Supporting Information

Sterically Demanding Csp^2 (*ortho*-Substitution)−Csp^3 (Tertiary) Bond Formation via Carboxylate Directed Mizoroki-Heck Reaction Under Extra Ligand-Free Conditions

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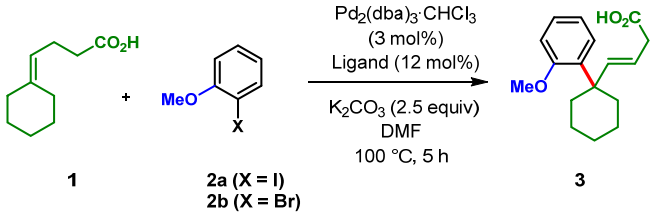
General Experimental

Unless otherwise noted, all experiments were performed under argon atmosphere and stirred magnetically. THF and DMF were obtained by passing the previously degassed solvent through an activated alumina column. Other solvents, starting materials, and reagents are commercially available and used directly as received, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) and NMR of the crude mixture. Evaporations were conducted under reduced pressure at temperatures less than 40 °C. Further dryings of the residues were accomplished using a high vacuum pump. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material. NMR spectra were recorded on Bruker Avance III 400, Avance III 500, Avance III 600 and Avance III 800 instruments. Chemical shifts are given in ppm and calibrated using the residual undeuterated solvent peaks (Chloroform-*d* ^{1}H, δ = 7.26 ppm, ^{13}C, δ = 77.2 ppm, Methanol-d_4 ^{1}H, δ = 3.31 ppm, ^{13}C, δ = 49.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant *J*, integration. High-resolution mass spectra were recorded on Agilent 1290/6545 UHPLC-QTOF/MS and Thermo DFS mass spectrometer. Melting points were recorded on a SGWX-4A melting point apparatus (Shanghai instrument physical optics instrument Co., LTD.).

Optimization Details

Table S1: ligand screen

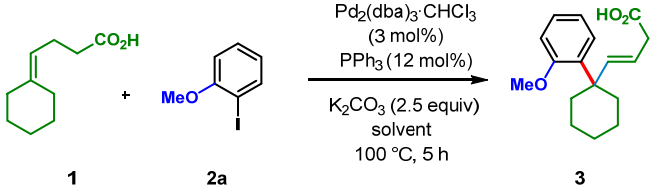


1 **2a (X = I)** **2b (X = Br)** **3**

Entry	ArX	Ligand (12 mol% if added)	Yield (%)[a]
1	ArBr	TrixiePhos	N.D.
2	ArI	TrixiePhos	30
3	ArI	PPh_3	39
4	ArI	P(*o*-tol)$_3$	<10
5	ArI	JohnPhos	<10
6	ArI	DavePhos	33
7	ArI	dppp	<10
8	ArI	dppb	N.D.
9	ArI	dpph	N.D.
10	ArI	-	15

Note: 1 (0.1 mmol), **2** (0.15 mmol). 0.5 mL DMF [a] Yield determined by ^{1}H NMR analysis using 1,3,5-Trimethoxybenzene as internal standard.

Table S2: screen of solvent



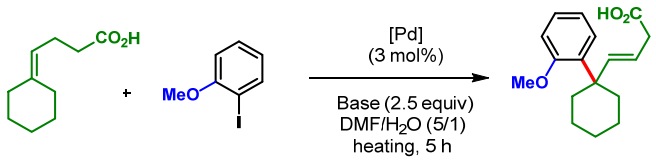
1 **2a** **3**

Entry	Ligand (12 mol% if added)	Solvent[b]	Yield (%)[a]
1	PPh_3	DMF	39
2	PPh_3	DMA	N.D.
3	PPh_3	DMSO	N.D.
4	PPh_3	1,4-dioxane	N.D.
5	PPh_3	0.5 mL DMF, 0.1 mL H_2O	39
6	TriexiePhos	0.5 mL DMF, 0.1 mL H_2O	36
7	DavePhos	0.5 mL DMF, 0.1 mL H_2O	39
8	-	0.5 mL DMF, 0.1 mL H_2O	60
9	-	0.5 mL DMA, 0.1 mL H_2O	32
10	-	0.5 mL 1,4-dioxane, 0.1 mL H_2O	30

11	-	0.5 mL DMSO, 0.1 mL H_2O	60
12	-	0.4 mL DMF, 0.2 mL H_2O	52
13	-	0.3 mL DMF, 0.3 mL H_2O	44
14	-	0.2 mL DMF, 0.4 mL H_2O	45
15	-	0.1 mL DMF, 0.5 mL H_2O	22
16	-	DMA	<5
17	-	1,4-dioxane	<5
18	-	DMSO	<5

Note: 1 (0.1 mmol), **2a** (0.15 mmol). [a] Yield determined by ^{1}H NMR analysis using 1,3,5-Trimethoxybenzene as internal standard. [b] 0.5 mL except otherwise noted

Table S3: screen of more conditions

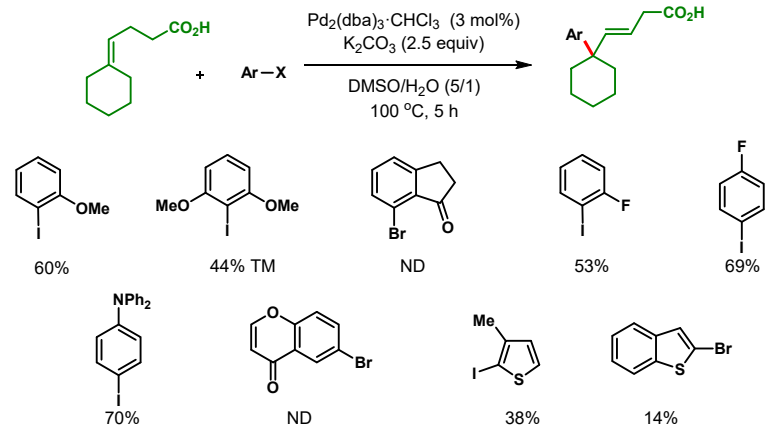


1 **2a (X = I)** **3**

Entry	Palladium source	Base	Temp. (°C)	Yield (%)[a]
1	$Pd_2(dba)_3{\cdot}CHCl_3$	K_2CO_3	90	47
2	$Pd_2(dba)_3{\cdot}CHCl_3$	K_2CO_3	110	51
3	$Pd(OAc)_2$	K_2CO_3	100	42
4	$PdCl_2$	K_2CO_3	100	45
5	$PdCl_2(PPh_3)_2$	K_2CO_3	100	12
6	$Pd(PPh_3)_4$	K_2CO_3	100	23
7	$Pd_2(dba)_3{\cdot}CHCl_3$	$NaHCO_3$	100	25
8	$Pd_2(dba)_3{\cdot}CHCl_3$	Na_2CO_3	100	28
9	$Pd_2(dba)_3{\cdot}CHCl_3$	Cs_2CO_3	100	45
10	$Pd_2(dba)_3{\cdot}CHCl_3$	*t*-BuONa	100	15
11	$Pd_2(dba)_3{\cdot}CHCl_3$	Et_3N	100	23

Note: 1 (0.1 mmol), **2a** (0.15 mmol). [a] Yield determined by ^{1}H NMR analysis using 1,3,5-Trimethoxybenzene as internal standard.

Table S4: substrates tested using DMSO/H_2O (5/1) as solvent[a]



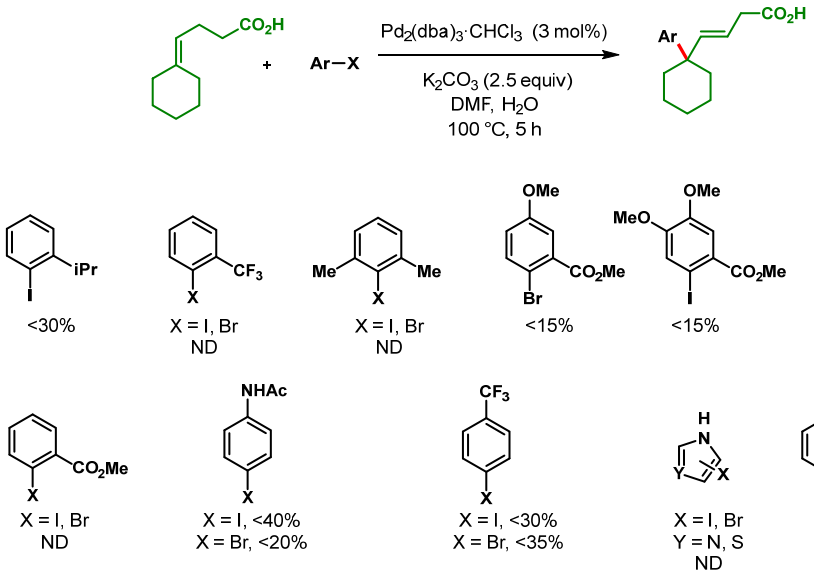
60% | 44% TM | ND | 53% | 69%

70% | ND | 38% | 14%

[a]Yields determined by ^{1}H NMR analysis using 1,3,5-Trimethoxybenzene as internal standard

Table S5: methodology limitations

Reactions with some aryl coupling partners were found to be unsatisfying or ineffective and are listed as below.[a]



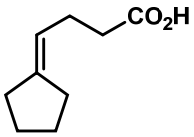
[a]Yields determined by ^{1}H NMR analysis using 1,3,5-Trimethoxybenzene as internal standard

Experimental Procedure and Characterization Data for Compound S1

The olefin substrates except **S1** were prepared according to literature procedure.[1],[2]

Compound S1

4-cyclopentylidenebutanoic acid



To a solution of (3-carboxypropyl)triphenylphosphonium bromide (1.0 equiv, 10 mmol, 4.29 g) in THF (140 mL) was added KHMDS (1.0 M in THF, 20 mL, 2.0 equiv) at room temperature under Ar atmosphere. The resulting mixture was stirred at the same temperature for 30 minutes. Cyclopentanone (1.68 g, 2.0 equiv) was added and the reaction was heated to reflux overnight. After cooling to room temperature, most of the THF was removed under reduced pressure. Aqueous NaOH (1.0 M, 200 mL) was added, and the resulting solution was washed with Et_2O for three times. The aqueous layer was then acidified with HCl (con.) until pH < 2 and extracted with Et_2O for three times. The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by flash column chromatography (silica gel, acetone/hexanes, 1/20 to 1/10) to afford 0.37 g (24%) of the title compound **S1**.

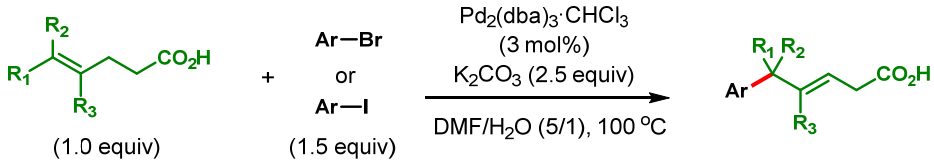
Physical State: colorless oil.

^{1}H NMR (600 MHz, Chloroform-d) δ 5.24 – 5.18 (m, 1H), 2.38 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 2H), 2.32 – 2.26 (m, 2H), 2.23 – 2.16 (m, 4H), 1.68 – 1.62 (m, 2H), 1.62 – 1.55 (m, 2H).

^{13}C NMR (151 MHz, Chloroform-d) δ 179.9, 145.3, 117.6, 34.3, 33.7, 28.7, 26.5, 26.4, 25.0.

HRMS (ESI-TOF): calculated for $C_9H_{13}O_2^-$ $[M-H]^-$: 153.0921; Found 153.0921.

General Procedure for the Carboxylate Directed Heck Reaction

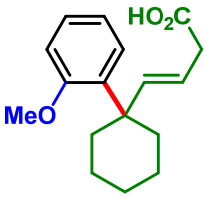


To a reaction tube equipped a stir bar were added olefin substrate (1.0 equiv), potassium carbonate (2.5 equiv), $Pd_2(dba)_3$•$CHCl_3$ (3 mol%), and aryl halide (1.5 equiv). The tube was evacuated and backfilled with argon for three times. Premixed and degassed DMF/H_2O (5/1, 0.6 mL for 0.1 mmol scale) was added and the resulting mixture was heated to 100 ℃ in an oil bath for 5-12 hours. After cooling to room temperature, saturated aqueous NH_4Cl was added, followed by addition of 1N HCl to ajust the pH to 2-4. The aqueous layer was extracted with Et_2O for three times. The combined organic extracts were dried over anhydrous Na_2SO_4, evaporated, and purified by flash column chromatography (silica gel) to afford the desired product.

Experimental Procedures and Characterization Data

Compound 3

(E)-4-(1-(2-methoxyphenyl)cyclohexyl)but-3-enoic acid



16.0 mg, 58% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-iodo-2-methoxybenzene (35.1 mg, 0.15 mmol).

Physical State: colorless oil.

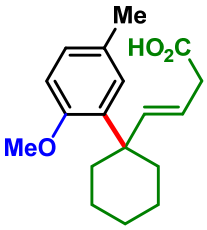
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.52 – 7.48 (m, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.15 – 7.09 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.11 (d, *J* = 15.9 Hz, 1H), 5.35 – 5.24 (m, 1H), 3.94 (s, 3H), 3.25 (d, *J* = 6.7 Hz, 2H), 2.25 – 2.12 (m, 4H), 1.85 – 1.57 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.5, 158.3, 143.2, 136.3, 127.5, 127.4, 120.6, 118.8, 112.4, 55.4, 43.6, 38.4, 35.8, 26.6, 22.9.

HRMS (ESI-TOF): calculated for $C_{17}H_{22}NaO_3^+$ $[M+Na]^+$: 297.1459; Found 297.1461.

Compound 4

(E)-4-(1-(2-methoxy-5-methylphenyl)cyclohexyl)but-3-enoic acid



17.2 mg, 60% yield. Prepared following the **General Procedure** (except the modification of concentration: 1.2 mL solvent) from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 2-iodo-1-methoxy-4-methylbenzene (37.2 mg, 0.15 mmol).

Physical State: colorless oil.

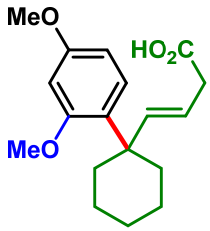
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.11 (d, *J* = 2.2 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 5.93 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.31 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.72 (s, 3H), 3.07 (dd, *J* = 7.1, 1.3 Hz, 2H), 2.29 (s, 3H), 2.04 – 1.92 (m, 4H), 1.56 (m, 6H).

^{13}C NMR (151 MHz, Chloroform-*d*): δ 177.6, 156.1, 143.3, 136.2, 129.6, 128.3, 127.5, 118.7, 112.5, 55.6, 43.5, 38.4, 35.8, 26.6, 22.9, 21.0.

HRMS (ESI-TOF): calculated for $C_{18}H_{24}NaO_3^+$ $[M+Na]^+$: 311.1616; Found 311.1618.

Compound 5

(E)-4-(1-(2,4-dimethoxyphenyl)cyclohexyl)but-3-enoic acid



22.2 mg, 73% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-iodo-2,4-dimethoxybenzene (39.6 mg, 0.15 mmol).

Physical State: colorless oil

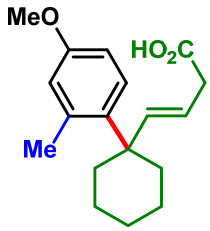
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.18 (m, 1H), 6.47 – 6.41 (m, 2H), 5.86 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.29 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.06 (dd, *J* = 7.1, 1.4 Hz, 2H), 2.02 – 1.90 (m, 4H), 1.59 – 1.45 (m, 5H), 1.39 – 1.29 (m, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.3, 159.2, 159.2, 143.5, 128.7, 128.0, 118.5, 103.7, 100.2, 55.4, 55.3, 43.1, 38.3, 35.9, 26.6, 22.9.

HRMS (ESI-TOF): calculated for $C_{18}H_{23}O_4^-$ [M-H]$^-$: 303.1602; Found 303.1601.

Compound 6

(E)-4-(1-(4-methoxy-2-methylphenyl)cyclohexyl)but-3-enoic acid



18.7 mg, 65% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-iodo-4-methoxy-2-methylbenzene (37.2 mg, 0.15 mmol).

Physical State: colorless oil.

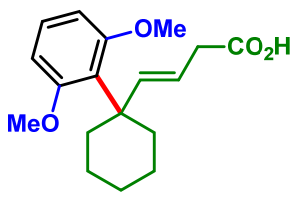
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.32 (d, *J* = 8.5 Hz, 1H), 6.73 – 6.66 (m, 2H), 5.88 (dd, *J* = 15.8, 1.4 Hz, 1H), 5.22 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.79 (s, 3H), 3.06 (d, *J* = 7.0 Hz, 2H), 2.32 (s, 3H), 2.02 – 1.93 (m, 2H), 1.93 – 1.81 (m, 2H), 1.67 – 1.46 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.2, 157.5, 143.4, 138.8, 137.5, 128.4, 119.3, 118.5, 110.1, 55.2, 44.3, 38.1, 37.5, 26.4, 23.4, 22.7.

HRMS (ESI-TOF): calculated for $C_{18}H_{24}NaO_3^+$ [M+Na]$^+$: 311.1616; Found 311.1618.

Compound 7

(E)-4-(1-(2,6-dimethoxyphenyl)cyclohexyl)but-3-enoic acid



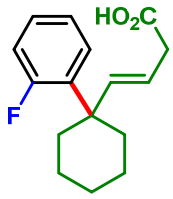
10.0 mg, 33% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 2-iodo-1,3-dimethoxybenzene (39.6 mg, 0.15 mmol).

Physical State: colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.12 (t, *J* = 8.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 2H), 6.06 (d, *J* = 15.7 Hz, 1H), 5.29 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.73 (s, 6H), 3.05 (dd, *J* = 7.2, 1.3 Hz, 2H), 2.63 – 2.52 (m, 2H), 1.79 – 1.72 (d, 2H), 1.60 – 1.53 (m, 2H), 1.46 – 1.34 (m, 4H).
^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.2, 159.9, 146.0, 127.3, 123.9, 116.3, 106.9, 56.2, 46.2, 38.3, 38.0, 26.6, 23.7.
HRMS (ESI-TOF): calculated for $C_{18}H_{23}O_4^-$ [M-H]$^-$: 303.1603; Found 303.1602.

Compound 8

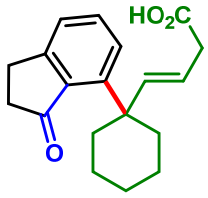
(E)-4-(1-(2-fluorophenyl)cyclohexyl)but-3-enoic acid



11.0 mg, 42% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-fluoro-2-iodobenzene (33.3 mg, 0.15 mmol).
65 mg, 50% yield. Prepared following the **General Procedure** (except the modification of concentration: totally 5 mL DMF and 1 mL water were used) from 4-cyclohexylidenebutanoic acid (84 mg, 0.5 mmol) and 1-fluoro-2-iodobenzene (166 mg, 0.75 mmol).
Physical State: colorless oil.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.33 (td, *J* = 8.1, 1.8 Hz, 1H), 7.22 – 7.14 (m, 1H), 7.08 (td, *J* = 7.5, 1.5 Hz, 1H), 7.00 – 6.92 (m, 1H), 5.83 – 5.75 (m, 1H), 5.42 – 5.33 (m, 1H), 3.09 (dd, *J* = 7.0, 1.4 Hz, 2H), 2.10 – 1.98 (m, 2H), 1.97 – 1.86 (m, 2H), 1.62 – 1.54 (m, 2H), 1.53 – 1.44 (m, 3H), 1.42 – 1.34 (m, 1H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.4, 161.8 (*J* = 249.2 Hz), 141.8, 134.4 (*J* = 10.5 Hz), 128.4 (*J* = 5.3 Hz), 127.9 (*J* = 3.7 Hz), 123.9 (3.2), 120.0, 116.7 (*J* = 24.4 Hz), 43.4, 43.4, 38.0, 35.8, 35.8, 26.4, 22.7.
^{19}F NMR (471 MHz, Chloroform-*d*) δ -107.8.
HRMS (ESI-TOF): calculated for $C_{16}H_{18}FO_2^-$ [M-H]$^-$: 261.1295; Found 261.1296.

Compound 9

(E)-4-(1-(3-oxo-2,3-dihydro-1H-inden-4-yl)cyclohexyl)but-3-enoic acid



11.9 mg, 40% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 7-bromo-2,3-dihydro-1H-inden-1-one (31.7 mg, 0.15 mmol).
Physical State: pale yellow oil.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.51 – 7.47 (m, *J* = 7.6 Hz, 1H), 7.42 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.46 – 6.37 (m, 1H), 5.00 (dt, *J* = 16.0, 7.1 Hz, 1H), 3.08 – 3.04 (m, 2H),

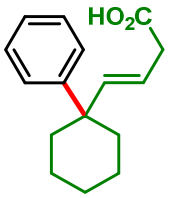
3.02 (dd, *J* = 7.0, 1.3 Hz, 2H), 2.62 – 2.56 (m, 2H), 2.13 (d, *J* = 13.0 Hz, 2H), 1.87 – 1.79 (m, 2H), 1.71 – 1.46 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 206.3, 177.6, 158.7, 150.4, 143.5, 134.4, 134.2, 125.07, 125.0, 118.8, 44.0, 38.2, 37.3, 37.0, 26.1, 25.8, 22.9.

HRMS (ESI-TOF): calculated for $C_{19}H_{21}O_3^-$ [M-H]$^-$: 297.1496; Found 297.1496.

Compound 10

(E)-4-(1-phenylcyclohexyl)but-3-enoic acid



13.2 mg, 54% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and iodobenzene (30.6 mg, 0.15 mmol).

Physical State: colorless oil.

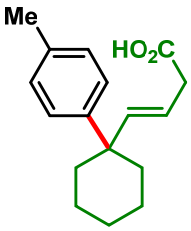
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.37 – 7.28 (m, 4H), 7.20 – 7.15 (m, 1H), 5.58 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.40 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.09 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.06 – 1.95 (m, 2H), 1.88 – 1.79 (m, 2H), 1.60 – 1.36 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.7, 147.1, 144.0, 128.4, 126.9, 125.8, 119.3, 44.3, 38.0, 36.3, 26.4, 22.6.

HRMS (ESI-TOF): calculated for $C_{16}H_{19}O_2^-$ [M-H]$^-$: 243.1391; Found 243.1391.

Compound 11

(E)-4-(1-(p-tolyl)cyclohexyl)but-3-enoic acid



15.2 mg, 59% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-iodo-4-methylbenzene (32.7 mg, 0.15 mmol).

Physical State: colorless oil.

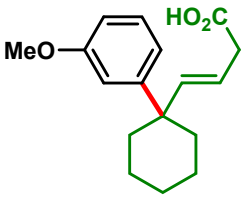
^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.25 – 7.21 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.57 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.40 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.08 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.32 (s, 3H), 2.00 – 1.95 (m, 2H), 1.86 – 1.79 (m, 2H), 1.60 – 1.37 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.1, 144.2, 144.1, 135.3, 129.1, 126.8, 119.0, 43.9, 38.1, 36.3, 26.5, 22.7, 21.0.

HRMS (ESI-TOF): calculated for $C_{17}H_{21}O_2^-$ [M-H]$^-$: 257.1546; Found 257.1547.

Compound 12

(E)-4-(1-(3-methoxyphenyl)cyclohexyl)but-3-enoic acid



12.1 mg, 44% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-iodo-3-methoxybenzene (35.1 mg, 0.15 mmol).

Physical State: colorless oil.

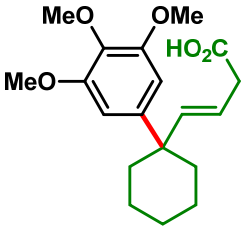
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.24 (t, *J* = 8.0 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.91 (t, *J* = 2.2 Hz, 1H), 6.74 – 6.70 (m, 1H), 5.56 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.42 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.80 (s, 3H), 3.09 (dd, *J* = 6.8, 1.2 Hz, 2H), 2.02 – 1.94 (m, 2H), 1.87 – 1.78 (m, 2H), 1.59 – 1.37 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.1, 159.7, 149.1, 143.8, 129.3, 119.4, 119.3, 113.6, 110.5, 55.3, 44.4, 37.9, 36.3, 26.4, 22.7.

HRMS (ESI-TOF): calculated for $C_{17}H_{21}O_3^-$ $[M-H]^-$: 273.1493; Found 273.1496.

Compound 13

(E)-4-(1-(3,4,5-trimethoxyphenyl)cyclohexyl)but-3-enoic acid



14.7 mg, 44% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 5-iodo-1,2,3-trimethoxybenzene (44.1 mg, 0.15 mmol).

Physical State: colorless oil.

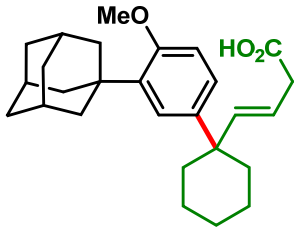
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.58 (s, 2H), 5.55 (d, *J* = 16.0 Hz, 1H), 5.48 (dt, *J* = 15.8, 6.3 Hz, 1H), 3.84 (s, 6H), 3.83 (s, 3H), 3.13 (d, *J* = 6.2 Hz, 2H), 1.96 – 1.79 (m, 4H), 1.63 – 1.48 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.7, 152.9, 143.4, 143.4, 136.2, 119.8, 104.3, 61.0, 56.3, 44.6, 38.0, 36.6, 26.3, 22.7.

HRMS (ESI-TOF): calculated for $C_{19}H_{26}NaO_5^+$ $[M+Na]^+$: 357.1672; Found 357.1672.

Compound 14

(E)-4-(1-(3-(1-adamantyl)-4-methoxyphenyl)cyclohexyl)but-3-enoic acid



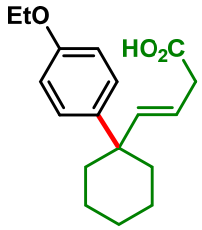
20.0 mg, 49% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-(5-bromo-2-methoxyphenyl)adamantane (48.2 mg, 0.15 mmol).

Physical State: colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.20 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 5.55 (d, *J* = 15.9 Hz, 1H), 5.45 (dt, *J* = 15.8, 6.7 Hz, 1H), 3.81 (s, 3H), 3.10 (d, *J* = 6.6 Hz, 2H), 2.10 – 2.04 (m, 9H), 1.92 – 1.82 (m, 4H), 1.76 (s, 6H), 1.64 – 1.40 (m, 6H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.2, 156.8, 144.1, 138.9, 138.0, 125.4, 124.7, 119.0, 111.2, 55.0, 43.9, 40.7, 38.2, 37.3, 36.5, 29.3, 26.5, 22.8.
HRMS (ESI-TOF): calculated for $C_{27}H_{36}NaO_3^+$ $[M+Na]^+$: 431.2557; Found 431.2560.

Compound 15

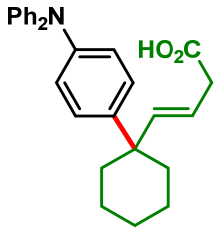
(E)-4-(1-(4-ethoxyphenyl)cyclohexyl)but-3-enoic acid



18.5 mg, 64% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-ethoxy-4-iodobenzene (37.2 mg, 0.15 mmol).
Physical State: colorless oil.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.26 – 7.20 (m, 2H), 6.87 – 6.82 (m, 2H), 5.56 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.37 (dt, *J* = 15.8, 6.9 Hz, 1H), 4.02 (q, *J* = 7.0 Hz, 2H), 3.08 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.00 – 1.90 (m, *J* = 11.7, 8.2, 3.1 Hz, 2H), 1.85 – 1.75 (m, 2H), 1.60 – 1.37 (m, 9H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.3, 156.9, 144.4, 139.0, 127.9, 118.9, 114.2, 63.4, 43.7, 38.1, 36.4, 26.5, 22.6, 15.1.
HRMS (ESI-TOF): calculated for $C_{18}H_{23}O_3^-$ $[M-H]^-$: 287.1652; Found 287.1653.

Compound 16

(E)-4-(1-(4-(diphenylamino)phenyl)cyclohexyl)but-3-enoic acid

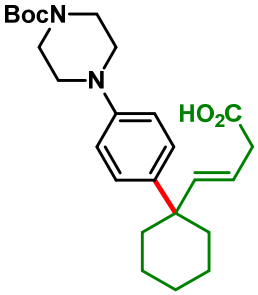


26.3 mg, 64% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 4-iodo-N,N-diphenylaniline (55.7 mg, 0.15 mmol).
24.6 mg, 60% yield. Following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 4-bromo-N,N-diphenylaniline (48.6 mg, 0.15 mmol).
Physical State: pale yellow oil.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.25 – 7.15 (m, 6H), 7.10 – 7.05 (m, 4H), 7.02 – 6.95 (m, 4H), 5.57 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.44 (dt, *J* = 15.9, 6.8 Hz, 1H), 3.11 (dd, *J* = 6.7, 1.2 Hz, 2H), 1.98 – 1.88 (m, 2H), 1.87 – 1.78 (m, 2H), 1.61 – 1.44 (m, 6H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 175.9, 148.0, 145.4, 143.9, 129.3, 127.6, 124.2, 123.8, 122.6, 119.3, 43.9, 37.8, 36.4, 26.5, 22.7.

HRMS (ESI-TOF): calculated for $C_{28}H_{26}NO_2^-$ [M-H]$^-$: 410.2124; Found 410.2126.

Compound 17

(E)-4-(1-(4-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)cyclohexyl)but-3-enoic acid



31.3 mg, 73% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and tert-butyl 4-(4-iodophenyl)piperazine-1-carboxylate (58.2 mg, 0.15 mmol).

Physical State: orange oil.

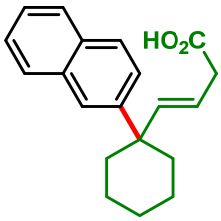
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.25 – 7.21 (m, 2H), 6.91 – 6.86 (m, 2H), 5.54 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.38 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.57 (t, *J* = 5.2 Hz, 4H), 3.11 (t, *J* = 5.1 Hz, 4H), 3.07 (dd, *J* = 6.9, 1.2 Hz, 2H), 2.00 – 1.91 (m, 2H), 1.84 – 1.72 (m, 2H), 1.55 – 1.35 (m, 15H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.6, 154.9, 148.9, 144.1, 138.9, 127.7, 119.0, 116.5, 80.1, 49.6, 44.1, 43.6, 38.1, 36.3, 28.6, 26.5, 22.6.

HRMS (ESI-TOF): calculated for $C_{25}H_{35}N_2O_4^-$ [M-H]$^-$: 427.2601; Found 427.2602.

Compound 18

(E)-4-(1-(naphthalen-2-yl)cyclohexyl)but-3-enoic acid



16.2 mg, 55% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 2-iodonaphthalene (38.11 mg, 0.15 mmol).

19.7 mg, 67% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 2-bromonaphthalene (31.1 mg, 0.15 mmol).

Physical State: colorless oil.

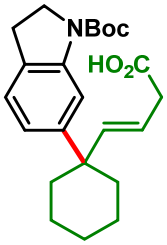
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.83 – 7.76 (m, 4H), 7.50 – 7.41 (m, 3H), 5.66 (d, *J* = 15.8 Hz, 1H), 5.45 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.10 (dd, *J* = 7.0, 1.3 Hz, 2H), 2.18 – 2.07 (m, 2H), 1.99 – 1.88 (m, 2H), 1.66 – 1.40 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.1, 144.5, 143.9, 133.6, 131.9, 128.1, 127.9, 127.5, 126.0, 125.9, 125.6, 125.1, 119.7, 44.4, 38.1, 36.3, 26.5, 22.7.

HRMS (ESI-TOF): calculated for $C_{20}H_{21}O_2^-$ [M-H]$^-$: 293.1549; Found 293.1547.

Compound 19

Benzyl (2-formyl-4,5-dimethoxyphenyl)carbamateyl)cyclohexyl)but-3-enoic acid



14.2 mg, 37% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and tert-butyl 6-bromoindoline-1-carboxylate (44.7 mg, 0.15 mmol).

Physical State: pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 9.05 (br s, 1H), 7.91 – 7.50 (br s, 0.5H), 7.48 – 7.27 (br s, 0.5H), 7.16 – 7.05 (m, 2H), 5.53 (d, *J* = 15.8 Hz, 1H), 5.38 (dt, *J* = 15.1, 6.8 Hz, 1H), 3.96 (br s, 2H), 3.15 – 2.97 (m, 4H), 2.00 – 1.89 (m, 2H), 1.86 – 1.72 (m, 2H), 1.62 – 1.42 (m, 15H).

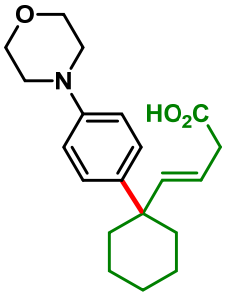
^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.2, 152.9 (152.7), 144.1, 141.1, 140.8 (139.9), 131.9 (131.0), 125.9, 123.6 (123.3), 119.1, 114.4, 81.5 (80.3), 47.8 (47.7), 43.8, 38.4, 36.4, 28.6, 27.7 (27.2), 26.4, 22.6.

Extra splitting due to the existence of rotamerism.

HRMS (ESI-TOF): calculated for $C_{23}H_{30}NO_4^-$ $[M-H]^-$: 384.2181; Found 384.2180.

Compound 20

(E)-4-(1-(4-morpholinophenyl)cyclohexyl)but-3-enoic acid



21.4 mg, 65% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 4-(4-iodophenyl)morpholine (43.4 mg, 0.15 mmol).

Physical State: pale yellow oil.

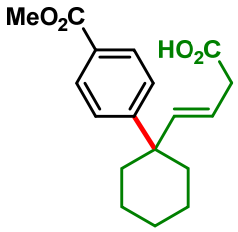
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.26 – 7.19 (m, 2H), 6.90 – 6.83 (m, 2H), 5.55 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.38 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.88 – 3.83 (m, 4H), 3.18 – 3.12 (m, 4H), 3.07 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.03 – 1.91 (m, 2H), 1.86 – 1.74 (m, 2H), 1.57 – 1.36 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.5, 149.0, 144.3, 138.5, 127.7, 118.9, 115.6, 67.1, 49.5, 43.6, 38.1, 36.3, 26.5, 22.7.

HRMS (ESI-TOF): calculated for $C_{20}H_{28}NO_3^+$ $[M+H]^+$: 330.2064; Found 330.2065.

Compound 21

(E)-4-(1-(4-(methoxycarbonyl)phenyl)cyclohexyl)but-3-enoic acid



17.8 mg, 59% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and methyl 4-bromobenzoate (32.3 mg, 0.15 mmol).

Physical State: colorless oil.

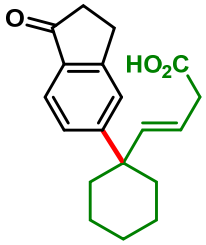
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.99 – 7.95 (m, 2H), 7.43 – 7.39 (m, 2H), 5.57 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.39 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.90 (s, 3H), 3.08 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.06 – 1.96 (m, 2H), 1.89 – 1.78 (m, 2H), 1.63 – 1.54 (m, 2H), 1.51 – 1.36 (m, 4H).

^{13}C NMR (151 MHz, Chloroform-*d*): δ 177.3, 167.3, 152.7, 143.3, 129.7, 127.7, 127.0, 120.1, 52.1, 44.7, 37.9, 36.3, 26.3, 22.6.

HRMS (ESI-TOF): calculated for $C_{18}H_{21}O_4^-$ [M-H]$^-$: 301.1445; Found 301.1445.

Compound 22

(E)-4-(1-(1-oxo-2,3-dihydro-1H-inden-5-yl)cyclohexyl)but-3-enoic acid



19.9 mg, 67% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 5-bromo-2,3-dihydro-1H-inden-1-one (31.7 mg, 0.15 mmol).

Physical State: colorless oil.

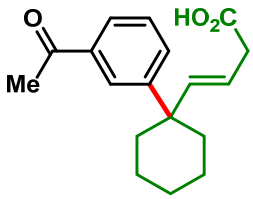
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.69 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.6 Hz, 1H), 5.62 – 5.51 (m, 1H), 5.44 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.15 – 3.04 (m, 4H), 2.72 – 2.60 (m, 2H), 2.08 – 1.95 (m, 2H), 1.93 – 1.81 (m, 2H), 1.67 – 1.34 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*): δ 207.1, 177.1, 155.8, 155.1, 143.0, 135.0, 126.6, 125.0, 123.6, 120.4, 45.0, 37.9, 36.7, 36.4, 26.3, 26.1, 22.6.

HRMS (ESI-TOF): calculated for $C_{19}H_{21}O_3^-$ [M-H]$^-$: 297.1495; Found 297.1496.

Compound 23

(E)-4-(1-(3-acetylphenyl)cyclohexyl)but-3-enoic acid



16.0 mg, 56% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-(3-bromophenyl)ethan-1-one (29.9 mg, 0.15 mmol).

Physical State: colorless oil.

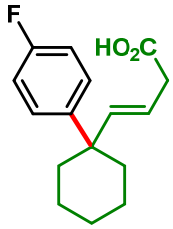
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.97 (d, *J* = 2.1 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 5.58 (d, *J* = 15.9 Hz, 1H), 5.42 (dt, *J* = 15.1, 6.9 Hz, 1H), 3.09 (d, *J* = 6.9 Hz, 2H), 2.60 (s, 3H), 2.02 – 1.97 (m, 2H), 1.92 – 1.84 (m, 2H), 1.62 – 1.36 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 198.8, 177.8, 148.0, 143.4, 137.3, 132.0, 128.6, 126.8, 126.2, 120.2, 44.4, 38.0, 36.4, 26.8, 26.3, 22.6.

HRMS (ESI-TOF): calculated for $C_{18}H_{21}O_3^-$ [M-H]$^-$: 285.1498; Found 285.1496.

Compound 24

(E)-4-(1-(4-fluorophenyl)cyclohexyl)but-3-enoic acid



14.2 mg, 54% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-fluoro-4-iodobenzene (33.3 mg, 0.15 mmol).

Physical State: colorless oil.

^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.32 – 7.26 (m, 2H), 7.03 – 6.95 (m, 2H), 5.56 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.37 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.09 (dd, *J* = 7.0, 1.3 Hz, 2H), 2.01 – 1.92 (m, 2H), 1.86 – 1.78 (m, 2H), 1.59 – 1.37 (m, 6H).

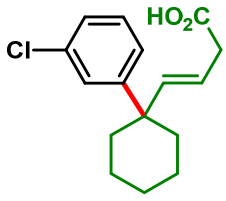
^{13}C NMR (126 MHz, Chloroform-*d*): δ 176.9, 161.1 (*J* = 244.8 Hz), 143.9, 142.8, 128.5 (*J* = 7.7 Hz), 119.5, 115.0 (*J* = 20.9 Hz), 43.9, 37.8, 36.5, 26.4, 22.6.

^{19}F NMR (471 MHz, Chloroform-*d*) δ -118.0.

HRMS (ESI-TOF): calculated for $C_{16}H_{18}FO_2^-$ [M-H]$^-$: 261.1295; Found 261.1296.

Compound 25

(E)-4-(1-(3-chlorophenyl)cyclohexyl)but-3-enoic acid



19.8 mg, 71% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 1-bromo-3-chlorobenzene (28.7 mg, 0.15 mmol).

Physical State: colorless oil.

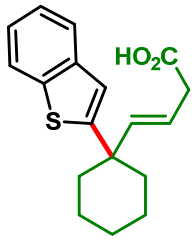
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.33 – 7.30 (m, 1H), 7.24 – 7.21 (m, 2H), 7.16 (dt, *J* = 6.6, 2.3 Hz, 1H), 5.60 – 5.49 (m, 1H), 5.41 (dt, *J* = 15.9, 6.8 Hz, 1H), 3.10 (dd, *J* = 6.8, 1.3 Hz, 2H), 2.00 – 1.91 (m, 2H), 1.87 – 1.78 (m, 2H), 1.61 – 1.36 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.2, 149.5, 143.3, 134.3, 129.6, 127.3, 126.0, 125.2, 120.0, 44.4, 38.0, 36.3, 26.3, 22.6.

HRMS (ESI-TOF): calculated for $C_{16}H_{18}ClO_2^-$ [M-H]$^-$: 277.1001; Found 277.1001.

Compound 26

(E)-4-(1-(benzo[b]thiophen-2-yl)cyclohexyl)but-3-enoic acid



9.9 mg, 33% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 2-bromobenzo[b]thiophene (31.9 mg, 0.15 mmol).

Physical State: yellow solid.

m.p.: 125 – 126 ℃.

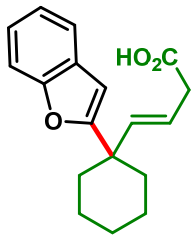
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.76 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.32 – 7.22 (m, 2H), 7.07 (d, *J* = 0.8 Hz, 1H), 5.69 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.52 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.10 (dd, *J* = 7.0, 1.3 Hz, 2H), 2.15 – 2.00 (m, 2H), 1.95 – 1.84 (m, 2H), 1.64 – 1.56 (m, 4H), 1.51 – 1.40 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.4, 154.2, 143.1, 140.2, 139.3, 124.1, 123.7, 123.2, 122.3, 120.06, 120.0, 44.0, 37.8, 37.8, 26.0, 22.6.

HRMS (ESI-TOF): calculated for $C_{18}H_{19}O_2S^-$ [M-H]$^-$: 299.1111; Found 299.1111.

Compound 27

(E)-4-(1-(benzofuran-2-yl)cyclohexyl)but-3-enoic acid



10.2 mg, 36% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 2-iodobenzofuran (36.6 mg, 0.15 mmol).

Physical State: colorless oil.

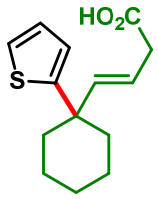
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.52 – 7.44 (m, 1H), 7.44 – 7.38 (m, 1H), 7.23 – 7.14 (m, 2H), 6.45 (d, *J* = 0.9 Hz, 1H), 5.68 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.47 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.08 (dd, *J* = 6.9, 1.4 Hz, 2H), 2.20 – 2.11 (m, 2H), 1.80 – 1.71 (m, 2H), 1.65 – 1.55 (m, 2H), 1.54 – 1.38 (m, 4H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.0, 163.1, 154.7, 141.1, 128.9, 123.3, 122.5, 120.6, 120.4, 111.1, 102.4, 42.7, 37.8, 34.9, 26.1, 22.5.

HRMS (ESI-TOF): calculated for $C_{18}H_{19}O_3^-$ [M-H]$^-$: 283.1339; Found 283.1340.

Compound 28

(E)-4-(1-(thiophen-2-yl)cyclohexyl)but-3-enoic acid



9.5 mg, 38% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 2-iodothiophene (31.5 mg, 0.15 mmol).

Physical State: pale yellow oil.

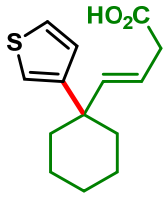
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.16 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.83 (dd, *J* = 3.6, 1.2 Hz, 1H), 5.65 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.45 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.09 (dd, *J* = 7.0, 1.4 Hz, 2H), 2.00 – 1.93 (m, 2H), 1.92 – 1.83 (m, 2H), 1.61 – 1.40 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.6, 153.7, 143.6, 123.4, 123.2, 119.6, 43.4, 38.2, 37.9, 26.1, 22.6.

HRMS (ESI-TOF): calculated for $C_{14}H_{17}O_2S^-$ [M-H]$^-$: 249.0954; Found 249.0955.

Compound 29

(E)-4-(1-(thiophen-3-yl)cyclohexyl)but-3-enoic acid



12.3 mg, 49% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 3-iodothiophene (31.5 mg, 0.15 mmol).

Physical State: pale yellow oil.

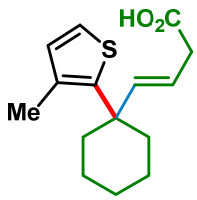
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.26 – 7.24 (m, 1H), 7.01 – 6.97 (m, 2H), 5.61 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.38 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.08 (dd, *J* = 6.9, 1.4 Hz, 2H), 1.97 – 1.88 (m, 2H), 1.85 – 1.77 (m, 2H), 1.58 – 1.37 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.7, 149.0, 143.5, 127.2, 125.2, 119.9, 119.2, 42.9, 38.0, 37.0, 26.3, 22.6.

HRMS (ESI-TOF): calculated for $C_{14}H_{17}O_2S^-$ [M-H]$^-$: 249.0954; Found 249.0955.

Compound 30

(E)-4-(1-(3-methylthiophen-2-yl)cyclohexyl)but-3-enoic acid



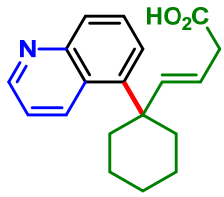
7.9 mg, 30% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 2-iodo-3-methylthiophene (33.6 mg, 0.15 mmol).

Physical State: pale yellow oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.02 (d, *J* = 5.1 Hz, 1H), 6.76 (d, *J* = 5.1 Hz, 1H), 5.67 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.44 (dt, *J* = 15.7, 7.0 Hz, 1H), 3.11 (dd, *J* = 7.0, 1.4 Hz, 2H), 2.19 (s, 3H), 2.06 – 1.98 (m, 2H), 1.98 – 1.89 (m, 2H), 1.66 – 1.45 (m, 6H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.9, 144.7, 141.0, 132.8, 132.5, 120.6, 119.8, 43.7, 38.00, 37.1, 26.2, 22.7, 16.4.
HRMS (ESI-TOF): calculated for $C_{15}H_{19}O_2S^-$ [M-H]$^-$: 263.1108; Found 263.1111.

Compound 31

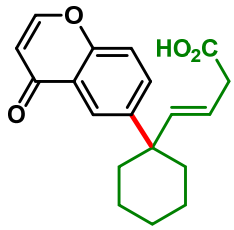
(E)-4-(1-(quinolin-5-yl)cyclohexyl)but-3-enoic acid



8.0 mg, 27% yield. Prepared following the **General Procedure** (except modification of extraction: extract the first time after aqueous NH_4Cl added, second time when pH = 5 after adding 1 N HCl, third time when pH = 3) from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 5-bromoquinoline (31.2 mg, 0.15 mmol).
Physical State: colorless oil.
^{1}H NMR (600 MHz, Methanol-d_4) δ 8.75 (dd, *J* = 10.0, 6.5 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.78 – 7.75 (m, 1H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 8.8, 4.2 Hz, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 5.21 (dt, *J* = 16.0, 7.1 Hz, 1H), 2.99 (d, *J* = 7.1 Hz, 2H), 2.22 – 2.17 (m, 2H), 2.08 – 2.02 (m, 2H), 1.82 – 1.74 (m, 2H), 1.69 – 1.64 (m, 1H), 1.64 – 1.58 (m, 2H), 1.46 – 1.40 (m, 1H).
^{13}C NMR (126 MHz, Methanol-d_4) δ 175.6, 150.4, 149.7, 147.0, 143.4, 139.1, 130.2, 128.3, 127.7, 126.5, 124.3, 120.4, 45.8, 40.3, 39.0, 27.4, 23.6.
HRMS (ESI-TOF): calculated for $C_{19}H_{22}NO_2^+$ [M+H]$^+$: 296.1645; Found 296.1647.

Compound 32

(E)-4-(1-(4-oxo-4H-chromen-6-yl)cyclohexyl)but-3-enoic acid

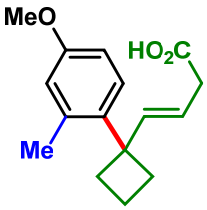


14.0 mg, 45% yield. Prepared following the **General Procedure** from 4-cyclohexylidenebutanoic acid (16.8 mg, 0.1 mmol) and 6-bromo-4H-chromen-4-one (33.8 mg, 0.15 mmol).
Physical State: pale yellow oil.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.18 (d, *J* = 2.5 Hz, 1H), 7.84 (d, *J* = 6.0 Hz, 1H), 7.67 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 1H), 6.35 (d, *J* = 6.0 Hz, 1H), 5.60 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.42 (dt, *J* = 15.9, 7.0 Hz, 1H), 3.09 (dd, *J* = 6.9, 1.3 Hz, 2H), 2.11 – 2.01 (m, 2H), 2.01 – 1.85 (m, 2H), 1.62 – 1.37 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.2, 175.8, 155.4, 155.0, 144.9, 143.2, 133.5, 124.5, 123.4, 120.5, 118.2, 113.0, 44.4, 37.8, 36.4, 26.3, 22.6.
HRMS (ESI-TOF): calculated for $C_{19}H_{19}O_4^-$ [M-H]$^-$: 311.1288; Found 311.1289.

Compound 33

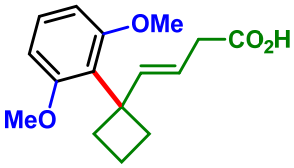
(E)-4-(1-(4-methoxy-2-methylphenyl)cyclobutyl)but-3-enoic acid



11.0 mg, 42% yield. Prepared following the **General Procedure** from 4-cyclobutylidenebutanoic acid (14.0 mg, 0.1 mmol) and 1-iodo-4-methoxy-2-methylbenzene (37.2 mg, 0.15 mmol).
Physical State: colorless oil.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.95 (d, *J* = 8.4 Hz, 1H), 6.70 (dd, *J* = 8.5, 2.9 Hz, 1H), 6.64 (d, *J* = 2.9 Hz, 1H), 5.96 (dt, *J* = 15.4, 1.5 Hz, 1H), 5.30 (dt, *J* = 15.6, 7.0 Hz, 1H), 3.78 (d, *J* = 2.1 Hz, 3H), 3.08 (dd, *J* = 7.0, 1.4 Hz, 2H), 2.52 – 2.42 (m, 2H), 2.31 (dt, *J* = 8.5, 2.7 Hz, 2H), 2.15 – 2.07 (m, 4H), 1.82 – 1.73 (m, 1H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.2, 157.9, 140.7, 138.4, 137.5, 127.4, 117.7, 116.6, 110.7, 55.3, 49.2, 37.7, 34.0, 20.4, 16.5.
HRMS (ESI-TOF): calculated for $C_{16}H_{19}O_3^-$ [M-H]$^-$: 259.1338; Found 259.1340.

Compound 34

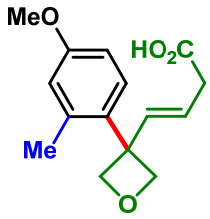
(E)-4-(1-(2,6-dimethoxyphenyl)cyclobutyl)but-3-enoic acid



13.3 mg, 48% yield. Prepared following the **General Procedure** from 4-cyclobutylidenebutanoic acid (14.0 mg, 0.1 mmol) and 2-iodo-1,3-dimethoxybenzene (39.6 mg, 0.15 mmol).
Physical State: white solid.
m.p.: 118 – 119 ℃.
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.11 (t, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 2H), 6.02 (d, *J* = 15.3 Hz, 1H), 5.52 (dt, *J* = 14.7, 6.8 Hz, 1H), 3.74 (s, 6H), 3.09 (d, *J* = 6.9 Hz, 2H), 2.50 – 2.42 (m, 2H), 2.42 – 2.36 (m, 2H), 2.00 – 1.92 (m, 1H), 1.70 – 1.63 (m, 1H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.4, 158.3, 139.5, 127.1, 124.2, 116.7, 104.8, 55.7, 46.9, 38.0, 35.5, 17.9.
HRMS (ESI-TOF): calculated for $C_{16}H_{19}O_4^-$ [M-H]$^-$: 275.1291; Found 275.1289.

Compound 35

(E)-4-(3-(4-methoxy-2-methylphenyl)oxetan-3-yl)but-3-enoic acid



13.1 mg, 50% yield. Prepared following the **General Procedure** from 4-(oxetan-3-ylidene)butanoic acid (14.2 mg, 0.1 mmol) and 1-iodo-4-methoxy-2-methylbenzene (37.2 mg, 0.15 mmol).

Physical State: colorless oil.

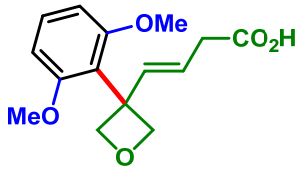
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.78 – 6.69 (m, 3H), 6.40 (dt, *J* = 15.3, 1.4 Hz, 1H), 5.19 (dt, *J* = 15.4, 7.0 Hz, 1H), 5.14 (d, *J* = 5.9 Hz, 2H), 4.69 (d, *J* = 5.8 Hz, 2H), 3.80 (s, 3H), 3.11 (dd, *J* = 7.0, 1.4 Hz, 2H), 1.96 (s, 3H).

^{13}C NMR (151 MHz, Chloroform-*d*): δ 176.6, 158.6, 139.0, 137.2, 133.0, 127.8, 121.4, 116.8, 111.2, 81.9, 55.3, 49.8, 37.4, 19.7.

HRMS (ESI-TOF): calculated for $C_{15}H_{17}O_4^-$ [M-H]$^-$: 261.1135; Found 261.1132.

Compound 36

(E)-4-(3-(2,6-dimethoxyphenyl)oxetan-3-yl)but-3-enoic acid



13.1 mg, 47% yield. Prepared following the **General Procedure** from 4-(oxetan-3-ylidene)butanoic acid (14.2 mg, 0.1 mmol) and 2-iodo-1,3-dimethoxybenzene (39.6 mg, 0.15 mmol).

Physical State: colorless oil.

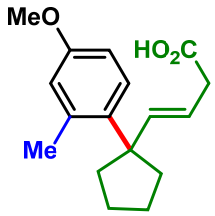
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.19 (t, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 2H), 6.27 (dt, *J* = 15.3, 1.4 Hz, 1H), 5.46 (dt, *J* = 15.4, 7.0 Hz, 1H), 5.03 (d, *J* = 6.8 Hz, 2H), 4.63 (d, *J* = 6.9 Hz, 2H), 3.73 (s, 6H), 3.11 (dd, *J* = 6.9, 1.5 Hz, 2H).

^{13}C NMR (151 MHz, Chloroform-*d*): δ 176.8, 157.6, 137.3, 128.4, 119.6, 118.6, 104.4, 81.7, 55.8, 47.3, 37.7.

HRMS (ESI-TOF): calculated for $C_{15}H_{17}O_5^-$ [M-H]$^-$: 277.1083; Found 277.1081.

Compound 37

(E)-4-(1-(4-methoxy-2-methylphenyl)cyclopentyl)but-3-enoic acid



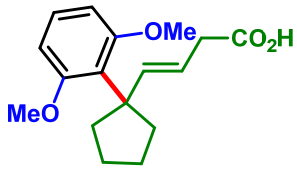
13.9 mg, 51% yield. Prepared following the **General Procedure** from 4-cyclopentylidenebutanoic acid (15.4 mg, 0.1 mmol) and 1-iodo-4-methoxy-2-methylbenzene (37.2 mg, 0.15 mmol).

Physical State: colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.25 – 7.21 (m, 1H), 6.70 – 6.65 (m, 2H), 5.64 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.29 (dt, *J* = 15.5, 7.0 Hz, 1H), 3.78 (s, 3H), 3.05 (dd, *J* = 7.0, 1.4 Hz, 2H), 2.30 (s, 3H), 2.16 – 2.09 (m, 2H), 1.95 – 1.86 (m, 2H), 1.75 – 1.66 (m, 4H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.0, 157.8, 142.0, 139.1, 137.9, 127.7, 118.2, 117.7, 110.2, 55.2, 53.1, 38.0, 37.8, 23.4, 22.4.
HRMS (ESI-TOF): calculated for $C_{17}H_{21}O_3^-$ [M-H]$^-$: 273.1496; Found 273.1496.

Compound 38

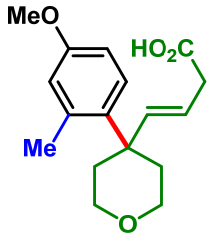
(E)-4-(1-(2,6-dimethoxyphenyl)cyclopentyl)but-3-enoic acid



13.8 mg, 48% yield. Prepared following the **General Procedure** from 4-cyclopentylidenebutanoic acid (15.4 mg, 0.1 mmol) and 2-iodo-1,3-dimethoxybenzene (39.6 mg, 0.15 mmol).
Physical State: colorless oil.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.12 (t, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 2H), 5.79 (dt, *J* = 15.5, 1.4 Hz, 1H), 5.39 (dt, *J* = 15.5, 7.0 Hz, 1H), 3.75 (s, 6H), 3.03 (dd, *J* = 7.1, 1.3 Hz, 2H), 2.65 – 2.57 (m, 2H), 1.93 – 1.82 (m, 2H), 1.62 – 1.56 (m, 4H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.9, 159.5, 141.3, 127.3, 124.7, 116.8, 106.1, 56.0, 52.0, 38.6, 38.1, 23.0.
HRMS (ESI-TOF): calculated for $C_{17}H_{21}O_4^-$ [M-H]$^-$: 289.1443; Found 289.1445.

Compound 39

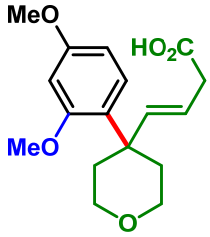
(E)-4-(4-(4-methoxy-2-methylphenyl)tetrahydro-2H-pyran-4-yl)but-3-enoic acid



14.5 mg, 50% yield. Prepared following the **General Procedure** from 4-(tetrahydro-4H-pyran-4-ylidene)butanoic acid (17.0 mg, 0.1 mmol) and 1-iodo-4-methoxy-2-methylbenzene (37.2 mg, 0.15 mmol).
Physical State: colorless oil.
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.25 – 7.22 (m, 1H), 6.74 – 6.68 (m, 2H), 5.89 (d, *J* = 15.7 Hz, 1H), 5.38 – 5.27 (m, 1H), 3.82 – 3.74 (m, 7H), 3.09 (dd, *J* = 7.0, 2.1 Hz, 2H), 2.32 (d, *J* = 2.4 Hz, 3H), 2.18 – 2.12 (m, 2H), 2.06 – 2.00 (m, 2H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 175.9, 157.9, 141.5, 138.7, 136.2, 127.9, 121.1, 118.9, 110.3, 64.5, 55.2, 42.1, 37.7, 37.2, 23.1.
HRMS (ESI-TOF): calculated for $C_{17}H_{21}O_4^-$ [M-H]$^-$: 289.1446; Found 289.1445.

Compound 40

(E)-4-(4-(2,4-dimethoxyphenyl)tetrahydro-2H-pyran-4-yl)but-3-enoic acid



16.5 mg, 54% yield. Prepared following the **General Procedure** from 4-(tetrahydro-4H-pyran-4-ylidene)butanoic acid (17.0 mg, 0.1 mmol) and 1-iodo-2,4-dimethoxybenzene (39.6 mg, 0.15 mmol).

Physical State: colorless oil.

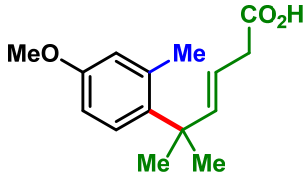
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.16 – 7.09 (m, 1H), 6.49 – 6.39 (m, 2H), 5.85 (dt, *J* = 15.8, 1.4 Hz, 1H), 5.37 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.74 (m, 4H), 3.73 (s, 3H), 3.08 (dd, *J* = 7.0, 1.4 Hz, 2H), 2.23 – 2.15 (m, 2H), 2.14 – 2.04 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.2, 159.5, 159.2, 140.9, 127.5, 127.2, 120.2, 103.7, 100.2, 64.7, 55.4, 55.2, 40.8, 38.1, 35.8.

HRMS (ESI-TOF): calculated for $C_{17}H_{21}O_5^-$ [M-H]$^-$: 305.1394; Found 305.1394.

Compound 41

(E)-5-(4-methoxy-2-methylphenyl)-5-methylhex-3-enoic acid



12.4 mg, 50% yield. Prepared following the **General Procedure** from 5-methylhex-4-enoic acid (12.8 mg, 0.1 mmol) and 1-iodo-4-methoxy-2-methylbenzene (37.2 mg, 0.15 mmol).

Physical State: colorless oil.

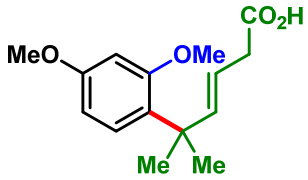
^{1}H NMR (600 MHz, Chloroform-*d*): δ 7.29 – 7.26 (m, 1H), 6.71 – 6.65 (m, 2H), 5.79 (dt, *J* = 15.6, 1.4 Hz, 1H), 5.43 (dt, *J* = 15.6, 7.0 Hz, 1H), 3.78 (s, 3H), 3.10 (dd, *J* = 7.1, 1.4 Hz, 2H), 2.35 (s, 3H), 1.43 (s, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 178.1, 157.8, 145.1, 138.8, 138.0, 127.2, 118.1, 117.5, 110.3, 55.2, 40.8, 37.9, 29.3, 22.6.

HRMS (ESI-TOF): calculated for $C_{15}H_{19}O_3^-$ [M-H]$^-$: 247.1339; Found 247.1340.

Compound 42

(E)-5-(2,4-dimethoxyphenyl)-5-methylhex-3-enoic acid



12.1 mg, 46% yield. Prepared following the **General Procedure** from 5-methylhex-4-enoic acid (12.8 mg, 0.1 mmol) and 1-iodo-2,4-dimethoxybenzene (39.6 mg, 0.15 mmol).

Physical State: colorless oil.

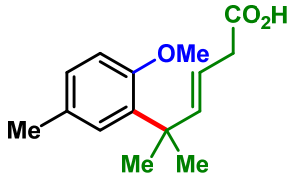
^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.16 (d, *J* = 8.5 Hz, 1H), 6.46 (d, *J* = 2.6 Hz, 1H), 6.42 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.92 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.42 (dt, *J* = 15.6, 7.1 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.09 (dd, *J* = 7.1, 1.4 Hz, 2H), 1.42 (s, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 176.4, 159.5, 159.1, 145.3, 128.8, 127.4, 116.7, 103.7, 100.0, 55.4, 55.3, 39.6, 38.0, 27.8.

HRMS (ESI-TOF): calculated for $C_{15}H_{19}O_4^-$ [M-H]$^-$: 263.1290; Found 263.1289.

Compound 43

(E)-5-(2-methoxy-5-methylphenyl)-5-methylhex-3-enoic acid



136 mg, 55% yield. Prepared following the **General Procedure** from 5-methylhex-4-enoic acid (128 mg, 1.0 mmol) and 2-iodo-1-methoxy-4-methylbenzene (372 mg, 1.5 mmol).

Physical State: colorless oil.

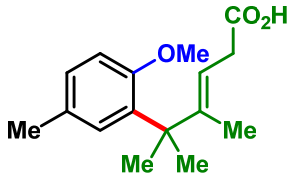
^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.06 (d, *J* = 2.2 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.95 (dt, *J* = 15.7, 1.4 Hz, 1H), 5.43 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.75 (s, 3H), 3.09 (dd, *J* = 7.1, 1.4 Hz, 2H), 2.28 (s, 3H), 1.45 (s, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*): δ 177.1, 156.1, 145.2, 136.0, 129.6, 127.9, 127.8, 116.7, 112.2, 55.5, 40.0, 38.1, 27.7, 20.9.

HRMS (ESI-TOF): calculated for $C_{15}H_{19}O_3^-$ [M-H]$^-$: 247.1339; Found 247.1340.

Compound 45

(E)-5-(2-methoxy-5-methylphenyl)-4,5-dimethylhex-3-enoic acid



9.7 mg, 37% yield. Prepared following the **General Procedure** with 4,5-dimethylhex-4-enoic acid (14.2 mg, 0.1 mmol, 1.0 equiv), 2-iodo-1-methoxy-4-methylbenzene (74.4 mg, 0.3 mmol, 3.0 equiv) , $Pd_2(dba)_3 \cdot CHCl_3$ (10.4 mg, 10 mol%).

Physical State: colorless oil.

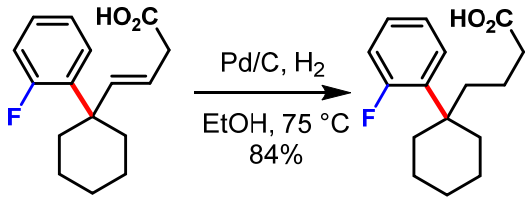
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.08 (d, *J* = 2.2 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 5.44 (t, *J* = 7.6 Hz, 1H), 3.71 (s, 3H), 3.14 (d, *J* = 7.5 Hz, 2H), 2.30 (s, 3H), 1.48 (s, 3H), 1.43 (s, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.5, 155.7, 150.2, 136.4, 130.0, 128.0, 127.8, 112.4, 112.1, 55.9, 43.9, 34.2, 27.5, 21.0, 14.4.

HRMS (ESI-TOF): calculated for $C_{16}H_{21}O_3^-$ [M-H]$^-$: 261.1496; Found 261.1496.

Compound 46

4-(1-(2-fluorophenyl)cyclohexyl)butanoic acid



8 **46**

Pd/C (5% Pd, 7.9 mg, 30 wt%) was added to a 25 mL flask containing a solution of compound **8** (26.2 mg, 0.1 mmol) in EtOH (2.0 mL). The flask was evacuated and backfilled with hydrogen for three times, before heated to 75 ℃ and stirred vigorously for 1 hour with a hydrogen balloon equipped. After cooling to room temperature, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated under vaccum and purified by flash column chromatography (silica gel, acetone/hexanes, 1/20) to afford the title compound **46** (22.1 mg, 84%).

Physical State: colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (td, *J* = 8.2, 1.8 Hz, 1H), 7.20 – 7.14 (m, 1H), 7.07 (td, *J* = 7.5, 1.5 Hz, 1H), 7.00 – 6.92 (m, 1H), 2.25 – 2.10 (m, 4H), 1.75 – 1.67 (m, 2H), 1.67 – 1.54 (m, 4H), 1.49 – 1.34 (m, 4H), 1.30 – 1.24 (m, 2H).

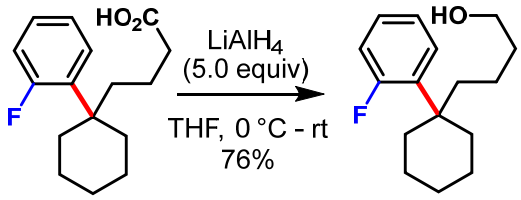
^{13}C NMR (126 MHz, Chloroform-*d*) δ 179.4, 162.2 (*J* = 248.1 Hz), 133.1 (*J* = 10.7 Hz), 130.0 (*J* = 6.1 Hz), 127.7 (*J* = 9.1 Hz), 123.8 (*J* = 2.9 Hz), 116.7 (*J* = 12.7 Hz), 41.6 (*J* = 3.4 Hz), 39.3, 35.9 (*J* = 3.8 Hz), 34.5, 26.7, 22.6, 19.6.

^{19}F NMR (471 MHz, Chloroform-*d*) δ -108.6.

HRMS (ESI-TOF): calculated for $C_{16}H_{20}FO_2^-$ [M-H]$^-$: 263.1453; Found 263.1455.

Compound 47

4-(1-(2-fluorophenyl)cyclohexyl)butan-1-ol



46 **47**

Compound **46** (50 mg, 0.19 mmol, 1.0 equiv) was dissolved in THF (5.0 mL) and $LiAlH_4$ (2.5 N in THF, 0.38 mL, 5.0 equiv) was added dropwise at 0 ℃ under Ar atmosphere. The resulting mixture was allowed to stir at room temperature for 4 hours, before cooled again to 0 ℃ and added NaOH (1.0 M, 0.5 mL). After stirring, the reaction mixture was filtered, concentrated and purified by flash column chromatography (silica gel, acetone/hexanes, 1/30 to 1/20) to afford the title compound **47** (36 mg, 76%).

Physical State: colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (td, *J* = 8.1, 1.8 Hz, 1H), 7.20 – 7.13 (m, 1H), 7.07 (td, *J* = 7.5, 1.5 Hz, 1H), 7.00 – 6.92 (m, 1H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.21 – 2.11 (m, 2H), 1.74 – 1.67 (m, 2H), 1.65 – 1.54 (m, 4H), 1.47 – 1.36 (m, 6H), 1.06 – 0.93 (m, 2H).

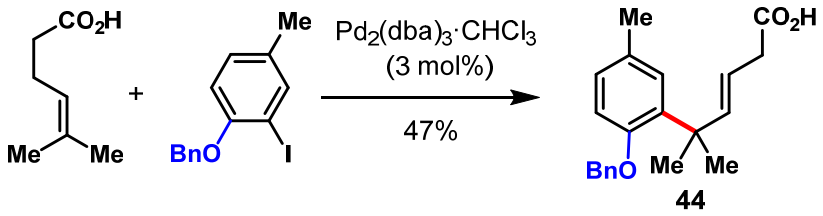
^{13}C NMR (126 MHz, Chloroform-*d*) δ 162.2 (*J* = 248.1 Hz), 133.5 (*J* = 10.7 Hz), 130.1 (*J* = 6.2 Hz), 127.5 (*J* = 9.1 Hz), 123.7 (*J* = 2.9 Hz), 116.6 (*J* = 25.3 Hz), 63.0, 41.8 (*J* = 3.5 Hz), 39.9, 36.1 (*J* = 3.9 Hz), 33.5, 26.8, 22.7, 20.3.

^{19}F NMR (471 MHz, Chloroform-*d*) δ -108.7.

HRMS (EI-DFS): calculated for $C_{16}H_{23}O_1F_1$ $[M]^+$: 250.1727; Found 250.1719.

Compound 44

(E)-5-(2-(benzyloxy)-5-methylphenyl)-5-methylhex-3-enoic acid



44

152 mg, 47% yield. Prepared following the **General Procedure** with 1-(benzyloxy)-2-iodo-4-methylbenzene[3] (324 mg, 1.0 mmol, 1.0 equiv) and 5-methylhex-4-enoic acid (192 mg, 1.5 equiv).

Physical State: colorless oil.

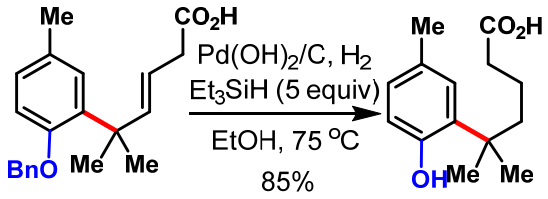
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.35 (m, 4H), 7.32 – 7.28 (m, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 7.00 – 6.96 (m, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.96 (dt, *J* = 15.7, 1.5 Hz, 1H), 5.40 (dt, *J* = 15.7, 7.0 Hz, 1H), 5.04 (s, 2H), 3.00 (dd, *J* = 7.0, 1.4 Hz, 2H), 2.29 (s, 3H), 1.48 (s, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.1, 155.2, 144.7, 137.7, 136.3, 129.7, 128.6, 128.1, 127.8, 127.7, 127.3, 116.8, 112.8, 70.4, 40.0, 38.0, 27.9, 20.9.

HRMS (ESI-TOF): calculated for $C_{21}H_{23}O_3^-$ $[M-H]^-$: 323.1654; Found 323.1653.

Compound 48

5-(2-hydroxy-5-methylphenyl)-5-methylhexanoic acid



44 **48**

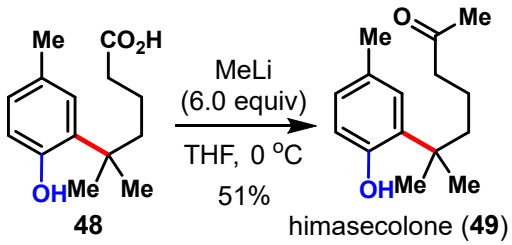
To a 50 mL round-bottom flask containing a solution of compound **44** (32.4 mg, 0.1 mmol, 1.0 equiv) in EtOH (4.0 mL) was added $Pd(OH)_2/C$ (20% Pd, 9.7 mg, 30 wt%) and Et_3SiH (80 μL, 5.0 equiv). The flask was evacuated and backfilled with hydrogen for three times, before heated to 75 °C and stirred vigorously for 3 hours with a hydrogen balloon equipped. After cooling to room temperature, the reaction mixture was filtered through a pad of celite. The filtrate was concentrated under vaccum and purified by flash column chromatography (silica gel, acetone/hexanes, 1/20 to 1/5) to afford the title compound **48** (20.0 mg, 85%).

Physical State: colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.99 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 1H), 2.28 – 2.20 (m, *J* = 7.0 Hz, 5H), 1.93 – 1.84 (m, 2H), 1.39 – 1.30 (m, 8H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 108.1, 152.0, 134.0, 129.7, 129.0, 127.5, 116.6, 40.2, 37.9, 34.7, 28.3, 21.0, 20.9.
HRMS (ESI-TOF): calculated for $C_{14}H_{19}O_3^-$ [M-H]$^-$: 235.1340; Found 235.1340.

Compound 49

6-(2-hydroxy-5-methylphenyl)-6-methylheptan-2-one



To a solution of compound **51** (29.5 mg, 0.125 mmol, 1.0 equiv) in THF (1.0 mL) was added MeLi (1.3 M in Et_2O, 0.58 mL, 6.0 equiv) quickly in one portion (no more than 3 seconds) at 0 ℃ under Ar atmosphere. The reaction mixture was stirred at the same temperature for 2 hours before TMSCl (475 μL, 30 equiv) was added quickly in one portion (no more than 3 seconds).[4] The mixture was warmed to room temperature, and 1 N HCl (2.0 mL) was added. After stirring for another 30 minutes, the reaction was diluted with water, extracted with Et_2O for three times. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography (silica gel, acetone/hexanes, 1/20 to 1/5) to afford the title compound **52** (15.0 mg, 51%).
Physical State: colorless oil.
^{1}H NMR (400 MHz, Chloroform-*d*): δ 6.99 (d, *J* = 2.2 Hz, 1H), 6.86 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 4.90 (br s, 1H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 2.07 (s, 3H), 1.84 – 1.79 (m, 2H), 1.36 (s, 6H), 1.33 – 1.29 (m, 2H).
^{13}C NMR (126 MHz, Chloroform-*d*): δ 210.2, 152.0, 134.3, 129.8, 129.0, 127.5, 116.9, 44.5, 40.3, 37.9, 29.9, 28.4, 21.0, 20.0.
HRMS (ESI-TOF): calculated for $C_{15}H_{21}O_2^-$ [M-H]$^-$: 233.1548; Found 233.1547.

Reference

[1] J. Lei, X. Liu, S. Zhang, S. Jiang, M. Huang, X. Wu, Q. Zhu, *Chemistry – A European Journal* **2015**, *21*, 6700-6703.

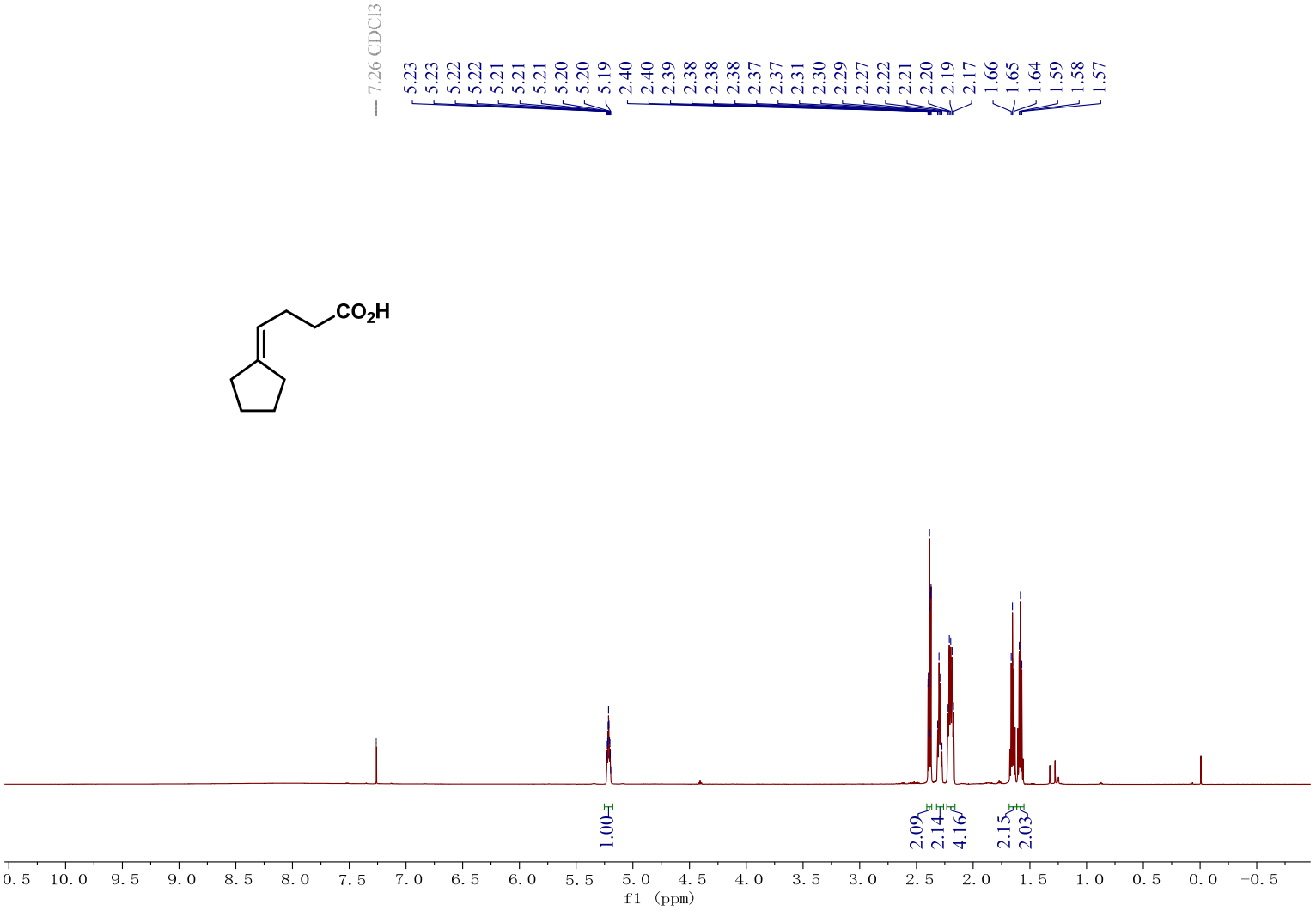
[2] T. R. Huffman, Y. Wu, A. Emmerich, R. A. Shenvi, *Angewandte Chemie International Edition* **2019**, *58*, 2371-2376.

[3] X. Zhou, Y. He, M. Wang, Y. Ding, *Phosphorus, Sulfur, and Silicon and the Related Elements* **2009**, *184*, 651-659.

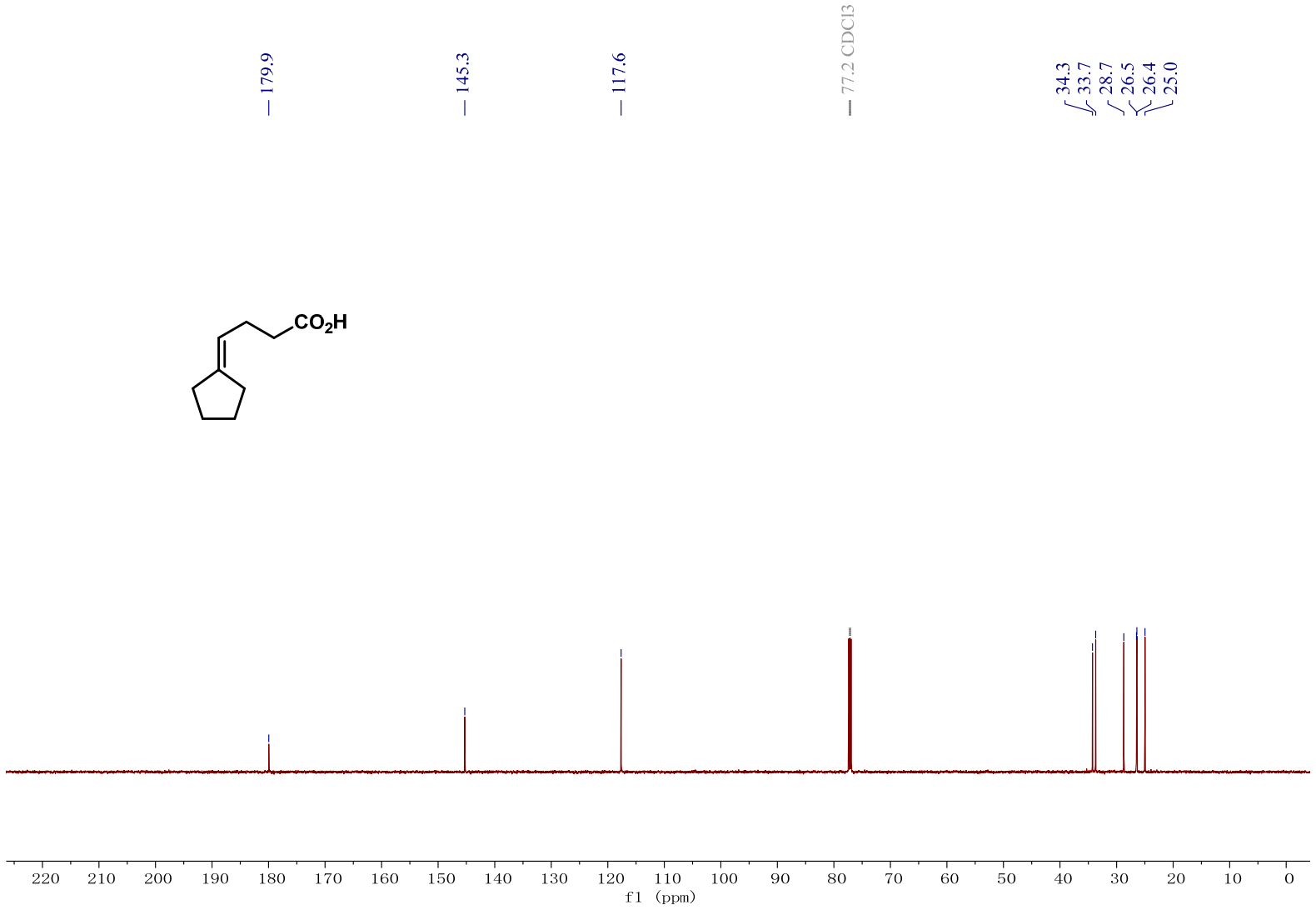
[4] G. M. Rubottom, C. Kim, *The Journal of Organic Chemistry* **1983**, *48*, 1550-1552.

NMR Spectra

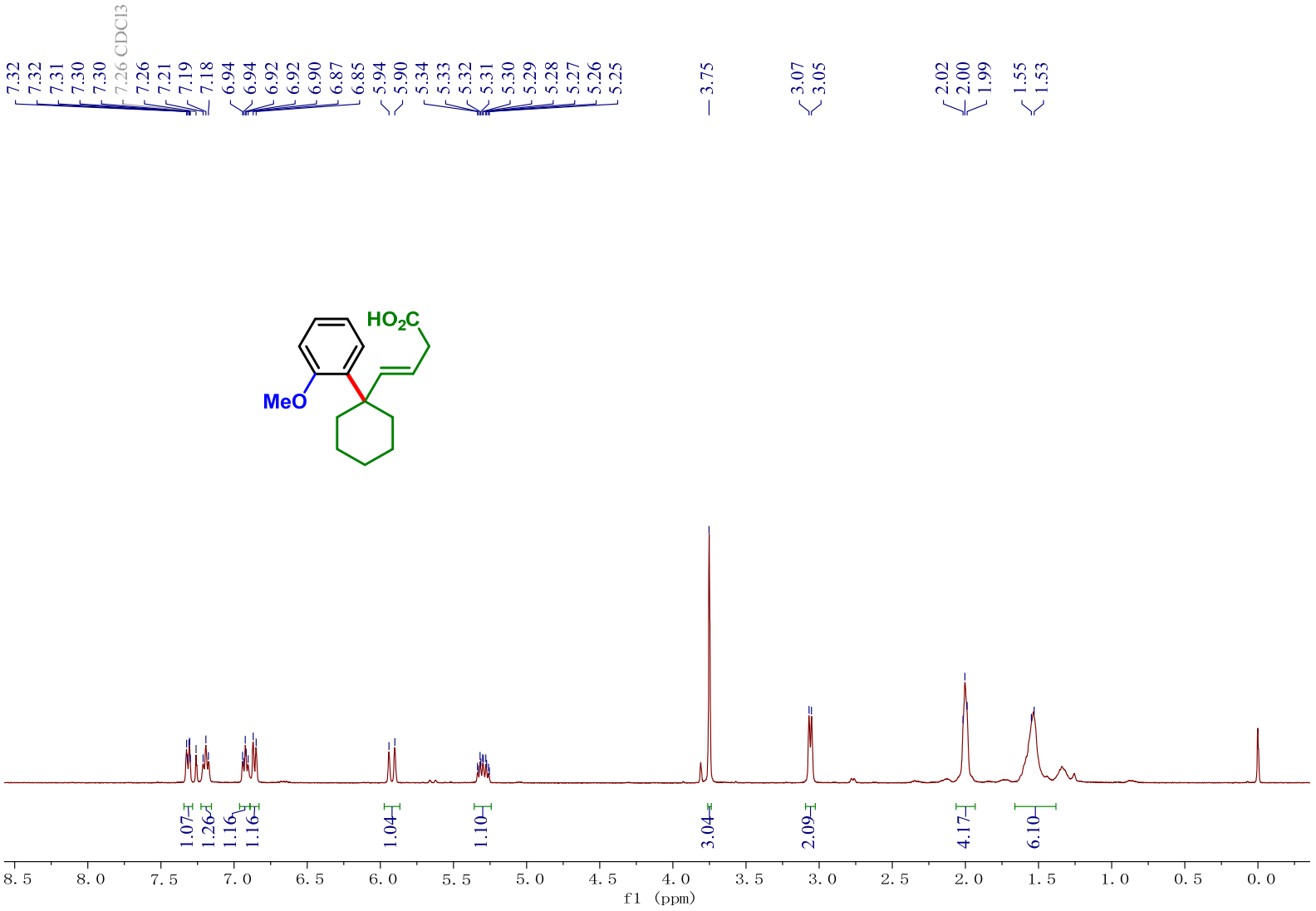
Compound S1 ^{1}H NMR



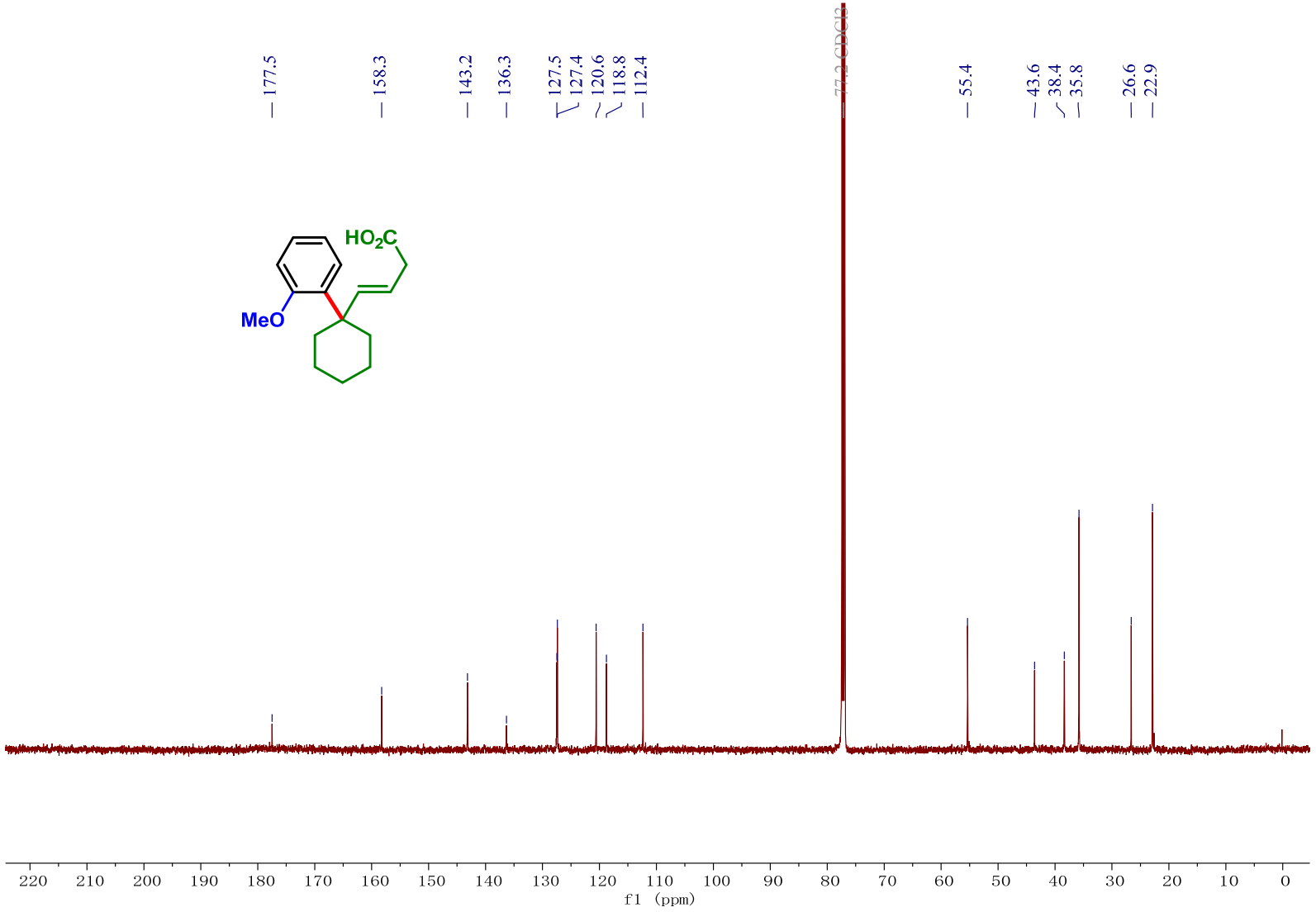
Compound S1 ^{13}C NMR



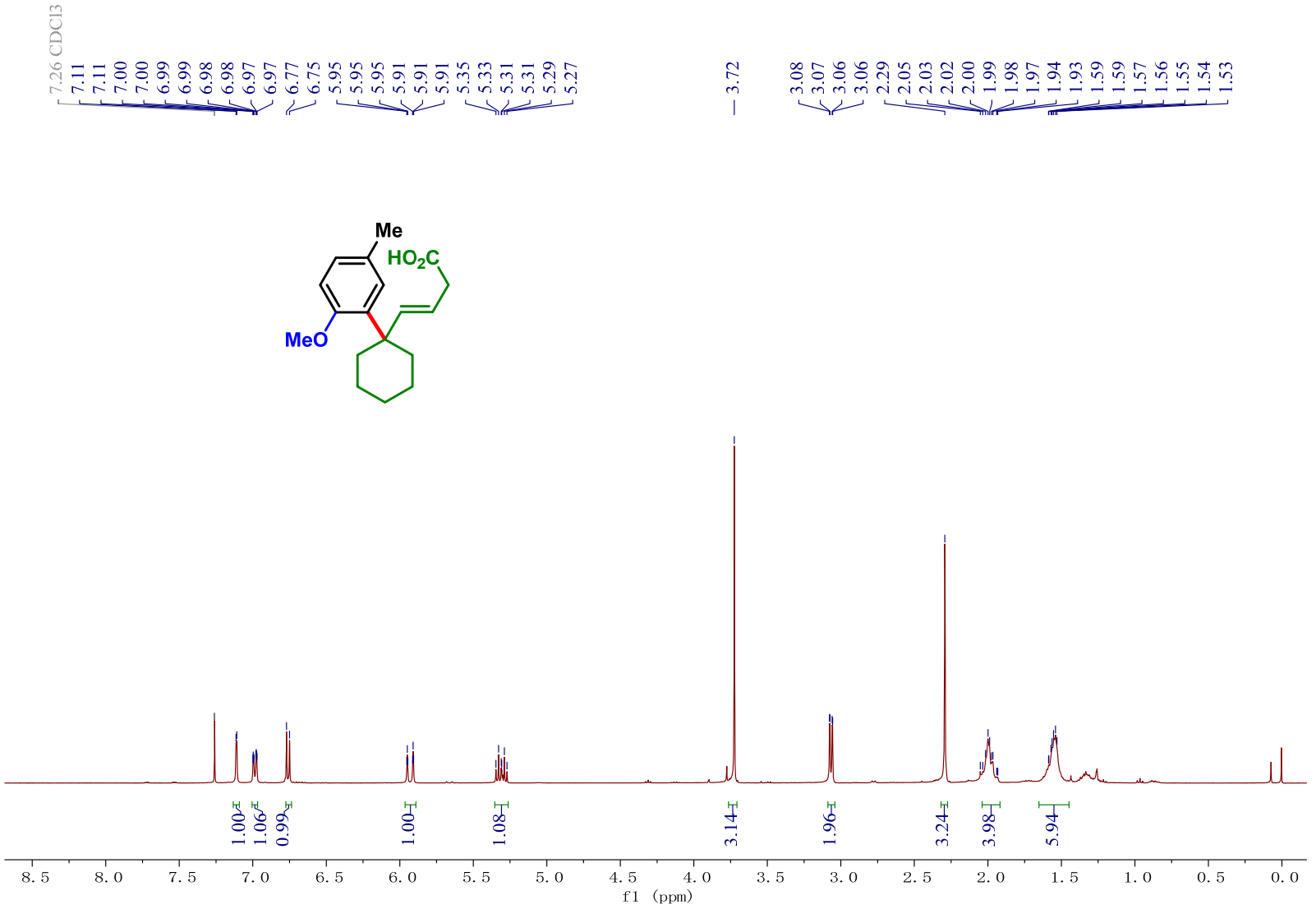
Compound 3 ^{1}H NMR



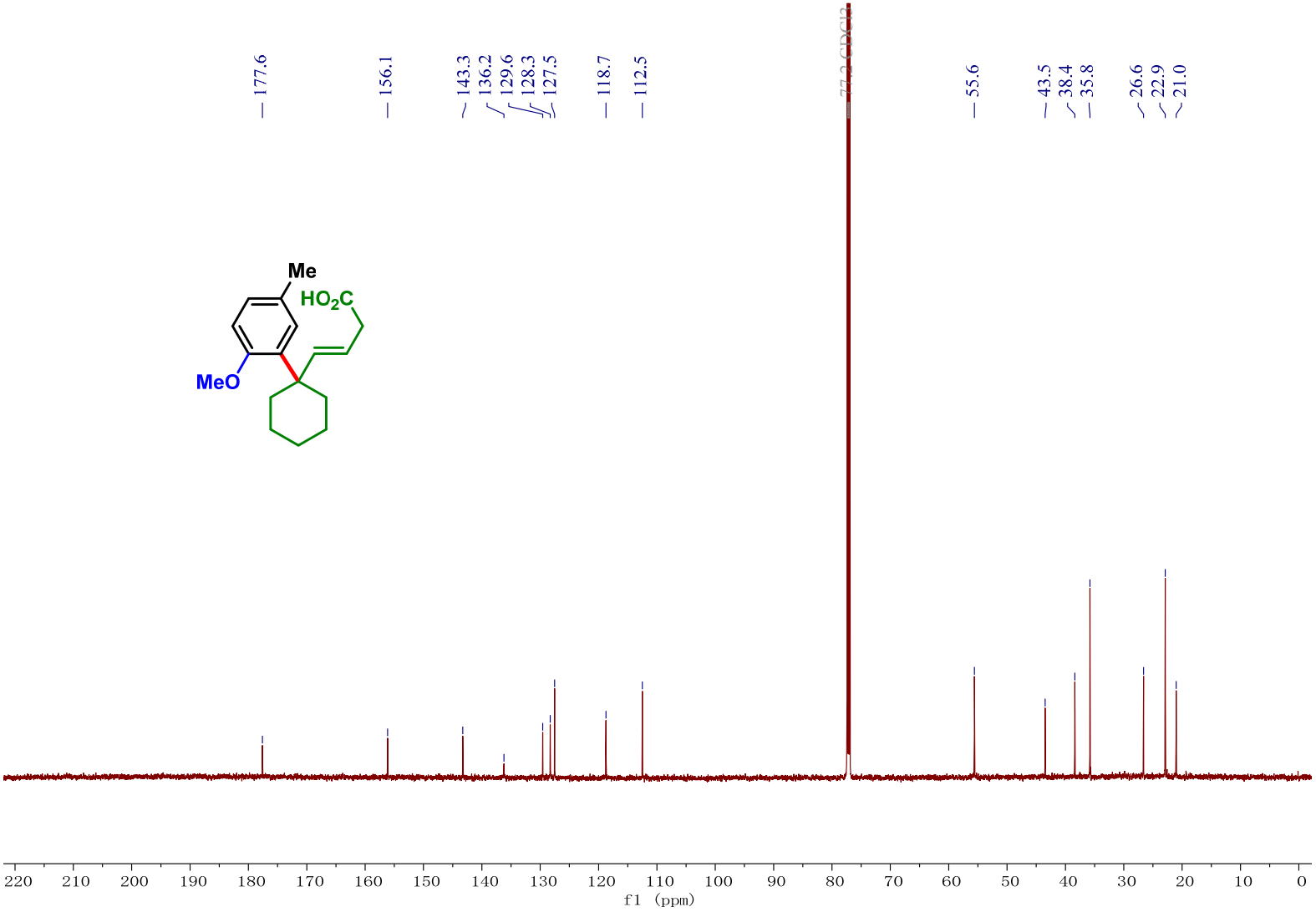
Compound 3 ^{13}C NMR



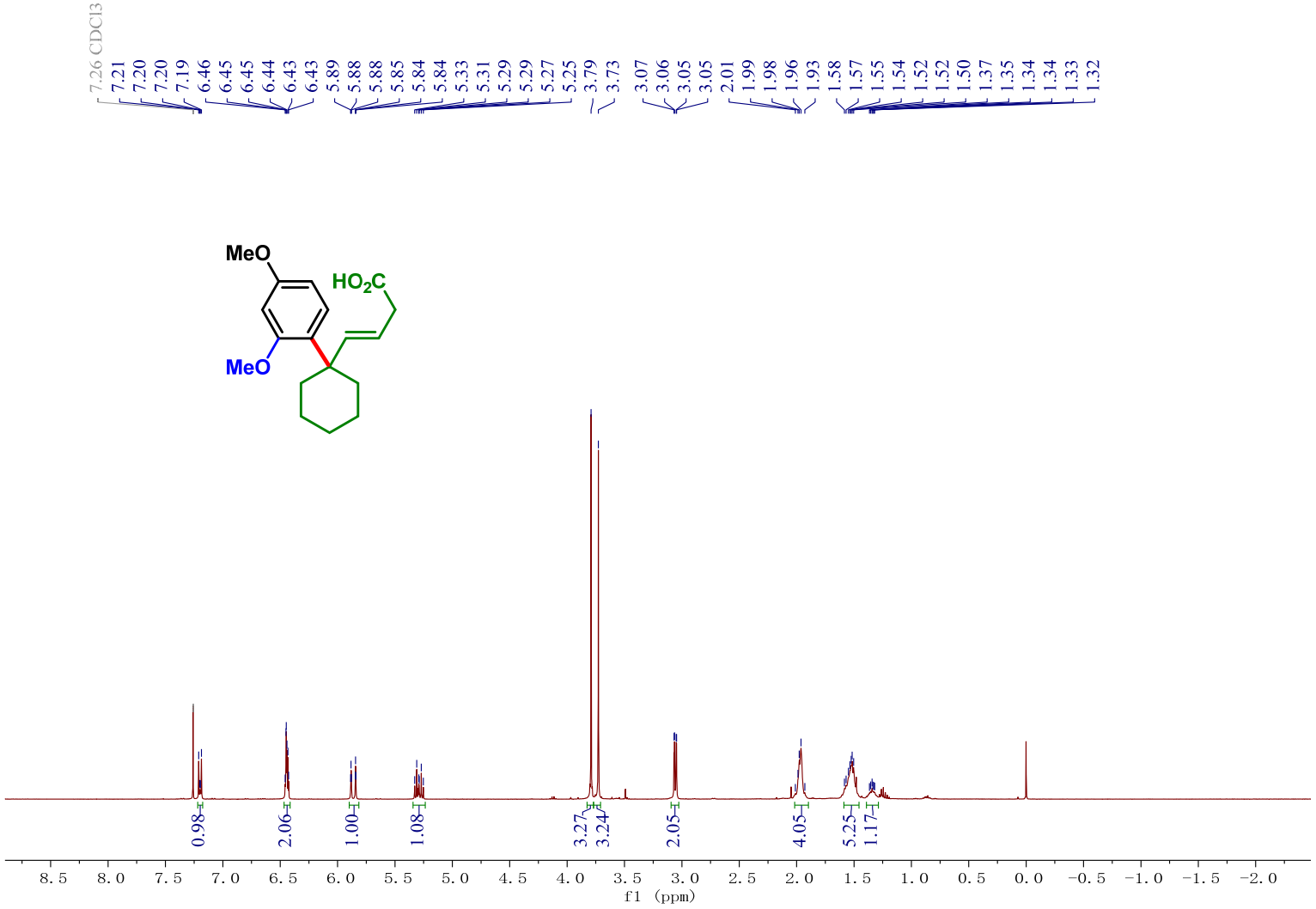
Compound 4 ^{1}H NMR



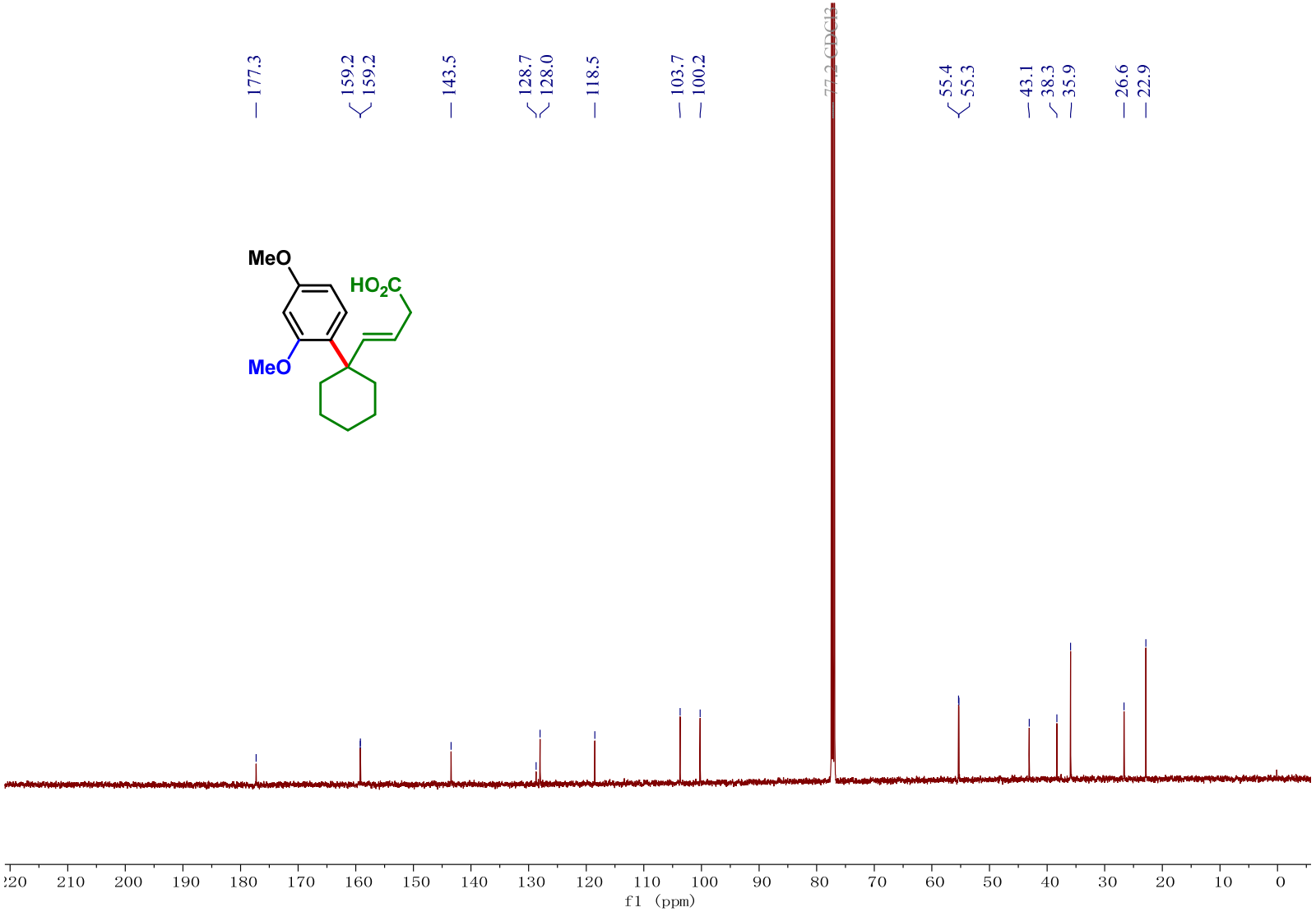
Compound 4 ^{13}C NMR



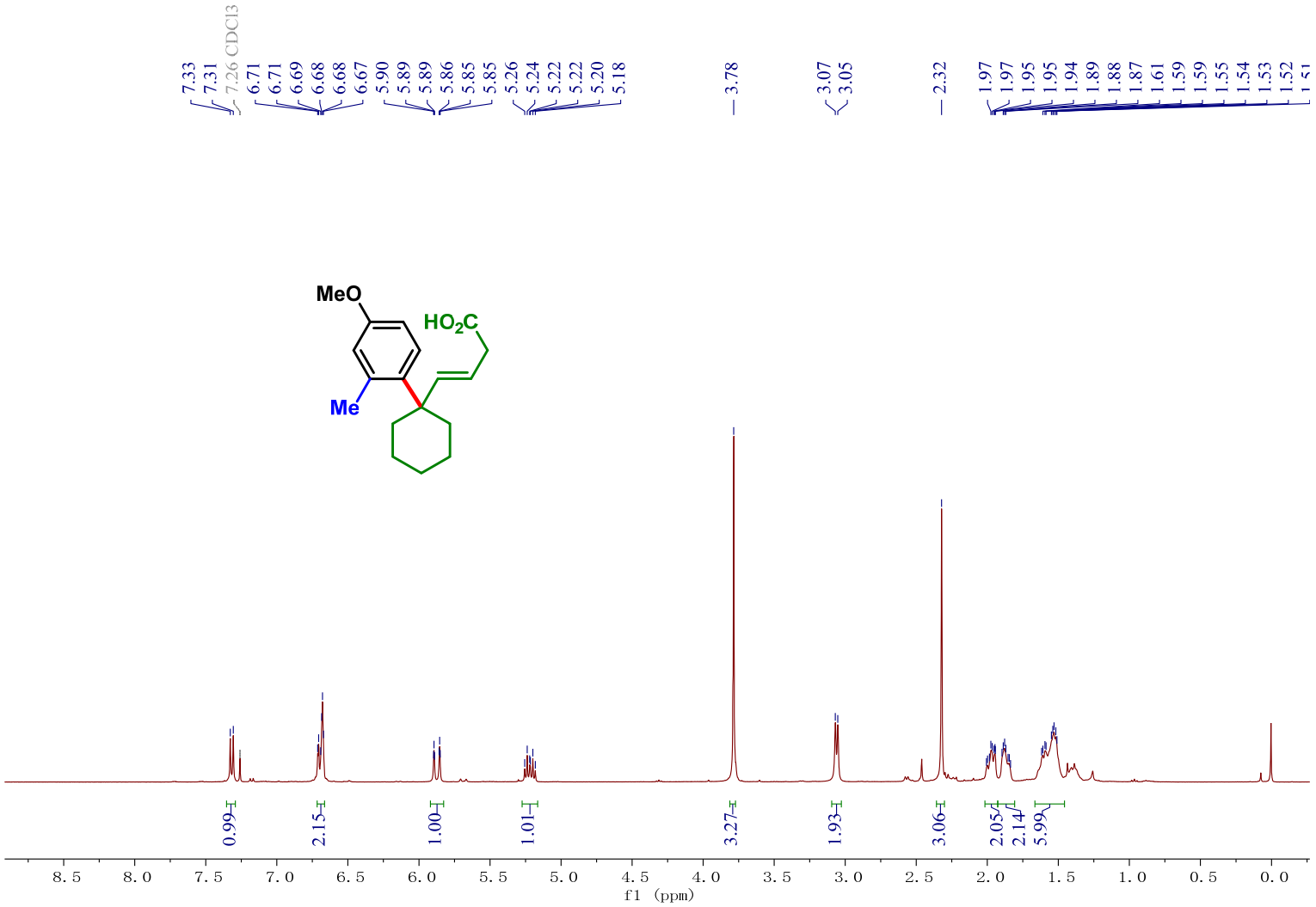
Compound 5 ^{1}H NMR



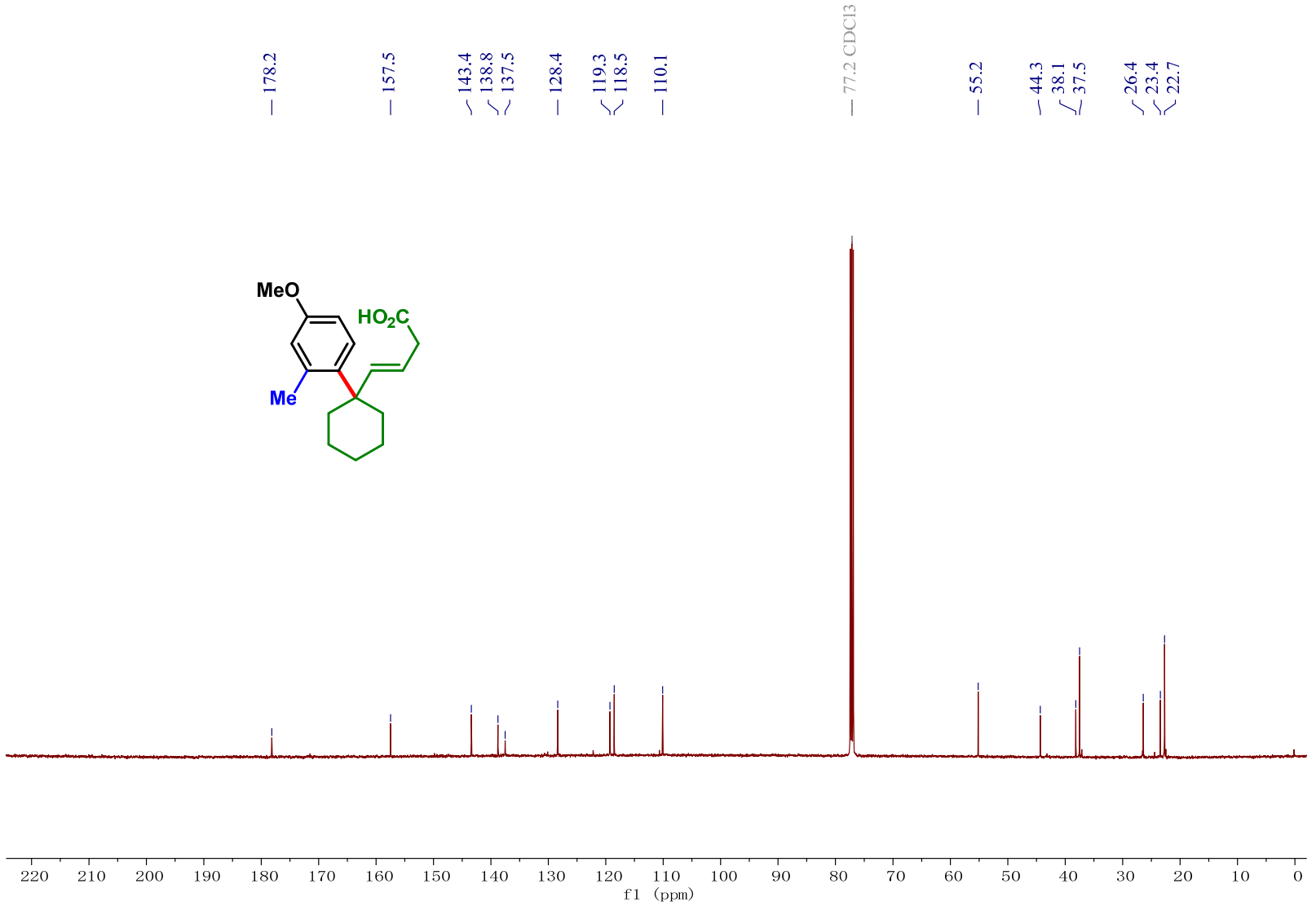
Compound 5 ^{13}C NMR



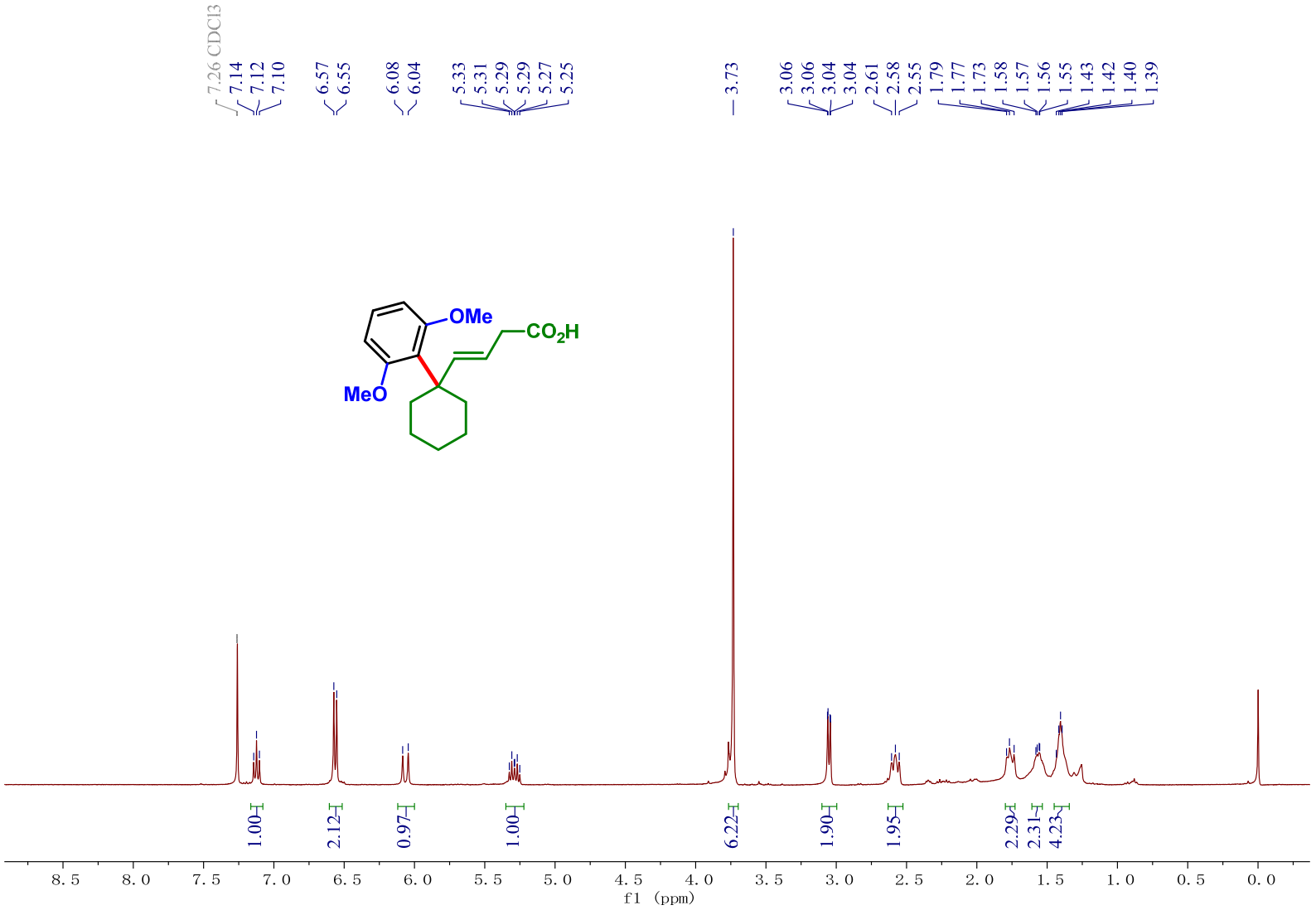
Compound 6 ^{1}H NMR



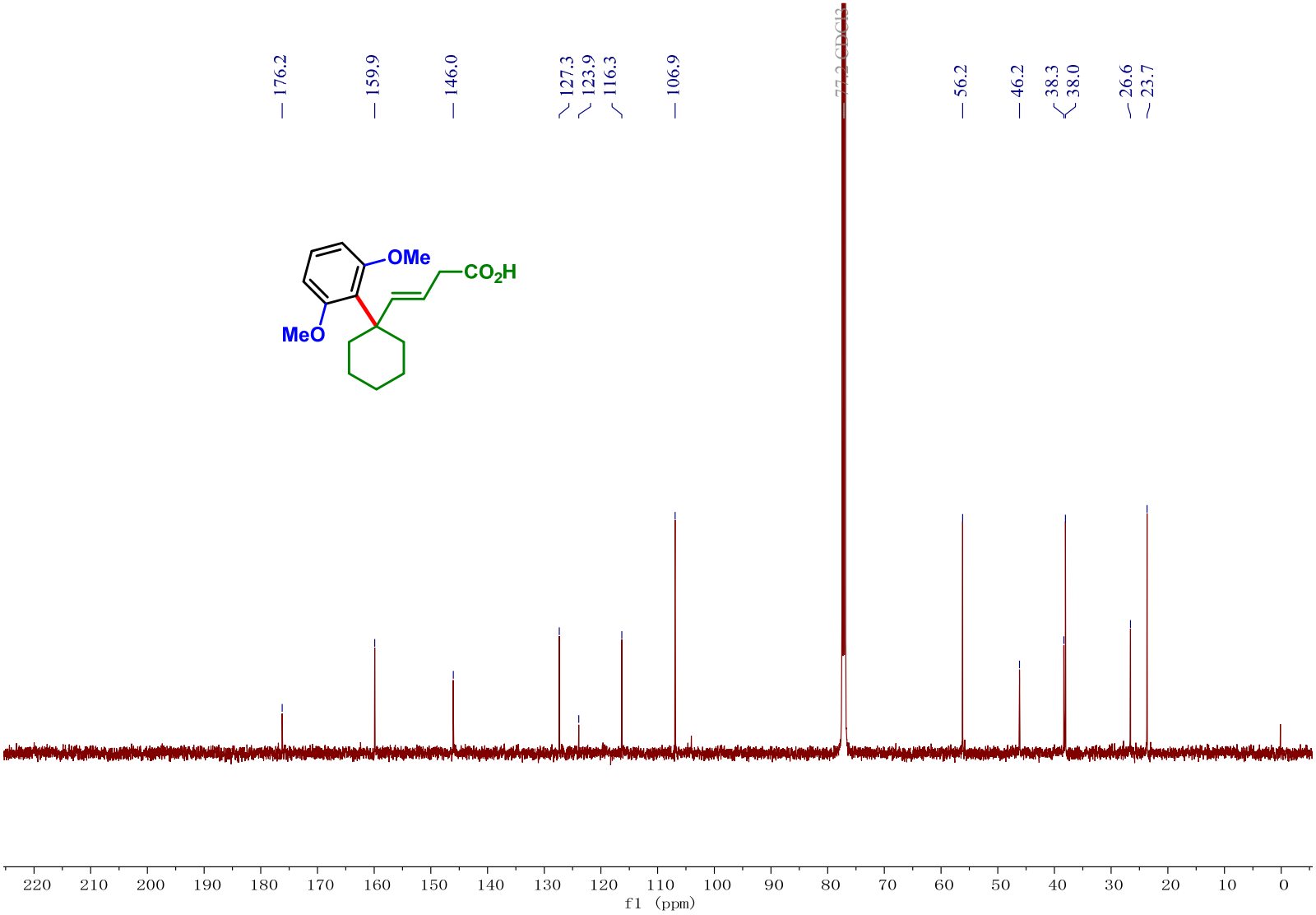
Compound 6 ^{13}C NMR



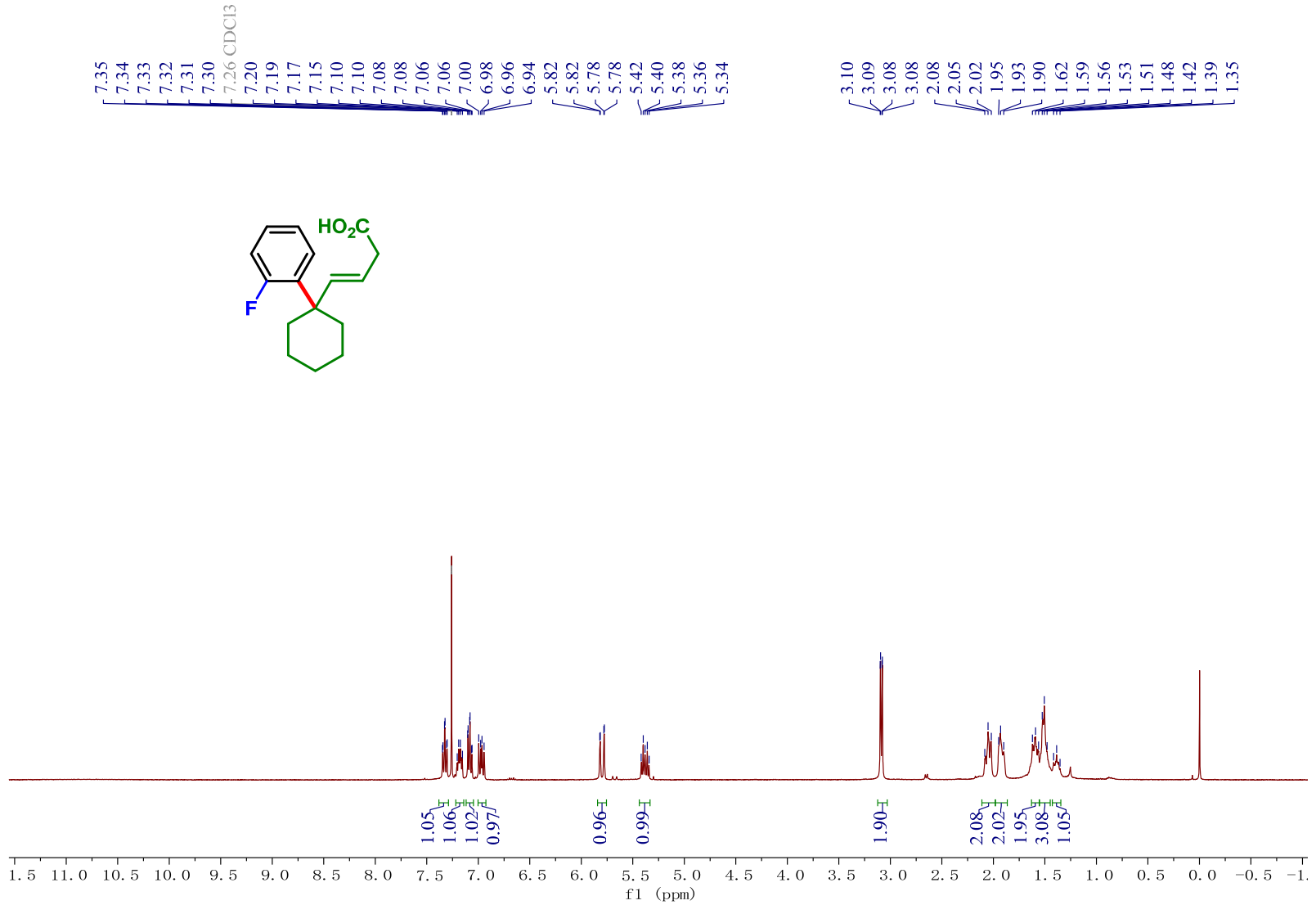
Compound 7 ^{1}H NMR



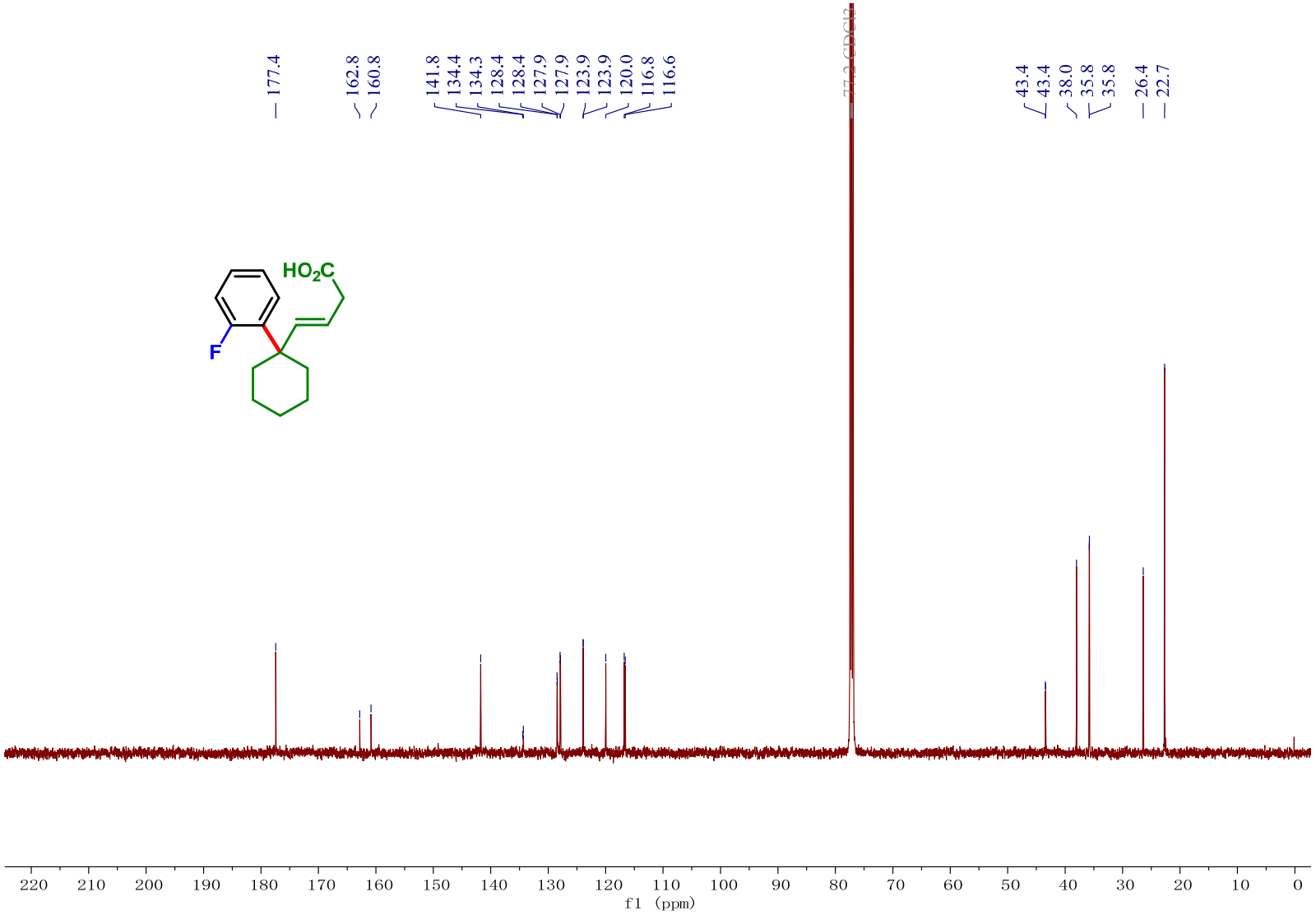
Compound 7 ^{13}C NMR



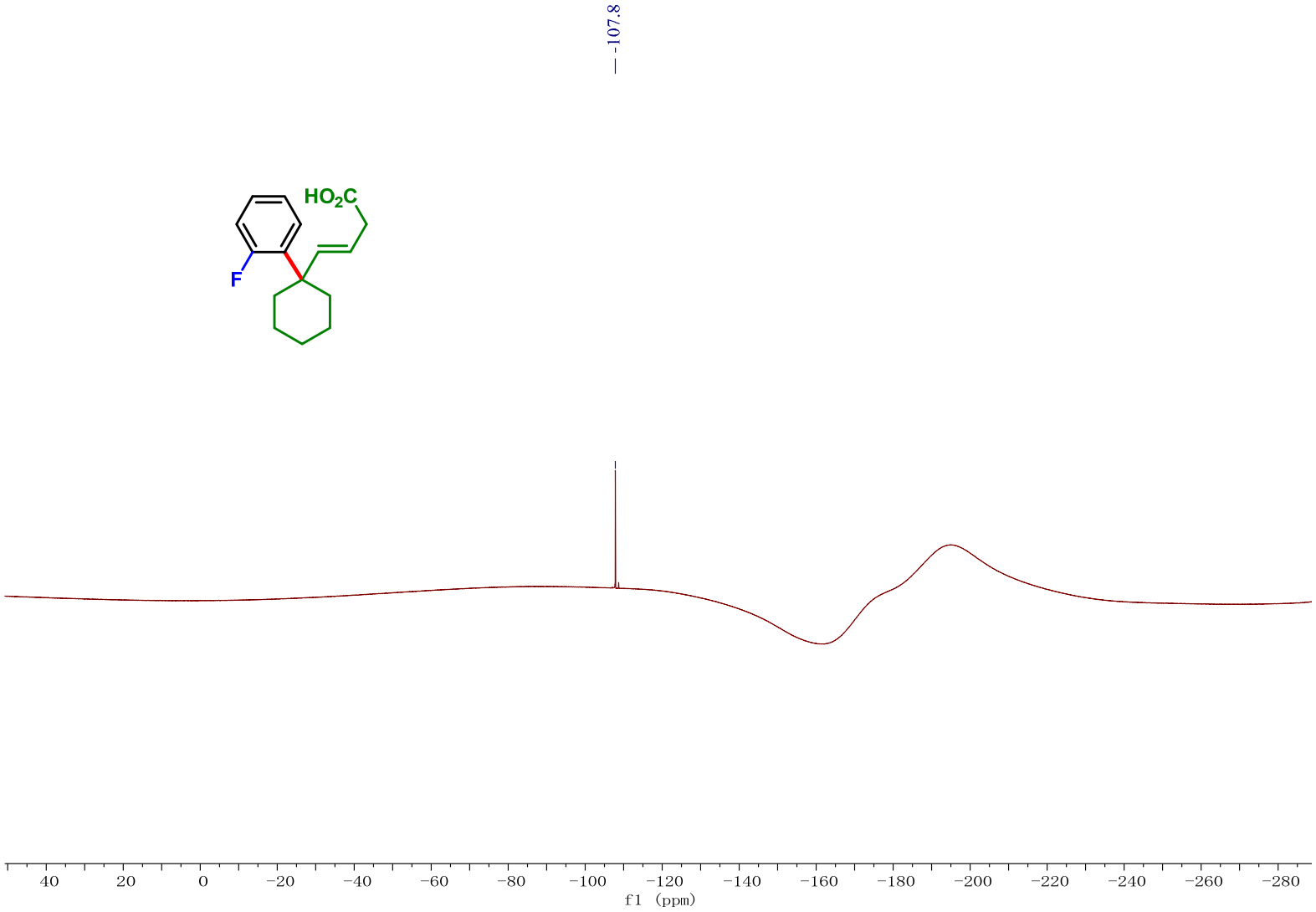
Compound 8 ^{1}H NMR



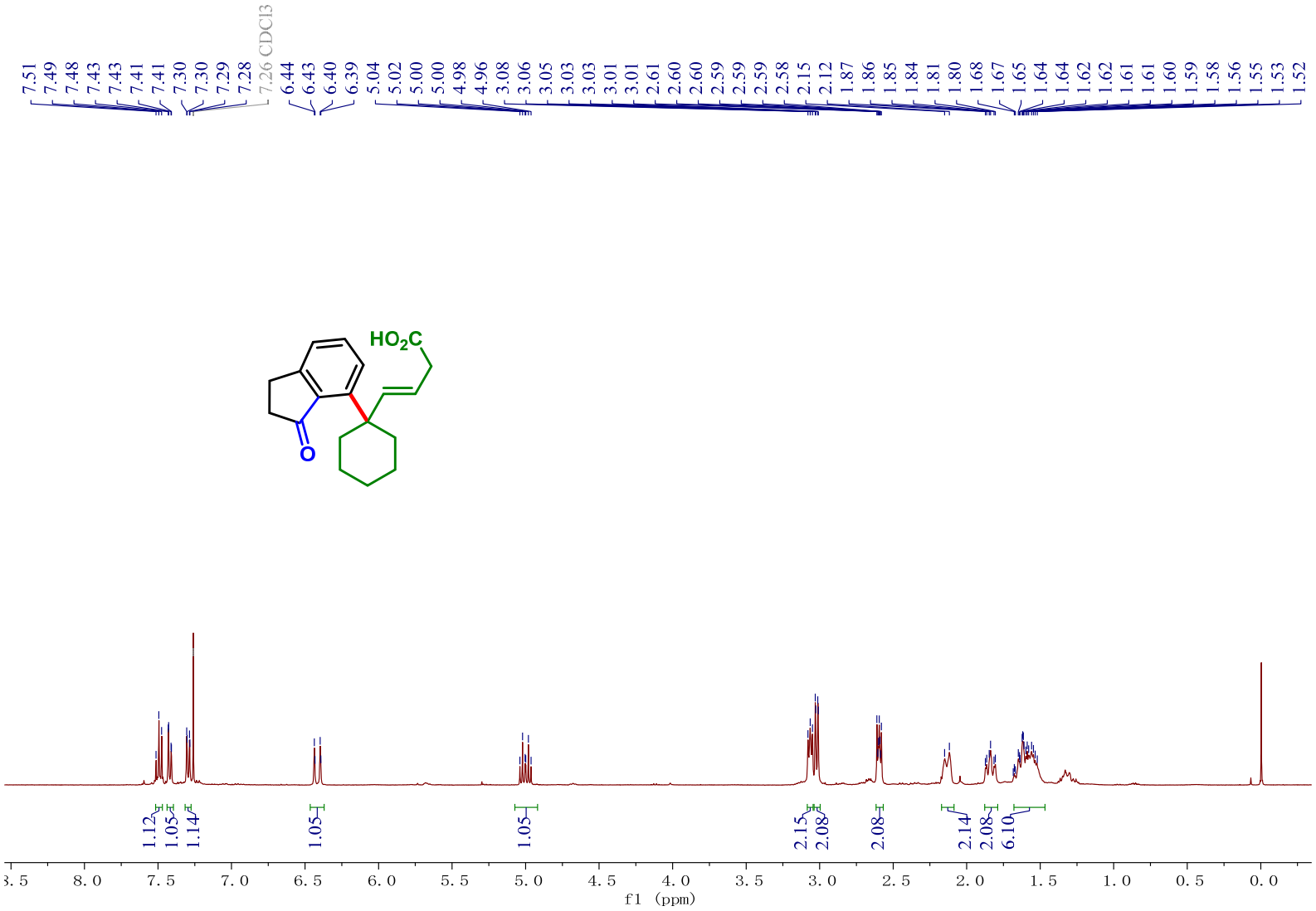
Compound 8 ^{13}C NMR



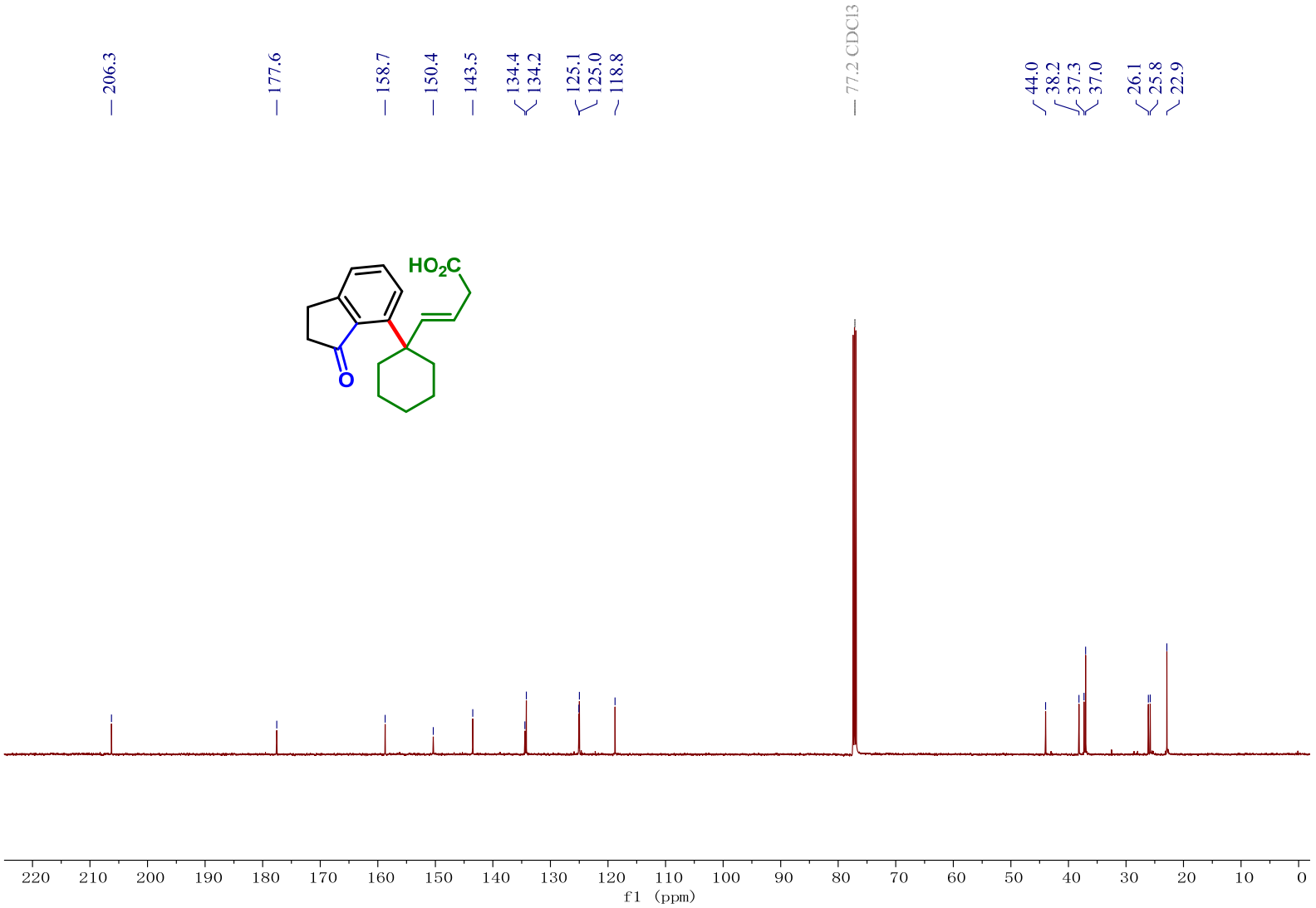
Compound 8 ^{19}F NMR



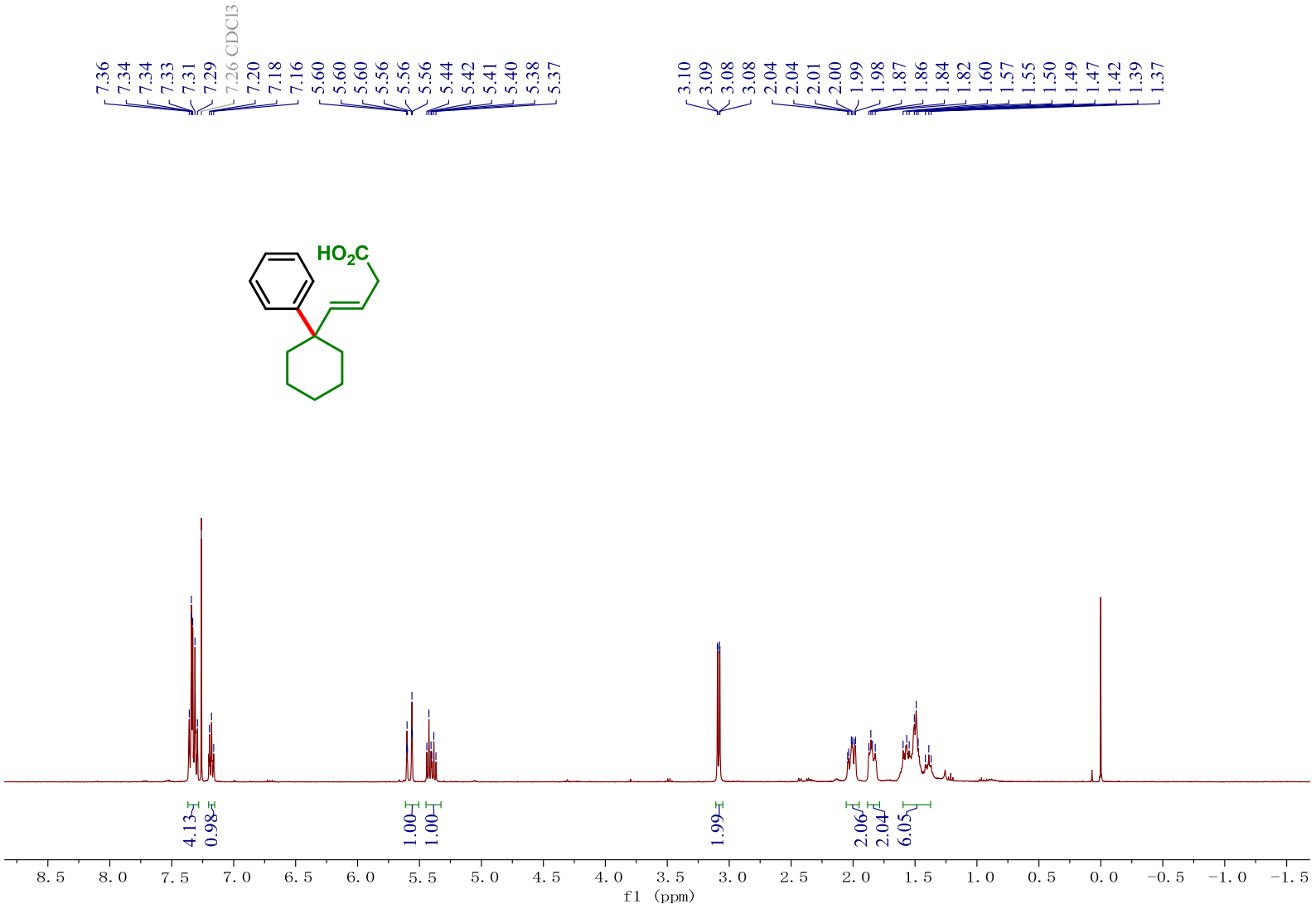
Compound 9 ^{1}H NMR



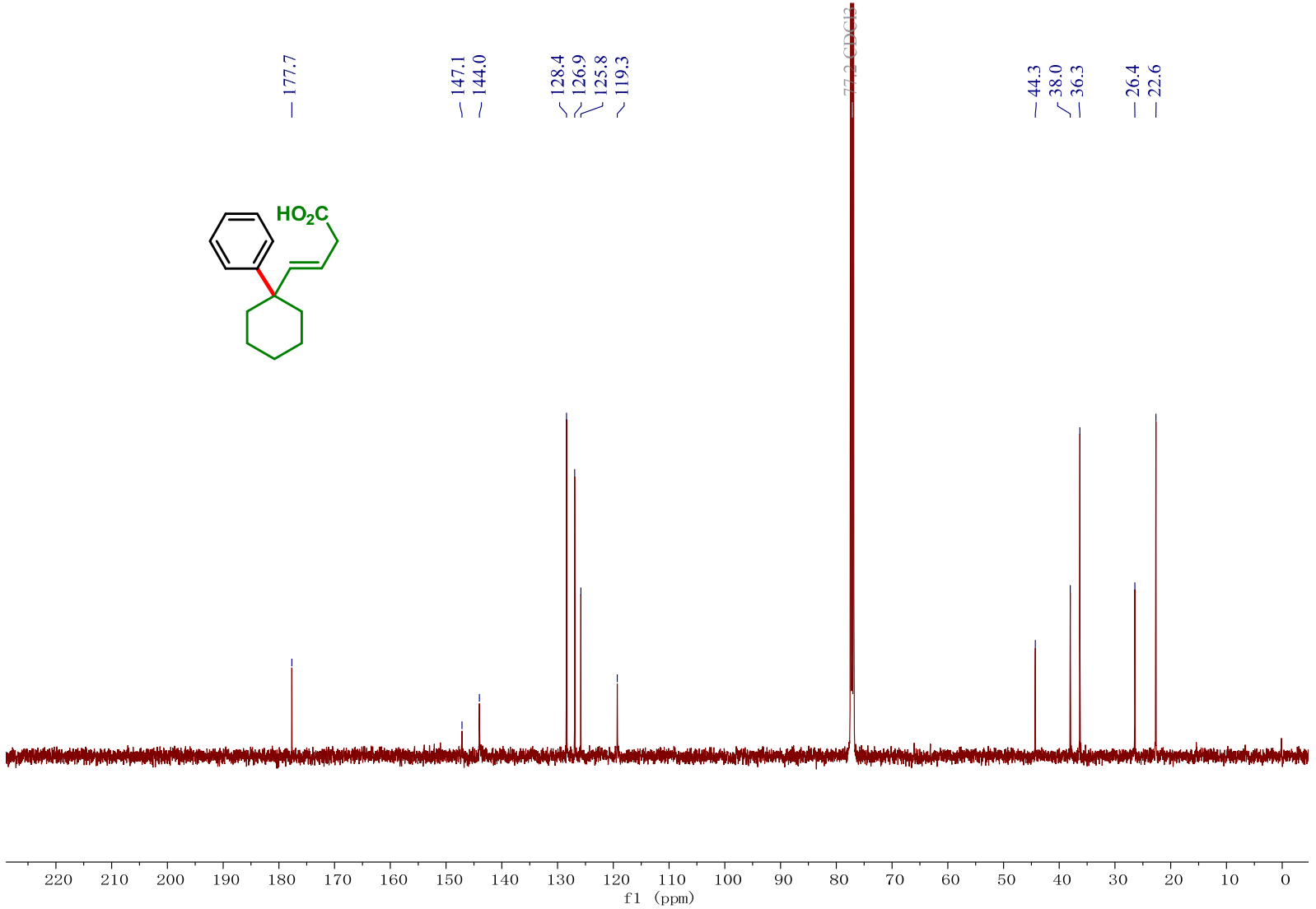
Compound 9 ^{13}C NMR



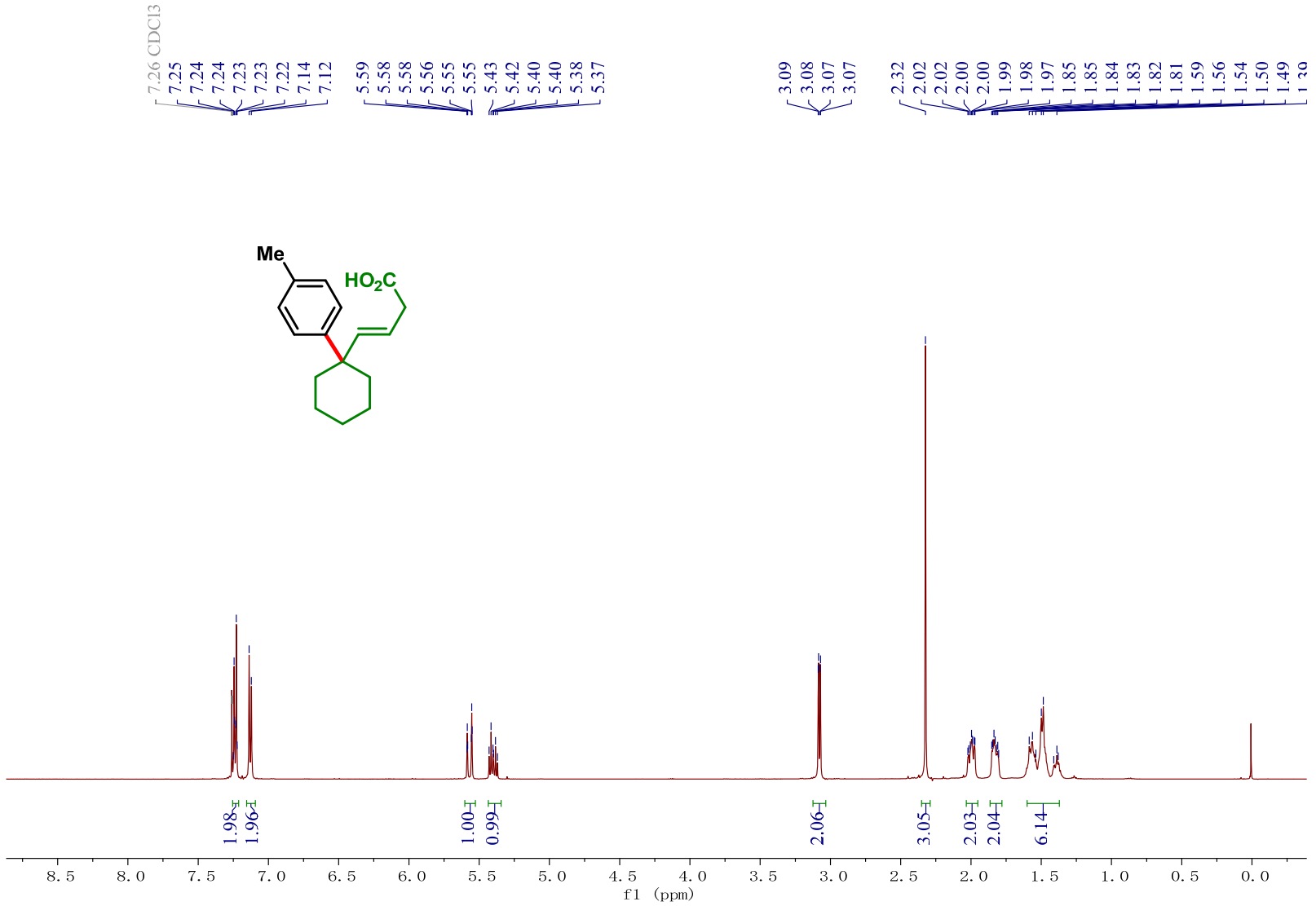
Compound 10 ^{1}H NMR



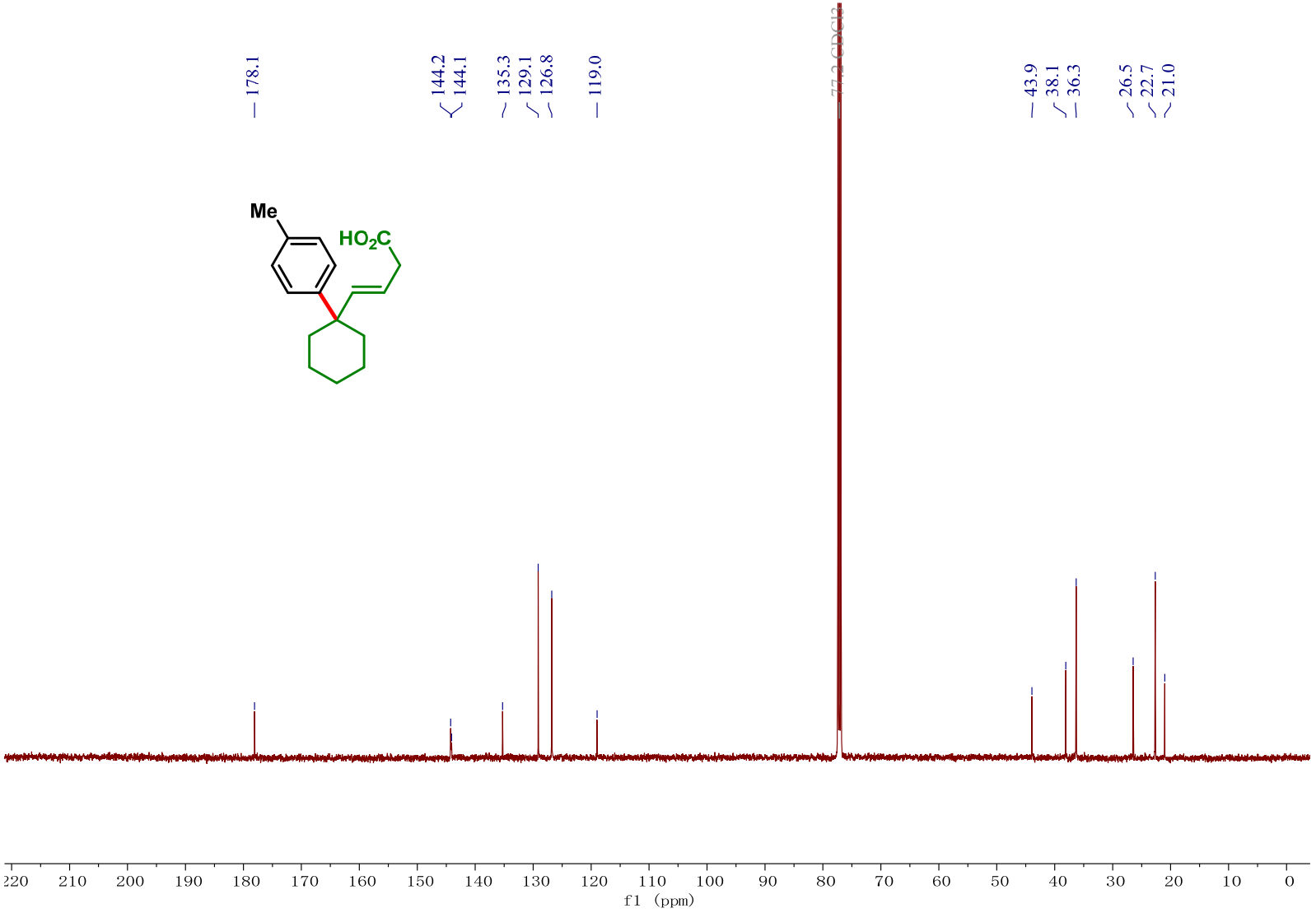
Compound 10 ^{13}C NMR



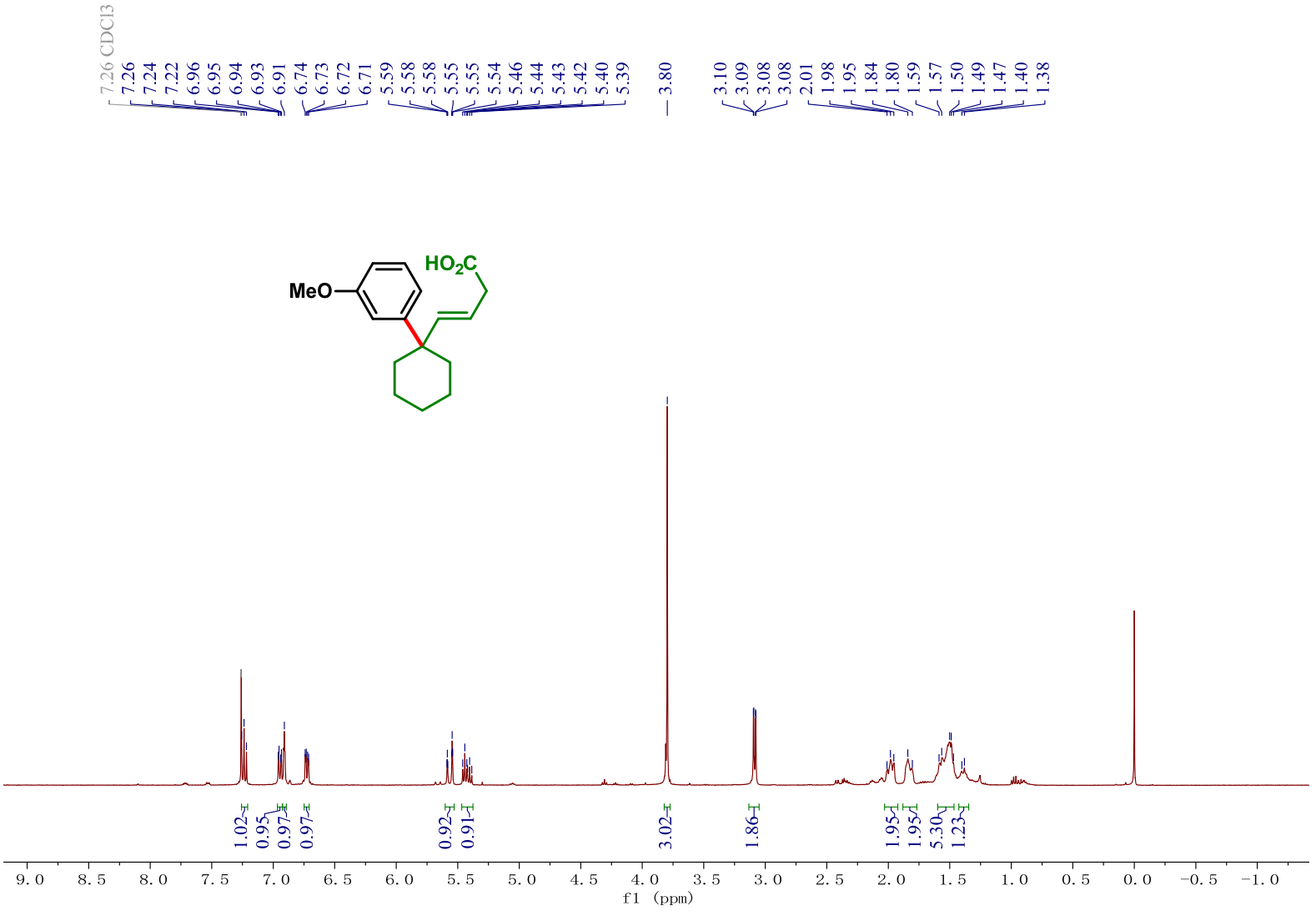
Compound 11 ^{1}H NMR



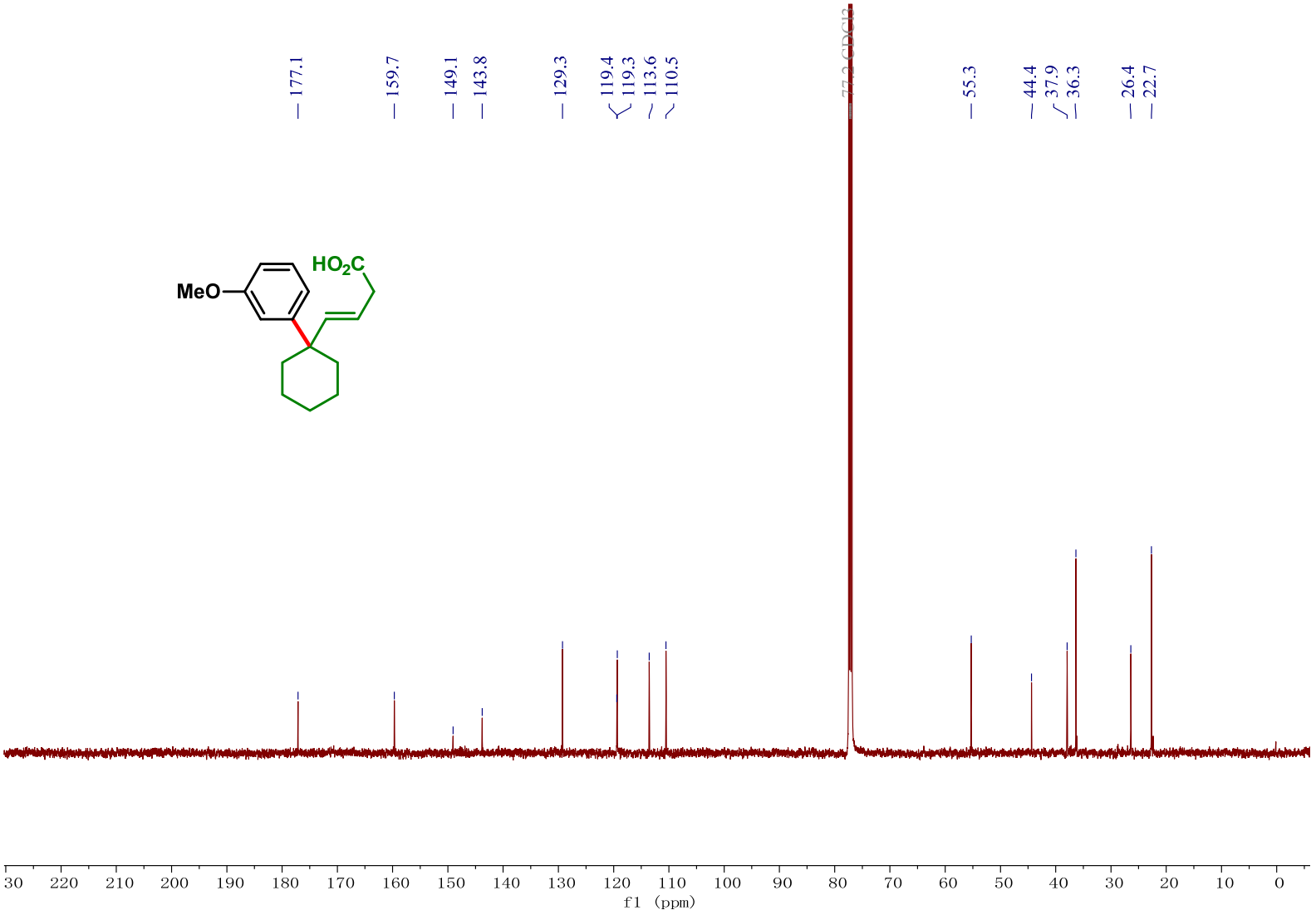
Compound 11 ^{13}C NMR



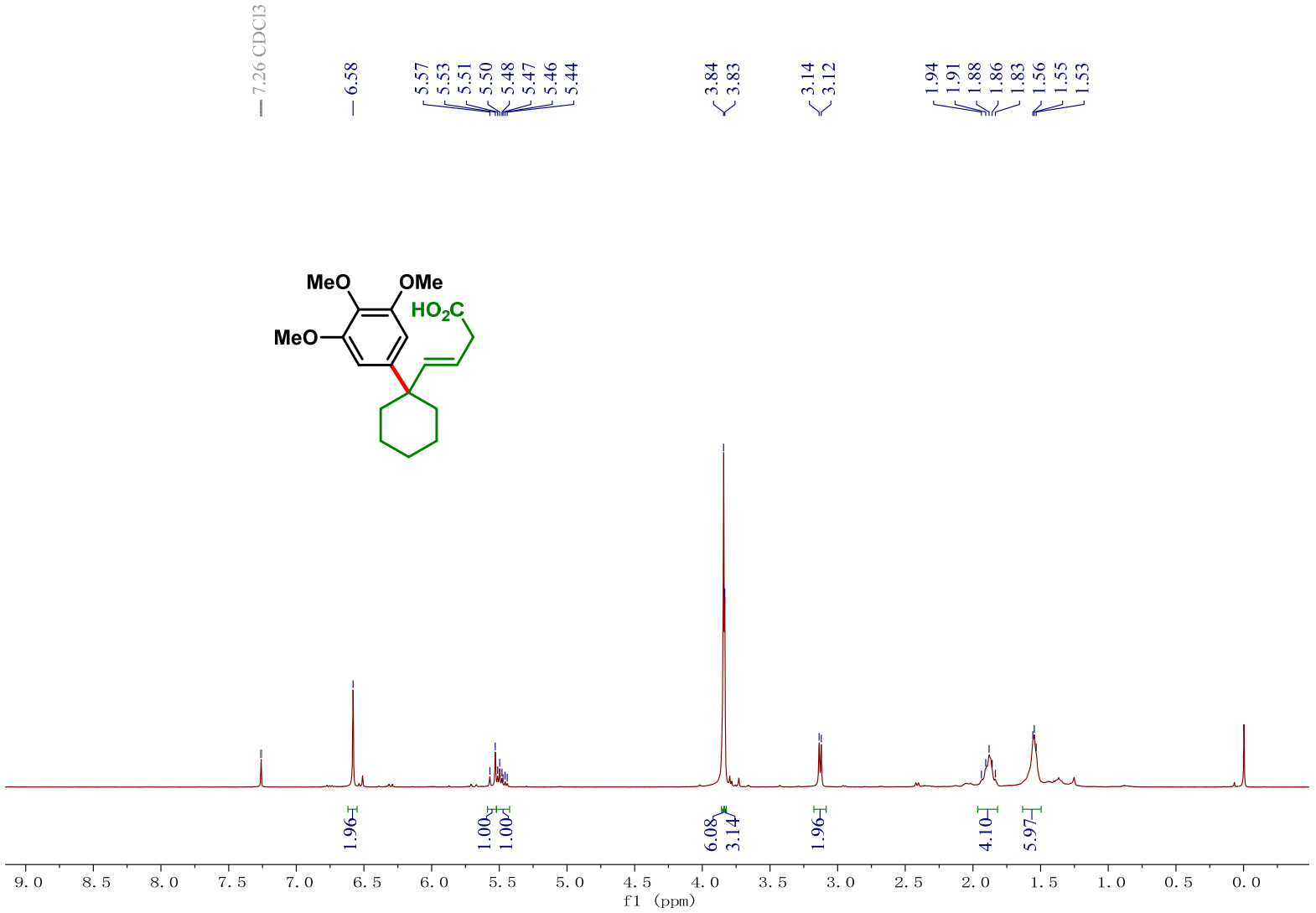
Compound 12 ^{1}H NMR



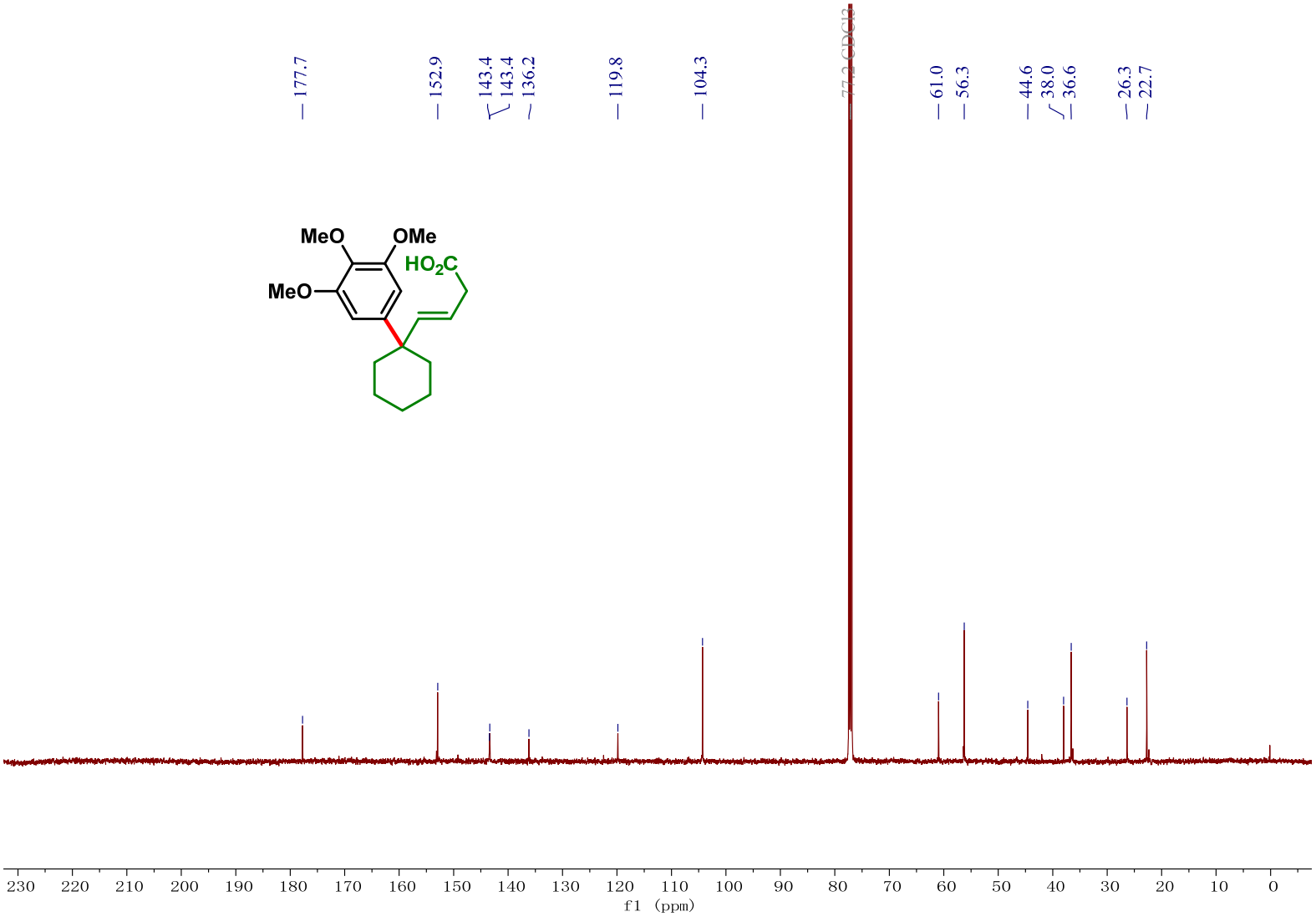
Compound 12 ^{13}C NMR



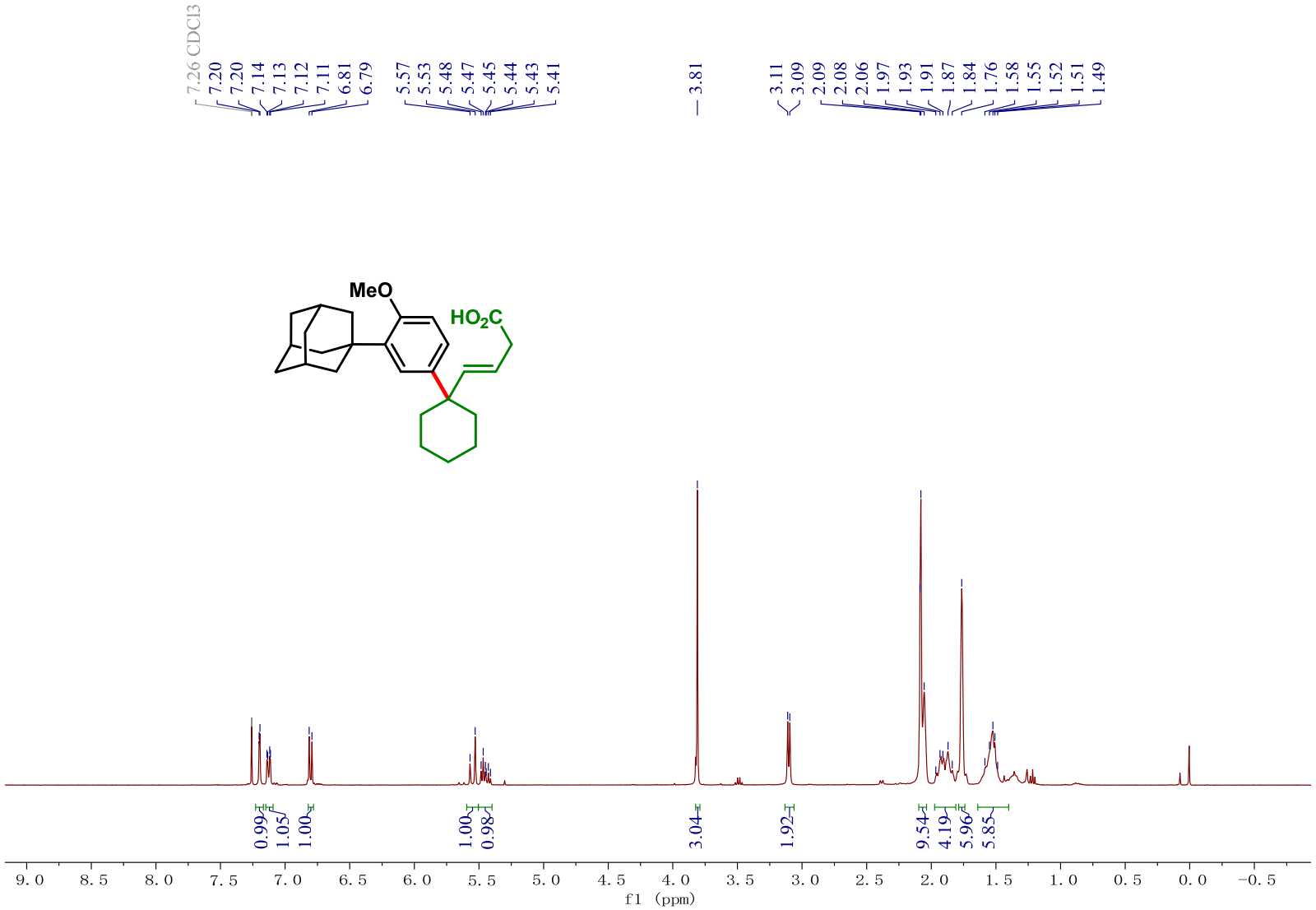
Compound 13 ^{1}H NMR



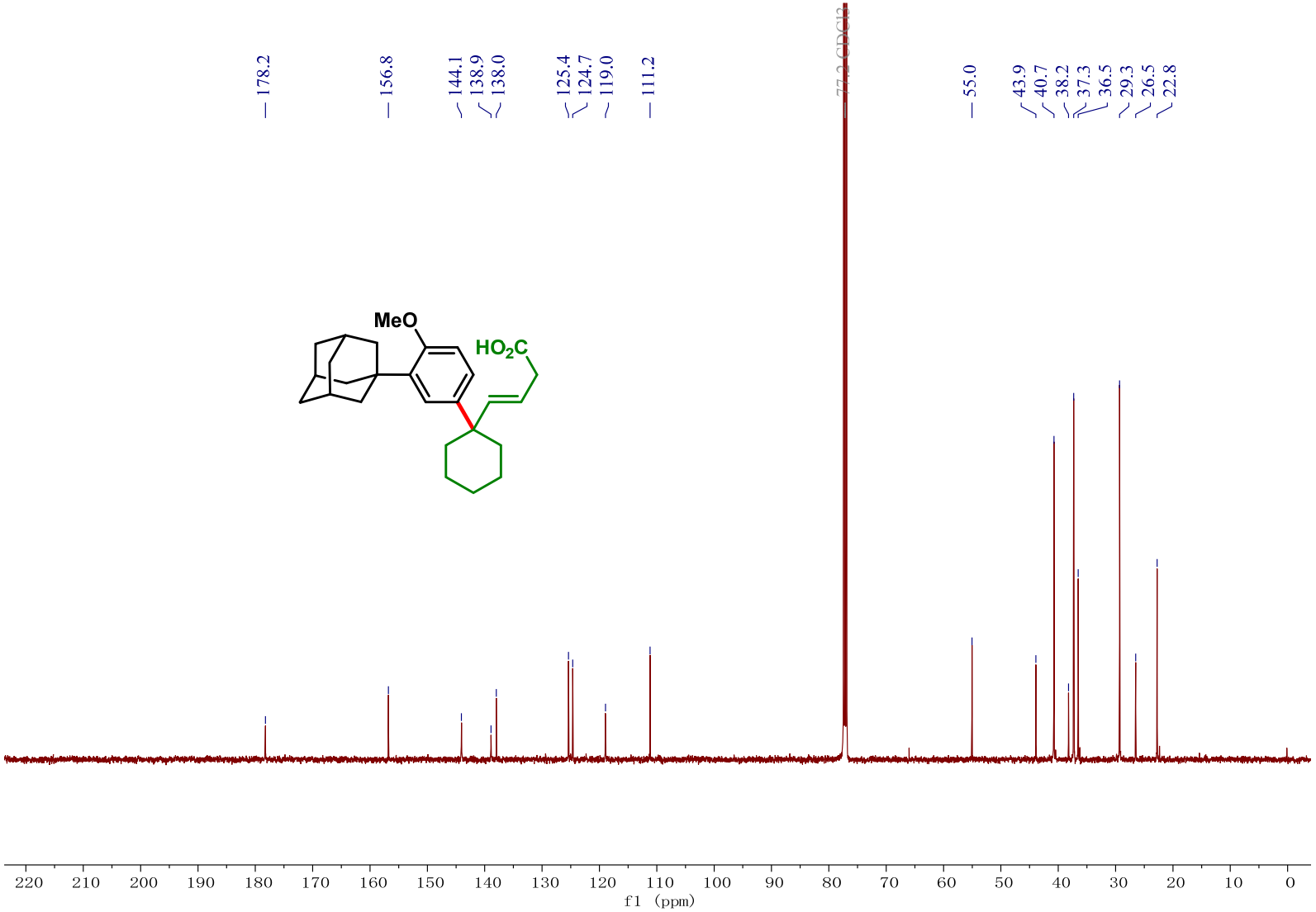
Compound 13 ^{13}C NMR



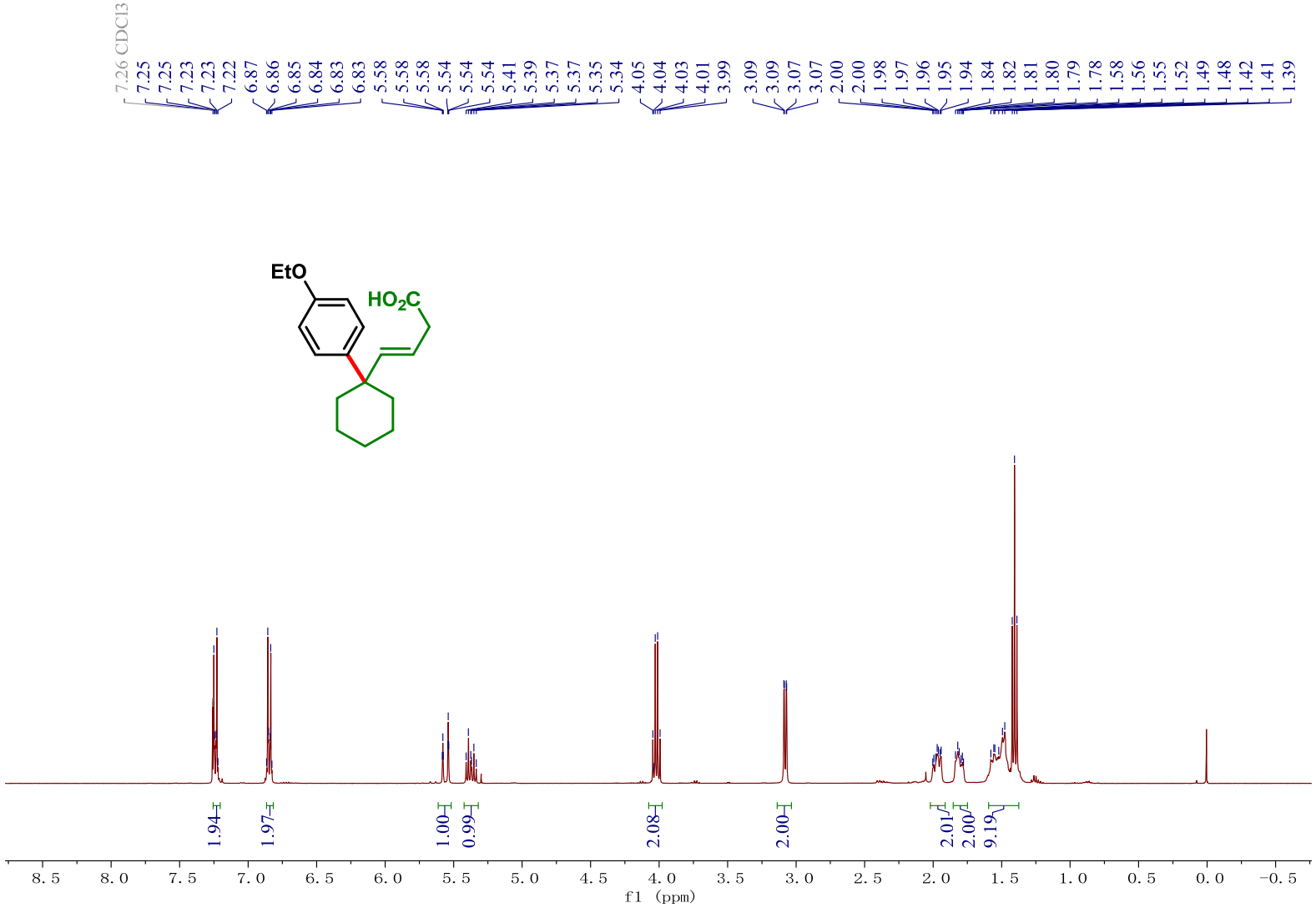
Compound 14 ^{1}H NMR



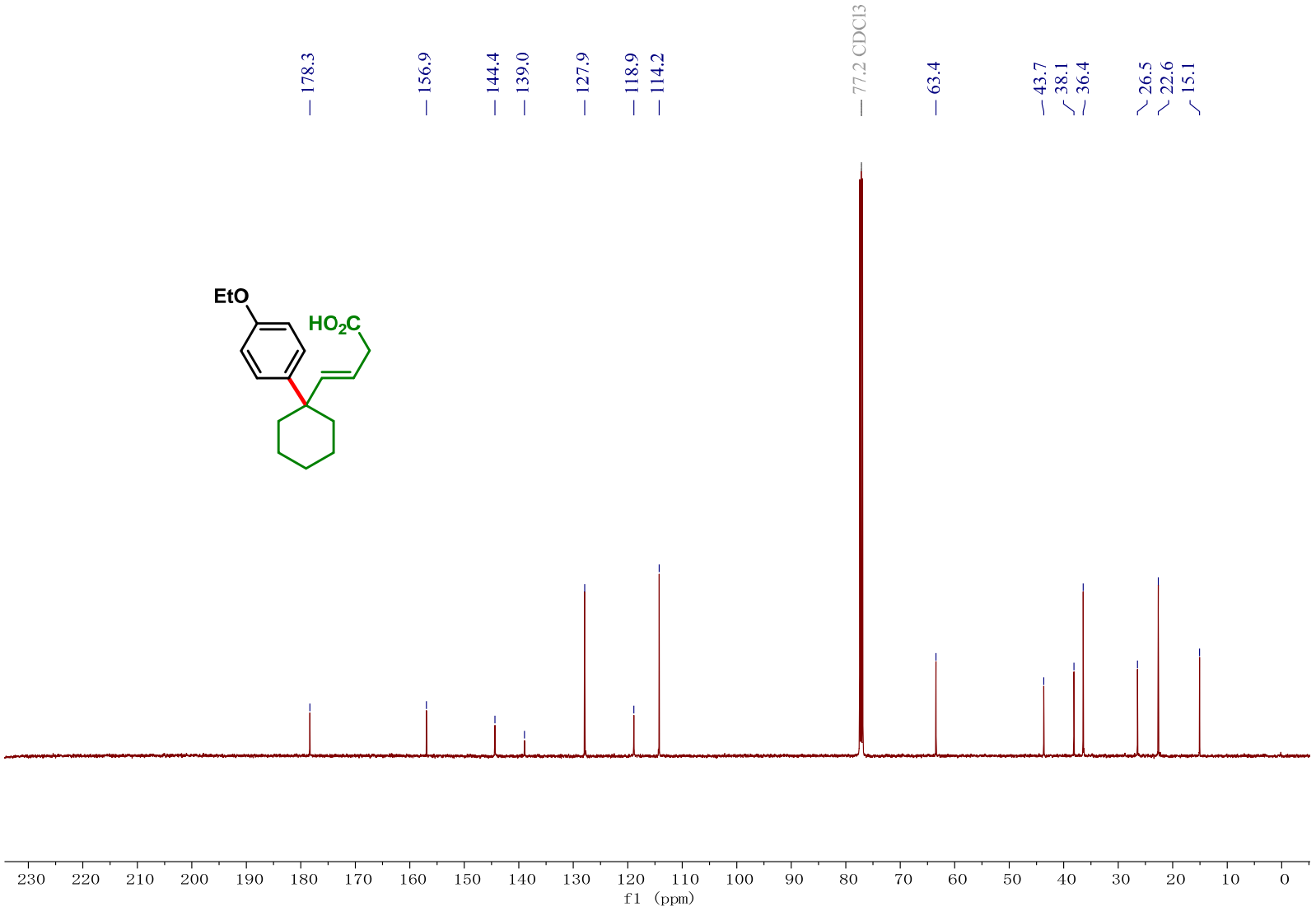
Compound 14 ^{13}C NMR



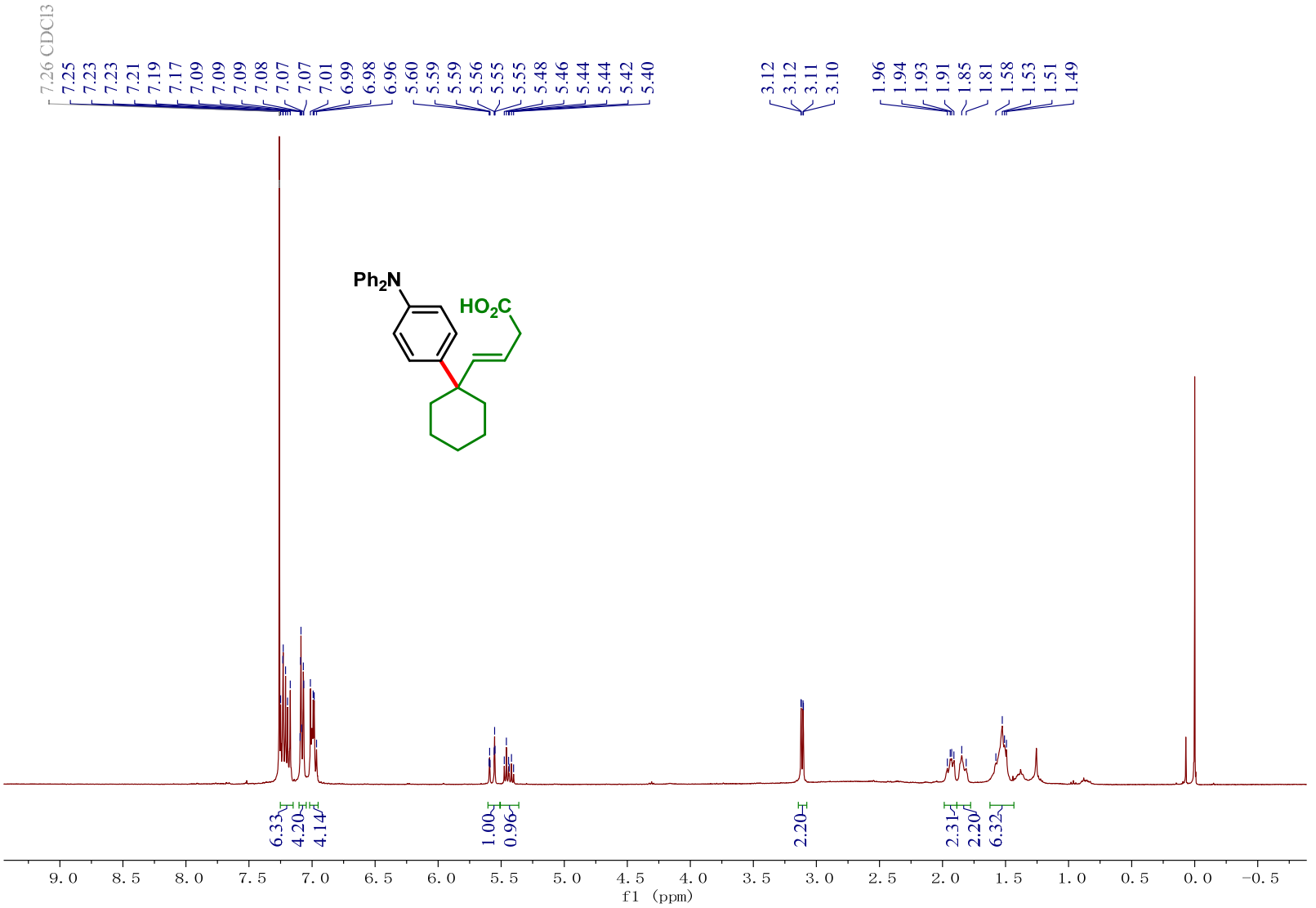
Compound 15 ^{1}H NMR



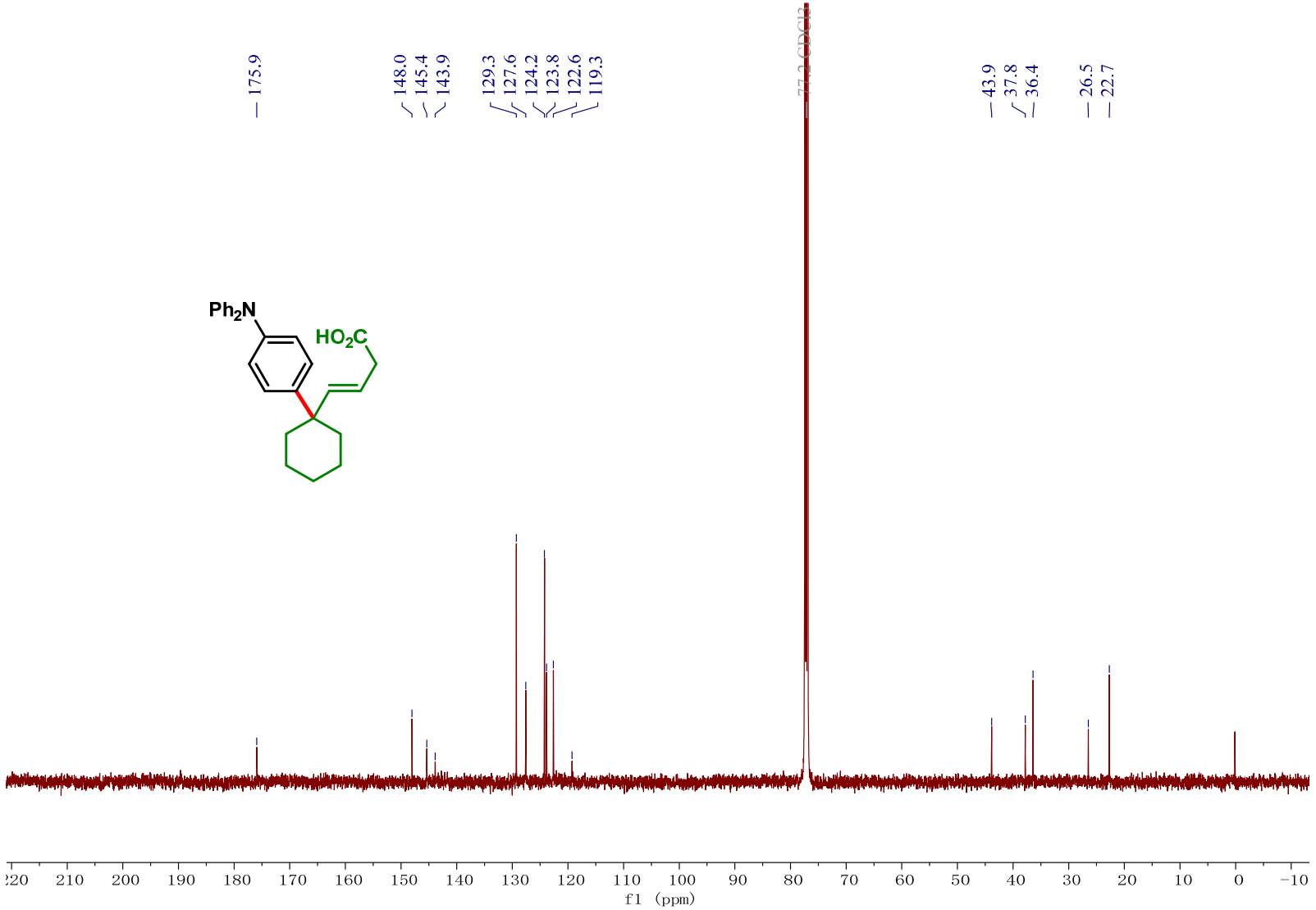
Compound 15 ^{13}C NMR



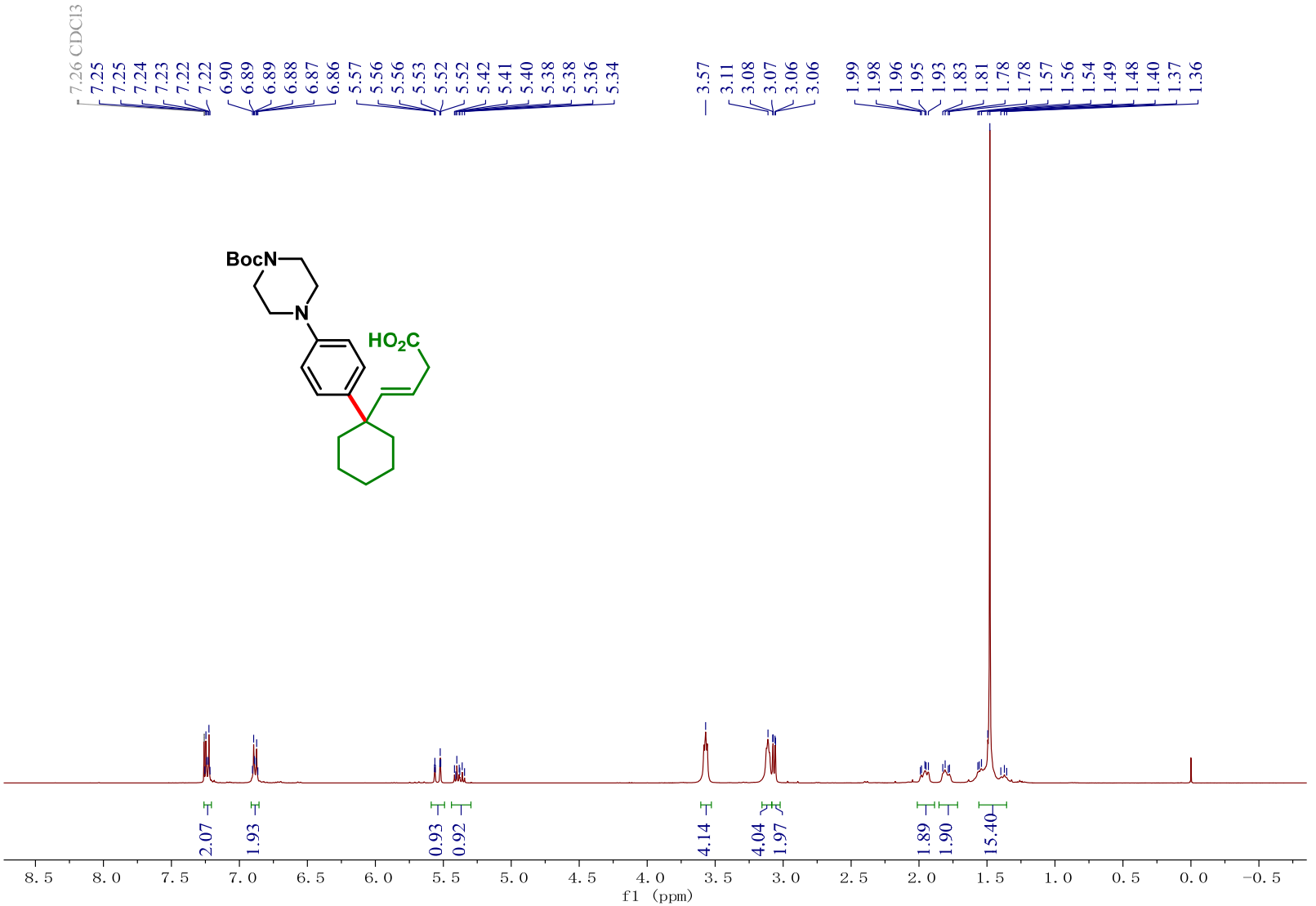
Compound 16 ^{1}H NMR



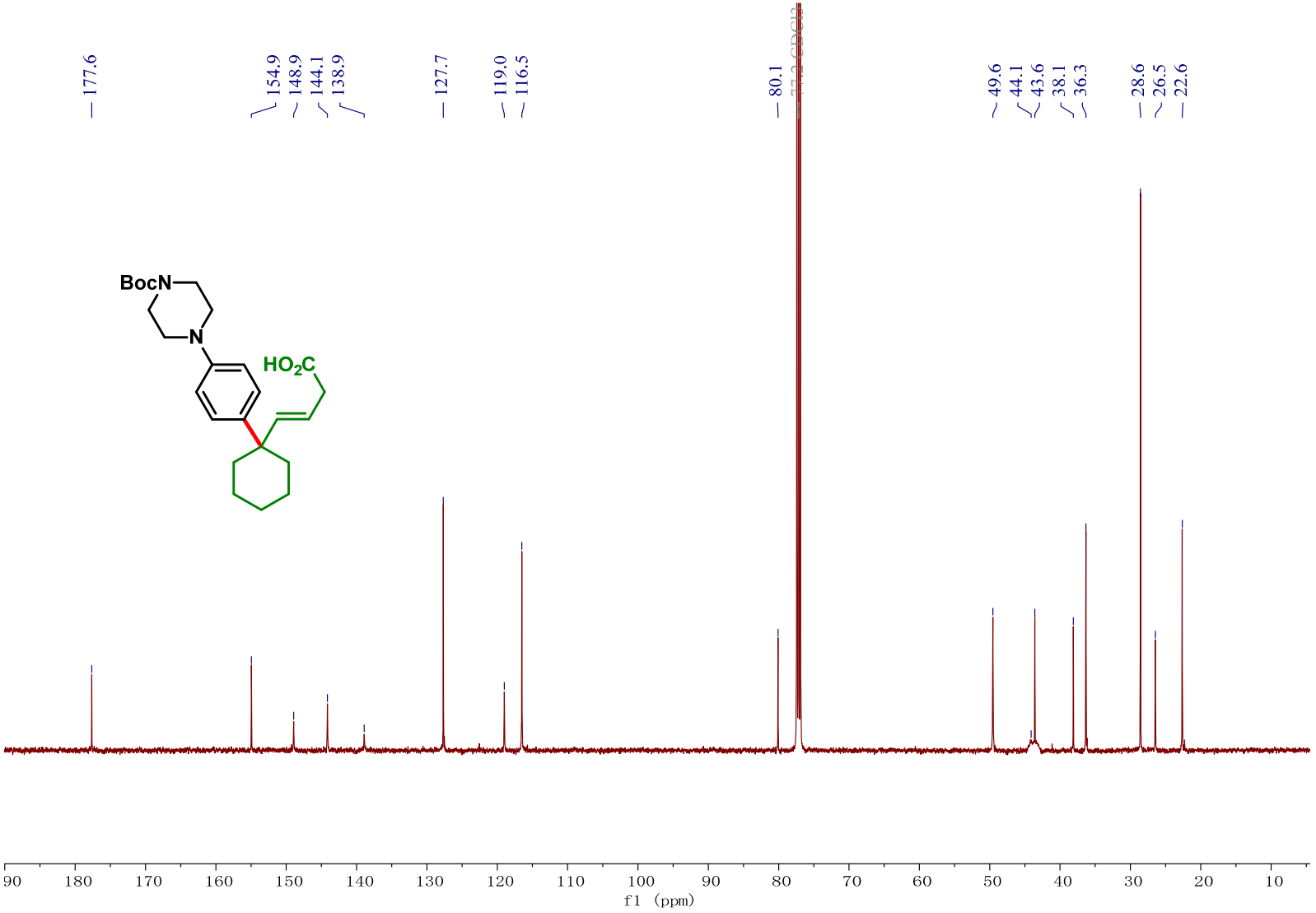
Compound 16 ^{13}C NMR



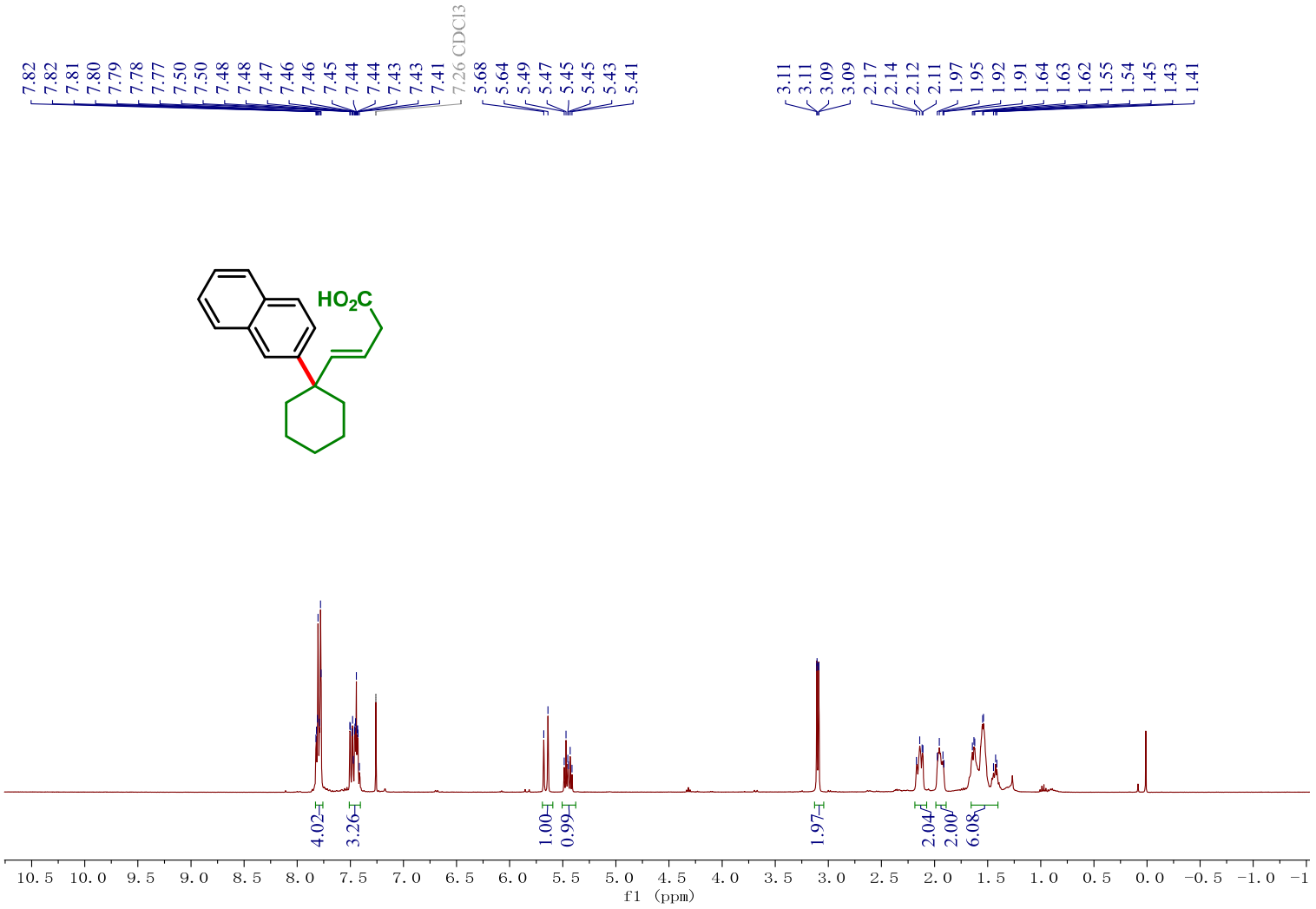
Compound 17 ^{1}H NMR



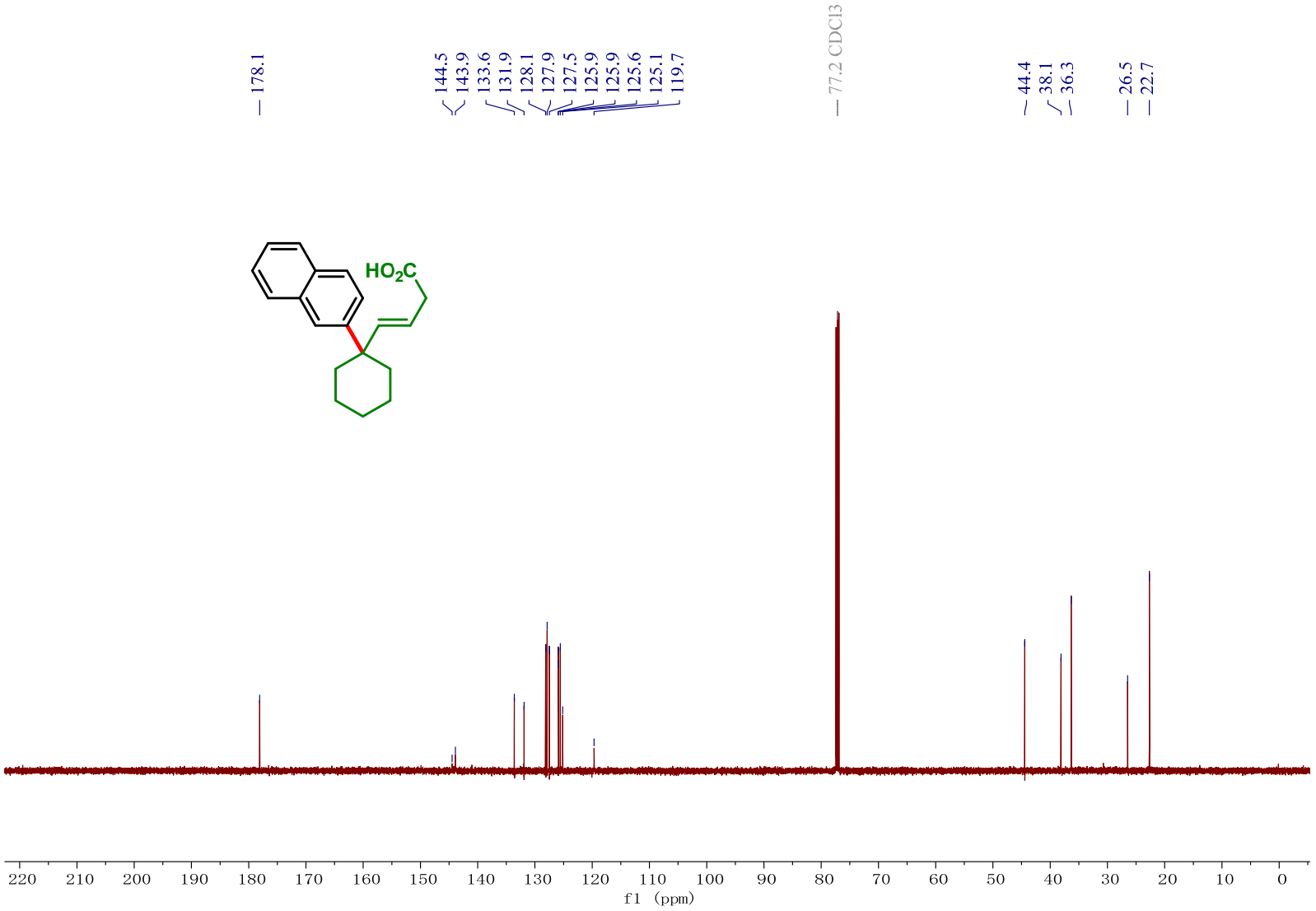
Compound 17 ^{13}C NMR



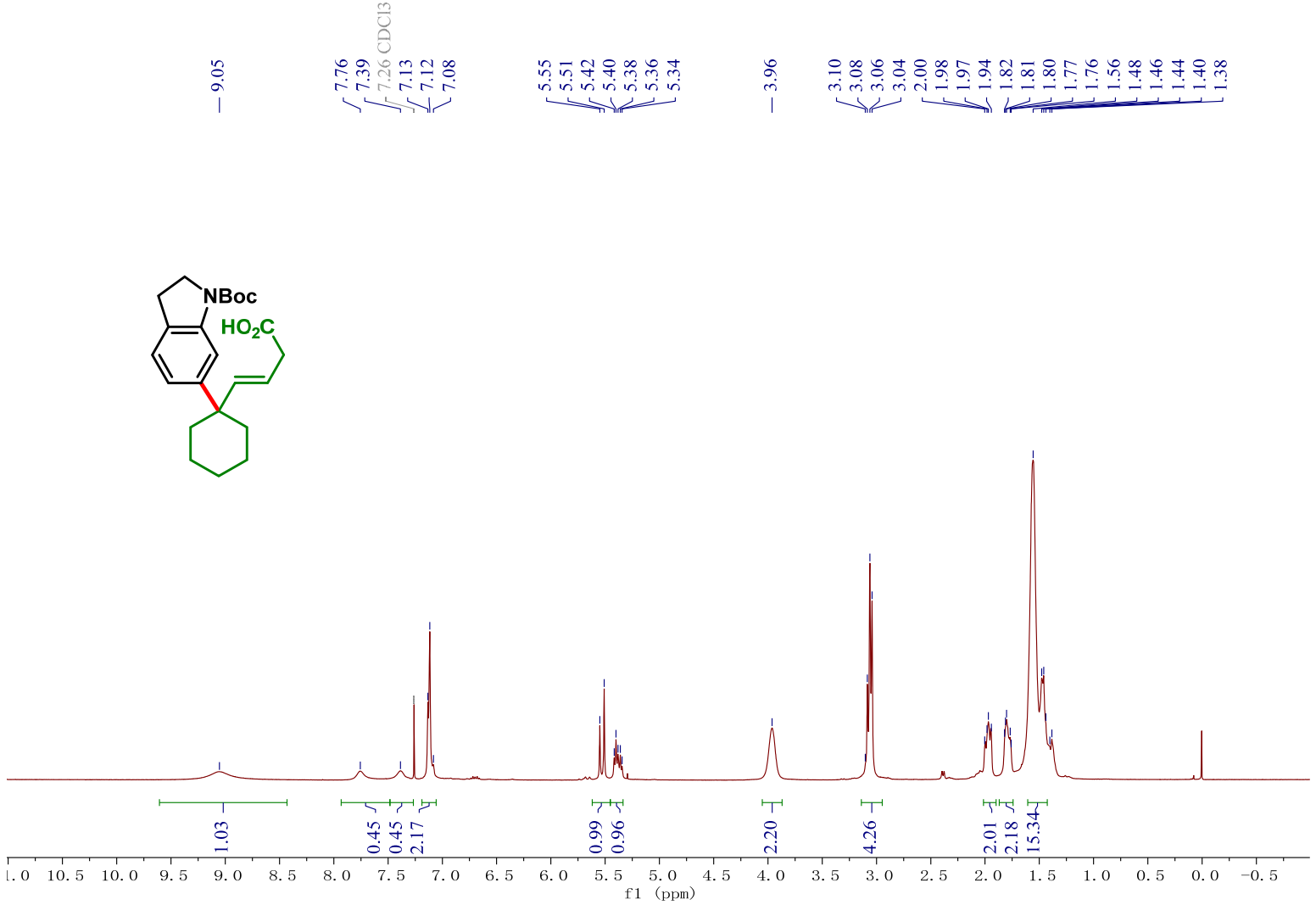
Compound 18 ^{1}H NMR



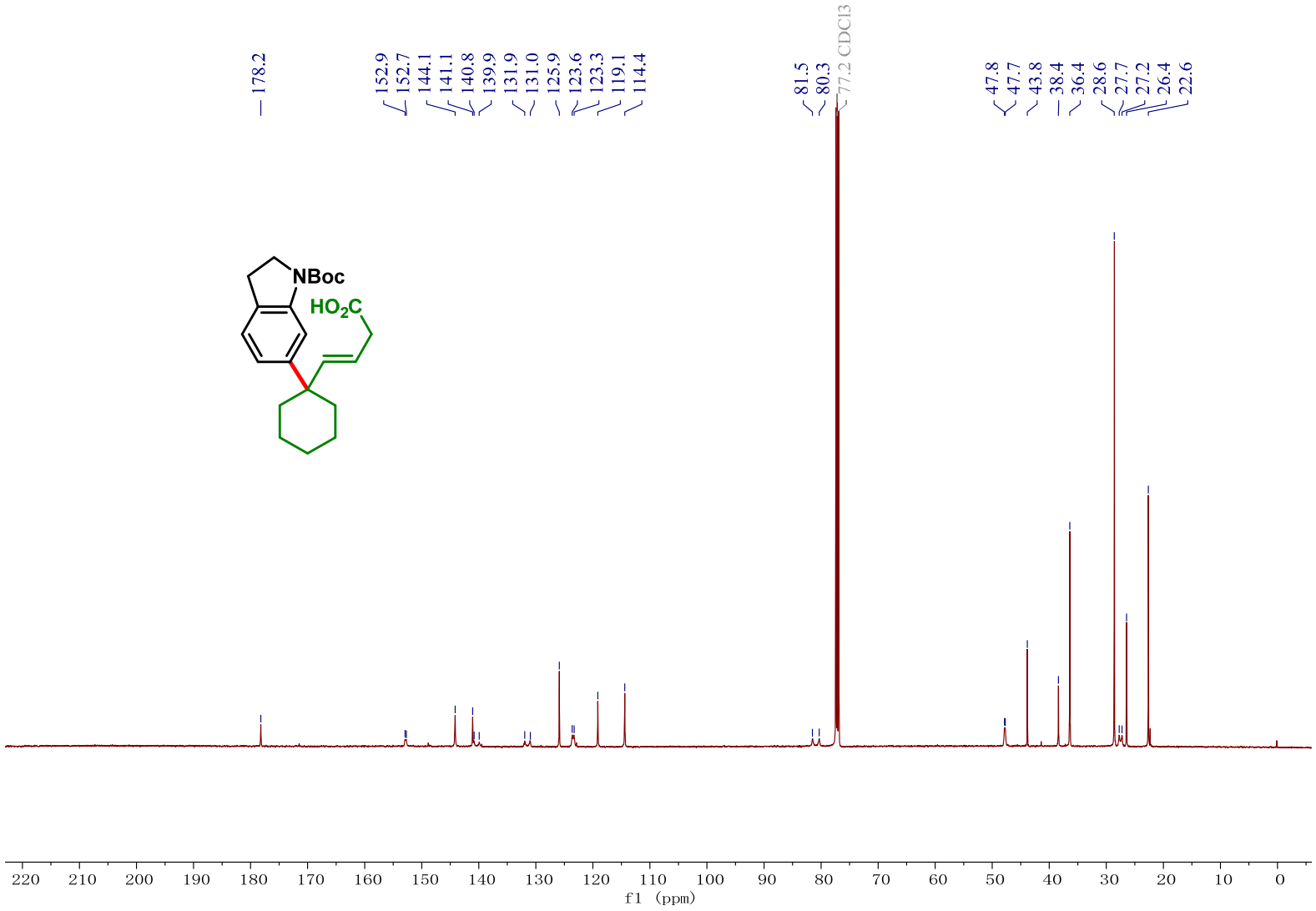
Compound 18 ^{13}C NMR



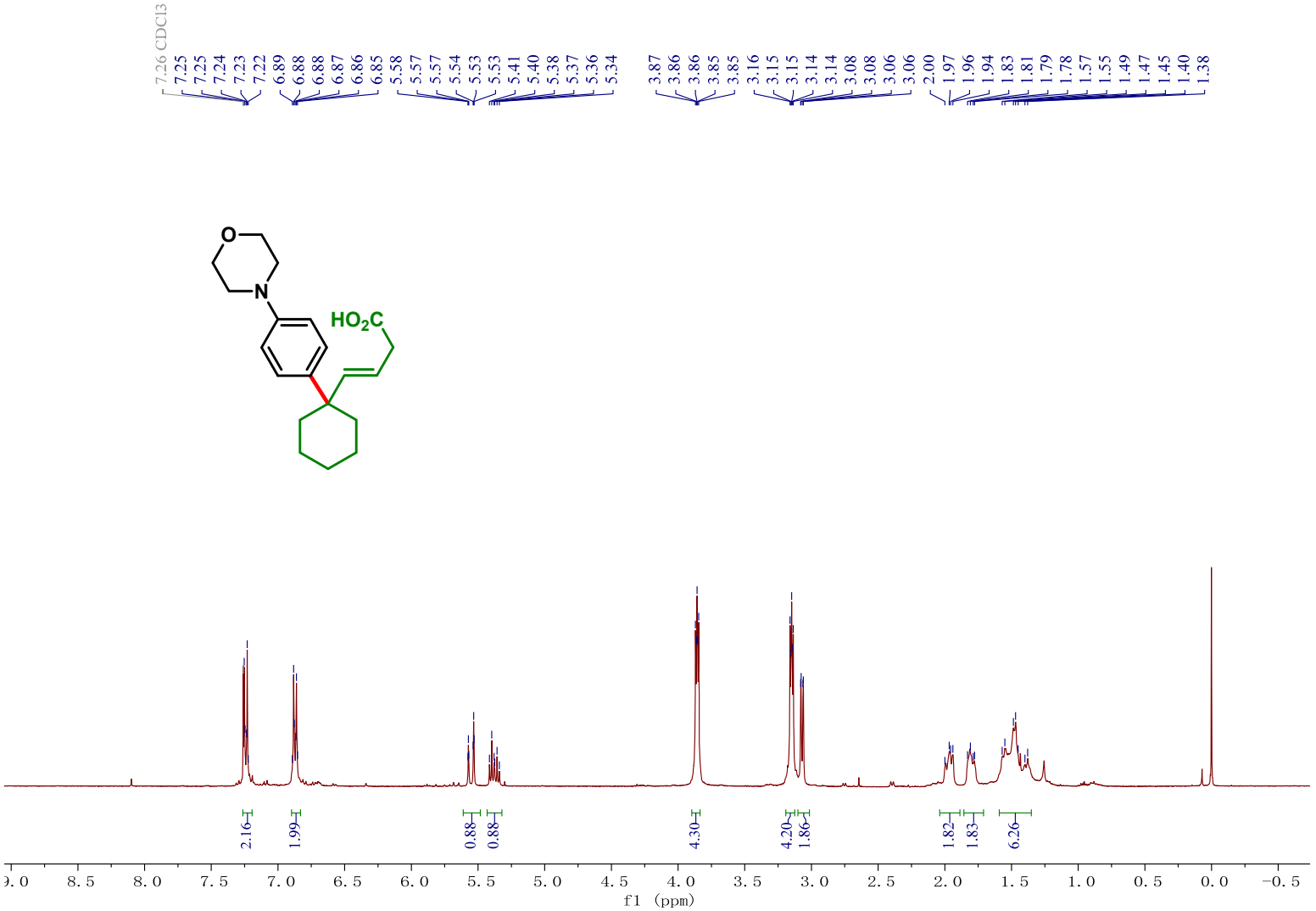
Compound 19 ^{1}H NMR



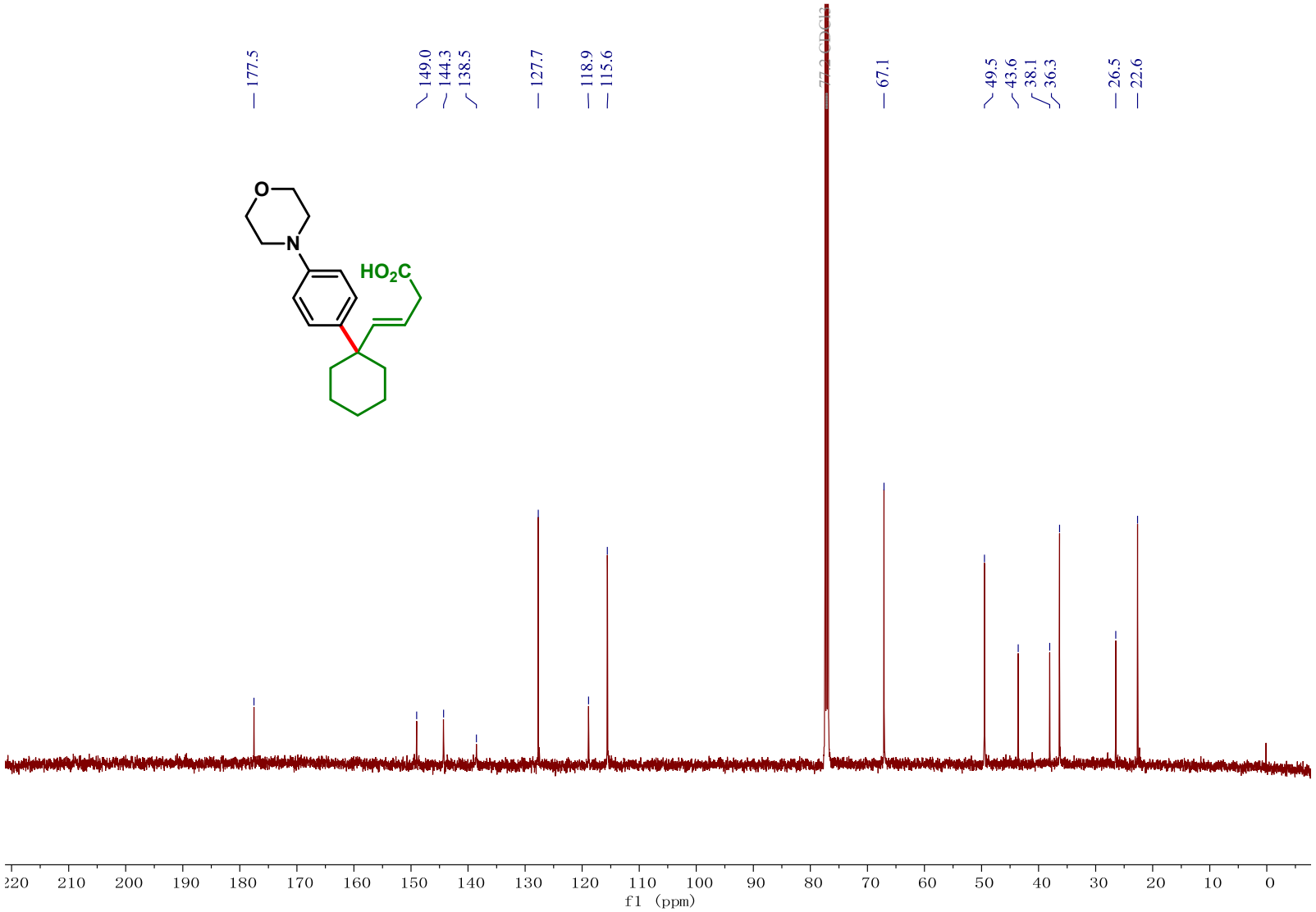
Compound 19 ^{13}C NMR



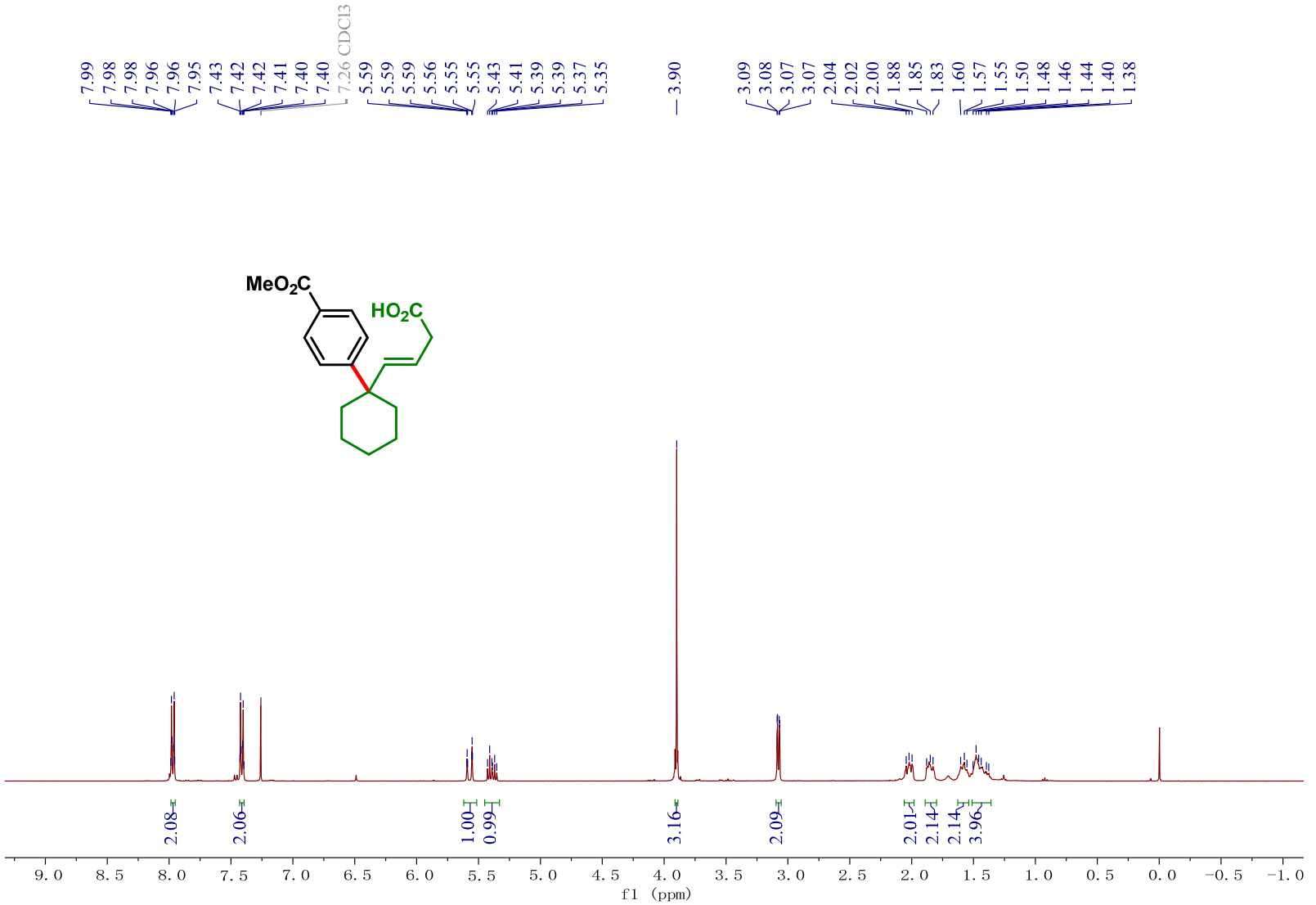
Compound 20 ^{1}H NMR



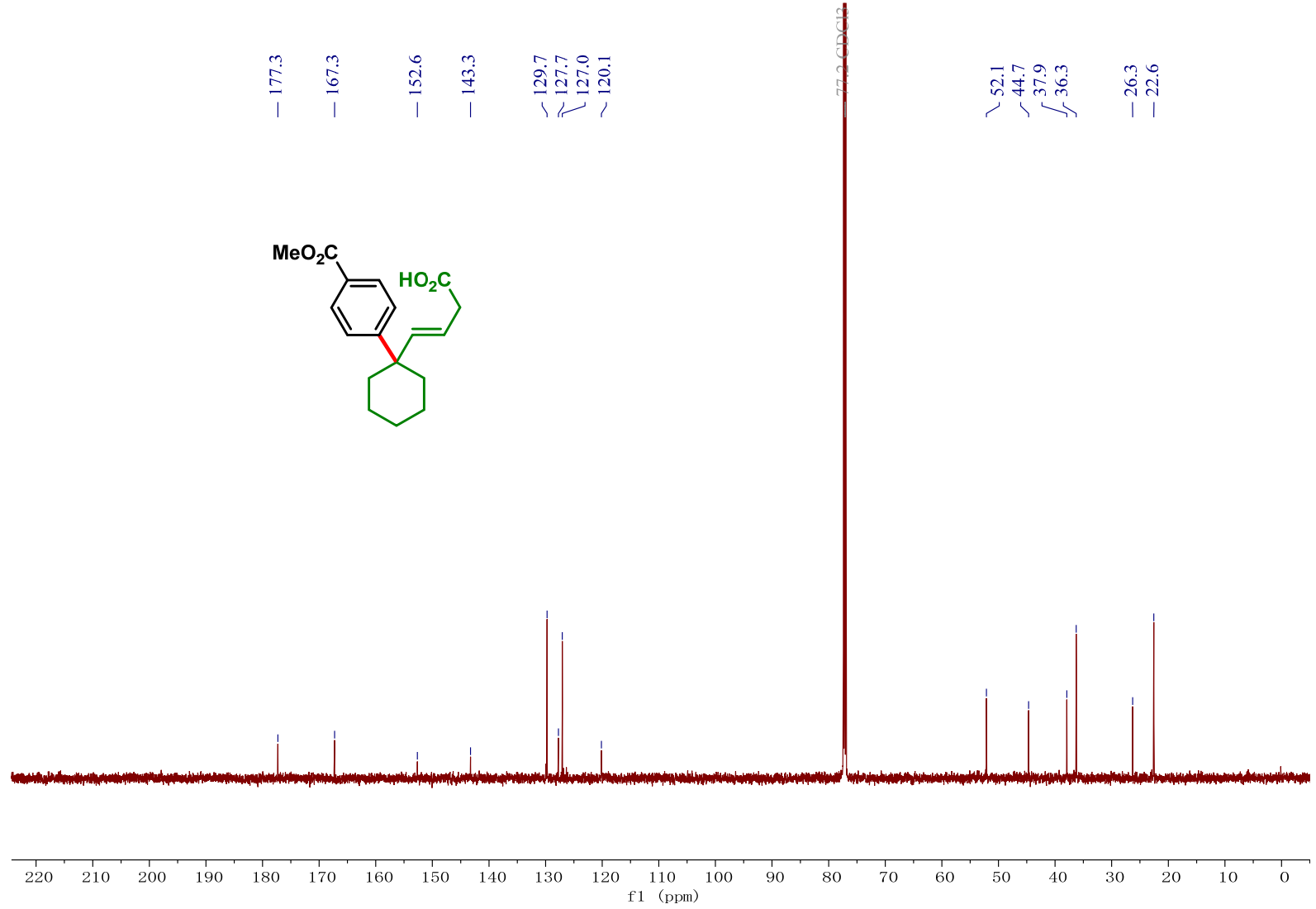
Compound 20 ^{13}C NMR



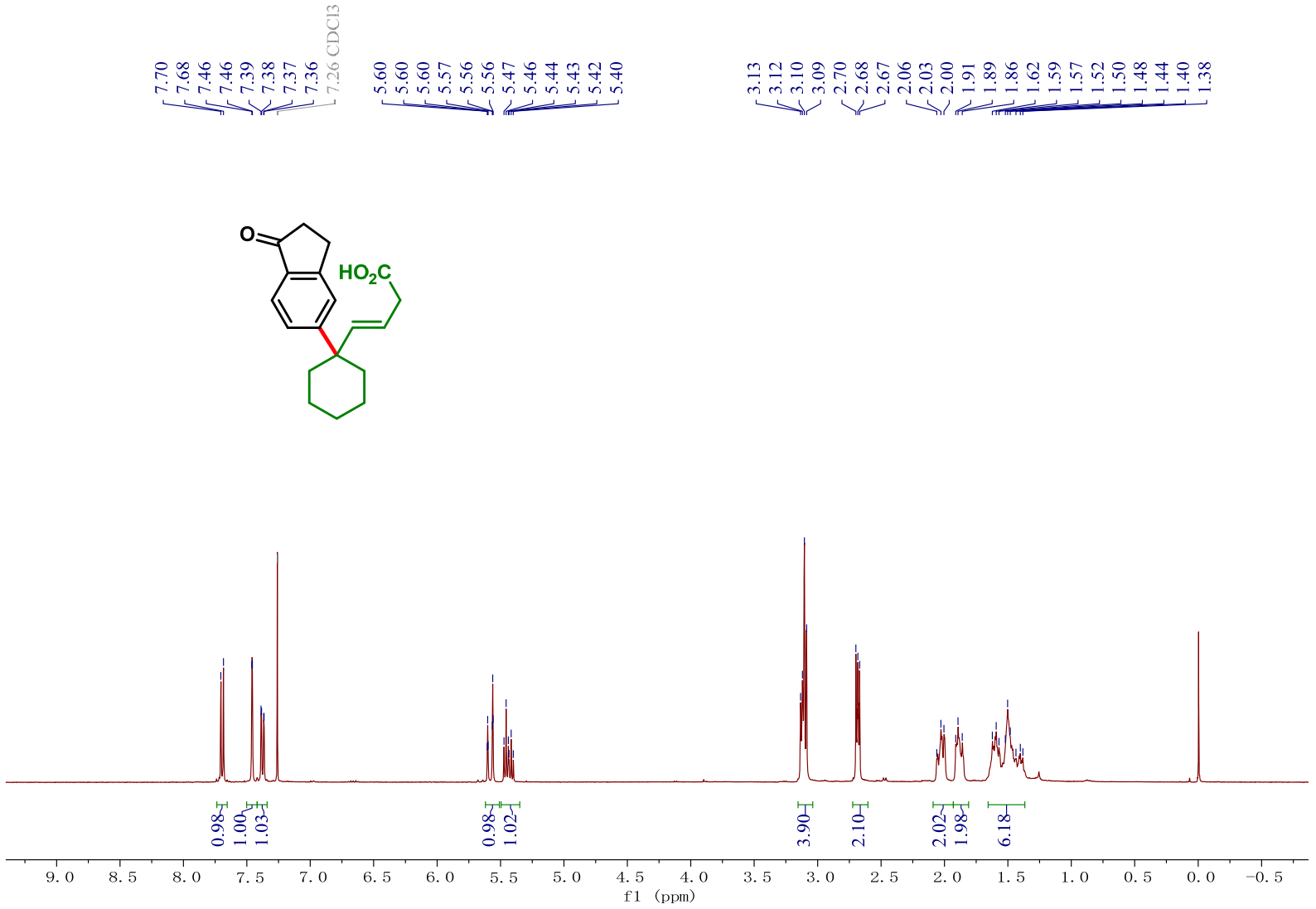
Compound 21 ^{1}H NMR



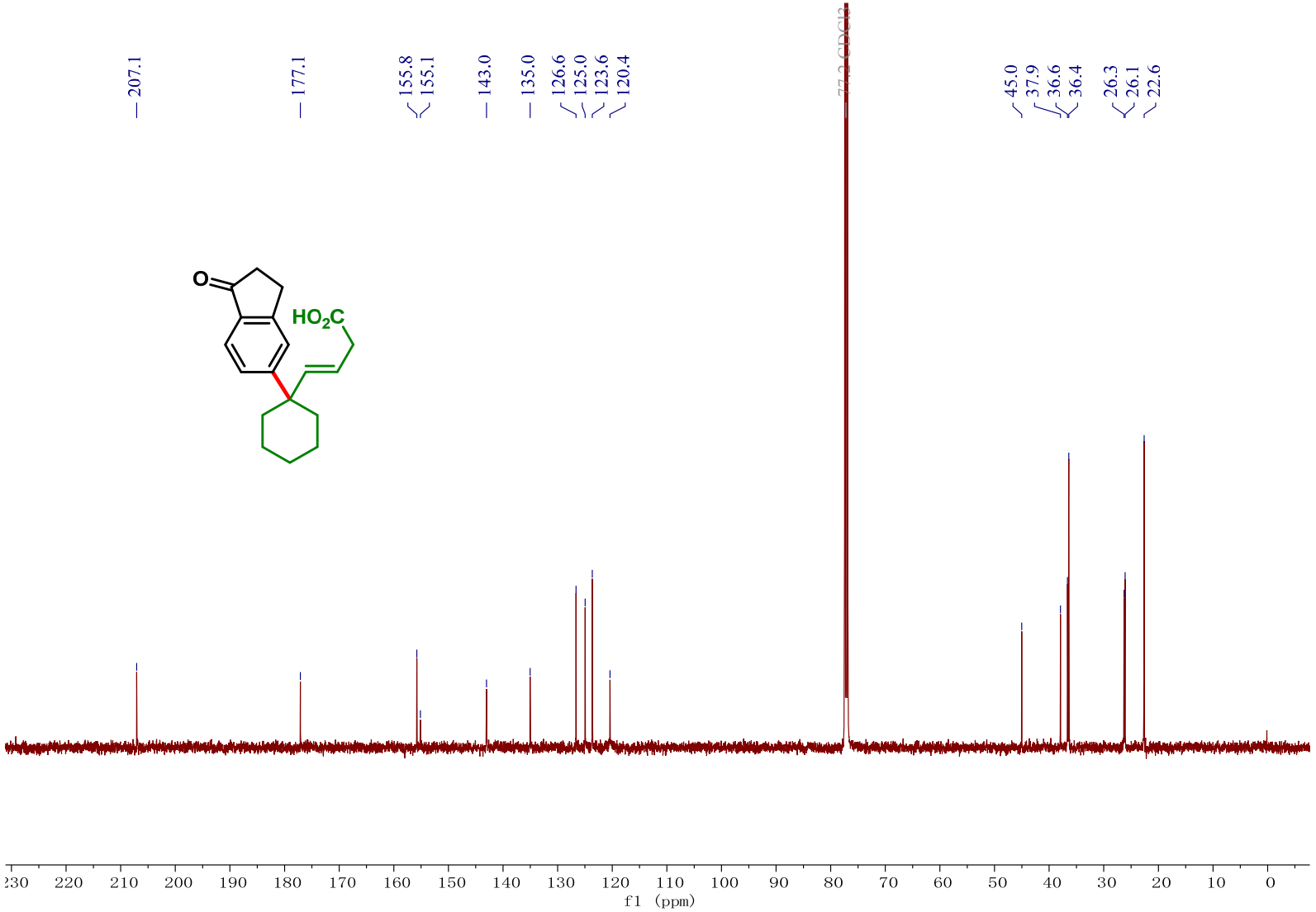
Compound 21 ^{13}C NMR



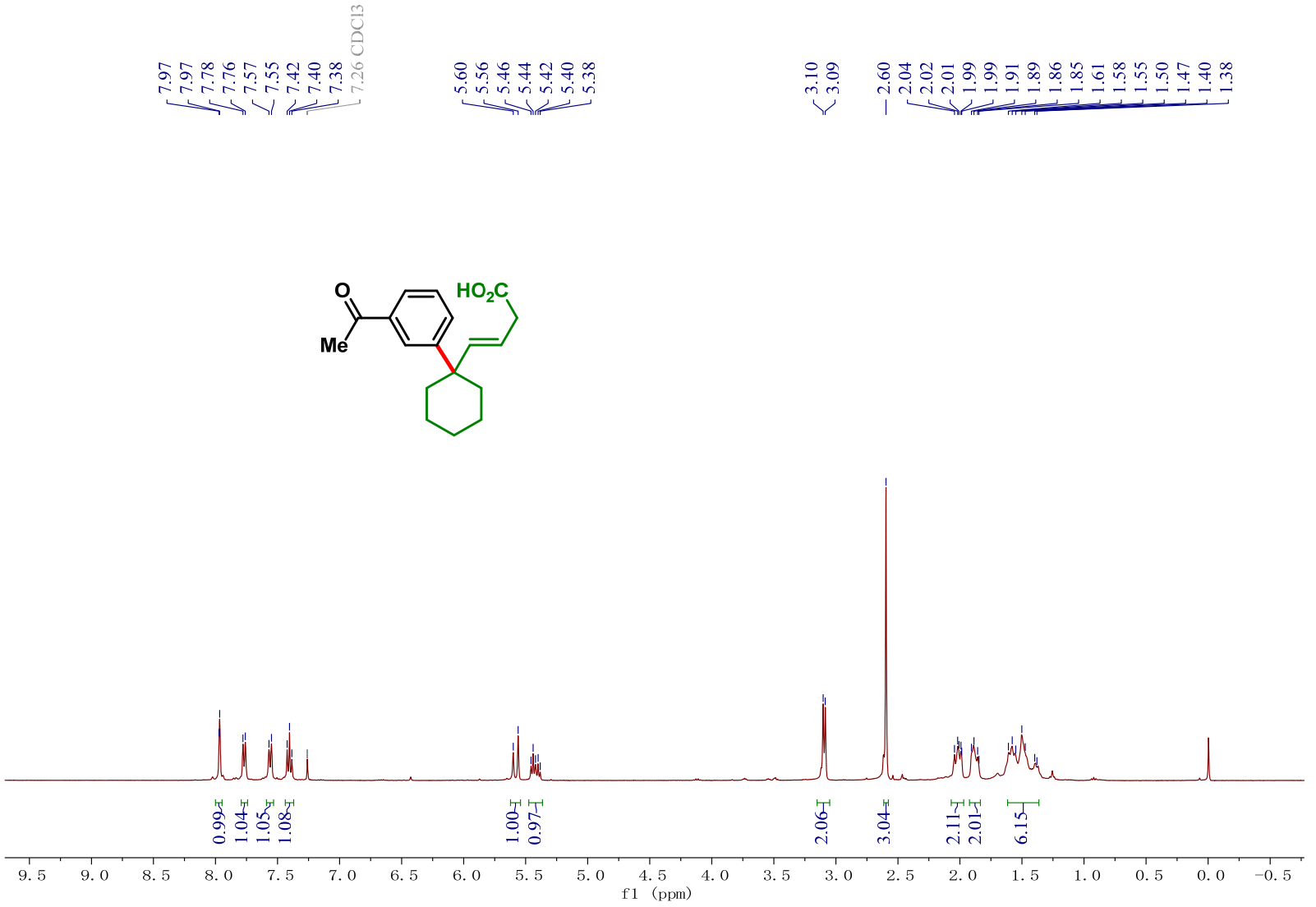
Compound 22 ^{1}H NMR



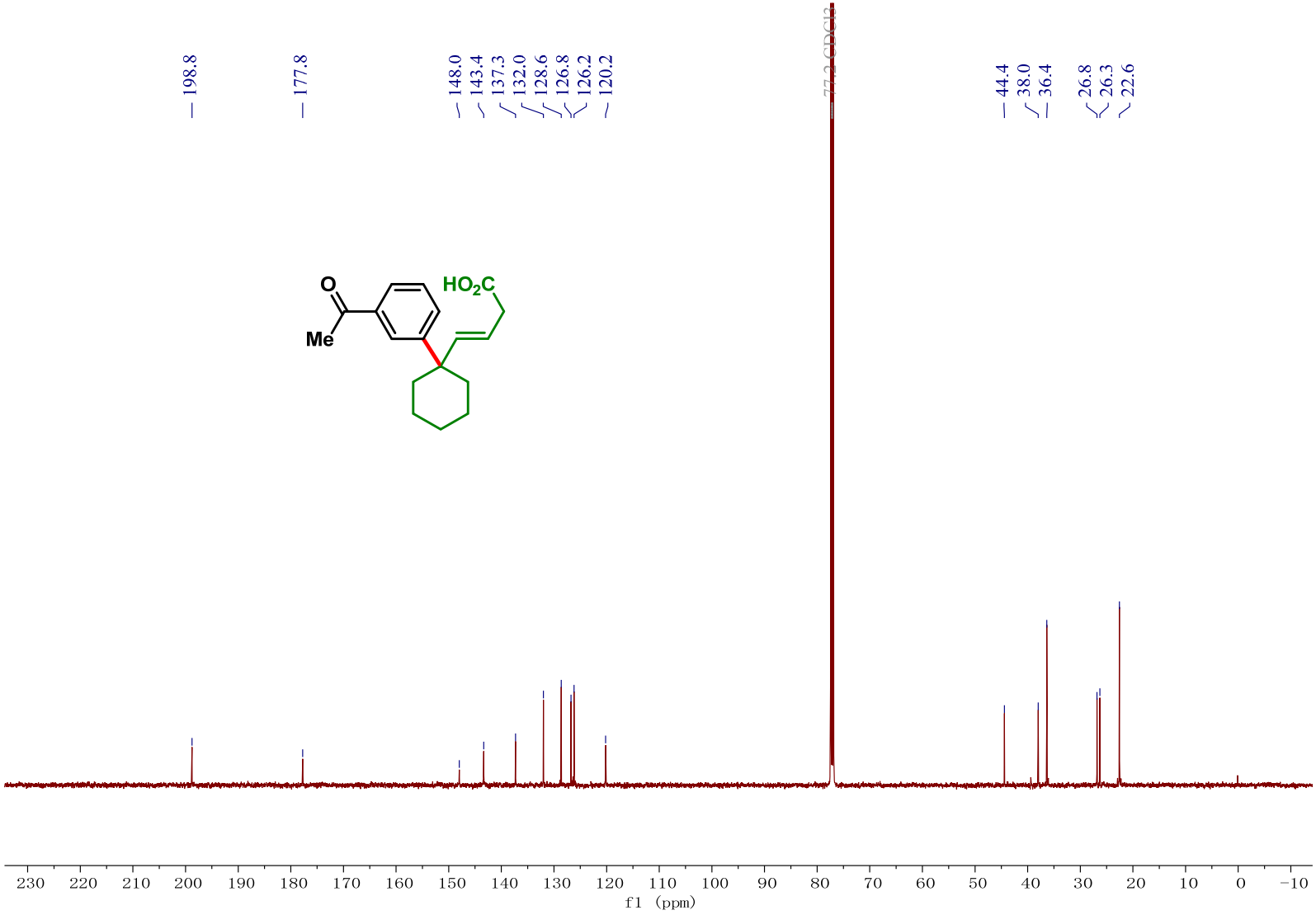
Compound 22 ^{13}C NMR



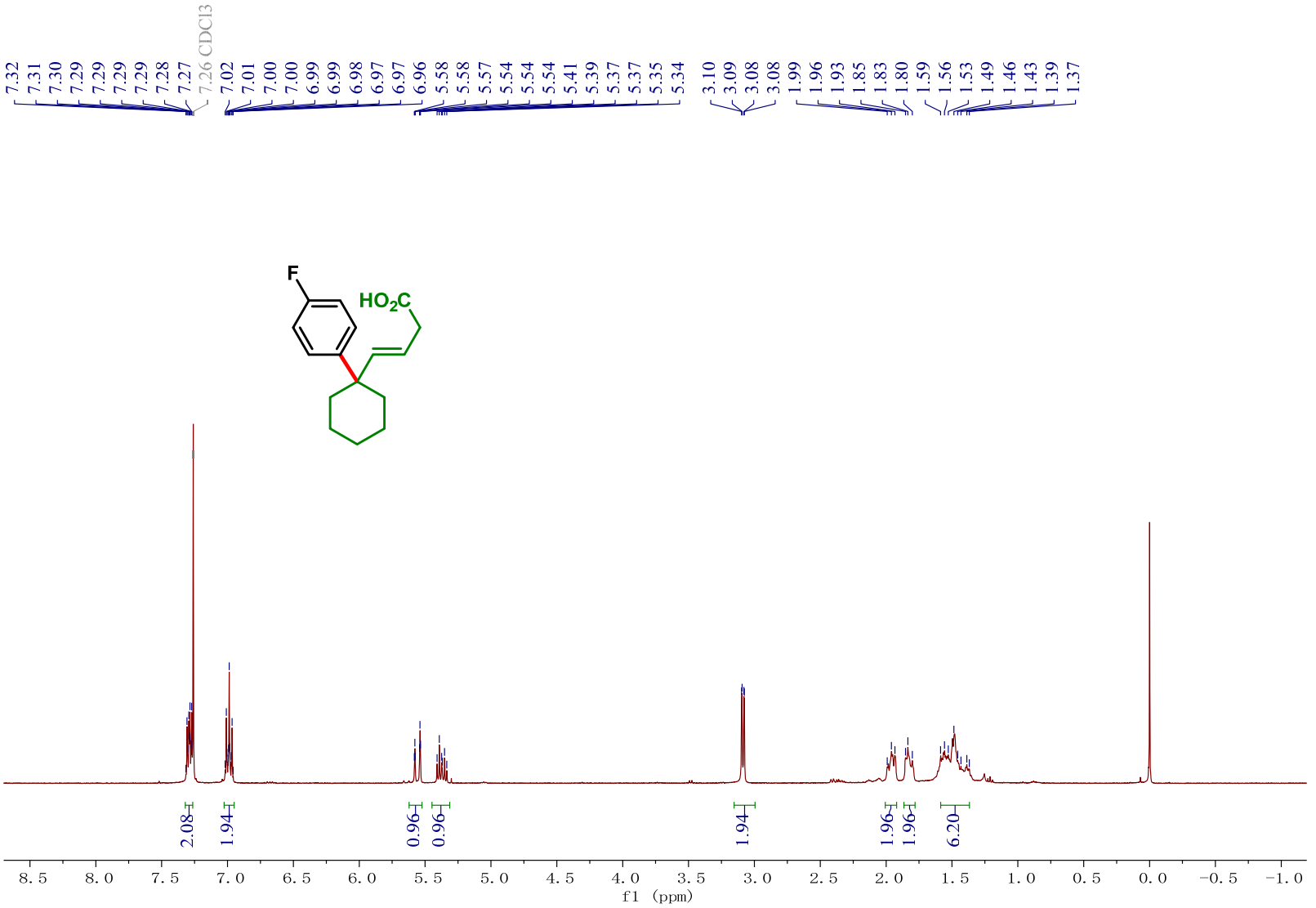
Compound 23 ^{1}H NMR



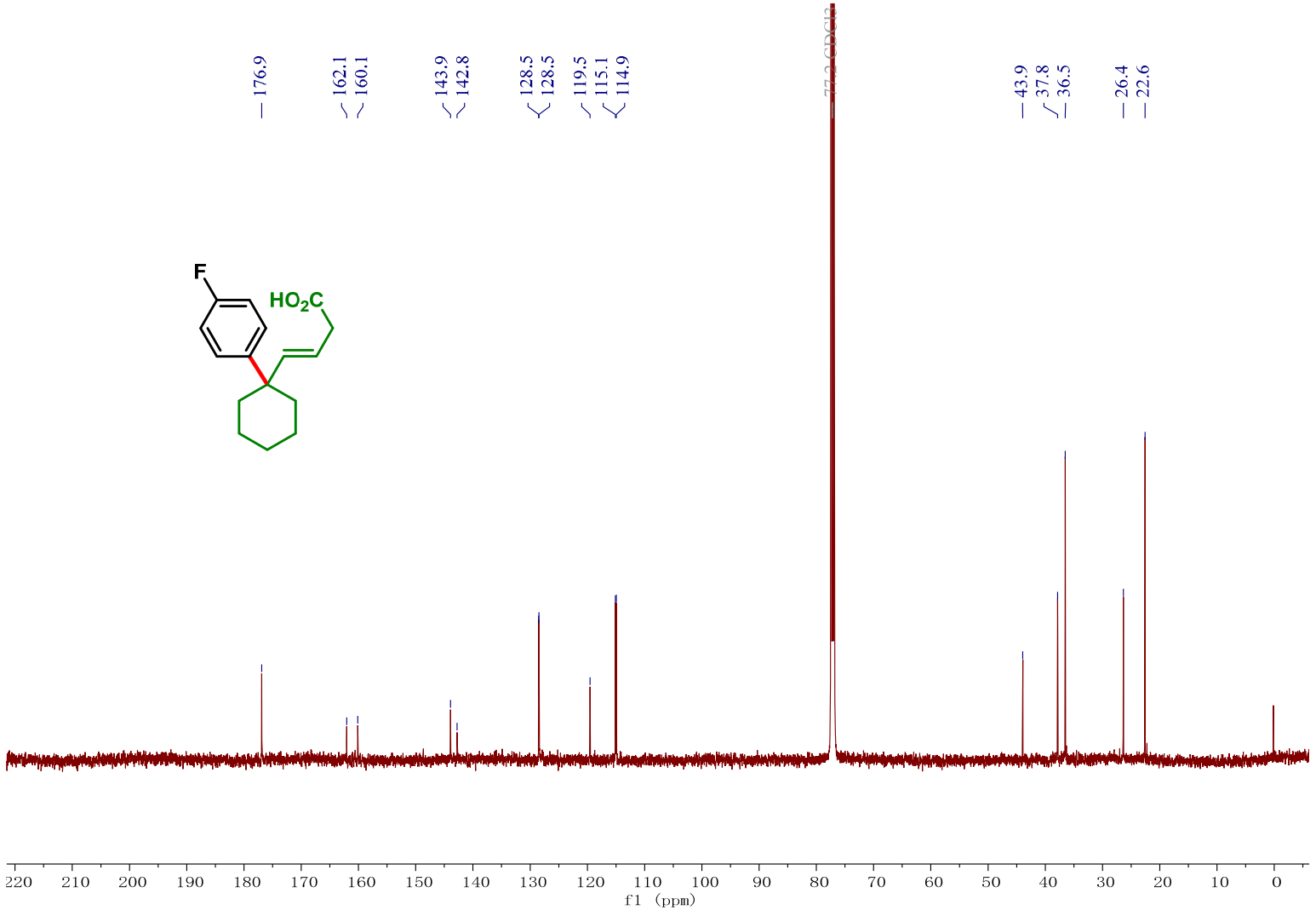
Compound 23 ^{13}C NMR



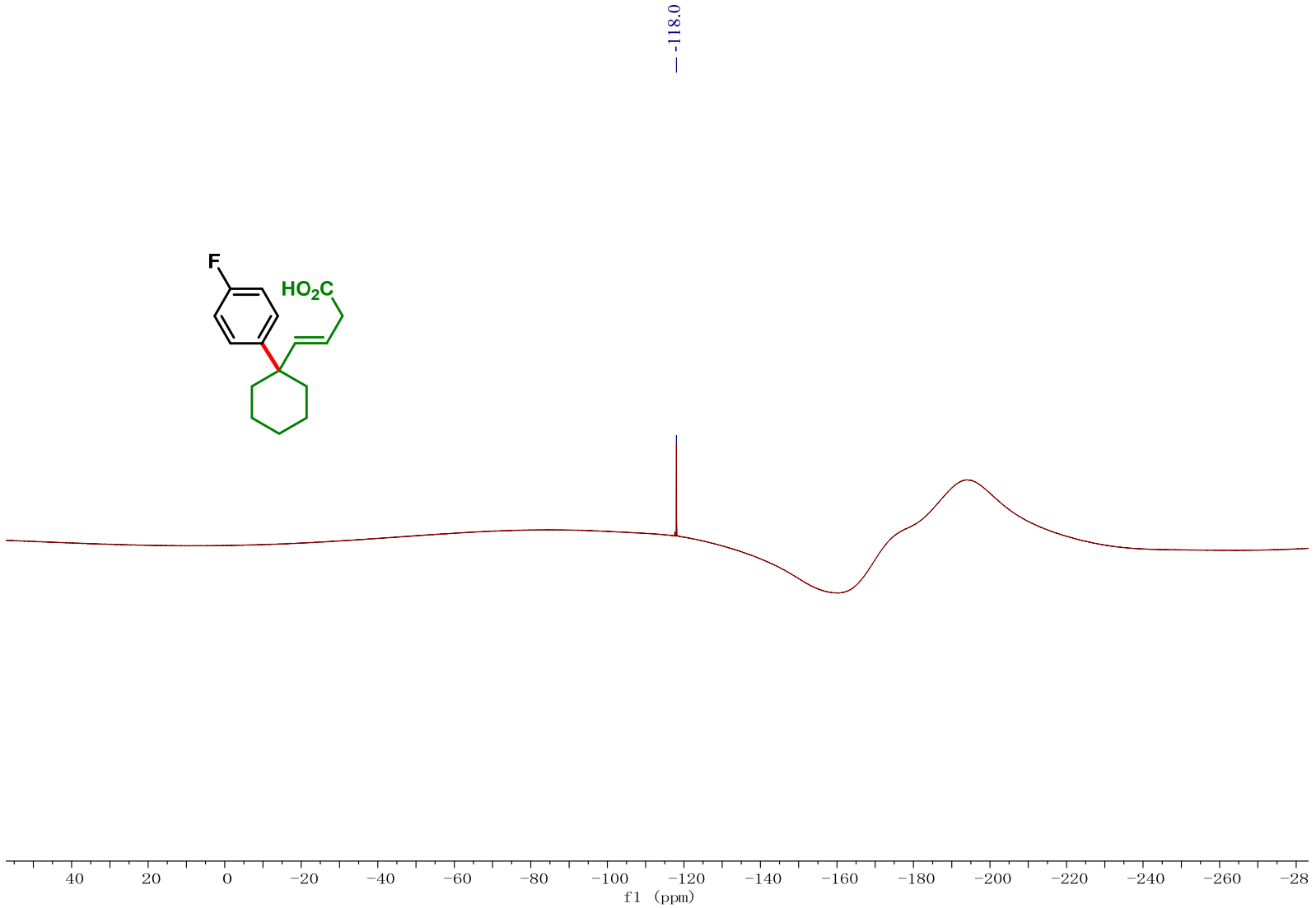
Compound 24 ^{1}H NMR



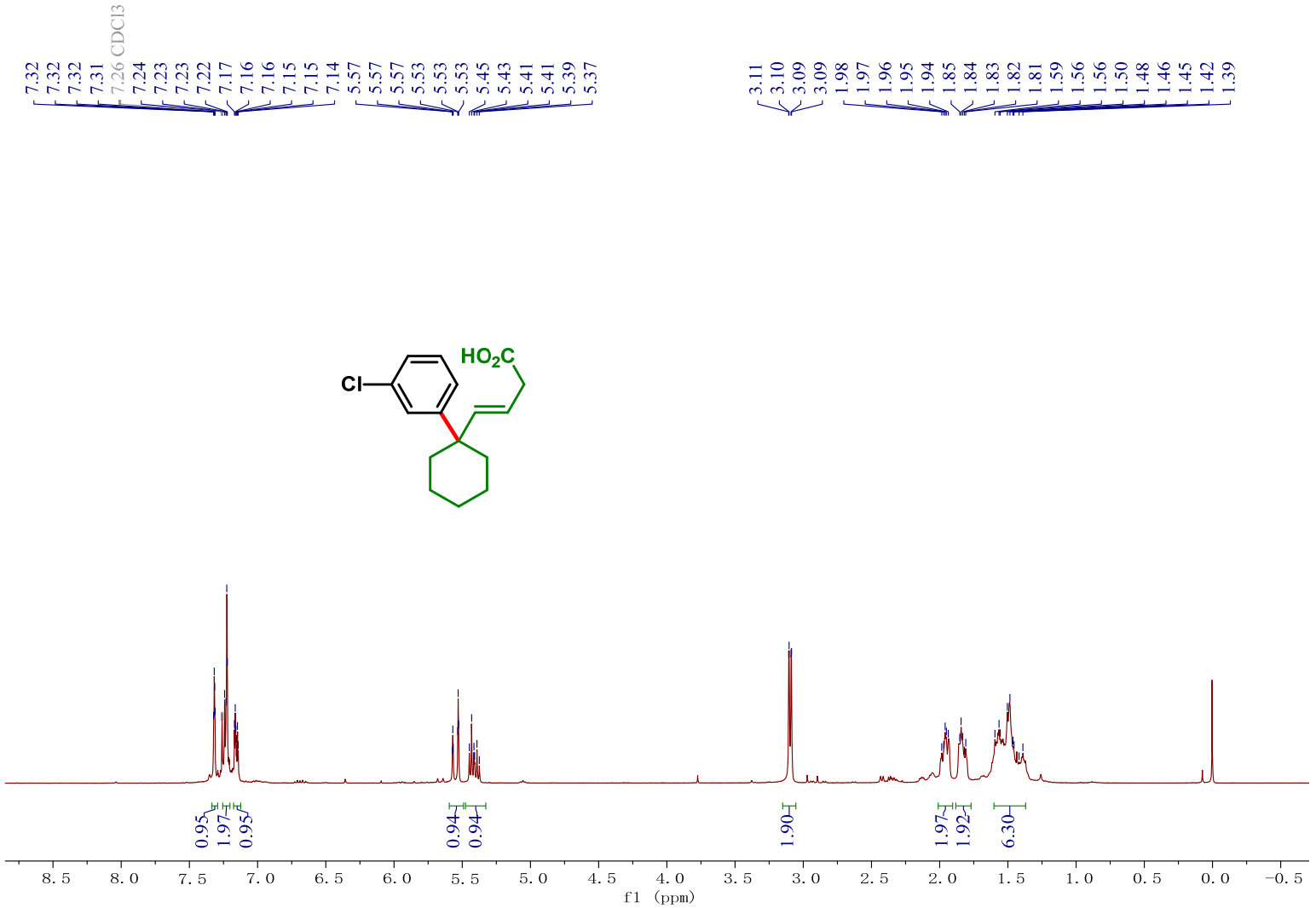
Compound 24 ^{13}C NMR



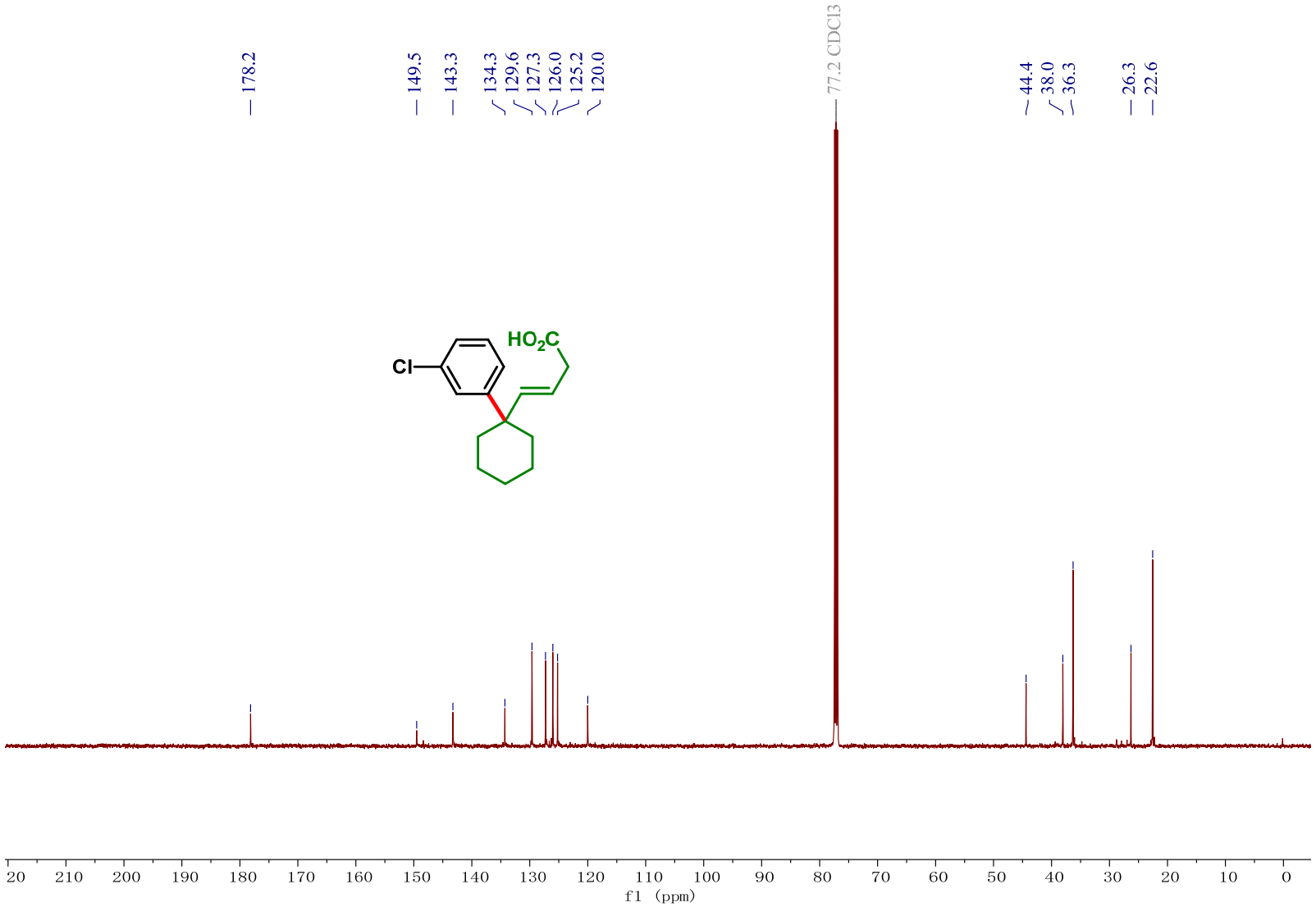
Compound 24 ^{19}F NMR



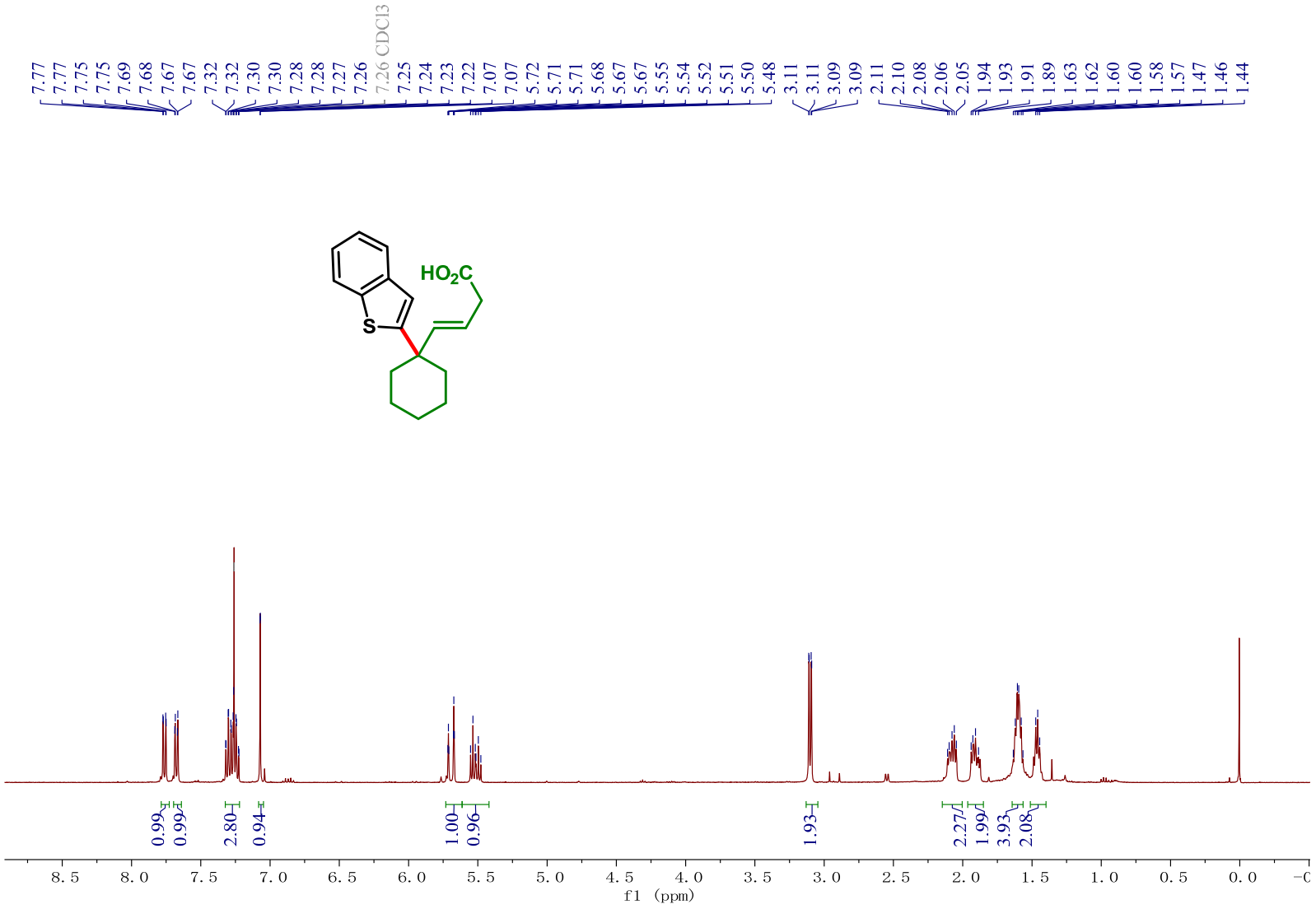
Compound 25 ^{1}H NMR



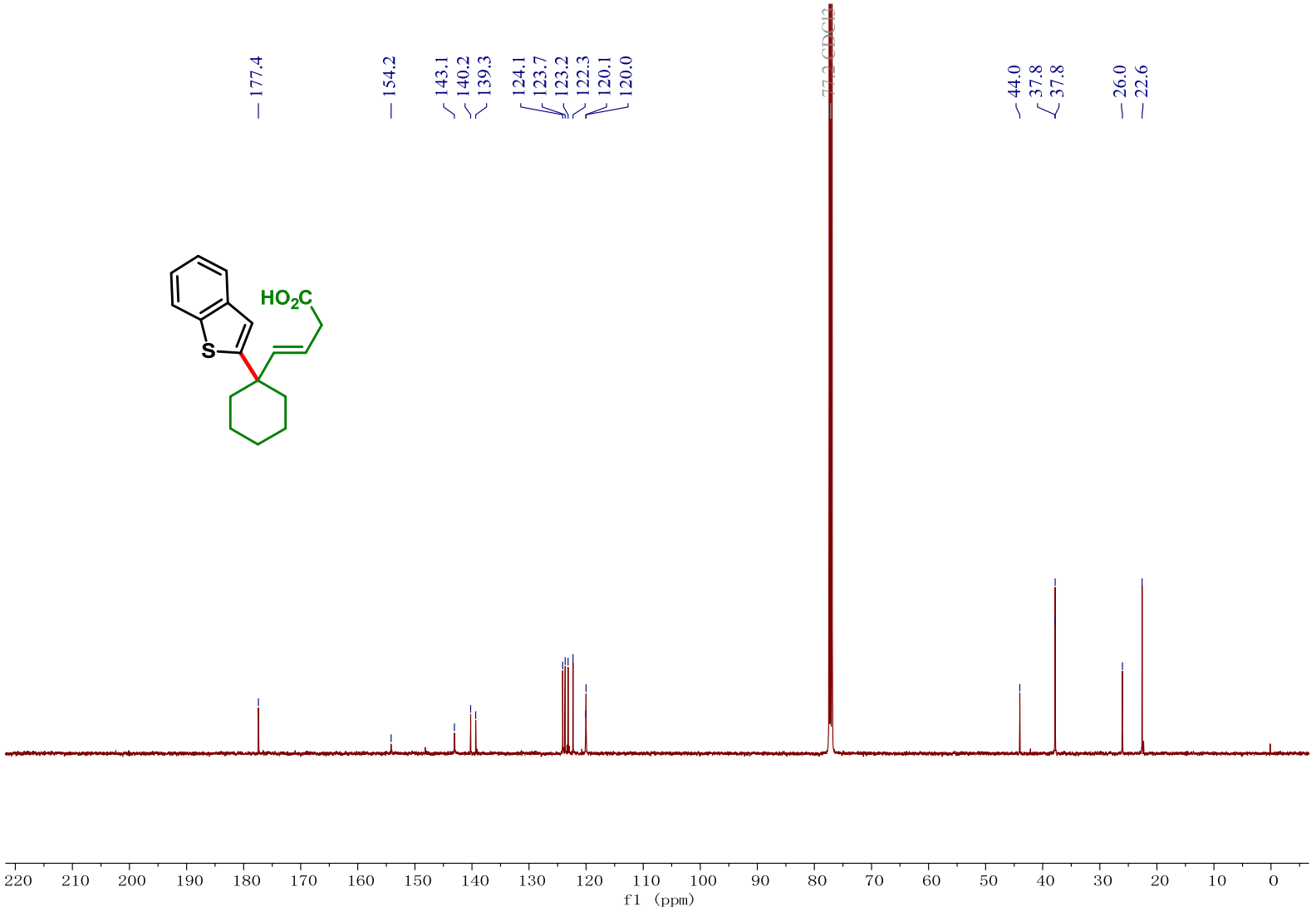
Compound 25 ^{13}C NMR



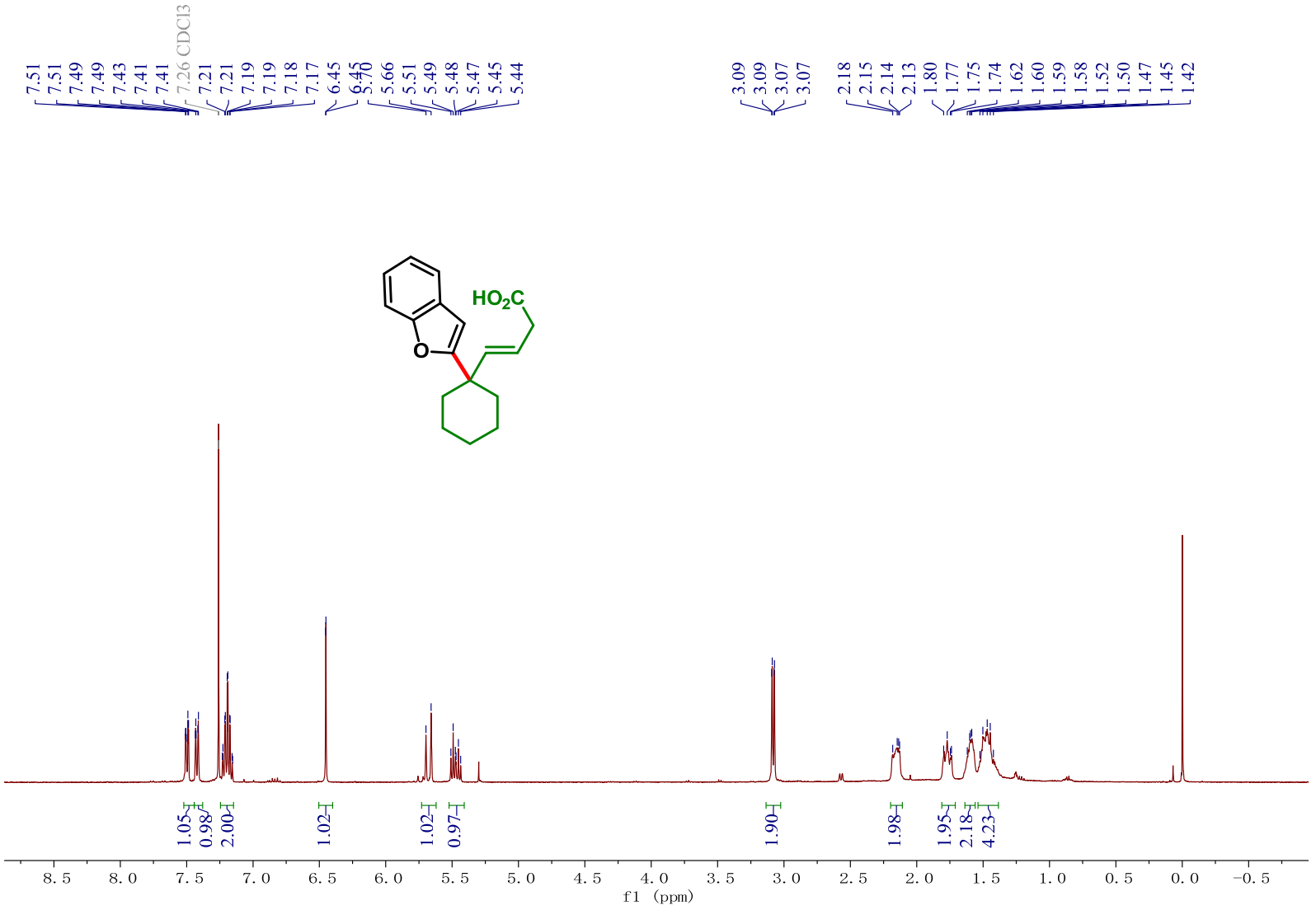
Compound 26 ^{1}H NMR



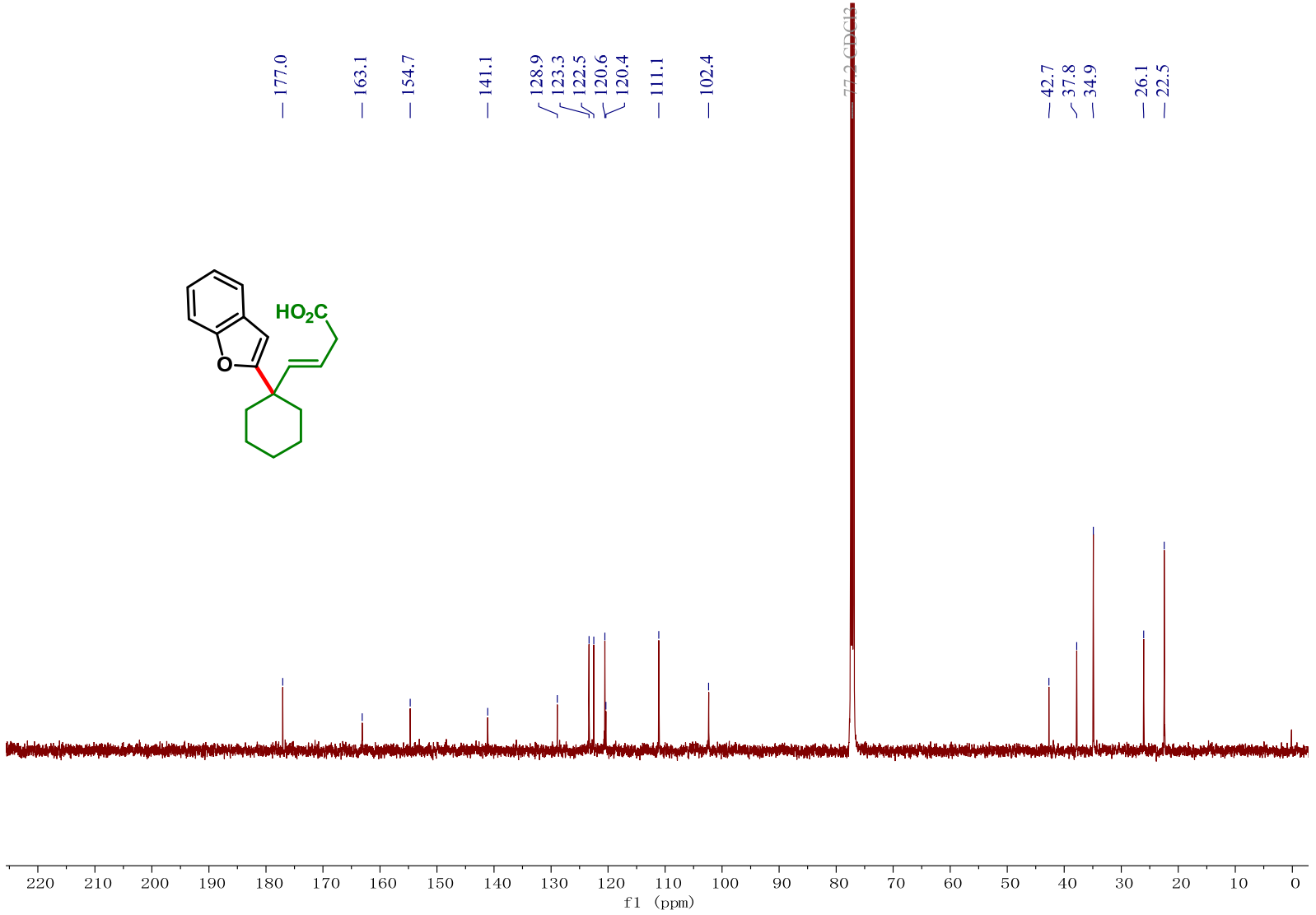
Compound 26 ^{13}C NMR



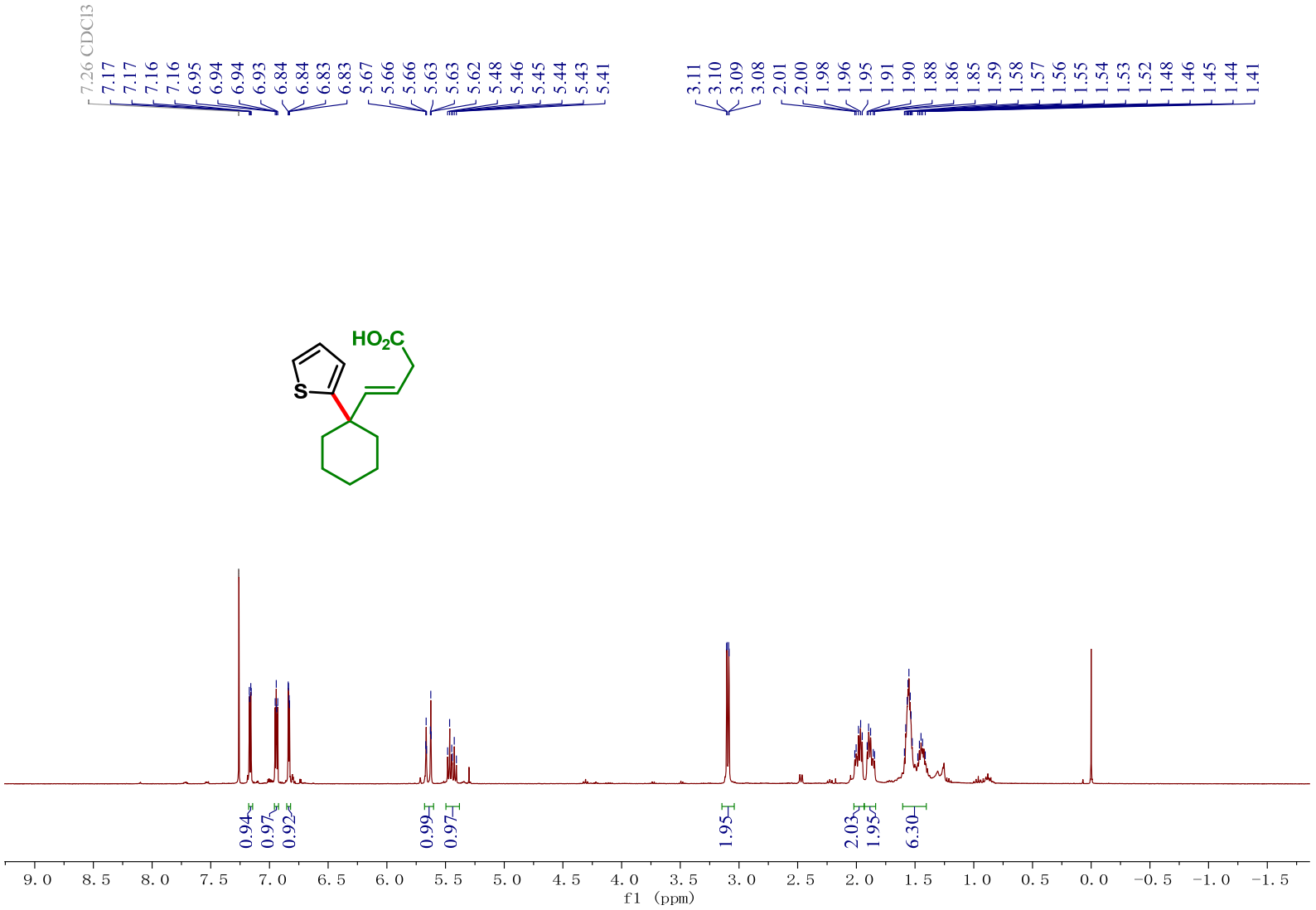
Compound 27 ^{1}H NMR



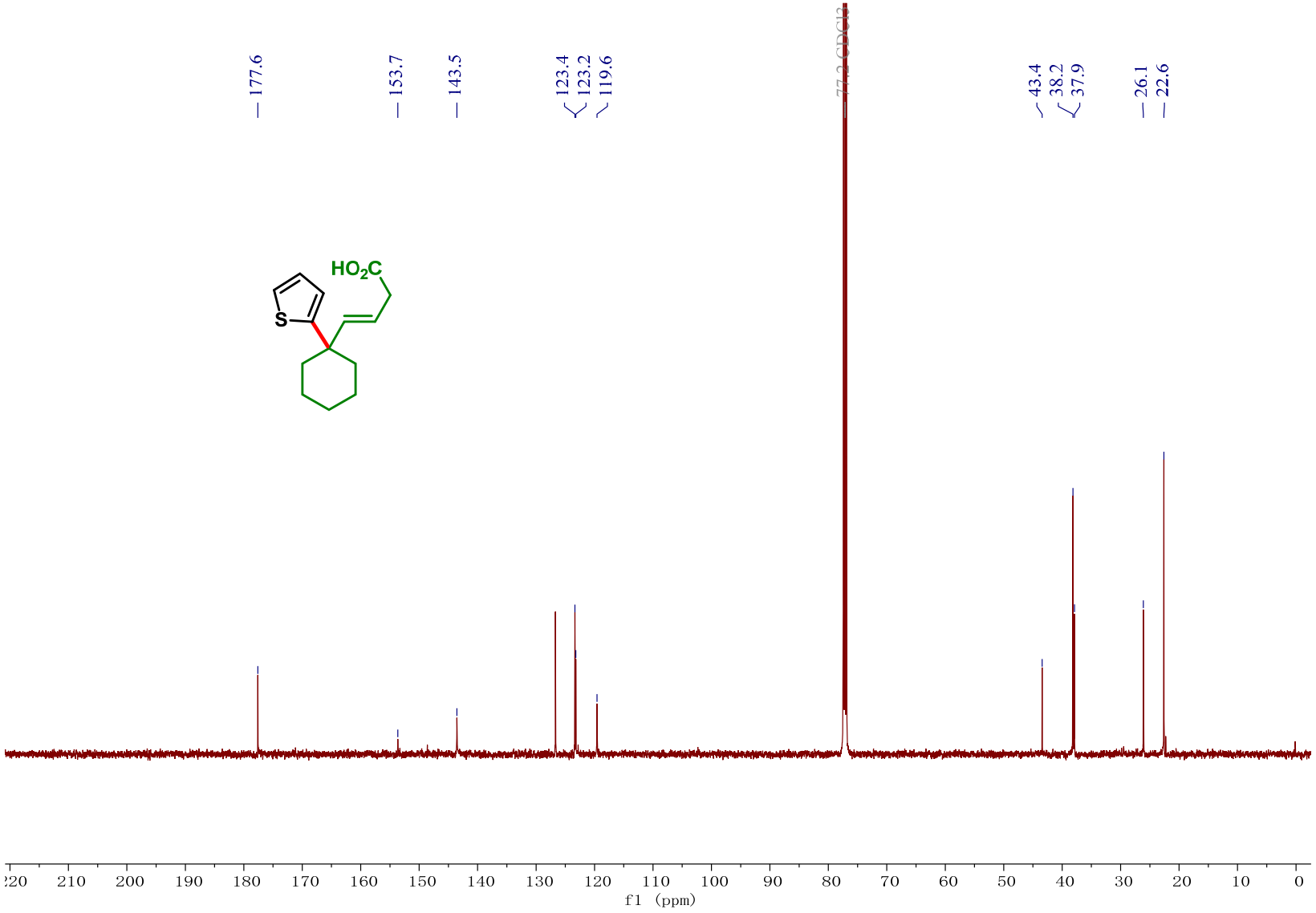
Compound 27 ^{13}C NMR



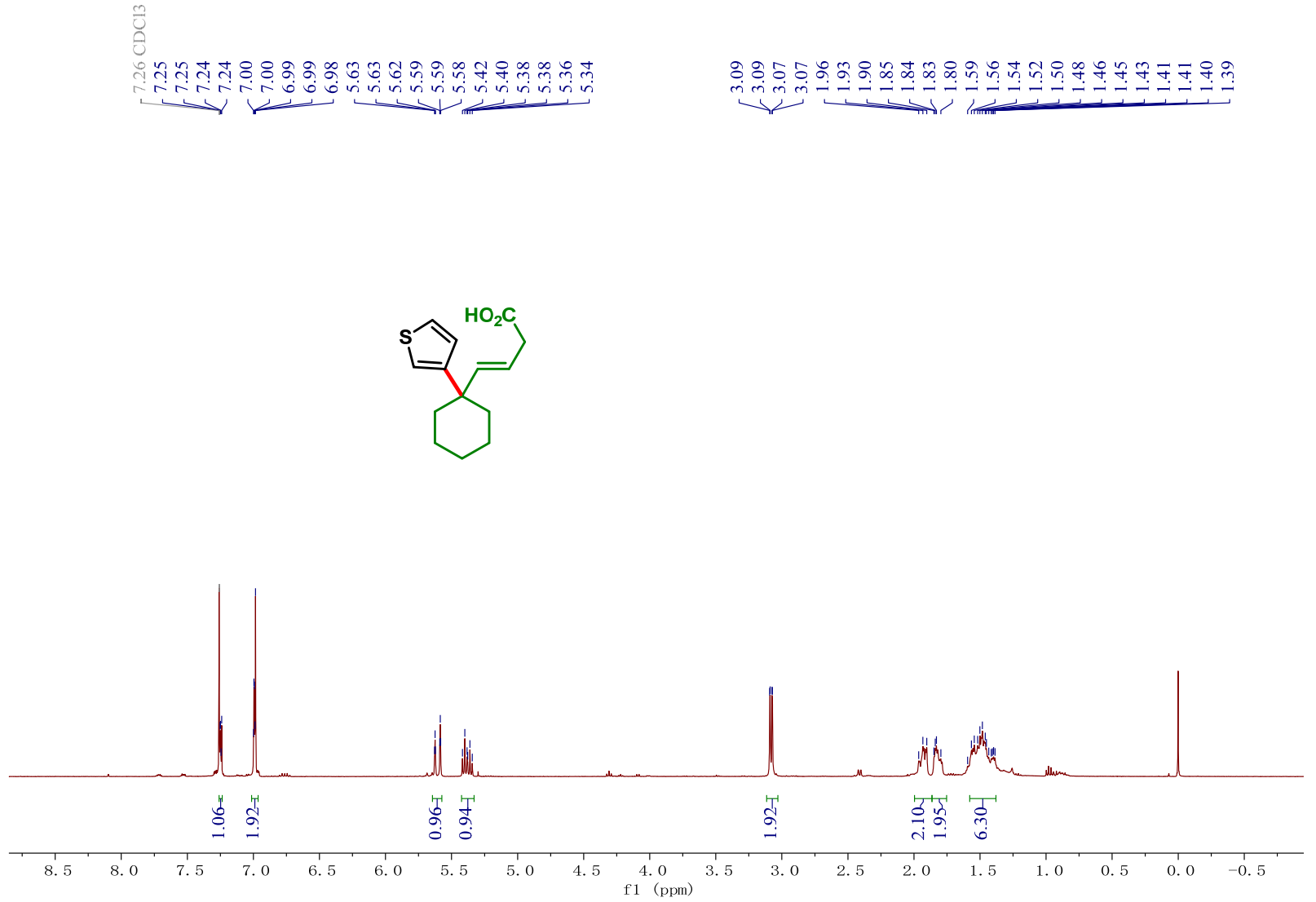
Compound 28 ^{1}H NMR



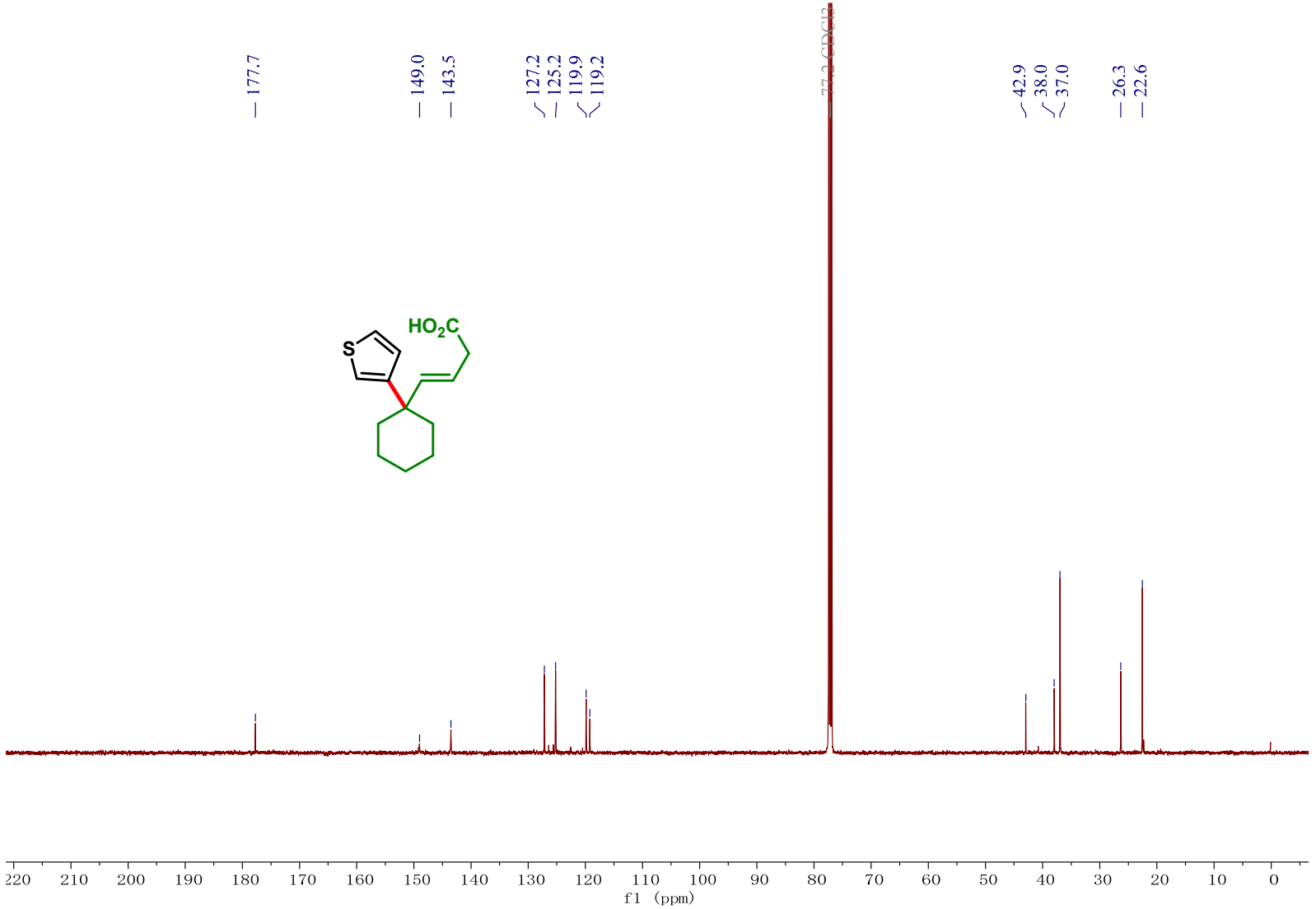
Compound 28 ^{13}C NMR



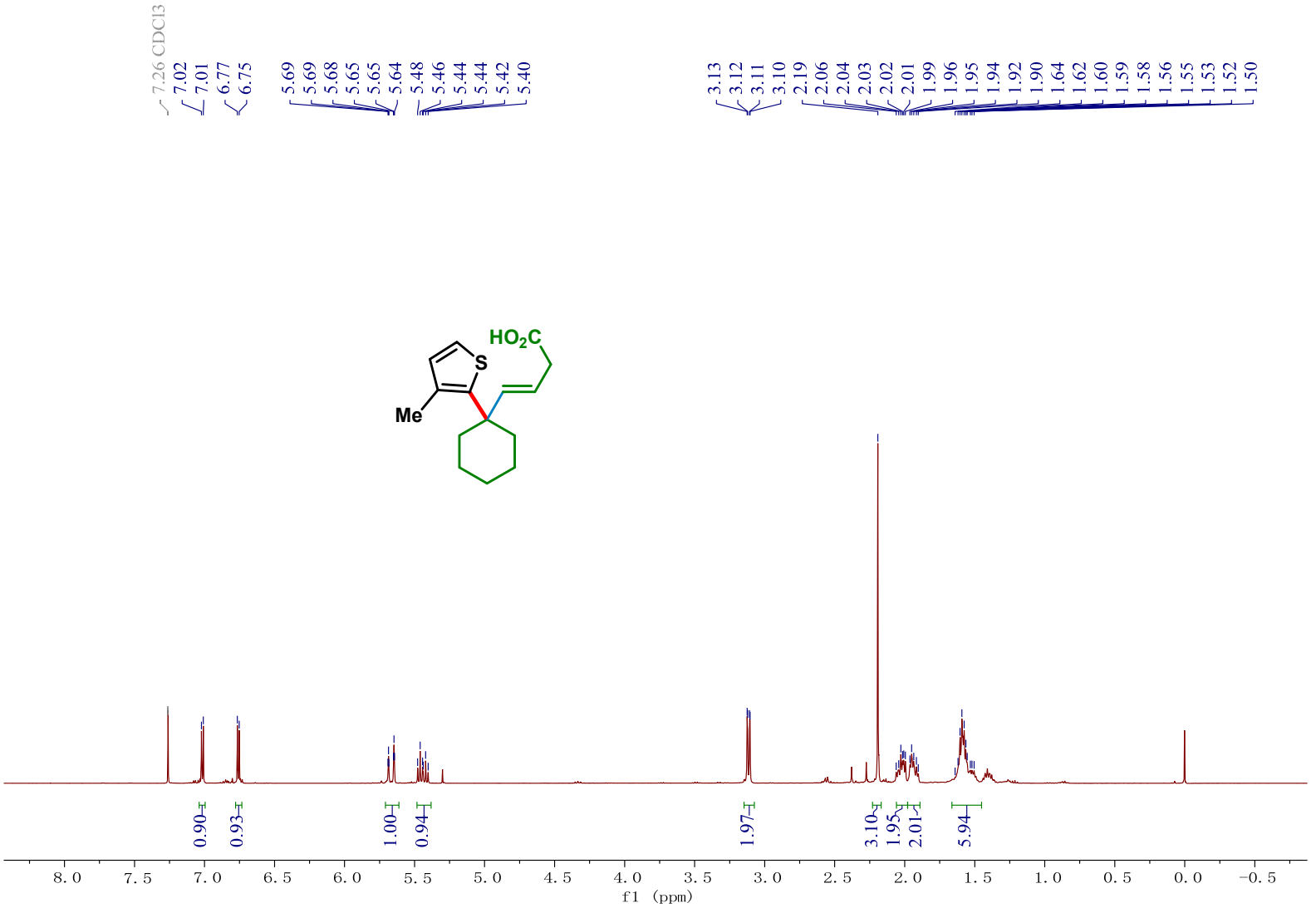
Compound 29 ^{1}H NMR



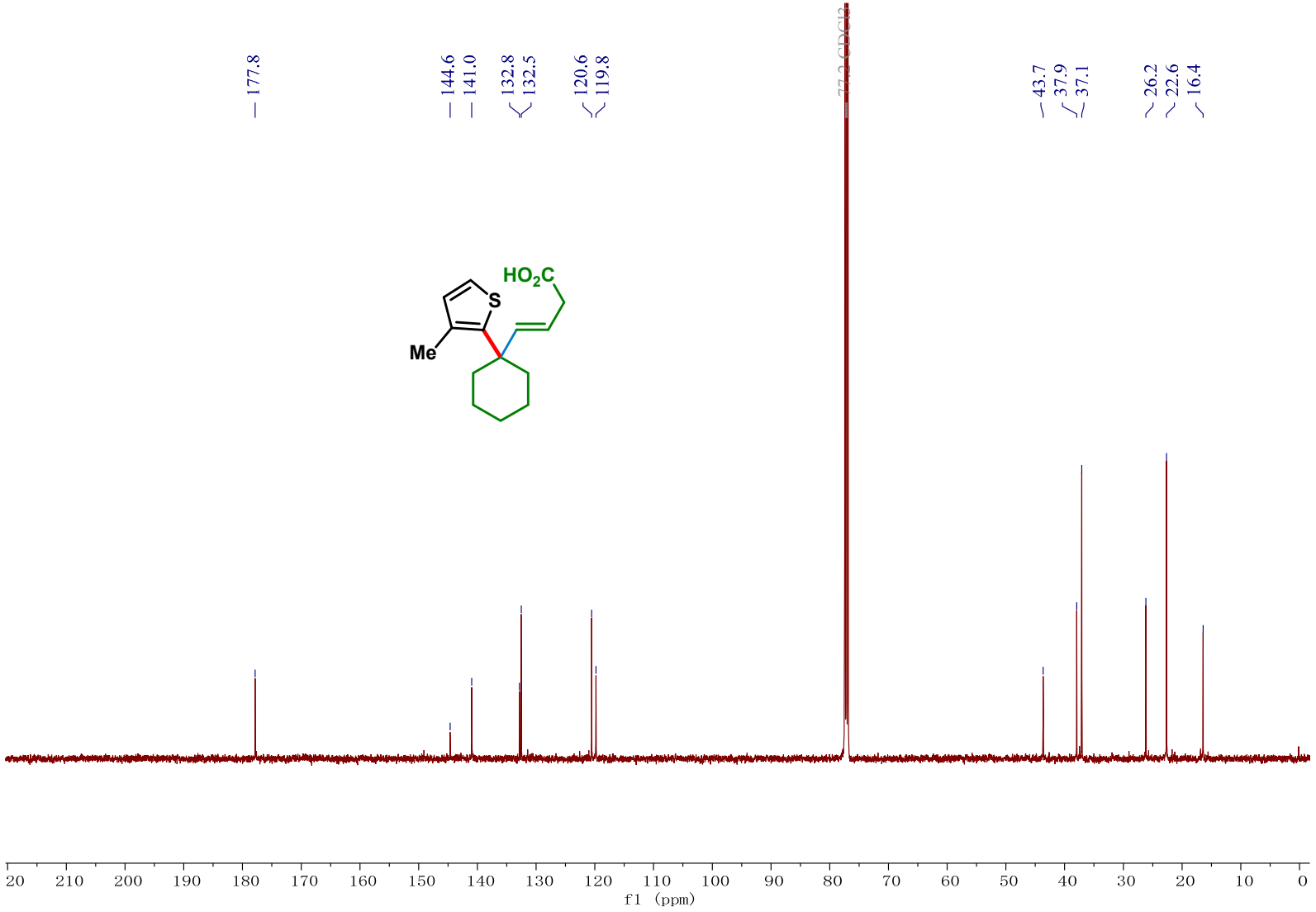
Compound 29 ^{13}C NMR



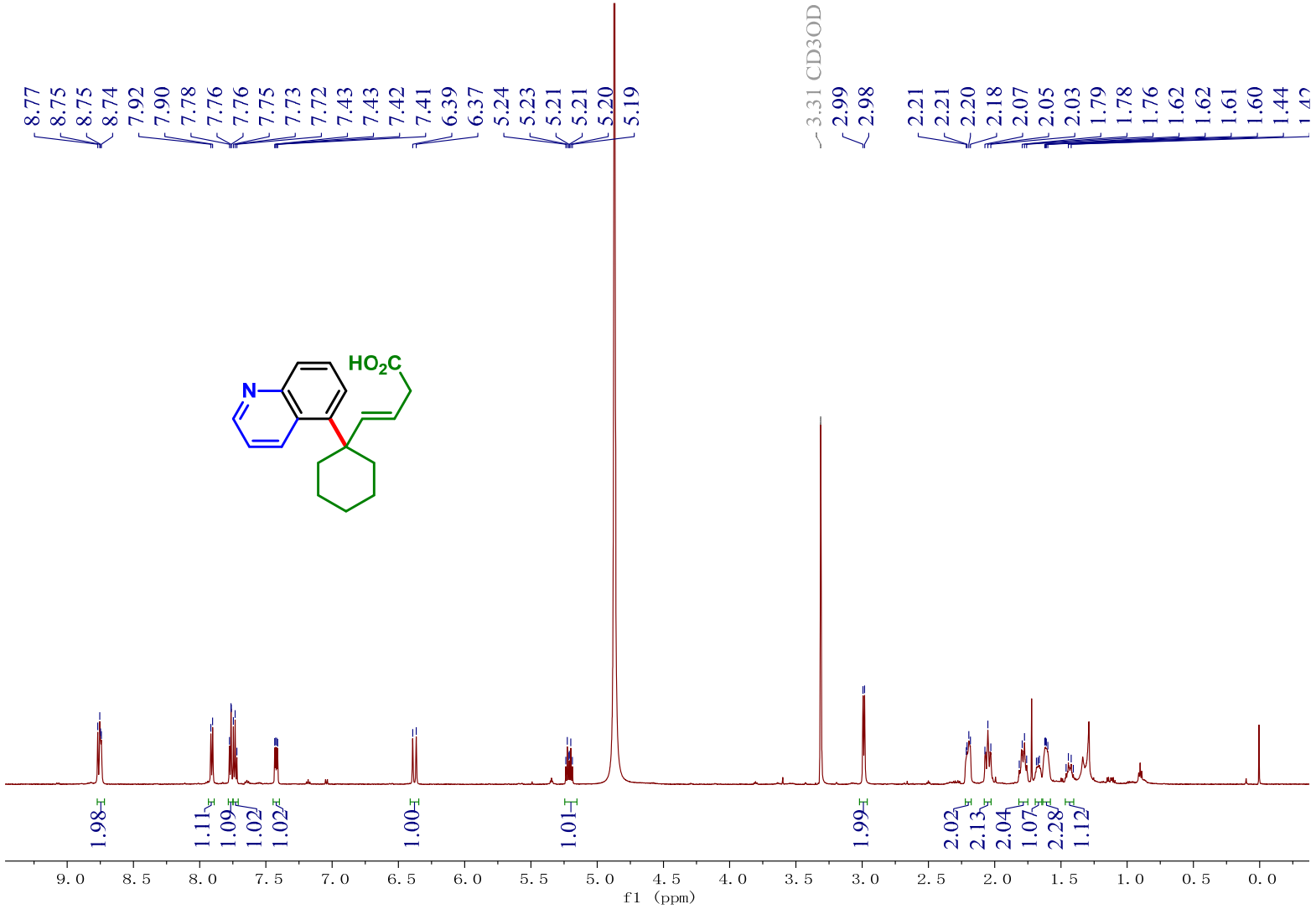
Compound 30 ^{1}H NMR



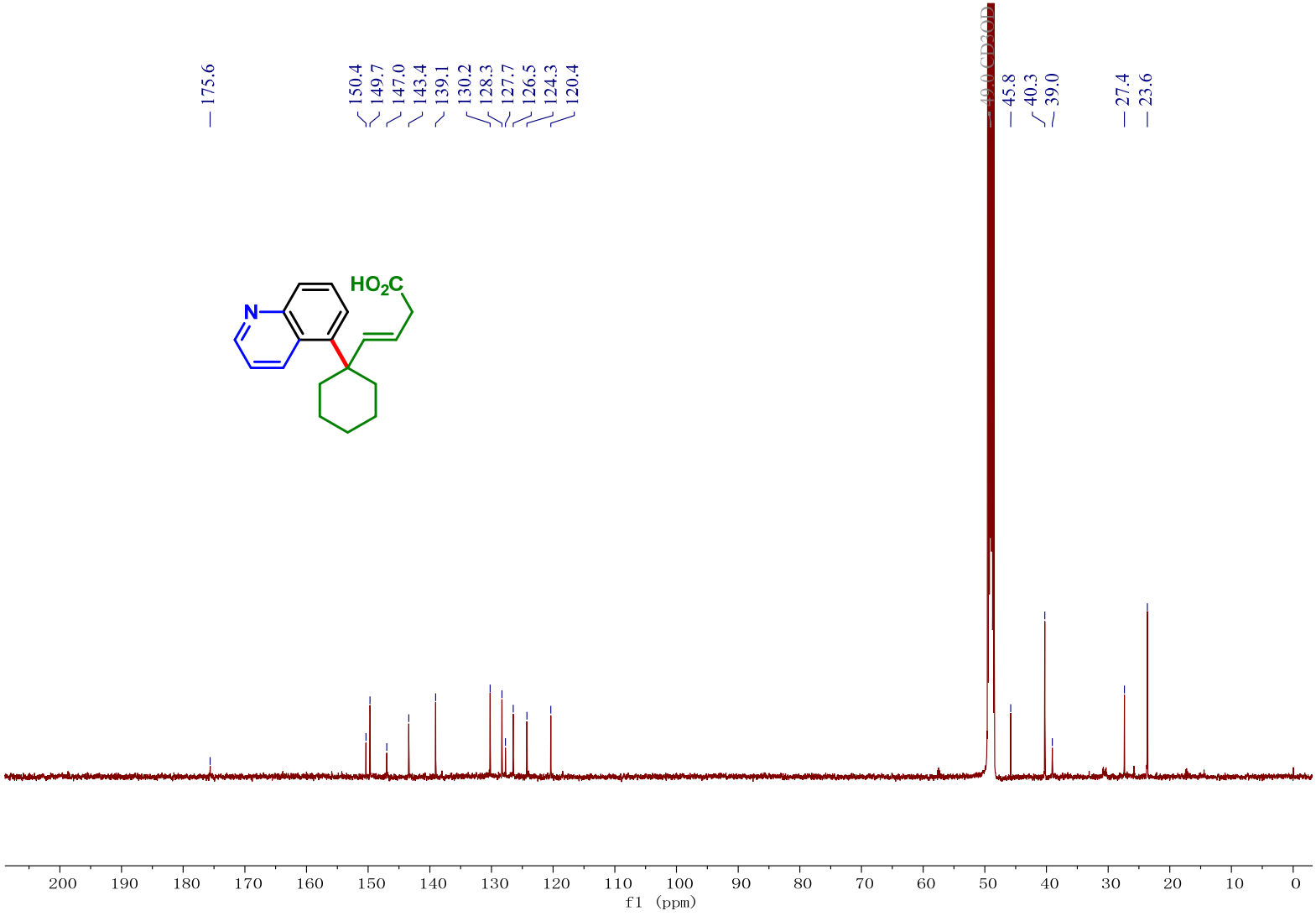
Compound 30 ^{13}C NMR



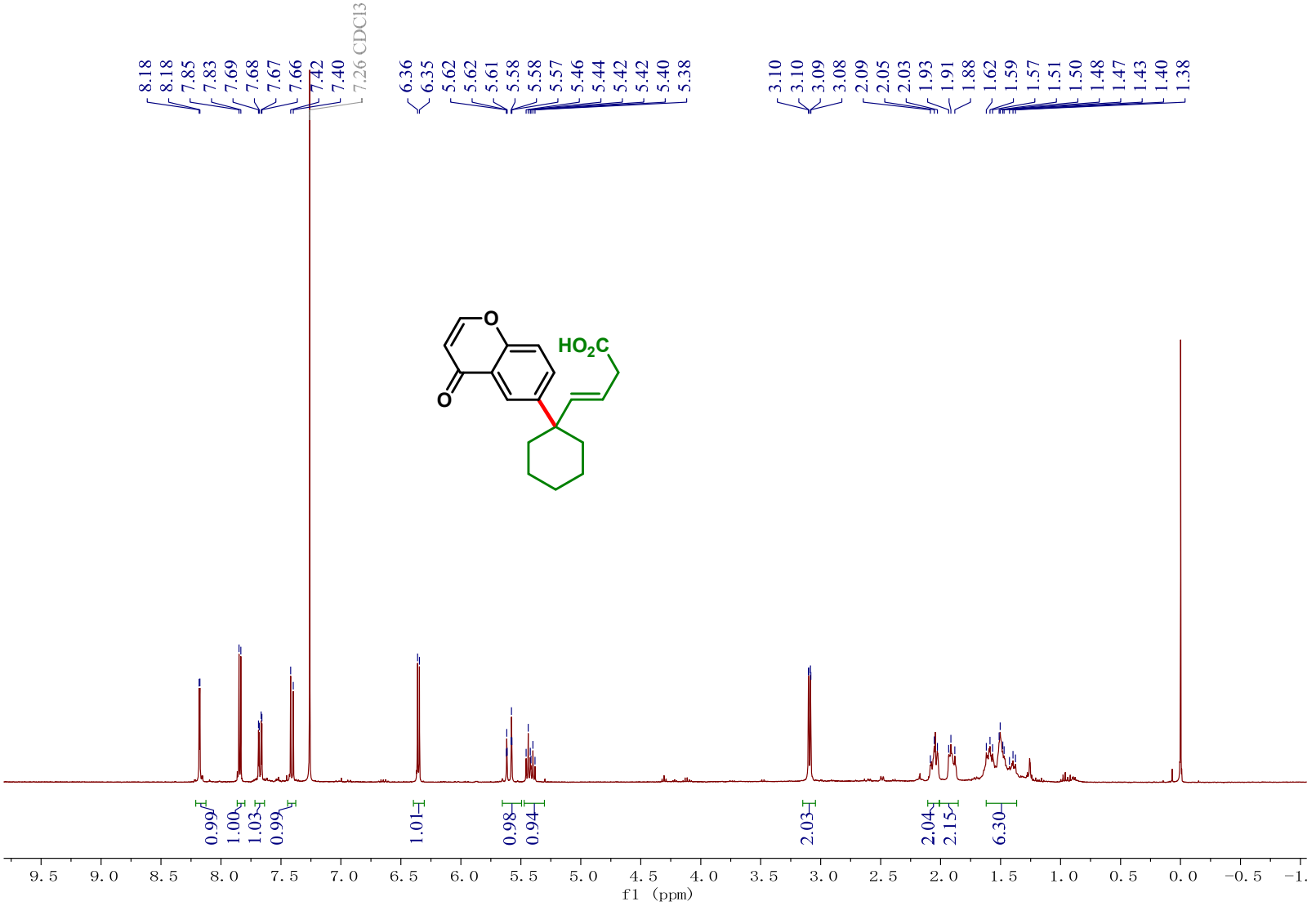
Compound 31 ^{1}H NMR



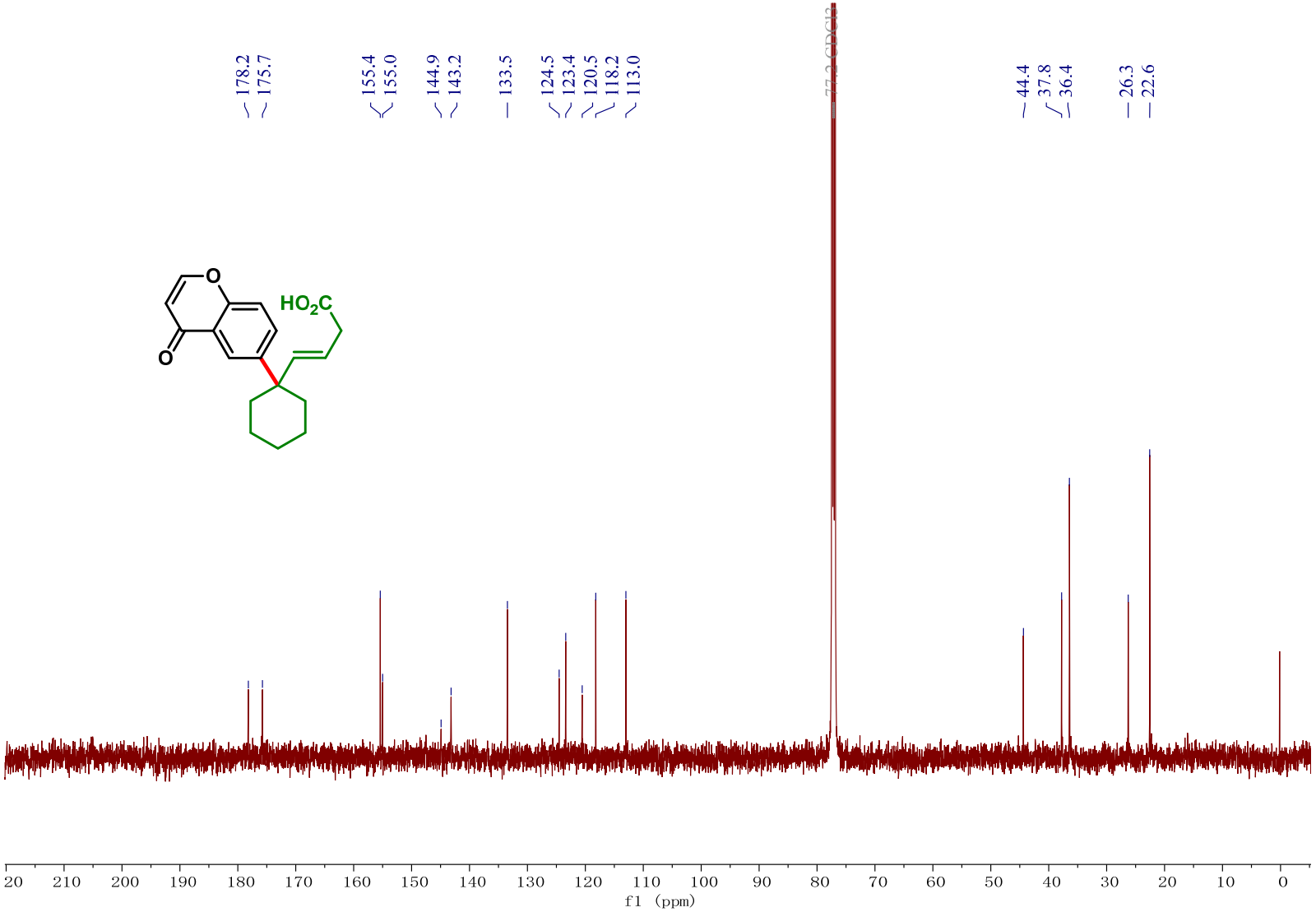
Compound 31 ^{13}C NMR



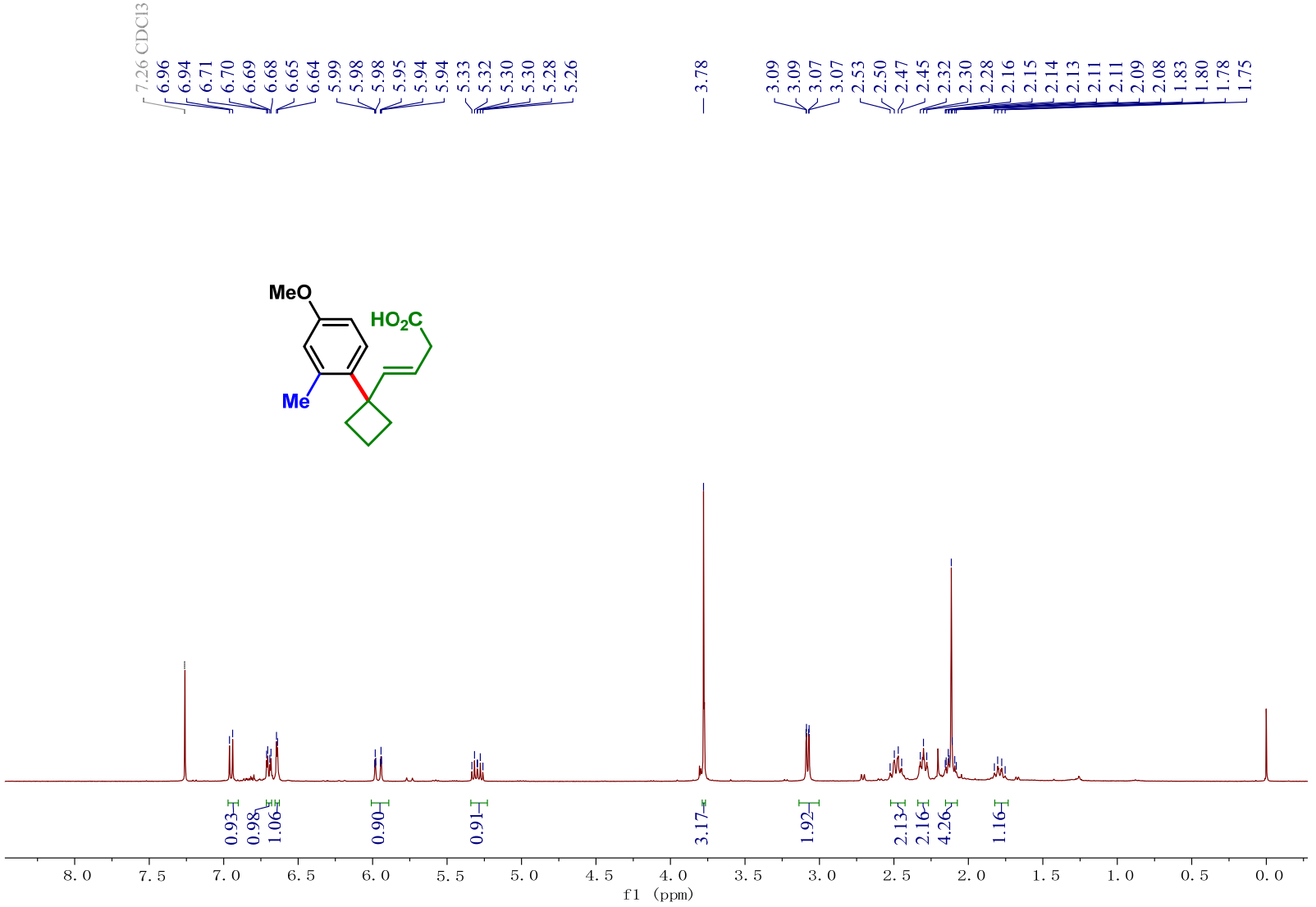
Compound 32 ^{1}H NMR



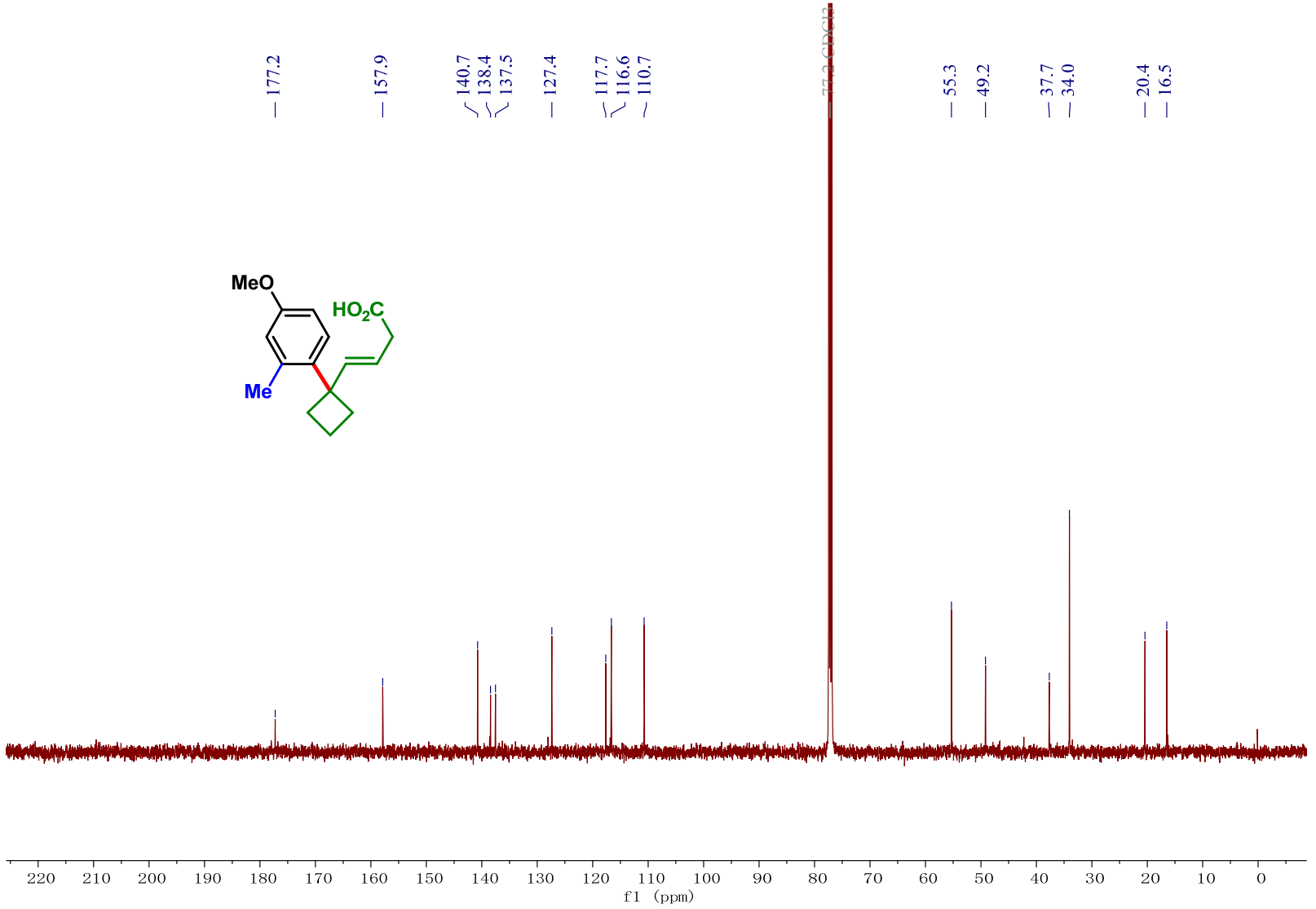
Compound 32 ^{13}C NMR



Compound 33 ^{1}H NMR



Compound 33 ^{13}C NMR



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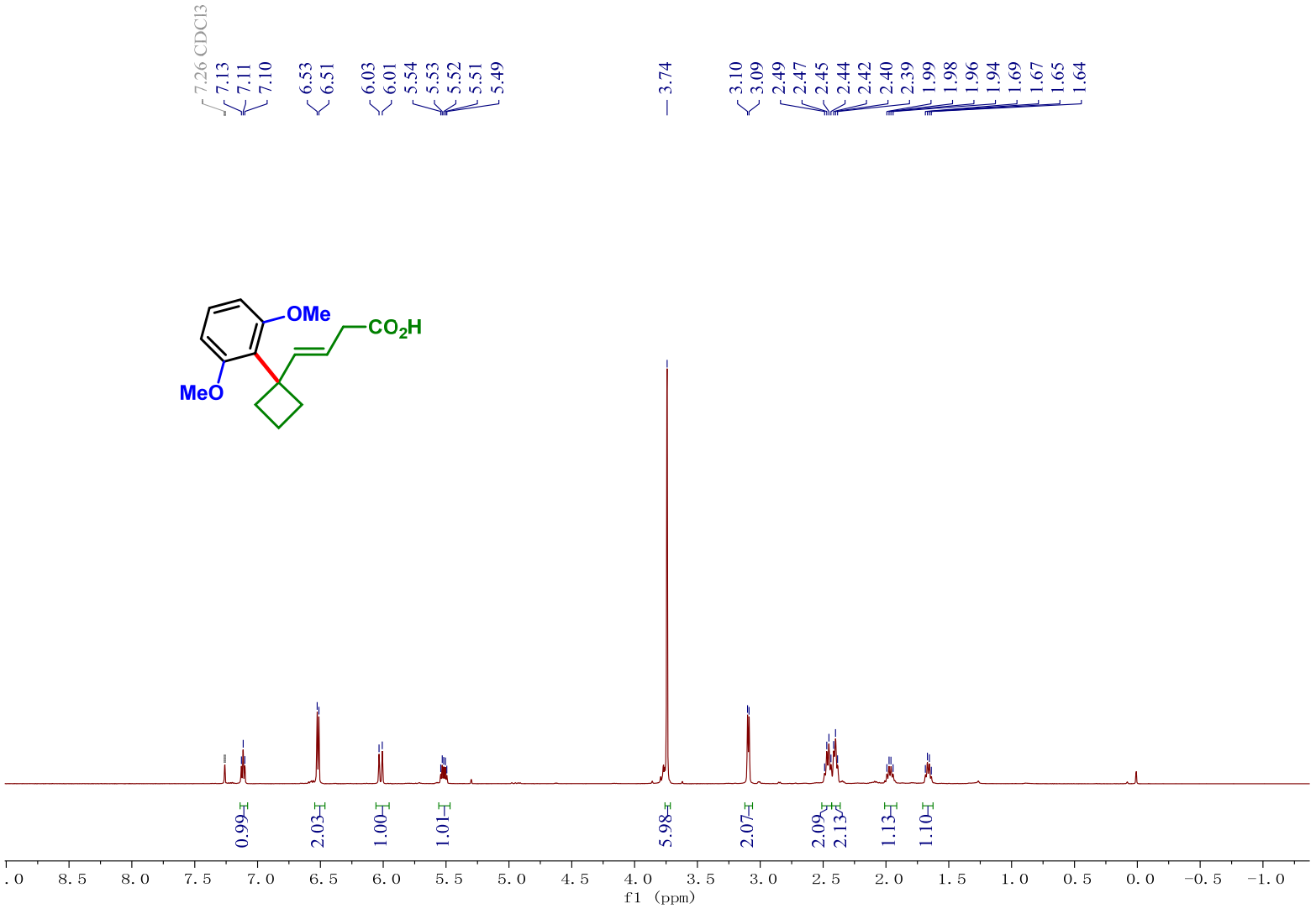
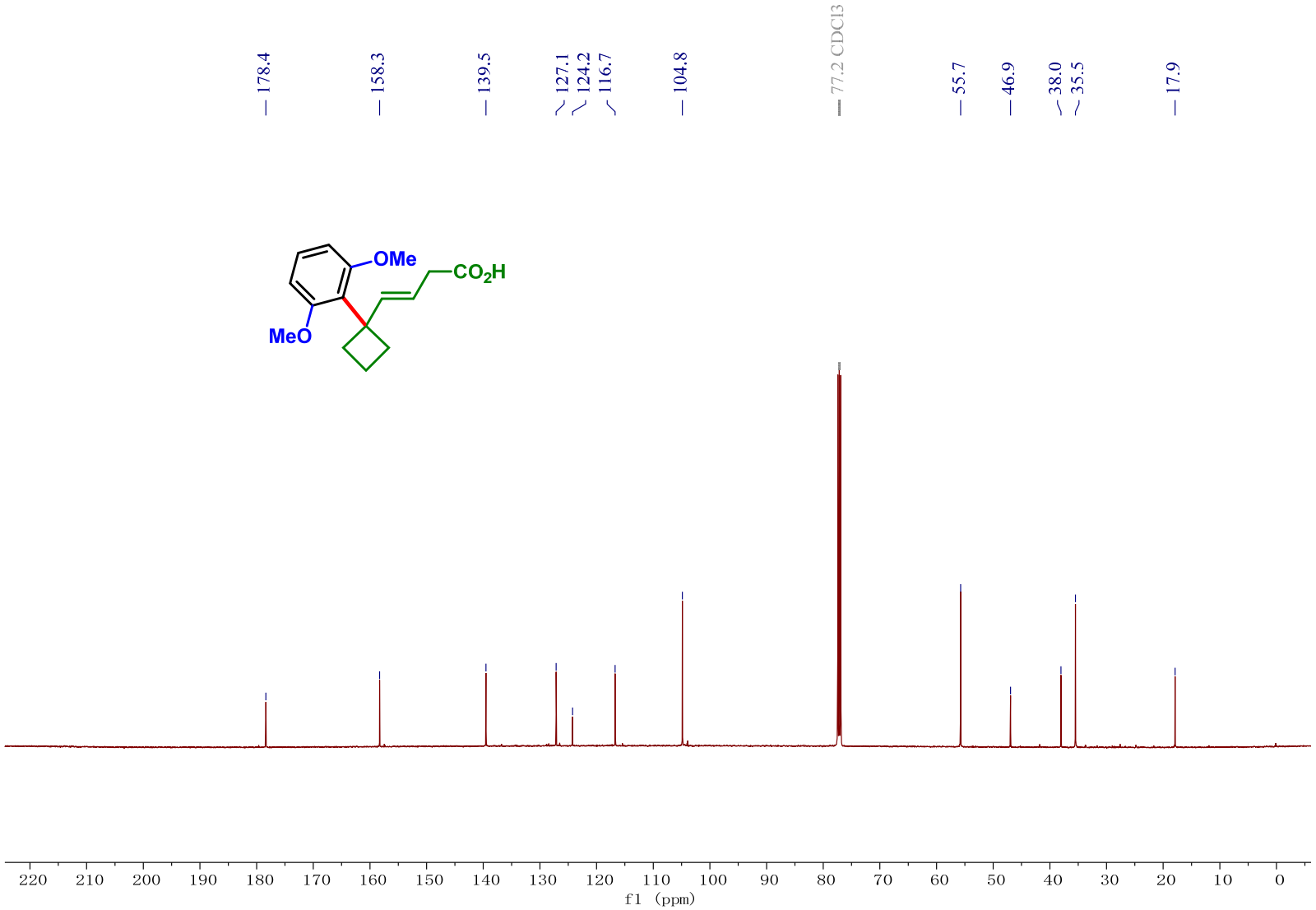


Compound 34 ^{13}C NMR



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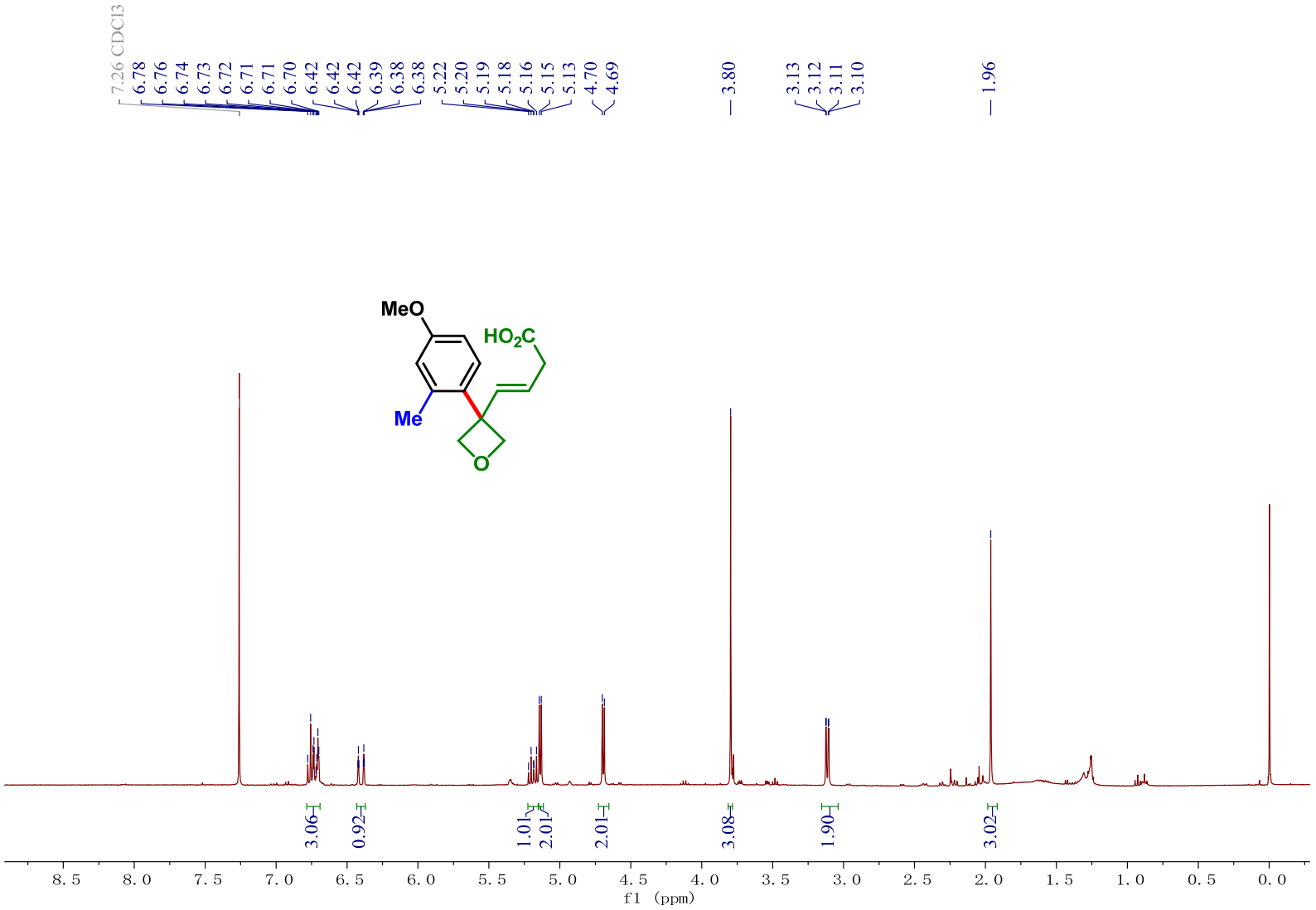
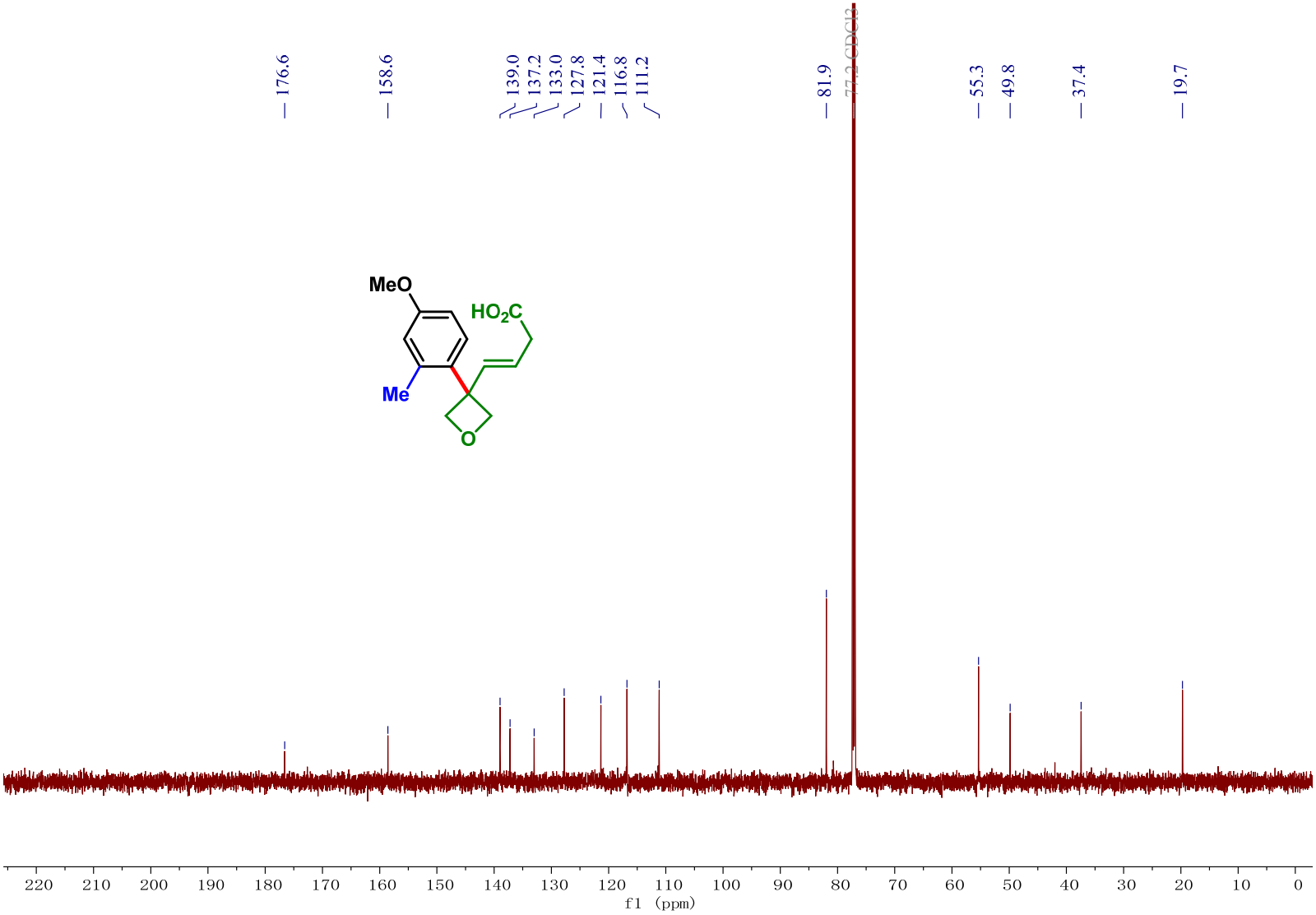


Compound 35 ^{13}C NMR



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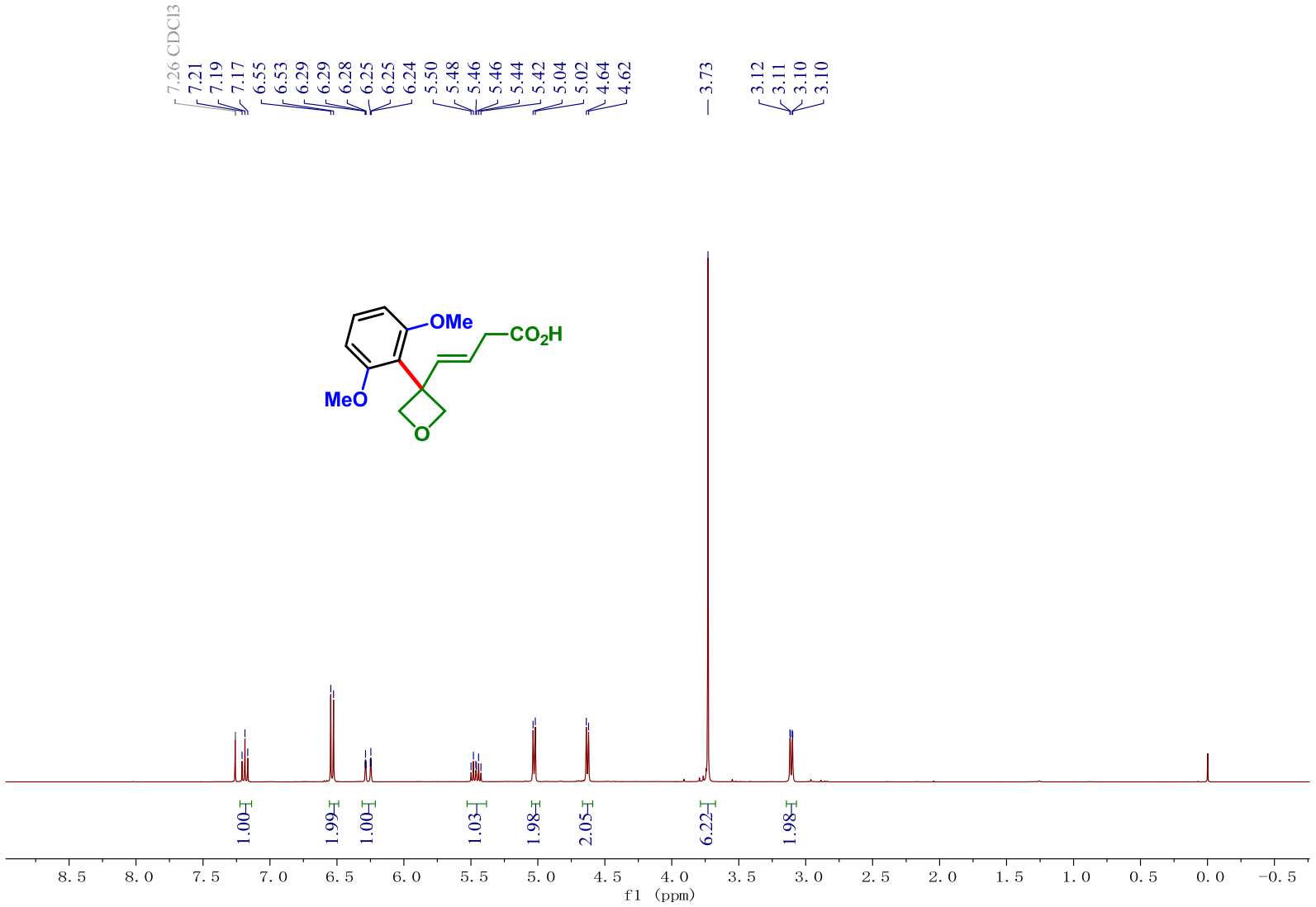
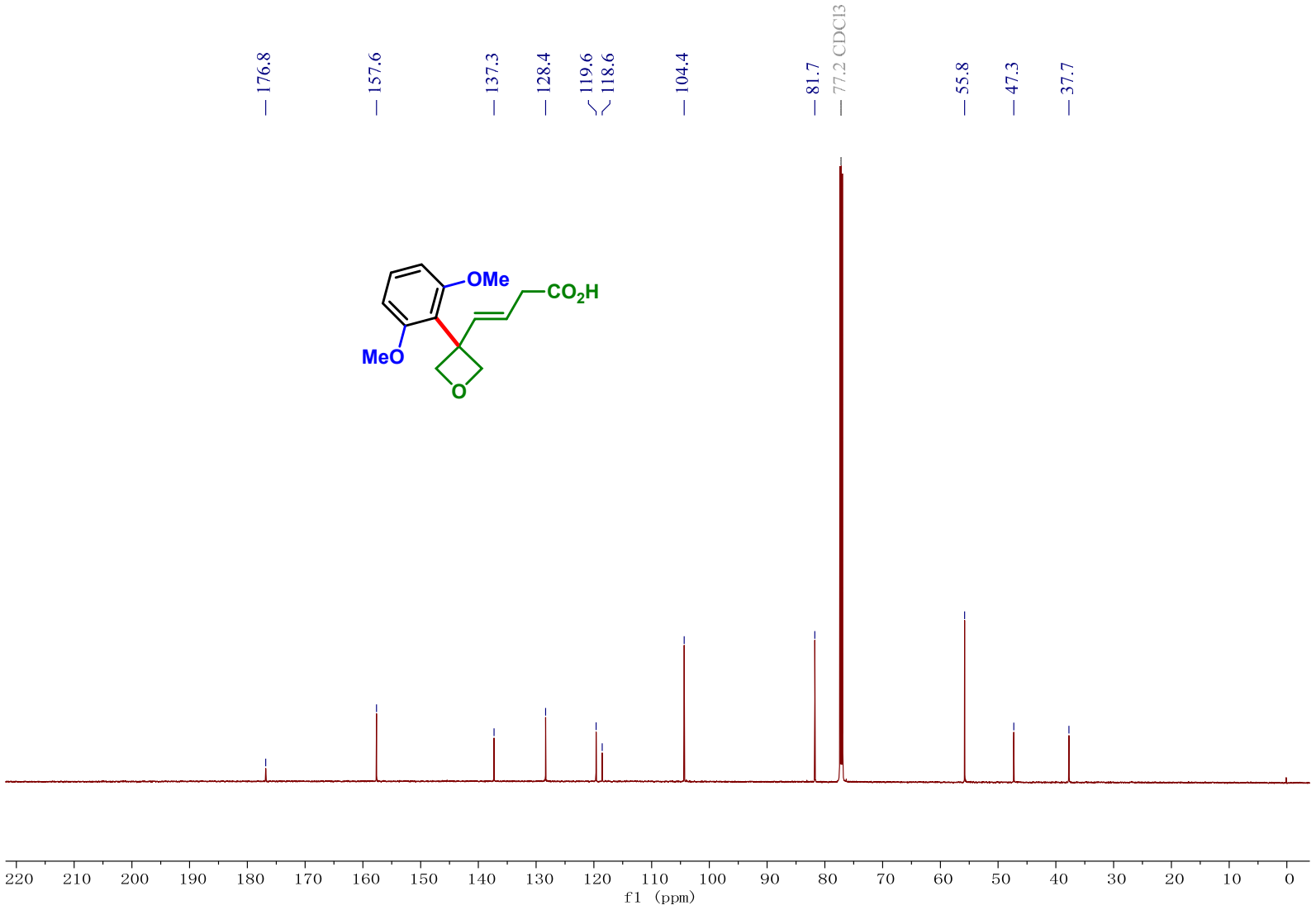
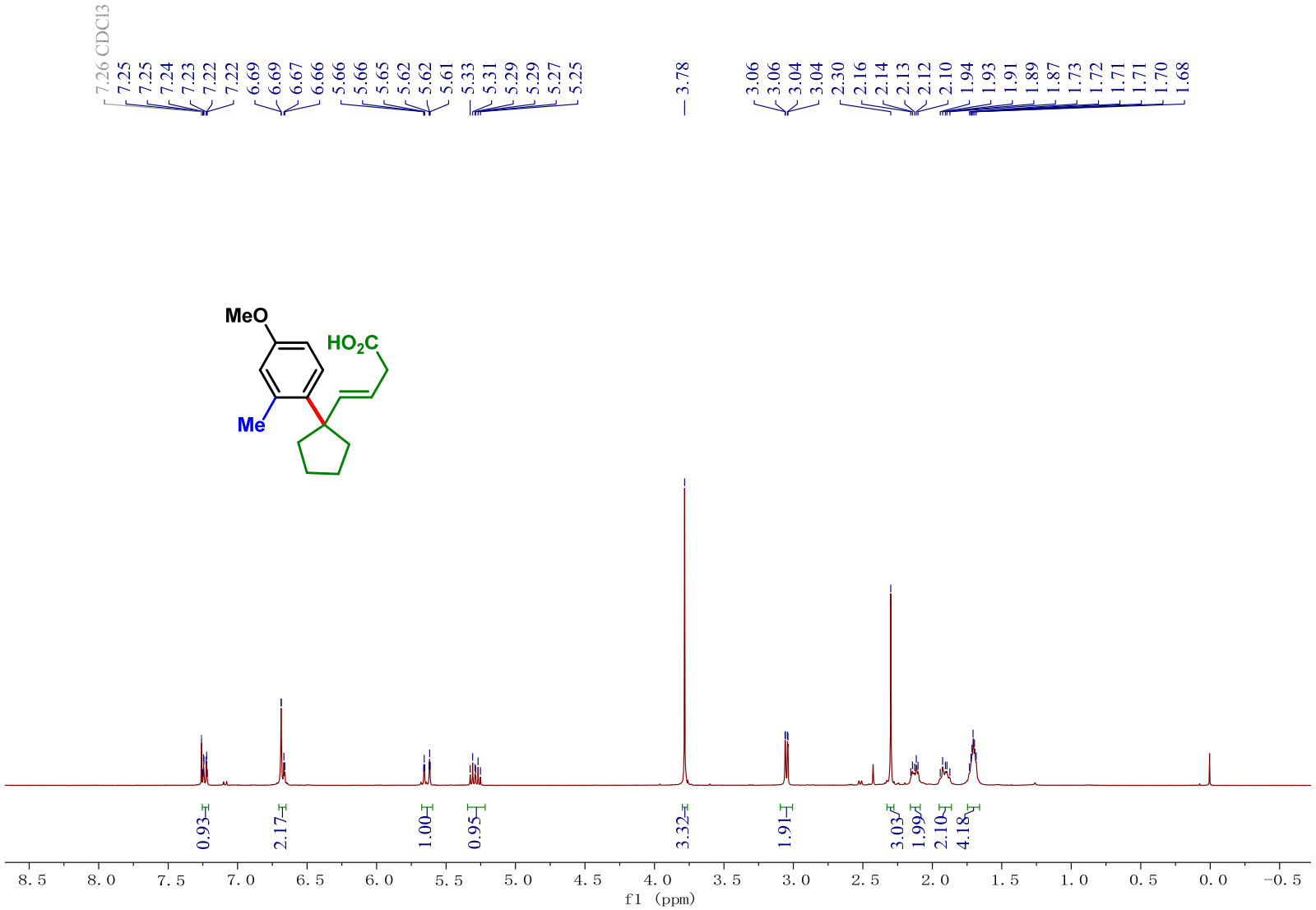


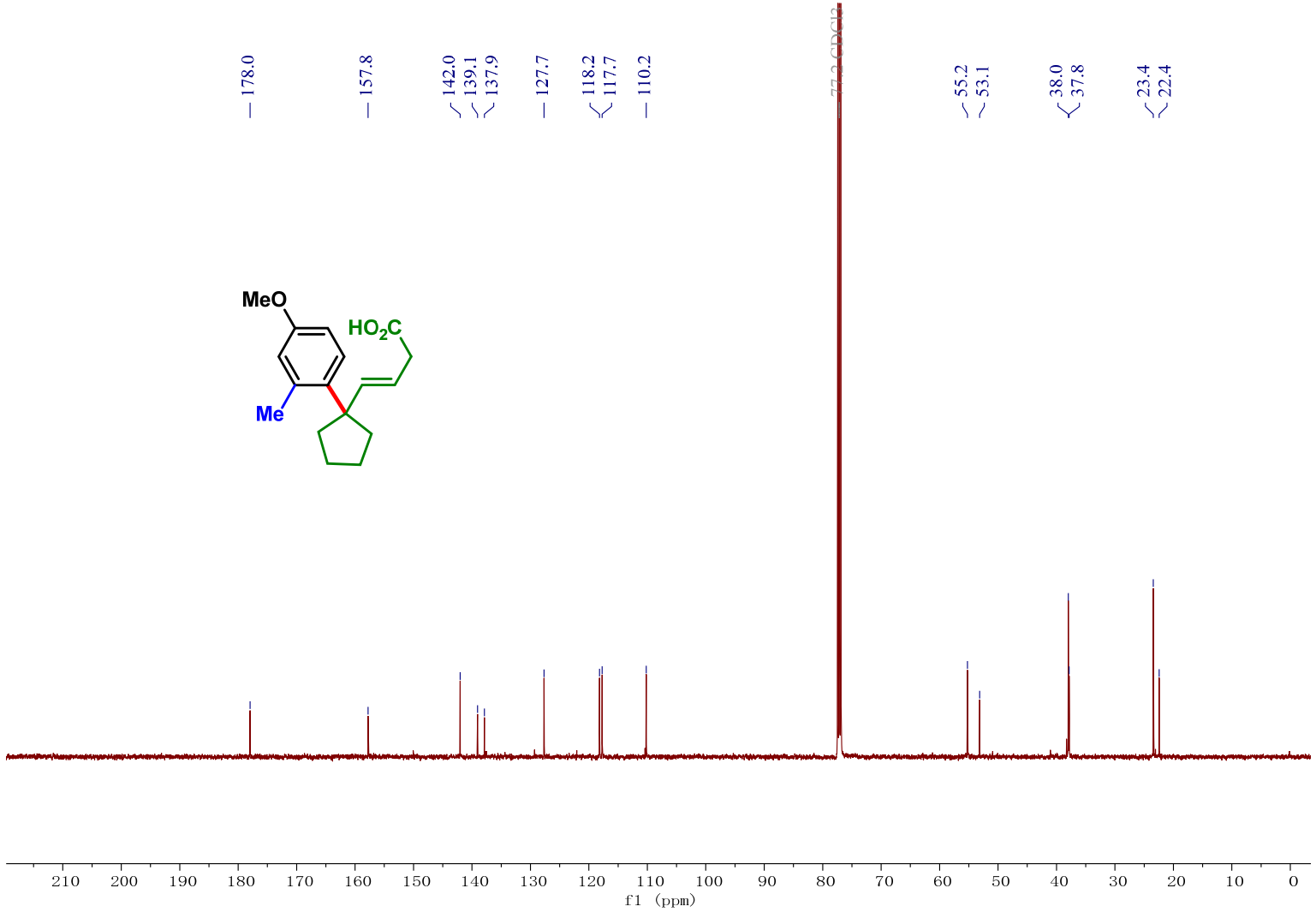
Compound 36 ^{13}C NMR



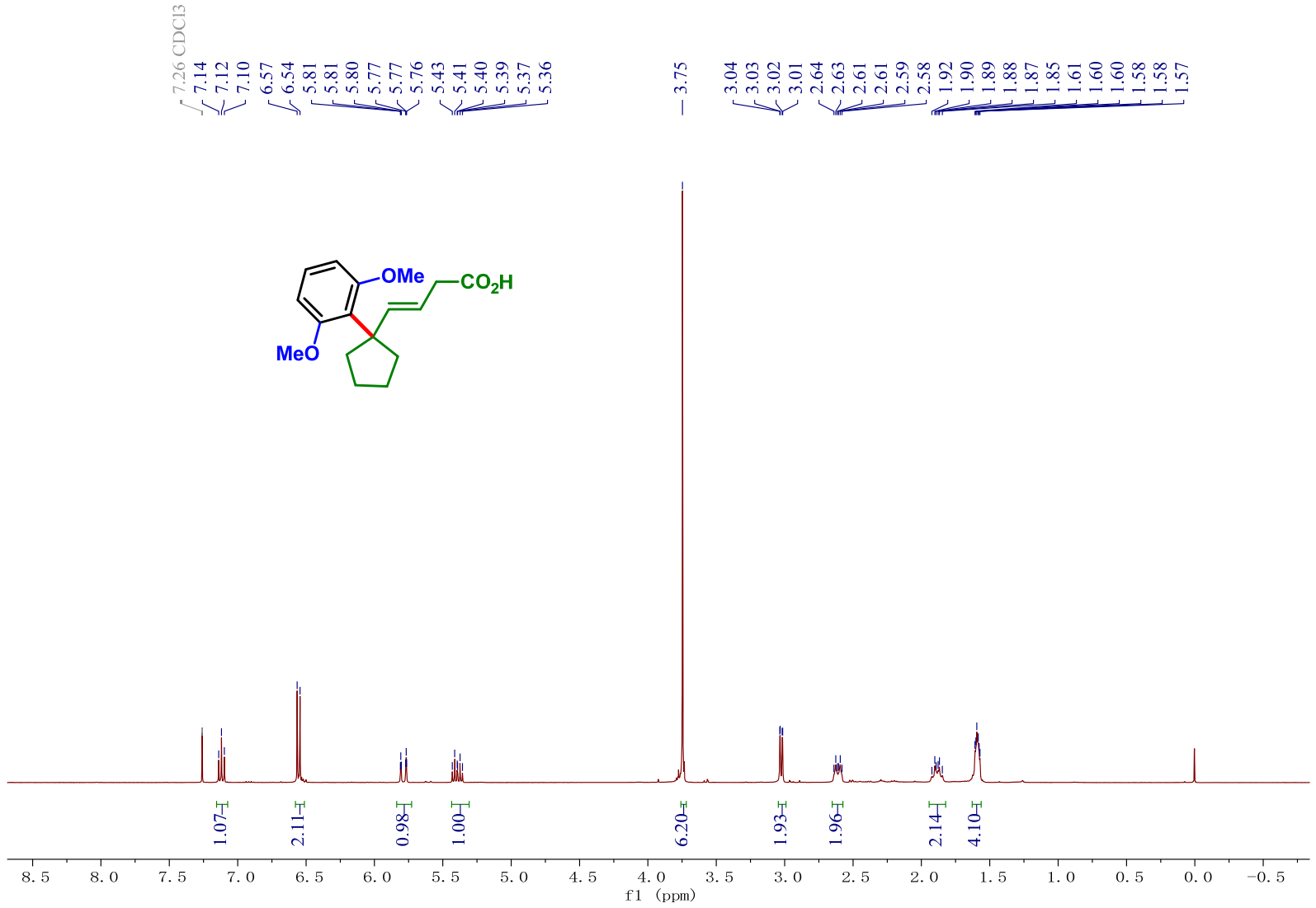
Compound 37 ^{1}H NMR



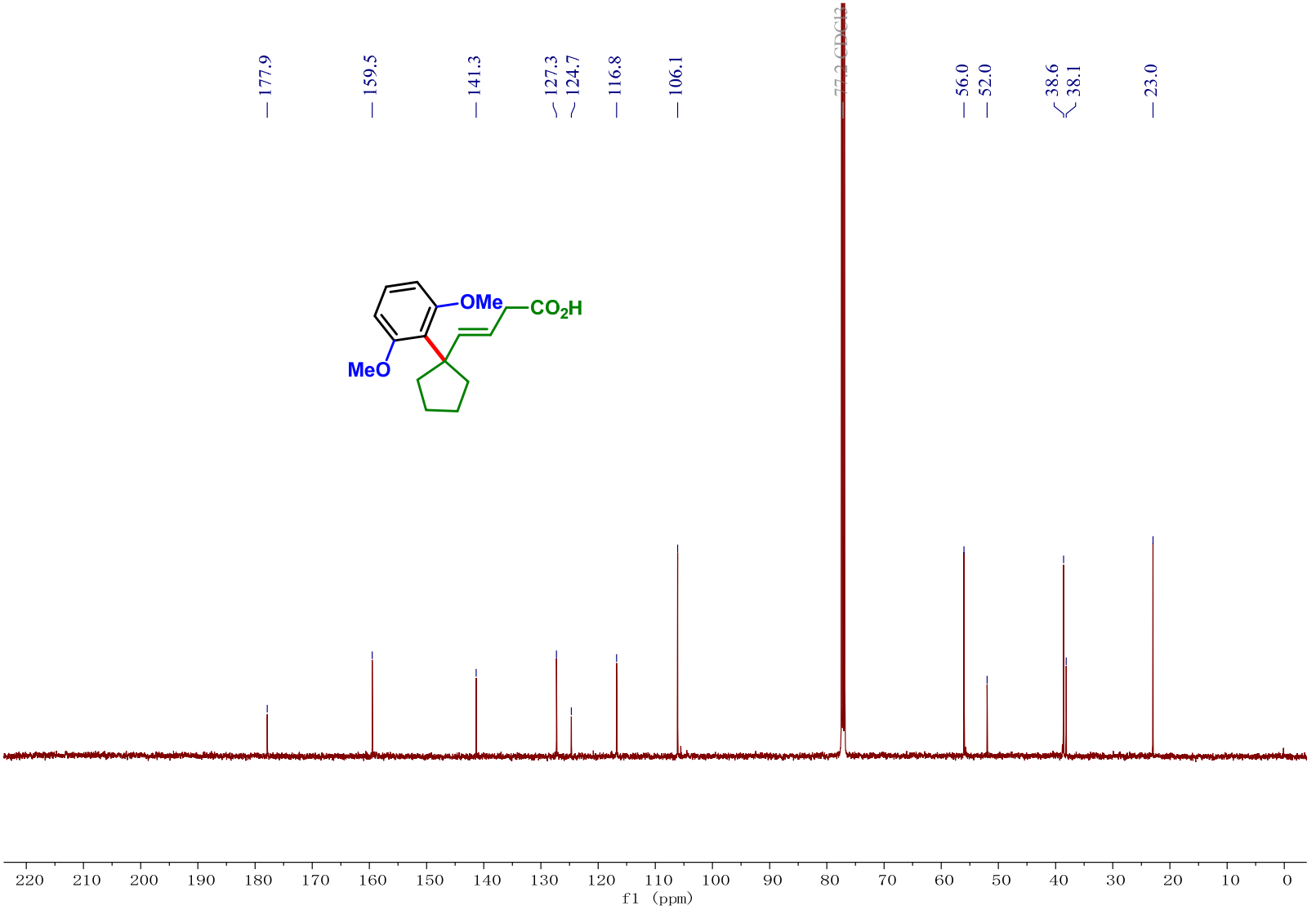
Compound 37 ^{13}C NMR



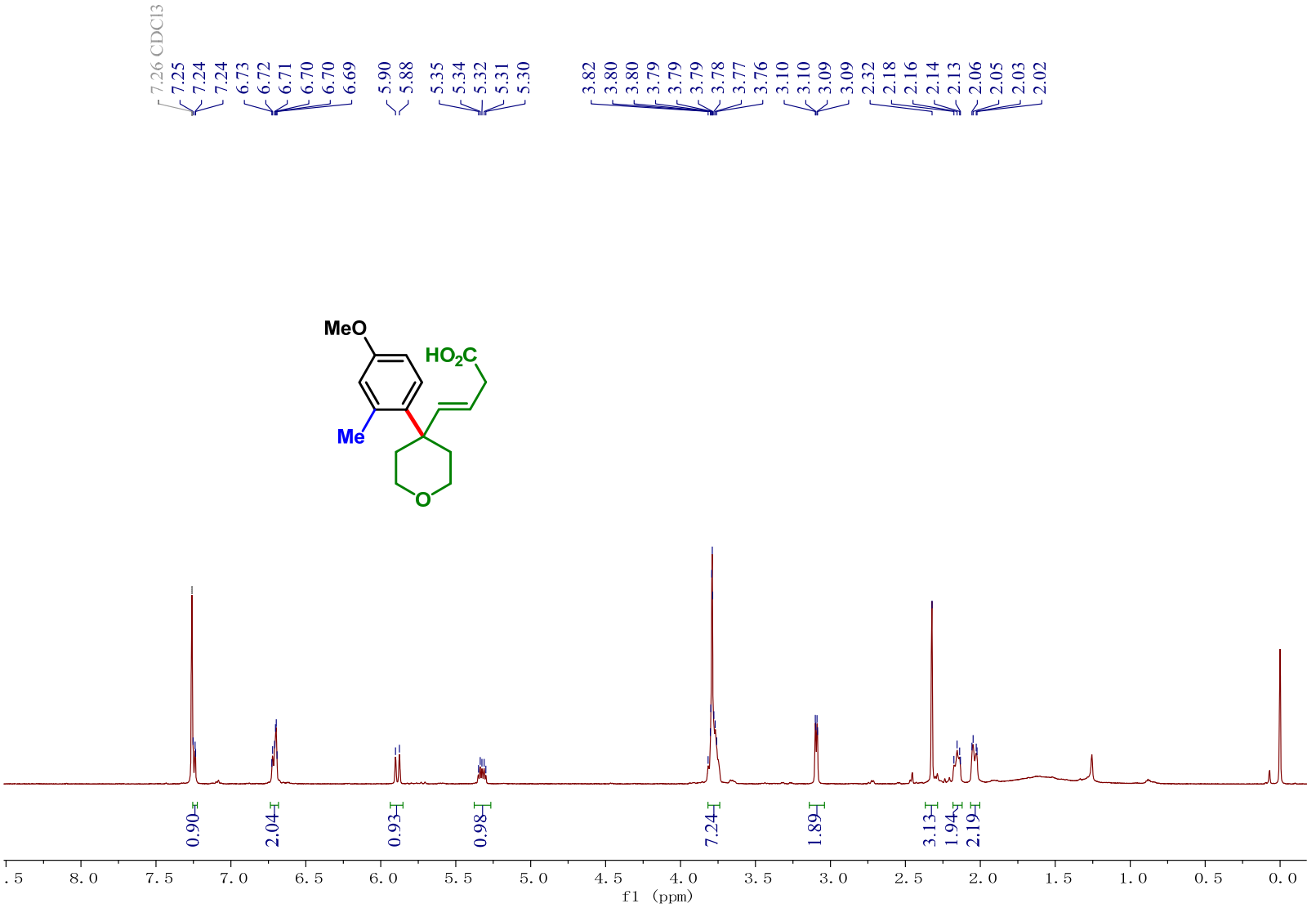
Compound 38 ^{1}H NMR



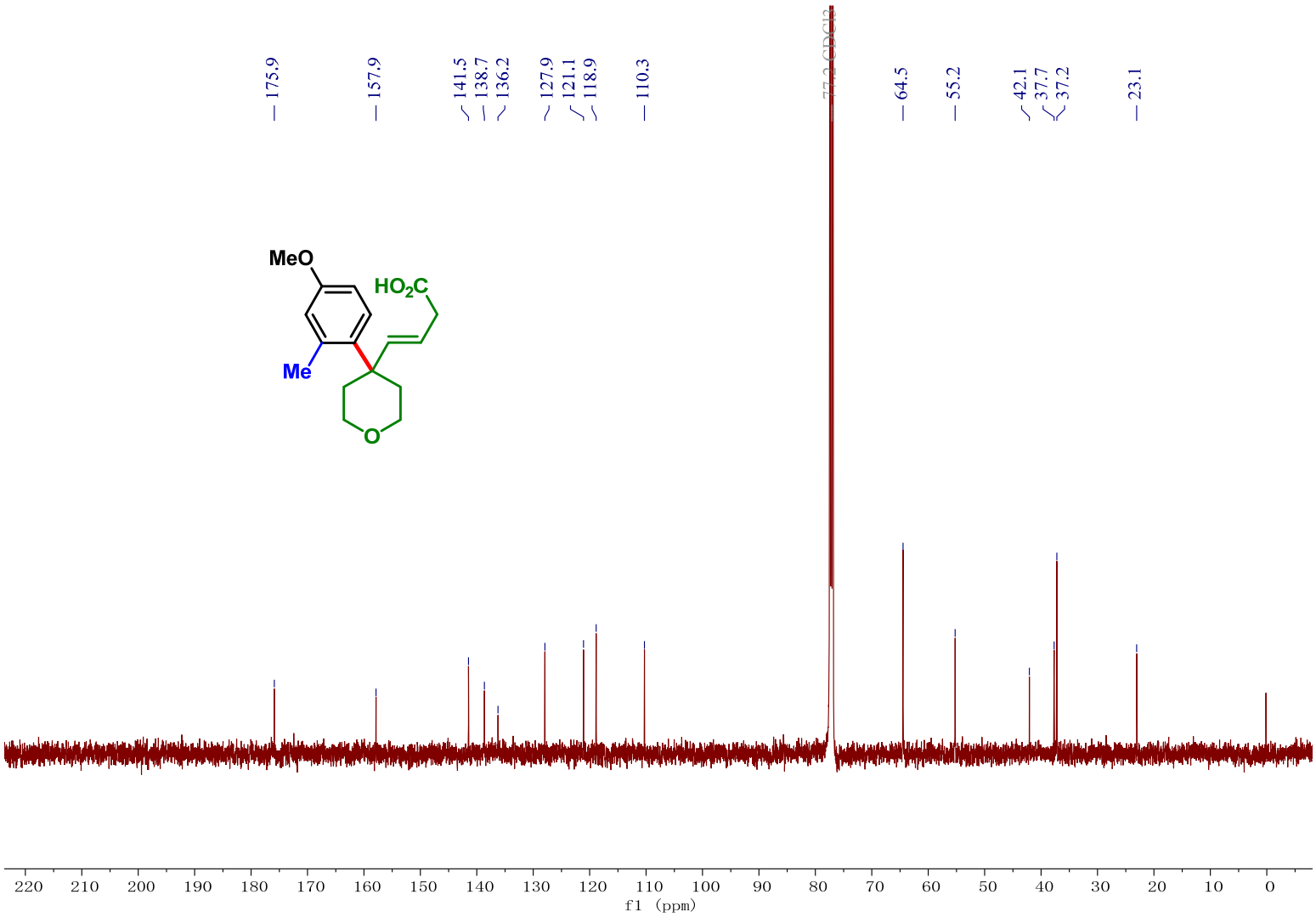
Compound 38 ^{13}C NMR



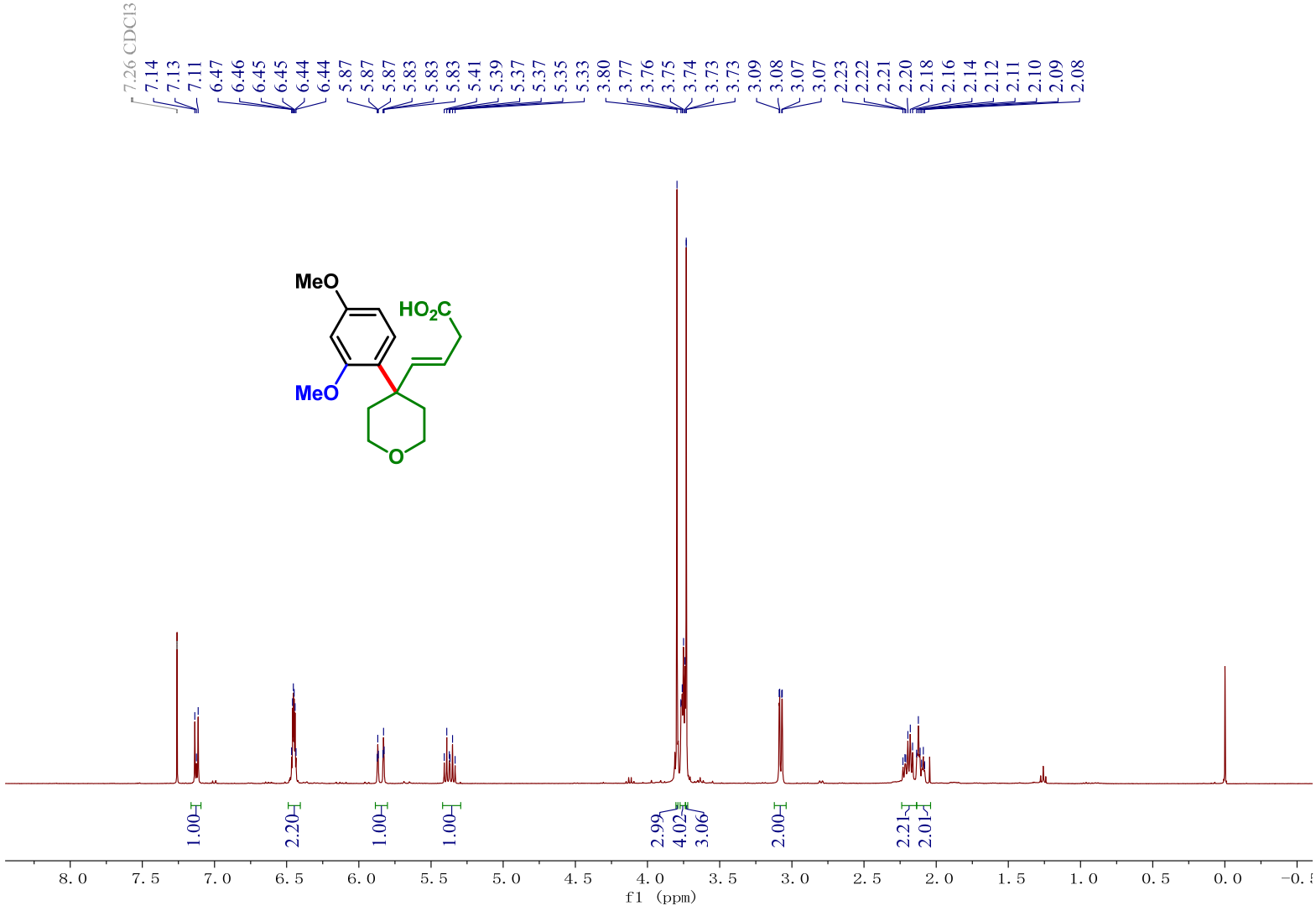
Compound 39 ^{1}H NMR



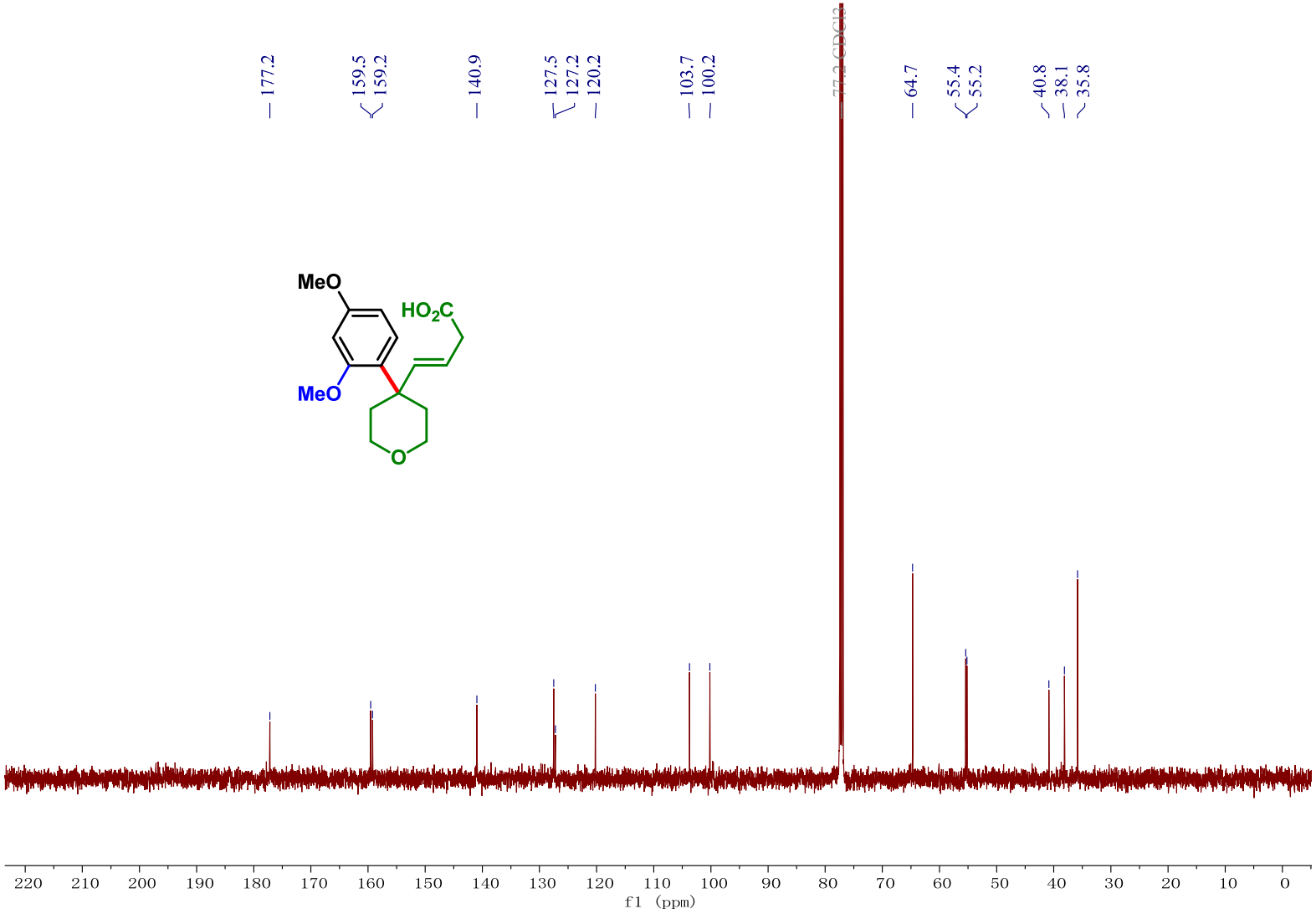
Compound 39 ^{13}C NMR



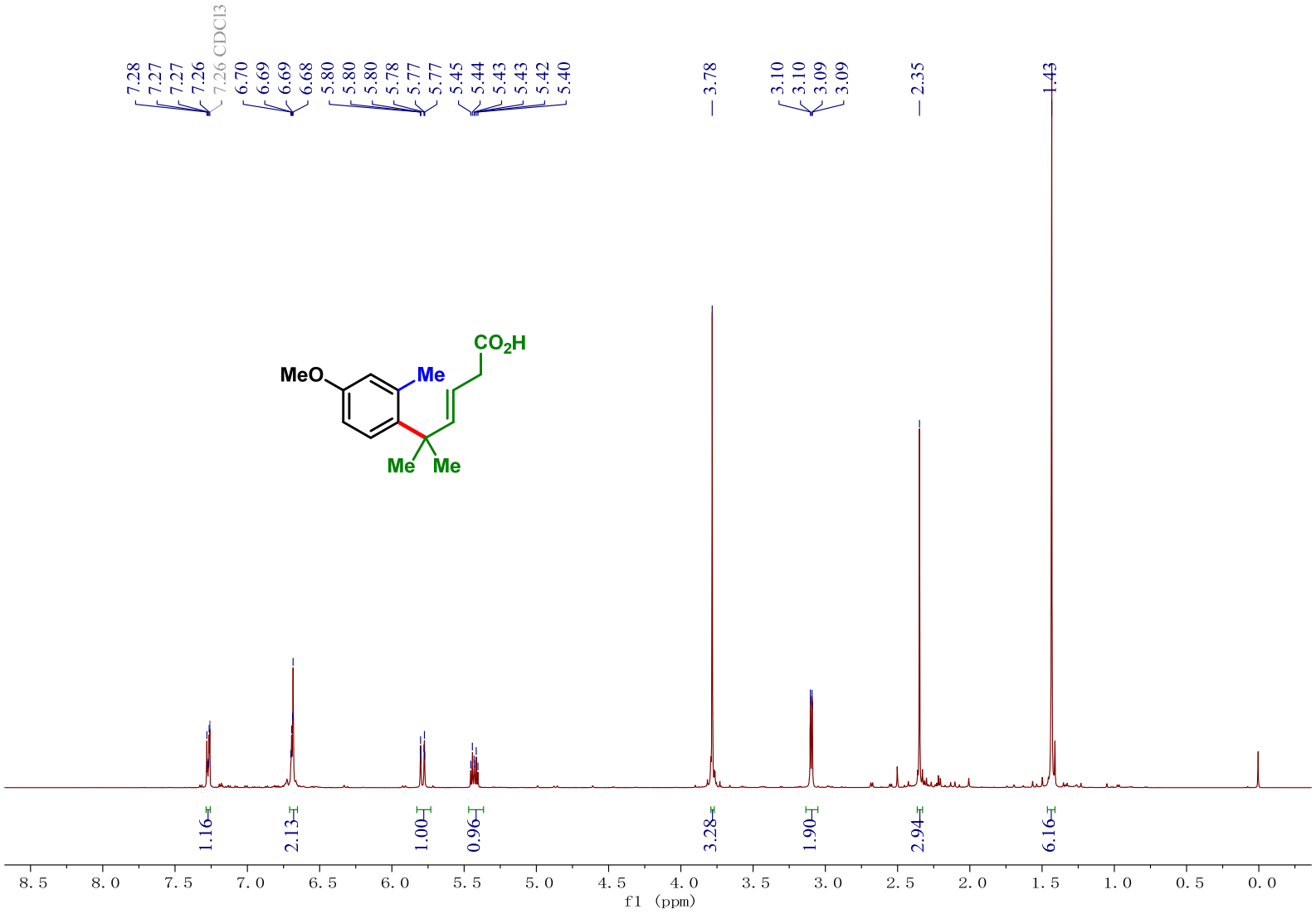
Compound 40 ^{1}H NMR



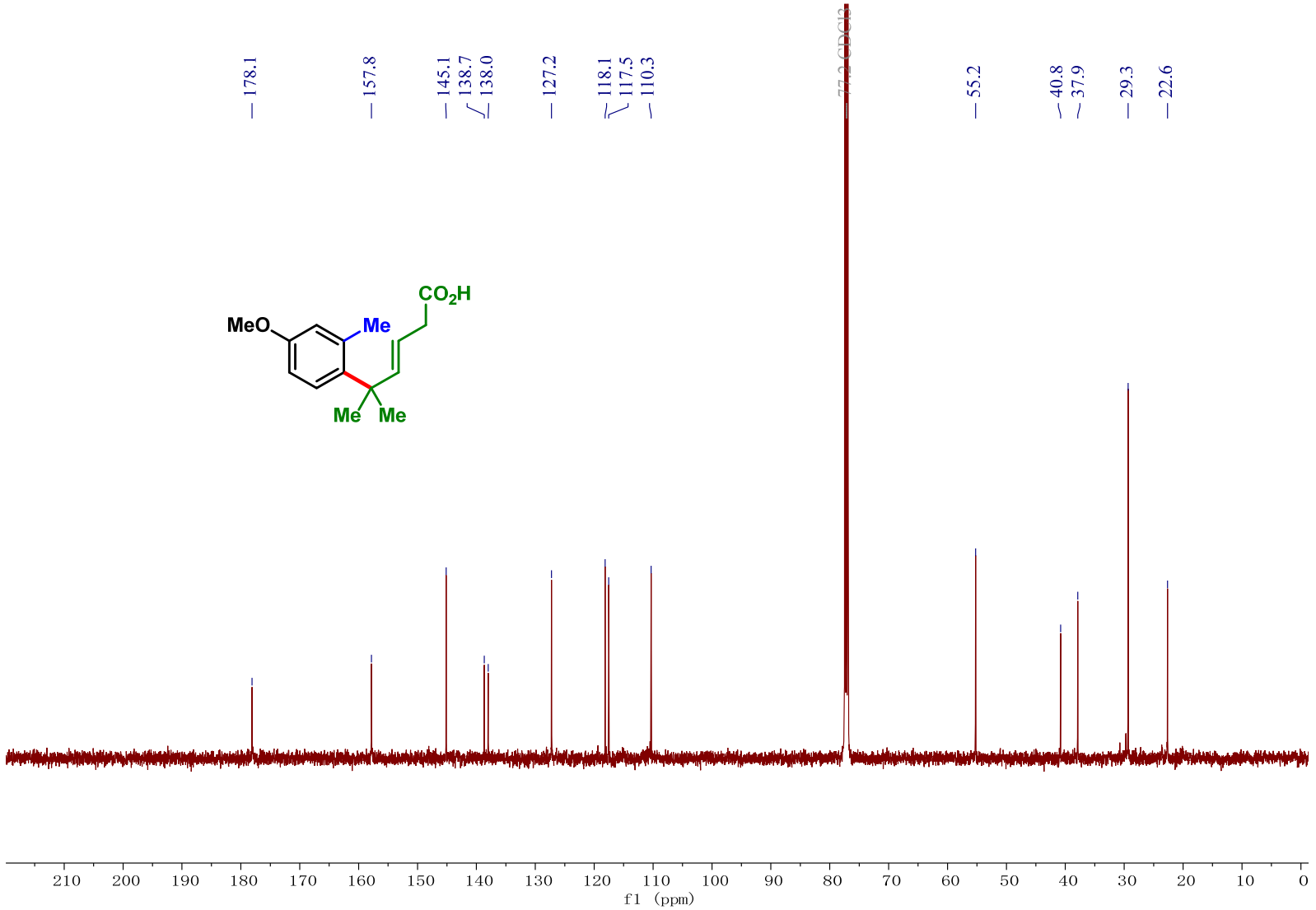
Compound 40 ^{13}C NMR



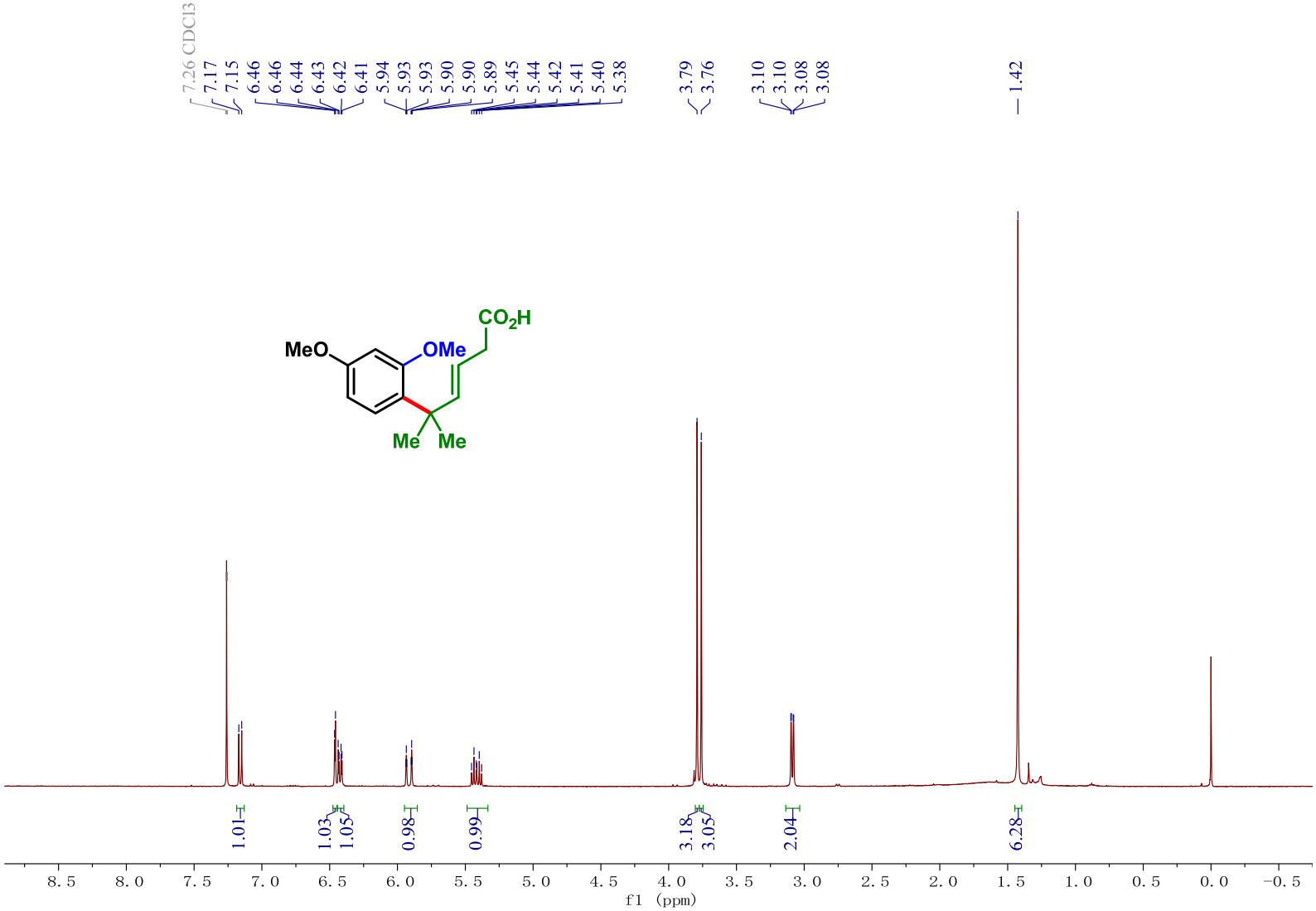
Compound 41 ^{1}H NMR



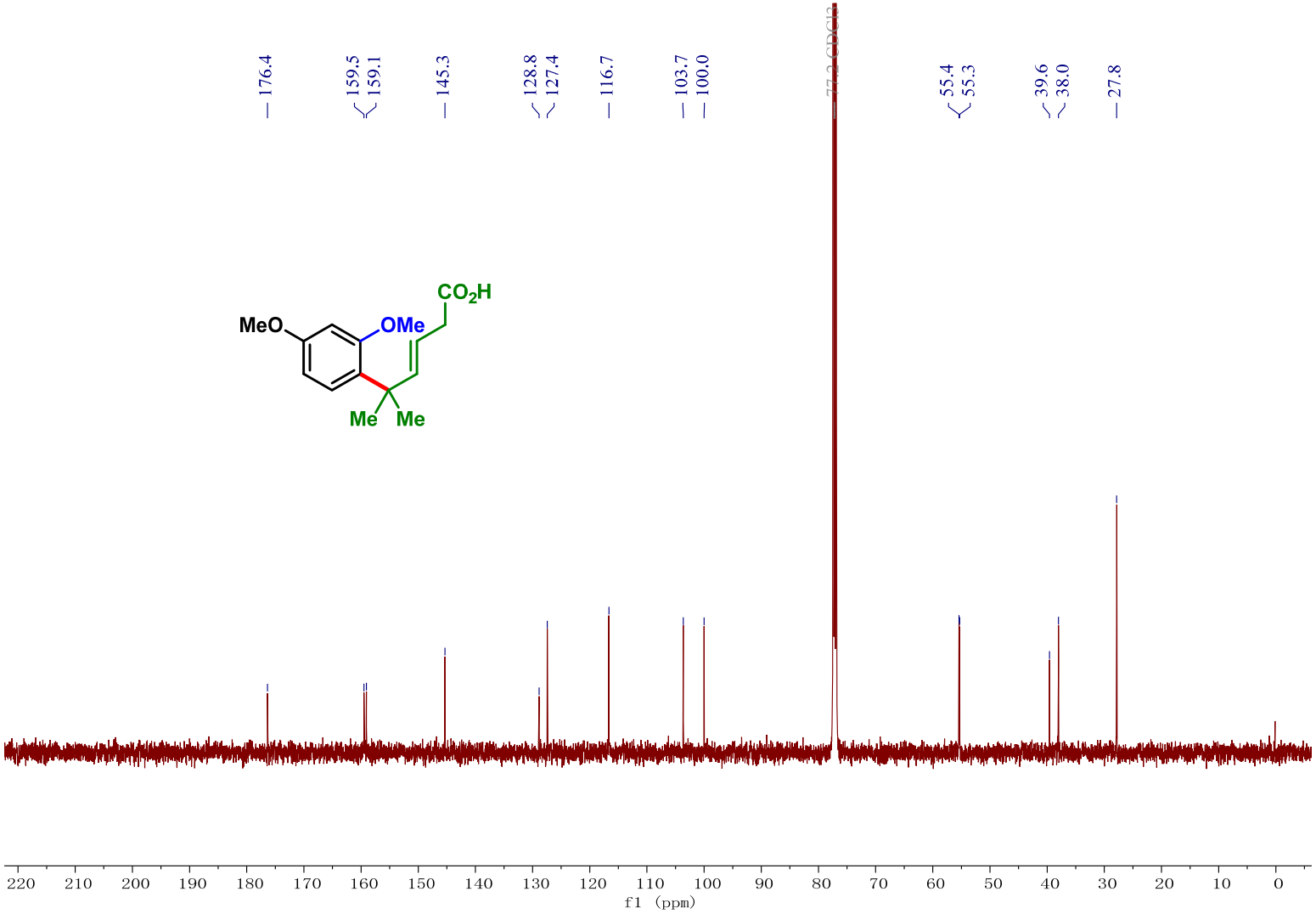
Compound 41 ^{13}C NMR



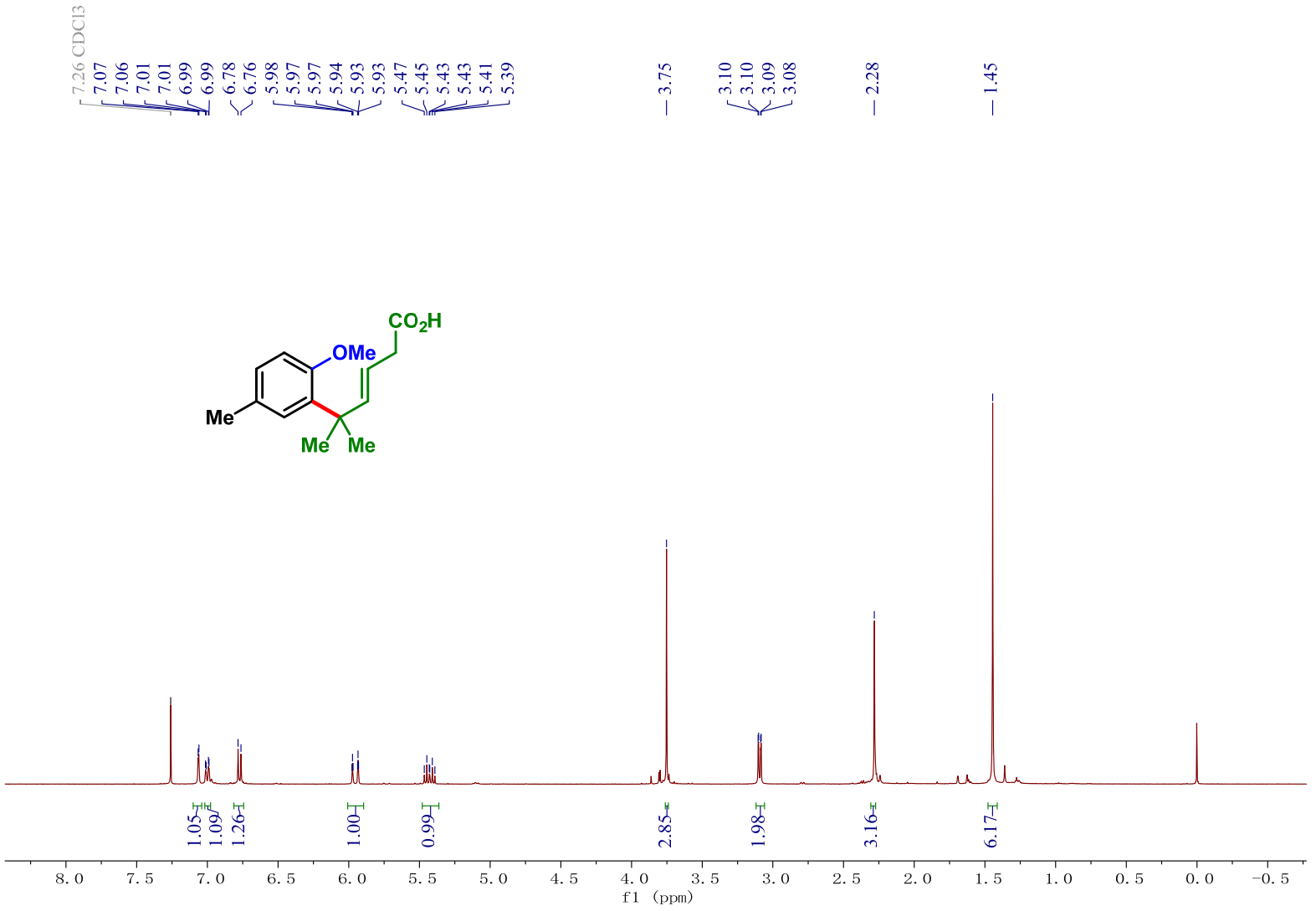
Compound 42 ^{1}H NMR



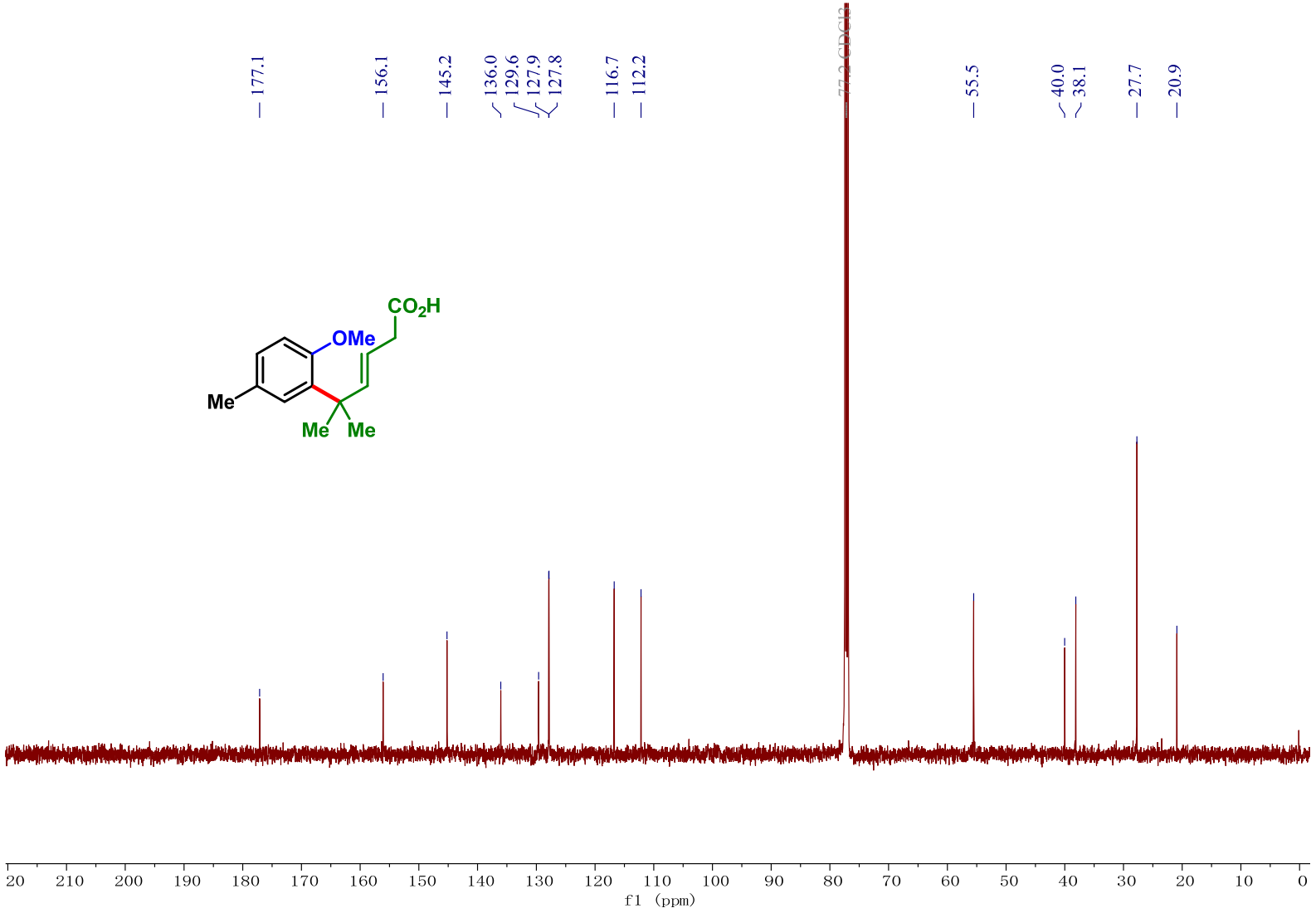
Compound 42 ^{13}C NMR



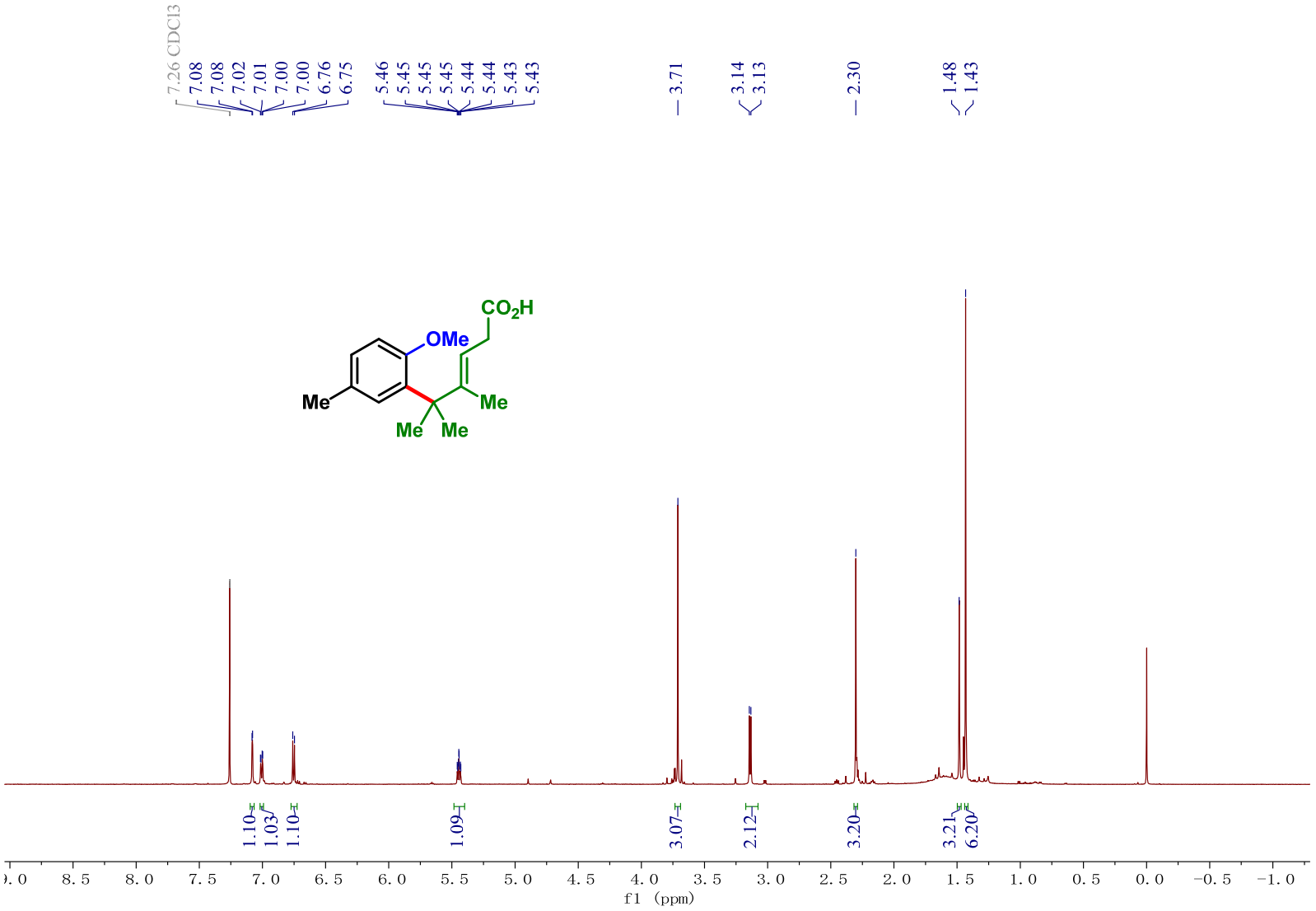
Compound 43 ^{1}H NMR



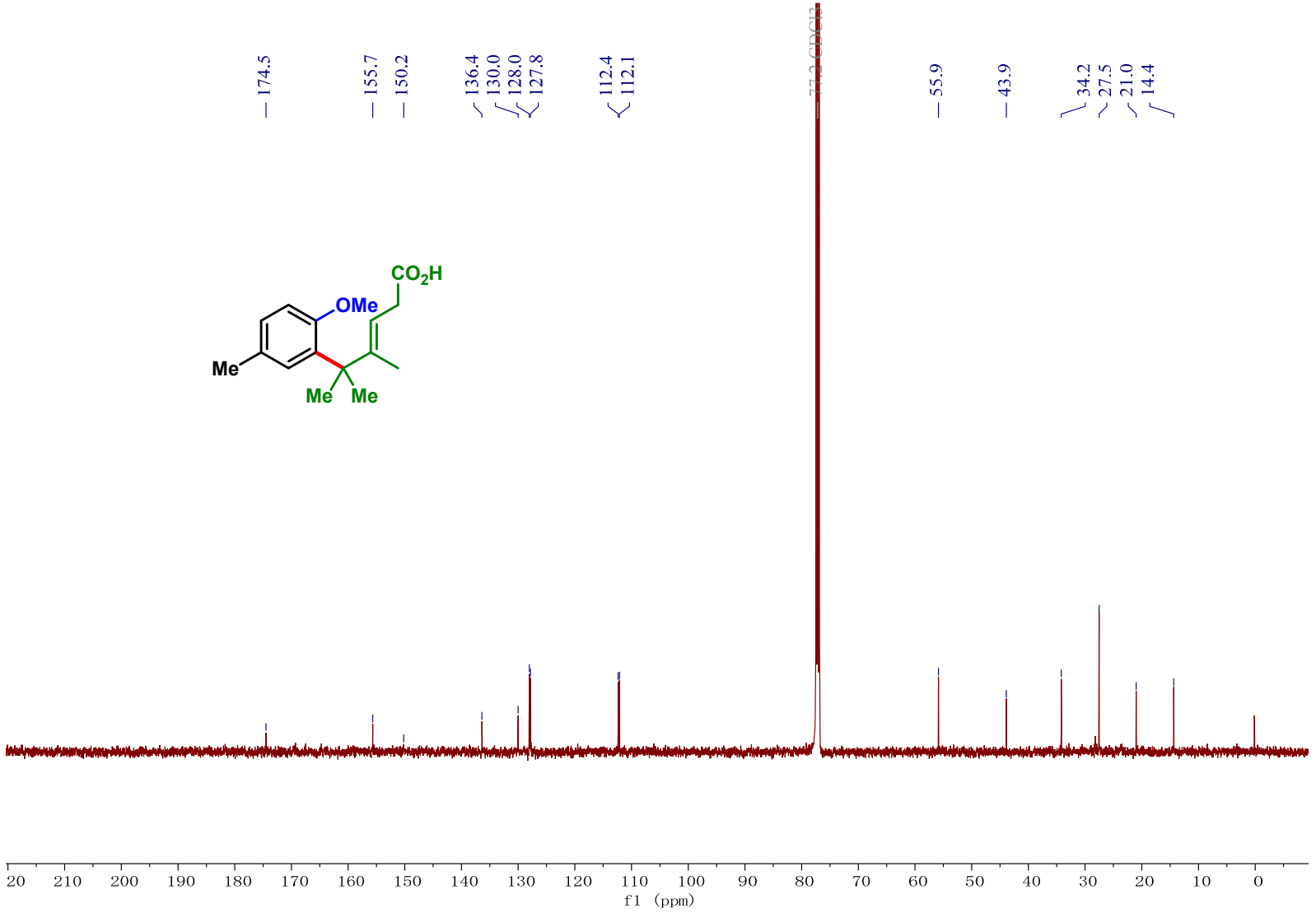
Compound 43 ^{13}C NMR



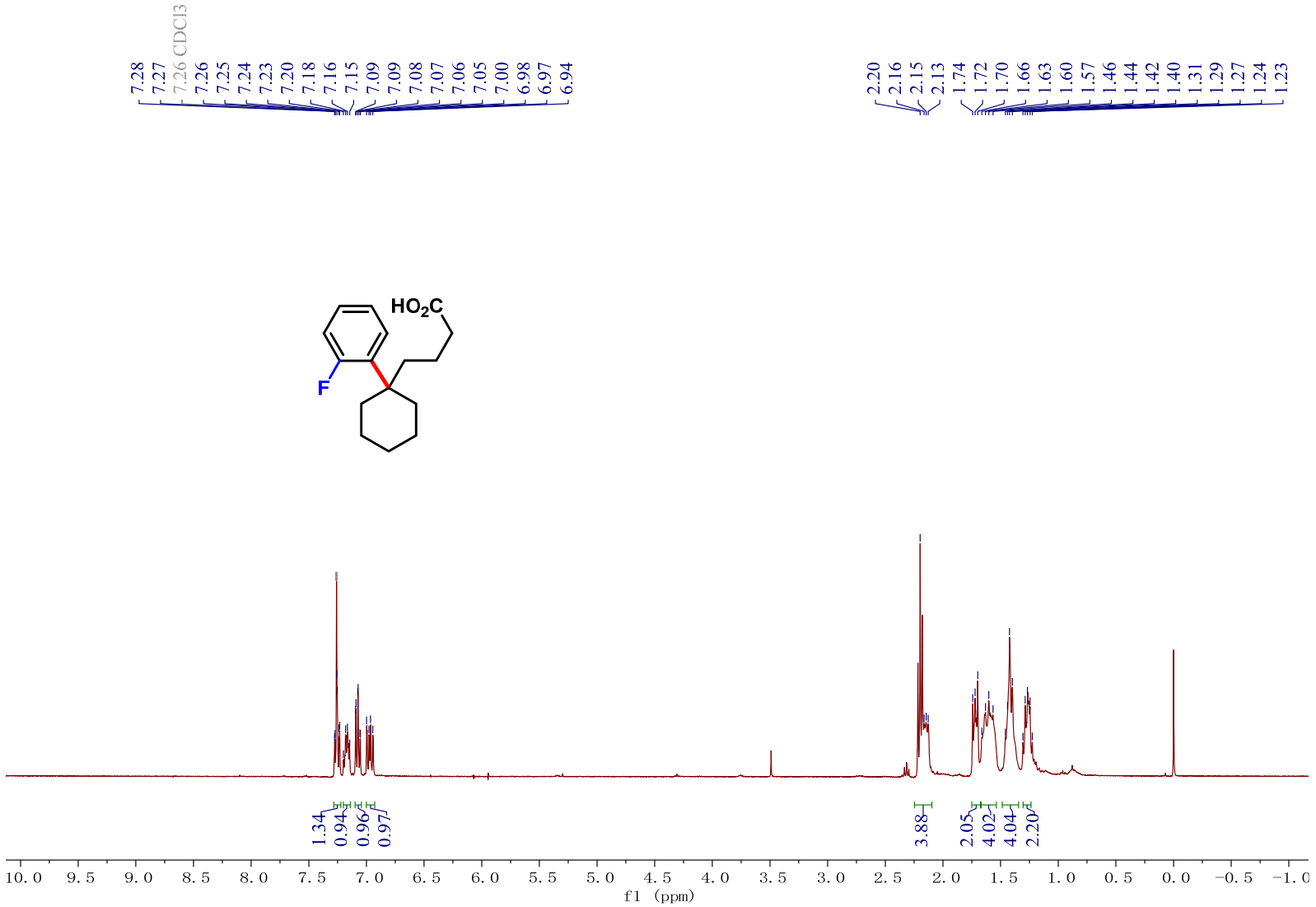
Compound 45 ^{1}H NMR



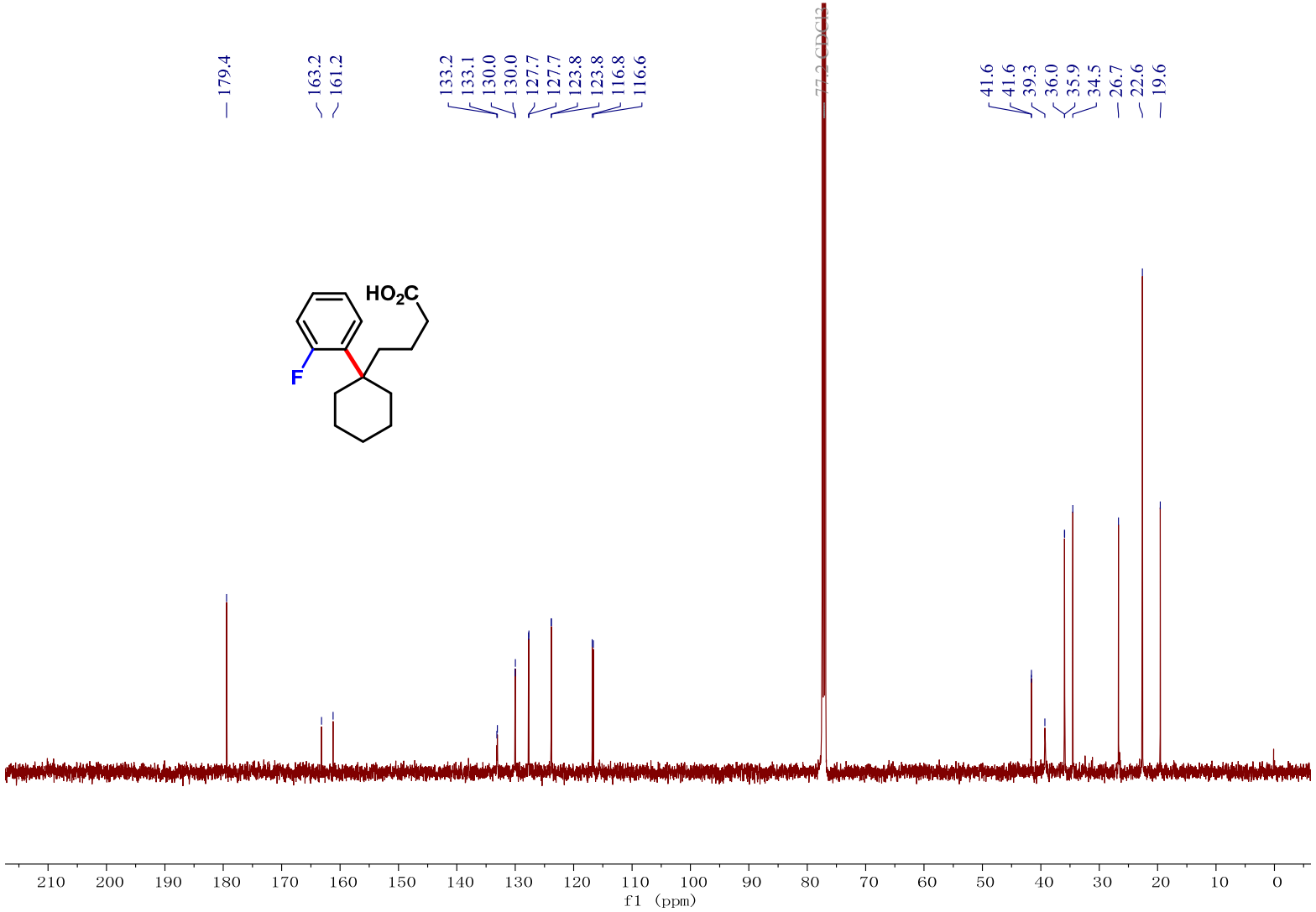
Compound 45 ^{13}C NMR



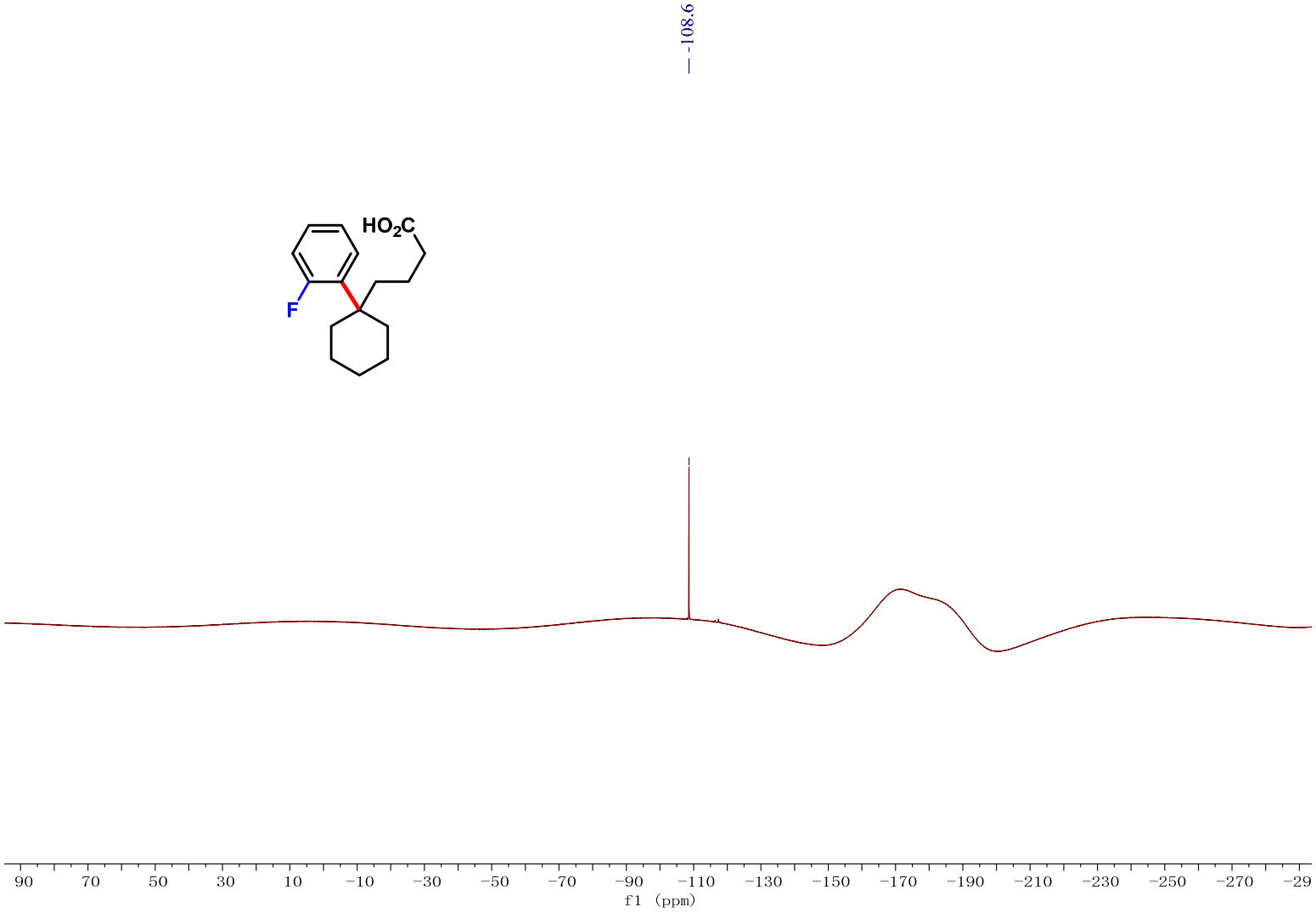
Compound 46 ^{1}H NMR



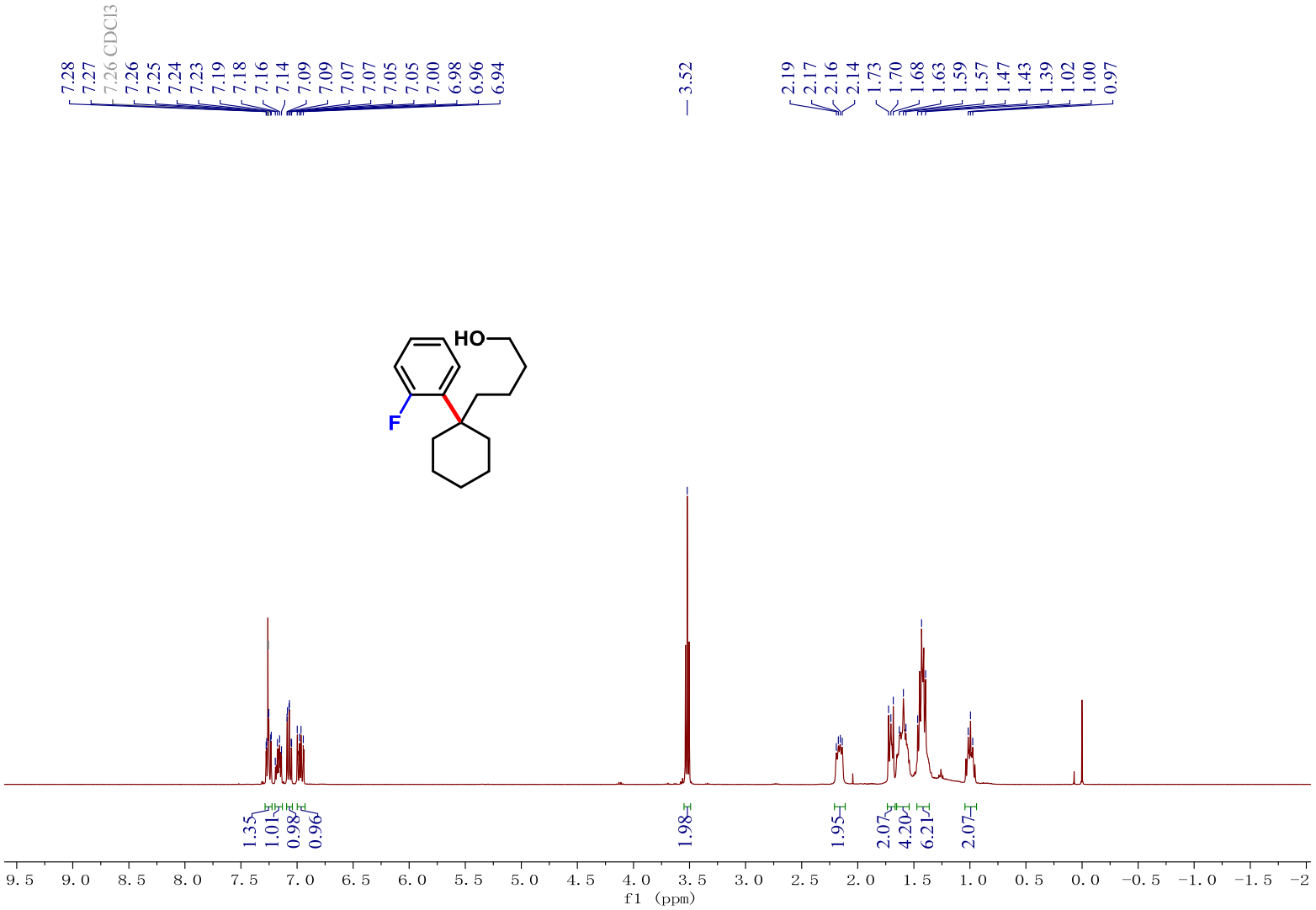
Compound 46 ^{13}C NMR



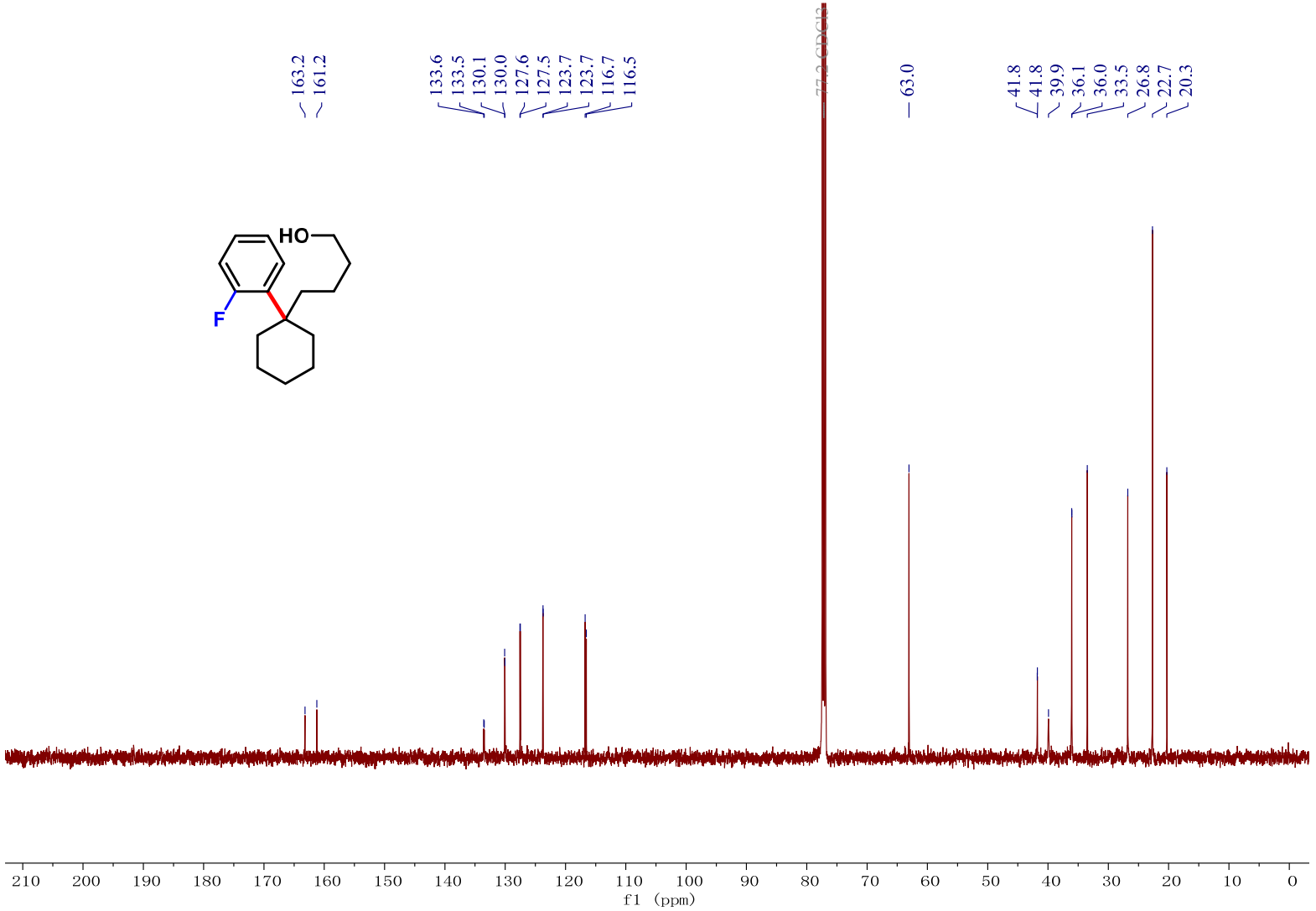
Compound 46 ^{19}F NMR



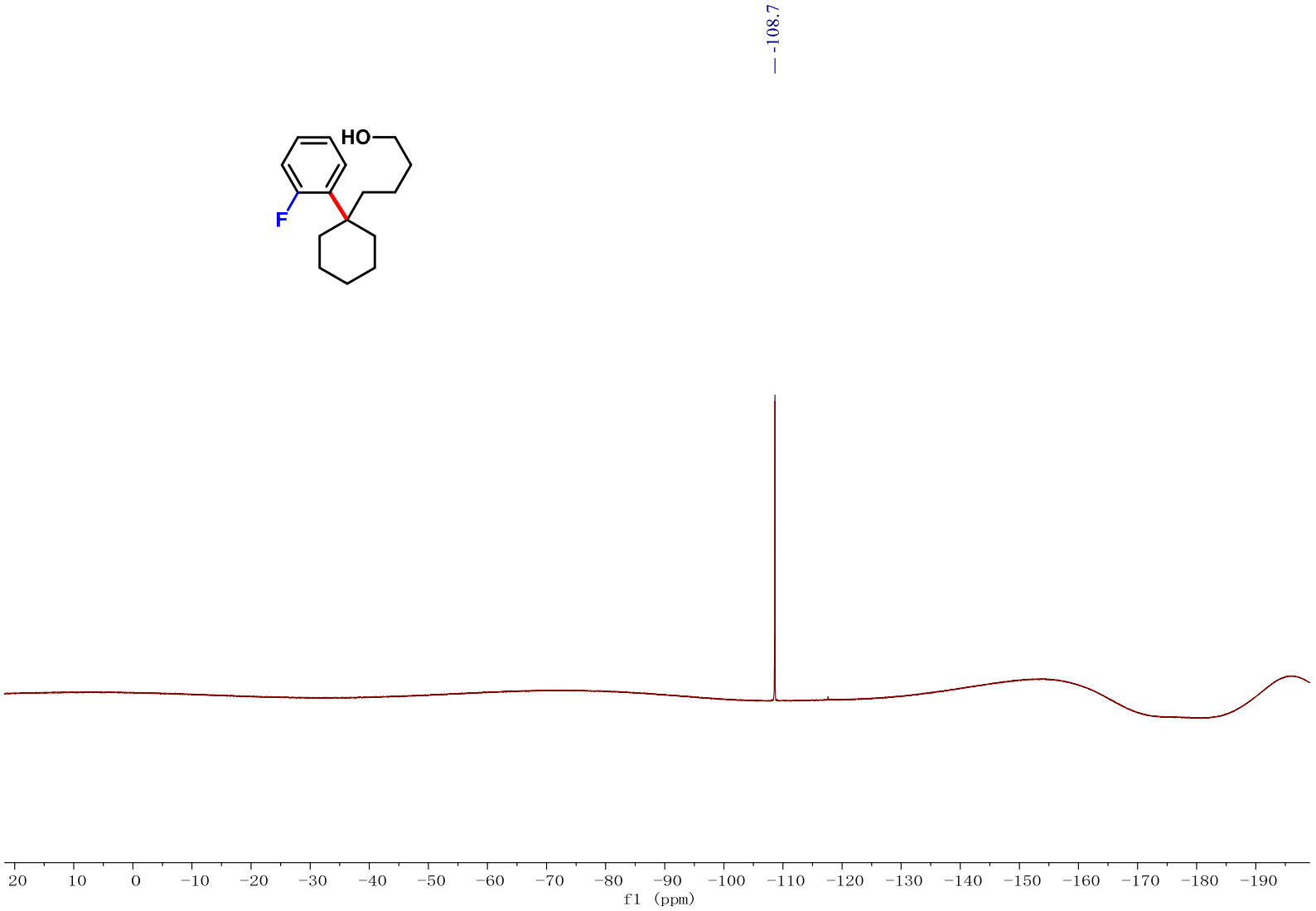
Compound 47 ^{1}H NMR



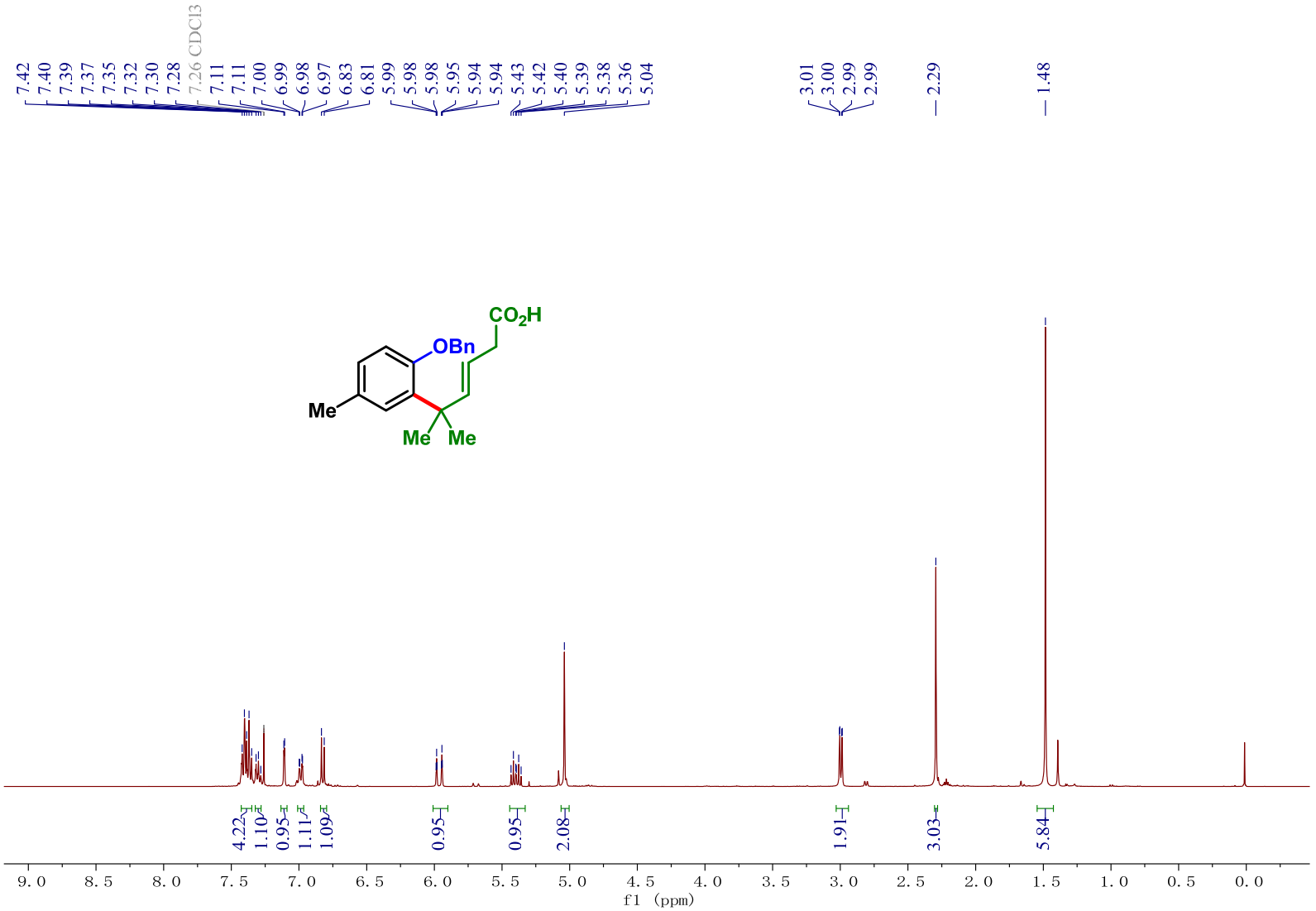
Compound 47 ^{13}C NMR



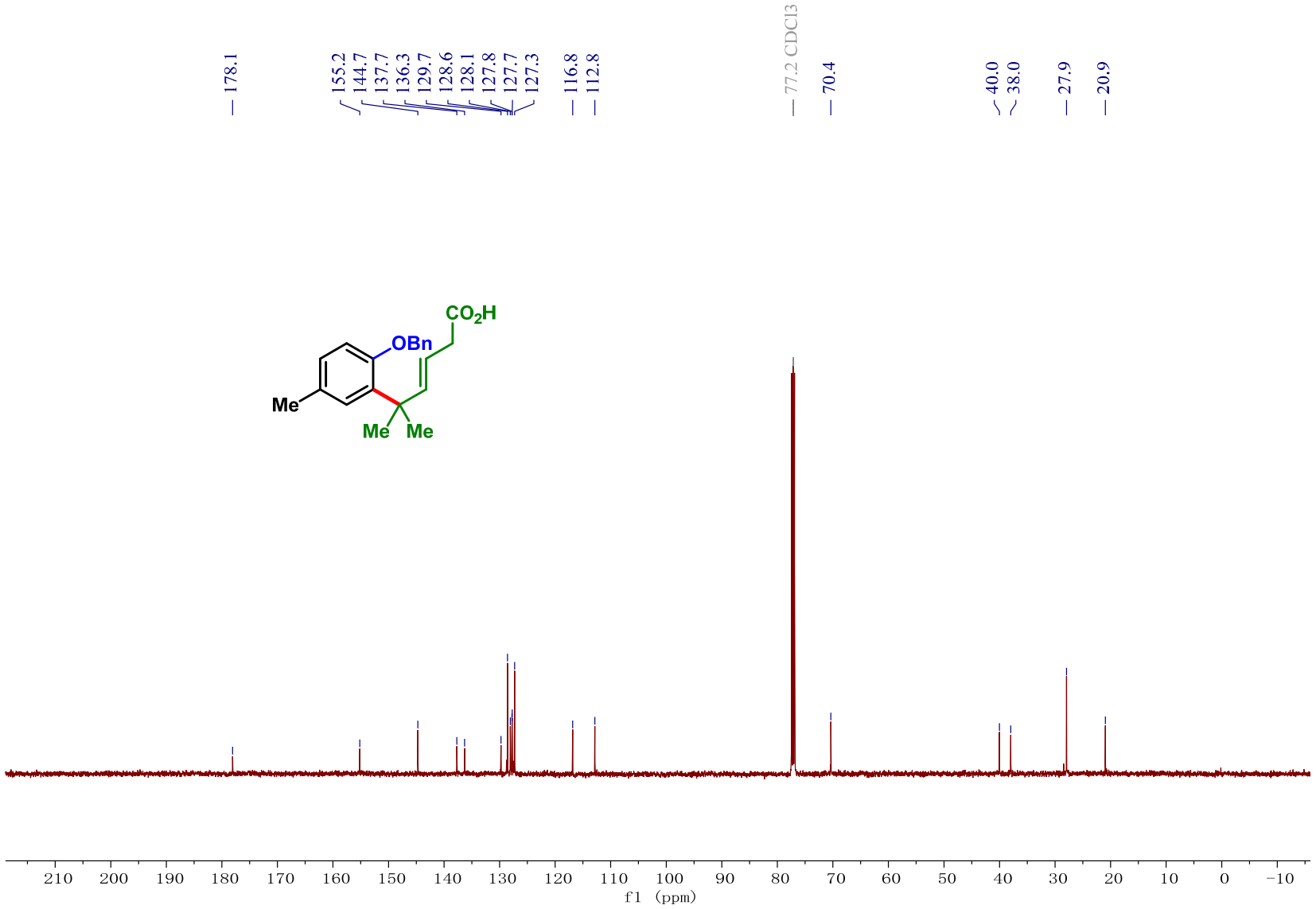
Compound 47 ^{19}F NMR



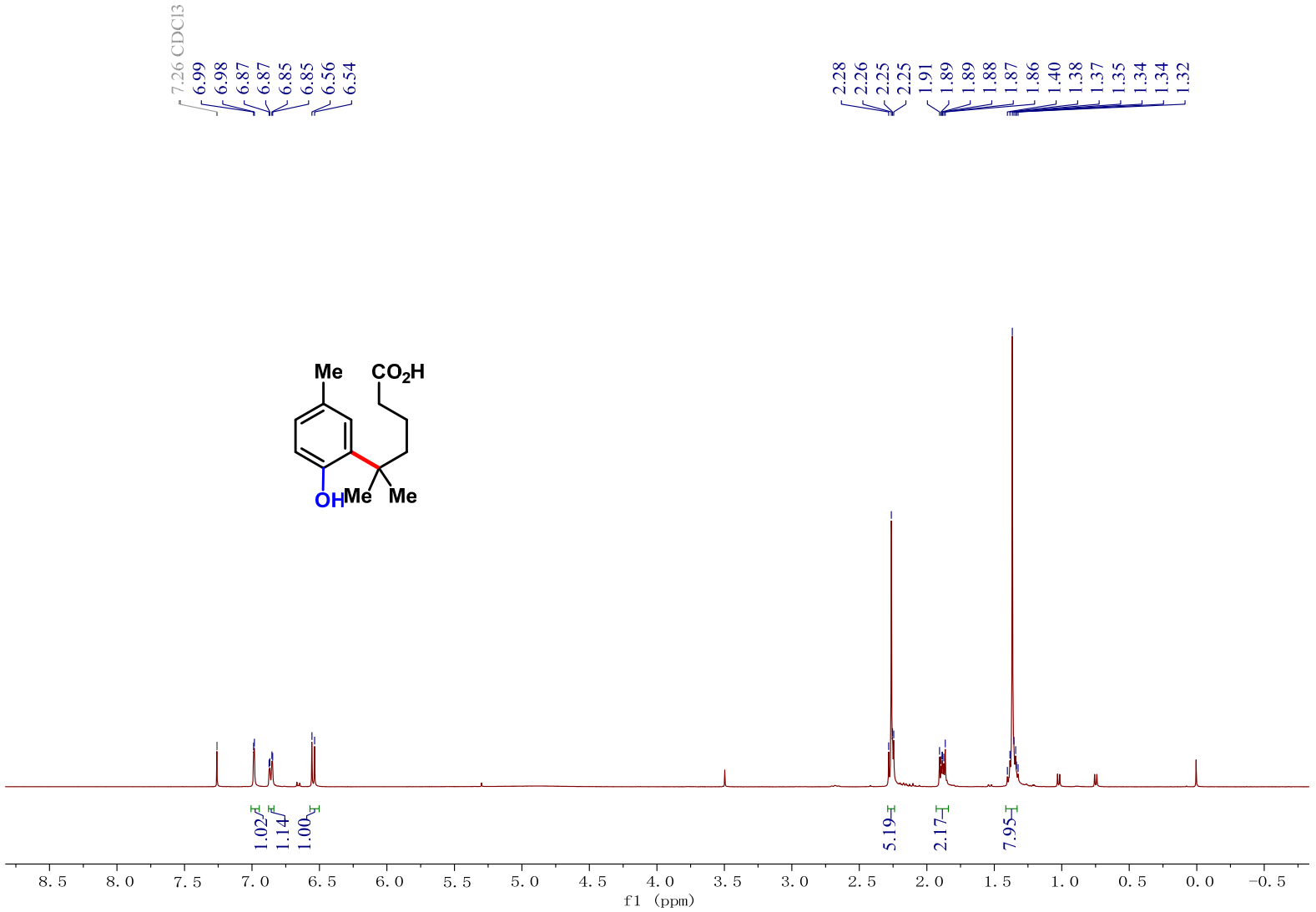
Compound 44 ^{1}H NMR



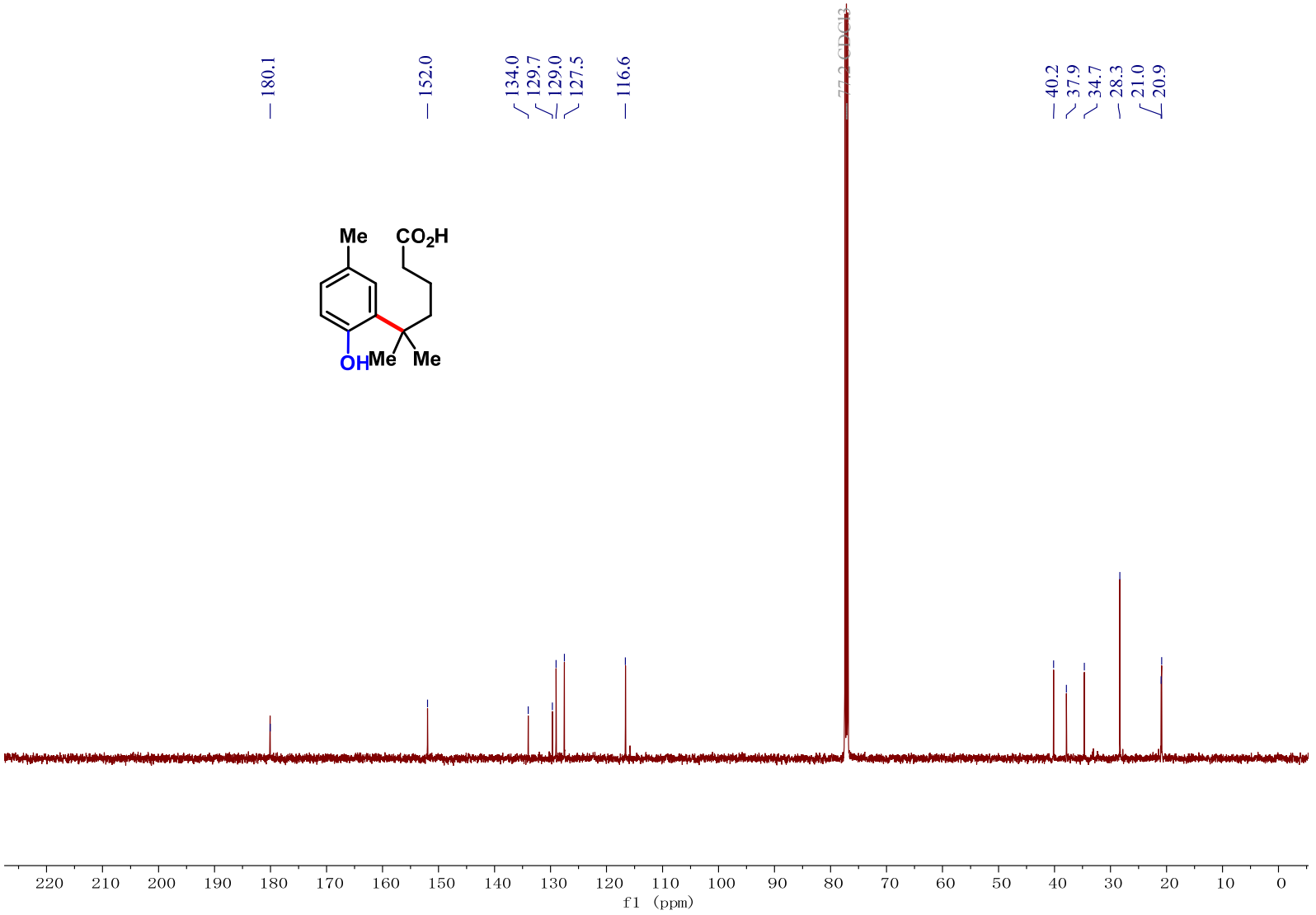
Compound 44 ^{13}C NMR



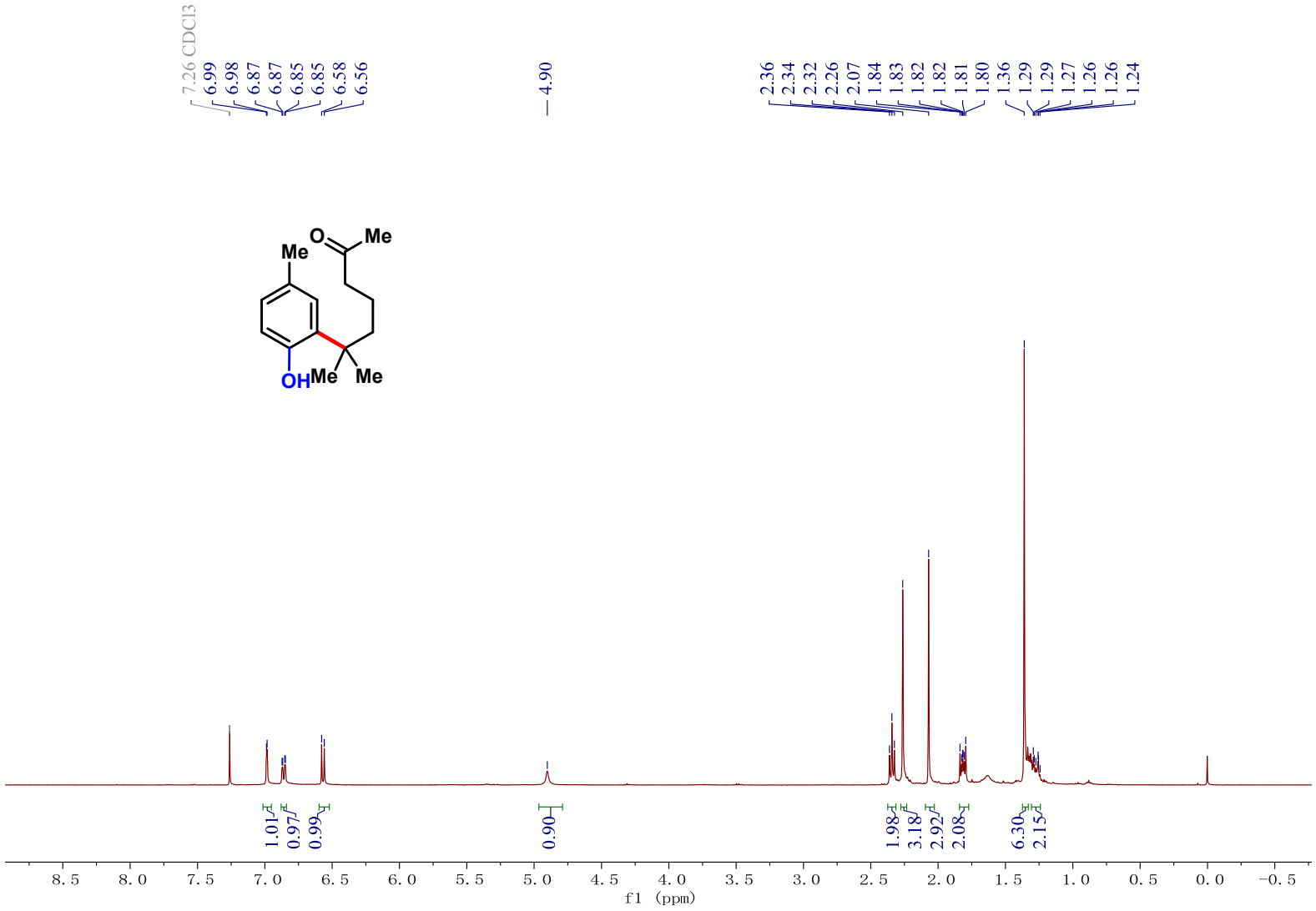
Compound 48 ^{1}H NMR



Compound 48 ^{13}C NMR



Compound 49 ^{1}H NMR



Compound 49 ^{13}C NMR