Practical Synthesis of PC190723, An Inhibitor of the Bacterial Cell Division Protein FtsZ

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Supporting Information

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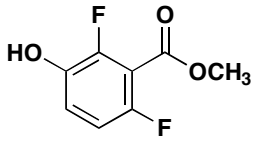
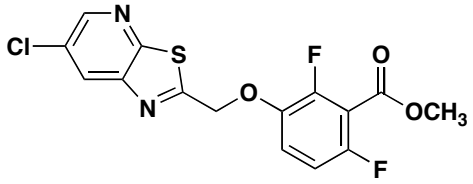
Materials: Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. Instrumentation: ^{1}H and ^{13}C NMR spectra were obtained on a 300, 400, 600MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS or DMSO-d ($CHCl_3$, s, δ 0.00), (DMSO-d, m, δ 2.50) . Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplet), m (multiplet), brs (broad singlet). ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (t, δ 77.16) DMSO-d (m, δ 40.0) unless otherwise noted. For the ^{19}F NMR data, trifluoroacetic acid (TFA) was used as an internal standard. High resonance mass spectra were recorded on positive and negative ESI mode in methanol or acetonitrile unless otherwise noted. Melting points were taken on an EZ-melting apparatus and were uncorrected. Infrared spectra were taken neat. Silica gel chromatographic purifications were performed by flash chromatography with silica gel (Silicycle, 40–63 μm) packed in glass columns. The eluting solvent for each purification was determined by thin layer chromatography (TLC) on glass plates coated with EMD silica gel 50F254 and visualized by ultraviolet. The following abbreviations are used throughout: ethyl acetate (EtOAc), diisopropylethylamine ($(i\text{-Pr})_2$NEt).

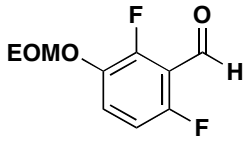
Experimental:



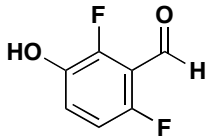
2,6-Difluoro-3-hydroxy-benzoic acid methyl ester (5). Compound **11** (0.461 g, 1.99 mmol) was dissolved in a 50:50 mixture of MeOH and concentrated H_2SO_4 (20 mL total volume) the mixture was allowed to stir overnight. The solvent was evaporated *in vacuo* and then extracted 3x with CH_2Cl_2 yielding a light brown oil (0.342 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (td, *J* = 9.3, 5.2, 1H), 6.81 (td, *J* = 9.2, 2.0, 1H), 6.45 (brs, 1H), 3.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 153.6 (dd, *J* = 249.7, 4.6), 148.7 (dd, *J* = 250.5, 6.4), 140.6 (dd, *J* = 13.9, 3.4), 120.5 (dd, *J* = 9.6, 3.9), 111.8 (dd, *J* = 23.4, 4.1), 110.4 (dd, *J* = 19.1, 15.0), 53.1 (d, *J* = 2.7); IR (neat) 3408, 1751, 1633 cm^{-1}; R_f 0.708 in 50% EtOAc/hexanes; HRMS (ESI) *m / z* calcd for $C_8H_6F_2O_3$ $(M + H)^+$ 189.0360, found 189.0358.



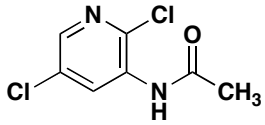
3-(6-Chloro-thiazolo[5,4-b]pyridin-2-ylmethoxy)-2,6-difluoro-benzoic acid methyl ester (19). Phenol **5** (0.053 g, 0.282 mmol) was dissolved in 5 mL of dry CH_3CN followed by the addition of Cs_2CO_3 (0.275 g, 0.844 mmol). Compound **2** (0.053 g, 0.242 mmol) was added to the mixture and stirred for 1.5 h at 65 ºC. The solution was filtered and the filtrate was concentrated and purified by flash chromatography (100% CH_2Cl_2), yielding a yellow solid (0.056 g, 62%): mp 144-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.1, 1H), 8.24 (d, *J* = 2.1, 1H), 7.18 (td, *J* = 9.0, 5.0, 1H), 6.89 (td, *J* = 9.0, 1.8, 1H), 5.49 (s, 2H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 161.7 (d, *J* = 1.3), 156.1, 155.3 (dd, *J* = 248.46, 5.05), 151.1 (dd, *J* = 258.7, 6.6), 146.7, 146.4, 142.4 (dd, *J* = 11.2, 3.8), 130.2, 129.9, 119.5 (dd, *J* = 9.8, 2.8, 1H), 112.4 (dd, *J* = 19.9, 15.6), 111.5 (dd, *J* = 23.4, 4.4), 70.6 (d, *J* = 1.4), 53.1 (d, *J* = 2.3); IR 1732, 1251, 728 cm^{-1}; R_f 0.814 in 50% EtOAc/hexanes; HRMS (ESI) *m / z* calcd for $C_{15}H_9ClF_2N_2O_3S$ $(M + H)^+$ 371.0068, found 371.0058.



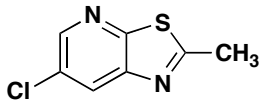
3-Ethoxymethoxy-2,6-difluoro-3-hydroxy-benzaldehyde (13). A solution of **9** (0.945 g, 5.02 mmol) in 30 mL dry THF was cooled to -78 °C. To this solution, *n*-BuLi (2.2 mL, 5.50 mmol, 2.5M in hexanes) was added dropwise at -78 °C. After the reaction had stirred for 30 min at -78 °C, dry DMF (8.00 mL, 10.0 mmol) was added dropwise and stirred for an additional 30 min at -78 °C. The reaction mixture was warmed to 0 °C and stirred for an additional 30 min. Water was added to the solution and extracted 3x with diethyl ether. The organic layers were combined and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the crude mixture was purified by flash chromatography (10 to 30% EtOAc/hexanes) yielding a yellow oil (0.619 g, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.46 (td, *J* = 9.1, 5.3 Hz, 1H), 6.92 (t, *J* = 9.5 Hz, 1H), 5.25 (s, 2H), 3.79 (q, *J* = 7.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 185.4 – 183.7 (m), 157.4 (dd, *J* = 257.2, 4.5 Hz), 153.5 (dd, *J* = 264.0, 6.0 Hz), 142.2 (dd, *J* = 10.3, 3.8 Hz), 124.6 (dd, *J* = 10.4, 3.8 Hz), 114.8 (dd, *J* = 12.1, 8.7 Hz), 111.7 (dd, *J* = 22.2, 4.5 Hz), 95.1, 65.0, 15.1; IR (neat) 3433, 1687 cm^{-1}; R_f 0.689 in 30% EtOAc/hexanes; HRMS (ESI) *m / z* calcd for $C_{10}H_{10}F_2O_3$ (M - EOM)$^-$ 157.0101, found 157.0115.



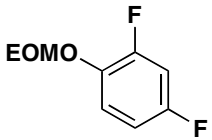
2,6-Difluoro-3-hydroxy-benzaldehyde (3). The EOM-protected aldehyde **13** (0.564 g, 2.61 mmol) was dissolved in a 50:50 mixture of 6M HCl and MeOH (~30 mL total volume). After 1 h, the solvent was evaporated in *vacuo* yielding a white solid (0.380 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.33 (s, 1H), 7.30-7.22 (m, 1H), 6.96-689 (m, 1H), 5.53 (brs, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.2, 156.8 (dd, *J* = 255.2, 4.6 Hz), 150.1 (d, *J* = 255.8 Hz), 140.8 (dd, *J* = 13.3, 3.5 Hz), 123.8, 114.6 – 113.3 (m), 112.3 (dd, *J* = 22.6, 4.3 Hz); IR (neat) 3179, 1675 cm^{-1}; R_f 0.703 in 50% EtOAc/hexanes ; HRMS (ESI) *m / z* calcd for $C_7H_4F_2O_2$ (M - H)$^-$ 157.0101, found 157.0115.



N-(2,5-Dichloro-pyridin-3-yl)-acetamide (14). 3-amino-2,5-dichloropyridine (0.316 g, 1.94 mmol) was dissolved in CH_2Cl_2 (30 mL). The mixture was cooled to 0 °C and acetyl chloride (0.275 mL, 3.87 mmol) was added dropwise. This was followed by the addition of $(i\text{-Pr})_2NEt$. (0.70 mL, 4.08 mmol). After 3 h, the solvent was evaporated *in vacuo* and the crude mixture was purified by flash chromatography (100% CH_2Cl_2) yielding a white solid (0.265 g, 65%): mp 120-121°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 2.4 Hz, 1H), 7.64 (brs, 1H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 142.2, 137.2, 132.3, 131.7, 128.36, 25.1; IR (neat) 3270, 1652, 1507 cm^{-1}; R_f 0.666 in 50% EtOAc/hexanes; HRMS (ESI) *m / z* calcd for $C_7H_6Cl_2N_2O$ $(M + H)^+$ 204.9935, found 204.9922.



6-Chloro-2-methyl-thiazolo[5,4-b]pyridine (15). Compound **14** (0.227 g, 1.12 mmol) was dissolved in dry toluene (20 mL) followed by the addition of phosphorus pentasulfide (0.369 g, 1.66 mmol). The reaction mixture was stirred overnight at 110 °C. The crude mixture was passed through a plug of silica gel and washed with CH_2Cl_2. The solvent was evaporated *in vacuo* and the crude mixture was purified by flash chromatography (100% CH_2Cl_2) yielding a white solid (0.153 g, 75%): mp 108-109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 2.1 Hz, 1H), 8.14 (d, J = 2.2 Hz, 1H), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 156.9, 147.0, 145.7, 129.8, 129.0, 21.4; R_f 0.703 in 50% EtOAc/hexanes; HRMS (ESI) *m / z* calcd for $C_7H_5ClN_2S$ $(M + H)^+$ 184.9940, found 184.9929.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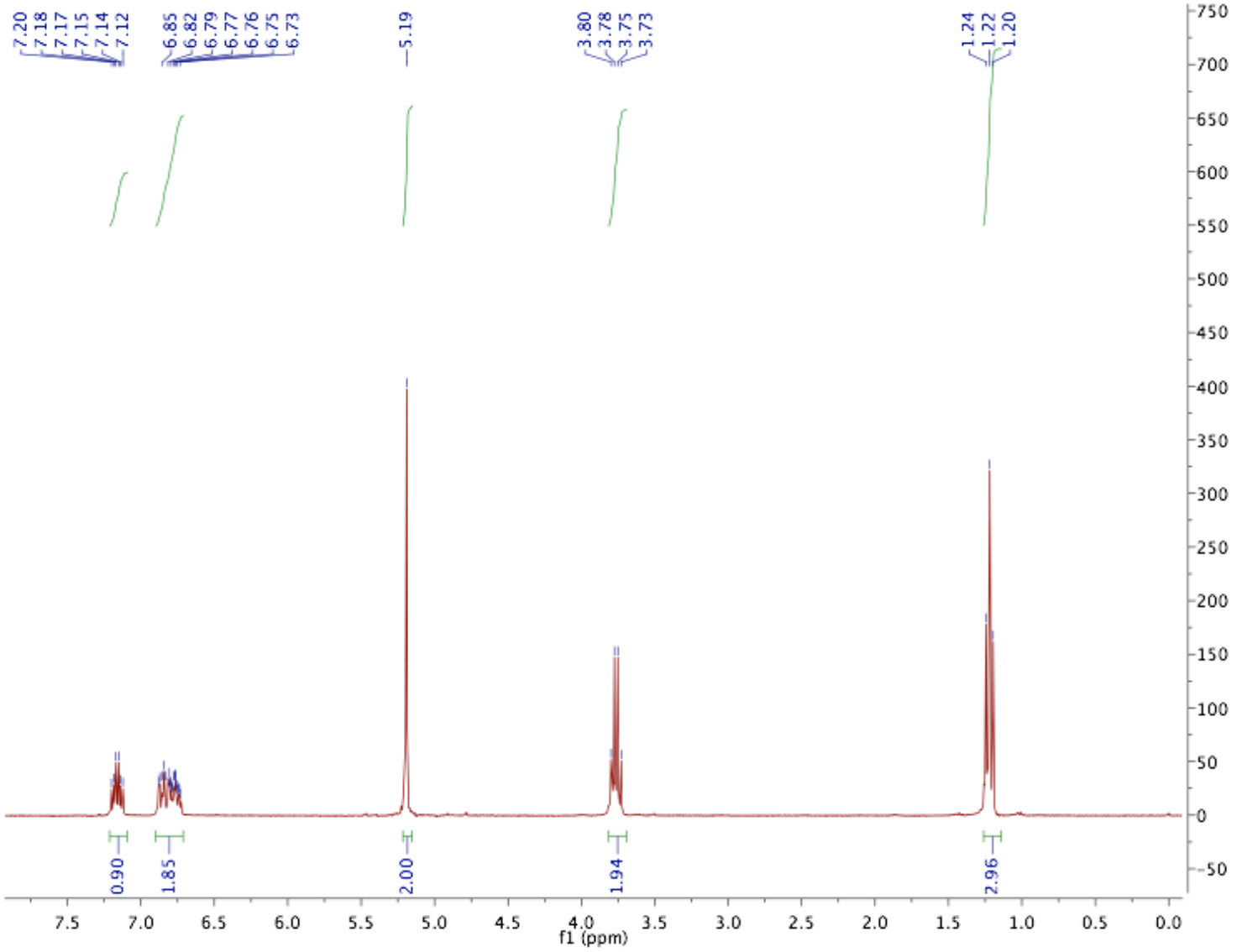
F

9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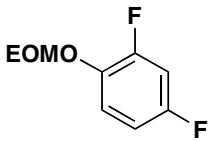
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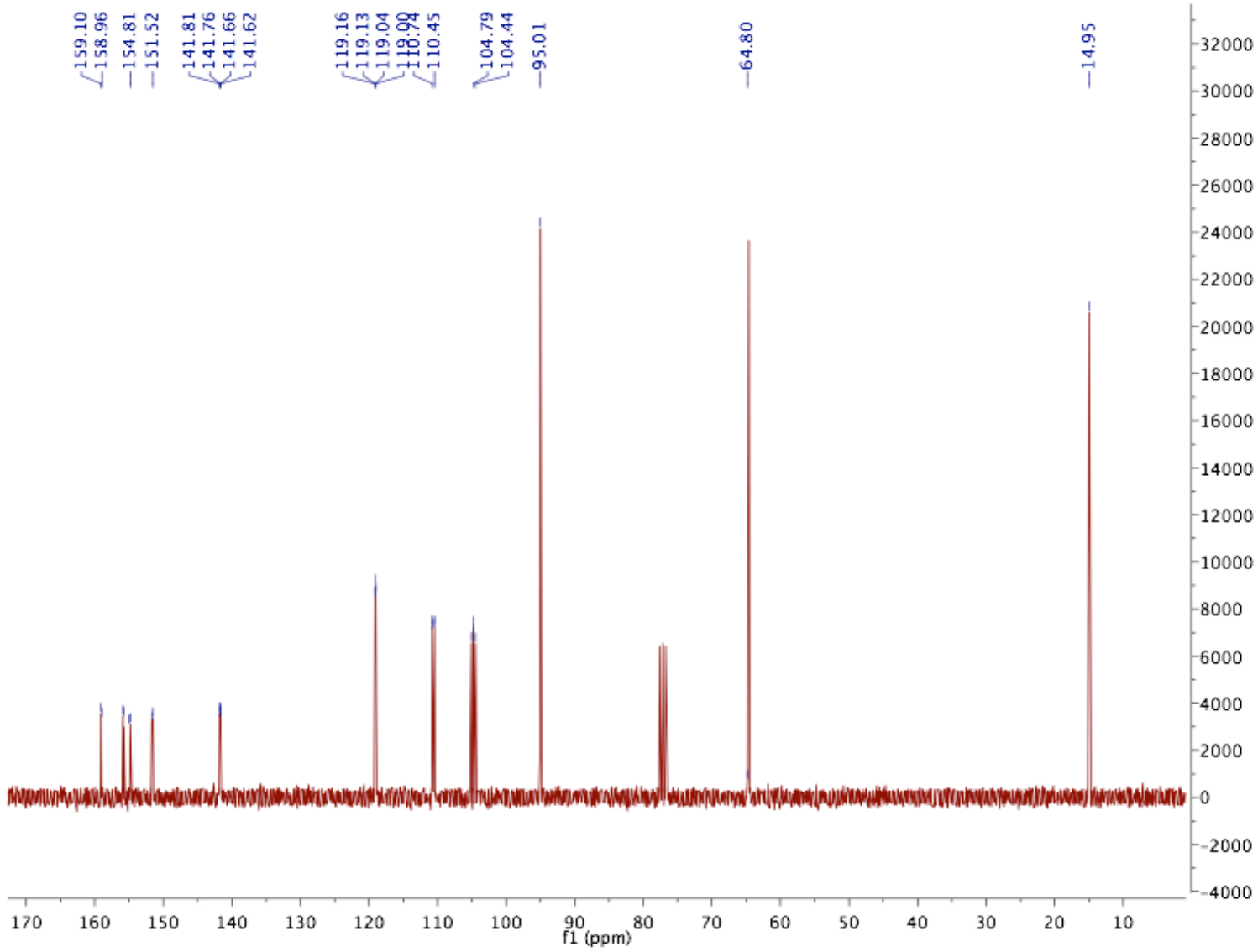
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95.01
64.80
14.95
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
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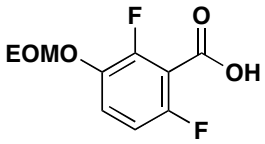
30
20
10
f1 (ppm)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O
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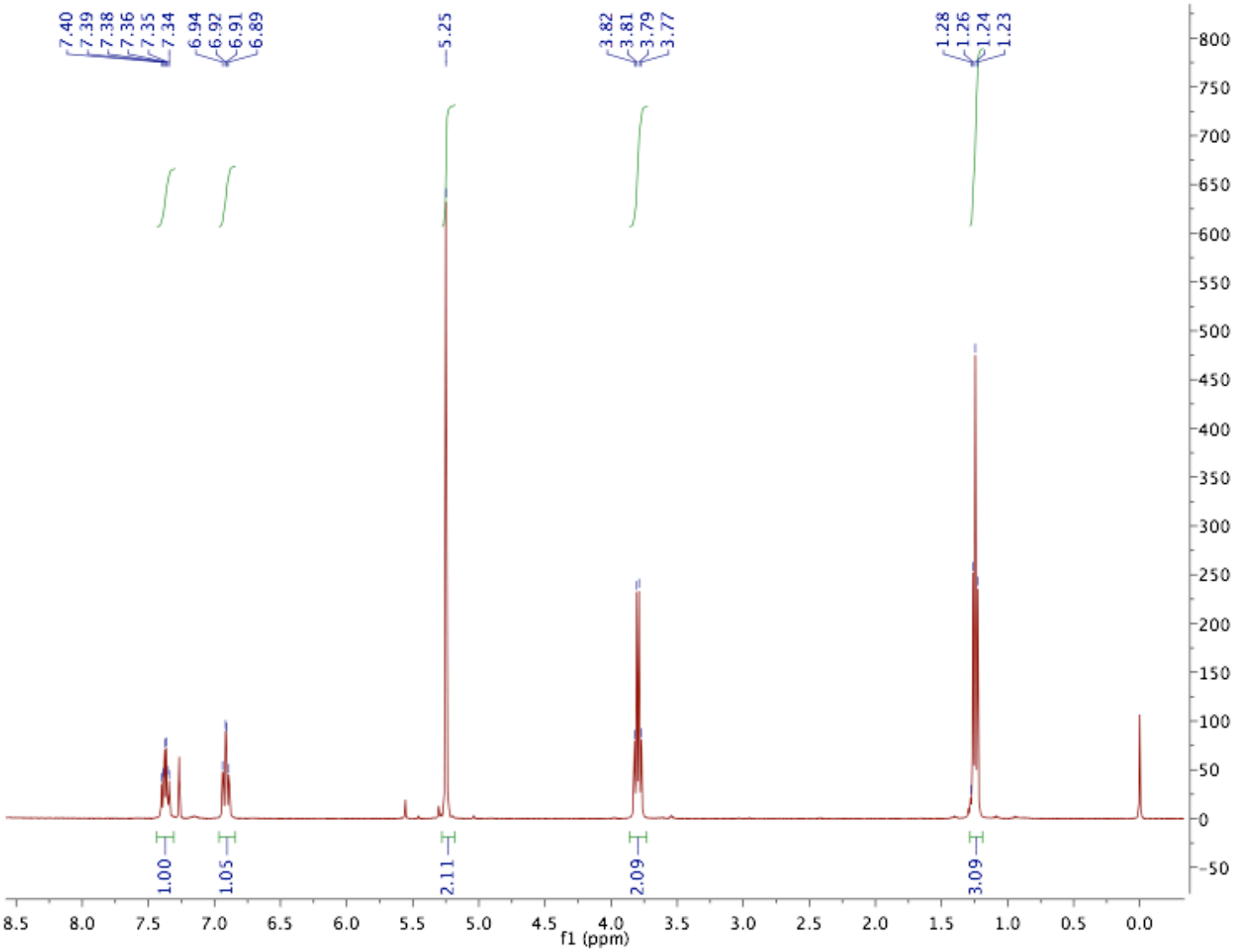
OH
F

11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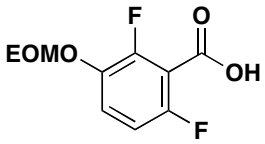
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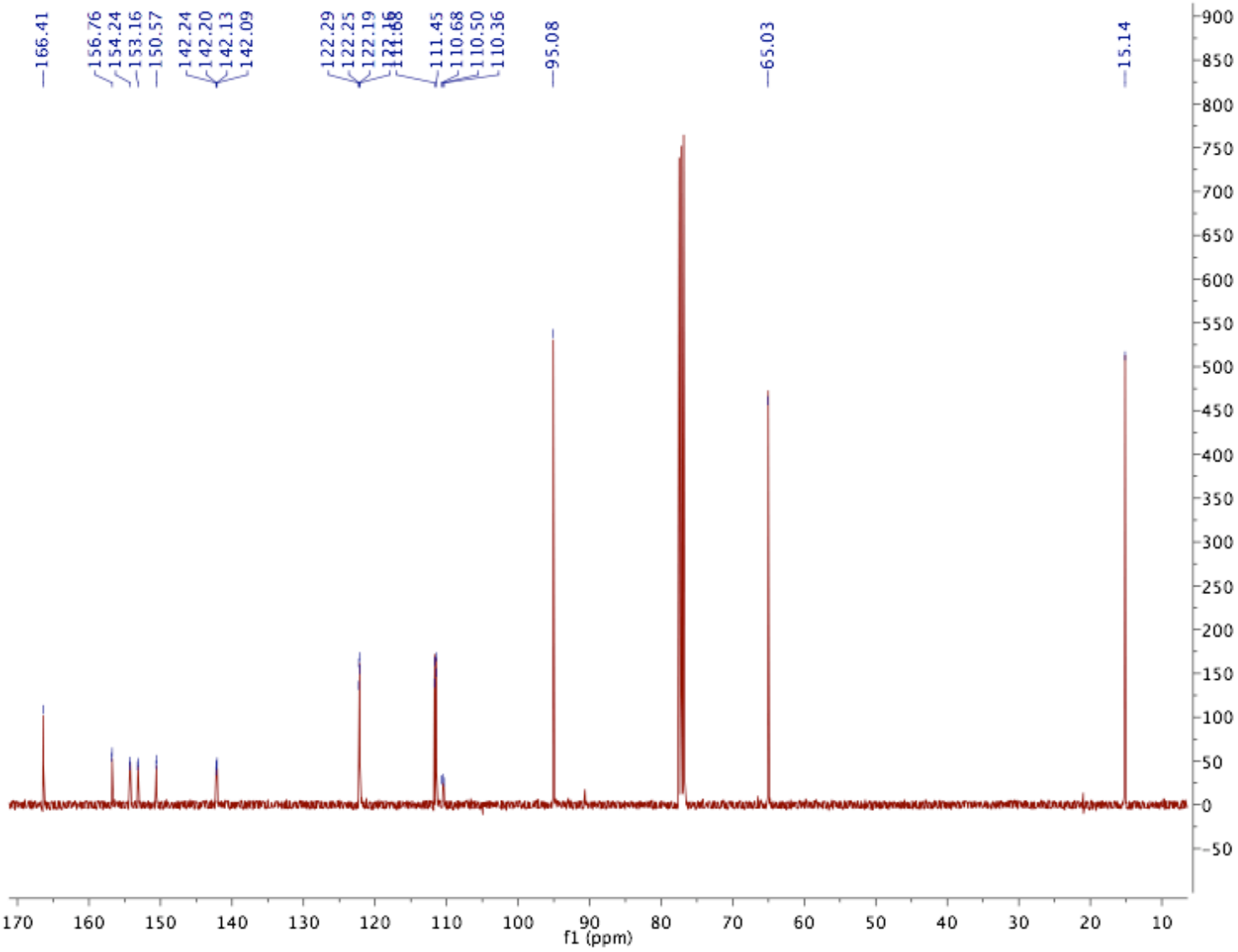
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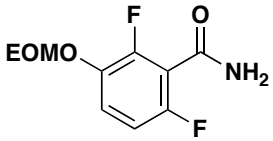
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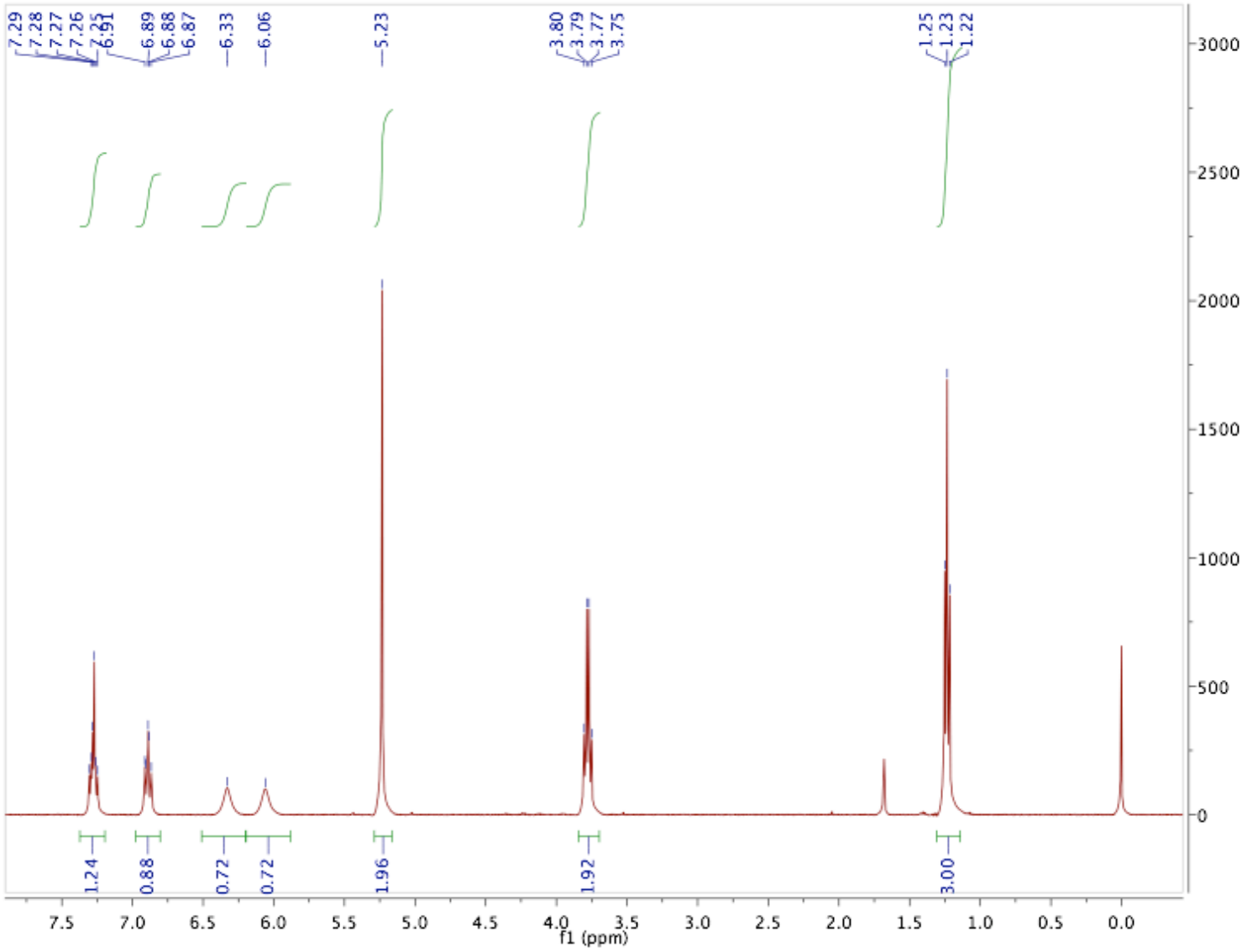
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1.23
1.22
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2500
2000
1500
1000
500
0
1.24
0.88
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0.72
1.96
1.92
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7.0
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6.0
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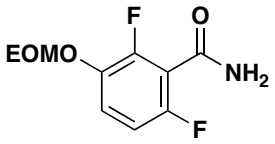
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O
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NH2
F

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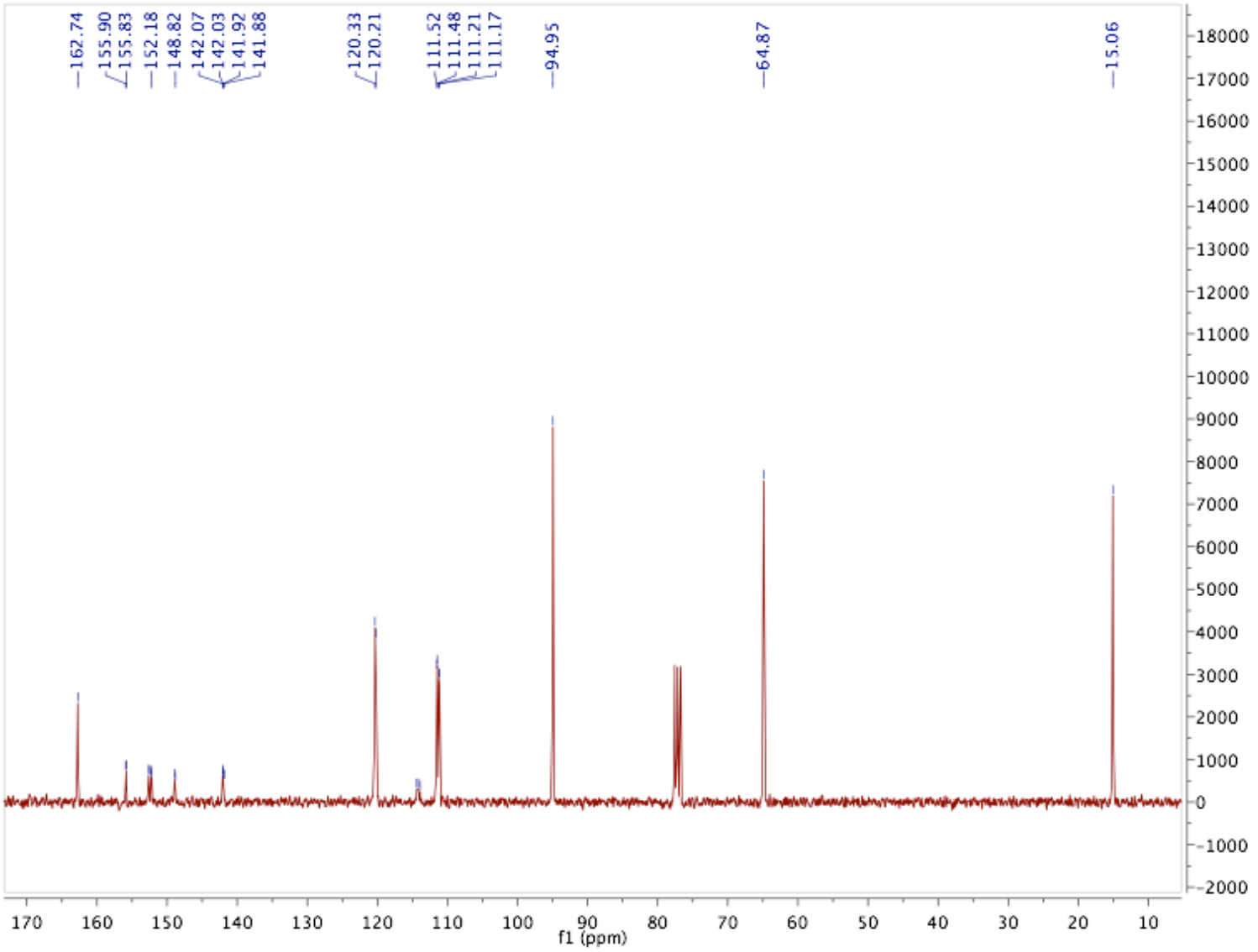
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14000
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1000
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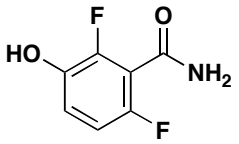
f1 (ppm)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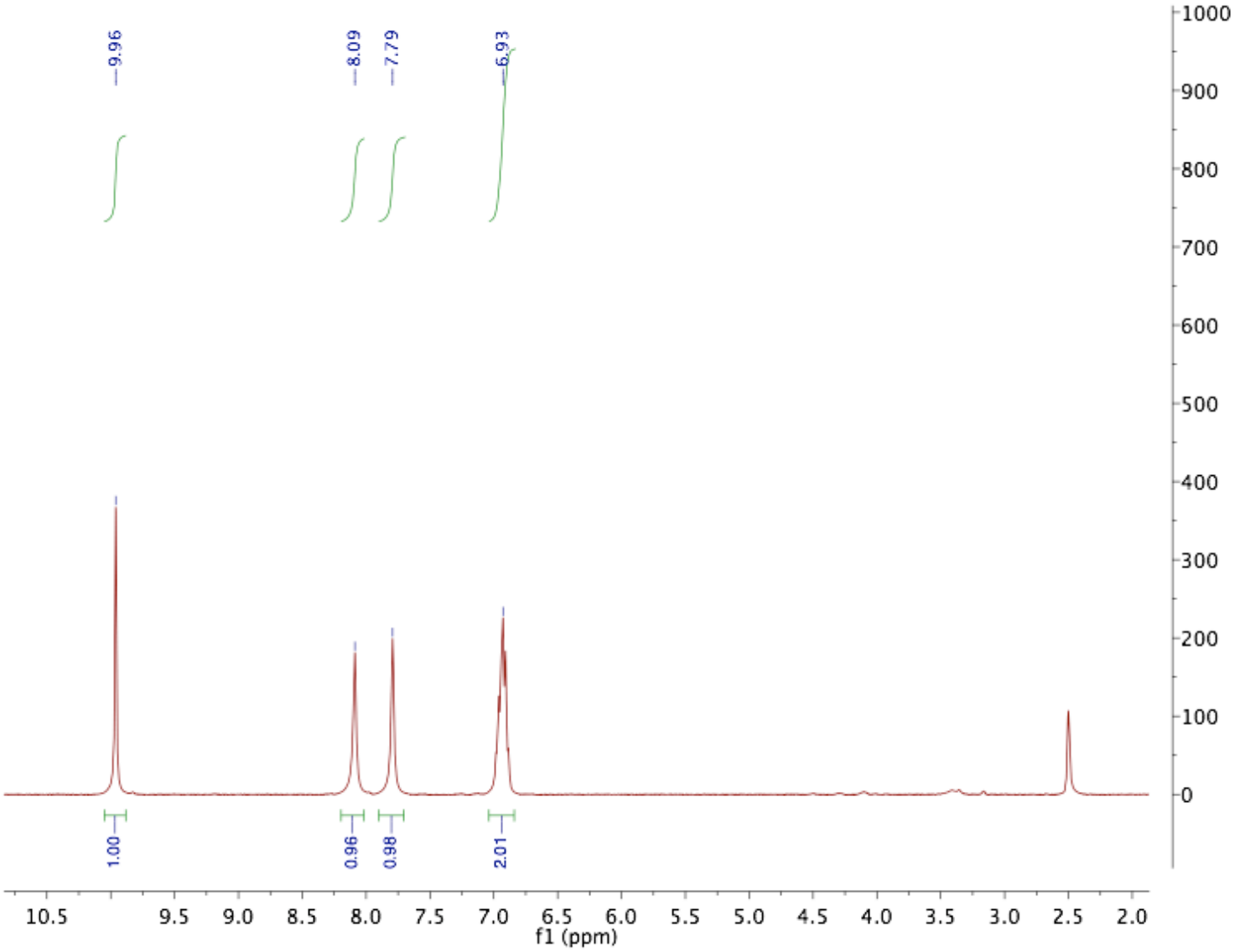
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200
100
0
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9.5
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8.5
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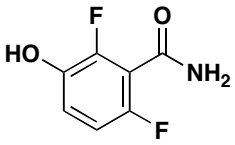
f1 (ppm)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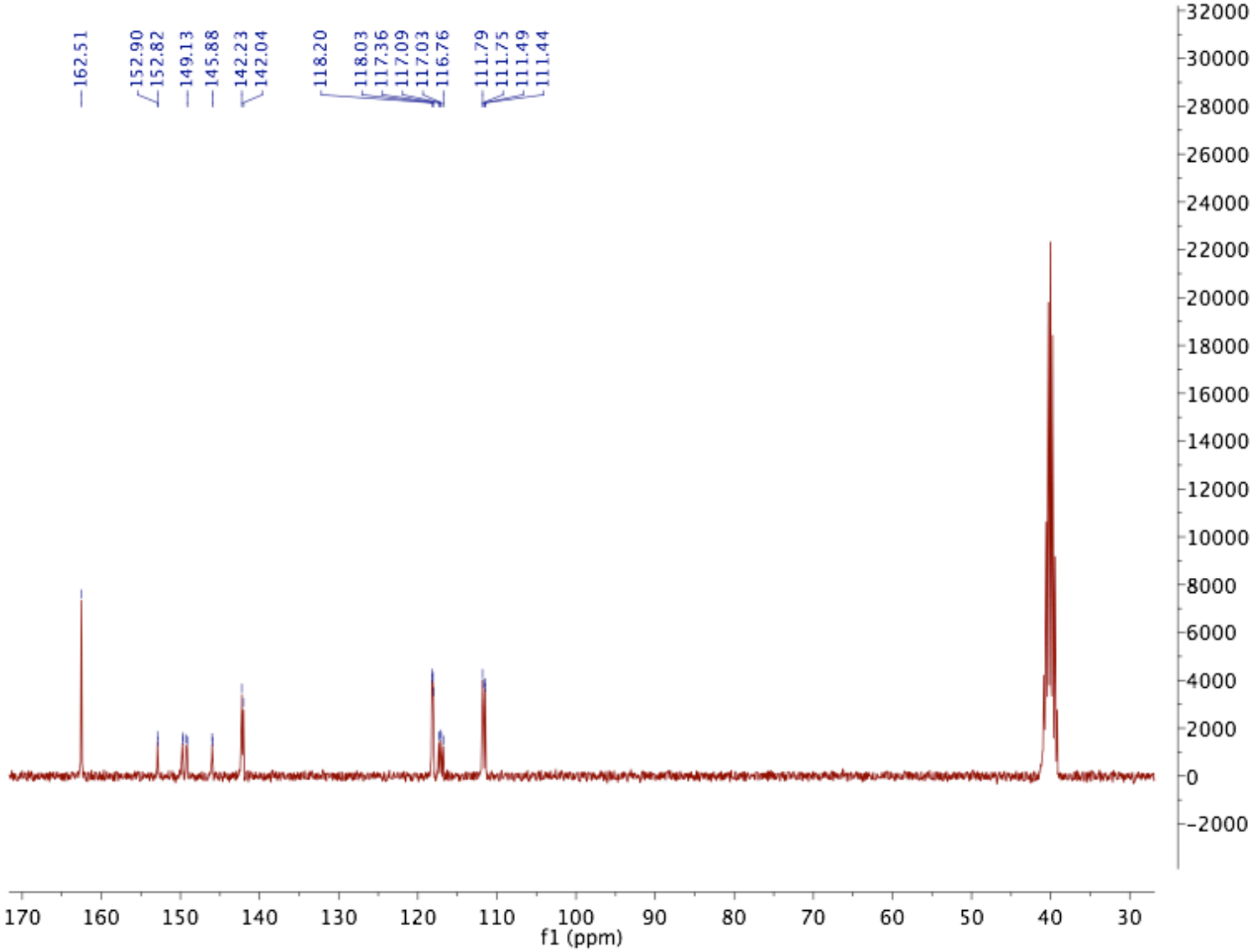
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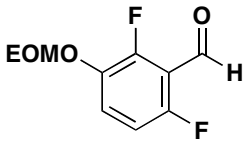
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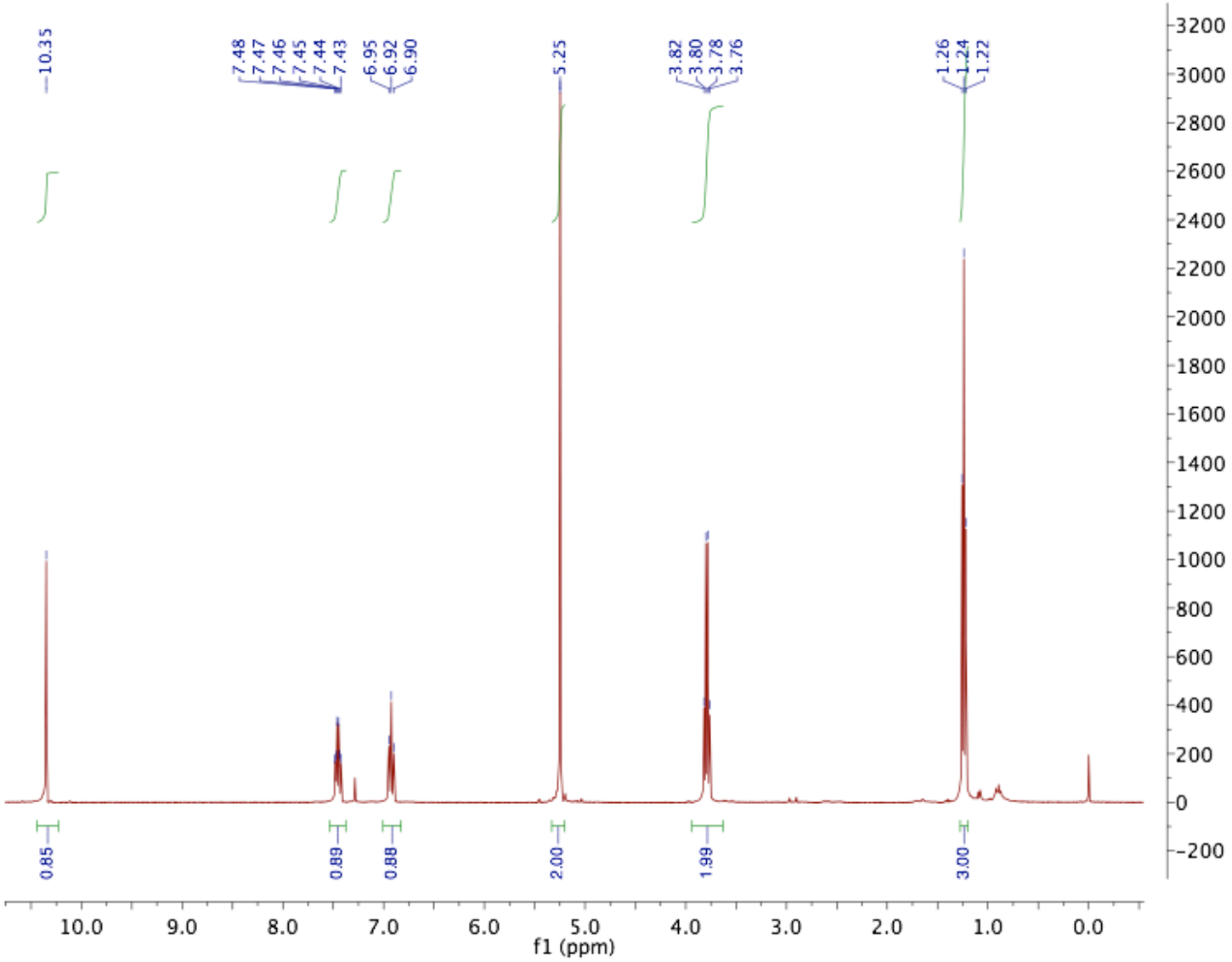
H
F

13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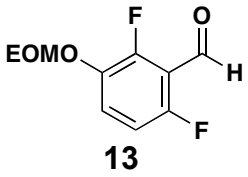
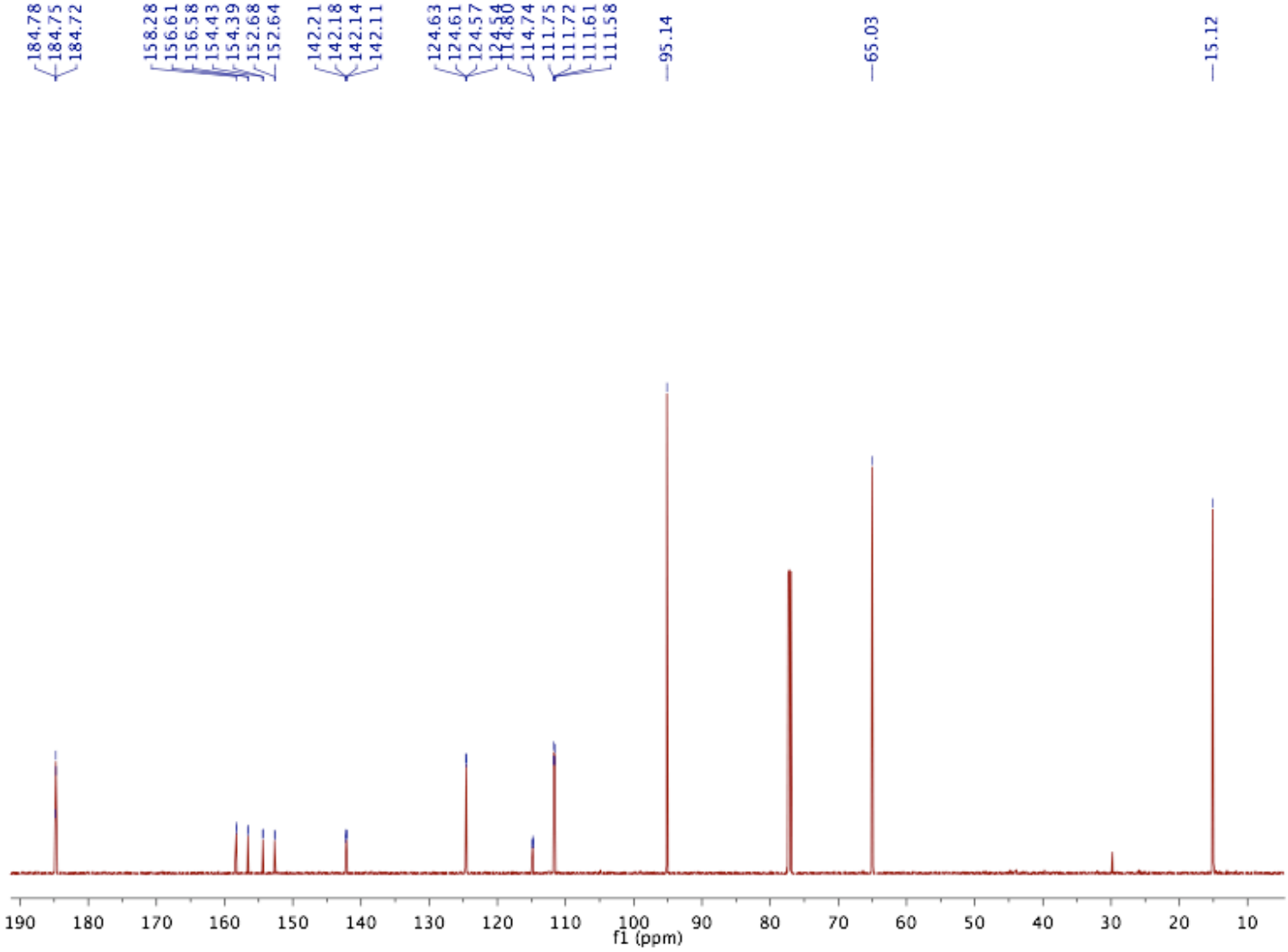
f1 (ppm)


F
O
EOMO
H
F

13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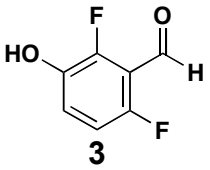
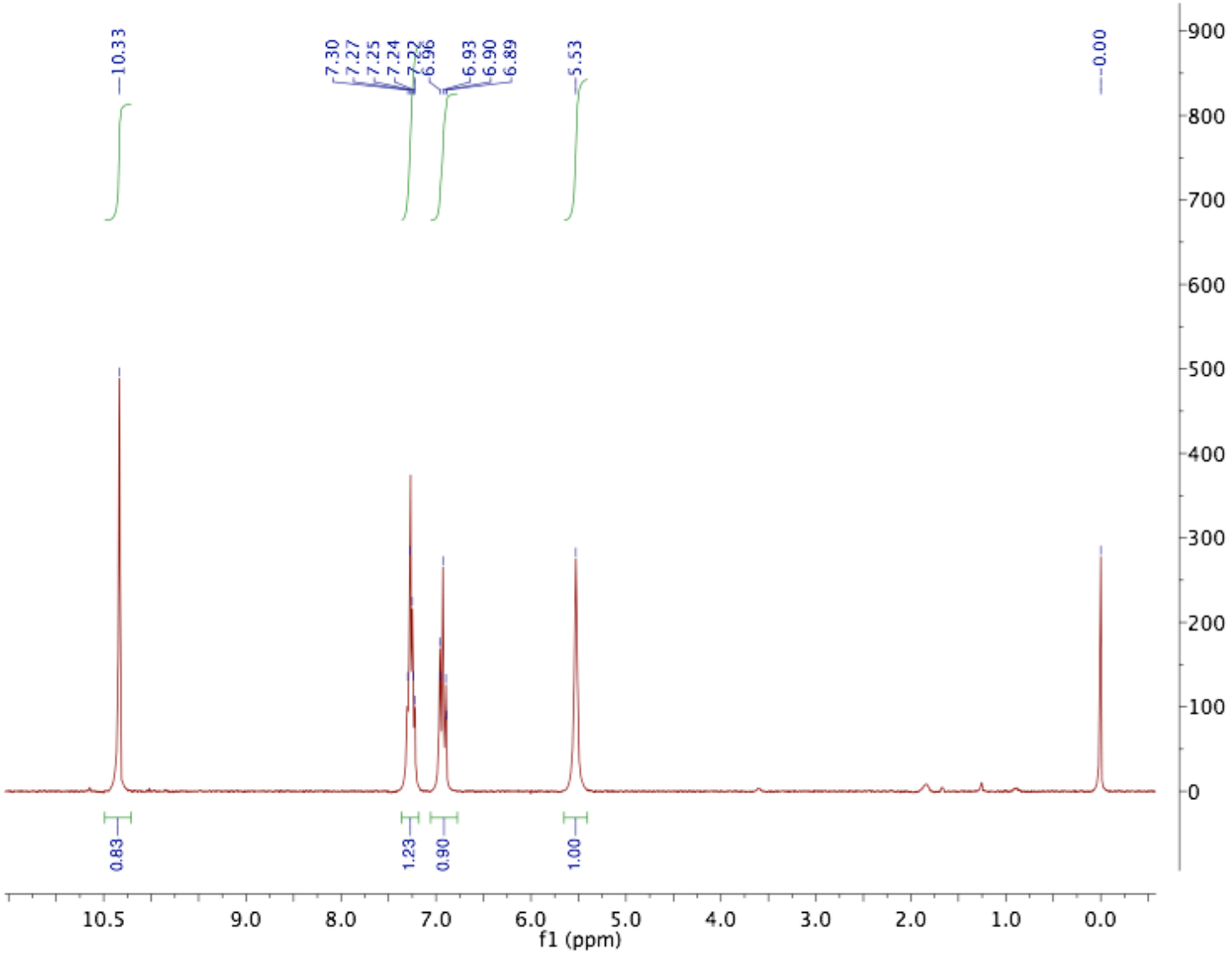
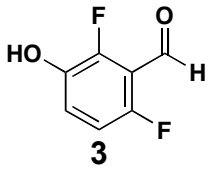
156.58
154.43
154.39
152.68
152.64
142.21
142.18
142.14
142.11
124.63
124.61
124.57
114.80
114.74
111.75
111.72
111.61
111.58
95.14
65.03
15.12
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

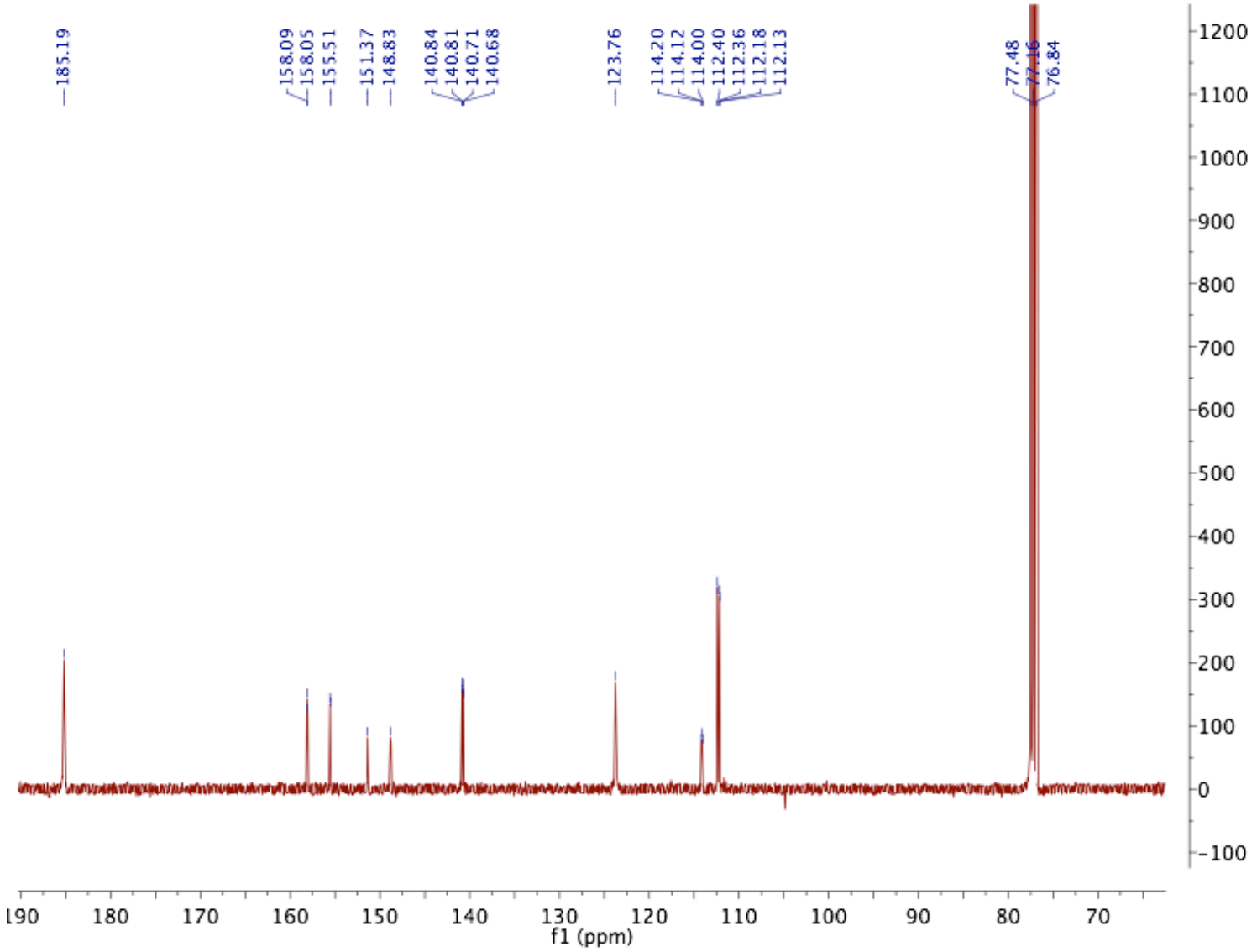

F
O
HO
H
F

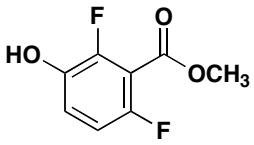
3


10.33
7.30
7.27
7.25
7.24
7.22
6.96
6.93
6.90
6.89
5.53
0.00
0.83
1.23
0.90
1.00
900
800
700
600
500
400
300
200
100
0
10.5
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

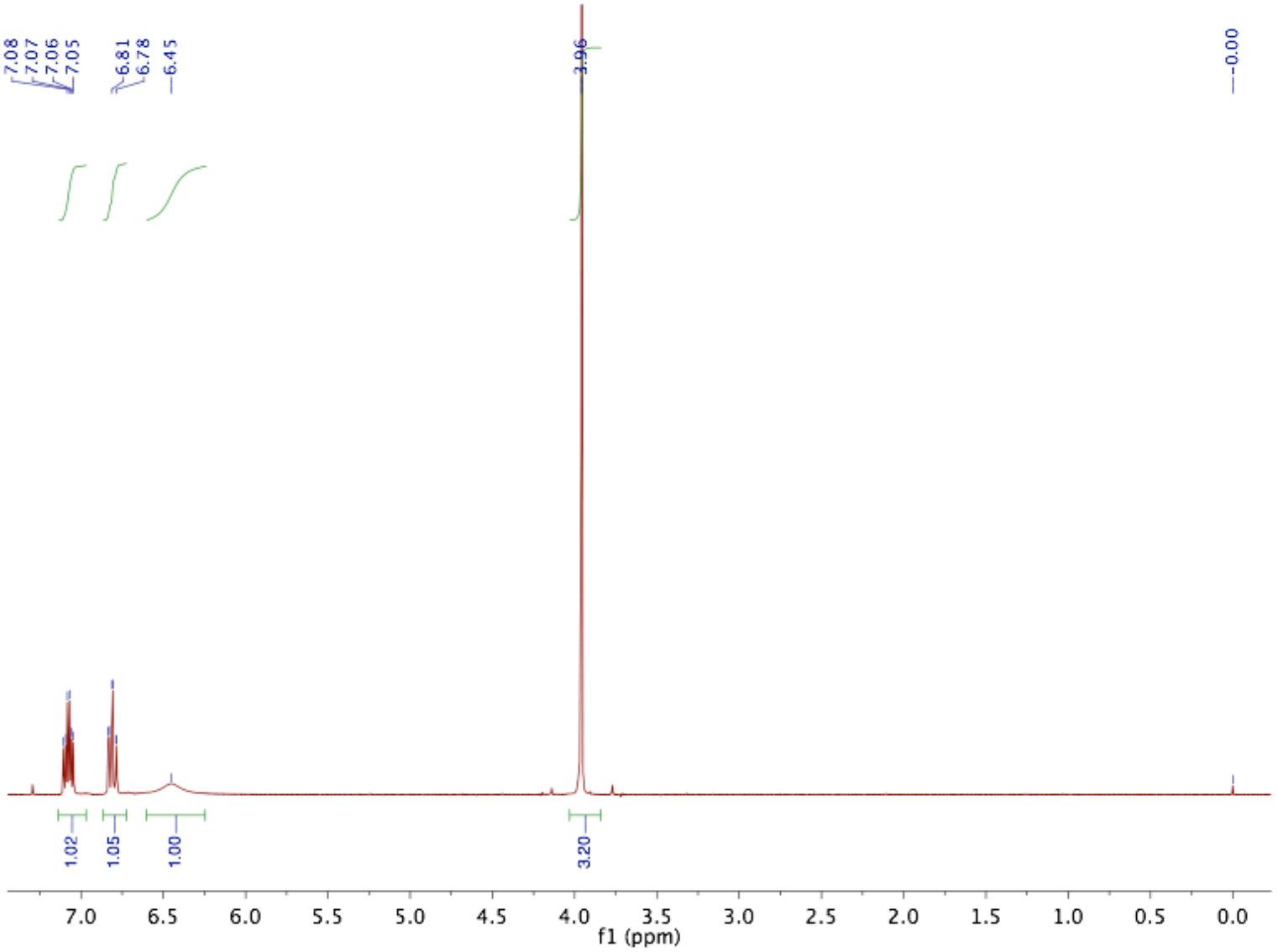

F
O
HO
H
F

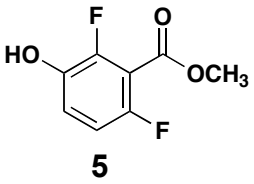
3


185.19
158.09
158.05
155.51
151.37
148.83
140.84
140.81
140.71
140.68
123.76
114.20
114.12
114.00
112.40
112.36
112.18
112.13
77.48
77.16
76.84
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
190
180
170
160
150
140
130
120
110
100
90
80
70
f1 (ppm)

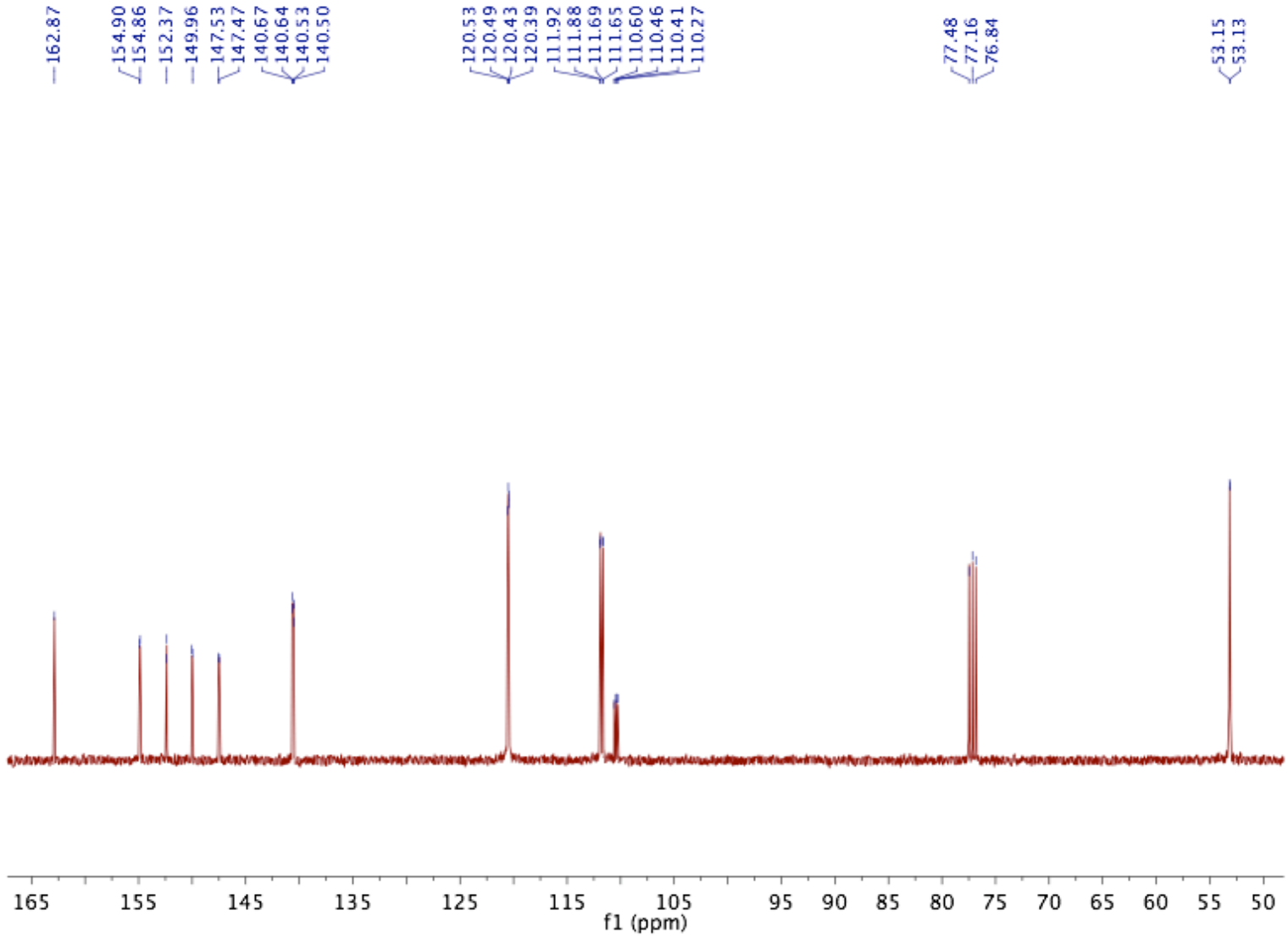

F
O
HO
OCH3
F

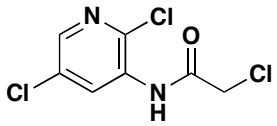
5


7.08
7.07
7.06
7.05
6.81
6.78
6.45
3.96
0.00
1.02
1.05
1.00
3.20
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)


F
O
HO
OCH3
F

5


162.87
154.90
154.86
152.37
149.96
147.53
147.47
140.67
140.64
140.53
140.50
120.53
120.49
120.43
120.39
111.92
111.88
111.69
111.65
110.60
110.46
110.41
110.27
77.48
77.16
76.84
53.15
53.13
165
155
145
135
125
115
105
95
90
85
80
75
70
65
60
55
50
f1 (ppm)



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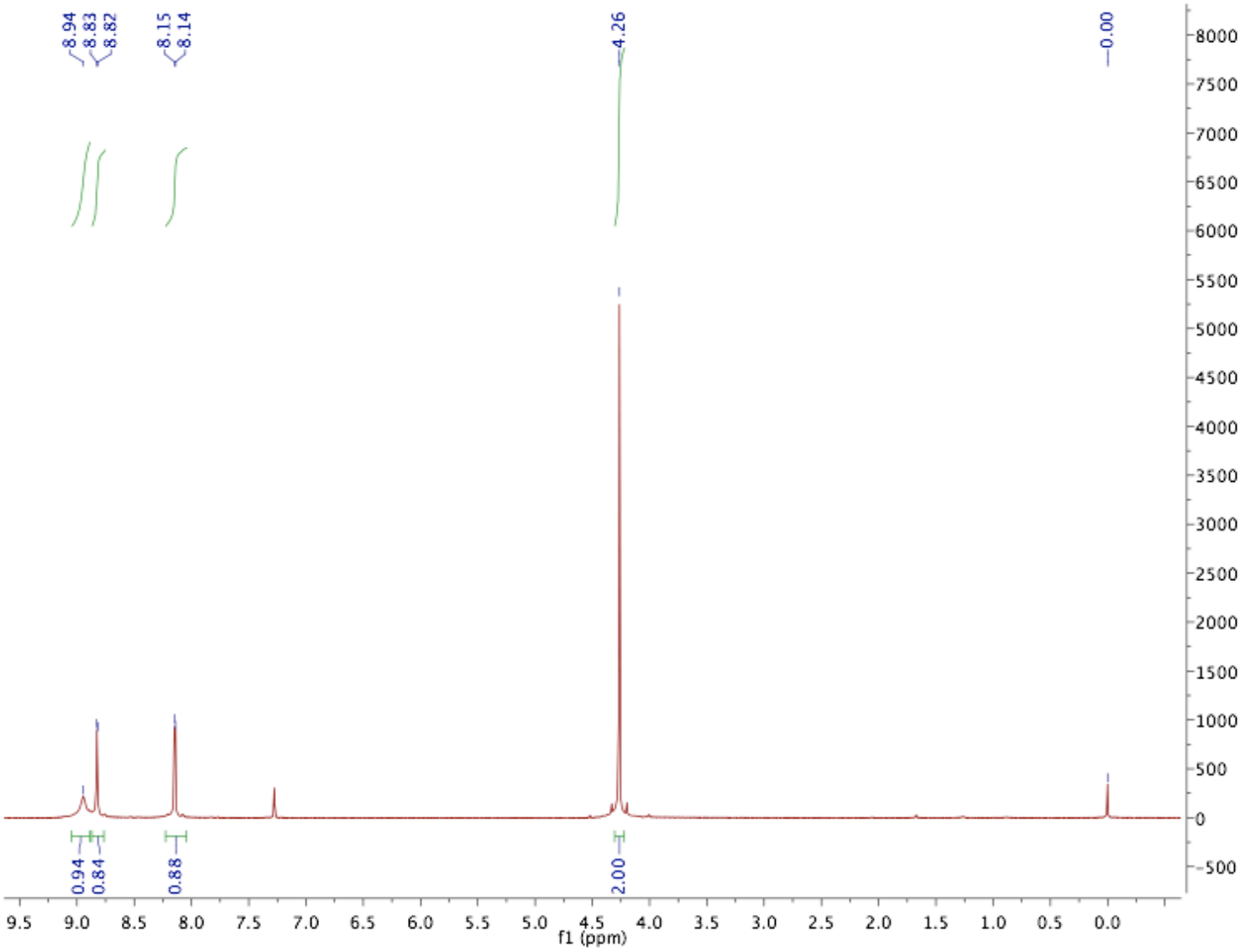
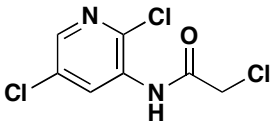
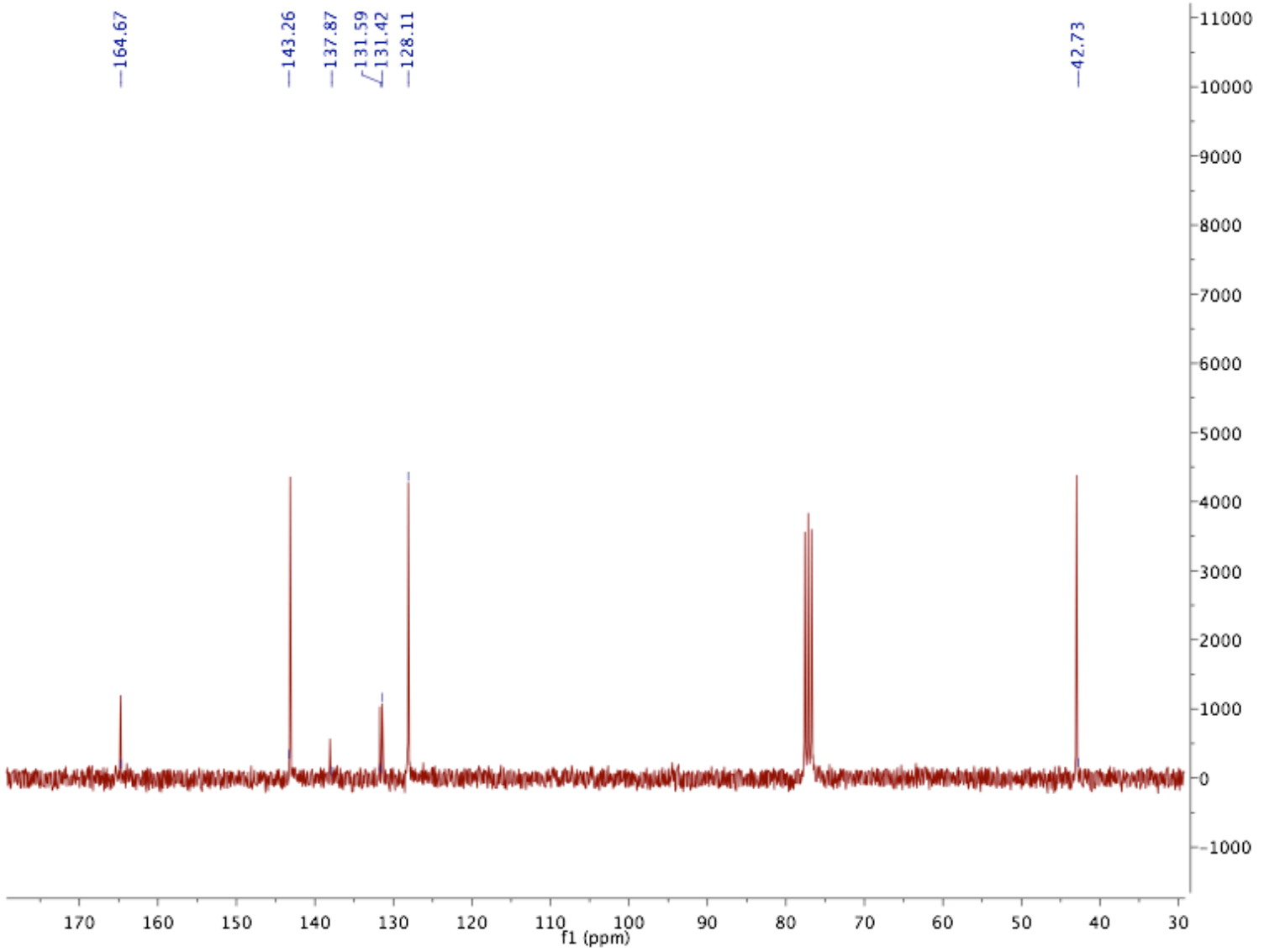
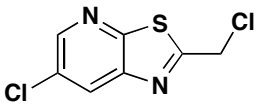


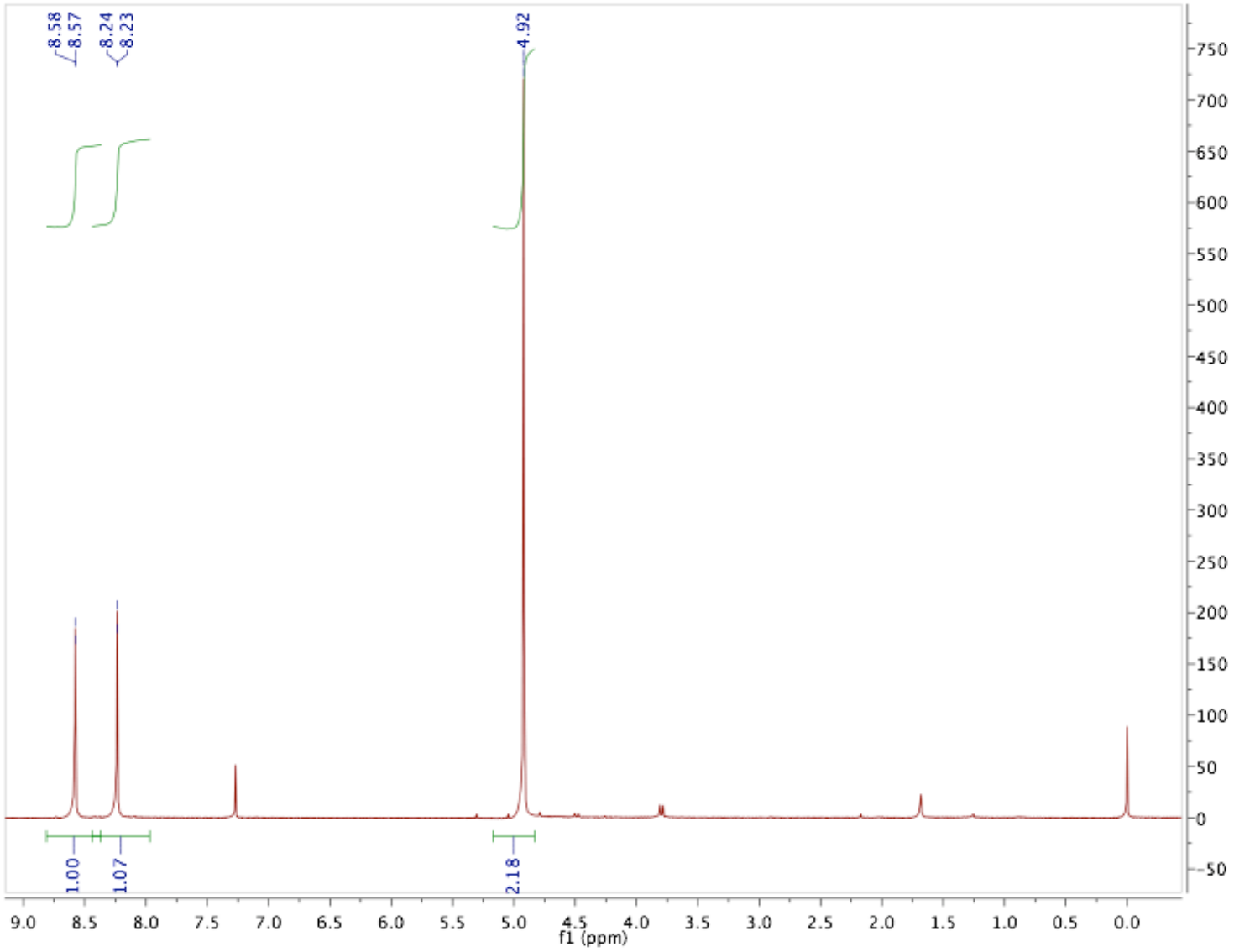

N
Cl
O
Cl
Cl
N
H

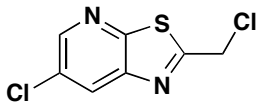
7


164.67
143.26
137.87
131.59
131.42
128.11
42.73
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

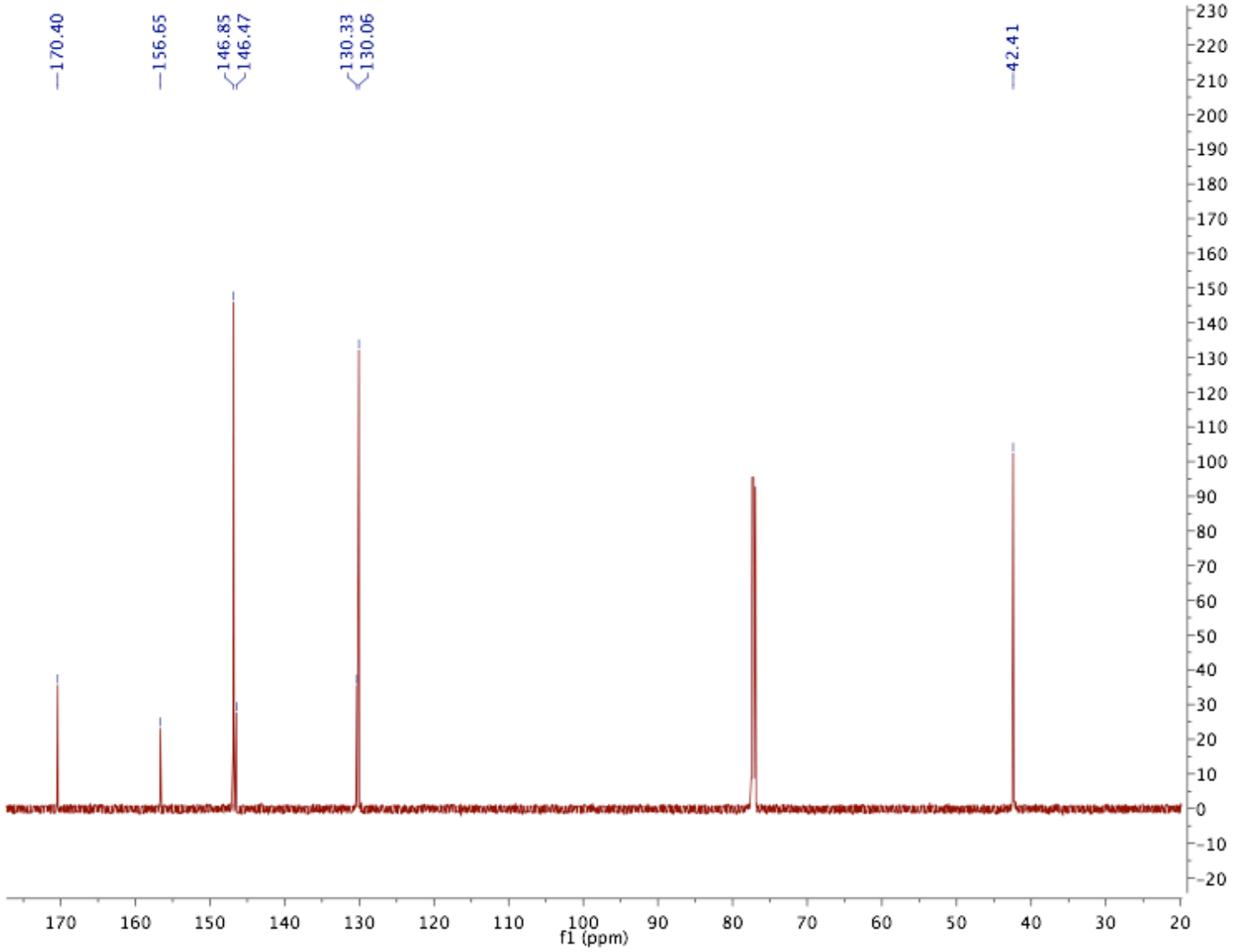


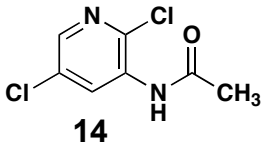
2



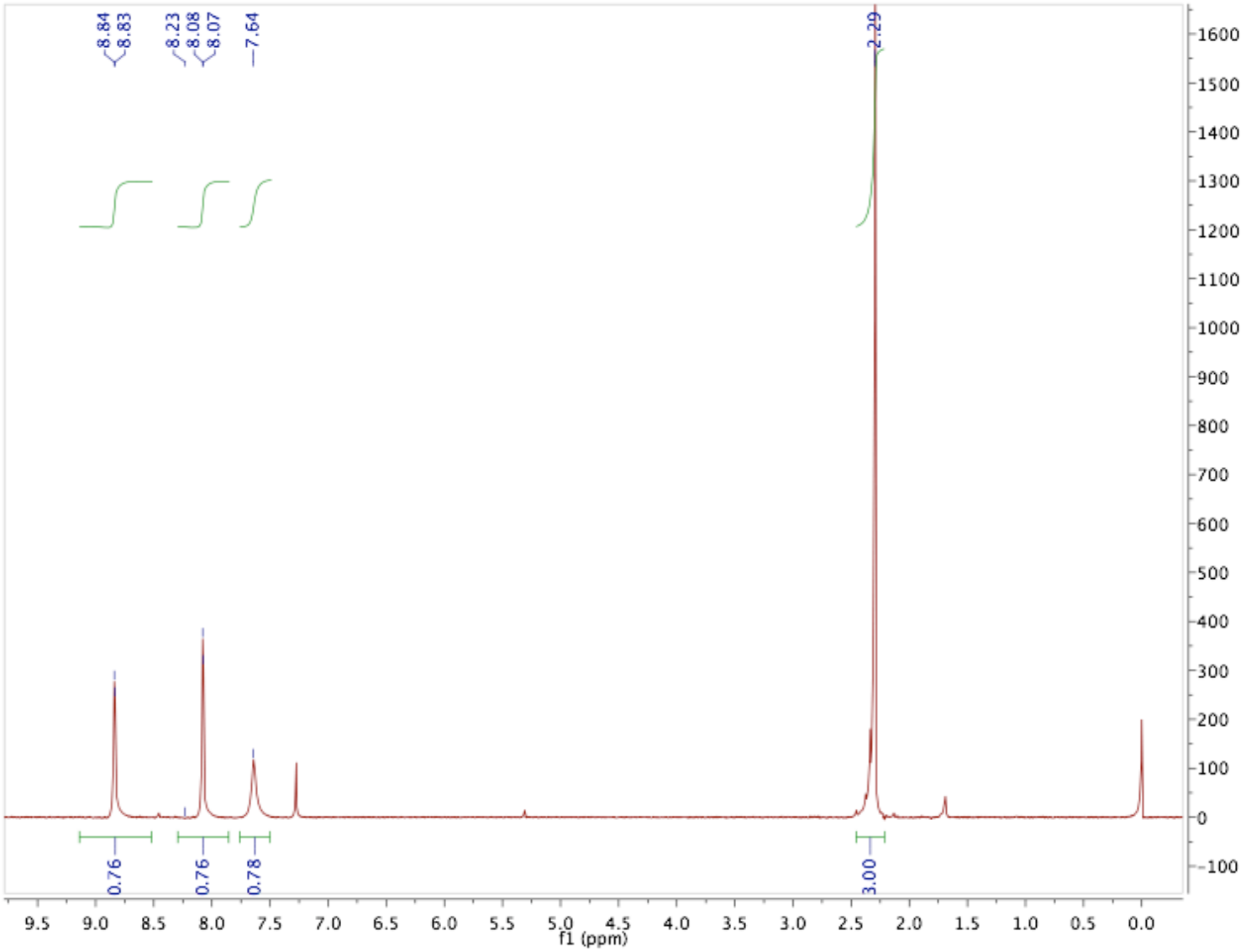

N
S
Cl
Cl
N

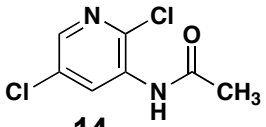
2


170.40
156.65
146.85
146.47
130.33
130.06
42.41
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

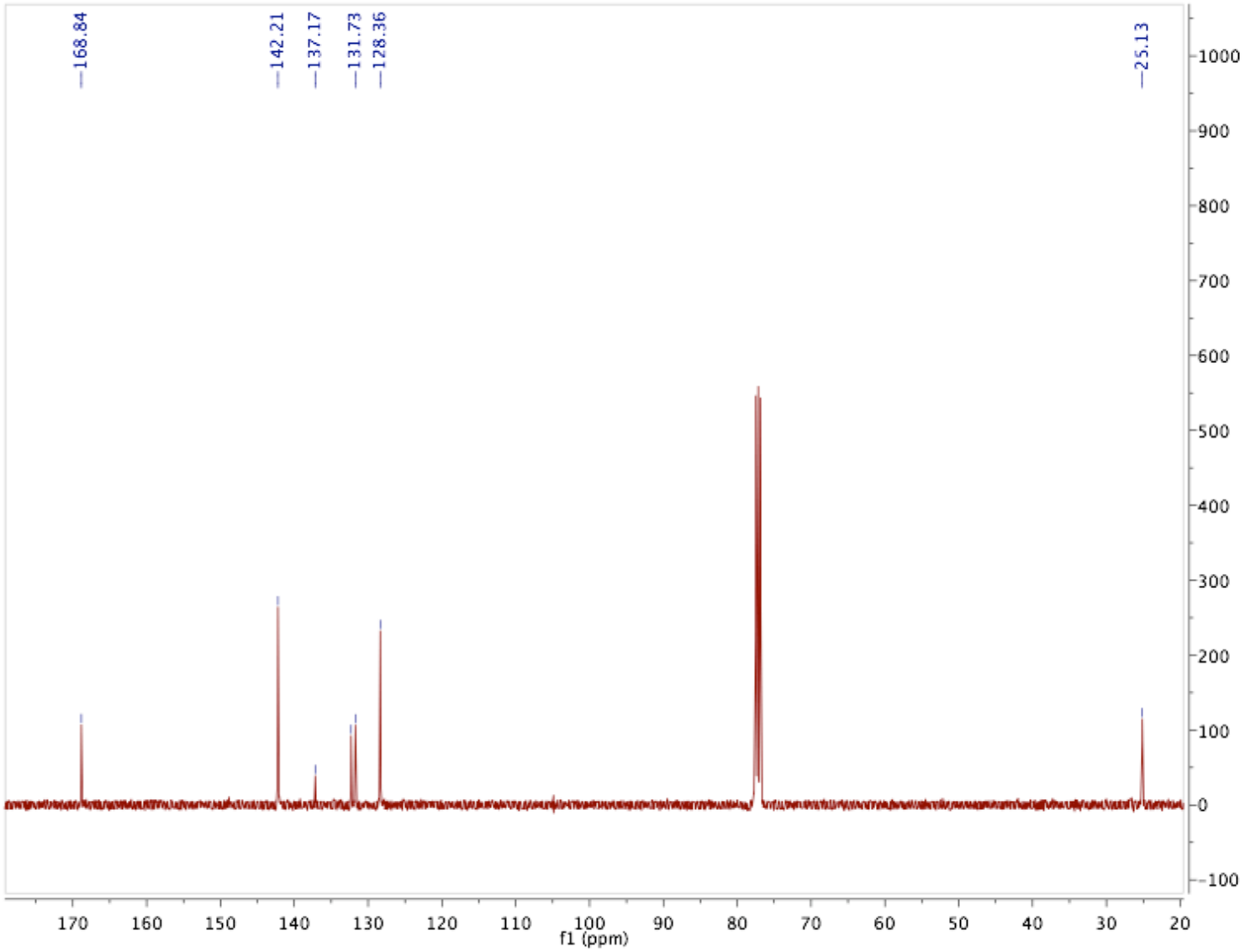


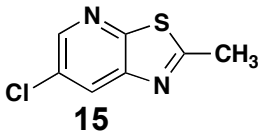
14



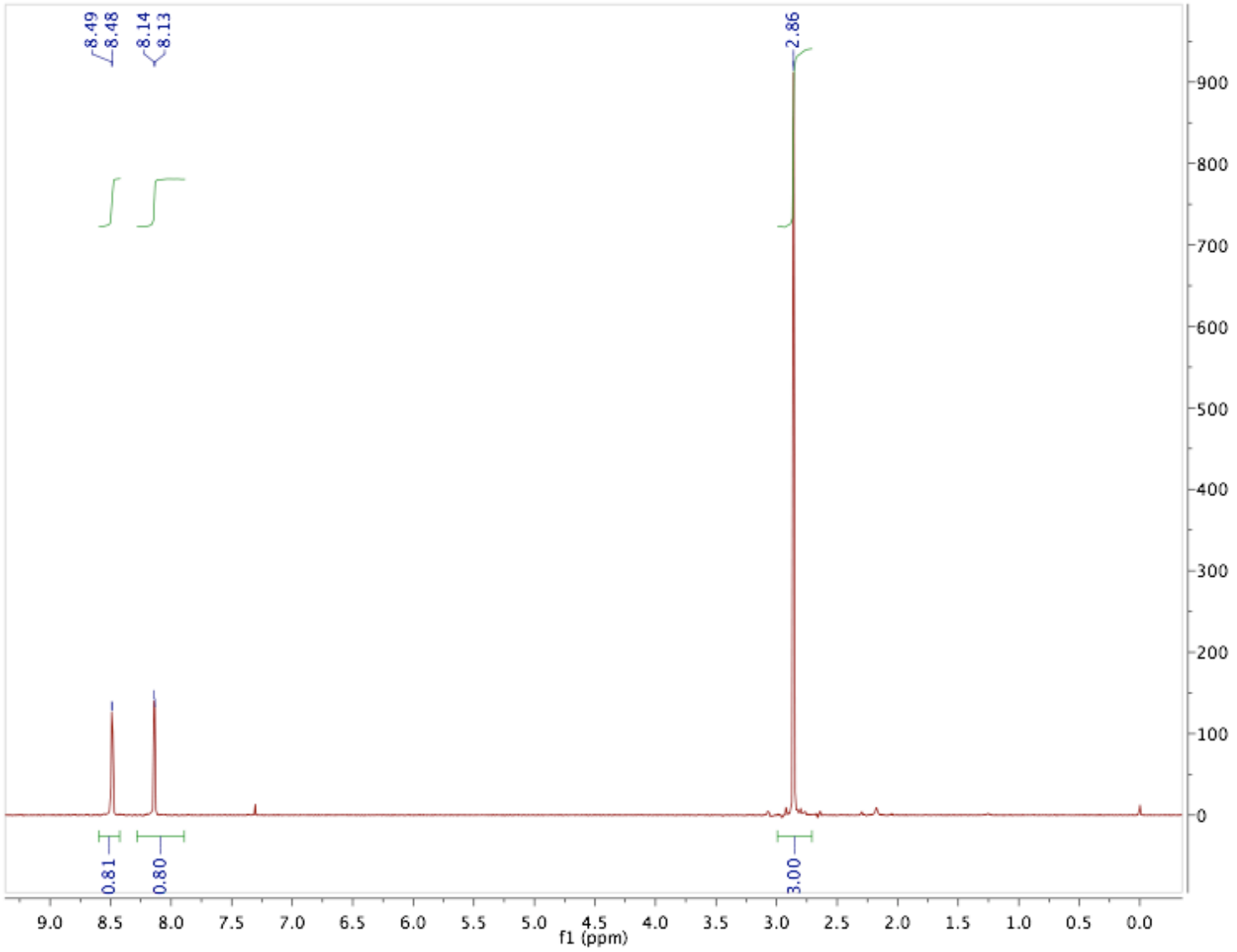

N
Cl
O
Cl
N
H
CH3

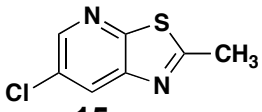
14


168.84
142.21
137.17
131.73
128.36
25.13
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
f1 (ppm)

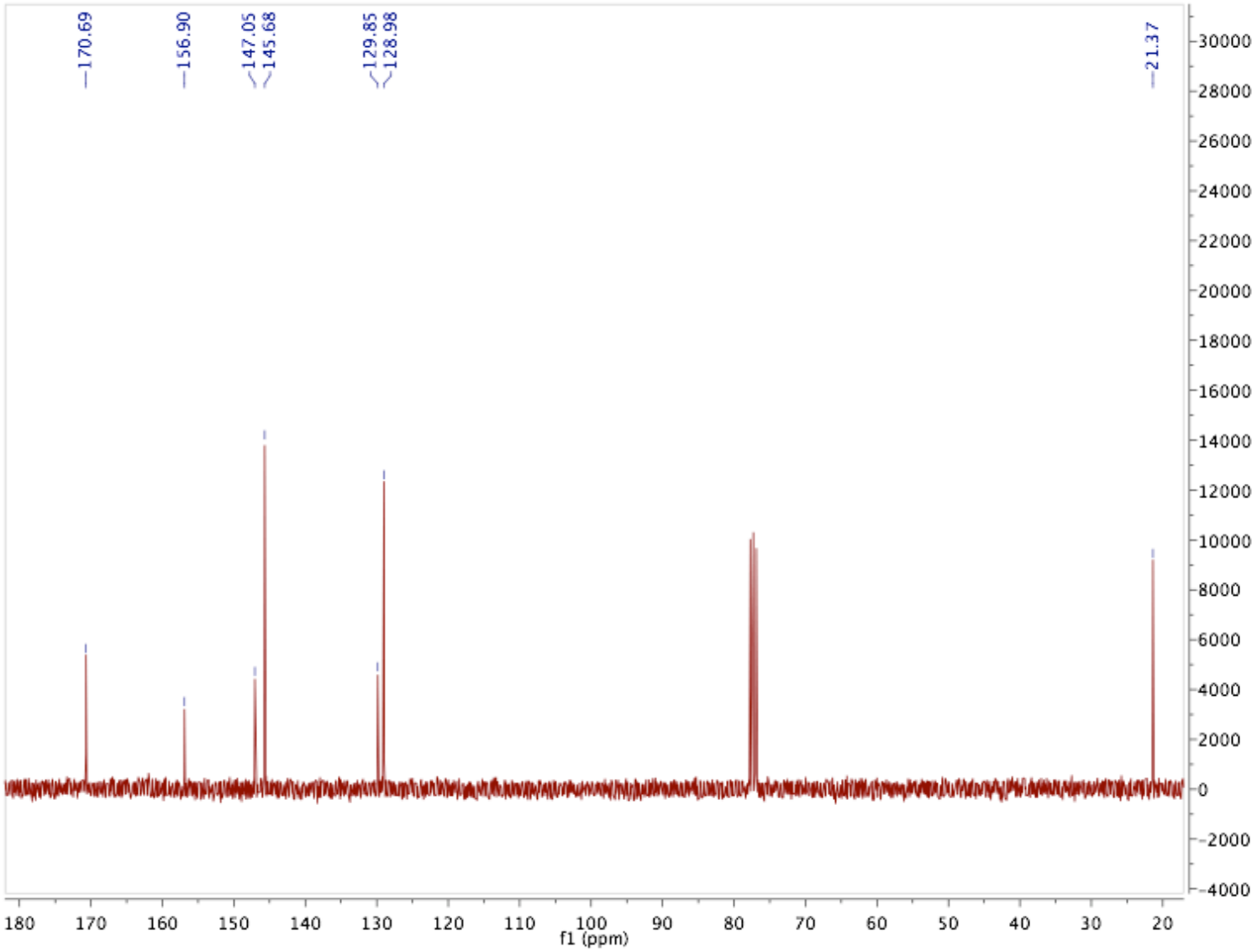

N
S
CH3
Cl
N

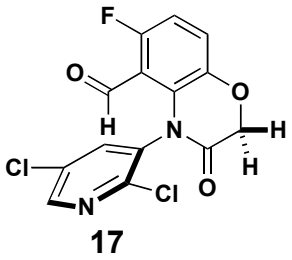
15


8.49
8.48
8.14
8.13
2.86
900
800
700
600
500
400
300
200
100
0
0.81
0.80
3.00
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)

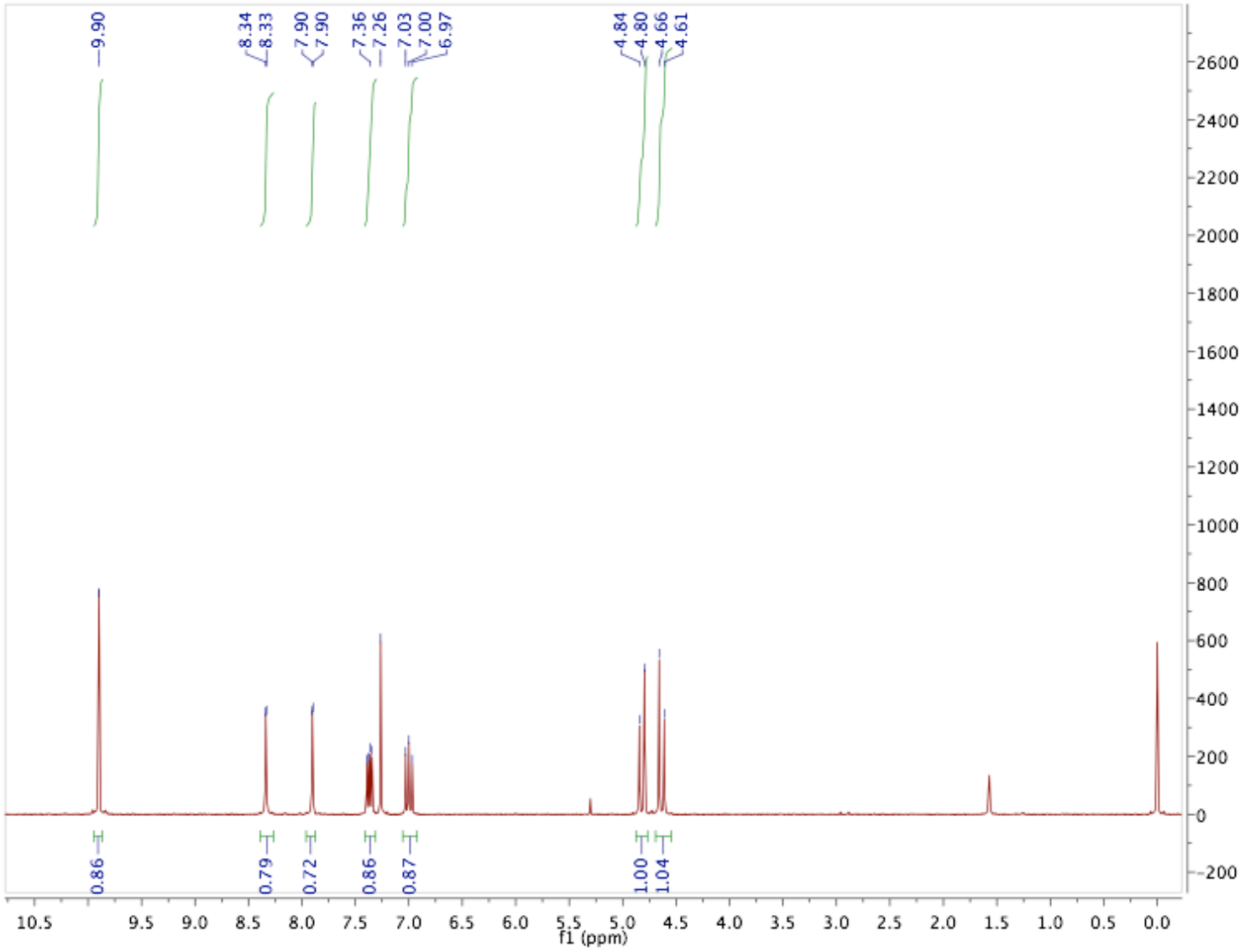

N
S
CH3
Cl
N

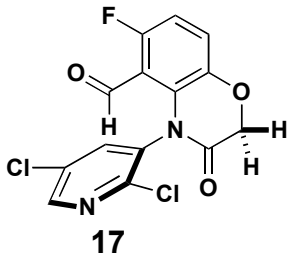
15


170.69
156.90
147.05
145.68
129.85
128.98
21.37
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

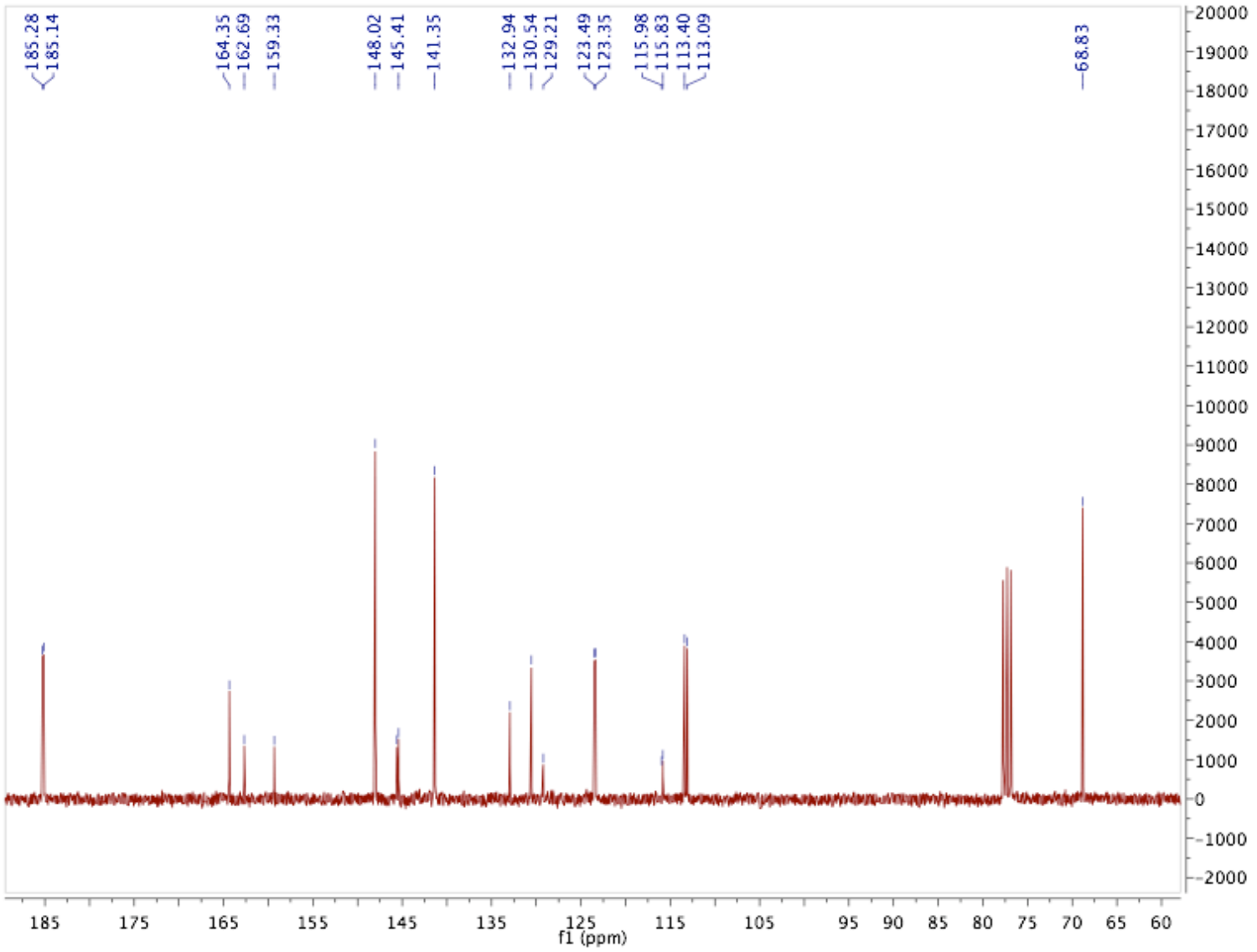

F
O
H
N
O
H
Cl
O
H
N
Cl

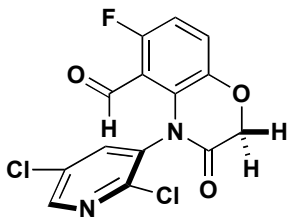
17


9.90
8.34
8.33
7.90
7.90
7.36
7.26
7.03
7.00
6.97
4.84
4.80
4.66
4.61
0.86
0.79
0.72
0.86
0.87
1.00
1.04
f1 (ppm)

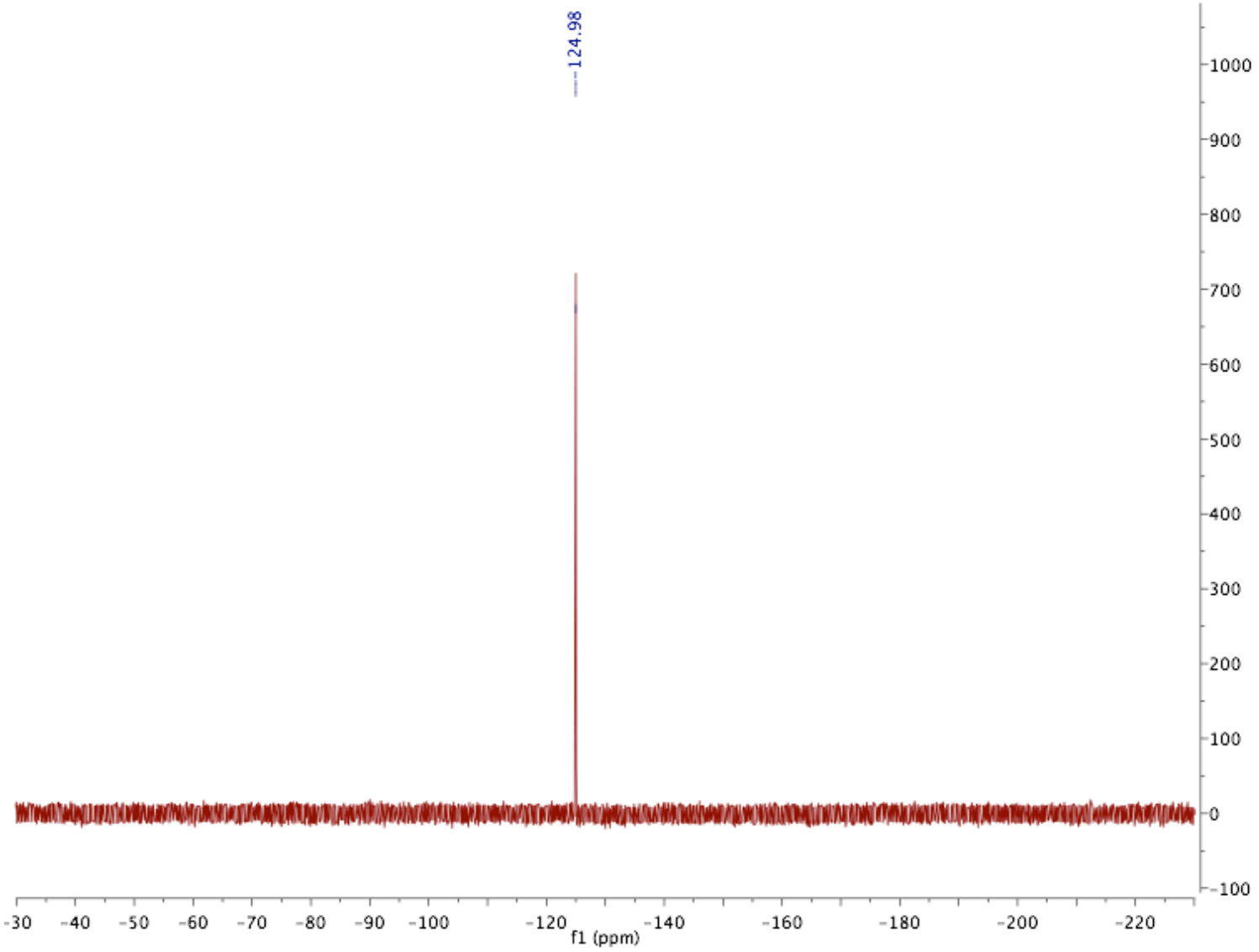

F
O
H
N
O
H
Cl
O
H
Cl
N

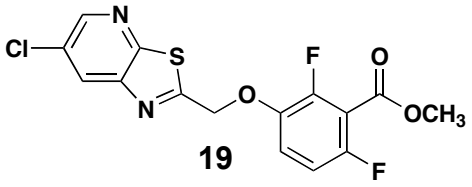
17


185.28
185.14
164.35
162.69
159.33
148.02
145.41
141.35
132.94
130.54
129.21
123.49
123.35
115.98
115.83
113.40
113.09
68.83
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
185
175
165
155
145
135
125
115
105
95
90
85
80
75
70
65
60
f1 (ppm)

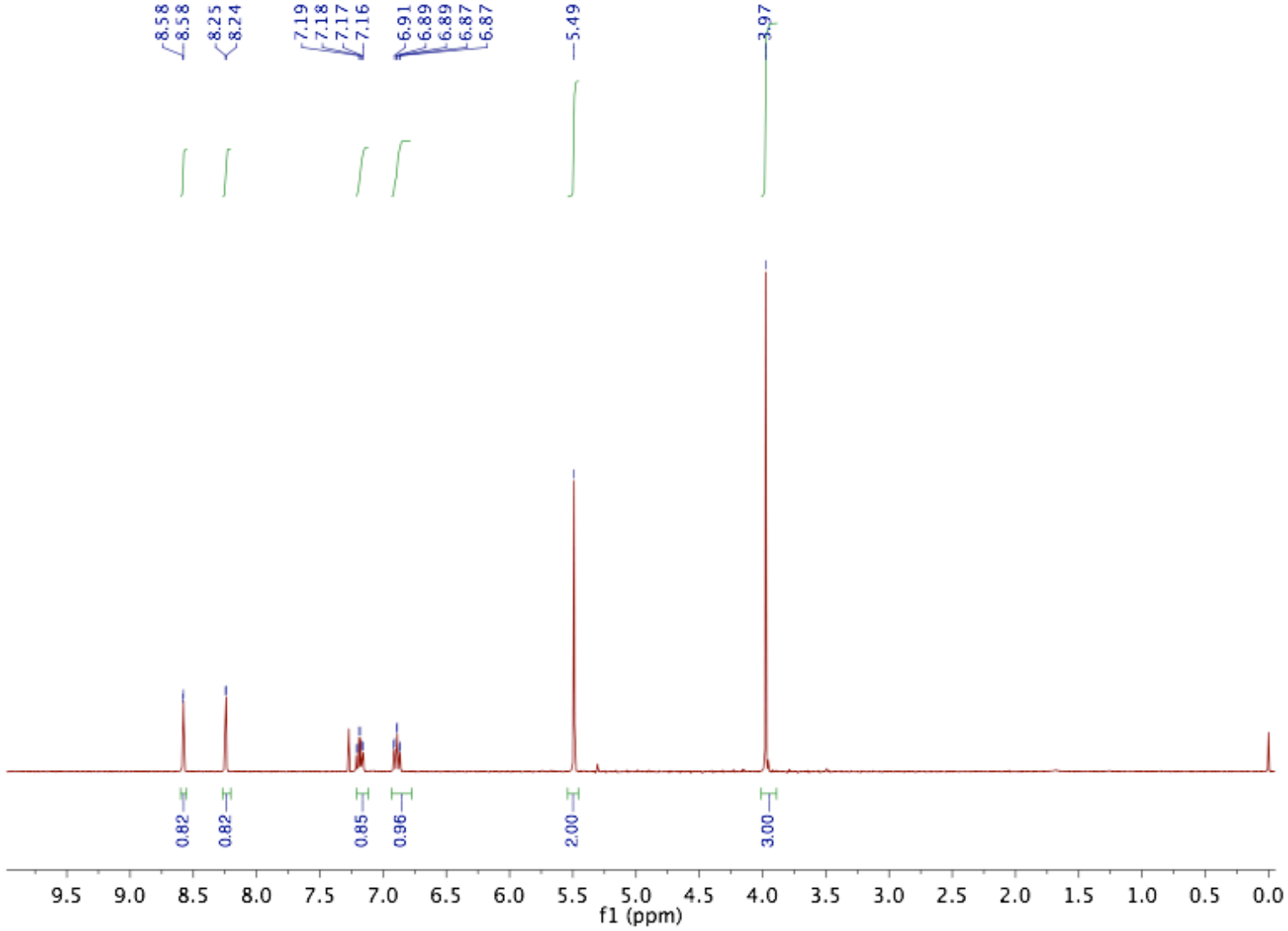

F
O
H
N
O
H
H
O
Cl
Cl
N

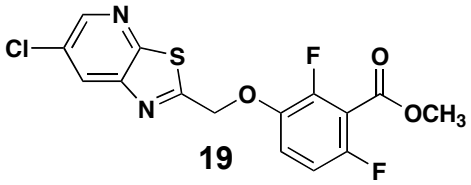
17


124.98
1000
900
800
700
600
500
400
300
200
100
0
-100
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)

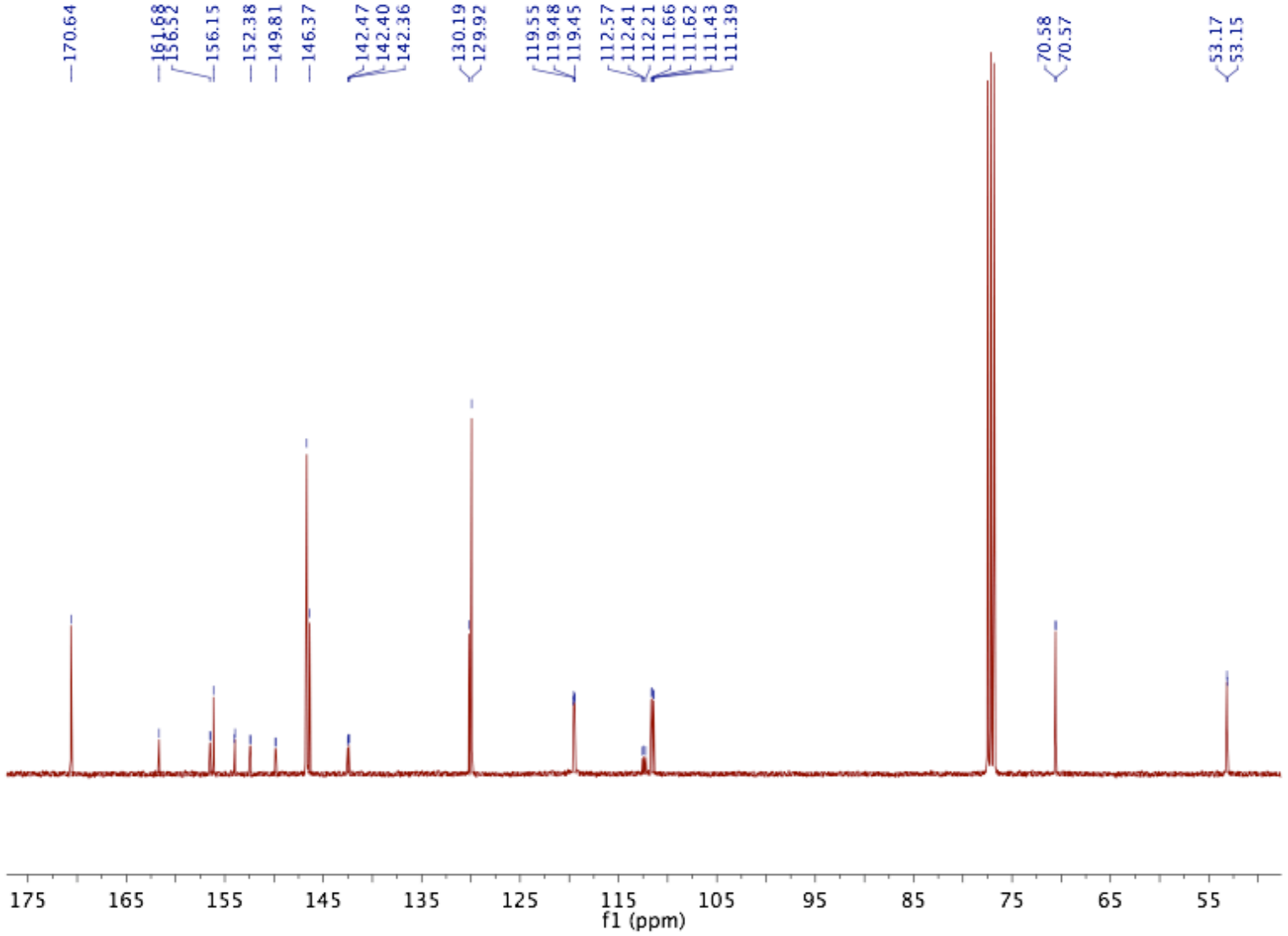

Cl
N
S
N
O
F
O
OCH3
F

19


8.58
8.58
8.25
8.24
7.19
7.18
7.17
7.16
6.91
6.89
6.89
6.87
6.87
5.49
3.97
0.82
0.82
0.85
0.96
2.00
3.00
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)


Cl
N
S
N
O
F
O
OCH3
F

19


170.64
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156.52
156.15
152.38
149.81
146.37
142.47
142.40
142.36
130.19
129.92
119.55
119.48
119.45
112.57
112.41
112.21
111.66
111.62
111.43
111.39
70.58
70.57
53.17
53.15
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155
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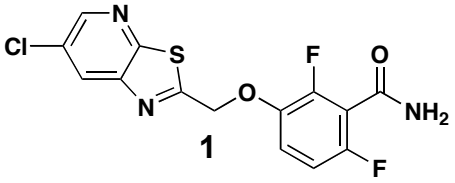
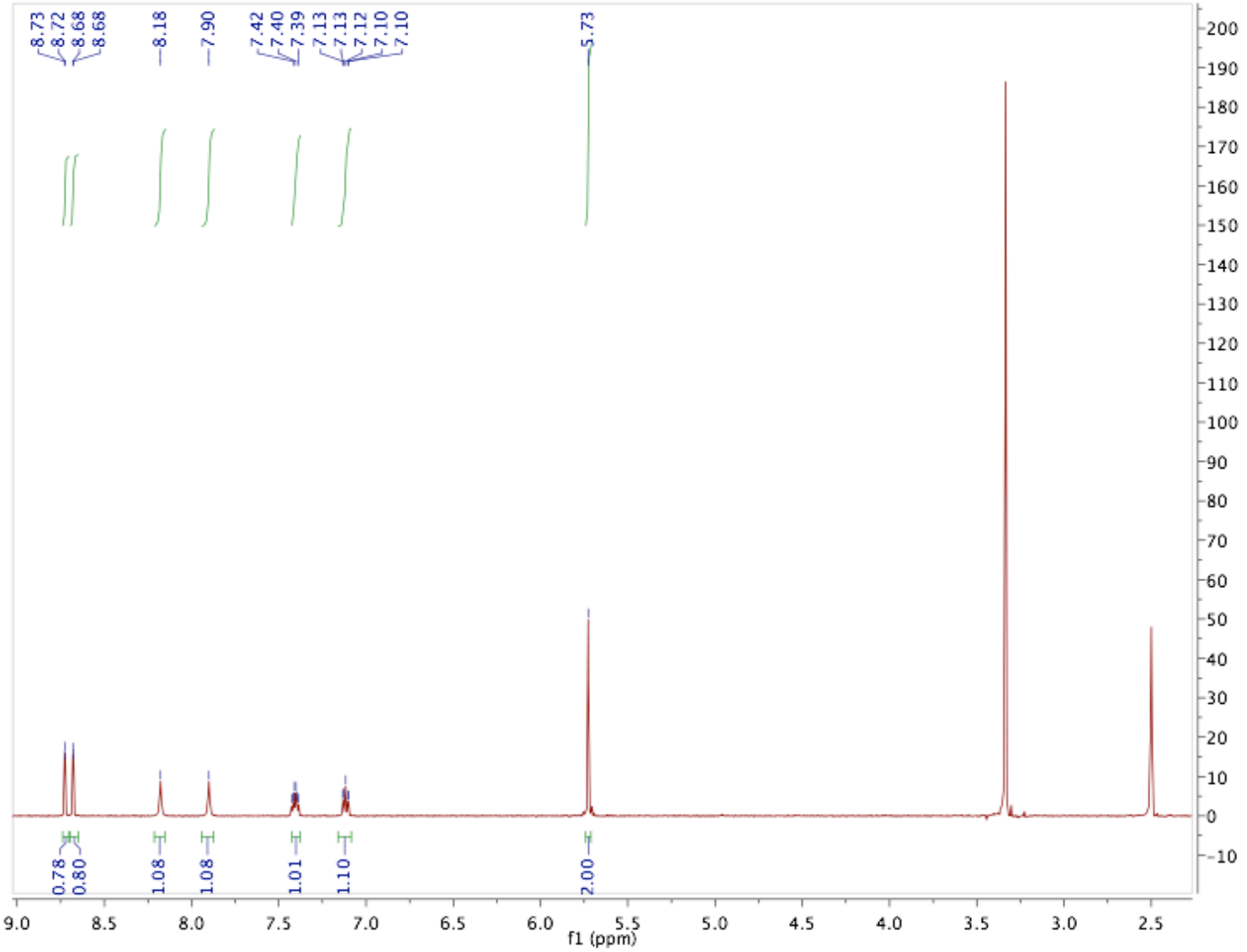
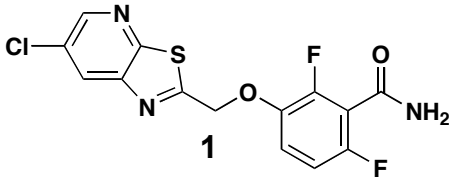
125
115
105
95
85
75
65
55
f1 (ppm)

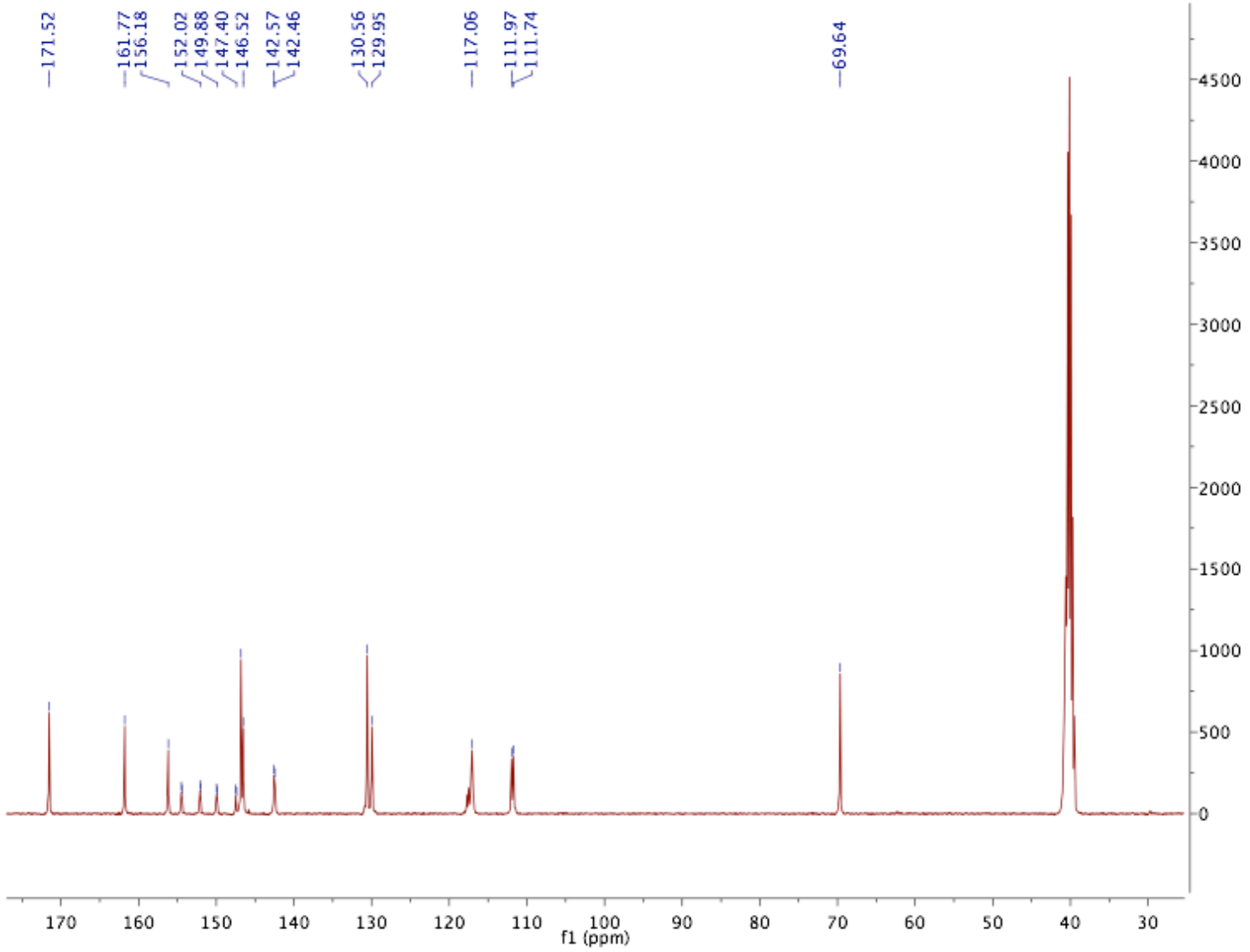

Cl
N
S
N
O
F
O
NH2
F

1


8.73
8.72
8.68
8.68
8.18
7.90
7.42
7.40
7.39
7.13
7.13
7.12
7.10
7.10
5.73
0.78
0.80
1.08
1.08
1.01
1.10
2.00
f1 (ppm)


Cl
N
S
N
O
F
O
NH2
F

1


171.52
161.77
156.18
152.02
149.88
147.40
146.52
142.57
142.46
130.56
129.95
117.06
111.97
111.74
69.64
4500
4000
3500
3000
2500
2000
1500
1000
500
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
f1 (ppm)

Complete References 7a,b & 10:

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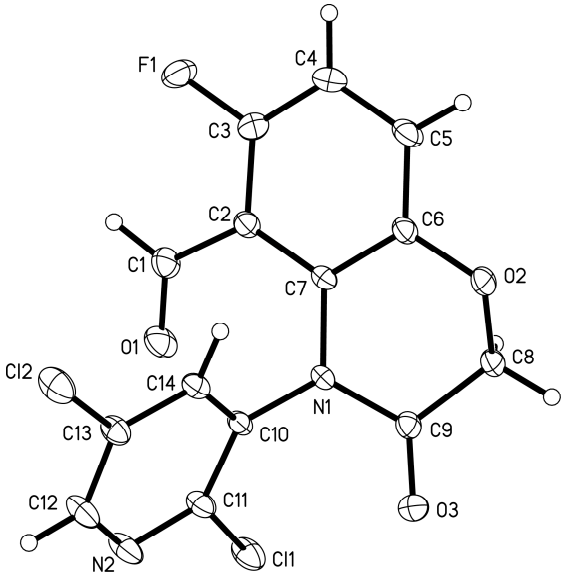
X-ray Crystallography and Data Collection. The crystals were obtained by slow evaporation of an acetone solution. A suitable crystal was removed from the vial and mounted on a MiTeGen mount and placed in the CRYO Industries N_2 cold stream of a Bruker SMART Apex II DUO X-ray diffractometer. Data collection was carried out with Mo Kα radiation, data reduction was carried out with SAINT, and a correction for absorption was applied using SADABS.[1] The structure was solved with the use of SHELXS97 and refined with SHELXL97.[2] Hydrogen atoms were added geometrically and refined with a riding model. Crystal data and selected data collection and refinement parameters are presented in Table S1.



(1) Bruker AXS, **2010**. APEX2, SAINT, SADABS, TWINABS. Bruker AXS Inc. Madison, Wisconsin, USA.

(2) Sheldrick, G. M. *Acta Crystallogr. Sect. A* **2008**, *64*, 112.

Table S1. Crystal data and structure refinement for Compound **17**.

Identification code	mn2021	
Empirical formula	$C_{14}H_7Cl_2FN_2O_3$	
Formula weight	341.12	
Temperature	87(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	*P*$\bar{1}$	
Unit cell dimensions	a = 8.4638(11) Å	α= 63.0260(10)°.
	b = 9.5592(13) Å	β= 77.877(2)°.
	c = 10.0336(14) Å	γ = 71.216(2)°.
Volume	682.97(16) Å^3	
Z	2	
Density (calculated)	1.659 Mg/m^3	
Absorption coefficient	0.501 mm^{-1}	
F(000)	344	
Crystal size	0.41 x 0.34 x 0.22 mm^3	
Crystal color and habit	colorless block	
Diffractometer	Bruker SMART Apex DUO	
θ range for data collection	2.28 to 29.13°.	
Index ranges	-11≤h≤11, -13≤k≤13, -13≤l≤13	
Reflections collected	9949	
Independent reflections	3652 [R(int) = 0.0232]	
Observed reflections (I > 2σ(I))	3535	
Completeness to θ = 29.13°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.898 and 0.821	
Solution method	SHELXS97 (Sheldrick, 2008)	
Refinement method	SHELXL97 (Sheldrick, 2008)	
Data / restraints / parameters	3652 / 0 / 199	
Goodness-of-fit on F^2	1.084	
Final R indices [I>2σ(I)]	R1 = 0.0319, wR2 = 0.0865	
R indices (all data)	R1 = 0.0327, wR2 = 0.0871	
Largest diff. peak and hole	0.542 and -0.392 e.Å^{-3}	