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

An Aryne-Based Three-Component Access to α-Aroylamino Amides

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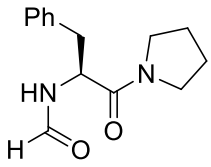
1. Table of contents

2. HPLC chromatograms for enantioenriched compounds

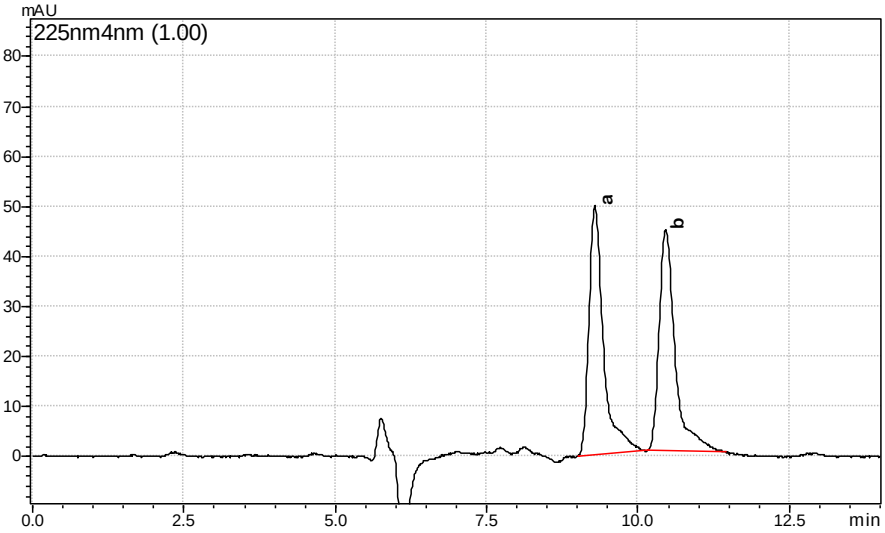
Chiral separation was performed by high performance liquid chromatography using a Shimadzu HPLC system (Shimadzu, Kyoto, Japan), consisting in two LC-10AD Vp module pumps, a DGU-14-A on-line vacuum degasser, and a photodiode array (PDA) detector. Separation of the enantiomers was performed in both normal phase or polar organic modes using a cellulose tris(3-chloro-4-methylphenylcarbamate) chiral stationary phase (CPS) Lux Cellulose-2 (Phenomenex, Torrance, CA, USA).

(14a) (S)-*N*-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)formamide



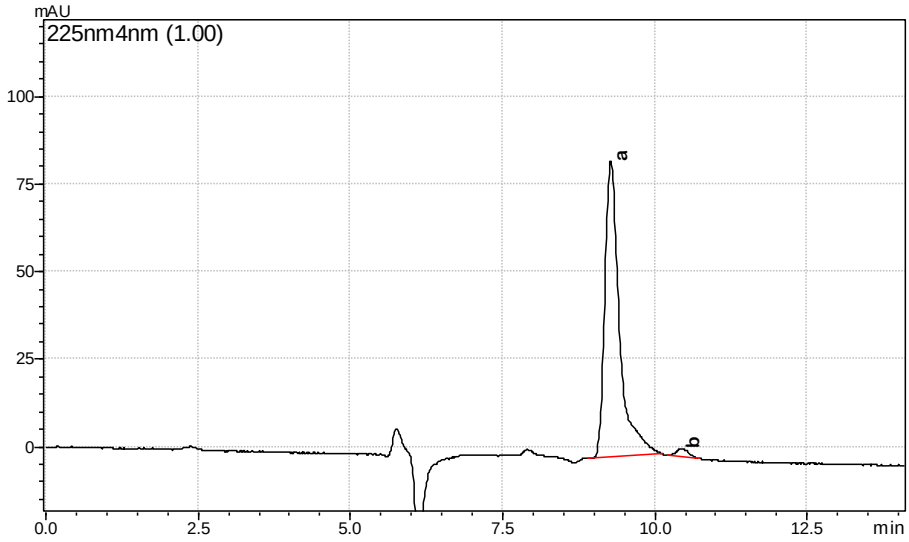
a) HPLC-UV analysis of the isolated racemic compound

Column: Phenomemex Lux 5µ Cellulose-2 250 x 4.6 mm (kept at 40°C)
eluant A: isopropanol [10%]
eluant B: methanol + 0.1% formic acid [90%]
flow rate: 0.5 mL min^{-1}
Volume injected: 5 µL (solution 0.33 mg mL^{-1} in ethanol)
λ: 225 nm



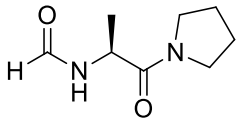
enantiomer	*r.t. (min)*	*area*	*area%*
a	9.280	828,833	50.7%
b	10.438	805,397	49.3%

b) HPLC-UV of the isolated enantioenriched pure compound **14a**



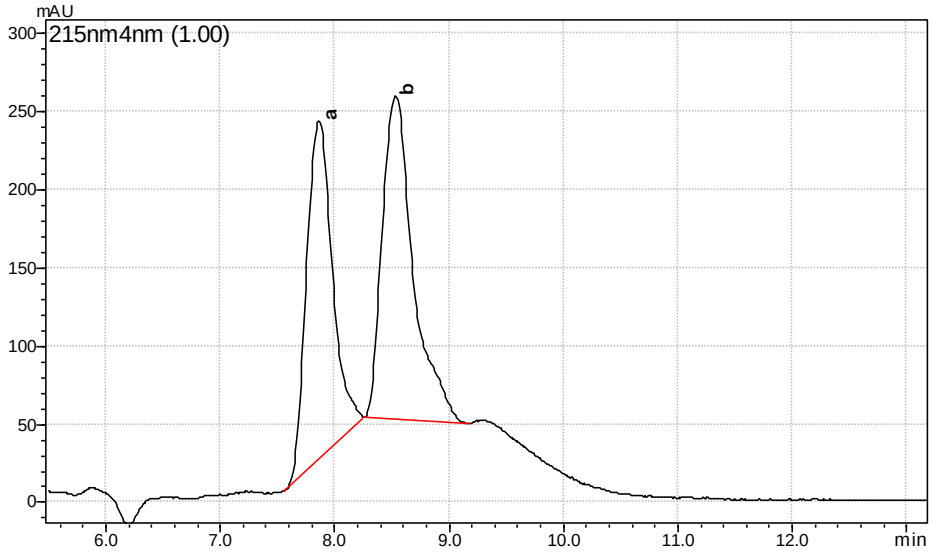
enantiomer	*r.t. (min)*	*area*	*area%*
a	9.270	1,421,118	97.9%
b	10.436	31,134	2.1%

(14b) (S)-*N*-(1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)formamide



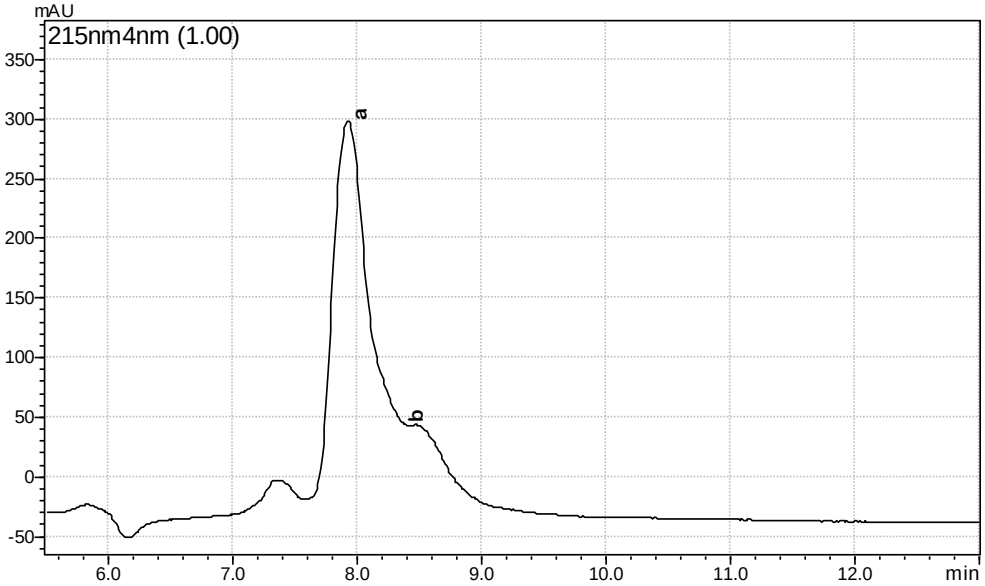
a) HPLC-UV analysis of the isolated racemic compound

Column: Phenomemex Lux 5µ Cellulose-2 250 x 4.6 mm (kept at 40°C)
eluant A: isopropanol [10%]
eluant B: methanol + 0.1% formic acid [90%]
flow rate: 0.5 mL min^{-1}
Volume injected: 5 µL (solution 0.33 mg mL^{-1} in ethanol)
λ: 215 nm



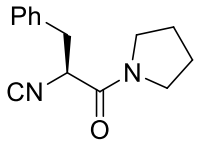
enantiomer	*r.t. (min)*	*area*	*area%*
a	7.856	3,429,916	47.0%
b	8.528	3,864,689	53.0%

b) HPLC analysis of the isolated enantioenriched pure compound **14b**



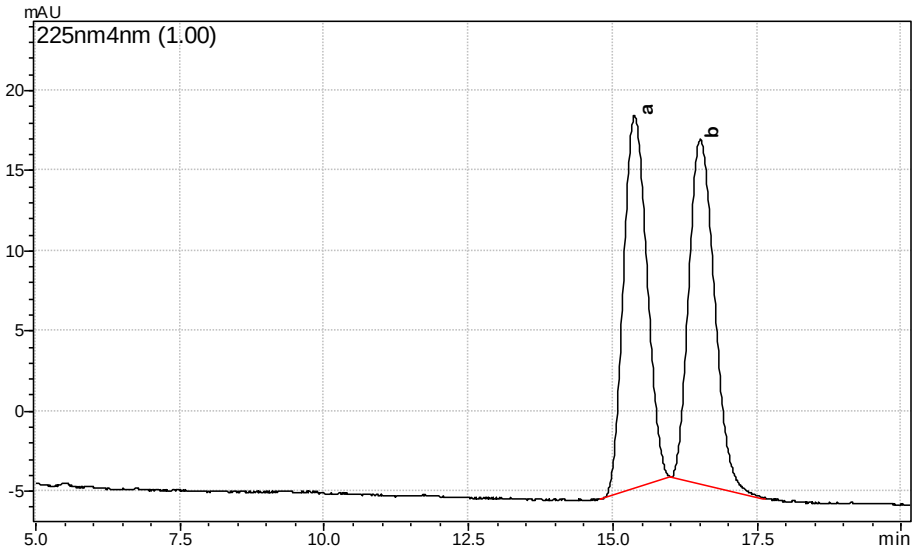
enantiomer	*r.t. (min)*	*area*	*area%*
a	7.845	8,007,496	97.7%
b	8.532	192,221	2.3%

(15a) (S)-2-isocyano-3-phenyl-1-(pyrrolidin-1-yl)propan-1-one



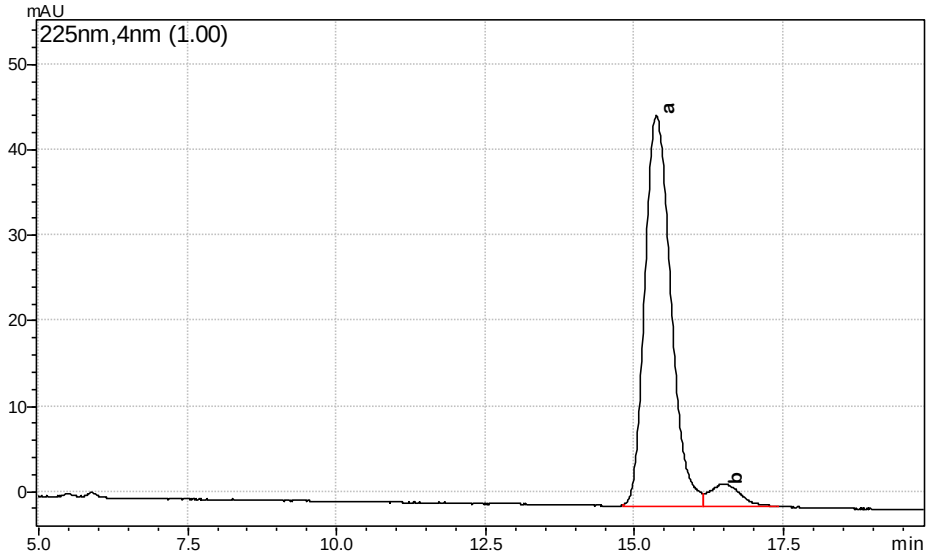
a) HPLC analysis of the isolated racemic compound

Column: Phenomemex Lux 5µ Cellulose-2 250 x 4.6 mm (kept at 40°C)
eluant A: ethanol 99.8 [15%]
eluant B: n-exane [85%]
flow rate: 1 mL min^{-1}
Volume injected: 5 µL (solution 0.50 mg mL^{-1} in ethanol)
λ: 225 nm



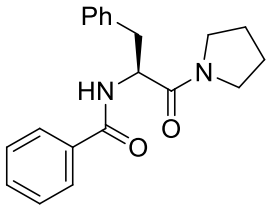
enantiomer	*r.t. (min)*	*area*	*area%*
a	15.365	663,002	49.9%
b	16.511	665,673	50.1%

b) HPLC-UV analysis of the isolated enantioenriched pure compound **15a**



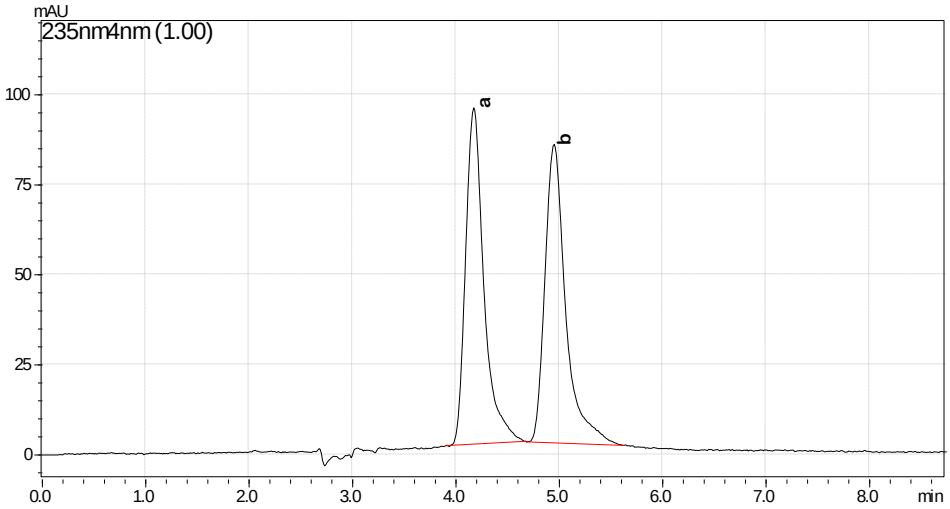
enantiomer	*r.t. (min)*	*area*	*area%*
a	15.360	1,394,200	93.6%
b	16.493	95,423	6.4%

(16a) (*S*)-*N*-(1-Oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide



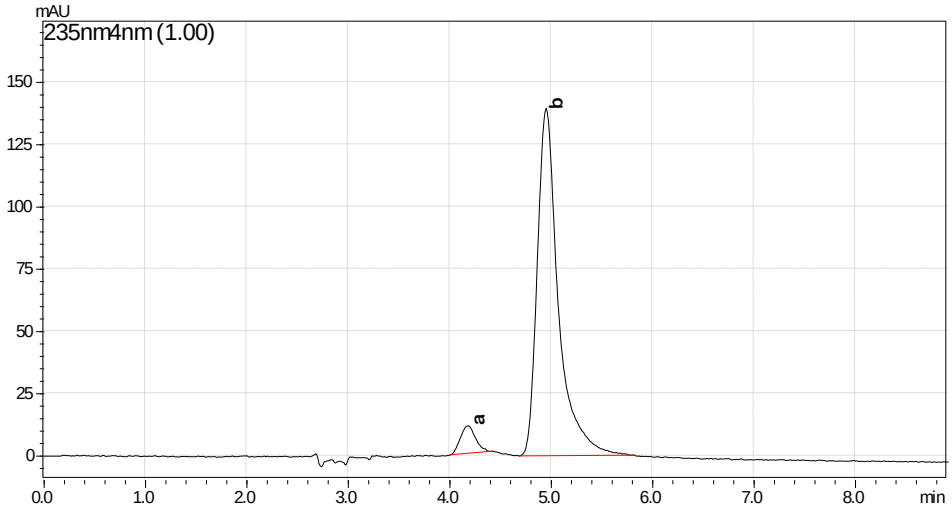
a) HPLC-UV analysis of the isolated racemic compound **8a**

Column: Phenomemex Lux 5µ Cellulose-2 250 x 4.6 mm
eluant A: methanol [90%]
eluant B: 2-propanol [10%]
flow rate: 1 mL min^{-1}
Volume injected: 5 µL (solution 0.33 mg mL^{-1} in methanol)
λ: 235 nm



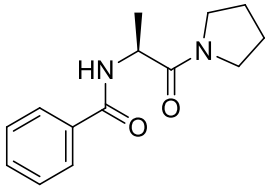
enantiomer	*r.t. (min)*	*area*	*area%*
a	4.168	1,145,971	48.8%
b	4.943	1,155,968	50.2%

b) HPLC-UV of the isolated enantioenriched pure compound **16a**



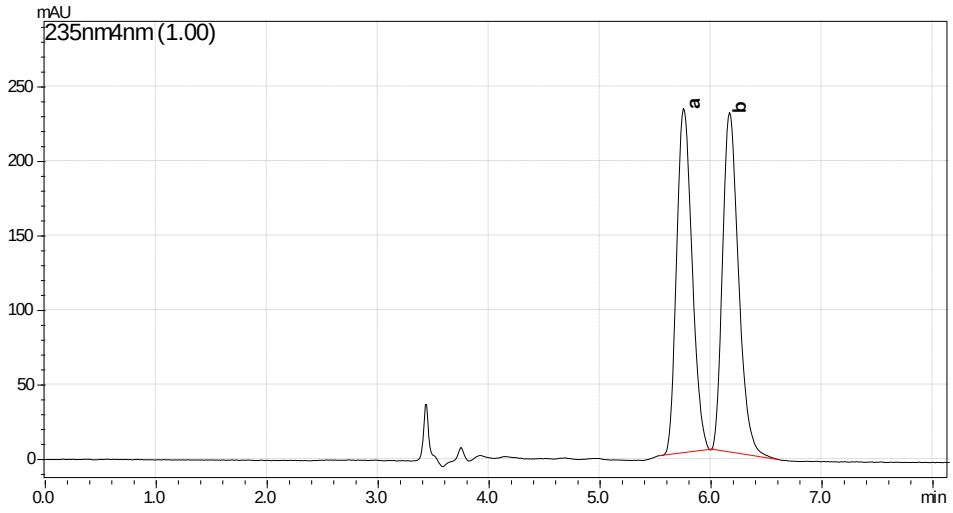
enantiomer	*r.t. (min)*	*area*	*area%*
a	4.176	114,292	5.4%
b	4.945	2,010,297	94.6%

(16b) (S)-*N*-(1-Oxo-1-(pyrrolidin-1-yl)propan-2-yl)benzamide



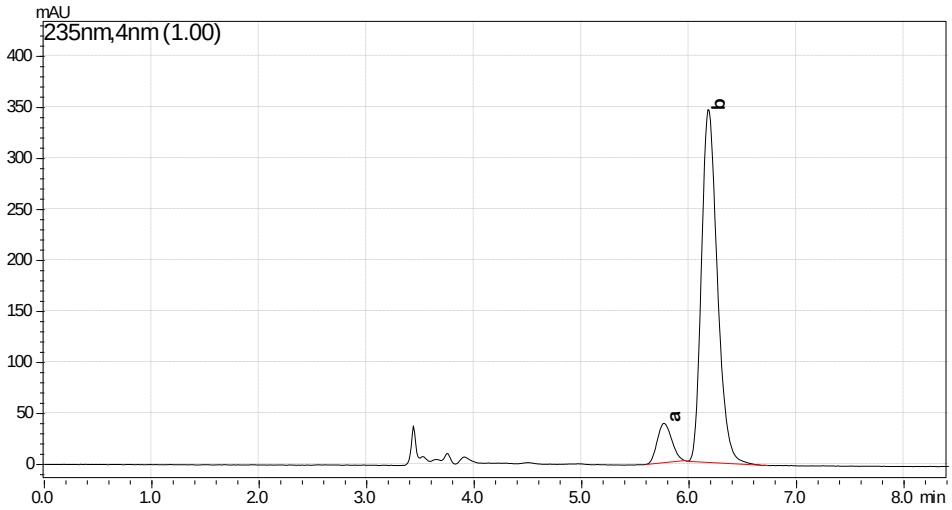
a) HPLC-UV analysis of the isolated racemic compound **8b**

Column: Phenomemex Lux 5µ Cellulose-2 250 x 4.6 mm
eluant A: acetonitrile [90%]
eluant B: 2-propanol [10%]
flow rate: 0.85 mL min^{-1}
Volume injected: 5 µL (solution 0.5 mg mL^{-1} in methanol)
λ: 235 nm



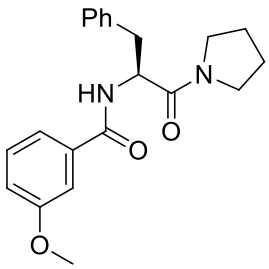
enantiomer	*r.t. (min)*	*area*	*area%*
a	5.747	2,246,658	49.6%
b	6.161	2,286,182	50.4%

b) HPLC analysis of the isolated enantioenriched pure compound **16b**



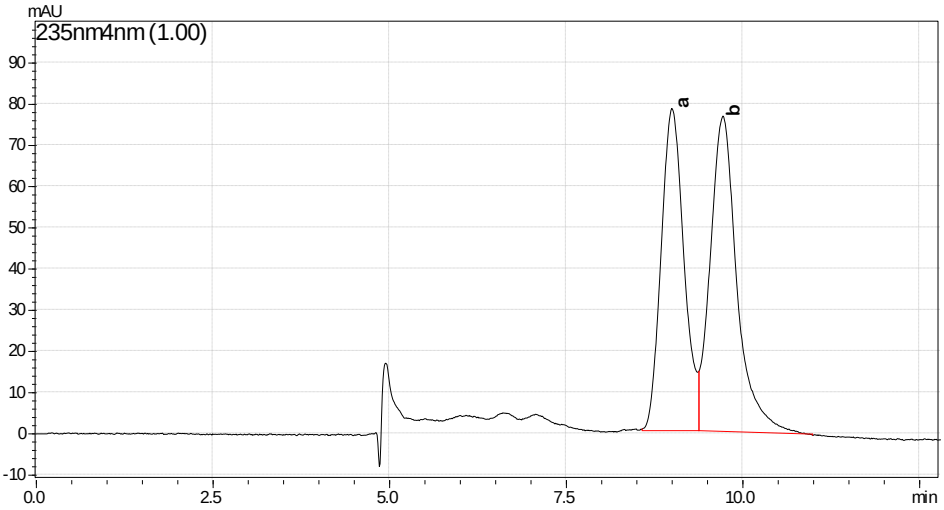
enantiomer	*r.t. (min)*	*area*	*area%*
a	5.760	361,853	9.2%
b	6.175	3,558,119	90.8%

(16c) (S)-3-Methoxy-N-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)benzamide



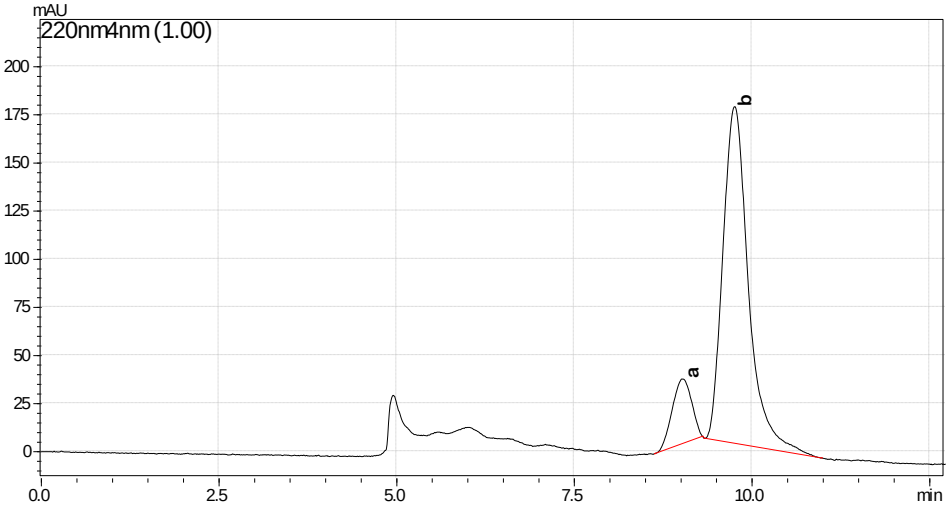
a) HPLC analysis of the isolated racemic compound **8l**

Column: Phenomemex Lux 5µ Cellulose-2 250 x 4.6 mm
eluant A: methanol [7%]
eluant B: acetonitrile [93%]
flow rate: 0.6 mL min^{-1}
Volume injected: 5 µL (solution 0.33 mg mL^{-1} in methanol)
λ: 235 nm



enantiomer	*r.t. (min)*	*area*	*area%*
a	8.989	1,762,386	46.7%
b	9.712	2,009,439	53.3%

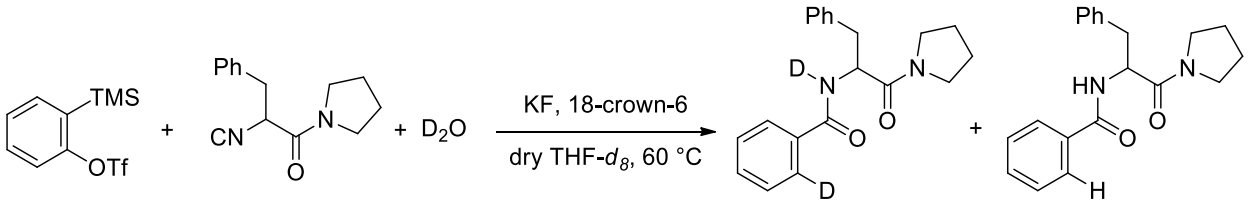
b) HPLC-UV analysis of the isolated enantioenriched pure compound **16c**



enantiomer	*r.t. (min)*	*area*	*area%*
a	9.010	502,290	9.9%
b	9.751	4,593,928	90.1%

3. Deuterium-labelling studies

3.1. Procedure for the synthesis of compound *d*-8a



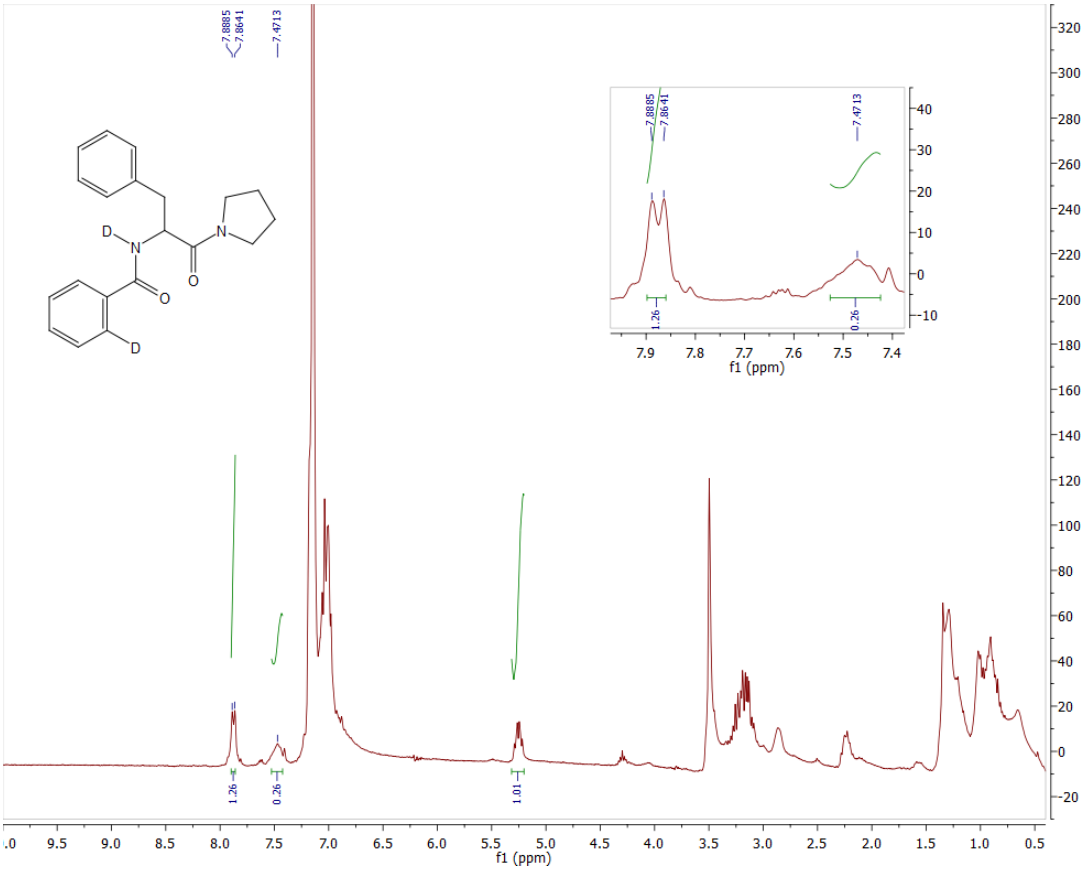
1a **7a** ***d*-8a** **71.4 %** **8a** **28.6 %**

To a flame-dried screw capped containing a solution of anhydrous KF (3 equiv, 3.99 mmol, 232 mg), 18-crown-6 (3 equiv, 3.99 mmol, 1.05 g) and **7a** (1 equiv, 1.33 mmol, 304 mg) in dry THF-*d*8 (6.5 mL), **1a** (1.5 equiv, 1.99 mmol, 595 mg) and deuterated water (2 equiv, 1 mmol) are added under nitrogen atmosphere. After stirring for 3 h at 60 °C, the reaction is filtered over a pad of silica gel and washed with dry CH_2Cl_2. The volatile is removed under vacuo.

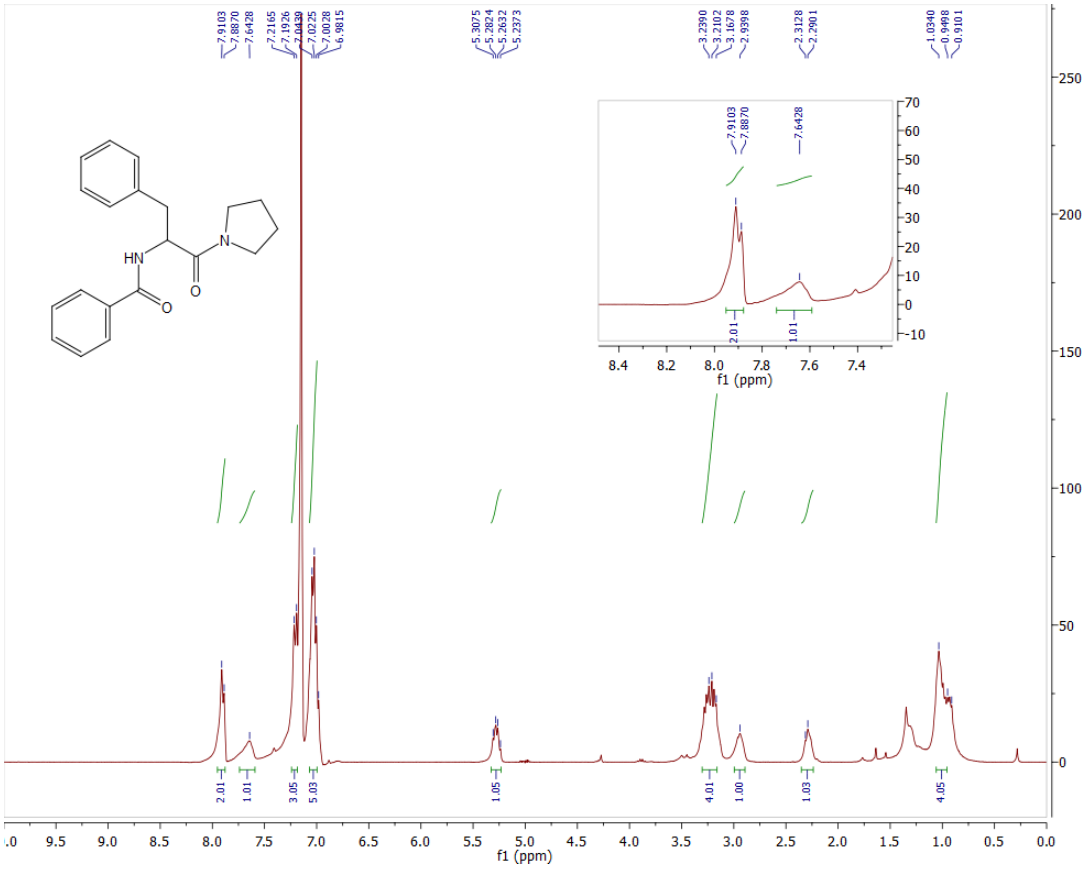
3.2. ^{1}H-NMR analysis on the crude material

The deuterium incorporation on the nitrogen of ***d*-8a** was detected and quantified by integration of the signal at 7.47 ppm on the crude material and comparison with the signal at 7.64 ppm on the purified **8a**.

d-8a: ^{1}H (C_6D_6)



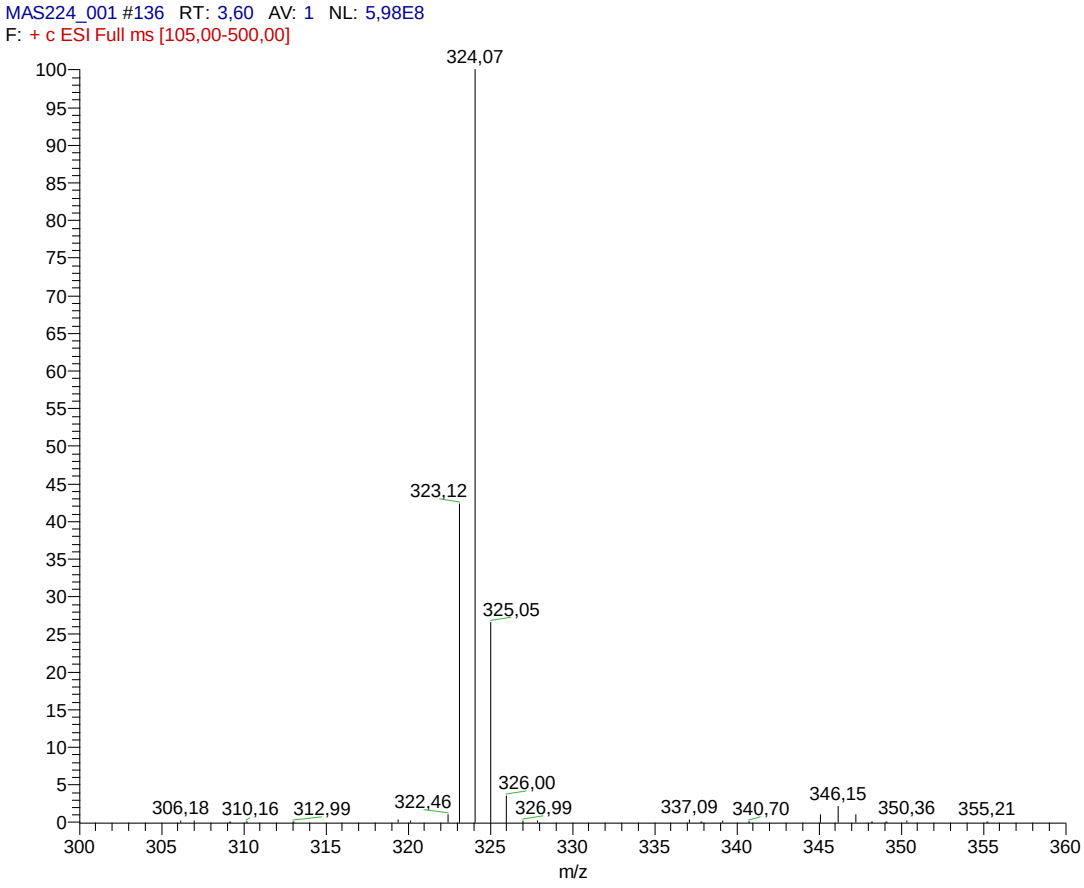
8a: ^{1}H (C_6D_6)


7.9103
7.8870
7.6428
7.2165
7.1926
7.0439
7.0225
7.0028
6.9815
5.3075
5.2824
5.2632
5.2373
3.2390
3.2102
3.1678
2.9398
2.3128
2.2901
1.0340
0.9498
0.9101
HN
O
N
O
2.01
1.01
3.05
5.03
1.05
4.01
1.00
1.03
4.05
f1 (ppm)

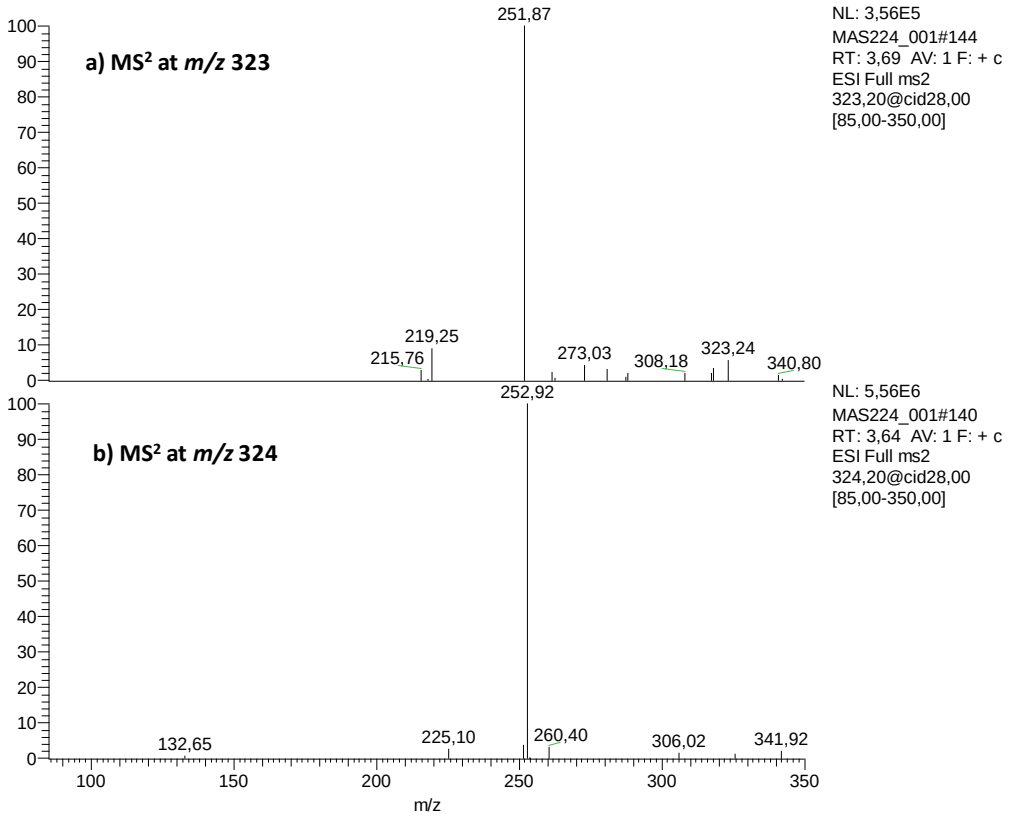
3.3. LC-ESI-MS analysis on the purified compound 8a, *d*-8a

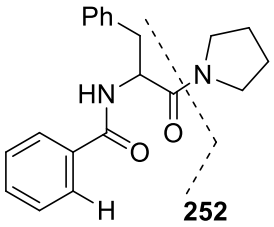
The resulting crude material was purified by gravimetric column using PE/EtOAc 6/4 to afford a mixture of **8a** and ***d*-8a** (292 mg, 68% yield). Deuterium incorporation on the aromatic ring was investigated by liquid chromatograpy-low resolution mass spectrometry (LC-LRMS) using a Thermo Finningan LCQ Deca XP *plus* system (Thermo Electron Corporation, Waltham, MA) equipped with an electrospray ion source (ESI).Aliquots (5.0 µl) of 10 ppm ***d*-8a** solution were injected onto the system and eluted with a mobile phase (flow rate 0.2 mL/min) consisting of a A: 0.2% formic acid solution, B: acetonitrile (A:B= 50-50) using a Luna 5µ C18(2) 150 x 2 mm column (Phenomenex Torrance, CA, USA) as a stationary phase.

Positive full mass



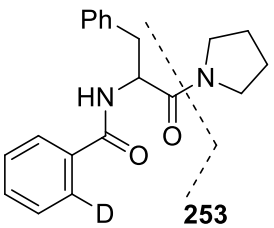
Positive MS^2 spectra of ions at *m/z* 323 (a) and 324 (b)





252

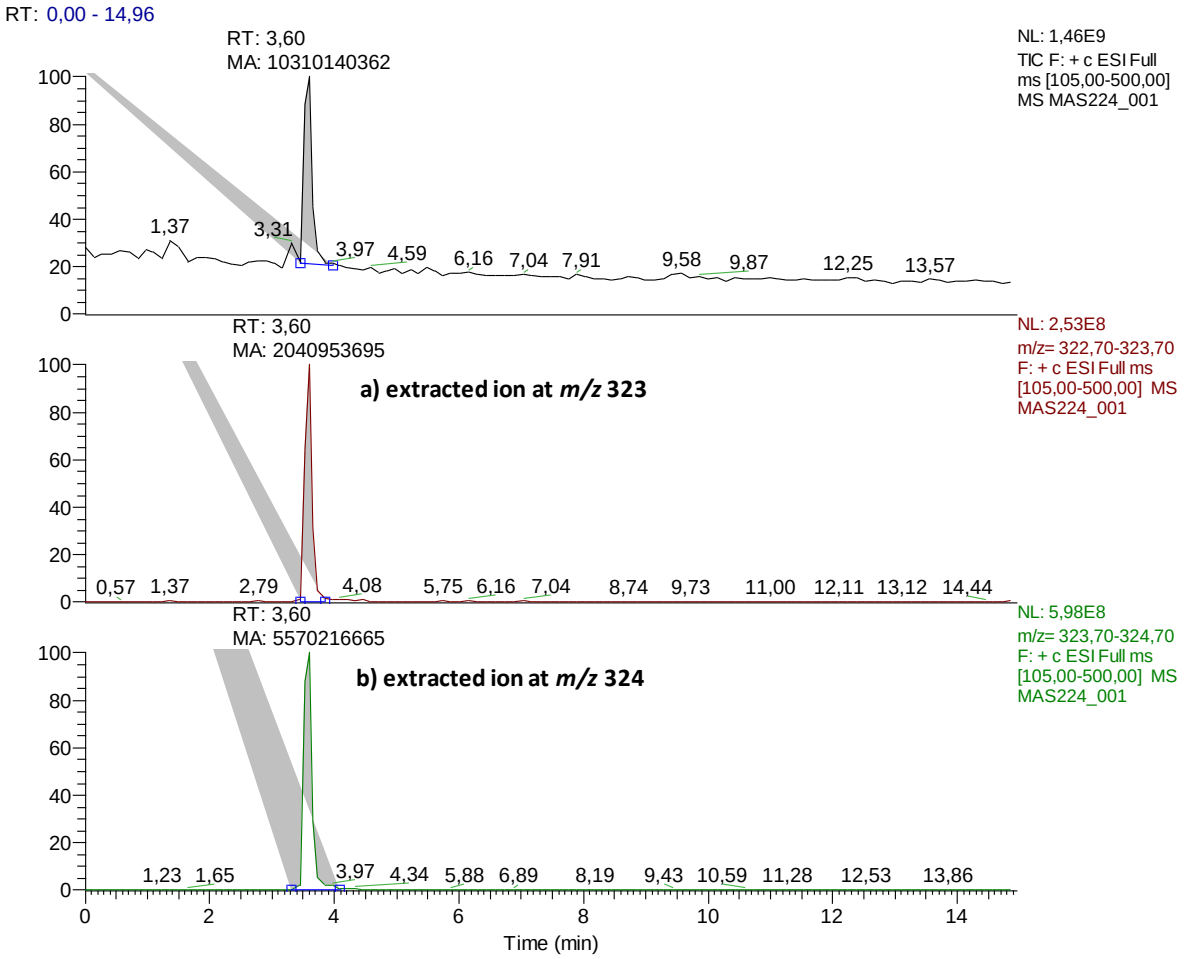
8a $[M+H]^+$ = 323.18

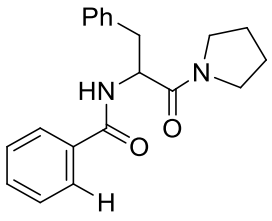


253

***d*-8a** $[M+H]^+$ = 324.18

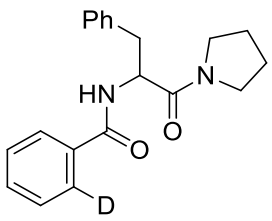
LC-ESI-MS: positive full mass chromatogram (a), extracted ions at *m/z* 323 (b) and 324 (c)





8a

Chemical Formula: $C_{20}H_{22}N_2O_2$
Exact Mass: 322,17
LRMS $(M+H)^+$ = 323,20



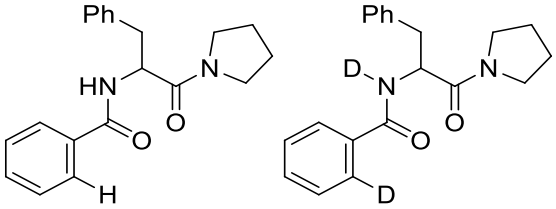
***d*-8a**

Chemical Formula: $C_{20}H_{21}DN_2O_2$
Exact Mass: 323,17
LRMS $(M+H)^+$ = 324,18

Peak *m/z*	Intensity	Relative %
323,2	2,040,953,695	28.6
324,2	5,104,879,223 [a]	71.4

a) Subtracted to 22.8%; relative to peak ^{13}C of ion at *m/z* 323

3.4. NMR assignments on the purified compound 8a, *d*-8a

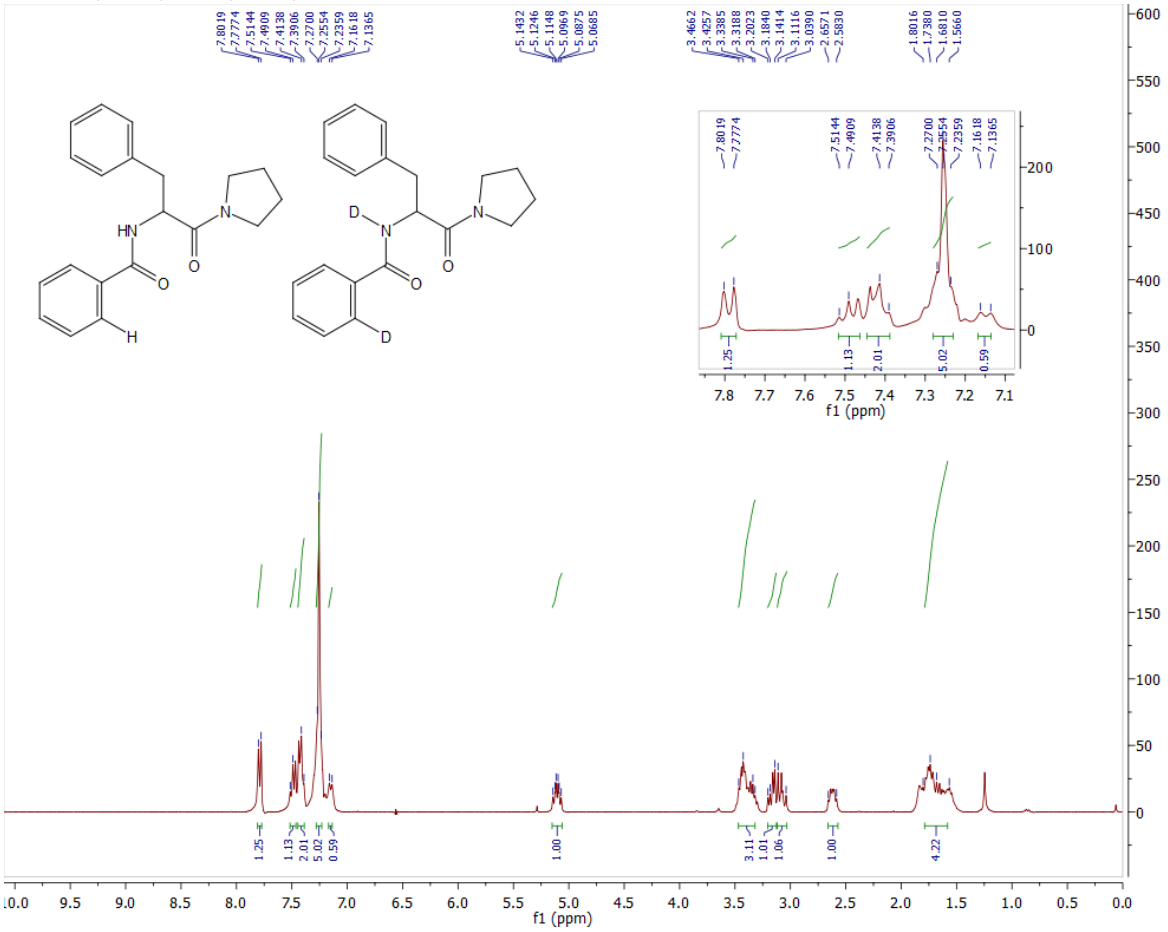


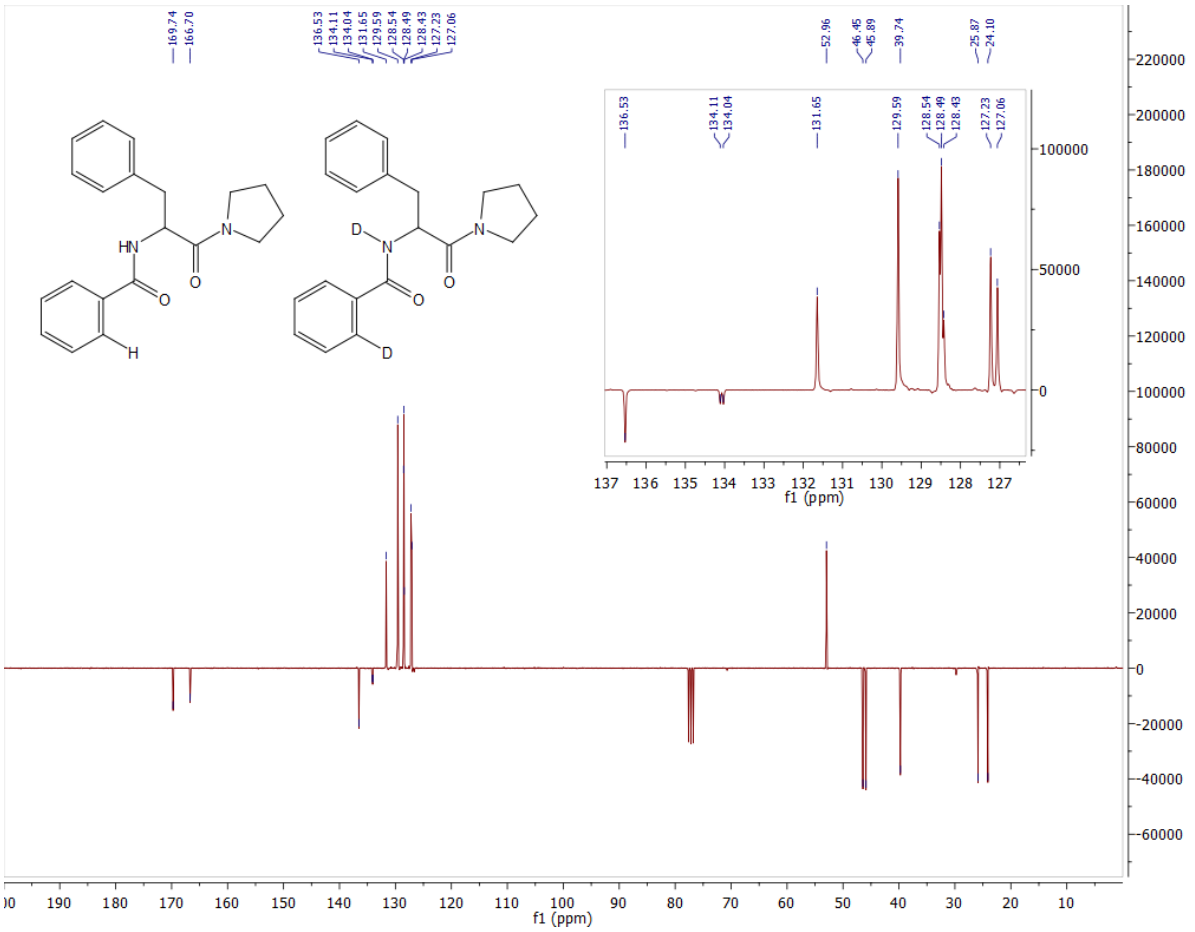
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.4 Hz), 7.51-7.39 (m), 7.27-7.24 (m), 7.15 (br d, *J* = 7.6 Hz), 5.11 (td, *J* = 7.6, 5.6 Hz), 3.47-3.32 (m), 3.17 (dd, *J* = 12.9, 5.6 Hz), 3.08 (dd, *J* = 12.9, 5.6 Hz), 2.66-2.58 (m), 1.80-1.58 (m)

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 166.7, 136.5, 134.1, 134.0, 131.7, 129.6, 128.5 (2C), 128.4, 127.3, 127.1, 53.0, 46.5, 45.9, 39.7, 25.9, 24.1

3.5. ^{1}H and APT spectra

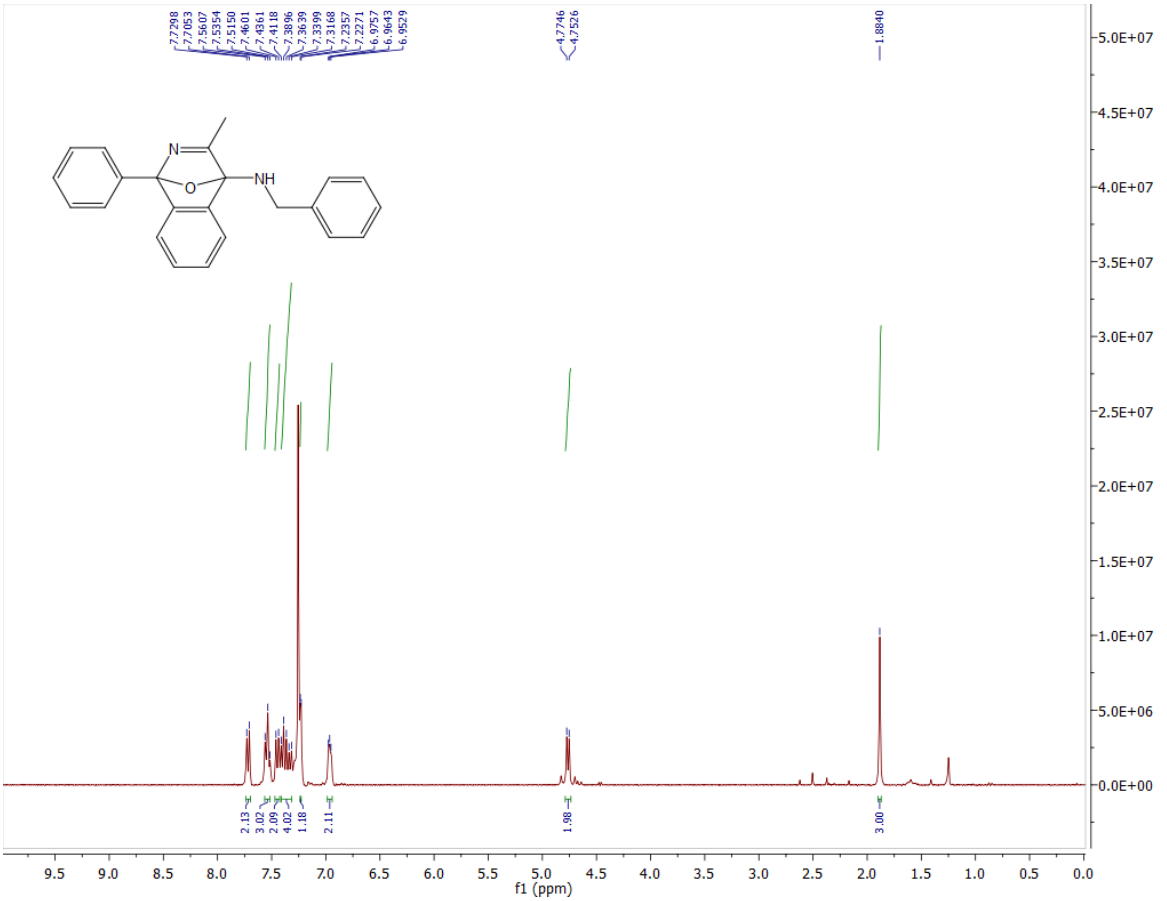
8a, *d*-8a: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

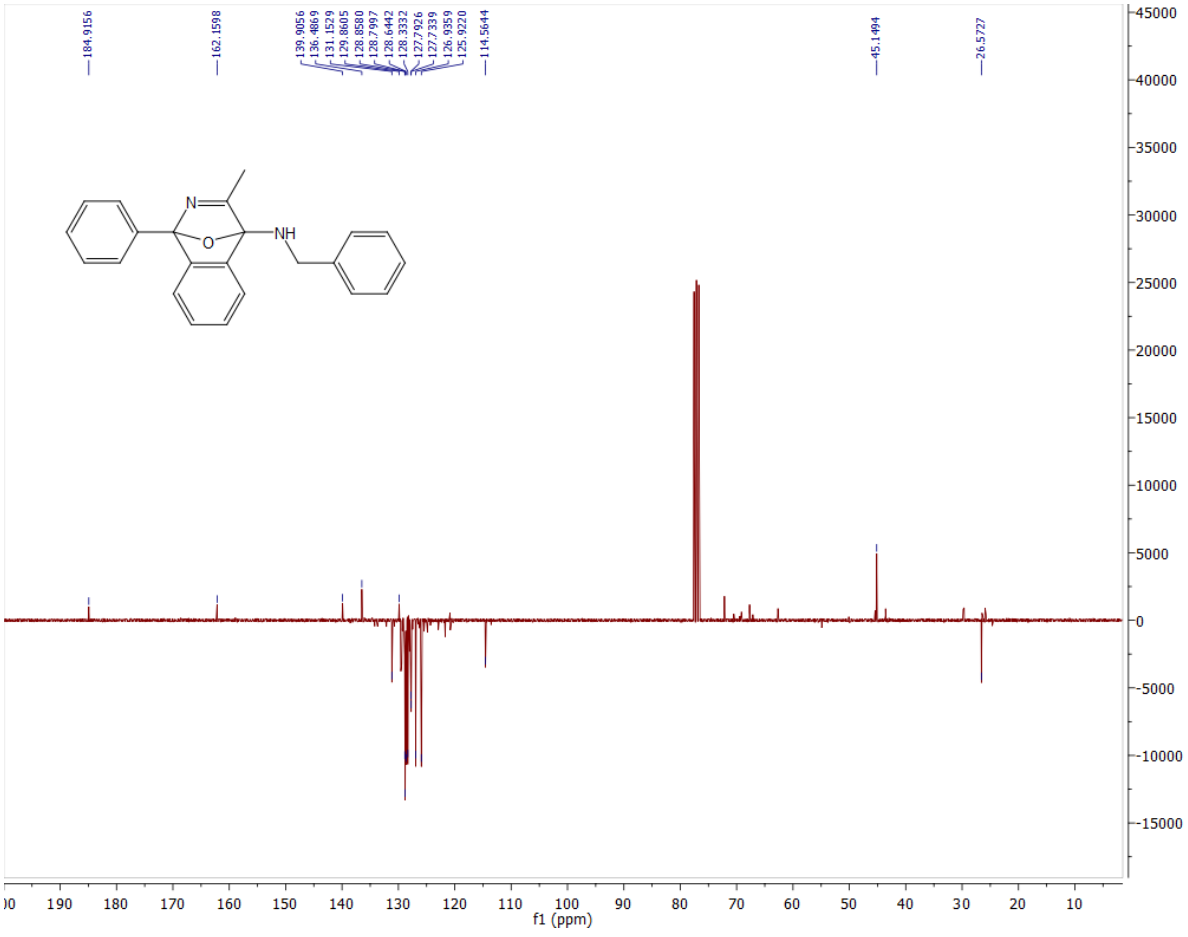



169.74
166.70
136.53
134.11
134.04
131.65
129.59
128.54
128.49
128.43
127.23
127.06
52.96
46.45
45.89
39.74
25.87
24.10
HN
O
N
H
D
f1 (ppm)

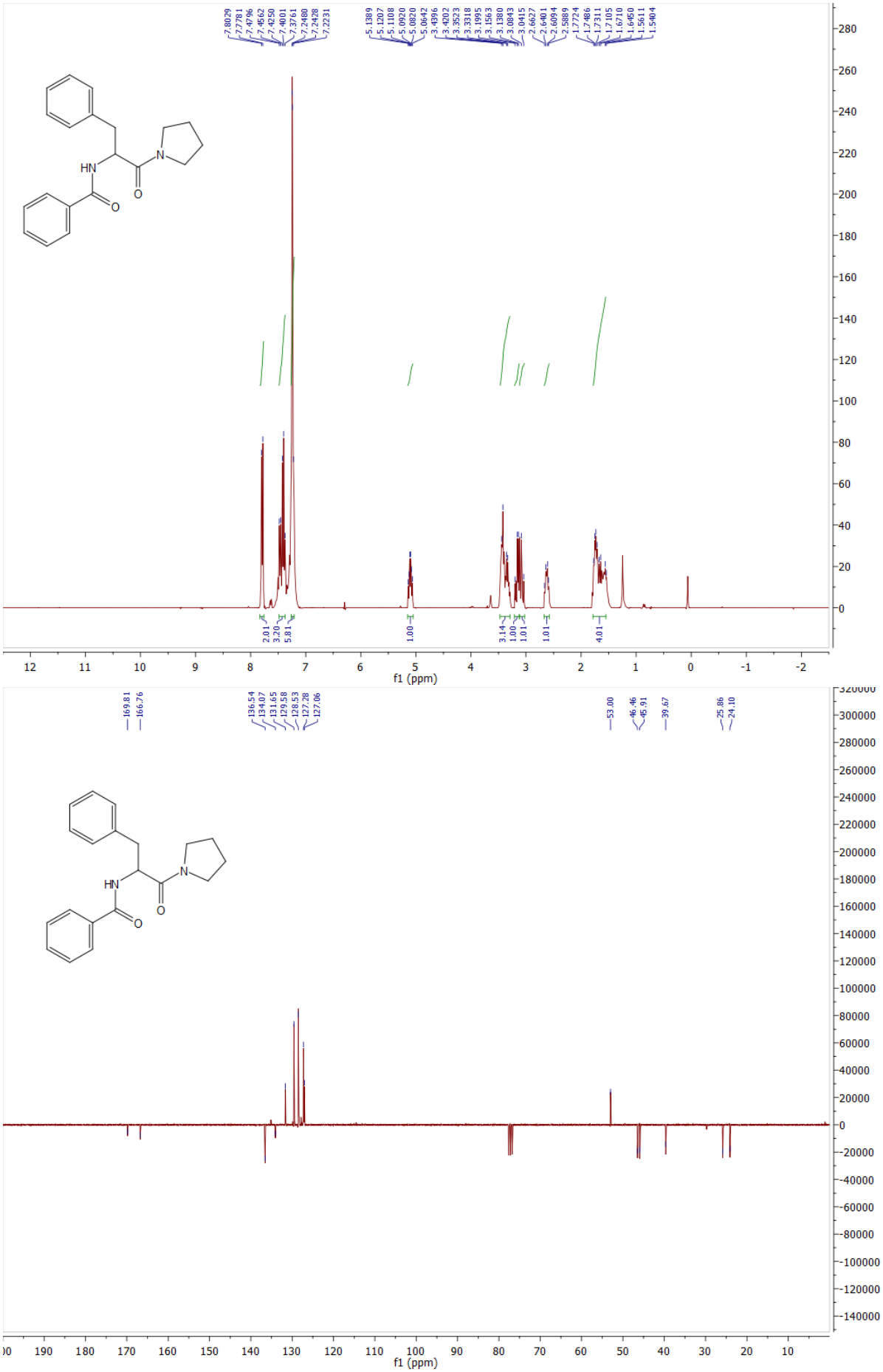
4. ^{1}H and ^{13}C/APT spectra of final products

5: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

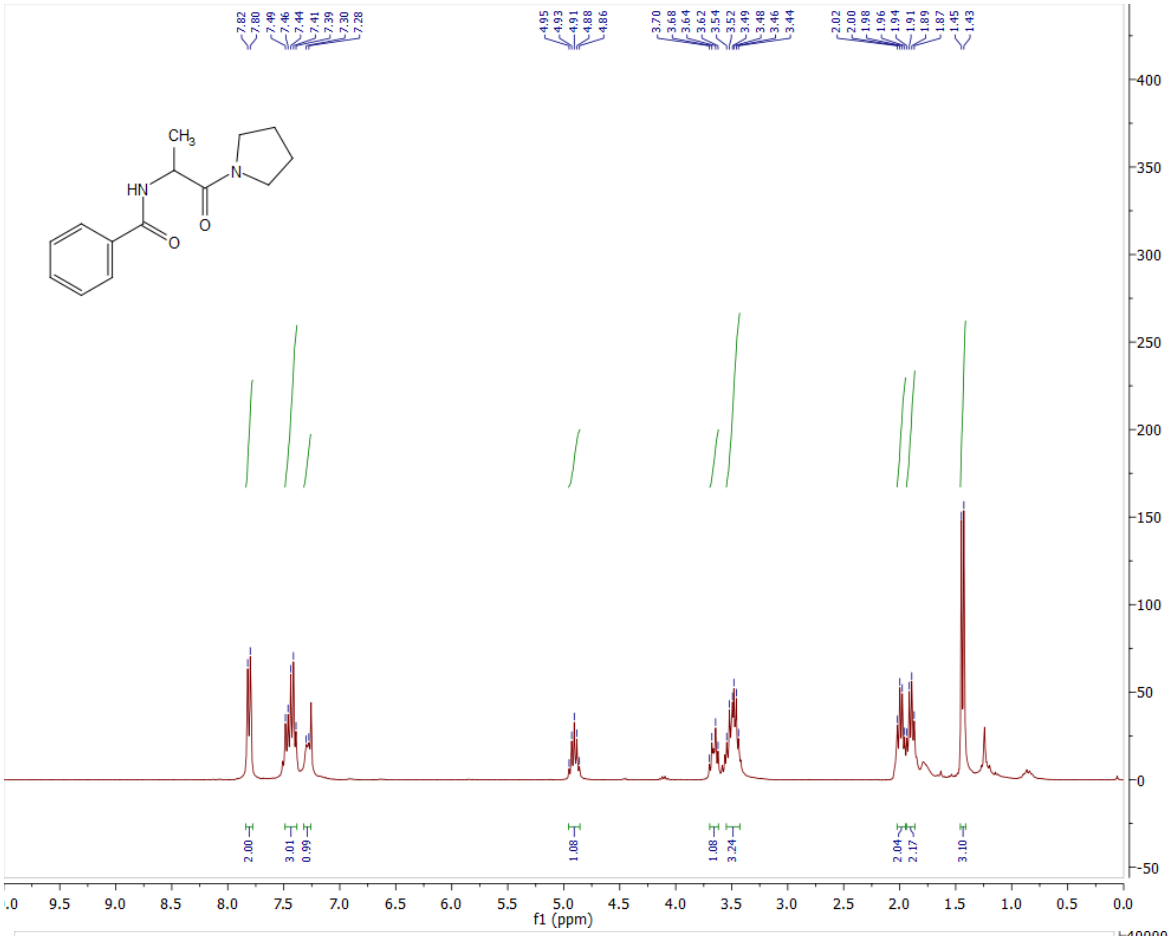


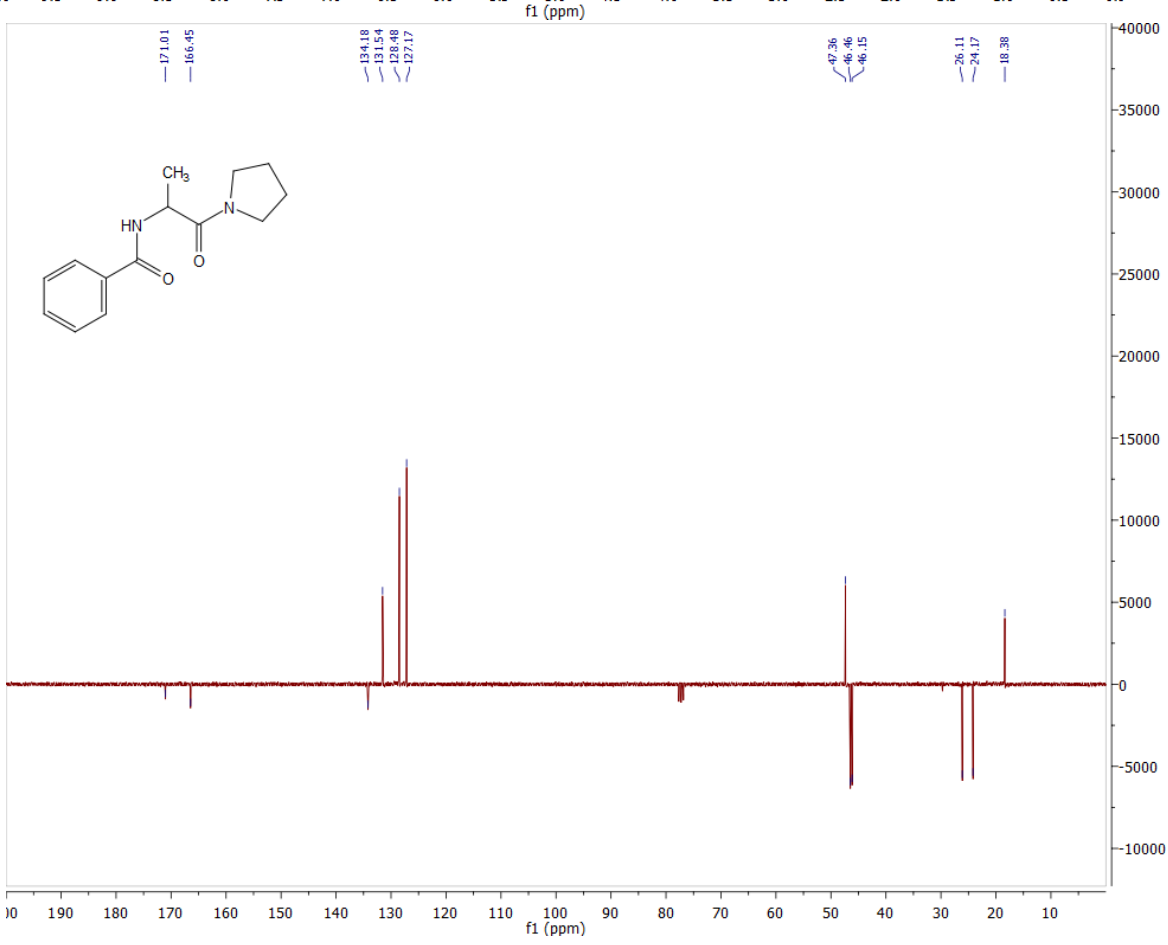


8a: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

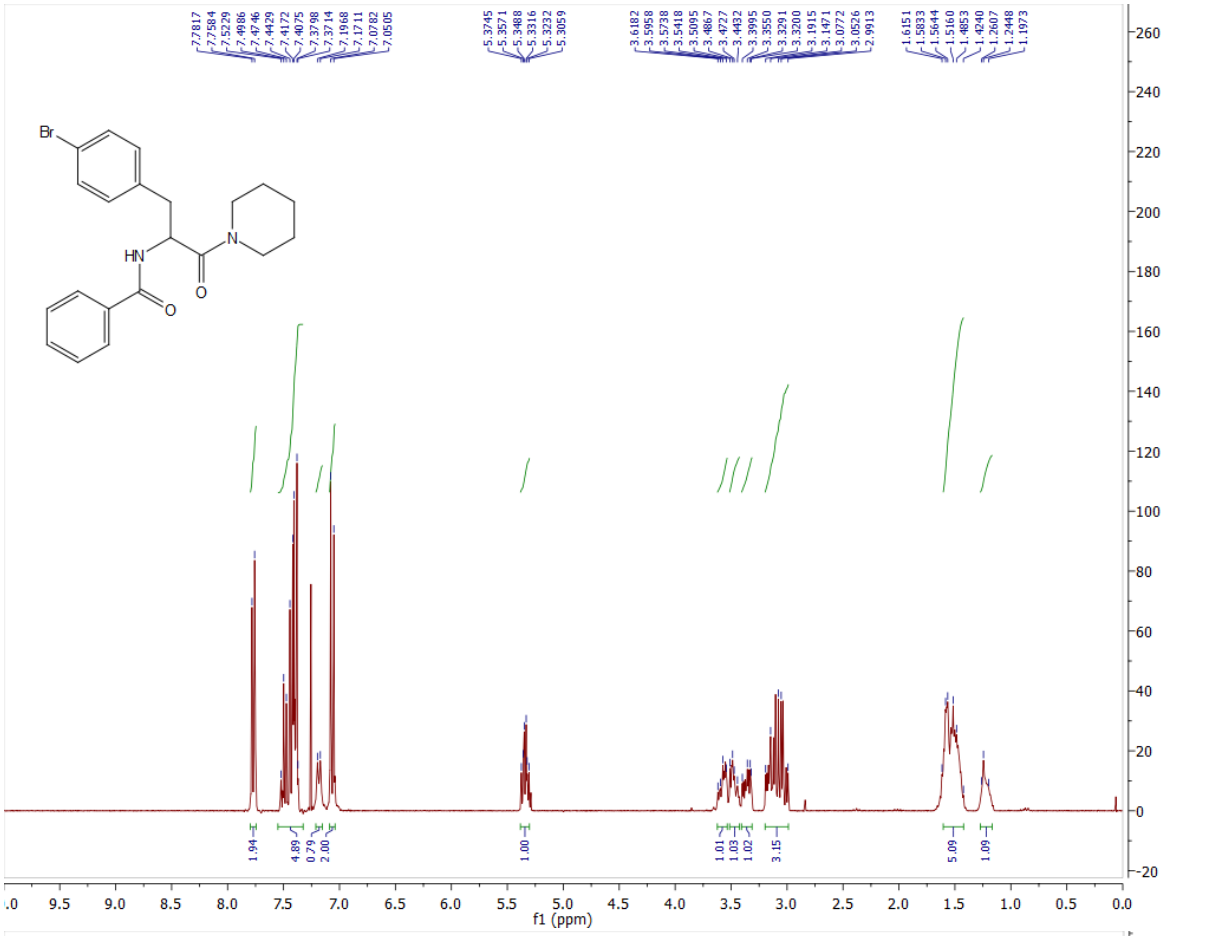


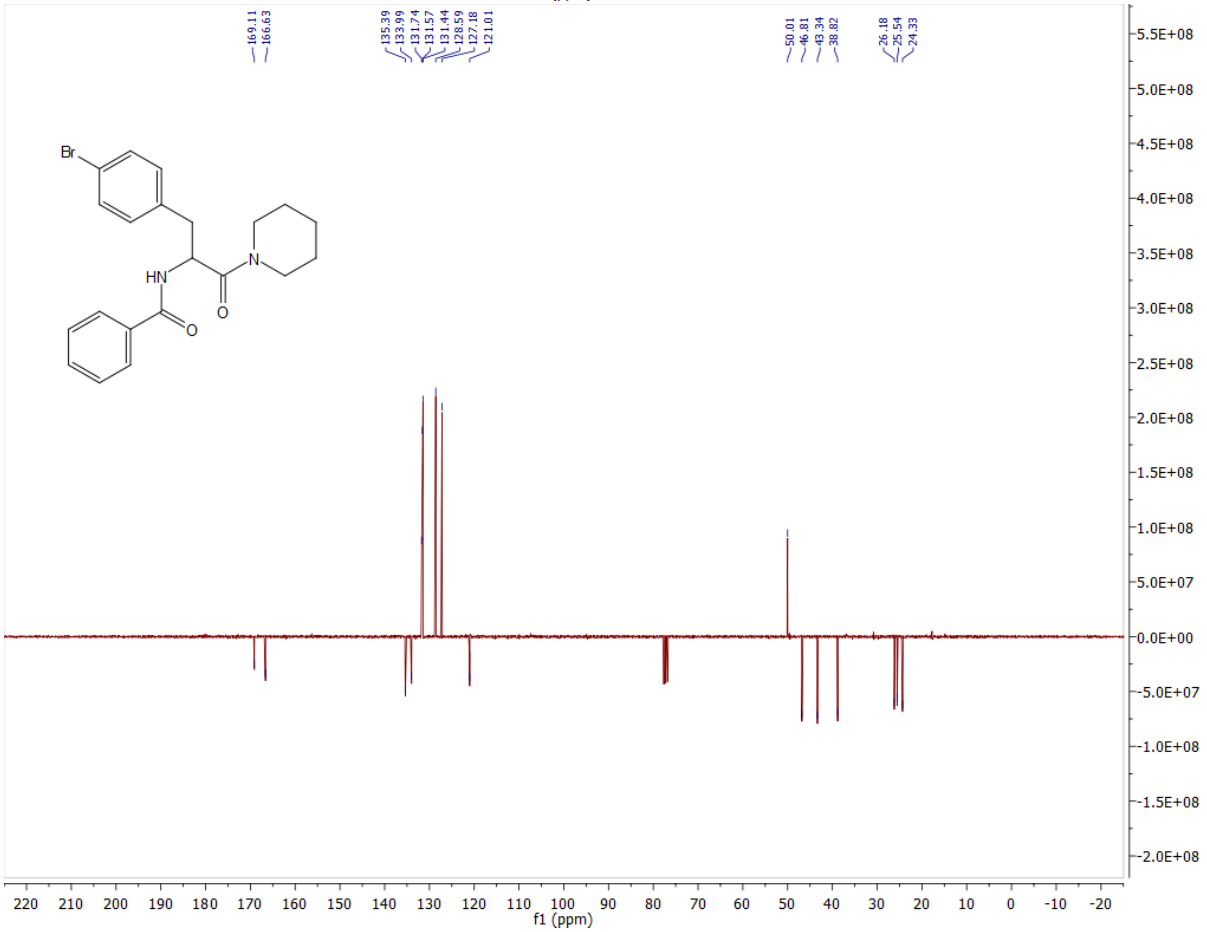
8b: ^{1}H ($CDCl_3$), APT ($CDCl_3$)



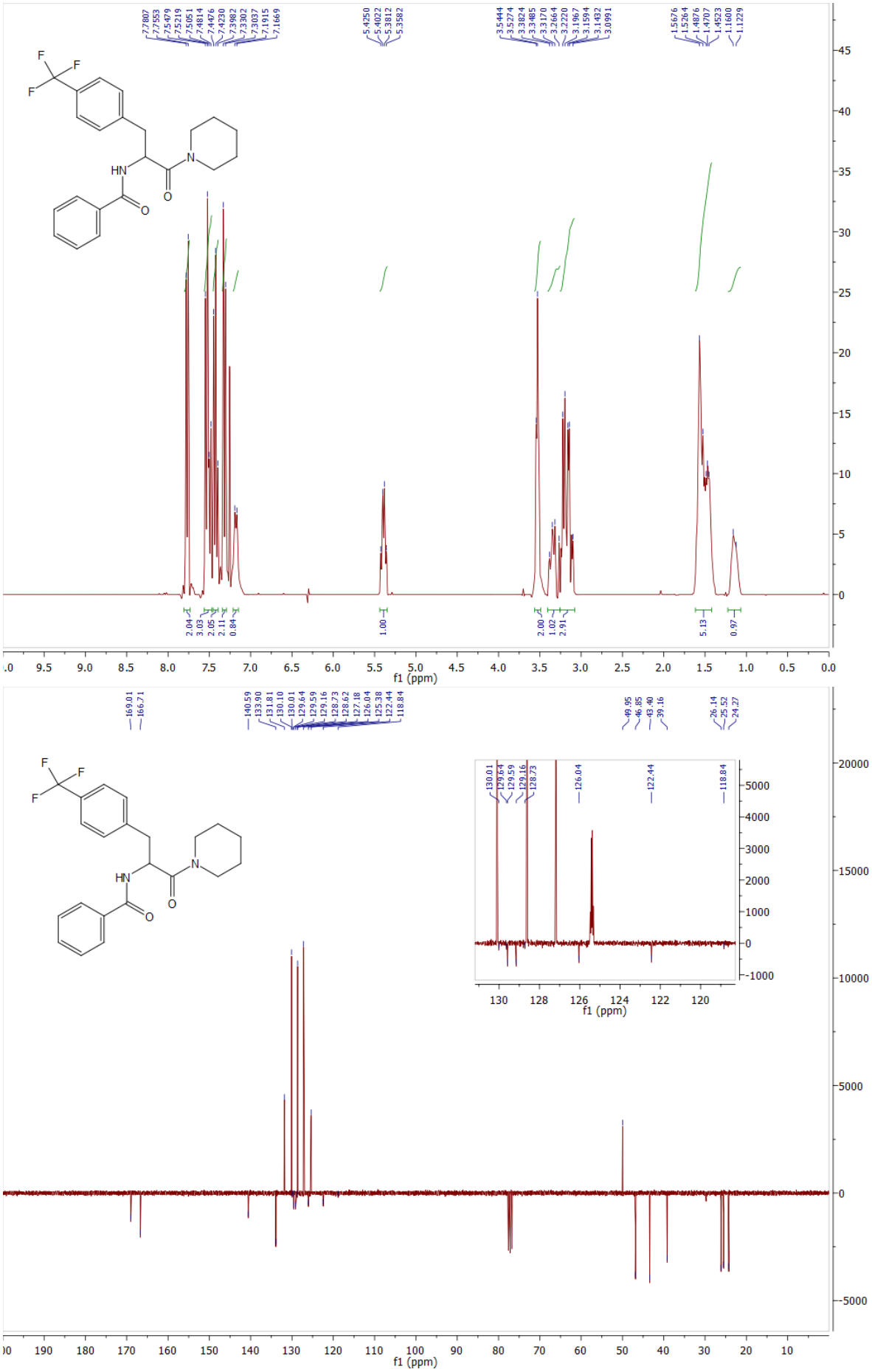


8c: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

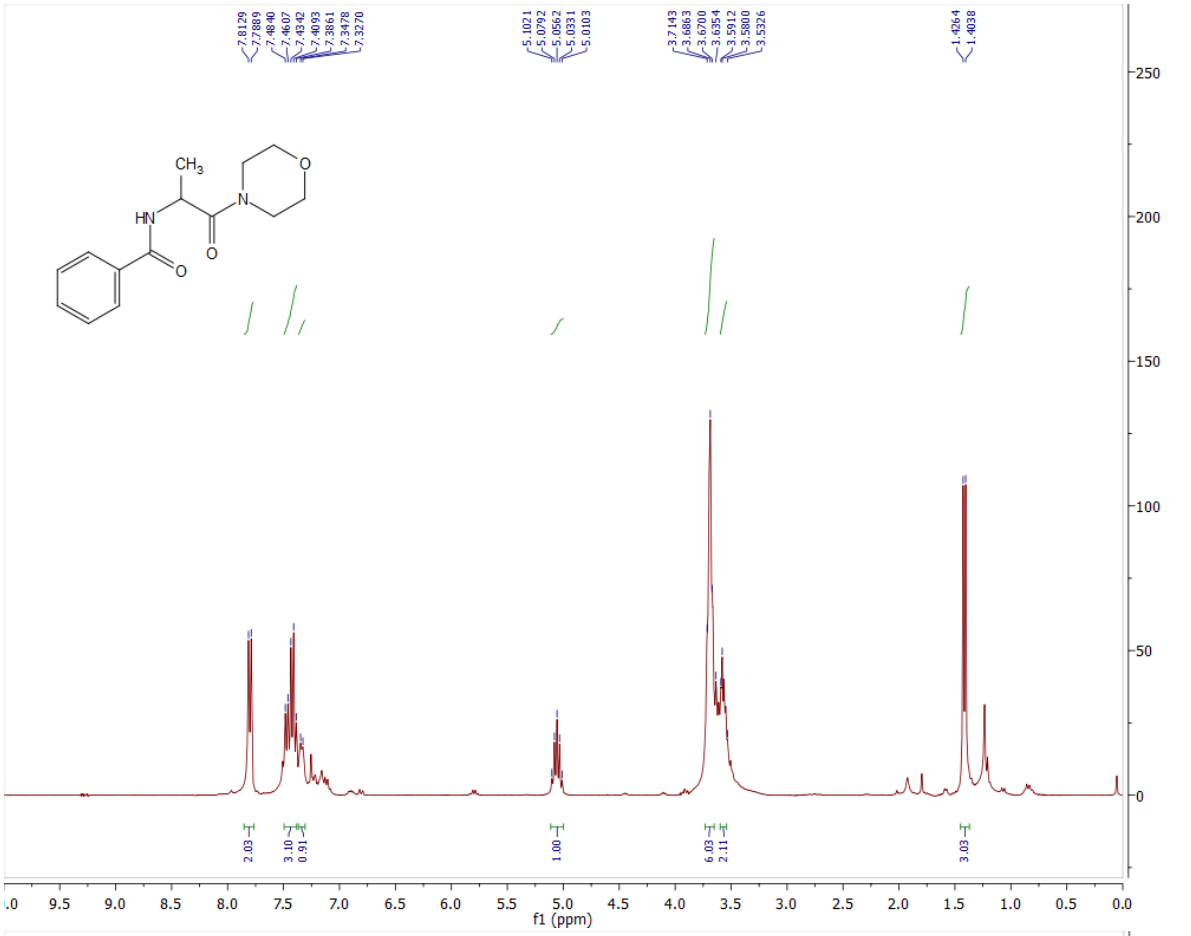


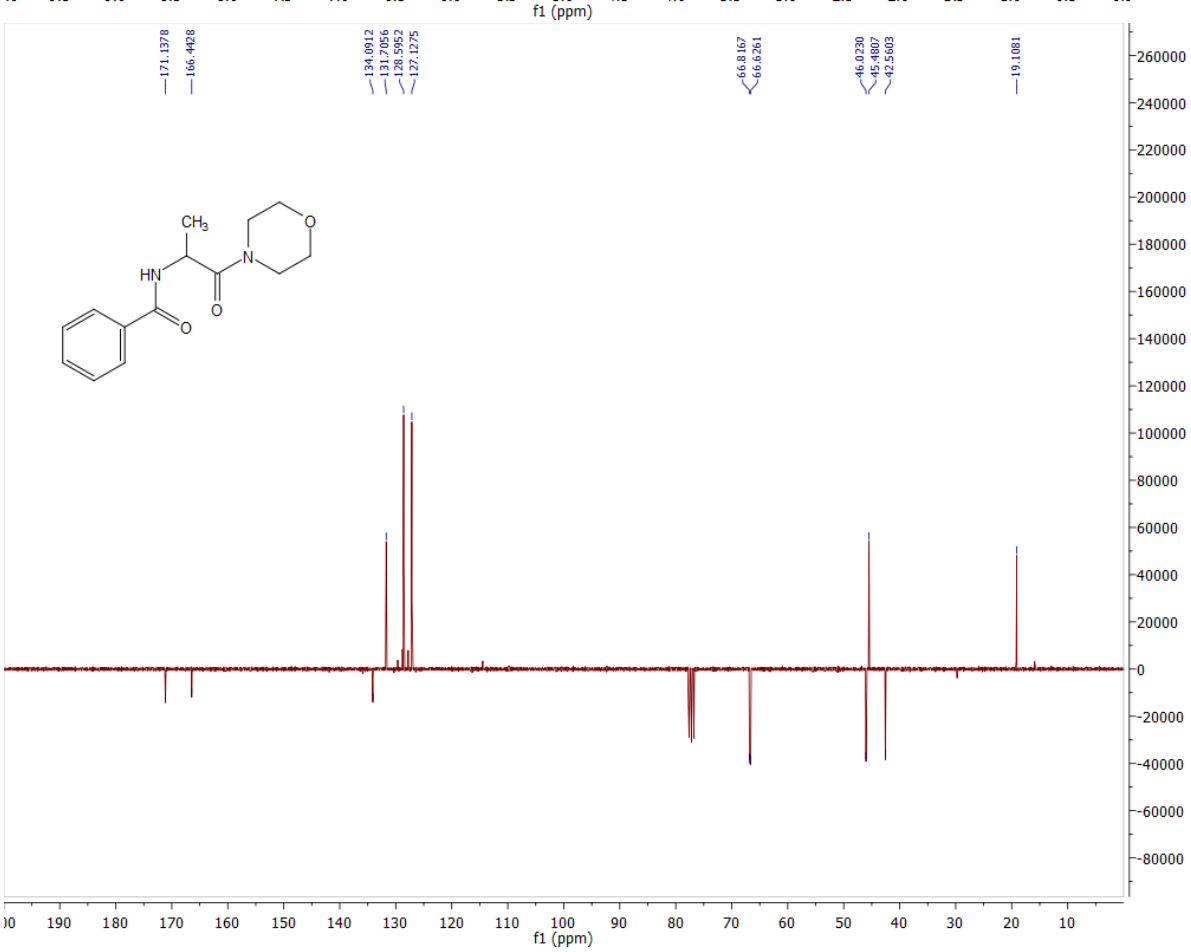


8d: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

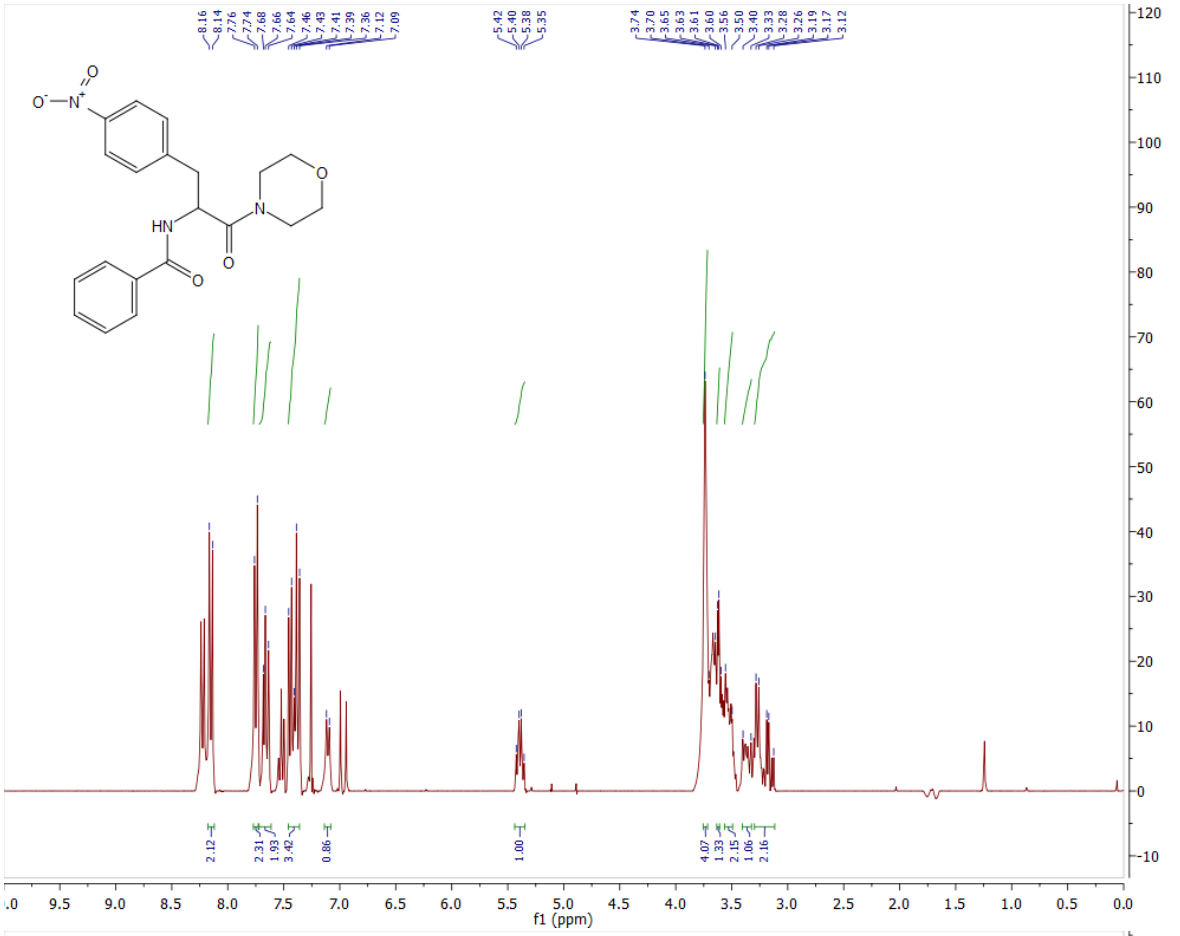


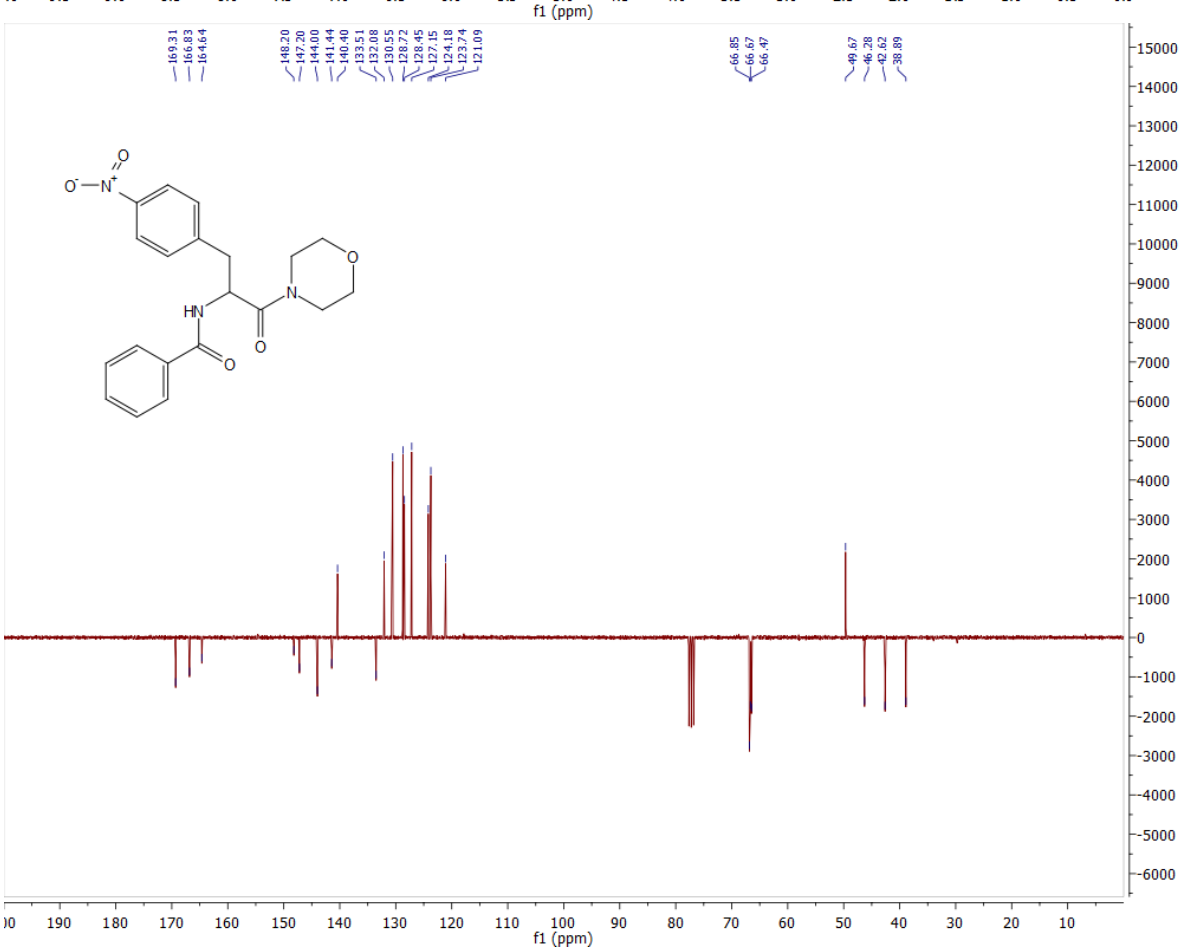
8e: ^{1}H ($CDCl_3$), APT ($CDCl_3$)



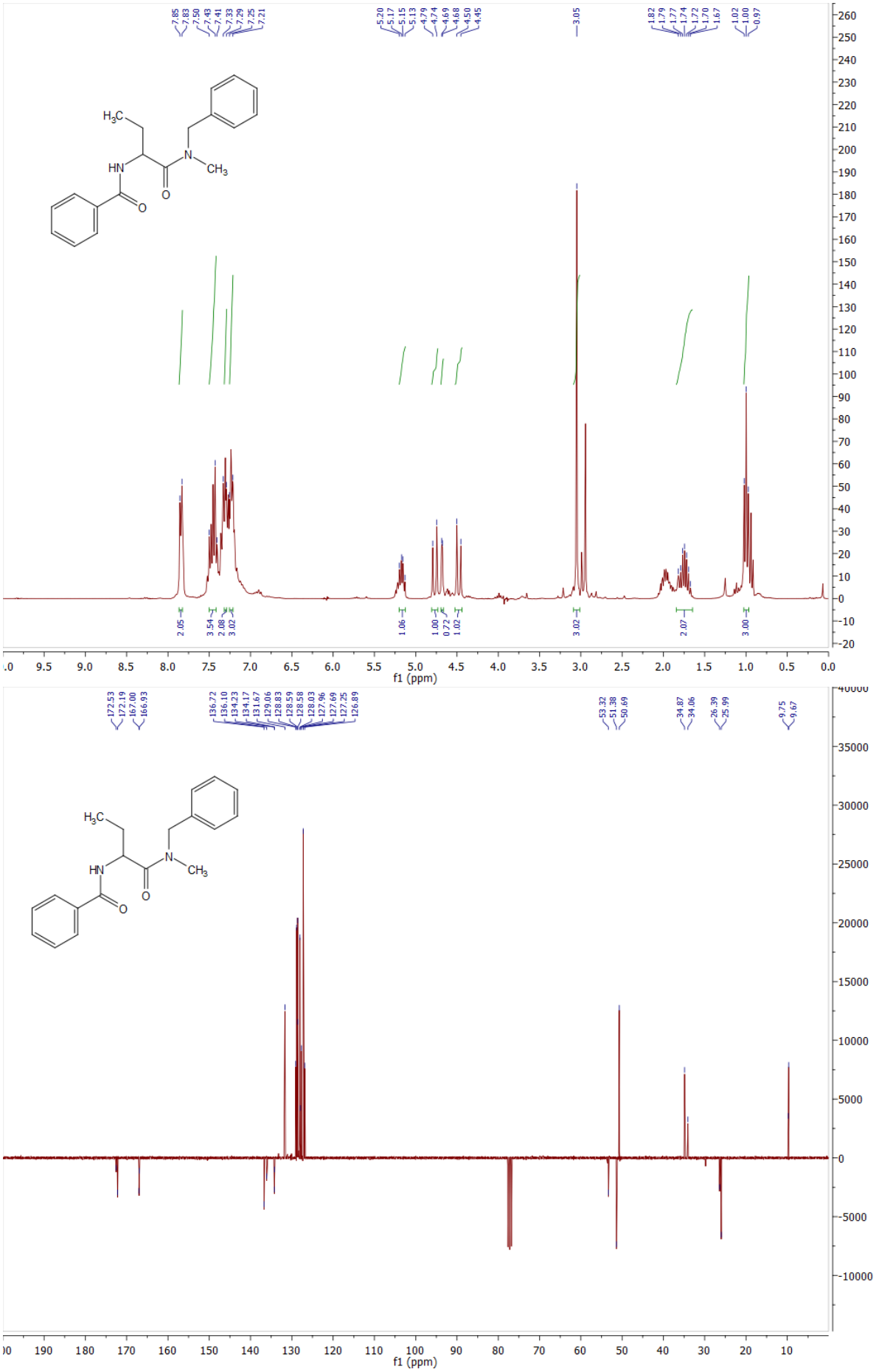


8f: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

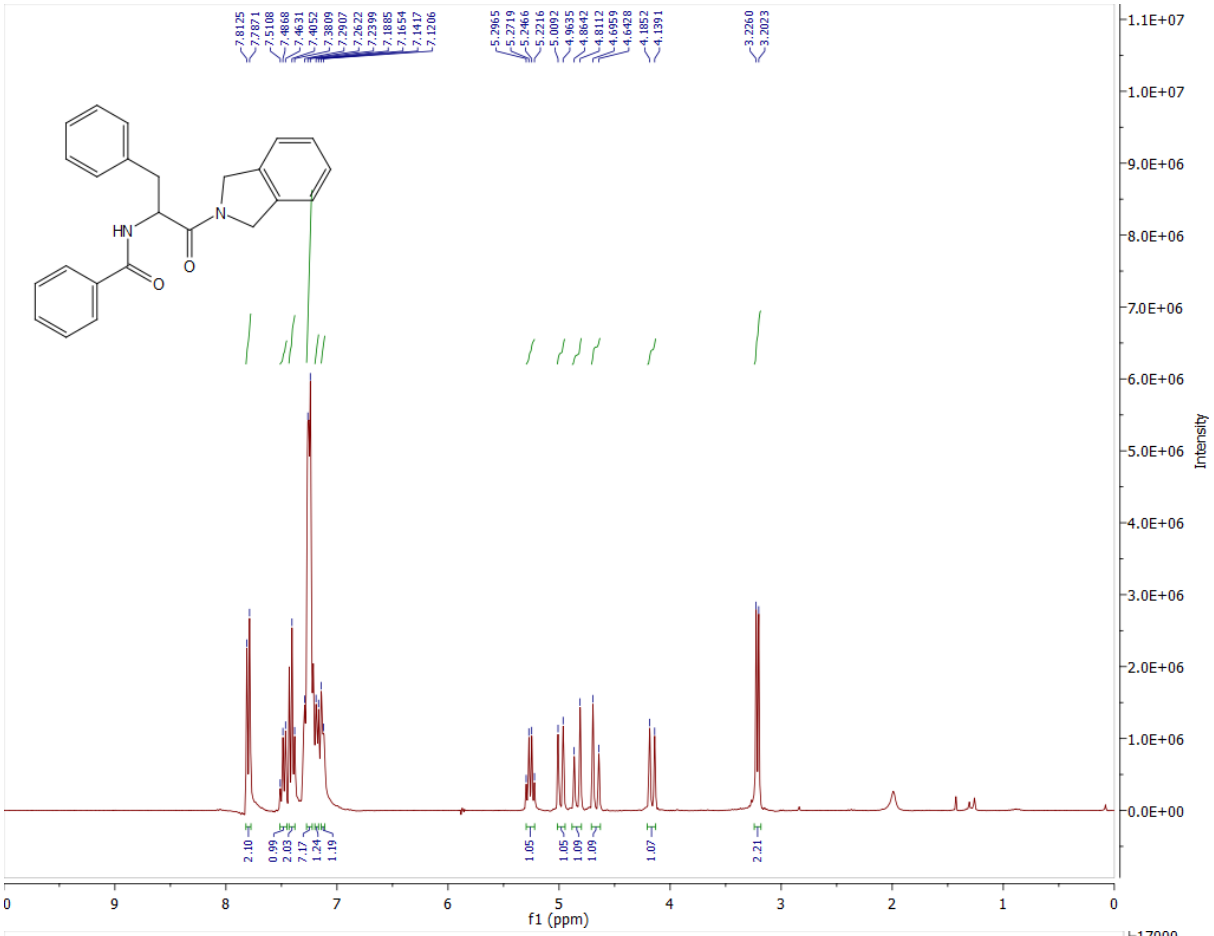


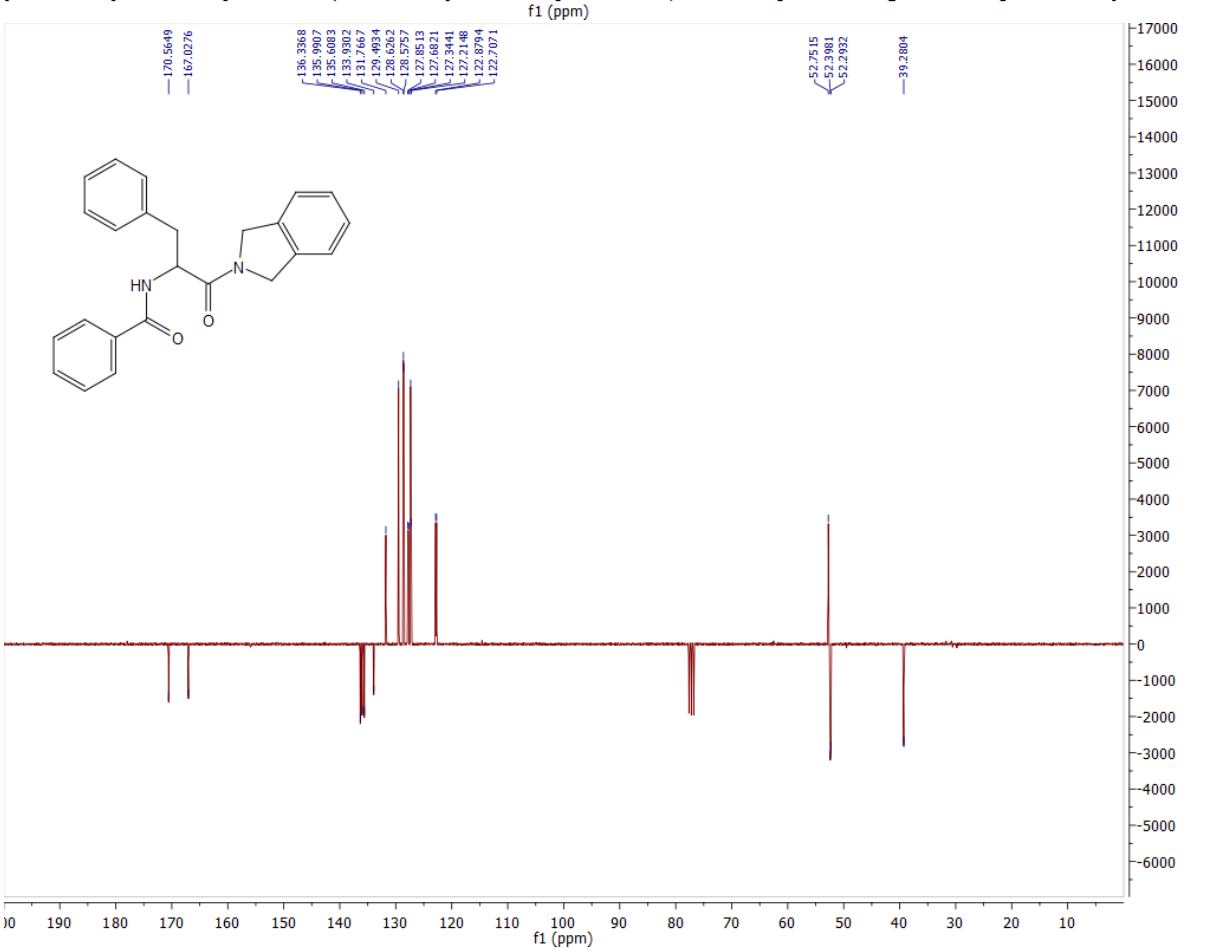


8g: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

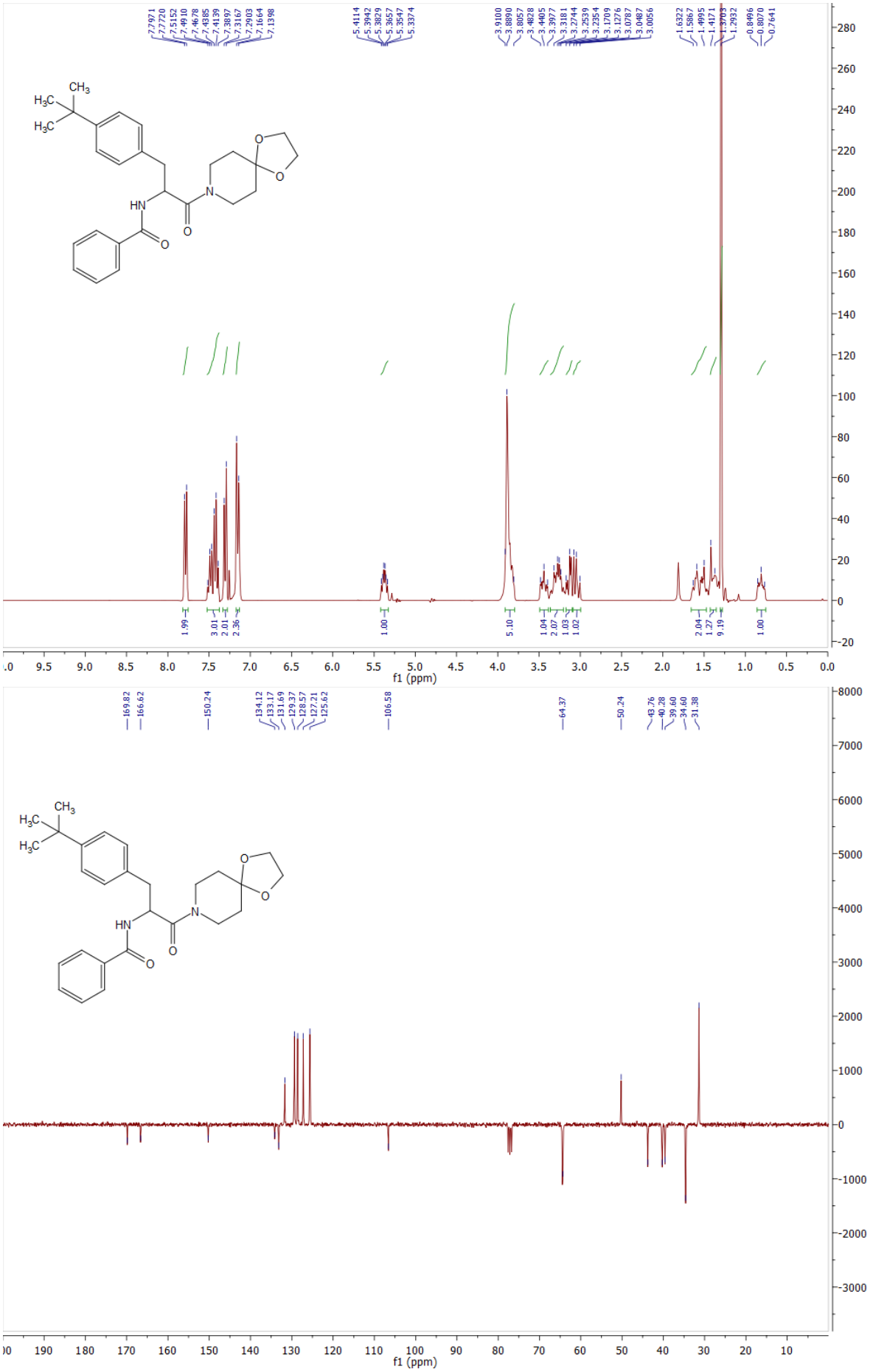


8h: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

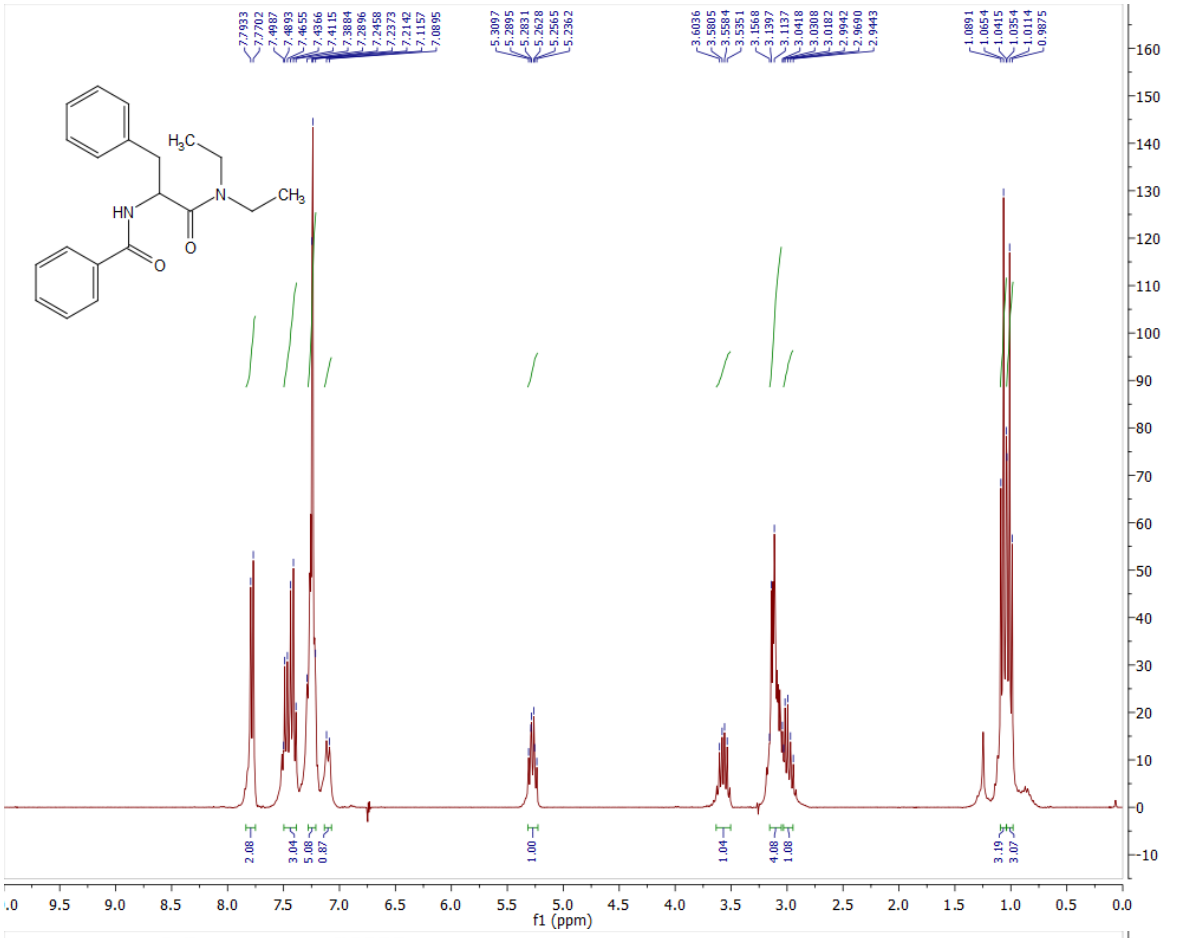


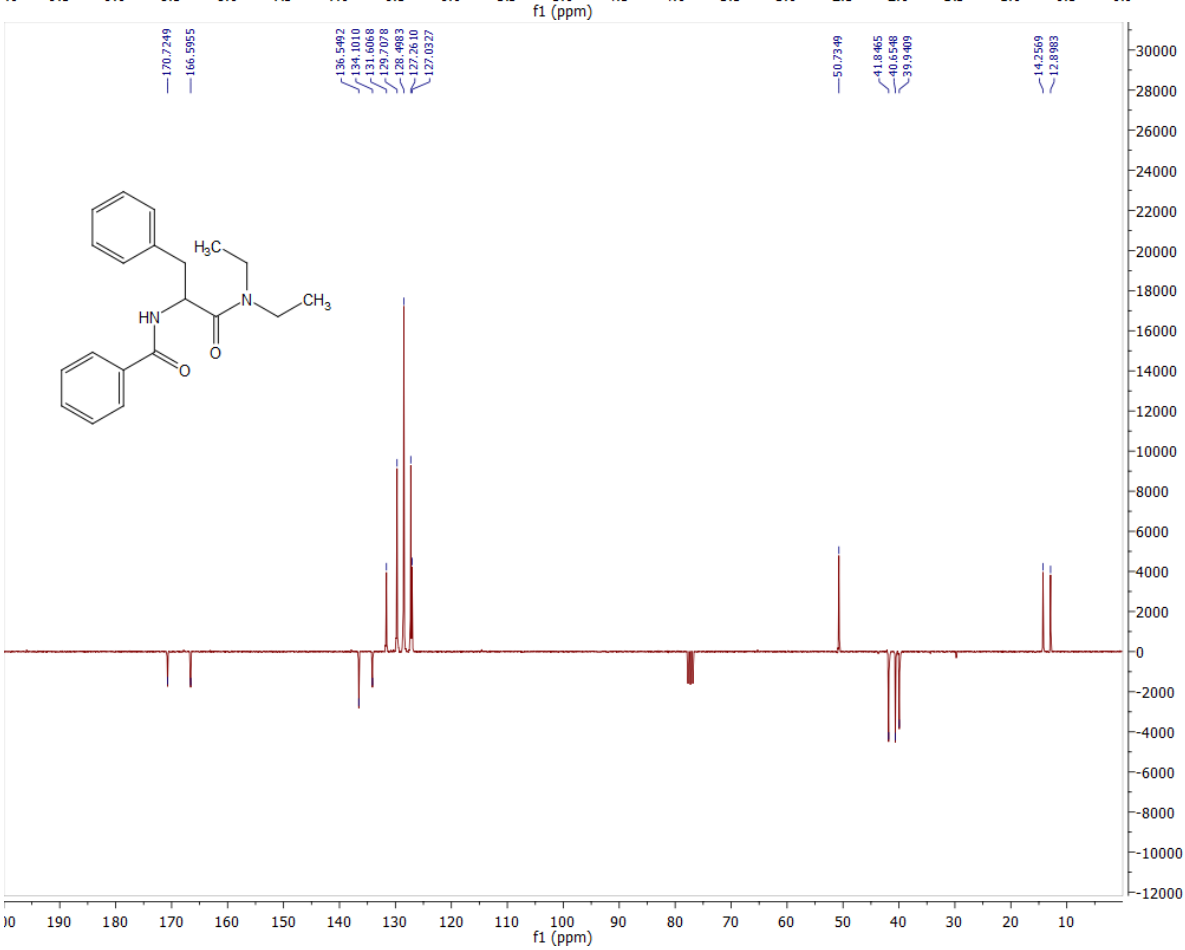


8i: ^{1}H ($CDCl_3$), APT ($CDCl_3$)

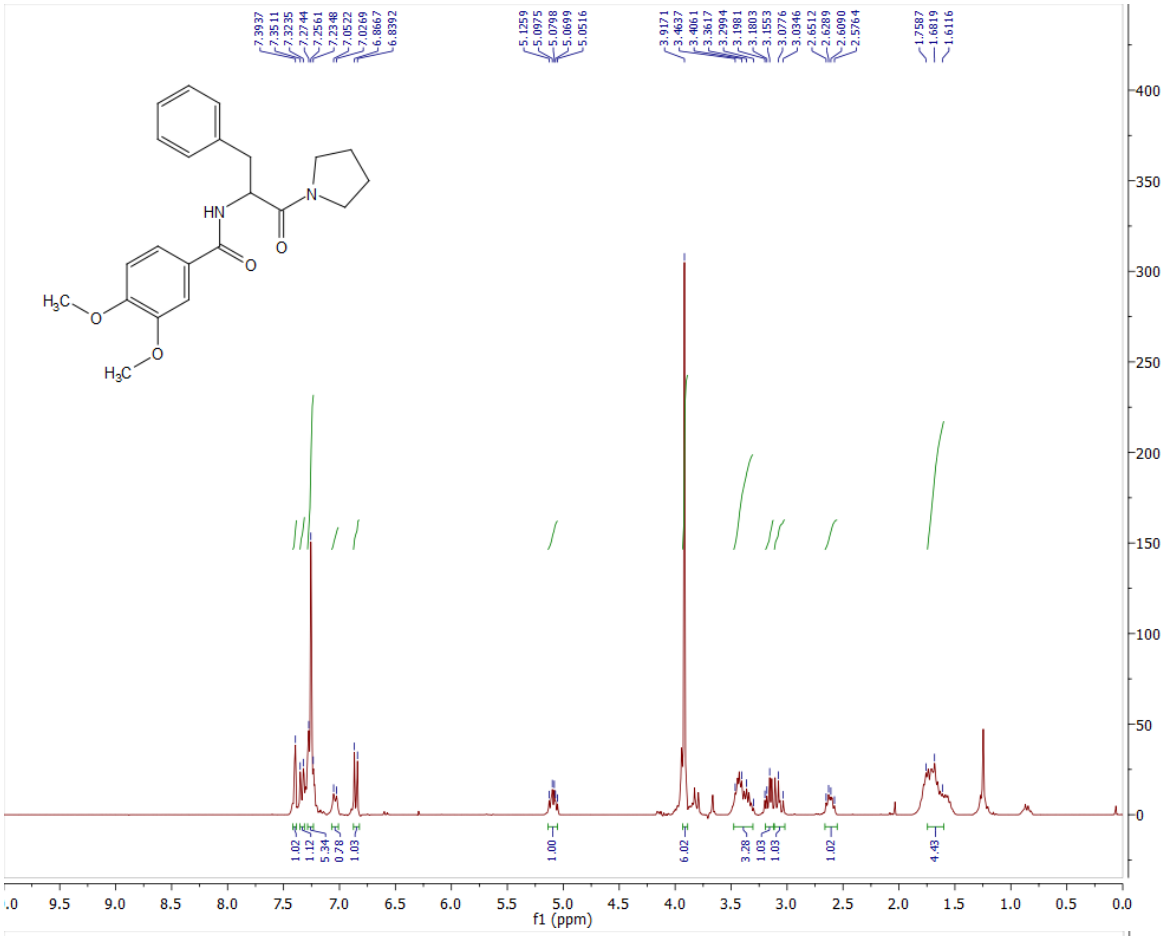


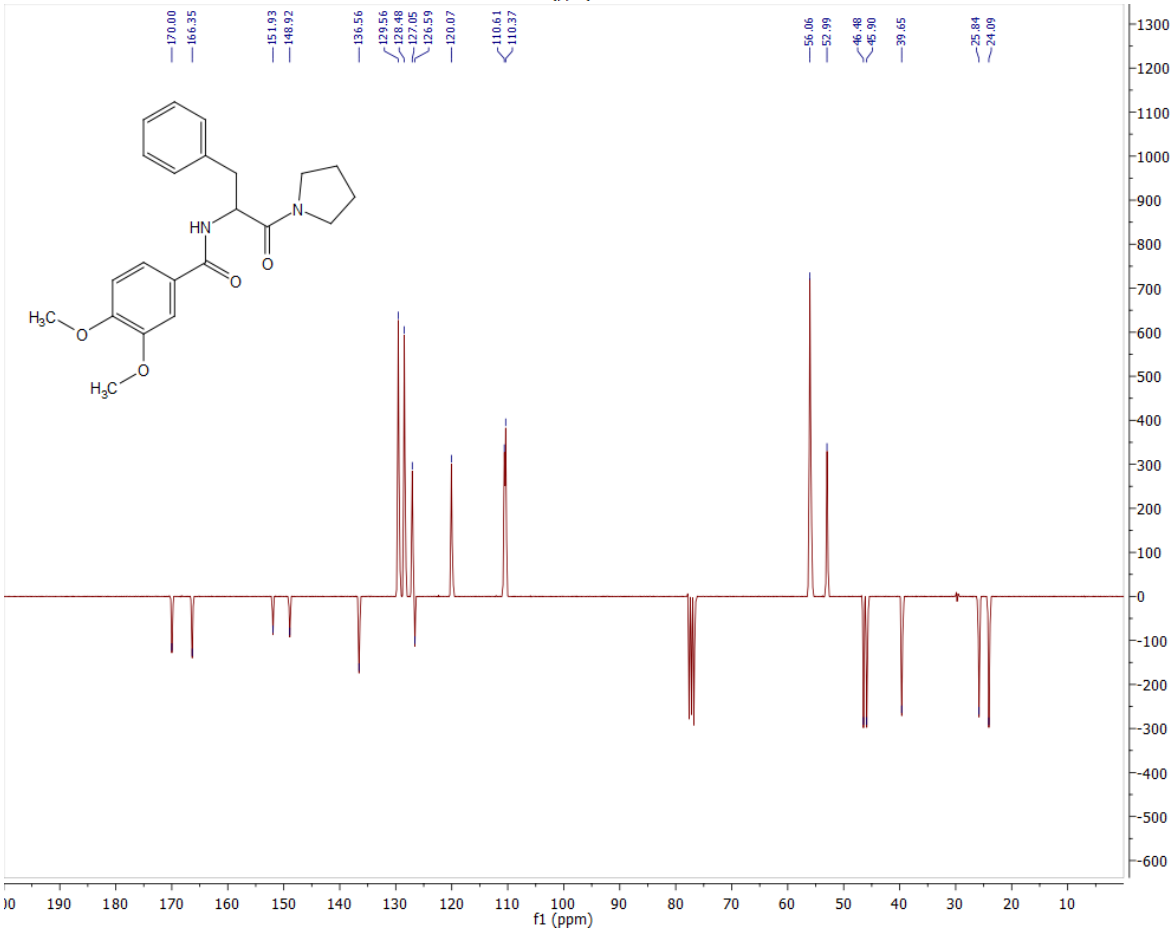
8j: ^{1}H ($CDCl_3$), APT ($CDCl_3$)



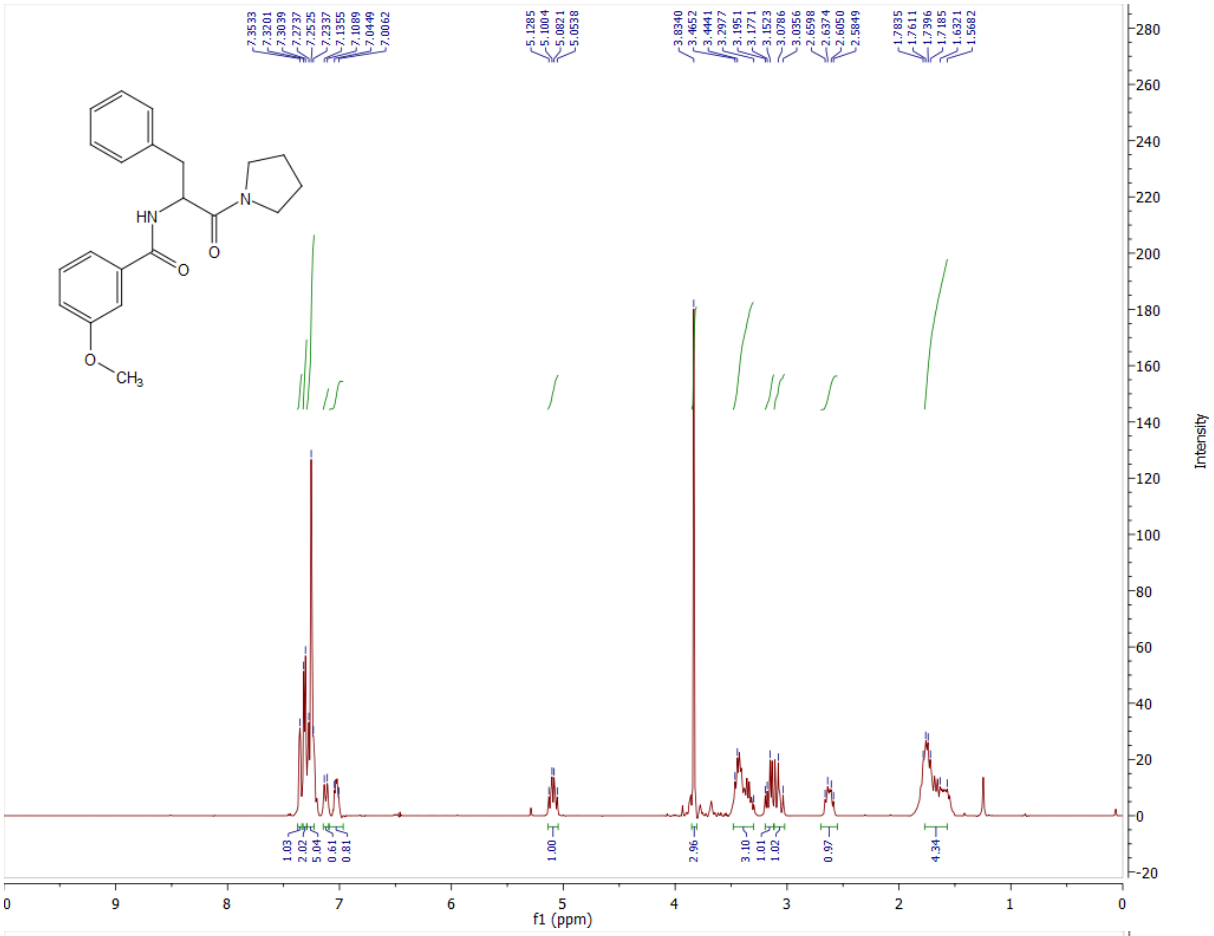


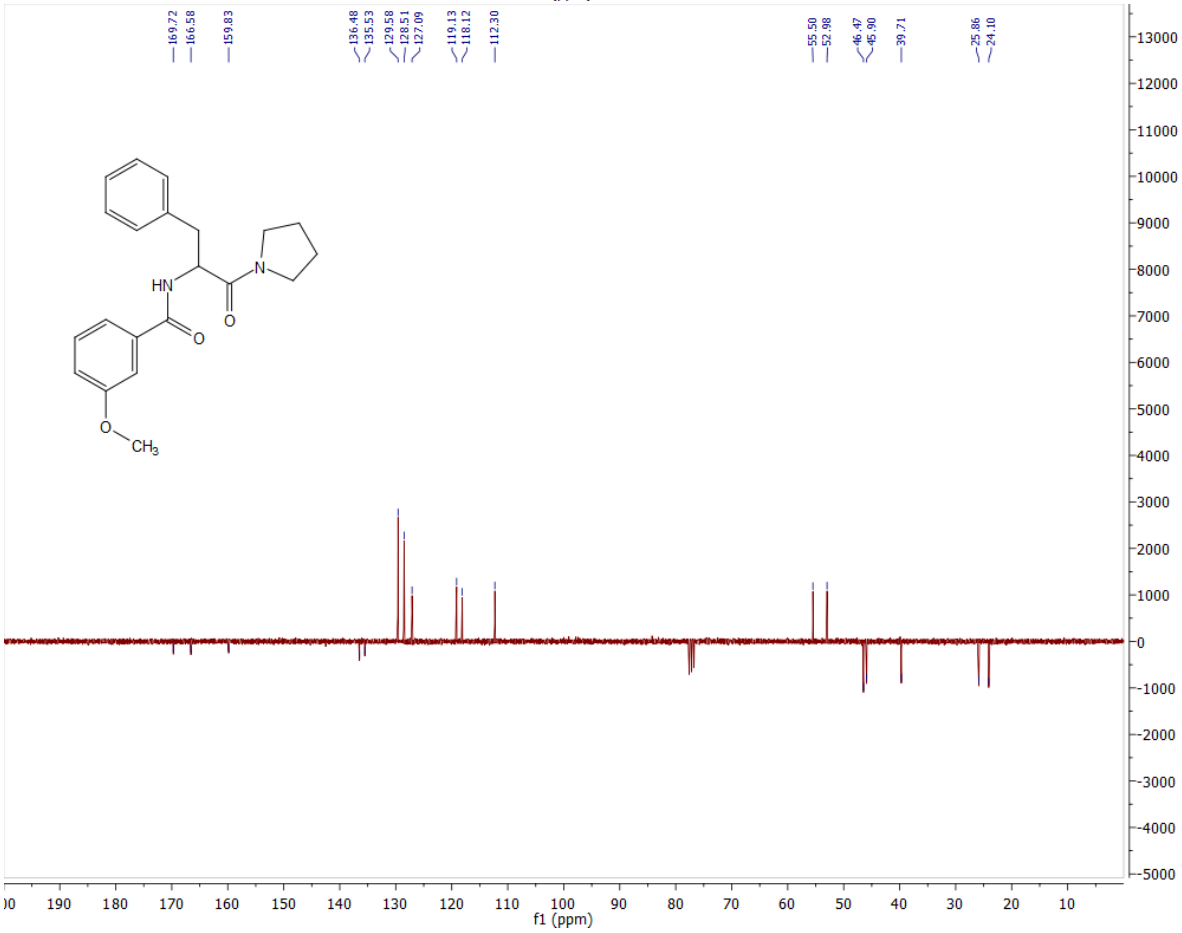
8k: ^{1}H ($CDCl_3$), APT ($CDCl_3$)



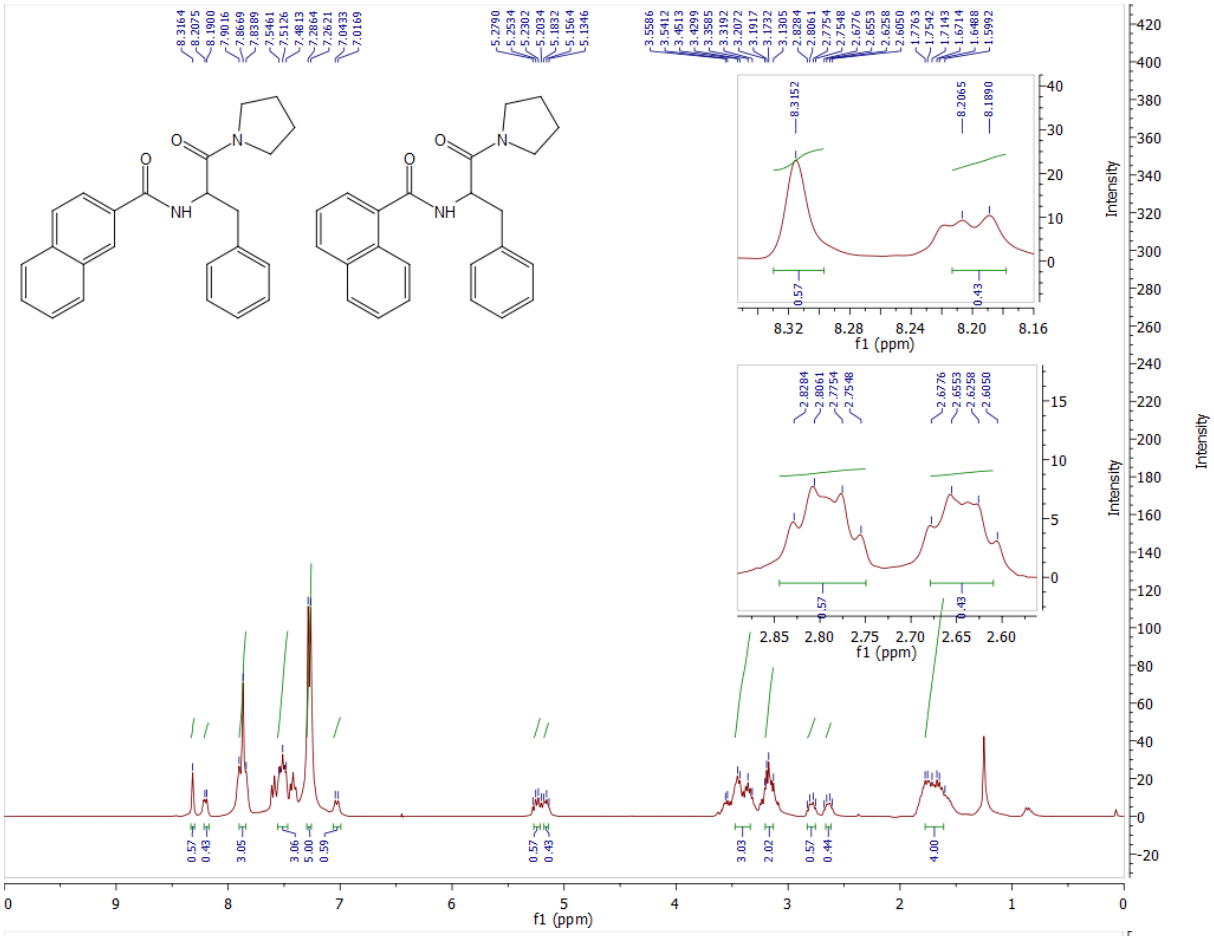


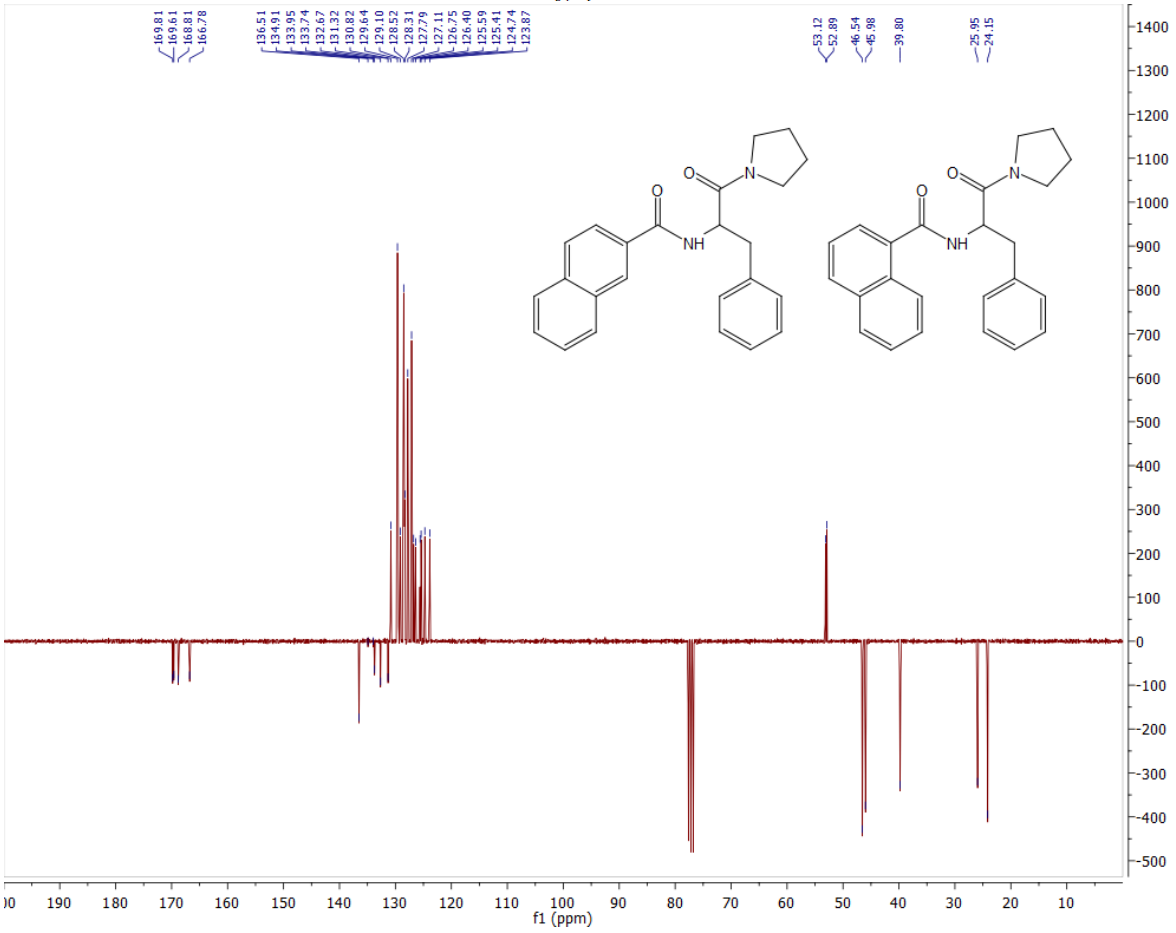
8l: ^{1}H ($CDCl_3$), APT ($CDCl_3$)



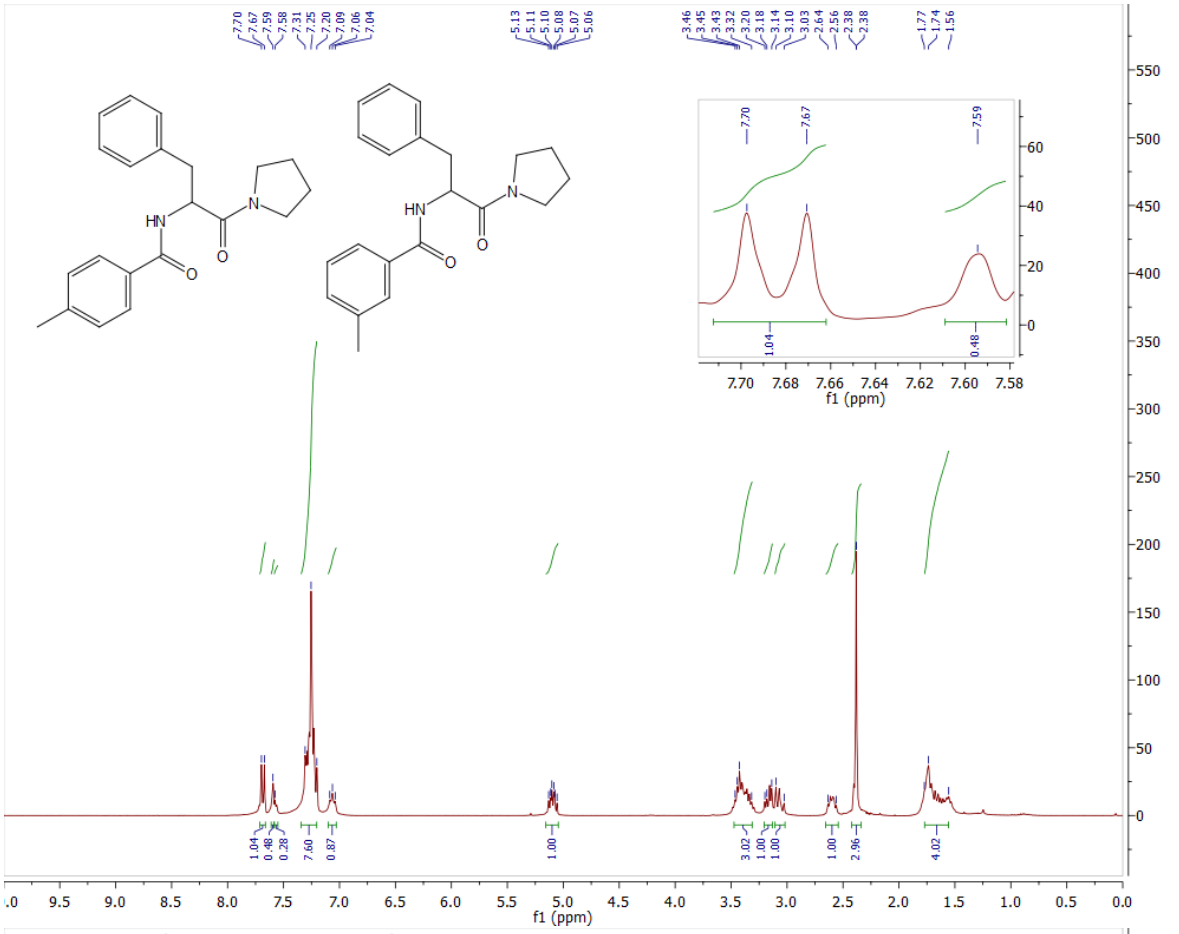


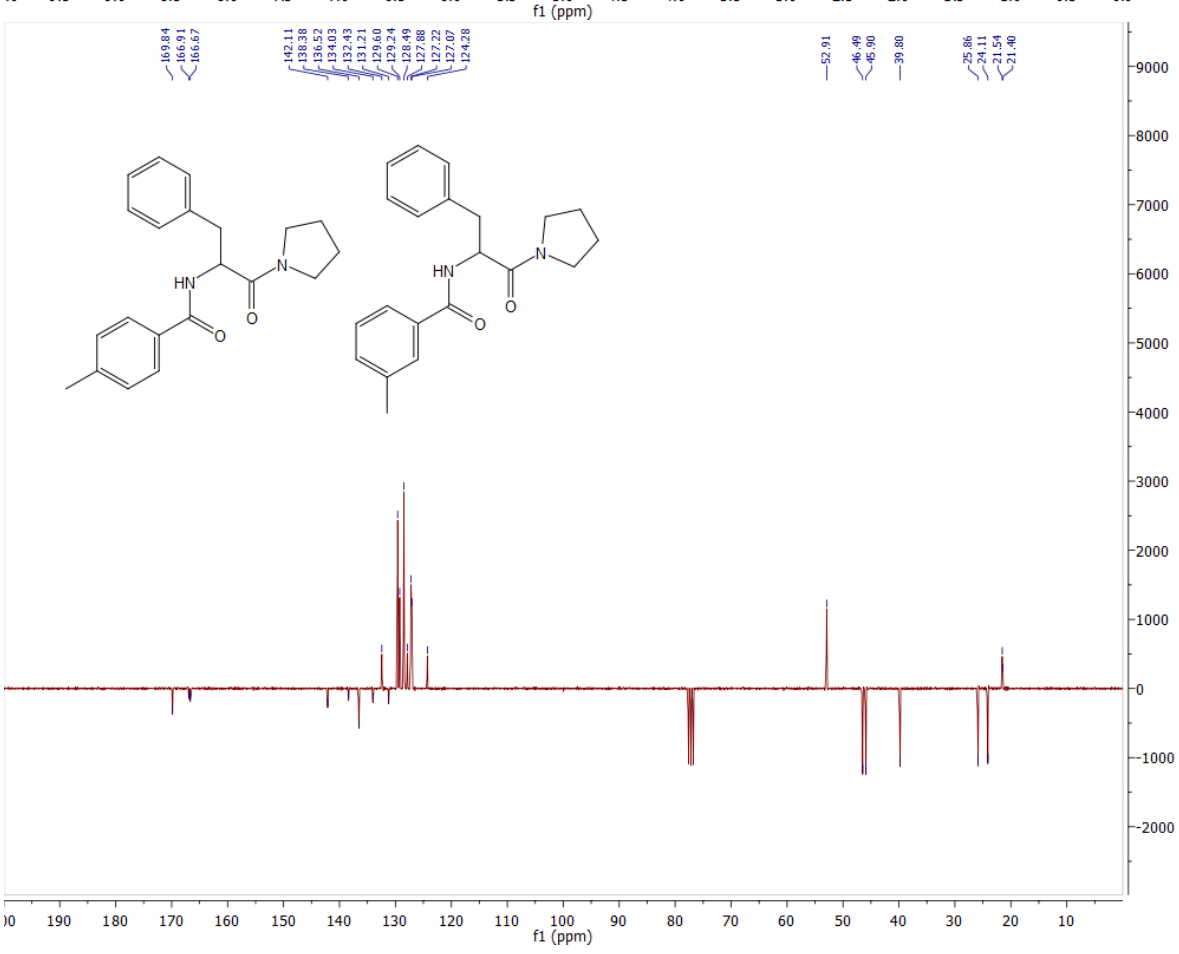
8m: ^{1}H ($CDCl_3$), APT ($CDCl_3$)





8n: ^{1}H ($CDCl_3$), APT ($CDCl_3$)





8o: ^{1}H (CD_3OD), APT (DMSO-d_6)