SUPPLEMENTARY MATERIALS

SYNTHESIS OF NOVEL 2-(HET)ARYLPYRROLIDINE DERIVATIVES AND EVALUATION OF THEIR ANTICANCER AND ANTI-BIOFILM ACTIVITY

Andrey Smolobochkin,[1] Almir Gazizov,[1]* Marina Sazykina,[2] Nurgali Akylbekov,[3] Elena Chugunova,[1,4]* Ivan Sazykin,[2] Anastasiya Gildebrant,[2] Julia Voronina,[5] Alexander Burilov,[1] Shorena Karchava,[2] Maria Klimova,[2] Alexandra Voloshina,[1] Anastasia Sapunova,[1] Elena Klimanova,[6] Tatyana Sashenkova,[6] Ugulzhan Allayarova,[6] Anastasiya Balakina,[6,7] Denis Mishchenko[6,7]

Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of RAS, Russia, 420088, Kazan, Arbuzov str., 8

[2] *Southern Federal University, Russia, 344090, Rostov-on-Don, Stachki Avenue, 194/2*

[3] *Institute of Chemical Research and Technology of Korkyt Ata Kyzylorda State University, The Republic of Kazakhstan, 120014, Kyzylorda, Aiteke bie str., 29A*

[4] *Kazan Federal University, Russia, 420008, Kazan, Kremlyovskaya str., 18*

[5] *N. S. Kurnakov Institute of General and Inorganic Chemistry, RAS, 31 Leninsky Av., 119991 Moscow, Russian Federation*

[6] *Institute of Problems of Chemical Physics RAS, Chernogolovka 142432, Russia*

[7] *Scientific and Educational Center in Chernogolovka of Moscow Region State University, Mytishi, 141014, Russia*

*** *Correspondence: chugunova.e.a@gmail.com, Tel.: +7 843 272 7324 (Elena Chugunova); agazizov@iopc.ru; Tel.: +7 843 272 7324 (Almir Gazizov)*

Contents

Anti-biofilm activity studies

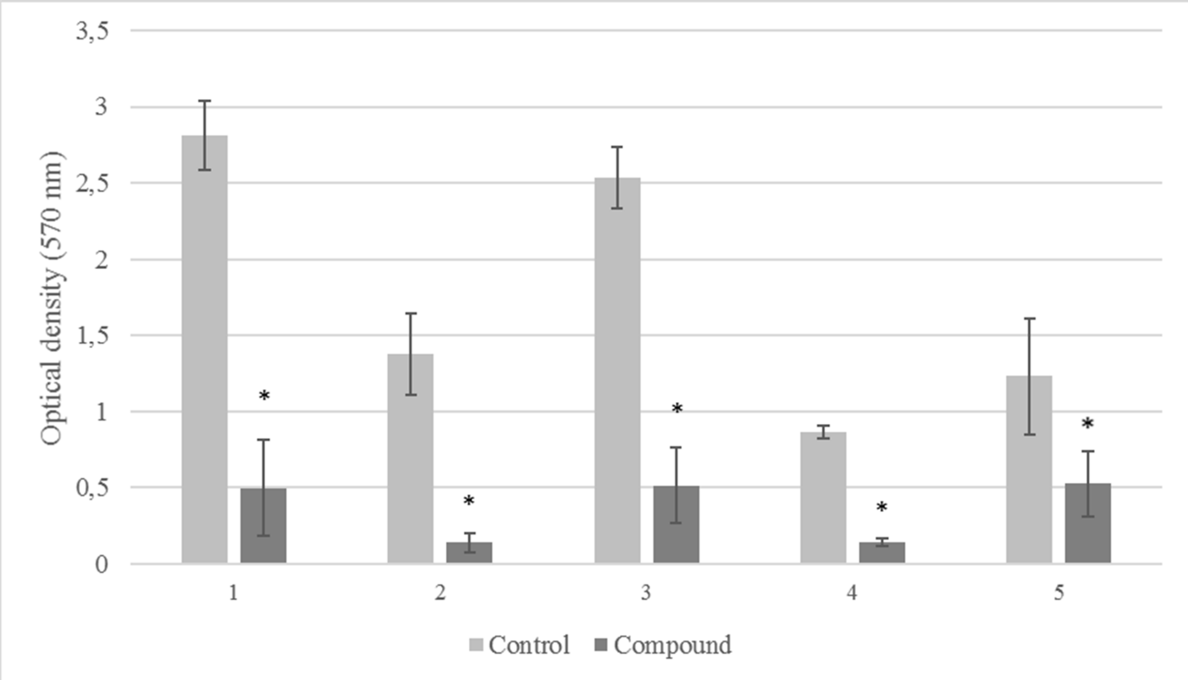


Figure S 1. Antibiofilm activity of pyrrolidine **6a** against *V. aquamarinus* DSM 26054: 1 – **6a** ($1{\times}10^{-9}$ M); 2 – **6a** ($1{\times}10^{-8}$ M); 3 – **6a** ($1{\times}10^{-7}$ M); 4 – **6a** ($1{\times}10^{-6}$ M); 5 – **6a** ($1{\times}10^{-5}$ M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean ± SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

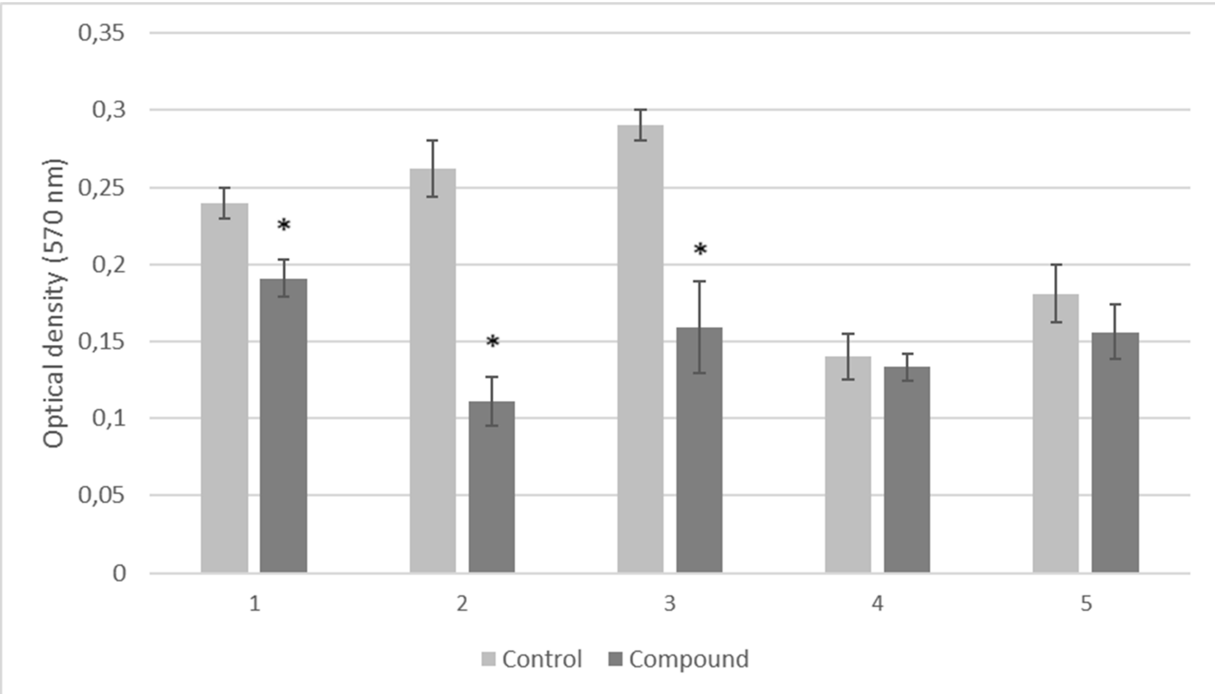


Figure S 2. Antibiofilm activity of pyrrolidine **6a** against *A. calcoaceticus* VKPM B-10353: 1 – **6a** ($1{\times}10^{-9}$ M); 2 – **6a** ($1{\times}10^{-8}$ M); 3 – **6a** ($1{\times}10^{-7}$ M); 4 – **6a** ($1{\times}10^{-6}$ M); 5 – **6a** ($1{\times}10^{-5}$ M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean ± SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

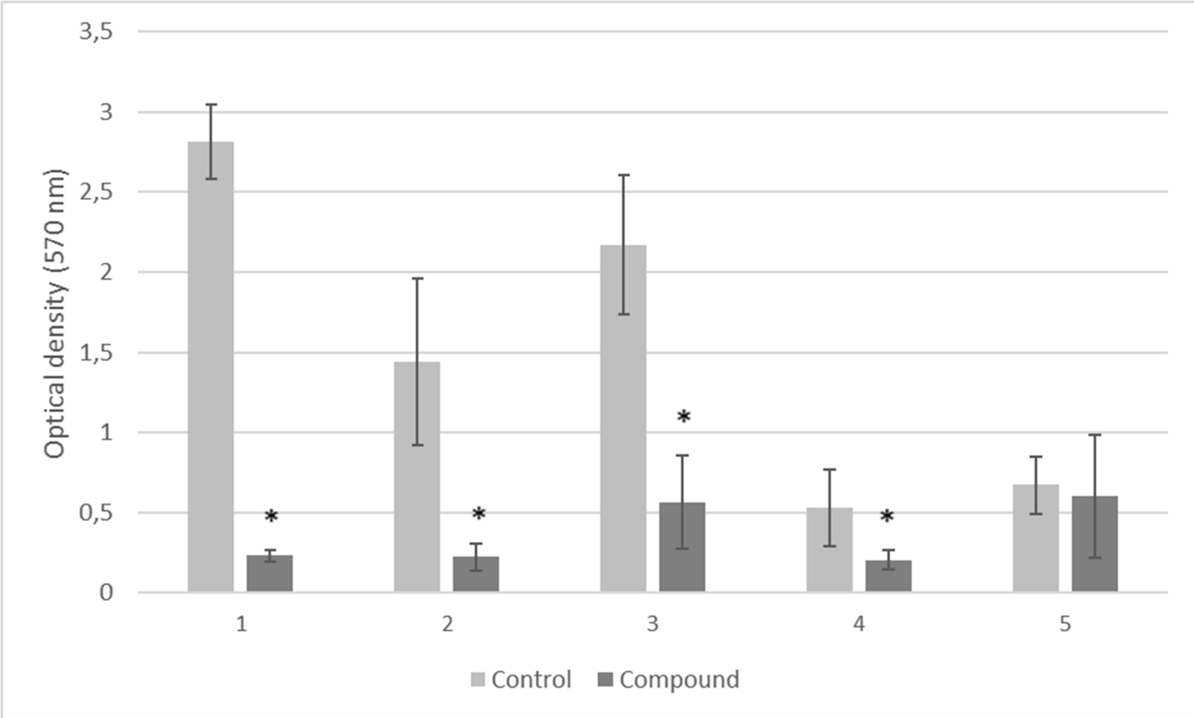


Figure S 3. Antibiofilm activity of pyrrolidine **6b** against *V. aquamarinus* DSM 26054: 1 – **6b** (1×10^{-9} M); 2 – **6b** (1×10^{-8} M); 3 – **6b** (1×10^{-7} M); 4 – **6b** (1×10^{-6} M); 5 – **6b** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean $\pm$ SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

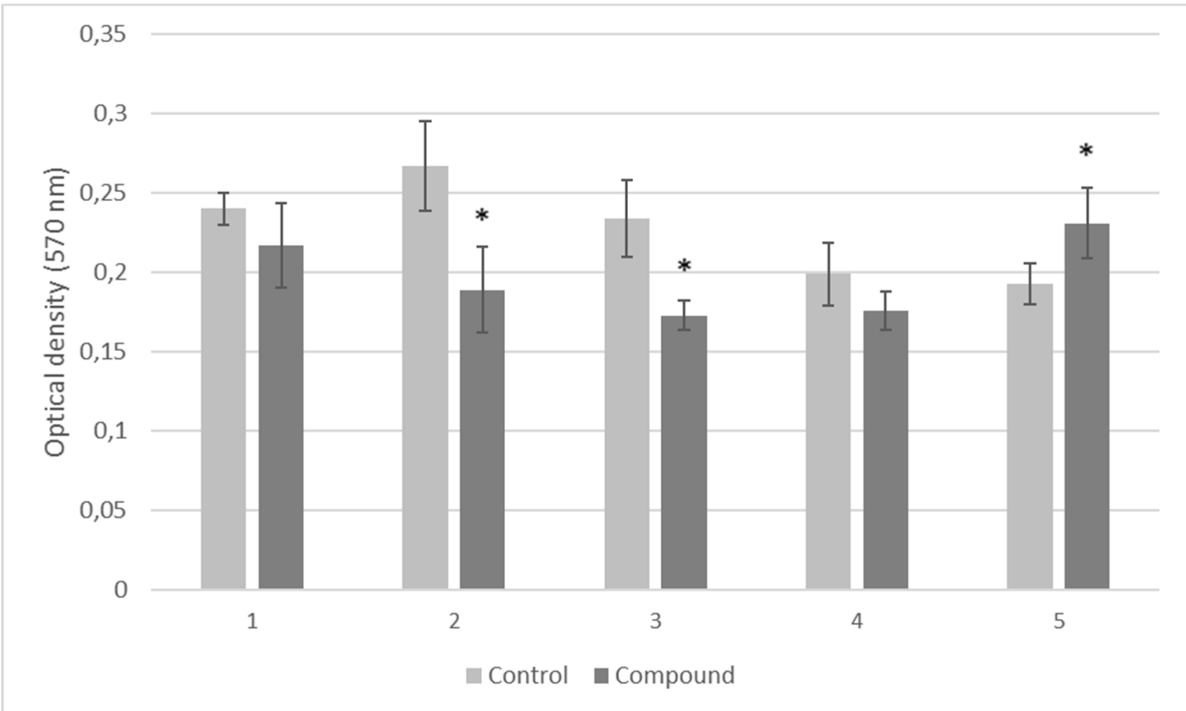


Figure S 4. Antibiofilm activity of pyrrolidine **6b** against *A. calcoaceticus* VKPM B-10353: 1 – **6b** (1×10^{-9} M); 2 – **6b** (1×10^{-8} M); 3 – **6b** (1×10^{-7} M); 4 – **6b** (1×10^{-6} M); 5 – **6b** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean $\pm$ SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

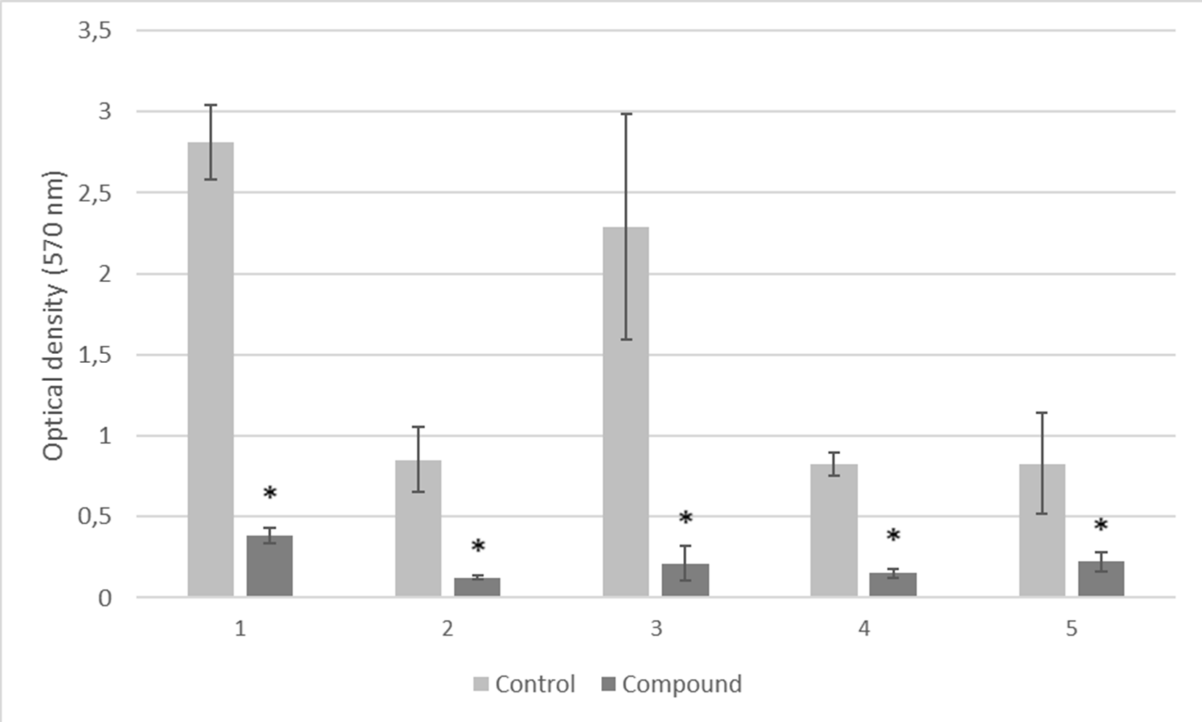


Figure S 5. Antibiofilm activity of pyrrolidine **6c** against V. aquamarinus DSM 26054: 1 – **6c** (1×10^{-9} M); 2 – **6c** (1×10^{-8} M); 3 – **6c** (1×10^{-7} M); 4 – **6c** (1×10^{-6} M); 5 – **6c** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean $\pm$ SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

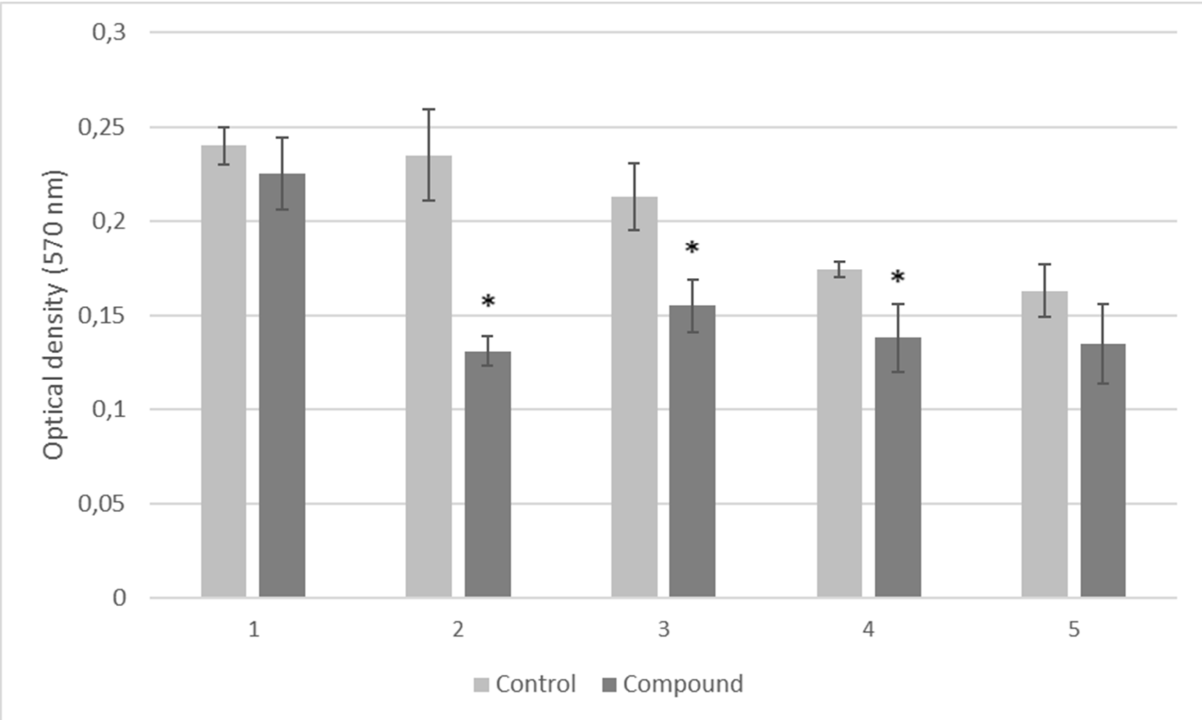


Figure S 6. Antibiofilm activity of pyrrolidine **6c** against *A. calcoaceticus* VKPM B-10353: 1 – **6c** (1×10^{-9} M); 2 – **6c** (1×10^{-8} M); 3 – **6c** (1×10^{-7} M); 4 – **6c** (1×10^{-6} M); 5 – **6c** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean $\pm$ SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

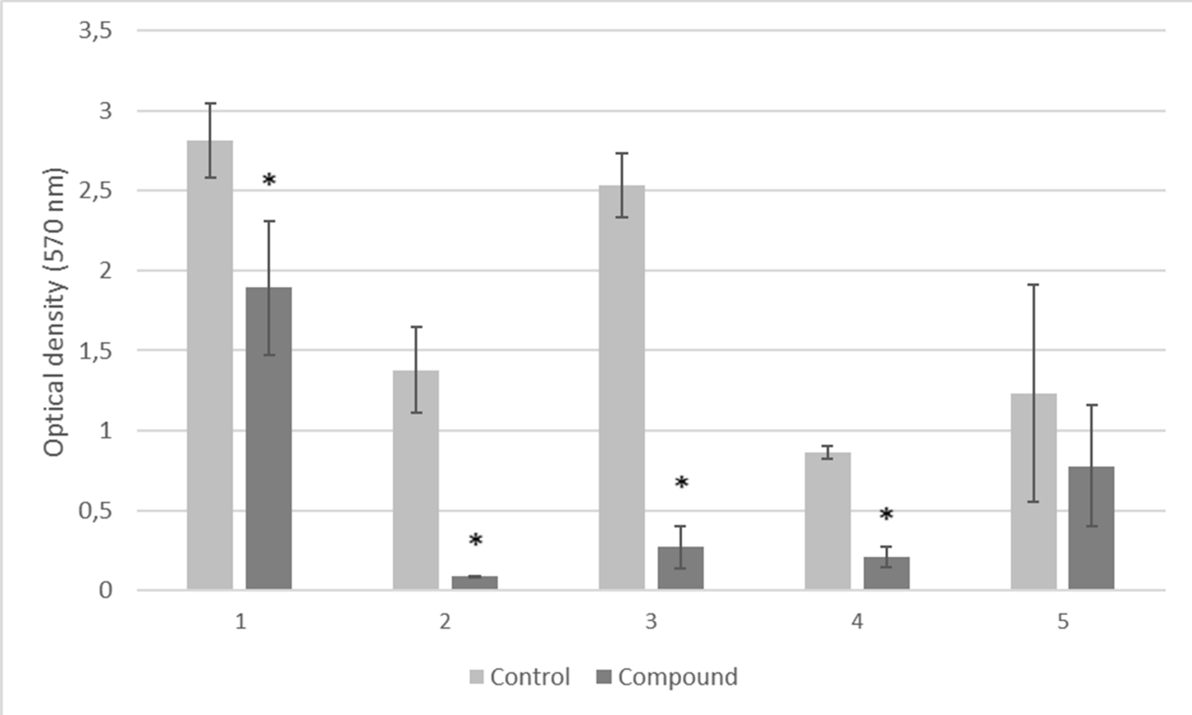


Figure S 7. Antibiofilm activity of pyrrolidine **6d** against *V. aquamarinus* DSM 26054: 1 – **6d** (1×10^{-9} M); 2 – **6d** (1×10^{-8} M); 3 – **6d** (1×10^{-7} M); 4 – **6d** (1×10^{-6} M); 5 – **6d** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean $\pm$ SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

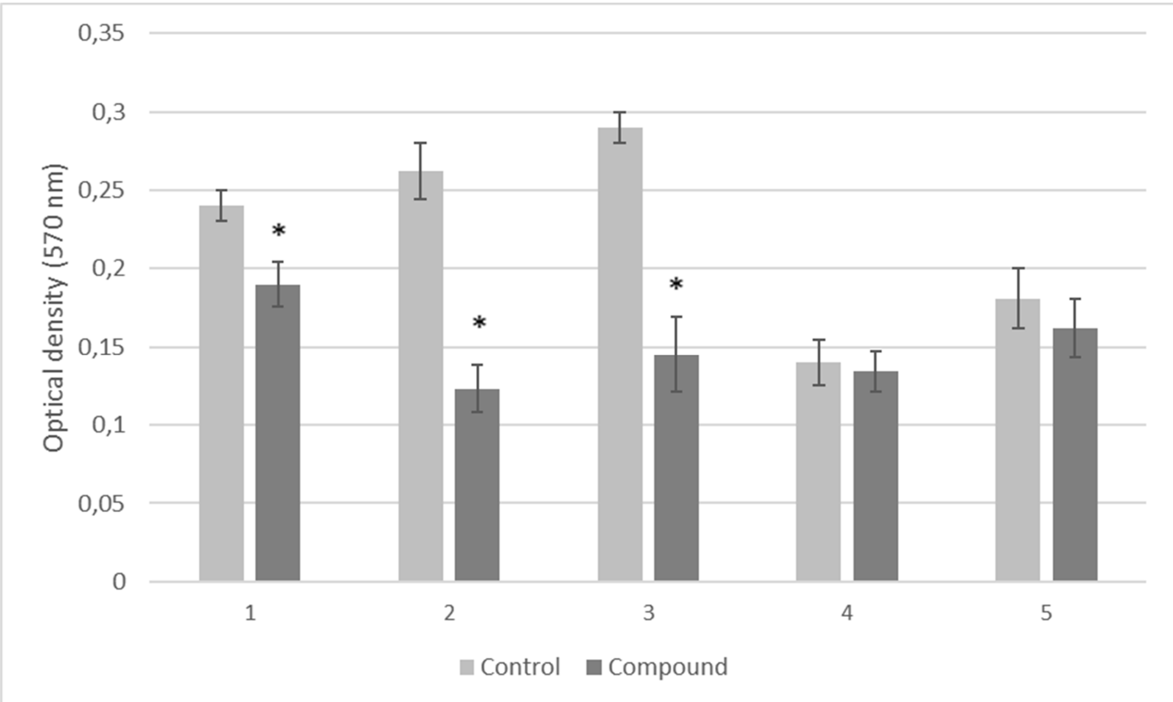


Figure S 8. Figure 4 – Antibiofilm activity of pyrrolidine **6d** against *A. calcoaceticus* VKPM B-10353: 1 – **6d** (1×10^{-9} M); 2 – **6d** (1×10^{-8} M); 3 – **6d** (1×10^{-7} M); 4 – **6d** (1×10^{-6} M); 5 – **6d** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean $\pm$ SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

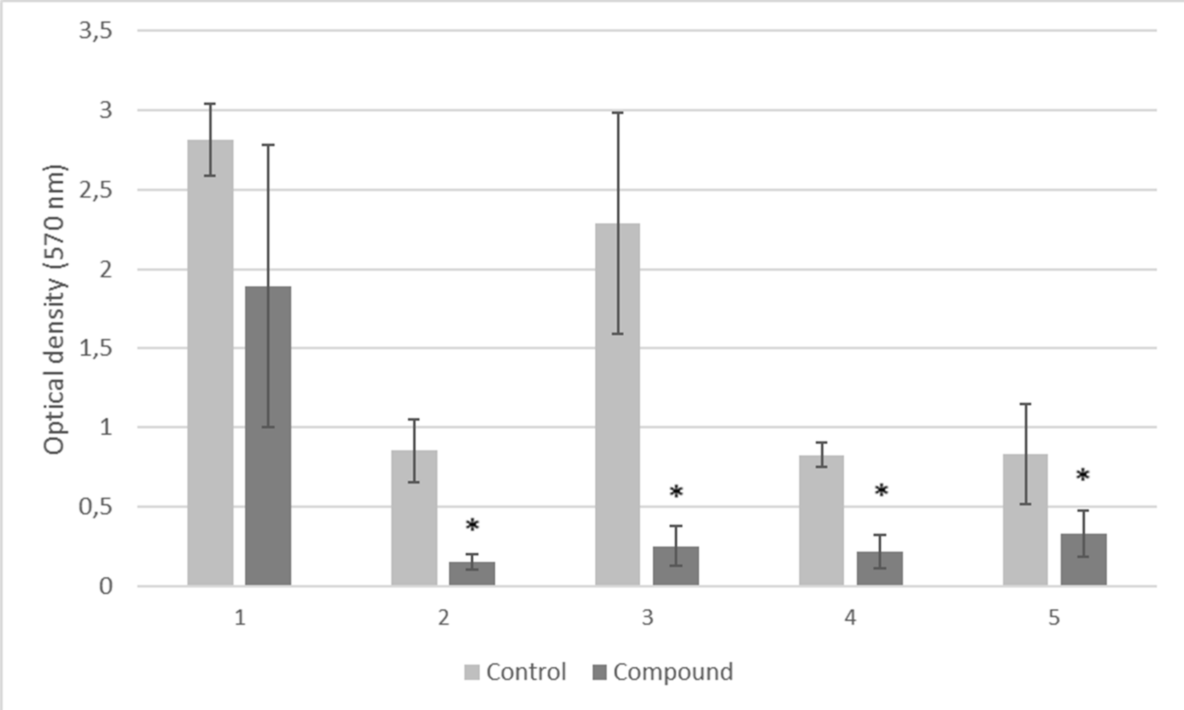


Figure S 9. Antibiofilm activity of pyrrolidine **6e** against *V. aquamarinus* DSM 26054: 1 – **6e** (1×10^{-9} M); 2 – **6e** (1×10^{-8} M); 3 – **6e** (1×10^{-7} M); 4 – **6e** (1×10^{-6} M); 5 – **6e** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean ± SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

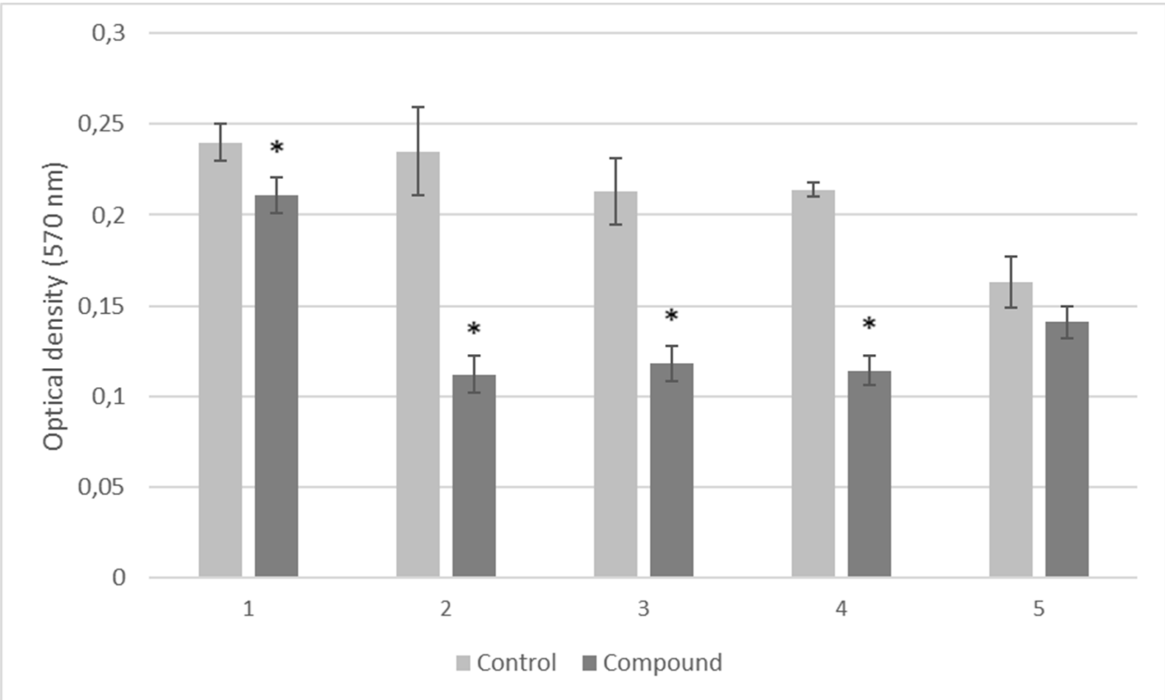


Figure S 10. Antibiofilm activity of pyrrolidine **6e** against *A. calcoaceticus* VKPM B-10353: 1 – **6e** (1×10^{-9} M); 2 – **6e** (1×10^{-8} M); 3 – **6e** (1×10^{-7} M); 4 – **6e** (1×10^{-6} M); 5 – **6e** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean ± SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

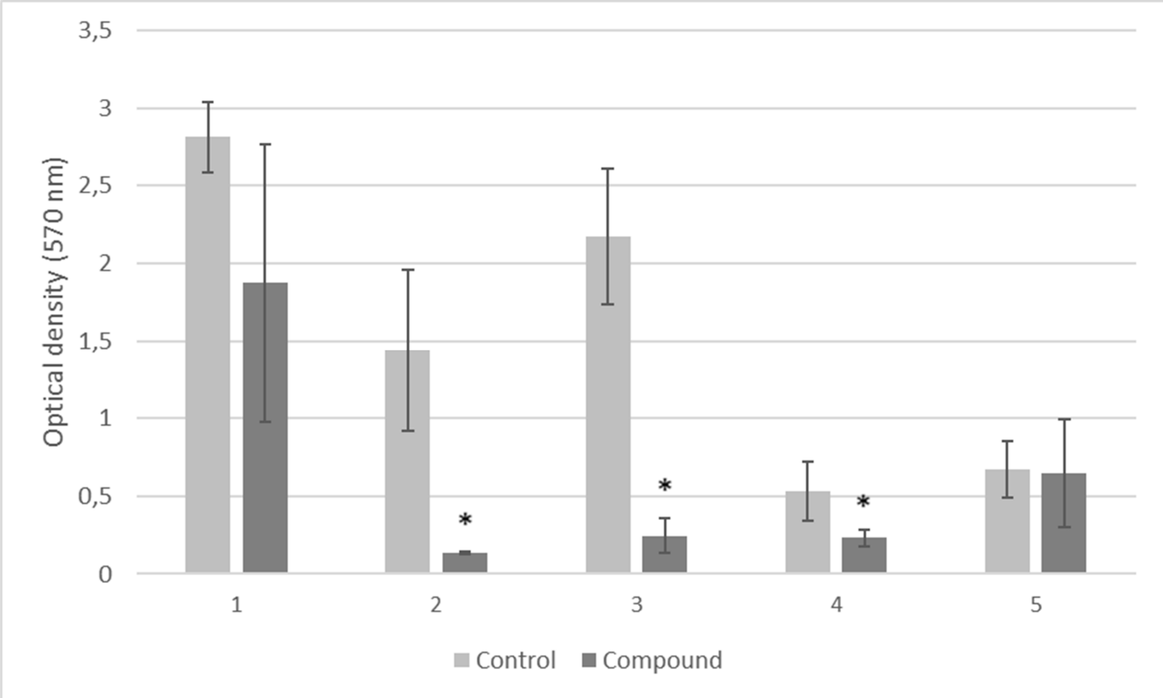


Figure S 11. Antibiofilm activity of phenol **4** against *V. aquamarinus* DSM 26054: 1 – **4** (1×10^{-9} M); 2 –**4** (1×10^{-8} M); 3 – **4** (1×10^{-7} M); 4 – **4** (1×10^{-6} M); 5 – **4** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean + SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at p < 0.05.

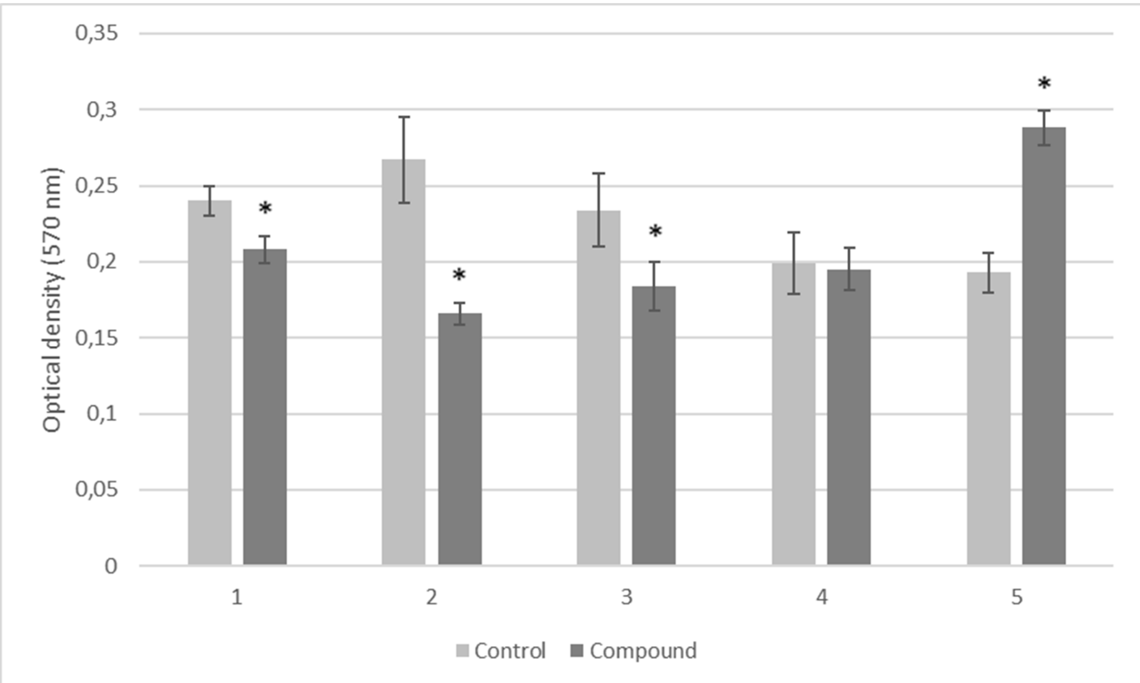


Figure S 12. Figure 12 – Antibiofilm activity of phenol **4** against *A. calcoaceticus* VKPM B-10353: 1 – **4** (1×10^{-9} M); 2 – **4** (1×10^{-8} M); 3 – **4** (1×10^{-7} M); 4 – **4** (1×10^{-6} M); 5 – **4** (1×10^{-5} M). The solutions of appropriate solvent in ethanol with the same concentration were used as controls. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean $\pm$ SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

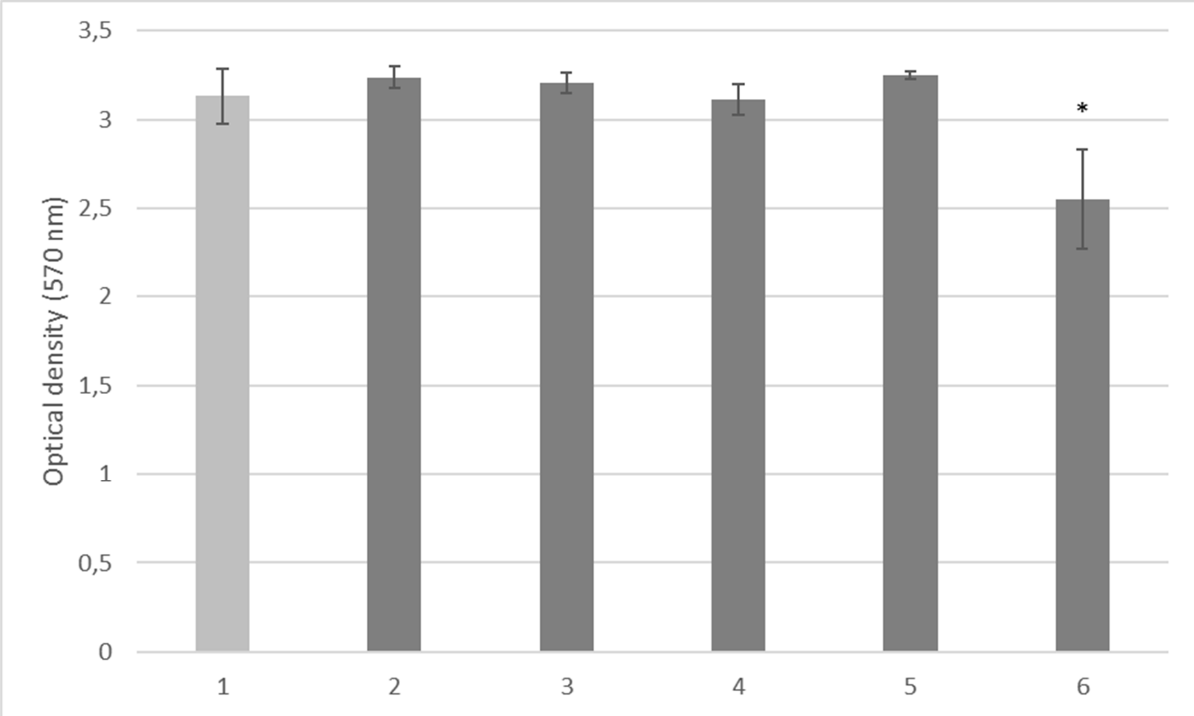


Figure S 13. Antibiofilm activity of azithromycin against *V. aquamarinus* DSM 26054: 1 – control; 2 – azithromycin (1×10^{-9} M); 3 – azithromycin (1×10^{-8} M); 4 – azithromycin (1×10^{-7} M); 5 – azithromycin (1×10^{-6} M); 6 – azithromycin (1×10^{-5} M). Deionized H_2O was used as control. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean + SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at p < 0.05.

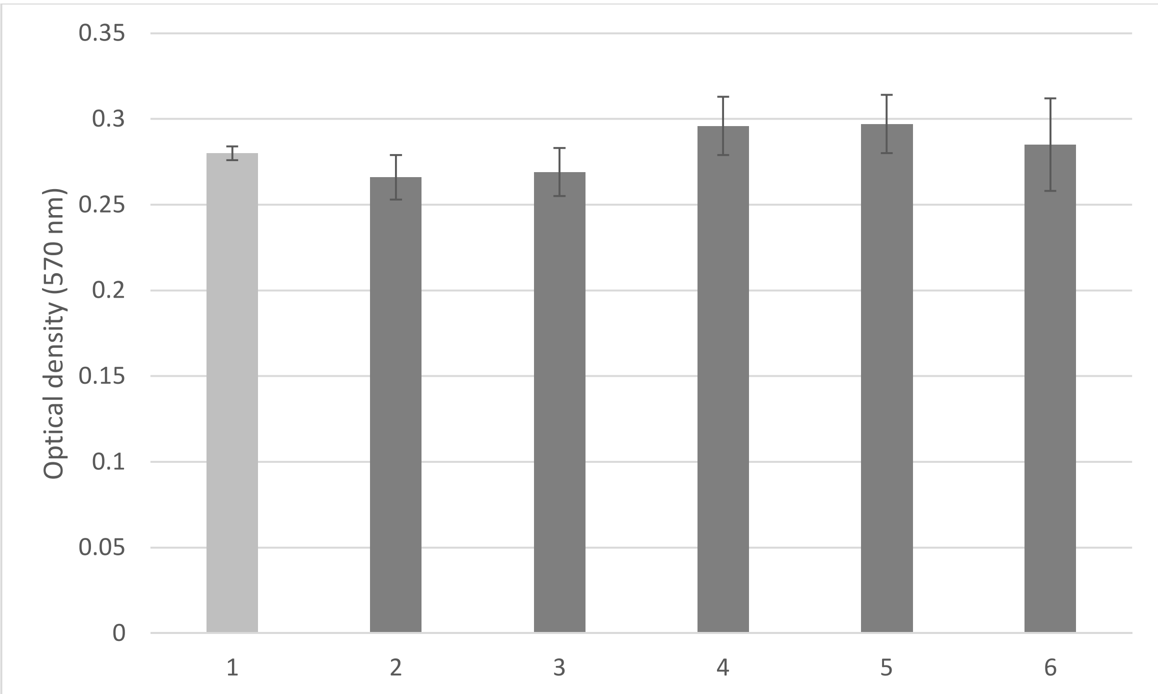


Figure S 14. Antibiofilm activity of azithromycin against *A. calcoaceticus* VKPM B-10353: 1 – control; 2 – azithromycin (1×10^{-9} M); 3 – azithromycin (1×10^{-8} M); 4 – azithromycin (1×10^{-7} M); 5 – azithromycin (1×10^{-6} M); 6 – azithromycin (1×10^{-5} M). Deionized H_2O was used as control. Each experiment was performed in triplicate and repeated in six different occasions. The values were expressed as mean $\pm$ SD. Student's T-test was used to compare these values. *Differences were considered statistically significant at $p < 0.05$.

X-ray studies

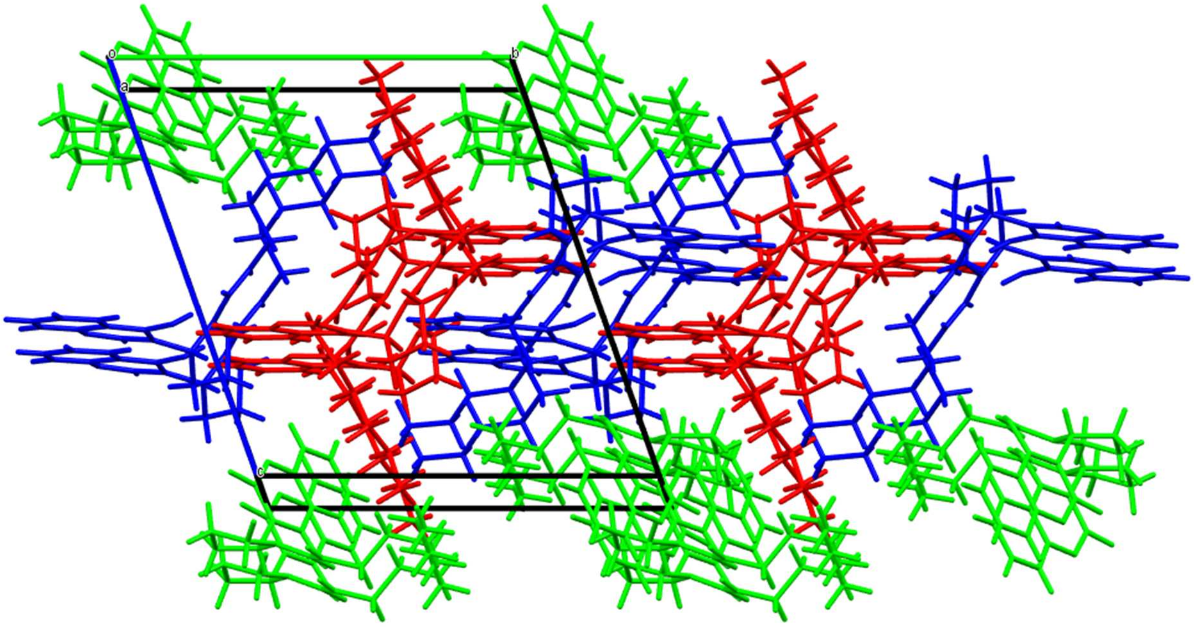


Figure S 15. Crystal packing of compound **8f** (molecules of different symmetry equivalents are shown in different colors).

Table S 1. Torsion angles in pyrrolidine and hexane substituents in compound **8f**.

Torsion angle	a	b	c	Torsion angle	a	b	c
N1-C2-C3-C4	18.0(3)	21.0(3)	36.1(3)	C16-N17-C18-C19	83.4(3)	98.6(3)	90.2(3)
C2-C3-C4-C5	30.0(3)	33.6(3)	35.3(3)	N17-C18-C19-C20	173.5(2)	171.8(3)	54.8(3)
C3-C4-C5-N1	29.7(3)	32.6(3)	20.6(3)	C18-C19-C20-C21	66.5(4)	49.3(5)	170.3(2)
C5-N1-C2-C3	0.8(3)	0.6(3)	23.9(3)	C19-C20-C21-C22	61.3(4)	179.0(3)	173.3(2)
C2-N1-C5-C4	19.0(3)	19.9(3)	2.1(3)	C20-C21-C22-C23	172.4(3)	175.8(4)	174.4(3)

Table S 2. H-bonds in crystal of compound **8f**.

H-bond	D-H	H...A	D...A	D-H...A
O15B-H15B...O16B	0.86	1.68	2.536(3)	173
O15C-H15C...O16C	0.85	1.72	2.550(3)	165
O15A-H16A...O16A	0.85	1.66	2.508(3)	171
N17A-H17A...O7A	0.88	2.10	2.921(3)	156
N17B-H17B...O7B	1.02	1.91	2.842(3)	151
N17C-H17C...O7C	0.89	1.98	2.867(3)	171
C2A-H2AA...O15A	1.00	2.48	2.882(3)	103
C3A-H3AB...O7A	0.99	2.44	2.914(3)	109
C4A-H4AB...O7A	0.99	2.54	3.131(3)	118
C5A-H5AB...O7A	0.99	2.52	3.338(3)	140

H-bond	D-H	H...A	D...A	D-H...A
C2B-H2BA...O15B	1.00	2.49	2.893(3)	104
C3B-H3BB...O7B	0.99	2.31	3.003(4)	126
C12B-H12B...O16C	0.95	2.38	3.251(3)	152
C18B-H18D...O16B	0.99	2.42	2.765(3)	100
C4C-H4CA...O7C	0.99	2.32	3.006(3)	126
C5C-H5CA...O15C	1.00	2.48	2.890(3)	104

Table S 3. π…π interactions in crystal of compound **8f**.

Π...π	Cg-Cg	Alpha	CgI_Perp	CgJ_Perp
Cg2...Cg3	3.4890(16)	0.88(13)	3.4838(11)	3.4858(11)
Cg3...Cg2	3.4890(16)	0.88(13)	3.4858(11)	3.4838(11)
Cg7...Cg11	3.7432(16)	1.41(13)	-3.4105(11)	-3.3934(11)
Cg11...Cg7	3.7432(16)	1.41(13)	-3.3934(11)	-3.4105(11)

Table S 4. CH…π interactions in crystal of compound **8f**.

C-H…π	H..Cg	H-Perp	Gamma	X-H..Cg
C2A-H2AA...Cg11	2.89	2.86	7.89	143
C21A-H21B...Cg6	2.78	2.73	10.66	144
C22C-H22E...Cg3	2.66	-2.65	6.12	168

In vivo anti-cancer activity

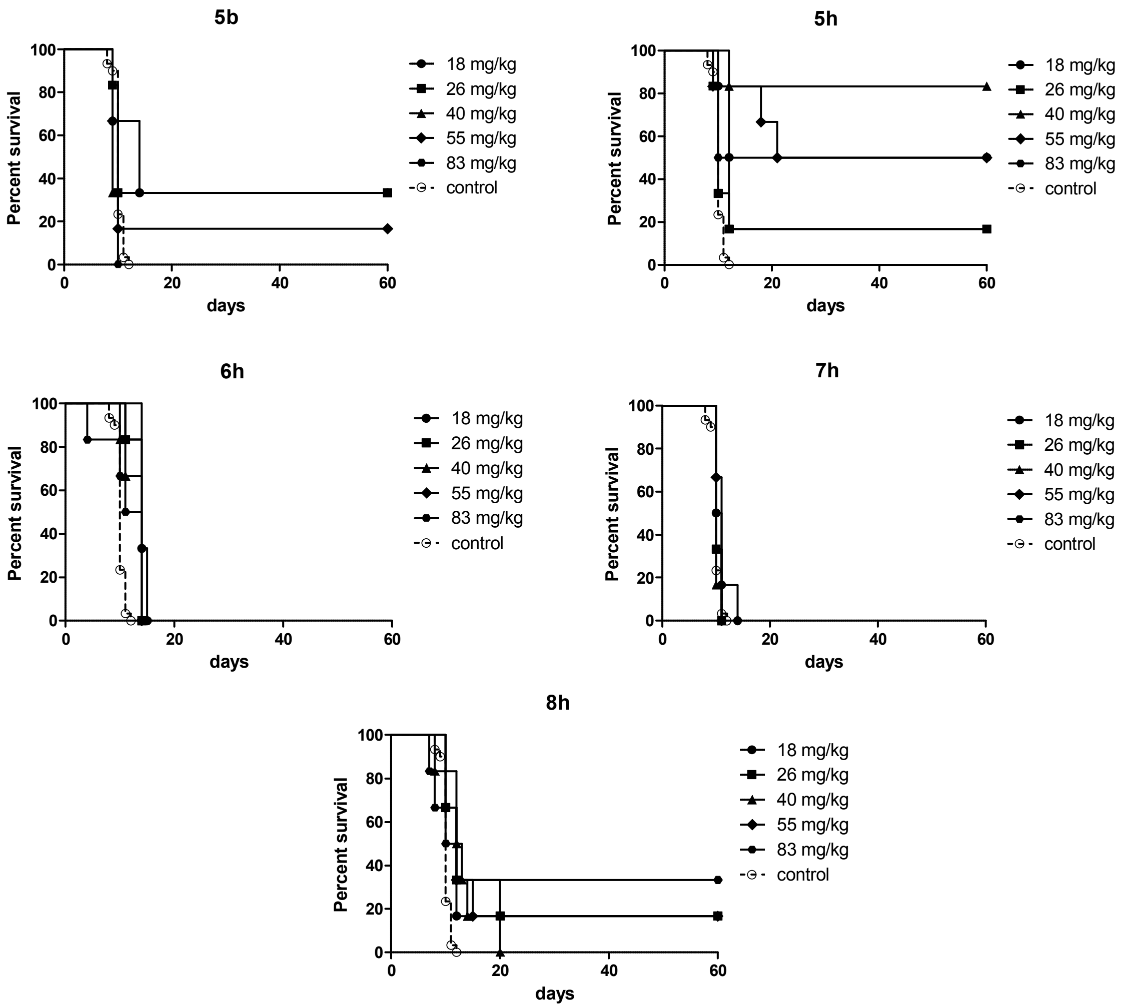


Figure S 16. The Kaplan-Meier curves demonstrating the percentage of survival of mice bearing P388 leukemia as a function of time.

In vitro anti-cancer activity

Table S 5. Cytotoxic effects of pyrrolidines **7b–8h** on the cancer and normal human cell lines.[1]

Test compounds	IC_{50} (μM)		Test compounds	IC_{50} (μM)	
	Cancer cell line	Normal cell line		Cancer cell line	Normal cell line
	M-Hela	Chang liver		M-Hela	Chang liver
7b	>100	>100	**8b**	>100	>100
7c	>100	>100	**8c**	>100	>100
7d	>100	>100	**8d**	>100	>100
7e	>100	>100	**8e**	>100	>100
7f	>100	>100	**8f**	>100	>100
7g	>100	>100	**8g**	>100	>100
7h	>100	>100	**8h**	>100	>100

[1] Three independent experiments were carried out

Copies of NMR spectra

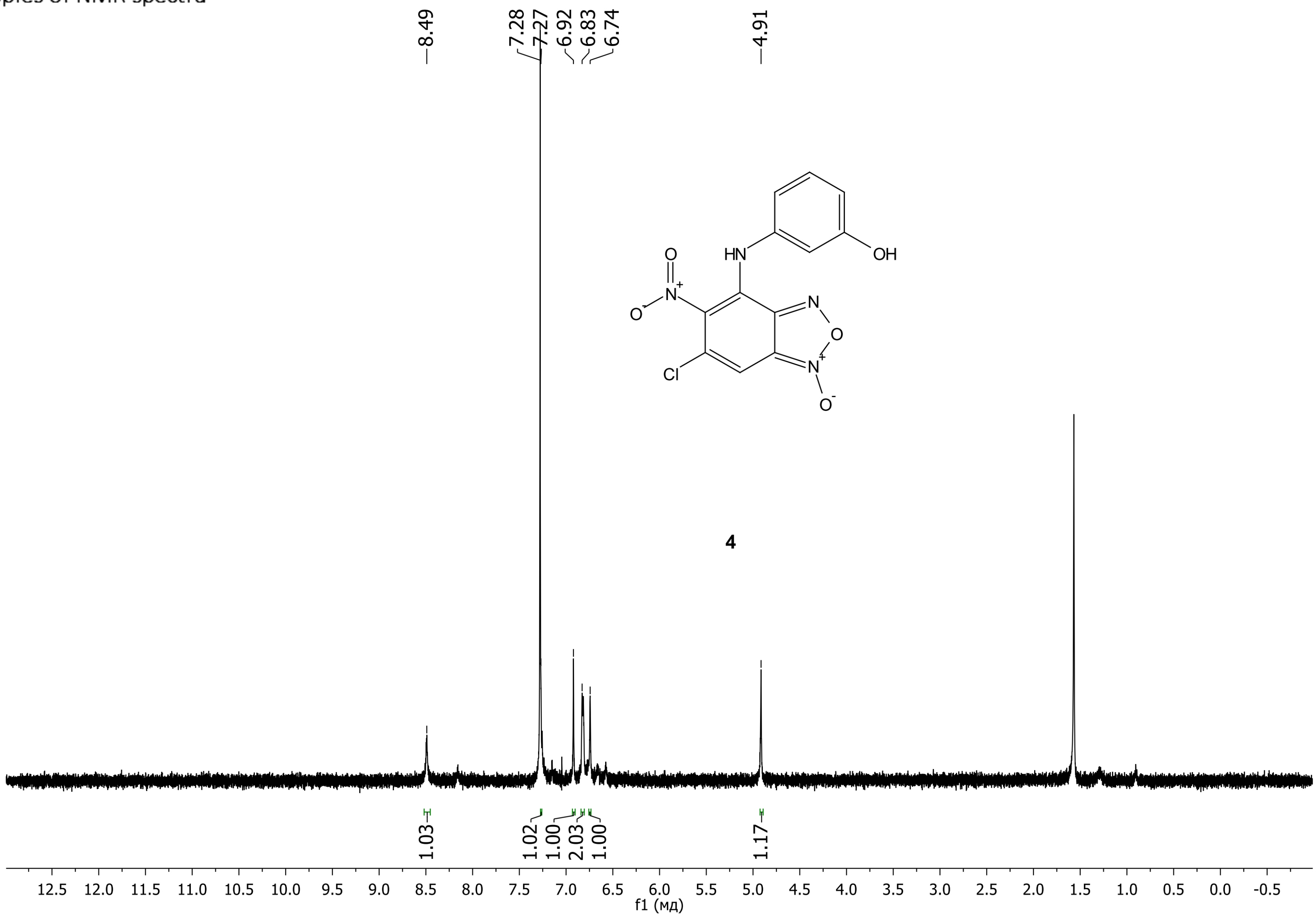
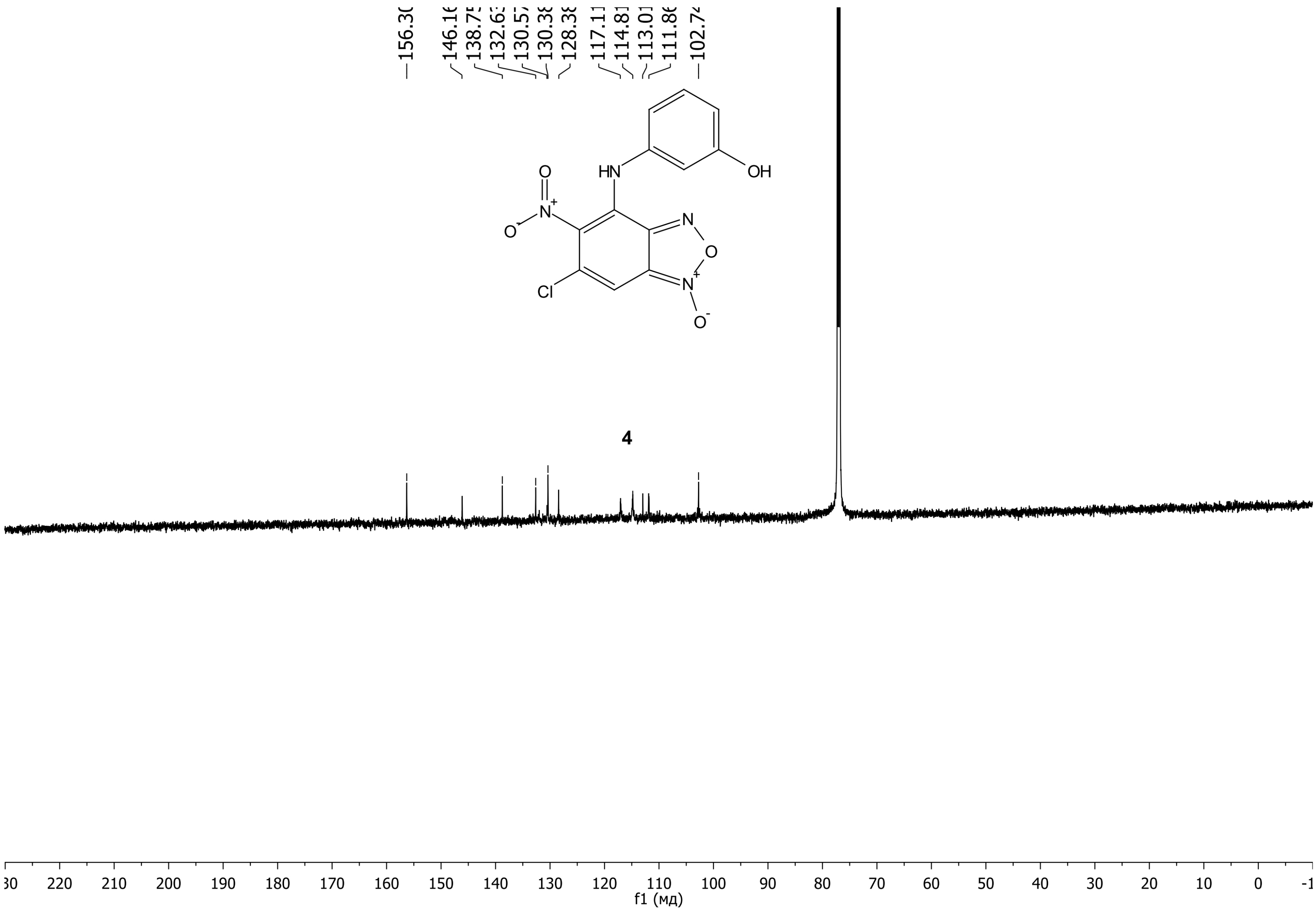


Figure S 17.



156.30
146.16
138.75
132.63
130.57
130.38
128.38
117.11
114.81
113.01
111.86
102.74
HN
OH
O
N+
O-
N
O
N+
O-
Cl
4
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 (мд)

Figure S 18.

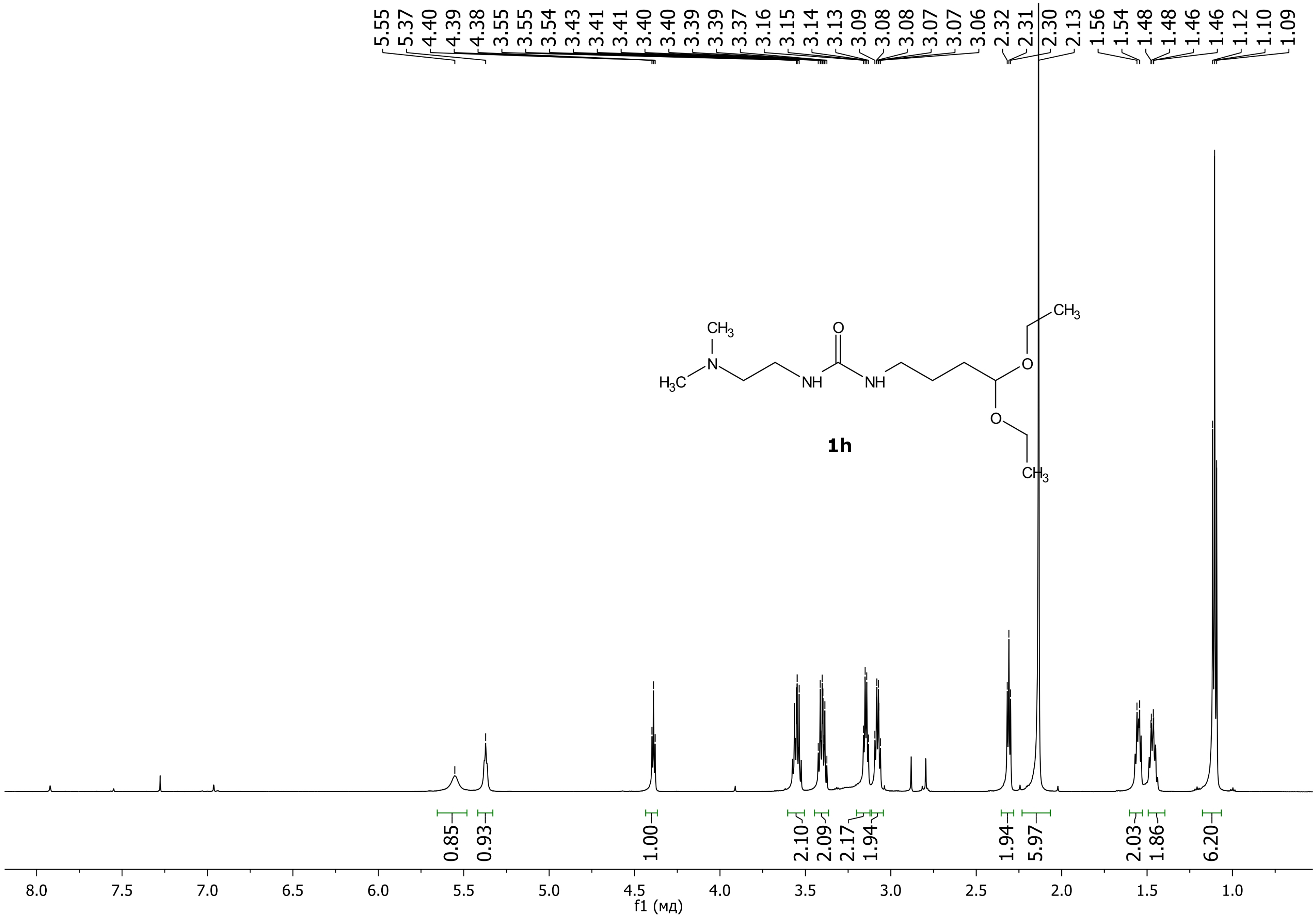


Figure S 19.


159.09
102.81
61.24
59.27
45.20
40.02
38.05
31.05
25.45
15.23
CH_3
O
H_3C
N
NH
NH
O
O
CH_3
CH_3
1h
f1 (мд)

Figure S 20.

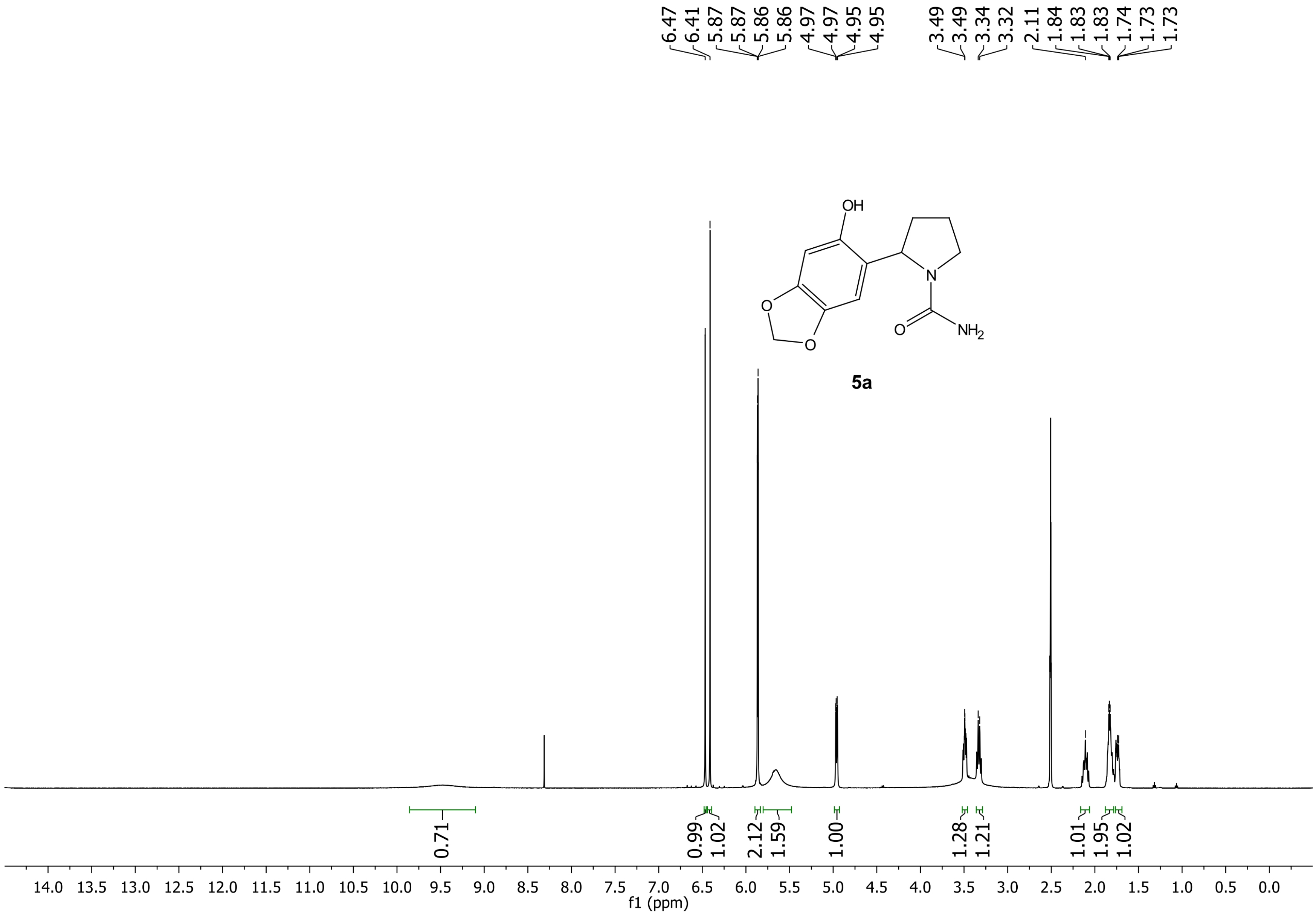

6.47
6.41
5.87
5.87
5.86
5.86
4.97
4.97
4.95
4.95
3.49
3.49
3.34
3.32
2.11
1.84
1.83
1.83
1.74
1.73
1.73
OH
N
O
O
O
NH2
5a
0.71
0.99
1.02
2.12
1.59
1.00
1.28
1.21
1.01
1.95
1.02
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

Figure S 21.

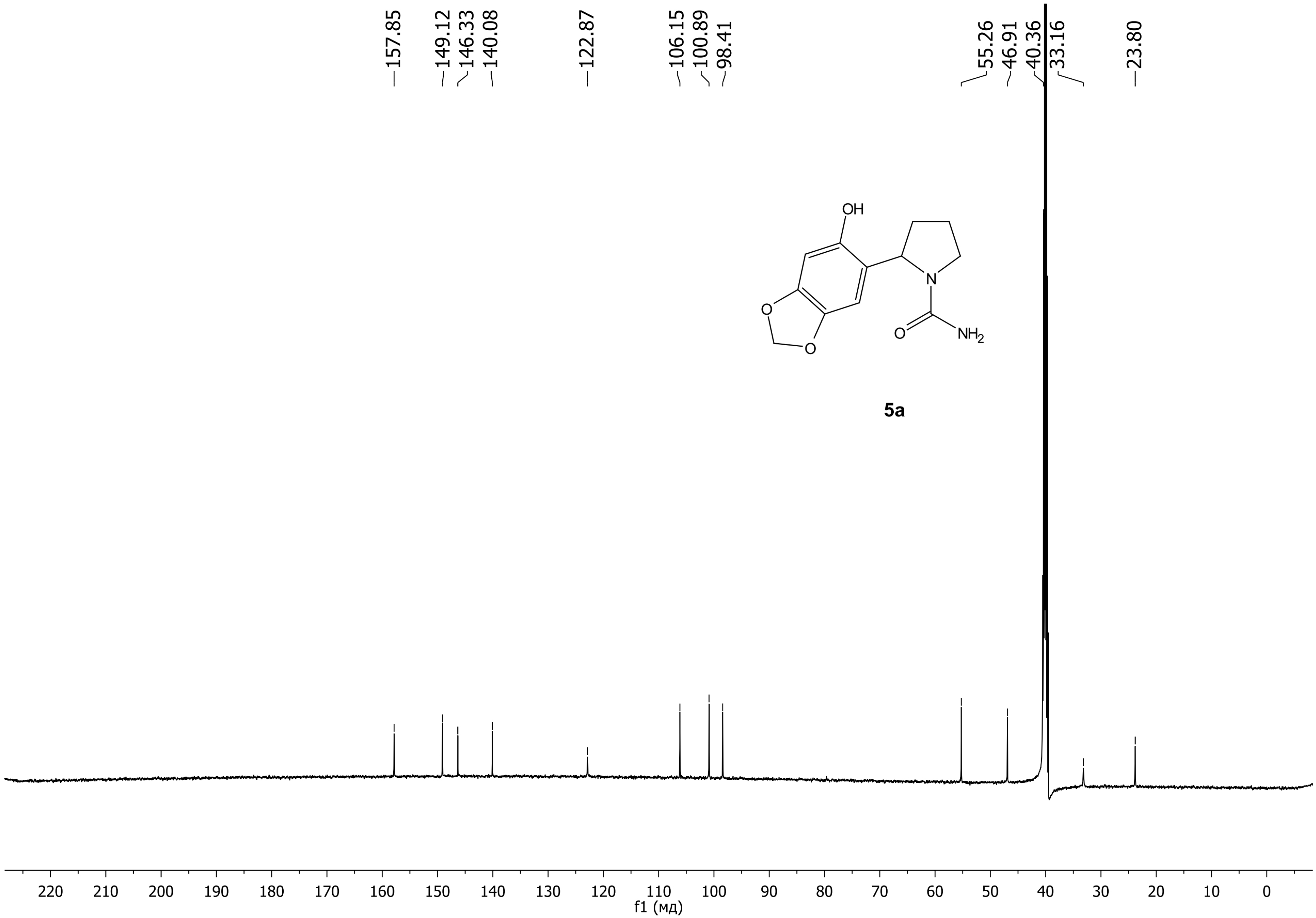
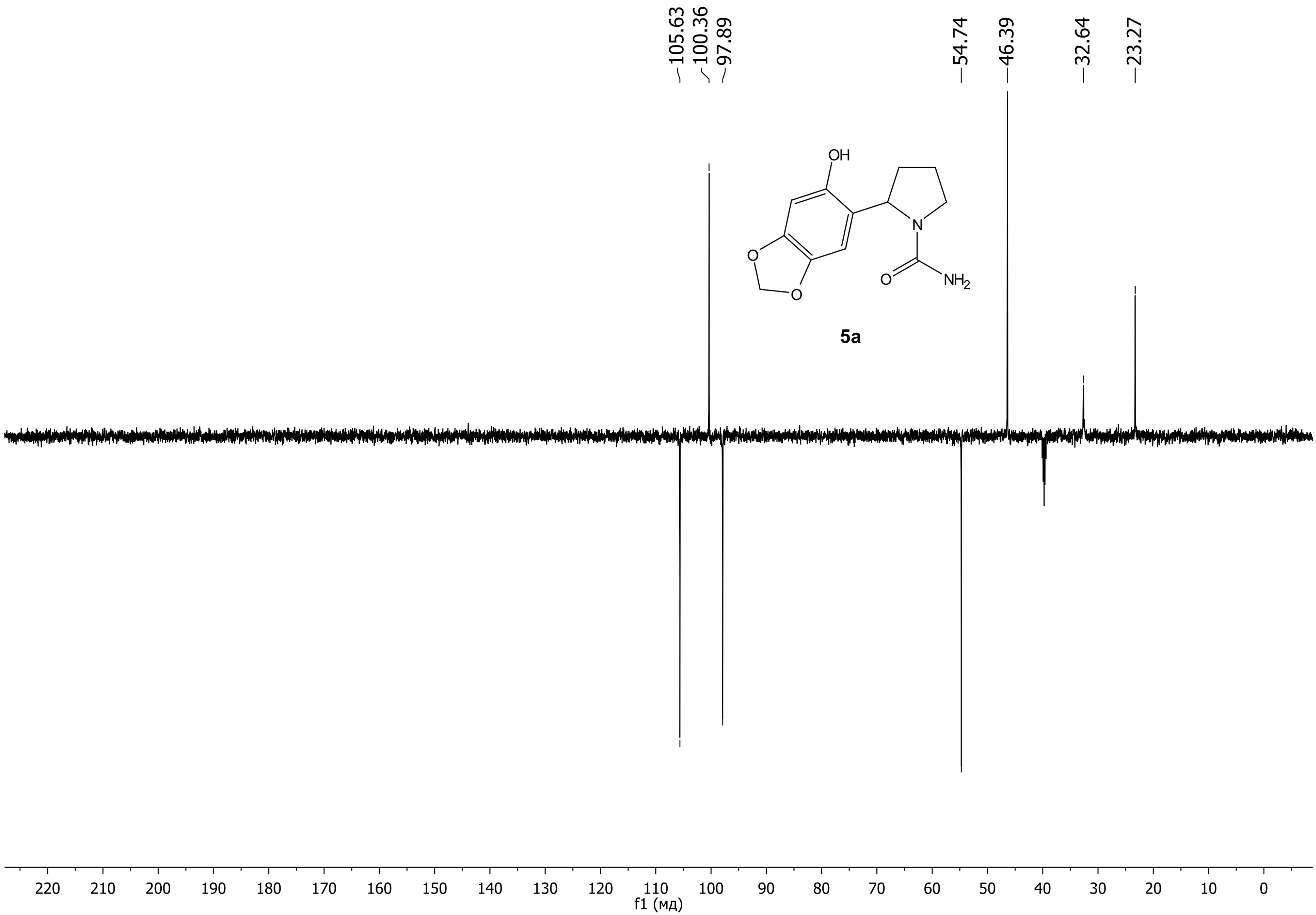
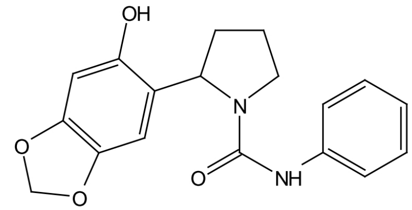

157.85
149.12
146.33
140.08
122.87
106.15
100.89
98.41
55.26
46.91
40.36
33.16
23.80
OH
O
O
N
O
NH2
5a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)

Figure S 22.



105.63
100.36
97.89
54.74
46.39
32.64
23.27
OH
O
O
N
O
NH2
5a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)

Figure S 23.



5b

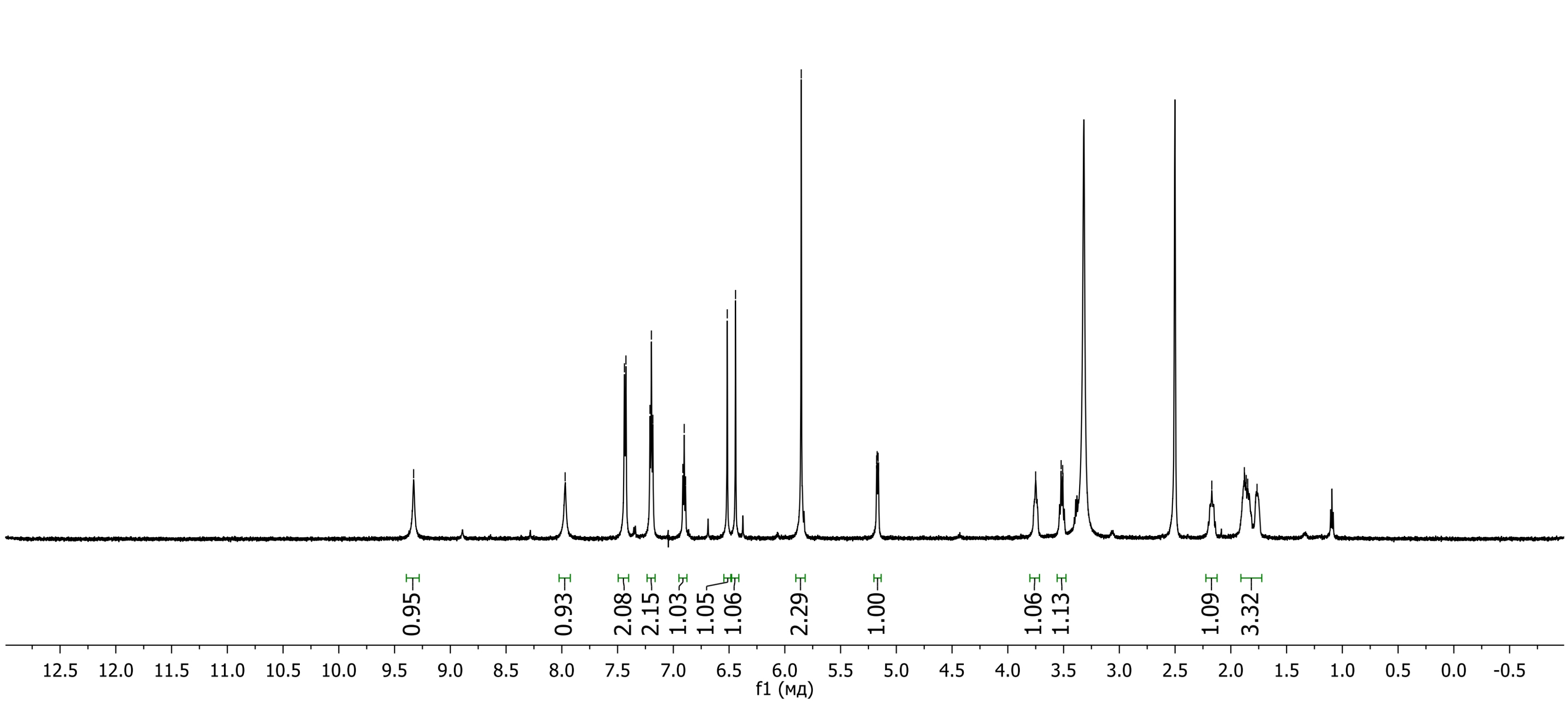
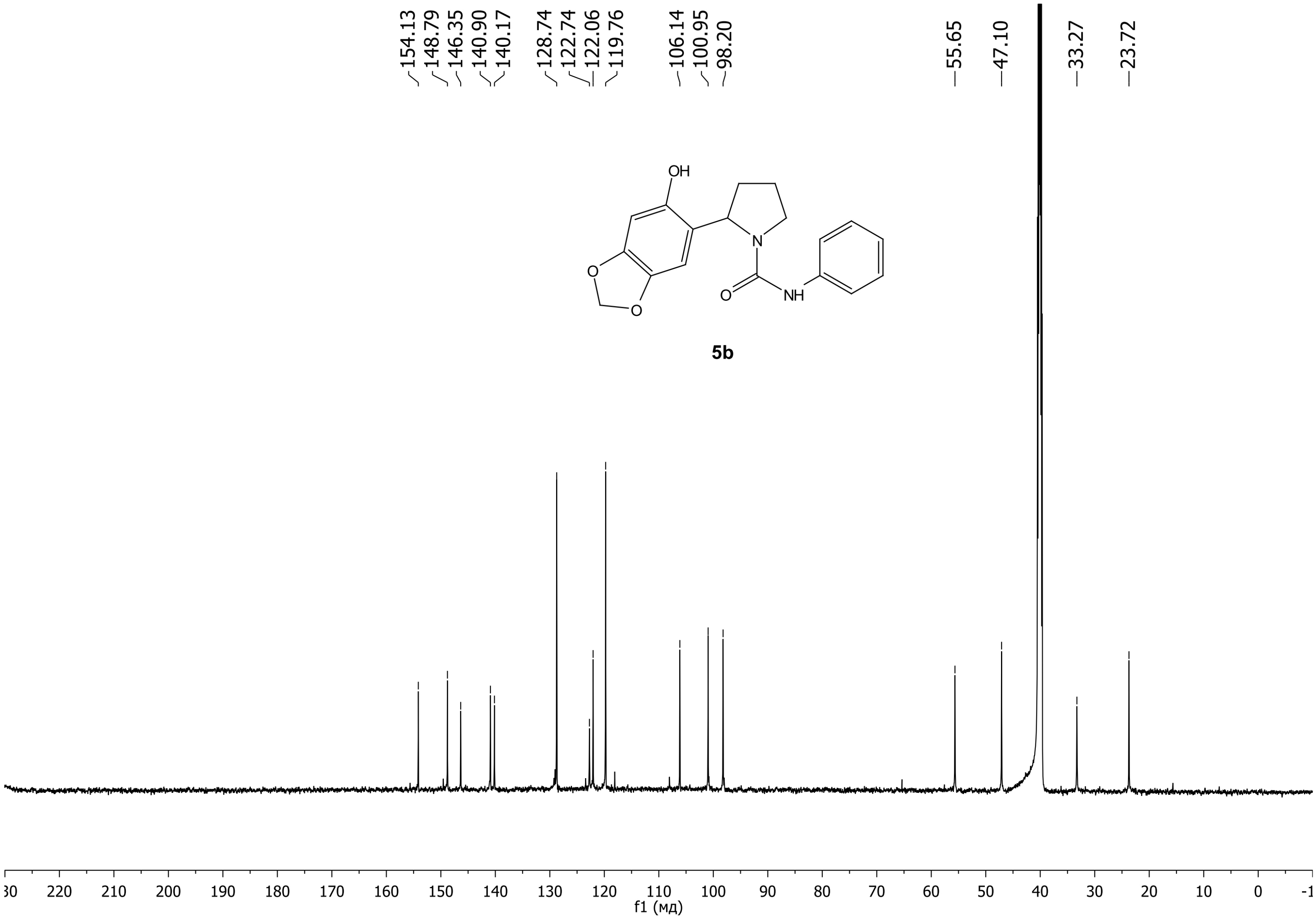


Figure S 24.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148.79
146.35
140.90
140.17
128.74
122.74
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100.95
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55.65
47.10
33.27
23.72
OH
O
O
N
O
NH
5b
f1 (мд)

Figure S 25.

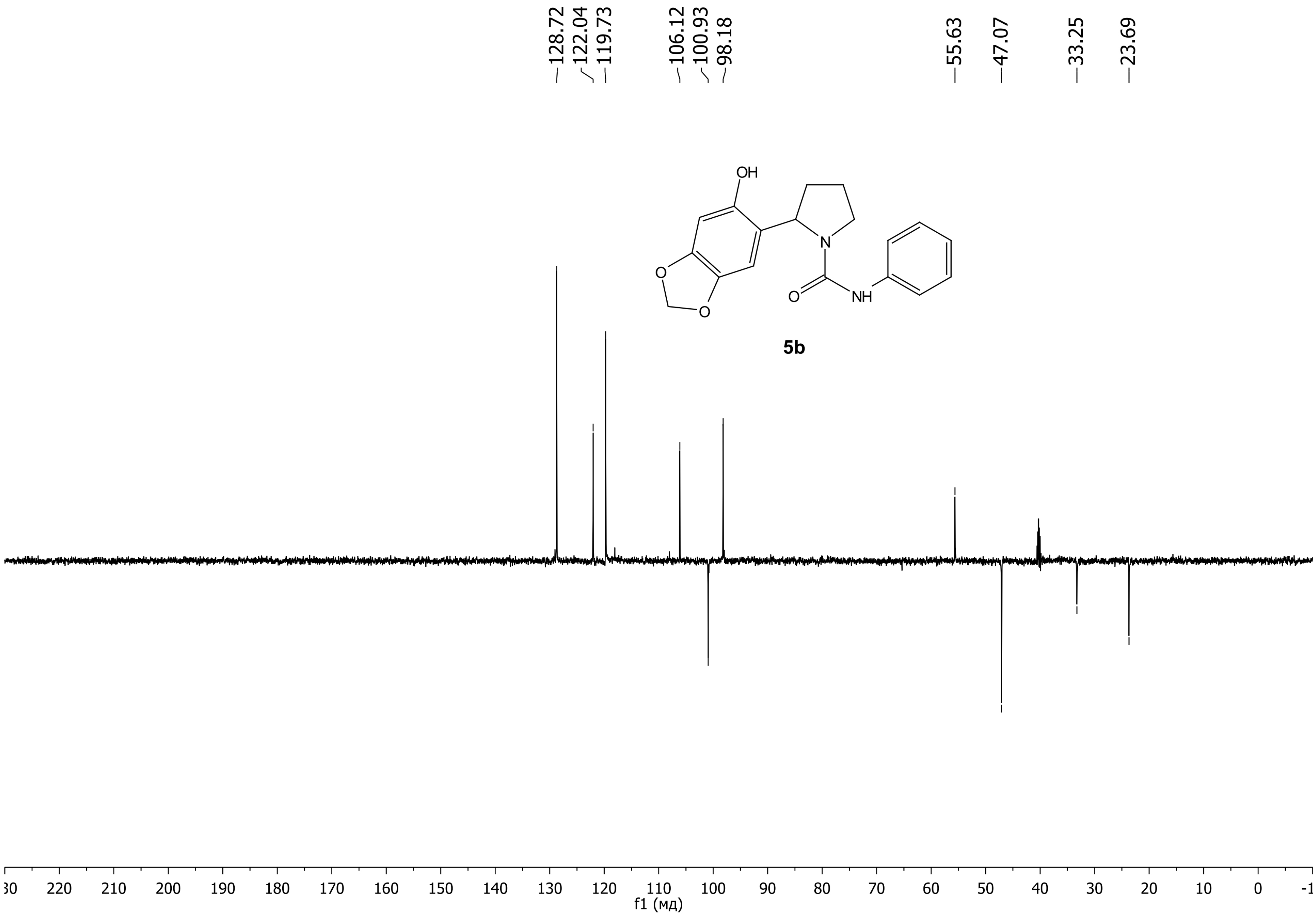
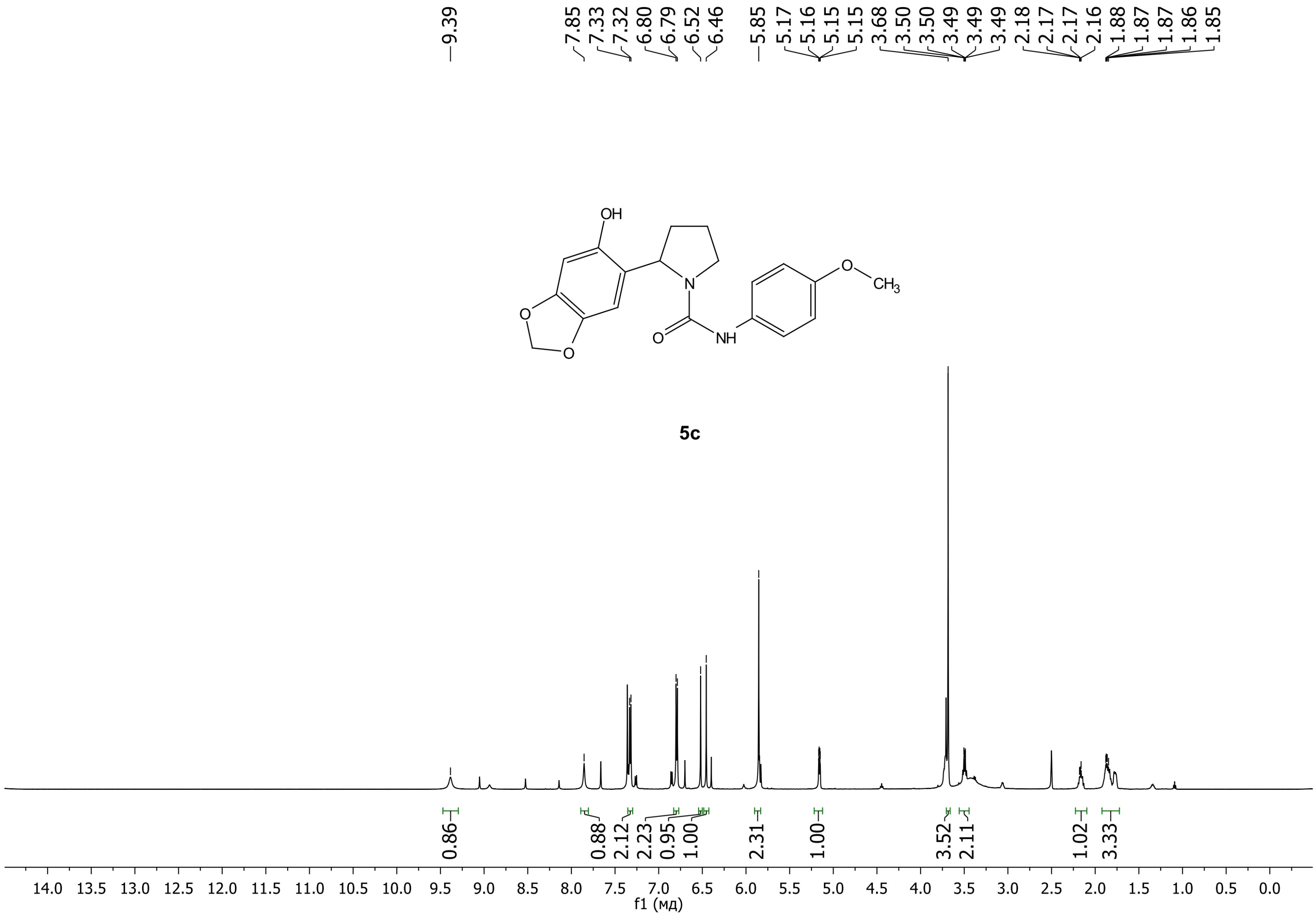

128.72
122.04
119.73
106.12
100.93
98.18
55.63
47.07
33.25
23.69
OH
O
O
N
O
NH
5b
f1 (мд)

Figure S 26.



9.39
7.85
7.33
7.32
6.80
6.79
6.52
6.46
5.85
5.17
5.16
5.15
5.15
3.68
3.50
3.50
3.49
3.49
3.49
2.18
2.17
2.17
2.16
1.88
1.87
1.87
1.86
1.85
OH
O
O
N
O
NH
O
CH3
5c
0.86
0.88
2.12
2.23
0.95
1.00
2.31
1.00
3.52
2.11
1.02
3.33
14.0 13.5 13.0 12.5 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 (мд)

Figure S 27.

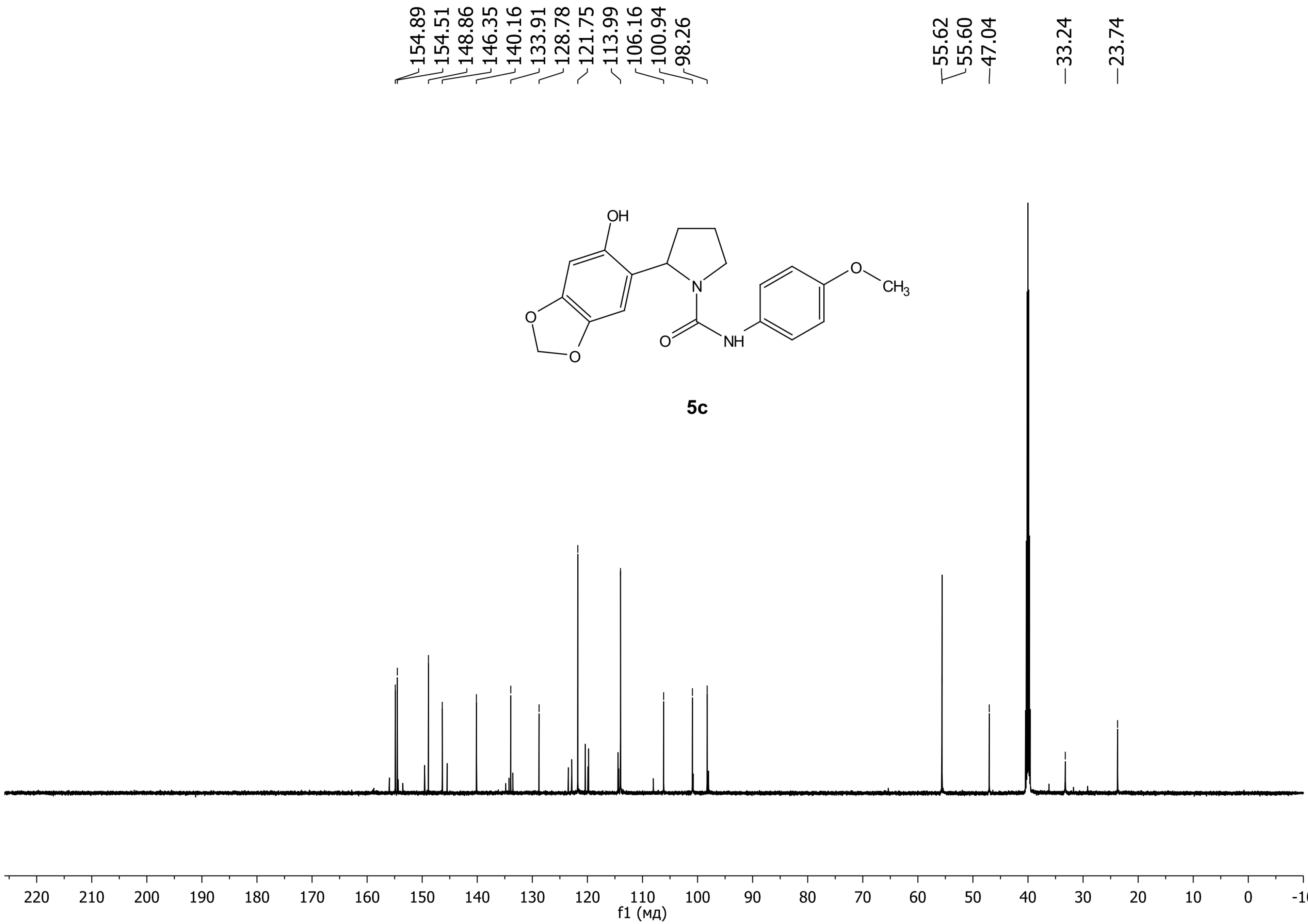
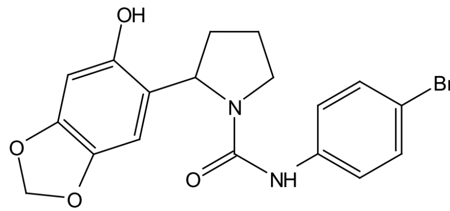

154.89
154.51
148.86
146.35
140.16
133.91
128.78
121.75
113.99
106.16
100.94
98.26
55.62
55.60
47.04
33.24
23.74
OH
O
O
N
O
NH
O
CH3
5c
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (мд)

Figure S 28.



5d

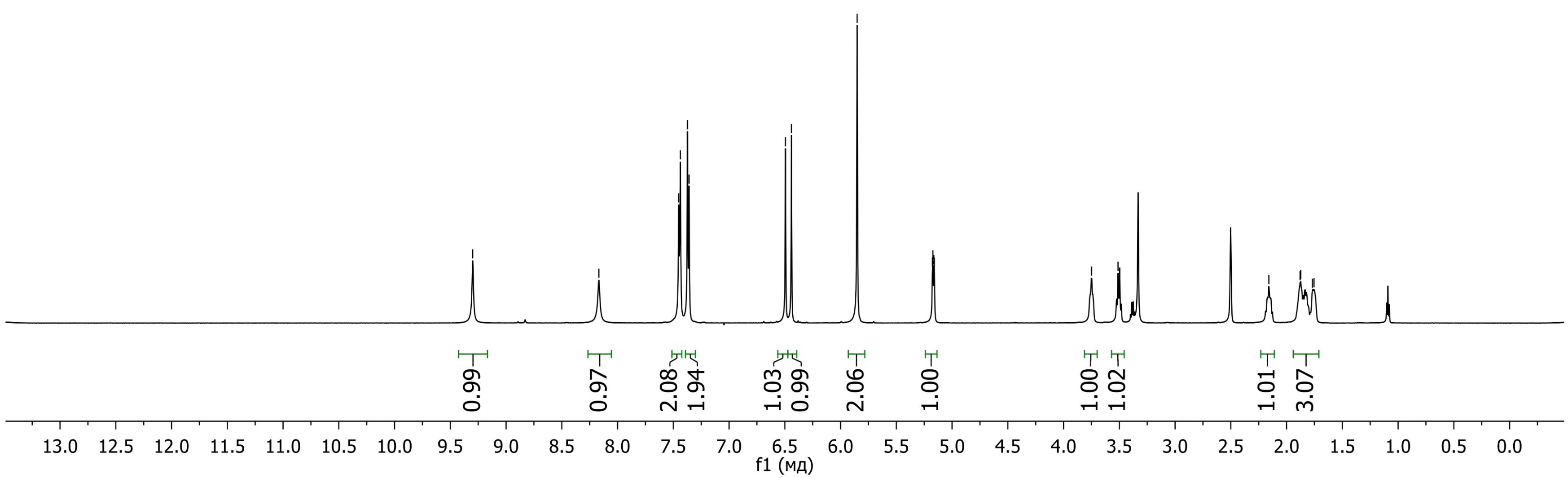


Figure S 29.

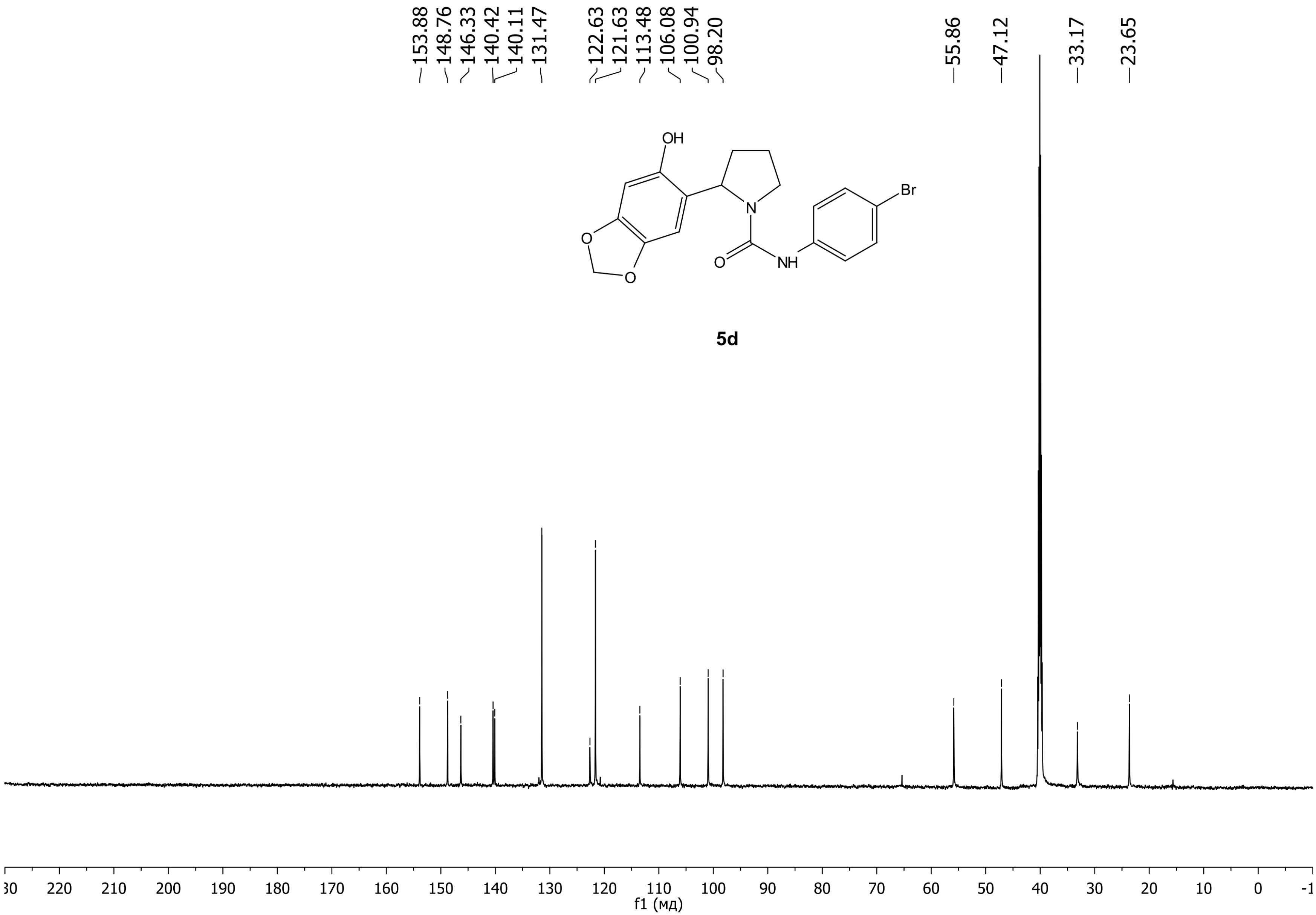
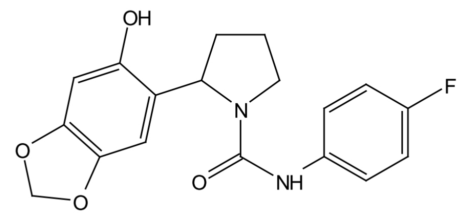

153.88
148.76
146.33
140.42
140.11
131.47
122.63
121.63
113.48
106.08
100.94
98.20
55.86
47.12
33.17
23.65
OH
Br
N
O
O
O
NH
5d
f1 (мд)

Figure S 30.



5e

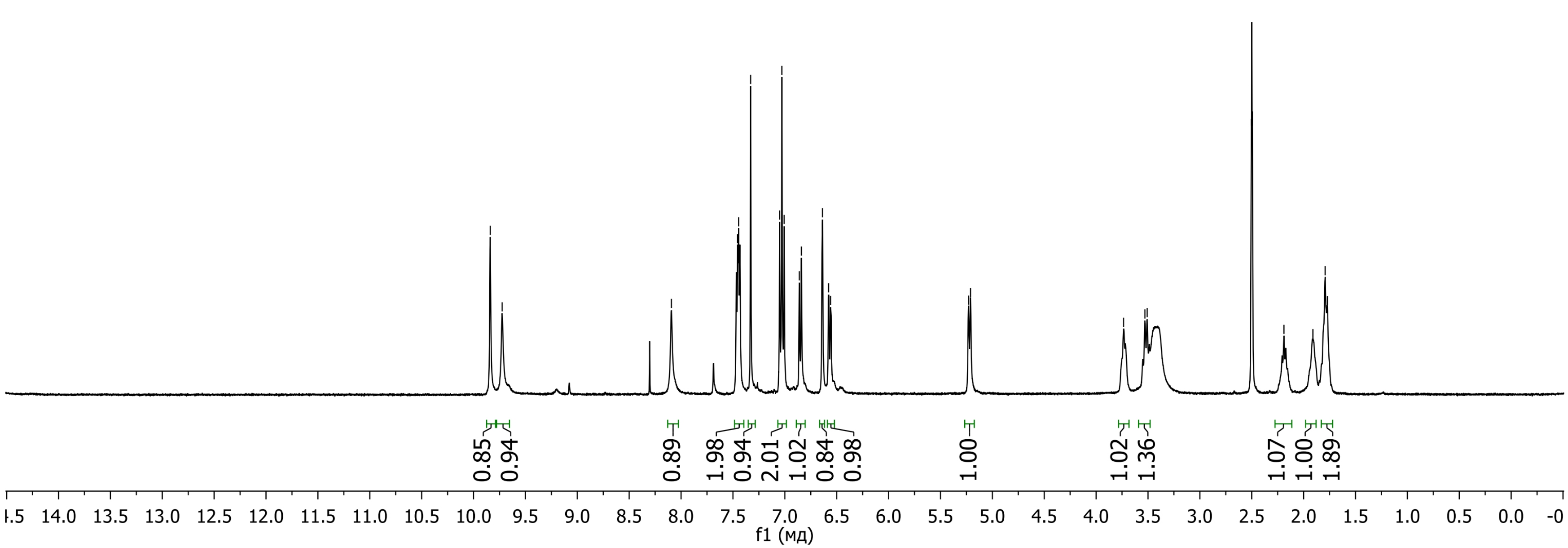
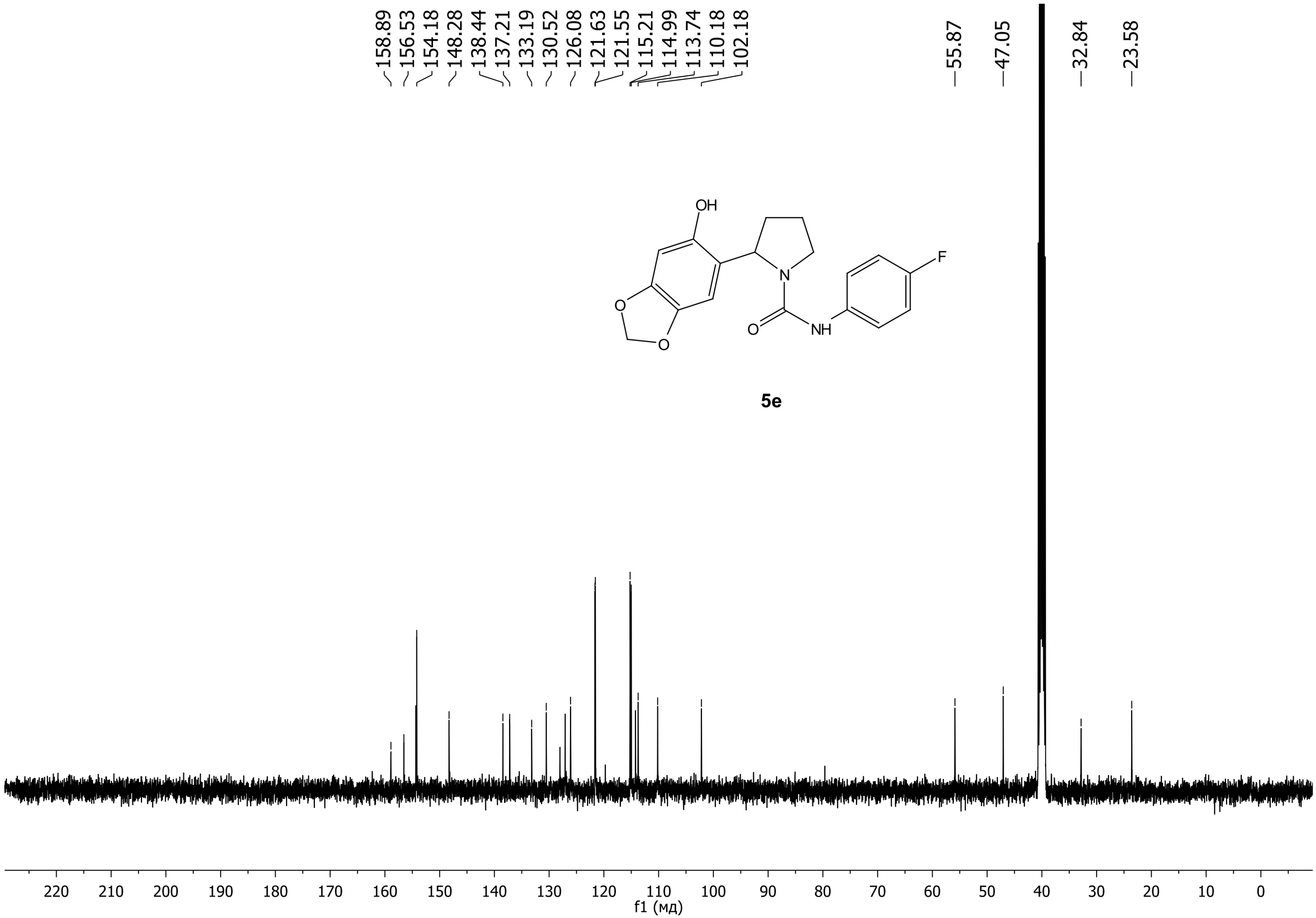


Figure S 31.



5e

Figure S 32.

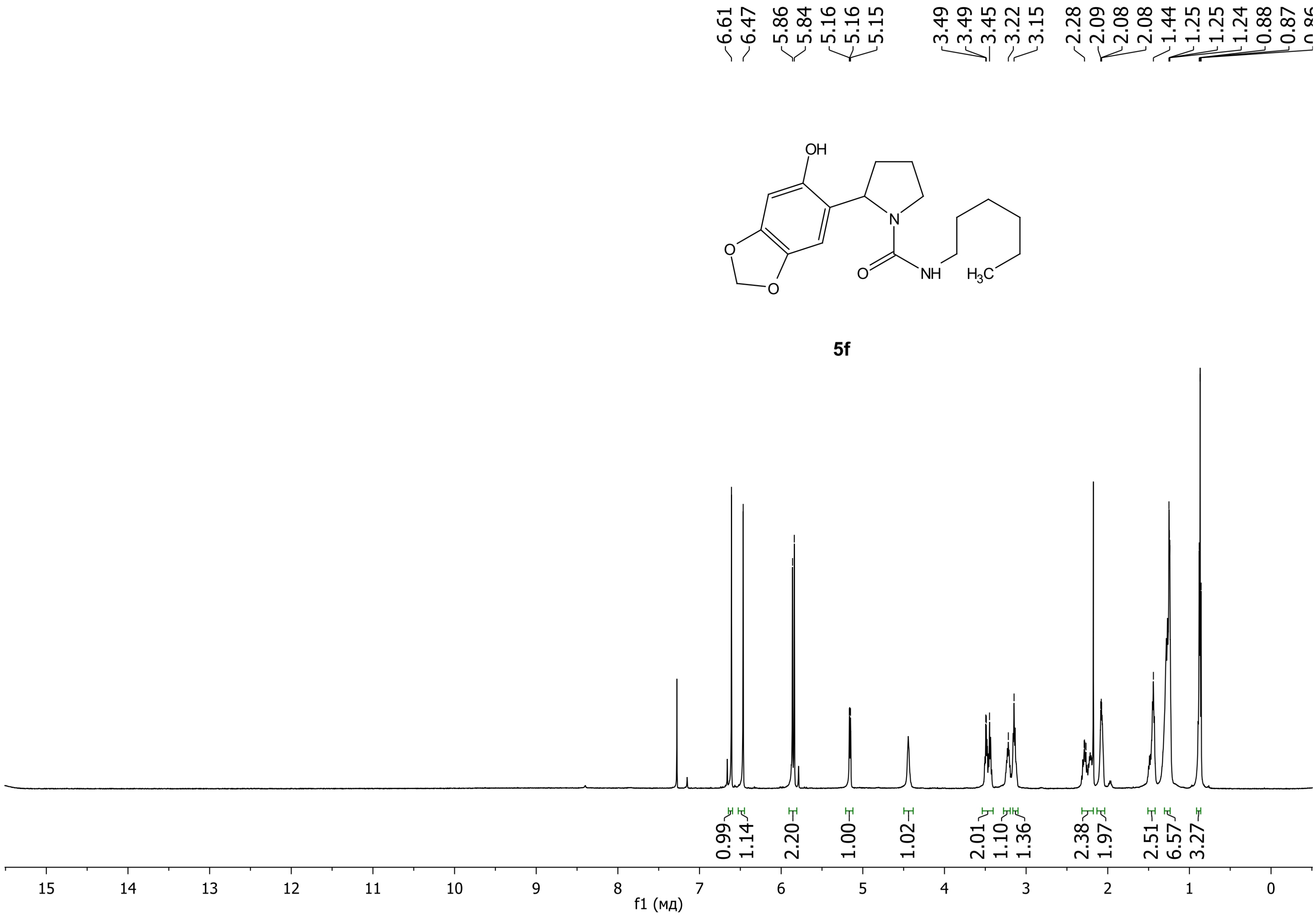

6.61
6.47
5.86
5.84
5.16
5.16
5.15
3.49
3.49
3.45
3.22
3.15
2.28
2.09
2.08
2.08
1.44
1.25
1.25
1.24
0.88
0.87
OH
O
O
N
O
NH
H_3C
5f
0.99
1.14
2.20
1.00
1.02
2.01
1.10
1.36
2.38
1.97
2.51
6.57
3.27
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (мд)

Figure S 33.

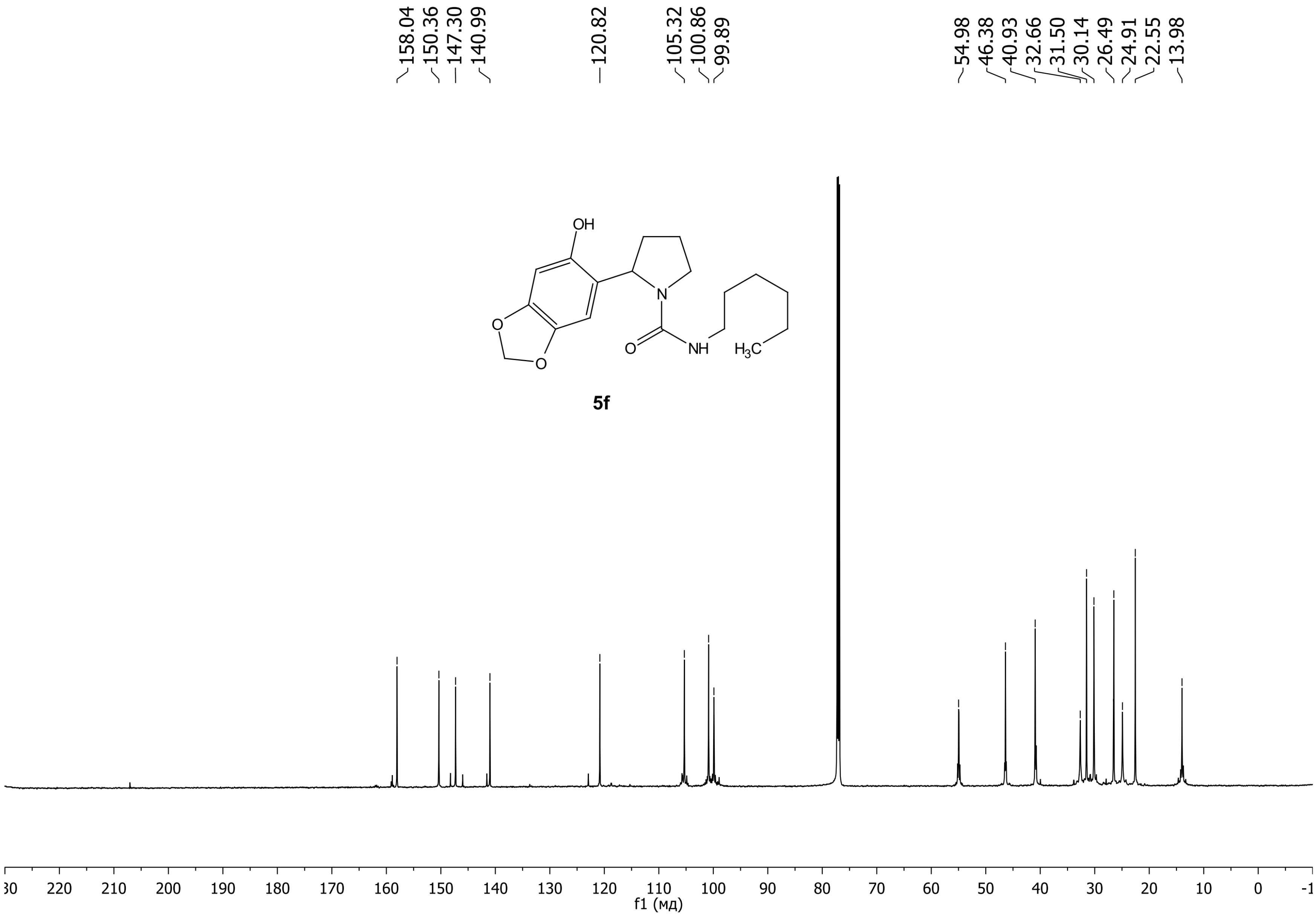
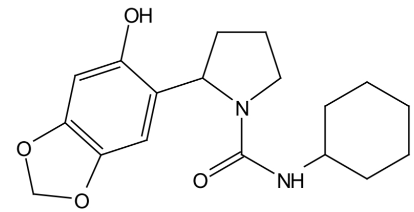

158.04
150.36
147.30
140.99
120.82
105.32
100.86
99.89
54.98
46.38
40.93
32.66
31.50
30.14
26.49
24.91
22.55
13.98
OH
O
O
N
O
NH
H_3C
5f
f1 (мд)

Figure S 34.



5g

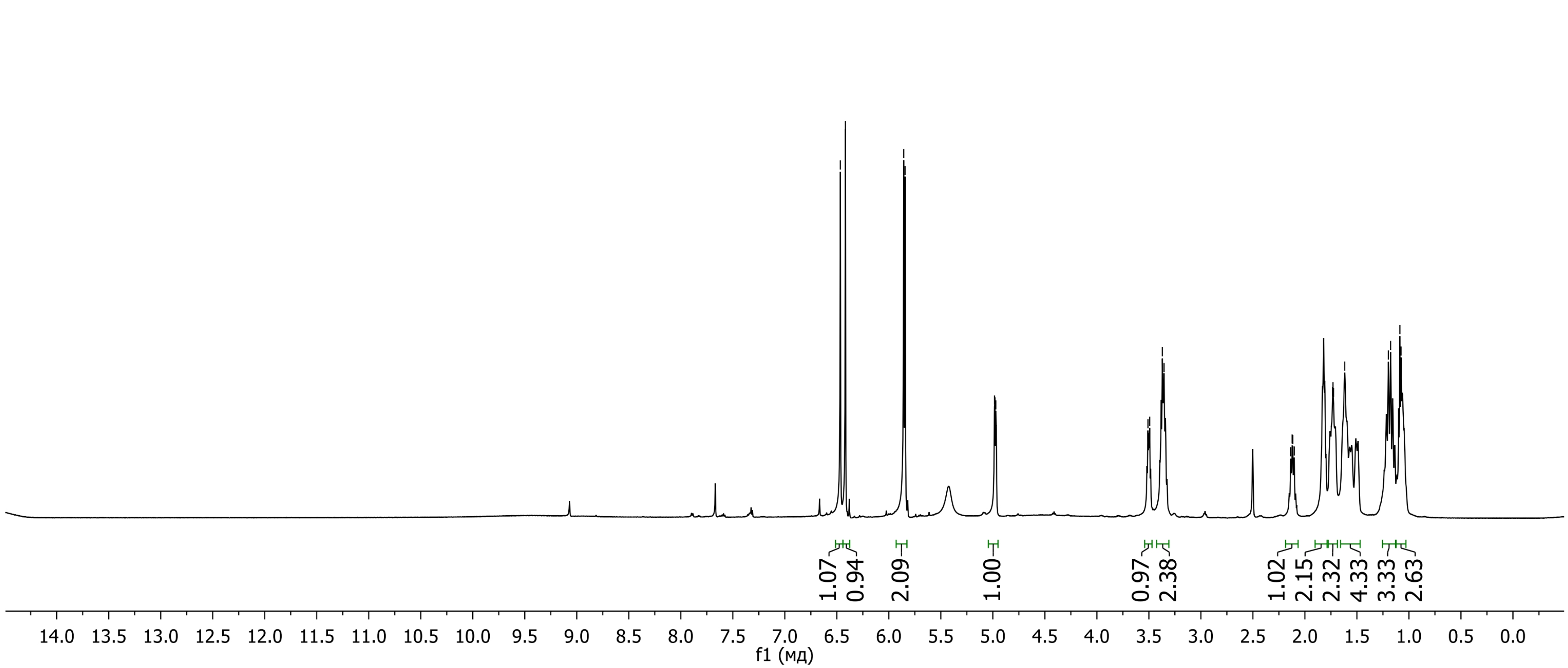
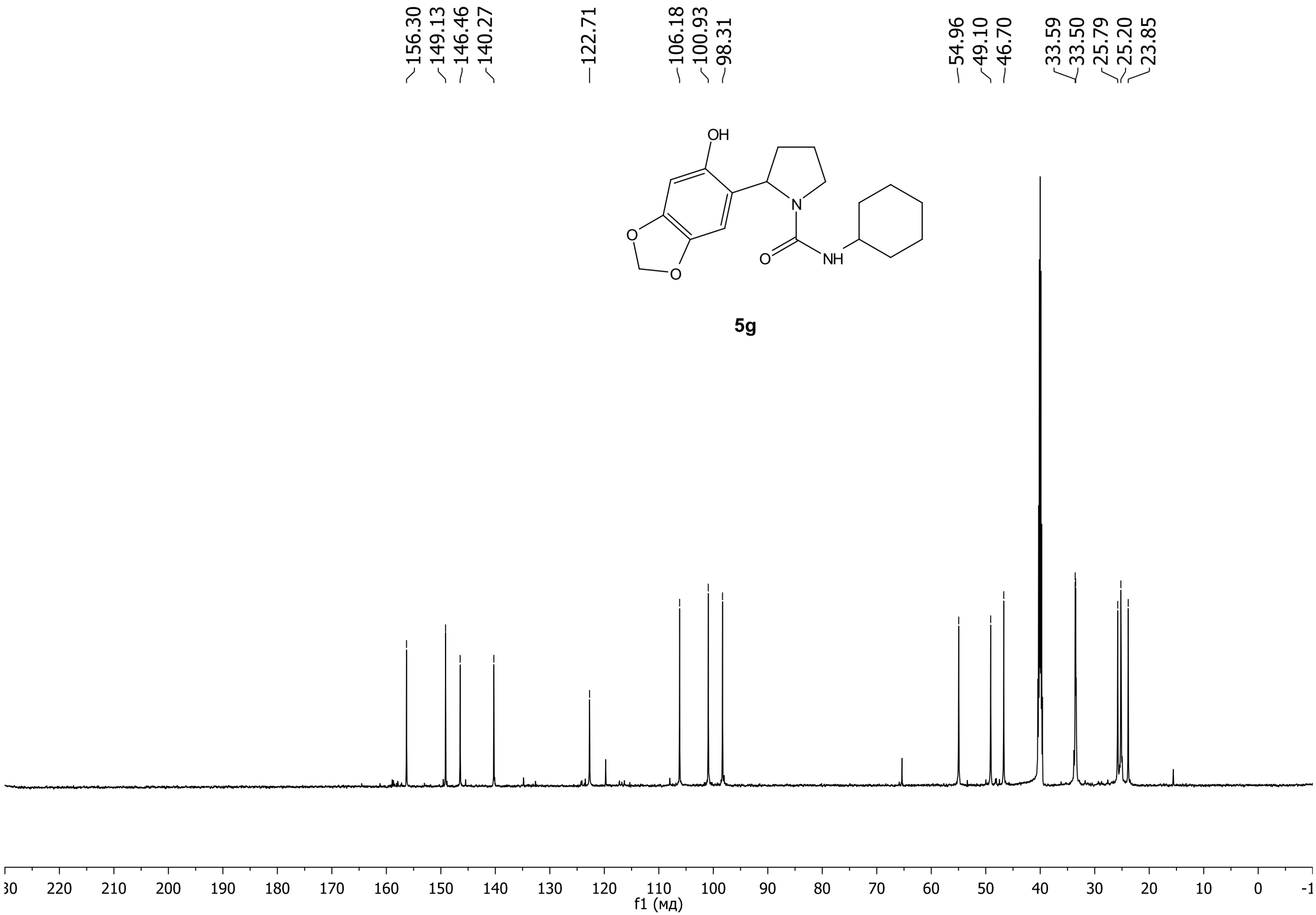


Figure S 35.



156.30
149.13
146.46
140.27
122.71
106.18
100.93
98.31
54.96
49.10
46.70
33.59
33.50
25.79
25.20
23.85
OH
O
O
N
O
NH
5g
f1 (мд)

Figure S 36.

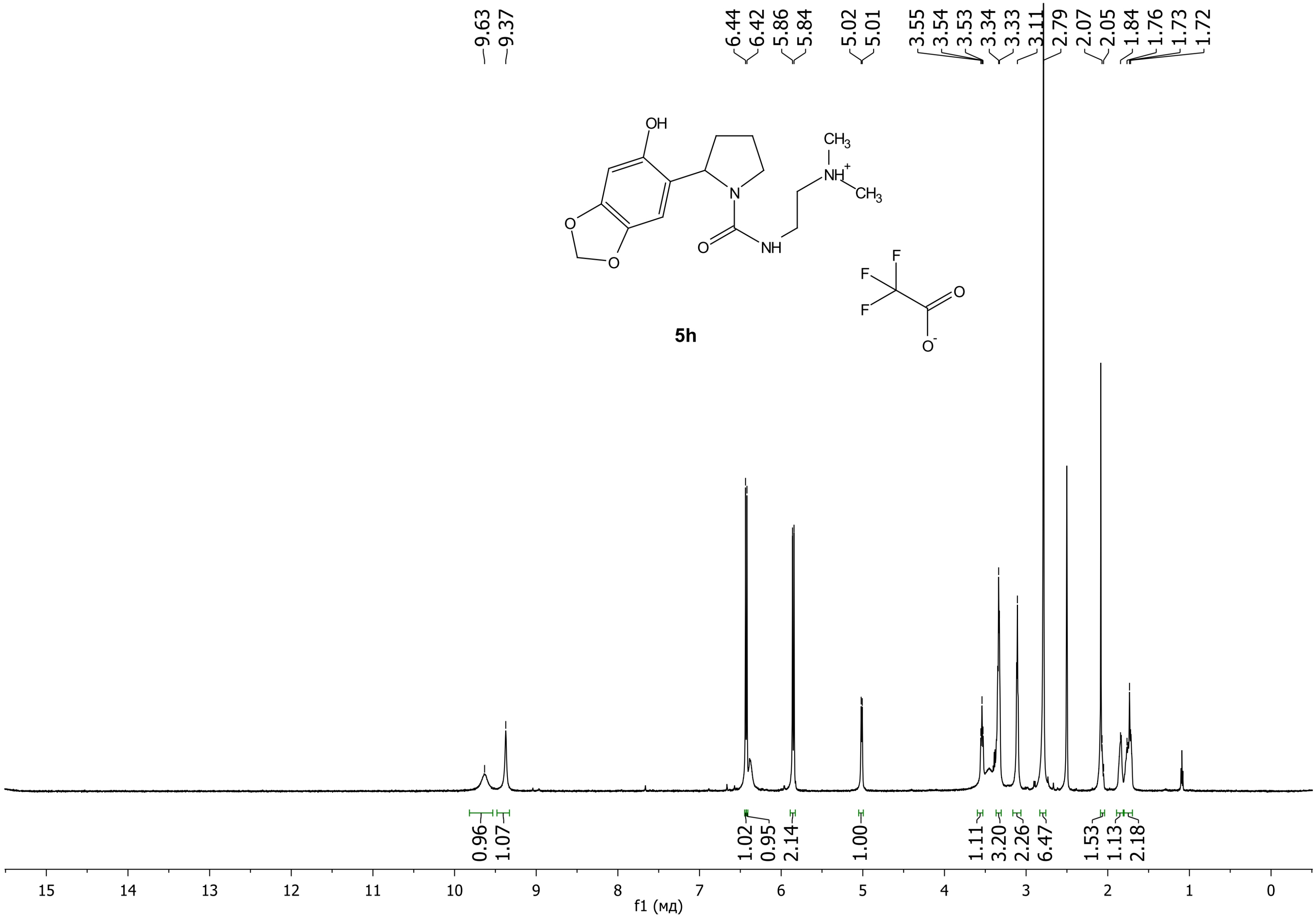
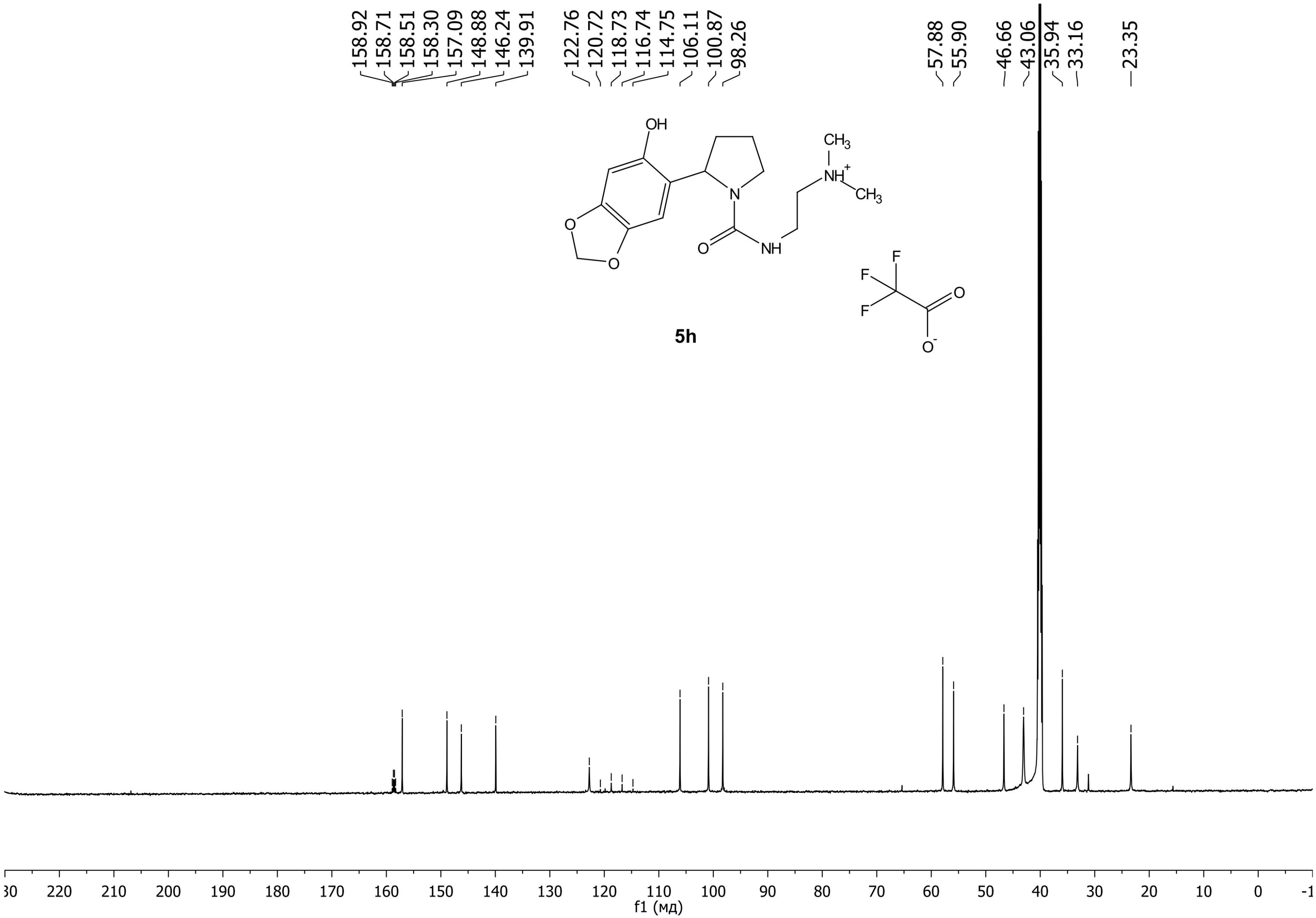

9.63
9.37
6.44
6.42
5.86
5.84
5.02
5.01
3.55
3.54
3.53
3.34
3.33
3.11
2.79
2.07
2.05
1.84
1.76
1.73
1.72
OH
O
O
N
O
NH
CH_3
NH^+
CH_3
F
F
F
O
O^-
5h
0.96
1.07
1.02
0.95
2.14
1.00
1.11
3.20
2.26
6.47
1.53
1.13
2.18
f1 (мд)

Figure S 37.



158.92
158.71
158.51
158.30
157.09
148.88
146.24
139.91
122.76
120.72
118.73
116.74
114.75
106.11
100.87
98.26
57.88
55.90
46.66
43.06
35.94
33.16
23.35
OH
N
O
NH
CH3
NH+
CH3
F
O
O-
5h
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 (мд)

Figure S 38.

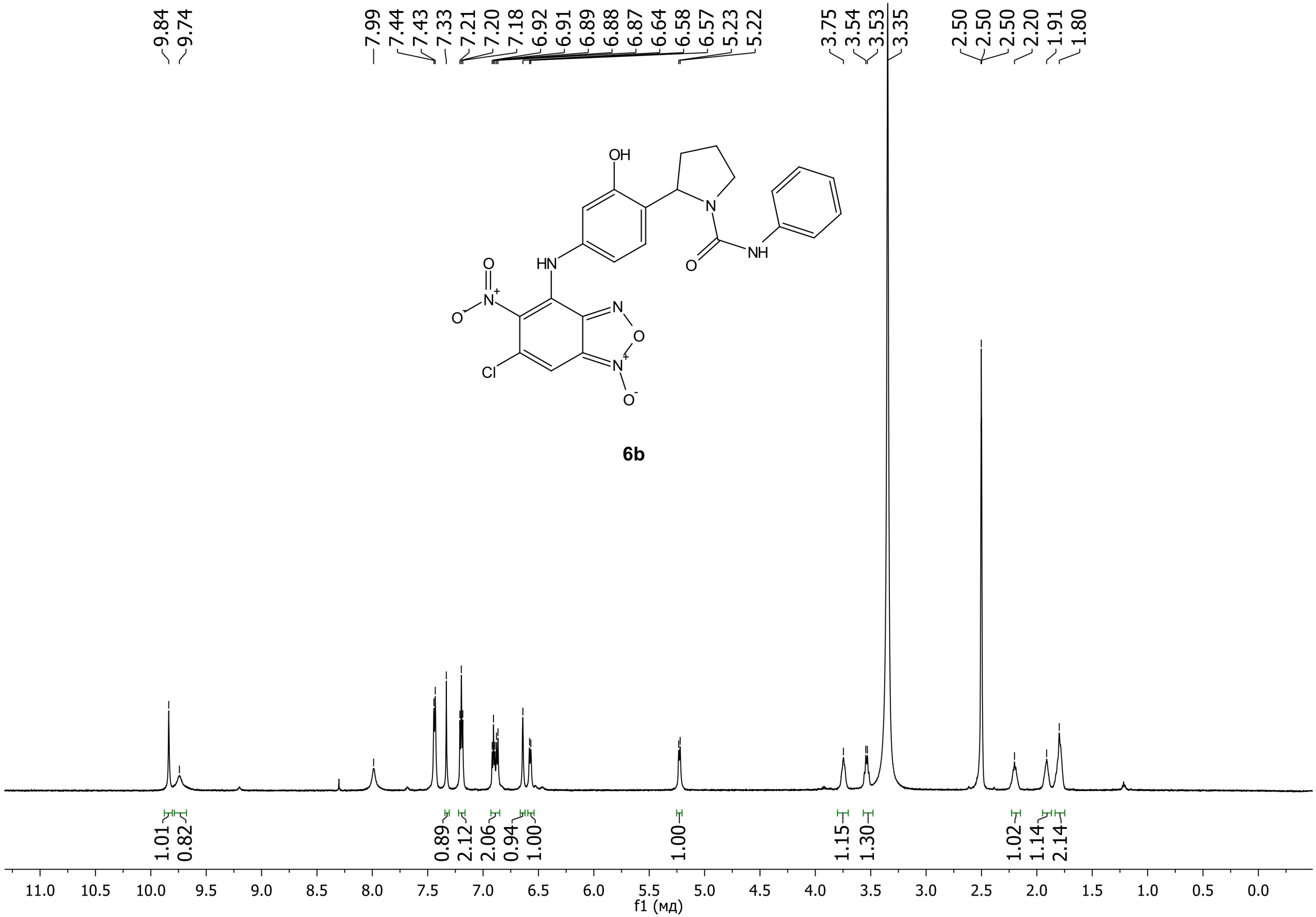

9.84
9.74
7.99
7.44
7.43
7.33
7.21
7.20
7.18
6.92
6.91
6.89
6.88
6.87
6.64
6.58
6.57
5.23
5.22
3.75
3.54
3.53
3.35
2.50
2.50
2.50
2.20
1.91
1.80
OH
N
HN
NH
O
N+
O-
N
O
N+
O-
Cl
6b
1.01
0.82
0.89
2.12
2.06
0.94
1.00
1.00
1.15
1.30
1.02
1.14
2.14
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (мд)

Figure S 39.

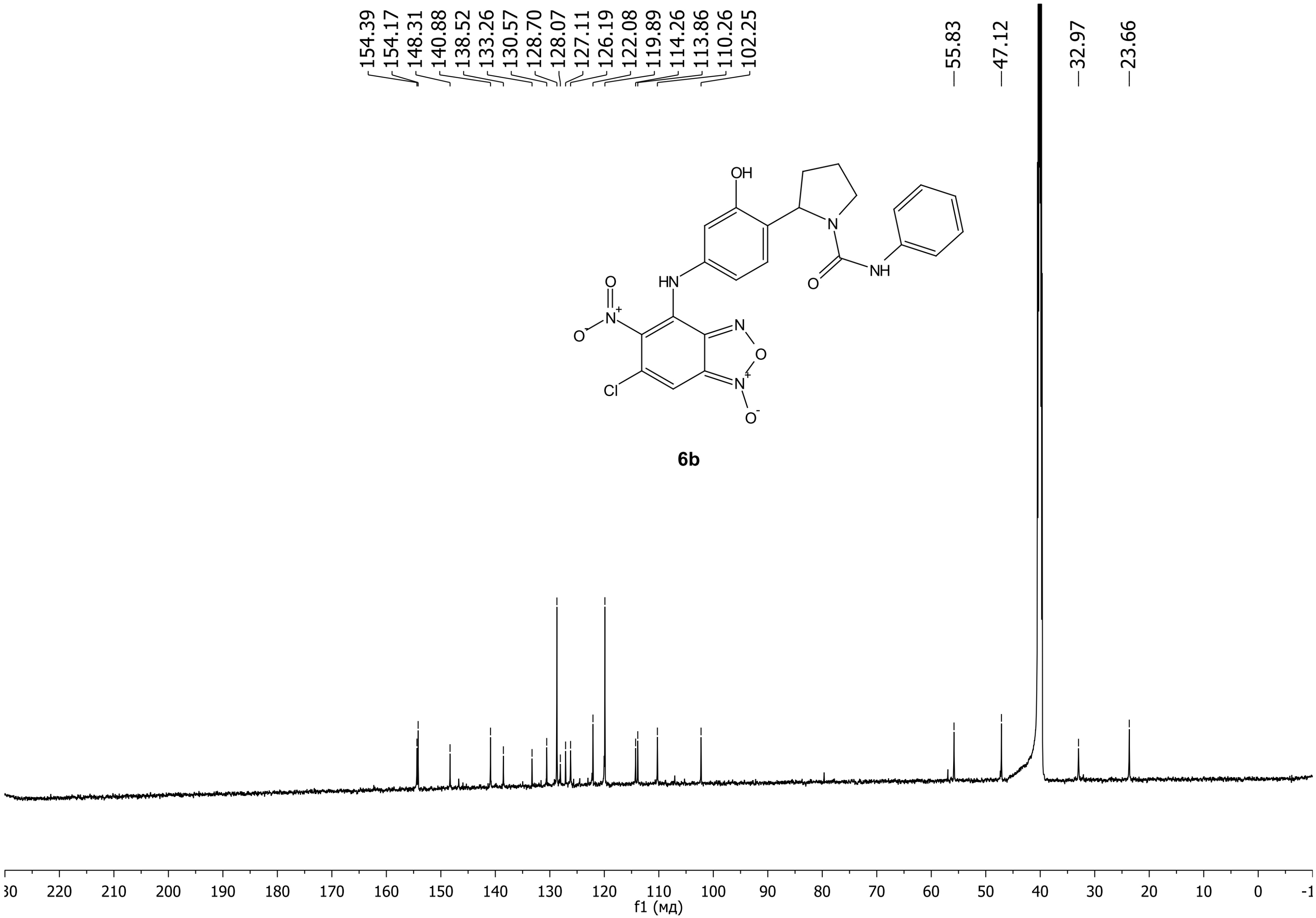

154.39
154.17
148.31
140.88
138.52
133.26
130.57
128.70
128.07
127.11
126.19
122.08
119.89
114.26
113.86
110.26
102.25
55.83
47.12
32.97
23.66
OH
N
NH
O
HN
O
N+
O-
N
O
N+
O-
Cl
6b
f1 (мд)

Figure S 40.

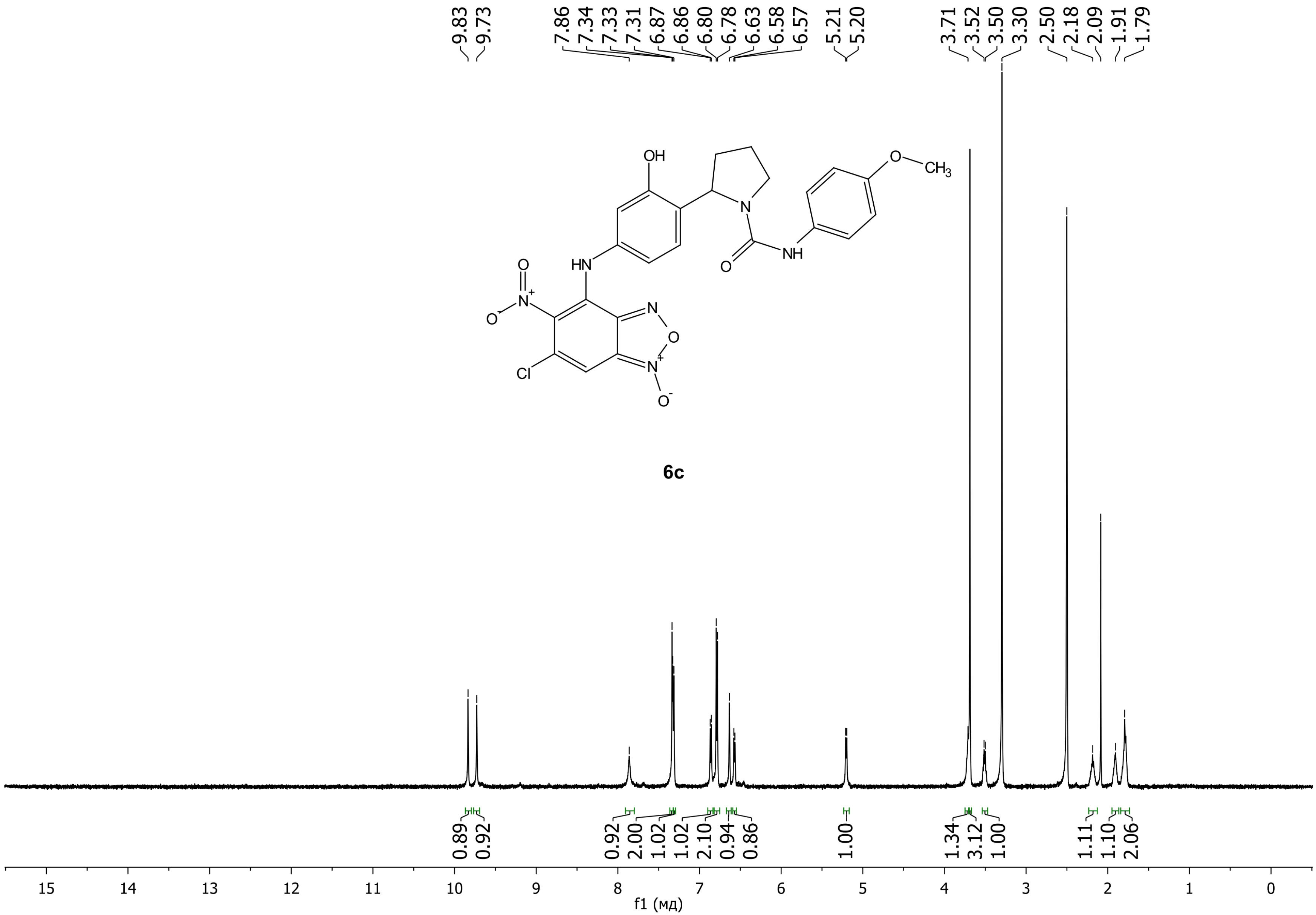

9.83
9.73
7.86
7.34
7.33
7.31
6.87
6.86
6.80
6.78
6.63
6.58
6.57
5.21
5.20
3.71
3.52
3.50
3.30
2.50
2.18
2.09
1.91
1.79
OH
O
CH3
N
HN
NH
O
N+
O-
N
O
N+
O-
Cl
6c
0.89
0.92
0.92
2.00
1.02
1.02
2.10
0.94
0.86
1.00
1.34
3.12
1.00
1.11
1.10
2.06
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (мд)

Figure S 41.

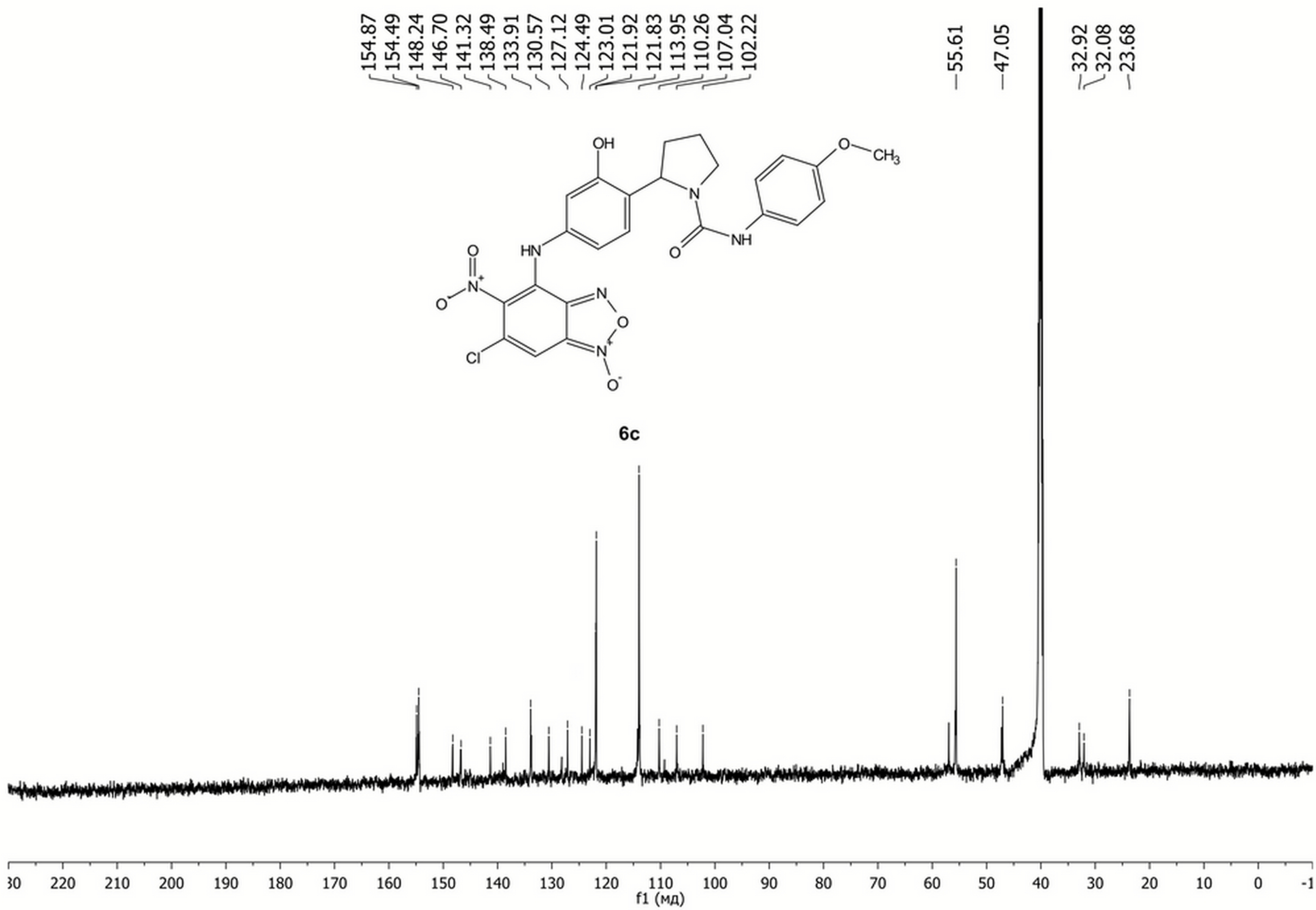

154.87
154.49
148.24
146.70
141.32
138.49
133.91
130.57
127.12
124.49
123.01
121.92
121.83
113.95
110.26
107.04
102.22
55.61
47.05
32.92
32.08
23.68
6c
f1 (мд)

Figure S 42.

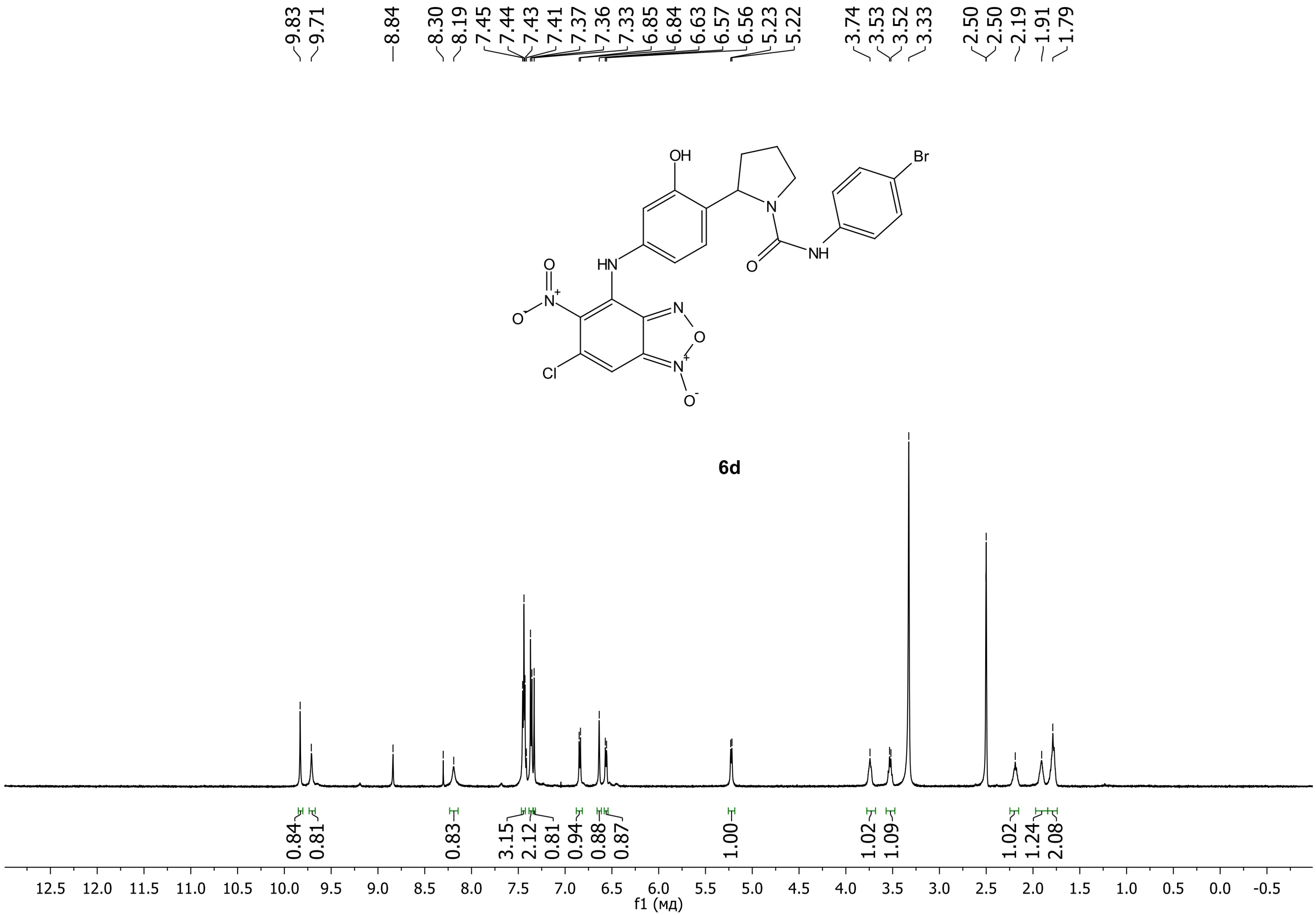

9.83
9.71
8.84
8.30
8.19
7.45
7.44
7.43
7.41
7.37
7.36
7.33
6.85
6.84
6.63
6.57
6.56
5.23
5.22
3.74
3.53
3.52
3.33
2.50
2.50
2.19
1.91
1.79
OH
Br
N
NH
O
HN
O
N+
O-
N
O
N+
Cl
O-
6d
0.84
0.81
0.83
3.15
2.12
0.81
0.94
0.88
0.87
1.00
1.02
1.09
1.02
1.24
2.08
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 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 -0.5
f1 (мд)

Figure S 43.

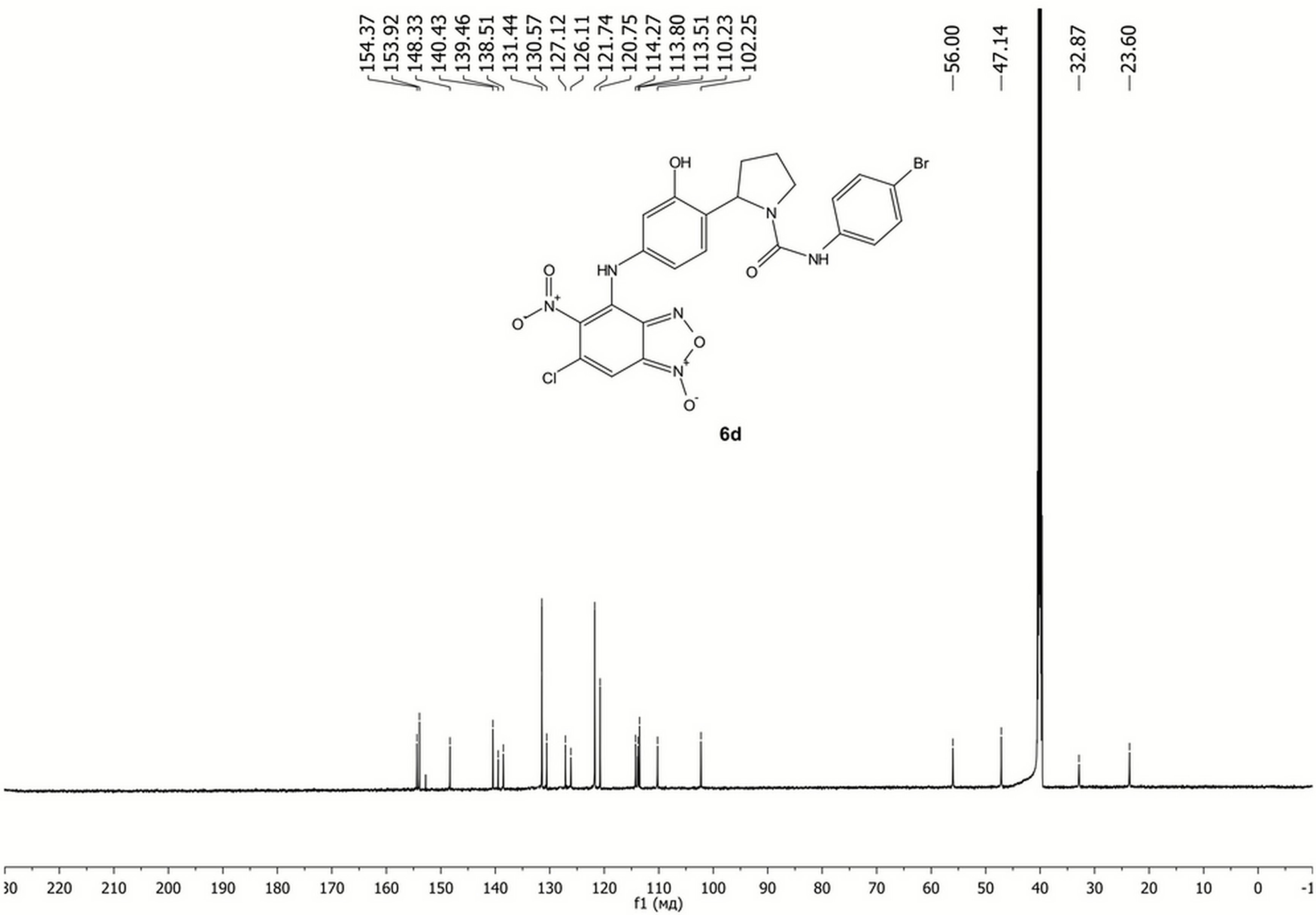
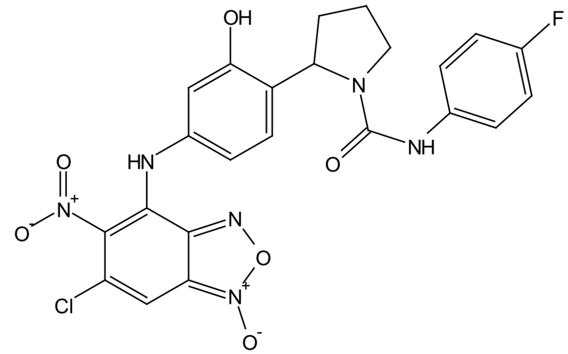

154.37
153.92
148.33
140.43
139.46
138.51
131.44
130.57
127.12
126.11
121.74
120.75
114.27
113.80
113.51
110.23
102.25
56.00
47.14
32.87
23.60
OH
Br
N
NH
O
HN
O
N
O
N
O
N
Cl
O
6d
f1 (мд)

Figure S 44.



6e

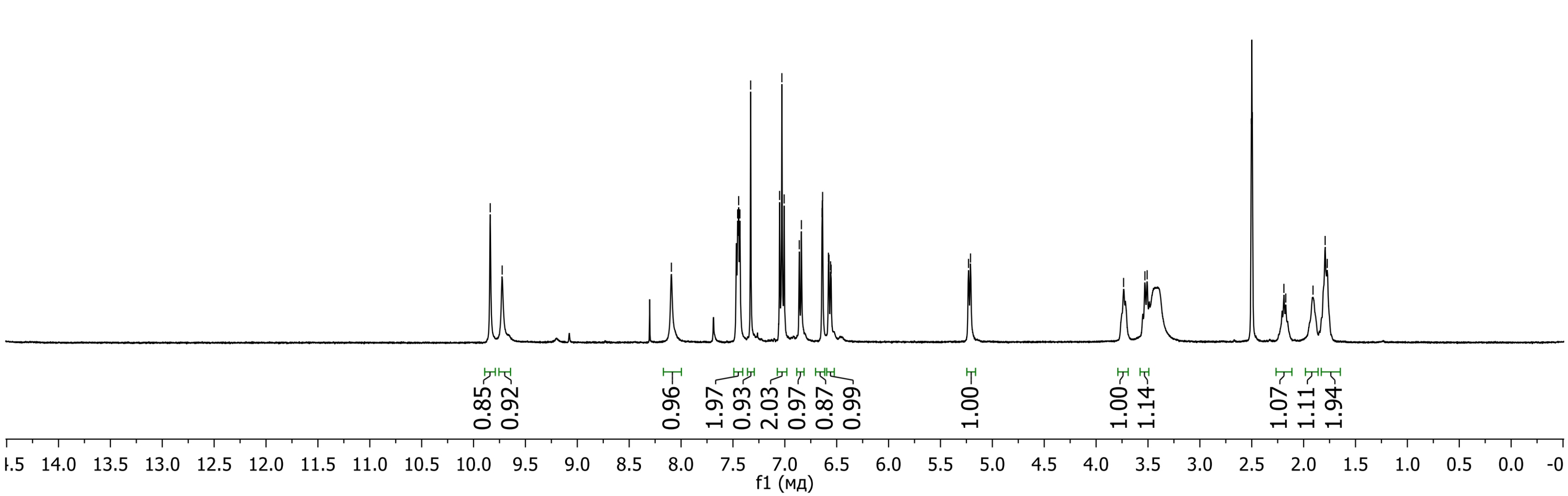


Figure S 45.

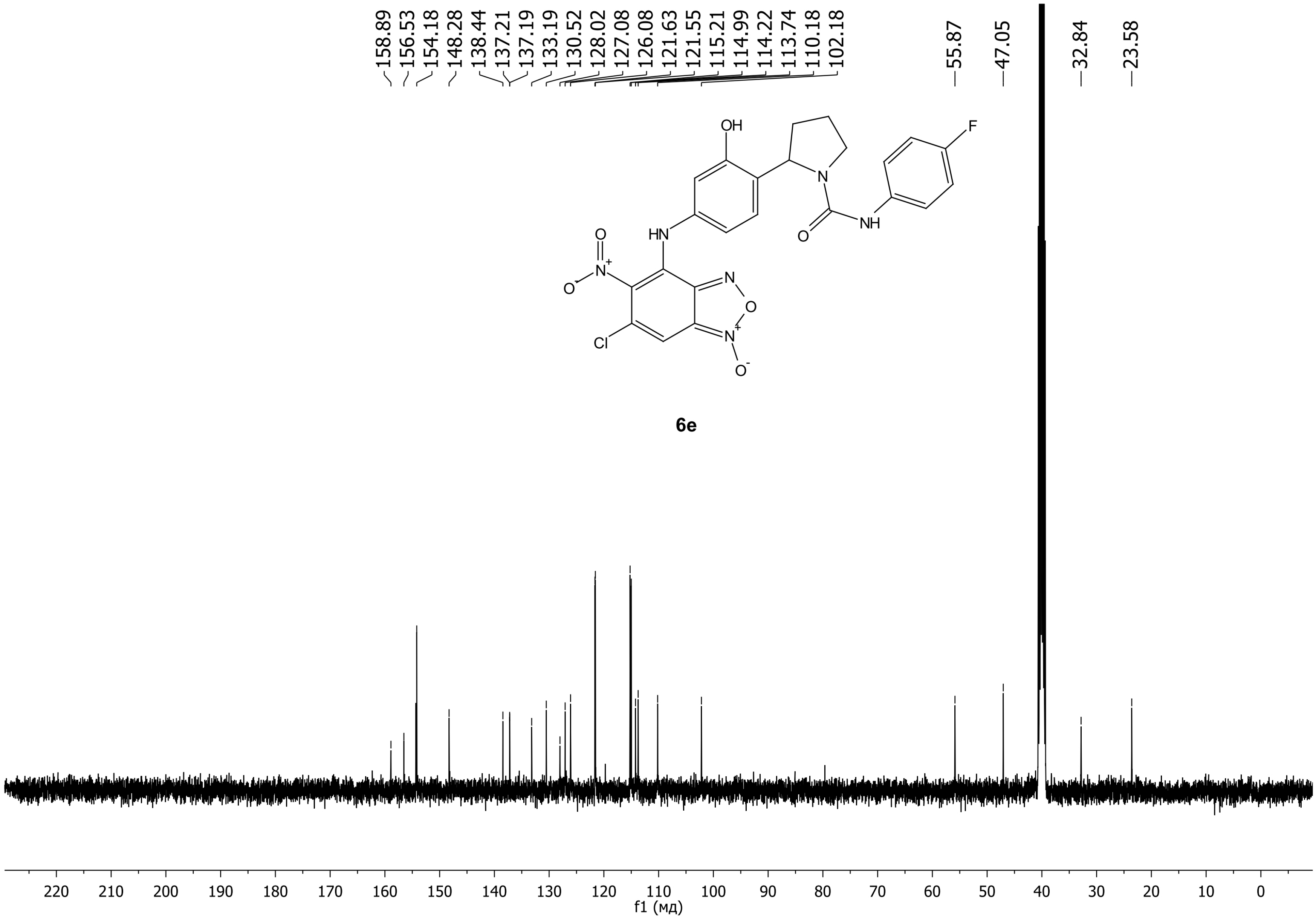

158.89
156.53
154.18
148.28
138.44
137.21
137.19
133.19
130.52
128.02
127.08
126.08
121.63
121.55
115.21
114.99
114.22
113.74
110.18
102.18
55.87
47.05
32.84
23.58
OH
F
N
HN
NH
O
N+
O-
N
O
N+
O-
Cl
6e
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)

Figure S 46.

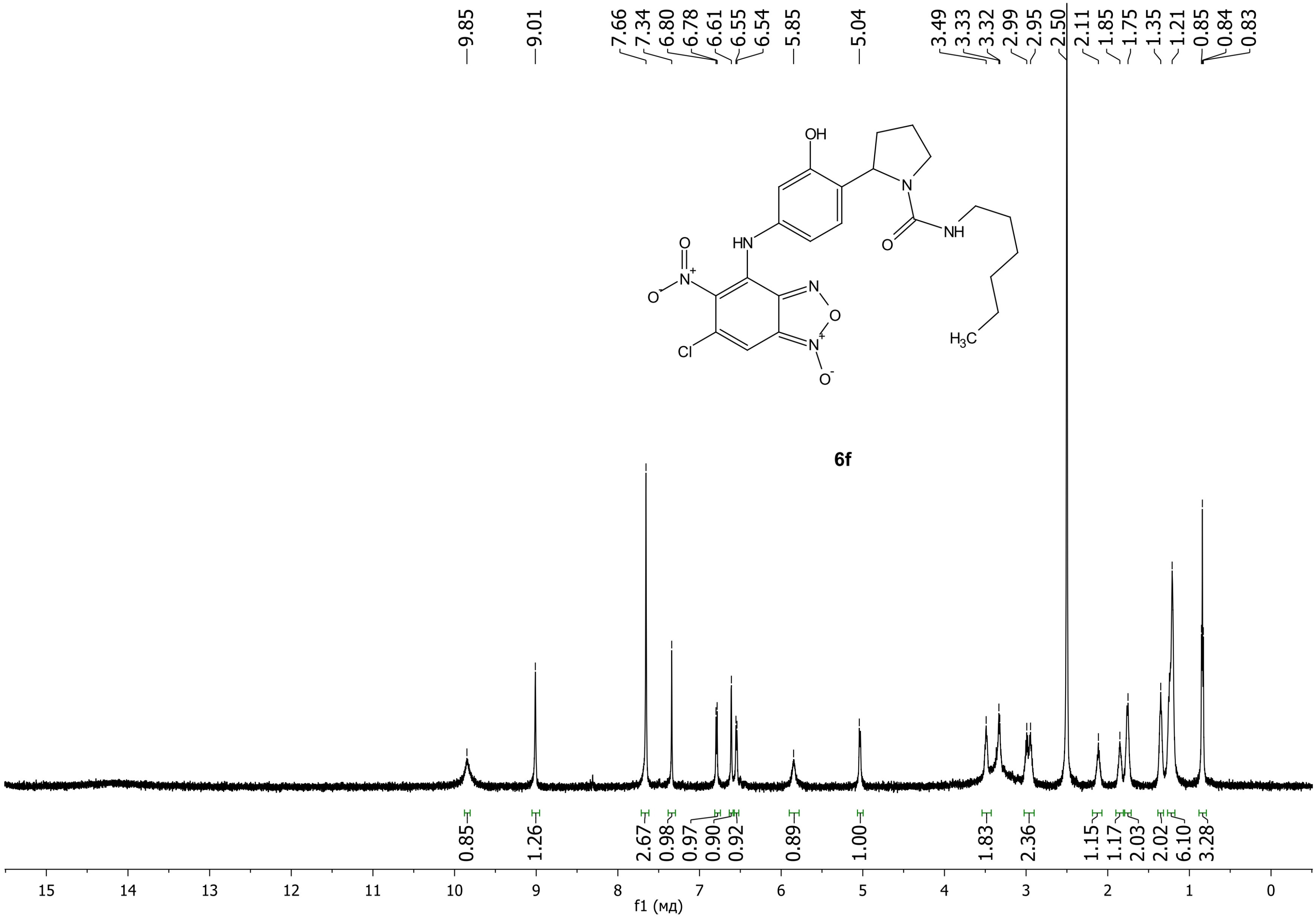

9.85
9.01
7.66
7.34
6.80
6.78
6.61
6.55
6.54
5.85
5.04
3.49
3.33
3.32
2.99
2.95
2.50
2.11
1.85
1.75
1.35
1.21
0.85
0.84
0.83
OH
HN
N
NH
O
H_3C
Cl
6f
0.85
1.26
2.67
0.98
0.97
0.90
0.92
0.89
1.00
1.83
2.36
1.15
1.17
2.03
2.02
6.10
3.28
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (мд)

Figure S 47.

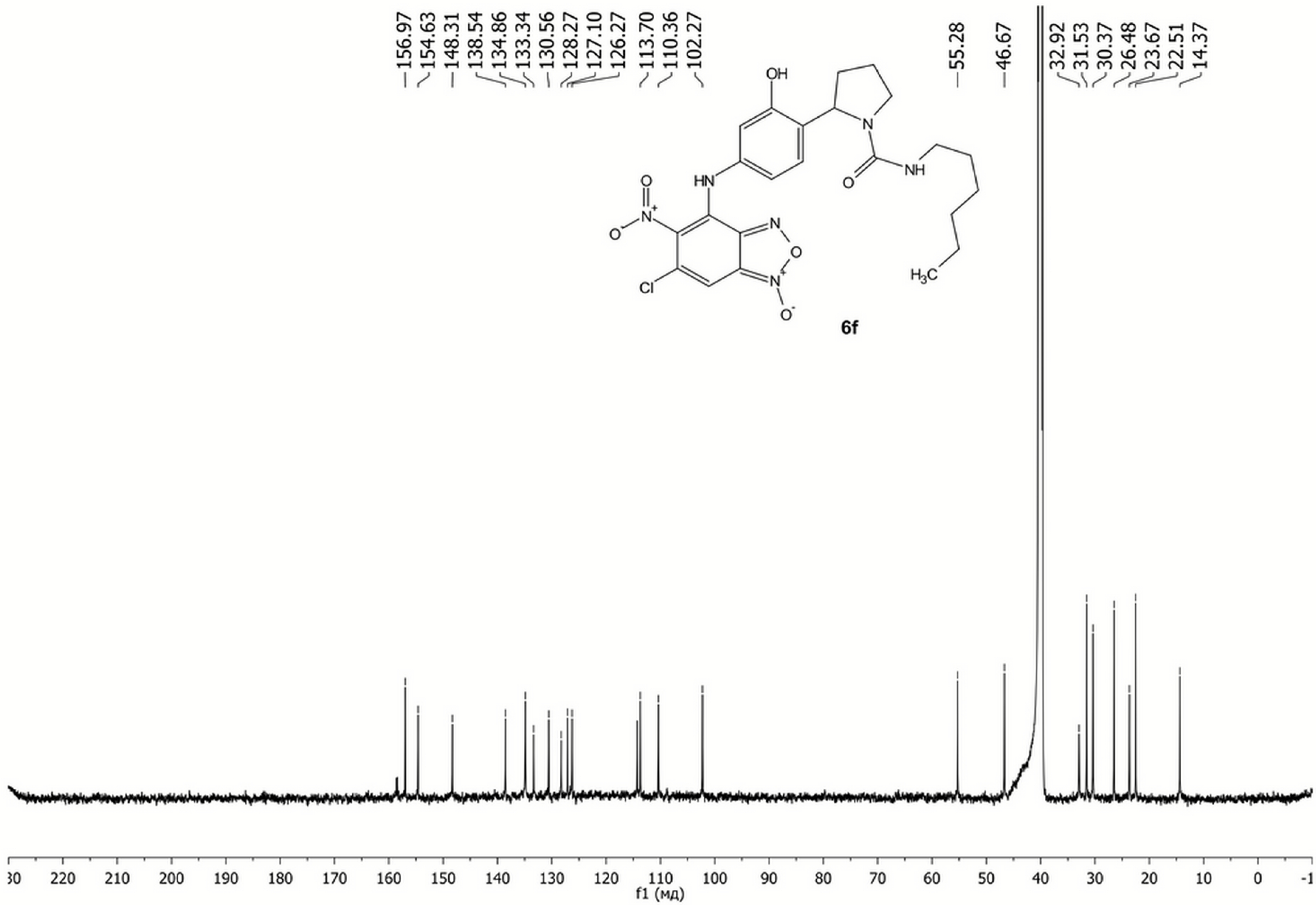

156.97
154.63
148.31
138.54
134.86
133.34
130.56
128.27
127.10
126.27
113.70
110.36
102.27
55.28
46.67
32.92
31.53
30.37
26.48
23.67
22.51
14.37
OH
HN
N
NH
O
H3C
Cl
6f
f1 (мд)

Figure S 48.

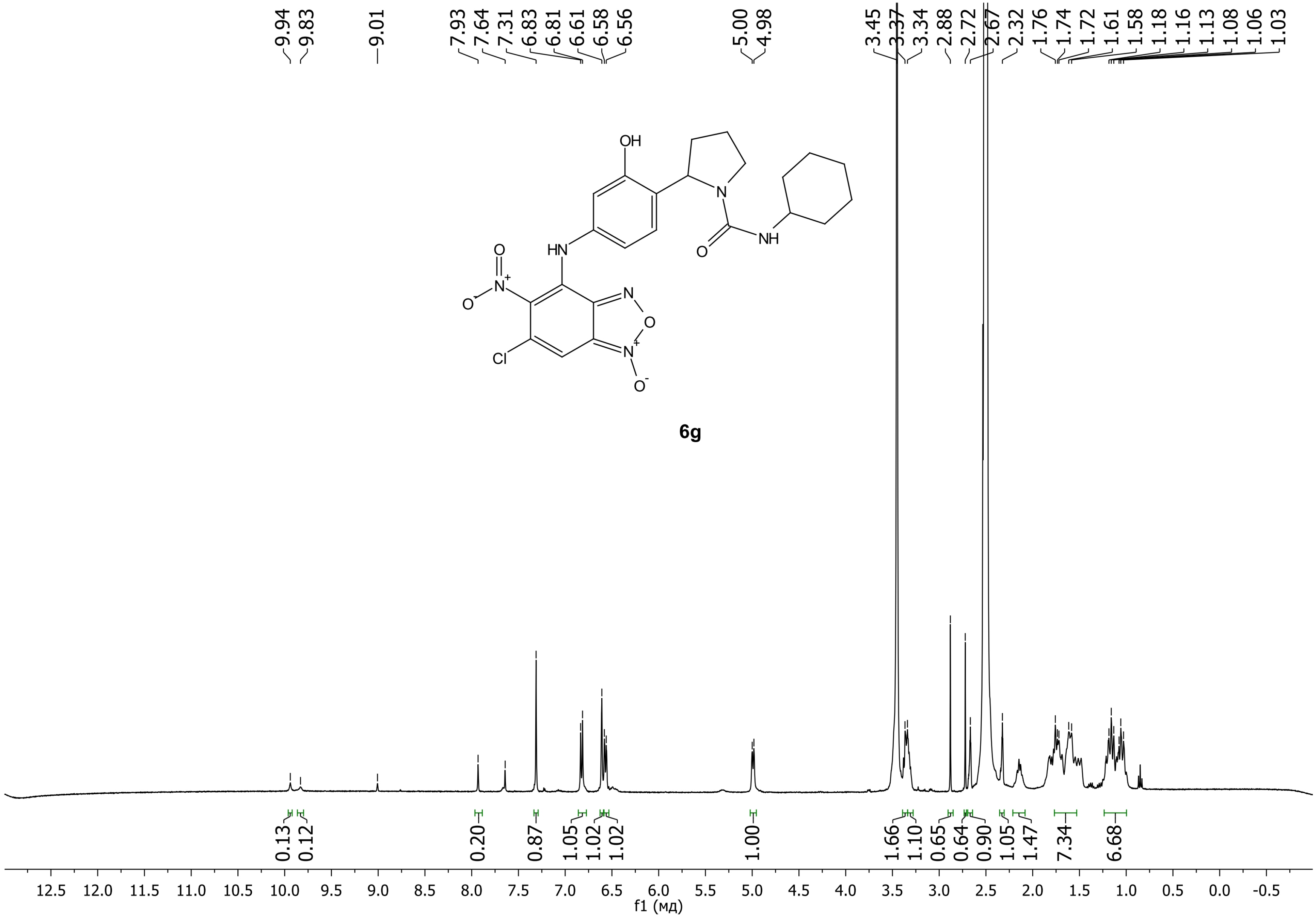


Figure S 49.

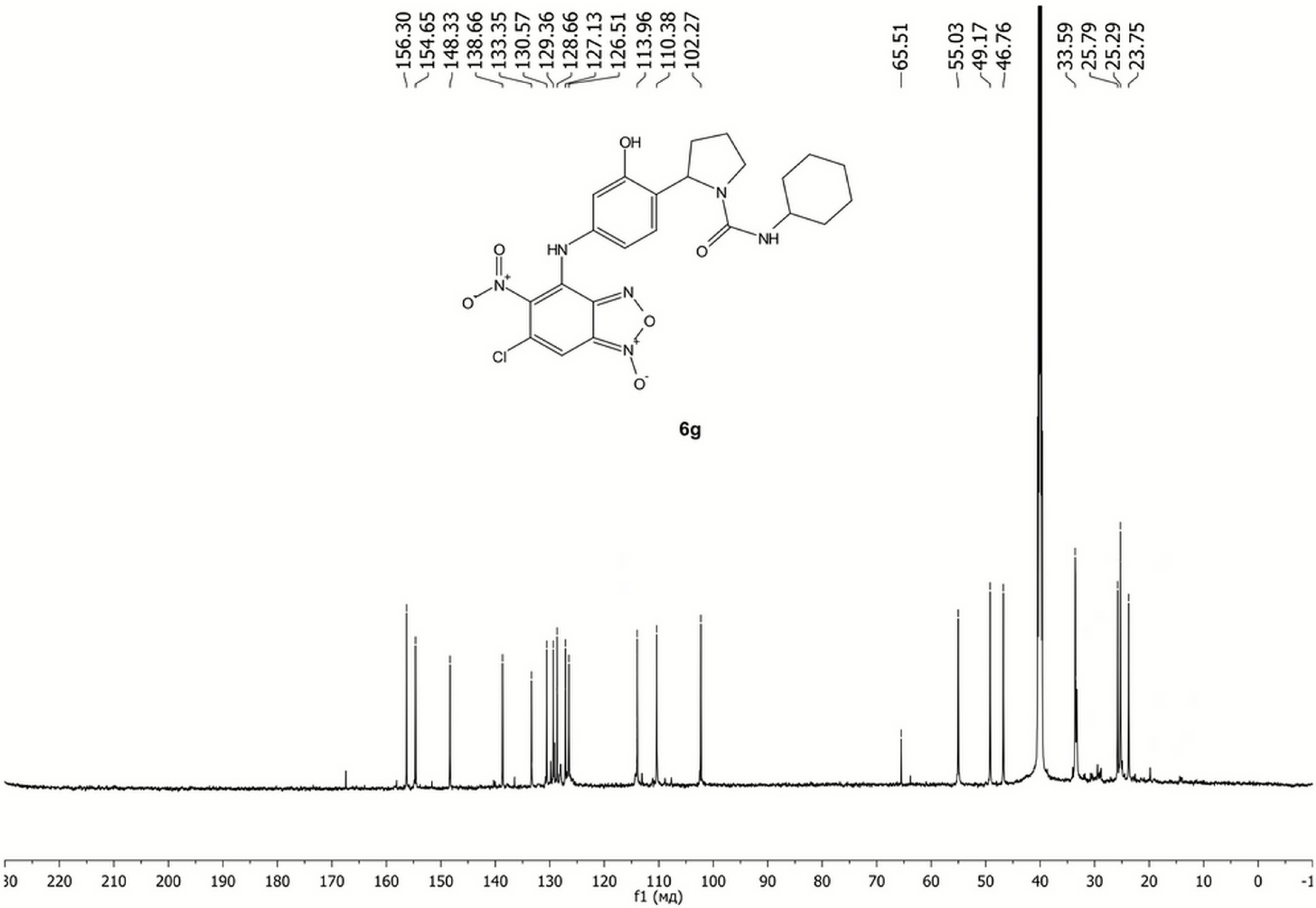

156.30
154.65
148.33
138.66
133.35
130.57
129.36
128.66
127.13
126.51
113.96
110.38
102.27
65.51
55.03
49.17
46.76
33.59
25.79
25.29
23.75
6g
f1 (мд)

Figure S 50.

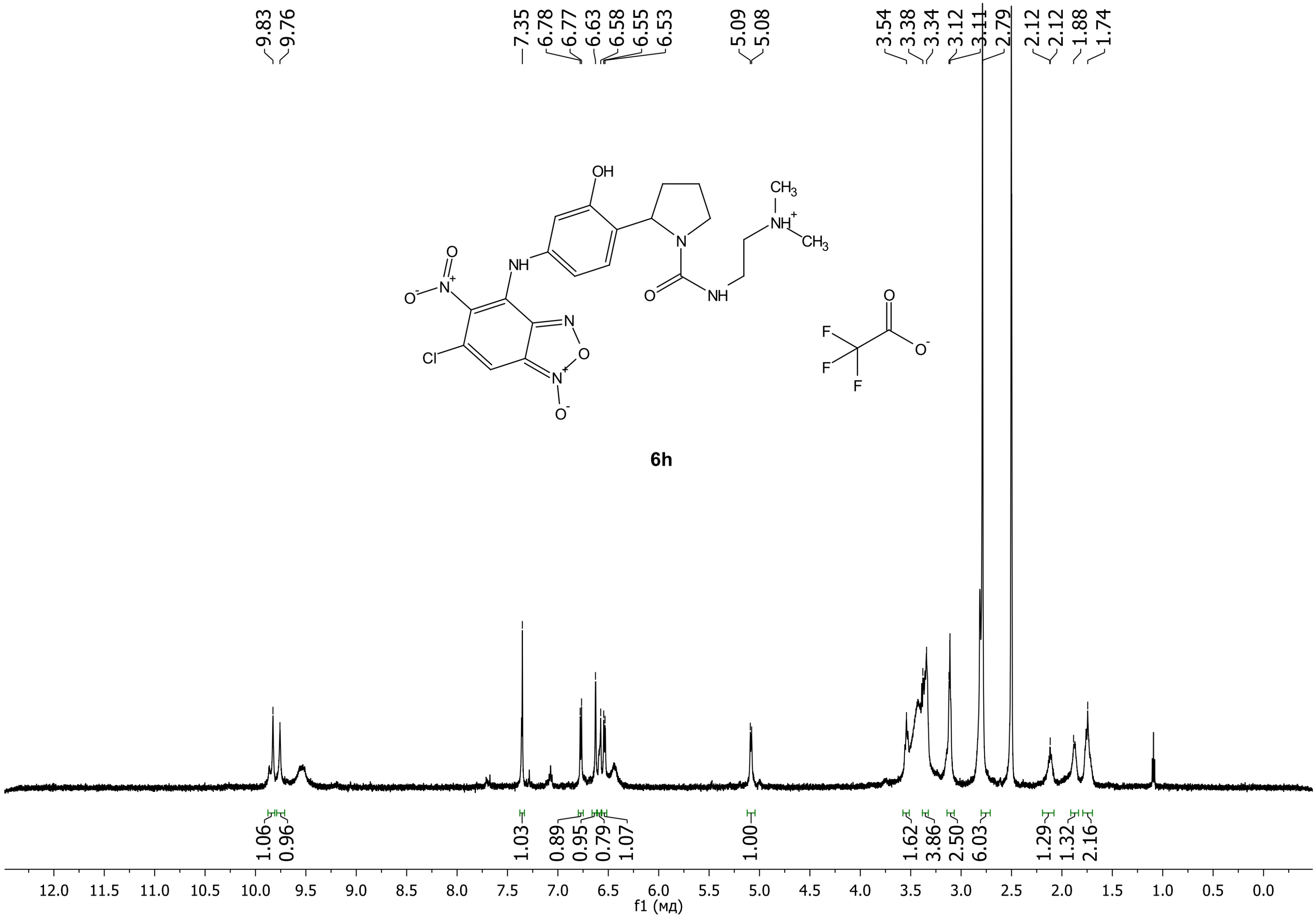
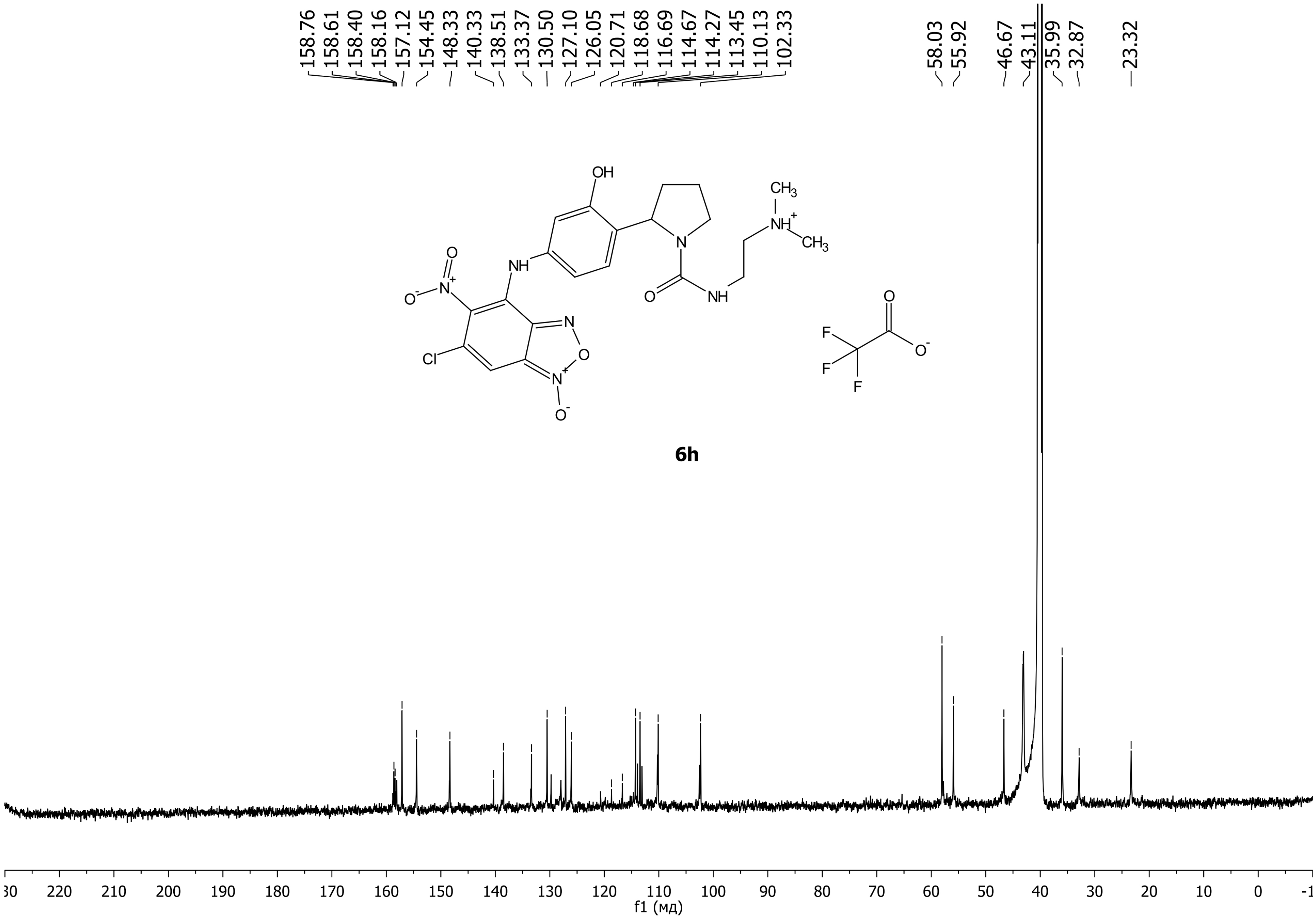
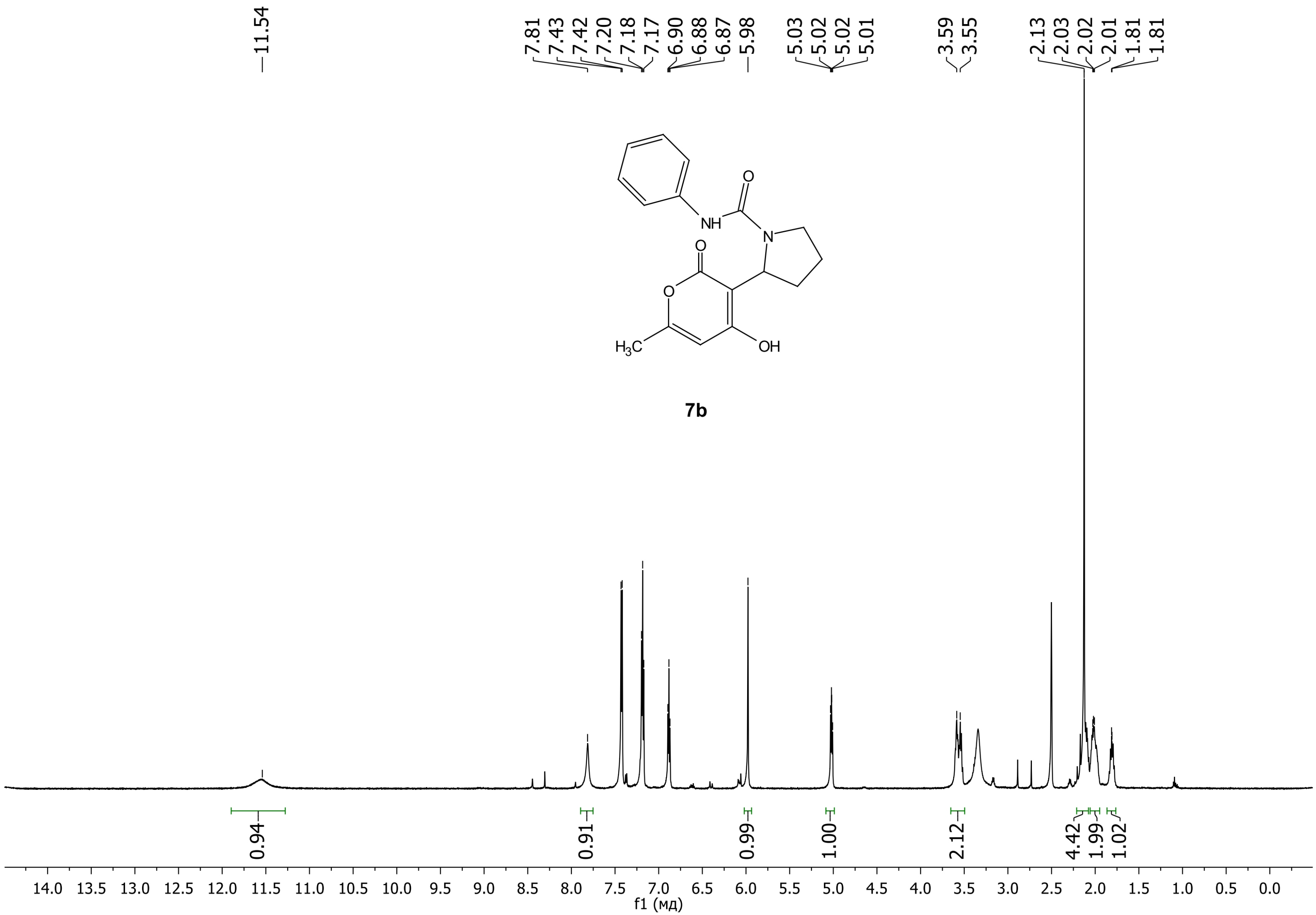


Figure S 51.



6h

Figure S 52.



11.54
7.81
7.43
7.42
7.20
7.18
7.17
6.90
6.88
6.87
5.98
5.03
5.02
5.02
5.01
3.59
3.55
2.13
2.03
2.02
2.01
1.81
1.81
7b
0.94
0.91
0.99
1.00
2.12
4.42
1.99
1.02
14.0 13.5 13.0 12.5 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 (мд)

Figure S 53.

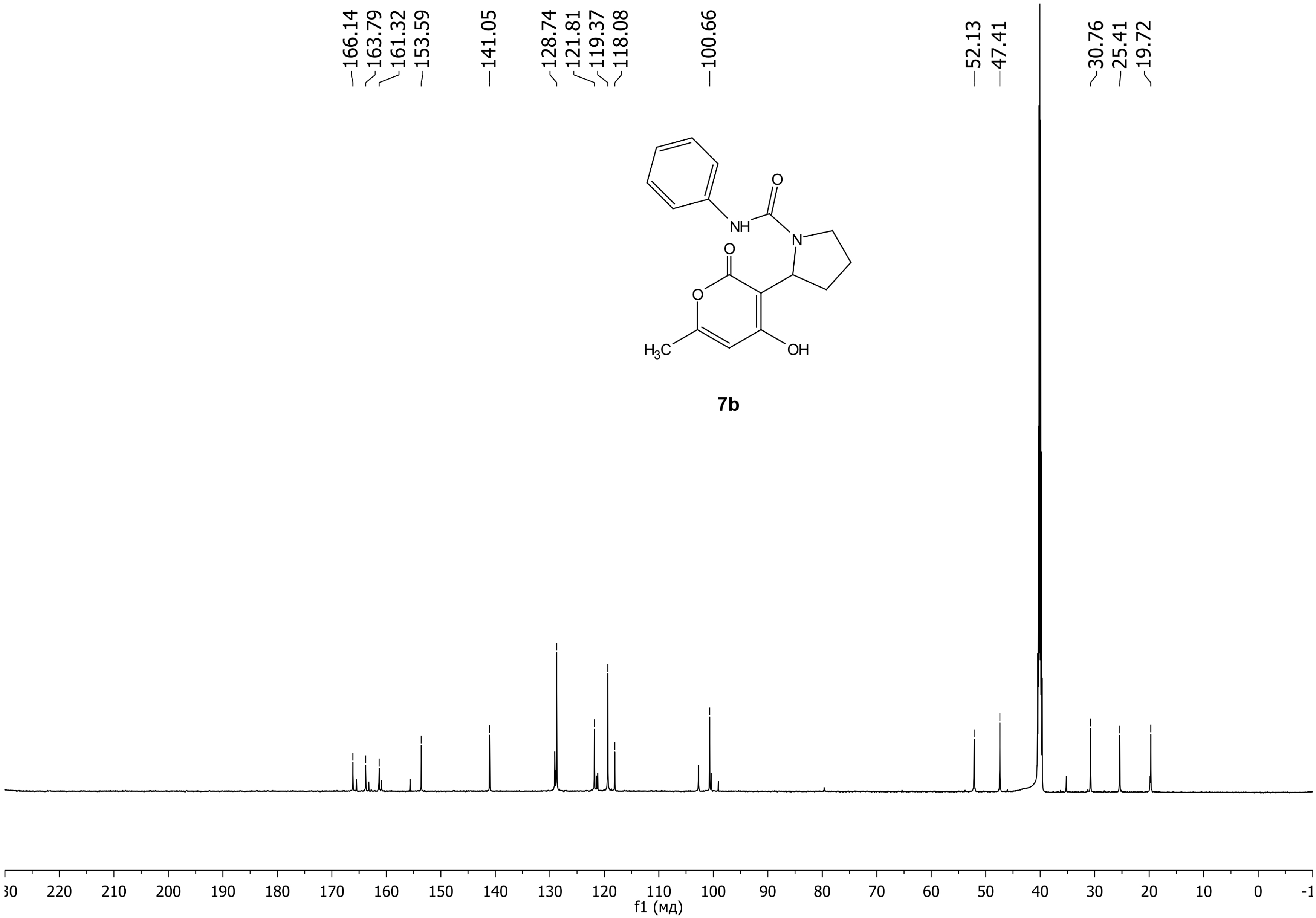

166.14
163.79
161.32
153.59
141.05
128.74
121.81
119.37
118.08
100.66
52.13
47.41
30.76
25.41
19.72
NH
O
N
O
O
H3C
OH
7b
f1 (мд)

Figure S 54.

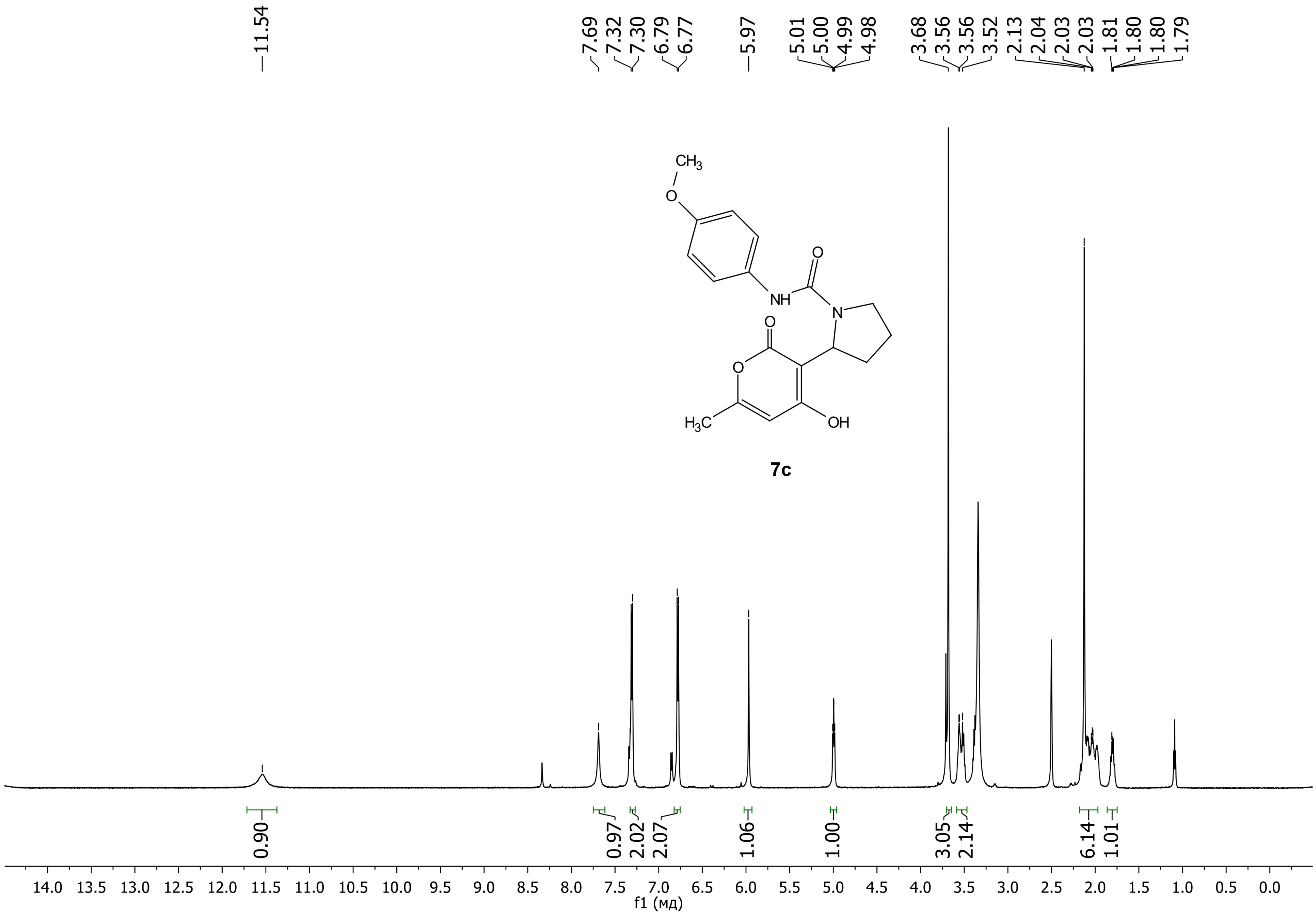


Figure S 55.

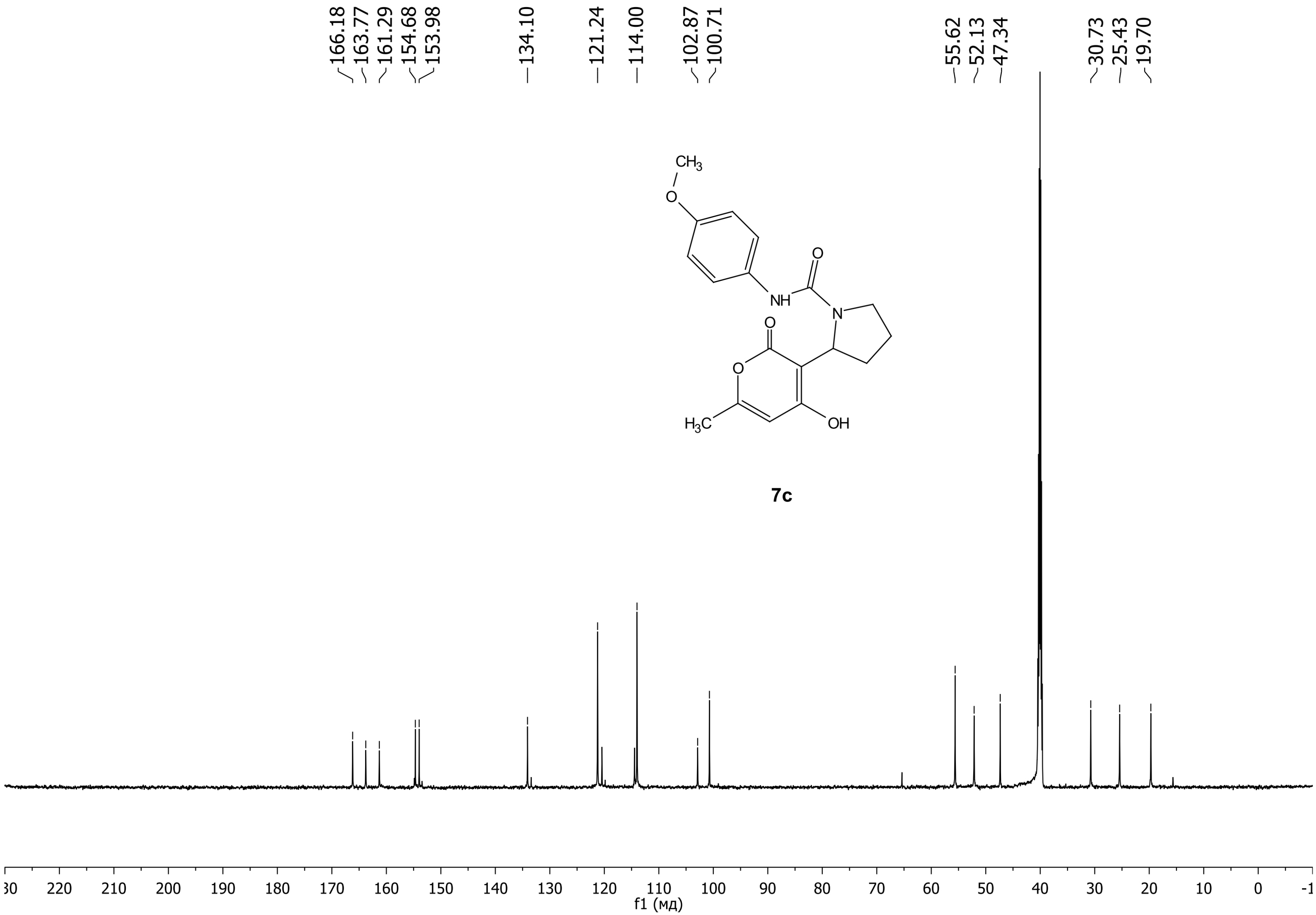
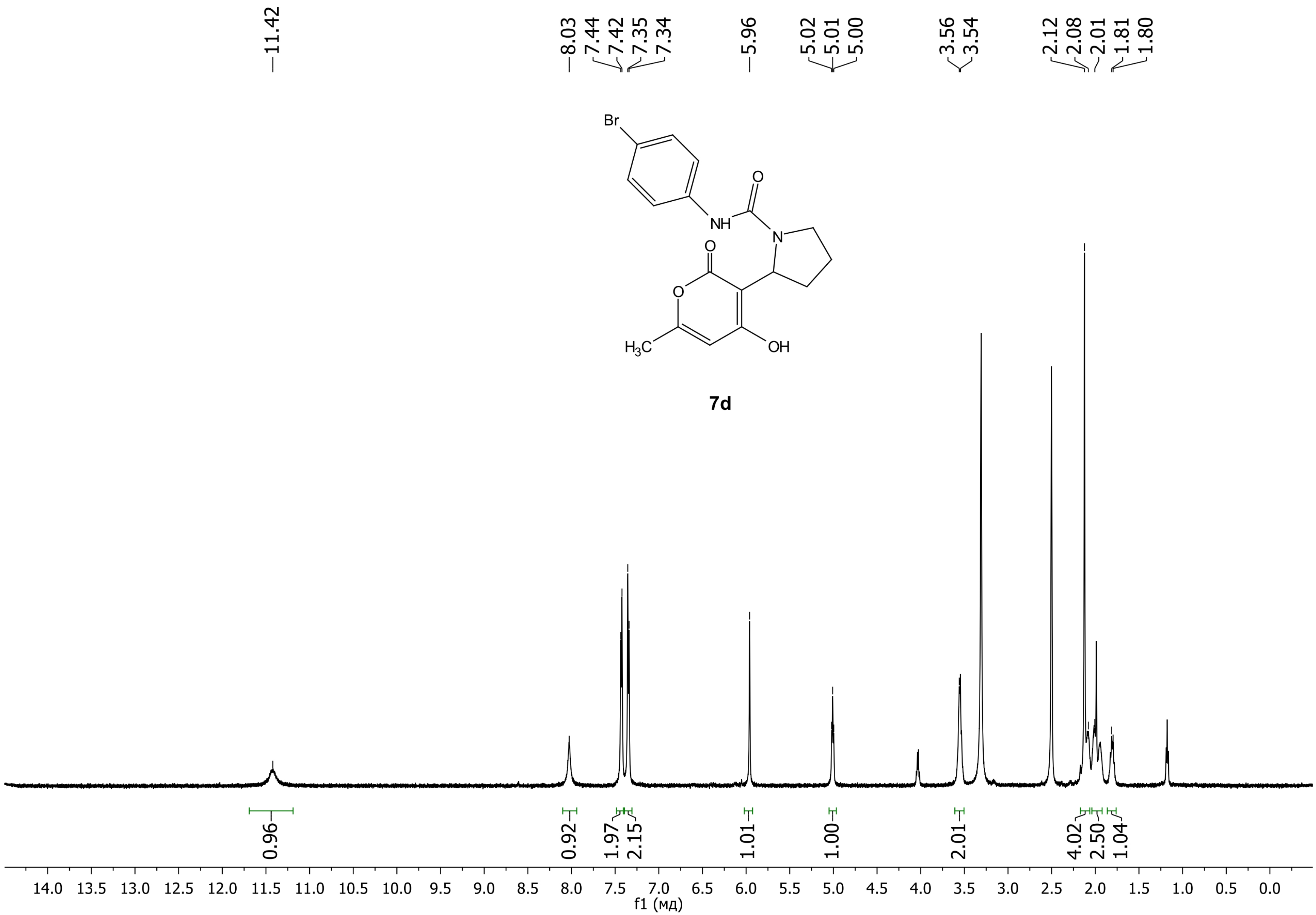

166.18
163.77
161.29
154.68
153.98
134.10
121.24
114.00
102.87
100.71
55.62
52.13
47.34
30.73
25.43
19.70
CH3
O
O
NH
N
O
O
H3C
OH
7c
f1 (мд)

Figure S 56.



11.42
8.03
7.44
7.42
7.35
7.34
5.96
5.02
5.01
5.00
3.56
3.54
2.12
2.08
2.01
1.81
1.80
Br
NH
O
N
O
O
H3C
OH
7d
0.96
0.92
1.97
2.15
1.01
1.00
2.01
4.02
2.50
1.04
14.0
13.5
13.0
12.5
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 (мд)

Figure S 57.

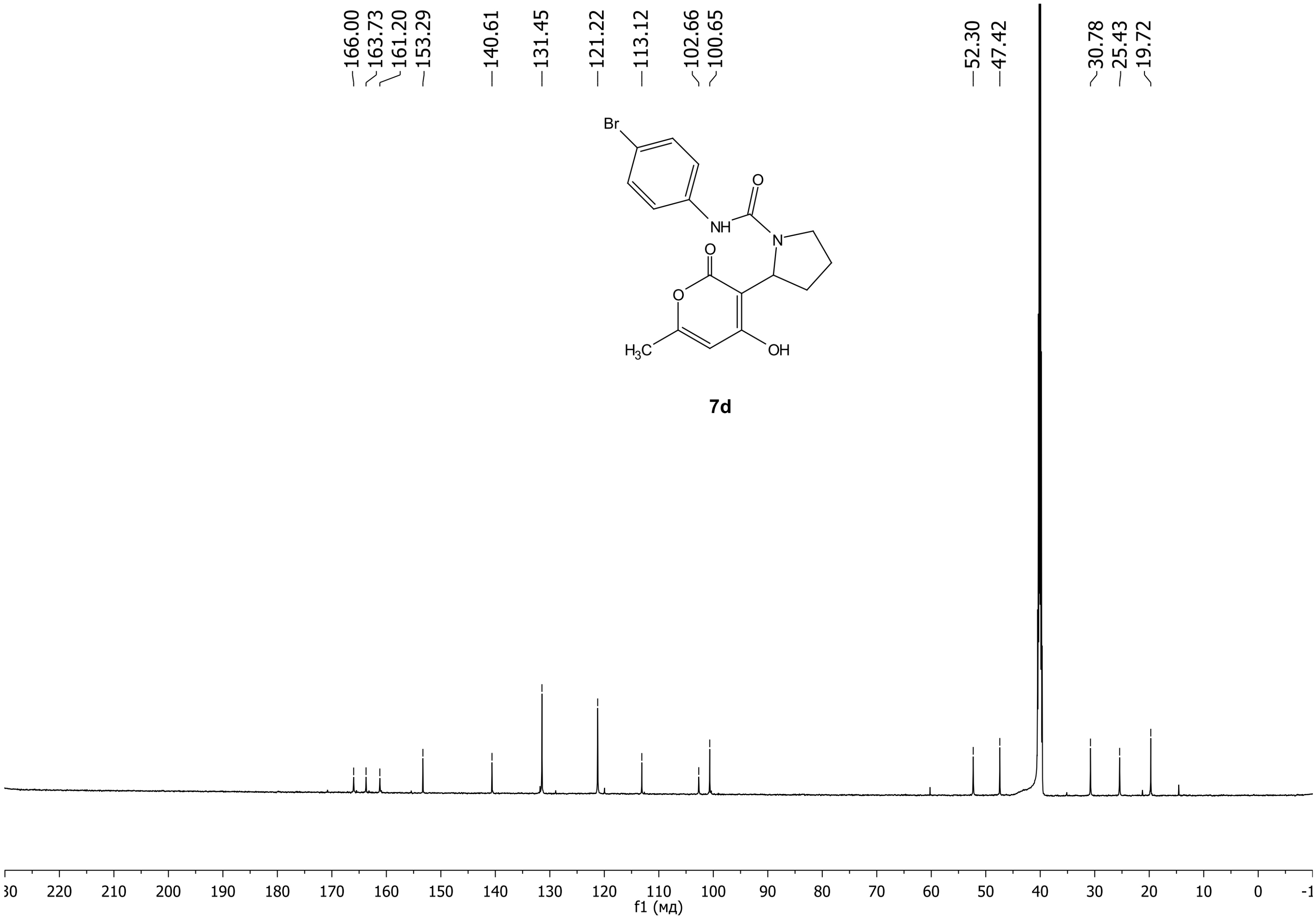
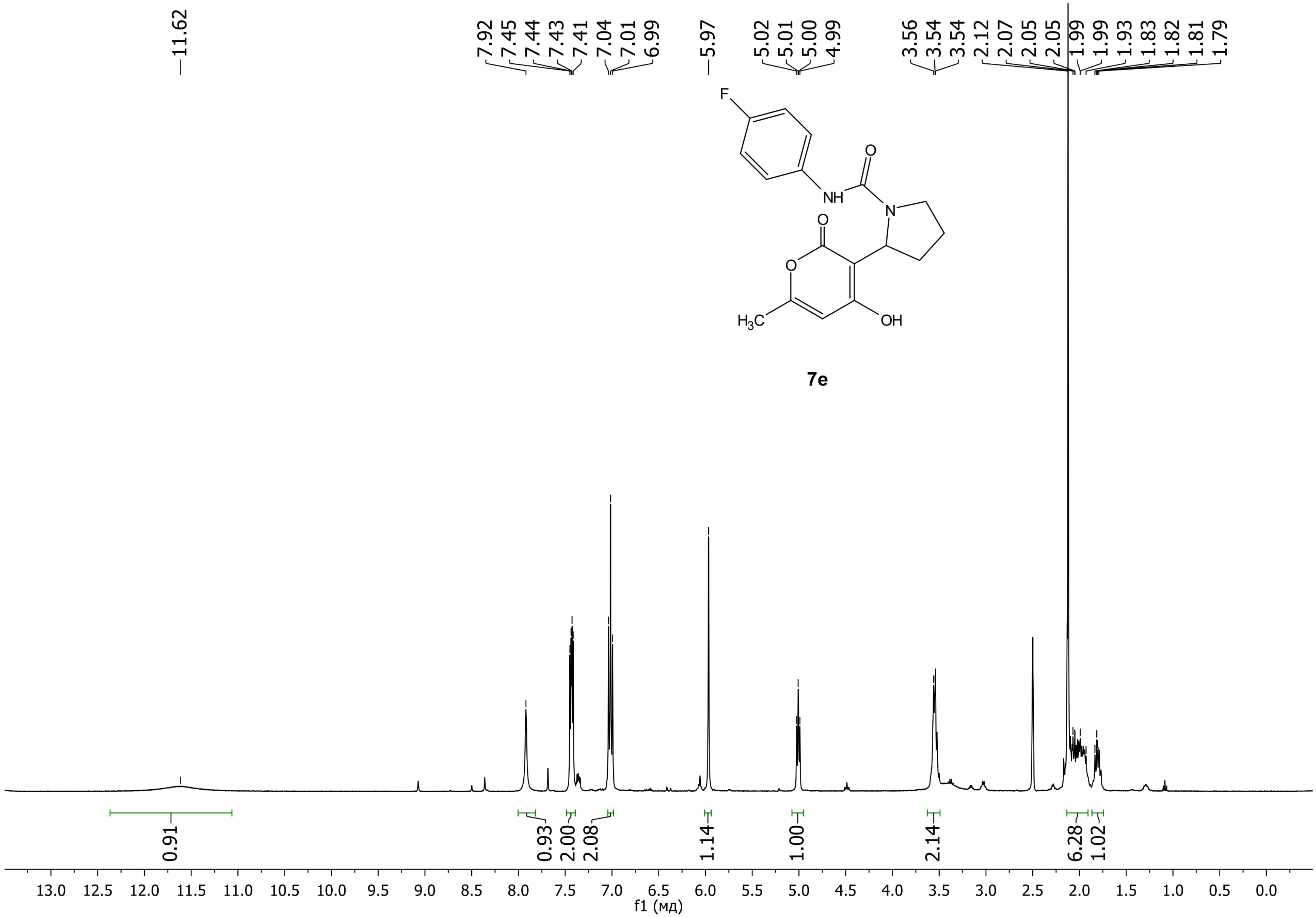

166.00
163.73
161.20
153.29
140.61
131.45
121.22
113.12
102.66
100.65
52.30
47.42
30.78
25.43
19.72
Br
O
NH
N
O
O
H3C
OH
7d
f1 (мд)

Figure S 58.



7e

Figure S 59.

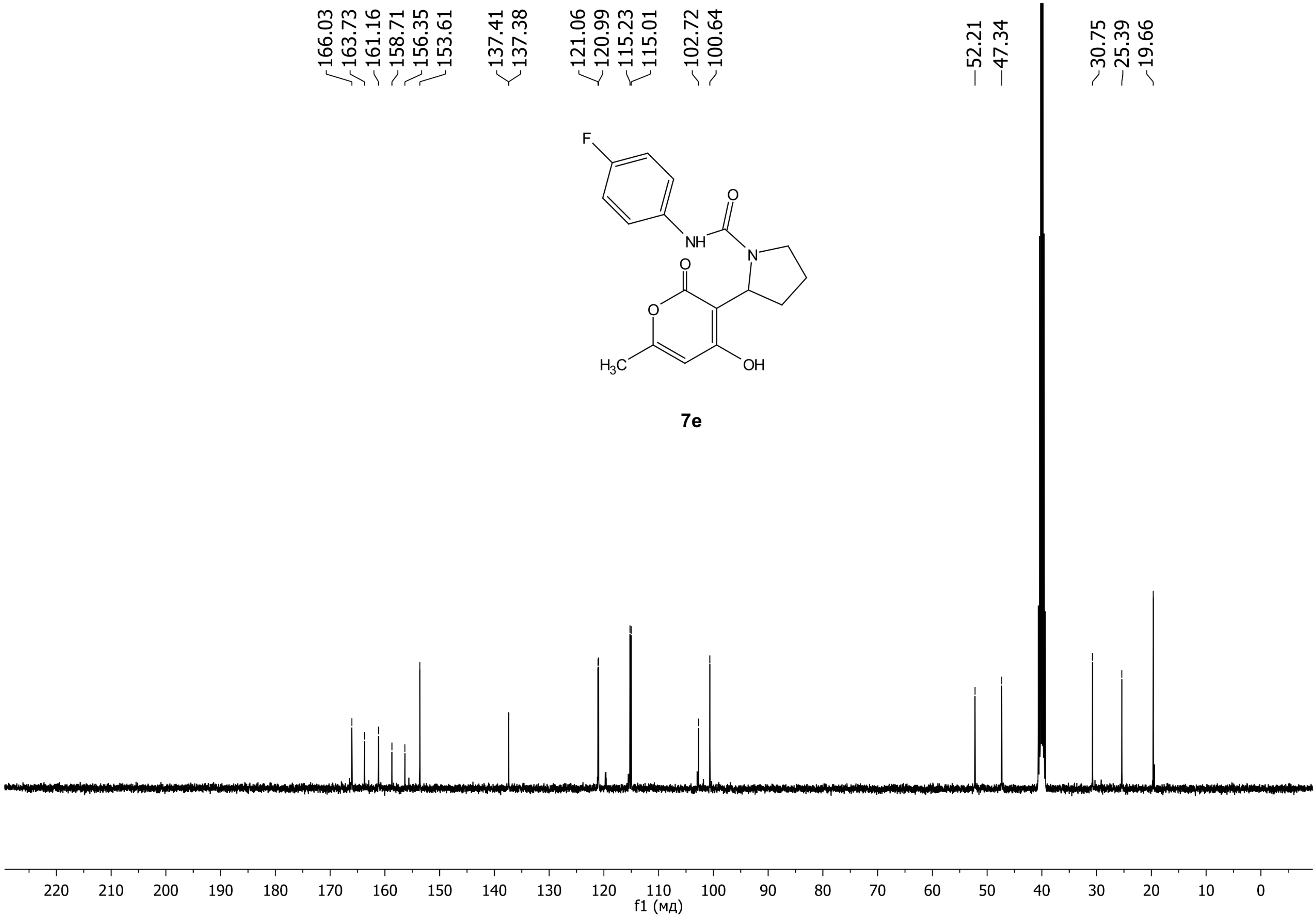
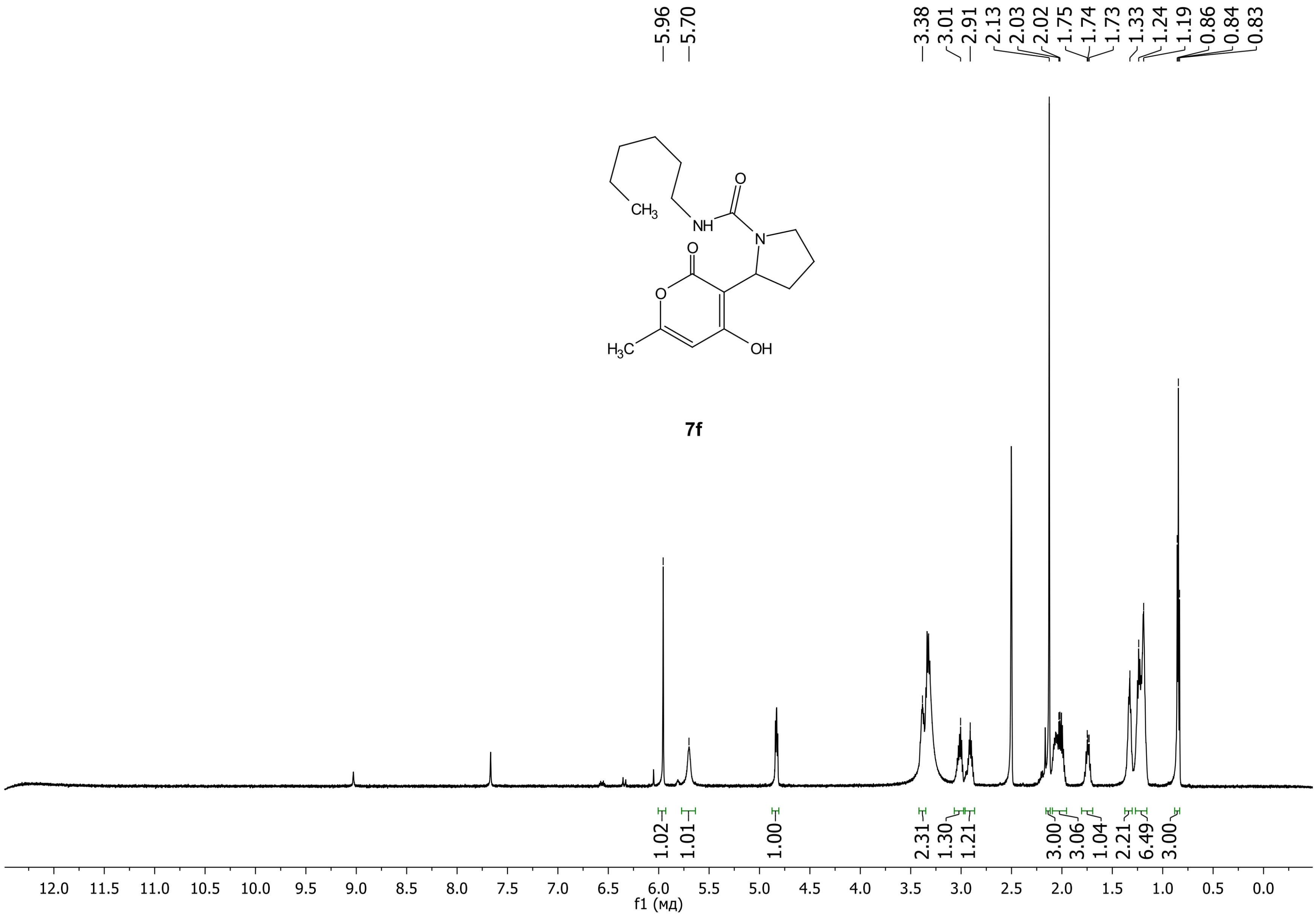
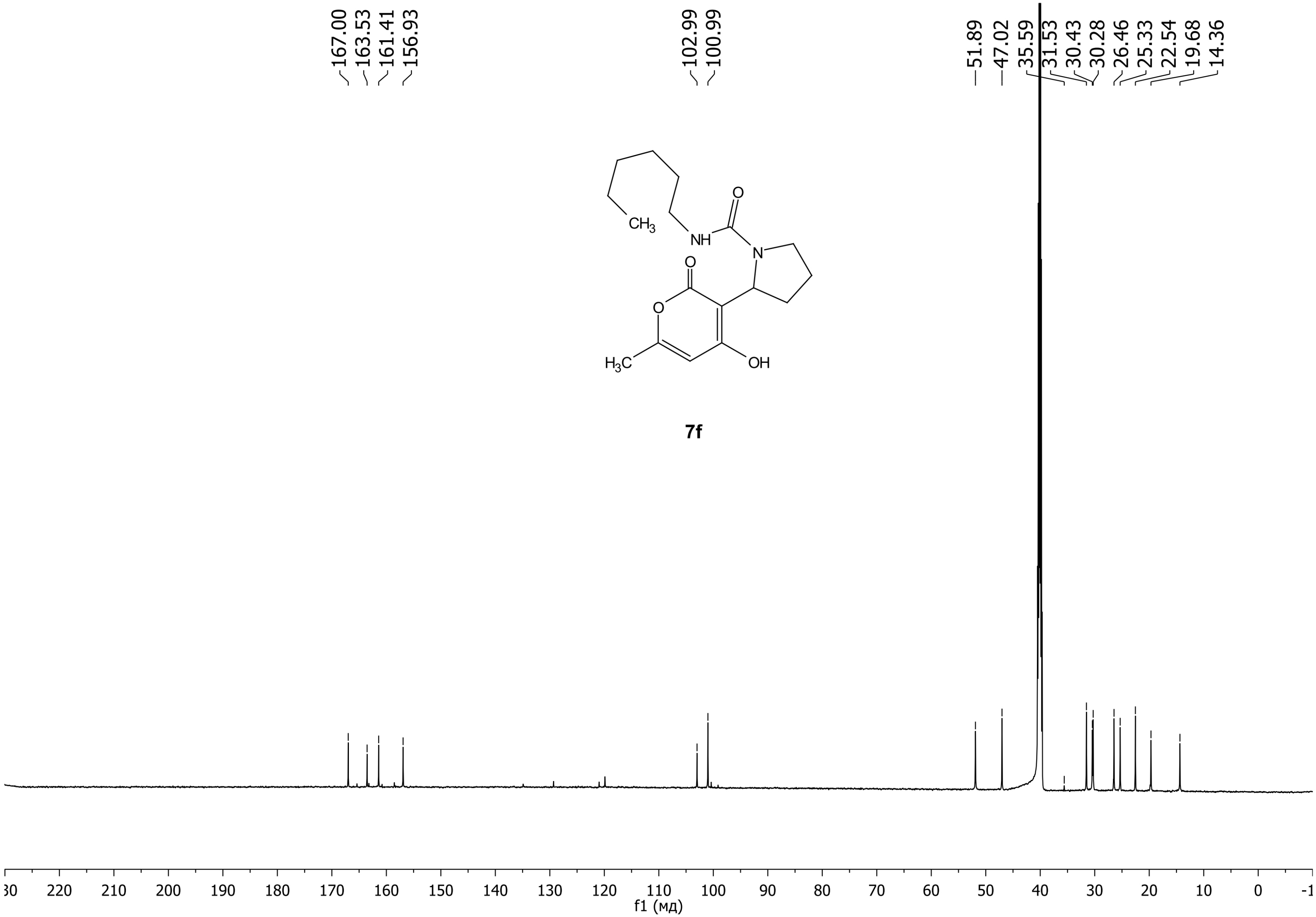

166.03
163.73
161.16
158.71
156.35
153.61
137.41
137.38
121.06
120.99
115.23
115.01
102.72
100.64
52.21
47.34
30.75
25.39
19.66
F
O
NH
N
O
O
H3C
OH
7e
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)

Figure S 60.



5.96
5.70
3.38
3.01
2.91
2.13
2.03
2.02
1.75
1.74
1.73
1.33
1.24
1.19
0.86
0.84
0.83
7f
1.02
1.01
1.00
2.31
1.30
1.21
3.00
3.06
1.04
2.21
6.49
3.00
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 (мд)

Figure S 61.



167.00
163.53
161.41
156.93
102.99
100.99
51.89
47.02
35.59
31.53
30.43
30.28
26.46
25.33
22.54
19.68
14.36
O
CH3
NH
N
O
O
H3C
OH
7f
30
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-1
f1 (мд)

Figure S 62.

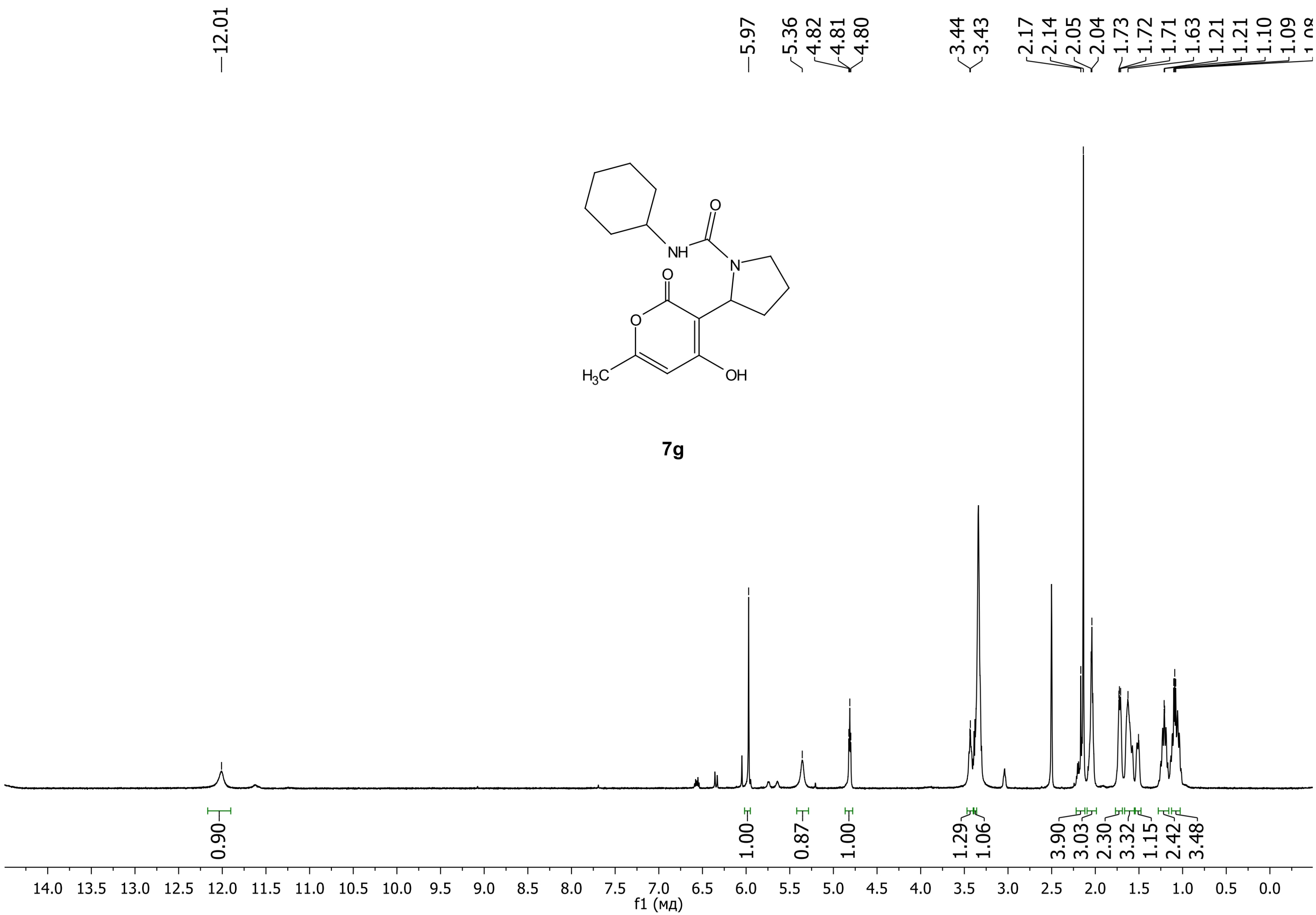
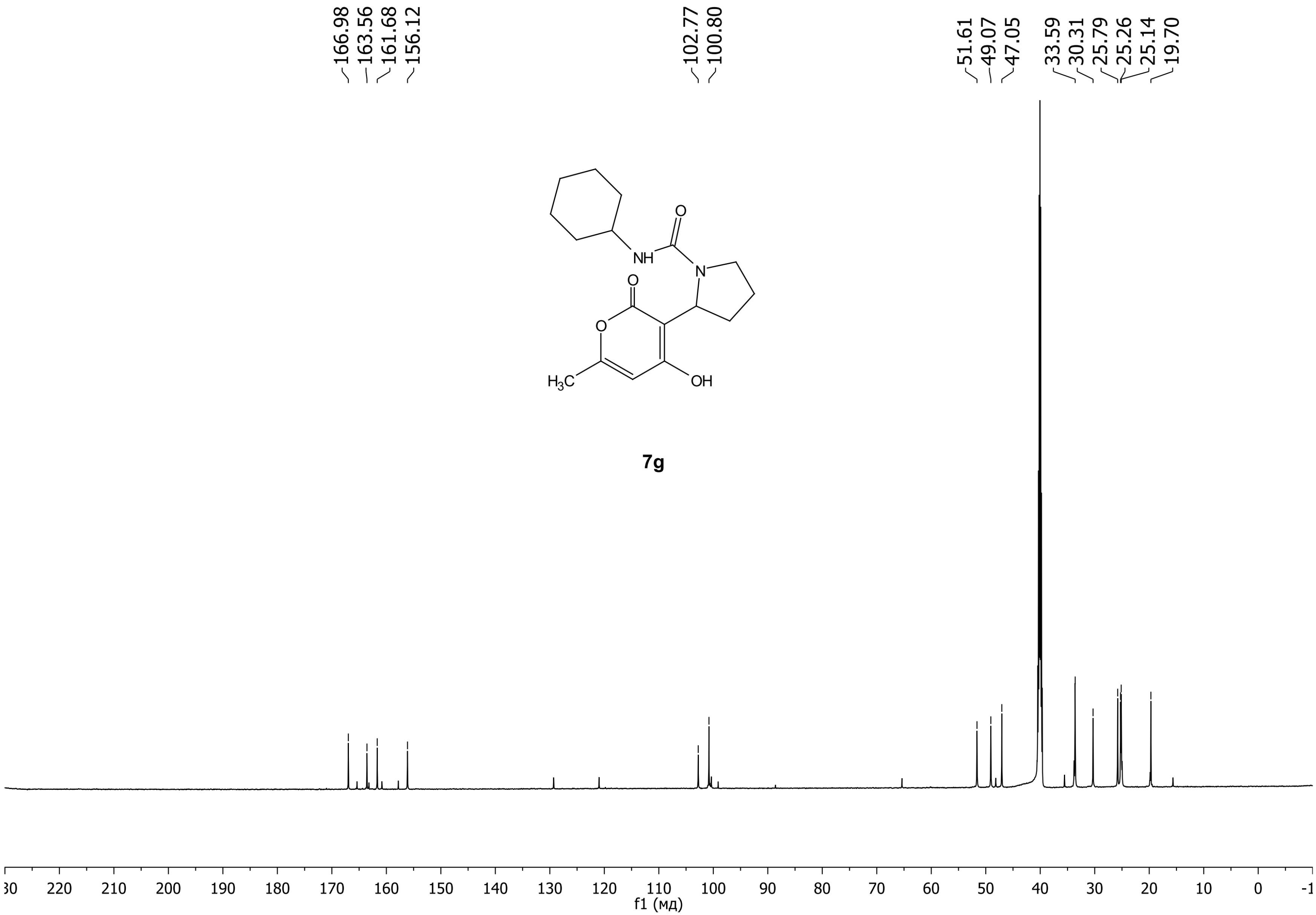

12.01
5.97
5.36
4.82
4.81
4.80
3.44
3.43
2.17
2.14
2.05
2.04
1.73
1.72
1.71
1.63
1.21
1.21
1.10
1.09
NH
O
N
O
O
H3C
OH
7g
0.90
1.00
0.87
1.00
1.29
1.06
3.90
3.03
2.30
3.32
1.15
2.42
3.48
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (мд)

Figure S 63.



7g

Figure S 64.

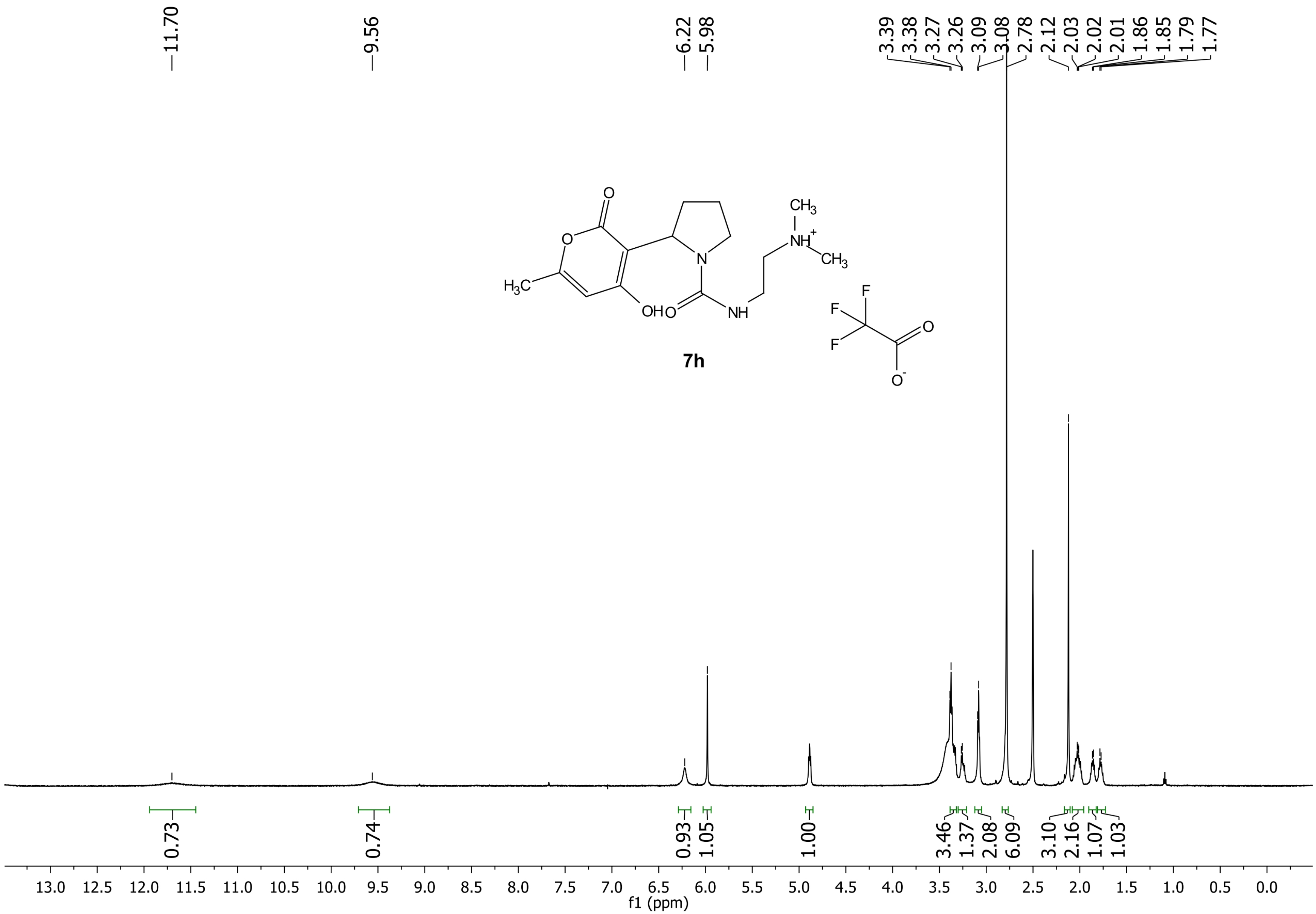
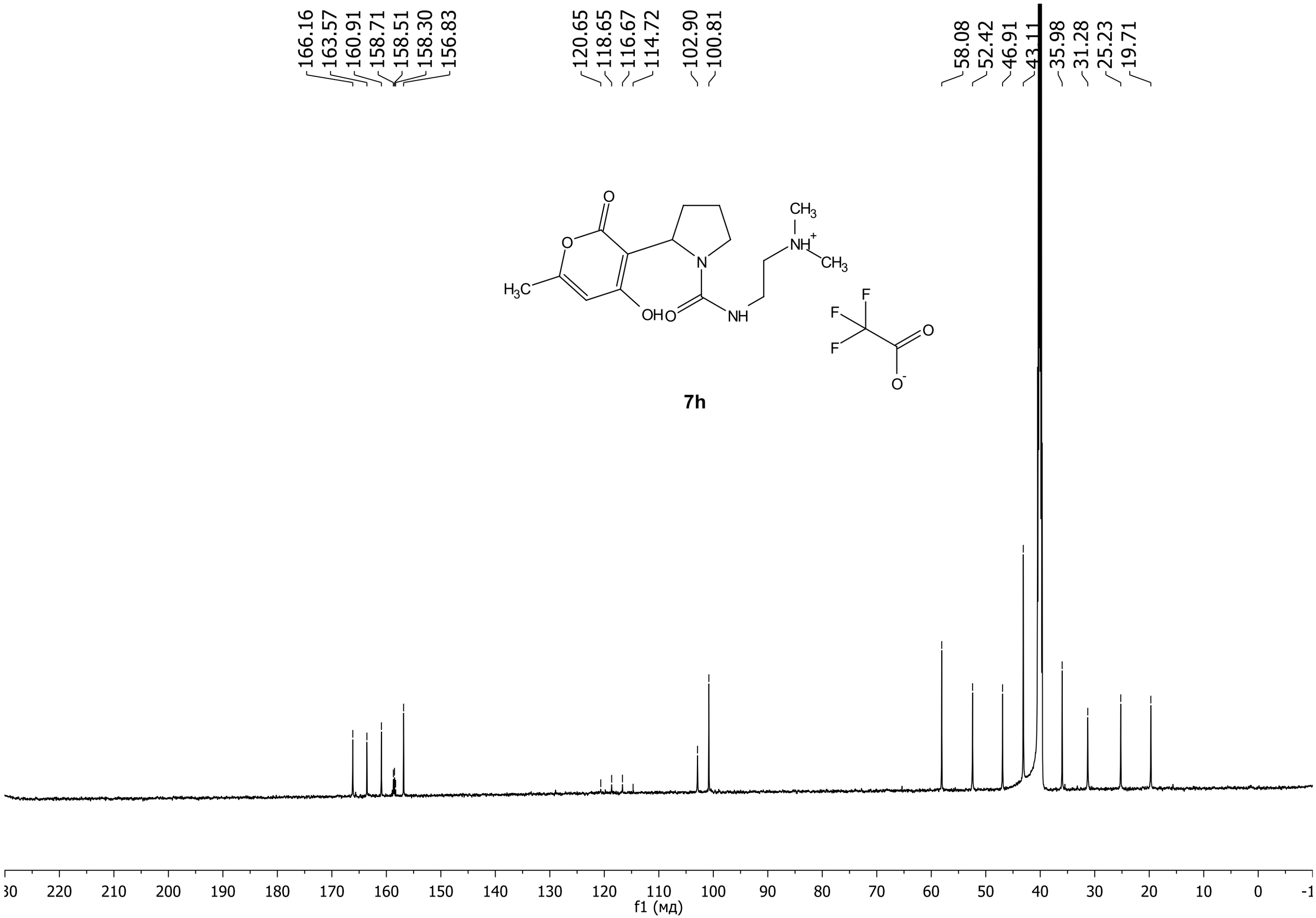

11.70
9.56
6.22
5.98
3.39
3.38
3.27
3.26
3.09
3.08
2.78
2.12
2.03
2.02
2.01
1.86
1.85
1.79
1.77
7h
0.73
0.74
0.93
1.05
1.00
3.46
1.37
2.08
6.09
3.10
2.16
1.07
1.03
f1 (ppm)

Figure S 65.



166.16
163.57
160.91
158.71
158.51
158.30
156.83
120.65
118.65
116.67
114.72
102.90
100.81
58.08
52.42
46.91
43.11
35.98
31.28
25.23
19.71
7h
f1 (мд)

Figure S 66.

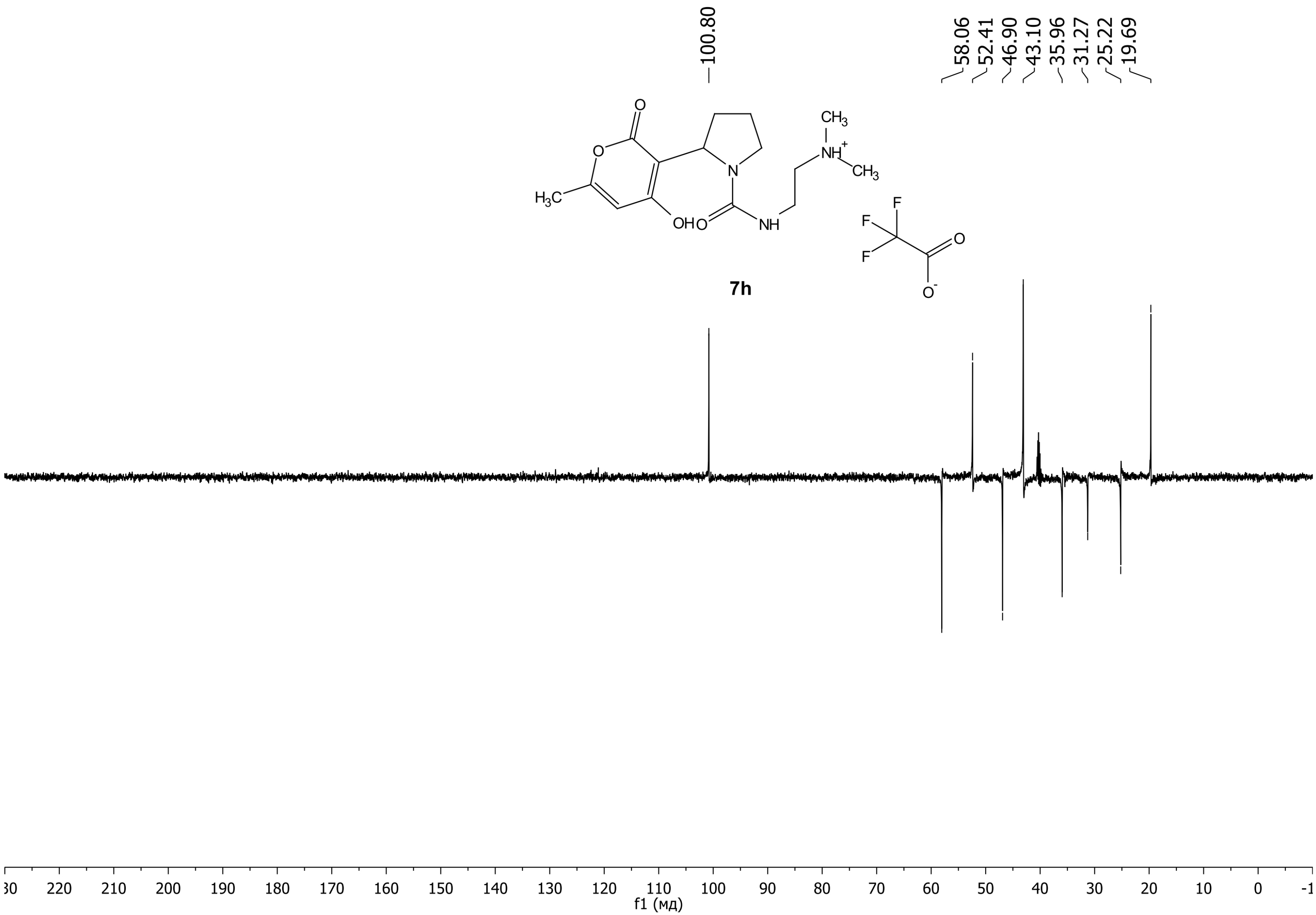


Figure S 67.

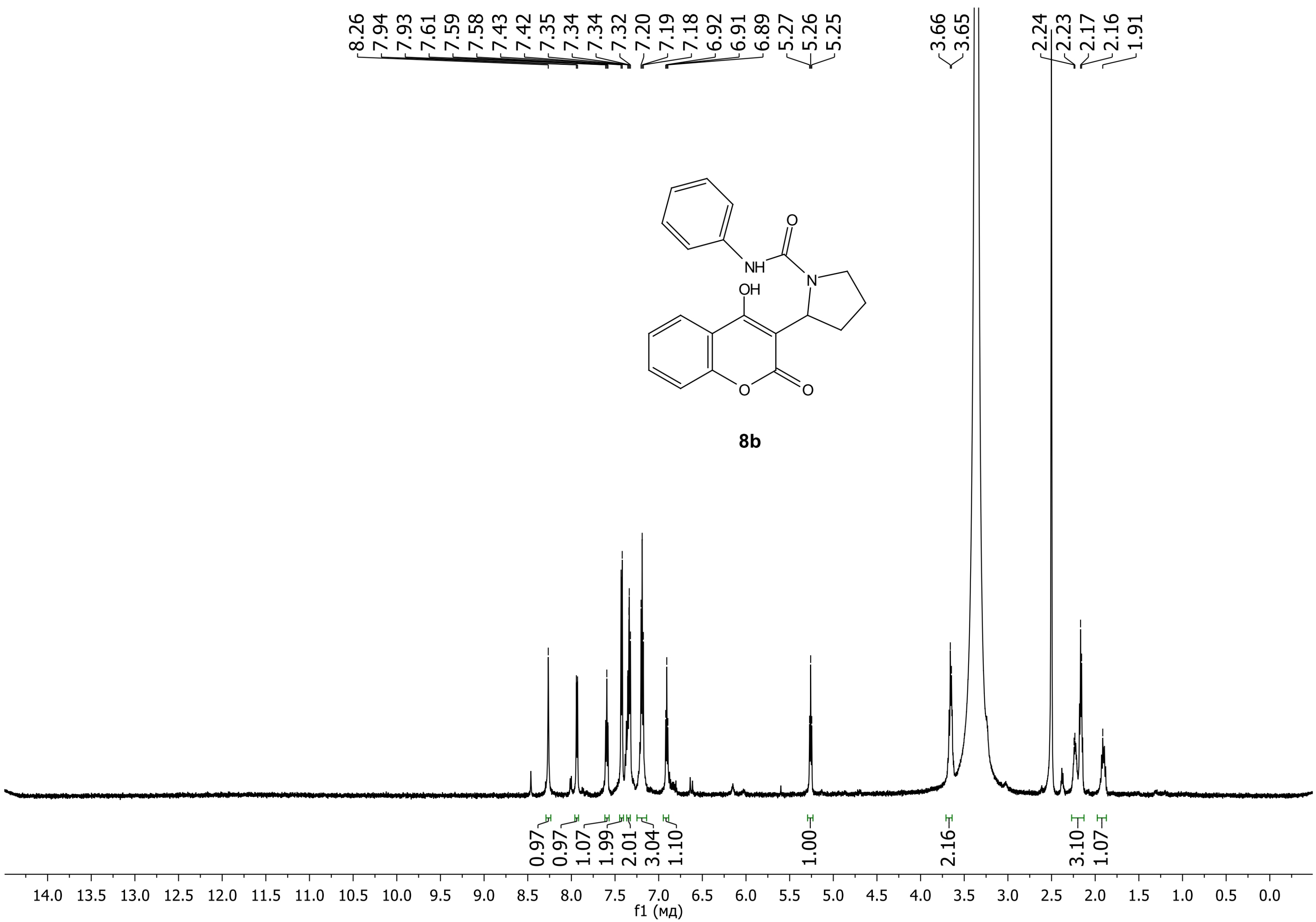

8.26
7.94
7.93
7.61
7.59
7.58
7.43
7.42
7.35
7.34
7.34
7.32
7.20
7.19
7.18
6.92
6.91
6.89
5.27
5.26
5.25
3.66
3.65
2.24
2.23
2.17
2.16
1.91
O
NH
N
OH
O
O
8b
0.97
0.97
1.07
1.99
2.01
3.04
1.10
1.00
2.16
3.10
1.07
14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (мд)

Figure S 68.

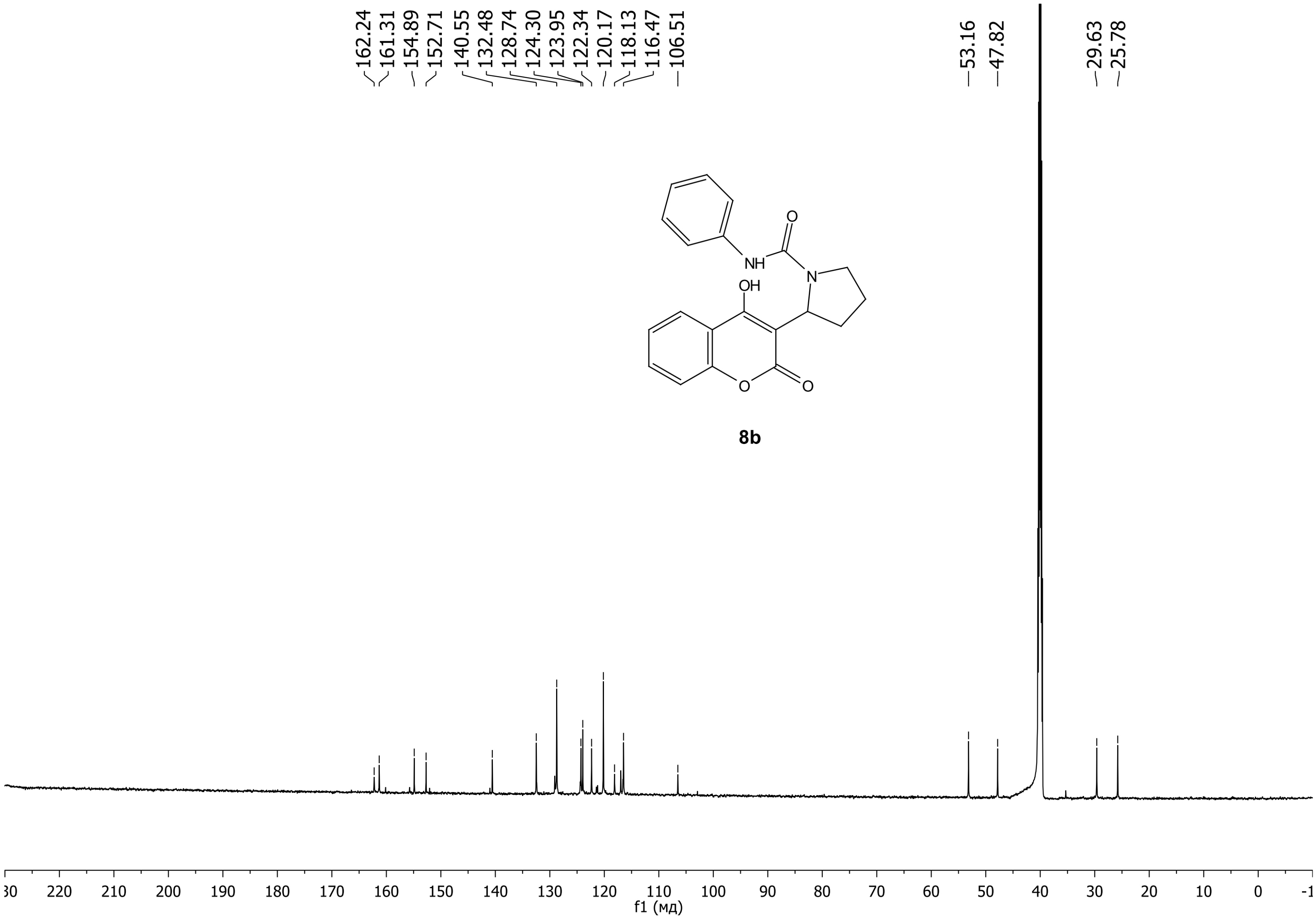
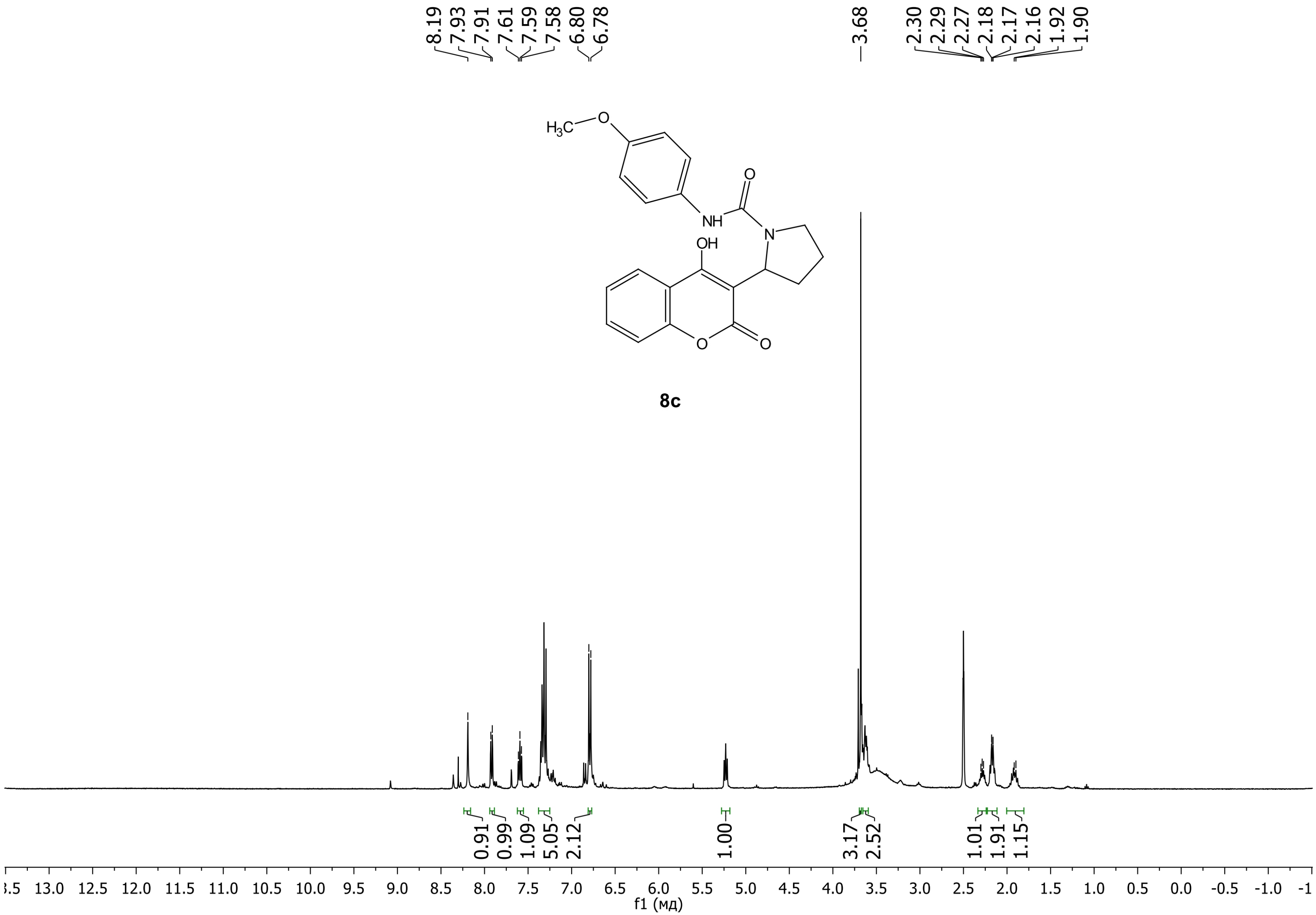

162.24
161.31
154.89
152.71
140.55
132.48
128.74
124.30
123.95
122.34
120.17
118.13
116.47
106.51
53.16
47.82
29.63
25.78
O
NH
N
OH
O
O
8b
f1 (мд)

Figure S 69.



8.19
7.93
7.91
7.61
7.59
7.58
6.80
6.78
3.68
2.30
2.29
2.27
2.18
2.17
2.16
1.92
1.90
H_3C
O
NH
OH
N
8c
0.91
0.99
1.09
5.05
2.12
1.00
3.17
2.52
1.01
1.91
1.15
f1 (мд)

Figure S 70.

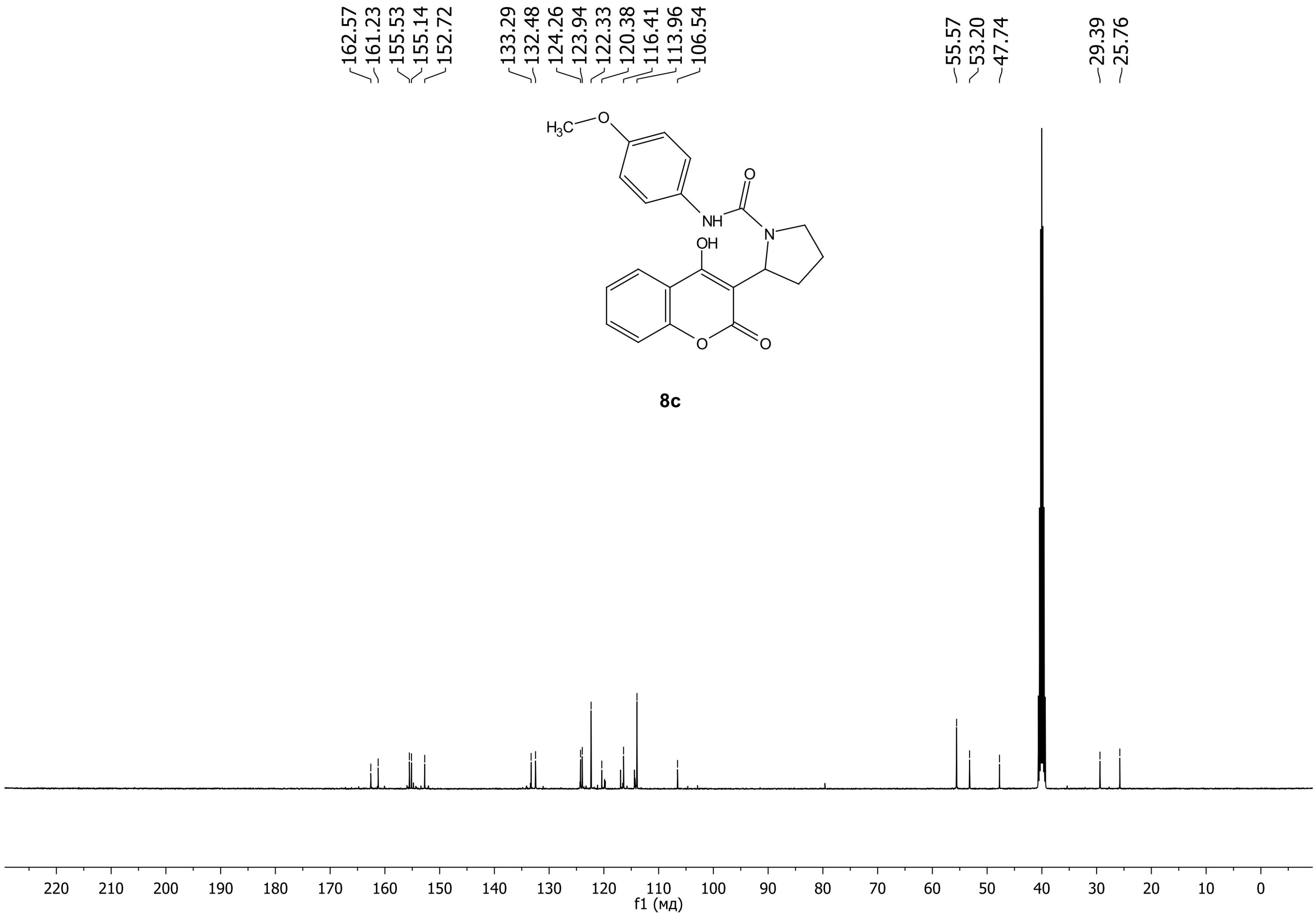

162.57
161.23
155.53
155.14
152.72
133.29
132.48
124.26
123.94
122.33
120.38
116.41
113.96
106.54
55.57
53.20
47.74
29.39
25.76
H3C
O
O
NH
N
OH
O
O
8c
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)

Figure S 71.

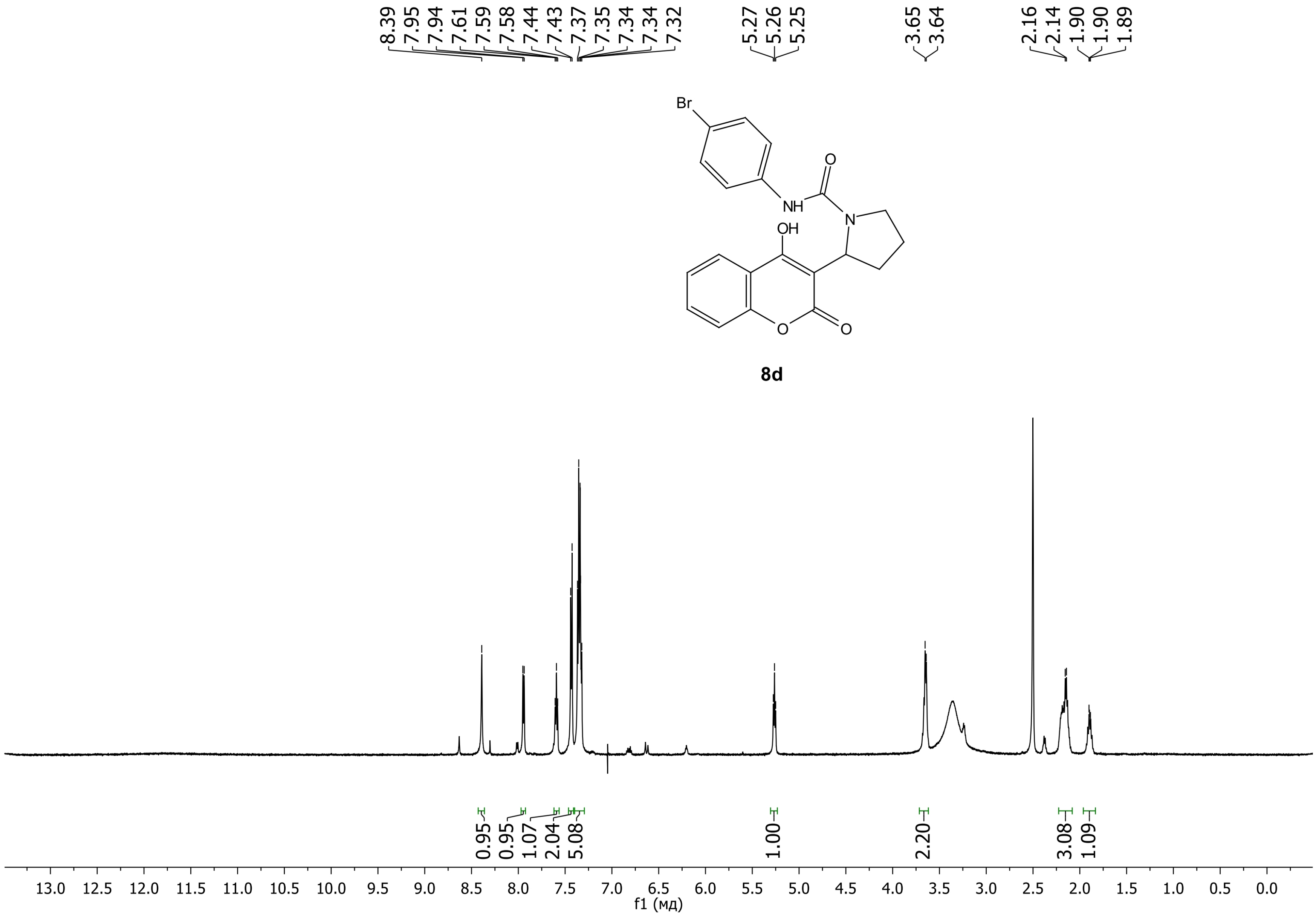

8.39
7.95
7.94
7.61
7.59
7.58
7.44
7.43
7.37
7.35
7.34
7.34
7.32
5.27
5.26
5.25
3.65
3.64
2.16
2.14
1.90
1.90
1.89
Br
O
NH
N
OH
O
O
8d
0.95
0.95
1.07
2.04
5.08
1.00
2.20
3.08
1.09
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (мд)

Figure S 72.

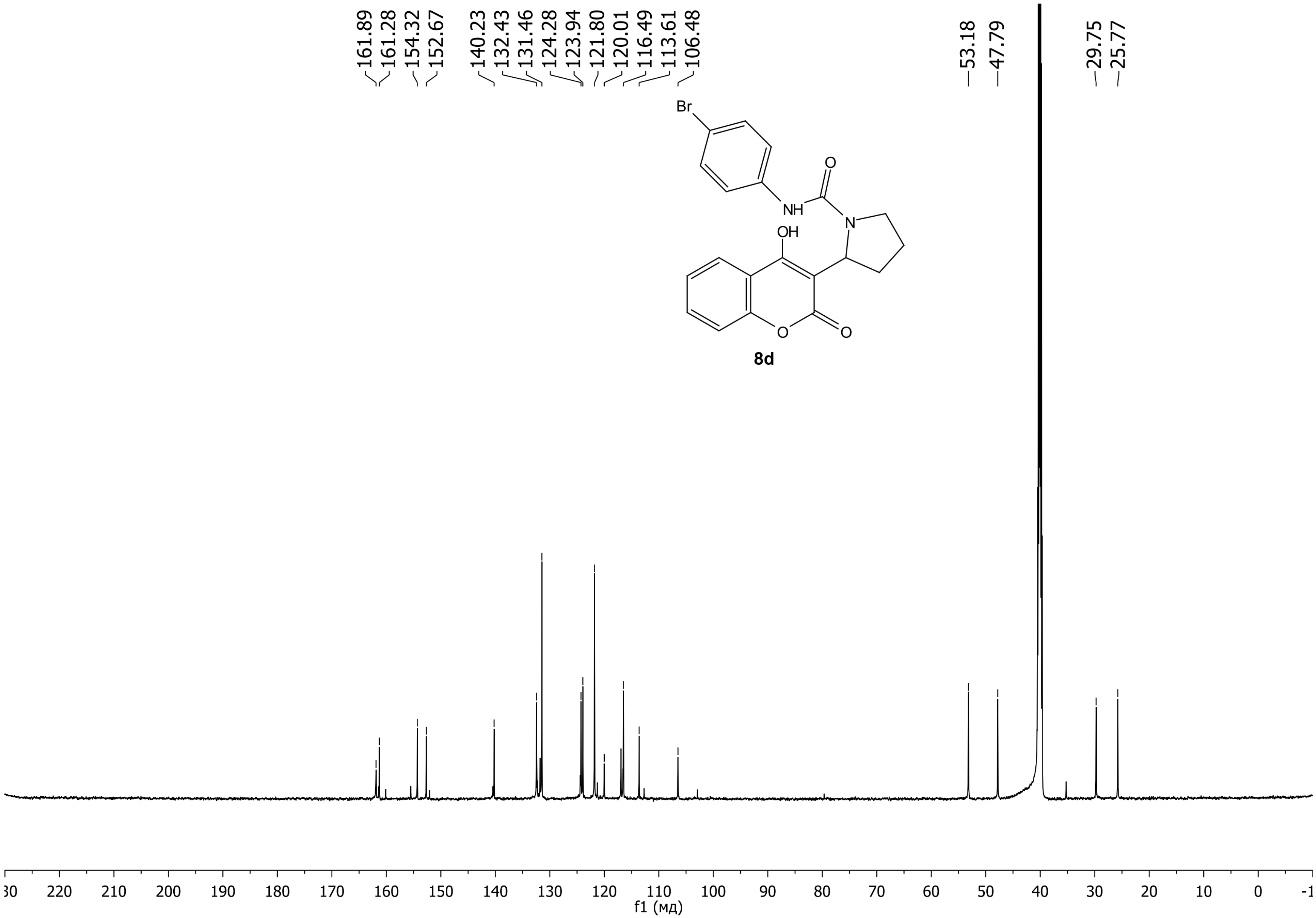
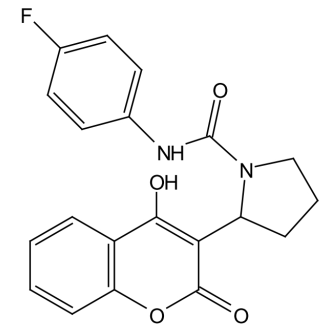

161.89
161.28
154.32
152.67
140.23
132.43
131.46
124.28
123.94
121.80
120.01
116.49
113.61
106.48
53.18
47.79
29.75
25.77
Br
O
NH
N
OH
O
O
8d
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (мд)

Figure S 73.



8e

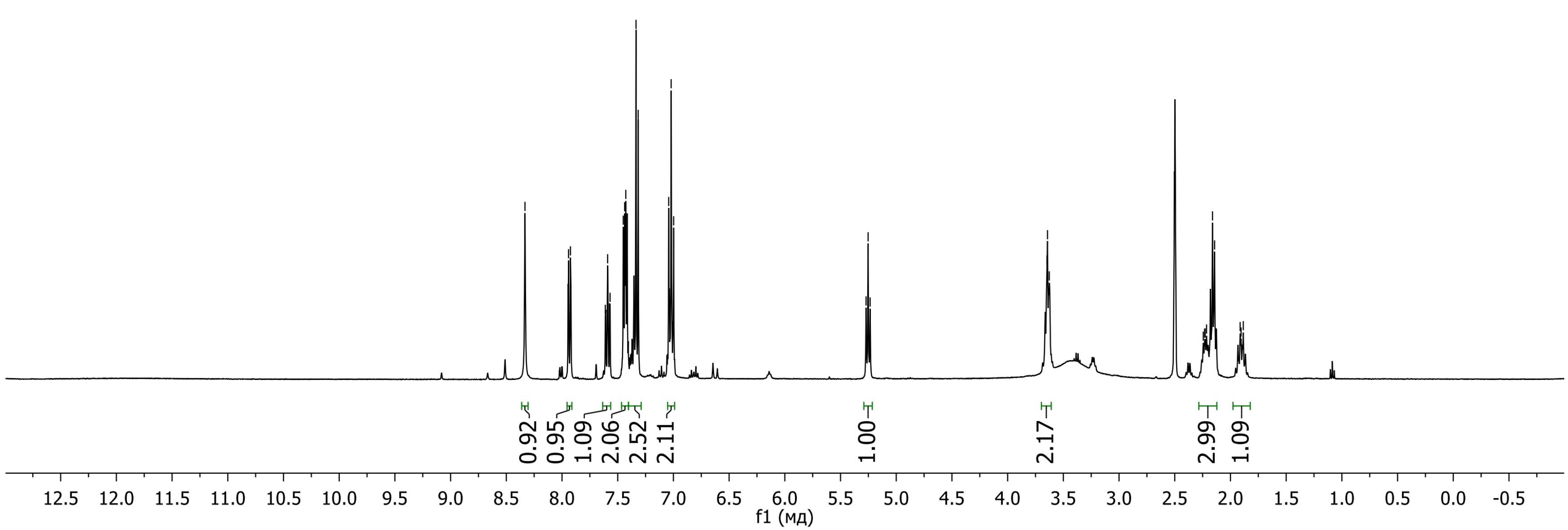


Figure S 74.

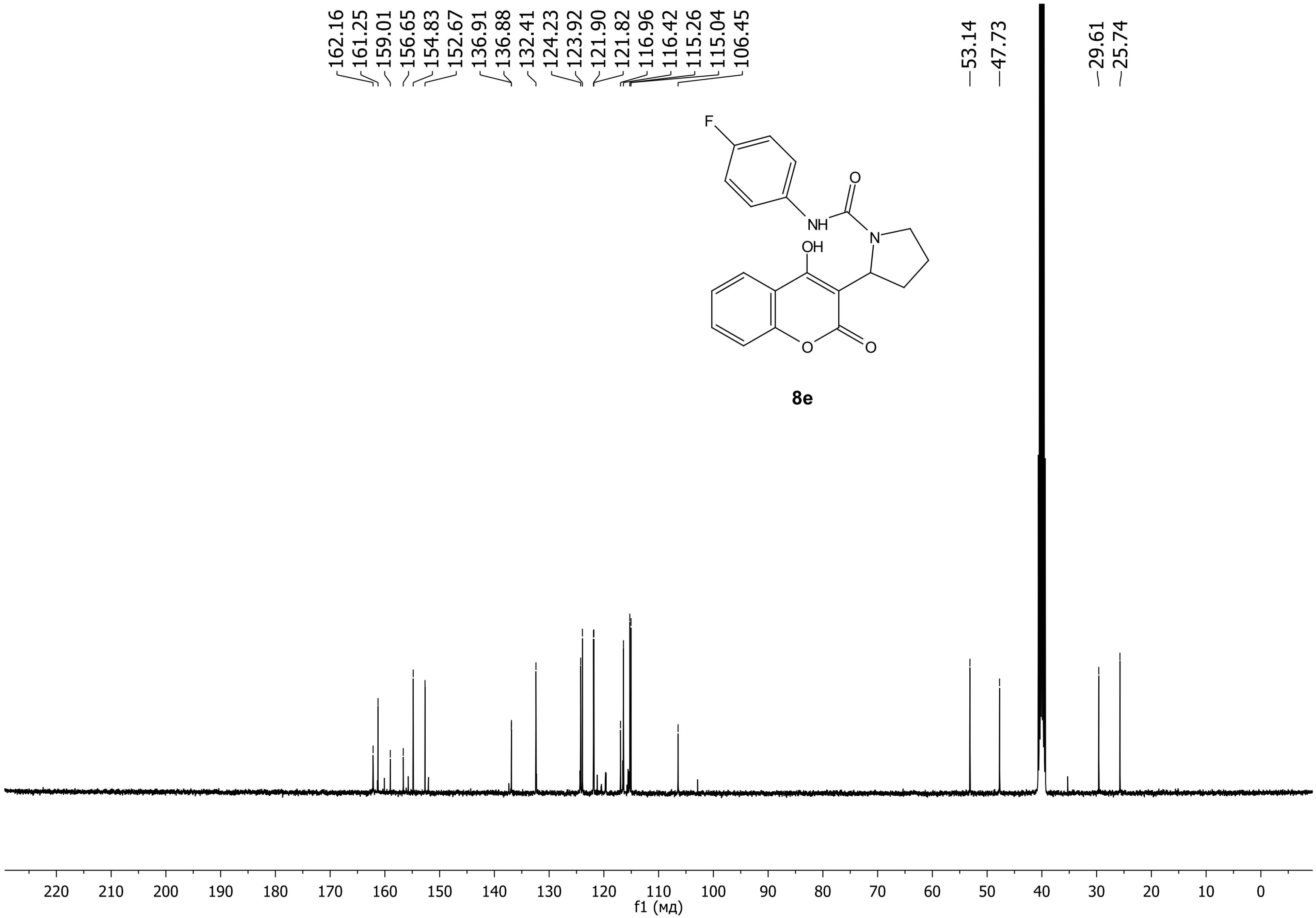

162.16
161.25
159.01
156.65
154.83
152.67
136.91
136.88
132.41
124.23
123.92
121.90
121.82
116.96
116.42
115.26
115.04
106.45
53.14
47.73
29.61
25.74
F
O
NH
N
OH
O
O
8e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (мд)

Figure S 75.

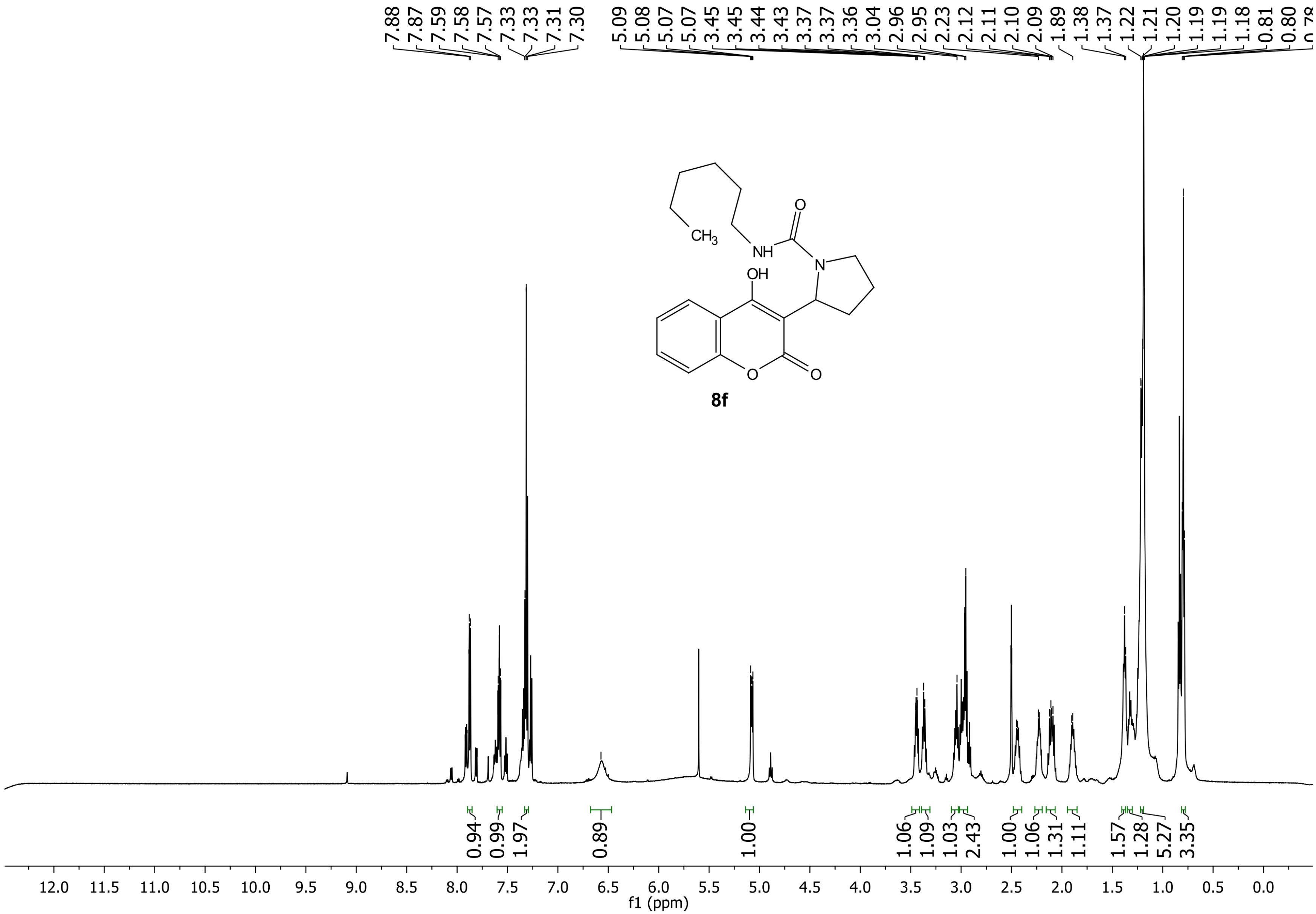
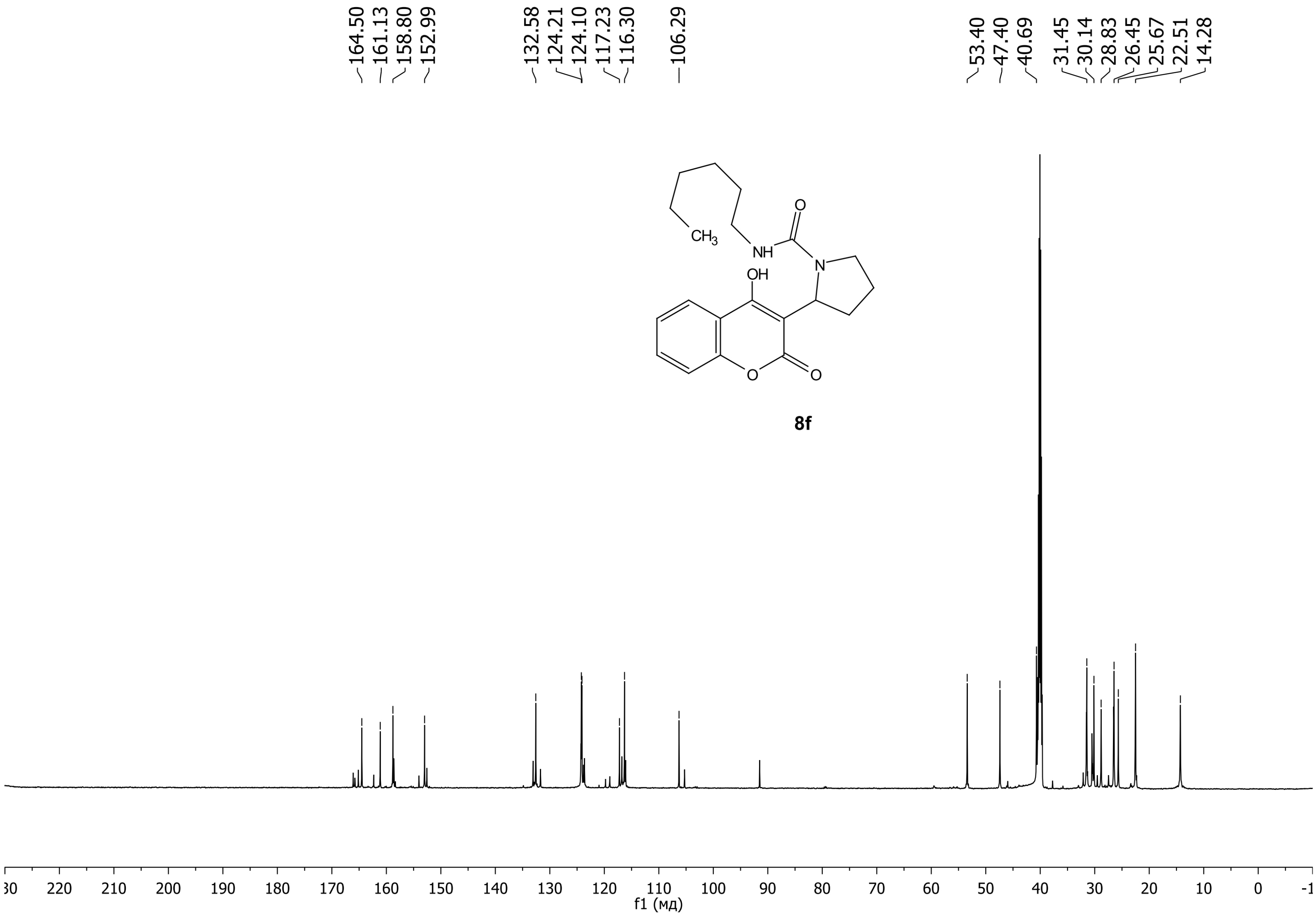


Figure S 76.



8f

Figure S 77.

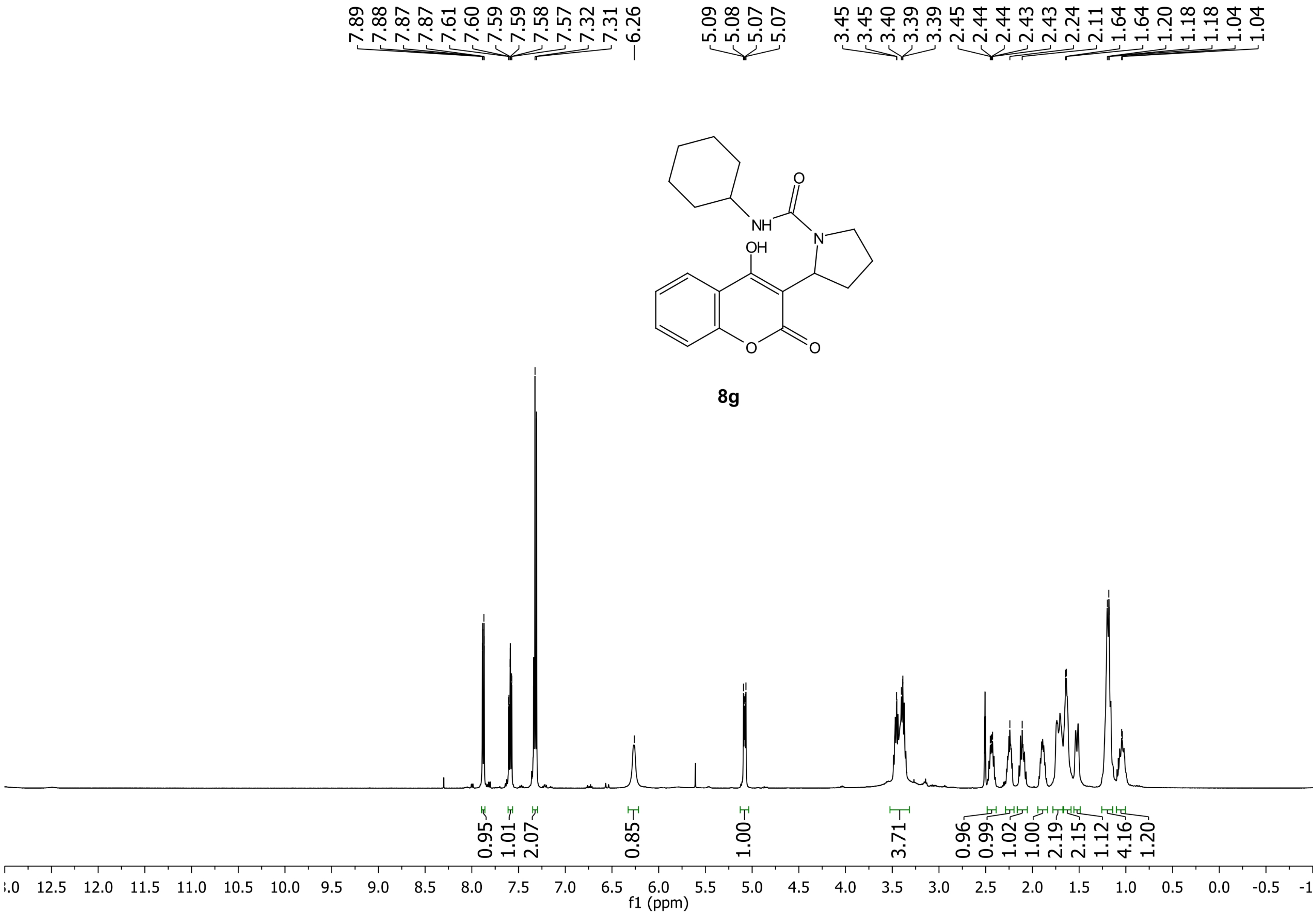
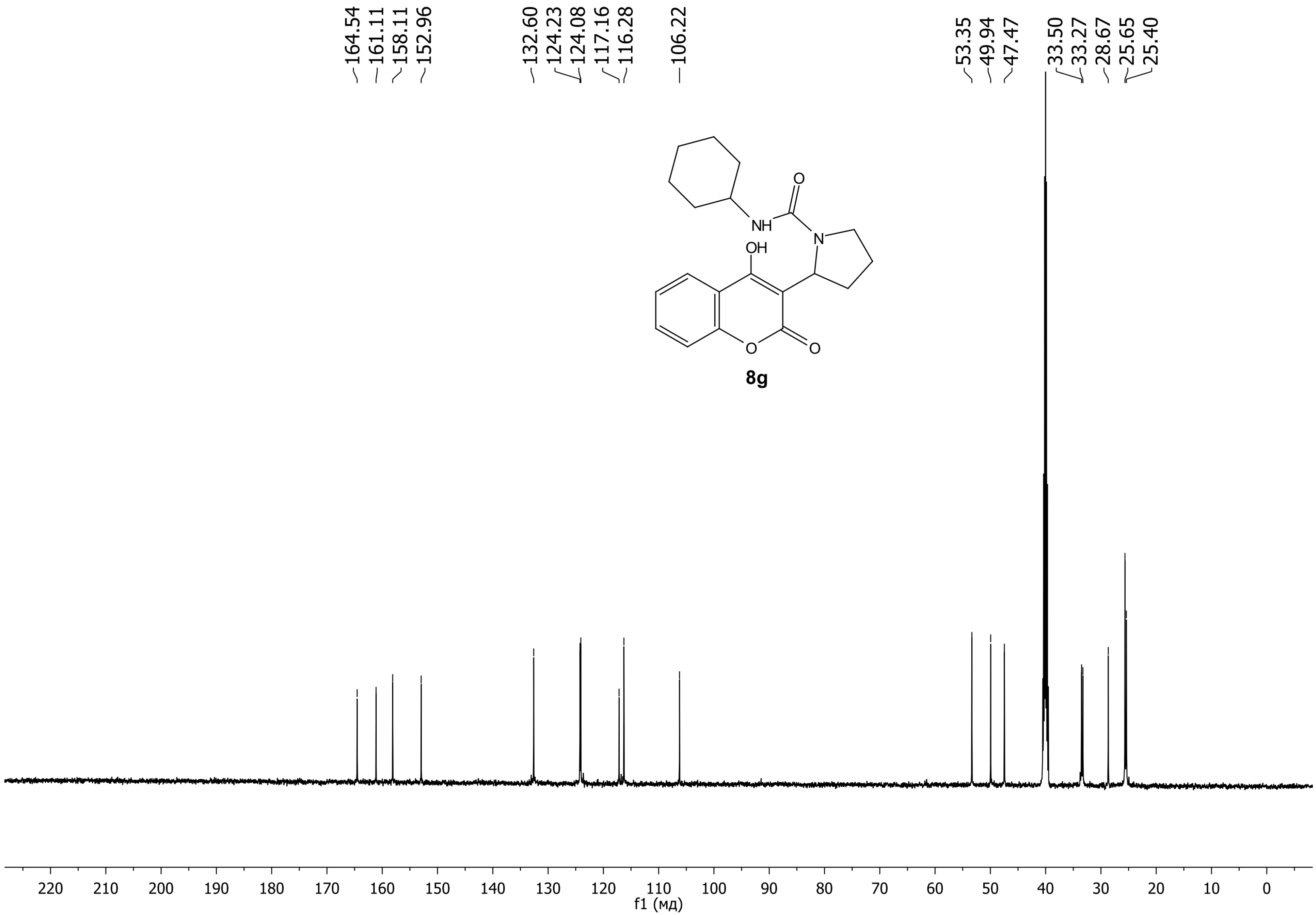

7.89
7.88
7.87
7.87
7.61
7.60
7.59
7.59
7.58
7.57
7.32
7.31
6.26
5.09
5.08
5.07
5.07
3.45
3.45
3.40
3.39
3.39
2.45
2.44
2.44
2.43
2.43
2.24
2.11
1.64
1.64
1.20
1.18
1.18
1.04
1.04
NH
O
N
OH
O
O
8g
0.95
1.01
2.07
0.85
1.00
3.71
0.96
0.99
1.02
1.00
2.19
2.15
1.12
4.16
1.20
f1 (ppm)

Figure S 78.



164.54
161.11
158.11
152.96
132.60
124.23
124.08
117.16
116.28
106.22
53.35
49.94
47.47
33.50
33.27
28.67
25.65
25.40
O
NH
N
OH
O
O
8g
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (мд)

Figure S 79.

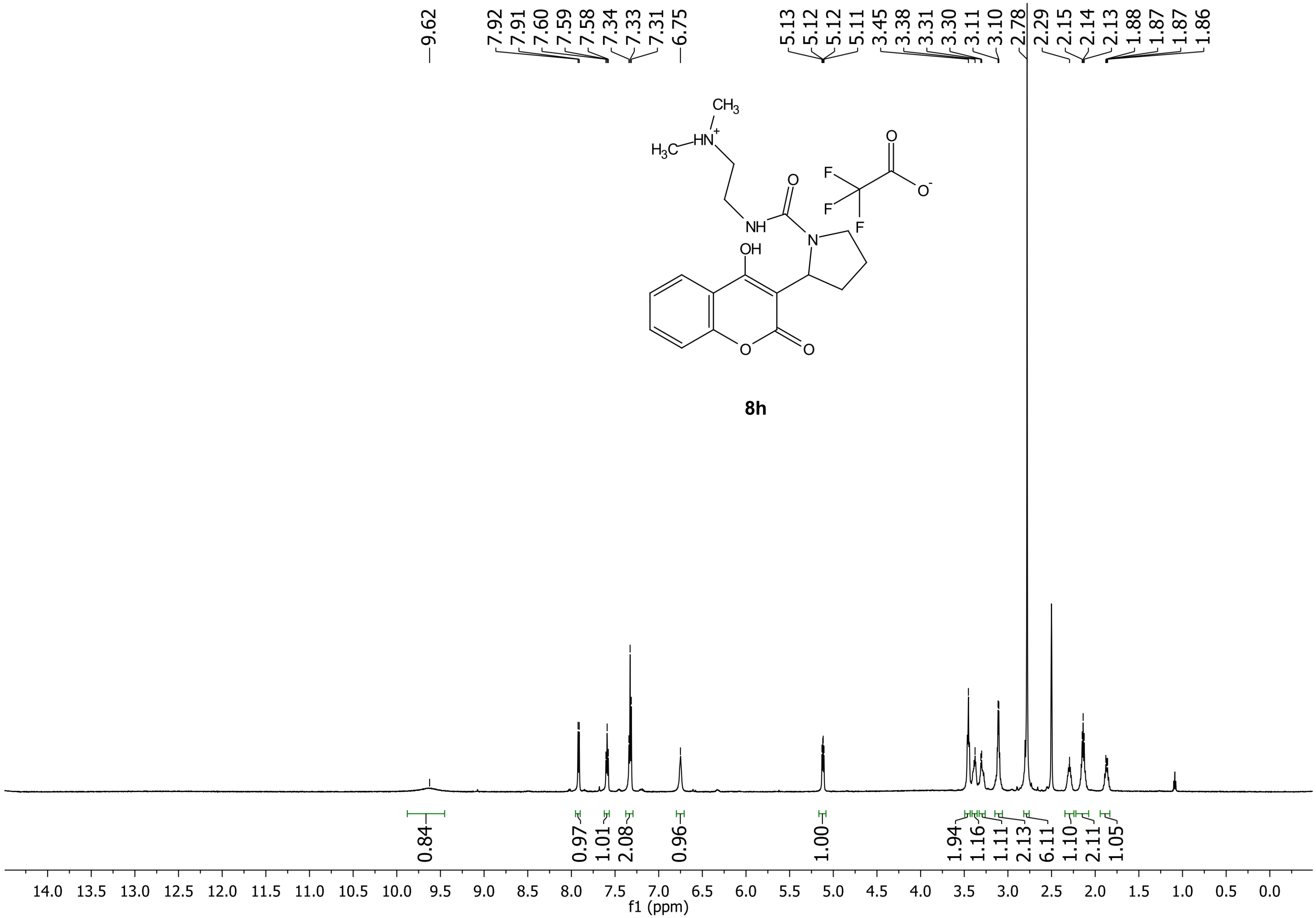

9.62
7.92
7.91
7.60
7.59
7.58
7.34
7.33
7.31
6.75
5.13
5.12
5.12
5.11
3.45
3.38
3.31
3.30
3.11
3.10
2.78
2.29
2.15
2.14
2.13
1.88
1.87
1.87
1.86
CH3
H3C
HN+
O
F
O-
NH
N
OH
O
O
8h
0.84
0.97
1.01
2.08
0.96
1.00
1.94
1.16
1.11
2.13
6.11
1.10
2.11
1.05
14.0
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
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)

Figure S 80.

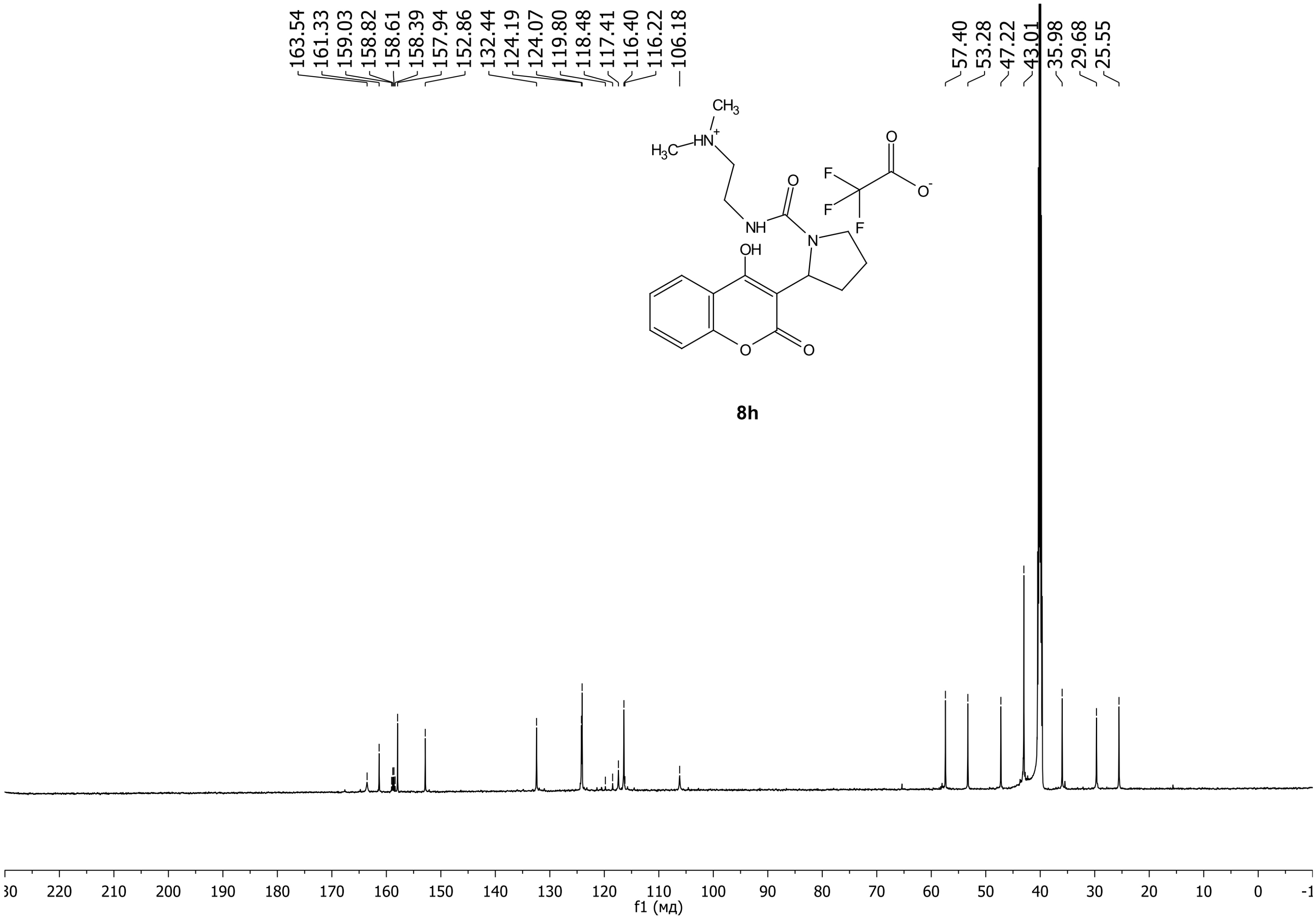

163.54
161.33
159.03
158.82
158.61
158.39
157.94
152.86
132.44
124.19
124.07
119.80
118.48
117.41
116.40
116.22
106.18
57.40
53.28
47.22
43.01
35.98
29.68
25.55
CH3
H3C
HN+
O
F
F
F
O-
NH
N
OH
O
O
8h
f1 (мд)

Figure S 81.