Palladium-Catalyzed Double Carbonylation Using Near Stoichiometric Carbon Monoxide: Expedient Access to Substituted $^{13}C_2$-Labeled Phenethylamines

*Dennis U. Nielsen, Karoline Neumann, Rolf H. Taaning, Anders T. Lindhardt, Amalie Modvig, Troels Skrydstrup**

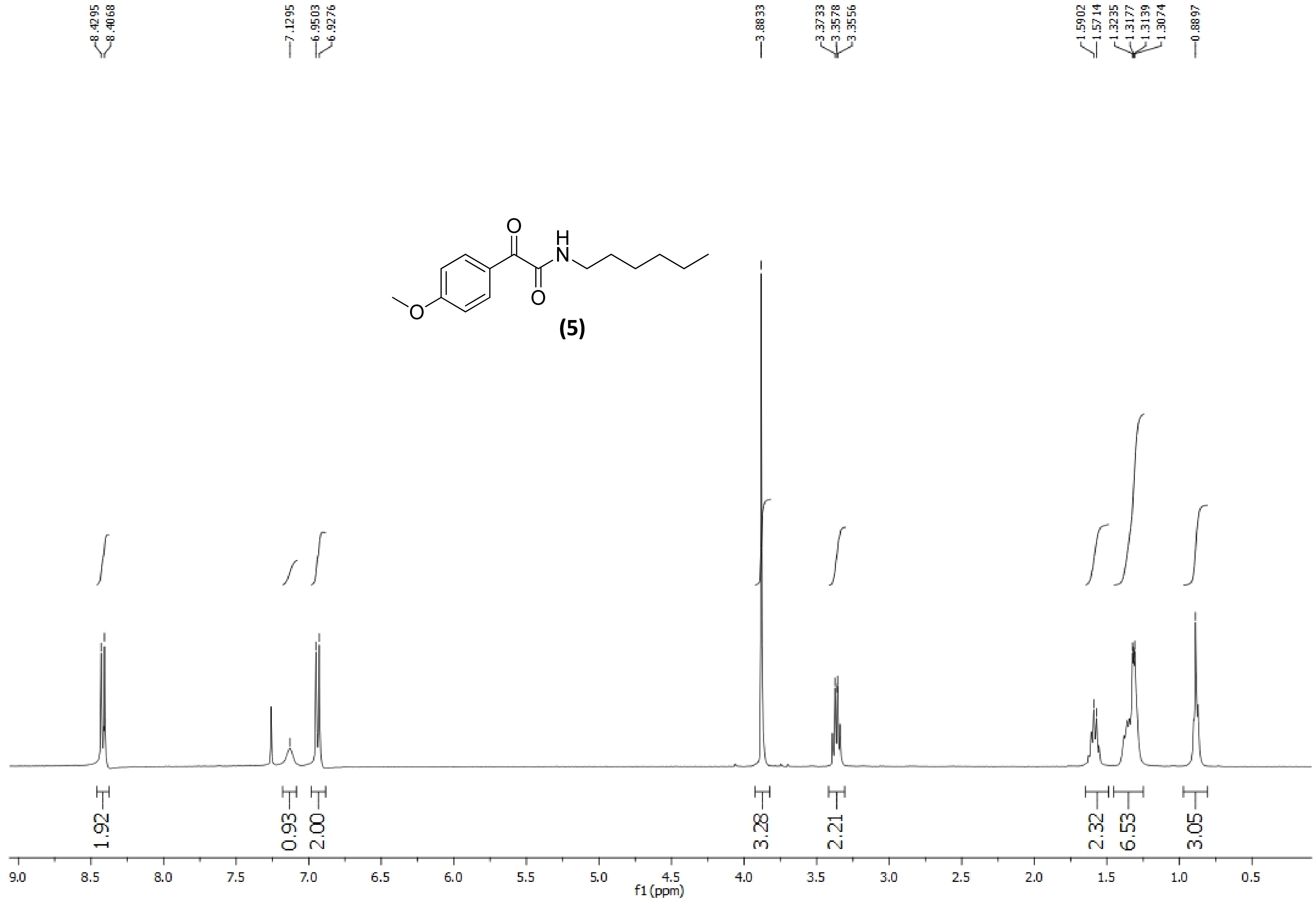
Department of Chemistry, Center for Insoluble Protein Structures (InSPIN), and the Interdisciplinary Nanoscience Center (iNANO),

Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark

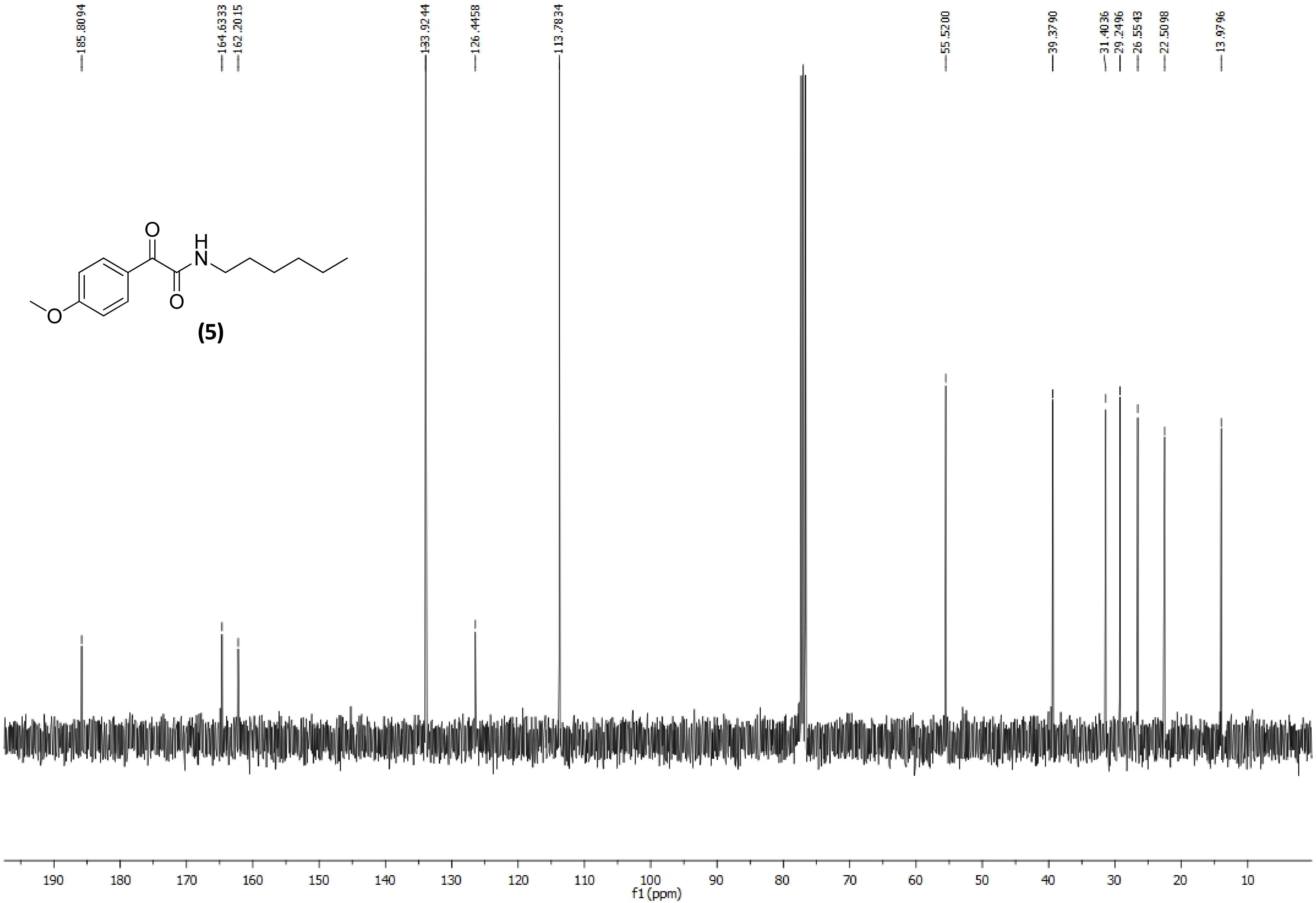
ts@chem.au.dk

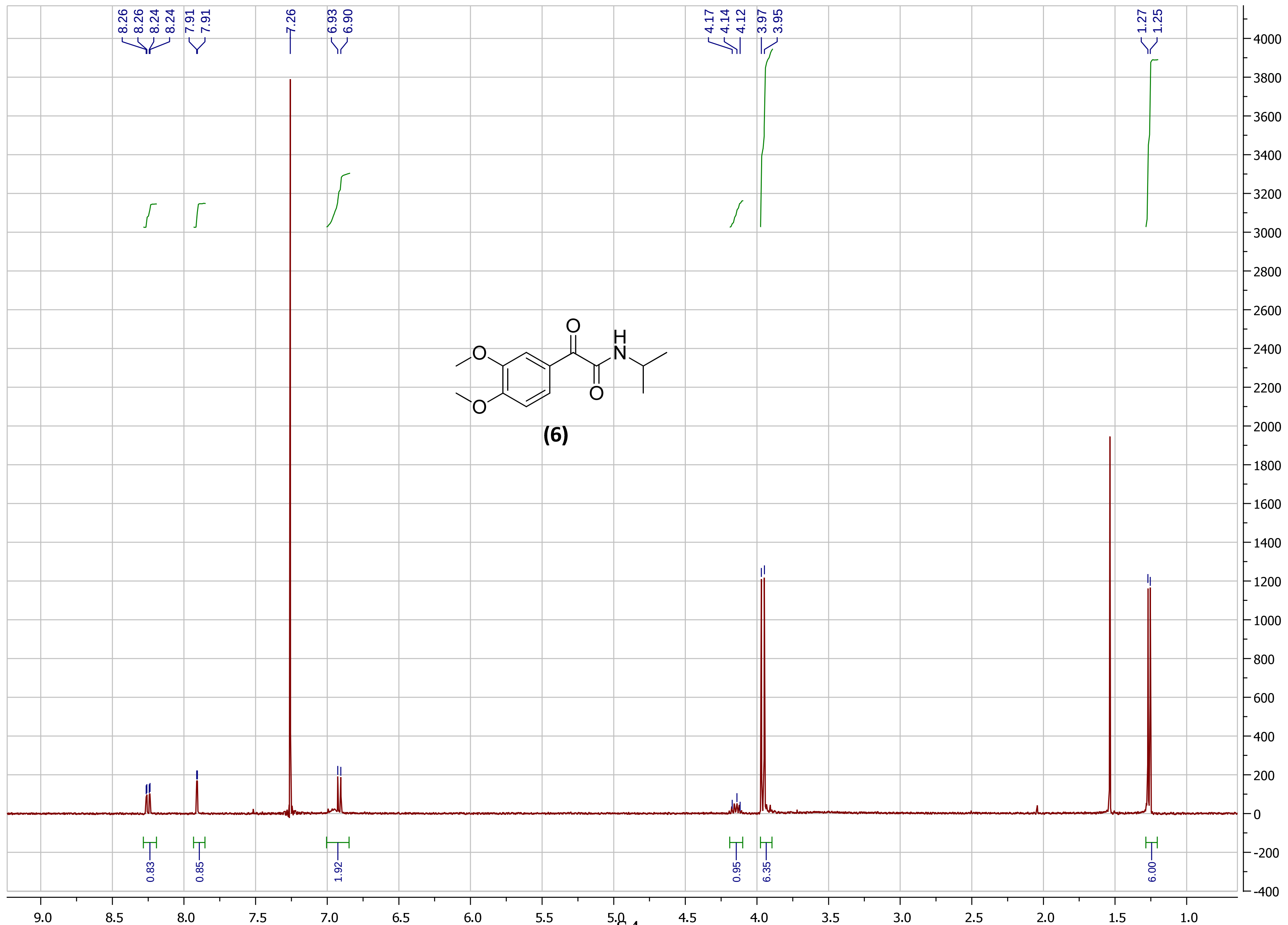
Supporting Information

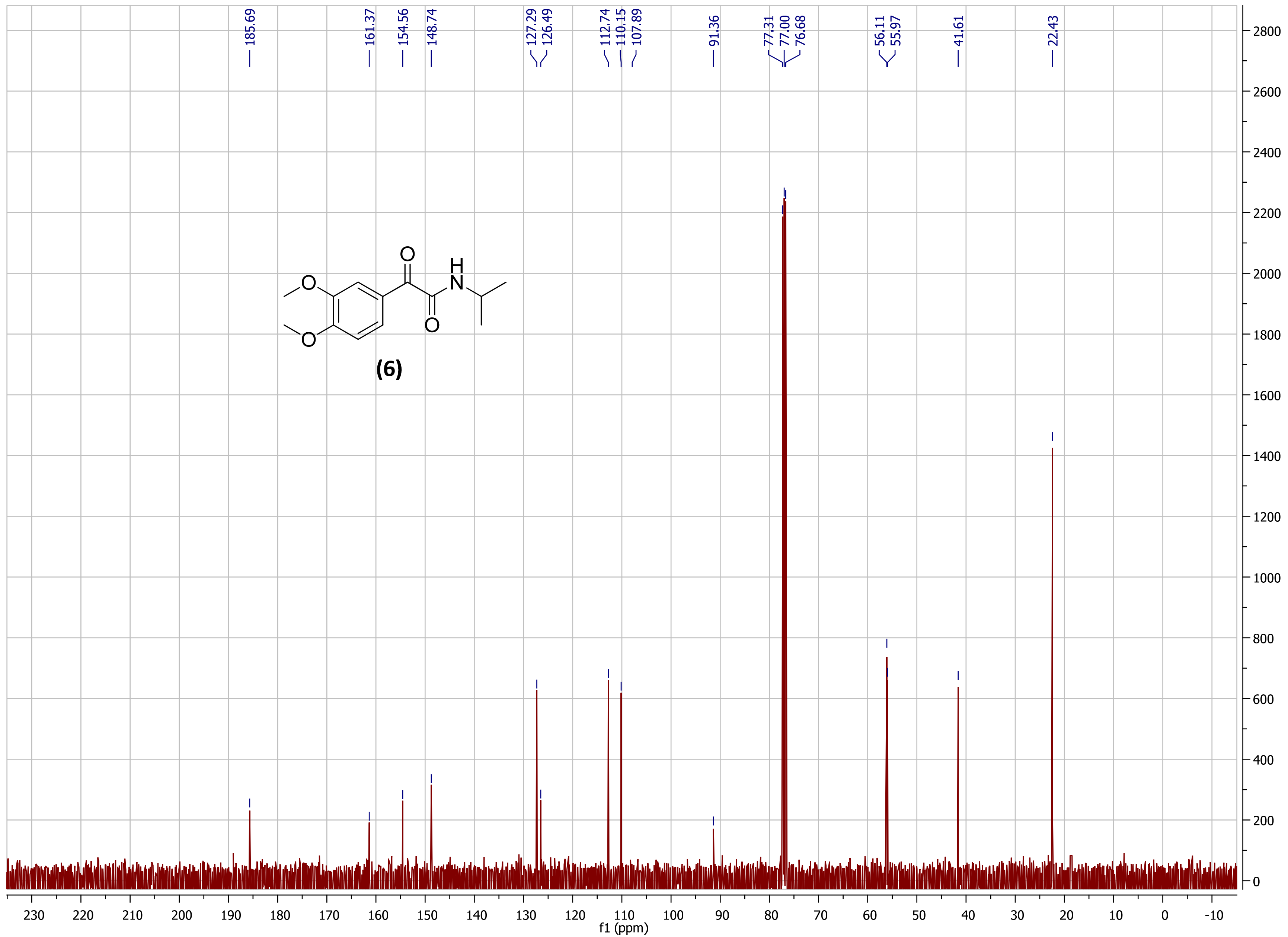
Table of contents

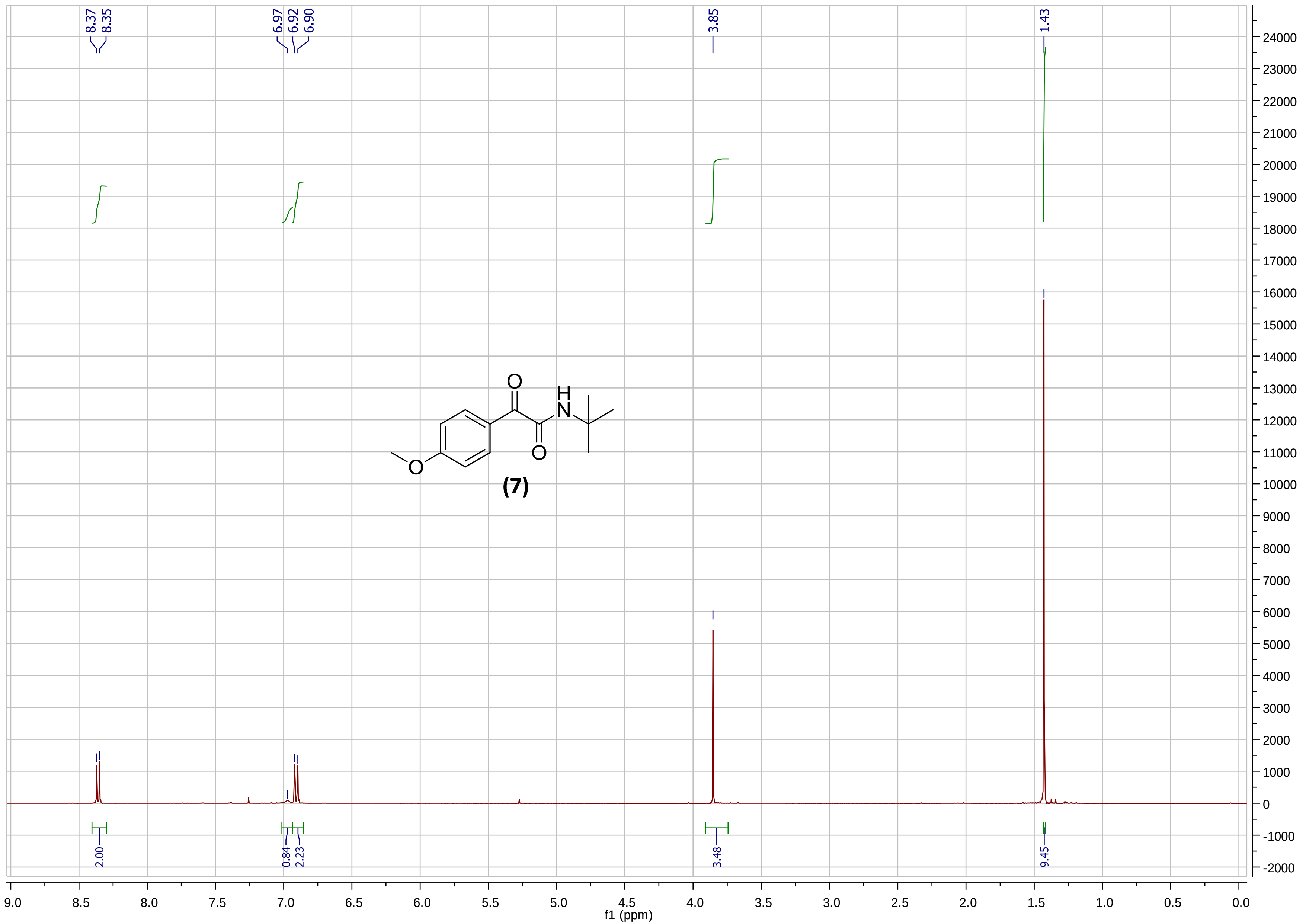


(5)

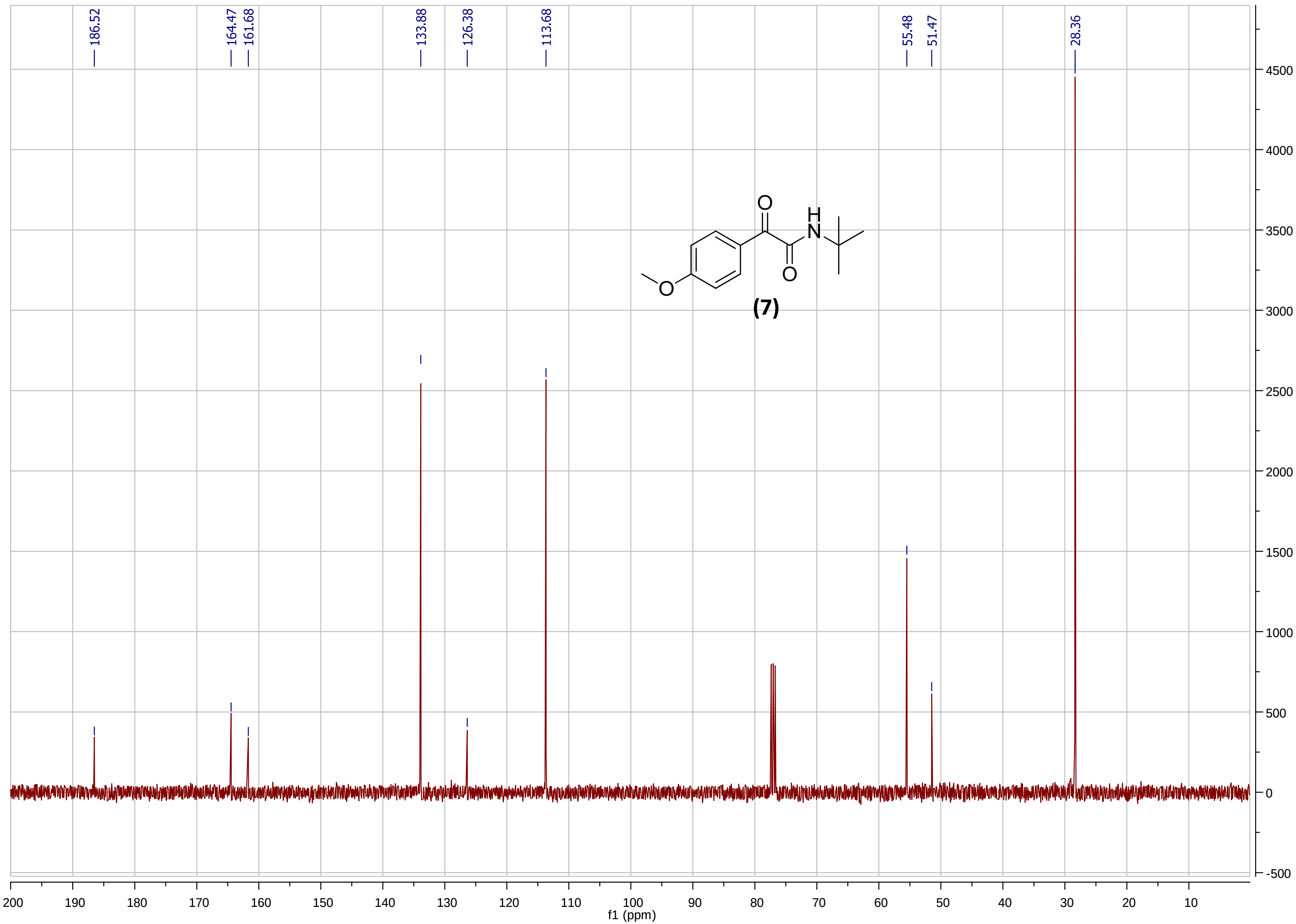

185.8094
164.6333
162.2015
133.9244
126.4458
113.7834
55.5200
39.3790
31.4036
29.2496
26.5543
22.5098
13.9796
O
H
N
O
O
(5)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

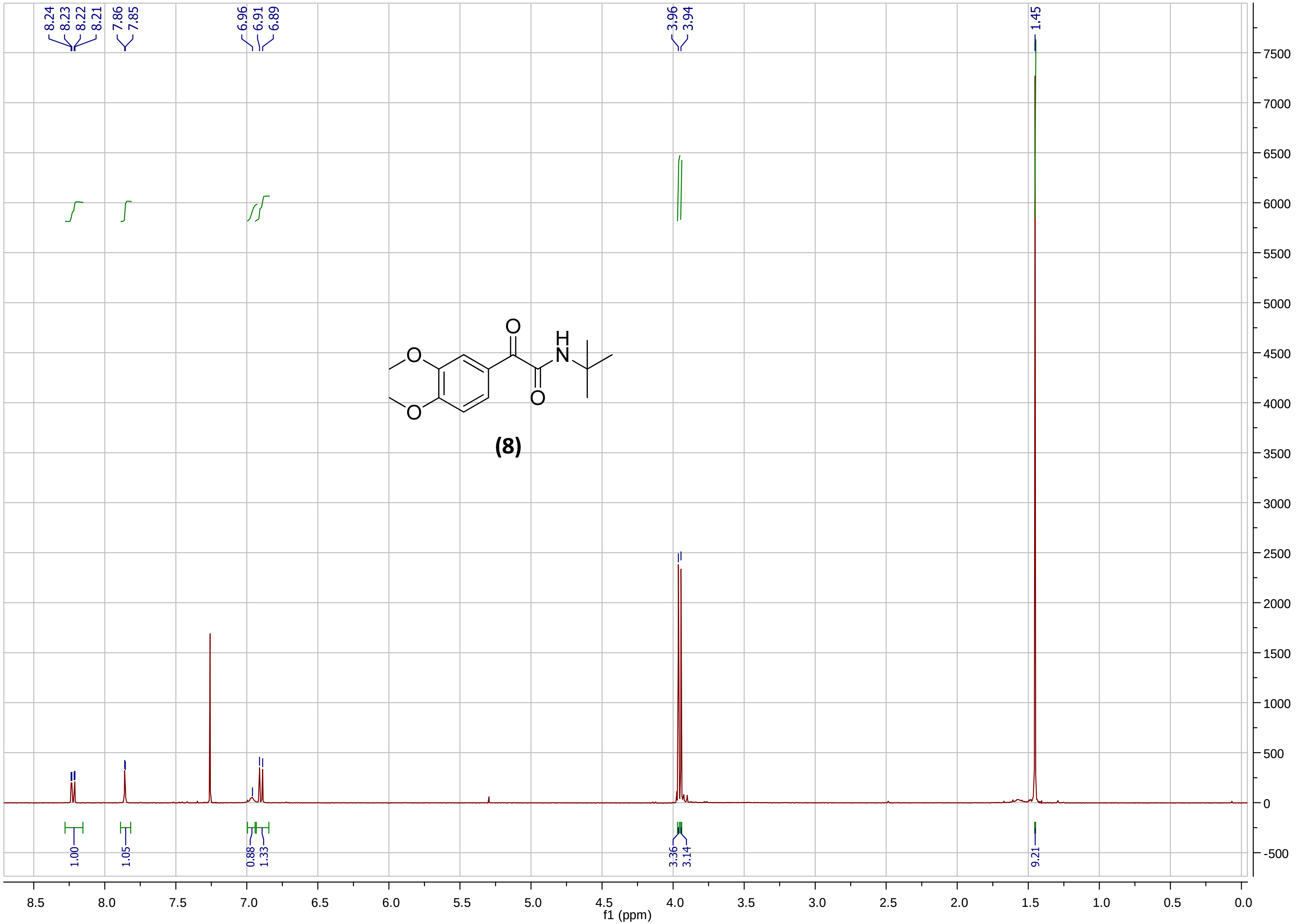

8.26
8.26
8.24
8.24
7.91
7.91
7.26
6.93
6.90
4.17
4.14
4.12
3.97
3.95
1.27
1.25
(6)
0.83
0.85
1.92
0.95
6.35
6.00
f1 (ppm)

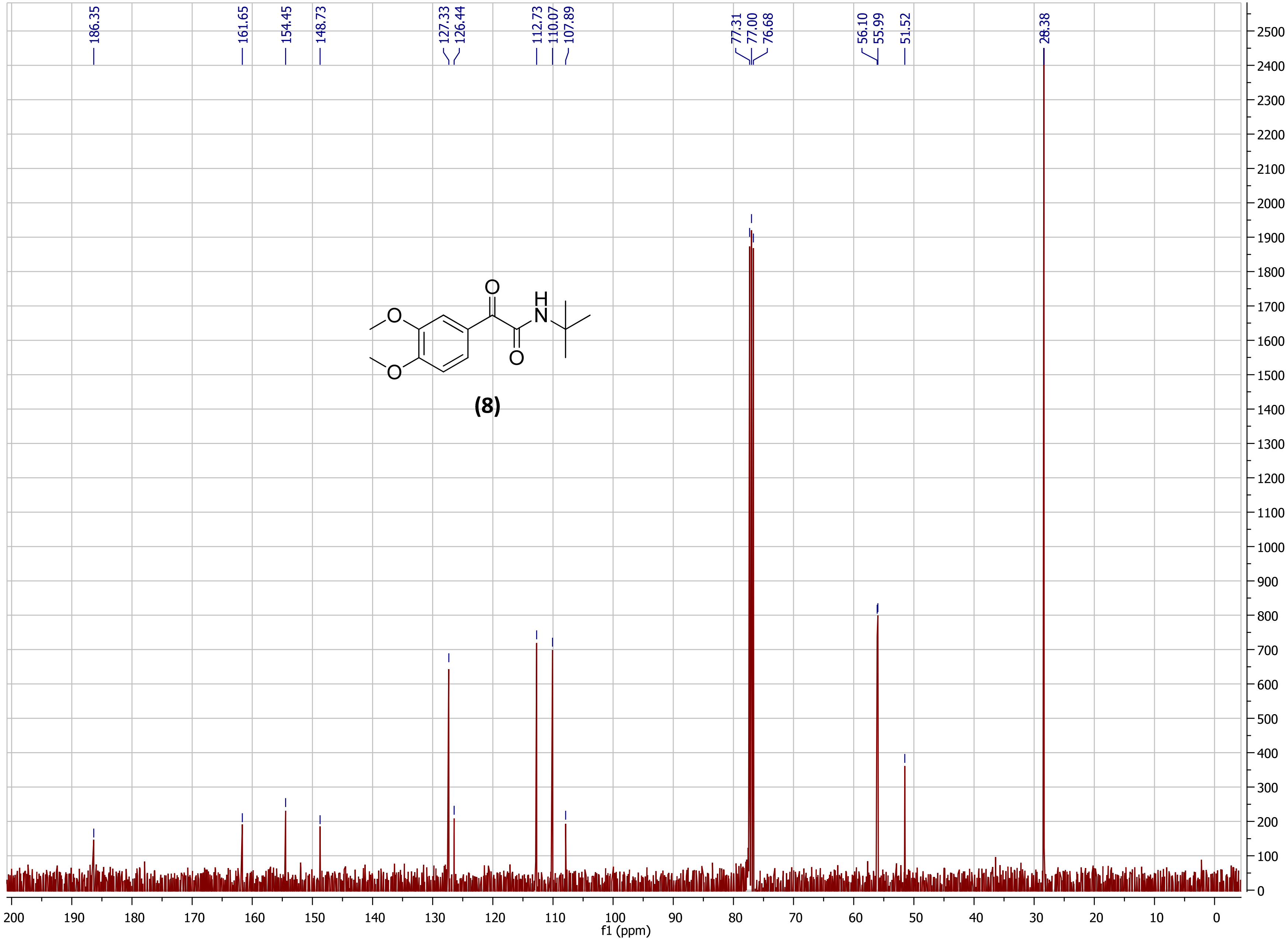

185.69
161.37
154.56
148.74
127.29
126.49
112.74
110.15
107.89
91.36
77.31
77.00
76.68
56.11
55.97
41.61
22.43
(6)
f1 (ppm)

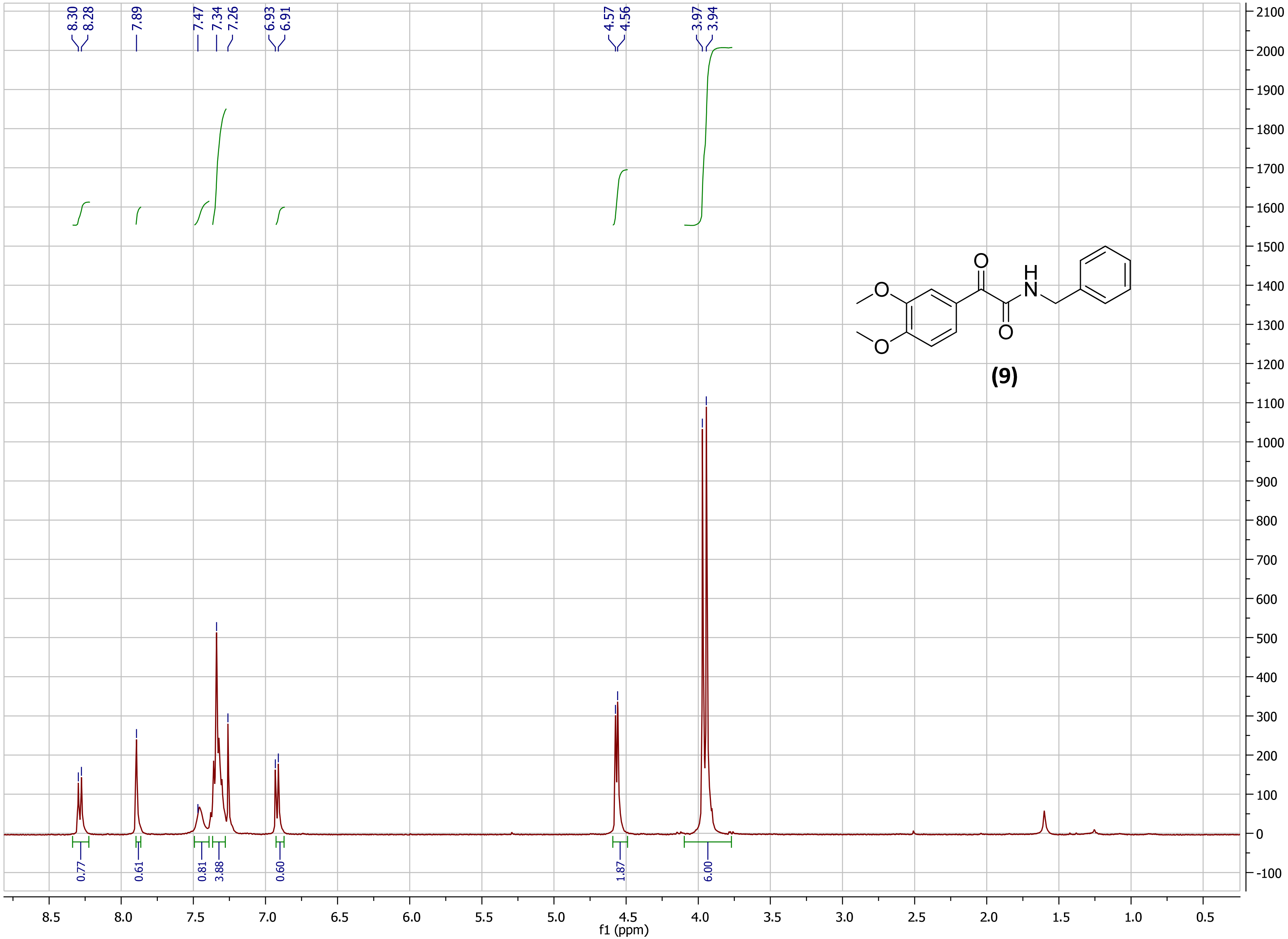


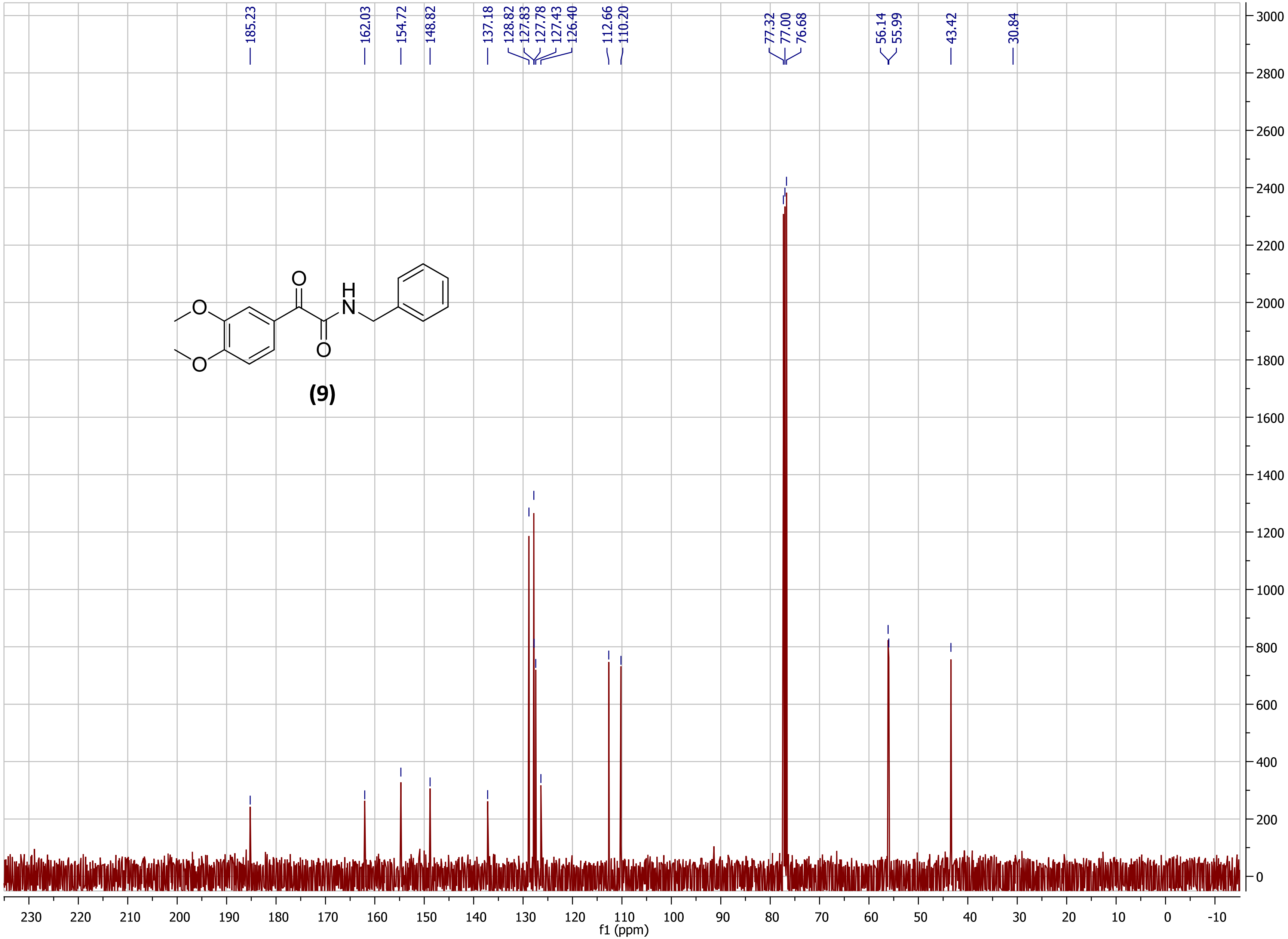
8.37
8.35
6.97
6.92
6.90
3.85
1.43
2.00
0.84
2.23
3.48
9.45
(7)
f1 (ppm)


186.52
164.47
161.68
133.88
126.38
113.68
55.48
51.47
28.36
O
H
N
O
O
(7)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

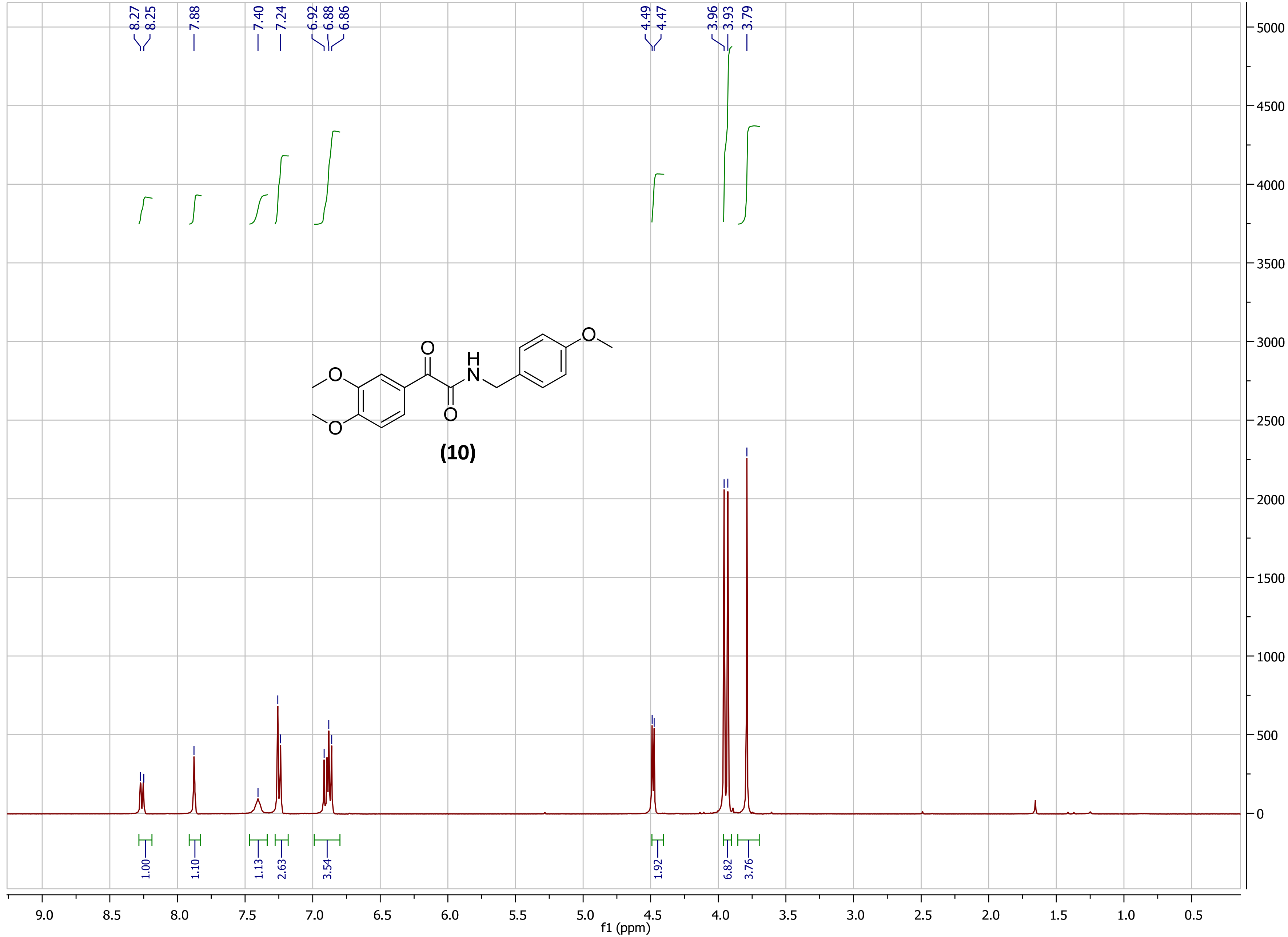

8.24
8.23
8.22
8.21
7.86
7.85
6.96
6.91
6.89
3.96
3.94
1.45
O
H
N
O
O
O
(8)
1.00
1.05
0.88
1.33
3.36
3.14
9.21
f1 (ppm)

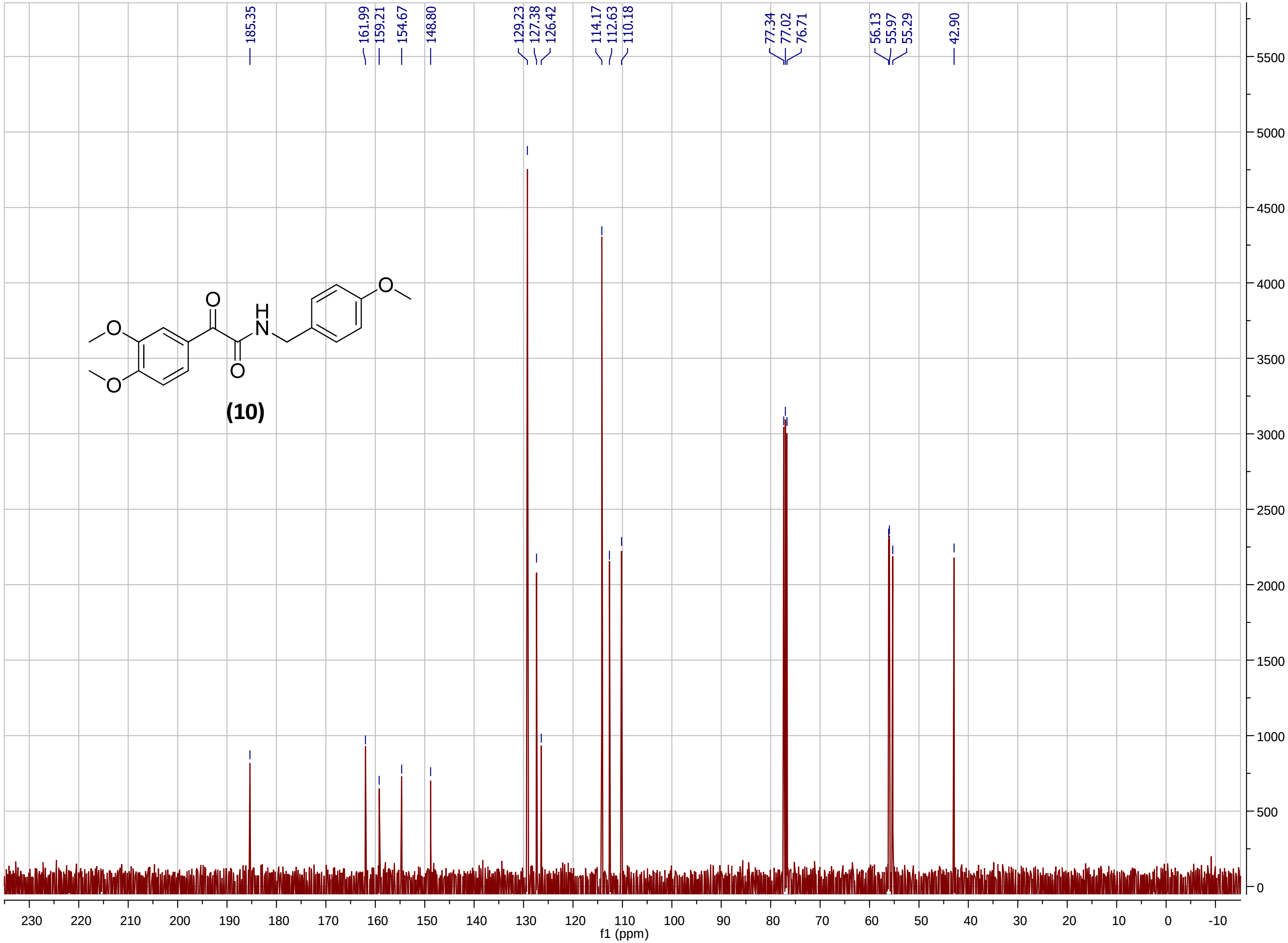

186.35
161.65
154.45
148.73
127.33
126.44
112.73
110.07
107.89
77.31
77.00
76.68
56.10
55.99
51.52
28.38
(8)
f1 (ppm)


8.30
8.28
7.89
7.47
7.34
7.26
6.93
6.91
4.57
4.56
3.97
3.94
O
H
N
O
O
O
(9)
0.77
0.61
0.81
3.88
0.60
1.87
6.00
f1 (ppm)

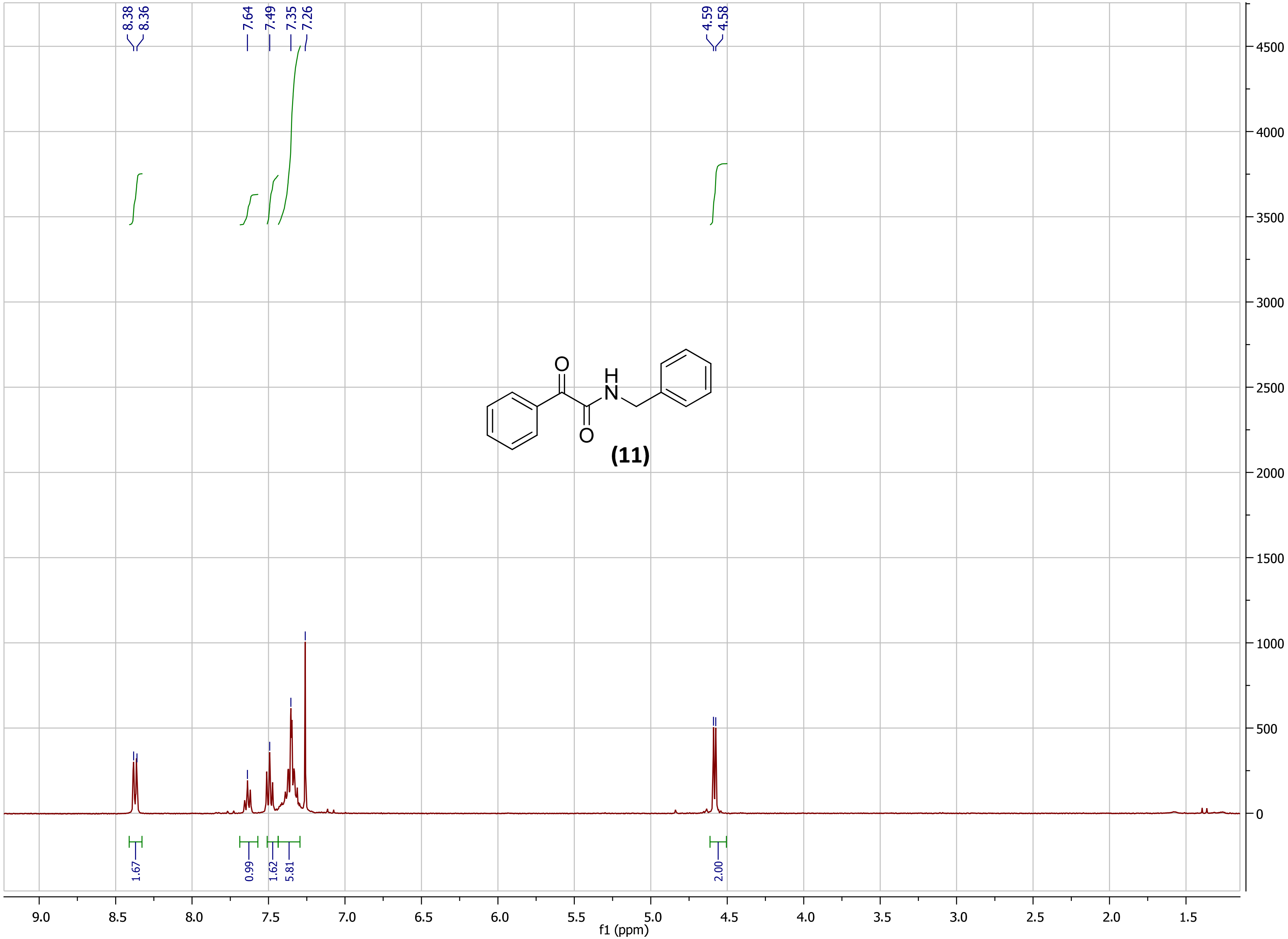


185.23
162.03
154.72
148.82
137.18
128.82
127.83
127.78
127.43
126.40
112.66
110.20
77.32
77.00
76.68
56.14
55.99
43.42
30.84
O
H
N
O
O
O
(9)
f1 (ppm)


8.27
8.25
7.88
7.40
7.24
6.92
6.88
6.86
4.49
4.47
3.96
3.93
3.79
(10)
1.00
1.10
1.13
2.63
3.54
1.92
6.82
3.76
f1 (ppm)

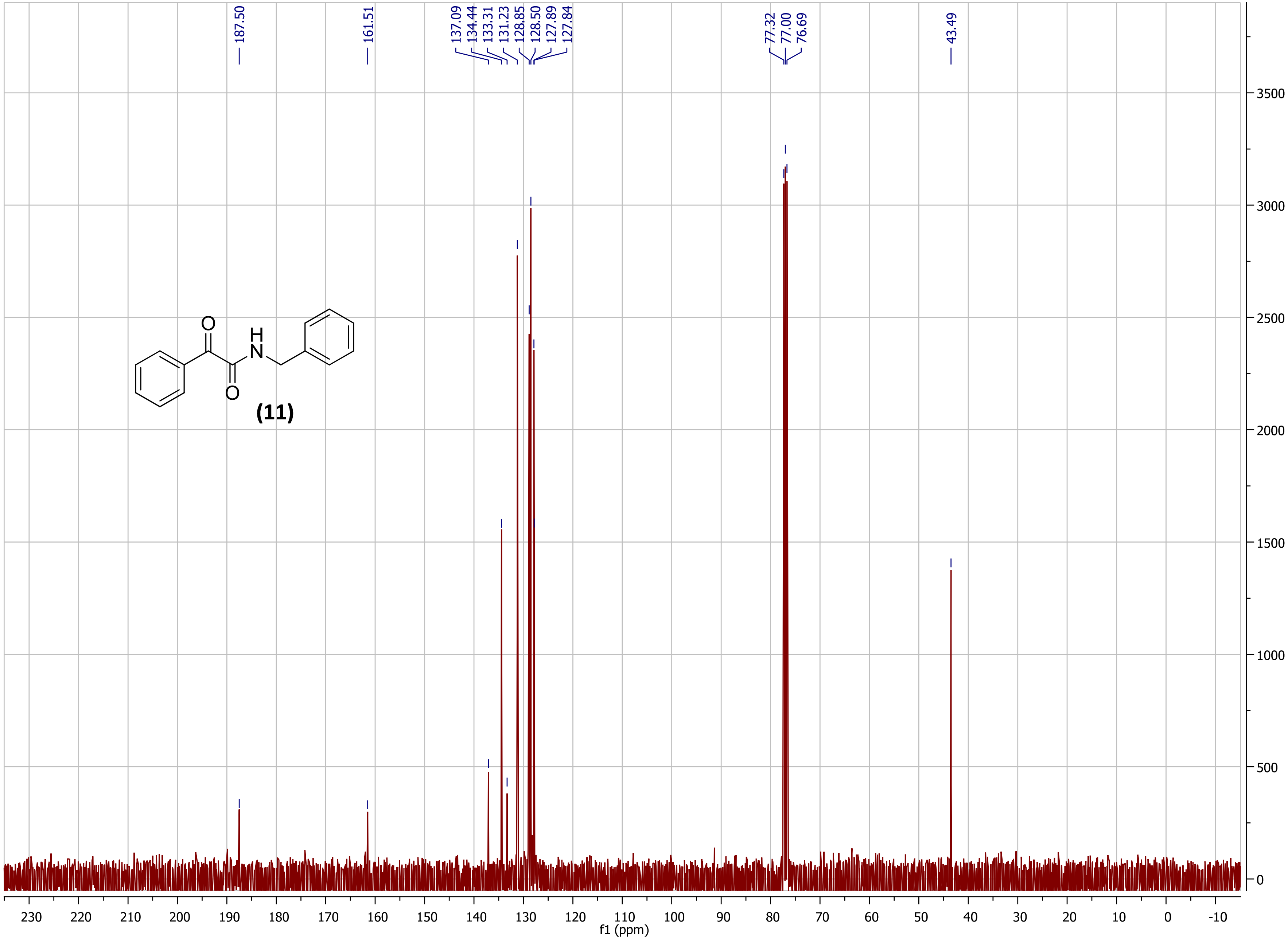

185.35
161.99
159.21
154.67
148.80
129.23
127.38
126.42
114.17
112.63
110.18
77.34
77.02
76.71
56.13
55.97
55.29
42.90
f1 (ppm)

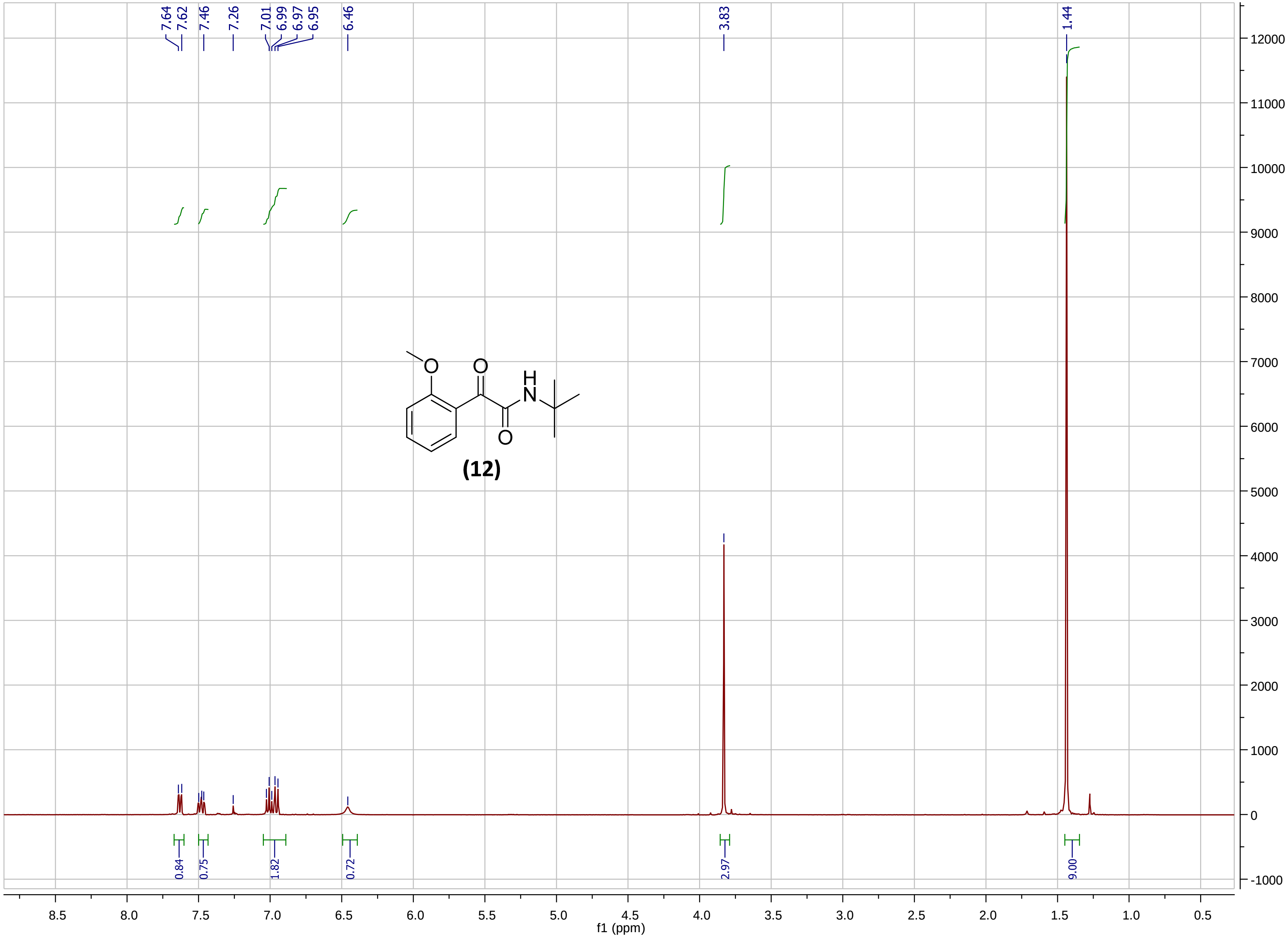
(10)

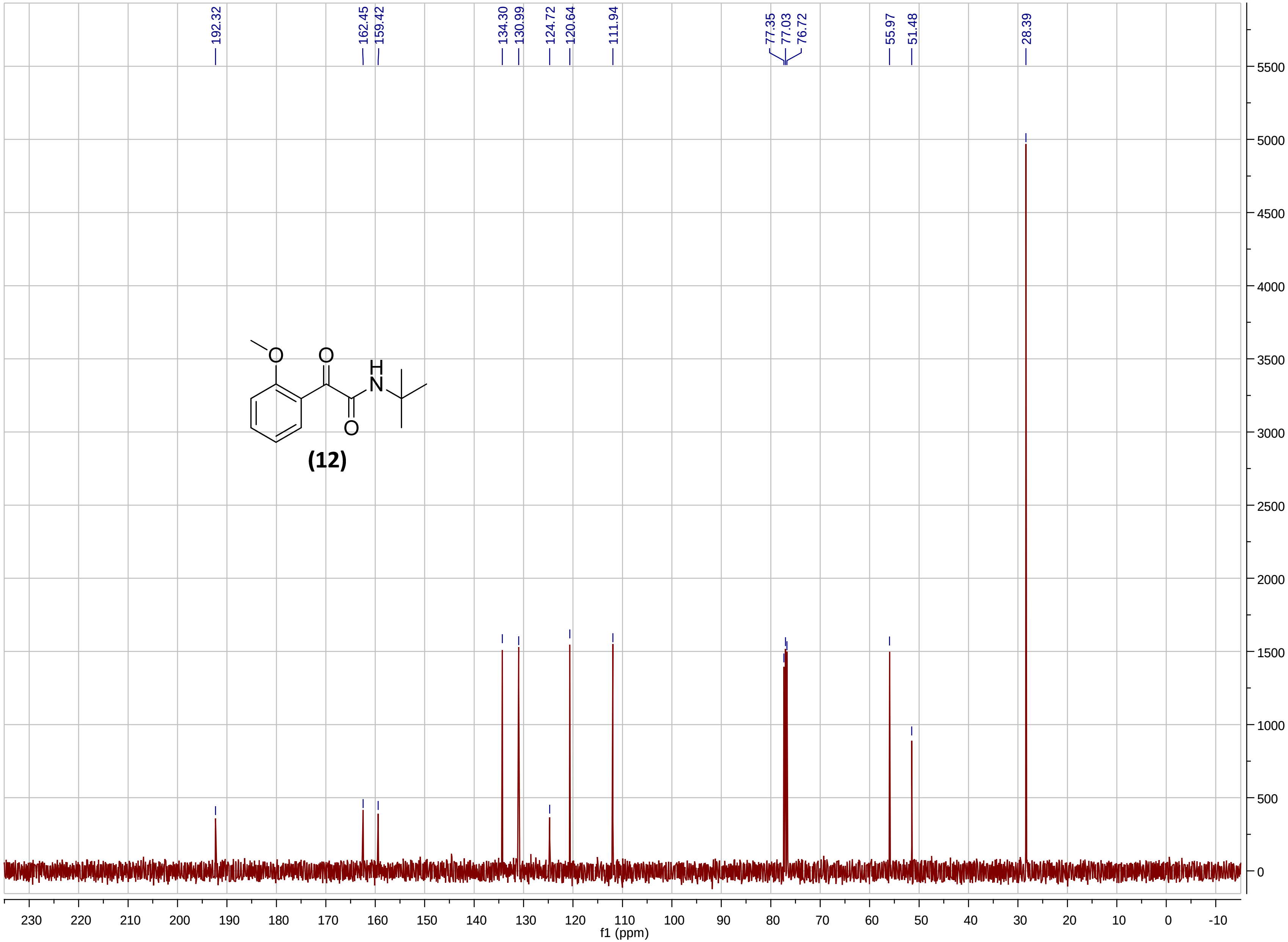


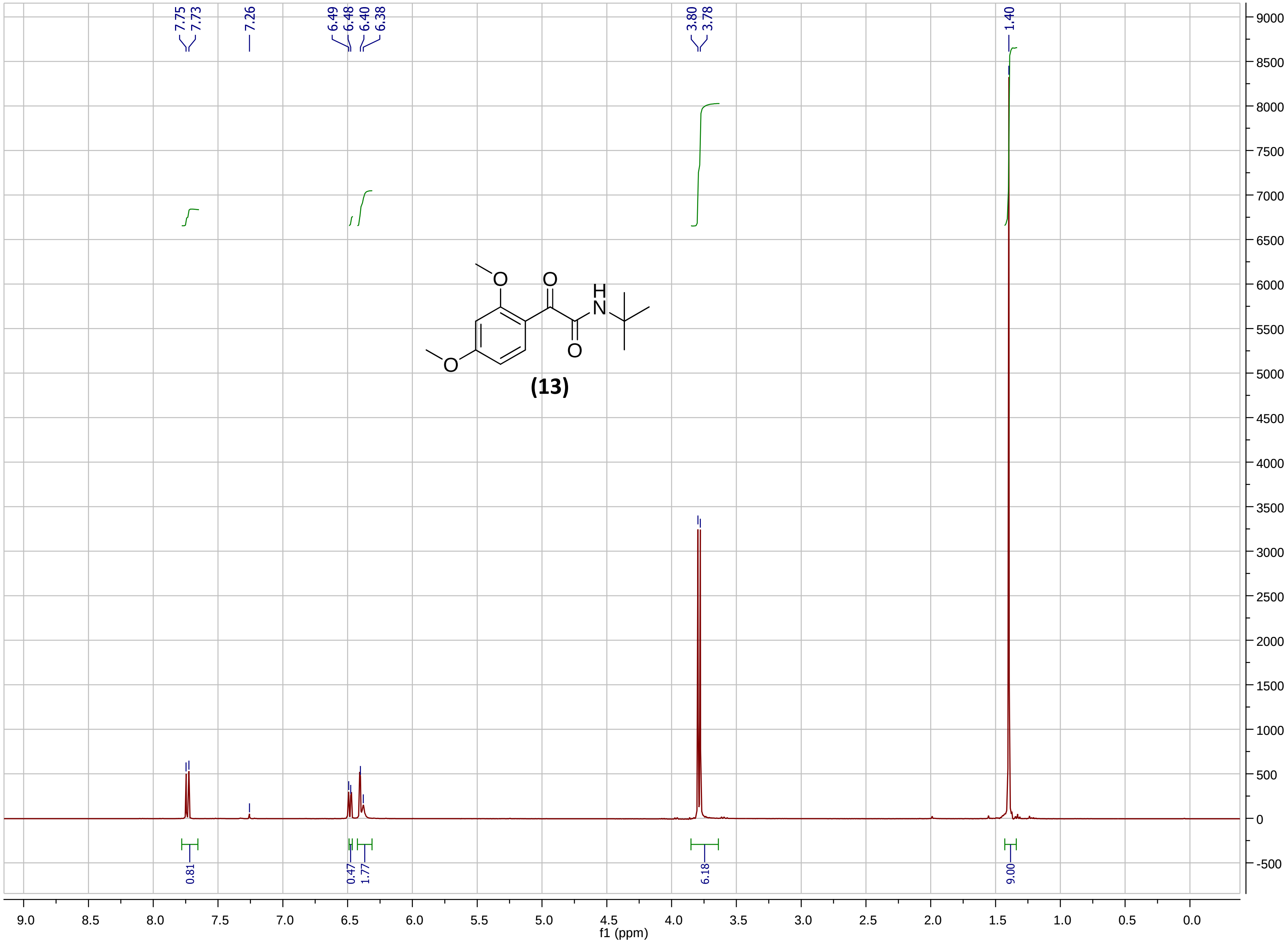
8.38
8.36
7.64
7.49
7.35
7.26
4.59
4.58
4500
4000
3500
3000
2500
2000
1500
1000
500
0
O
H
N
O
1.67
0.99
1.62
5.81
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

(11)

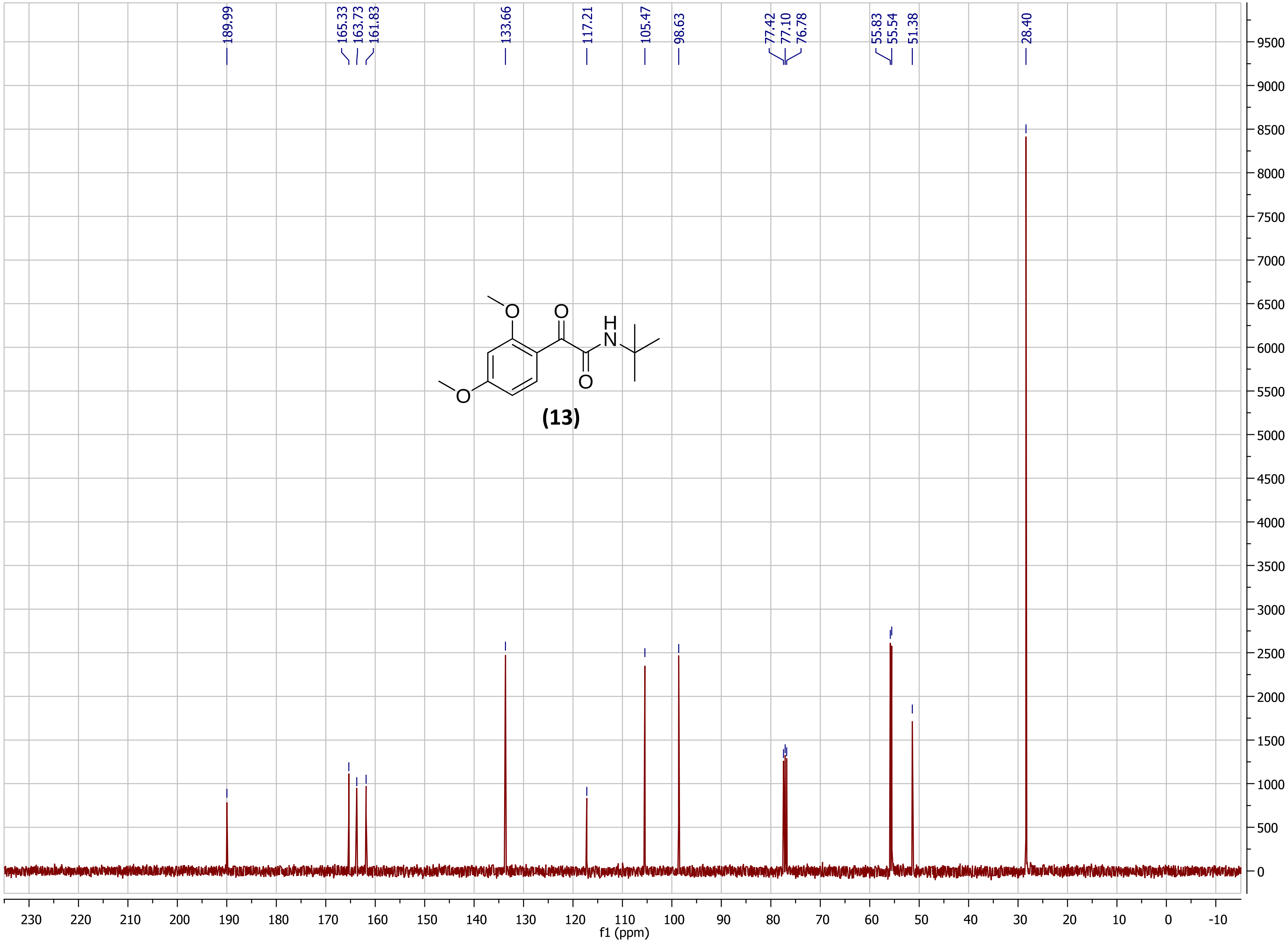

187.50
161.51
137.09
134.44
133.31
131.23
128.85
128.50
127.89
127.84
77.32
77.00
76.69
43.49
(11)
f1 (ppm)


7.64
7.62
7.46
7.26
7.01
6.99
6.97
6.95
6.46
3.83
1.44
(12)
0.84
0.75
1.82
0.72
2.97
9.00
f1 (ppm)

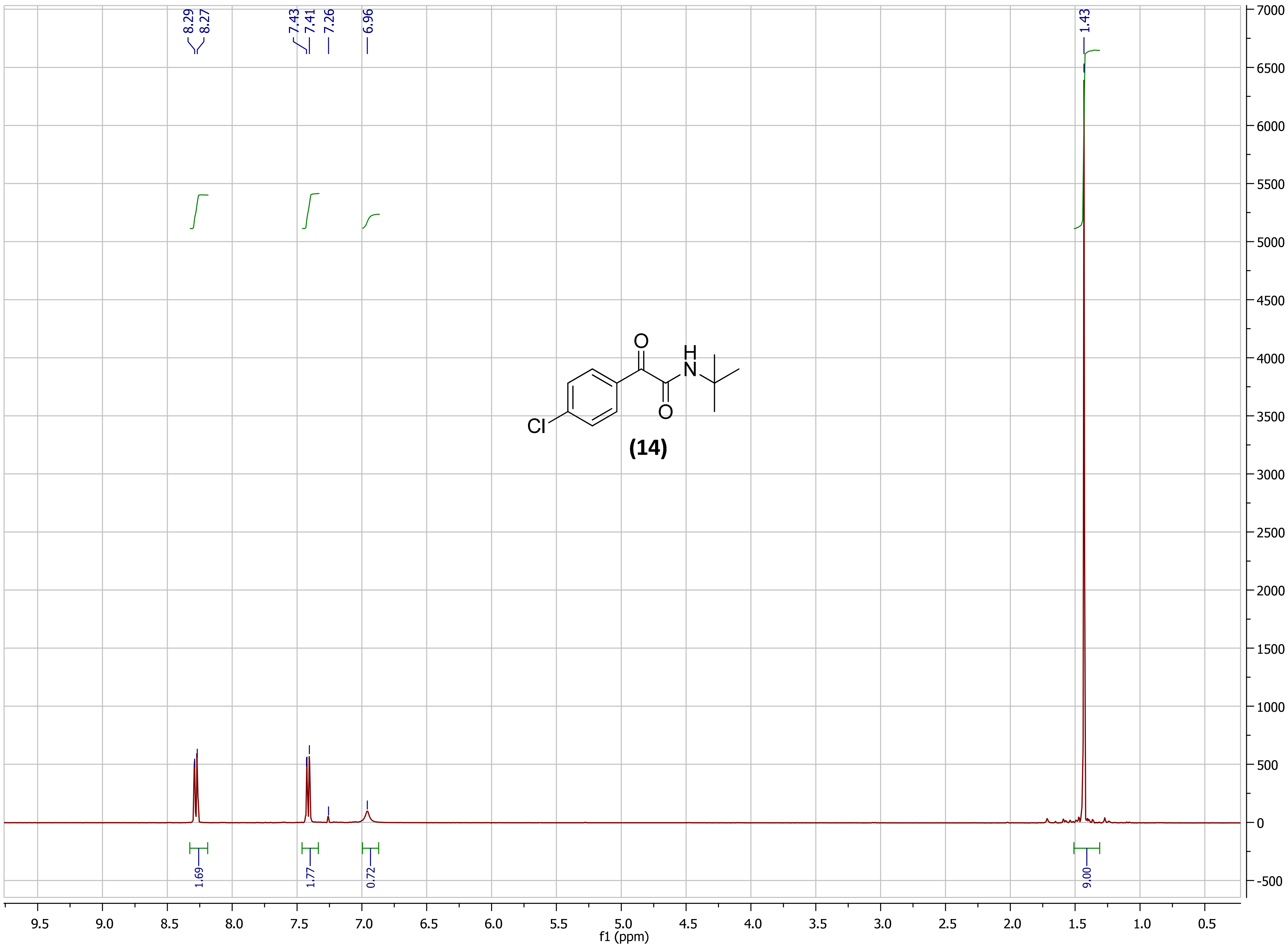

192.32
162.45
159.42
134.30
130.99
124.72
120.64
111.94
77.35
77.03
76.72
55.97
51.48
28.39
(12)
f1 (ppm)



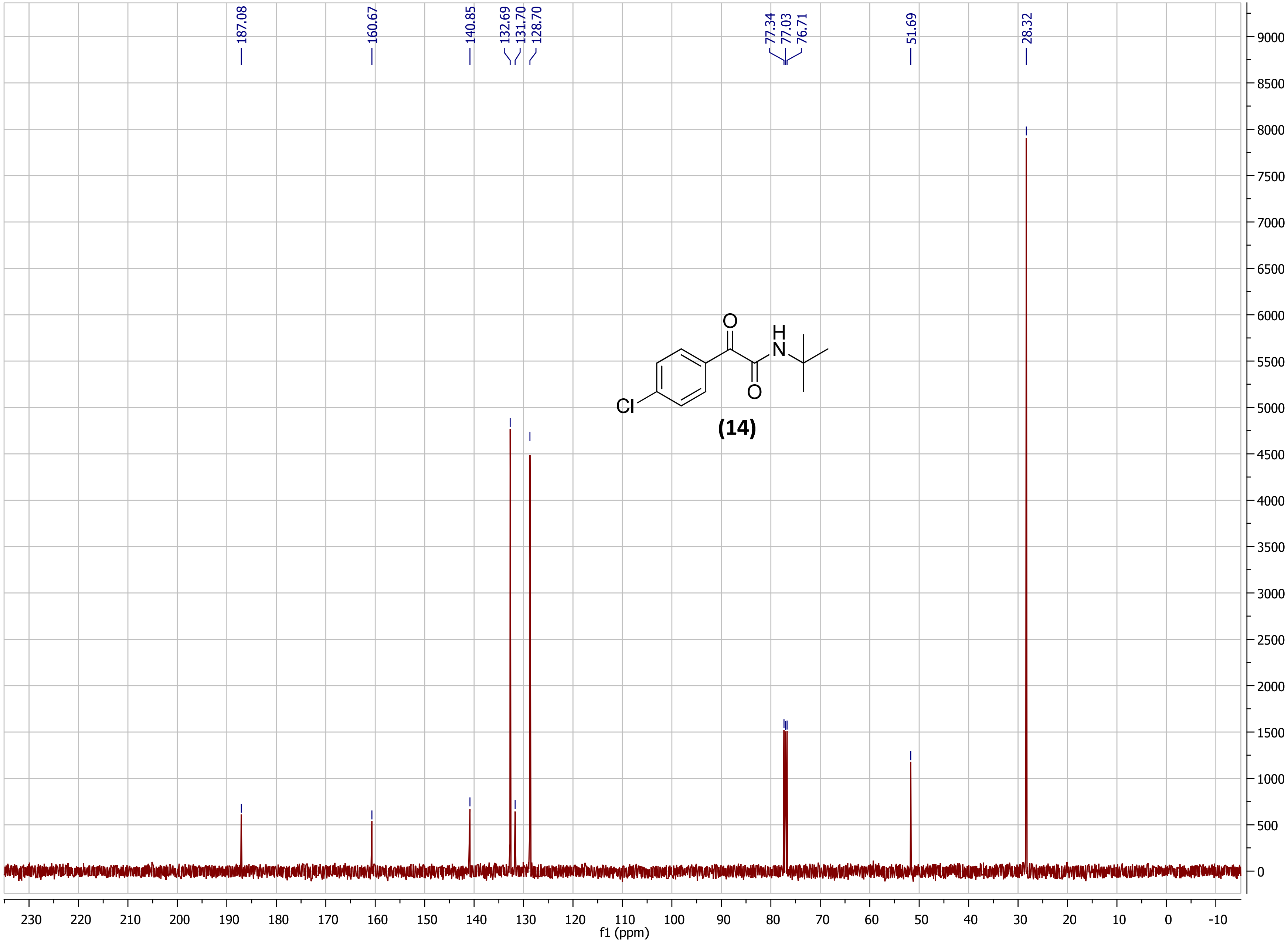
7.75
7.73
7.26
6.49
6.48
6.40
6.38
3.80
3.78
1.40
O
O
H
N
O
O
(13)
0.81
0.47
1.77
6.18
9.00
f1 (ppm)

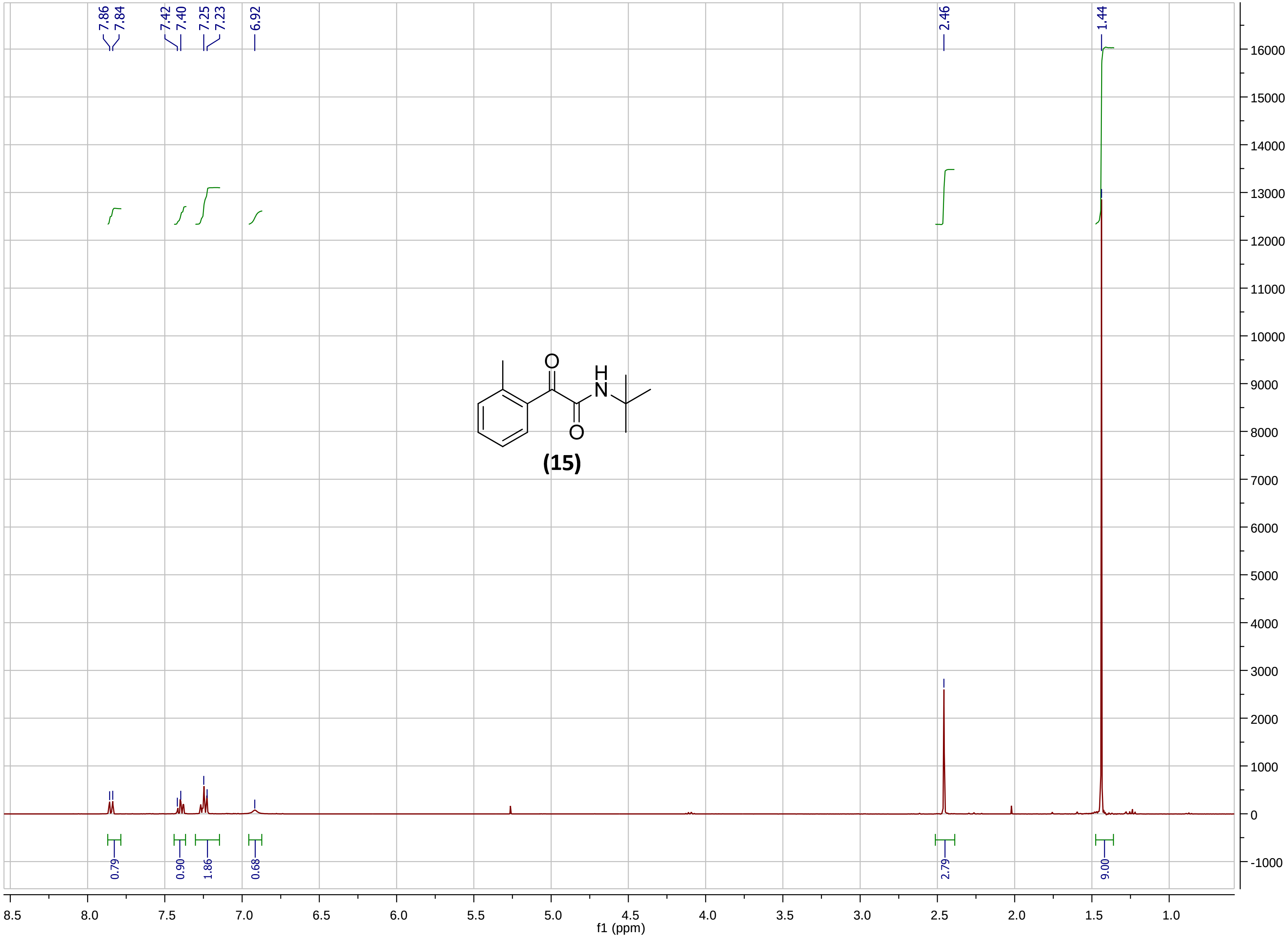


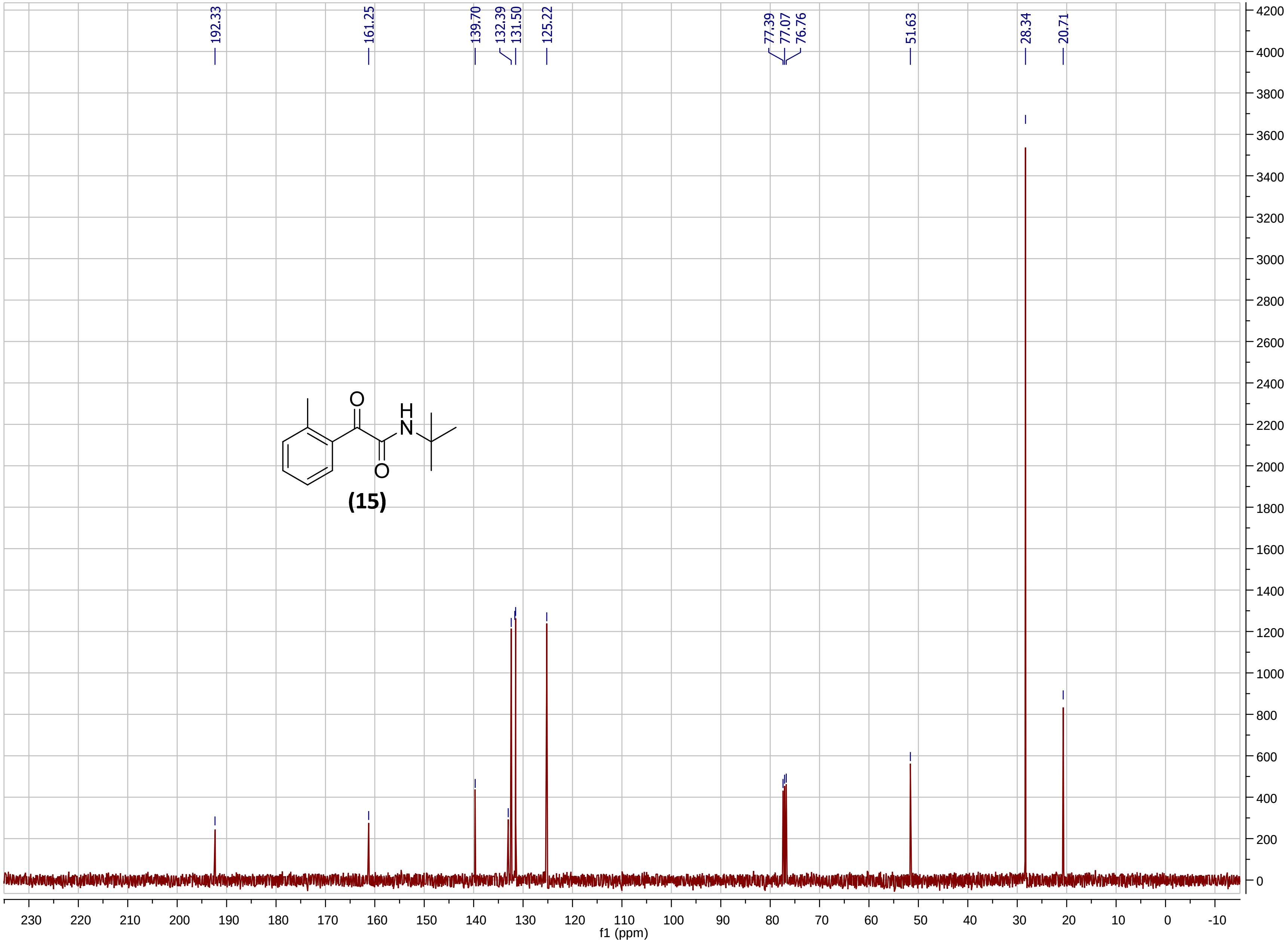
189.99
165.33
163.73
161.83
133.66
117.21
105.47
98.63
77.42
77.10
76.78
55.83
55.54
51.38
28.40
(13)
f1 (ppm)

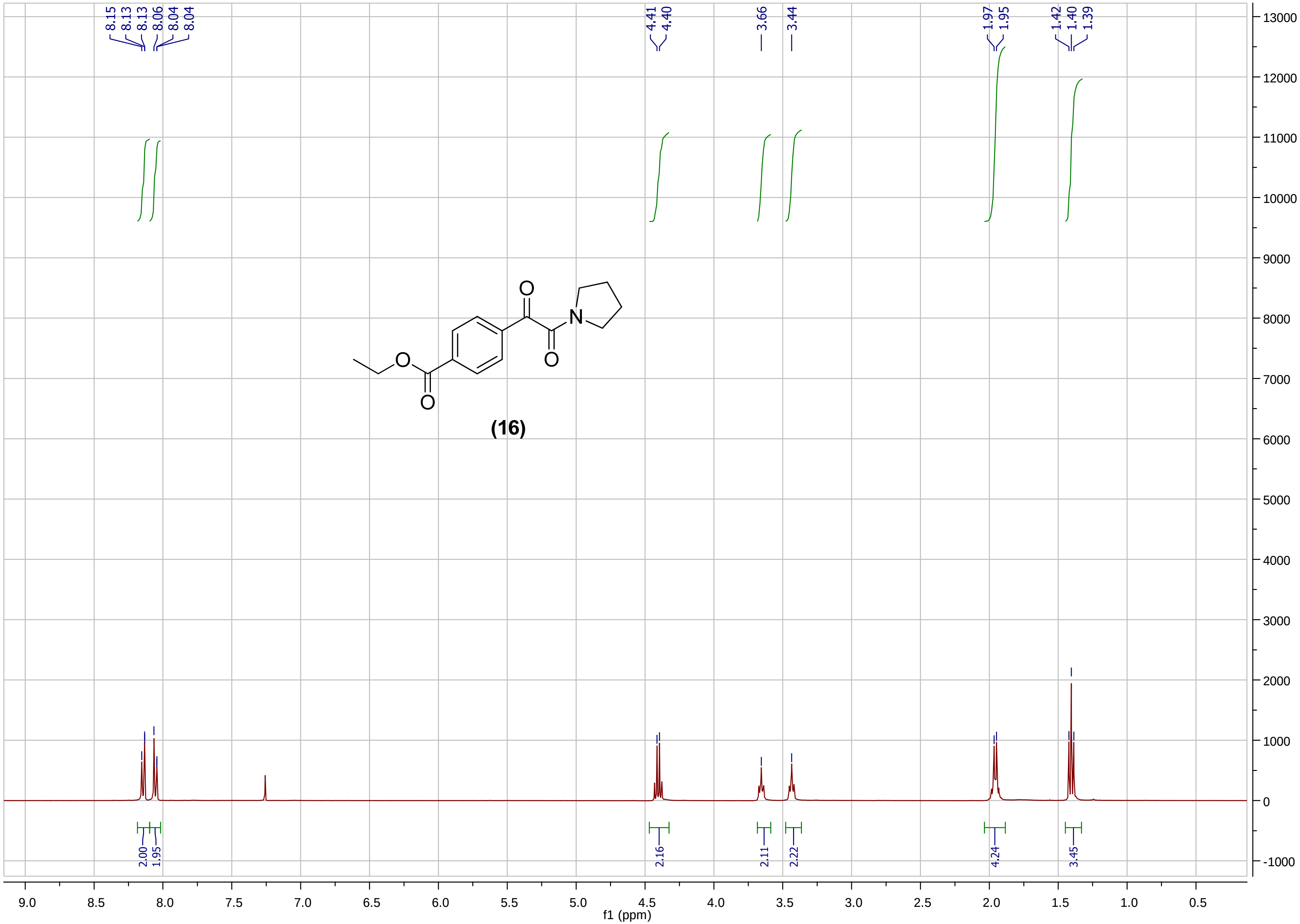


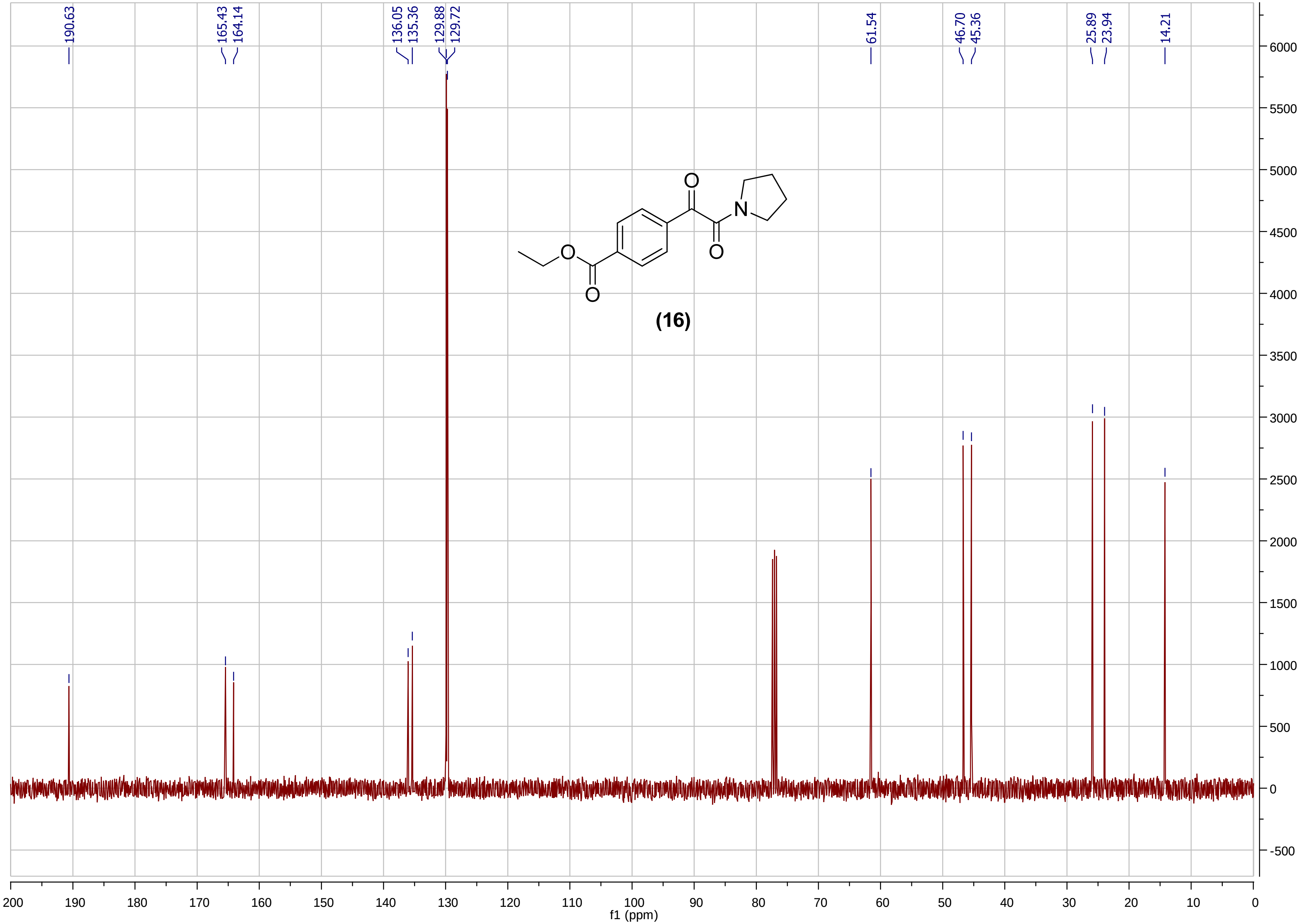
(14)

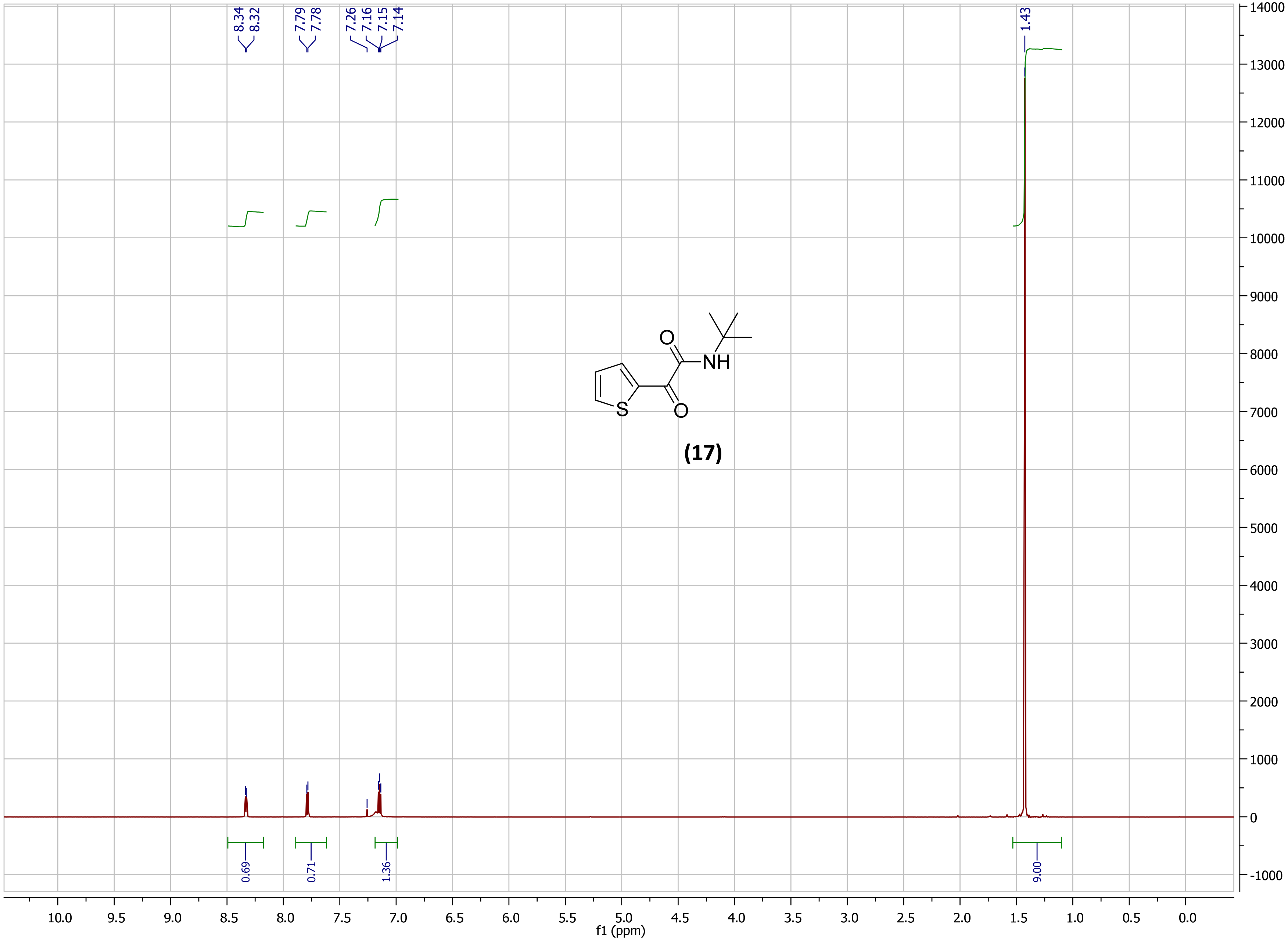

187.08
160.67
140.85
132.69
131.70
128.70
77.34
77.03
76.71
51.69
28.32
O
H
N
O
Cl
(14)
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.86
7.84
7.42
7.40
7.25
7.23
6.92
2.46
1.44
(15)
0.79
0.90
1.86
0.68
2.79
9.00
f1 (ppm)

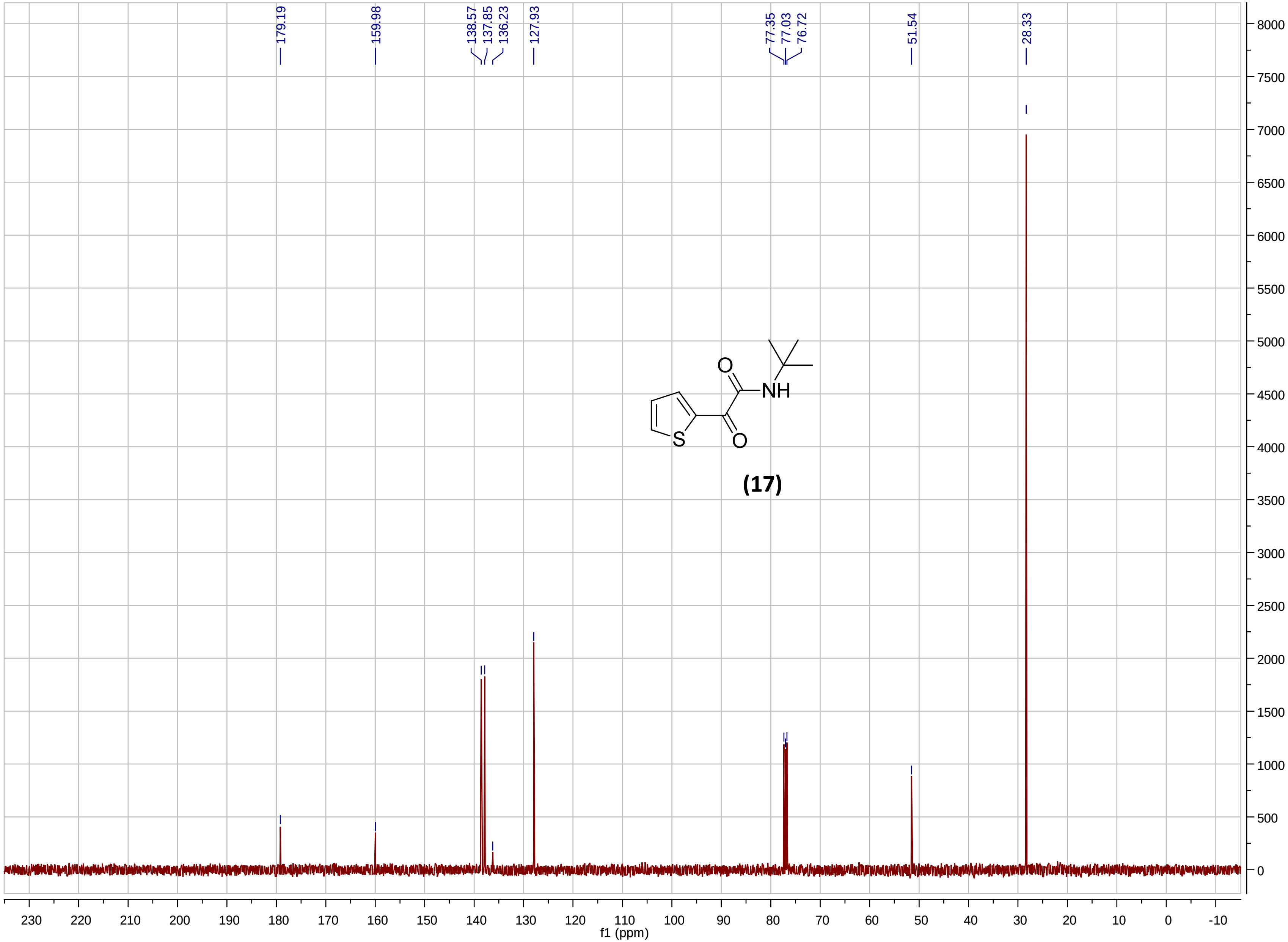

192.33
161.25
139.70
132.39
131.50
125.22
77.39
77.07
76.76
51.63
28.34
20.71
(15)
f1 (ppm)


8.15
8.13
8.13
8.06
8.04
8.04
4.41
4.40
3.66
3.44
1.97
1.95
1.42
1.40
1.39
2.00
1.95
2.16
2.11
2.22
4.24
3.45
f1 (ppm)
(16)

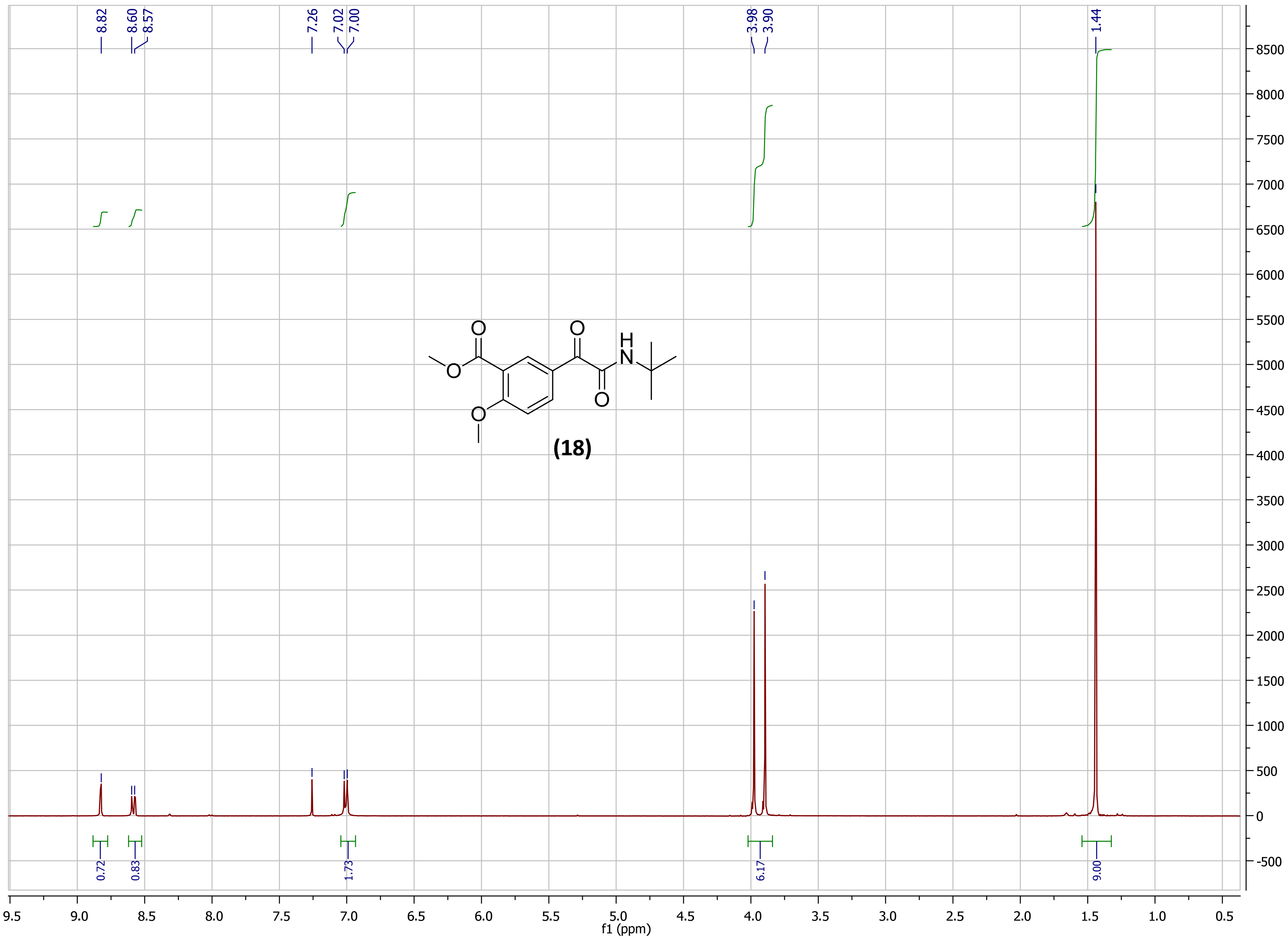

190.63
165.43
164.14
136.05
135.36
129.88
129.72
61.54
46.70
45.36
25.89
23.94
14.21
(16)
f1 (ppm)

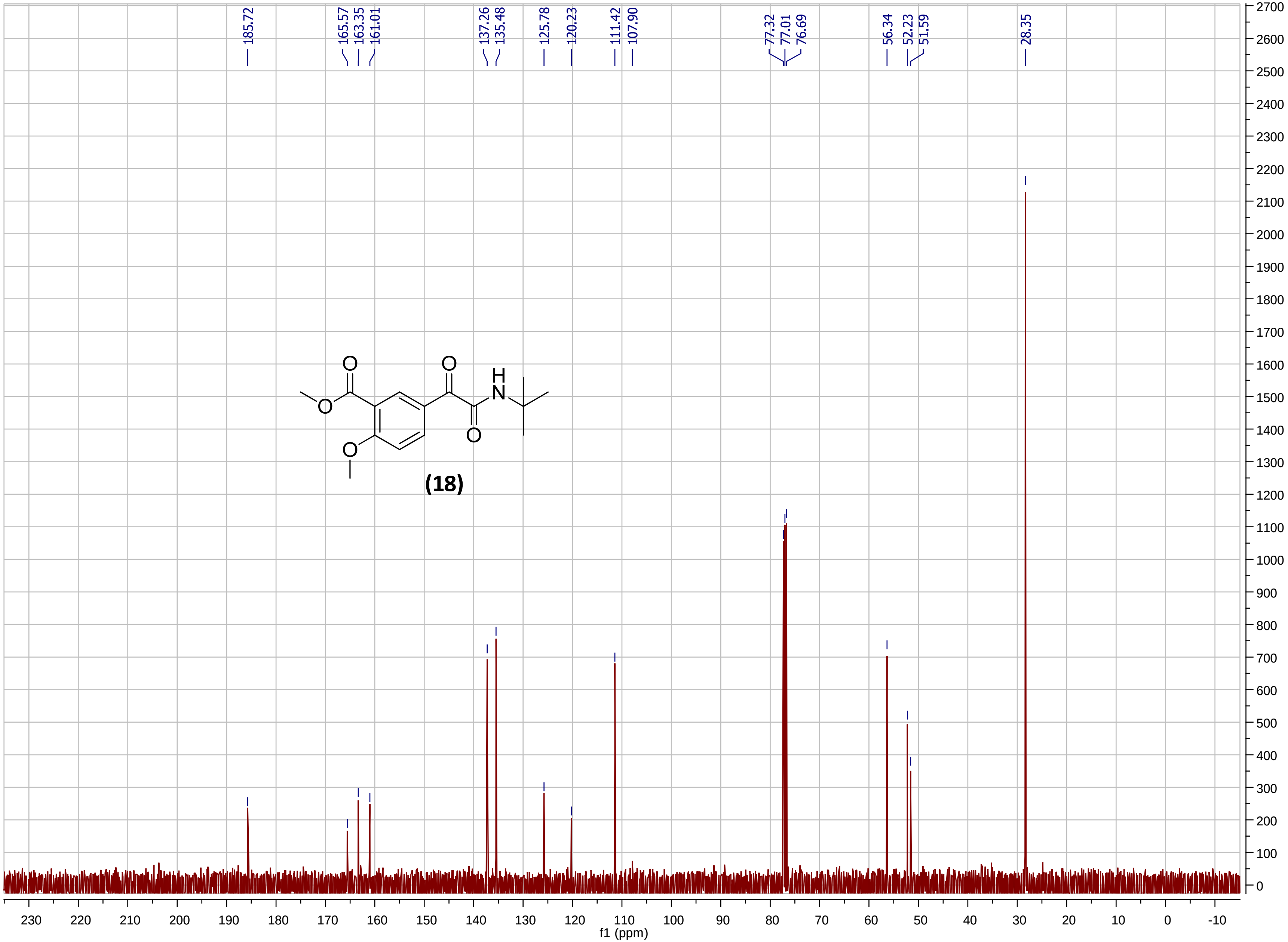


8.34
8.32
7.79
7.78
7.26
7.16
7.15
7.14
1.43
0.69
0.71
1.36
9.00
O
NH
S
O
(17)
f1 (ppm)

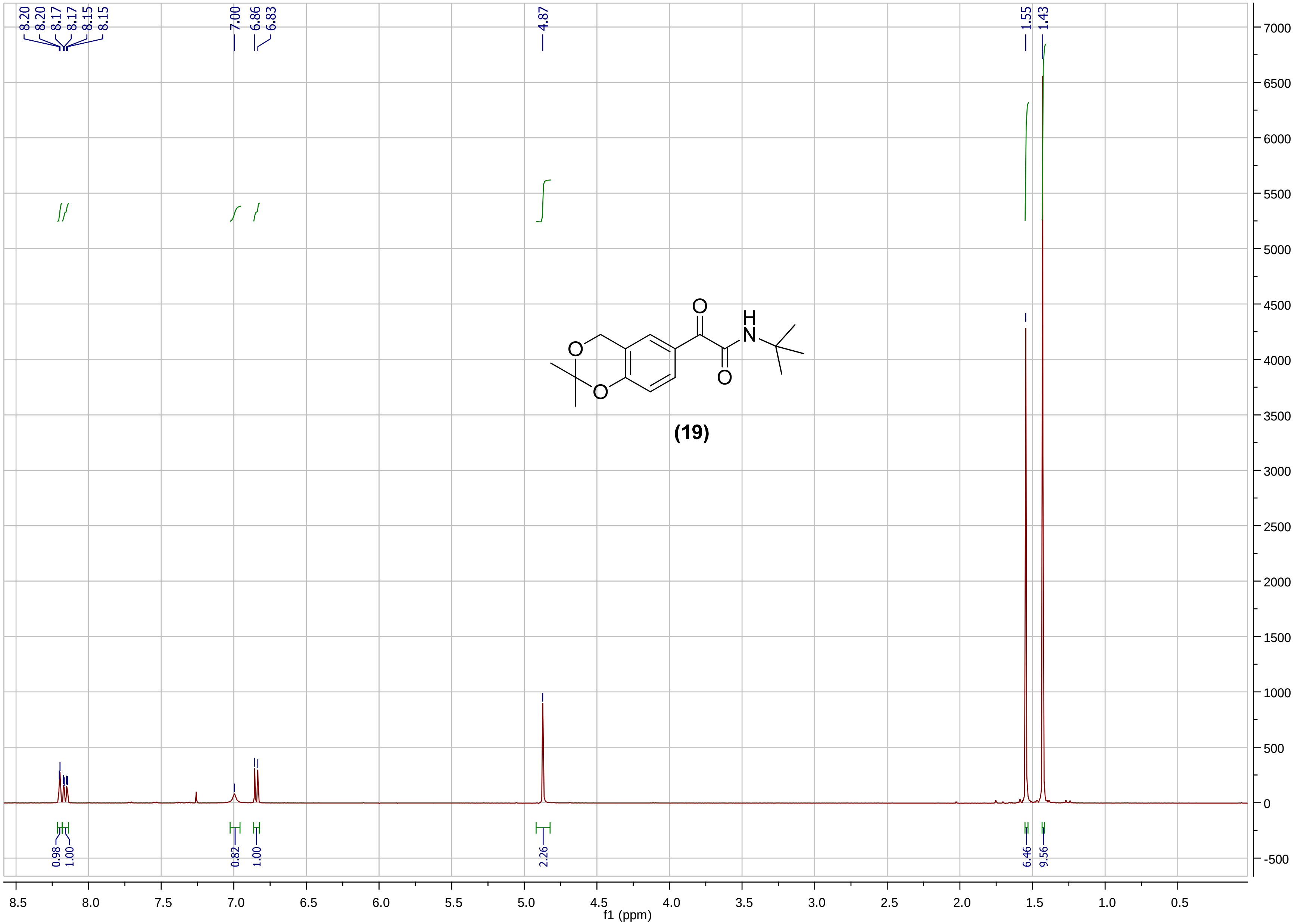

179.19
159.98
138.57
137.85
136.23
127.93
77.35
77.03
76.72
51.54
28.33
O
NH
S
O
f1 (ppm)

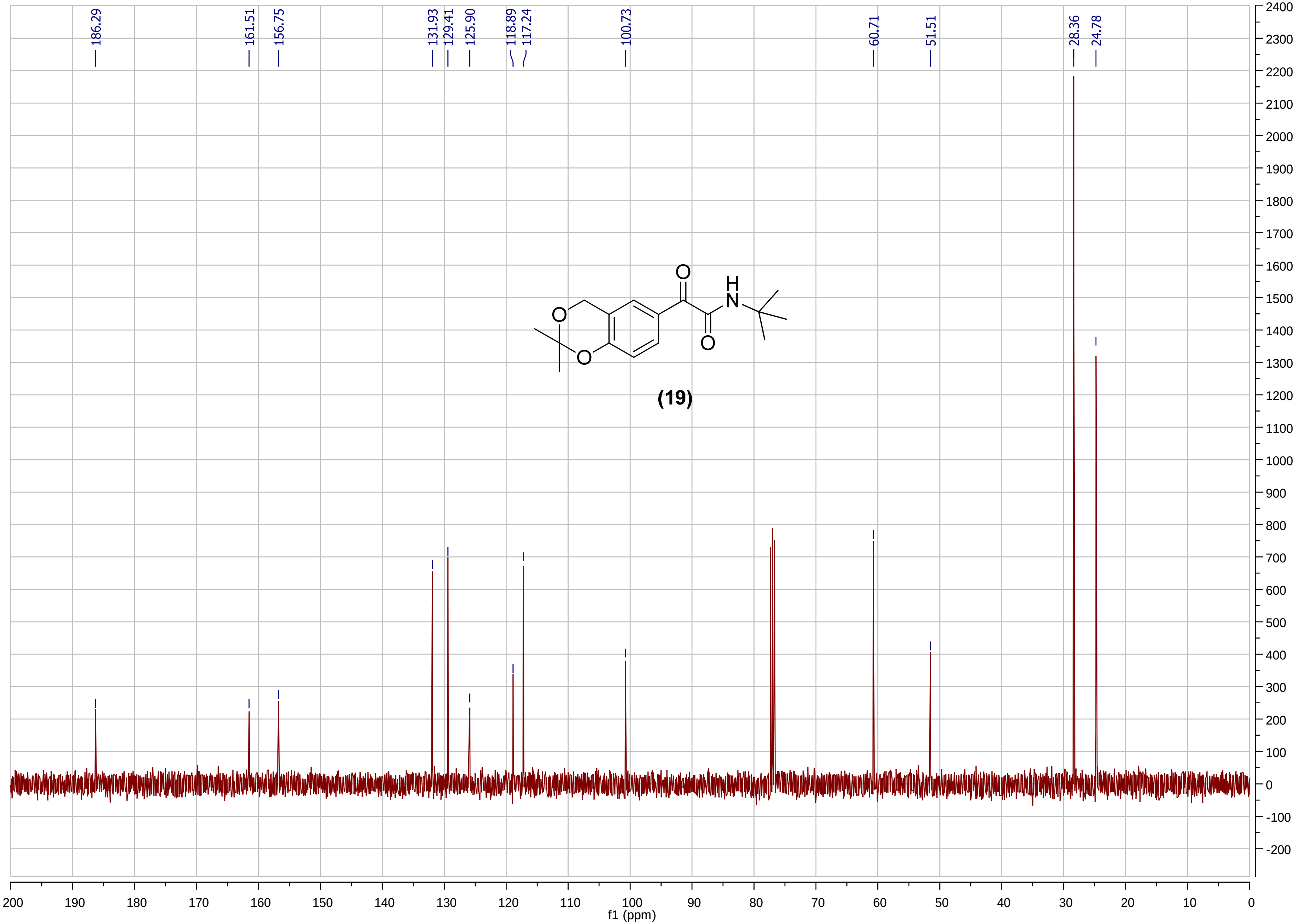
(17)

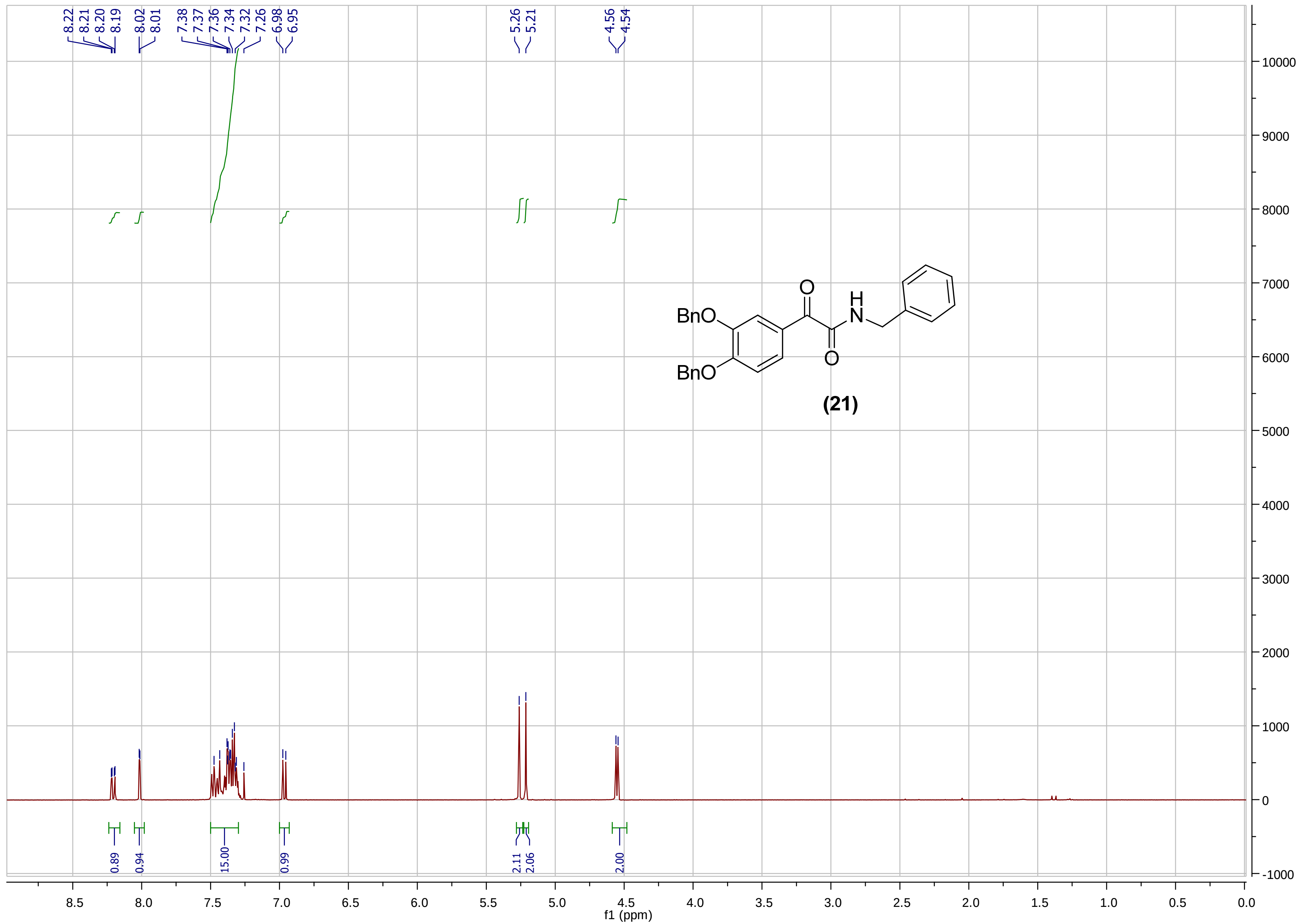

8.82
8.60
8.57
7.26
7.02
7.00
3.98
3.90
1.44
(18)
0.72
0.83
1.73
6.17
9.00
f1 (ppm)

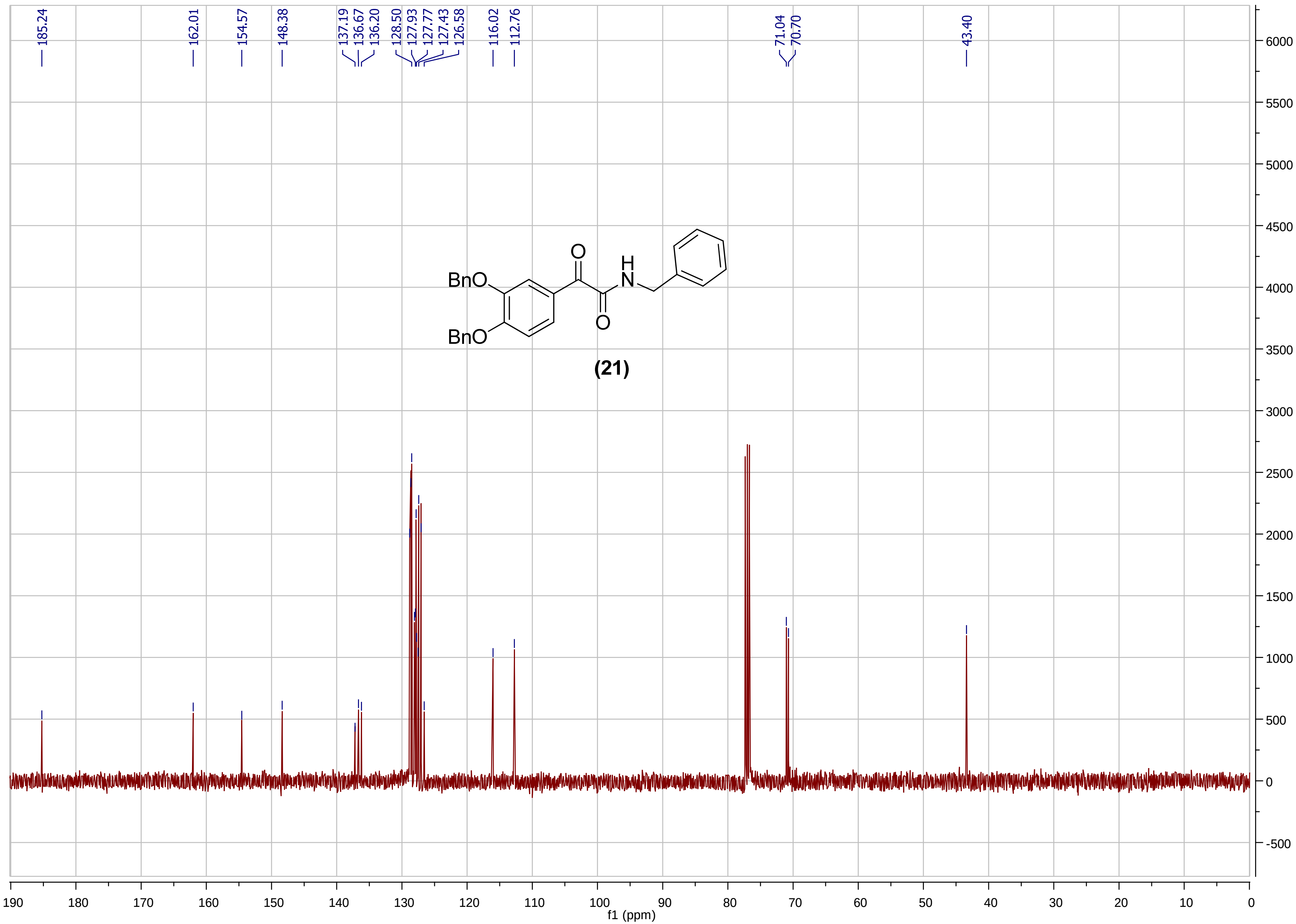


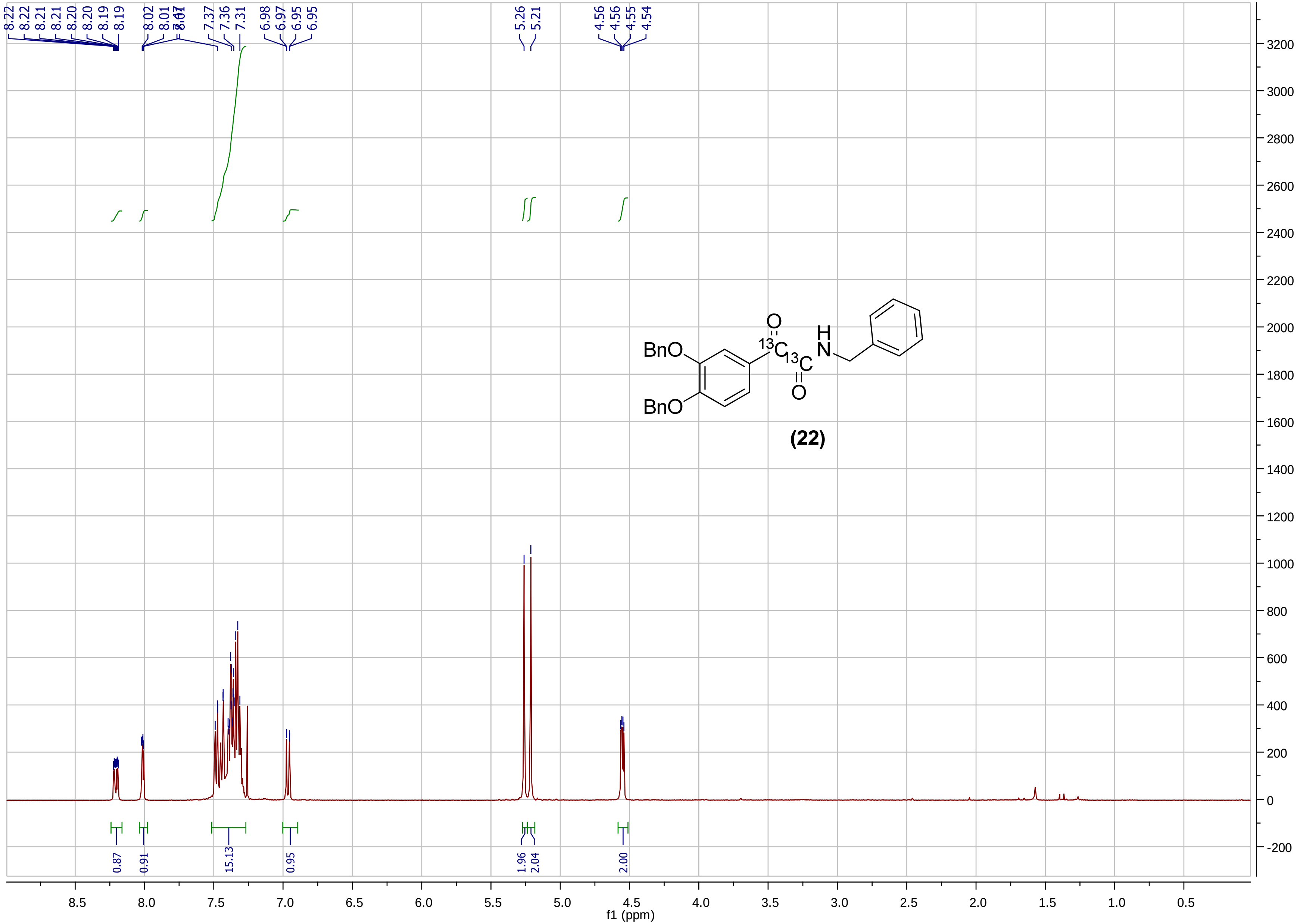
185.72
165.57
163.35
161.01
137.26
135.48
125.78
120.23
111.42
107.90
77.32
77.01
76.69
56.34
52.23
51.59
28.35
(18)
f1 (ppm)

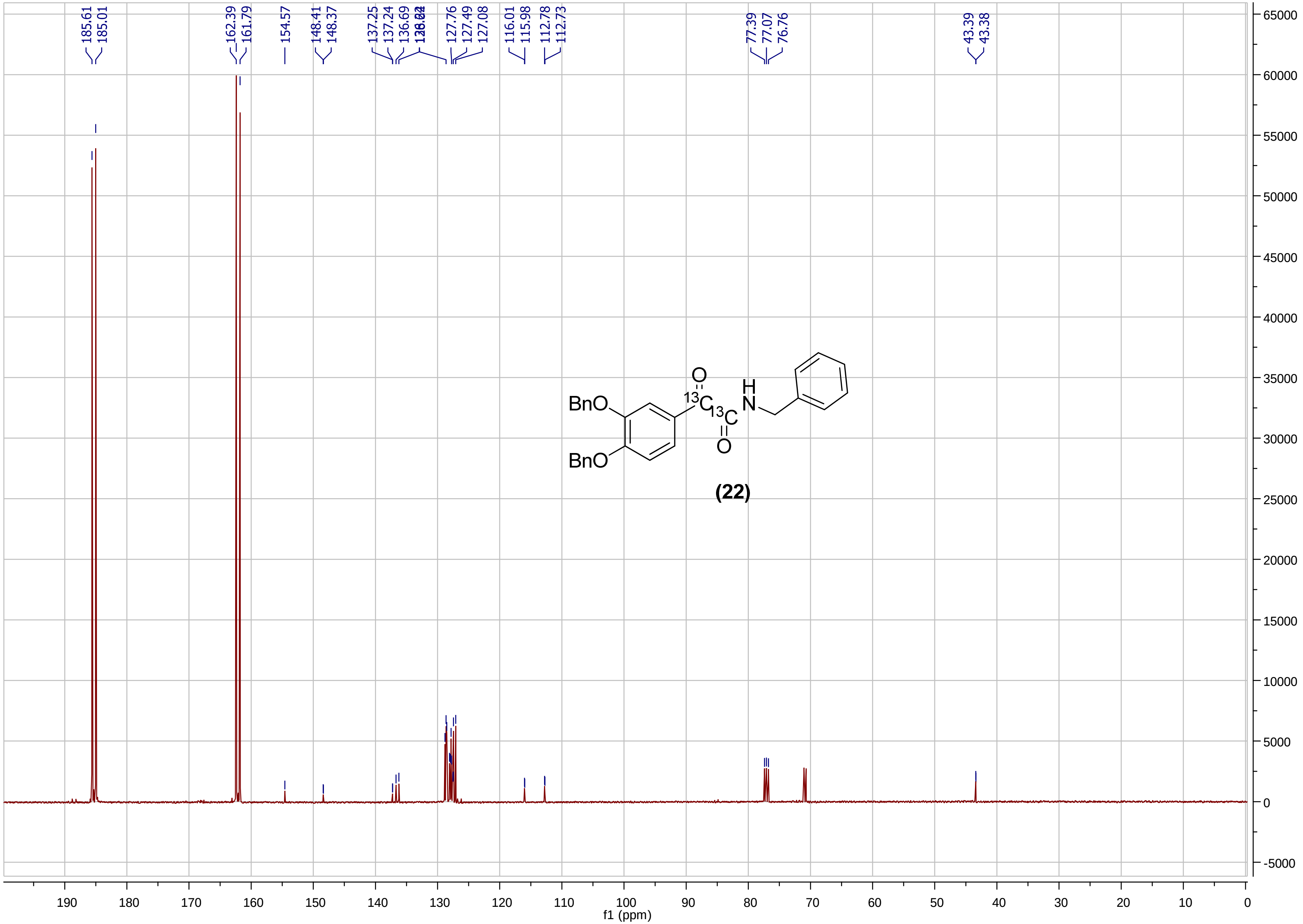

8.20
8.20
8.17
8.17
8.15
8.15
7.00
6.86
6.83
4.87
1.55
1.43
0.98
1.00
0.82
1.00
2.26
6.46
9.56
f1 (ppm)
(19)

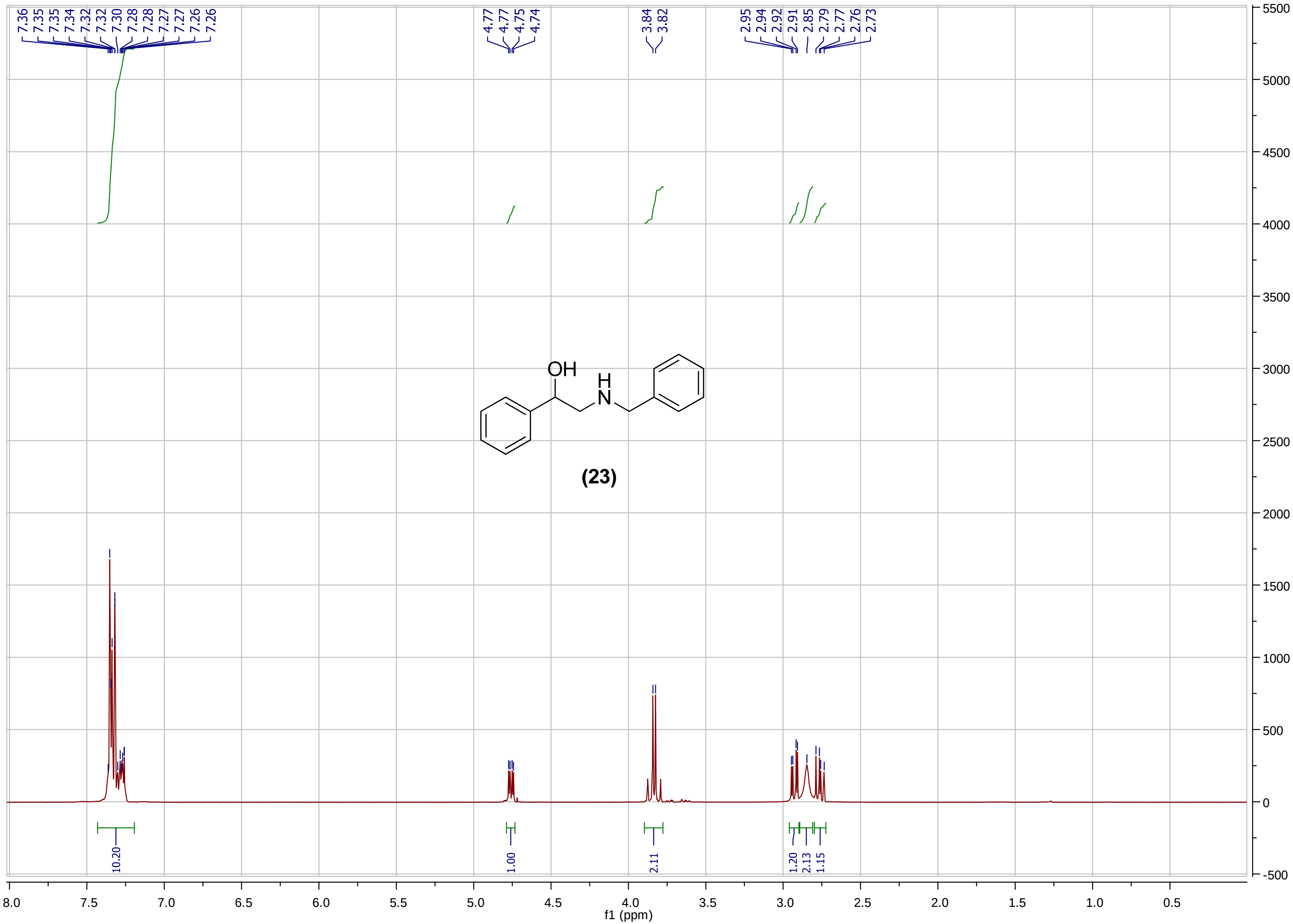

186.29
161.51
156.75
131.93
129.41
125.90
118.89
117.24
100.73
60.71
51.51
28.36
24.78
O
H
N
O
O
O
(19)
f1 (ppm)


8.22
8.21
8.20
8.19
8.02
8.01
7.38
7.37
7.36
7.34
7.32
7.26
6.98
6.95
5.26
5.21
4.56
4.54
BnO
BnO
O
O
H
N
(21)
0.89
0.94
15.00
0.99
2.11
2.06
2.00
f1 (ppm)

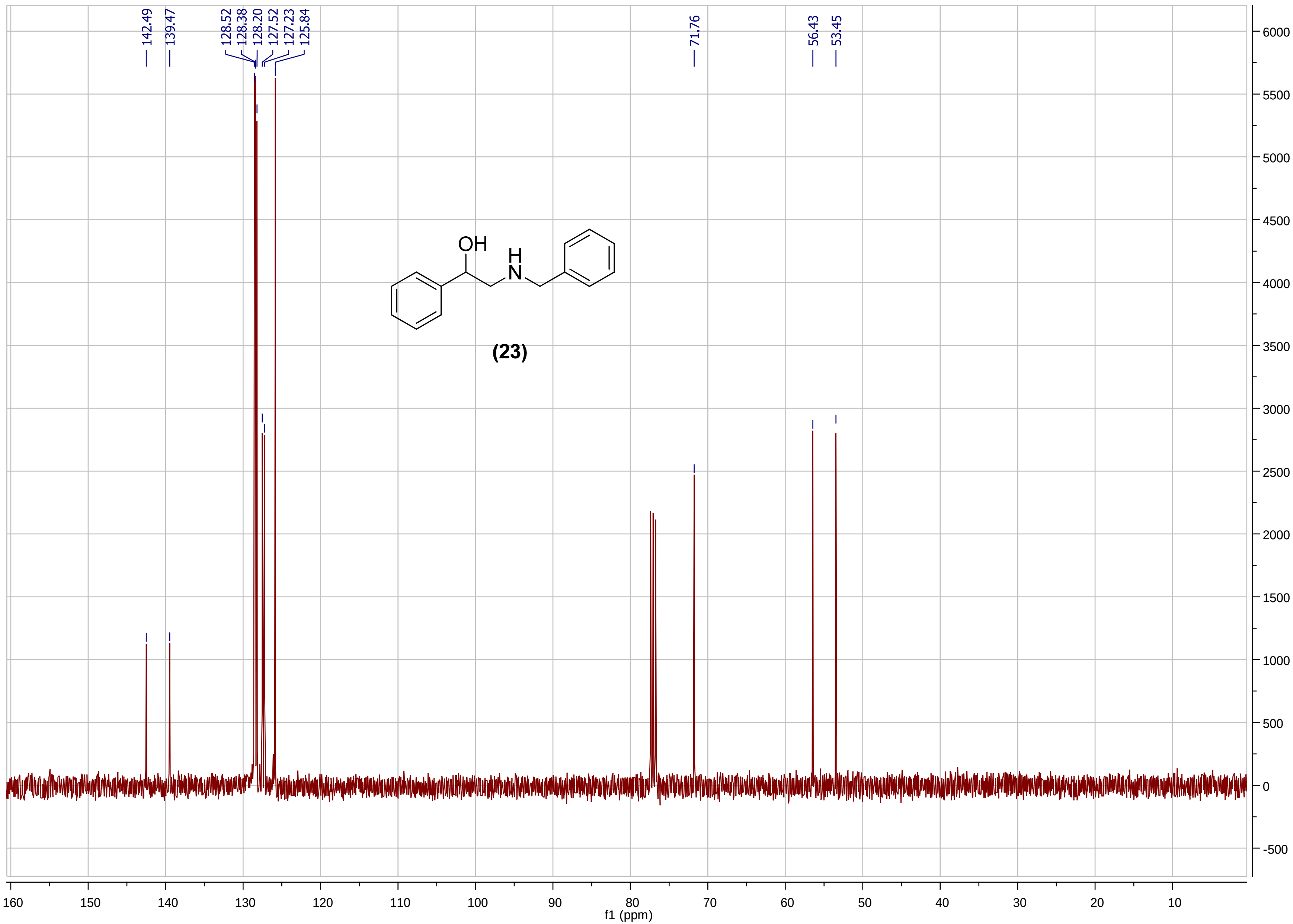

185.24
162.01
154.57
148.38
137.19
136.67
136.20
128.50
127.93
127.77
127.43
126.58
116.02
112.76
71.04
70.70
43.40
BnO
BnO
O
H
N
O
(21)
f1 (ppm)

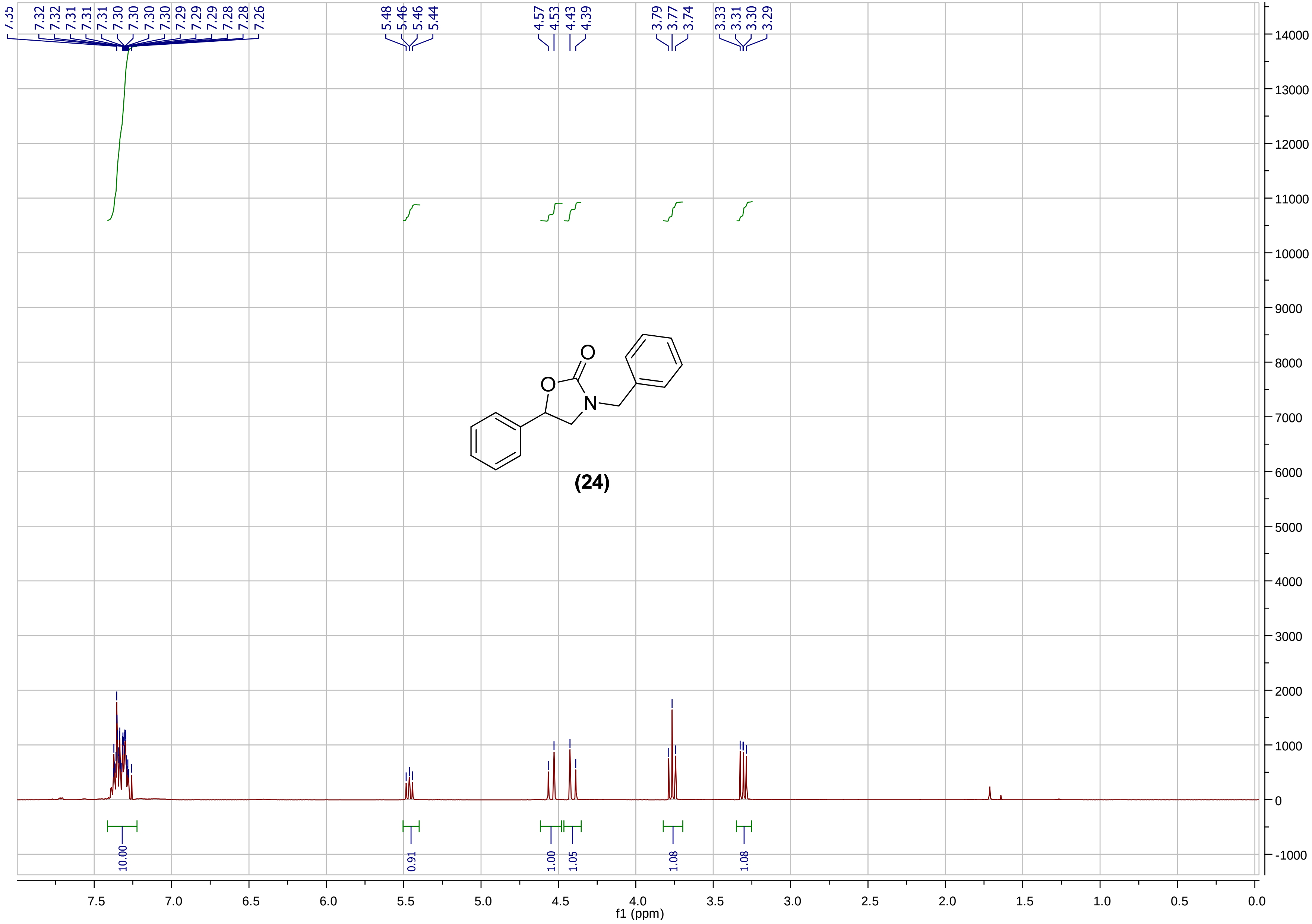


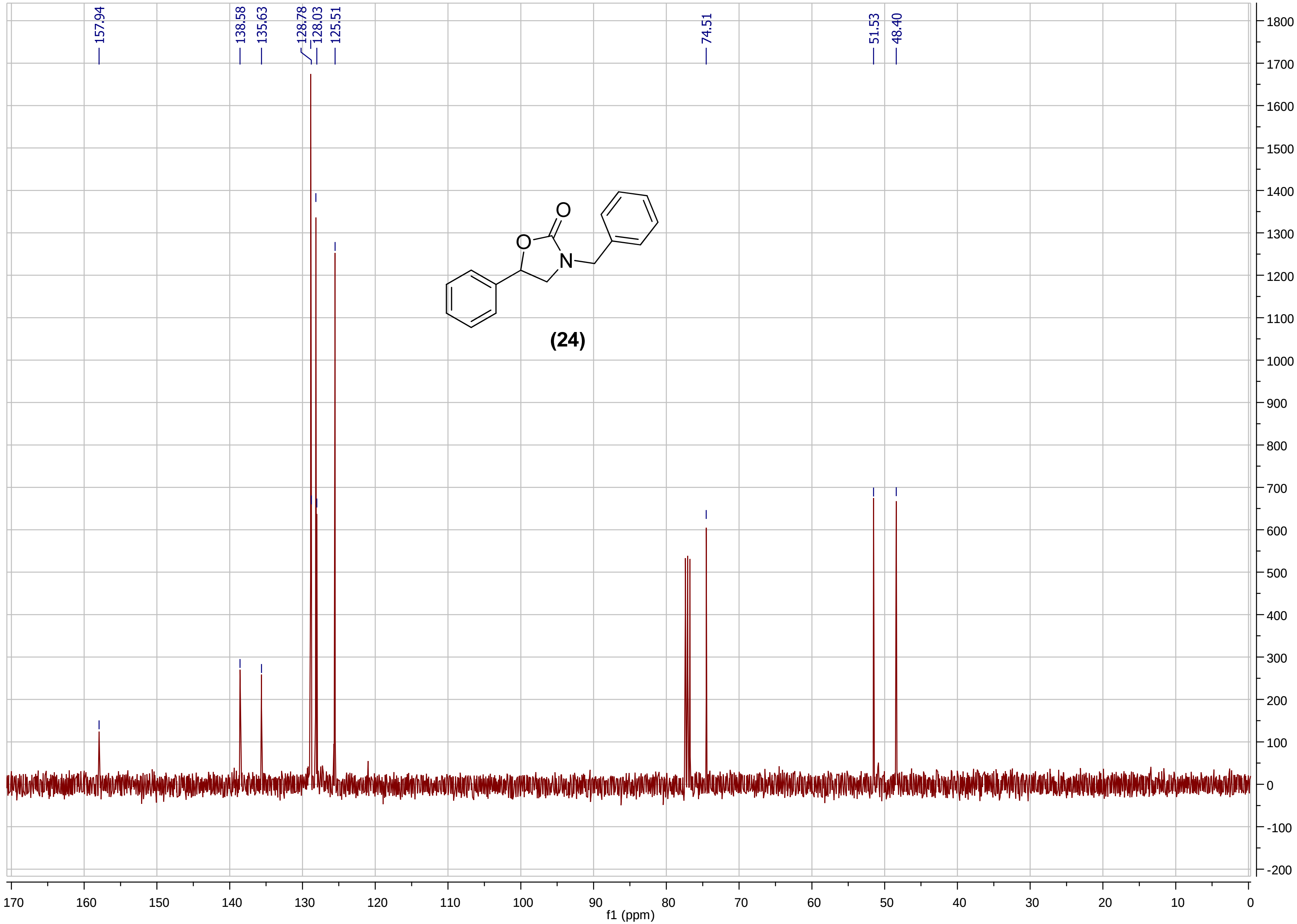

185.61
185.01
162.39
161.79
154.57
148.41
148.37
137.25
137.24
136.69
127.76
127.49
127.08
116.01
115.98
112.78
112.73
77.39
77.07
76.76
43.39
43.38
BnO
BnO
O
^{13}C
^{13}C
O
H
N
(22)
f1 (ppm)

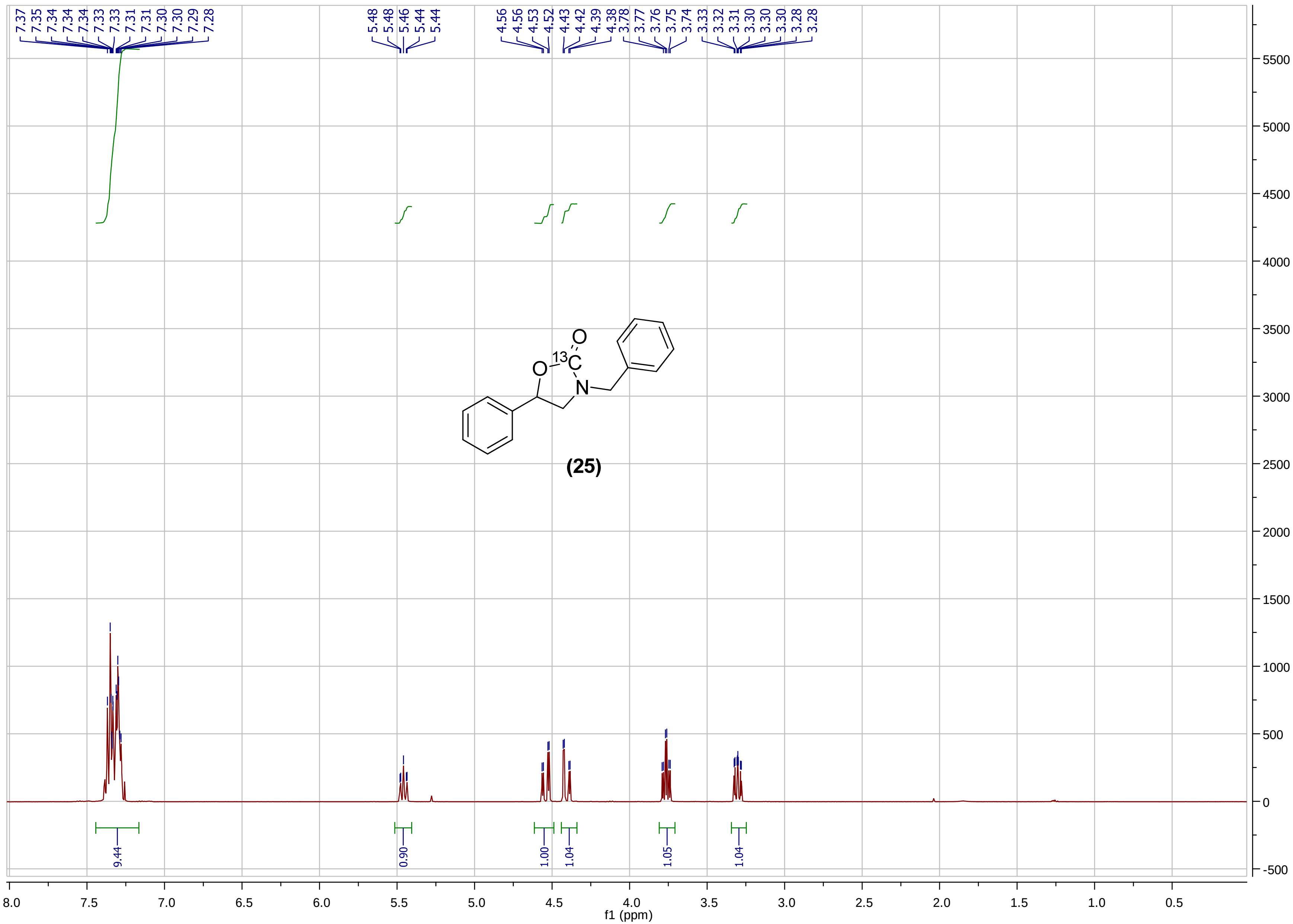


7.36
7.35
7.35
7.34
7.32
7.32
7.30
7.28
7.28
7.27
7.27
7.26
7.26
4.77
4.77
4.75
4.74
3.84
3.82
2.95
2.94
2.92
2.91
2.85
2.79
2.77
2.76
2.73
OH
H
N
(23)
10.20
1.00
2.11
1.20
2.13
1.15
f1 (ppm)

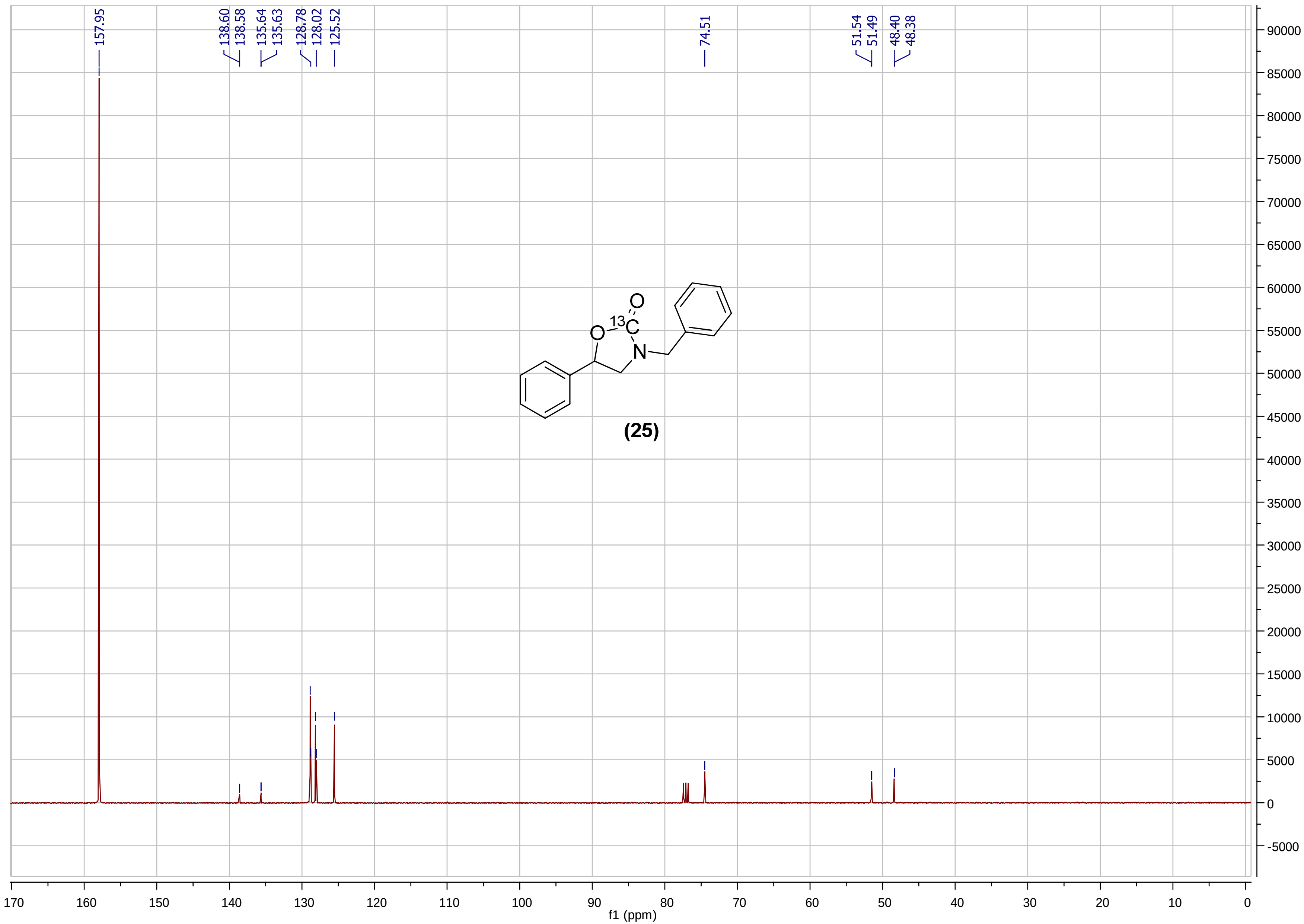

142.49
139.47
128.52
128.38
128.20
127.52
127.23
125.84
71.76
56.43
53.45
OH
H
N
(23)
f1 (ppm)

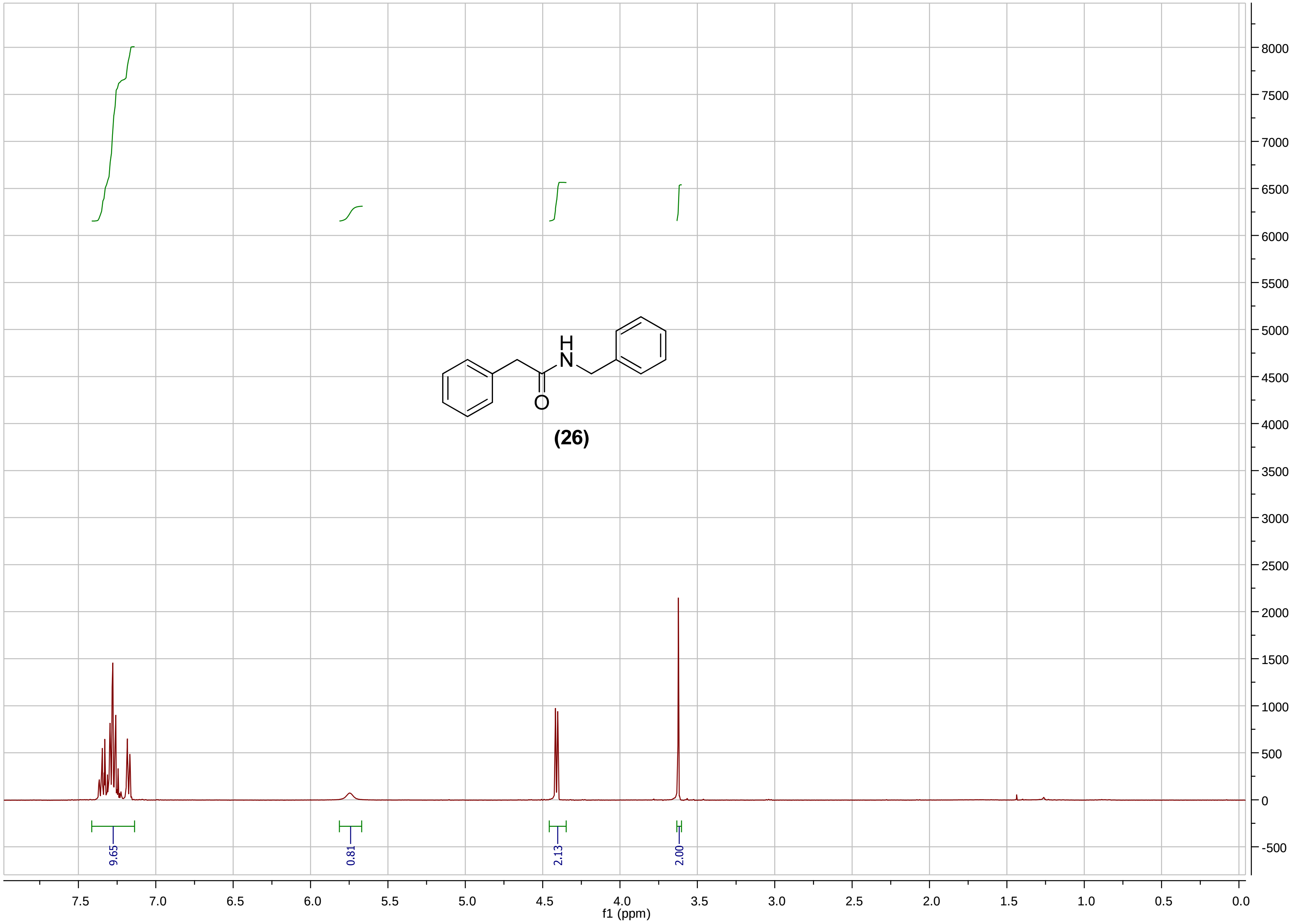

7.35
7.32
7.32
7.31
7.31
7.31
7.30
7.30
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.26
5.48
5.46
5.46
5.44
4.57
4.53
4.43
4.39
3.79
3.77
3.74
3.33
3.31
3.30
3.29
O
O
N
(24)
10.00
0.91
1.00
1.05
1.08
1.08
f1 (ppm)


157.94
138.58
135.63
128.78
128.03
125.51
74.51
51.53
48.40
O
O
N
(24)
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

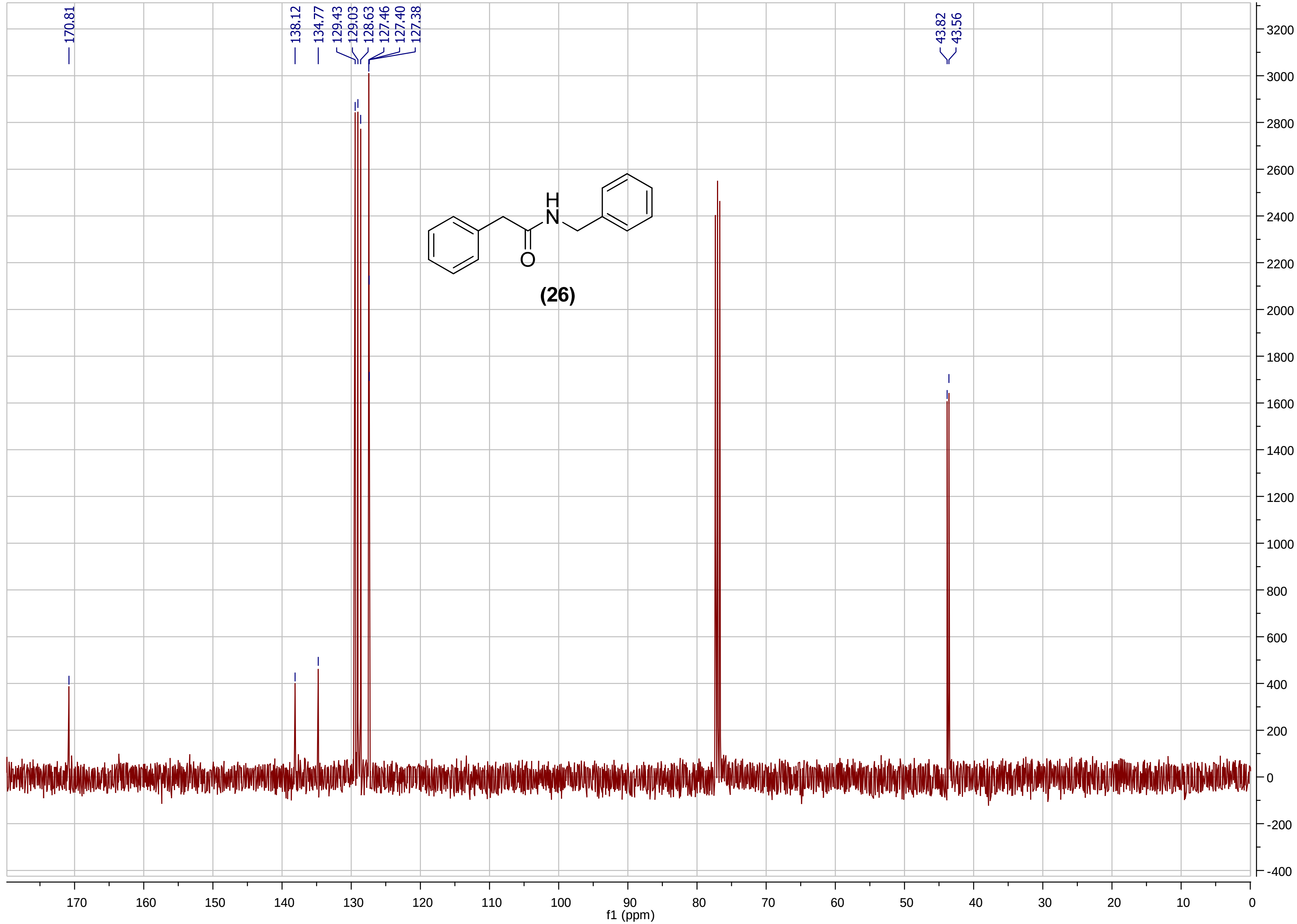


7.37
7.35
7.34
7.34
7.34
7.33
7.33
7.31
7.30
7.30
7.29
7.28
5.48
5.48
5.46
5.44
5.44
4.56
4.56
4.53
4.52
4.43
4.42
4.39
4.38
3.78
3.77
3.76
3.75
3.74
3.33
3.32
3.31
3.30
3.30
3.30
3.28
3.28
O
^{13}C
O
N
(25)
9.44
0.90
1.00
1.04
1.05
1.04
f1 (ppm)

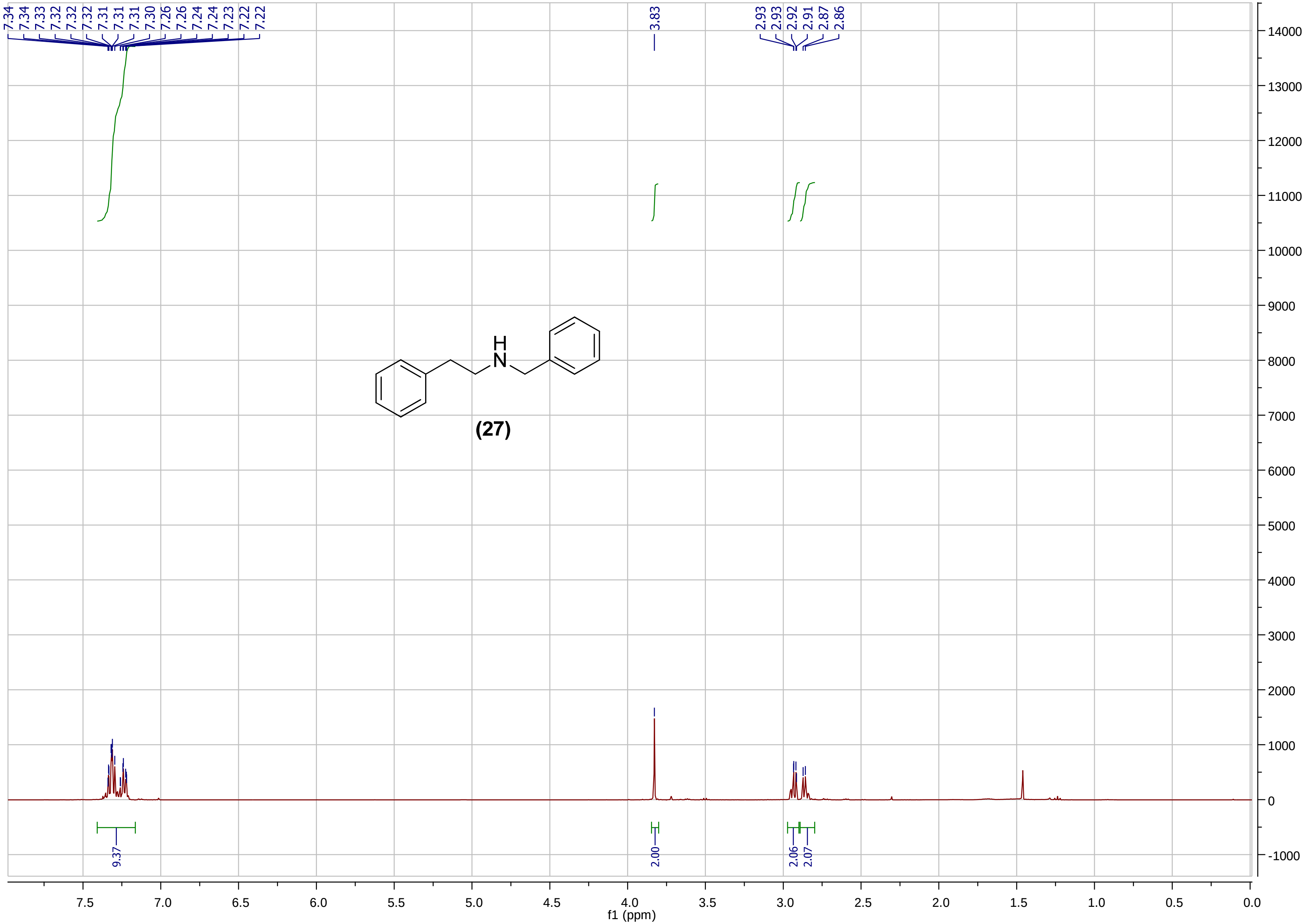

157.95
138.60
138.58
135.64
135.63
128.78
128.02
125.52
74.51
51.54
51.49
48.40
48.38
O
13C
O
N
(25)
f1 (ppm)

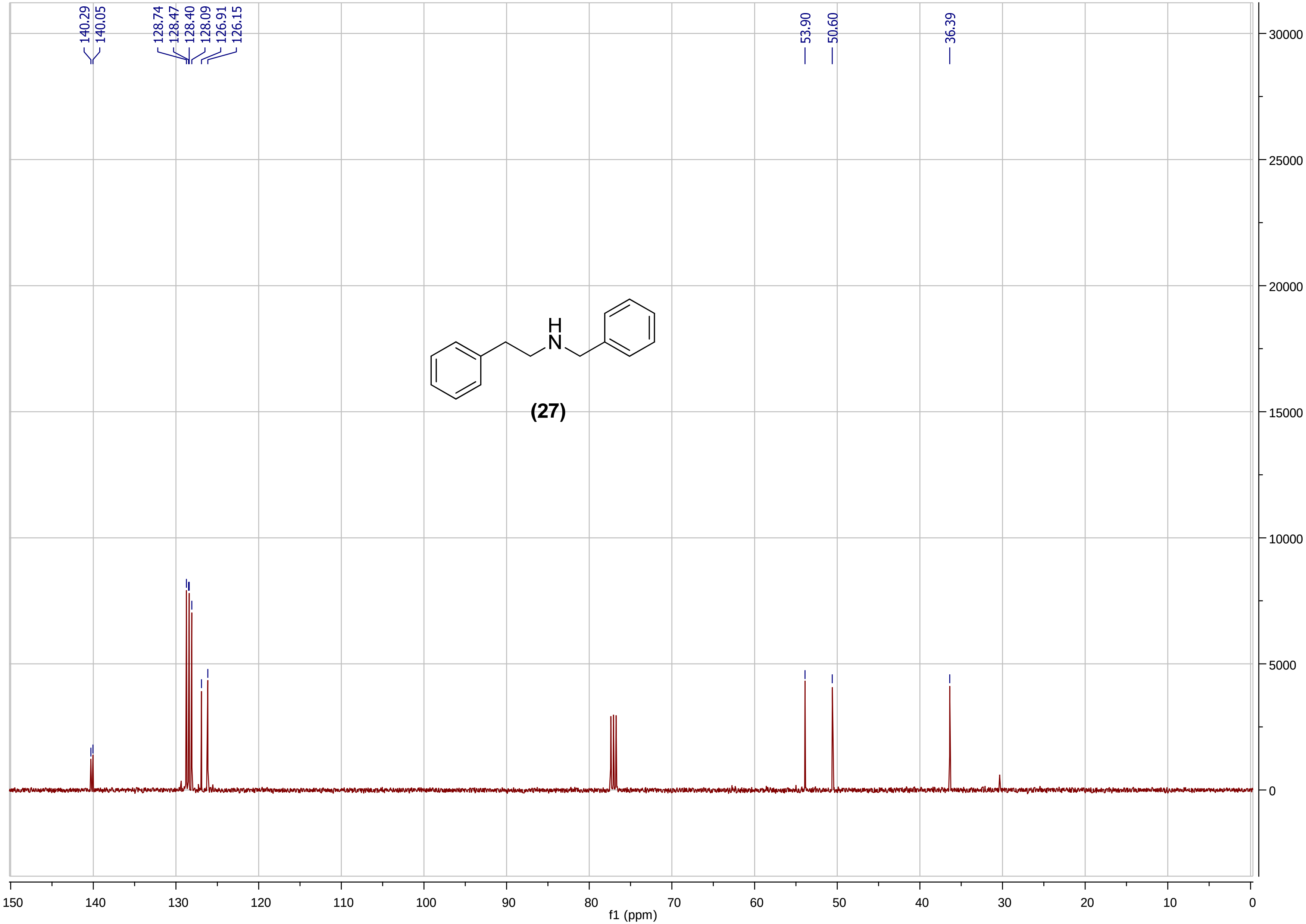


(26)
9.65
0.81
2.13
2.00
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

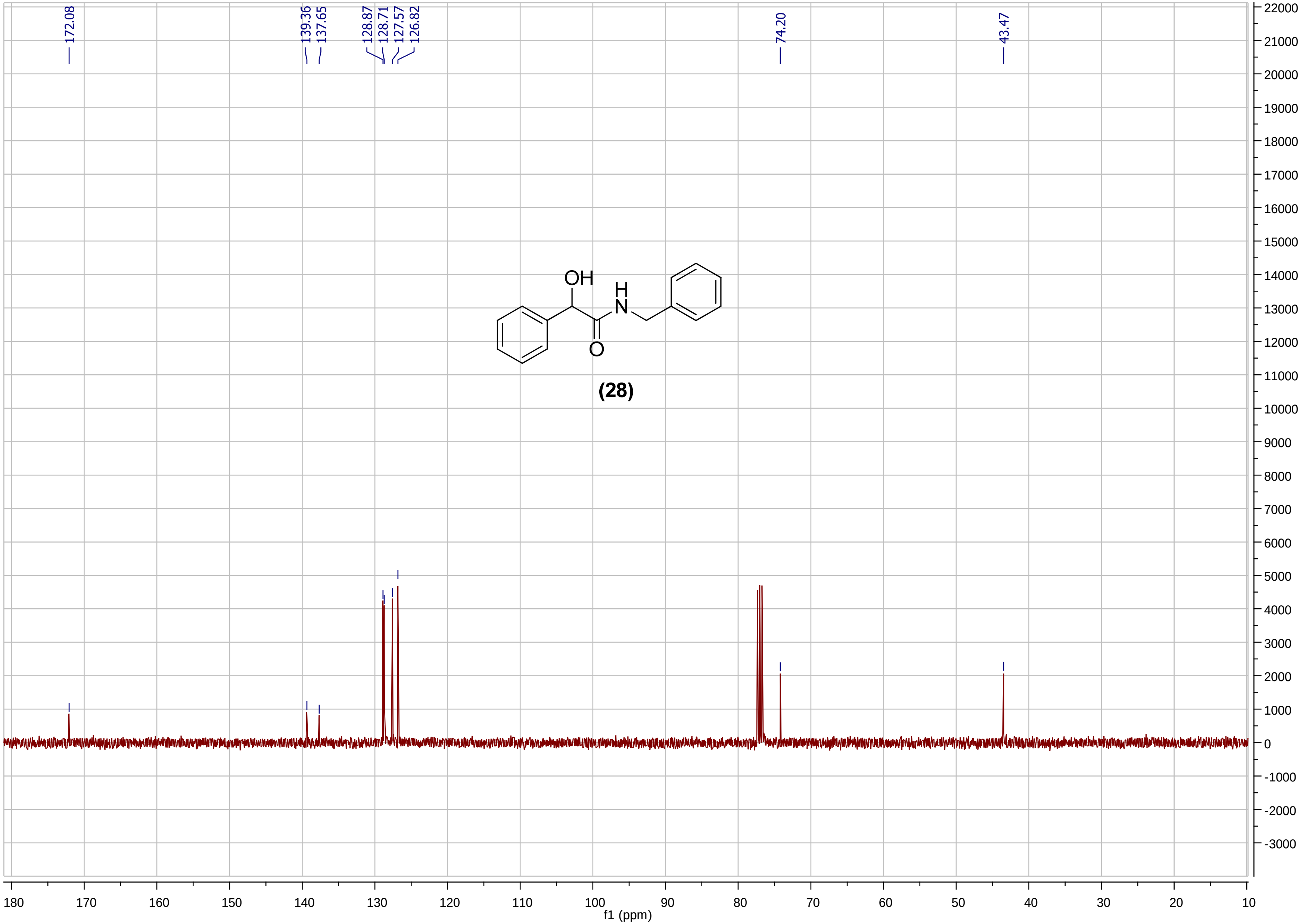

170.81
138.12
134.77
129.43
129.03
128.63
127.46
127.40
127.38
43.82
43.56
f1 (ppm)

(26)

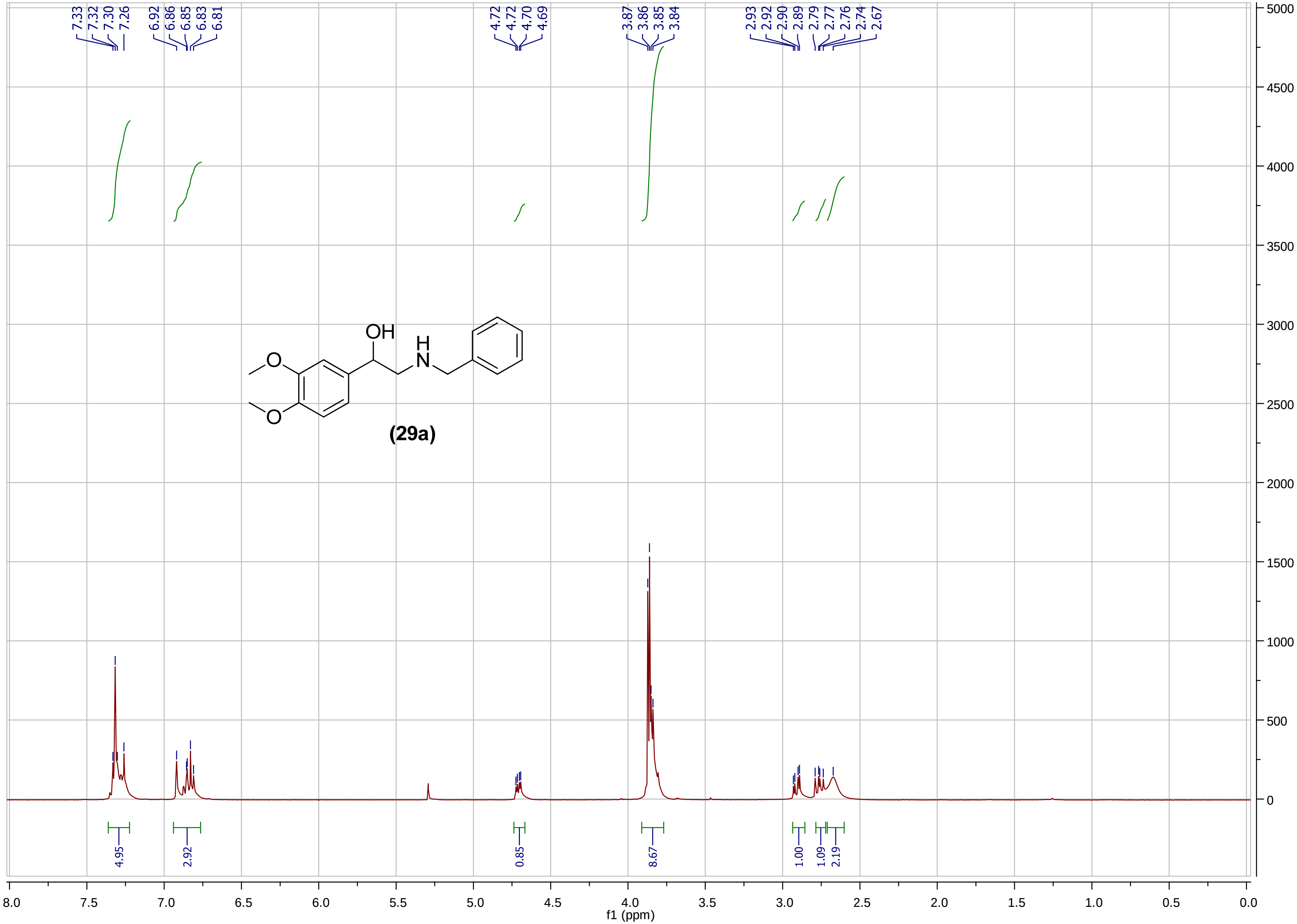

7.34
7.34
7.33
7.32
7.32
7.32
7.31
7.31
7.31
7.30
7.26
7.26
7.24
7.24
7.23
7.22
7.22
3.83
2.93
2.93
2.92
2.91
2.87
2.86
H
N
(27)
9.37
2.00
2.06
2.07
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

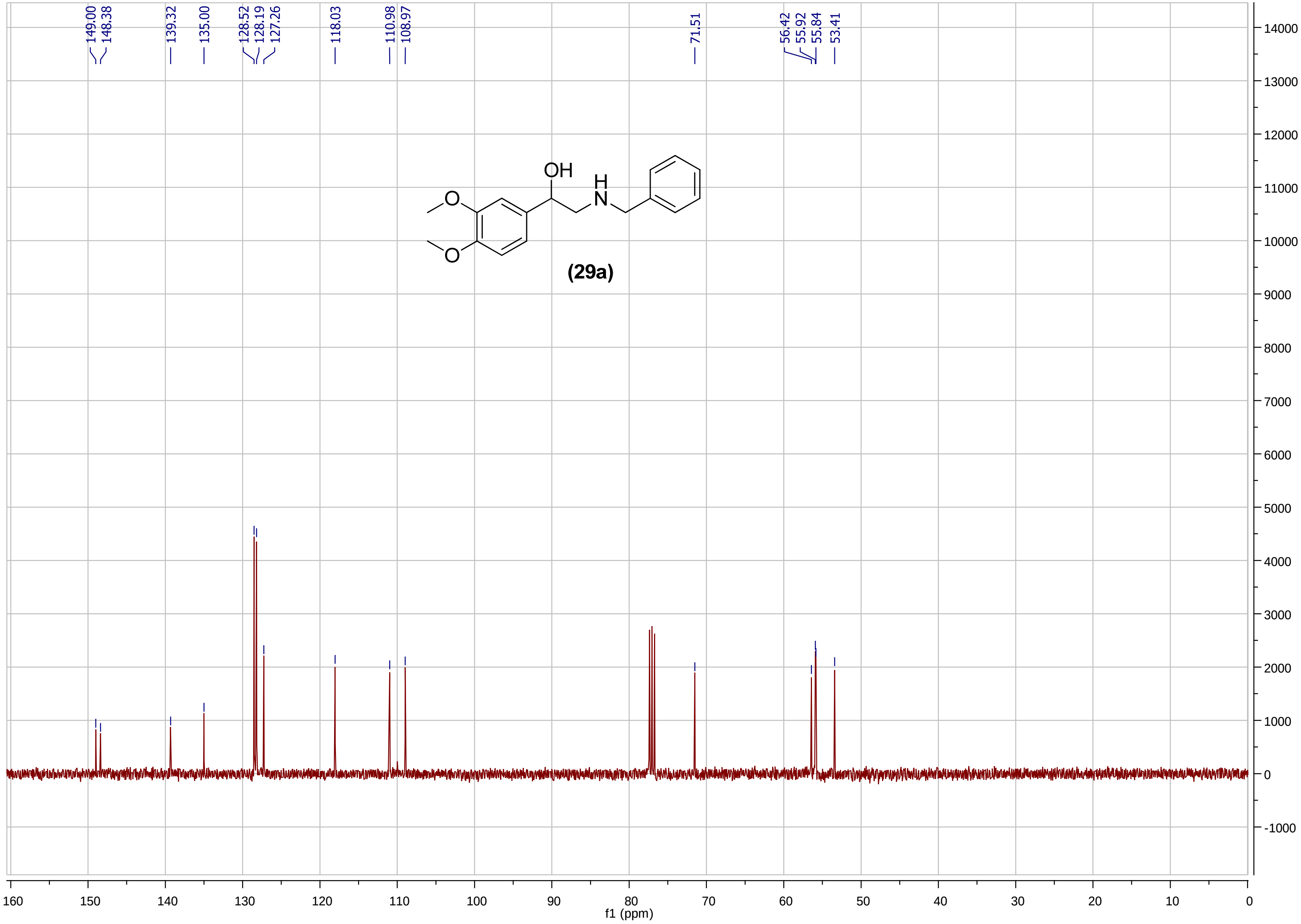

140.29
140.05
128.74
128.47
128.40
128.09
126.91
126.15
53.90
50.60
36.39
H
N
(27)
30000
25000
20000
15000
10000
5000
0
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

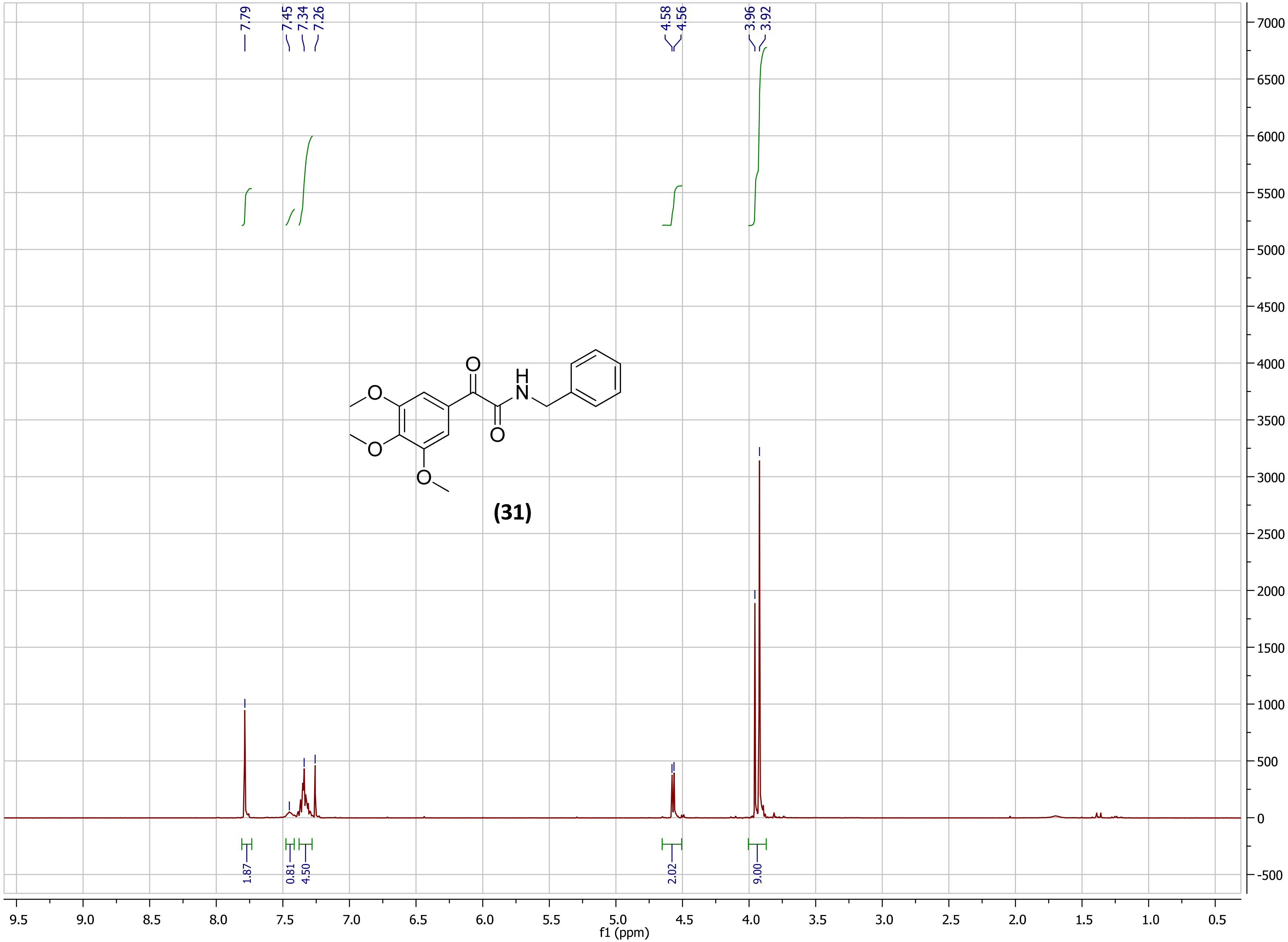

7.40
7.38
7.36
7.36
7.31
7.29
7.19
7.19
7.19
7.17
7.17
7.17
6.42
5.08
4.47
4.46
4.45
4.43
OH
H
N
O
(28)
7.89
2.01
0.87
1.00
2.28
f1 (ppm)



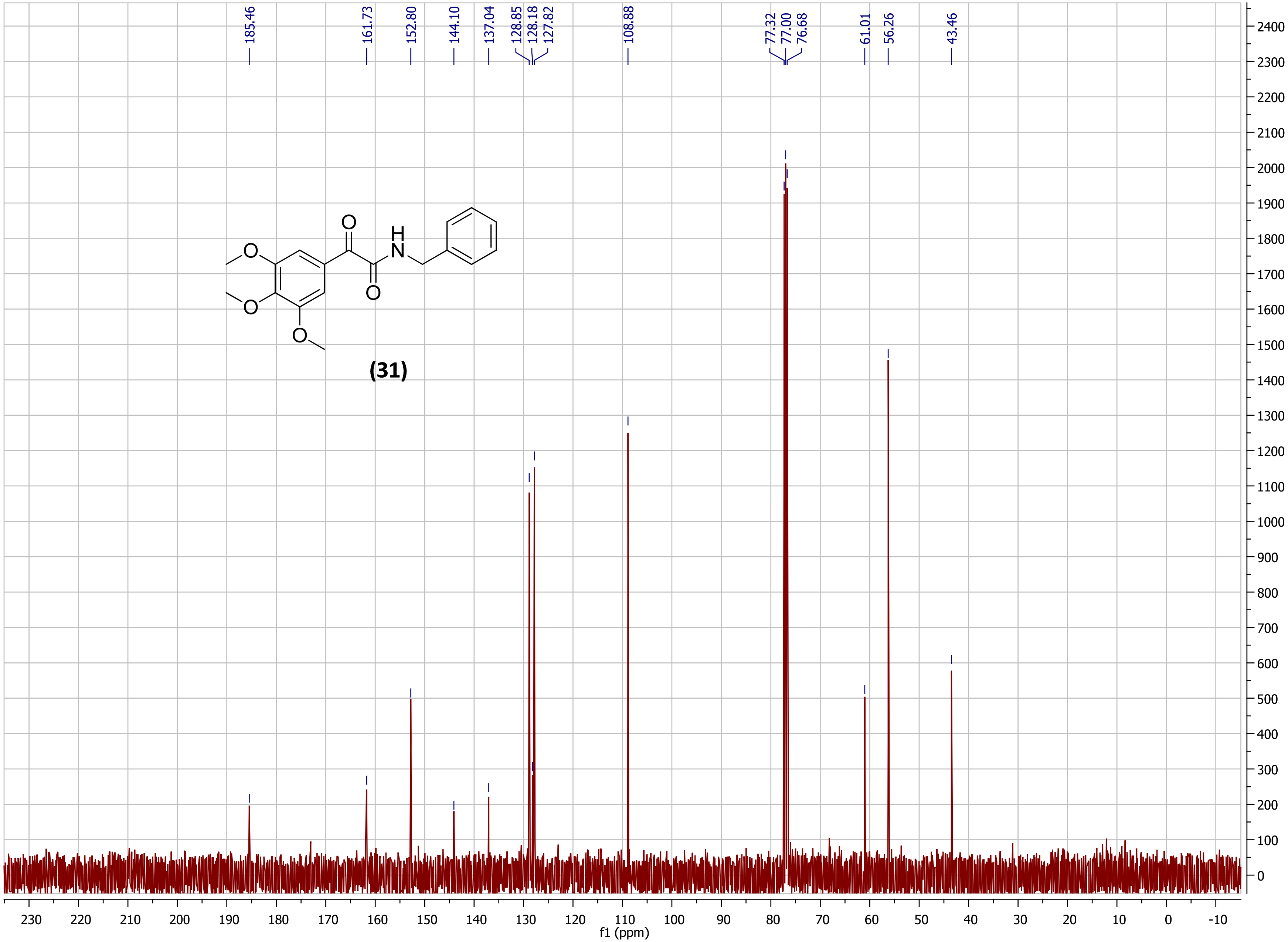
172.08
139.36
137.65
128.87
128.71
127.57
126.82
74.20
43.47
OH
H
N
O
(28)
f1 (ppm)

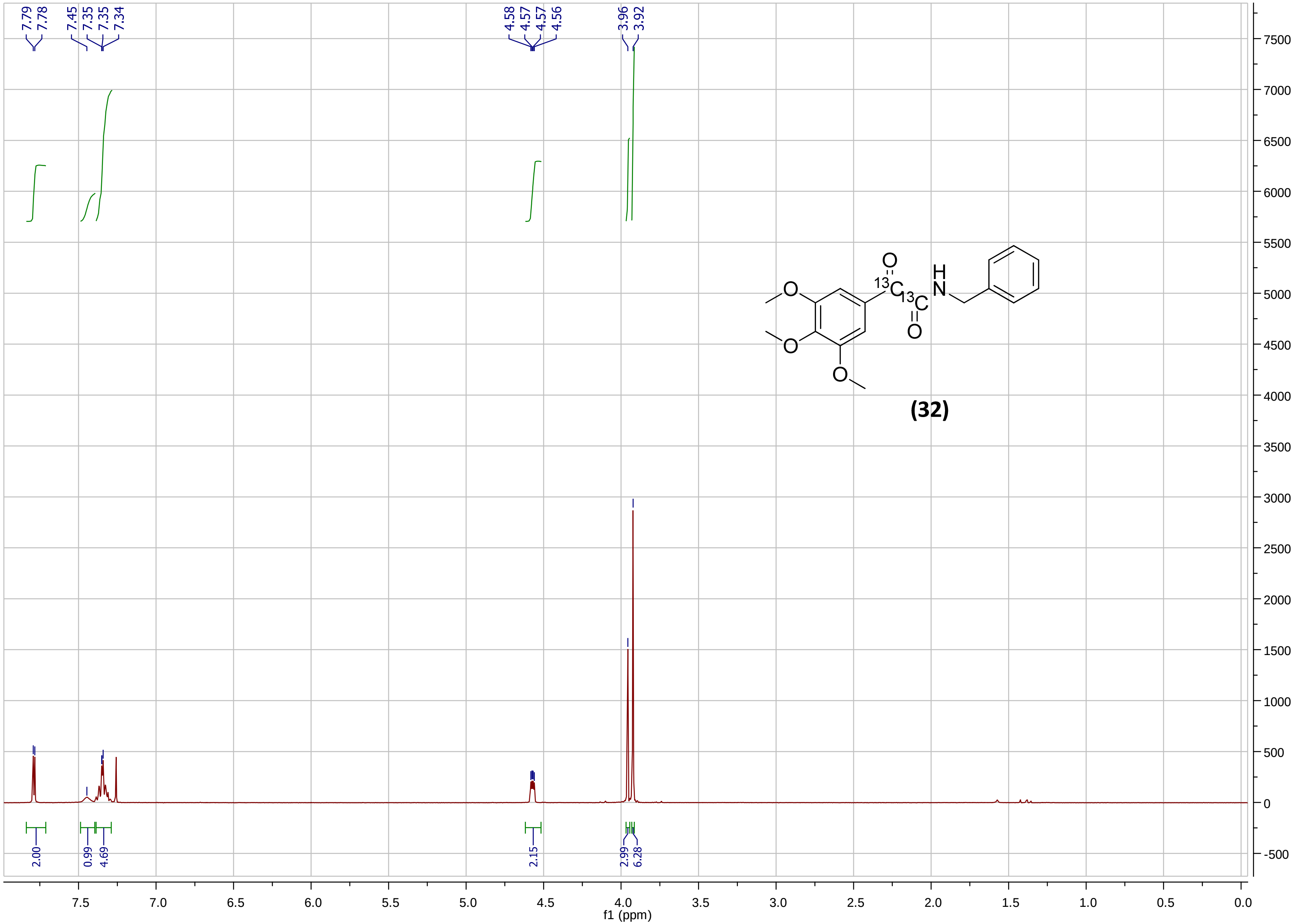

7.33
7.32
7.30
7.26
6.92
6.86
6.85
6.83
6.81
4.72
4.72
4.70
4.69
3.87
3.86
3.85
3.84
2.93
2.92
2.90
2.89
2.79
2.77
2.76
2.74
2.67
OH
H
N
O
O
(29a)
4.95
2.92
0.85
8.67
1.00
1.09
2.19
f1 (ppm)


149.00
148.38
139.32
135.00
128.52
128.19
127.26
118.03
110.98
108.97
71.51
56.42
55.92
55.84
53.41
OH
H
N
O
O
(29a)
f1 (ppm)

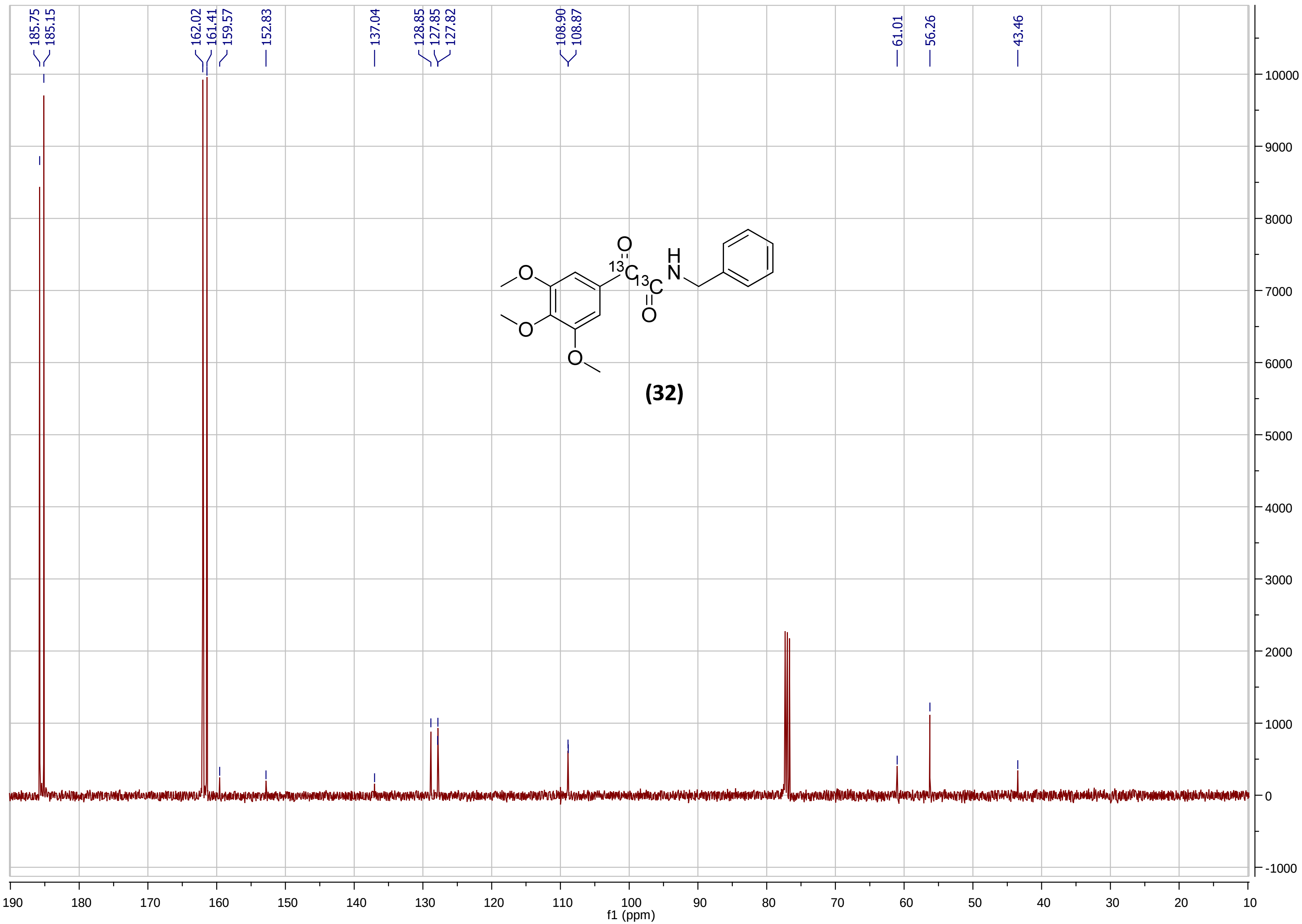


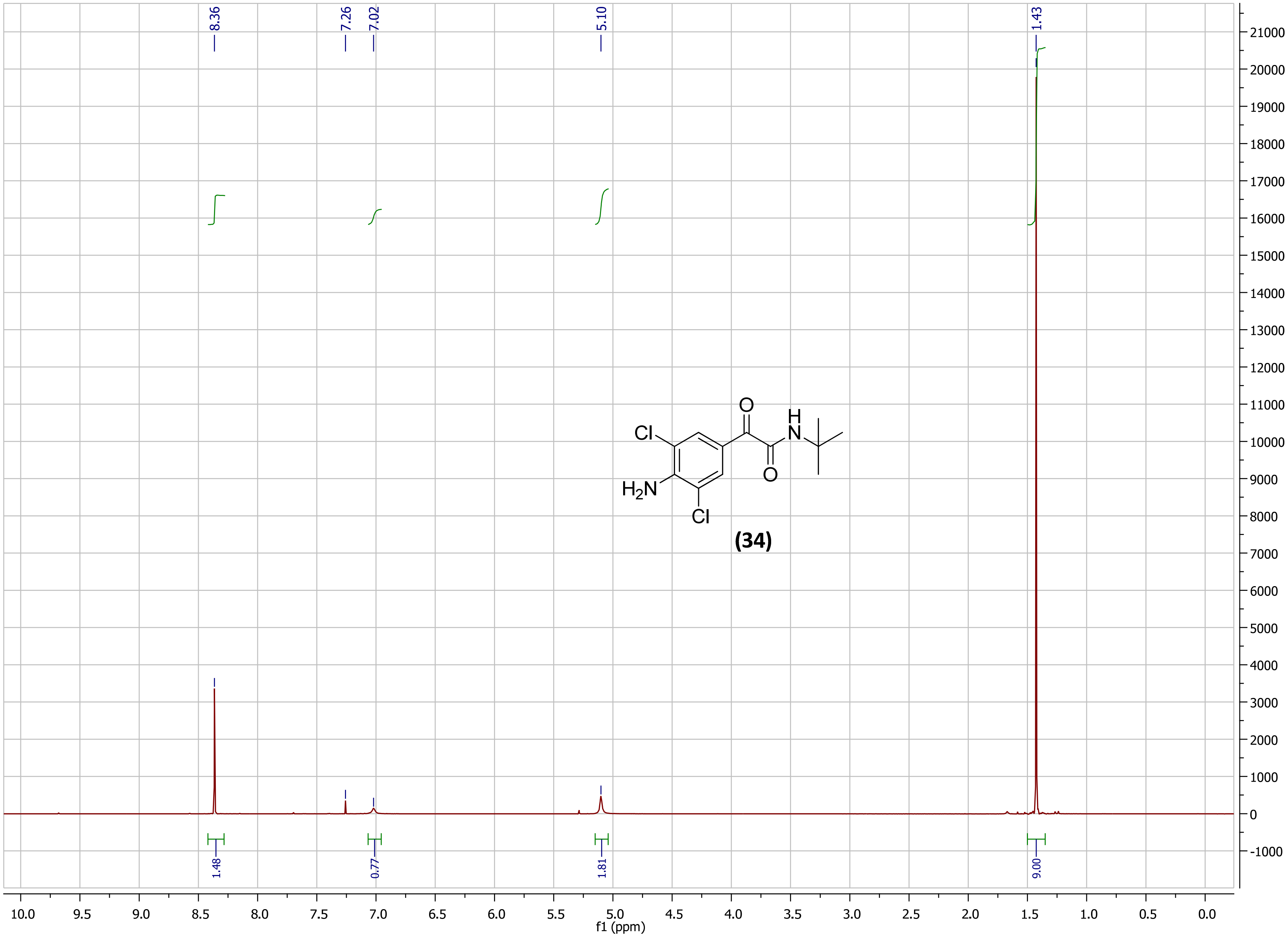
(31)

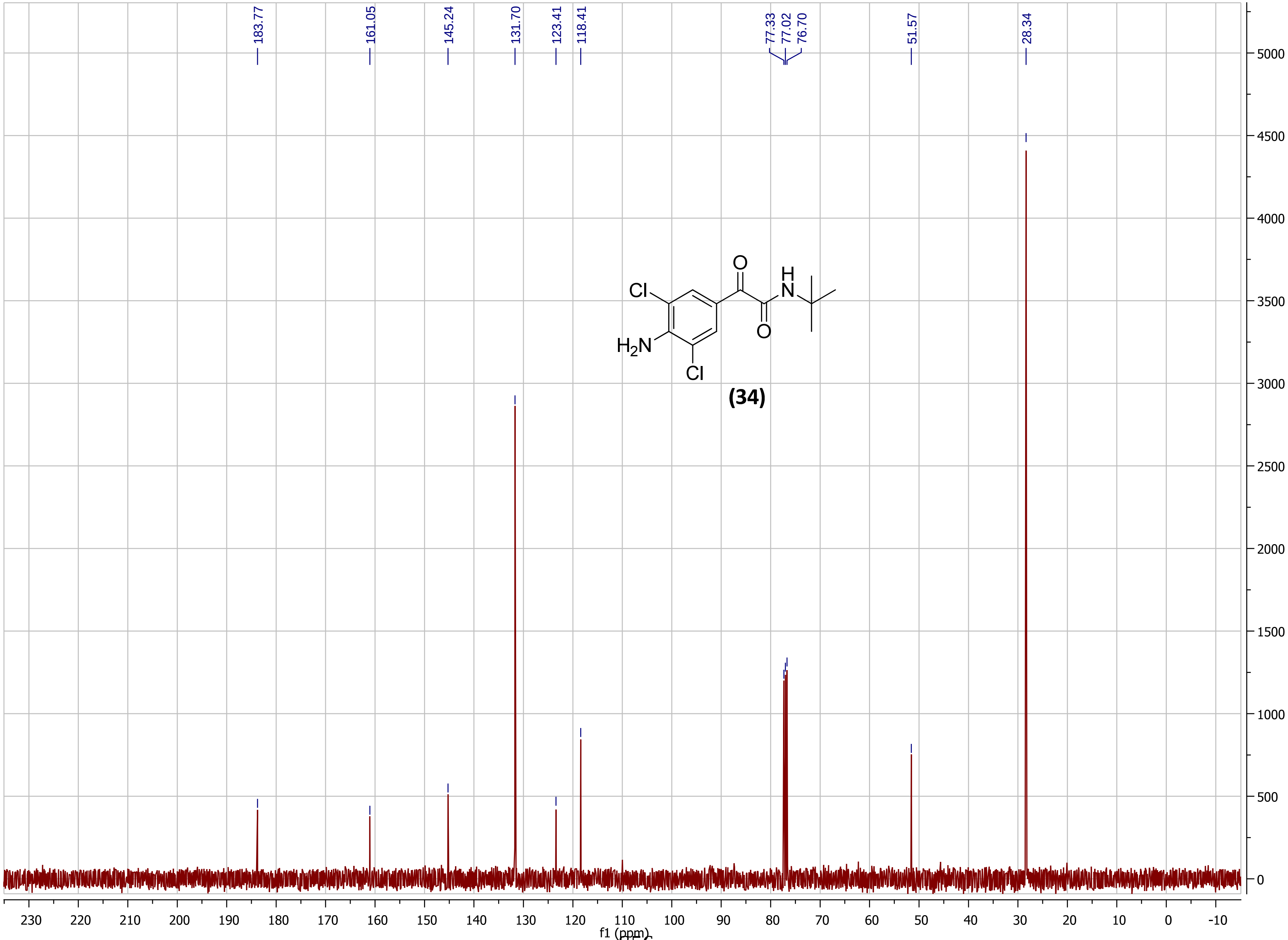

185.46
161.73
152.80
144.10
137.04
128.85
128.18
127.82
108.88
77.32
77.00
76.68
61.01
56.26
43.46
(31)
f1 (ppm)

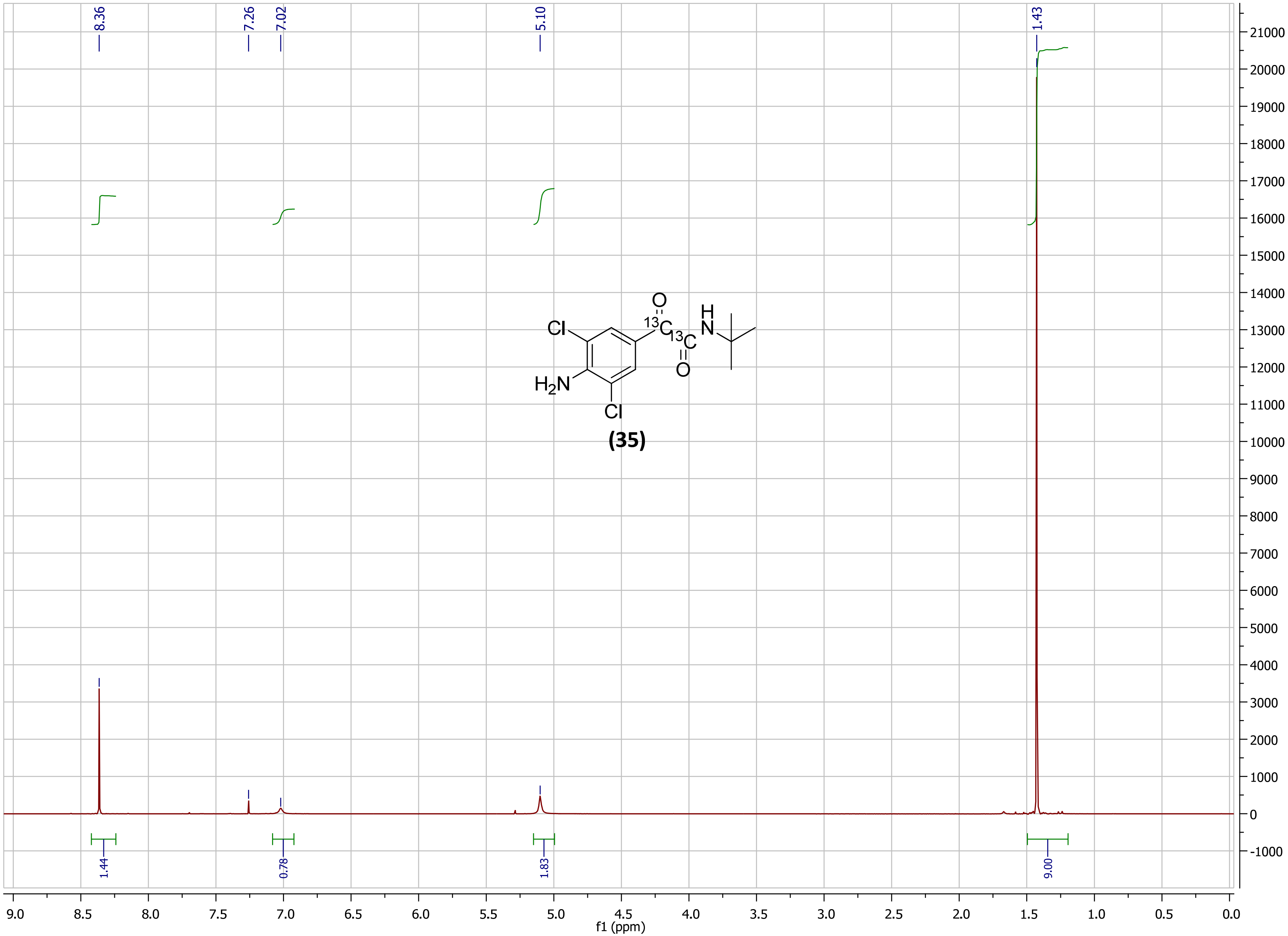


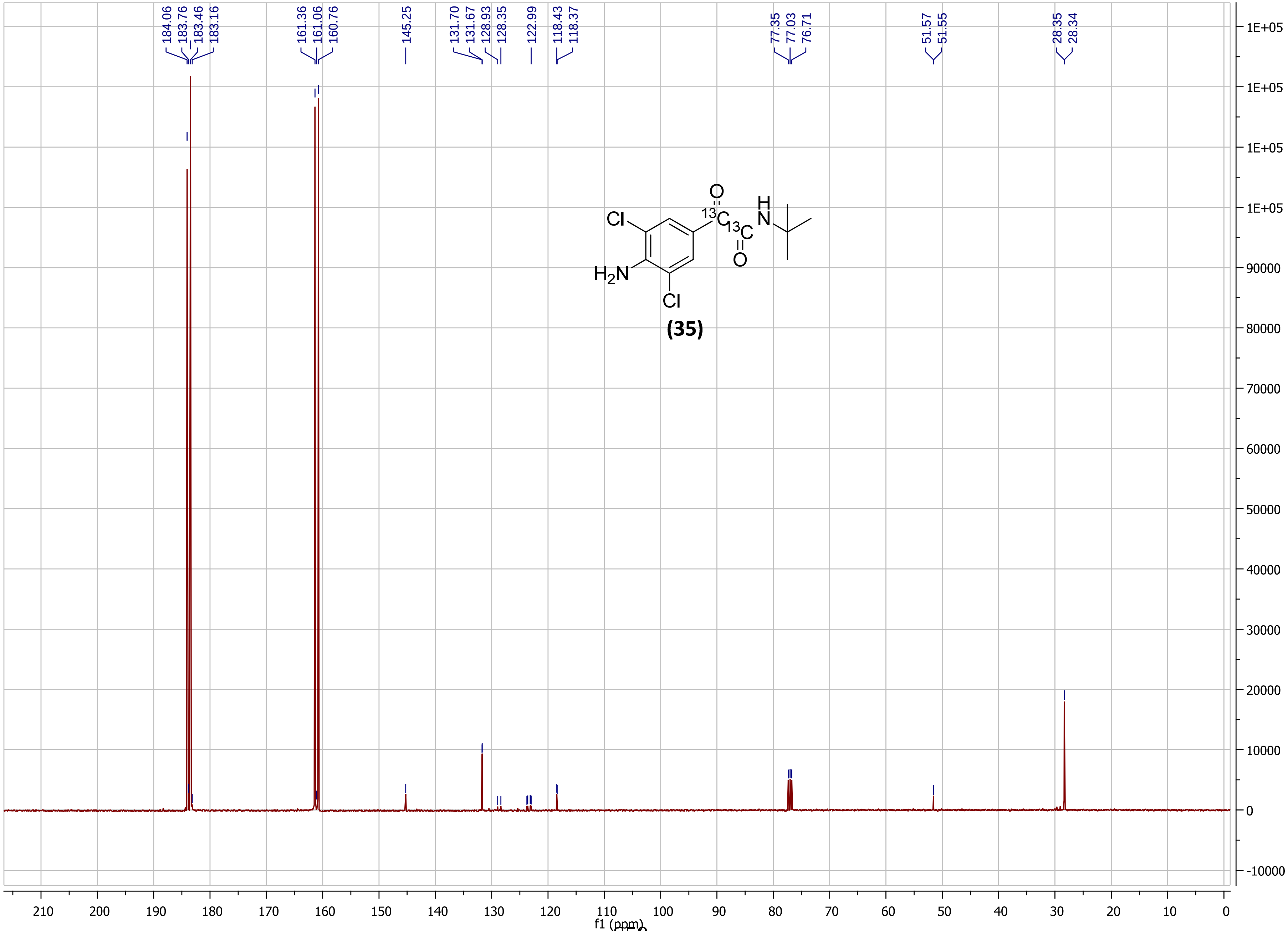
7.79
7.78
7.45
7.35
7.35
7.34
4.58
4.57
4.57
4.56
3.96
3.92
2.00
0.99
4.69
2.15
2.99
6.28
(32)
f1 (ppm)


185.75
185.15
162.02
161.41
159.57
152.83
137.04
128.85
127.85
127.82
108.90
108.87
61.01
56.26
43.46
(32)
f1 (ppm)

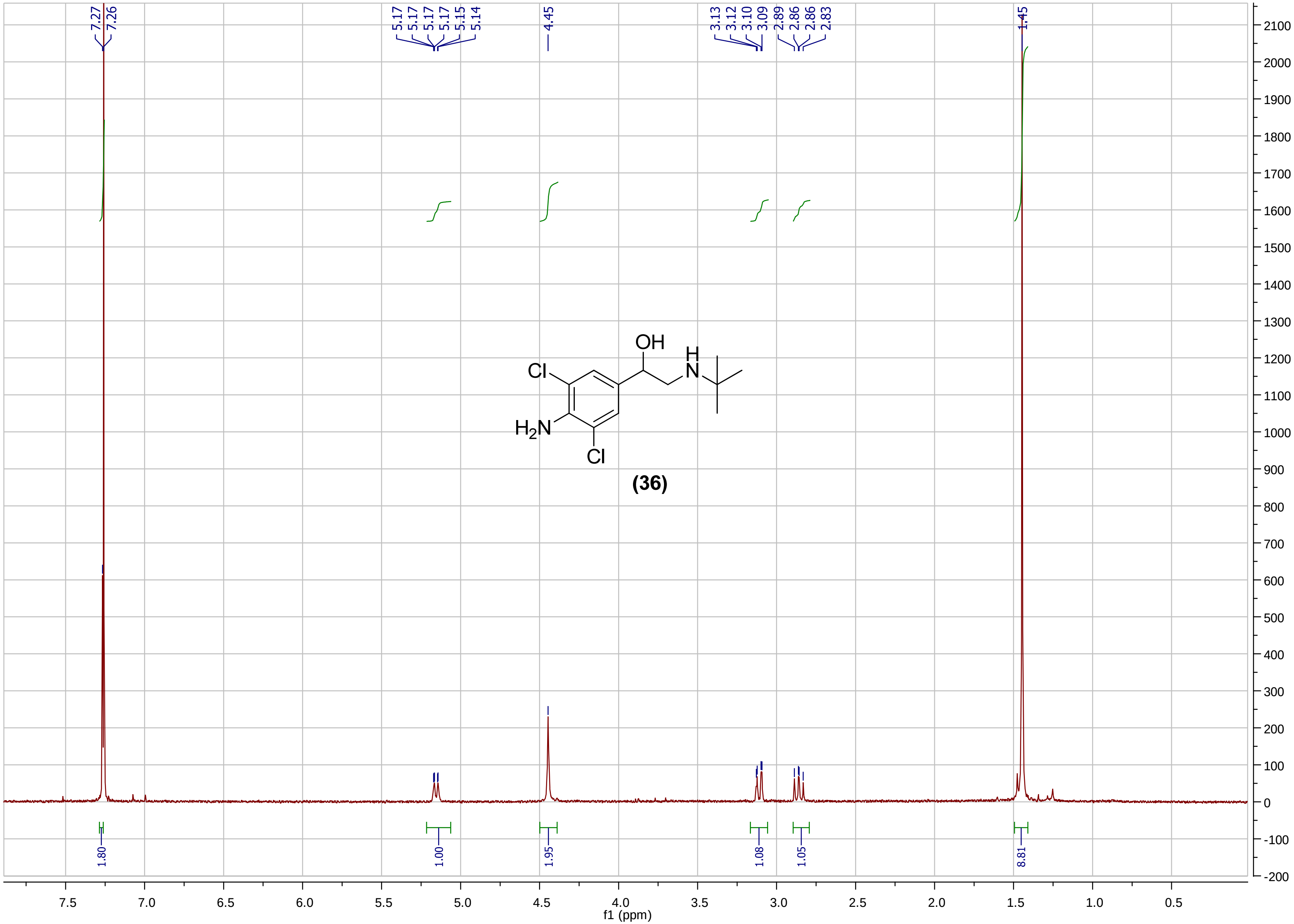

8.36
7.26
7.02
5.10
1.43
1.48
0.77
1.81
9.00
f1 (ppm)
Cl
H2N
Cl
O
O
H
N
(34)

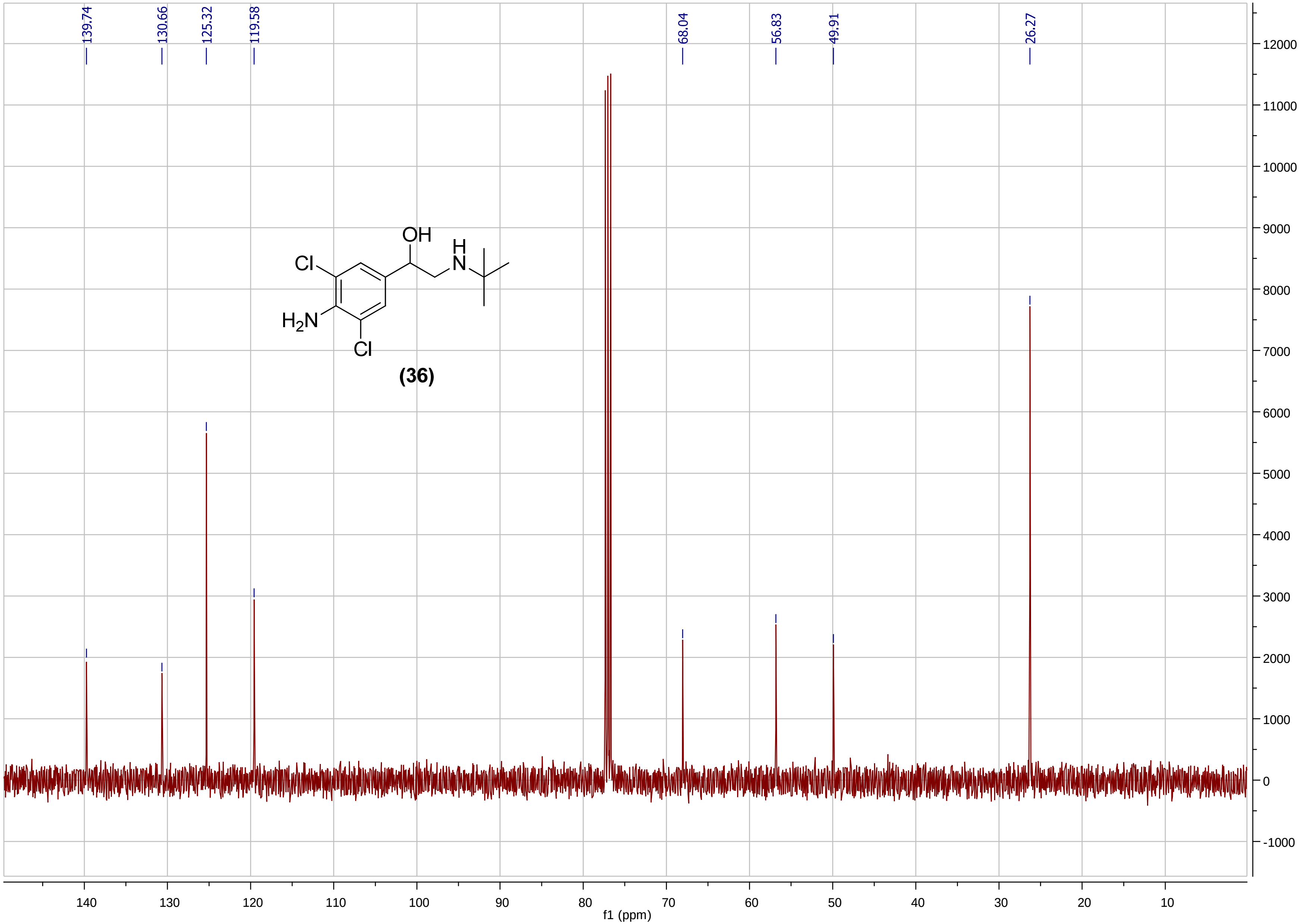

183.77
161.05
145.24
131.70
123.41
118.41
77.33
77.02
76.70
51.57
28.34
Cl
H
N
O
O
H2N
Cl
(34)
f1 (ppm)

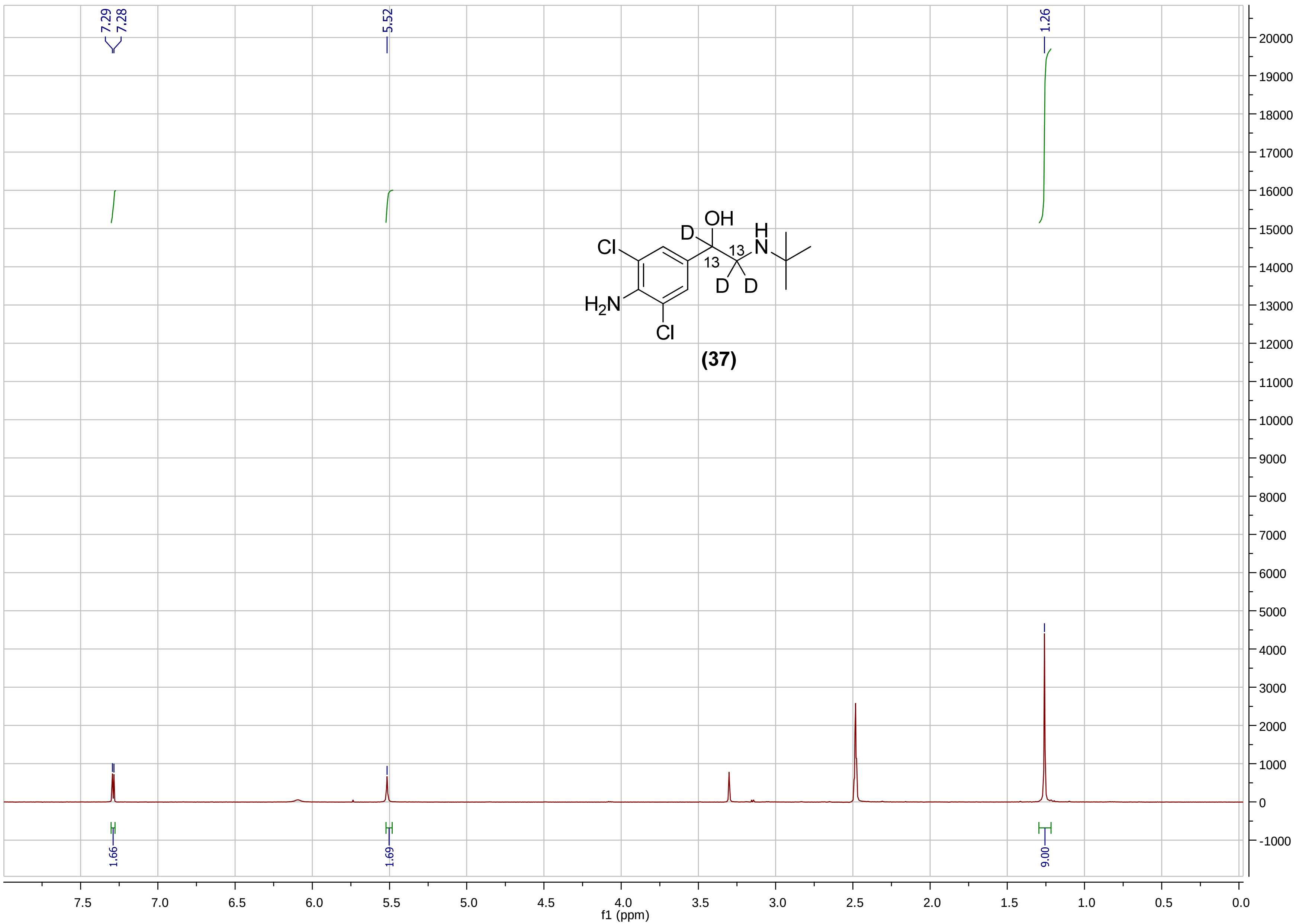

8.36
7.26
7.02
5.10
1.43
1.44
0.78
1.83
9.00
Cl
H2N
Cl
13C
13C
O
O
H
N
(35)
f1 (ppm)



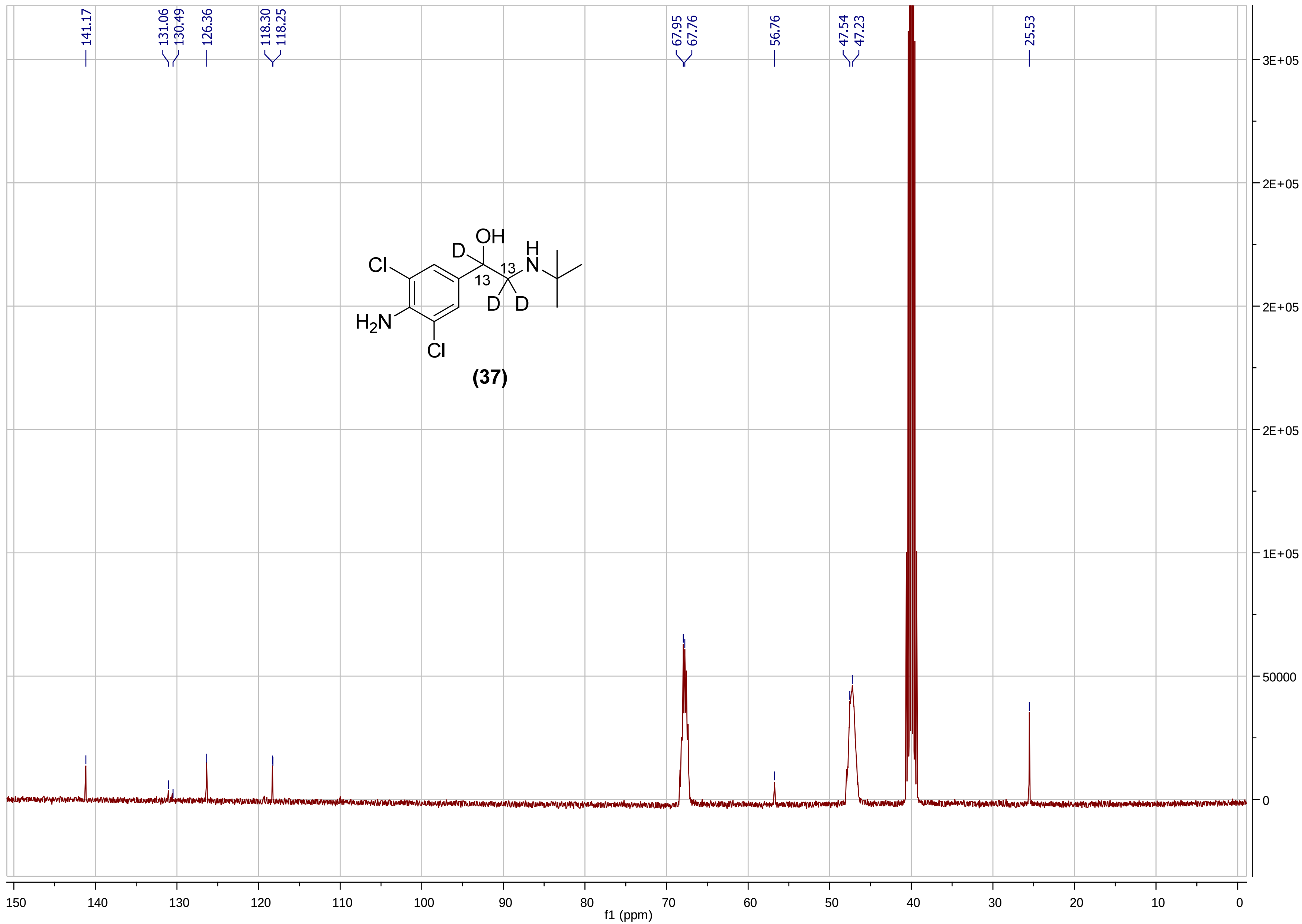
184.06
183.76
183.46
183.16
161.36
161.06
160.76
145.25
131.70
131.67
128.93
128.35
122.99
118.43
118.37
77.35
77.03
76.71
51.57
51.55
28.35
28.34
Cl
H2N
Cl
13C
13C
O
O
H
N
(35)
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.27
7.26
5.17
5.17
5.17
5.17
5.15
5.14
4.45
3.13
3.12
3.10
3.09
2.89
2.86
2.86
2.83
1.45
OH
H
N
Cl
H2N
Cl
(36)
1.80
1.00
1.95
1.08
1.05
8.81
f1 (ppm)


139.74
130.66
125.32
119.58
68.04
56.83
49.91
26.27
OH
H
N
Cl
H2N
Cl
(36)
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

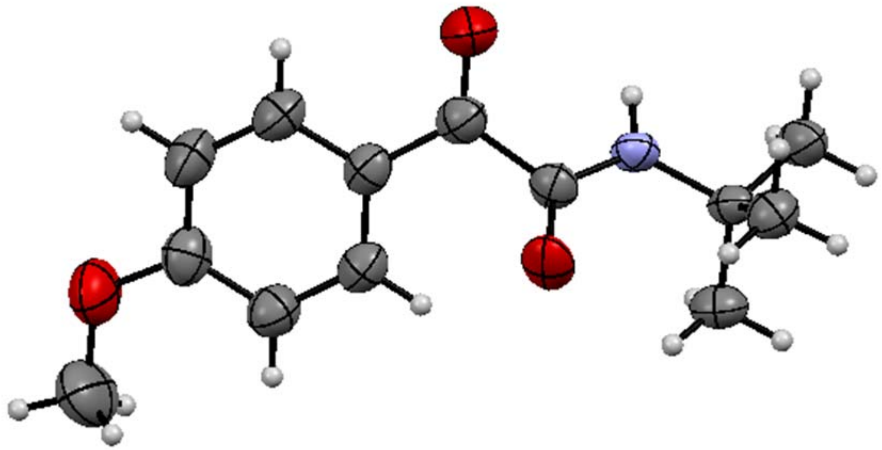


7.29
7.28
5.52
1.26
OH
D
H
N
Cl
13
13
H2N
D
D
Cl
(37)
1.66
1.69
9.00
f1 (ppm)



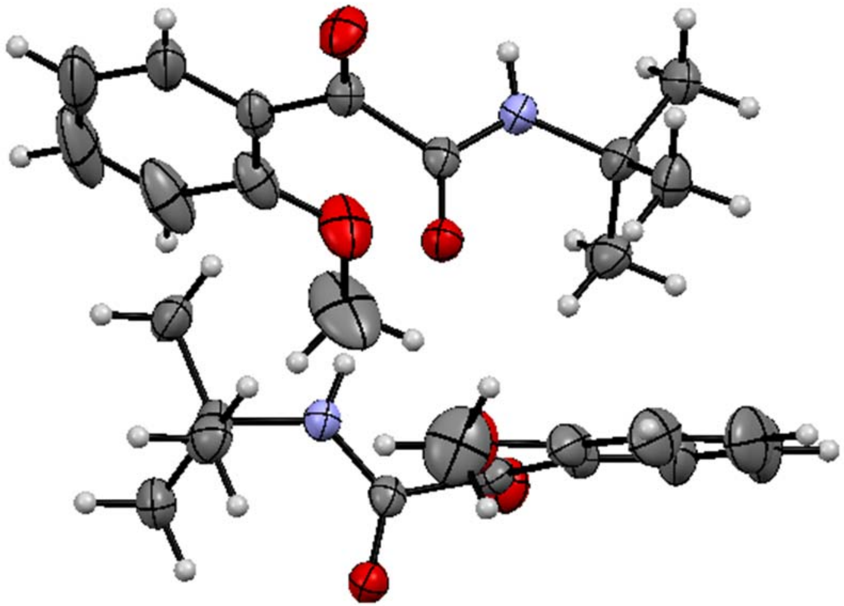
141.17
131.06
130.49
126.36
118.30
118.25
67.95
67.76
56.76
47.54
47.23
25.53
OH
D
H
N
Cl
13
13
H2N
D
D
Cl
(37)
3E+05
2E+05
2E+05
2E+05
1E+05
50000
0
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

ORTEP Diagram for compound **7**



Item	Value
Molecular formula	C13 H17 N O3
Formula weight	235.28
Crystal system	monoclinic
Space Group	P 1 21/c 1
a (Å)	12.3286
b (Å)	10.3522
c (Å)	10.205
α (°)	90
β (°)	96.066
γ (°)	90
Volume (Å^3)	1295.16
Z	4
T (K)	250
ρ (g cm^{-1})	1.207
λ (Å)	0.7107
μ (mm^{-1})	0.086
# measured refl	20601
# unique refl	3161
R_{int}	0.0423
# parameters	159
R(F^2), all refl	0.0552
R_w(F^2), all refl	0.1108
Goodness of fit	1.038

ORTEP Diagram for compound **12**



Item	Value
Molecular formula	C13 H17 N O3
Formula weight	235.28
Crystal system	triclinic
Space Group	P -1
a (Å)	9.2335
b (Å)	10.93
c (Å)	14.245
α (°)	95.14
β (°)	90.06
γ (°)	112.38
Volume ($Å^3$)	1323
Z	4
T (K)	160
ρ (g cm^{-1})	1.181
λ (Å)	0.71073
μ (mm^{-1})	0.084
# measured refl	10353
# unique refl	10353
R_{int}	0
# parameters	307
$R(F^2)$, all refl	0.0827
$R_w(F^2)$, all refl	0.1488
Goodness of fit	1.032

CO-release measurements general procedure[1]:

$Pd(dba)_2$ (14 mg, 0.025 mmol), ligand (0.025 mmol), COgen (9-methylfluorene-9-carbonyl chloride) (121.4mg, 0.500 mmol) and solvent (3 mL) was mixed in a crimp cap vial followed by addition of base (1.0 mmol) before it was sealed in a glove box under argon atmosphere. This was connected to a gas-volumeter (Figure 1), through the septum *via* a needle. The water level was noted and the reaction left stirring at 22 ^{o}C while the water level monitored over time, with continuous alignment of the water level in the two tubes, gives a time resolved measure of gas evolution. When the water level was constant in time the final water level was noted, giving a measure of the complete gas evolution of the reaction.

Finally the gas volumes were converted into amount of CO utilizing the ideal gas equation[2] and plotted as percent of theoretical amount of CO against time.

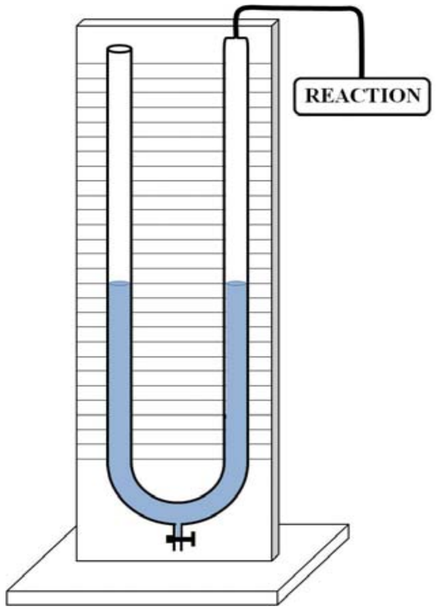


Figure 1. Gas-volumeter

Table 1

Entry	Ligand	Base	Solvent	Gas Yield / % (10 min)	Gas Yield / % (45 min)
1	$HBF_4P(tBu)_3$	DIPEA	dioxane	4%	4%
2	$P(tBu)_3$	DIPEA	DMF	27%	49%
3	$P(tBu)_3$	Cy_2NMe	DMF	49%	60%

[1] Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup T. *J. Am. Chem. Soc.*, **2011**, *133*, 18114–18117.
[2] The atmospheric pressure measured by the National Danish Whether Service (DMI) at the time and place of the experiment was used.

Gas calculation example

Calculation of the gas volume

$$V = (d - d_0) \cdot r^2 \cdot \pi$$

d = water level at a given time
d_0= water level before heating
r = 0.71 cm (inner radius of the gas volumeter used)

Using the ideal gas equation the molar amount of CO was calculated

$$n_{CO} = \frac{p \cdot V}{R \cdot T}$$

n_{CO} = molar amount of CO
p = atmospheric pressure, as given by the National Danish Whether Service (DMI) at the time and place of the experiment was used.
T = laboratory temperature – approximately 295 K.

Percentage gas release:

$$\text{Gas Yield } \% = \frac{n_{CO}}{n_{Theoretical}} \cdot 100\%$$

n_{CO} = molar amount of CO
$n_{theoretical}$ = theoretical amount of CO produced

Calculation example for entry 3 in table 1, at 45 min:

$$V = (3.1\text{ cm} - 7.7\text{ cm}) \cdot (0.71\text{cm})^2 \cdot \pi - 3.009\text{ cm}^3$$

$$V = 7.29\ \mathrm{cm}^3 = 0.00729\ \mathrm{L}$$

$$n_{CO} = \frac{1006.5\ \mathrm{hPa} \cdot 0.00729\ \mathrm{L}}{83.14472\ \frac{\mathrm{hPa} \cdot \mathrm{L}}{\mathrm{K} \cdot \mathrm{mol}} \cdot 295\ \mathrm{K}}$$

$$n_{CO} = 2.99\ \cdot 10^{-4}\ \mathrm{mol}$$

$$\text{Gas Yield }\% = \frac{2.99 \cdot 10^{-4}\ \mathrm{mol}}{5.00\ \cdot 10^{-4}\ \mathrm{mol}} \cdot 100\%$$

Gas Yield % = 60%