Synthesis and bioactivity of reduced chalcones containing sulfonamide side chains

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Synthesis of compound **5a**…….S2

Synthesis of compound **6a**…….S2

Synthesis of compound **7a**…….S3

Supporting Information

4-(3-Phenylpropyl)phenol (5a)

To a solution of (*E*)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one (1 g, 0.04 mol) in EtOAc (3 mL) and water (9 mL) 20% $Pd(OH)_2/C$ (600 mg, 60 wt %) was added. The flask was sealed and hydrogen gas was passed through the reaction mixture. After stirring overnight at room temperature, the reaction mixture was filtered through silica gel. The filtrate was dissolved in EtOAc followed by extraction with EtOAc (2 x 50 mL). The organic layer was washed with water (2 x 30 mL), dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure.

The title compound was obtained as a brown oil (700 mg, 23%). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.38 – 7.18 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 7.08 (2H, d, *J* = 8.6 Hz, H-2′, H-6′), 6.79 (2H, d, *J* = 8.6 Hz, H-3′, H-5′), 4.87 (1H, s, 1 x OH), 2.67 (2H, t, *J* = 7.8 Hz, H-3), 2.62 (2H, t, *J* = 7.8 Hz, H-1), 2.00 – 1.89 (2H, m, H-2) (Plate S17). ^{13}C NMR δ (600 MHz, $CDCl_3$, Me_4Si) 153.5 (C-4′), 142.4 (C-1″), 134.6 (C-1′), 129.5 (C-2′/C-6′), 128.5 (C-3″/C-5″), 128.3 (C-2″/C-6″), 125.8 (C-4″), 115.2 (C-3′/C-5′), 35.4 (C-1), 34.5 (C-3), 33.2 (C-2) (Plate S18).

2,6-bis((dimethylamino)methyl)-4-(3-phenylpropyl)phenol (6a)

A mixture of 4-(3-phenylpropyl)phenol (**5a**) (0.212 g, 0.001 mol), paraformaldehyde (0.040 g, 0.01 mol) and dimethylamine (0.045 g, 1 mL, 0.01 mol) in dry acetonitrile (10 mL) was refluxed overnight. The reaction mixture was purified by TLC chromatography (H:EtOAc 7:3). LREIMS m/z 327.3 (calcd for $C_{21}H_{30}N_2O$, 326.5). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.35 – 7.16 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 6.87 (2H, s, H-2′, H-6′), 3.54 (4H, s, 2 x -C**H**$_2$N), 2.66 (2H, t, *J* = 7.8 Hz, H-3), 2.58 (2H, t, *J* = 7.8 Hz, H-1), 2.31 (12H, s, 4 x -NC**H**$_3$),

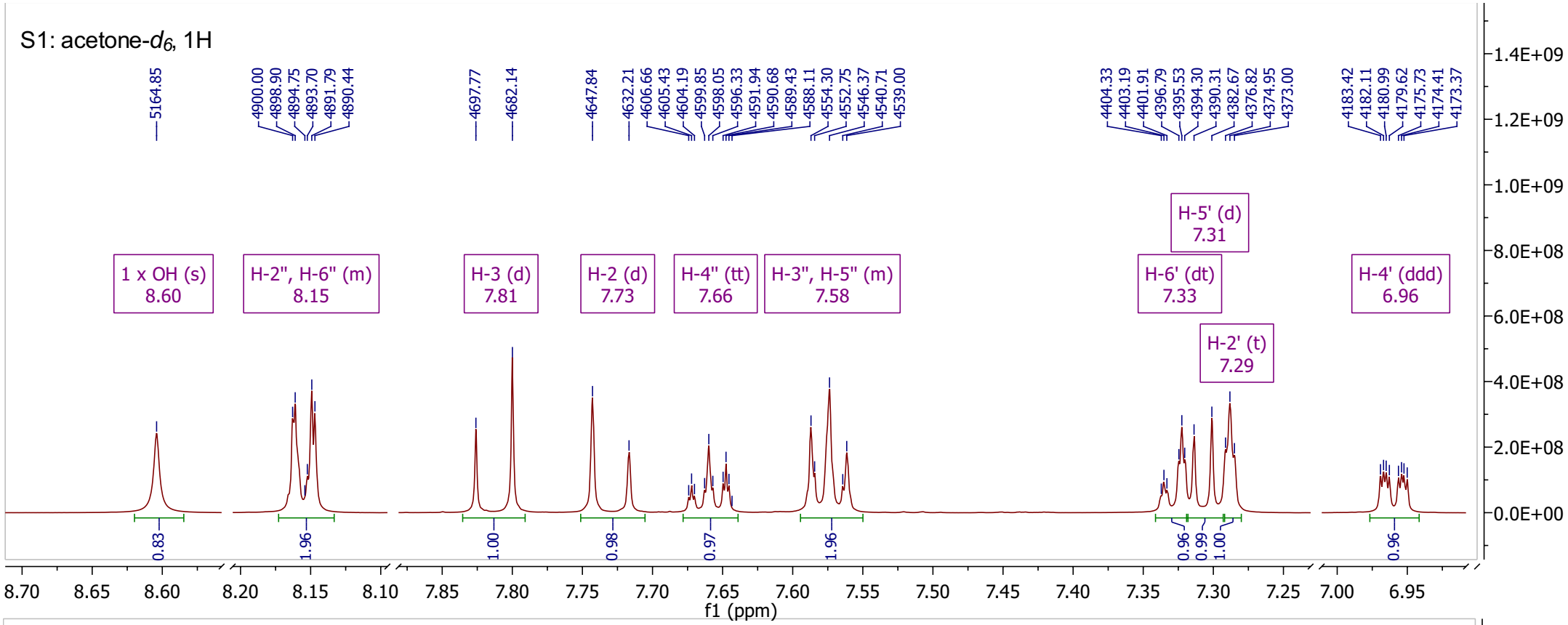
1.98 – 1.90 (2H, m, H-2) (Plate S19). ^{13}C NMR δ (600 MHz, $CDCl_3$, Me_4Si) 154.6 (C-4′), 142.6 (C-1″), 131.9 (C-1′), 128.7 (C-2′/C-6′), 128.5 (C-2″/C-6″), 128.3 (C-3″/C-5″), 125.7 (C-4″), 123.2 (C-3′/C-5′), 60.6 (2 x -**C**H_2N), 45.0 (4 x -N**C**H_3), 35.7 (C-3), 34.7 (C-1), 33.5 (C-2) (Plate S20).

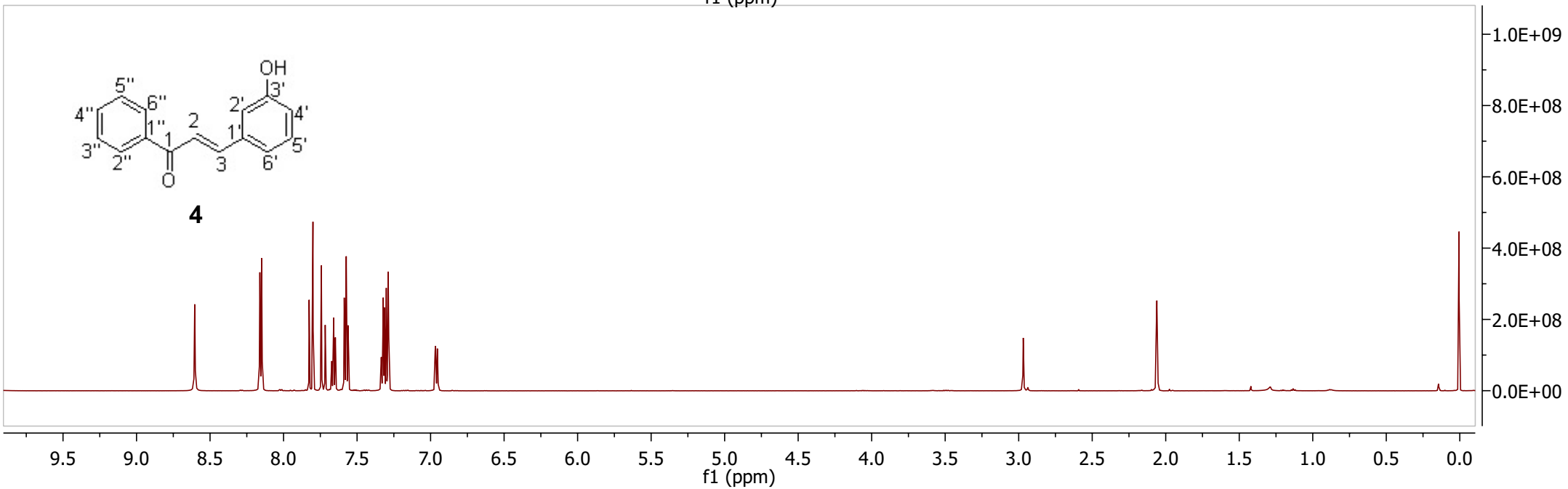
1,1'-(2-hydroxy-5-(3-phenylpropyl)-1,3-phenylene)bis(N,N-dimethylmethanaminium) chloride (7a)

2,6-bis((dimethylamino)methyl)-4-(3-phenylpropyl)phenol (**6a**) (0.240 g, 0.7 mmol) was dissolved in hexane (5 mL) at 0 ºC. HCl gas was bubbled through the reaction mixture for 60 min. to obtain the HCl salt as white crystals (0.30 g, 98%).

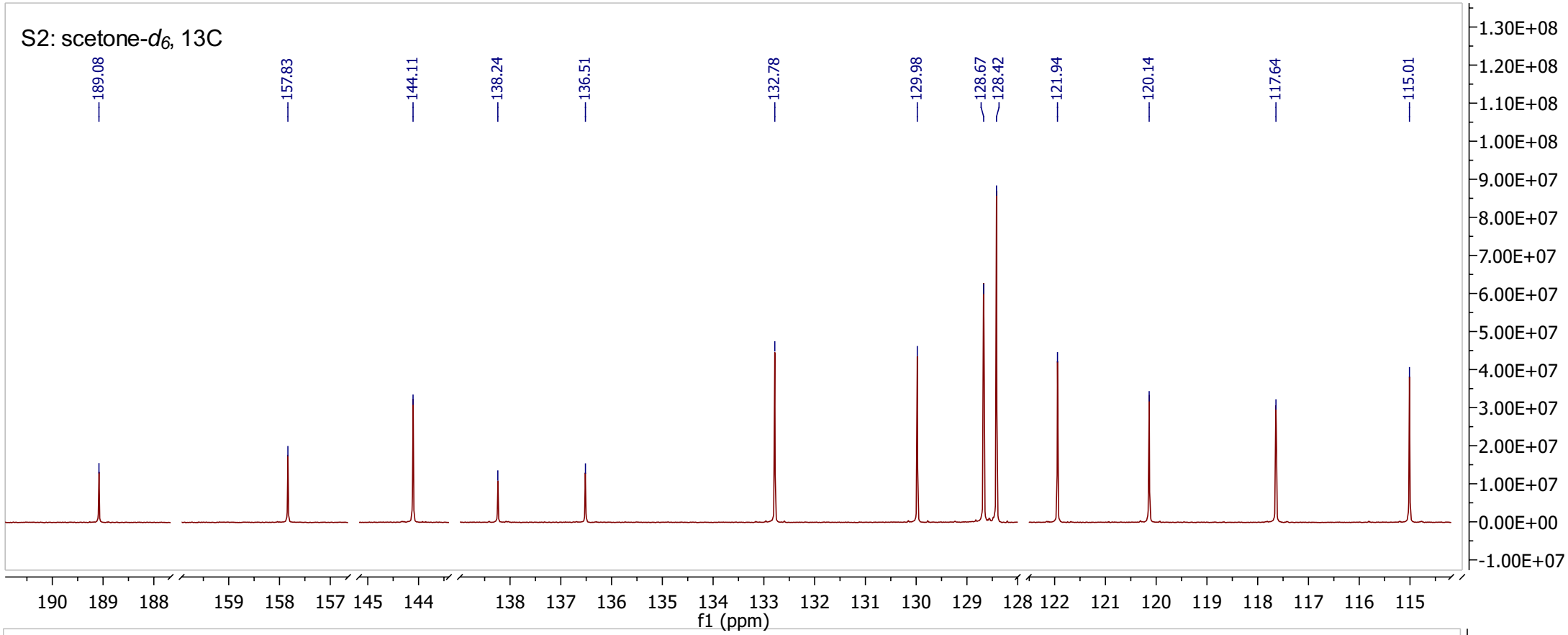
LREIMS *m/z* 397.3 and 399.5 (calcd for $C_{21}H_{32}Cl_2N_2O$, 399.4). ^{1}H NMR δ (600 MHz, $CDCl_3$, Me_4Si) 7.33 (2H, bs, H-2′, H-6′), 7.30 (2H, d, *J* = 8.1 Hz, H-2″, H-6″), 7.20 – 7.17 (3H, m, H-3″, H-4″, H-5″), 4.16 (4H, s, 2 x -C**H**$_2$N), 2.75 (12H, bs, 4 x -NC**H**$_3$), 2.67 (2H, t, *J* = 8.2 Hz, H-3), 2.63 (2H, t, *J* = 8.2 Hz, H-1), 2.00 – 1.91 (2H, m, H-2) (Plate S21). ^{13}C NMR δ (600 MHz, $CDCl_3$, Me_4Si) 154.1 (C-4′), 141.9 (C-1″), 134.2 (C-1′), 128.5 – 128.4 (C-2′/C-6′/C-2″/C-6″/C-3″/C-5″), 125.9 (C-3′/C-5′), 120.4 (C-4″), 57.2 (2 x -**C**H_2N-), 42.8 (4 x - N**C**H_3), 35.5 (C-3), 34.3 (C-1), 32.9 (C-2) (Plate S22).

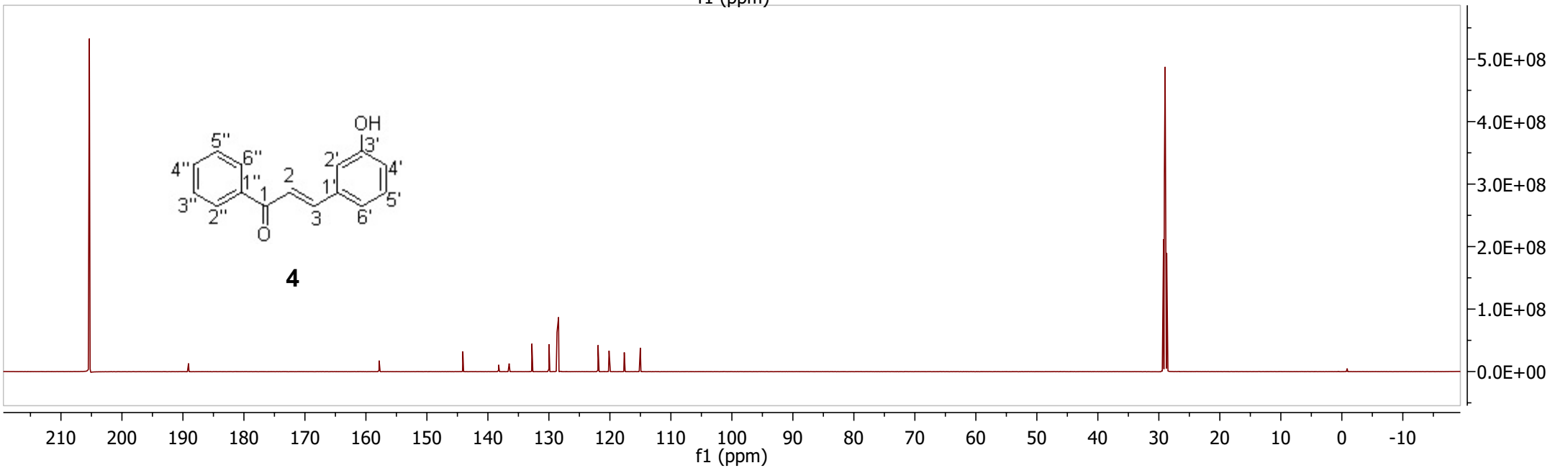
S1: acetone-d_6, 1H



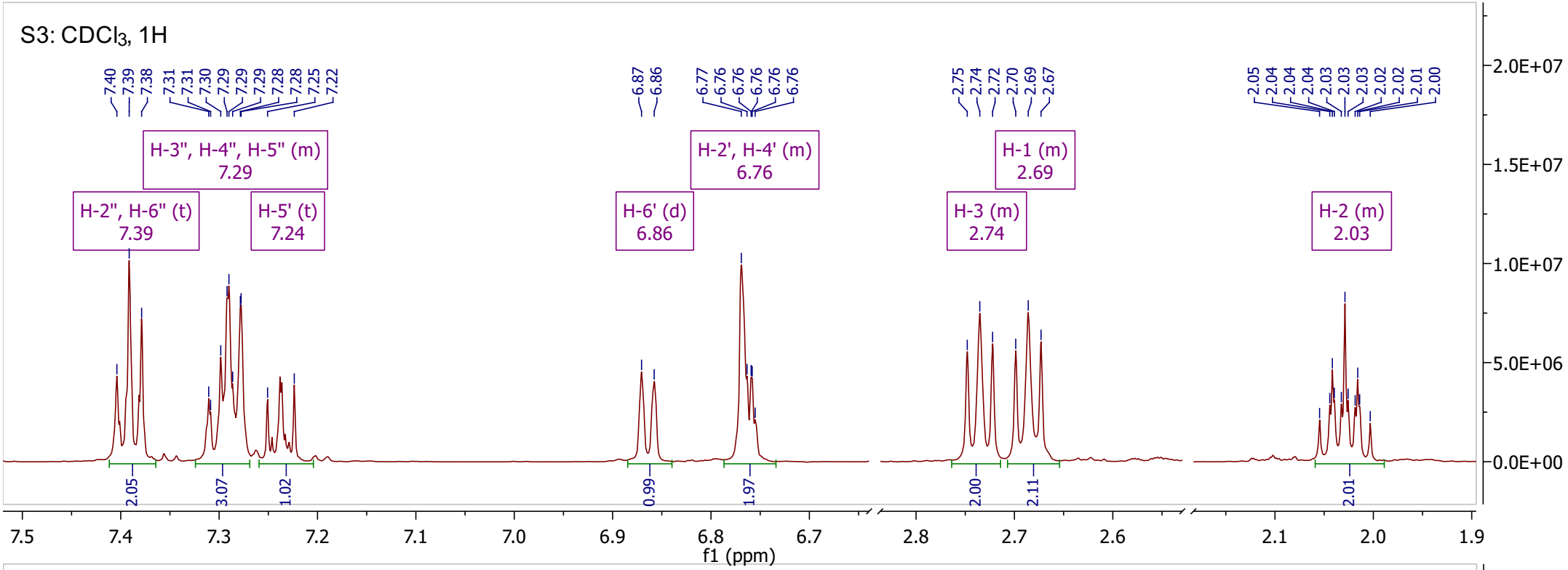


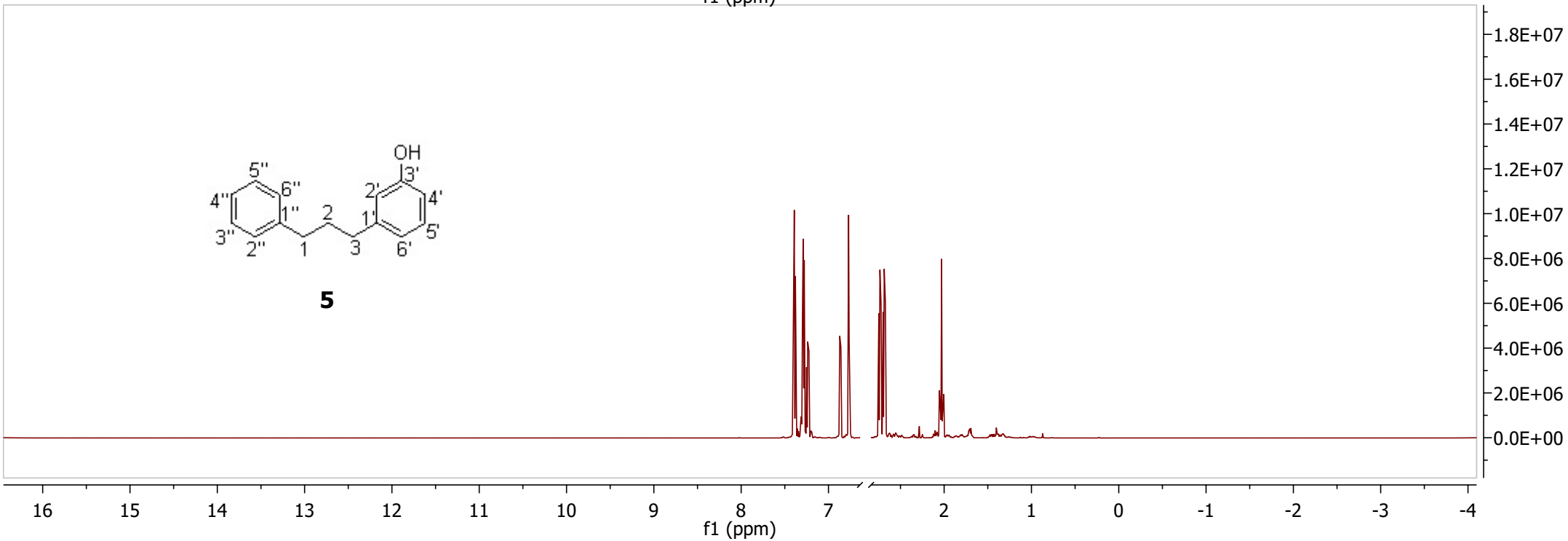
S2: scetone-d_6, 13C



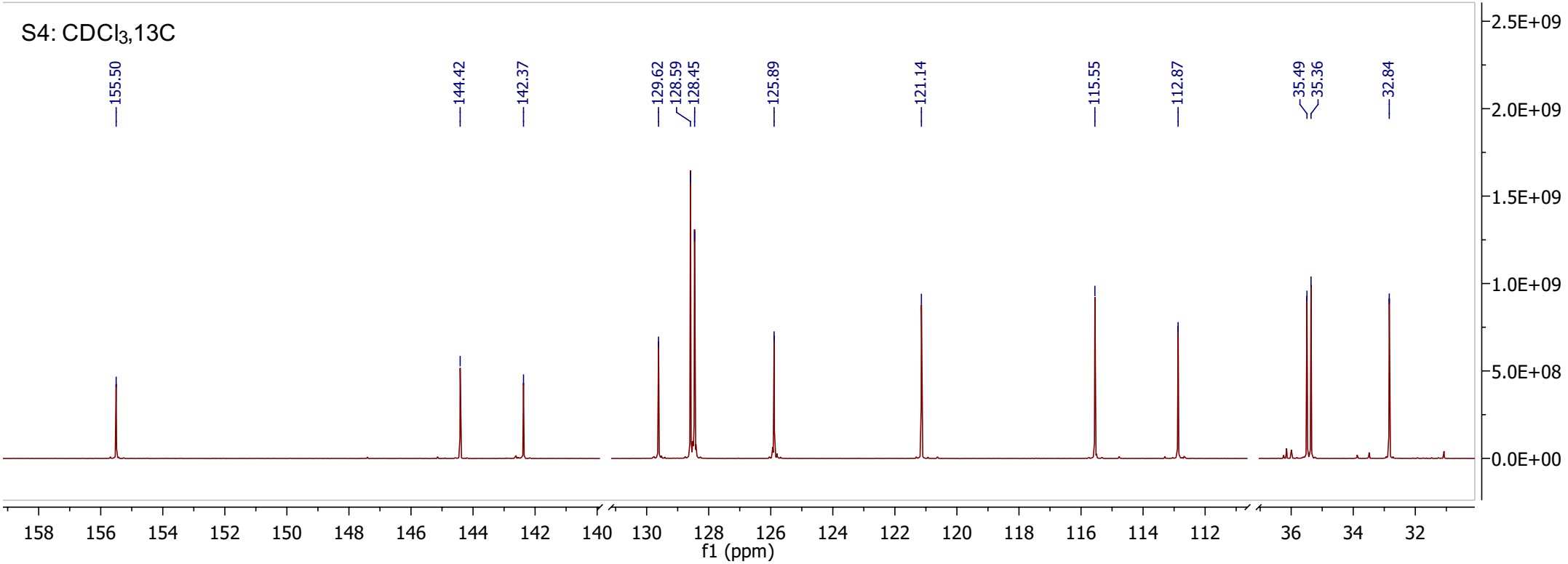


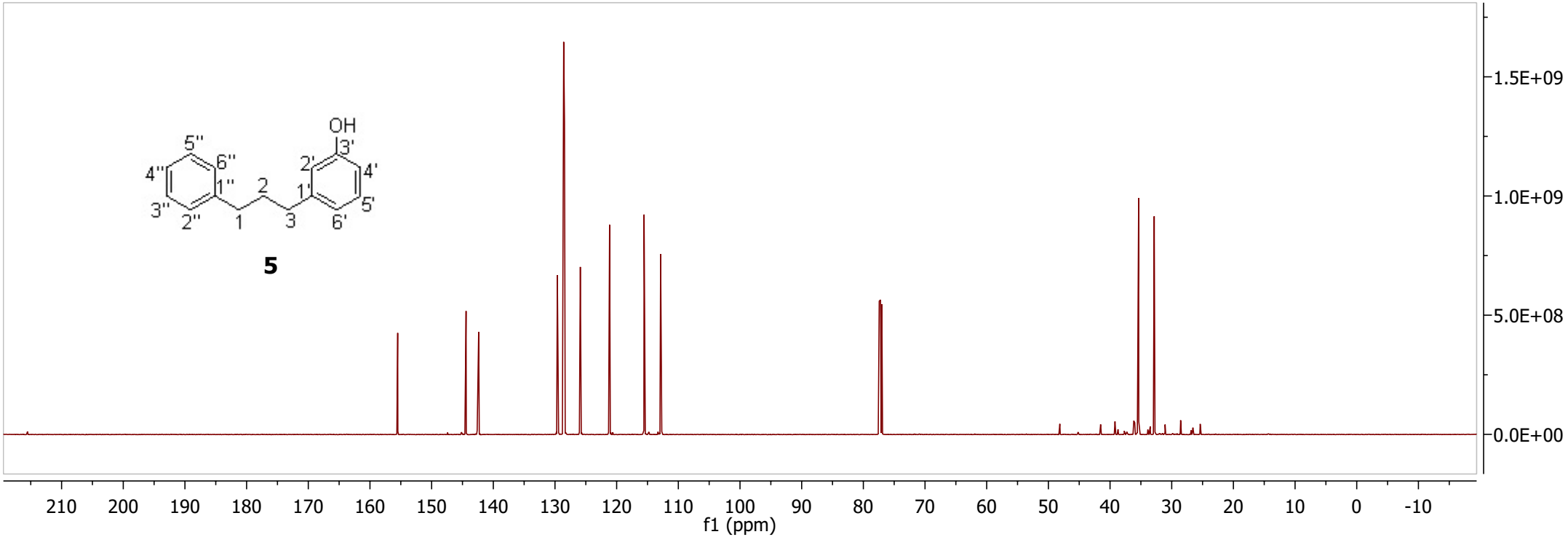
S3: $CDCl_3$, 1H


7.40 7.39 7.38 7.31 7.31 7.30 7.29 7.29 7.29 7.28 7.28 7.25 7.22
6.87 6.86
6.77 6.76 6.76 6.76 6.76 6.76
2.75 2.74 2.72 2.70 2.69 2.67
2.05 2.04 2.04 2.04 2.03 2.03 2.03 2.02 2.02 2.01 2.00
H-3", H-4", H-5" (m)
7.29
H-2", H-6" (t)
7.39
H-5' (t)
7.24
H-6' (d)
6.86
H-2', H-4' (m)
6.76
H-3 (m)
2.74
H-1 (m)
2.69
H-2 (m)
2.03
2.05
3.07
1.02
0.99
1.97
2.00
2.11
2.01
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 2.8 2.7 2.6 2.1 2.0 1.9
f1 (ppm)

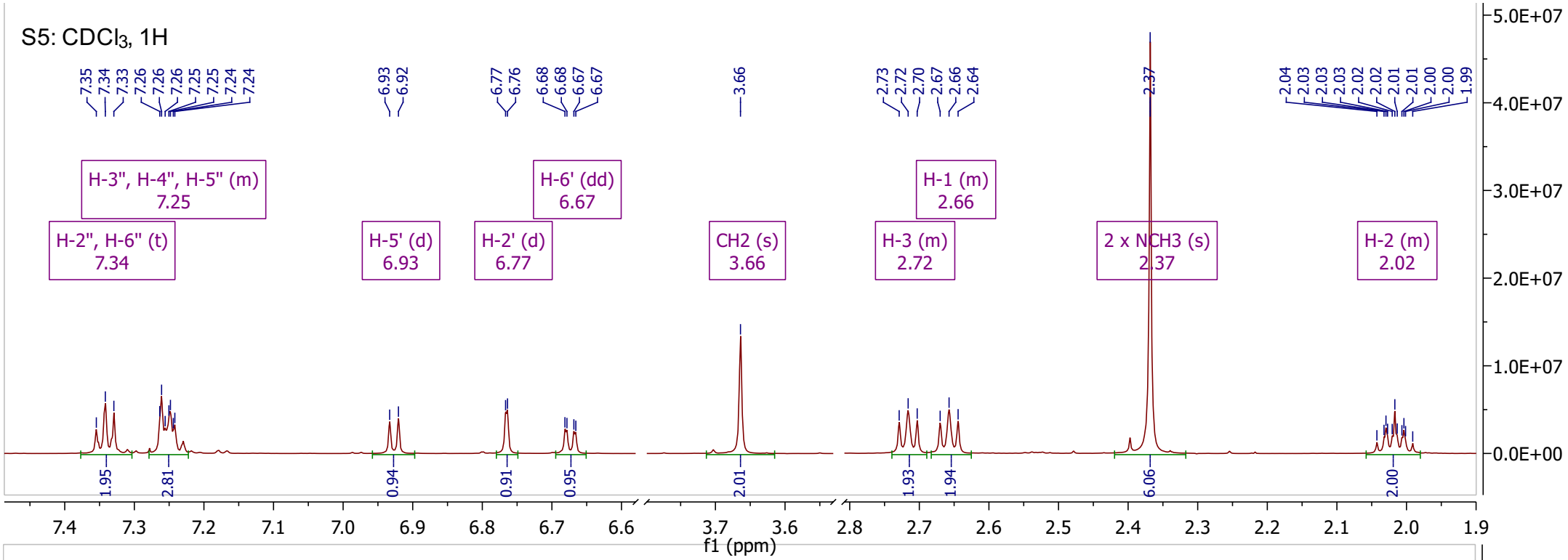

OH
5''
6''
4''
1''
2
2'
3'
4'
1'
5'
3''
2''
1
3
6'
5
1.8E+07
1.6E+07
1.4E+07
1.2E+07
1.0E+07
8.0E+06
6.0E+06
4.0E+06
2.0E+06
0.0E+00
16 15 14 13 12 11 10 9 8 7 2 1 0 -1 -2 -3 -4
f1 (ppm)

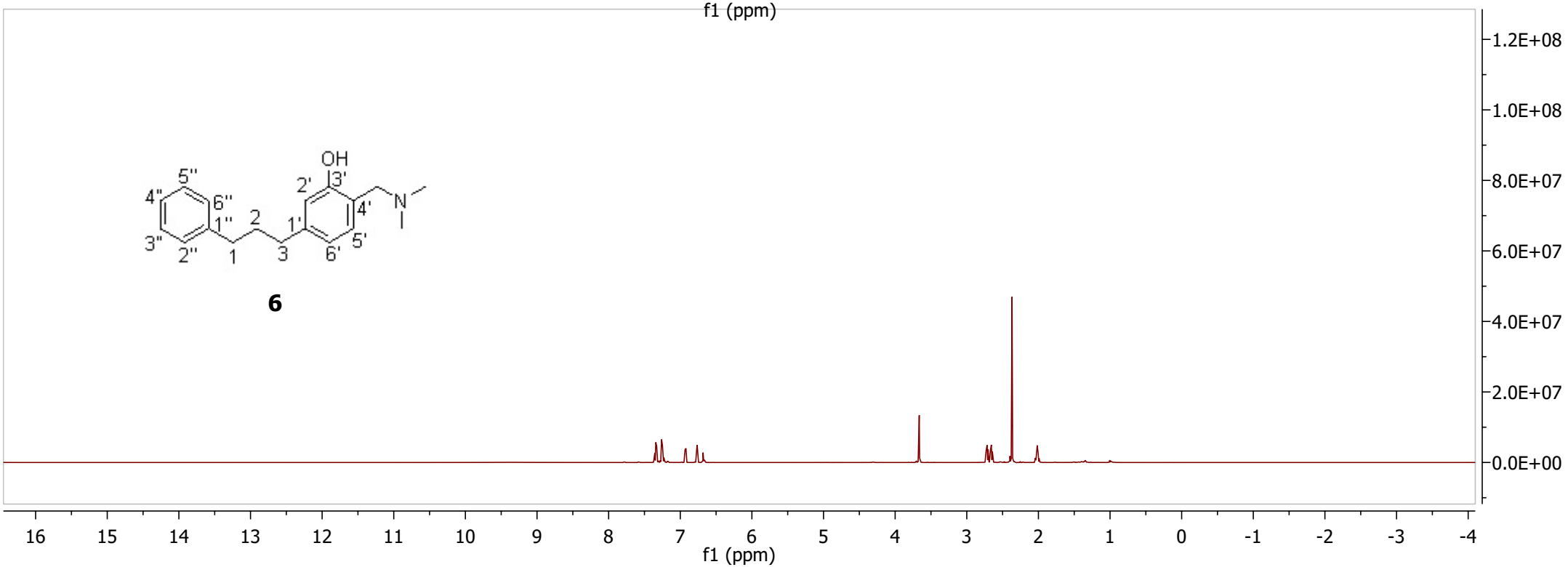
S4: $CDCl_3$,13C


155.50
144.42
142.37
129.62
128.59
128.45
125.89
121.14
115.55
112.87
35.49
35.36
32.84
2.5E+09
2.0E+09
1.5E+09
1.0E+09
5.0E+08
0.0E+00
158 156 154 152 150 148 146 144 142 140 130 128 126 124 122 120 118 116 114 112 36 34 32
f1 (ppm)

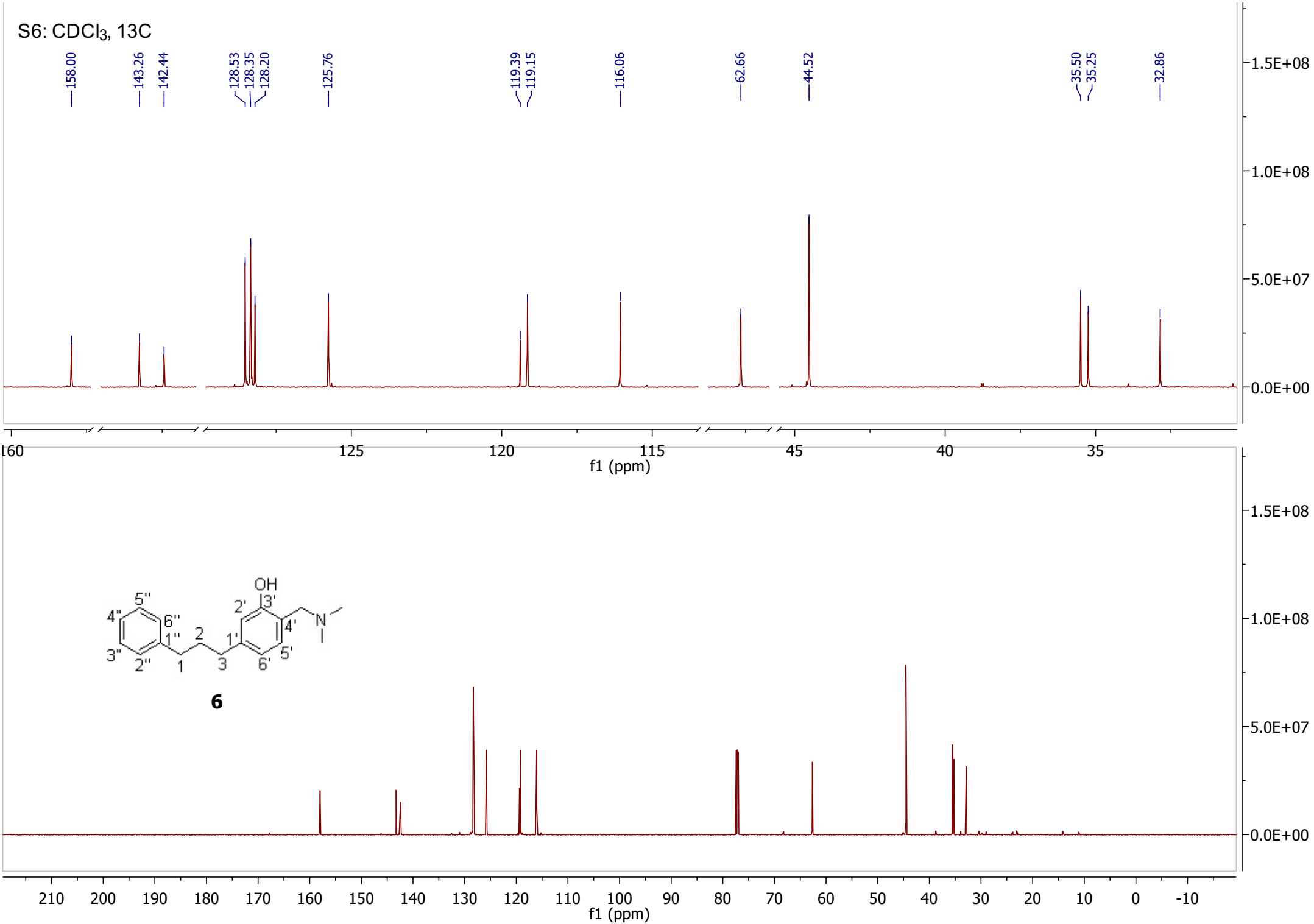

OH
5''
6''
4''
1''
2
2'
3'
4'
1'
5'
3''
2''
1
3
6'
5
1.5E+09
1.0E+09
5.0E+08
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

S5: $CDCl_3$, 1H

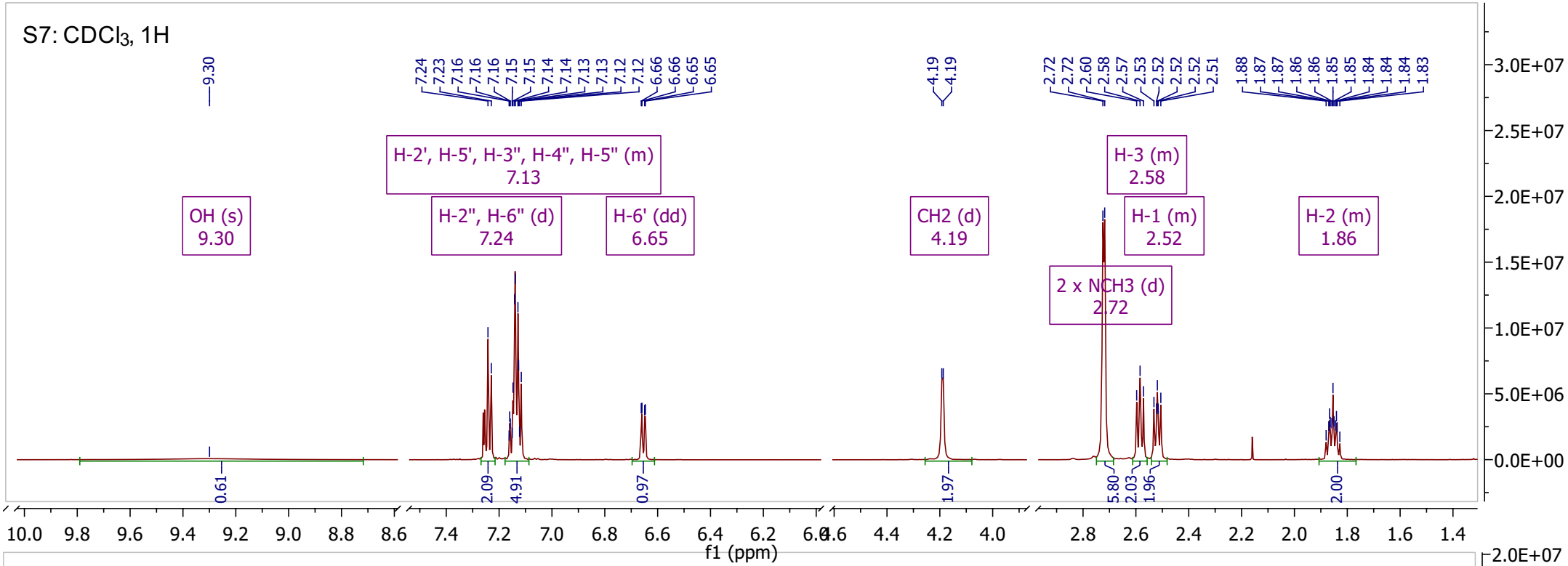

7.35 7.34 7.33 7.26 7.26 7.26 7.25 7.25 7.24 7.24
6.93 6.92
6.77 6.76
6.68 6.68 6.67 6.67
3.66
2.73 2.72 2.70 2.67 2.66 2.64
2.37
2.04 2.03 2.03 2.02 2.02 2.01 2.01 2.00 2.00 1.99
H-3", H-4", H-5" (m) 7.25
H-2", H-6" (t) 7.34
H-5' (d) 6.93
H-2' (d) 6.77
H-6' (dd) 6.67
CH2 (s) 3.66
H-1 (m) 2.66
H-3 (m) 2.72
2 x NCH3 (s) 2.37
H-2 (m) 2.02
1.95 2.81 0.94 0.91 0.95 2.01 1.93 1.94 6.06 2.00
5.0E+07 4.0E+07 3.0E+07 2.0E+07 1.0E+07 0.0E+00
7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 3.7 3.6 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9
f1 (ppm)

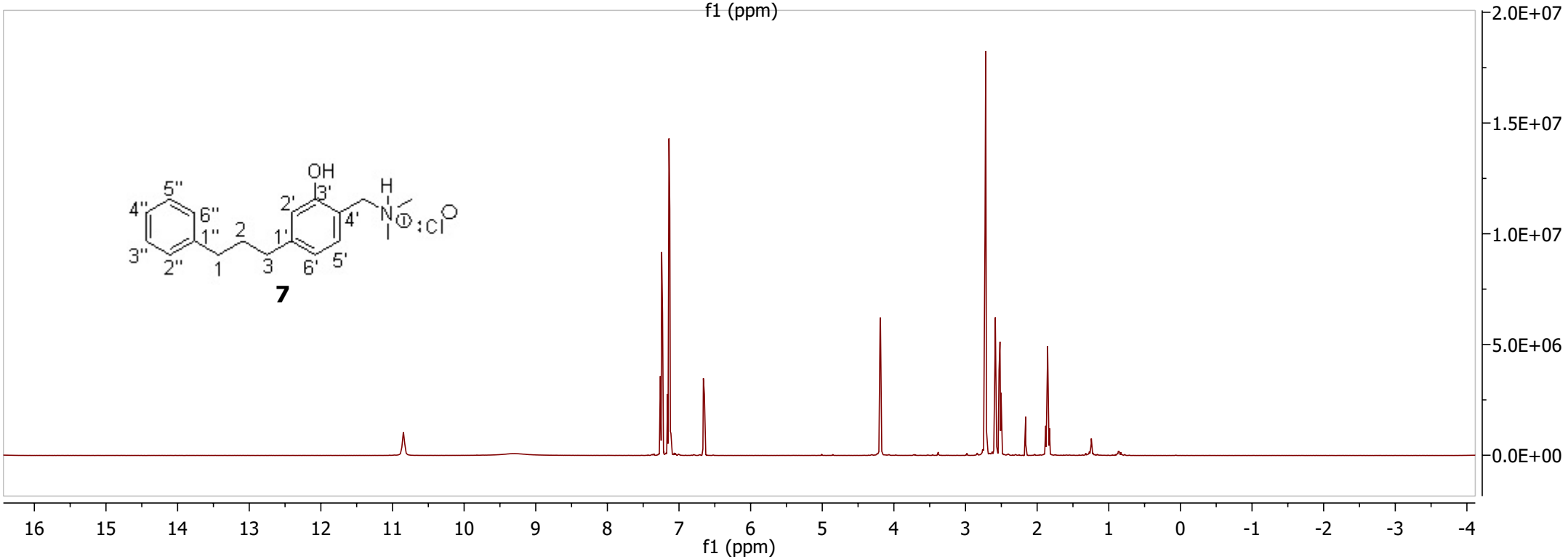

OH
5''
4''
6''
1''
2
1'
2'
3'
4'
N
3''
2''
1
3
6'
5'
6
1.2E+08 1.0E+08 8.0E+07 6.0E+07 4.0E+07 2.0E+07 0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

S6: $CDCl_3$, 13C

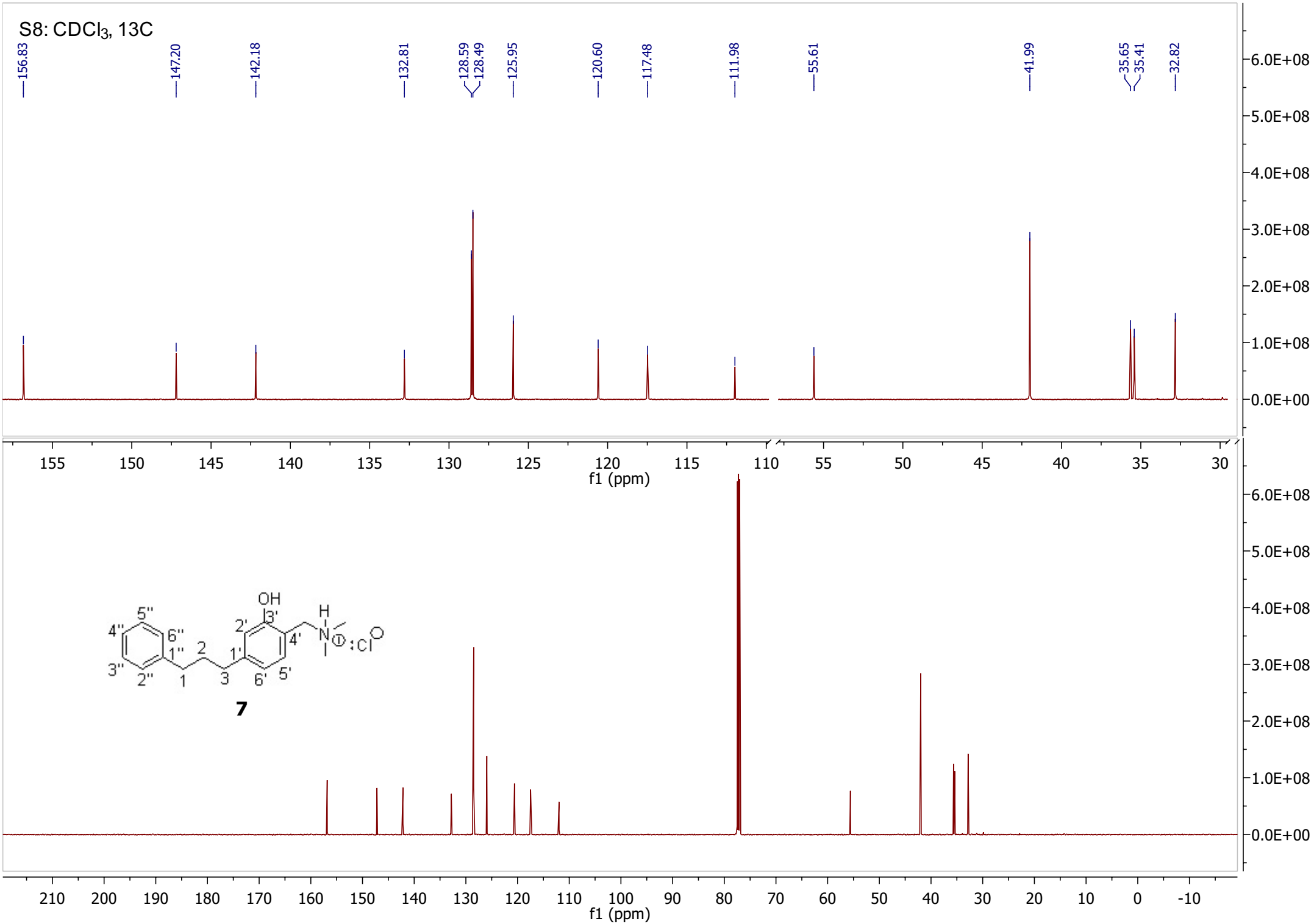

158.00
143.26
142.44
128.53
128.35
128.20
125.76
119.39
119.15
116.06
62.66
44.52
35.50
35.25
32.86
1.5E+08
1.0E+08
5.0E+07
0.0E+00
160
125
120
115
45
40
35
f1 (ppm)
OH
N
6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

S7: $CDCl_3$, 1H

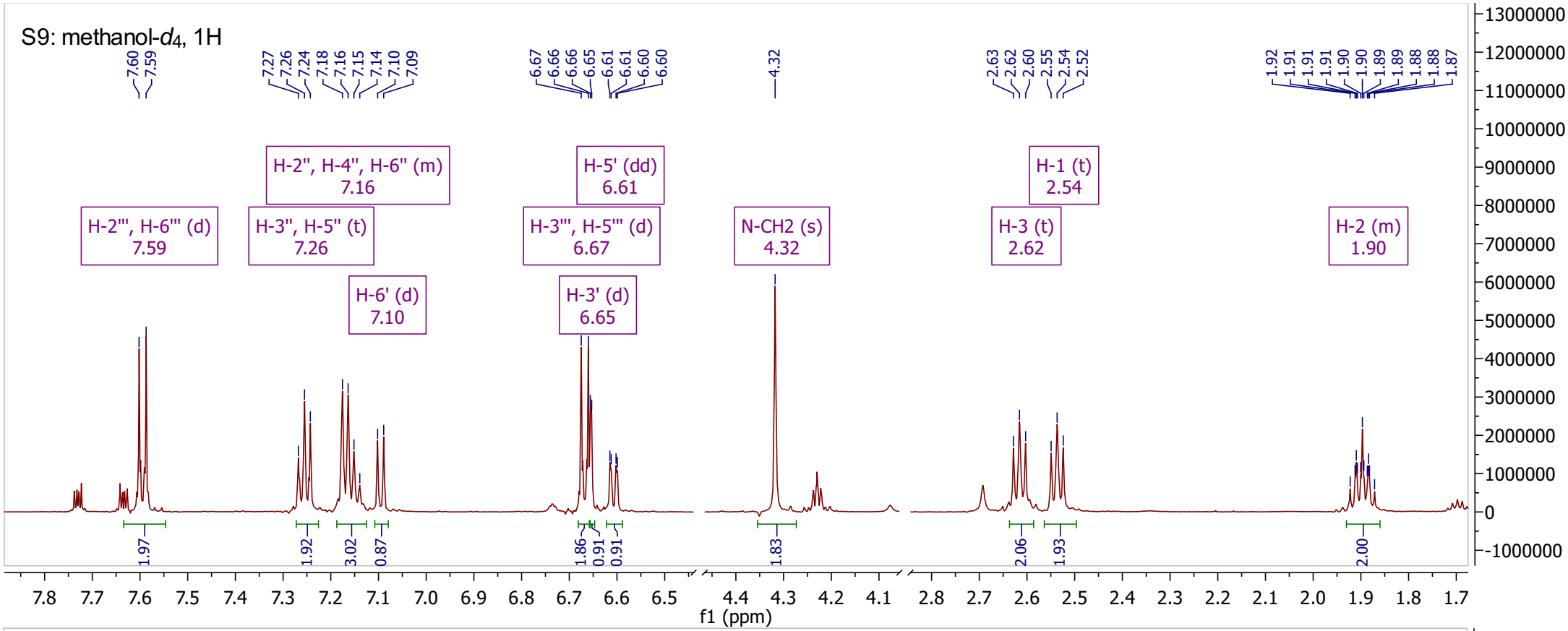

9.30
7.24 7.23 7.16 7.16 7.16 7.15 7.15 7.14 7.14 7.13 7.13 7.12 7.12 6.66 6.66 6.65 6.65
4.19 4.19
2.72 2.72 2.60 2.58 2.57 2.53 2.52 2.52 2.52 2.51
1.88 1.87 1.87 1.86 1.86 1.85 1.85 1.84 1.84 1.84 1.83
OH (s) 9.30
H-2', H-5', H-3", H-4", H-5" (m) 7.13
H-2", H-6" (d) 7.24
H-6' (dd) 6.65
CH2 (d) 4.19
H-3 (m) 2.58
H-1 (m) 2.52
2 x NCH3 (d) 2.72
H-2 (m) 1.86
0.61
2.09
4.91
0.97
1.97
5.80
2.03
1.96
2.00
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 4.6 4.4 4.2 4.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4
f1 (ppm)

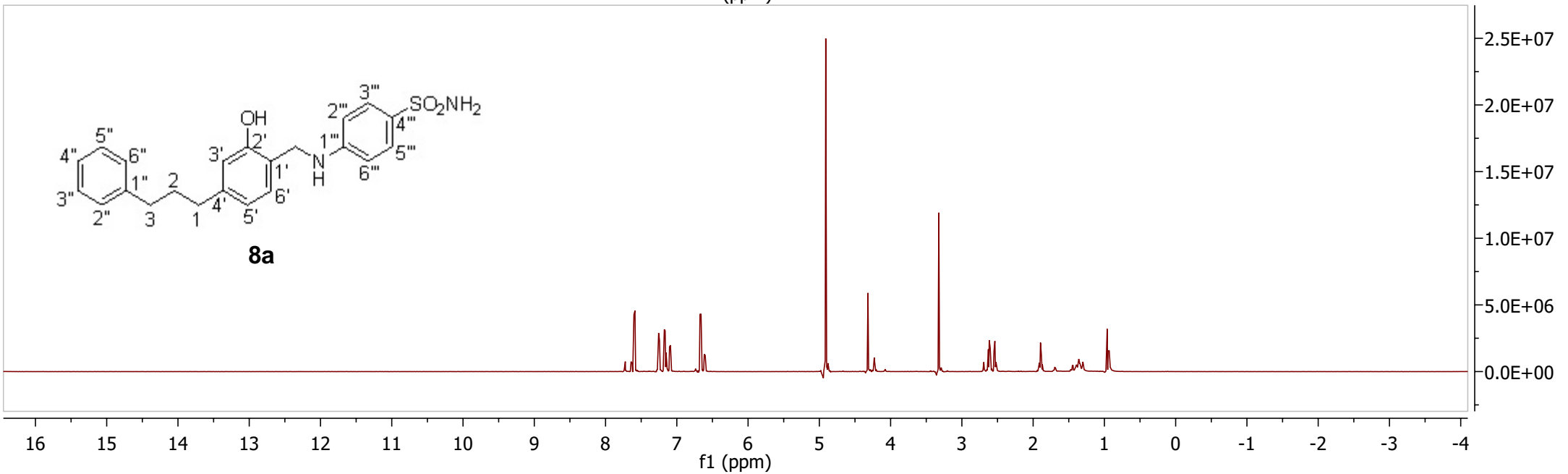

OH
H
N
Cl
5"
4"
6"
3"
2"
1"
1
2
3
1'
2'
3'
4'
5'
6'
7
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

S8: $CDCl_3$, 13C

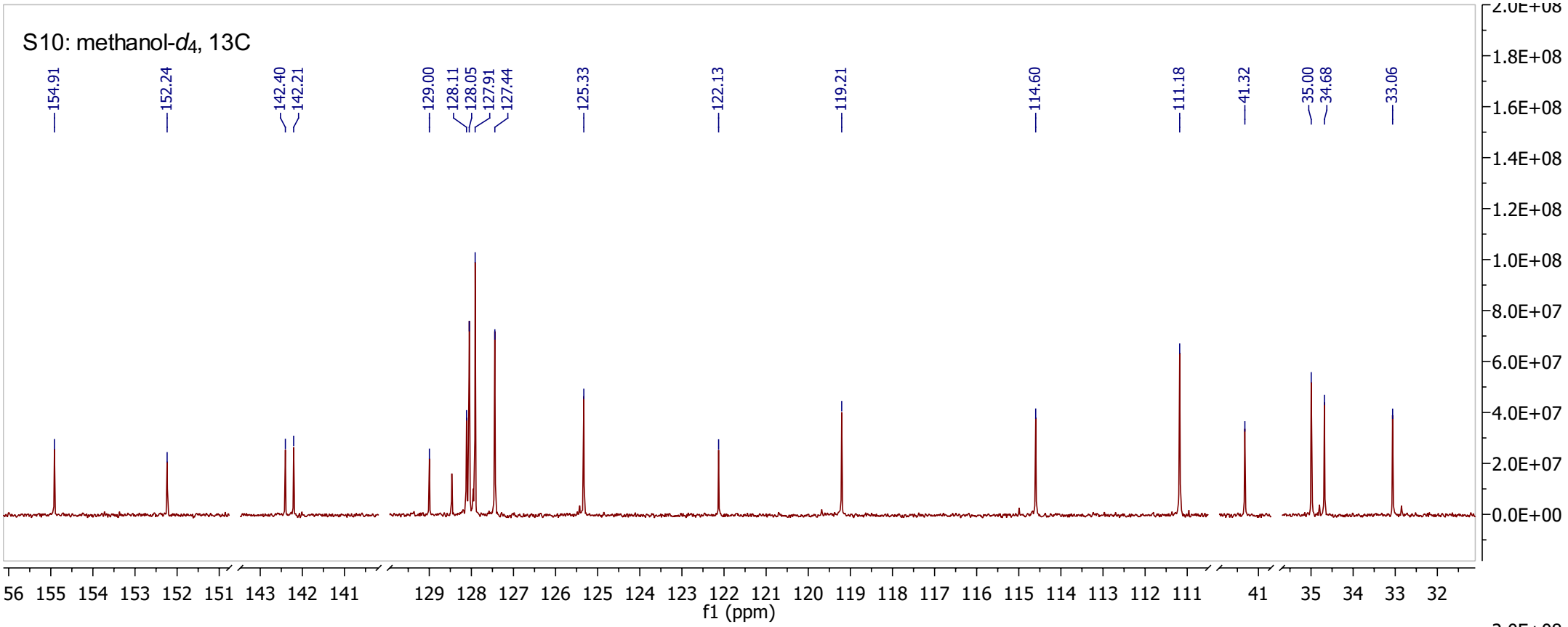

156.83
147.20
142.18
132.81
128.59
128.49
125.95
120.60
117.48
111.98
55.61
41.99
35.65
35.41
32.82
6.0E+08
5.0E+08
4.0E+08
3.0E+08
2.0E+08
1.0E+08
0.0E+00
155 150 145 140 135 130 125 120 115 110 55 50 45 40 35 30
f1 (ppm)
OH
H
N
Cl
1 2 3
1' 2' 3' 4' 5' 6'
1'' 2'' 3'' 4'' 5'' 6''
7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

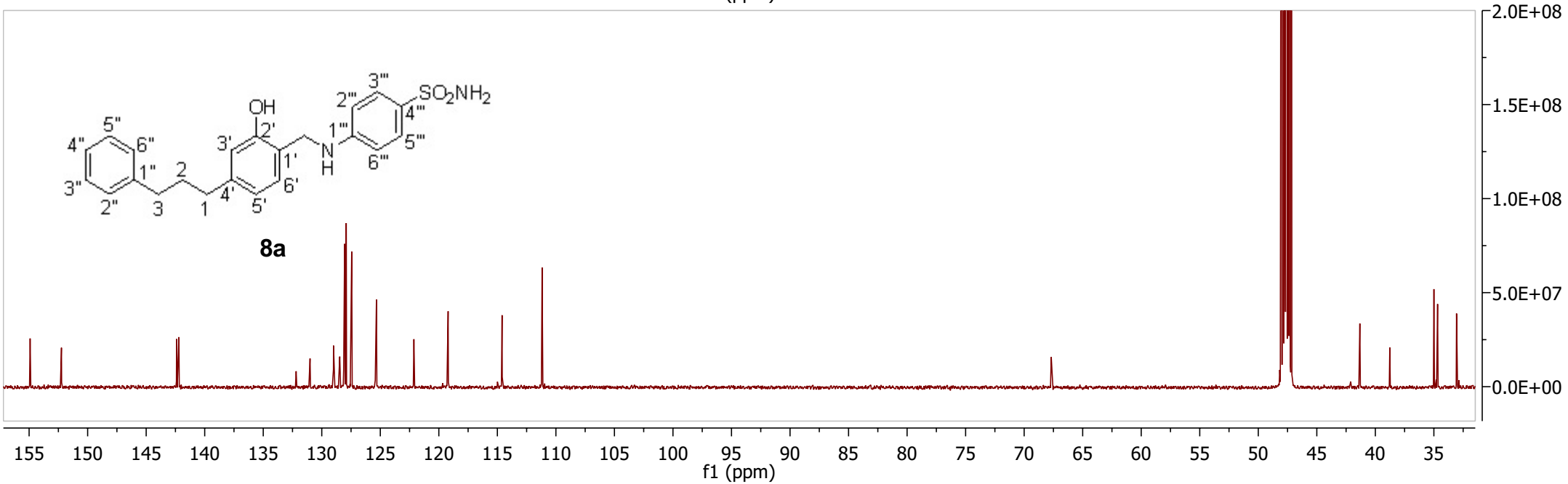
S9: methanol-d_4, 1H



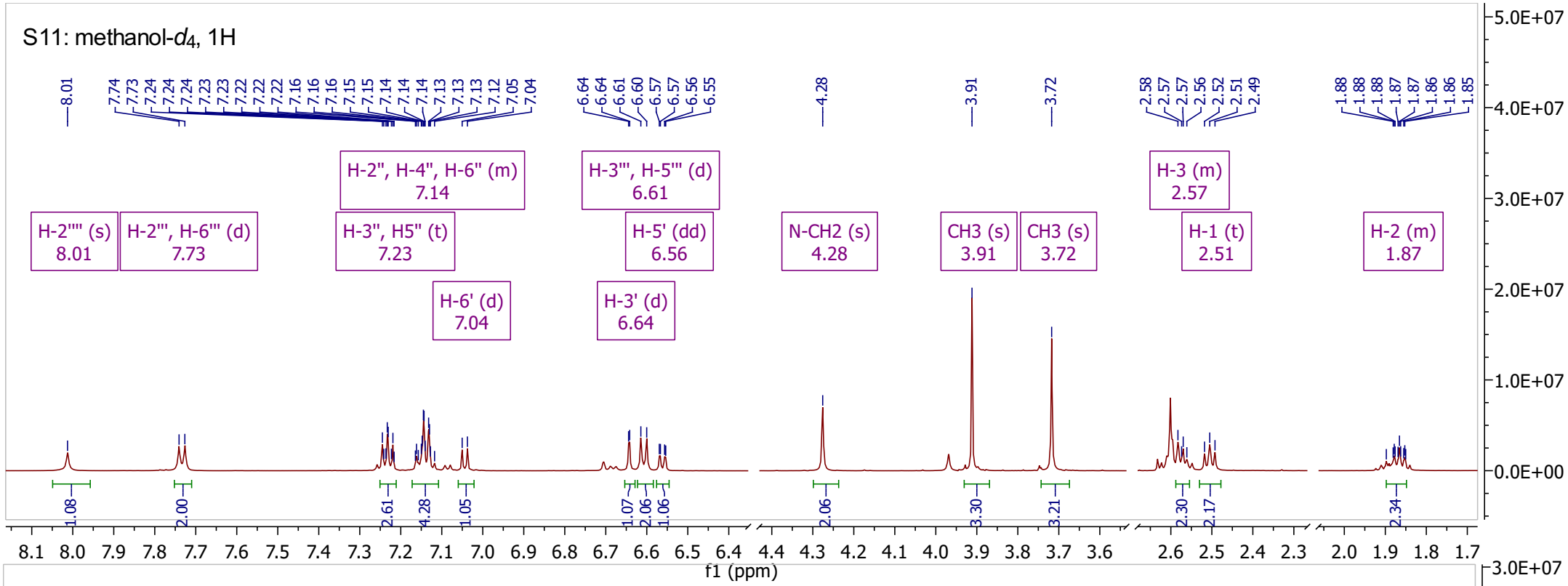


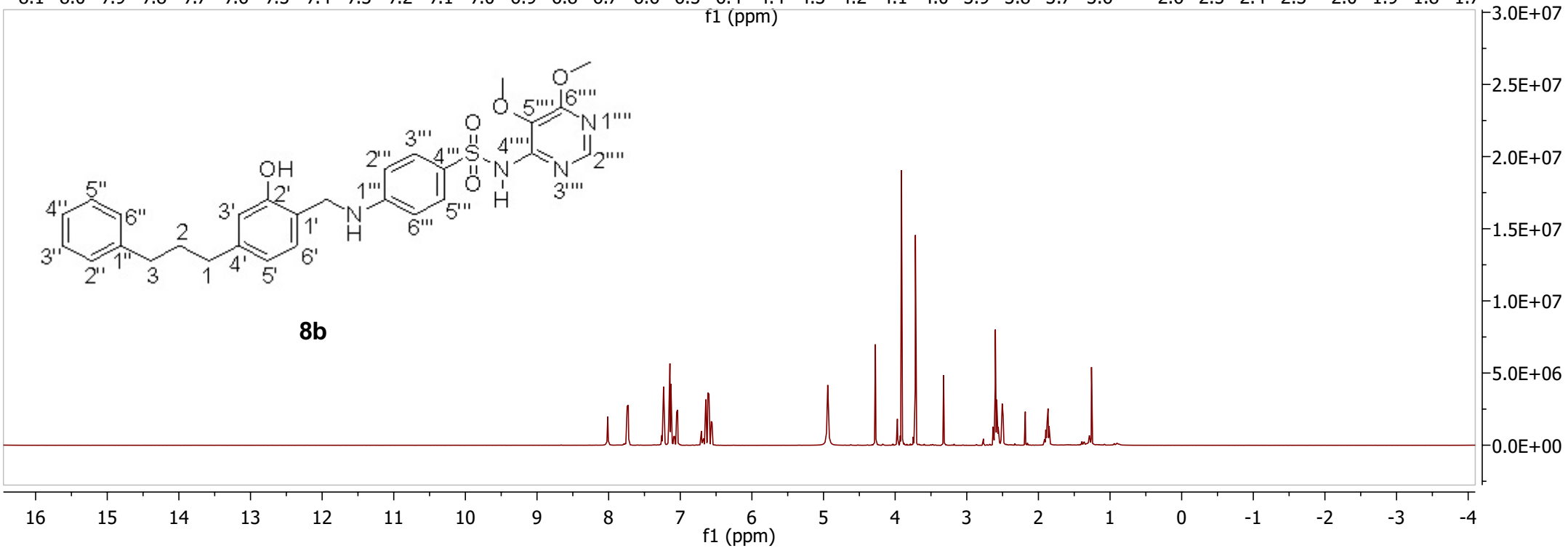
S10: methanol-d_4, 13C



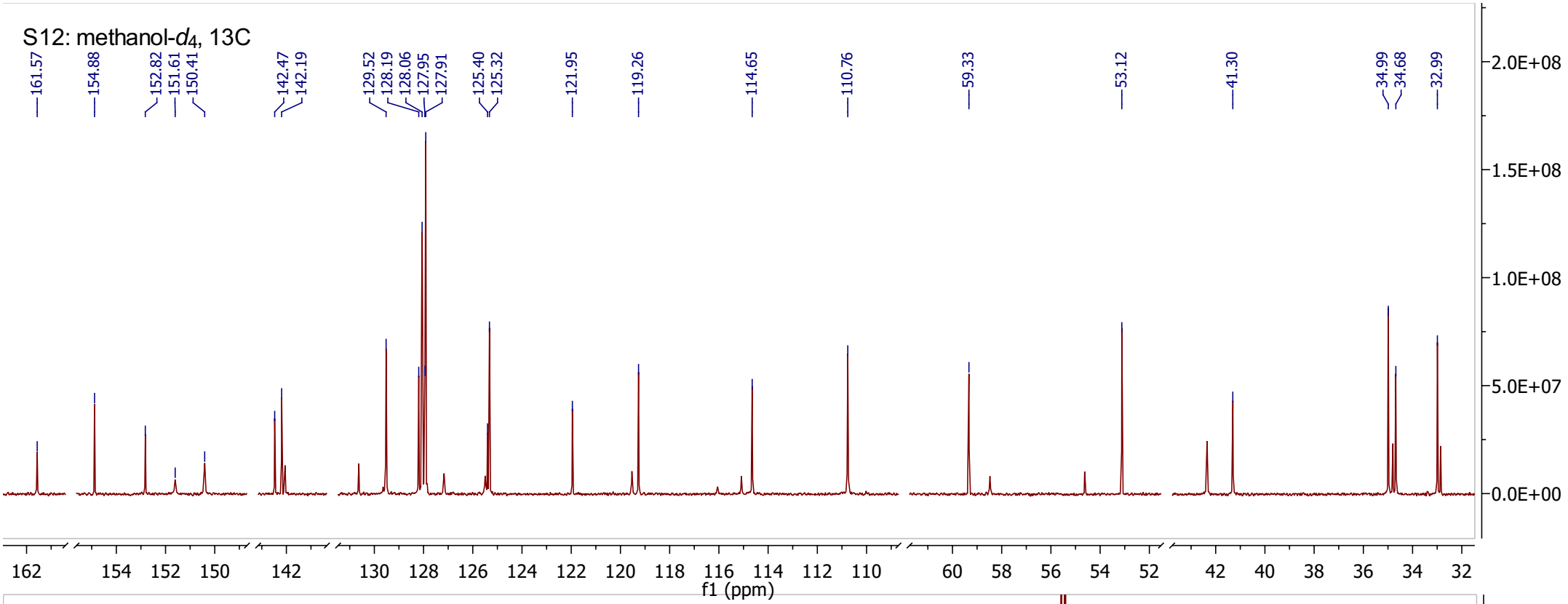


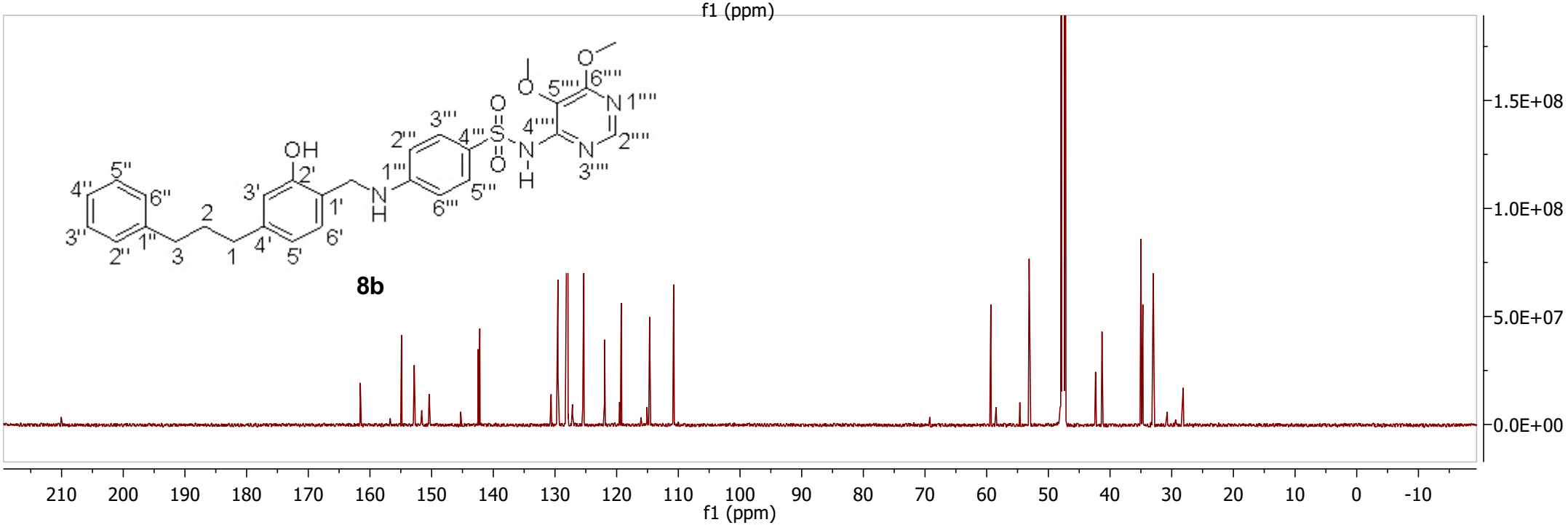
S11: methanol-d_4, 1H

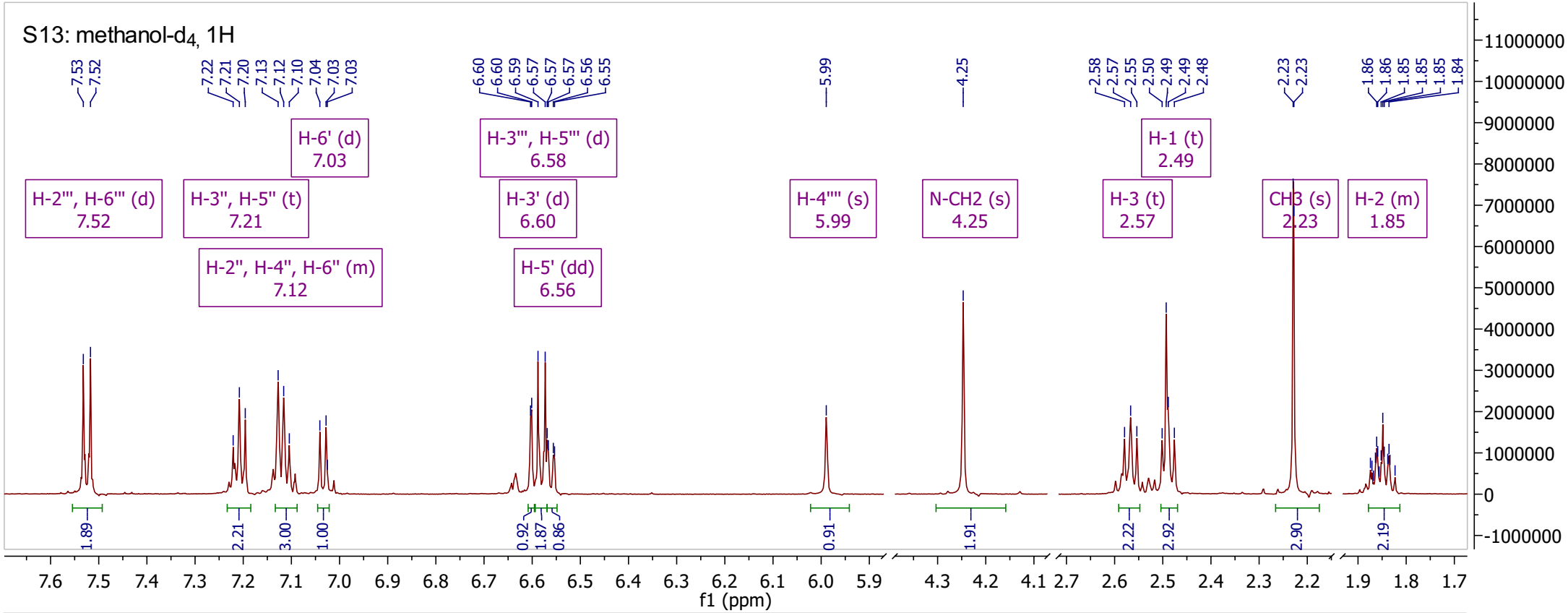


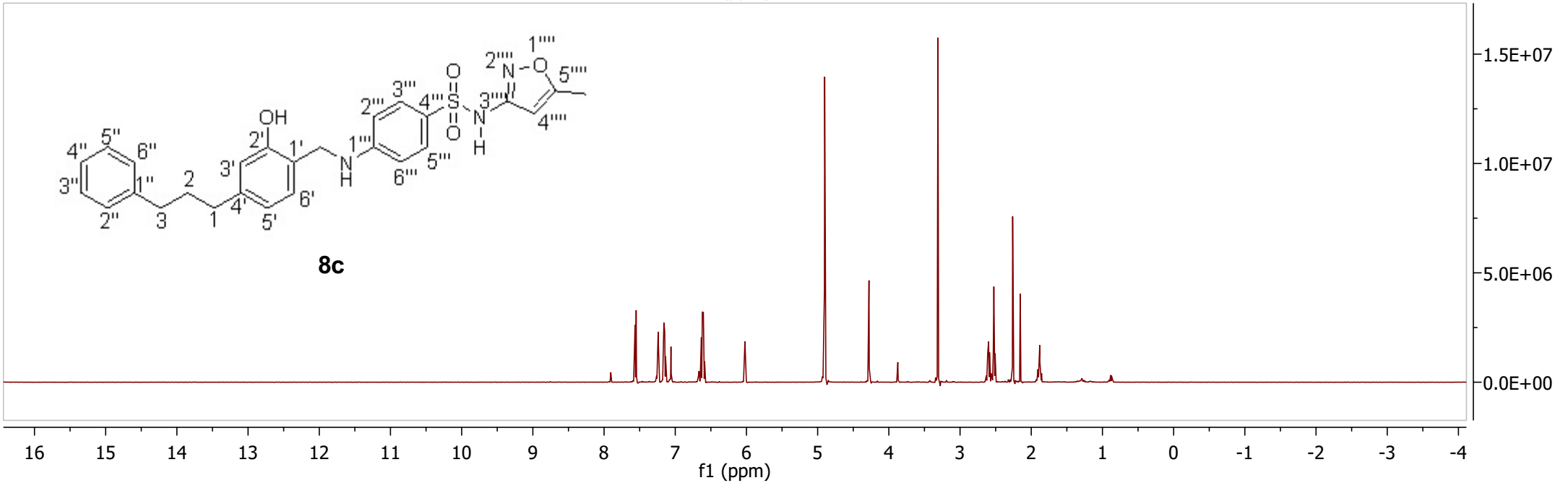


S12: methanol-d_4, 13C

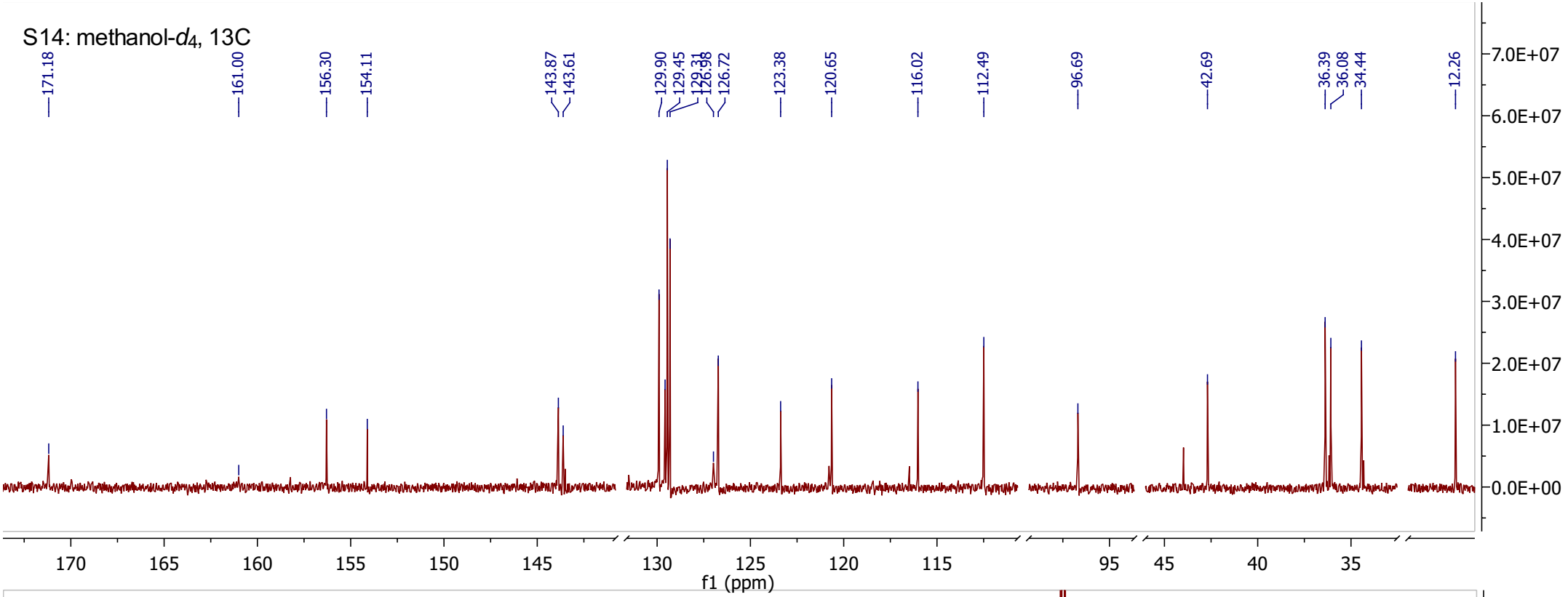


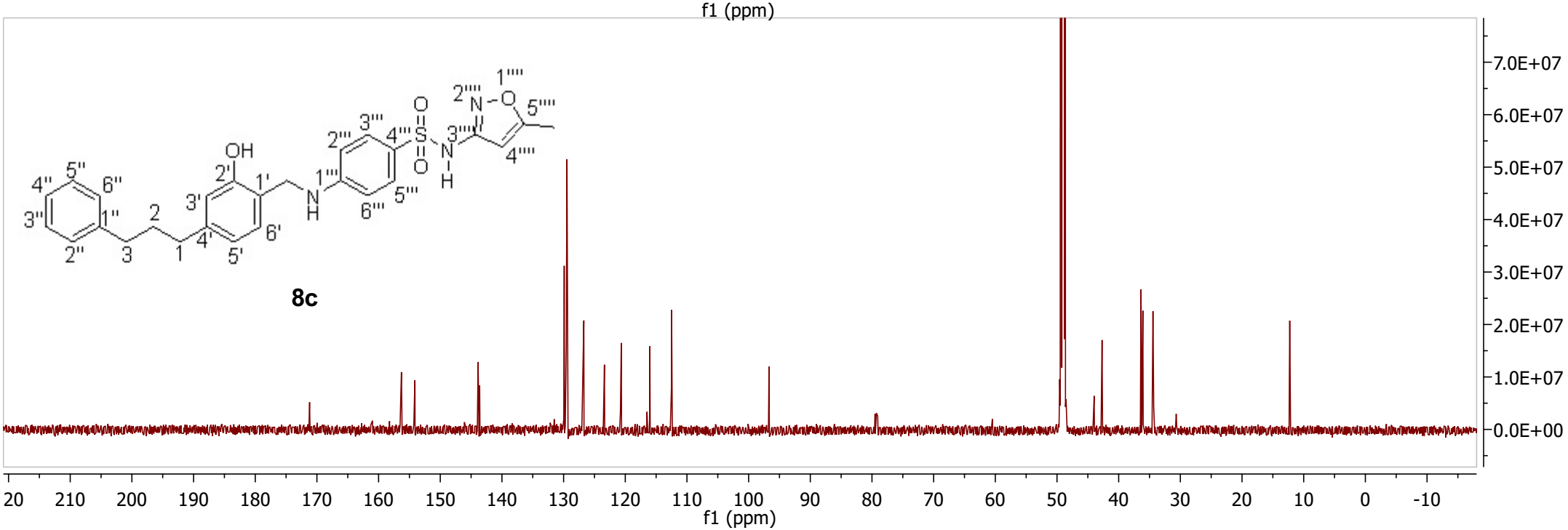



S13: methanol-d4, 1H
H-2''', H-6''' (d) 7.52
H-3'', H-5'' (t) 7.21
H-6' (d) 7.03
H-2'', H-4'', H-6'' (m) 7.12
H-3''', H-5''' (d) 6.58
H-3' (d) 6.60
H-5' (dd) 6.56
H-4'''' (s) 5.99
N-CH2 (s) 4.25
H-1 (t) 2.49
H-3 (t) 2.57
CH3 (s) 2.23
H-2 (m) 1.85
f1 (ppm)

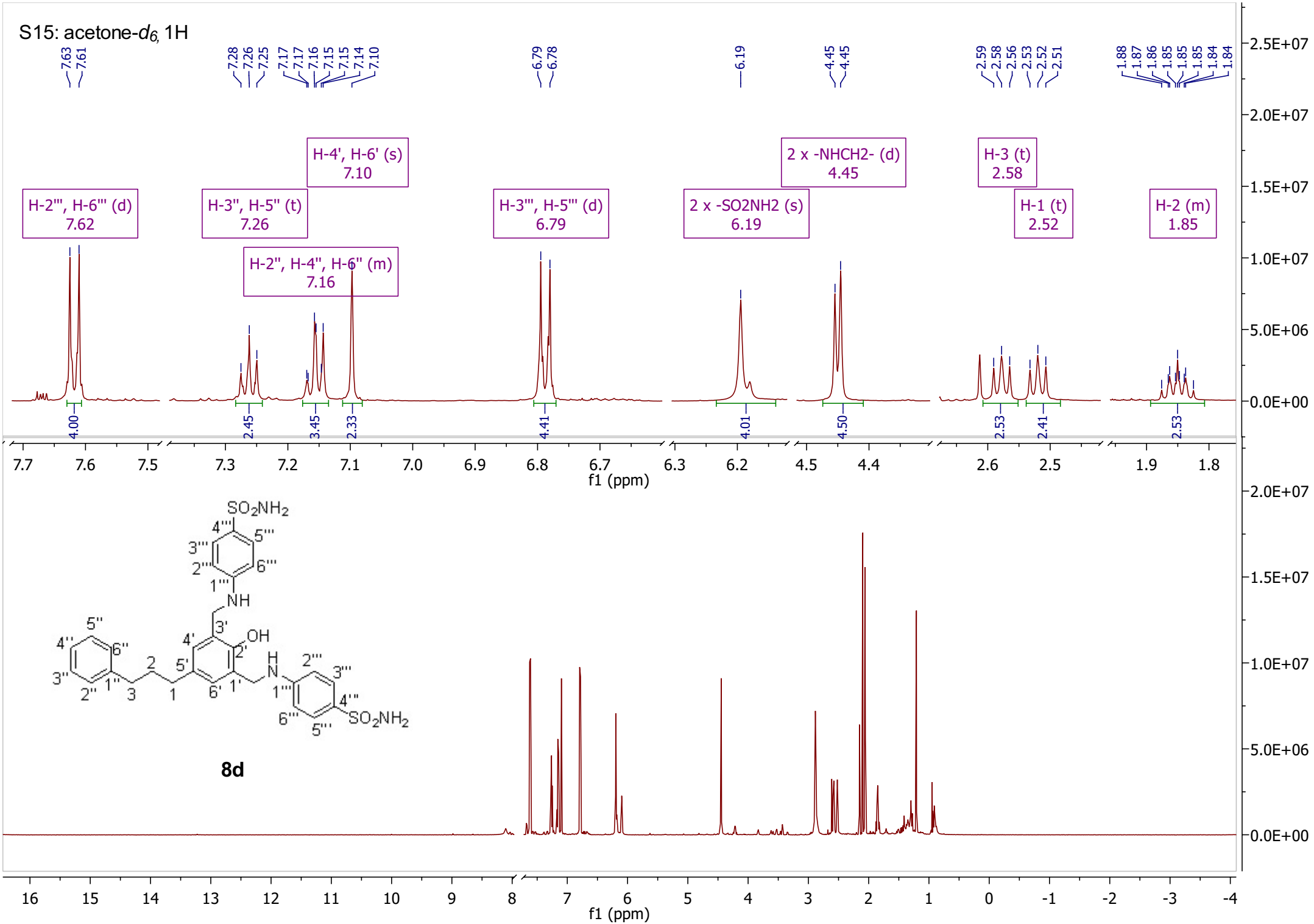

8c
f1 (ppm)

S14: methanol-d_4, 13C

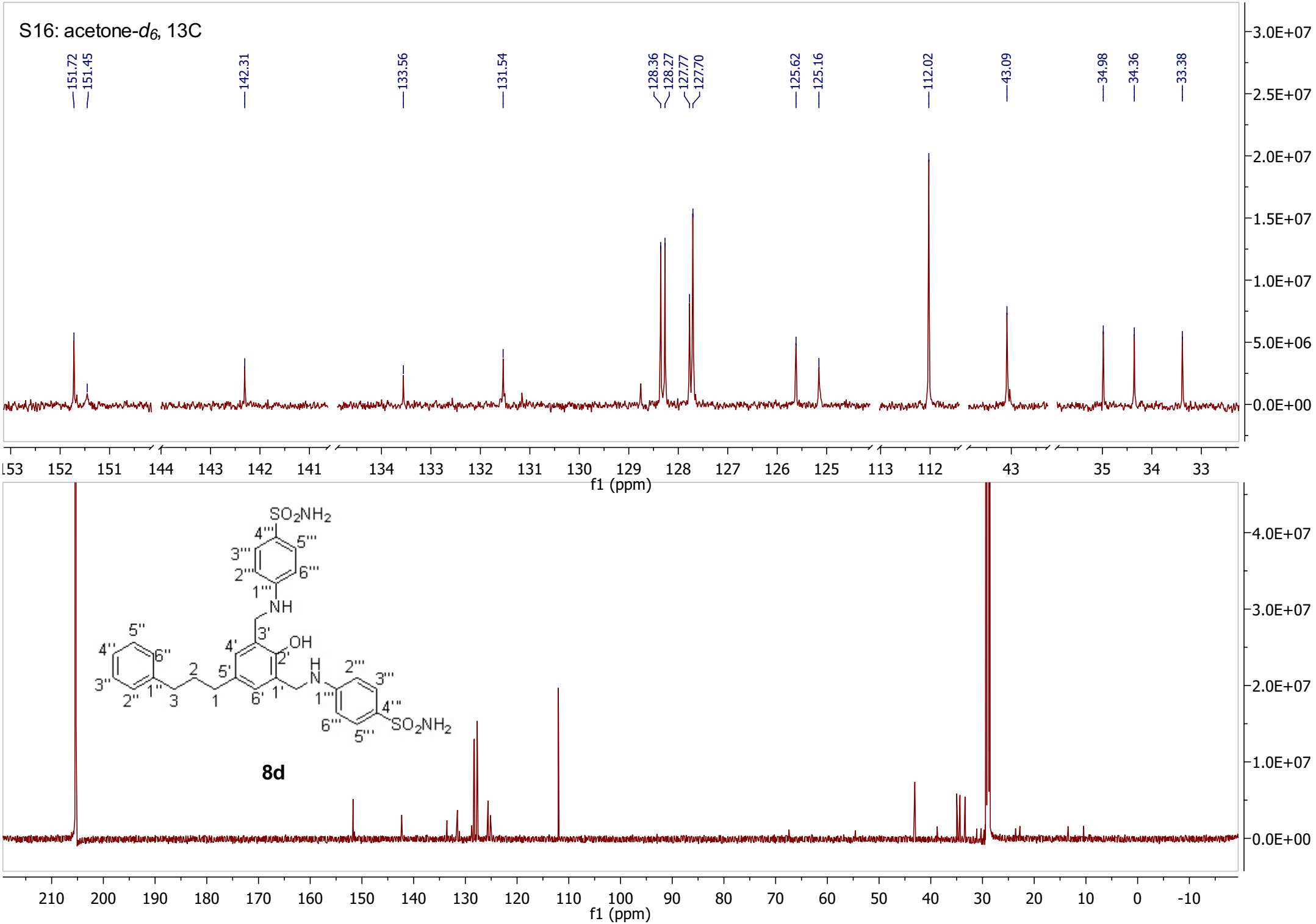




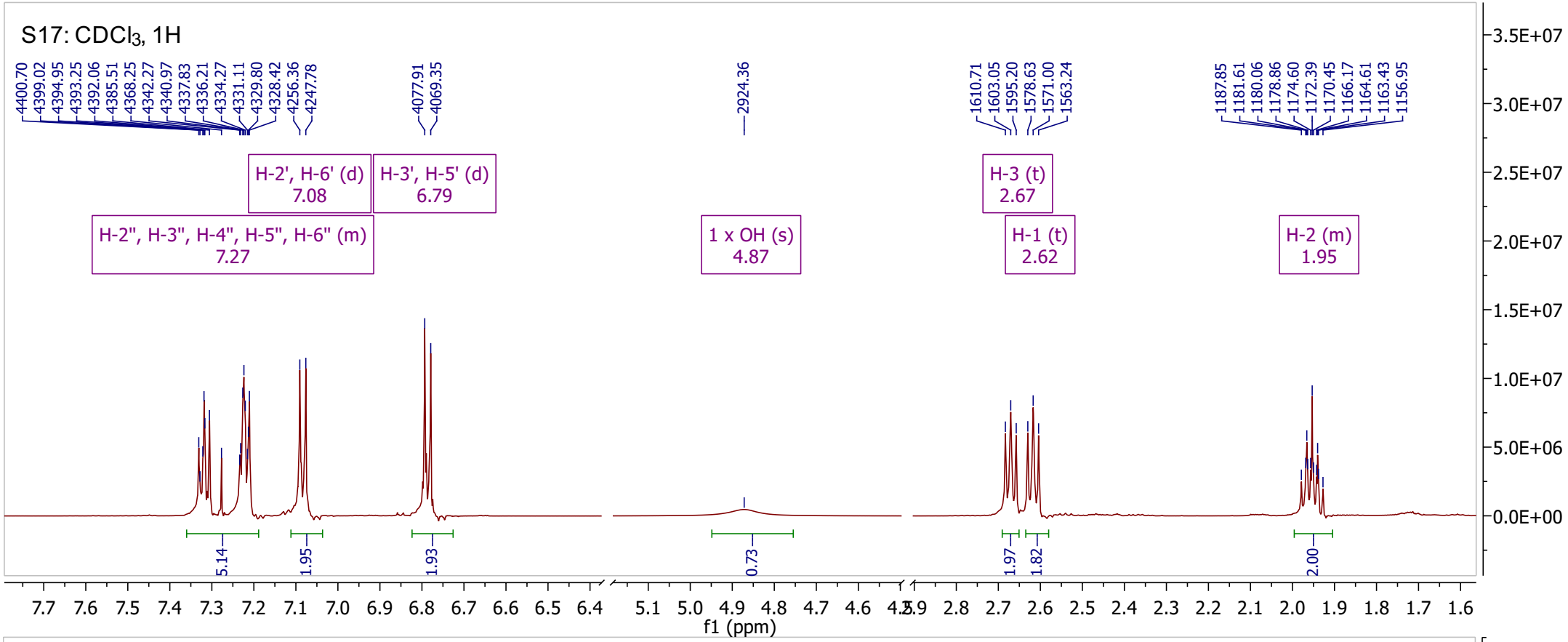
S15: acetone-d_6, 1H

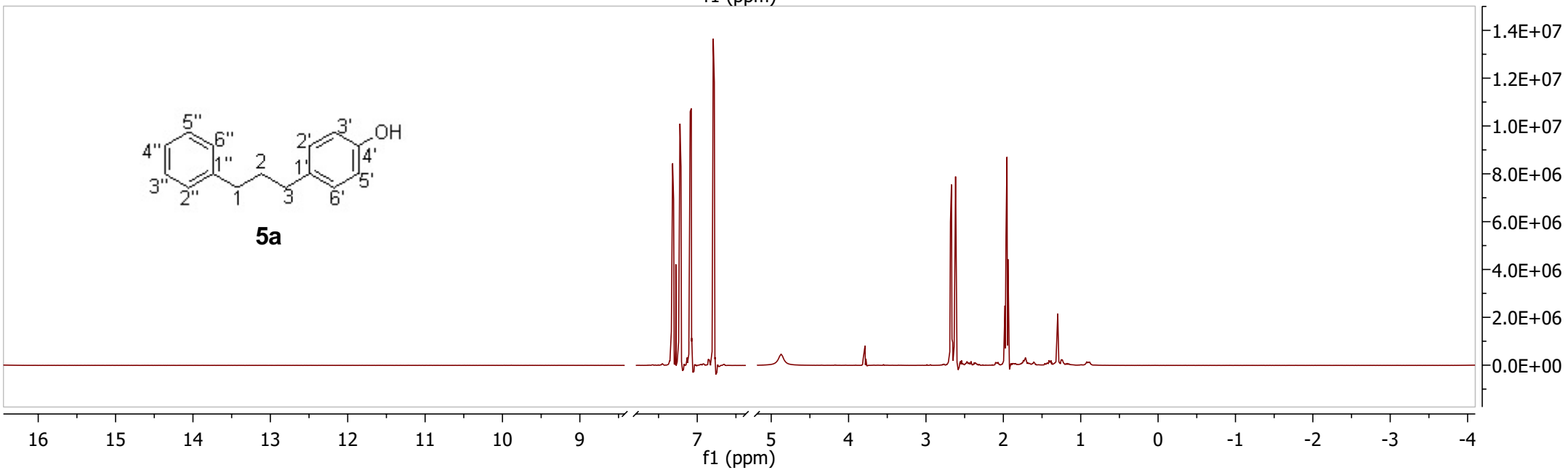


S16: acetone-d_6, 13C

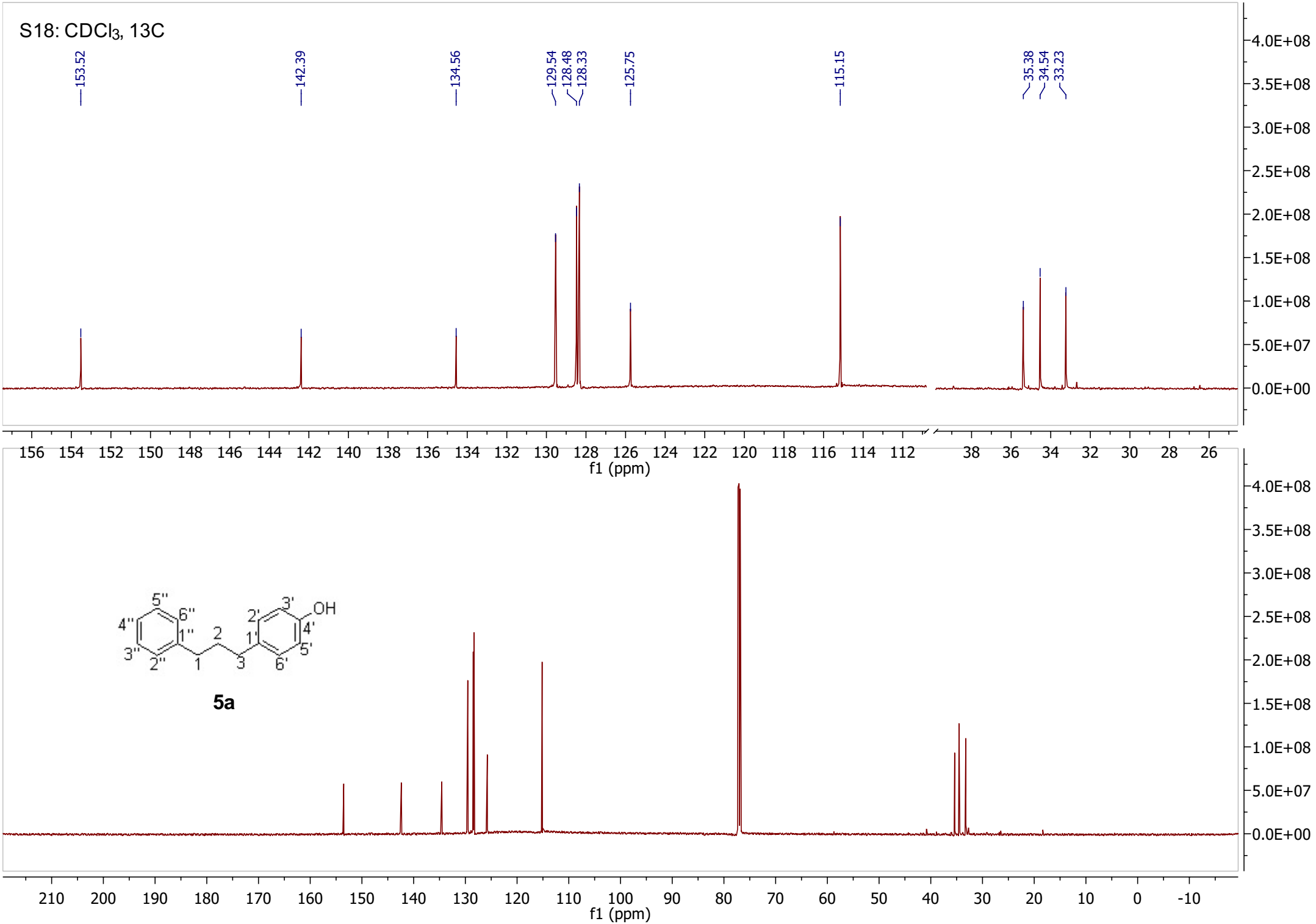


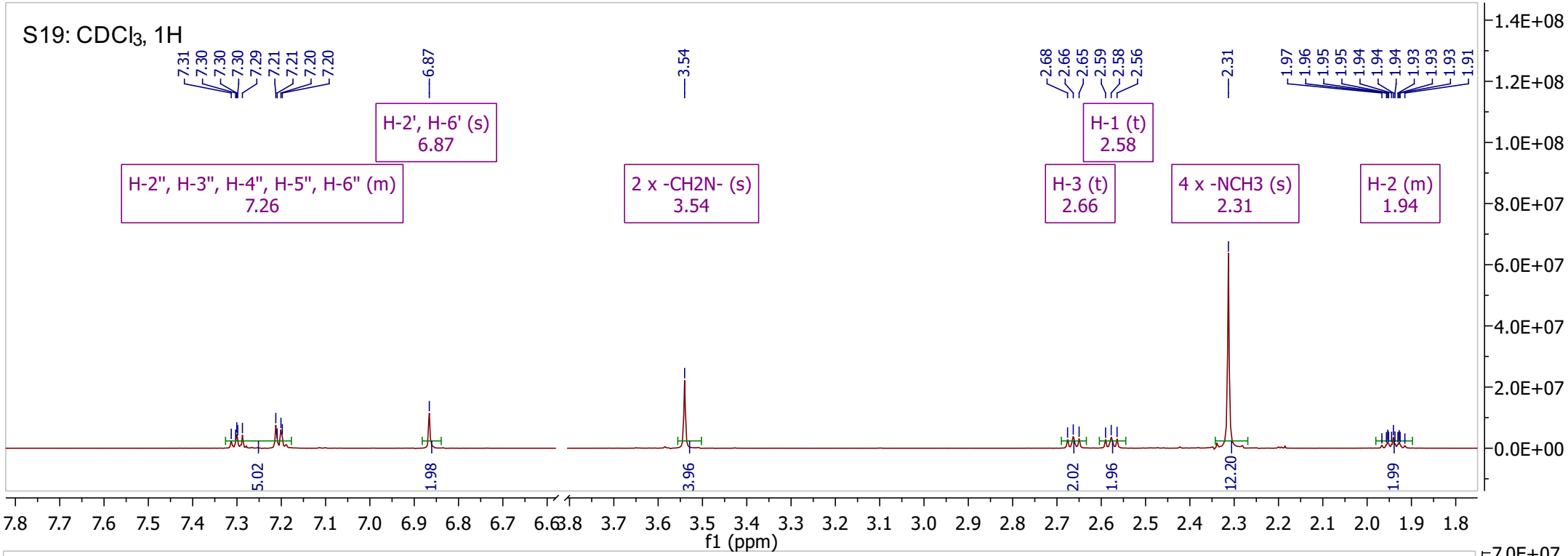
S17: $CDCl_3$, 1H

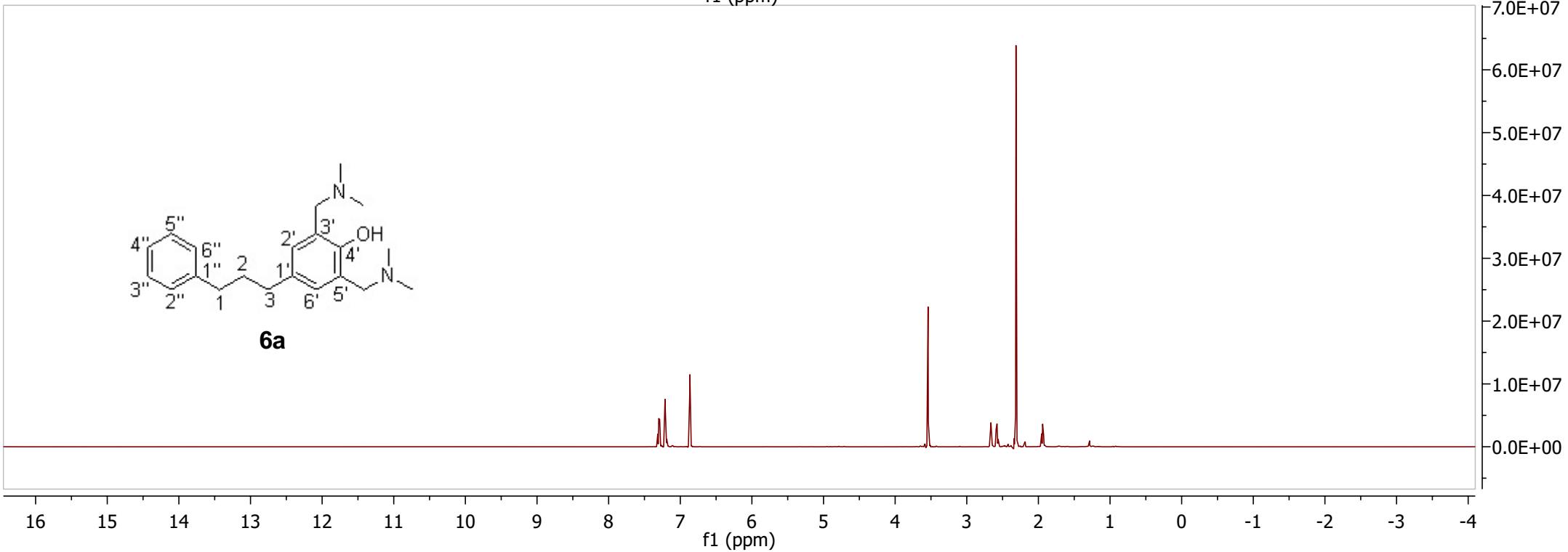

4400.70
4399.02
4394.95
4393.25
4392.06
4385.51
4368.25
4342.27
4340.97
4337.83
4336.21
4334.27
4331.11
4329.80
4328.42
4256.36
4247.78
4077.91
4069.35
2924.36
1610.71
1603.05
1595.20
1578.63
1571.00
1563.24
1187.85
1181.61
1180.06
1178.86
1174.60
1172.39
1170.45
1166.17
1164.61
1163.43
1156.95
H-2', H-6' (d)
7.08
H-3', H-5' (d)
6.79
H-2", H-3", H-4", H-5", H-6" (m)
7.27
1 x OH (s)
4.87
H-3 (t)
2.67
H-1 (t)
2.62
H-2 (m)
1.95
5.14
1.95
1.93
0.73
1.97
1.82
2.00
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 5.1 5.0 4.9 4.8 4.7 4.6 4.5 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6
f1 (ppm)


5"
6"
4"
1"
2
2'
3'
OH
4'
1'
5'
3"
2"
1
3
6'
5a
1.4E+07
1.2E+07
1.0E+07
8.0E+06
6.0E+06
4.0E+06
2.0E+06
0.0E+00
16 15 14 13 12 11 10 9 7 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

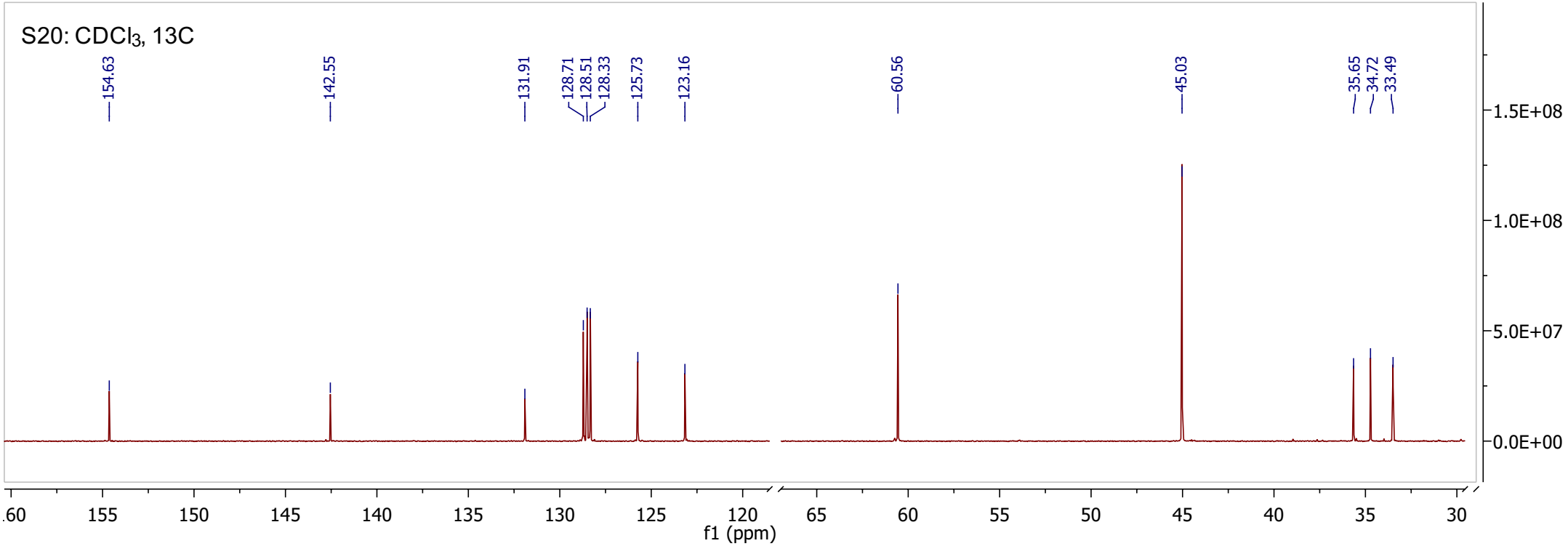
S18: $CDCl_3$, 13C

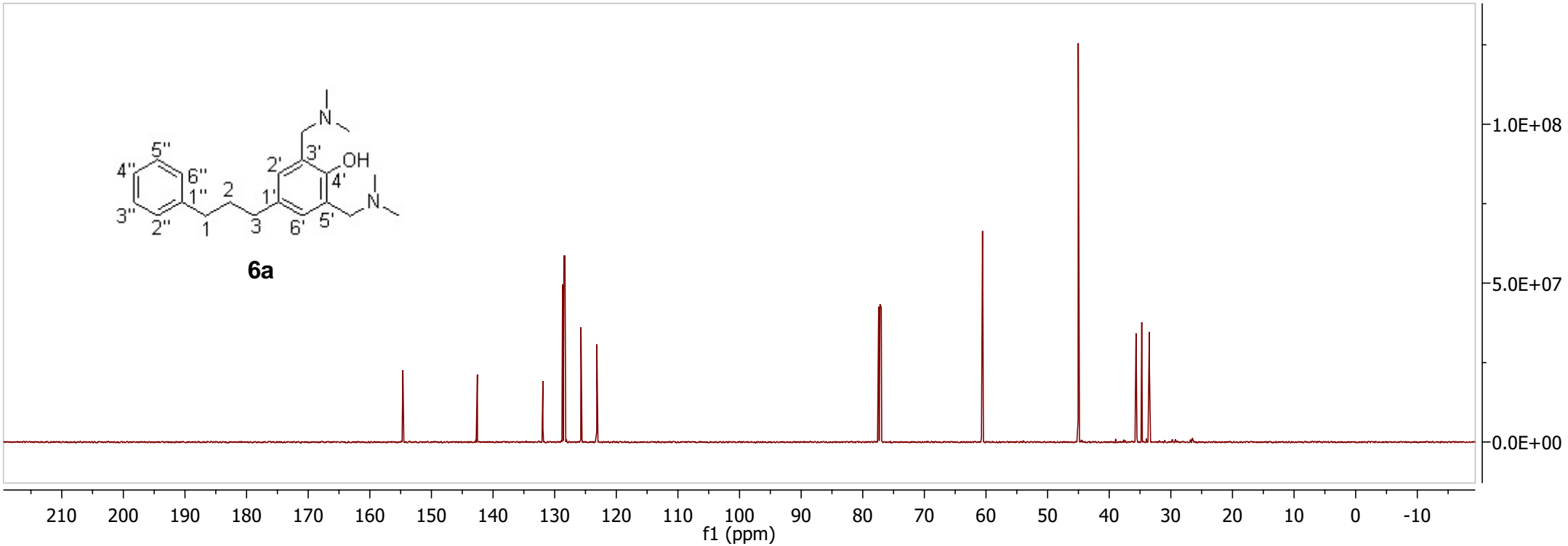



S19: CDCl3, 1H
7.31 7.30 7.30 7.30 7.29 7.21 7.21 7.20 7.20
6.87
3.54
2.68 2.66 2.65 2.59 2.58 2.56
2.31
1.97 1.96 1.95 1.95 1.94 1.94 1.94 1.93 1.93 1.93 1.91
H-2', H-6' (s)
6.87
H-1 (t)
2.58
H-2", H-3", H-4", H-5", H-6" (m)
7.26
2 x -CH2N- (s)
3.54
H-3 (t)
2.66
4 x -NCH3 (s)
2.31
H-2 (m)
1.94
5.02
1.98
3.96
2.02
1.96
12.20
1.99
1.4E+08
1.2E+08
1.0E+08
8.0E+07
6.0E+07
4.0E+07
2.0E+07
0.0E+00
7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)


N
5''
4''
6''
1''
2
2'
3'
OH
4'
1'
N
3''
2''
1
3
6'
5'
6a
7.0E+07
6.0E+07
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

S20: $CDCl_3$, 13C





S21: $CDCl_3$, 1H

H-2'', H-6'' (d) 7.30

H-2', H-6' (s) 7.33

H-3'', H-4'', H-5'' (m) 7.19

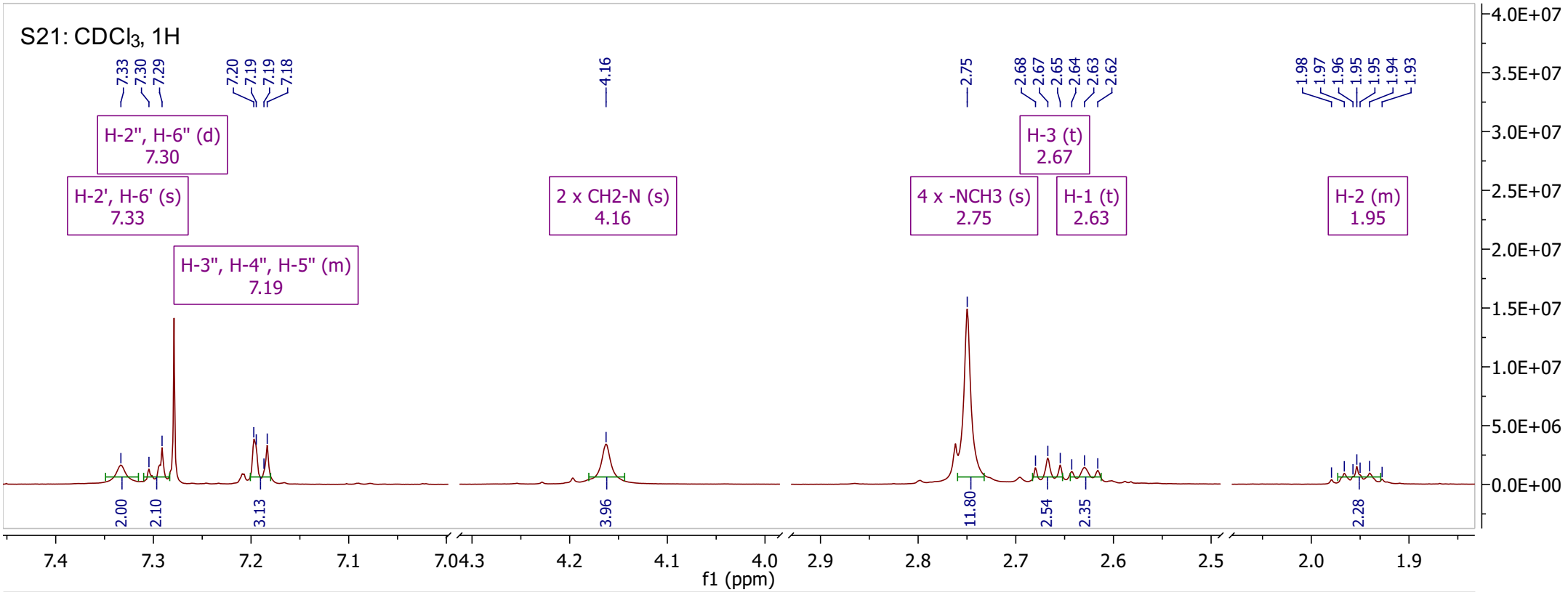
2 x CH2-N (s) 4.16

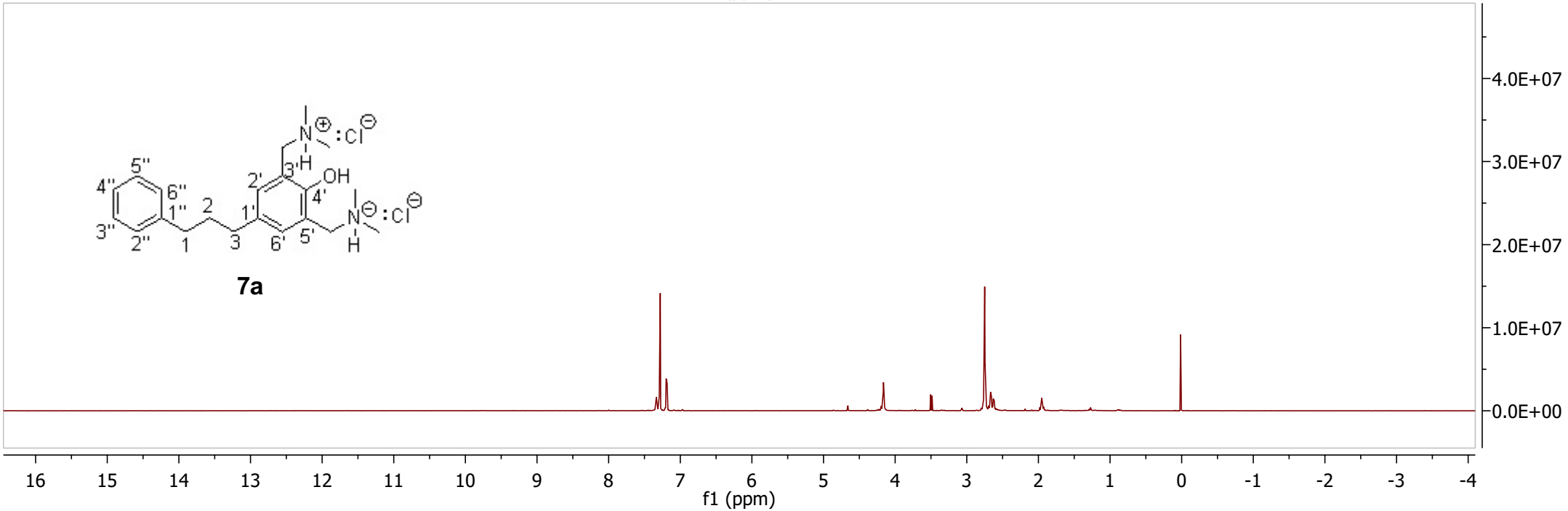
4 x -NCH3 (s) 2.75

H-3 (t) 2.67

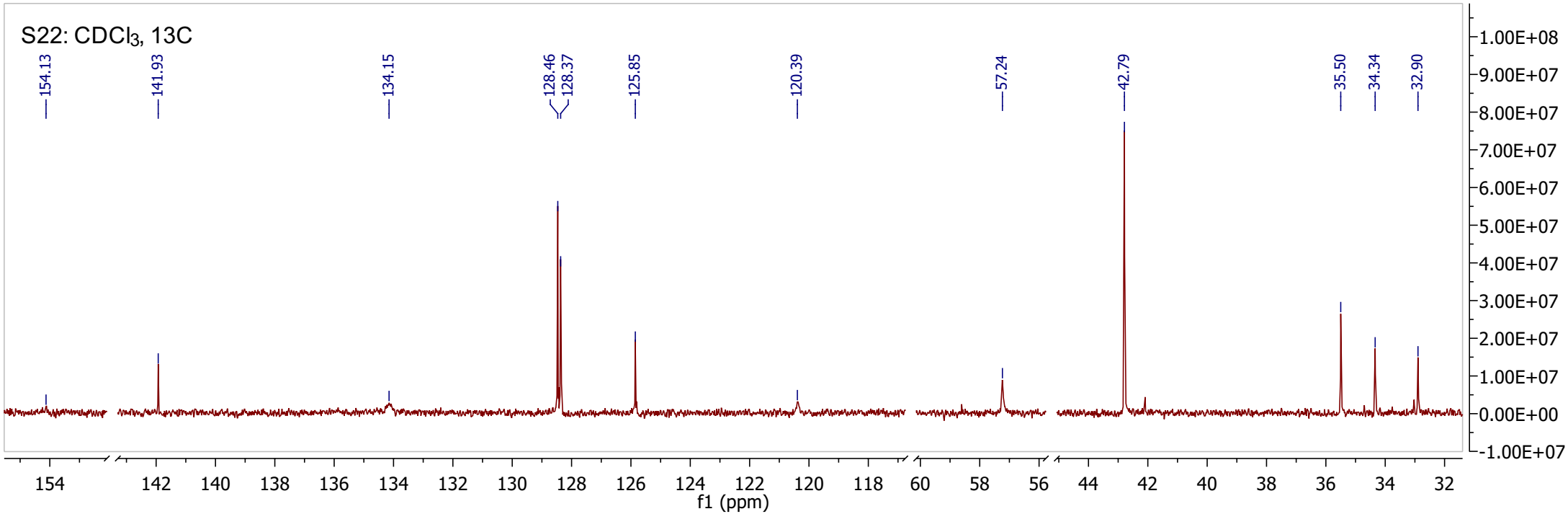
H-1 (t) 2.63

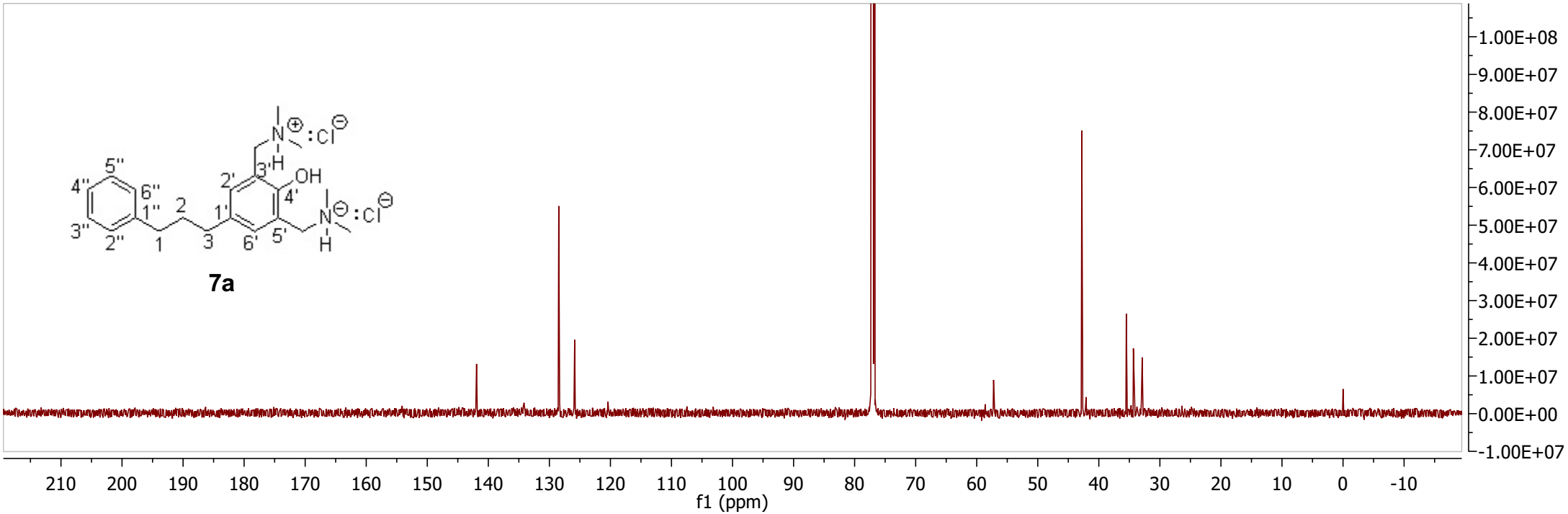
H-2 (m) 1.95





7a


S22: CDCl3, 13C
154.13
141.93
134.15
128.46
128.37
125.85
120.39
57.24
42.79
35.50
34.34
32.90
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
154 142 140 138 136 134 132 130 128 126 124 122 120 118 60 58 56 44 42 40 38 36 34 32
f1 (ppm)


7a
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
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)