Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Synthesis of highly substituted 2-spiropiperidines

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Contents

3-Oxo-5-phenyl-5-(toluene-4-sulfonylamino)-pentanoic acid methyl ester (2)

To a solution of diisopropylamine (824 µL, 5.89 mmol) in THF (10 mL) at -78 °C was added *n*-BuLi (2.41 mL, 5.79 mmol) dropwise. The mixture was warmed to 0 °C for 15 mins, then re-cooled to -78 °C. A solution of methyl acetoacetate (312 µL, 2.90 mmol) in THF (2 mL) was added *via* syringe pump over 20 mins. The mixture was warmed to -50 °C, and a solution of *N*-Benzylidene-4-methyl-benzenesulfonamide (250 mg, 0.965 mmol) in THF (2 mL) was added fast. The reaction was stirred for 40 mins, then quenched with sat. aq. NH_4Cl (4 mL). The mixture was warmed to rt, and layers were separated. The aqueous was extracted with EtOAc (2 x 20 mL). Organics were combined, washed with water (10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The residue was purified by column chromatography (10-30% EtOAc/hexane) to afford the title compound (225 mg, 0.600 mmol, 62% yield) as a colourless oil. Spectroscopic data was identical to that previously reported.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.54 (m, 2H), 7.20-7.11 (m, 5H), 7.09-7.04 (m, 2H), 5.69 (d, *J* = 7.2 Hz, 1H), 4.73 (dt, *J* = 7.2, 6.3 Hz, 1H), 3.65 (s, 3H), 3.36 (d, *J* = 15.5 Hz, 1H), 3.31 (d, *J* = 15.5 Hz, 1H), 3.17 (dd, *J* = 17.4, 6.3 Hz, 1H), 3.01 (dd, *J* = 17.4, 6.3 Hz, 1H-4), 2.36 (s, 3H) ppm.

2-Isopropylidene-3-oxo-5-phenyl-5-(toluene-4-sulfonylamino)-pentanoic acid methyl ester (3)

To a 0.5 M solution of $TiCl_4$ in THF (2 mL, 1.07 mmol) at 0 °C was added a solution of **2** (400 mg, 1.07 mmol), acetone (156 µL, 2.13 mmol), and pyridine (345 µL, 4.26 mmol) in THF (2 mL). The reaction was stirred overnight at rt. The reaction mixture was partitioned between water (10 mL) and EtOAc (30 mL). The aqueous was extracted with EtOAc (2 x 15 mL). Organics were combined, washed with $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (15% EtOAc/hexane) to afford the title compound (115 mg, 0.277 mmol, 26% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.54 (m, 2H), 7.19-7.12 (m, 5H), 7.11-7.05 (m, 2H), 5.71 (d, *J* = 7.0 Hz, 1H), 4.74 (dt, *J* = 7.0, 6.2 Hz, 1H), 3.60 (s, 3H), 3.12 (dd, *J* = 17.5, 6.2 Hz, 1H), 2.96 (dd, *J* = 17.5, 6.2 Hz, 1H), 2.36 (s, 3H), 2.05 (s, 3H), 1.65 (s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 201.1, 165.5, 156.1, 143.3, 139.8, 137.4, 130.9, 129.5, 128.5, 127.7, 127.3, 126.8, 54.3, 51.9, 49.4, 23.5, 23.1, 21.6 ppm; IR (ATR): ν_{max} 3278, 2952, 1726, 1694, 1156 cm^{-1}; HRMS (ESI) 438.1338 (M + Na^+. $C_{22}H_{25}NNaO_5S$ requires 438.1346).

2-Isopropylidene-3-oxo-5-phenyl-pent-4-enoic acid methyl ester (4)

To a 0.5 M solution of $TiCl_4$ in THF (1.5 mL, 0.735 mmol) at 0 °C was added a solution of **5** (150 mg, 0.735 mmol), acetone (108 µL, 1.47 mmol), and pyridine (240 µL, 2.94 mmol) in THF (1 mL). The reaction was stirred overnight at rt. The reaction mixture was partitioned between water (5 mL) and EtOAc (30 mL). The aqueous was extracted with EtOAc (2 x 15 mL). Organics were combined, washed with $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/hexane) to afford the title compound (23 mg, 0.0942 mmol, 13% yield) as a yellow oil.

[1] P. A. Clarke, A. V. Zaytsev, T. W. Morgan, A. C. Whitwood and C. Wilson, *Org. Lett.* 2008, **10**, 2877-2880.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 – 7.49 (m, 2H), 7.42 – 7.35 (m, 3H), 7.42 (d, *J* = 16.2 Hz, 1H), 6.80 (d, *J* = 16.2 Hz, 1H), 3.69 (s, 3H), 2.26 (s, 3H), 1.87 (s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 195.5, 165.5, 154.8, 145.6, 134.5, 130.9, 129.5, 129.1, 128.6, 127.6, 51.9, 24.2, 22.5 ppm; IR (ATR): ν_{max} 3063, 2912, 1708, 1641, 1620, 1596, 1435, 1301, 1238, 1217, 1201, 1097, 1033 cm^{-1}; HRMS (ESI) 267.0992 (M + Na^+. $C_{16}H_{16}NaO_3$ requires 267.0992).

3-Hydroxy-5-phenyl-penta-2,4-dienoic acid methyl ester (5)

To a solution of **6**[2] (500 mg, 2.25 mmol) in CH_2Cl_2 (3 mL) was added acetic anhydride (223 µL, 2.36 mmol), Et_3N (470 µL, 3.38 mmol) and DMAP (cat.). The reaction was stirred for 2h at rt. MeOH (400 µL) was added, and the mixture stirred for 15 mins. The mixture was diluted with CH_2Cl_2 (8 mL) and partitioned with 0.1 M HCl (10 mL). Organics were combined, washed with water (10 mL), $CuSO_4$ (10 mL), and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (5% EtOAc/hexane) to afford title compound (201 mg, 0.905 mmol, 44% yield) as a white solid.

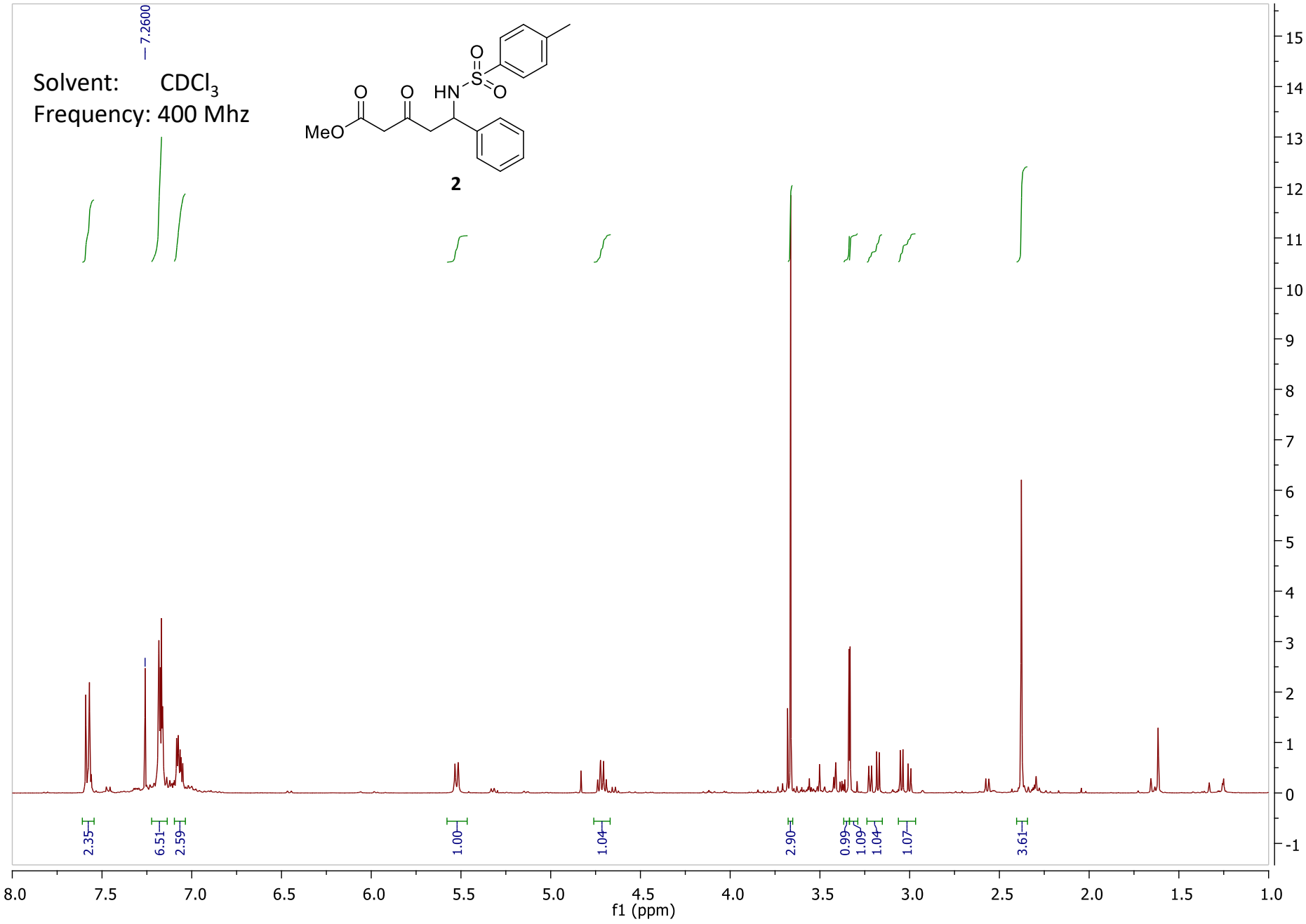
mp 93-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.9 (s, 1H), 7.51-7.47 (m, 2H), 7.44 (d, *J* = 16.0 Hz, 1H), 7.39-7.31 (m, 3H), 6.44 (dd, *J* = 16.0, 1.5 Hz, 1H), 5.18 (s, 1H), 3.77 (s, 3H) ppm; ^{13}C-NMR (101 MHz, $CDCl_3$): δ 173.4, 169.4, 137.1, 135.4, 129.5, 128.9, 127.7, 121.9, 91.7, 51.5 ppm; IR (ATR): ν_{max} 3027, 2953, 1634, 1590, 1445, 1202 cm^{-1}; HRMS (ESI) 227.0695 (M + Na^+. $C_{14}H_{16}NNaO_5$ requires 227.0679).

[Benzenesulfonyl-(4-trifluoromethyl-phenyl)-methyl]-carbamic acid tert-butyl ester (7k)

Following the general procedure: 4-(Trifluoromethyl)benzaldehye (6.00 g, 34.5 mmol), *tert*-butyl carbamate (2.69 g, 23.0 mmol) and benzenesulfinic acid sodium salt (7.54 g, 46.0 mmol). The white precipitate was triturated by stirring in diethyl ether (50 mL) for 1h at rt. Filtration gave the title compound, (6.87 g, 16.6 mmol, 72% yield) as a white solid. Spectroscopic data was identical to that previously reported.[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 7.8 Hz, 2H), 7.70-7.65 (m, 3H), 7.63-7.53 (m, 4H), 6.02 (d, *J* = 10.5 Hz, 1H), 5.93 (d, *J* = 10.5 Hz, 1H), 1.23 (s, 9H) ppm.

[2] P. A. Clarke, W. H. C. Martin, J. M. Hargreaves, C. Wilson and A. J. Blake, *Org. Biomol. Chem.* 2005, *3*, 3551-3563.
[3] L. Huang and W. D. Wulff, *J. Am. Chem. Soc.* 2011, **133**, 8892-8895.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O
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2.59
1.00
1.04
2.90
0.99
1.09
1.04
1.07
3.61
8.0
7.5
7.0
6.5
6.0
5.5
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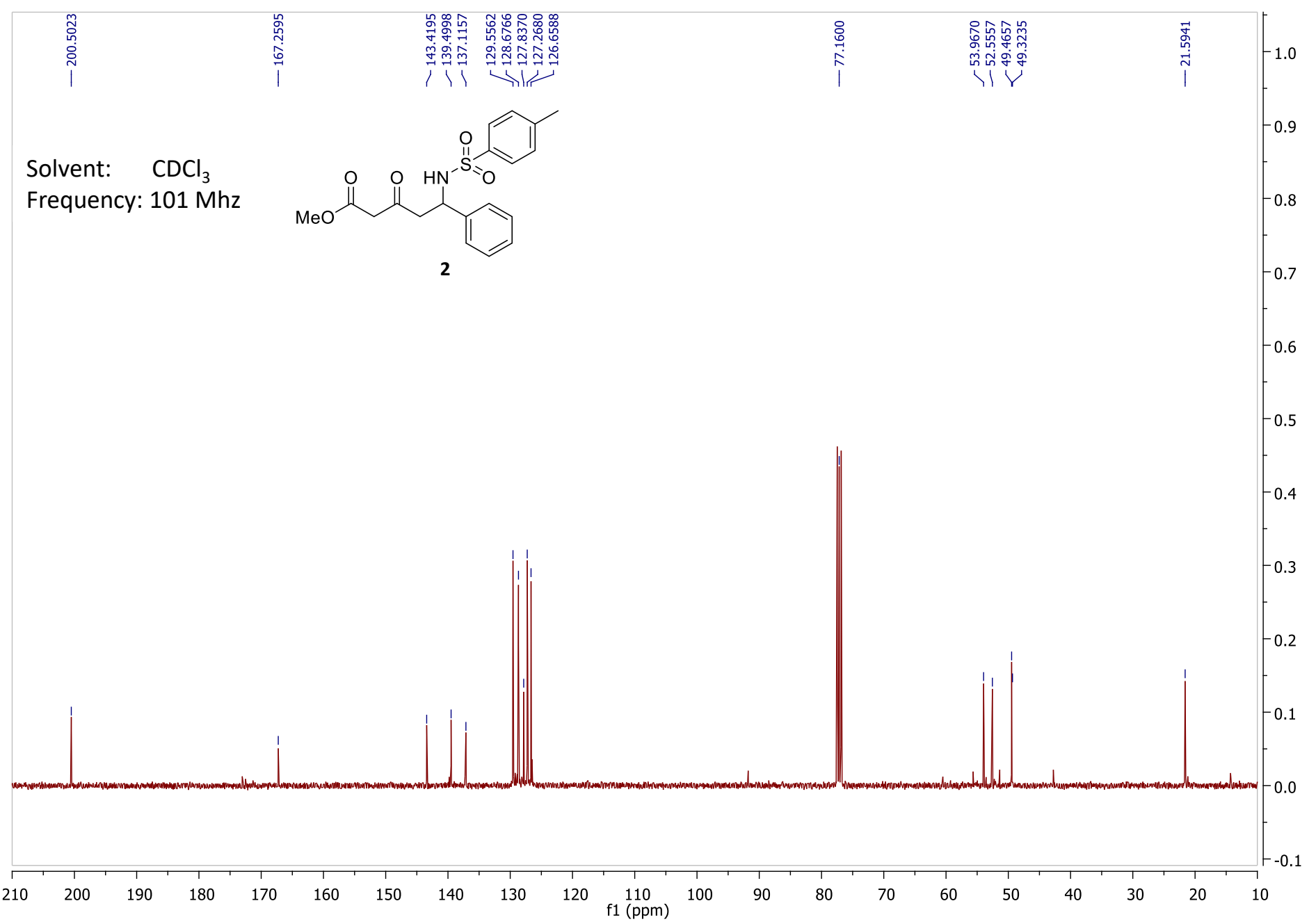
2.0
1.5
1.0
f1 (ppm)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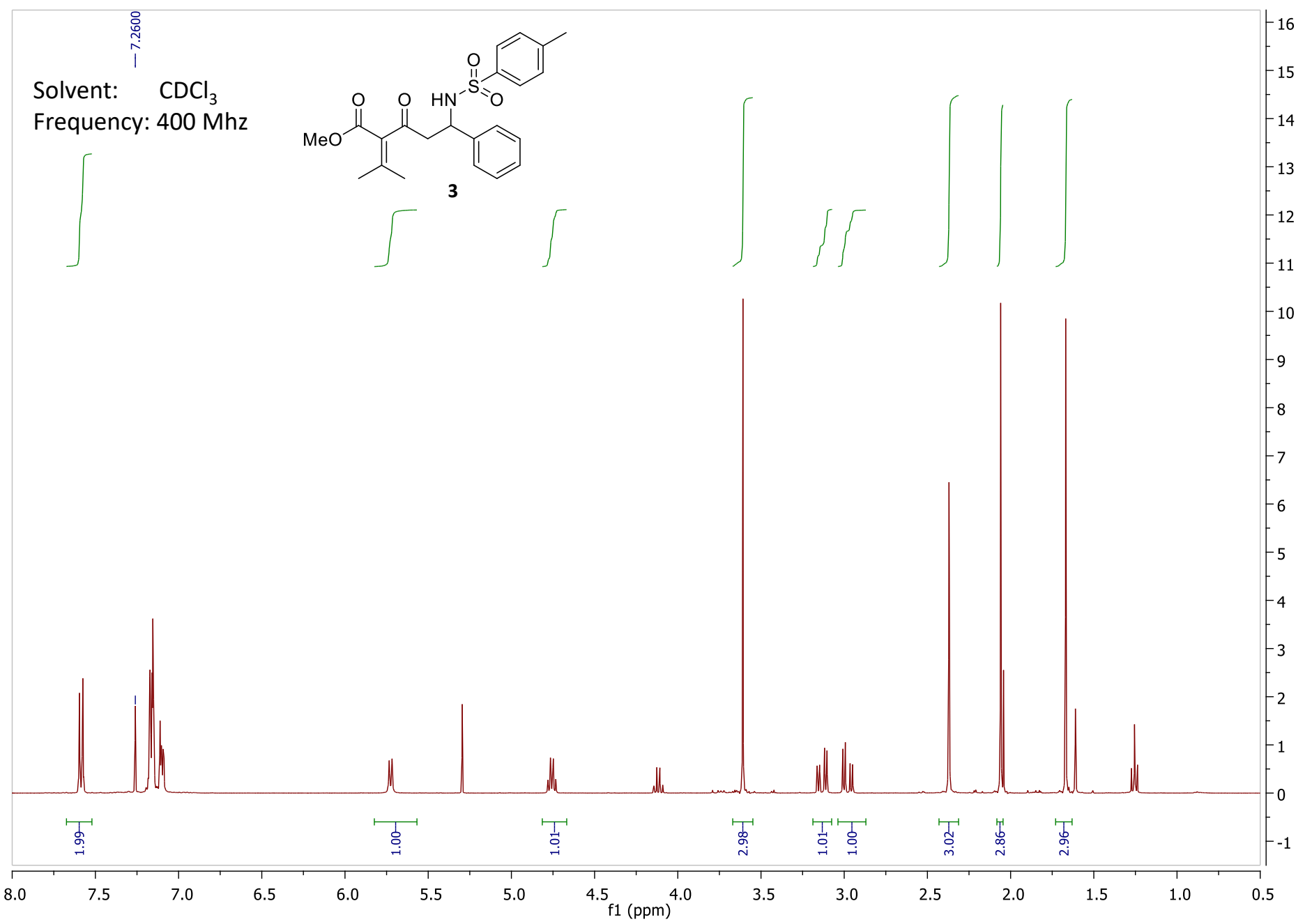
HN
2
f1 (ppm)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O
HN
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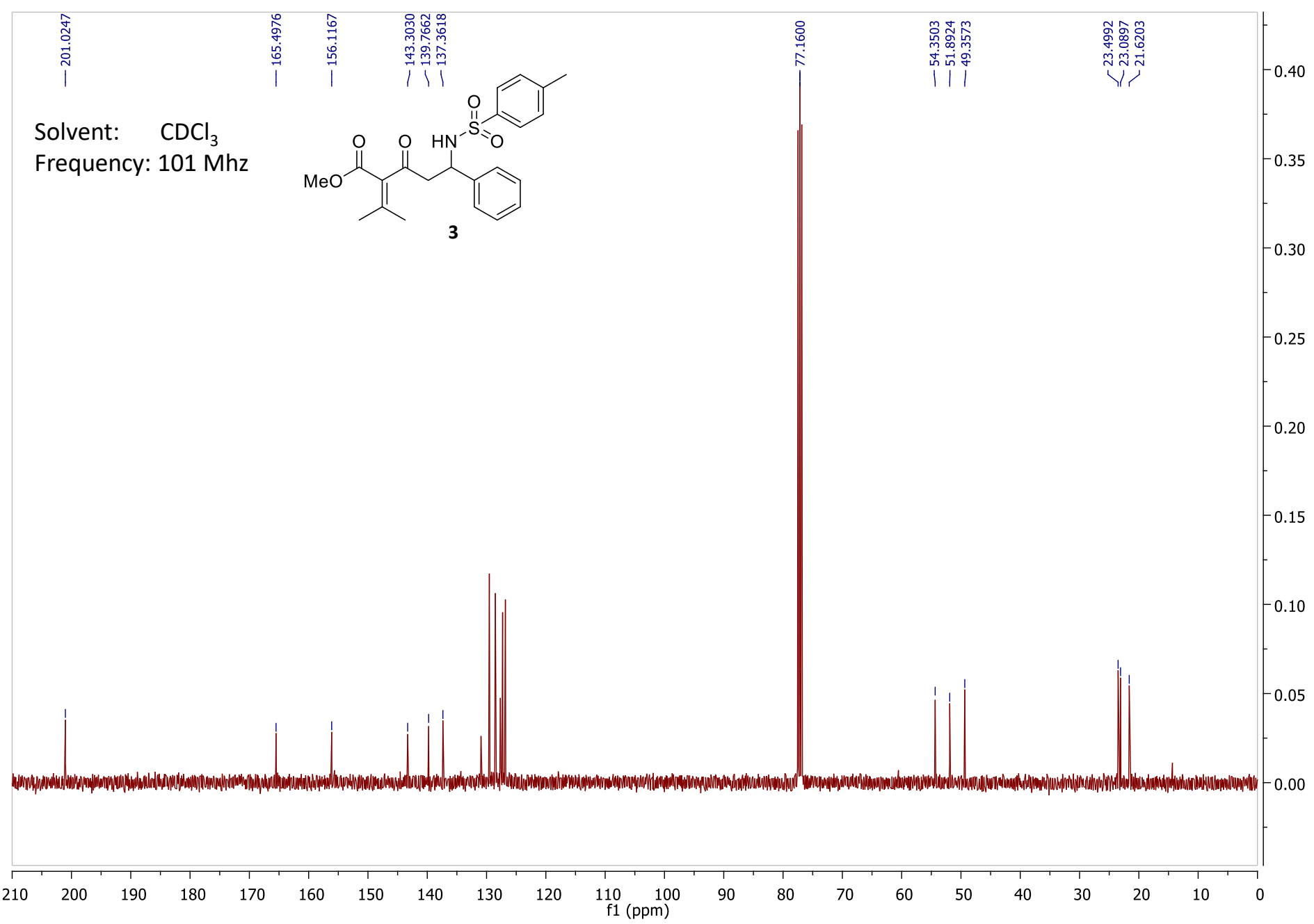
f1 (ppm)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O
HN
S
O
O
3
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0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
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20
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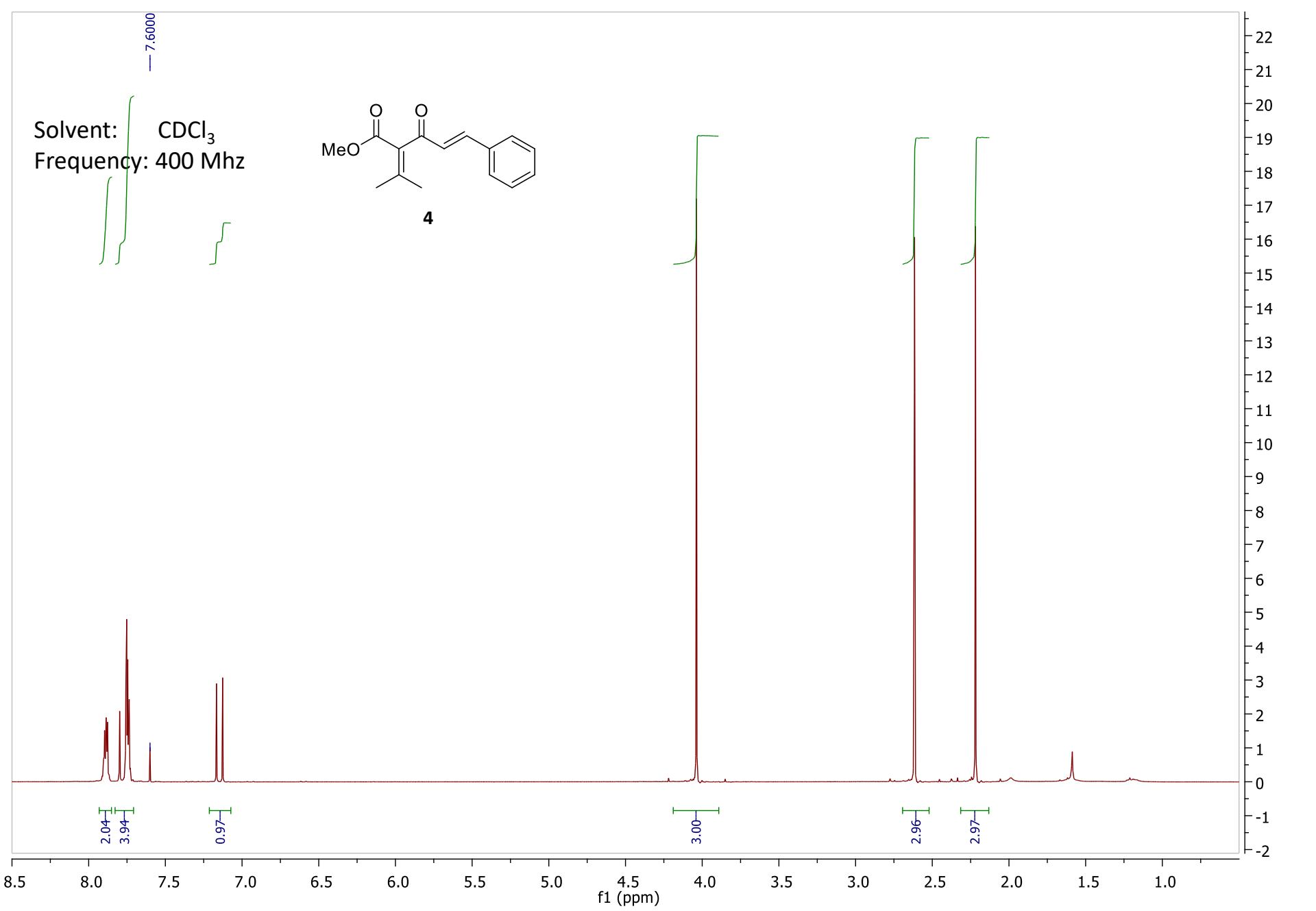
f1 (ppm)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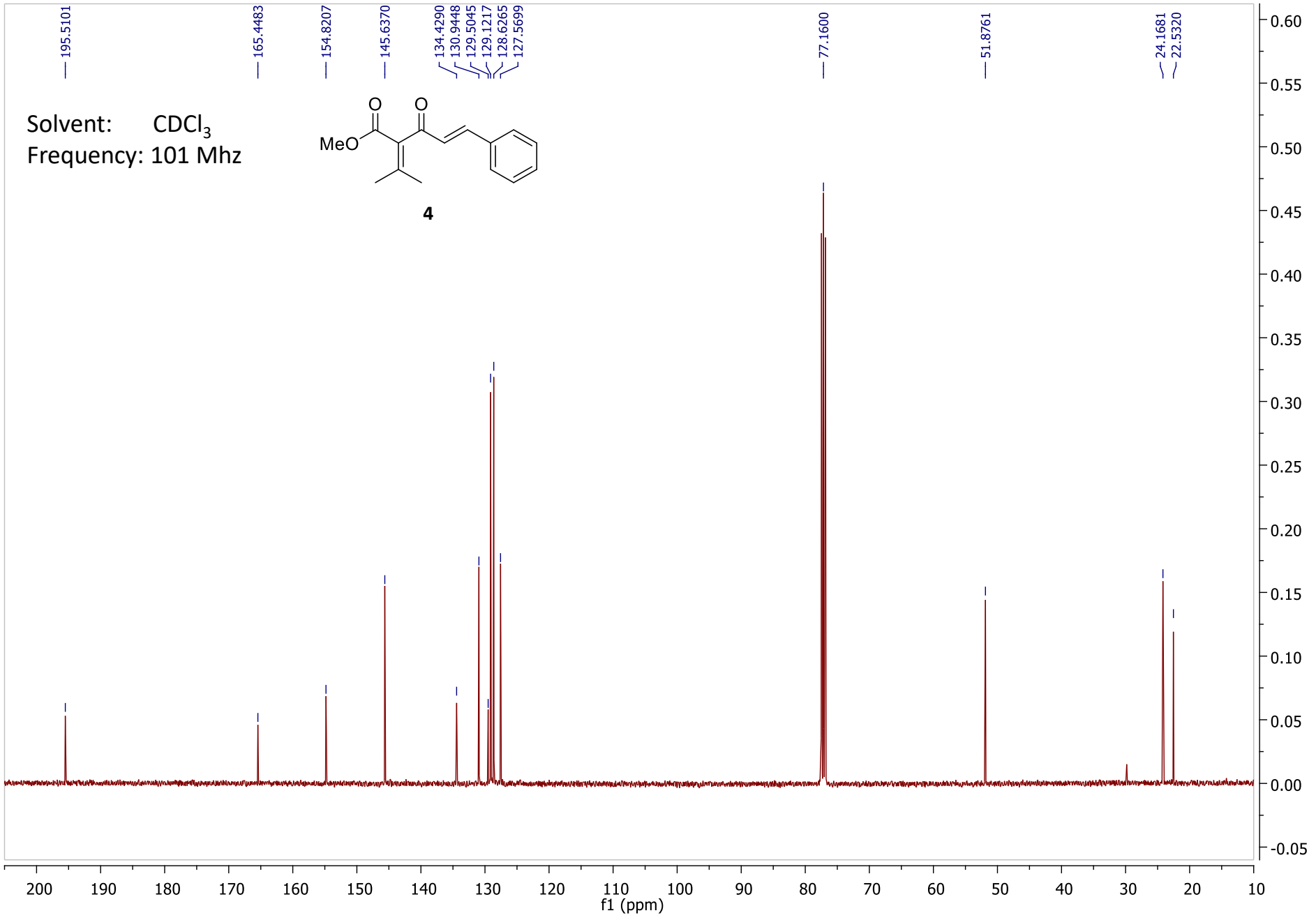
2.97
f1 (ppm)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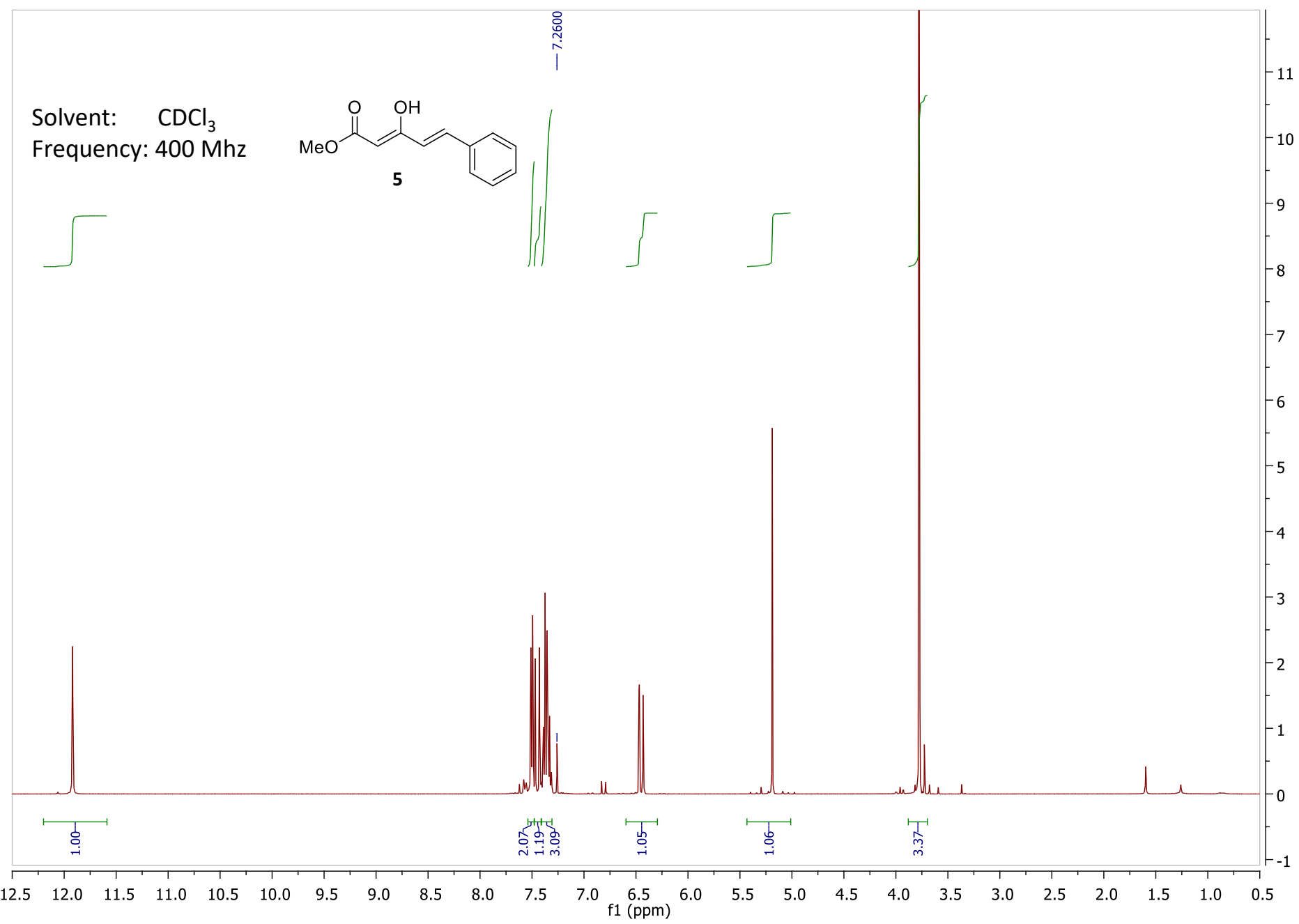
O
O
4
f1 (ppm)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1.06
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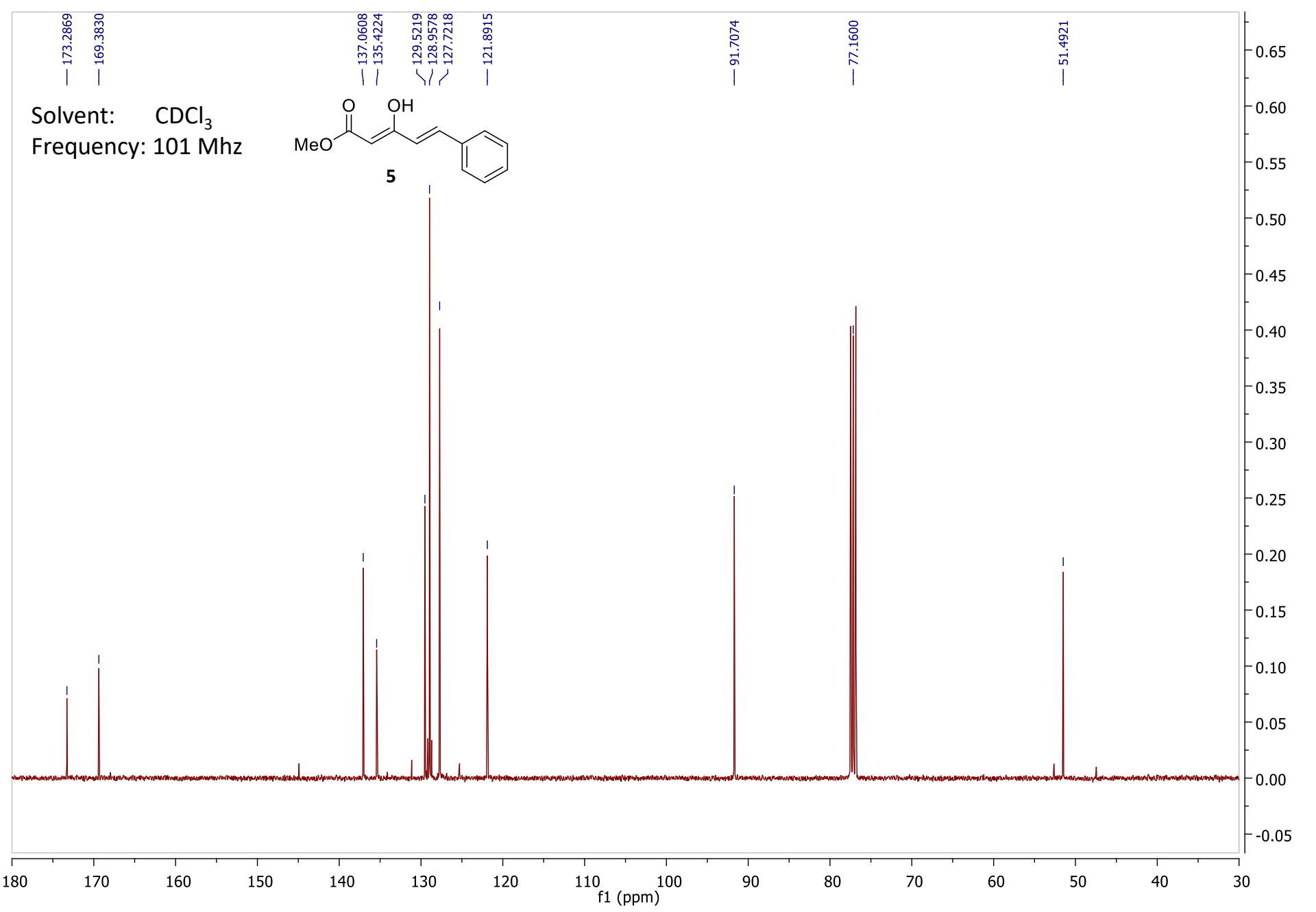
f1 (ppm)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Solvent: CDCl3
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OH
MeO
5
0.65
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0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
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70
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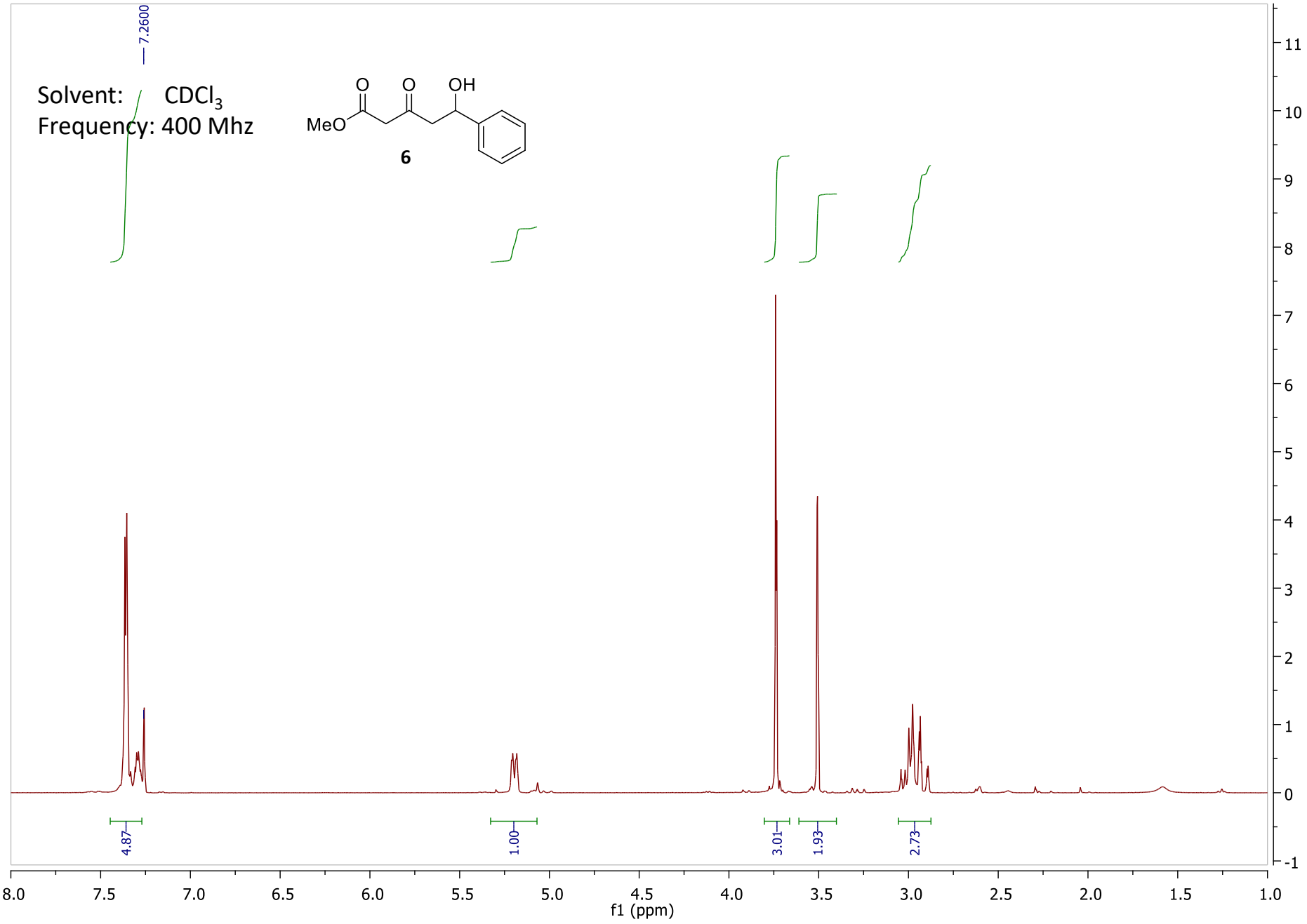
40
30
f1 (ppm)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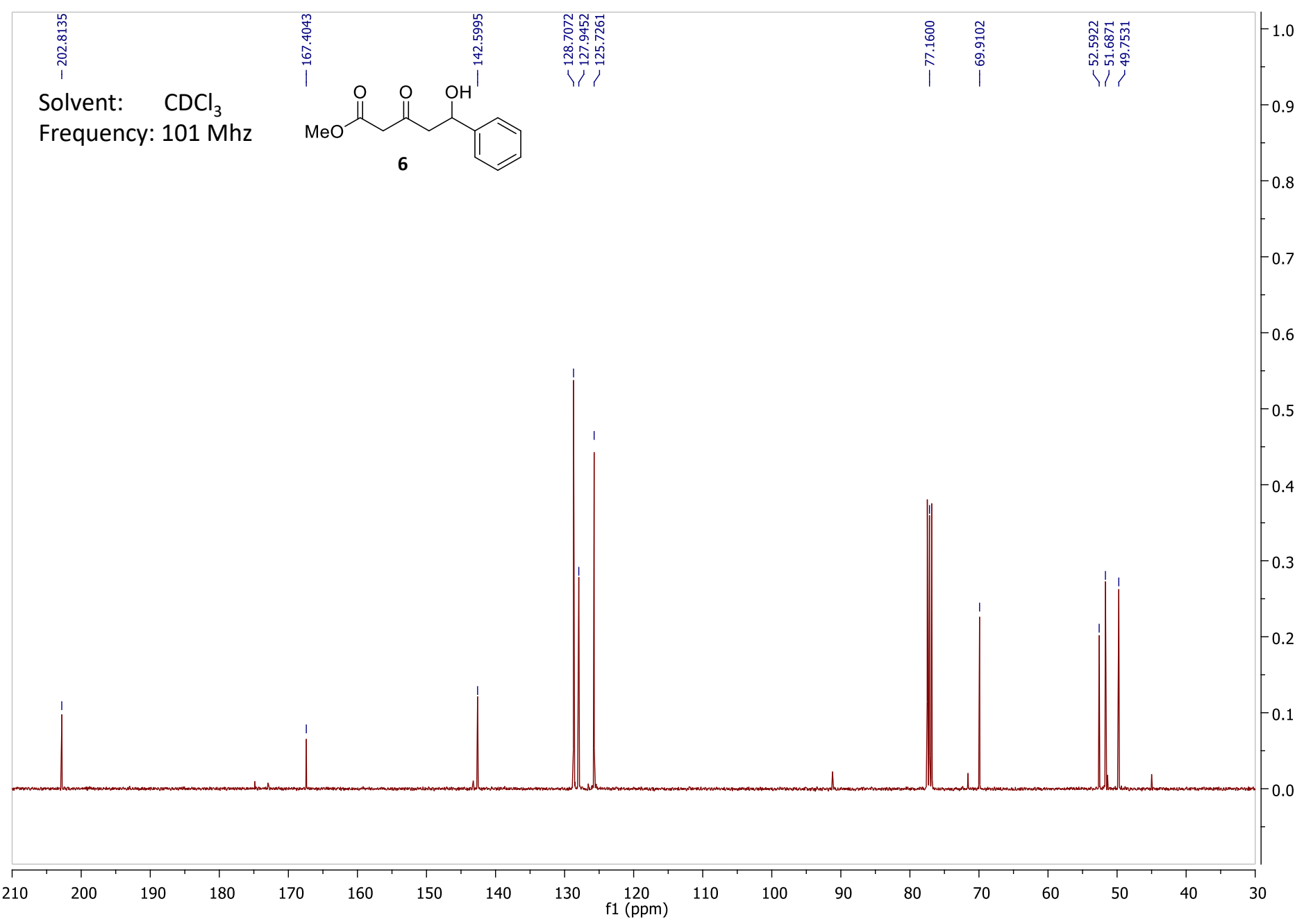
f1 (ppm)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O
OH
MeO
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0.6
0.5
0.4
0.3
0.2
0.1
0.0
210
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80
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40
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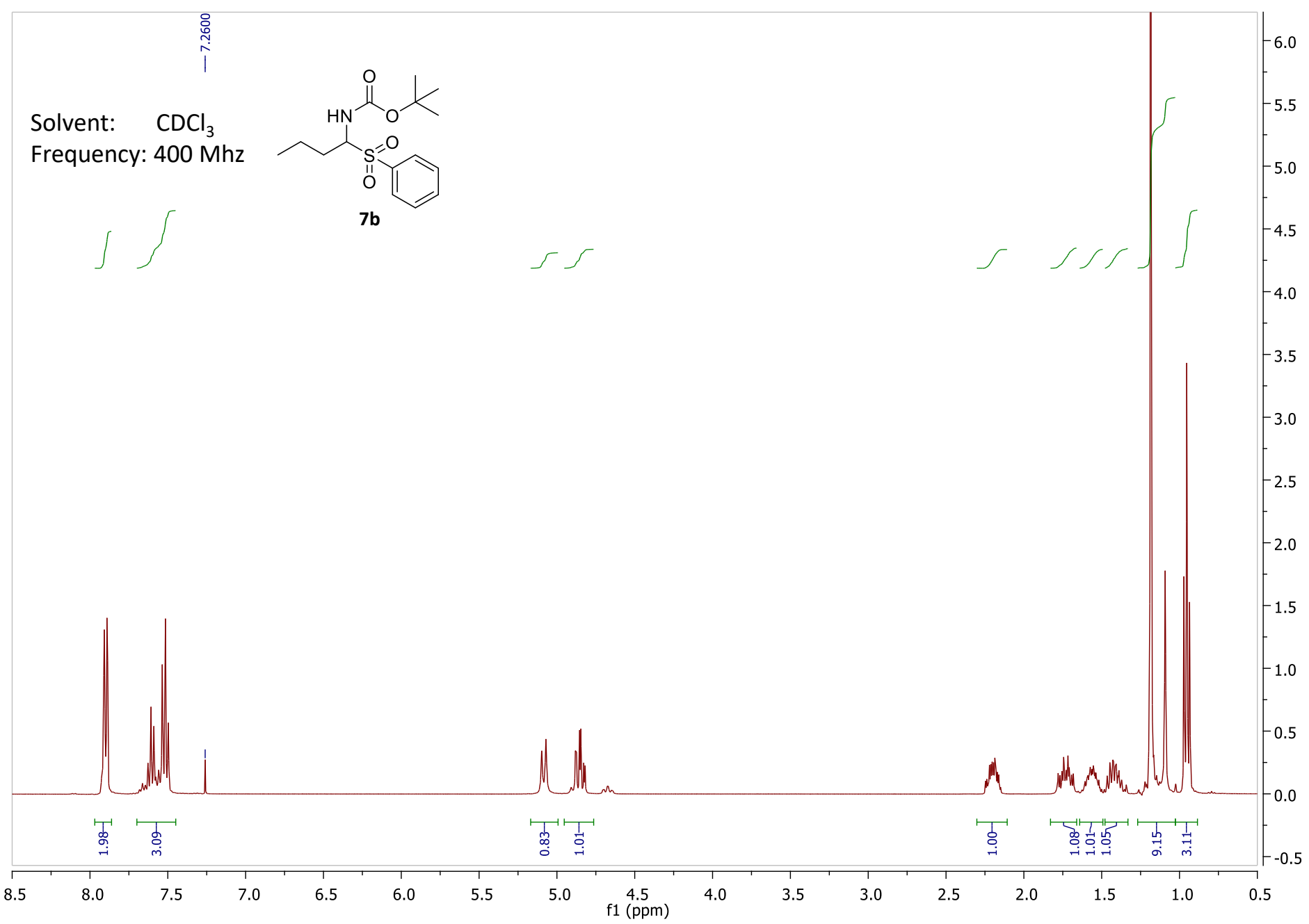
f1 (ppm)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S
O
O
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1.00
1.08
1.01
1.05
9.15
3.11
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)
6.0
5.5
5.0
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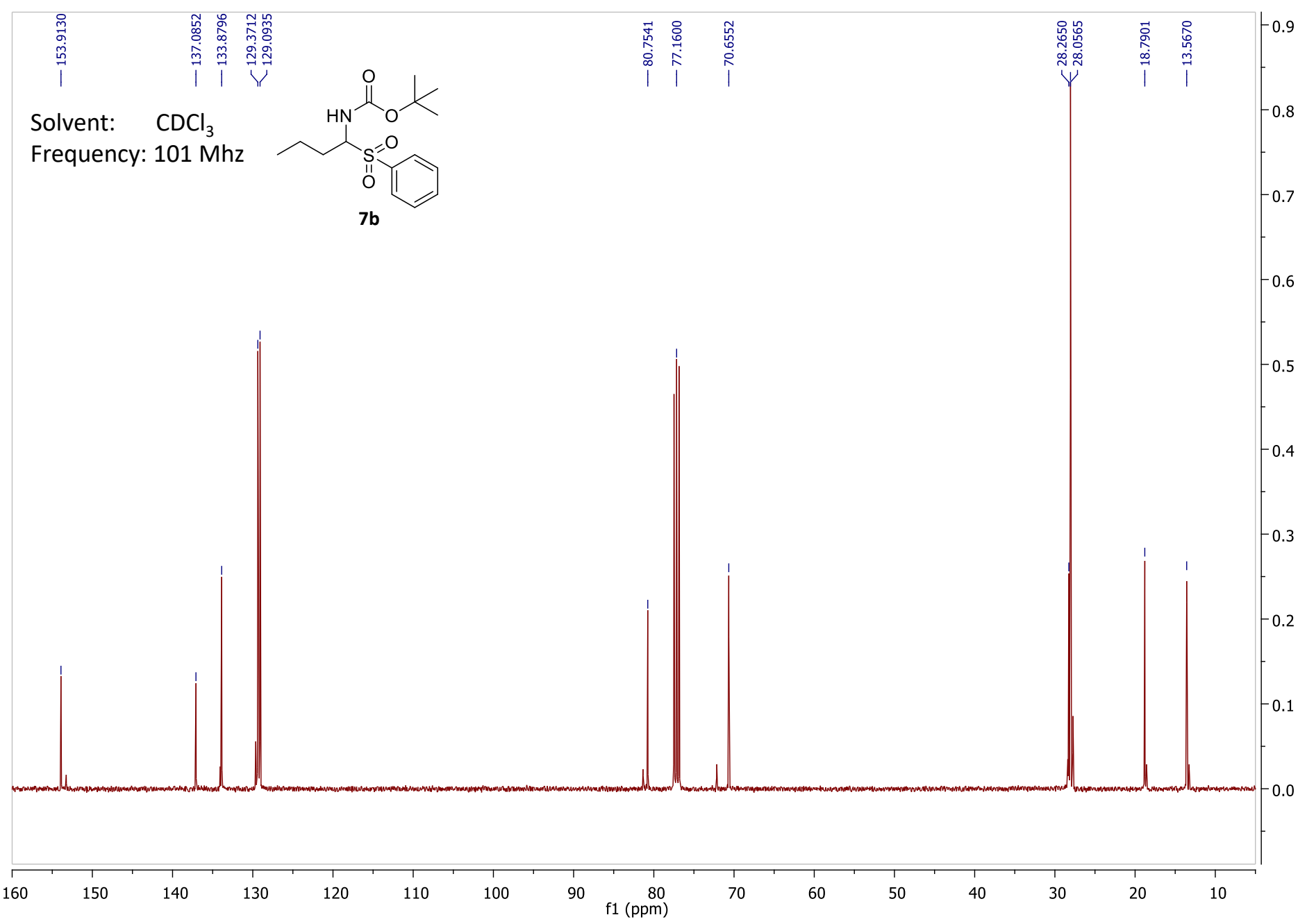
0.0
-0.5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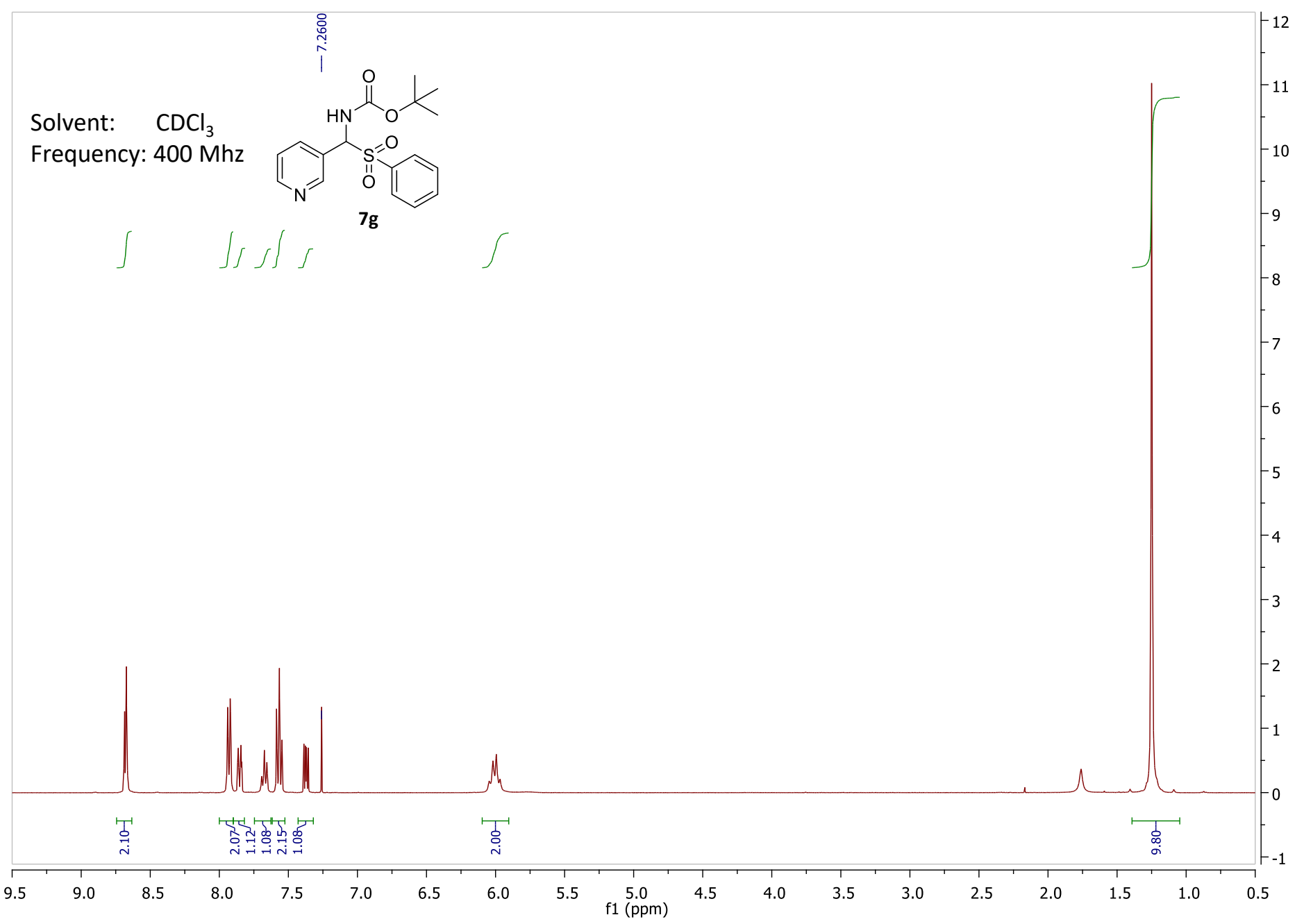
O
S
O
O
7b
f1 (ppm)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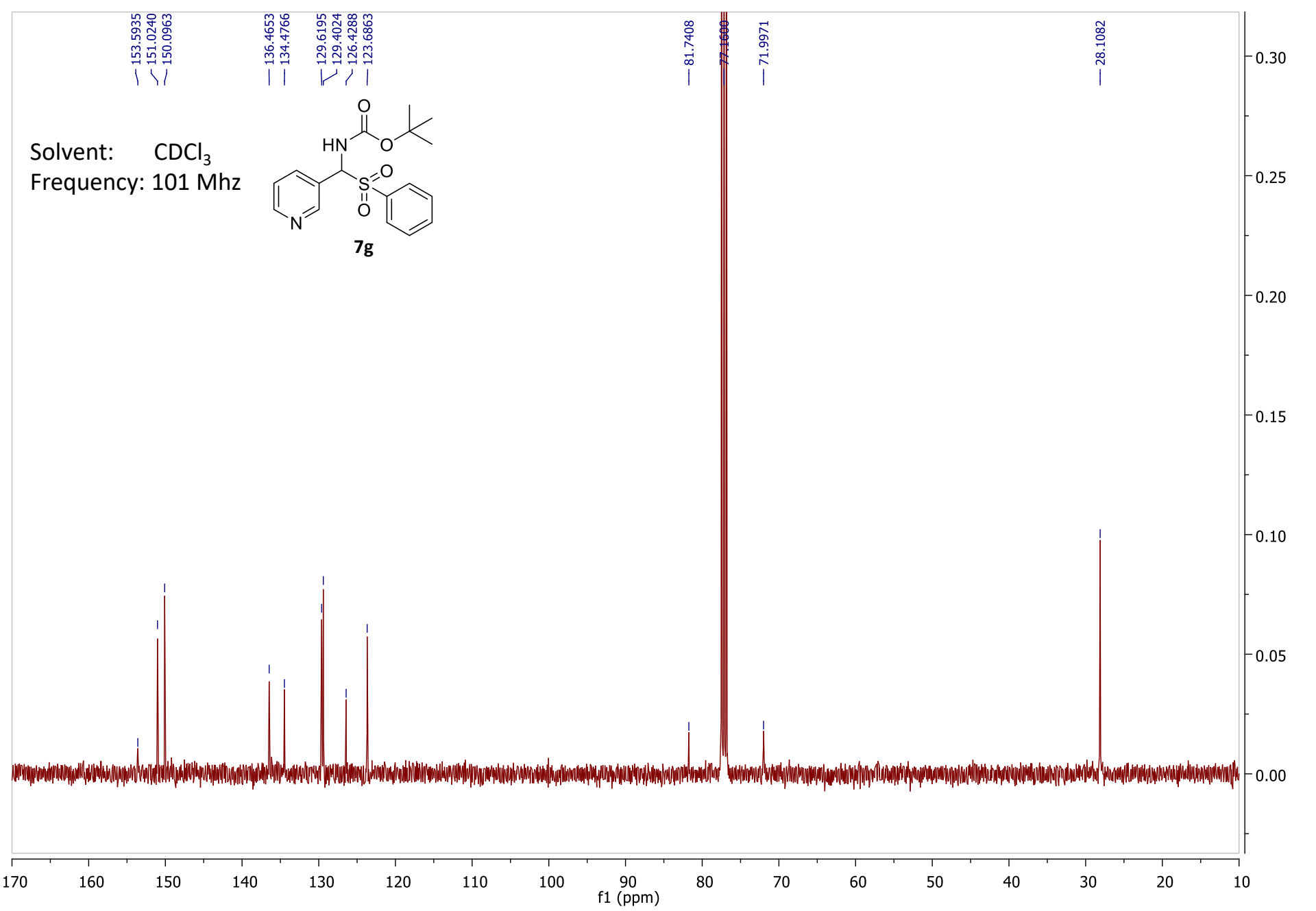
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S
O
O
N
7g
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0.15
0.10
0.05
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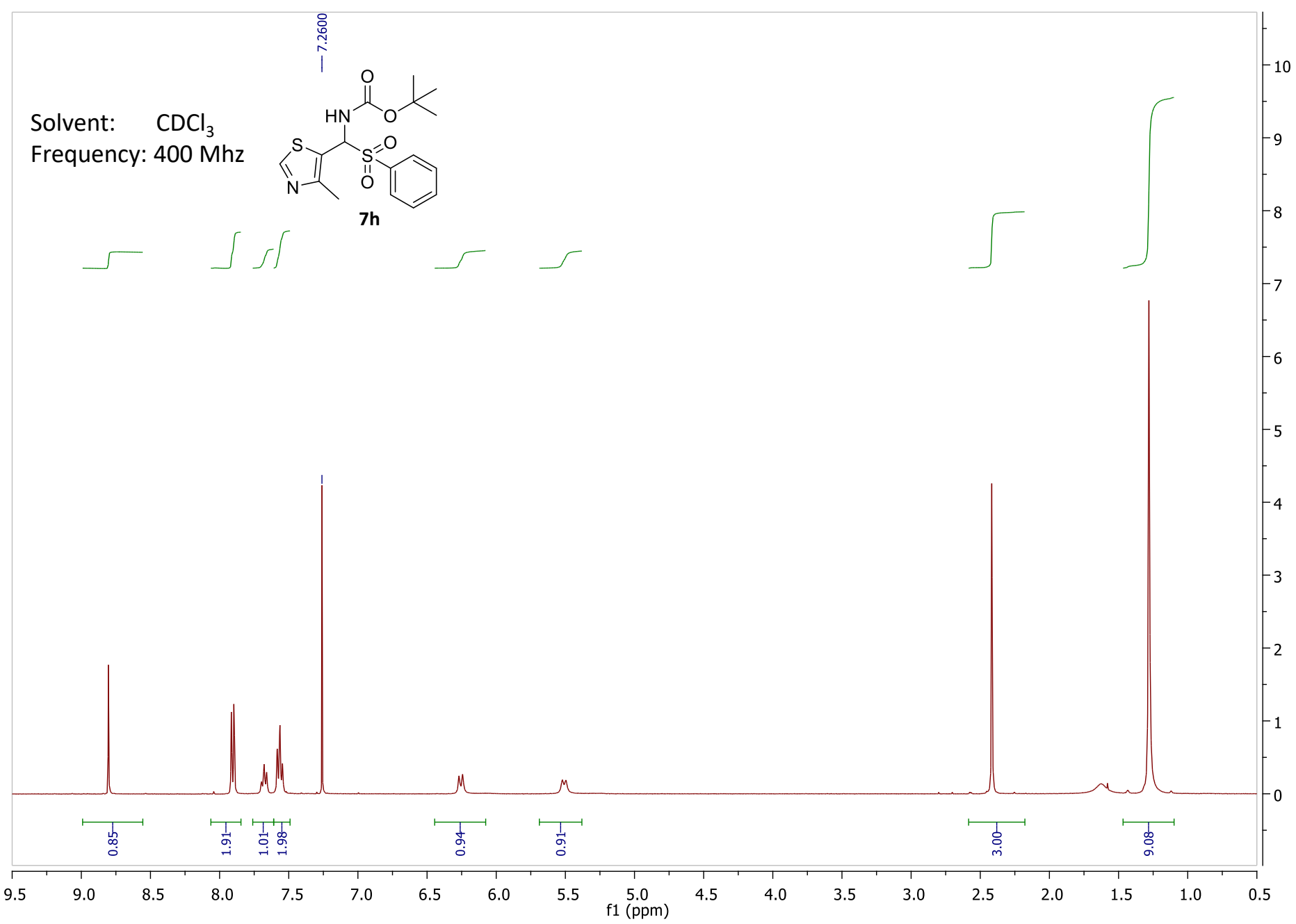
f1 (ppm)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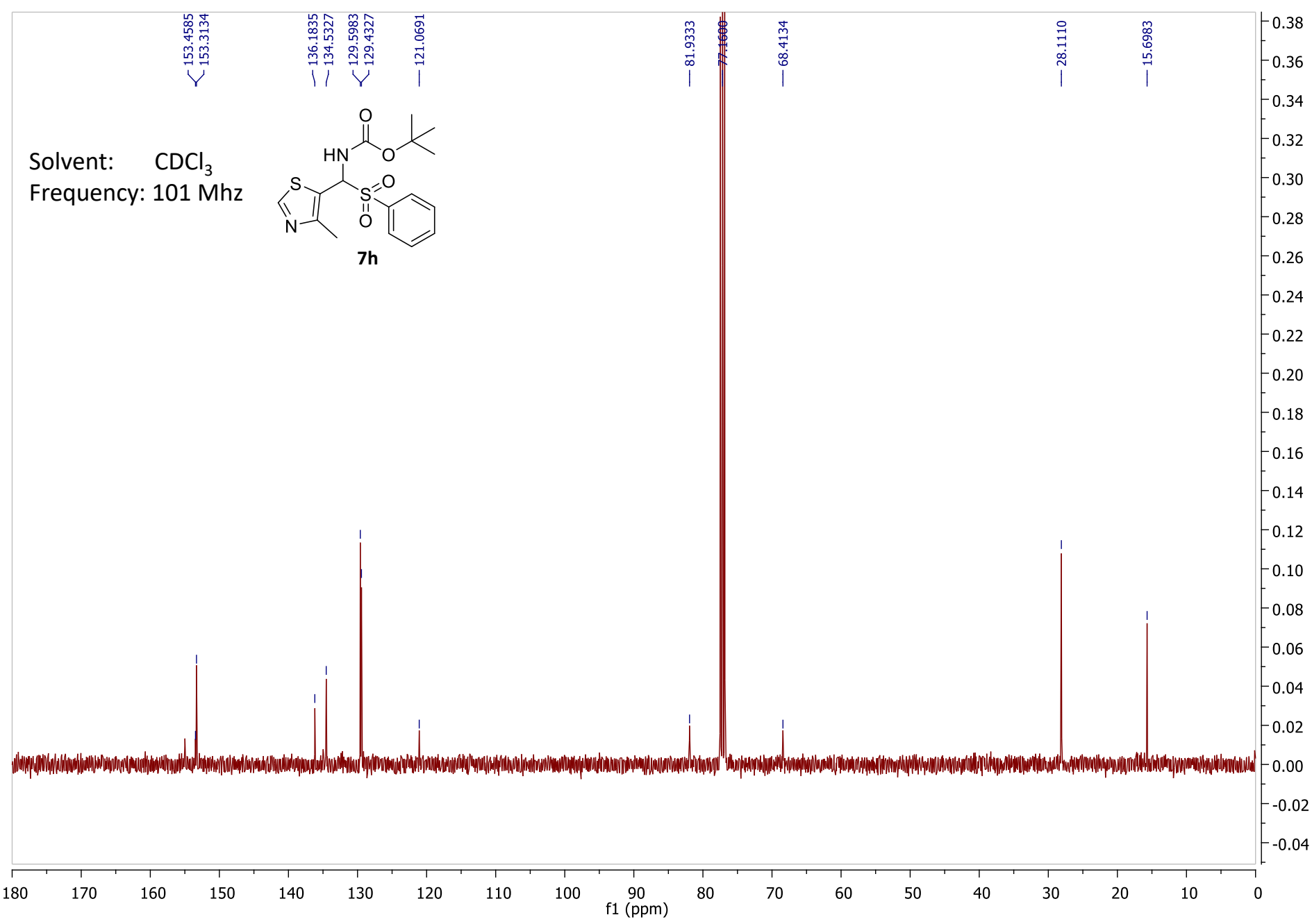
9.08
f1 (ppm)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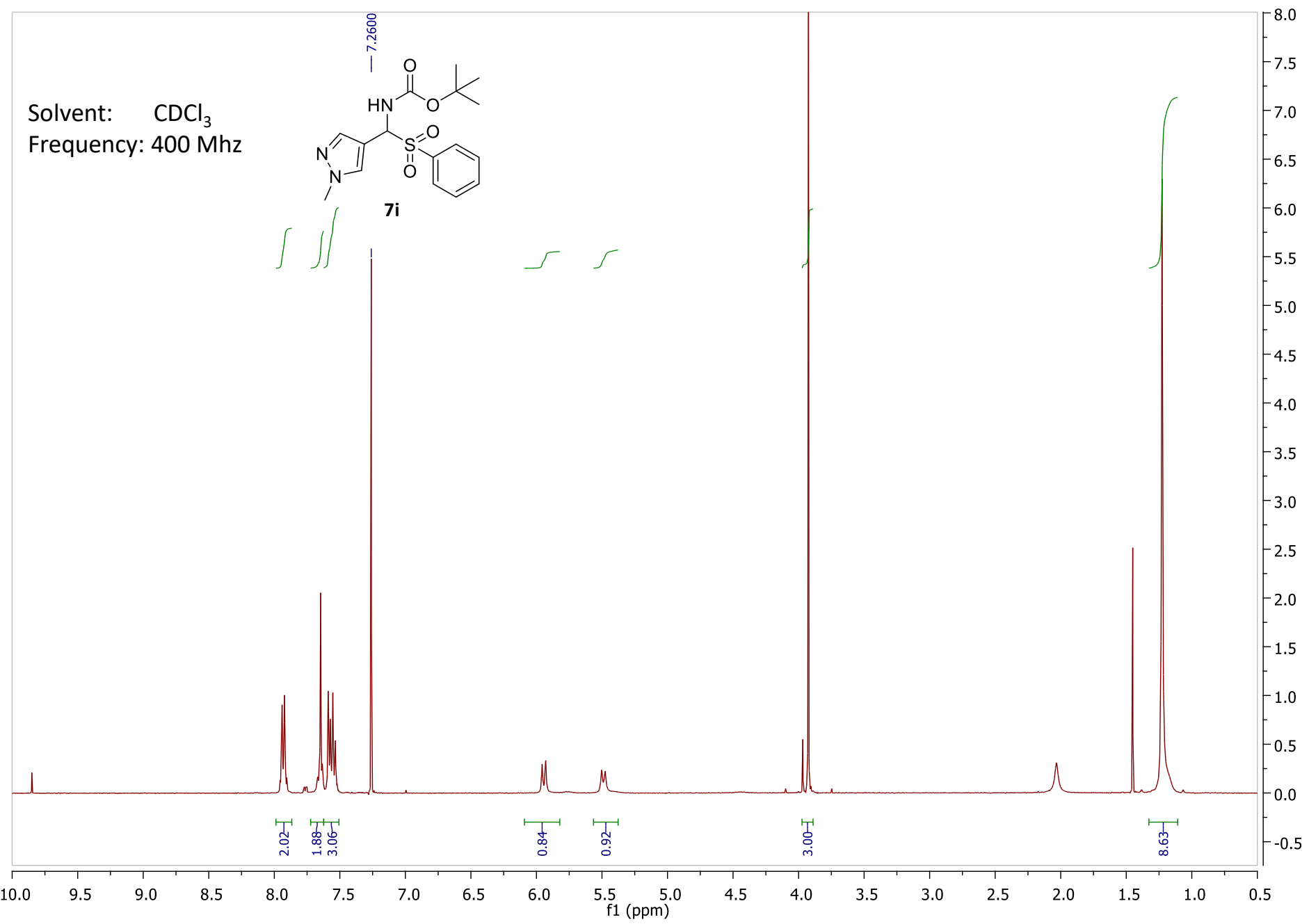
7h
f1 (ppm)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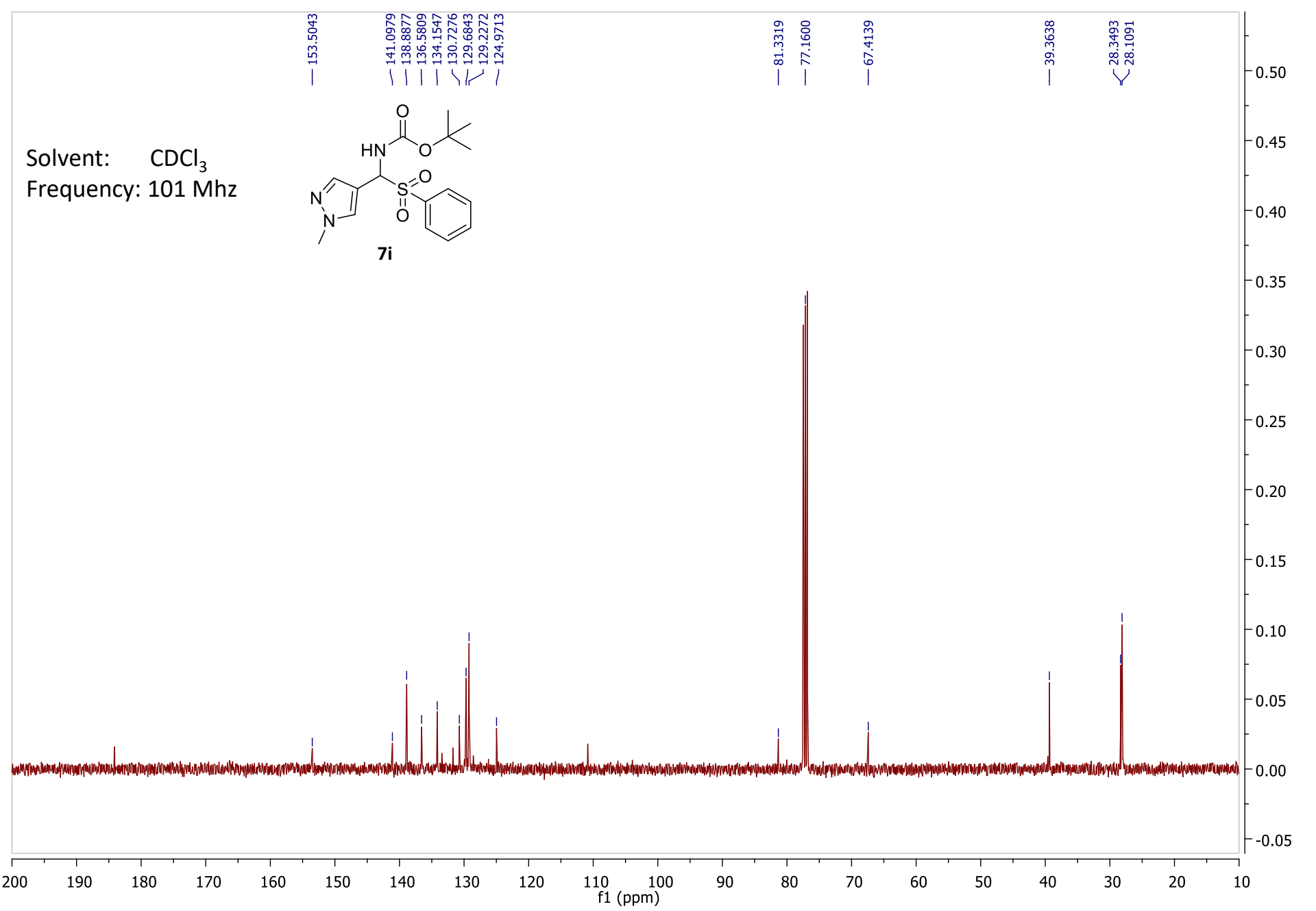
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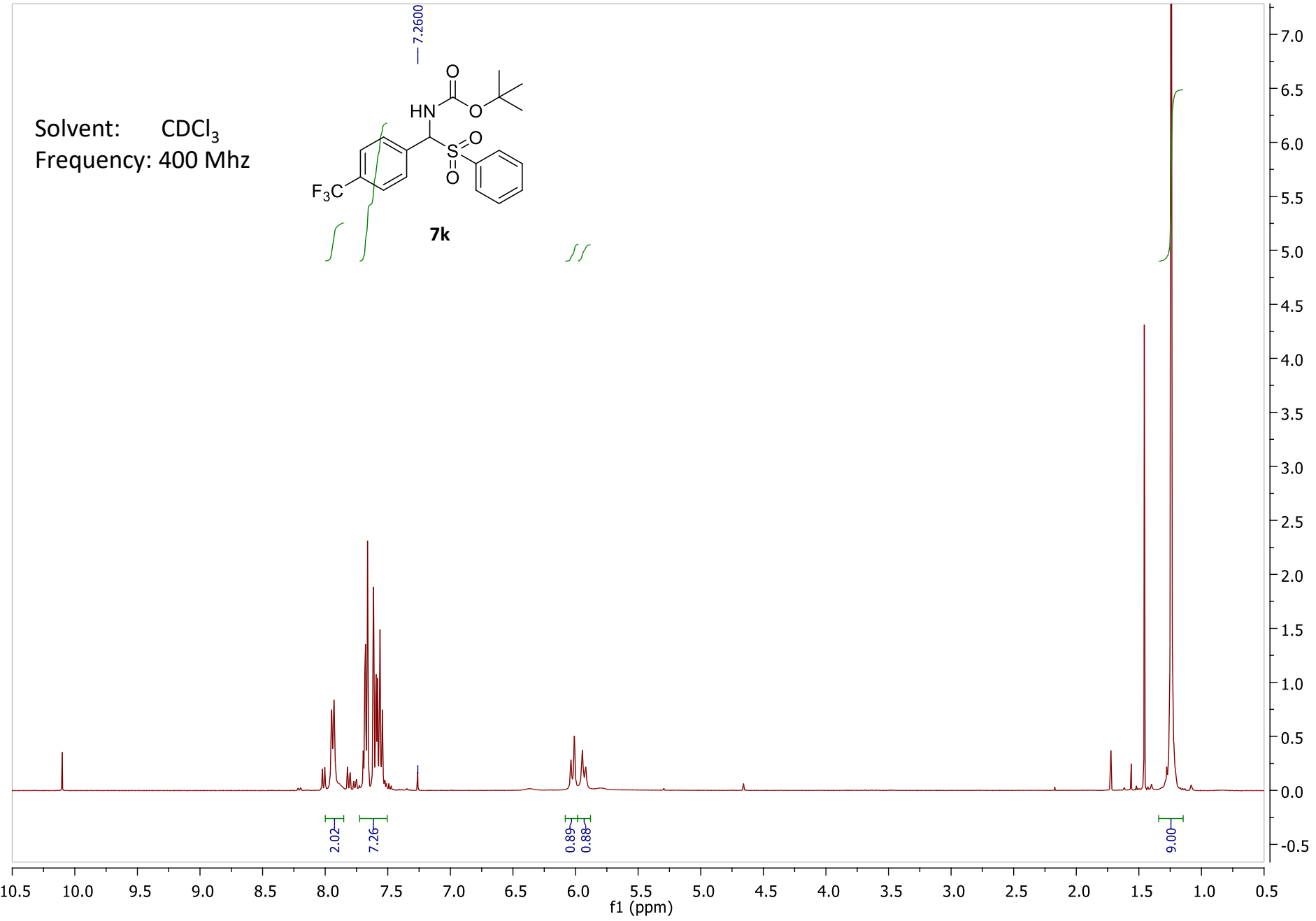
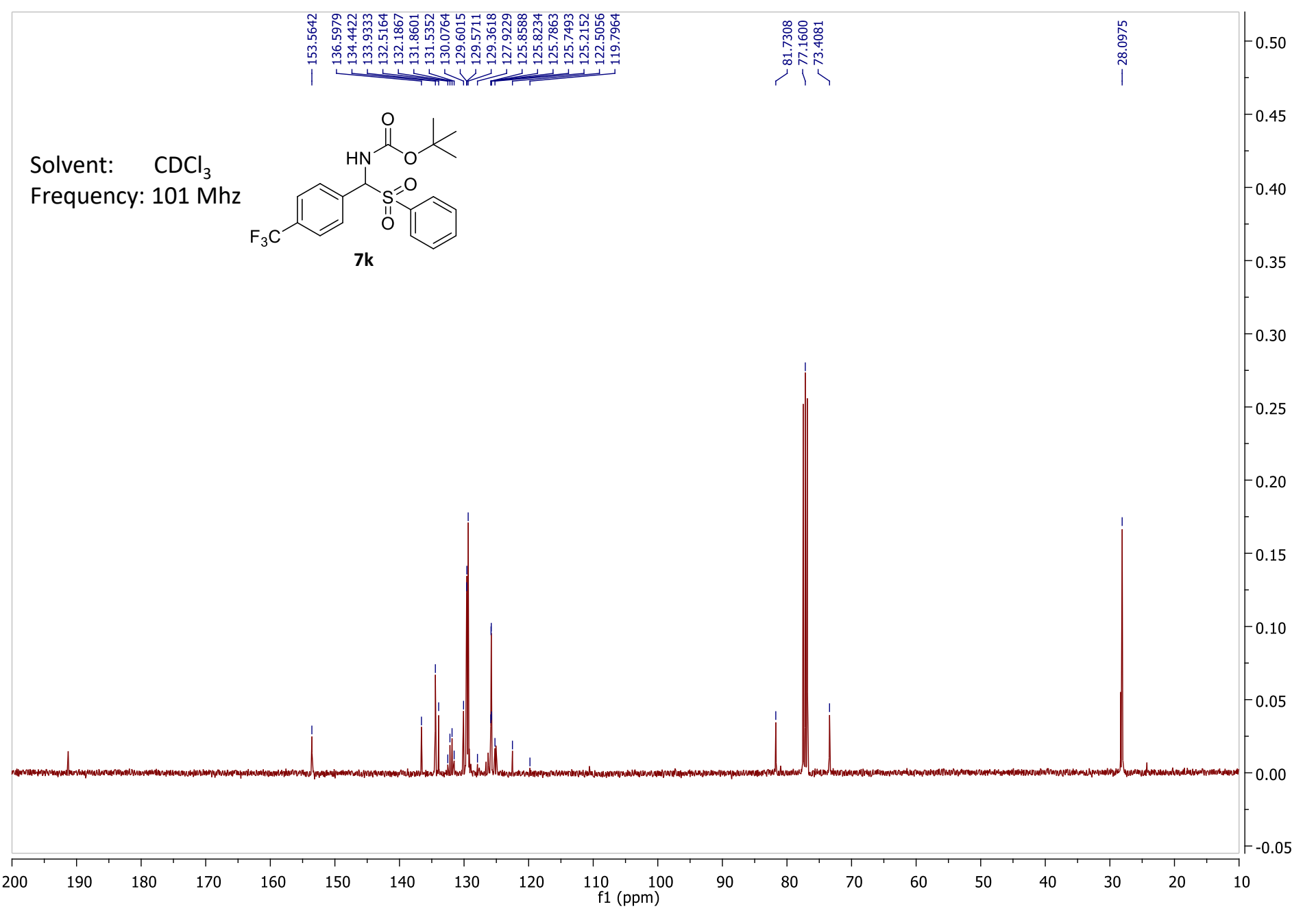
77.1600
67.4139
39.3638
28.3493
28.1091
Solvent: CDCl3
Frequency: 101 Mhz
HN
O
O
S
O
O
N
N
7i
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Solvent: $CDCl_3$
Frequency: 400 Mhz

7k

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125.8234
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125.2152
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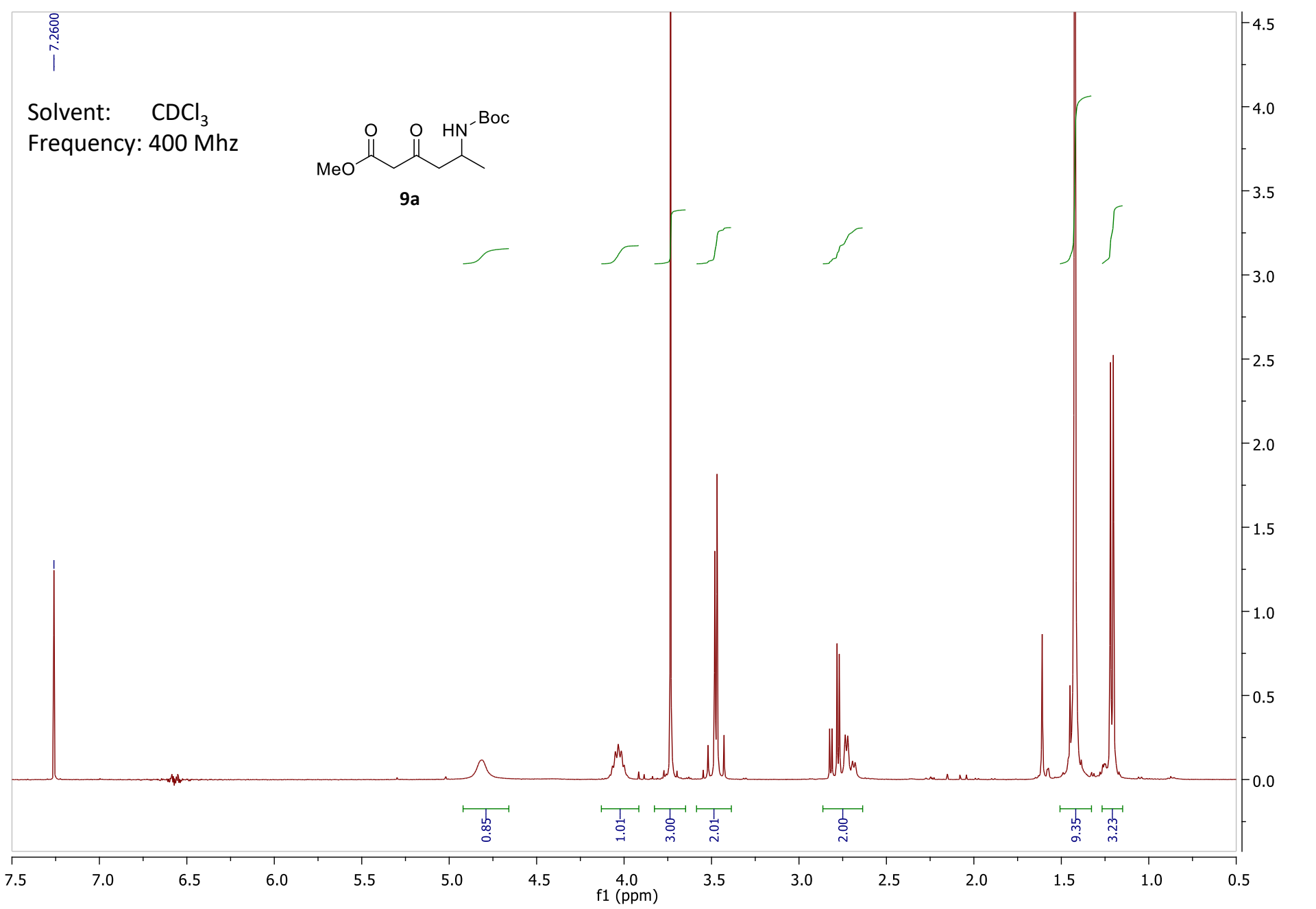
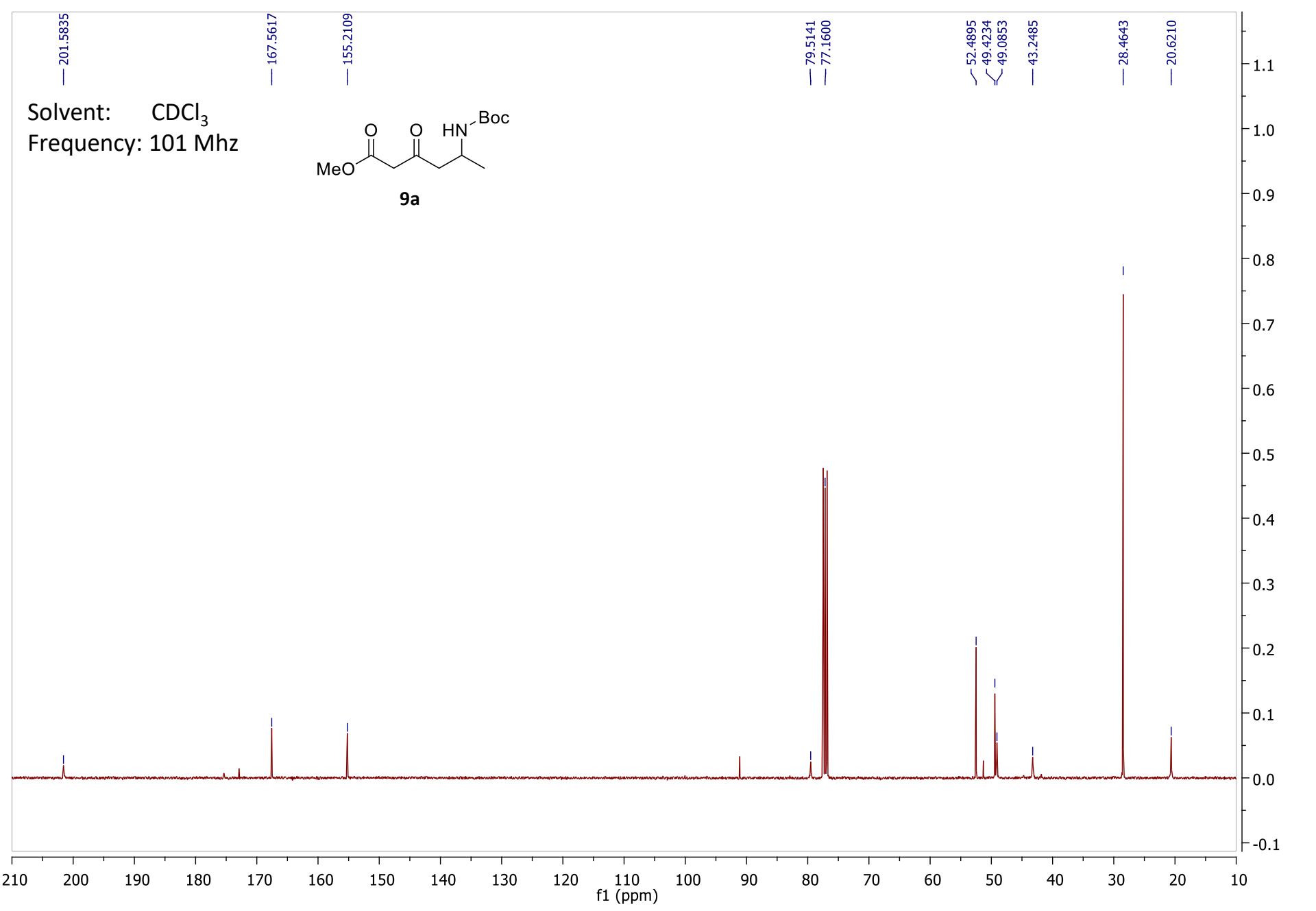
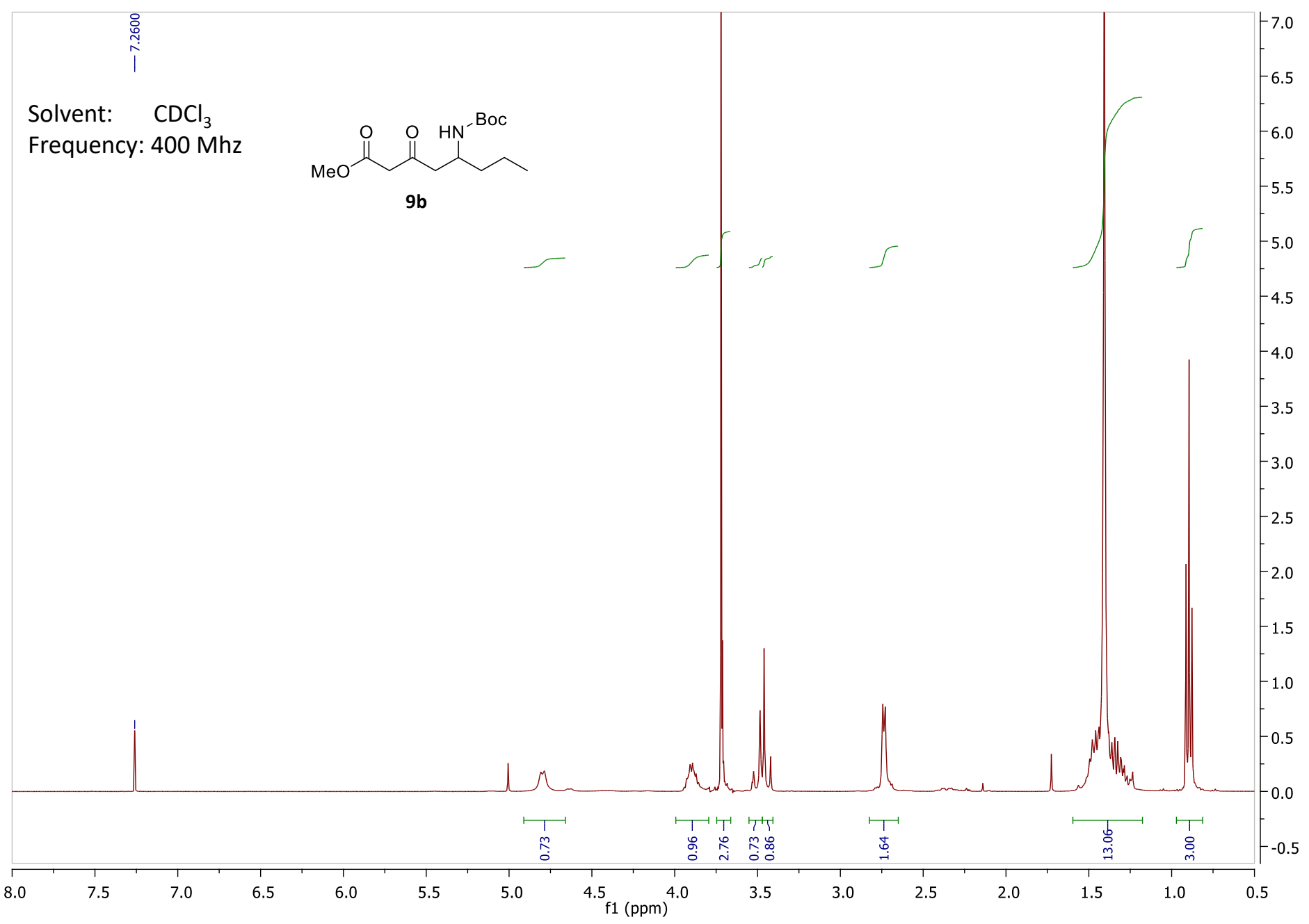
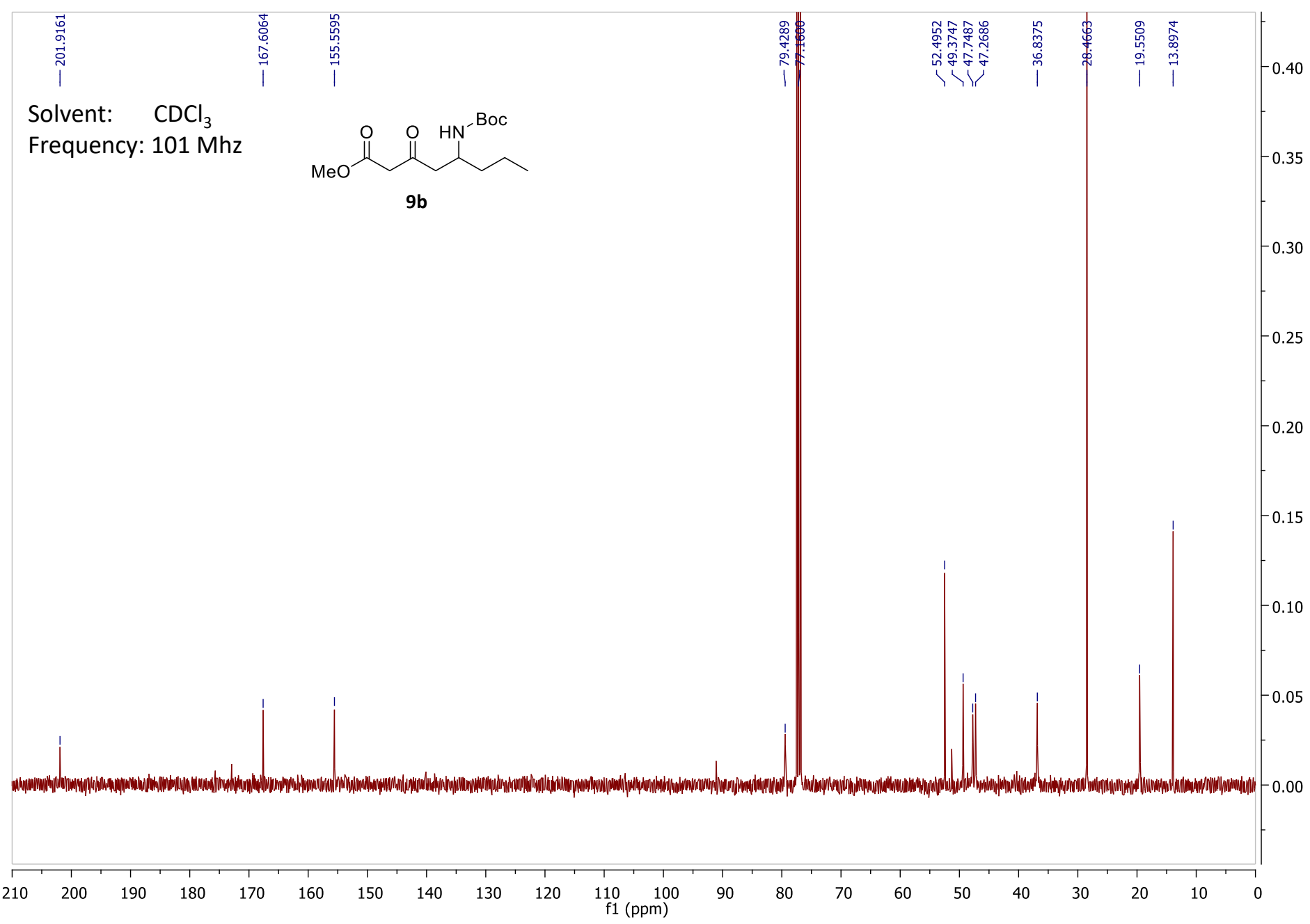
73.4081
28.0975
Solvent: CDCl3
Frequency: 101 Mhz
HN
O
O
O
S
O
F3C
7k
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

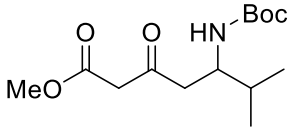

7.2600
Solvent: $CDCl_3$
Frequency: 400 Mhz
MeO
O
O
HN
Boc
9a
0.85
1.01
3.00
2.01
2.00
9.35
3.23
f1 (ppm)


201.5835
167.5617
155.2109
79.5141
77.1600
52.4895
49.4234
49.0853
43.2485
28.4643
20.6210
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
9a
f1 (ppm)

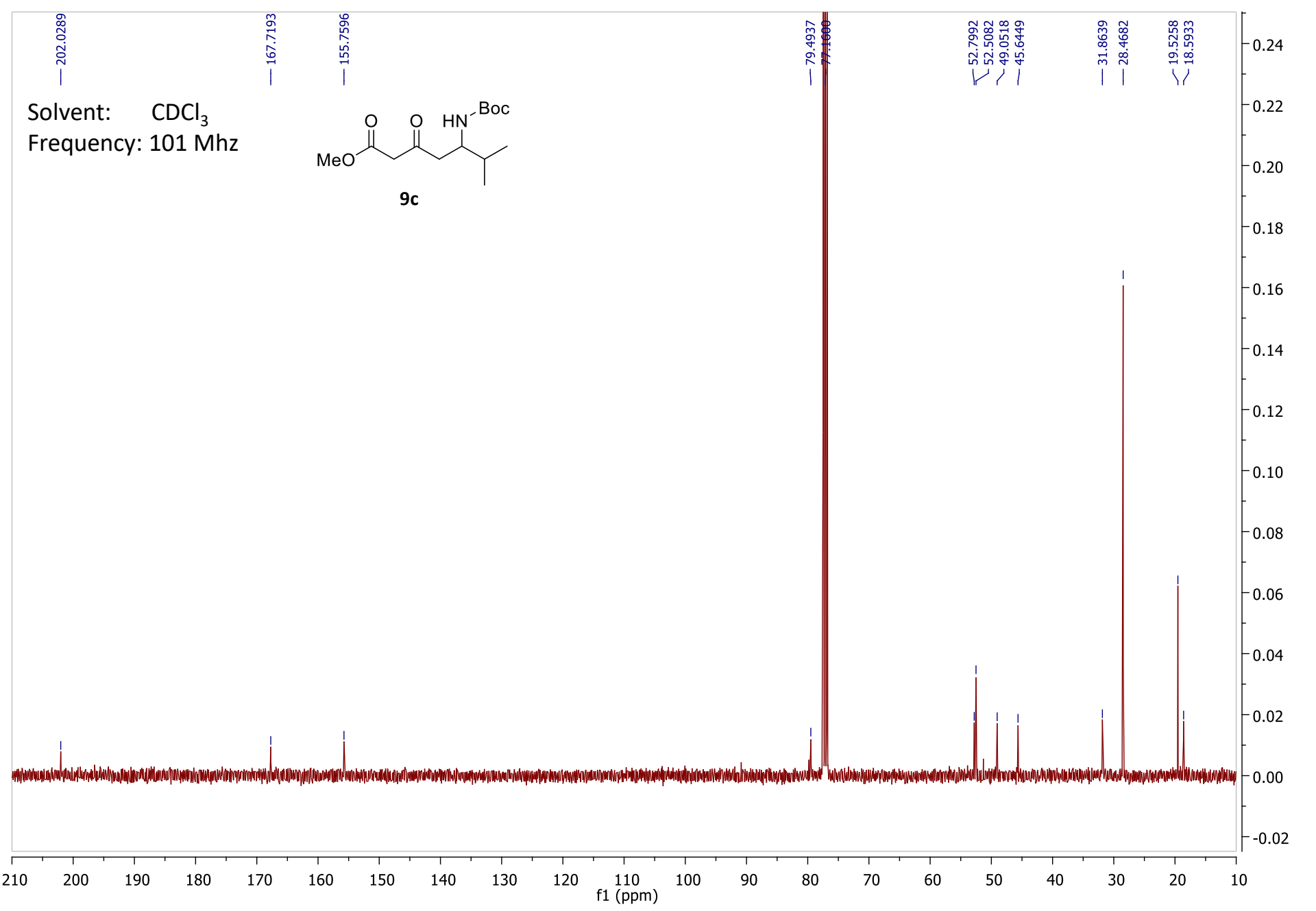

7.2600
Solvent: $CDCl_3$
Frequency: 400 Mhz
MeO
O
O
HN
Boc
9b
0.73
0.96
2.76
0.73
0.86
1.64
13.06
3.00
f1 (ppm)

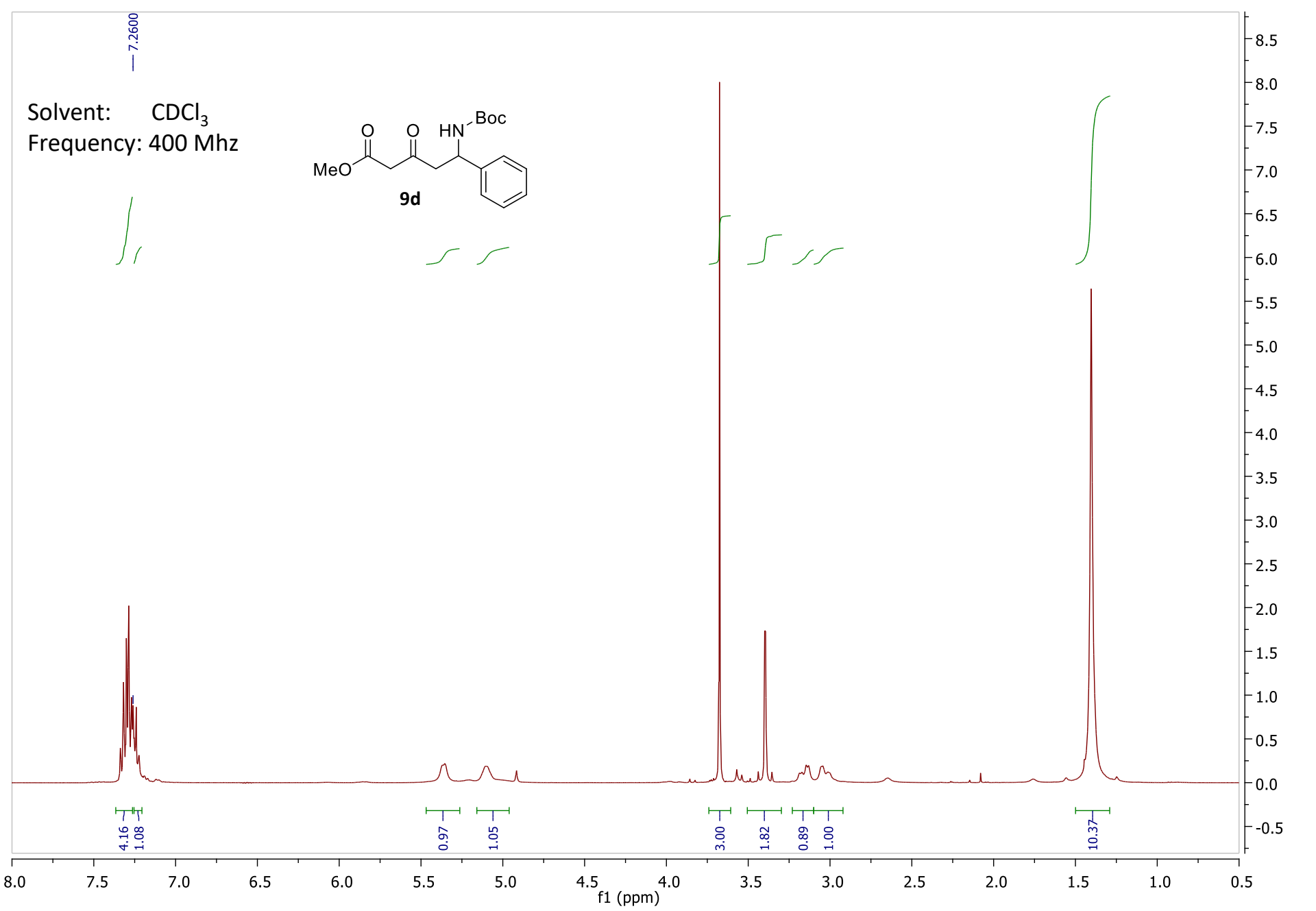

201.9161
167.6064
155.5595
79.4289
77.1600
52.4952
49.3747
47.7487
47.2686
36.8375
28.4663
19.5509
13.8974
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
9b
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

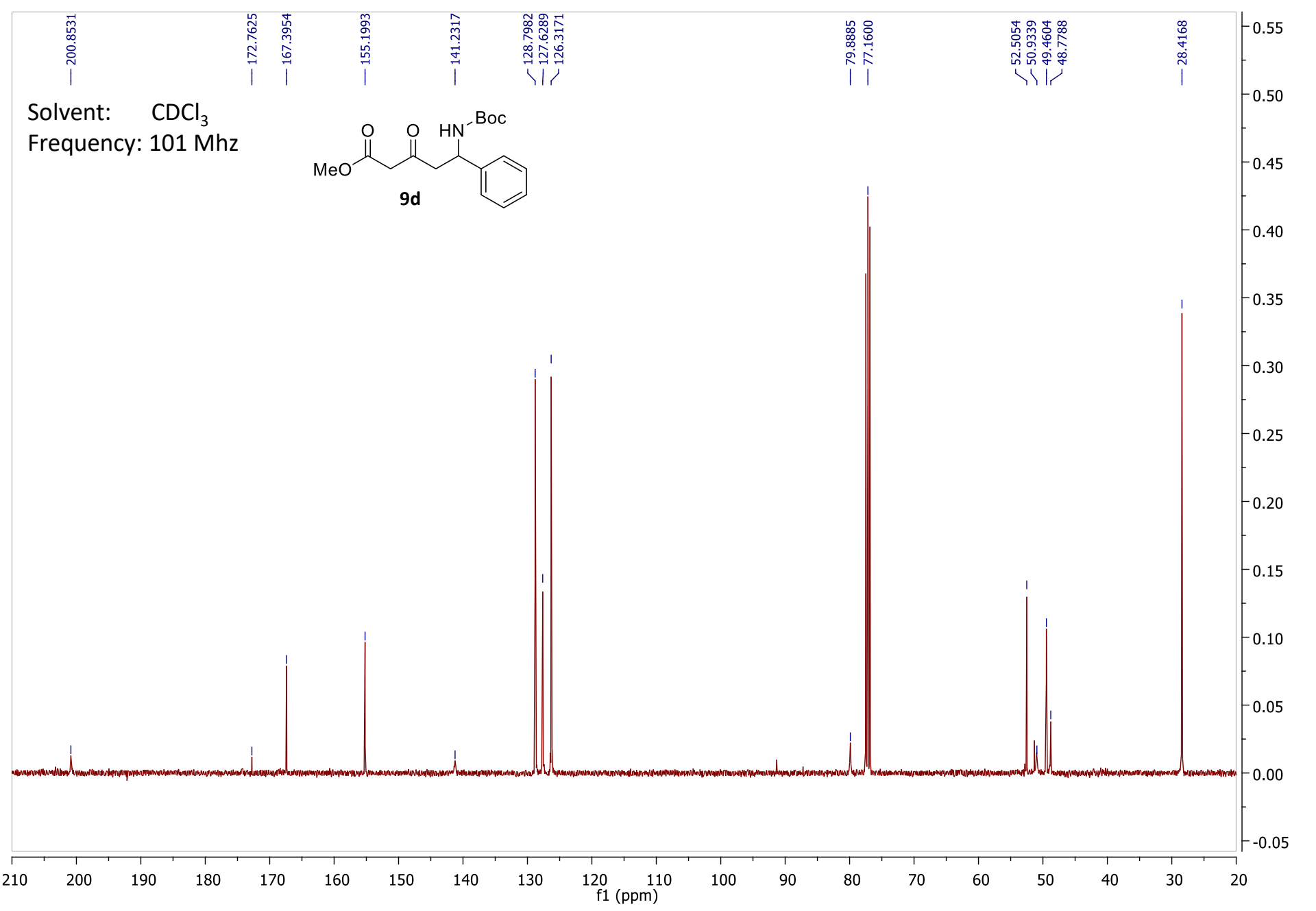
Solvent: $CDCl_3$
Frequency: 400 Mhz

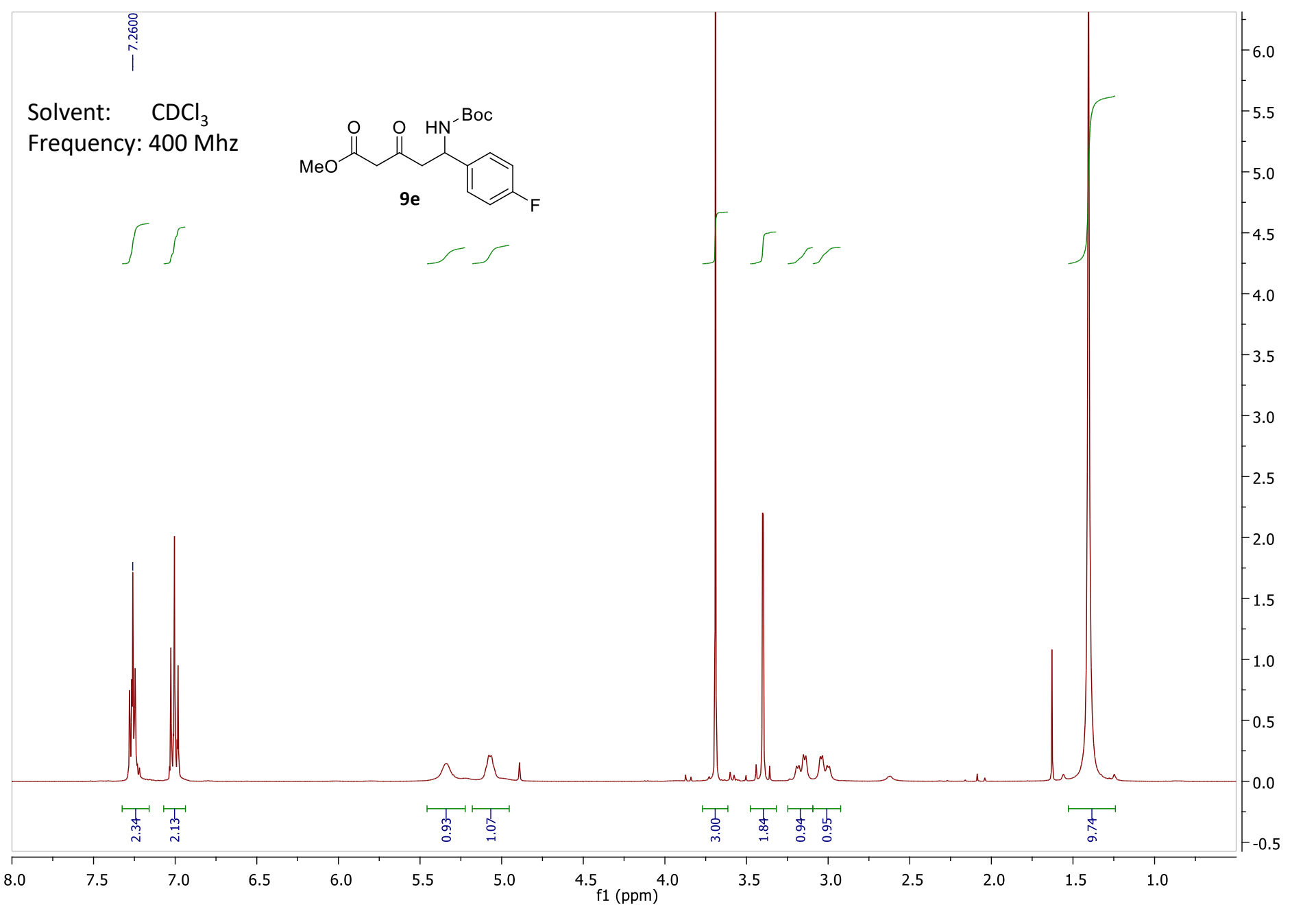


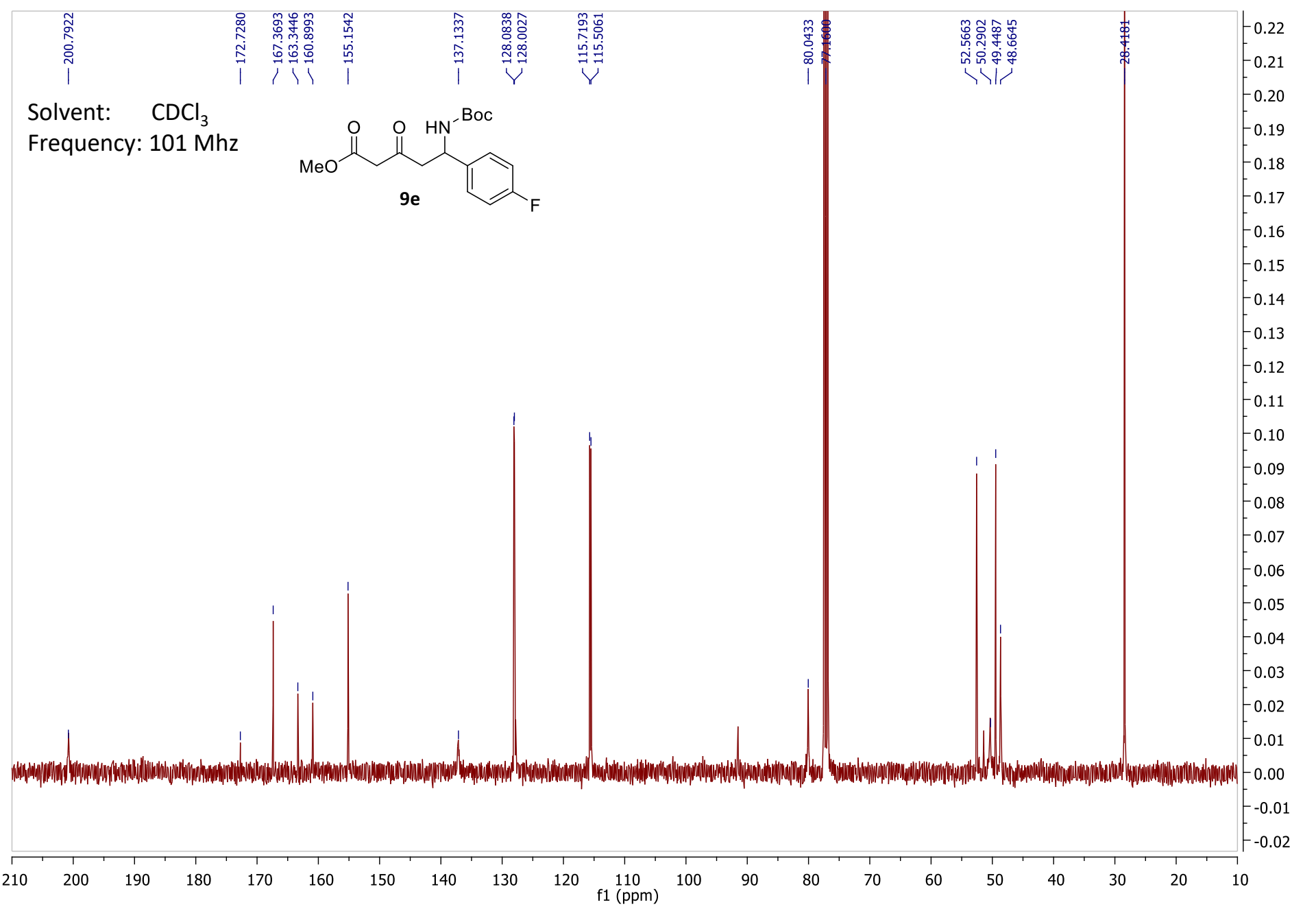
9c


202.0289
167.7193
155.7596
79.4937
77.1600
52.7992
52.5082
49.0518
45.6449
31.8639
28.4682
19.5258
18.5933
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
9c
f1 (ppm)


7.2600
Solvent: $CDCl_3$
Frequency: 400 Mhz
MeO
O
O
HN
Boc
9d
4.16
1.08
0.97
1.05
3.00
1.82
0.89
1.00
10.37
f1 (ppm)

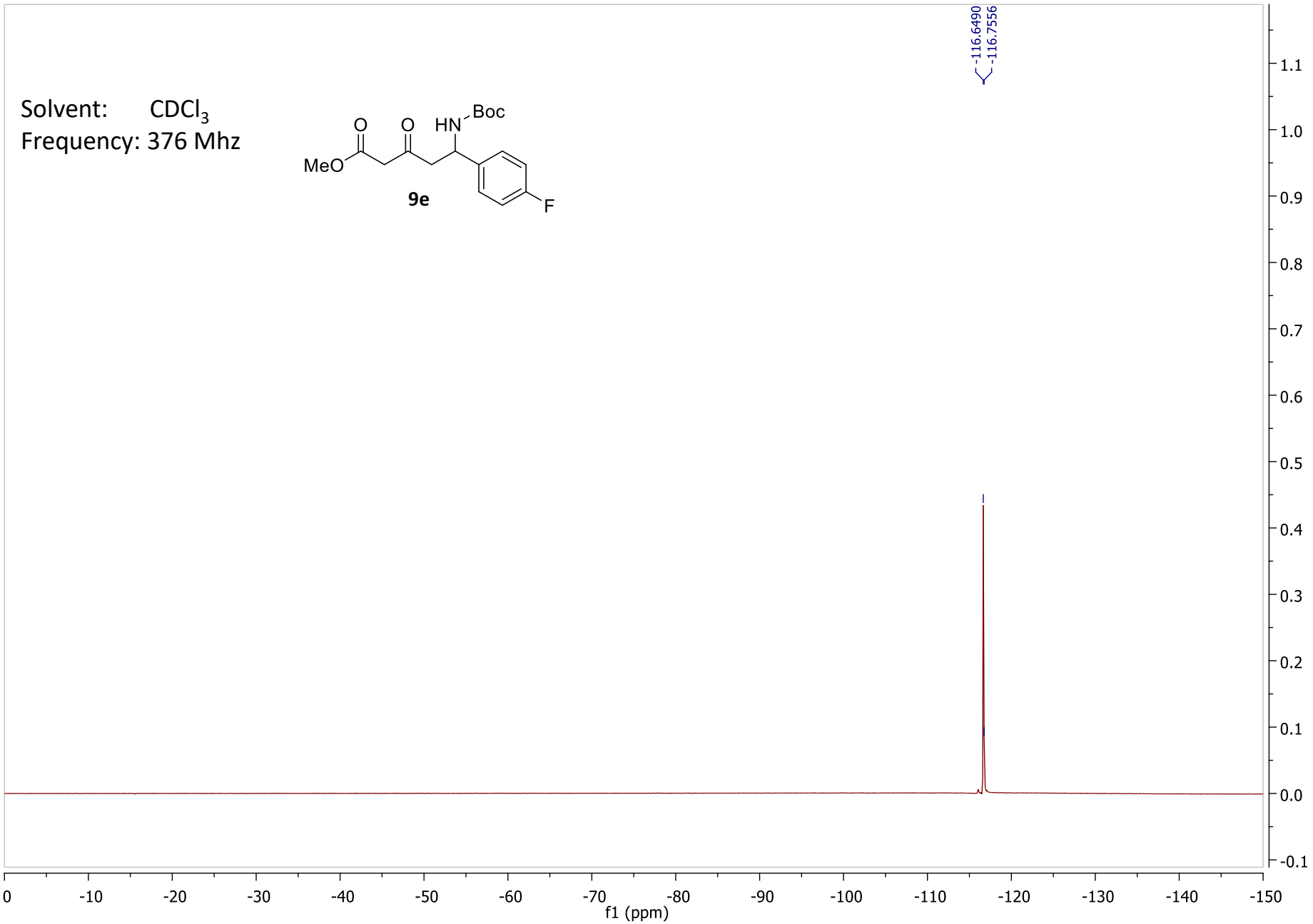

200.8531
172.7625
167.3954
155.1993
141.2317
128.7982
127.6289
126.3171
79.8885
77.1600
52.5054
50.9339
49.4604
48.7788
28.4168
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
9d
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

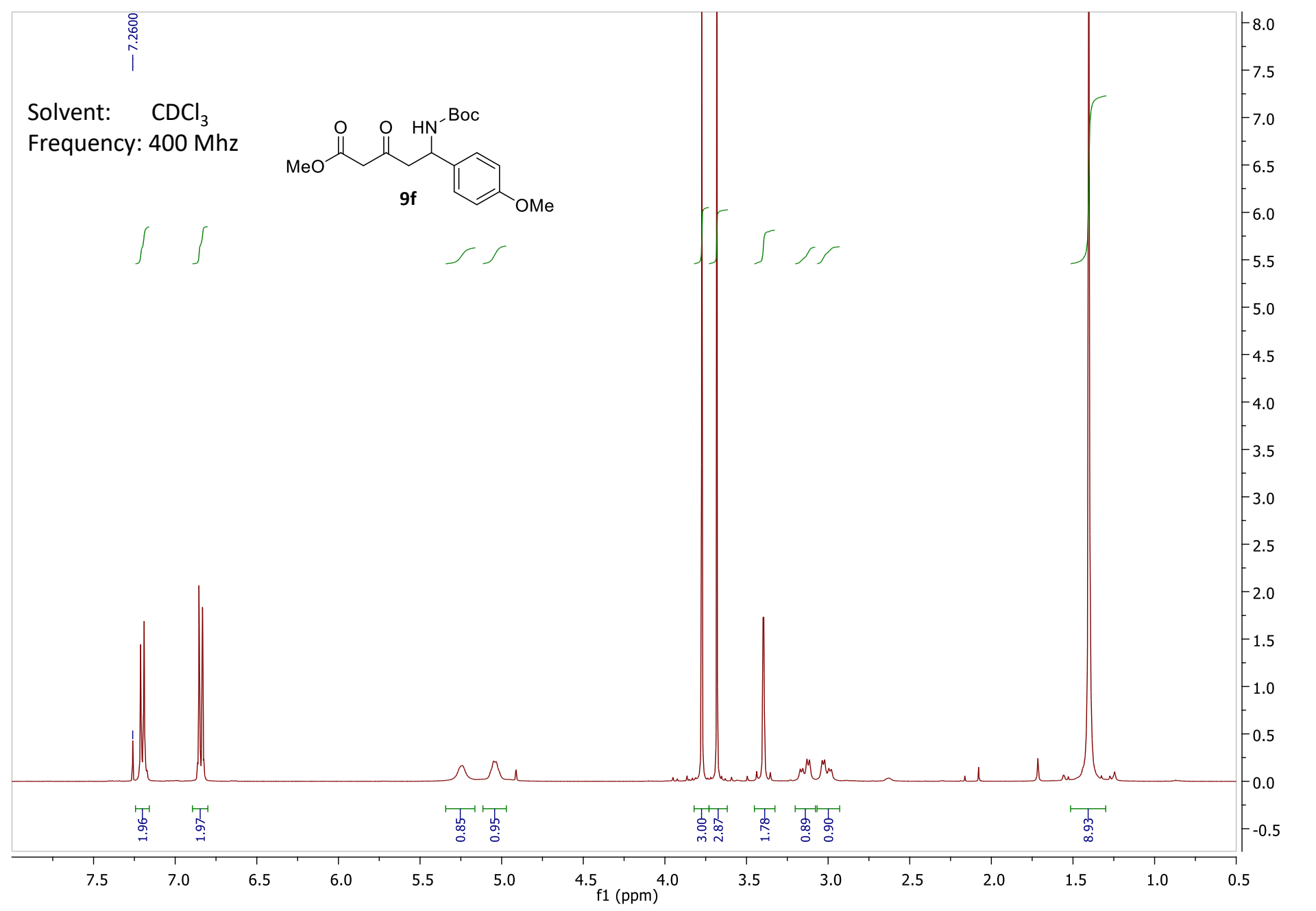

7.2600
Solvent: CDCl3
Frequency: 400 Mhz
MeO
O
O
HN
Boc
F
9e
2.34
2.13
0.93
1.07
3.00
1.84
0.94
0.95
9.74
f1 (ppm)

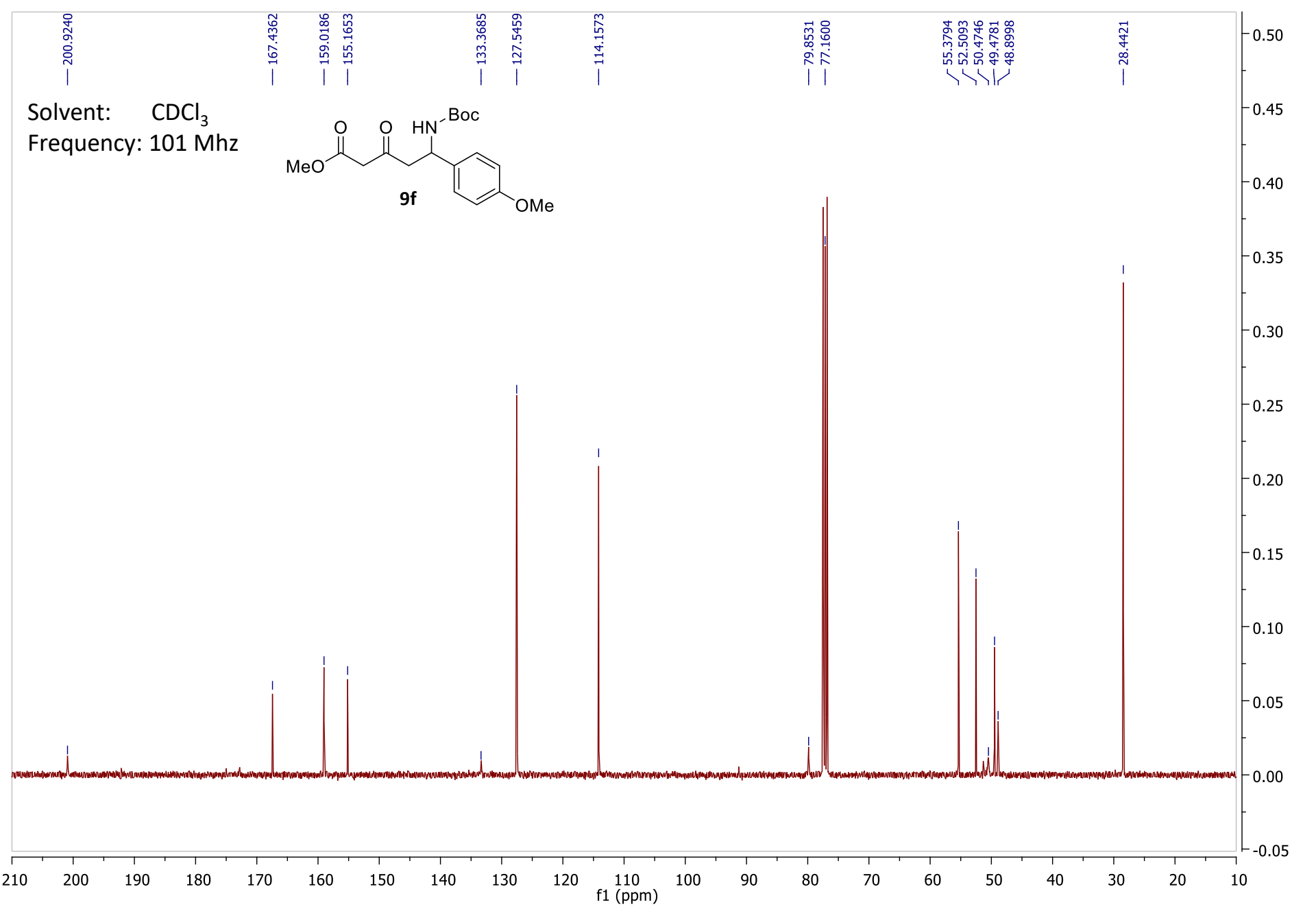

200.7922
172.7280
167.3693
163.3446
160.8993
155.1542
137.1337
128.0838
128.0027
115.7193
115.5061
80.0433
77.1600
52.5663
50.2902
49.4487
48.6645
28.4181
Solvent: CDCl3
Frequency: 101 Mhz
MeO
O
O
HN
Boc
F
9e
f1 (ppm)

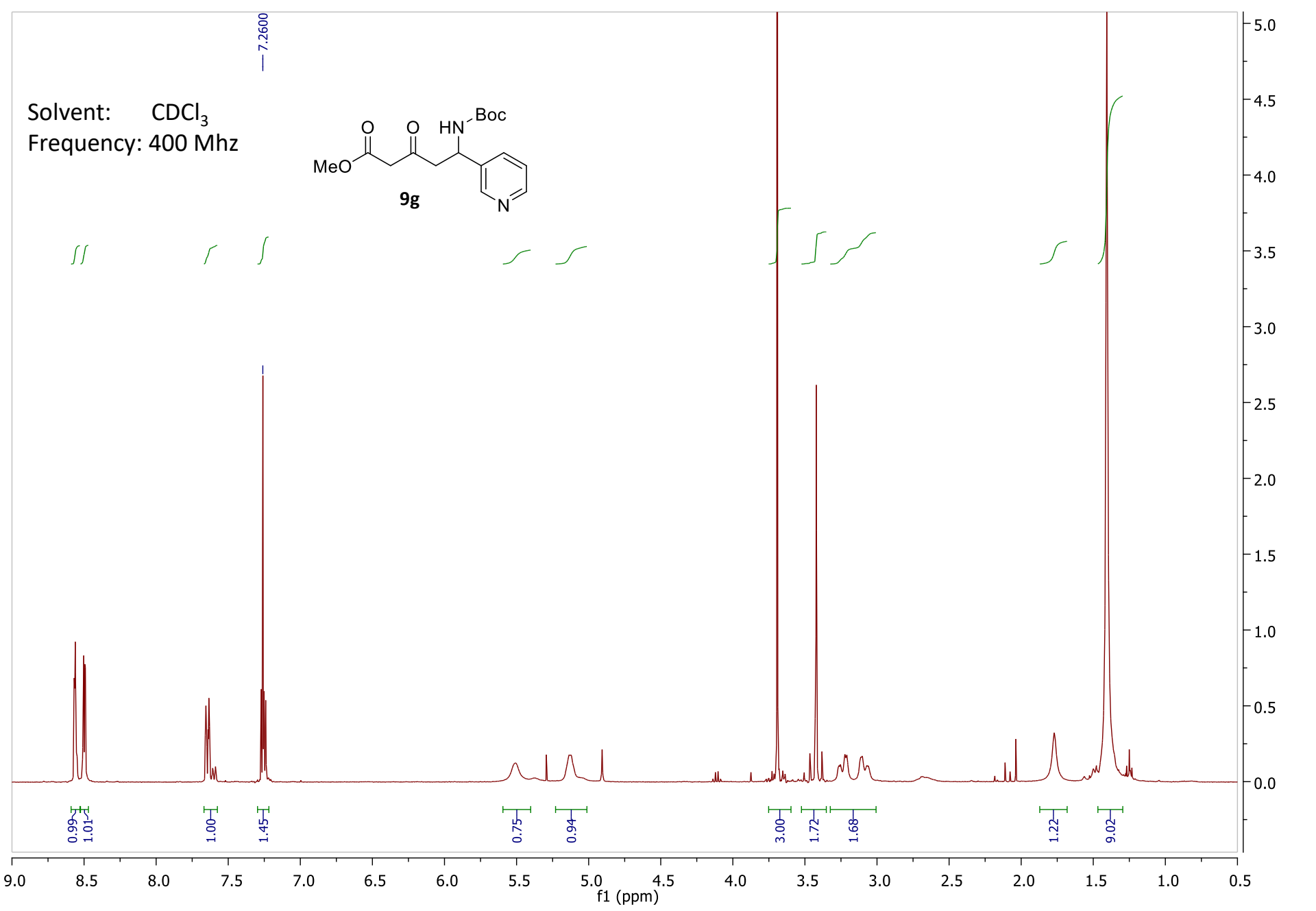
Solvent: $CDCl_3$
Frequency: 376 Mhz

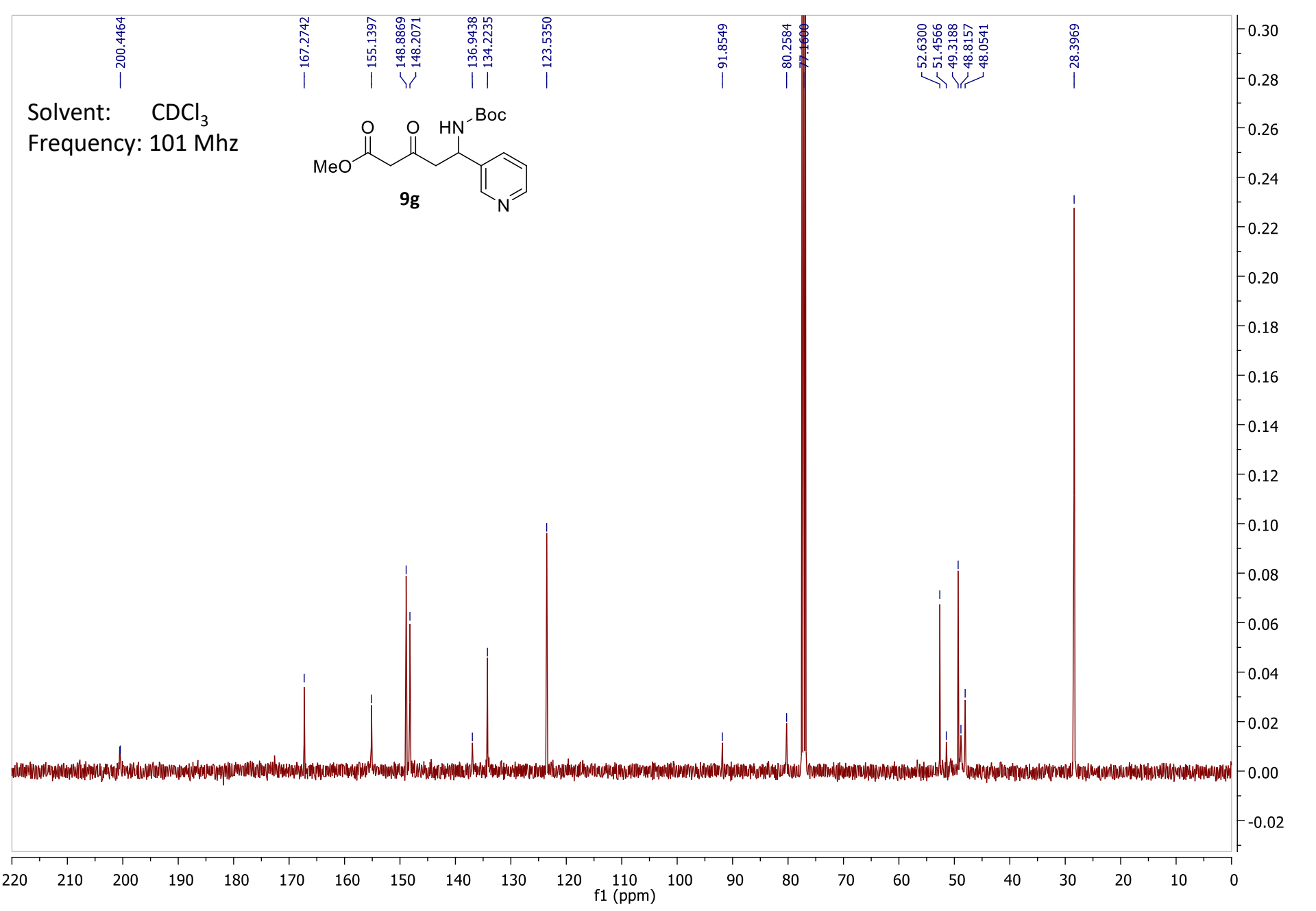
9e

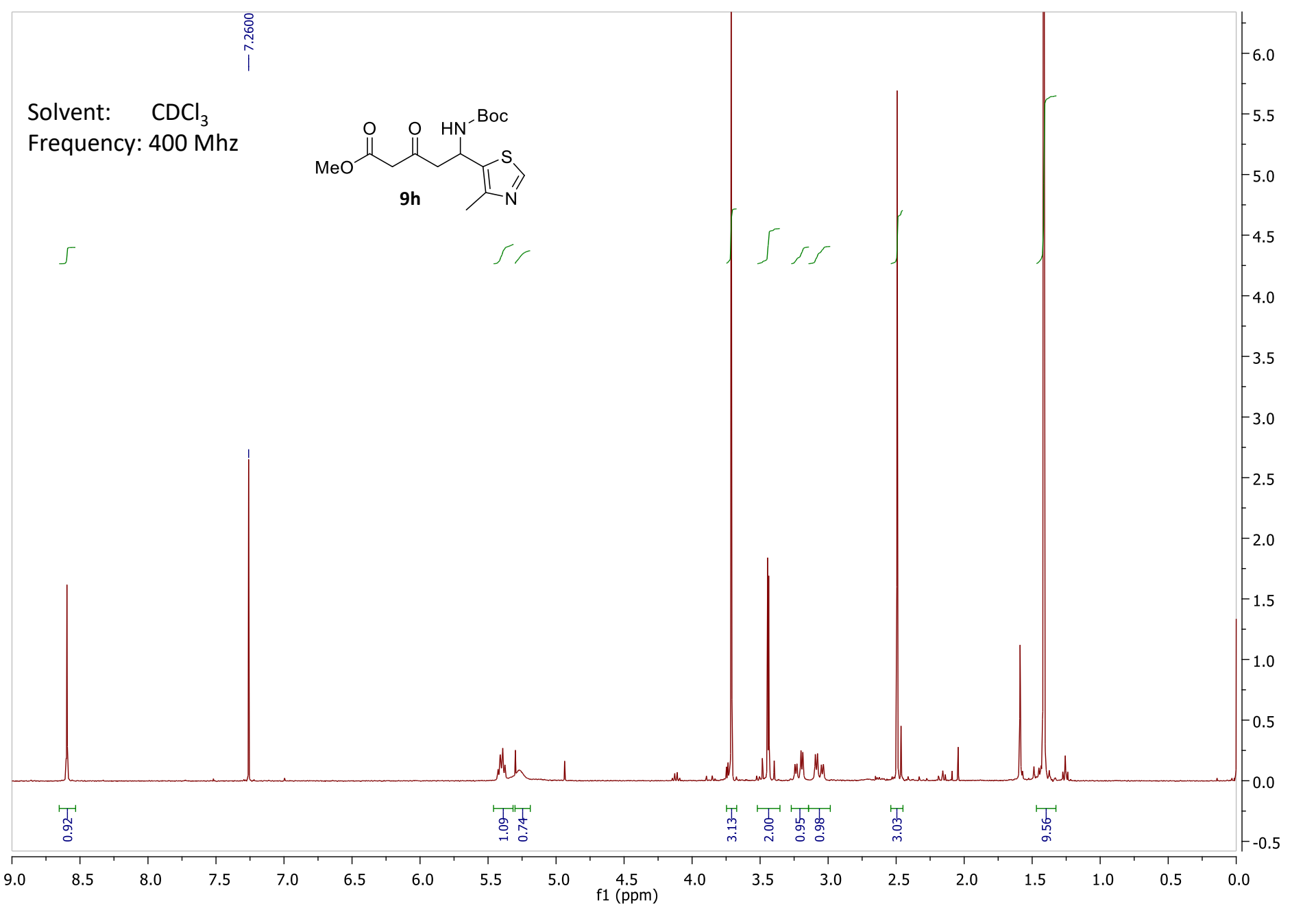


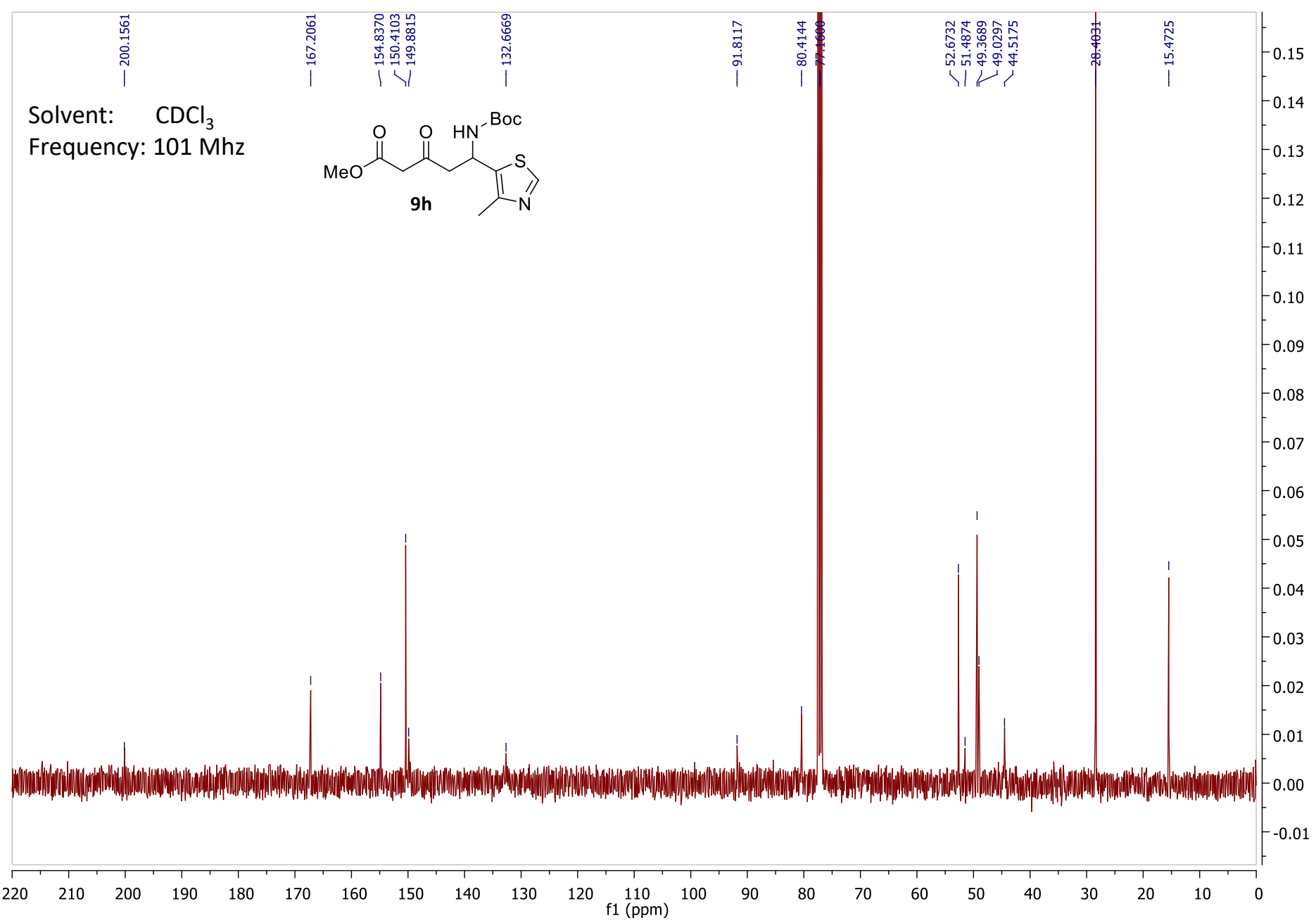

7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
HN
Boc
MeO
OMe
9f
1.96
1.97
0.85
0.95
3.00
2.87
1.78
0.89
0.90
8.93
f1 (ppm)

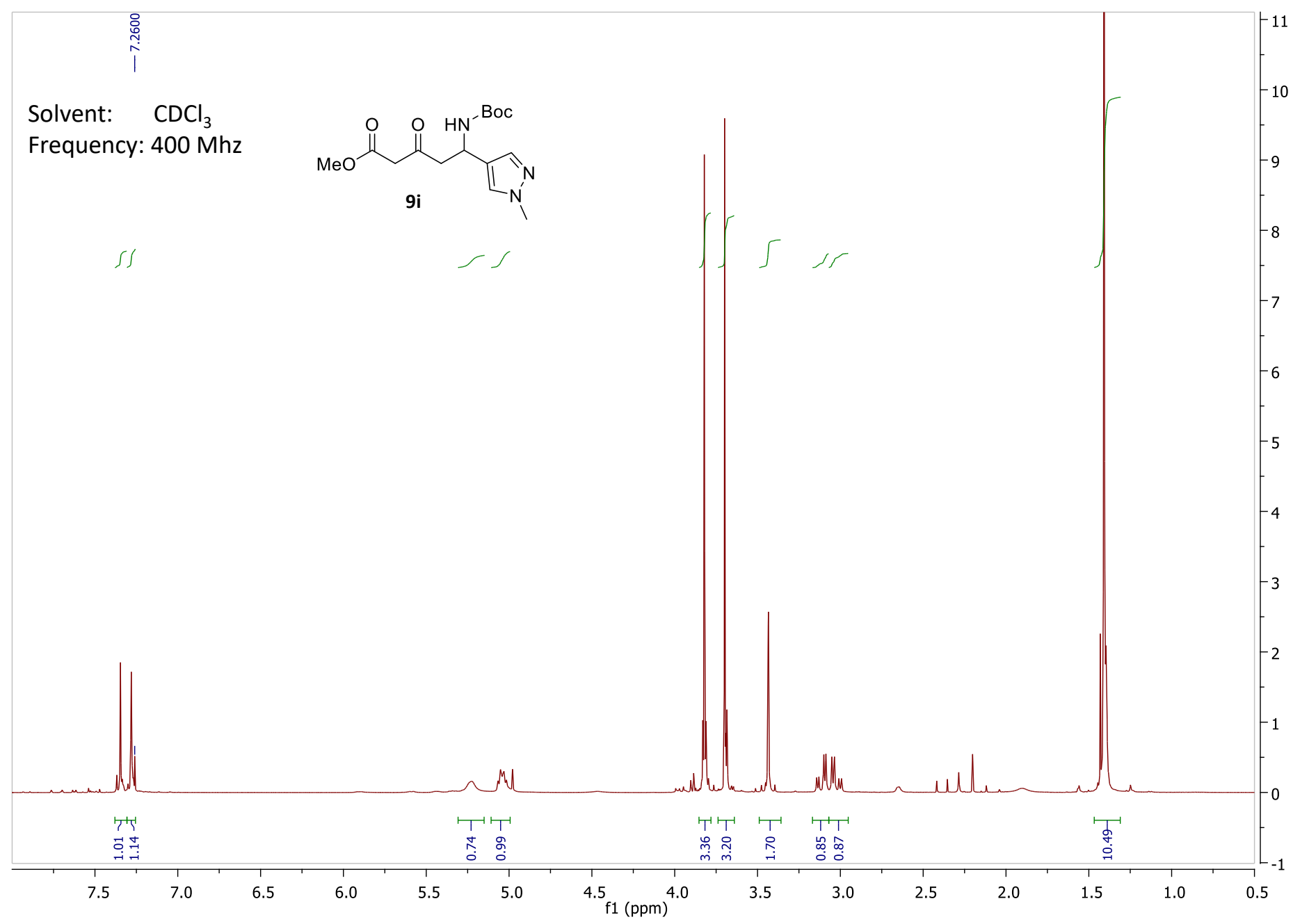

200.9240
167.4362
159.0186
155.1653
133.3685
127.5459
114.1573
79.8531
77.1600
55.3794
52.5093
50.4746
49.4781
48.8998
28.4421
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
OMe
9f
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

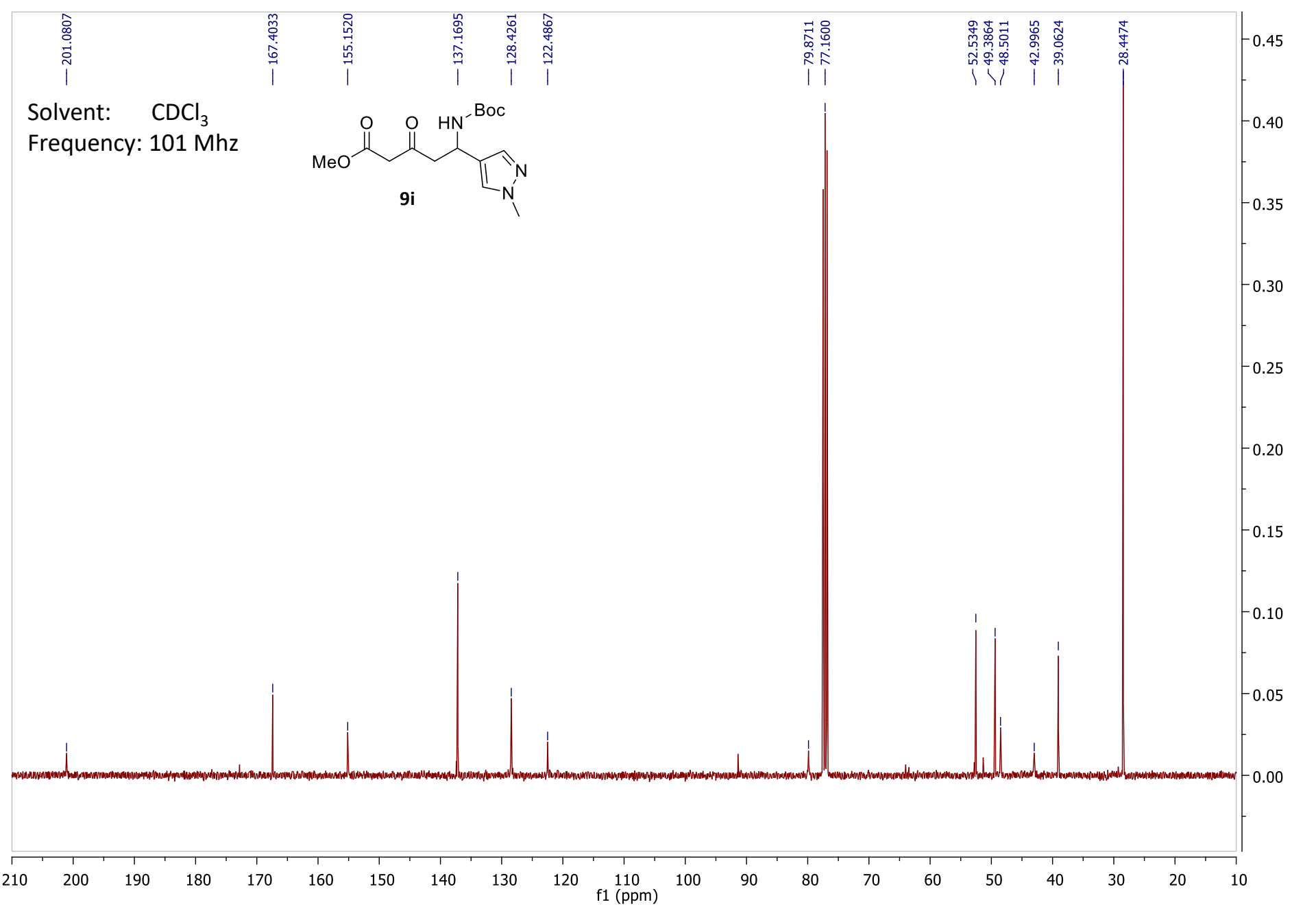

Solvent: CDCl3
Frequency: 400 Mhz
MeO
O
O
HN
Boc
N
9g
7.2600
f1 (ppm)

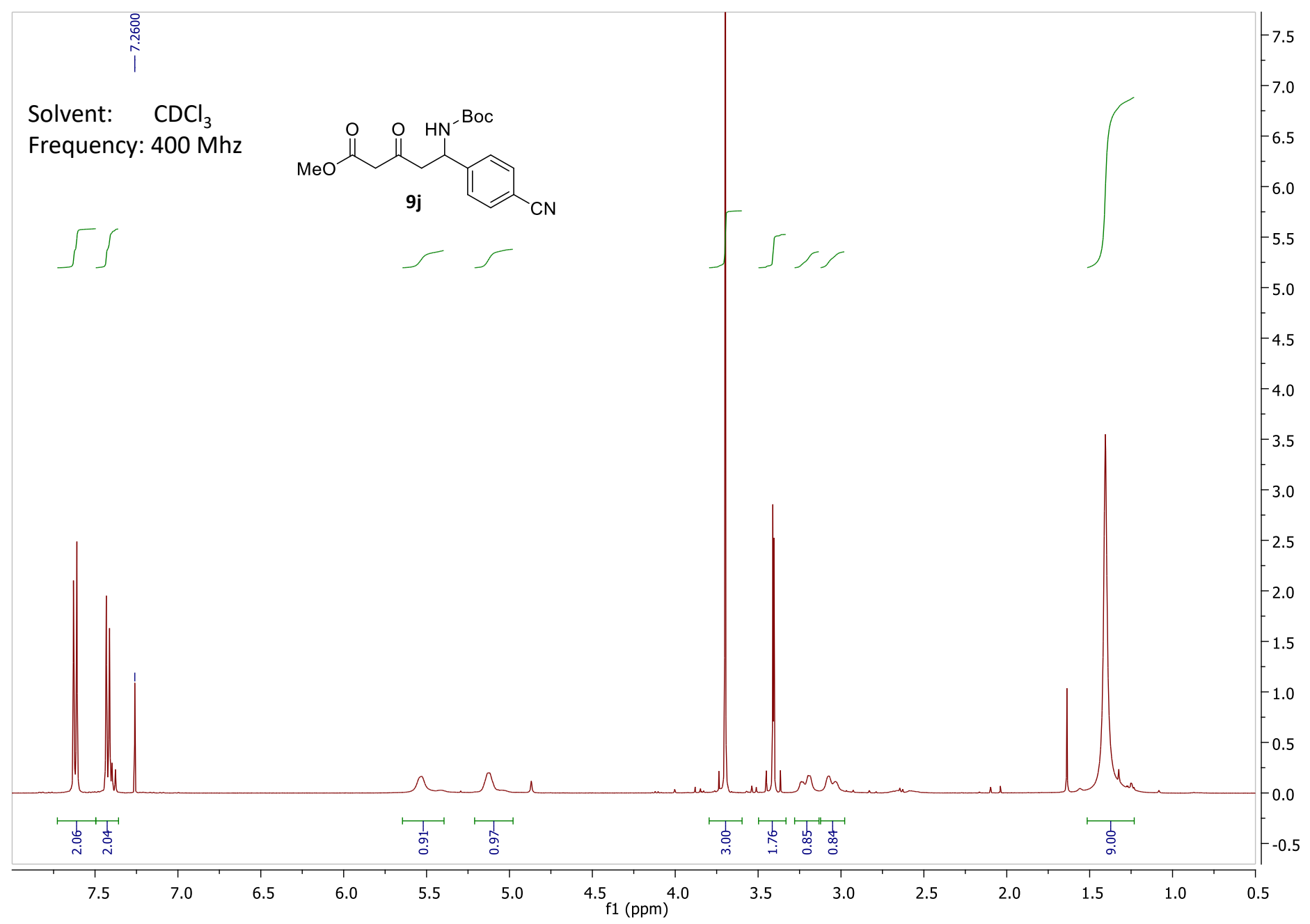

200.4464
167.2742
155.1397
148.8869
148.2071
136.9438
134.2235
123.5350
91.8549
80.2584
77.1600
52.6300
51.4566
49.3188
48.8157
48.0541
28.3969
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
N
9g
0.30
0.28
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

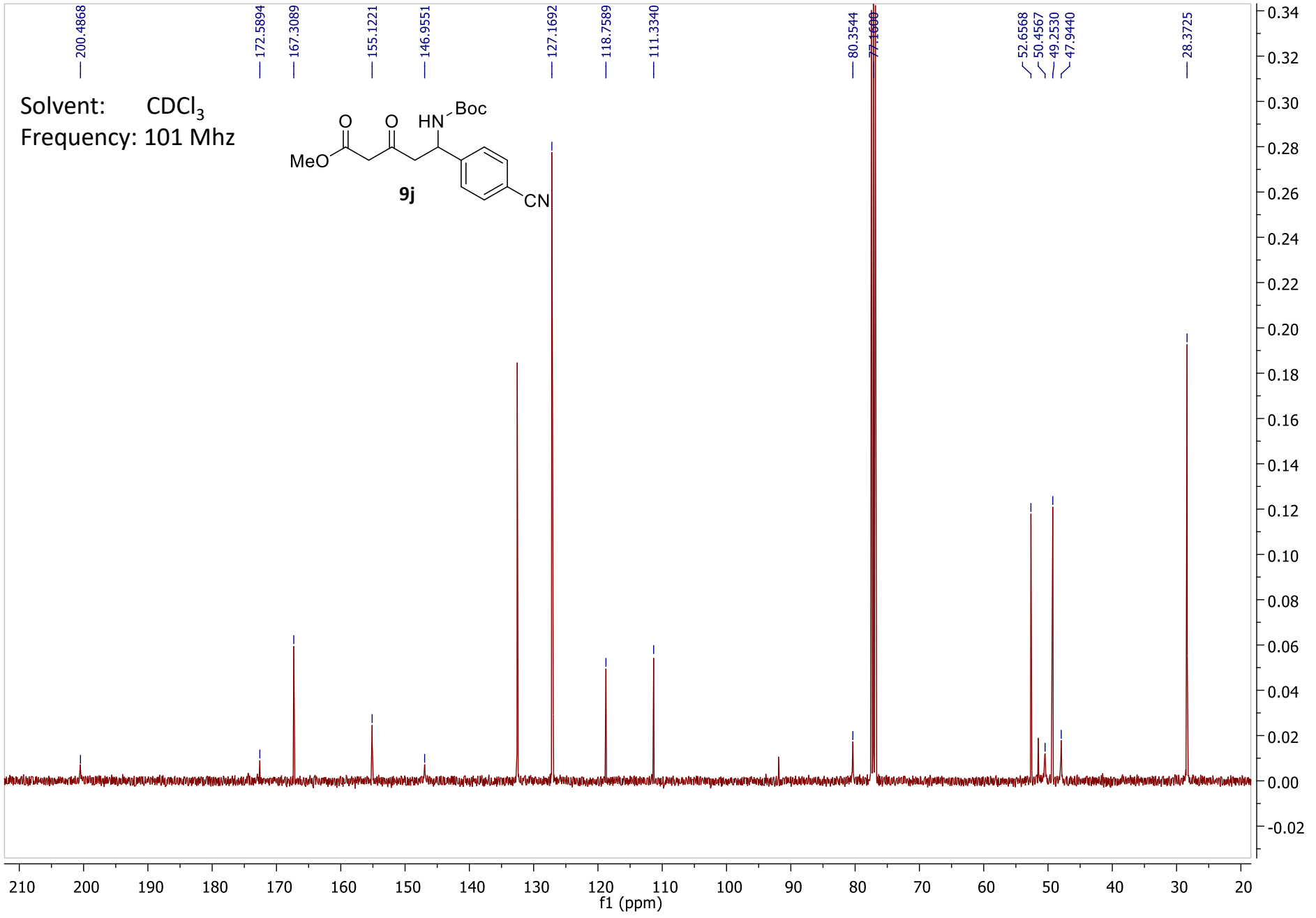

Solvent: CDCl3
Frequency: 400 Mhz
MeO
O
O
HN
Boc
S
N
9h
7.2600
0.92
1.09
0.74
3.13
2.00
0.95
0.98
3.03
9.56
f1 (ppm)


200.1561
167.2061
154.8370
150.4103
149.8815
132.6669
91.8117
80.4144
77.1600
52.6732
51.4874
49.3689
49.0297
44.5175
28.4031
15.4725
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
S
N
9h
f1 (ppm)


7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
HN
Boc
MeO
N
N
9i
1.01
1.14
0.74
0.99
3.36
3.20
1.70
0.85
0.87
10.49
f1 (ppm)

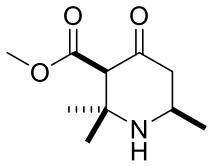

201.0807
167.4033
155.1520
137.1695
128.4261
122.4867
79.8711
77.1600
52.5349
49.3864
48.5011
42.9965
39.0624
28.4474
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
N
N
9i
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
HN
Boc
MeO
CN
9j
2.06
2.04
0.91
0.97
3.00
1.76
0.85
0.84
9.00
f1 (ppm)


200.4868
172.5894
167.3089
155.1221
146.9551
127.1692
118.7589
111.3340
80.3544
77.1600
52.6568
50.4567
49.2530
47.9440
28.3725
Solvent: CDCl3
Frequency: 101 Mhz
O
O
HN
Boc
MeO
CN
9j
f1 (ppm)

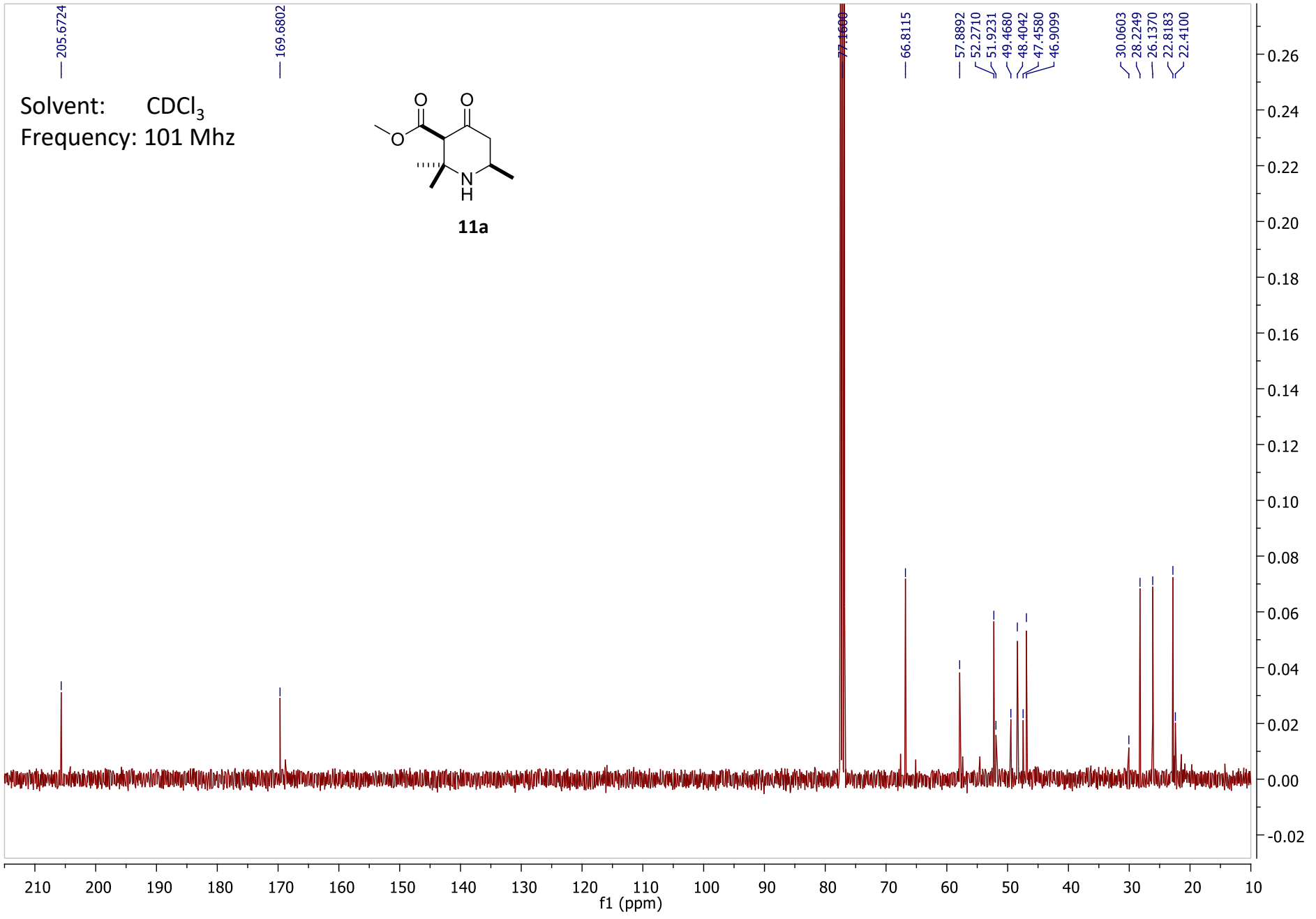
Solvent: $CDCl_3$

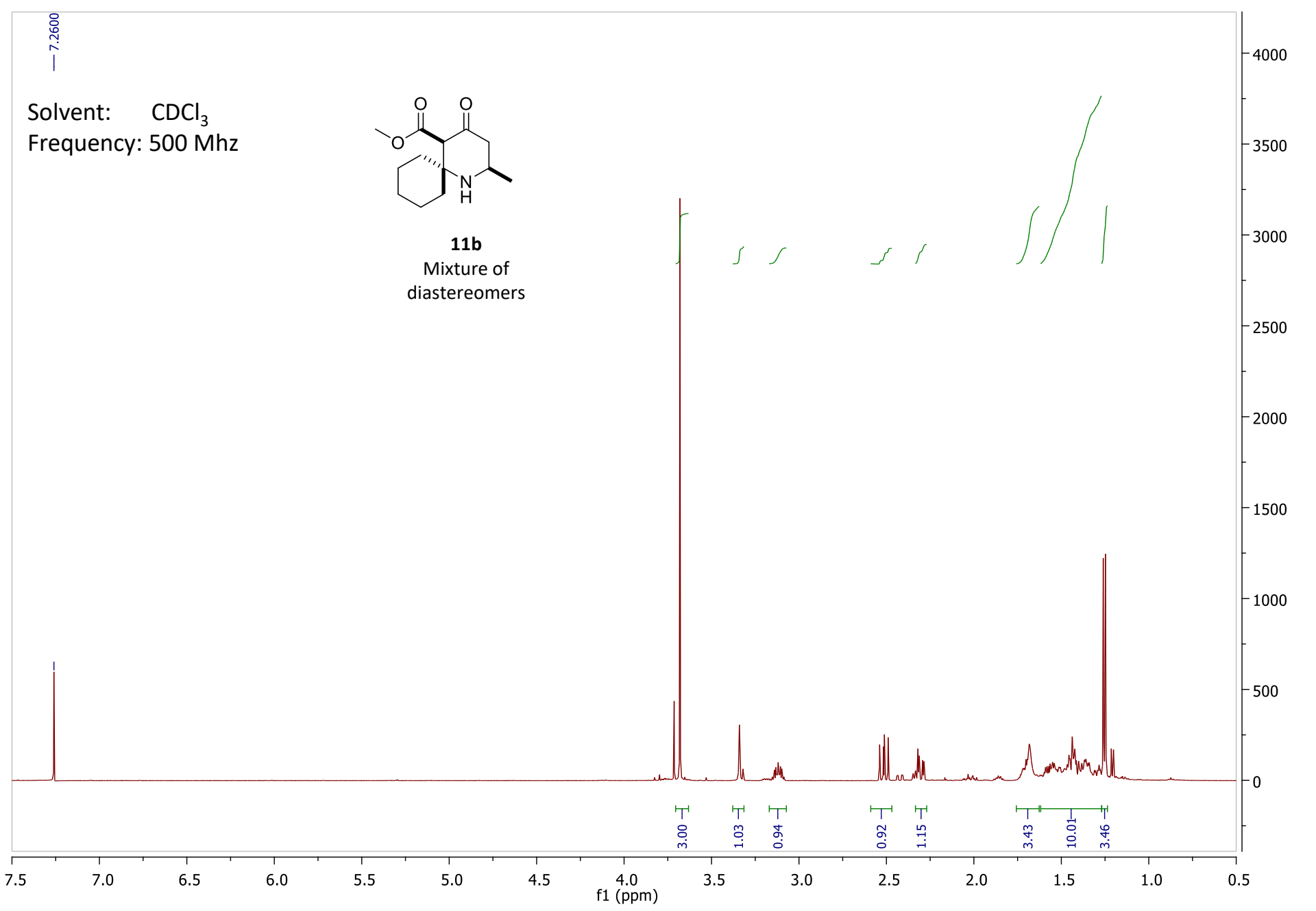
Frequency: 500 Mhz

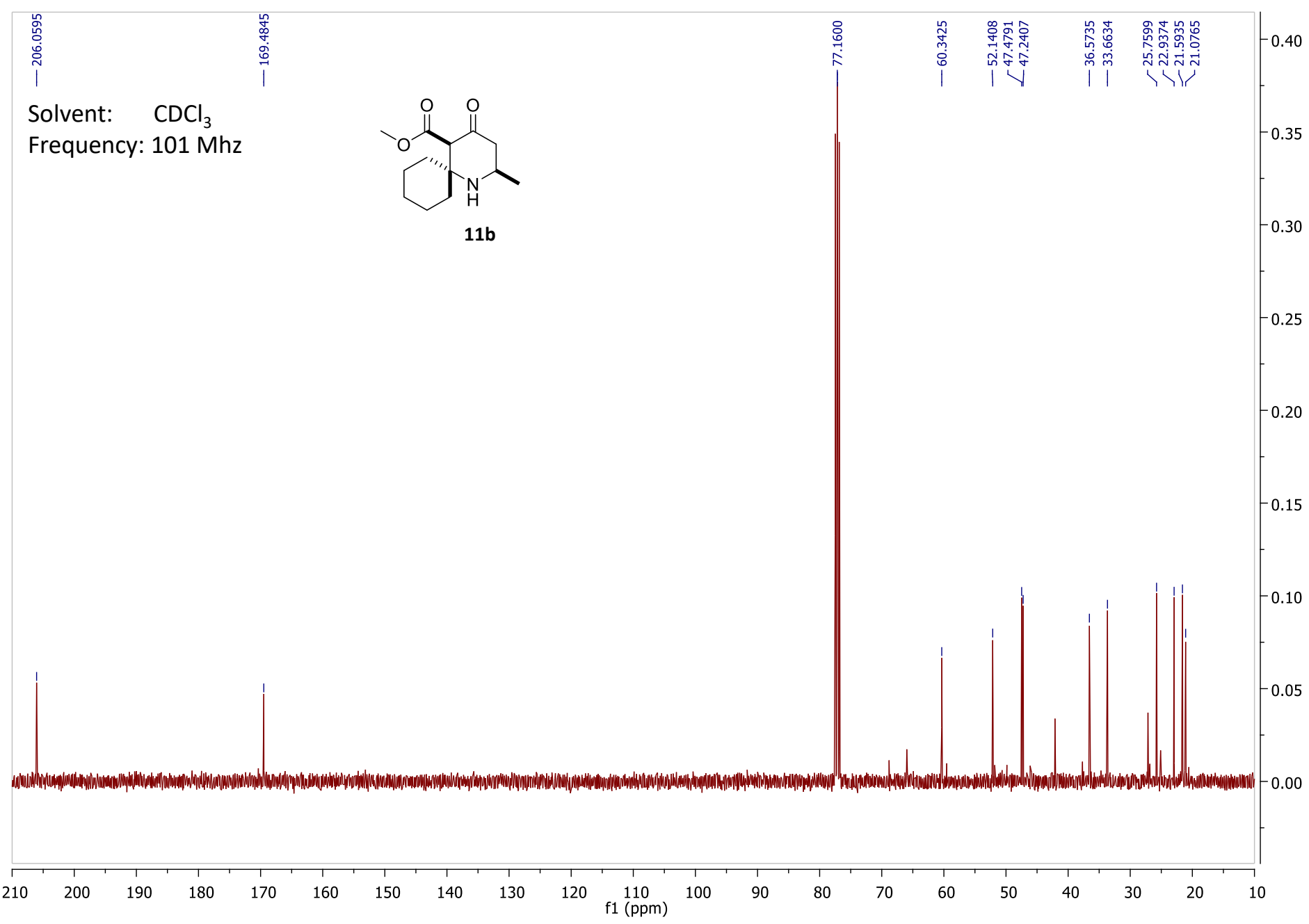


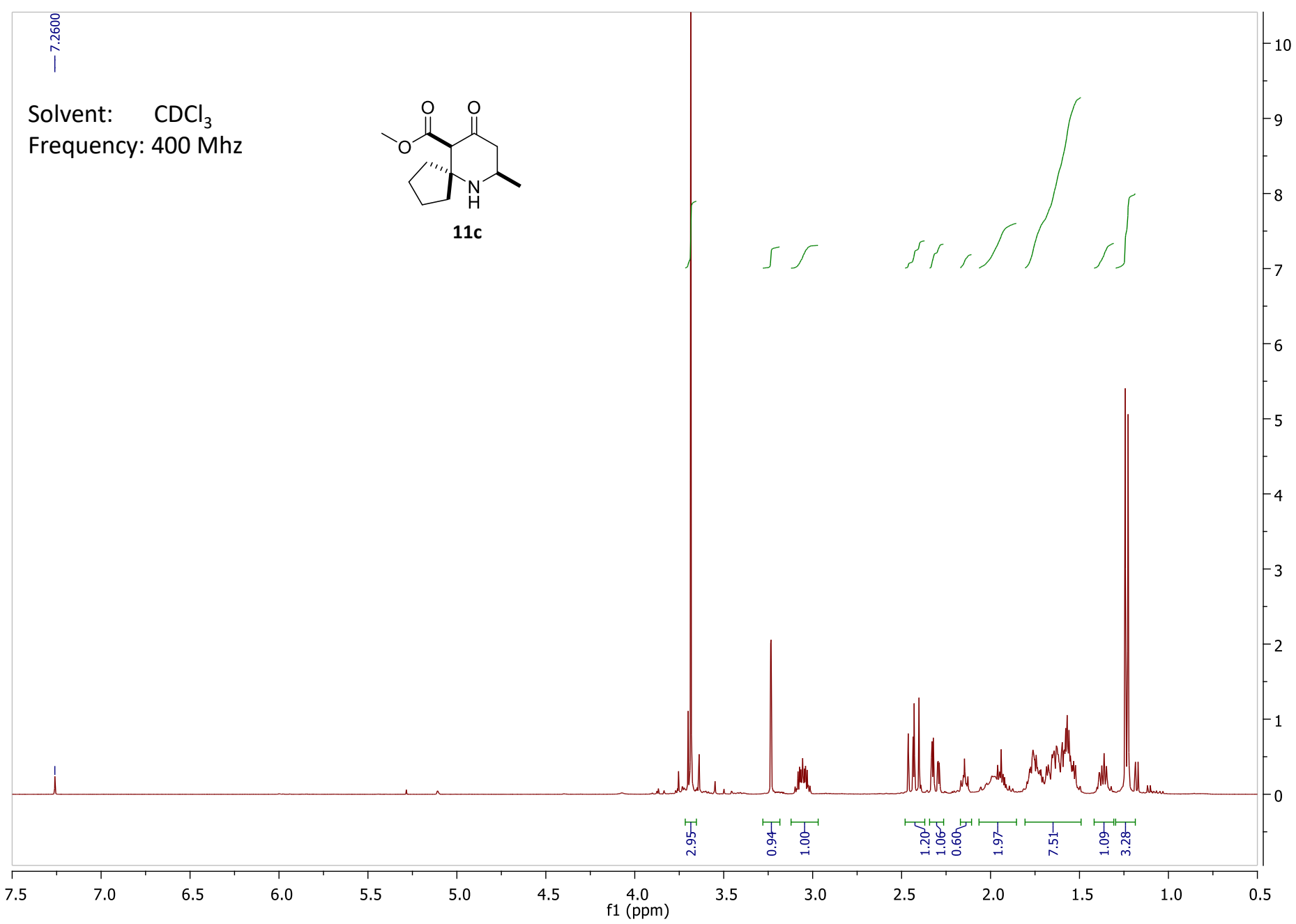
11a

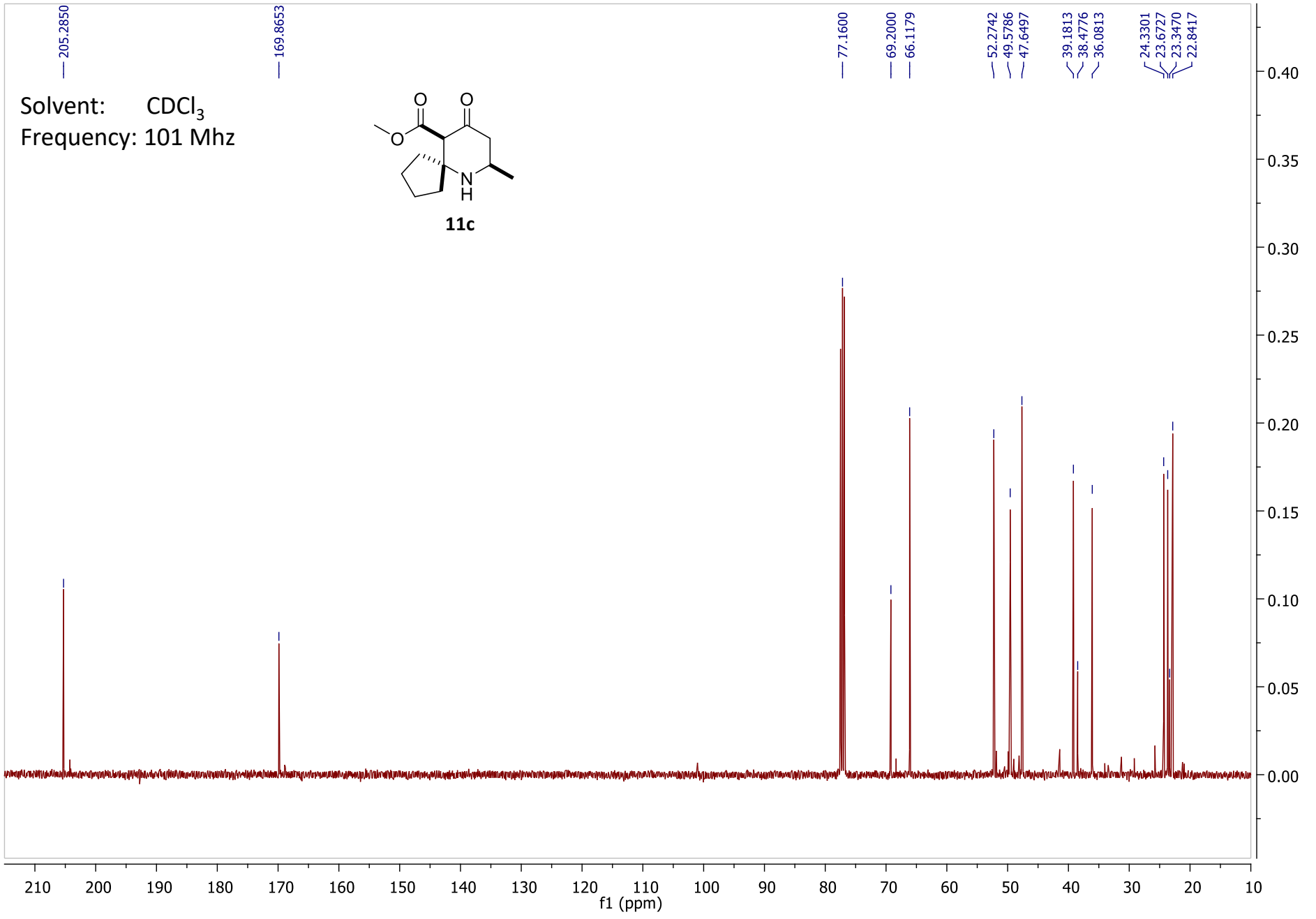
Mixture of diastereomers

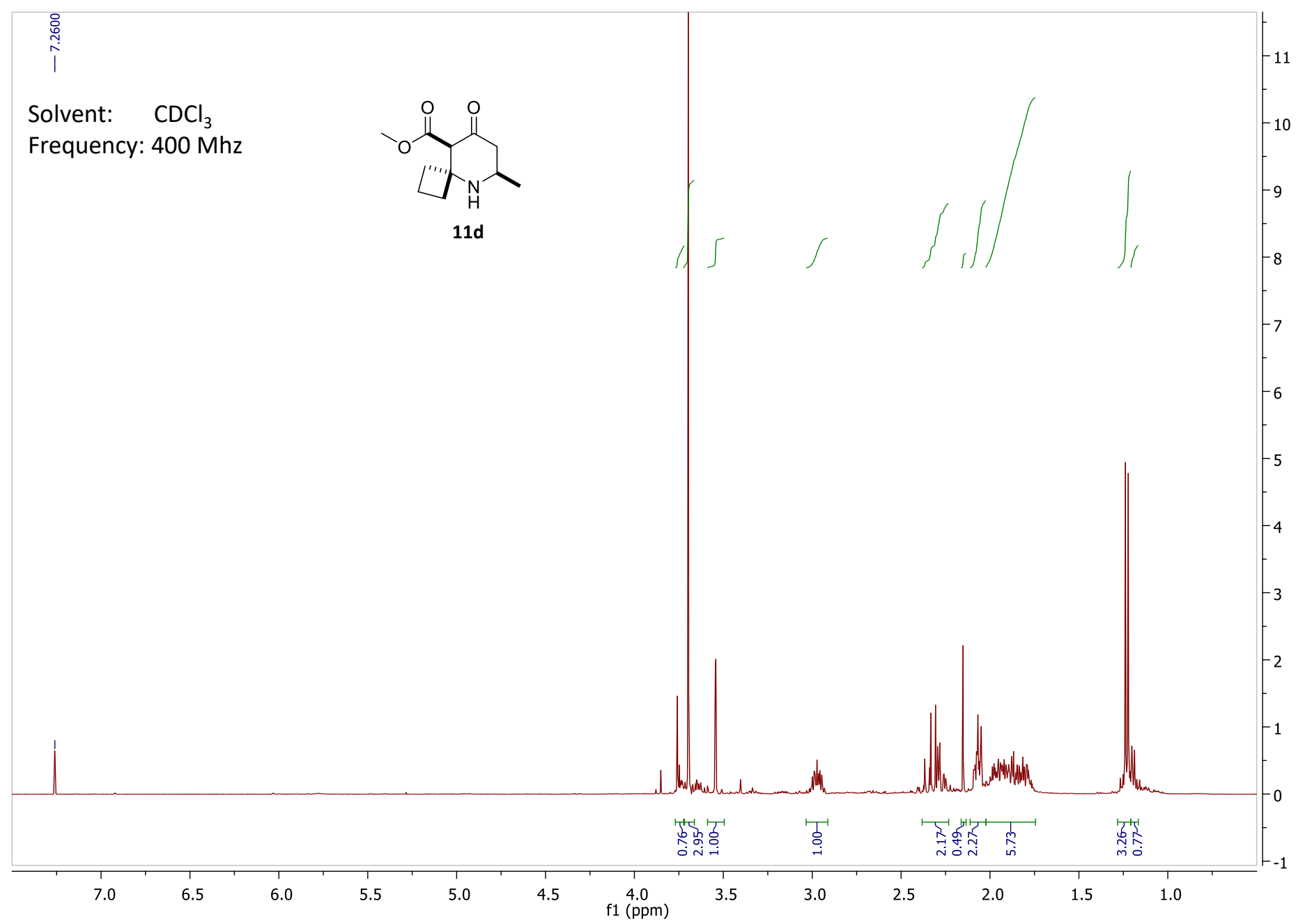

205.6724
169.6802
77.1600
66.8115
57.8892
52.2710
51.9231
49.4680
48.4042
47.4580
46.9099
30.0603
28.2249
26.1370
22.8183
22.4100
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
11a
0.26
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

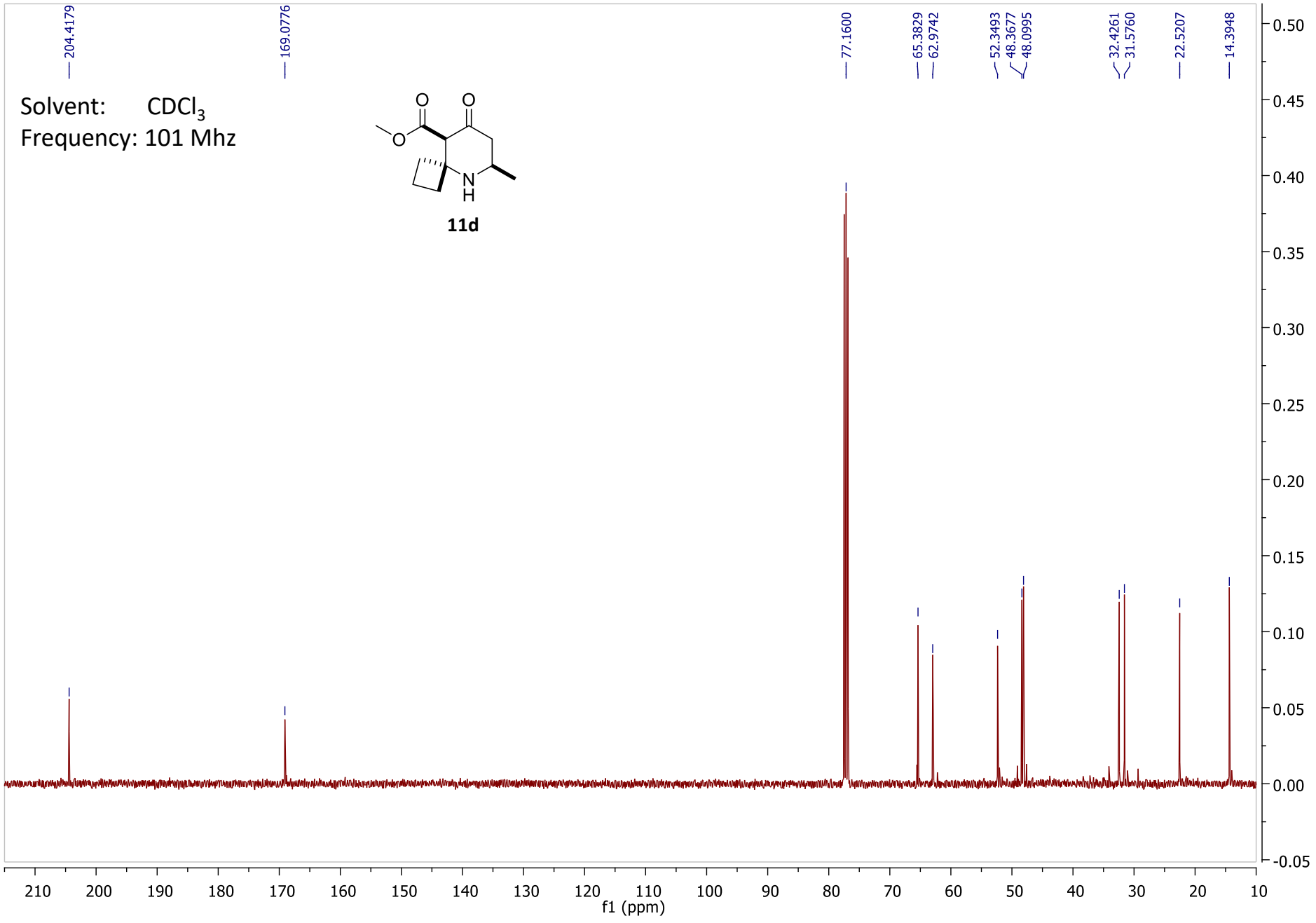

7.2600
Solvent: CDCl3
Frequency: 500 Mhz
O
O
O
N
H
11b
Mixture of
diastereomers
4000
3500
3000
2500
2000
1500
1000
500
0
3.00
1.03
0.94
0.92
1.15
3.43
10.01
3.46
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

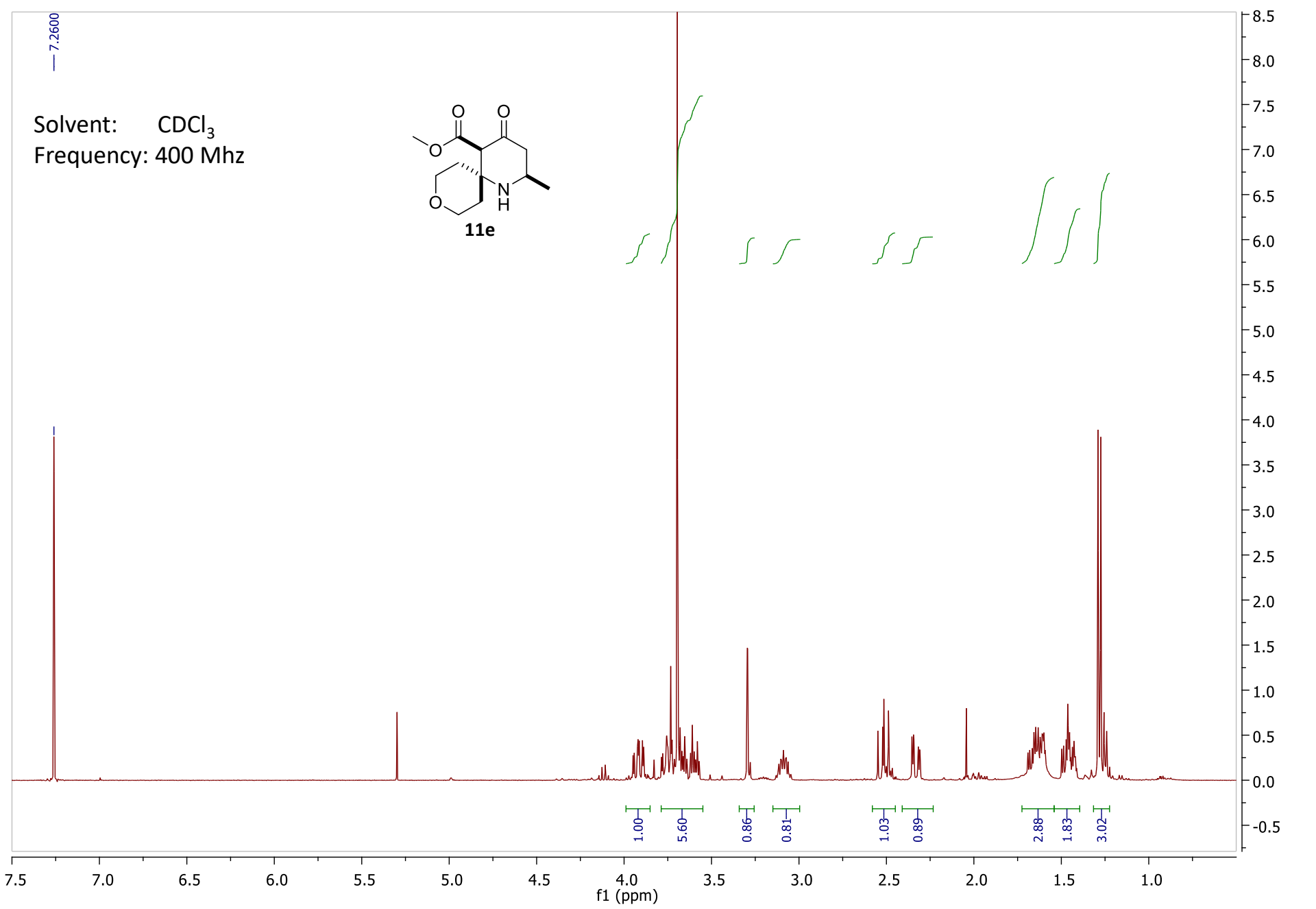

206.0595
169.4845
77.1600
60.3425
52.1408
47.4791
47.2407
36.5735
33.6634
25.7599
22.9374
21.5935
21.0765
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
11b
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
O
N
H
11c
2.95
0.94
1.00
1.20
1.06
0.60
1.97
7.51
1.09
3.28
f1 (ppm)


205.2850
169.8653
77.1600
69.2000
66.1179
52.2742
49.5786
47.6497
39.1813
38.4776
36.0813
24.3301
23.6727
23.3470
22.8417
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
11c
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

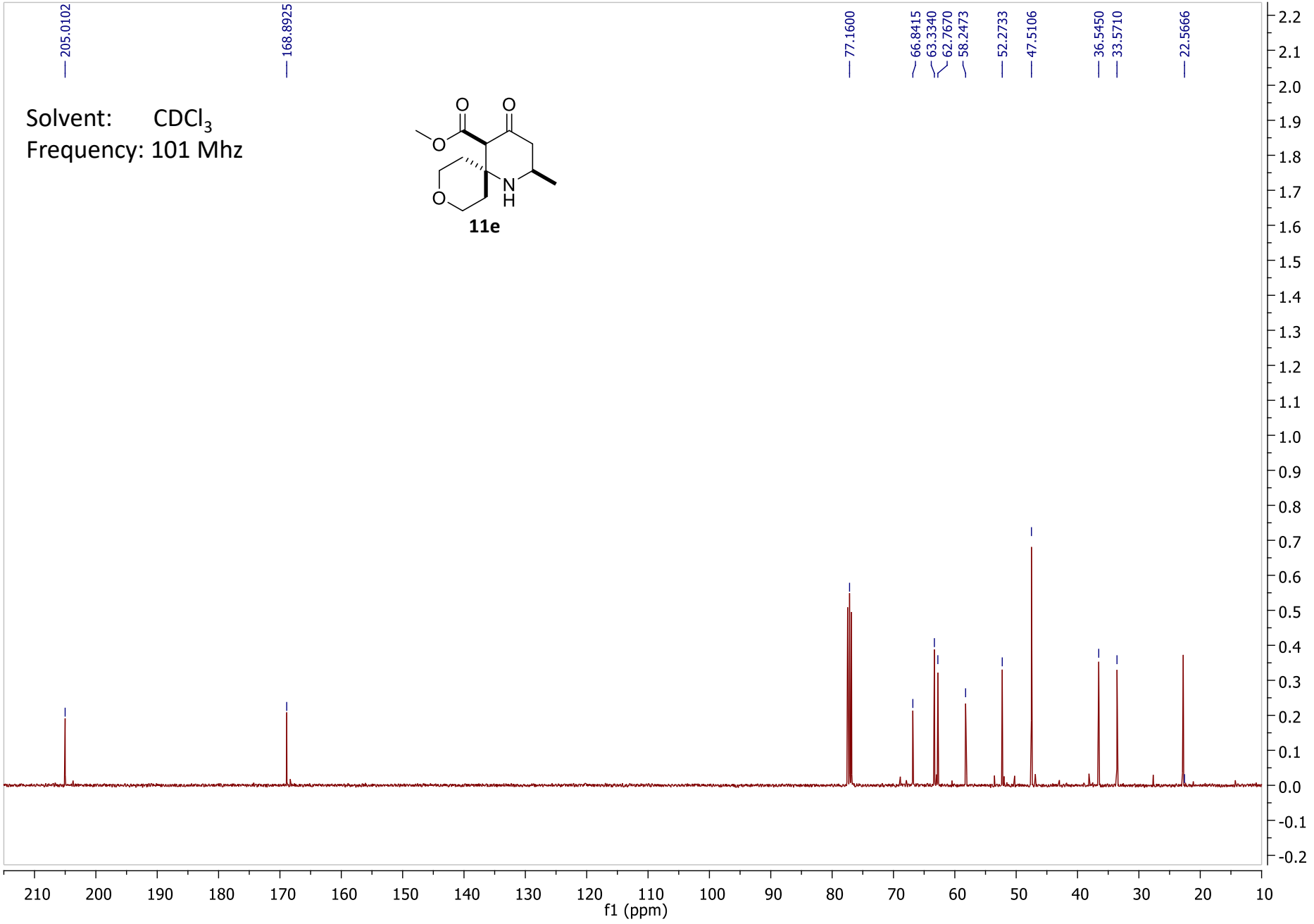

7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
O
N
H
11d
0.76
2.95
1.00
1.00
2.17
0.49
2.27
5.73
3.26
0.77
11
10
9
8
7
6
5
4
3
2
1
0
-1
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

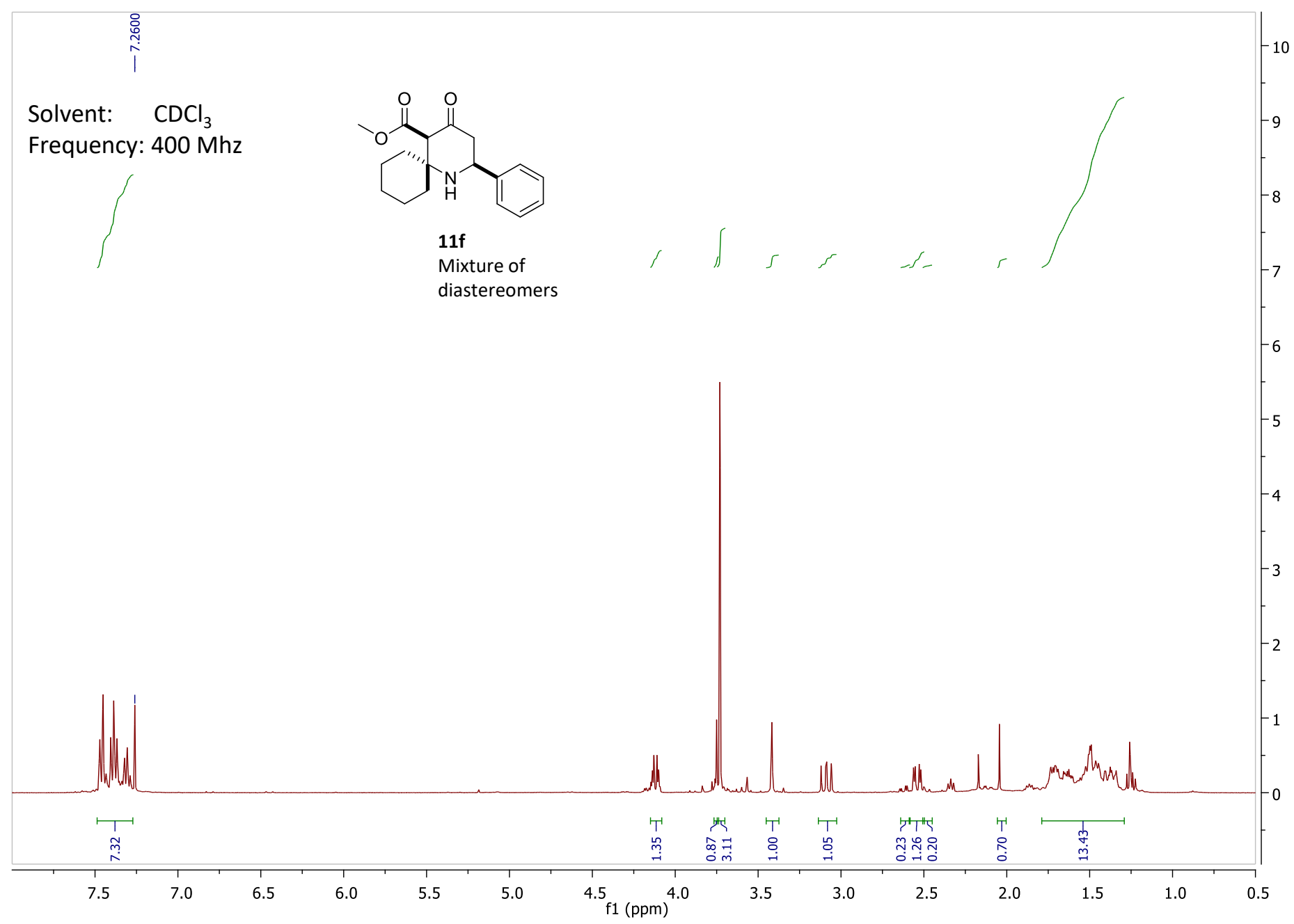

204.4179
169.0776
77.1600
65.3829
62.9742
52.3493
48.3677
48.0995
32.4261
31.5760
22.5207
14.3948
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
11d
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

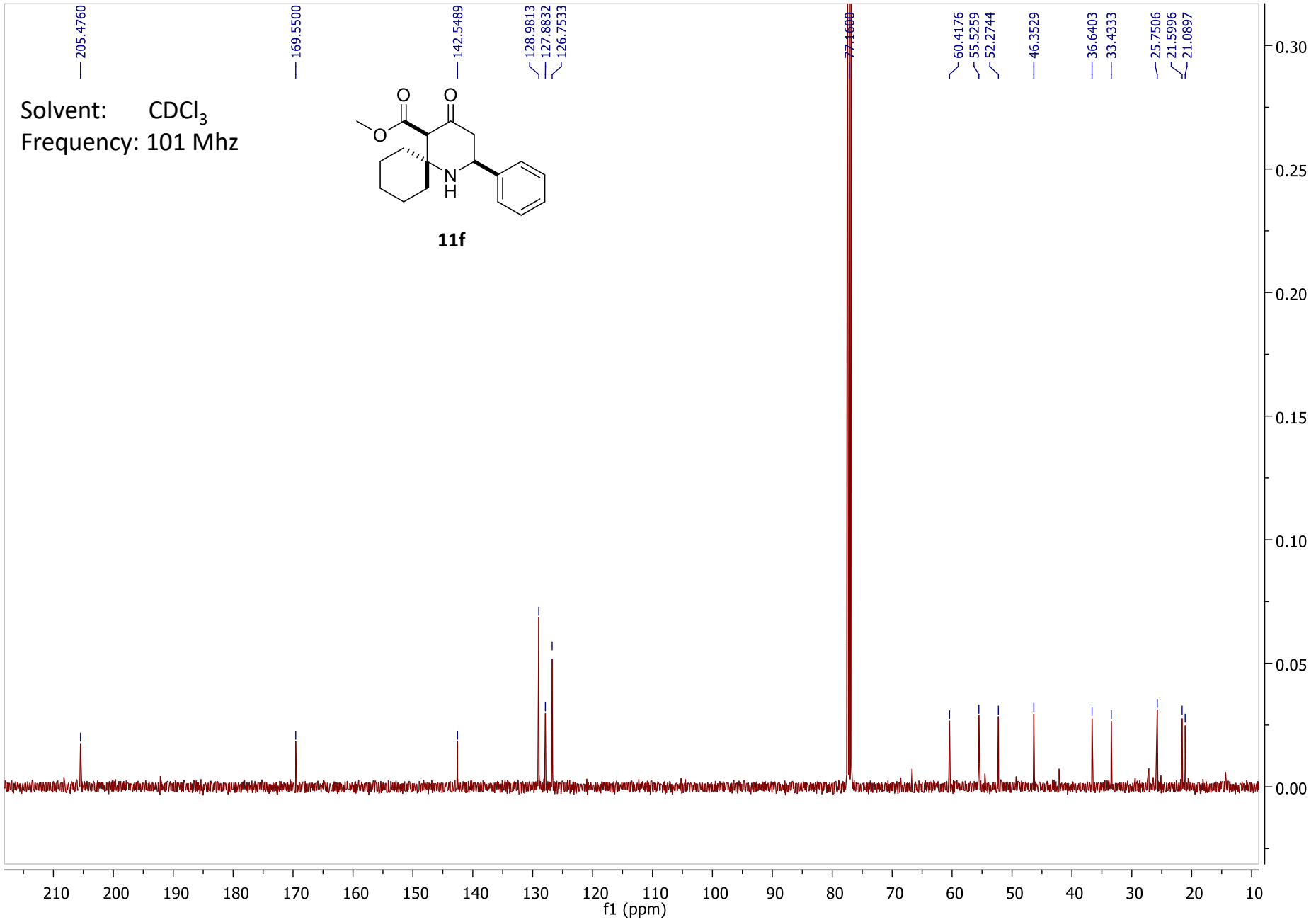

7.2600
Solvent: $CDCl_3$
Frequency: 400 Mhz
11e
1.00
5.60
0.86
0.81
1.03
0.89
2.88
1.83
3.02
f1 (ppm)

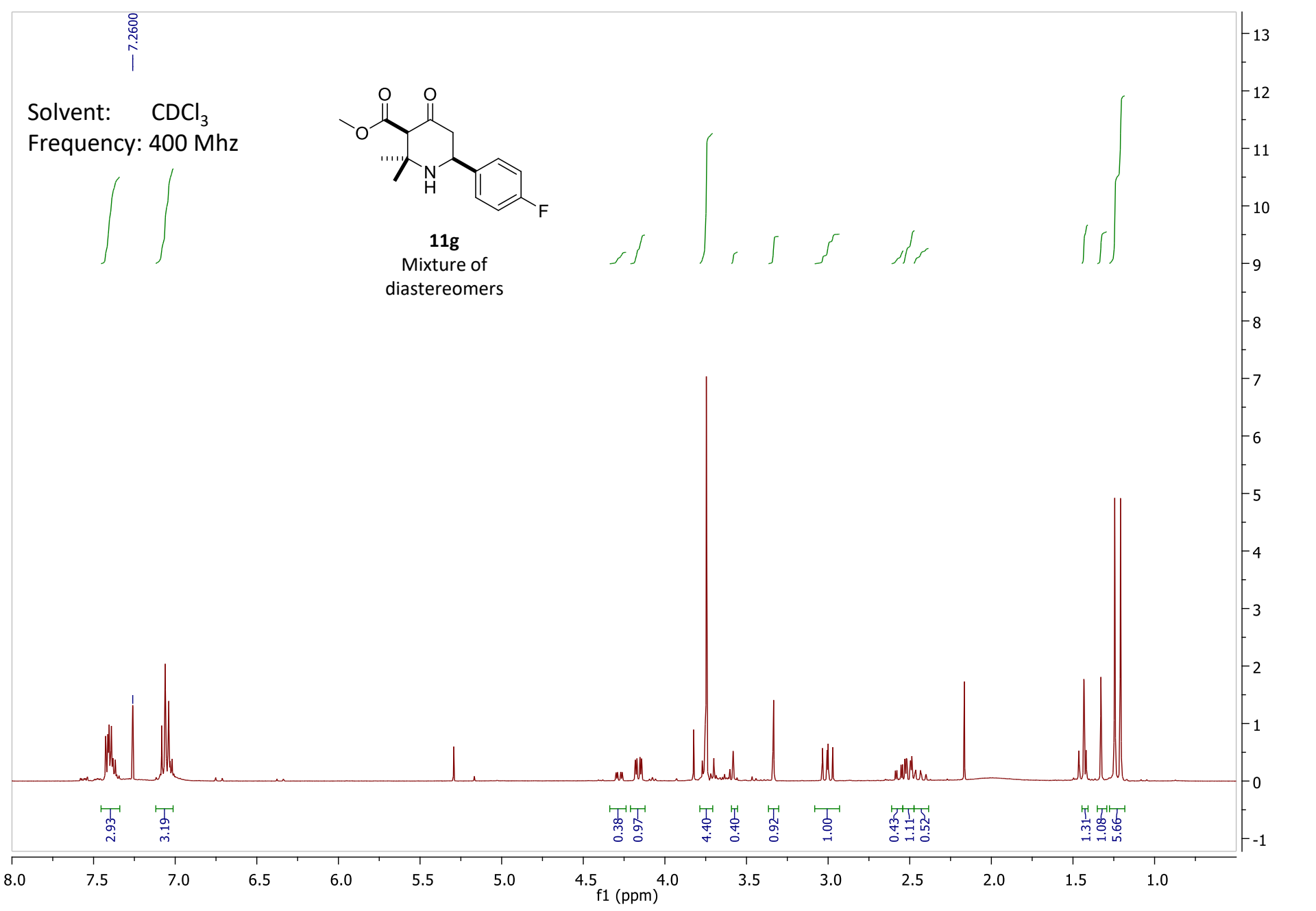
Solvent: $CDCl_3$
Frequency: 101 Mhz

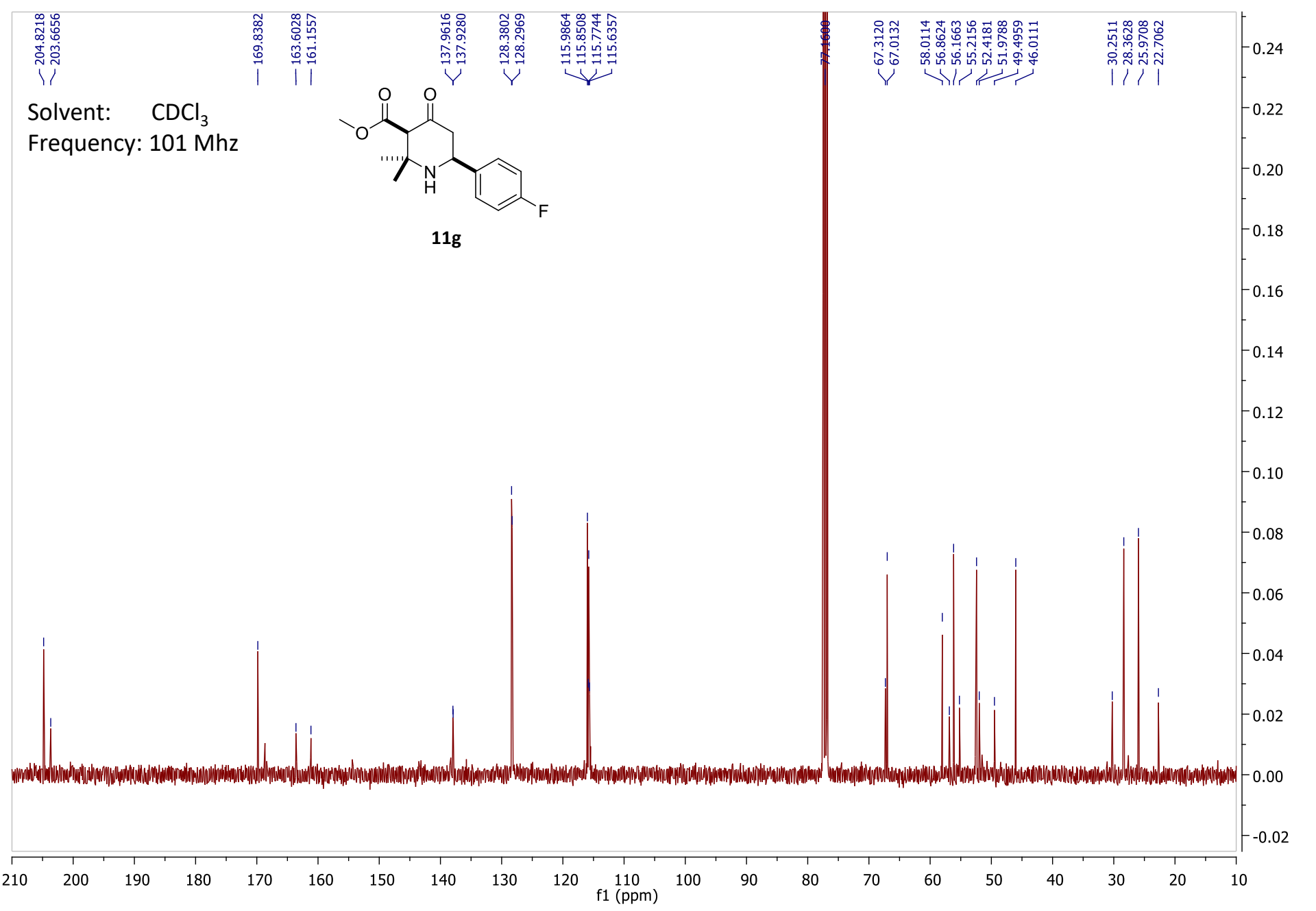
11e




7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
O
N
H
11f
Mixture of
diastereomers
7.32
1.35
0.87
3.11
1.00
1.05
0.23
1.26
0.20
0.70
13.43
f1 (ppm)


205.4760
169.5500
142.5489
128.9813
127.8832
126.7533
77.1600
60.4176
55.5259
52.2744
46.3529
36.6403
33.4333
25.7506
21.5996
21.0897
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
11f
0.30
0.25
0.20
0.15
0.10
0.05
0.00
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

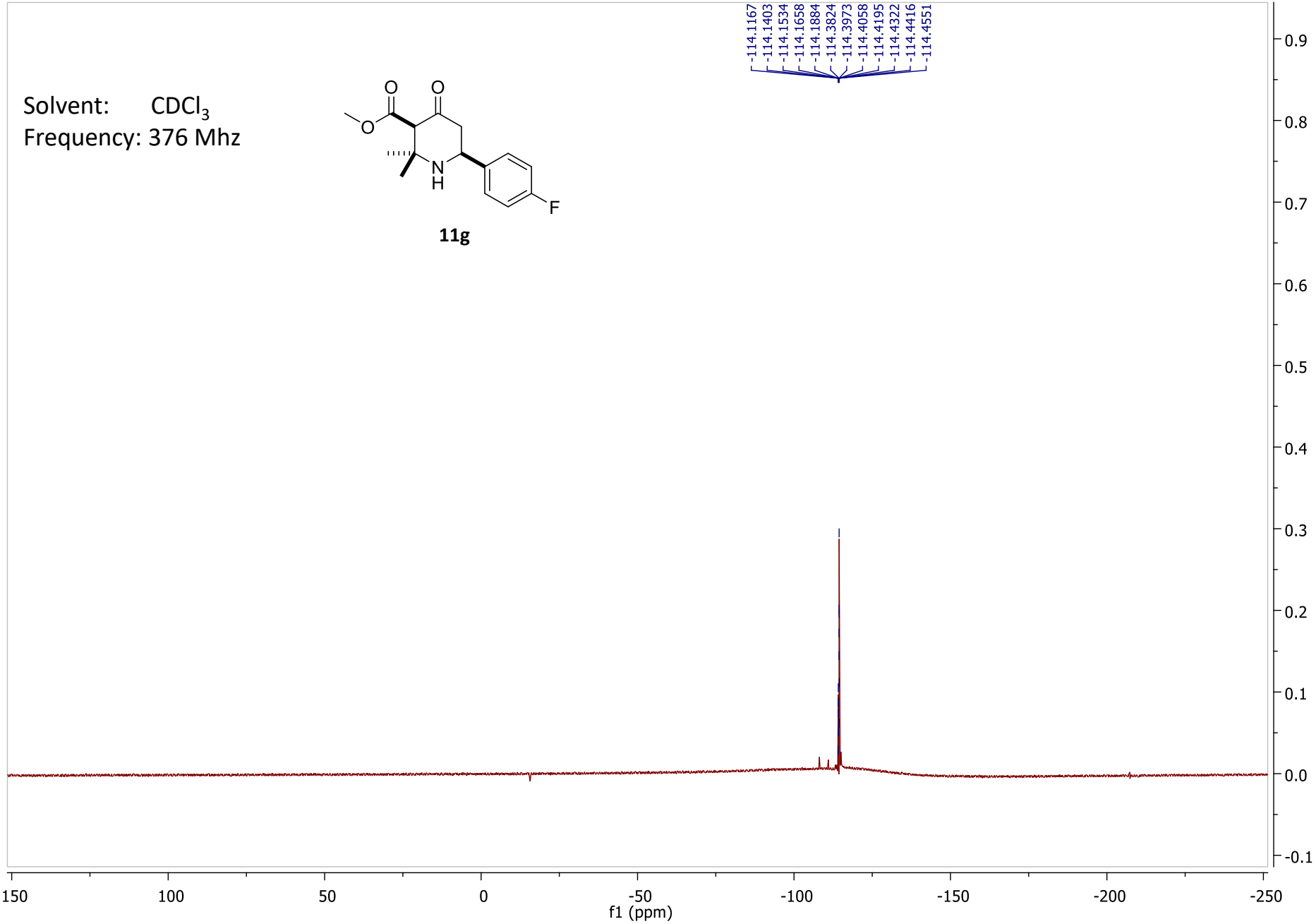

7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
O
N
H
F
11g
Mixture of
diastereomers
2.93
3.19
0.38
0.97
4.40
0.40
0.92
1.00
0.43
1.11
0.52
1.31
1.08
5.66
f1 (ppm)

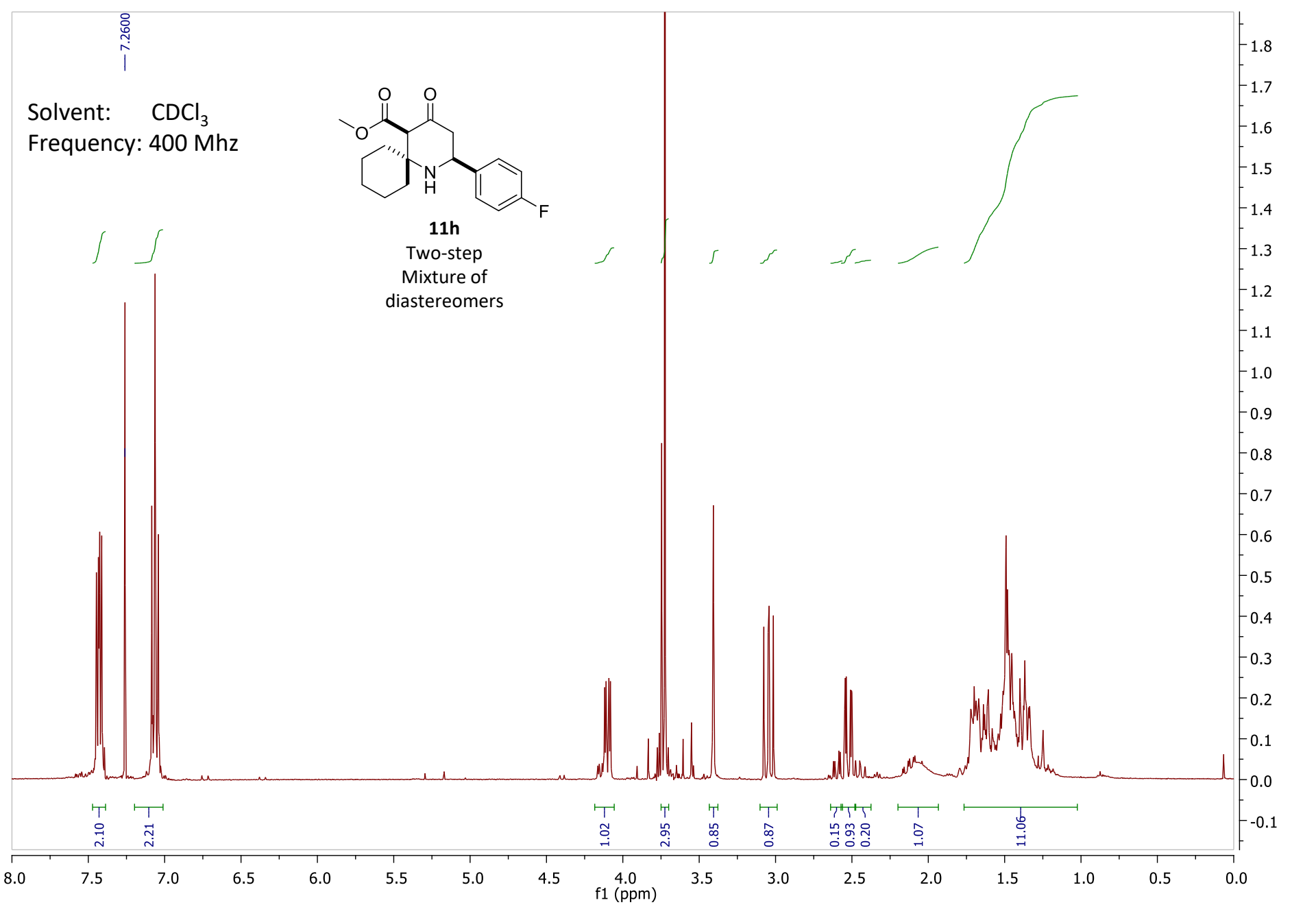

204.8218
203.6656
169.8382
163.6028
161.1557
137.9616
137.9280
128.3802
128.2969
115.9864
115.8508
115.7744
115.6357
77.1600
67.3120
67.0132
58.0114
56.8624
56.1663
55.2156
52.4181
51.9788
49.4959
46.0111
30.2511
28.3628
25.9708
22.7062
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
F
11g
0.24
0.22
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Solvent: $CDCl_3$

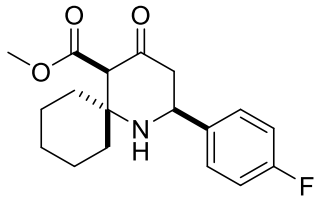
Frequency: 376 Mhz

11g

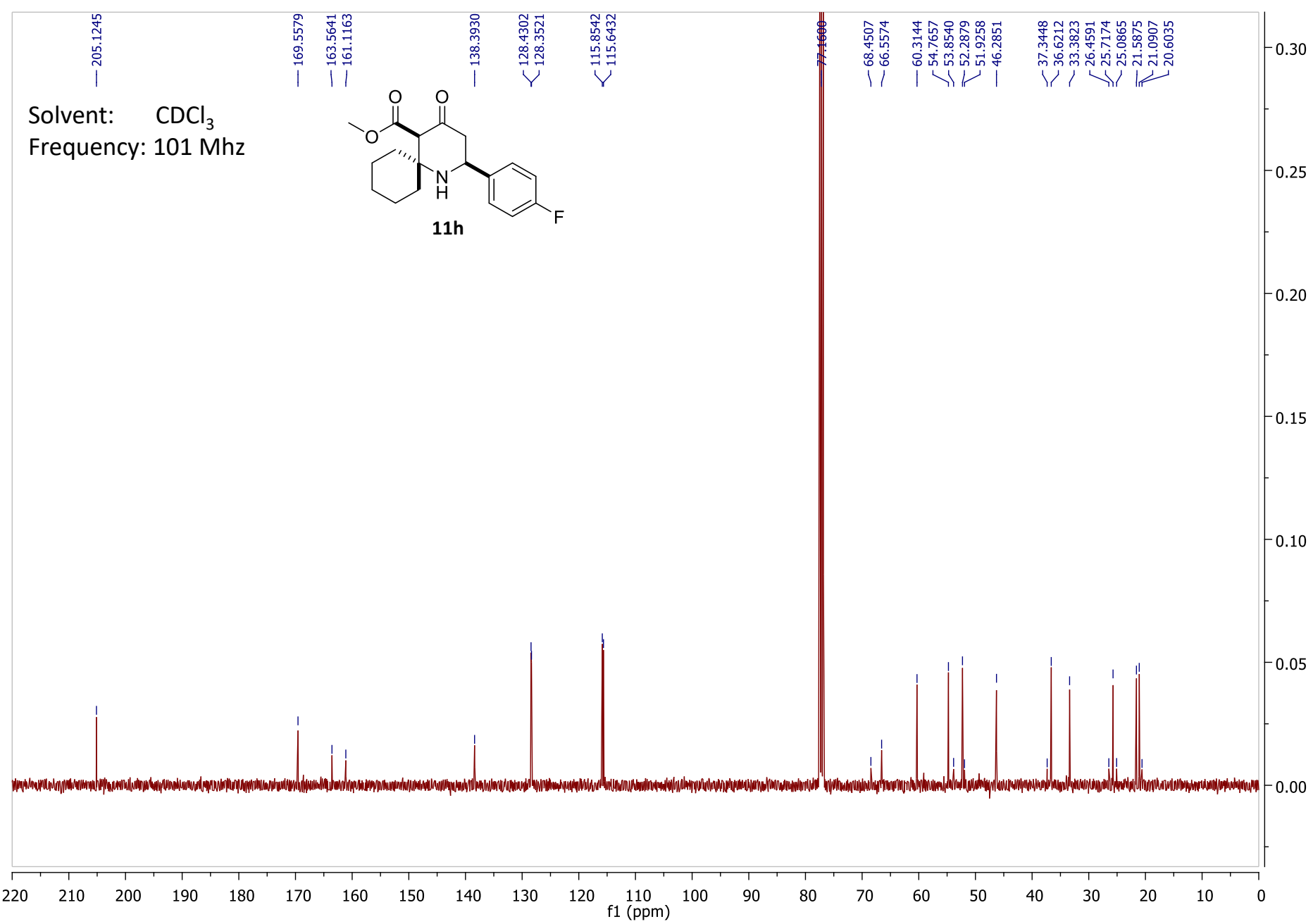



7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
O
N
H
F
11h
Two-step
Mixture of
diastereomers
2.10
2.21
1.02
2.95
0.85
0.87
0.15
0.93
0.20
1.07
11.06
f1 (ppm)

Solvent: $CDCl_3$
Frequency: 400 Mhz

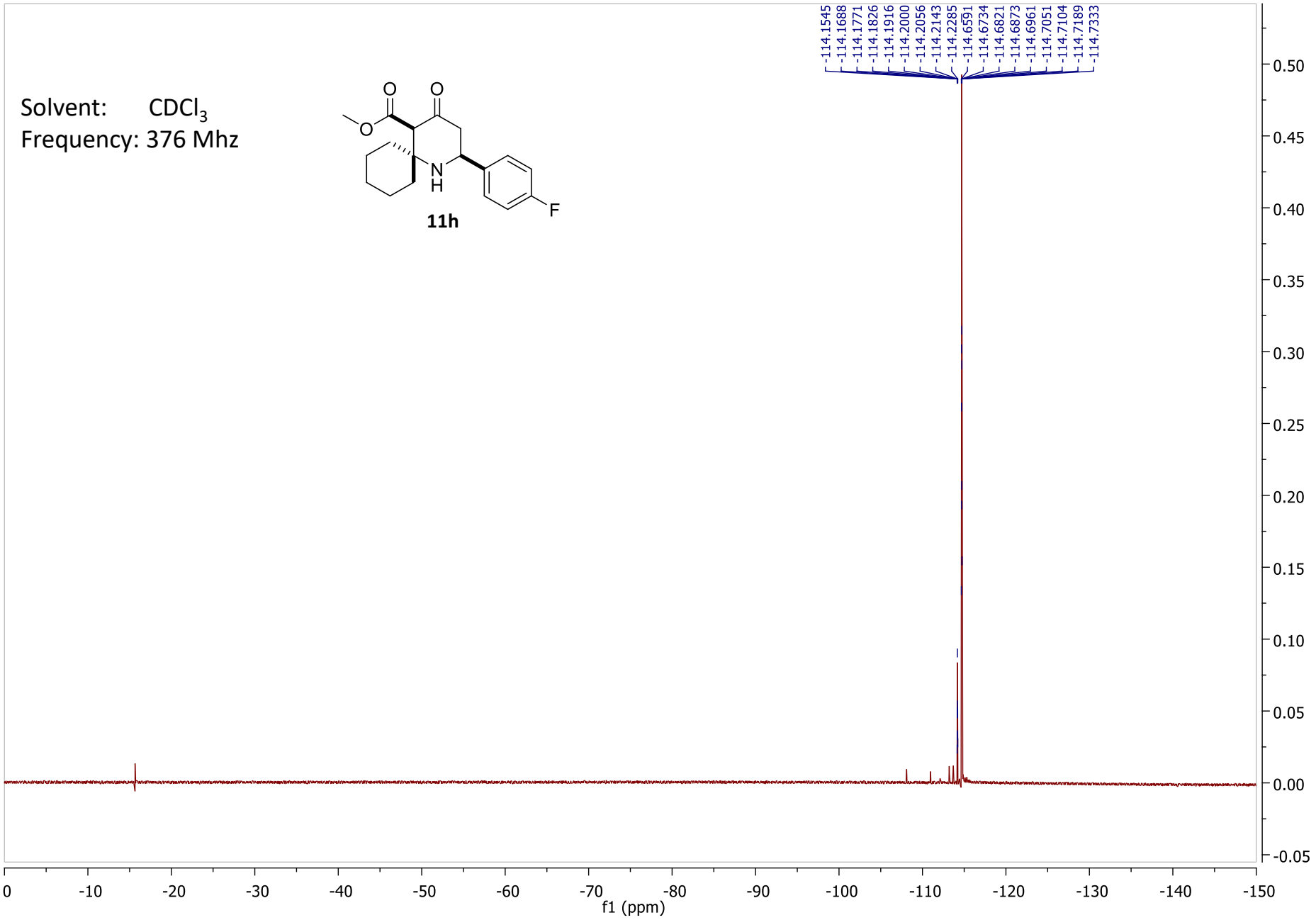


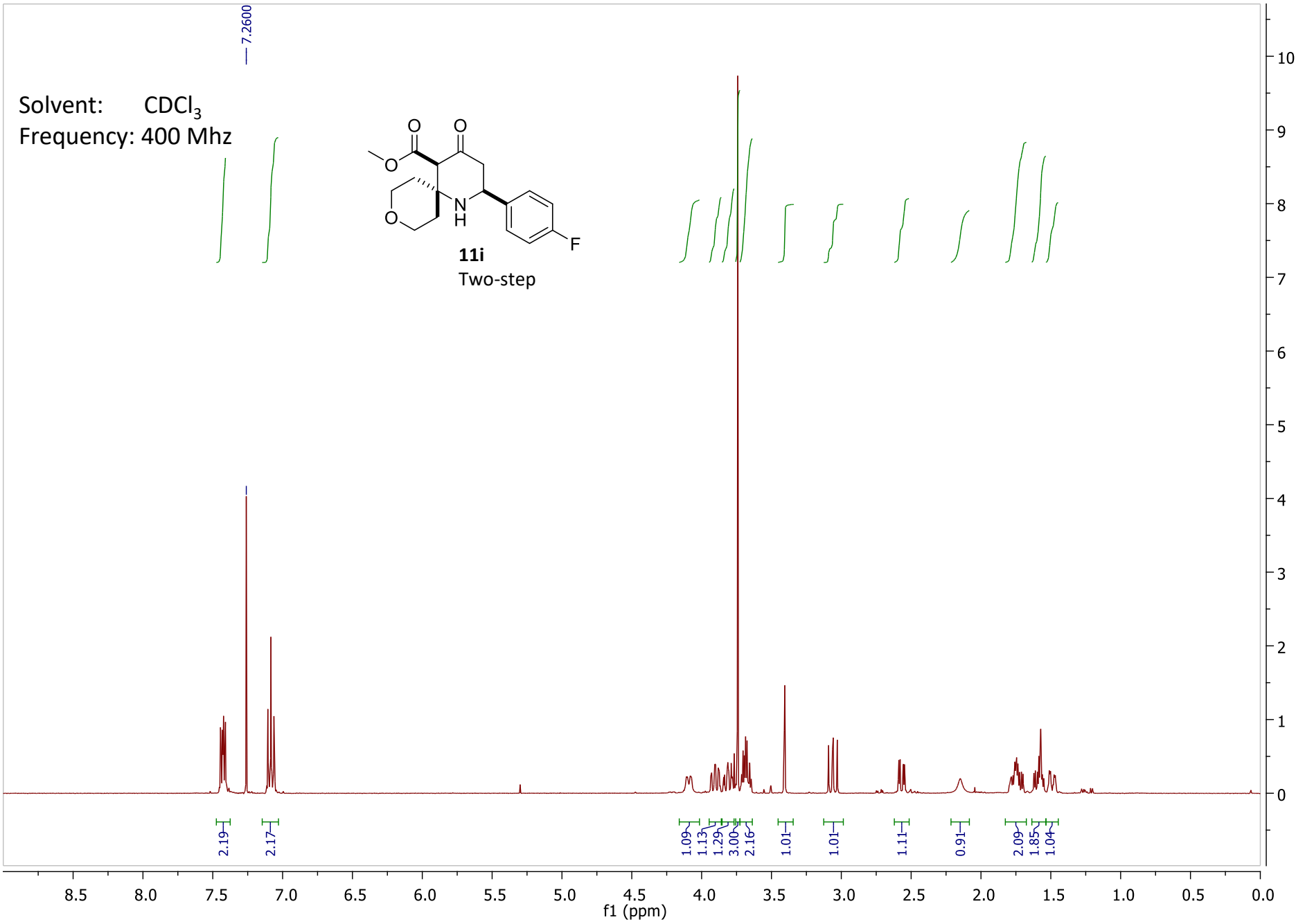
11h
One-pot
Mixture of
diastereomers


205.1245
169.5579
163.5641
161.1163
138.3930
128.4302
128.3521
115.8542
115.6432
77.1600
68.4507
66.5574
60.3144
54.7657
53.8540
52.2879
51.9258
46.2851
37.3448
36.6212
33.3823
26.4591
25.7174
25.0865
21.5875
21.0907
20.6035
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
F
11h
0.30
0.25
0.20
0.15
0.10
0.05
0.00
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Solvent: $CDCl_3$
Frequency: 376 Mhz

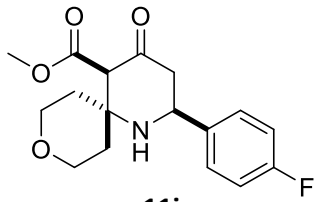
11h




Solvent: $CDCl_3$
Frequency: 400 Mhz
7.2600
O
O
O
N
H
F
11i
Two-step
2.19
2.17
1.09
1.13
1.29
3.00
2.16
1.01
1.01
1.11
0.91
2.09
1.85
1.04
f1 (ppm)

Solvent: $CDCl_3$

Frequency: 400 Mhz

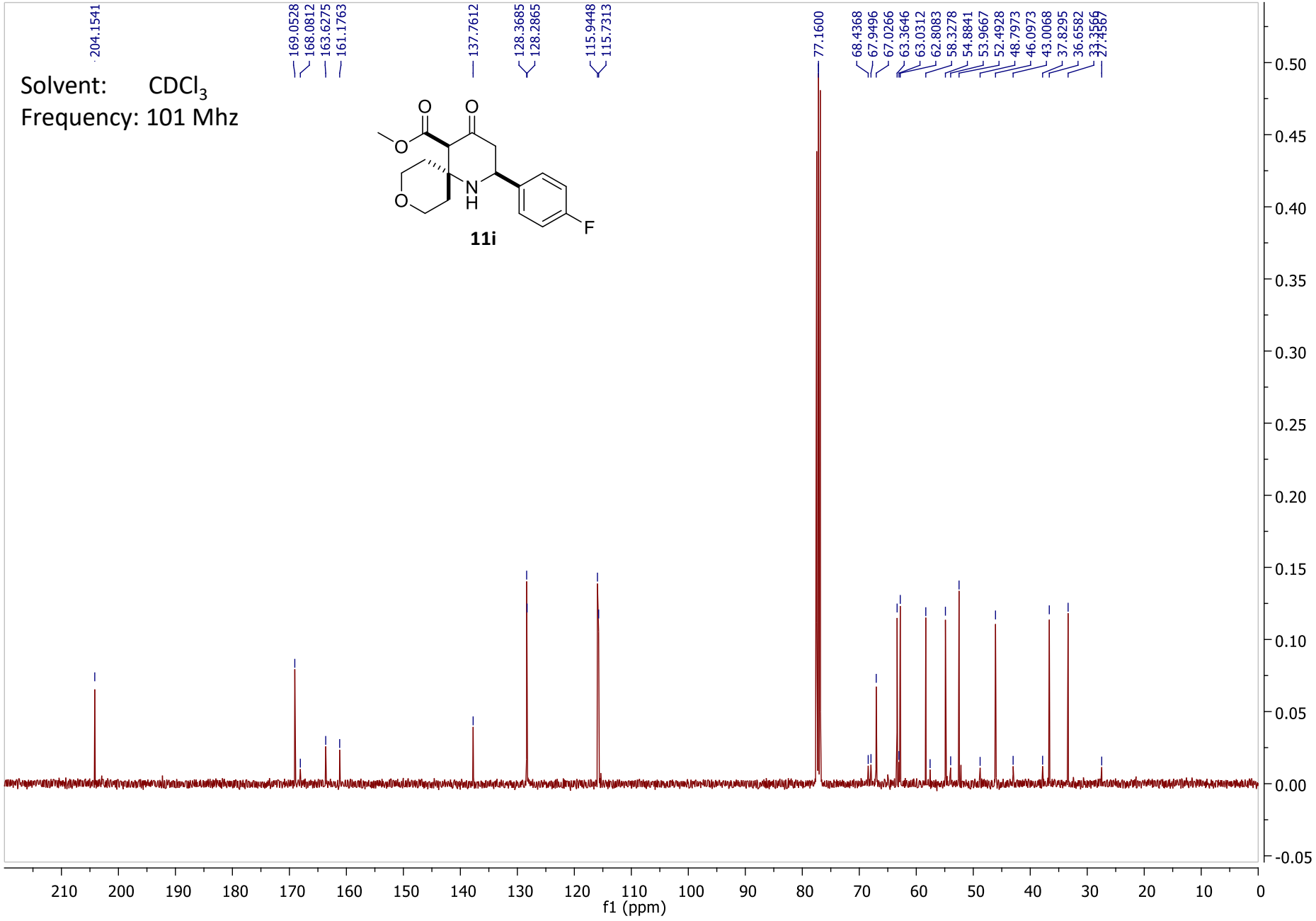


11i

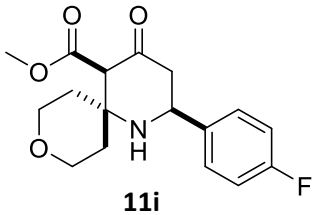
One-pot

Mixture of

diastereomers


Solvent: CDCl3
Frequency: 101 Mhz
204.1541
169.0528
168.0812
163.6275
161.1763
137.7612
128.3685
128.2865
115.9448
115.7313
77.1600
68.4368
67.9496
67.0266
63.3646
63.0312
62.8083
58.3278
54.8841
53.9667
52.4928
48.7973
46.0973
43.0068
37.8295
36.6582
33.3566
27.4567
O
O
O
N
H
F
11i
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Solvent: $CDCl_3$
Frequency: 376 Mhz

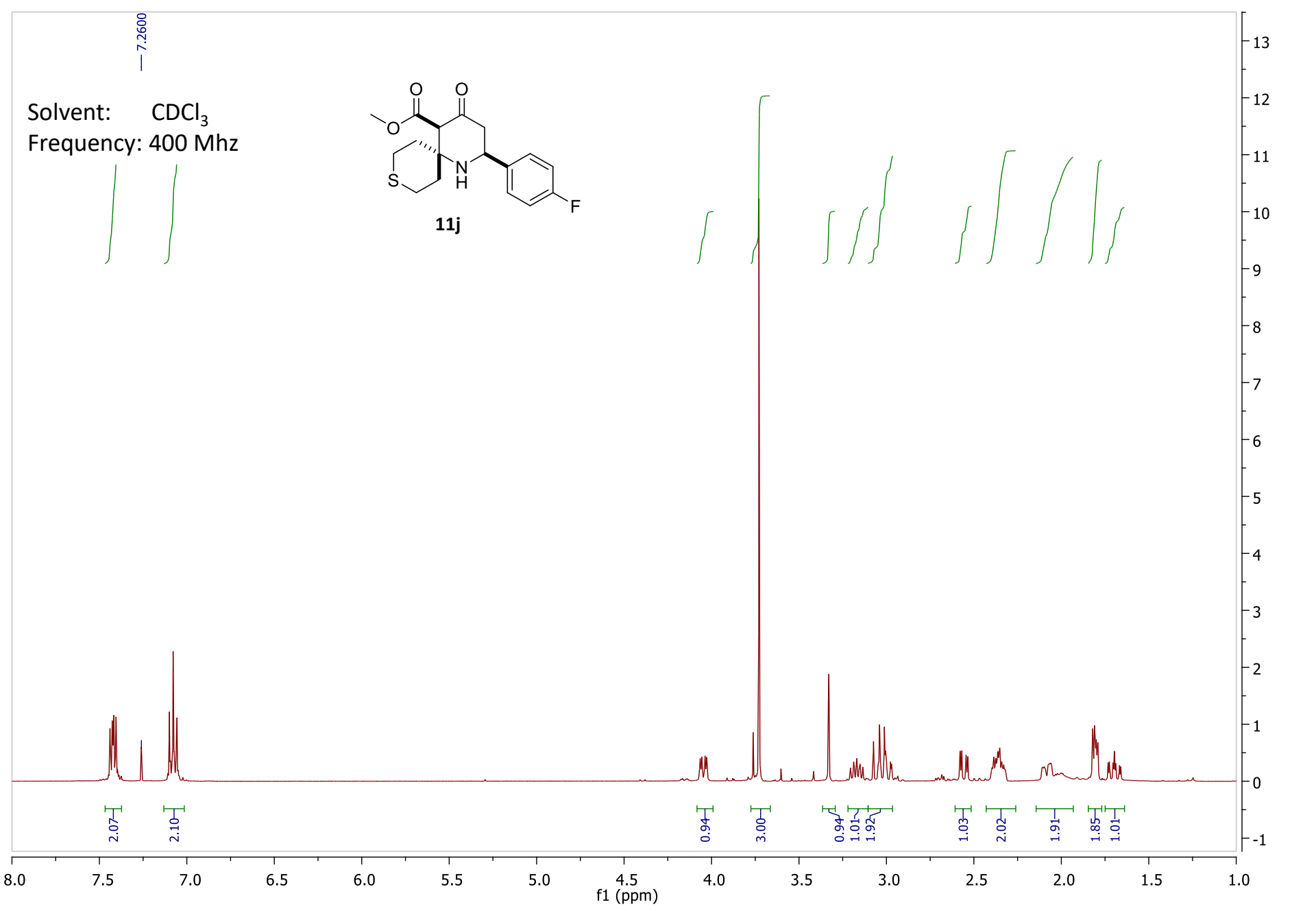


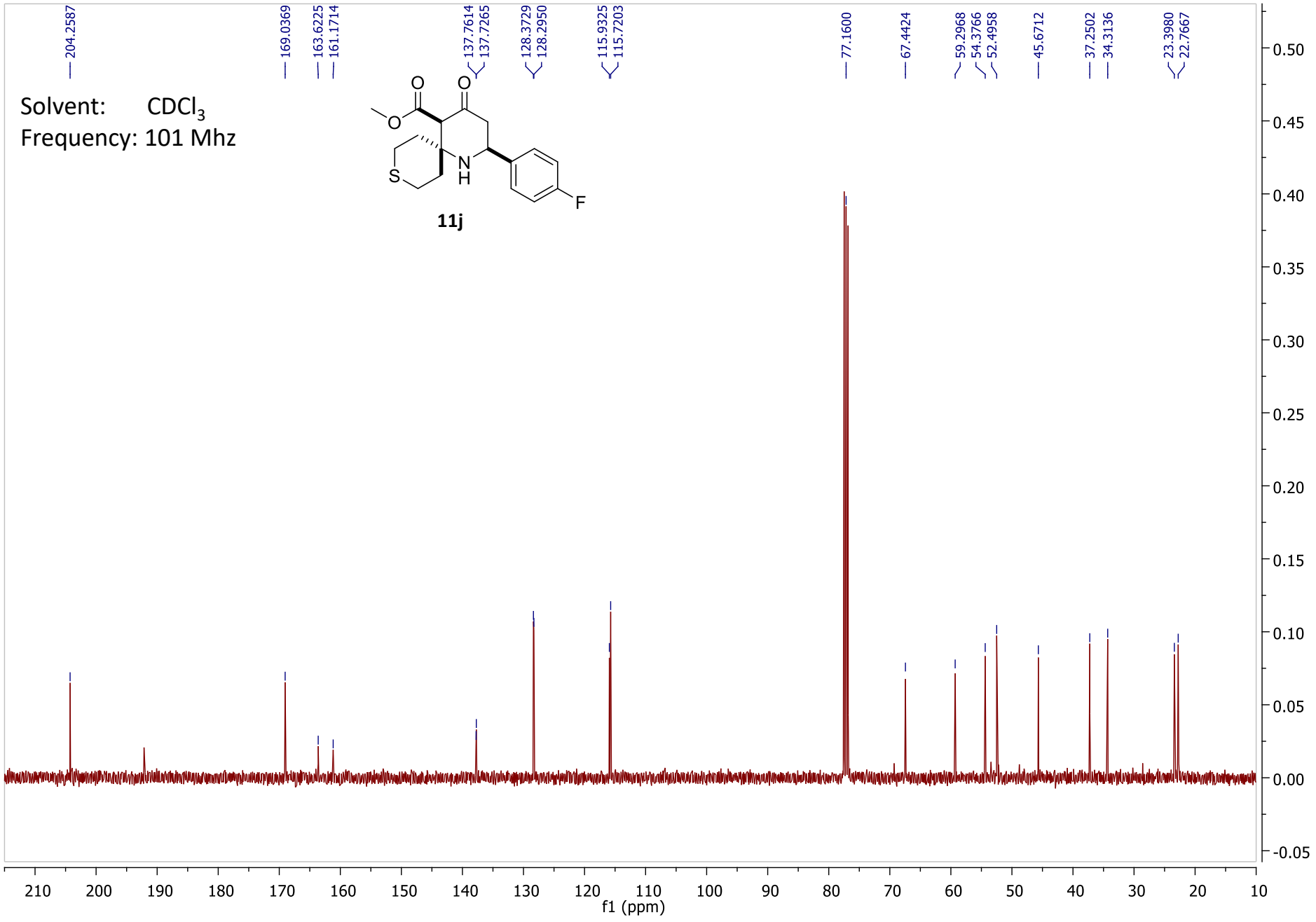
11i

-113.8822
-113.8979
-113.9190
-113.9312
-113.9414
-113.9543
-113.9661
-113.9805
-113.9884
-114.2659
-114.2825
-114.2894
-114.3016
-114.3151
-114.3228
-114.3383

1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1

0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150
f1 (ppm)

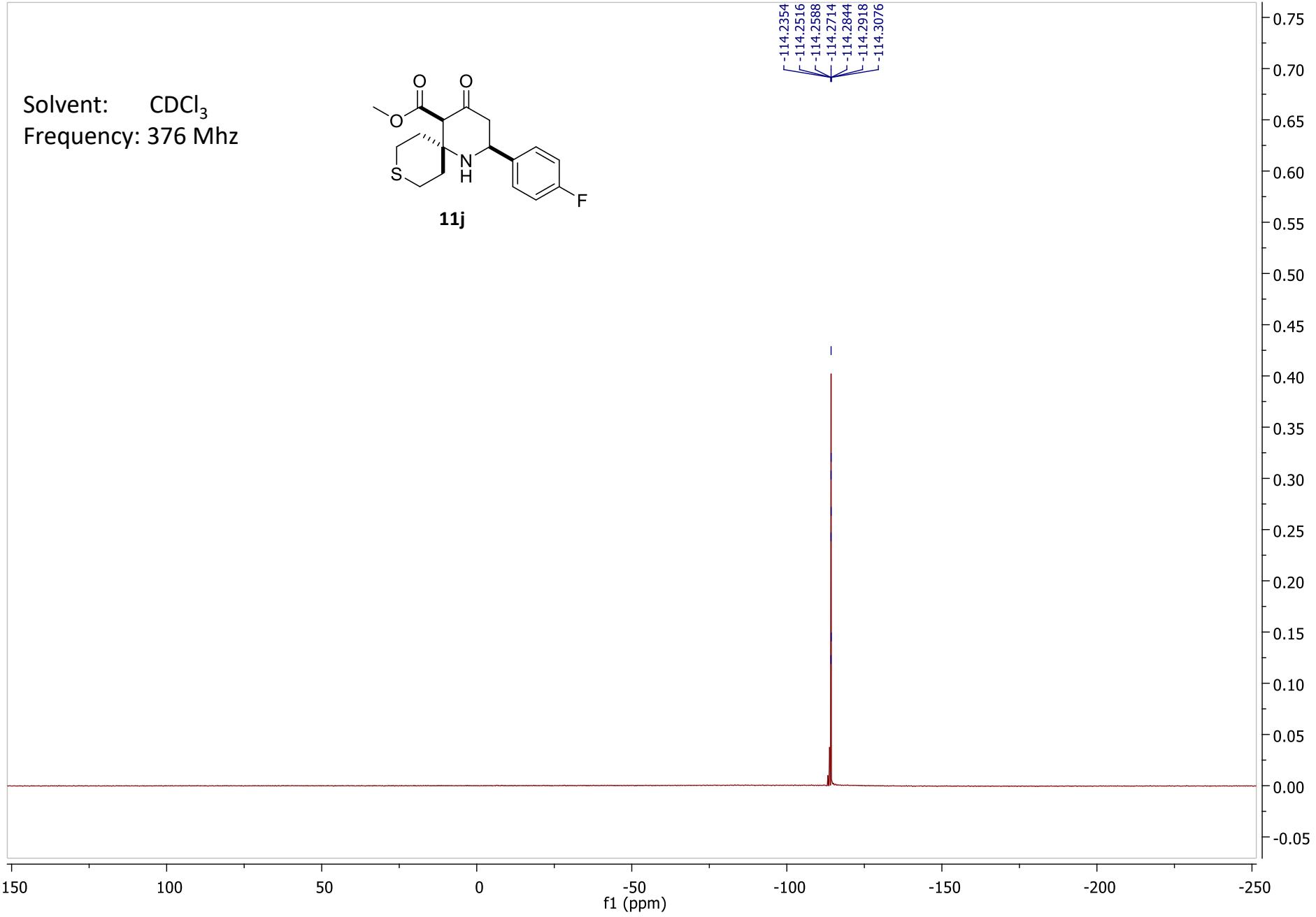

7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
O
N
H
S
F
11j
2.07
2.10
0.94
3.00
0.94
1.01
1.92
1.03
2.02
1.91
1.85
1.01
f1 (ppm)

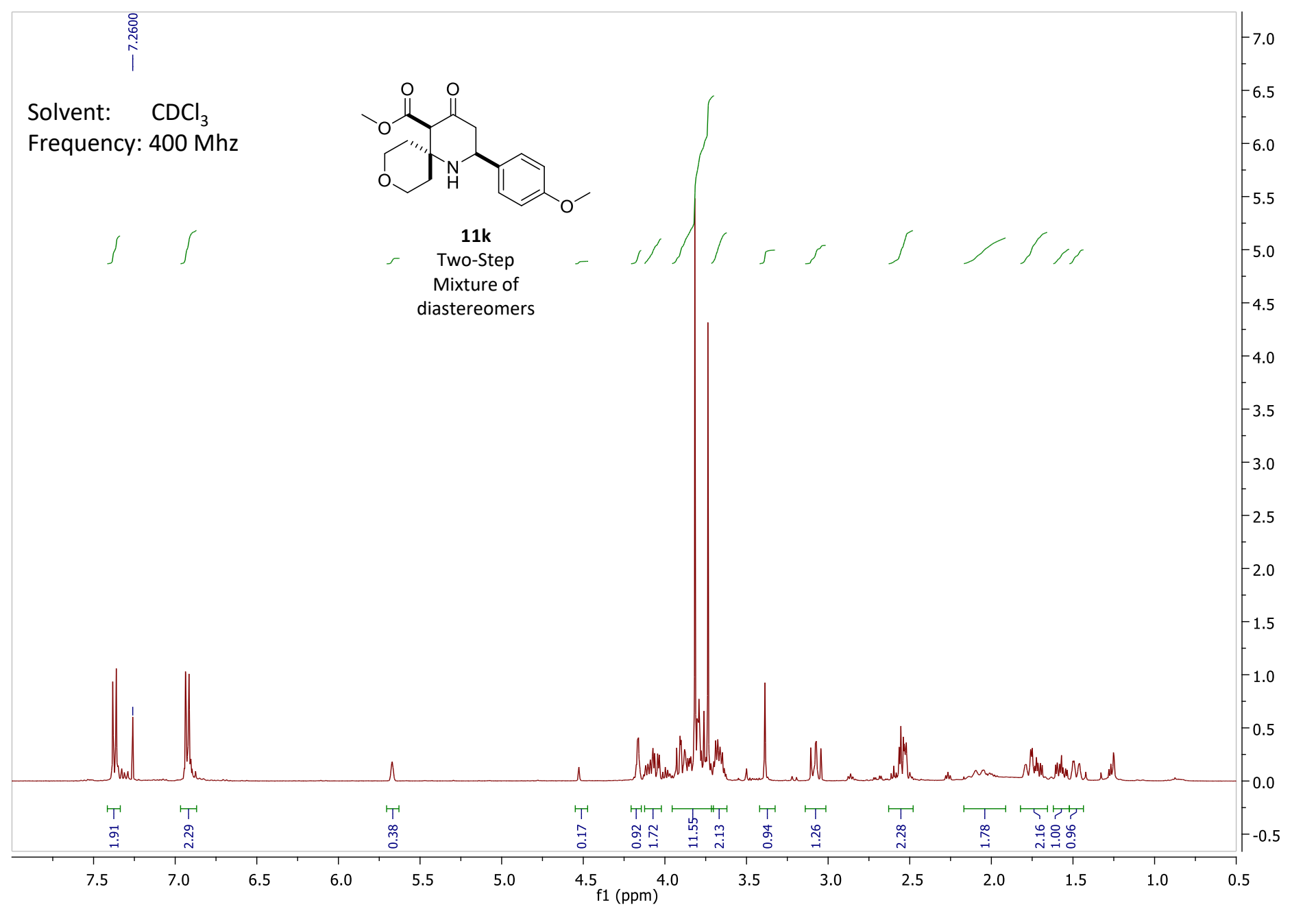

204.2587
169.0369
163.6225
161.1714
137.7614
137.7265
128.3729
128.2950
115.9325
115.7203
77.1600
67.4424
59.2968
54.3766
52.4958
45.6712
37.2502
34.3136
23.3980
22.7667
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
S
F
11j
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

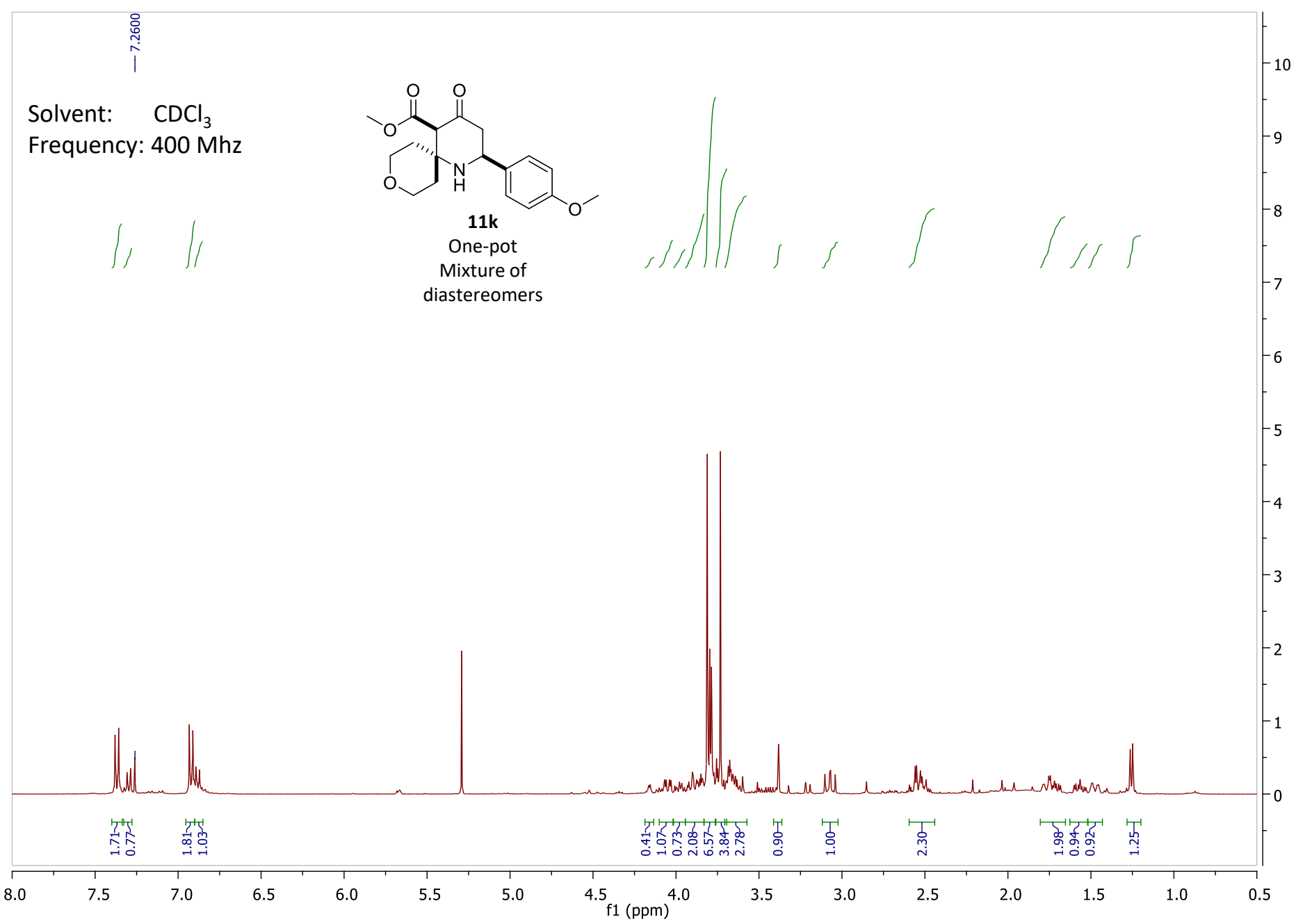
Solvent: $CDCl_3$

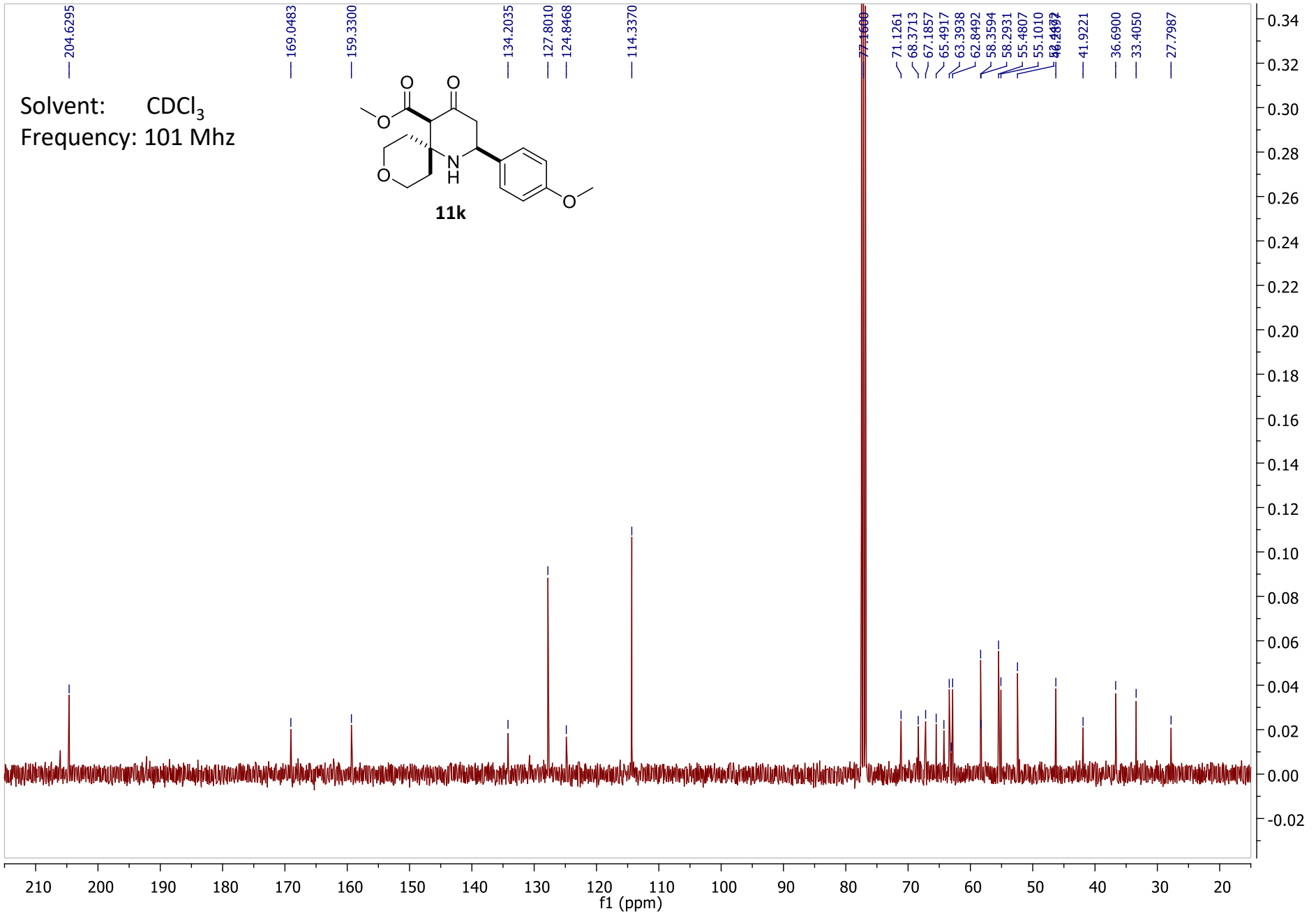
Frequency: 376 Mhz

11j



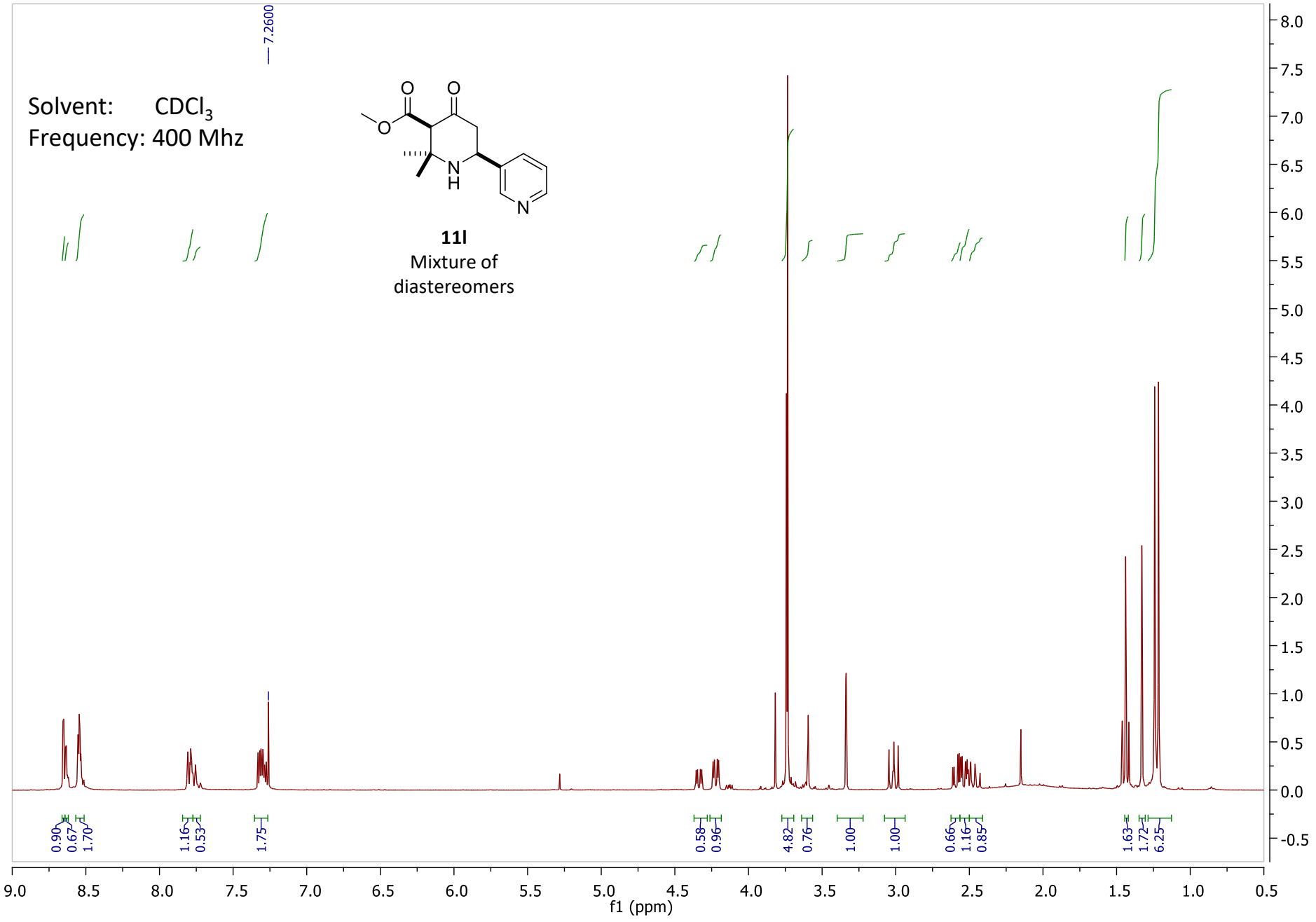

7.2600
Solvent: $CDCl_3$
Frequency: 400 Mhz
11k
Two-Step
Mixture of
diastereomers
1.91
2.29
0.38
0.17
0.92
1.72
11.55
2.13
0.94
1.26
2.28
1.78
2.16
1.00
0.96
f1 (ppm)

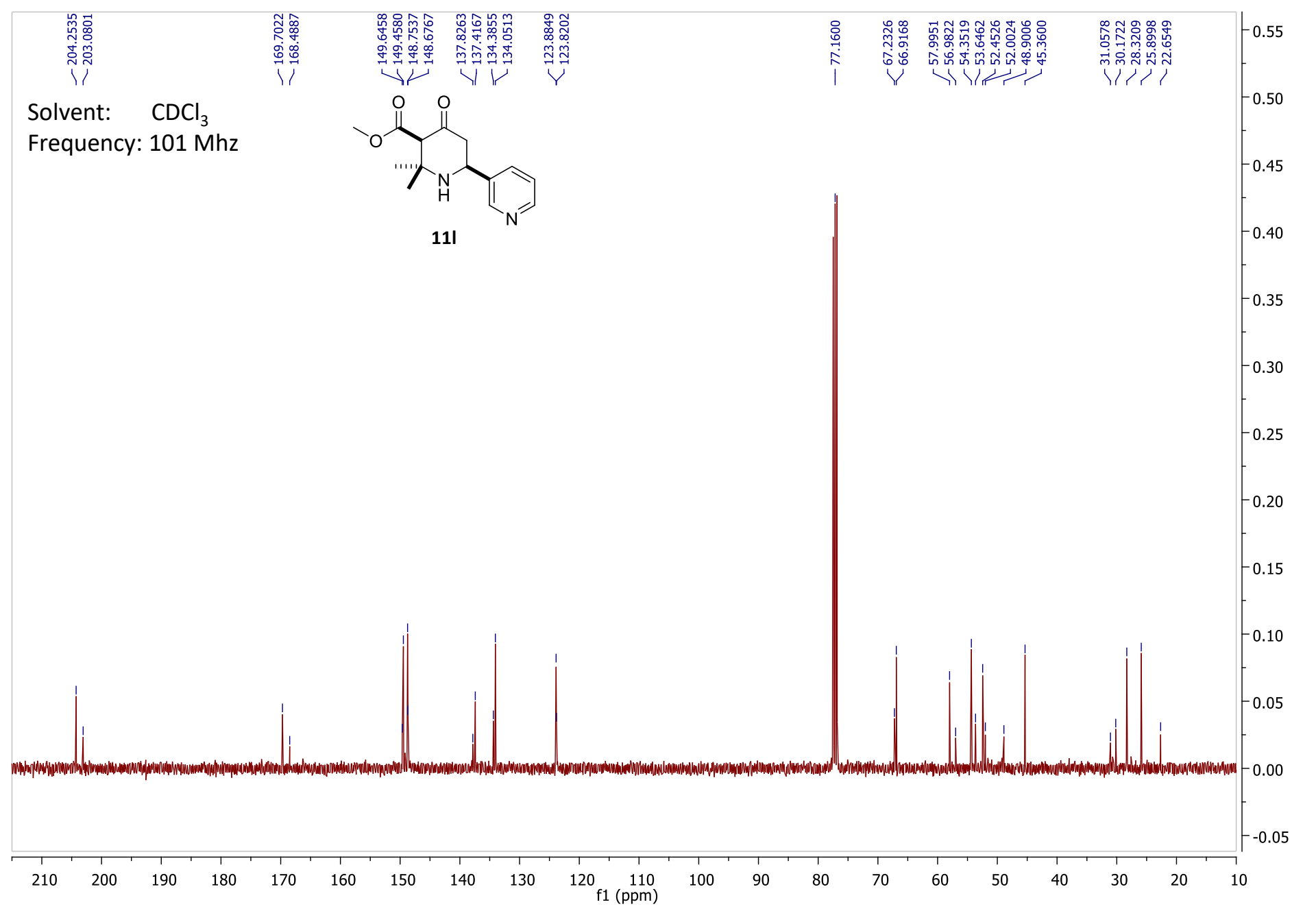

7.2600
Solvent: $CDCl_3$
Frequency: 400 Mhz
11k
One-pot
Mixture of
diastereomers
1.71
0.77
1.81
1.03
0.41
1.07
0.73
2.08
6.57
3.84
2.78
0.90
1.00
2.30
1.98
0.94
0.92
1.25
f1 (ppm)

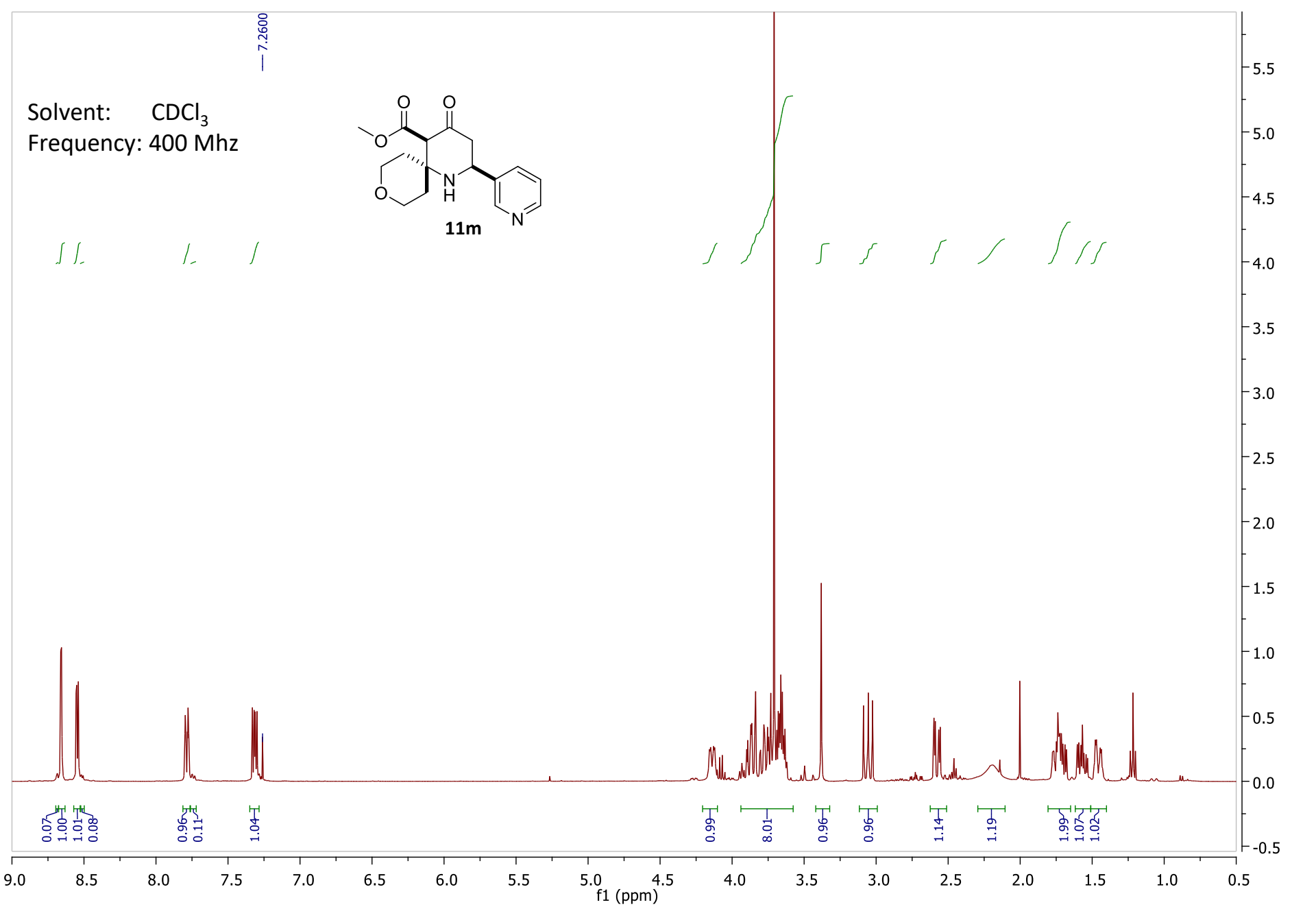

204.6295
169.0483
159.3300
134.2035
127.8010
124.8468
114.3370
77.1600
71.1261
68.3713
67.1857
65.4917
63.3938
62.8492
58.3594
58.2931
55.4807
55.1010
41.9221
36.6900
33.4050
27.7987
Solvent: CDCl3
Frequency: 101 Mhz
11k
f1 (ppm)

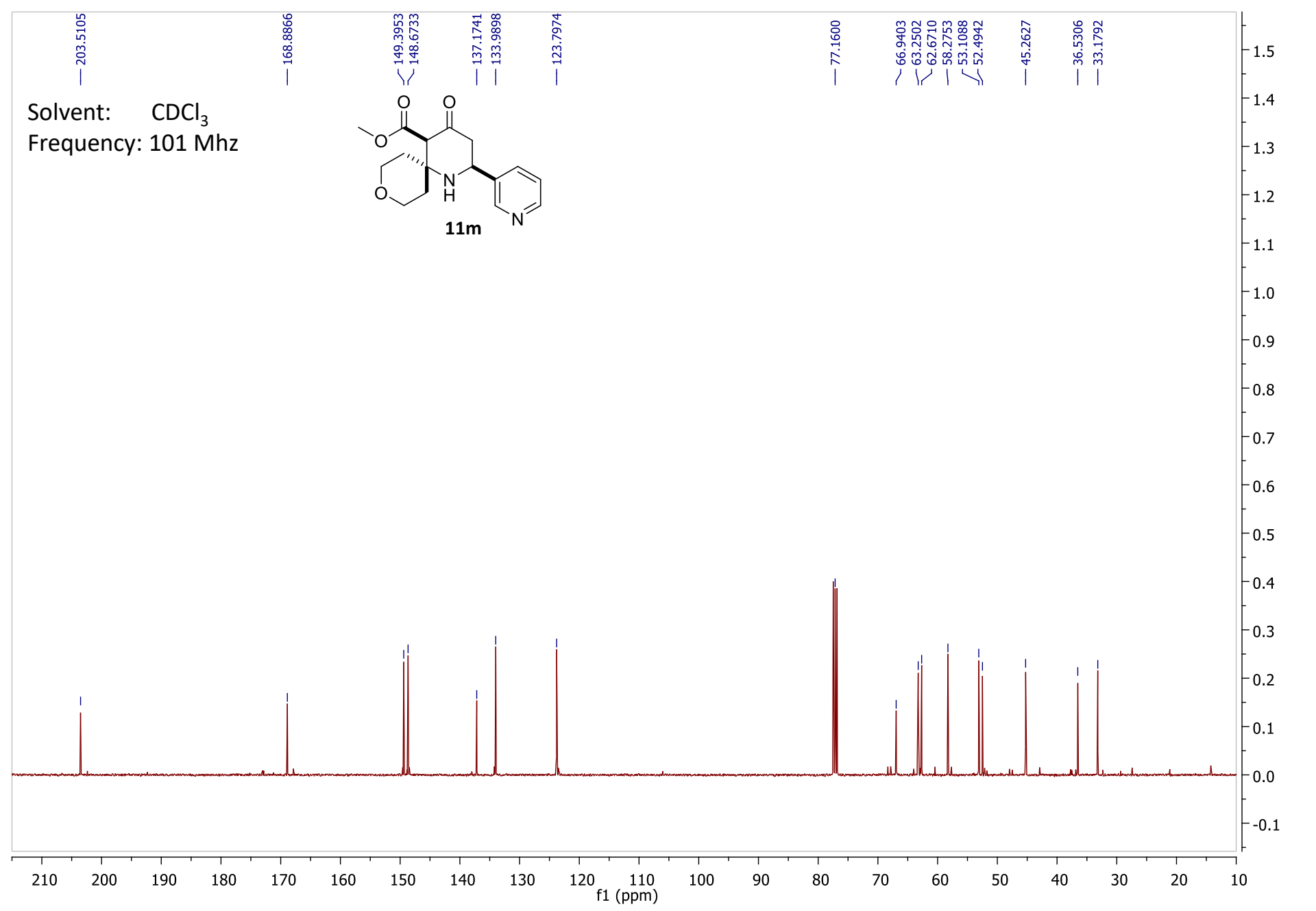
Solvent: $CDCl_3$
Frequency: 400 Mhz

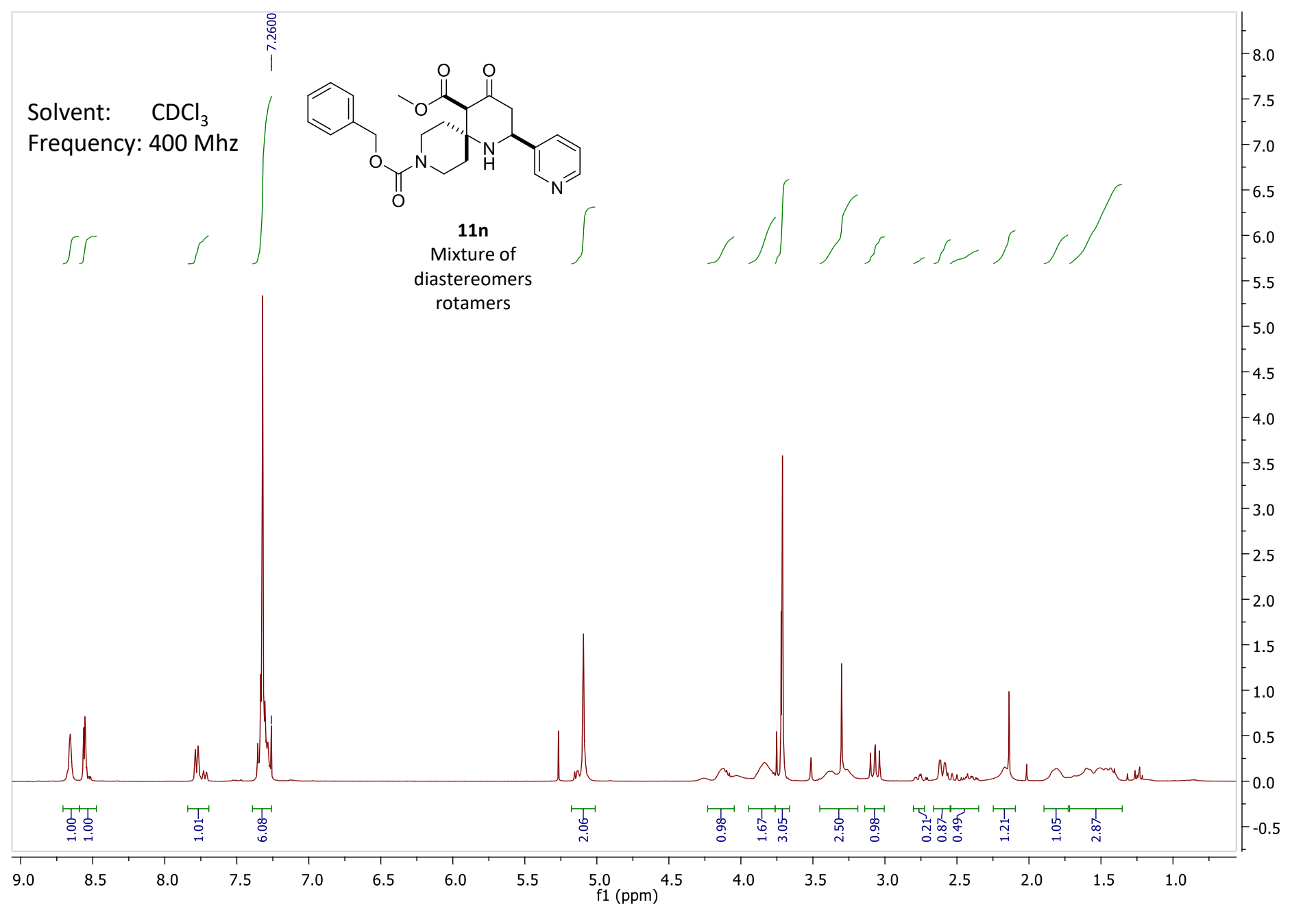
11l
Mixture of
diastereomers

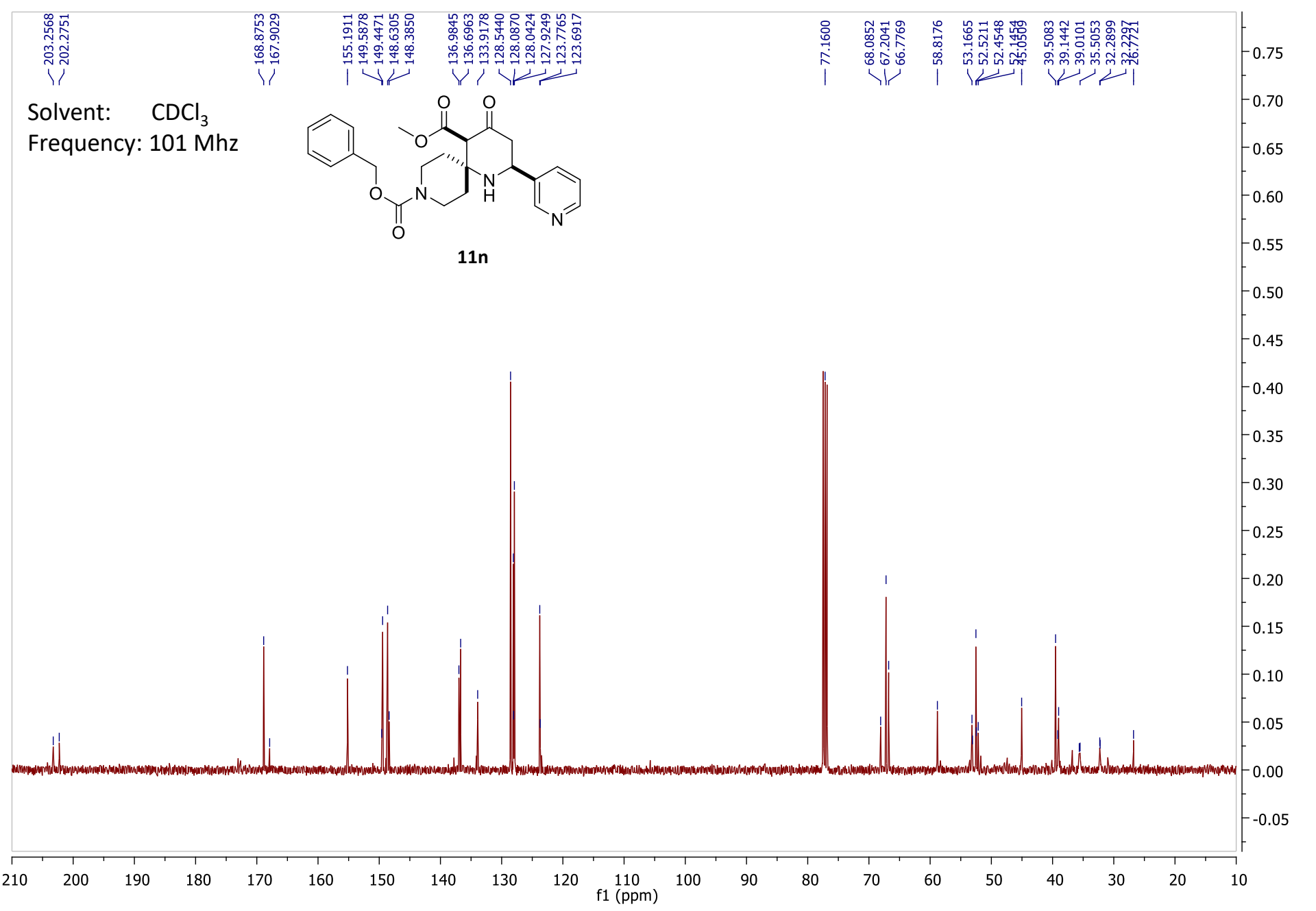



204.2535
203.0801
169.7022
168.4887
149.6458
149.4580
148.7537
148.6767
137.8263
137.4167
134.3855
134.0513
123.8849
123.8202
77.1600
67.2326
66.9168
57.9951
56.9822
54.3519
53.6462
52.4526
52.0024
48.9006
45.3600
31.0578
30.1722
28.3209
25.8998
22.6549
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
N
11l
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

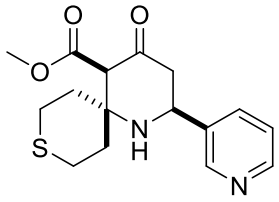

7.2600
Solvent: CDCl3
Frequency: 400 Mhz
11m
0.07
1.00
1.01
0.08
0.96
0.11
1.04
0.99
8.01
0.96
0.96
1.14
1.19
1.99
1.07
1.02
f1 (ppm)


203.5105
168.8866
149.3953
148.6733
137.1741
133.9898
123.7974
77.1600
66.9403
63.2502
62.6710
58.2753
53.1088
52.4942
45.2627
36.5306
33.1792
Solvent: CDCl3
Frequency: 101 Mhz
11m
f1 (ppm)

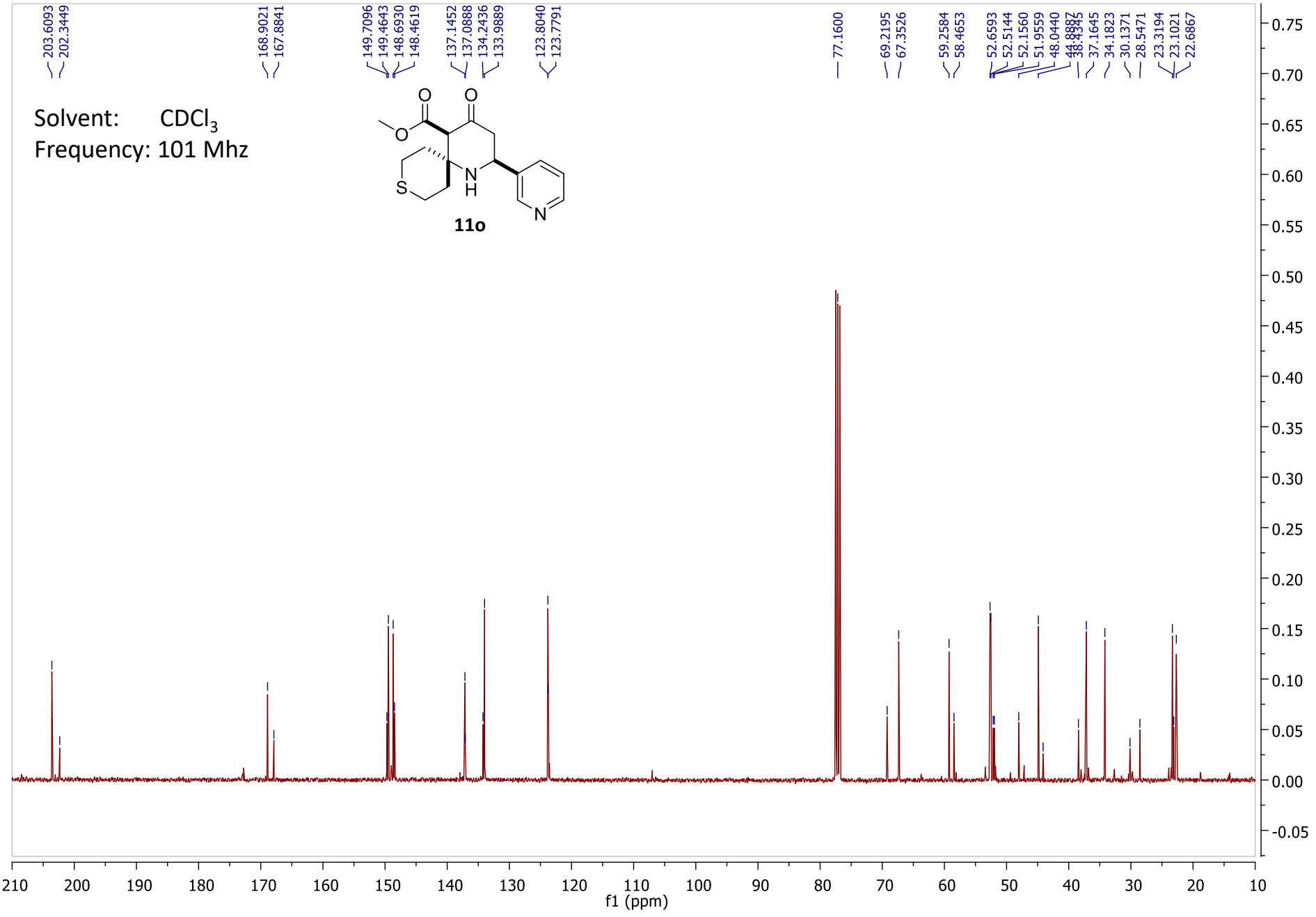

Solvent: CDCl3
Frequency: 400 Mhz
7.2600
11n
Mixture of
diastereomers
rotamers
1.00
1.00
1.01
6.08
2.06
0.98
1.67
3.05
2.50
0.98
0.21
0.87
0.49
1.21
1.05
2.87
f1 (ppm)

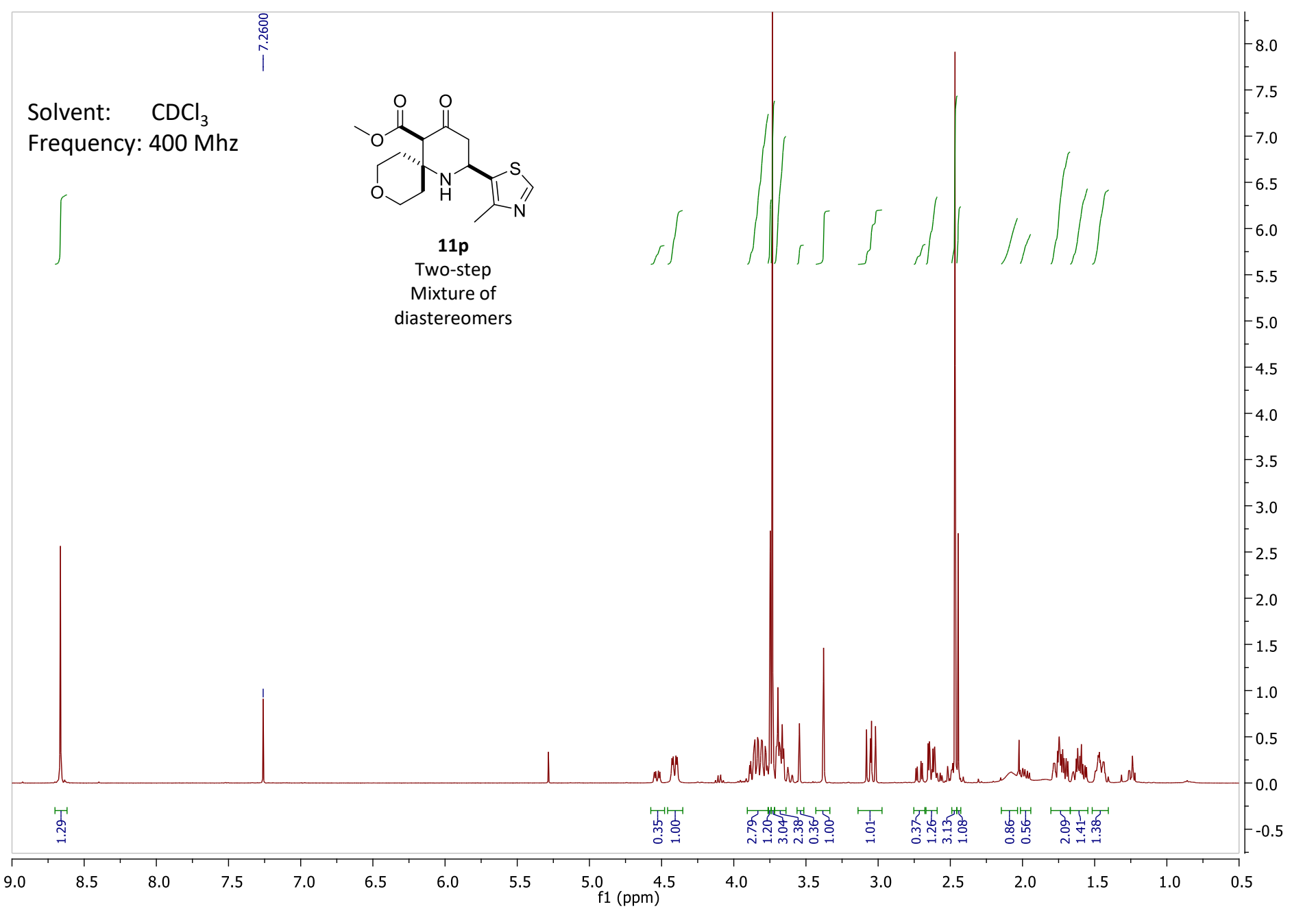

Solvent: CDCl3
Frequency: 101 Mhz
11n
f1 (ppm)

Solvent: $CDCl_3$
Frequency: 400 Mhz

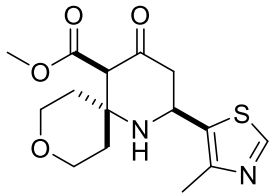


11o
Mixture of
diastereomers

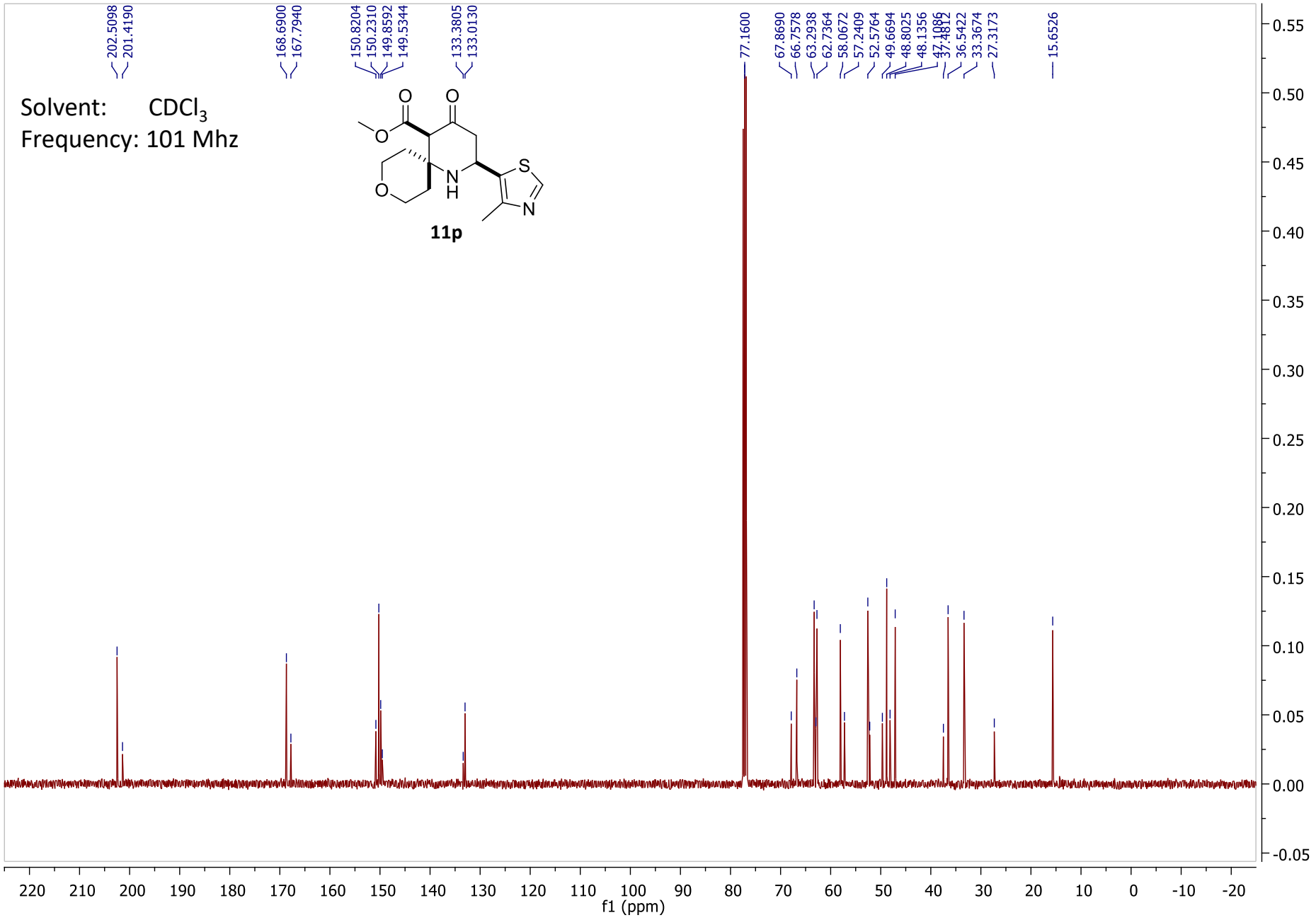

203.6093
202.3449
168.9021
167.8841
149.7096
149.4643
148.6930
148.4619
137.1452
137.0888
134.2436
133.9889
123.8040
123.7791
77.1600
69.2195
67.3526
59.2584
58.4653
52.6593
52.5144
52.1560
51.9559
48.0440
44.8887
38.4345
37.1645
34.1823
30.1371
28.5471
23.3194
23.1021
22.6867
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
S
N
H
N
11o
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Solvent: CDCl3
Frequency: 400 Mhz
7.2600
11p
Two-step
Mixture of
diastereomers
f1 (ppm)

Solvent: $CDCl_3$
Frequency: 400 Mhz

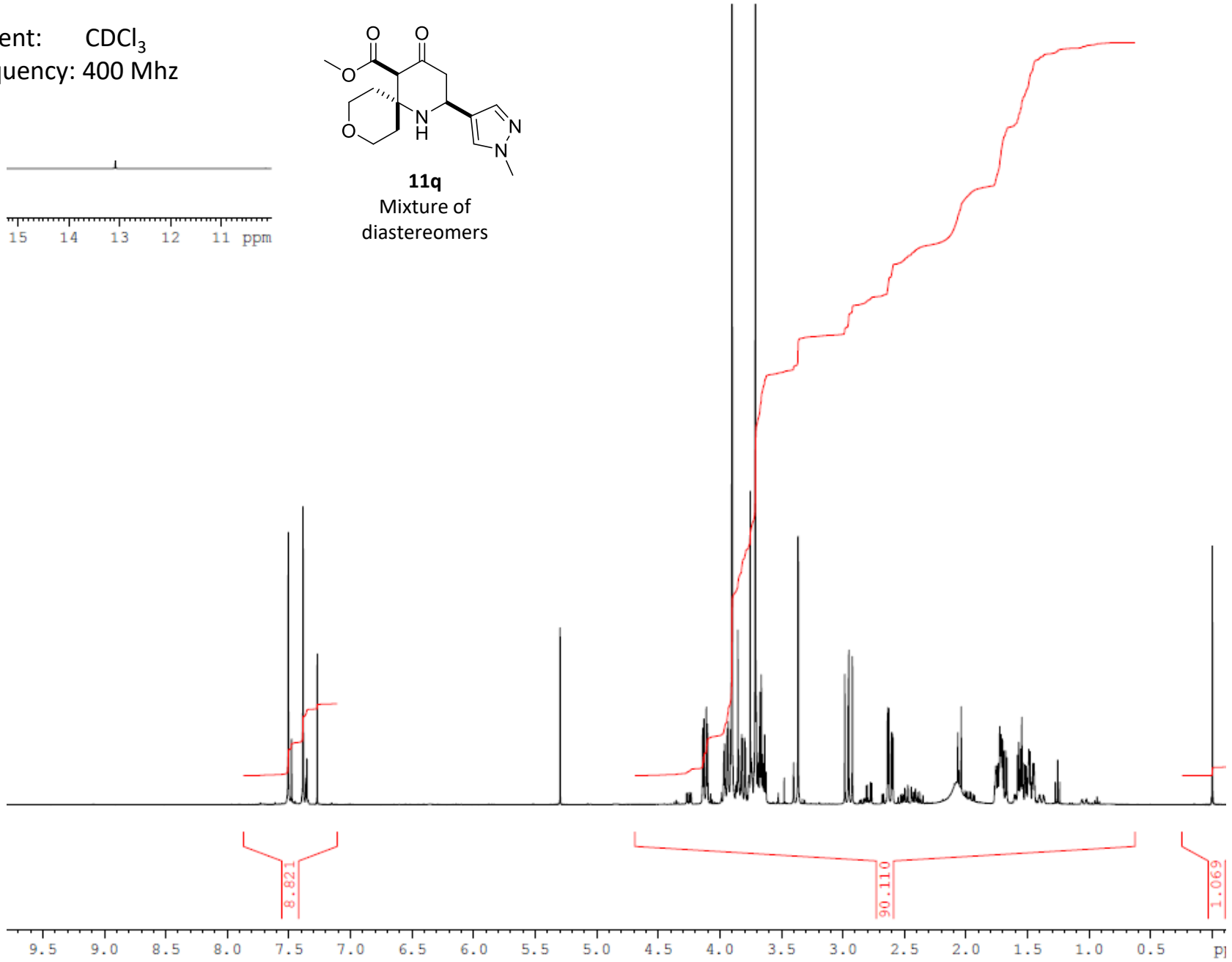


11p
One-pot
Mixture of
diastereomers


Solvent: CDCl3
Frequency: 101 Mhz
11p
202.5098
201.4190
168.6900
167.7940
150.8204
150.2310
149.8592
149.5344
133.3805
133.0130
77.1600
67.8690
66.7578
63.2938
62.7364
58.0672
57.2409
52.5764
49.6694
48.8025
48.1356
36.5422
33.3674
27.3173
15.6526
f1 (ppm)

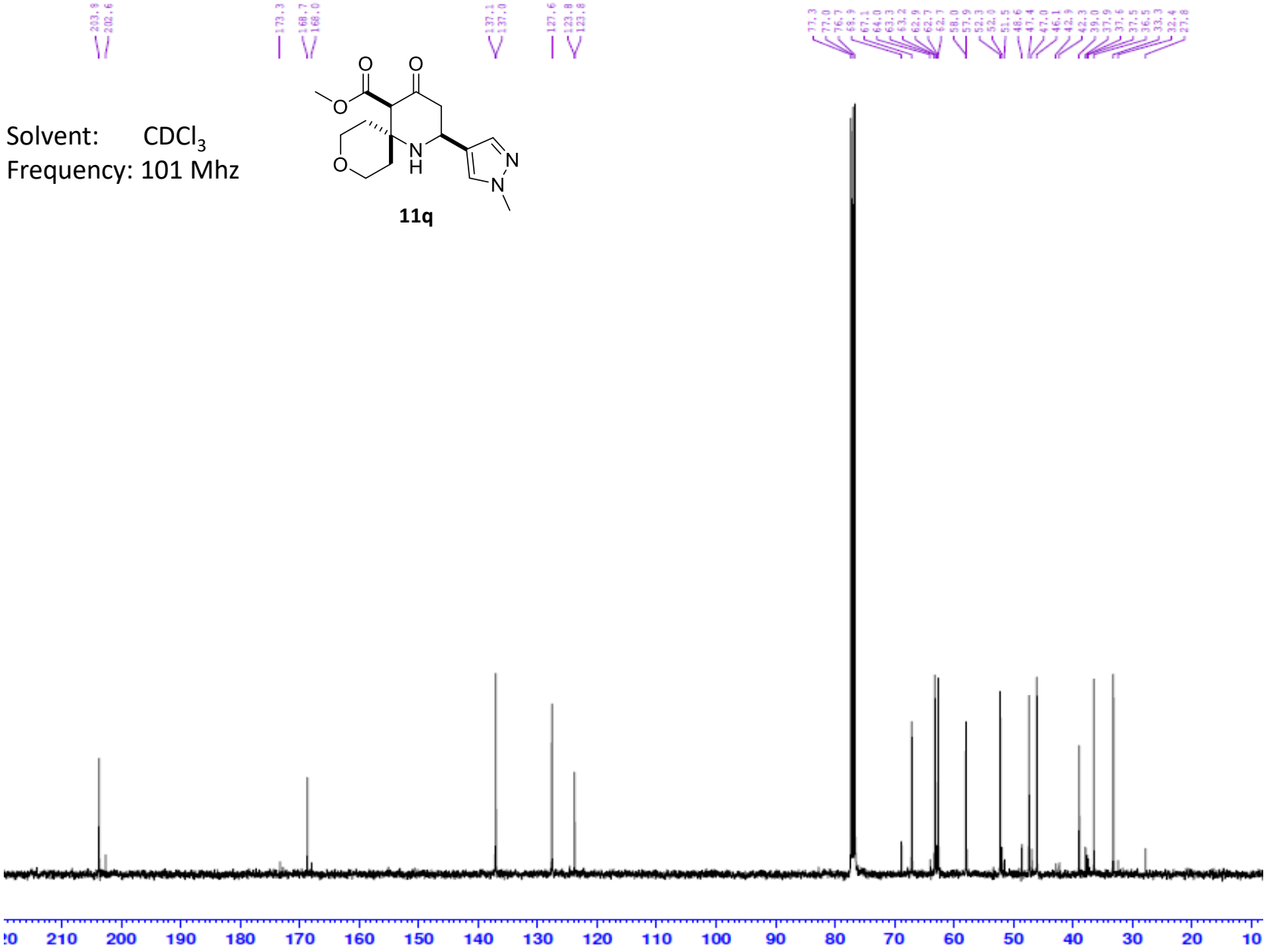
Solvent: $CDCl_3$
Frequency: 400 Mhz

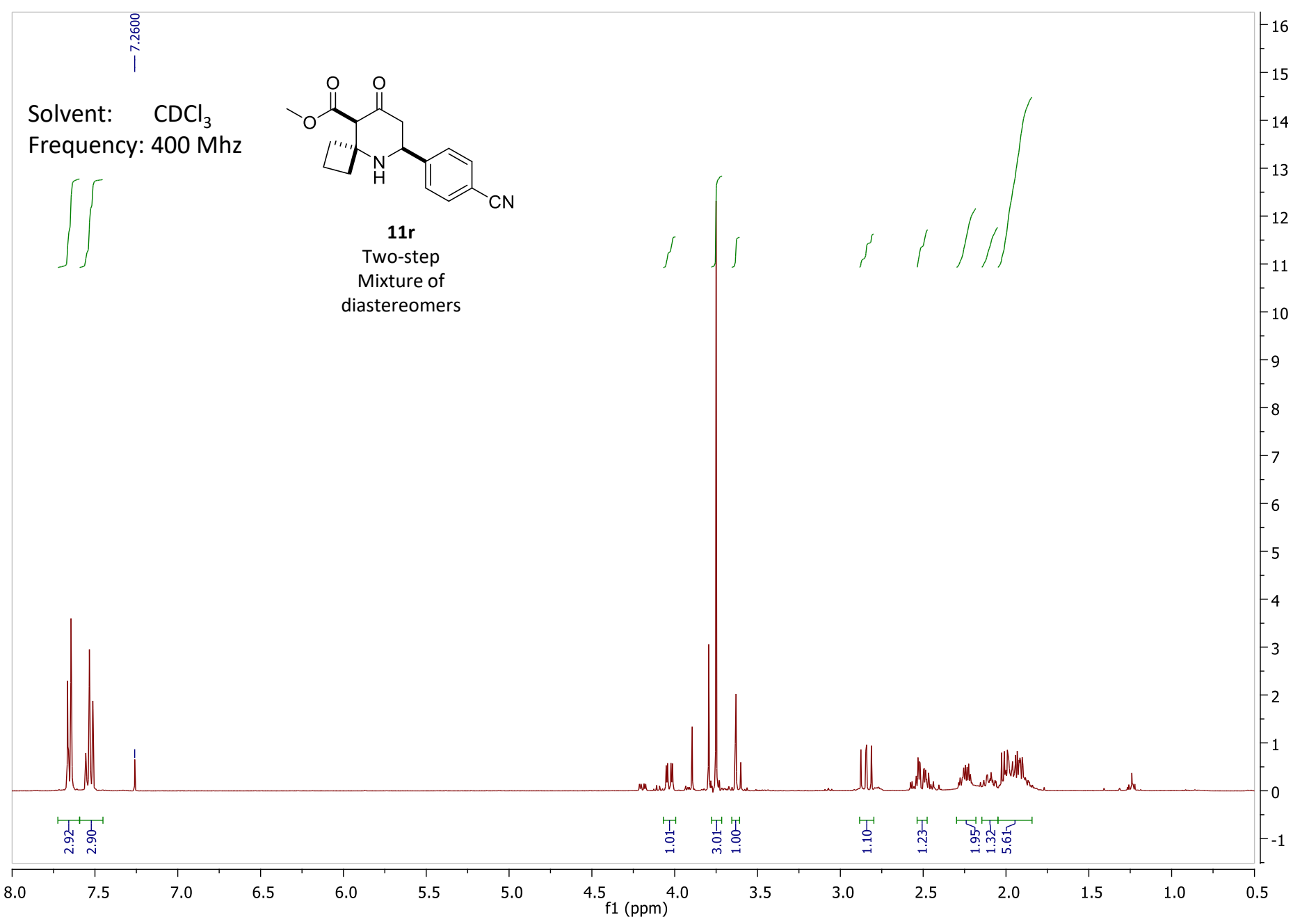
11q
Mixture of diastereomers

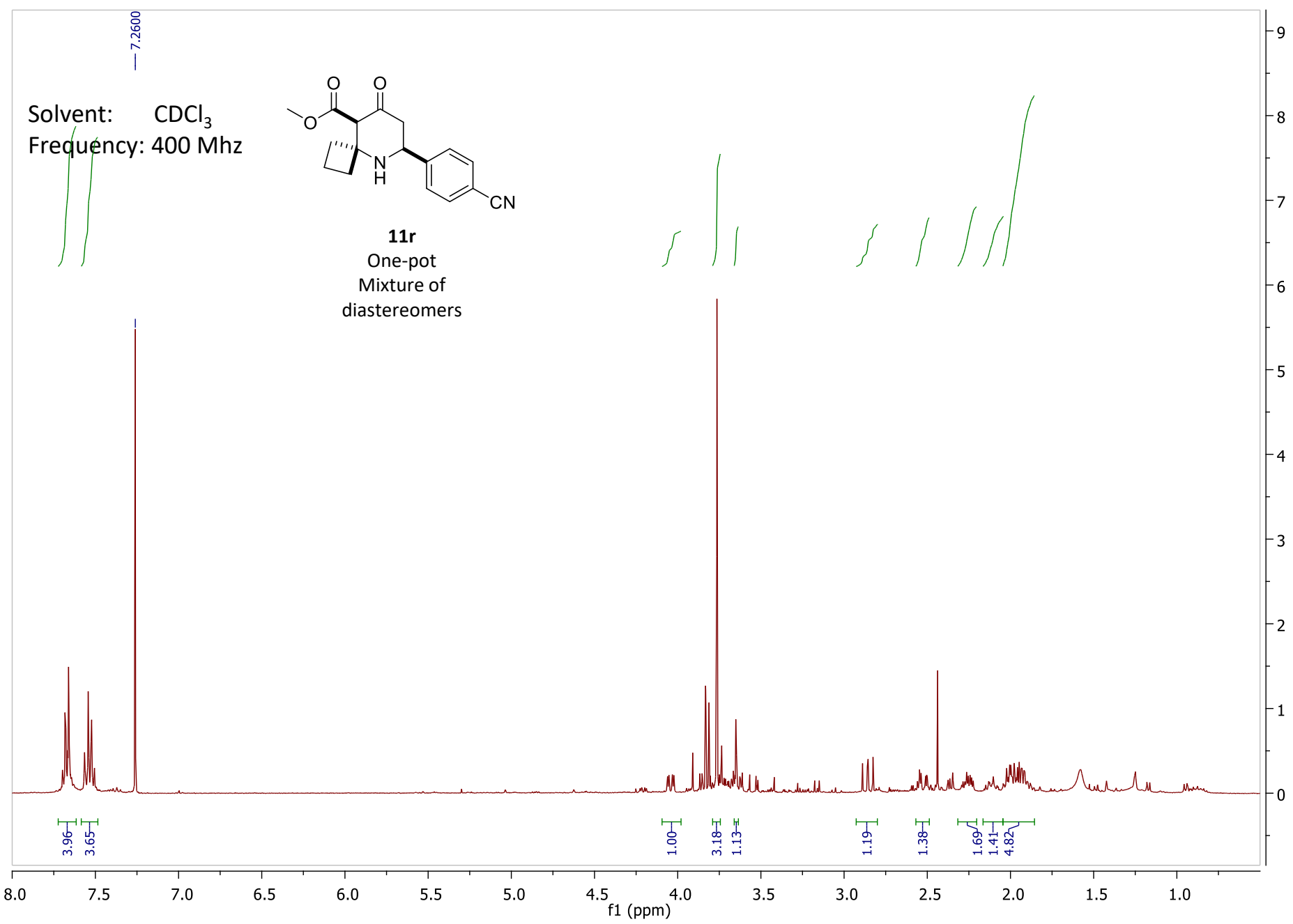


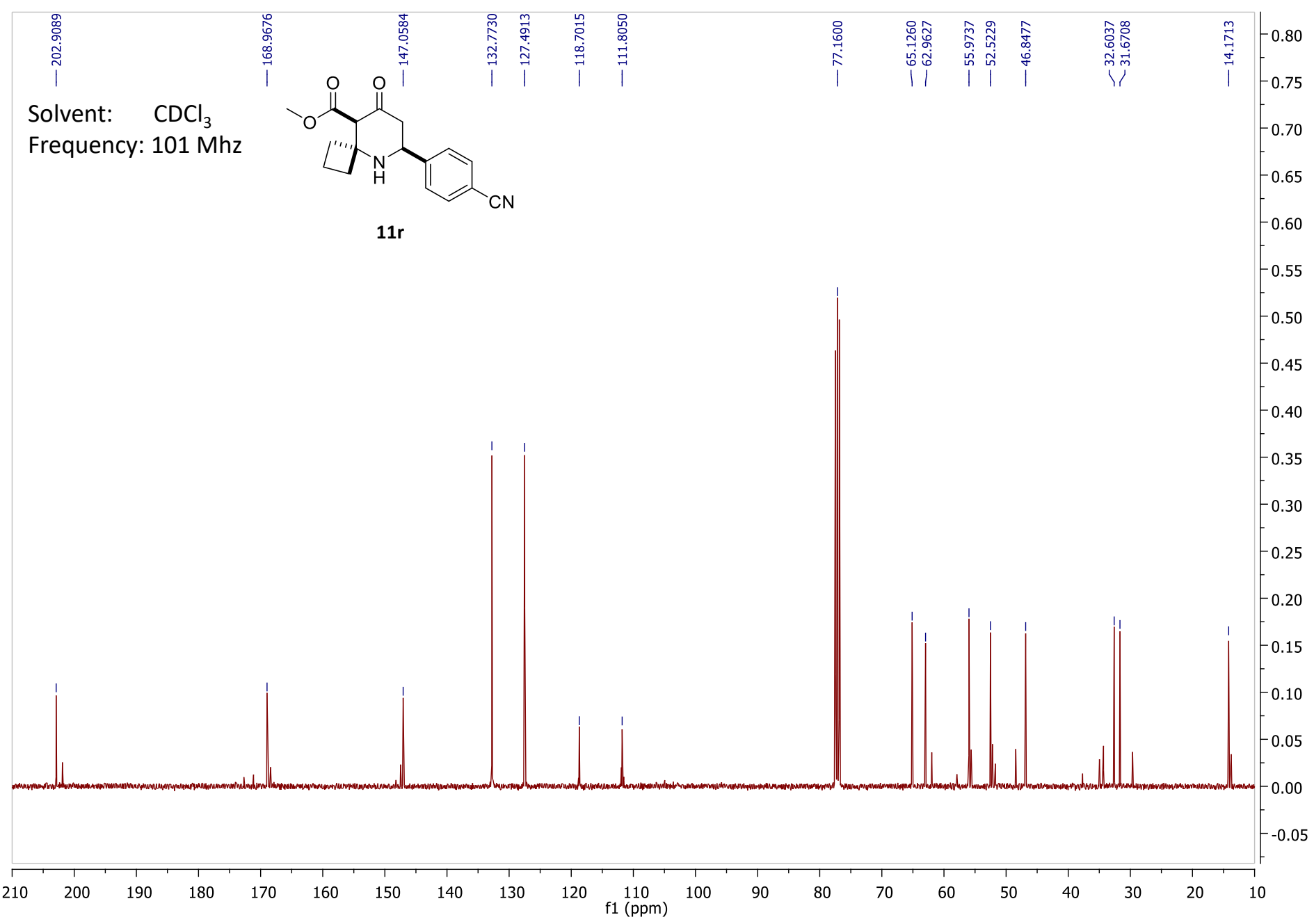
Solvent: $CDCl_3$
Frequency: 101 Mhz

11q



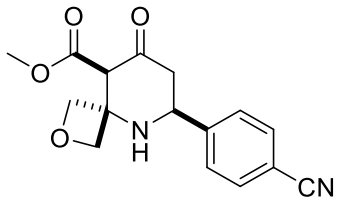

7.2600
Solvent: $CDCl_3$
Frequency: 400 Mhz
O
O
O
N
H
CN
11r
Two-step
Mixture of
diastereomers
2.92
2.90
1.01
3.01
1.00
1.10
1.23
1.95
1.32
5.61
f1 (ppm)


7.2600
Solvent: CDCl3
Frequency: 400 Mhz
O
O
O
N
H
CN
11r
One-pot
Mixture of
diastereomers
3.96
3.65
1.00
3.18
1.13
1.19
1.38
1.69
1.41
4.82
f1 (ppm)


202.9089
168.9676
147.0584
132.7730
127.4913
118.7015
111.8050
77.1600
65.1260
62.9627
55.9737
52.5229
46.8477
32.6037
31.6708
14.1713
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
CN
11r
f1 (ppm)

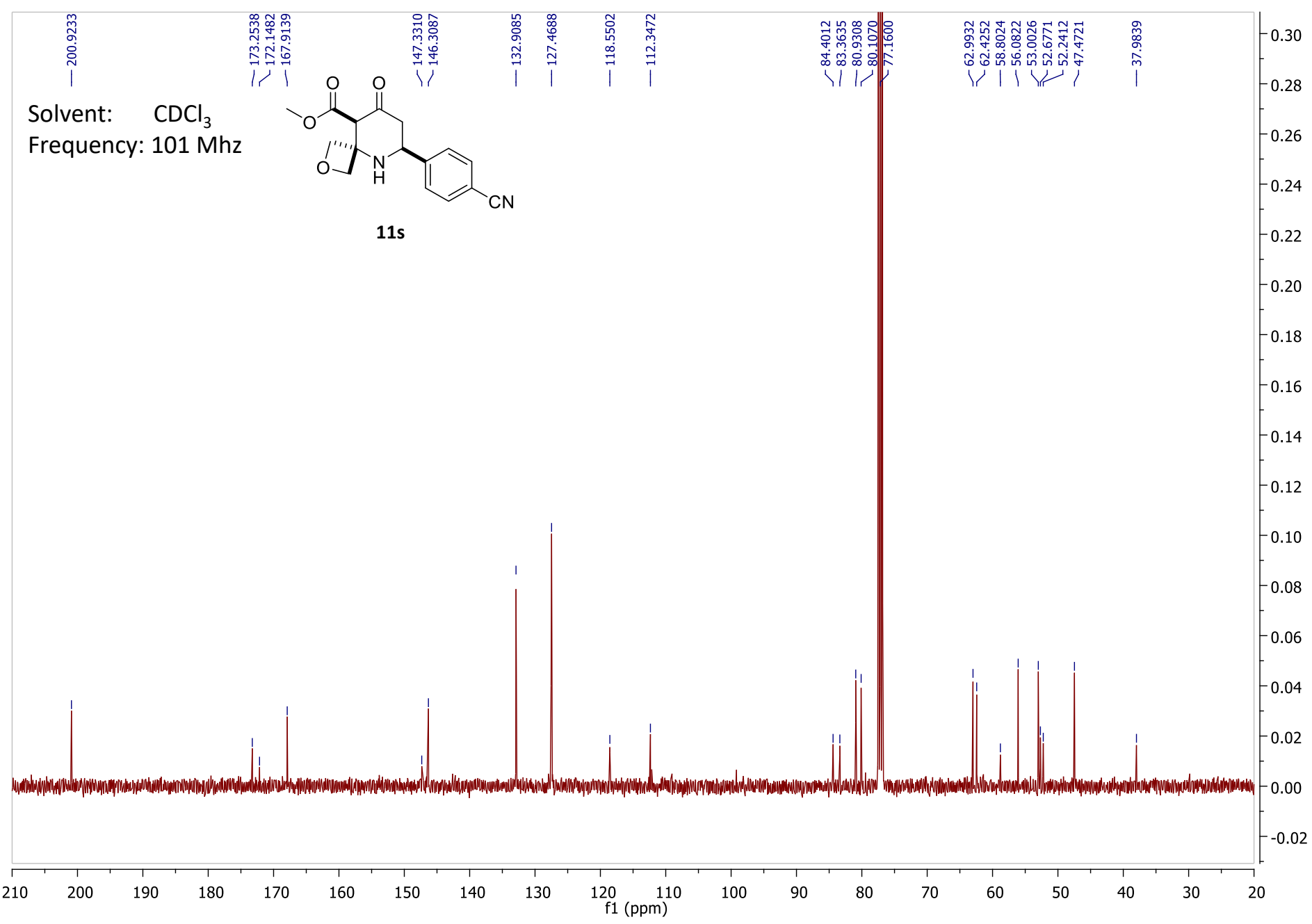
Solvent: $CDCl_3$

Frequency: 400 Mhz



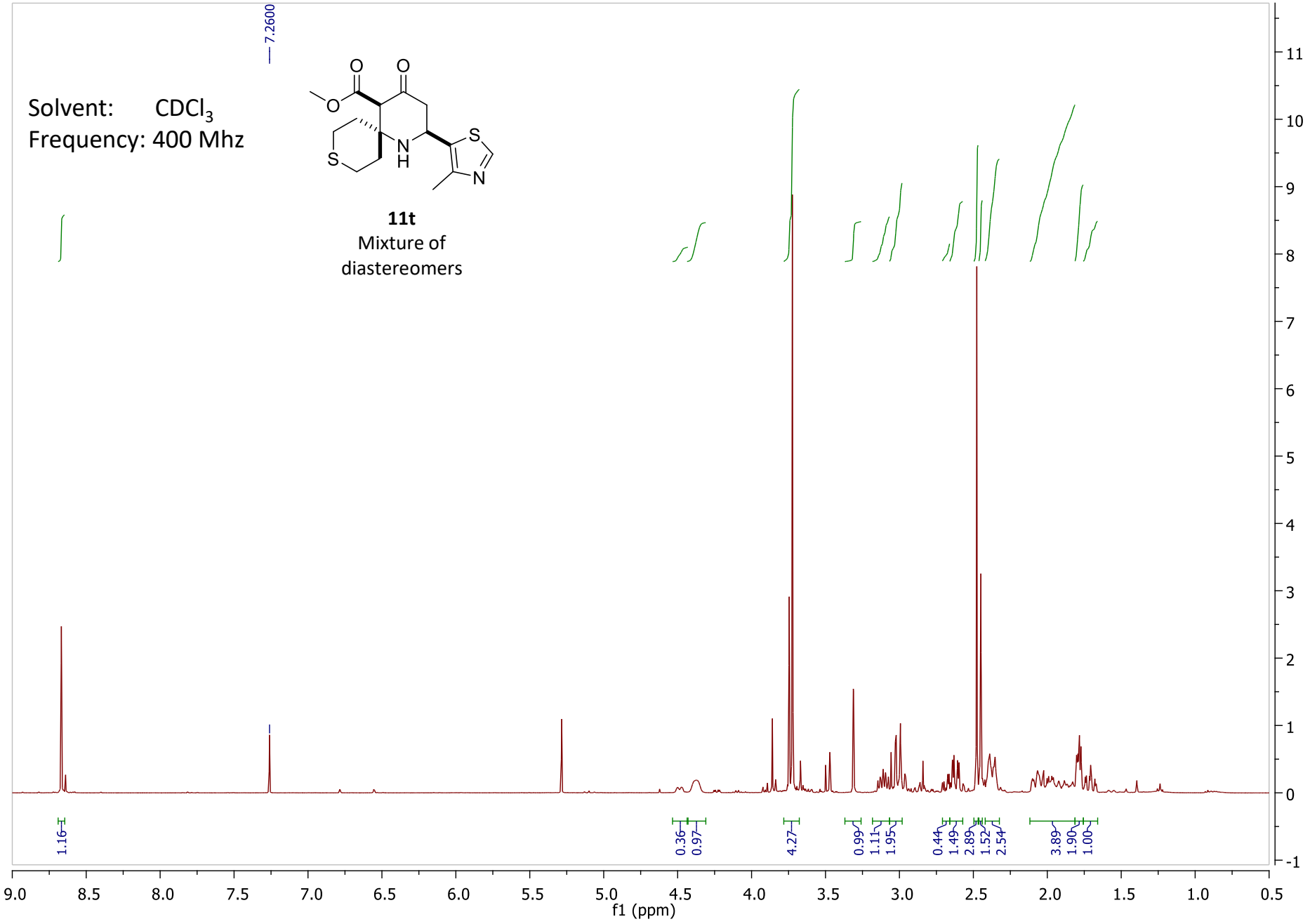
11s

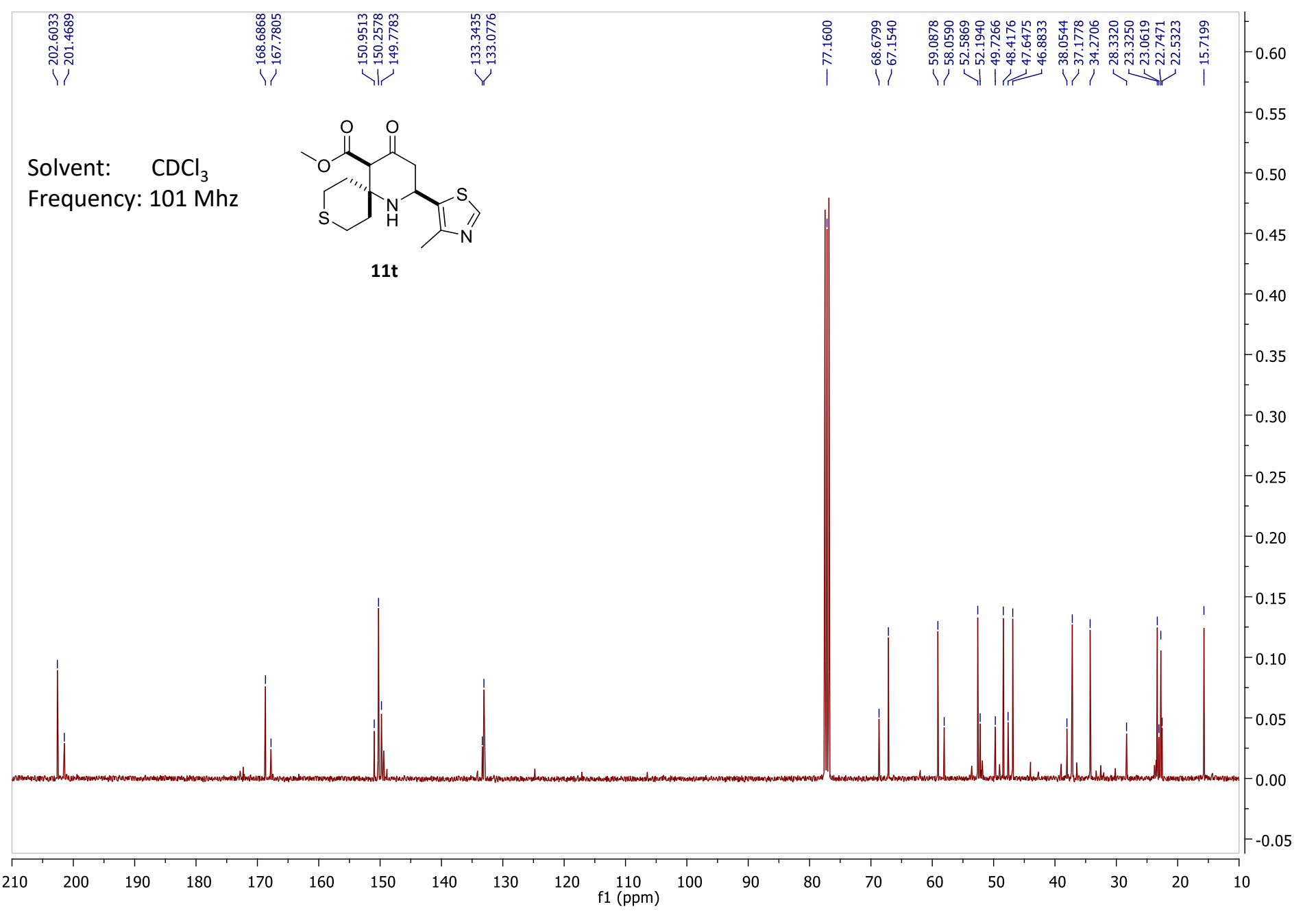
Mixture of diastereomers

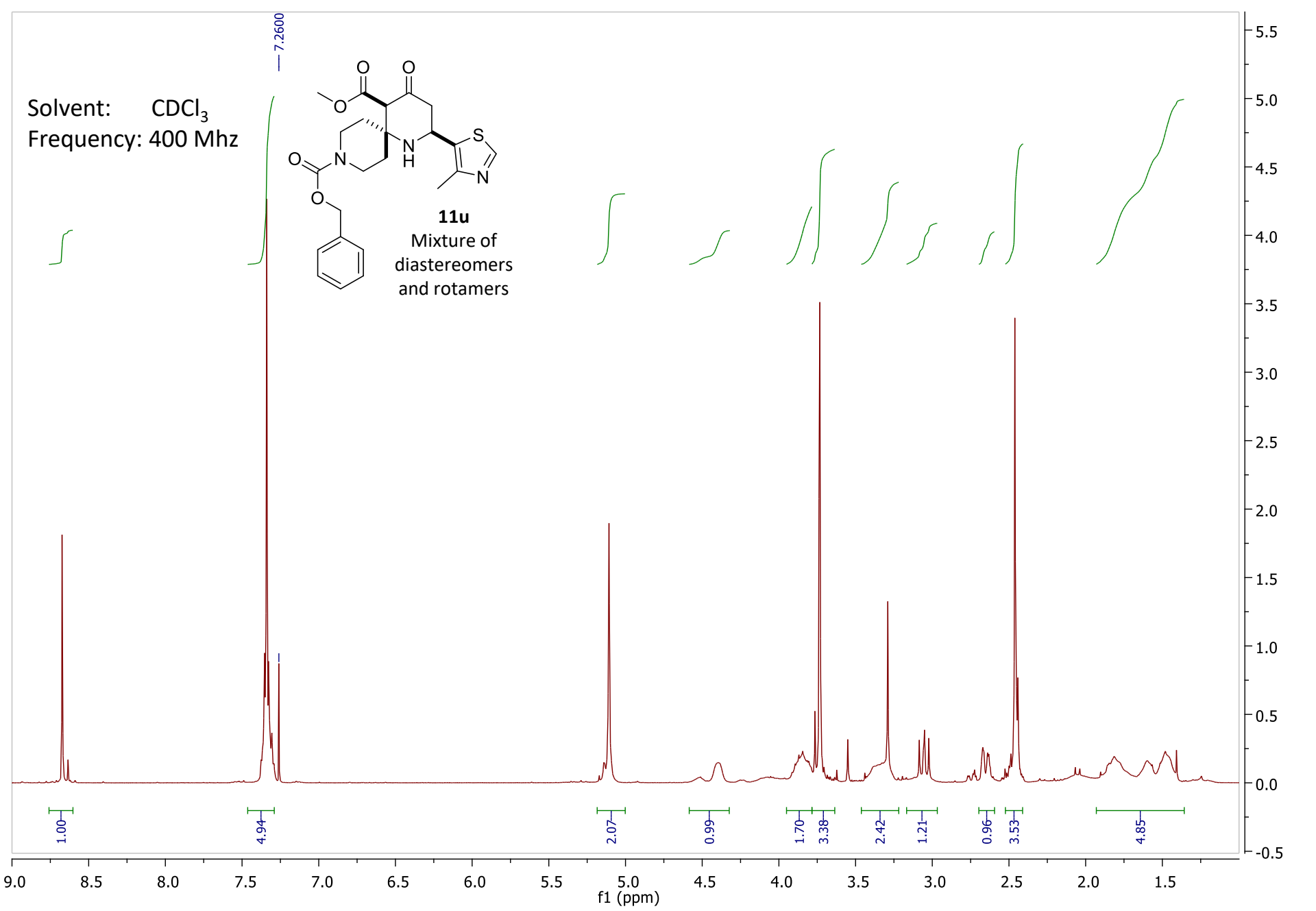

200.9233
173.2538
172.1482
167.9139
147.3310
146.3087
132.9085
127.4688
118.5502
112.3472
84.4012
83.3635
80.9308
80.1070
77.1600
62.9932
62.4252
58.8024
56.0822
53.0026
52.6771
52.2412
47.4721
37.9839
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
CN
11s
f1 (ppm)

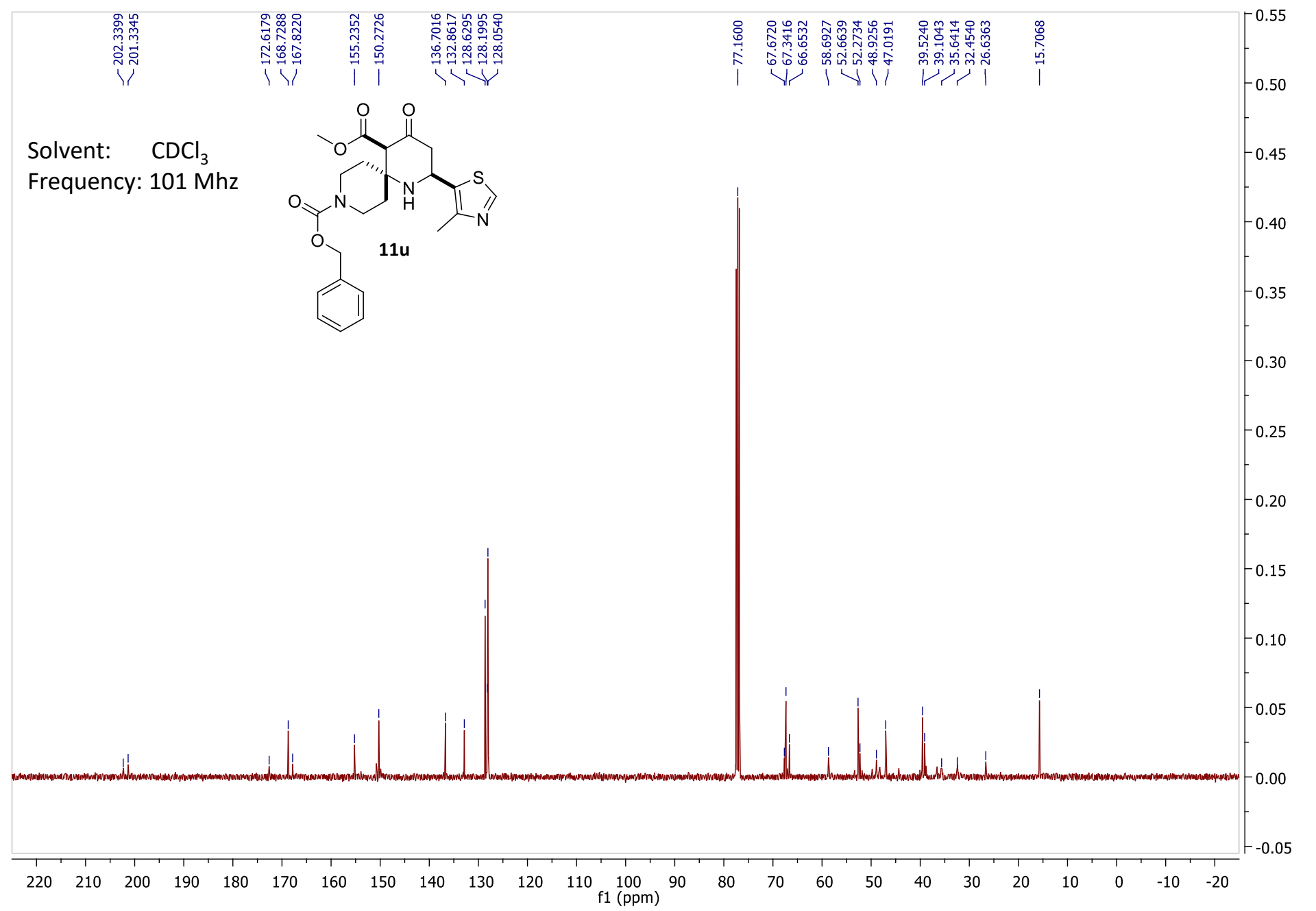
Solvent: $CDCl_3$
Frequency: 400 Mhz

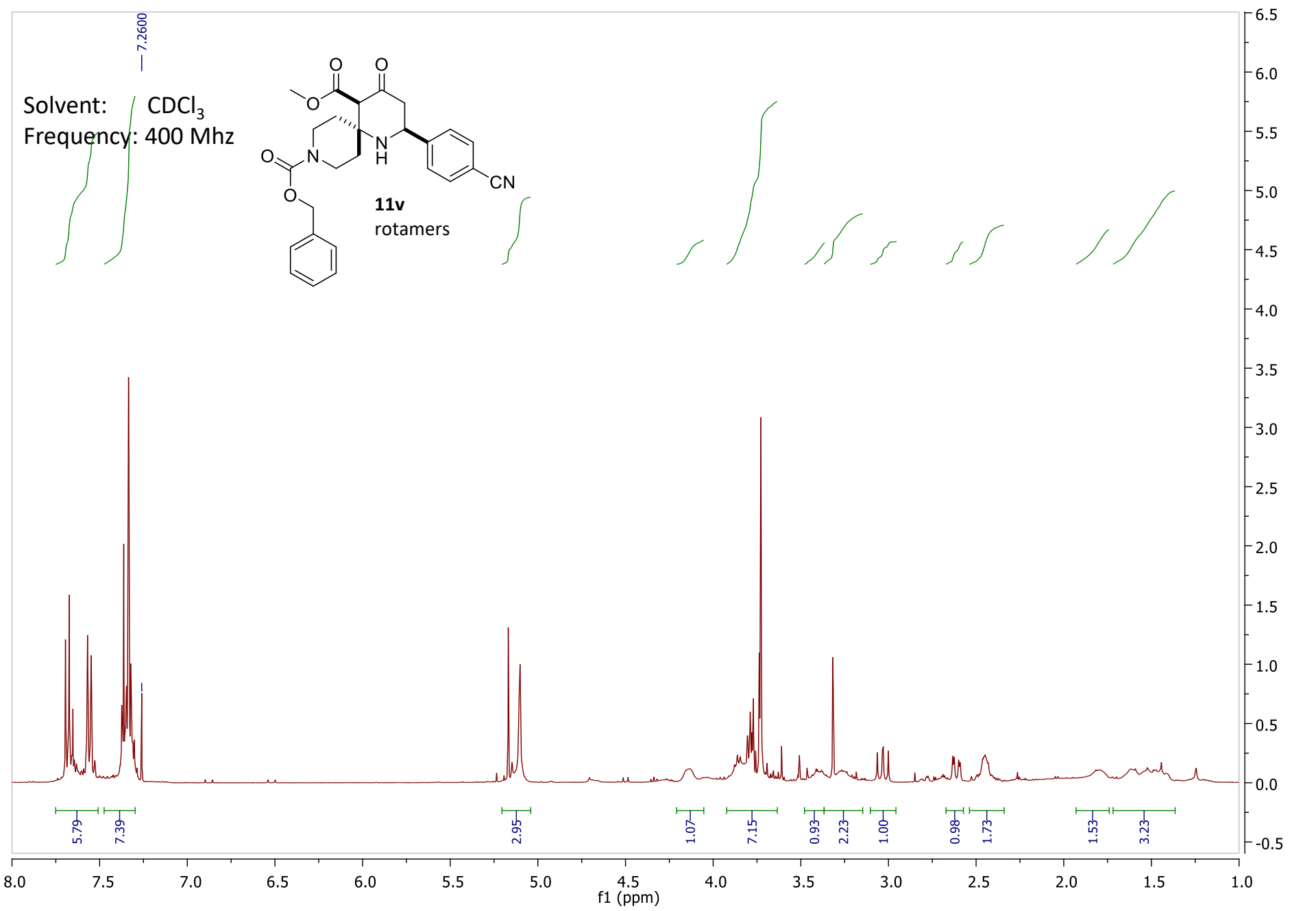
11t
Mixture of
diastereomers

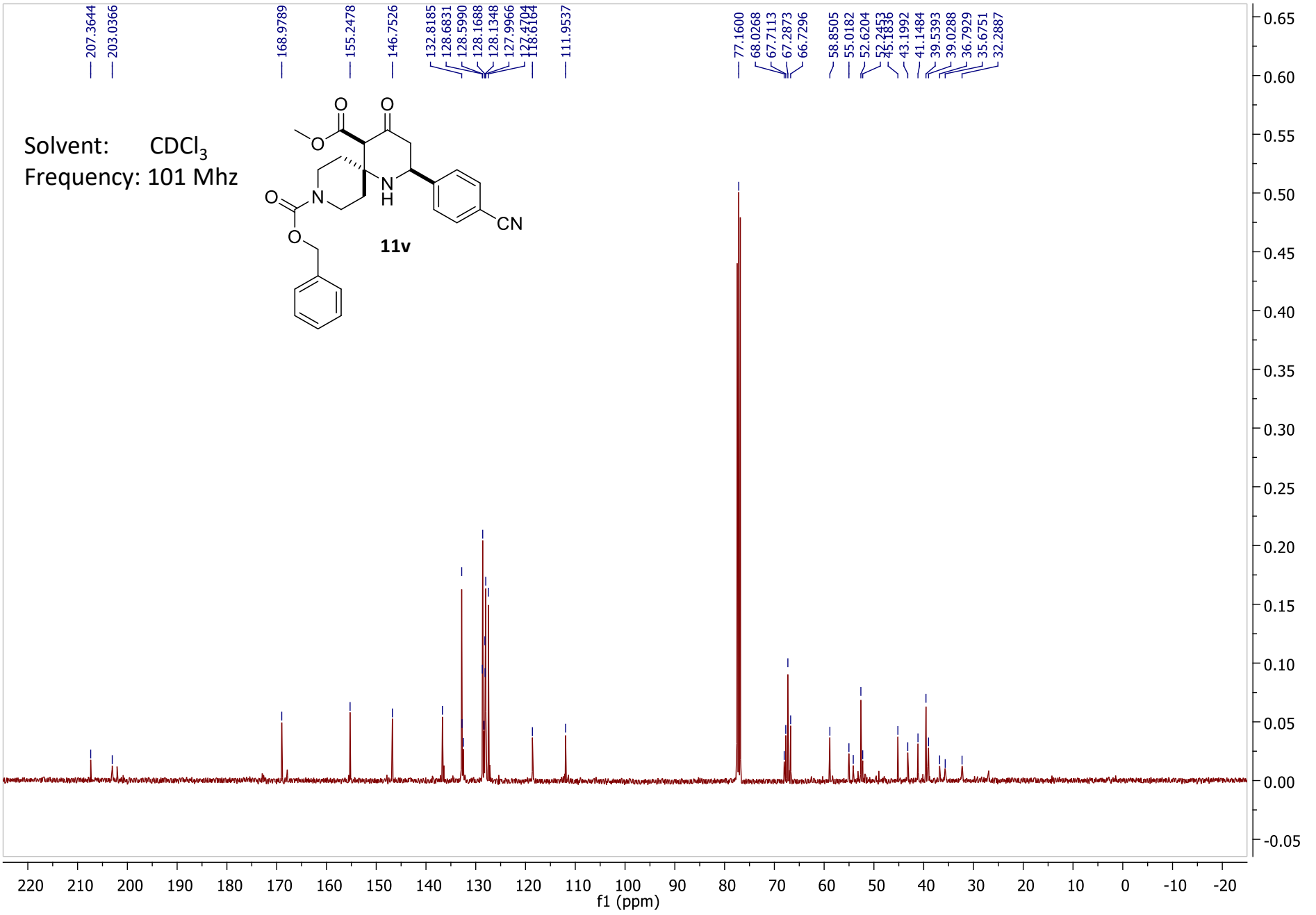



202.6033
201.4689
168.6868
167.7805
150.9513
150.2578
149.7783
133.3435
133.0776
77.1600
68.6799
67.1540
59.0878
58.0590
52.5869
52.1940
49.7266
48.4176
47.6475
46.8833
38.0544
37.1778
34.2706
28.3320
23.3250
23.0619
22.7471
22.5323
15.7199
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
S
S
N
11t
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Solvent: CDCl3
Frequency: 400 Mhz
7.2600
11u
Mixture of diastereomers and rotamers
1.00
4.94
2.07
0.99
1.70
3.38
2.42
1.21
0.96
3.53
4.85
f1 (ppm)

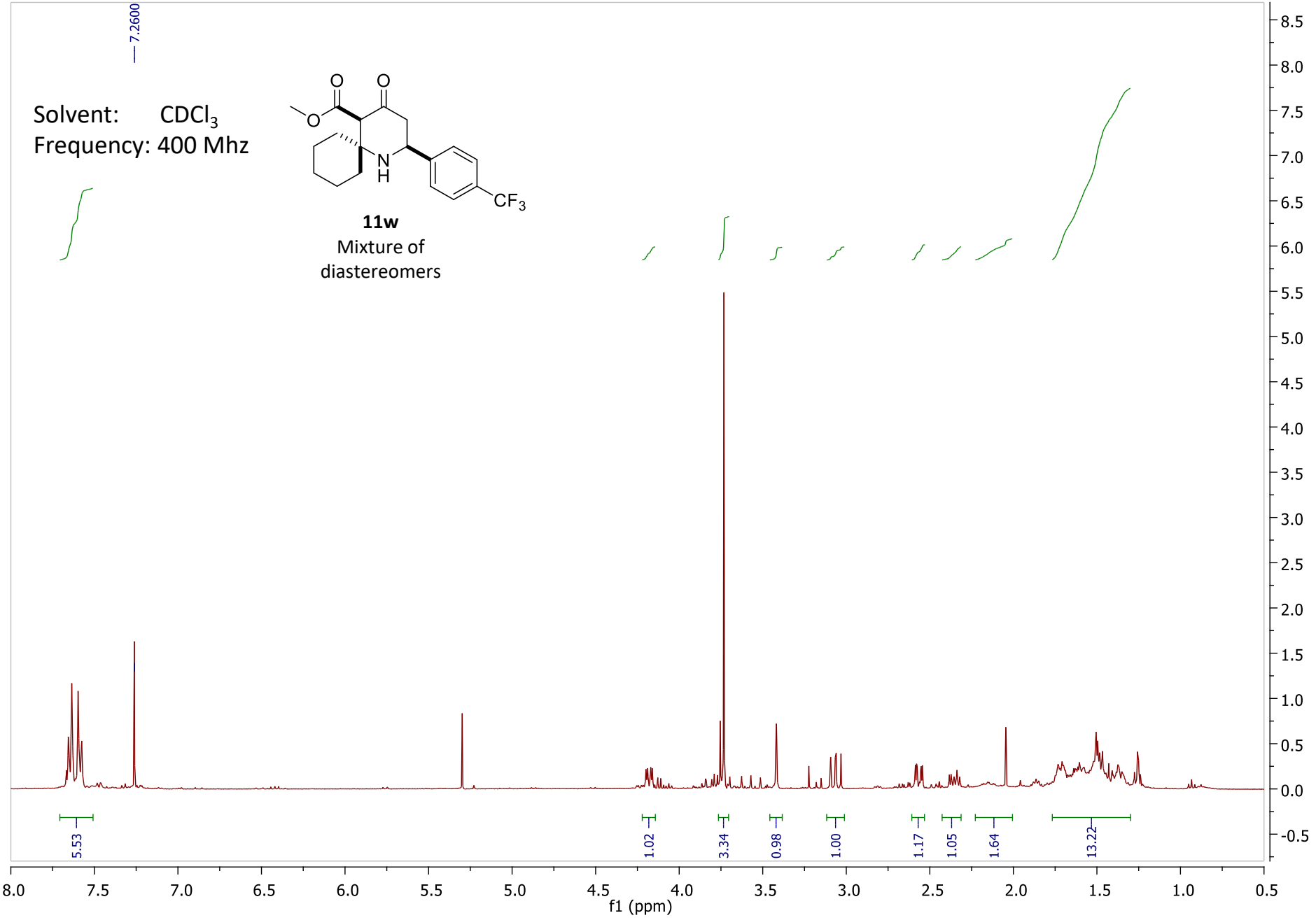

202.3399
201.3345
172.6179
168.7288
167.8220
155.2352
150.2726
136.7016
132.8617
128.6295
128.1995
128.0540
77.1600
67.6720
67.3416
66.6532
58.6927
52.6639
52.2734
48.9256
47.0191
39.5240
39.1043
35.6414
32.4540
26.6363
15.7068
Solvent: CDCl3
Frequency: 101 Mhz
11u
f1 (ppm)

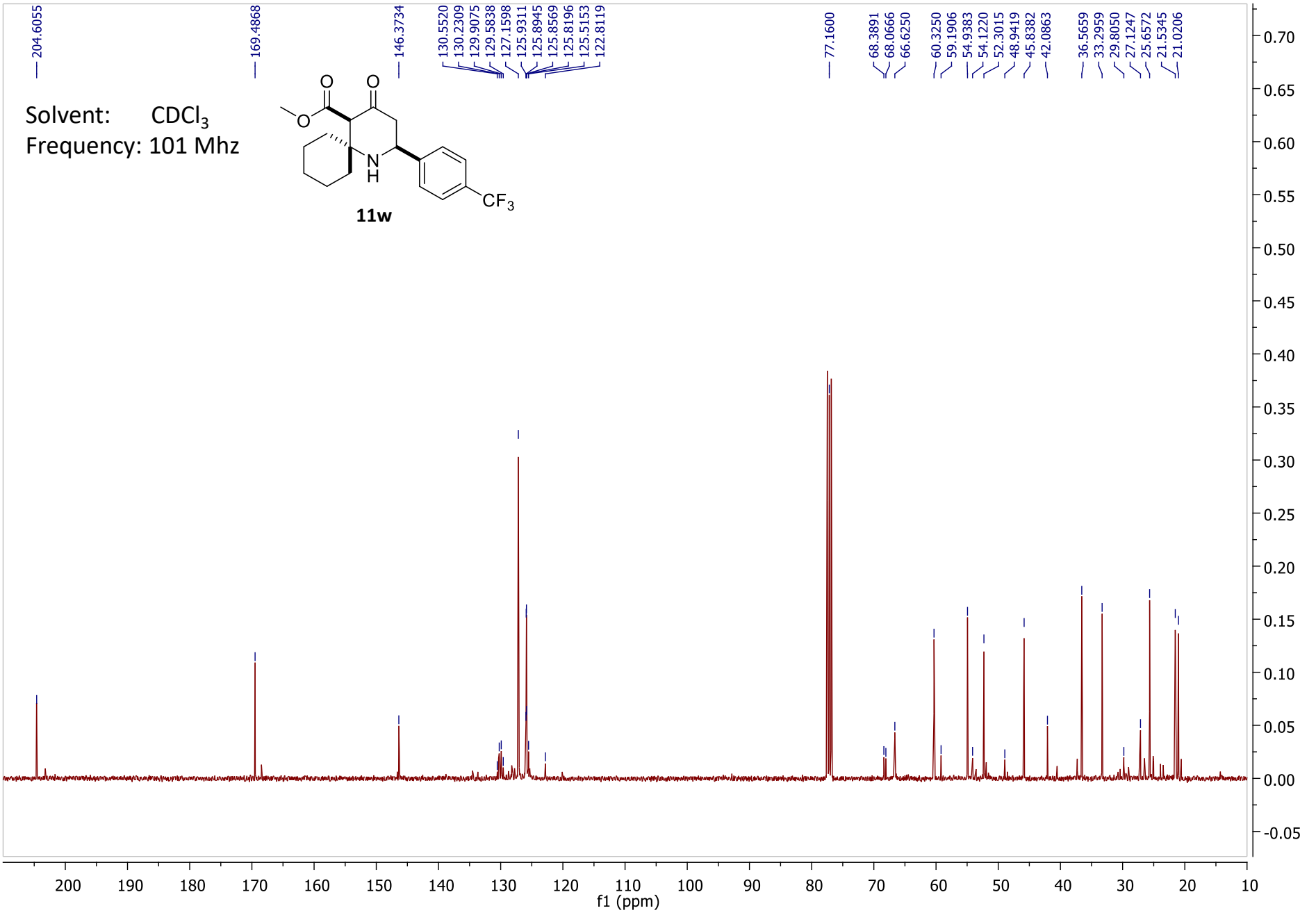

Solvent: $CDCl_3$
Frequency: 400 Mhz
7.2600
O
O
O
N
N
H
O
O
CN
11v
rotamers
5.79
7.39
2.95
1.07
7.15
0.93
2.23
1.00
0.98
1.73
1.53
3.23
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


207.3644
203.0366
168.9789
155.2478
146.7526
132.8185
128.6831
128.5990
128.1688
128.1348
127.9966
127.4704
118.6184
111.9537
77.1600
68.0268
67.7113
67.2873
66.7296
58.8505
55.0182
52.6204
52.2453
45.1836
43.1992
41.1484
39.5393
39.0288
36.7929
35.6751
32.2887
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
N
H
O
O
CN
11v
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

Solvent: $CDCl_3$
Frequency: 400 Mhz

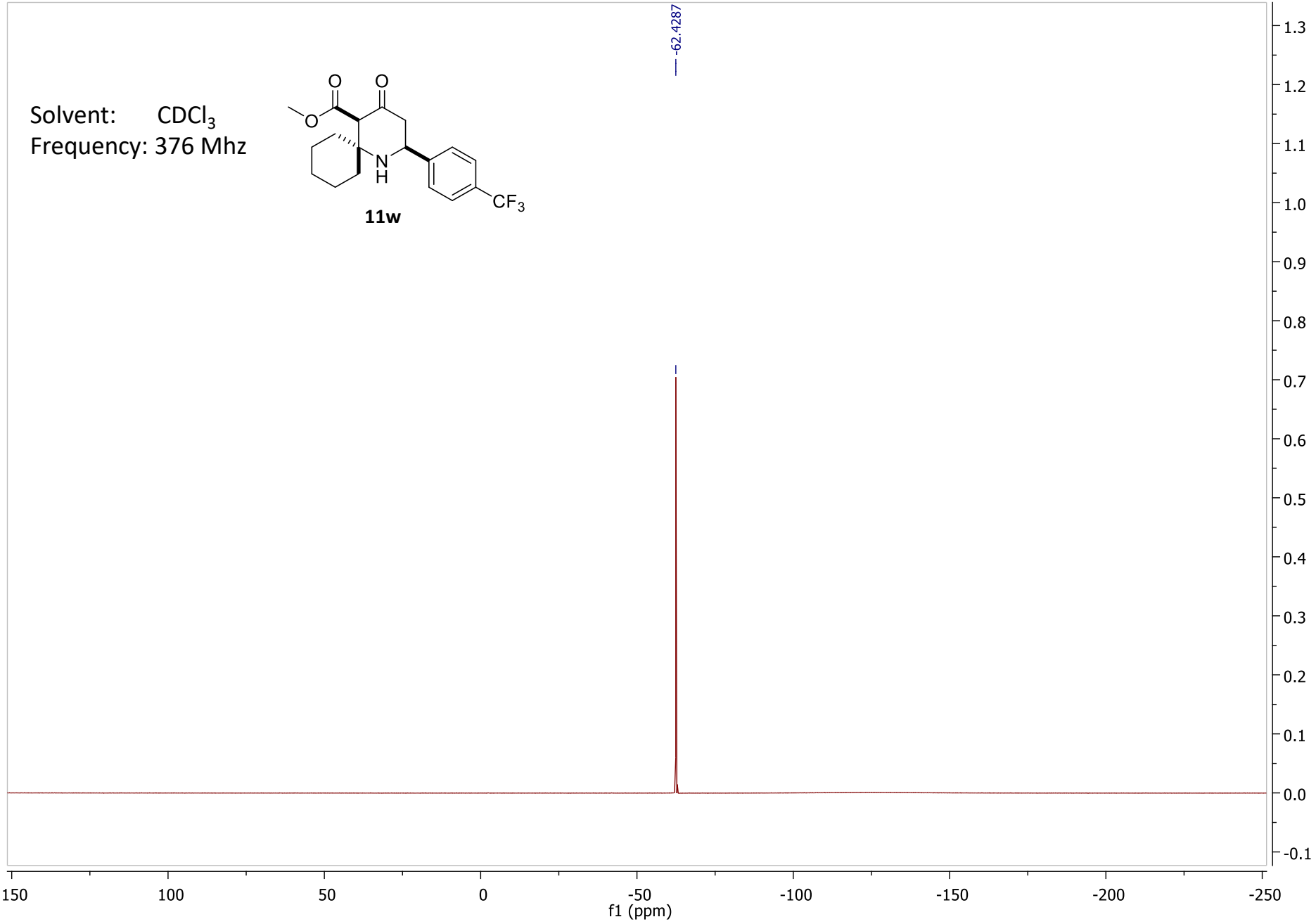
11w
Mixture of
diastereomers



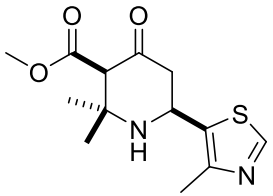

204.6055
169.4868
146.3734
130.5520
130.2309
129.9075
129.5838
127.1598
125.9311
125.8945
125.8569
125.8196
125.5153
122.8119
77.1600
68.3891
68.0666
66.6250
60.3250
59.1906
54.9383
54.1220
52.3015
48.9419
45.8382
42.0863
36.5659
33.2959
29.8050
27.1247
25.6572
21.5345
21.0206
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
CF3
11w
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Solvent: $CDCl_3$
Frequency: 376 Mhz

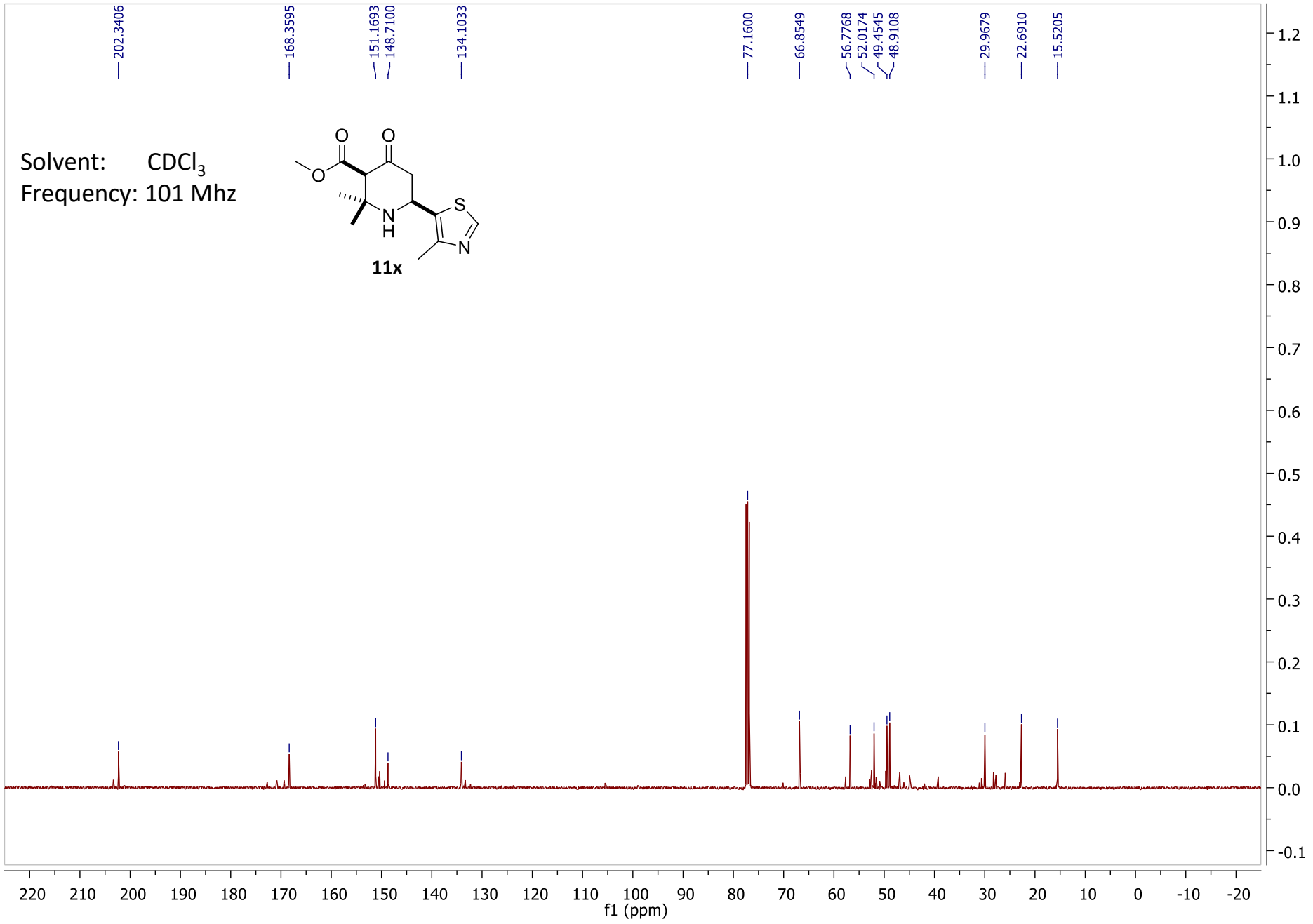
11w

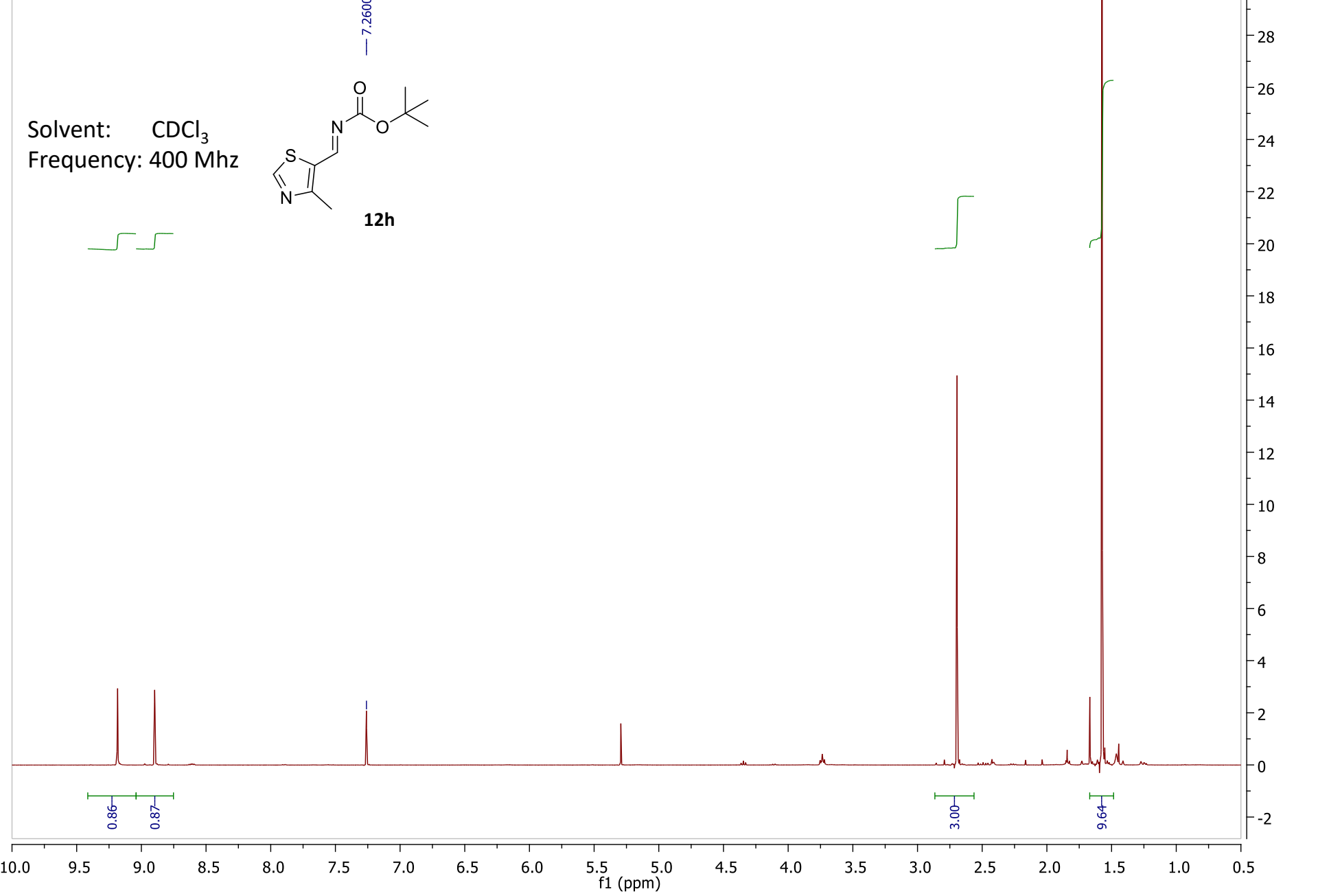


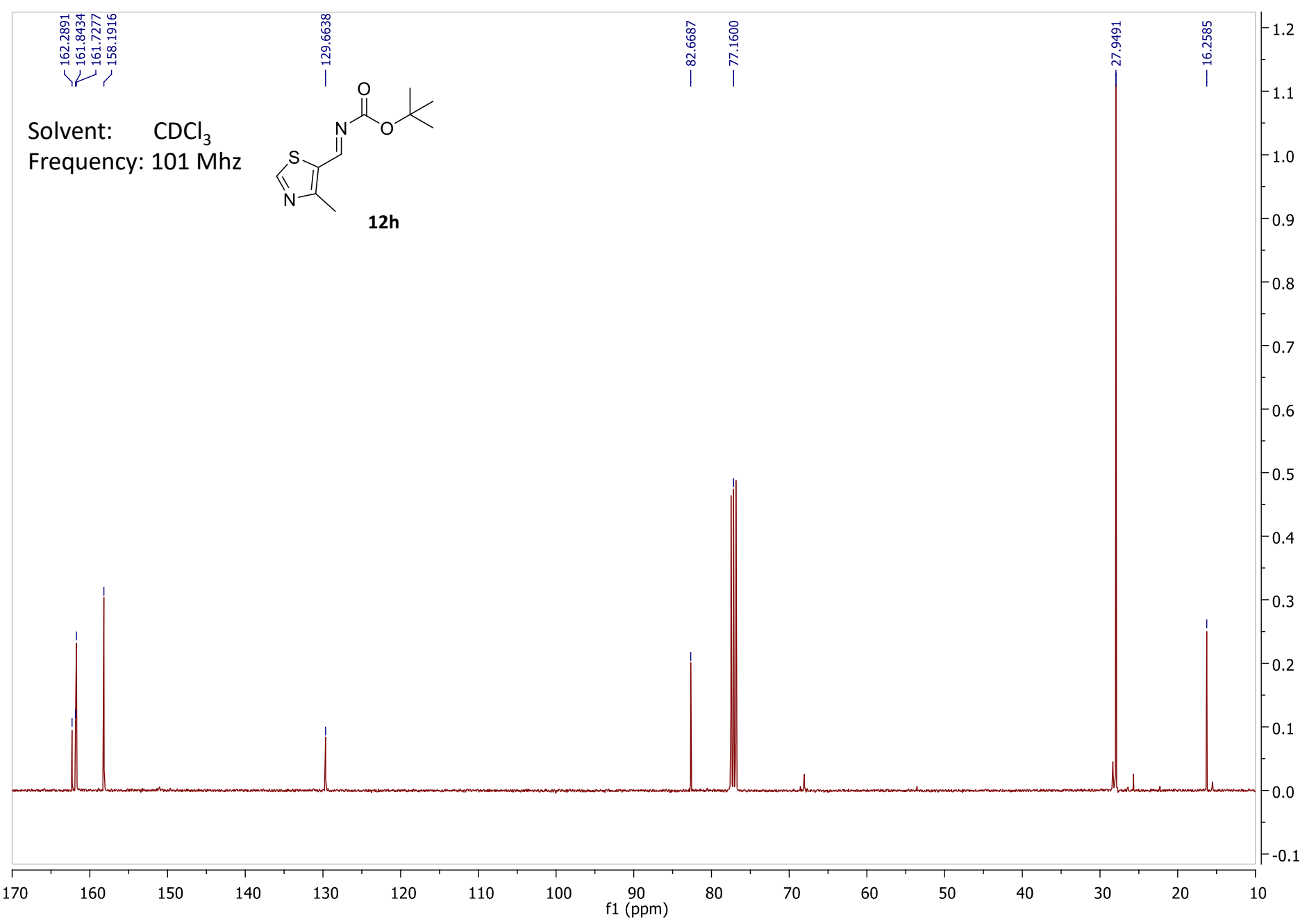
Solvent: $CDCl_3$
Frequency: 400 Mhz



11x
Mixture of
diastereomers


202.3406
168.3595
151.1693
148.7100
134.1033
77.1600
66.8549
56.7768
52.0174
49.4545
48.9108
29.9679
22.6910
15.5205
Solvent: CDCl3
Frequency: 101 Mhz
O
O
O
N
H
S
N
11x
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


Solvent: CDCl3
Frequency: 400 Mhz
12h
7.260
0.86
0.87
3.00
9.64
f1 (ppm)


162.2891
161.8434
161.7277
158.1916
129.6638
82.6687
77.1600
27.9491
16.2585
Solvent: CDCl3
Frequency: 101 Mhz
O
N
O
S
N
12h
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
-0.1
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)