Solvent-free double aza-Michael under ultrasound irradiations: diastereoselective sequential one-pot scalable synthesis of pyrrolidine Lobelia alkaloids analogues

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Electronic supplementary information

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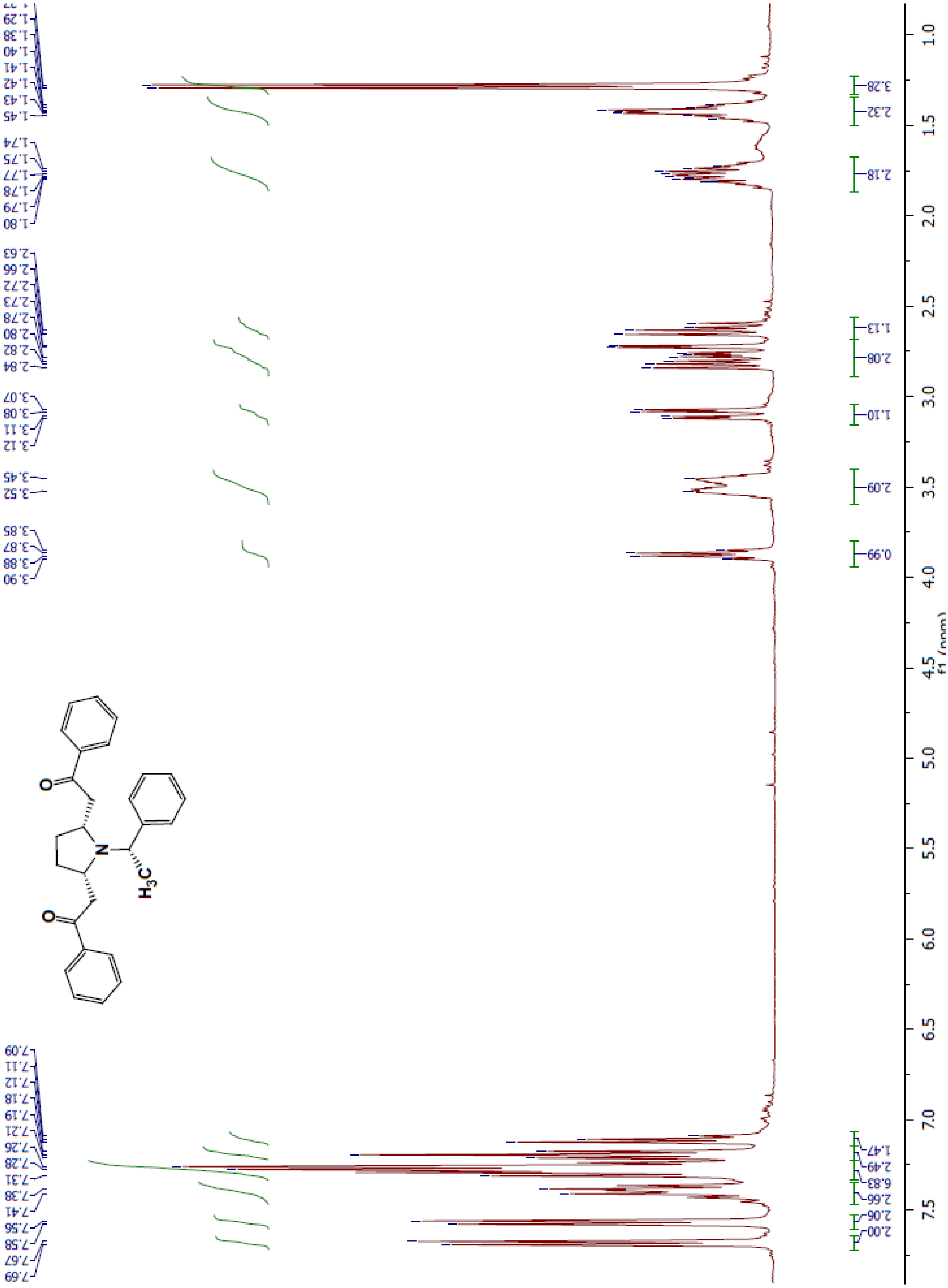
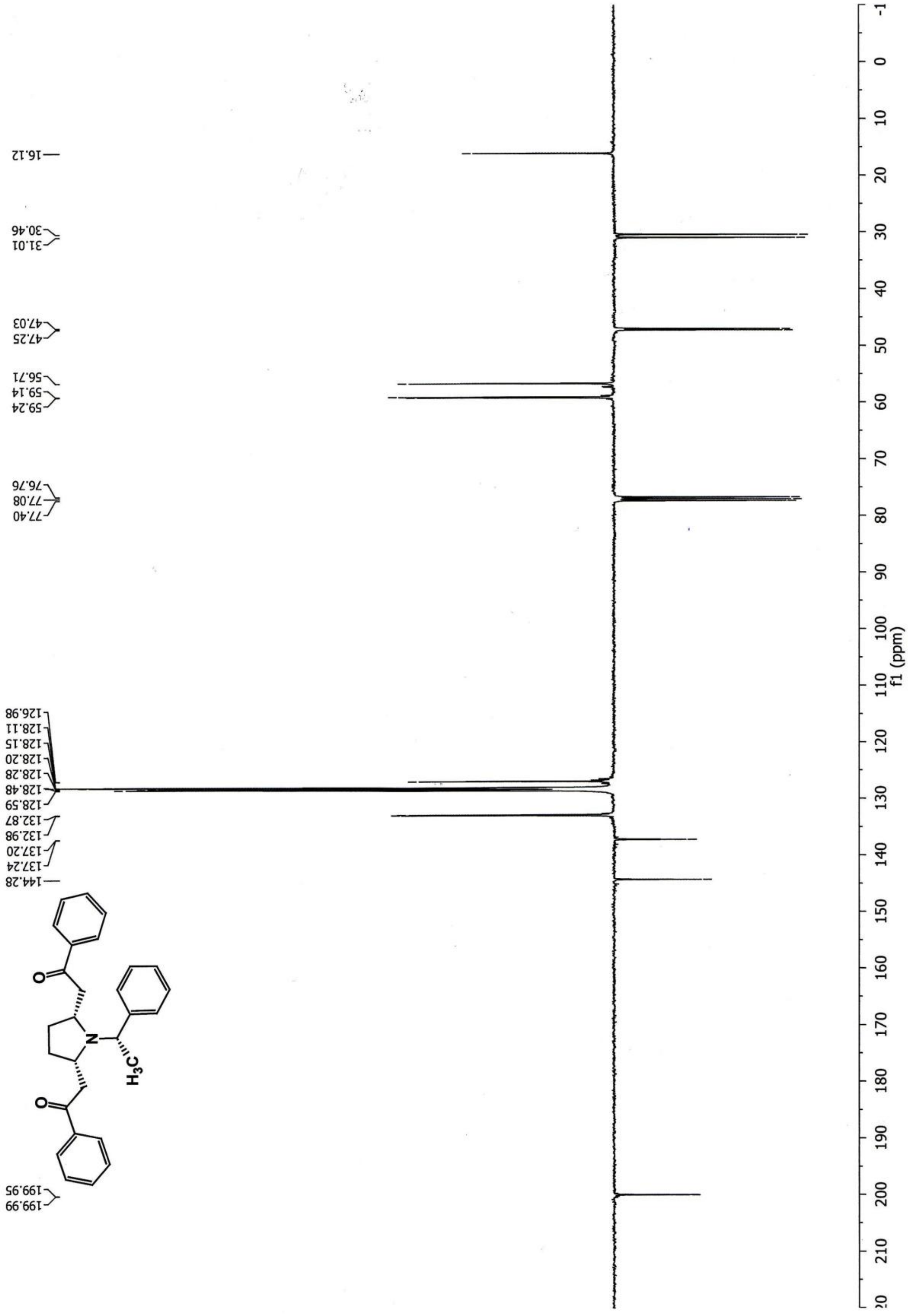
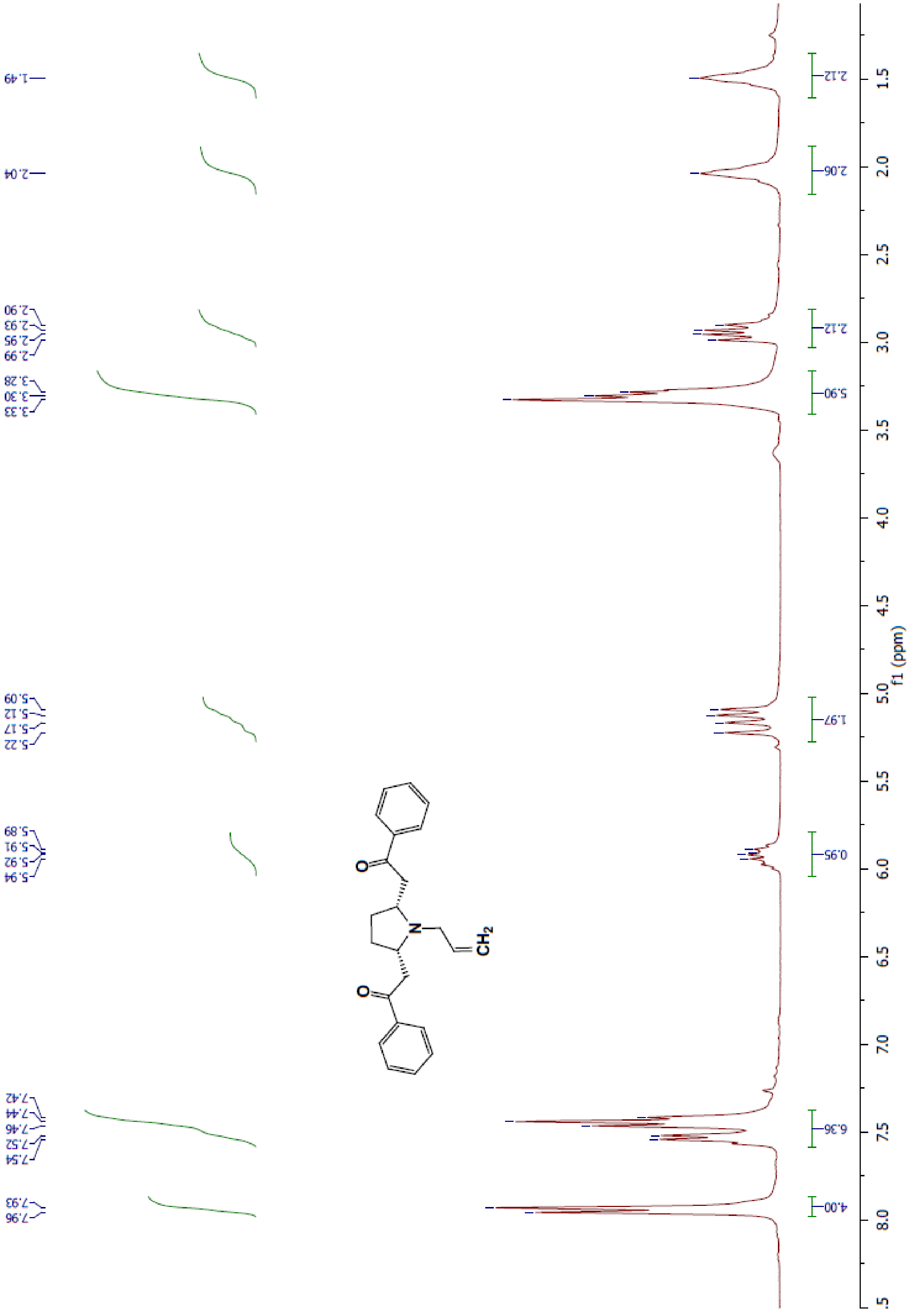
1. Copies of ^{1}H and ^{13}C NMR spectra

1.1 ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **13a**





1.2. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **13b**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2.93
2.95
2.99
3.28
3.30
3.33
5.09
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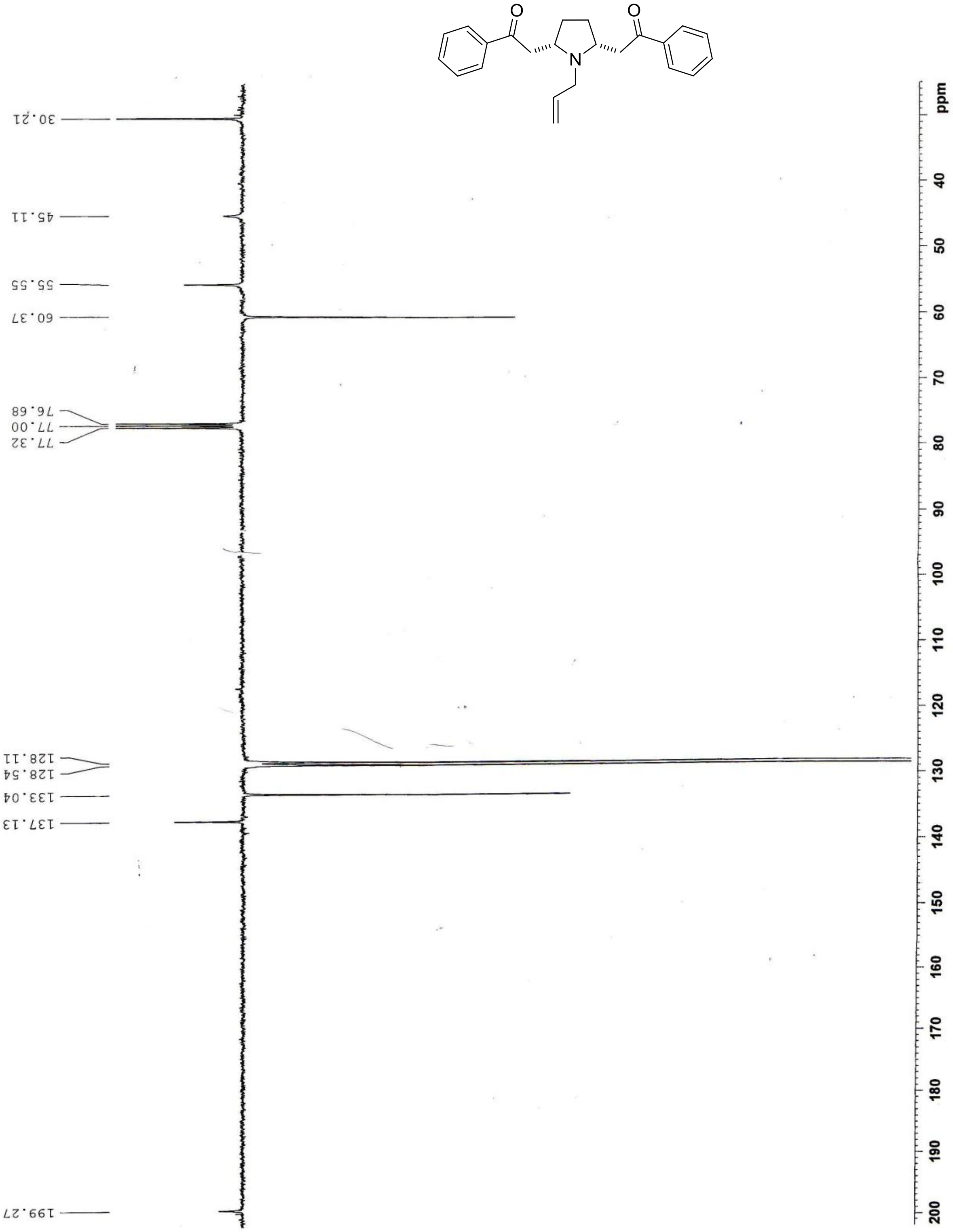
5.22
5.89
5.91
5.92
5.94
7.42
7.44
7.46
7.52
7.54
7.93
7.96
2.12
2.06
2.12
5.90
1.97
0.95
6.36
4.00
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
.5
f1 (ppm)
O
O
N
CH2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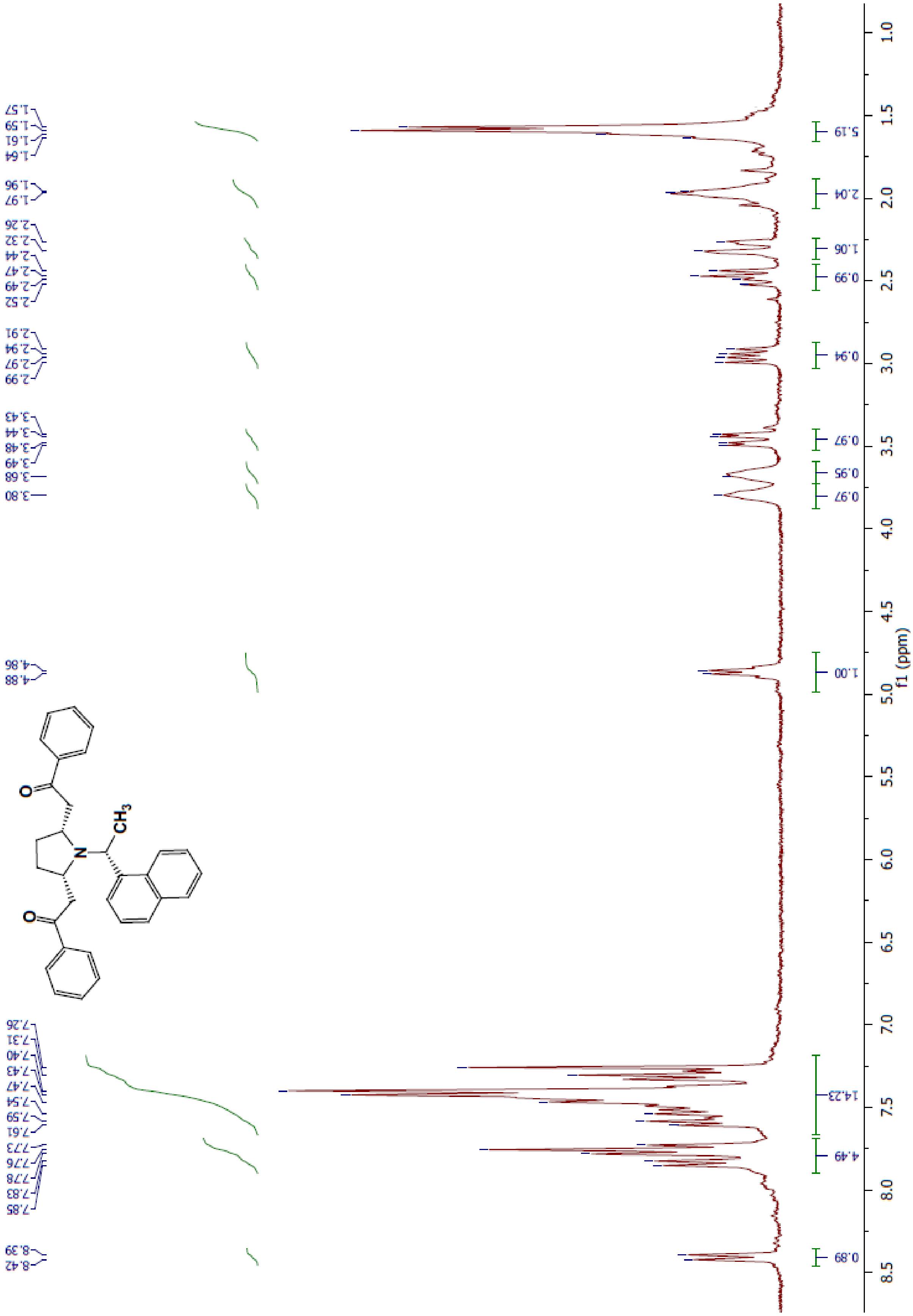
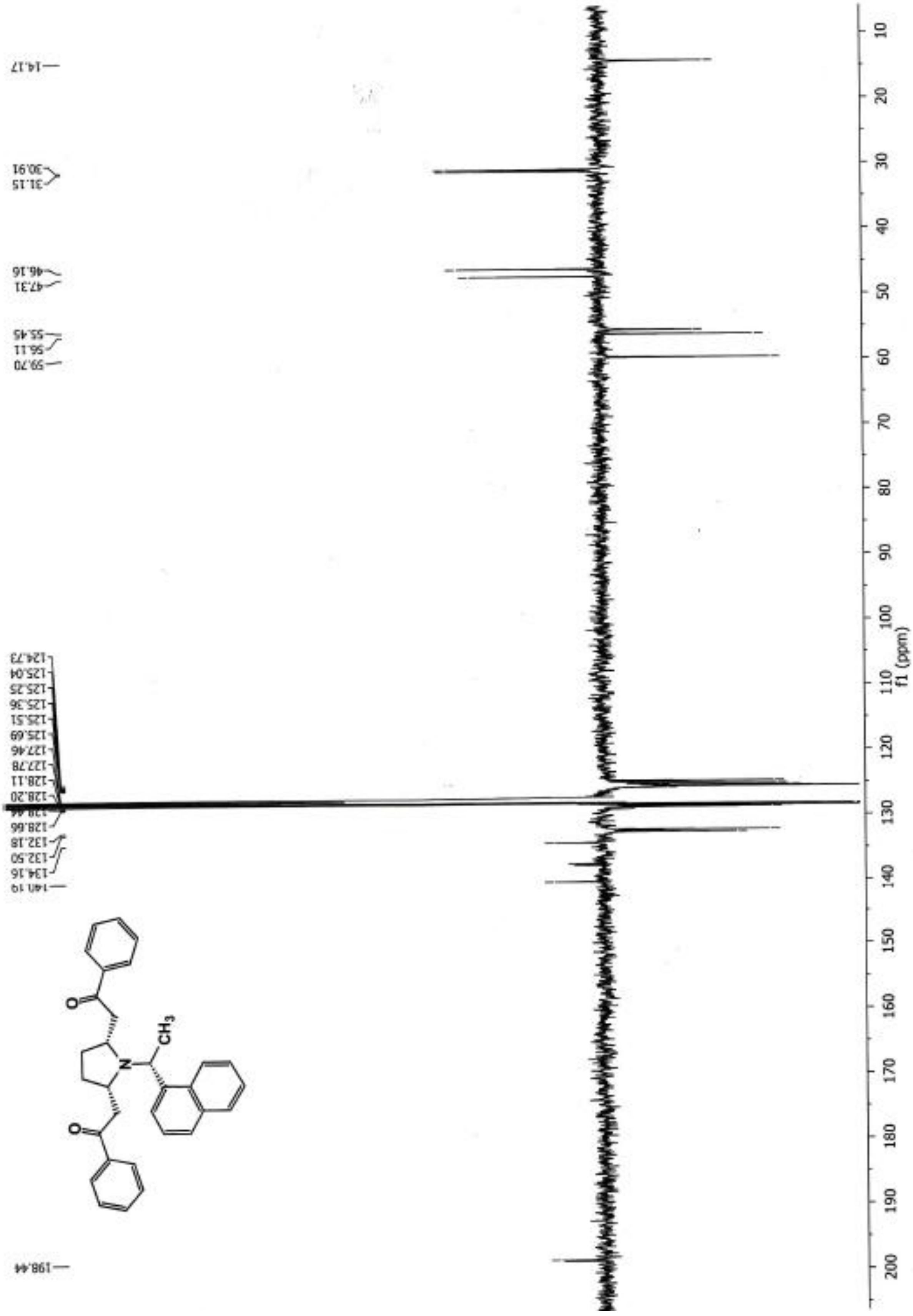
O
N
30.21
45.11
55.55
60.37
76.68
77.00
77.32
128.11
128.54
133.04
137.13
199.27
ppm
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200

1.3. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **13c**

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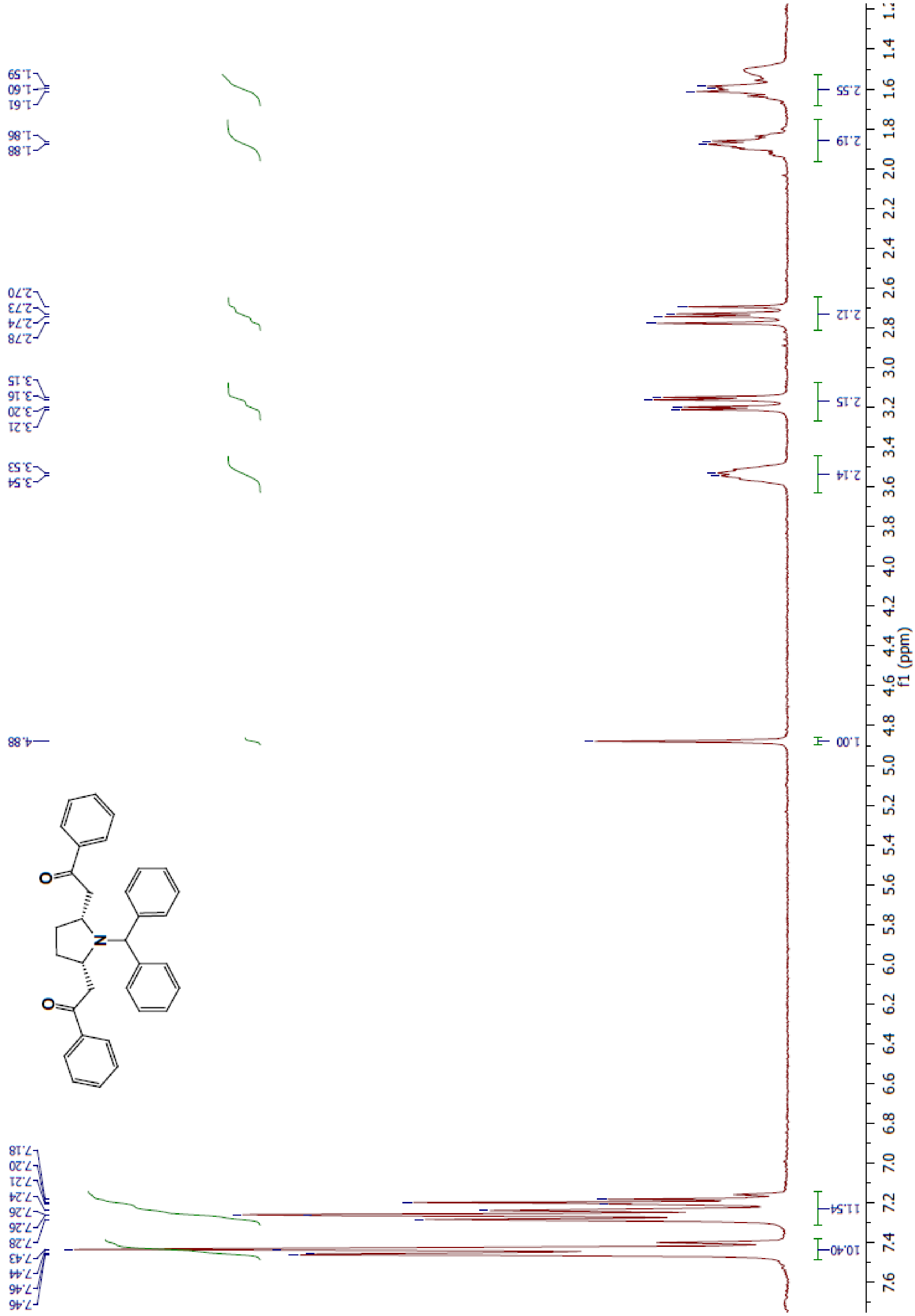
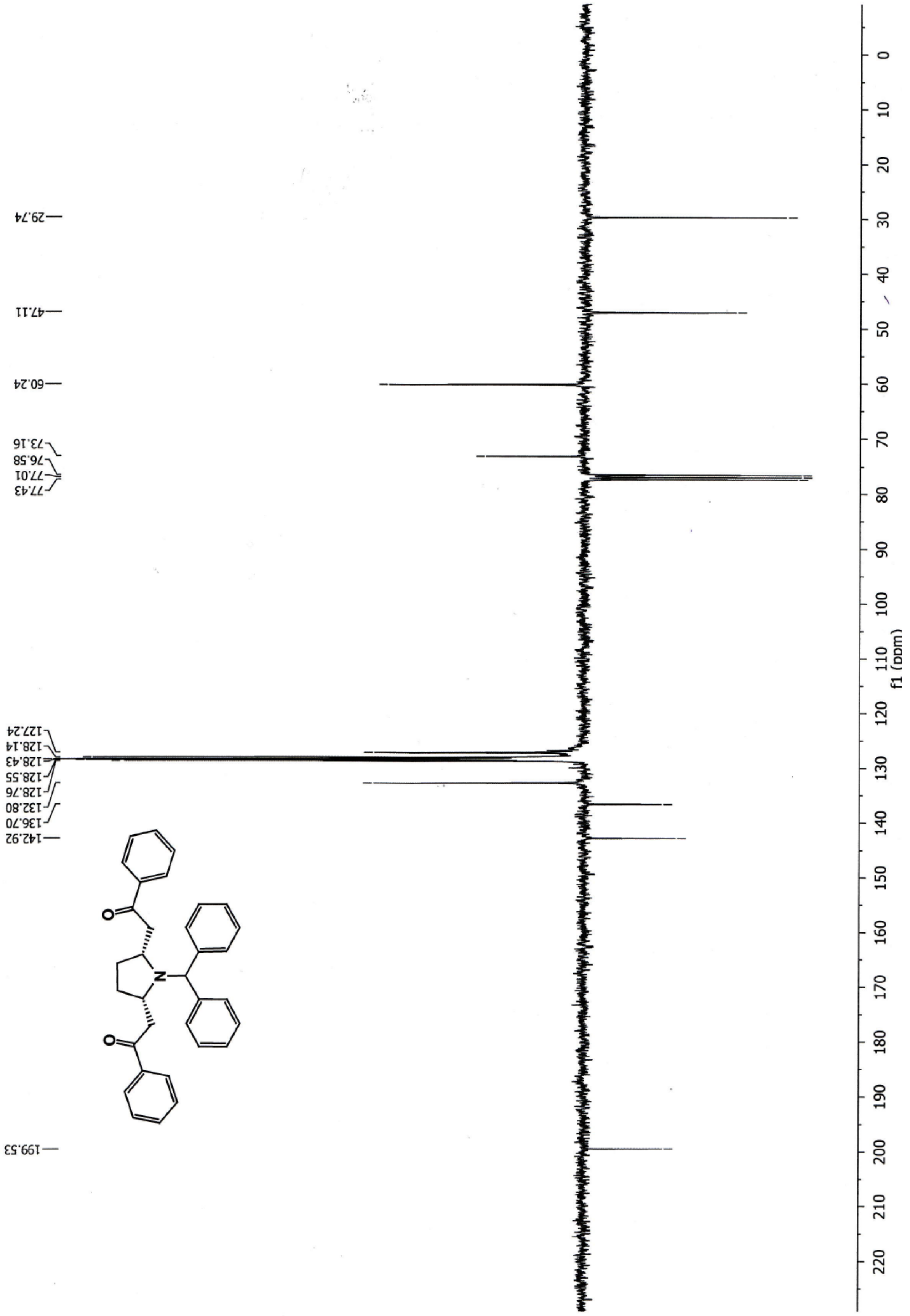
30.91
31.15
46.16
47.31
55.45
56.11
59.70
124.73
125.04
125.25
125.36
125.51
125.69
127.46
127.78
128.11
128.20
128.44
128.66
132.18
132.50
134.16
140.19
198.44
O
O
N
CH3
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

1.4. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **13d**

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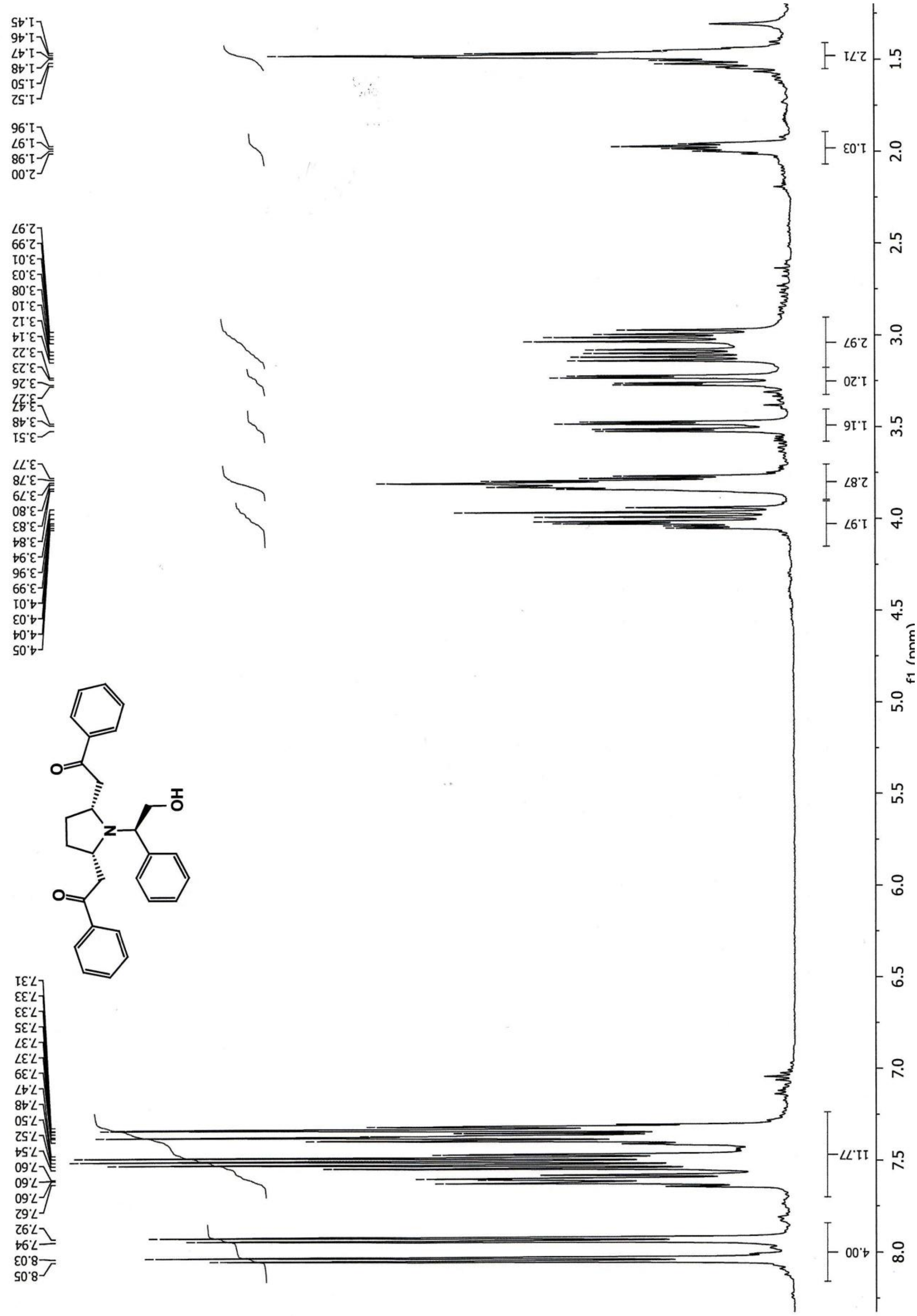
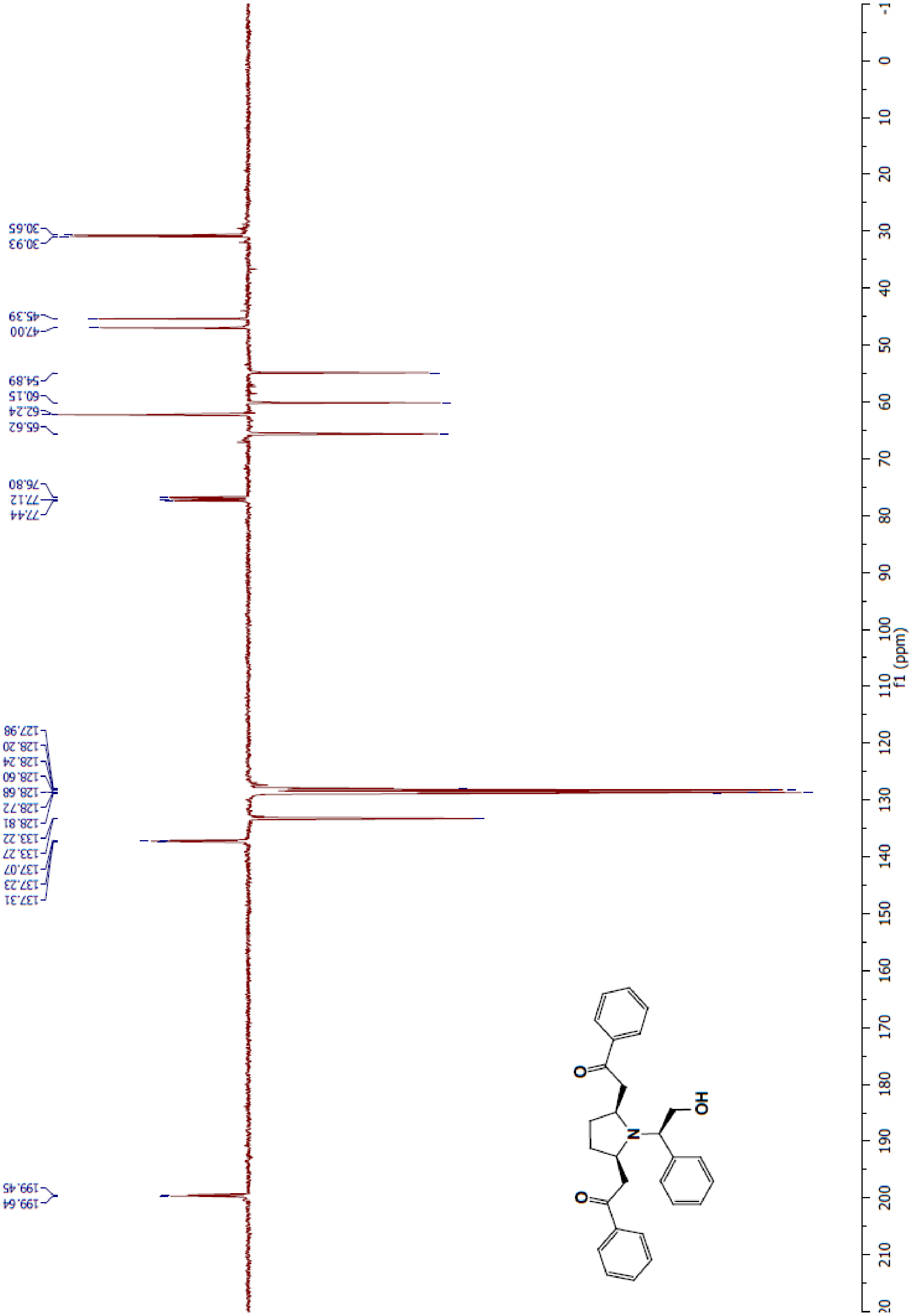
60.24
73.16
76.58
77.01
77.43
127.24
128.14
128.43
128.55
128.76
132.80
136.70
142.92
199.53
O
N
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

1.5. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **13e**

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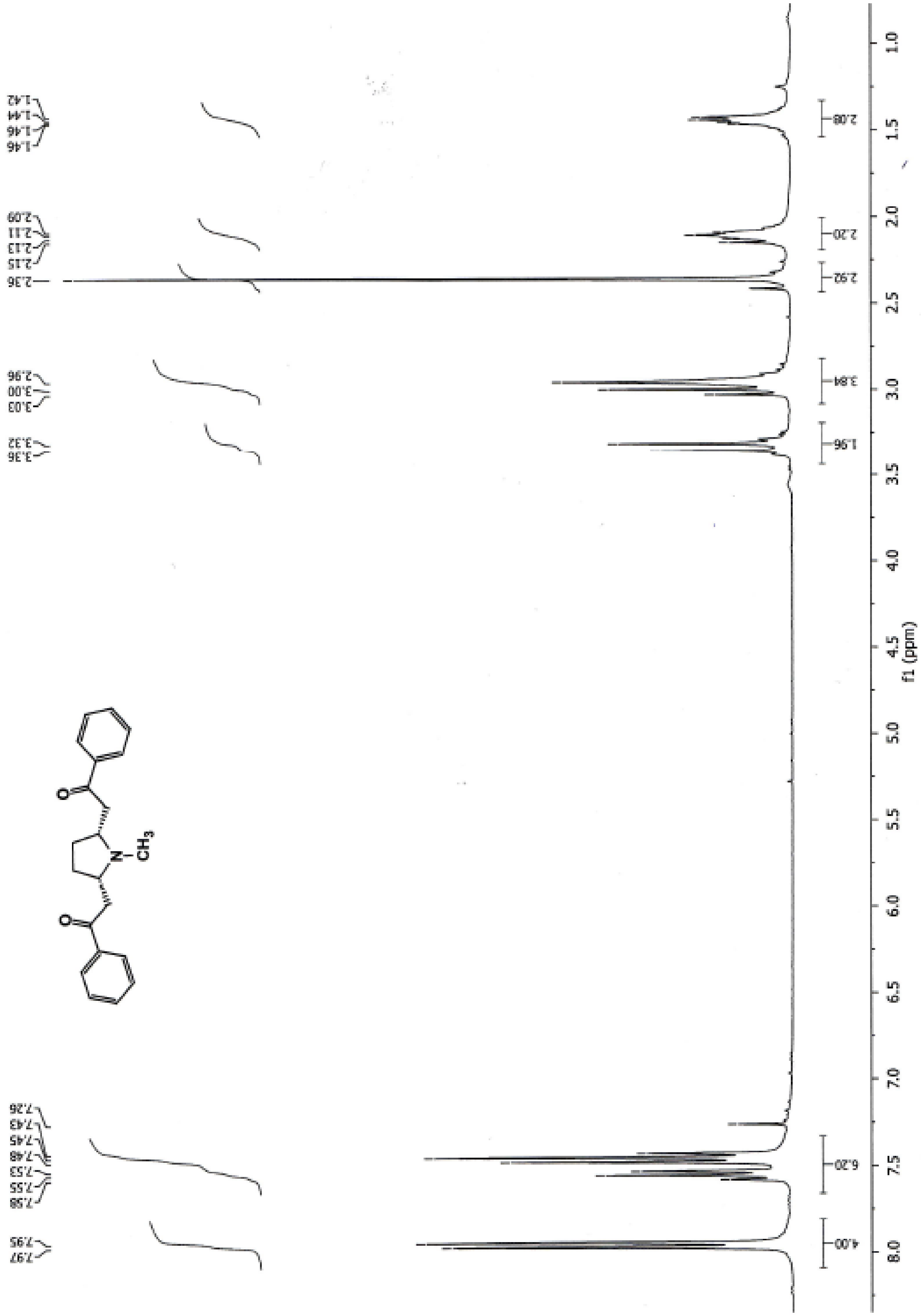
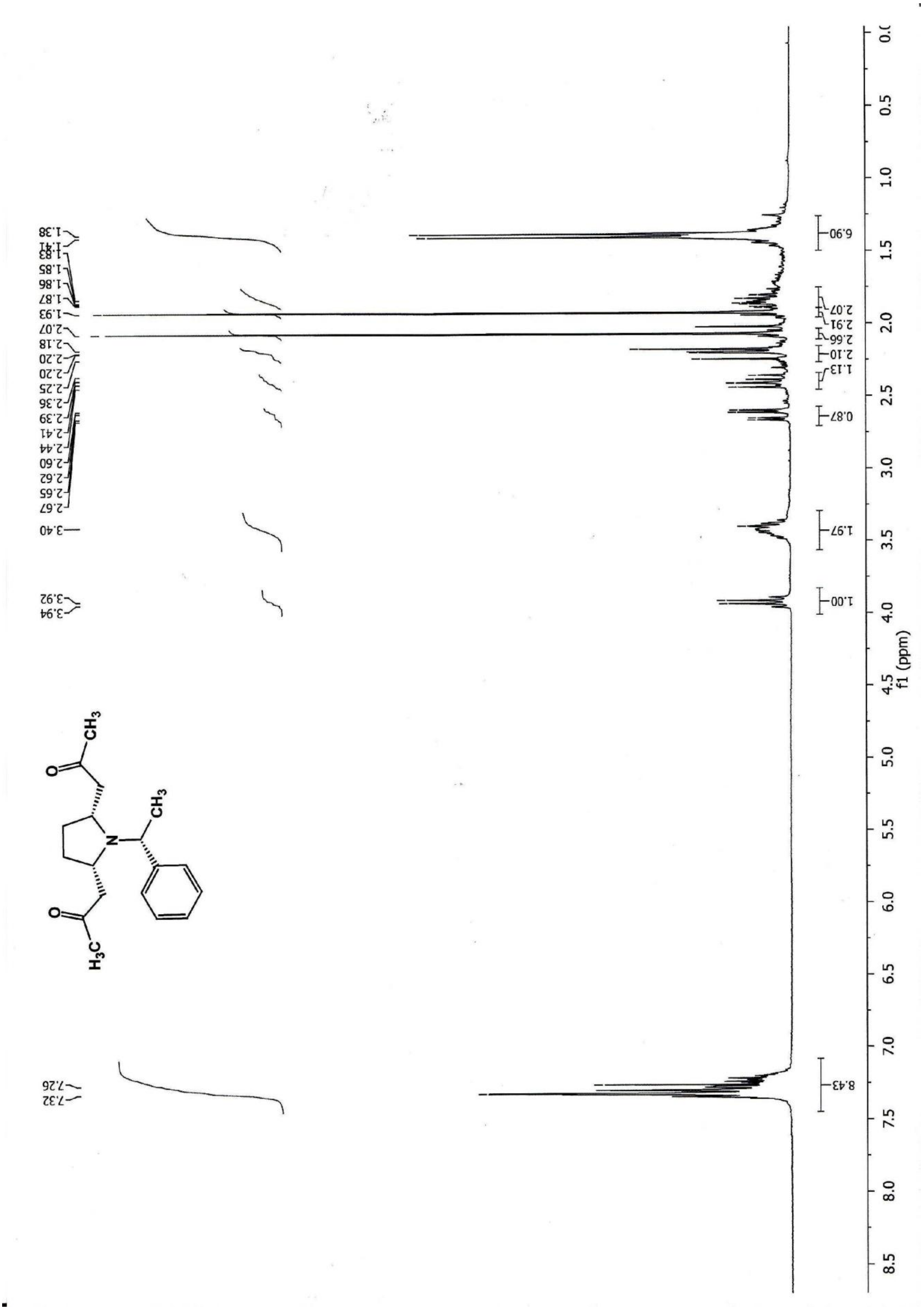
30.93
45.39
47.00
54.89
60.15
62.24
65.62
76.80
77.12
77.44
127.98
128.20
128.24
128.60
128.68
128.72
128.81
133.22
133.27
137.07
137.23
137.31
199.45
199.64
O
N
OH
O
-1
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

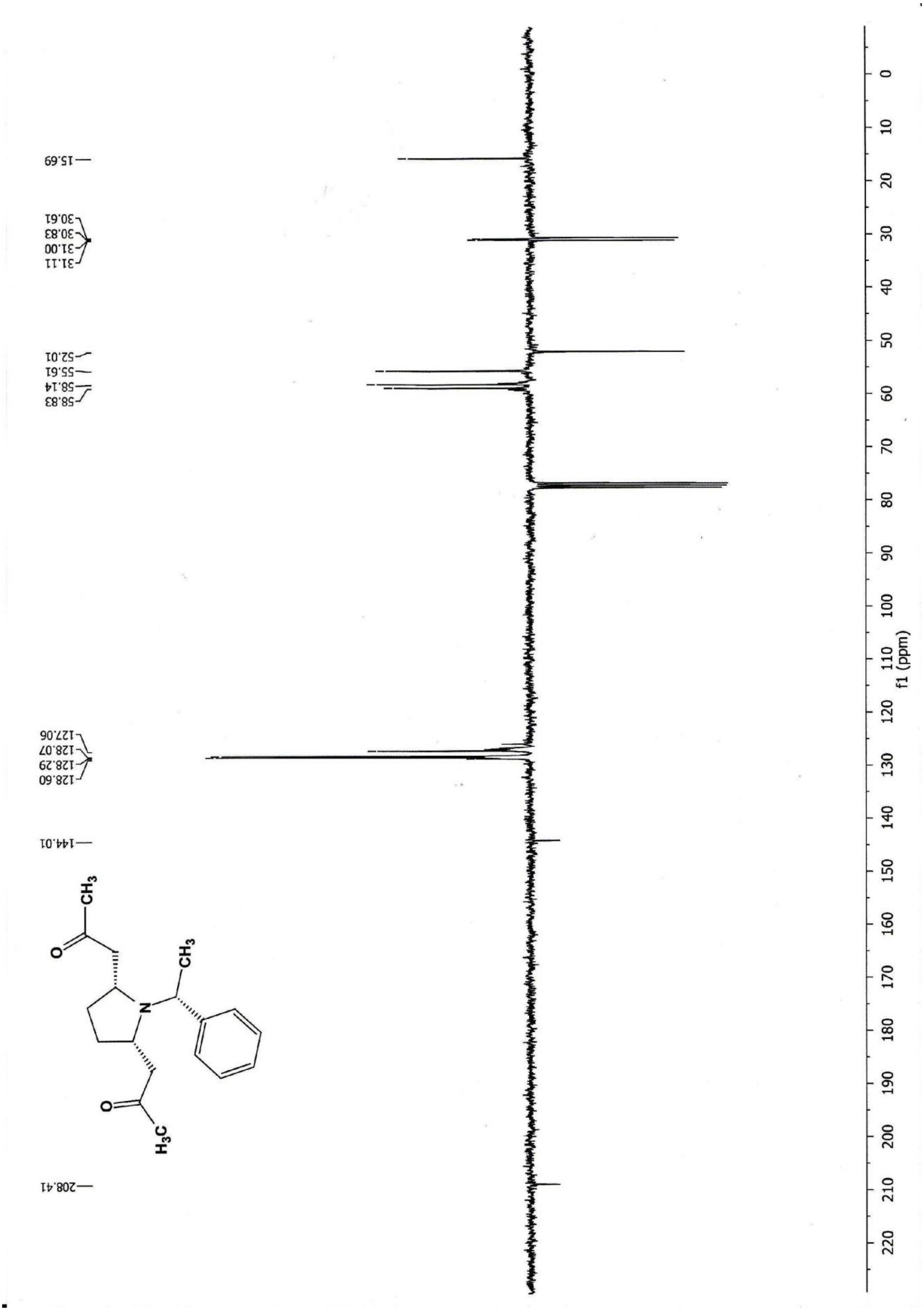
1.6. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **13f**



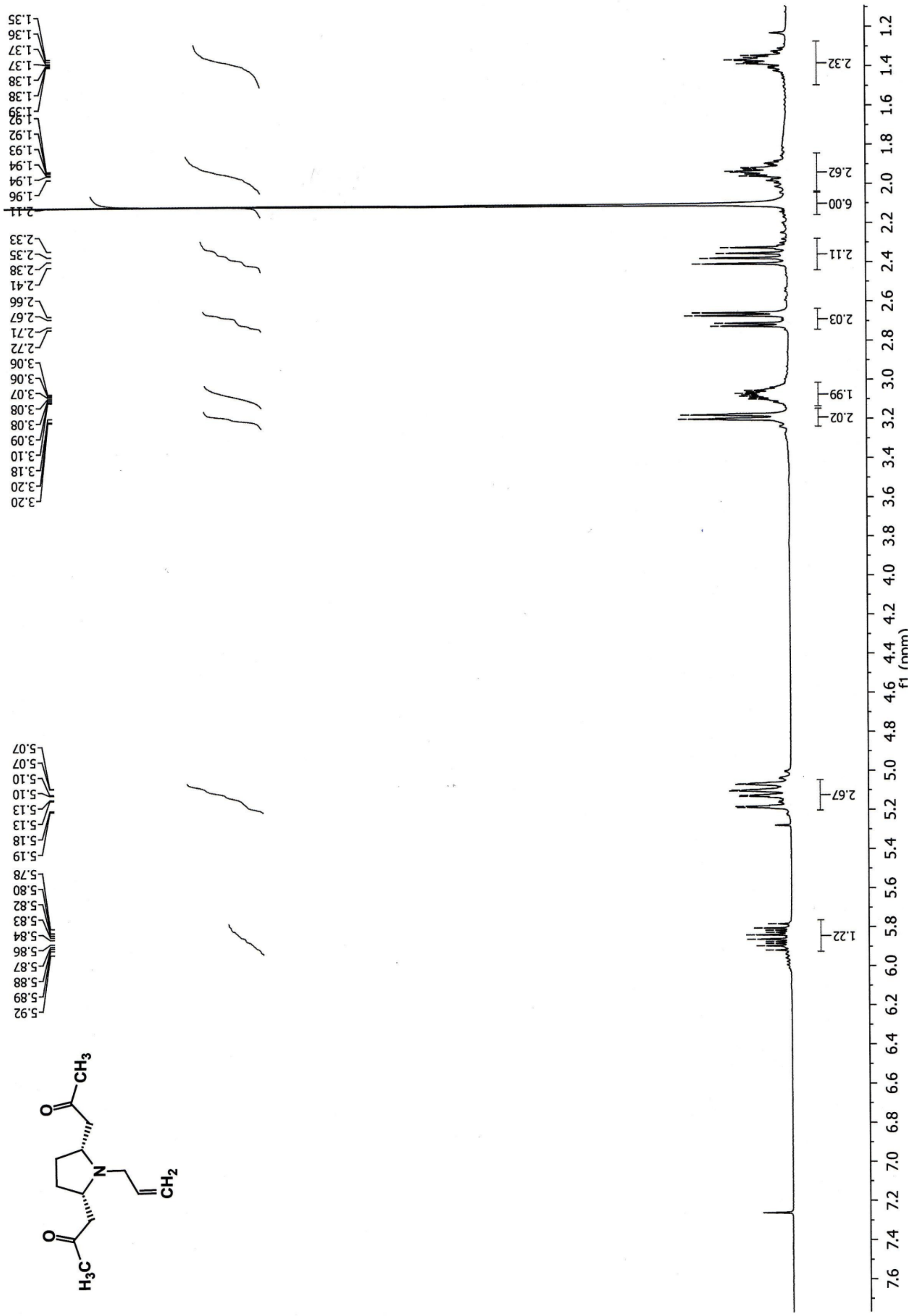

29.91
39.31
44.20
63.00
76.60
77.02
77.45
128.04
128.58
133.05
137.19
199.16
O
N
CH3
O
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

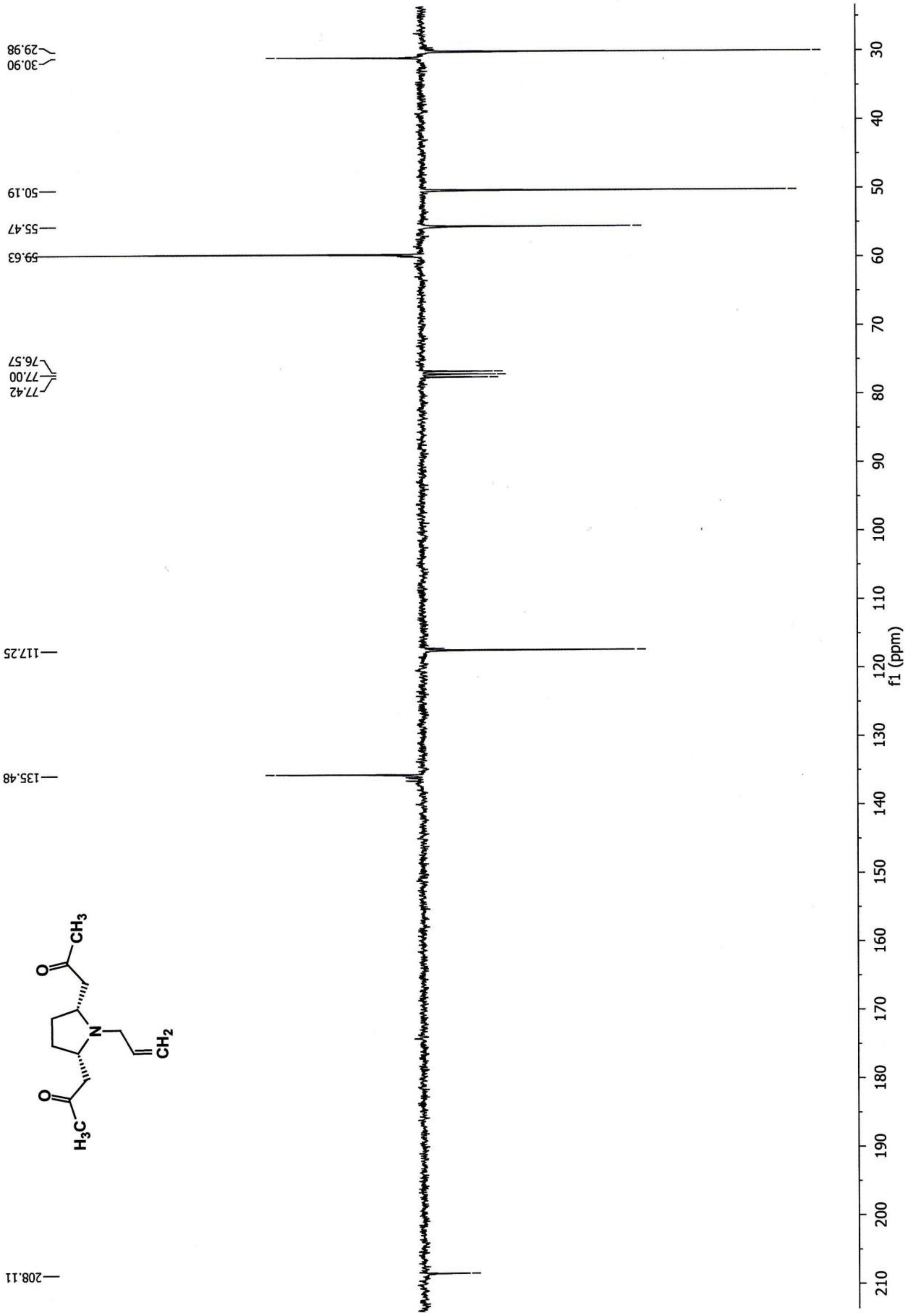
1.7. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **15a**



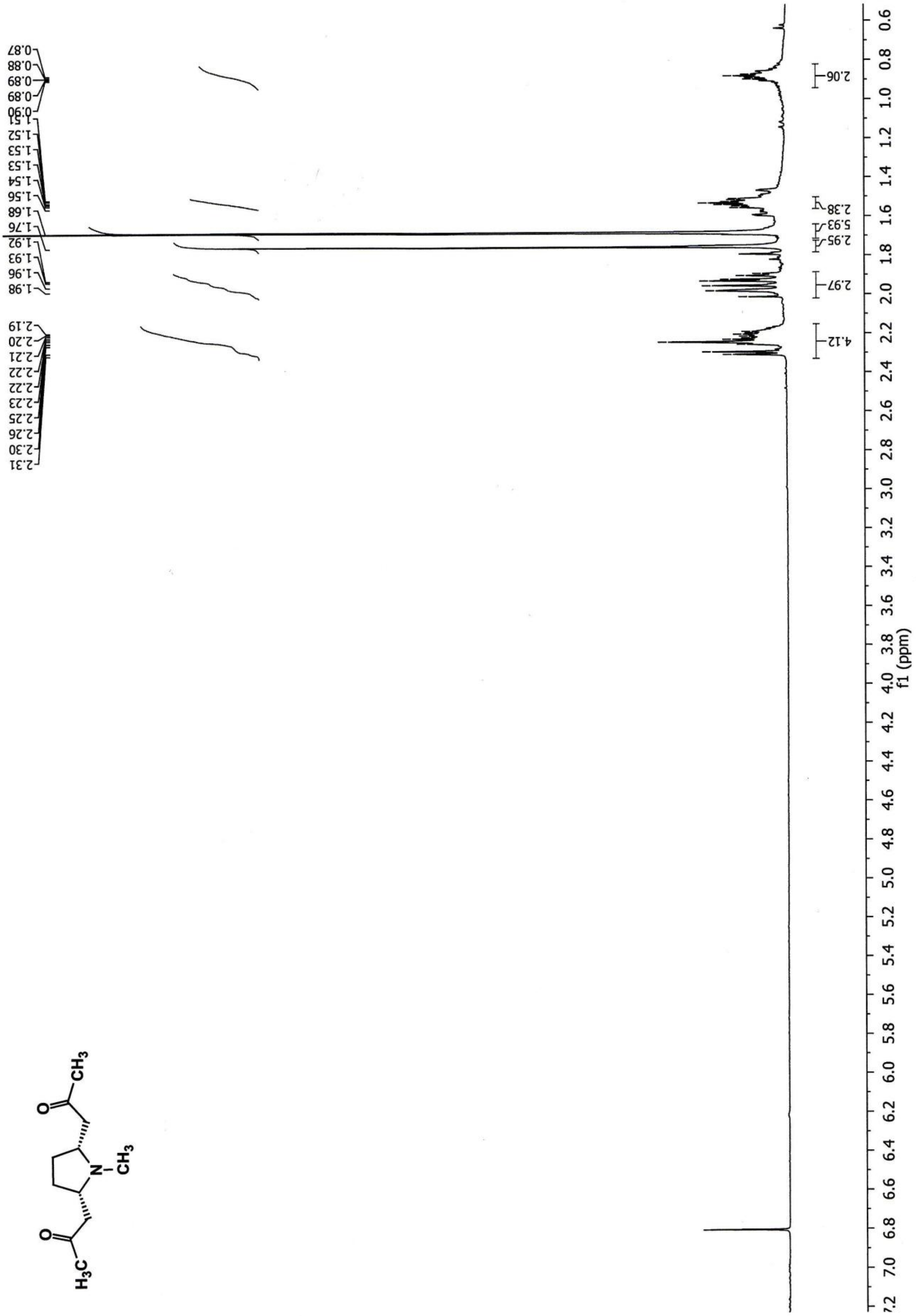

15.69
30.61
30.83
31.00
31.11
52.01
55.61
58.14
58.83
127.06
128.07
128.29
128.60
144.01
208.41
O
CH3
N
CH3
O
H3C
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
f1 (ppm)

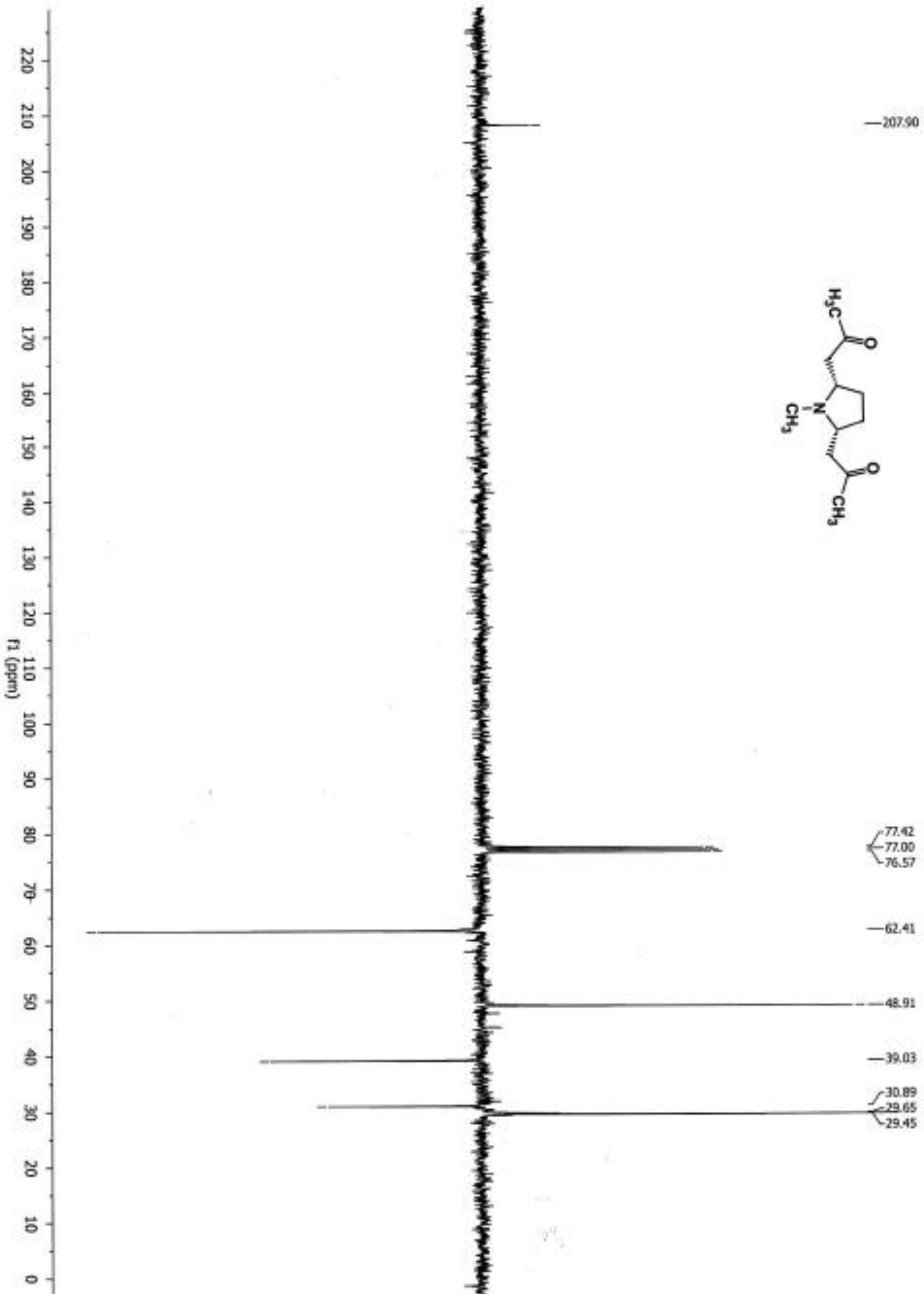
1.8. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **15b**



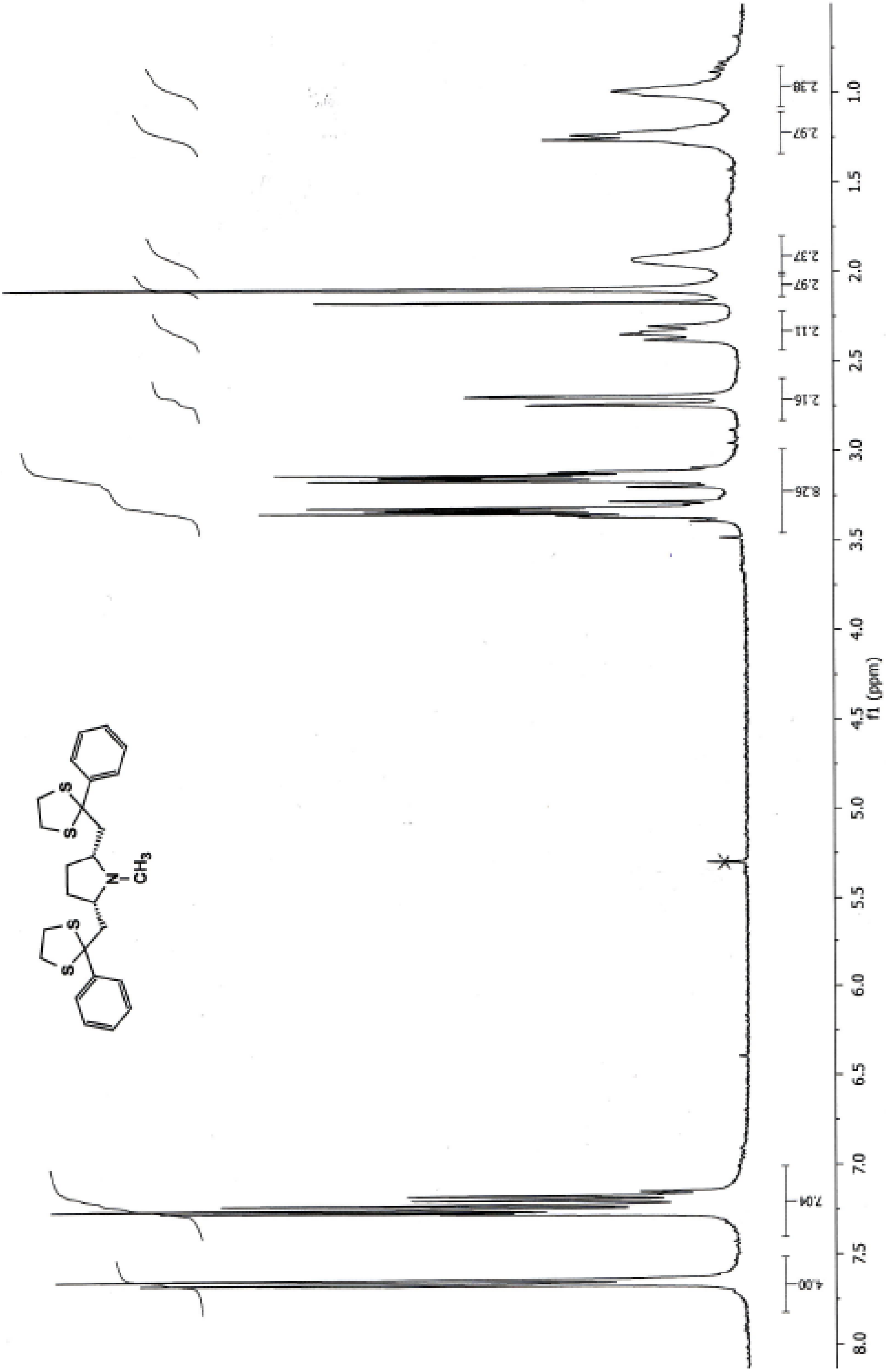

29.98
30.90
50.19
55.47
59.63
76.57
77.00
77.42
117.25
135.48
208.11
CH3
O
N
CH2
O
H3C
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
f1 (ppm)

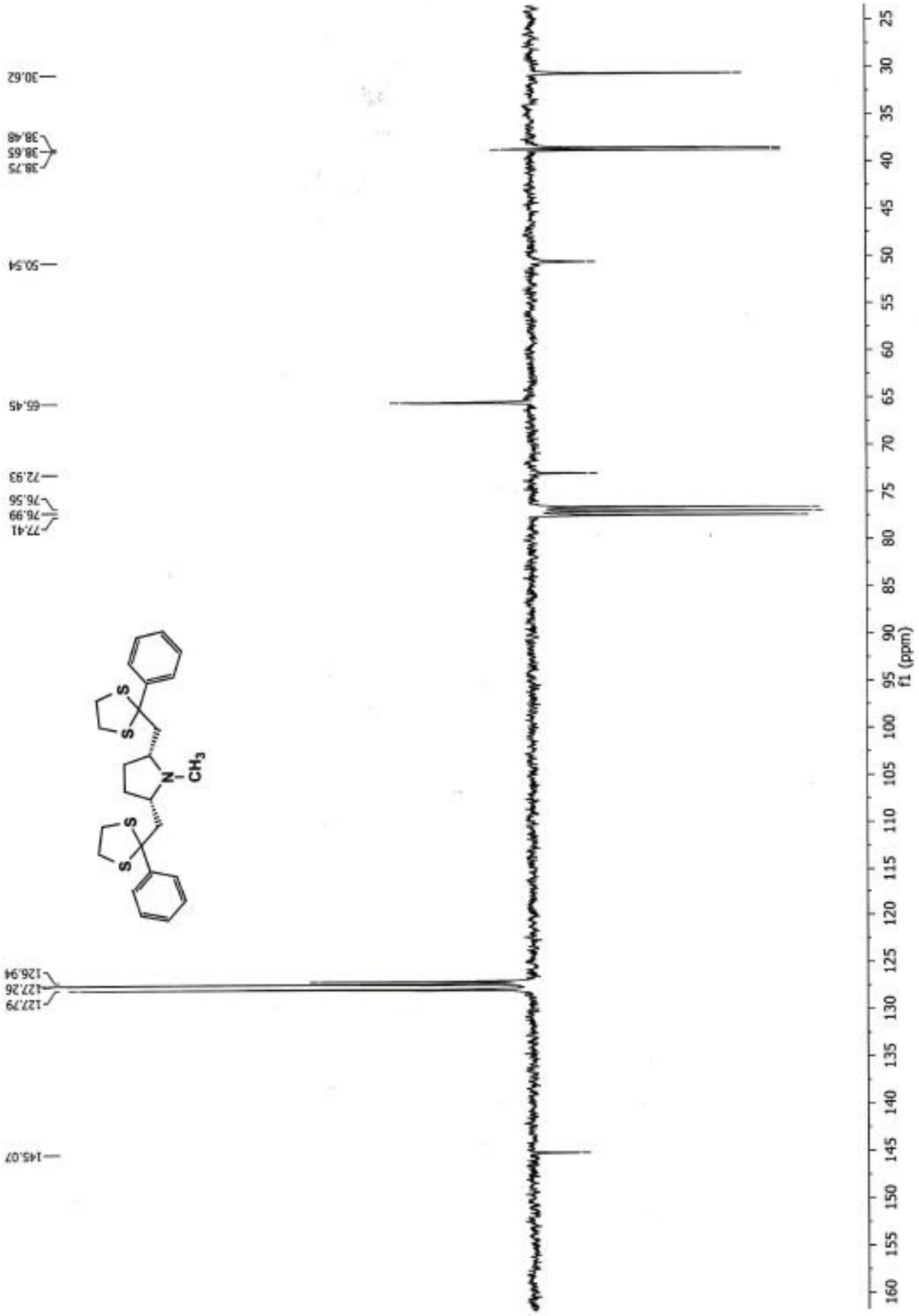
1.9. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **15c**




207.90
77.42
77.00
76.57
62.41
48.91
39.03
30.89
29.65
29.45
H3C
O
N
CH3
O
CH3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

1.10. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **17**

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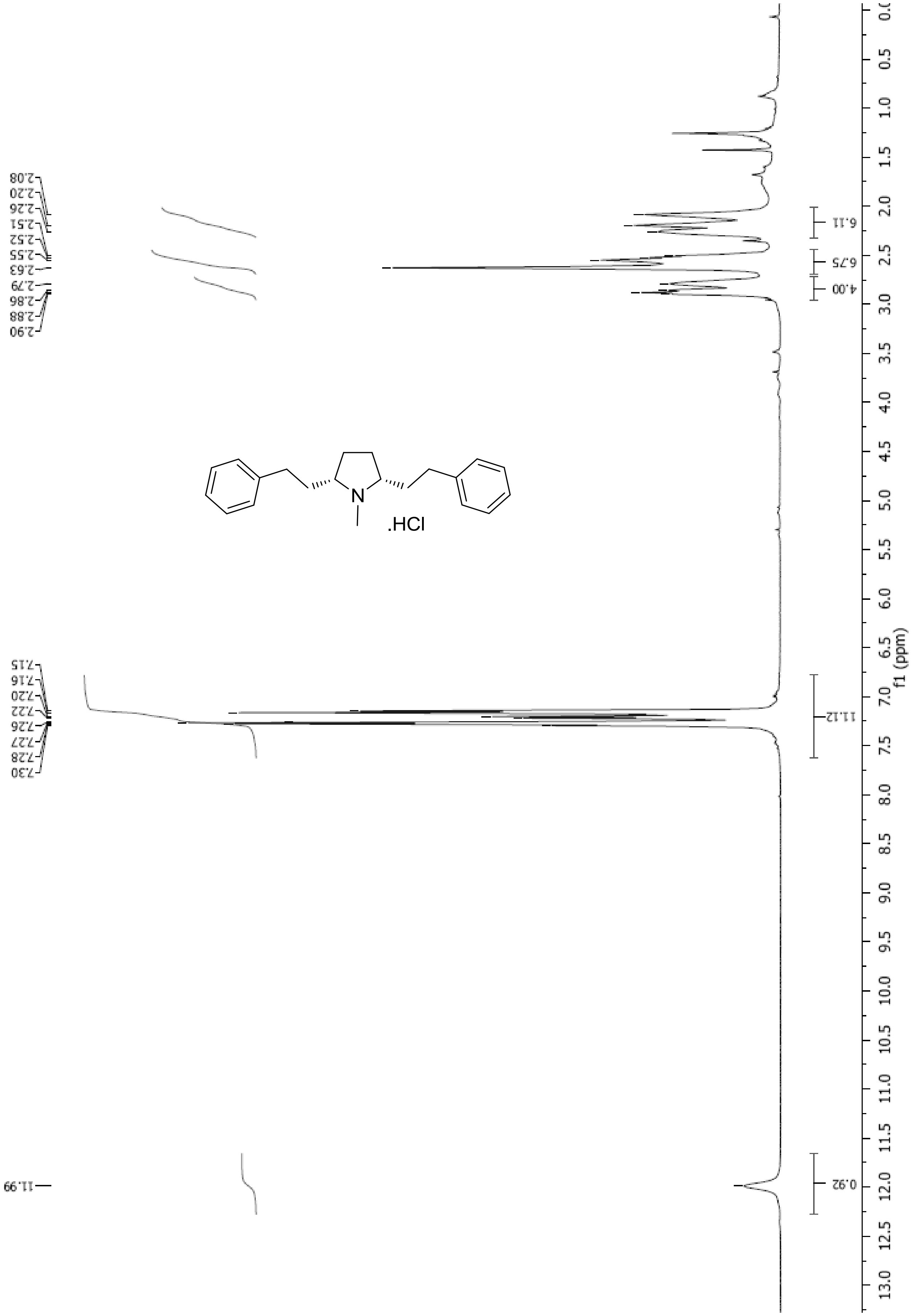
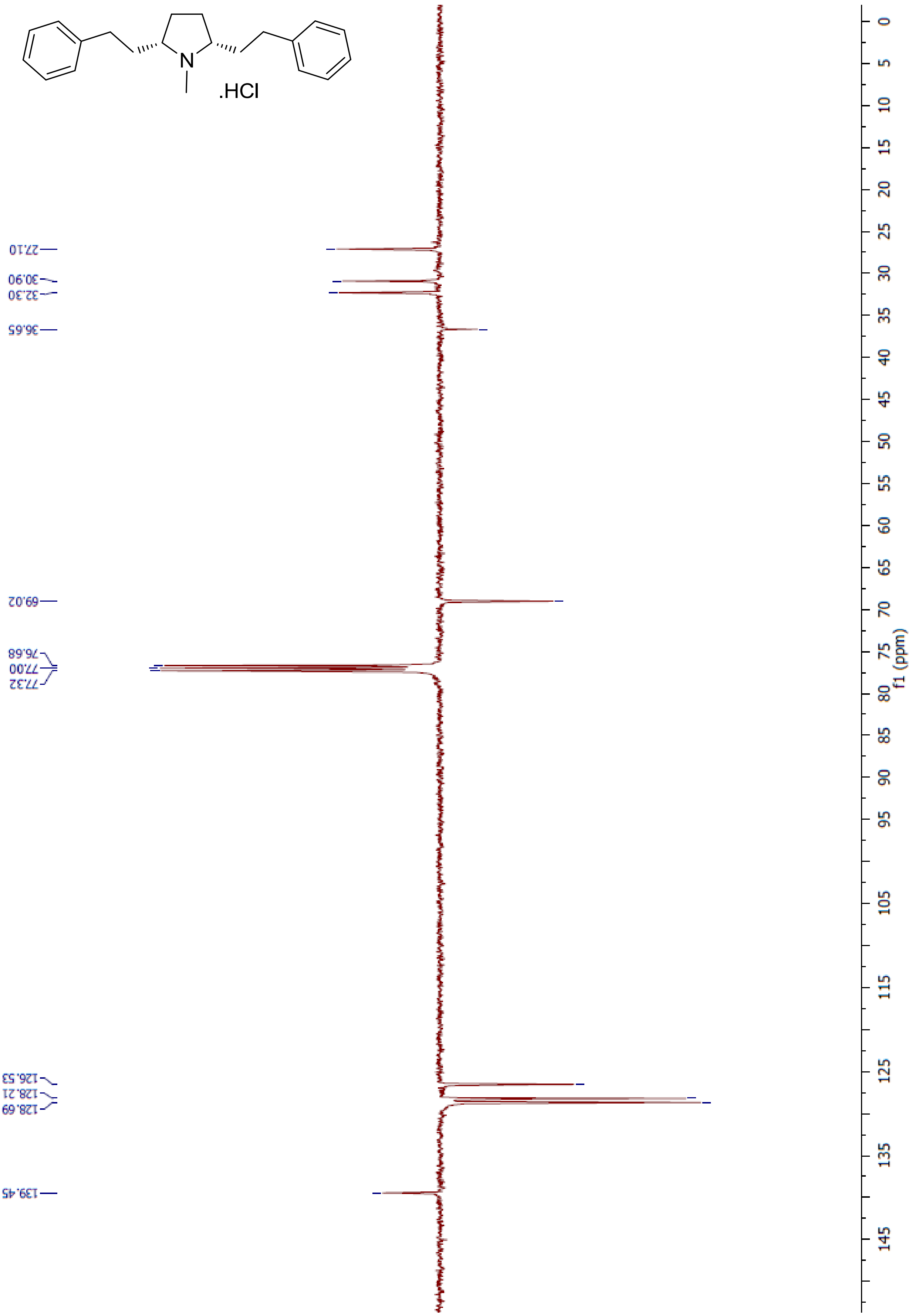
38.48
38.65
38.75
50.54
65.45
72.93
76.56
76.99
77.41
126.94
127.26
127.79
145.07
S
S
N
CH3
S
S
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
105
110
115
120
125
130
135
140
145
150
155
160
f1 (ppm)

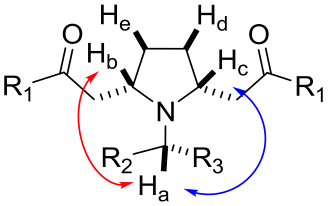
1.11. ^{1}H and ^{13}C NMR spectra for compound at respectively 300 MHz and 75 MHz **18**



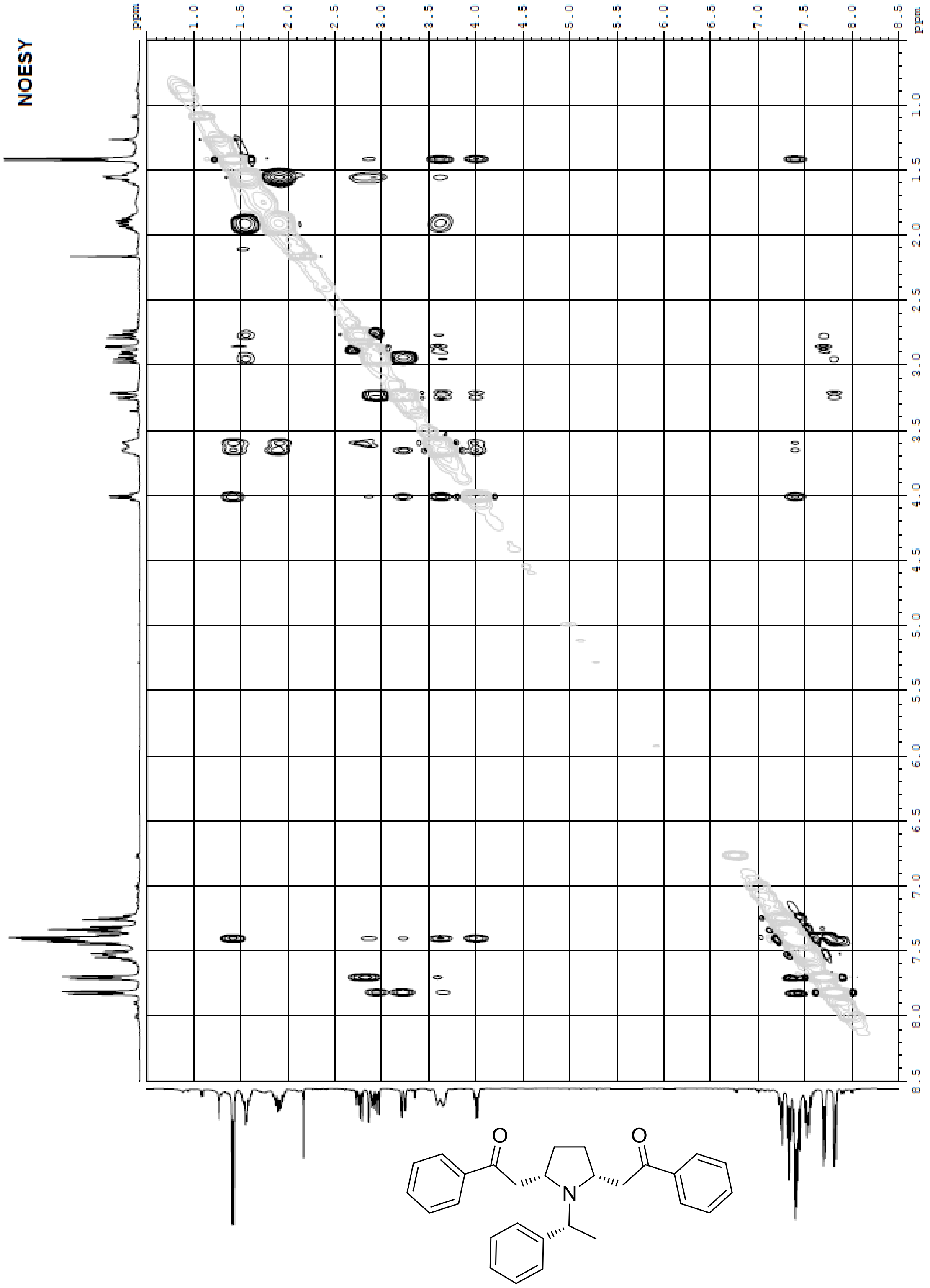

N
.HCl
27.10
30.90
32.30
36.65
69.02
76.68
77.00
77.32
126.53
128.21
128.69
139.45
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
105
115
125
135
145
f1 (ppm)

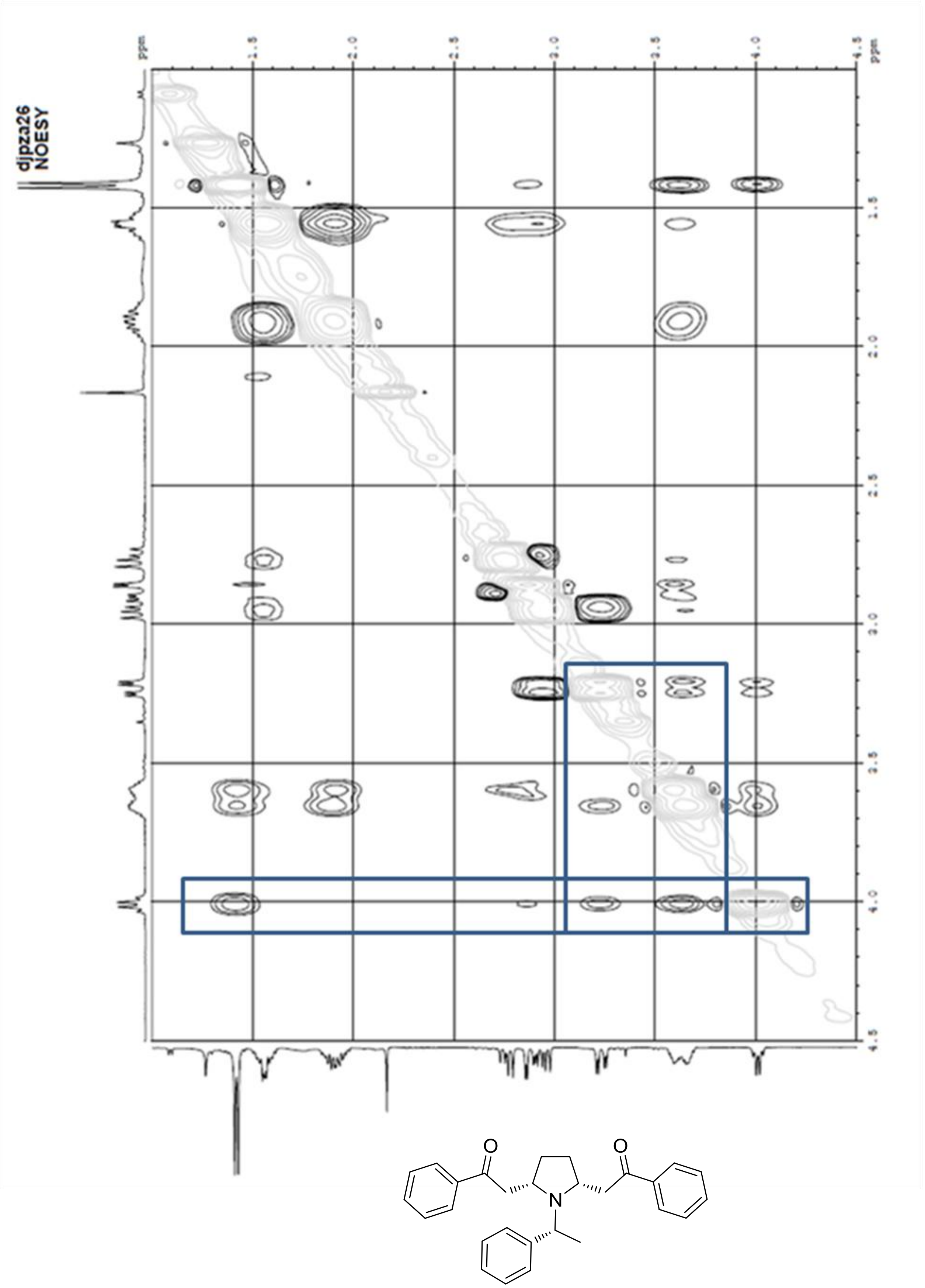
2. nOesy correlation spectra of 13a,c,e for relative configuration determination

Relative stereochemistry has been assigned by nOesy correlations between H_a and H_b, H_a and H_c, H_b and H_c. General characterization of the *cis*-stereochemistry is highlighted on spectra.

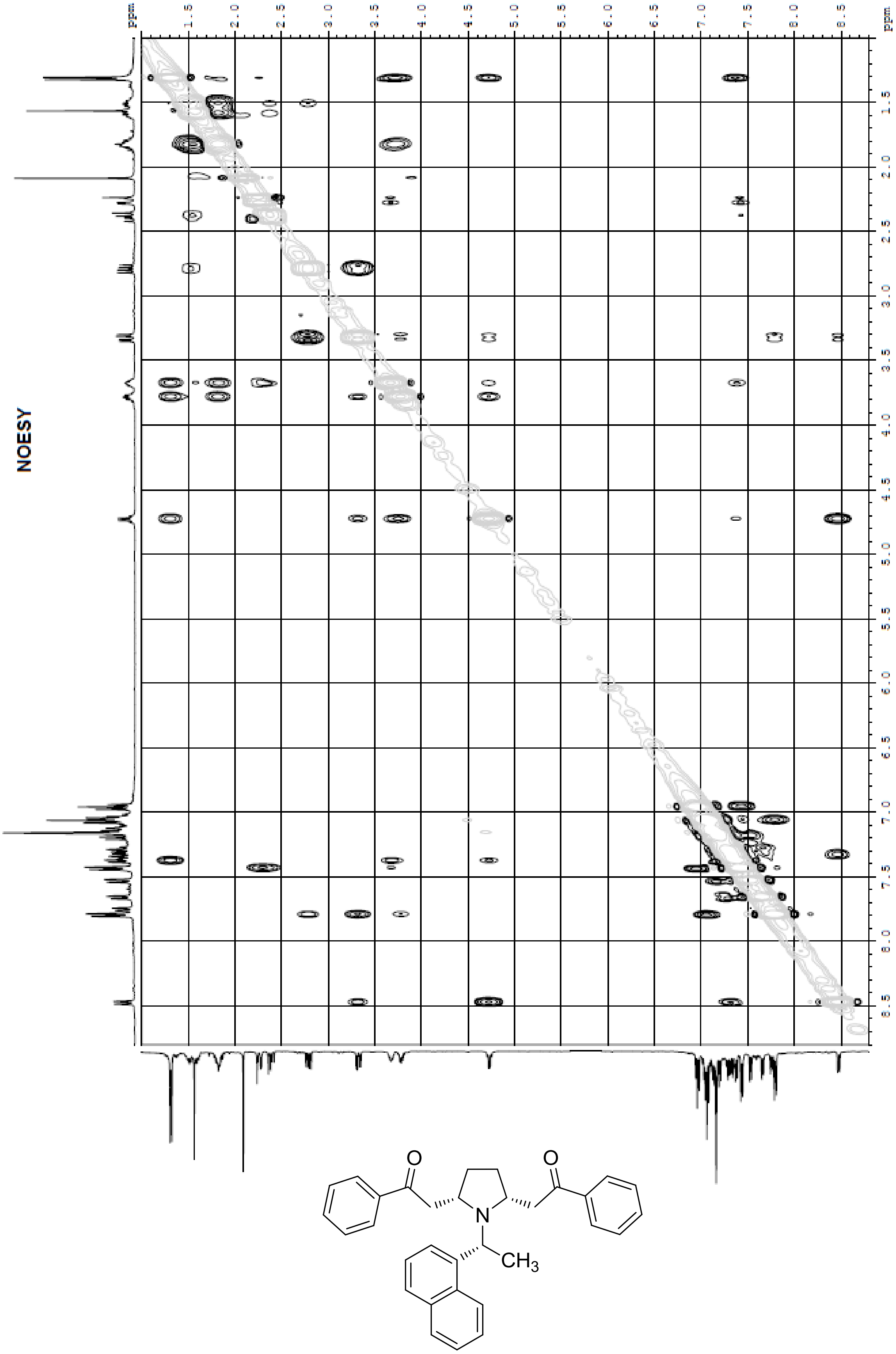


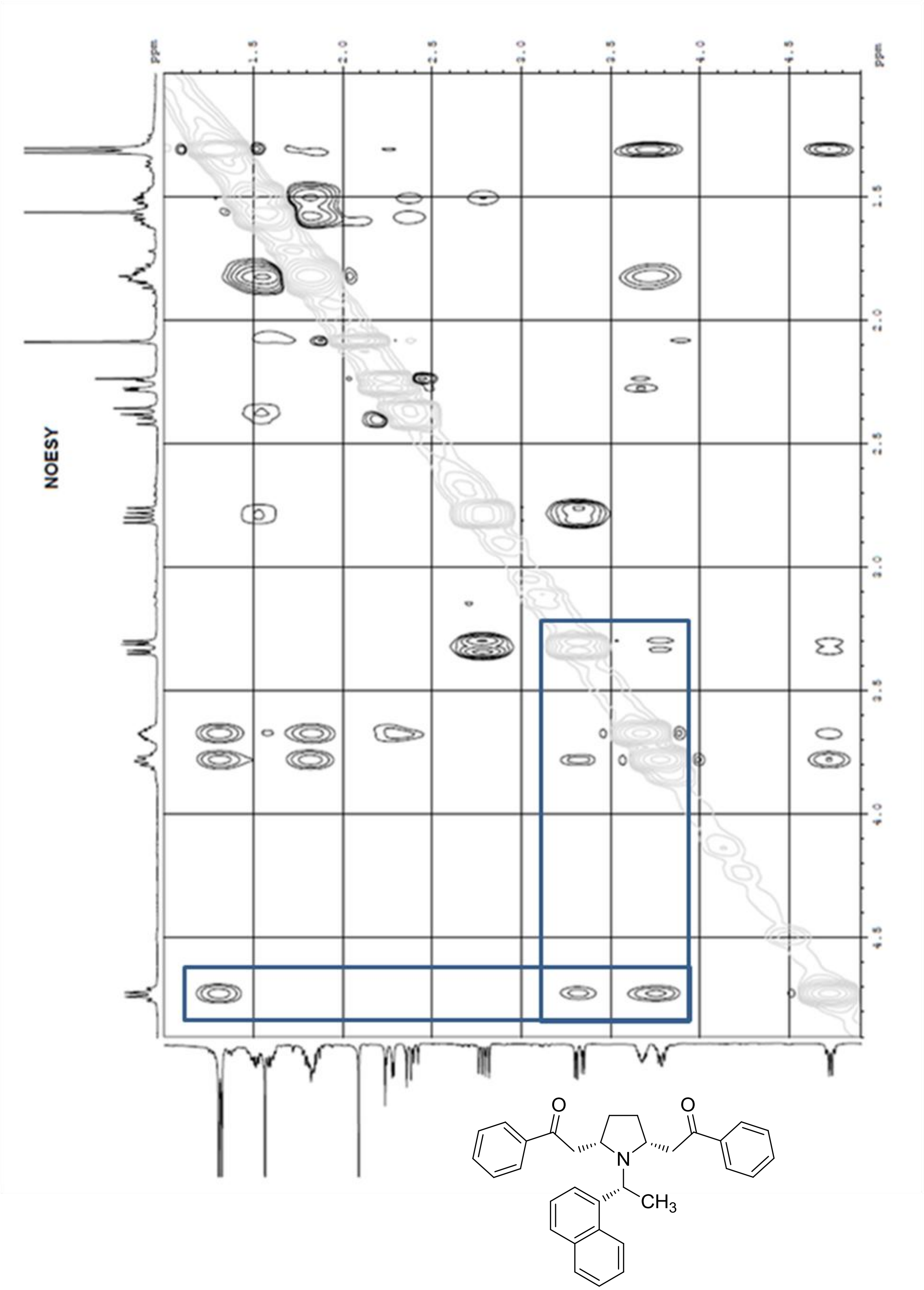
2.1 nOesy correlation spectra of **13a** for relative configuration determination




djpza26
NOESY
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
O
O
N

2.2. nOesy correlation spectra of **13c** for relative configuration determination




NOESY
ppm
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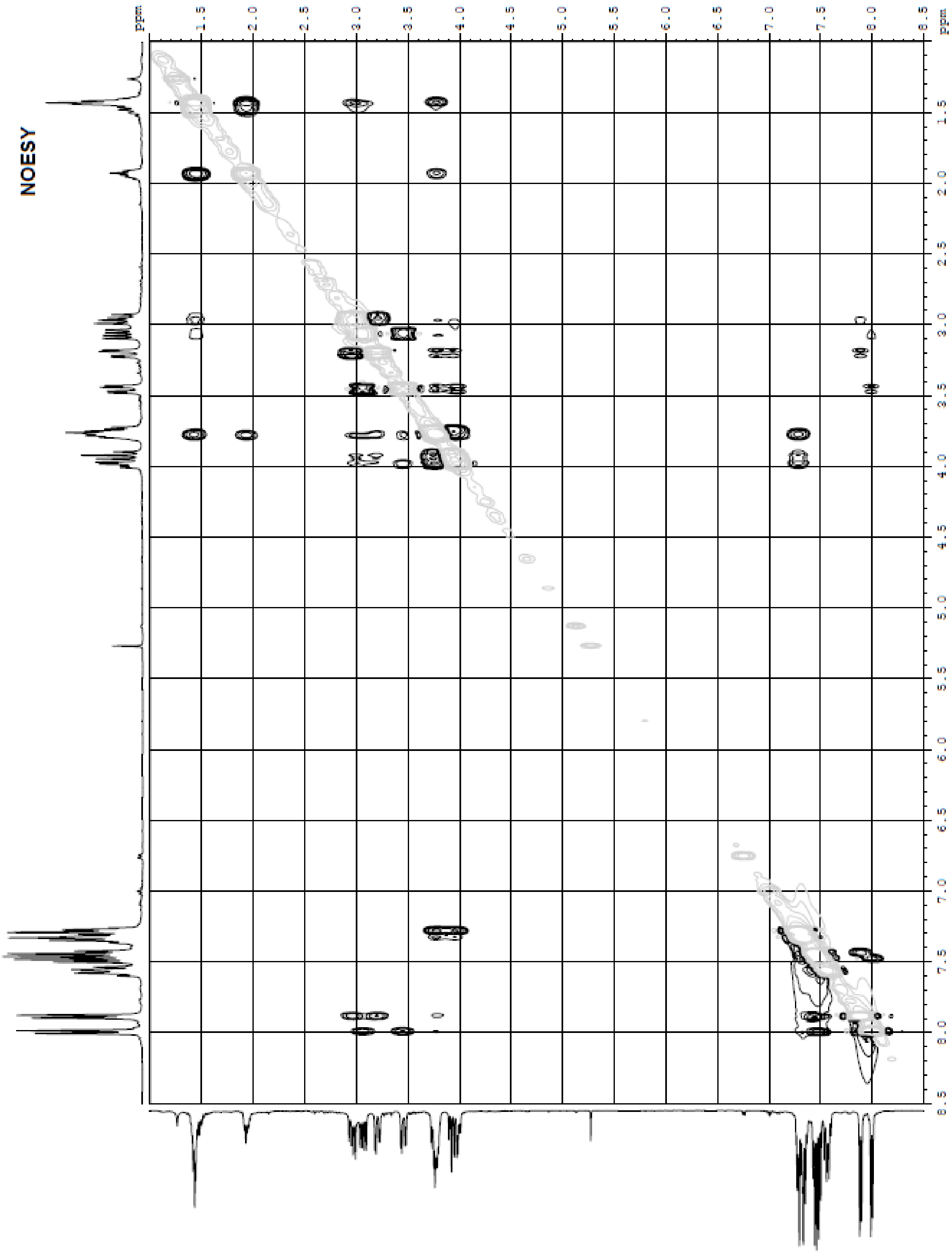
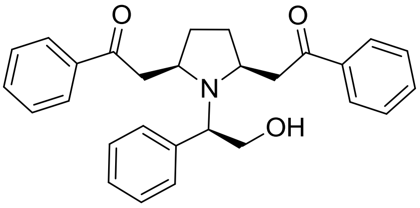
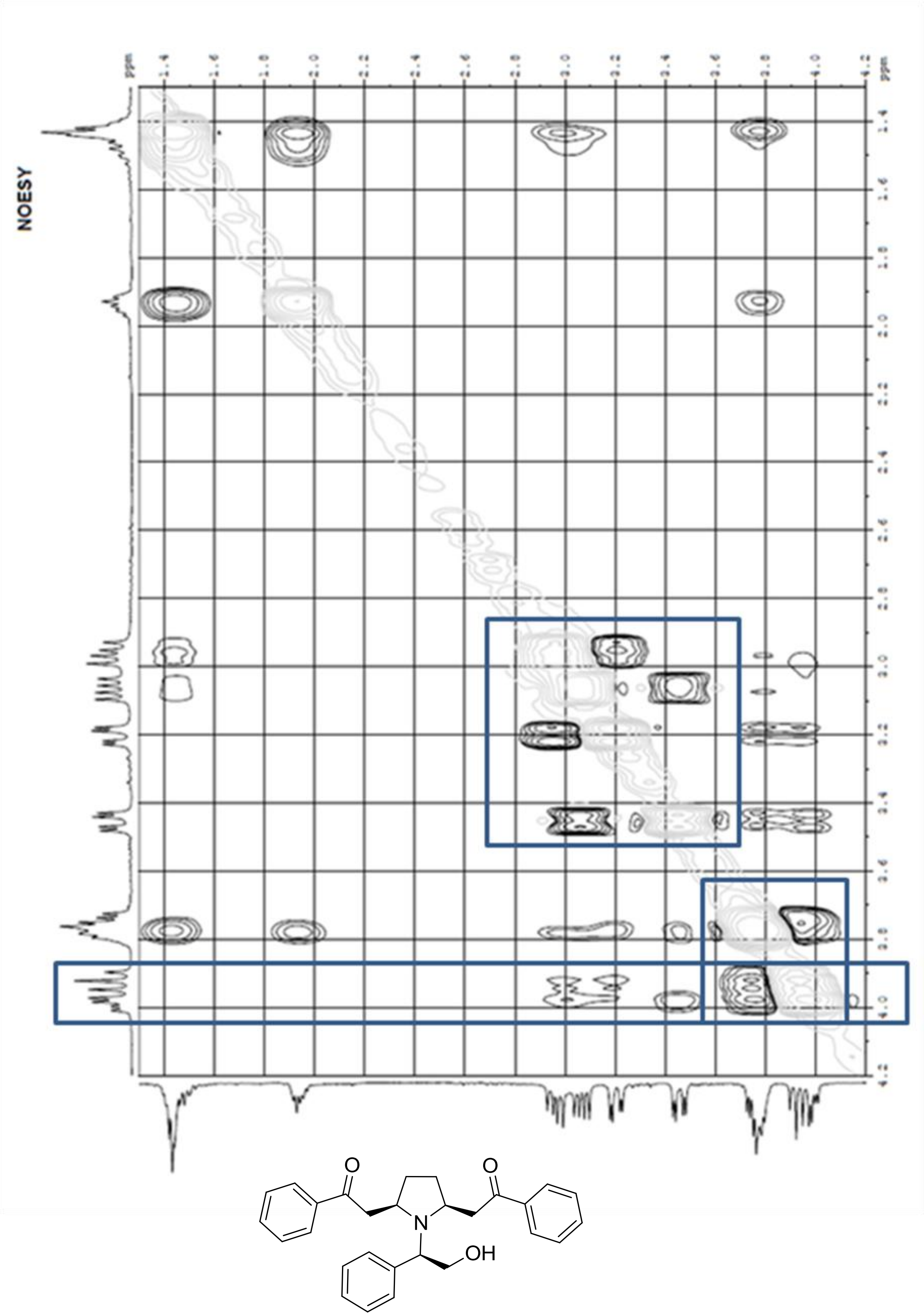
2.0
2.5
3.0
3.5
4.0
4.5
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
O
O
N
CH3

2.3. nOesy correlation spectra of **13e** for relative configuration determination






NOESY
ppm
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.2
O
O
N
OH

3. X-Ray structures for compounds 13d and 18

3.1. Crystal data of 2-[1-benzhydryl-5-(2-oxo-2-phenylethyl)pyrrolidin-2-yl]acetophenone **13d**.

A colourless plate-like single crystal (0.60 x 0.46 x 0.10 mm) grown from cyclohexane was mounted on an Enraf-Nonius Kappa-CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71069 Å) at ambient temperature (293(2)K). A preliminary orientation matrix and unit cell parameters were determined from a 10° φ–scan of 1°-oscillation, followed by spot integration and least-squares refinement.[1] A φ–scan of a 179° range with 1.3° oscillation, followed by two ω-scans of successive lengths: 38.1, 62.5°, with the detector at a distance of 41.9 mm from the crystal and at θ= 7.453° (respectively -7.166°) was designed for complete collection of data in *mmm* Laue system with significant measured intensities up to a resolution of 0.90 Å. «Dezingering» was accomplished by measuring each frame twice with exposure of 40s per degree. Data reduction and cell dimension post-refinement were performed, altogether with multi-scan absorption correction with *SCALEPACK*.[2]
The structure was solved using direct methods *(SIR97)*[3]and all non-hydrogen atoms were refined with anisotropic displacement parameters using *SHELX-L97*[4] by full-matrix least squares on F^2 values. All hydrogen atoms were located on difference–Fourier syntheses but were refined with a riding model and with U_{iso} set to 1.2 times that of the attached C-atom. One low-resolution reflection shaded by the beamstop was omitted during the stage of the model refinement using the OMIT instruction in *SHELX-L97.*

The crystallographic data are summarized as follows: thin colourless plate of dimensions 0.60 x 0.46 x 0.10 mm, $C_{33}H_{29}NO_2$, Mr = 471.57, orthorhombic system, space group $P\ b\ c$ m, Z = 4, a = 8.806 (4), b = 11.377 (5) Å, c = 26.118 (8) Å, V = 2616.7(2) Å^3, D_{calcd} =1.197 g/cm^3, F(000) = 1000, μ = 0.074 mm^{-1}, 11516 collected reflections (1.98° ≤ θ ≤ 46.58°), $-9 \leq h \leq 9$, $-12 \leq k \leq 12$, $-28 \leq l \leq 28$), 1920 independent reflections (R_{int} = 0.0245), goodness-of-fit on F^2: S = 1.050, R_1 = 0.0885 and wR_2 = 0.1925 for all 1919 reflections, R_1 = 0.0635 and wR_2 = 0.1708 for 1361 observed reflections [$I > 2\sigma(I)$], refining 167 parameters, semi-empirical absorption correction from multi-scans (T_{min} = 0.89, T_{max} = 0.99), final electron density between -0.180 and 0.385 e Å^{-3}. The programs used in the crystallographic study were as follows: data collection, cell refinement and data reduction: COLLECT[i] / HKL2000;[2] structure solution: SIR97;[3] structure refinement: SHELXL97[4] within CRYSTALBUILDER;[5] molecular graphics: ORTEP[6] within PLATON.[7]

CCDC 854591 (compound **13d**) contains the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.ac.uk).

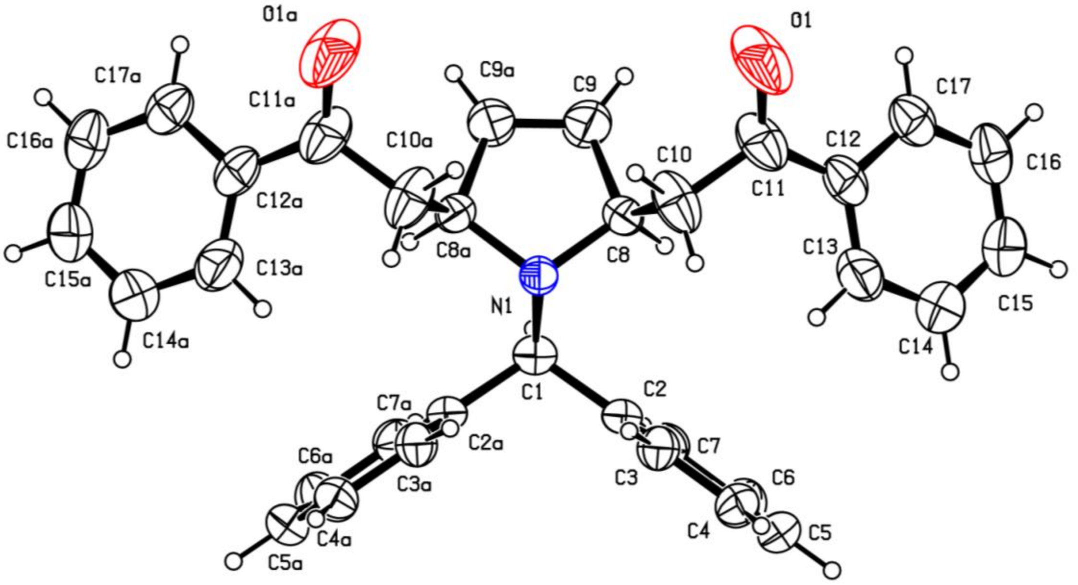


Figure 1. ORTEP diagram (30% probability ellipsoids) showing crystallographic atom numbering and solid-state conformation for compound **13d**.

3.2. Crystal data of *N*-methyl-2,5-*cis*-di-(2-phenethyl)-pyrrolidine hydrochloride **18.**

The X-ray crystallographic data were measured on a Rigaku MM007 HF copper (λ = 1.54187 Å) rotating-anode generator equipped with Osmic confocal optics and a rapid II Curved Image Plate at 200(2)K. A total of 42 oscillation images were collected in two sweeps using ω oscillations from 20.0 to 200.0° and from 70 to 100°, respectively, in 5.0° steps. The exposure rate was 120.0 sec./°. The crystal-to-detector distance was 127.40 mm and the configuration set-up allowed the measurement of data to a maximum 2θ value of 136.5°. Out of the 12865 reflections that were collected, 1894 were unique (R_{int} = 0.0359). The linear absorption coefficient, μ, for Cu-Kα radiation is 1.721 cm^{-1}. An empirical absorption correction was applied which resulted in transmission factors ranging from 0.648 to 0.866. The data were corrected for Lorentz and polarization effects.

Compound (**18**) crystallized in the orthorhombic system (from diethylether). From the manner in which the data were integrated (with a < b < c), the systematic absences allowed the space group to be either *C2cb* or *Cmca.* Both possibilities were examined and the non-centrosymmetric spacegroup *C2cb* shown to be correct, allowing the structure to be solved by conventional direct methods and refined by full-matrix least-squares on F^2. The *C2cb* system was then transformed to the equivalent standard *Aba2* system before the final refinement. The *meso*-molecules were subjected to a 2-fold rotational crystallographically imposed symmetry, passing through the pyrrolidine group, and the chloride ion, thus in special position. This heterocycle ring adopts an envelope conformation, folded across the line C2 ... C2_a, with atom N1 at the apex out of the least-squares plane defined by the other non-H atoms of the ring, by 0.610 (6) Å, and oriented toward the chloride ion (N1–H1 ... Cl1 2.155 Å and 170.8 °). Phenacyl substituents at the opposite sides of the ring are in bisectional positions and in *syn* conformation but in *anti* with respect to the methyl substituent also in bisectional position. All non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were located from difference Fourier maps but refined as a riding model with U_{iso} set to 1.5 (methyl) and 1.2 (other) times the equivalent isotropic displacement parameter of their parent atoms. Soft restraints were applied on distances (by the use of the DFIX and DANG instructions) to regularize the geometry of the pyrrolidine group and its alkyl substituents, which appear also disordered over two possible orientations with occupancy factors freely refined to 0.548(12)/0.452(12).

The crystallographic data are summarized as follows: elongated rectangular cuboid of dimensions

0.59 x 0.18 x 0.16 mm, $C_{21}H_{28}N^{+}$, Cl^{-}, $Mr = 329.89$, orthorhombic system, space group $A\ b\ a\ 2$, $Z = 4$, $a = 25.438(2)$ $b = 10.6710\ (5)$ Å, $c = 7.1250\ (2)$ Å, $V = 1934.07(19)$ Å^3, $D_{calcd} = 1.133$ g/cm^3, $F(000) = 712$, $\mu = 1.721$ mm^{-1}, 12865 collected reflections ($6.96° \leq \theta \leq 73.14°$), $-31 \leq h \leq 31$, $-12 \leq k \leq 8$, $-8 \leq l \leq 8$), 1894 independent reflections ($R_{int} = 0.0375$), goodness-of-fit on F^2: $S = 1.136$, $R_1 = 0.0718$ and $wR_2 = 0.1763$ for all 1891 reflections, $R_1 = 0.0544$ and $wR_2 = 0.1467$ for 1405 observed reflections [$I > 2\sigma(I)$], refining 131 parameters and 4 restraints on bond lengths with respect the pyrrolidine group, semi-empirical absorption correction from multi ω-scans ($T_{min} = 0.680$, $T_{max} = 1.000$), final electron density between -0.312 and 0.205 e Å^{-3}. The programs used in the crystallographic study were as follows: data collection, cell refinement and data reduction: CRYSTALCLEAR™ software package;[8] structure solution: SHELXS97;[4] structure refinement: SHELXL97[4] within CRYSTALBUILDER;[5] molecular graphics: ORTEP [6] within PLATON. [7]

CCDC 828848 (compound **18**) contains the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336033; or deposit@ccdc.cam.ac.uk).

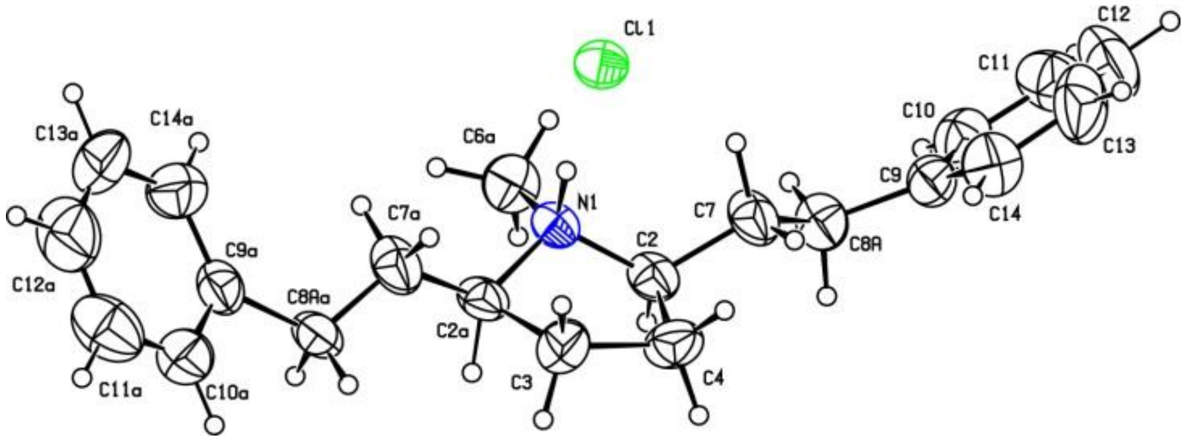
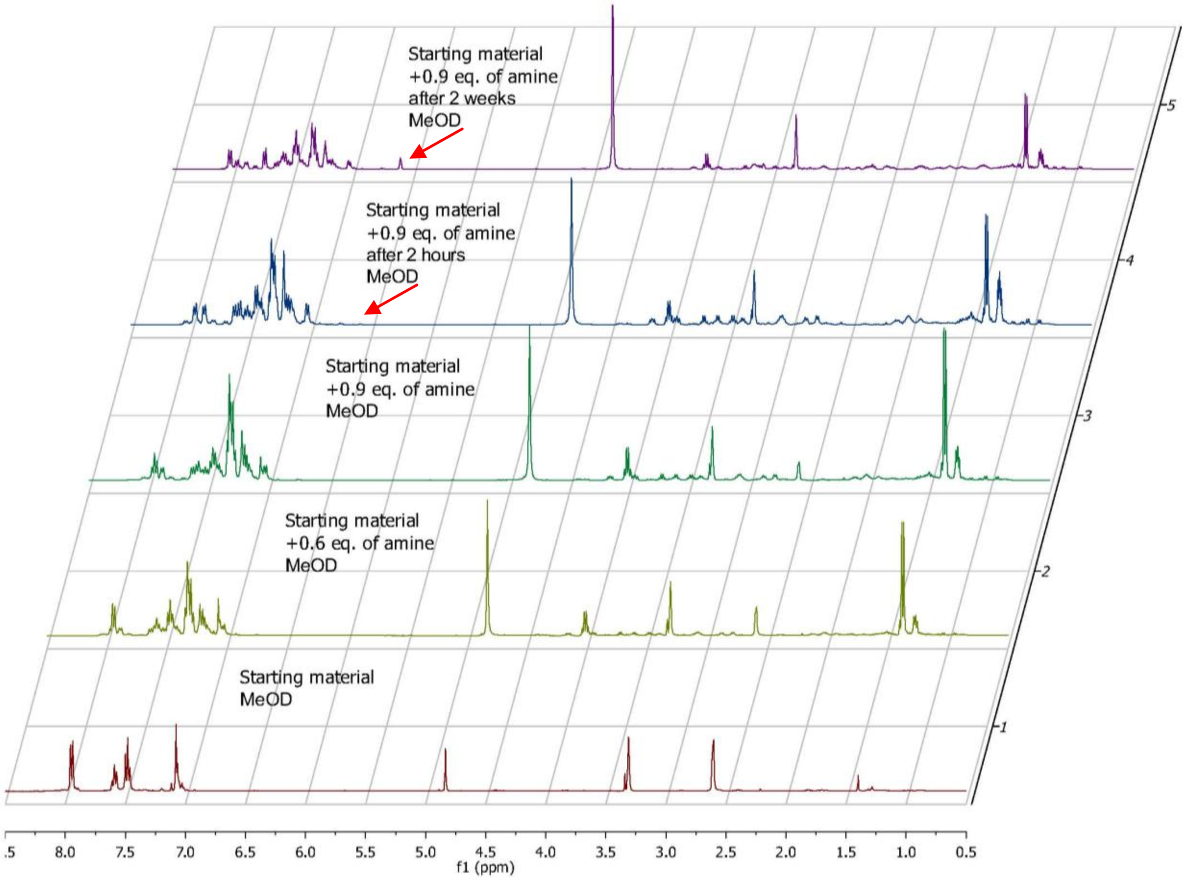


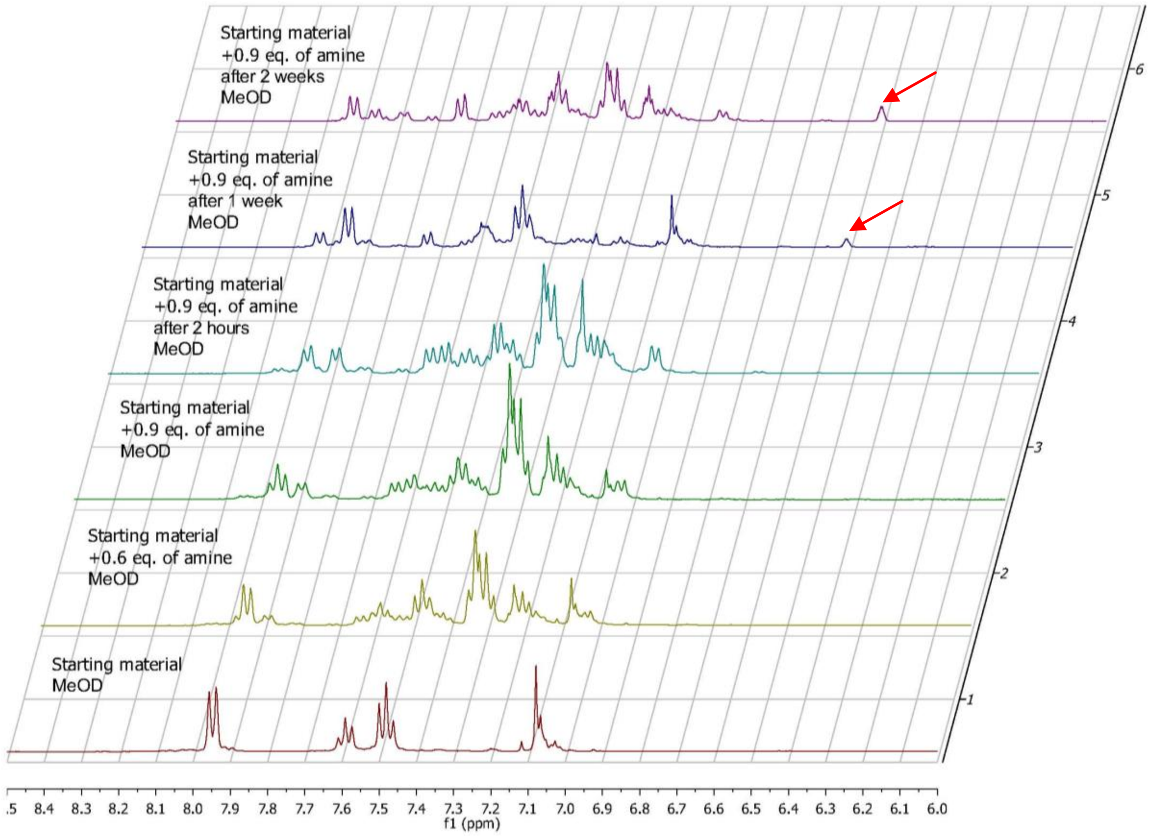
Figure 2. ORTEP diagram (30% probability ellipsoids) showing crystallographic atom numbering and solid-state conformation for compound **18**. For clarity the disordered part of the molecule was not shown.

References :
(1) B. V. Nonius, (1999). *Collect*, data collection software, Nonius BV, Delft, The Netherlands.
(2) Z. Otwinowski, W. Minor, (1997). *Processing of X-ray Diffraction data Collected in Oscillation Mode, Methods in Enzymology*, in *Macromolecular Crystallography A*, Vol. 276, edited by C.W. Carter, Jr. & R.M. Sweet, pp. 307-326. New York: Academic Press.
(3) A. Altomare, M. C. Burla, M. Camalli, G. L.Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Cryst.*, 1999, **32**, 115.
(4) G. M. Sheldrick, *Acta Cryst.*, 2008, **A**64, 112.
(5) R. Welter, *Acta Cryst.*, 2006, **A**62, s252.
(6) M. N. Burnett, C. K. Johnson, "ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Il- lustrations," Oak Ridge National Laboratory Report No. ORNL-6895, 1996 (unpublished).
(7) A. L. Spek, *J. Appl. Cryst.*, 2003, **36**, 7-13.
(8) Copyright © 2006-2009, Rigaku Americas Corporation.

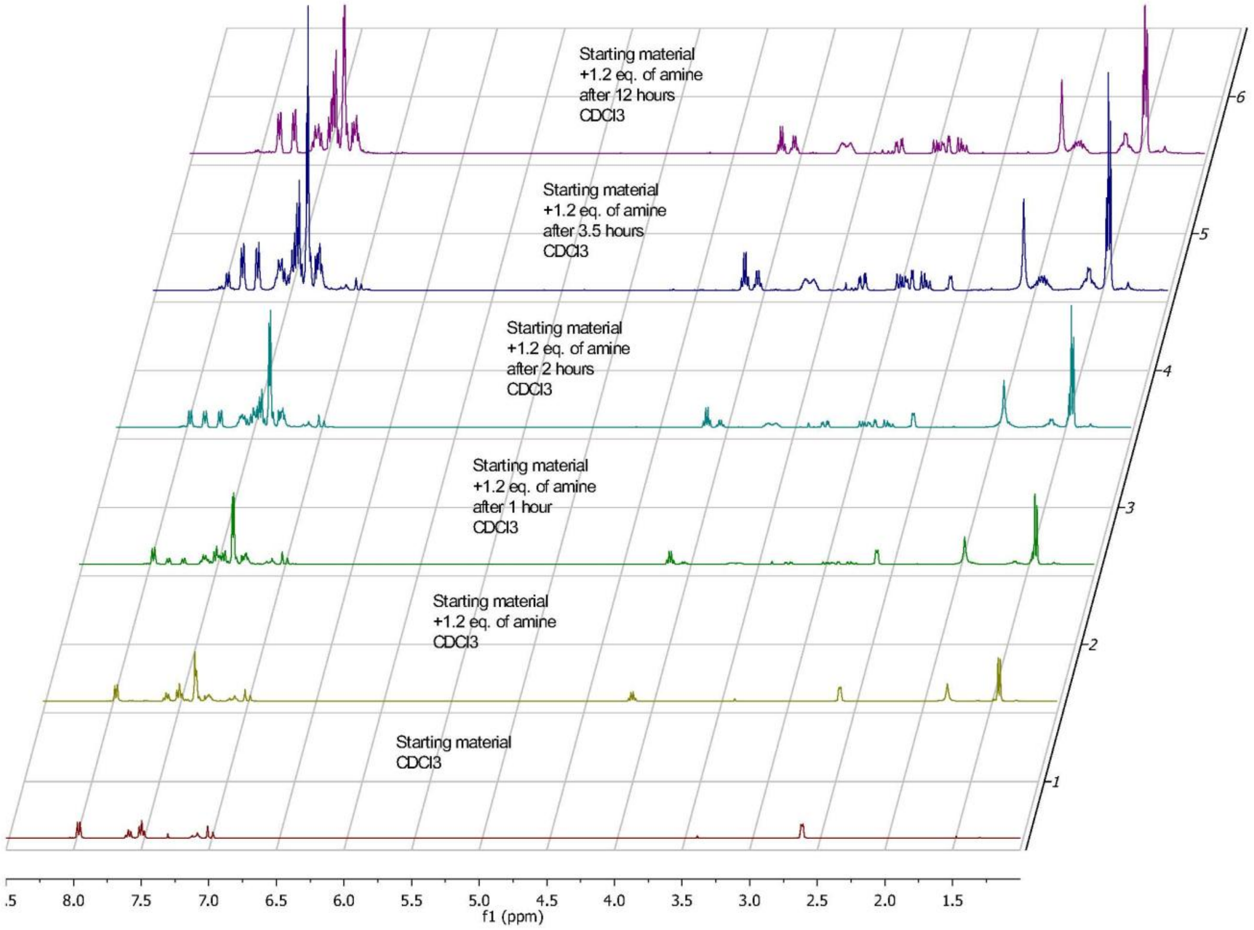
4. ^{1}H NMR monitoring of double conjugate addition of (+)-phenylethylamine to 12a

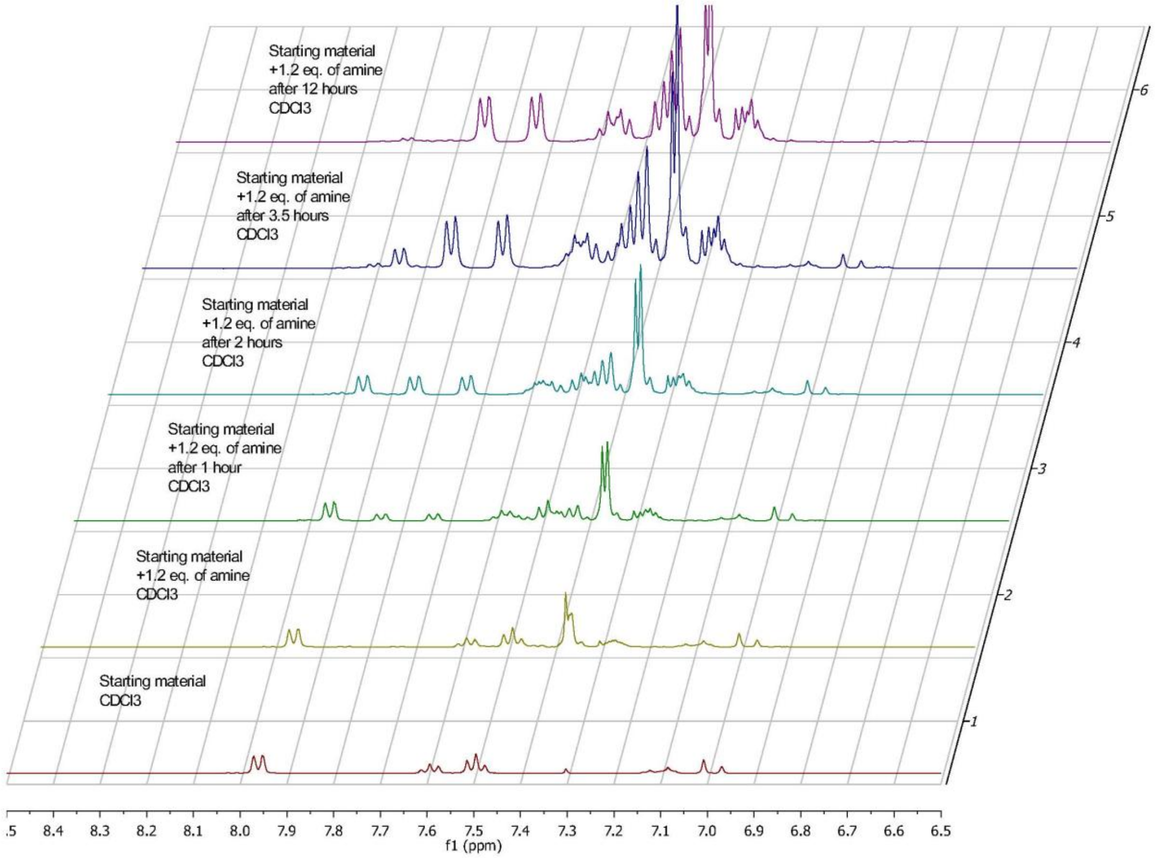
4.1. ^{1}H NMR monitoring of double aza-Michael reaction in methanol-*d*^{4}

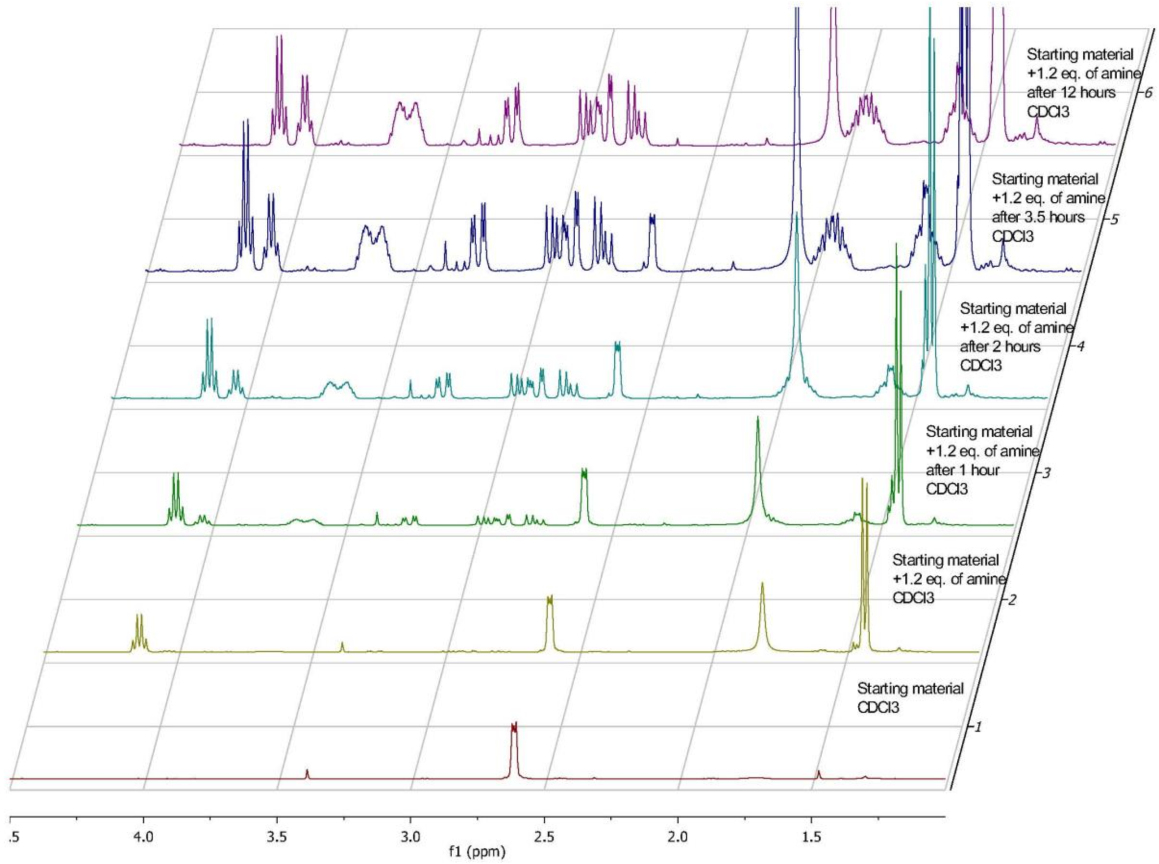




4.2. ^{1}H NMR monitoring of double aza-Michael reaction in chloroform-*d*[1]




Starting material
+1.2 eq. of amine
after 12 hours
CDCl3
Starting material
+1.2 eq. of amine
after 3.5 hours
CDCl3
Starting material
+1.2 eq. of amine
after 2 hours
CDCl3
Starting material
+1.2 eq. of amine
after 1 hour
CDCl3
Starting material
+1.2 eq. of amine
CDCl3
Starting material
CDCl3
6
5
4
3
2
1
.5
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
f1 (ppm)


Starting material
+1.2 eq. of amine
after 12 hours
CDCl3
Starting material
+1.2 eq. of amine
after 3.5 hours
CDCl3
Starting material
+1.2 eq. of amine
after 2 hours
CDCl3
Starting material
+1.2 eq. of amine
after 1 hour
CDCl3
Starting material
+1.2 eq. of amine
CDCl3
Starting material
CDCl3
6
5
4
3
2
1
.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)