Identification of Psychoplastogenic *N,N*-Dimethylaminoisotryptamine (isoDMT) Analogs Through Structure-Activity Relationship Studies

Supplemental Material
(62 pages)

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Figure S2
Figure S3
Spectral Data

Compound	MPO Score	% Efficacy
1	4.1	79%
2	4.4	87%
4	4.4	26%
5	4.4	65%
6	4.4	95%
7	4.4	92%
8	3.9	38%
9	3.9	78%
10	3.9	65%
11	3.9	131%
12	4.4	37%
13	4.4	75%
14	4.4	88%
15	4.4	85%
16	4.4	104%
17	4.4	84%
18	4.4	62%
19	5.4	85%
20	4.4	117%
21	5.5	72%
22	4.9	50%
23	4.4	64%
24	4.1	86%
25	3.5	17%
26	4.2	70%
27	4.3	73%
28	4.6	80%
29	4.2	81%
30	4.6	72%

Figure S1. CNS MPO Scores and Maximum Psychoplastogenicity. Central nervous system (CNS) multiparameter optimization (MPO) scores were determined by the method described in reference 21. Maximum psychoplastogenicity is expressed as percent efficacy of the N_{max} value relative to the vehicle (0%) and positive (ketamine, 100%) controls.

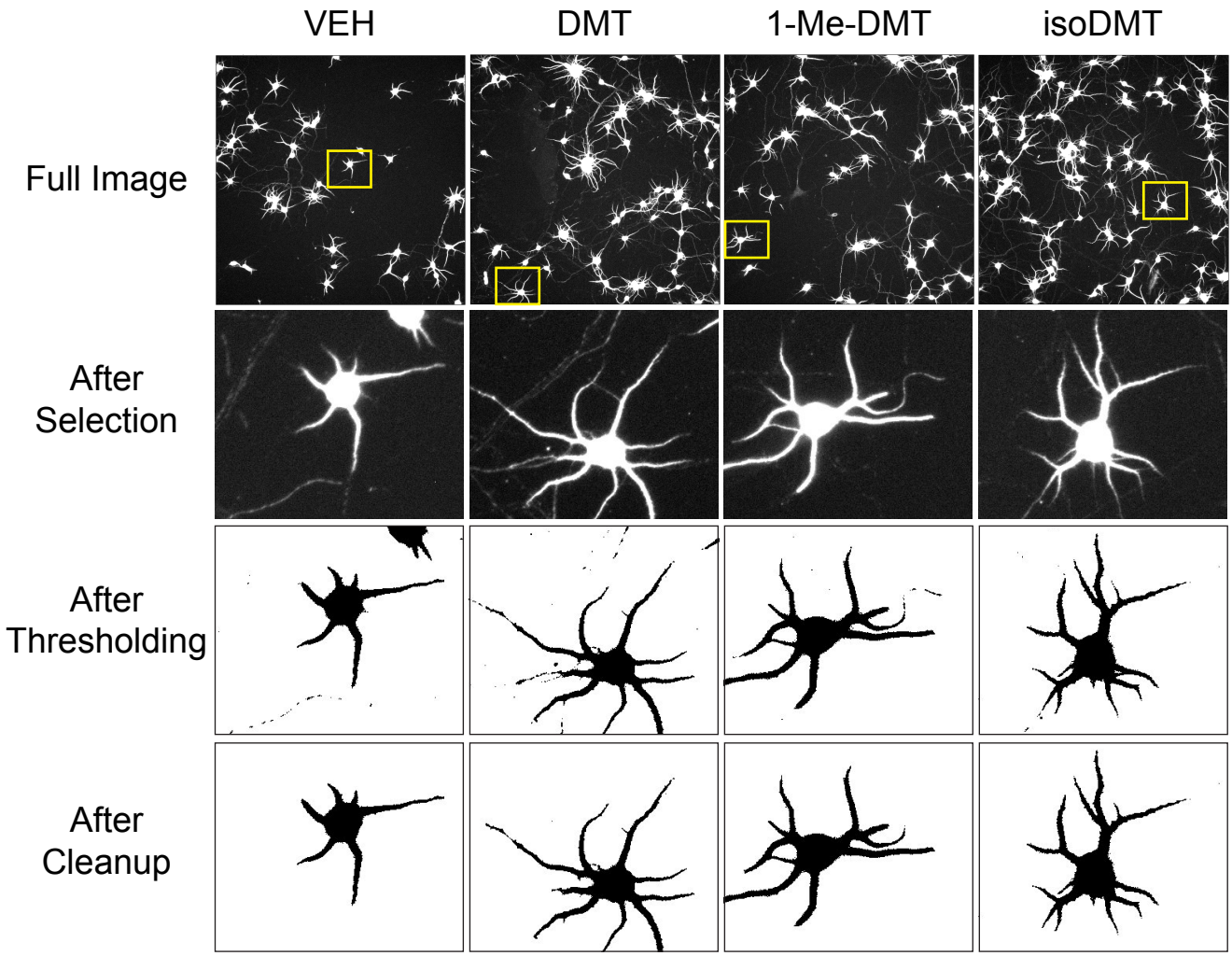


Figure S2. Process for converting images into files suitable for data analysis. Images were acquired on a high content confocal microscope using a 20x objective. Then, well defined pyramidal-like neurons were selected (yellow boxes). Predetermined thresholding values were applied to all images. Finally, adjacent cells and signals noncontiguous with the neuron being analyzed were removed prior to running the Sholl analysis macro. All data processing was performed by experimenters blinded to treatment conditions. The examples shown here correspond to the representative images depicted in Figure 4.

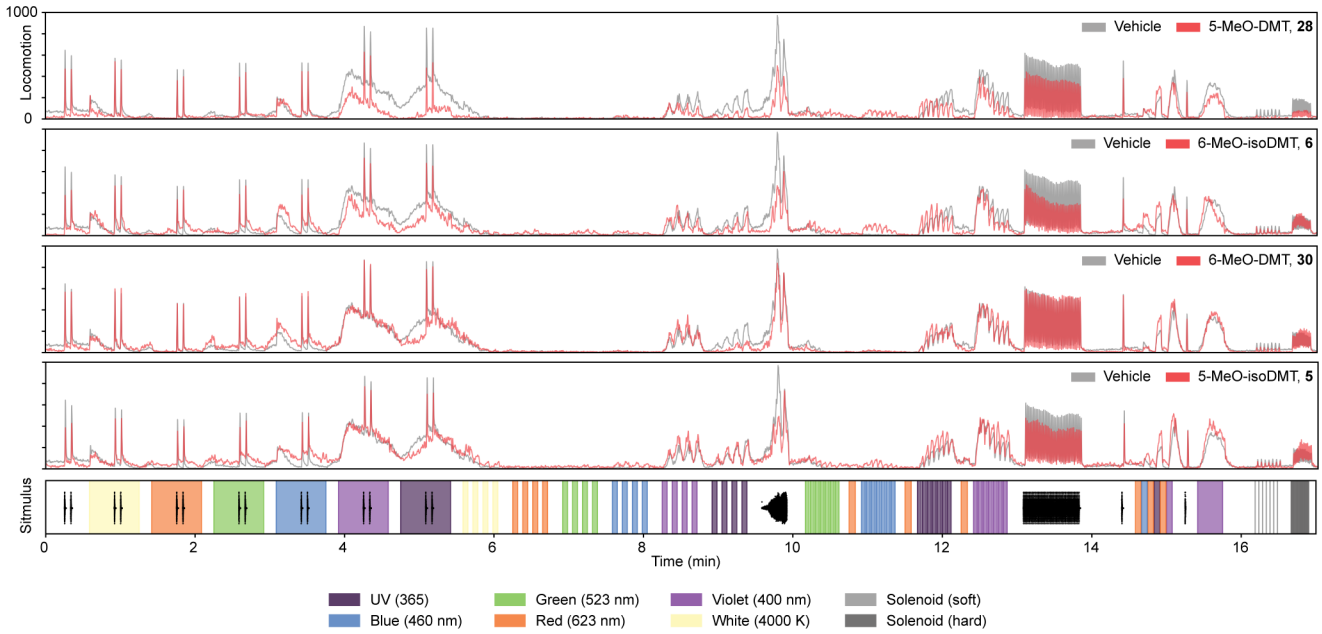
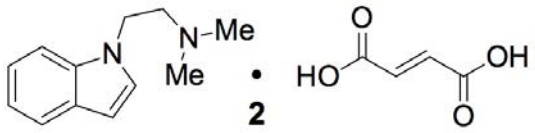
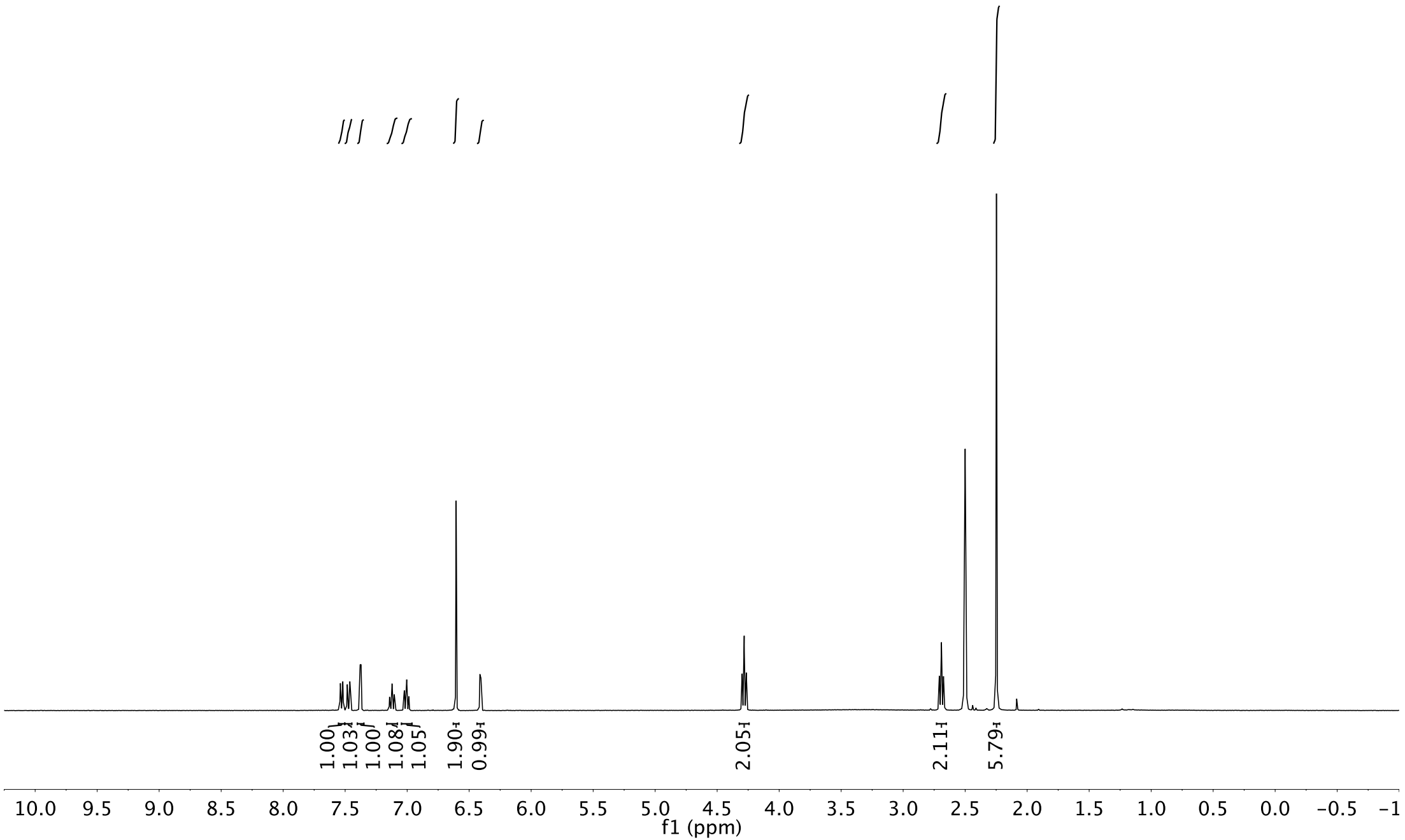


Figure S3. Zebrafish motion traces with associated stimuli. Top: Locomotion in wells treated with vehicle (gray) or compounds (200 µM, red). Bottom: Stimuli applied over time. Colors indicate bright LED light of respective colors. Black traces represent the waveform of acoustic stimuli, and gray vertical lines indicate physical tapping as secondary acoustic stimuli.

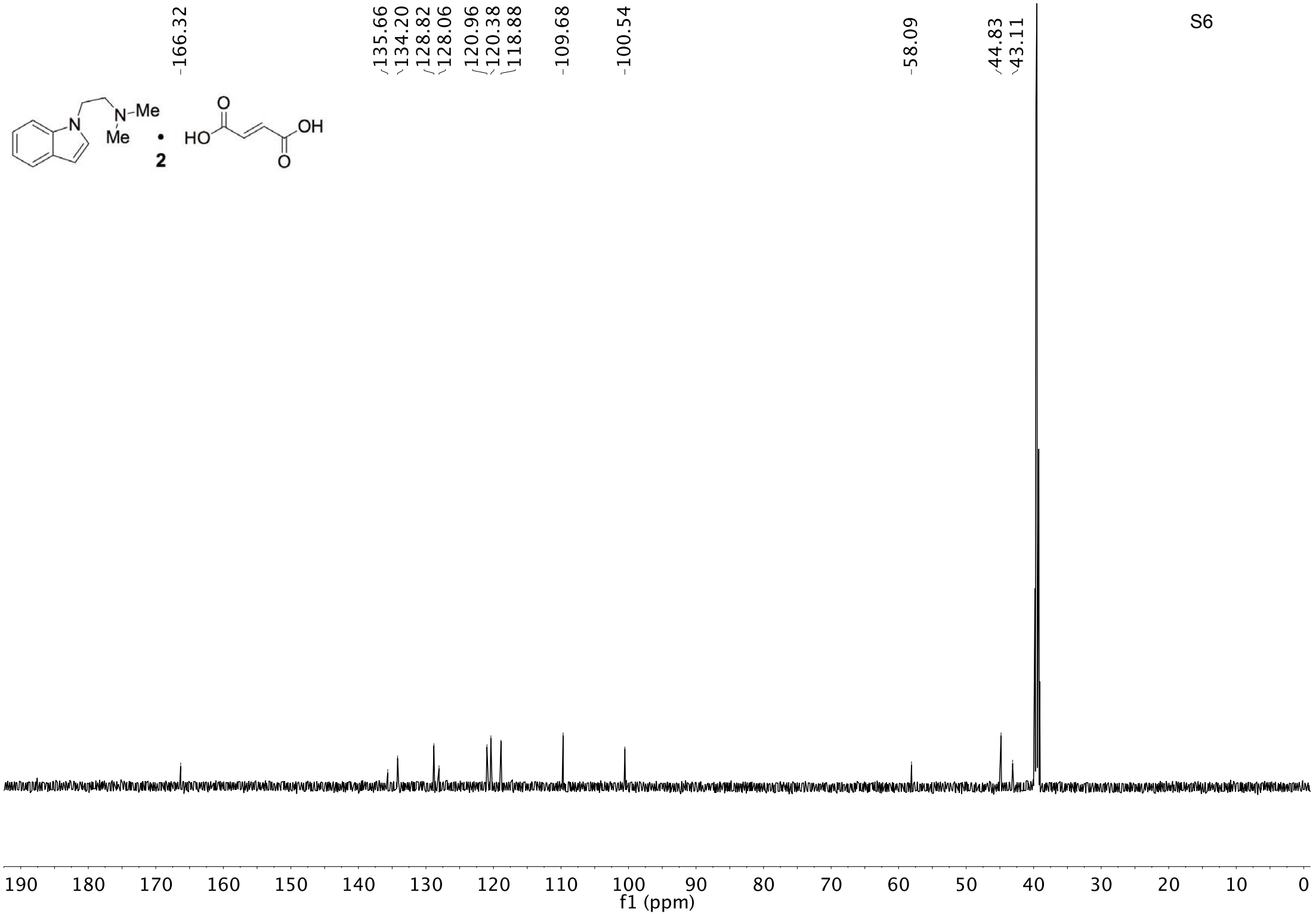

N
N–Me
Me
HO
OH
O
O

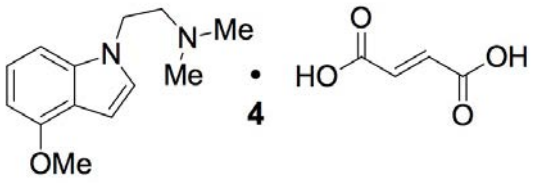
2


1.00
1.03
1.00
1.08
1.05
1.90
0.99
2.05
2.11
5.79
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 0.0 −0.5 −1
f1 (ppm)

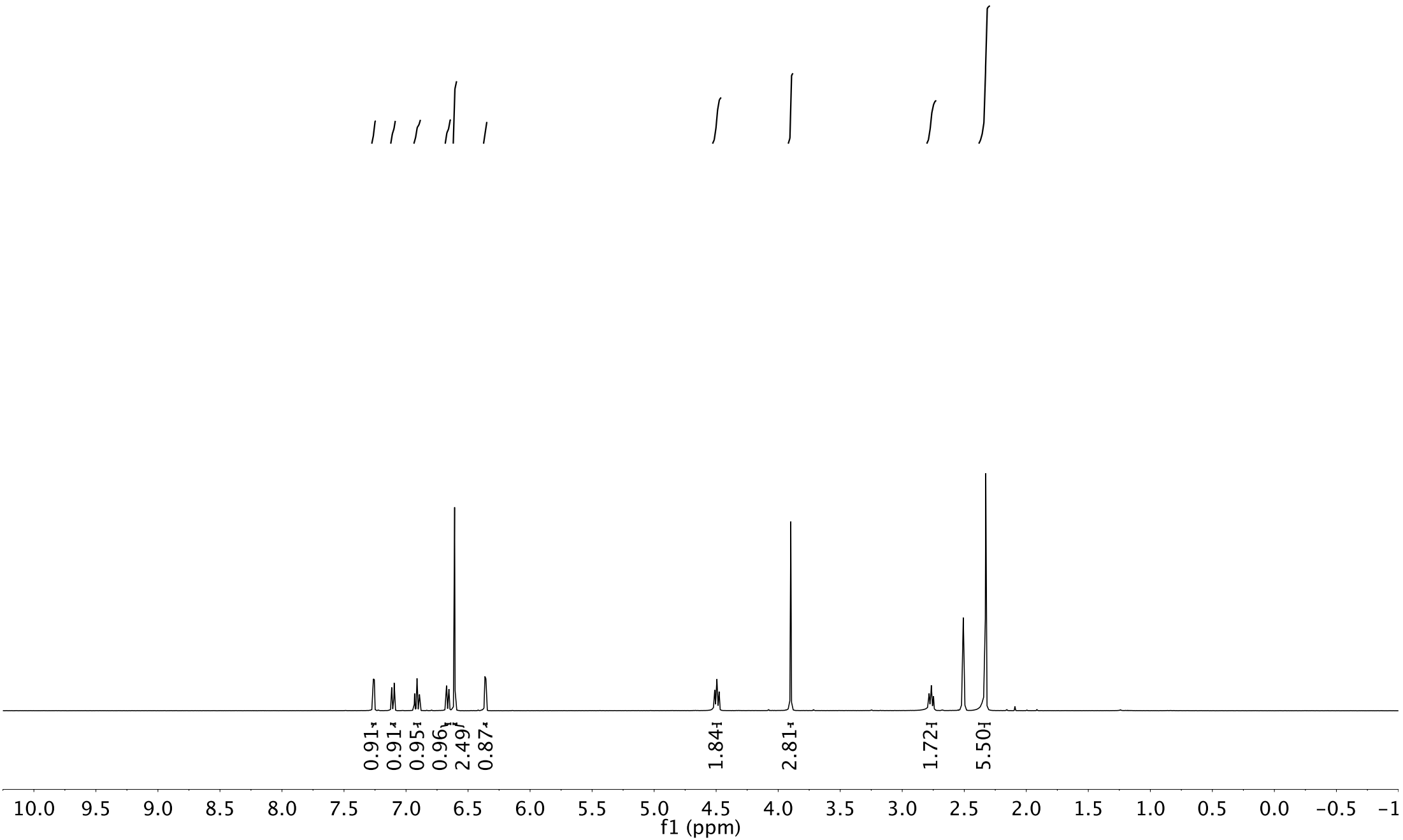
2

166.32
135.66
134.20
128.82
128.06
120.96
120.38
118.88
109.68
100.54
58.09
44.83
43.11




N
N-Me
Me
OMe
HO
O
OH
O

4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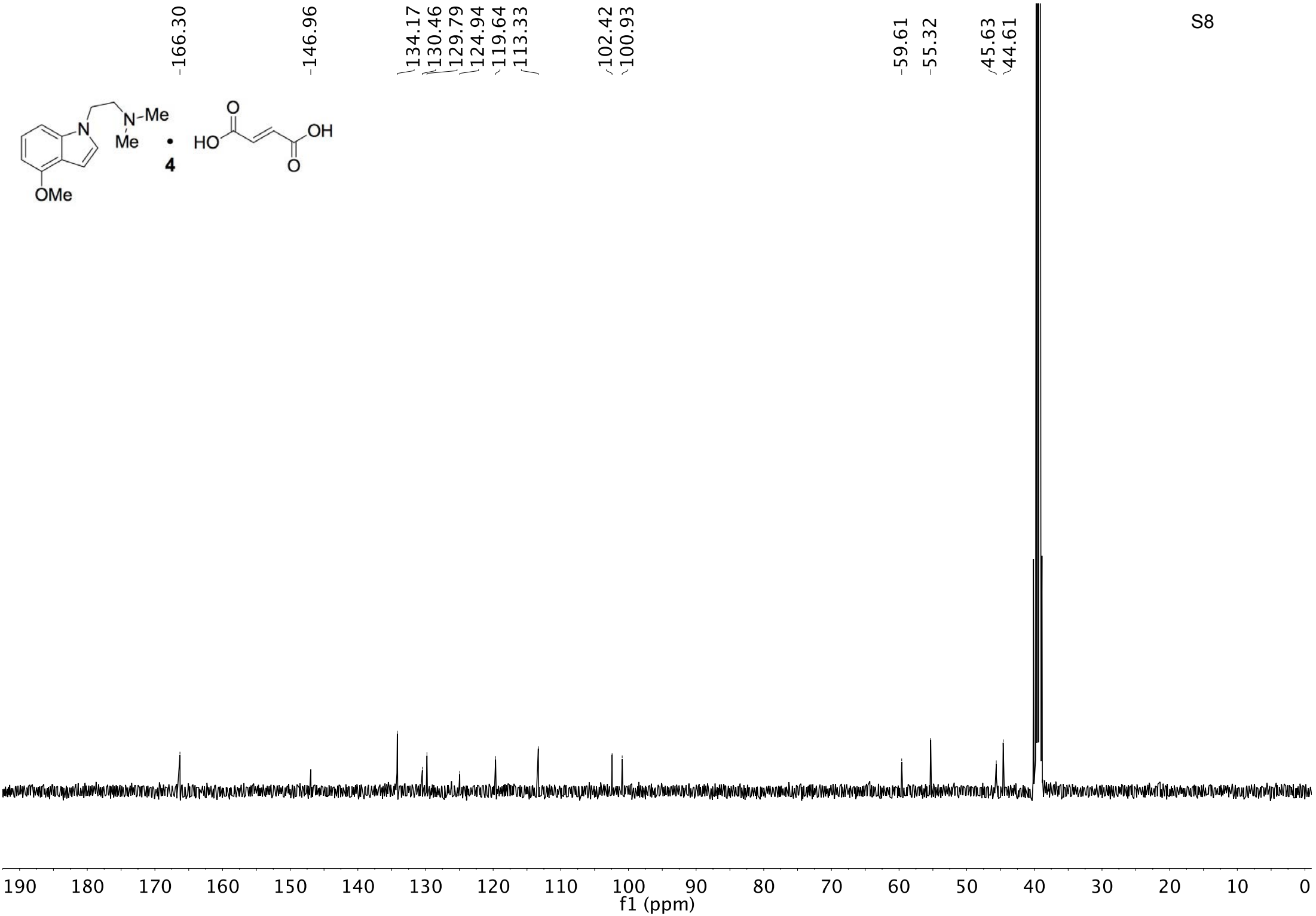
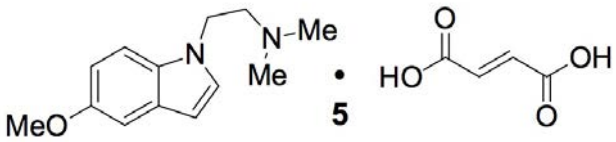
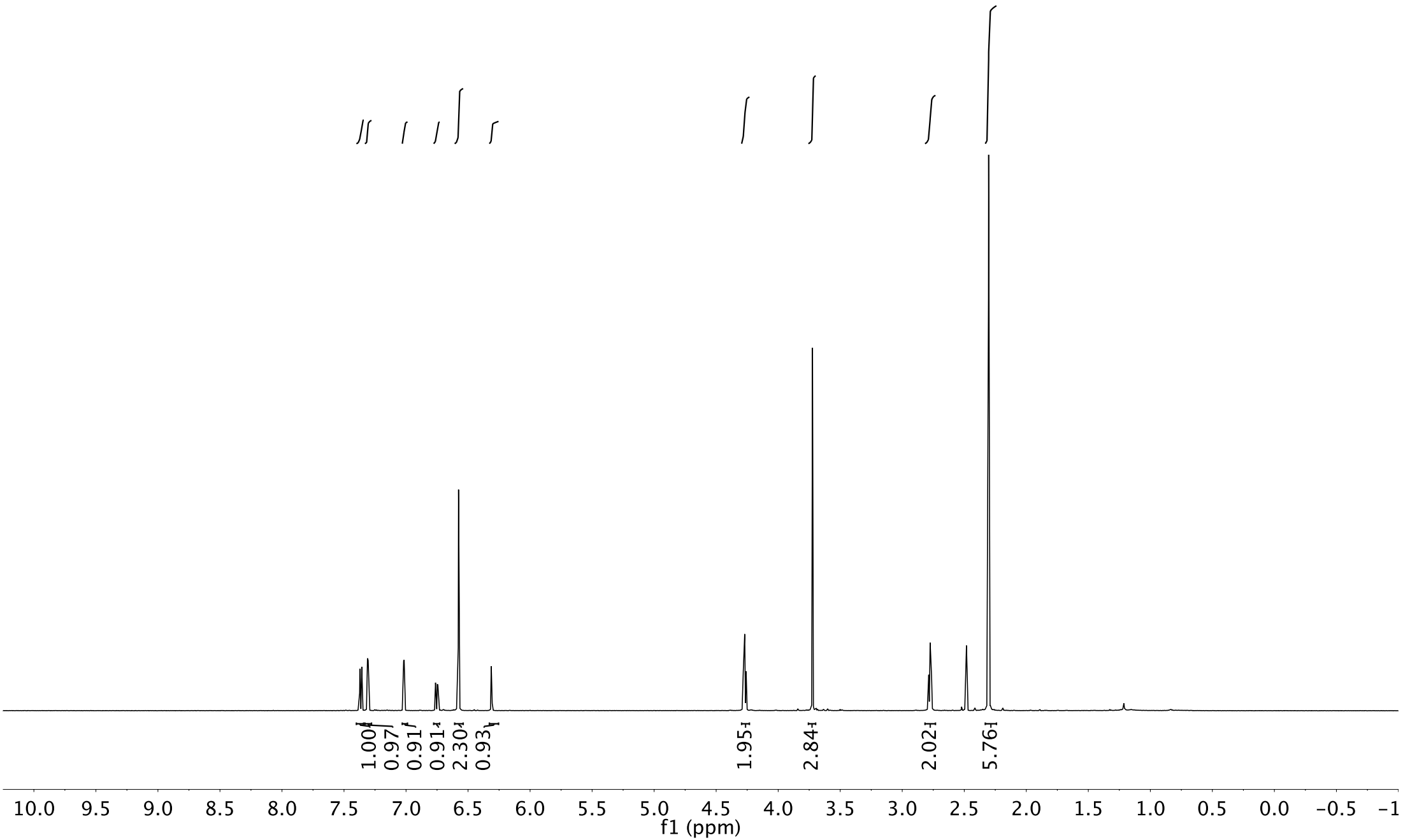
0.91
0.95
0.96
2.49
0.87
1.84
2.81
1.72
5.50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)

4

166.30
146.96
134.17
130.46
129.79
124.94
119.64
113.33
102.42
100.93
59.61
55.32
45.63
44.61




N
N–Me
Me
MeO
•
HO
OH
O
O
5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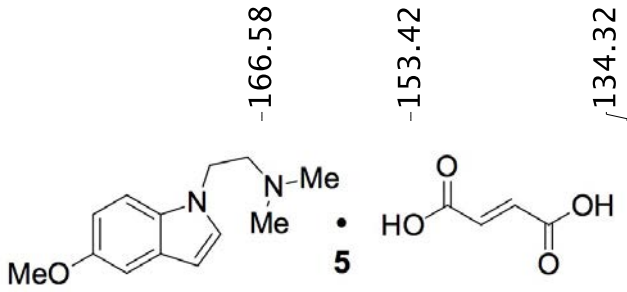
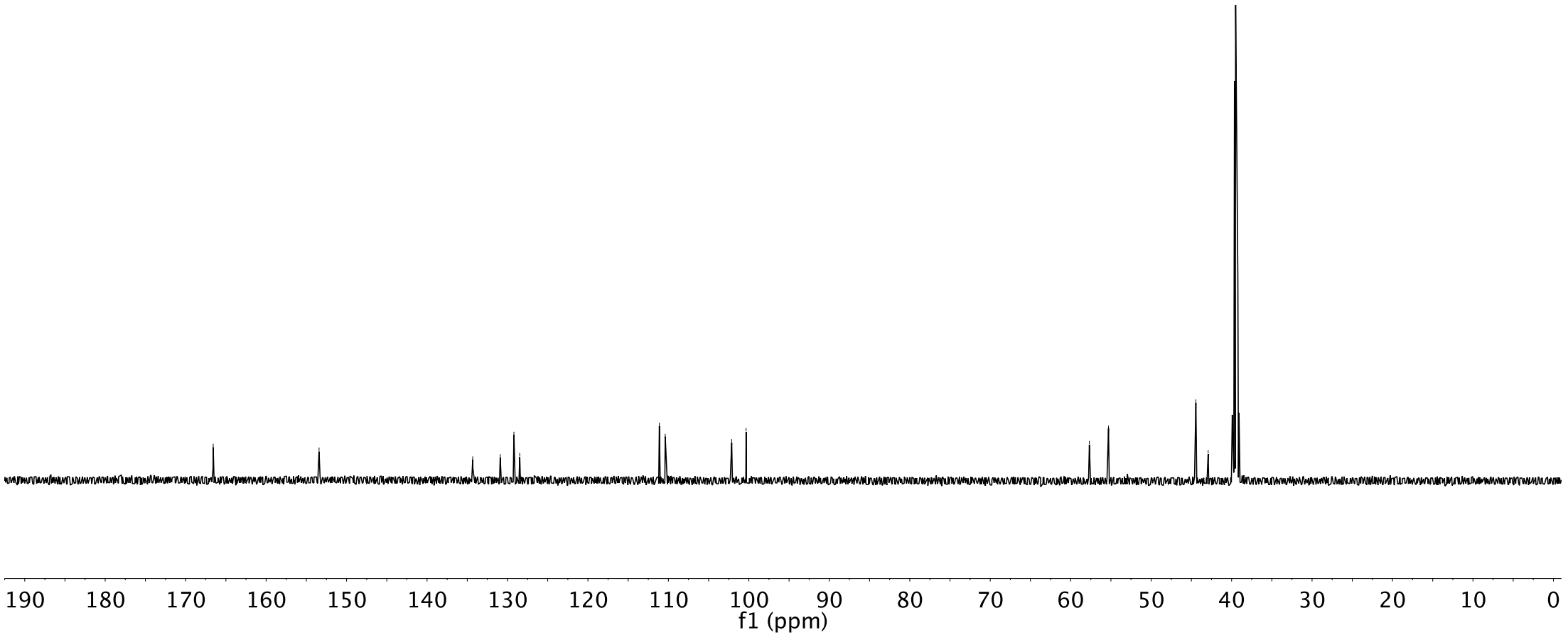
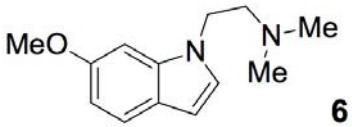
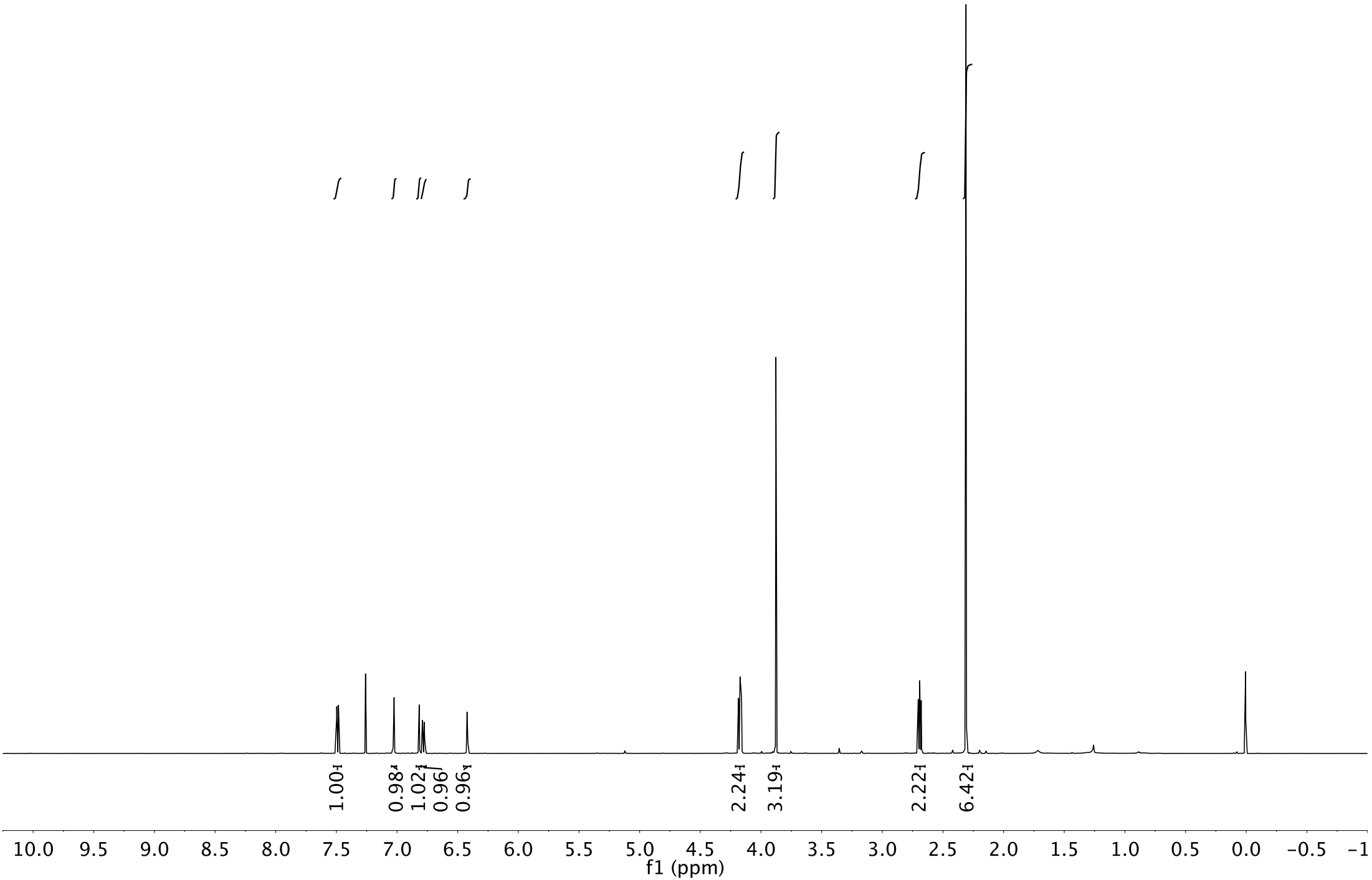
0.97
0.91
0.91
2.30
0.93
1.95
2.84
2.02
5.76
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)


166.58
153.42
134.32
130.90
129.20
128.48
111.12
110.39
102.13
100.34
57.68
55.30
44.44
42.91
N
N–Me
Me
MeO
5
HO
O
OH
O


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

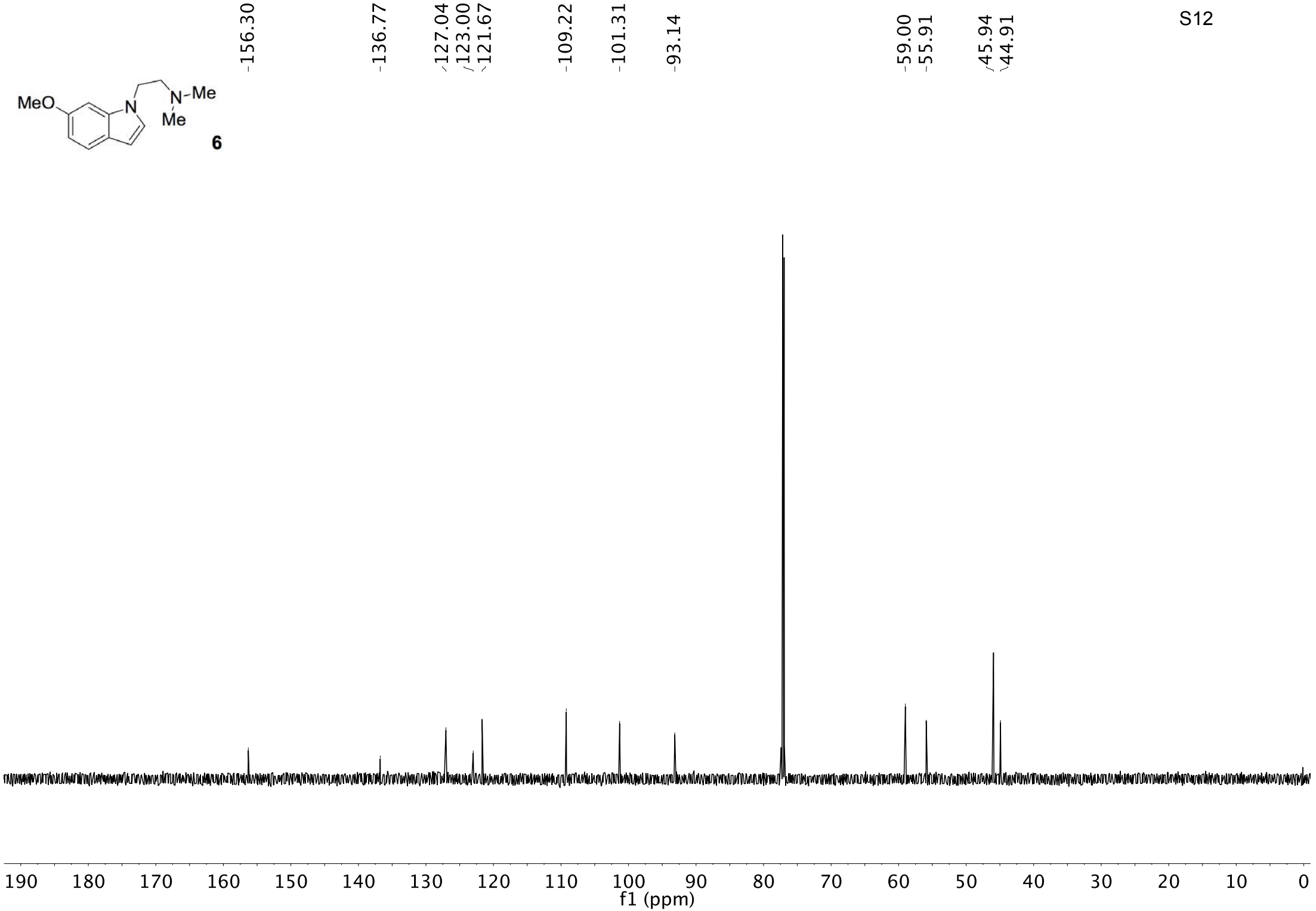

MeO
N
N-Me
Me

6


1.00
0.98
1.02
0.96
0.96
2.24
3.19
2.22
6.42
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 0.0 -0.5 -1
f1 (ppm)

MeO
N
N-Me
Me

6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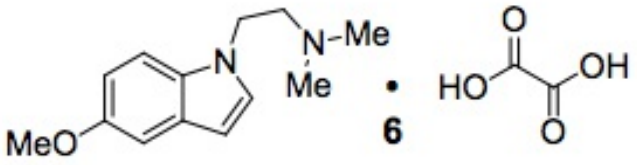
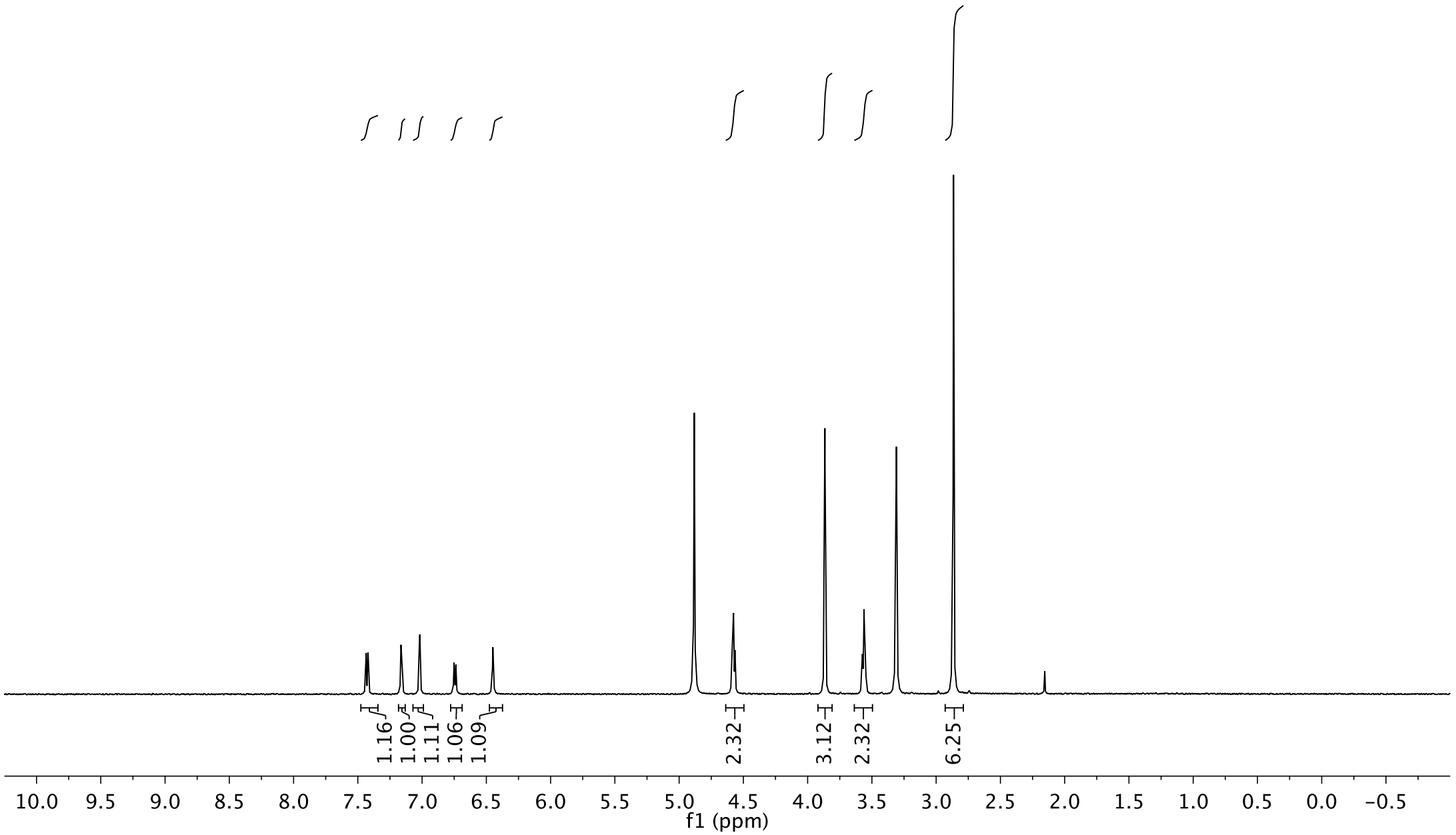
136.77
127.04
123.00
121.67
109.22
101.31
93.14
59.00
55.91
45.94
44.91
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N
N-Me
Me
MeO
HO
OH
O
O

6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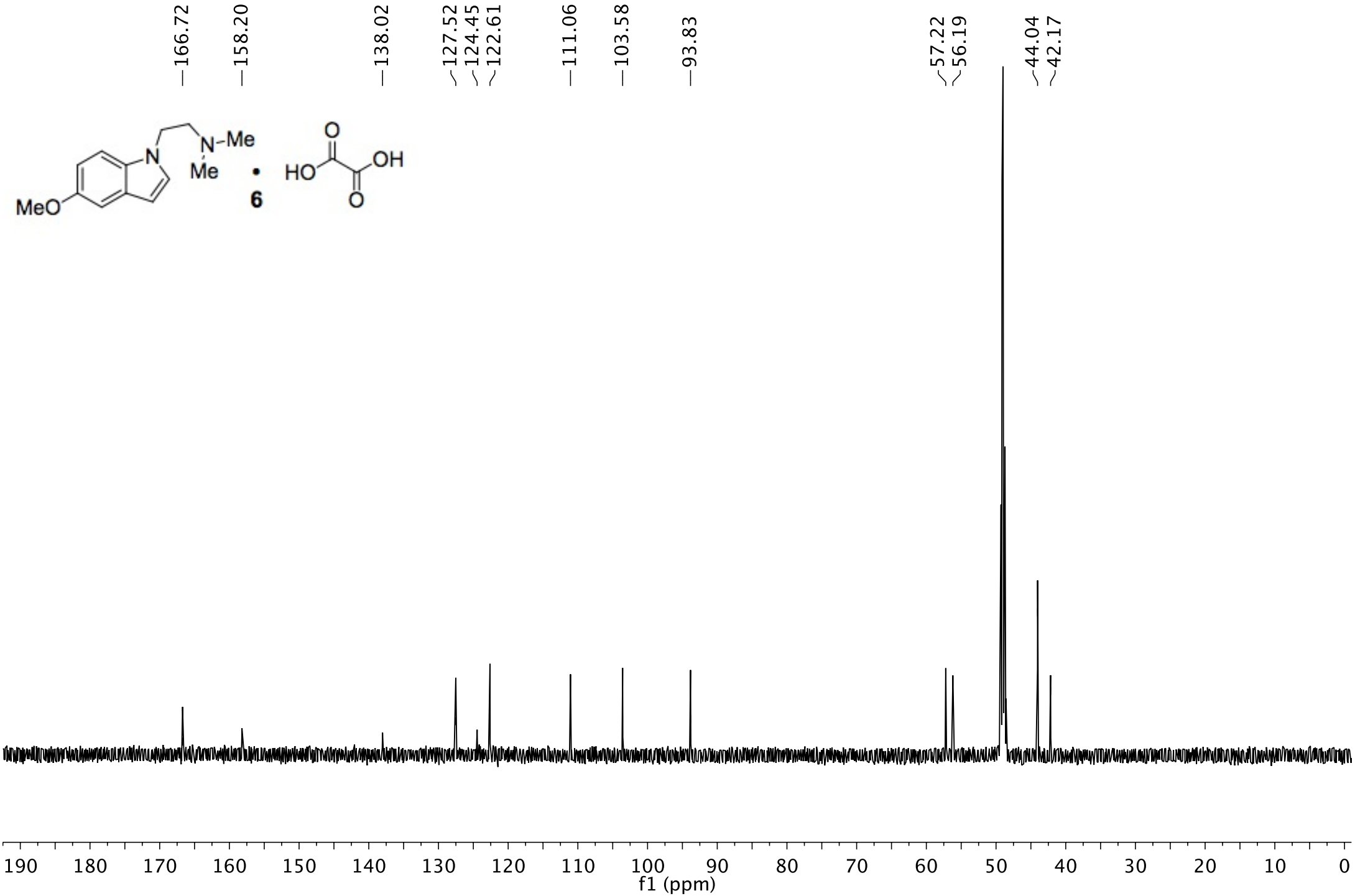
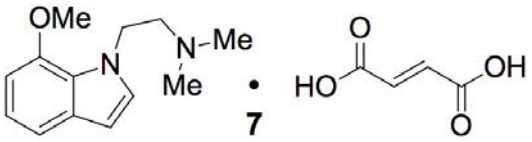
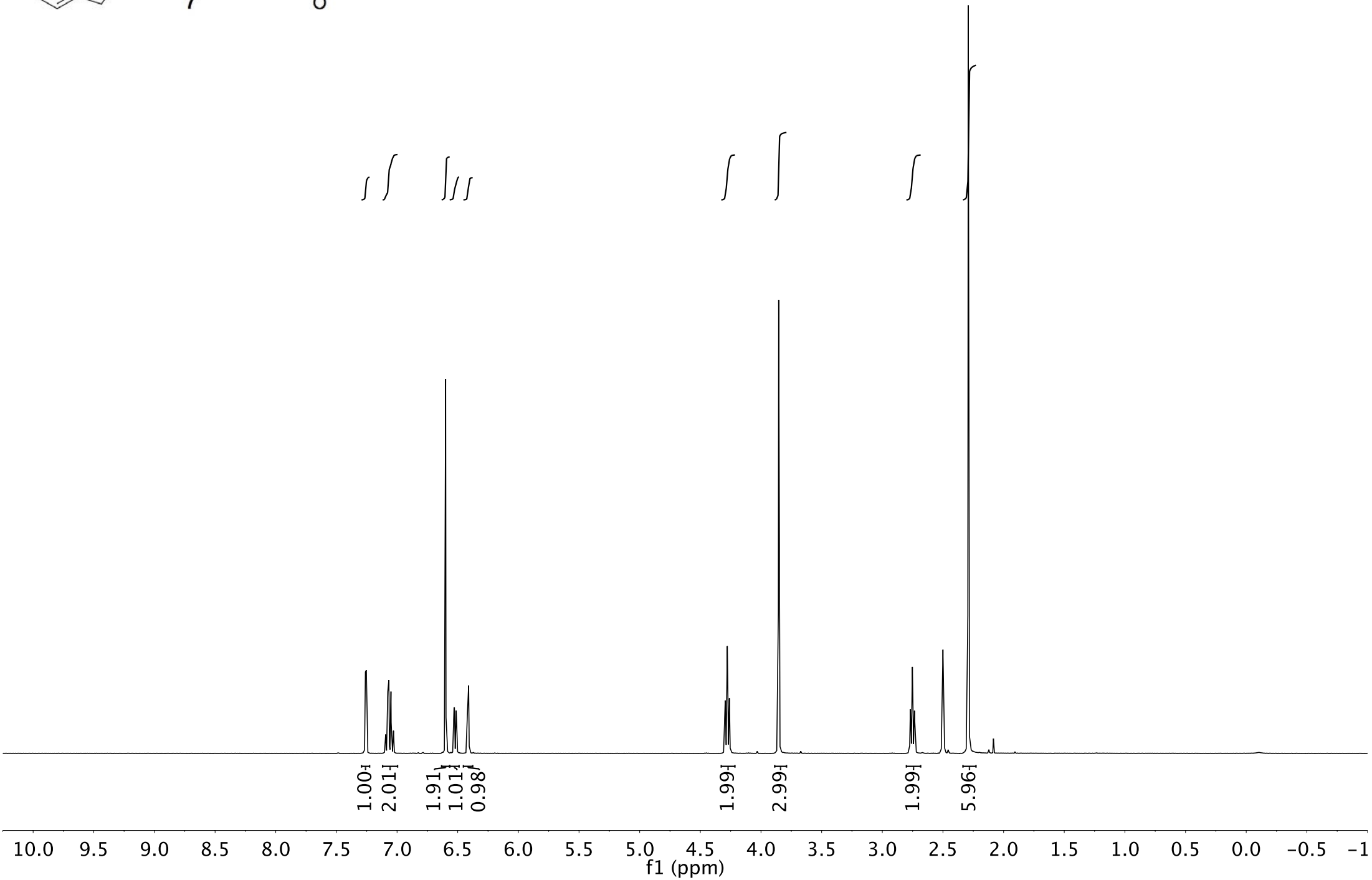
1.00
1.11
1.06
1.09
2.32
3.12
2.32
6.25
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


166.72
158.20
138.02
127.52
124.45
122.61
111.06
103.58
93.83
57.22
56.19
44.04
42.17
N
N-Me
Me
MeO
6
HO
OH
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OMe
N
N-Me
Me
•
HO
O
OH
O

7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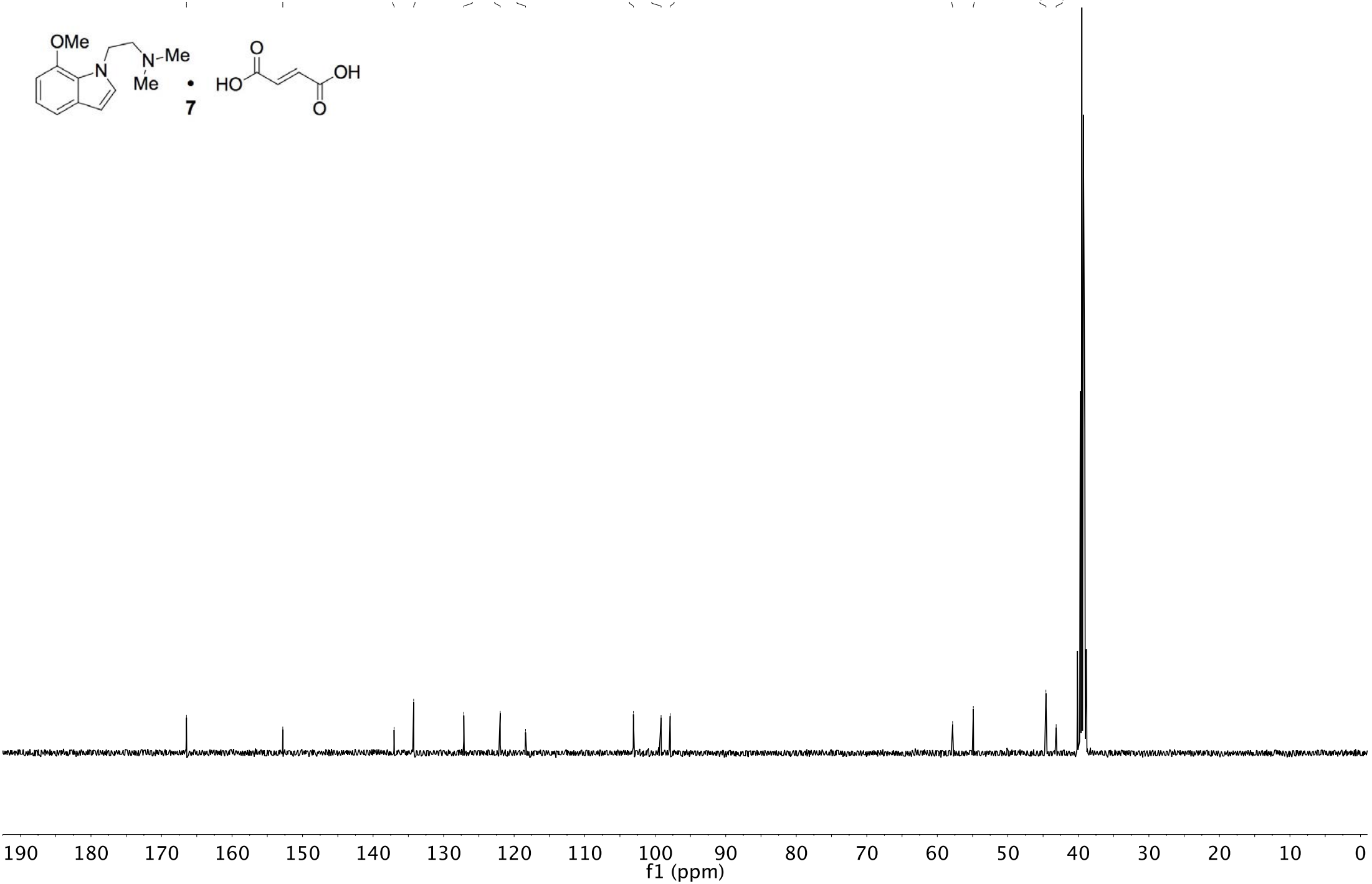
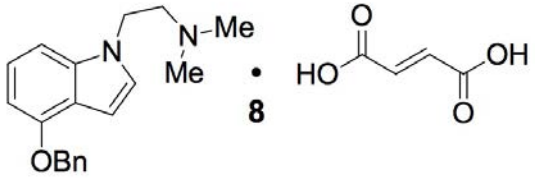
2.01
1.91
1.01
0.98
1.99
2.99
1.99
5.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)

166.46
152.80
137.02
134.24
127.14
121.98
118.38
103.09
99.16
97.88
57.83
54.89
44.60
43.15

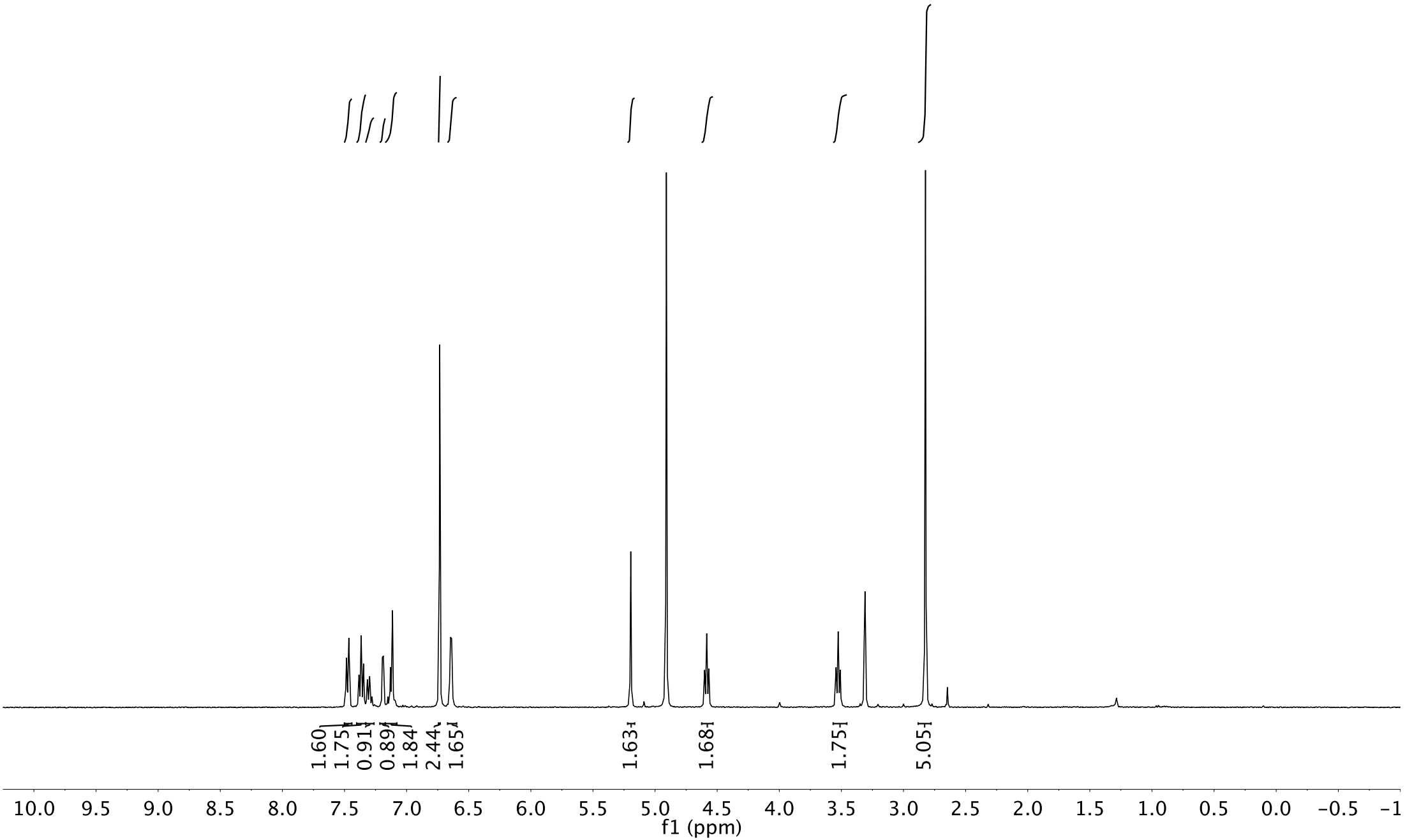
•

7




N
N-Me
Me
OBn
HO
OH
O
O

8


1.60
1.75
0.91
0.89
1.84
2.44
1.65
1.63
1.68
1.75
5.05
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 0.0 −0.5 −1
f1 (ppm)

169.90
153.99
139.05
138.85
135.75
129.47
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128.47
127.21
124.18
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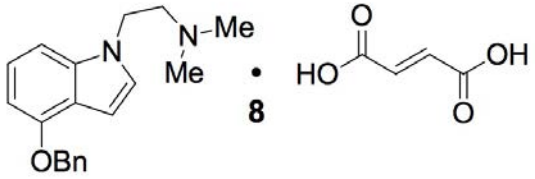
42.46



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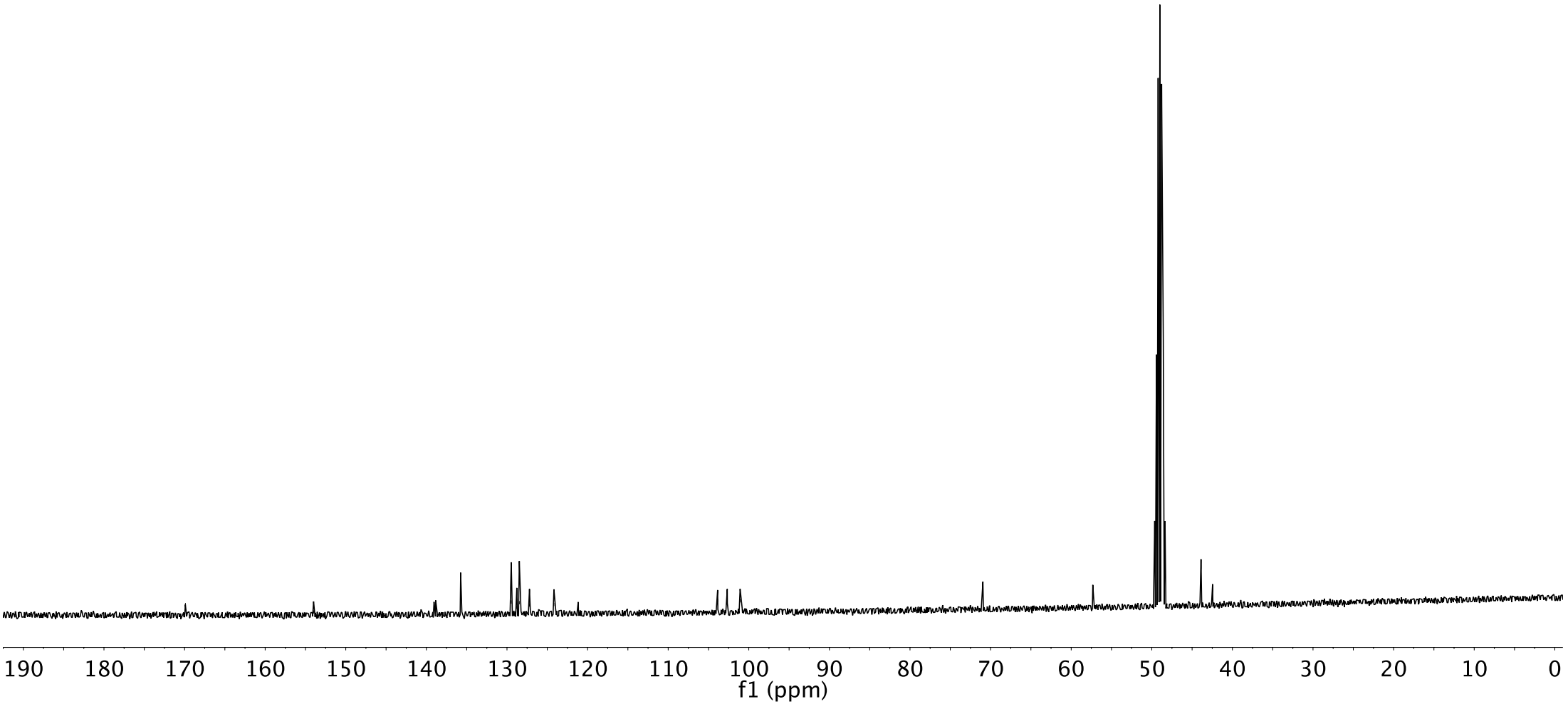
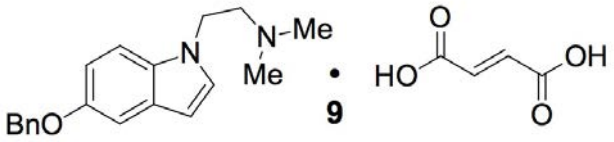
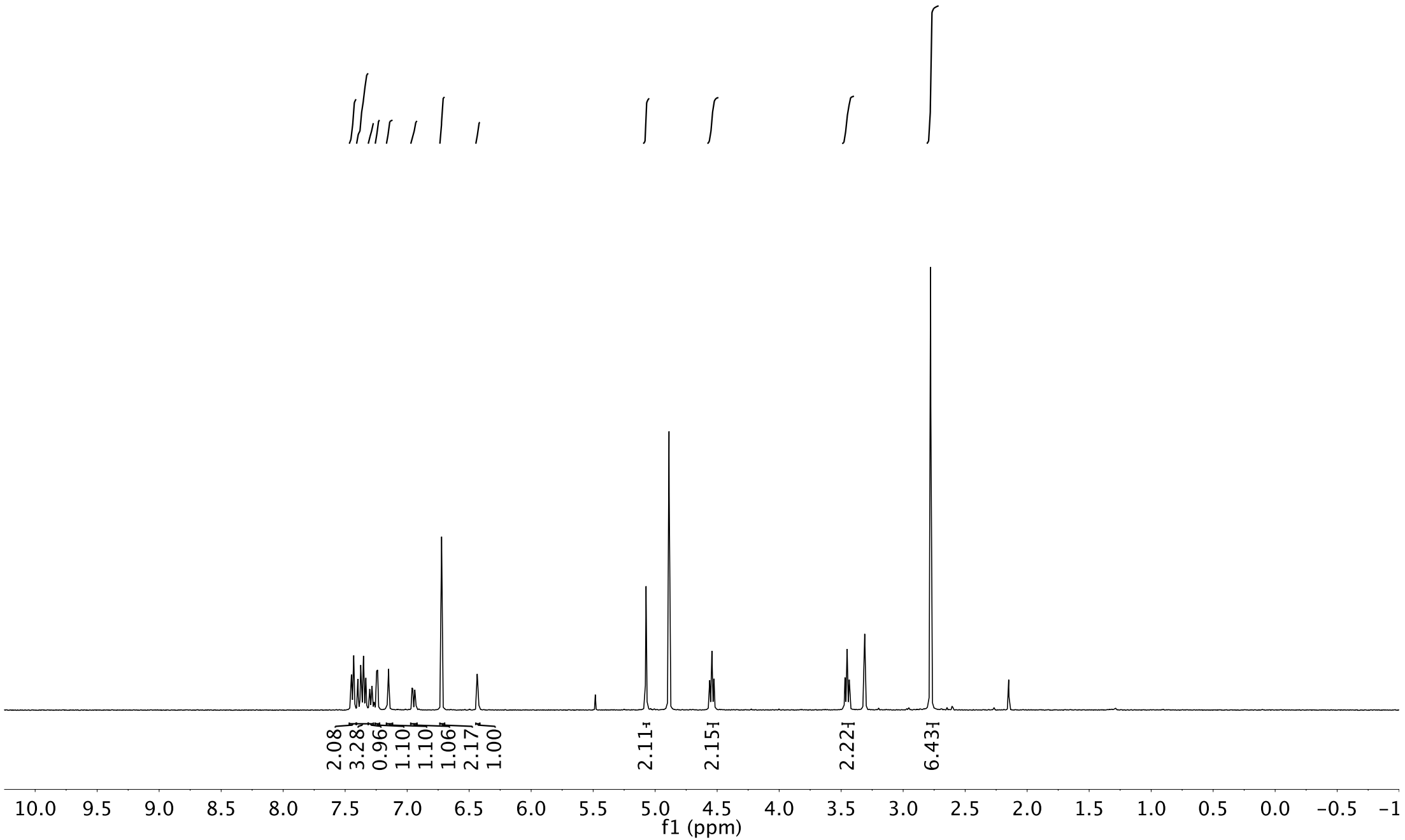



N
N-Me
Me
BnO
HO
OH
O
O

9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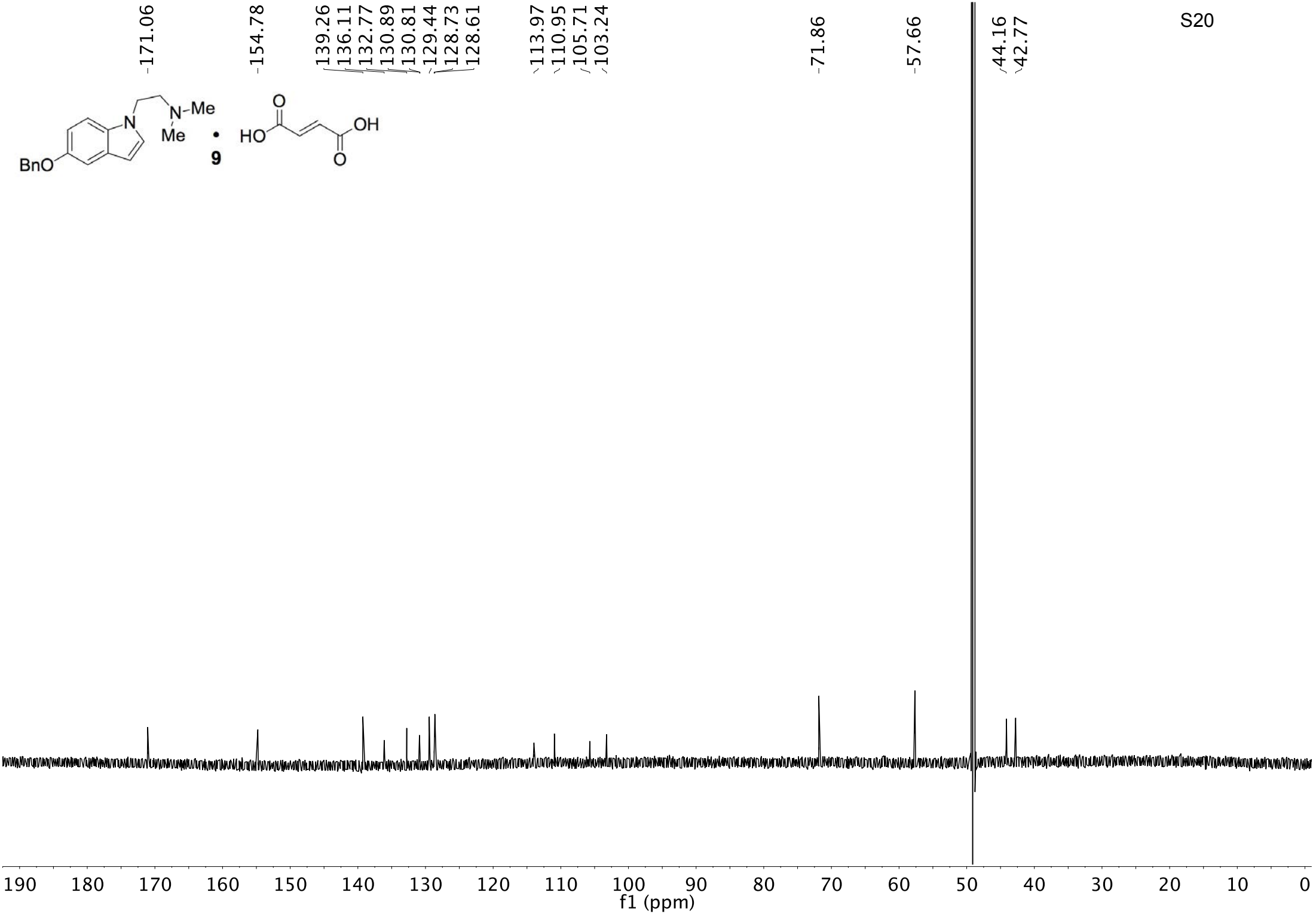
0.96
1.10
1.10
1.06
2.17
1.00
2.11
2.15
2.22
6.43
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1
f1 (ppm)

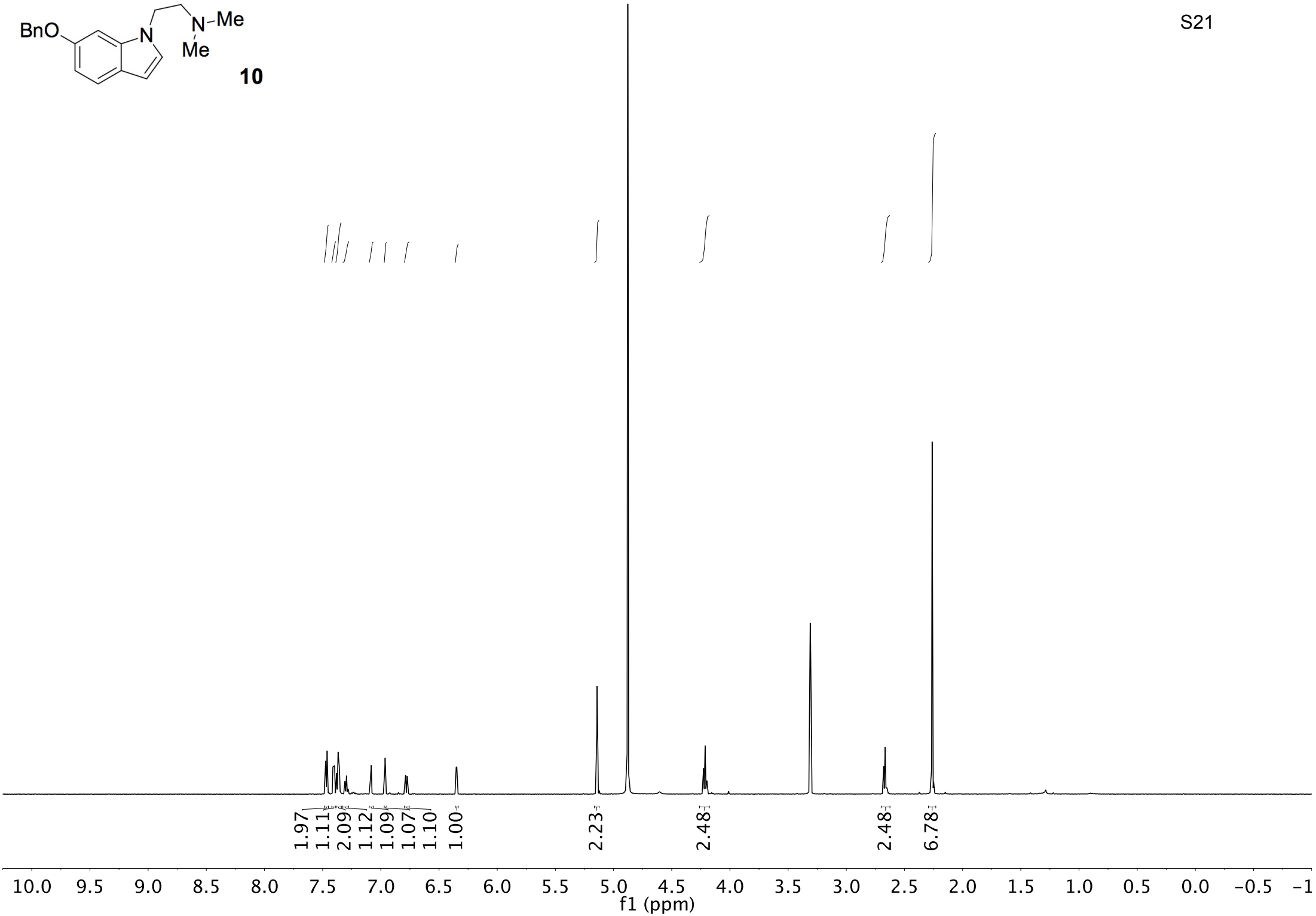
9

171.06
154.78
139.26
136.11
132.77
130.89
130.81
129.44
128.73
128.61
113.97
110.95
105.71
103.24
71.86
57.66
44.16
42.77



BnO
N
N-Me
Me

10


1.97
1.11
2.09
1.12
1.09
1.07
1.10
1.00
2.23
2.48
2.48
6.78
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 0.0 -0.5 -1
f1 (ppm)

155.39
137.60
136.66
128.69
127.97
127.67
127.22
123.24
121.68
109.95
101.31
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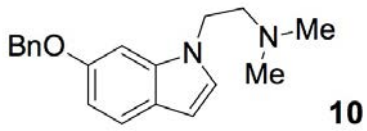
45.91
44.90



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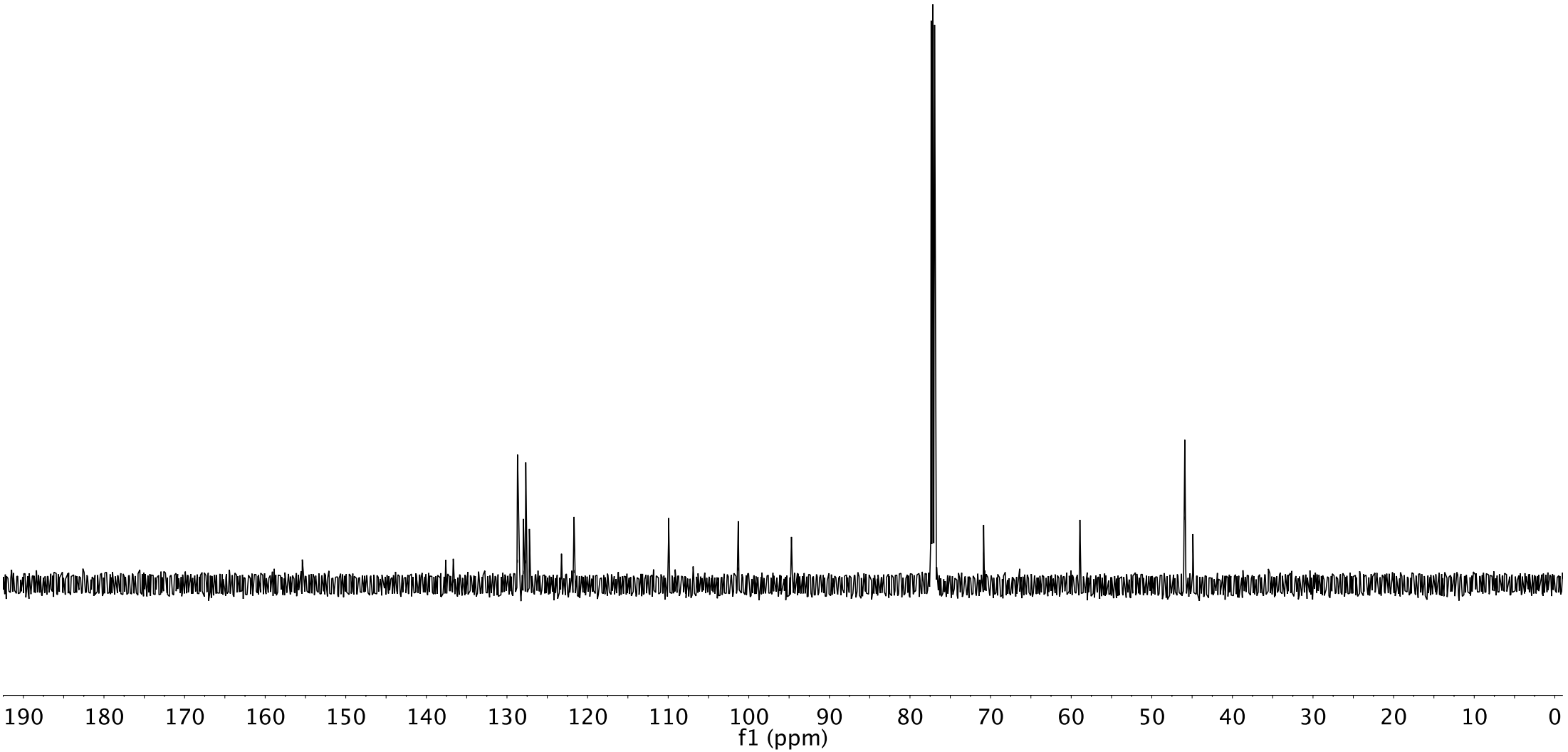
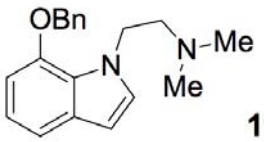
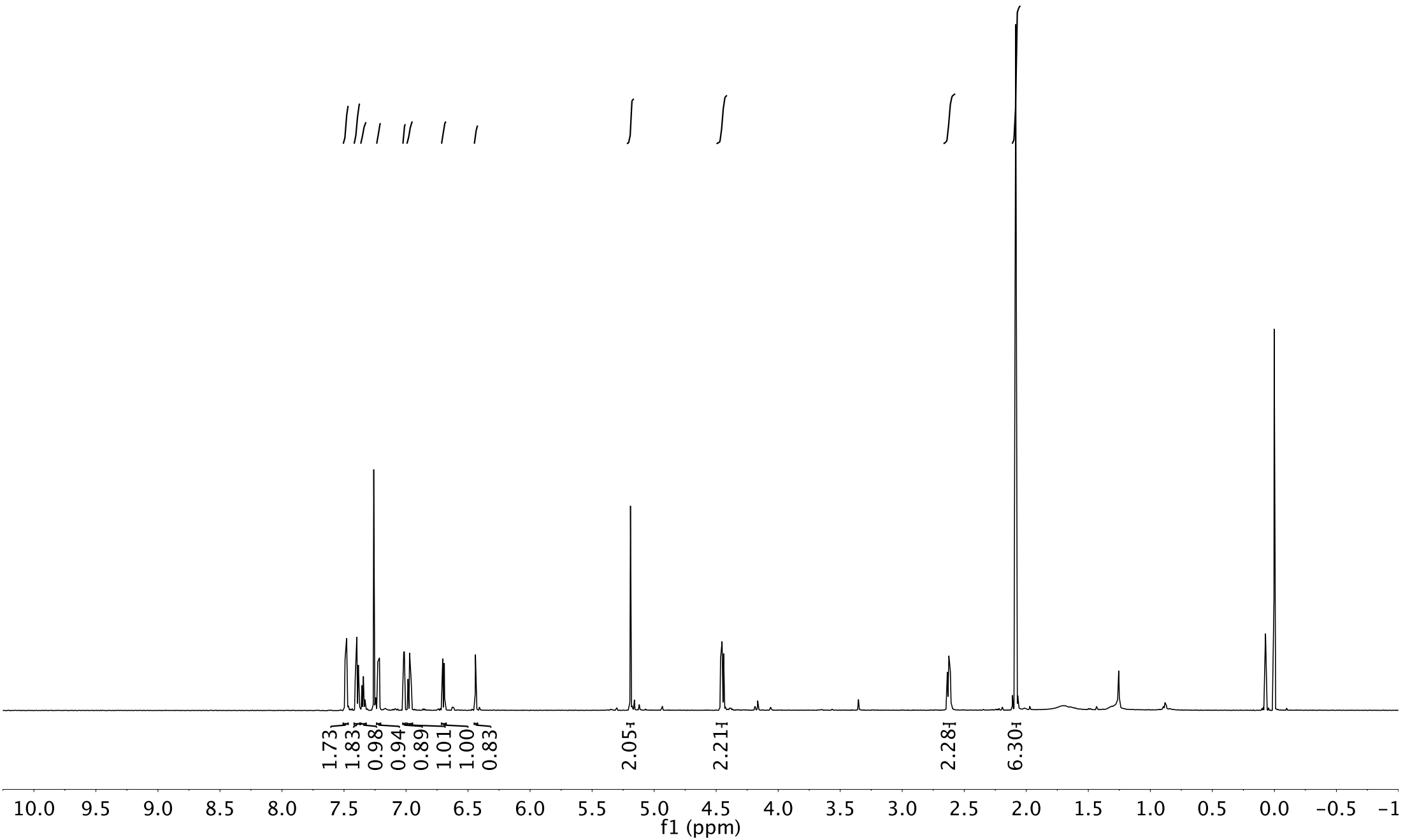
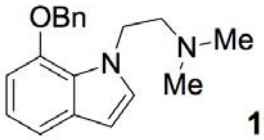



OBn
N
N-Me
Me

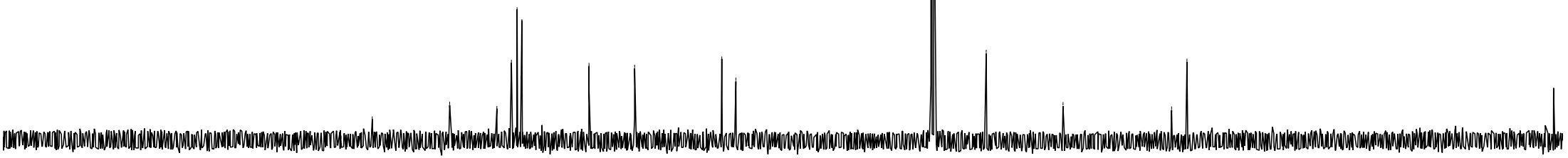
11

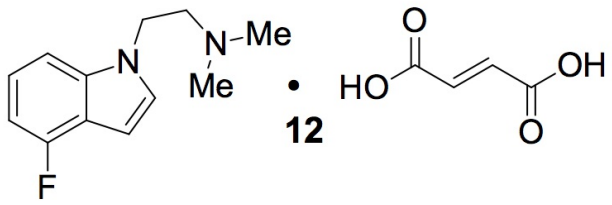

1.73
1.83
0.98
0.94
0.89
1.01
1.00
0.83
2.05
2.21
2.28
6.30
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)

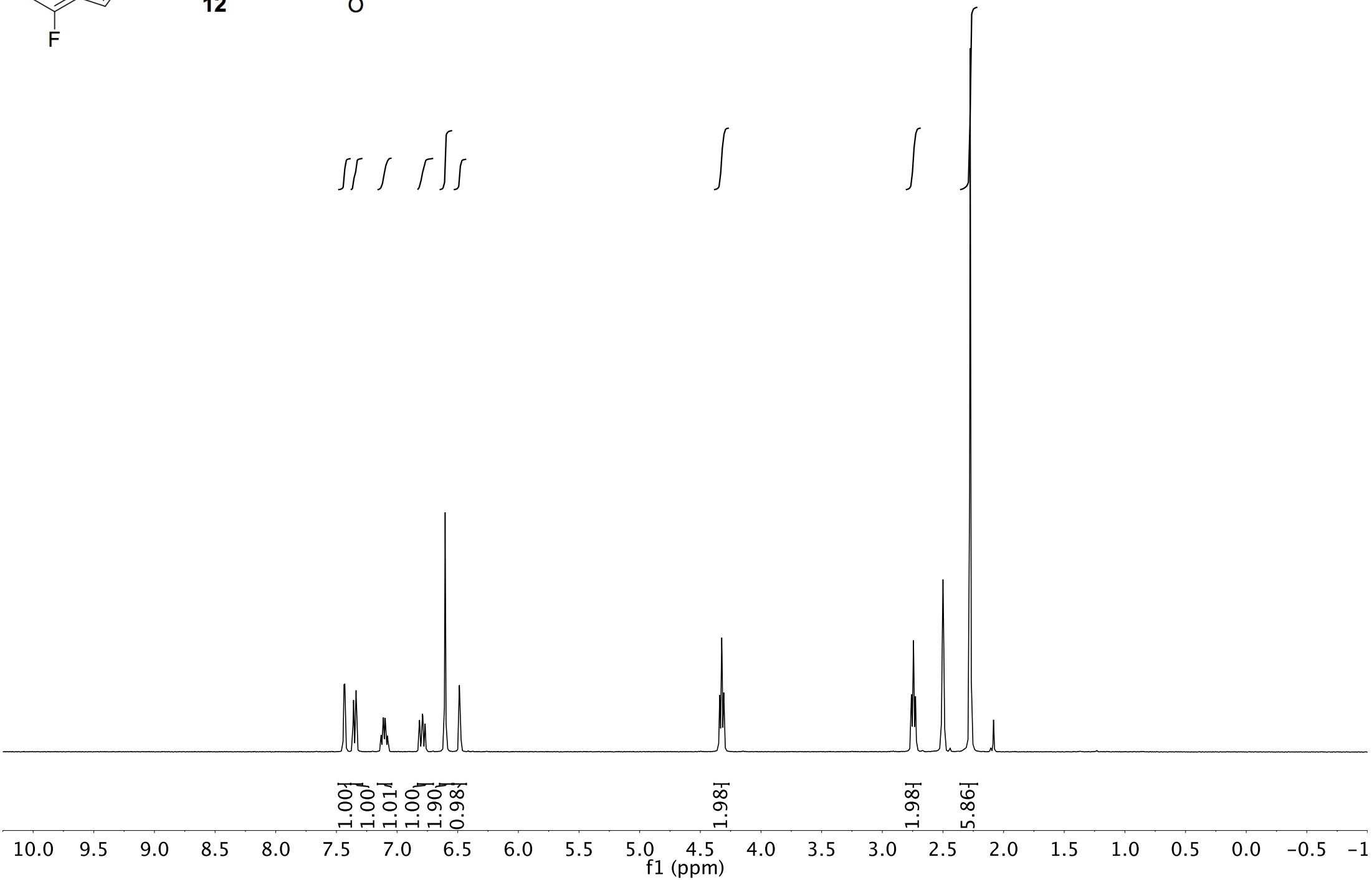


11

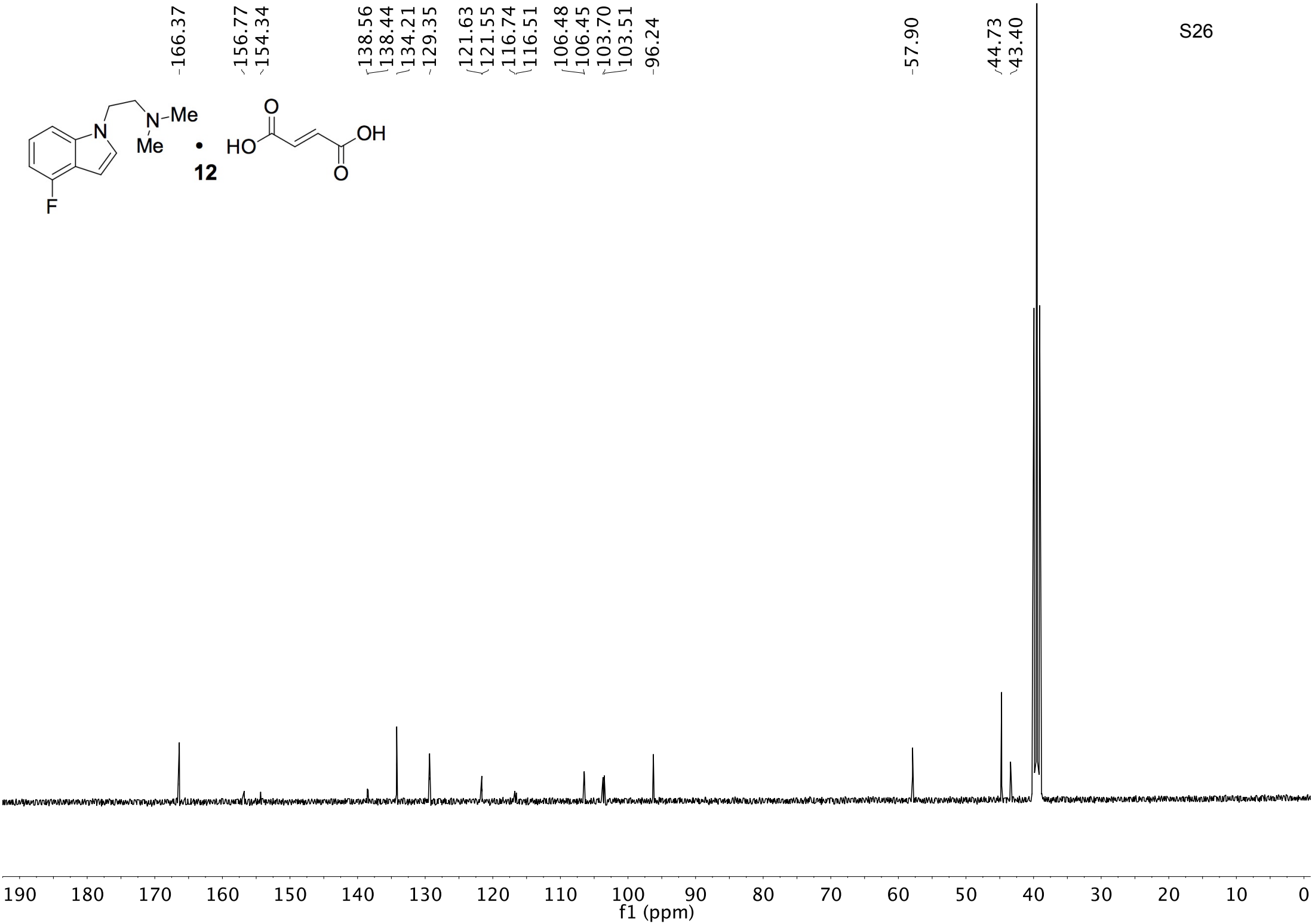
150.59
146.71
137.11
131.25
129.45
128.75
128.24
128.15
119.82
114.16
103.35
101.60
70.55
61.02
47.54
45.64

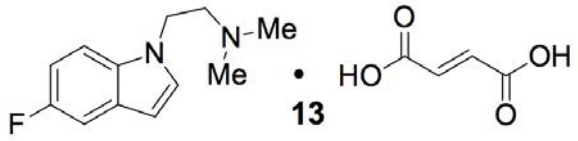



N
N-Me
Me
F
12
HO
O
OH
O

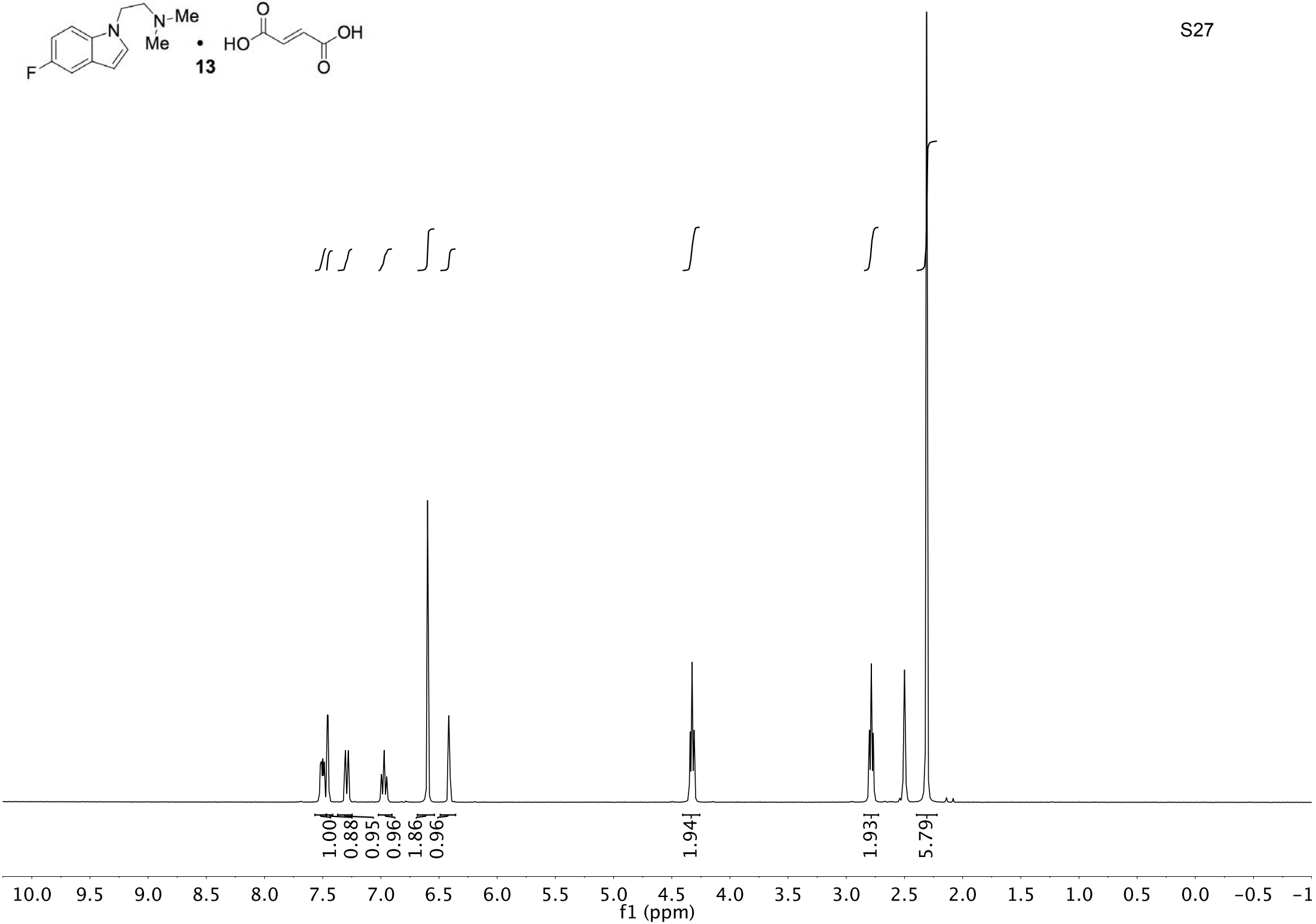

1.00
1.00
1.01
1.00
1.90
0.98
1.98
1.98
5.86
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1
f1 (ppm)

166.37
156.77
154.34
138.56
138.44
134.21
129.35
121.63
121.55
116.74
116.51
106.48
106.45
103.70
103.51
96.24
57.90
44.73
43.40



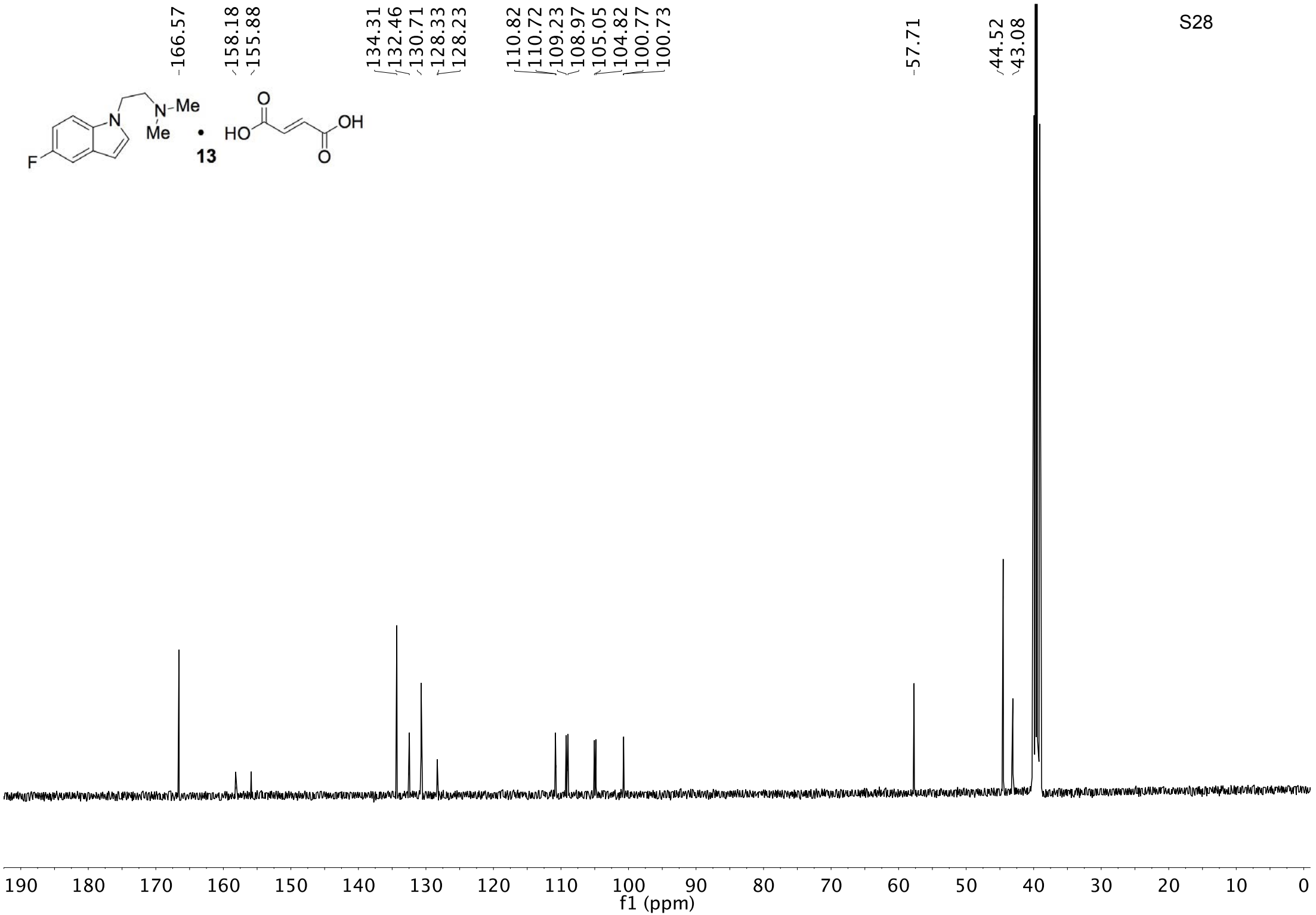

N
N-Me
Me
F
HO
OH
O
O

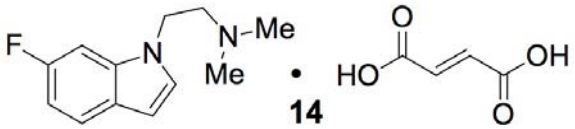
13


1.00
0.88
0.95
0.96
1.86
0.96
1.94
1.93
5.79
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
0.0
−0.5
−1
f1 (ppm)

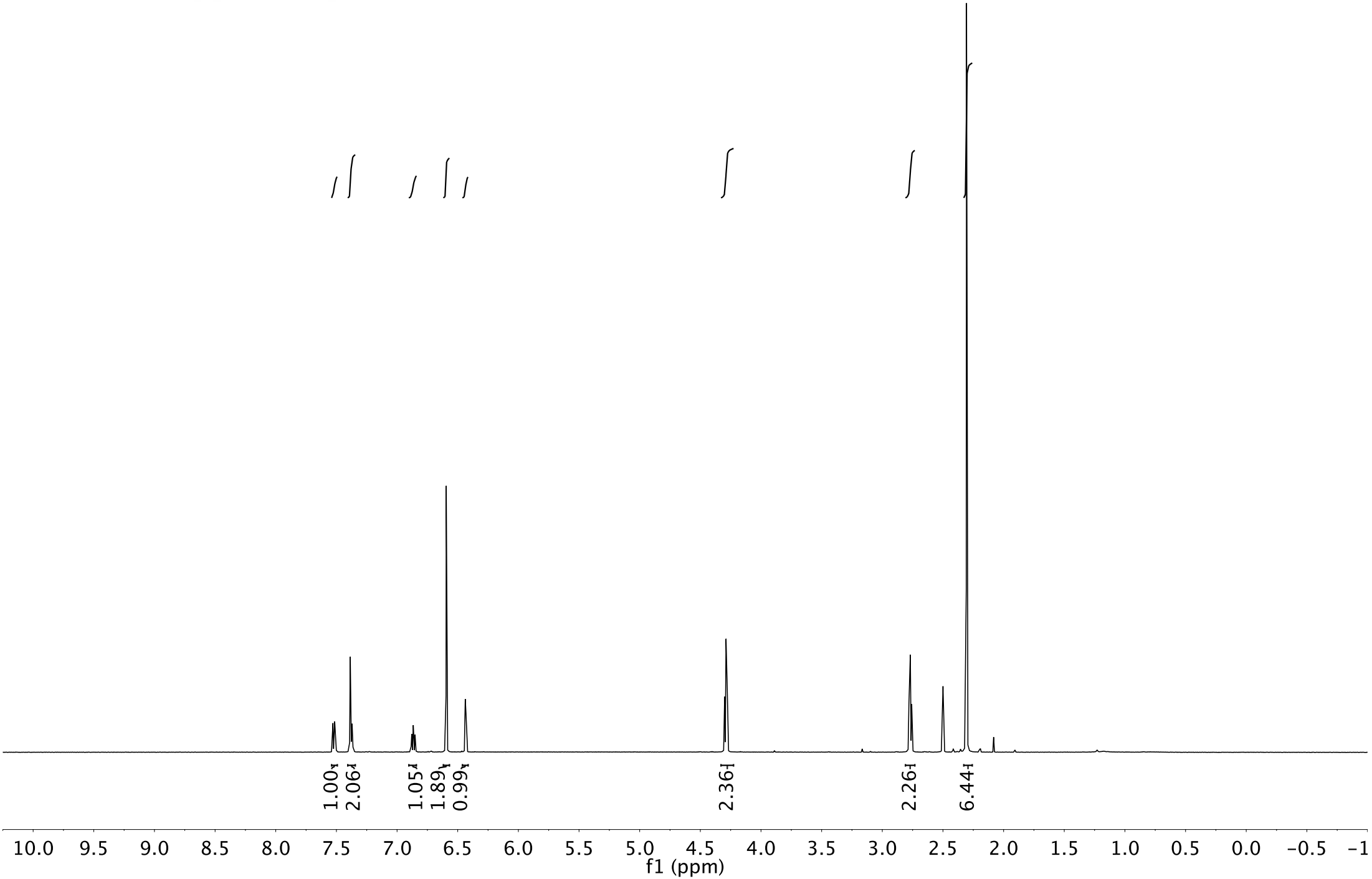
13

166.57
158.18
155.88
134.31
132.46
130.71
128.33
128.23
110.82
110.72
109.23
108.97
105.05
104.82
100.77
100.73
57.71
44.52
43.08



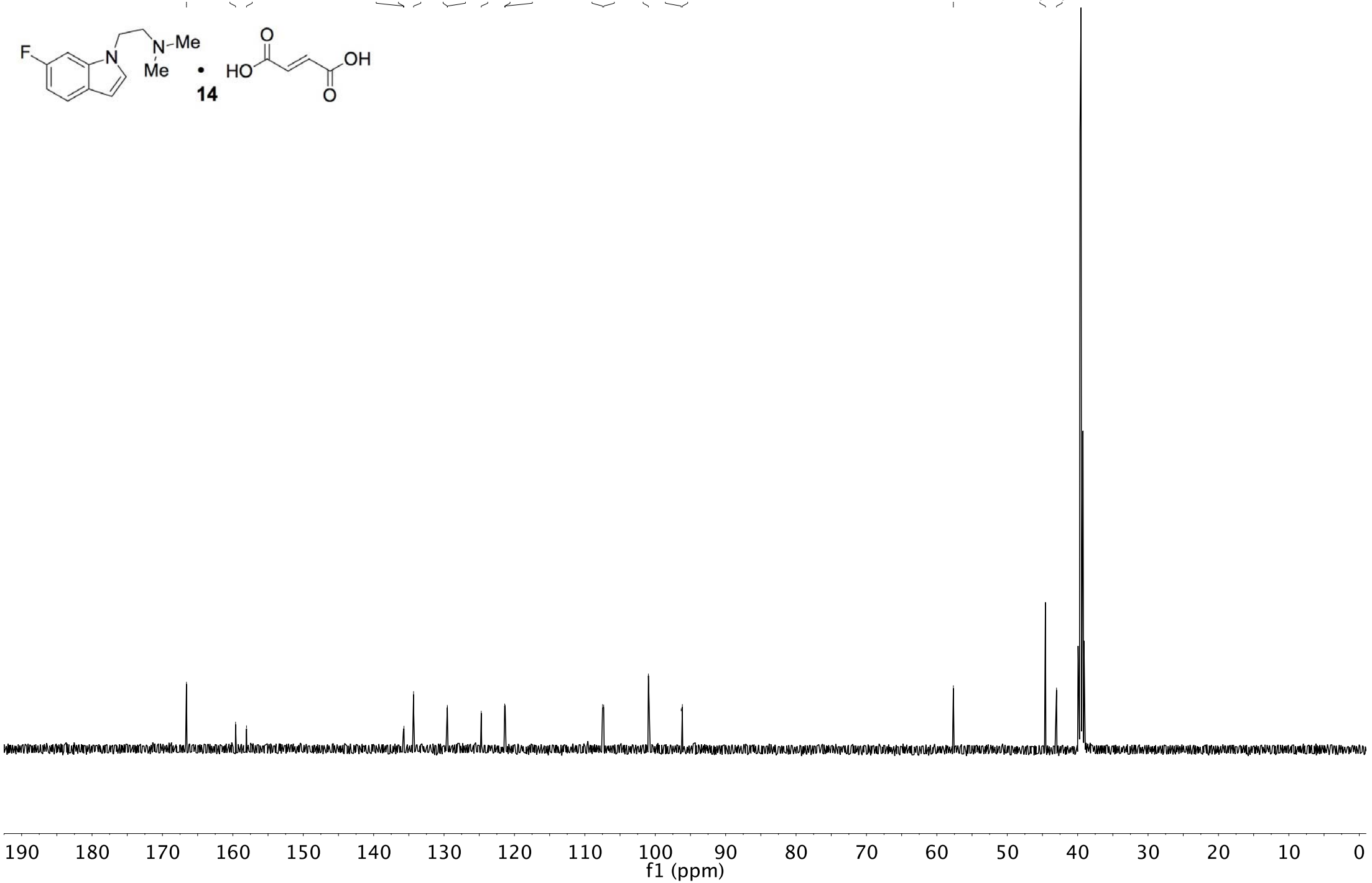

F
N
N-Me
Me
HO
OH
O
O

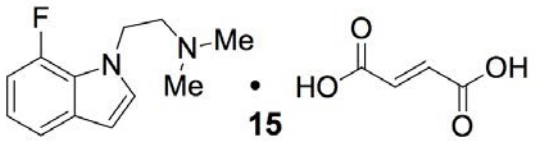
14


1.00
2.06
1.05
1.89
0.99
2.36
2.26
6.44
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 0.0 −0.5 −1
f1 (ppm)

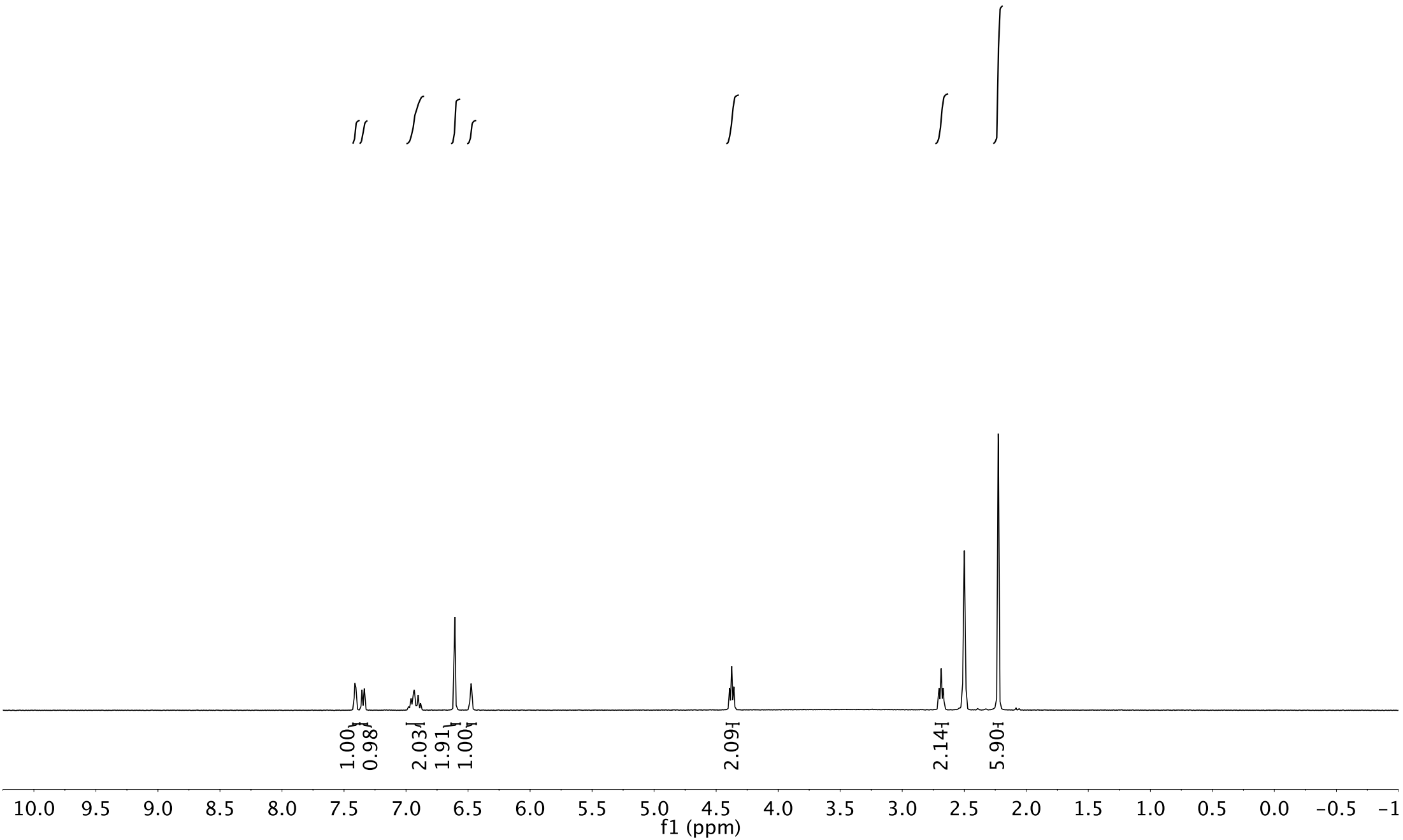
14

166.59
159.61
158.06
135.77
135.69
134.33
129.54
129.51
124.72
121.39
121.32
107.48
107.32
100.97
96.32
96.15
57.66
44.58
43.00



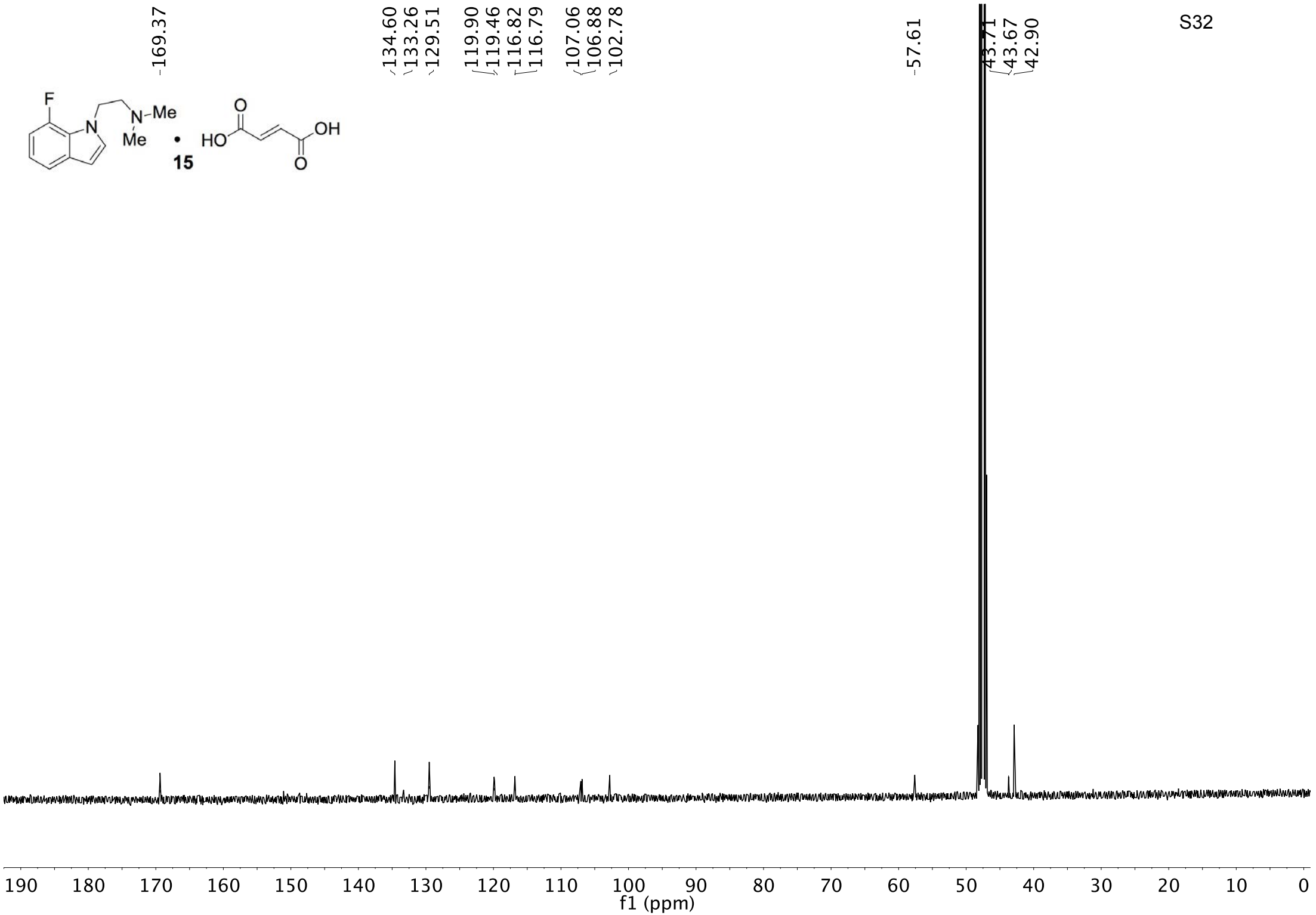

F
N
N-Me
Me
HO
O
OH
O

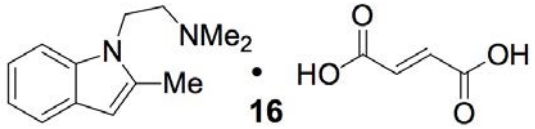
15


1.00
0.98
2.03
1.91
1.00
2.09
2.14
5.90
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 0.0 −0.5 −1
f1 (ppm)

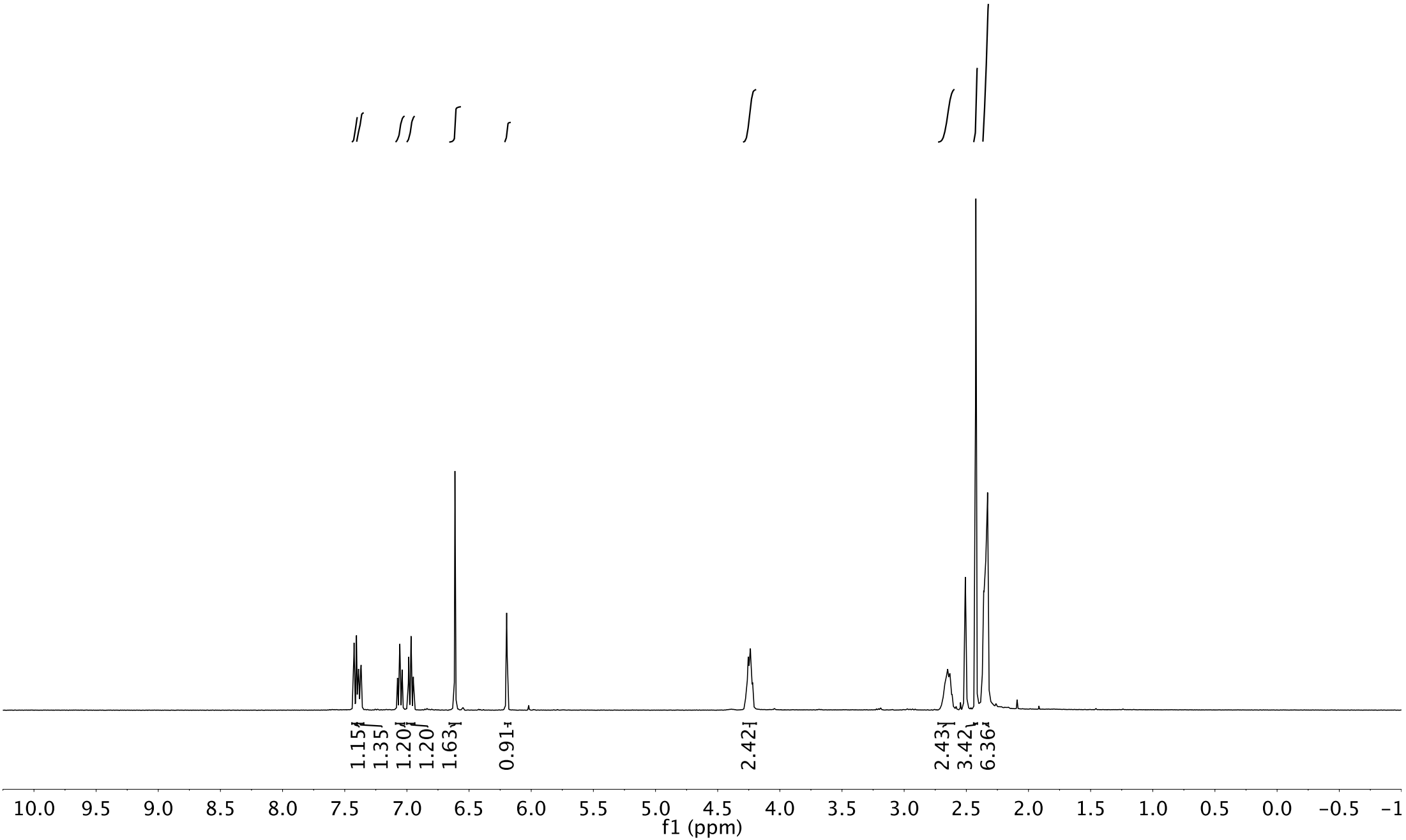
15

169.37
134.60
133.26
129.51
119.90
119.46
116.82
116.79
107.06
106.88
102.78
57.61
43.71
43.67
42.90



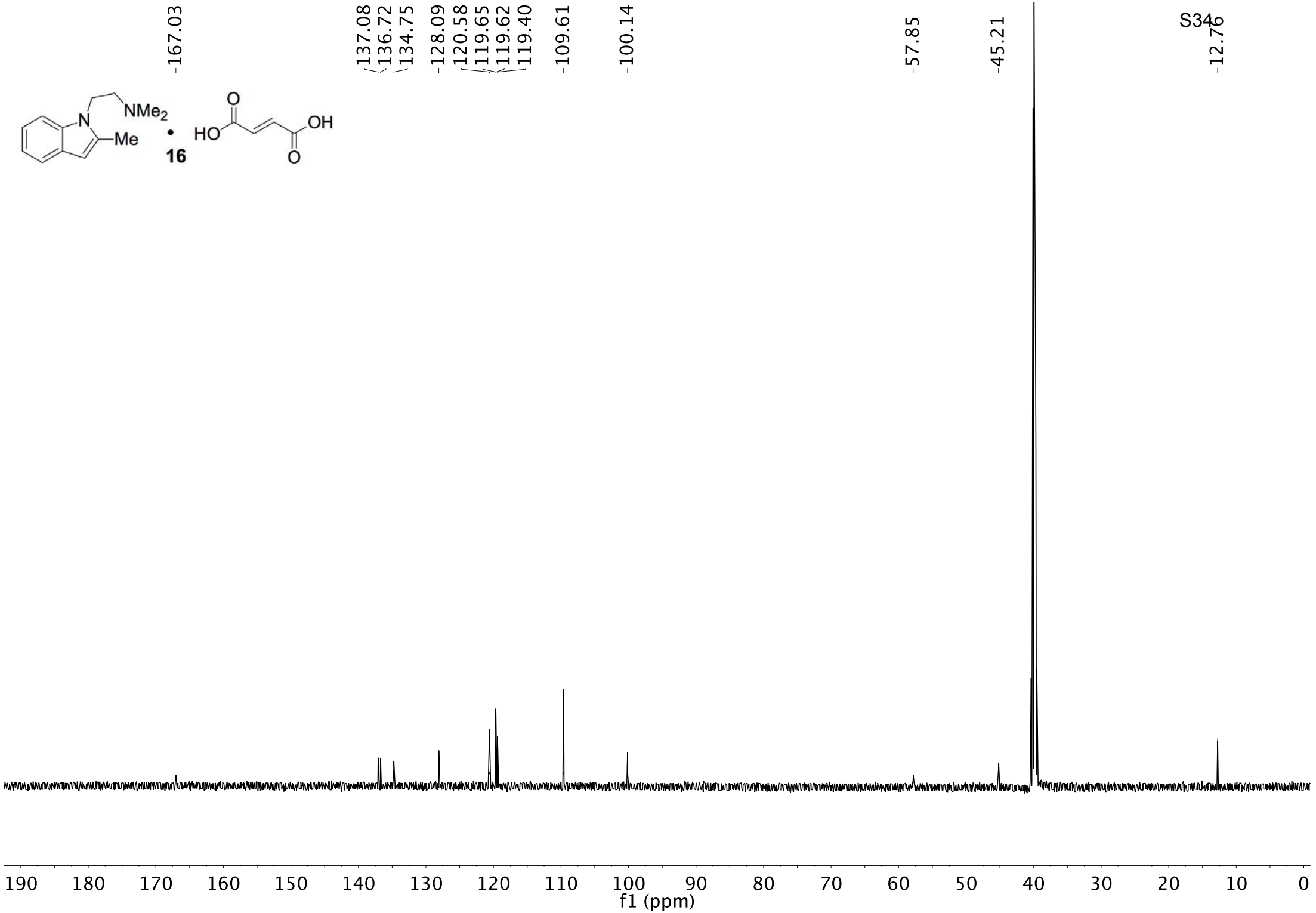

N
NMe2
Me
HO
OH
O
O

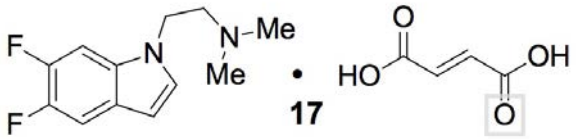
16


1.15
1.35
1.20
1.20
1.63
0.91
2.42
2.43
3.42
6.36
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 0.0 −0.5 −1
f1 (ppm)

NMe2
N
Me
HO
OH
O
O

16


167.03
137.08
136.72
134.75
128.09
120.58
119.65
119.62
119.40
109.61
100.14
57.85
45.21
12.76
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



17

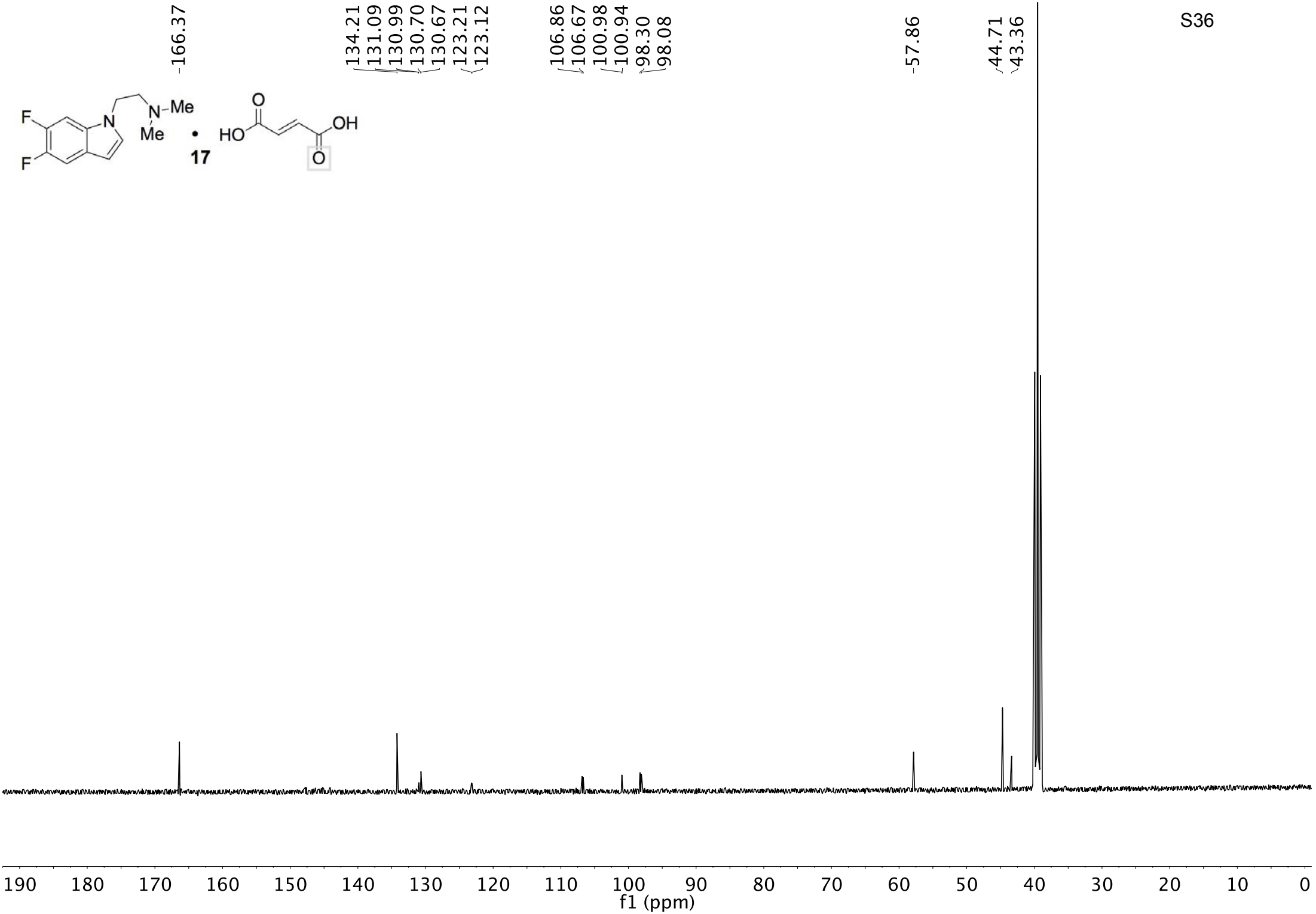
1.00
0.95
0.95
1.96
1.03
1.95
1.94
5.73

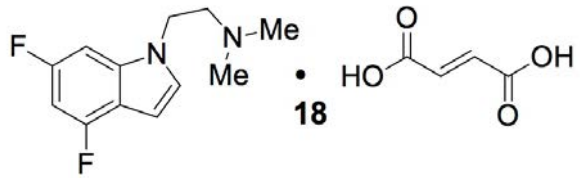
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1

f1 (ppm)

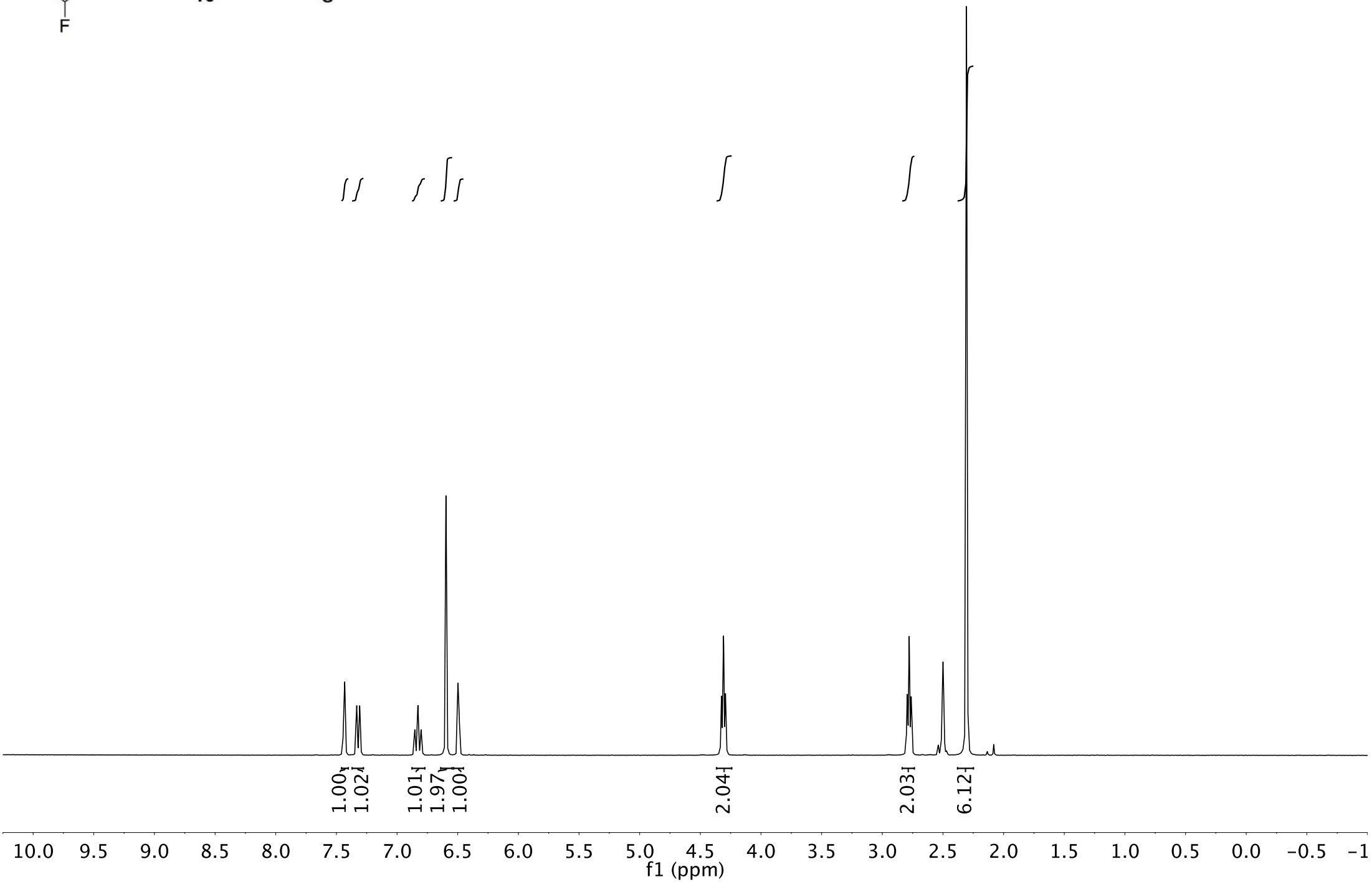
17

166.37
134.21
131.09
130.99
130.70
130.67
123.21
123.12
106.86
106.67
100.98
100.94
98.30
98.08
57.86
44.71
43.36



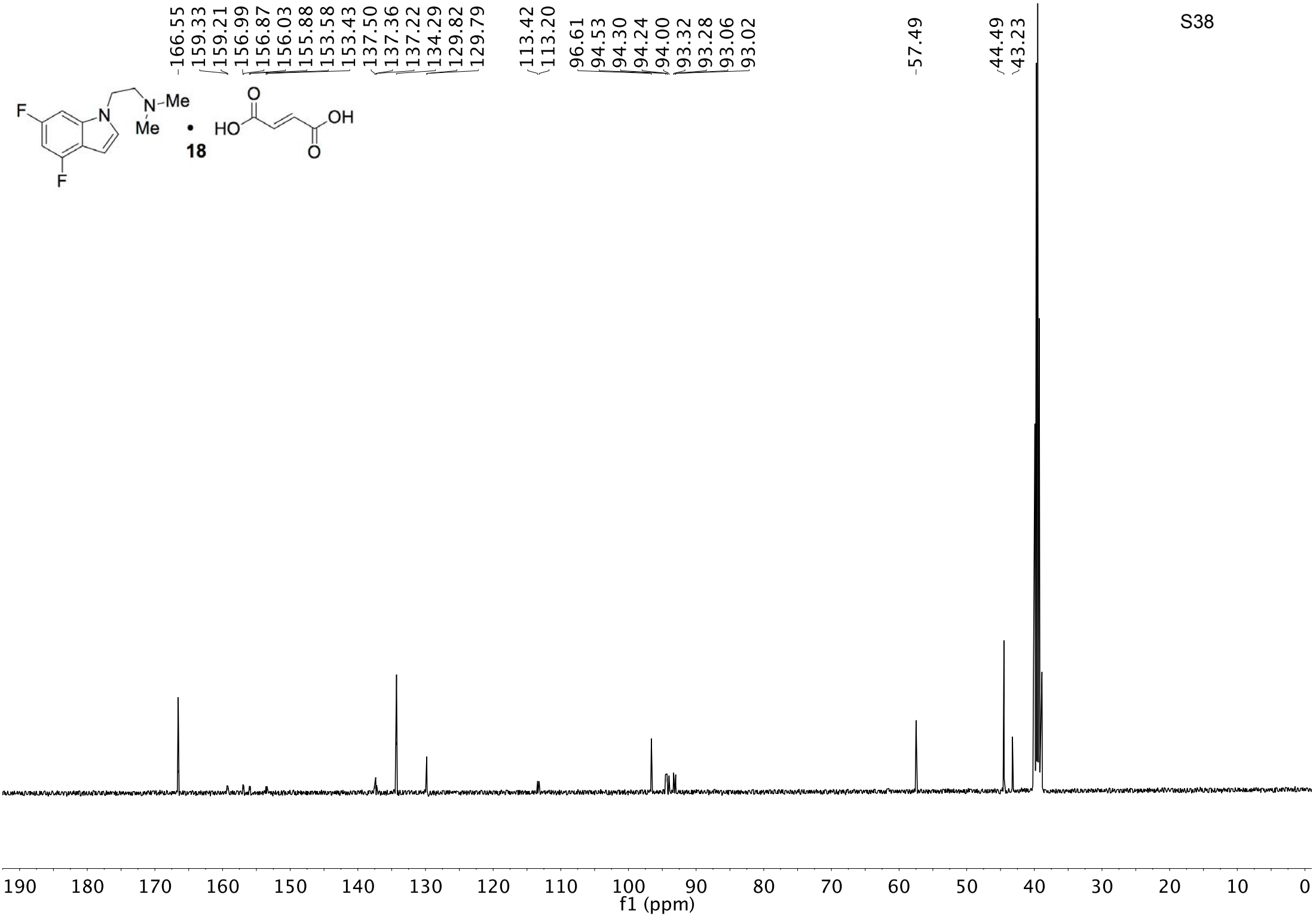

F
N
N-Me
Me
F
HO
O
OH
O

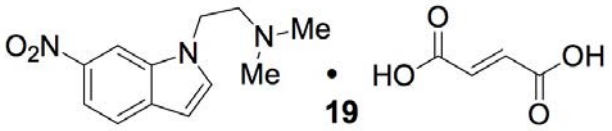
18


1.00
1.02
1.01
1.97
1.00
2.04
2.03
6.12
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 0.0 −0.5 −1
f1 (ppm)

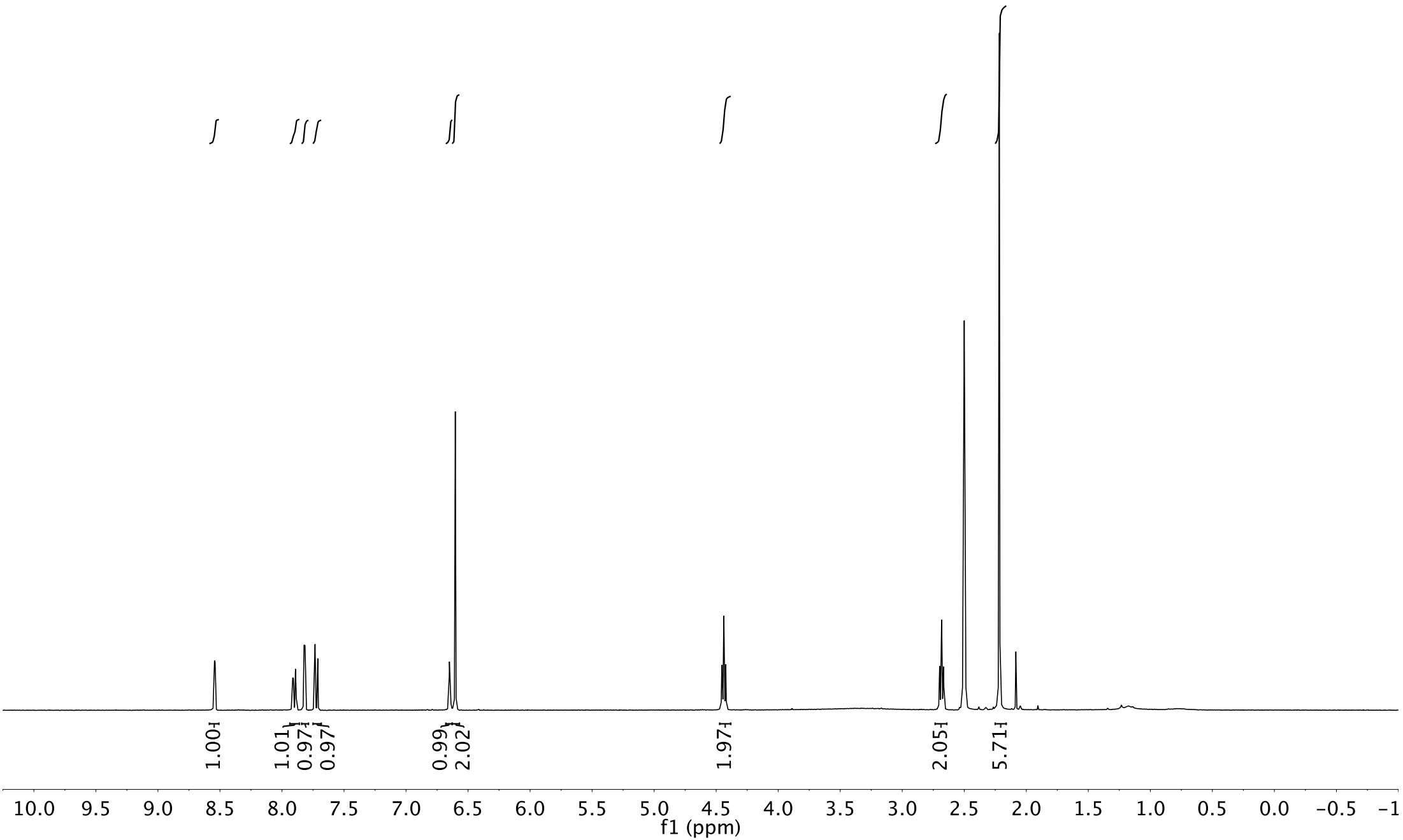
18

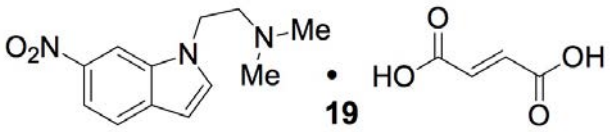
166.55
159.33
159.21
156.99
156.87
156.03
155.88
153.58
153.43
137.50
137.36
137.22
134.29
129.82
129.79
113.42
113.20
96.61
94.53
94.30
94.24
94.00
93.32
93.28
93.06
93.02
57.49
44.49
43.23




O2N
N
N-Me
Me
HO
OH
O
O

19

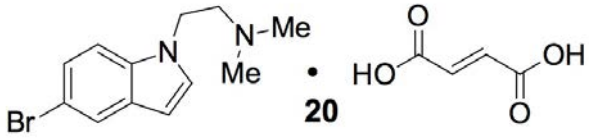

1.00
1.01
0.97
0.97
0.99
2.02
1.97
2.05
5.71
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)



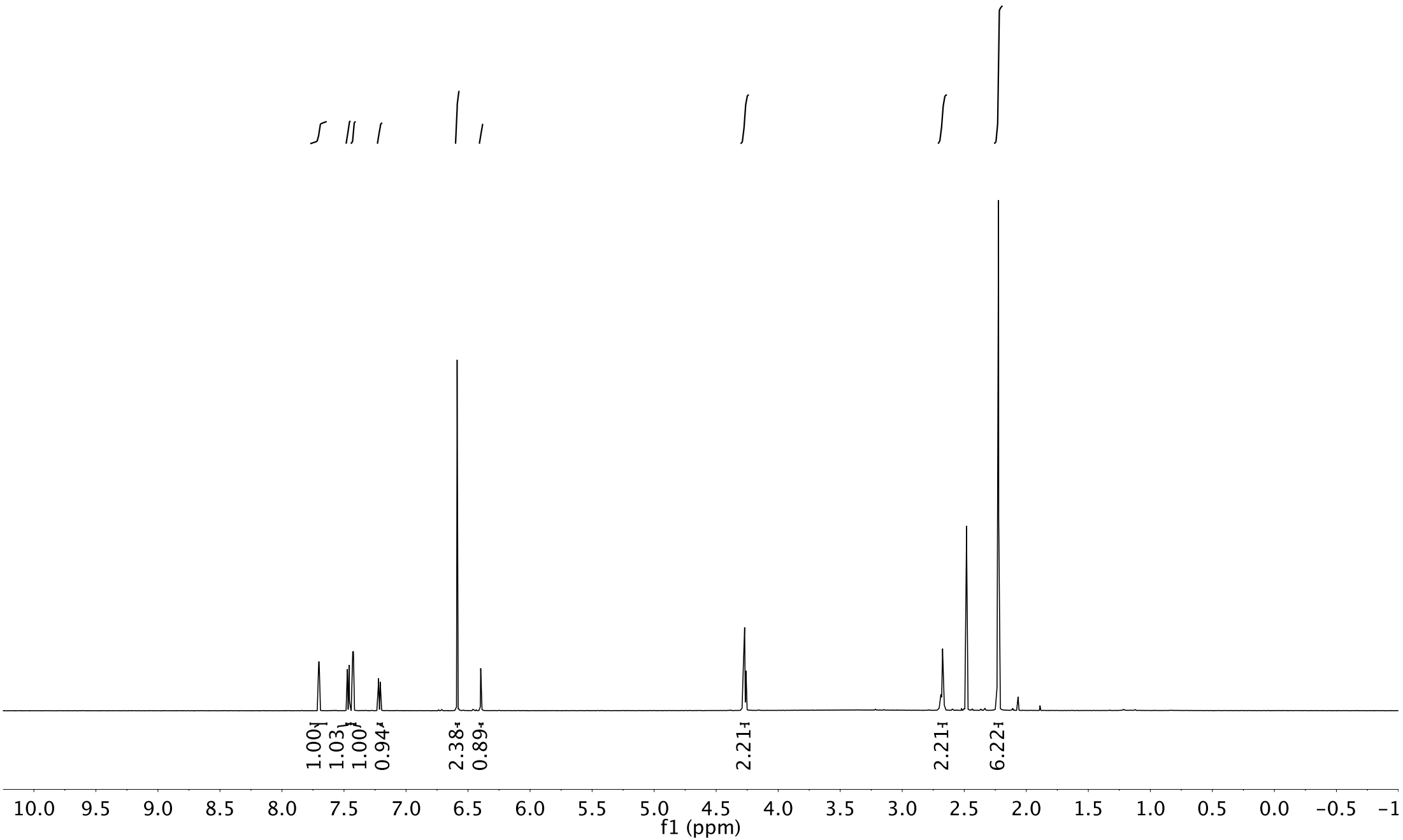
19

166.66
136.18
134.76
134.59
133.41
121.04
114.52
107.53
102.25
58.98
45.50
44.18
18.59

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

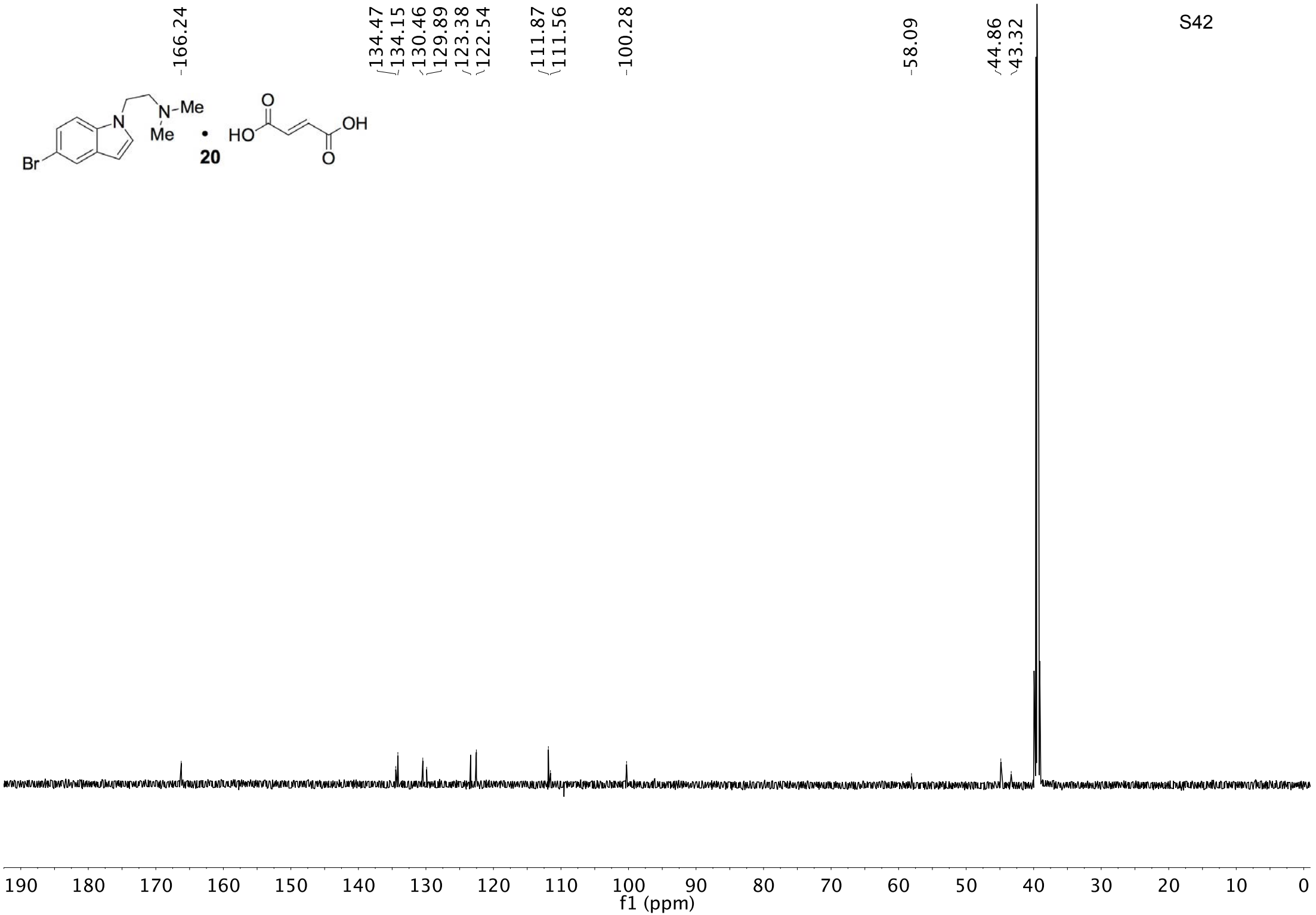

N
N-Me
Me
Br
HO
OH
O
O

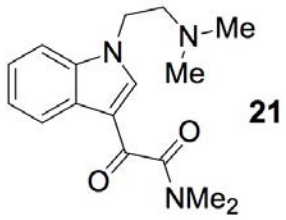
20


1.00
1.03
1.00
0.94
2.38
0.89
2.21
2.21
6.22
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 0.0 −0.5 −1
f1 (ppm)

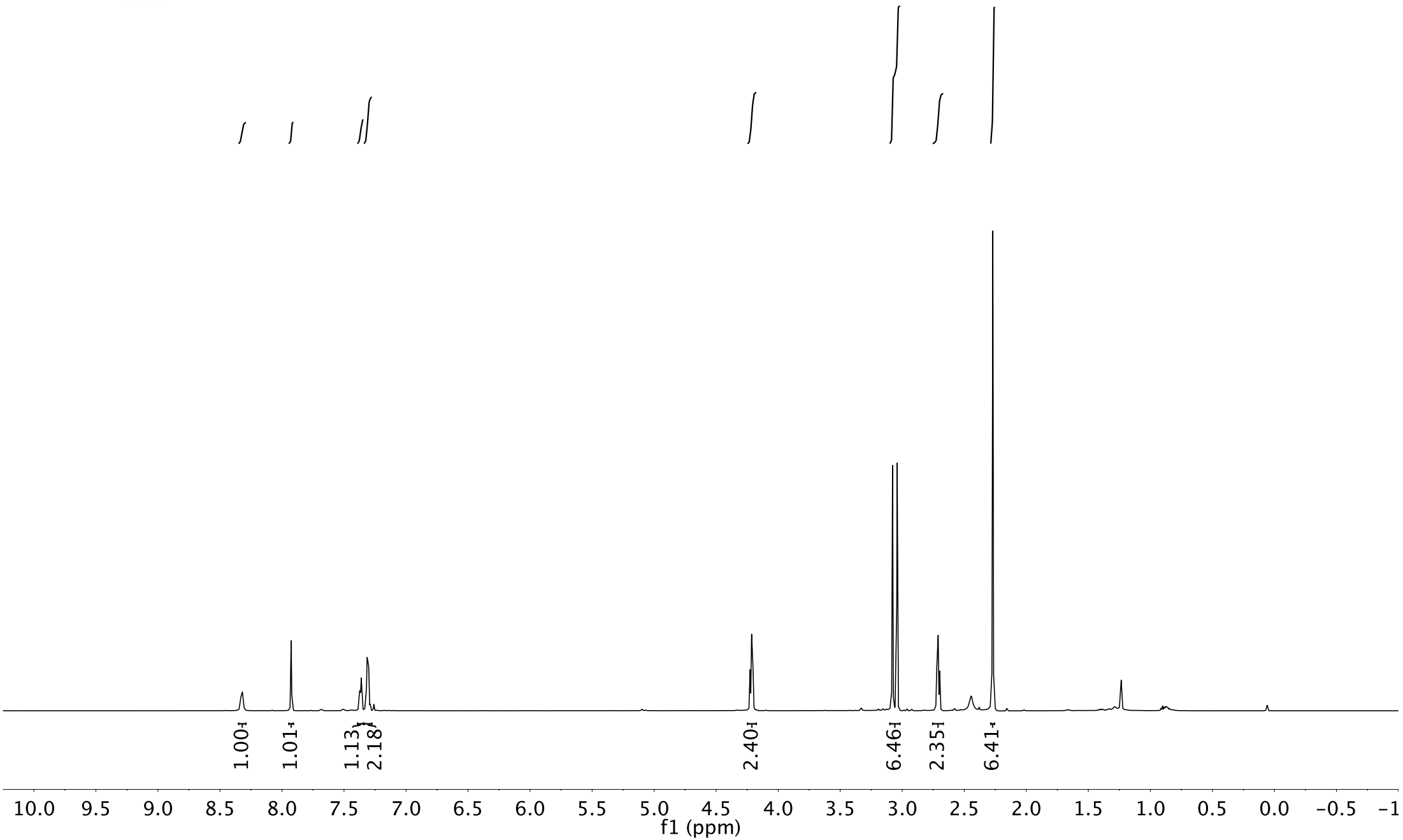
20

166.24
134.47
134.15
130.46
129.89
123.38
122.54
111.87
111.56
100.28
58.09
44.86
43.32

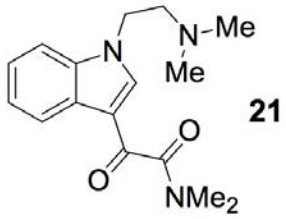



N
N-Me
Me
O
O
NMe2

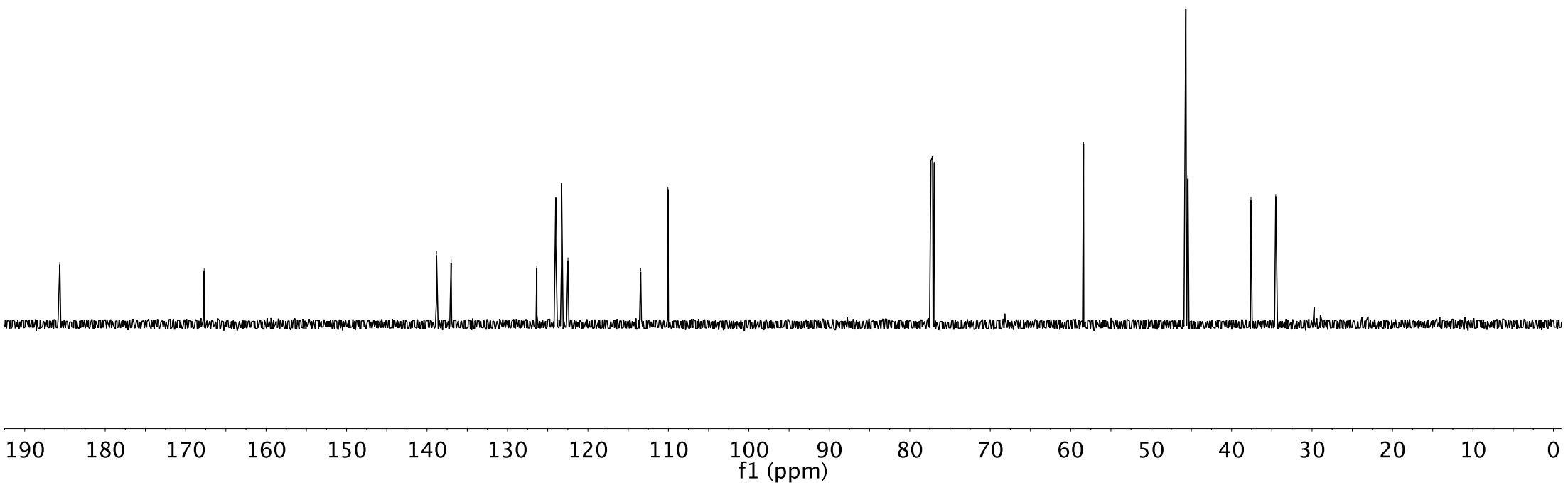
21

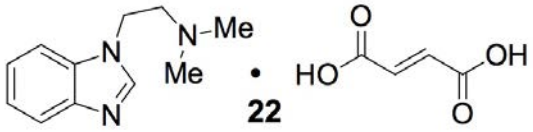

1.00
1.01
1.13
2.18
2.40
6.46
2.35
6.41
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)

185.64
167.70
138.82
137.01
126.36
124.00
123.28
122.48
113.45
110.06
58.40
45.68
45.43
37.59
34.51

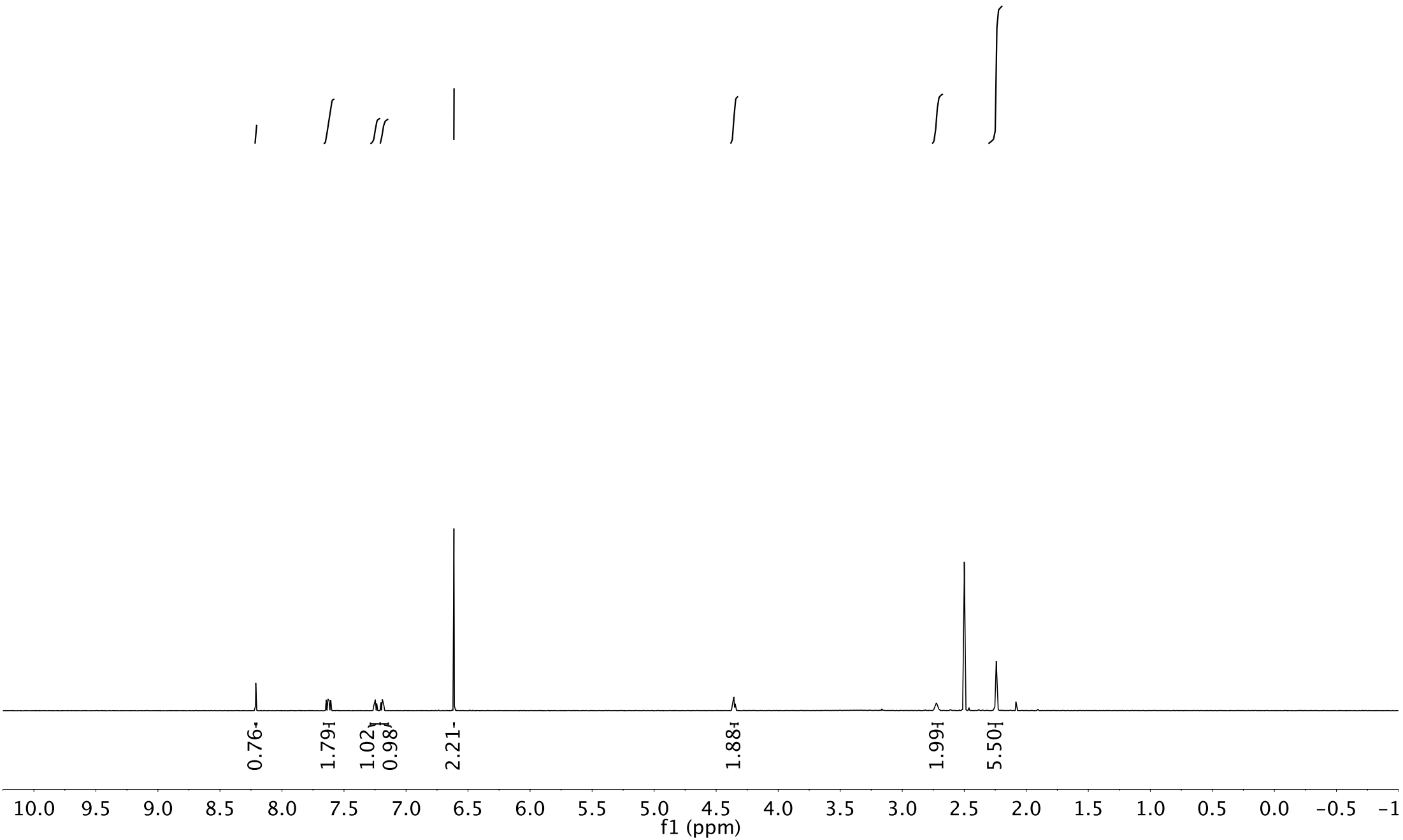


21



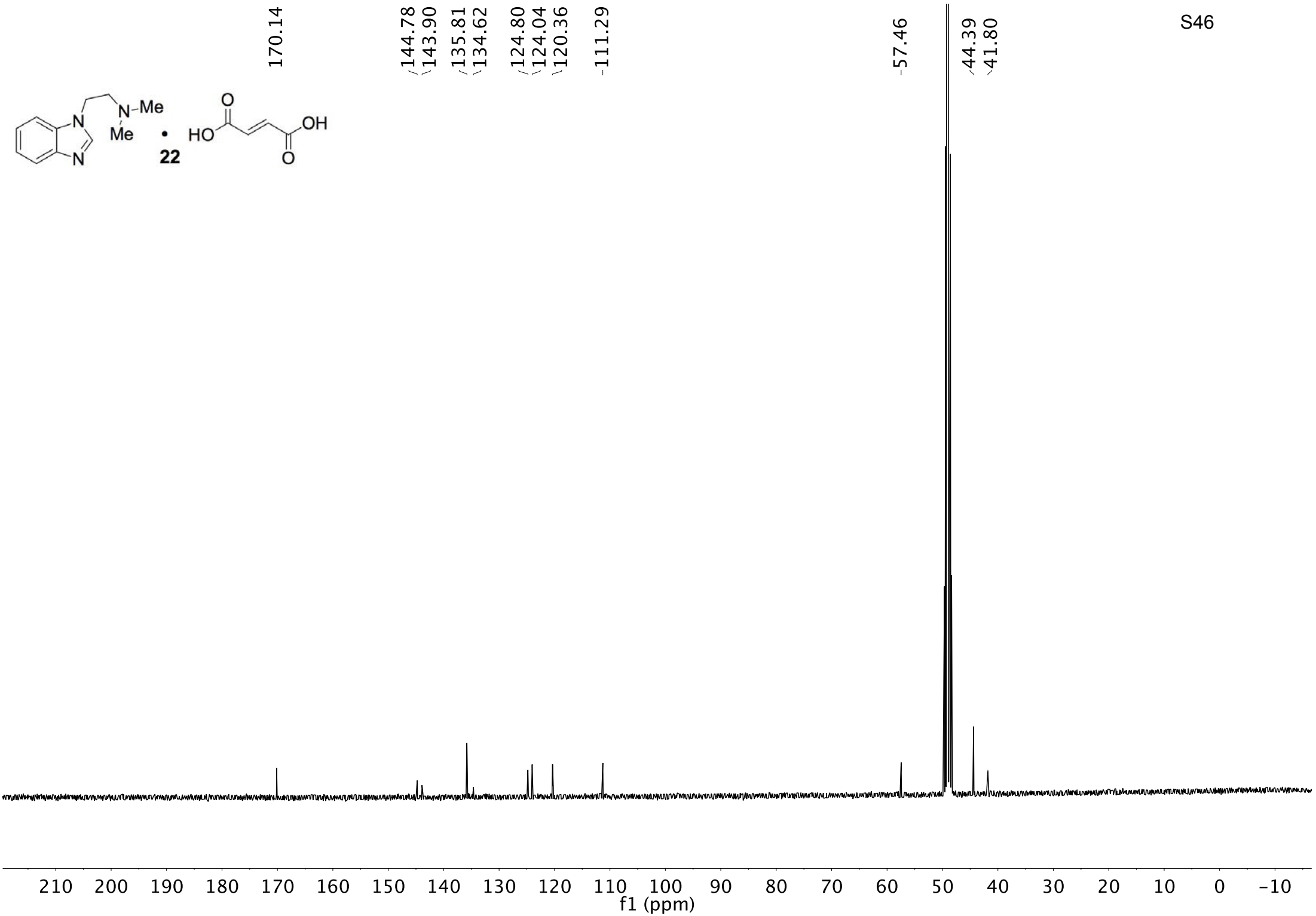

N
N
N-Me
Me
•
HO
O
OH
O

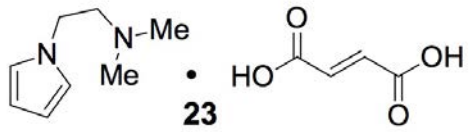
22


0.76
1.79
1.02
0.98
2.21
1.88
1.99
5.50
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 0.0 −0.5 −1
f1 (ppm)

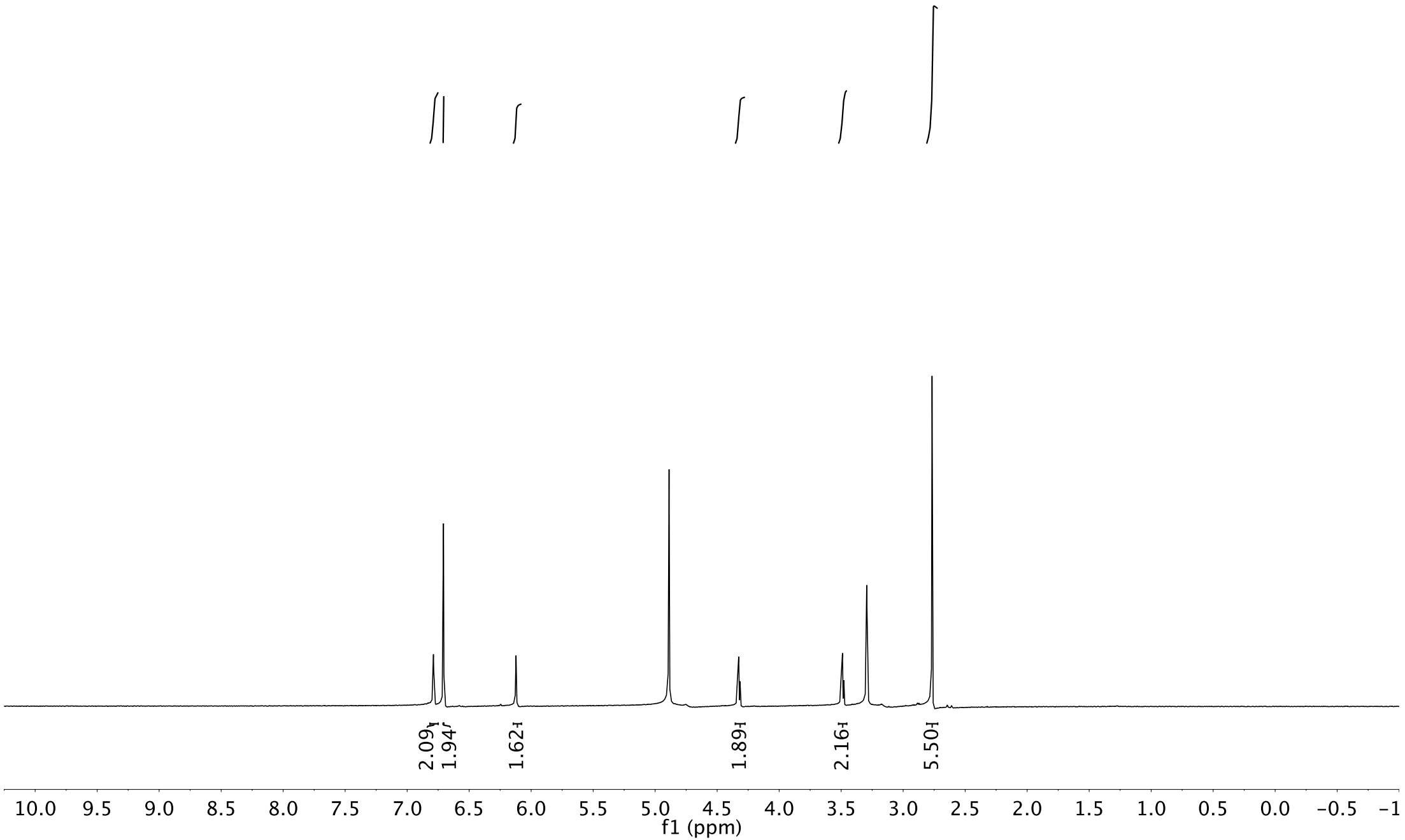
22

170.14
144.78
143.90
135.81
134.62
124.80
124.04
120.36
111.29
57.46
44.39
41.80



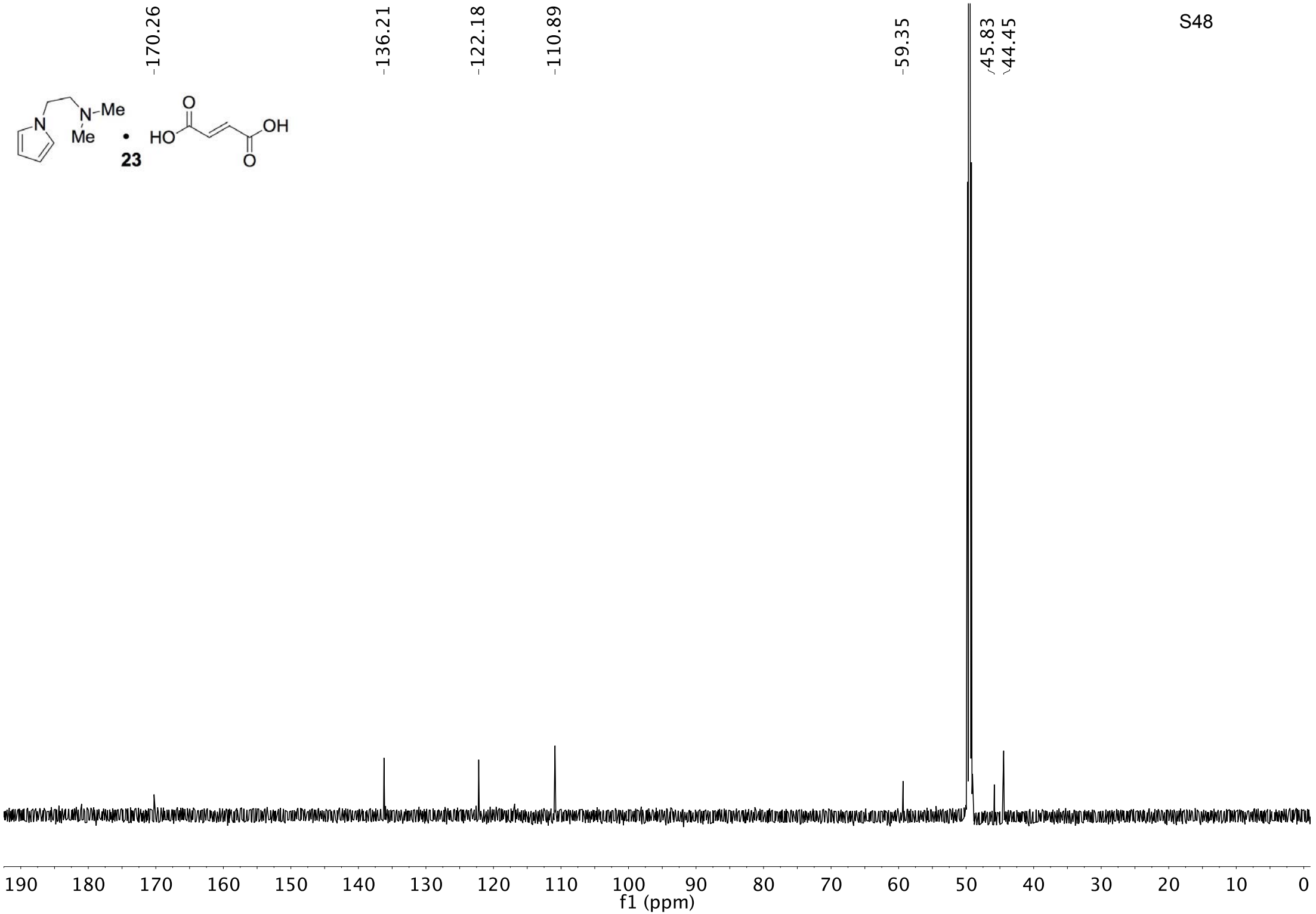

N
N–Me
Me
HO
OH
O
O

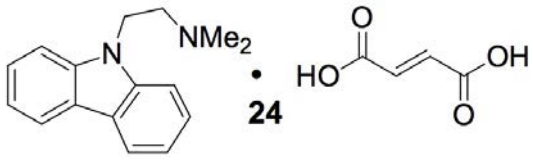
23


2.09
1.94
1.62
1.89
2.16
5.50
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 0.0 −0.5 −1
f1 (ppm)

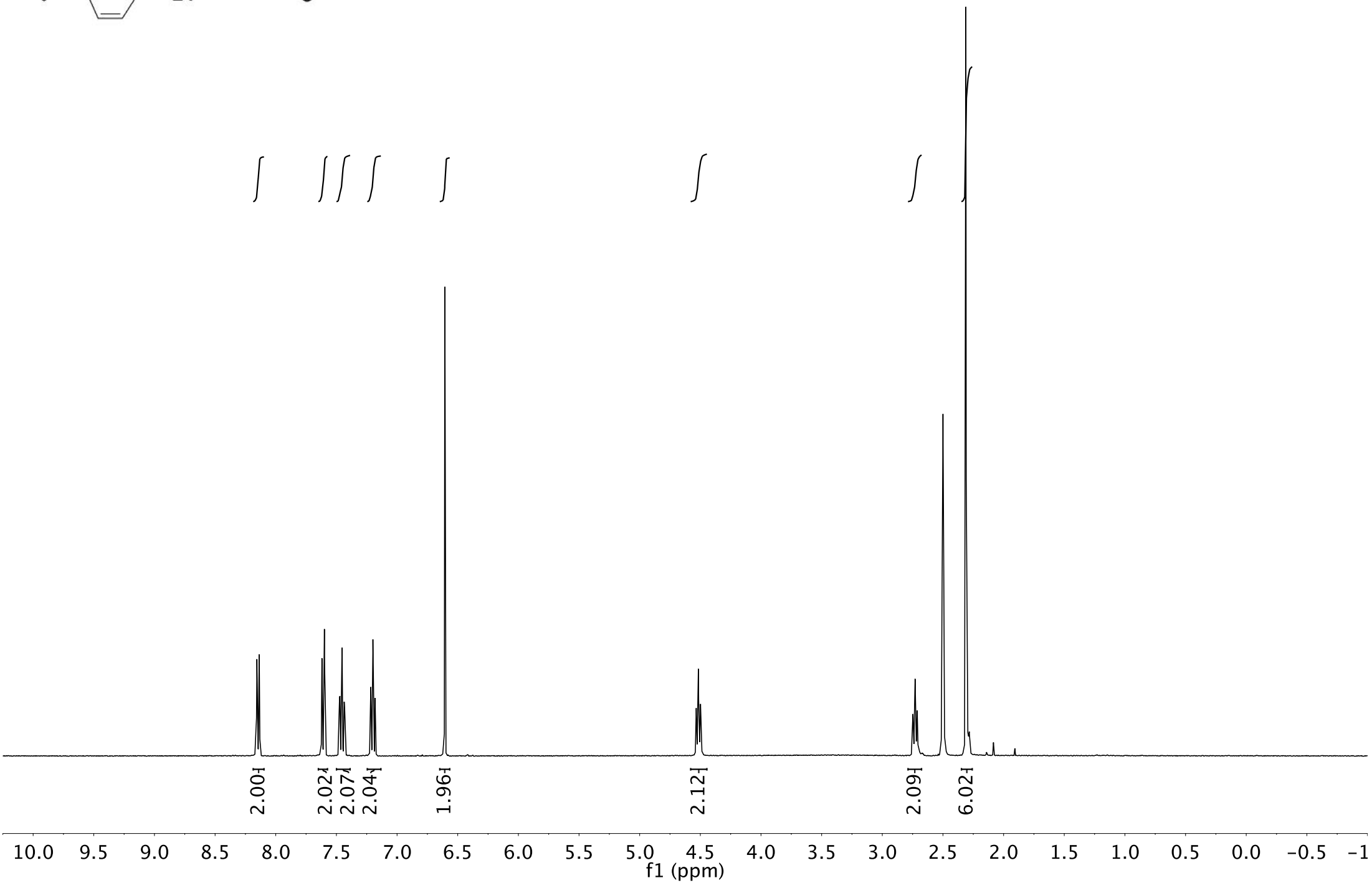
N
N–Me
Me
•
HO
O
OH
O

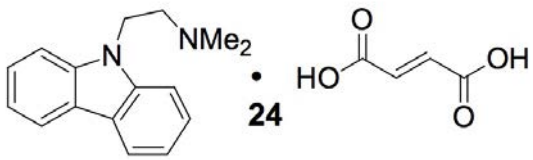
23


170.26
136.21
122.18
110.89
59.35
45.83
44.45
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NMe2
N
HO
OH
O
O

24


2.00
2.02
2.07
2.04
1.96
2.12
2.09
6.02
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 0.0 −0.5 −1
f1 (ppm)

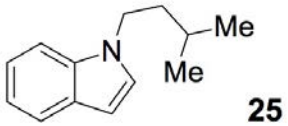


24

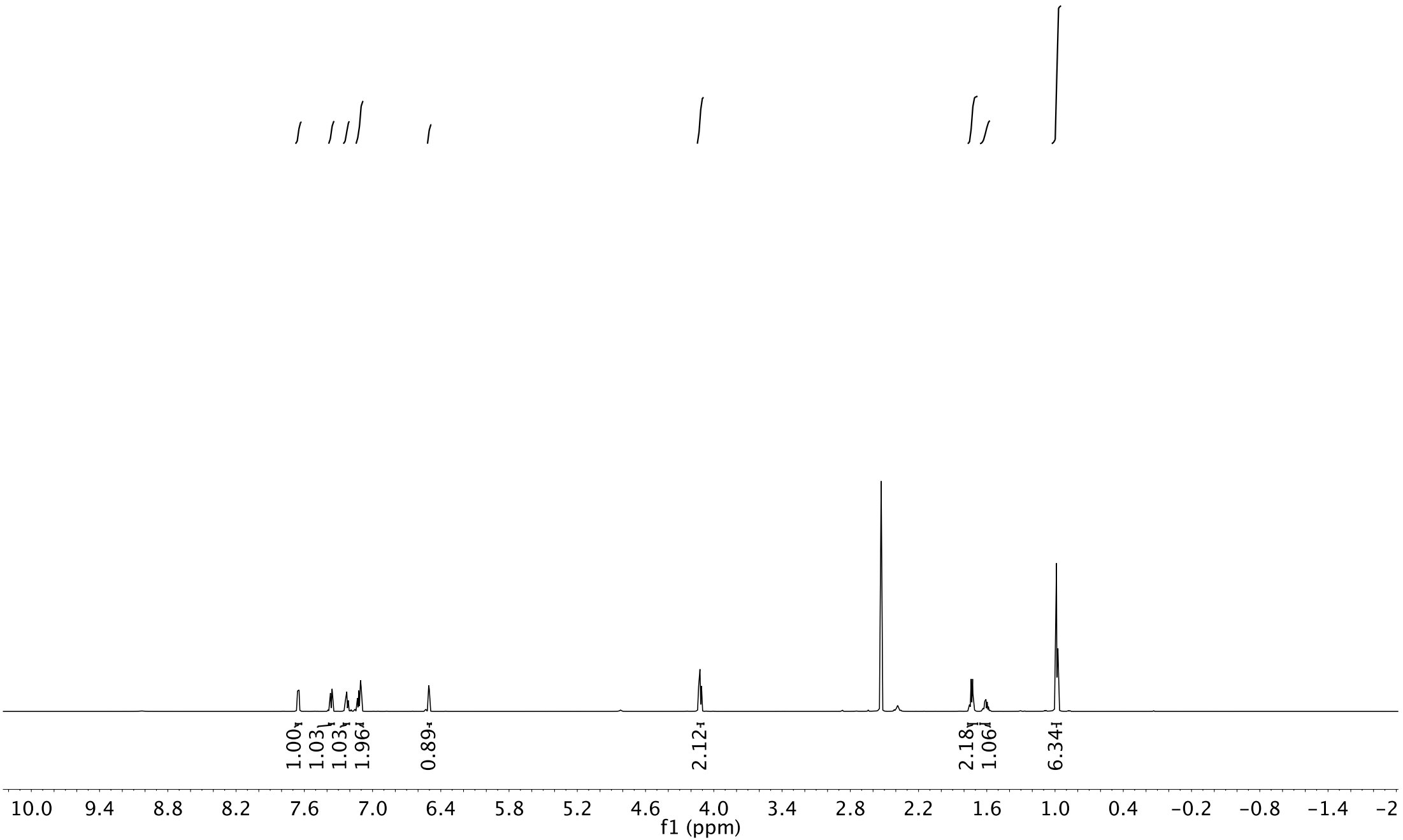
169.78
139.86
134.76
125.83
123.17
119.99
119.39
108.34
54.39
42.61
37.85

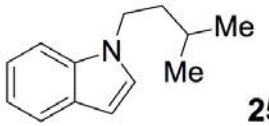
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10

f1 (ppm)


N
Me
Me

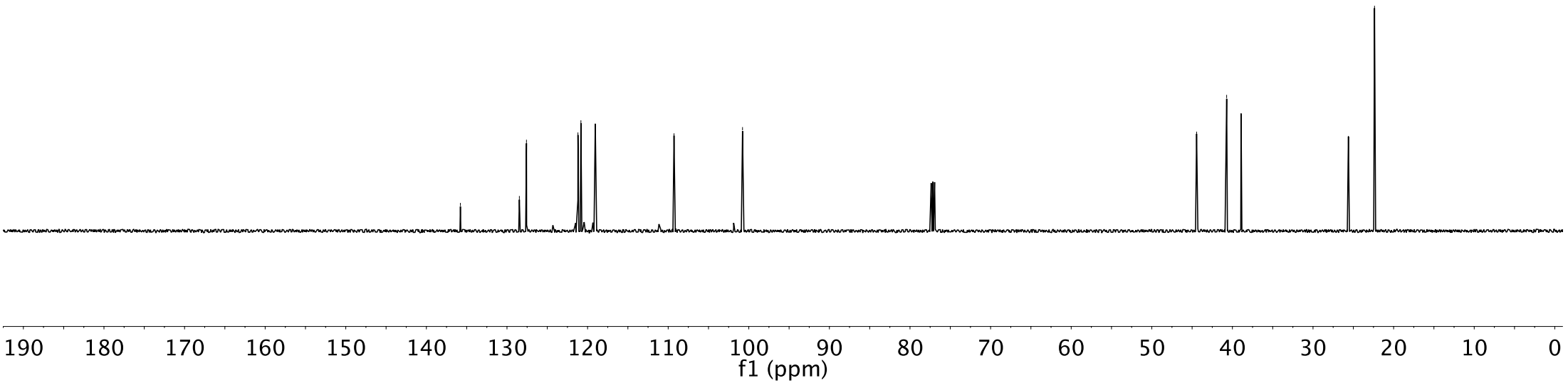
25

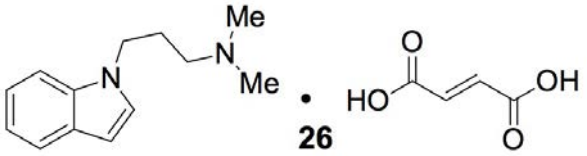

1.00
1.03
1.03
1.96
0.89
2.12
2.18
1.06
6.34
10.0
9.4
8.8
8.2
7.6
7.0
6.4
5.8
5.2
4.6
4.0
3.4
2.8
2.2
1.6
1.0
0.4
-0.2
-0.8
-1.4
-2
f1 (ppm)



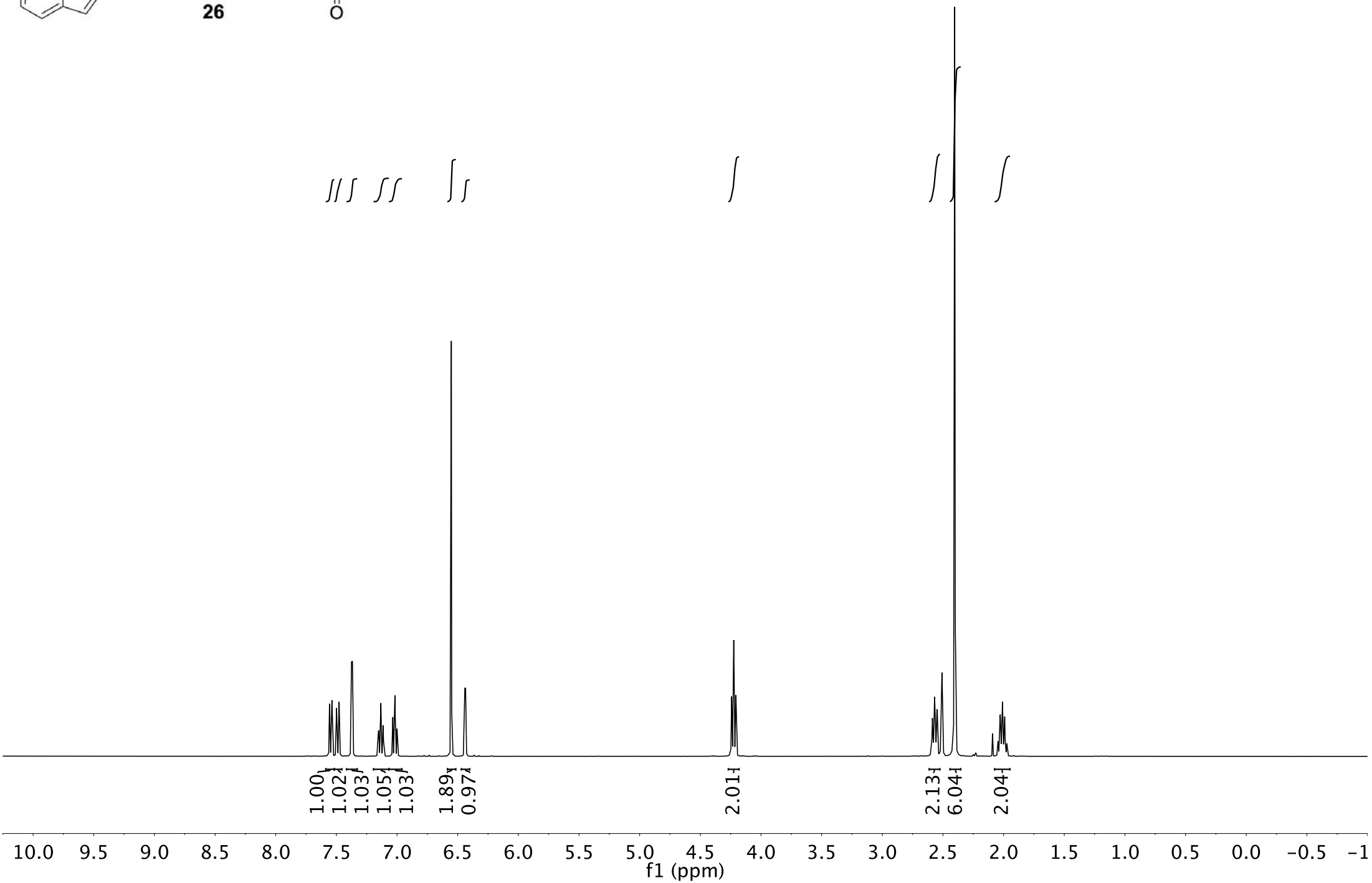
25

135.78
128.46
127.58
121.20
120.83
119.05
109.28
100.78
44.44
40.72
38.92
25.61
22.37



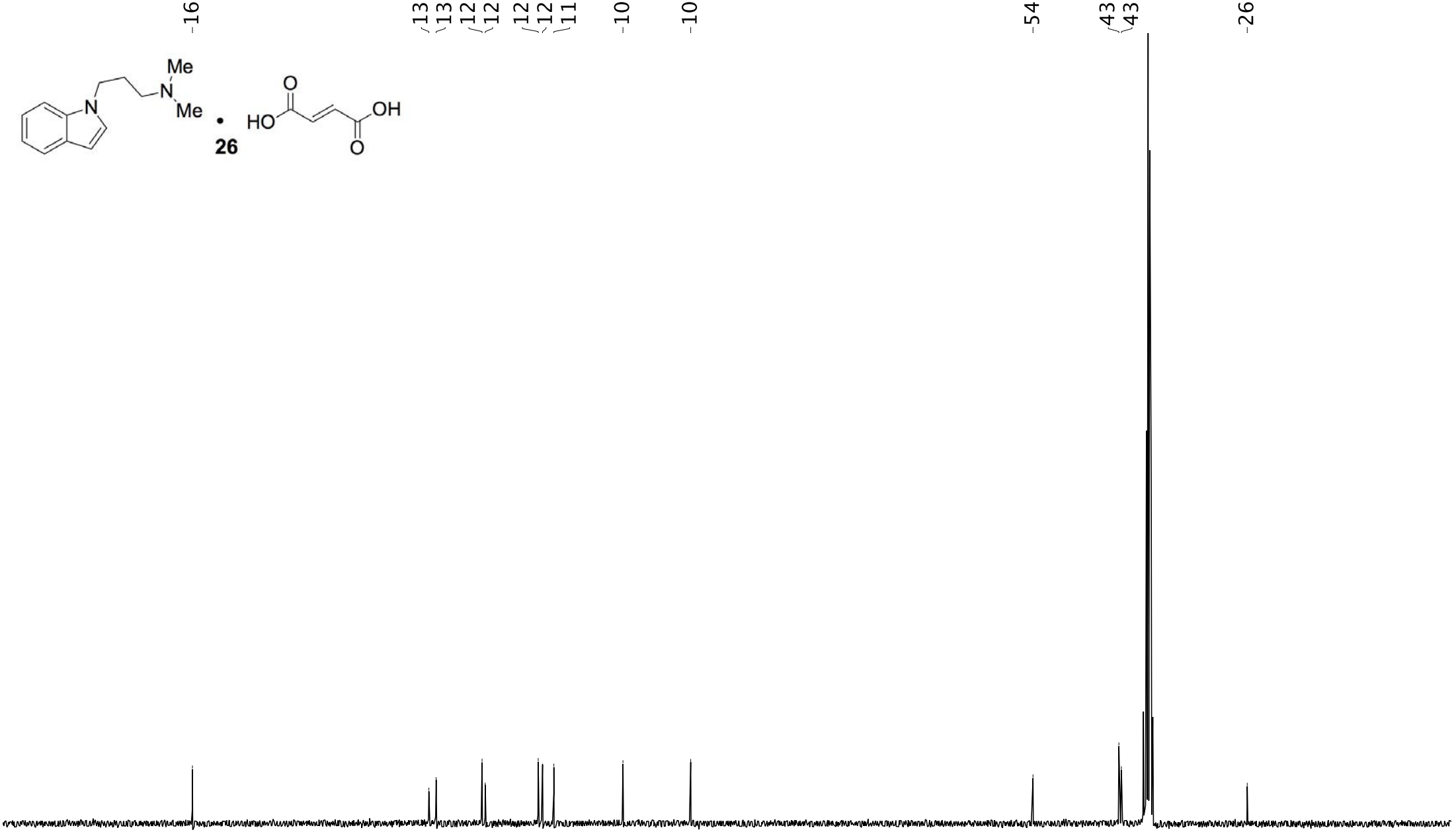

Me
N
Me
N
•
HO
O
OH
O

26


1.00
1.02
1.03
1.05
1.03
1.89
0.97
2.01
2.13
6.04
2.04
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
0.0
−0.5
−1
f1 (ppm)

26

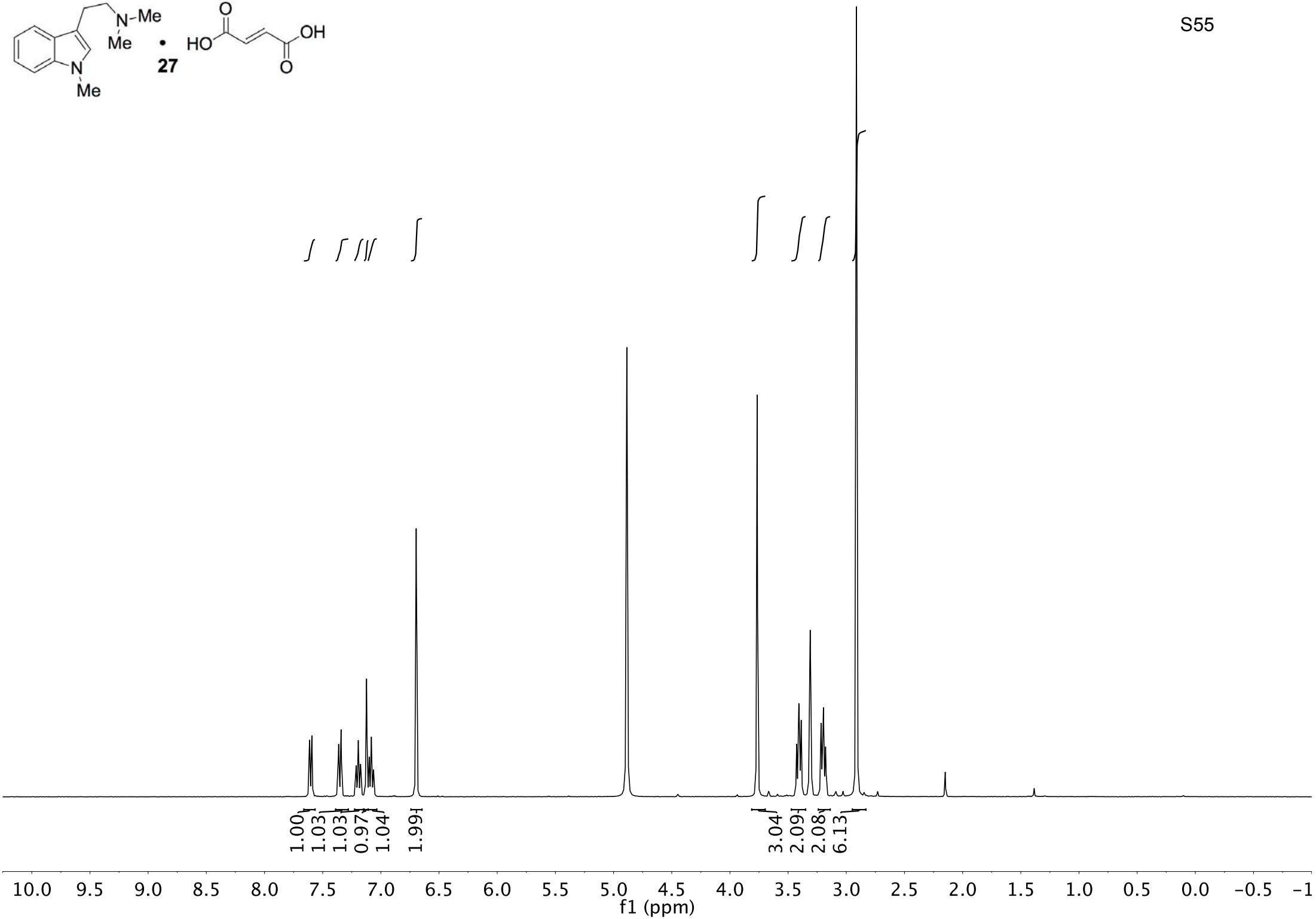
-167.19
135.60
134.62
128.49
128.07
120.99
120.41
118.90
-109.67
-100.61
-54.88
43.41
43.07
-26.26



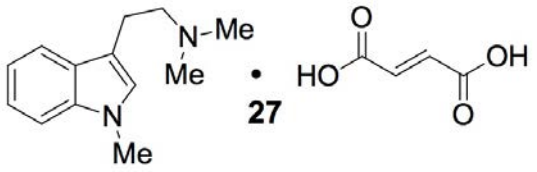
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

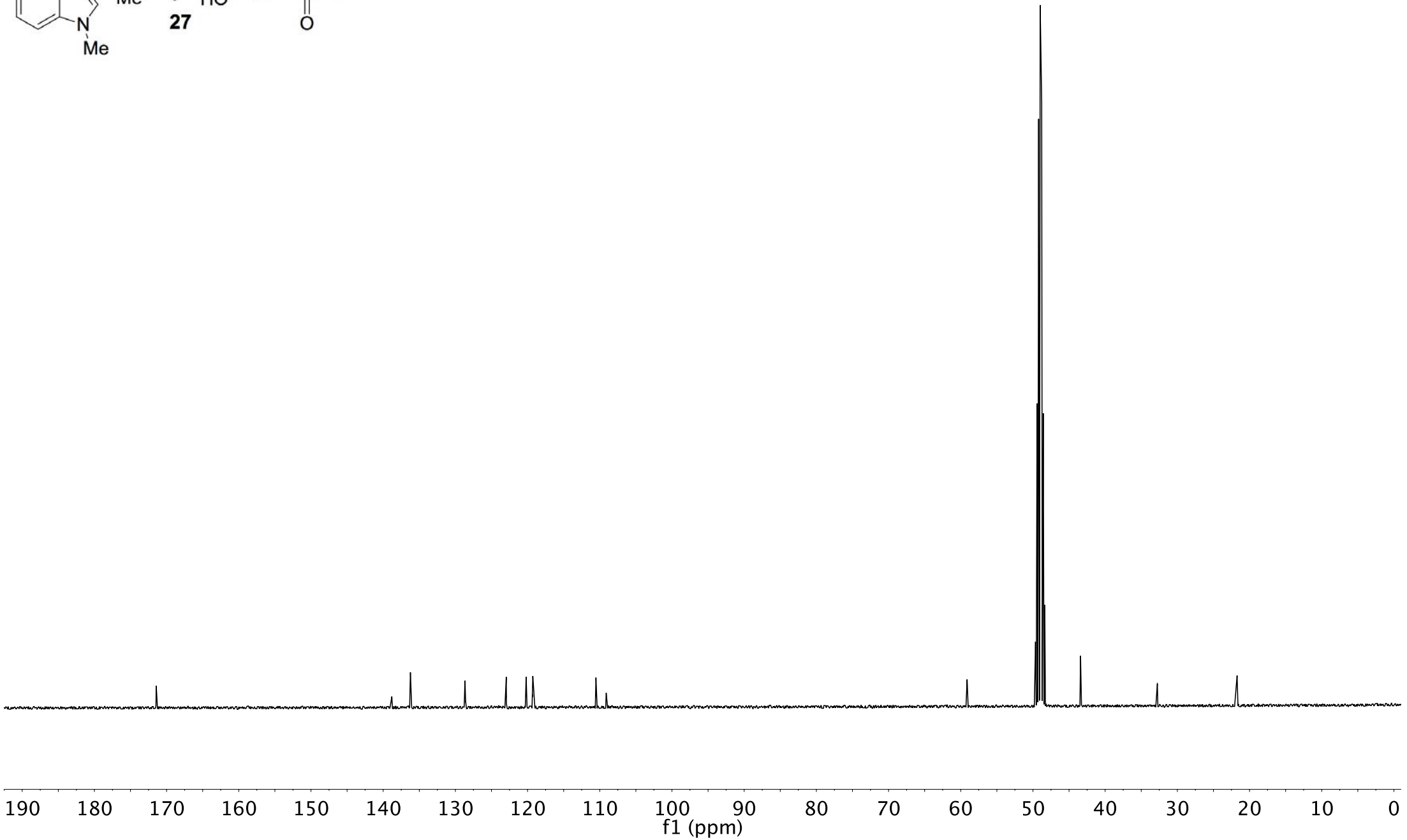
N-Me
Me
N
Me
27
HO
O
OH
O

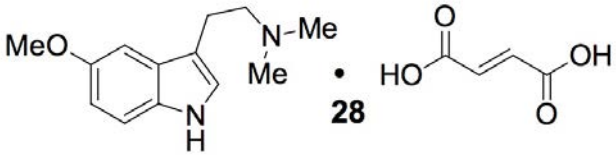

1.00
1.03
1.03
0.97
1.04
1.99
3.04
2.09
2.08
6.13
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)

171.44
138.80
136.23
128.67
128.59
122.95
120.20
119.27
110.53
109.11
59.12
43.41
32.77
21.72

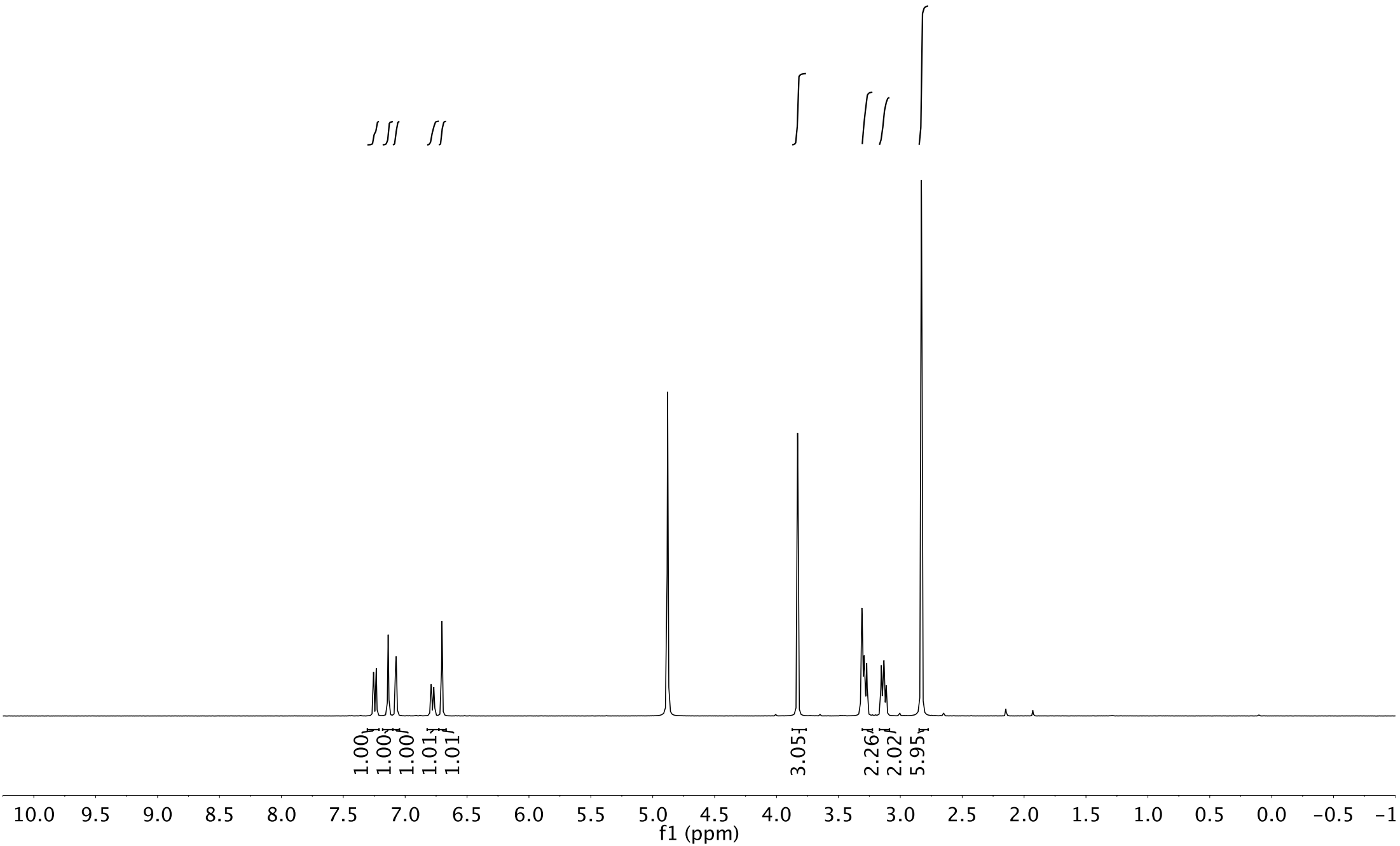


27

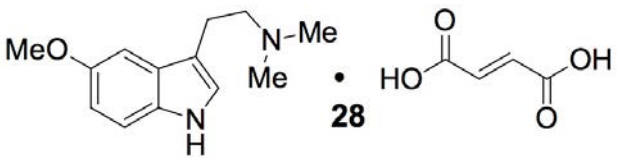



MeO
N-Me
Me
N
H
•
HO
OH
O
O

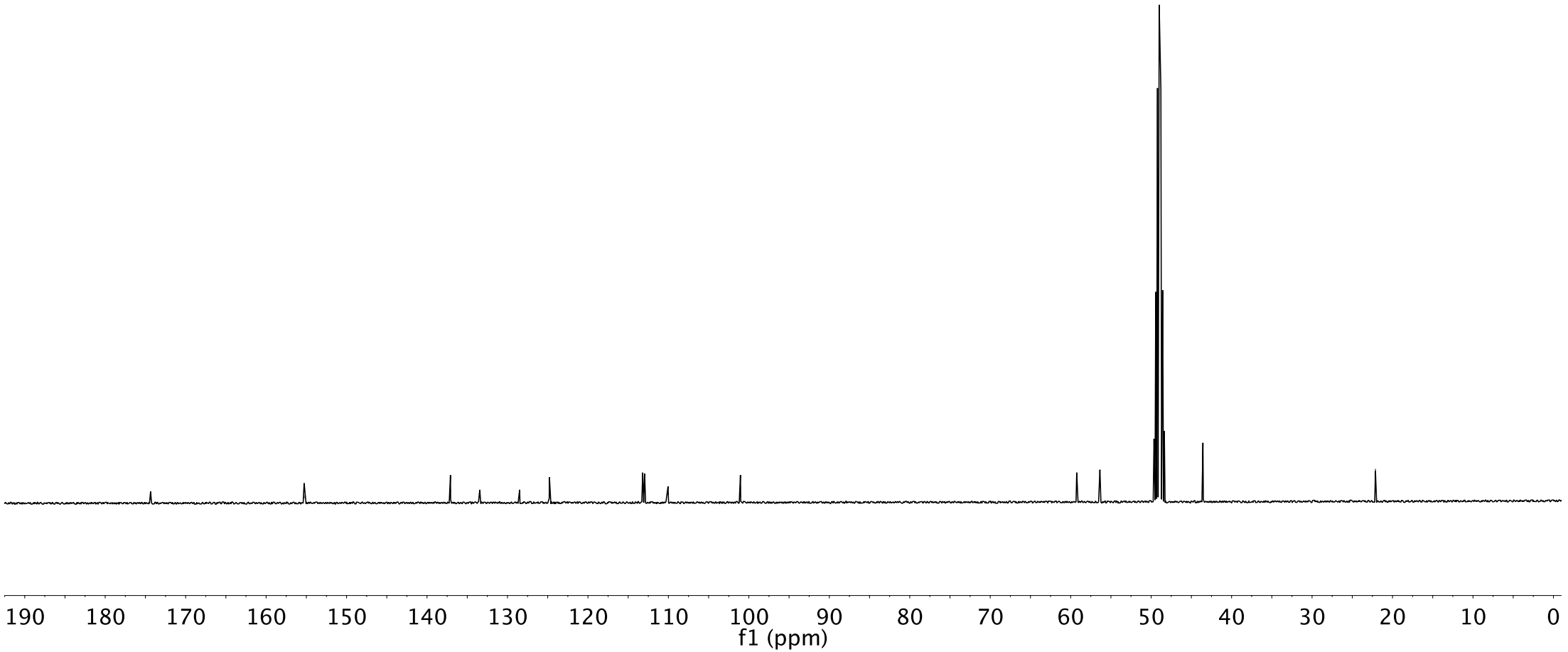
28

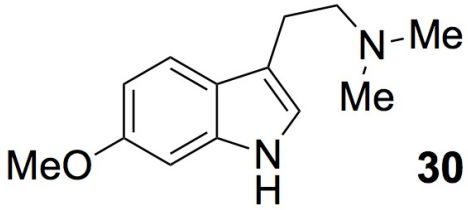

1.00
1.00
1.00
1.01
1.01
3.05
2.26
2.02
5.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)

174.36
155.27
137.09
133.44
128.49
124.79
113.20
112.96
110.05
101.05
59.25
56.37
43.56
22.12

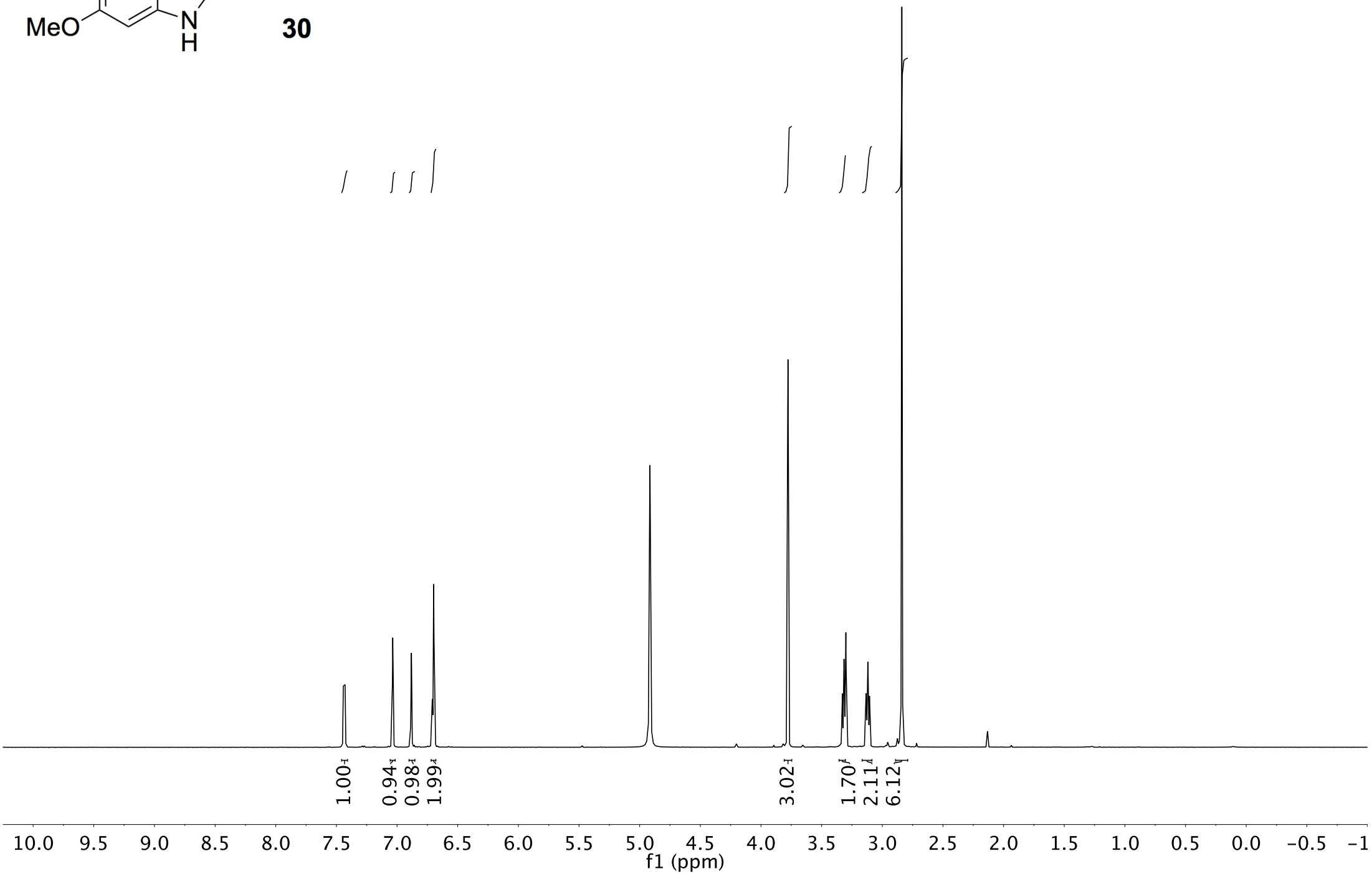


28



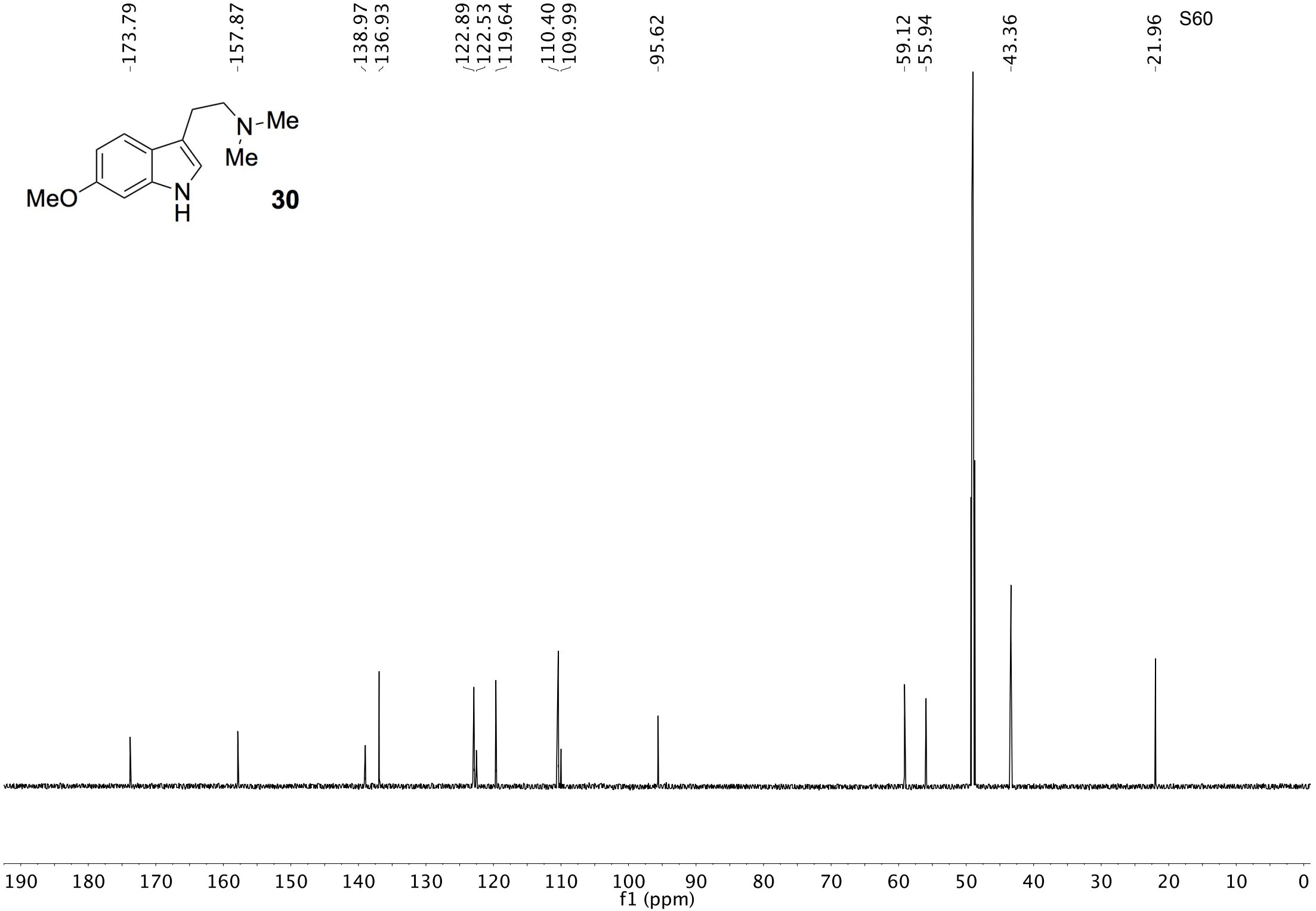

N-Me
Me
MeO
N
H

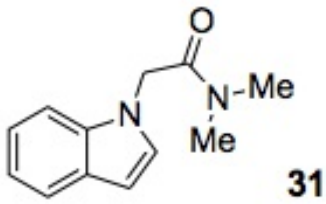
30


1.00
0.94
0.98
1.99
3.02
1.70
2.11
6.12
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 0.0 −0.5 −1
f1 (ppm)

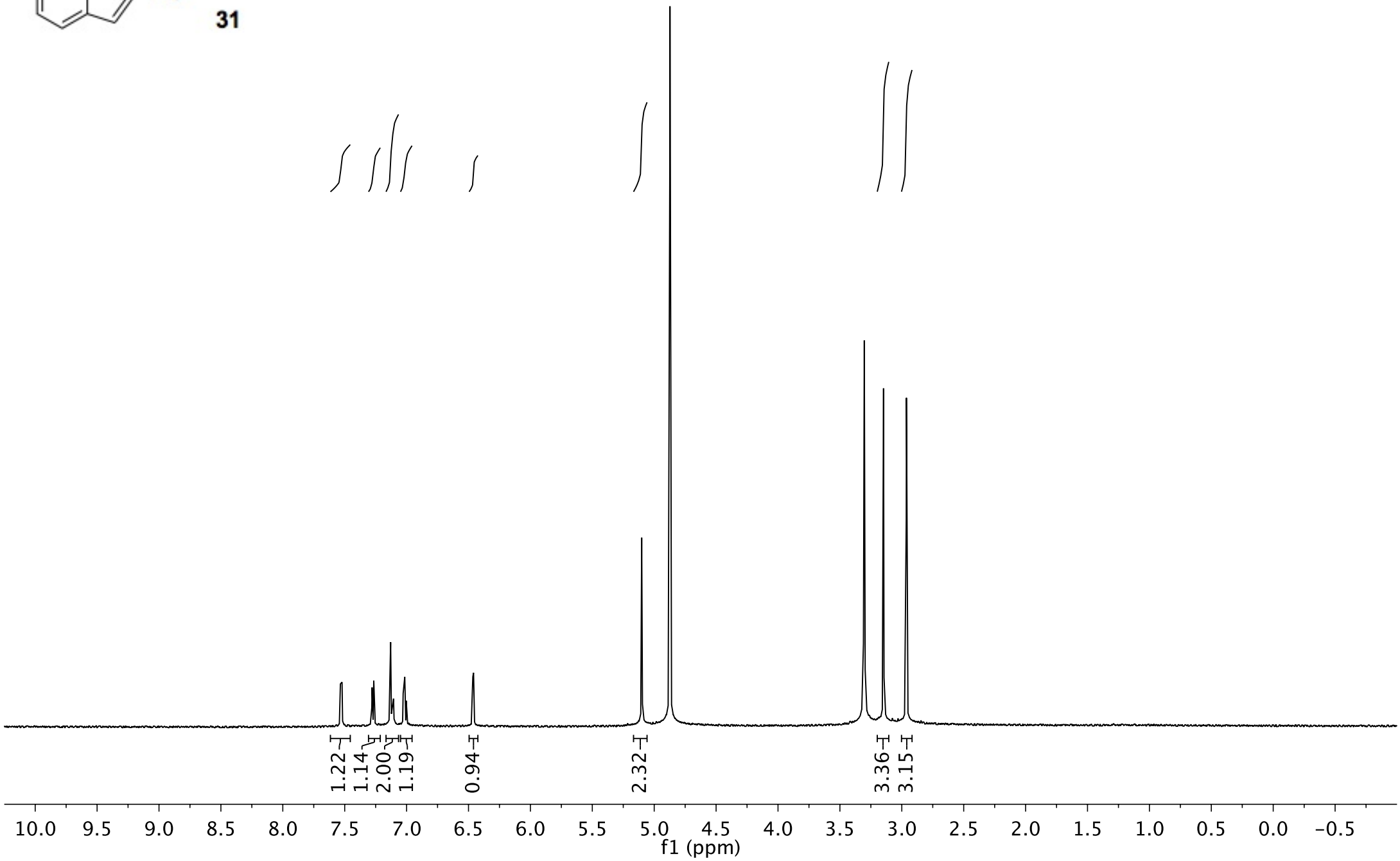
N-Me
Me
MeO
N
H

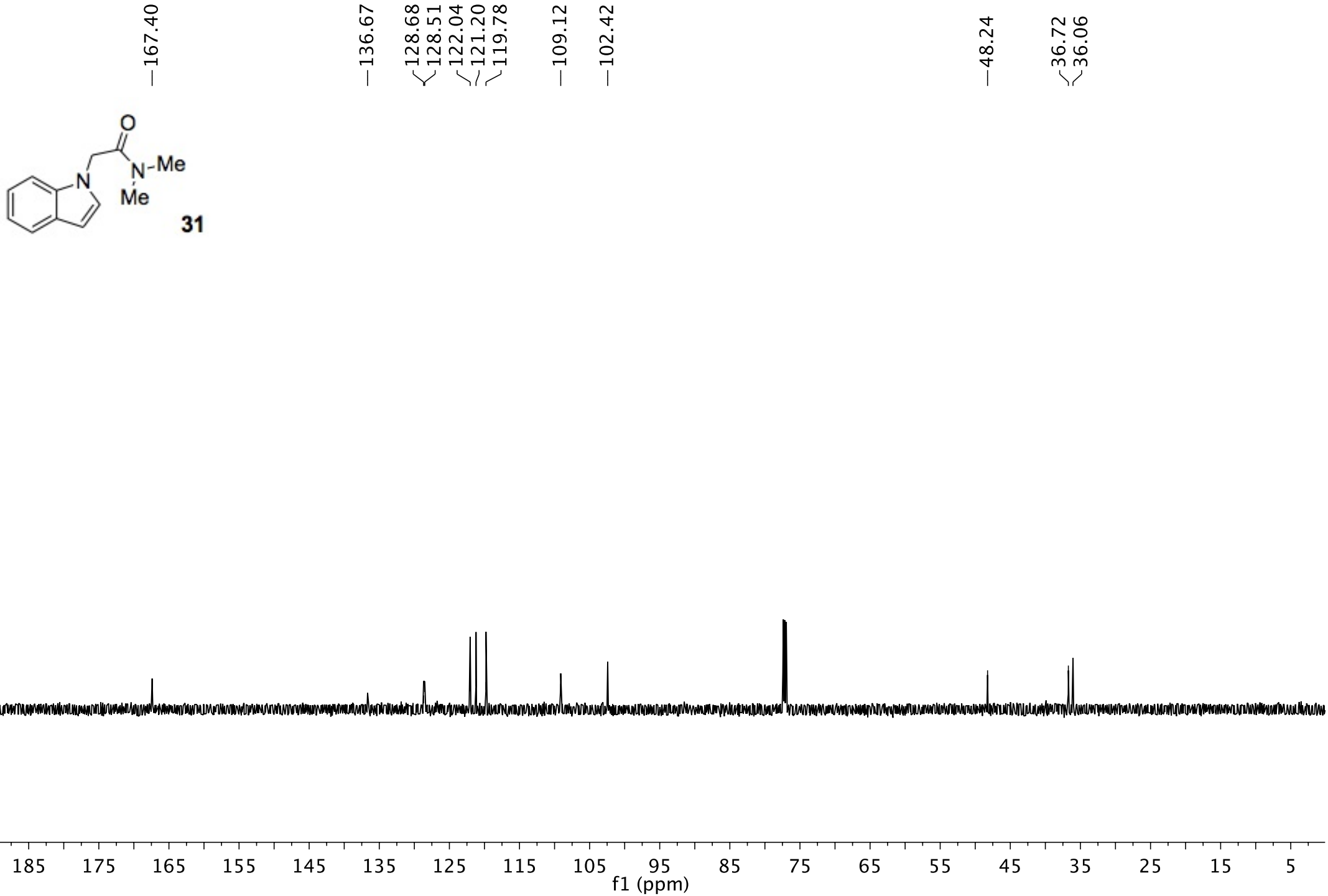
30


173.79
157.87
138.97
136.93
122.89
122.53
119.64
110.40
109.99
95.62
59.12
55.94
43.36
21.96
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N-Me
N
Me

31


1.22
1.14
2.00
1.19
0.94
2.32
3.36
3.15
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 0.0 -0.5
f1 (ppm)


167.40
136.67
128.68
128.51
122.04
121.20
119.78
109.12
102.42
48.24
36.72
36.06
O
N
N-Me
Me
31
185
175
165
155
145
135
125
115
105
95
85
75
65
55
45
35
25
15
5
f1 (ppm)