Electronic Supplementary Material (ESI) for RSC Advances.

Bio-inspired NHC-organocatalyzed Stetter reaction in aqueous conditions.

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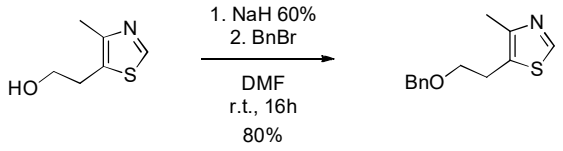
All reagent-grade chemicals were obtained from commercial suppliers and were used as received, unless otherwise stated. Milli-Q© water was used to perform Stetter reaction in water.
^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker Avance 300 (^{1}H: 300 MHz, ^{13}C: 75.46 MHz) spectrometer using $CDCl_3$ as internal reference and at 293K. FT-IR spectra were recorded on a Perkin-Elmer FT spectrometer Spectrum two (UATR two). HRMS were recorded with a Waters Q-TOF 2 spectrometer in the electrospray ionization (ESI) mode, a Bruker maxis 4G or Thermo Fisher Q-Exactive. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous materials, unless otherwise stated. Analytical thin layer chromatography was performed using silica gel 60 F254 pre-coated plates (Merck) with visualization by ultraviolet light, potassium permanganate or sulfuric acid. Flash chromatography was performed on silica gel (0.043-0.063 mm).

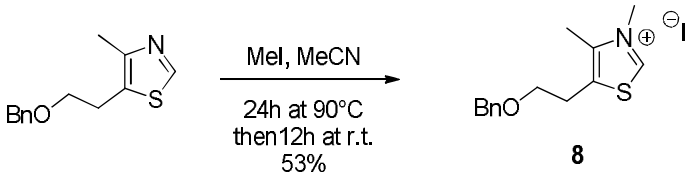
I -Synthesis of the thiazolium salts

Two-step sequence synthesis of 8

Step1: synthesis of 5-methyl-4-[2-(phenylmethoxy)ethyl]-thiazole



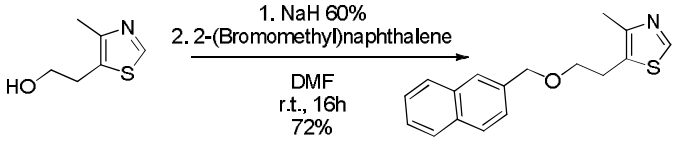
Step 2: Synthesis of 1,5-dimethyl-4-[2-(phenylmethoxy)ethyl]-thiazolium iodide



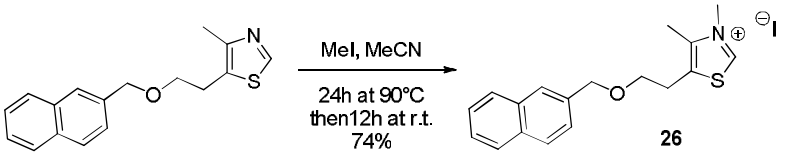
8

Two-step sequence synthesis of 26

Step1



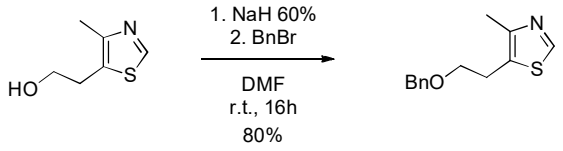
Step 2



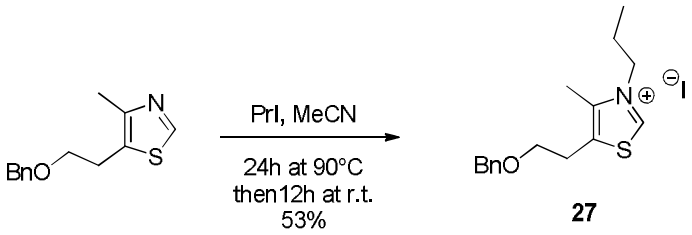
26

Two-step sequence synthesis of 27

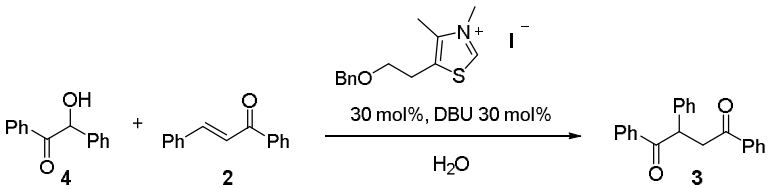
Step1: synthesis of 5-methyl-4-[2-(phenylmethoxy)ethyl]-thiazole



Step 2: Synthesis of 1-propyl-5-methyl-4-[2-(phenylmethoxy)ethyl]-thiazolium iodide



II- Stetter reaction in water at 40°C and 95°C



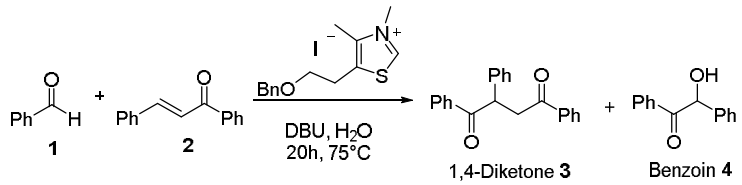
Ratios at 40°C

Reaction time (h)	Benzoin **4** (%)	1,4-diketone **3** (%)	PhCHO **1** (%)
0	0	0	100
2	71	25	4
6	71	25	4
15	64	31	4
24	63	32	4
36	59	37	3
48	52	45	3
72	42	55	3

Ratios at 95°C

Reaction time (h)	Benzoin **4** (%)	1,4-diketone **3** (%)	PhCHO **1** (%)
0	0	0	100
0,25	38	45	16
0,5	37	51	13
1	29	57	13
2	27	60	11
4	27	64	8
6	13	79	8
8	9	85	6

III- Study of the influence of the catalytic loading

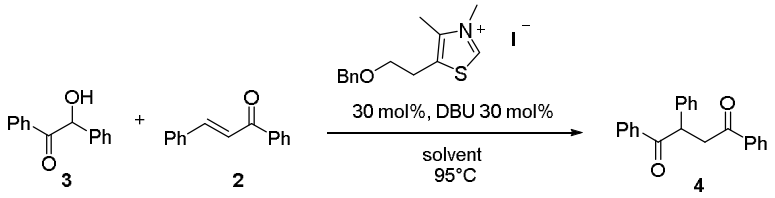


The influence of catalytic loading was explored according to the table below from 10% to 30% following the general procedure for Stetter reaction in water.

Entry	Catalyst loading	Conversion[a)]	Diketone[b)]	Benzoïn[b)]
1	10 mol %	65%	63%	10%
2	20 mol %	72%	69%	9%
3	30 mol %	75%	74%	6%

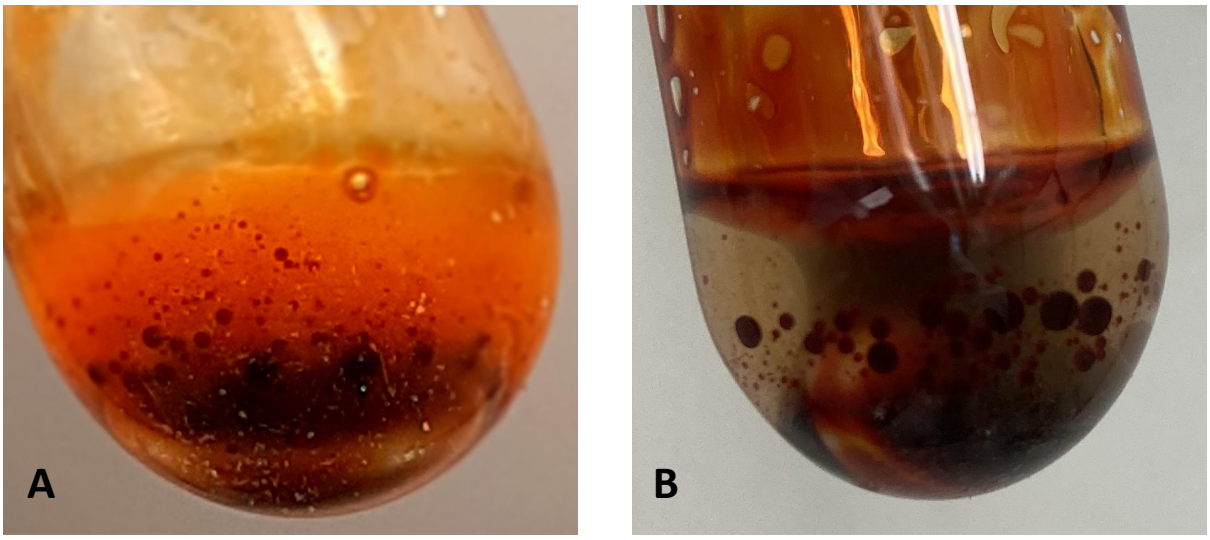
[a)] Based on the quantity of chalcone limiting reagent remaining. [b)] Yields calculated after purification by flash chromatography on silica-gel.

IV- General procedure for the Stetter reaction starting from benzoin substrate

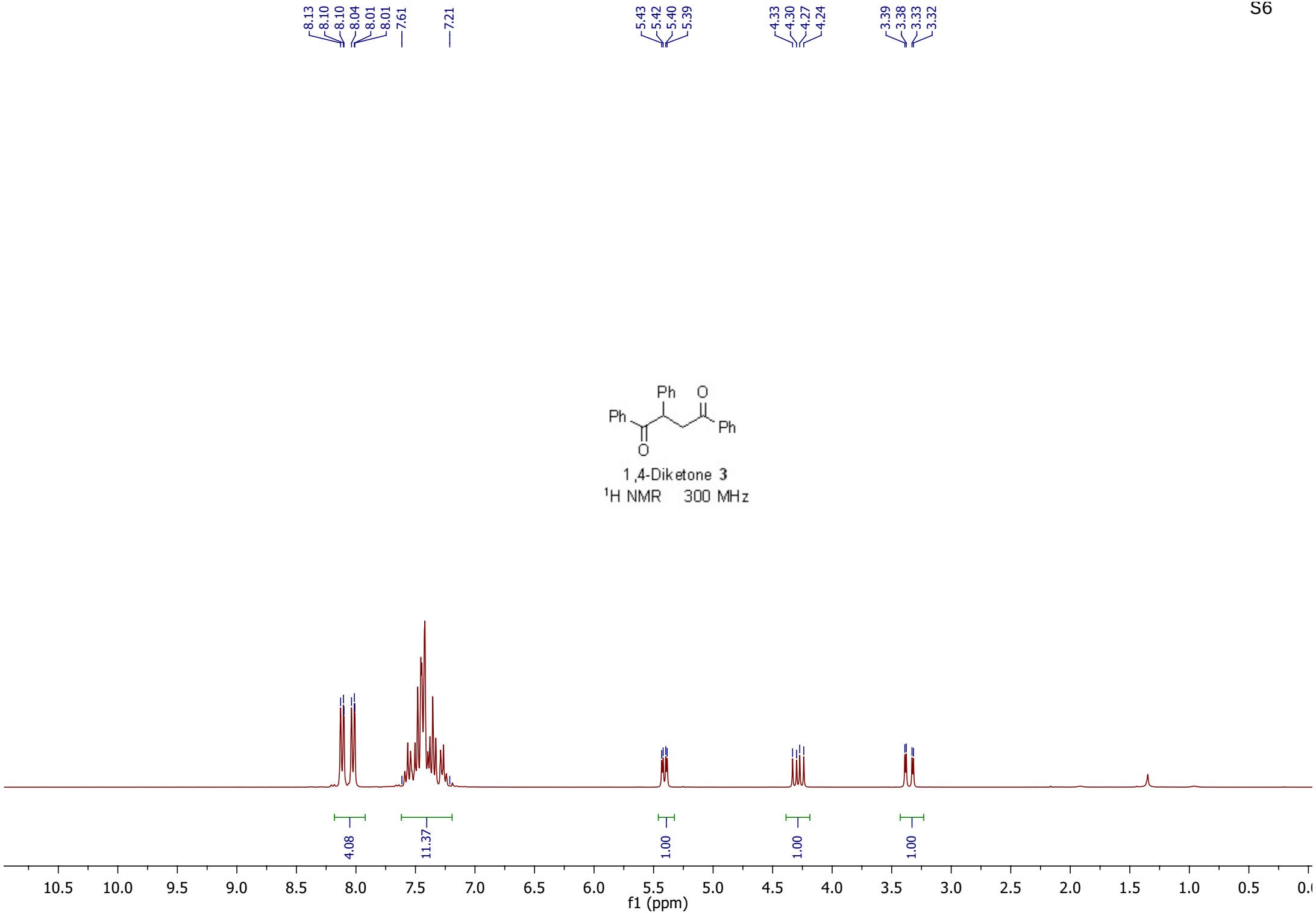


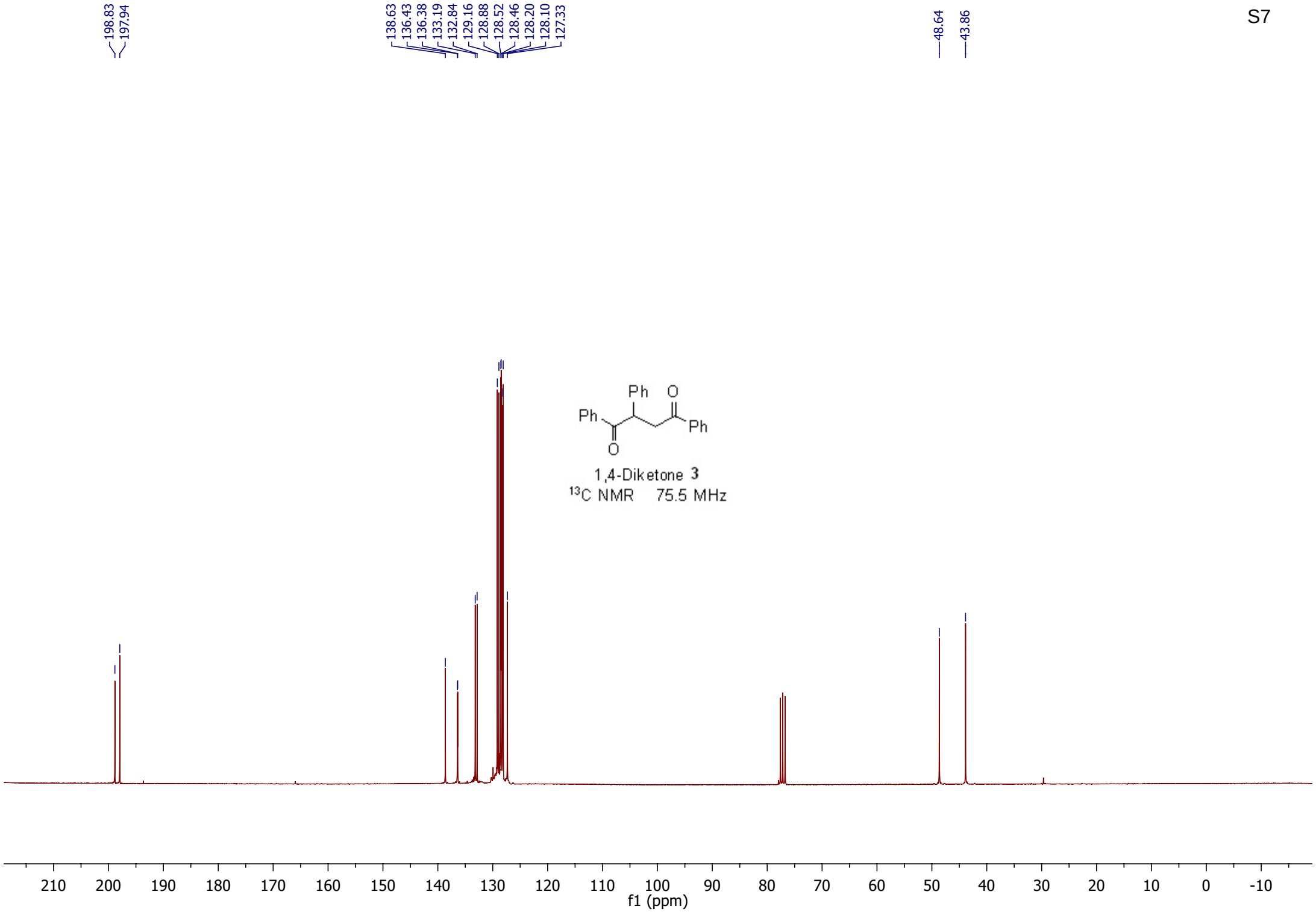
Entry	Reaction time	Solvent	Benzoin	diketone	PhCHO
1	2h	H_2O	75%	24%	1%
2	2h	THF	12%	82%	6%
3	6h	H_2O	69%	26%	5%
4	6h	THF	2%	95%	3%
5	15h	H_2O	59%	34%	7%
6	15h	THF	0%	98%	2%
7	24h	H_2O	52%	40%	8%
8	24h	THF	0%	100%	0%

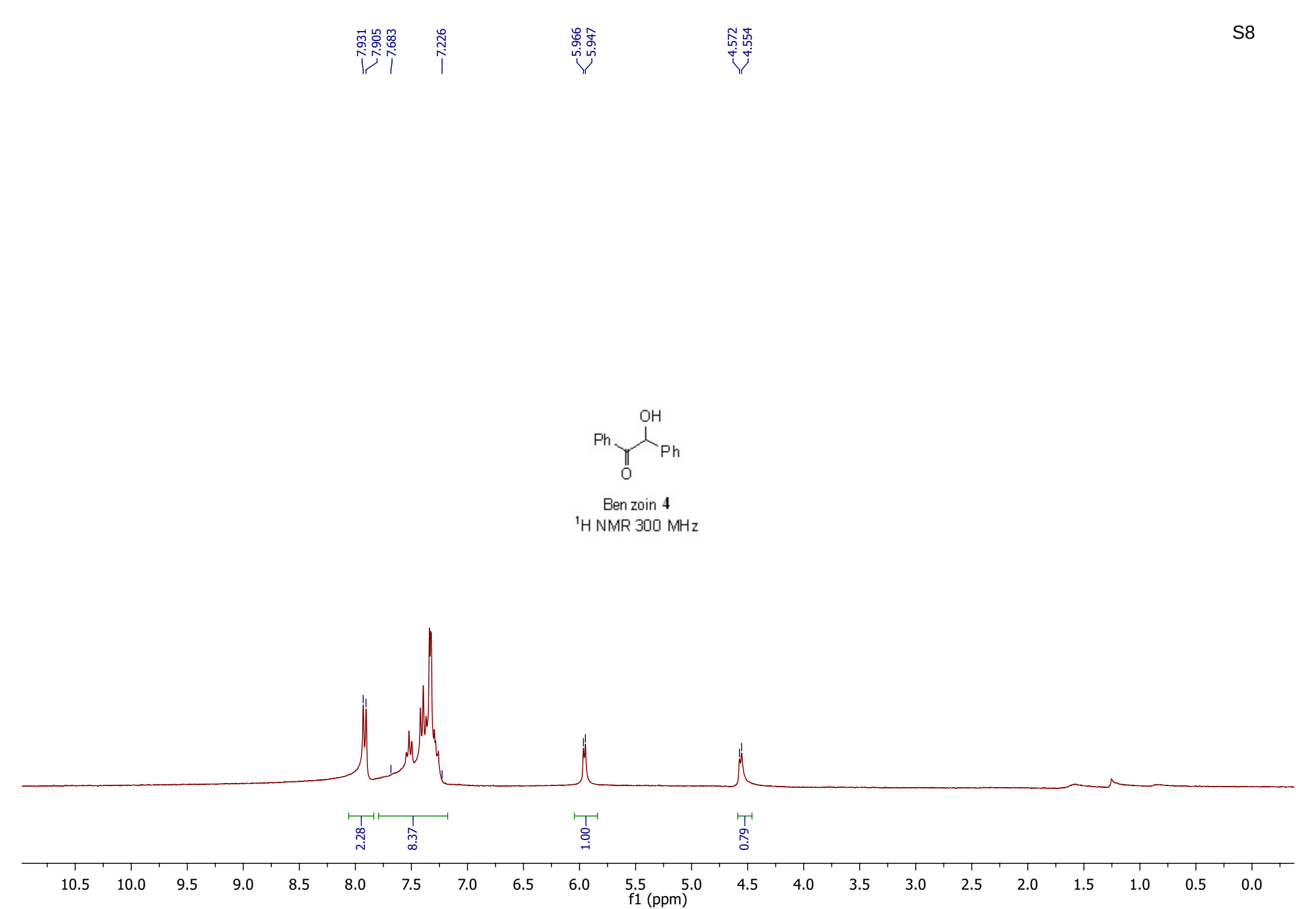
V- Pictures of the heterogeneous reaction medium highlighting the formation of organic droplets.

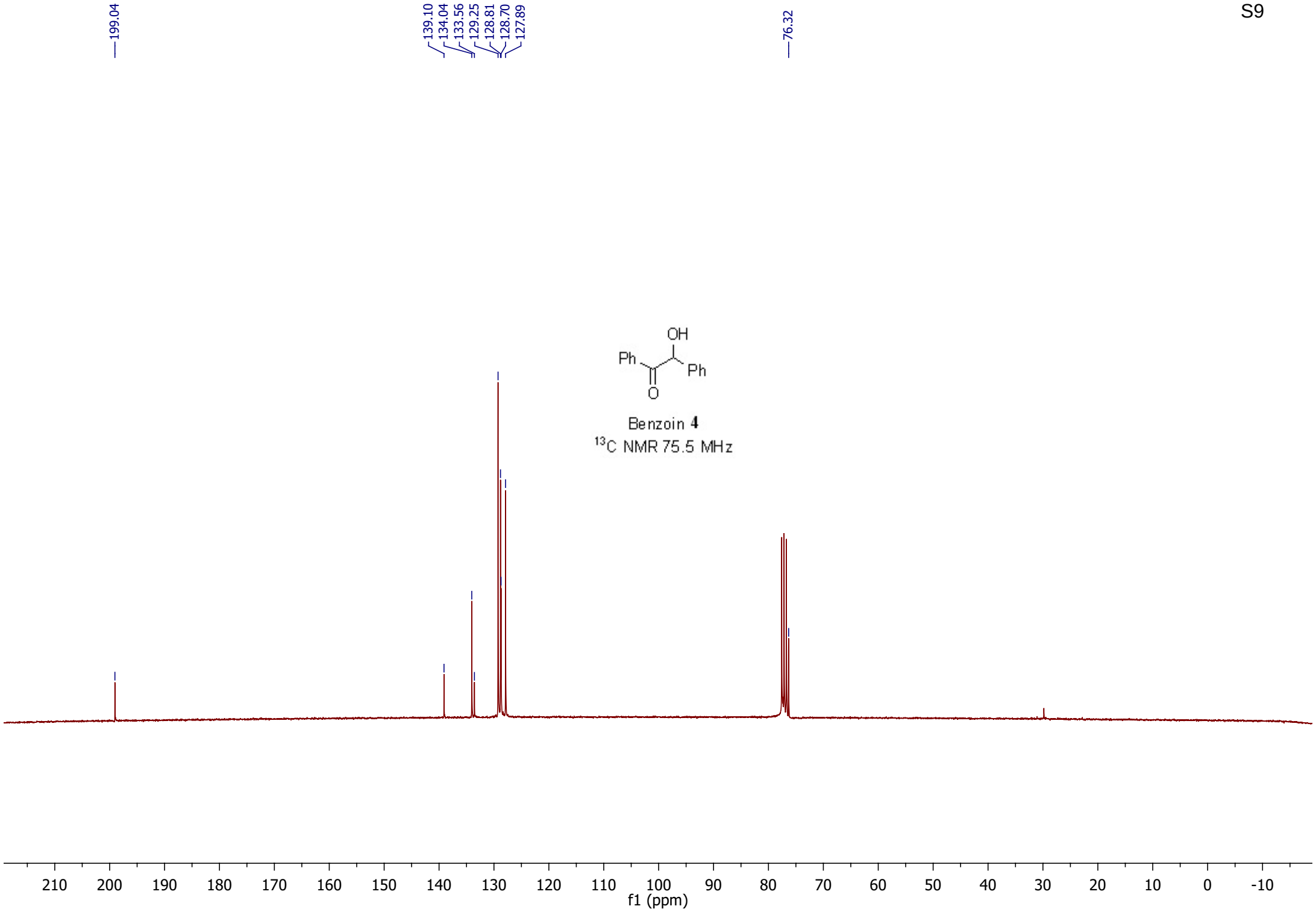


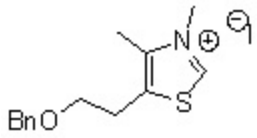
Formation of organic droplets under stirring
A: reaction between benzaldehyde **1** and chalcone **2**
B: reaction between anisaldehyde **15** and chalcone **2**


8.13
8.10
8.10
8.04
8.01
8.01
7.61
7.21
5.43
5.42
5.40
5.39
4.33
4.30
4.27
4.24
3.39
3.38
3.33
3.32
Ph
O
Ph
Ph
O
1,4-Diketone 3
1H NMR 300 MHz
4.08
11.37
1.00
1.00
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


198.83
197.94
138.63
136.43
136.38
133.19
132.84
129.16
128.88
128.52
128.46
128.20
128.10
127.33
48.64
43.86
Ph
O
Ph
Ph
O
1,4-Diketone 3
13C NMR 75.5 MHz
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)

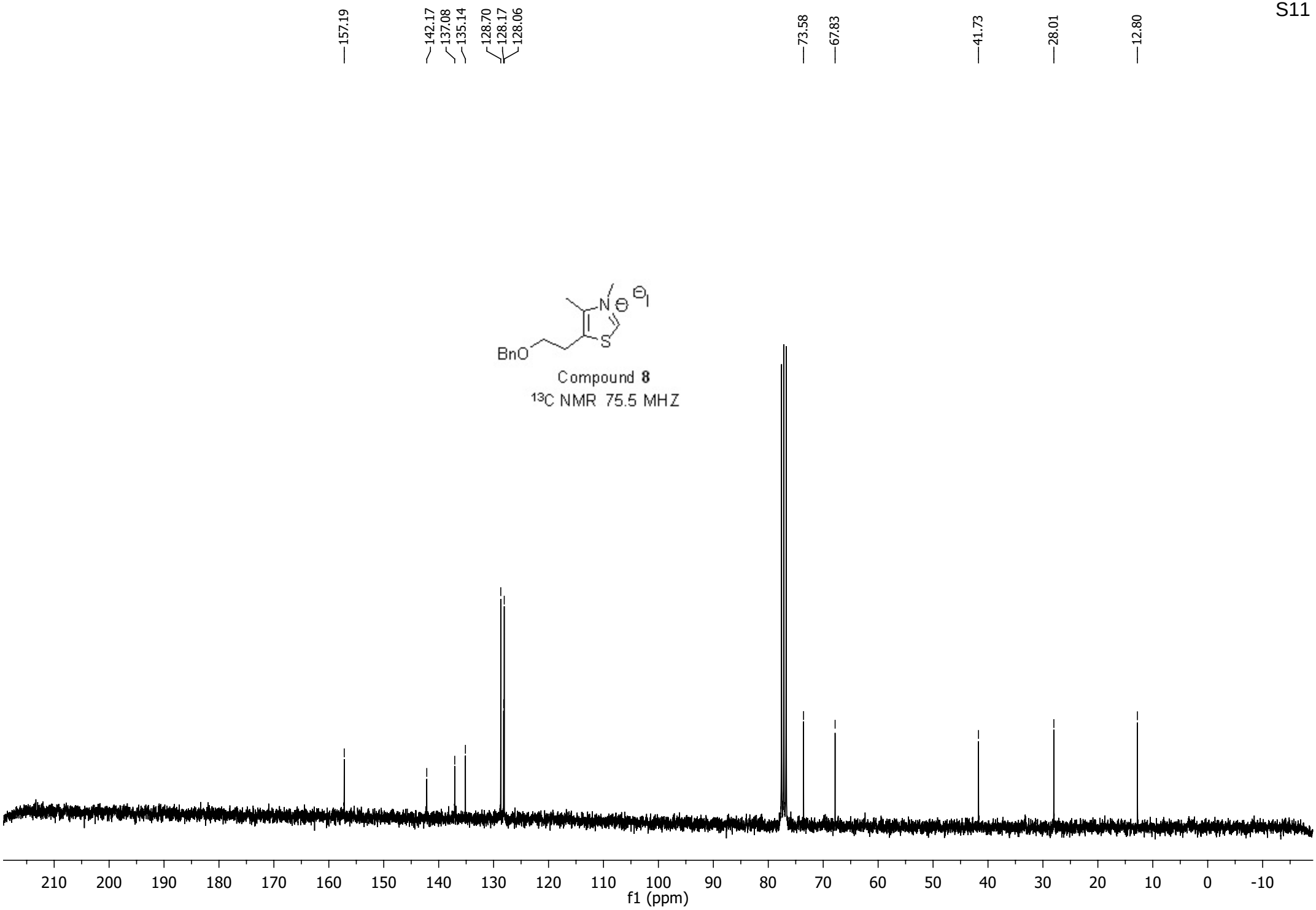

7.931
7.905
7.683
7.226
5.966
5.947
4.572
4.554
OH
Ph
Ph
O
Ben zoin 4
1H NMR 300 MHz
2.28
8.37
1.00
0.79
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

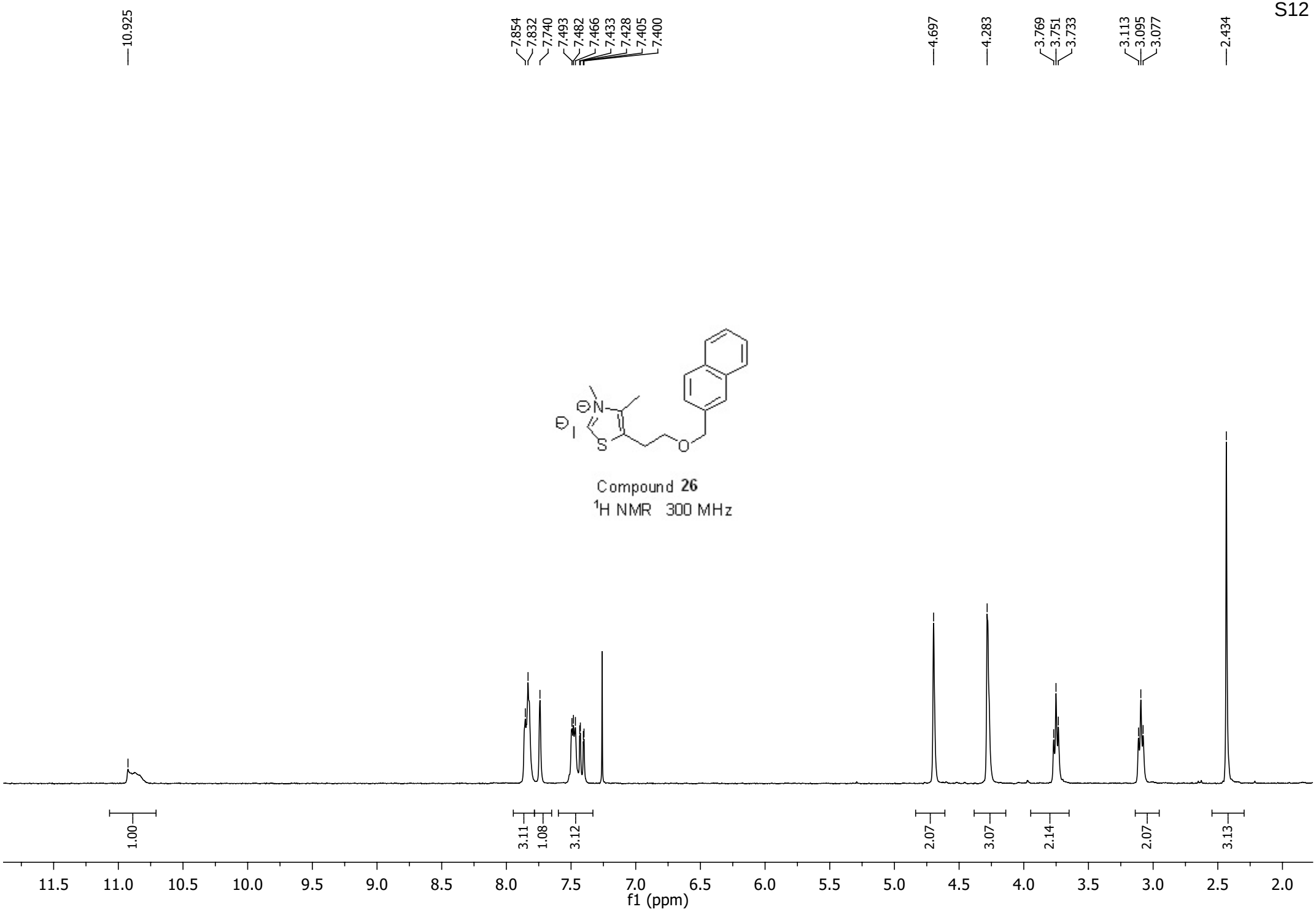

199.04
139.10
134.04
133.56
129.25
128.81
128.70
127.89
76.32
OH
Ph
Ph
O
Benzoin 4
13C NMR 75.5 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

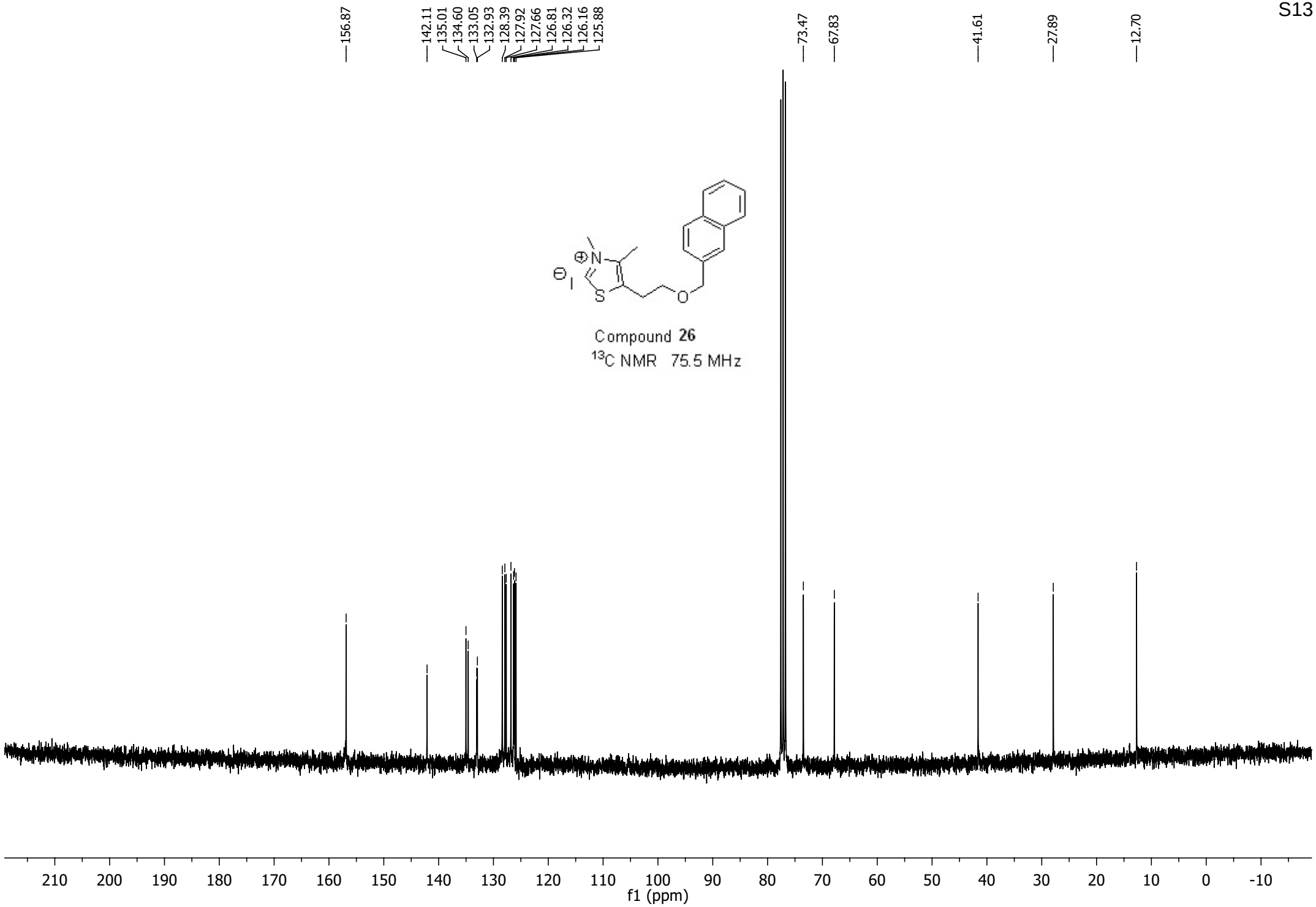


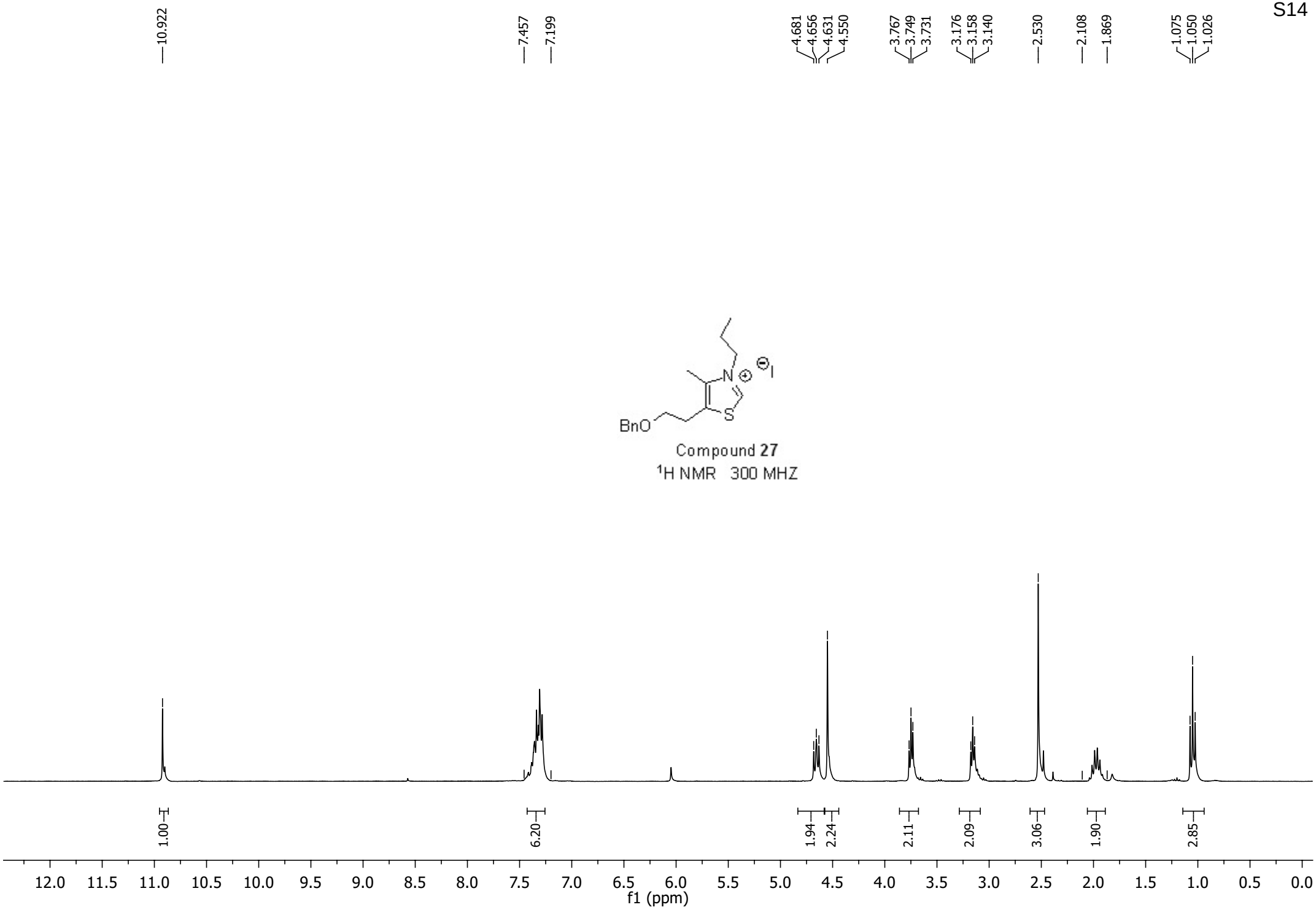
Compound **8**

^{1}H NMR 300 MHZ


157.19
142.17
137.08
135.14
128.70
128.17
128.06
73.58
67.83
41.73
28.01
12.80
BnO
N
S
Compound 8
13C NMR 75.5 MHZ
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)


10.925
7.854
7.832
7.740
7.493
7.482
7.466
7.433
7.428
7.405
7.400
4.697
4.283
3.769
3.751
3.733
3.113
3.095
3.077
2.434
Compound 26
1H NMR 300 MHz
1.00
3.11
1.08
3.12
2.07
3.07
2.14
2.07
3.13
11.5
11.0
10.5
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
f1 (ppm)


156.87
142.11
135.01
134.60
133.05
132.93
128.39
127.92
127.66
126.81
126.32
126.16
125.88
73.47
67.83
41.61
27.89
12.70
Compound 26
13C NMR 75.5 MHz
f1 (ppm)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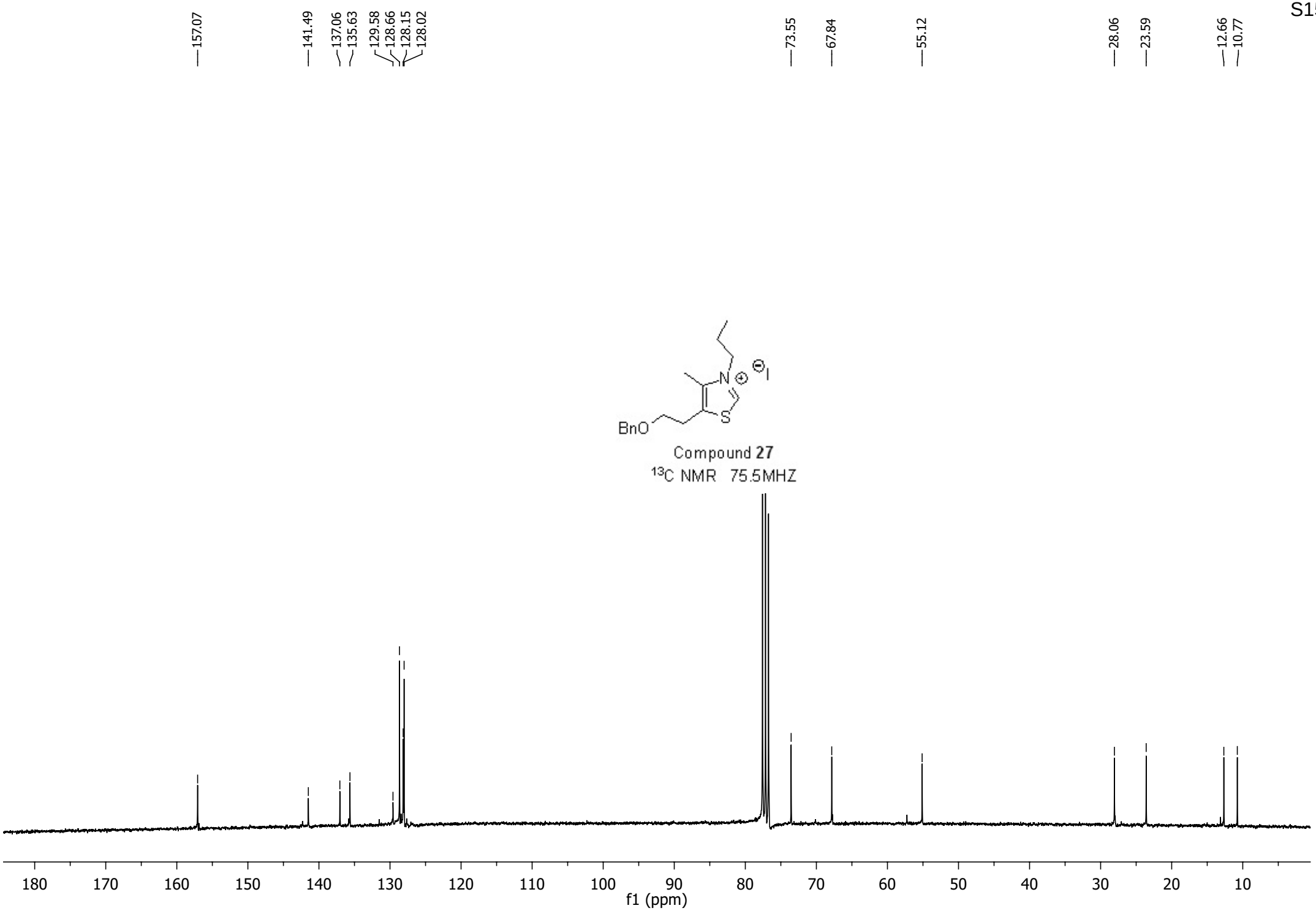
7.457
7.199
4.681
4.656
4.631
4.550
3.767
3.749
3.731
3.176
3.158
3.140
2.530
2.108
1.869
1.075
1.050
1.026
BnO
N
S
I
Compound 27
1H NMR 300 MHZ
1.00
6.20
1.94
2.24
2.11
2.09
3.06
1.90
2.85
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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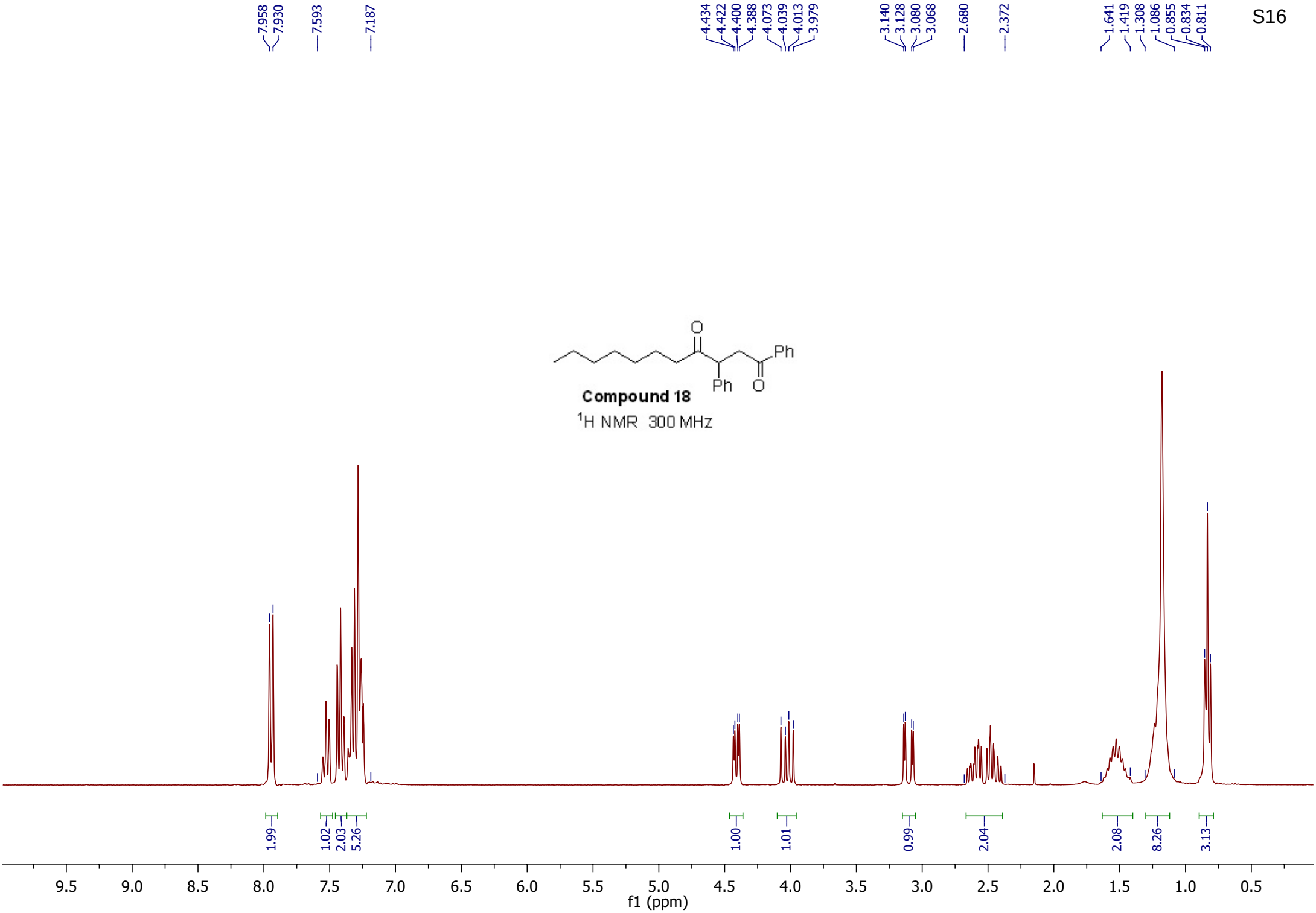
137.06
135.63
129.58
128.66
128.15
128.02
73.55
67.84
55.12
28.06
23.59
12.66
10.77
BnO
N
S
I
Compound 27
13C NMR 75.5MHZ
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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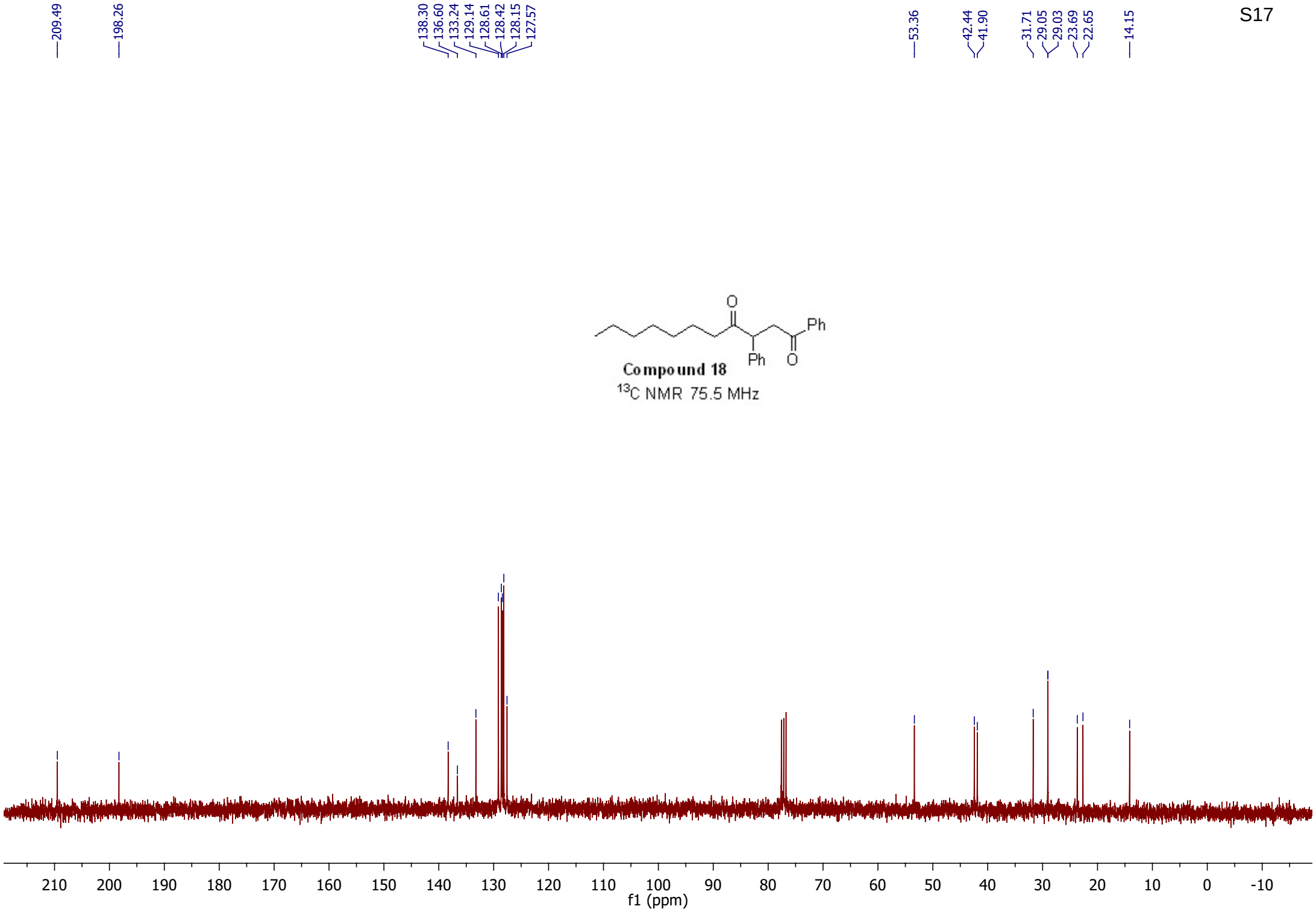
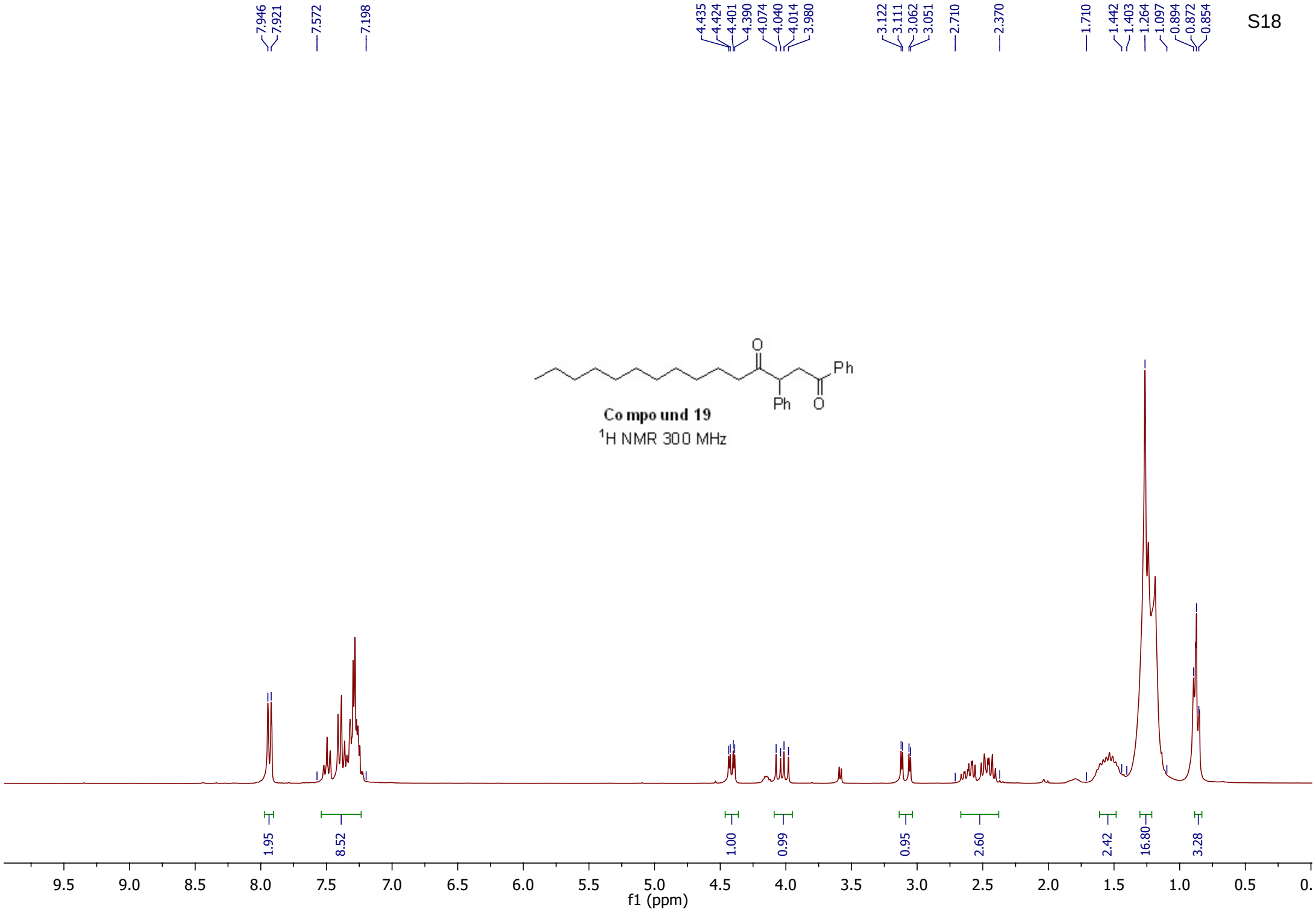
7.593
7.187
4.434
4.422
4.400
4.388
4.073
4.039
4.013
3.979
3.140
3.128
3.080
3.068
2.680
2.372
1.641
1.419
1.308
1.086
0.855
0.834
0.811
O
Ph
Ph
O
Compound 18
1H NMR 300 MHz
1.99
1.02
2.03
5.26
1.00
1.01
0.99
2.04
2.08
8.26
3.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


209.49
198.26
138.30
136.60
133.24
129.14
128.61
128.42
128.15
127.57
53.36
42.44
41.90
31.71
29.05
29.03
23.69
22.65
14.15
O
Ph
Ph
O
Compound 18
13C NMR 75.5 MHz
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)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4.074
4.040
4.014
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3.122
3.111
3.062
3.051
2.710
2.370
1.710
1.442
1.403
1.264
1.097
0.894
0.872
0.854
O
Ph
Ph
O
Co mpo und 19
1H NMR 300 MHz
1.95
8.52
1.00
0.99
0.95
2.60
2.42
16.80
3.28
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
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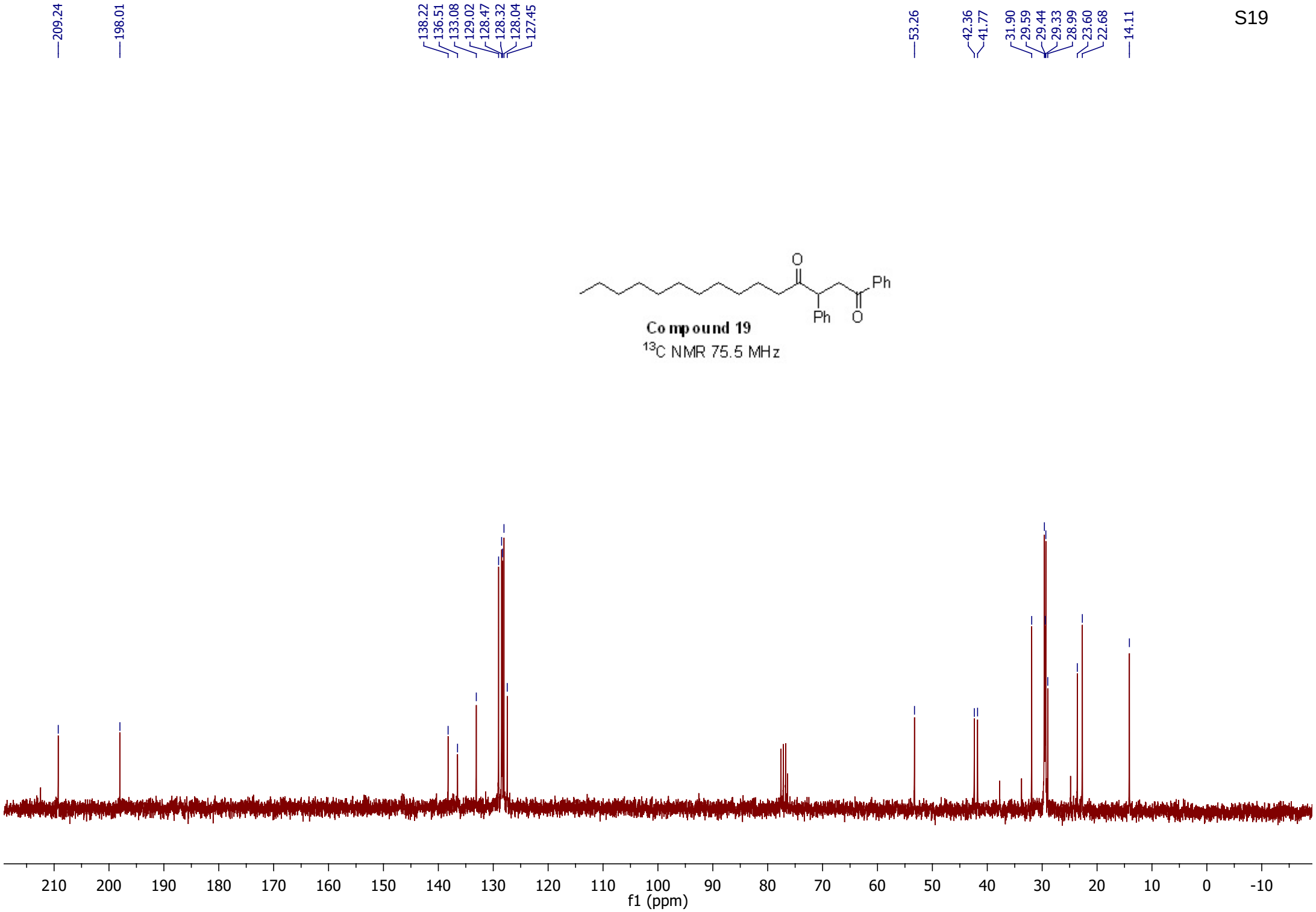
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)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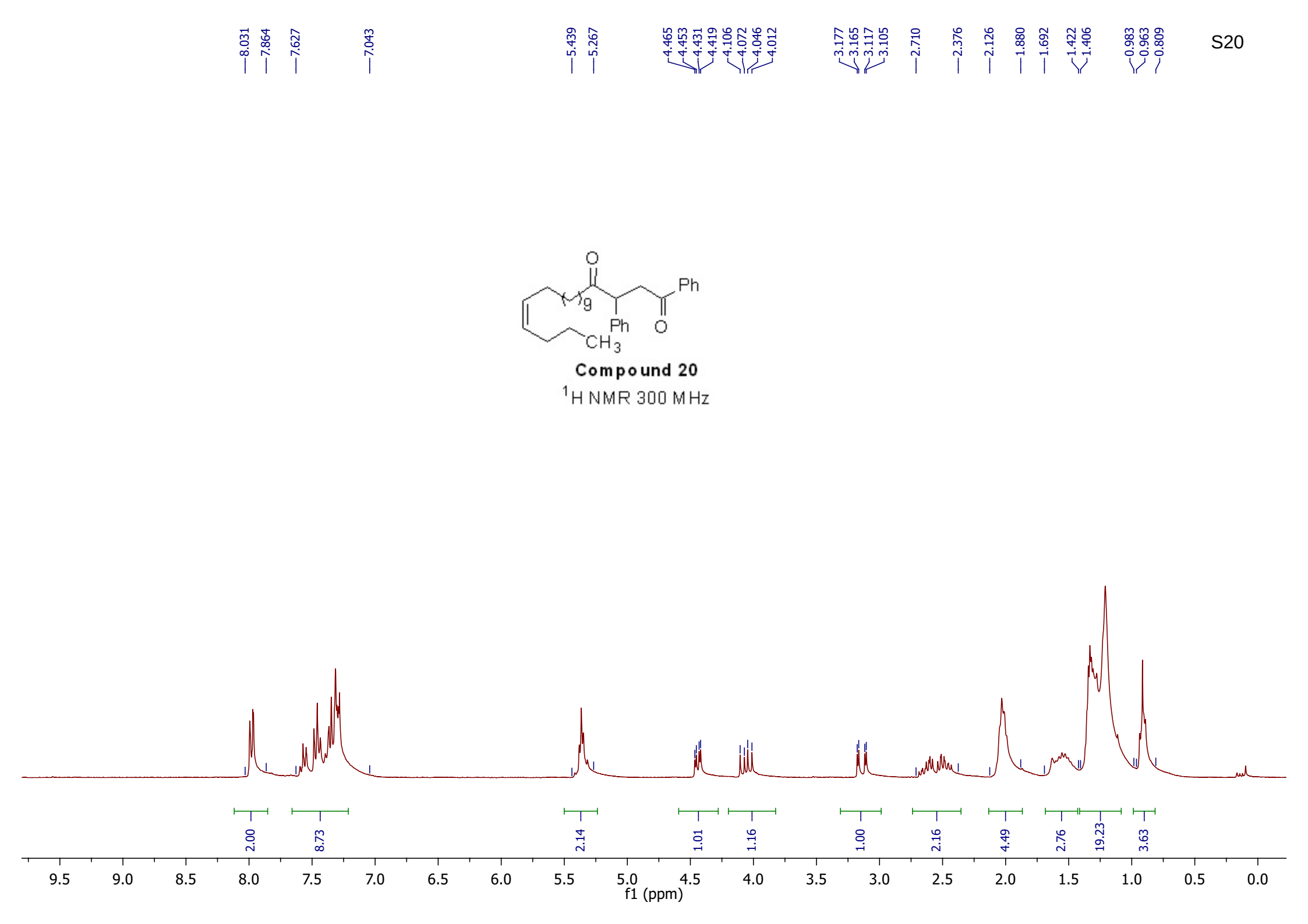
136.51
133.08
129.02
128.47
128.32
128.04
127.45
53.26
42.36
41.77
31.90
29.59
29.44
29.33
28.99
23.60
22.68
14.11
O
Ph
Ph
O
Compound 19
13C NMR 75.5 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.864
7.627
7.043
5.439
5.267
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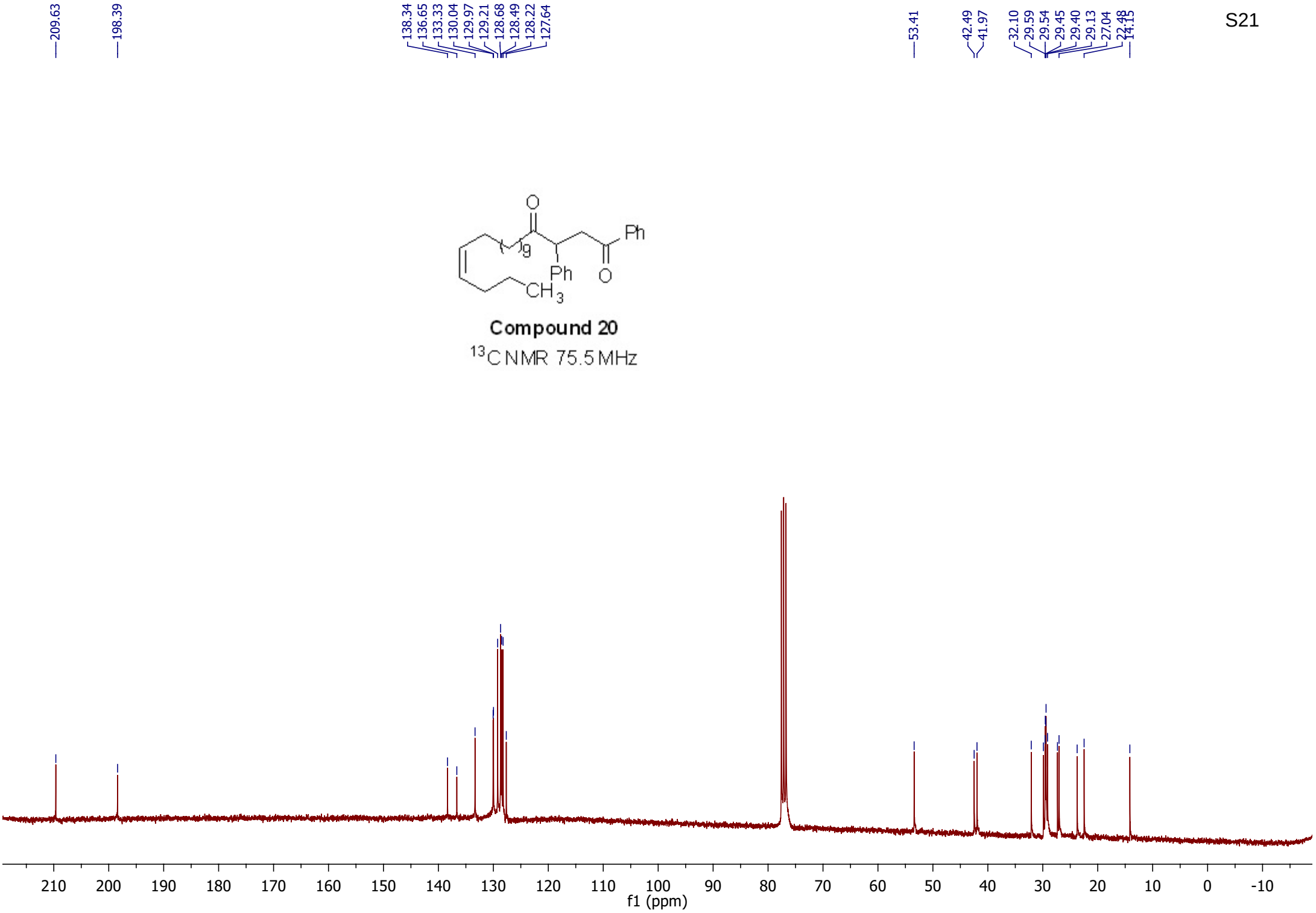
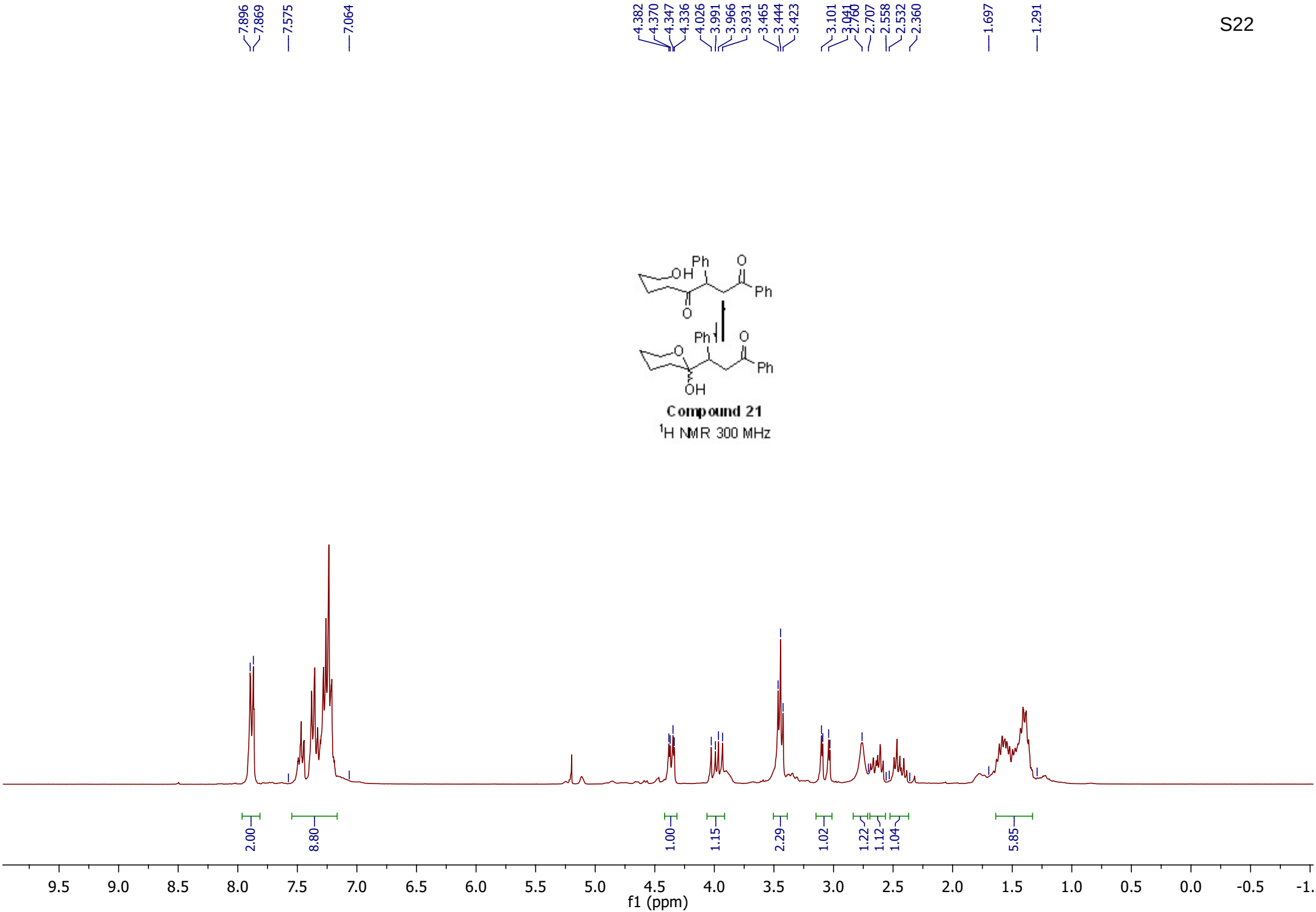
4.453
4.431
4.419
4.106
4.072
4.046
4.012
3.177
3.165
3.117
3.105
2.710
2.376
2.126
1.880
1.692
1.422
1.406
0.983
0.963
0.809
O
Ph
g
Ph
O
CH3
Compound 20
1H NMR 300 MHz
2.00
8.73
2.14
1.01
1.16
1.00
2.16
4.49
2.76
19.23
3.63
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

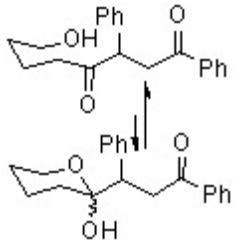

209.63
198.39
138.34
136.65
133.33
130.04
129.97
129.21
128.68
128.49
128.22
127.64
53.41
42.49
41.97
32.10
29.59
29.54
29.45
29.40
29.13
27.04
22.48
14.15
O
Ph
g
Ph
O
CH3
Compound 20
13C NMR 75.5 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



Compound 21

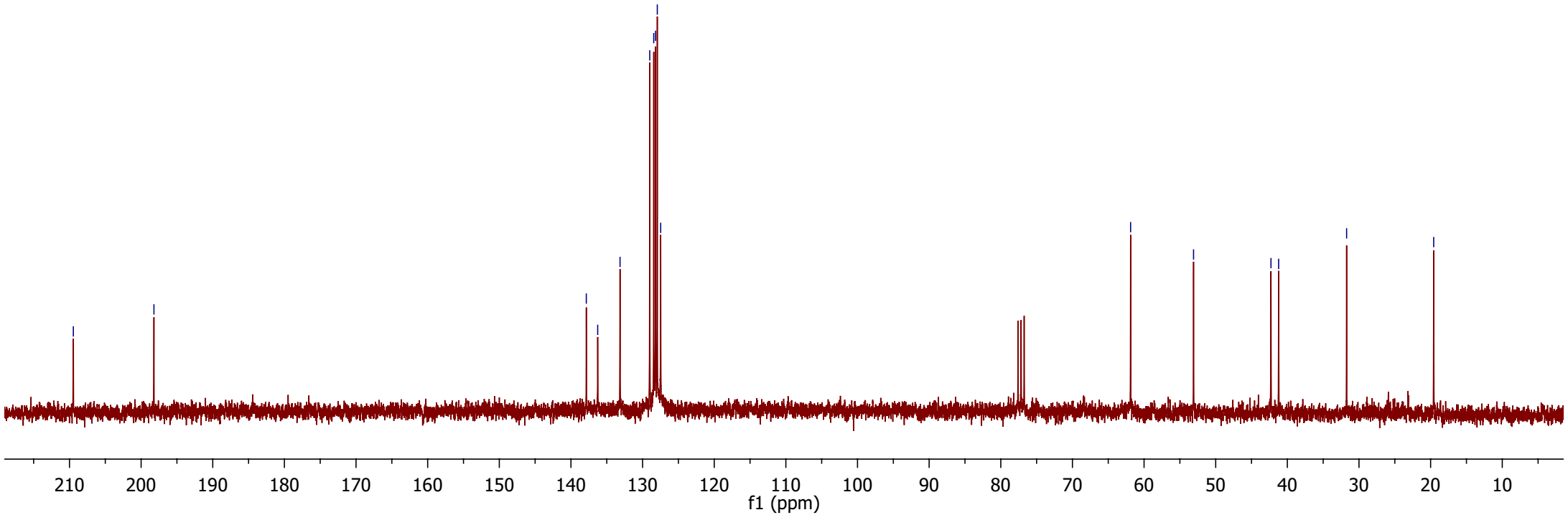
^{1}H NMR 300 MHz

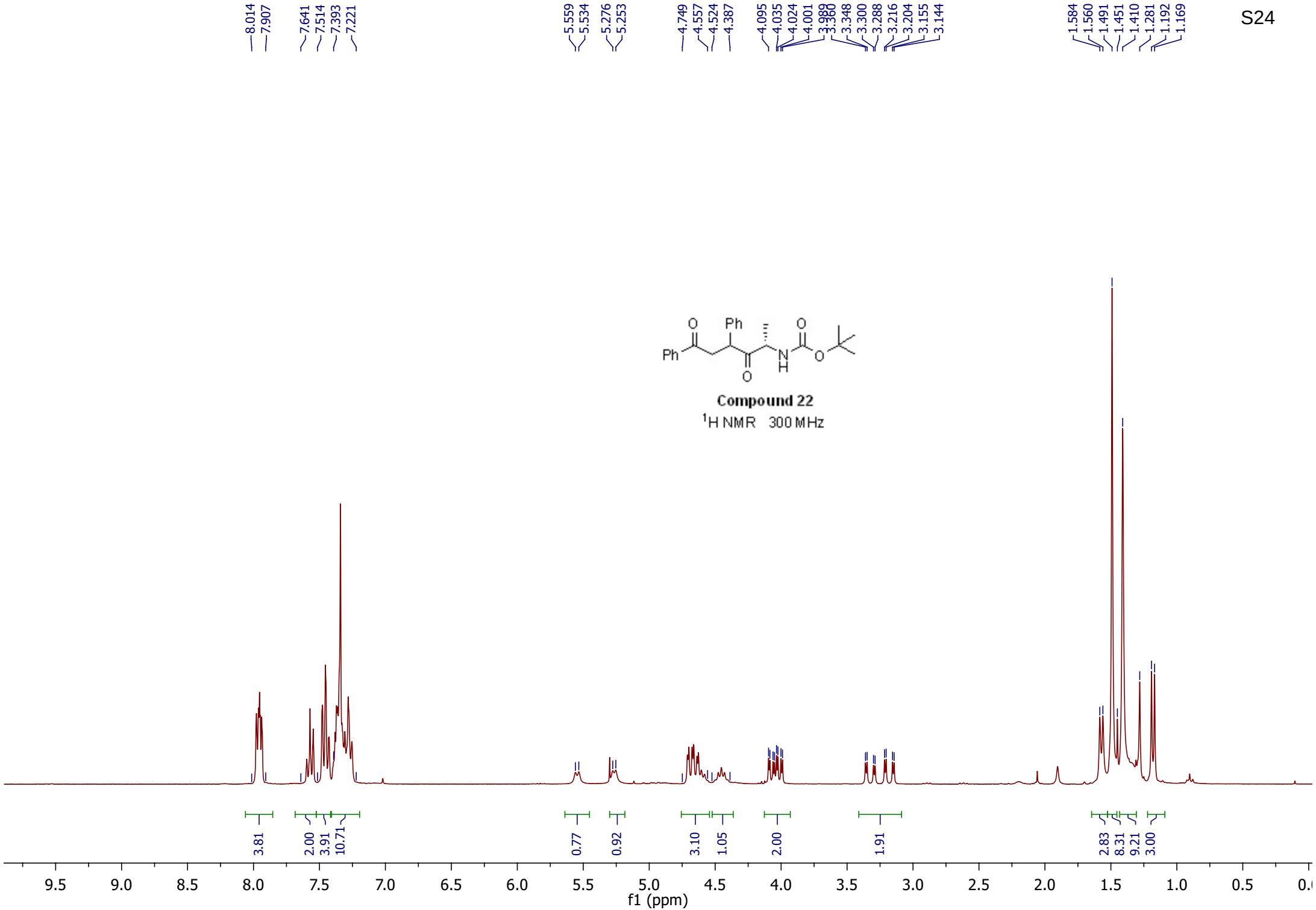
209.46
198.21
137.86
136.27
133.15
129.00
128.44
128.19
127.95
127.47
61.88
53.09
42.29
41.21
31.73
19.57



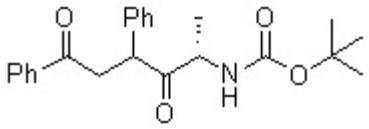
Compound 21

^{13}C NMR 300 MHz



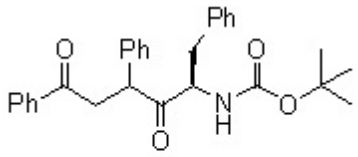

8.014
7.907
7.641
7.514
7.393
7.221
5.559
5.534
5.276
5.253
4.749
4.557
4.524
4.387
4.095
4.035
4.024
4.001
3.989
3.348
3.300
3.288
3.216
3.204
3.155
3.144
1.584
1.560
1.491
1.451
1.410
1.281
1.192
1.169
Ph
Ph
O
N
H
O
O
O
Compound 22
1H NMR 300 MHz
3.81
2.00
3.91
10.71
0.77
0.92
3.10
1.05
2.00
1.91
2.83
8.31
9.21
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

208.91
207.75
198.11
197.66
155.23
154.84
133.35
129.36
129.12
128.64
128.38
128.35
128.15
128.10
127.91
127.70
79.63
79.42
65.14
54.70
54.03
49.75
49.38
44.14
42.53
30.34
29.72
28.44
28.37
18.55
17.44



Compound 22

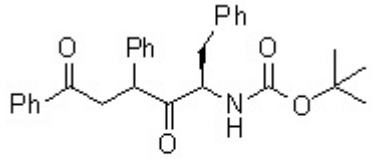
^{1}3C NMR 75;5 MHz



Compound 23

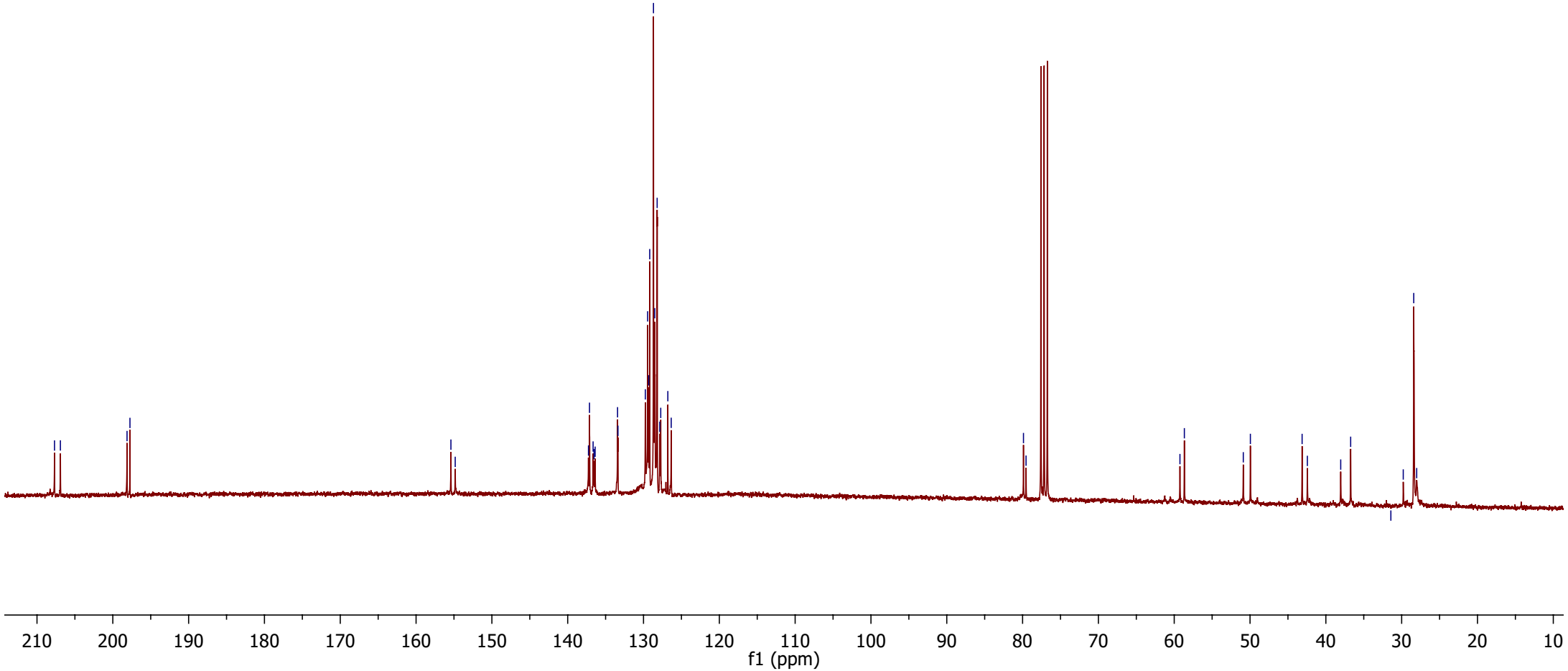
^{1}H NMR 300 MHz

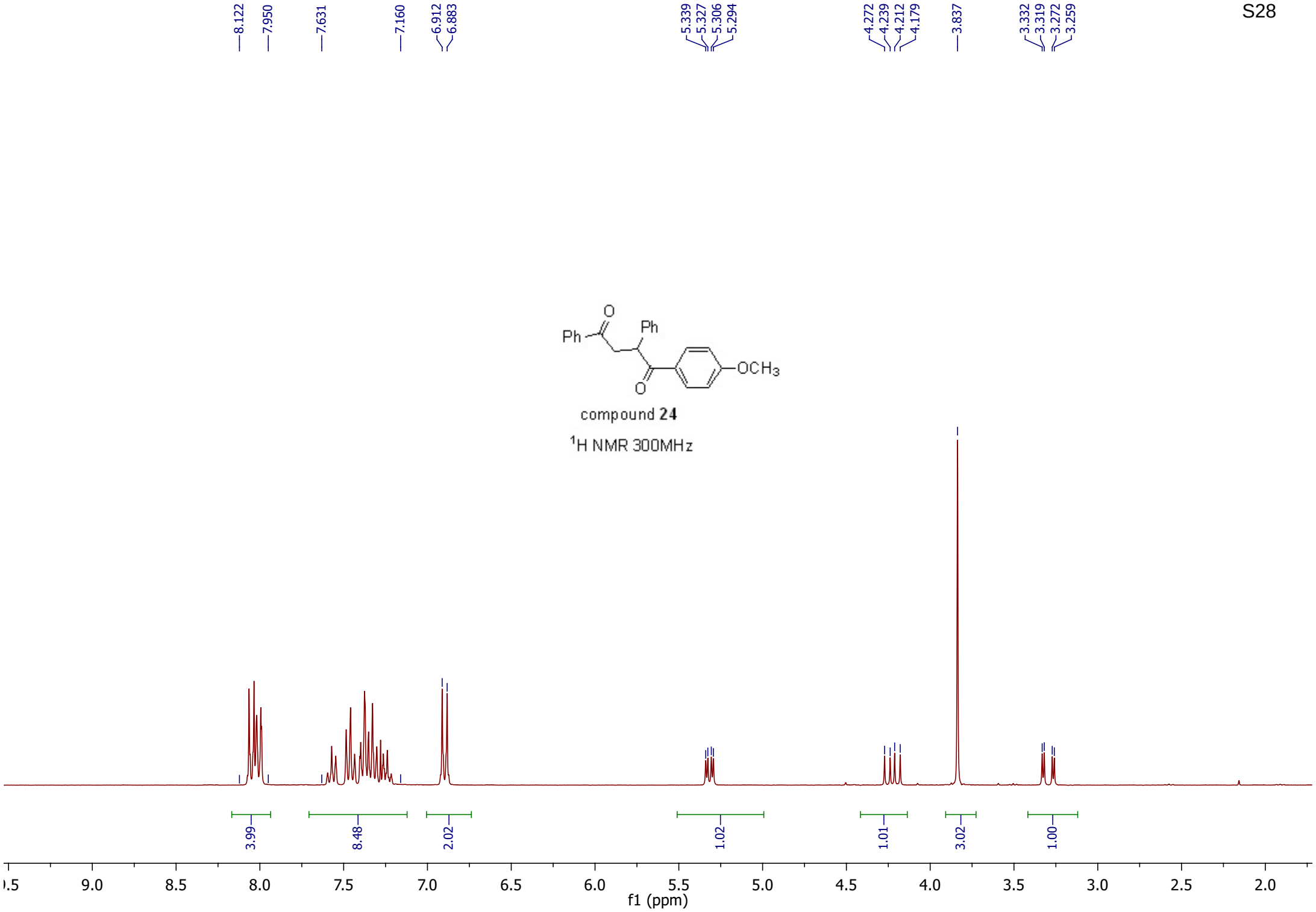
207.69
206.91
198.12
197.74
155.40
154.84
137.26
137.13
136.65
136.53
136.38
133.42
133.37
129.76
129.46
129.31
129.18
128.69
128.52
128.20
127.86
127.73
126.79
126.35
79.88
79.54
59.25
58.66
50.89
49.95
43.13
42.44
38.04
36.73
31.42
29.79
28.41
28.02



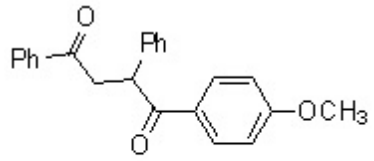
Compound 23

^{13}C NMR 75;5 MHz



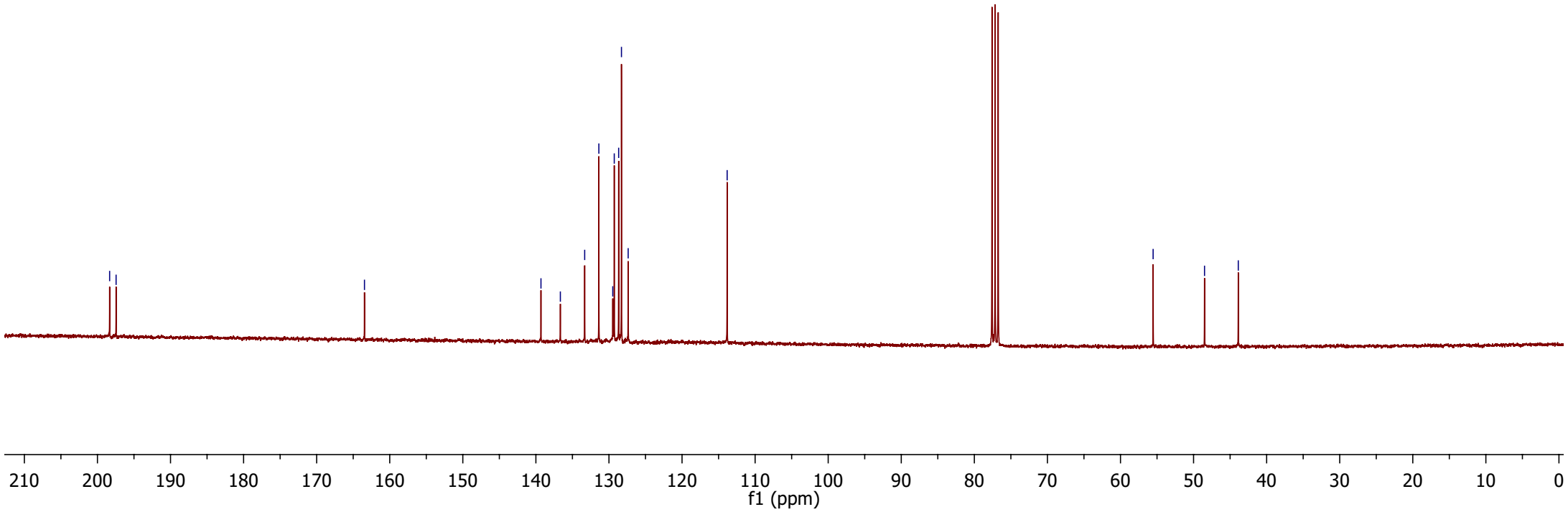

8.122
7.950
7.631
7.160
6.912
6.883
5.339
5.327
5.306
5.294
4.272
4.239
4.212
4.179
3.837
3.332
3.319
3.272
3.259
O
Ph
Ph
O
OCH3
compound 24
1H NMR 300MHz
3.99
8.48
2.02
1.02
1.01
3.02
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

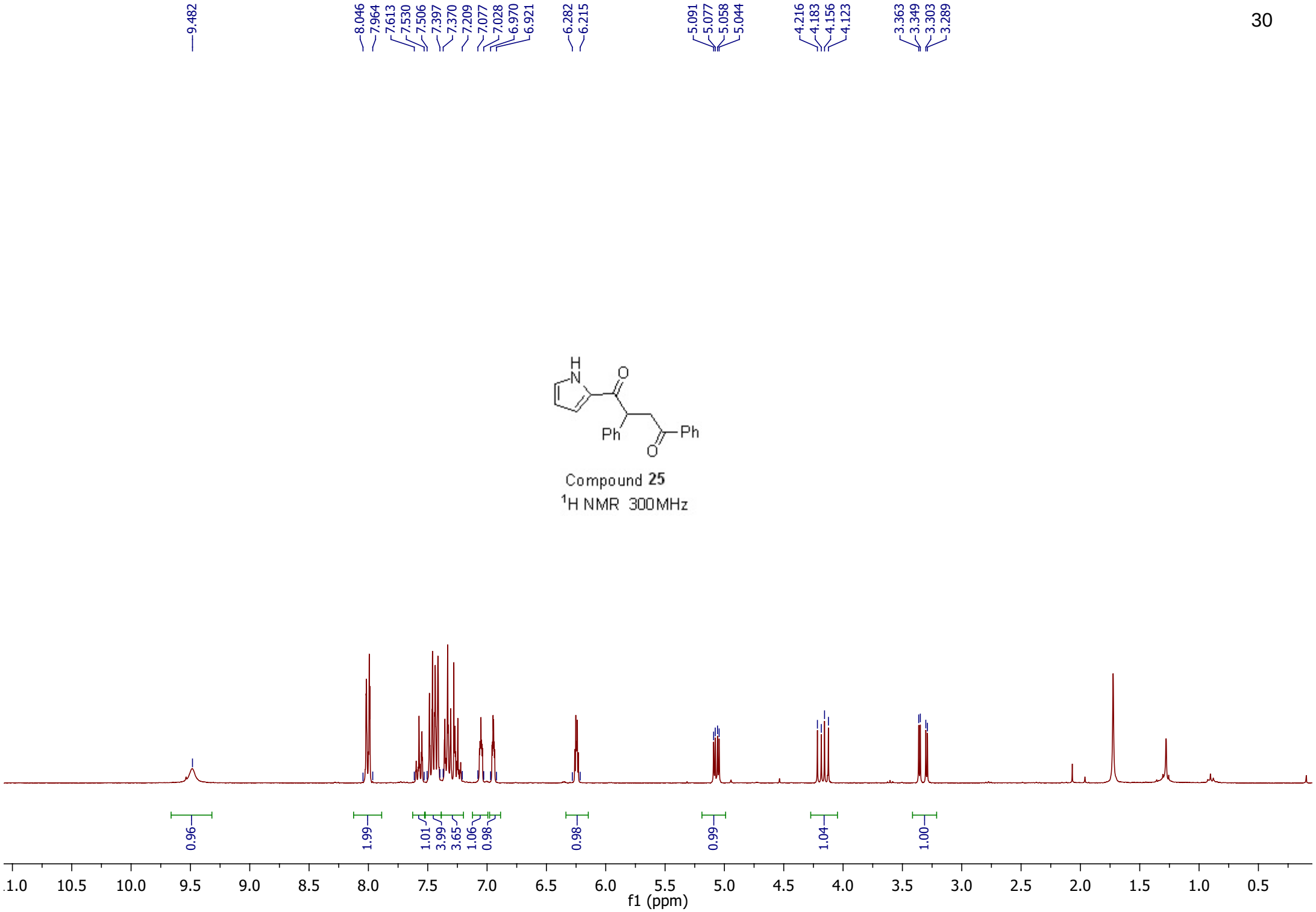
198.33
197.45
163.46
139.31
136.65
133.32
131.38
129.48
129.28
128.67
128.29
127.37
113.83
55.53
48.50
43.88

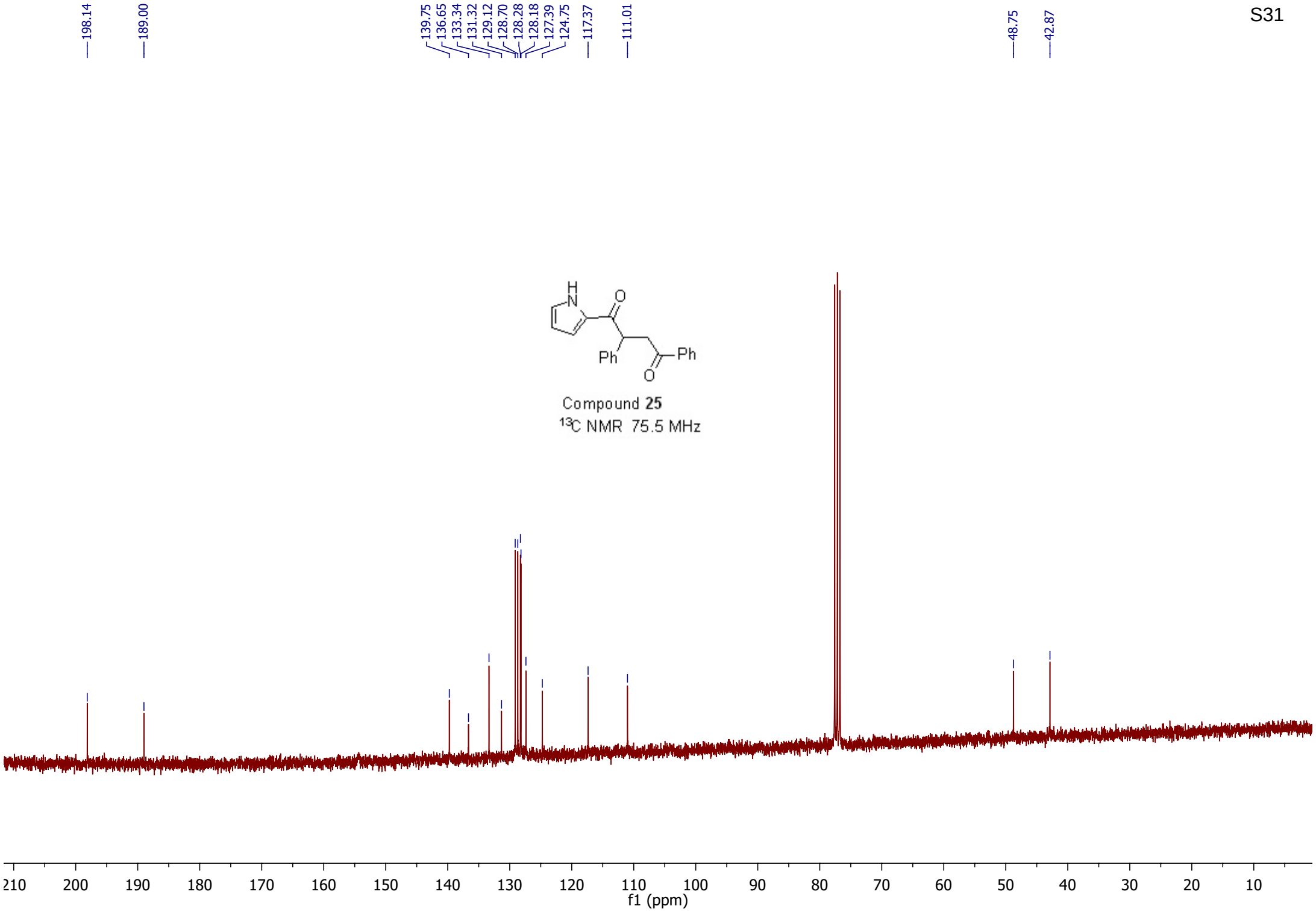


compound **24**

^{13}C NMR 75.5 MHz




9.482
8.046
7.964
7.613
7.530
7.506
7.397
7.370
7.209
7.077
7.028
6.970
6.921
6.282
6.215
5.091
5.077
5.058
5.044
4.216
4.183
4.156
4.123
3.363
3.349
3.303
3.289
H
N
O
Ph
Ph
O
Compound 25
1H NMR 300MHz
0.96
1.99
1.01
3.99
3.65
1.06
0.98
0.98
0.99
1.04
1.00
f1 (ppm)


198.14
189.00
139.75
136.65
133.34
131.32
129.12
128.70
128.28
128.18
127.39
124.75
117.37
111.01
48.75
42.87
H
N
O
Ph
O
Ph
Compound 25
13C NMR 75.5 MHz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)