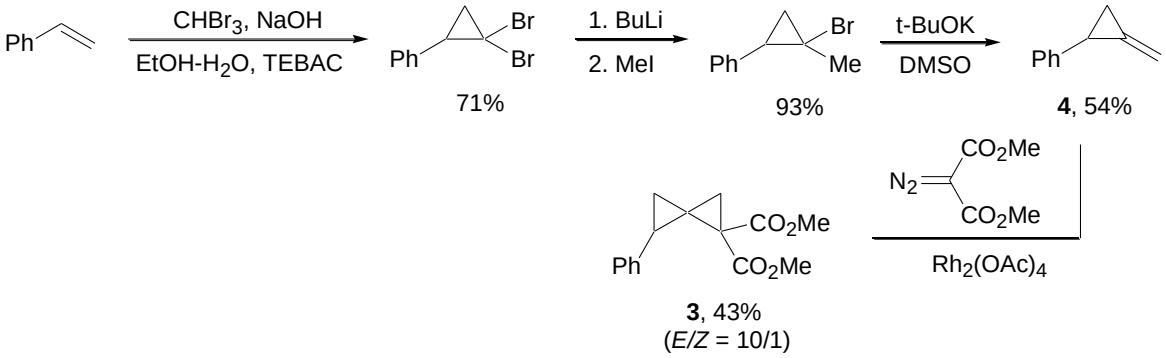
Electronic supplementary materials *Mendeleev Commun.*, 2019, **29**, 417–418

4-Phenylspiro[2.2]pentane-1,1-dicarboxylate: synthesis and reactions with $EtAlCl_2$ and 4,5-diazaspiro[2.4]hept-4-ene derivative

Dmitry A. Denisov, Denis D. Borisov, Konstantin V. Potapov, Roman A. Novikov and Yury V. Tomilov



Intermediate (2,2-dibromocyclopropyl)benzene and (2-bromo-2-methylcyclopropyl)benzene were prepared according known procedures. [S1, S2]

(2-Bromo-2-methylcyclopropyl)benzene.

A 2.5 *M* solution of *n*-BuLi (1.45 ml, 3.6 mmol) in hexane was added dropwise to a stirred solution of (2,2-dibromocyclopropyl)benzene (1 g, 3.6 mmol) in THF (5 ml) at –95 ºC. The mixture was stirred at this temperature for 10 min, and then iodomethane (1.53 g, 10.9 mmol) was added dropwise. Then the mixture was warmed to room temperature and water was added. Resulting mixture was extracted with Et_2O (twice), washed with water, washed with brine, and dried over anhydrous $MgSO_4$. The title compound was obtained in yield 0.713 g (93%) and was used without further purification for the preparation of known 1-methylidene-2-phenylcyclopropane **4**. [S2]

*Dimethyl 4-phenylspiro[2.2]pentane-1,1-dicarboxylate (**3**).*

Catalyst $Rh_2(OAc)_4$ (24 mg, 0.055 mmol) was added to a solution of 1-methylidene-2-phenylcyclopropane **4** (662 mg, 5.09 mmol) in dry CH_2Cl_2 (1.5 ml), and the mixture was stirred for 10

min. Then a solution of dimethyl diazomalonate (724 mg, 4.58 mmol) in CH_2Cl_2 (10 ml) was added via syringe pump over a period of 4 h. The mixture was stirred at room temperature for 2 days, then filtered through silica gel and concentrated on a rotary evaporator. Product **3** was isolated by chromatography on silica gel (light petroleum – EtOAc, 8:1) in yield 564 mg (43%) as a mixture of *E*- and *Z*-isomers in ratio 10:1. IR ($CHCl_3$): $\tilde{\nu}$ = 3685, 3033, 2955, 2849, 1732, 1605, 1522, 1498, 1477, 1438, 1425, 1333, 1233, 1198, 1126, 1091 cm^{-1}. HRMS, *m/z*: 283.0942 (calc. for $C_{15}H_{16}NaO_4$, *m/z*: 283.0941 $[M+Na]^+$)

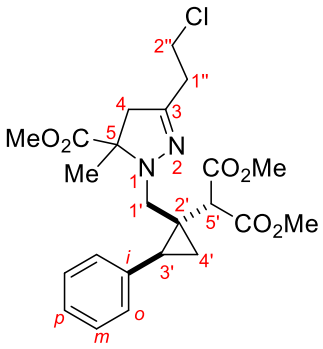
E-Isomer. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* 5.6 Hz, 1H, H_a from $H_2C(5)$), 1.65 (dd, *J* 8.8, 5.6 Hz, 1H, H_b from $H_2C(5)$), 1.80 (d, *J* 4.4 Hz, 1H, H_a from $H_2C(2)$), 2.01 (d, *J* 4.4 Hz, 1H, H_b from $H_2C(2)$), 2.53 (dd, *J* 8.8, 5.6 Hz, 1H, H(4)), 3.73 and 3.77 (both s, 2×3H, 2 OMe), 7.02–7.34 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0 (C(5)), 20.1 (C(2)), 22.8 (C(4)), 32.7 (C(3)), 34.6 (C(1)), 52.5 and 52.6 (2 OMe), 126.3 (*p*-Ph), 126.7 and 128.4 (*o*-Ph and *m*-Ph), 140.1 (*i*-Ph), 169.2 and 169.4 (2 COO).

Z-Isomer. ^1H NMR (300 MHz, $CDCl_3$) δ 1.26–1.58 (m, 2H, $H_2C(5)$), 1.88 (d, *J* 4.2 Hz, 1H, H_a from $H_2C(2)$), 2.14 (d, *J* 4.2 Hz, 1H, H_b from $H_2C(2)$), 3.75 and 3.82 (both s, 2×3H, 2 OMe). The remaining signals overlap with the signals of the major *E*-isomer.

[S1] J. Hu, Y. Xie and H. Huang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7272.

[S2] T. Kippo, K. Hamaoka and I. Ryu, *J. Am. Chem. Soc.*, 2013, **135**, 632.

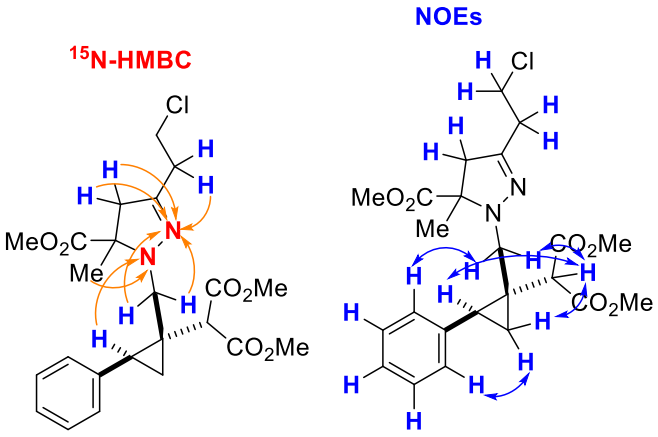
*General synthetic procedure and spectroscopic data for compounds **7–10**.* All operations with $EtAlCl_2$ were performed under dry argon atmosphere. A 1.0 *M* solution of $EtAlCl_2$ (0.6 mmol) in hexane was added to a solution of dimethyl 4-phenylspiro[2.2]pentane-1,1-dicarboxylate **3** (50 mg, 0.3 mmol) and the pyrazoline **5** (101 mg, 0.4 mmol) in dry CH_2Cl_2 (2 ml) and the mixture was stirring at reflux for 30 min. Then an aqueous solution of HCl (5%) was added at room temperature until pH 3 was achieved and the reaction mixture was extracted with CH_2Cl_2 (3×10 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (benzene–EtOAc (30:1) to benzene–EtOAc (10:1)) on silica gel to afford the pure product **7** and by-products **8** and **9**.

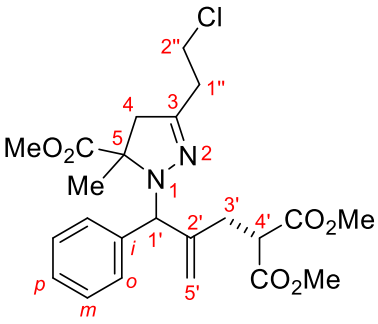


*Dimethyl 2-(1-{[3-(2-chloroethyl)-5-methoxycarbonyl-5-methyl-4,5-dihydro-1H-pyrazol-1-yl]methyl}-2-phenylcyclopropyl)malonate **(7)*** was prepared in yield 48% (67 mg, *cis/trans* > 10:1 and *dr* ~1.1:1) as a colorless oil. IR (KBr) $\tilde{\nu}$ 3084, 3059, 3026, 3000, 2954, 2846, 1734 br. (C=O), 1604, 1498, 1435, 1319, 1288, 1197, 1155 cm^{-1}. HRMS, *m/z*: 487.1591 (calc. for $C_{23}H_{29}N_2NaO_6Cl$, *m/z*: 487.1606 (for ^{35}Cl) $[M+Na]^+$)

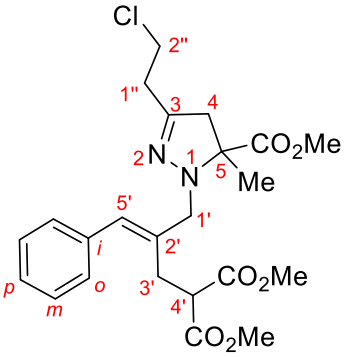
<u>*cis*-Diastereomer A</u>: ^1H NMR (300 MHz, $CDCl_3$): δ 1.02–1.13 (m, $H_a(4')$), 1.08 (s, Me), 1.35 (t, $^2J = {}^3J$ 6.5 Hz, $H_b(4')$), 2.08 (d, ^2J 13.3 Hz, H_a from CH_2N), 2.41–2.51 (m, H(3′) and $H_a(4)$), 2.70 (t, ^3J 6.4 Hz, $H_2C(1'')$), 3.10 (d, ^2J 11.8 Hz, $H_b(4)$), 3.19 (d, ^2J 13.3 Hz, H_b from CH_2N), 3.64, 3.74 and 3.80 (all s, 3 OMe), 3.72 (t, ^3J 6.4 Hz, CH_2Cl), 4.31 (s, H(5′)), 7.15–7.23 (m, *p*-Ph), 7.24–7.34 (m, *m*-Ph), 7.35–7.46 (m, *o*-Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.5 (C(4′)), 18.3 (Me), 24.5 (C(2′)), 24.8 (C(3′)), 33.5 (C(1′′)), 41.3 (C(2′′)), 46.9 (C(4)), 51.8 (C(1′)), 51.8, 52.0 and 52.1 (3 OMe), 53.8 (C(5′)), 71.4 (C(5)), 126.0 (*p*-Ph), 127.9 (*m*-Ph), 129.5 (*o*-Ph), 138.2 (*i*-Ph), 148.1 (C(3)), 169.0, 169.3, and 173.0 (3 COO). ^{15}N NMR (30.5 MHz, $CDCl_3$): δ 142.7 (N(1)), 339.4 (N(2)).

<u>*cis*-Diastereomer B</u>: ^1H NMR (300 MHz, $CDCl_3$): δ 1.02–1.13 (m, $H_a(4')$), 1.13 (s, Me), 1.29 (t, $^2J = {}^3J$ 6.5 Hz, $H_b(4')$), 2.22 (d, ^2J 13.4 Hz, H_a from CH_2N), 2.41–2.51 (m, H(3′) and $H_a(4)$), 2.72 (t, ^3J 6.4 Hz, $H_2C(1'')$), 3.06 (d, ^2J 11.8 Hz, $H_b(4)$), 3.12 (d, ^2J 13.4 Hz, H_b from CH_2N), 3.54, 3.75 and 3.79 (all s, 3 OMe), 3.70 (t, ^3J 6.4 Hz, CH_2Cl), 4.33 (s, H(5′)), 7.15–7.23 (m, *p*-Ph), 7.24–7.34 (m, *m*-Ph), 7.35–7.46 (m, *o*-Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7 (C(4′)), 19.2 (Me), 24.7 (C(2′)), 25.6 (C(3′)), 33.5 (C(1′′)), 41.1 (C(2′′)), 47.0 (C(4)), 51.9 (C(1′)), 51.7, 51.9 and 52.2 (3 OMe), 54.3 (C(5′)), 71.5 (C(5)), 126.1 (*p*-Ph), 127.8 (*m*-Ph), 129.4 (*o*-Ph), 138.0 (*i*-Ph), 148.5 (C(3)), 168.9, 169.2, and 173.1 (3 COO). ^{15}N NMR (30.5 MHz, $CDCl_3$): δ 142.5 (N(1)), 340.9 (N(2)).

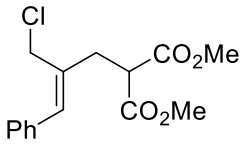




Dimethyl 2-[3-(2-chloroethyl)-5-methoxycarbonyl-5-methyl-4,5-dihydro-1H-pyrazol-1-yl](phenylmethyl)allylmalonate ***(8)*** was isolated together with compound **7** (ratio ~1:1.4) in yield ~7% (20 mg, *dr* = 4:1). Colorless oil. Major diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 3H, Me), 2.55 (d, 1H, ^{2}J = 16.9 Hz, H(4)), 3.37 (d, 1H, ^{2}J = 16.9 Hz, H(4)), 4.64 (s, 1H, H(5′)), 4.86 (s, 1H, H(1′)), 5.02 (s, 1H, H(5′)). Minor diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): 4.72 (s, 1H, H(5′)), 4.83 (s, 1H, H(1′)), 5.00 (s, 1H, H(5′)). The remaining signals overlap with the signals of the compound **9**. HRMS calcd for $C_{23}H_{29}N_2O_6Cl$ (*M*, for ^{35}Cl): *M+Na*, 487.1606. Found: *m/z* 487.1600.



Dimethyl (E)-{2-[3-(2-chloroethyl)-5-methoxycarbonyl-5-methyl-4,5-dihydro-1H-pyrazol-1-ylmethyl]-3-phenylallyl}malonate ***(9)*** was isolated together with compound **8** (ratio ~1:2) in yield ~4% (13 mg, mixture of *E*- and *Z*-isomers ~6:1). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.47 (s, 1H, H_{mn}(5′)), 6.60 (s, 1H, H_{mj}(5′)). The remaining signals overlap with the signals of the compounds **8**.

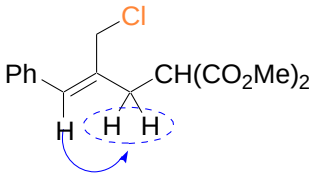


*Dimethyl 2-(chloromethyl)-3-phenylallylmalonate (**10**).*

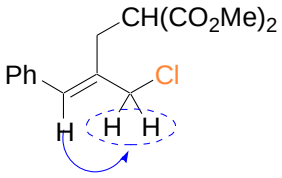
A 1.0 *M* solution of $EtAlCl_2$ (0.576 mmol) in hexane was added to a solution of dimethyl 4-phenylspiro[2.2]pentane-1,1-dicarboxylate **3** (150 mg, 0.576 mmol) in dry CH_2Cl_2 (5 ml), and the mixture was stirring at reflux for 30 min. Then an aqueous solution of HCl (5%) was added at room temperature until pH 3 was achieved, and the mixture was extracted with CH_2Cl_2 (3×10 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (Petrolium ether – EtOAc = 10:1) on silica gel to afford the compound **10** (67 mg, ~40%) as a colorless oil in a mixture of two isomers (*Z*/*E* = 2.6/1). IR ($CHCl_3$) $\tilde{\nu}$ 3006, 2956, 2847, 1751, 1734, 1437, 1334, 1284, 1238 cm^{-1}. HRMS: calcd. for $C_{15}H_{17}NaClO_4$ (*M*, for ^{35}Cl): *M*+*Na*, 319.0706. Found 319.0708.

Z-Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 2.96 (dd, 2H, ^3J = 7.9, ^4J = 1.0 Hz, CH_2), 3.66 and 3.76 (both s, 2×3H, 2 OMe), 3.78 (t, 1H, *J* = 7.9 Hz, CH), 4.21 (s, 2H, CH_2Cl), 6.57 (bd.s, 1H, =CH), 7.18–7.39 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.5 (CH_2), 43.2 (CH_2Cl), 50.6 (CH), 52.7 (2 OMe), 127.7 and 128.7 (*o*- and *m*-Ph), 128.6 (*p*-Ph), 133.1 (CH=), 133.7 (*i*-Ph), 136.0 (=C), 169.2 (2 COO).

E-Isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 3.08 (d, 2H, *J* = 7.9 Hz, CH_2), 4.23 (s, 2H, CH_2Cl), 6.72 (s, 1H, =CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.4 (CH_2), 49.5 (CH), 49.9 (CH_2Cl), 52.6 (2 OMe), 133.2 (=CH), 169.1 (2 COO). The remaining signals overlap with the signals of the major isomer.

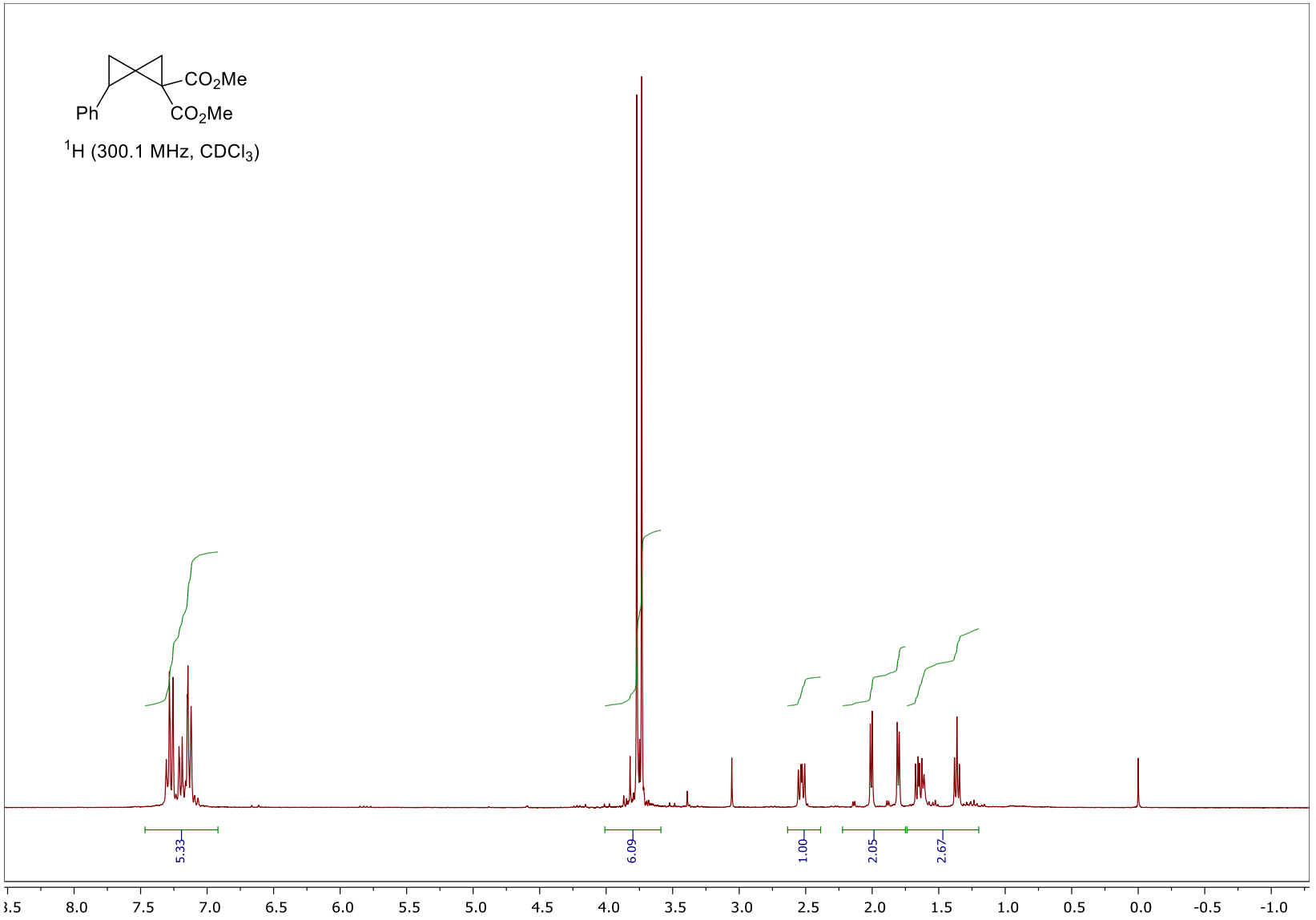


Major (*Z*)



Minor (*E*)

Key NOEs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Ph
CO2Me
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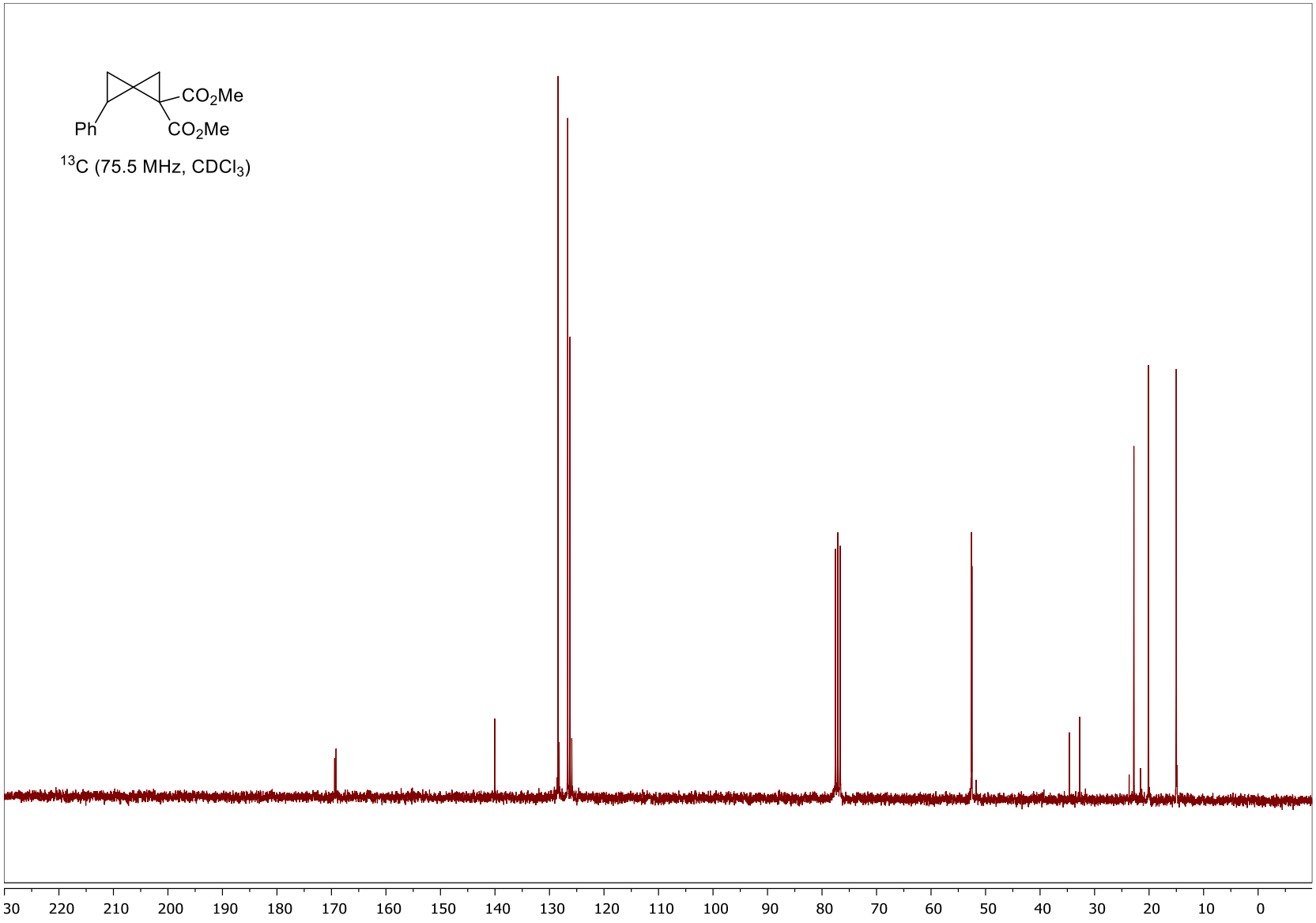
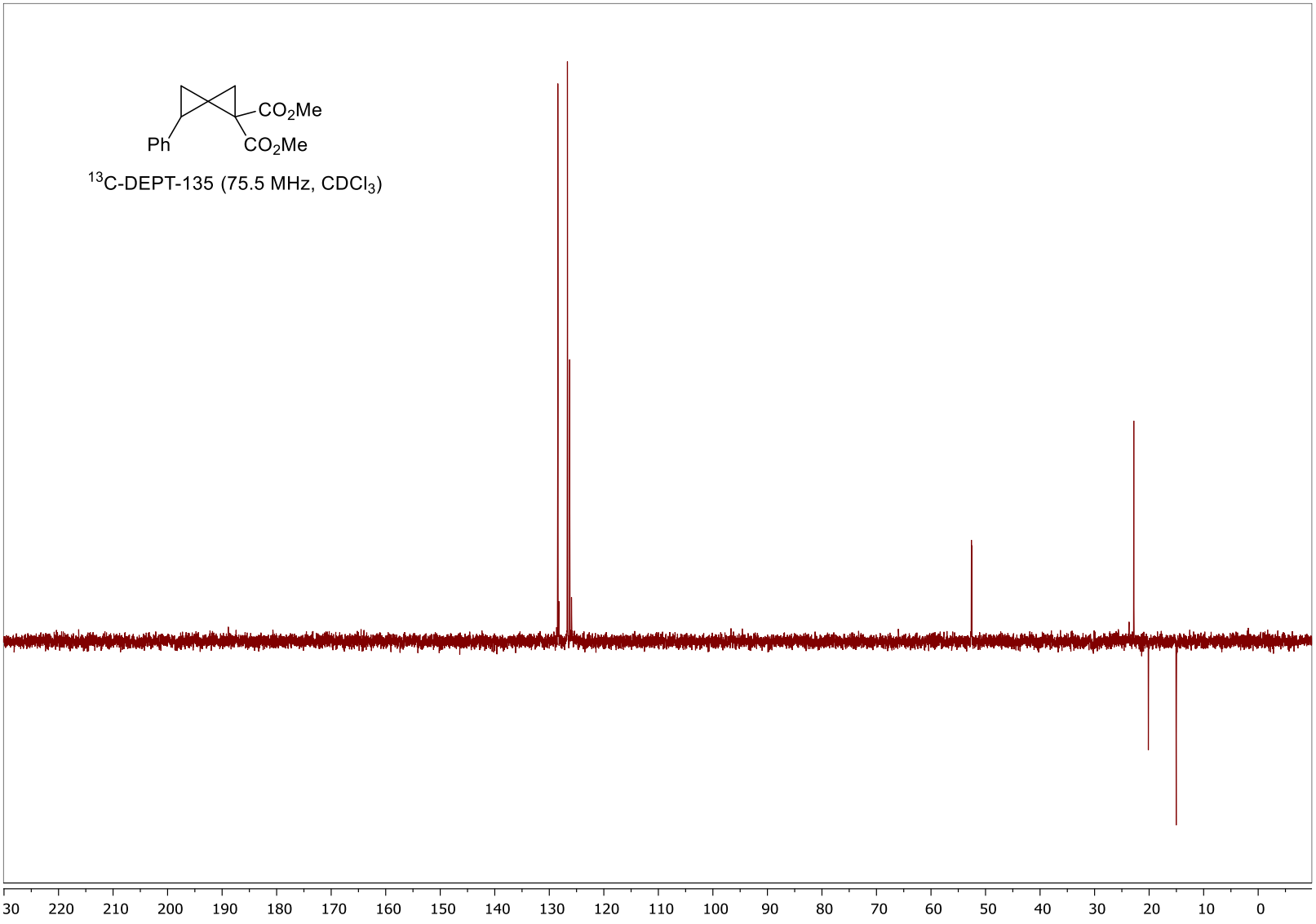
6.09
1.00
2.05
2.67
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0


CO2Me
Ph
CO2Me
13C (75.5 MHz, CDCl3)
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


CO2Me
Ph
CO2Me
13C-DEPT-135 (75.5 MHz, CDCl3)
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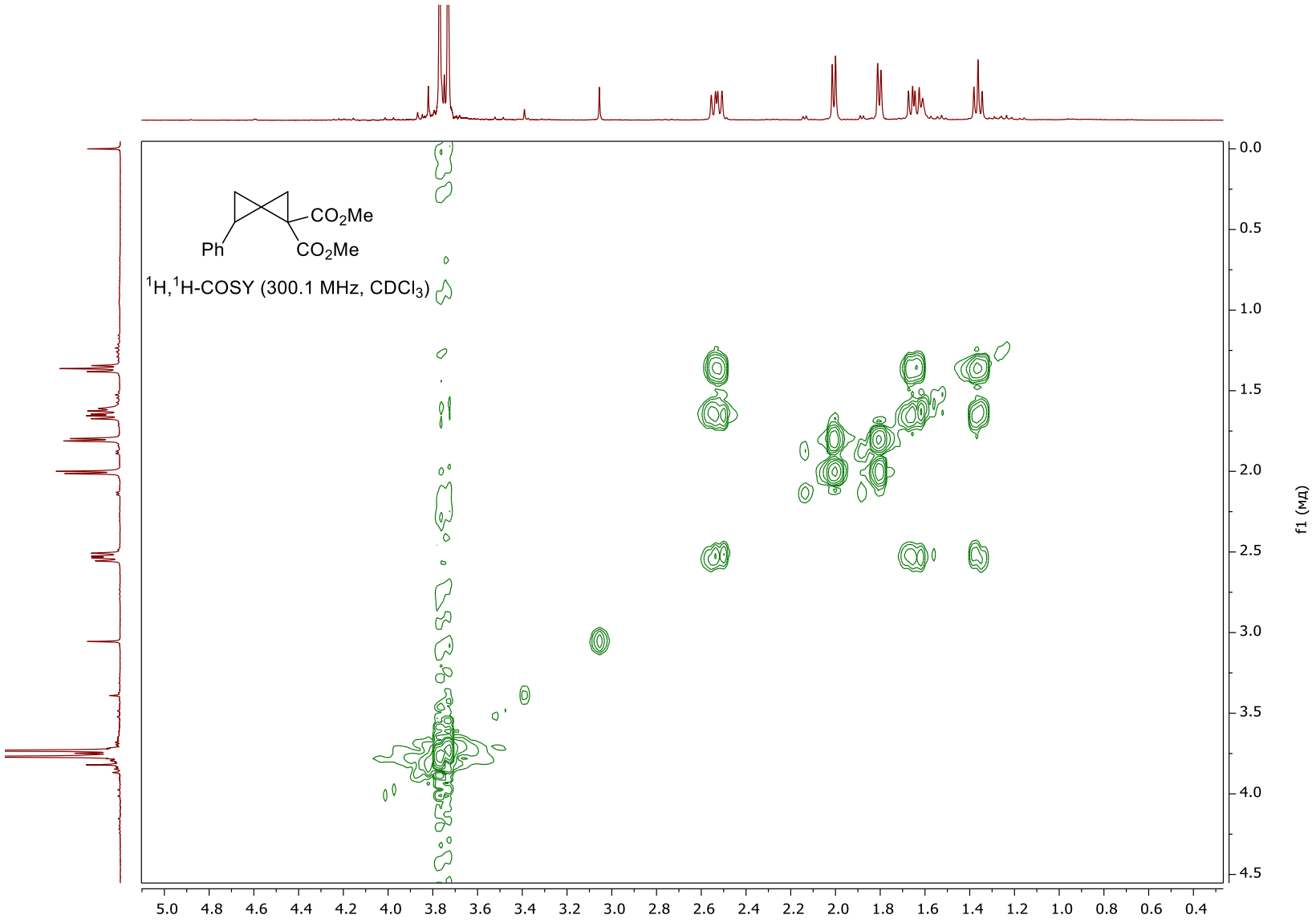
CO2Me
Ph
CO2Me
1H,1H-COSY (300.1 MHz, CDCl3)
f1 (мд)
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0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
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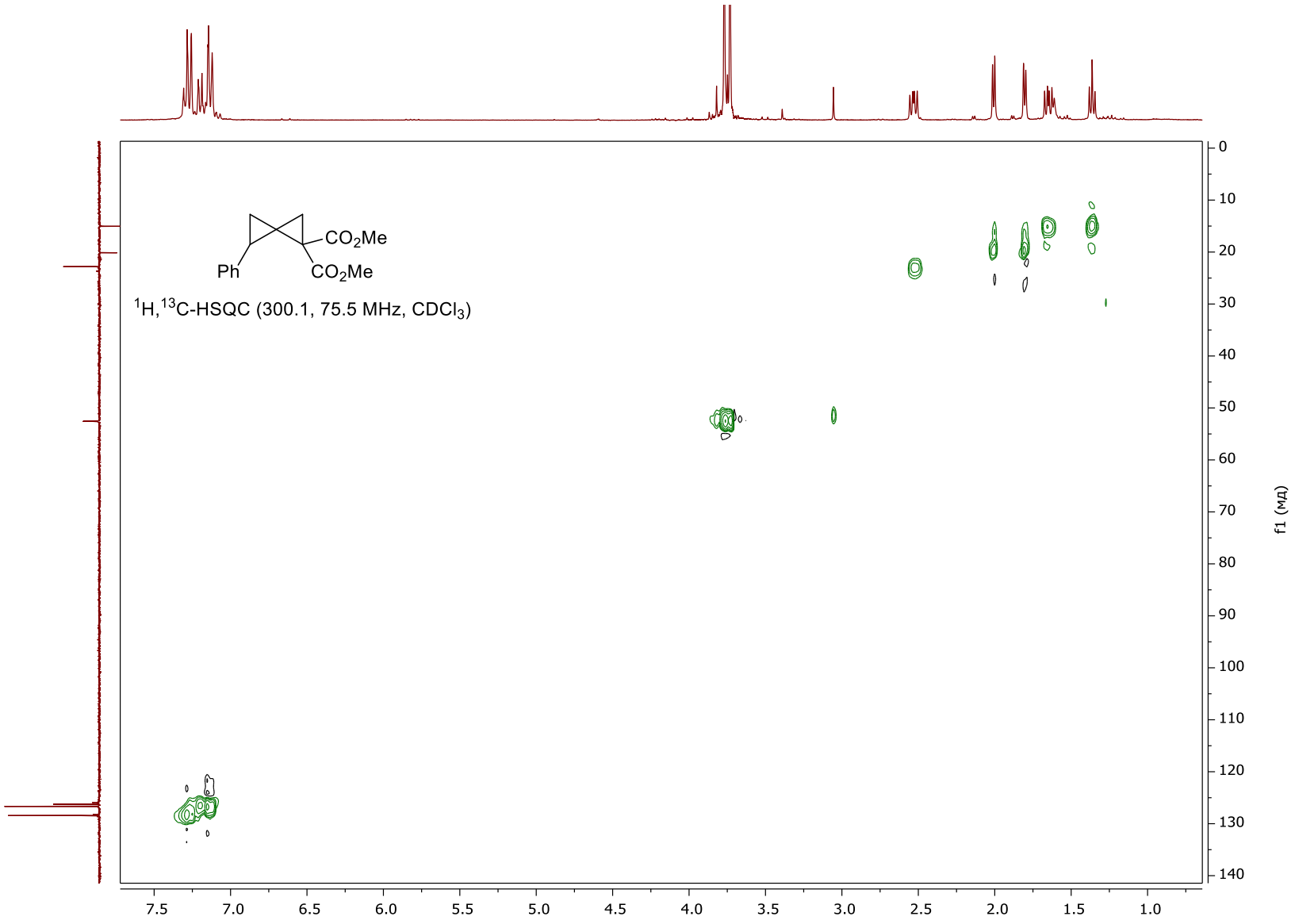
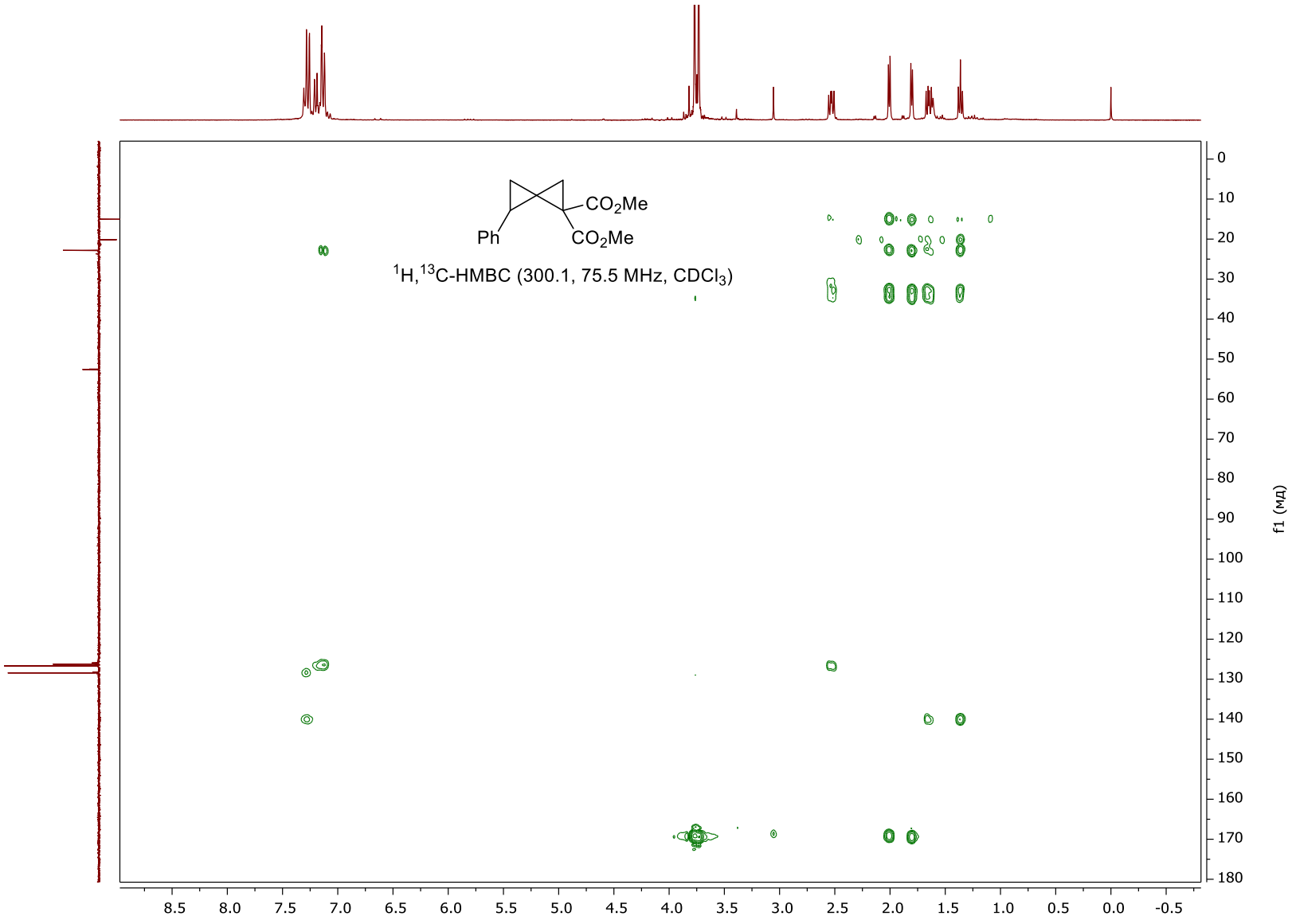
1.6
1.4
1.2
1.0
0.8
0.6
0.4


CO2Me
Ph
CO2Me
1H,13C-HSQC (300.1, 75.5 MHz, CDCl3)
f1 (мд)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
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


CO2Me
Ph
CO2Me
1H,13C-HMBC (300.1, 75.5 MHz, CDCl3)
f1 (мд)
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10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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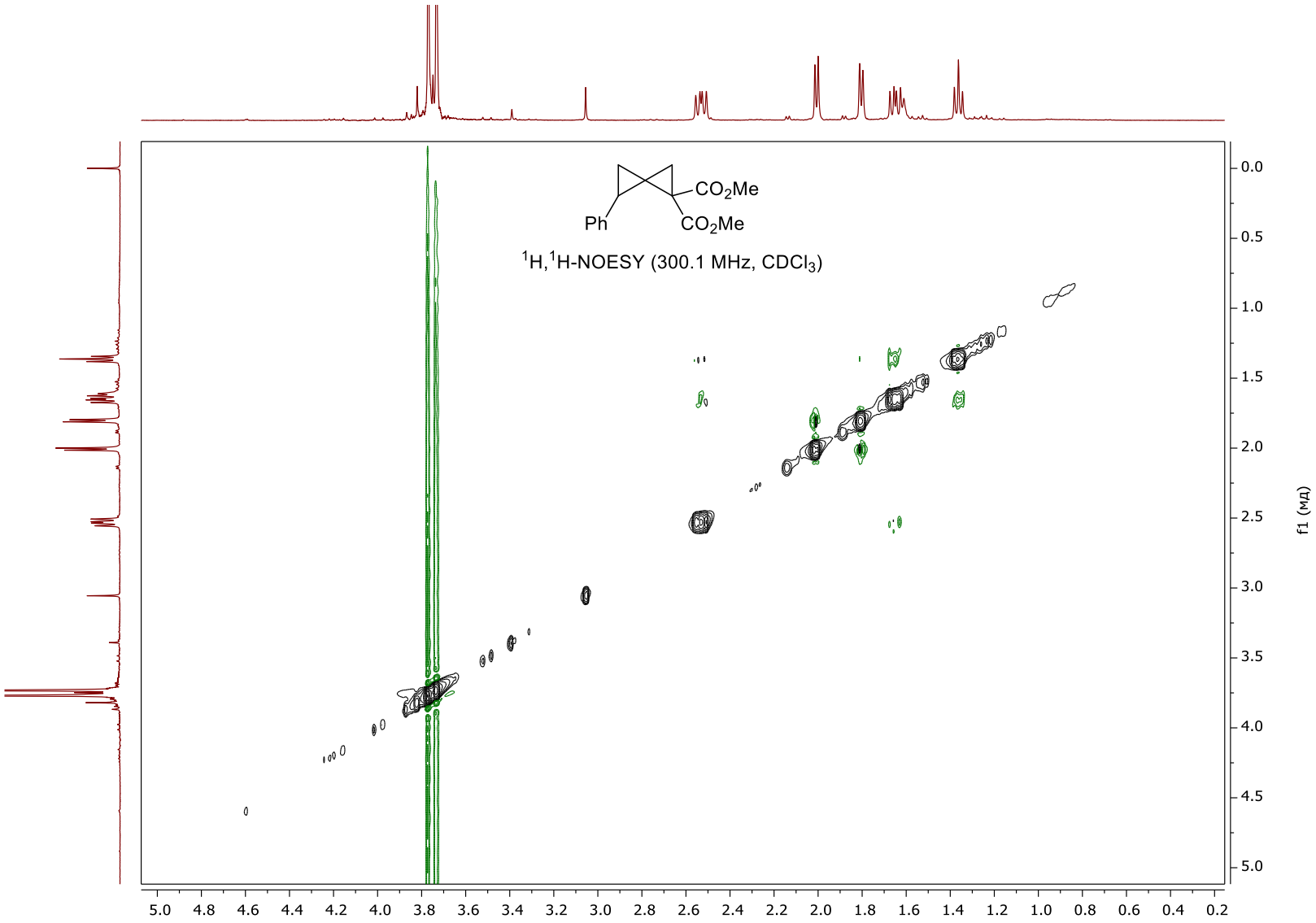
0.0
-0.5


CO2Me
Ph
CO2Me
1H,1H-NOESY (300.1 MHz, CDCl3)
f1 (мд)
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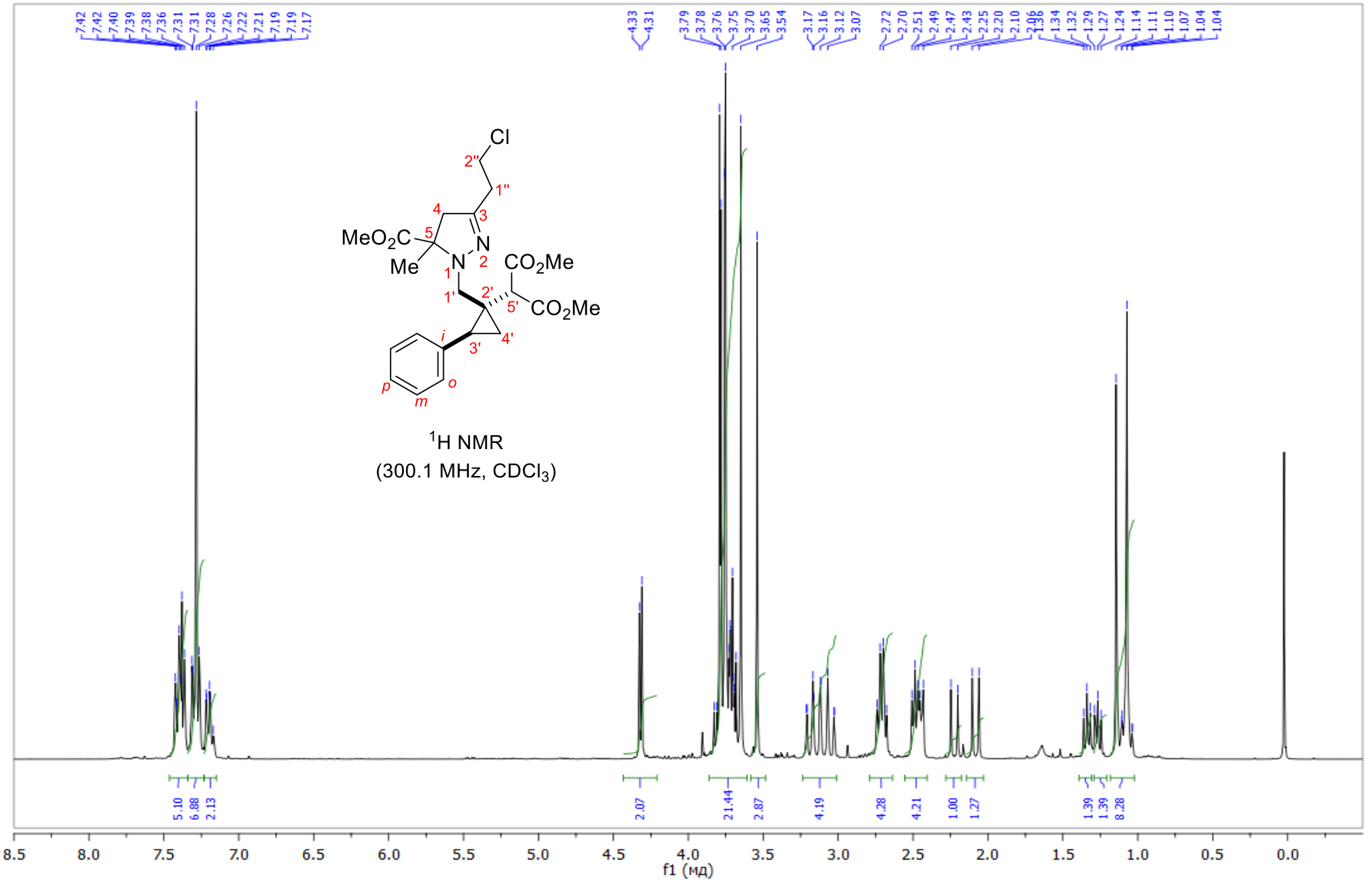
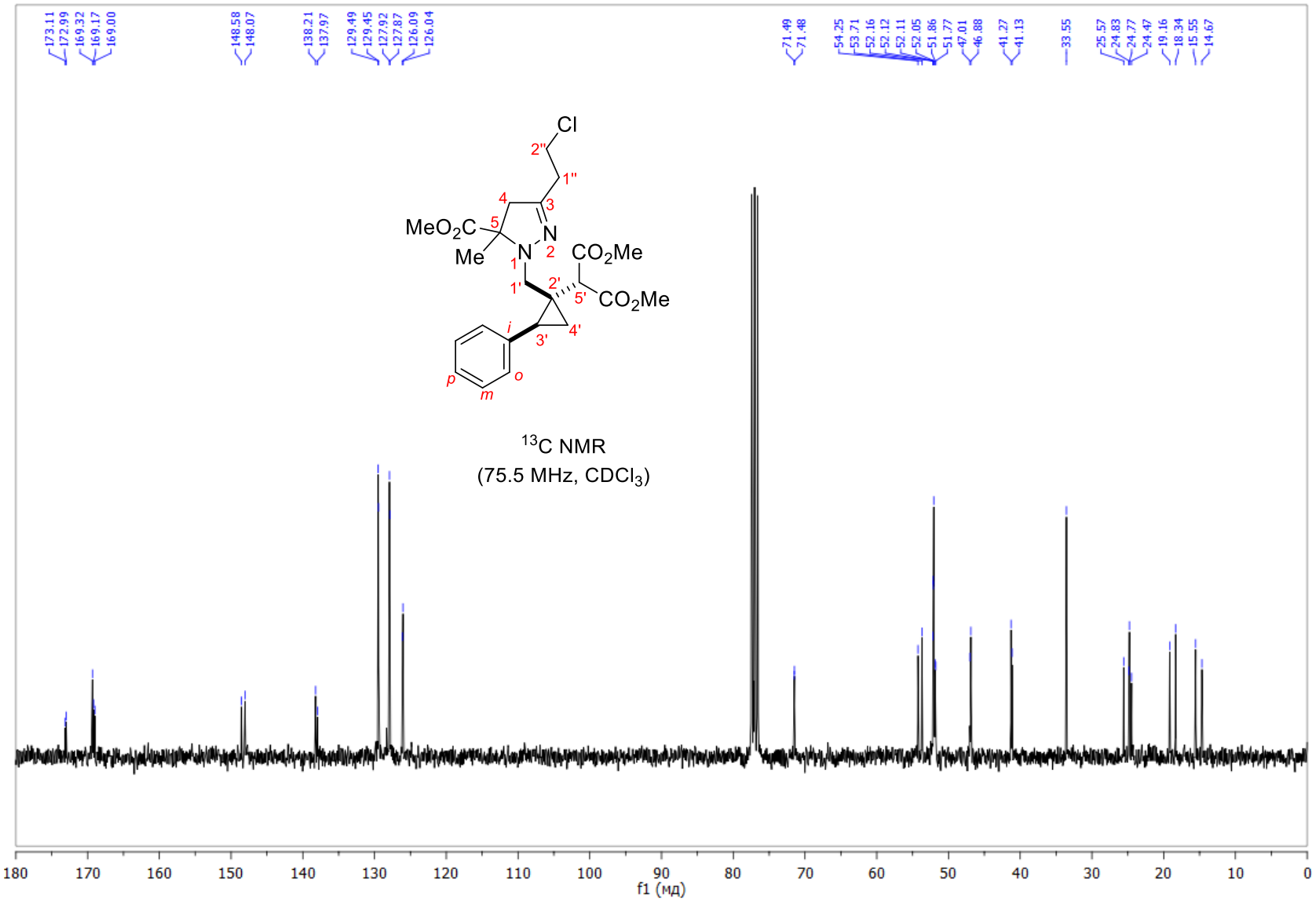
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2


Cl
2''
1''
4
3
MeO2C
5
N
Me
N
2
CO2Me
1
1'
2'
5'
CO2Me
i
3'
4'
p
o
m
1H NMR
(300.1 MHz, CDCl3)
7.42 7.42 7.40 7.39 7.38 7.36 7.31 7.31 7.28 7.26 7.22 7.21 7.19 7.19 7.17
4.33 4.31
3.79 3.78 3.76 3.75 3.70 3.65 3.54
3.17 3.16 3.12 3.07
2.72 2.70 2.51 2.49 2.47 2.43 2.25 2.20 2.10 2.06 1.36 1.34 1.32 1.29 1.27 1.24 1.14 1.11 1.10 1.07 1.04 1.04
5.10 6.88 2.13 2.07 21.44 2.87 4.19 4.28 4.21 1.00 1.27 1.39 1.39 8.28
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)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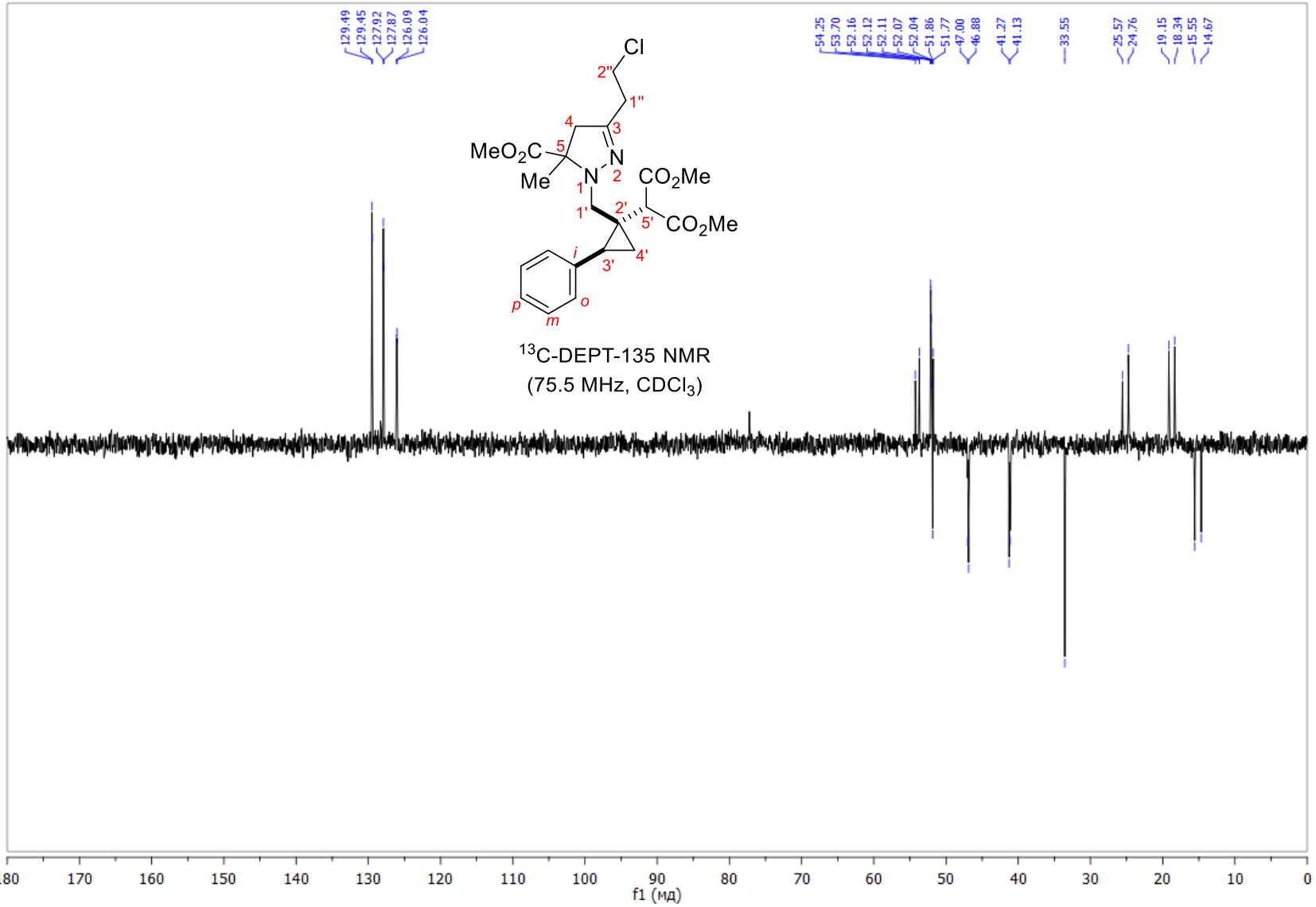
126.09
126.04
71.49
71.48
54.25
53.71
52.16
52.12
52.11
52.05
51.86
51.77
47.01
46.88
41.27
41.13
33.55
25.57
24.83
24.77
24.47
19.16
18.34
15.55
14.67
Cl
2"
1"
4
3
5
MeO2C
Me
N
2
1
CO2Me
1'
2'
5'
CO2Me
i
3'
4'
p
o
m
13C NMR
(75.5 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)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126.04
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25.57
24.76
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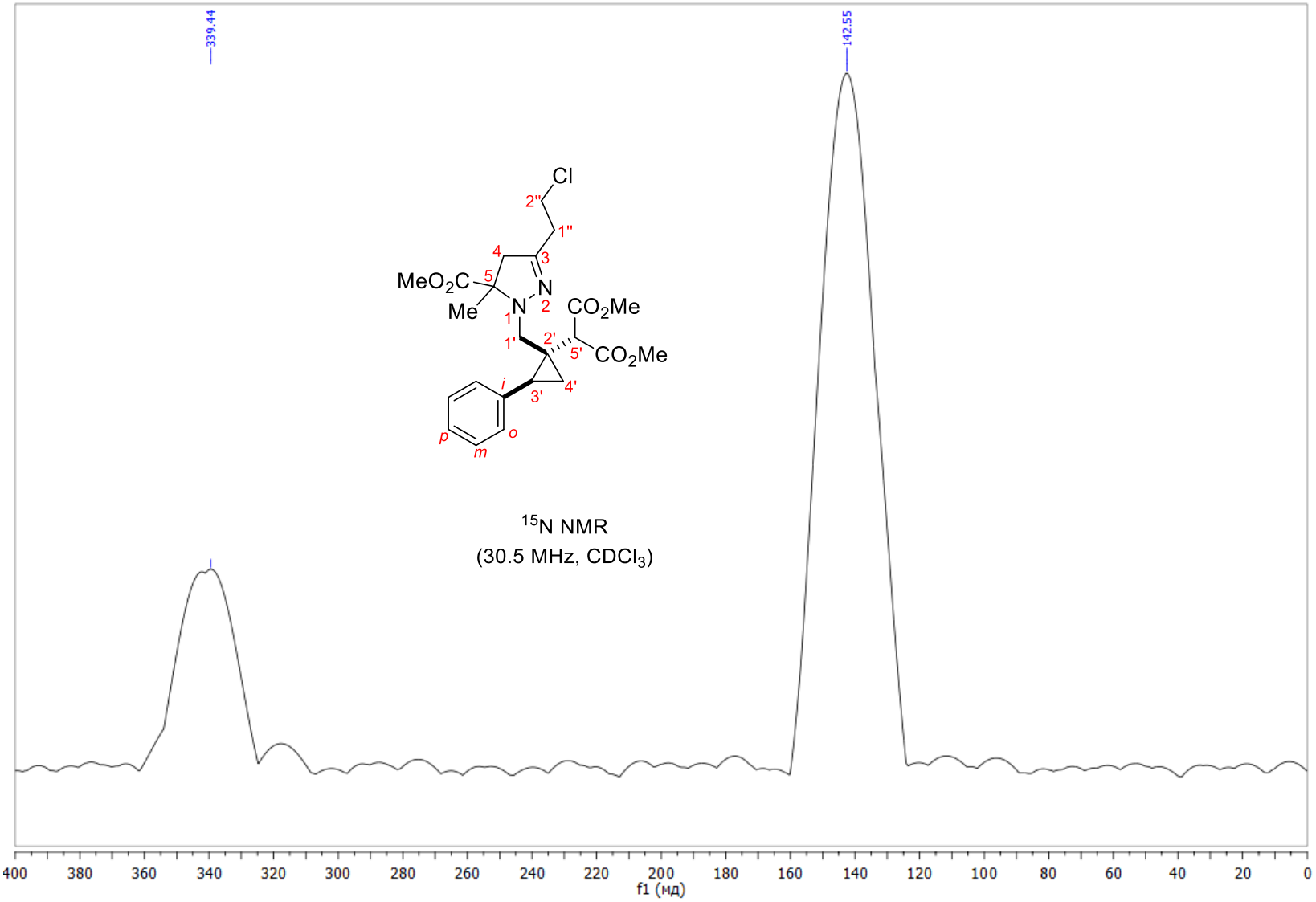
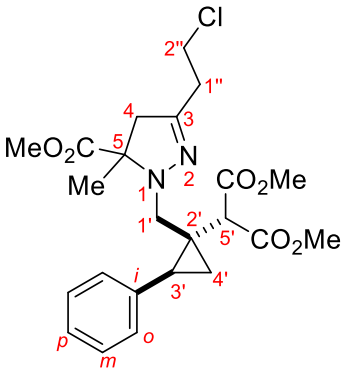
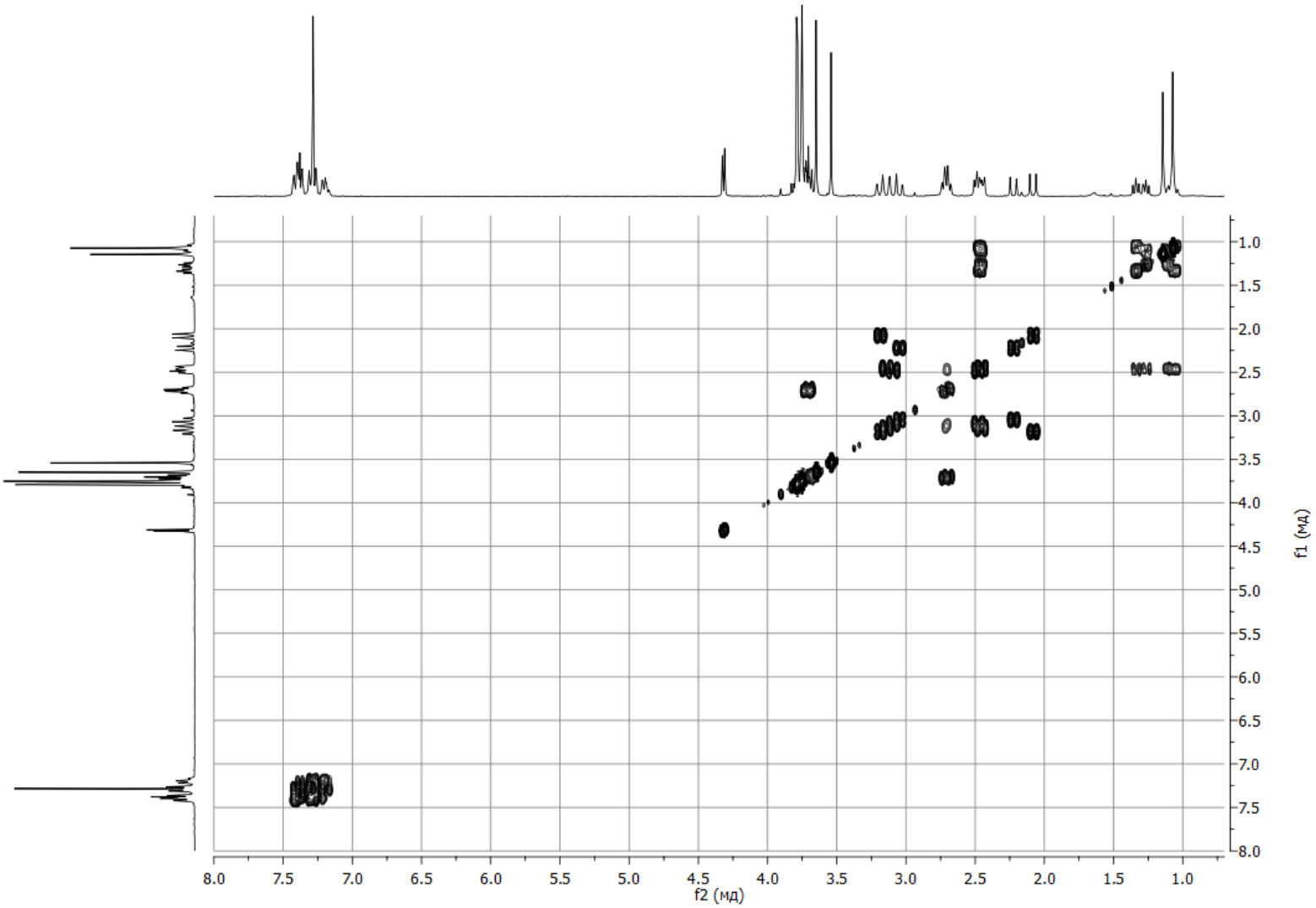
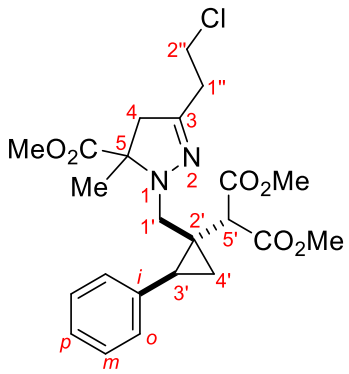
15.55
14.67
Cl
2''
1''
4
3
5
MeO2C
Me
N
2
N
1
CO2Me
1'
2'
5'
CO2Me
i
3'
4'
p
o
m
13C-DEPT-135 NMR
(75.5 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (мд)


339.44
142.55
Cl
2''
1''
4
3
MeO2C
5
N
Me
N
2
1
CO2Me
1'
2'
5'
CO2Me
i
3'
4'
p
o
m
15N NMR
(30.5 MHz, CDCl3)
400
380
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
f1 (мд)

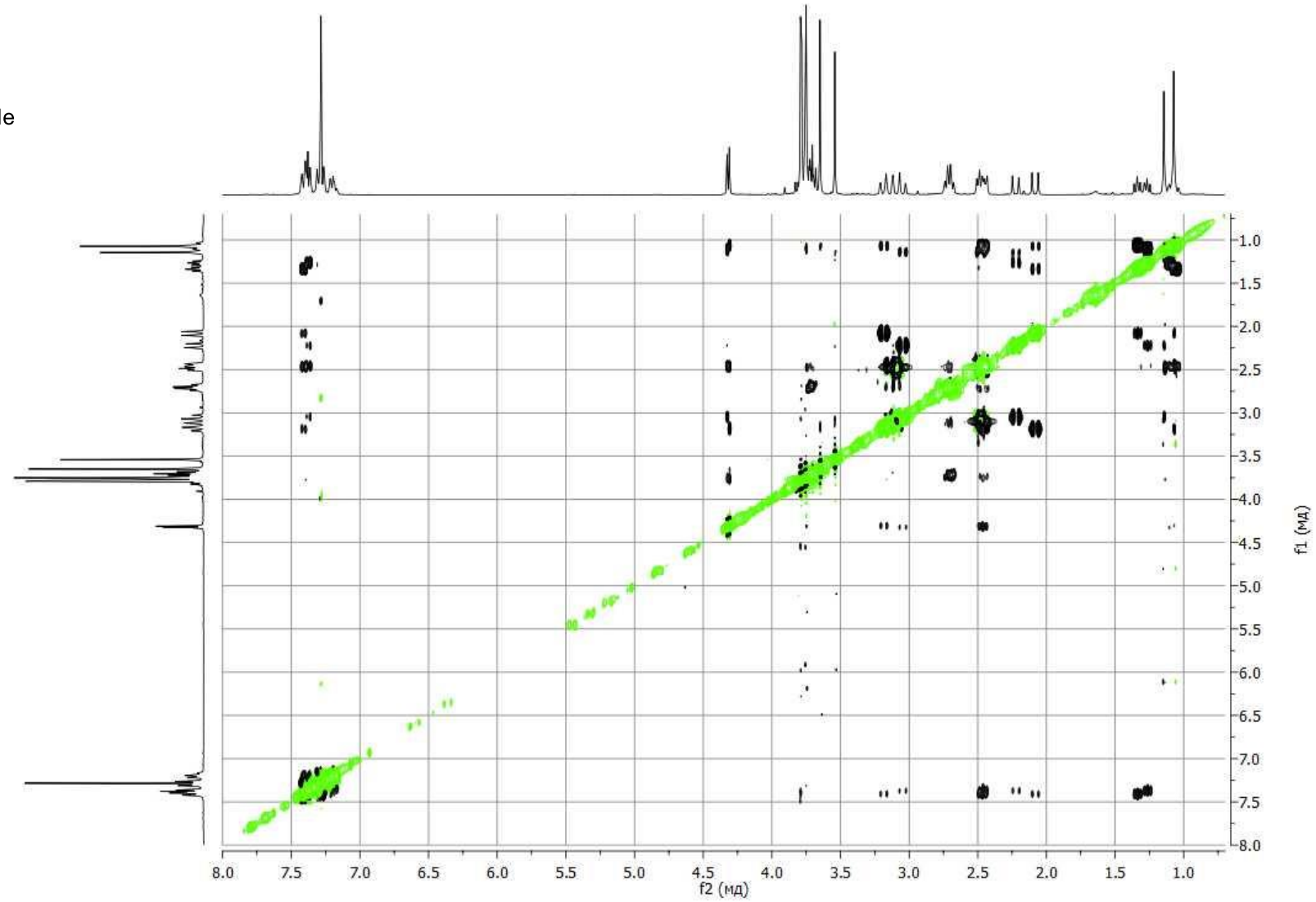


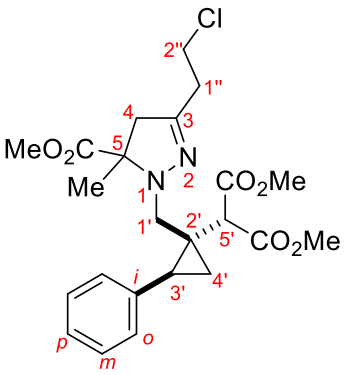
^{1}H, ^{1}H-COSY
(300.1 MHz, $CDCl_3$)



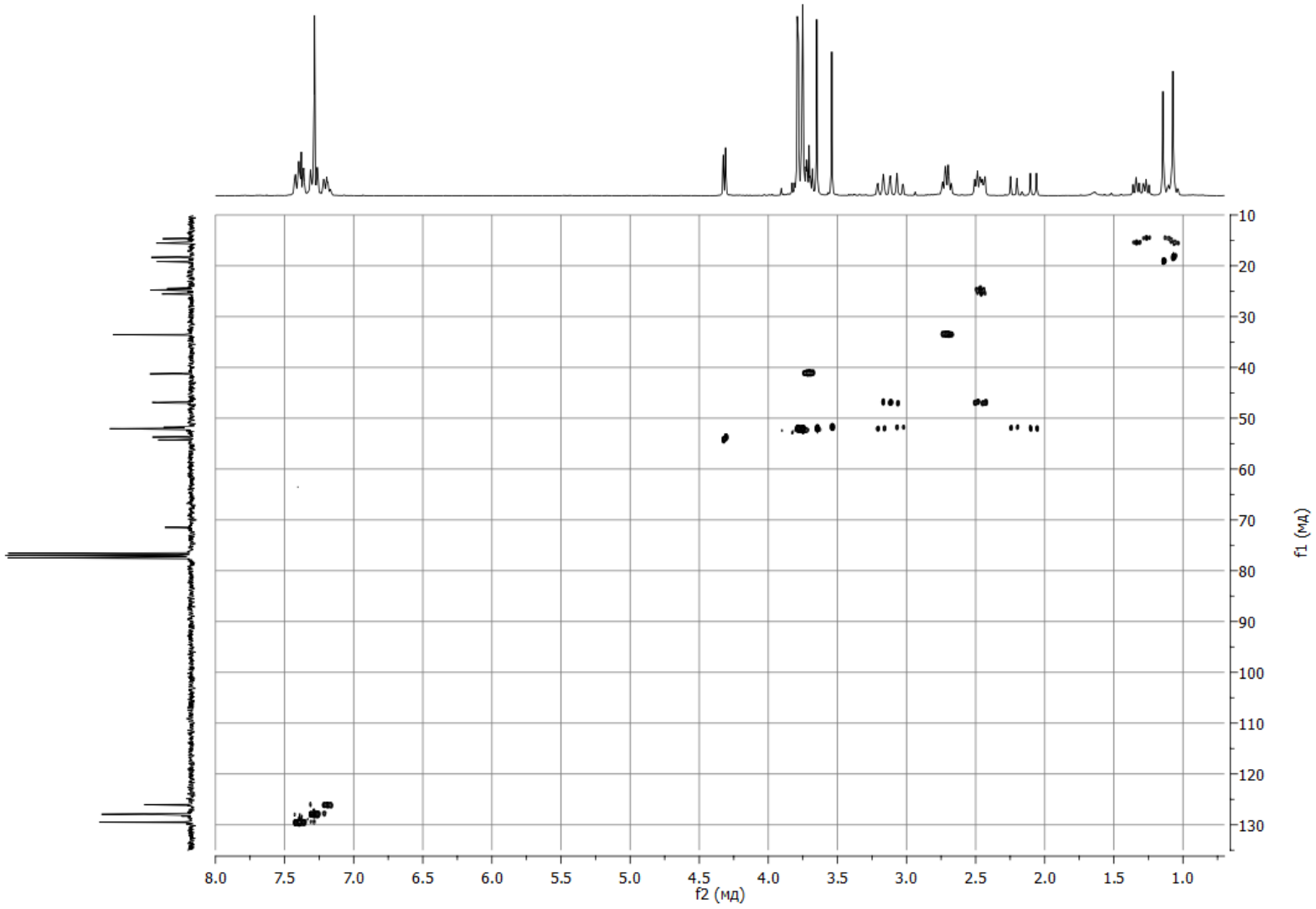


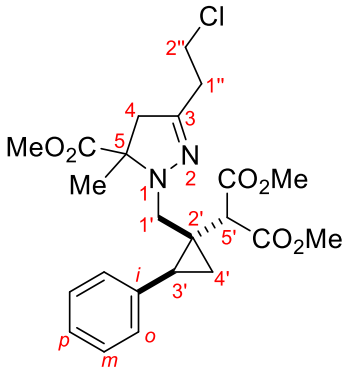
^{1}H, ^{1}H-NOESY
(300.1 MHz, $CDCl_3$)



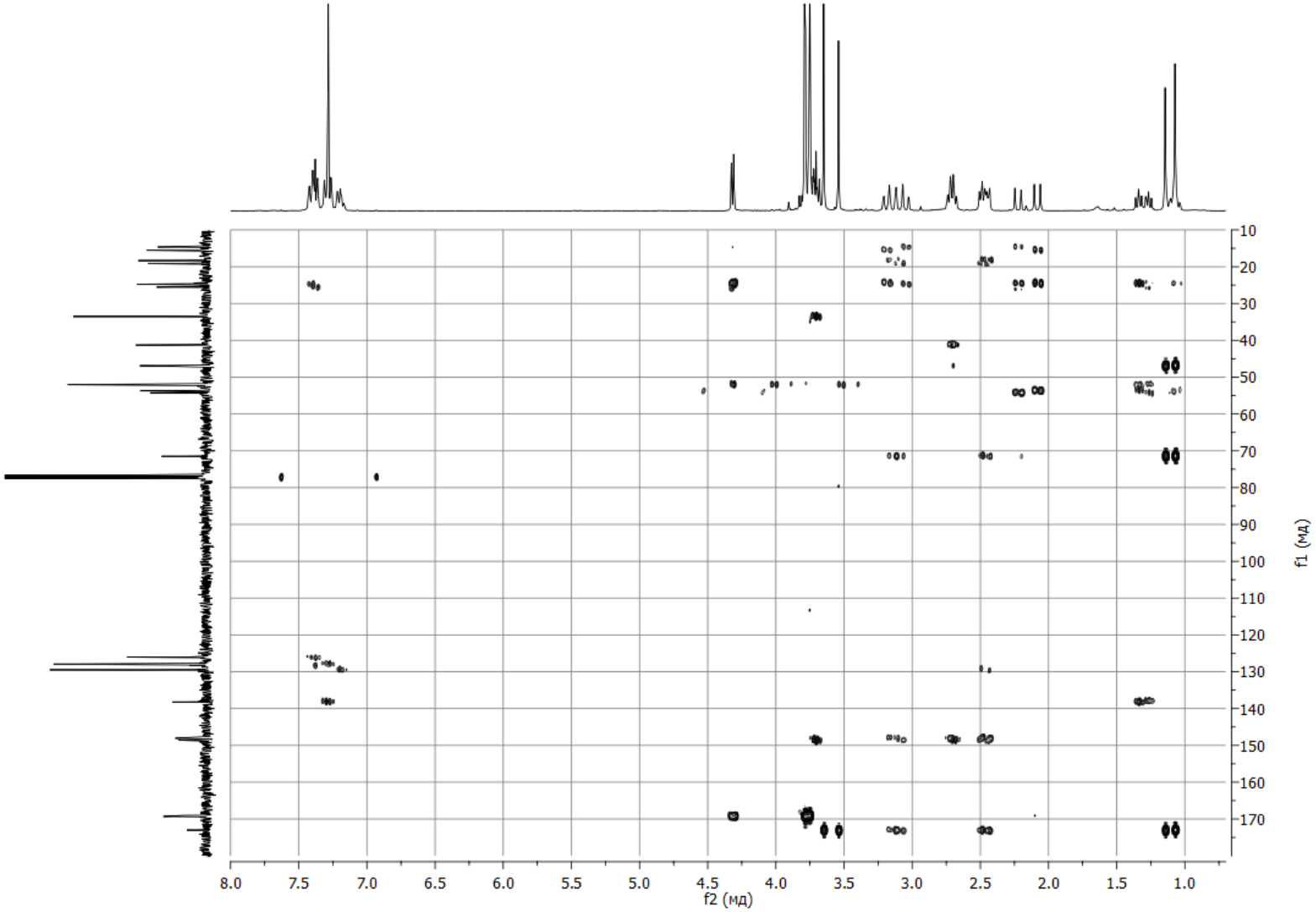


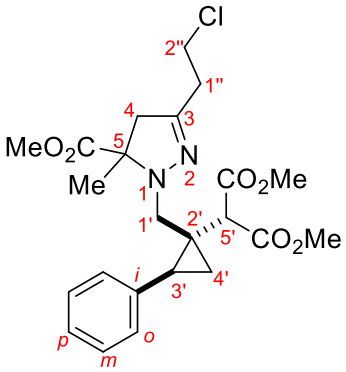
^{1}H,^{13}C-edited-HSQC
(^{1}H: 300.1 MHz,
^{13}C: 75.5 MHz
$CDCl_3$)



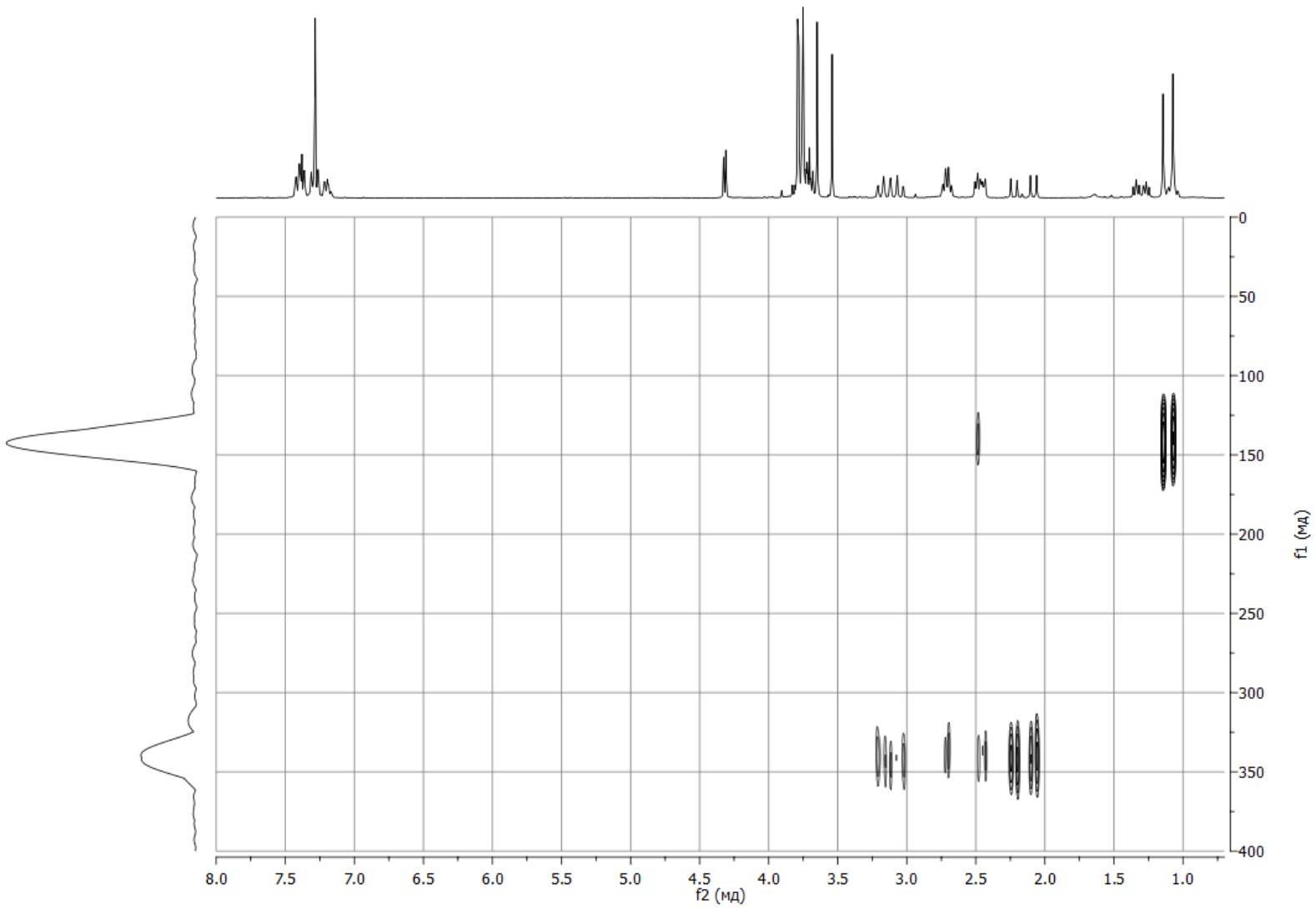


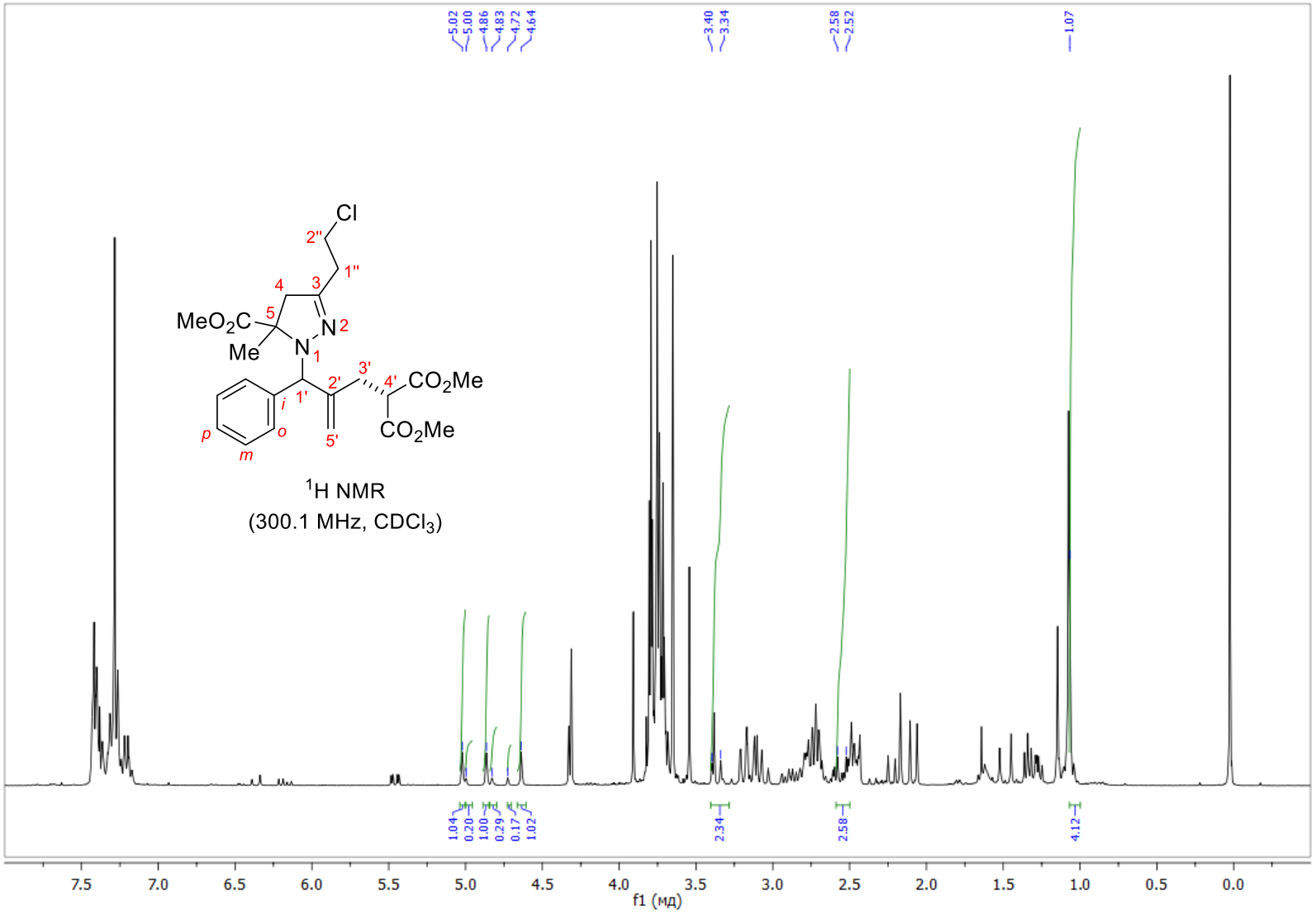
^{1}H,^{13}C-HMBC
(^{1}H: 300.1 MHz,
^{13}C: 75.5 MHz
$CDCl_3$)

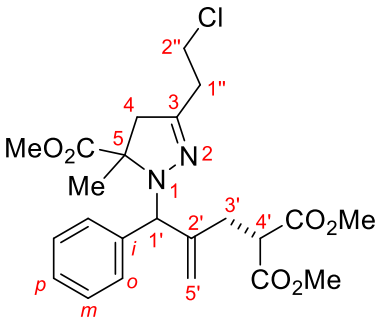




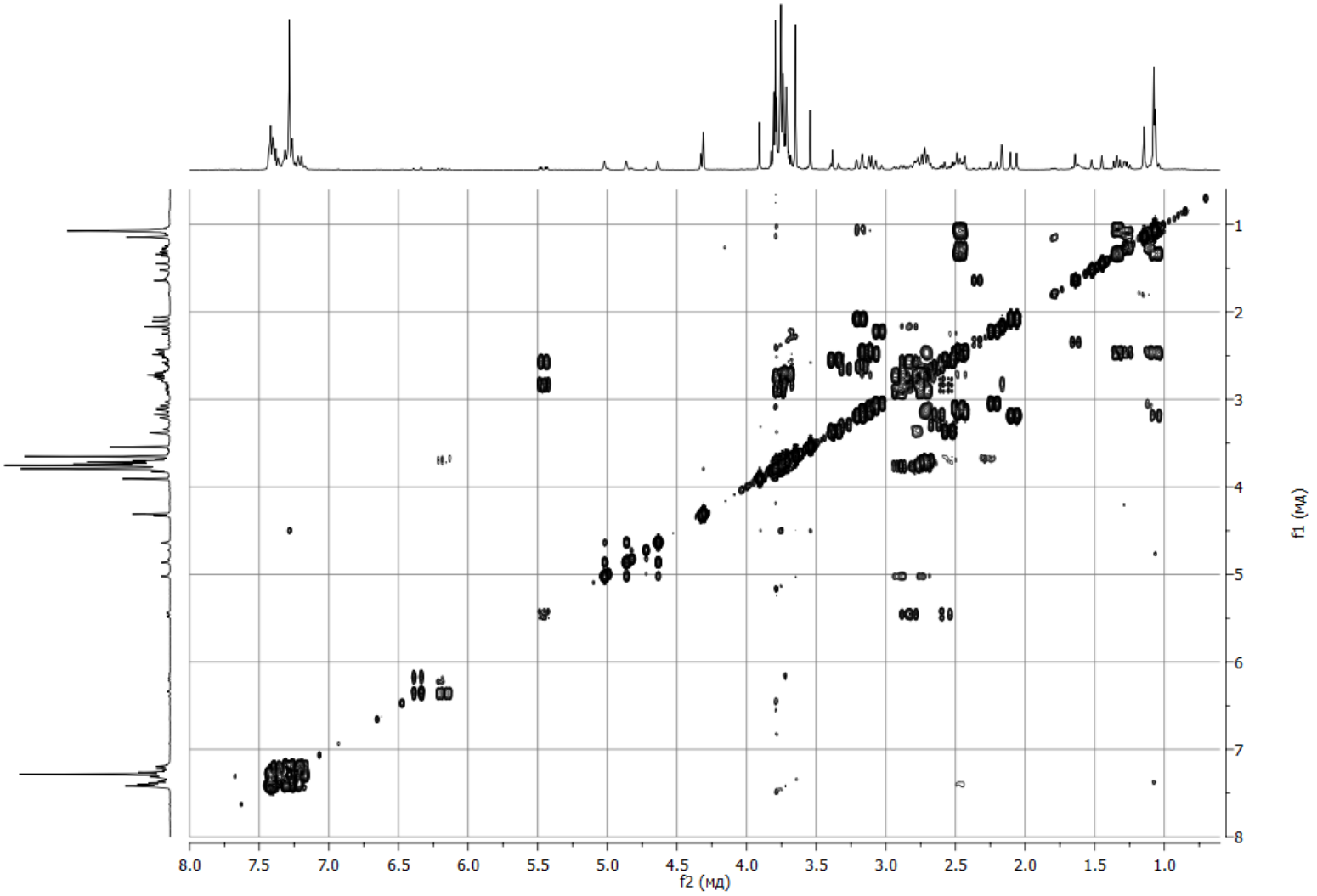
$^{1}H,^{15}N$-HMBC
(^{1}H: 300.1 MHz,
^{15}N: 30.5 MHz
$CDCl_3$)

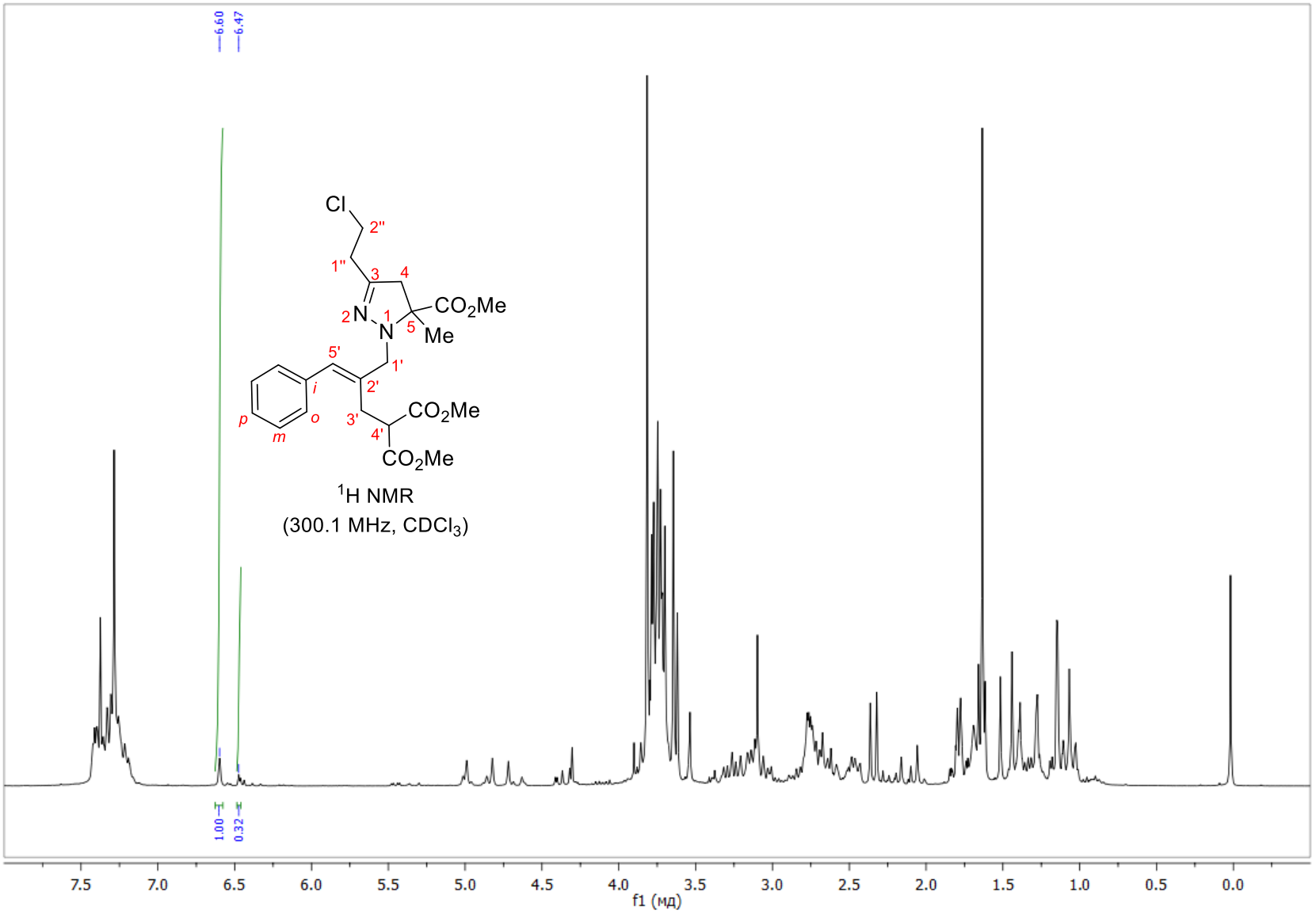


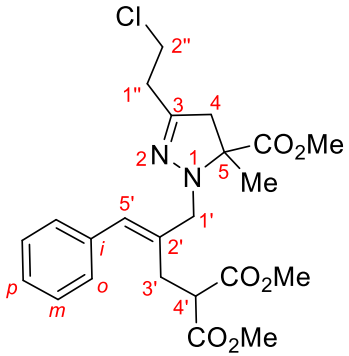

5.02
5.00
4.86
4.83
4.72
4.64
3.40
3.34
2.58
2.52
1.07
Cl
2''
1''
4
3
5
MeO2C
N
2
Me
N
1
3'
2'
4'
CO2Me
1'
i
p
o
5'
CO2Me
m
1H NMR
(300.1 MHz, CDCl3)
1.04
0.20
1.00
0.29
0.17
1.02
2.34
2.58
4.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (мд)



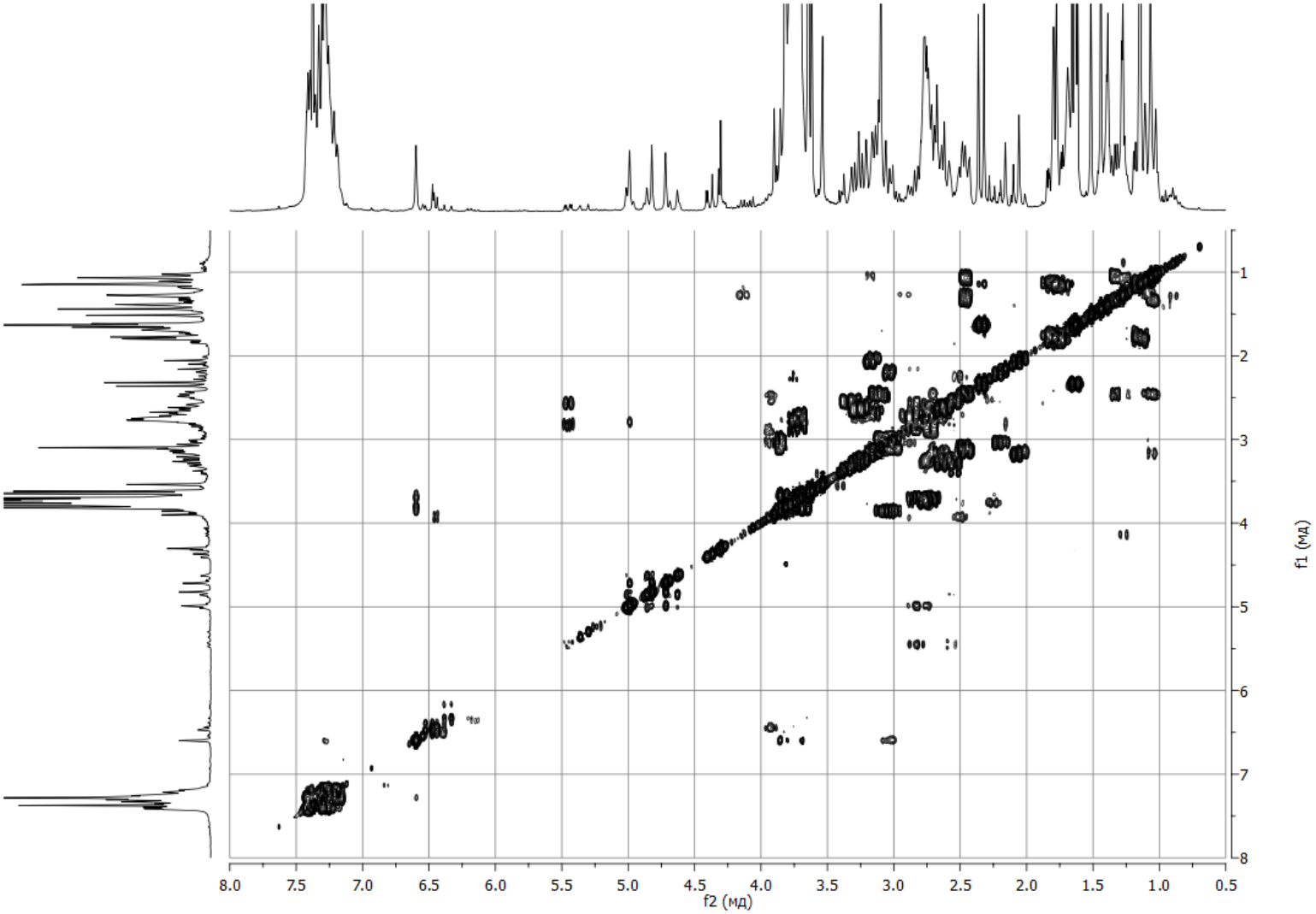
^{1}H, ^{1}H-COSY
(300.1 MHz, $CDCl_3$)

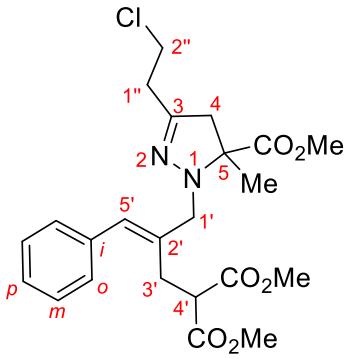



6.60
6.47
Cl
2"
1"
3
4
2
N
1
N
5
CO2Me
Me
5'
1'
2'
i
p
o
m
3'
4'
CO2Me
CO2Me
1H NMR
(300.1 MHz, CDCl3)
1.00
0.32
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (мд)

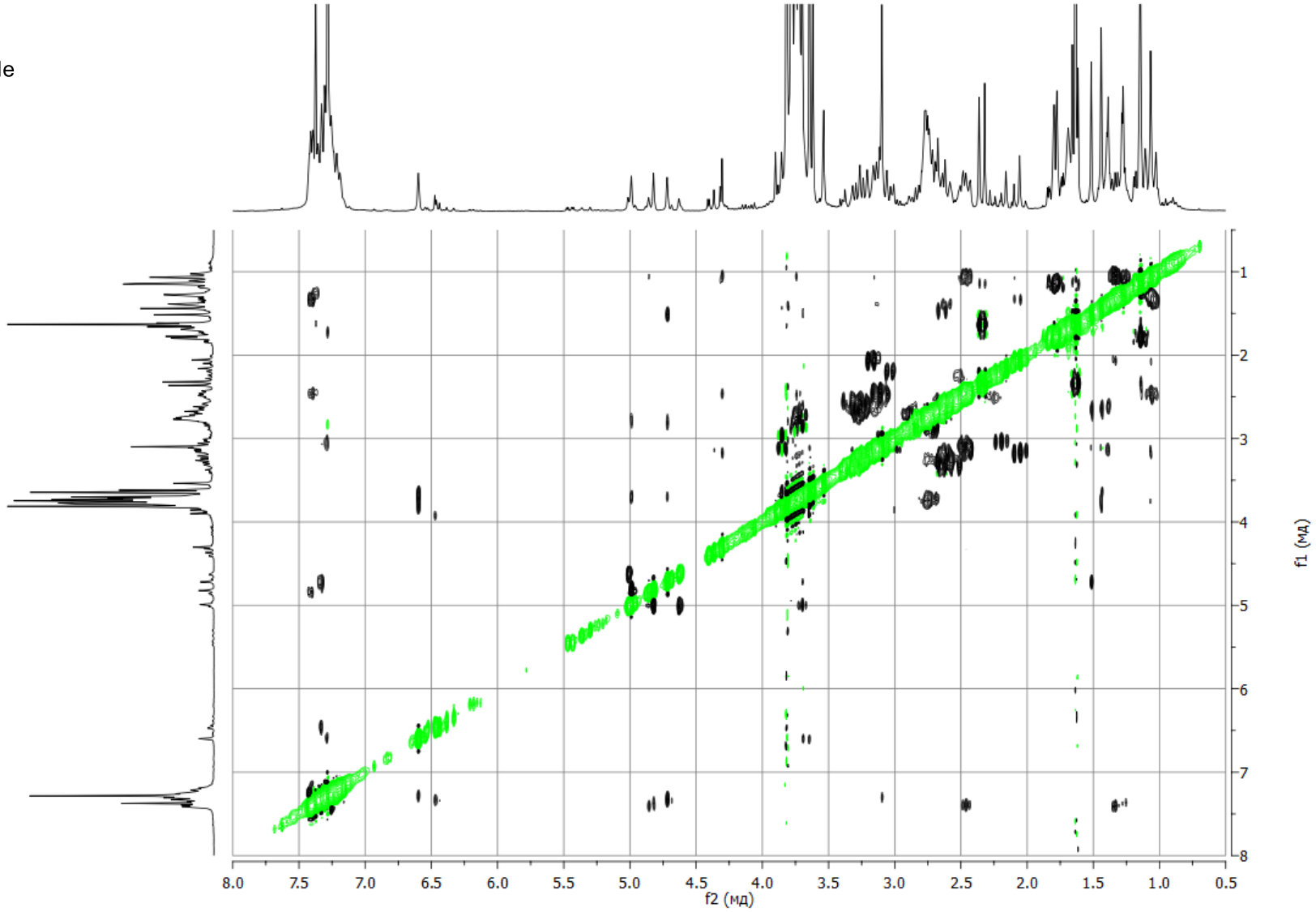


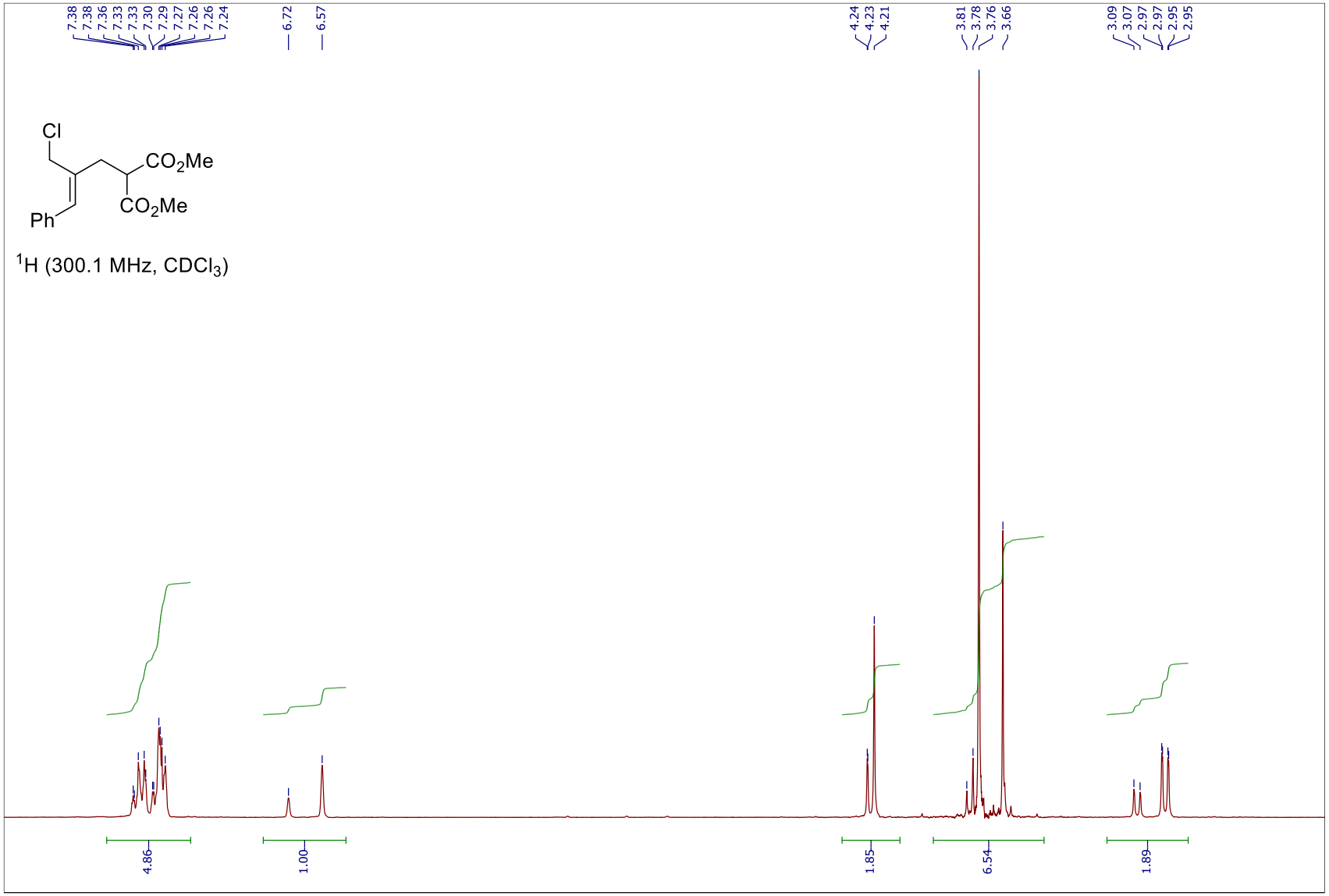
^{1}H, ^{1}H-COSY
(300.1 MHz, $CDCl_3$)

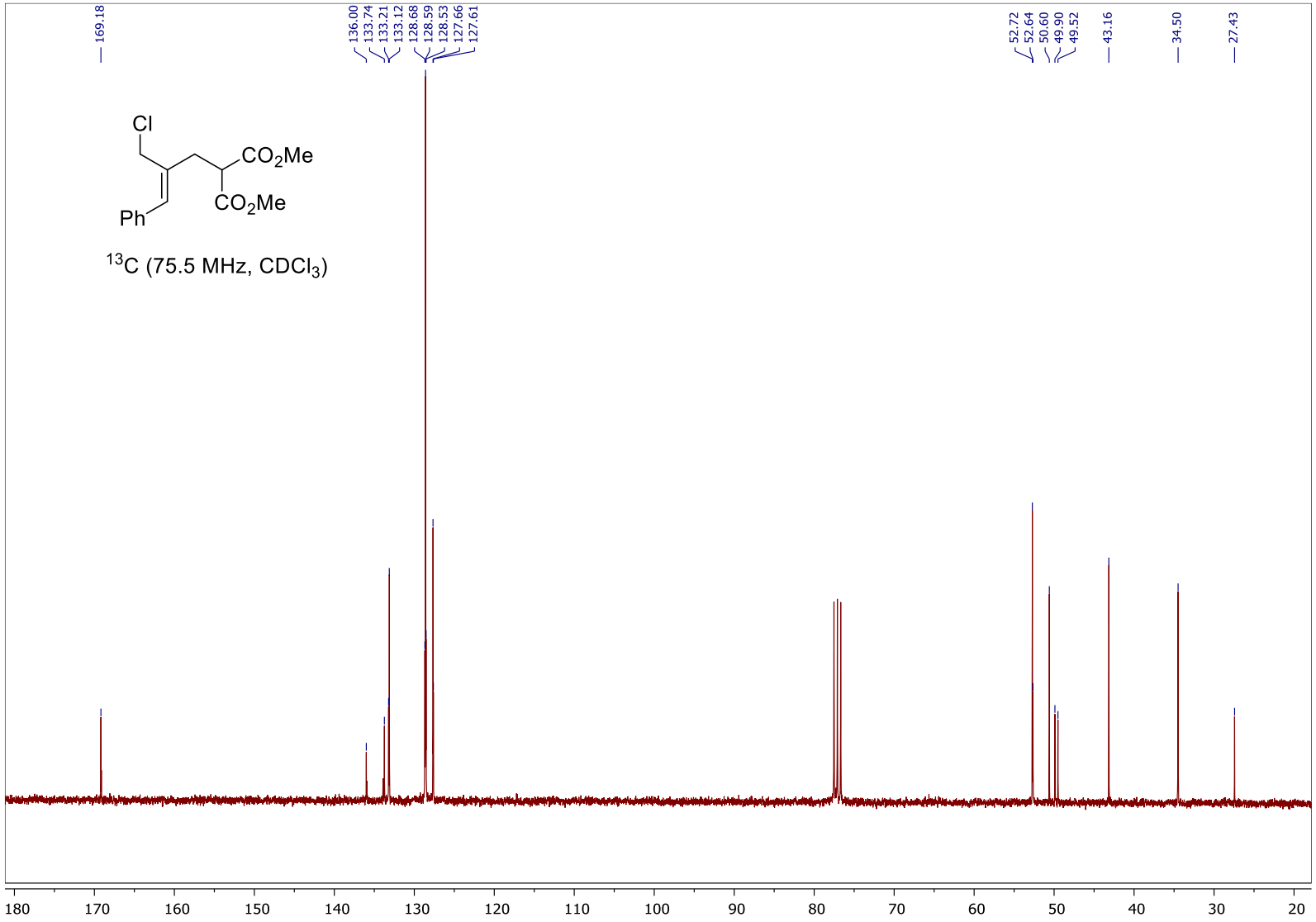


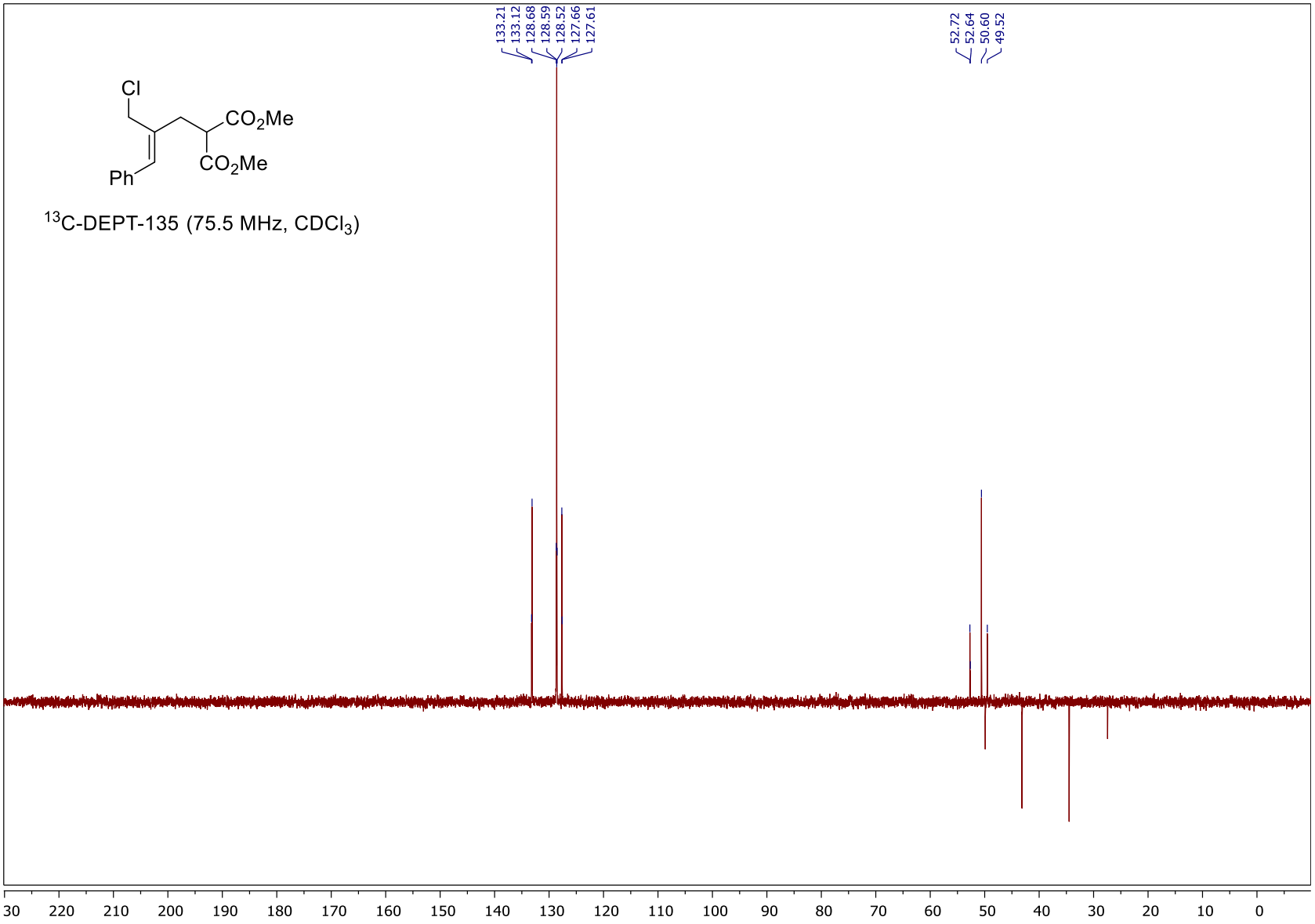


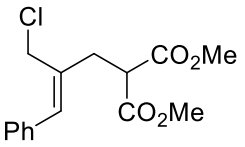
^{1}H, ^{1}H-NOESY
(300.1 MHz, $CDCl_3$)



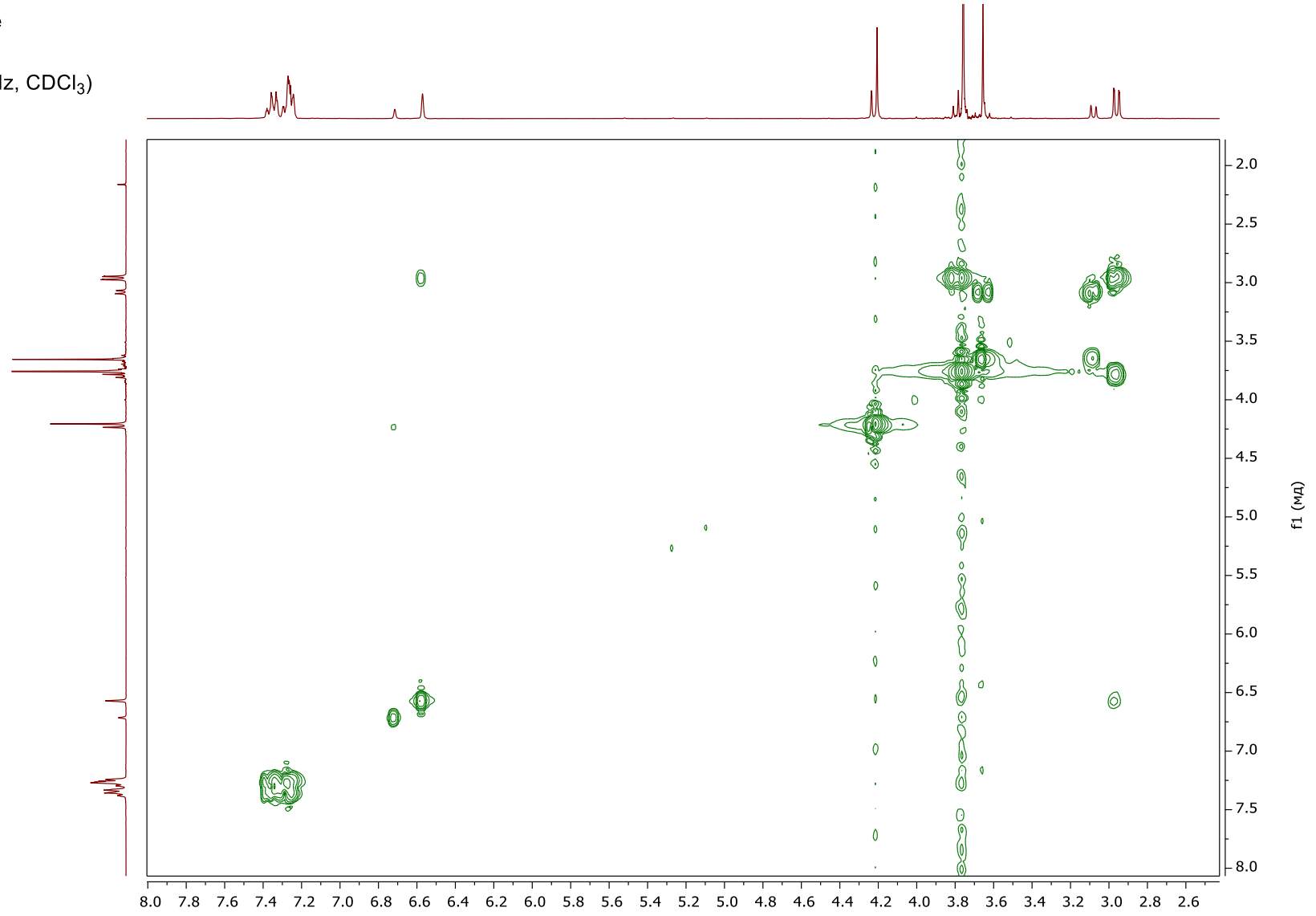

7.38
7.38
7.36
7.33
7.33
7.30
7.29
7.27
7.26
7.26
7.24
6.72
6.57
4.24
4.23
4.21
3.81
3.78
3.76
3.66
3.09
3.07
2.97
2.97
2.95
2.95
Cl
CO2Me
CO2Me
Ph
1H (300.1 MHz, CDCl3)
4.86
1.00
1.85
6.54
1.89
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4

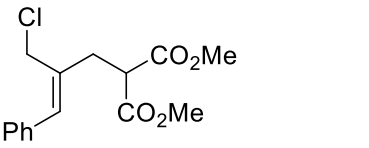

169.18
136.00
133.74
133.21
133.12
128.68
128.59
128.53
127.66
127.61
52.72
52.64
50.60
49.90
49.52
43.16
34.50
27.43
Cl
CO2Me
CO2Me
Ph
13C (75.5 MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20


133.21
133.12
128.68
128.59
128.52
127.66
127.61
52.72
52.64
50.60
49.52
Cl
CO2Me
CO2Me
Ph
13C-DEPT-135 (75.5 MHz, CDCl3)
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

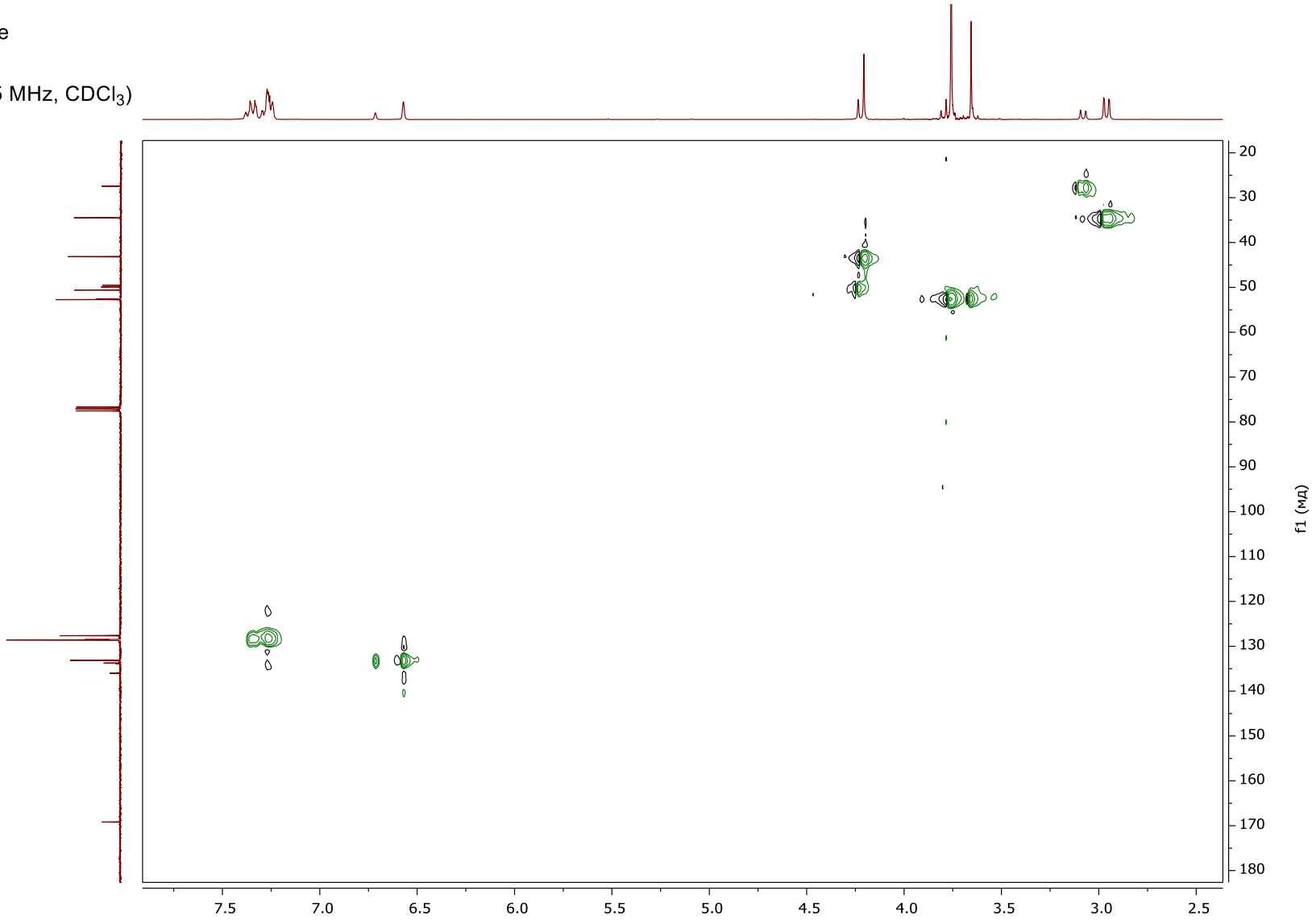


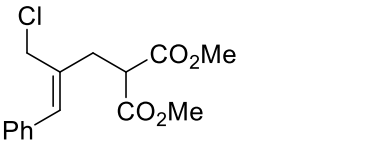
$^{1}H,^{1}H$-COSY (300.1 MHz, $CDCl_3$)



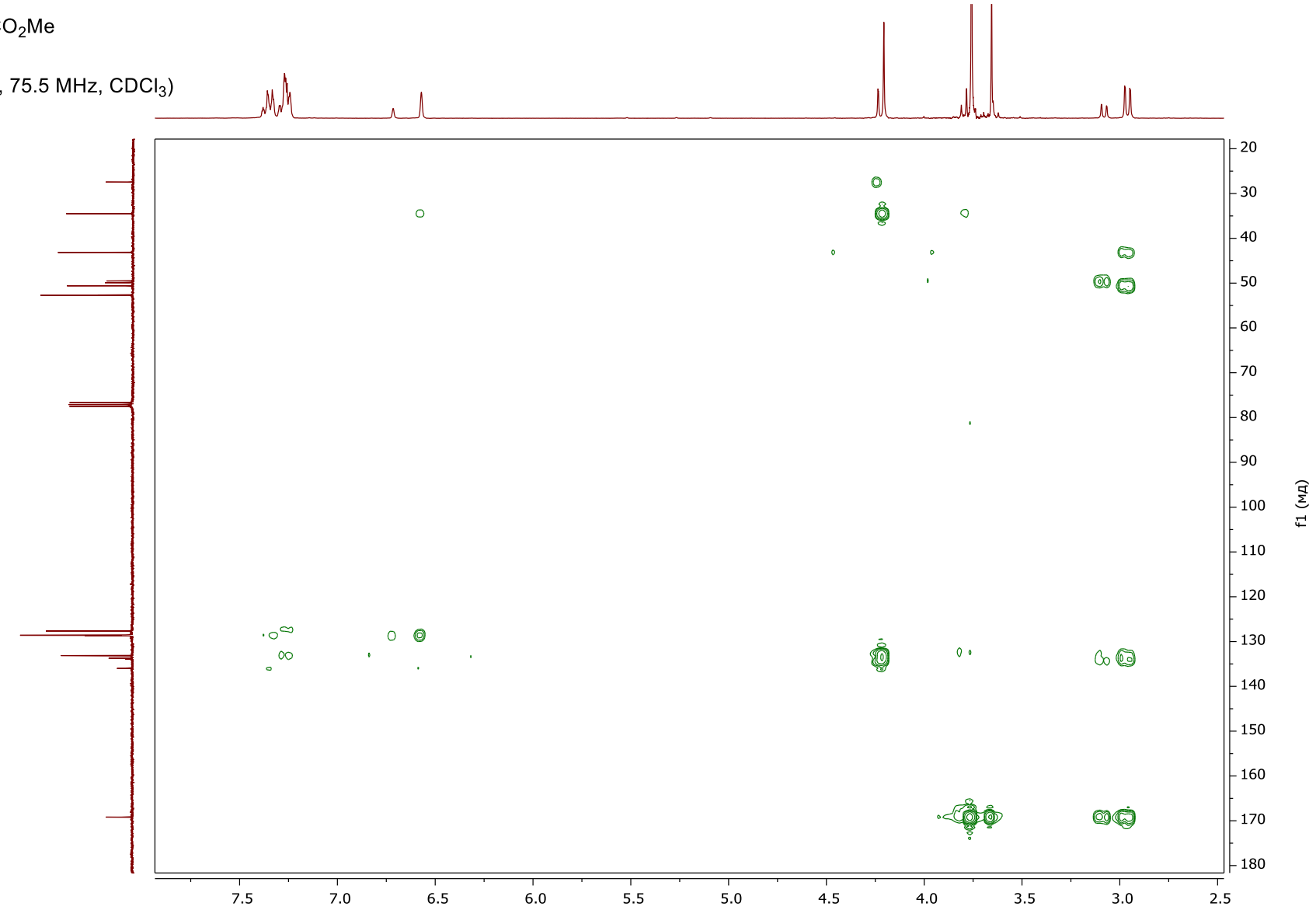


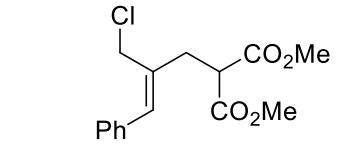
$^{1}H,^{13}C$-HSQC (300.1, 75.5 MHz, $CDCl_3$)





$^{1}H,^{13}C$-HMBC (300.1, 75.5 MHz, $CDCl_3$)





$^{1}H,^{1}H$-NOESY (300.1 MHz, $CDCl_3$)