Supporting Information

Chemoenzymatic synthesis of optically active phenolic 3,4-dihydropyridin-2-ones: a way to access enantioenriched 1,4-dihydropyridine and benzodiazepine derivatives

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I. Procedures implied in the assignment of the absolute configuration of optically active compounds (Scheme 2 of the manuscript).

*1. Transformation of (–)-**6a** into (R)-**13**.*

To a solution of (–)-**6a** (ee = 94%, 26 mg, 0.10 mmol) in DMF (0.54 mL), KOH (9.0 mg, 0.16 mmol) was added. After 10 min stirring at room temperature, methyl yodide (50 μL, 0.80 mmol) was added and the resulting mixture was allowed to react at room temperature during 6 h. Then, CH_2Cl_2 (10 mL) and water (10 mL) were added and both phases separated. The organic layer was washed with water (2 × 5.0 mL) and brine (5.0 mL). The crude product was purified by flash-chromatography (*n*-hexane/ethyl acetate 15:1 as the eluent) yielding (*R*)-**13** (19 mg, 69%). This compound was analysed by chiral-HPLC (Chiralpak IC; hexane/propan-2-ol 75:25, 0.8 mL/min, 215 nm, 20 ºC, t_R = 15.1 (*S*) and 18.4 (*R*) min; R_S = 3.9).[1]

*2. Transformation of (–)-**6c** into (R)-**6a**.*

To a sample of (–)-**6c** (3.5 mg, 10 μmol) dissolved in methanol (0.5 mL), Pd-C (10%, 1.0 mg) was added and the resulting mixture stirred at room temperature under a hydrogen atmosphere. After 7 h (TLC monitoring), the reaction mixture was filtered through Celite®, and the filtrate was evaporated. The resulting carboxylic acid was treated with an excess of a solution of diazomethane in a mixture of diethyl ether/methanol (40 mM). After 2-3 min, solvents were evaporated and the resulting methyl ester (*R*)-**6a** was analysed by chiral-HPLC (see section III for conditions).

II. Synthesis of racemic 1,4-DHP derivatives 14a-c and 15a-c involved in the screening of the enzymatic hydrolysis reactions (Table 3 of the manuscript)

Racemic 1,4-DHP derivatives (±)-**14a-c** were prepared from the corresponding racemic 3,4-DHP-2-one (±)-**10a-c** following the procedure indicated in the text for the optically active 1,4-DHP there described. The ^{1}H- and ^{13}C-NMR spectra of (±)-**14a** and (±)-**14c** were identical to those of the optically active samples. For (±)-**14b**, ^{1}H NMR ($CDCl_3$, 300.13 MHz), δ (ppm): 1.33 (s, 9 H, Bu^t), 2.27 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 5.07 (s, 1 H, H-4), 6.36 (b s, 1 H, NH), 6.90 (dd, 1 H, ^4J 2.2, ^3J 7.8 Hz, Ar), 7.00 (t, 1 H, ^4J 1.7, H-2′), 7.15 (b d, 1 H, ^3J 7.8 Hz, Ar), 7.24 (t, 1 H, ^3J 7.8 Hz, H-5′), 9.76 (s, 1 H, HC=O).

Racemic 1,4-DHP derivatives (±)-**15a-c** were prepared from the corresponding racemic acetyl derivative (±)-**14a-c** as follows: To a solution of (±)-**14** (0.10 mmol) in acetone (1.8 mL), 3 M aq NaOH (0.40 mmol) and water (3.5 mL) were added. Reaction was maintained at room temperature until disappearance of the starting material (TLC monitoring). Then, acetone was eliminated under reduced presure, the pH of the aqueous solution adjusted at 1-2 with 3 M aq HCl, and extracted with ethyl acetate (3 × 10 mL). After the usual work-up, the corresponding (±)-**15** was isolated (83-92% yield) and identified by ^{1}H-NMR spectrum analysis (CD_3OD, 300.13 MHz).

[1] S. Y. Torres, E. Ochoa, Y. Verdecia and F. Rebolledo, *Tetrahedron* 2014, **70**, 4675-4684.

For (±)-**15a**: δ 2.37 (s, 3 H, CH_3), 3.63 (s, 3 H, CH_3O), 4.99 (s, 1 H, H-4), 6.61-6.51 (m, 1 H, Ar), 6.78-6.62 (m, 2 H, Ar), 7.02 (t, 1 H, ^3J 7.6, H-5′), and 9.75 (s, 1 H, HC=O) ppm.

For (±)-**15b**: δ 1.36 (s, 9 H, Bu^t), 2.33 (s, 3 H, CH_3), 4.91 (s, 1 H, H-4), 6.60-6.52 (m, 1 H, Ar), 6.76-6.65 (m, 2 H, Ar), 7.03 (t, 1 H, ^3J 7.8 Hz, H-5′), and 9.72 (s, 1 H, HC=O) ppm.

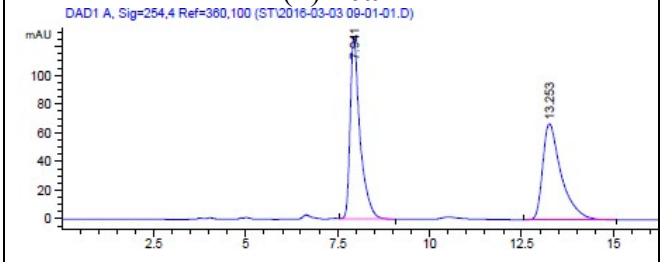
For (±)-**15c**: δ 2.39 (s, 3 H, CH_3), 5.16-4.98 [AB system + s, 3 H, CH_2 (AB system, 5.07, $|^2J|$ 12.6 Hz) and H-4 (s, 5.17)], 6.61-6.54 (m, 1 H, Ar), 6.71-6.64 (m, 2 H, Ar), 7.00 (t, 1 H, ^3J 8.1 Hz, Ar), 7.19-7.08 (m, 2 H, Ar), 7.33-7.21 (m, 3 H, Ar), and 9.74 (s, 1 H, HC=O) ppm.

III. Chiral HPLC conditions and chromatograms of the isolated optically active compounds:

*1. CRL-catalyzed hydrolysis of (±)-**10a*** (Table 1 of the manuscript, entries 3 and 4)

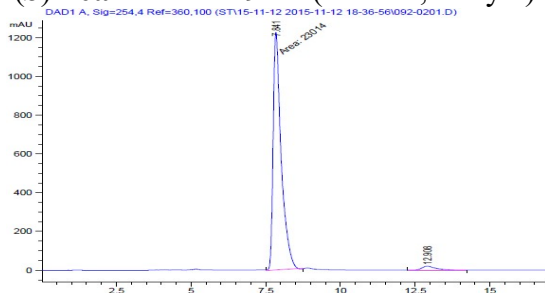
Substrate (±)-10a and the enantioenriched sample: Chiralcel OD; hexane/propan-2-ol 70:30, 0.8 mL/min, 254 nm, 30 °C; t_R = 7.9 (*S*) and 13.3 (*R*) min; R_S = 6.5.

(±)-**10a**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.941	BB	0.2712	2356.12451	126.57726	50.1784
2	13.253	BB	0.5136	2339.37280	66.95255	49.8216

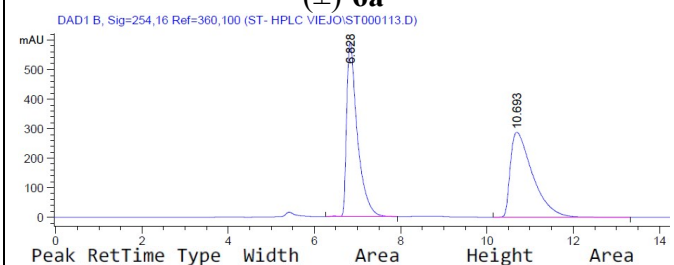
(*S*)-**10a** with ee = 94% (Table 1, entry 4)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.841	MM	0.3129	2.30140e4	1225.67261	97.2194
2	12.908	BB	0.4871	658.23273	19.94027	2.7806

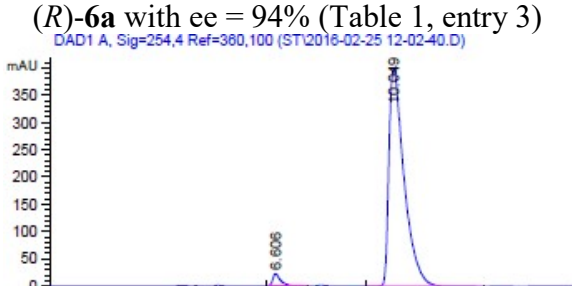
Product (±)-6a and the enantioenriched sample: Chiralcel OD; hexane/propan-2-ol 70:30, 0.8 mL/min, 254 nm, 30 °C; t_R = 6.8 (*S*) and 10.7 (*R*) min; R_S = 4.9.

(±)-**6a**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.828	VB R	0.2532	1.02214e4	590.96375	49.7855
2	10.693	BB	0.5395	1.03095e4	288.07355	50.2145

(*R*)-**6a** with ee = 94% (Table 1, entry 3)

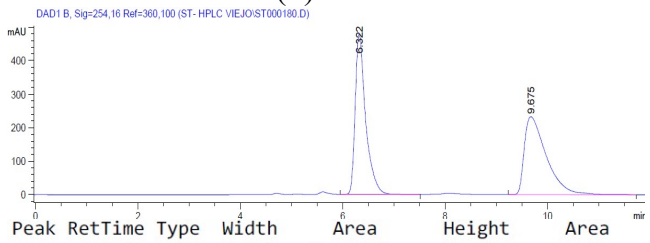


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.606	BB	0.2411	374.26208	22.61117	2.9562
2	10.049	BB	0.4593	1.22861e4	398.92078	97.0438

*2. CRL-catalyzed hydrolysis of (±)-**10b*** (Table 2 of the manuscript, entry 3)

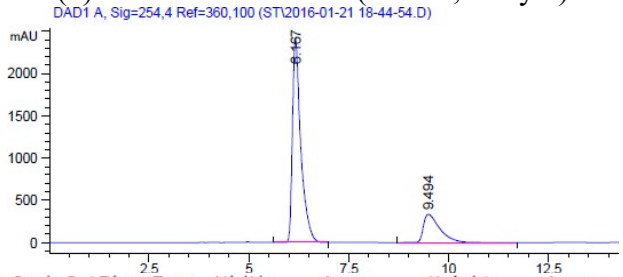
Substrate (±)-10b and the enantioenriched sample: Chiralcel OD; hexane/propan-2-ol 70:30, 0.8 mL/min, 254 nm, 30 °C; t_R = 6.3 (*S*) and 9.7 (*R*) min; R_S = 5.1.

(±)-**10b**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.322	BB	0.2095	6795.63379	479.12866	49.5811
2	9.675	BB	0.4507	6910.45068	232.51851	50.4189

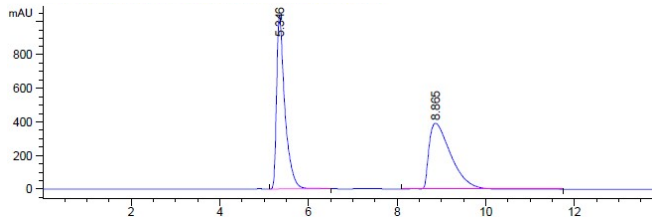
(*S*)-**10b** with ee = 58% (table 2, entry 3)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.167	BB	0.2141	3.51033e4	2407.71094	78.7969
2	9.494	BB	0.4239	9445.75391	334.00723	21.2031

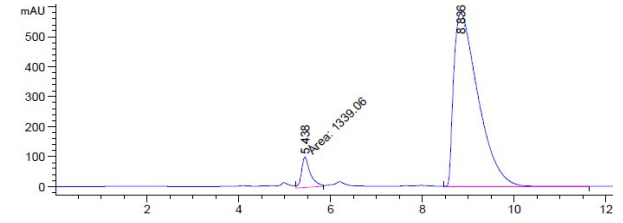
Product (±)-6b and the enantioenriched sample: Chiralcel OD; hexane/propan-2-ol 70:30, 0.8 mL/min, 254 nm, 30 °C; t_R = 5.3 (*S*) and 8.9 (*R*) min; R_S = 4.9.

(±)-**6b**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.346	BV R	0.1886	1.34364e4	1036.08008	49.9866
2	8.865	VB R	0.5238	1.34436e4	393.19232	50.0134

(*R*)-**6b** with ee = 88% (table 2, entry 3)

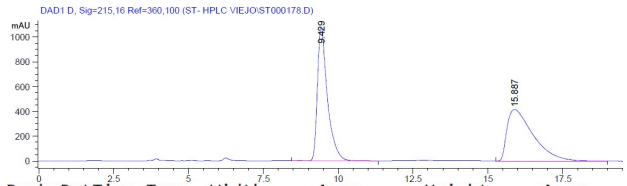


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.438	MM	0.2208	1339.05603	101.09353	5.9155
2	8.836	VB	0.5633	2.12972e4	578.81329	94.0845

*3. CRL-catalyzed hydrolysis of (±)-**10c*** (Table 2 of the manuscript, entries 4 and 5)

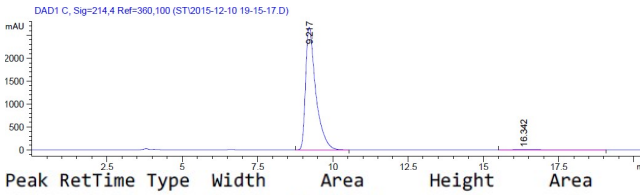
Substrate (±)-10c and the enantioenriched sample: Chiralcel OD; hexano/2-propanol 70:30, 0.8 mL/min, 215 nm, 30 °C; t_R = 9.4 (*S*) and 15.9 (*R*) min; R_S = 5.2.

(±)-**10c**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.429	VB R	0.3458	2.51282e4	1076.52454	49.9552
2	15.887	BB	0.8983	2.51733e4	415.82639	50.0448

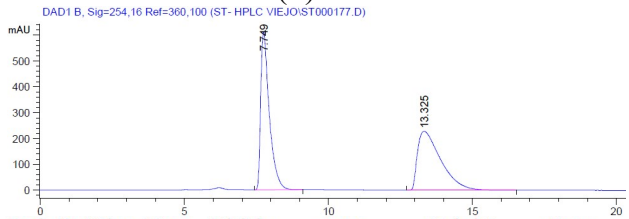
(*S*)-**10c** with ee = 99% (table 2, entry 5)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.217	BB	0.3485	6.28966e4	2673.38599	99.4528
2	16.342	BB	0.7593	346.04071	6.75911	0.5472

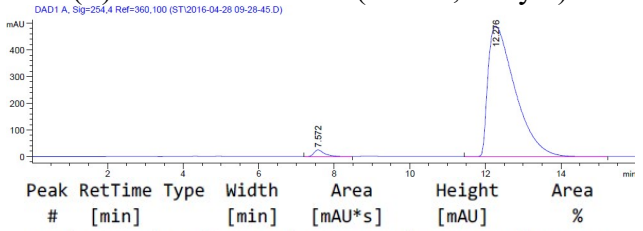
Product (±)-6c and the enantioenriched sample: Chiralcel OD; hexane/propan-2-ol 70:30, 0.8 mL/min, 254 nm, 30 °C; t_R = 7.7 (*S*) and 13.3 (*R*) min; R_S = 4.8.

(±)-**6c**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.749	BB	0.3062	1.27044e4	611.95020	49.7687
2	13.325	BB	0.8551	1.28225e4	228.34610	50.2313

(*R*)-**6c** with ee = 96% (table 2, entry 4)

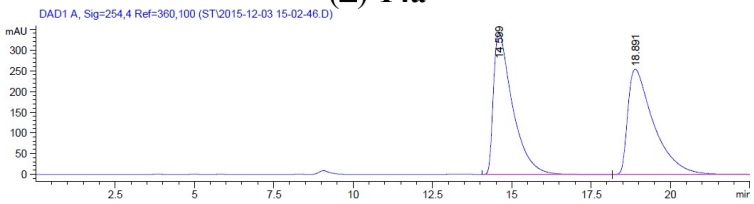


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.572	BB	0.2848	478.50739	24.83595	1.9382
2	12.276	BB	0.7576	2.42093e4	489.02179	98.0618

*4. The Vilsmeier-Haack reaction of **10a,c**: 1,4-dihydropyridines **14a,c***

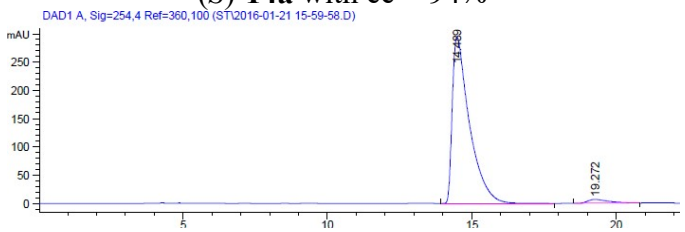
(±)-14a: Chiralcel OD; hexane/propan-2-ol 90:10, 0.8 mL/min, 254 nm, 30 ºC; t_R = 14.6 (*S*) and 18.9 (*R*) min; R_S = 3.0.

(±)-**14a**



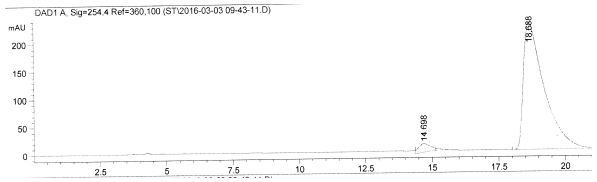
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.599	BB	0.6088	1.42102e4	341.97131	49.8630
2	18.891	BBA	0.8222	1.42883e4	254.04109	50.1370

(*S*)-**14a** with ee = 94%



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.489	BB	0.5996	1.21362e4	293.98135	97.2071
2	19.272	BB	0.7312	348.68491	6.92733	2.7929

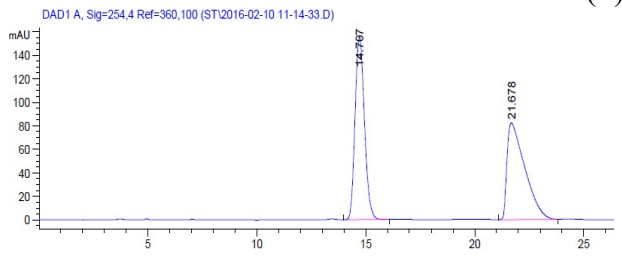
(*R*)-**14a** with ee = 93%



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.698	MM	0.5167	465.57370	15.01663	3.6017
2	18.688	BBA	0.7912	1.24611e4	229.60355	96.3983

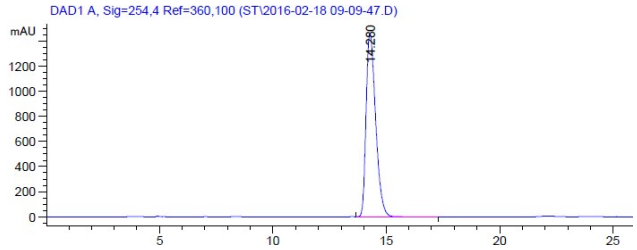
(±)-14c: Chiralpak AD-H; hexane/propan-2-ol 90:10, 0.8 mL/min, 254 nm, 30 ºC; t_R = 14.7 (*S*) and 21.7 (*R*) min; R_S = 5.3.

(±)-**14c**

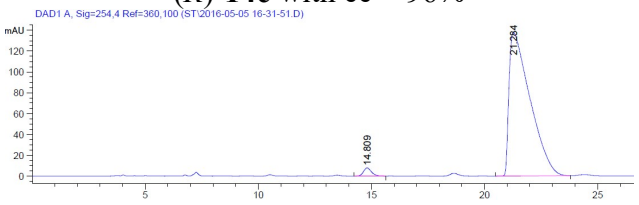


RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
14.707	BB	0.4706	4659.64111	155.05646	49.9864
21.678	BB	0.8378	4662.17725	82.18651	50.0136

(*S*)-**14c** with ee > 99%



(*R*)-**14c** with ee = 96%

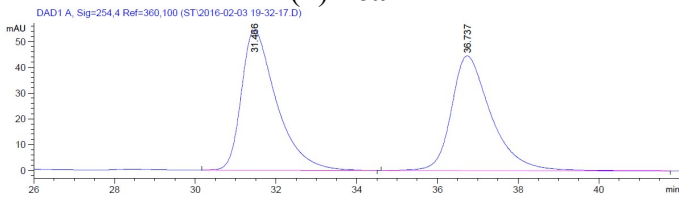


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.809	BB	0.3780	191.79919	7.82275	2.1153
2	21.284	BB	0.9476	8875.25977	138.13109	97.8847

*5. Hybrids 1,5-benzodiazepine-1,4-dihydropyridines **16a,c***

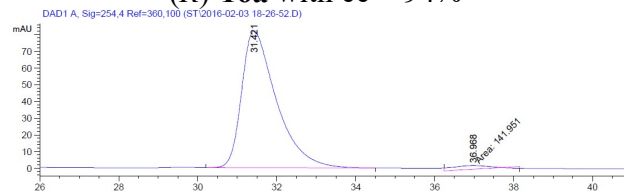
(±)-16a: Chiralpak IA; hexane/ethanol/diethylamine 90:10:0.2, 0.8 mL/min, 254 nm, 30 ºC; t_R = 31.5 (*R*) and 36.7 (*S*) min; R_S = 2.8.

(±)-**16a**



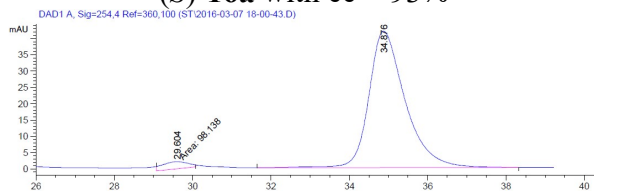
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.466	BB	0.9030	3272.42603	54.30397	51.8473
2	36.737	BB	1.0135	3039.22949	44.57248	48.1527

(*R*)-**16a** with ee = 94%



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.421	BB	0.9069	5007.22363	81.94304	97.2432
2	36.968	MM	1.0471	141.95128	2.25940	2.7568

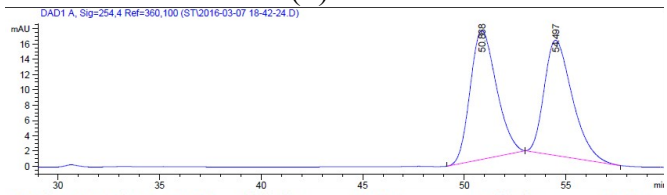
(*S*)-**16a** with ee = 93%



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.604	MM	0.7718	98.13800	2.11936	3.5133
2	34.876	BB	0.9618	2695.19189	41.82733	96.4867

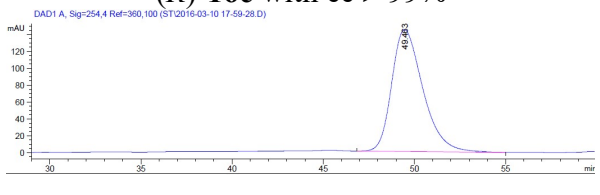
(±)-16c: Chiralpak IA; hexane/ethanol/diethylamine 90:10:0.2, 0.8 mL/min, 254 nm, 30 ºC; t_R = 50.9 (*R*) and 54.5 (*S*) min; R_S = 1.3.

(±)-**16c**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.868	BB	1.3665	1514.03601	16.84690	51.0644
2	54.497	BB	1.4510	1450.91602	15.07272	48.9356

(*R*)-**16c** with ee > 99%



Optimization of the separation of both peaks for the racemic sample (±)-**16c** was not possible. For this reason, only the HPLC-chromatogram of the enantiopure sample is shown.

IV. Chiral HPLC conditions for other compounds implied in the screening processes.

The following compounds were separated using a Chiralcel OD column; hexane/propan-2-ol 70:30, 0.8 mL/min, 30 °C:

For (±)-**7a**: t_R = 7.1 and 14.0 min; R_S = 5.6.

For (±)-**7c**: t_R = 7.9 and 19.8 min; R_S = 6.5.

For (±)-**9a**: t_R = 5.7 and 6.8 min; R_S = 2.1.

For (±)-**10d**: t_R = 6.8 and 10.4 min; R_S = 5.5.

For (±)-**11a**: t_R = 7.8 and 13.1 min; R_S = 6.5.

For (±)-**11c**: t_R = 8.8 and 16.1 min; R_S = 6.8.

For (±)-**12a**: t_R = 8.6 and 11.7 min; R_S = 4.4.

For (±)-**14b**: Chiralcel OD; hexane/propan-2-ol 95:5, 0.8 mL/min, 254 nm, 30 ºC; t_R = 20.8 (*S*) and 24.8 (*R*) min; R_S = 1.9.

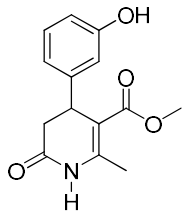
For (±)-**15a**: Chiralcel OD; hexane/propan-2-ol 90:10, 0.8 mL/min, 254 nm, 30 ºC; t_R = 18.9 (*S*) and 24.7 (*R*) min; R_S = 2.1.

For (±)-**15b**: Chiralcel OD; hexane/propan-2-ol 95:5, 0.8 mL/min, 254 nm, 30 ºC; t_R = 35.0 (*S*) and 41.6 (*R*) min; R_S = 1.7.

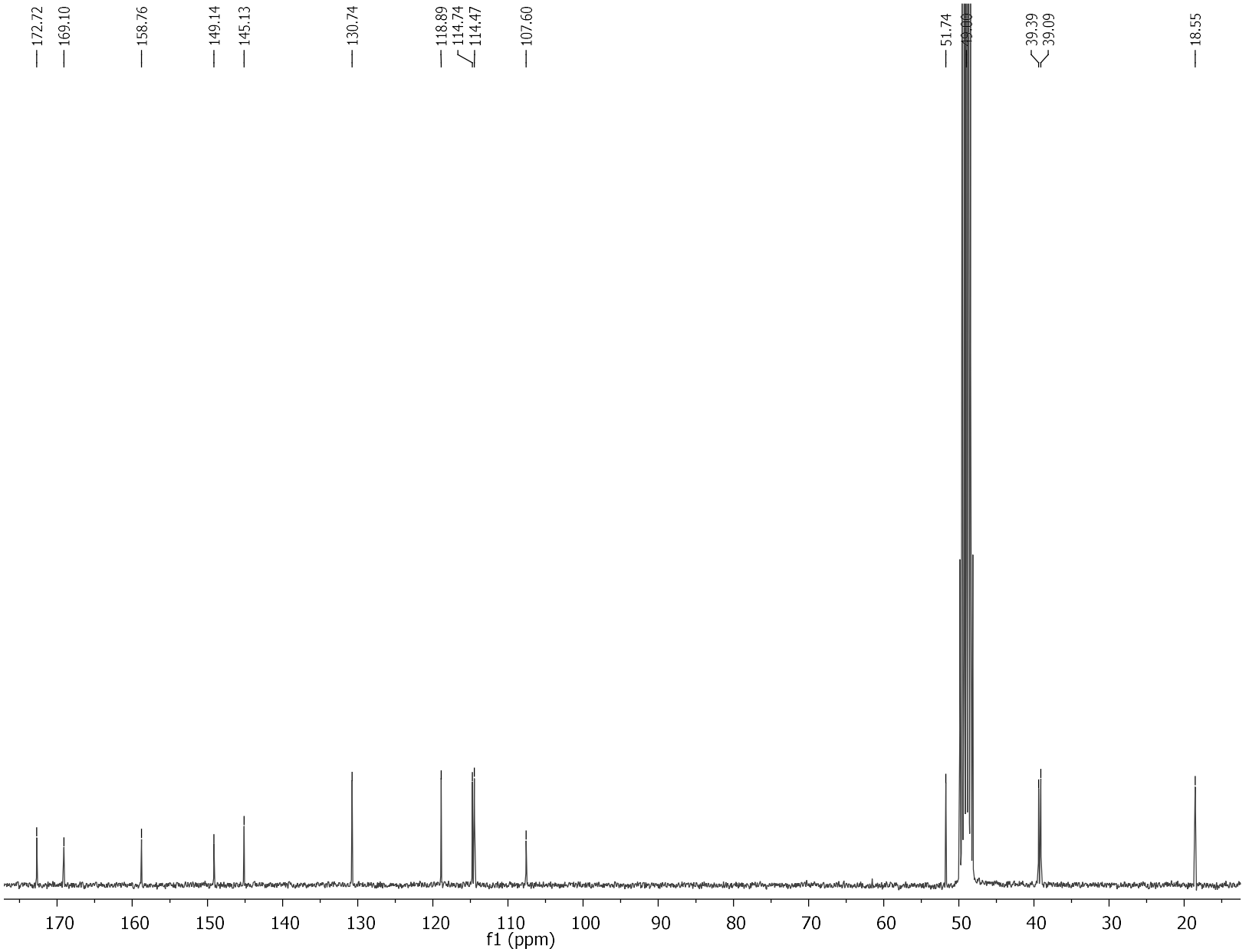
For (±)-**15c**: Chiralpak AD-H; hexane/propan-2-ol 90:10, 0.8 mL/min, 254 nm, 30 ºC; t_R = 27.8 (*R*) and 33.8 (*S*) min; R_S = 2.7.

V. ^{1}H and ^{13}C NMR spectra.

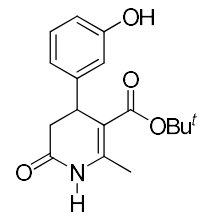
^{1}H- and ^{13}C-NMR spectra of **6a** in CD_3OD:



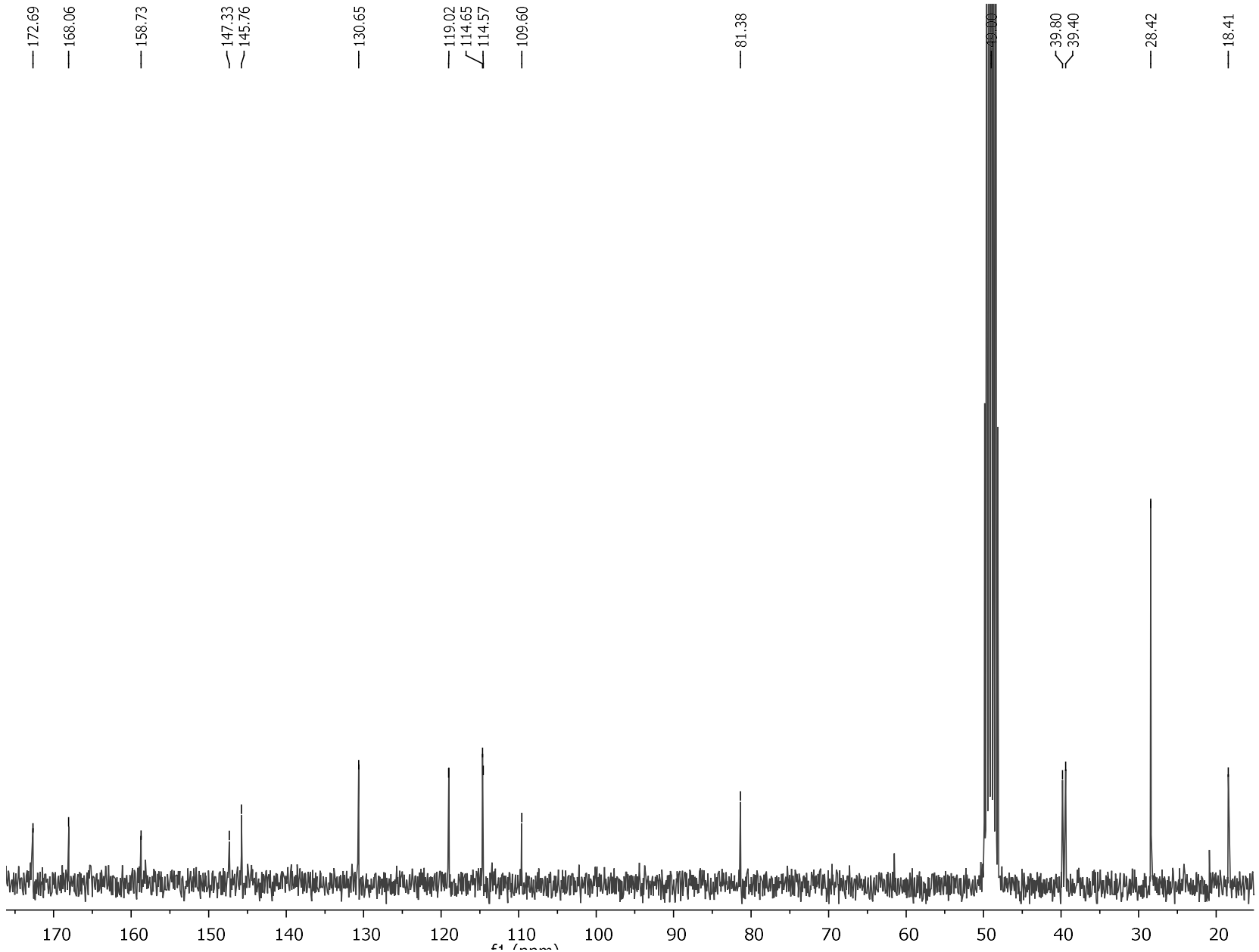
6a


172.72
169.10
158.76
149.14
145.13
130.74
118.89
114.74
114.47
107.60
51.74
49.00
39.39
39.09
18.55
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

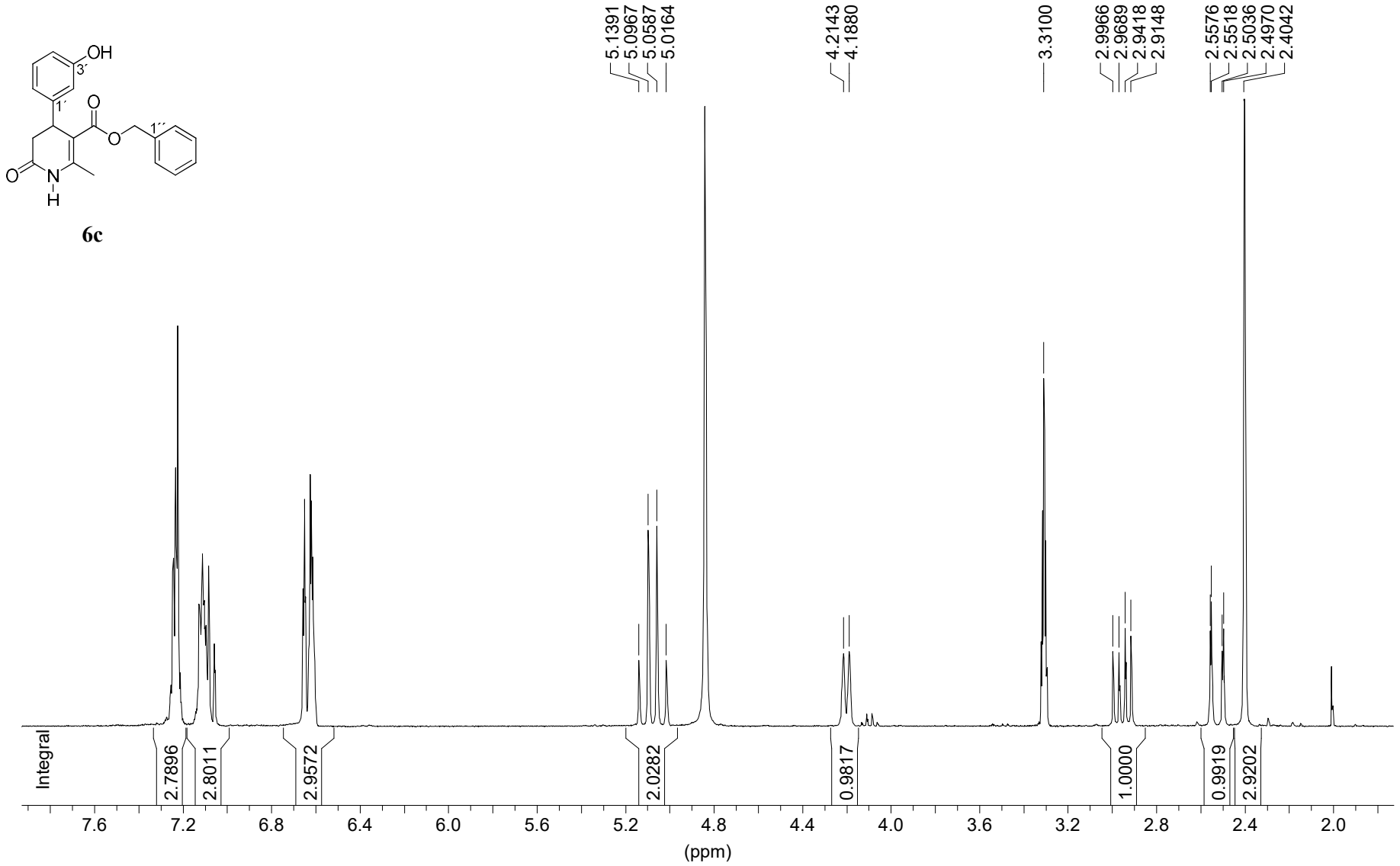
^{1}H- and ^{13}C-NMR spectra of **6b** in CD_3OD:

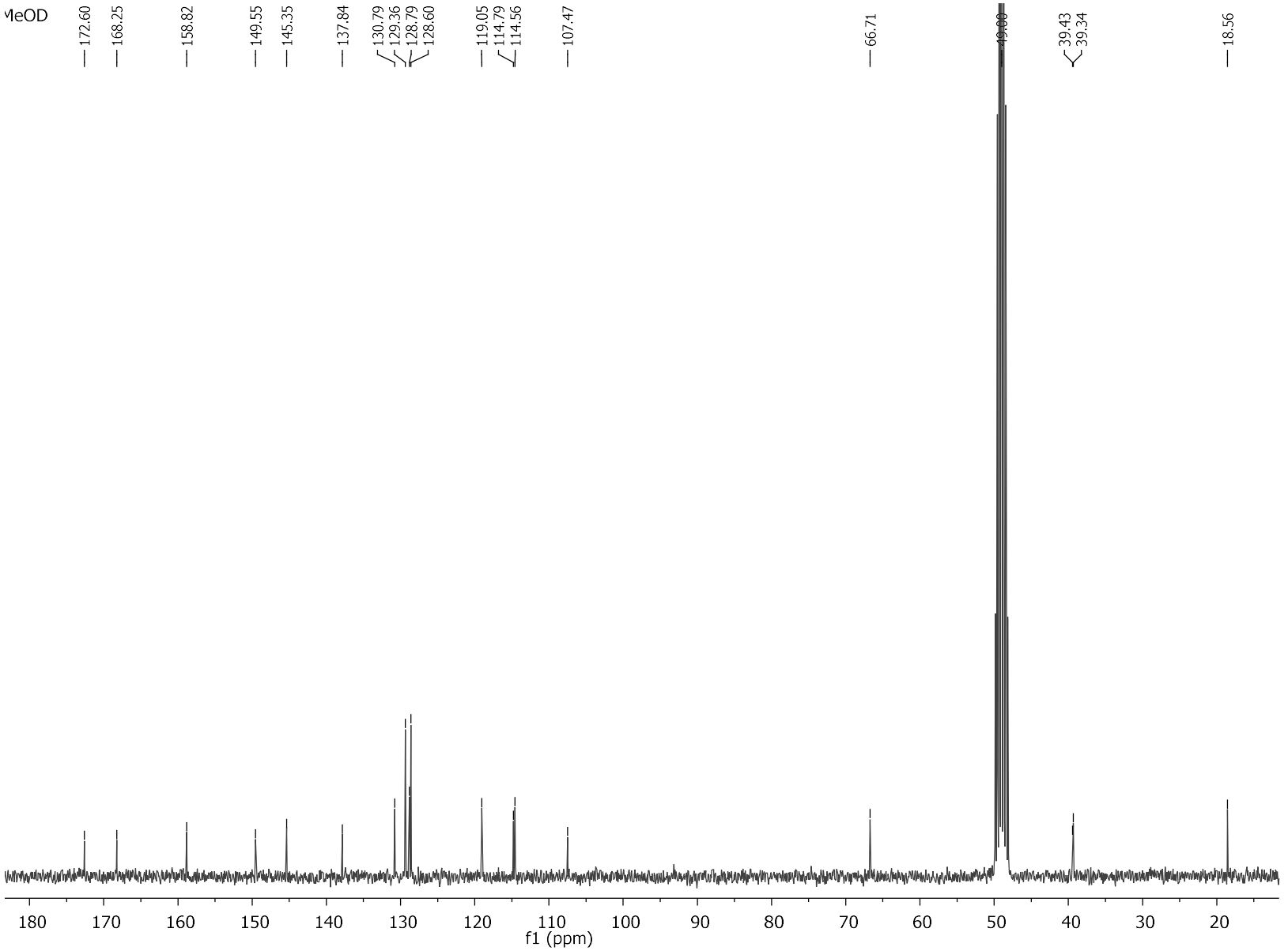


6b

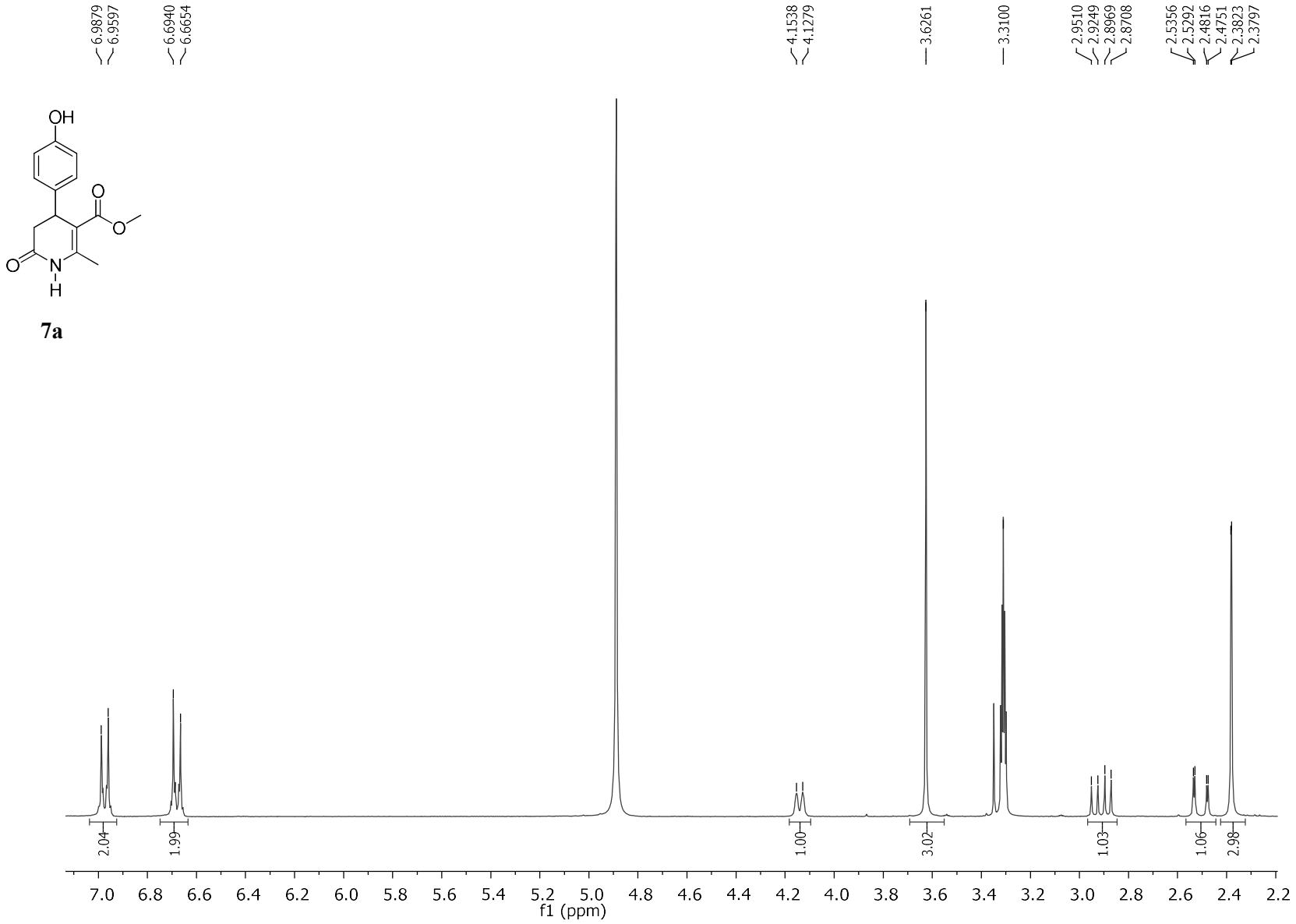

172.69
168.06
158.73
147.33
145.76
130.65
119.02
114.65
114.57
109.60
81.38
49.00
39.80
39.40
28.42
18.41
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

^{1}H- and ^{13}C-NMR spectra of **6c** in CD_3OD:

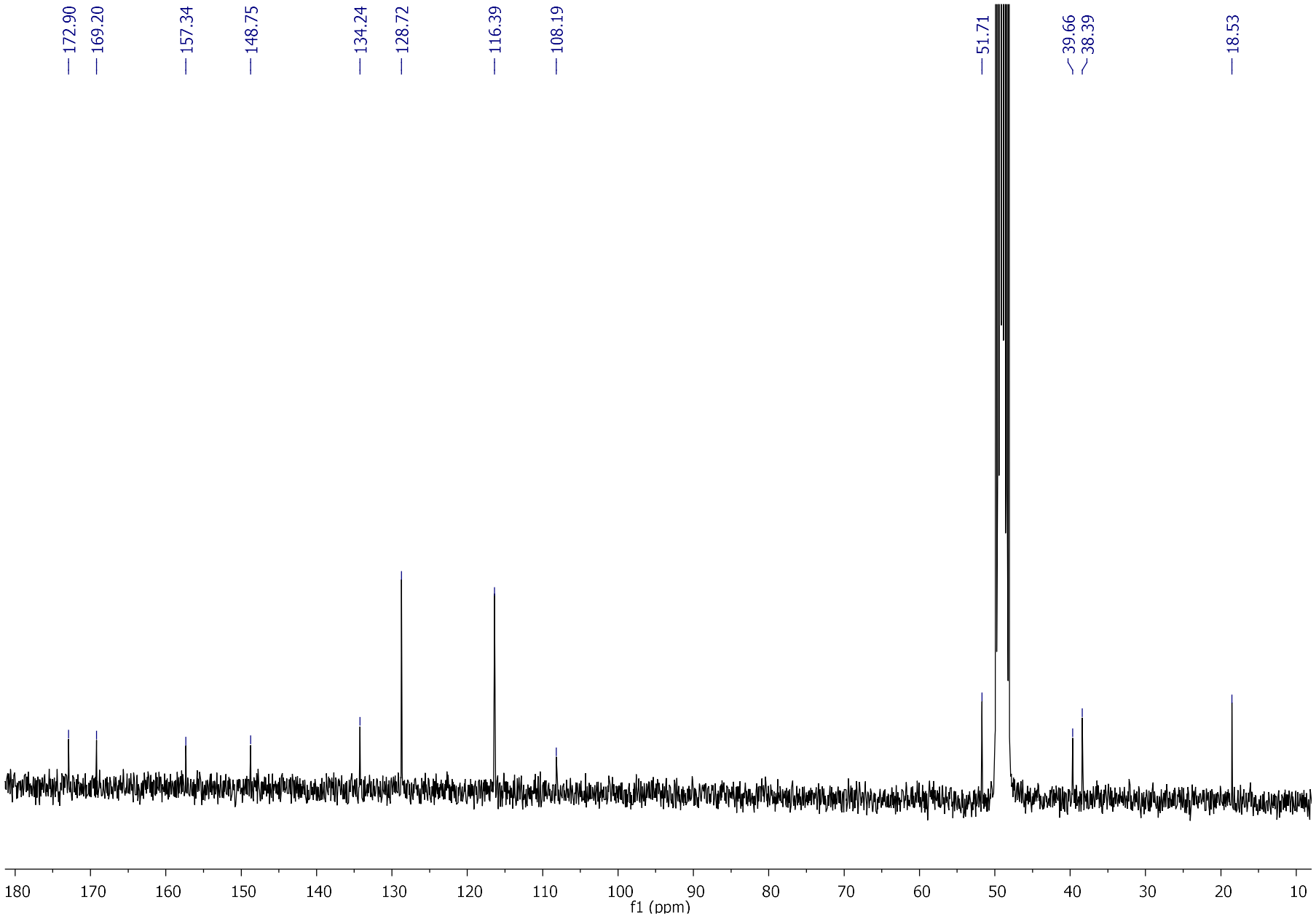



MeOD
172.60
168.25
158.82
149.55
145.35
137.84
130.79
129.36
128.79
128.60
119.05
114.79
114.56
107.47
66.71
49.00
39.43
39.34
18.56
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

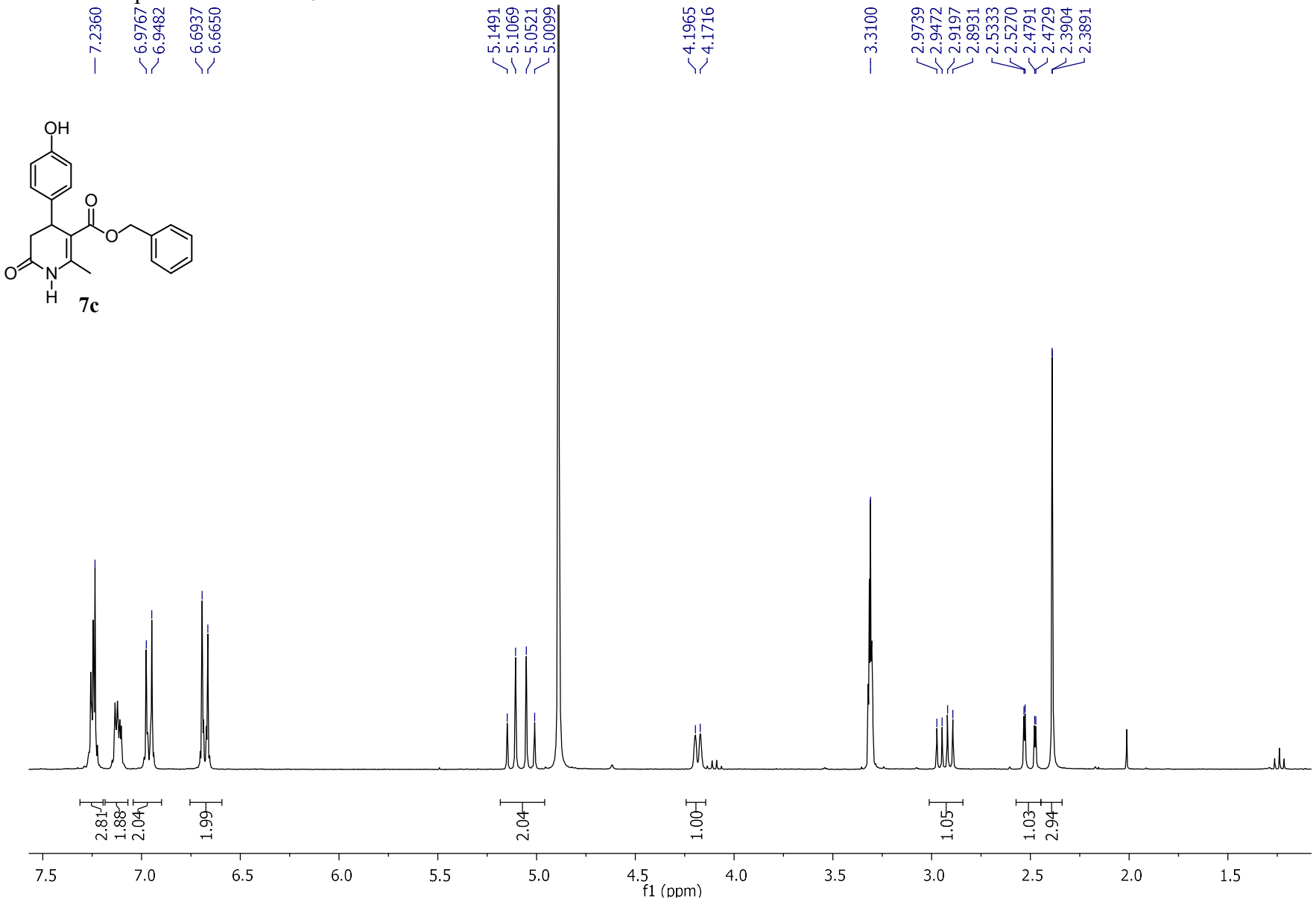
^{1}H- and ^{13}C-NMR spectra of **7a** in CD_3OD:

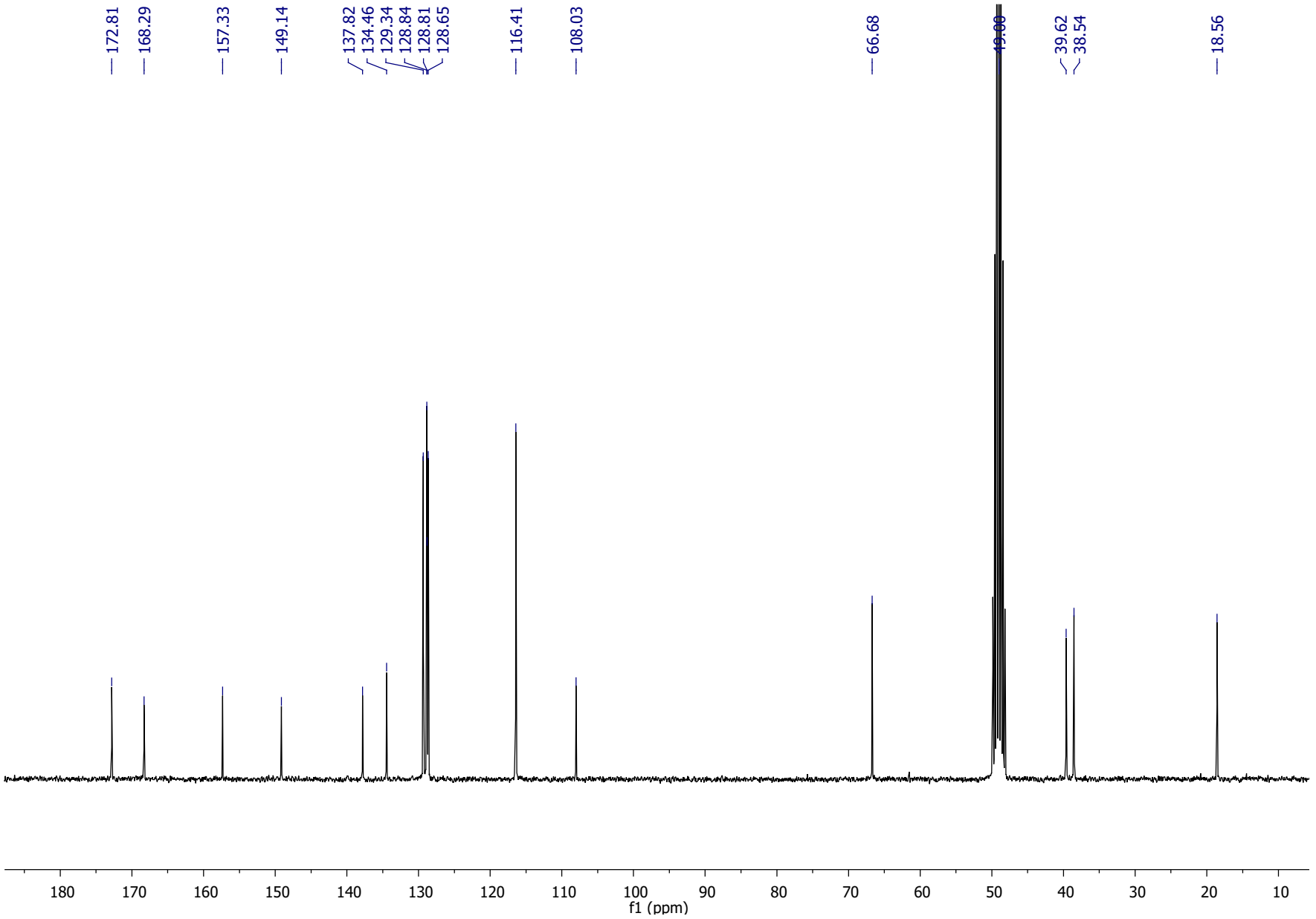


7a

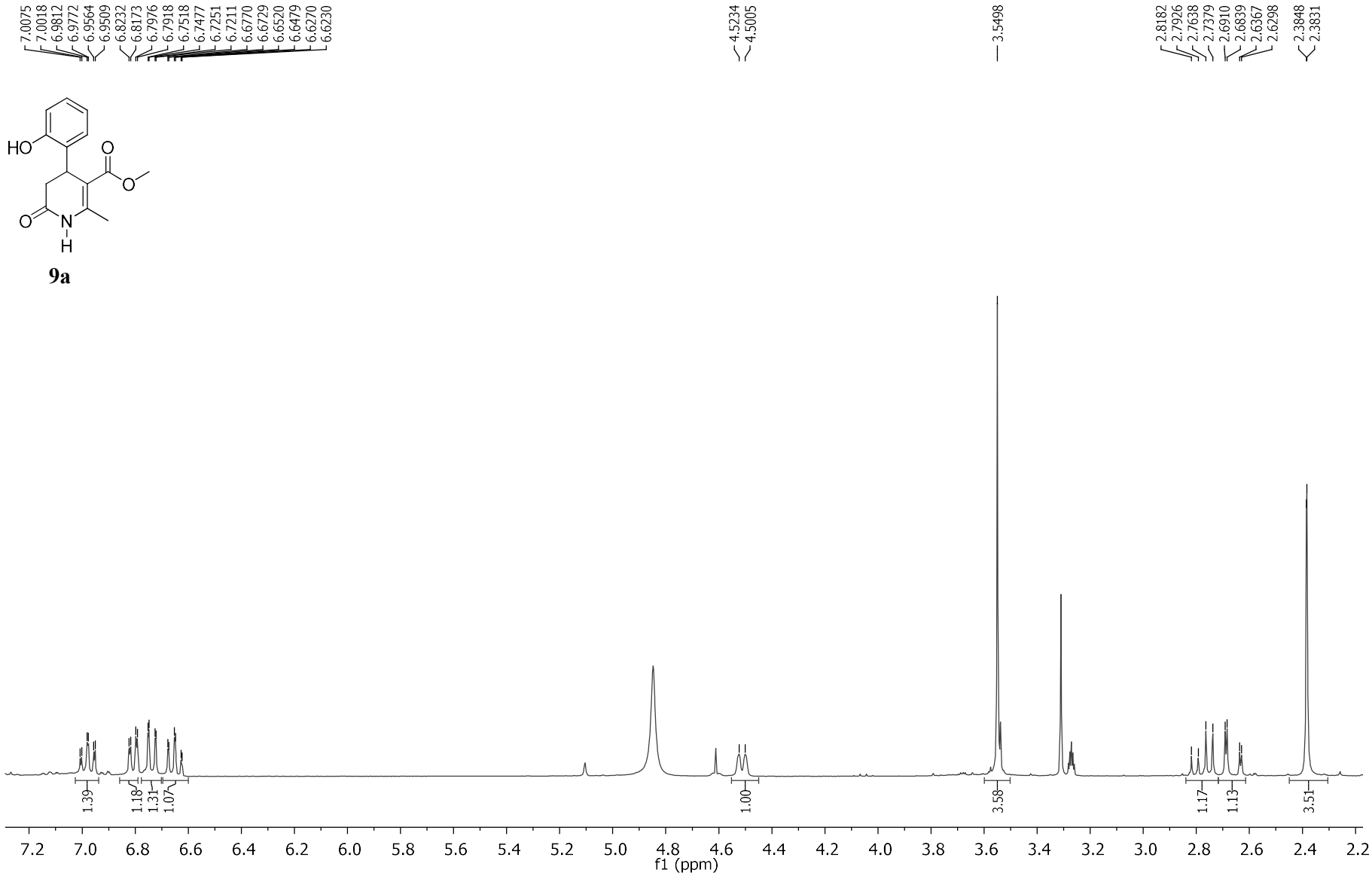

172.90
169.20
157.34
148.75
134.24
128.72
116.39
108.19
51.71
39.66
38.39
18.53
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

^{1}H- and ^{13}C-NMR spectra of **7c** in CD_3OD:

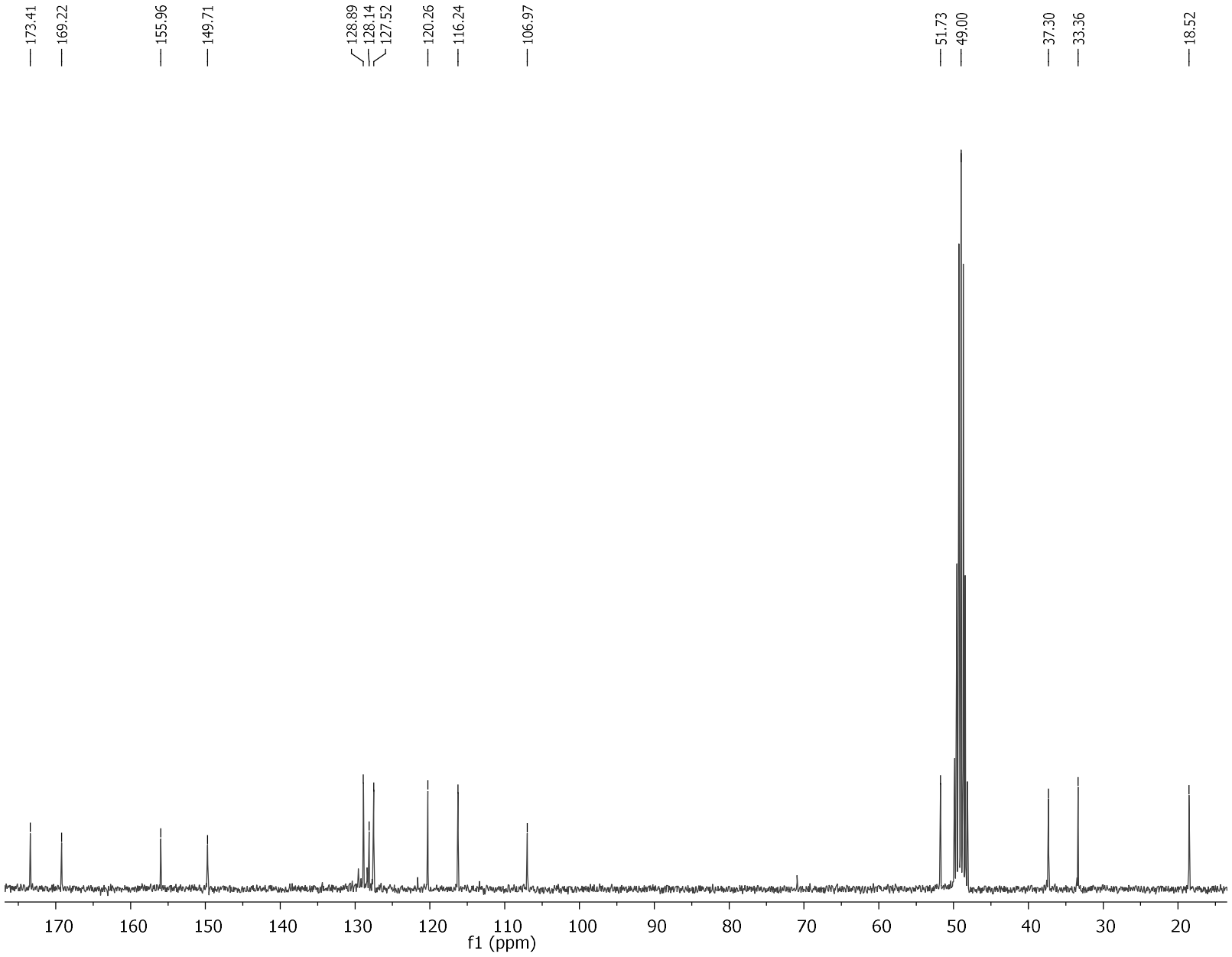



172.81
168.29
157.33
149.14
137.82
134.46
129.34
128.84
128.81
128.65
116.41
108.03
66.68
49.00
39.62
38.54
18.56
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

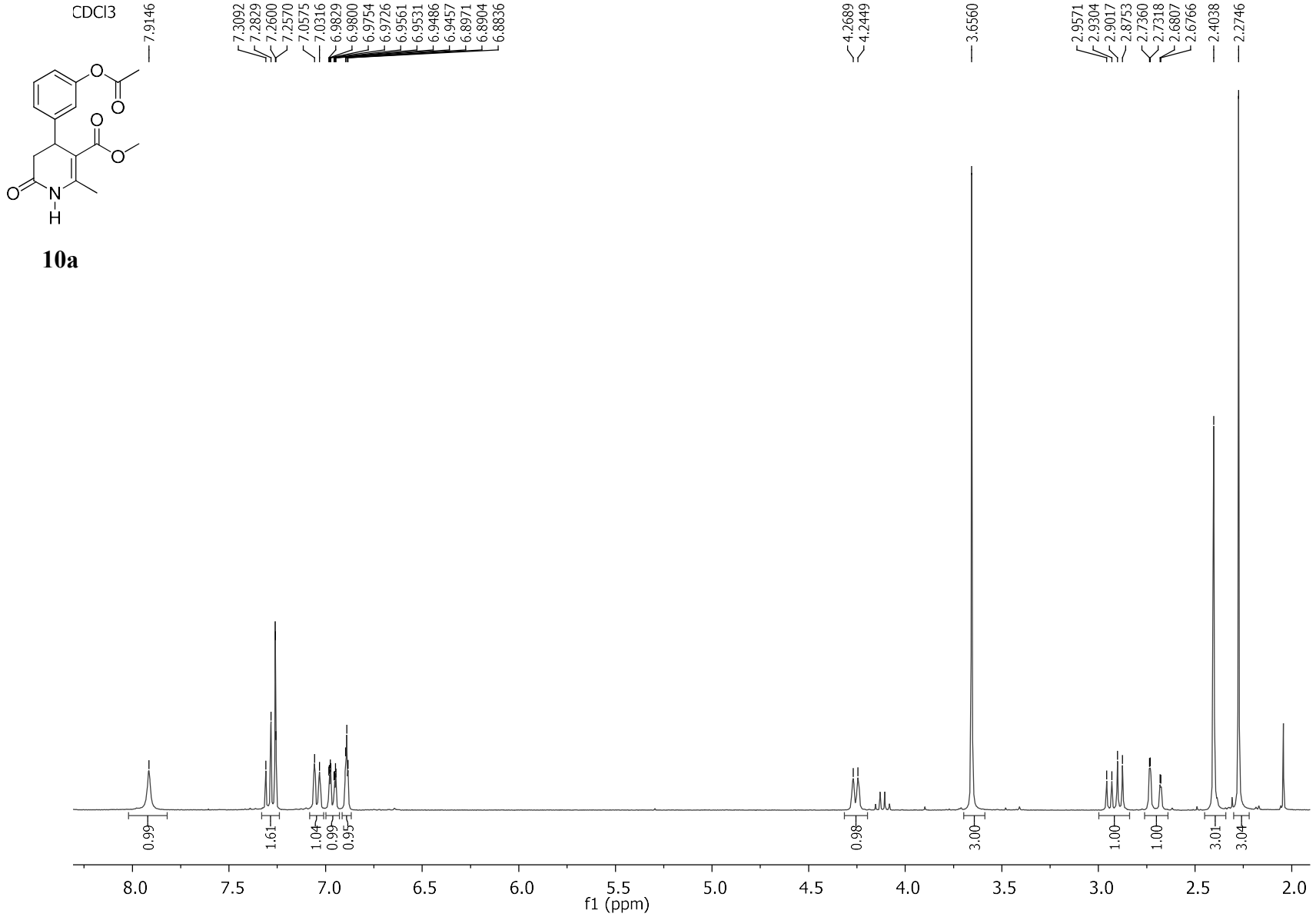
^{1}H- and ^{13}C-NMR spectra of **9a** in CD_3OD:



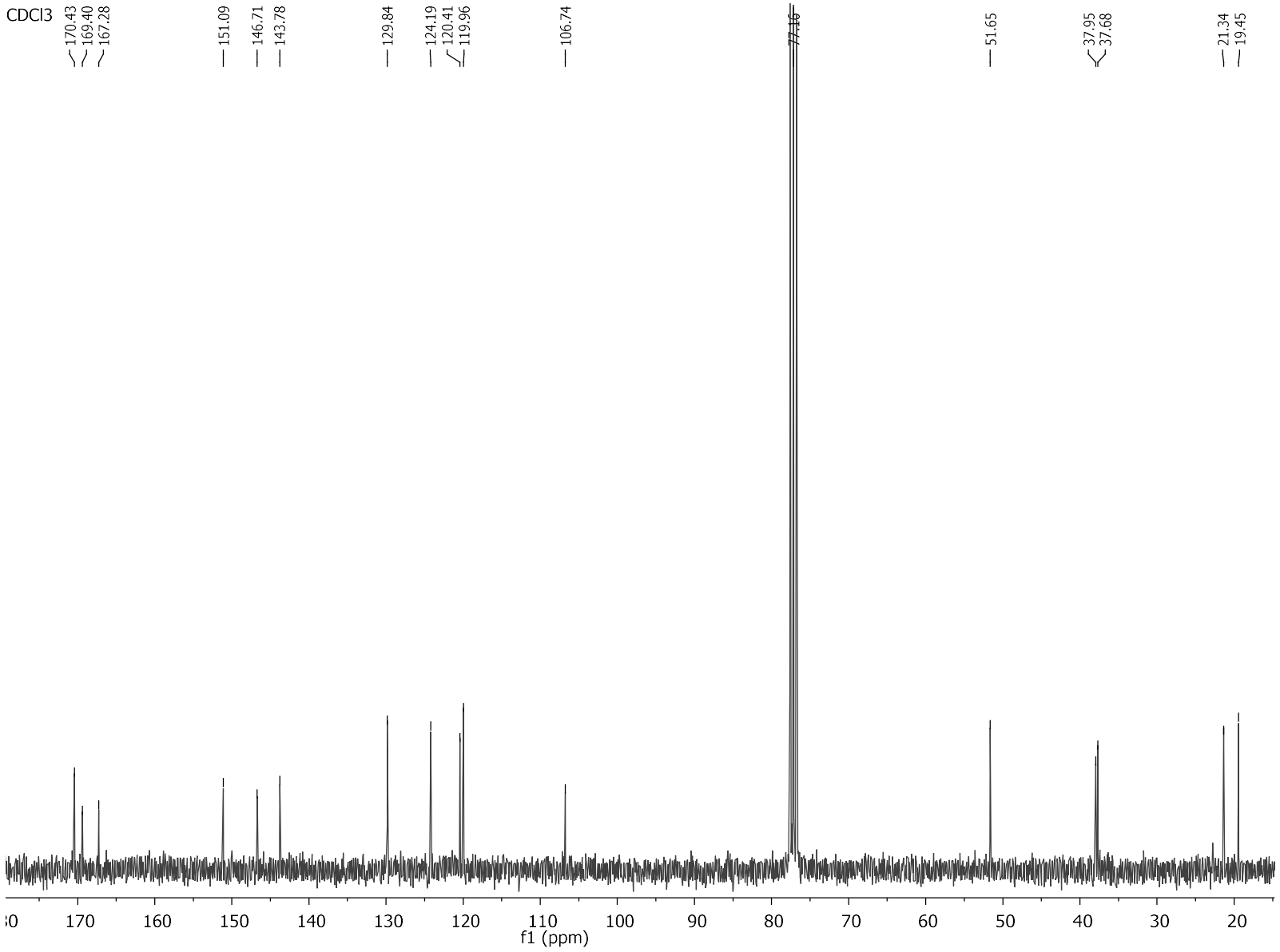
9a


173.41
169.22
155.96
149.71
128.89
128.14
127.52
120.26
116.24
106.97
51.73
49.00
37.30
33.36
18.52
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

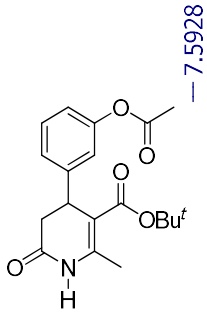
^{1}H- and ^{13}C-NMR spectra of **10a** in $CDCl_3$:



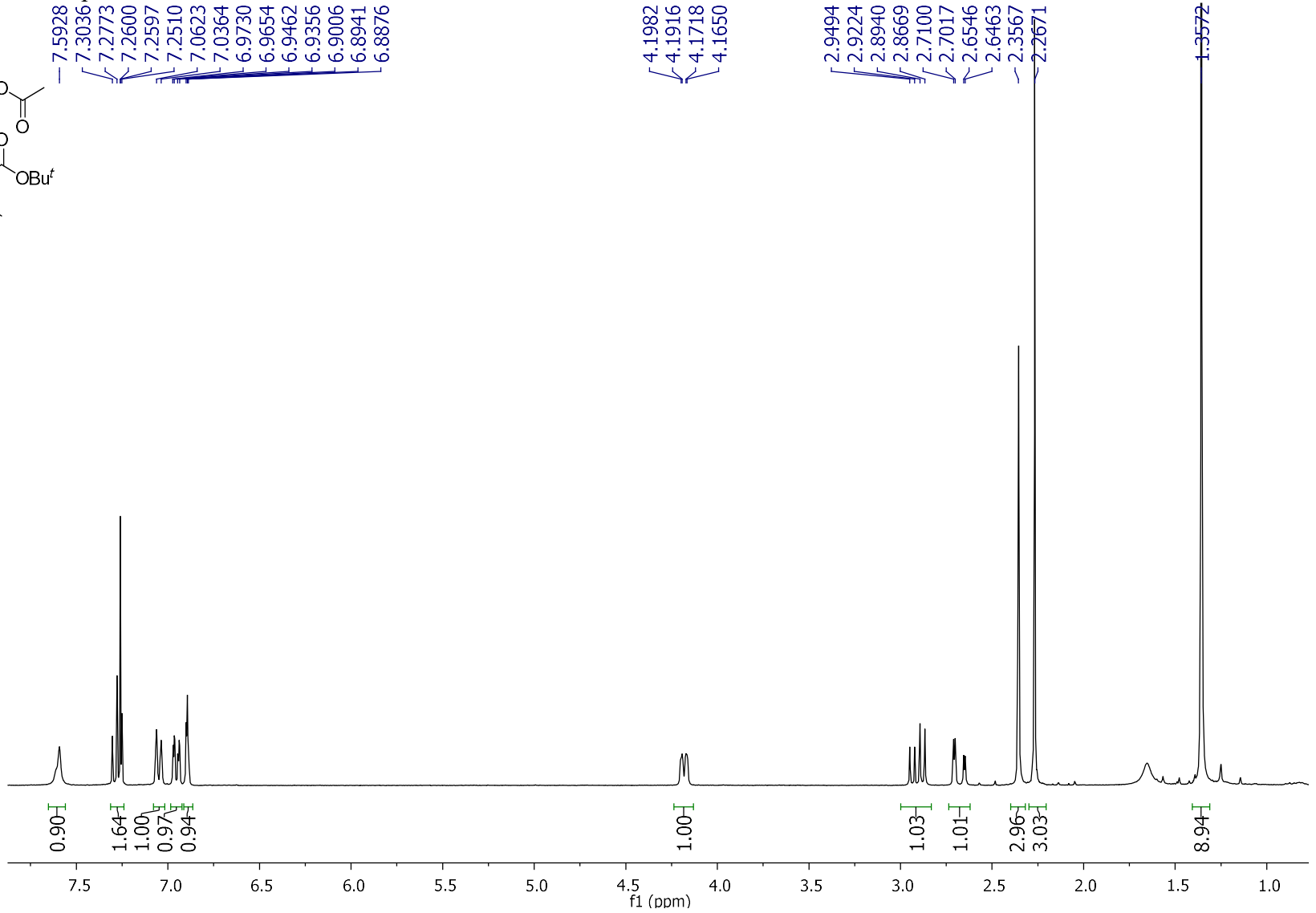
10a

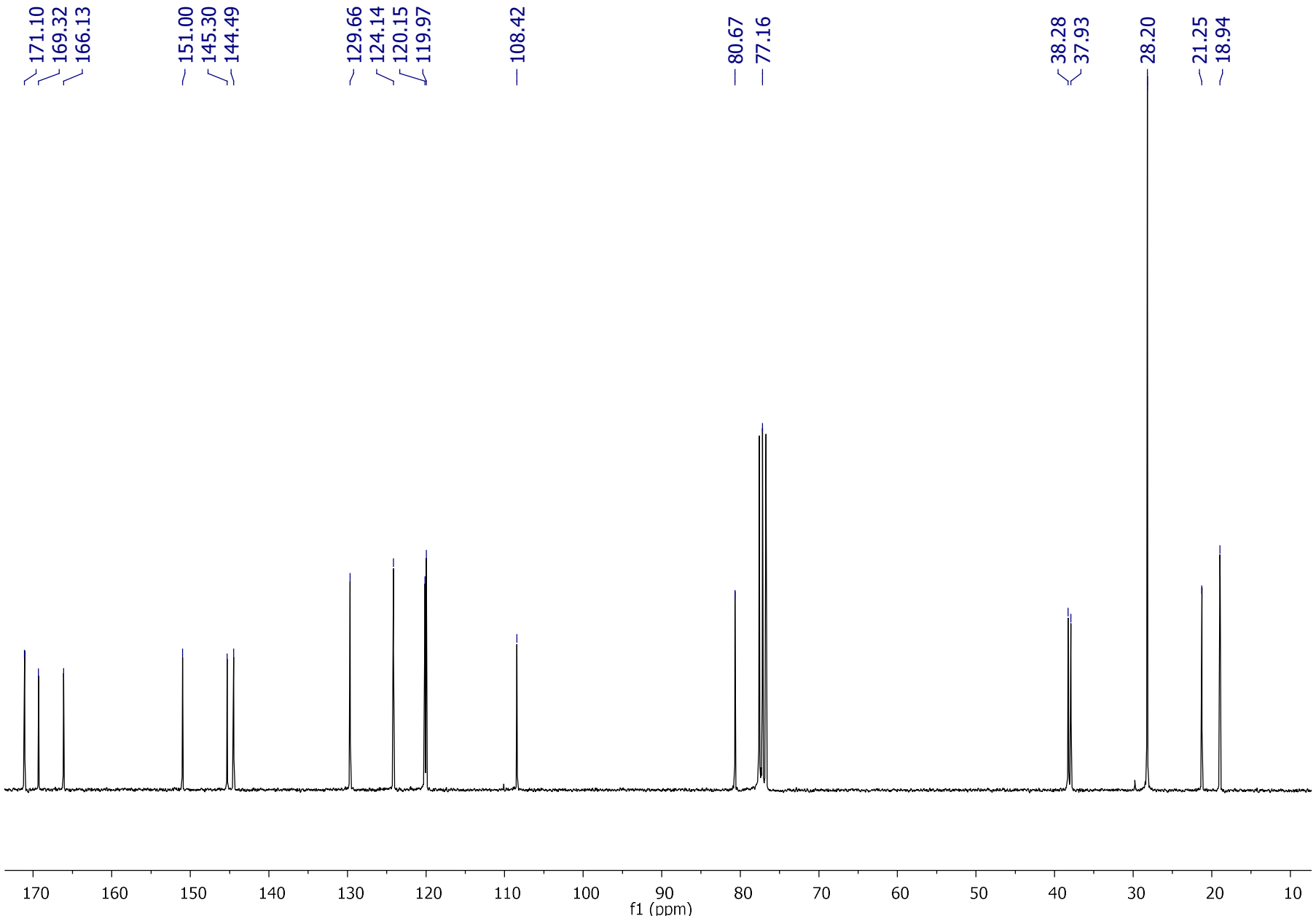

CDCl3
170.43
169.40
167.28
151.09
146.71
143.78
129.84
124.19
120.41
119.96
106.74
77.16
51.65
37.95
37.68
21.34
19.45
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

^{1}H- and ^{13}C-NMR spectra of **10b** in $CDCl_3$:

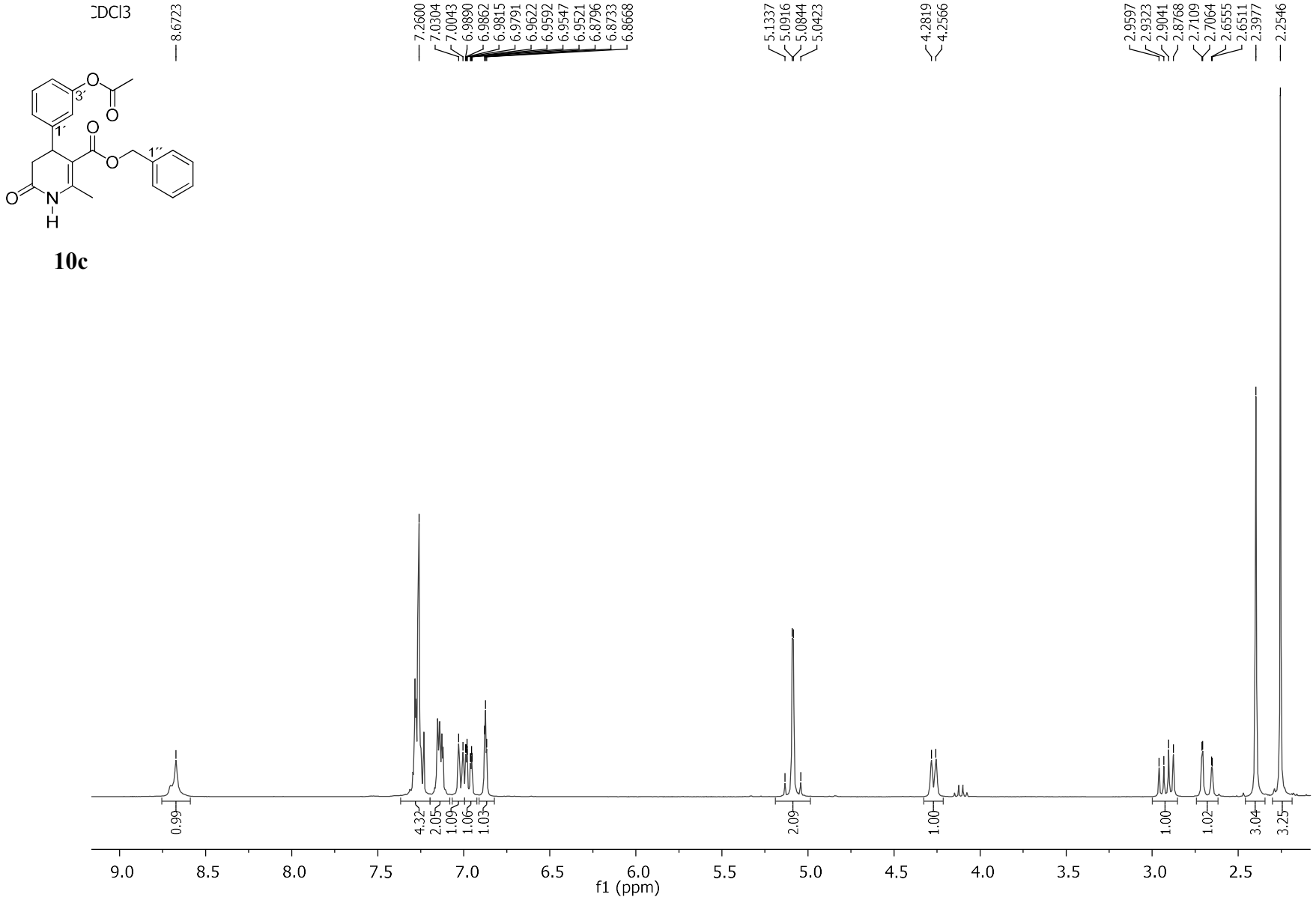


10b

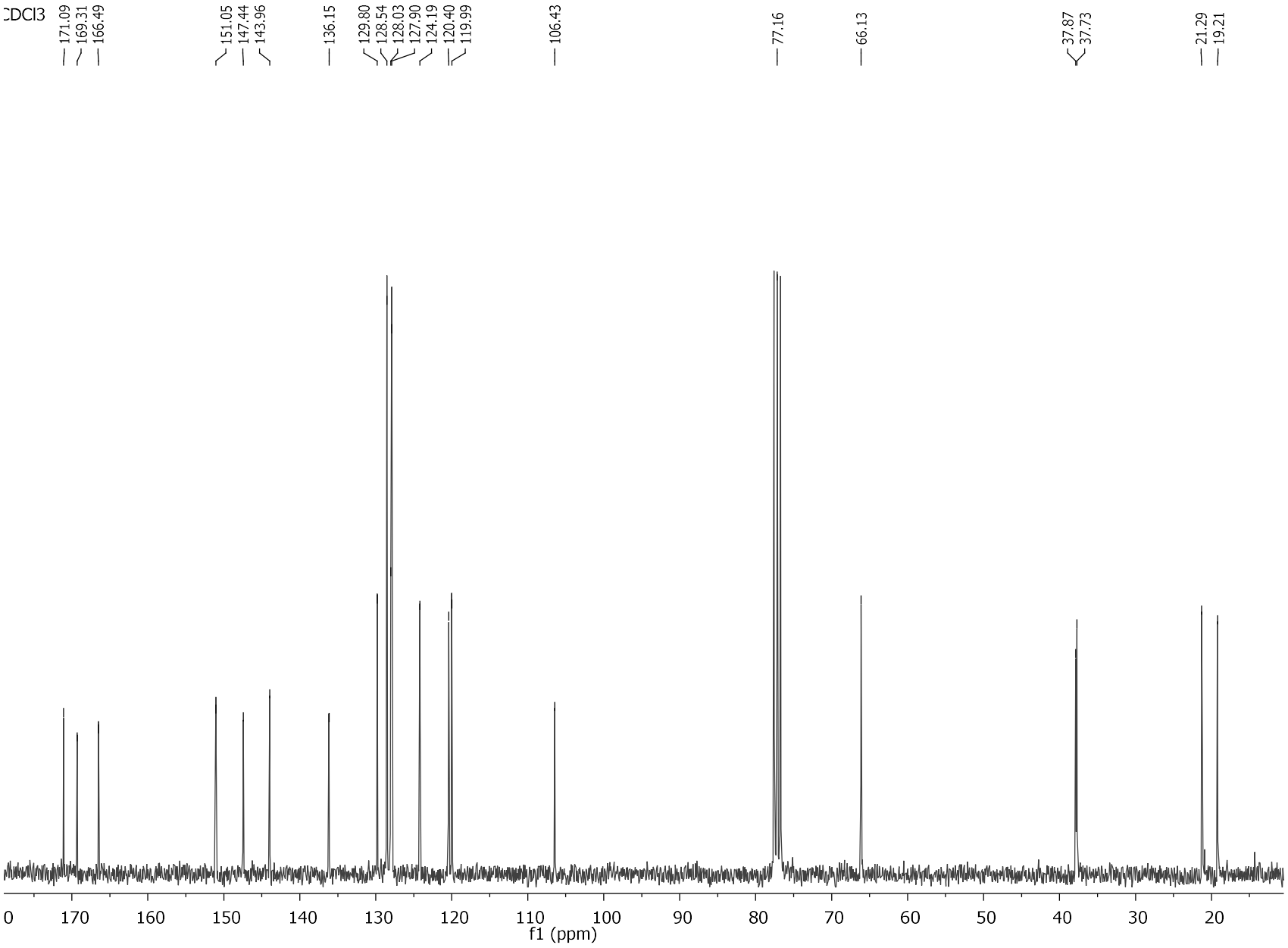



171.10
169.32
166.13
151.00
145.30
144.49
129.66
124.14
120.15
119.97
108.42
80.67
77.16
38.28
37.93
28.20
21.25
18.94
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

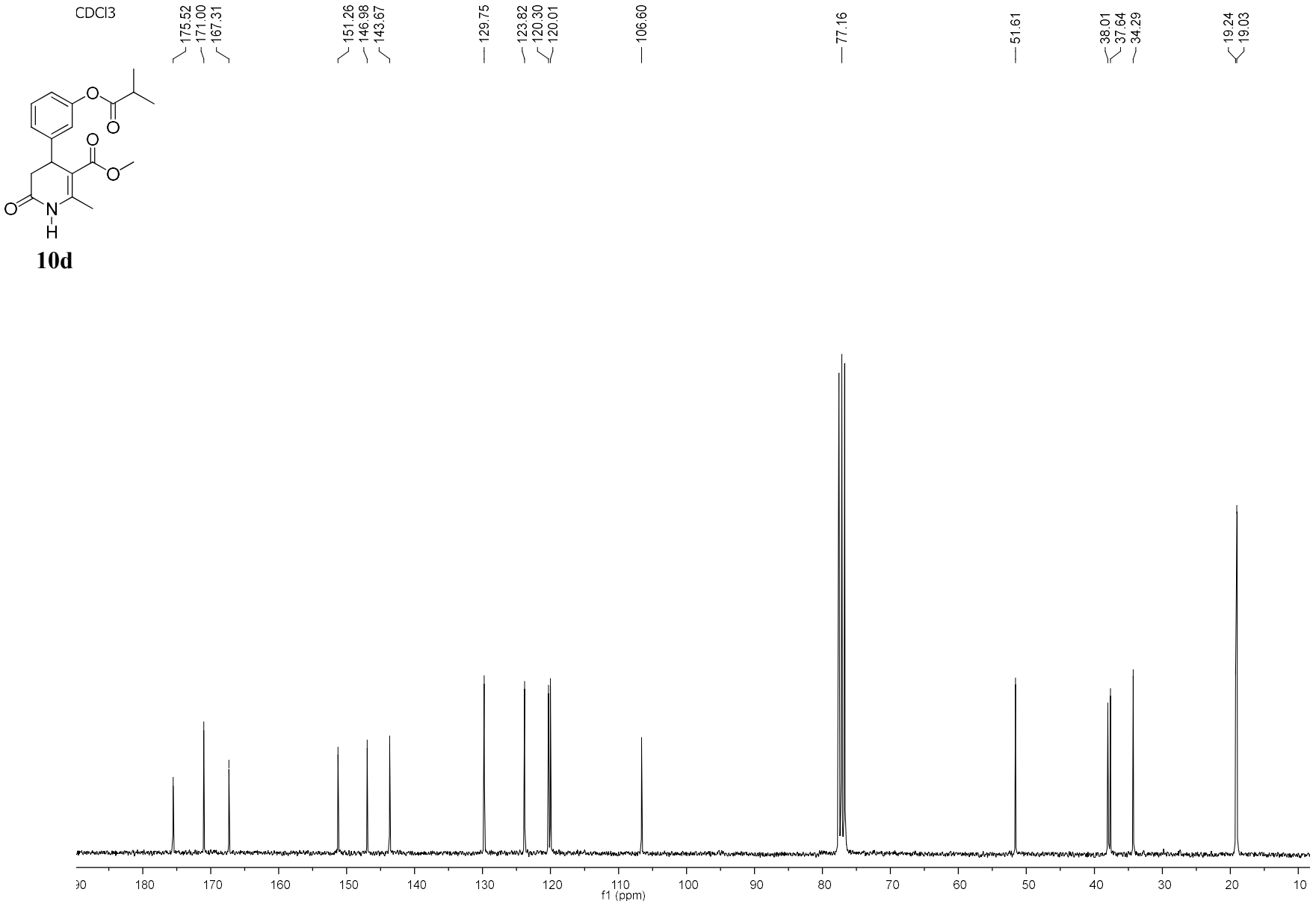
^{1}H- and ^{13}C-NMR spectra of **10c** in $CDCl_3$:



10c

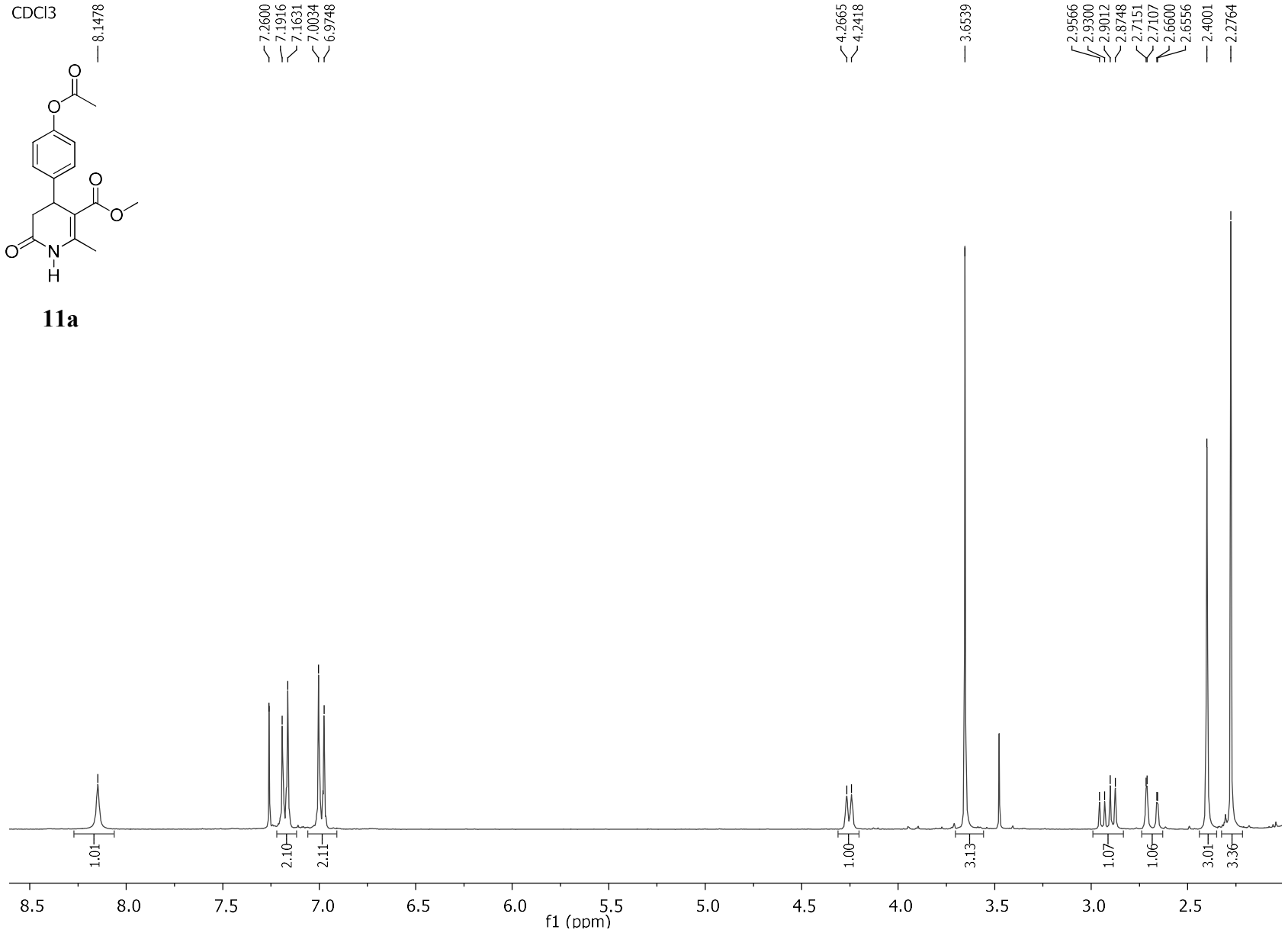

CDCl3
171.09
169.31
166.49
151.05
147.44
143.96
136.15
129.80
128.54
128.03
127.90
124.19
120.40
119.99
106.43
77.16
66.13
37.87
37.73
21.29
19.21
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

^{13}C-NMR spectrum of **10d** in $CDCl_3$:

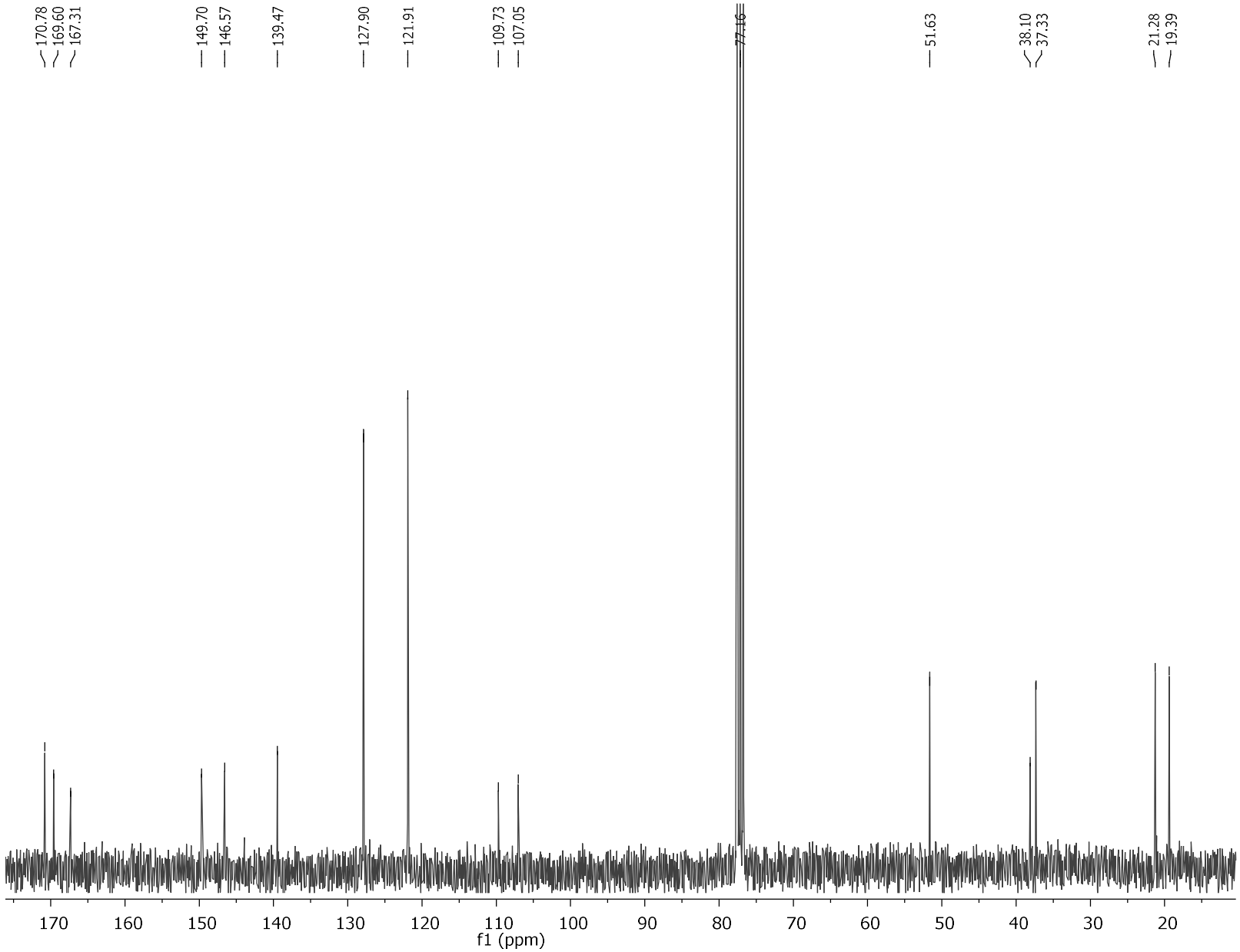


10d

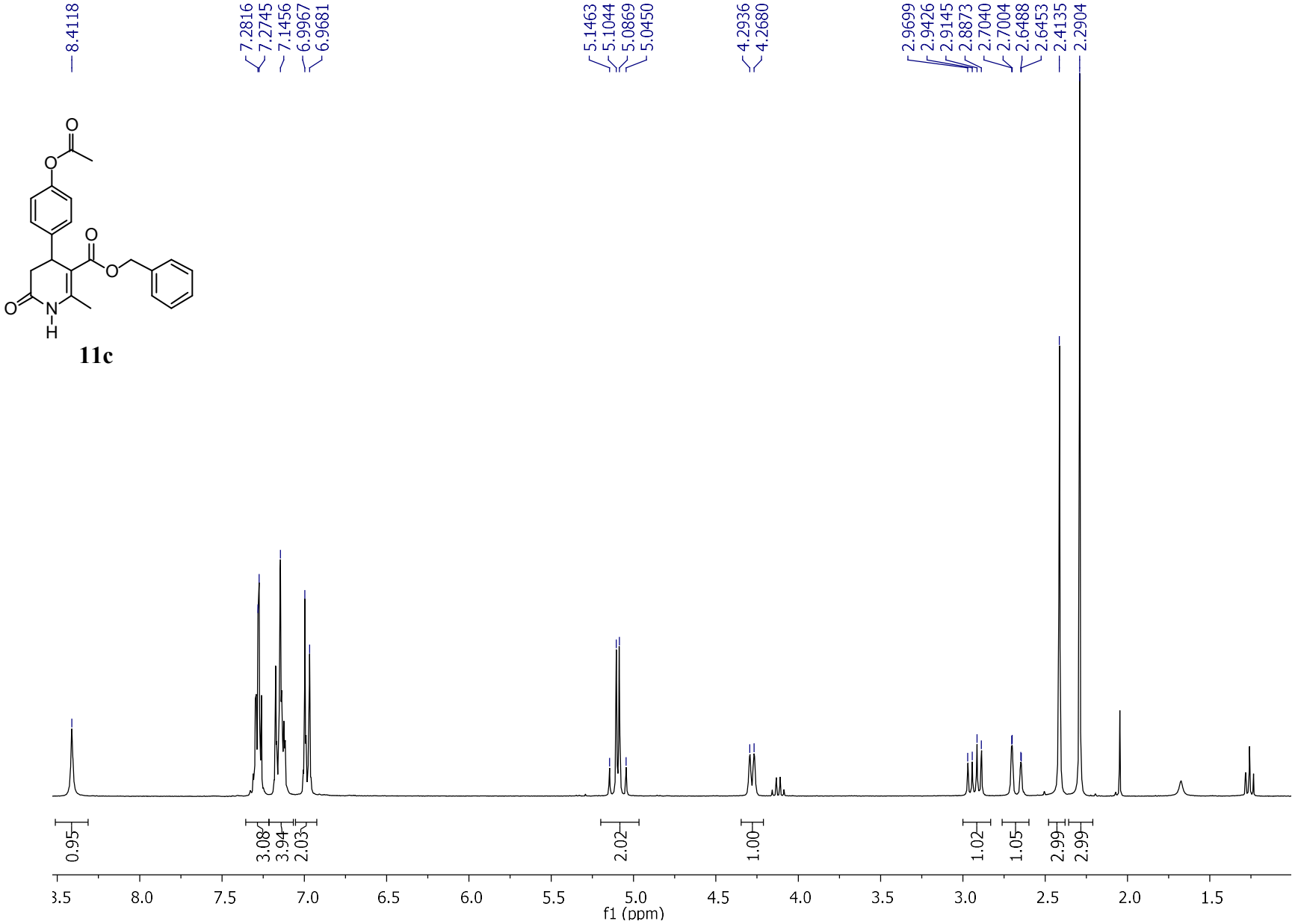
^{1}H- and ^{13}C-NMR spectra of **11a** in $CDCl_3$:



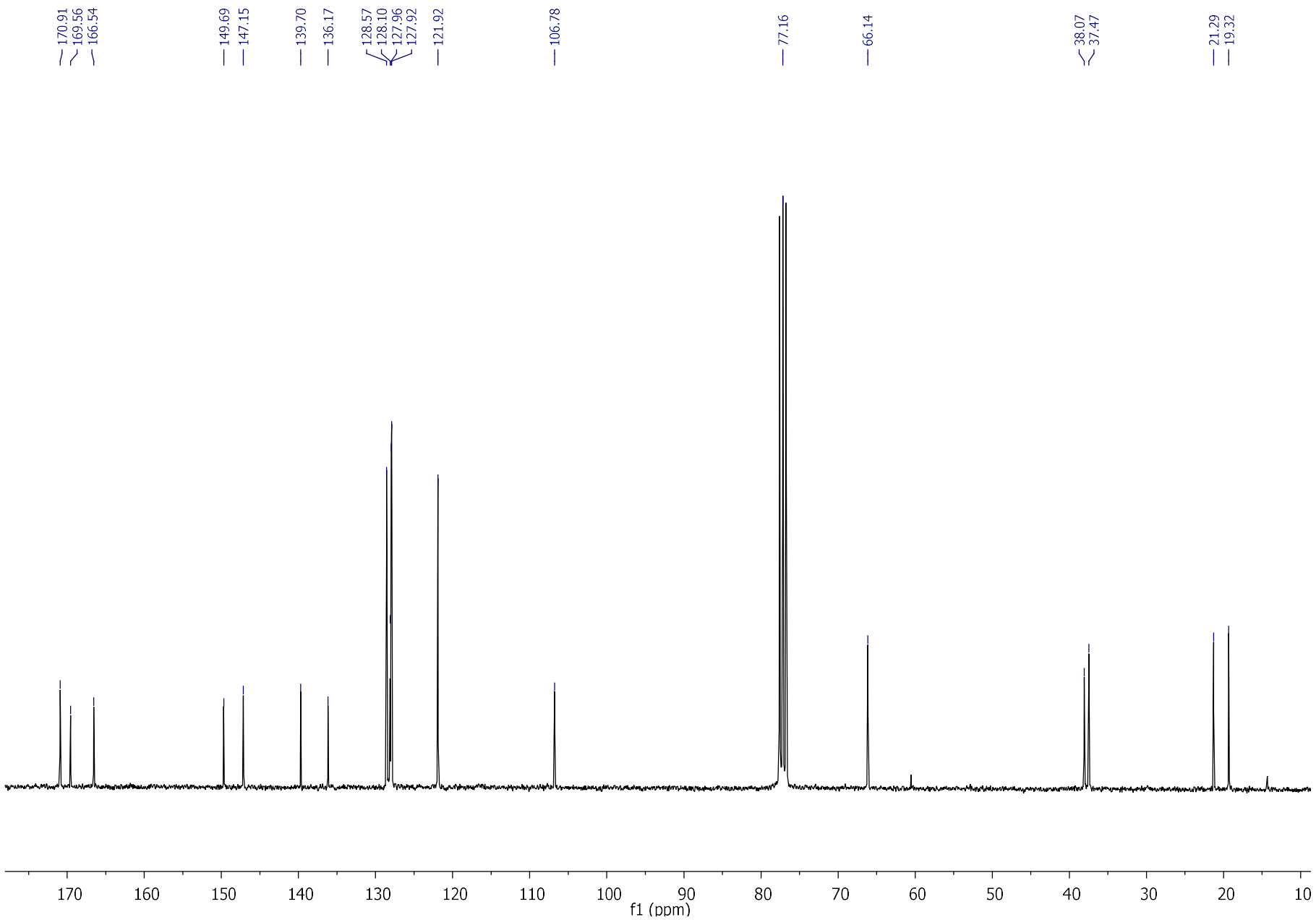
11a


170.78
169.60
167.31
149.70
146.57
139.47
127.90
121.91
109.73
107.05
77.16
51.63
38.10
37.33
21.28
19.39
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

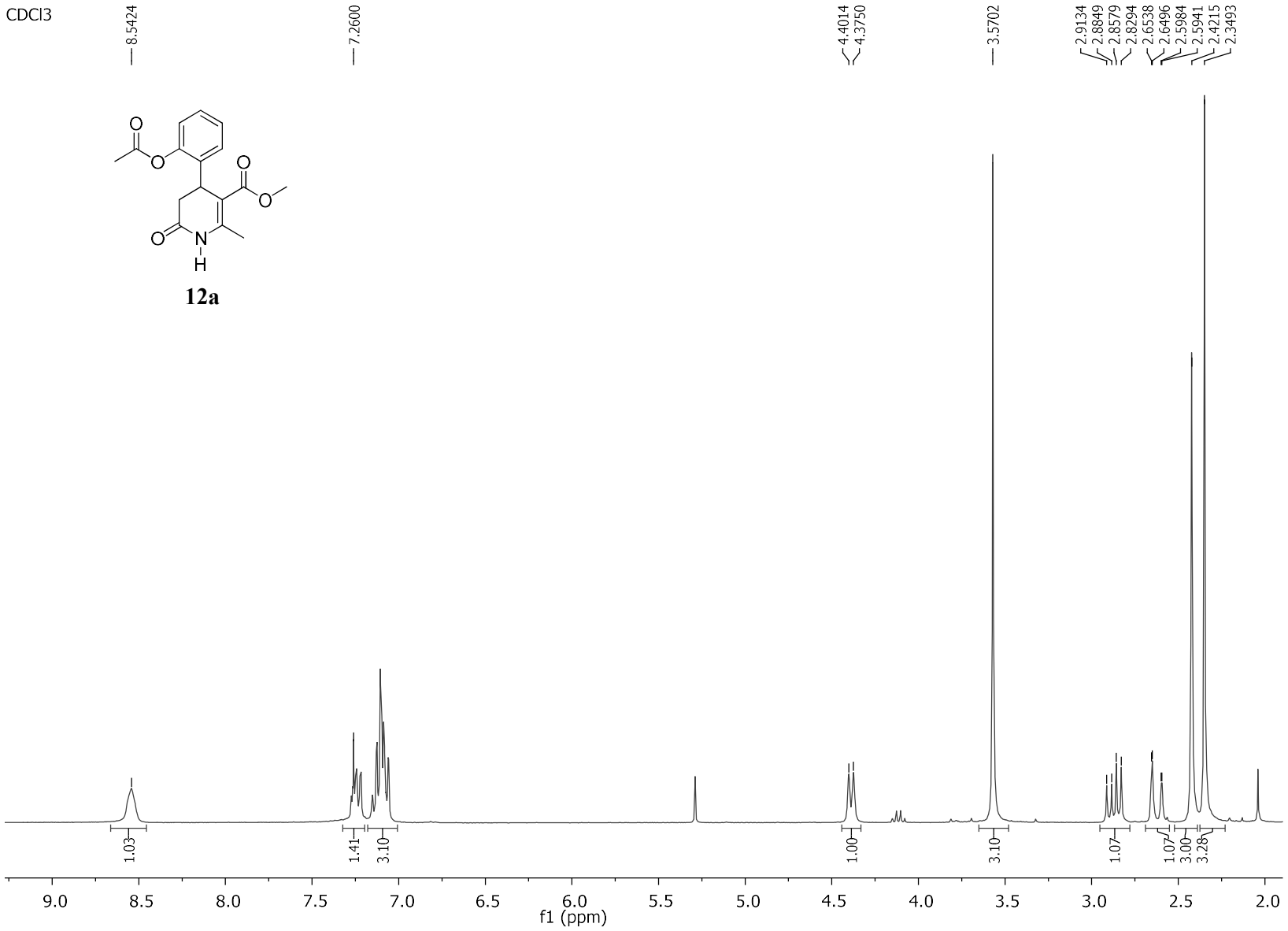
^{1}H- and ^{13}C-NMR spectra of **11c** in $CDCl_3$:



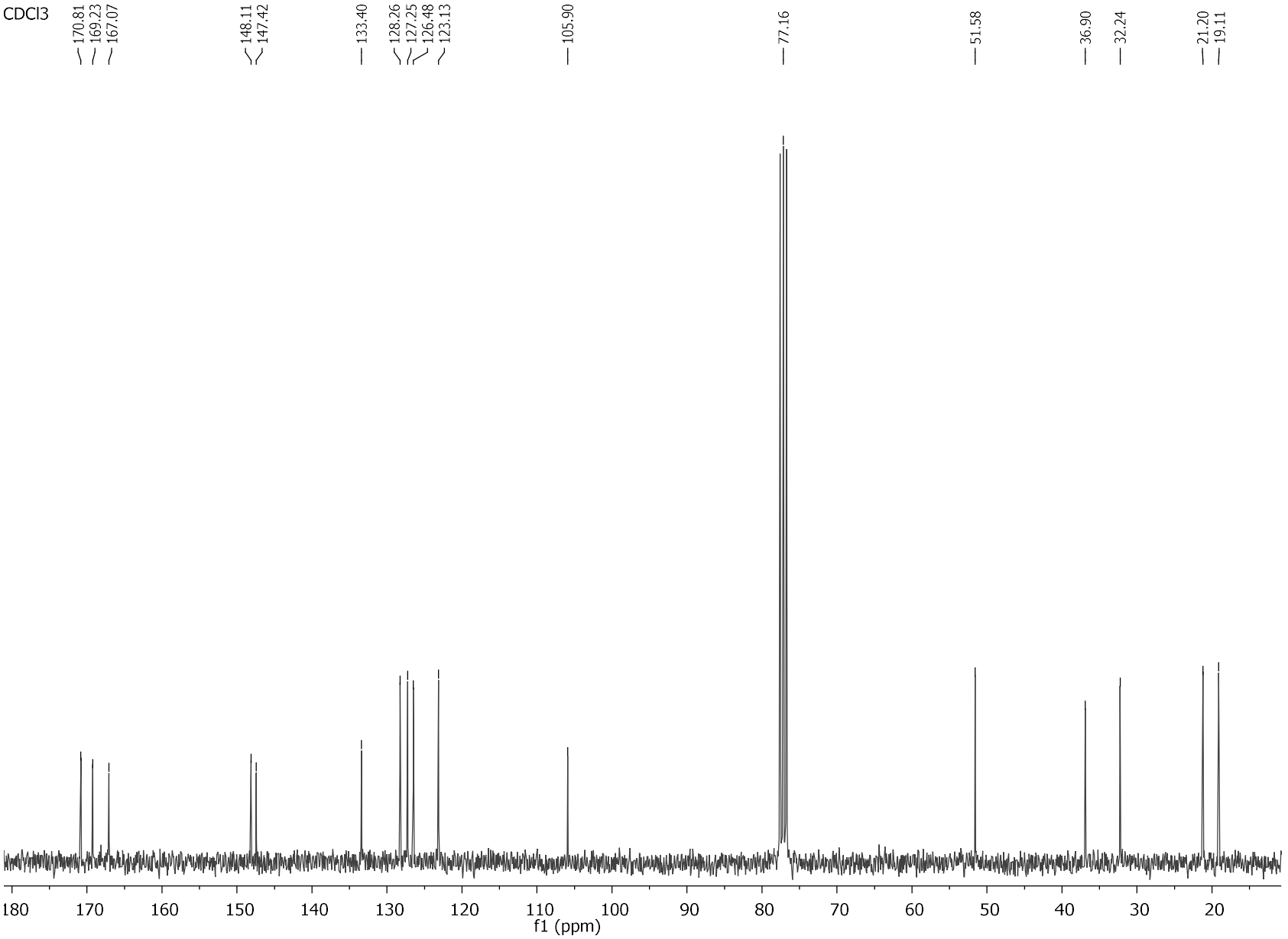
11c


170.91
169.56
166.54
149.69
147.15
139.70
136.17
128.57
128.10
127.96
127.92
121.92
106.78
77.16
66.14
38.07
37.47
21.29
19.32
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

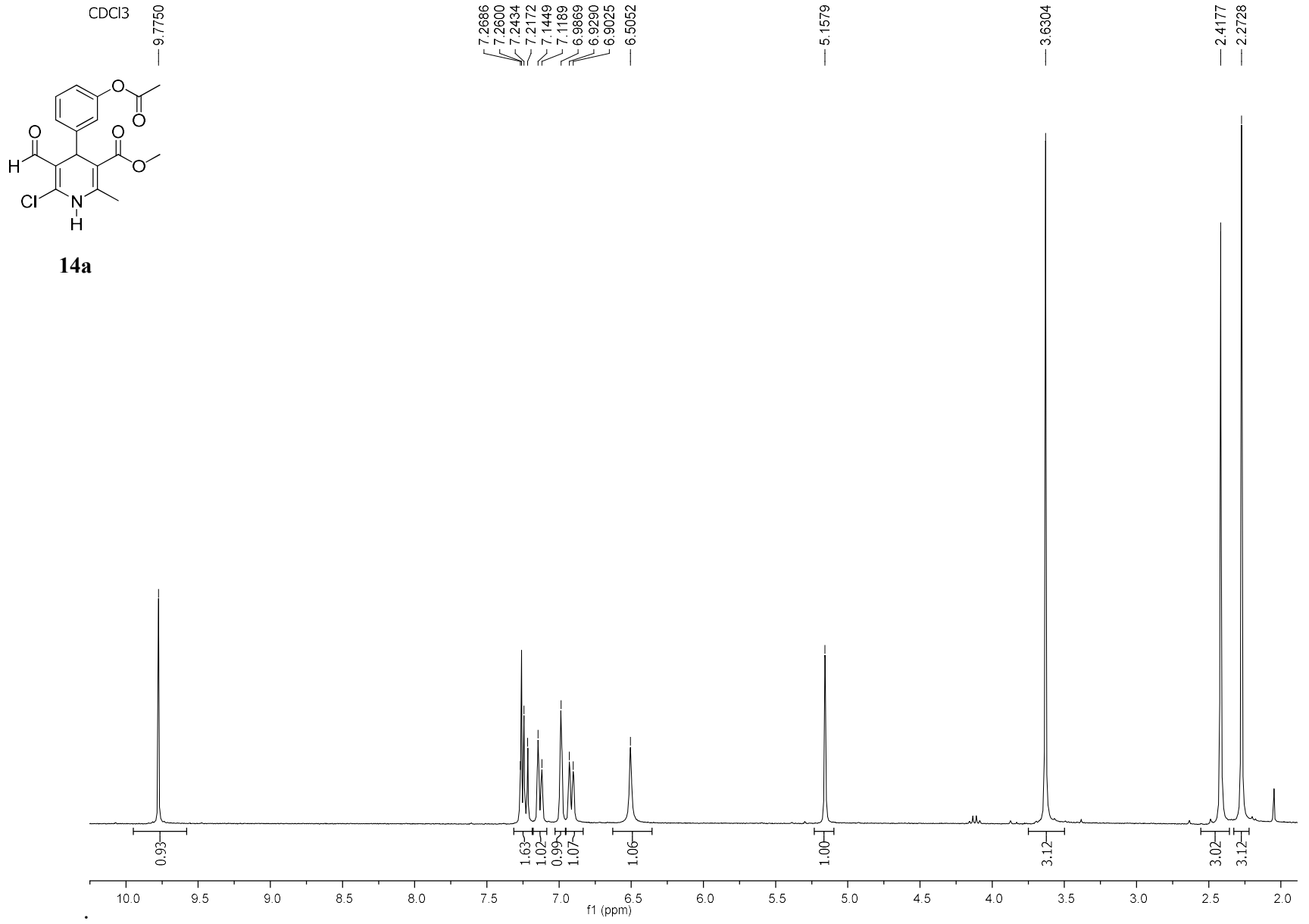
^{1}H- and ^{13}C-NMR spectra of **12a** in $CDCl_3$:



12a

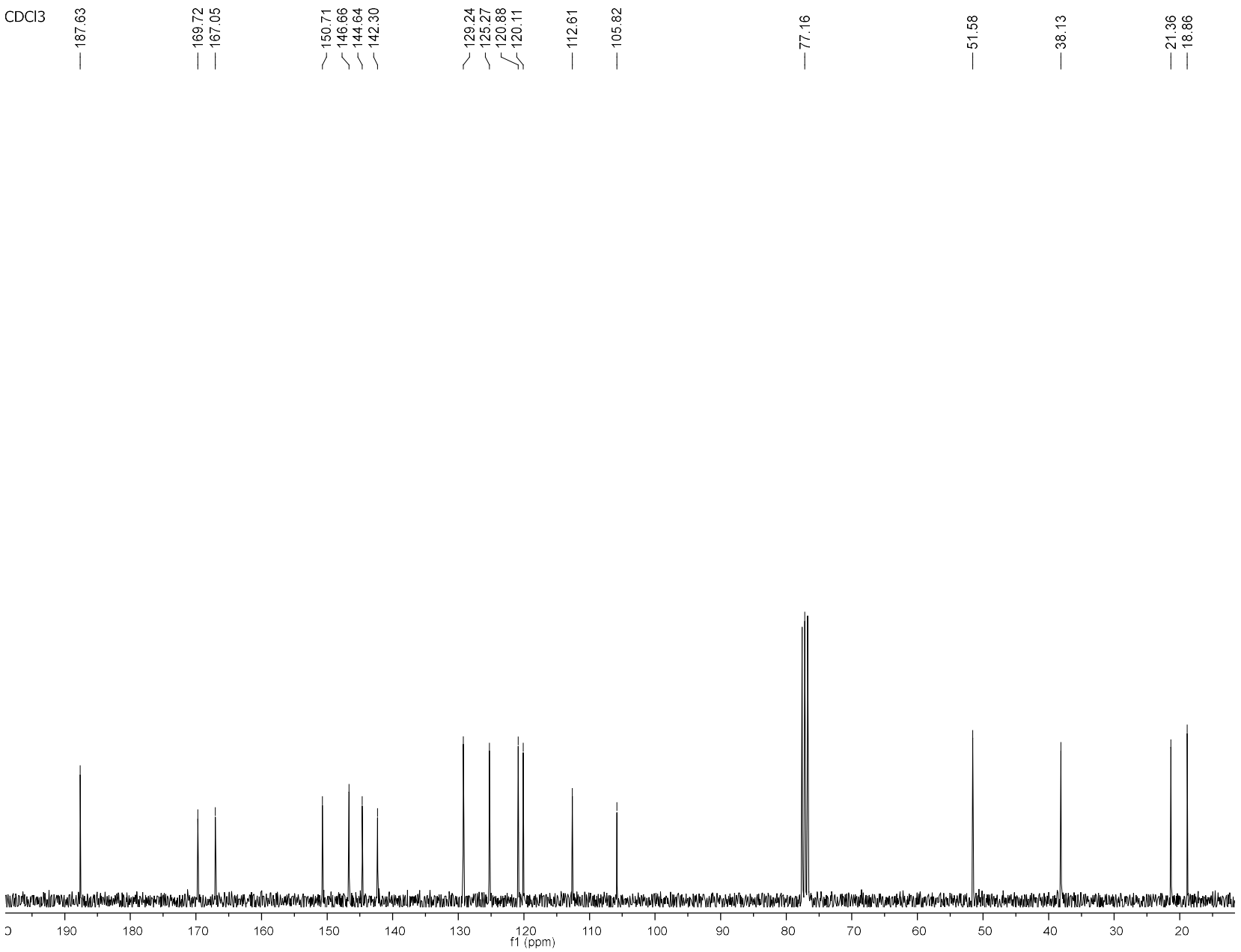

CDCl3
170.81
169.23
167.07
148.11
147.42
133.40
128.26
127.25
126.48
123.13
105.90
77.16
51.58
36.90
32.24
21.20
19.11
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

^{1}H- and ^{13}C-NMR spectra of **14a** in $CDCl_3$:

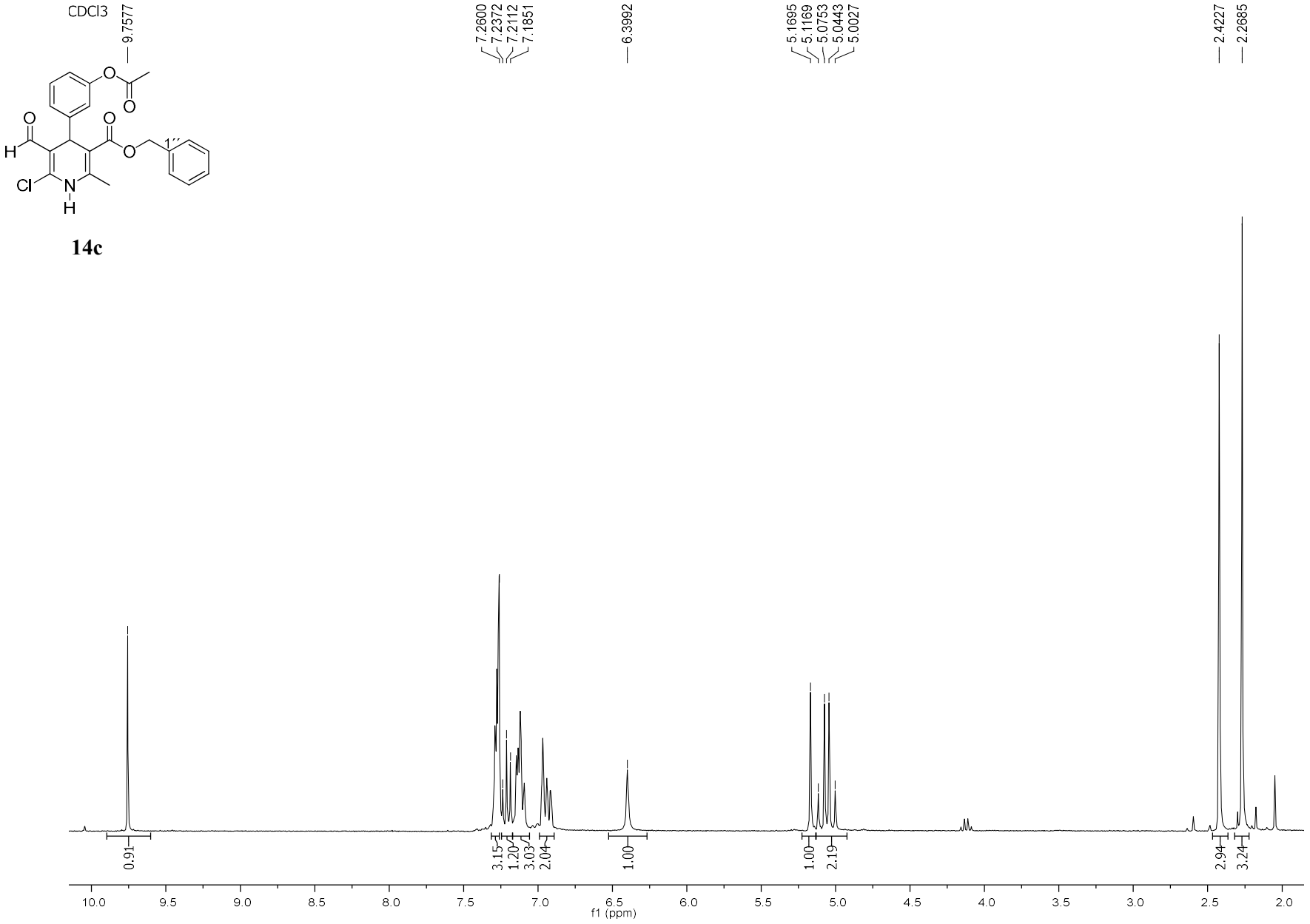


14a

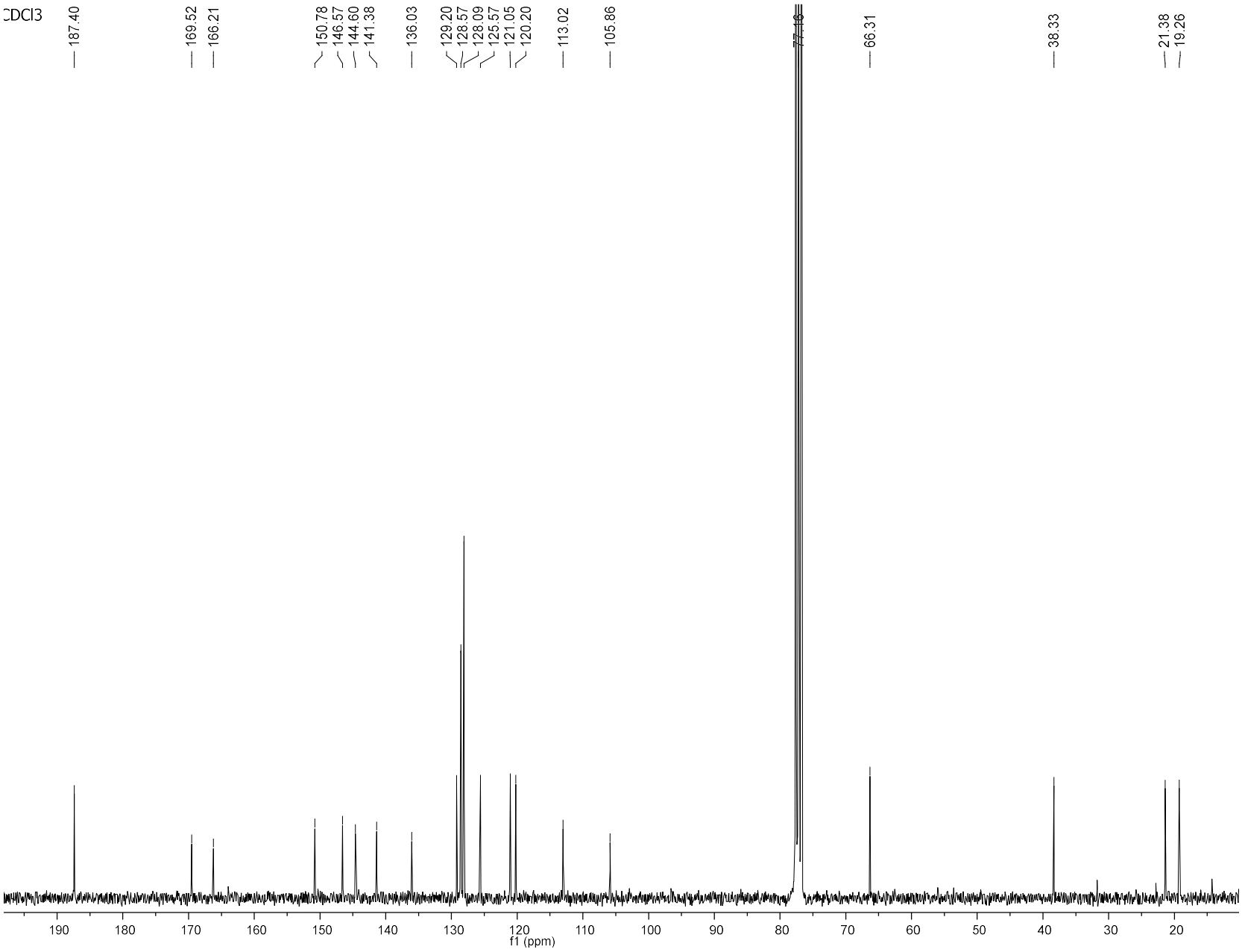
:


CDCl3
187.63
169.72
167.05
150.71
146.66
144.64
142.30
129.24
125.27
120.88
120.11
112.61
105.82
77.16
51.58
38.13
21.36
18.86
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

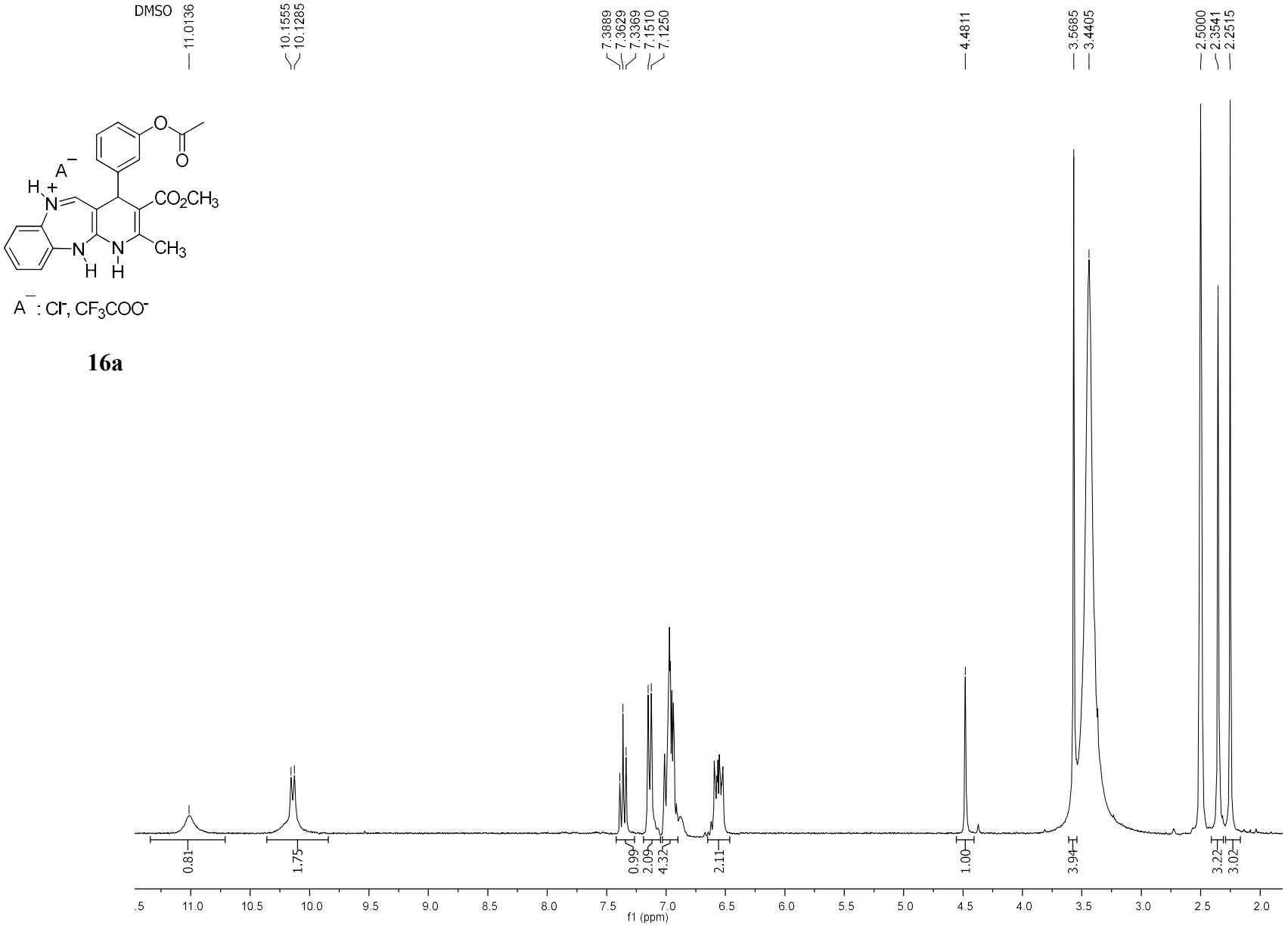
^{1}H- and ^{13}C-NMR spectra of **14c** in $CDCl_3$:



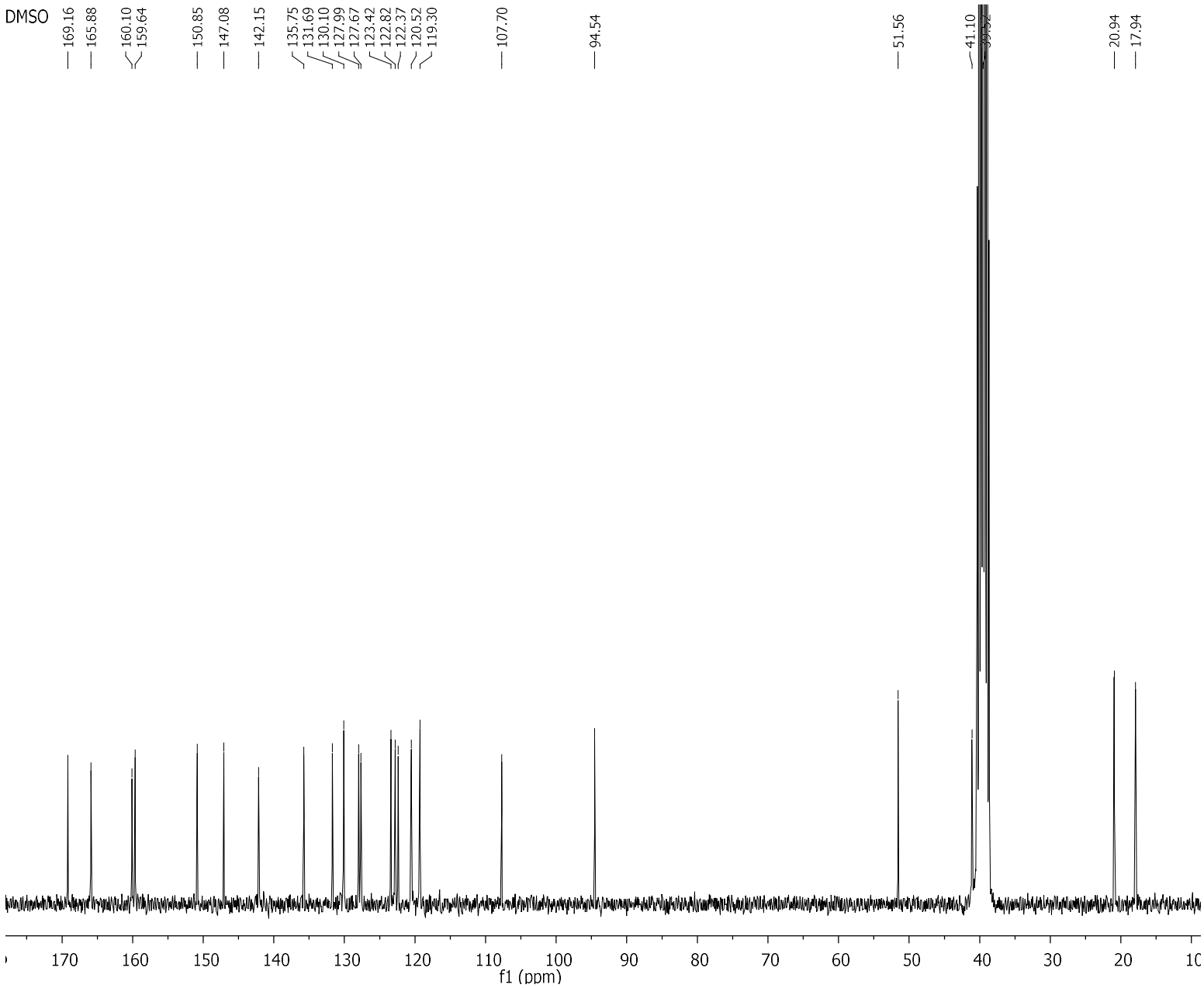
14c


CDCl3
187.40
169.52
166.21
150.78
146.57
144.60
141.38
136.03
129.20
128.57
128.09
125.57
121.05
120.20
113.02
105.86
77.16
66.31
38.33
21.38
19.26
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

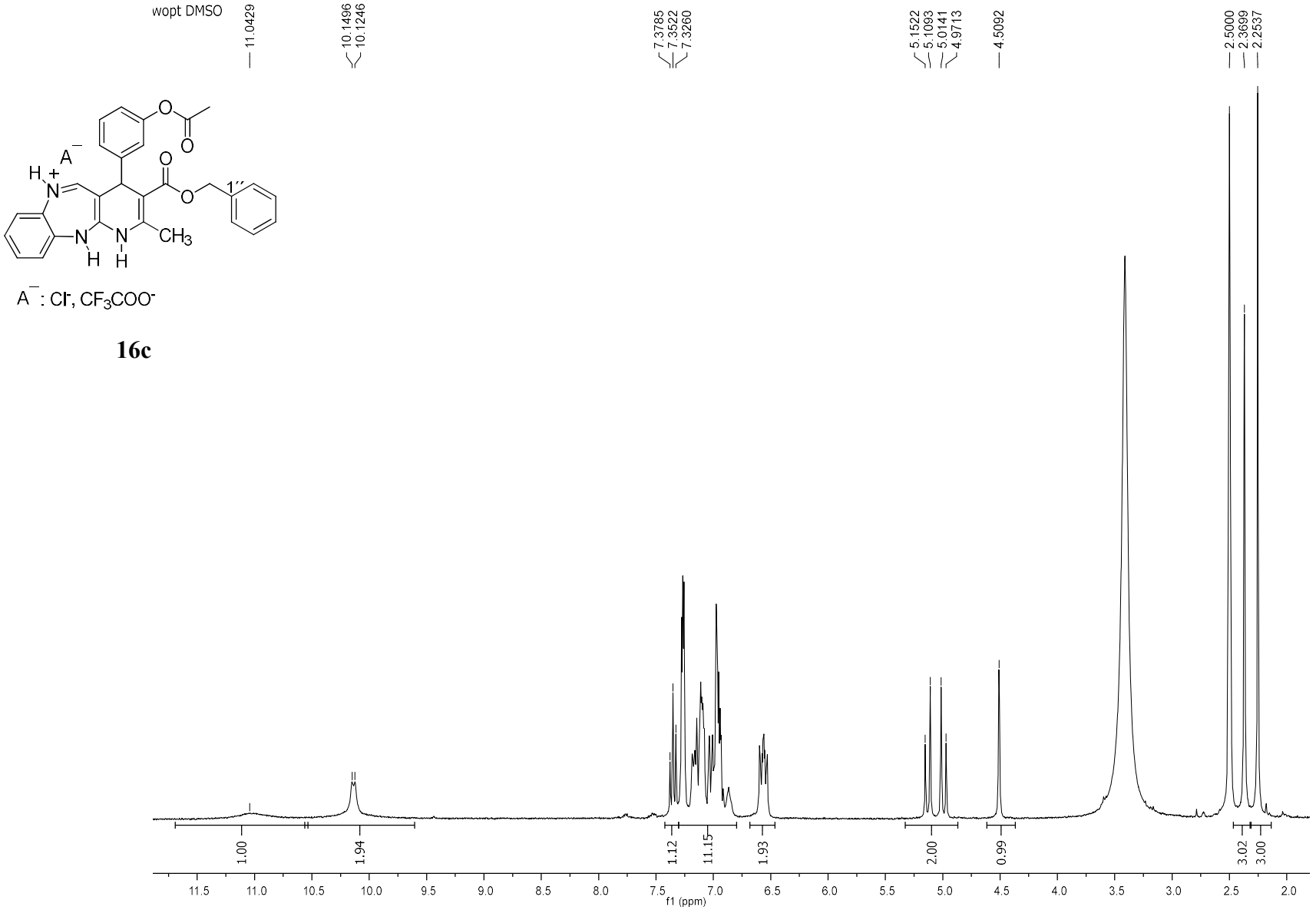
^{1}H- and ^{13}C-NMR spectra of **16a** in DMSO-d_6:



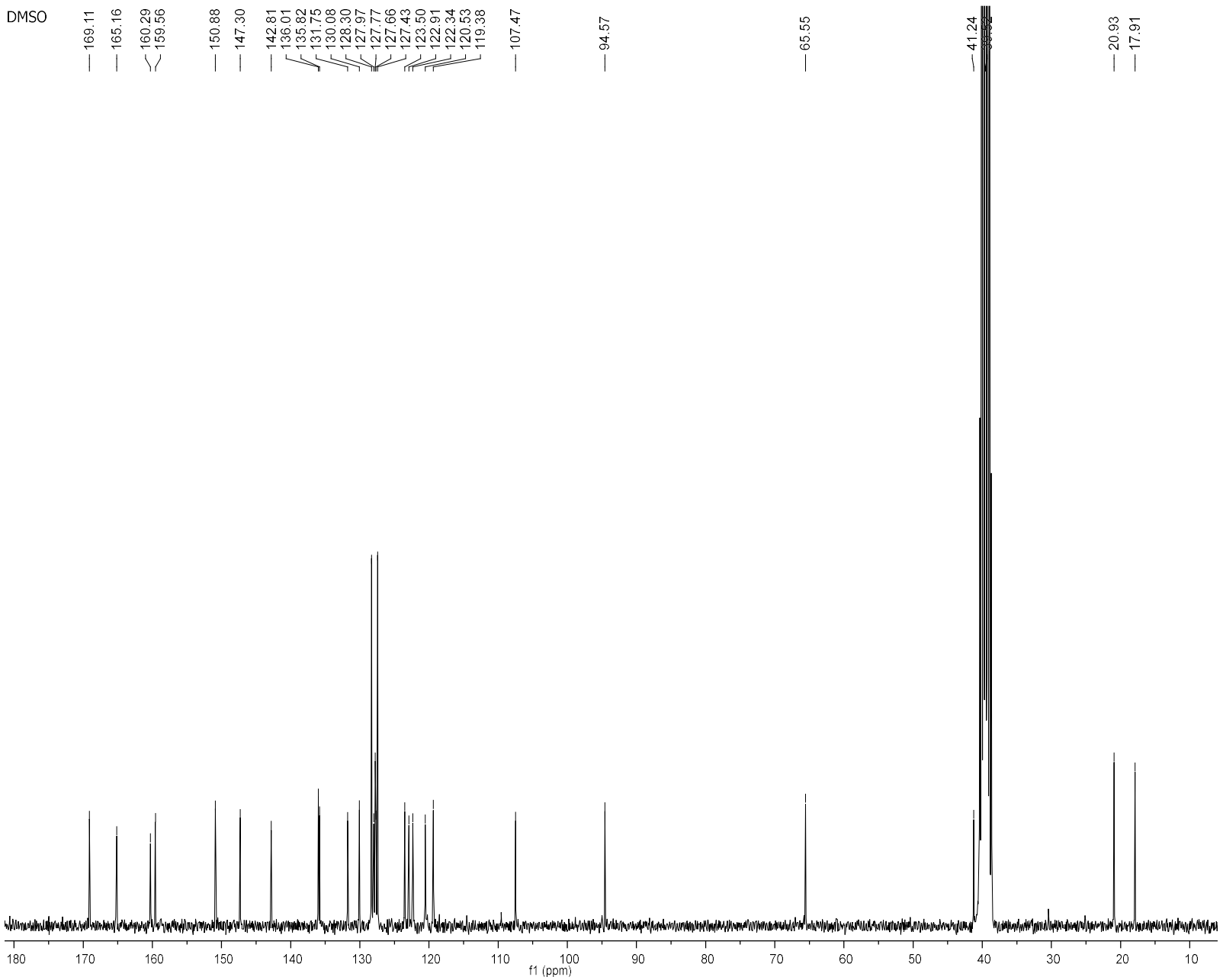
16a


DMSO
169.16
165.88
160.10
159.64
150.85
147.08
142.15
135.75
131.69
130.10
127.99
127.67
123.42
122.82
122.37
120.52
119.30
107.70
94.54
51.56
41.10
20.94
17.94
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

^{1}H- and ^{13}C-NMR spectra of **16c** in DMSO-d_6:



16c


DMSO
169.11
165.16
160.29
159.56
150.88
147.30
142.81
136.01
135.82
131.75
130.08
128.30
127.97
127.77
127.66
127.43
123.50
122.91
122.34
120.53
119.38
107.47
94.57
65.55
41.24
20.93
17.91
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)