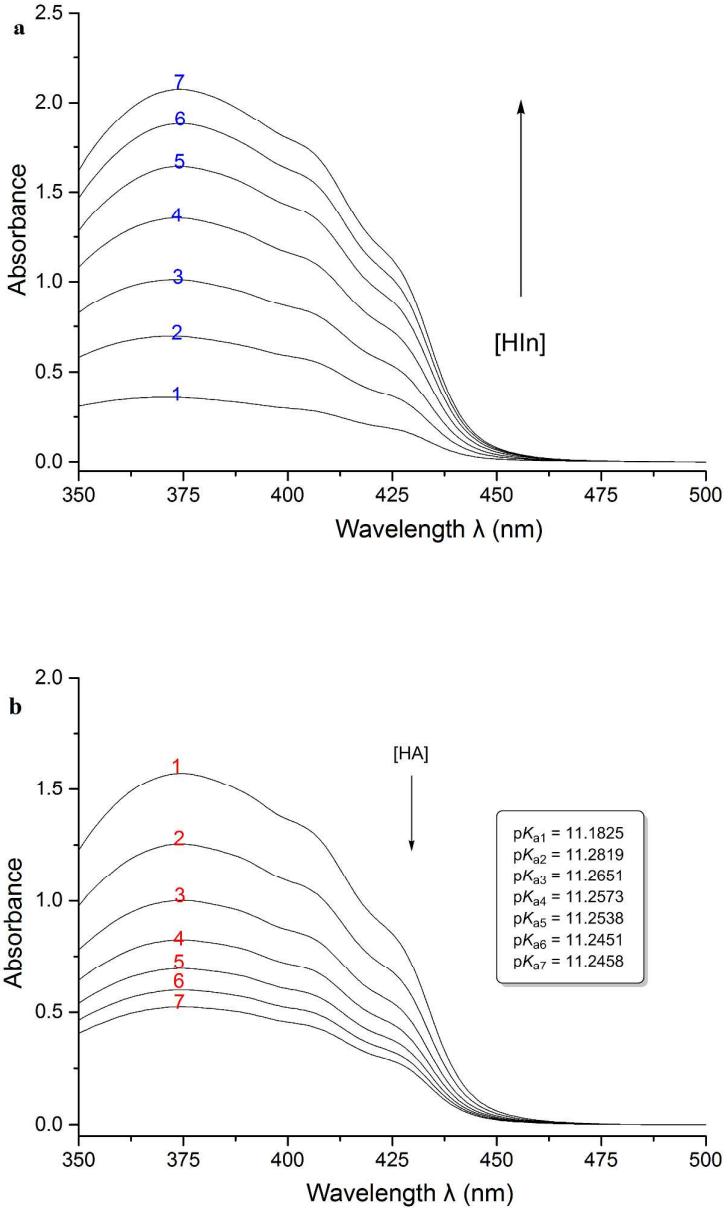


Figure S-3 (a) Absorption spectra of the incicator anion derived from 9-PhSO_2FH for various added amount of 9-PhSO_2FH during the **Third** titration. (b) Absorption spectra of the indicator anion for various added amount of Proline Tetrazole (1) during the **Third** titration

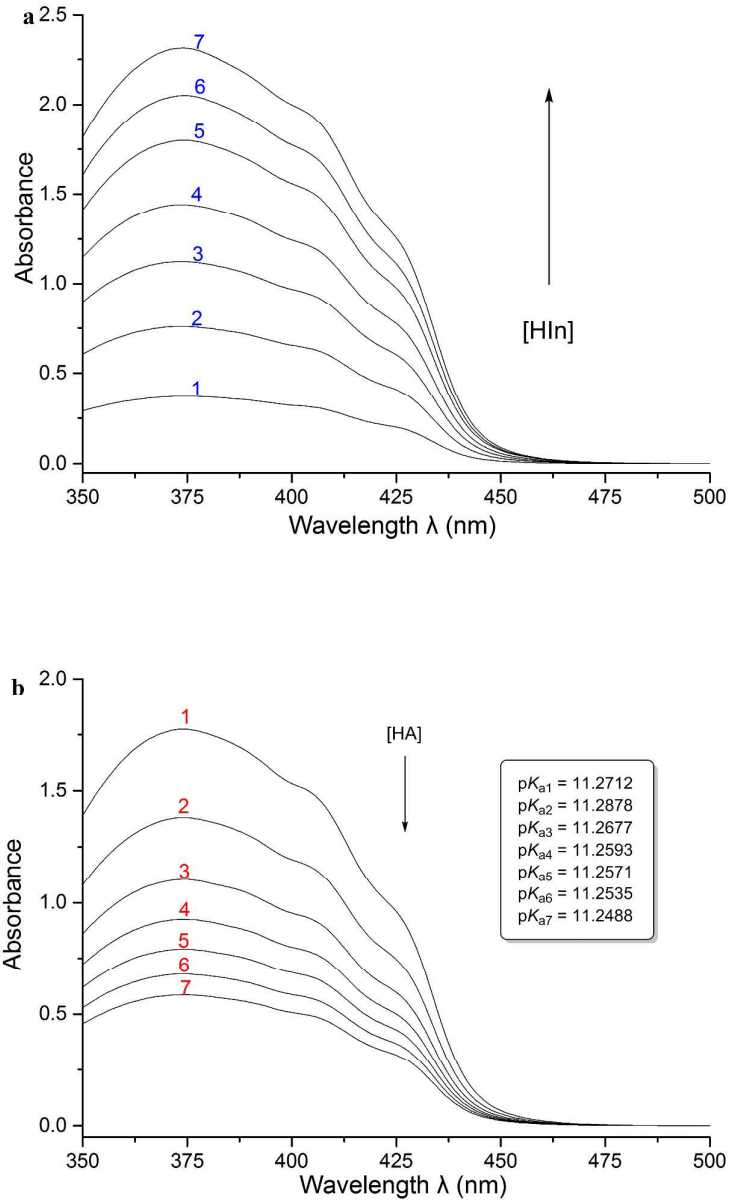
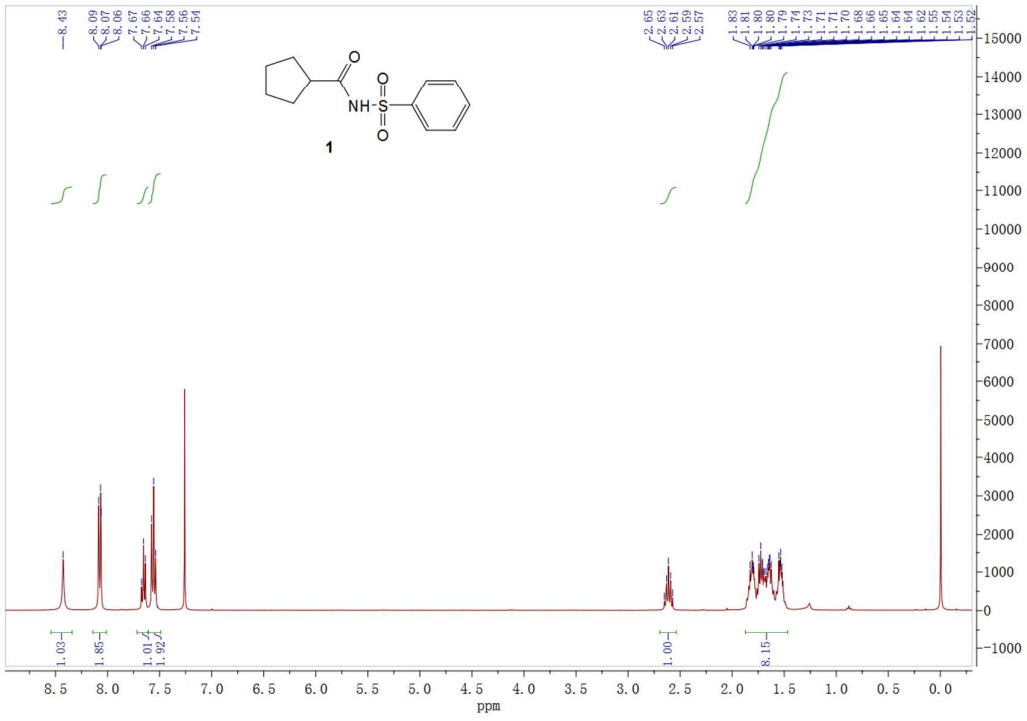
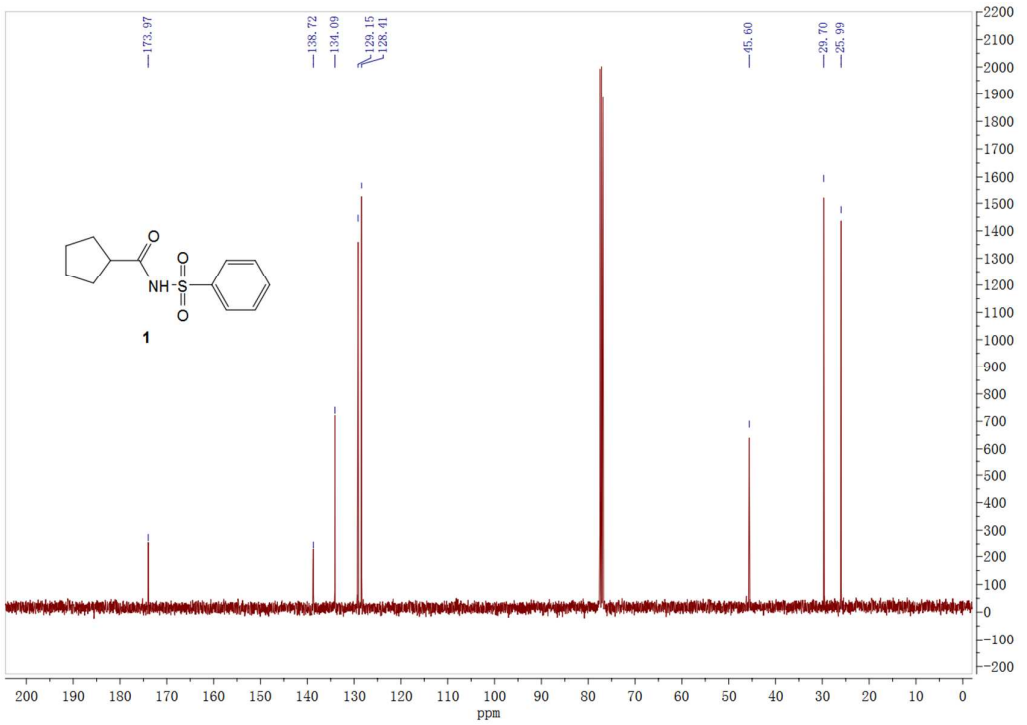
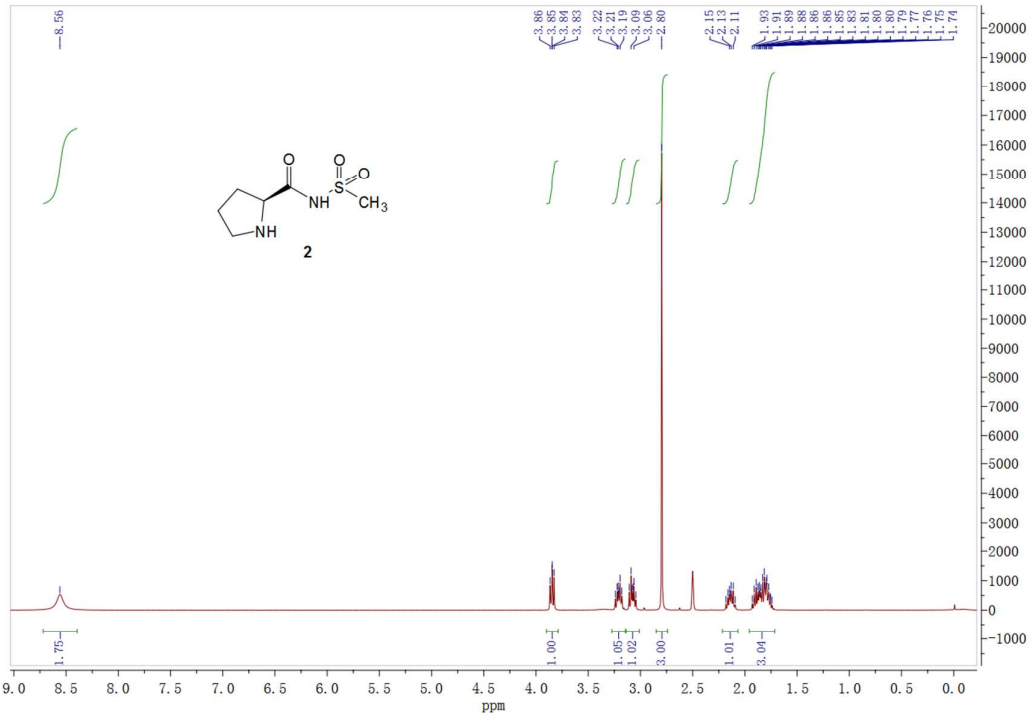


Figure S-4 (a) Absorption spectra of the incicator anion derived from 9-PhSO_2FH for various added amount of 9-PhSO_2FH during the **Fourth** titration. (b) Absorption spectra of the indicator anion for various added amount of Proline Tetrazole (1) during the **Fourth** titration

^{1}H & ^{13}C NMR spectra:



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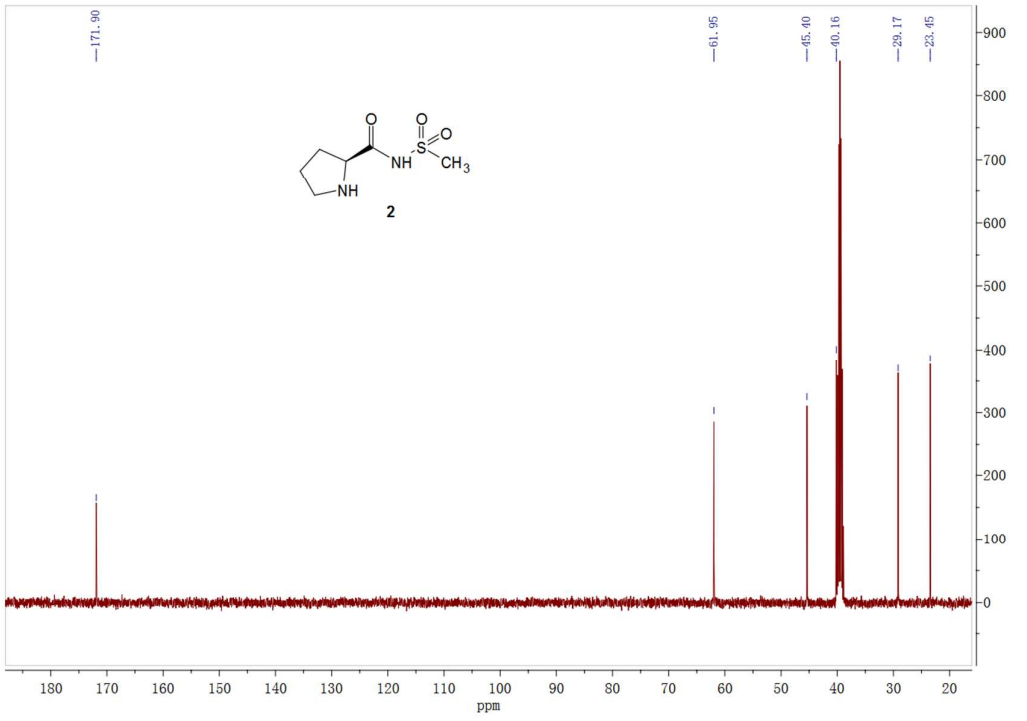
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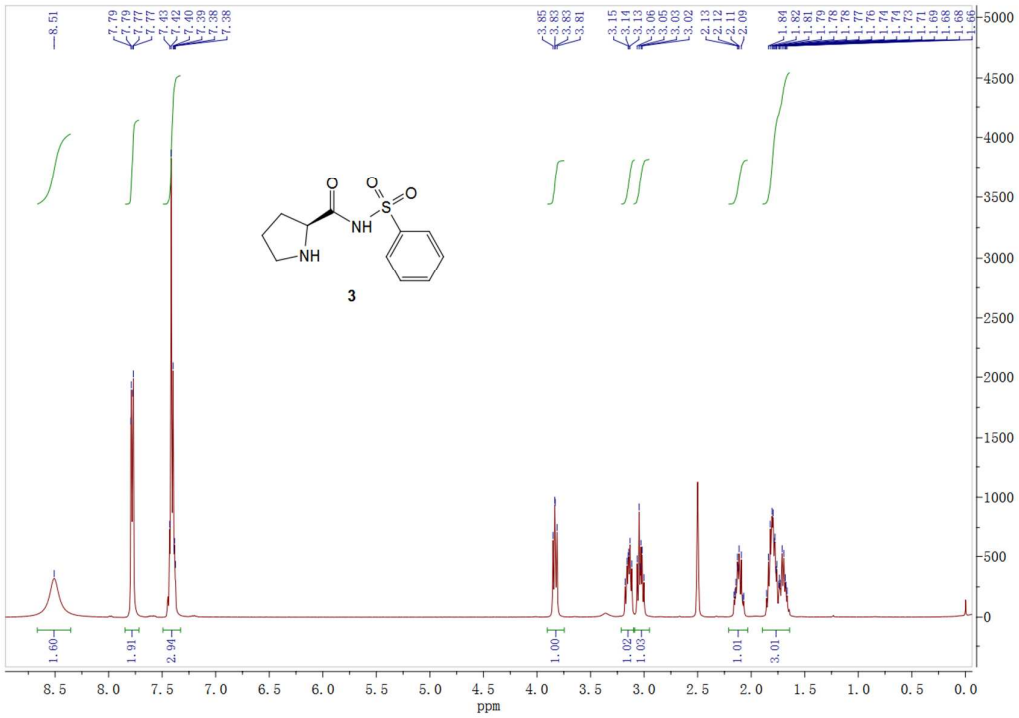
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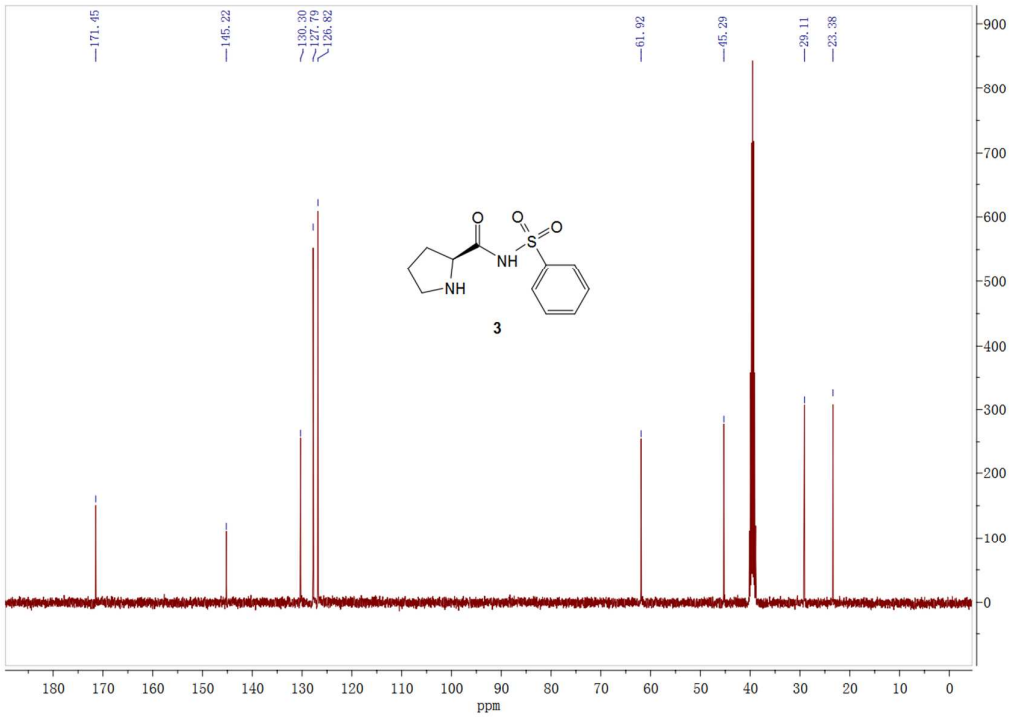
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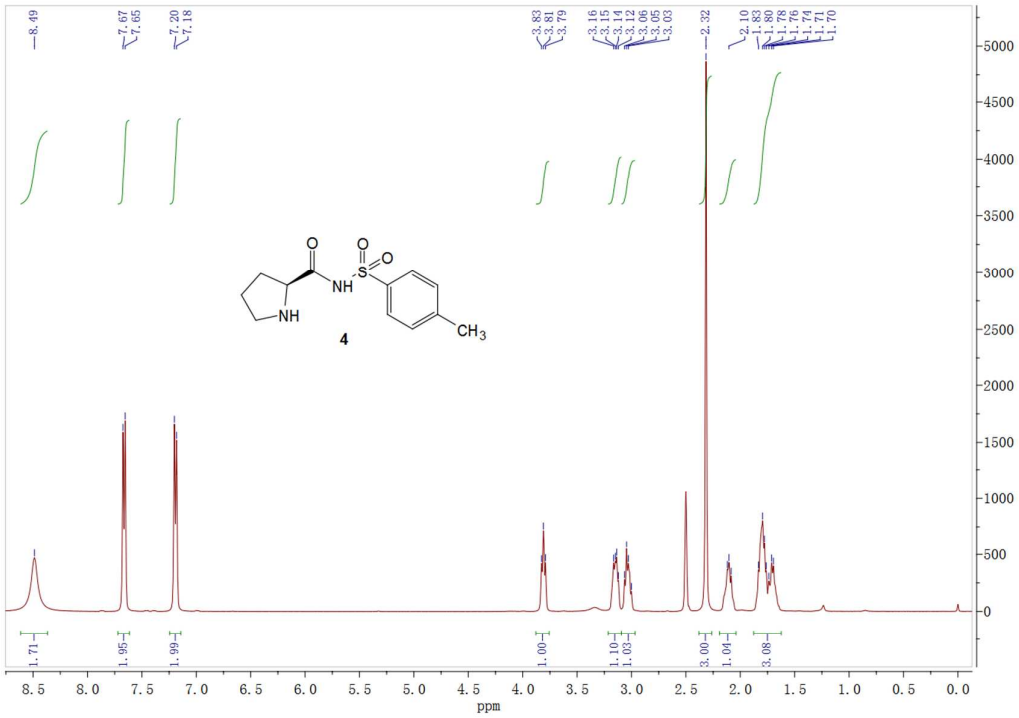
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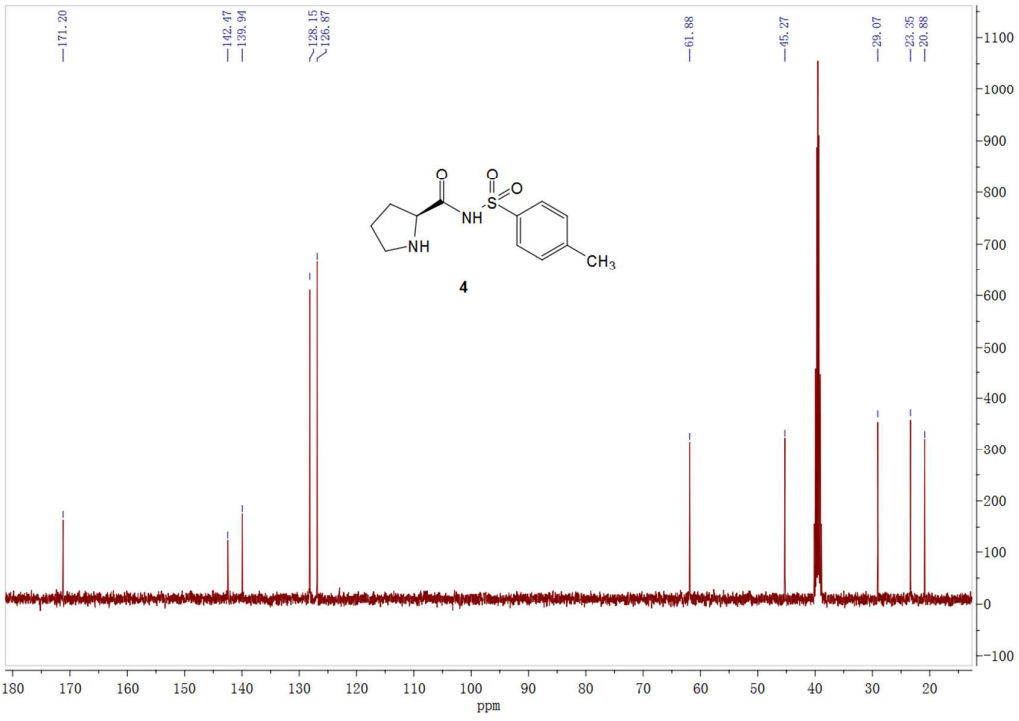
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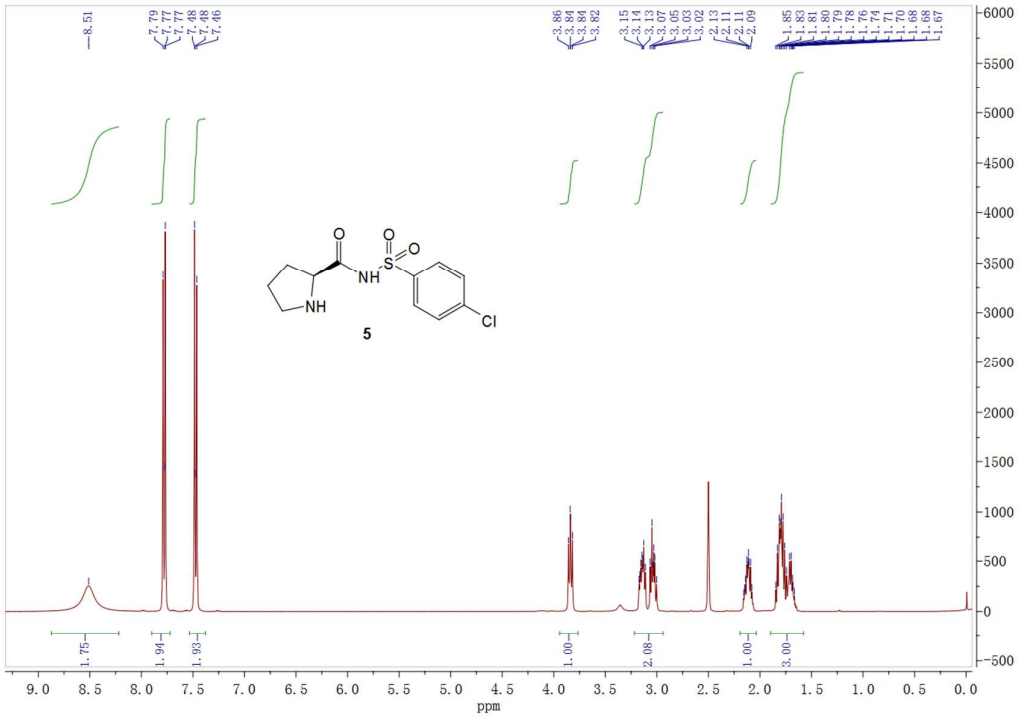
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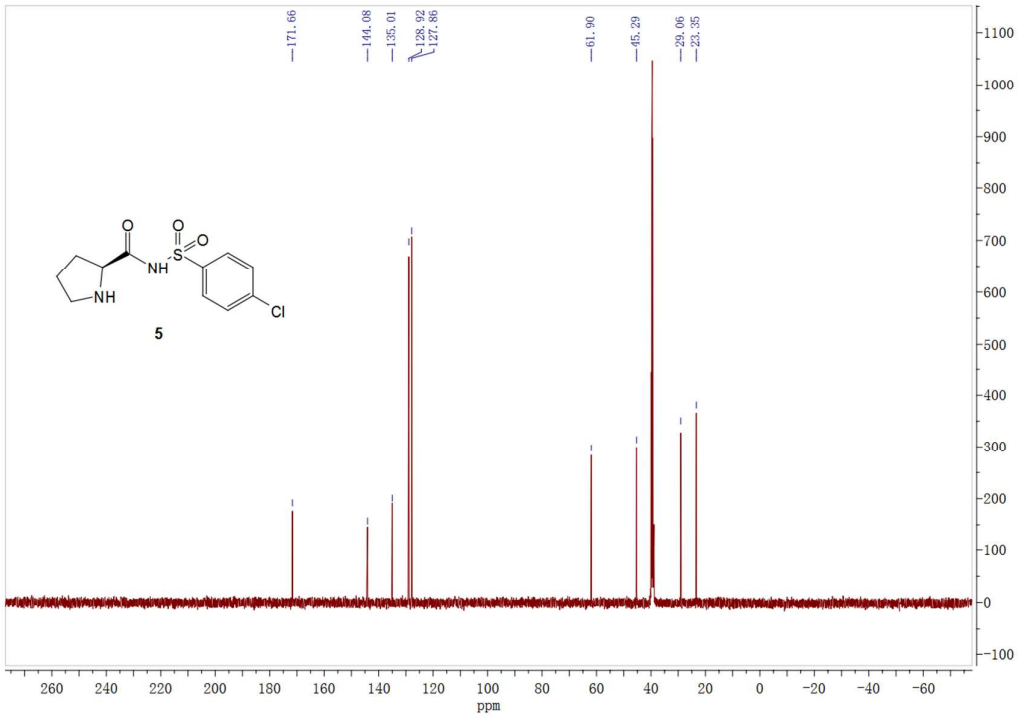
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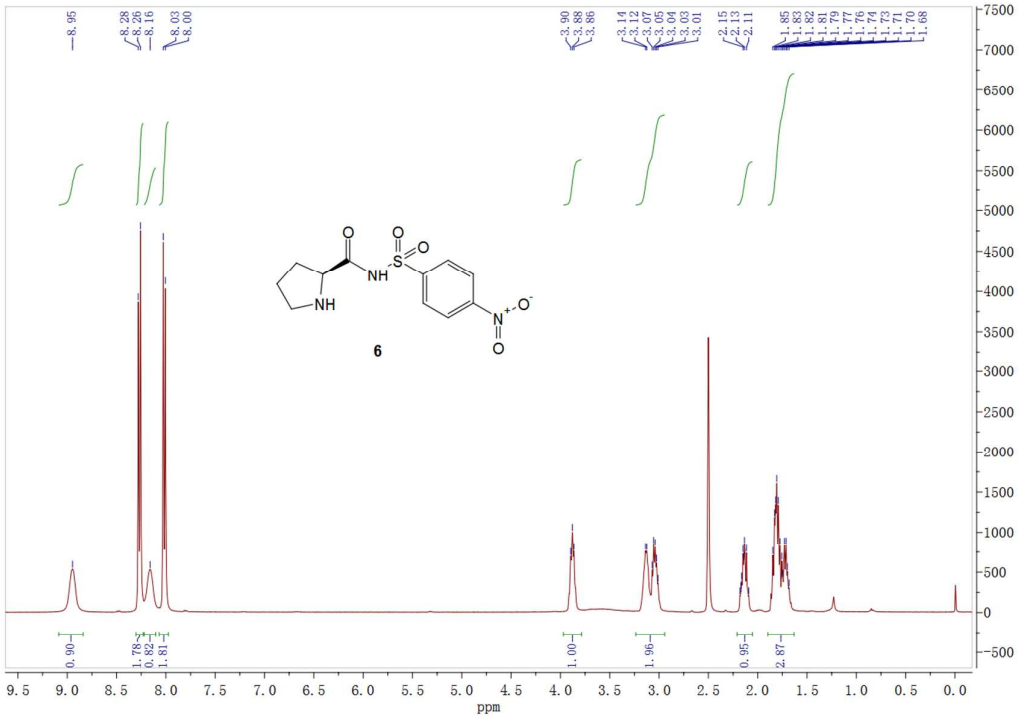
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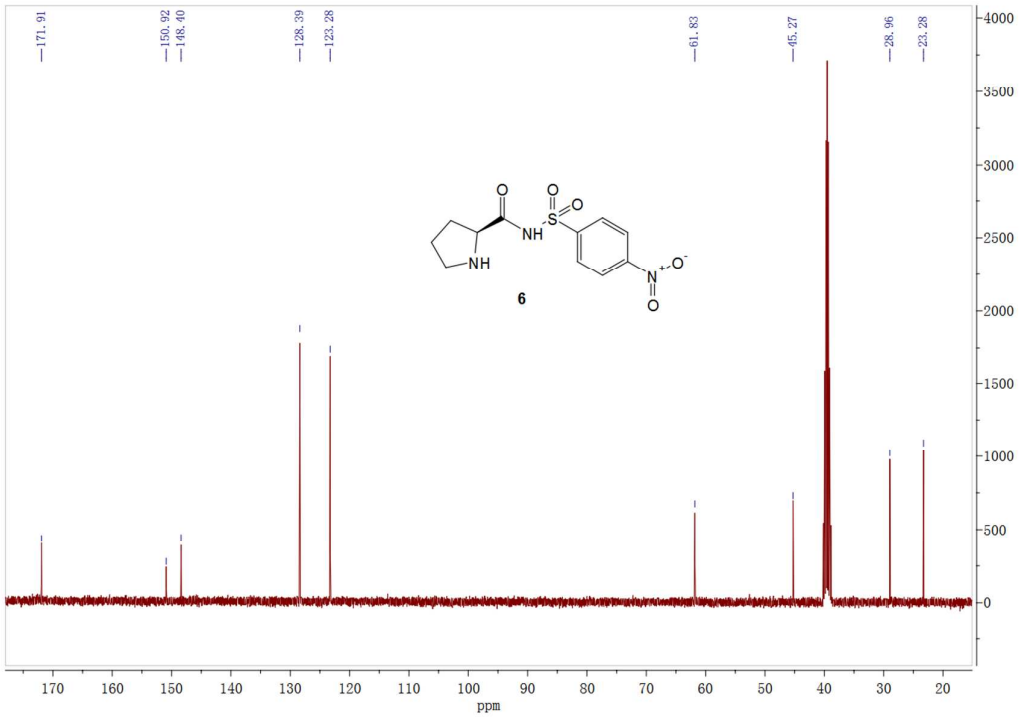
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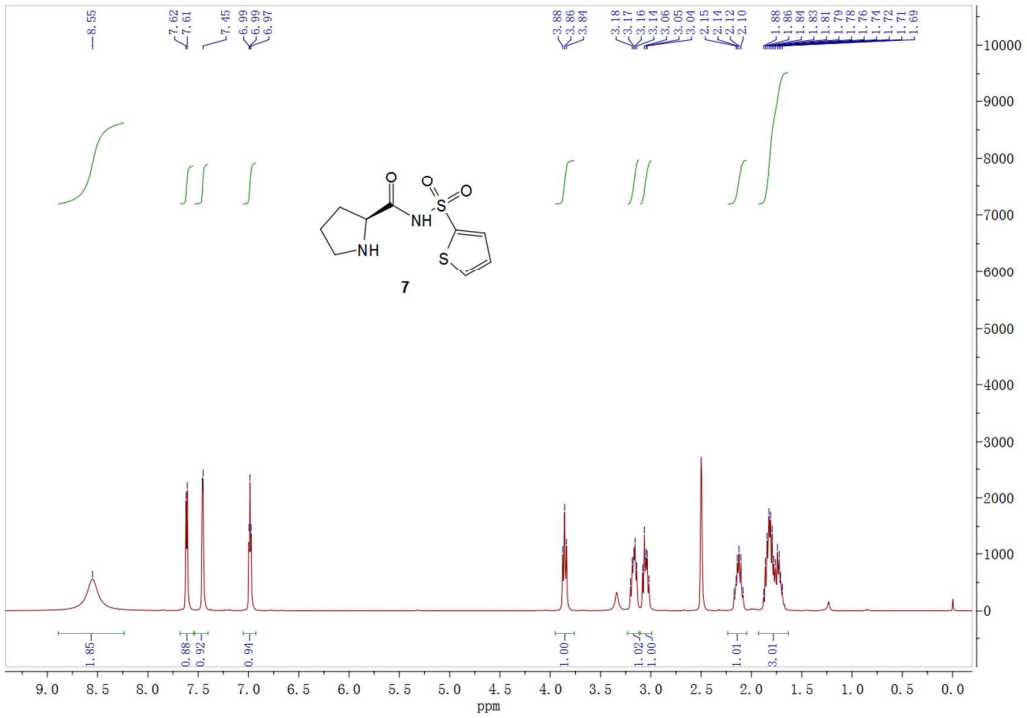
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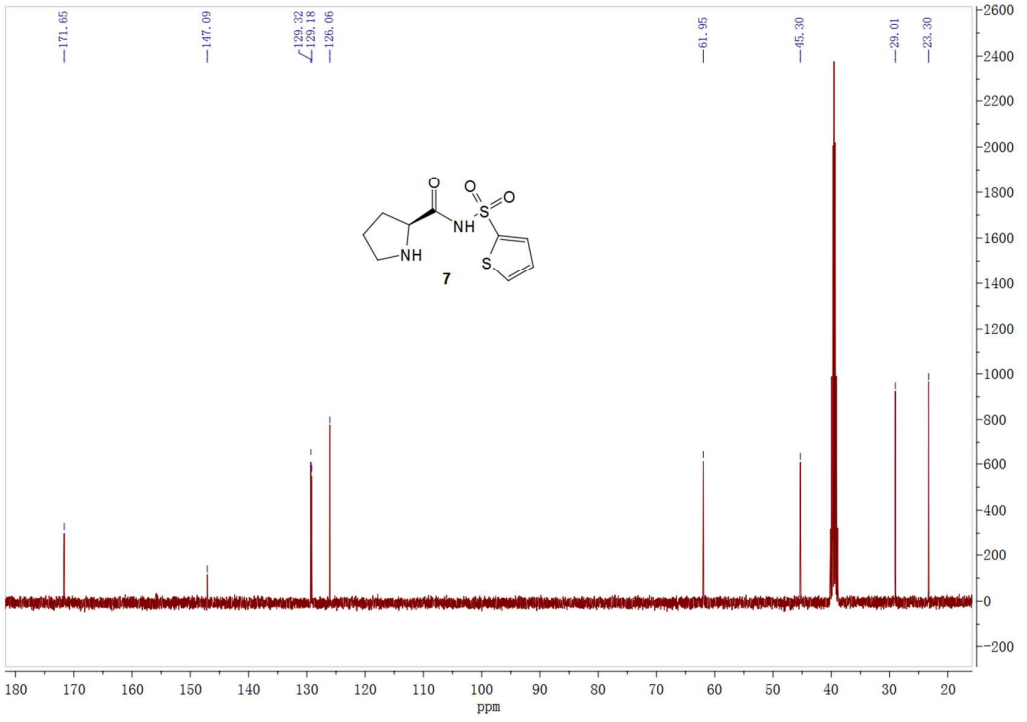
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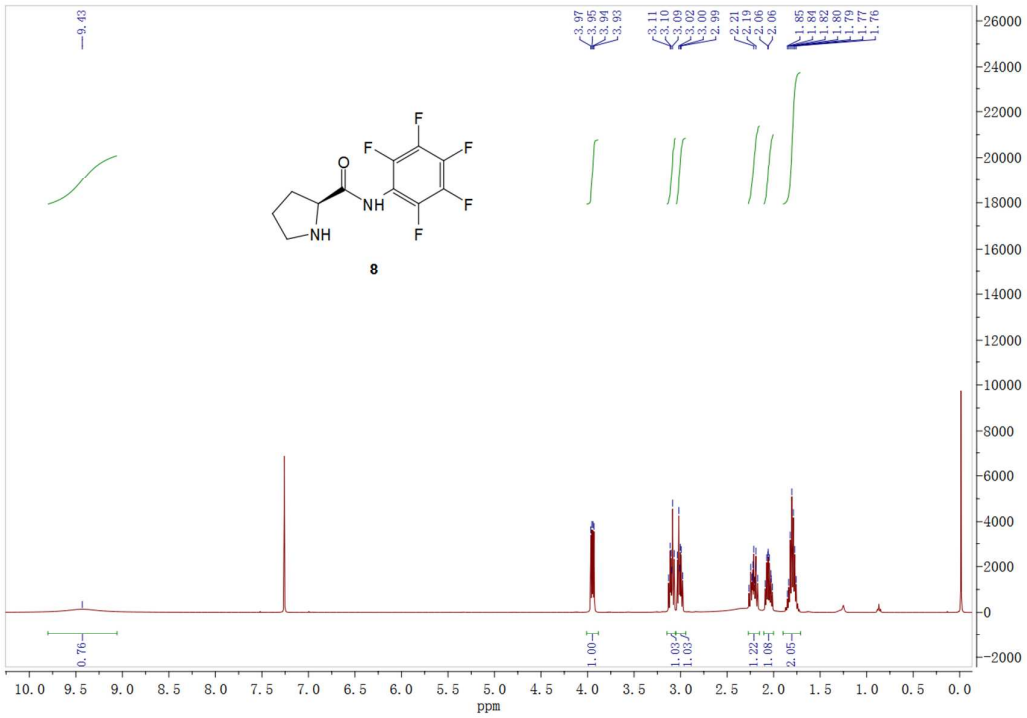
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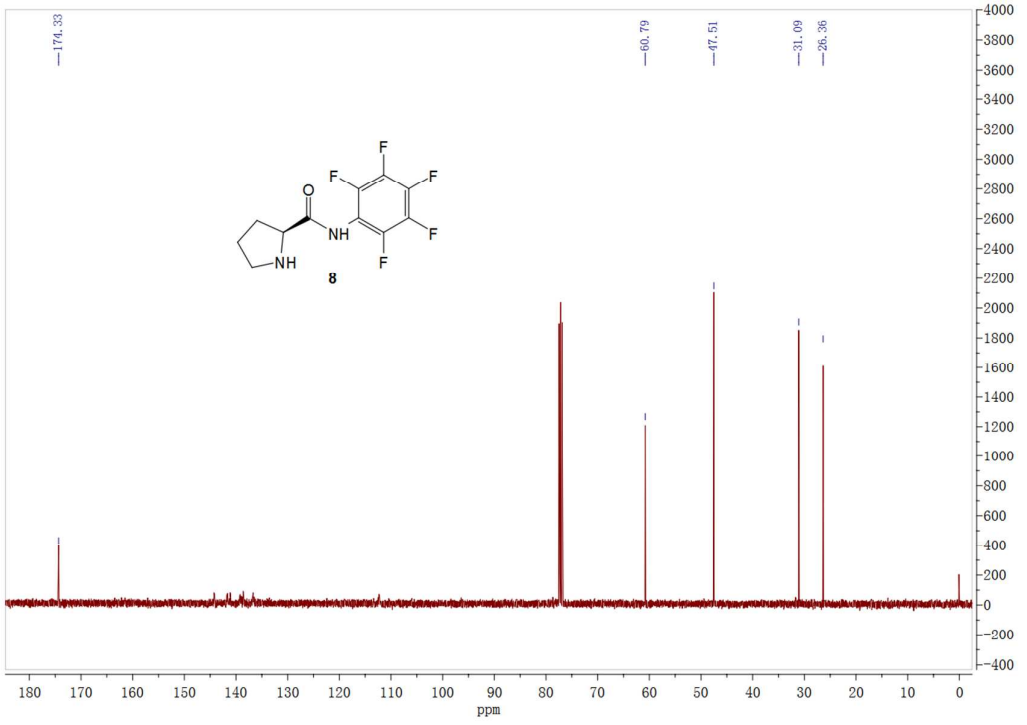
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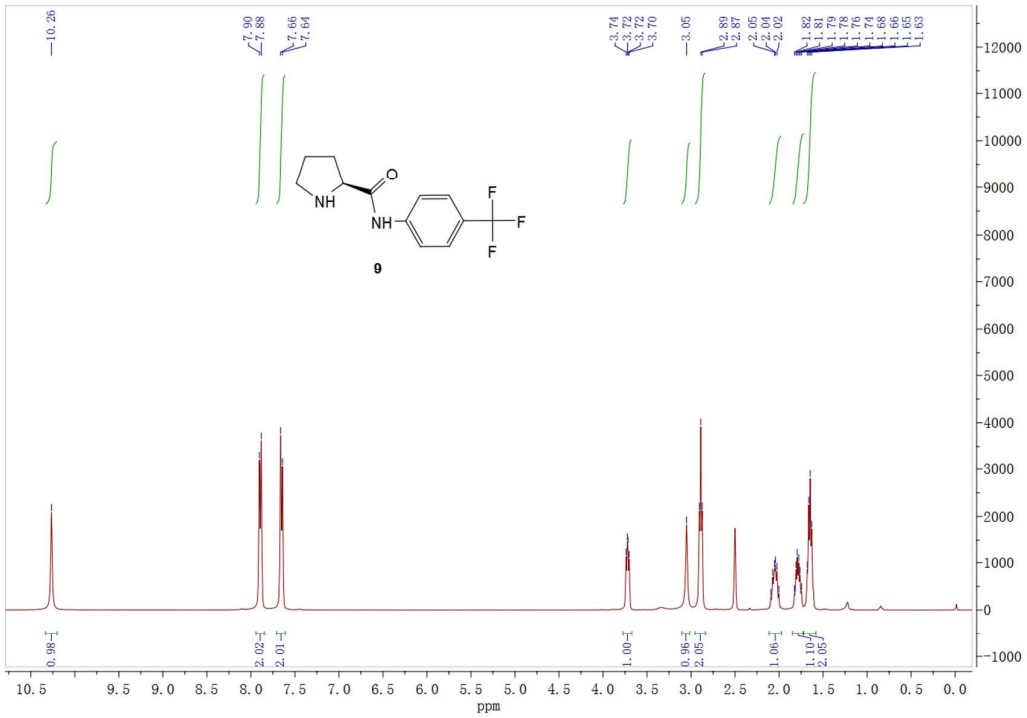
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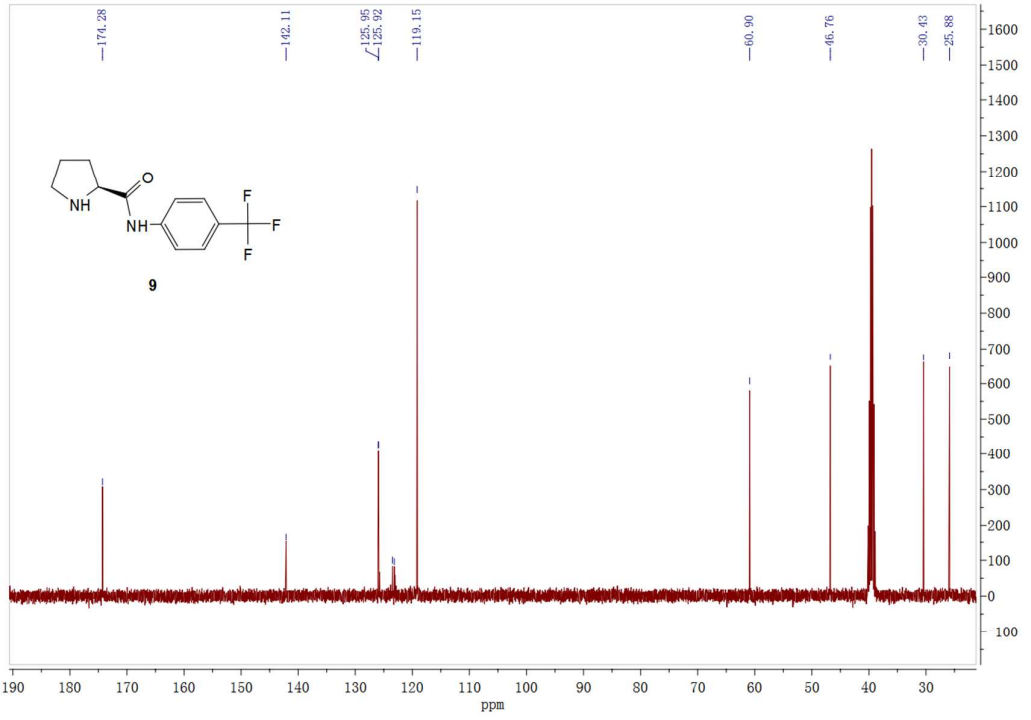
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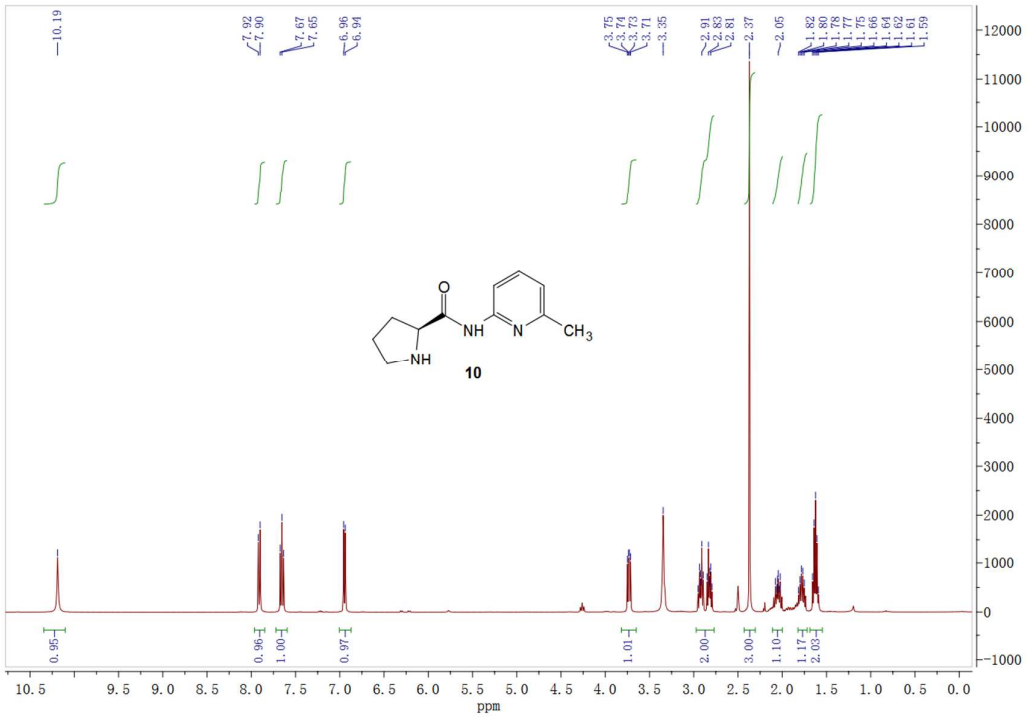
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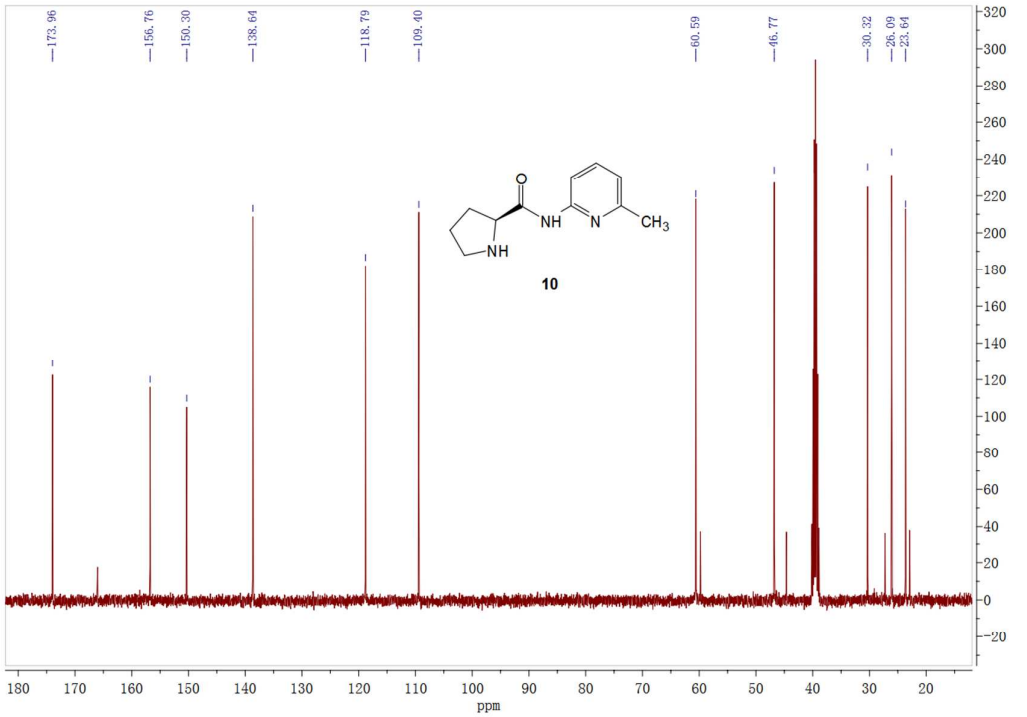
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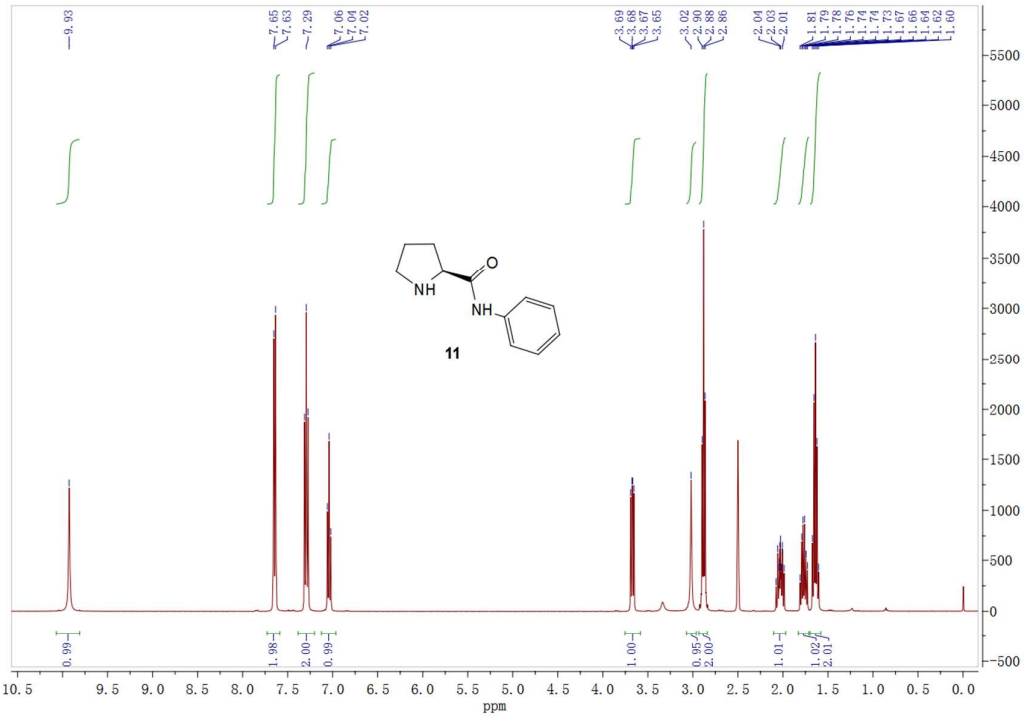
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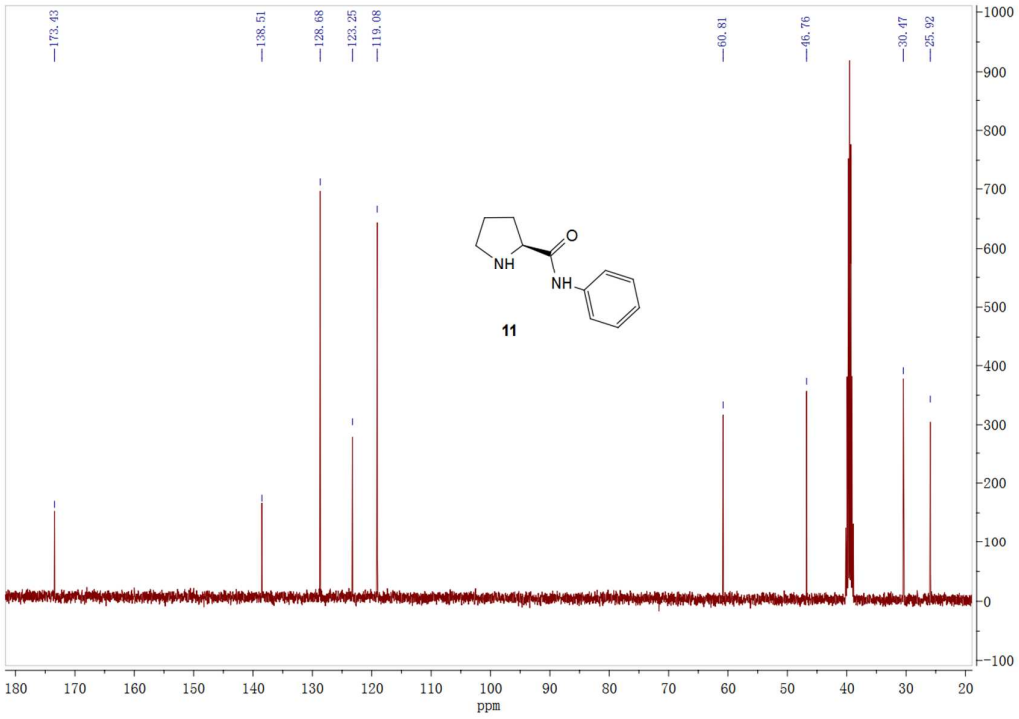
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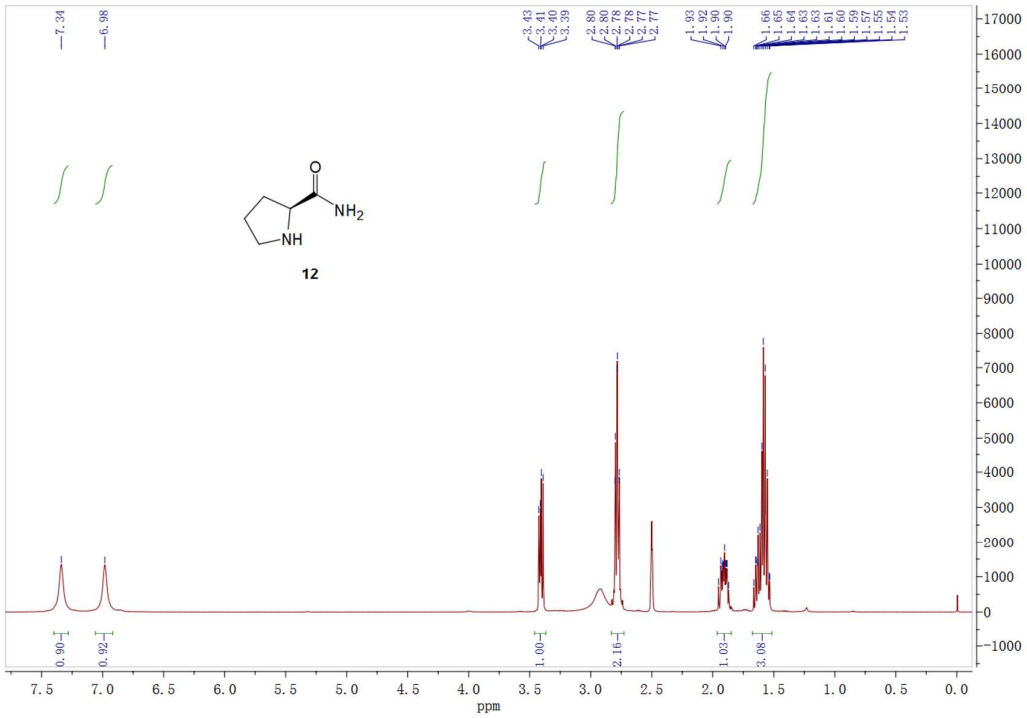
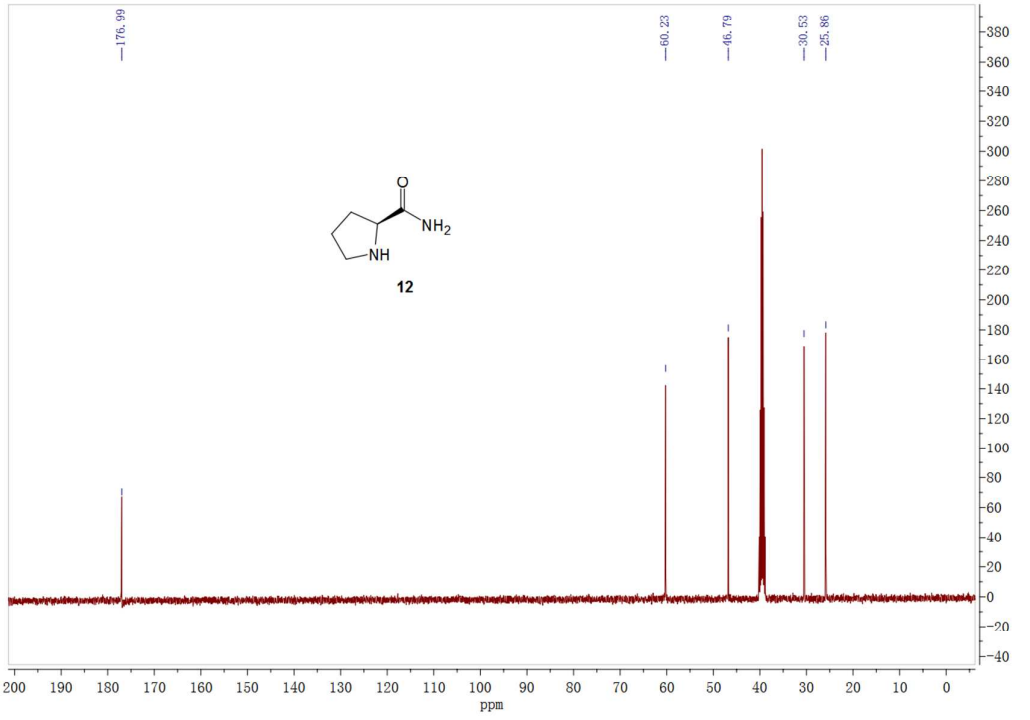
128.68
123.25
119.08
60.81
46.76
30.47
25.92
NH
O
NH
11
ppm


7.34
6.98
3.43
3.41
3.40
3.39
2.80
2.78
2.77
2.77
1.93
1.92
1.90
1.90
1.66
1.65
1.64
1.63
1.63
1.61
1.60
1.59
1.57
1.55
1.54
1.53
O
NH2
NH
12
0.90
0.92
1.00
2.16
1.03
3.08
ppm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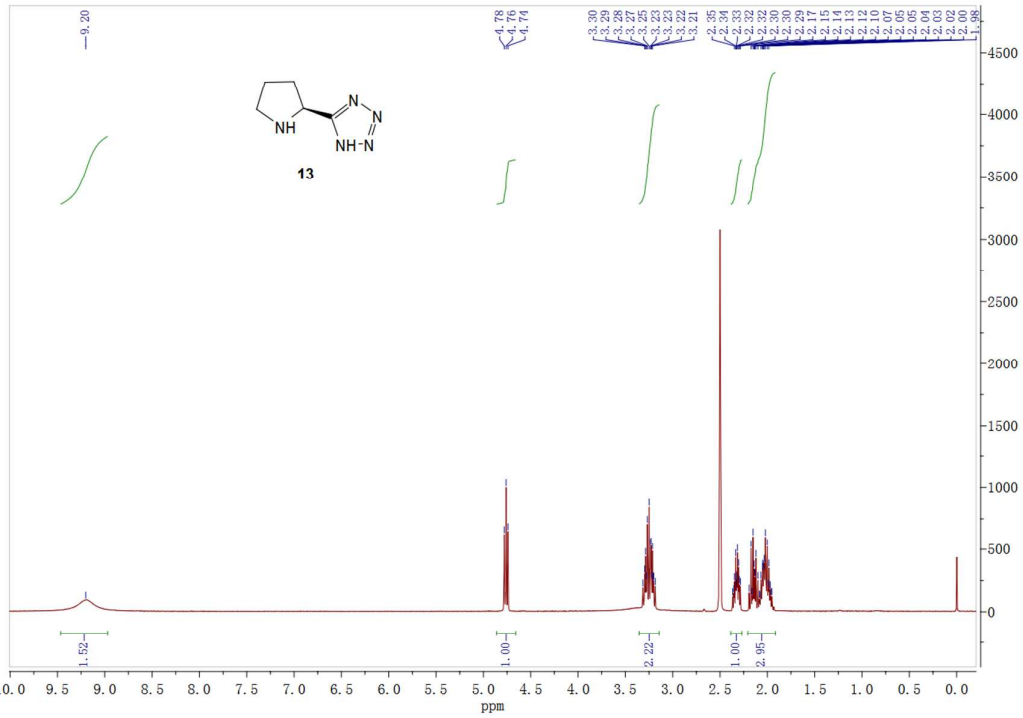
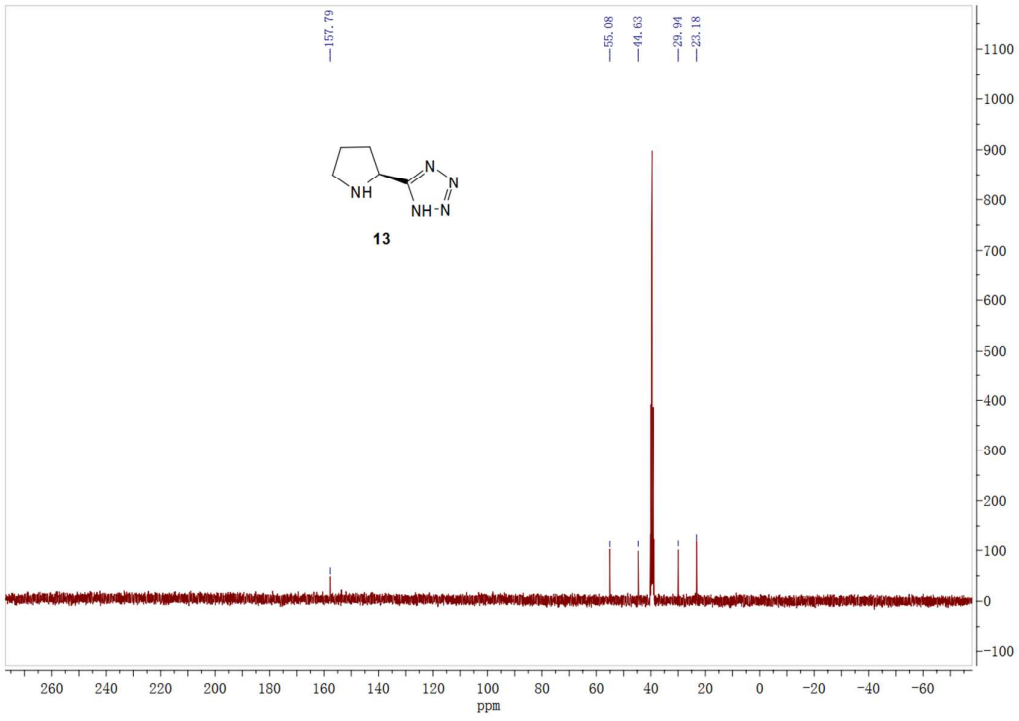
O
NH2
NH
12
ppm


9.20
4.78
4.76
4.74
3.30
3.29
3.28
3.27
3.25
3.23
3.22
3.21
2.35
2.34
2.33
2.32
2.30
2.29
2.17
2.15
2.14
2.13
2.12
2.10
2.07
2.05
2.04
2.03
2.02
2.00
1.98
NH
N
N
NH-N
13
1.52
1.00
2.22
1.00
2.95
ppm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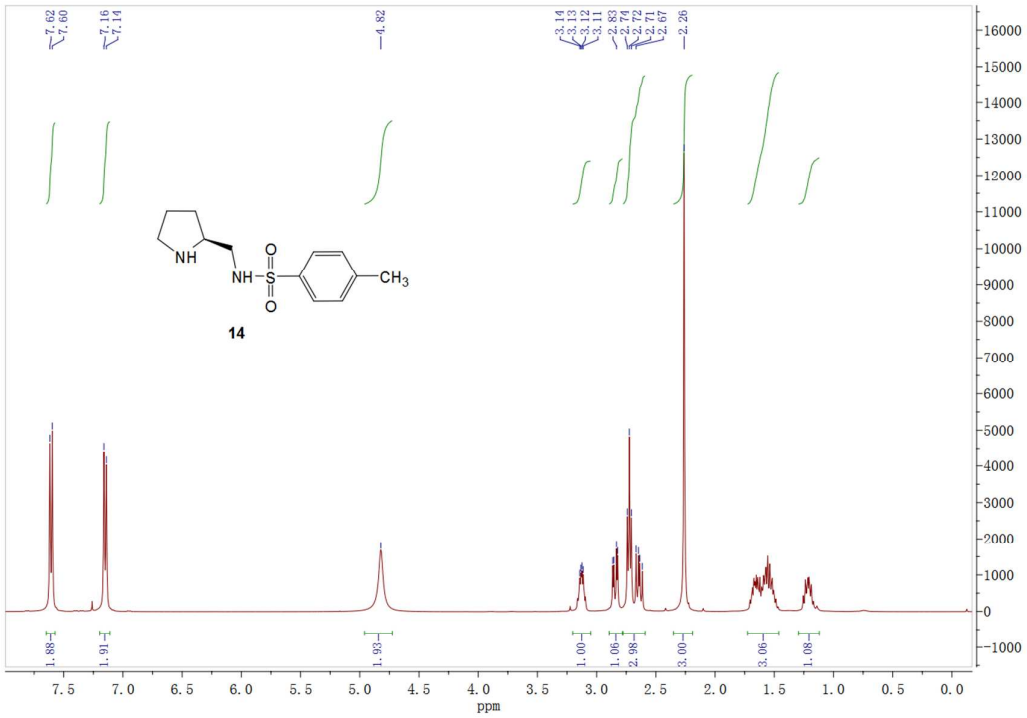
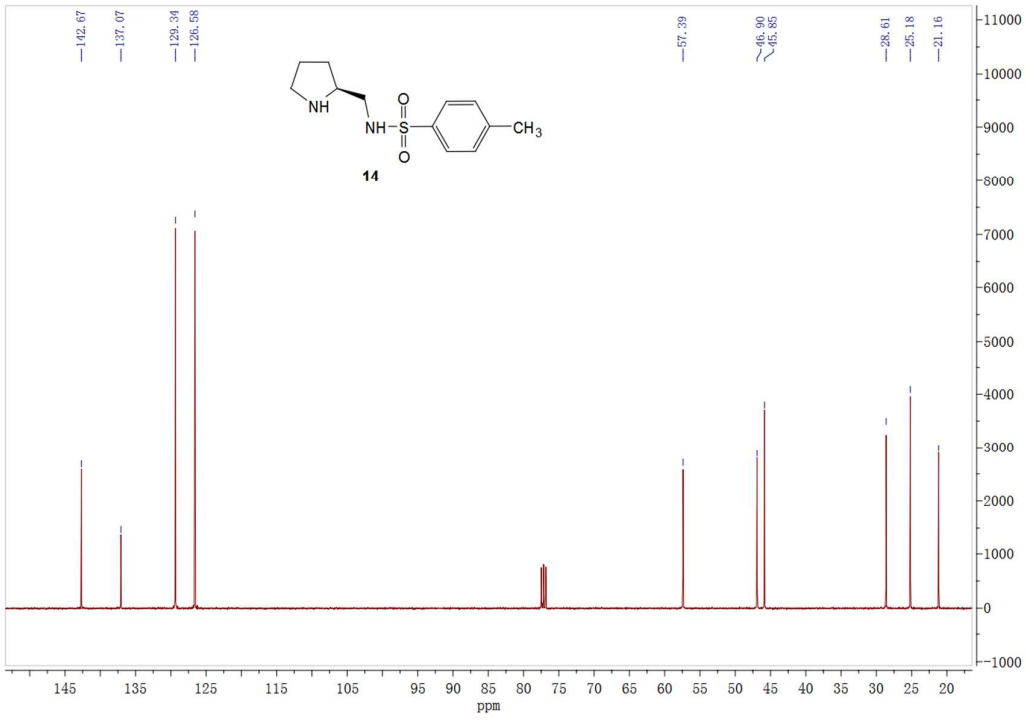
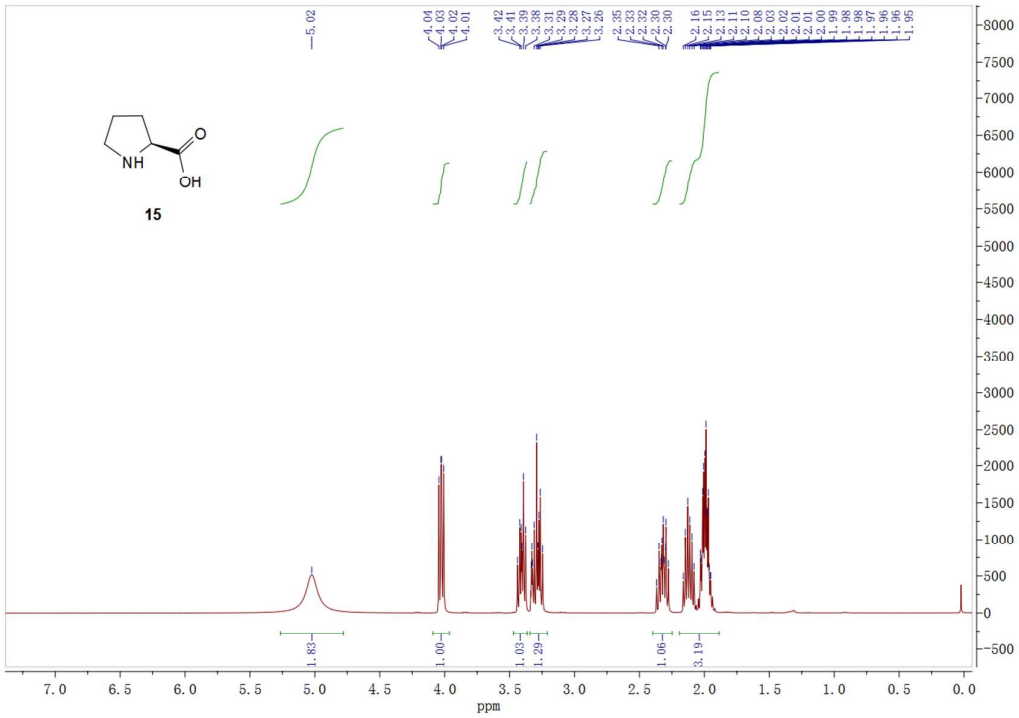
55.08
44.63
29.94
23.18
NH
N
N
NH-N
13
ppm


7.62
7.60
7.16
7.14
4.82
3.14
3.13
3.12
3.11
2.83
2.74
2.72
2.71
2.67
2.26
NH
NH
S
O
O
CH3
14
1.88
1.91
1.93
1.00
1.06
2.98
3.00
3.06
1.08
ppm


142.67
137.07
129.34
126.58
57.39
46.90
45.85
28.61
25.18
21.16
NH
NH
S
O
O
CH3
14
ppm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4.04
4.03
4.02
4.01
3.42
3.41
3.39
3.38
3.31
3.29
3.28
3.27
3.26
2.35
2.33
2.32
2.30
2.30
2.16
2.15
2.13
2.11
2.10
2.08
2.03
2.02
2.01
2.01
2.00
1.99
1.98
1.98
1.97
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1.95
NH
OH
O
15
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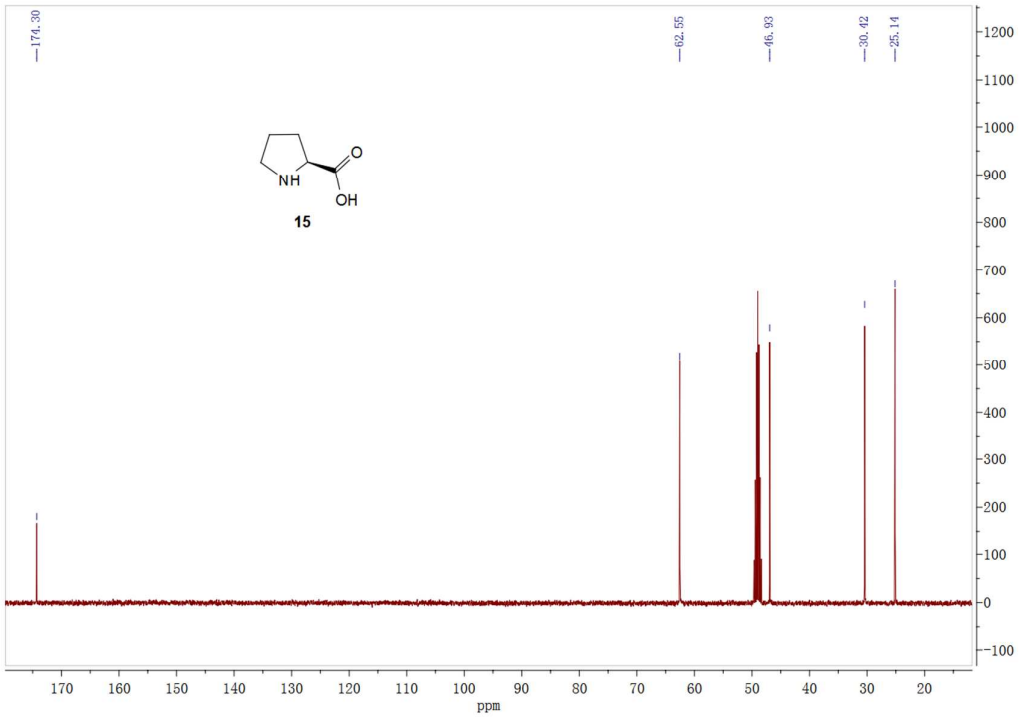
1.03
1.29
1.06
3.19
ppm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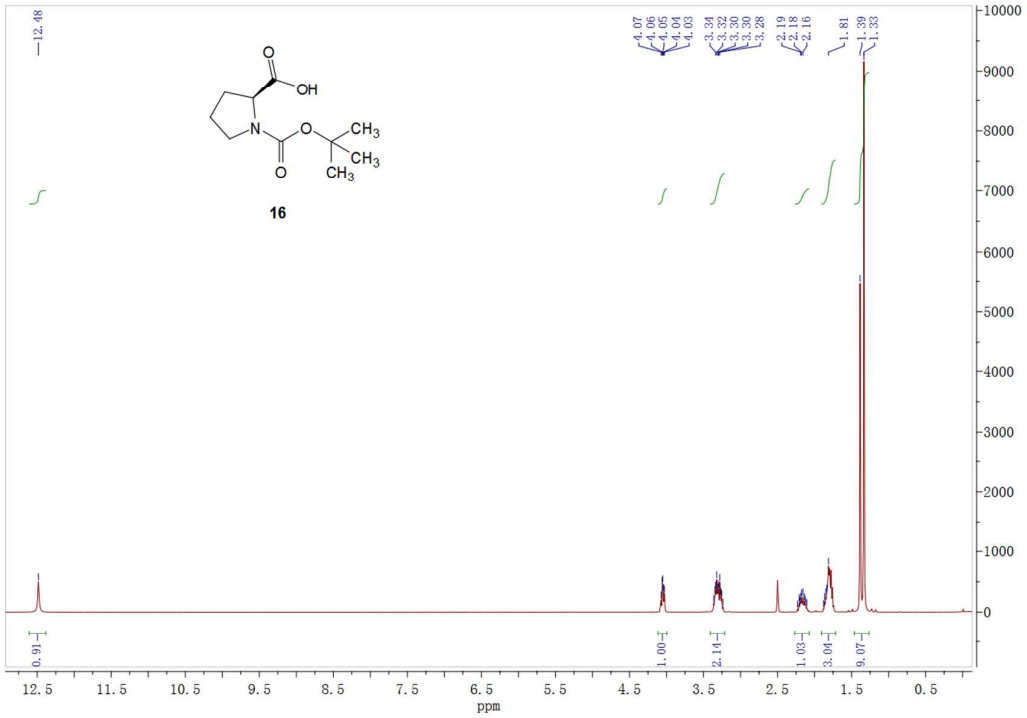
62.55
46.93
30.42
25.14
NH
OH
O
15
ppm


12.48
4.07
4.06
4.05
4.04
4.03
3.34
3.32
3.30
3.28
2.19
2.18
2.16
1.81
1.39
1.33
OH
N
O
CH3
CH3
CH3
16
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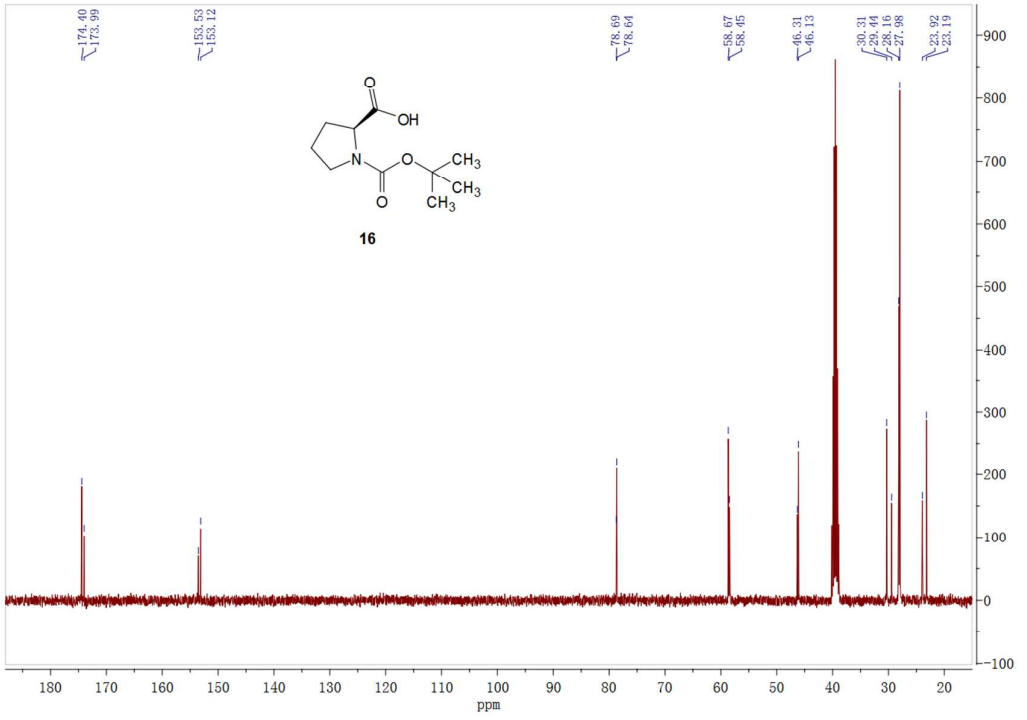
1.00
2.14
1.03
3.04
9.07
ppm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173.99
153.53
153.12
78.69
78.64
58.67
58.45
46.31
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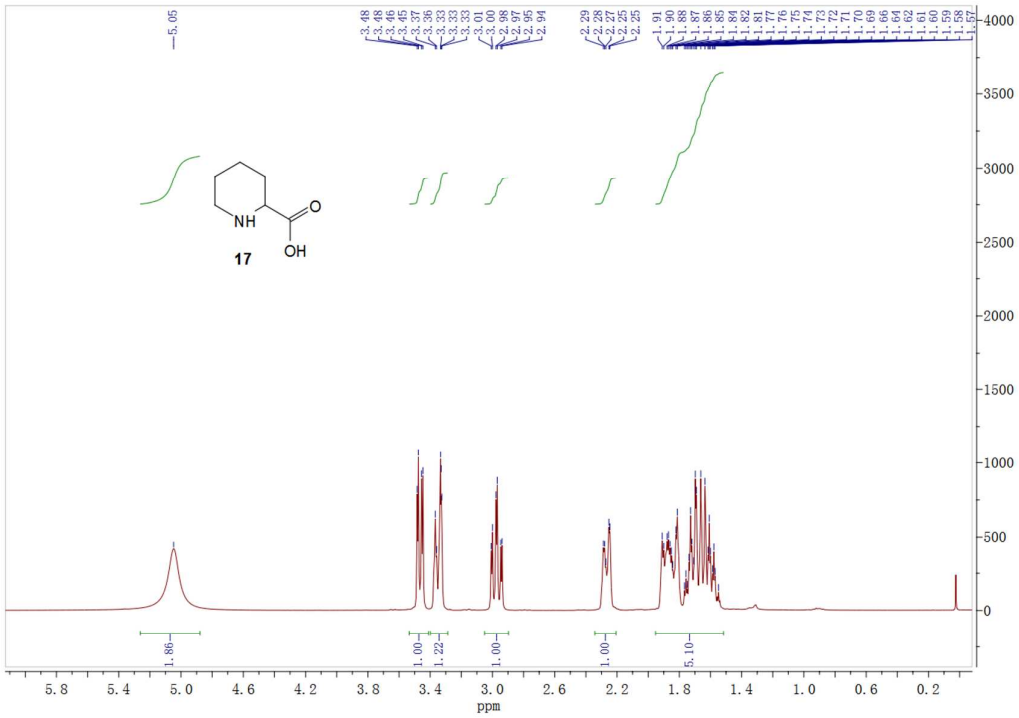
30.31
29.44
28.16
27.98
23.92
23.19
OH
N
O
CH3
CH3
CH3
16
ppm


5.05
3.48
3.46
3.45
3.37
3.36
3.33
3.33
3.01
3.00
2.98
2.97
2.95
2.94
2.29
2.28
2.27
2.25
2.25
1.91
1.90
1.88
1.87
1.86
1.85
1.84
1.82
1.81
1.77
1.76
1.75
1.74
1.73
1.72
1.71
1.70
1.69
1.66
1.64
1.62
1.61
1.60
1.59
1.58
1.57
NH
O
OH
17
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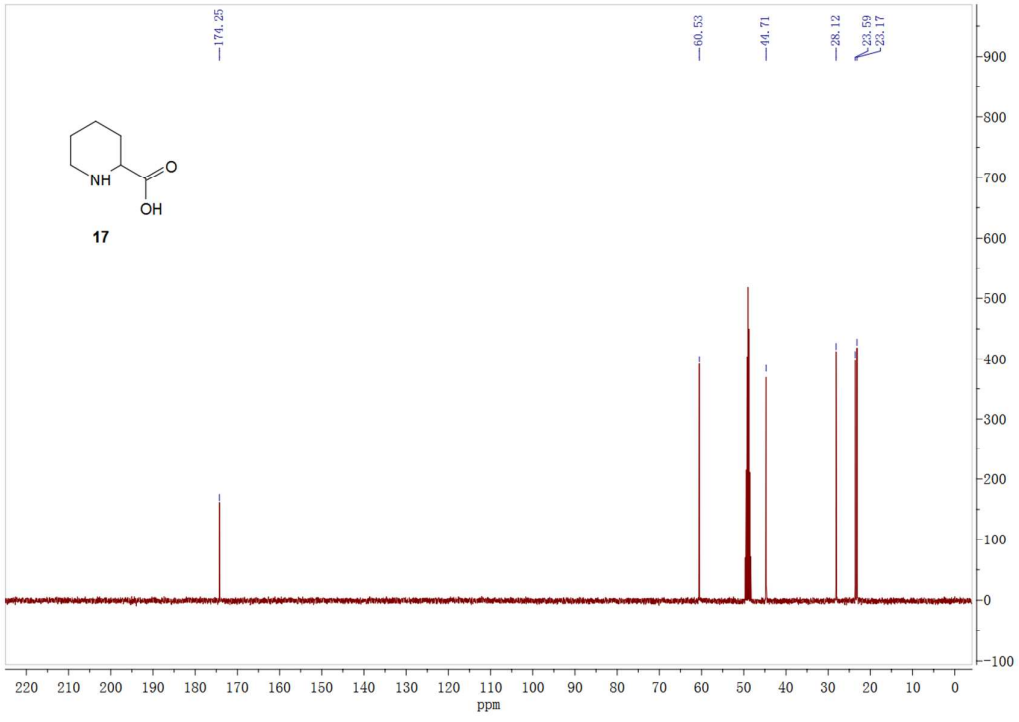
1.22
1.00
1.00
5.10
ppm


174.25
60.53
44.71
28.12
23.59
23.17
NH
O
OH
17
ppm

Reference

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