Supporting Information:

Hexafluoroisopropanol: a powerful solvent for the hydrogenation of indole derivatives. Selective access to tetrahydroindoles or *cis*-fused octahydroindoles.

Damien Clarisse,[a] Bernard Fenet[b] and Fabienne Fache*[a]

[a] *Université de Lyon, Université Lyon 1, ICBMS, équipe SURCOOF, CNRS, UMR 5246, Bât. Raulin, 43 Bd du 11 Nov. 1918, 69622 Villeurbanne cedex France. Fax: 33 472448136; Tel: 33472448521; E-mail: fache@univ-lyon1.fr.*

[b] *Centre Commun de Résonnance Magnétique Nucléaire, Bâtiment Curien, 3 rue Victor Grignard, 69622 Villeurbanne cedex France.*

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Part1 : Experimental part

General Informations: NMR spectra were recorded on a Bruker AC300, 400 or a Bruker Advance III 500 MHz. Chemical shifts δ are given in ppm, coupling constant *J* are in Hz. The chemical shifts are reported in ppm on scale upfield from TMS as an internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; dt, doublet of triplet; t, triplet; m, multiplet, br, broad singlet. High resolution mass spectrometry (HRMS) analyses were conducted using a ThermoFinigan-MAT 95 XL instrument. IR spectra (neat) were recorded on a Nicolet IS 100. Melting points were measured with a B-540 Büchi. Rf were calculated using TLC silicagel 60 F254 Merck and were visualized with UV light, phosphomolybdic acid or *p*-anisaldehyde solution. Column chromatographies were performed on silica gel (40-63 µm) using technical grade ethyl acetate (EtOAc) and petroleum ether (EP). When appropriate, solvents and reagents were dried by distillation over appropriate drying agent prior to use. Diethyl ether and tetrahydrofuran (THF) were distilled from Na/benzophenone and used fresh. Dichloromethane was distilled from CaH_2. All the reactions were performed under an atmosphere of nitrogen in flame or oven-dried glassware with magnetic stirring.

NMR Assignment Method

Sometimes, several further NMR analyses performed on a Bruker Avance III 500 MHz spectrometer were necessary to identify the different isomers. The first step of the analysis consisted in the attribution of all protons and carbons with a HSQC-TOCSY 2D experiments acquired with high resolution and good signal to noise. We used a homemade HSQC-TOCSY IPAP[1] experiment which suppress line distortion after addition/subtraction of the normal and the edited spectra, where TOCSY relays appear negative. This technique allowed the complete attribution of all protons including the CH_2 of the ring packed in a very crowded region and affected by second order effects. However, if H_2 and H_{7a} appear at low field and generally exhibit a good spectral separation, H_{3a} if often superposed with H_3, and solvent and temperature adjustments where often necessary to get a good spreading.

The configuration determination of each diastereoisomer was based on the interactions between H_2, H_3, H_{3a} and H_{7a}. The analysis of coupling constants between those protons should theoretically allow fixing some relative configurations. However, very complex coupling pattern for H_{3a} and H_{7a} alleviate the possibility to measure all coupling constants.

So, the configuration where determined with internuclear distances driven from dipolar interactions NOESY experiments. It can be shown[2,3] that in rigid molecule, the integrated NOESY matrix can easily be converted into a distance matrix calculating each r_{ij}, where a_{ii} are the integral volumes of the diagonal, and a_{ij} the cross peaks.

$$r_{ij} = r_{ij}^{ref}\left(\frac{\ln\left[\frac{a_{ii}^{ref} + a_{ij}^{ref}}{a_{ii}^{ref} - a_{ij}^{ref}}\right]}{\ln\left[\frac{a_{ii} + a_{ij}}{a_{ii} - a_{ij}}\right]}\right)^{1/6}$$

After the selection of n diagonal peaks of interest, a C program integrates the n*n integration region matrix, calculates distances and creates an Excel file for visualizing. An excel view with conditional formatted cells with colors sensible to cells values gave a nice color array, which allowed a straightforward interpretation.

Synthesis of starting materials

1-*tert*-butyl 2-methyl 6-methoxy-1H-indole-1,2-dicarboxylate 12f

To a solution of 1H-indole **8a** (2 mmol, 410 mg) in THF (5 mL) were added DMAP (3 mmol, 367 mg) and di-*t*-butyl dicarbonate (4 mmol, 873 mg). After 2 hours of stirring, the reaction mixture was concentrated, the residue taken up in dichloromethane and the organic phase washed successively with a 1N HCl solution in water, washed until pH 7, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/ petroleum ether 20/80) to afford product **12f** with 96% isolated yield.

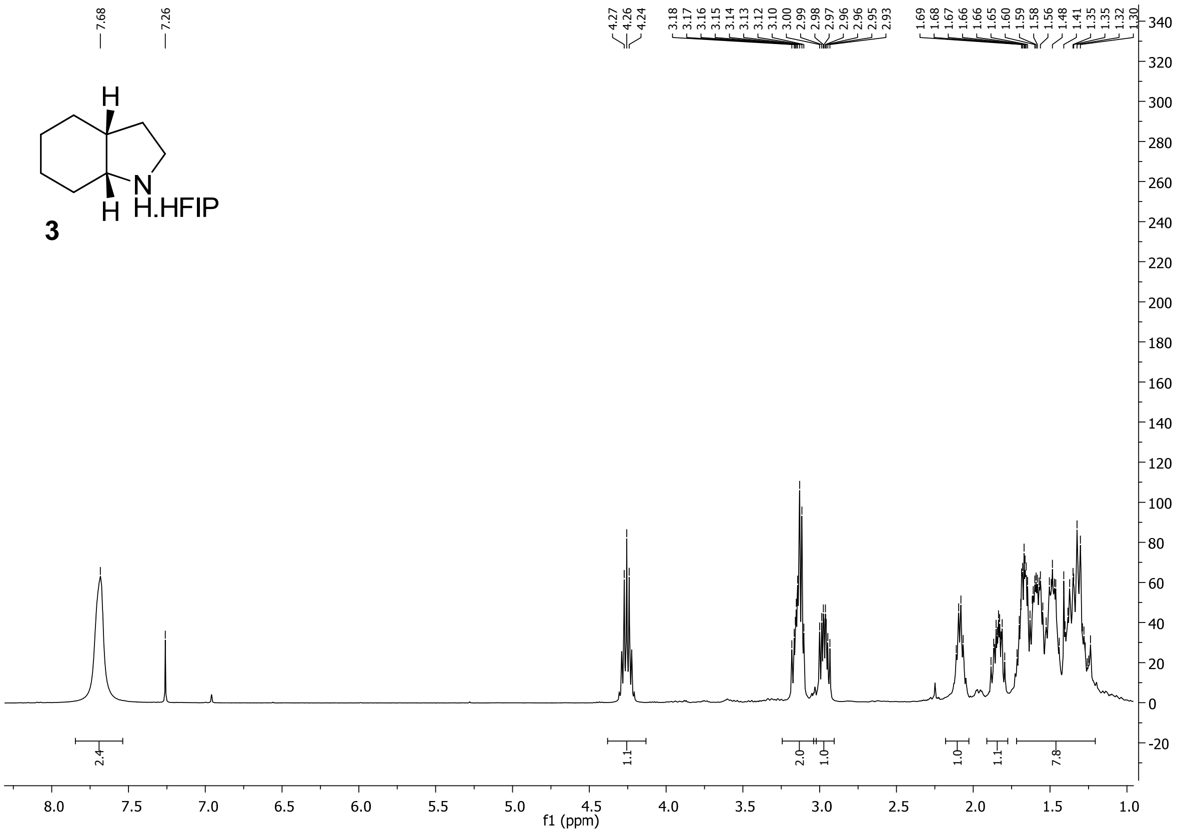
Colorless oil; $R_f = 0.78$ (ethyl acetate/petroleum ether 30/70); **^{1}H NMR:** (300 MHz, $CDCl_3$) δ 7.62 (1H, d, *J* = 2.3 Hz), 7.44 (1H, d, *J* = 8.7 Hz), 7.06 (1H, d, *J* = 0.6 Hz), 6.88 (1H, dd, *J* = 8.7, 2.3 Hz), 3.88 (3H, s), 3.87 (3H, s), 1.61 (9H, s); **^{13}C NMR**: (75 MHz, $CDCl_3$) δ 162.2, 159.9, 149.6, 139.6, 129.1, 122.9, 121.1, 115.9, 113.6, 98.1, 84.5, 55.6, 52.2, 27.8; **IR:** *ν* 3057, 2982, 2952, 2938, 1733, 1618, 1491, 1439, 1069, 1029, 845, 737 cm^{-1}; **HRMS** (ESI): calculated for $C_{16}H_{19}NO_5Na$ $[M+Na]^+$: 328.1155 found 328.1157.

Synthesis of products 16c and 16d

To a solution of indole-2-carboxylic acid (10 mmol, 1.61 g) and oxalyl chloride (30 mmol, 2.58 mL) in dichloromethane (40 mL), was added dropwise dimethylformamide (7 mmol, 536 µL). After 1.5 hours of stirring under reflux, the reaction mixture was concentrated and the residue was taken up in 50 mL of dichloromethane. The amine was then added dropwise at 0 ° C and the solution was stirred for 1.5 hours at room temperature. The organic phase was washed 3 times with a 1N HCl solution, washed until pH7, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate/petroleum ether 30/70) to afford the desired product.

***N,N*-diethyl-1H-indole-2-carboxamide 16c** 63% isolated yield; white solid; $R_f = 0.25$ (ethyl acetate/ petroleum ether 30/70); **Mp:** 163-164°C; **^{1}H NMR:** (400 MHz, DMSO, 50°C) δ 11.33 (1H, br s), 7.61 (1H, d, *J* = 7.8 Hz), 7.44 (1H, dd, *J* = 8.2, 1.0 Hz), 7.17 (1H, t, *J* = 7.8 Hz), 7.06 – 7.00 (1H, m), 6.76 (1H, d, *J* = 1.0 Hz), 3.59 (4H, q, *J* = 7.0 Hz), 1.23 (6H, t, *J* = 7.0 Hz,). **^{13}C NMR:** (100 MHz, DMSO, 50°C) δ 162.0, 135.5, 130.4, 127.0, 122.8, 121.1, 119.4, 111.7, 102.5, 41.1, 13.4. **IR:** *ν* 3247, 3061, 2931, 1600, 1525, 1383, 737 cm^{-1}. **HRMS** (ESI): calculated for $C_{13}H_{16}N_2ONa$ $[M+Na]^+$: 239.1155 found 239.1148.

(*S*)-*N*-(1-cyclohexylethyl)-1H-indole-2-carboxamide 16d 37% isolated yield; white solid; R_f 0.38 (ethyl acetate/ petroleum ether 30/70); $[\alpha_D]^{20} = 57.0$ (c = 0.34, $CHCl_3$); **Mp:** 167-169°C; **^{1}H NMR:** (300 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 7.7 Hz), 7.35 (1H, d, *J* = 8.2 Hz), 7.23 – 7.12 (1H, m), 7.03 (1H, t, *J* = 7.7 Hz), 6.93 (1H, s), 3.96 (1H, q, *J* = 6.6 Hz), 3.81 (2H, br s), 1.83 – 1.47 (5H, m), 1.46 – 1.28 (1H, m), 1.27 – 0.83 (8H, m); **^{13}C NMR:** (75 MHz, $CDCl_3$/ MeOD 9/1) δ 161.6, 136.5, 130.8, 127.4, 124.1, 121.7, 120.2, 111.9, 102.9, 49.8, 43.1, 29.2, 29.1, 26.2, 26.1, 17.6; **IR:** *ν* 3382, 3304, 3001, 2945, 2918, 2848, 1636, 1589, 1548, 1188 cm^{-1}; **HRMS** (ESI): calculated for $C_{17}H_{23}N_2O$ $[M+H]^+$: 271.1805 found 271.1809.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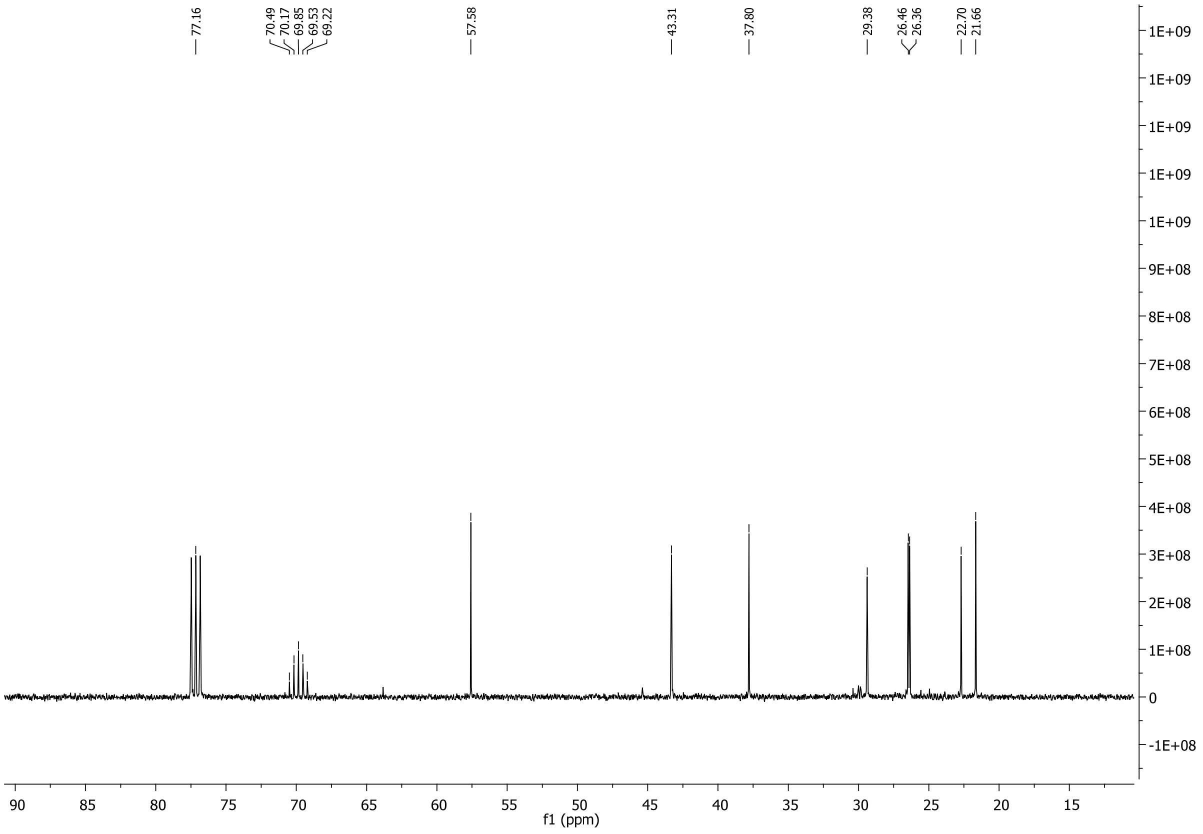
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20
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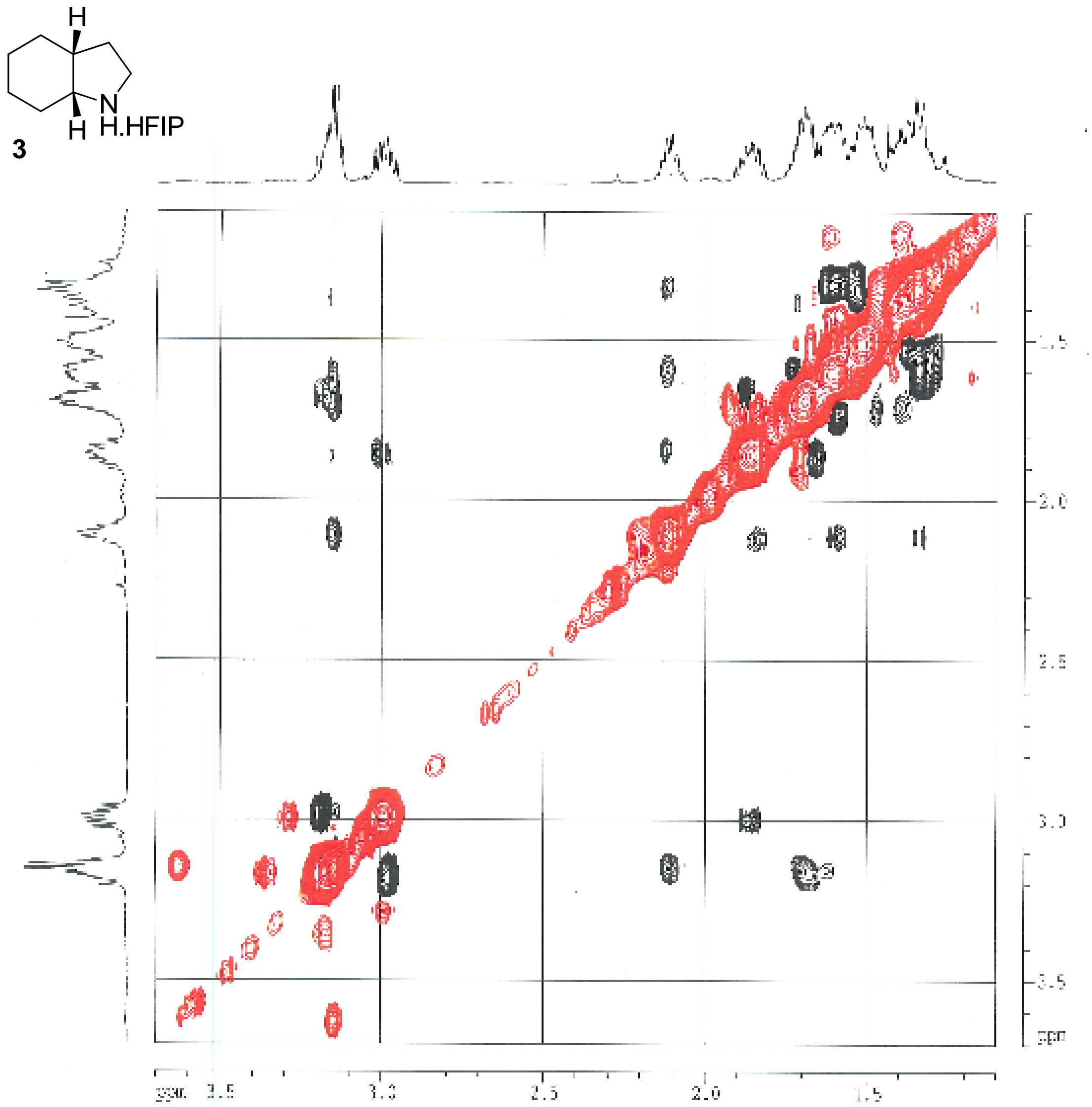
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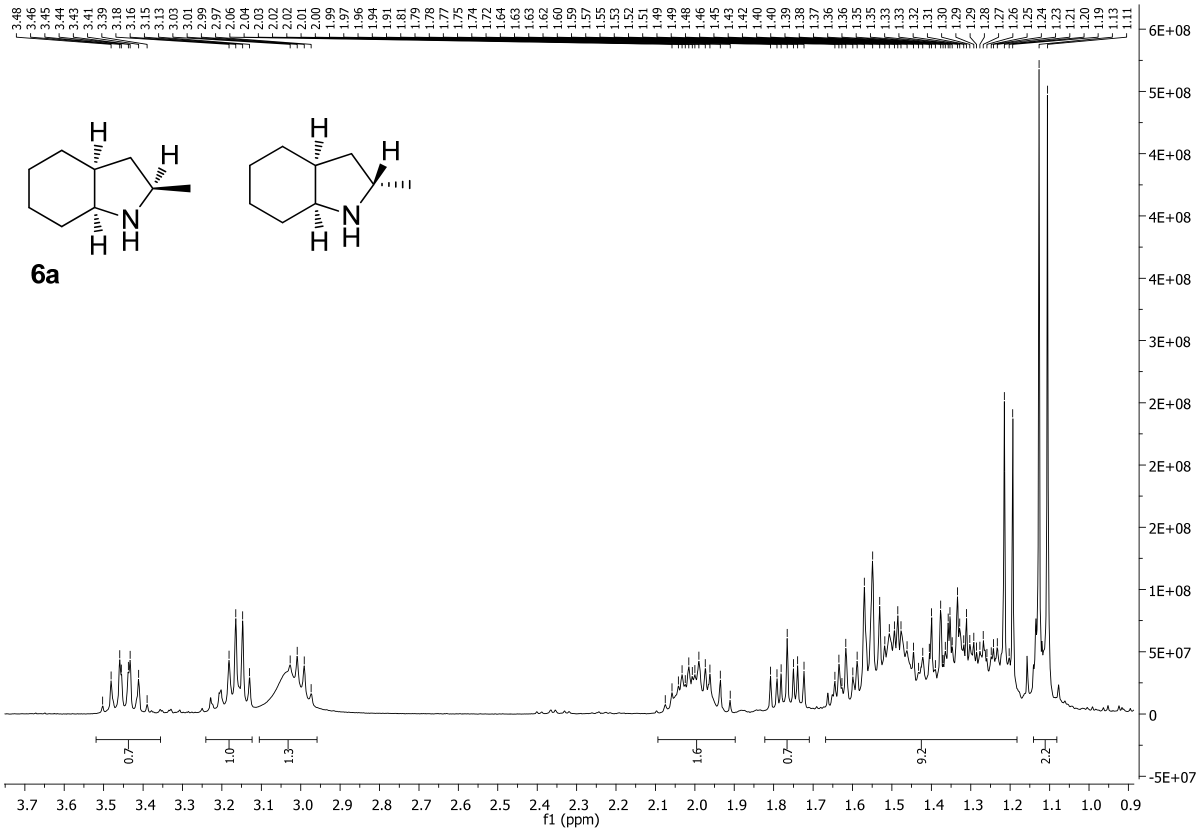
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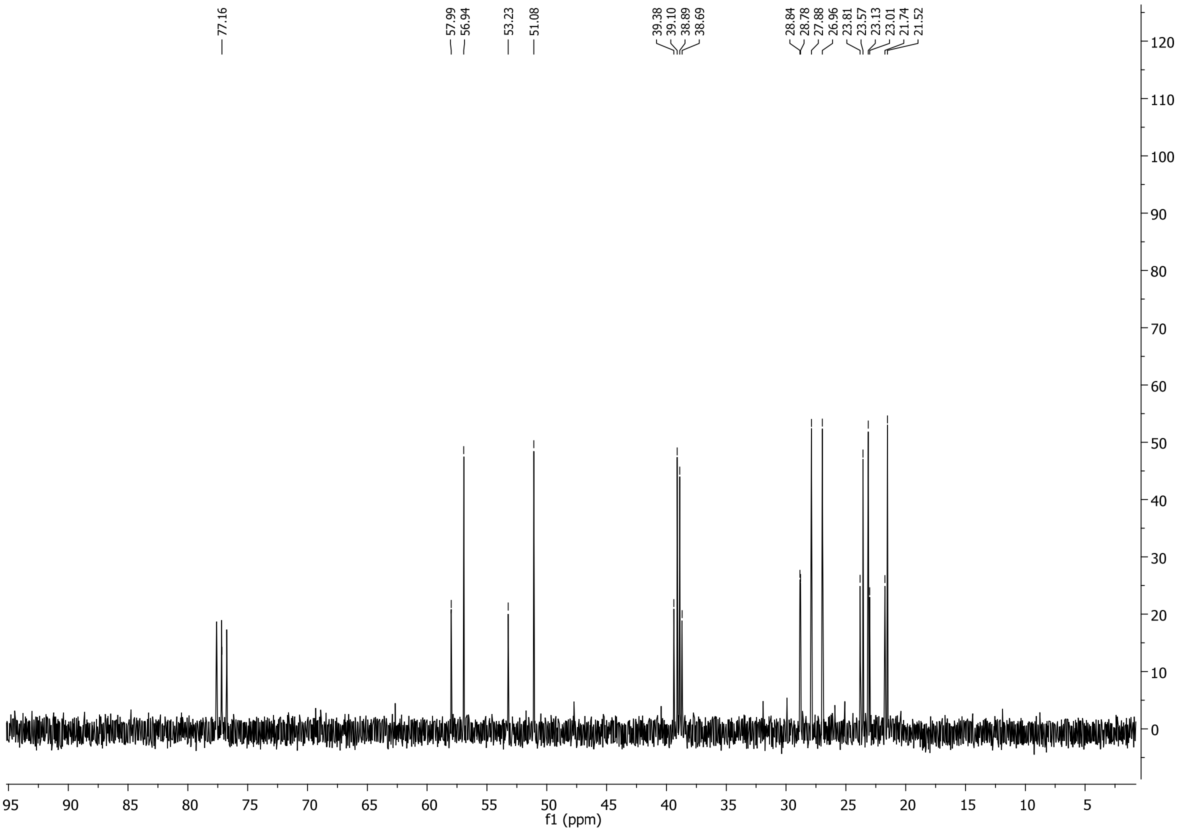
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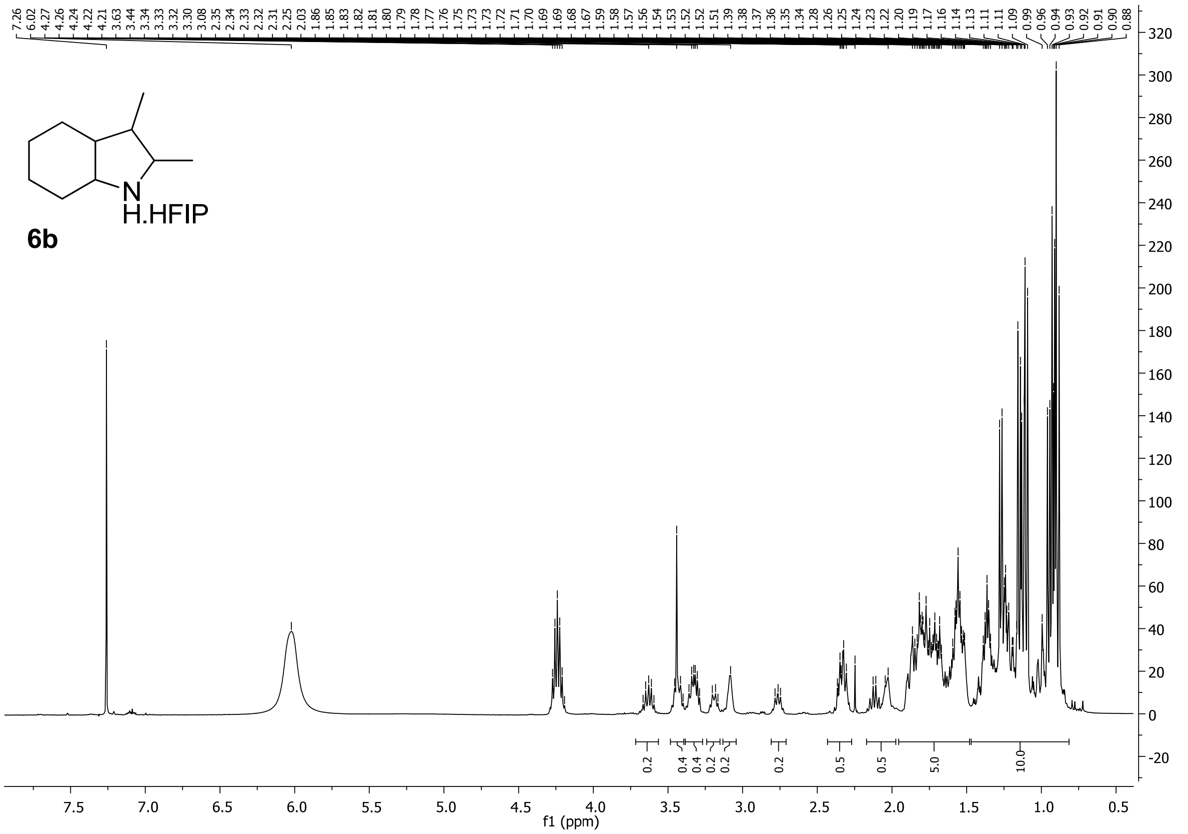
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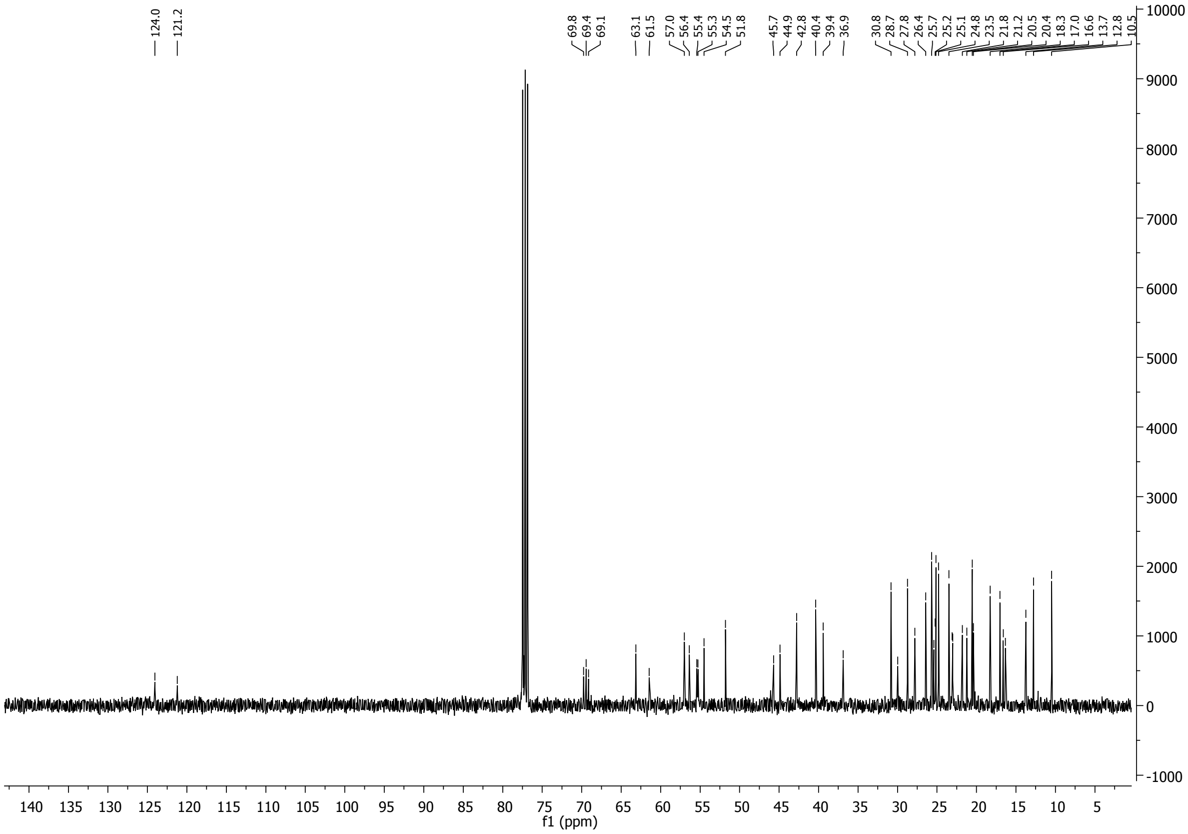
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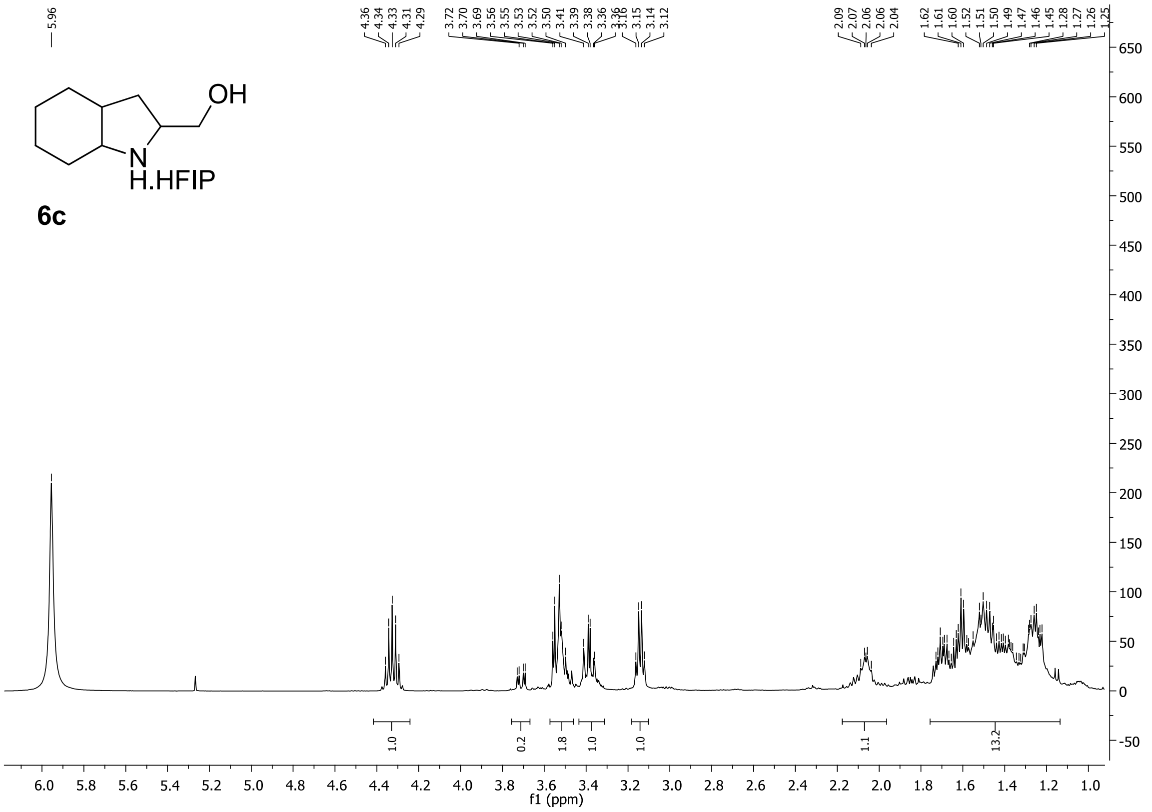
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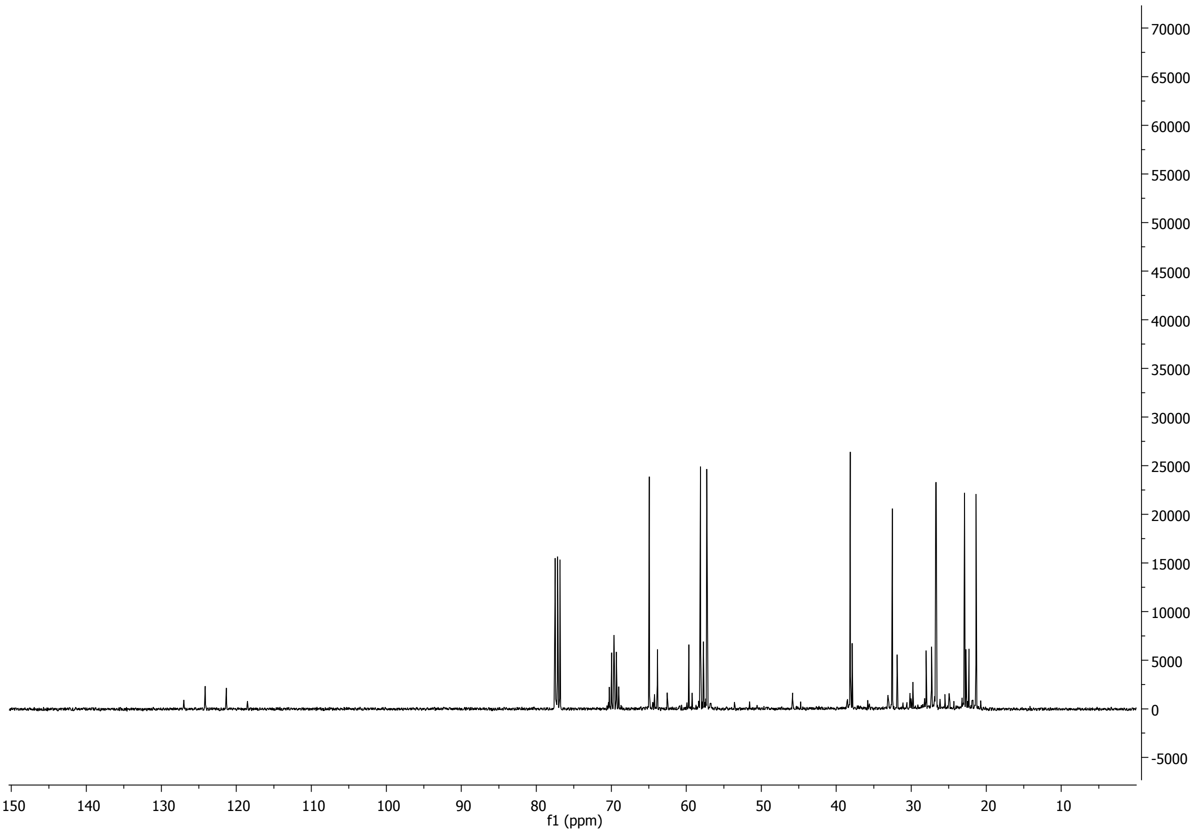
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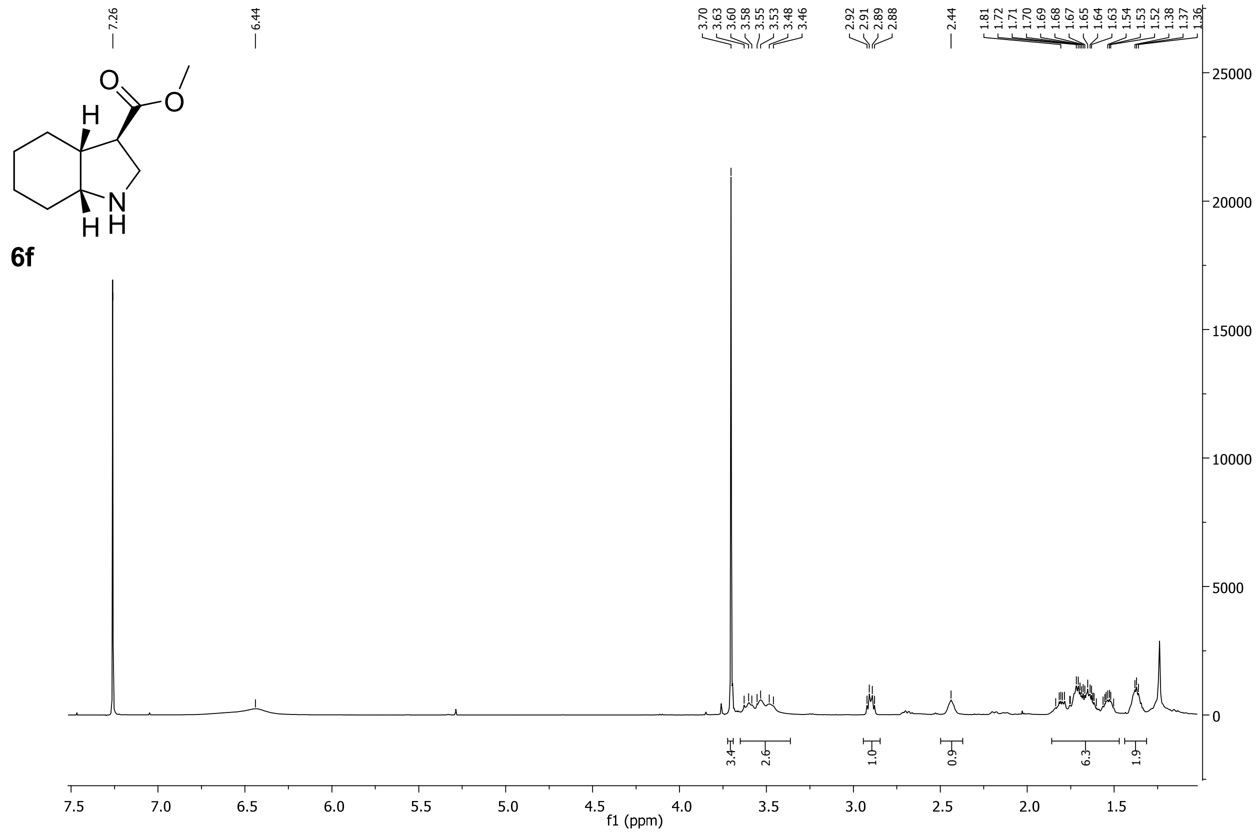
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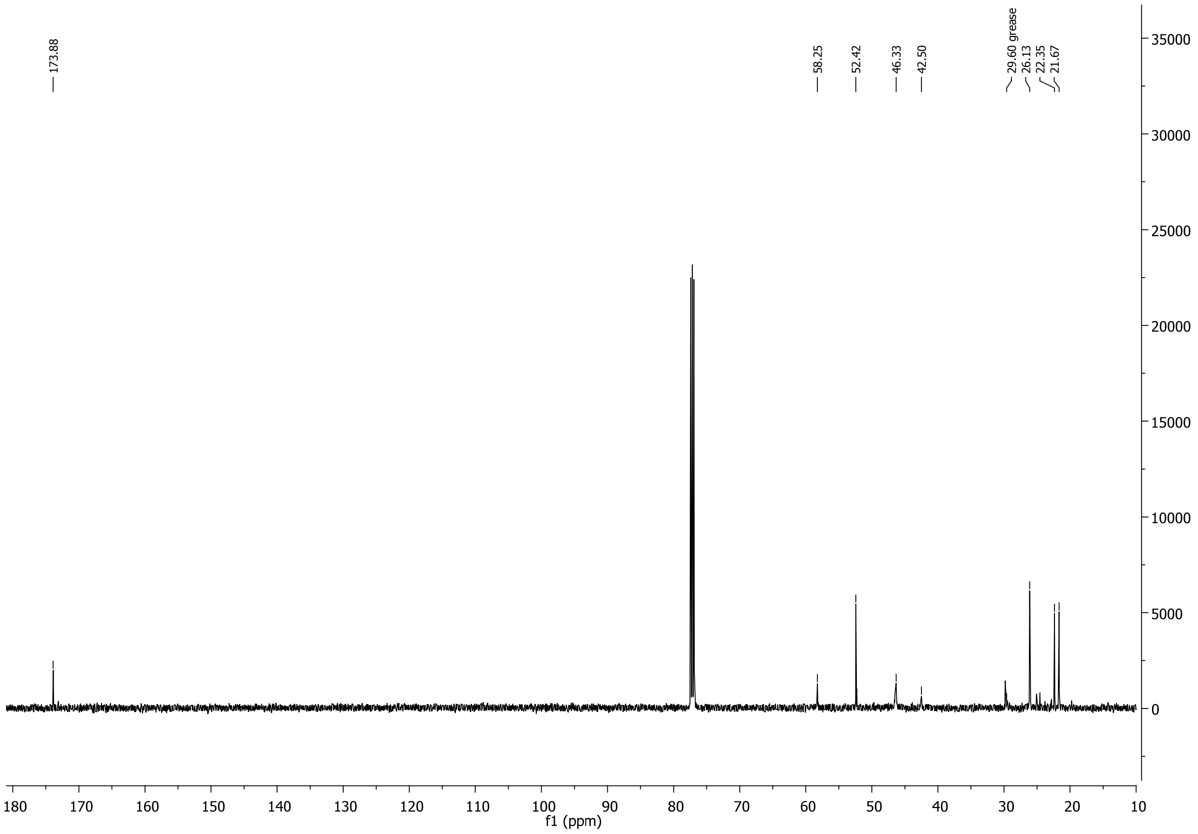
6f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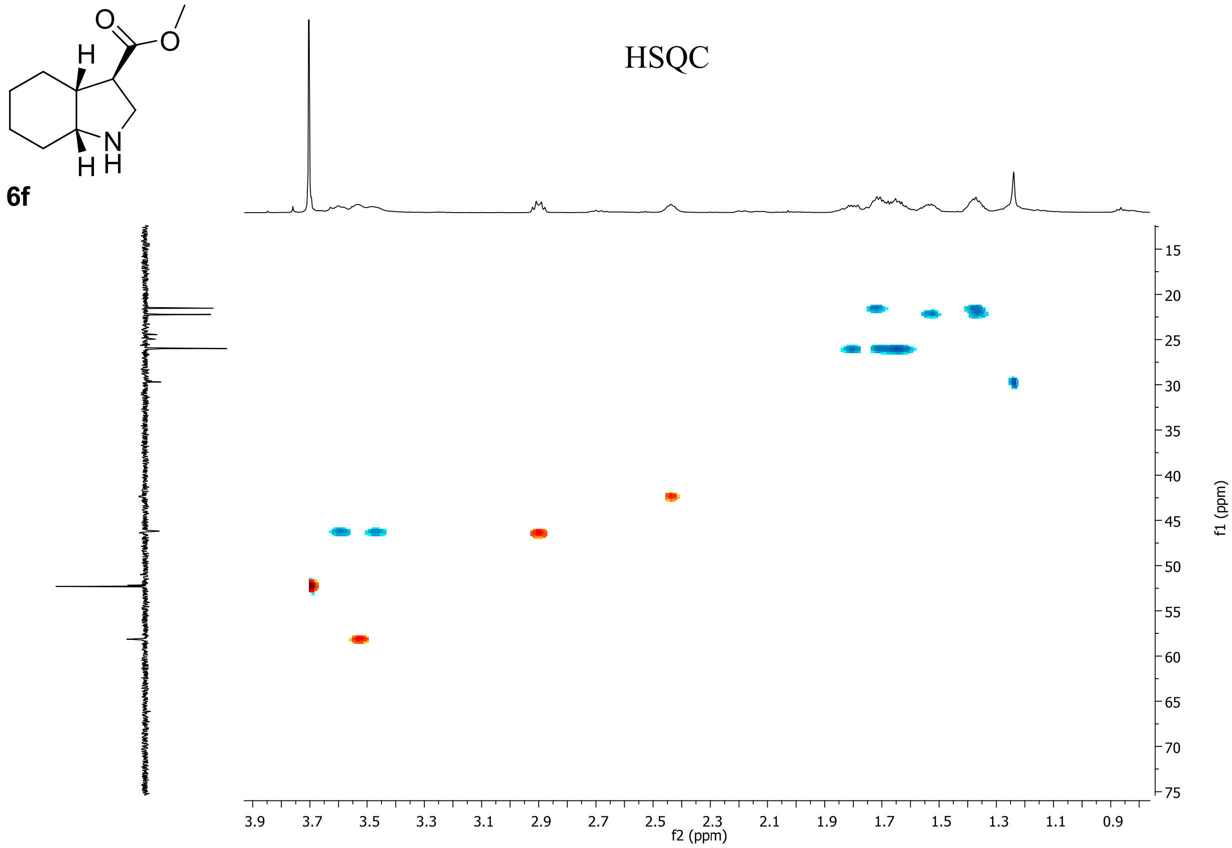
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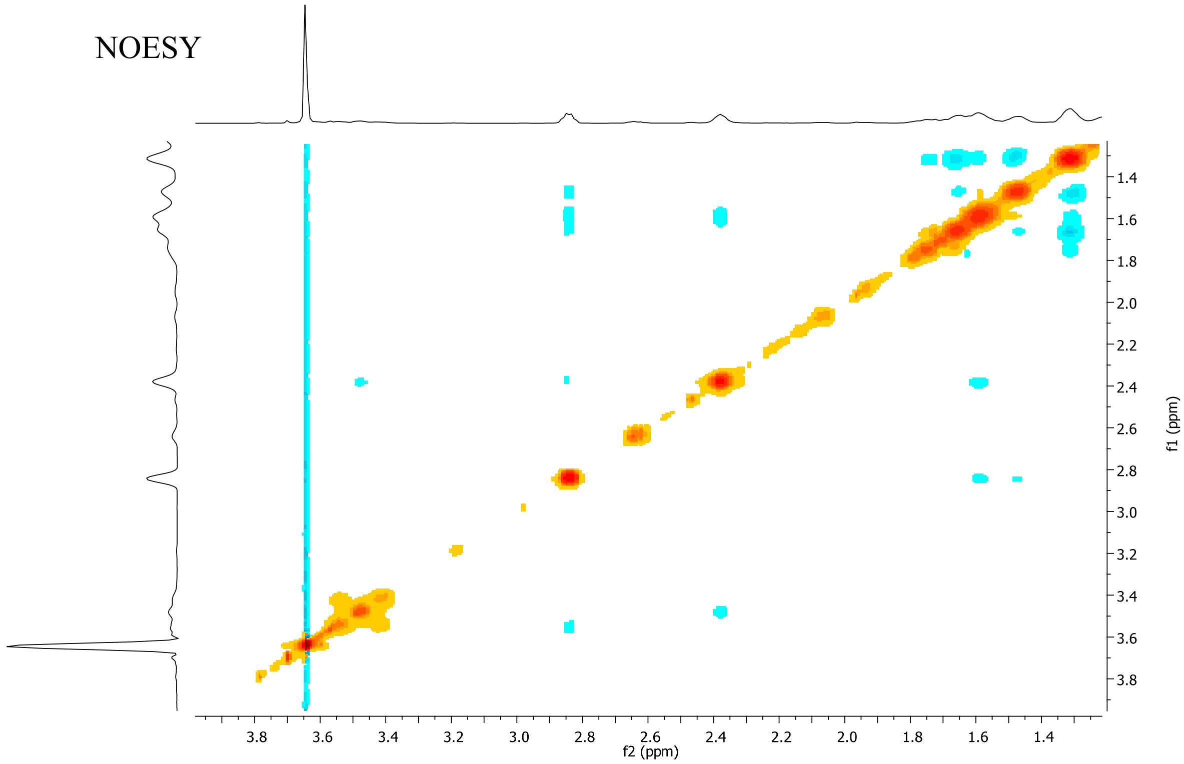
6f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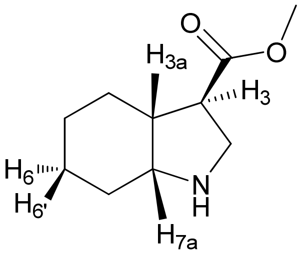
3.0
3.2
3.4
3.6
3.8

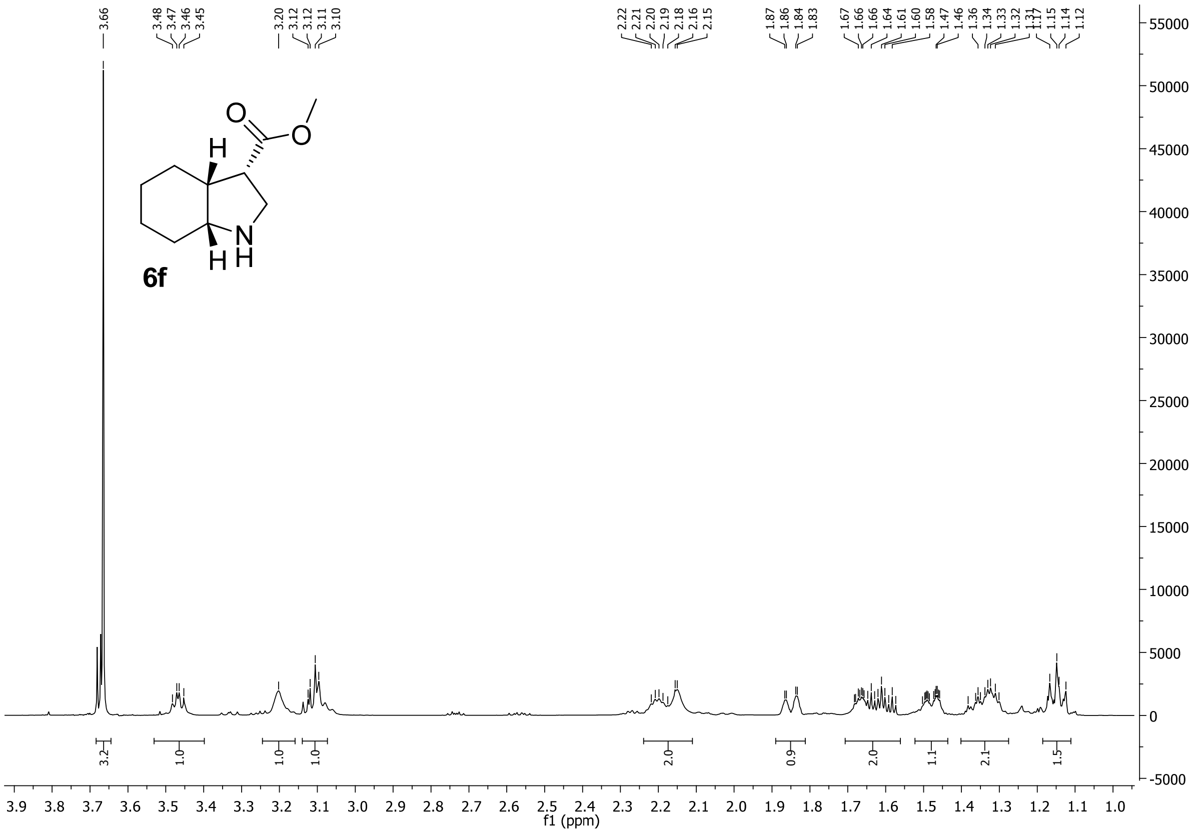
Internuclear distances driven from dipolar interactions NOESY experiments
Fixed value for H_6-$H_{6'}$ = 1.8 Å (measured by molecular modelisation)
- Grey values: outliers due to superposition of signals.
- The smaller the value, the darker the color is.



6f

(3*S**,3a*S**,7a*S**)

protons	H_{7a}	H_3	H_{3a}	H_6	$H_{6'}$
$H_{6'}$	3,2	-	2,8	1,8	$H_{6'}$
H_6	2,8	2,6	2,8	H_6	1,8
H_{3a}	2,4	3,1	H_{3a}	2,7	2,7
H_3	3,3	H_3	3,2	2,6	-
H_{7a}	H_{7a}	2,7	2,0	2,4	2,7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1.14
1.12
O
O
H
N
H H
6f
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1.0
2.0
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2.1
1.5
f1 (ppm)
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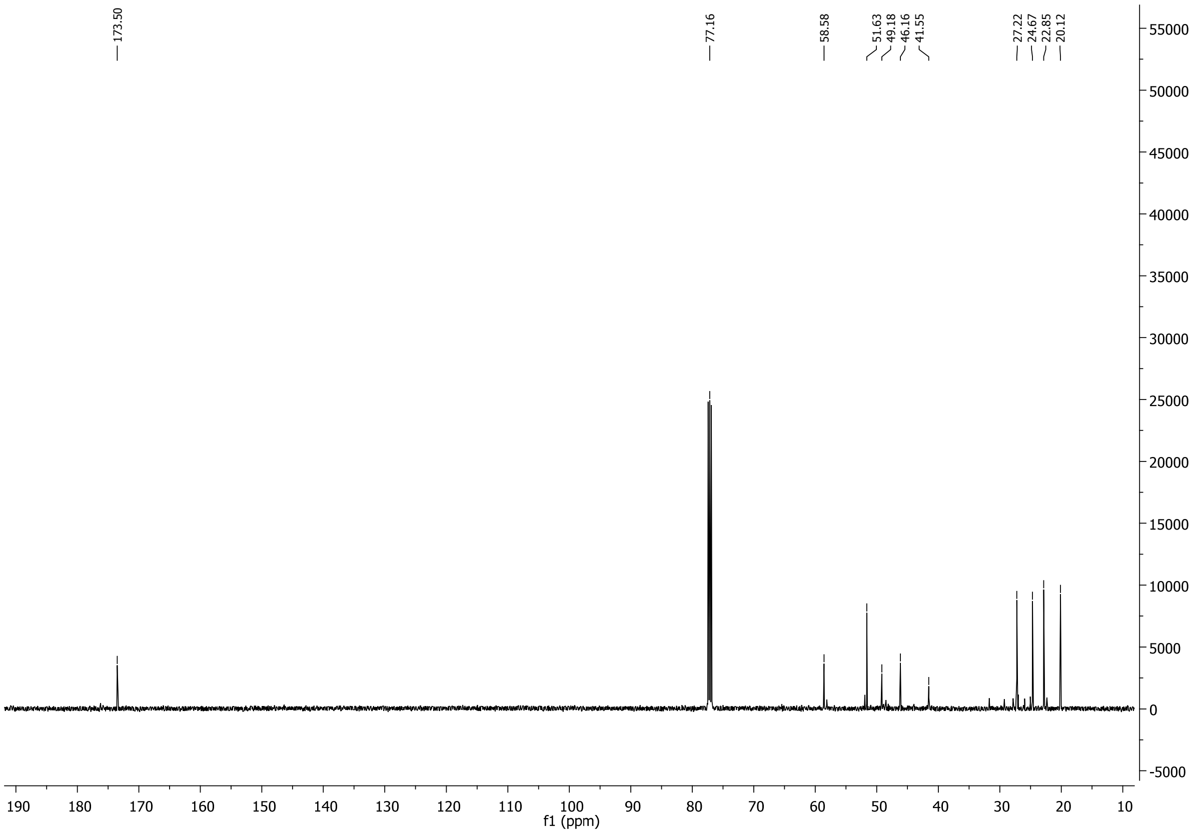
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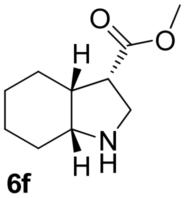
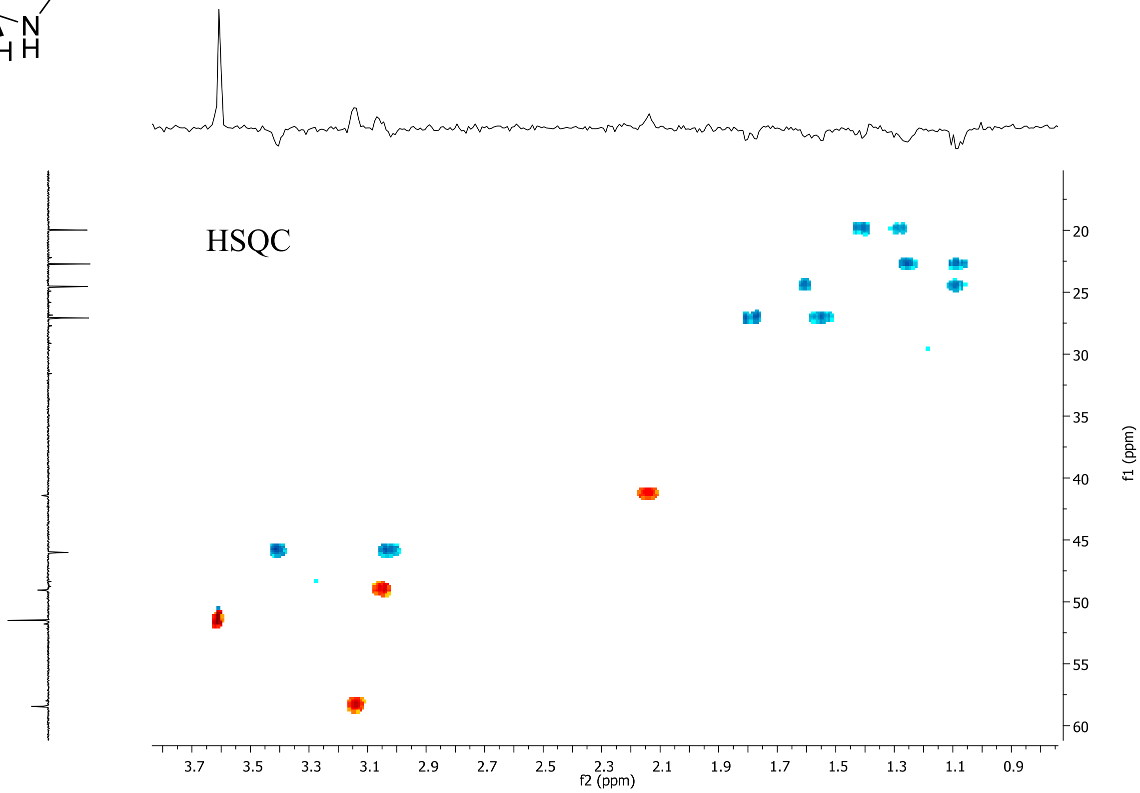
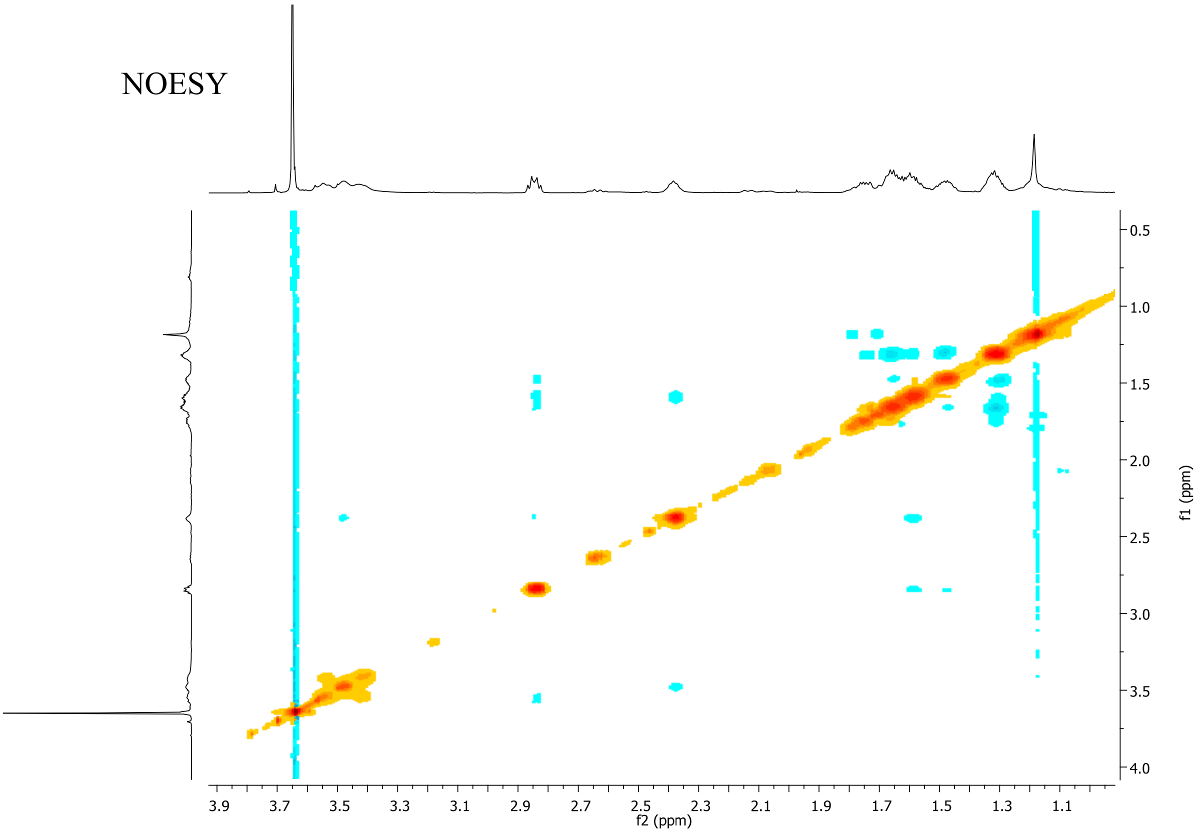
0
-5000

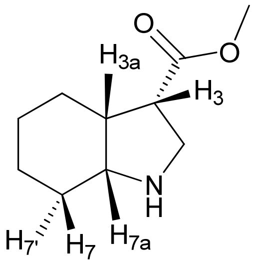

O
O
H
N
H H

6f


HSQC
20
25
30
35
40
45
50
55
60
f1 (ppm)
3.7
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
1.3
1.1
0.9
f2 (ppm)


NOESY
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
f1 (ppm)
3.9
3.7
3.5
3.3
3.1
2.9
2.7
2.5
2.3
2.1
1.9
1.7
1.5
1.3
1.1
f2 (ppm)

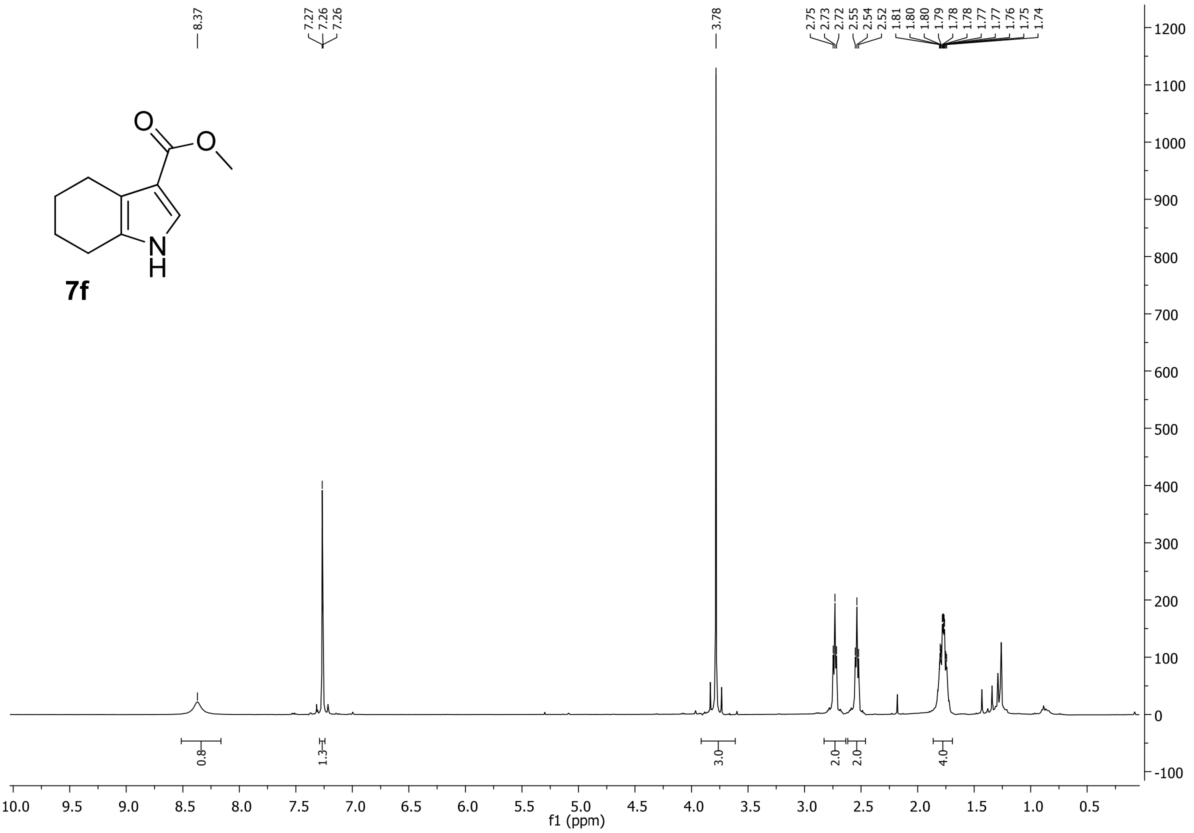
Internuclear distances driven from dipolar interactions NOESY experiments
Fixed value for H_7-$H_{7'}$ = 1.8 Å (measured by molecular modelisation)
- Grey values: outliers due to superposition of signals.
- The smaller the value, the darker the color is.

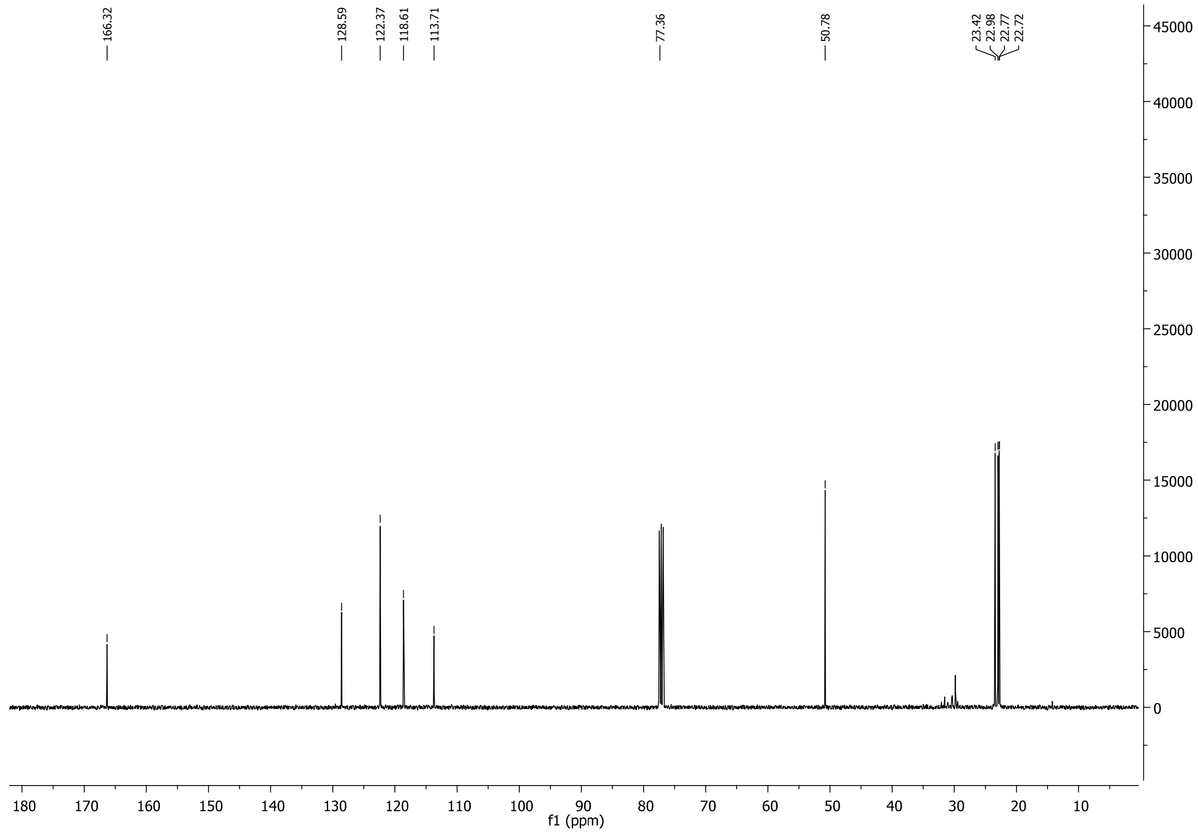


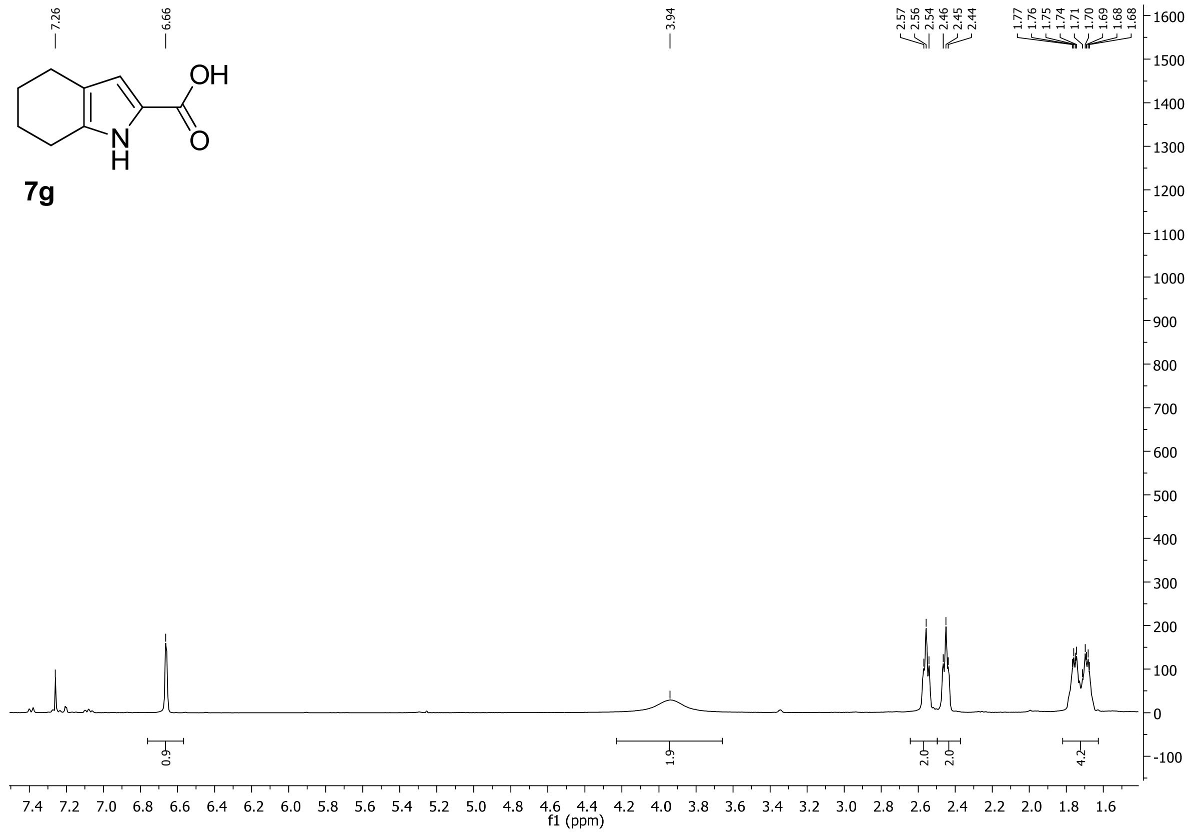
6f

(3*R**,3a*S**,7a*S**)

protons	H_{7a}	H_3	H_{3a}	H_7	$H_{7'}$
$H_{7'}$	2,3	-	2,7	1,8	$H_{7'}$
H_7	2,4	4,5	2,9	H_7	1,8
H_{3a}	2,5	2,5	H_{3a}	3,1	2,9
H_3	-	H_3	2,4	4,8	-
H_{7a}	H_{7a}	-	2,3	2,4	2,3

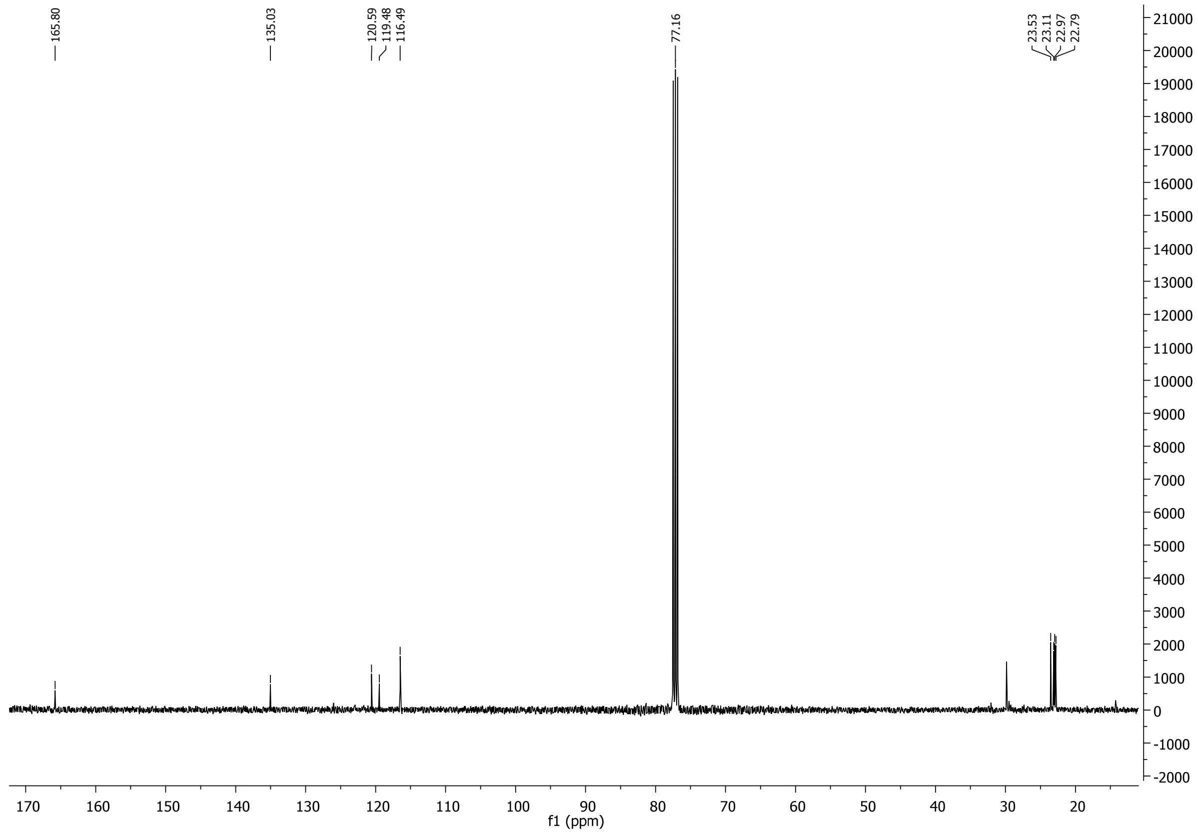

7f
8.37
7.27
7.26
7.26
3.78
2.75
2.73
2.72
2.55
2.54
2.52
1.81
1.80
1.80
1.79
1.78
1.78
1.77
1.77
1.76
1.75
1.74
O
O
N
H
0.8
1.3
3.0
2.0
2.0
4.0
f1 (ppm)


166.32
128.59
122.37
118.61
113.71
77.36
50.78
23.42
22.98
22.77
22.72
f1 (ppm)

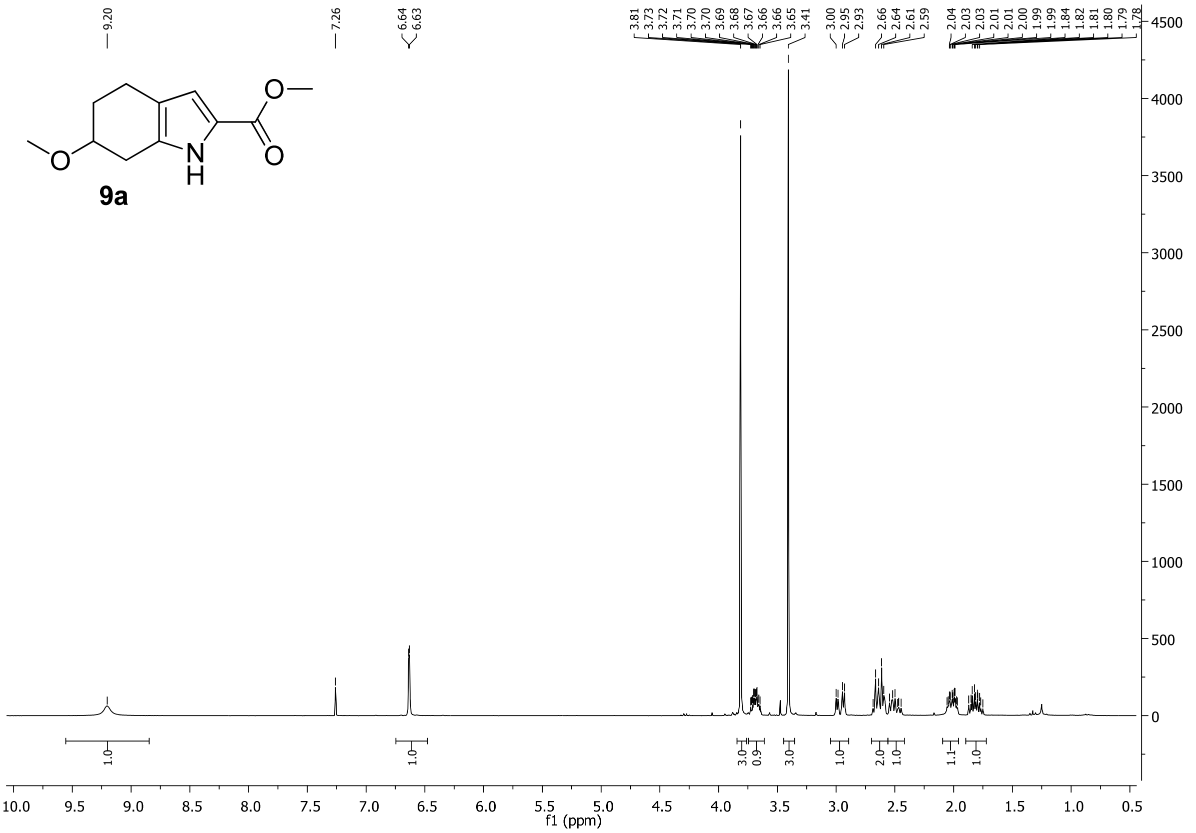


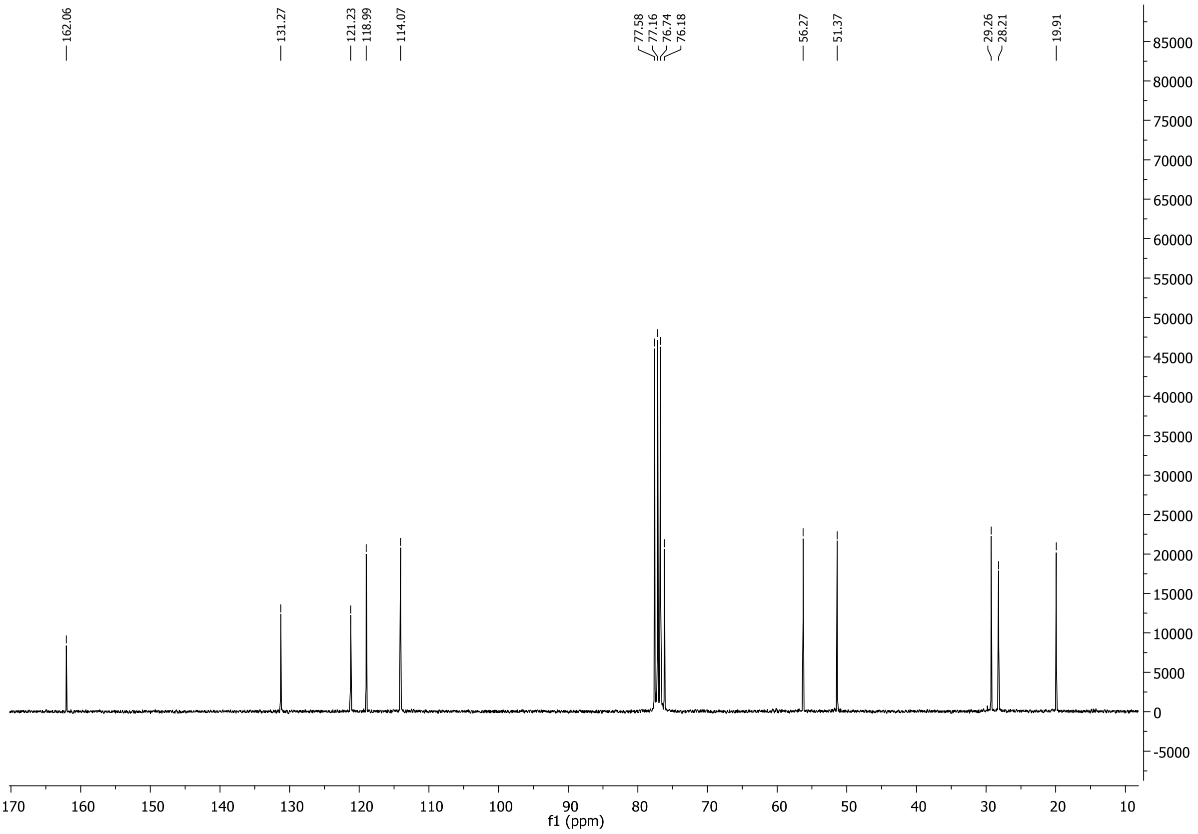
7g

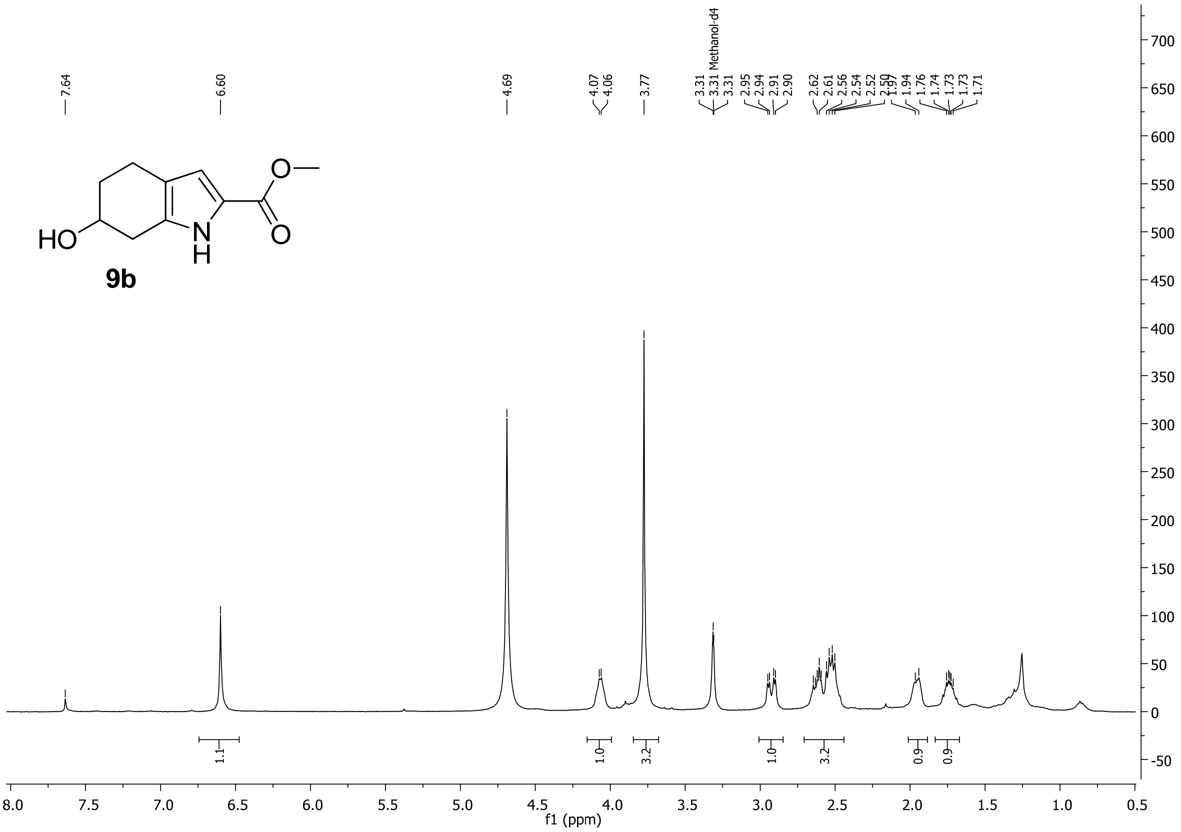
7.26
6.66
3.94
2.57
2.56
2.54
2.46
2.45
2.44
1.77
1.76
1.75
1.74
1.71
1.70
1.69
1.68
1.68
OH
O
N
H
0.9
1.9
2.0
2.0
4.2
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)

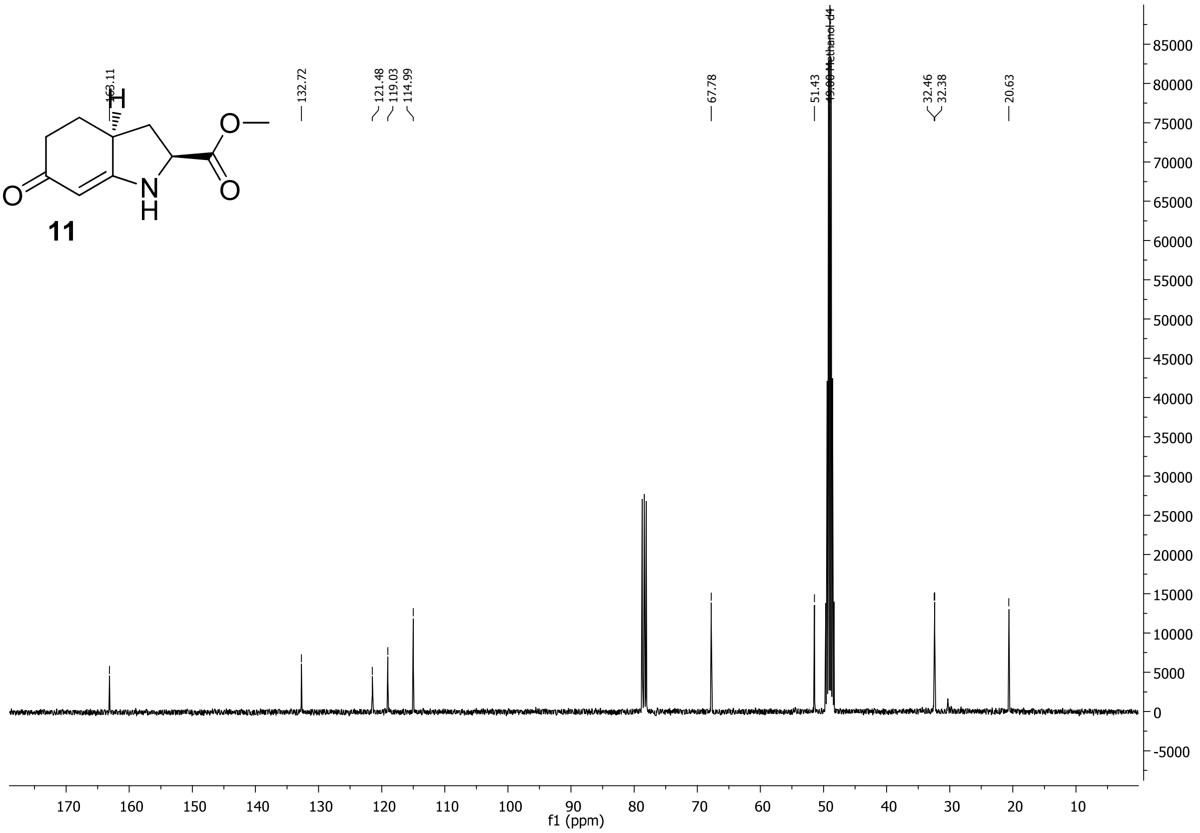


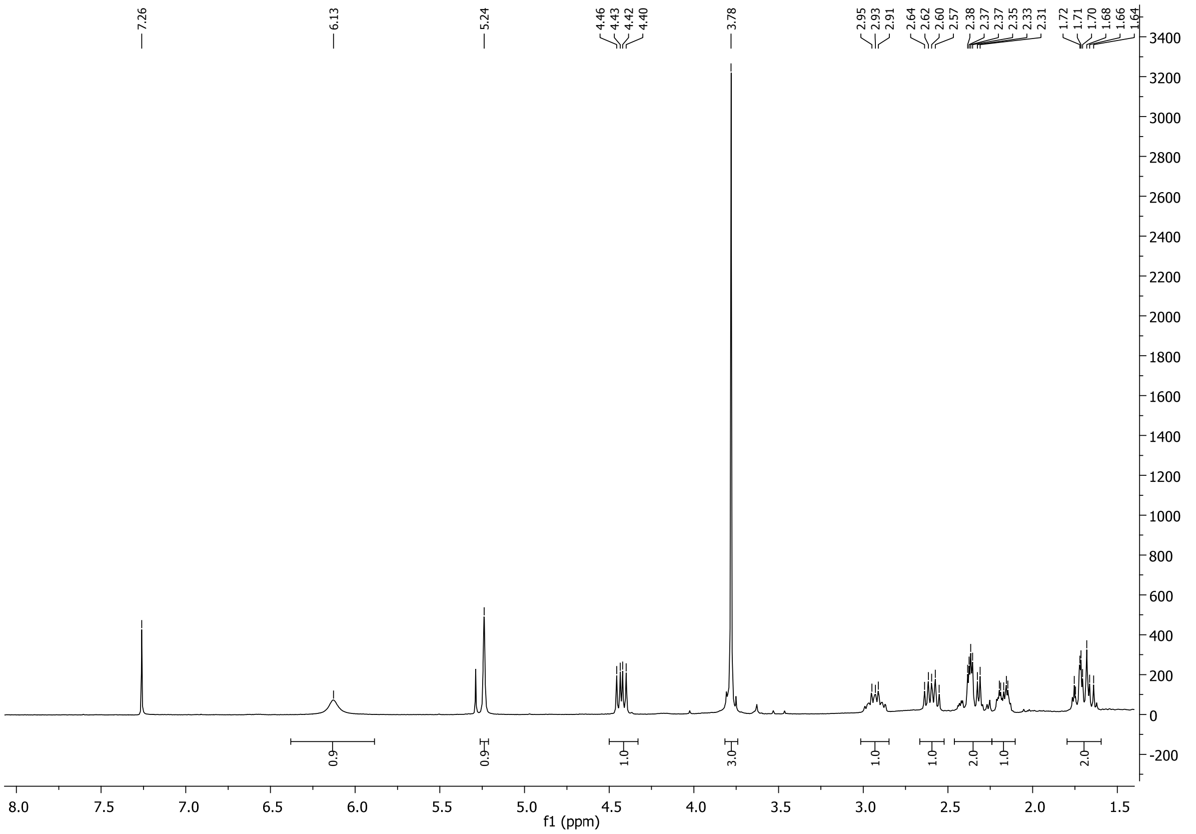
165.80
135.03
120.59
119.48
116.49
77.16
23.53
23.11
22.97
22.79
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

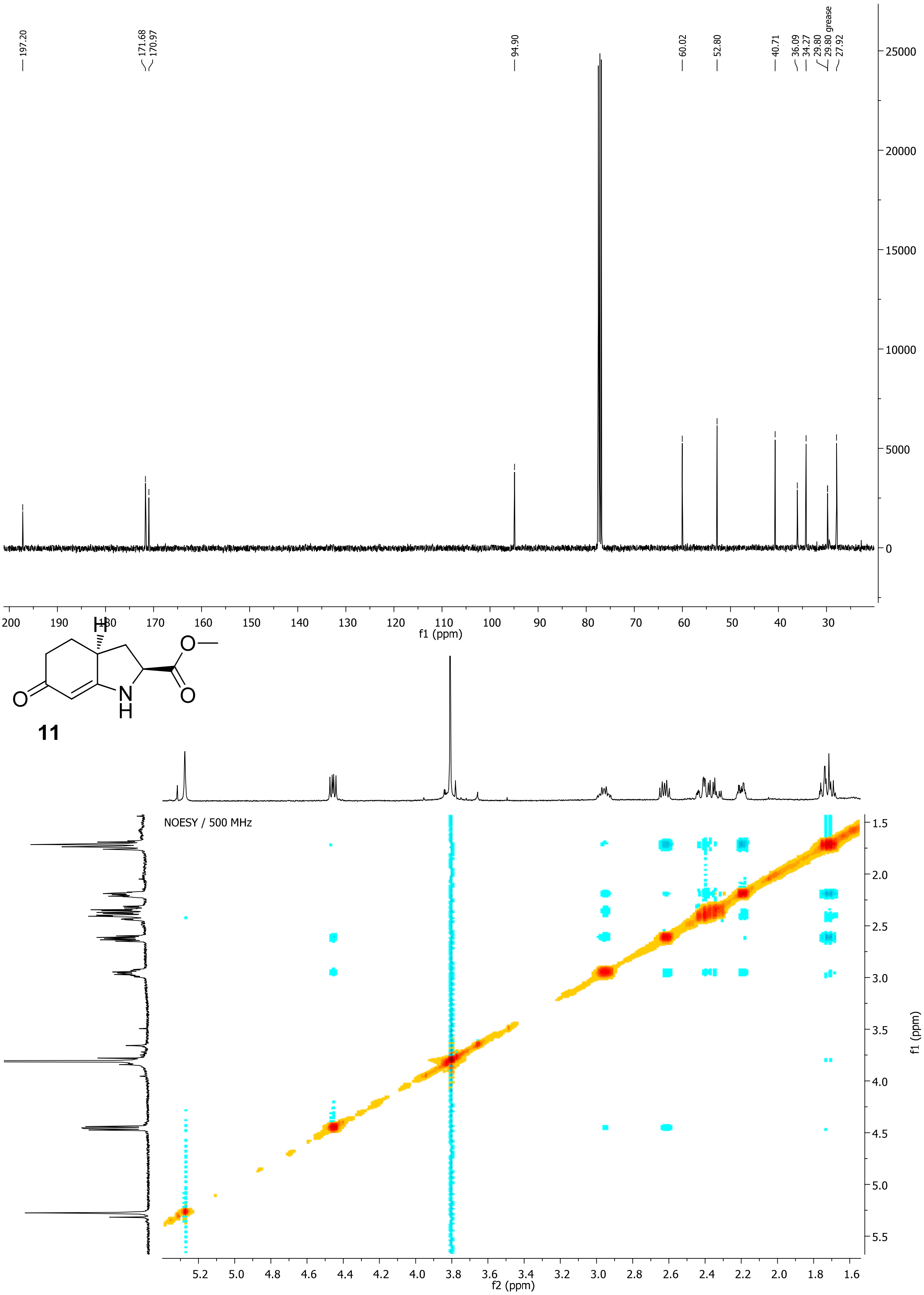

9a
9.20
7.26
6.64
6.63
3.81
3.73
3.72
3.71
3.70
3.70
3.69
3.68
3.67
3.66
3.66
3.65
3.41
3.00
2.95
2.93
2.66
2.64
2.61
2.59
2.04
2.03
2.03
2.01
2.01
2.00
1.99
1.99
1.84
1.82
1.81
1.80
1.79
1.78
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1.0
1.0
3.0
0.9
3.0
1.0
2.0
1.0
1.1
1.0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
O
N
H
O
O


162.06
131.27
121.23
118.99
114.07
77.58
77.16
76.74
76.18
56.27
51.37
29.26
28.21
19.91
85000
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

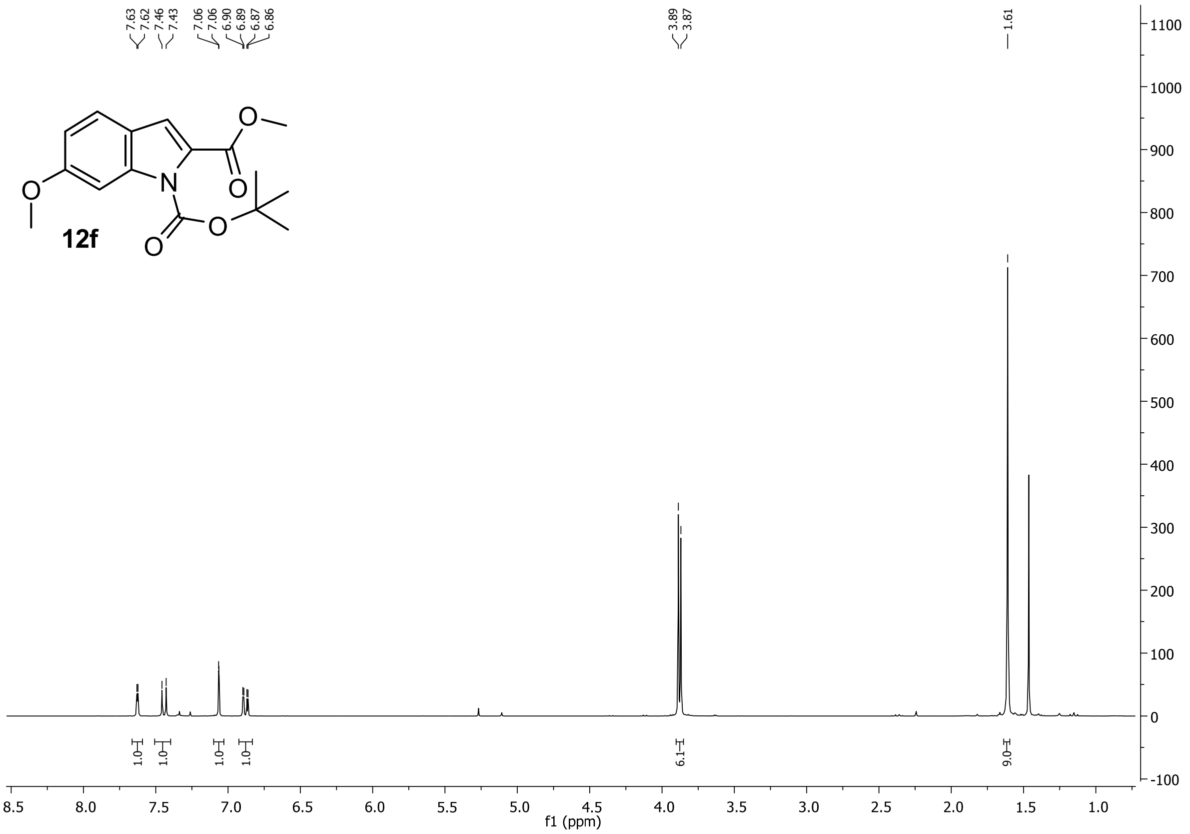

7.64
6.60
4.69
4.07
4.06
3.77
3.31
3.31 Methanol-d4
3.31
2.95
2.94
2.91
2.90
2.62
2.61
2.56
2.54
2.52
2.50
1.97
1.94
1.76
1.74
1.73
1.73
1.71
HO
N
H
O
O
9b
1.1
1.0
3.2
1.0
3.2
0.9
0.9
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

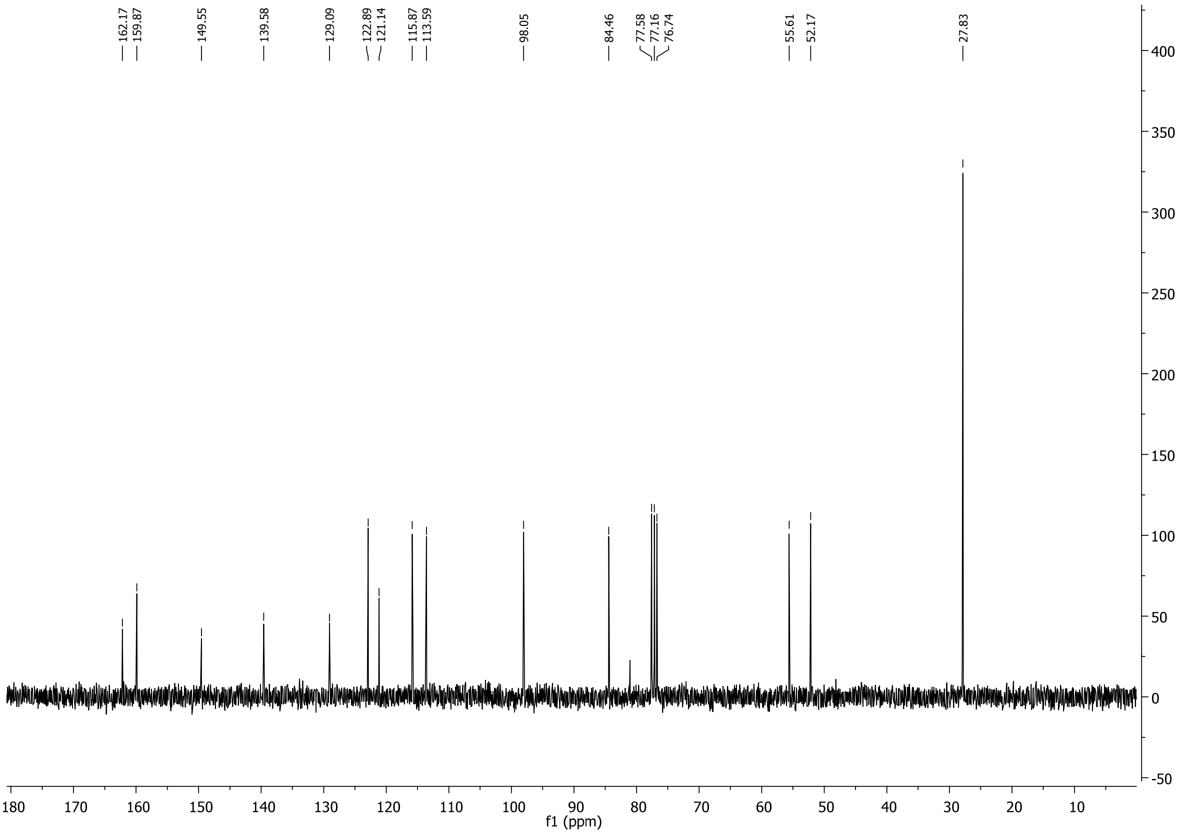

H
O
N
H
O
O
11
163.11
132.72
121.48
119.03
114.99
67.78
51.43
49.00 Methanol-d4
32.46
32.38
20.63
85000
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

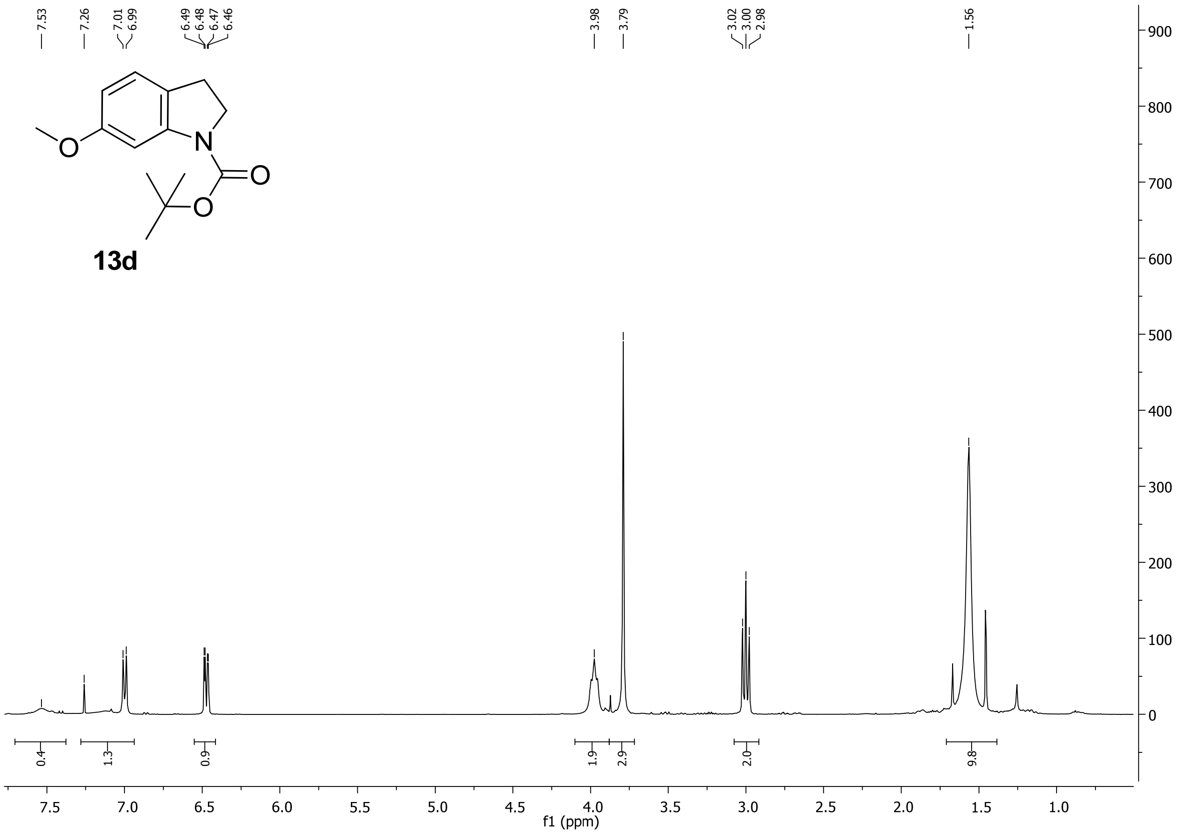

7.26
6.13
5.24
4.46
4.43
4.42
4.40
3.78
2.95
2.93
2.91
2.64
2.62
2.60
2.57
2.38
2.37
2.37
2.35
2.33
2.31
1.72
1.71
1.70
1.68
1.66
1.64
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
0.9
0.9
1.0
3.0
1.0
1.0
2.0
1.0
2.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


197.20
171.68
170.97
94.90
60.02
52.80
40.71
36.09
34.27
29.80
29.80 grease
27.92
25000
20000
15000
10000
5000
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)
H
O
N
H
O
O
NOESY / 500 MHz
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
f1 (ppm)
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
f2 (ppm)

11

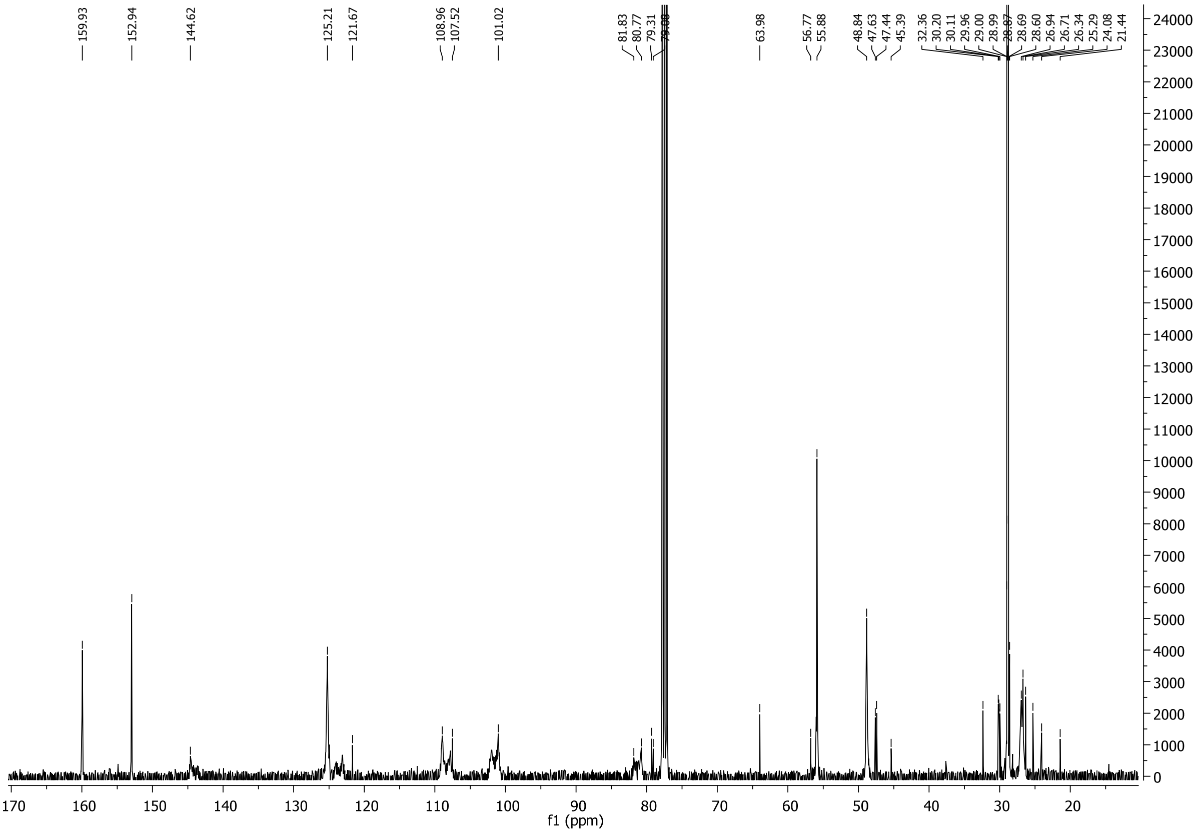

7.63
7.62
7.46
7.43
7.06
7.06
6.90
6.89
6.87
6.86
3.89
3.87
1.61
12f
1.0
1.0
1.0
1.0
6.1
9.0
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


162.17
159.87
149.55
139.58
129.09
122.89
121.14
115.87
113.59
98.05
84.46
77.58
77.16
76.74
55.61
52.17
27.83
400
350
300
250
200
150
100
50
0
-50
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

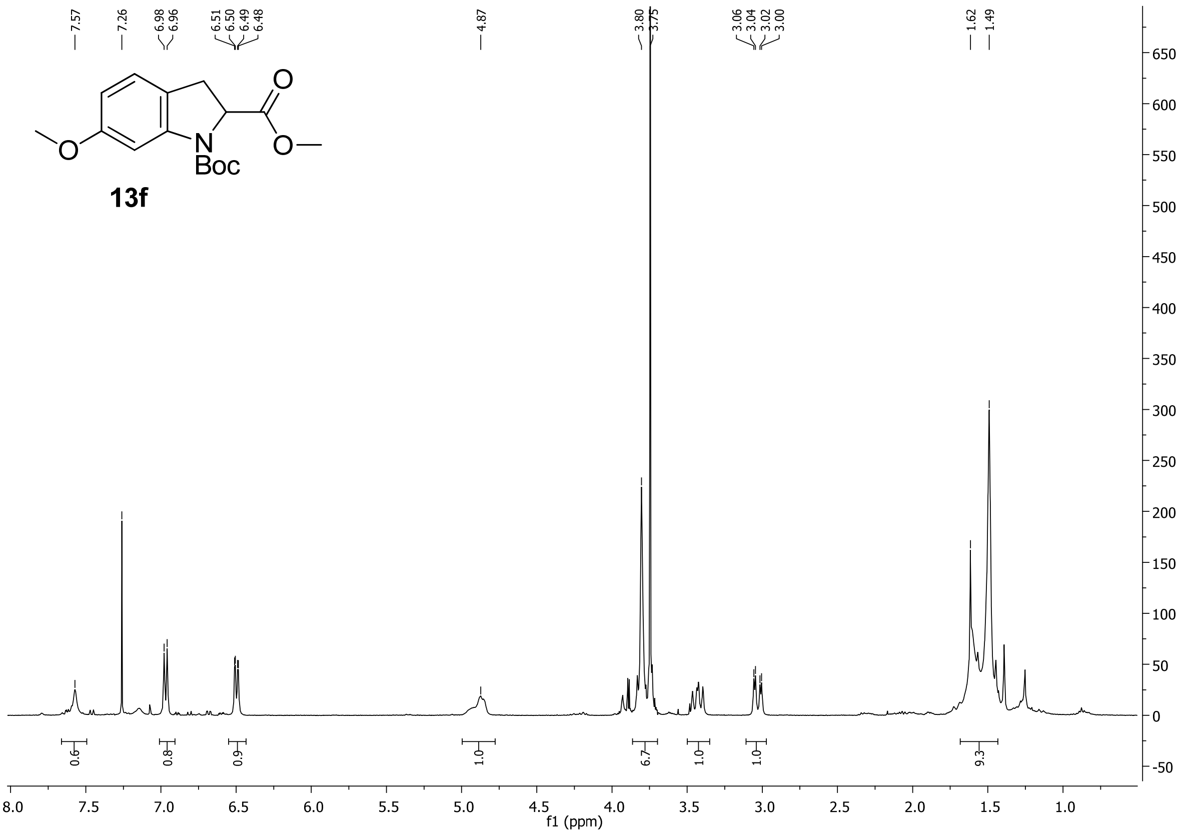


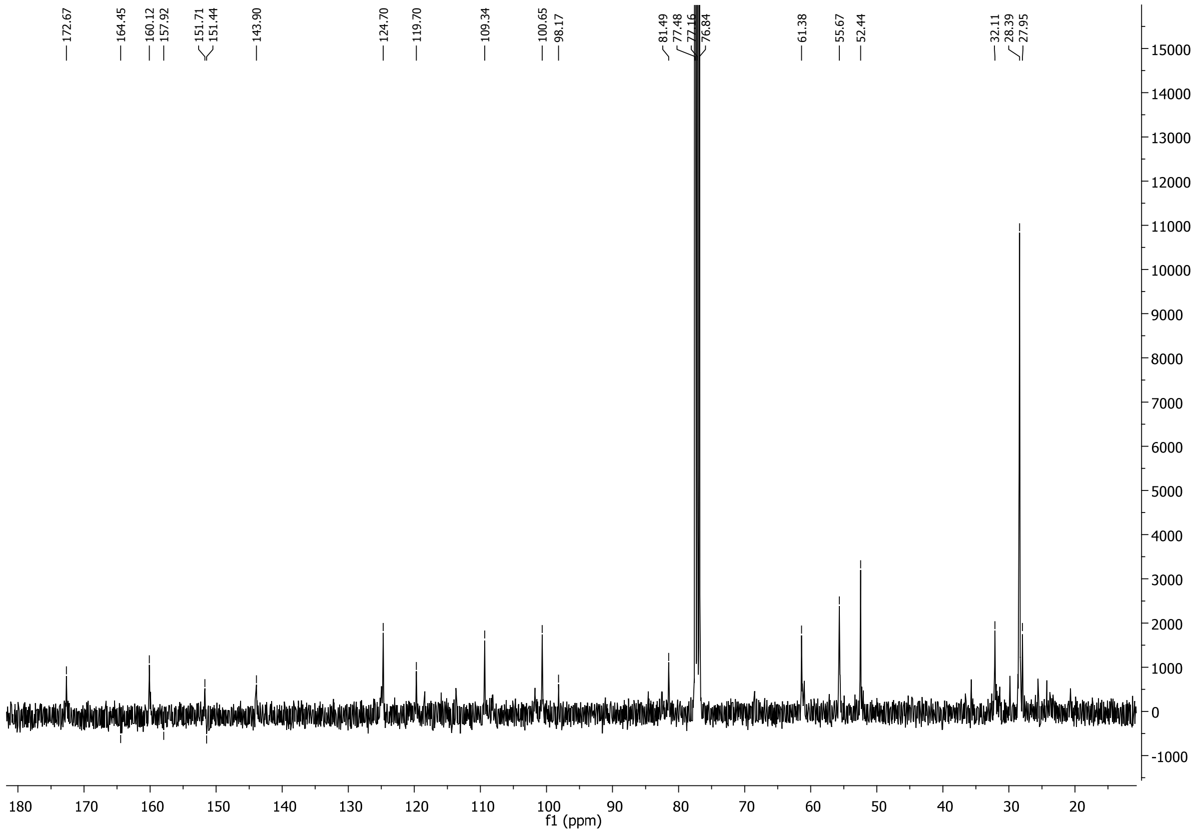
13d

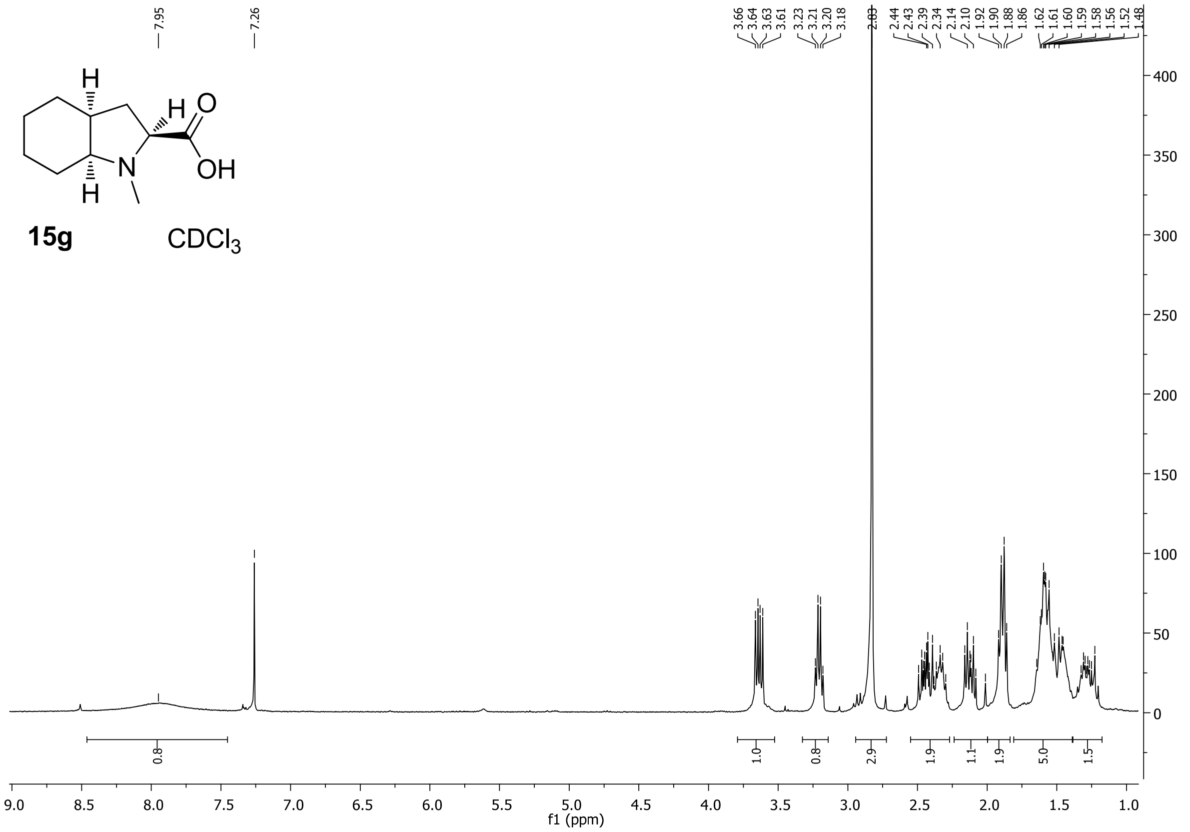
7.53
7.26
7.01
6.99
6.49
6.48
6.47
6.46
3.98
3.79
3.02
3.00
2.98
1.56
O
N
O
O
0.4
1.3
0.9
1.9
2.9
2.0
9.8
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
900
800
700
600
500
400
300
200
100
0



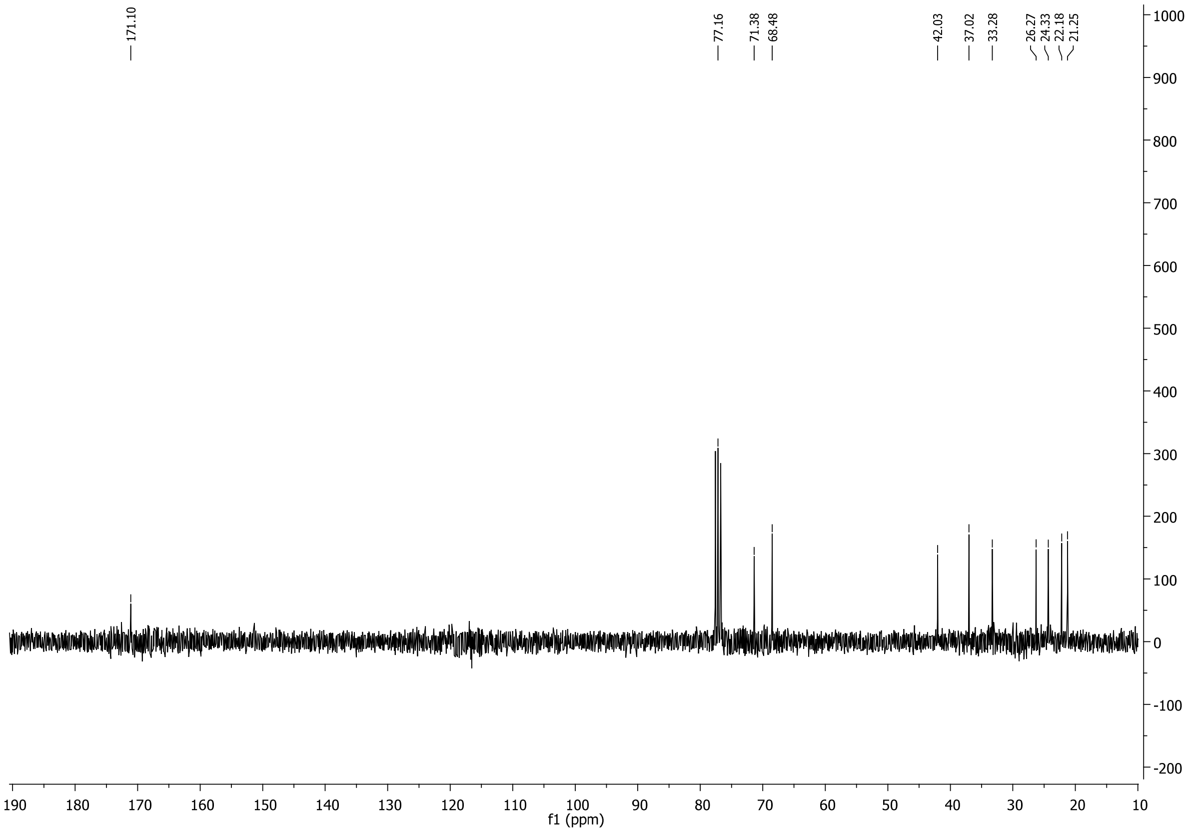
159.93
152.94
144.62
125.21
121.67
108.96
107.52
101.02
81.83
80.77
79.31
79.00
63.98
56.77
55.88
48.84
47.63
47.44
45.39
32.36
30.20
30.11
29.96
29.00
28.99
28.87
28.69
28.60
26.94
26.71
26.34
25.29
24.08
21.44
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0


13f
7.57
7.26
6.98
6.96
6.51
6.50
6.49
6.48
4.87
3.80
3.75
3.06
3.04
3.02
3.00
1.62
1.49
O
N
Boc
O
O
0.6
0.8
0.9
1.0
6.7
1.0
1.0
9.3
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

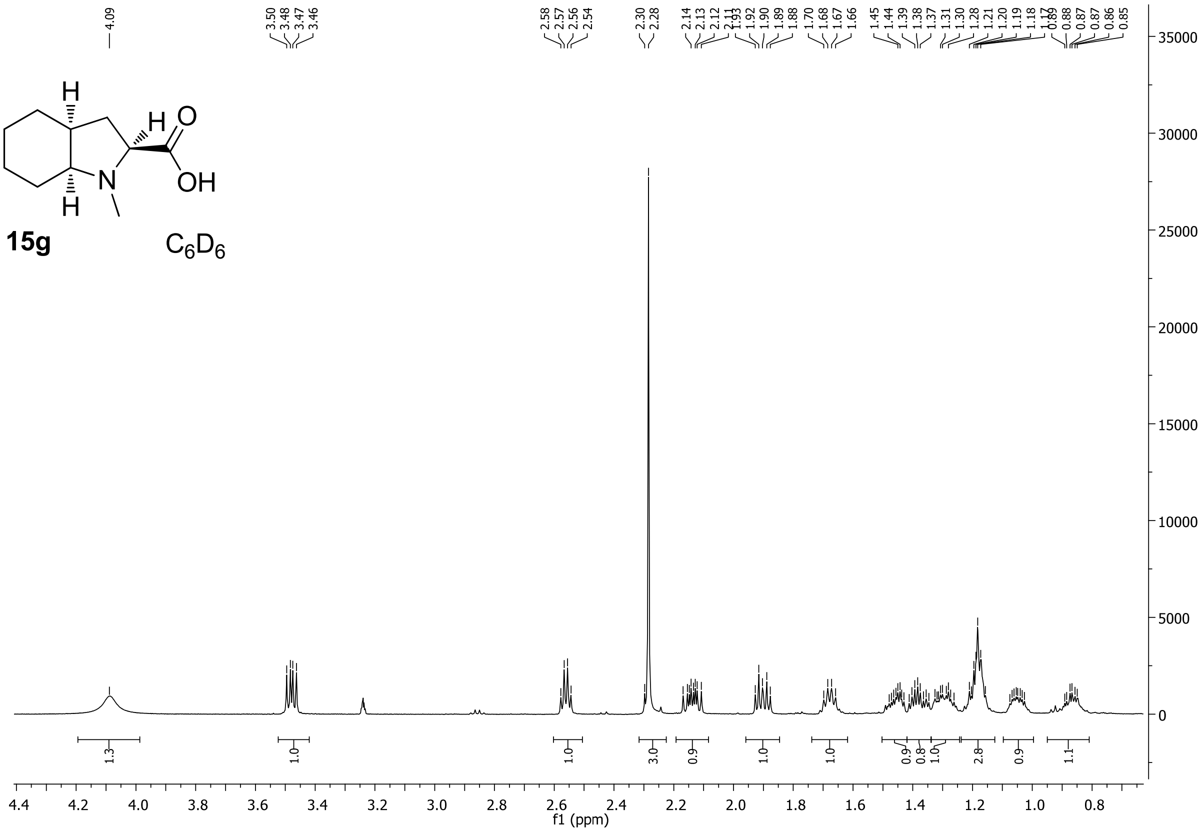

172.67
164.45
160.12
157.92
151.71
151.44
143.90
124.70
119.70
109.34
100.65
98.17
81.49
77.48
77.16
76.84
61.38
55.67
52.44
32.11
28.39
27.95
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

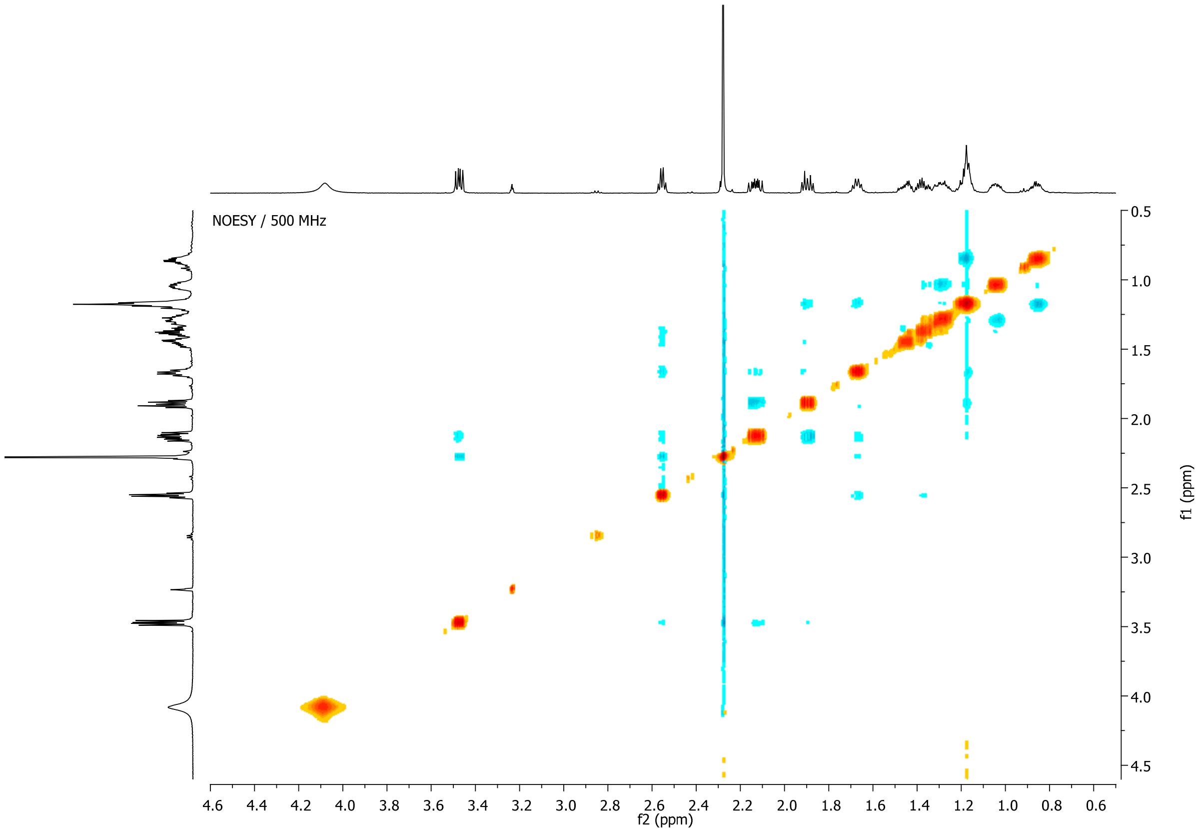


15g
CDCl3
7.95
7.26
3.66
3.64
3.63
3.61
3.23
3.21
3.20
3.18
2.83
2.44
2.43
2.39
2.34
2.14
2.10
1.92
1.90
1.88
1.86
1.62
1.61
1.60
1.59
1.58
1.56
1.52
1.48
0.8
1.0
0.8
2.9
1.9
1.1
1.9
5.0
1.5
400
350
300
250
200
150
100
50
0
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

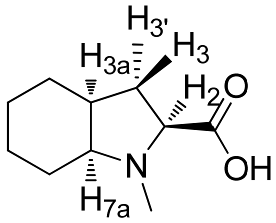


171.10
77.16
71.38
68.48
42.03
37.02
33.28
26.27
24.33
22.18
21.25
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


4.09
3.50 3.48 3.47 3.46
2.58 2.57 2.56 2.54
2.30 2.28
2.14 2.13 2.12 2.11 1.93 1.92 1.90 1.89 1.88 1.70 1.68 1.67 1.66 1.45 1.44 1.39 1.38 1.37 1.31 1.30 1.28 1.21 1.20 1.19 1.18 1.17 0.89 0.88 0.87 0.86 0.85
H
H
O
N
OH
H
15g
C_6D_6
35000
30000
25000
20000
15000
10000
5000
0
1.3
1.0
1.0
3.0
0.9
1.0
1.0
0.9
0.8
1.0
2.8
0.9
1.1
4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8
f1 (ppm)

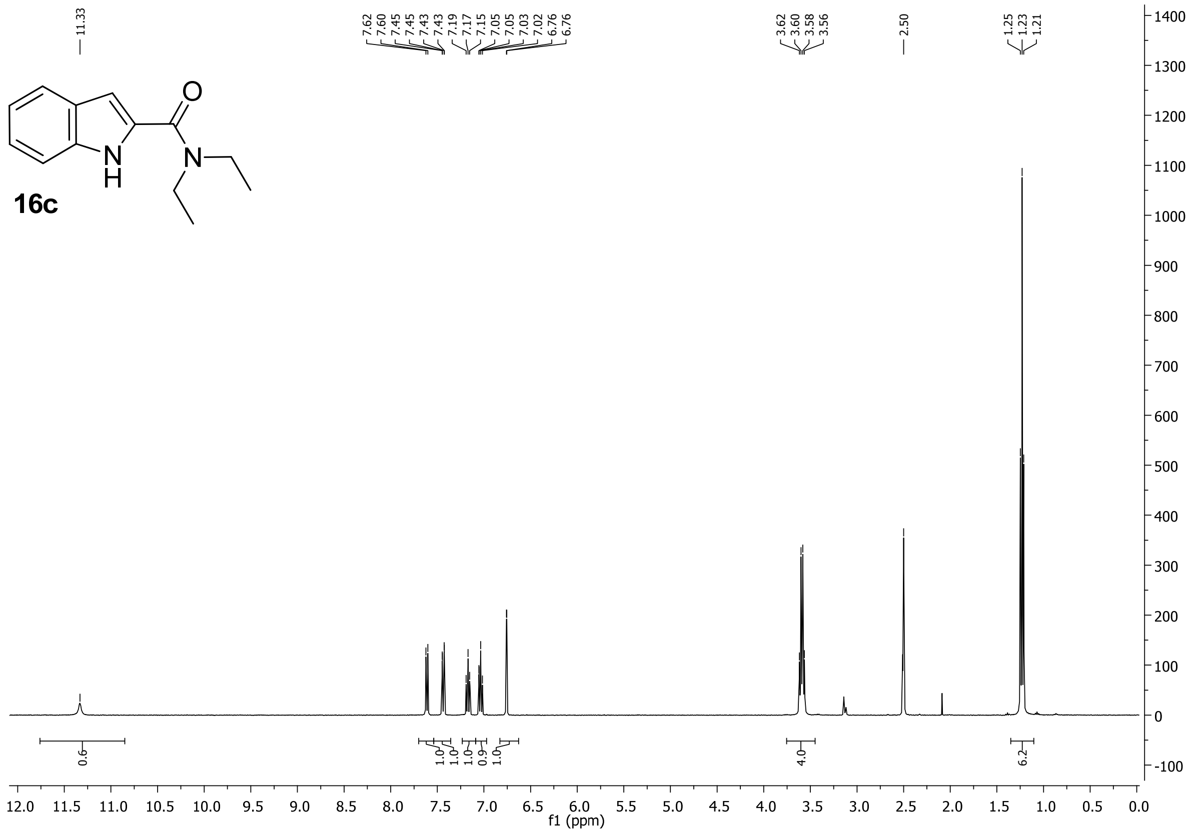

NOESY / 500 MHz
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)
4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f2 (ppm)

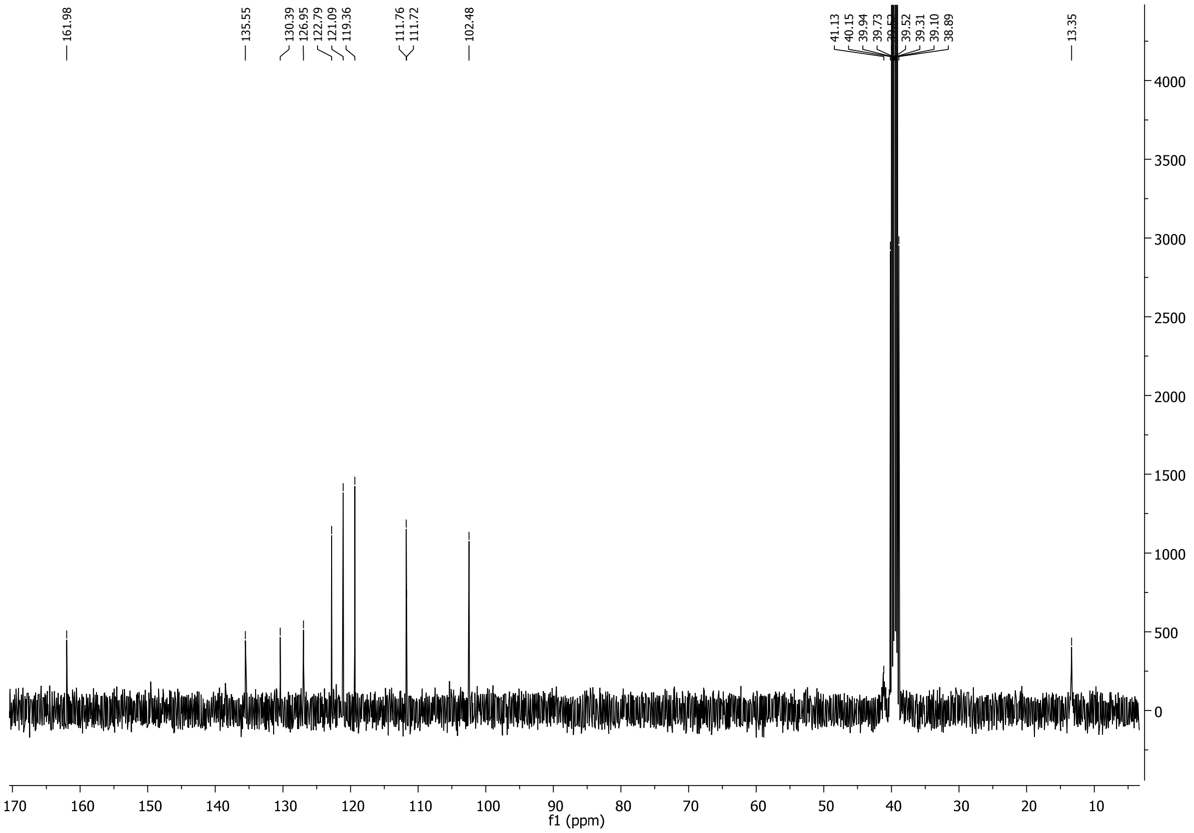
Internuclear distances driven from dipolar interactions NOESY experiments
Fixed value for H_{3a}-H_{7a} = 2.2 Å (measured by molecular modelisation)
- Grey values: outliers due to superposition of signals.
- The smaller the value, the darker the color is.

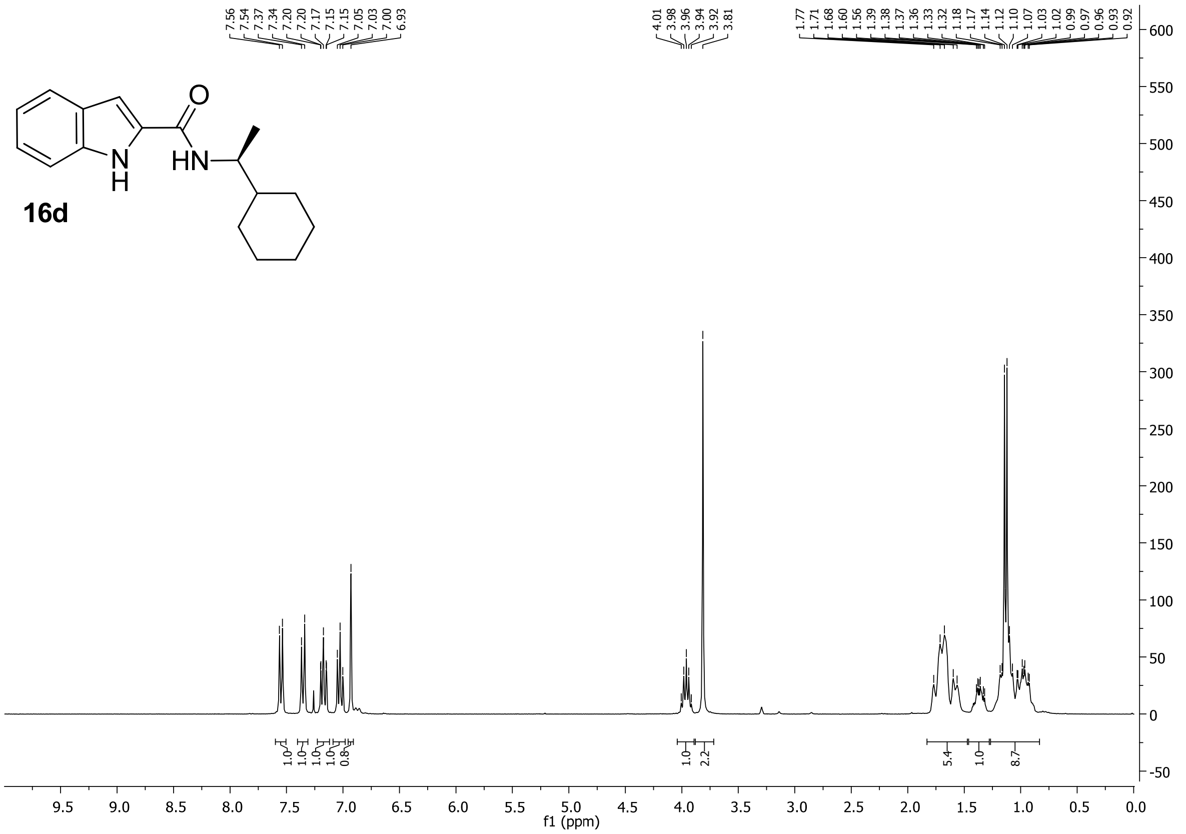


15g

protons	H_2	H_{7a}	$H_{3'}$	H_3	H_{3a}
H_{3a}	2,9	2,2	2,1	-	H_{3a}
H_3	3,0	-	1,6	H_3	-
$H_{3'}$	2,1	2,7	$H_{3'}$	1,7	2,2
H_{7a}	3,1	H_{7a}	3,2	-	2,2
H_2	H_2	2,8	2,3	3,2	3,0

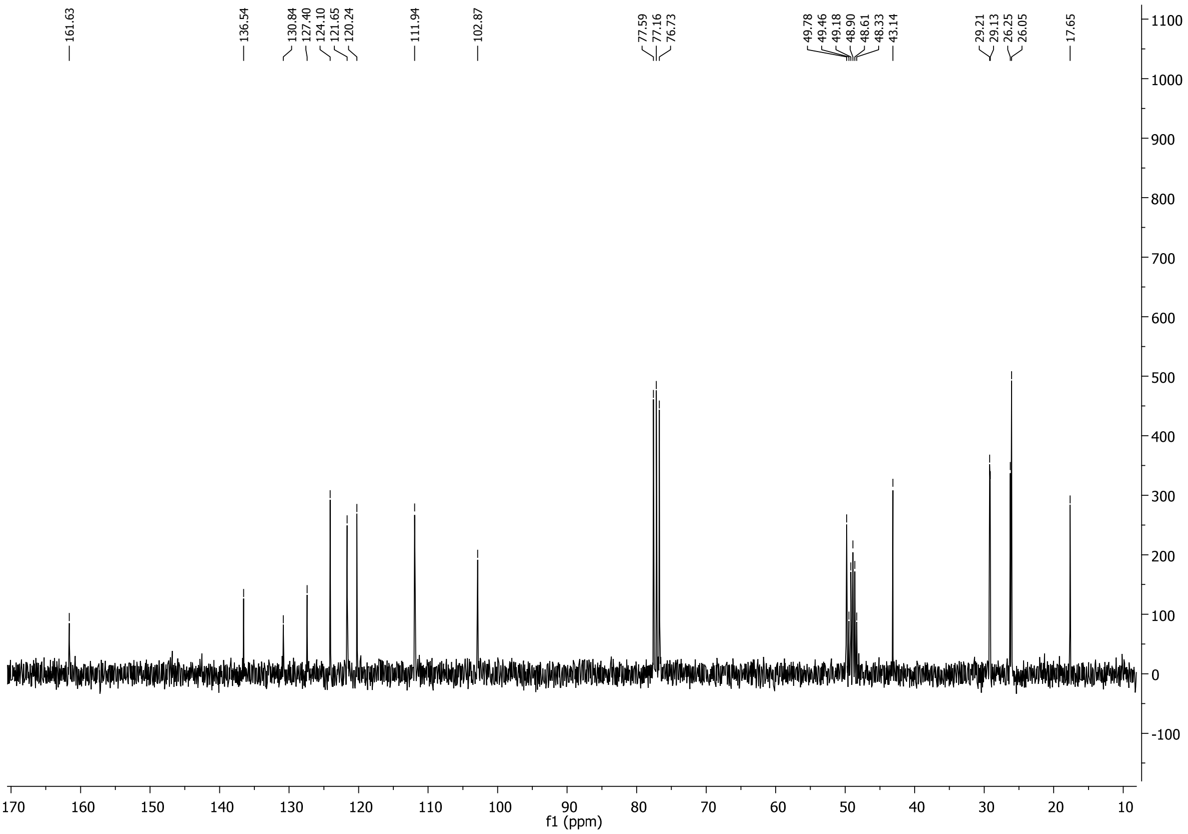

11.33
7.62
7.60
7.45
7.45
7.43
7.43
7.19
7.17
7.15
7.05
7.05
7.03
7.02
6.76
6.76
3.62
3.60
3.58
3.56
2.50
1.25
1.23
1.21
16c
O
N
N
H
0.6
1.0
1.0
1.0
0.9
1.0
4.0
6.2
f1 (ppm)


161.98
135.55
130.39
126.95
122.79
121.09
119.36
111.76
111.72
102.48
41.13
40.15
39.94
39.73
39.52
39.31
39.10
38.89
13.35
f1 (ppm)

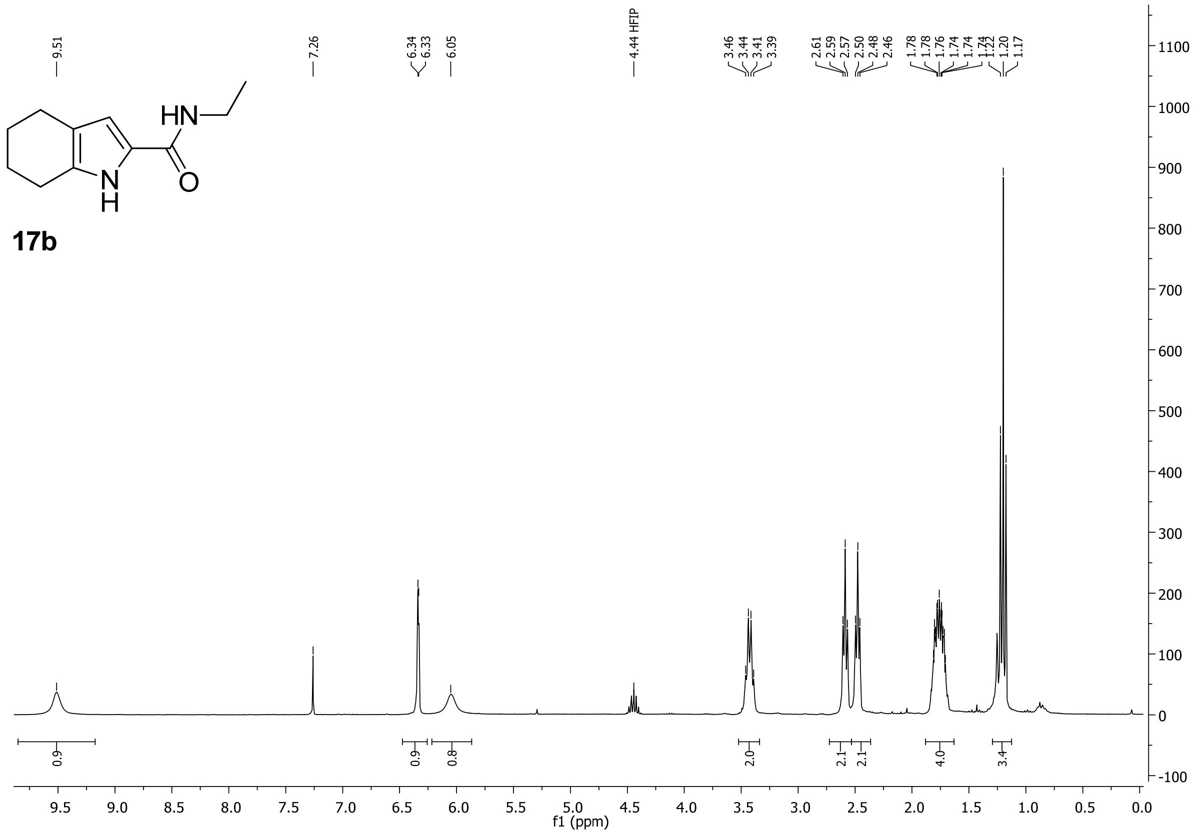


16d

7.56
7.54
7.37
7.34
7.20
7.20
7.17
7.15
7.15
7.05
7.03
7.00
6.93
4.01
3.98
3.96
3.94
3.92
3.81
1.77
1.71
1.68
1.60
1.56
1.39
1.38
1.37
1.36
1.33
1.32
1.18
1.17
1.14
1.12
1.10
1.07
1.03
1.02
0.99
0.97
0.96
0.93
0.92
1.0
1.0
1.0
1.0
0.8
1.0
2.2
5.4
1.0
8.7
O
N
H
HN
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

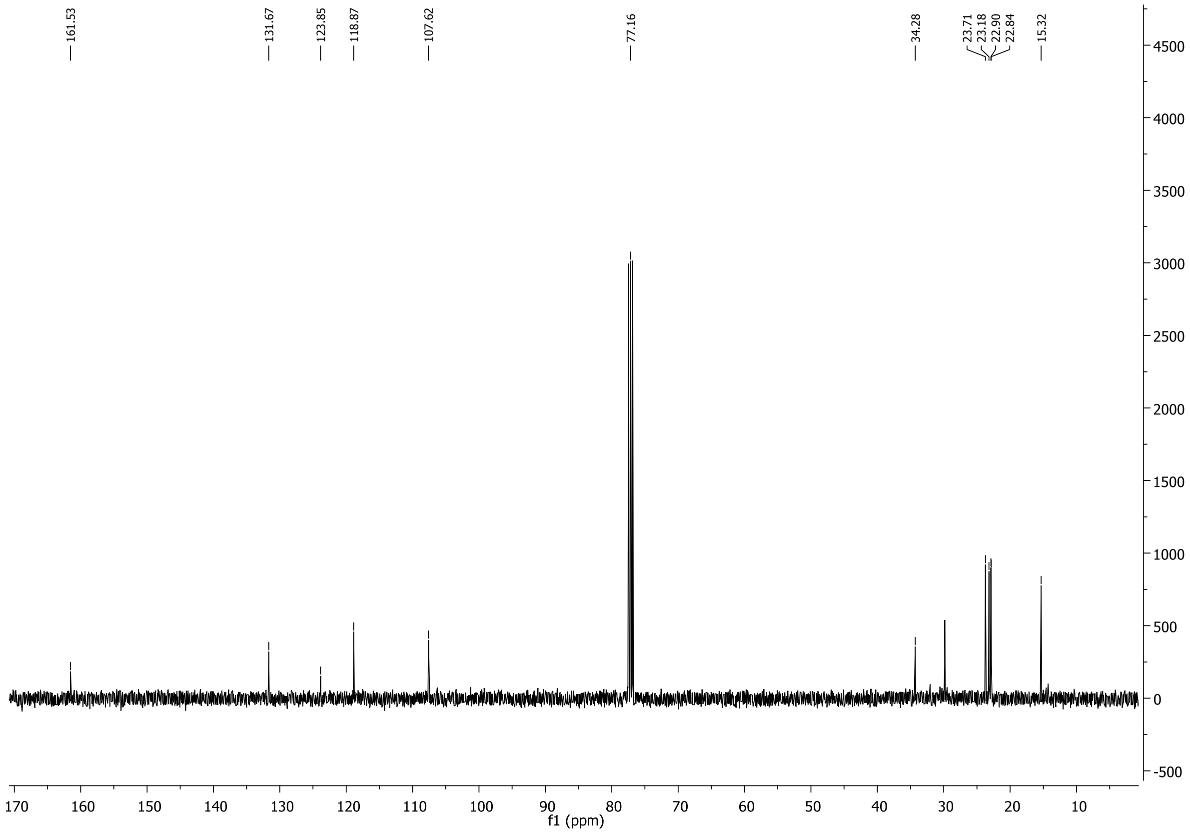


161.63
136.54
130.84
127.40
124.10
121.65
120.24
111.94
102.87
77.59
77.16
76.73
49.78
49.46
49.18
48.90
48.61
48.33
43.14
29.21
29.13
26.25
26.05
17.65
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

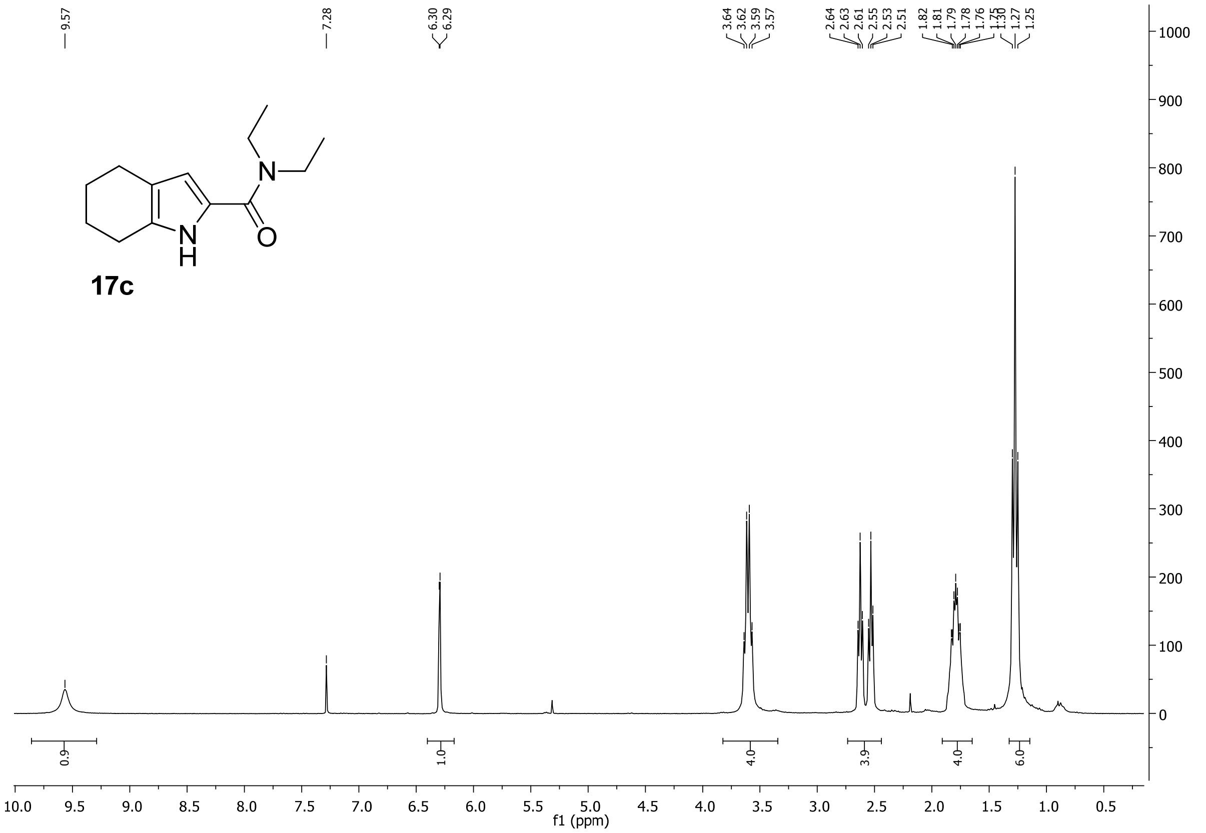


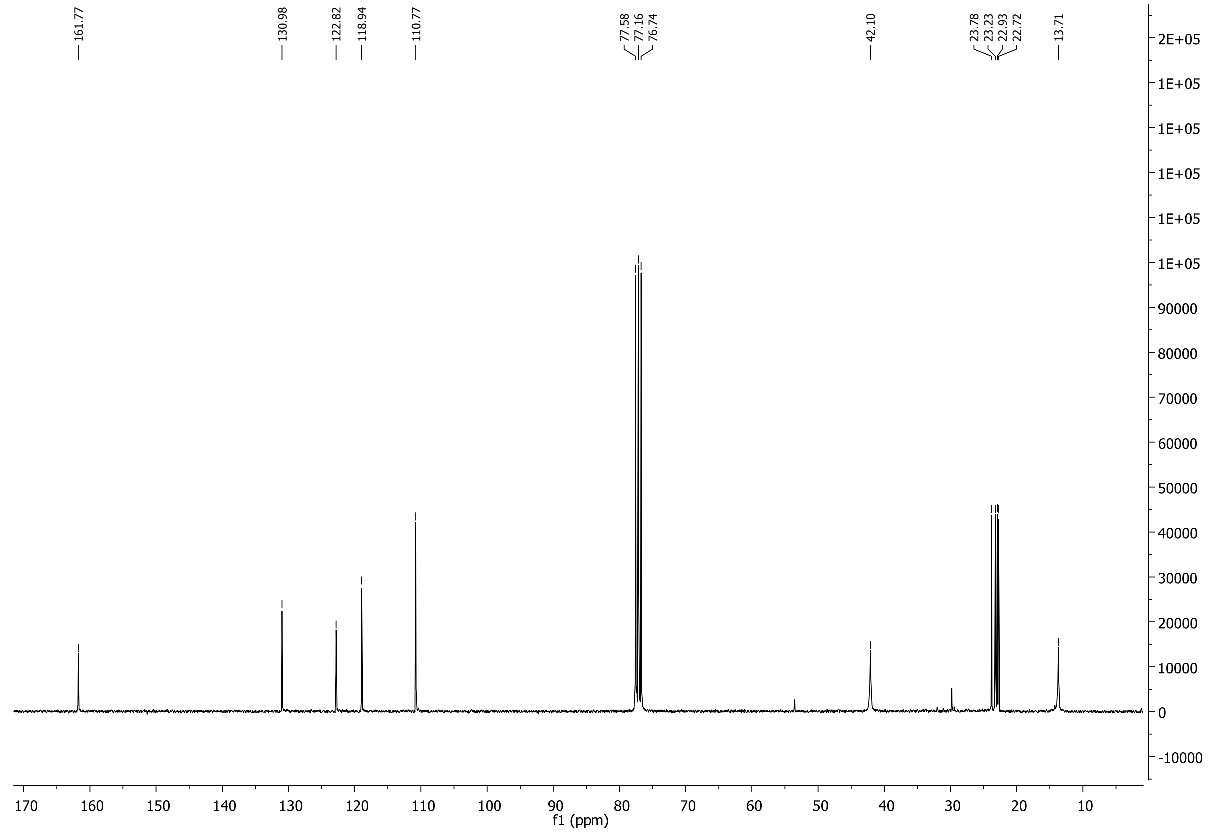
17b

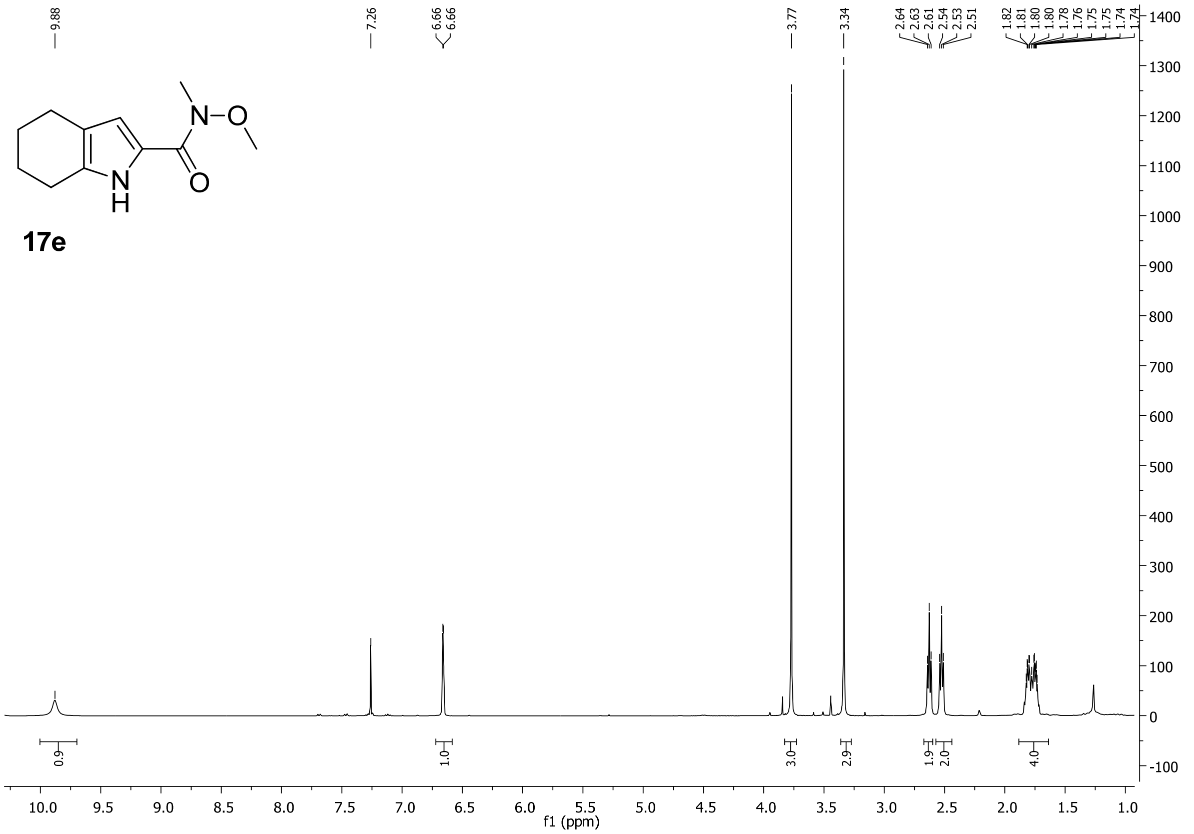
HN
N
H
O
9.51
7.26
6.34
6.33
6.05
4.44 HFIP
3.46
3.44
3.41
3.39
2.61
2.59
2.57
2.50
2.48
2.46
1.78
1.78
1.76
1.74
1.74
1.74
1.22
1.20
1.17
0.9
0.9
0.8
2.0
2.1
2.1
4.0
3.4
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

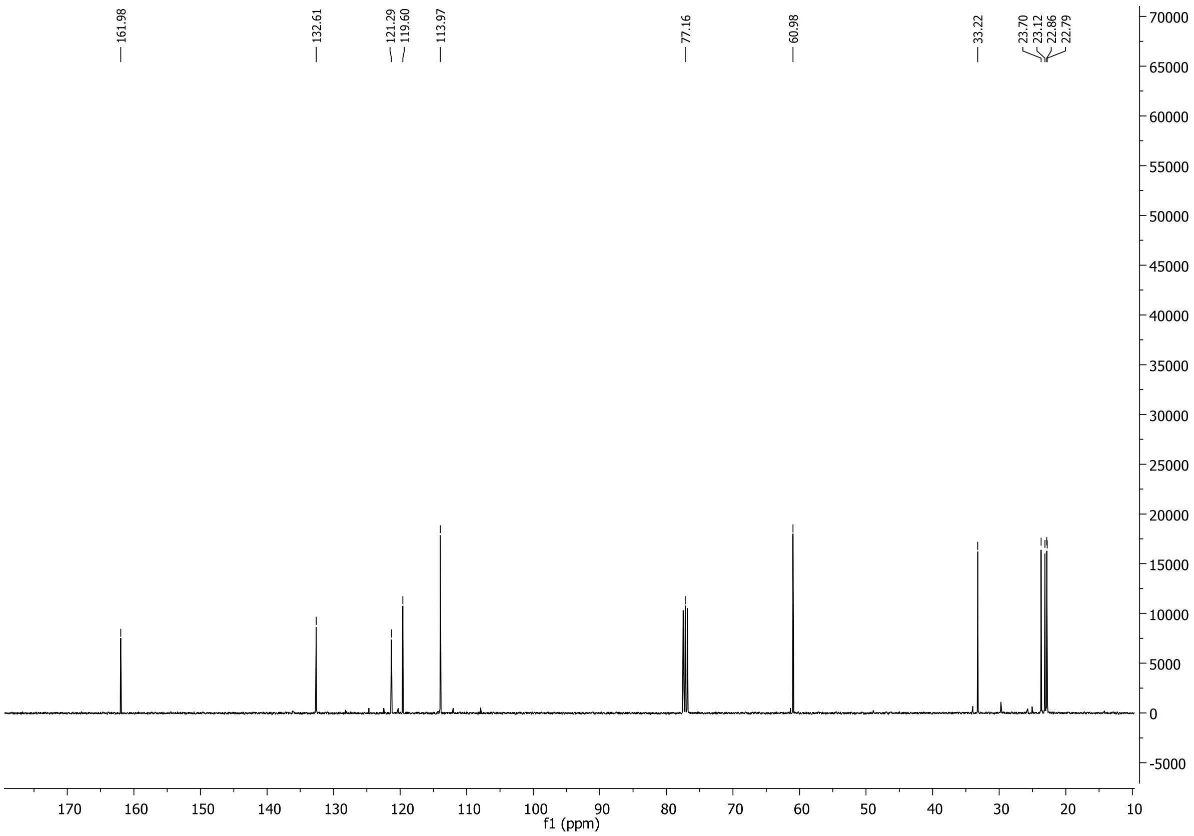


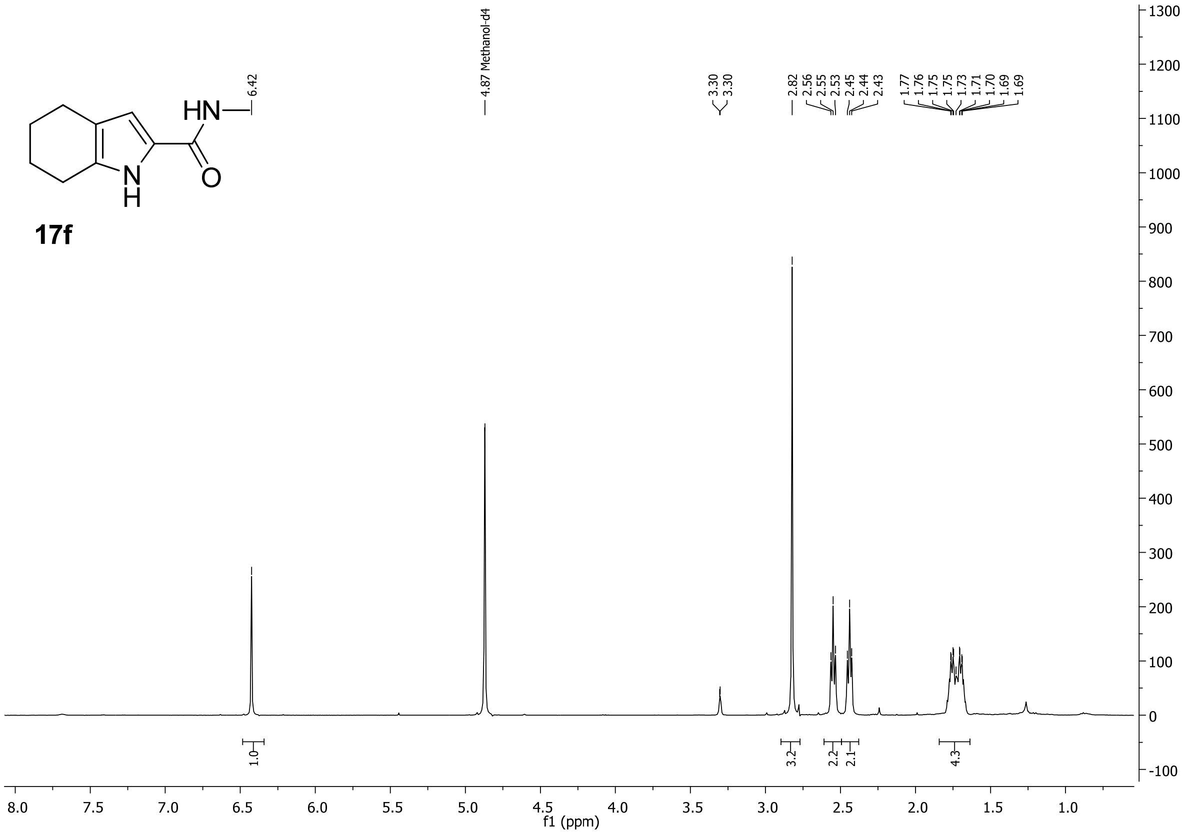
161.53
131.67
123.85
118.87
107.62
77.16
34.28
23.71
23.18
22.90
22.84
15.32
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

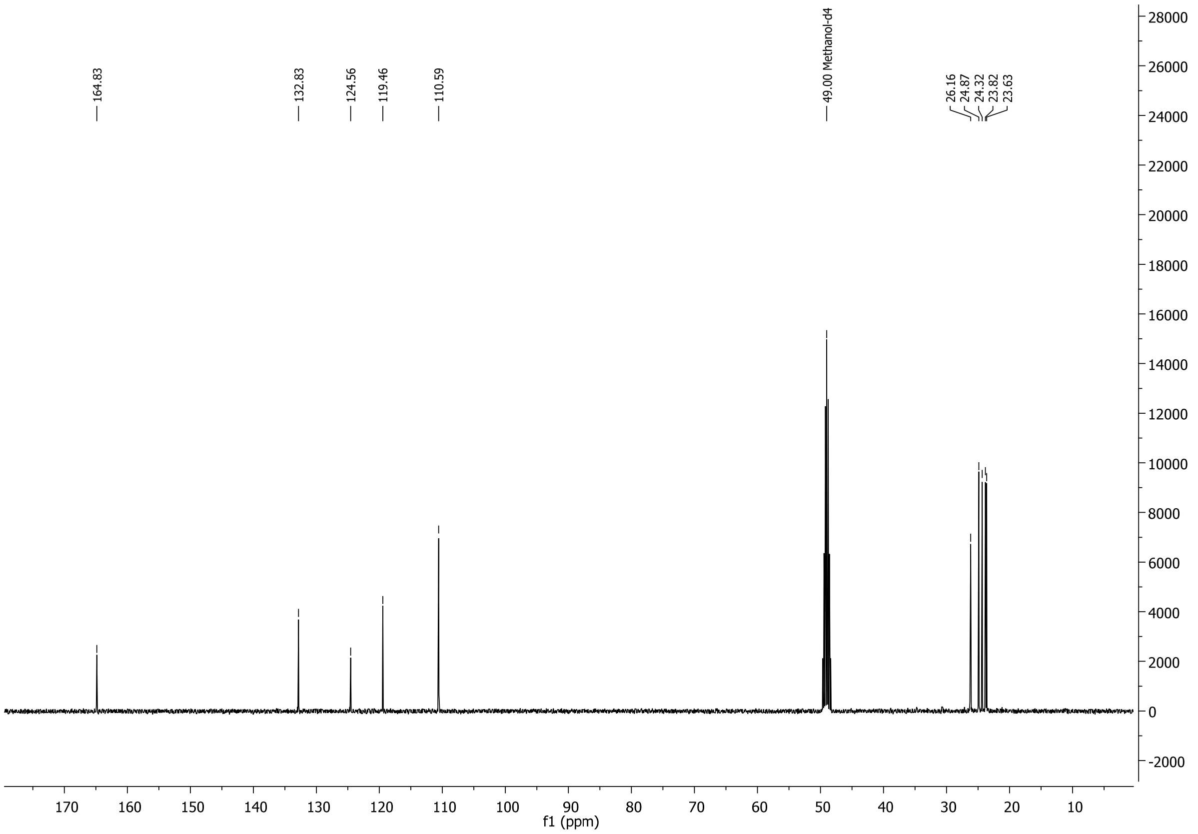

9.57
7.28
6.30
6.29
3.64
3.62
3.59
3.57
2.64
2.63
2.61
2.55
2.53
2.51
1.82
1.81
1.79
1.78
1.76
1.75
1.30
1.27
1.25
N
O
N
H
17c
0.9
1.0
4.0
3.9
4.0
6.0
1000
900
800
700
600
500
400
300
200
100
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

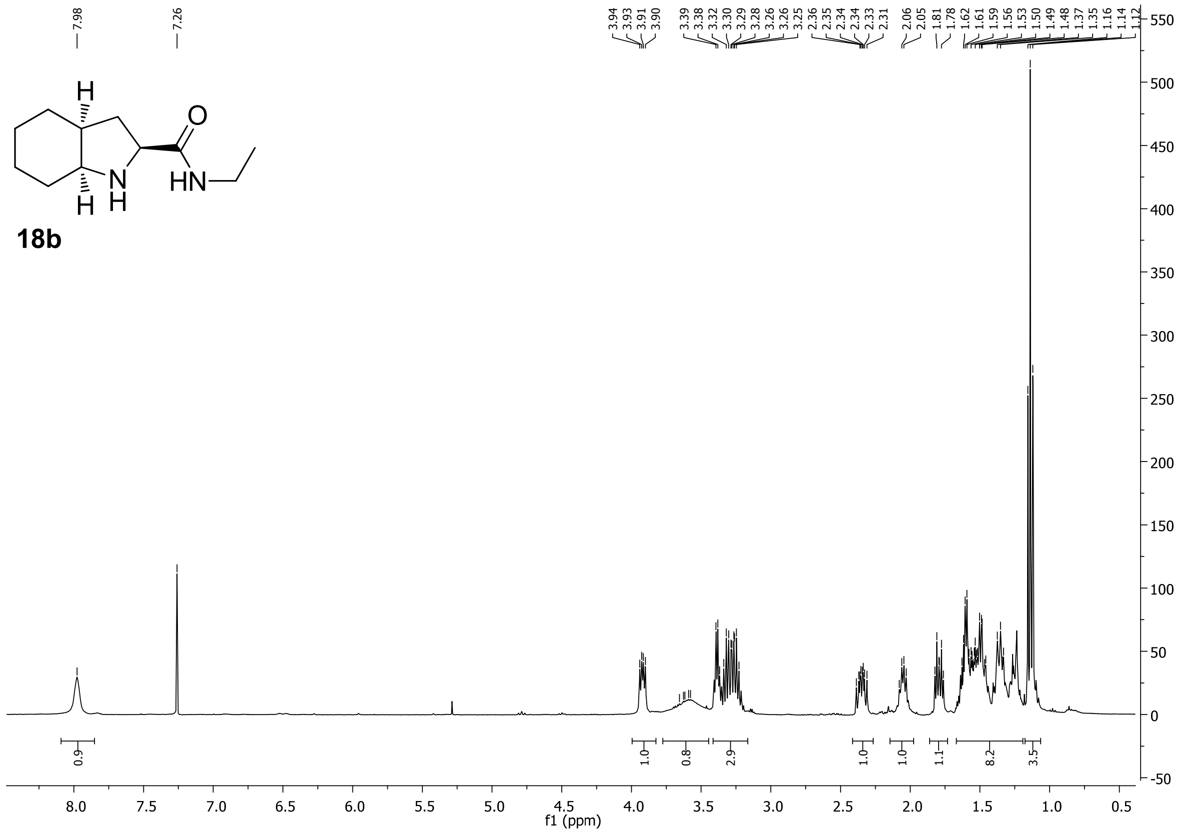

161.77
130.98
122.82
118.94
110.77
77.58
77.16
76.74
42.10
23.78
23.23
22.93
22.72
13.71
2E+05
1E+05
1E+05
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

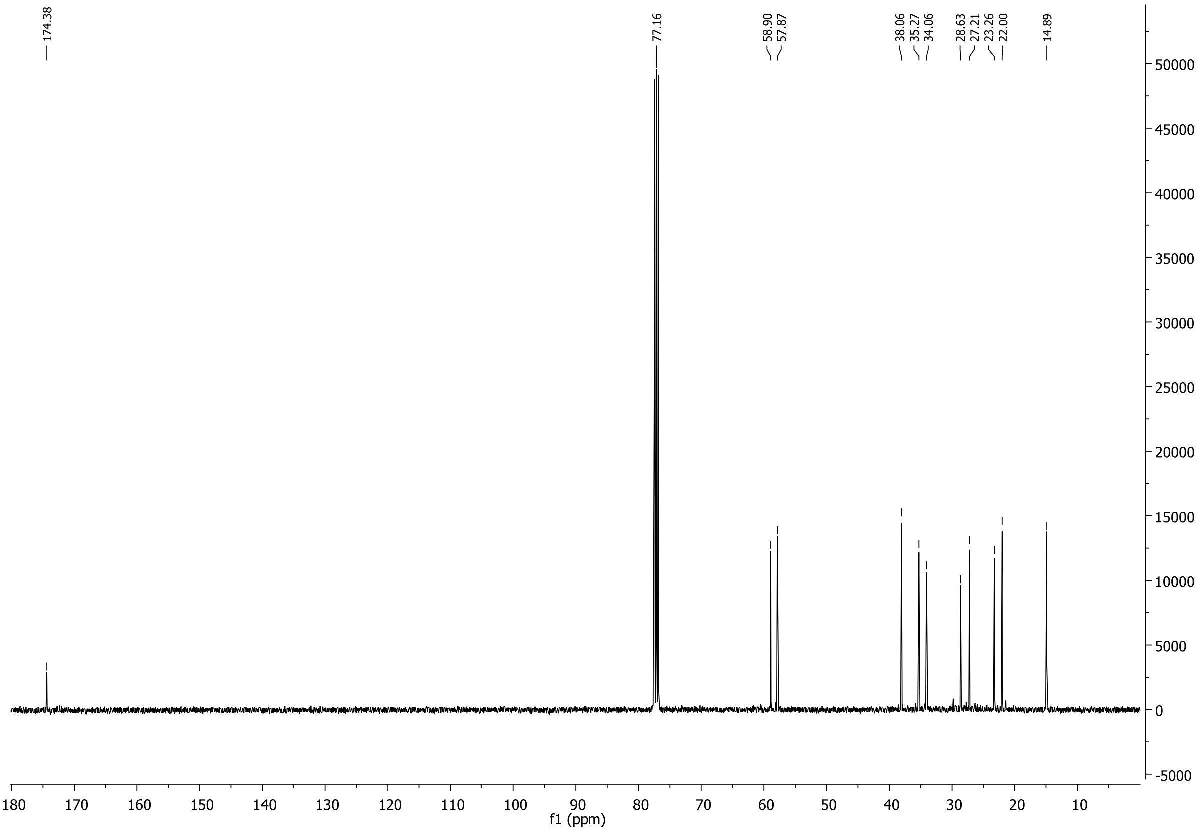

17e
9.88
7.26
6.66
6.66
3.77
3.34
2.64
2.63
2.61
2.54
2.53
2.51
1.82
1.81
1.80
1.80
1.78
1.76
1.75
1.75
1.74
1.74
N
O
N
H
O
0.9
1.0
3.0
2.9
1.9
2.0
4.0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

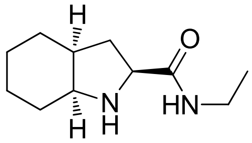

161.98
132.61
121.29
119.60
113.97
77.16
60.98
33.22
23.70
23.12
22.86
22.79
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000


HN
N
H
O
17f
6.42
4.87 Methanol-d4
3.30
3.30
2.82
2.56
2.55
2.53
2.45
2.44
2.43
1.77
1.76
1.75
1.75
1.73
1.71
1.70
1.69
1.69
1.0
3.2
2.2
2.1
4.3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100

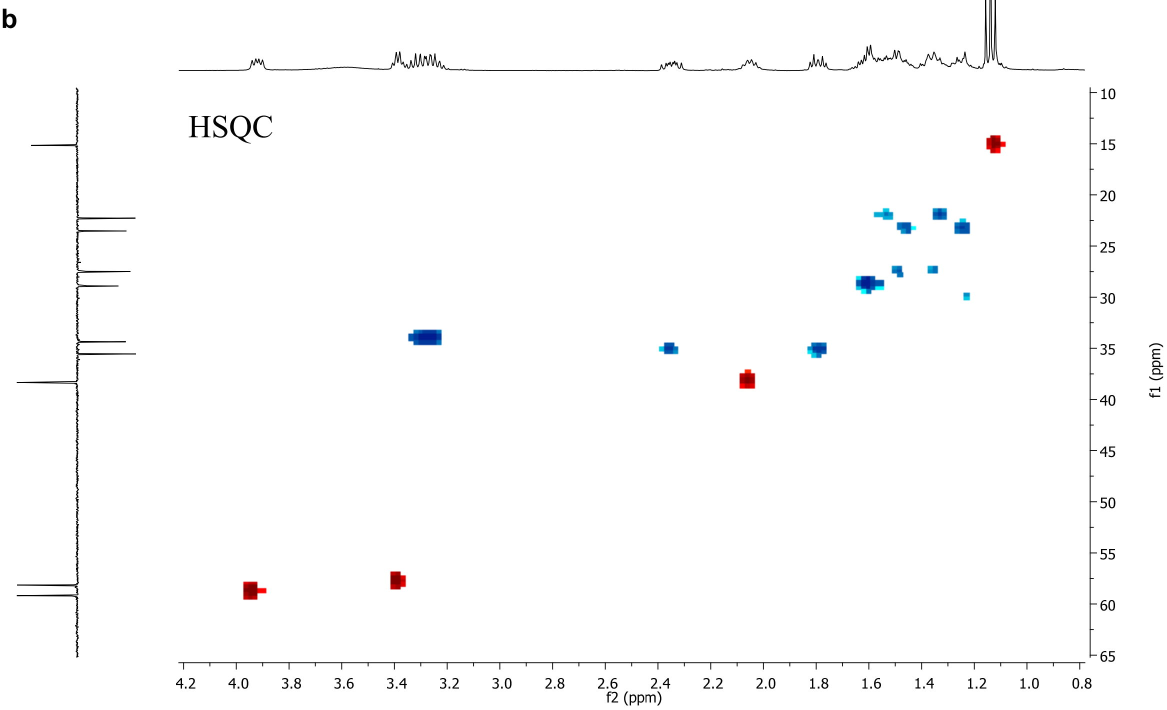

164.83
132.83
124.56
119.46
110.59
49.00 Methanol-d4
26.16
24.87
24.32
23.82
23.63
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000

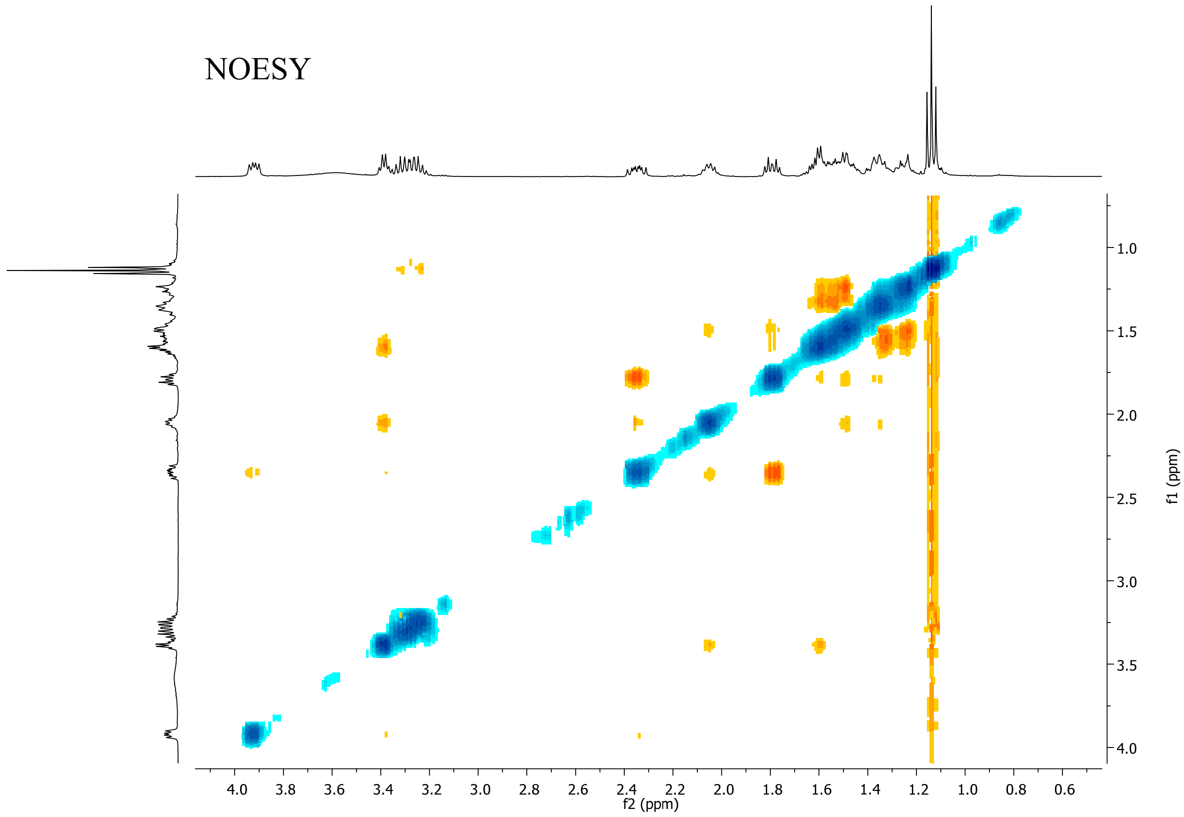

18b
H
O
N
H
HN
H
7.98
7.26
3.94
3.93
3.91
3.90
3.39
3.38
3.32
3.30
3.29
3.28
3.26
3.26
3.25
2.36
2.35
2.34
2.34
2.33
2.31
2.06
2.05
1.81
1.78
1.62
1.61
1.59
1.56
1.53
1.50
1.49
1.48
1.37
1.35
1.16
1.14
1.12
0.9
1.0
0.8
2.9
1.0
1.0
1.1
8.2
3.5
550
500
450
400
350
300
250
200
150
100
50
0
-50
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

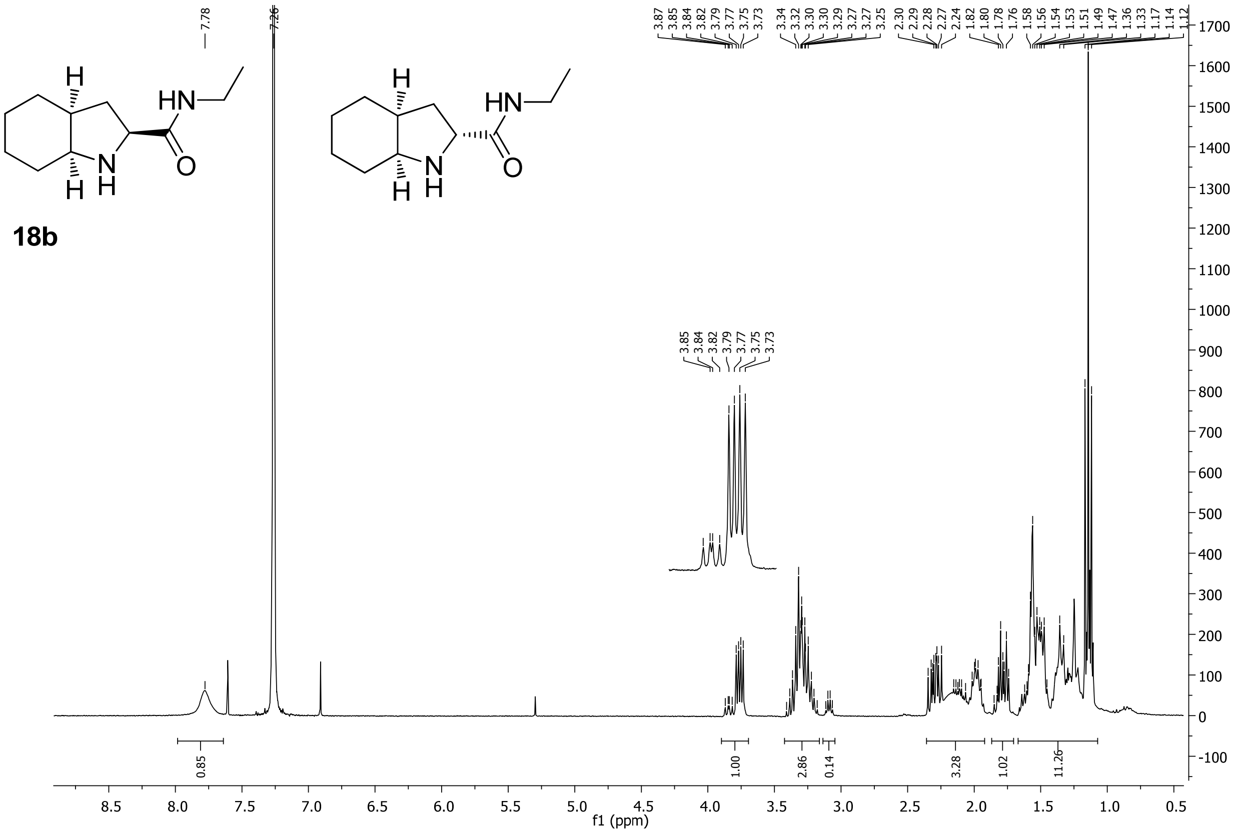

174.38
77.16
58.90
57.87
38.06
35.27
34.06
28.63
27.21
23.26
22.00
14.89
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


H
O
N
H
HN
H

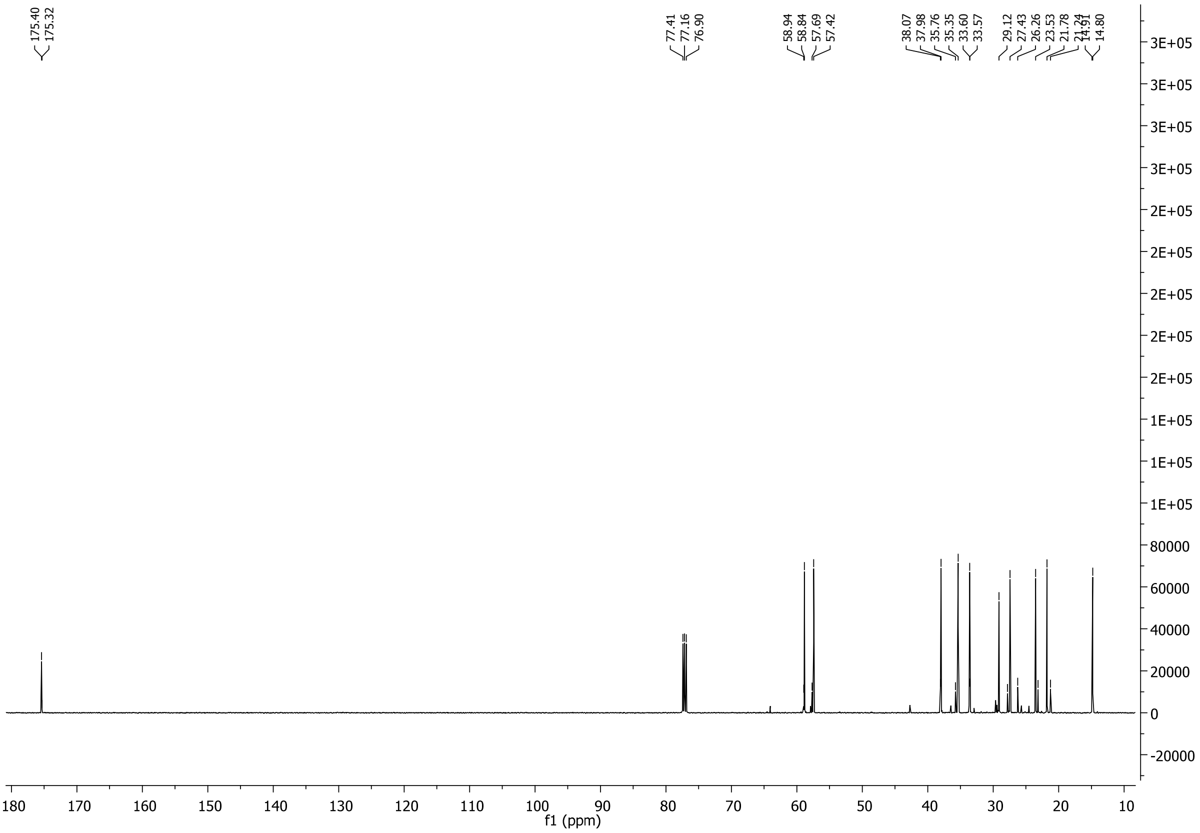
18b

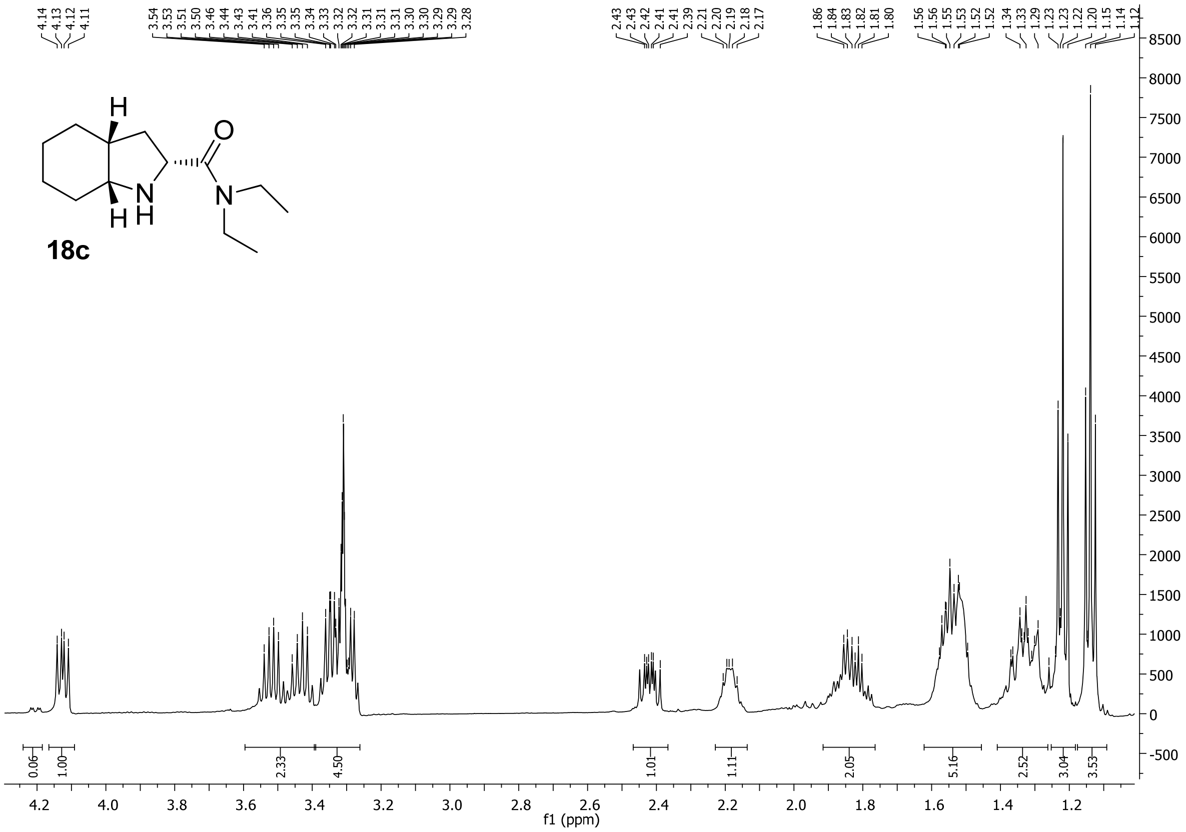

HSQC
f1 (ppm)
10
15
20
25
30
35
40
45
50
55
60
65
f2 (ppm)
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8

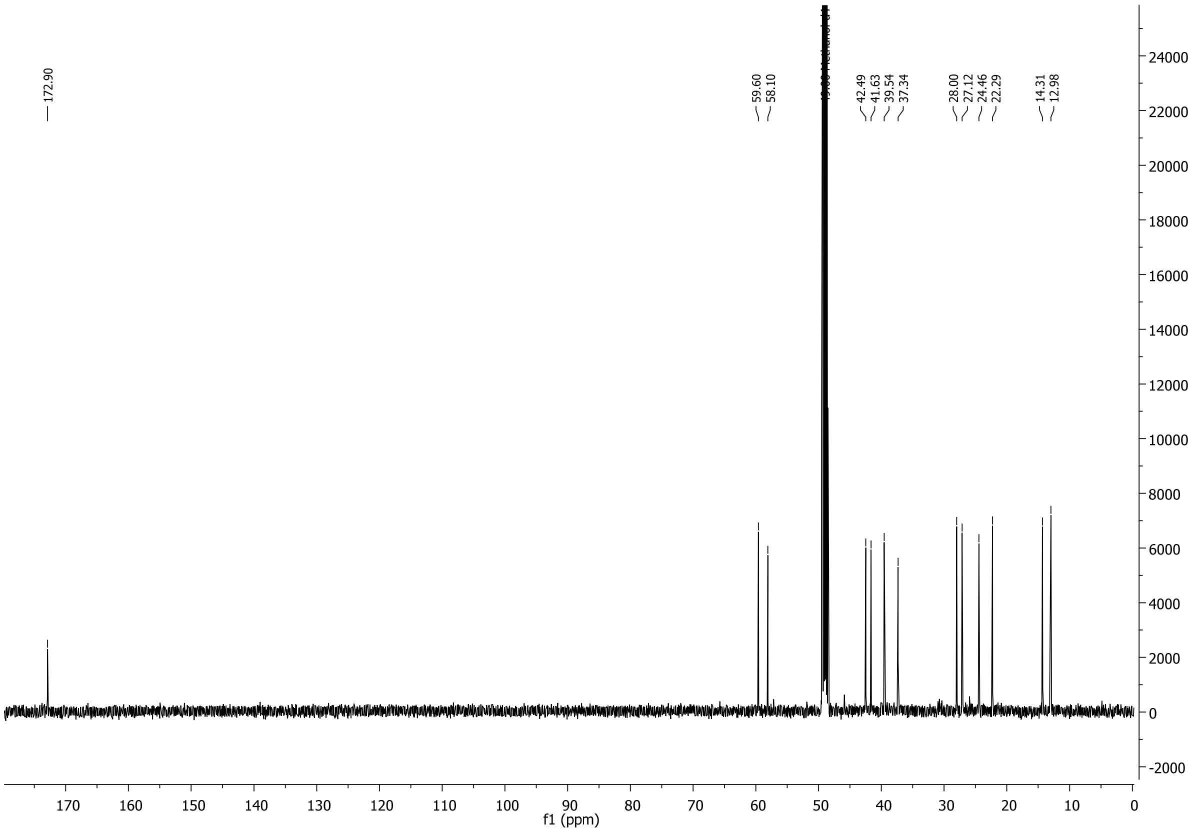

NOESY
f1 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
f2 (ppm)
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6

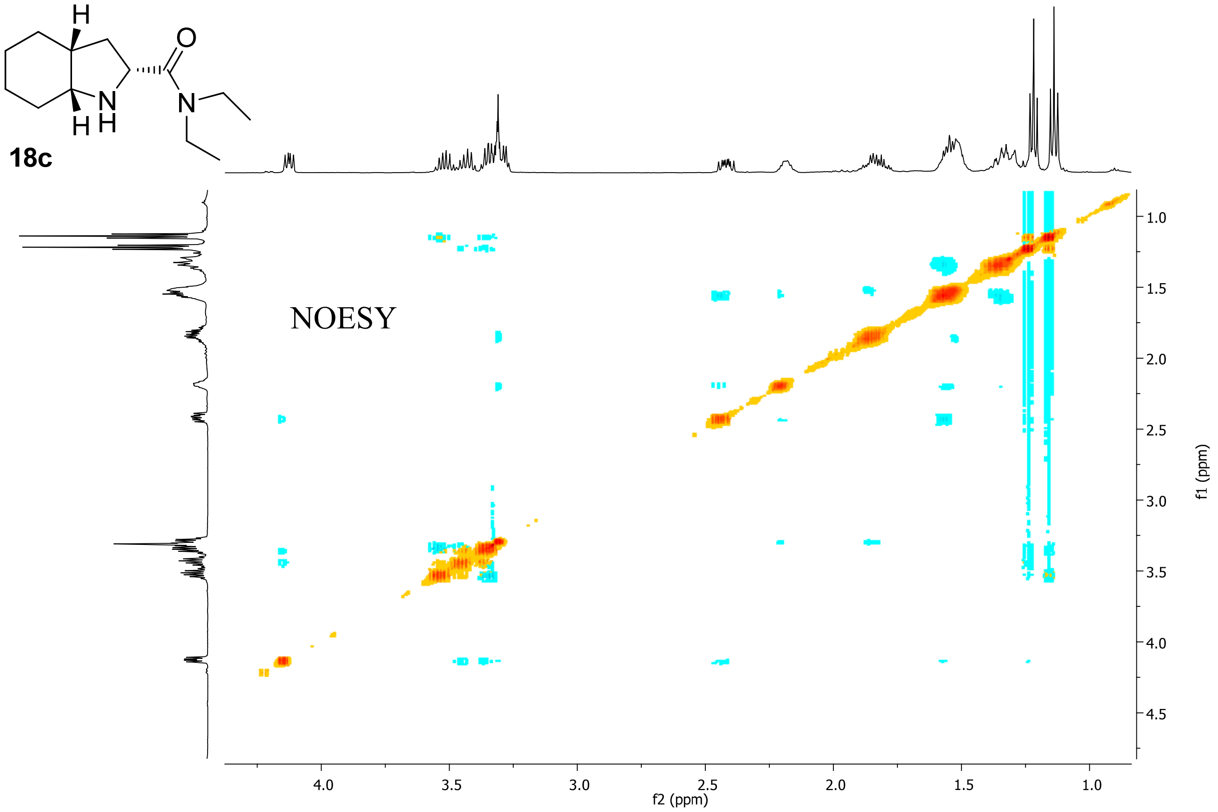

HN
N
H
H
H
O
7.78
7.26
3.87
3.85
3.84
3.82
3.79
3.77
3.75
3.73
3.34
3.32
3.30
3.30
3.29
3.27
3.27
3.25
2.30
2.29
2.28
2.27
2.24
1.82
1.80
1.78
1.76
1.58
1.56
1.54
1.53
1.51
1.49
1.47
1.36
1.33
1.17
1.14
1.12
0.85
1.00
2.86
0.14
3.28
1.02
11.26
f1 (ppm)

18b


175.40
175.32
77.41
77.16
76.90
58.94
58.84
57.69
57.42
38.07
37.98
35.76
35.35
33.60
33.57
29.12
27.43
26.26
23.53
21.78
21.24
14.91
14.80
f1 (ppm)

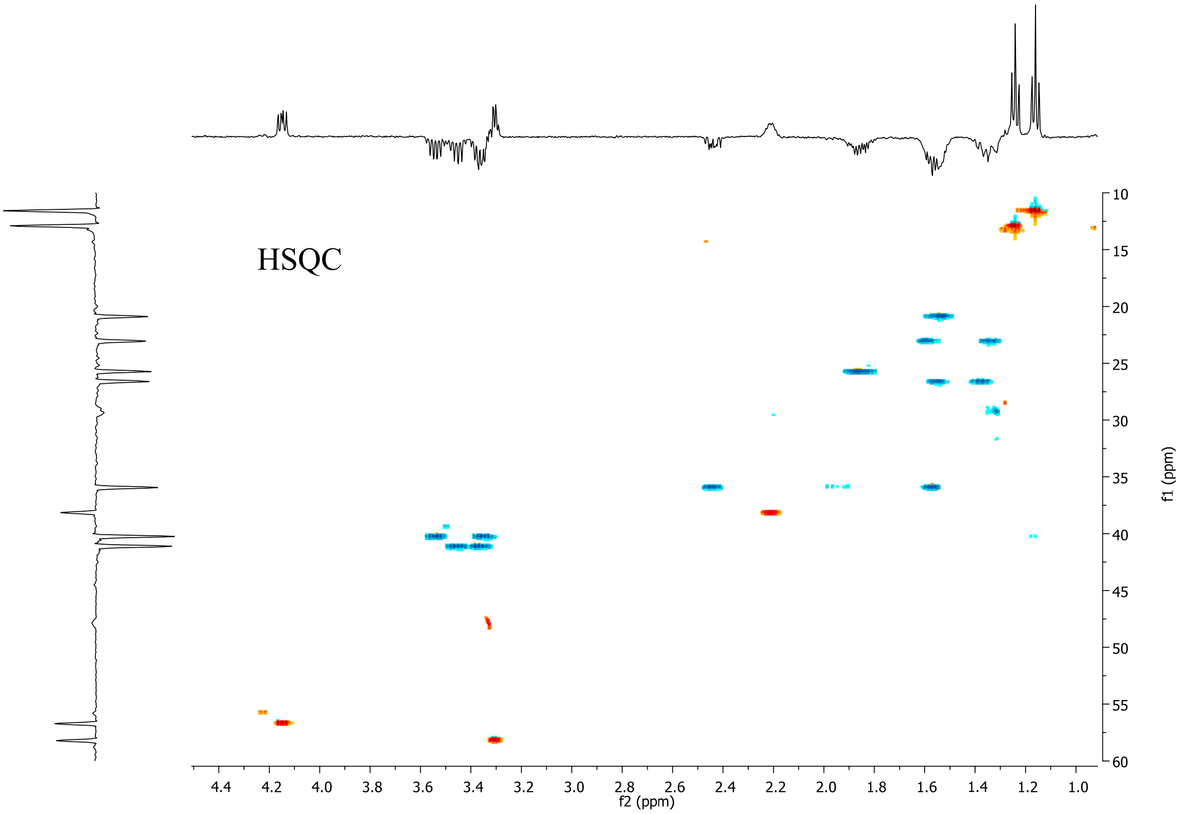

4.14
4.13
4.12
4.11
3.54
3.53
3.51
3.50
3.46
3.44
3.43
3.41
3.36
3.35
3.35
3.34
3.33
3.32
3.32
3.31
3.31
3.31
3.30
3.29
3.29
3.28
2.43
2.43
2.42
2.41
2.41
2.39
2.21
2.20
2.19
2.18
2.17
1.86
1.84
1.83
1.82
1.81
1.80
1.56
1.56
1.55
1.53
1.52
1.52
1.34
1.33
1.29
1.23
1.23
1.22
1.20
1.15
1.14
1.12
18c
0.06
1.00
2.33
4.50
1.01
1.11
2.05
5.16
2.52
3.04
3.53
f1 (ppm)


172.90
59.60
58.10
42.49
41.63
39.54
37.34
28.00
27.12
24.46
22.29
14.31
12.98
f1 (ppm)



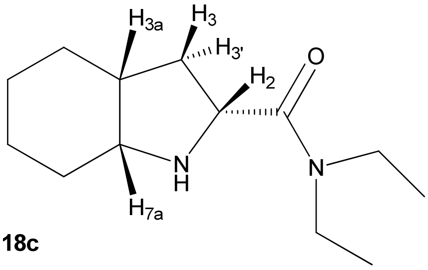
18c

H
O
N
N
H
H H
NOESY
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
f1 (ppm)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)



HSQC
10
15
20
25
30
35
40
45
50
55
60
f1 (ppm)
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
f2 (ppm)

Internuclear distances driven from dipolar interactions NOESY experiments
Fixed value for H_{3a}-H_{7a} = 2.2 Å (measured by molecular modelisation)
- Grey values: outliers due to superposition of signals.
- The smaller the value, the darker the color is.



18c

protons	H_2	H_{7a}	H_3	H_{3a}	$H_{3'}$
$H_{3'}$	3,4	3,2	1,9	-	$H_{3'}$
H_{3a}	3,0	2,2	2,3	H_{3a}	-
H_3	2,1	2,6	H_3	2,2	1,5
H_{7a}	2,8	H_{7a}	2,8	2,2	2,8
H_2	H_2	2,3	2,0	2,7	2,7

References

1 P. Chen, B. Fenet, S. Michaud, N. Tomczyk, E. Véricel, M. Lagarde, M. Guichardant, *FEBS Letters*, 2009, **583**, 3478.

2 Esposito and A. Pastore, *J. Magn. Reson.*, 1988, **76**, 331.

3 E. Ämmälathi, M. Bardet, D. Molko, and J. Cadet, *J. Magn. Reson.,* 1996*,* **122,** 230.