marine drugs

Supplementary Material for:

Design, Synthesis and In Vitro Experimental Validation of Novel TRPV4 Antagonists Inspired by Labdane Diterpenes

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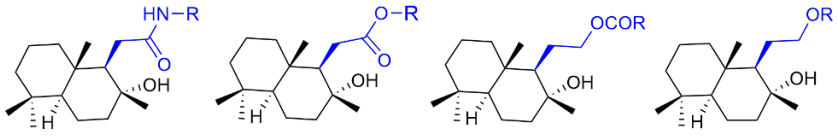
‡ Antonella Brizzi and Luciano De Petrocellis are joint senior authors.

Contents

Table S1. Results of TRPV1 assay of compounds **1-16**, **18-20**, **22-25**.[a]



1-16 18-20 22-24 21, 25

Cpd.	R	Efficacy[b] %	Potency EC_{50} (μM)	IC_{50} (μM)[c] inh TRPV1	Cpd.	R	Efficacy[b] %	Potency EC_{50} (μM)	IC_{50} (μM)[c] inh TRPV1
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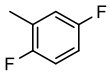
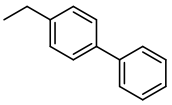
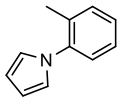
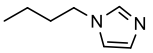
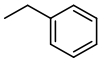
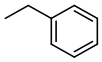
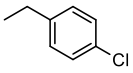
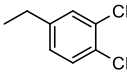
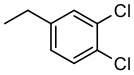
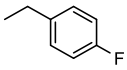
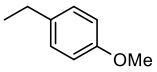
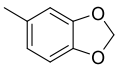
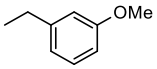
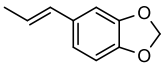
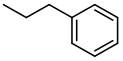
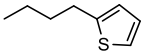
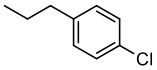
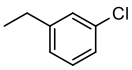
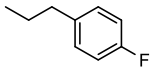
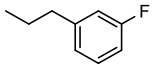
2		< 10	NA[d]	> 100	**15**		< 10	NA	> 100
3		32.0 ± 1.2	4.7 ± 0.4	> 100	**16**		< 10	NA	> 100
4		36.8 ± 0.2	> 10	> 10	**18**		< 10	NA	>10
5		< 10	NA	> 100	**19**		17.5 ± 2.7	>10	> 100
6		16.9 ± 0.3	> 10	> 100	**20**	Me	< 10	NA	> 100
7		24.5± 0.2	9.9 ± 0.1	>50	**21**	H	< 10	NA	> 100
8		19.7 ± 1.1	> 10	> 100	**22**		<10	NA	>100
9		< 10	NA	> 100	**23**		< 10	NA	> 100
10		< 10	NA	>10	**24**		< 10	NA	> 100
11		< 10	NA	> 100	**25**		< 10	>10	> 100
12		< 10	NA	> 100	**Scd**[e]	-	12.6 ± 0.5	> 10	> 100
13		20.8 ± 1.6	> 10	>50					

[a] Data are means ± SEM of at least N = 3 determinations. [b] As percent of the effect of ionomycin (4 μM). Inh = inhibitory activity. [c] Determined against the effect of Capsaicin (100 nM) after a 5 min pre-incubation with each compound. [d]NA = not active, if the efficacy is lower than 10% the potency is not calculated, [e] Scd = (+)-Sclareolide. Capsaicin efficacy 78.6 +/- 0.6 EC50 5.3 +/- 0.4 nM [1]

[1] Del Prete D, Caprioglio D, Appendino G, Minassi A, Schiano-Moriello A, Di Marzo V, De Petrocellis L. Discovery of non-electrophilic capsaicinoid-type TRPA1 ligands. Bioorg Med Chem Lett. 2015 Mar 1;25(5):1009-11. doi: 10.1016/j.bmcl.2015.01.039. Epub 2015 Jan 28. PMID: 25666822.

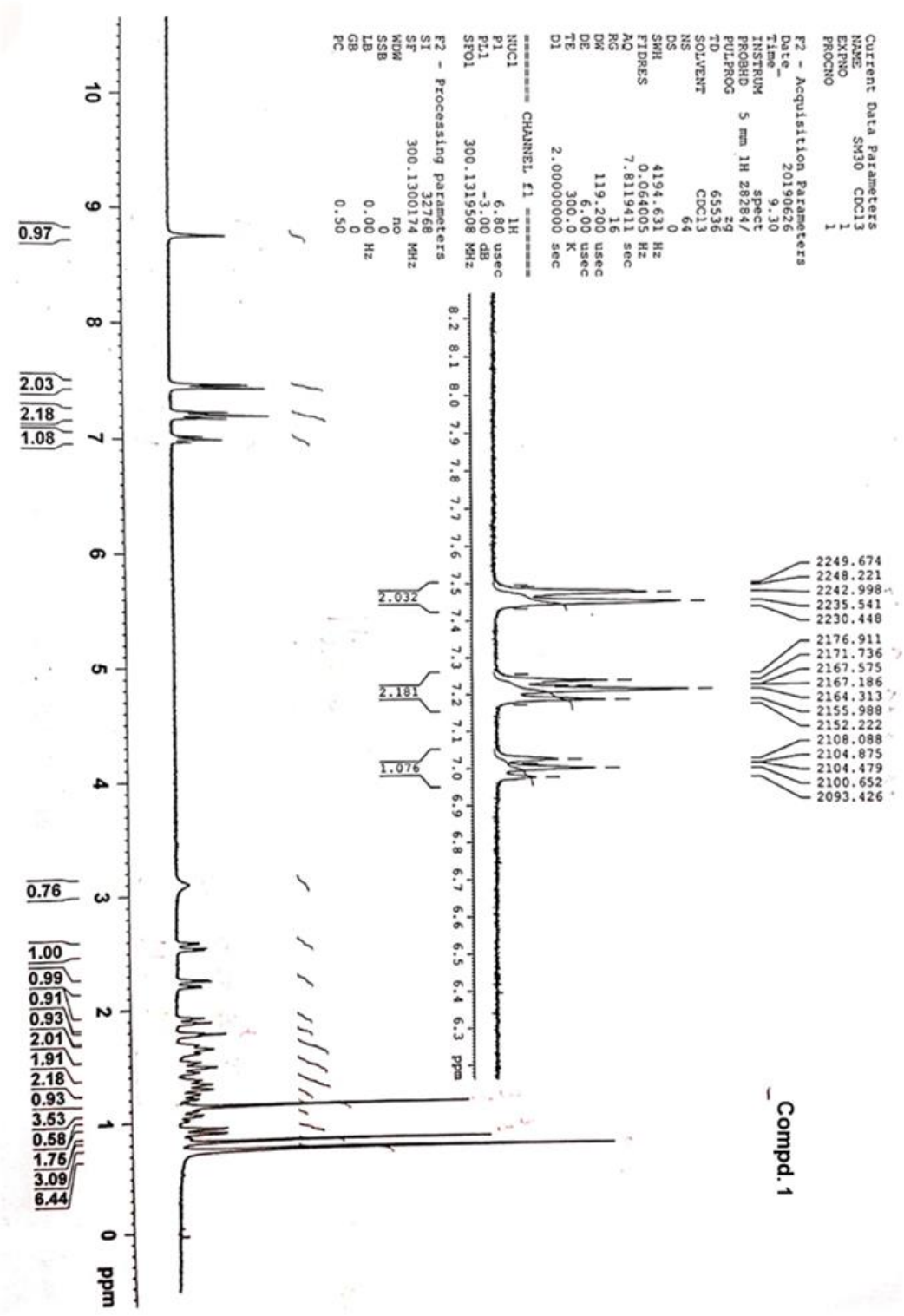
Synthesis of methyl ester derivative (20).

A well stirred methanolic solution of (+)-sclareolide (100 mg, 3 mL) was heated at 45 ℃ for 72 h. After that, the mixture was evaporated to dryness and the pure compound obtained after flash column chromatography using a gradient of PE/EtOAc. The compound was isolated as a white solid. Mp 72-73 ℃ (G). NMR data are in agreement with those reported. [1] Anal. Calcd. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.56; H, 10.75.

[1] Carmna, R.M. and Deeth, H.C. Diterpenoids XXVII. The Synthesis of α-Onoceradiene from Abienol. *Aust. J. Chem.* **1971**, *24*, 1099-1102.

Synthesis of (1*R*,2*R*,4a*S*,8a*S*)-1-(2-hydroxyethyl)-2,5,5,8a-tetramethyldecahydronaphthalen-2-ol (homodrimanyl diol) (21). (+)-Sclareolide (300 mg, 1.2 mmol, 1.0 eq.) was dissolved in dry THF (50 mL) under argon and cooled to 0 ℃. Then, $LiAlH_4$ (455.4 mg, 12.0 mmol, 10.0 eq.) was added to the solution. The reaction mixture was stirred at rt for 6 h, then quenched with EtOAc (30 mL) and evaporated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL) and the organic phase washed twice with 1 N HCl (30 mL), with staturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL). The organic phase was finally dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give homodrimanyl diol **21** as a white crystalline solid in quantitative yield. Mp 129.5-130.5 ℃. ^{1}H-NMR data are in agreement with those reported. [2] Anal. Calcd. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.56; H, 10.75.

[2] Li, D.; Zhang, S.; Song, Z.; Wang, G.; Li, S. Bioactivity-Guided Mixed Synthesis Accelerate the Serendipity in Lead Optimization: Discovery of Fungicidal Homodrimanyl Amides. *Eur. J. Med. Chem.* **2017**, *136* (31401777), 114–121. https://doi.org/10.1016/j.ejmech.2017.04.073.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1.076
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0.93
2.01
1.91
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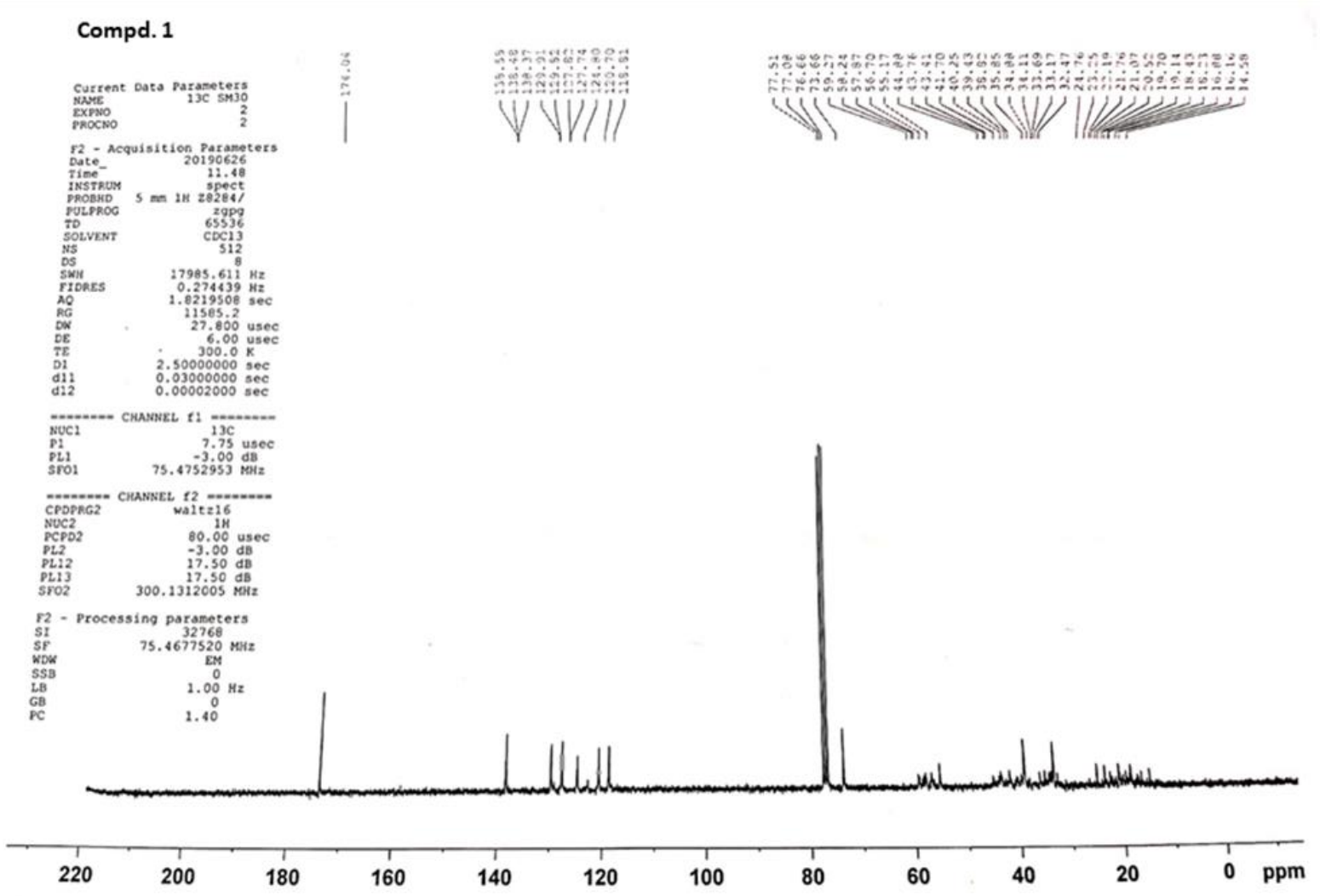
Compd.1

Compd. 1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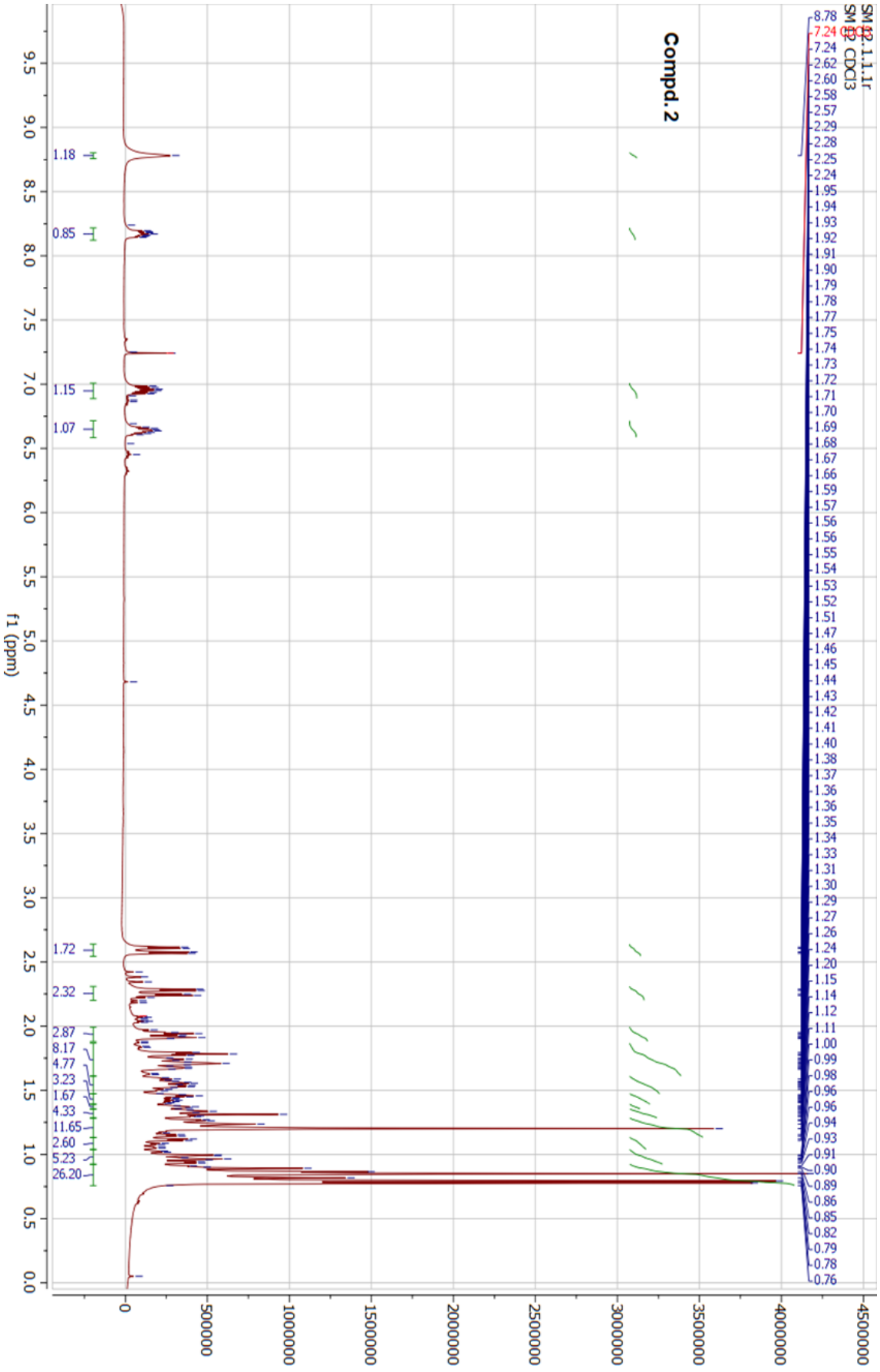
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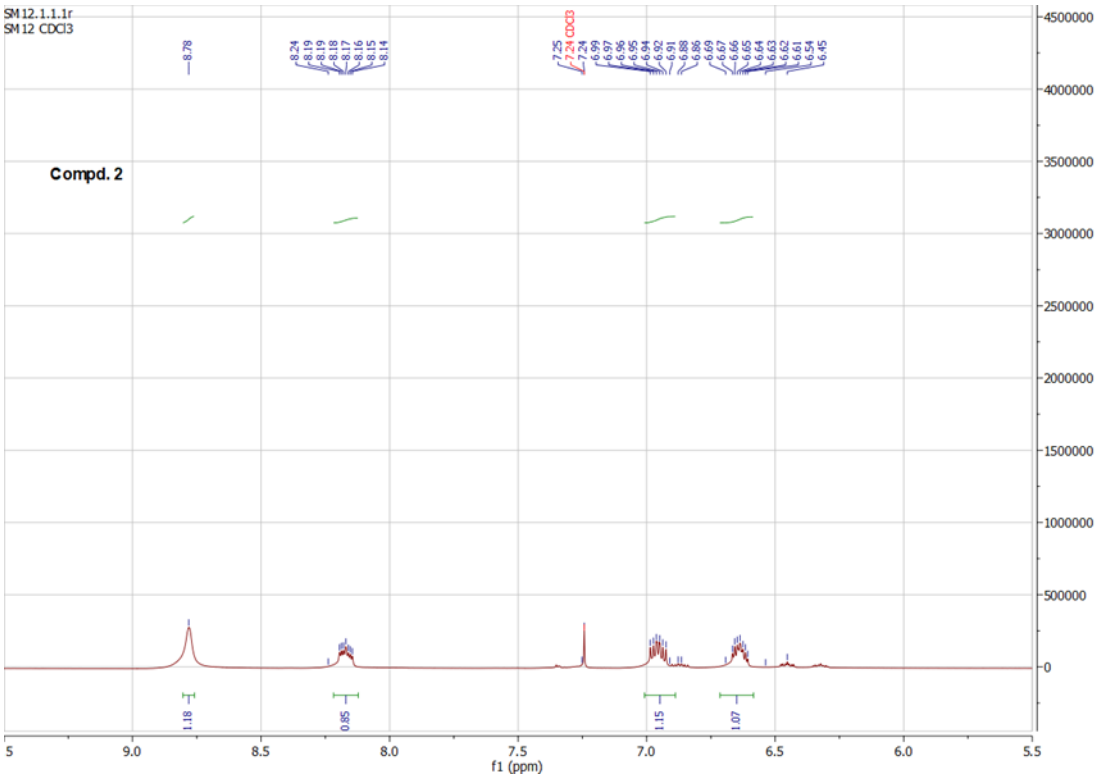
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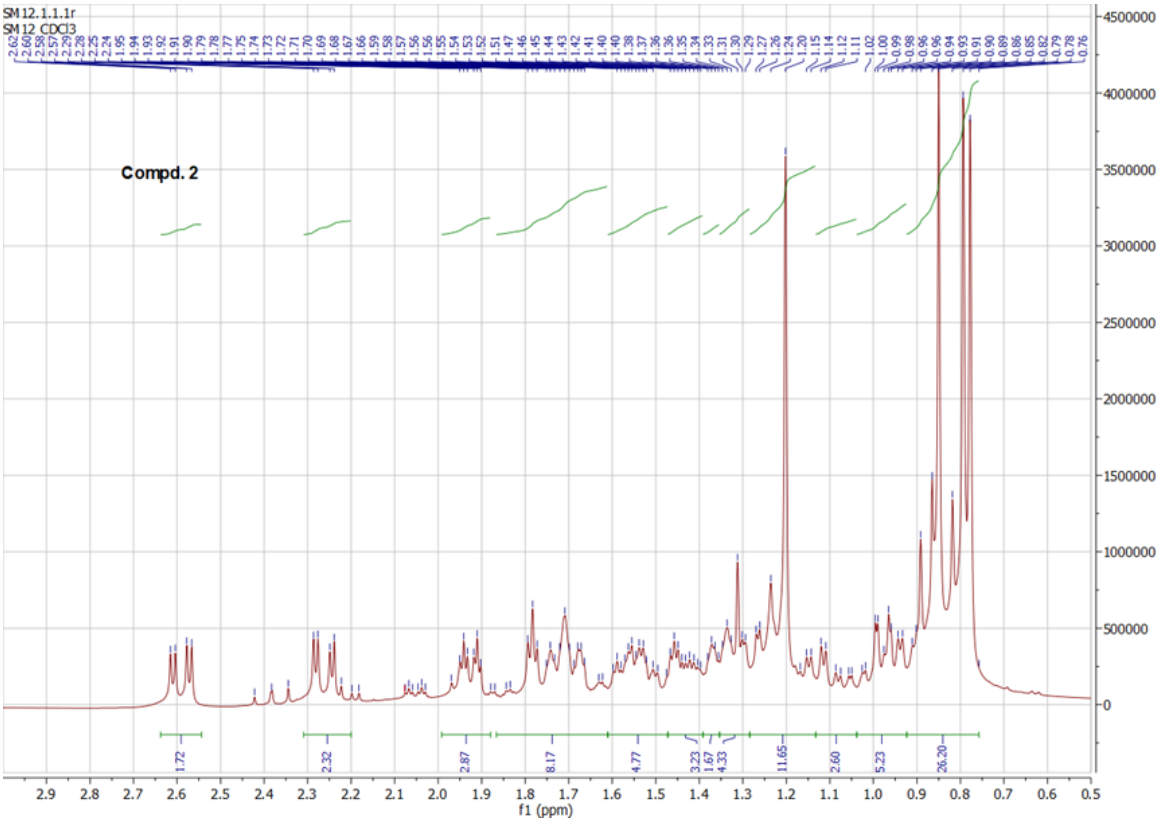
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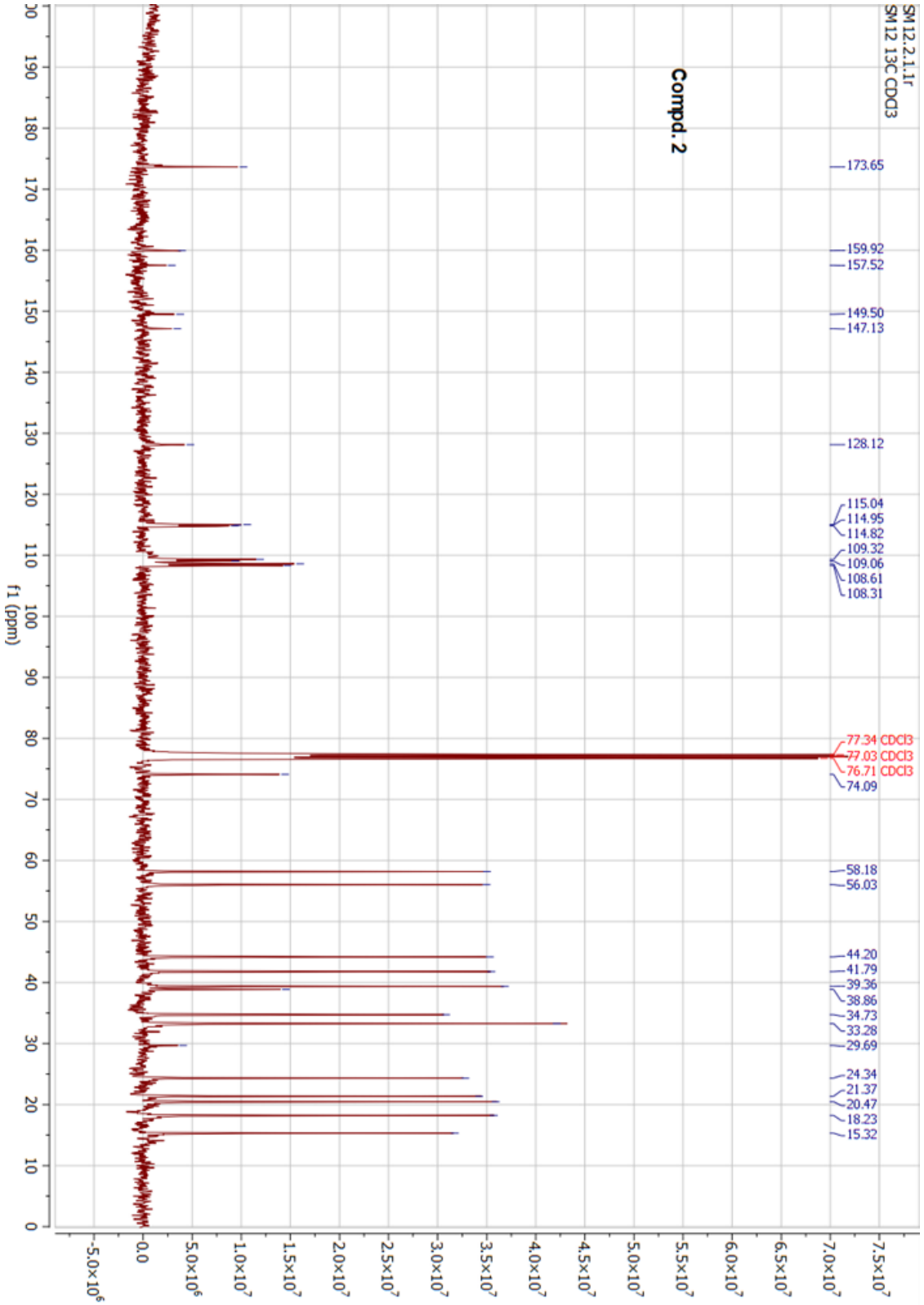
f1 (ppm)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114.82
109.32
109.06
108.61
108.31
77.34 CDCl3
77.03 CDCl3
76.71 CDCl3
74.09
58.18
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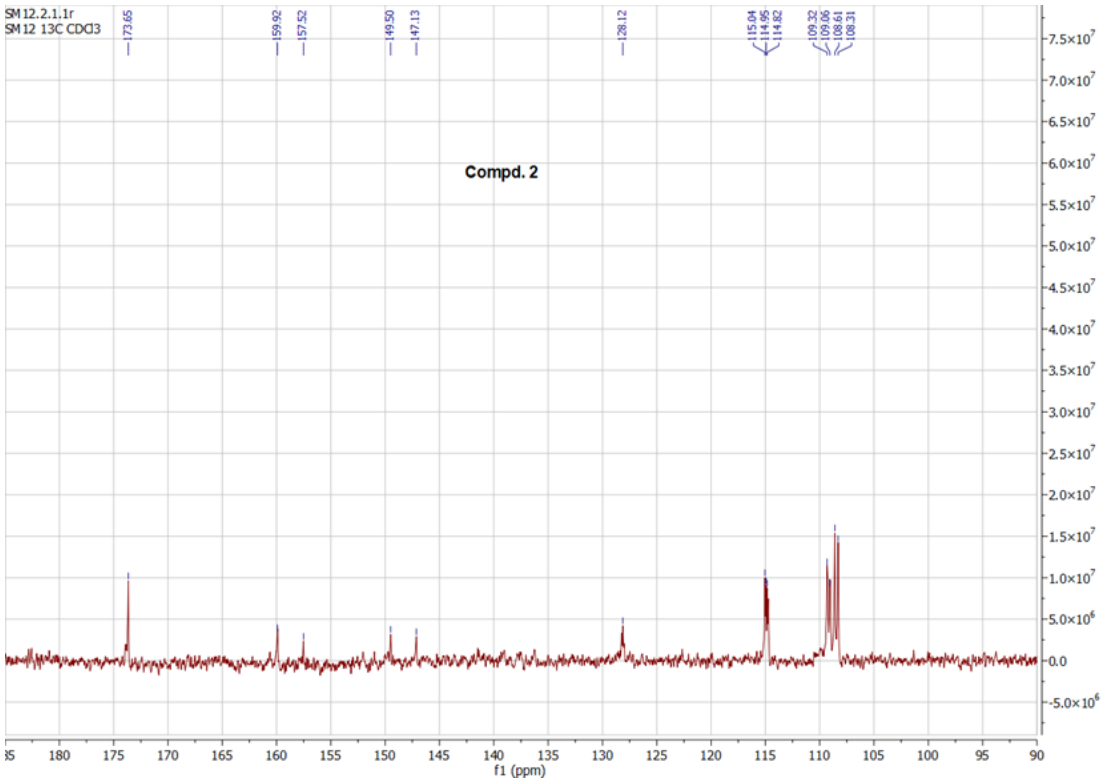
f1 (ppm)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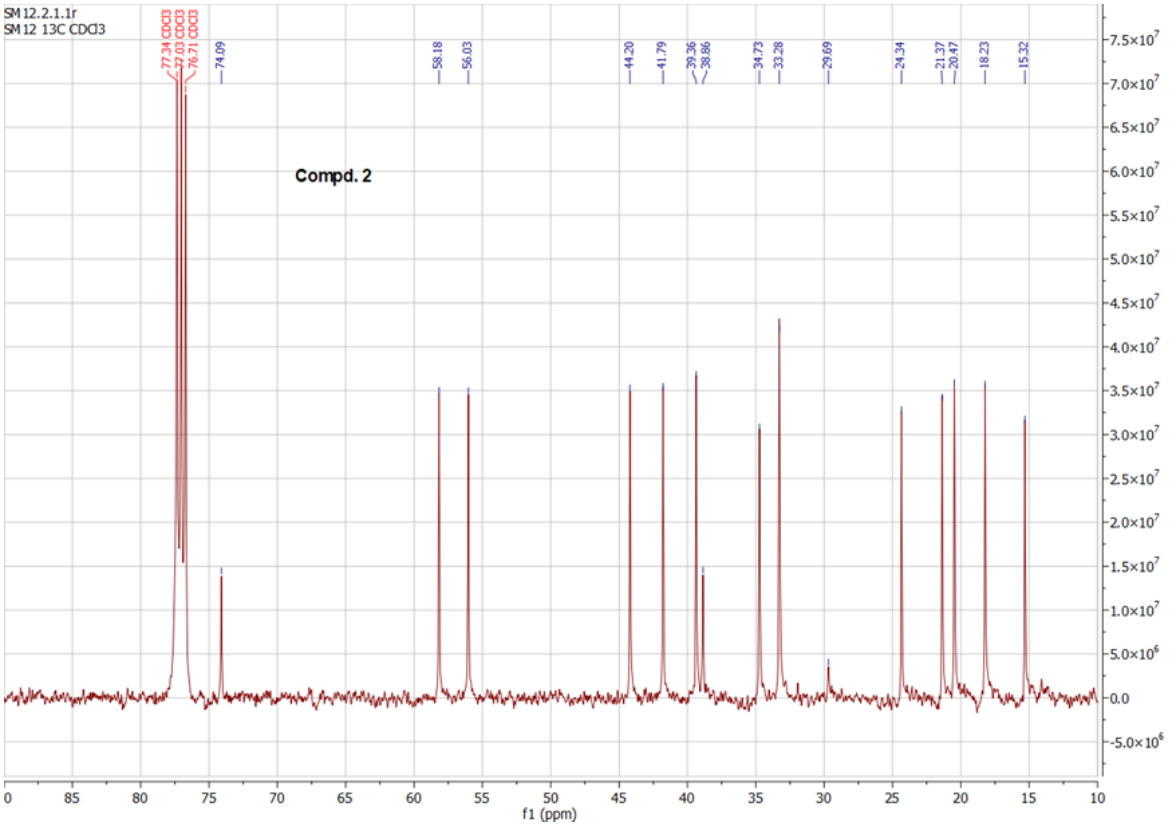
108.61
108.31
Compd. 2
f1 (ppm)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18.23
15.32
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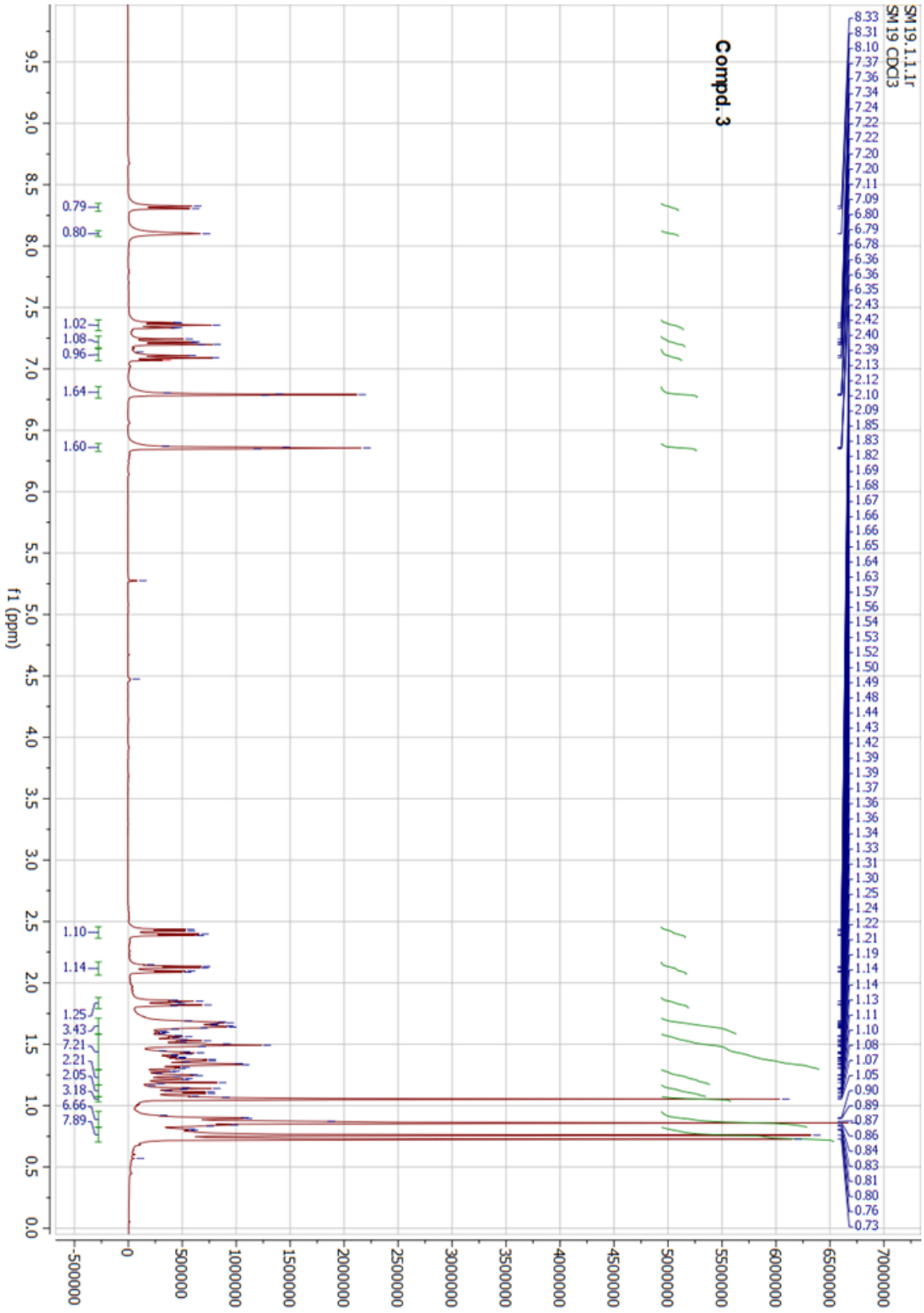
f1 (ppm)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1.14
1.25
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2.21
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3.18
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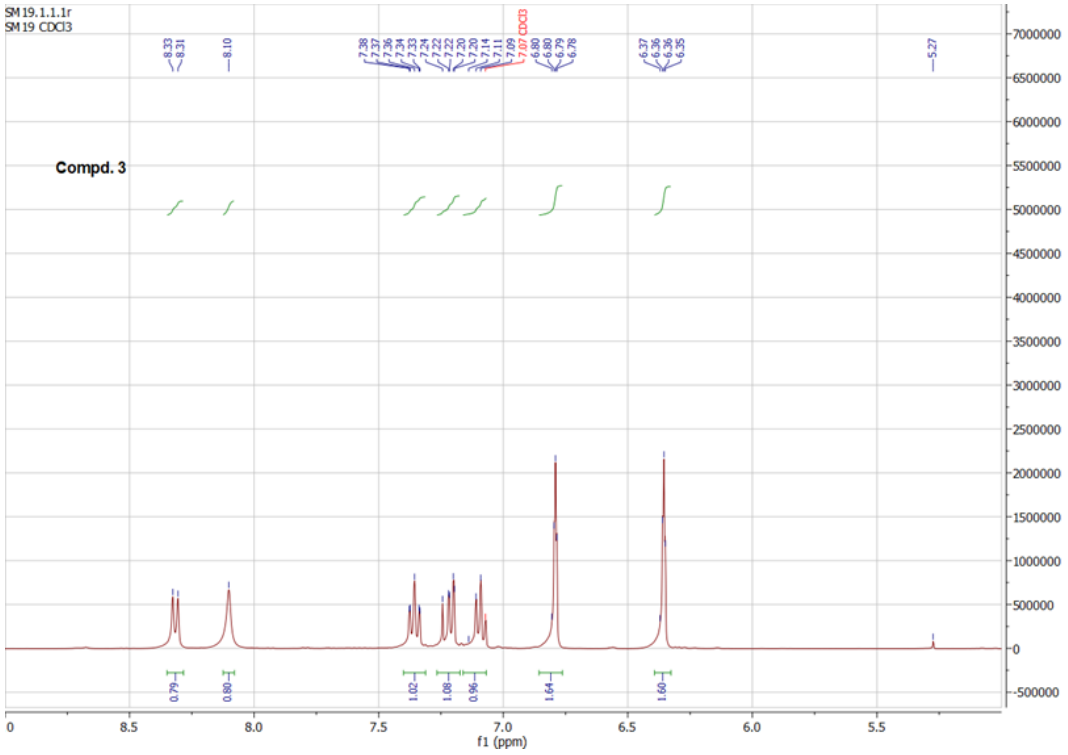
7.89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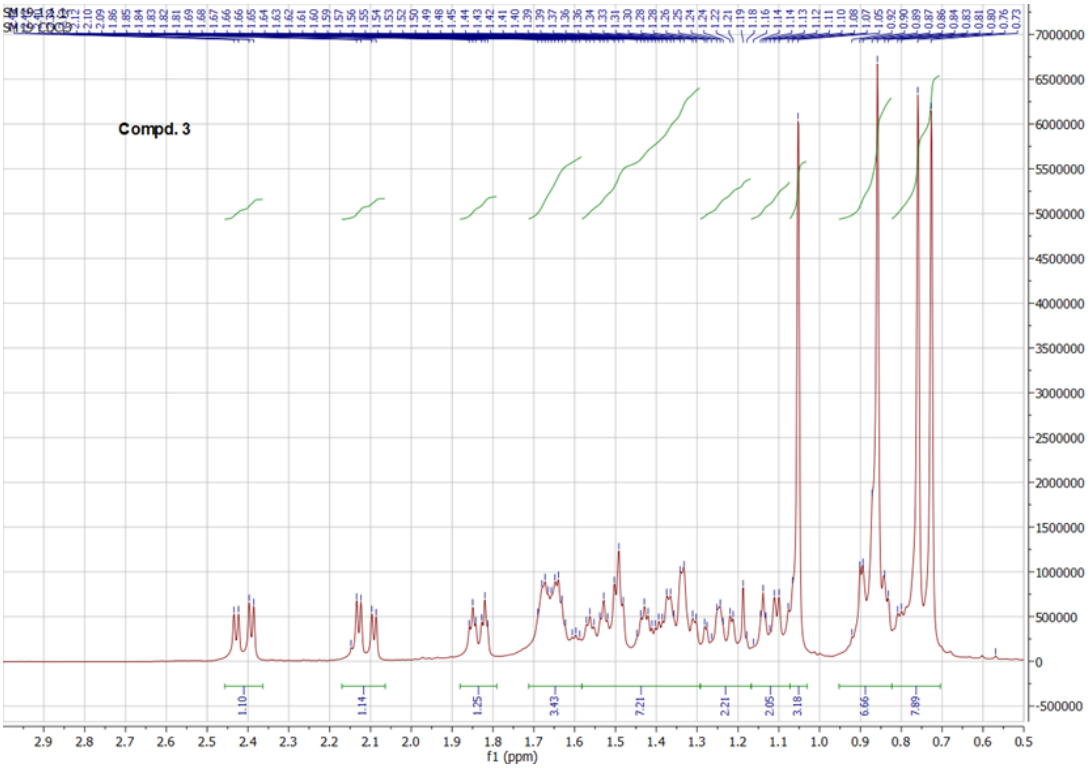
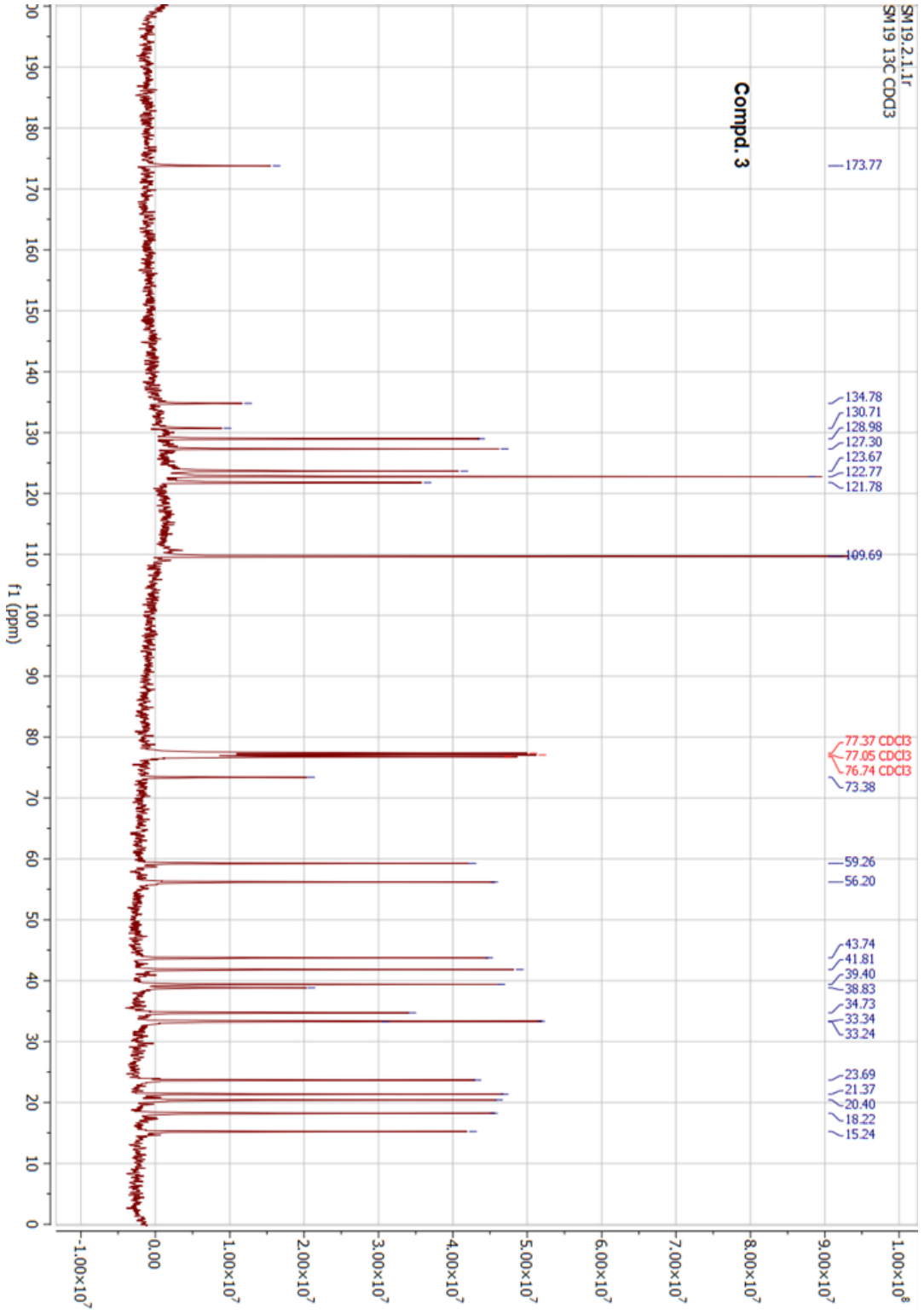
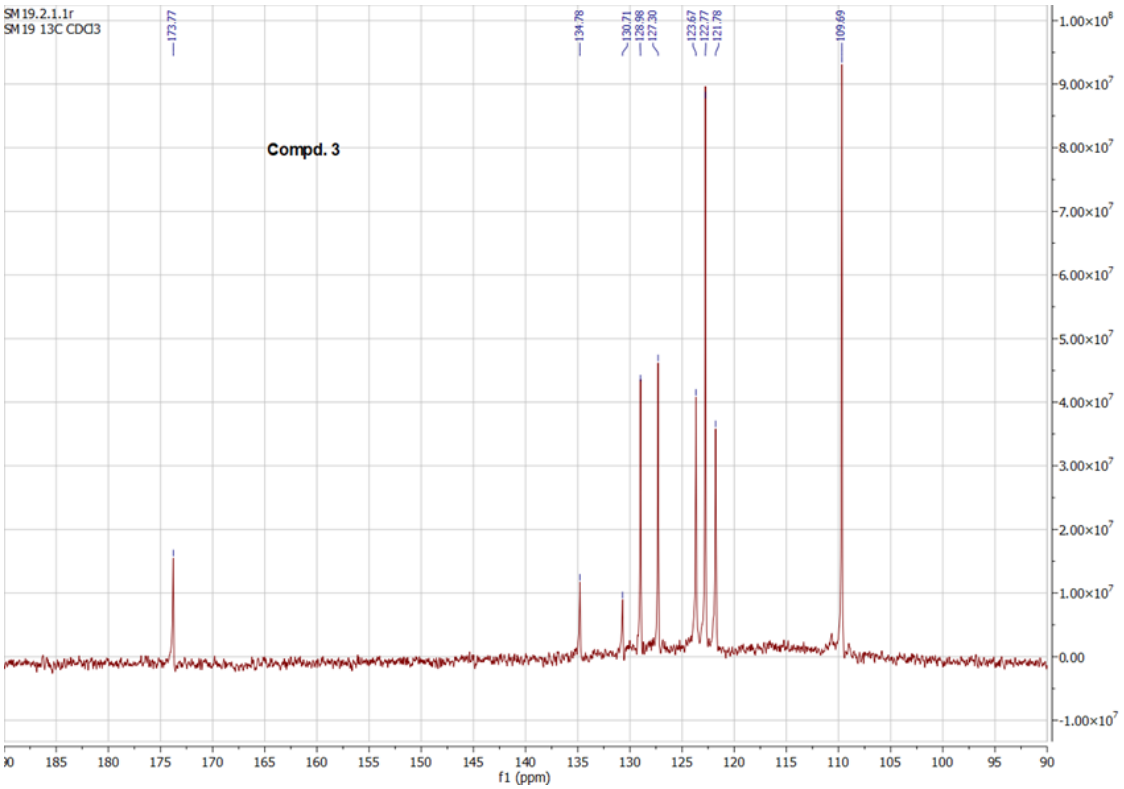
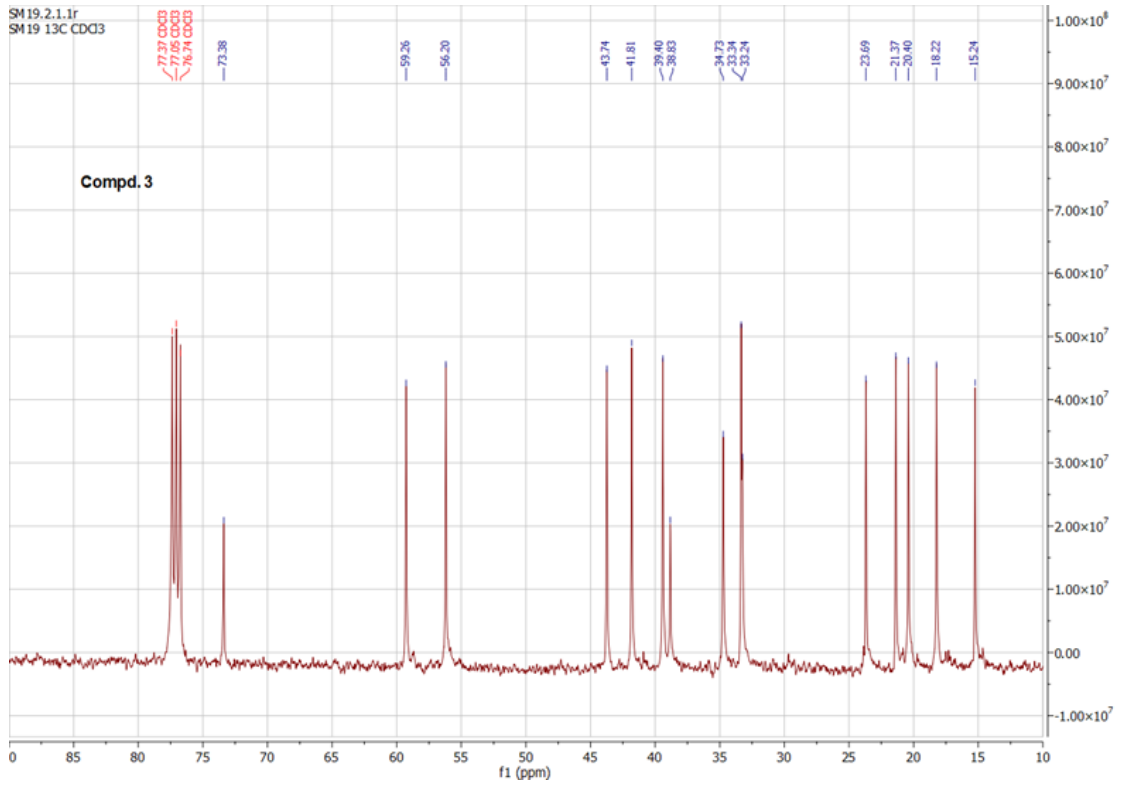
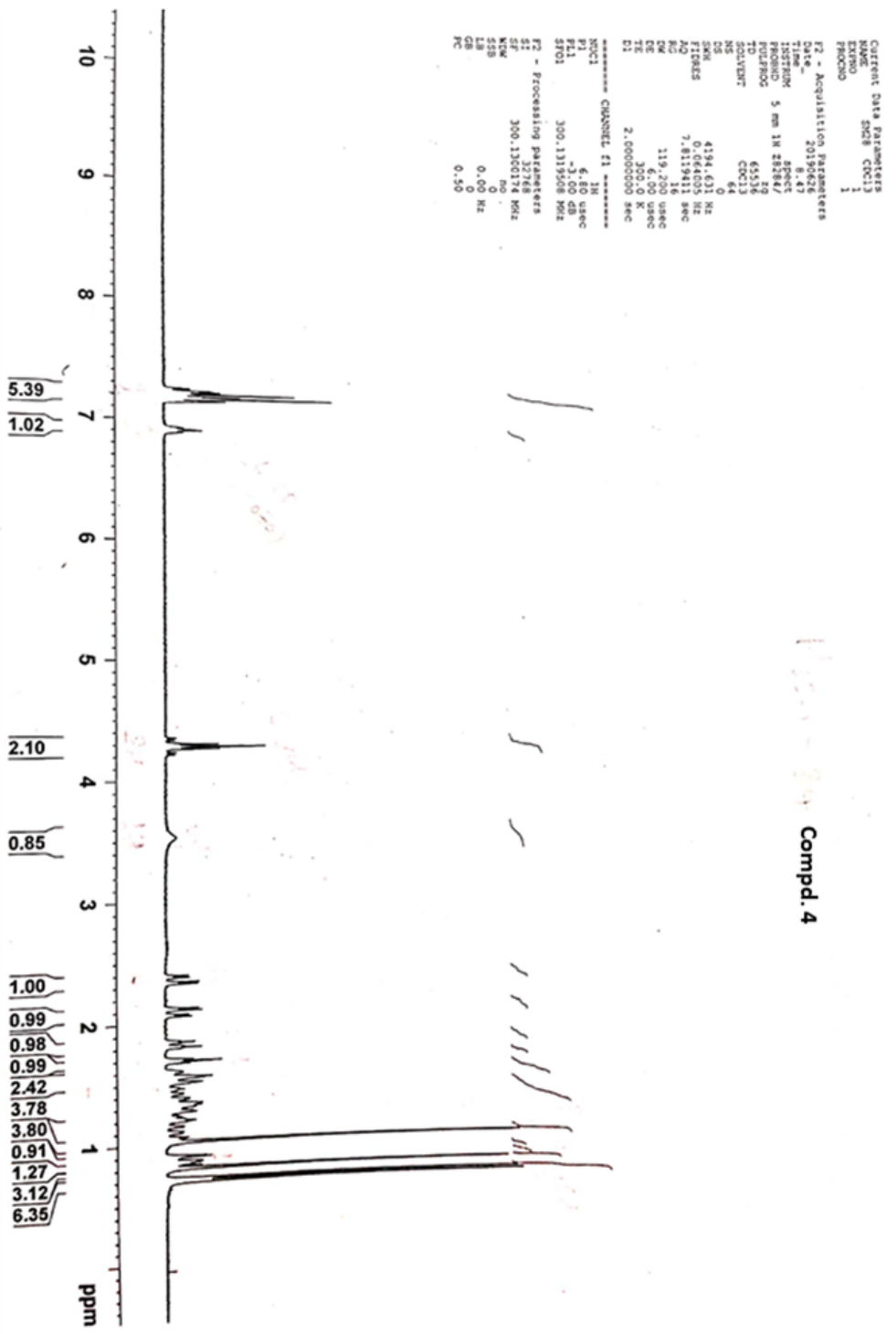
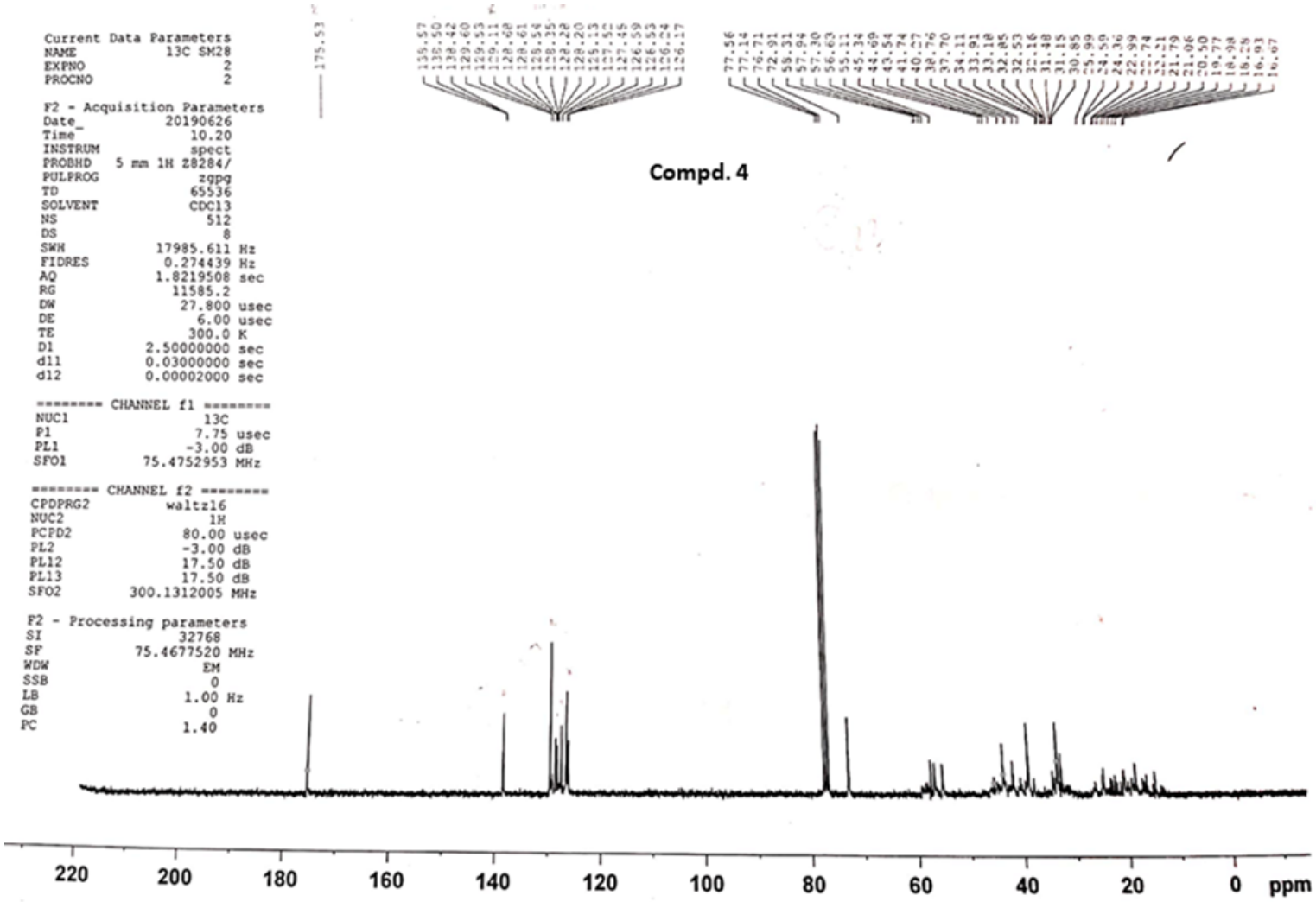

Compd. 3
f1 (ppm)

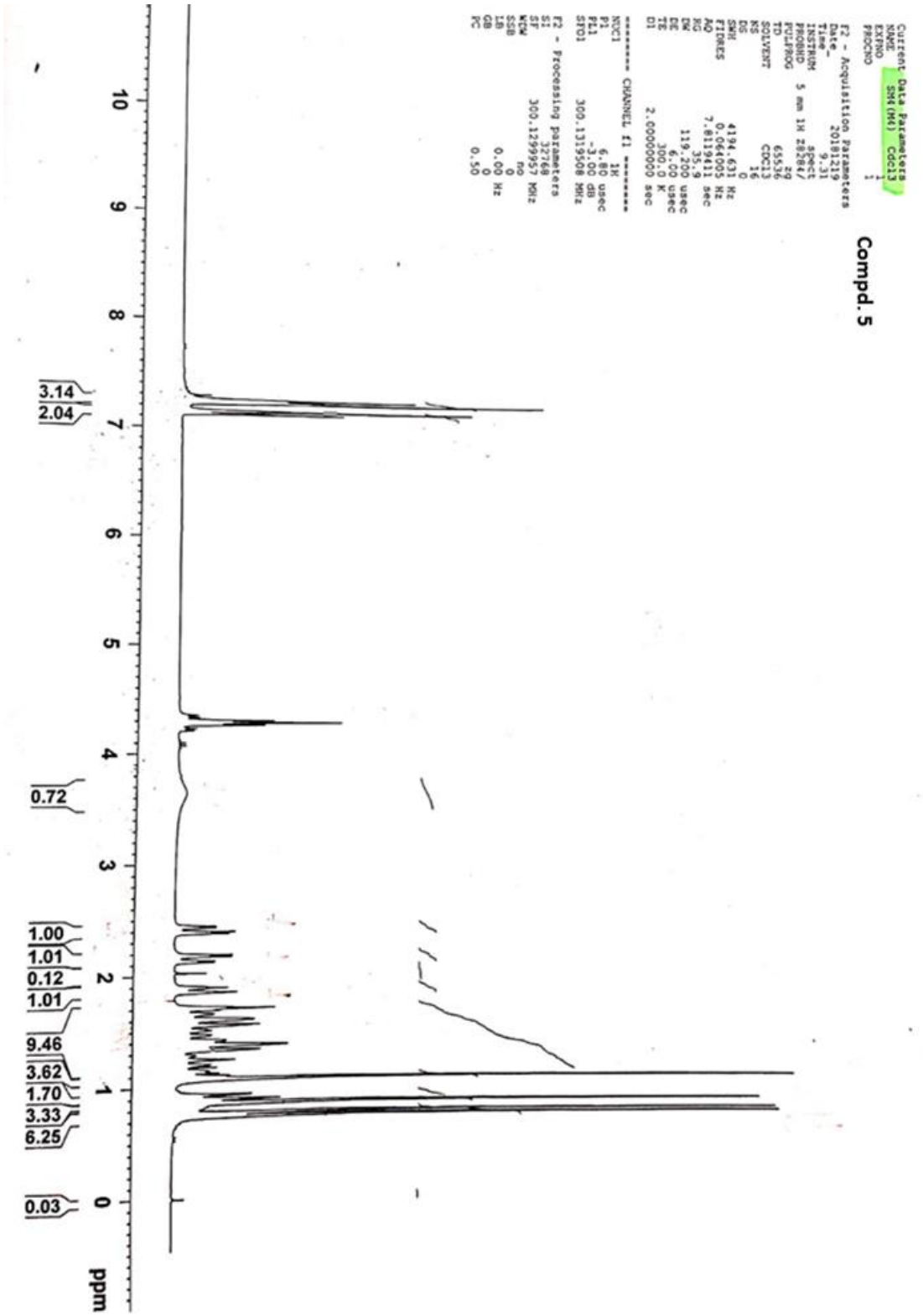

SM 19.2.1.1r
SM 19 13C CDCl3
Compd. 3
173.77
134.78
130.71
128.98
127.30
123.67
122.77
121.78
109.69
77.37 CDCl3
77.05 CDCl3
76.74 CDCl3
73.38
59.26
56.20
43.74
41.81
39.40
38.83
34.73
33.34
33.24
23.69
21.37
20.40
18.22
15.24
f1 (ppm)

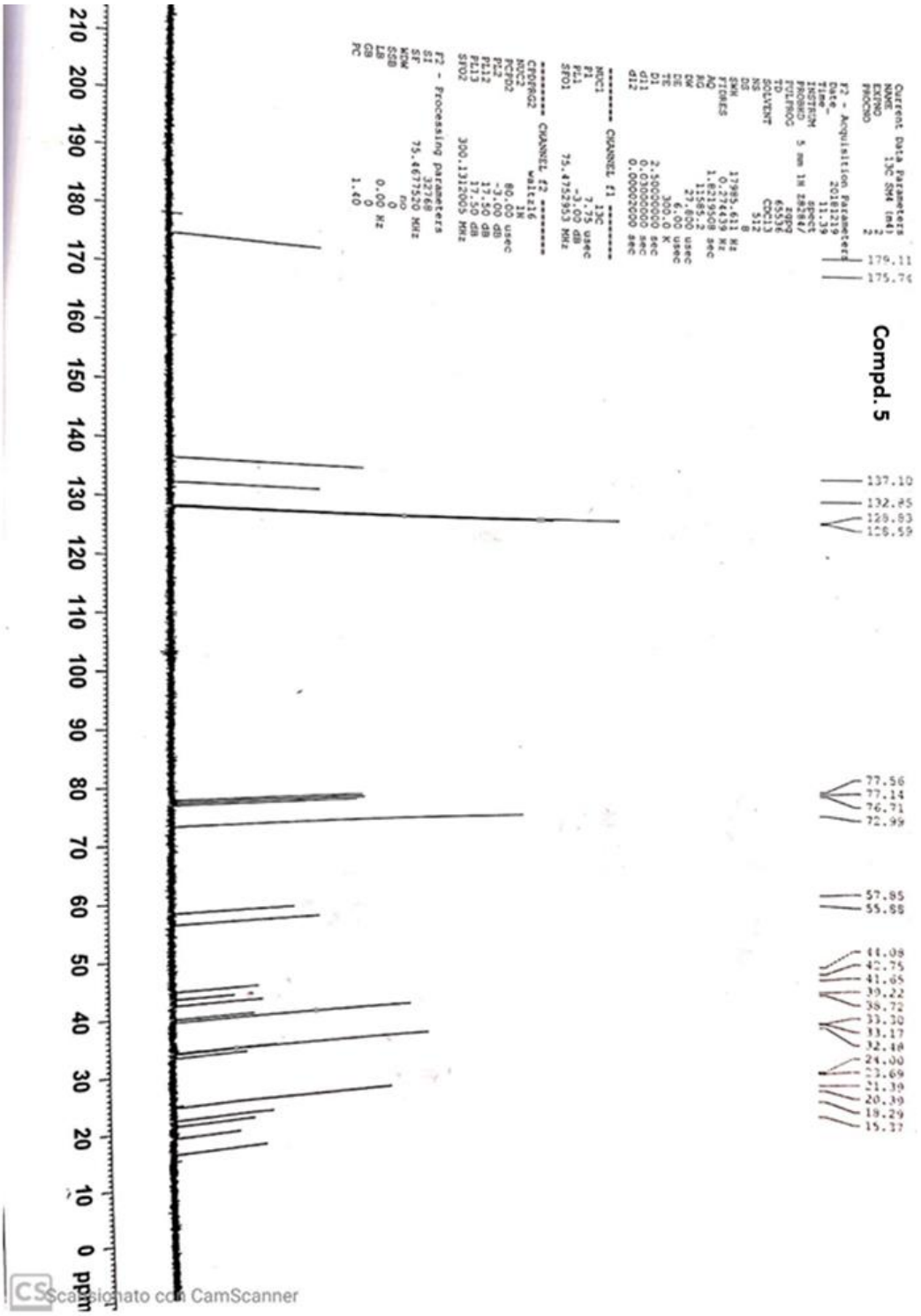

SM19.2.1.1r
SM19 13C CDCl3
173.77
134.78
130.71
128.98
127.30
123.67
122.77
121.78
109.69
Compd. 3
f1 (ppm)


SM19.2.1.1r
SM19 13C CDCl3
77.37 CDCl3
77.05 CDCl3
76.74 CDCl3
73.38
59.26
56.20
43.74
41.81
39.40
38.83
34.73
33.34
33.24
23.69
21.37
20.40
18.22
15.24
Compd. 3
f1 (ppm)

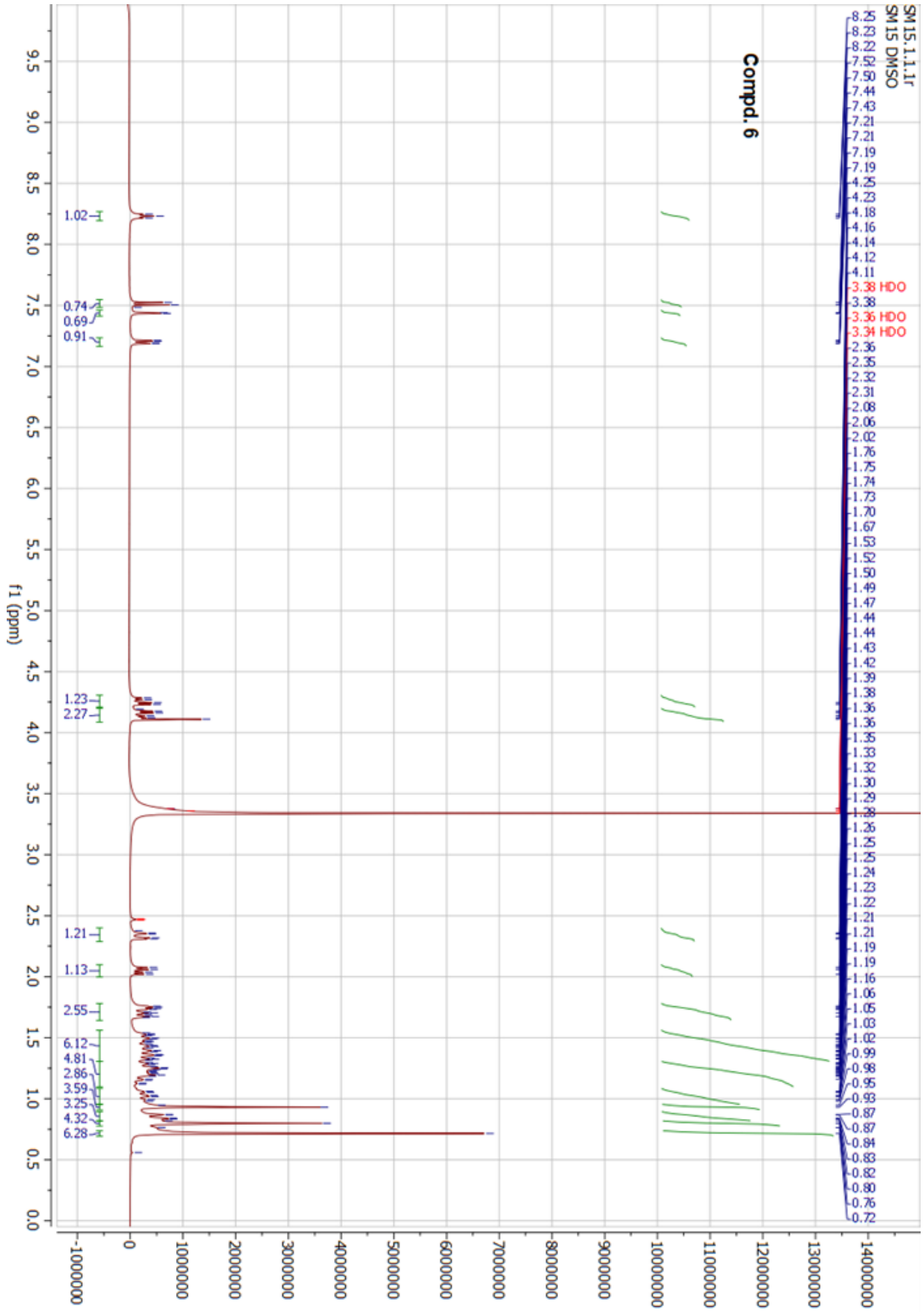

Compd.4
5.39
1.02
2.10
0.85
1.00
0.99
0.98
0.99
2.42
3.78
3.80
0.91
1.27
3.12
6.35
ppm

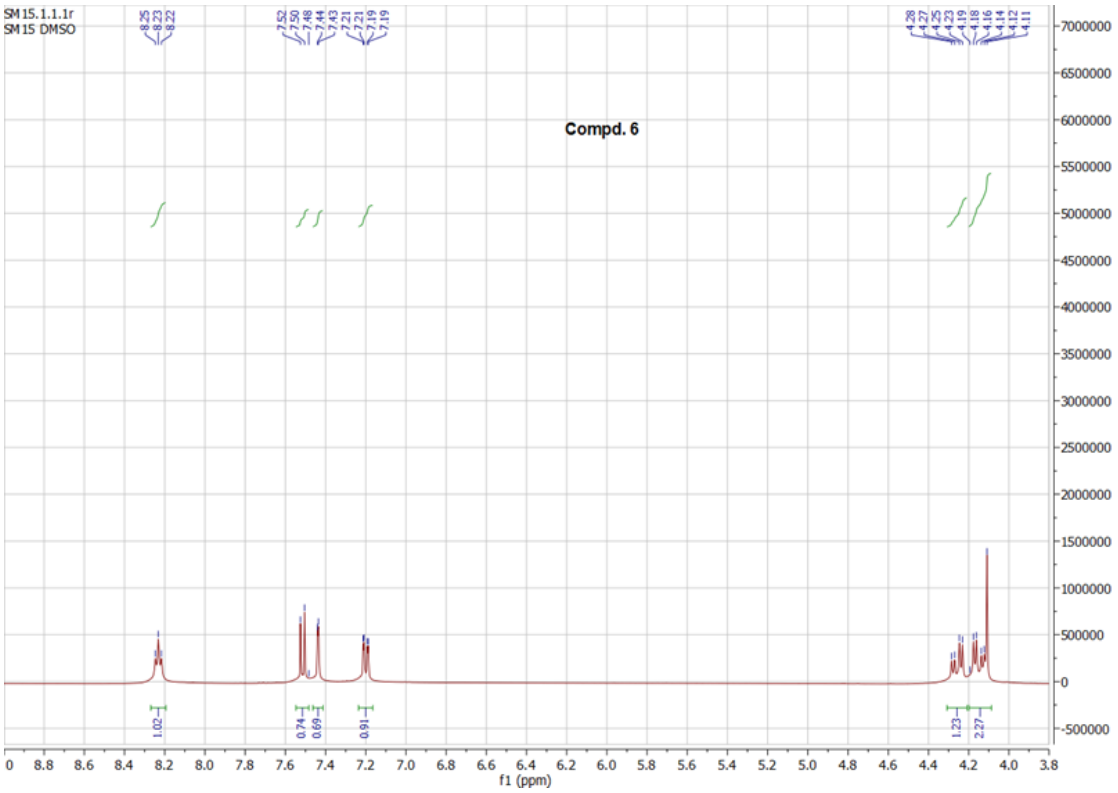

Current Data Parameters
NAME 13C SM28
EXPNO 2
PROCNO 2
F2 - Acquisition Parameters
Date_ 20190626
Time 10.20
INSTRUM spect
PROBHD 5 mm 1H Z8284/
PULPROG zgpg
TD 65536
SOLVENT CDCl3
NS 512
DS 8
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 11585.2
DW 27.800 usec
DE 6.00 usec
TE 300.0 K
D1 2.50000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.75 usec
PL1 -3.00 dB
SFO1 75.4752953 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 17.50 dB
PL13 17.50 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677520 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
175.53
159.57
136.50
130.42
129.60
129.53
129.11
128.68
128.61
128.54
128.35
128.28
128.20
125.13
117.55
117.45
126.59
126.55
126.24
126.17
77.56
77.14
76.71
72.91
59.31
57.94
57.30
56.63
55.11
45.34
44.69
43.54
41.74
40.27
38.76
37.70
34.11
33.91
33.18
32.85
32.53
32.16
31.48
31.15
30.85
25.99
24.59
24.36
22.99
22.74
22.21
21.79
21.06
20.50
19.77
18.98
16.25
16.93
16.67
Compd. 4
220
200
180
160
140
120
100
80
60
40
20
0
ppm

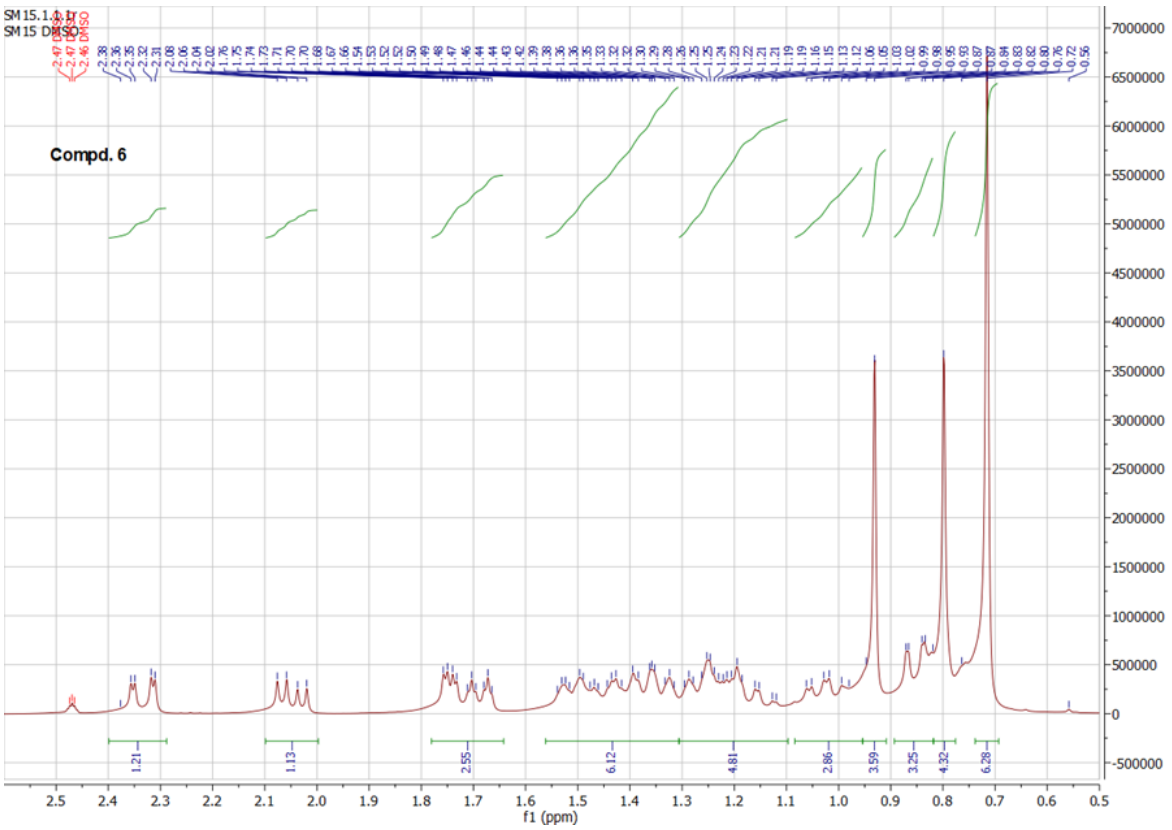

Compd.5
3.14
2.04
0.72
1.00
1.01
0.12
1.01
9.46
3.62
1.70
3.33
6.25
0.03
ppm

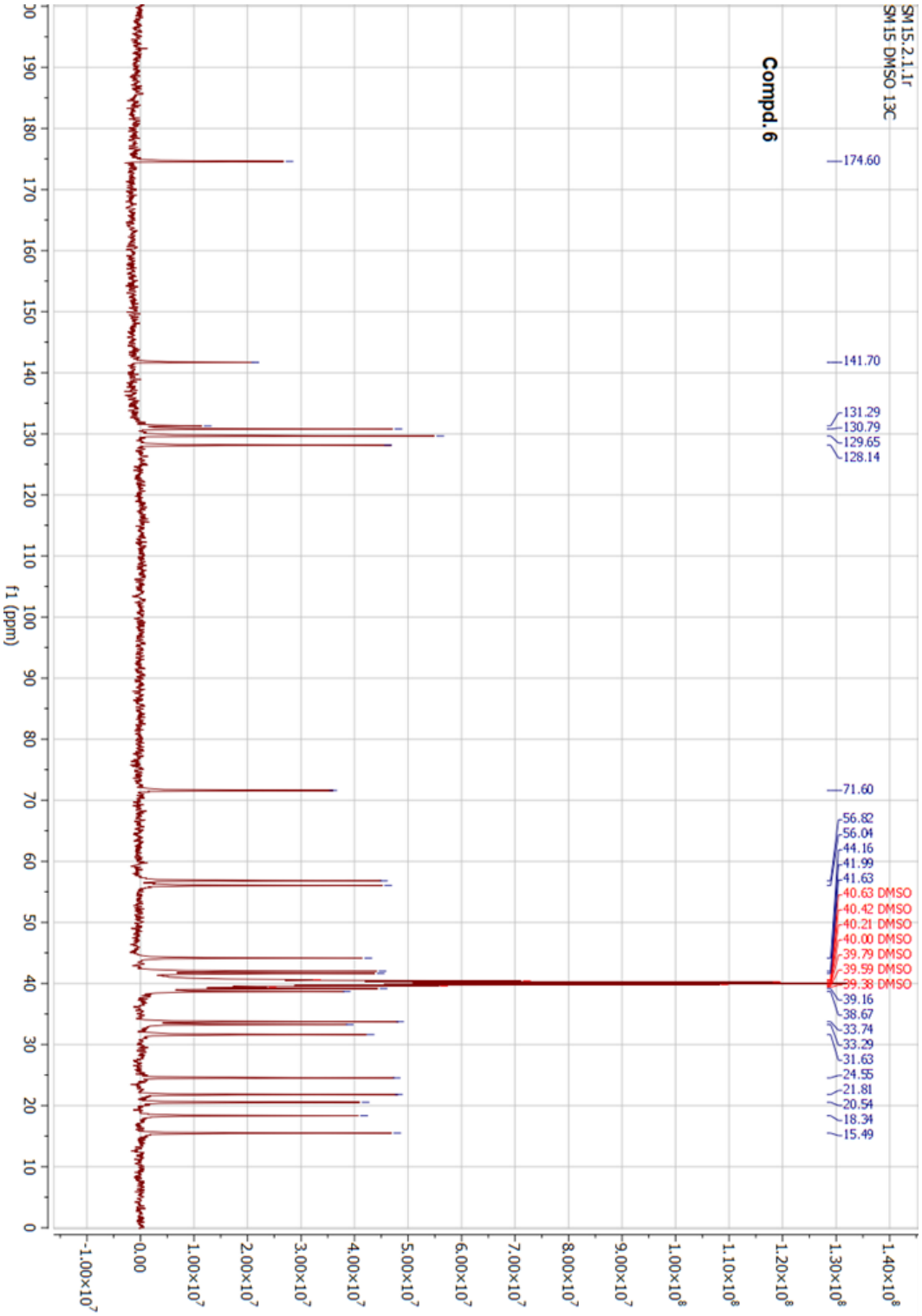


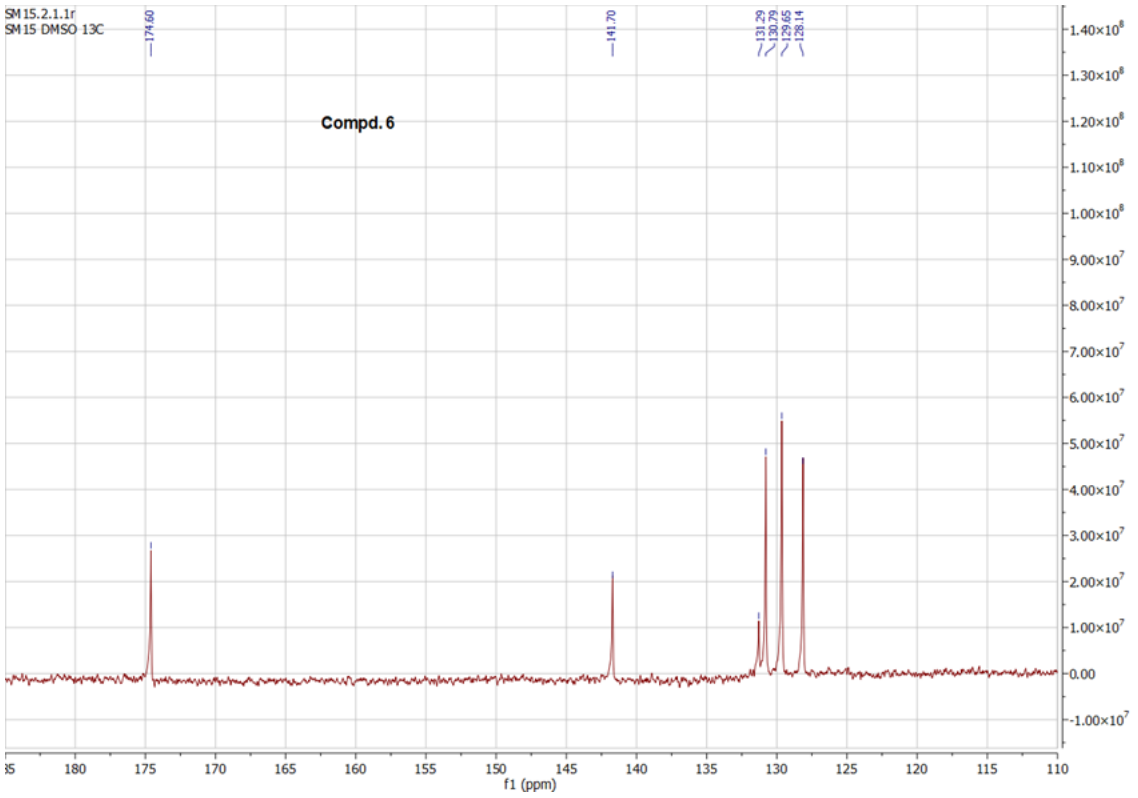
Scansionato con CamScanner

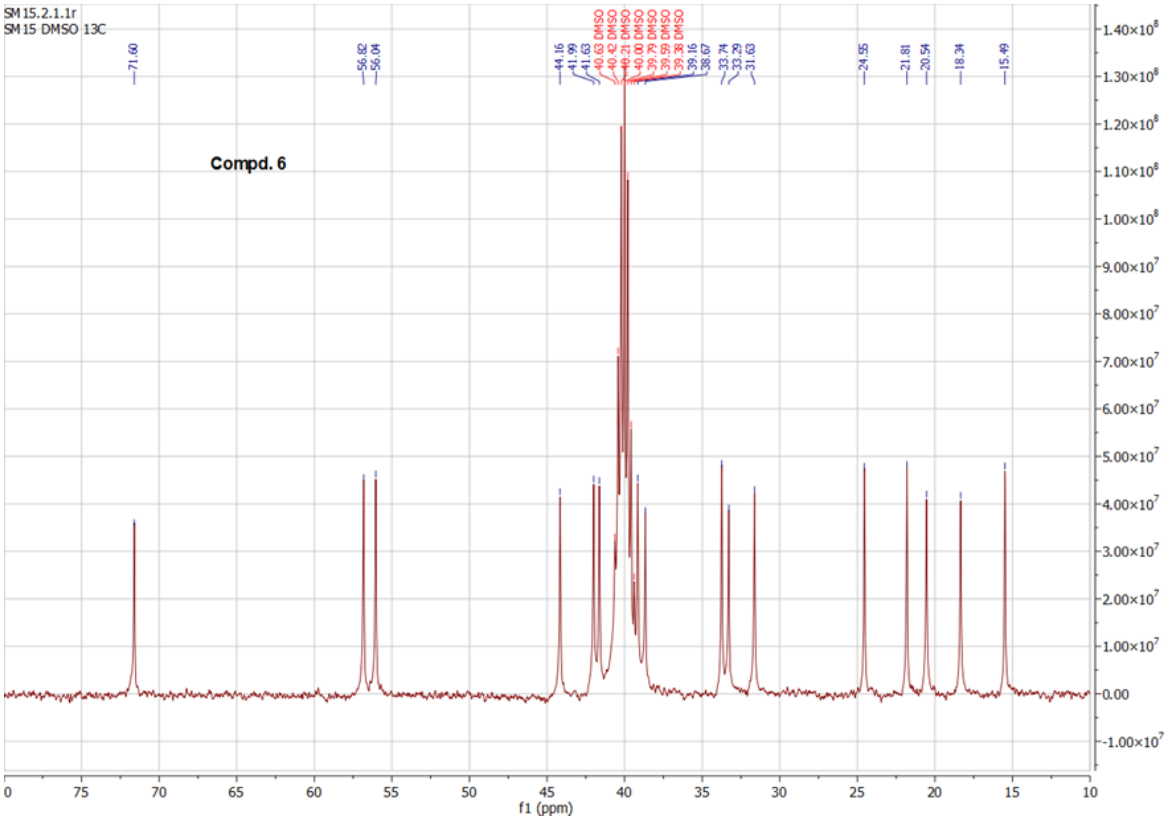

SM15.1.1.1r
SM15 DMSO
Compd. 6
f1 (ppm)
1.02
0.74
0.69
0.91
1.23
2.27
1.21
1.13
2.55
6.12
4.81
2.86
3.59
3.25
4.32
6.28
3.38 HDO
3.36 HDO
3.34 HDO

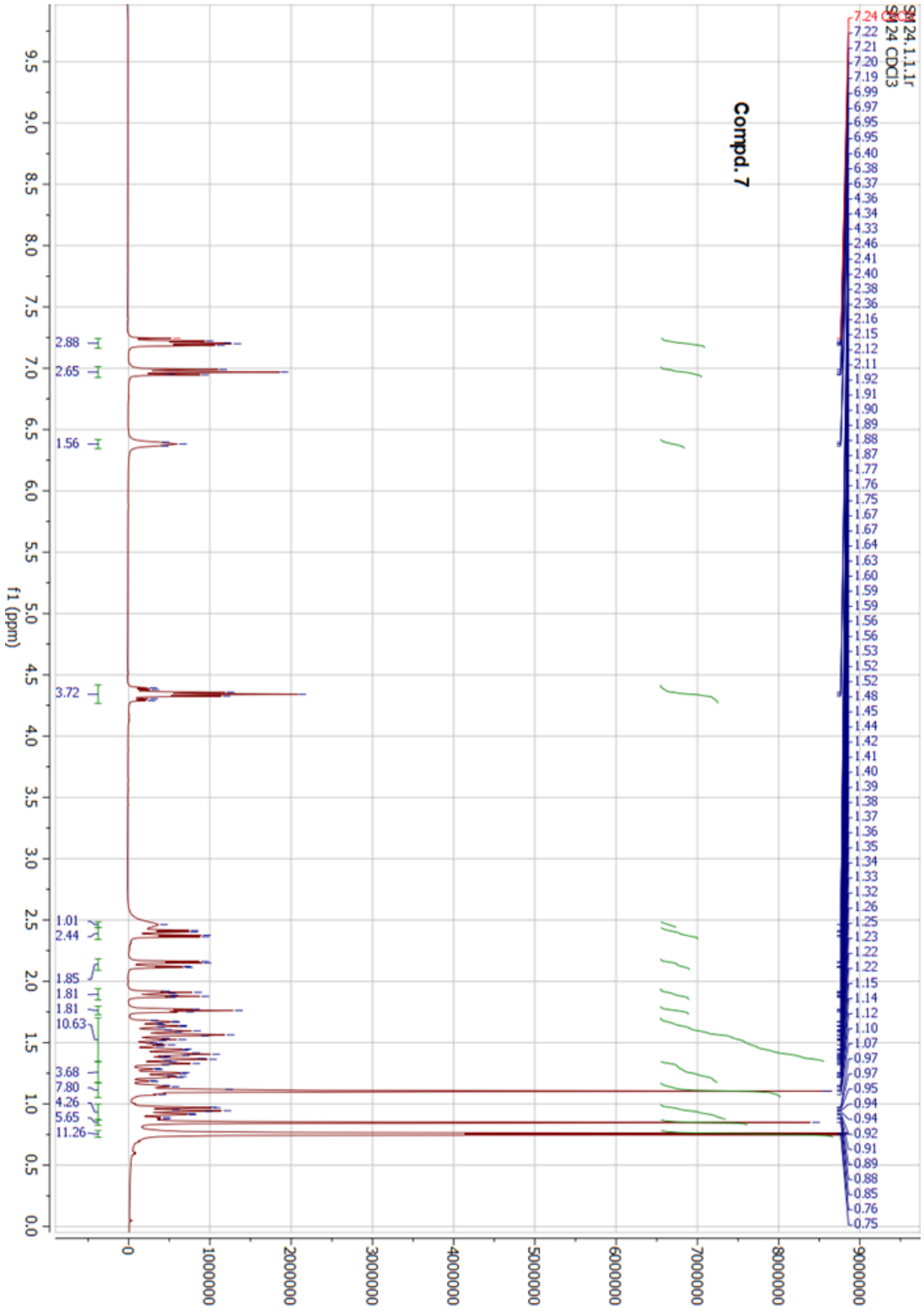

SM15.1.1.1r
SM15 DMSO
Compd. 6
f1 (ppm)

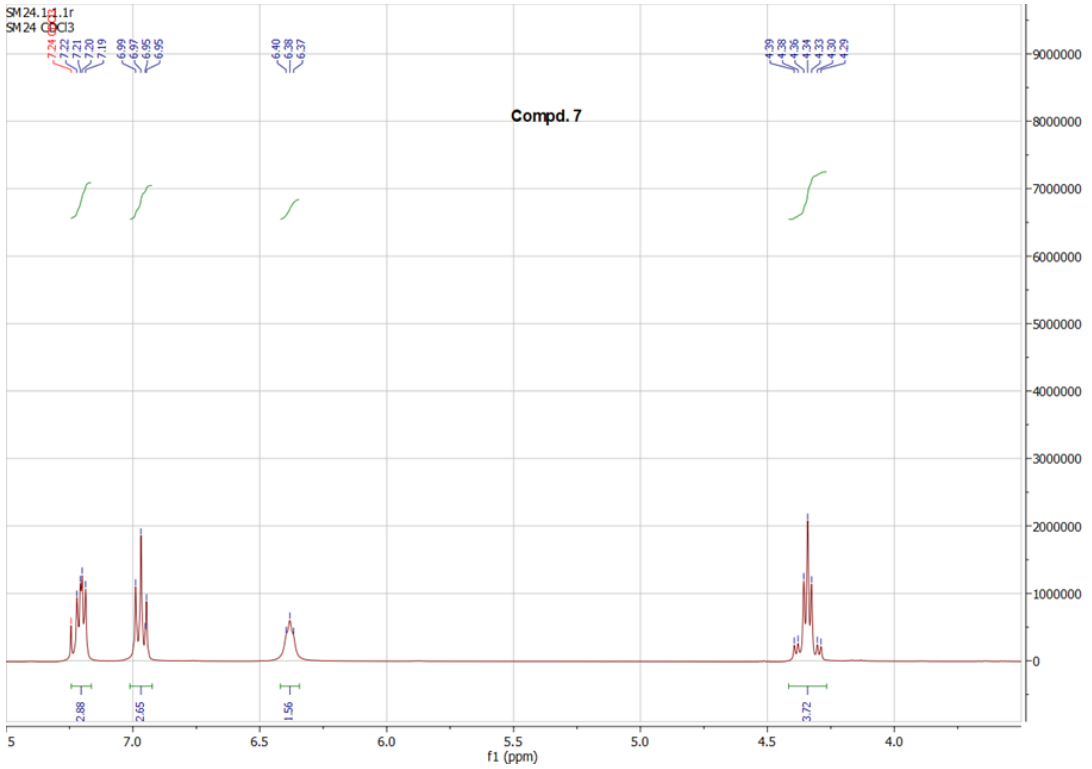

SM15.1.1.1r
SM15 DMSO
Compd. 6
f1 (ppm)

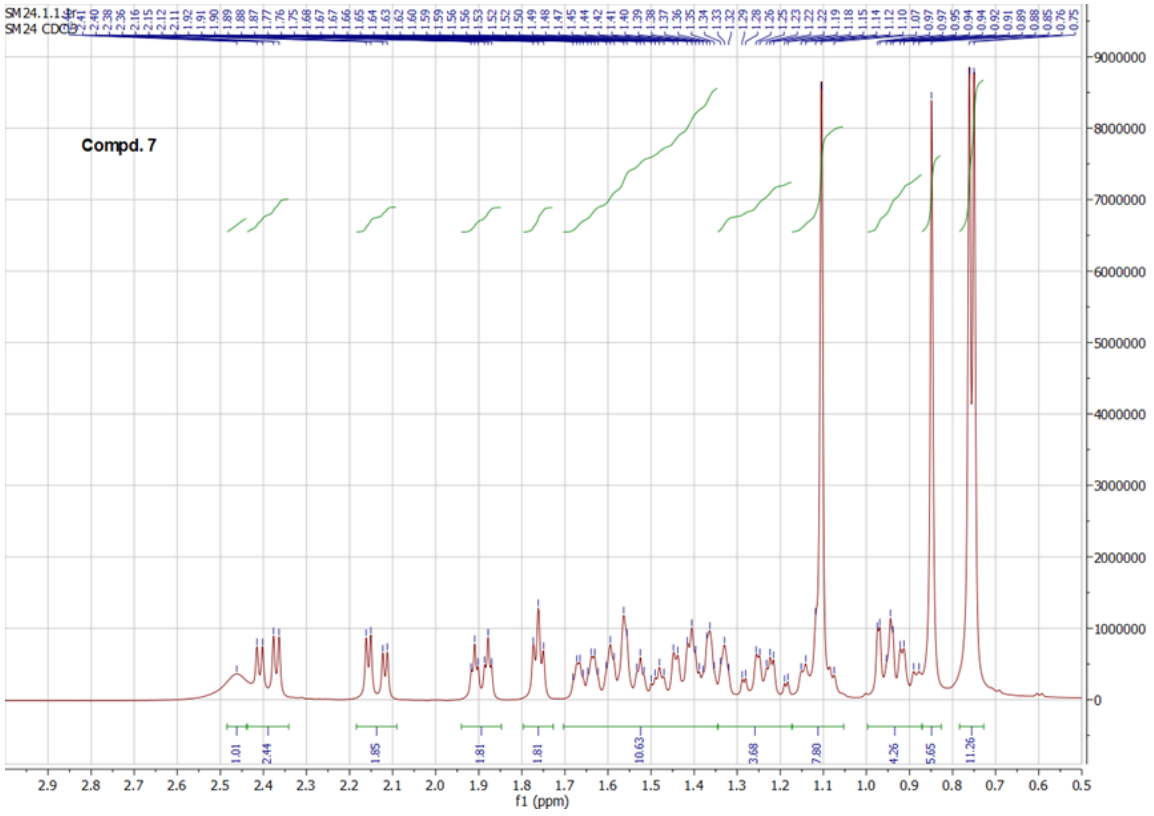

SM15.2.1.1r
SM15 DMSO 13C
Compd. 6
174.60
141.70
131.29
130.79
129.65
128.14
71.60
56.82
56.04
44.16
41.99
41.63
40.63 DMSO
40.42 DMSO
40.21 DMSO
40.00 DMSO
39.79 DMSO
39.59 DMSO
39.38 DMSO
39.16
38.67
33.74
33.29
31.63
24.55
21.81
20.54
18.34
15.49
f1 (ppm)

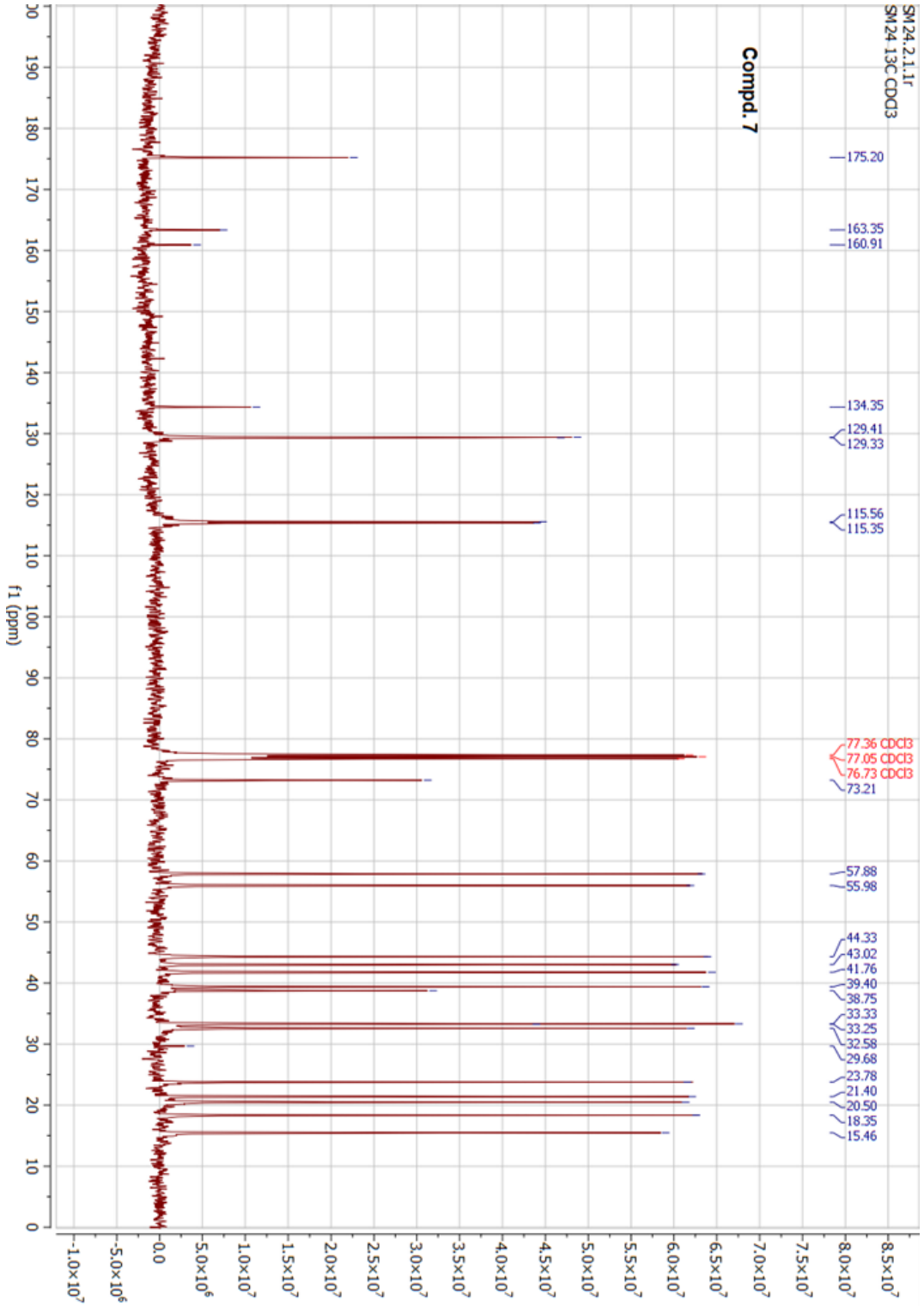

SM15.2.1.1r
SM15 DMSO 13C
174.60
141.70
131.29
130.79
129.65
128.14
Compd. 6
f1 (ppm)

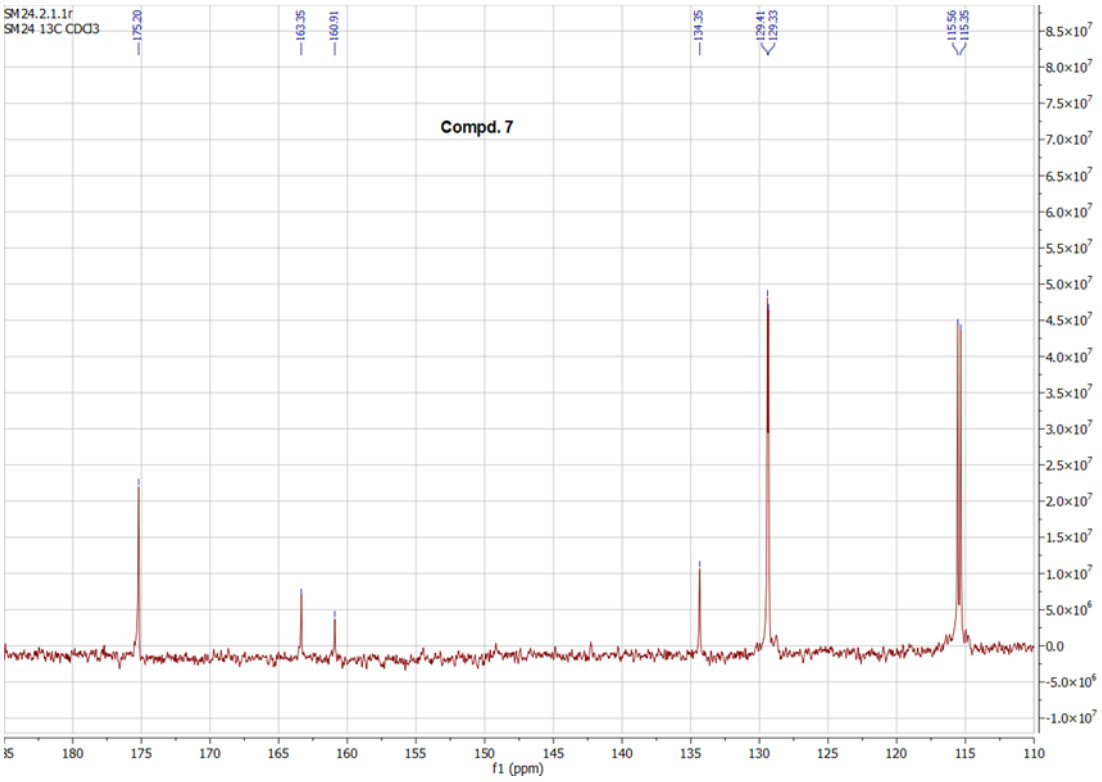

SM15.2.1.1r
SM15 DMSO 13C
71.60
56.82
56.04
44.16
41.99
41.63
40.63 DMSO
40.42 DMSO
40.21 DMSO
40.00 DMSO
39.79 DMSO
39.59 DMSO
39.38 DMSO
39.16
38.67
33.74
33.29
31.63
24.55
21.81
20.54
18.34
15.49
Compd. 6
f1 (ppm)

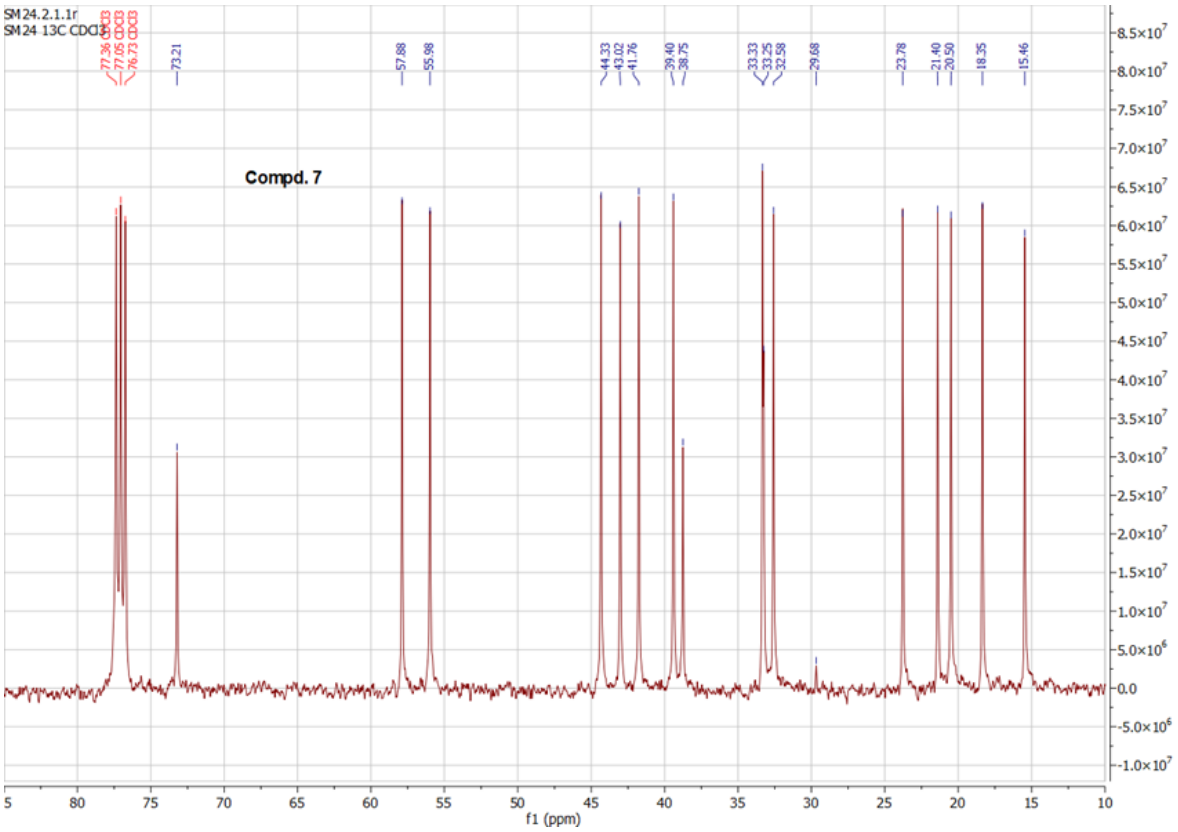

Compd. 7
f1 (ppm)
2.88
2.65
1.56
3.72
1.01
2.44
1.85
1.81
1.81
10.63
3.68
7.80
4.26
5.65
11.26

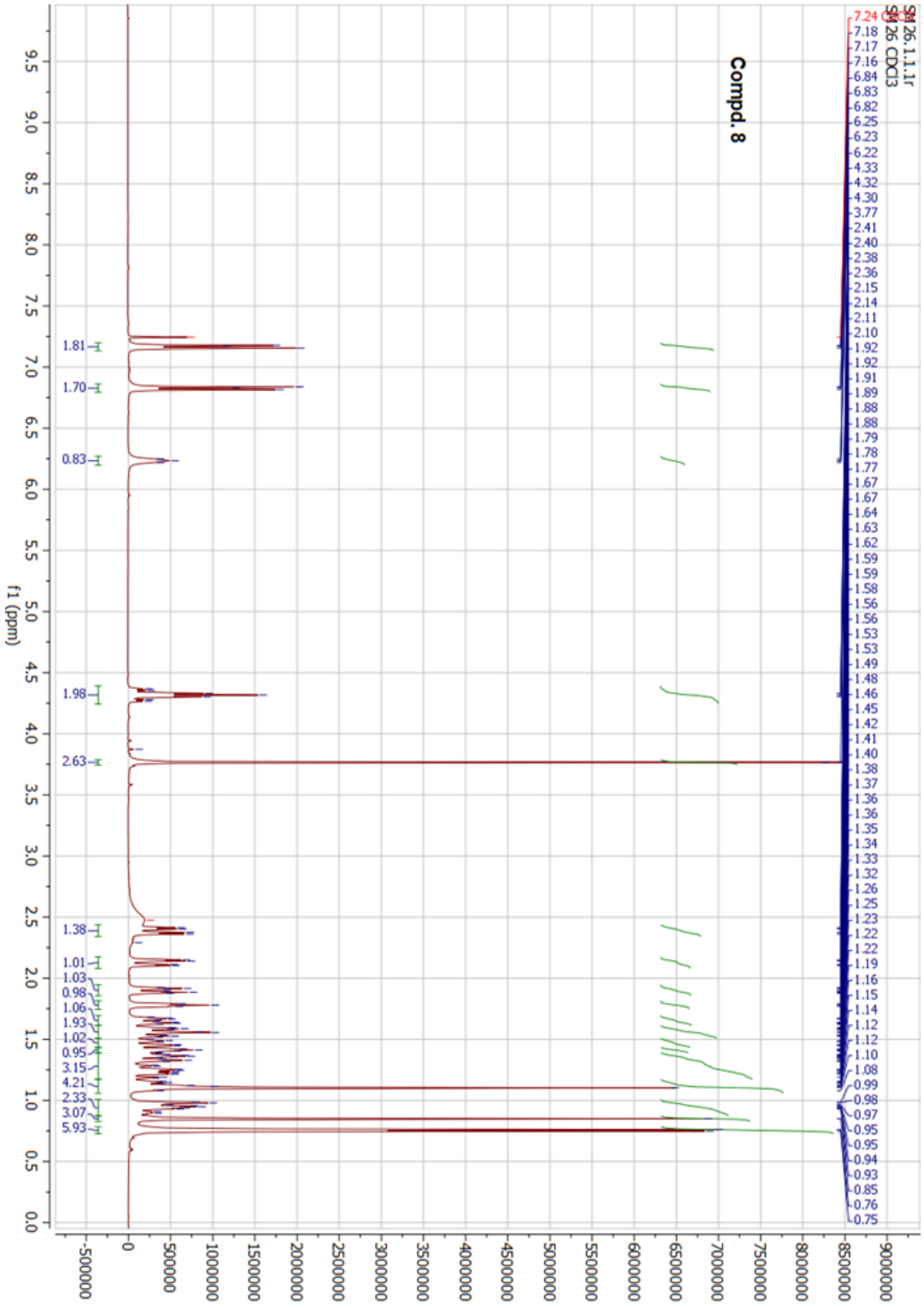

SM24.1.1.1r
SM24 CDCl3
Compd. 7
f1 (ppm)

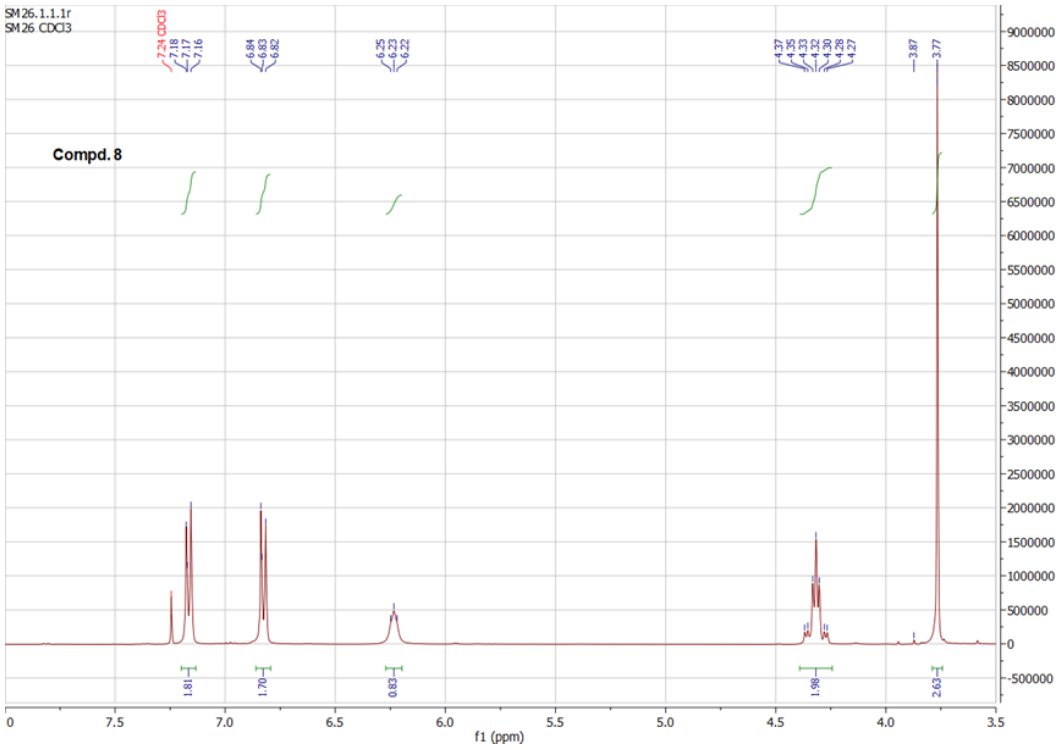

SM24.1.1.1r
SM24 CDCl3
Compd. 7
f1 (ppm)

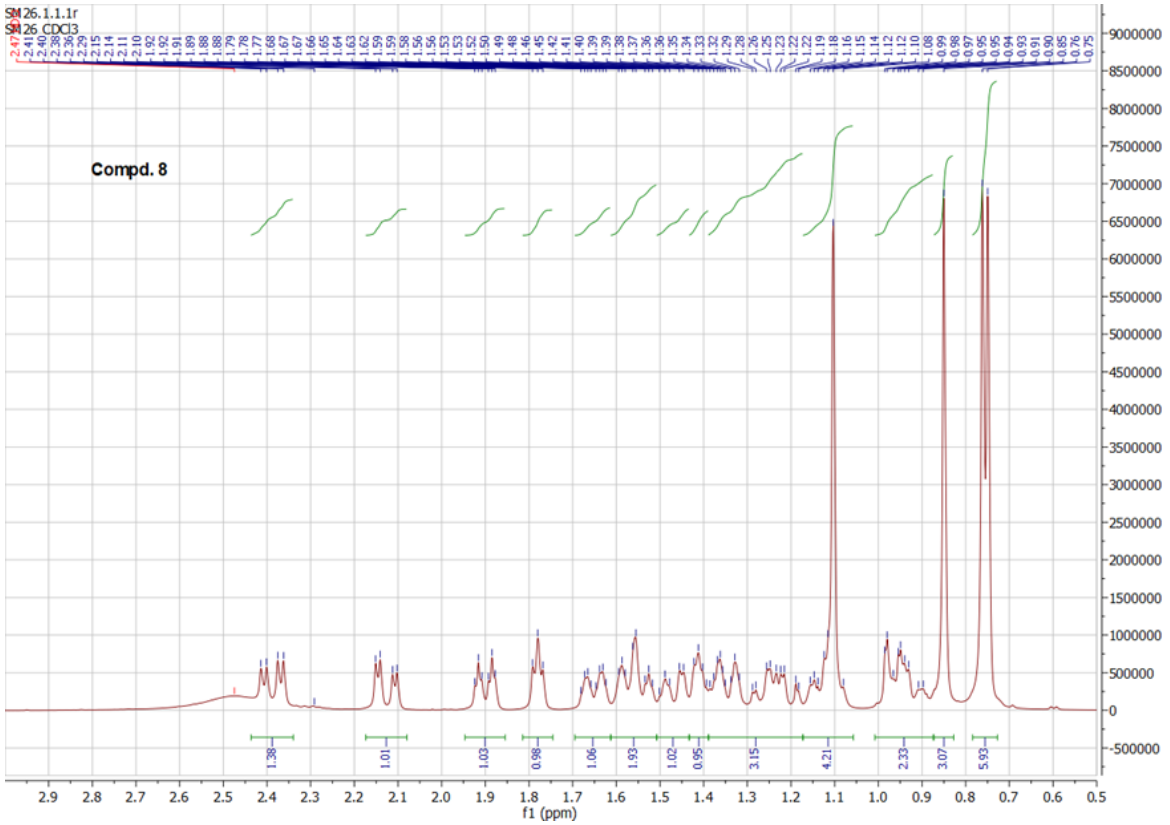

SM24.2.1.1r
SM24 13C CDCl3
Compd. 7
175.20
163.35
160.91
134.35
129.41
129.33
115.56
115.35
77.36 CDCl3
77.05 CDCl3
76.73 CDCl3
73.21
57.88
55.98
44.33
43.02
41.76
39.40
38.75
33.33
33.25
32.58
29.68
23.78
21.40
20.50
18.35
15.46
f1 (ppm)

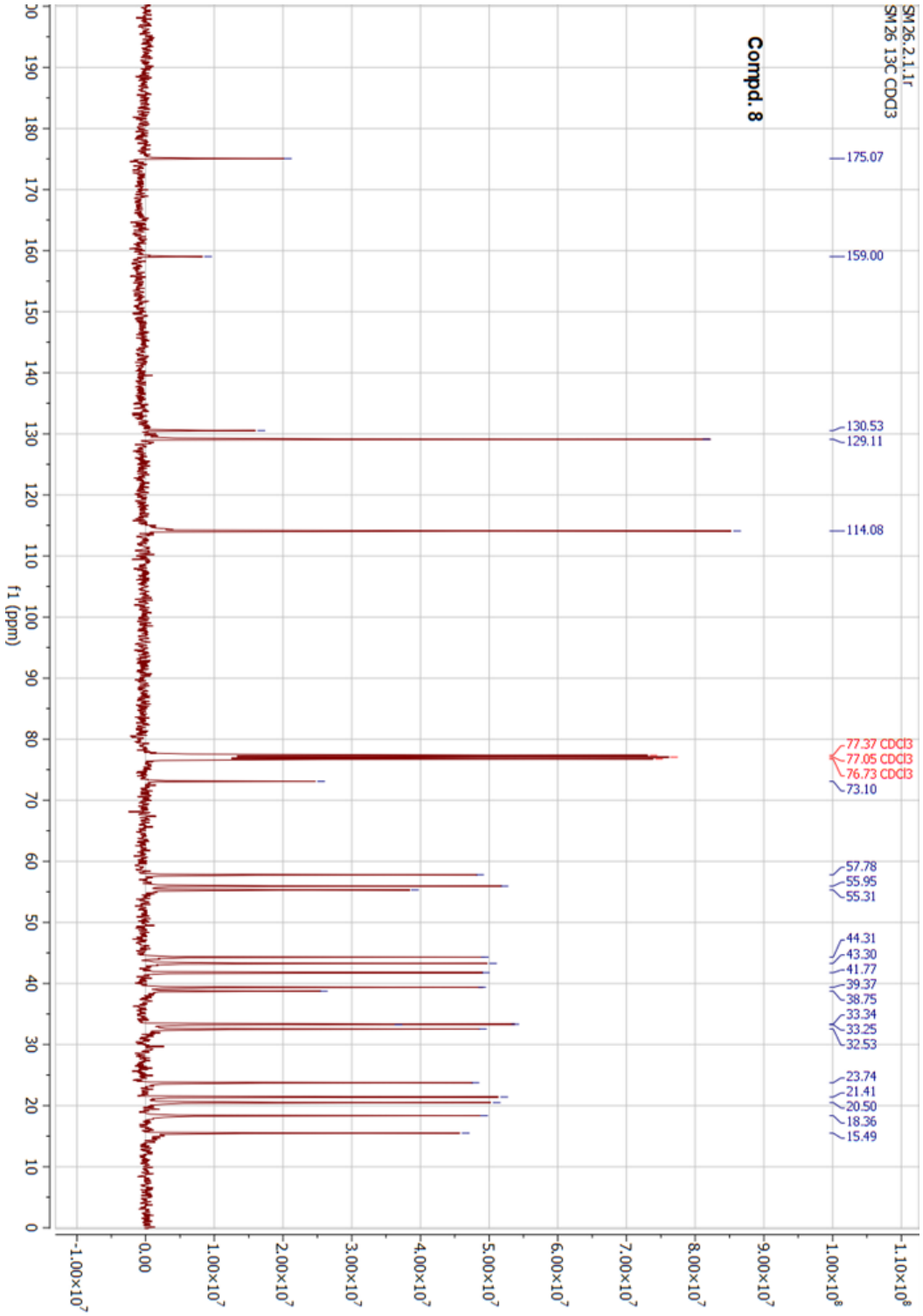

SM24.2.1.1r
SM24 13C CDCl3
175.20
163.35
160.91
134.35
129.41
129.33
115.56
115.35
Compd. 7
f1 (ppm)

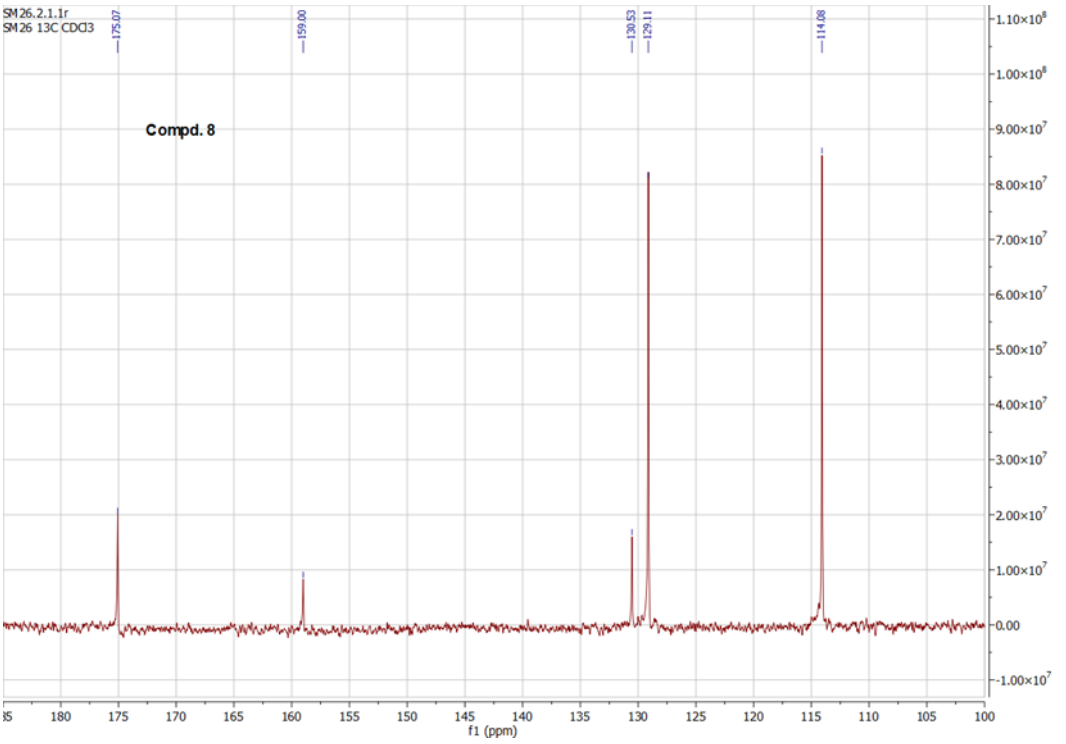

SM24.2.1.1r
SM24 13C CDCl3
77.36 CDCl3
77.05 CDCl3
76.73 CDCl3
73.21
57.88
55.98
44.33
43.02
41.76
39.40
38.75
33.33
33.25
32.58
29.68
23.78
21.40
20.50
18.35
15.46
Compd. 7
f1 (ppm)

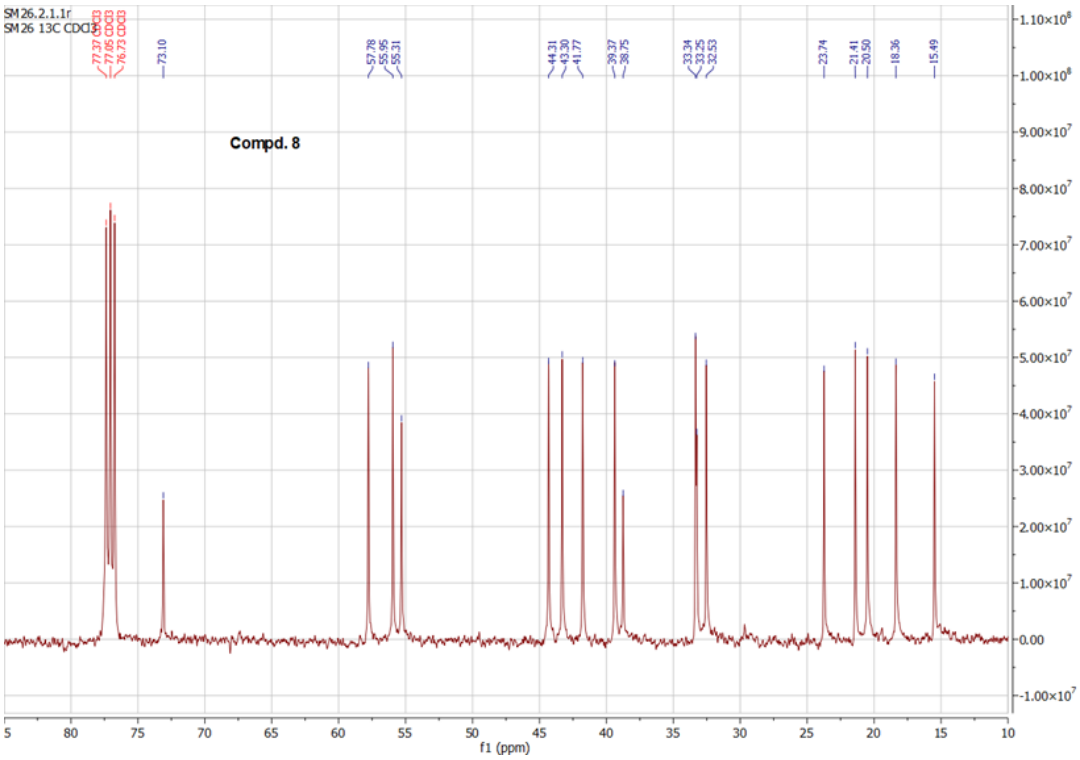

Compd. 8
f1 (ppm)

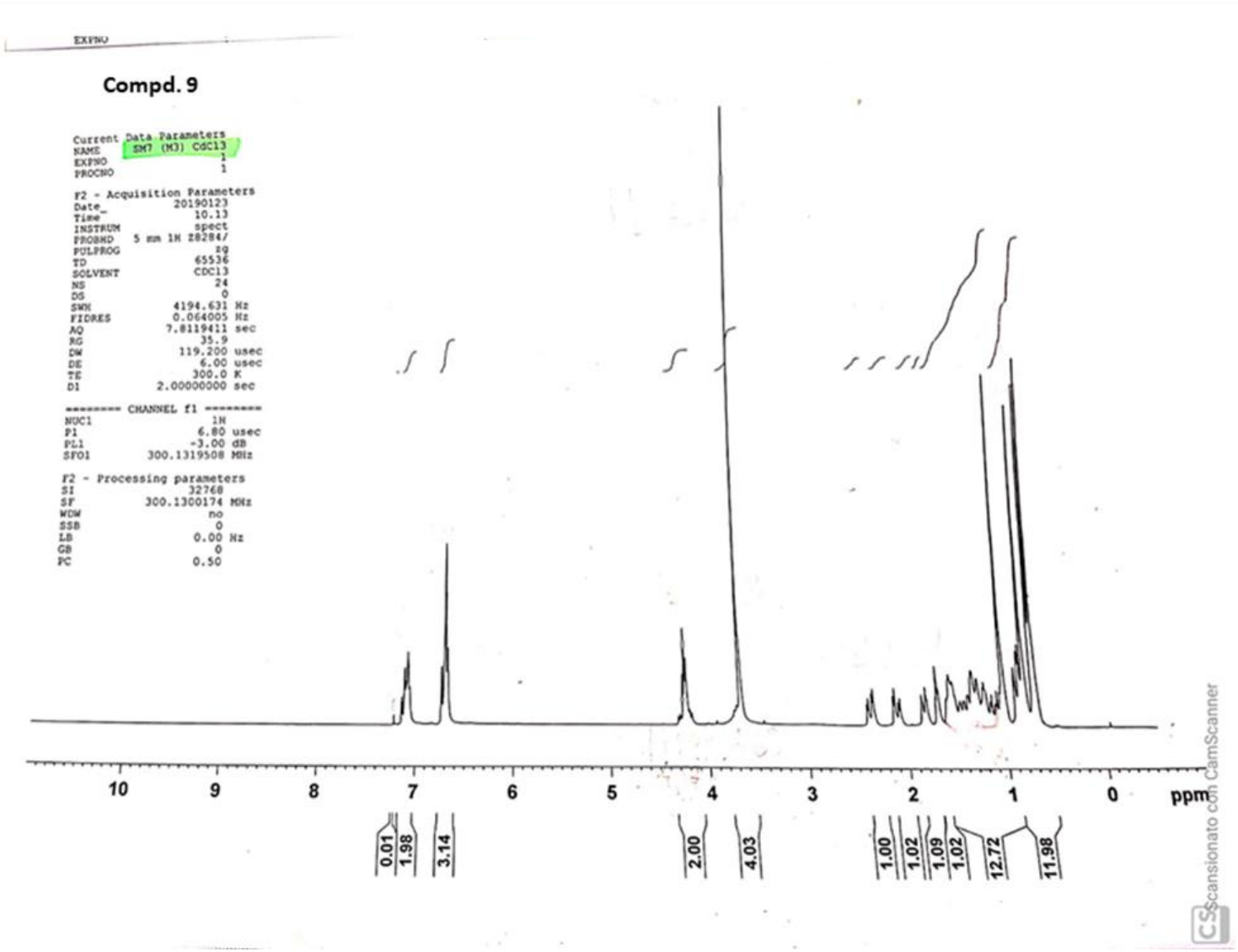

SM26.1.1.1r
SM26 CDCl3
Compd. 8
f1 (ppm)

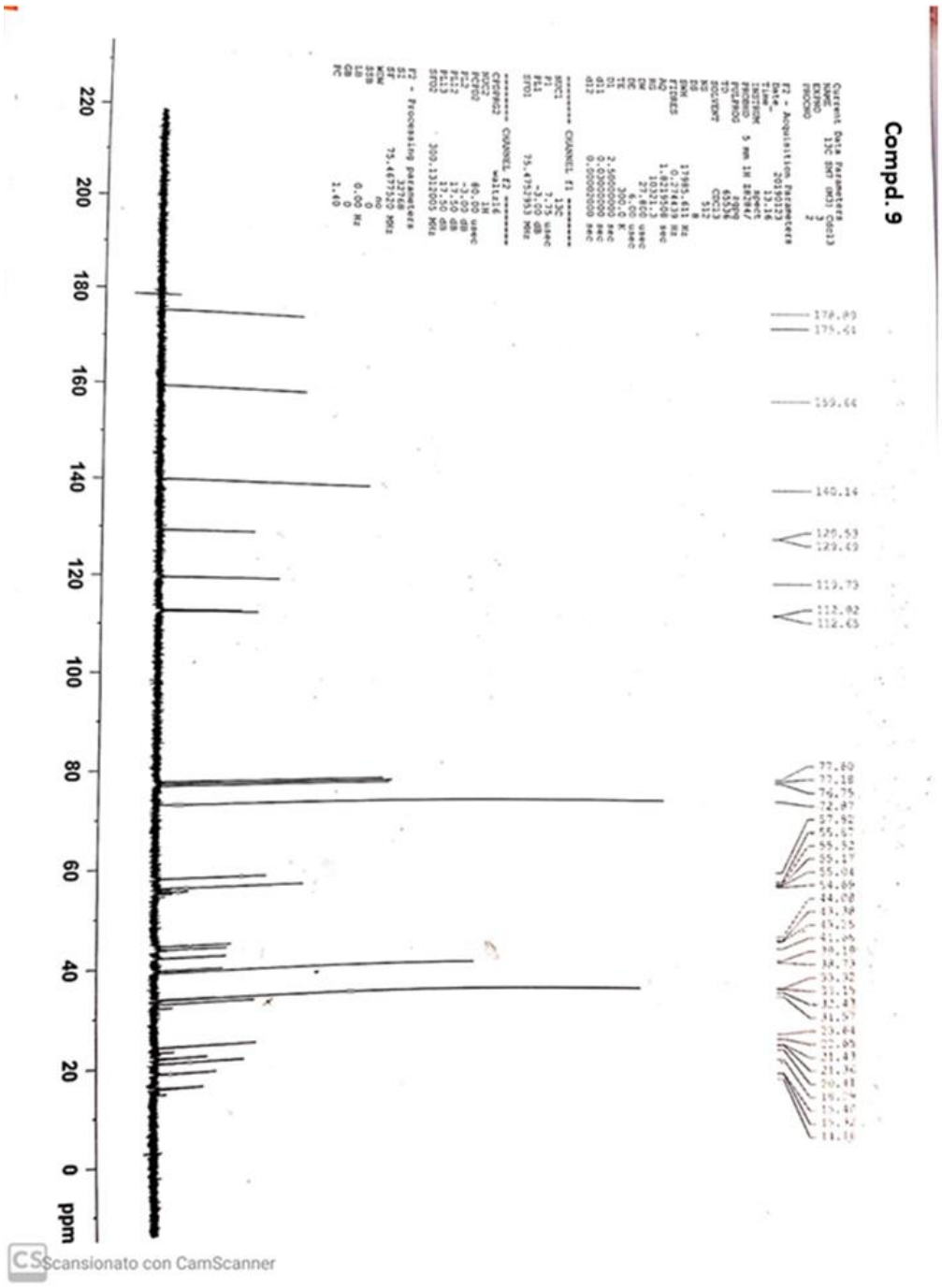

SM26.1.1.1r
SM26 CDCl3
Compd. 8
f1 (ppm)


SM26.2.1.1r
SM26 13C CDCl3
Compd. 8
175.07
159.00
130.53
129.11
114.08
77.37 CDCl3
77.05 CDCl3
76.73 CDCl3
73.10
57.78
55.95
55.31
44.31
43.30
41.77
39.37
38.75
33.34
33.25
32.53
23.74
21.41
20.50
18.36
15.49
f1 (ppm)

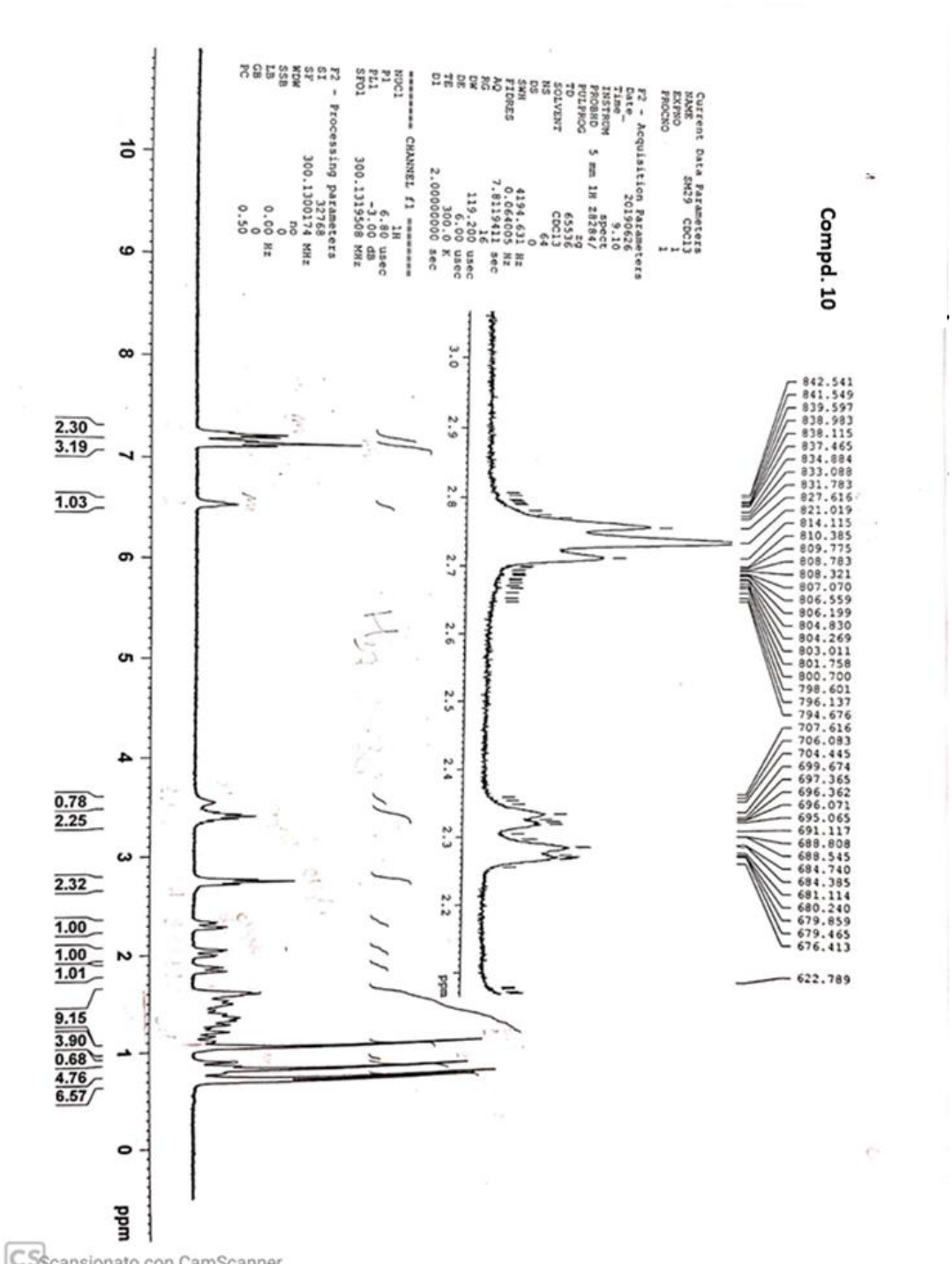

SM26.2.1.1r
SM26 13C CDCl3
175.07
159.00
130.53
129.11
114.08
Compd. 8
f1 (ppm)


SM26.2.1.1r
SM26 13C CDCl3
77.37 CDCl3
77.05 CDCl3
76.73 CDCl3
73.10
57.78
55.95
55.31
44.31
43.30
41.77
39.37
38.75
33.34
33.25
32.53
23.74
21.41
20.50
18.36
15.49
Compd. 8
f1 (ppm)

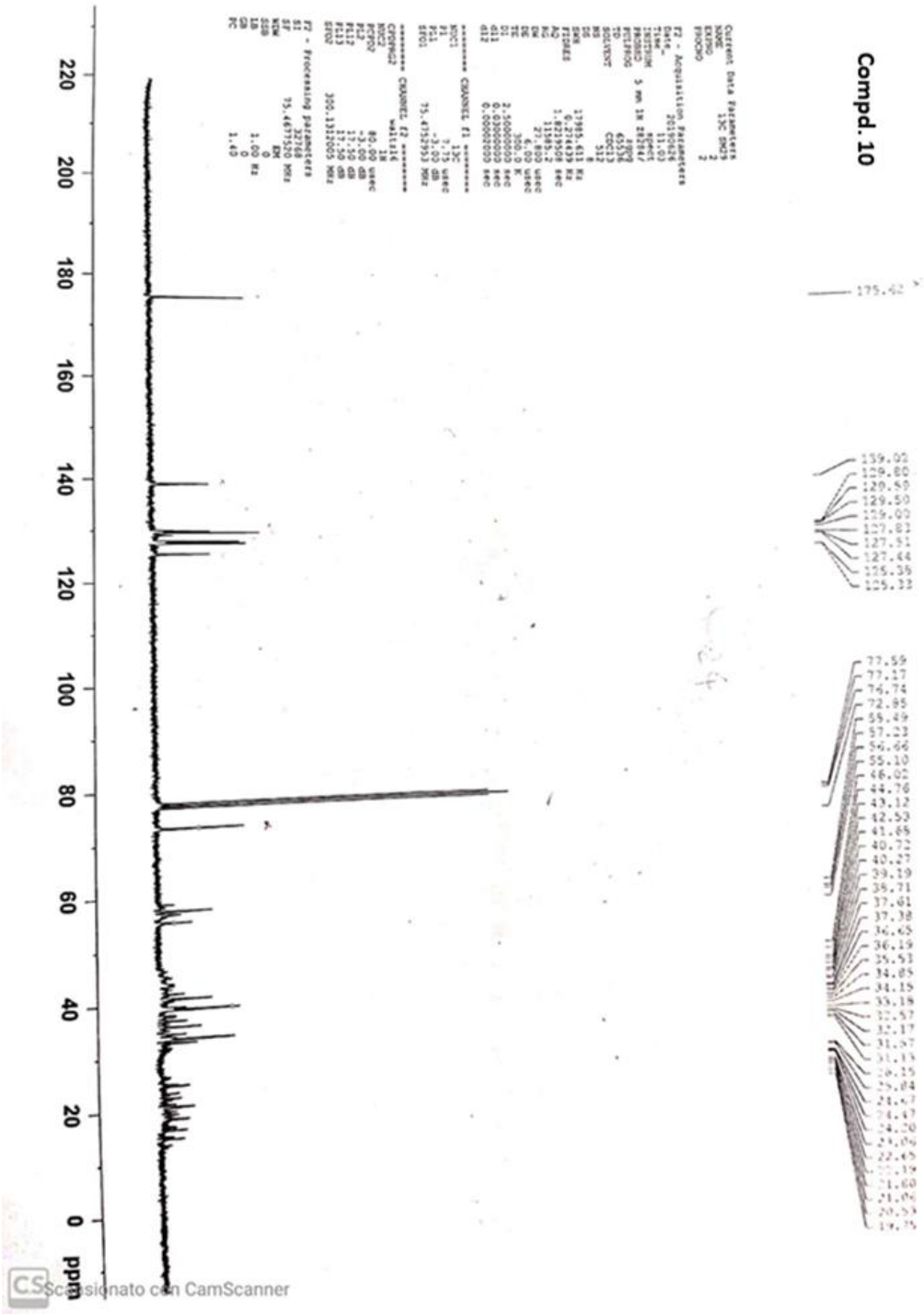

EXPNO
Compd. 9
Current Data Parameters
NAME SM7 (M3) CdCl3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190123
Time 10.13
INSTRUM spect
PROBHD 5 mm 1H Z8284/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 24
DS 0
SWH 4194.631 Hz
FIDRES 0.064005 Hz
AQ 7.8119411 sec
RG 35.9
DW 119.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 6.80 usec
PL1 -3.00 dB
SFO1 300.1319508 MHz
F2 - Processing parameters
SI 32768
SF 300.1300174 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 0.50
10
9
8
7
6
5
4
3
2
1
0
ppm
0.01
1.98
3.14
2.00
4.03
1.00
1.02
1.09
1.02
12.72
11.98
Scansionato con CamScanner



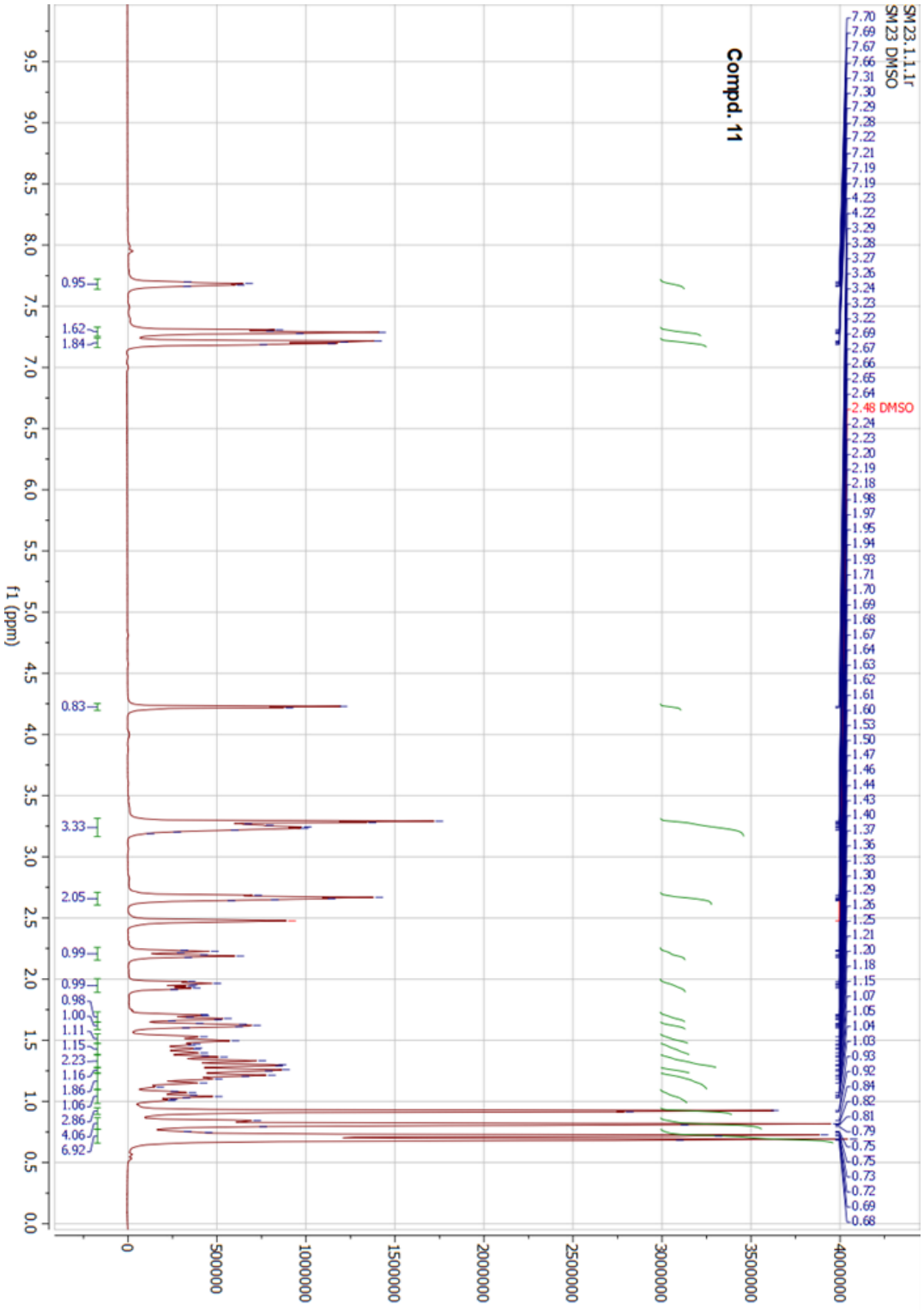
Scansionato con CamScanner

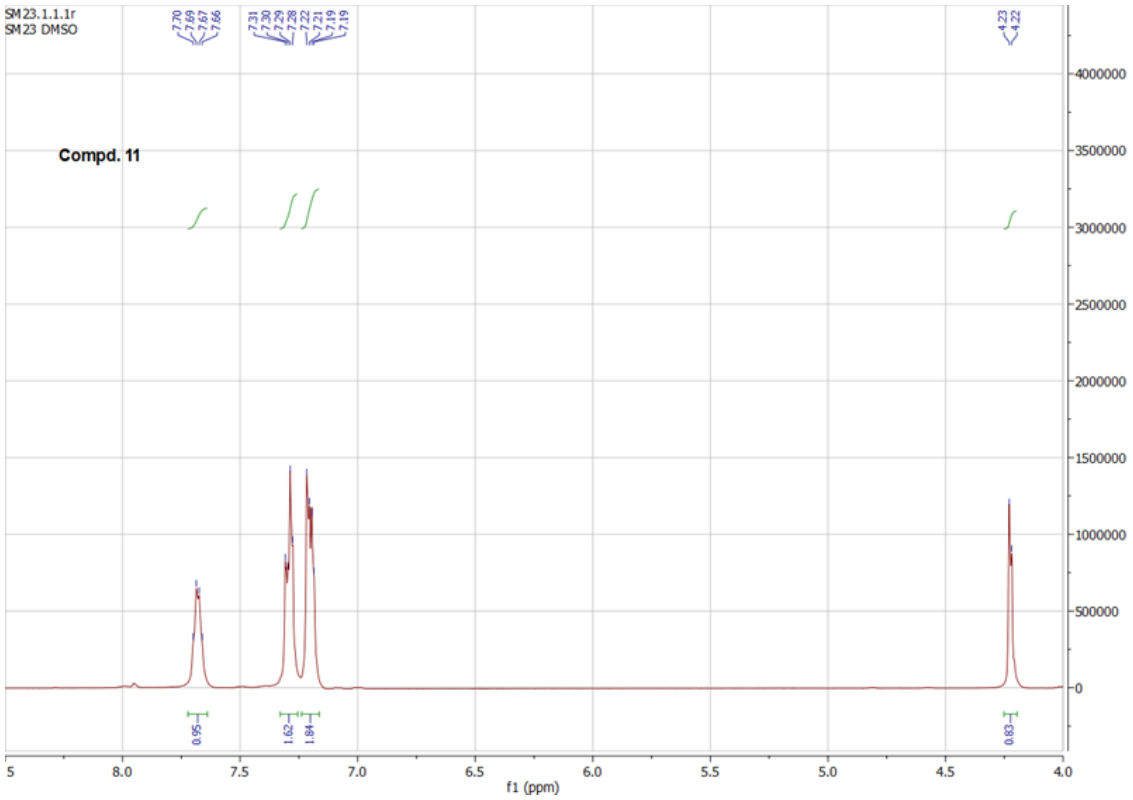


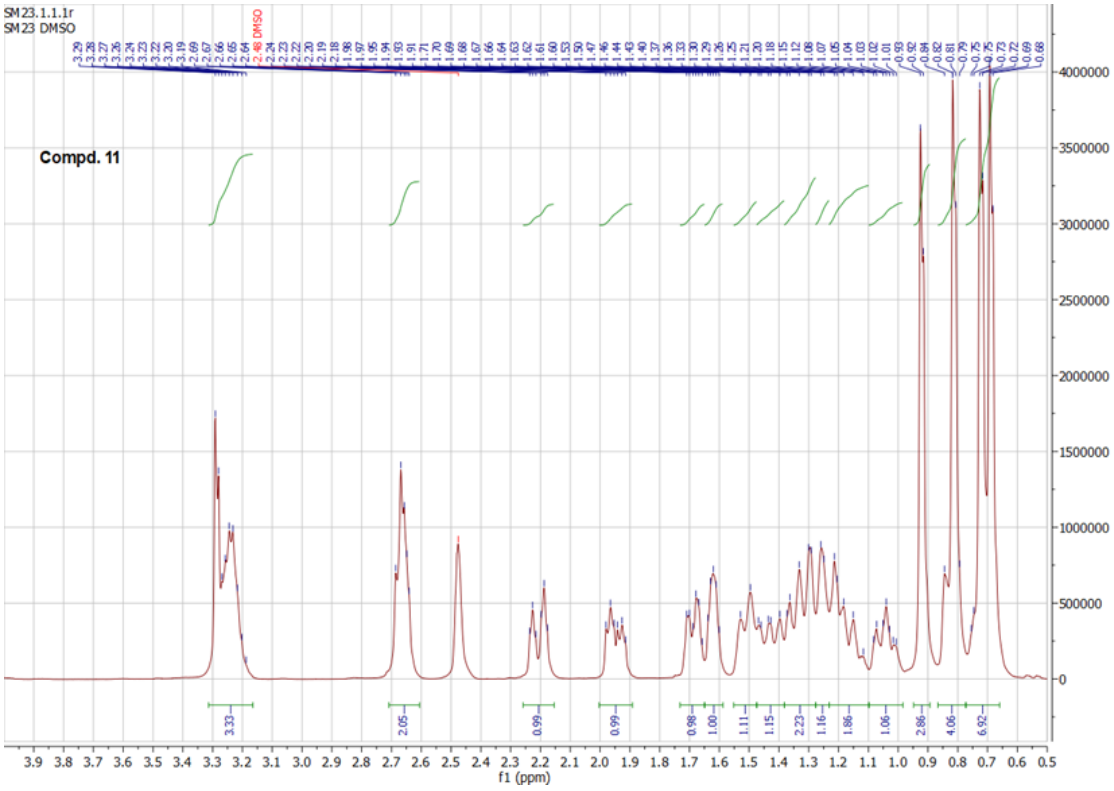
Scansionato con CamScanner

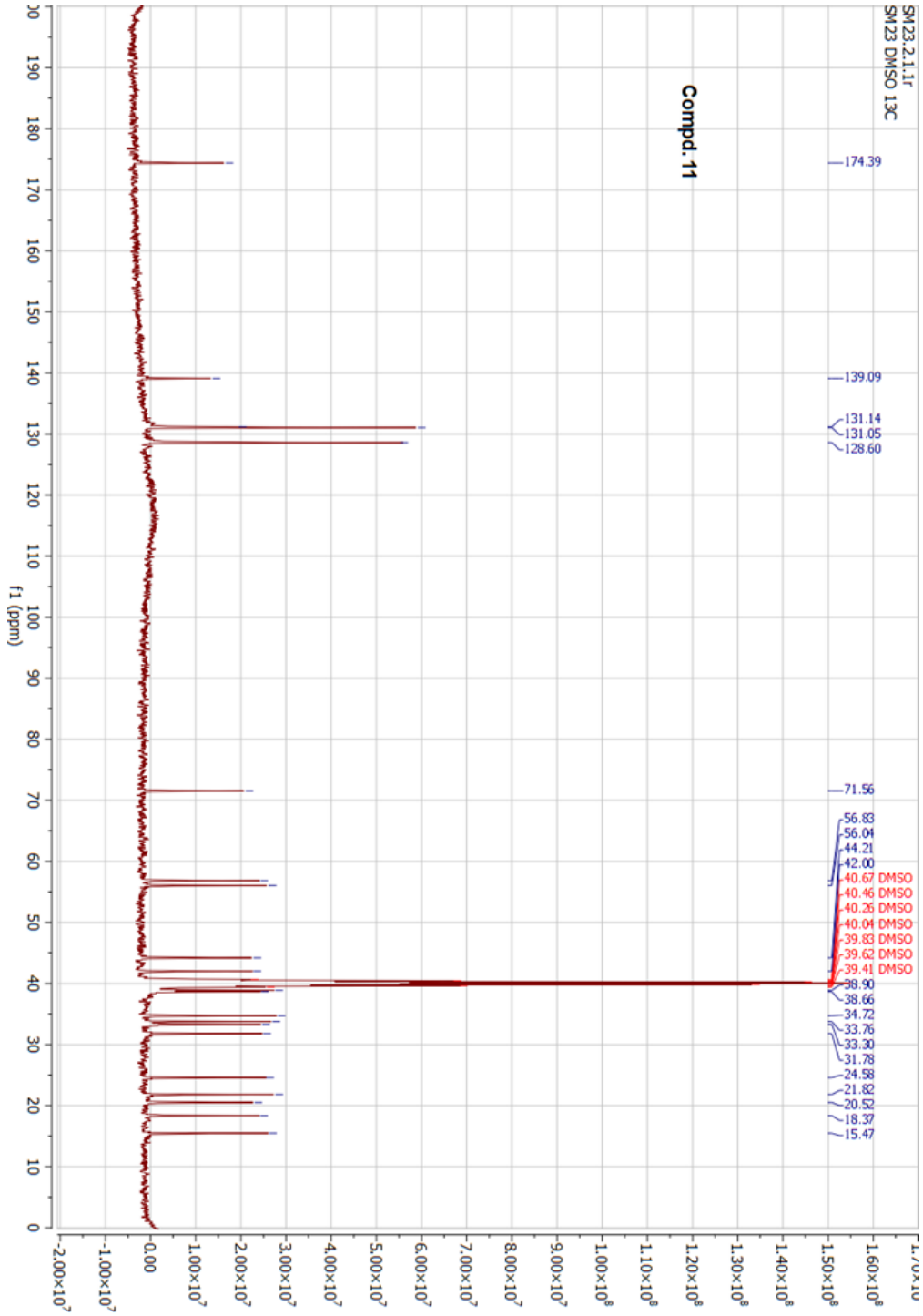


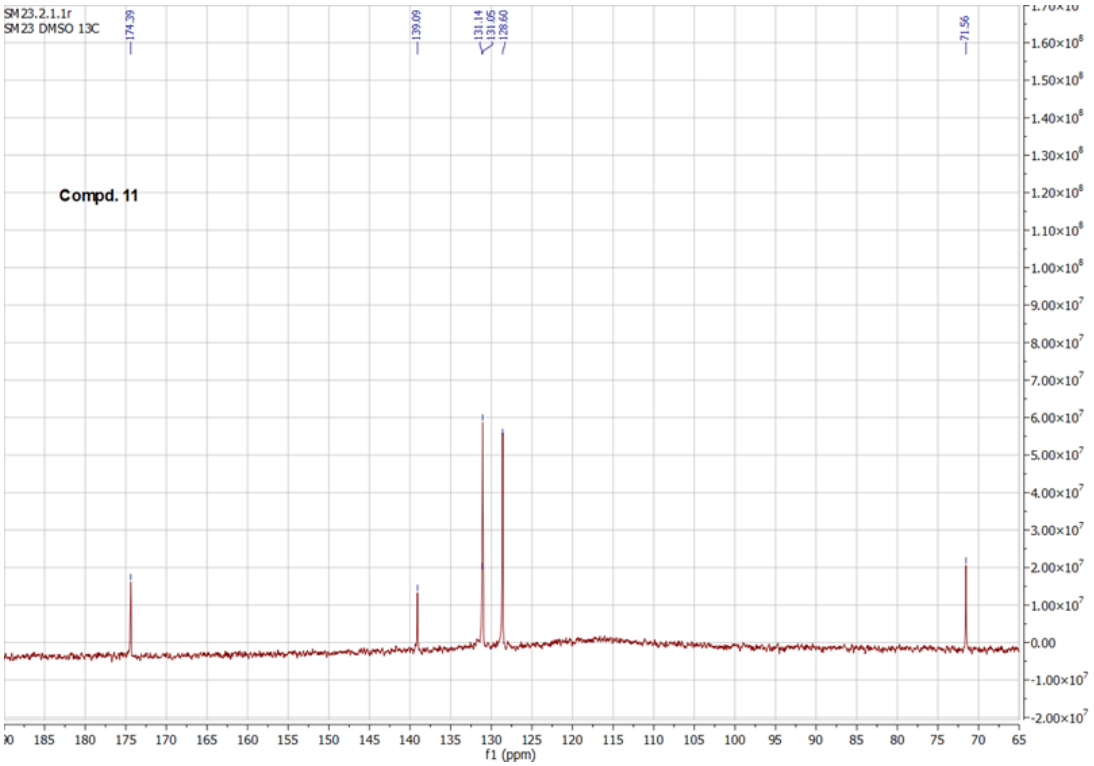
Scansionato con CamScanner

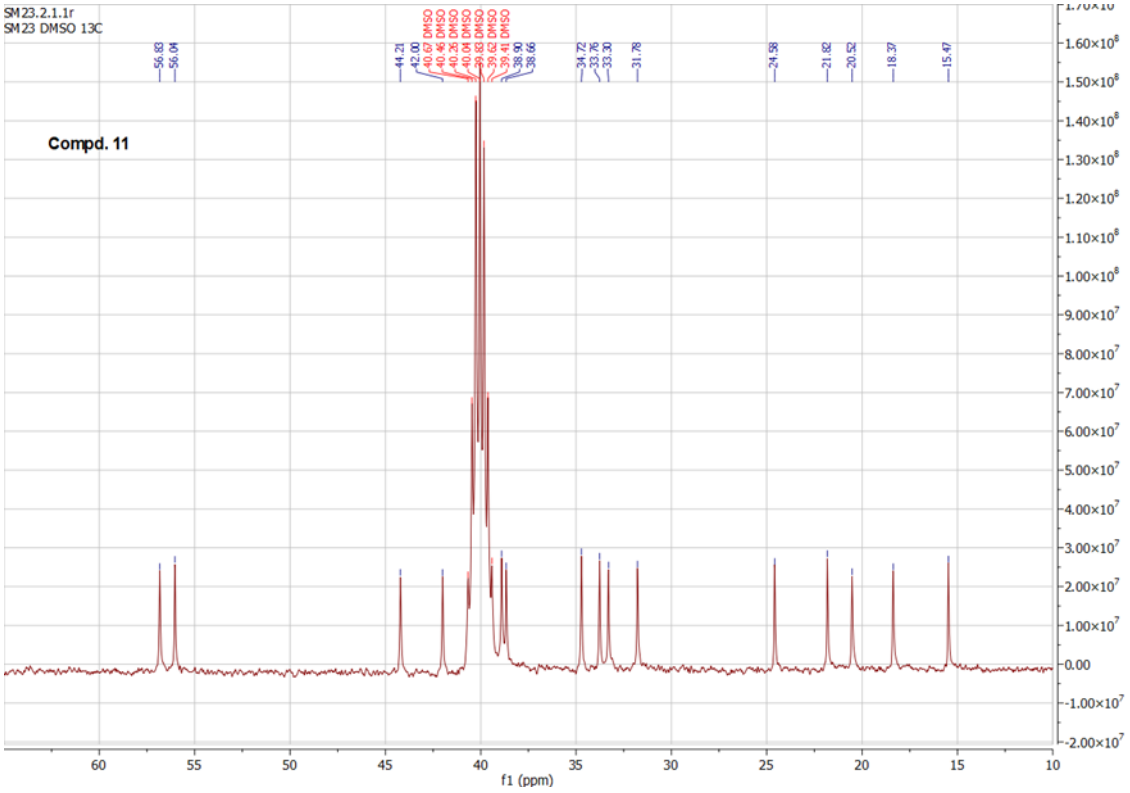

Compd. 11
SM 23.1.1.1r
SM 23 DMSO
2.48 DMSO
f1 (ppm)
0.95
1.62
1.84
0.83
3.33
2.05
0.99
0.99
0.98
1.00
1.11
1.15
2.23
1.16
1.86
1.06
2.86
4.06
6.92

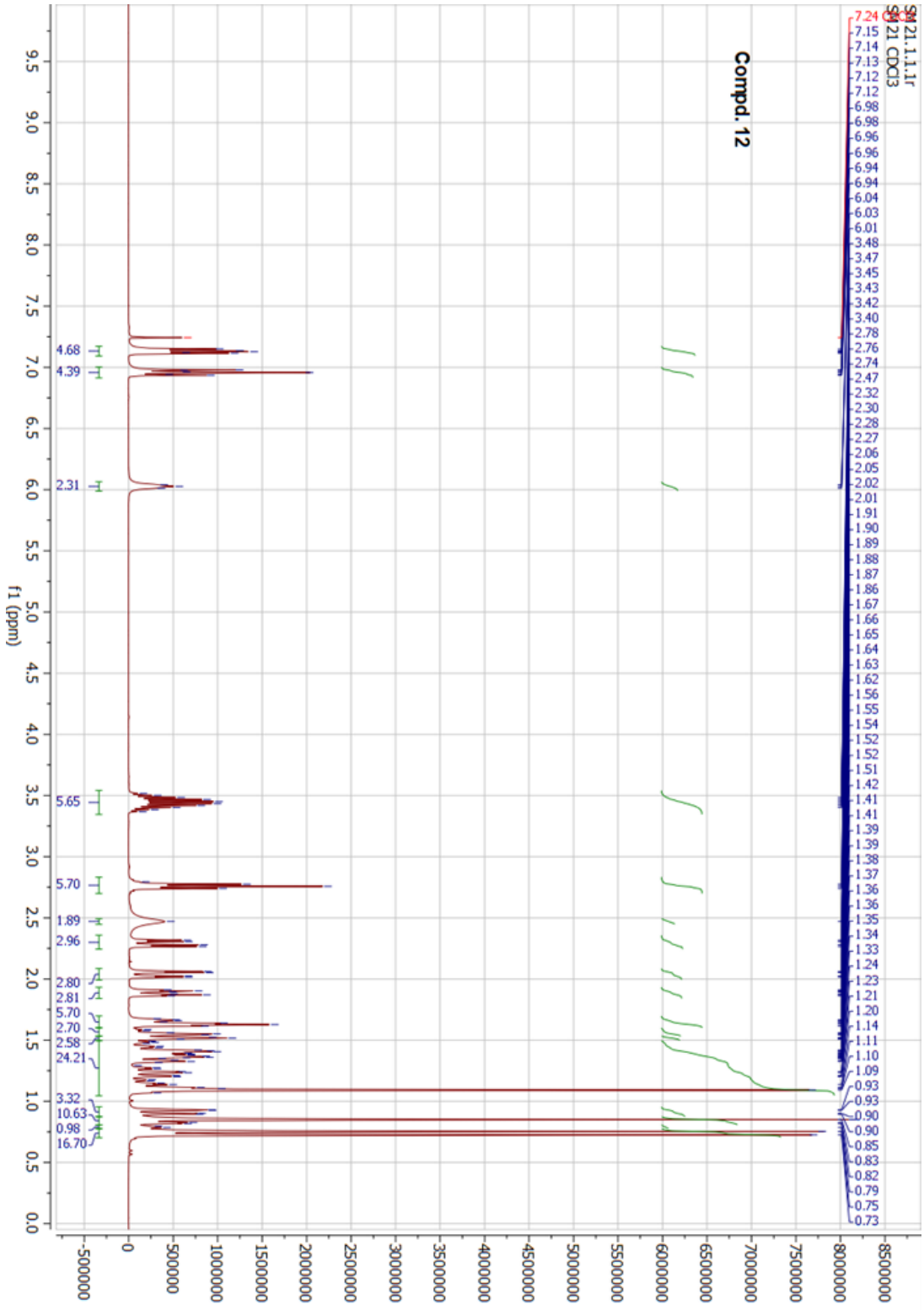

SM23.1.1.1r
SM23 DMSO
Compd. 11
f1 (ppm)

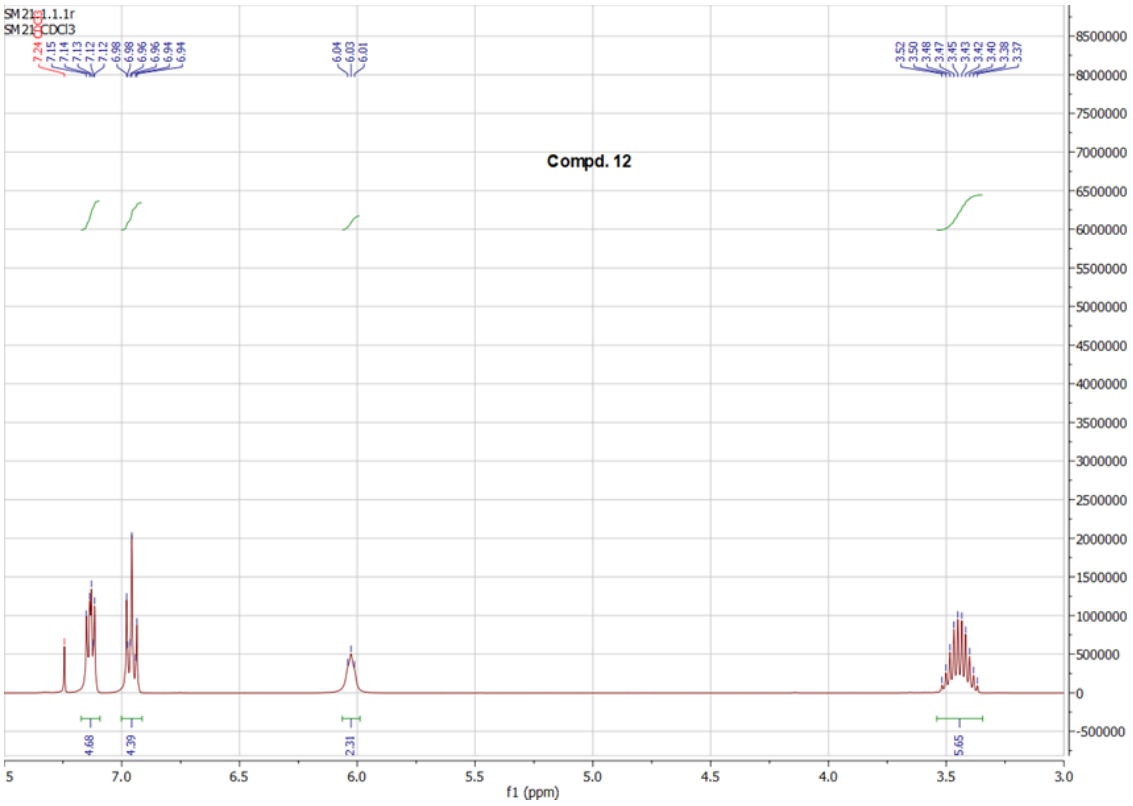

SM23.1.1.1r
SM23 DMSO
Compd. 11
f1 (ppm)

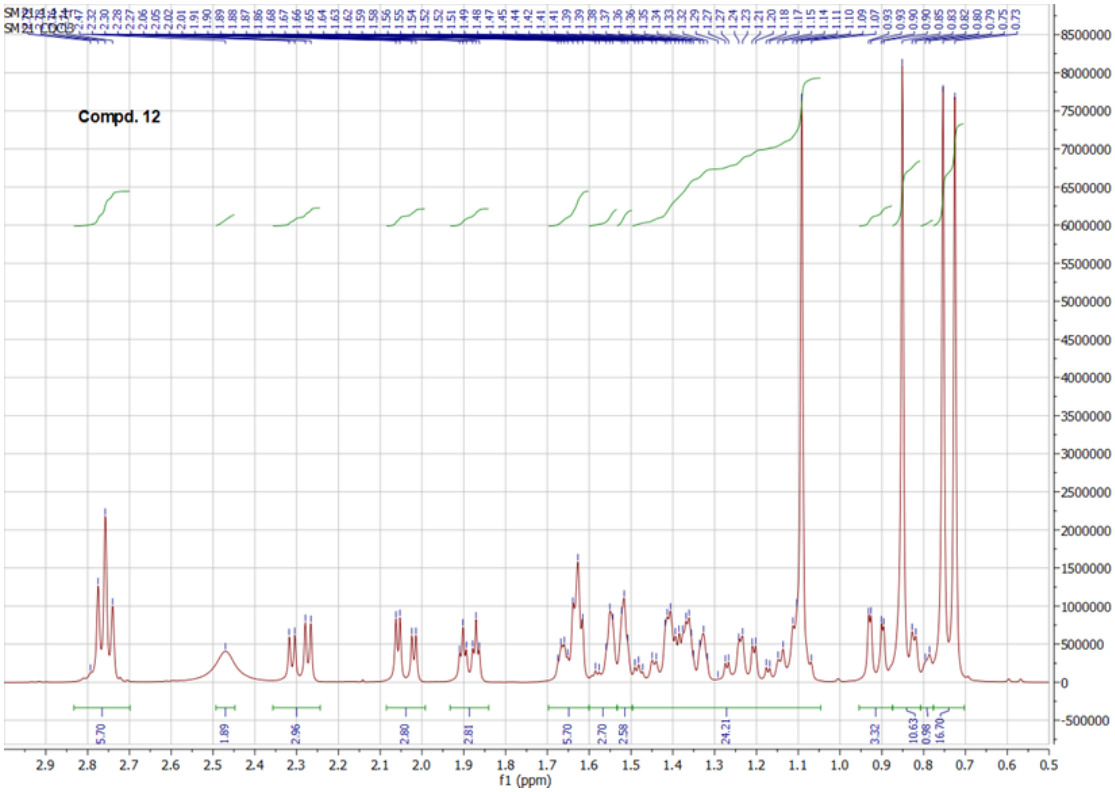

SM23.2.1.1r
SM23 DMSO 13C
Compd.11
174.39
139.09
131.14
131.05
128.60
71.56
56.83
56.04
44.21
42.00
40.67 DMSO
40.46 DMSO
40.26 DMSO
40.04 DMSO
39.83 DMSO
39.62 DMSO
39.41 DMSO
38.90
38.66
34.72
33.76
33.30
31.78
24.58
21.82
20.52
18.37
15.47
f1 (ppm)

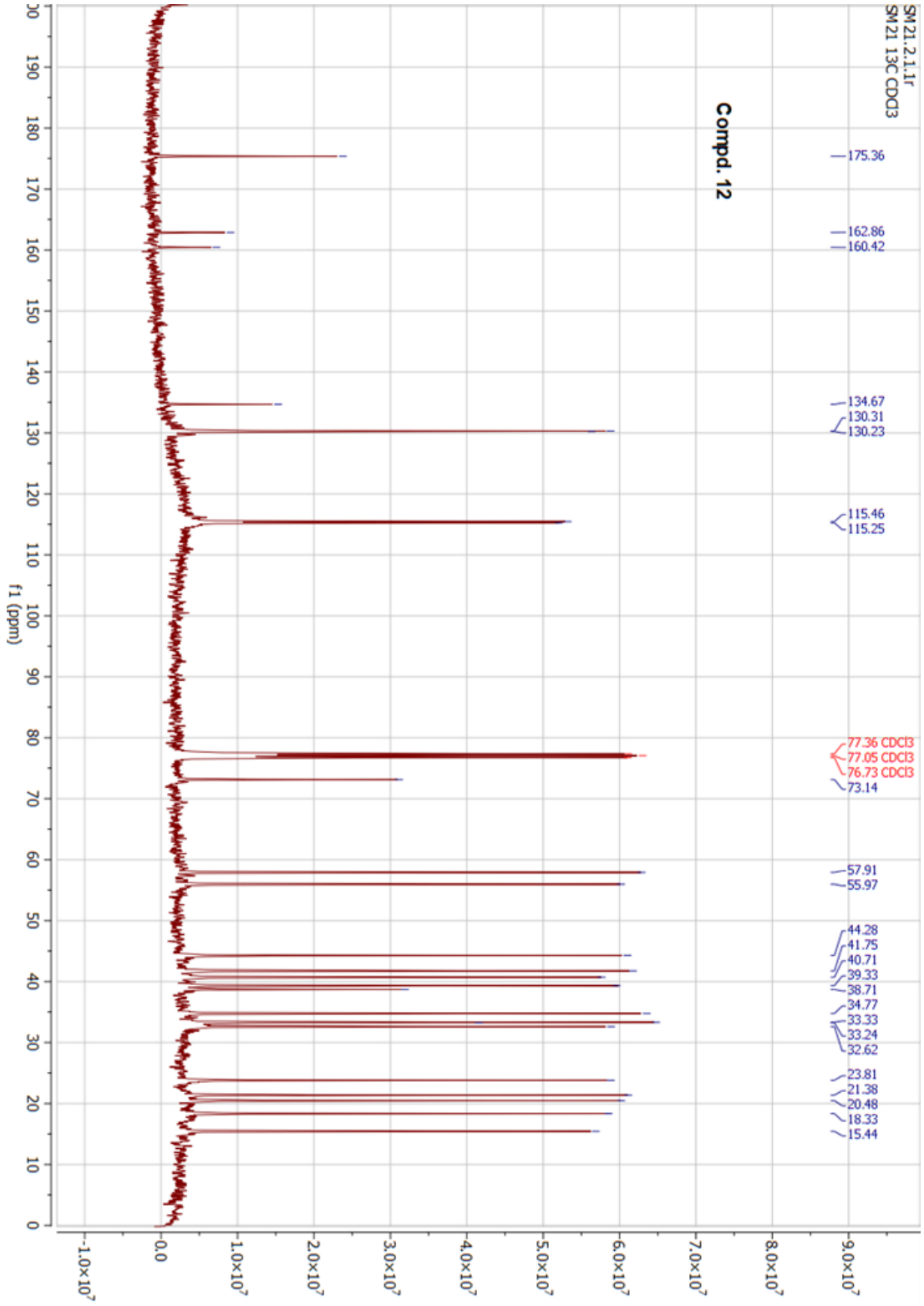

SM23.2.1.1r
SM23 DMSO 13C
174.39
139.09
131.14
131.05
128.60
71.56
Compd. 11
f1 (ppm)

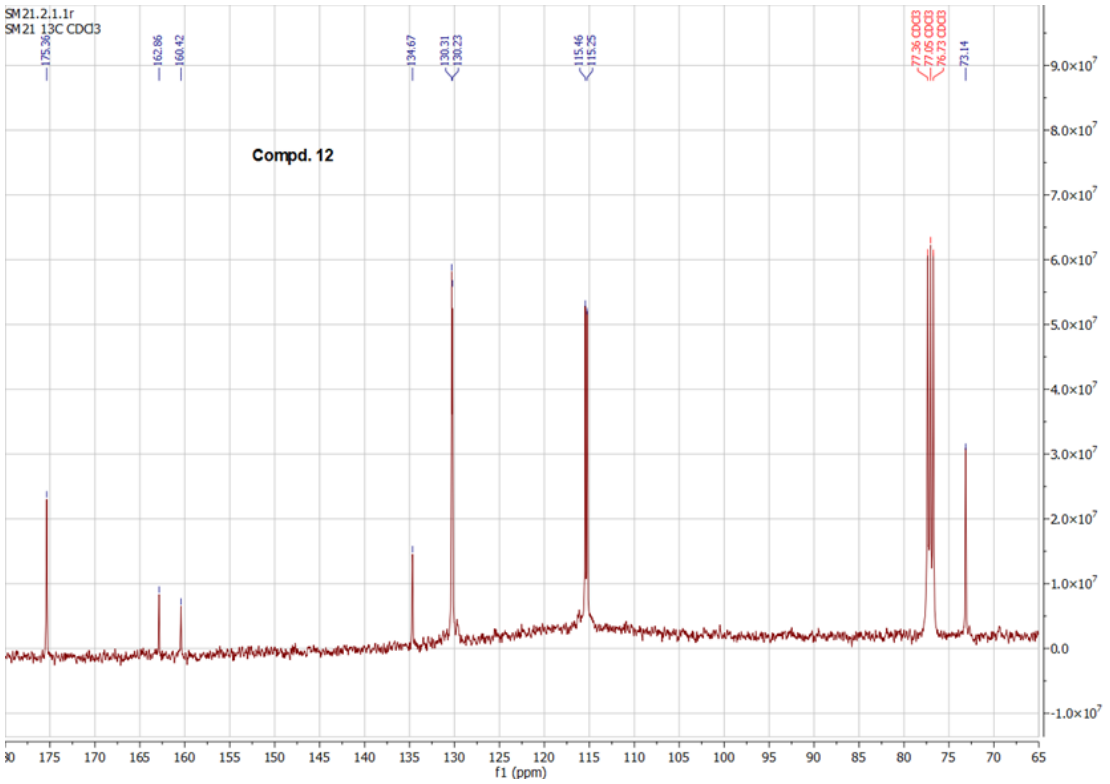

SM23.2.1.1r
SM23 DMSO 13C
56.83
56.04
44.21
42.00
40.67 DMSO
40.46 DMSO
40.25 DMSO
40.04 DMSO
39.83 DMSO
39.62 DMSO
39.41 DMSO
38.90
38.66
34.72
33.76
33.30
31.78
24.58
21.82
20.52
18.37
15.47
Compd. 11
f1 (ppm)

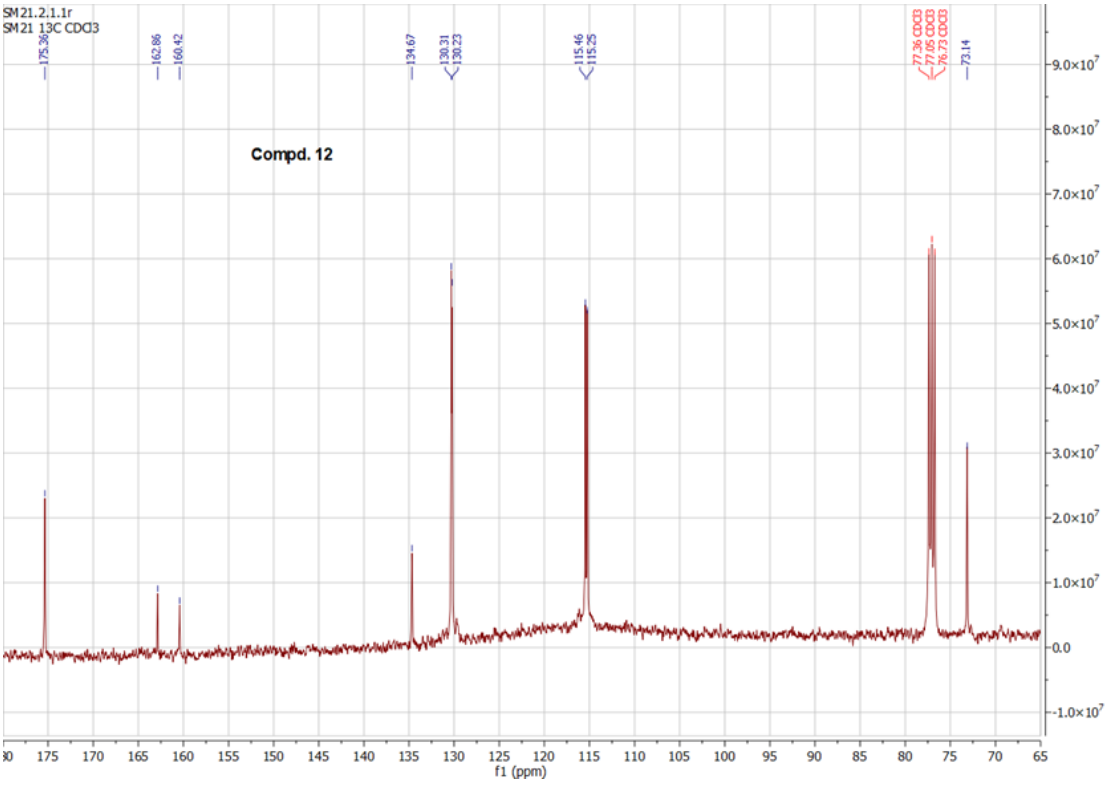

Compd. 12
f1 (ppm)
4.68
4.39
2.31
5.65
5.70
1.89
2.96
2.80
2.81
5.70
2.70
2.58
24.21
3.32
10.63
0.98
16.70


Compd. 12
f1 (ppm)


Compd. 12
f1 (ppm)


SM21.2.1.1r
SM21 13C CDCl3
Compd. 12
175.36
162.86
160.42
134.67
130.31
130.23
115.46
115.25
77.36 CDCl3
77.05 CDCl3
76.73 CDCl3
73.14
57.91
55.97
44.28
41.75
40.71
39.33
38.71
34.77
33.33
33.24
32.62
23.81
21.38
20.48
18.33
15.44
f1 (ppm)

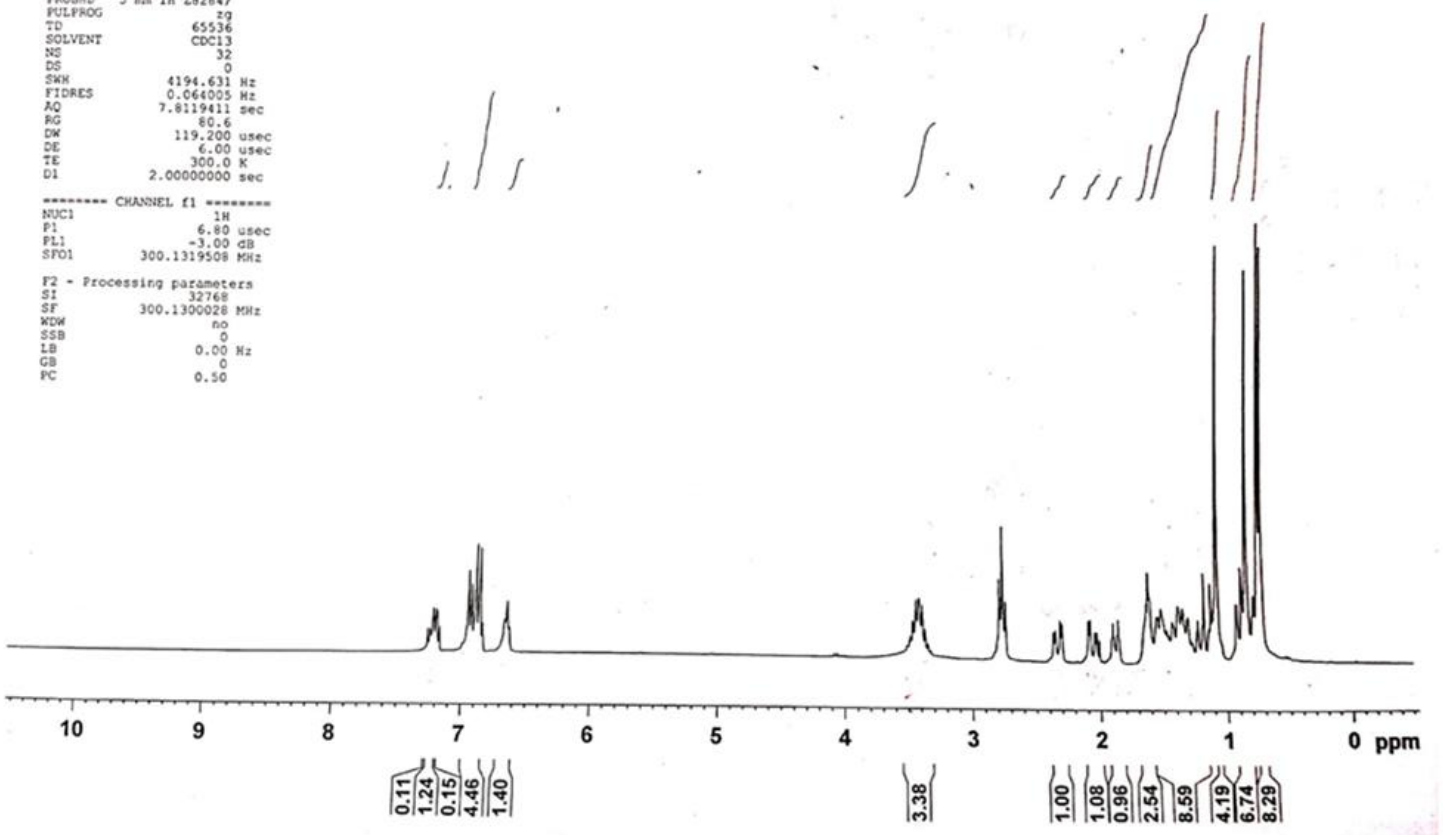

SM21.2.1.1r
SM21 13C CDCl3
175.36
162.86
160.42
134.67
130.31
130.23
115.46
115.25
77.36 CDCl3
77.05 CDCl3
76.73 CDCl3
73.14
Compd. 12
f1 (ppm)

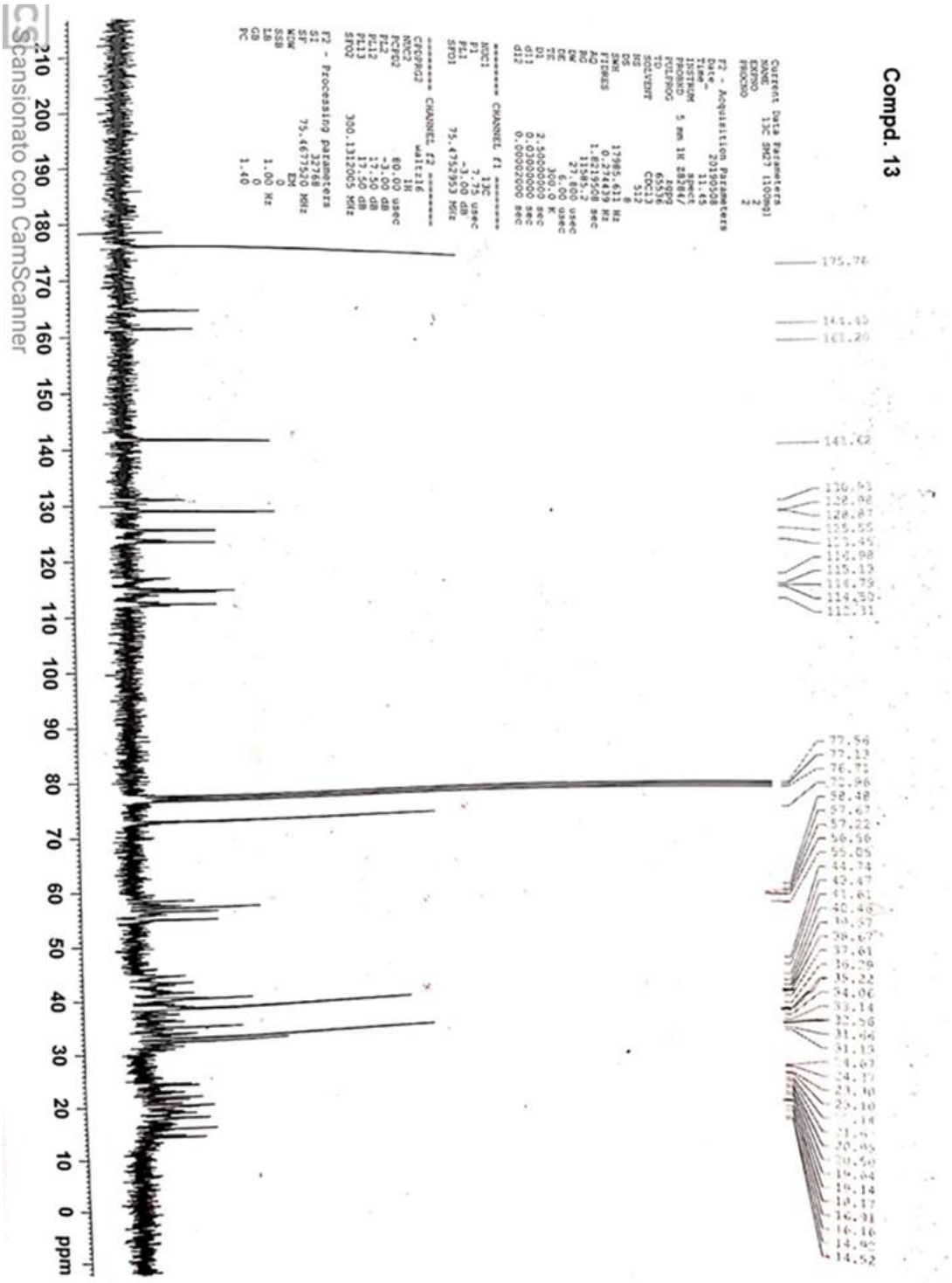

SM21.2.1.1r
SM21 13C CDCl3
175.36
162.86
160.42
134.67
130.31
130.23
115.46
115.25
77.36 CDCl3
77.05 CDCl3
76.73 CDCl3
73.14
Compd. 12
f1 (ppm)

zansionato con CamScanner

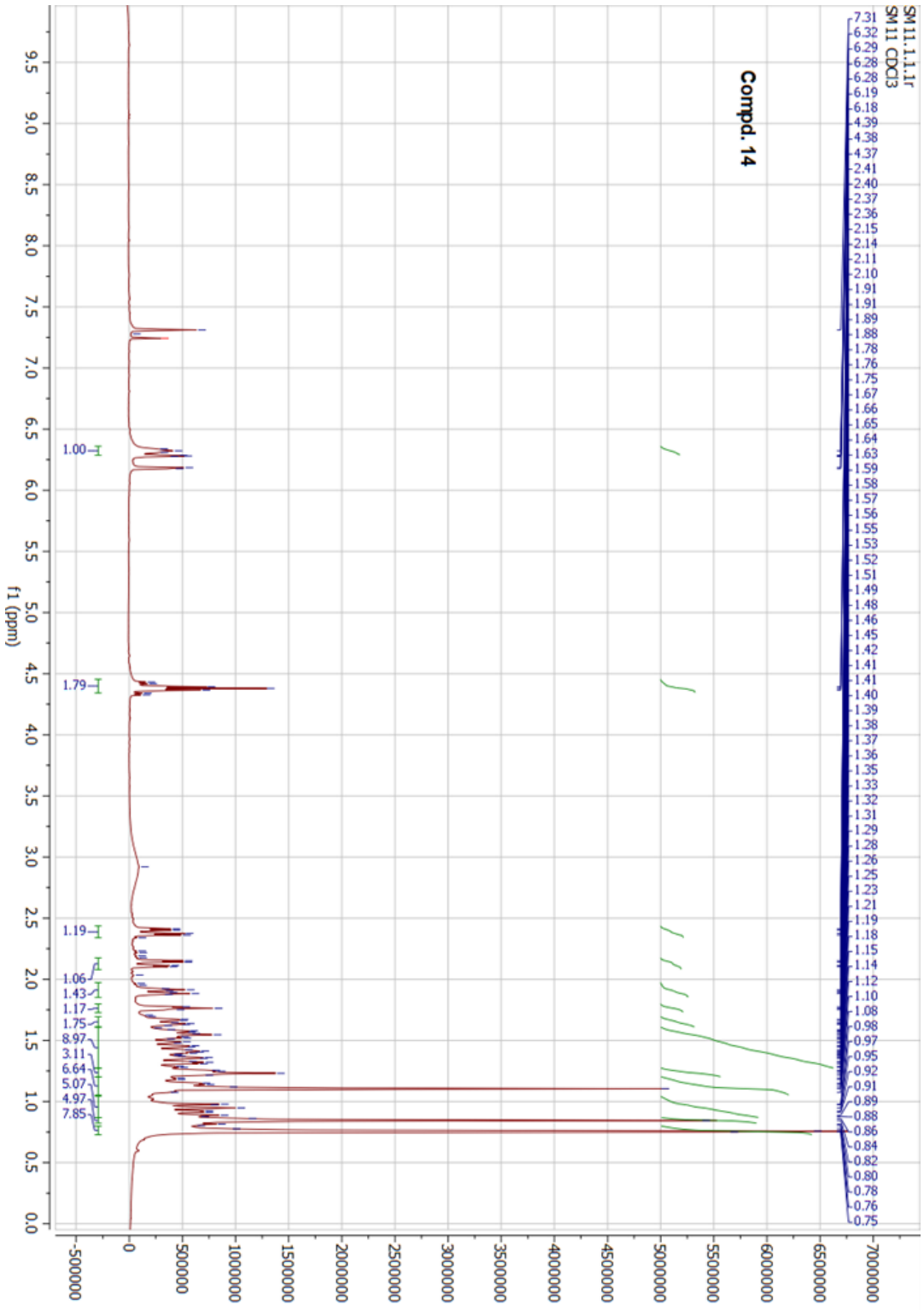
Compd. 13

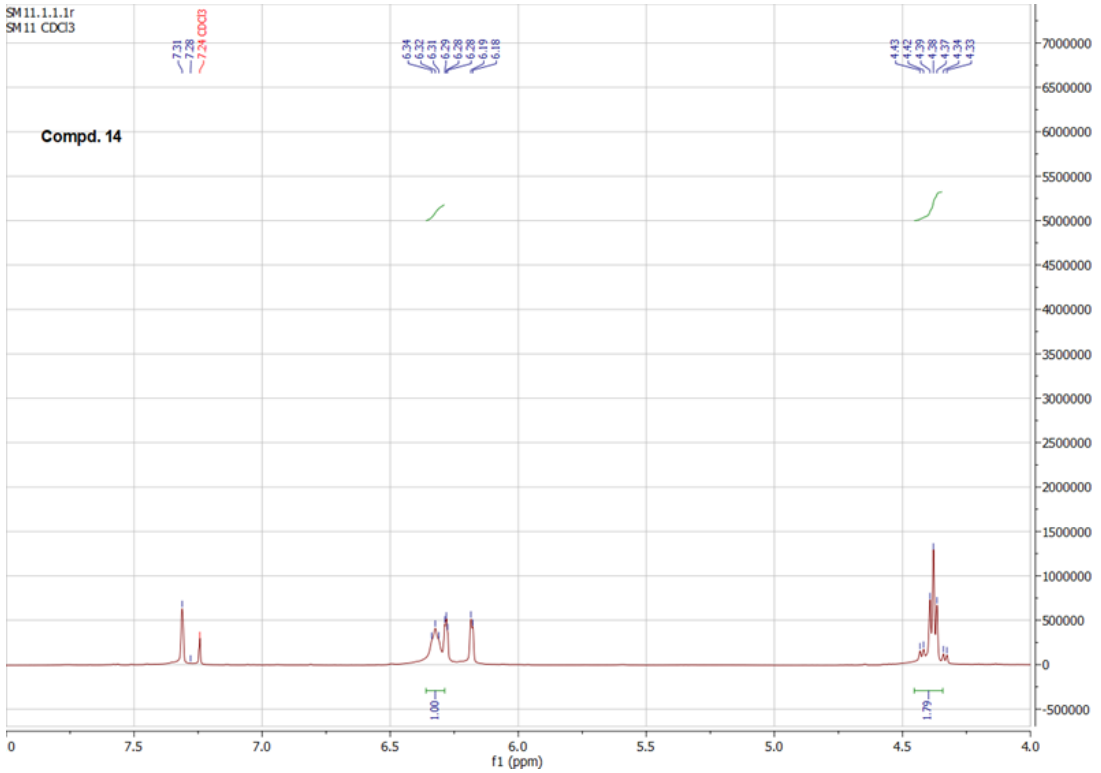
```
Current Data Parameters
NAME      SM27 100 mg CDC13
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_          20190508
Time              10.58
INSTRUM           spect
PROBHD   5 mm 1H Z8284/
PULPROG             zg
TD                65536
SOLVENT           CDC13
NS                   32
DS                    0
SWH            4194.631 Hz
FIDRES         0.064005 Hz
AQ             7.8119411 sec
RG                 80.6
DW               119.200 usec
DE                 6.00 usec
TE               300.0 K
D1            2.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                6.80 usec
PL1              -3.00 dB
SFO1        300.1319508 MHz

F2 - Processing parameters
SI                32768
SF          300.1300028 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 0.50
```

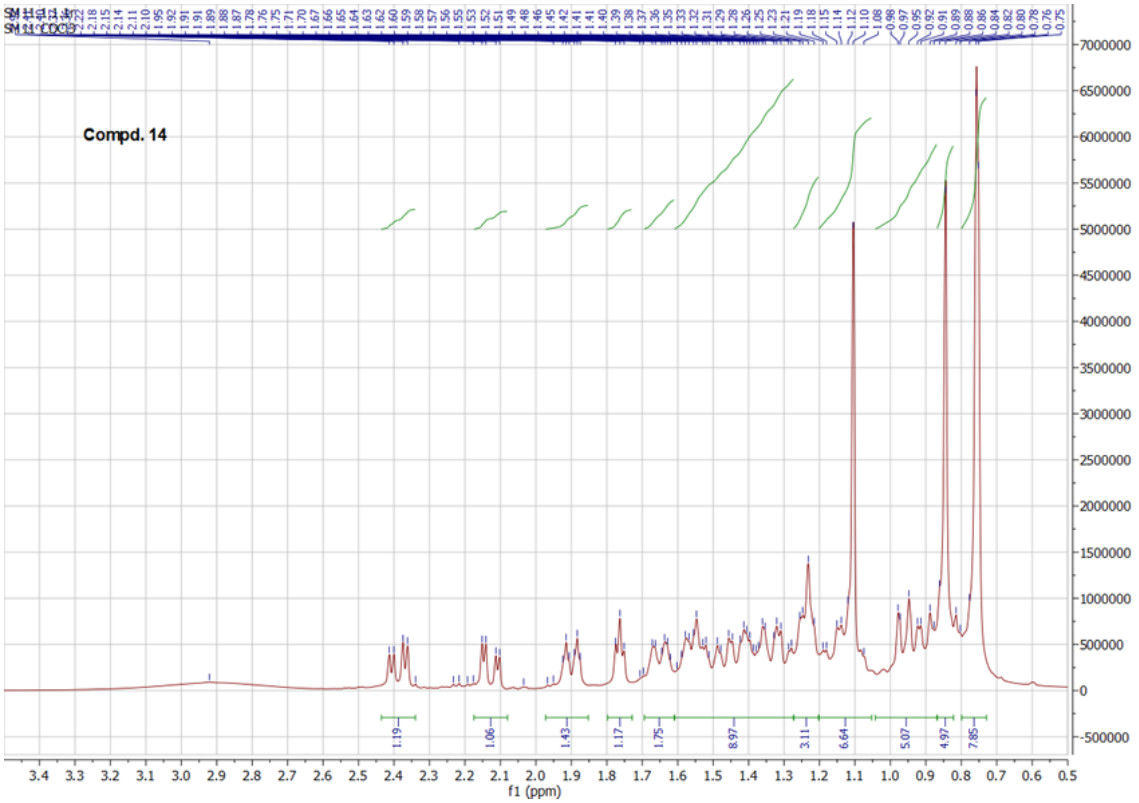


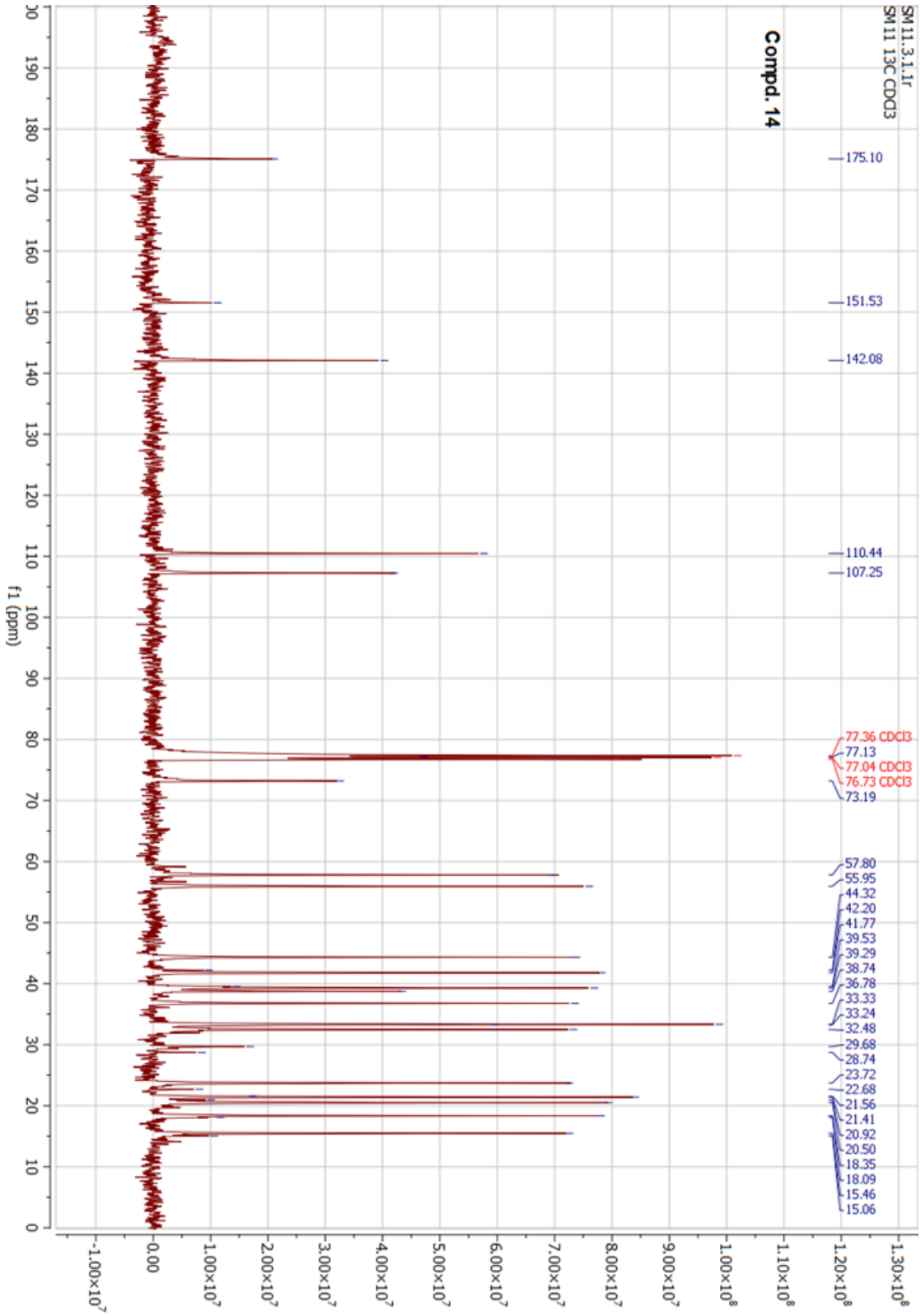


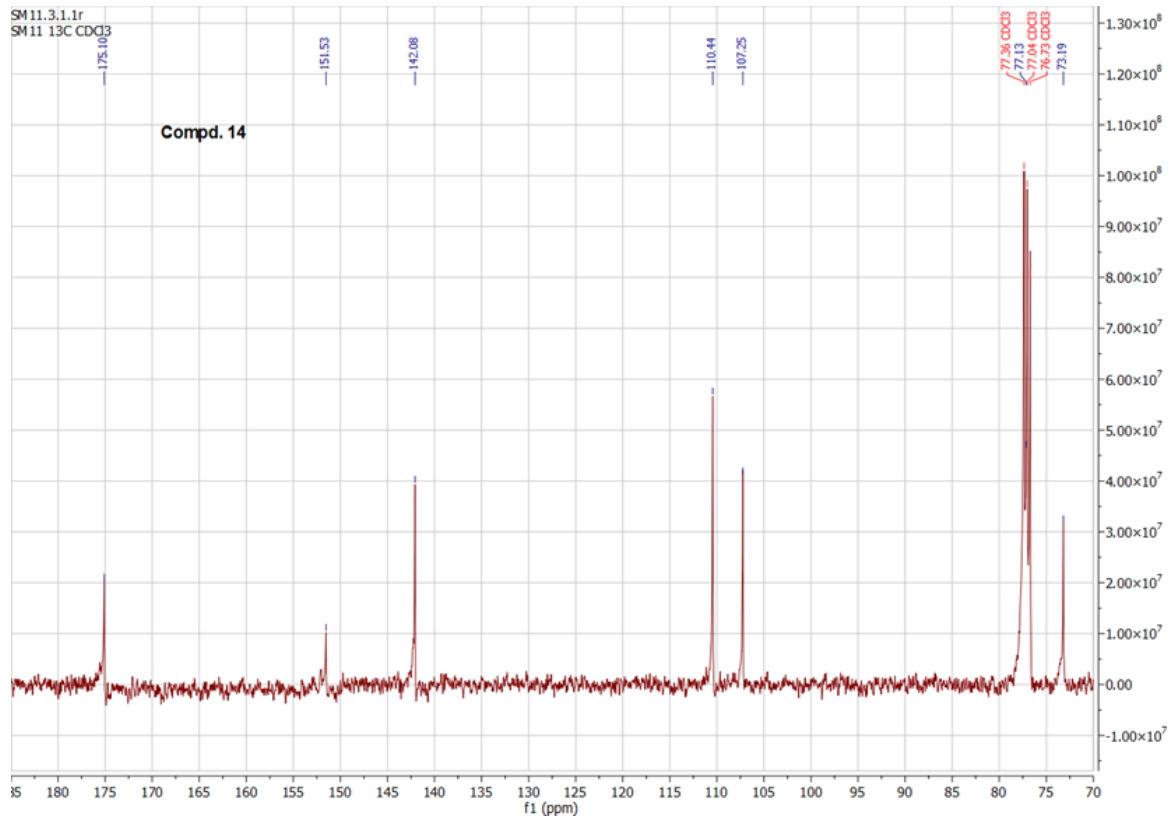
CS Scansionato con CamScanner

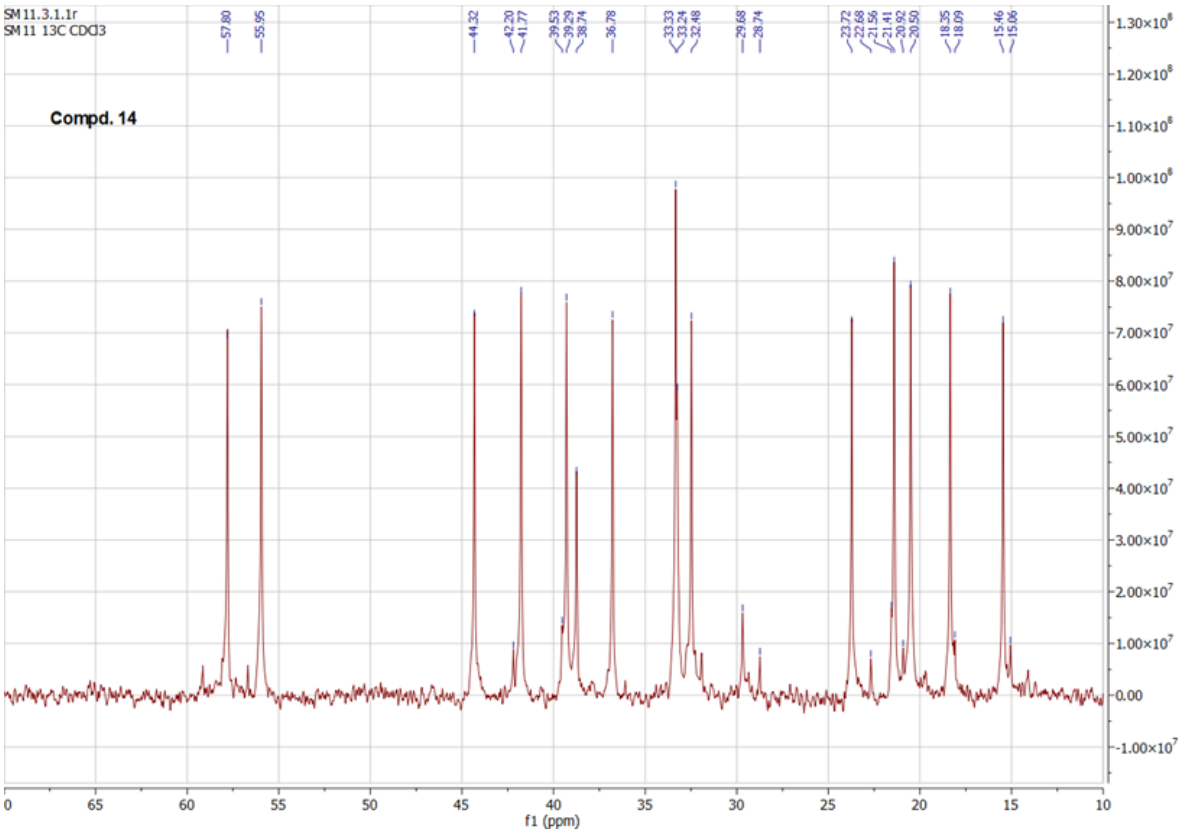

SM11.1.1.1r
SM11 CDCl3
Compd. 14
f1 (ppm)
1.00
1.79
1.19
1.06
1.43
1.17
1.75
8.97
3.11
6.64
5.07
4.97
7.85


SM11.1.1.1r
SM11 CDCl3
Compd. 14
f1 (ppm)


Compd. 14
f1 (ppm)

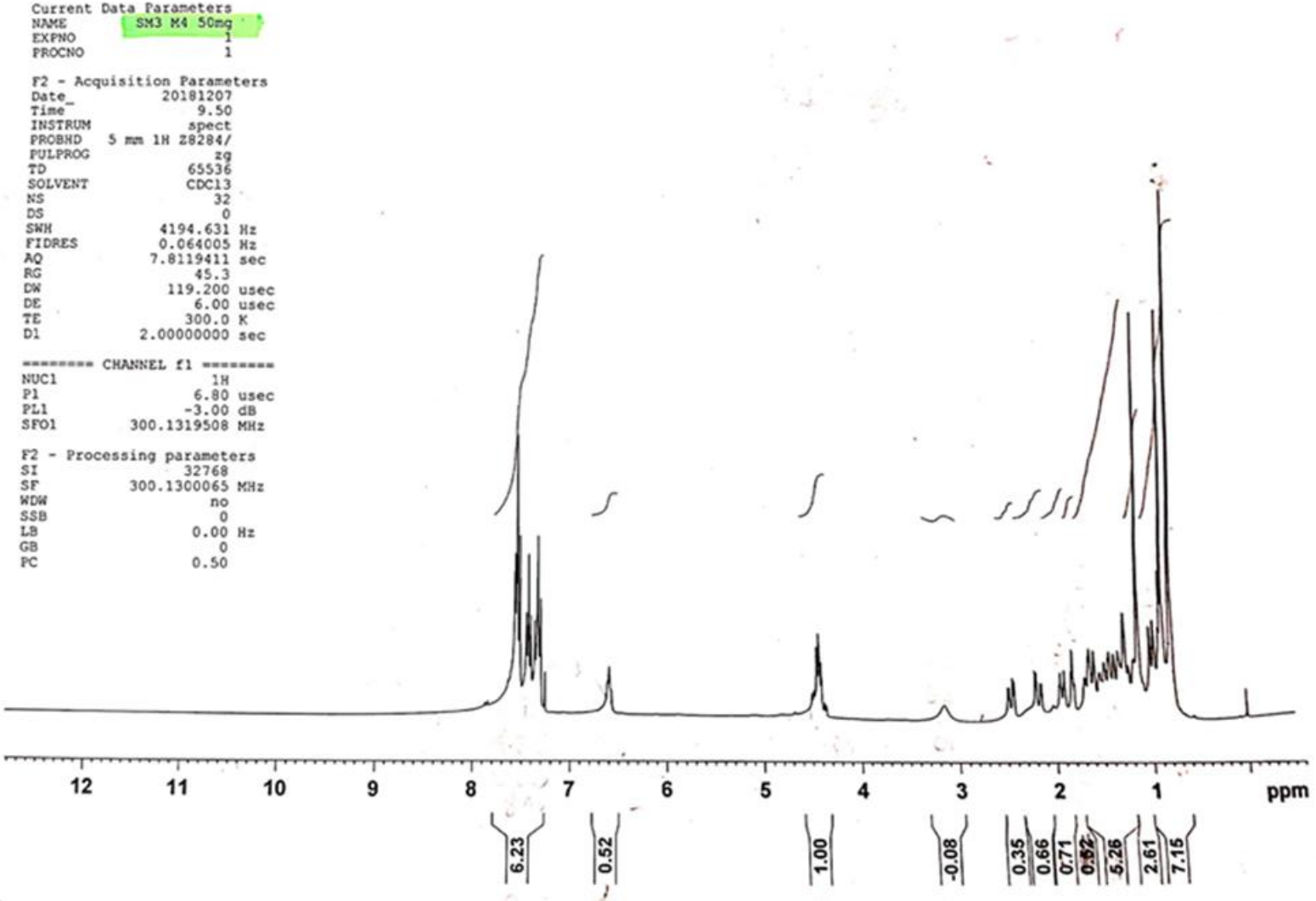

SM11.3.1.1r
SM11 13C CDCl3
Compd. 14
175.10
151.53
142.08
110.44
107.25
77.36 CDCl3
77.13
77.04 CDCl3
76.73 CDCl3
73.19
57.80
55.95
44.32
42.20
41.77
39.53
39.29
38.74
36.78
33.33
33.24
32.48
29.68
28.74
23.72
22.68
21.56
21.41
20.92
20.50
18.35
18.09
15.46
15.06
f1 (ppm)

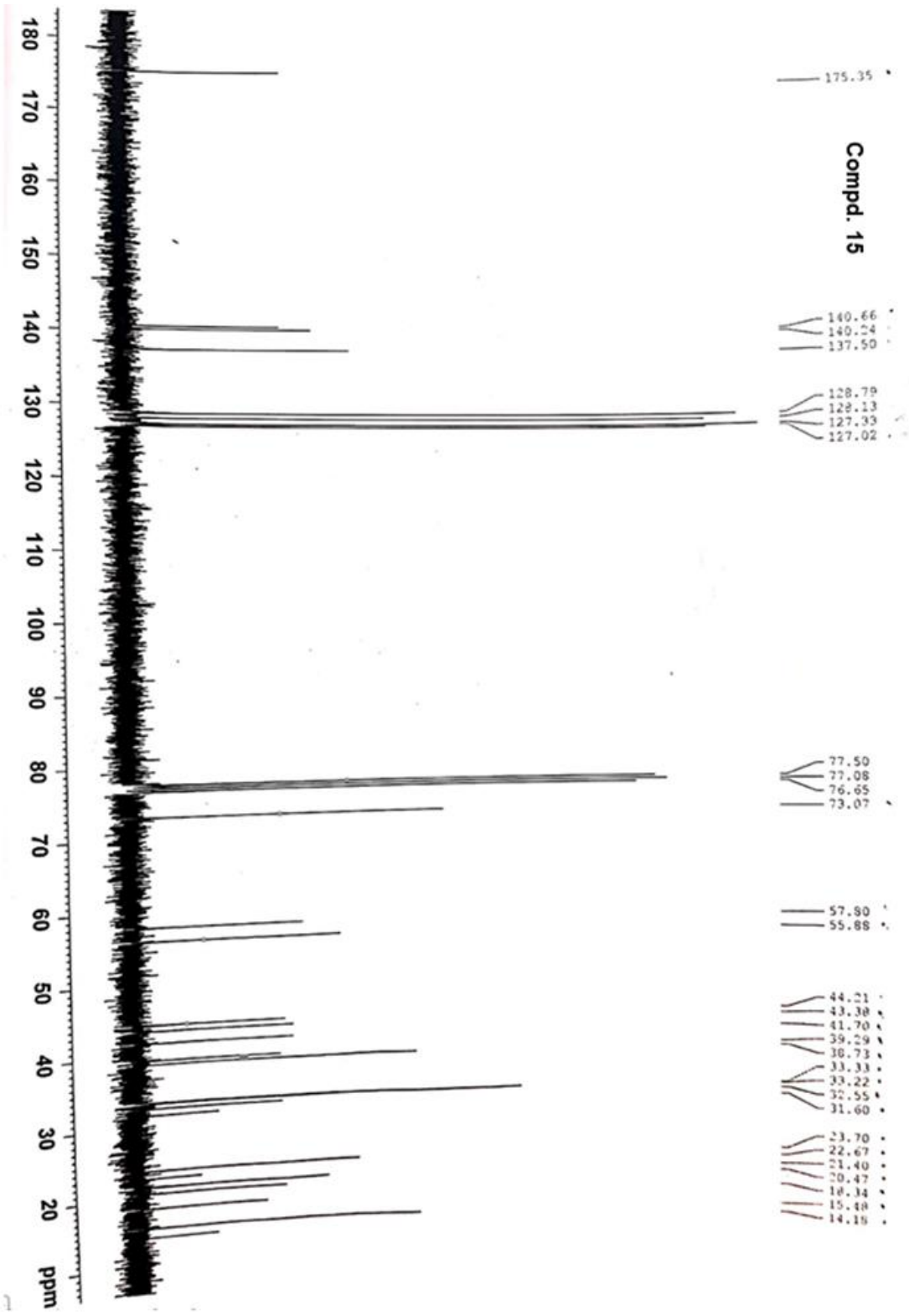

SM11.3.1.1r
SM11 13C CDCl3
175.10
151.53
142.08
110.44
107.25
77.36 CDCl3
77.13
77.04 CDCl3
76.73 CDCl3
73.19
Compd. 14
f1 (ppm)

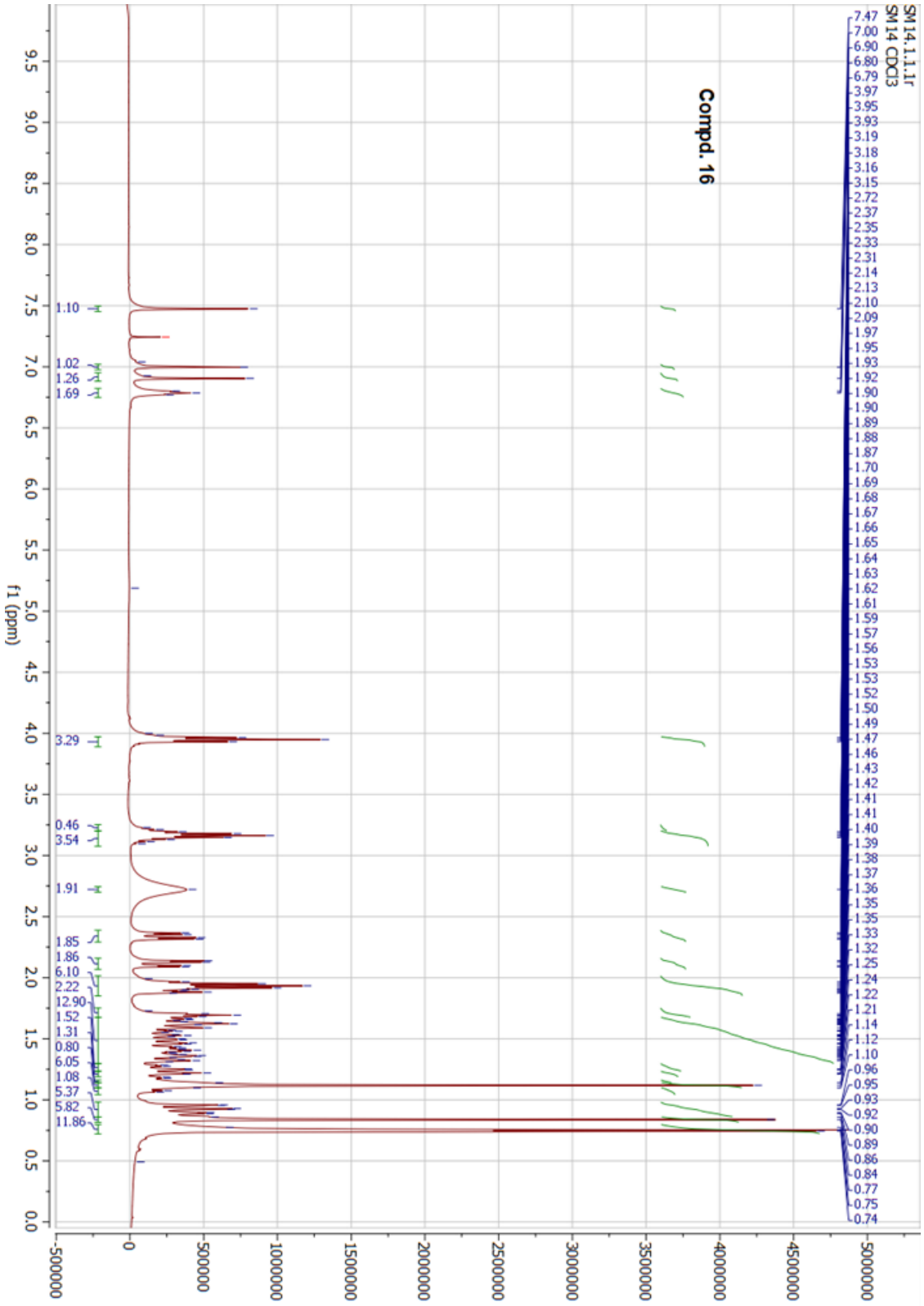

SM11.3.1.1r
SM11 13C CDCl3
57.80
55.95
44.32
42.20
41.77
39.53
39.29
38.74
36.78
33.33
33.24
32.48
29.68
28.74
23.72
22.68
21.56
21.41
20.92
20.50
18.35
18.09
15.46
15.06
Compd. 14
f1 (ppm)

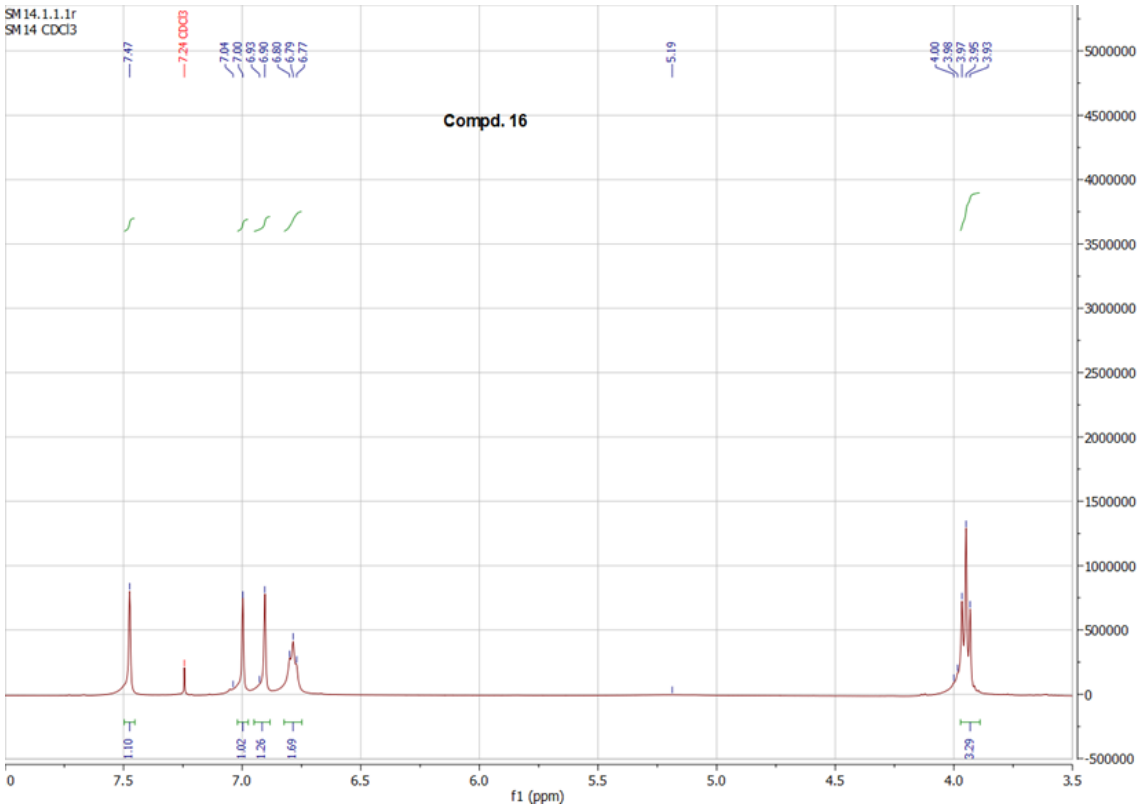
Compd. 15

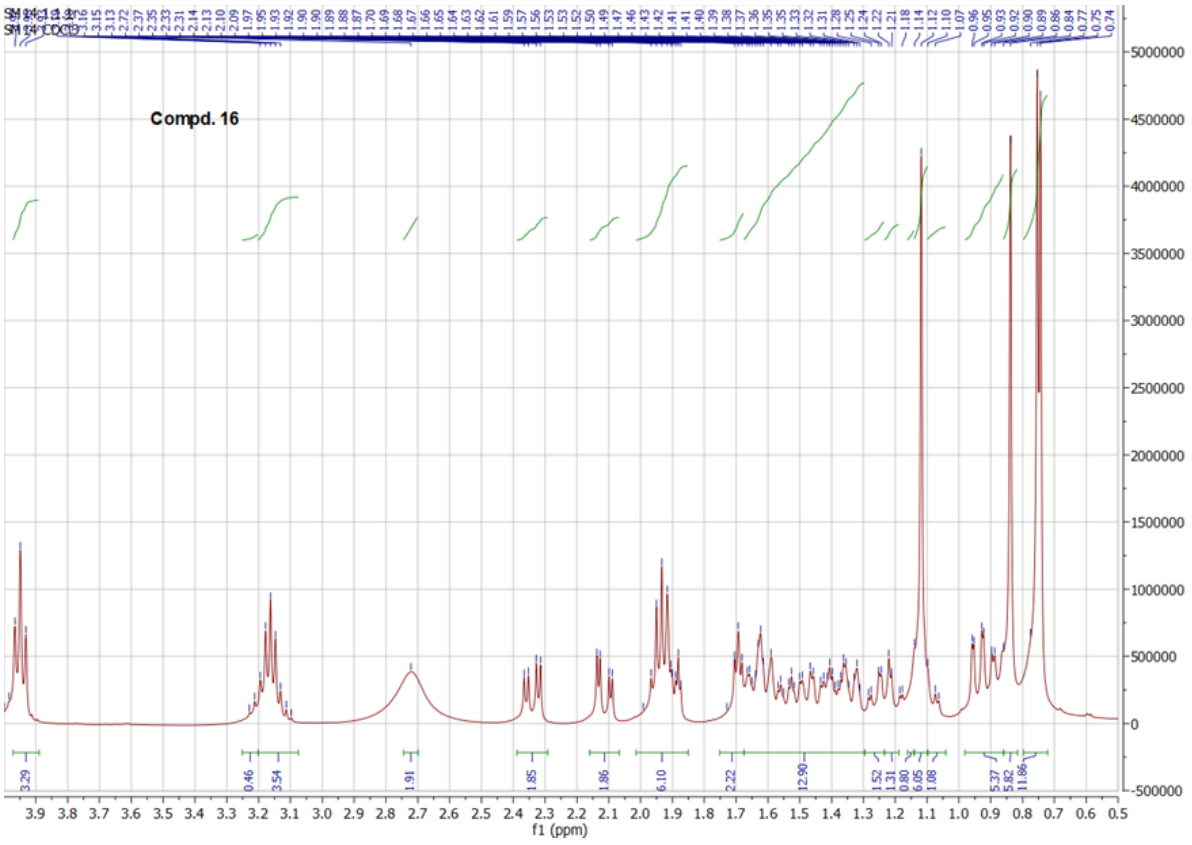
```
Current Data Parameters
NAME          SM3 M4 50mg
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_          20181207
Time               9.50
INSTRUM           spect
PROBHD   5 mm 1H Z8284/
PULPROG             zg
TD                65536
SOLVENT           CDCl3
NS                   32
DS                    0
SWH           4194.631 Hz
FIDRES        0.064005 Hz
AQ            7.8119411 sec
RG                45.3
DW             119.200 usec
DE               6.00 usec
TE              300.0 K
D1           2.00000000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                6.80 usec
PL1              -3.00 dB
SFO1        300.1319508 MHz

F2 - Processing parameters
SI                32768
SF          300.1300065 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 0.50
```

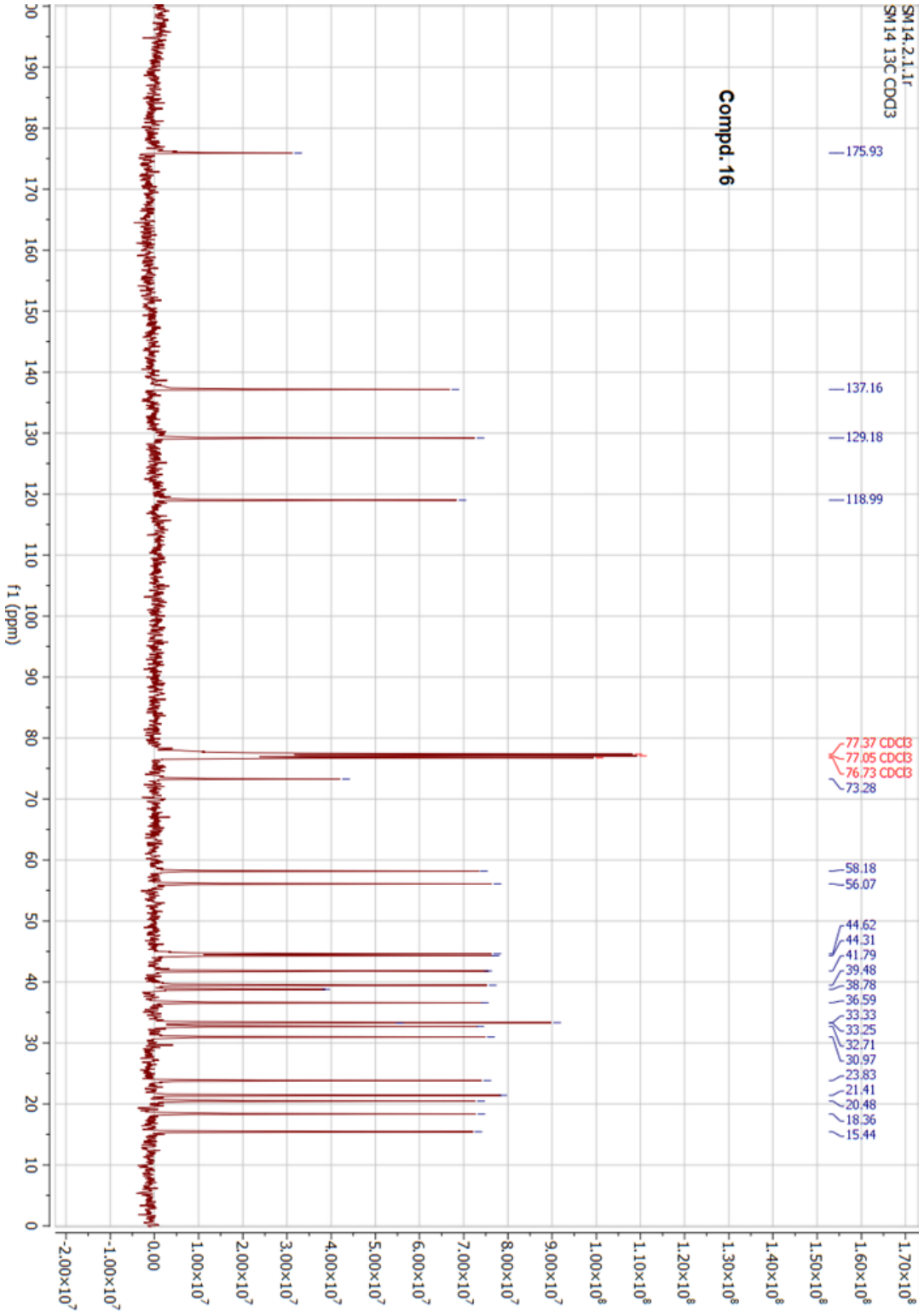


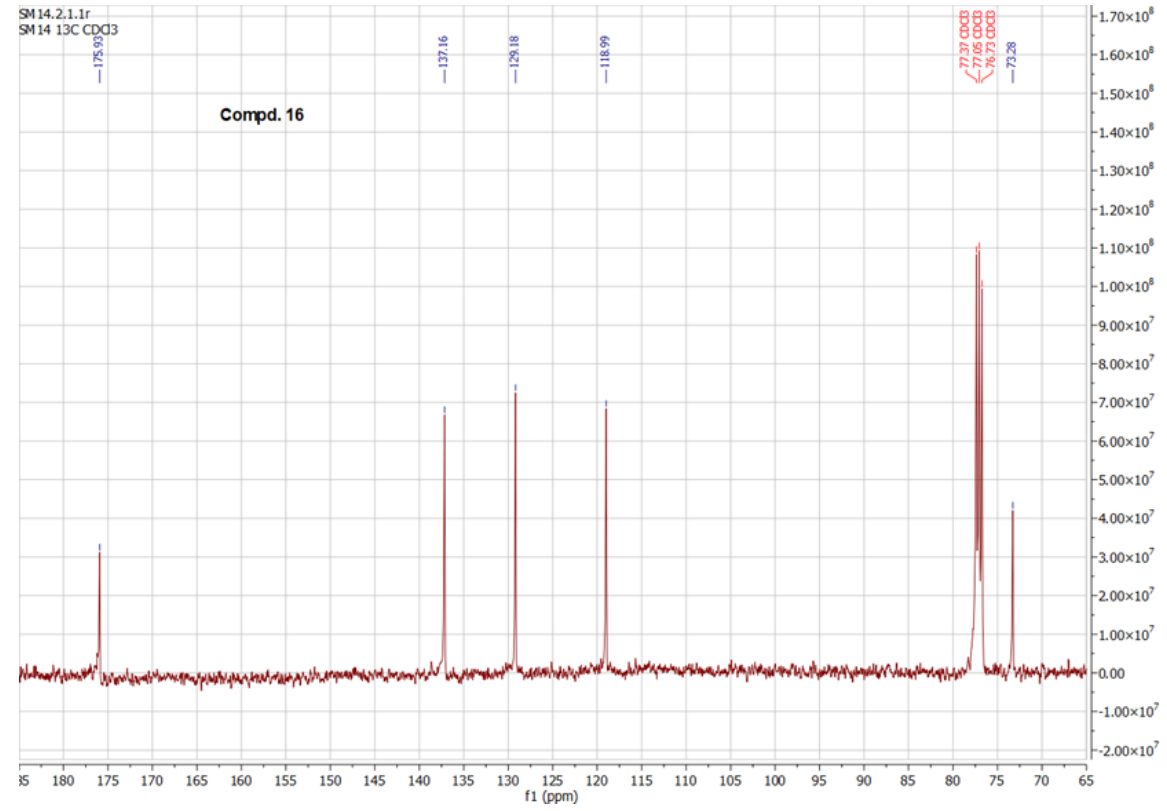

Compd. 15
175.35
140.66
140.24
137.50
128.79
128.13
127.33
127.02
77.50
77.08
76.65
73.07
57.80
55.88
44.21
43.38
41.70
39.29
38.73
33.33
33.22
32.55
31.60
23.70
22.67
21.40
20.47
14.34
13.48
14.15
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

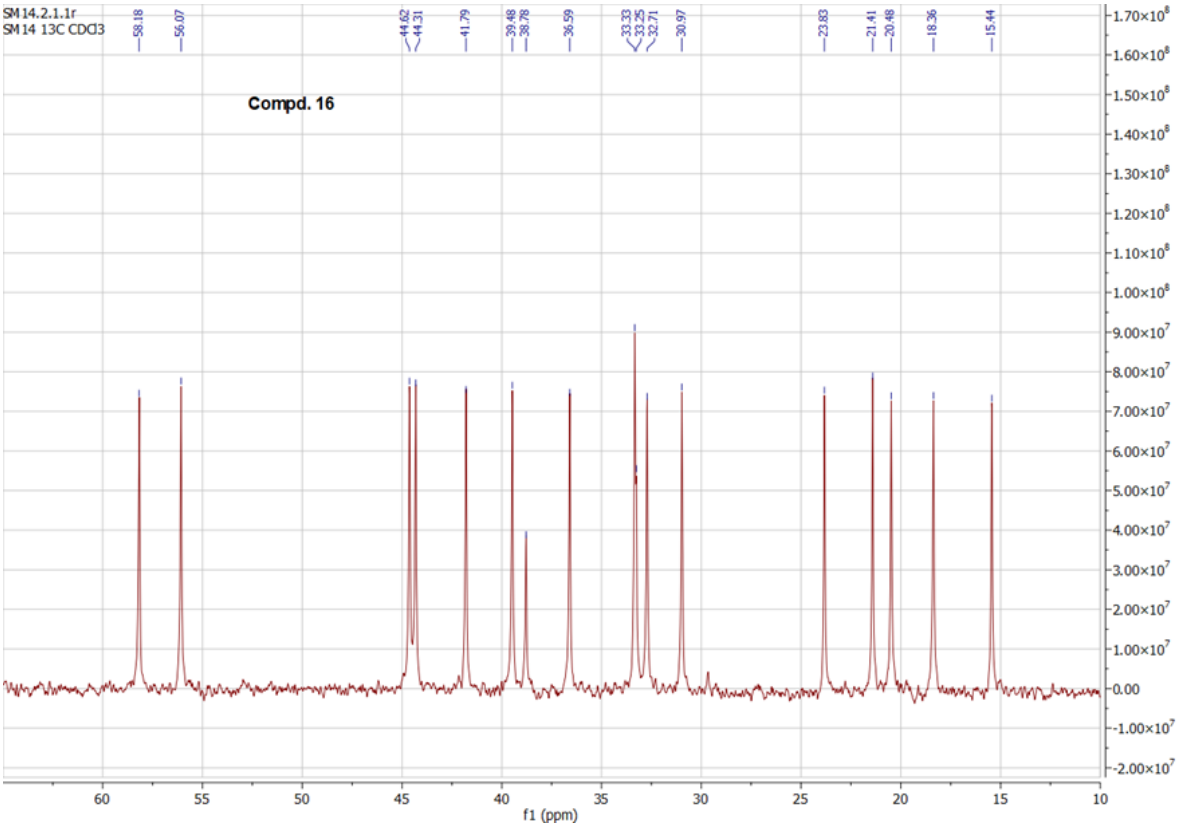

SM14.1.1.1r
SM14 CDCl3
Compd. 16
f1 (ppm)

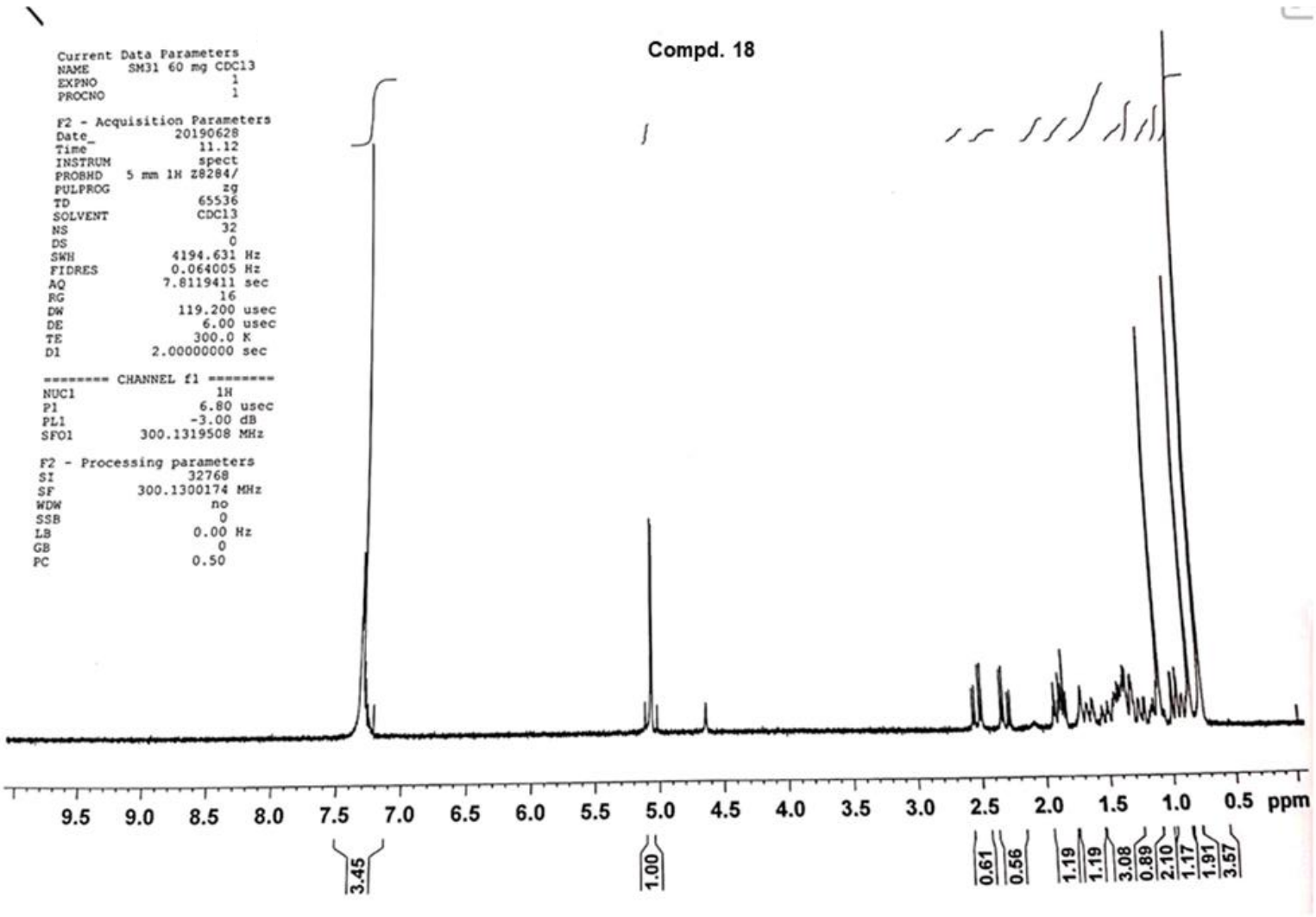

SM14.1.1.1r
SM14 CDCl3
Compd. 16
f1 (ppm)

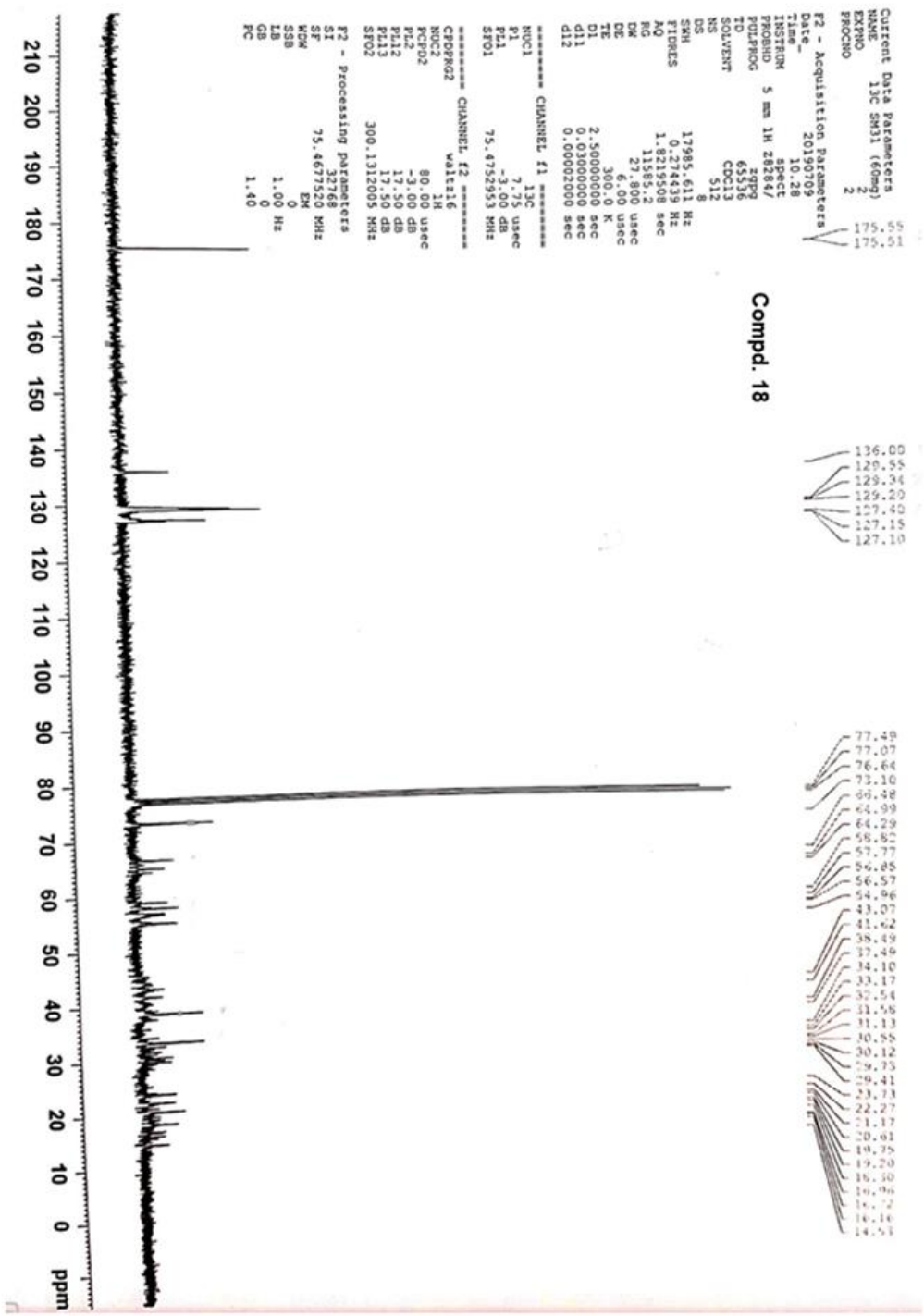

Compd. 16
f1 (ppm)

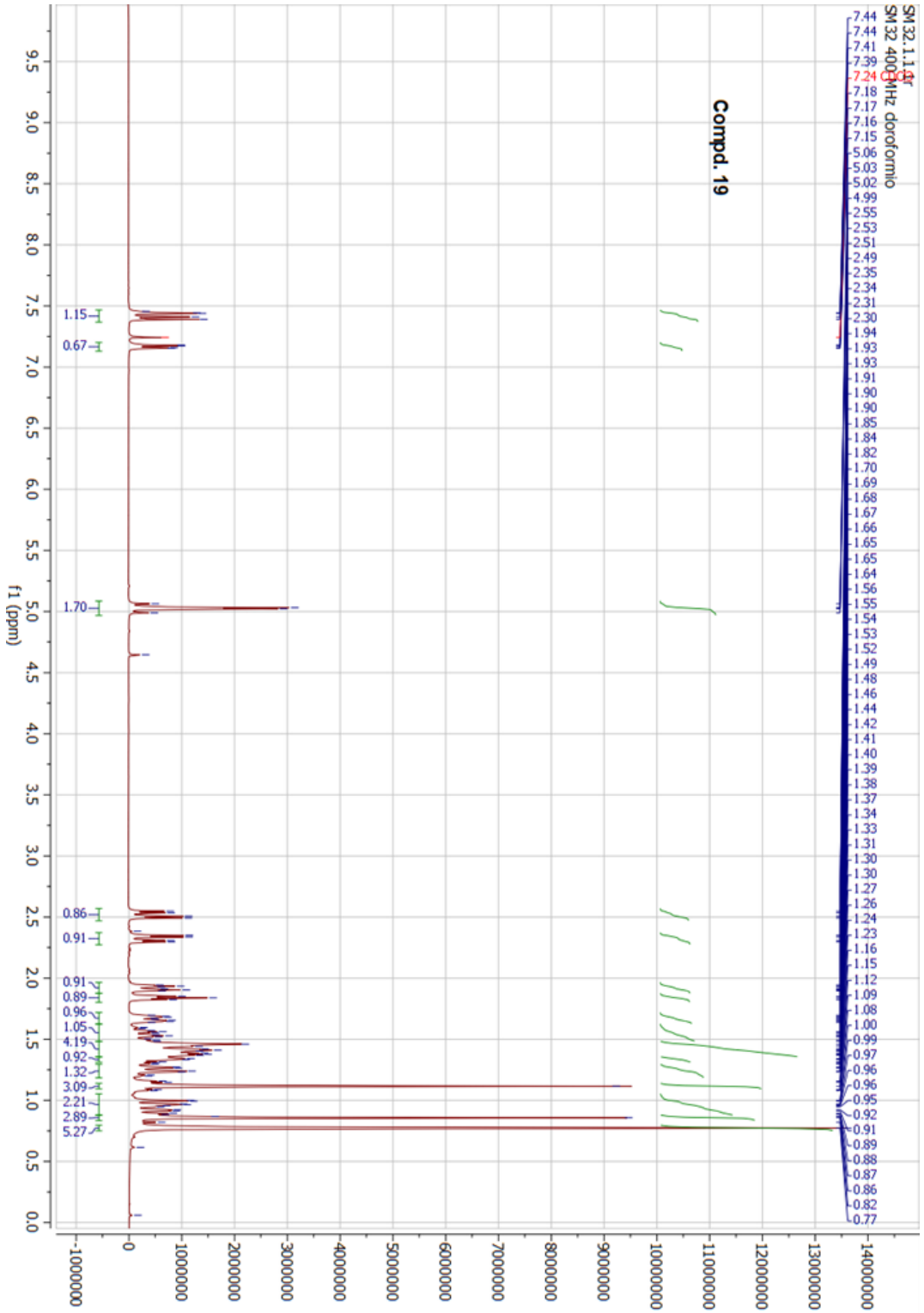

SM14.2.1.1r
SM14 13C CDCl3
Compd. 16
175.93
137.16
129.18
118.99
77.37 CDCl3
77.05 CDCl3
76.73 CDCl3
73.28
58.18
56.07
44.62
44.31
41.79
39.48
38.78
36.59
33.33
33.25
32.71
30.97
23.83
21.41
20.48
18.36
15.44
f1 (ppm)

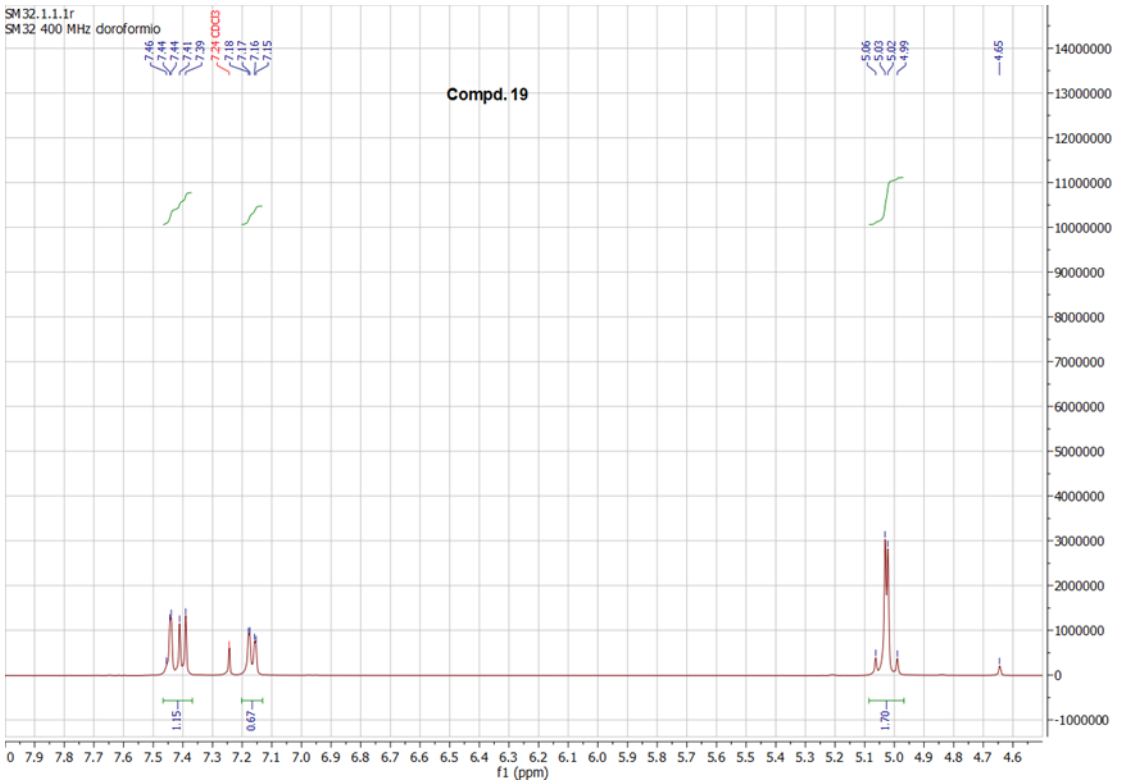

SM14.2.1.1r
SM14 13C CDCl3
Compd. 16
175.93
137.16
129.18
118.99
77.37 CDCl3
77.05 CDCl3
76.73 CDCl3
73.28
f1 (ppm)

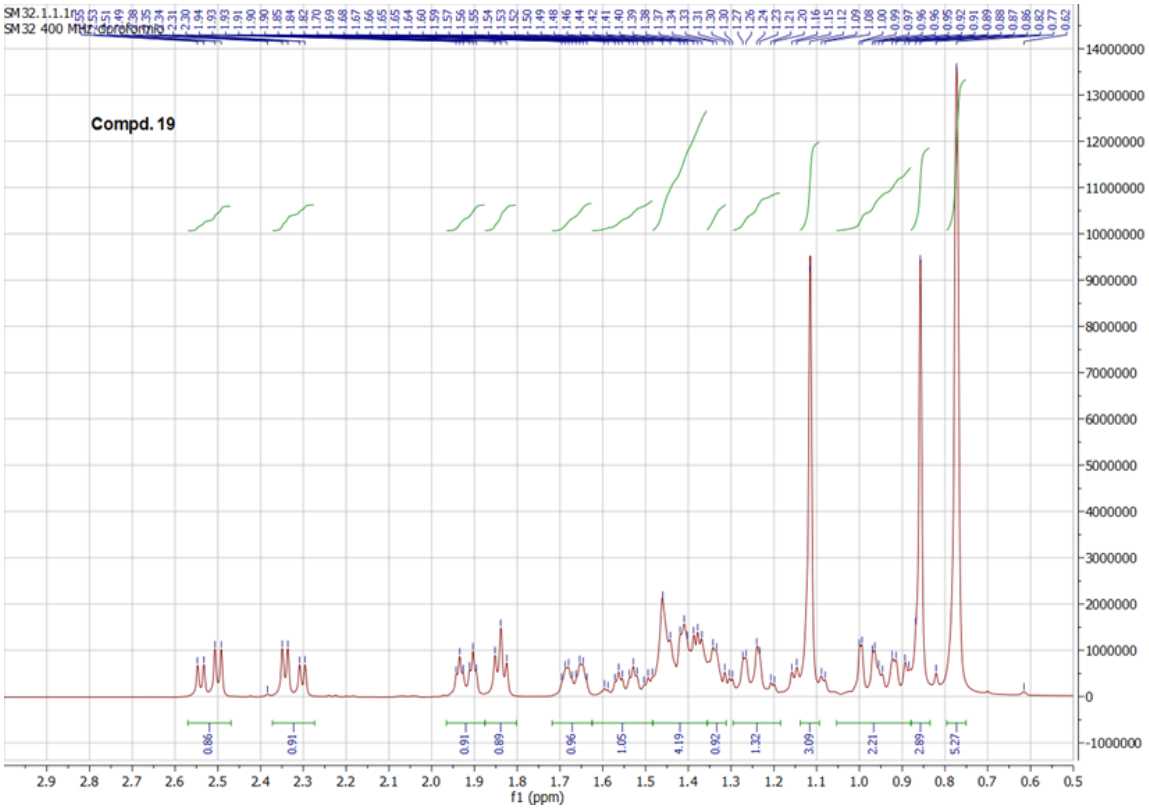

SM14.2.1.1r
SM14 13C CDCl3
Compd. 16
58.18
56.07
44.62
44.31
41.79
39.48
38.78
36.59
33.33
33.25
32.71
30.97
23.83
21.41
20.48
18.36
15.44
f1 (ppm)

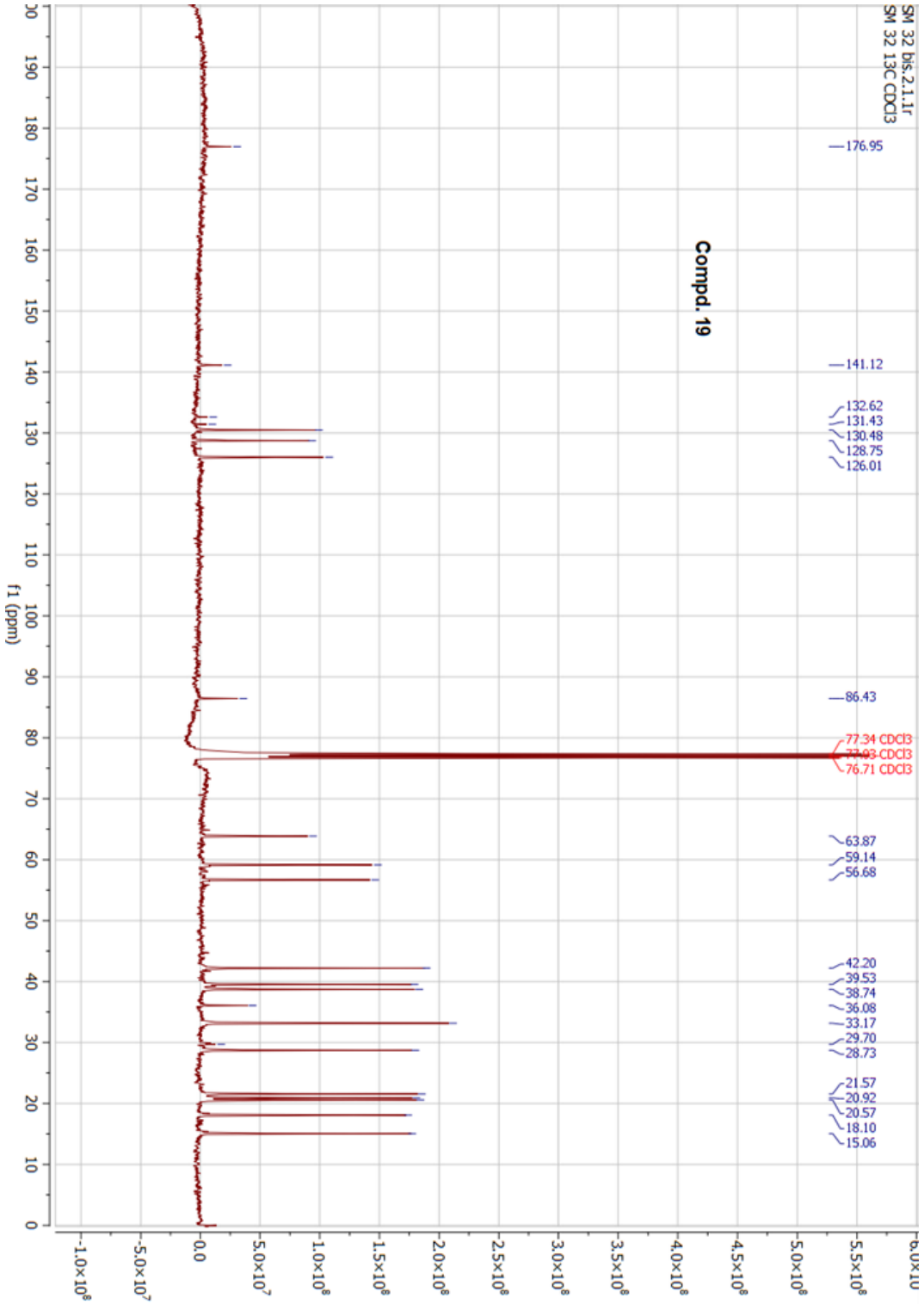

Compd. 18
Current Data Parameters
NAME SM31 60 mg CDCl3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190628
Time 11.12
INSTRUM spect
PROBHD 5 mm 1H Z8284/
PULPROG zg
TD 65536
SOLVENT CDCl3
NS 32
DS 0
SWH 4194.631 Hz
FIDRES 0.064005 Hz
AQ 7.8119411 sec
RG 16
DW 119.200 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 6.80 usec
PL1 -3.00 dB
SFO1 300.1319508 MHz
F2 - Processing parameters
SI 32768
SF 300.1300174 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 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 ppm
3.45
1.00
0.61
0.56
1.19
1.19
3.08
0.89
2.10
1.17
1.91
3.57

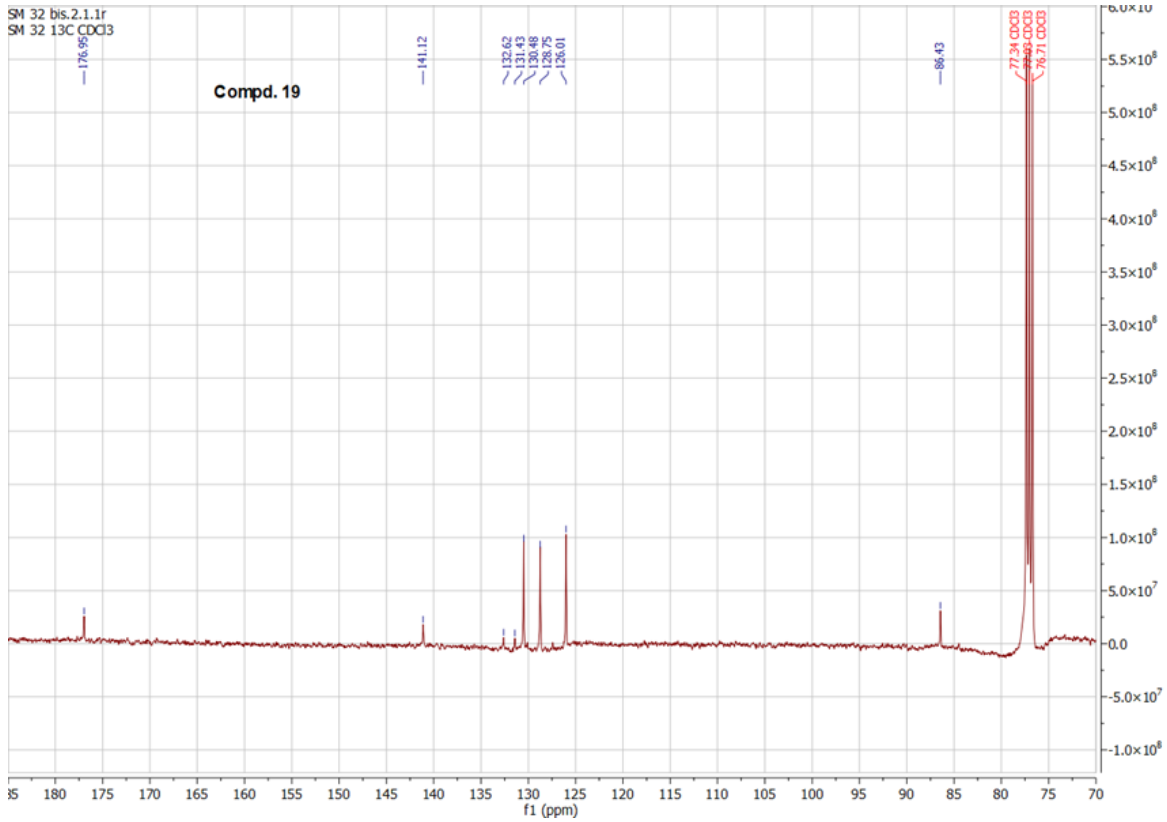

Compd. 18
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

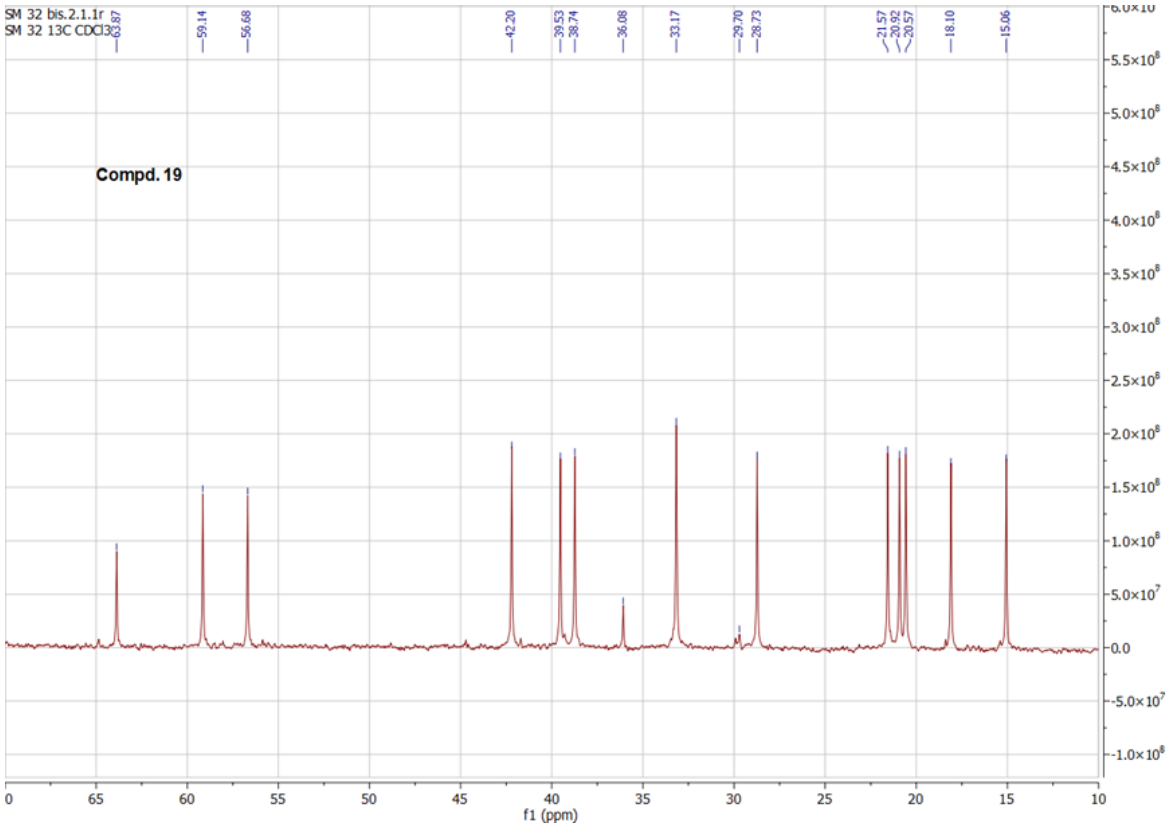

Compd. 19
SM 32.1.1.ser
SM 32 400MHz doroformio
f1 (ppm)
1.15
0.67
1.70
0.86
0.91
0.91
0.89
0.96
1.05
4.19
0.92
1.32
3.09
2.21
2.89
5.27

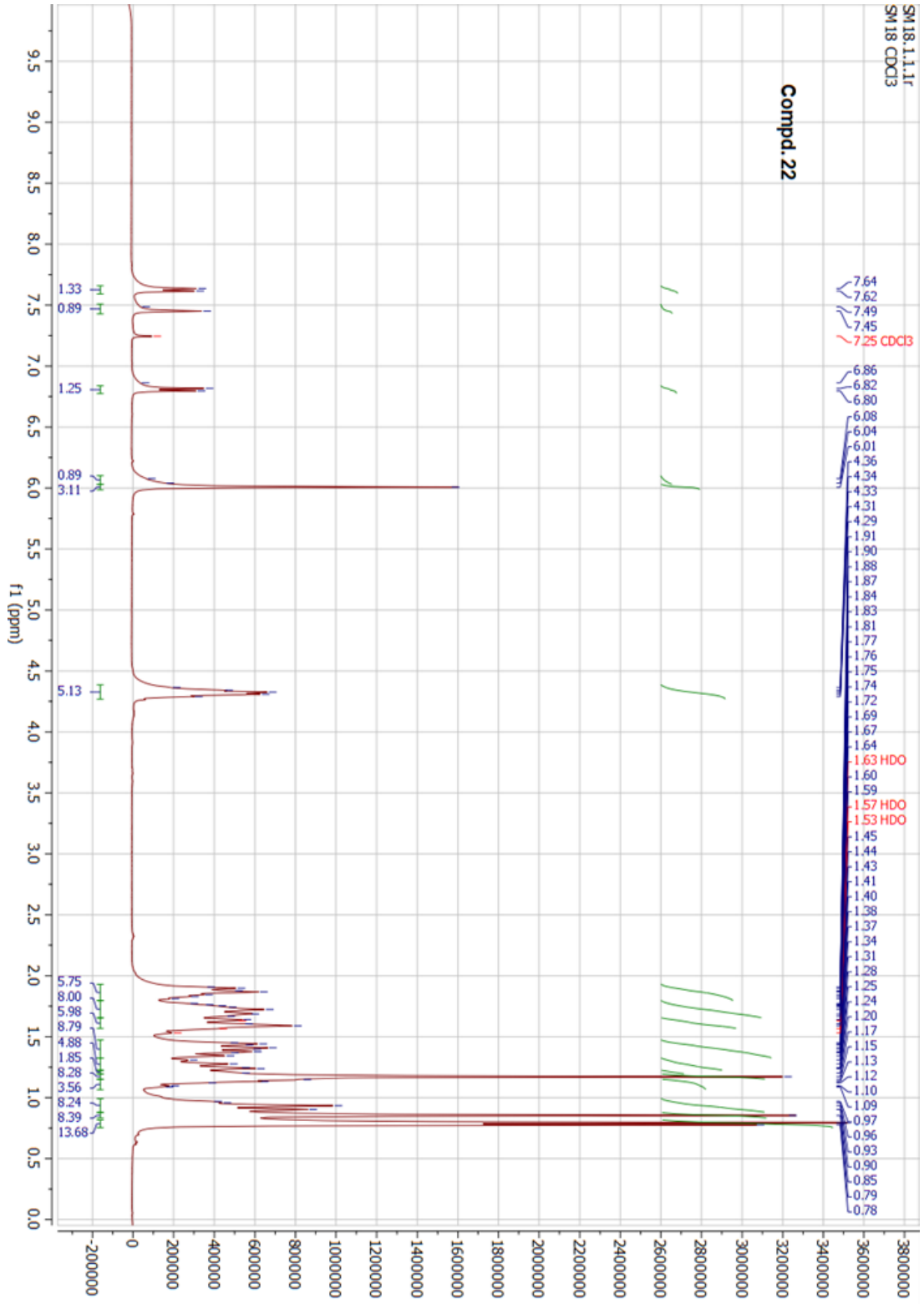

SM32.1.1.1r
SM32 400 MHz doroformio
Compd. 19
f1 (ppm)

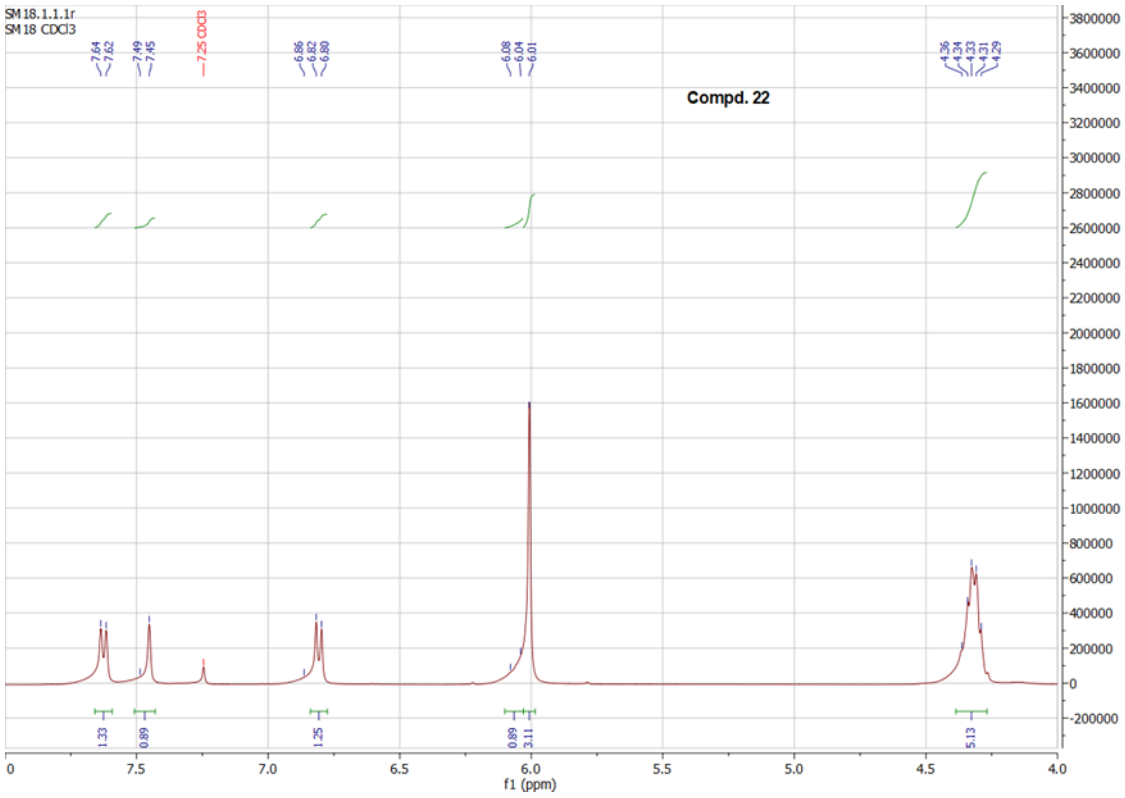

SM32.1.1.1r
SM32 400 MHz doroformio
Compd. 19
f1 (ppm)

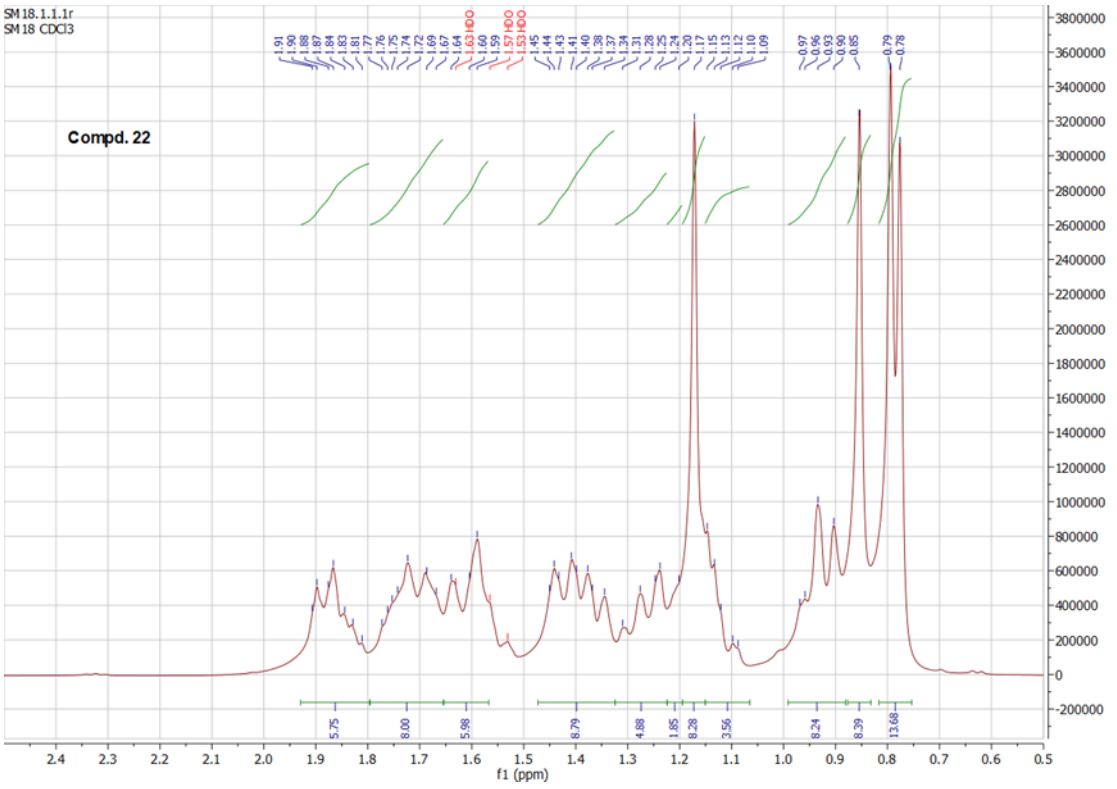

SM 32 bis.2.1.1r
SM 32 13C CDCl3
Compd. 19
176.95
141.12
132.62
131.43
130.48
128.75
126.01
86.43
77.34 CDCl3
77.03 CDCl3
76.71 CDCl3
63.87
59.14
56.68
42.20
39.53
38.74
36.08
33.17
29.70
28.73
21.57
20.92
20.57
18.10
15.06
f1 (ppm)

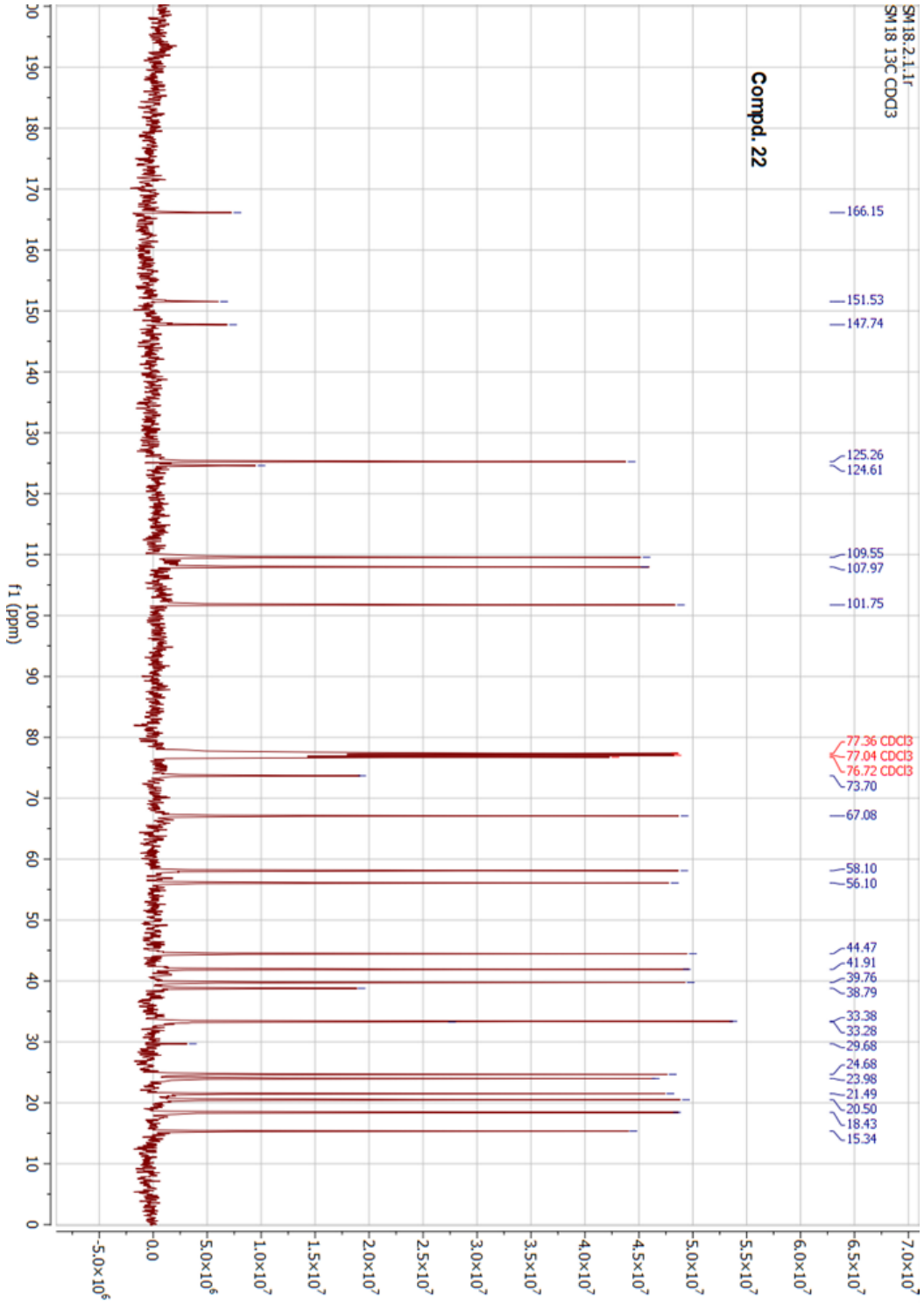

SM 32 bis.2.1.1r
SM 32 13C CDCl3
Compd. 19
176.95
141.12
132.62
131.43
130.48
128.75
126.01
86.43
77.34 CDCl3
77.03 CDCl3
76.71 CDCl3
f1 (ppm)

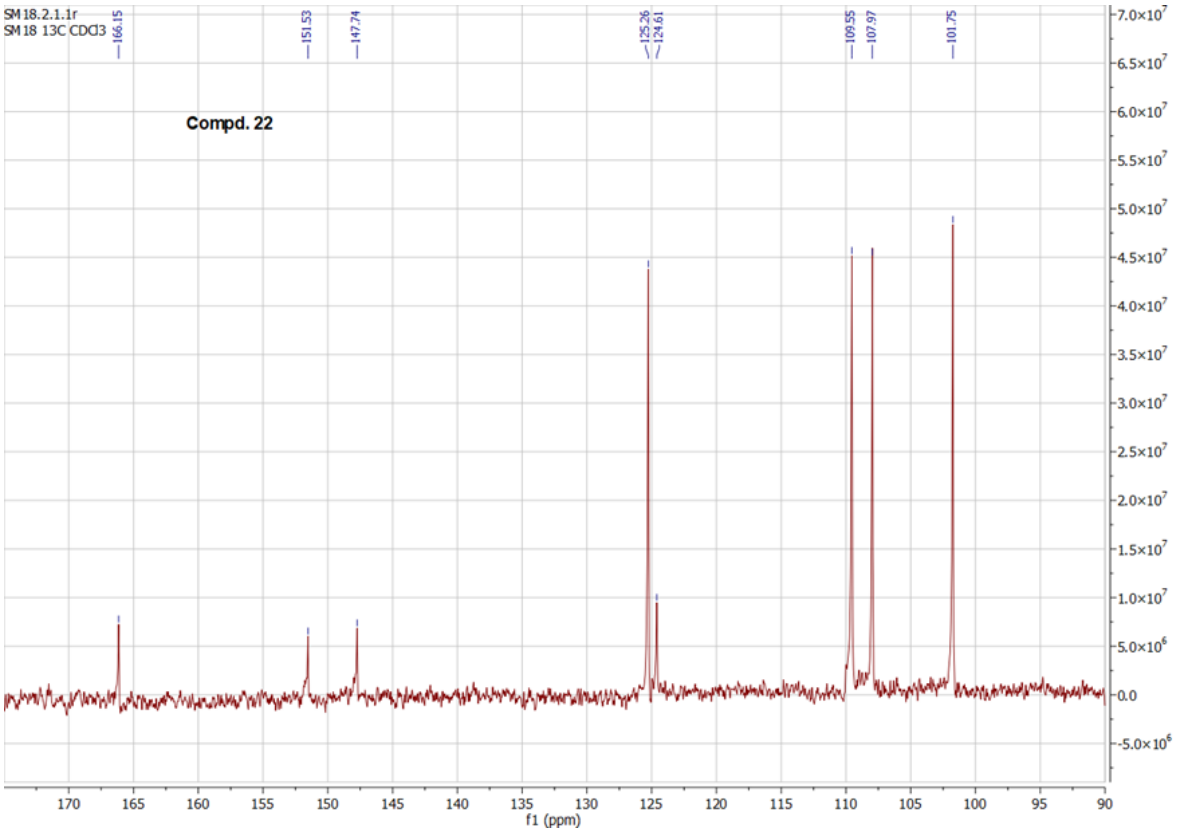

SM 32 bis.2.1.1r
SM 32 13C CDCl3
Compd. 19
63.87
59.14
56.68
42.20
39.53
38.74
36.08
33.17
29.70
28.73
21.57
20.92
20.57
18.10
15.06
f1 (ppm)

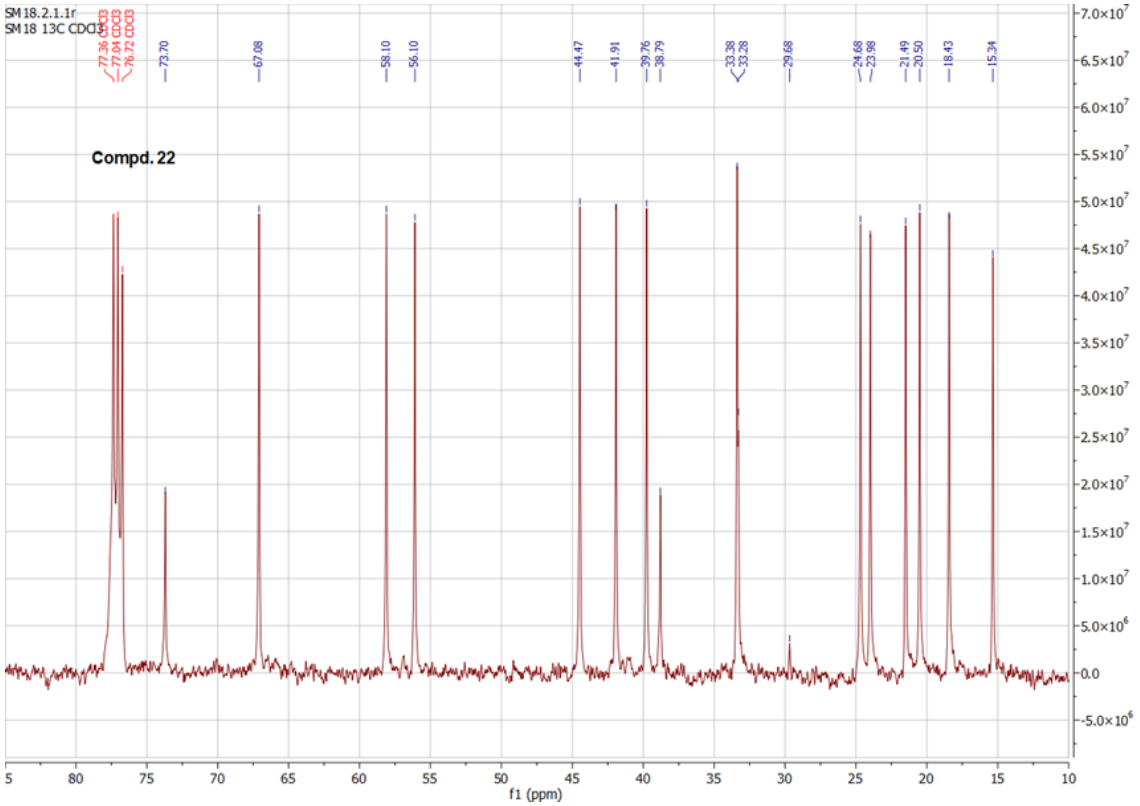

SM 18.1.1.1r
SM 18 CDCl3
Compd. 22
f1 (ppm)
1.33
0.89
1.25
0.89
3.11
5.13
5.75
8.00
5.98
8.79
4.88
1.85
8.28
3.56
8.24
8.39
13.68
7.64
7.62
7.49
7.45
7.25 CDCl3
6.86
6.82
6.80
6.08
6.04
6.01
4.36
4.34
4.33
4.31
4.29
1.91
1.90
1.88
1.87
1.84
1.83
1.81
1.77
1.76
1.75
1.74
1.72
1.69
1.67
1.64
1.63 HDO
1.60
1.59
1.57 HDO
1.53 HDO
1.45
1.44
1.43
1.41
1.40
1.38
1.37
1.34
1.31
1.28
1.25
1.24
1.20
1.17
1.15
1.13
1.12
1.10
1.09
0.97
0.96
0.93
0.90
0.85
0.79
0.78

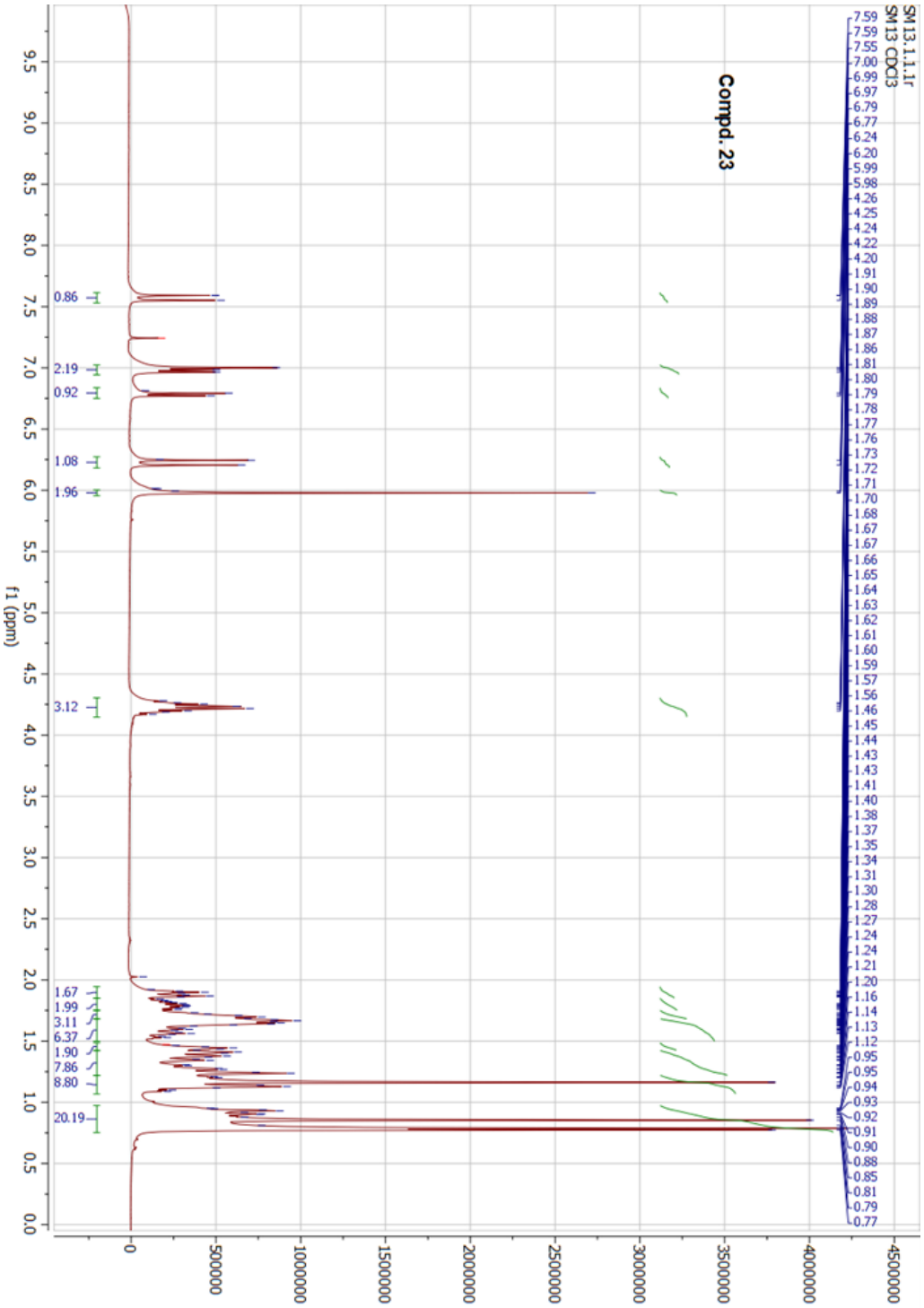

SM18.1.1.1r
SM18 CDCl3
Compd. 22
f1 (ppm)

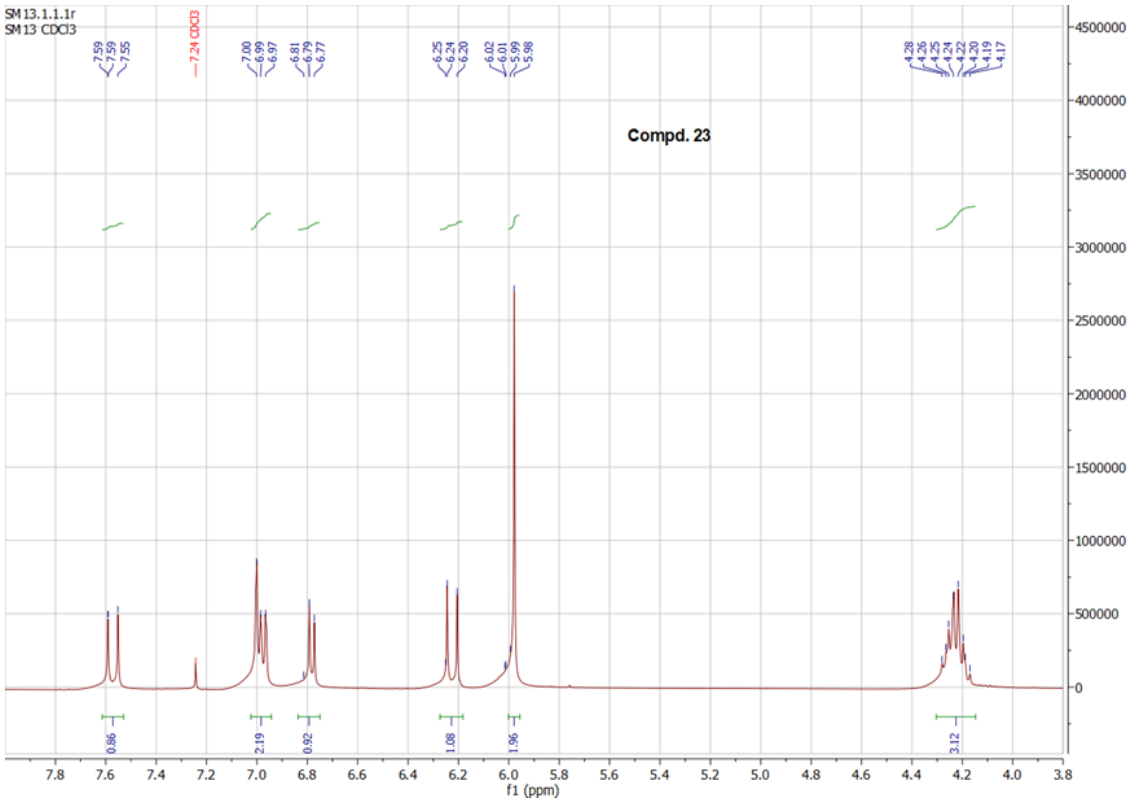

SM18.1.1.1r
SM18 CDCl3
Compd. 22
f1 (ppm)

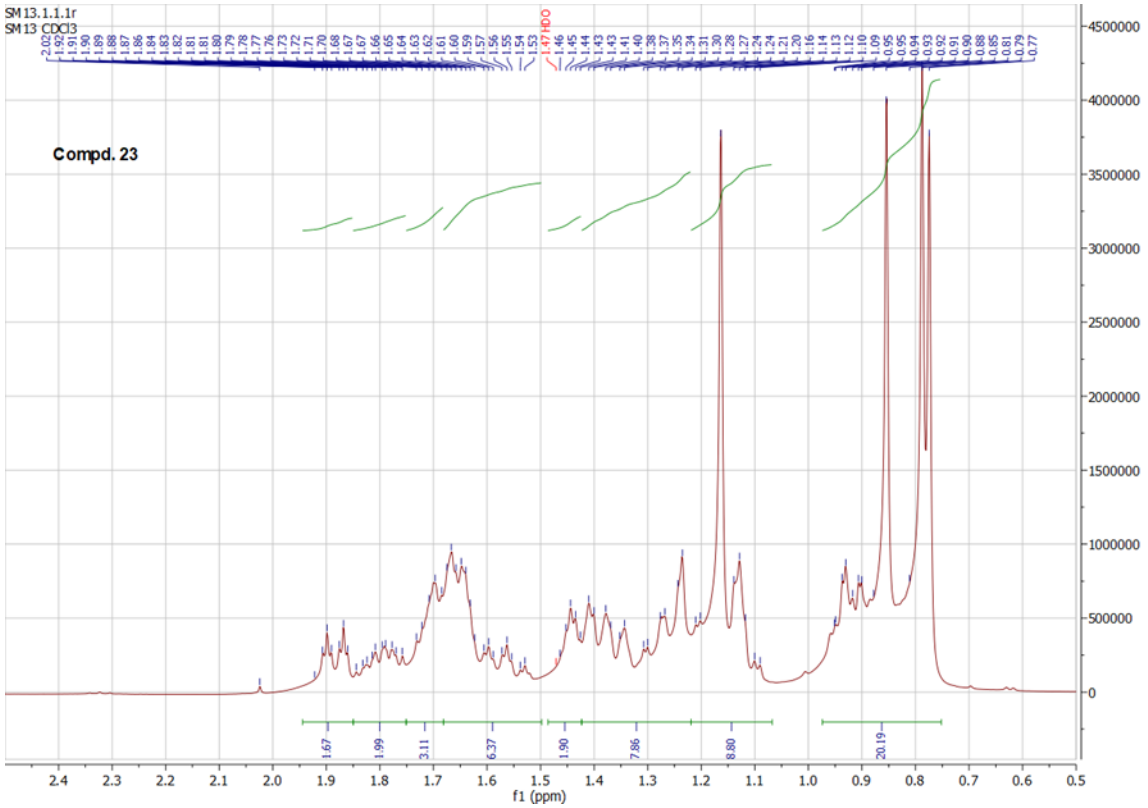

SM18.2.1.1r
SM18 13C CDCl3
Compd. 22
166.15
151.53
147.74
125.26
124.61
109.55
107.97
101.75
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
73.70
67.08
58.10
56.10
44.47
41.91
39.76
38.79
33.38
33.28
29.68
24.68
23.98
21.49
20.50
18.43
15.34
f1 (ppm)

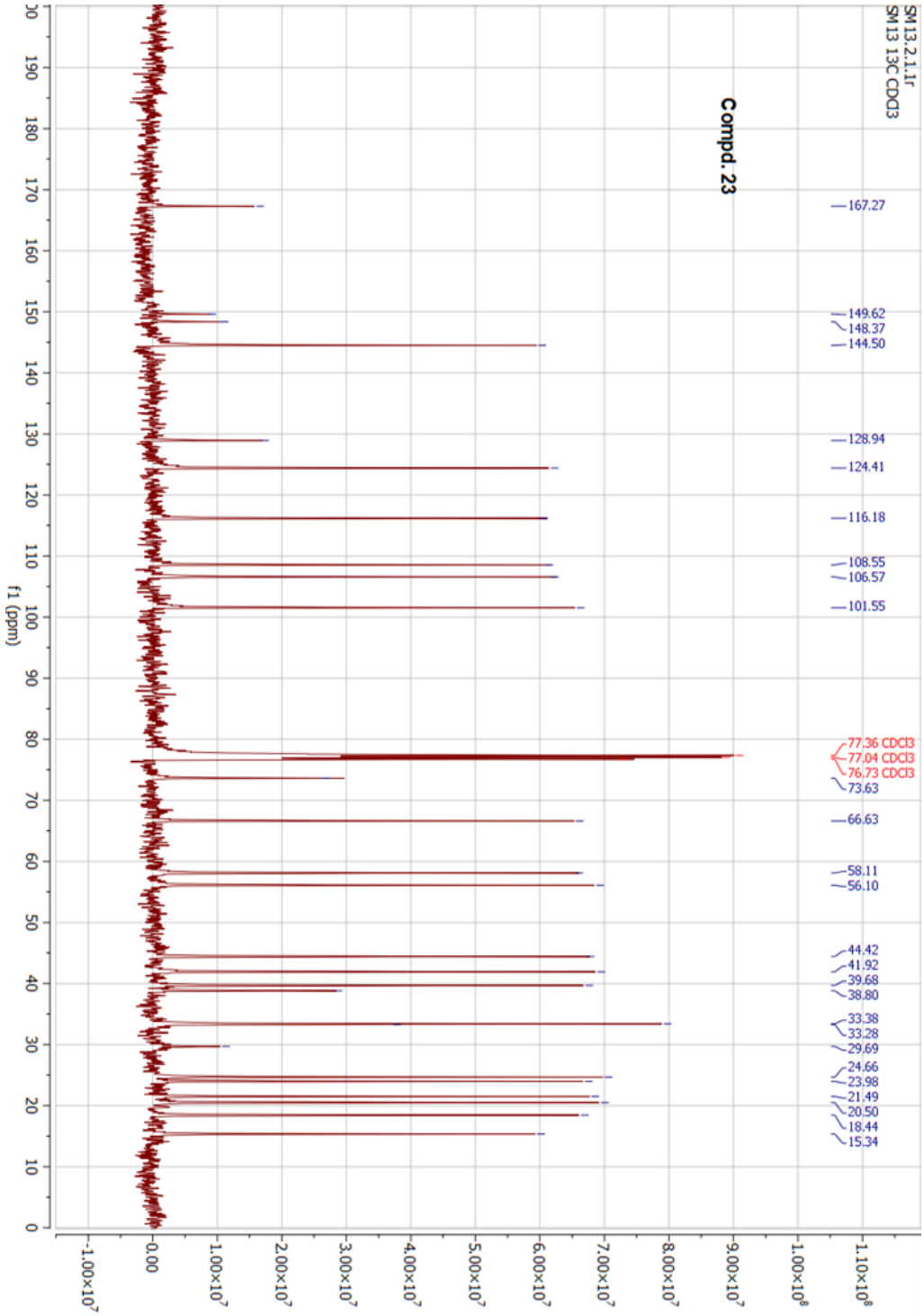

SM18.2.1.1r
SM18 13C CDCl3
166.15
151.53
147.74
125.26
124.61
109.55
107.97
101.75
Compd. 22
f1 (ppm)

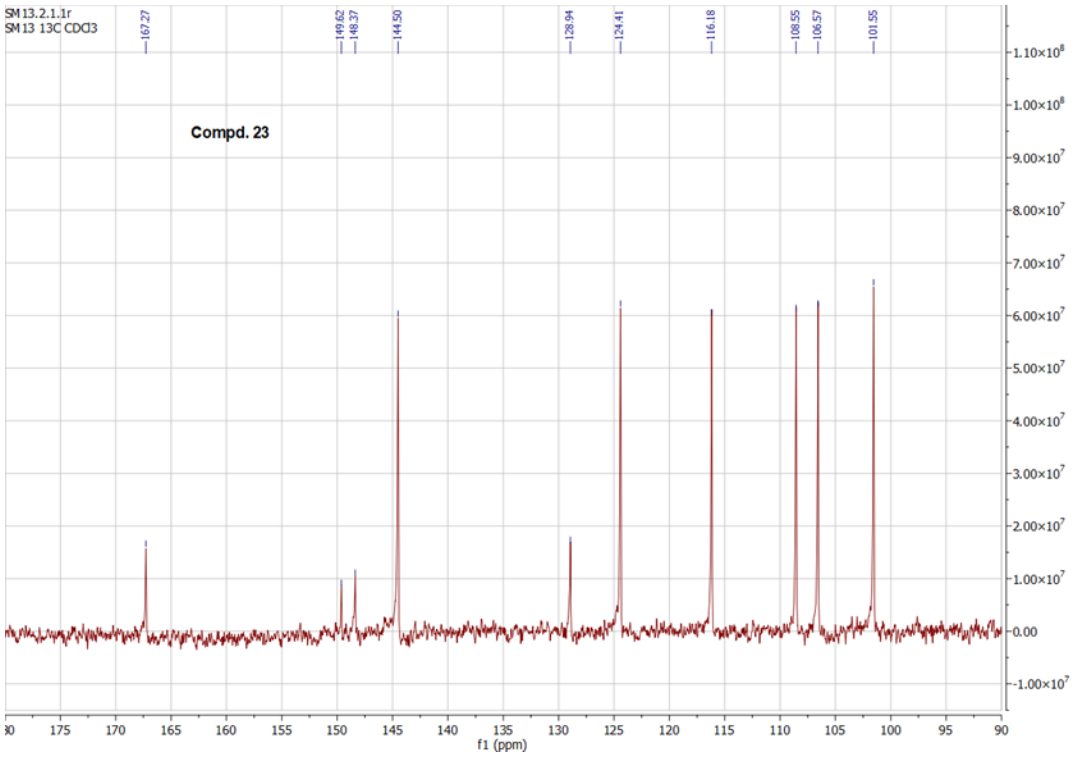

SM18.2.1.1r
SM18 13C CDCl3
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
73.70
67.08
58.10
56.10
44.47
41.91
39.76
38.79
33.38
33.26
29.68
24.68
23.98
21.49
20.50
18.43
15.34
Compd. 22
f1 (ppm)

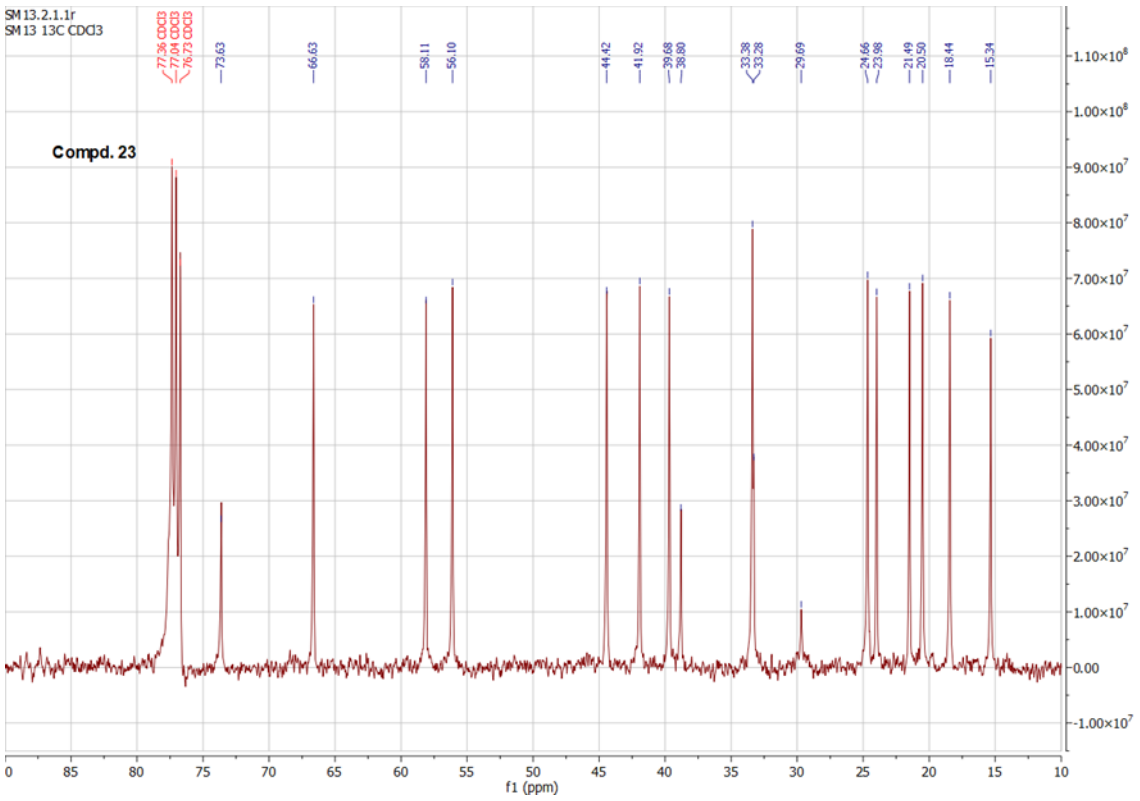

SM13_1_1.1r
SM13 CDCl3
Compd. 23
f1 (ppm)
0.86
2.19
0.92
1.08
1.96
3.12
1.67
1.99
3.11
6.37
1.90
7.86
8.80
20.19

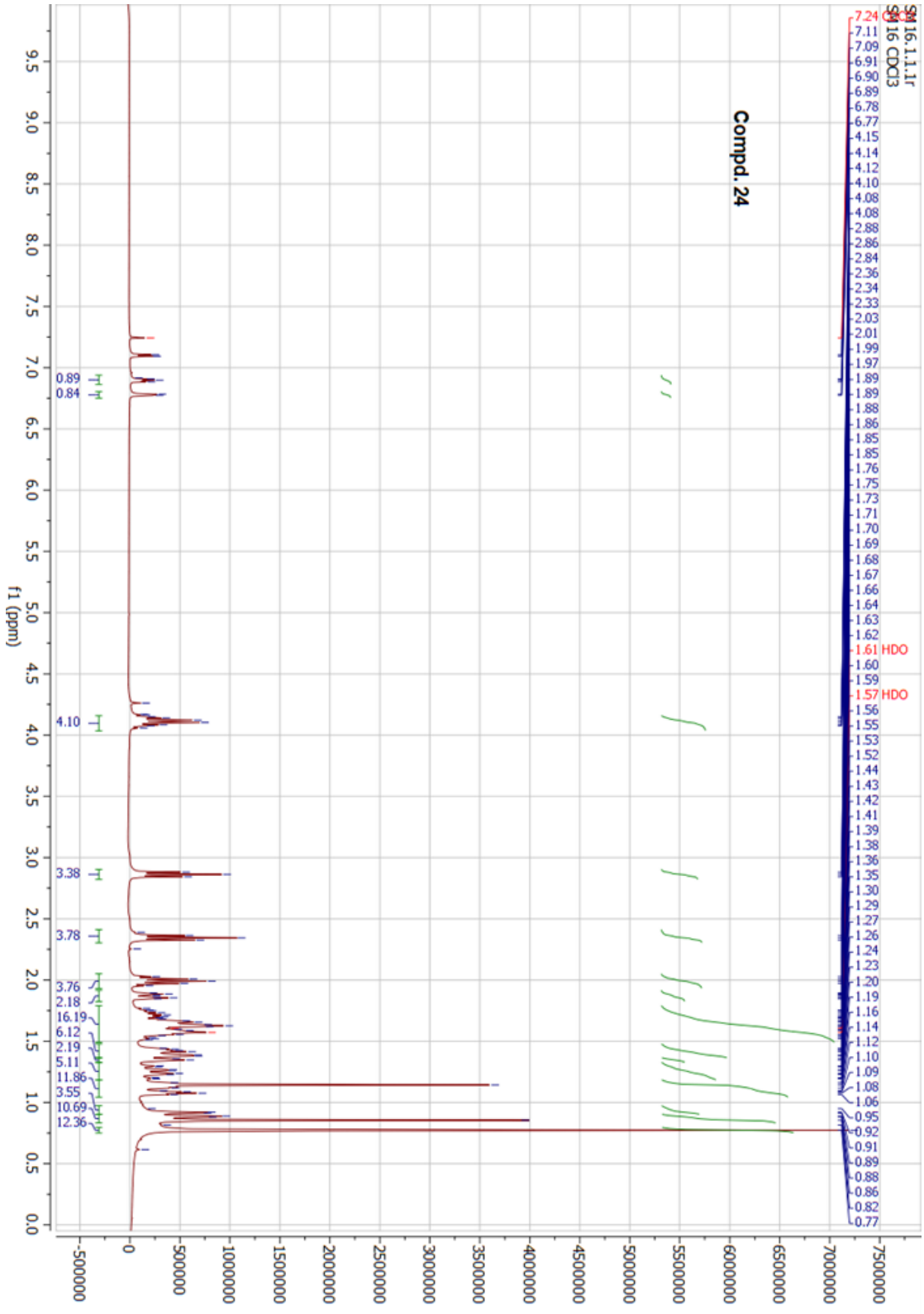

SM13.1.1.1r
SM13 CDCl3
Compd. 23
f1 (ppm)

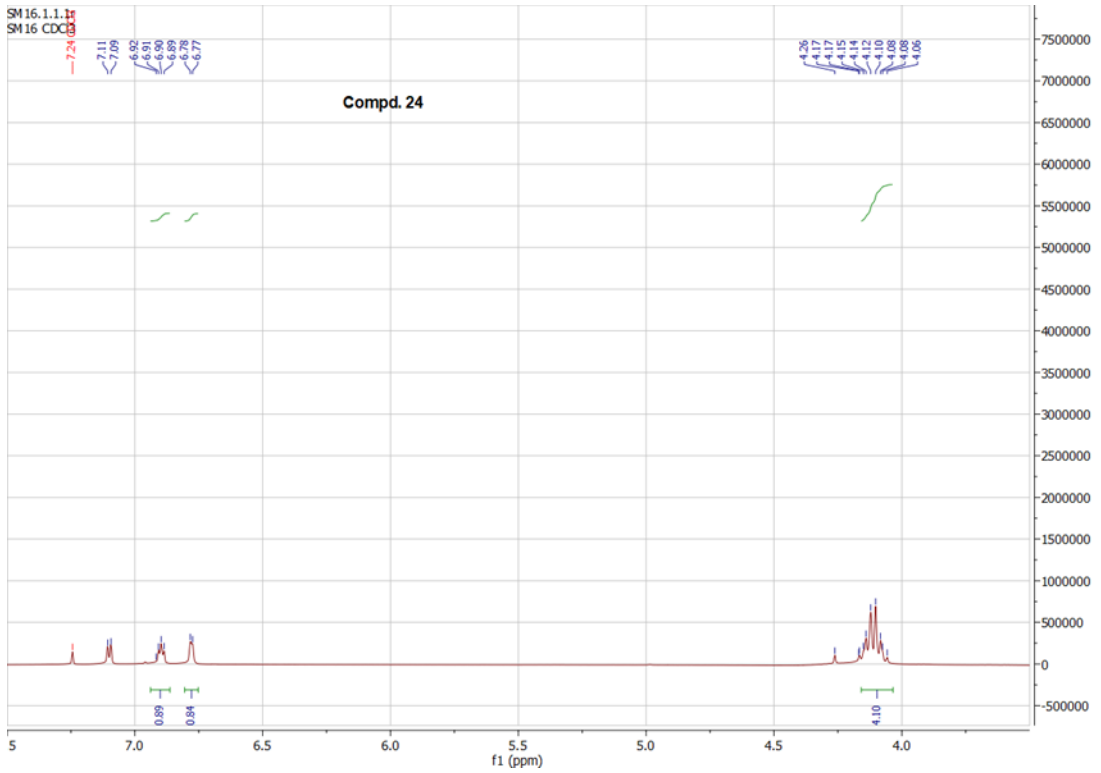

SM13.1.1.1r
SM13 CDCl3
Compd. 23
f1 (ppm)

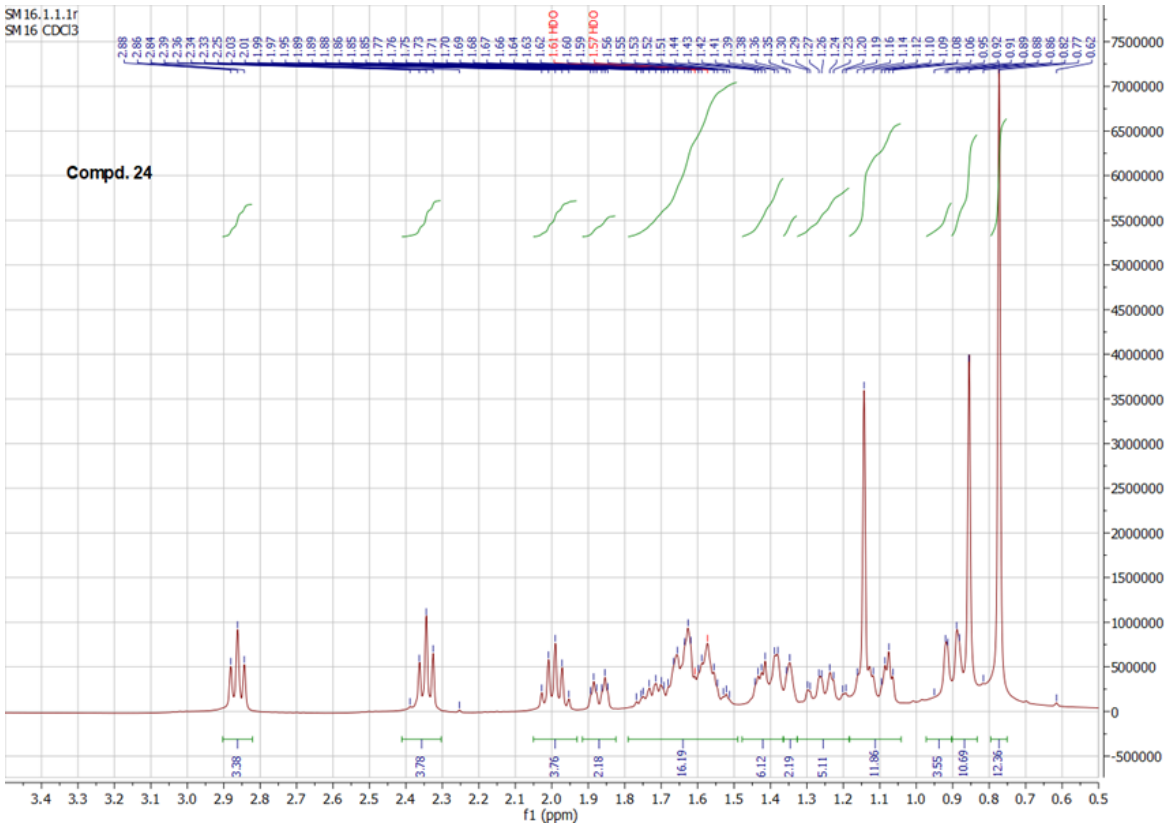

SM13.2.1.1r
SM13 13C CDCl3
Compd. 23
167.27
149.62
148.37
144.50
128.94
124.41
116.18
108.55
106.57
101.55
77.36 CDCl3
77.04 CDCl3
76.73 CDCl3
73.63
66.63
58.11
56.10
44.42
41.92
39.68
38.80
33.38
33.28
29.69
24.66
23.98
21.49
20.50
18.44
15.34
f1 (ppm)

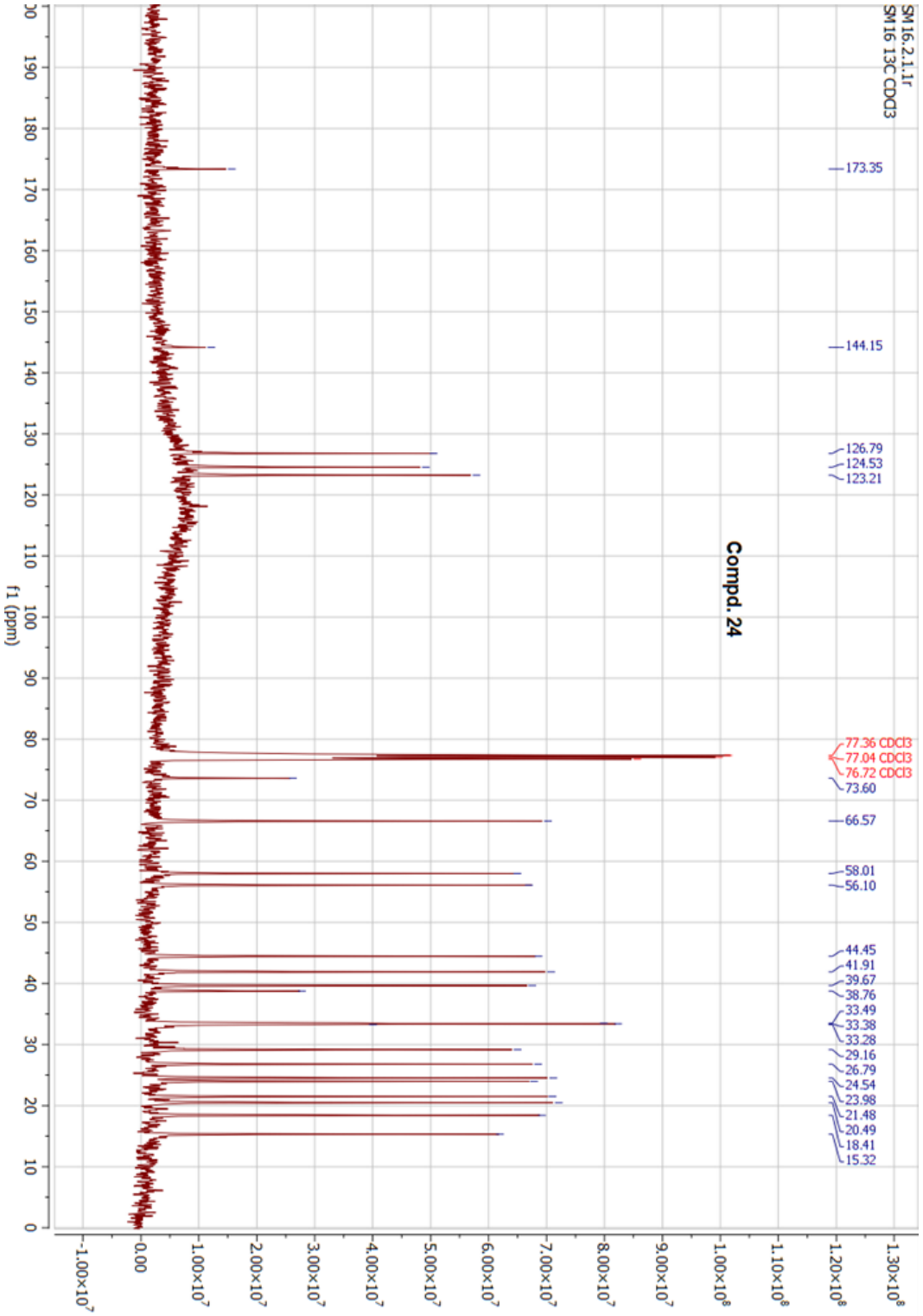

SM13.2.1.1r
SM13 13C CDCl3
167.27
149.62
148.37
144.50
128.94
124.41
116.18
106.55
106.57
101.55
Compd. 23
f1 (ppm)

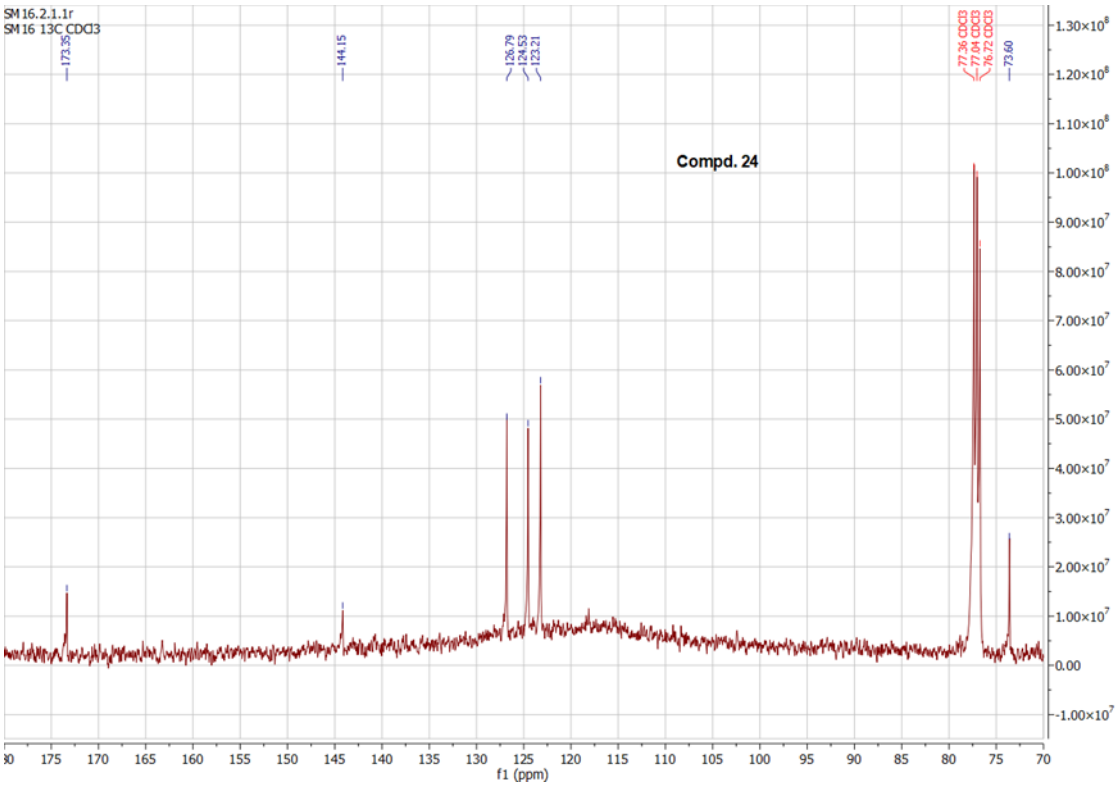

SM13.2.1.1r
SM13 13C CDCl3
77.36 CDCl3
77.04 CDCl3
76.73 CDCl3
73.63
66.63
58.11
56.10
44.42
41.92
39.68
38.80
33.38
33.28
29.69
24.66
23.98
21.49
20.50
18.44
15.34
Compd. 23
f1 (ppm)

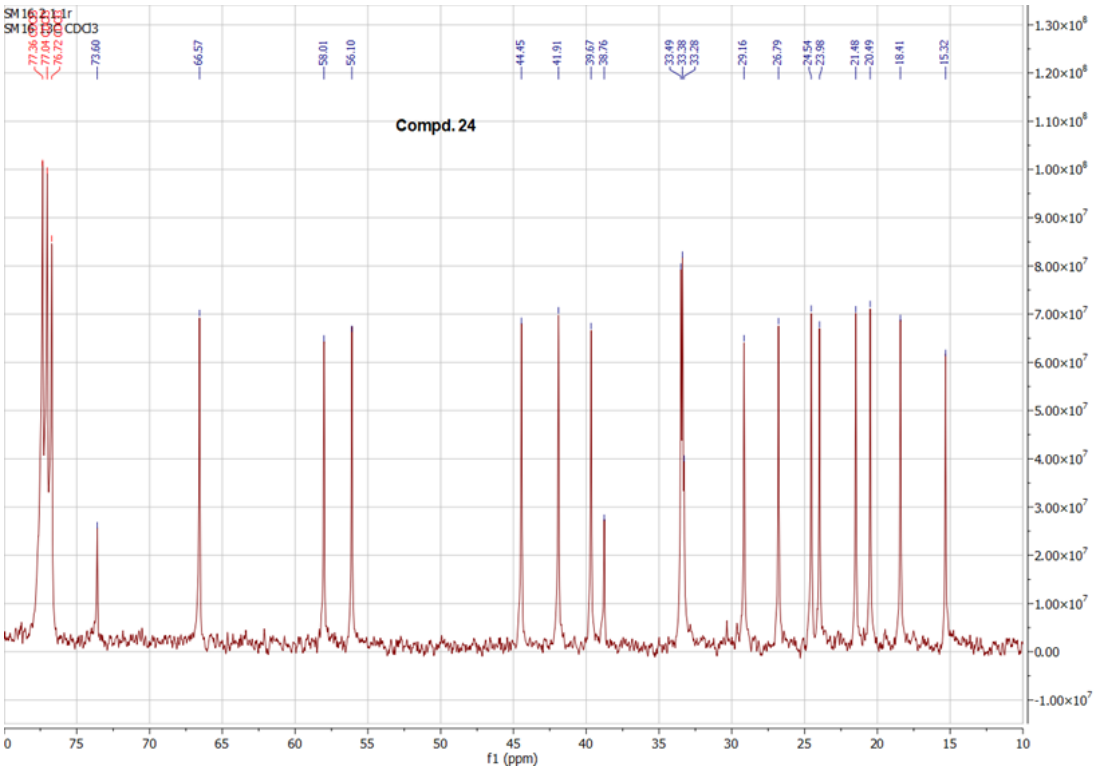

Compd. 24
f1 (ppm)
0.89
0.84
4.10
3.38
3.78
3.76
2.18
16.19
6.12
2.19
5.11
11.86
3.55
10.69
12.36
1.61 HDO
1.57 HDO

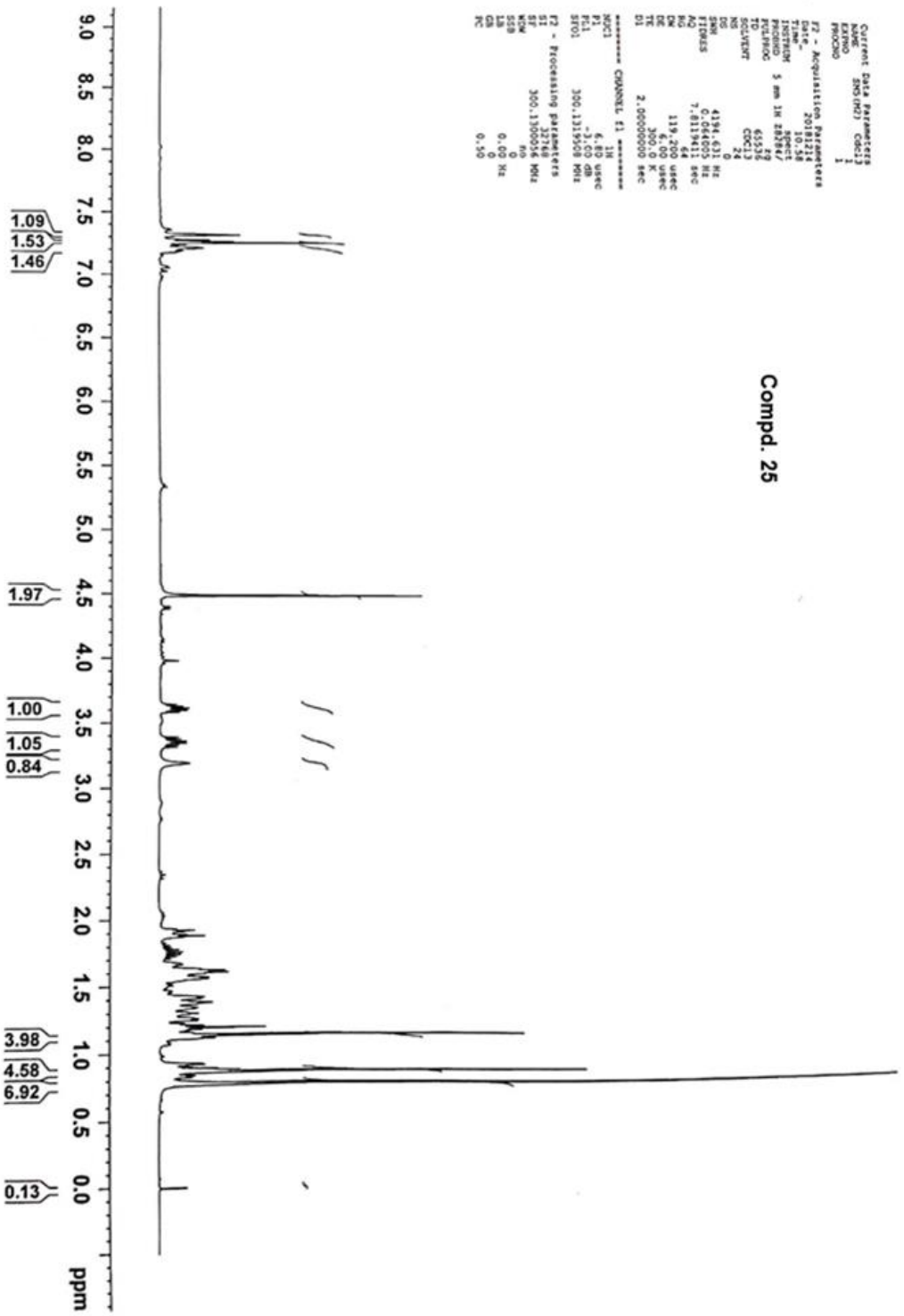

SM 16.1.1.1r
SM 16 CDCl3
Compd. 24
f1 (ppm)


SM 16.1.1.1r
SM 16 CDCl3
Compd. 24
f1 (ppm)


SM16.2.1.1r
SM16 13C CDCl3
Compd. 24
f1 (ppm)
173.35
144.15
126.79
124.53
123.21
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
73.60
66.57
58.01
56.10
44.45
41.91
39.67
38.76
33.49
33.38
33.28
29.16
26.79
24.54
23.98
21.48
20.49
18.41
15.32

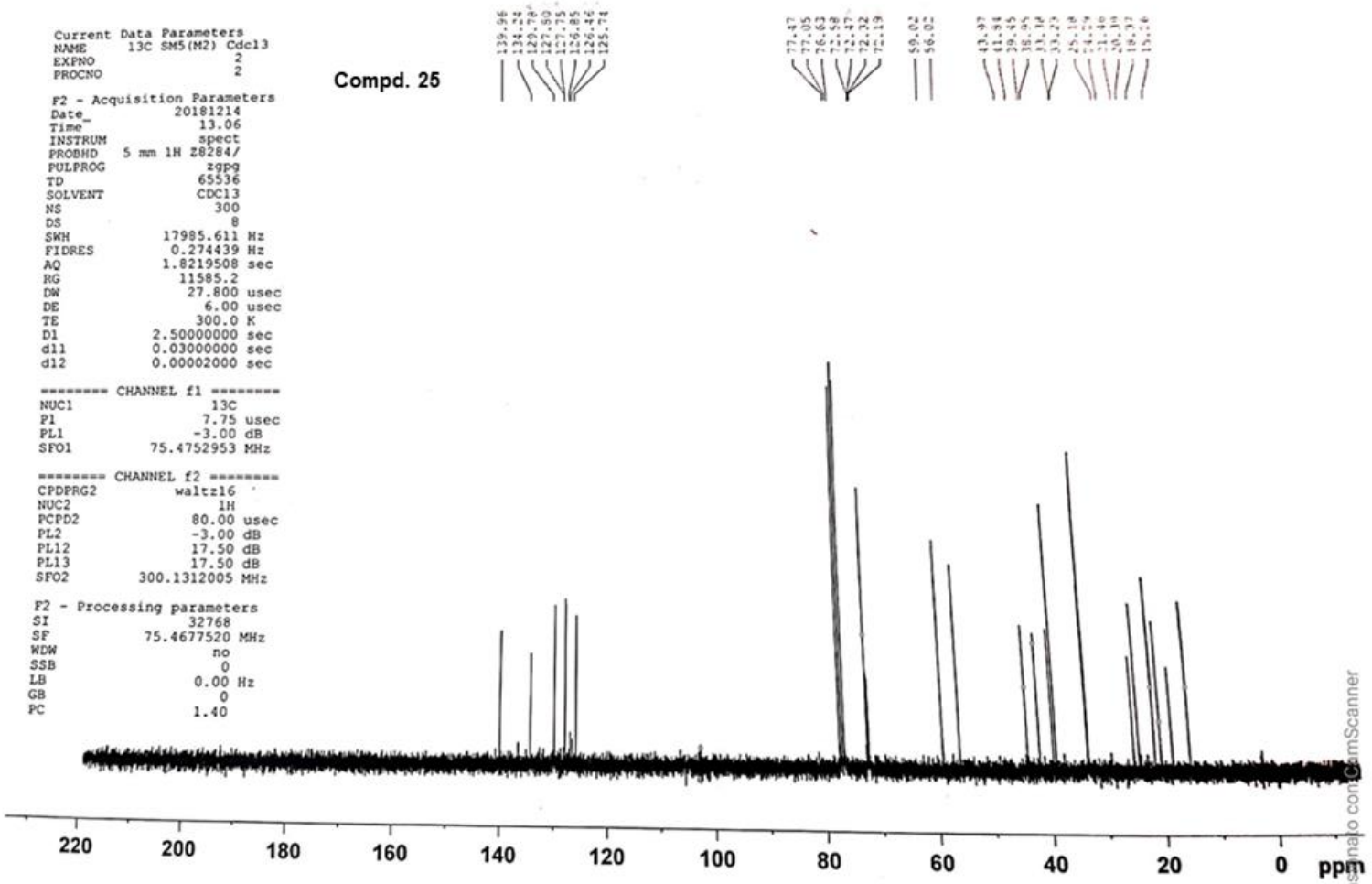

SM16.2.1.1r
SM16 13C CDCl3
173.35
144.15
126.79
124.53
123.21
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
73.60
Compd. 24
f1 (ppm)


SM16.2.1.1r
SM16 13C CDCl3
77.36 CDCl3
77.04 CDCl3
76.72 CDCl3
73.60
66.57
58.01
56.10
44.45
41.91
39.67
38.76
33.49
33.38
33.28
29.16
26.79
24.54
23.98
21.48
20.49
18.41
15.32
Compd. 24
f1 (ppm)


Compd. 25
1.09
1.53
1.46
1.97
1.00
1.05
0.84
3.98
4.58
6.92
0.13
ppm

Compd. 25

```
Current Data Parameters
NAME      13C SM5(M2) Cdcl3
EXPNO                    2
PROCNO                   2

F2 - Acquisition Parameters
Date_              20181214
Time                 13.06
INSTRUM              spect
PROBHD   5 mm 1H Z8284/
PULPROG                zgpg
TD                    65536
SOLVENT               CDCl3
NS                      300
DS                        8
SWH               17985.611 Hz
FIDRES             0.274439 Hz
AQ                1.8219508 sec
RG                  11585.2
DW                   27.800 usec
DE                    6.00 usec
TE                   300.0 K
D1              2.50000000 sec
d11             0.03000000 sec
d12             0.00002000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                    7.75 usec
PL1                  -3.00 dB
SFO1           75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2                80.00 usec
PL2                  -3.00 dB
PL12                 17.50 dB
PL13                 17.50 dB
SFO2          300.1312005 MHz

F2 - Processing parameters
SI                    32768
SF             75.4677520 MHz
WDW                      no
SSB                       0
LB                    0.00 Hz
GB                        0
PC                     1.40
```



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