Ligand-Enabled C–H Hydroxylation with Aqueous H_2O_2 at Room Temperature

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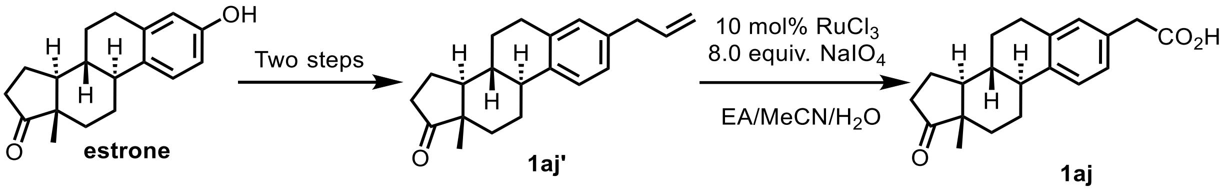
1. General Information:

Hydrogen peroxide (35 wt.% in H_2O) was purchased from Acros. Solvents were obtained from Sigma-Aldrich, Alfa-Aesar, and Acros, and used directly without further purification. Other reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254 or Merck pre-coated aluminium-backed silica gel F254 plates. ^{1}H NMR spectra were recorded on Bruker AMX-400 or Bruker DRX-600 instruments. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). ^{13}C NMR spectra were recorded on Bruker DRX-600 or JEOL instruments (100 MHz) and were fully decoupled by broad band proton decoupling. ^{19}F NMR Spectra were recorded on Bruker AMX-399 spectrometer (376 MHz) or JEOL-400 (376 MHz) and were fully decoupled by broad band proton decoupling. Chemical shifts were referenced to the appropriate residual solvent peaks. Column chromatography was carried out automated using Biotage Isolera One with Biotage SNAP Ultra Column. Automated reversed-phase chromatography was carried out using Biotage Isolera One with Biotage SNAP Samplet (C18). High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

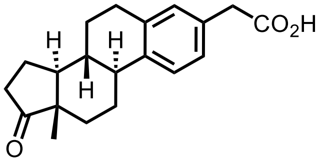
2. Experimental Section for C–H Hydroxylation

2.1. Preparation of Carboxylic Acids Substrates

Carboxylic acid substrates **1aa**, **3e** were obtained from the Bristol-Myers Squibb compounds collection. Substrates **1ak**[1], **3w**[2] were prepared following the reported procedures. Substrate **1aj** were prepared with the following procedure. Other substrates are commercially available.



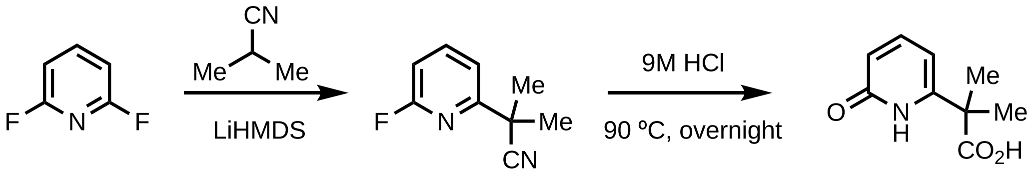
To a solution of **1aj'** (294 mg, 1.0 mmol) (compound **1aj'** was prepared by the known literature[3]) in EtOAc-MeCN-H_2O 2:2:3 (7 mL) was added $RuCl_3$ (20.6 mg, 0.1 mmol, 10 mol%). The mixture was stirred and $NaIO_4$ (1.711 g, 8.0 mmol, 8.0 equiv.) was added in two portions. The reaction solution was stirred vigorously for an additional 6 h. Upon completion, the mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were dried, filtered, and evaporated under reduced pressure. The residue was subjected to flash chromatography (Hexane-EtOAc 2:1 with 1% AcOH, v/v) to give **1aj** as a white solid (221.5 mg, 71%).



1aj

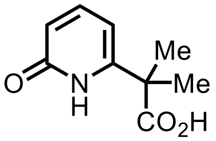
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.26 (d, J = 8.0 Hz, 1H), 7.08 (dd, J = 8.0, 2.0 Hz, 1H), 7.03 (d, J = 2.0 Hz, 1H), 3.59 (s, 2H), 2.93 – 2.90 (m, 2H), 2.58 – 2.47 (m, 1H), 2.46 – 2.38 (m, 1H), 2.33 – 2.25 (m, 1H), 2.21 – 2.13 (m, 1H), 2.09 – 1.94 (m, 3H), 1.68 – 1.59 (m, 2H), 1.56 – 1.39 (m, 4H), 0.91 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 221.42, 177.70, 138.88, 136.87, 130.84, 130.00, 126.81, 125.74, 50.51, 48.07, 44.31, 40.63, 38.10, 35.92, 31.59, 29.34, 26.49, 25.70, 21.63, 13.87. HRMS (ESI-TOF) Calcd for $C_{20}H_{23}O_3$ $[M-H]^-$: 311.1647; found: 311.1647.

2.2. Preparation of Bidentate Carboxyl-Pyridone(CarboxPyridone) Ligand



Step 1: A solution of LiHMDS (1.0 equiv.) in toluene was added to a solution of 2,6-difluoropyridine (1.5 equiv.) and isobutyronitrile (1.0 equiv.) in toluene at room temperature. The resulting mixture was heated to 80 ºC and stirred for overnight. After cooling the mixture to the room temperature, water was added to quench the reaction and toluene was removed under reduced pressure. The resulting mixture was extracted with ethyl acetate several times and combined organic layers were dried over Na_2SO_4 and concentrated to afford the product. In most cases, product was pure enough for the next step. If necessary, column chromatography was used for the purification.

Step 2: The 2-(6-fluoropyridin-2-yl)-2-methylpropanenitrile was weighed to the round bottom flask and was added 9M HCl aq. to make 0.3M solution. The resulting mixture was heated to 90 ºC and stirred for overnight. The reaction progress can be monitored through LCMS by consumption of the starting materials. After completion, the solution was concentrated under reduced pressure then diluted with H_2O. 4M NaOH solution was added until the pH reaches 2~3. The resulting aqueous solution was extracted with $CHCl_3$/IPA (3:1) several times and combined organic layers were dried and concentrated to afford the product. If the ligand is not pure in this stage, residue was purified by column chromatography on silica gel using DCM/MeOH (20:1with acetic acid) solution as eluent.



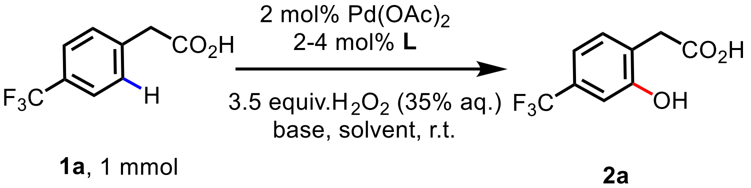
2-methyl-2-(6-oxo-1,6-dihydropyridin-2-yl) propanoic acid (L4)

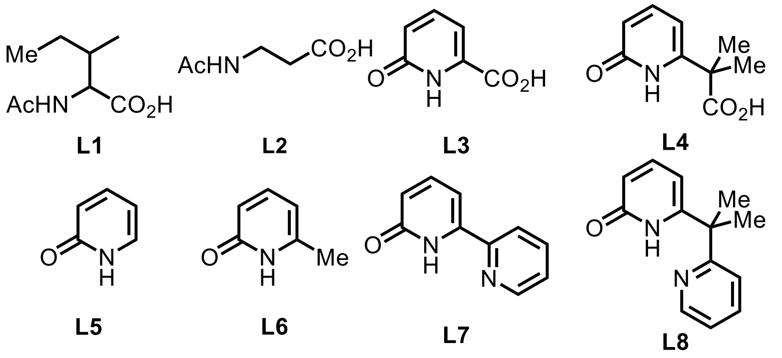
^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.54 (dd, *J* = 9.1, 7.2 Hz, 1H), 6.56 (dd, *J* = 9.1, 0.9 Hz, 1H), 6.40 (dd, *J* = 7.2, 0.9 Hz, 1H), 1.64 (s, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ

179.15, 165.25, 151.36, 142.81, 118.10, 105.13, 46.17, 25.45. HRMS (ESI-TOF) Calcd for $C_9H_{12}O_3$ $[M+H]^+$: 182.0812; found: 182.0807.

2.3. Optimization of the C–H Hydroxylation

Table S1. Ligand Effects

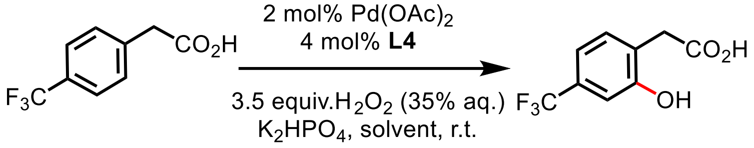




Entry	Ligand	Base	Solvent	Yield (%)
1[a]	**L1**	K_2HPO_4	DMA	37
2	**L1**	K_2HPO_4	DMA	0
3	**L2**	K_2HPO_4	DMA	0
4	**L3**	K_2HPO_4	DMA	0
5	**L4**	K_2HPO_4	DMA	65
6	**L5**	K_2HPO_4	DMA	trace
7	**L6**	K_2HPO_4	DMA	trace
8[b]	**L7**	K_2HPO_4	DMA	<5
9[b]	**L8**	K_2HPO_4	DMA	0
10	**No L**	K_2HPO_4	DMA	0

The reaction was performed with carboxylic acid **1a** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), H_2O_2 (35% aqueous solution, 3.5 mmol), and K_2HPO_4 (1.5 mmol) in DMA (3.0 mL) at room temperature for 24 h. Determined by ^1H NMR yield using CH_3NO_2 as the internal standard. [a] 90°C. [b] 2 mol% ligand.

Table S2. Solvent Effect



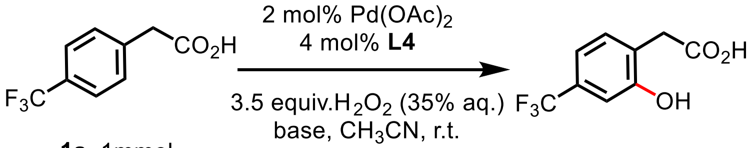
1a, 1mmol

2a

Entry	Solvent	Yield (%)
1	DMA	65
2	DMF	53
3	THF	16
4	NMP	46
5	DMSO	<2
6	HFIP	<2
7	CH_3CN	86
8	Acetone	50
9	*t*-Amyl-OH	37
10	DCE	35

The reaction was performed with carboxylic acid **1a** (1 mmol), Pd(OAc)$_2$ (0.02 mmol), ligand (0.04 mmol), H_2O_2 (35% aqueous solution, 3.5 mmol), and K_2HPO_4 (1.5 mmol) in solvent (3.0 mL) at room temperature for 24 h. Determined by ^{1}H NMR yield using CH_3NO_2 as the internal standard.

Table S3. Base Effect



1a, 1mmol

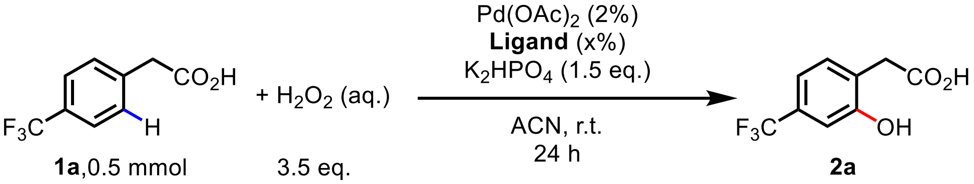
2a

Entry	Base	Solvent	Yield (%)
1	K_2HPO_4	CH_3CN	86
2	K_3PO_4	CH_3CN	<2
3	KH_2PO_4	CH_3CN	<2
4	K_2CO_3	CH_3CN	<2
5	$KHCO_3$	CH_3CN	<2
6	CsOAc	CH_3CN	60
7	NaOAc	CH_3CN	55
8	KOAc	CH_3CN	58
9	Na_3PO_4	CH_3CN	<2
10	/	CH_3CN	8

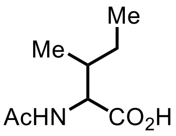
11	K_2HPO_4	DMA	65
12	$KHCO_3$	DMA	80
13	K_2CO_3	DMA	<2
14	K_3PO_4	DMA	17
15	NaOAc	DMA	42
16	Na_2HPO_4	DMA	25
17	KH_2PO_4	DMA	5
18	KOH	DMA	<2

The reaction was performed with carboxylic acid **1a** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), H_2O_2 (35% aqueous solution, 3.5 mmol), and base (1.5 mmol) in solvent(3.0 mL) at room temperature for 24 h. Determined by ^1H NMR yield using CH_3NO_2 as the internal standard.

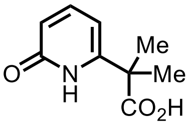
Table S4. Ligand loading effect



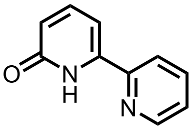
ligand loading	**L1**	**L4**	**L7**	**L8**
2%	No Product	73%	No Product	No Product
4%	No Product	87%	No Product	No Product
6%	No Product	77%	No Product	No Product
8%	No Product	77%	No Product	No Product
10%	No Product	65%	No Product	No Product



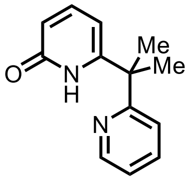
L1



L4



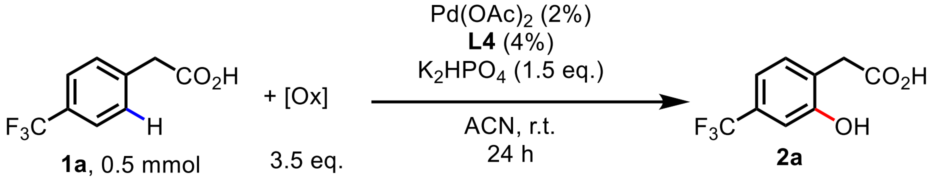
L7



L8

The reaction was performed with carboxylic acid **1a** (0.5 mmol), $Pd(OAc)_2$ (2 mol%), ligand (x mol%), H_2O_2 (35% aqueous solution, 3.5 eq and K_2HPO_4 (1.5 eq) in acetonitrile (1.5 mL) at room temperature for 24 h. Determined by ^1H NMR yield using CH_3NO_2 as the internal standard.

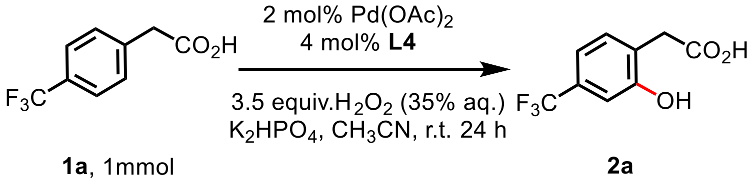
Table S5. Oxidant effect



Oxidant	Yield	Oxidant	Yield
$K_2S_2O_8$	No Product	TBHP in H_2O (70%)	8%
$(NH_4)_2S_2O_8$	No Product	TBHP in decane (~5.5M)	11%
$PhI(OAc)_2$	No Product	H_2O_2 in H_2O (35%)	87%
selectfluor	No Product	Na_2CO_3•$1.5H_2O_2$	trace
selectfluor+H_2O(150uL)	No Product	H_2O_2•Urea	24%

The reaction was performed with carboxylic acid **1a** (0.5 mmol), $Pd(OAc)_2$ (2 mol%), **L4** (4 mol%), oxidant (3.5 eq), and K_2HPO_4 (1.5 eq) in acetonitrile (1.5 mL) at room temperature for 24 h. Determined by ^1H NMR yield using CH_3NO_2 as the internal standard.

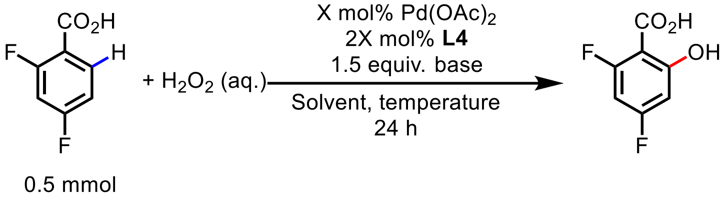
Table S6. Control experiments



Entry	Conditions	Yield (%)
1	/	86
2	w/o $Pd(OAc)_2$	0
3	w/o ligand	0
4	w/o H_2O_2	0
5	w/o K_2HPO_4	8
6	1 mol% $Pd(OAc)_2$	76
7	0.5 mol% $Pd(OAc)_2$	46
8	0.1 mol% $Pd(OAc)_2$	5
9	6 h	44
10	12 h	80

The reaction was performed with carboxylic acid **1a** (1 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), H_2O_2 (35% aqueous solution, 3.5 mmol), and K_2HPO_4 (1.5 mmol) in CH_3CN (3.0 mL) at room temperature for 24 h. Determined by ^1H NMR yield using CH_3NO_2 as the internal standard.

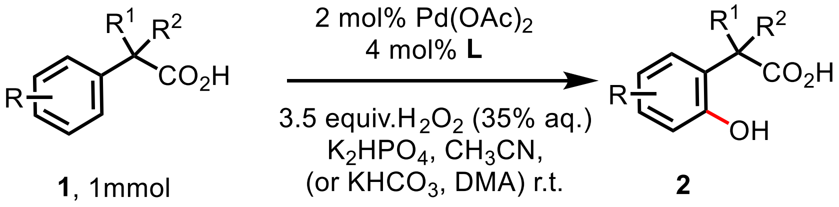
Table S7. Optimization using 2,4-difluorobenzoic acid as a substrate



Pd loading	Solvent	Base	Temp.	Yield
2%	ACN	K_2HPO_4	r.t.	No product
2%	ACN	K_2HPO_4•$3H_2O$	r.t.	No product
5%	ACN	K_2HPO_4•$3H_2O$	r.t.	trace
5%	ACN	K_2HPO_4•$3H_2O$	60 ºC	20%
5%	DMA	K_2HPO_4•$3H_2O$	60 ºC	33%
5%	DMA	$KHCO_3$	60 ºC	64%
5%	DMA	NaOAc	60 ºC	70%
5%	DMA	KOAc	60 ºC	25%
5%	DMA	CsOAc	60 ºC	78%

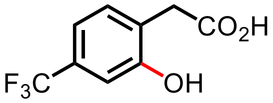
The reaction was performed with carboxylic acid **1a** (0.5 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.02 mmol), H_2O_2 (35% aqueous solution, 1.75 mmol), and base (0.75 mmol) in CH_3CN or DMA (1.5 mL) for 24 h. Determined by ^1H NMR yield using CH_3NO_2 as the internal standard.

2.4. General Procedures and Characterisation Data



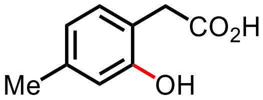
General Procedure for C(sp^2)–H hydroxylation of phenylacetic acids

$Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), **L4** (7.3 mg, 0.04 mmol, 4 mol%), carboxylic acid **1** (1.0 mmol), and K_2HPO_4 (260.0 mg, 1.5 mmol, 1.5 equiv.) were weighed and placed in an 8 mL vial. Then, CH_3CN (3.0 mL) was added and stirred for 10 min, followed by the addition of H_2O_2 (35% aq., 300 uL, 3.5 equiv.). The vial was sealed with a screw cap and stirred at ambient temperature for 24 h (typically ran at 25 °C unless otherwise noted). Upon completion, the reaction was diluted with methanol and acidified with 0.3 mL formic acid. The solution was filtered through a pad of Celite and washed with methanol then concentrated under vacuum (The organic phase should be tested by the potassium iodide starch test paper before concentration, and quenched with $Na_2S_2O_3$ aq. solution if necessary). The crude mixture was purified by flash chromatography (Hexane/EtOAc or DCM/MeOH with 1% AcOH, v/v).



2-(2-hydroxy-4-(trifluoromethyl)phenyl)acetic acid (**2a**)

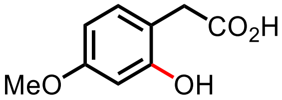
Substrate **1a** was hydroxylated following general procedure, the hydroxylated product **2a** was obtained as a greyish white solid (175 mg, 80%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.30 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 7.03 (s, 1H), 3.65 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 175.27, 157.32, 132.82, 131.44 (q, *J* = 32.2 Hz), 127.45, 125.60 (q, *J* = 271.4 Hz), 116.75 (q, *J* = 3.9 Hz), 112.20 (q, *J* = 3.8 Hz), 36.30. ^{19}F NMR (376 MHz, Methanol-*d*$_4$) δ -66.76. HRMS (ESI-TOF) Calcd for $C_9H_6F_3O_3$ [M-H]$^-$: 219.0269; found: 219.0270.



2-(2-hydroxy-4-methylphenyl)acetic acid (**2b**)

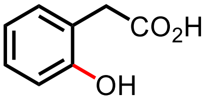
Substrate **1b** was hydroxylated following general procedure, the hydroxylated product **2b** was obtained as a white solid (145 mg, 87%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 6.97 (d, *J*

= 7.5 Hz, 1H), 6.63 – 6.56 (m, 2H), 3.53 (s, 2H), 2.24 (s, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 176.42, 156.54, 139.24, 131.83, 121.14, 119.76, 116.58, 36.18, 21.23. HRMS (ESI-TOF) Calcd for $C_9H_9O_3$ [M-H]$^-$: 165.0552; found: 165.0552.



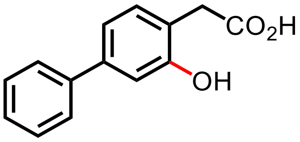
2-(2-hydroxy-4-methoxyphenyl)acetic acid (**2c**)

Substrate **1c** was hydroxylated following general procedure with $KHCO_3$ (200.2 mg, 2.0 mmol, 2.0 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, the hydroxylated product **2c** was obtained as a white solid (132 mg, 73%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 6.99 (d, *J* = 8.2 Hz, 1H), 6.40 – 6.34 (m, 2H), 3.72 (s, 3H), 3.50 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 176.61, 161.41, 157.55, 132.45, 115.27, 105.62, 102.22, 55.59, 35.87. HRMS (ESI-TOF) Calcd for $C_9H_9O_4$ [M-H]$^-$: 181.0501; found: 181.0502.



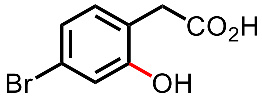
2-(2-hydroxyphenyl)acetic acid (**2d**)

Substrate **1d** was hydroxylated following general procedure, the hydroxylated product **2d** was obtained as a white solid (129 mg, 85%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.14 – 7.04 (m, 2H), 6.78 – 6.75 (m, 2H), 3.58 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 176.22, 156.77, 132.07, 129.25, 122.84, 120.41, 115.88, 36.53. HRMS (ESI-TOF) Calcd for $C_8H_7O_3$ [M-H]$^-$: 151.0395; found: 151.0393.



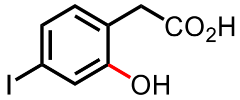
2-(3-hydroxy-[1,1'-biphenyl]-4-yl)acetic acid (**2e**)

Substrate **1e** was hydroxylated following general procedure with $KHCO_3$ (200.2 mg, 2.0 mmol, 1.5 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, the hydroxylated product **2e** was obtained as an ivory solid (179 mg, 79%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.58 – 7.52 (m, 2H), 7.42 – 7.36 (m, 2H), 7.32 – 7.25 (m, 1H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.07 – 7.01 (m, 2H), 3.63 (s, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.16, 157.06, 142.78, 142.32, 132.48, 129.71, 128.20, 127.80, 122.00, 119.09, 114.38, 36.26. HRMS (ESI-TOF) Calcd for $C_{14}H_{11}O_3$ $[M-H]^-$: 227.0708; found: 227.0714.



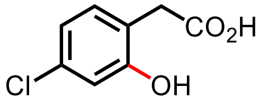
2-(4-bromo-2-hydroxyphenyl)acetic acid (**2f**)

Substrate **1f** was hydroxylated following general procedure, the hydroxylated product **2f** was obtained as white solid (200 mg, 87%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.03 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.92 (dd, *J* = 8.0, 2.0 Hz, 1H), 3.54 (s, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.56, 157.93, 133.46, 123.22, 122.44, 121.87, 118.80, 35.97. HRMS (ESI-TOF) Calcd for $C_8H_6BrO_3$ $[M-H]^-$: 228.9500; found: 228.9503.



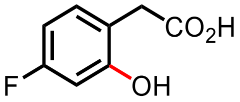
2-(2-hydroxy-4-iodophenyl)acetic acid (**2g**)

Substrate **1g** was hydroxylated following general procedure with $KHCO_3$ (200.2 mg, 2.0 mmol, 2.0 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, the hydroxylated product **2g** was obtained as a white solid (184 mg, 66%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.14 (d, *J* = 1.7 Hz, 1H), 7.11 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 3.53 (s, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 175.55, 157.81, 133.68, 129.48, 124.79, 123.05, 92.89, 36.07. HRMS (ESI-TOF) Calcd for $C_8H_6IO_3$ $[M-H]^-$: 276.9362; found: 276.9365.



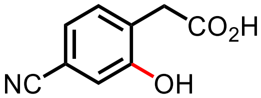
2-(4-chloro-2-hydroxyphenyl)acetic acid (**2h**)

Substrate **1h** was hydroxylated following general procedure, the hydroxylated product **2h** was obtained as a white solid (150 mg, 81%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.08 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 2.1 Hz, 1H), 6.77 (dd, *J* = 8.0, 2.2 Hz, 1H), 3.55 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 175.67, 157.75, 134.16, 133.10, 121.95, 120.21, 115.87, 35.90. HRMS (ESI-TOF) Calcd for $C_8H_6ClO_3$ [M-H]$^-$: 185.0005; found: 185.0005.



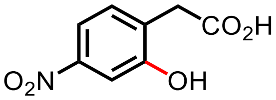
2-(4-fluoro-2-hydroxyphenyl)acetic acid (**2i**)

Substrate **1i** was hydroxylated following general procedure with $KHCO_3$ (200.2 mg, 2.0 mmol, 2.0 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, the hydroxylated product **2i** was obtained as a white solid (123 mg, 72%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.09 (dd, *J* = 8.3, 6.7 Hz, 1H), 6.56 – 6.44 (m, 2H), 3.54 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 176.04, 164.05 (d, *J* = 242.5 Hz), 158.05 (d, *J* = 11.0 Hz), 132.89 (d, *J* = 10.1 Hz), 119.03 (d, *J* = 3.2 Hz), 106.55 (d, *J* = 21.4 Hz), 103.04 (d, *J* = 24.3 Hz), 35.82. ^{19}F NMR (376 MHz, Methanol-*d*$_4$) δ -119.34. HRMS (ESI-TOF) Calcd for $C_8H_6FO_3$ [M-H]$^-$: 169.0301; found: 169.0306.



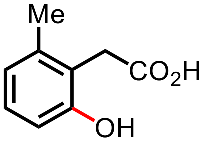
2-(4-cyano-2-hydroxyphenyl)acetic acid (**2j**)

Substrate **1j** was hydroxylated following general procedure at 60 ºC, the hydroxylated product **2j** was obtained as a yellow solid (131 mg, 74%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.30 (d, *J* = 7.7 Hz, 1H), 7.14 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.05 (d, *J* = 1.6 Hz, 1H), 3.65 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 174.80, 157.51, 133.34, 129.47, 124.14, 119.78, 118.45, 112.48, 36.44. HRMS (ESI-TOF) Calcd for $C_9H_6NO_3$ [M-H]$^-$: 176.0348; found: 176.0345.



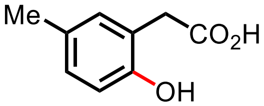
2-(2-hydroxy-4-nitrophenyl)acetic acid (**2k**)

Substrate **1k** was hydroxylated following general procedure at 60 ºC, the hydroxylated product **2k** was obtained as an orange solid (138 mg, 70%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.66 (dd, J = 8.3, 2.3 Hz, 1H), 7.62 (d, J = 2.3 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 3.69 (s, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 174.66, 157.60, 149.32, 132.74, 130.99, 115.08, 110.07, 36.33. HRMS (ESI-TOF) Calcd for $C_8H_6NO_5$ [M-H]$^-$: 196.0246; found: 196.0247.



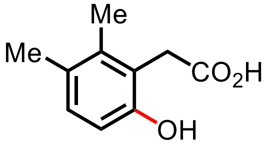
2-(2-hydroxy-6-methylphenyl)acetic acid (**2l**)

Substrate **1l** was hydroxylated following general procedure, the hydroxylated product **2l** was obtained as an ivory solid (143 mg, 86%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 6.95 (t, J = 7.8 Hz, 1H), 6.73 – 6.59 (m, 2H), 3.67 (s, 2H), 2.24 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.07, 156.75, 139.49, 128.48, 122.21, 121.57, 113.48, 32.42, 19.78. HRMS (ESI-TOF) Calcd for $C_9H_9O_3$ [M-H]$^-$: 165.0552; found: 165.0550.



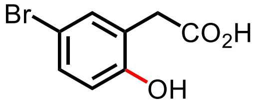
2-(2-hydroxy-5-methylphenyl)acetic acid (**2m**)

Substrate **1m** was hydroxylated following general procedure, the hydroxylated product **2m** was obtained as a white solid (131 mg, 79%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 6.92 (d, J = 2.2 Hz, 1H), 6.88 (dd, J = 8.1, 2.3 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 3.54 (s, 2H), 2.21 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.31, 154.34, 132.56, 129.59, 129.54, 122.47, 115.80, 36.52, 20.50. HRMS (ESI-TOF) Calcd for $C_9H_9O_3$ [M-H]$^-$: 165.0552; found: 165.0554.



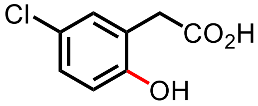
2-(6-hydroxy-2,3-dimethylphenyl)acetic acid (**2n**)

Substrate **1n** was hydroxylated following general procedure, the hydroxylated product **2n** was obtained as an ivory solid (128 mg, 71%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 6.85 (d, *J* = 8.2 Hz, 1H), 6.55 (d, *J* = 8.2 Hz, 1H), 3.71 (s, 2H), 2.17 (s, 3H), 2.13 (s, 3H),.^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 176.35, 154.70, 137.49, 129.84, 128.32, 121.50, 112.93, 32.70, 20.11, 15.89. HRMS (ESI-TOF) Calcd for $C_{10}H_{11}O_3$ [M-H]$^-$: 179.0708; found: 179.0710.



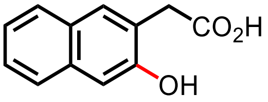
2-(5-bromo-2-hydroxyphenyl)acetic acid (**2o**)

Substrate **1o** was hydroxylated following general procedure, the hydroxylated product **2o** was obtained as a white solid (190 mg, 83%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.26 (d, *J* = 2.6 Hz, 1H), 7.19 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 3.56 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 175.43, 156.20, 134.66, 131.88, 125.46, 117.54, 111.74, 36.09. HRMS (ESI-TOF) Calcd for $C_8H_6BrO_3$ [M-H]$^-$: 228.9500; found: 228.9503.



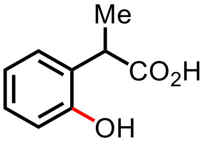
2-(5-chloro-2-hydroxyphenyl)acetic acid (**2p**)

Substrate **1p** was hydroxylated following general procedure, the hydroxylated product **2p** was obtained as a white solid (158 mg, 85%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.12 (d, *J* = 2.6 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 3.56 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 175.46, 155.68, 131.73, 128.86, 124.88, 124.72, 117.03, 36.17. HRMS (ESI-TOF) Calcd for $C_8H_6ClO_3$ [M-H]$^-$: 185.0005; found: 185.0008.



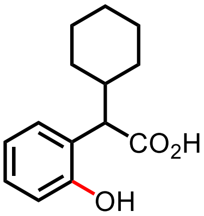
2-(3-hydroxynaphthalen-2-yl)acetic acid (**2q**)

Substrate **1q** was hydroxylated following general procedure with $KHCO_3$ (200.2 mg, 2.0 mmol, 2.0 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, the hydroxylated product **2q** was obtained as a white solid (166 mg, 82%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.68 (d, *J* = 8.2 Hz, 1H), 7.61 (s, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.33 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.23 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.10 (s, 1H), 3.75 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 176.03, 155.33, 135.86, 131.05, 129.85, 128.35, 126.81, 126.72, 125.85, 123.94, 109.53, 37.18. HRMS (ESI-TOF) Calcd for $C_{12}H_9O_3$ $[M-H]^-$: 201.0552; found: 201.0552.



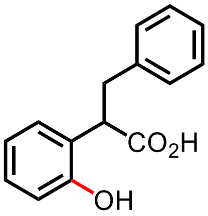
2-(2-hydroxyphenyl)propanoic acid (**2r**)

Substrate **1r** was hydroxylated following general procedure, the hydroxylated product **2r** was obtained as a colourless liquid (146 mg, 88%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.13 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.05 (td, *J* = 7.7, 1.7 Hz, 1H), 6.82 – 6.74 (m, 2H), 4.00 (q, *J* = 7.2 Hz, 1H), 1.41 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 179.44, 155.96, 129.10, 128.96, 128.83, 120.58, 116.17, 40.74, 17.70. HRMS (ESI-TOF) Calcd for $C_9H_9O_3$ $[M-H]^-$: 165.0552; found: 165.0552.



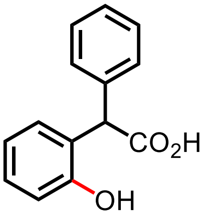
2-cyclohexyl-2-(2-hydroxyphenyl)acetic acid (**2s**)

Substrate **1s** was hydroxylated following general procedure, the hydroxylated product **2s** was obtained as a white solid (173 mg, 74%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.27 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.04 (td, *J* = 7.7, 1.6 Hz, 1H), 6.81 – 6.75 (m, 2H), 3.80 (d, *J* = 10.6 Hz, 1H), 1.98 – 1.88 (m, 2H), 1.78 – 1.74 (m, 1H), 1.66 – 1.60 (m, 2H), 1.36 – 1.28 (m, 2H), 1.21 – 1.08 (m, 3H), 0.89 – 0.82 (m, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 178.57, 156.67, 129.74, 128.85, 125.77, 120.61, 116.32, 51.59, 41.75, 33.24, 31.01, 27.53, 27.21. HRMS (ESI-TOF) Calcd for $C_{14}H_{17}O_3$ [M-H]$^-$: 233.1178; found: 233.1185.



2-(2-hydroxyphenyl)-3-phenylpropanoic acid (**2t**)

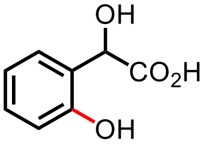
Substrate **1t** was hydroxylated following general procedure, the hydroxylated product **2t** was obtained as a white solid (171 mg, 71%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.21 – 7.10 (m, 6H), 7.05 (td, *J* = 7.6, 1.6 Hz, 1H), 6.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.77 – 6.72 (m, 1H), 4.25 (t, *J* = 7.6 Hz, 1H), 3.27 – 3.23 (m, 1H), 3.04 – 2.96 (m, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 177.79, 156.10, 141.35, 130.03, 129.53, 129.09, 129.05, 127.09, 127.04, 120.46, 116.23, 48.24, 39.44. HRMS (ESI-TOF) Calcd for $C_{15}H_{13}O_3$ [M-H]$^-$: 241.0865; found: 241.0872.



2-(2-hydroxyphenyl)-2-phenylacetic acid (**2u**)

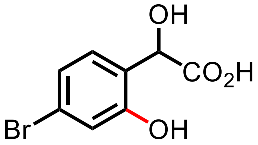
Substrate **1u** was hydroxylated following general procedure with $KHCO_3$ (200.2 mg, 2.0 mmol, 2.0 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, the hydroxylated product **2u** was obtained as a white solid (135 mg, 59%), ^{1}H NMR (600 MHz, Methanol-d_4)

δ 7.34 – 7.27 (m, 4H), 7.26 – 7.23 (m, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 1H), 6.73 (t, *J* = 7.5 Hz, 1H), 5.29 (s, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 177.02, 156.23, 139.88, 130.30, 130.12, 129.38, 129.14, 127.96, 127.49, 120.21, 115.82, 52.39. HRMS (ESI-TOF) Calcd for $C_{14}H_{11}O_3$ [M-H]$^-$: 227.0708; found: 227.0708.



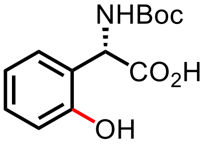
2-hydroxy-2-(2-hydroxyphenyl)acetic acid (2v)

Substrate **1v** was hydroxylated following general procedure, the hydroxylated product **2v** was obtained as a as viscous liquid (139 mg, 83%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.34 (d, *J* = 7.7 Hz, 1H), 7.18 – 7.07 (m, 1H), 6.90 – 6.73 (m, 2H), 5.39 (s, 1H). ^{13}C NMR (151 MHz, MeOD) δ 177.88, 156.25, 130.08, 128.79, 127.72, 120.62, 117.00, 70.52. HRMS (ESI-TOF) Calcd for $C_8H_7O_4$ [M-H]$^-$: 167.0344; found: 167.0346.



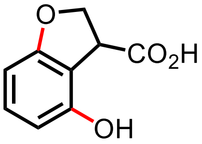
2-(4-bromo-2-hydroxyphenyl)-2-hydroxyacetic (2w)

Substrate **1w** was hydroxylated following general procedure at 60 ºC, the hydroxylated product **2w** was obtained as a as viscous liquid (115 mg, 47%), ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.30 (d, *J* = 8.2 Hz, 1H), 6.98 – 6.90 (m, 2H), 5.20 (s, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 178.80, 157.27, 129.64, 127.99, 123.52, 122.53, 120.38, 70.65. HRMS (ESI-TOF) Calcd for $C_8H_6BrO_4$ [M-H]$^-$: 244.9449; found: 244.9455.



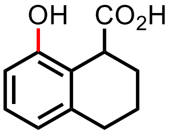
(*S*)-2-((*tert*-butoxycarbonyl)amino)-2-(2-hydroxyphenyl)acetic (2x)

Substrate **1x** was hydroxylated following general procedure, the hydroxylated product **2x** was obtained as a yellow solid (155 mg, 58%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.20 (dd, J = 7.8, 1.7 Hz, 1H), 7.15 – 7.10 (m, 1H), 6.83 – 6.78 (m, 2H), 5.38 (s, 1H), 1.44 (s, 9H). ^{13}C NMR (151 MHz, MeOD) δ 175.64, 157.65, 156.42, 130.23, 130.05, 128.51, 125.63, 120.63, 116.69, 80.71, 28.71. HRMS (ESI-TOF) Calcd for $C_{13}H_{16}NO_5$ [M-H]$^-$: 266.1034; found: 266.1034.



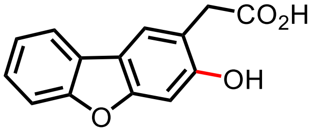
4-hydroxy-2,3-dihydrobenzofuran-3-carboxylic acid (**2y**)

Substrate **1y** was hydroxylated following general procedure, the hydroxylated product **2y** was obtained as a white solid (135 mg, 75%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 6.98 (t, J = 8.1, 1H), 6.33 (d, J = 8.1Hz, 1H), 6.28 (d, J = 7.9 Hz, 1H), 4.70 (dd, J = 9.1, 6.0 Hz, 1H), 4.64 (dd, J = 9.7, 9.0 Hz, 1H), 4.33 (dd, J = 9.7, 6.0 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.19, 163.18, 155.97, 131.25, 112.05, 109.13, 102.21, 74.80, 47.04. HRMS (ESI-TOF) Calcd for $C_9H_7O_4$ [M-H]$^-$: 179.0344; found: 179.0347.



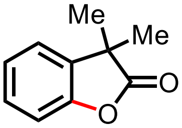
8-hydroxy-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (**2z**)

Substrate **1z** was hydroxylated following general procedure, the hydroxylated product **2z** was obtained as an ivory solid (123 mg, 64%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 6.95 (t, J = 7.8 Hz, 1H), 6.61 – 6.55 (m, 2H), 3.80 (dd, J = 6.8, 4.9 Hz, 1H), 2.81 – 2.63 (m, 2H), 2.12 – 2.06 (m, 1H), 2.04 – 1.99 (m, 1H), 1.88 – 1.81 (m, 1H), 1.76 – 1.69 (m, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 180.15, 156.71, 139.85, 128.20, 122.79, 121.15, 112.74, 41.29, 30.44, 28.49, 21.53. HRMS (ESI-TOF) Calcd for $C_{11}H_{11}O_3$ [M-H]$^-$: 191.0708; found: 191.0714.



2-(3-hydroxydibenzo[b,d]furan-2-yl)acetic acid (2aa)

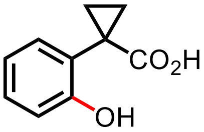
Substrate **1aa** was hydroxylated following general procedure with $KHCO_3$ (200.2 mg, 2.0 mmol, 2.0 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, the hydroxylated product **2aa** was obtained as a white solid (160 mg, 66%), ^1H NMR (600 MHz, Methanol-*d*$_4$) δ 7.81 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.71 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 6.98 (s, 1H), 3.72 (s, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 176.42, 158.04, 157.48, 157.23, 126.41, 125.84, 123.72, 123.44, 120.51, 119.40, 117.18, 111.97, 98.54, 36.81. HRMS (ESI-TOF) Calcd for $C_{14}H_9O_4$ $[M-H]^-$: 241.0501; found: 241.0503.



Compound **2ab** easily converts into the corresponding lactone during work-up and purification. The isolated yield is based on the lactone **2ab'** after following the produce below. Procedure: Upon completion of C–H hydroxylation, 0.5 mL concentrated sulfuric acid was added to the reaction mixture and stirred for 2h. The solution was quenched with saturated solution of Na_2SO_3 in water. The mixture was filtered through Celite, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography affording the product as colourless liquid, 130 mg, 80%. (Hexane/EtOAc = 10/1, v/v).

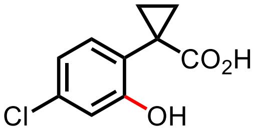
3,3-dimethylbenzofuran-2(3H)-one (**2ab'**)

^1H NMR (600 MHz, Chloroform-*d*) δ 7.38 (td, *J* = 7.8, 1.5 Hz, 1H), 7.31 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.25 (td, *J* = 7.5, 1.0 Hz, 1H), 7.21 (dt, *J* = 7.9, 0.8 Hz, 1H), 1.59 (s, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 181.07, 152.37, 133.82, 128.66, 124.40, 122.86, 110.96, 43.03, 25.40. The NMR data matches the reported data[4].



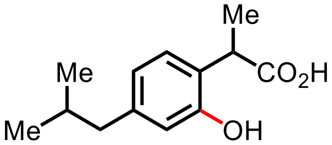
1-(2-hydroxyphenyl)cyclopropane-1-carboxylic acid (**2ac**)

Substrate **1ac** was hydroxylated following general procedure, the hydroxylated product **2ac** was obtained as a colourless oil (139 mg, 78%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.14 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.07 (td, *J* = 7.7, 1.7 Hz, 1H), 6.75 (m, 2H), 1.56 (q, *J* = 4.1 Hz, 2H), 1.11 (q, *J* = 4.0 Hz, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 178.73, 158.20, 131.85, 129.33, 127.74, 120.11, 116.03, 25.74, 17.19. HRMS (ESI-TOF) Calcd for $C_{10}H_9O_3$ [M-H]$^-$: 177.0552; found: 177.0550.



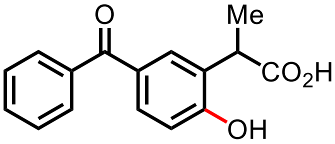
1-(4-chloro-2-hydroxyphenyl)cyclopropane-1-carboxylic acid (2ad)

Substrate **1ad** was hydroxylated following general procedure, the hydroxylated product **2ad** was obtained as a yellow solid (119 mg, 56%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.10 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 2.1 Hz, 1H), 6.75 (dd, *J* = 8.1, 2.1 Hz, 1H), 1.57 – 1.53 (m, 2H), 1.11 – 1.07 (m, 2H). ^{13}C NMR (151 MHz, MeOD) δ 178.38, 159.25, 134.28, 132.92, 127.02, 119.90, 116.07, 25.43, 17.06. HRMS (ESI-TOF) Calcd for $C_{10}H_8ClO_3$ [M-H]$^-$: 211.0162; found: 211.0157.



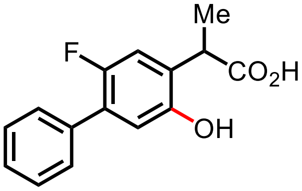
2-(2-hydroxy-4-isobutylphenyl)propanoic acid (**2ae**)

Substrate **1ae** was hydroxylated following general procedure, the hydroxylated product **2ae** was obtained as a white solid (195 mg, 88%), ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.06 (d, *J* = 7.8 Hz, 1H), 6.71 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.67 (d, *J* = 1.7 Hz, 1H), 3.93 (q, *J* = 7.2 Hz, 1H), 2.40 (d, *J* = 7.2 Hz, 2H), 1.85 – 1.81 (m, 1H), 1.55 (d, *J* = 7.3 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 182.11, 153.79, 143.13, 128.34, 122.83, 122.20, 118.02, 45.08, 40.84, 30.15, 22.55, 16.14. HRMS (ESI-TOF) Calcd for $C_{13}H_{17}O_3$ $[M-H]^-$: 221.1178; found: 221.1179.



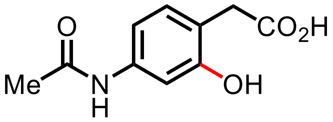
2-(5-benzoyl-2-hydroxyphenyl)propanoic acid (**2af**)

Substrate **1af** was hydroxylated following general procedure, the hydroxylated product **2af** was obtained as a white solid (151 mg, 56%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.75 – 7.67 (m, 3H), 7.63 – 7.58 (m, 2H), 7.54 – 7.48 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 1H), 1.44 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 197.81, 178.56, 161.20, 139.75, 133.12, 132.49, 132.33, 130.65, 129.88, 129.51, 129.37, 115.69, 40.53, 17.46. HRMS (ESI-TOF) Calcd for $C_{16}H_{13}O_4$ $[M-H]^-$: 269.0814; found: 269.0813.



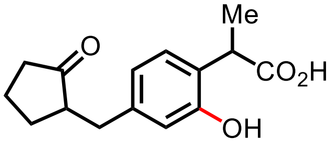
2-(2-fluoro-5-hydroxy-[1,1'-biphenyl]-4-yl)propanoic acid (**2ag**)

Substrate **1ag** was hydroxylated following general procedure, the hydroxylated product **2ag** was obtained as a pale-yellow solid (174 mg, 67%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.49 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.29 (m, 1H), 6.99 (d, *J* = 11.6 Hz, 1H), 6.85 (d, *J* = 6.8 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 1H), 1.46 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 178.54, 154.50 (d, *J* = 237.7 Hz), 152.24 (d, *J* = 2.1 Hz), 137.25, 129.95 (d, *J* = 7.2 Hz), 129.86 (d, *J* = 2.9 Hz), 129.40, 128.95 (d, *J* = 14.9 Hz), 128.57, 117.13 (d, *J* = 3.5 Hz), 116.29 (d, *J* = 25.2 Hz), 40.28, 17.62. ^{19}F NMR (376 MHz, Methanol-*d*$_4$) δ -134.88. HRMS (ESI-TOF) Calcd for $C_{15}H_{12}FO_3$ $[M-H]^-$: 259.0770; found: 259.0769.



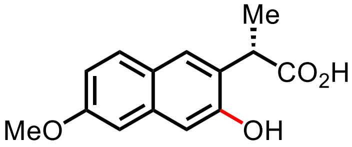
2-(4-acetamido-2-hydroxyphenyl)acetic acid (**2ah**)

Substrate **1ah** was hydroxylated following general procedure with $KHCO_3$ (200.2 mg, 2.0 mmol, 2.0 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, the hydroxylated product **2ah** was obtained as an ivory solid (140 mg, 67%), ^1H NMR (600 MHz, Methanol-*d*$_4$) δ 7.25 (d, *J* = 2.1 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.83 (dd, *J* = 8.1, 2.1 Hz, 1H), 3.53 (s, 2H), 2.08 (s, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 176.39, 171.55, 156.92, 139.83, 131.98, 118.82, 112.06, 108.17, 36.29, 23.80. HRMS (ESI-TOF) Calcd for $C_{10}H_{10}NO_4$ [M-H]$^-$: 208.0610; found: 208.0609.



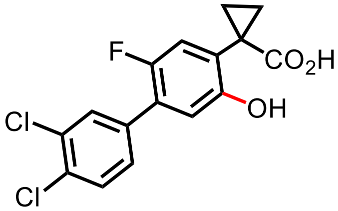
2-(2-hydroxy-4-((2-oxocyclopentyl)methyl)phenyl)propanoic acid (**2ai**)

Substrate **1ai** was hydroxylated following general procedure, the hydroxylated product **2ai** was obtained as an yellow oil (197 mg, 75%), ^1H NMR (600 MHz, Methanol-*d*$_4$) δ 7.04 (d, *J* = 8.3 Hz, 1H), 6.65 – 6.58 (m, 2H), 3.97 (q, *J* = 7.2 Hz, 1H), 2.98 – 2.94 (m, 1H), 2.47 – 2.42 (m, 1H), 2.39 – 2.25 (m, 2H), 2.12 – 2.03 (m, 2H), 1.96 – 1.91 (m, 1H), 1.79 – 1.70 (m, 1H), 1.60 – 1.53 (m, 1H), 1.39 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 222.98, 179.31, 155.85, 141.17, 128.87, 126.89, 121.19, 116.56, 52.04, 40.16, 39.03, 36.17, 30.08, 21.45, 17.72. HRMS (ESI-TOF) Calcd for $C_{15}H_{17}O_4$ [M-H]$^-$: 261.1127; found: 261.1129.



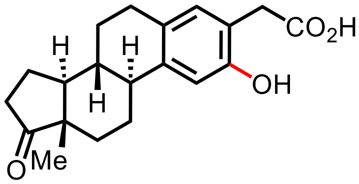
(*S*)-2-(3-hydroxy-6-methoxynaphthalen-2-yl)propanoic acid (**2aj**)

Substrate **1aj** was hydroxylated following general procedure, the hydroxylated product **2aj** was obtained as an orange solid (160 mg, 65%) with $KHCO_3$ (200.2 mg, 2.0 mmol, 2.0 equiv.) and DMA (3.0 mL) instead of CH_3CN and K_2HPO_4, ^1H NMR (600 MHz, Methanol-d_4) δ 7.57 (d, *J* = 8.9 Hz, 1H), 7.53 (s, 1H), 7.03 (s, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H), 3.84 (s, 3H), 1.52 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 179.32, 159.32, 155.24, 136.73, 129.97, 129.22, 127.84, 125.26, 116.47, 109.27, 105.03, 55.57, 40.99, 17.74. HRMS (ESI-TOF) Calcd for $C_{14}H_{13}O_4$ $[M-H]^-$: 245.0814; found: 245.0817.



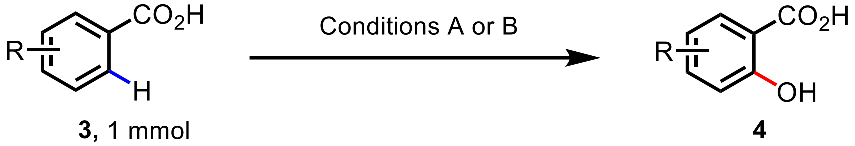
1-(3',4'-dichloro-2-fluoro-5-hydroxy-[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid (2ak)

Substrate **1ak** was hydroxylated following general procedure on 0.5 mmol scale, the hydroxylated product **2ak** was obtained as a white solid (126 mg, 74%), ^1H NMR (600 MHz, Methanol-d_4) δ 7.64 (dd, *J* = 2.0, 1.3 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.42 (dt, *J* = 8.3, 1.6 Hz, 1H), 7.00 (d, *J* = 11.2 Hz, 1H), 6.82 (d, *J* = 6.7 Hz, 1H), 1.62 – 1.55 (m, 2H), 1.18 – 1.11 (m, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 178.01, 154.83, 153.82 (d, *J* = 238.4 Hz), 137.55, 133.29, 132.52, 131.61 (d, *J* = 3.8 Hz), 131.54, 130.15 (d, *J* = 7.6 Hz), 129.62 (d, *J* = 3.3 Hz), 126.73 (d, *J* = 14.8 Hz), 119.18 (d, *J* = 24.8 Hz), 116.76 (d, *J* = 2.7 Hz), 26.00, 17.09. HRMS (ESI-TOF) Calcd for $C_{16}H_{10}Cl_2FO_3$ $[M-H]^-$: 338.9991; found: 338.9992.



(**2al**)

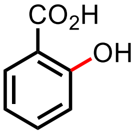
Substrate **1al** was hydroxylated following general procedure on 0.5 mmol scale, the hydroxylated product **2al** was obtained as a white solid (128 mg, 78%), ^{1}H NMR (600 MHz, Chloroform-*d*) δ 6.86 (s, 1H), 6.84 (s, 1H), 3.64 (s, 2H), 2.85 – 2.79 (m, 2H), 2.55 – 2.48 (m, 1H), 2.34 – 2.11 (m, 3H), 2.07 – 1.92 (m, 3H), 1.66 – 1.36 (m, 6H), 0.89 (s, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 221.65, 178.28, 152.52, 141.06, 131.63, 129.12, 118.02, 114.07, 50.59, 48.17, 44.45, 38.11, 36.77, 36.03, 31.66, 28.54, 26.71, 25.80, 21.72, 13.95. HRMS (ESI-TOF) Calcd for $C_{20}H_{23}O_4$ [M-H]$^-$: 327.1596; found: 327.1602.



General Procedure for hydroxylation of benzoic acids

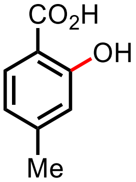
Conditions A: Pd(OAc)$_2$ (4.5 mg, 0.02 mmol, 2 mol%), **L4** (7.3 mg, 0.04 mmol, 4 mol%), carboxylic acid **3** (1.0 mmol), and K_2HPO_4•$3H_2O$ (342.3 mg, 1.5 mmol, 1.5 equiv.) were weighed and placed in an 8 mL vial. Then, CH_3CN (3.0 mL) was added and stirred for 10 min, followed by the addition of H_2O_2 (35% aq., 300 uL, 3.5 equiv.). The vial was sealed with a screw cap and stirred at room temperature for 24 h (typically ran at 25 °C unless otherwise noted). Upon completion, the reaction was quenched with saturated solution of Na_2SO_3 (or $Na_2S_2O_3$) in water until H_2O_2 was completely decomposed. (Tested by the potassium iodide starch test paper). The mixture was diluted with methanol and acidified with formic acid. The solution was filtered through a pad of Celite, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography (Hexane/EtOAc or DCM/MeOH with 1% AcOH, v/v).

Conditions B: Pd(OAc)$_2$ (11.0 mg, 0.05 mmol, 5 mol%), **L4** (18.2 mg, 0.10 mmol, 10 mol%), carboxylic acid **3** (1.0 mmol), and CsOAc (288.0 mg, 1.5 mmol, 1.5 equiv.) were weighed and placed in a reaction tube. Then, DMA (3.0 mL) was added and stirred for 10 min, followed by the addition of H_2O_2 (35% aq., 300 uL, 3.0 equiv.). The vial was sealed with a screw cap and stirred at 60 ºC for 24 h. Upon completion, the reaction was quenched with saturated solution of Na_2SO_3 (or $Na_2S_2O_3$) in water until H_2O_2 was completely decomposed. (Tested by the potassium iodide starch test paper). The mixture was diluted with methanol and acidified with formic acid. The solution was filtered through a pad of Celite, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography (Hexane/EtOAc or DCM/MeOH with 1% AcOH, v/v).



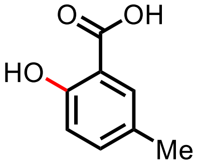
2-hydroxybenzoic acid (4a)

Substrate **3a** was hydroxylated following general procedure conditions A, the hydroxylated product **4a** was obtained as a white solid **(**130 mg, 94%), ^1H NMR (600 MHz, Methanol-*d*$_4$) δ 7.85 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.46 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H), 6.94 – 6.85 (m, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 173.51, 163.22, 136.60, 131.53, 120.04, 118.14, 113.88. HRMS (ESI-TOF) Calcd for $C_7H_5O_3$ $[M-H]^-$: 137.0244; found: 137.0240.



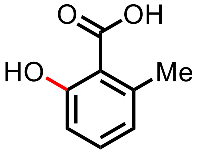
2-hydroxy-4-methylbenzoic acid (4b)

Substrate **3b** was hydroxylated following general procedure conditions A, the hydroxylated product **4b** was obtained as an ivory solid **(**140 mg, 92%),^1H NMR (600 MHz, Methanol-*d*$_4$) δ 7.72 (d, *J* = 8.0 Hz, 1H), 6.75 – 6.73 (m, 1H), 6.73 – 6.70 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 173.54, 163.14, 148.11, 131.37, 121.26, 118.22, 111.30, 21.79. HRMS (ESI-TOF) Calcd for $C_8H_7O_3$ $[M-H]^-$: 151.0395; found: 151.0399.



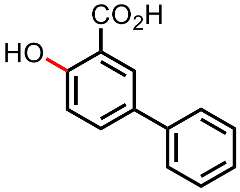
2-hydroxy-5-methylbenzoic acid (4c)

Substrate **3c** was hydroxylated following general procedure conditions A, the hydroxylated product **4c** was obtained as a white solid (130 mg, 85%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.64 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.26 (ddd, *J* = 8.3, 2.3, 0.6 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 173.50, 161.04, 137.42, 131.19, 129.35, 117.93, 113.42, 20.36 HRMS (ESI-TOF) Calcd for $C_8H_7O_3$ [M-H]$^-$: 151.0395; found: 151.0399.



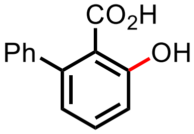
2-hydroxy-6-methylbenzoic acid (4d)

Substrate **3d** was hydroxylated following general procedure conditions A, the hydroxylated product **4d** was obtained as white solid (99.3 mg, 65%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.23 (dd, *J* = 8.3, 7.5 Hz, 1H), 6.76 – 6.70 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 174.86, 163.32, 142.45, 134.43, 123.44, 115.86, 115.07, 23.48. HRMS (ESI-TOF) Calcd for $C_8H_7O_3$ [M-H]$^-$: 151.0395; found: 151.0395.



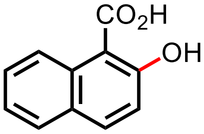
4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (4e)

Substrate **3e** was hydroxylated following general procedure conditions A, the hydroxylated product **4e** was obtained as a yellow solid (191 mg, 89%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.09 (d, *J* = 2.4 Hz, 1H), 7.74 (dt, *J* = 8.5, 2.2 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.44 – 7.39 (m, 2H), 7.34 – 7.26 (m, 1H), 7.01 (dd, *J* = 8.6, 2.1 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 173.33, 162.64, 141.28, 135.15, 133.59, 129.91, 129.54, 128.02, 127.47, 118.75, 114.21. HRMS (ESI-TOF) Calcd for $C_{13}H_9O_3$ $[M-H]^-$: 213.0552; found: 213.0555.



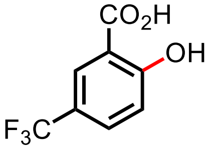
3-hydroxy-[1,1'-biphenyl]-2-carboxylic acid (4f)

Substrate **3f** was hydroxylated following general procedure conditions A, the hydroxylated product **4f** was obtained as a white solid (198 mg, 92%),^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.35 – 7.26 (m, 6H), 6.91 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.77 (dd, *J* = 7.5, 1.1 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 173.41, 159.78, 144.81, 143.20, 133.07, 129.37, 128.81, 128.02, 122.80, 117.72, 116.47. HRMS (ESI-TOF) Calcd for $C_{13}H_9O_3$ $[M-H]^-$: 213.0552; found: 213.0553.



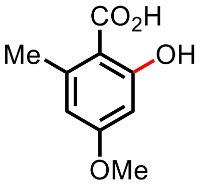
2-hydroxy-1-naphthoic acid (4g)

General procedure following conditions A, the hydroxylated product **4g** was obtained as a white solid (172 mg, 91%),^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 8.86 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.75 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.51 (dd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.33 (ddd, *J* = 8.0, 6.8, 1.1 Hz, 1H), 7.11 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 175.34, 165.31, 137.51, 133.63, 130.04, 129.93, 129.19, 126.49, 124.50, 119.95, 106.10. HRMS (ESI-TOF) Calcd for $C_{11}H_7O_3$ $[M-H]^-$: 187.0395; found: 187.0398.



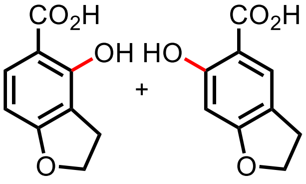
2-hydroxy-5-(trifluoromethyl)benzoic acid (4h)

Substrate **3h** was hydroxylated following general procedure conditions A but under 60 ºC, the hydroxylated product **4h** was obtained as an ivory solid (167 mg, 81%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 8.12 (dd, *J* = 2.4, 1.0 Hz, 1H), 7.73 (ddd, *J* = 8.8, 2.4, 0.7 Hz, 1H), 7.09 (dd, *J* = 8.8, 0.8 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 172.42, 165.75, 132.96 (q, *J* = 3.5 Hz), 128.96 (q, *J* = 4.2 Hz), 125.45 (q, *J* = 270.2 Hz), 122.32 (q, *J* = 33.1 Hz), 119.30, 114.17. ^{19}F NMR (376 MHz, Methanol-d_4) δ -65.77. HRMS (ESI-TOF) Calcd for $C_8H_4F_3O_3$ $[M-H]^-$: 205.0113; found: 205.0114.



2-hydroxy-4-methoxy-6-methylbenzoic acid (4i)

Substrate **3i** was hydroxylated following general procedure conditions A, the hydroxylated product **4i** was obtained as a yellow solid (127 mg, 70%),^{1}H NMR (600 MHz, Methanol-d_4) δ 6.34 – 6.30 (m, 2H), 3.80 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 174.96, 166.99, 165.37, 144.90, 111.46, 106.46, 99.61, 55.74, 24.29. HRMS (ESI-TOF) Calcd for $C_9H_9O_4$ $[M-H]^-$: 181.0501; found: 181.0505.

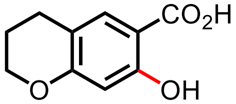


4-hydroxy-2,3-dihydrobenzofuran-5-carboxylic (4j, left)

6-hydroxy-2,3-dihydrobenzofuran-5-carboxylic acid (4j’, right)

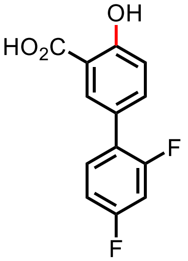
Substrate **3j** was hydroxylated following general procedure conditions A, the hydroxylated products **4j and 4j’** were obtained as inseparable mixture (1:1), (140 mg, 78%),^{1}H NMR (600 MHz, Methanol-d_4) δ 7.70 – 7.66 (m, 1H), 7.66 – 7.63 (m, 1H), 6.33 – 6.28 (m, 1H), 6.24 (d, *J* = 1.9 Hz, 1H), 4.66 – 4.62 (m, 2H), 4.61 – 4.57 (m, 2H), 3.16 – 3.08 (m, 4H). ^{13}C

NMR (151 MHz, Methanol-*d*$_4$) δ 173.46, 168.10, 167.78, 165.48, 160.69, 146.79, 133.11, 127.41, 120.30, 113.99, 107.68, 102.62, 98.21, 73.87, 73.81, 29.04, 27.09. (Peaks for –COOH are overlapped.) HRMS (ESI-TOF) Calcd for $C_9H_7O_4$ $[M-H]^-$: 179.0344; found: 179.0346.



7-hydroxychromane-6-carboxylic acid (4k)

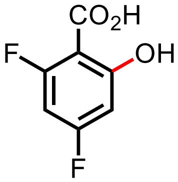
Substrate **3k** was hydroxylated following general procedure conditions A, the hydroxylated product **4k** was obtained as a brown solid (183 mg, 94%),^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.55 (t, *J* = 1.1 Hz, 1H), 6.22 (s, 1H), 4.34 – 3.98 (m, 2H), 2.85 – 2.49 (m, 2H), 2.11 – 1.82 (m, 2H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 173.34, 162.89, 162.37, 132.93, 115.48, 106.85, 104.33, 68.07, 25.15, 23.40. HRMS (ESI-TOF) Calcd for $C_{10}H_9O_4$ $[M-H]^-$: 193.0501; found: 193.0500.



2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (4l)

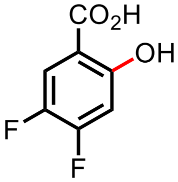
Substrate **3l** was hydroxylated following general procedure conditions A but under 60ºC, the hydroxylated product **4l** was obtained as a yellow solid (241 mg, 96%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.99 (s, 1H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.47 (td, *J* = 8.3, 5.9 Hz, 1H), 7.07 – 6.98 (m, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 172.76, 164.44 (dd, *J* = 247.6, 12.0 Hz), 162.98, 161.06 (dd, *J* = 248.7, 12.1 Hz), 137.01, 132.55 (d, *J* = 9.3 Hz), 132.51 (d, *J* = 9.6 Hz), 131.86, 127.14, 125.63 (dd, *J* = 13.6, 3.9 Hz), 118.57, 112.71 (dd, *J* = 21.4, 3.8 Hz), 105.13 (dd, *J* = 27.0, 25.8 Hz). ^{19}F NMR (376 MHz, Methanol-*d*$_4$) δ -113.68 (d, *J* = 6.8 Hz),

-115.69 (d, *J* = 7.3 Hz). HRMS (ESI-TOF) Calcd for $C_{13}H_7F_2O_3$ $[M-H]^-$: 249.0363; found: 249.0365.



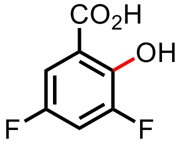
2,4-difluoro-6-hydroxybenzoic acid (4m)

Substrate **3m** was hydroxylated following general procedure conditions **B**, the hydroxylated product **4m** was obtained as a white solid **(**126 mg, 72%), ^{1}H NMR (600 MHz, Methanol-*d*4) δ 6.52 – 6.45 (m, 2H). ^{13}C NMR (151 MHz, Methanol-*d*4) δ 171.60 (d, *J* = 3.6 Hz), 167.79 (dd, *J* = 251.0, 15.5 Hz), 166.21 (dd, *J* = 16.5, 6.1 Hz), 165.19 (dd, *J* = 261.6, 17.2 Hz), 101.20 (dd, *J* = 13.5, 3.5 Hz), 101.03 (dd, *J* = 24.4, 4.4 Hz), 97.24 – 96.59 (m). ^{19}F NMR NMR (376 MHz, Methanol-*d*4) δ -102.64 (d, *J* = 12.7 Hz), -102.82 (d, *J* = 12.7 Hz). HRMS (ESI-TOF) Calcd for $C_7H_3F_2O_3$ $[M-H]^-$: 173.0050; found: 173.0054.



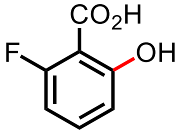
4,5-difluoro-2-hydroxybenzoic acid (4n)

Substrate **3n** was hydroxylated following general procedure conditions **B**, the hydroxylated product **4n** was obtained as an ivory solid **(**128 mg, 73%),^{1}H NMR (600 MHz, Methanol-*d*4) δ 7.72 – 7.65 (m, 1H), 6.87 – 6.79 (m, 1H). ^{13}C NMR (151 MHz, Methanol-*d*4) δ 171.97, 160.70 (dd, *J* = 11.8, 1.7 Hz), 156.11 (dd, *J* = 254.6, 14.3 Hz), 144.63 (dd, *J* = 240.2, 13.4 Hz), 118.84 (dd, *J* = 19.5, 2.6 Hz), 110.02, 106.78 (d, *J* = 20.3 Hz). ^{19}F NMR (376 MHz, Methanol-*d*4) δ -128.80 (d, *J* = 21.8 Hz), -151.10 (d, *J* = 21.7 Hz). HRMS (ESI-TOF) Calcd for $C_7H_3F_2O_3$ $[M-H]^-$: 173.0050; found: 173.0054.



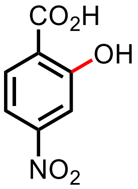
3,5-difluoro-2-hydroxybenzoic acid (4o)

Substrate **3o** was hydroxylated following general procedure conditions **B**, the hydroxylated product **4o** was obtained as a pink solid (113 mg, 65%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.38 (ddd, *J* = 8.7, 3.1, 2.0 Hz, 1H), 7.25 (ddd, *J* = 11.3, 8.3, 3.1 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 171.83, 154.95 (dd, *J* = 238.8, 10.5 Hz), 152.53 (d, *J* = 247.5 Hz), 148.38 (d, *J* = 12.5 Hz), 116.85, 111.73 (d, *J* = 23.8 Hz), 110.88 (dd, *J* = 27.6, 21.9 Hz). ^{19}F NMR (376 MHz, Methanol-d_4) δ -124.23, -134.42. HRMS (ESI-TOF) Calcd for $C_7H_3F_2O_3$ $[M-H]^-$: 173.0050; found: 173.0048.



2-fluoro-6-hydroxybenzoic acid (4p)

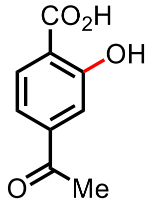
Substrate **3p** was hydroxylated following general procedure conditions **B**, the hydroxylated product **4p** was obtained as a yellow solid (96.2 mg, 62%),^{1}H NMR (600 MHz, Methanol-d_4) δ 7.40 (td, *J* = 8.5, 6.0 Hz, 1H), 6.74 (dt, *J* = 8.5, 1.0 Hz, 1H), 6.62 (ddd, *J* = 10.9, 8.2, 1.0 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 171.72, 164.40, 163.93 (d, *J* = 258.8 Hz), 136.16, 136.08, 113.96, 107.58 (d, *J* = 23.5 Hz). ^{19}F NMR (376 MHz, Methanol-d_4) δ -107.63. HRMS (ESI-TOF) Calcd for $C_7H_4FO_3$ $[M-H]^-$: 155.0144; found: 155.0147.



2-hydroxy-4-nitrobenzoic acid (4q)

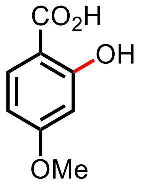
Substrate **3q** was hydroxylated following general procedure conditions **B**, the hydroxylated product **4q** was obtained as a yellow solid, (136 mg, 74%),^{1}H NMR (600 MHz, Methanol-

*d*₄) δ 8.09 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.74 – 7.69 (m, 2H). ^{13}C NMR (151 MHz, Methanol-*d*₄) δ 172.06, 163.45, 153.41, 133.04, 119.19, 114.29, 113.19. HRMS (ESI-TOF) Calcd for $C_7H_4NO_5$ [M-H]$^-$: 182.0089; found: 182.0090.



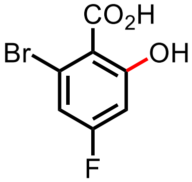
4-acetyl-2-hydroxybenzoic acid (4r)

Substrate **3r** was hydroxylated following general procedure conditions **B**, the hydroxylated product **4r** was obtained as an ivory solid (125 mg, 69%),^{1}H NMR (600 MHz, Methanol-*d*₄) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.48 – 7.44 (m, 2H), 2.60 (s, 3H). ^{13}C NMR (151 MHz, Methanol-*d*₄) δ 199.90, 163.00, 143.18, 132.16, 120.12, 119.04, 117.68, 26.95. (One peak corresponds –COOH was not detected) HRMS (ESI-TOF) Calcd for $C_9H_7O_4$ [M-H]$^-$: 179.0344; found: 179.0344.



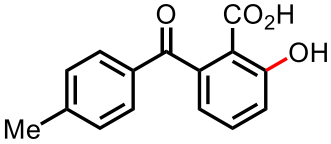
2-hydroxy-4-methoxybenzoic acid (4s)

Substrate **3s** was hydroxylated following general procedure conditions **B**, the hydroxylated product **4s** was obtained as an ivory solid (102 mg, 61%),^{1}H NMR (600 MHz, Methanol-*d*₄) δ 7.76 (d, *J* = 8.7 Hz, 1H), 6.49 – 6.40 (m, 2H), 3.82 (s, 3H). ^{13}C NMR (151 MHz, Methanol-*d*₄) δ 173.38, 167.14, 165.37, 132.89, 107.93, 106.78, 101.58, 55.97. HRMS (ESI-TOF) Calcd for $C_8H_7O_4$ [M-H]$^-$: 167.0344; found: 167.0346.



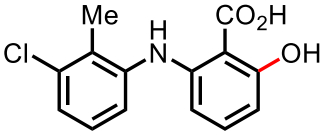
2-bromo-4-fluoro-6-hydroxybenzoic acid (4t)

Substrate **3t** was hydroxylated following general procedure conditions **B** but K_2HPO_4•$3H_2O$ was used instead of CsOAc and the reaction was run for 48 h, the hydroxylated product **4t** was obtained as an ivory solid (157 mg, 67%),^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 6.85 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.55 (dd, *J* = 10.2, 2.6 Hz, 1H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 173.96, 164.91 (d, *J* = 249.8 Hz), 164.81 (d, *J* = 14.0 Hz), 124.95 (d, *J* = 12.9 Hz), 118.13, 113.10 (d, *J* = 25.3 Hz), 103.64 (d, *J* = 23.2 Hz). ^{19}F NMR (376 MHz, Methanol-*d*$_4$) δ -111.12. HRMS (ESI-TOF) Calcd for $C_7H_3BrFO_3$ [M-H]$^-$: 232.9250; found: 232.9251.



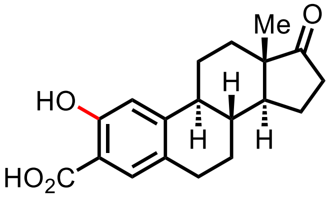
2-hydroxy-6-(4-methylbenzoyl)benzoic acid (4u)

Substrate **3u** was hydroxylated following general procedure conditions **B** to afford the hydroxylated product **4u** (244 mg, 95%), ^{1}H NMR (600 MHz, Methanol-*d*$_4$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.53 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.08 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.76 (dd, *J* = 7.4, 1.1 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (151 MHz, Methanol-*d*$_4$) δ 200.93, 162.72, 144.93, 144.57, 136.90, 133.57, 130.38, 130.06, 129.85, 118.45, 117.84, 21.57. (One peak corresponds –COOH was not detected) HRMS (ESI-TOF) Calcd for $C_{15}H_{11}O_4$ [M-H]$^-$: 255.0657; found: 255.0657.



2-((3-chloro-2-methylphenyl)amino)-6-hydroxybenzoic acid (4v)

Substrate **3v** was hydroxylated following general procedure conditions **B**, the hydroxylated product **4v** was obtained as a brown solid (255 mg, 92%),^{1}H NMR (400 MHz, Methanol-d_4) δ 7.26 – 7.19 (m, 1H), 7.11 – 7.03 (m, 2H), 6.97 (t, J = 8.2 Hz, 1H), 6.26 – 6.04 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, Methanol-d_4) δ 164.47, 150.04, 143.43, 136.18, 133.59, 131.48, 127.84, 125.18, 123.01, 106.38, 104.66, 104.18, 15.23. (One peak corresponds – COOH was not detected) HRMS (ESI-TOF) Calcd for $C_{14}H_{11}ClNO_3$ [M-H]$^-$: 276.0427; found: 276.0427.



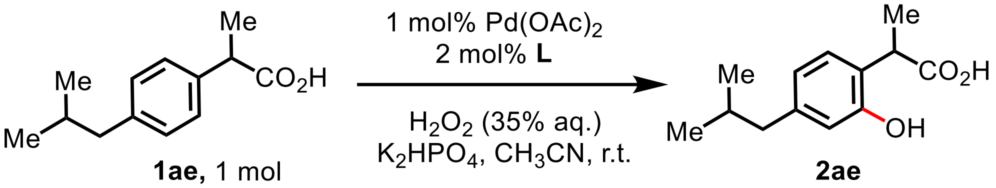
(8*R*,9*S*,13*S*,14*S*)-2-hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3-carboxylic acid (4w)

Substrate **3w** (0.5 mmol) was hydroxylated following general procedure conditions **B** but under room temperature, K_2HPO_4•$3H_2O$ was used instead of CsOAc. the hydroxylated product **4w** was obtained as an ivory solid (96.2 mg, 61%), ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.55 (s, 1H), 6.85 (s, 1H), 2.88 – 2.78 (m, 2H), 2.53 – 2.47 (m, 1H), 2.40 – 2.35 (m, 1H), 2.31 – 2.26 (m, 1H), 2.18 – 2.01 (m, 3H), 1.93 – 1.87 (m, 1H), 1.72 – 1.39 (m, 6H), 0.93 (s, 3H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 223.44, 173.40, 160.97, 149.76, 131.28, 128.61, 114.55, 111.70, 51.79, 49.17, 46.03, 39.11, 36.69, 32.71, 29.31, 27.61, 26.58, 22.51, 14.21. HRMS (ESI-TOF) Calcd for $C_{19}H_{21}O_4$ [M-H]$^-$: 313.1440; found: 313.1439.

3. Synthetic Application

3.1. Large Scale Reactions

Attention: Peroxides are particularly dangerous when they are concentrated. Large scale reactions should be quenched and tested by the potassium iodide starch test paper.



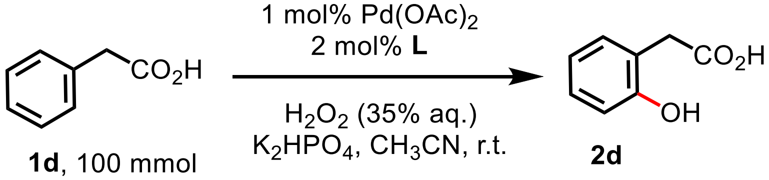
1ae, 1 mol

2ae

$Pd(OAc)_2$ (2.24 g, 0.01 mol, 1 mol%), **L4** (3.62 g, 0.02 mol, 2 mol%), carboxylic acid **1ae** (206 g, 1.0 mol), and K_2HPO_4 (260 g, 1.5 mol, 1.5 equiv.) were weighed and placed in a 3 L round bottom glass flask. Then, CH_3CN (2.0 L) was added and stirred vigorously for 30 min and H_2O_2 (35% aq., 300 mL, 3.5 equiv.) was carefully added in several portions. The mixture was stirred at ambient temperature for 24 h. After that, the reaction was monitored by LCMS and H_2O_2 (35% aq., 100 mL, 1.1 equiv.) was added and stirred vigorously for an additional 24 h. Upon completion, the reaction was carefully quenched with $Na_2S_2O_3$ aqueous solution until H_2O_2 was completely decomposed. The mixture was acidified with 1 M aqueous HCl and filtered through Celite then washed with EtOAc. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine then dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by multiple recrystallizations with Hexane/DCM. The mother liquor was further purified by flash chromatography (Hexane/EtOAc with 1% AcOH, v/v). The total hydroxylated product **2ae** was obtained as a white solid (179.2 g, 81%).

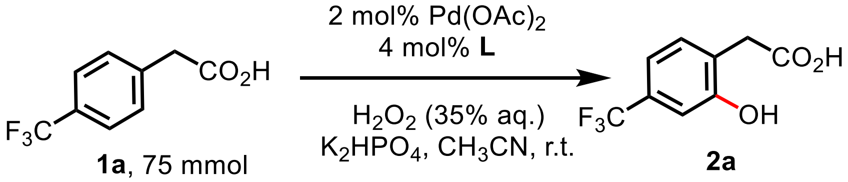
Reaction equipment Hydroxylated product **2ae**

Fig. S1. C(sp^2)–H hydroxylation of Ibuprofen

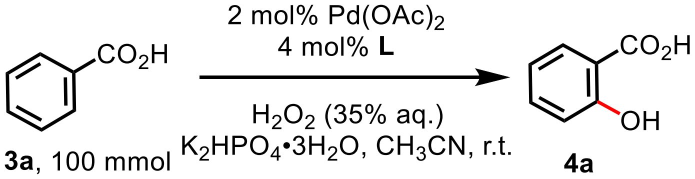


$Pd(OAc)_2$ (224 mg, 1 mmol, 1 mol%), **L4** (362 mg, 2 mmol, 2 mol%), carboxylic acid **1d** (13.6 g, 100 mmol), and K_2HPO_4 (26.0 g, 150 mmol, 1.5 equiv.) were weighed and placed in a 500 mL round bottom glass flask. Then, CH_3CN (250 mL) was added and stirred vigorously for 30 min and H_2O_2 (35% aq., 30 mL, 3.5 equiv.) was carefully added in several portions. The mixture was stirred at ambient temperature for 48 h. Upon completion, the reaction was carefully quenched with $Na_2S_2O_3$ aqueous solution until H_2O_2 was completely decomposed. The mixture was acidified with 1 M aqueous HCl and filtered through Celite then washed with EtOAc. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by multiple recrystallizations with Hexane/ EtOAc.

The mother liquor was further purified by flash chromatography (Hexane/EtOAc with 1% AcOH, v/v). The hydroxylated product **2d** was obtained as a white solid (12.4 g, 82%).



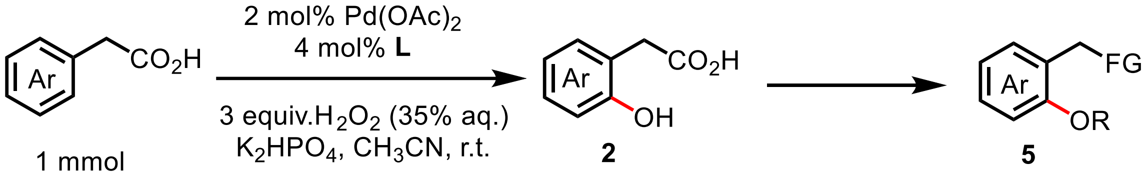
$Pd(OAc)_2$ (336 mg, 1.5 mmol, 2 mol%), **L4** (543 mg, 3 mmol, 2 mol%), carboxylic acid **1d** (15.3 g, 75 mmol), and K_2HPO_4 (19.7 g, 113 mmol, 1.5 equiv.) were weighed and placed in a 500 mL round bottom glass flask. Then, CH_3CN (200 mL) was added and stirred vigorously for 30 min and H_2O_2 (35% aq., 22.5 mL, 3.5 equiv.) was carefully added in several portions. The mixture was stirred at ambient temperature for 48 h. Upon completion, the reaction was carefully quenched with $Na_2S_2O_3$ aqueous solution until H_2O_2 was completely decomposed. The mixture was acidified with 1 M aqueous HCl and filtered through Celite then washed with EtOAc. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by flash chromatography (Hexane/EtOAc with 1% AcOH, v/v). The hydroxylated product **2d** was obtained as a yellow solid (12.6 g, 76%).



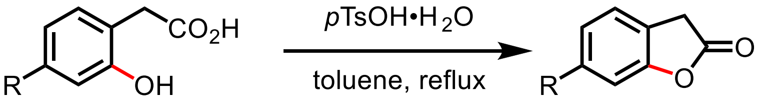
$Pd(OAc)_2$ (448 mg, 2 mmol, 2 mol%), **L4** (724 mg, 4 mmol, 4 mol%), carboxylic acid **1d** (12.2 g, 100 mmol), and K_2HPO_4 (26.0 g, 150 mmol, 1.5 equiv.) were weighed and placed in a 500 mL round bottom glass flask. Then, CH_3CN (250 mL) was added and stirred vigorously for 30 min and H_2O_2 (35% aq., 30 mL, 3.5 equiv.) was carefully added in several portions. The mixture was stirred at ambient temperature for 48 h. Upon completion, the reaction was carefully quenched with $Na_2S_2O_3$ aqueous solution until H_2O_2 was completely decomposed. The mixture was acidified with 1 M aqueous HCl and filtered through Celite then washed with EtOAc. The aqueous layer was extracted with ethyl acetate three times.

The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was purified by multiple recrystallizations. The hydroxylated product **2d** was obtained as a white solid (10.6 g, 77%).

3.2. Further Derivatizations of Phenolic Products

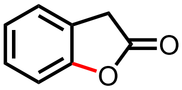


$Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), **L4** (7.3 mg, 0.04 mmol, 4 mol%), carboxylic acid **1d** or **1a** (1.0 mmol), and K_2HPO_4 (260.0 mg, 1.5 mmol, 1.5 equiv.) were weighed and placed in an 8 mL vial. Then, CH_3CN (3.0 mL) was added and stirred for 5 min, followed by the addition of H_2O_2 (35% aq., 300 uL, 3.5 equiv.). The vial was sealed with a screw cap and stirred at ambient temperature for 24 h. Upon completion, the reaction was quenched with aqueous Na_2SO_3 solution and acidified with 1 M aqueous HCl. The solution was filtered through a pad of Celite then washed with ethyl acetate. The aqueous layer was extracted with ethyl acetate three times and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture **2d** or **2a** was used in the next step without further purification.



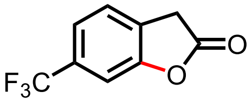
5a, **5b**

To a 25 mL flask provided with Dean-Stark tramp and magnetic stirrer was added crude **2d** or **2a** in 15 mL of toluene and catalytic amounts of *p*-TsOH (0.1 mmol). The mixture was refluxed for overnight with removal of water and then the residual solvent was removed at reduced pressure. The crude mixture was purified by flash column chromatography (Hexane/EtOAc) to give the corresponding lactone products.



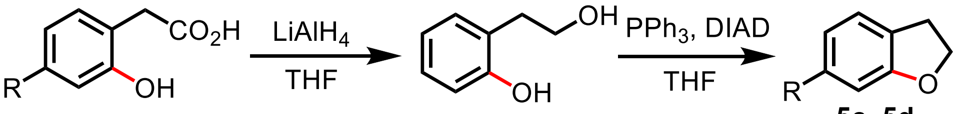
benzofuran-2(3*H*)-one (5a)

[CAS: 553-86-6] Yellow oil, 91.1 mg, 68%, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.27 (m, 2H), 7.17 – 7.09 (m, 2H), 3.74 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.29, 154.87, 129.07, 124.81, 124.27, 123.21, 110.97, 33.17. The NMR data matches the reported data[5].



6-(trifluoromethyl)benzofuran-2(3*H*)-one (5b)

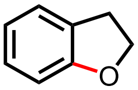
Yellow solid, 123.2 mg, 61%, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.39 (m, 2H), 7.38 – 7.34 (m, 1H), 3.81 (s, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 172.85, 154.84, 131.78 (q, *J* = 33.1 Hz), 127.17, 123.60 (q, *J* = 272.4 Hz), 125.23, 121.31 (q, *J* = 4.0 Hz), 108.23 (q, *J* = 3.9 Hz), 32.94. ^{19}F NMR (376 MHz, CDCl$_3$) δ -65.22. HRMS (ESI-TOF) Calcd for $C_9H_4F_3O_2$ [M-H]$^-$: 201.0169; found: 201.0168.



5c, **5d**

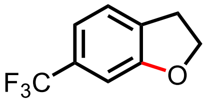
To a solution of crude **2d** or **2a** in THF (2.0 mL) was added lithium aluminum hydride solution (2.0 M in THF, 1.0 mL, 2 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 6 h. Upon completion, the mixture was diluted with 10 mL Et$_2$O and carefully quenched with 1 M aqueous HCl at 0 °C until the solution becomes clear. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine then dried and evaporated under reduced pressure. The crude product was used in the next step without further purification.

To a solution of the crude alcohol in THF (2.0 mL) was added PPh$_3$ (314.4 mg, 1.2 mmol) and diisopropyl azodicarboxylate (303.3 mg, 1.5 mmol). The mixture was stirred at ambient temperature until the diol was no longer apparent by TLC. Upon completion, the reaction was diluted with 20 mL diethyl ether and stirred for 30 min. The mixture was filtered through Celite and evaporated under reduced pressure. The crude product was purified by flash chromatography (Hexane/EtOAc = 10:1, v/v) to give the corresponding product.



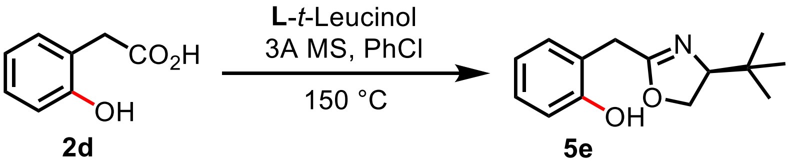
2,3-dihydrobenzofuran (5c)

[CAS: 496-16-2] Colourless liquid, 87.6 mg, 73%, ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.20 (d, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.84 (td, *J* = 7.4, 1.0 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 4.56 (t, *J* = 8.7 Hz, 2H), 3.21 (t, *J* = 8.6 Hz, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 160.14, 128.06, 127.00, 125.04, 120.46, 109.49, 71.14, 29.88. The NMR data matches the reported data[6].

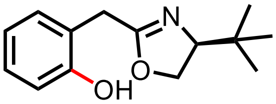


6-(trifluoromethyl)-2,3-dihydrobenzofuran (5d)

[CAS: 1391072-82-4] yellow liquid, 120.8 mg, 64%, ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.00 (s, 1H), 4.63 (t, *J* = 8.8 Hz, 2H), 3.25 (tt, *J* = 8.7, 1.3 Hz, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 160.47, 131.33, 131.71 (q, *J* = 32.2 Hz), 125.16, 124.28 (q, *J* = 272.1 Hz), 117.65 (q, *J* = 4.2 Hz), 106.47 (q, *J* = 3.8 Hz), 71.80, 29.65. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -64.91.The NMR data matches the reported data[7].

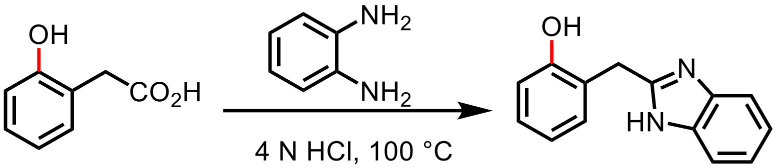


To a solution of crude **2d** in PhCl (4.0 mL) was added **L**-*tert*-Leucinol (156 uL, 1.2 mmol) and activated 3A molecule sieve (200 mg). The reaction mixture was heated to 150 °C and stirred for 24 h. After cooling down to room temperature, the reaction mixture was diluted with EtOAc, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc = 4:1, v/v) to give product **5e** as a white solid (177.1 mg, 76%).



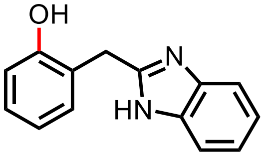
(*S*)-2-((4-(tert-butyl)-4,5-dihydrooxazol-2-yl)methyl)phenol (**5e**)

[CAS: 1816267-52-3] ^{1}H NMR (600 MHz, Chloroform-*d*) δ 10.60 (br s, 1H), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H), 7.05 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.98 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.83 (td, *J* = 7.4, 1.3 Hz, 1H), 4.25 (dd, *J* = 10.2, 8.8 Hz, 1H), 4.13 (t, *J* = 8.4 Hz, 1H), 3.89 (dd, *J* = 10.1, 8.0 Hz, 1H), 3.69 – 3.57 (m, 2H), 0.87 (s, 9H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.94, 156.60, 130.64, 129.16, 122.11, 120.25, 119.07, 74.93, 69.73, 33.65, 31.69, 25.72.The NMR data matches the reported data[8].



2d **5f**

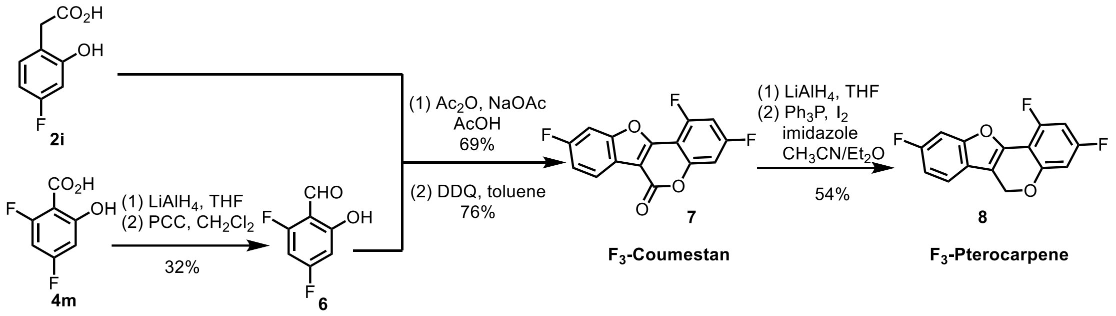
To a solution of crude **2d** in 4M aqueous HCl (2.0 mL) was added *o*-Phenylenediamine (129 mg, 1.2 mmol). The reaction mixture was heated to 100 °C and stirred for 24 h. After cooling down to room temperature, a saturated aqueous $NaHCO_3$ solution (20 mL) was added and extracted with EtOAc three times. The combined organic layers were washed with brine then dried and evaporated under reduced pressure. The crude product was purified by flash chromatography (DCM-MeOH 20:1, v/v) to give product **5f** as a white solid (105.3 mg, 47%).



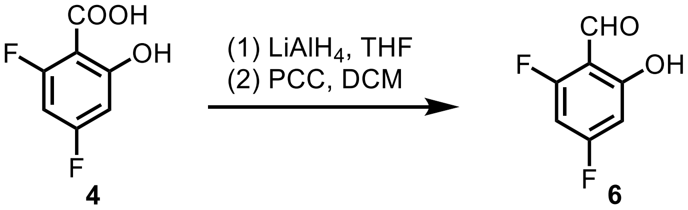
2-((1H-benzo[d]imidazol-2-yl)methyl)phenol (**5f**)

[CAS: 3416-07-7] ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.50 – 7.44 (m, 2H), 7.18 – 7.13 (m, 2H), 7.12 – 7.05 (m, 2H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.77 (td, *J* = 7.5, 1.2 Hz, 1H), 4.20 (s, 2H). ^{13}C NMR (151 MHz, Methanol-d_4) δ 155.13, 154.26, 138.15, 129.97, 127.95, 123.21, 121.71, 119.36, 114.82, 114.00, 29.40. The NMR data matches the reported data[9].

3.3. Synthesis of Coumestan and Ptercarpene Derivatives



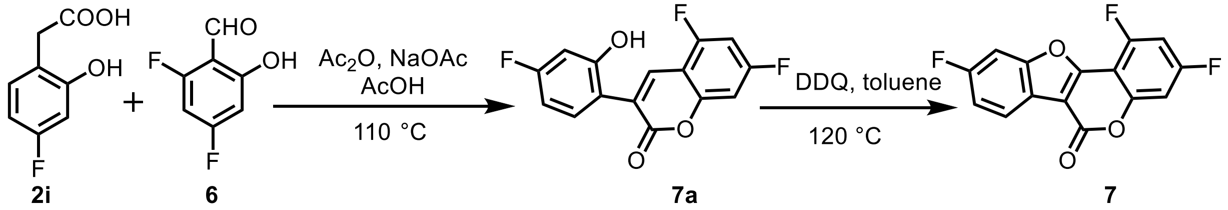
Synthesis of compound 6



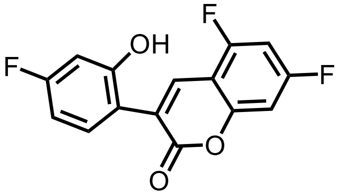
To a solution of **4** (1.044 g, 6 mmol) in THF (10.0 mL) was added lithium aluminum hydride solution (2.0 M in THF, 4.5 mL, 9 mmol) at 0 °C. The reaction mixture was heated to 50 °C and stirred for 6 h. After cooling down to room temperature, the mixture was diluted with 20 mL of Et_2O and carefully quenched with 1 M aqueous HCl at 0 °C until the solution becomes clear. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine then dried and evaporated under reduced pressure. The crude product was used in the next step without further purification.

To a solution of crude alcohol in DCM (20 mL) was added Pyridinium chlorochromate (1.293 mg, 6 mmol, 1.0 equiv.) and Celite (1 g). The mixture was stirred at room temperature for 2 h. Upon completion, the mixture was filtered and directly purified by flash chromatography (Hexane/EtOAc = 10:1 as eluent) to give compound **6** as a colorless oil (This compound is extremely volatile).

Synthesis of compound 7



To a solution of **2i** (170 mg, 1 mmol) and **6** (190 mg, 1.2 mmol) in AcOH (4.0 mL) was added NaOAc (410 mg, 5 mmol) and Ac_2O (227 uL, 2.4 mmol). The reaction mixture was heated to 110 °C and stirred for 20 h. After cooling down to room temperature, a saturated aqueous $NaHCO_3$ solution (20 mL) was added and extracted with EtOAc three times. The combined organic layers were washed with brine then dried and evaporated under reduced pressure. The crude product was purified by flash chromatography (Hexane/EtOAc = 5:1, v/v) to give product **7a** as a white solid (201.5 mg, 69%).

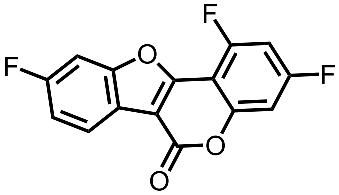


5,7-difluoro-3-(4-fluoro-2-hydroxyphenyl)-2*H*-chromen-2-one (7a)

^{1}H NMR (600 MHz, Acetone-d_6) δ 9.15 (s, 1H), 8.05 (s, 1H), 7.44 (dd, J = 8.5, 6.7 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.78 – 6.68 (m, 2H). ^{13}C NMR (151 MHz, Acetone-d_6) δ 164.85 (dd, J = 251.6, 14.8 Hz), 164.52 (d, J = 245.7 Hz), 159.90 (dd, J = 254.9, 15.4 Hz), 159.54, 157.54 (d, J = 11.6 Hz), 155.98 (dd, J = 15.6, 7.6 Hz), 134.76, 133.34 (d, J = 15.1 Hz), 125.49, 119.36 (d, J = 3.8 Hz), 107.39 (dd, J = 19.3, 3.3 Hz), 107.06 (d, J = 21.7 Hz), 104.01 (d, J =

24.3 Hz), 101.06 (dd, J = 26.0, 4.4 Hz), 100.72 (dd, J = 27.3, 24.3 Hz). ^{19}F NMR (376 MHz, Acetone-d_6) δ -105.29 (d, J = 7.8 Hz), -112.73, -117.22 (d, J = 7.8 Hz). HRMS (ESI-TOF) Calcd for $C_{15}H_8F_3O_3$ [M+H]$^+$: 293.0426; found: 293.0429.

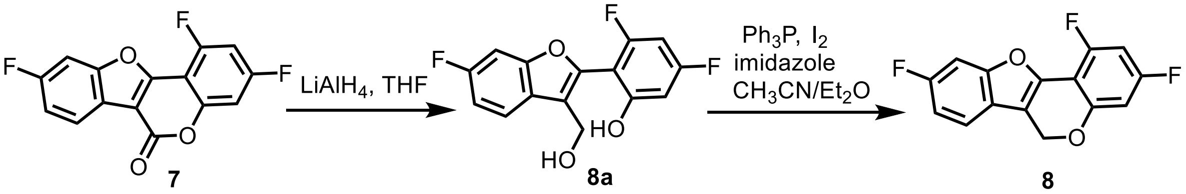
To a solution of **7a** (0.69 mmol) in toluene (8.0 mL) was added DDQ (317.8 mg, 1.4 mmol). The reaction mixture was heated to 120 °C and stirred for 12 h. After cooling down to room temperature, the mixture was filtered through Celite and evaporated under reduced pressure. The crude product was purified by flash chromatography (Hexane/EtOAc = 10:1, v/v) to give product **7** as a white solid (152.1 mg, 76%).



1,3,9-trifluoro-6*H*-benzofuro[3,2-*c*]chromen-6-one (7)

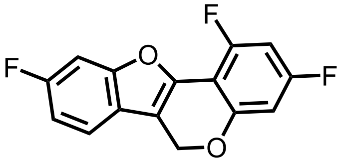
^{1}H NMR (600 MHz, Chloroform-d) δ 8.06 (dd, J = 8.6, 5.3 Hz, 1H), 7.44 (dd, J = 8.3, 2.2 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.08 (dt, J = 8.9, 2.0 Hz, 1H), 6.94 (ddd, J = 9.9, 8.8, 2.3 Hz, 1H). ^{13}C NMR (151 MHz, Chloroform-d) δ 164.25 (dd, J = 255.3, 13.7 Hz), 162.23 (d, J = 247.8 Hz), 157.88 (dd, J = 260.0, 15.0 Hz), 157.60, 156.85, 155.93 (d, J = 14.0 Hz), 154.77 (dd, J = 15.1, 7.7 Hz), 122.45 (d, J = 10.1 Hz), 118.91, 114.13 (d, J = 23.9 Hz), 105.39, 101.75 (dd, J = 26.1, 4.5 Hz), 101.42 (dd, J = 26.9, 23.0 Hz), 100.56 (d, J = 21.3 Hz) 100.42 (d, J = 27.6 Hz). ^{19}F NMR (376 MHz, Chloroform-d) δ -104.46 (d, J = 8.5 Hz), -112.27 (d, J = 8.4 Hz), -114.33. HRMS (ESI-TOF) Calcd for $C_{15}H_6F_3O_3$ [M+H]$^+$: 291.0269; found: 291.0268.

Synthesis of compound 8



To a solution of **7** (0.2 mmol) in THF (1.0 mL) was added lithium aluminum hydride solution (2.0 M in THF, 0.2 mL, 0.4 mmol) at 0 °C. The reaction mixture was heated to 50 °C and stirred for 6 h. After cooling down to room temperature, the mixture was diluted with 10 mL THF and carefully quenched with 1 M aqueous HCl at 0 °C until the solution becomes clear. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine then dried and evaporated under reduced pressure. The crude product was used in the next step without further purification.

To a solution of **8a**, imidazole (40.8 mg, 0.6 mmol) and PPh_3 (104.8 mg, 0.4 mmol) in CH_3CN/Et_2O (1.0/1.0 mL) was added I_2 (101.6 mg, 0.4 mmol) at 0 °C. The mixture was stirred at ambient temperature for 12 h. Upon completion, the reaction mixture was diluted with saturated aqueous NH_4Cl solution and extracted with EtOAc three times. The combined organic layers were washed with brine then dried and evaporated under reduced pressure. The crude product was purified by flash chromatography (Hexane/EtOAc = 20:1, v/v) to give product **8** as a white solid (30.0 mg, 54% yield in two steps).

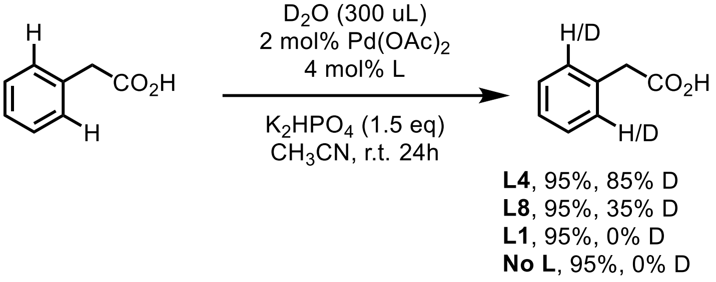


1,3,9-trifluoro-6*H*-benzofuro[3,2-*c*]chromene (8)

^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 2H), 7.04 (ddd, *J* = 9.4, 8.6, 2.3 Hz, 1H), 6.54 – 6.46 (m, 2H), 5.58 (s, 2H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 163.14 (dd, *J* = 249.3, 14.8 Hz), 161.10 (d, *J* = 243.9 Hz), 157.28 (dd, *J* = 253.2, 15.1 Hz), 155.86 (dd, *J* = 14.8, 6.6 Hz), 155.81 (dd, *J* = 15.4 Hz), 145.13, 121.12, 119.03 (d, *J* = 9.8 Hz), 111.98 (d, *J* = 24.2 Hz), 107.74, 102.44 (dd, *J* = 17.7, 3.9 Hz), 100.96 (dd, *J* = 25.8, 3.8 Hz), 100.08 (d, *J* = 27.0 Hz), 98.06 (dd, *J* = 26.4, 24.8 Hz), 65.70. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -107.59 (d, *J* = 6.5 Hz), -114.64 (d, *J* = 6.4 Hz), -115.60. HRMS (ESI-TOF) Calcd for $C_{15}H_8F_3O_2$ $[M+H]^+$: 277.0476; found: 277.0472.

4. Mechanistic Studies

4.1. Deuterium-Labeling Experiments



$Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), **Ligand** (4 mol%), carboxylic acid **1d** (1.0 mmol), and K_2HPO_4 (260.0 mg, 1.5 mmol, 1.5 equiv.) were weighed and placed in an 8 mL vial. Then, CH_3CN (3.0 mL) was added and stirred for 5 min, followed by the addition of D_2O (300 uL). The vial was sealed with a screw cap and stirred at ambient temperature for 24 h. Upon completion, the reaction mixture was diluted with EtOAc and acidified with formic acid. The mixture was filtered through Celite and evaporated under reduced pressure. The ratio of deuterium was analyzed by ^1H NMR with the corresponding pure compound.

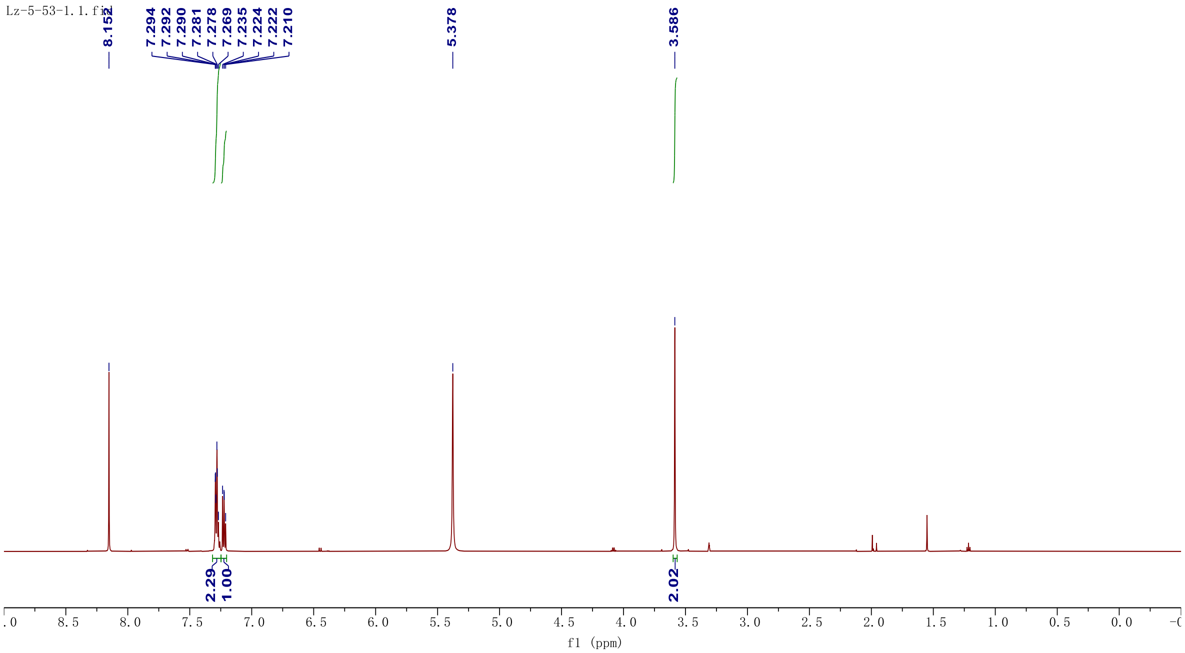


Fig. S2. ^1H NMR of H/D exchange experiment using L4

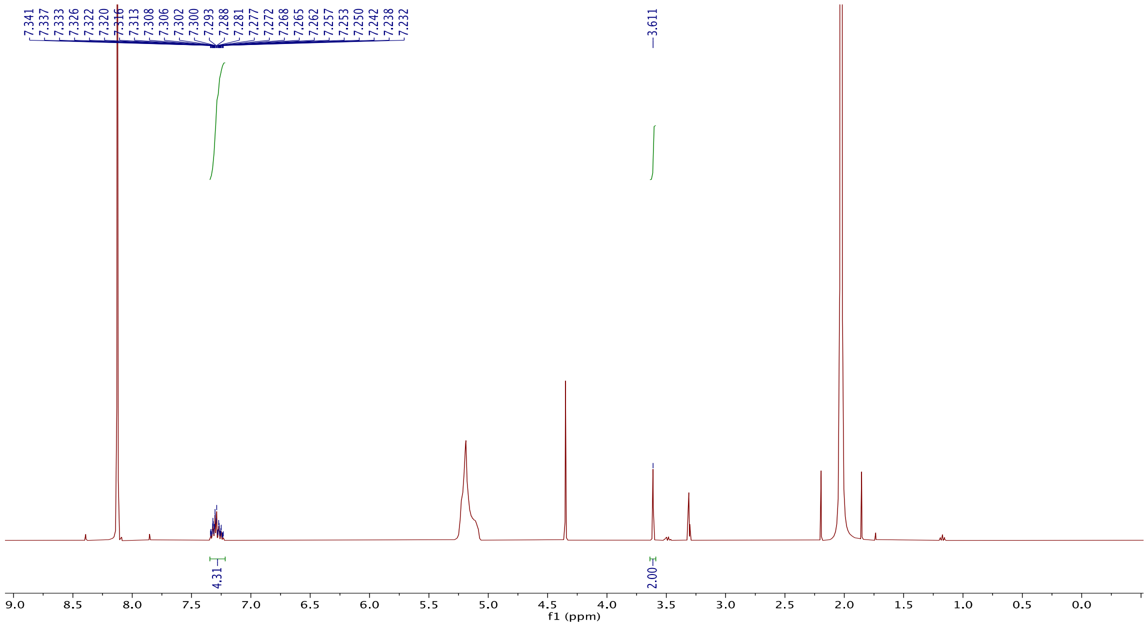


Fig. S3. ^{1}H NMR of H/D exchange experiment using L8

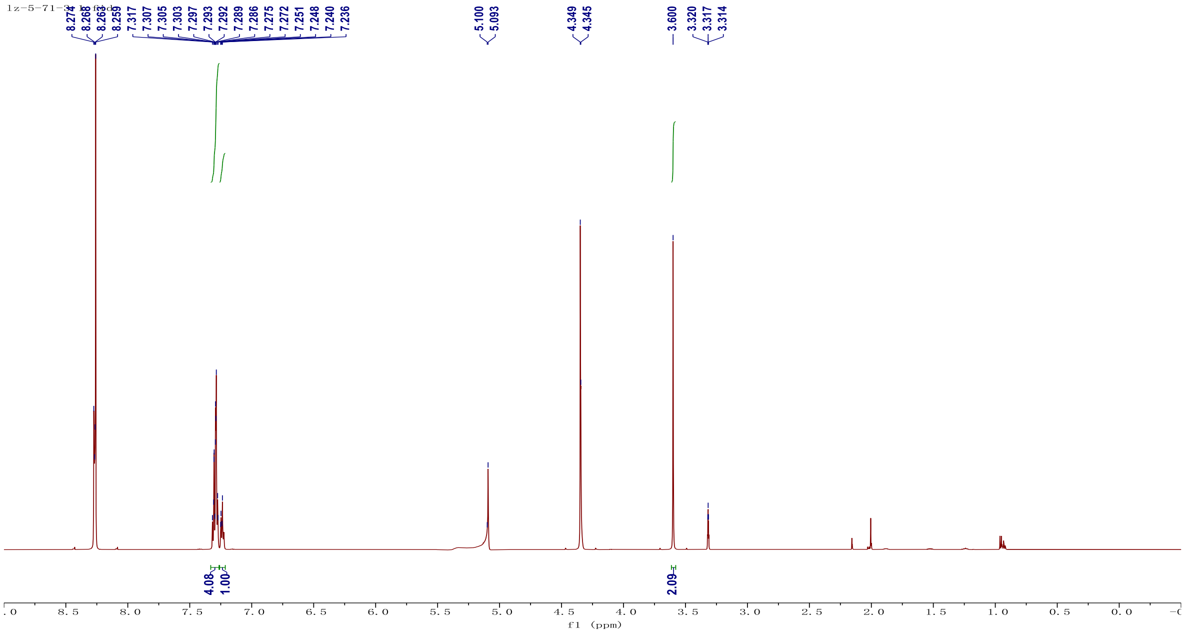


Fig. S4. ^{1}H NMR of H/D exchange experiment using L1

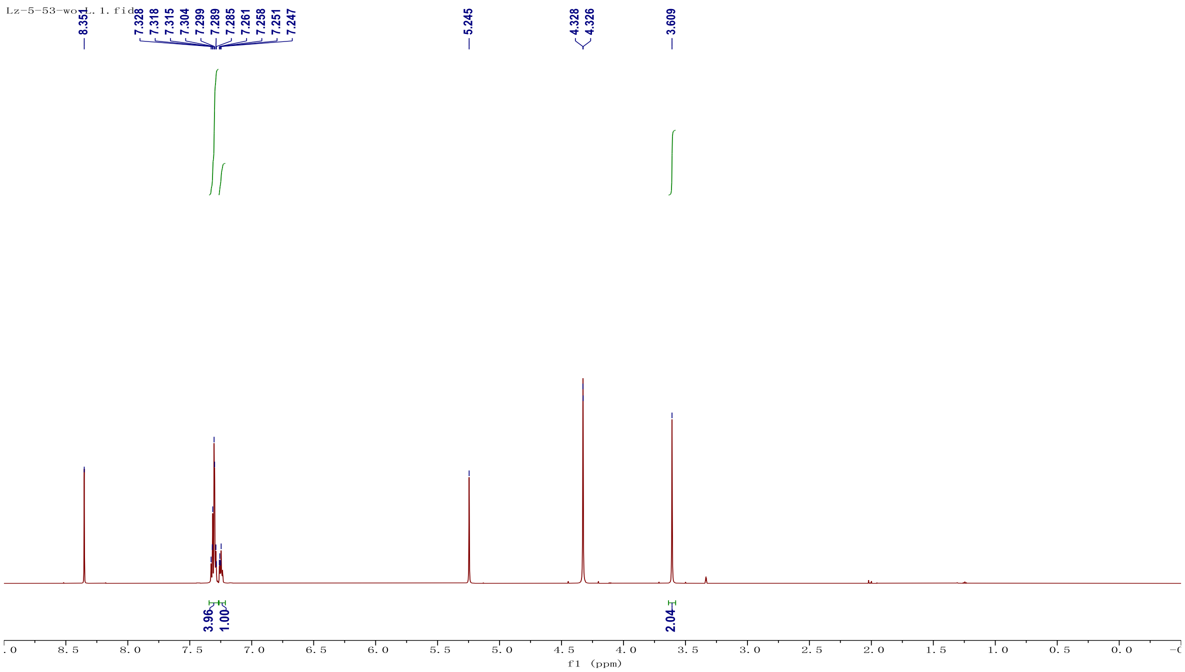
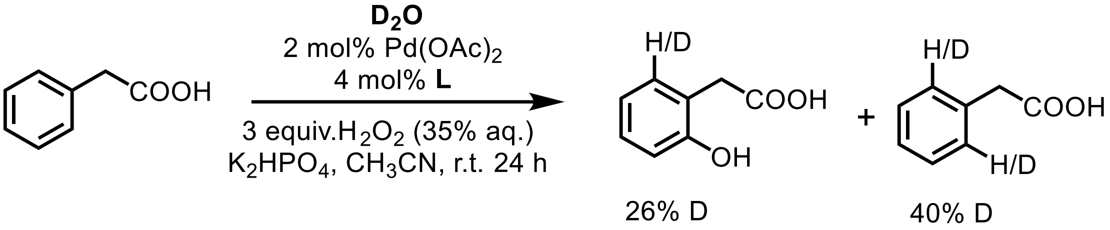


Fig. S5. ^{1}H NMR of H/D exchange experiment with no ligand



$Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), **L4** (7.3 mg, 0.04 mmol, 4 mol%), carboxylic acid **1d** (1.0 mmol), and K_2HPO_4 (260.0 mg, 1.5 mmol, 1.5 equiv.) were weighed and placed in an 8 mL vial. Then, CH_3CN (3.0 mL) was added and stirred for 5 min, followed by the addition of H_2O_2 (35% aq., 300 uL, 3.0 equiv.) and D_2O (300 uL). The vial was sealed with a screw cap and stirred at ambient temperature for 24 h. Upon completion, the reaction was quenched with saturated Na_2SO_3 solution. The mixture was diluted with EtOAc and acidified with formic acid. The solution was filtered through Celite, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The ratios of deuterium were analyzed by ^{1}H NMR with the corresponding pure compounds.

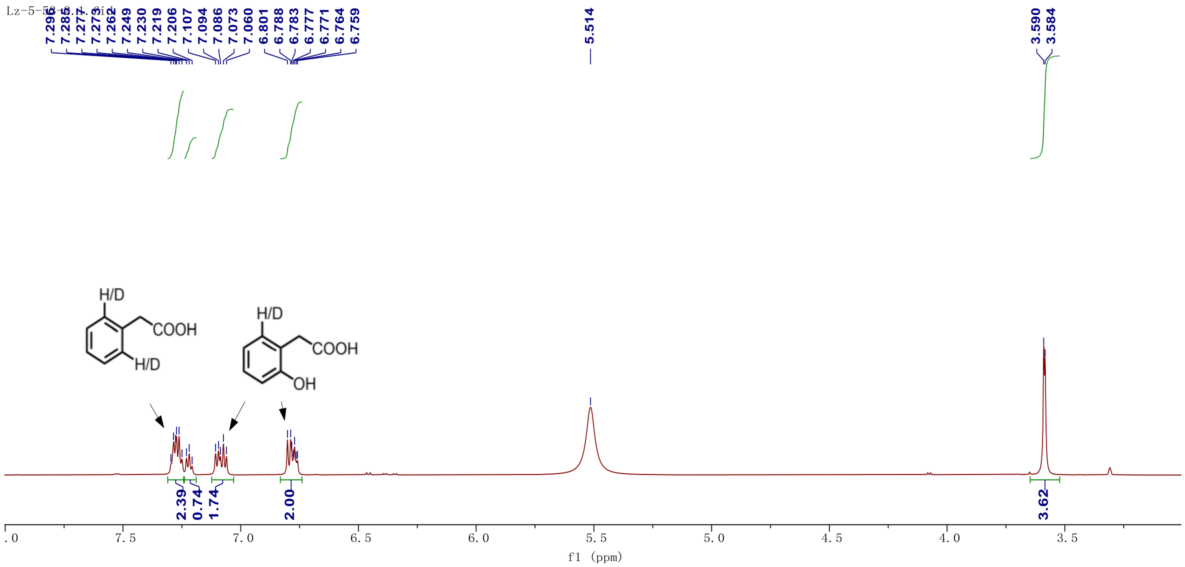
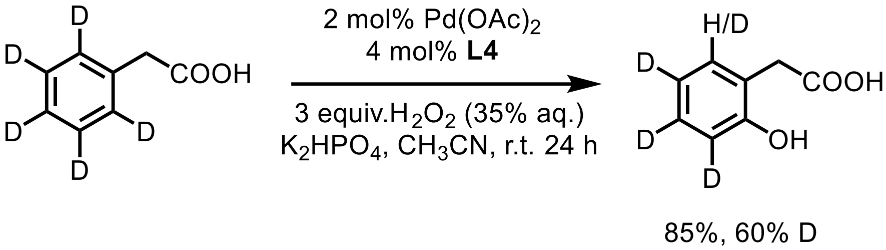


Fig. S6. ^{1}**H NMR of C–H hydroxylation in the presence of** D_2O



$Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), **L4** (7.3 mg, 0.04 mmol, 4 mol%), carboxylic acid **1d-**_d_5 (1.0 mmol), and K_2HPO_4 (260.0 mg, 1.5 mmol, 1.5 equiv.) were weighed and placed in an 8 mL vial. Then, CH_3CN (3.0 mL) was added and stirred for 5 min, followed by the addition of H_2O_2 (35% aq., 300 uL, 3.0 equiv.). The vial was sealed with a screw cap and stirred at ambient temperature for 24 h. Upon completion, the reaction was quenched with saturated Na_2SO_3 solution. The reaction mixture was diluted with EtOAc and acidified with formic acid. The solution was filtered through Celite, and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The ratios of deuterium were analyzed by ^{1}H NMR with the corresponding pure compounds.

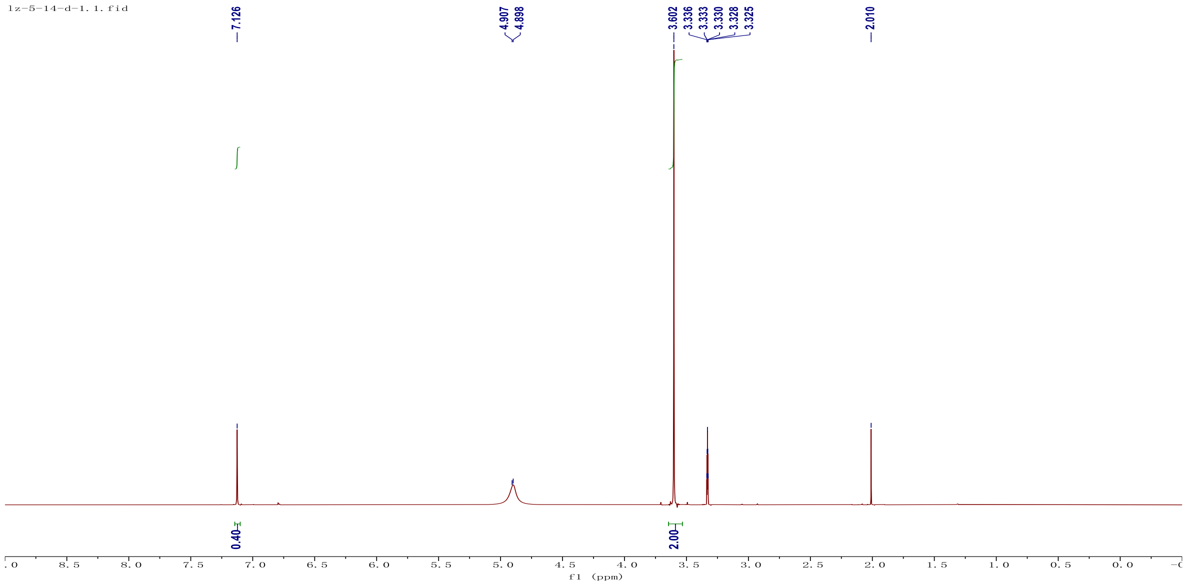
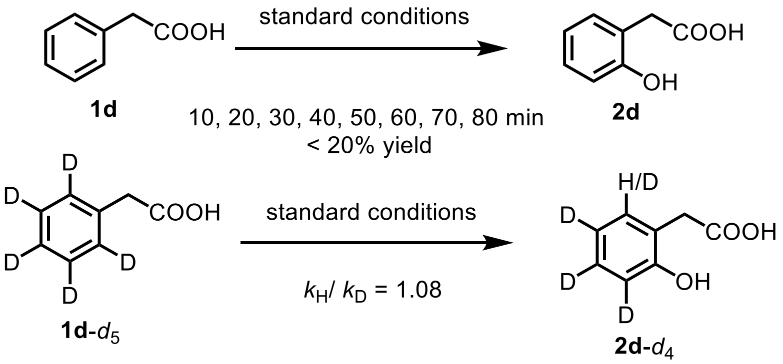


Fig. S7. ^{1}H NMR of C–H hydroxylation of 1d-*d*5

4.2. KIE Experiments



$Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), **L4** (7.3 mg, 0.04 mmol, 4 mol%), carboxylic acid **1d** (1.0 mmol) or **1d-***d*5 (1.0 mmol), and K_2HPO_4 (260.0 mg, 1.5 mmol, 1.5 equiv.) were weighed and placed in an 8 mL vial. Then, CH_3CN (3.0 mL) was added and stirred for 5 min, followed by the addition of H_2O_2 (35% aq., 300 uL, 3.0 equiv.) and CH_3NO_2 (54 uL, 1 mmol). The reaction mixture was stirred at ambient temperature. A 40 uL reaction mixture was taken at 10 min, 20 min, 30 min, 40 min, 50 min, 60 min, 70 min, 80 min and immediately diluted with formic acid (10 uL) in Methanol-d_4 (500 uL). The obtained yields were plotted as concentration vs. time (Table **S8-9**) and the following initial rates were calculated.

t (min)	**2d** (X10^{-3} mmol/mL)	**2d-*d*** (X10^{-3} mmol/mL)
10	6.67	5
20	13.33	13.33
30	23.33	23.33
40	33.33	31.67
50	40	38.33
60	48.33	43.33
70	55	55
80	66.67	60
k	0.8453	0.7857

Table S8. Reaction rate of hydroxylation of 2d

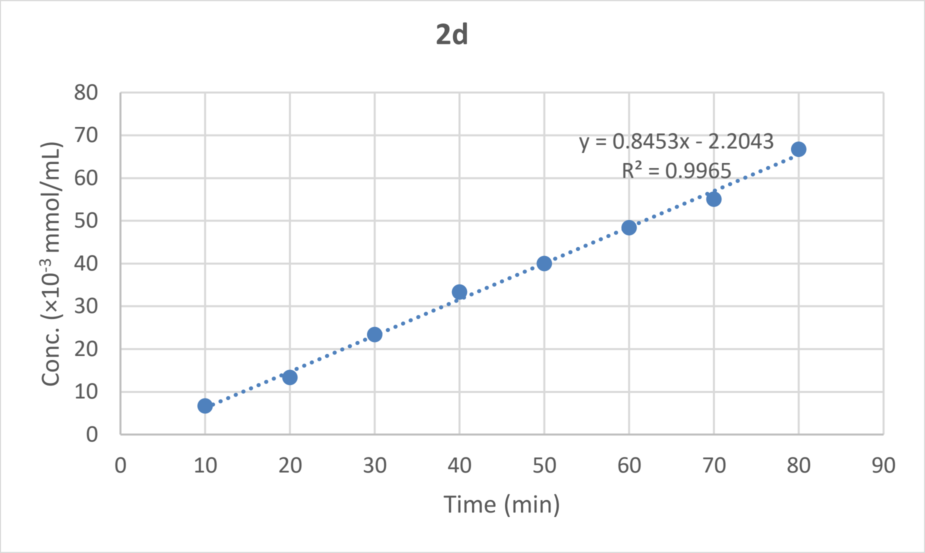


Fig. S8. Reaction rate of hydroxylation of 2d

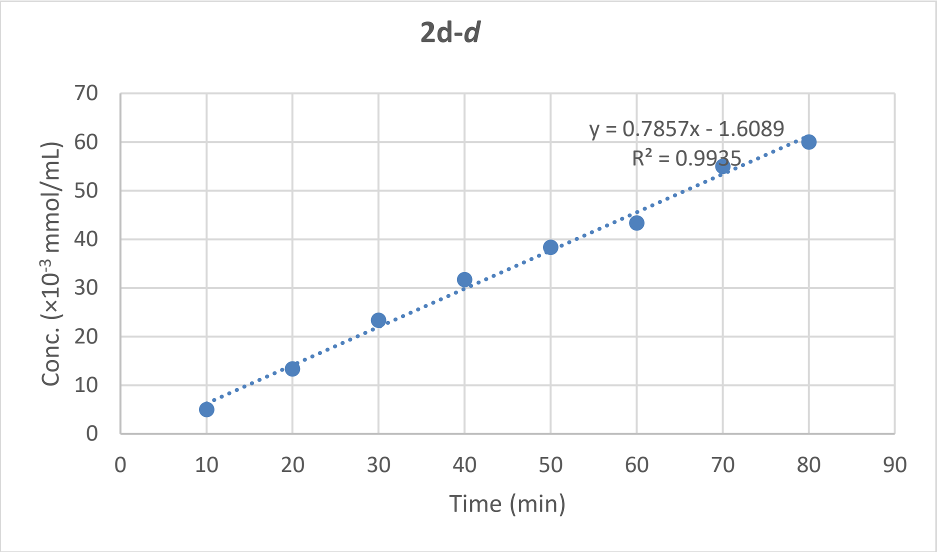
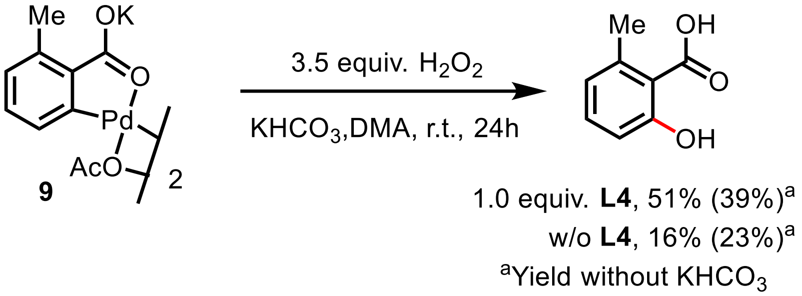


Fig. S9. Reaction rate of hydroxylation of 2d-d_4

4.3. Stoichiometric Reaction



1.0 equiv. **L4**, 51% (39%)[a]
w/o **L4**, 16% (23%)[a]
[a]Yield without $KHCO_3$

Complex **9**[10] (33.7 mg, 0.1 mmol, based on Pd), $KHCO_3$ (10 mg, 1.0 equiv) and **L4** (18.1 mg, 1.0 equiv) or without ligand were placed in an 8 mL vial. Then, DMA (0.5 mL) was added and stirred for 10 min, followed by the addition of H_2O_2 (35% aq., 30 uL, 3.5 equiv.). The reaction was stirred at ambient temperature. The aliquots were taken at 7 min, 14 min, 21min, 60 min and quenched with formic acid. The progress was monitored by ^1H NMR. After 24 hr, the reaction was cooled down to 0 °C and quenched with formic acid (50 uL) and diluted with EtOAc. The solution was filtered through a pad of Celite then concentrated under vacuum. The yield of hydroxylated product was analyzed by ^1H NMR (Figure **S10**).

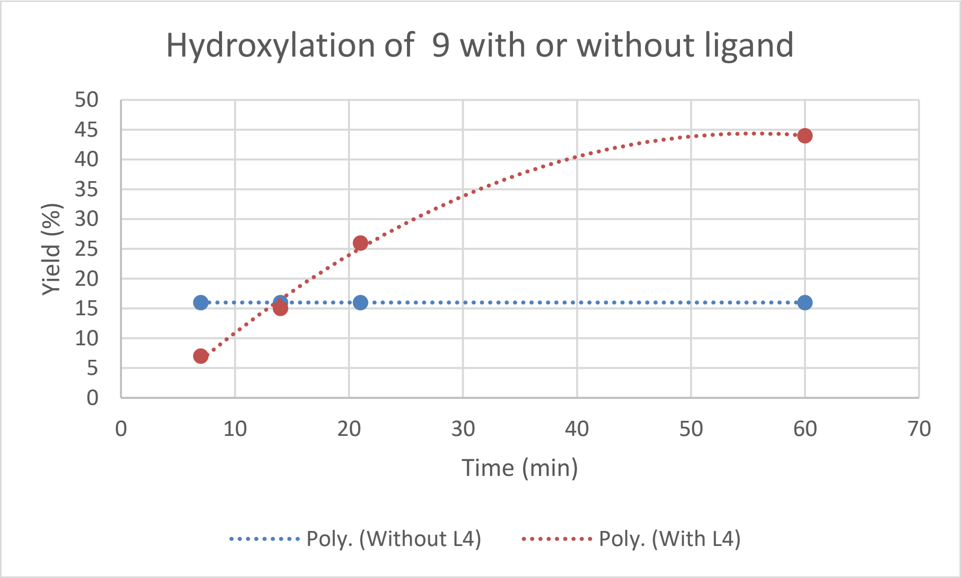
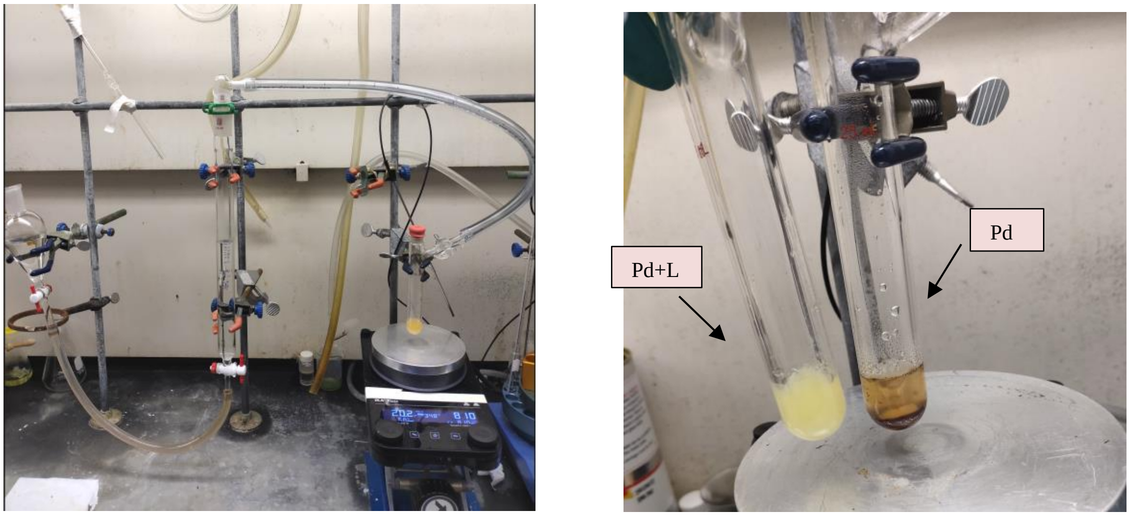


Fig. S10. Hydroxylation reaction of complex 9

4.4. Hydrogen Peroxide Decomposition Experiments

$$H_2O_2 \longrightarrow H_2O + {}^{1}/_{2}\, O_2$$



(a) Reaction measuring equipment

(b) Reaction vials with or w/o ligand after 30 min at r.t.

Fig. S11. Reaction equipment

The reactions were carried out in 25 mL Schlenk tubes under the corresponding conditions, $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2 mol%), **L1** or **L4** (0.04 mmol, 4 mol%), K_2HPO_4 (261 mg, 1.5 mmol, 1.5 equiv.) , Phenylacetic acid (S) (136 mg, 1 mmol), DMA (3 mL).

Each reaction mixture solution was stirred for 10 min before H_2O_2 (35% aq., 0.3 mL, 3.5 mmol, 3.5 equiv.) was added and stirred at r.t or 90 °C. The volume of oxygen was measured by gas volume measuring equipment (Fig. **S11**) and calibrated by standard volume using syringe. The amount of H_2O_2 (n) was calculated based on the volume of oxygen evolved ($PV_{O2} = nRT$, T = 298 K). The obtained average n for two trials were plotted as n vs. time (Fig. **S12-S14**).

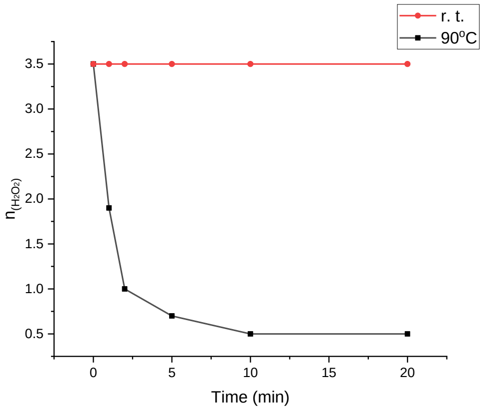


Fig. S12. H_2O_2 decomposition experiments with **L1** (Condition: Pd + K_2HPO_4 + **L1** +S)

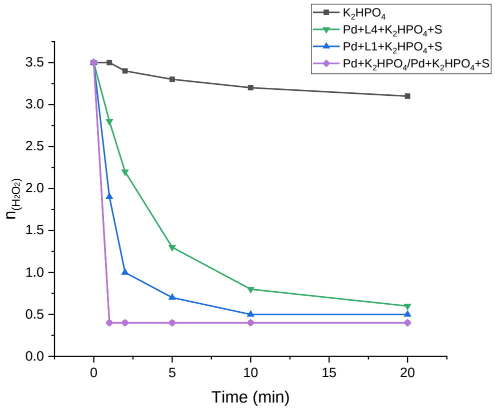
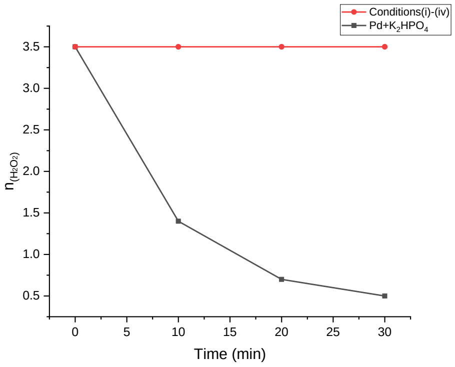


Fig. S13. H_2O_2 decomposition at 90 °C



Condition (i): K_2HPO_4
Condition (ii): Pd + K_2HPO_4 + L1
Condition (iii): Pd + K_2HPO_4 + L4
Condition (iv): Pd + K_2HPO_4 + S

Fig. S14. H_2O_2 decomposition at room temperature

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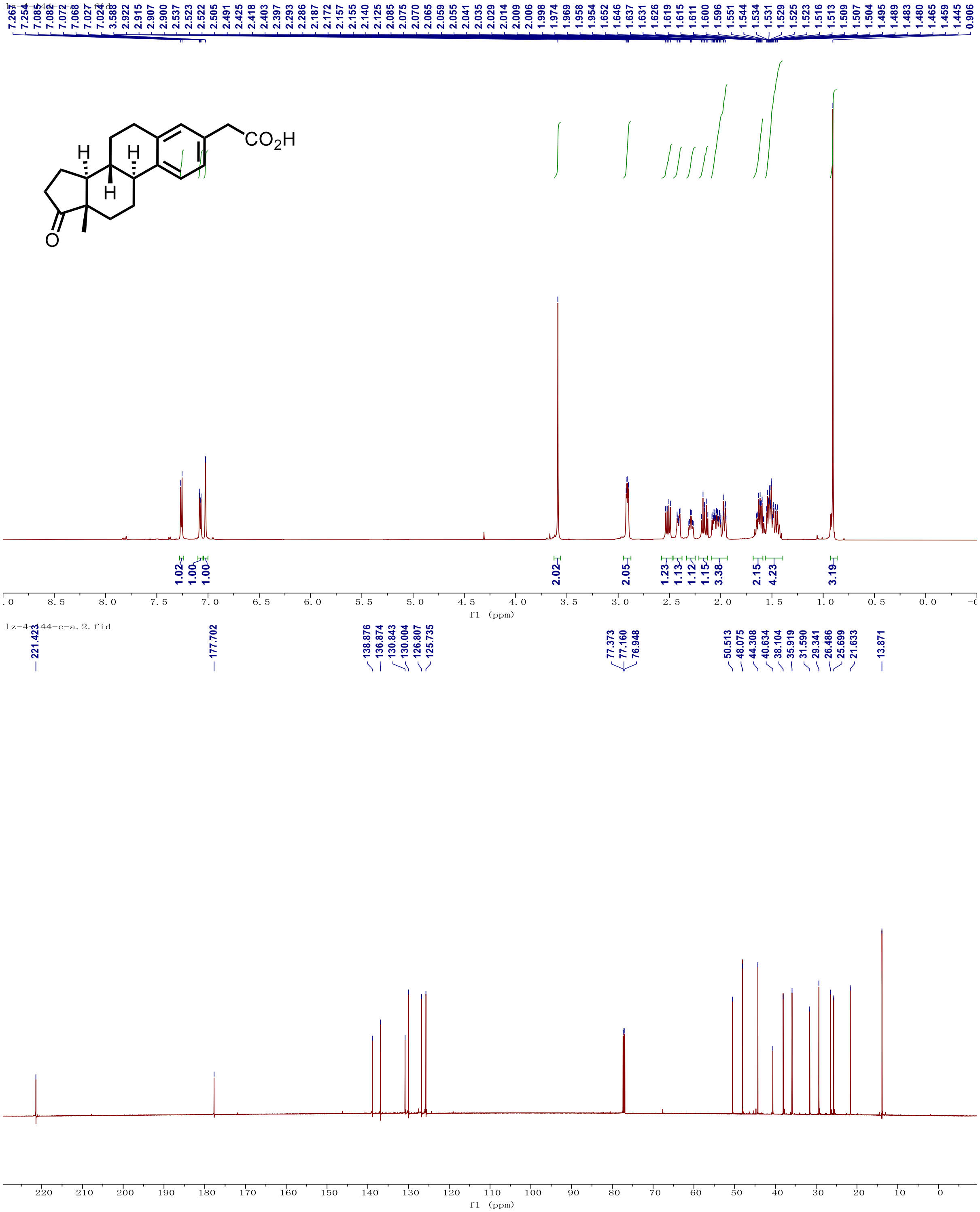
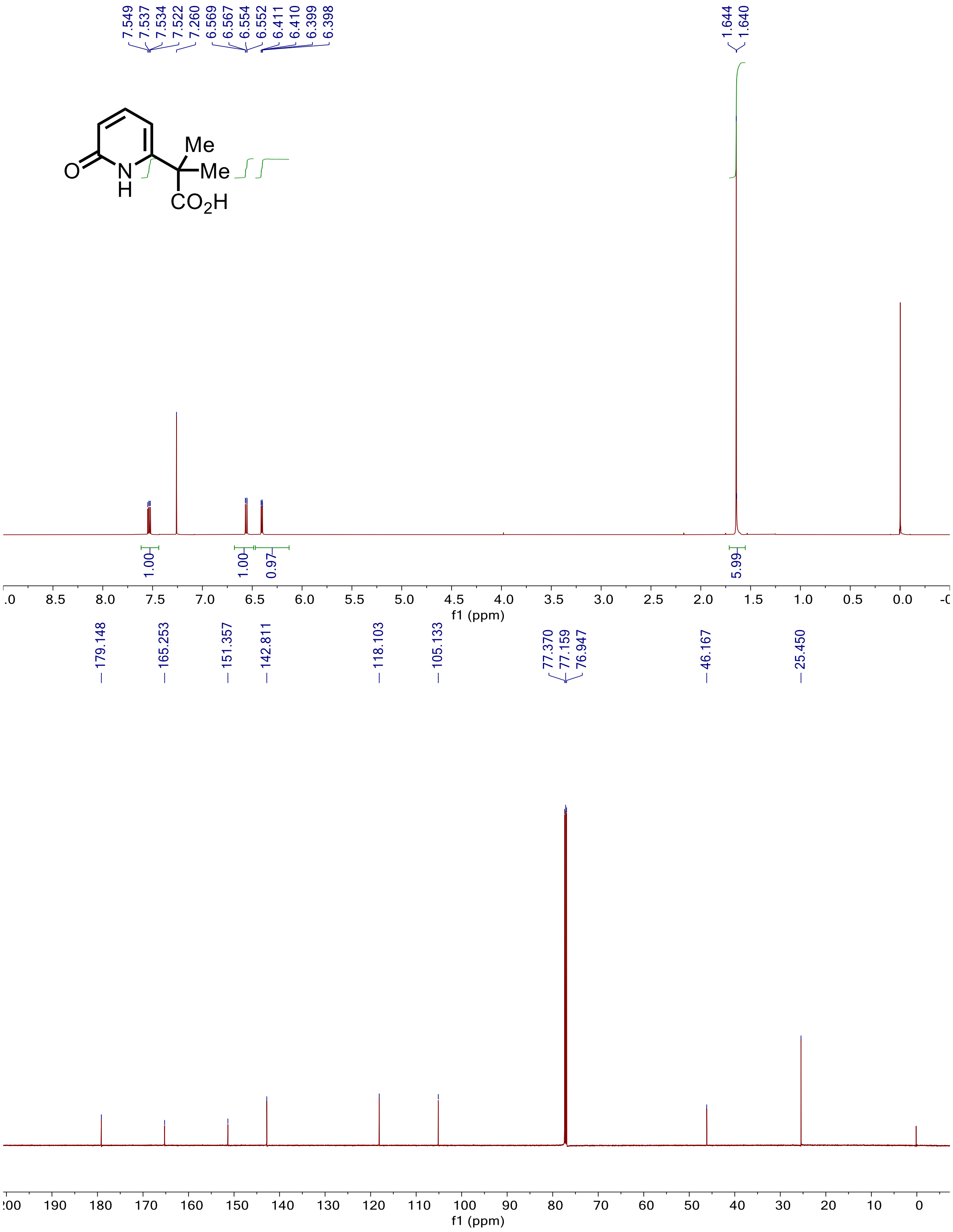
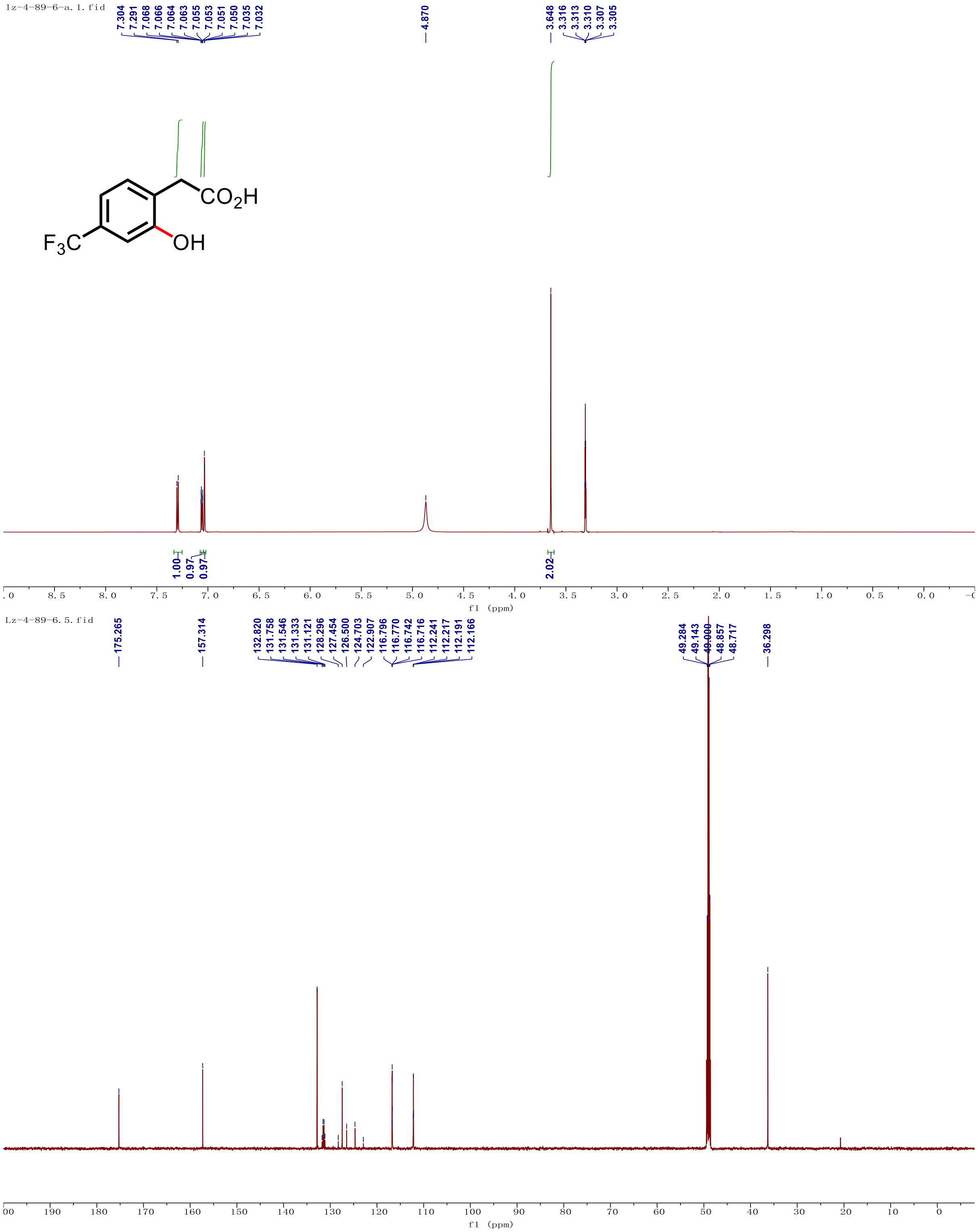
NMR Spectra



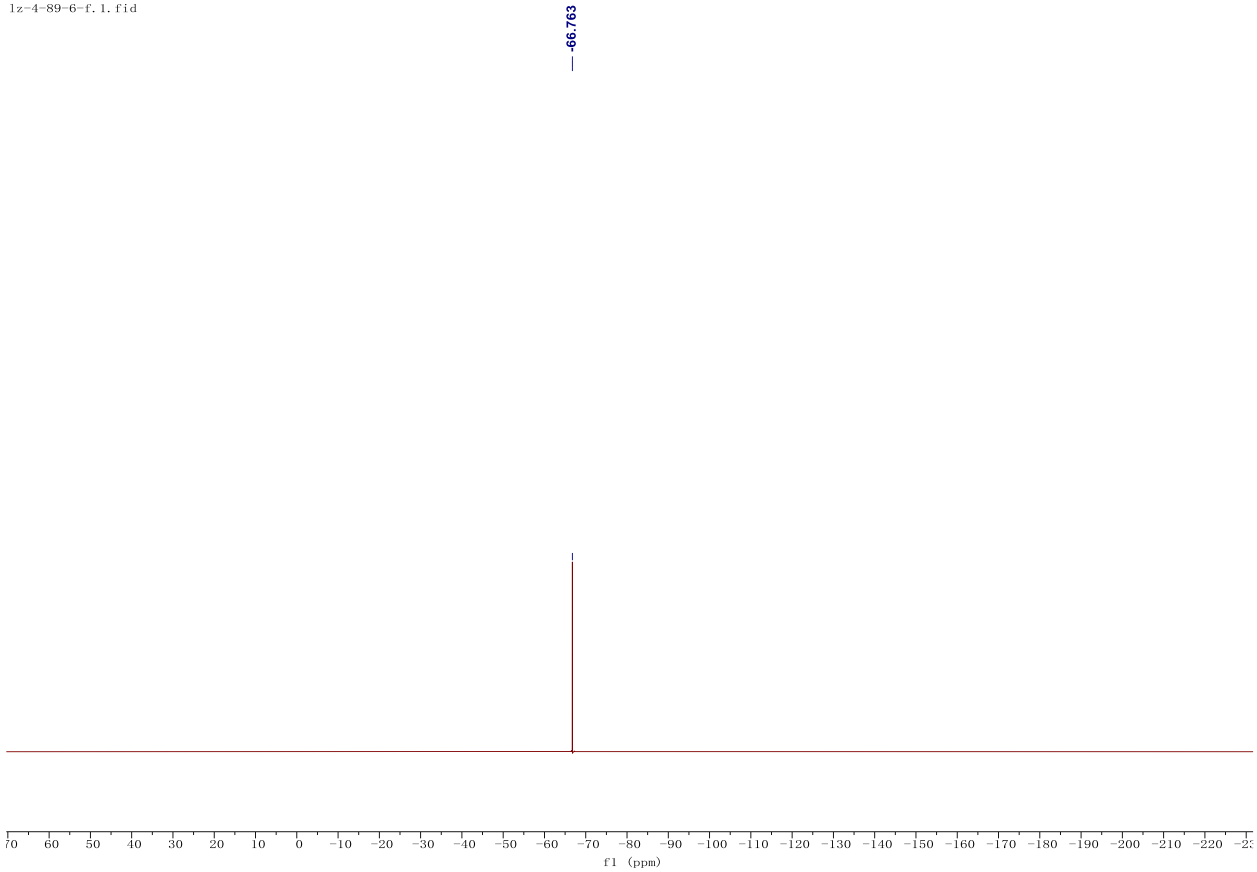
NMR Spectra of **1al**



NMR Spectra of **L4**



NMR Spectra of **2a**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60
50
40
30
20
10
0
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-20
-30
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-50
-60
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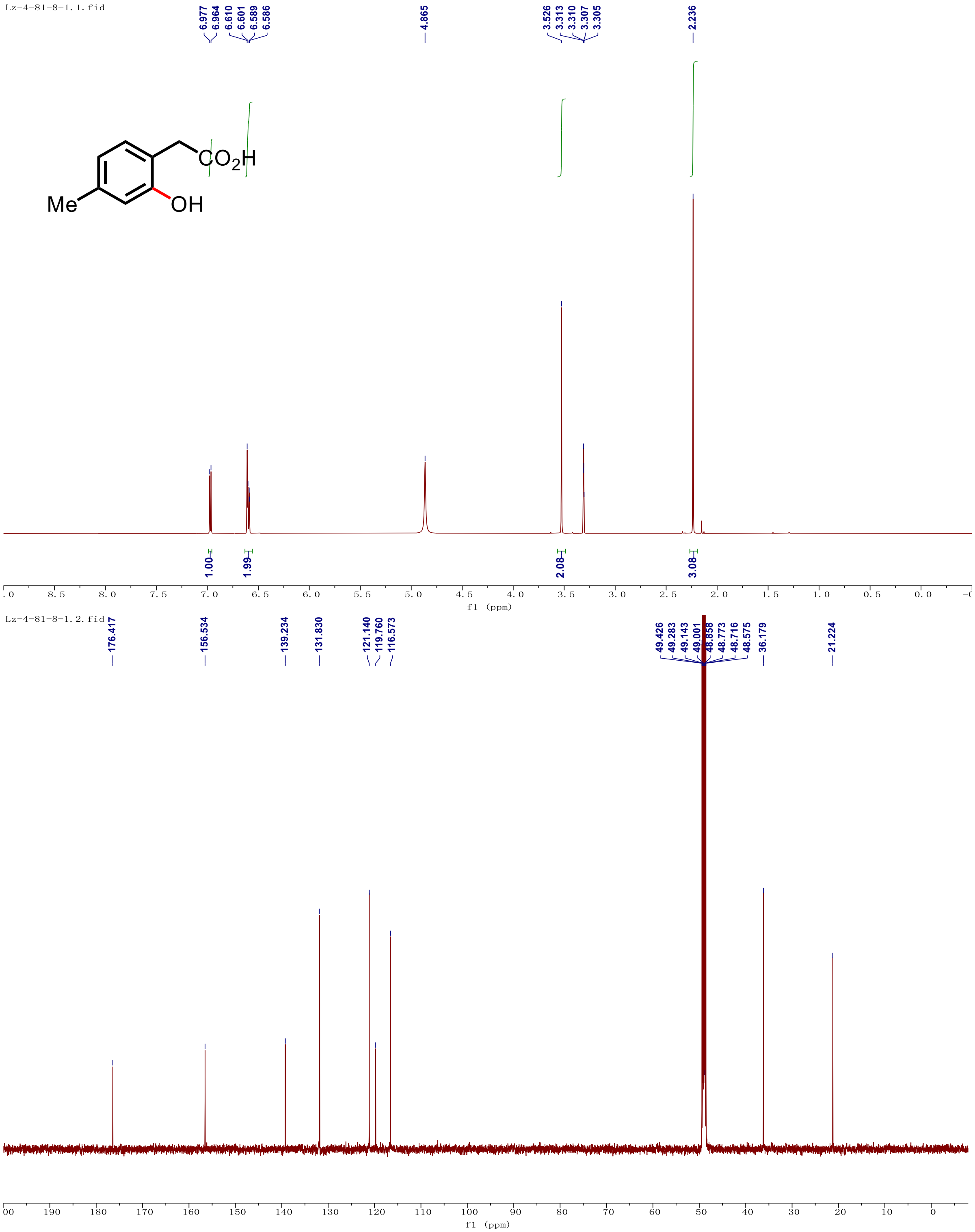
f1 (ppm)



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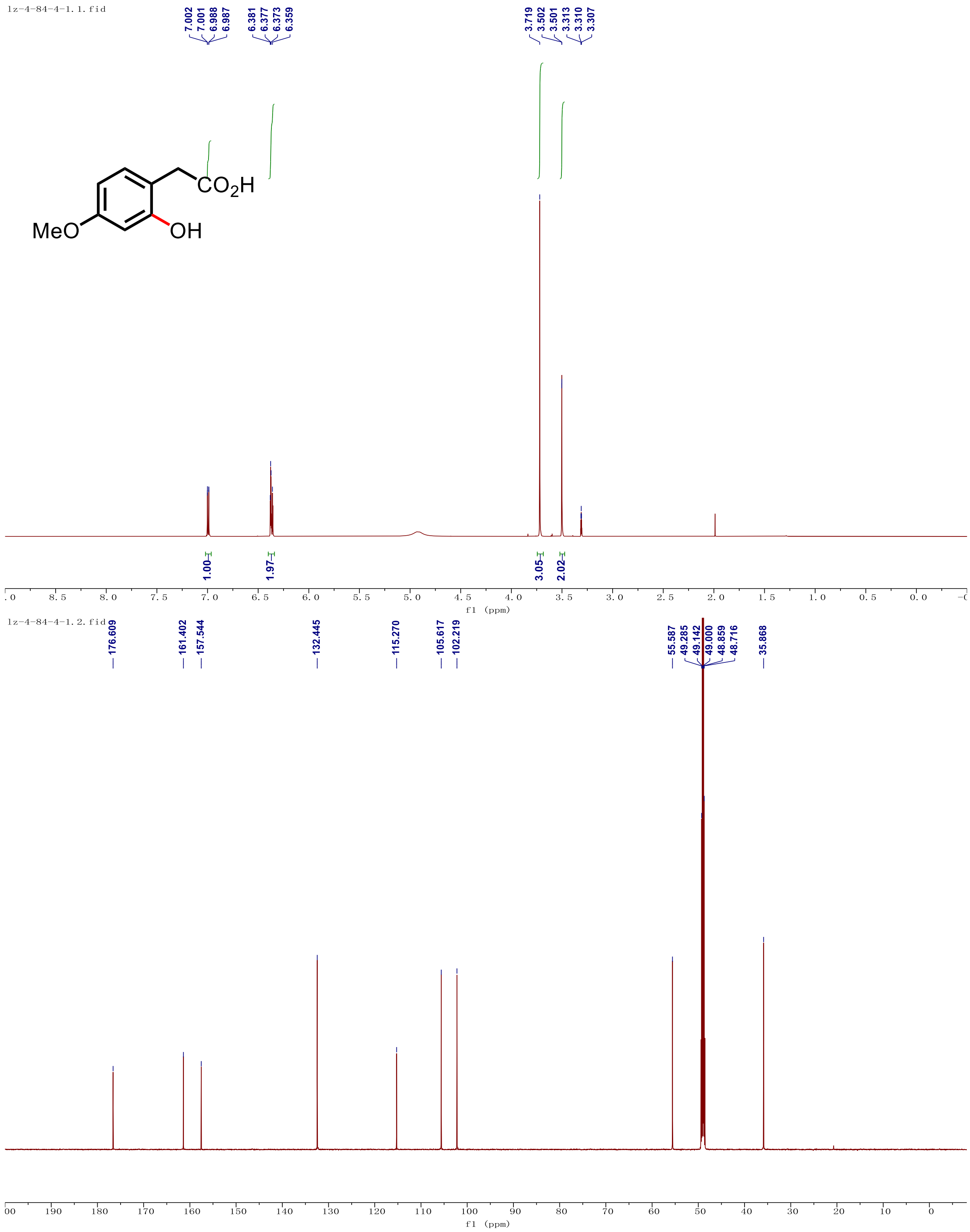

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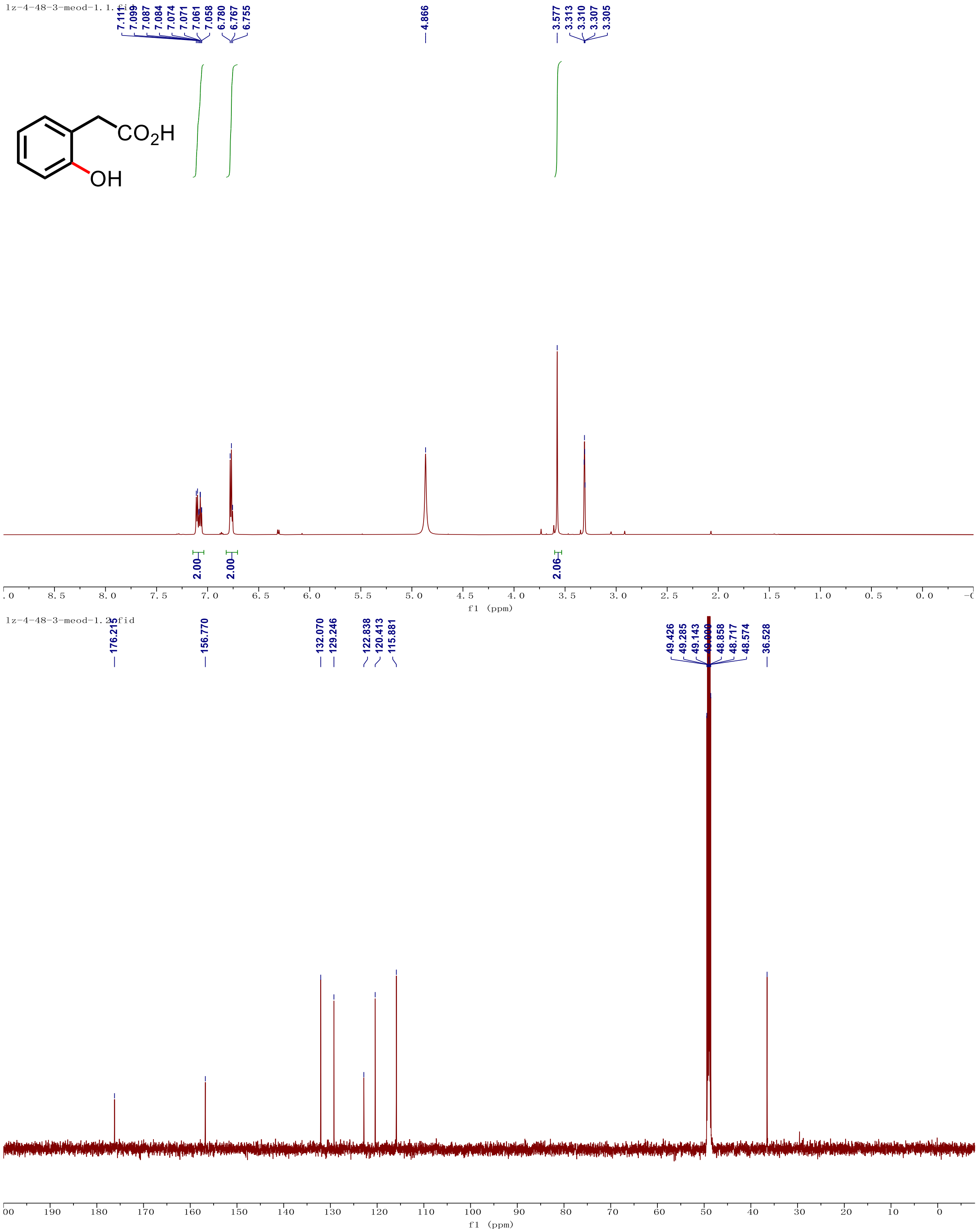
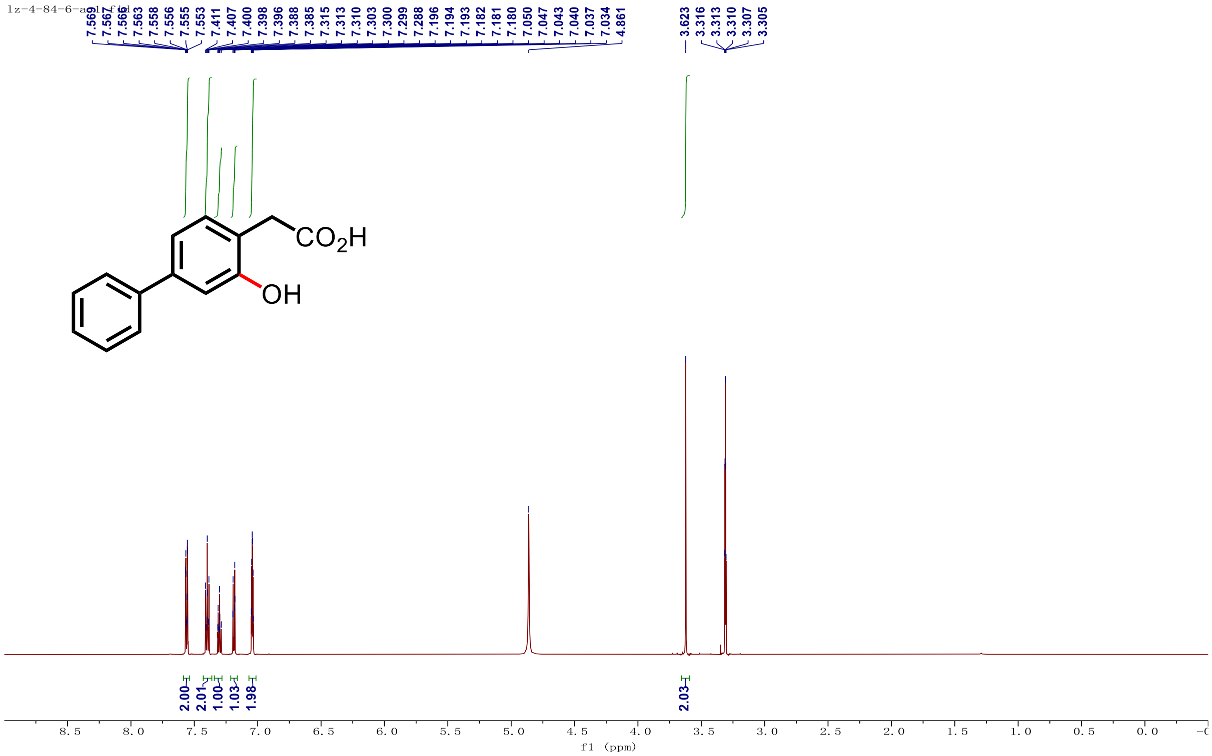
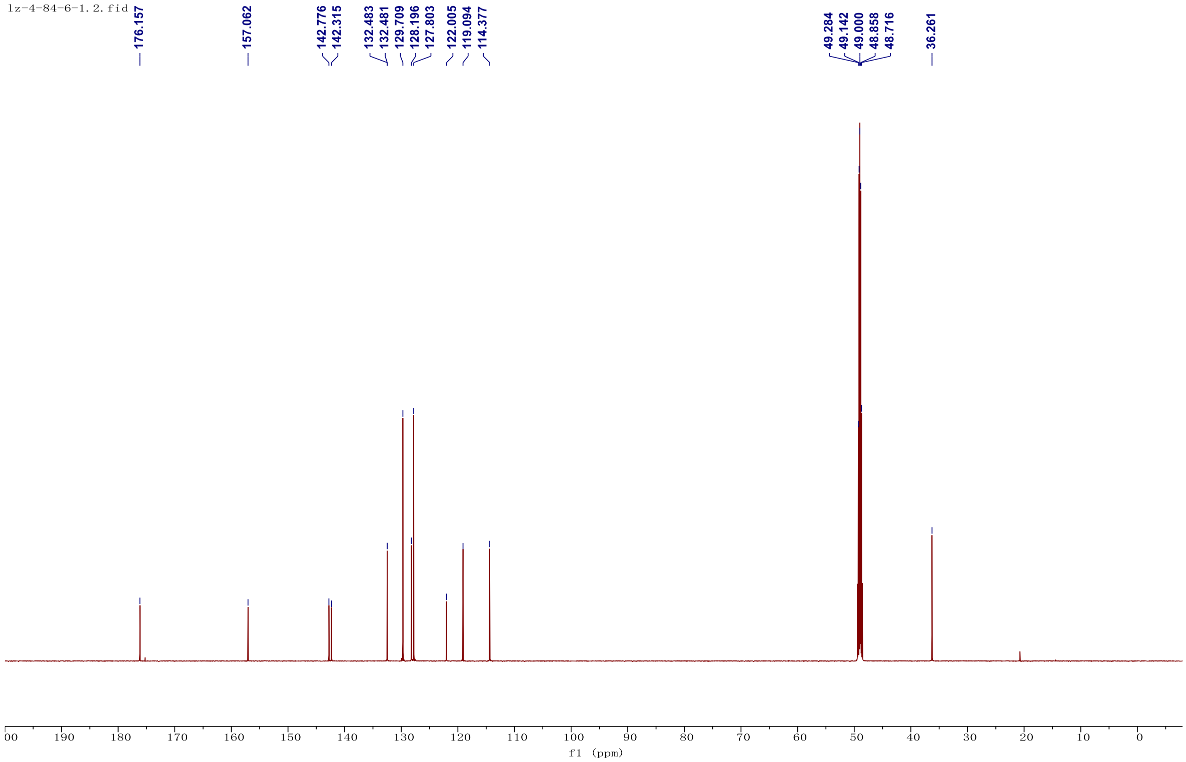


NMR Spectra of **2d**





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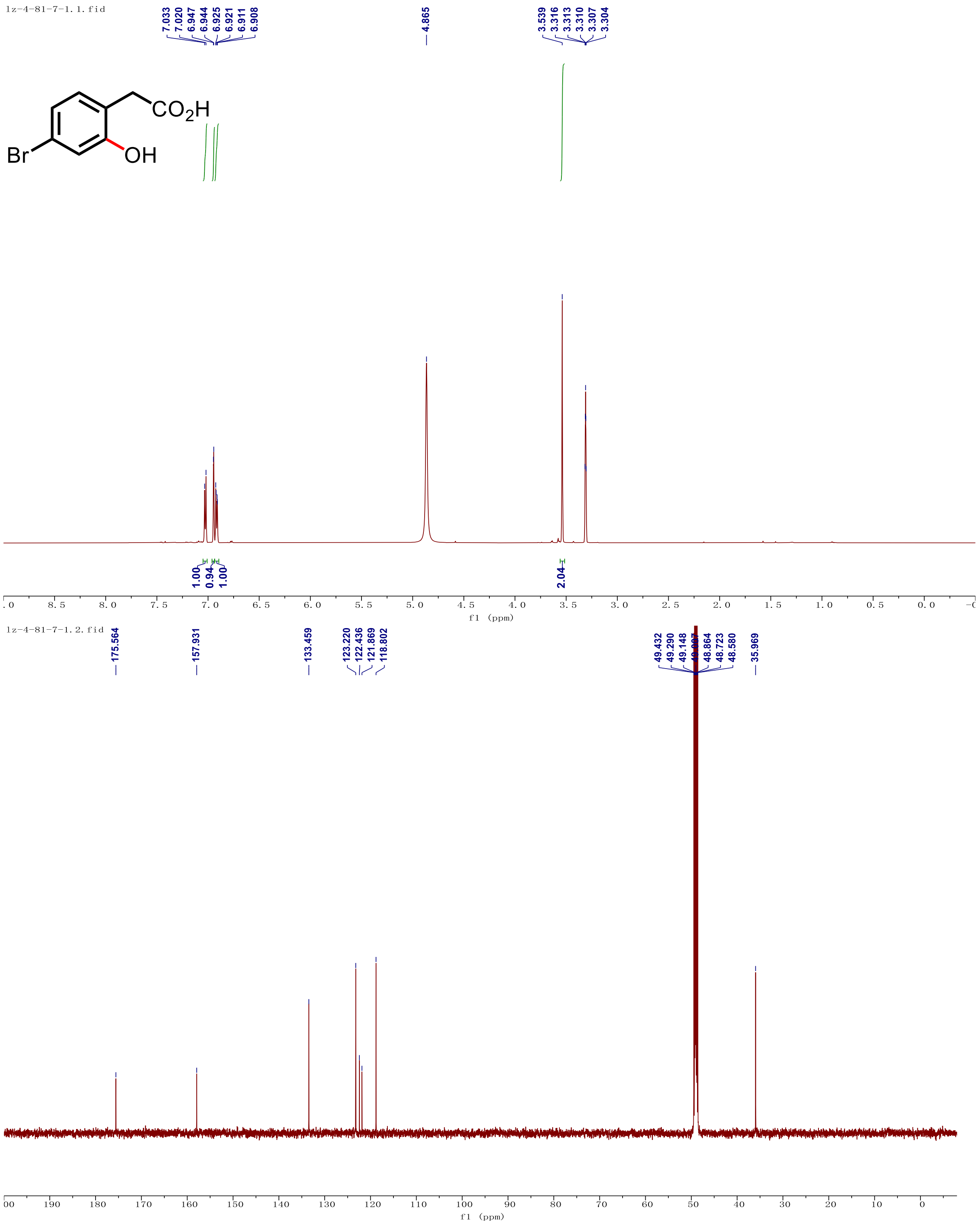

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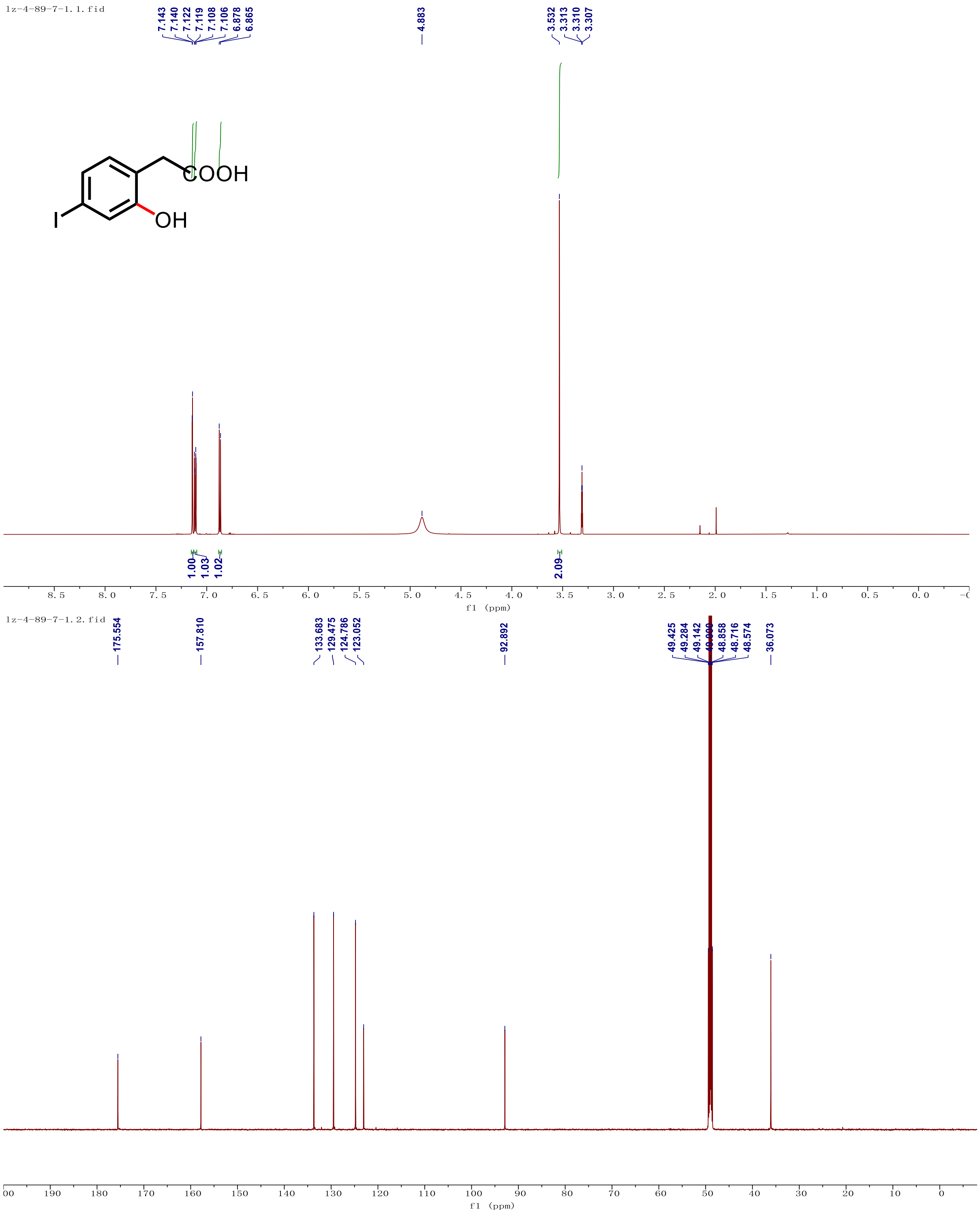

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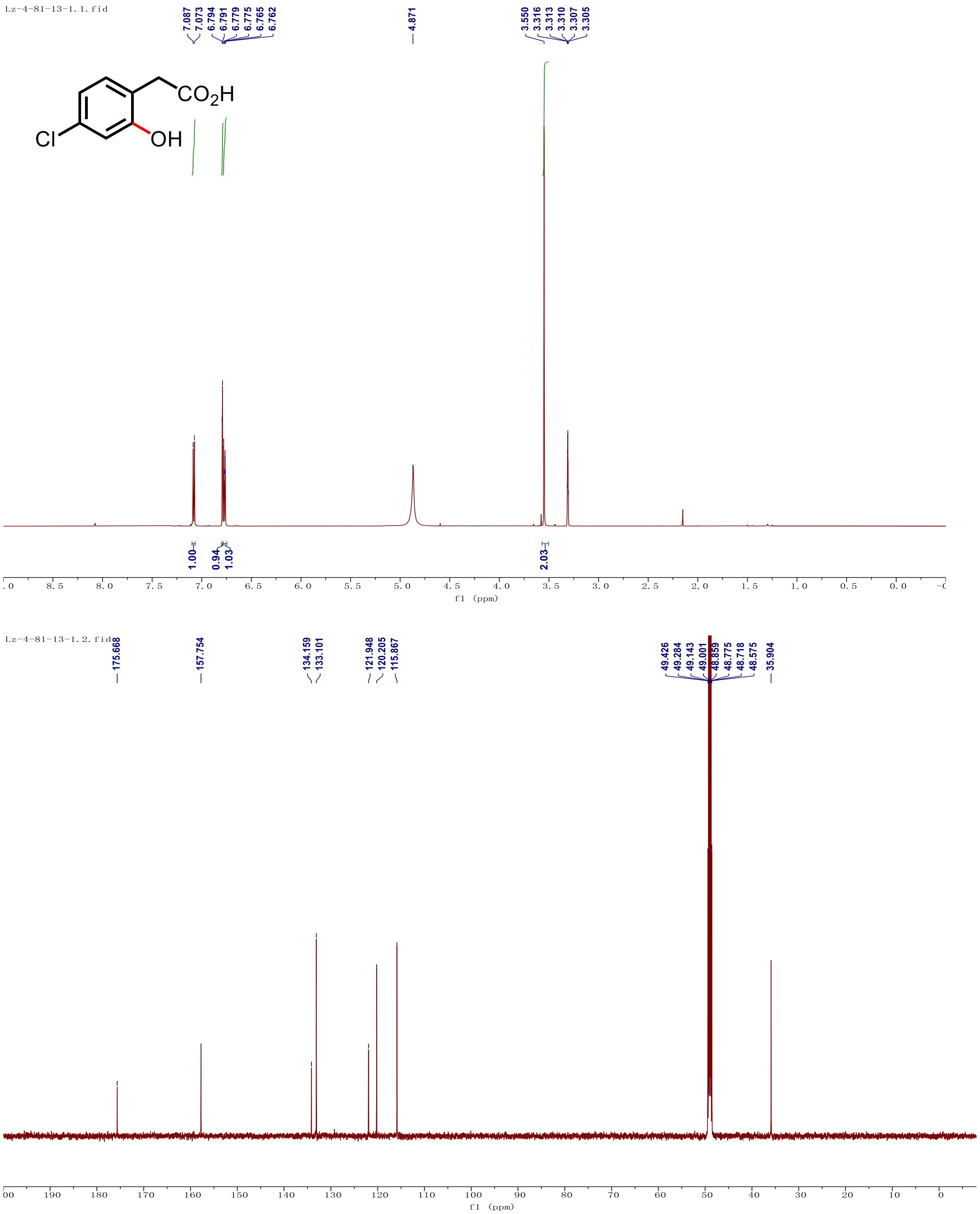

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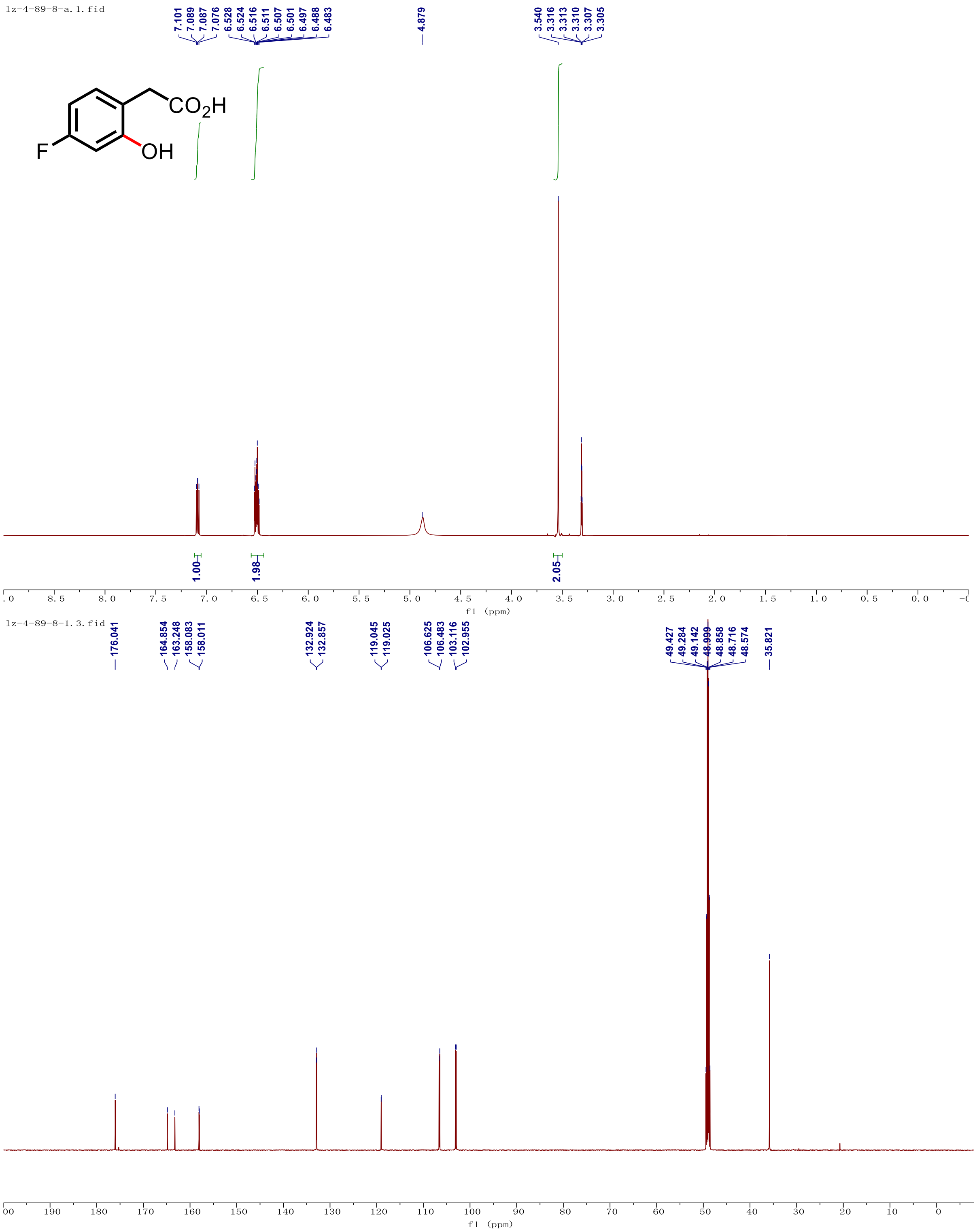

NMR Spectra of **2i**


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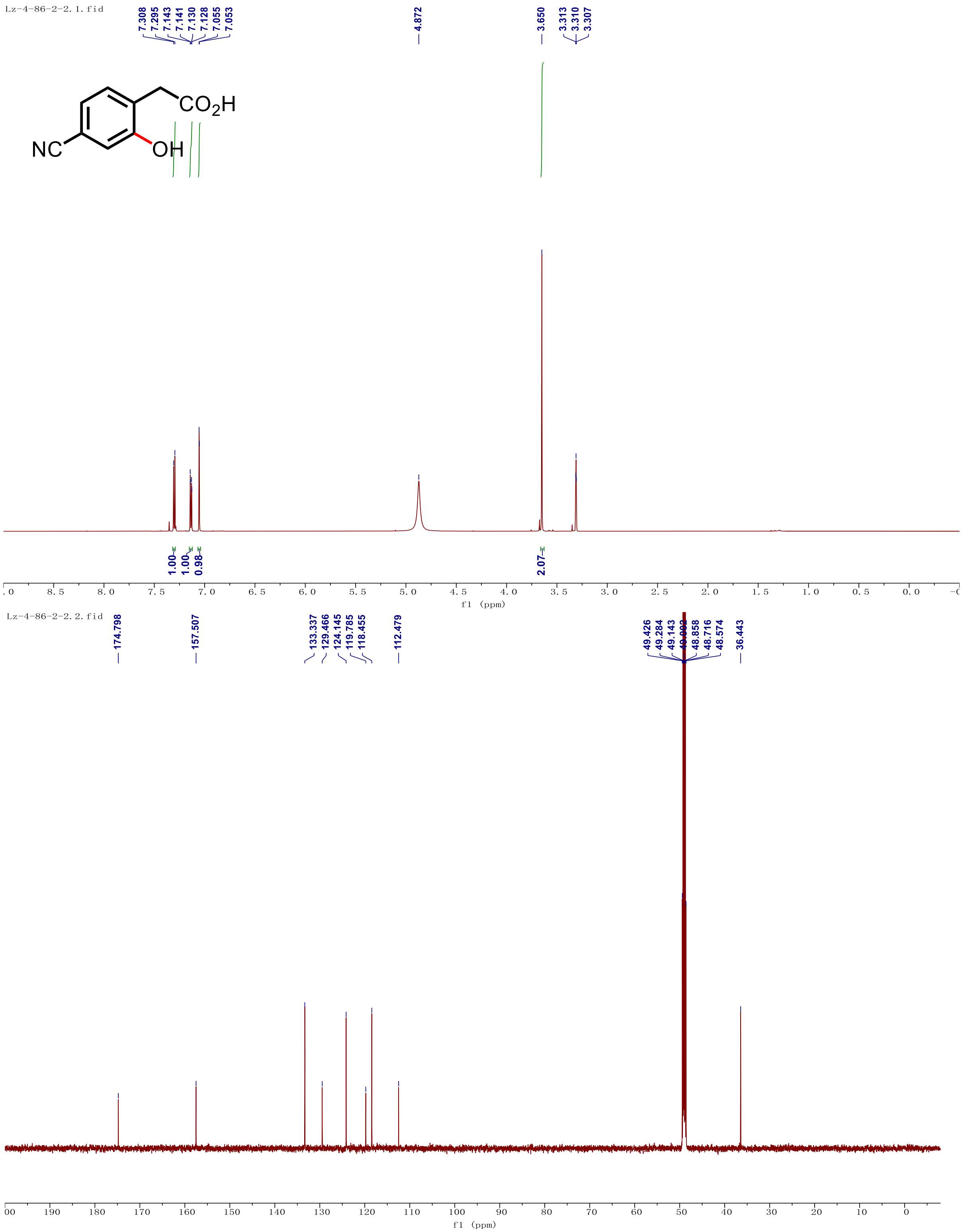
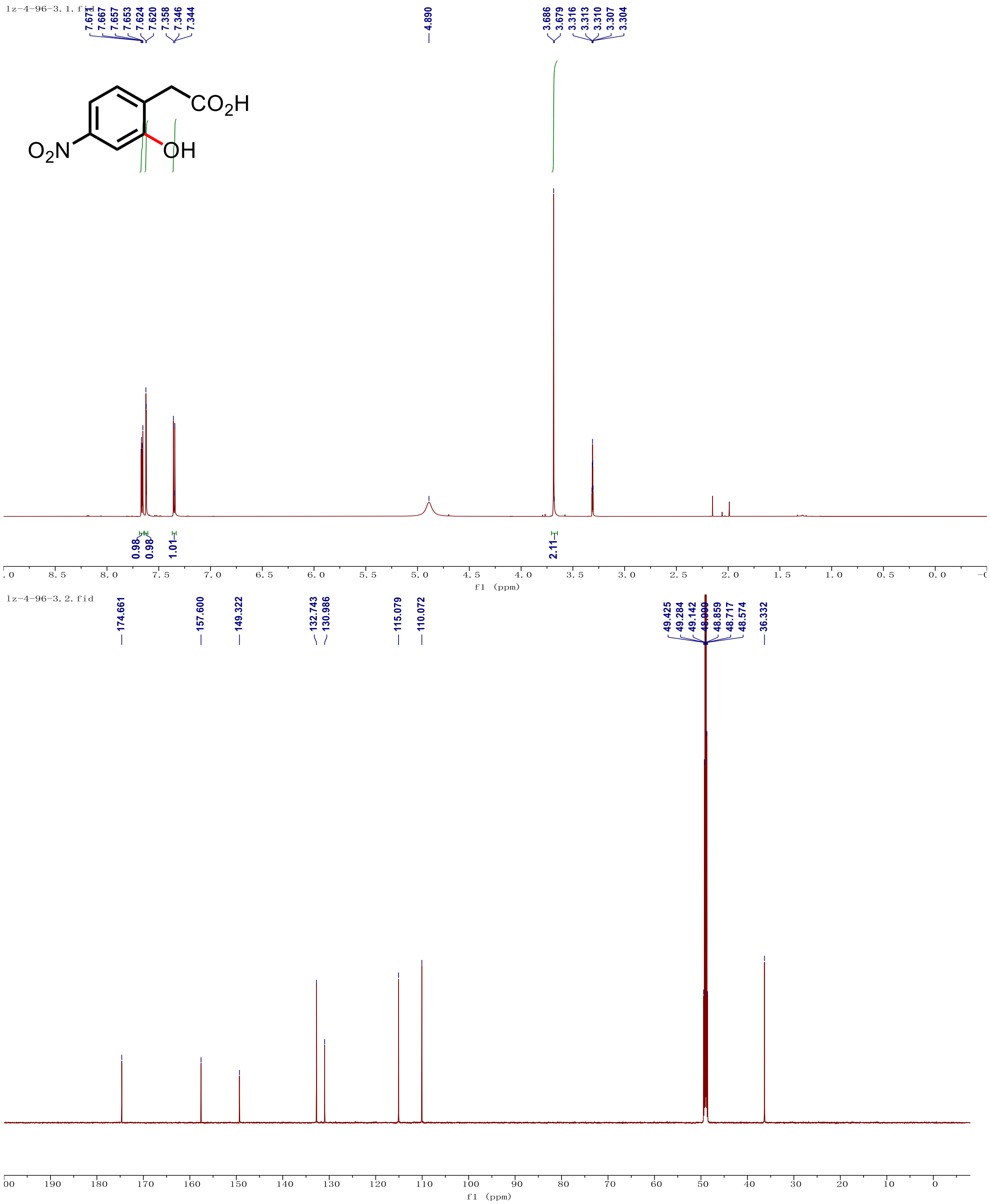
f1 (ppm)



NMR Spectra of **2j**



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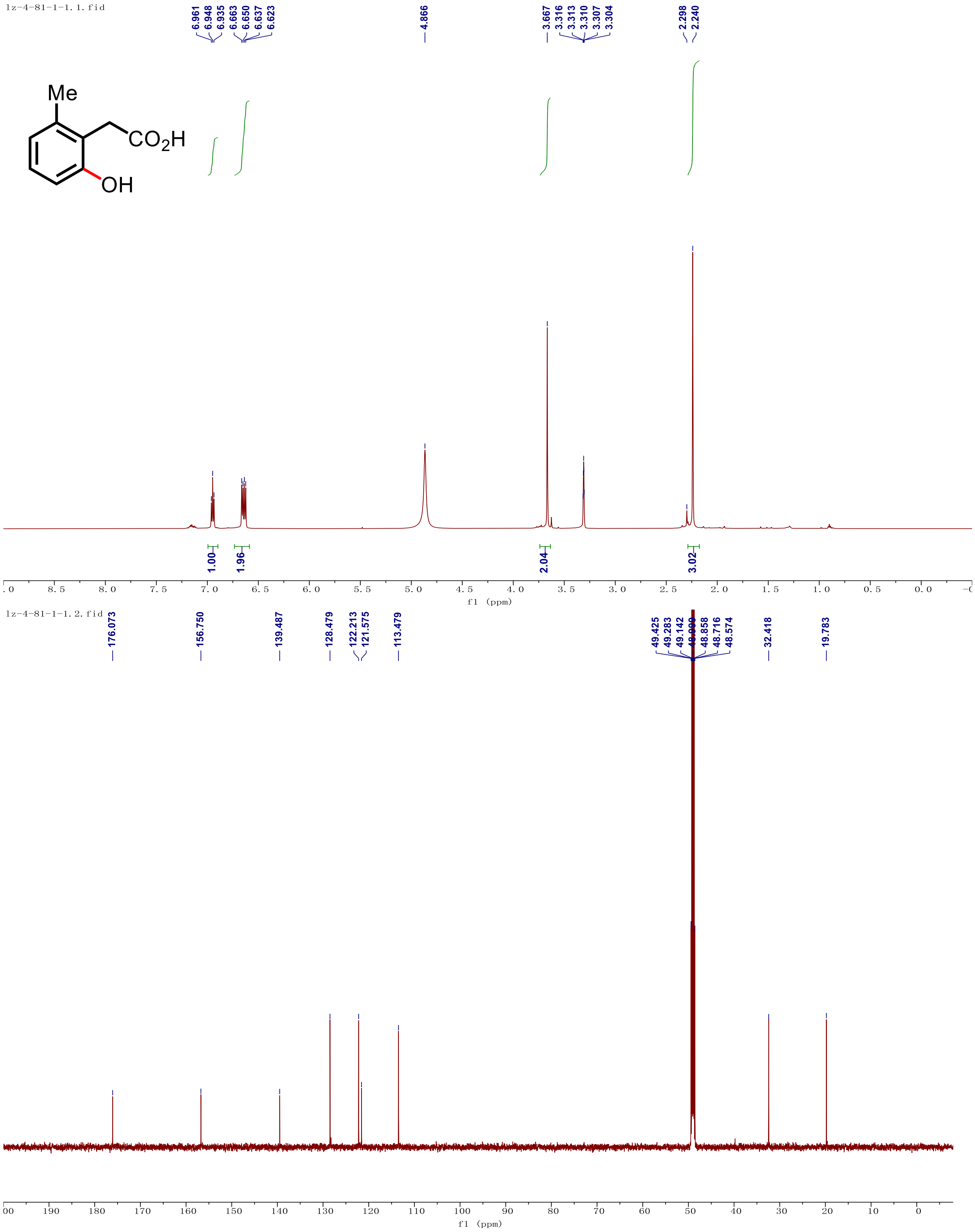

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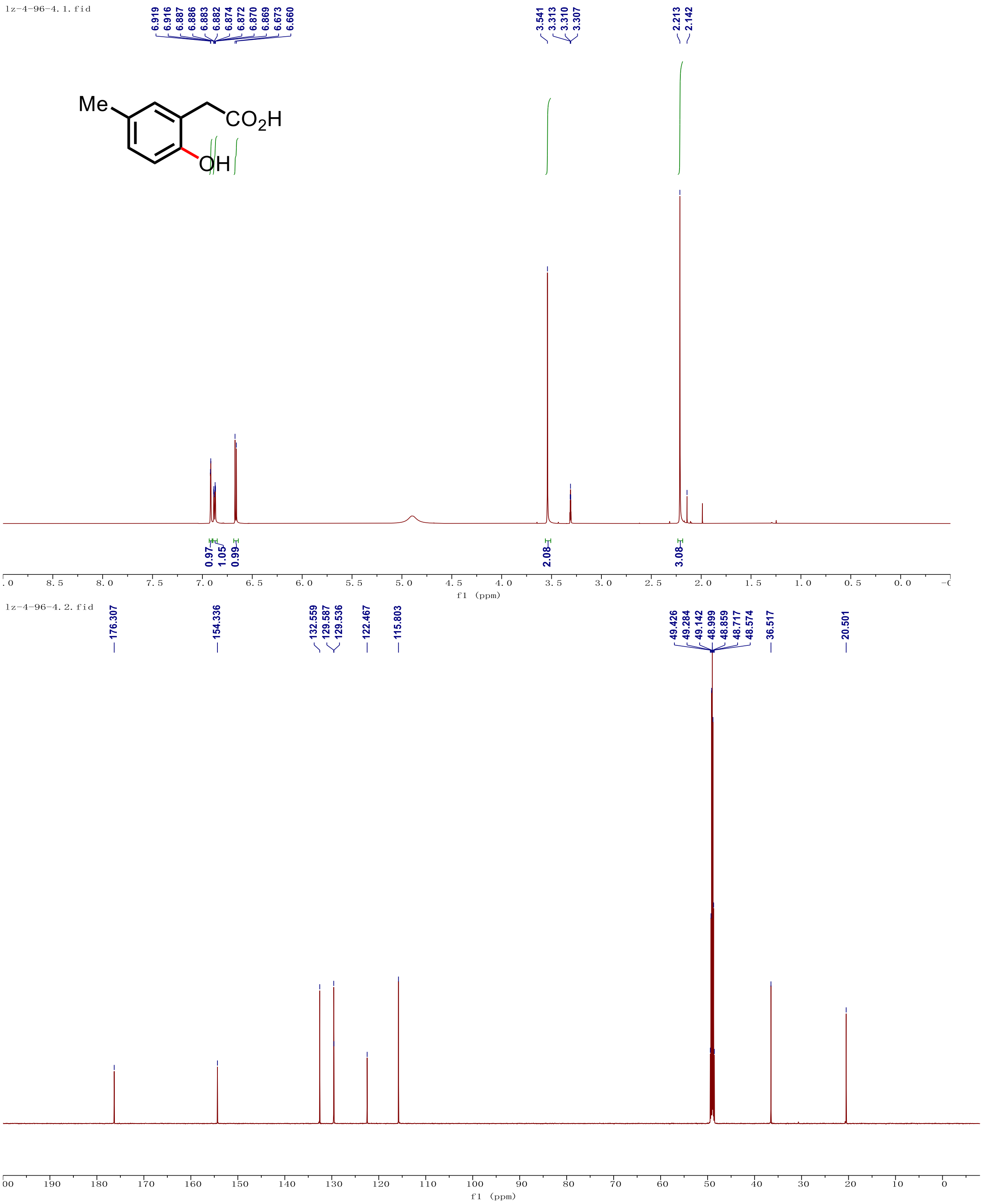

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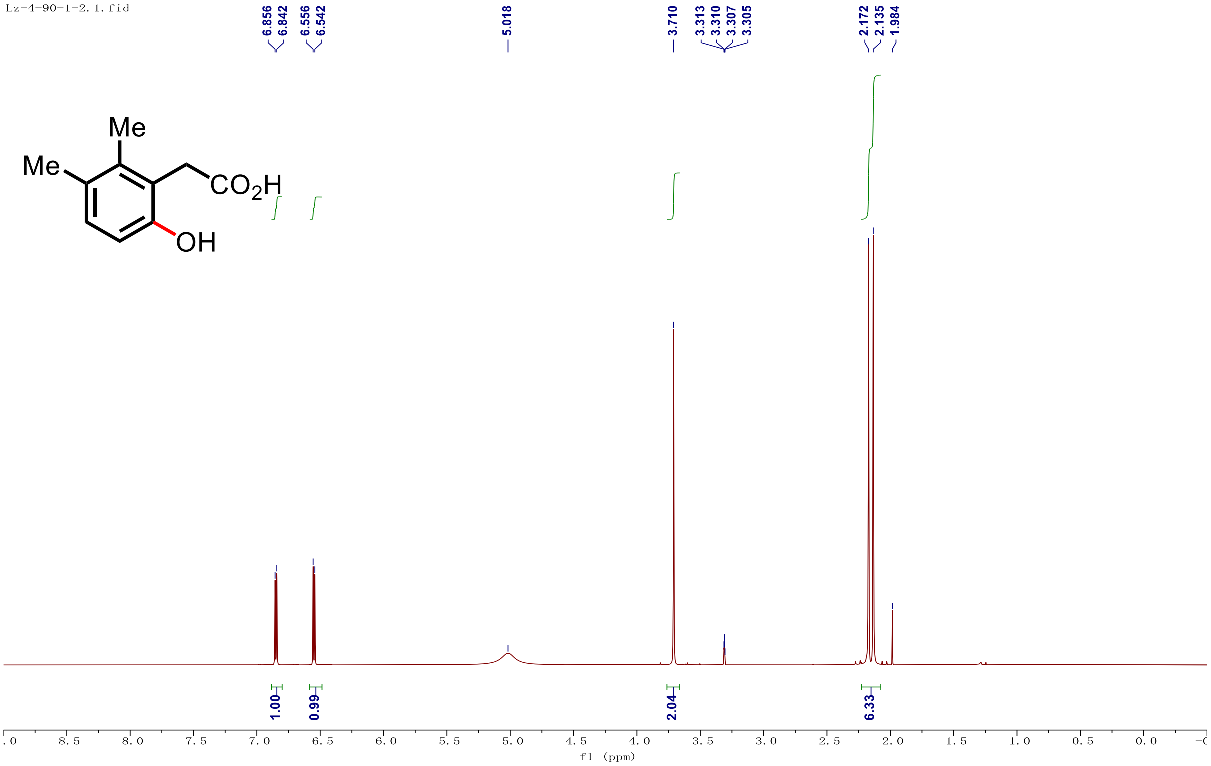
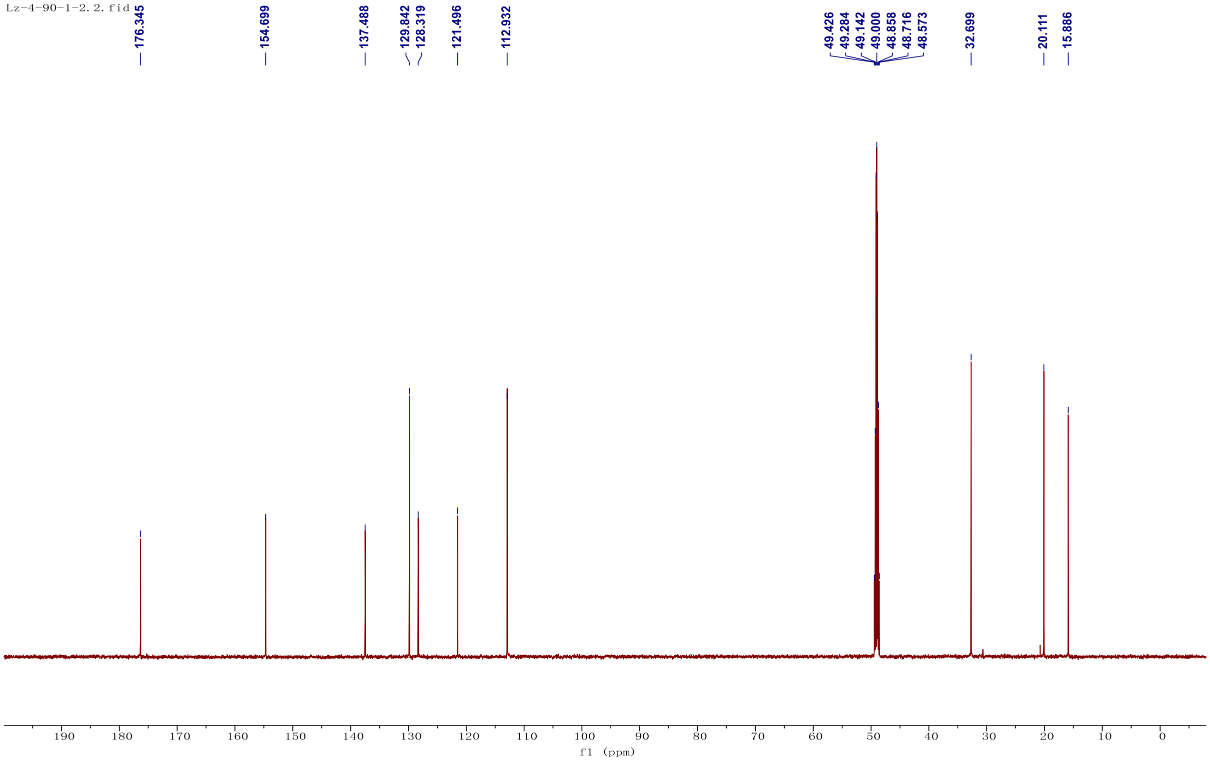
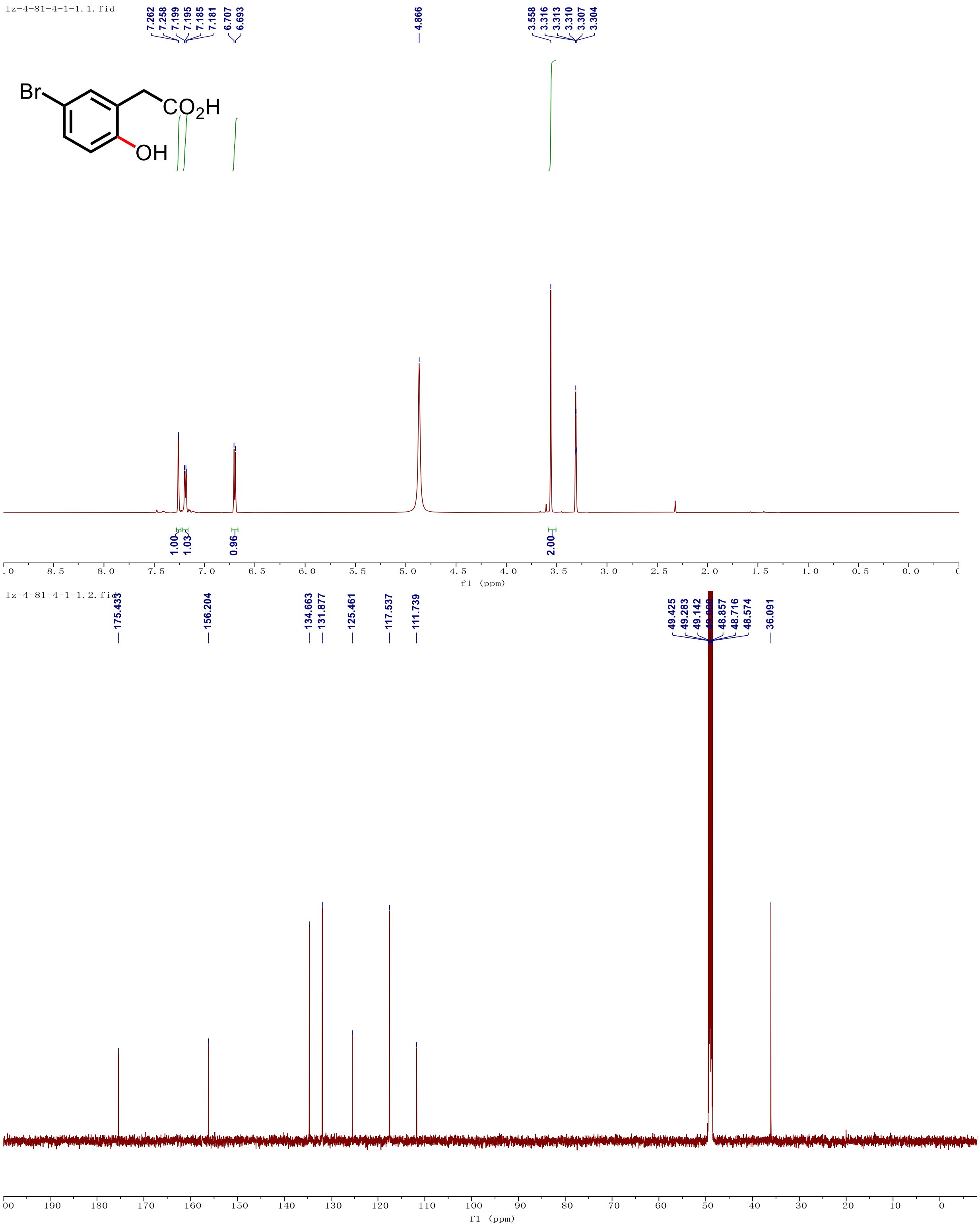




NMR Spectra of **2n**



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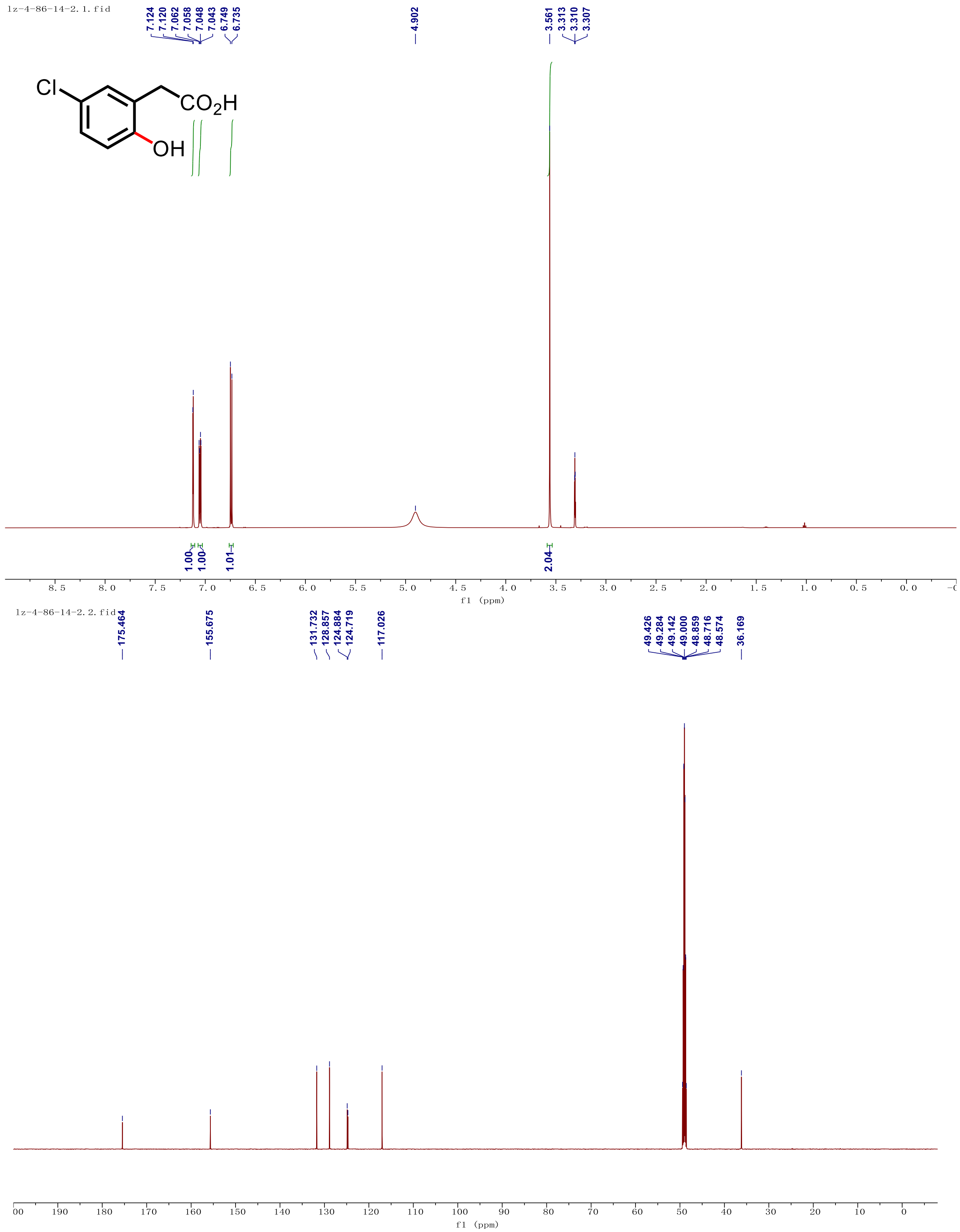

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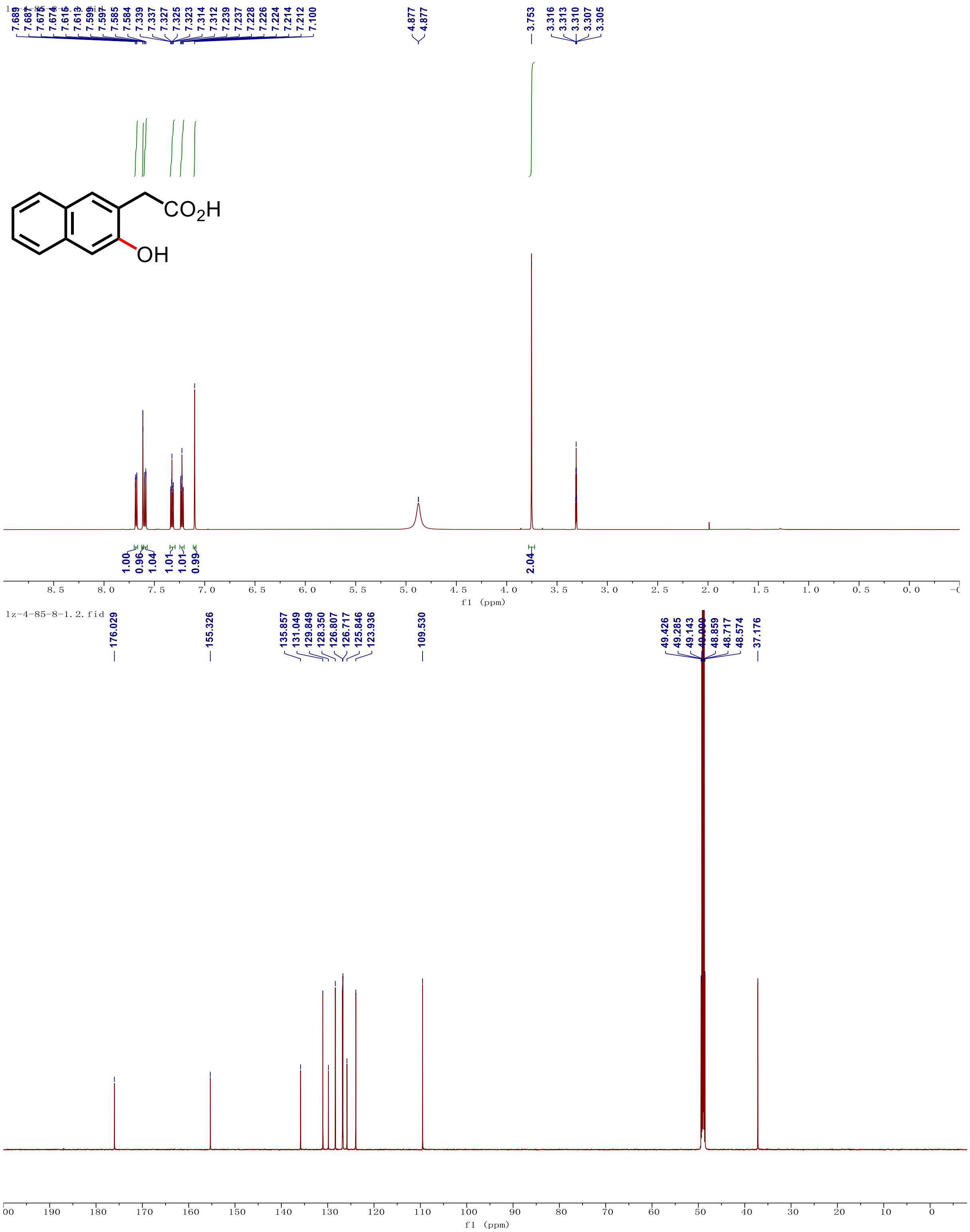
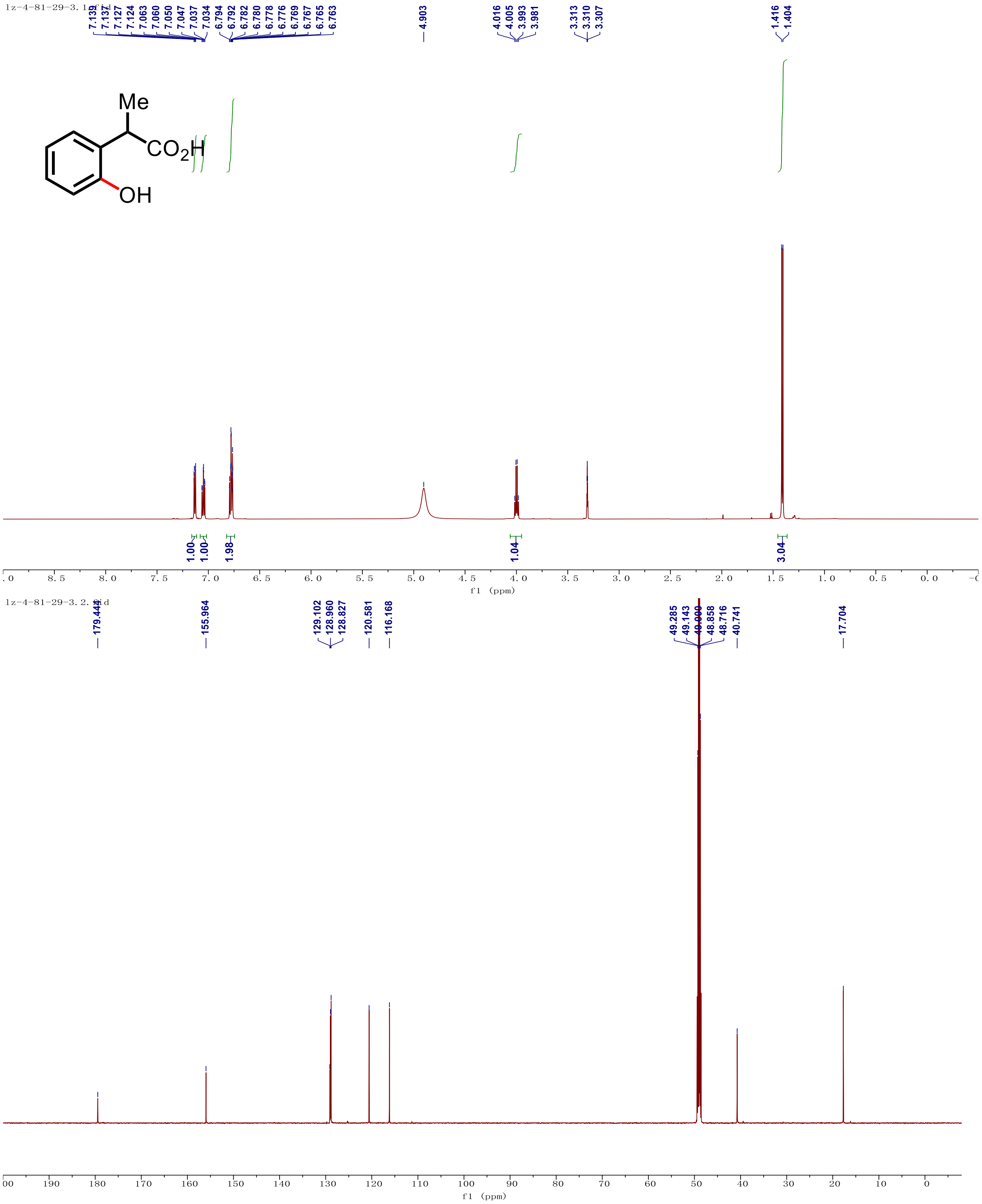
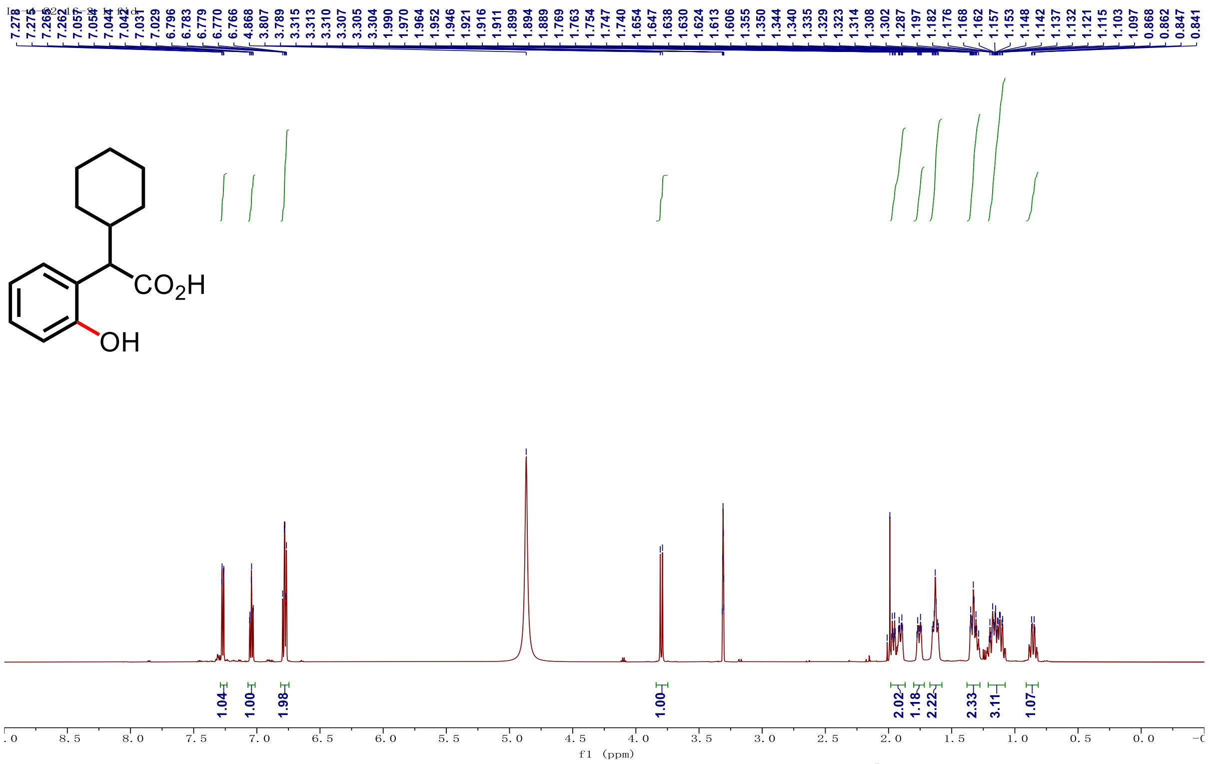
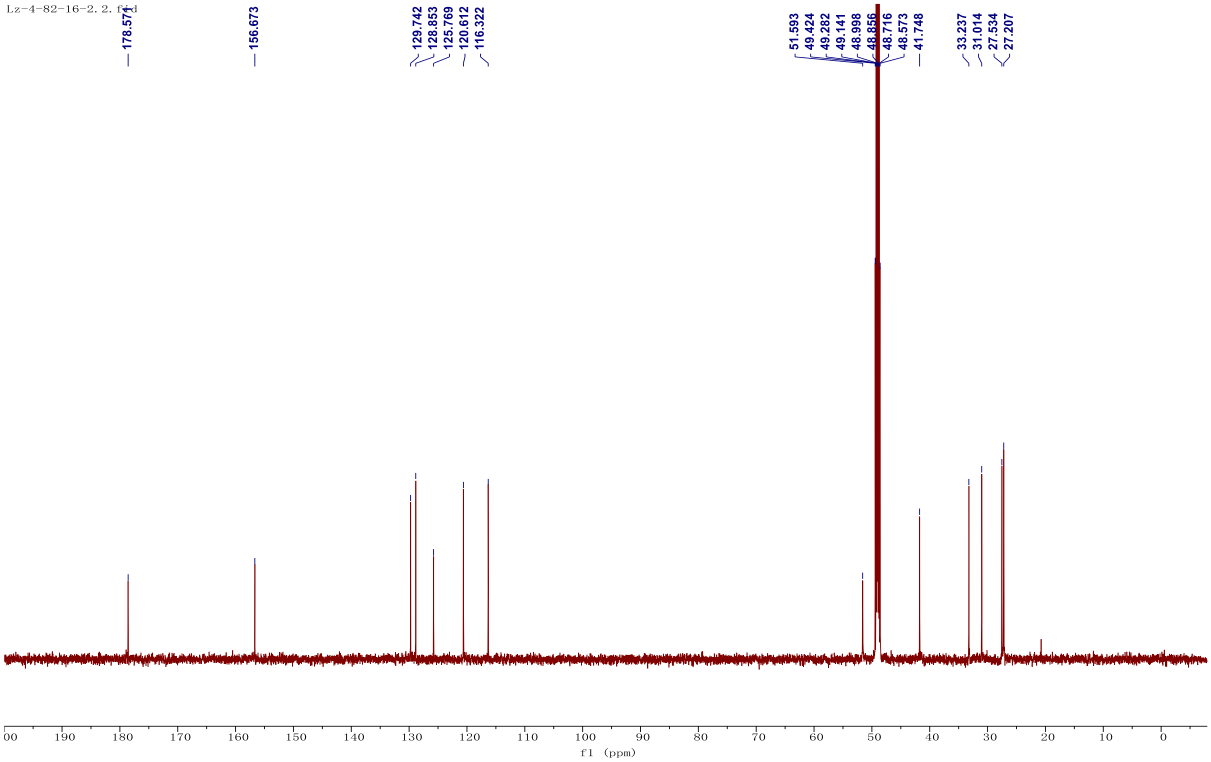


NMR Spectra of **2q**



NMR Spectra of **2r**





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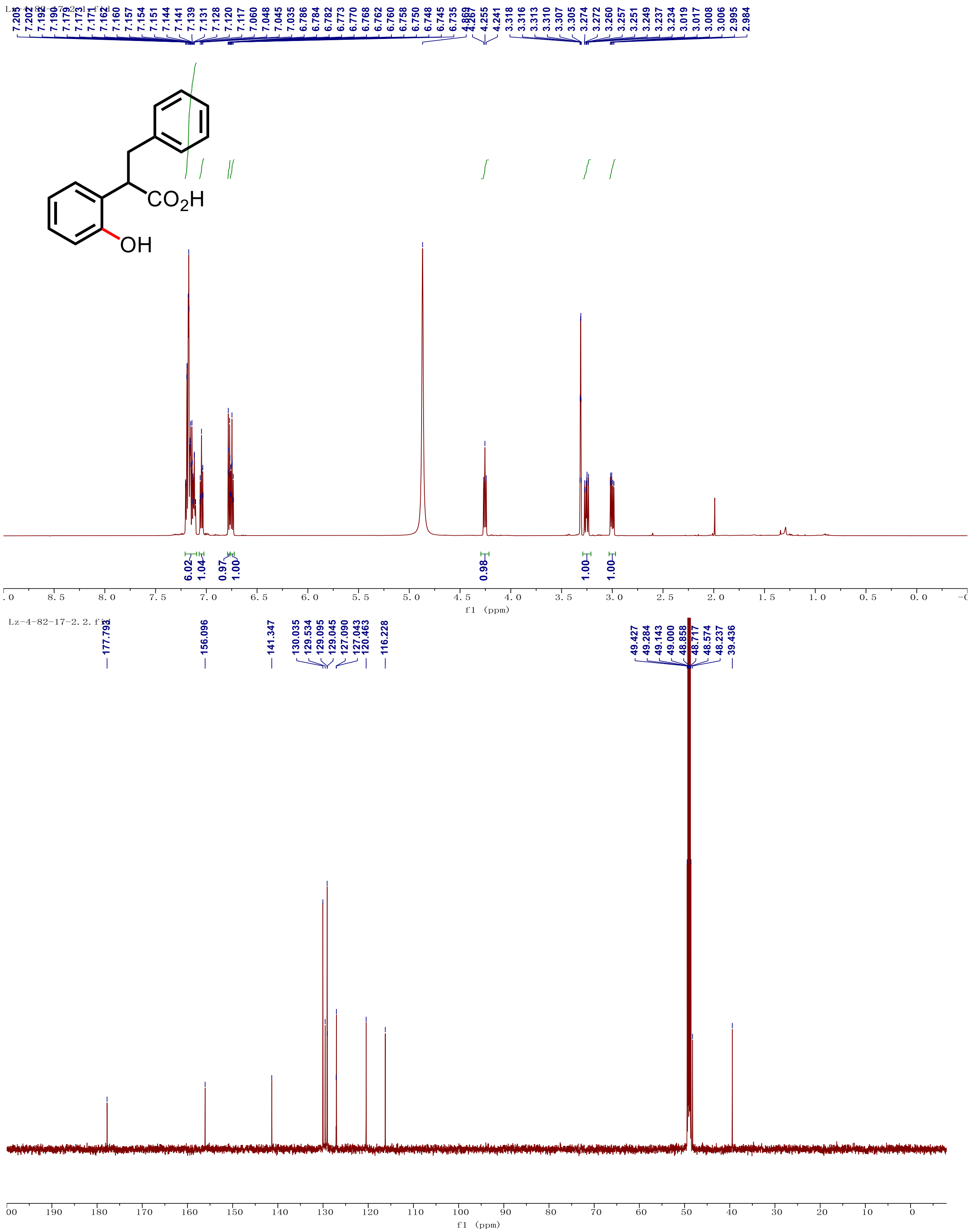

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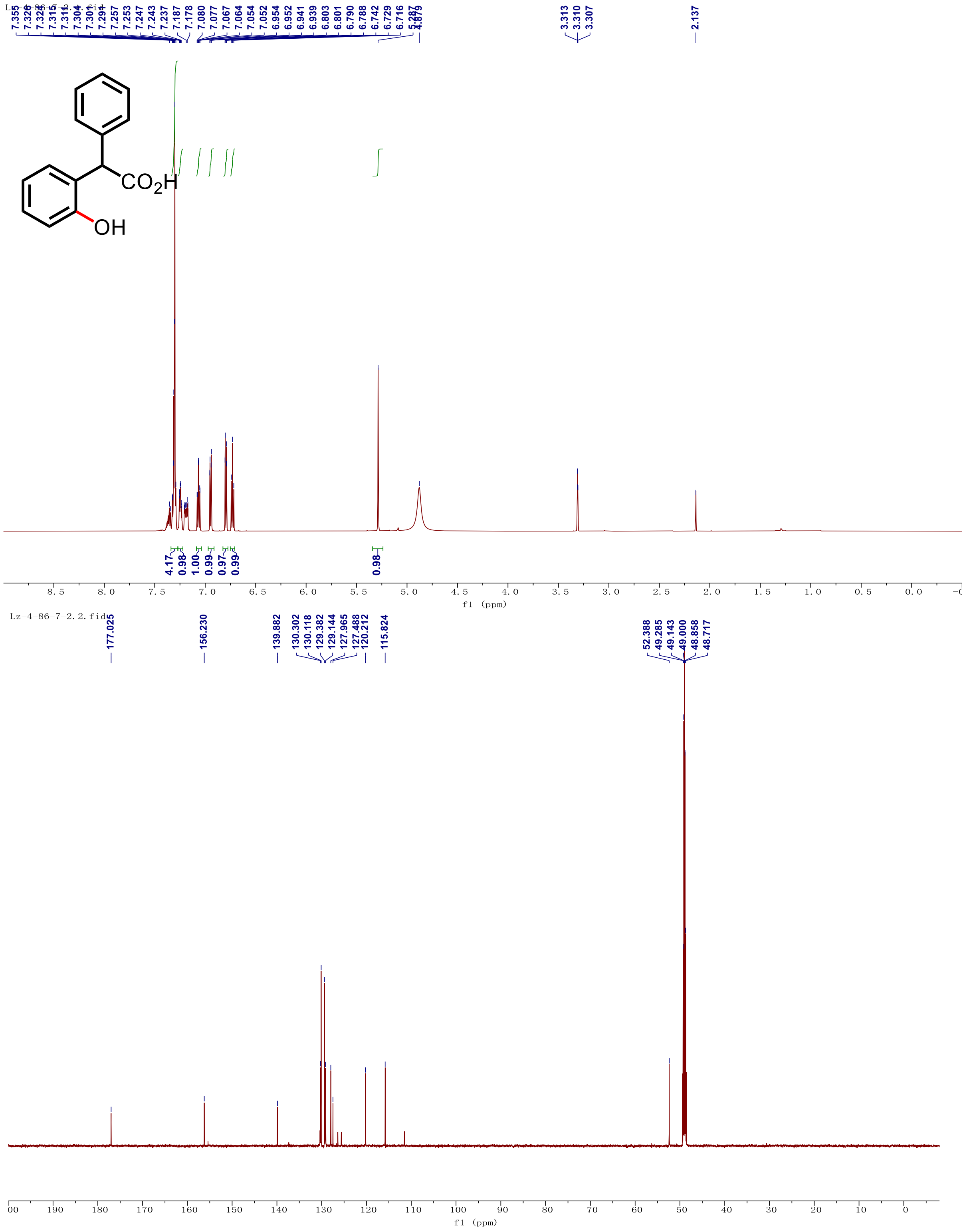

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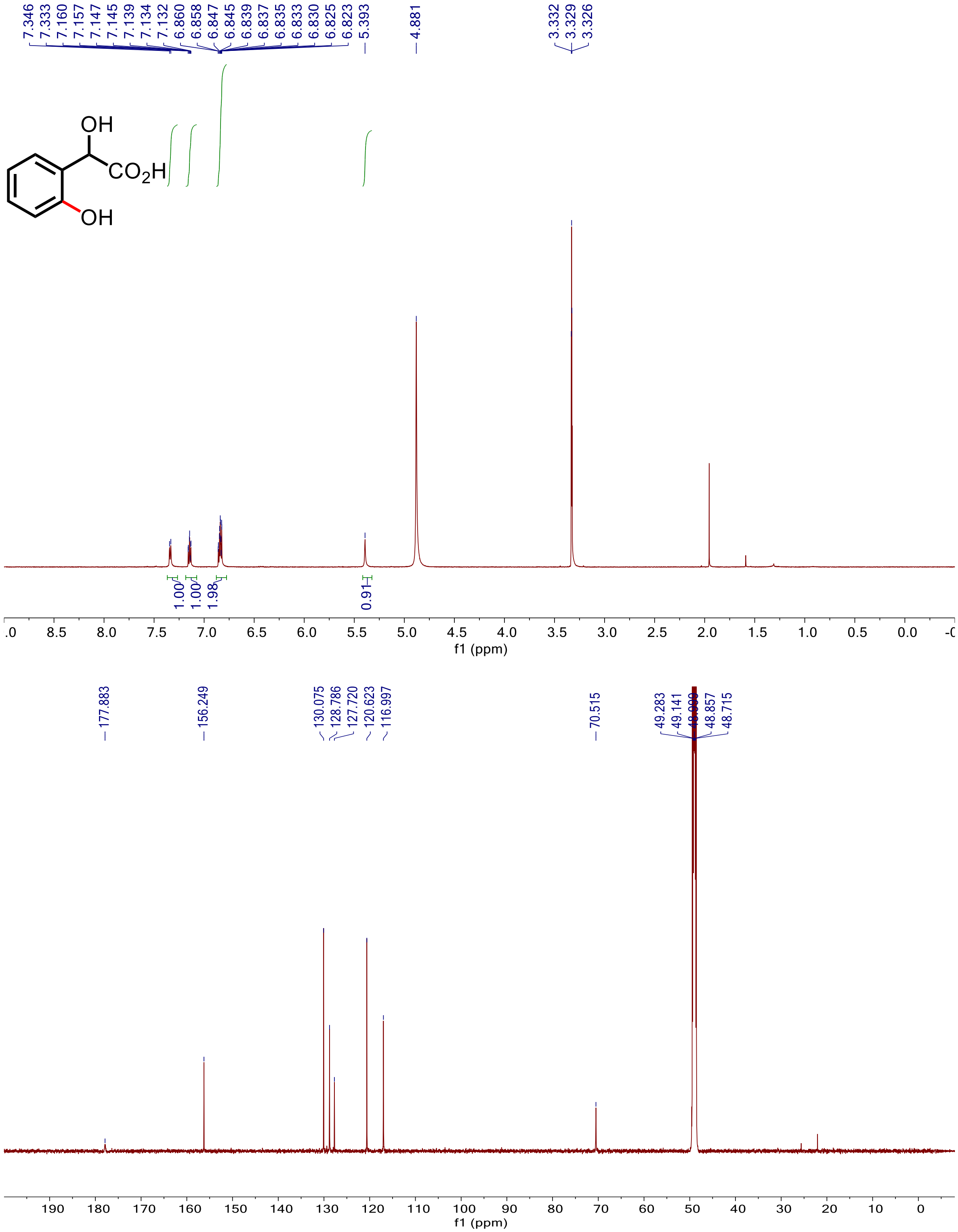

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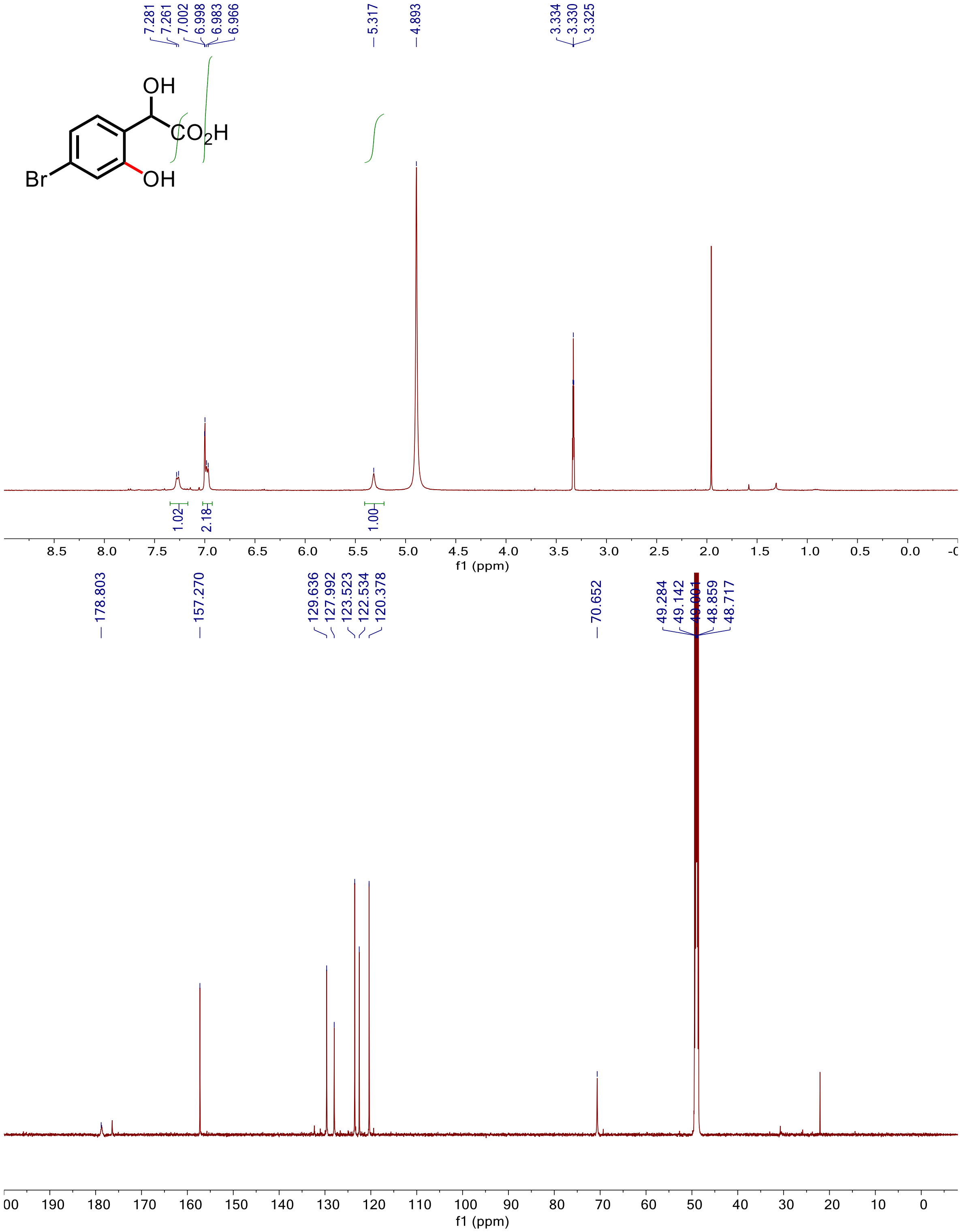
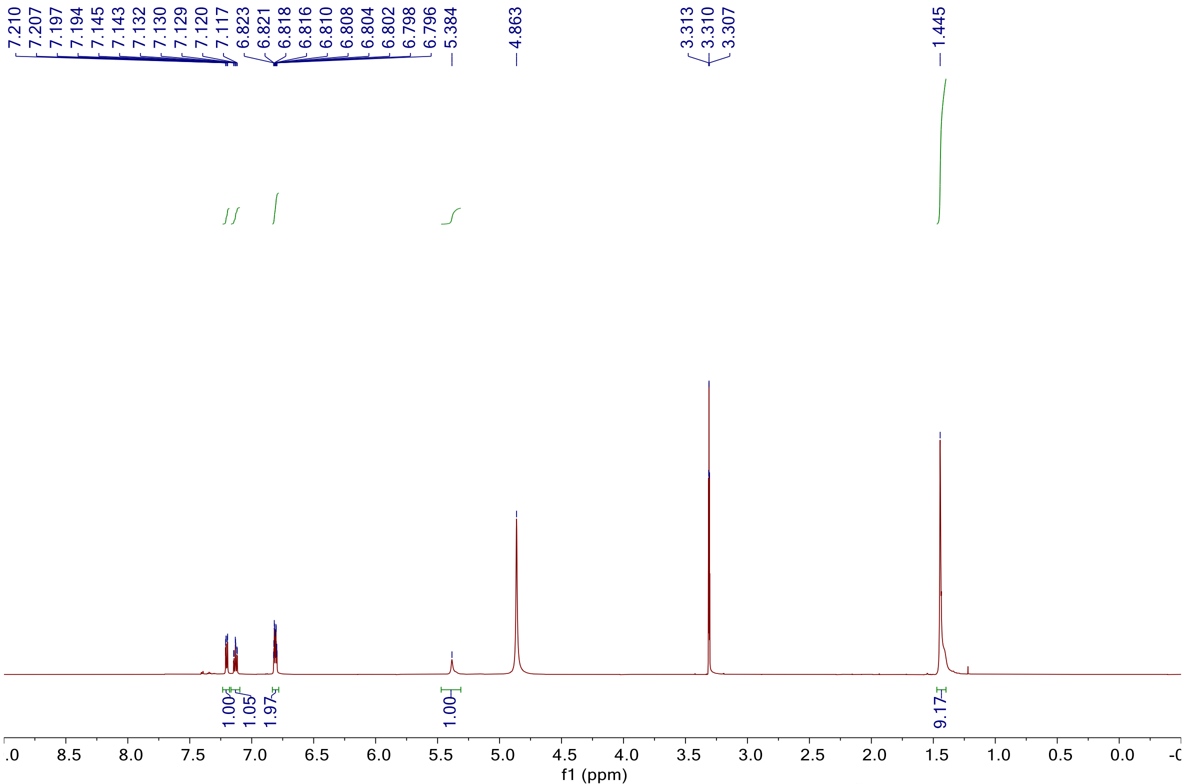
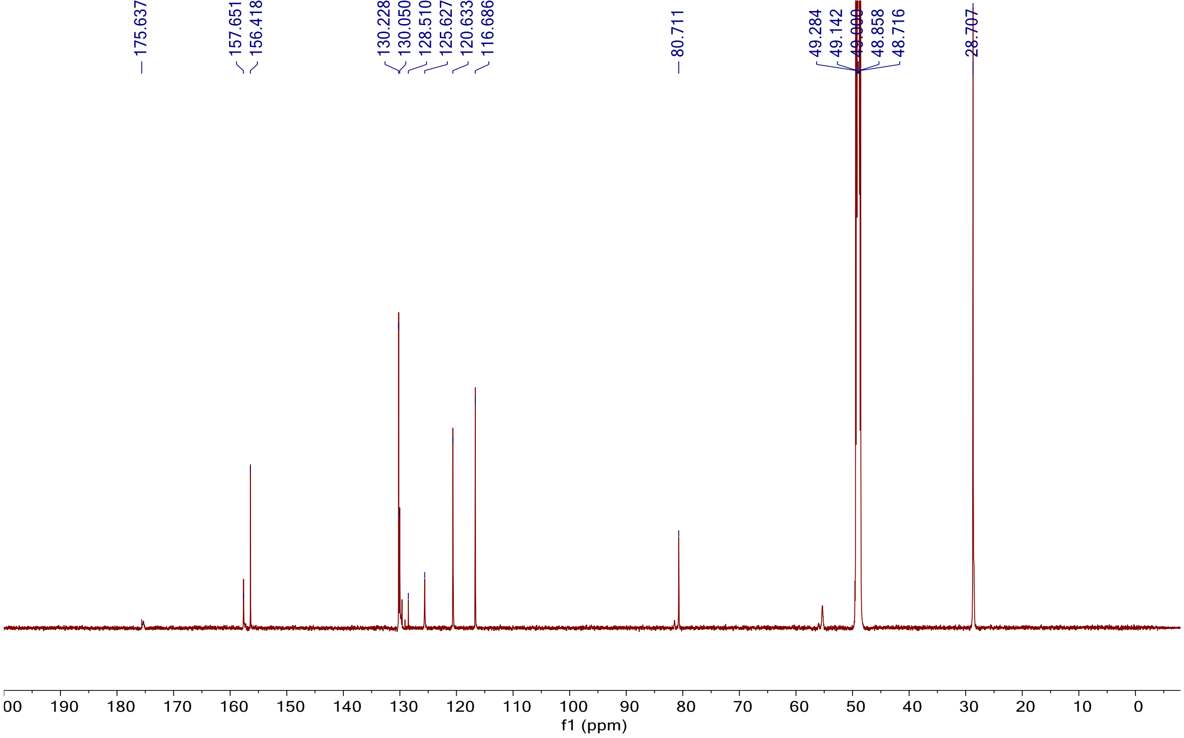
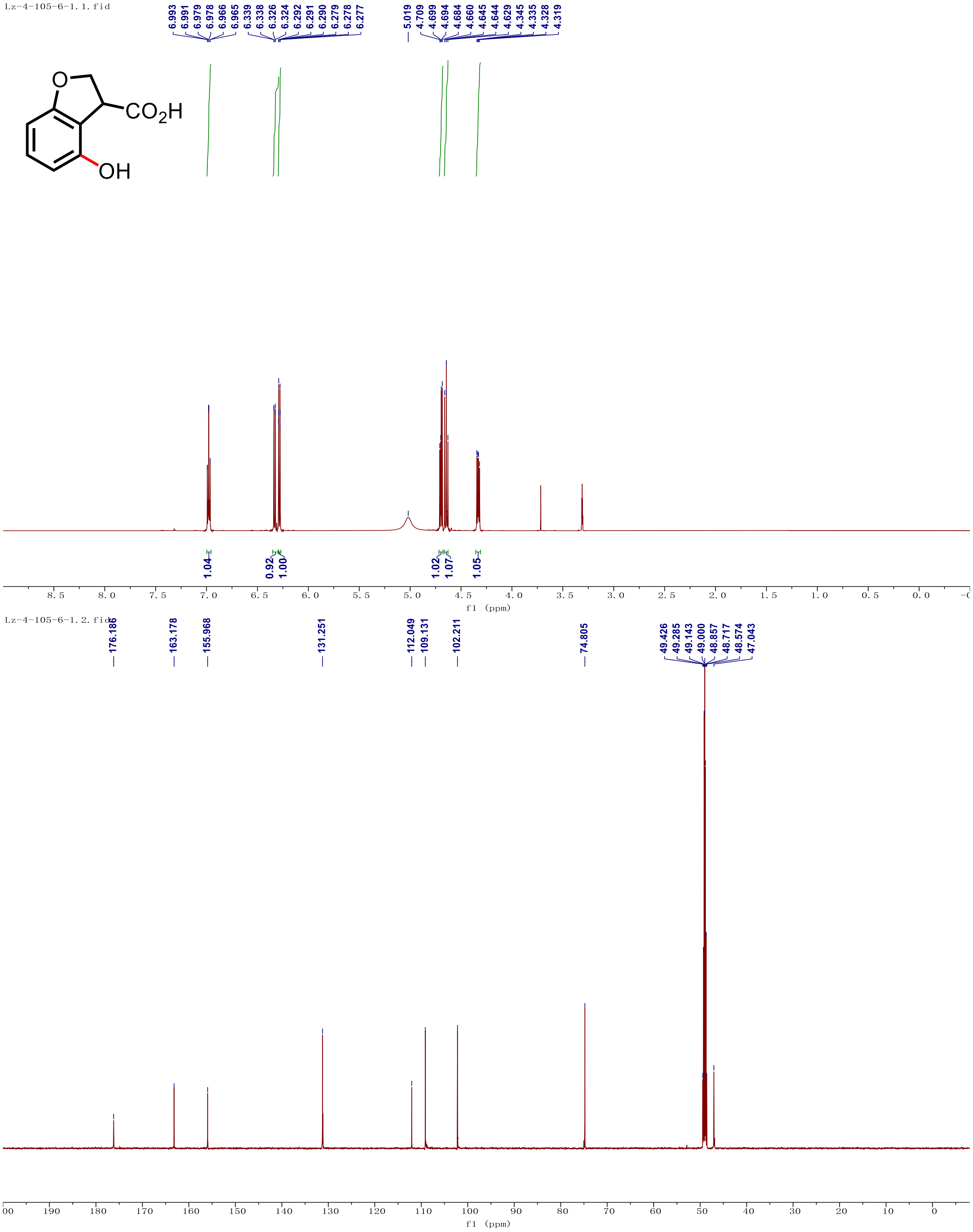


NMR Spectra of **2w**

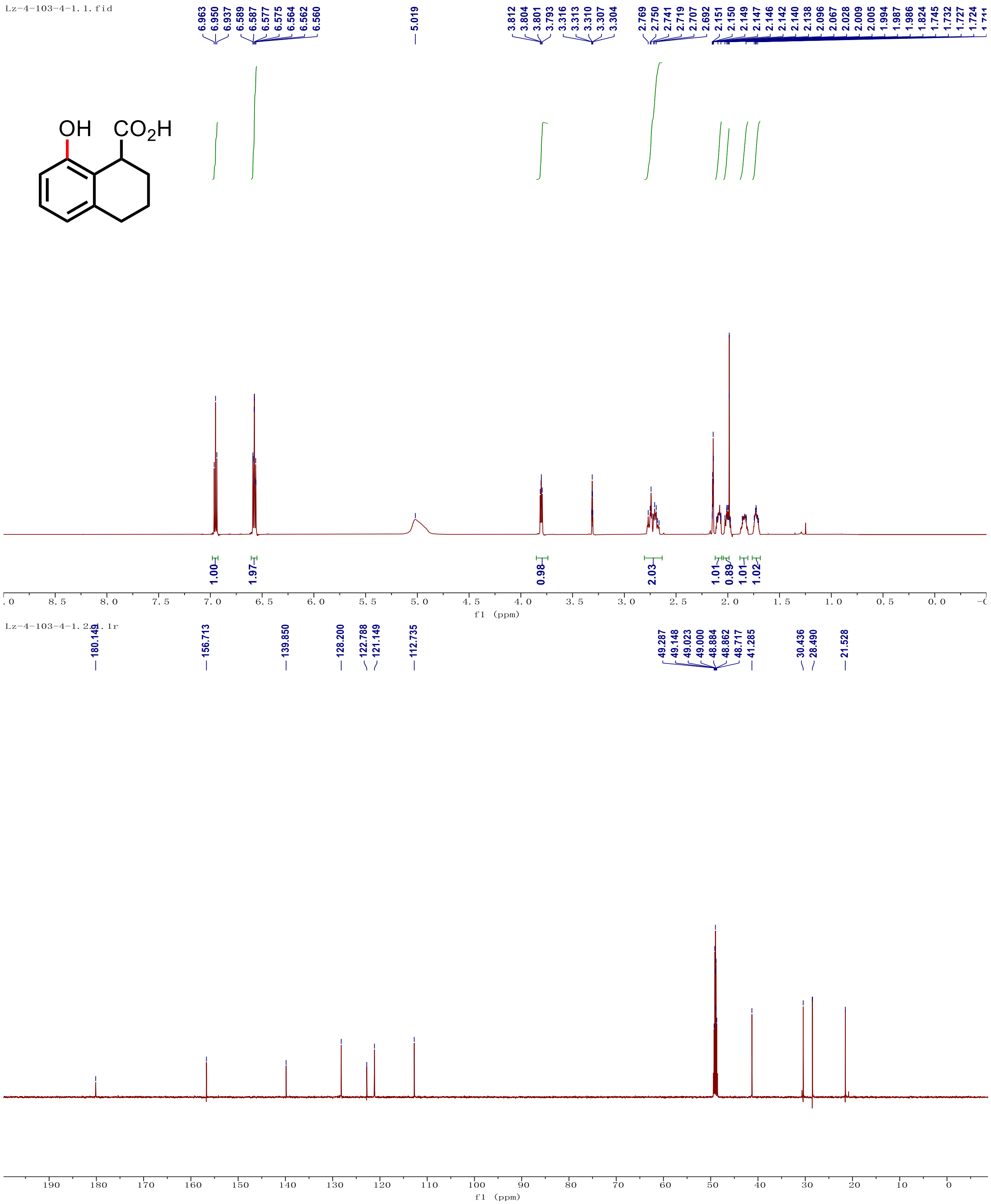




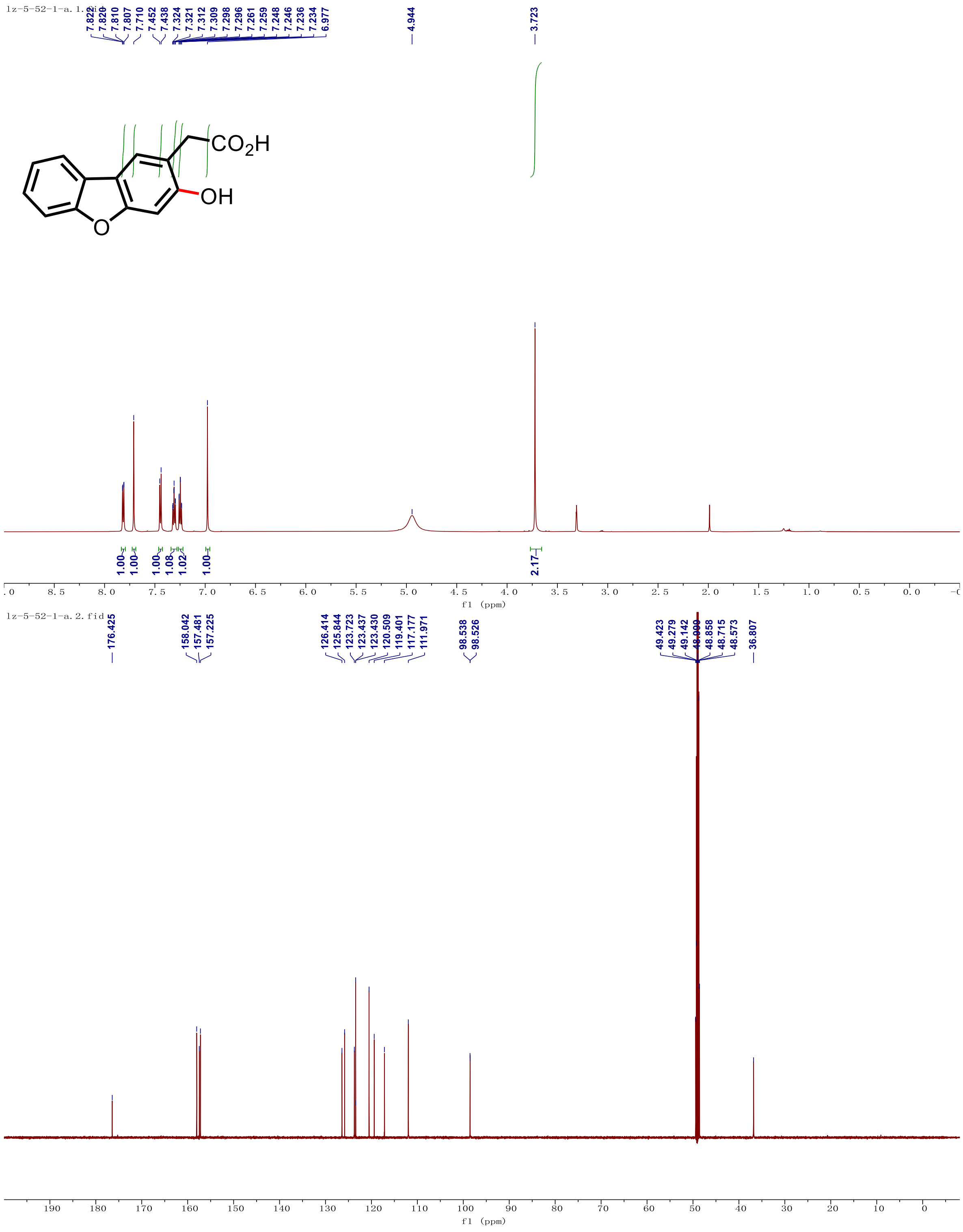
NMR Spectra of **2x**



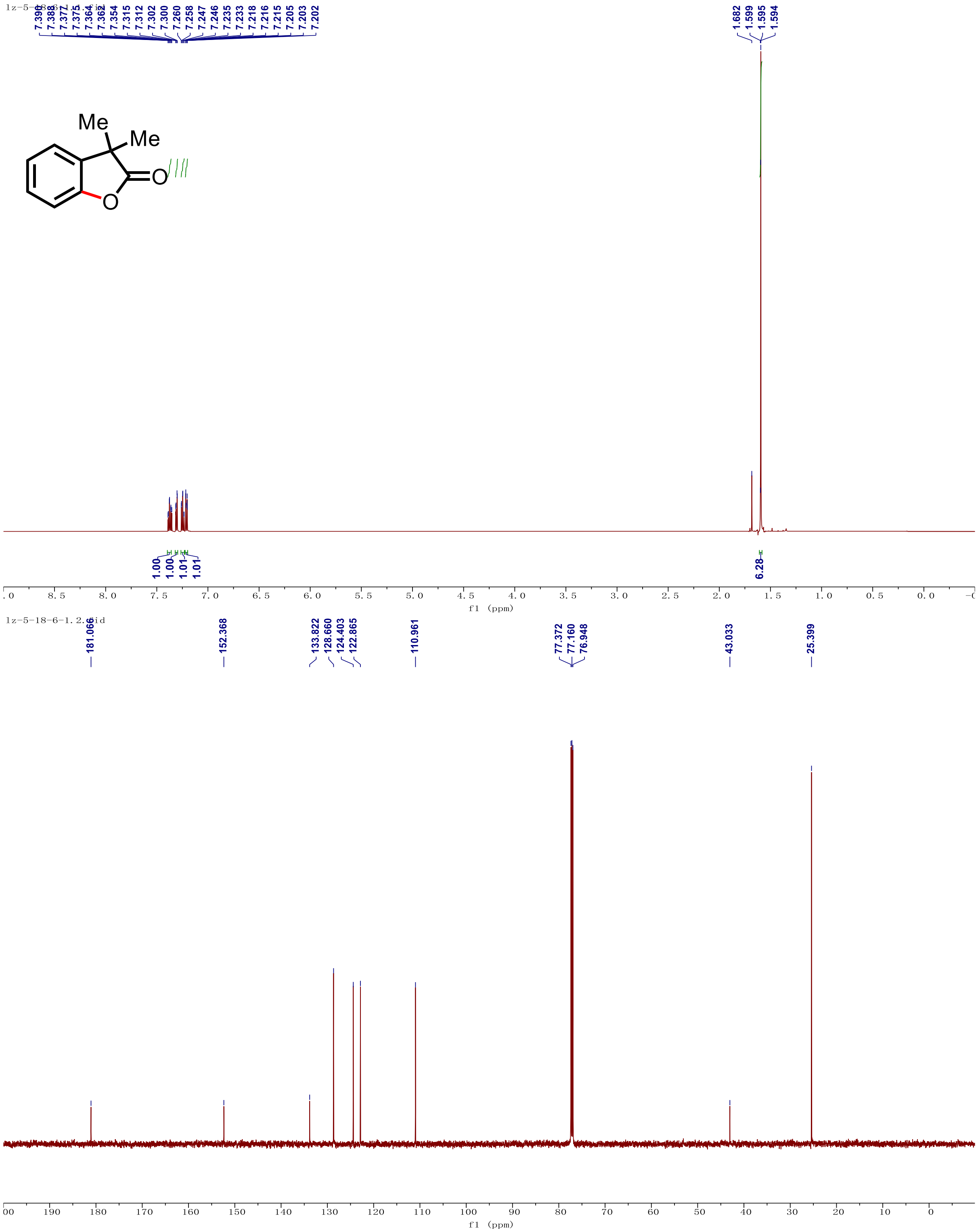
NMR Spectra of **2y**



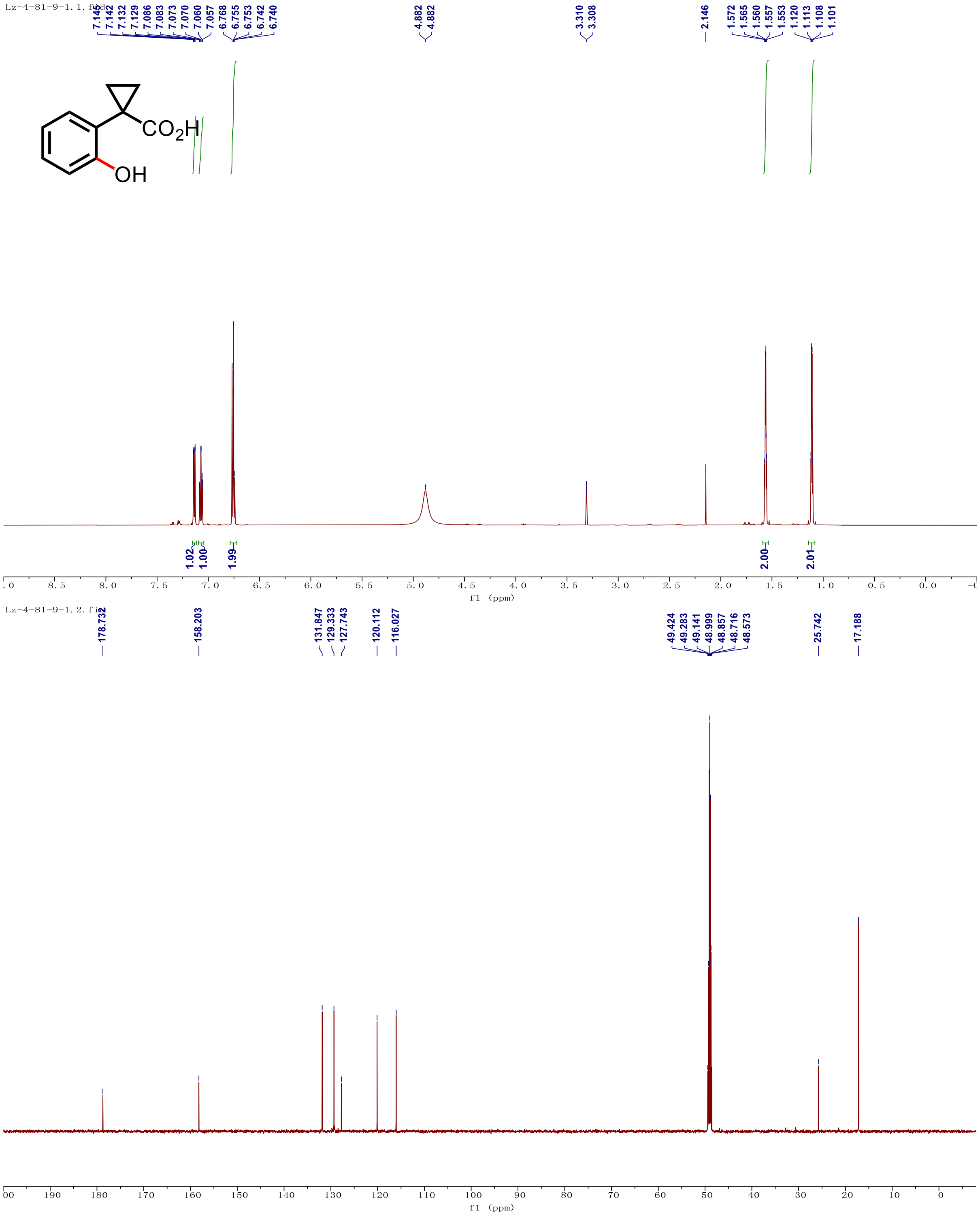
NMR Spectra of **2z**



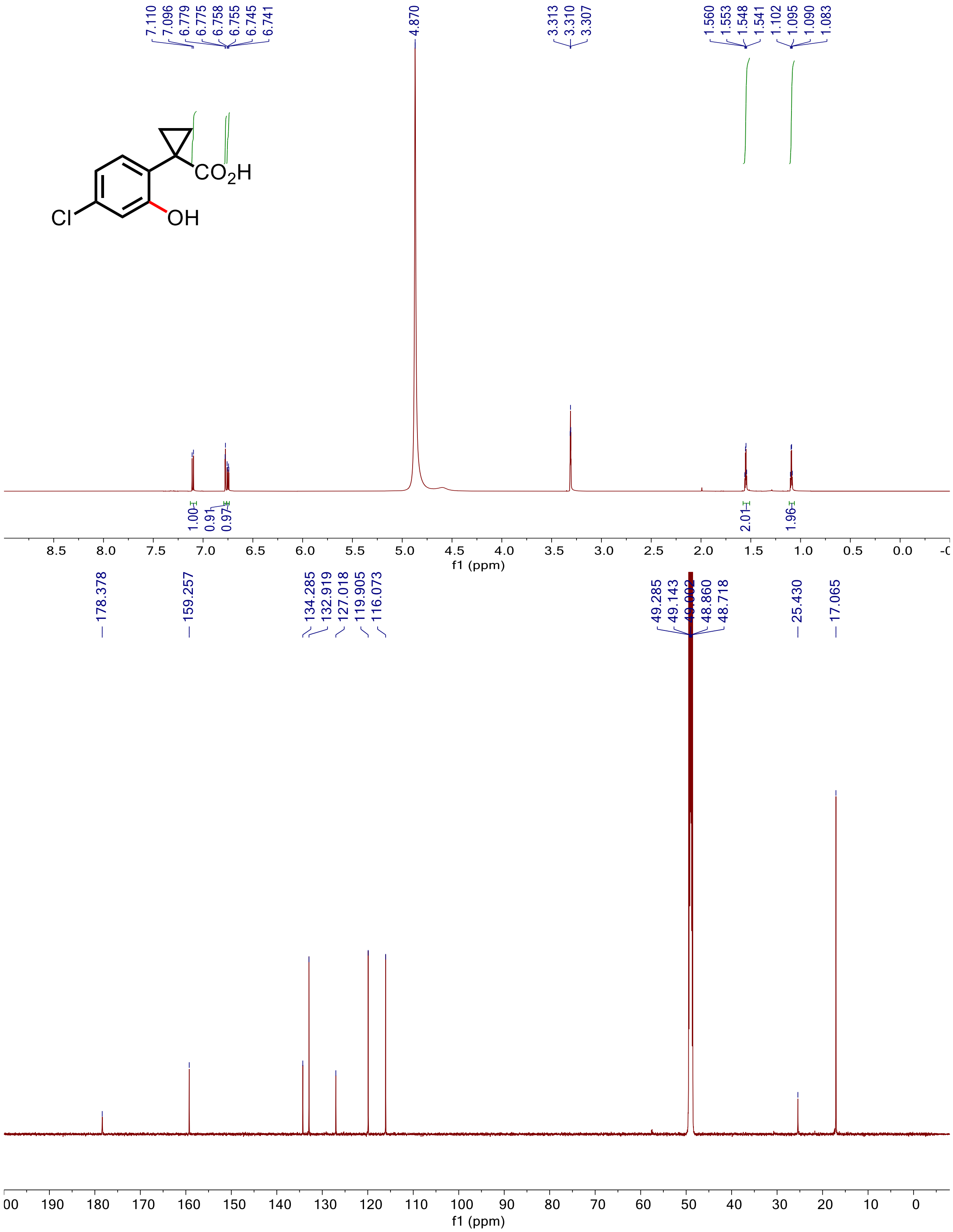
NMR Spectra of **2aa**



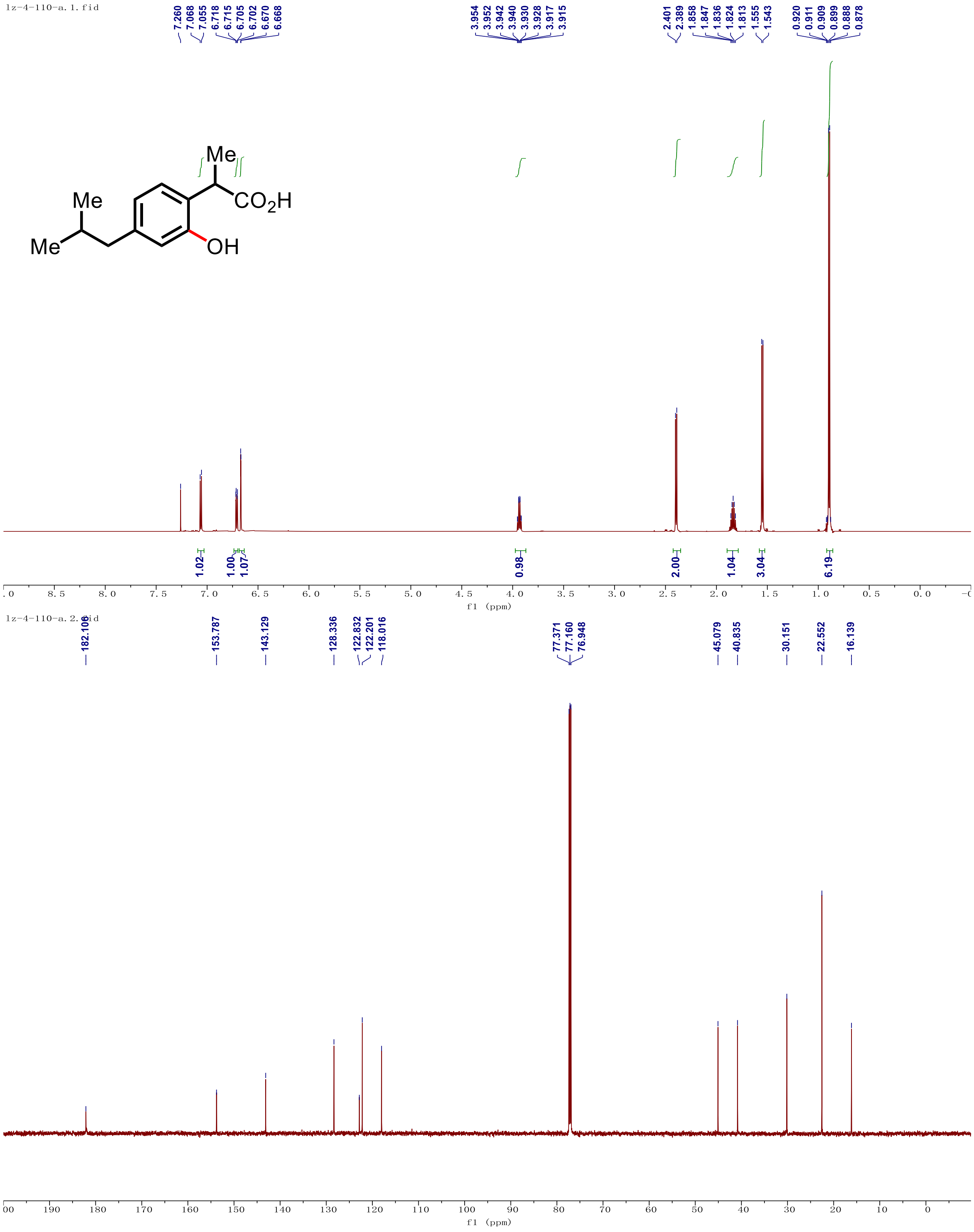
NMR Spectra of **2ab'**



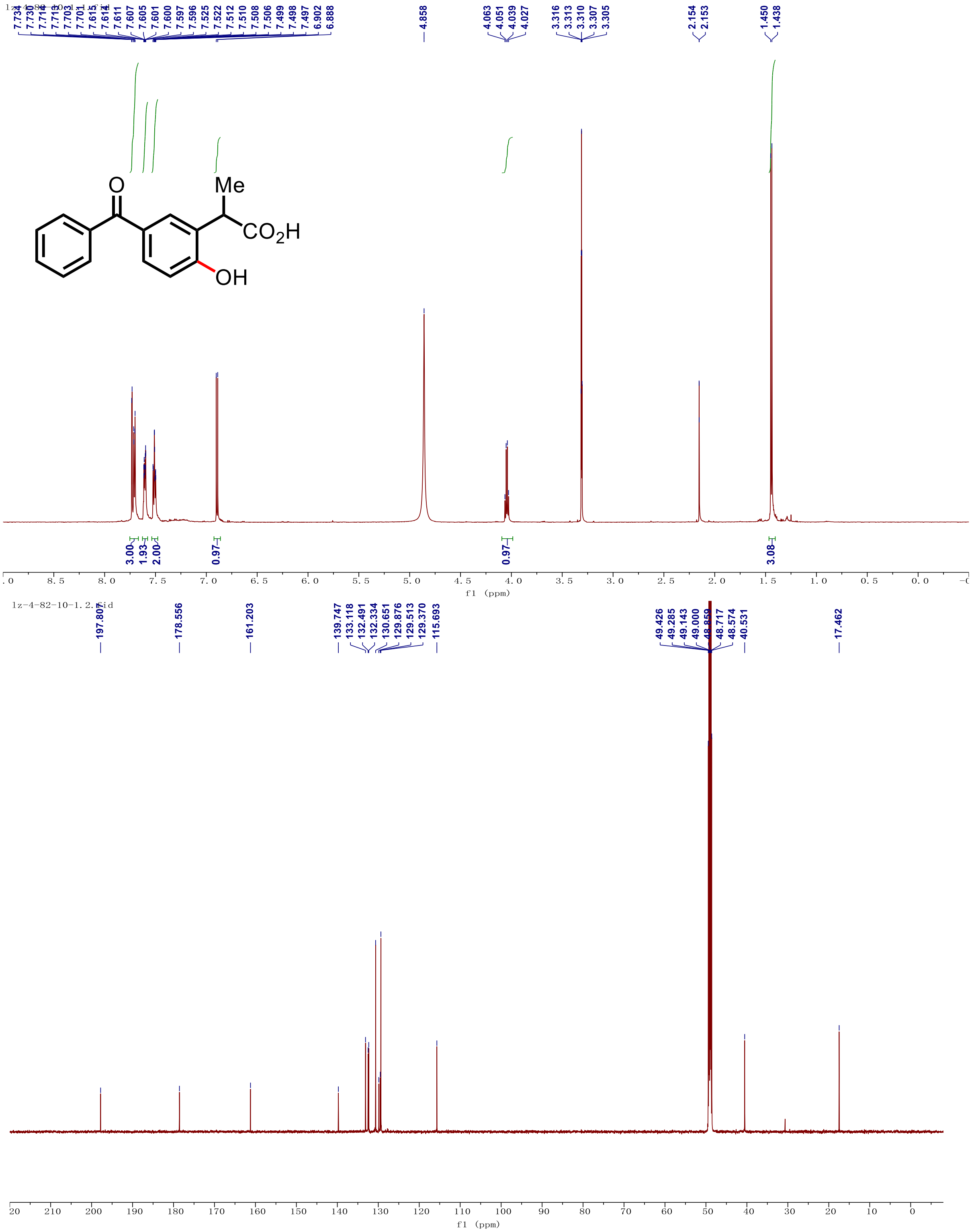
NMR Spectra of **2ac**



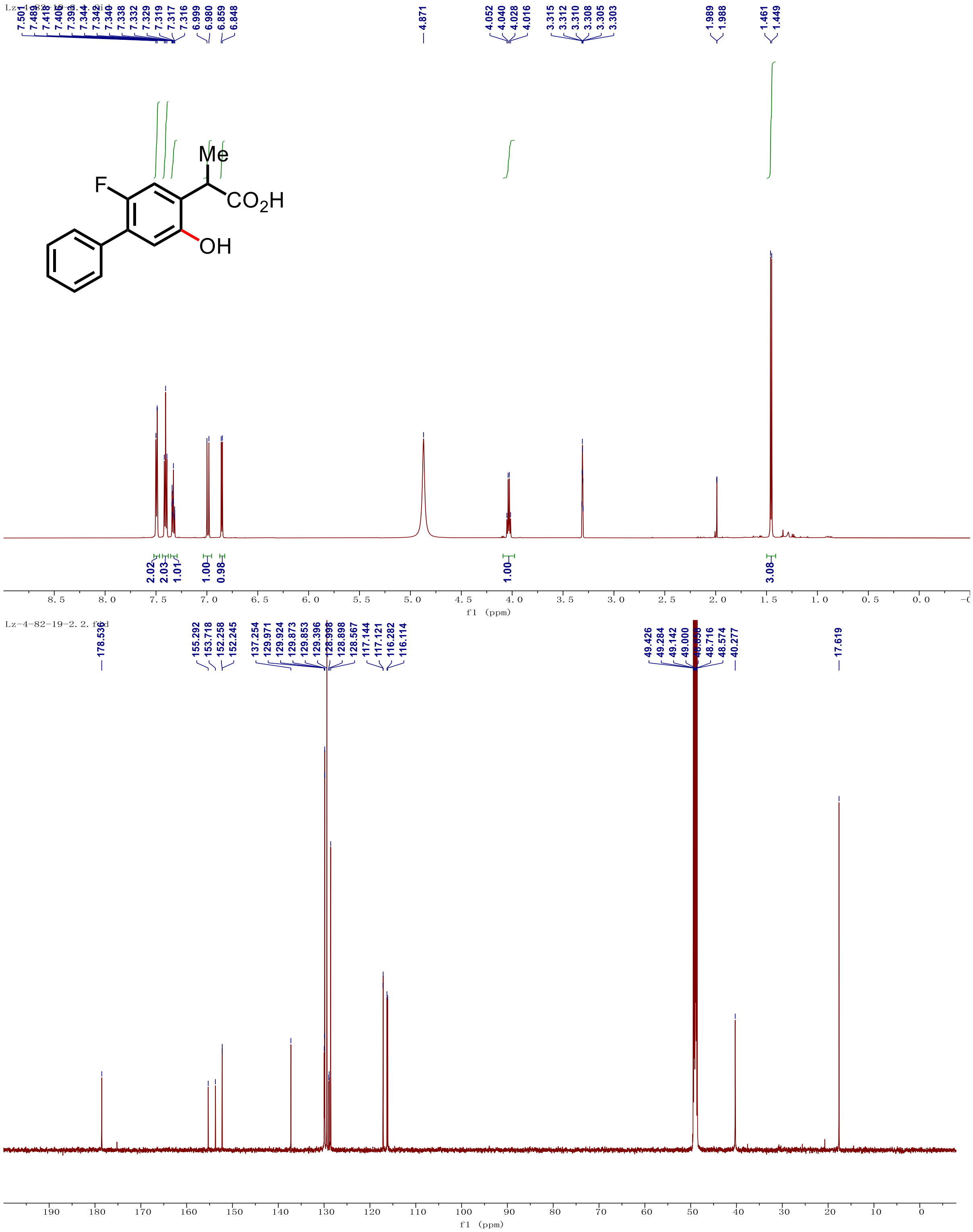
NMR Spectra of **2ad**



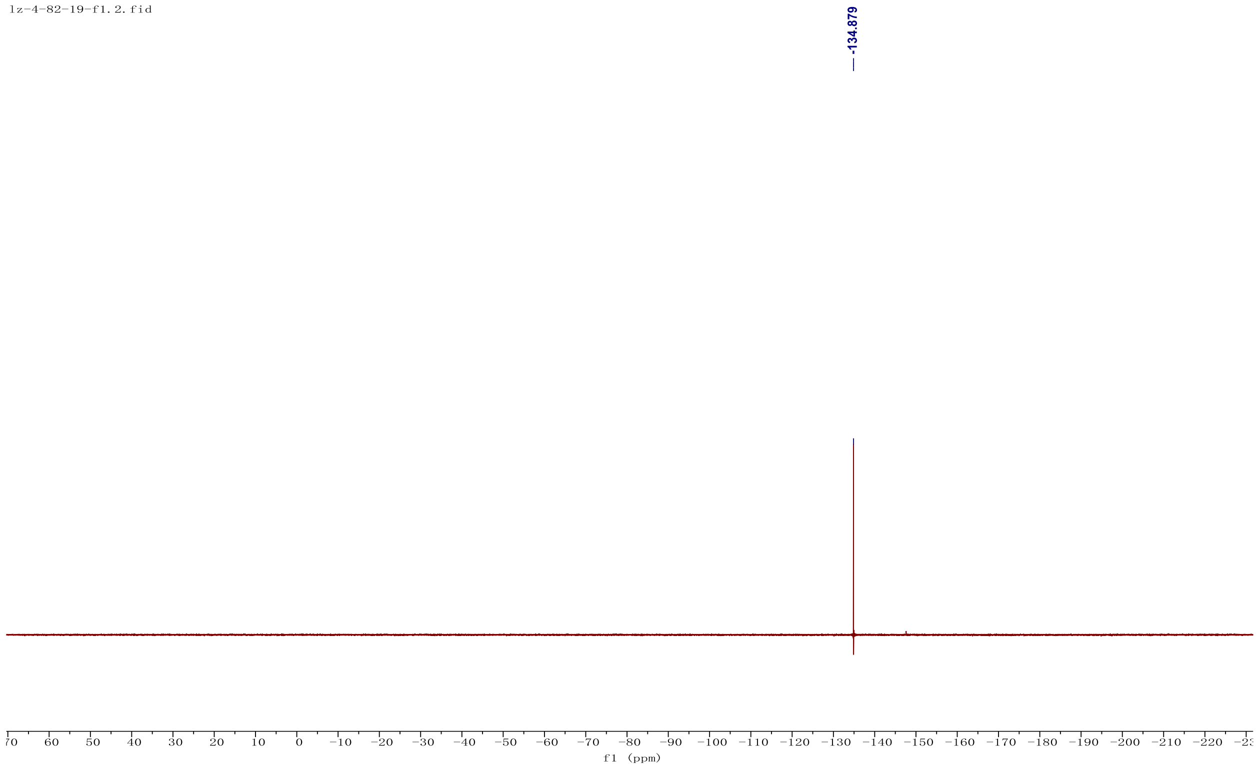
NMR Spectra of **2ae**



NMR Spectra of **2af**



NMR Spectra of **2ag**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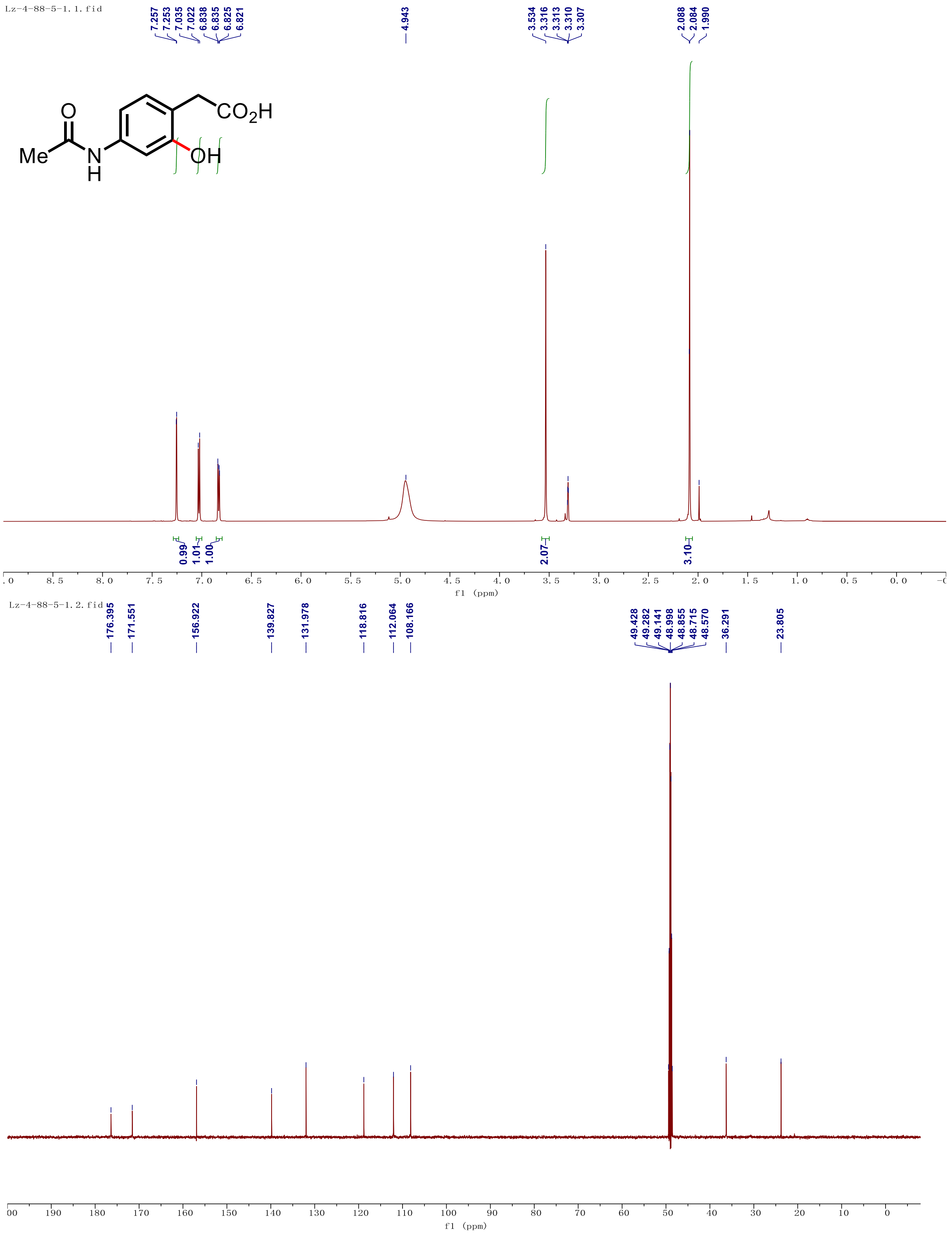
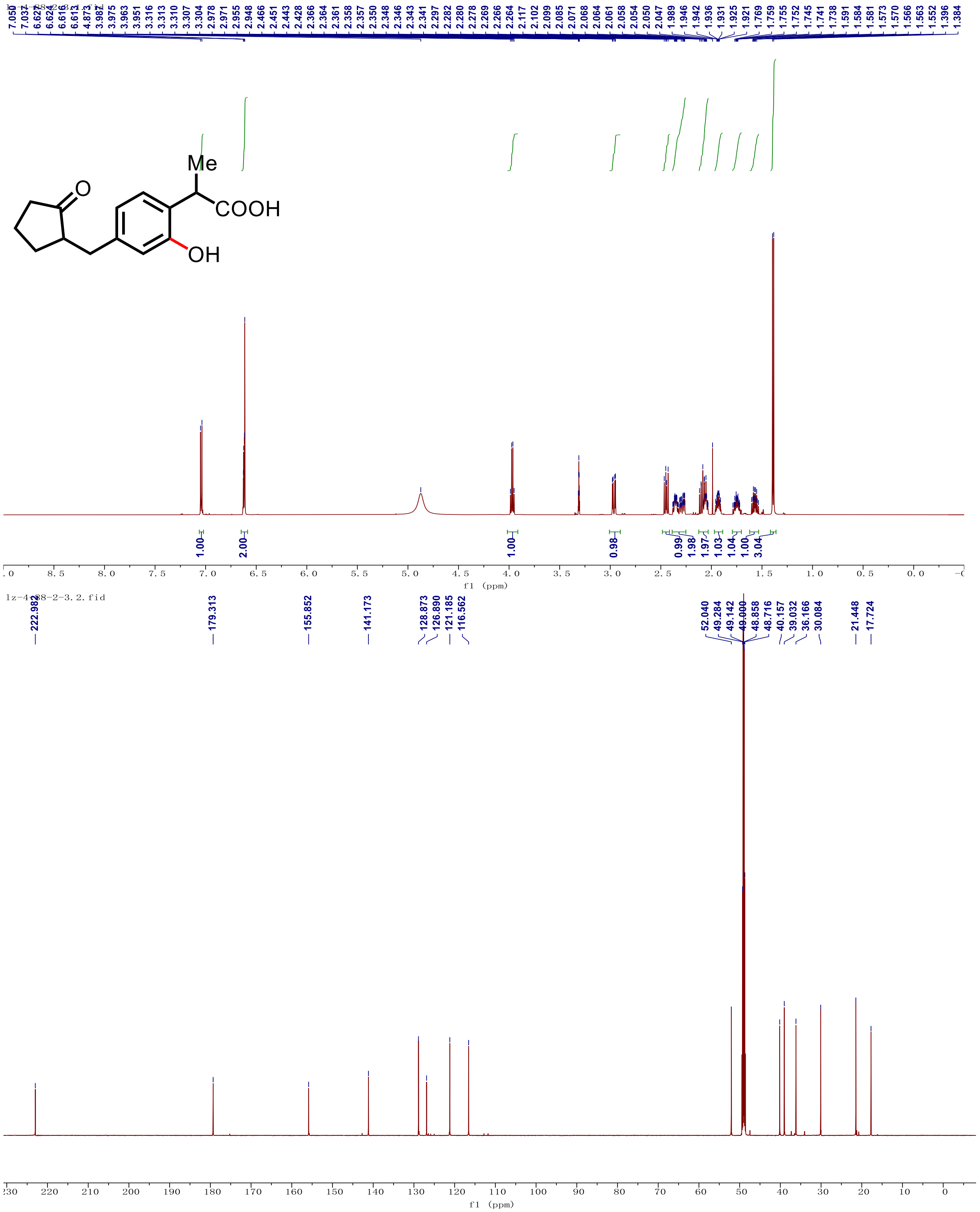
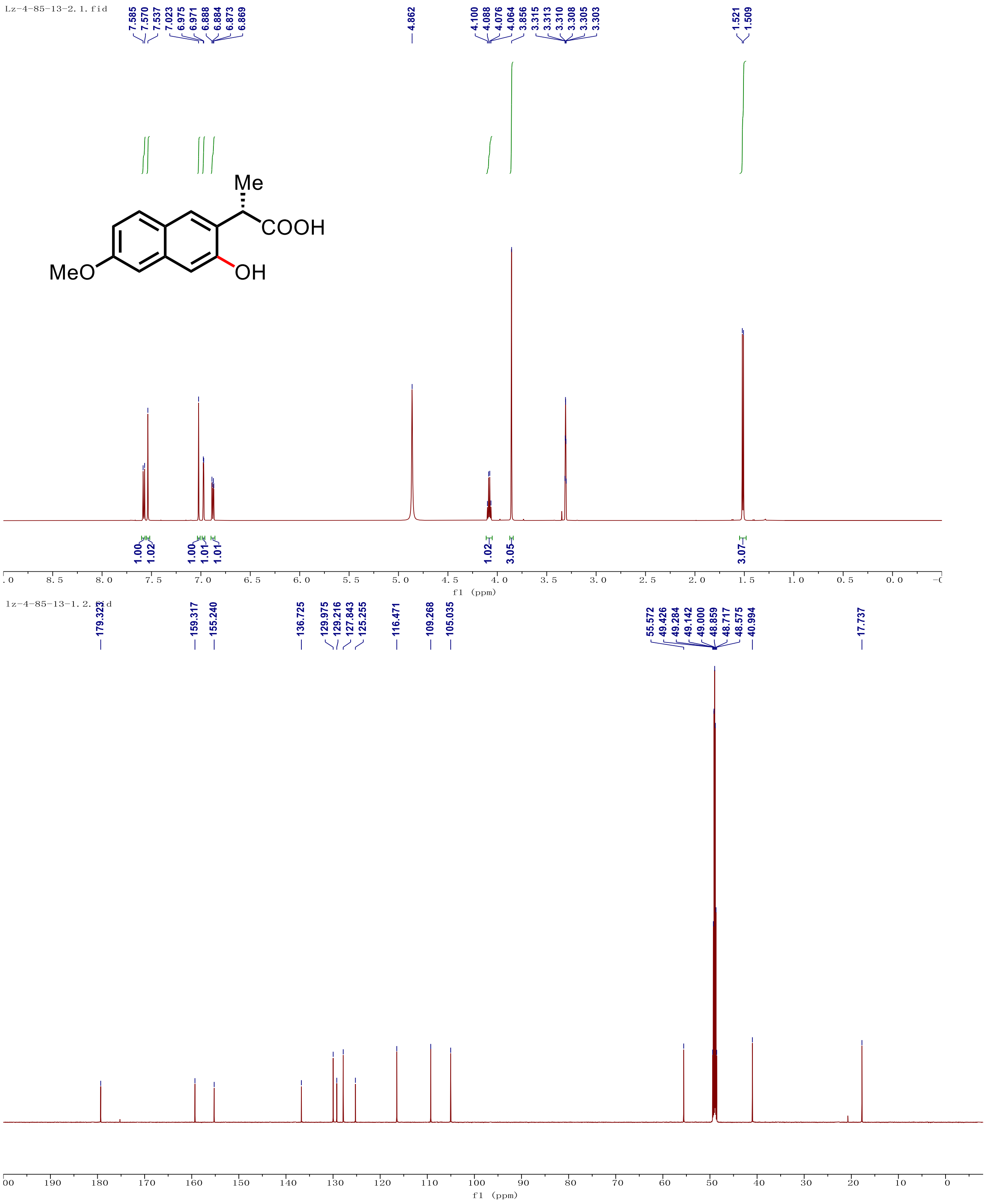
-210
-220
-23
f1 (ppm)



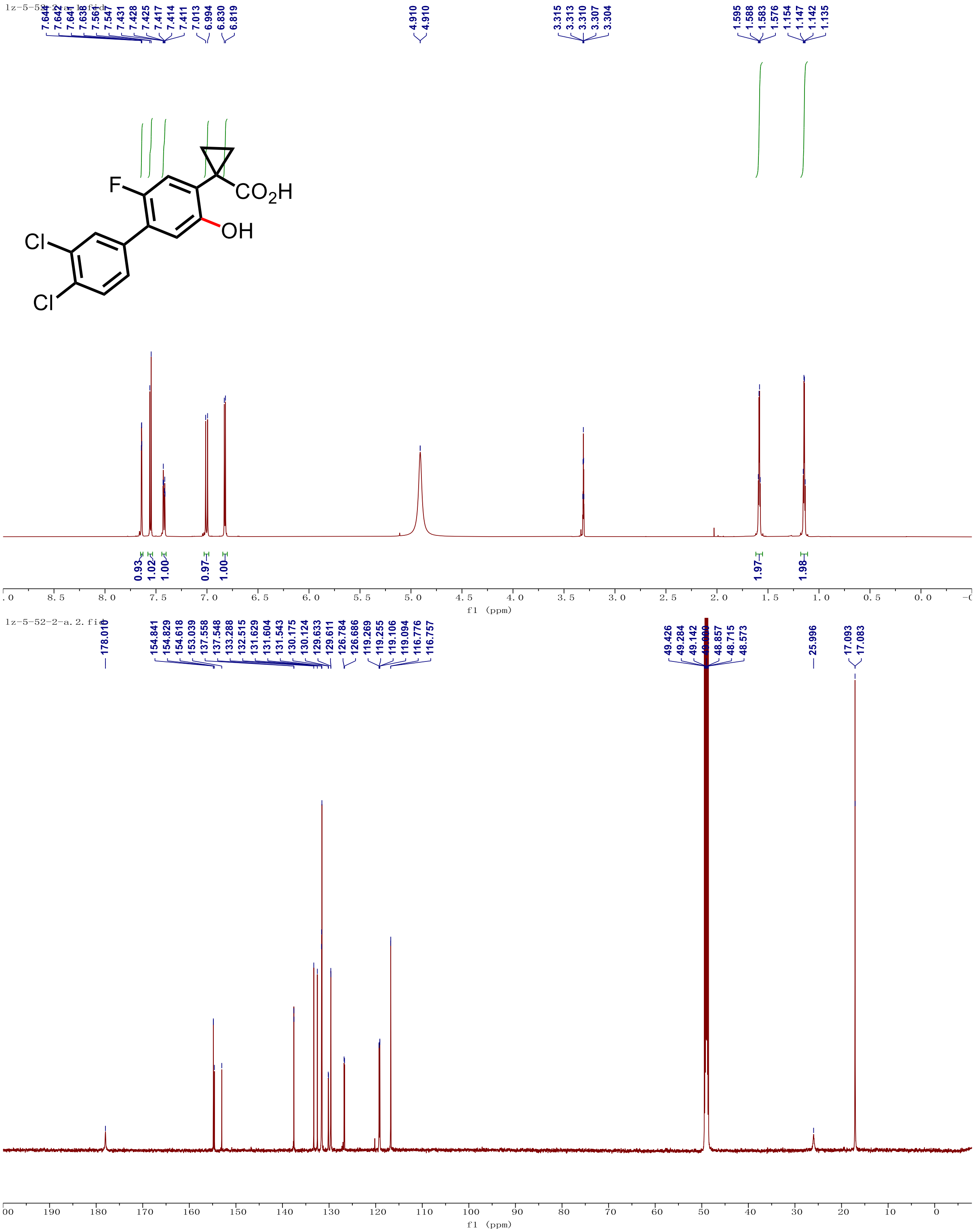
NMR Spectra of **2ah**



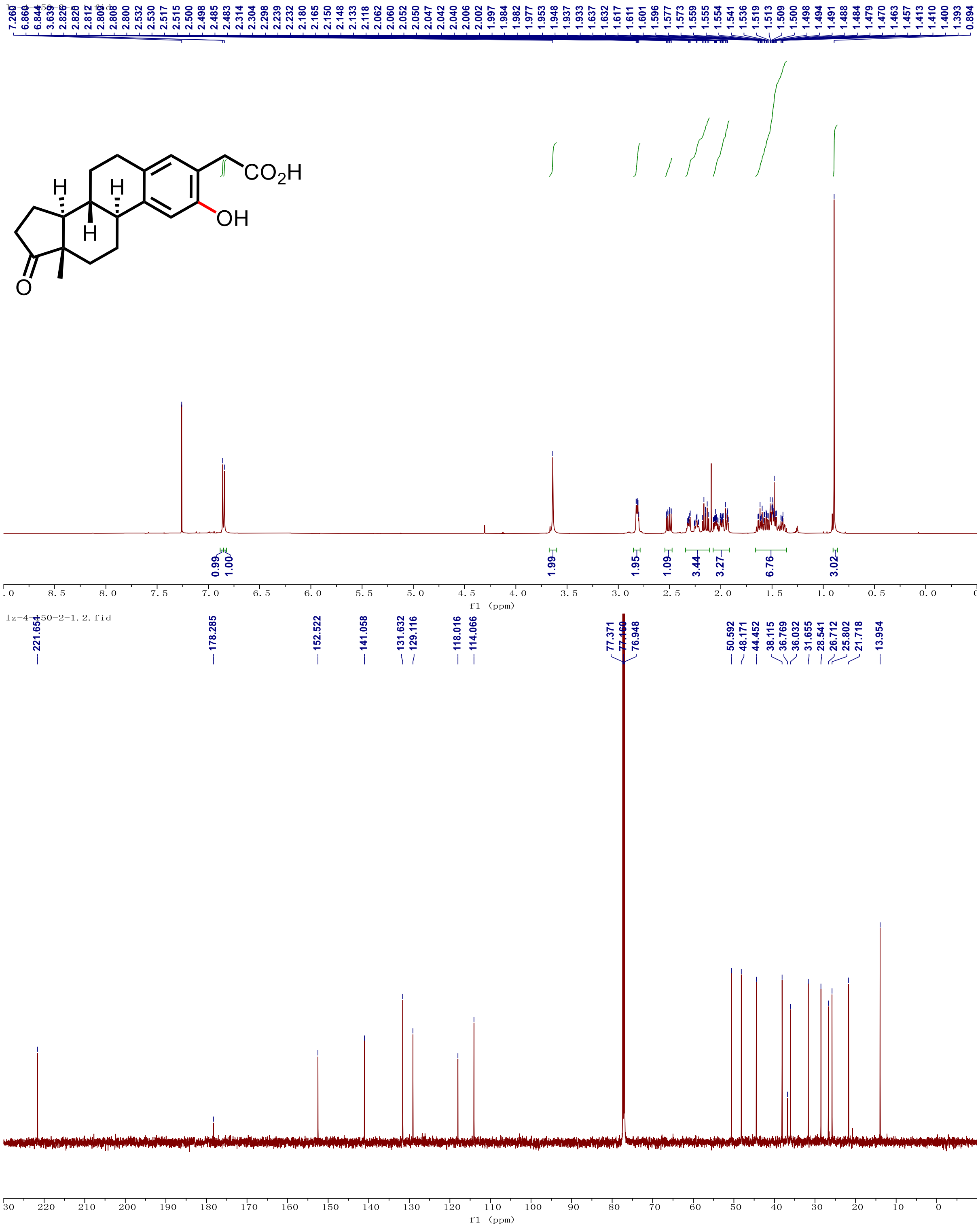
NMR Spectra of **2ai**



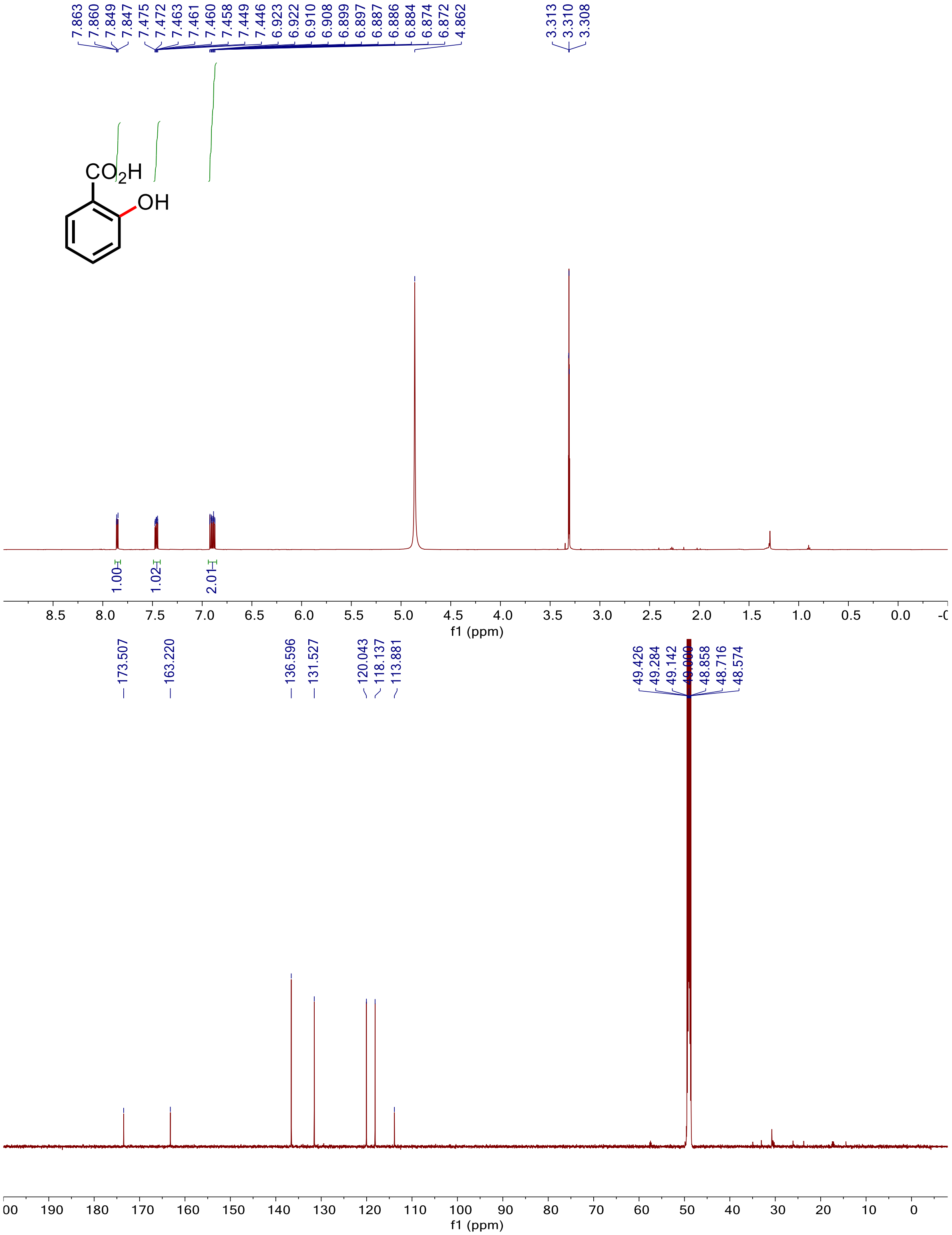
NMR Spectra of **2aj**



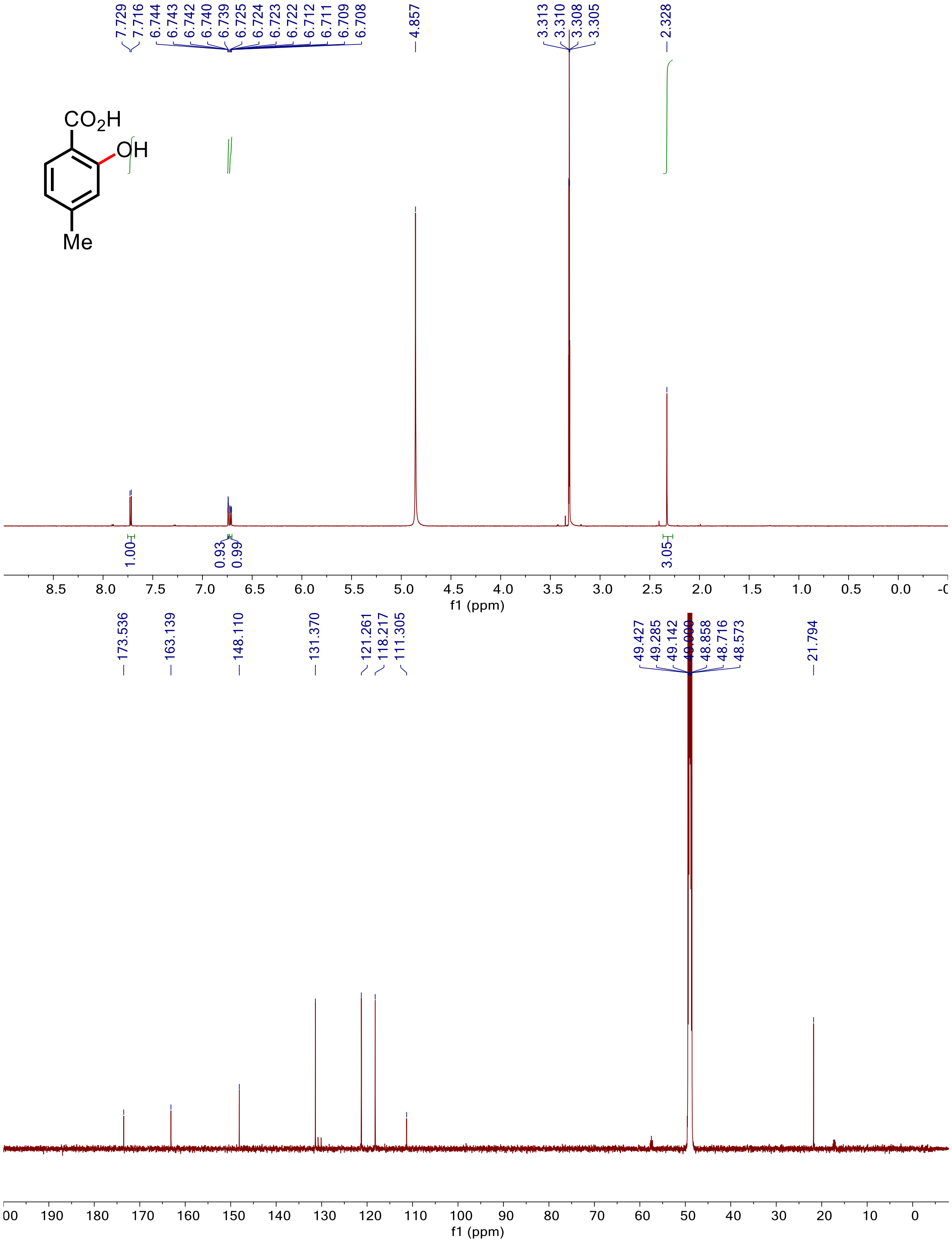
NMR Spectra of **2ak**



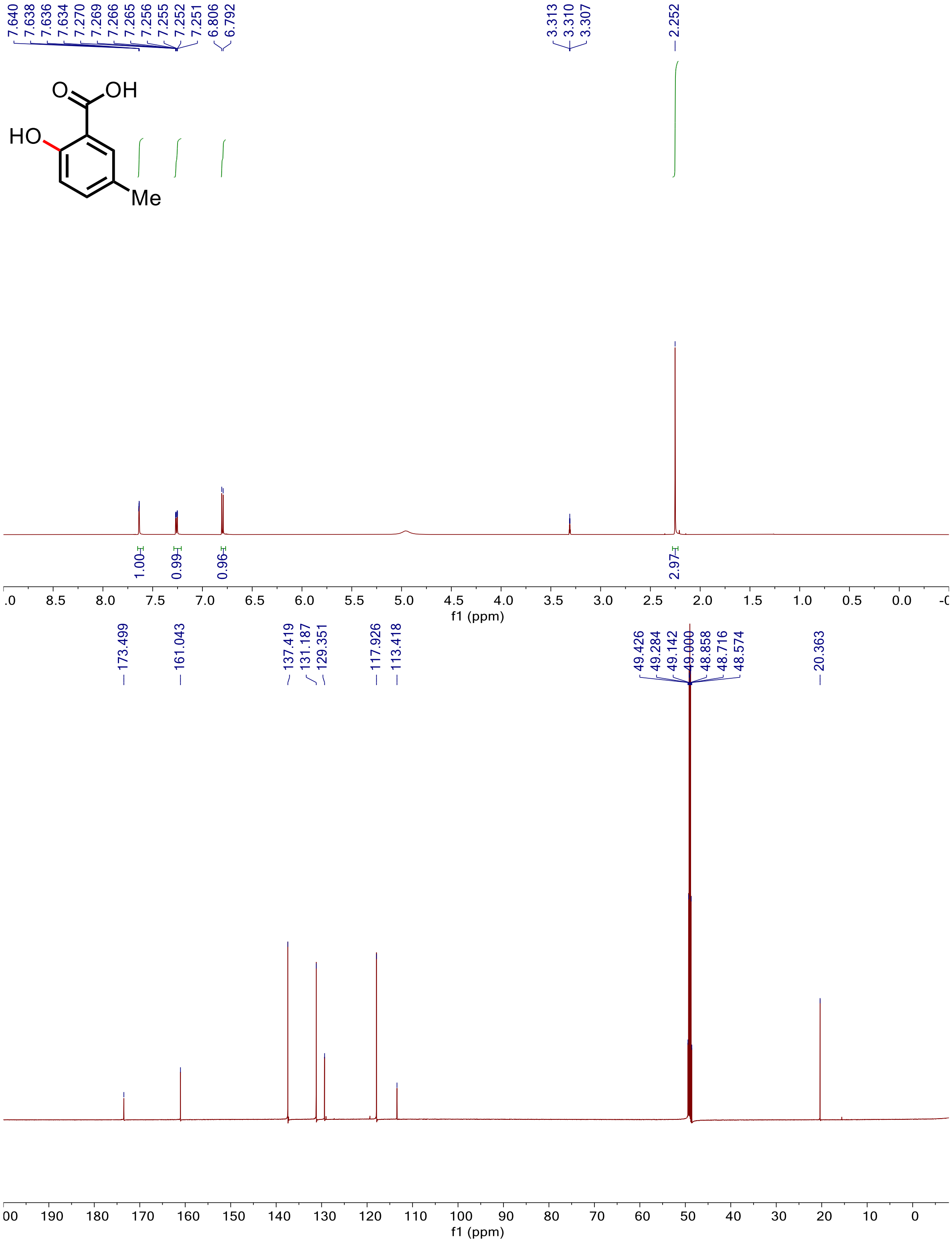
NMR Spectra of **2al**



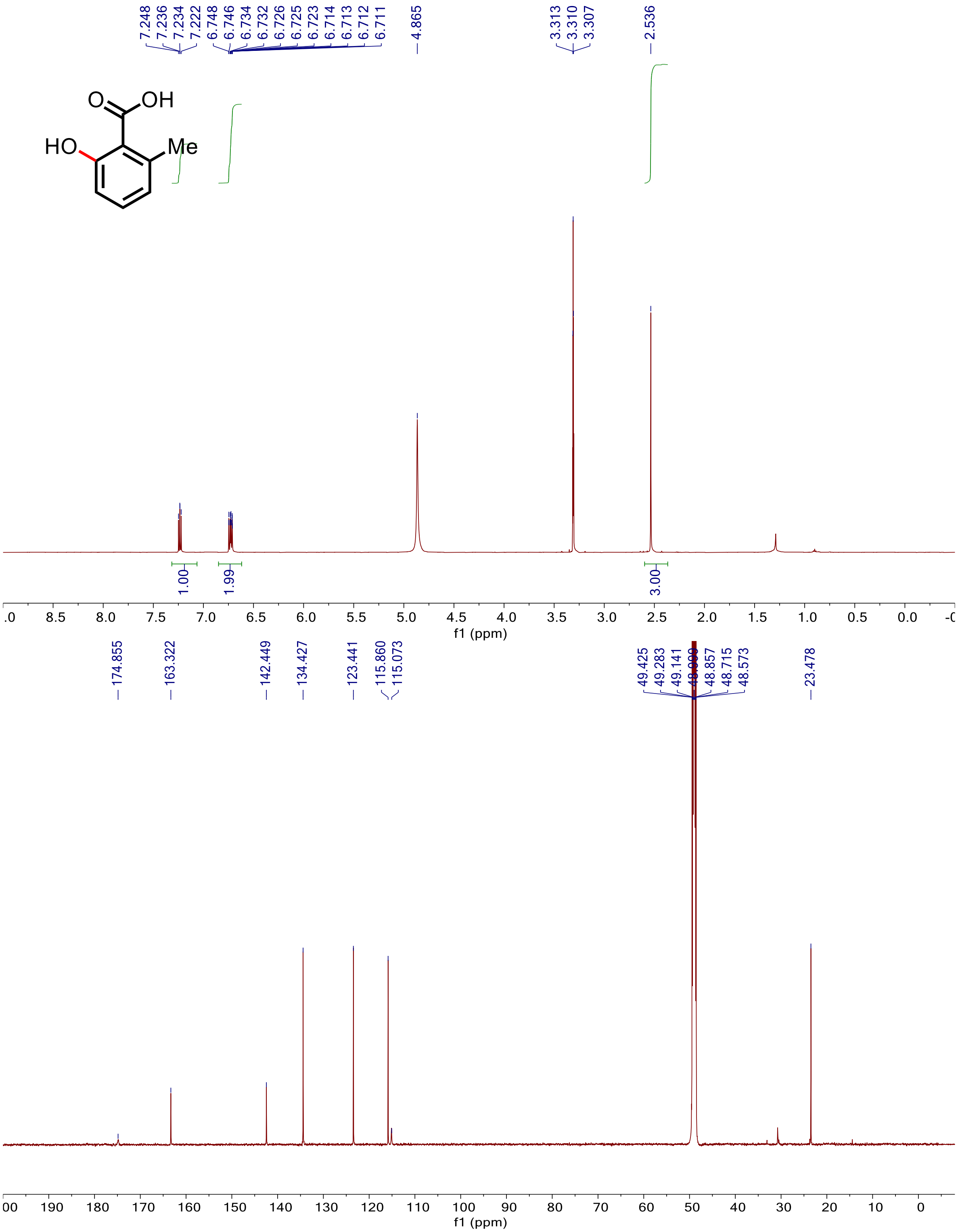
NMR Spectra of **4a**



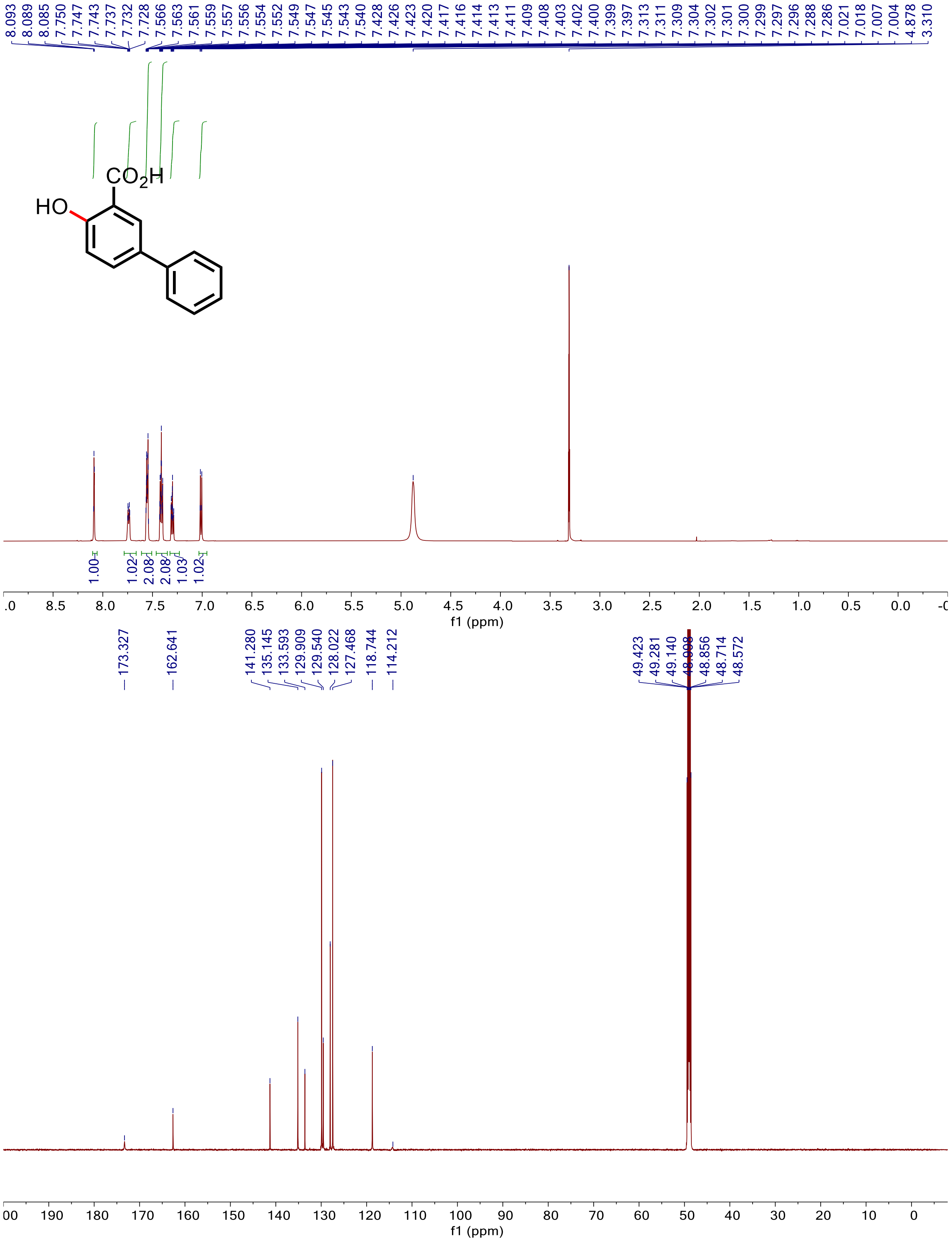
NMR Spectra of **4b**



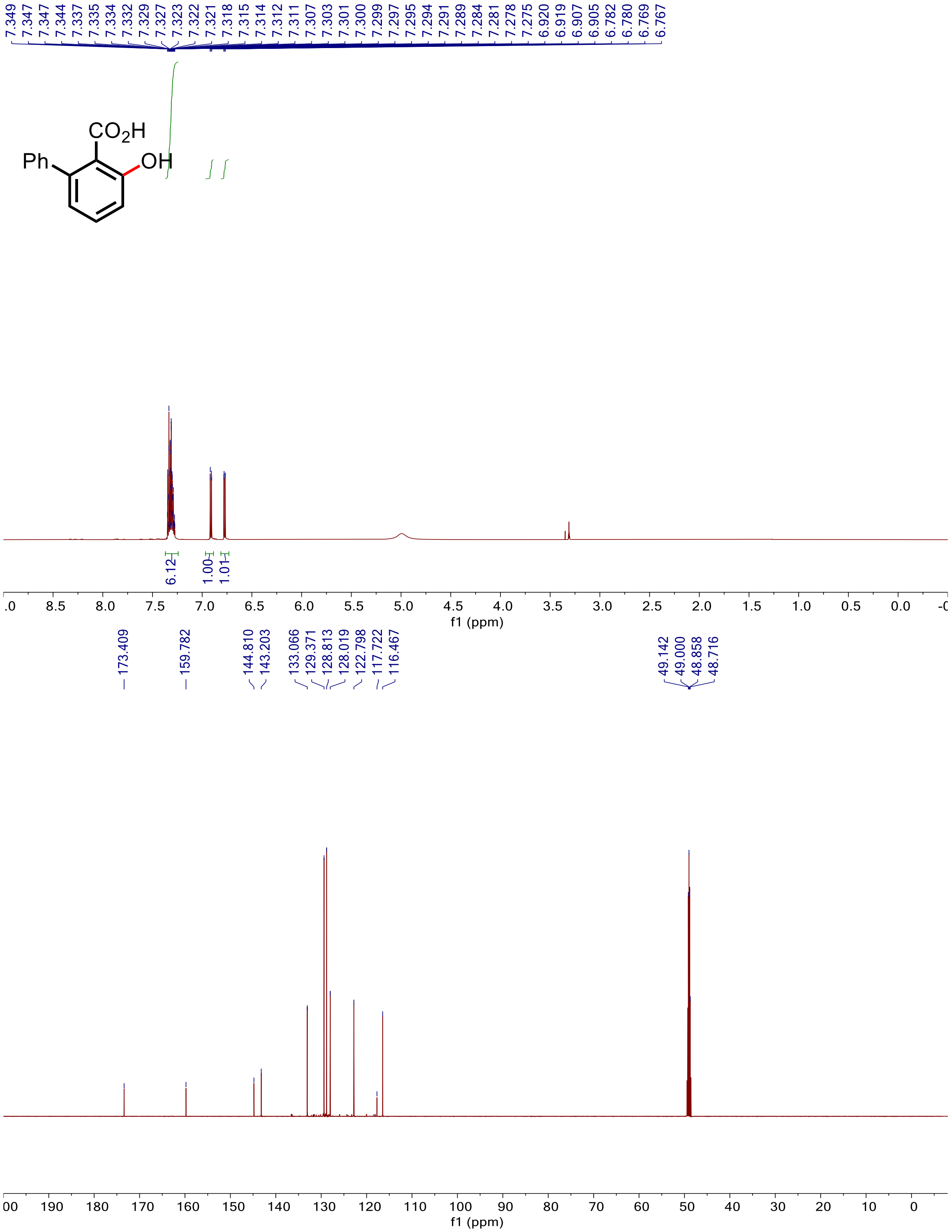
NMR Spectra of **4c**



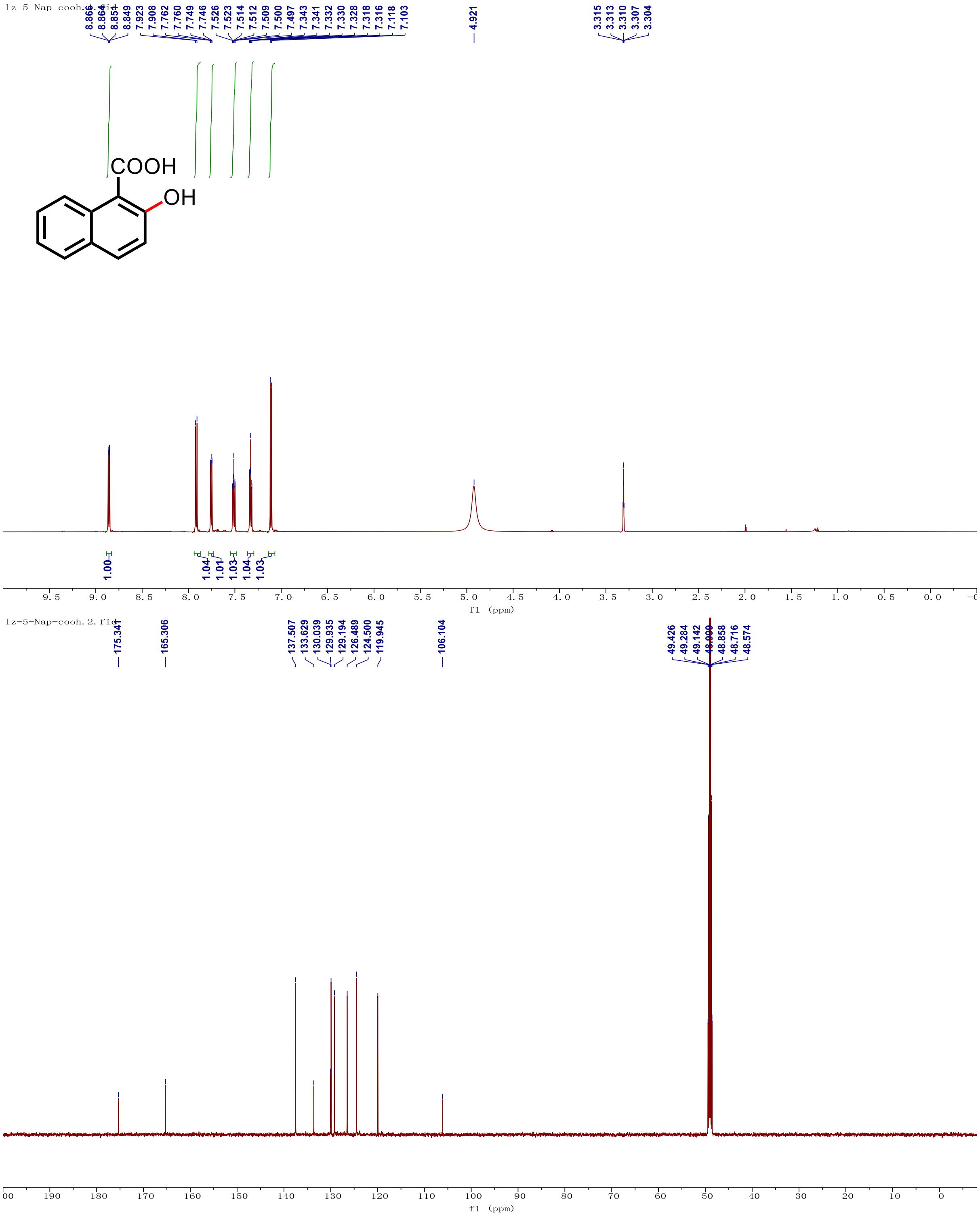
NMR Spectra of **4d**



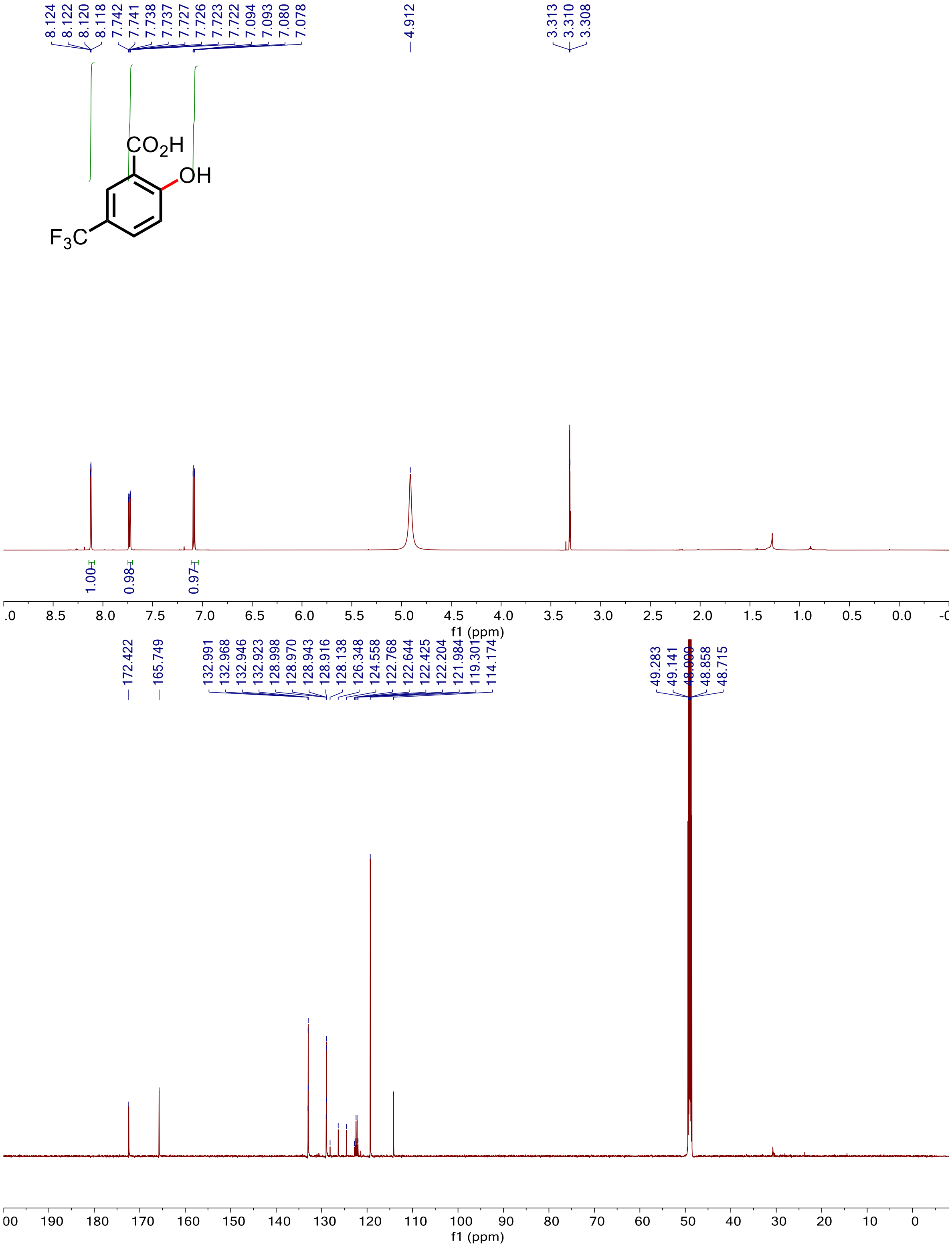
NMR Spectra of **4e**



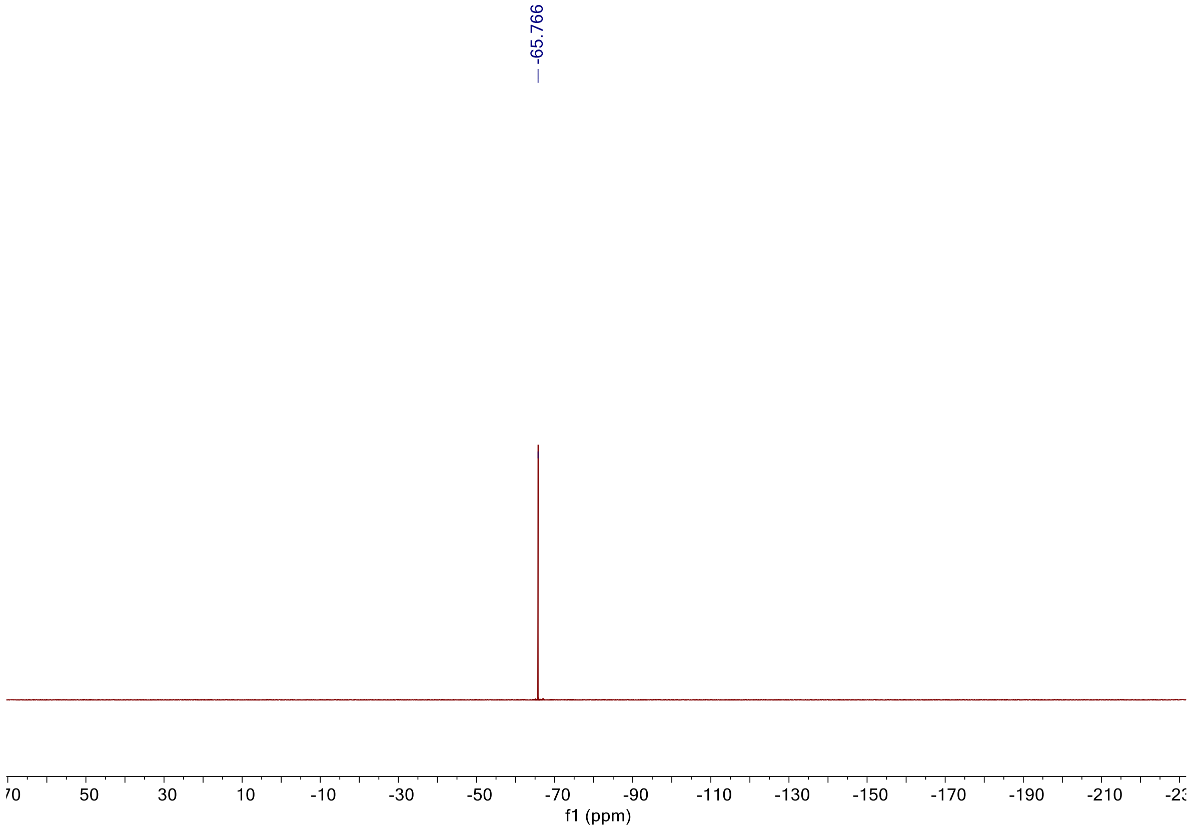
NMR Spectra of **4f**



NMR Spectra of **4g**



NMR Spectra of **4h**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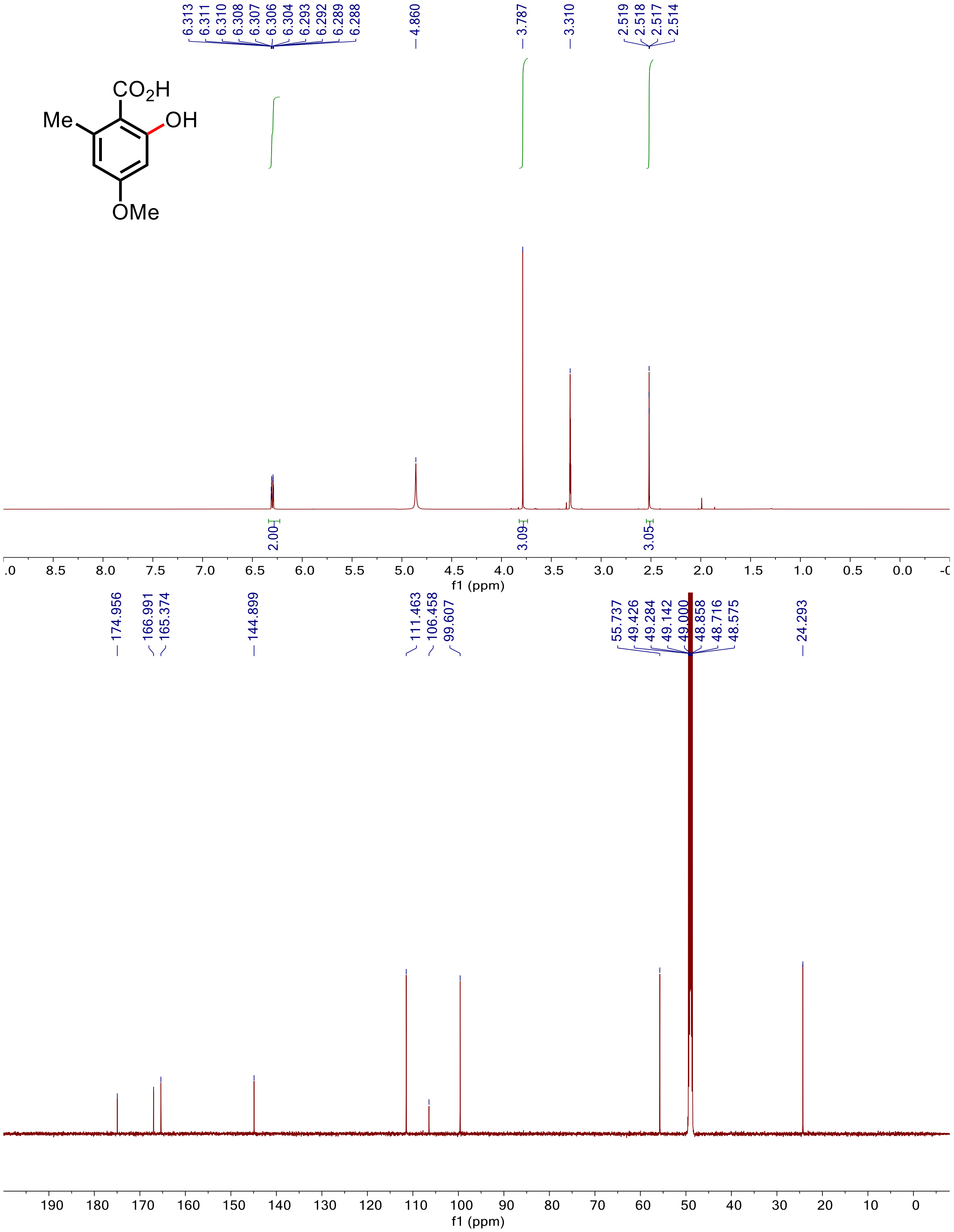
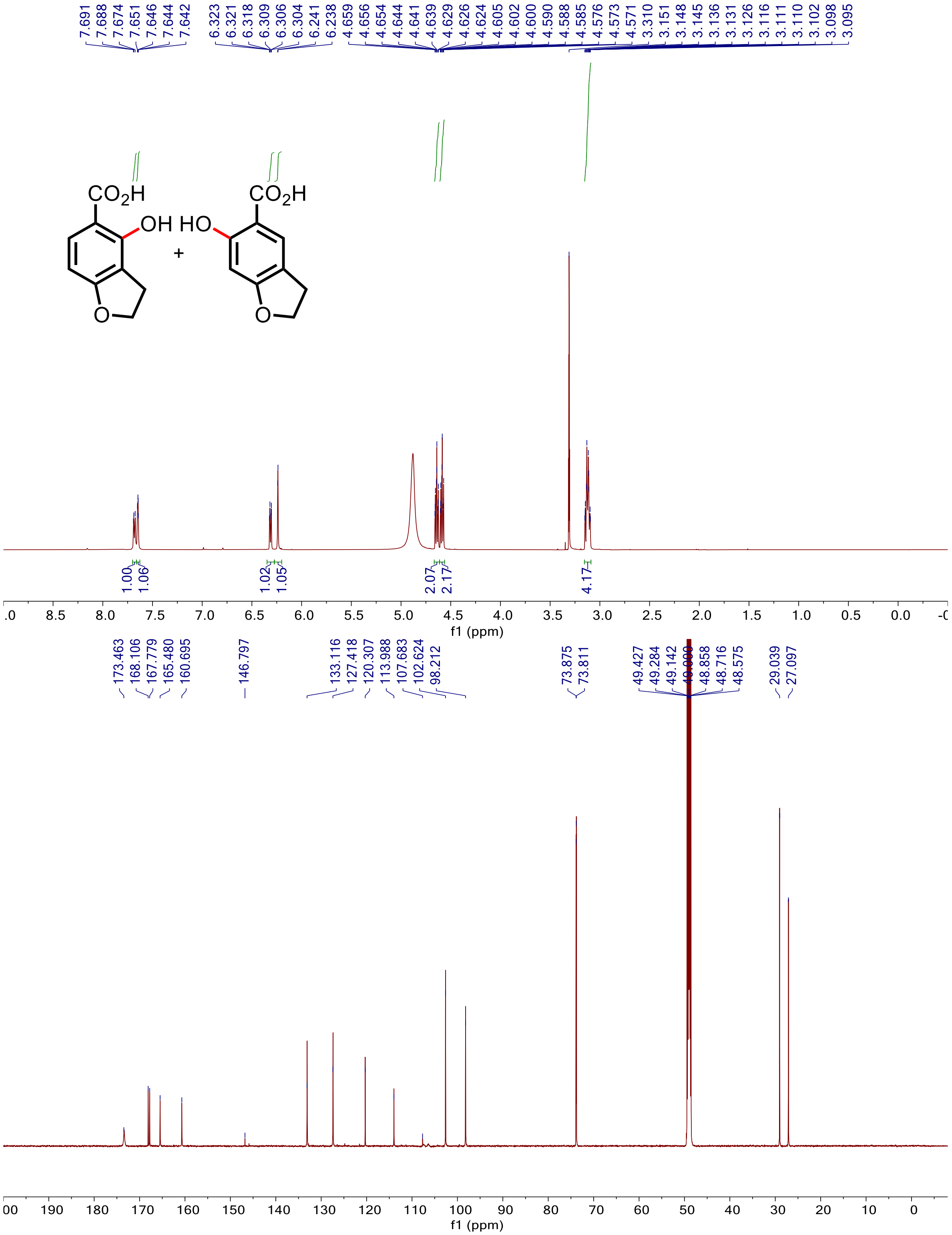
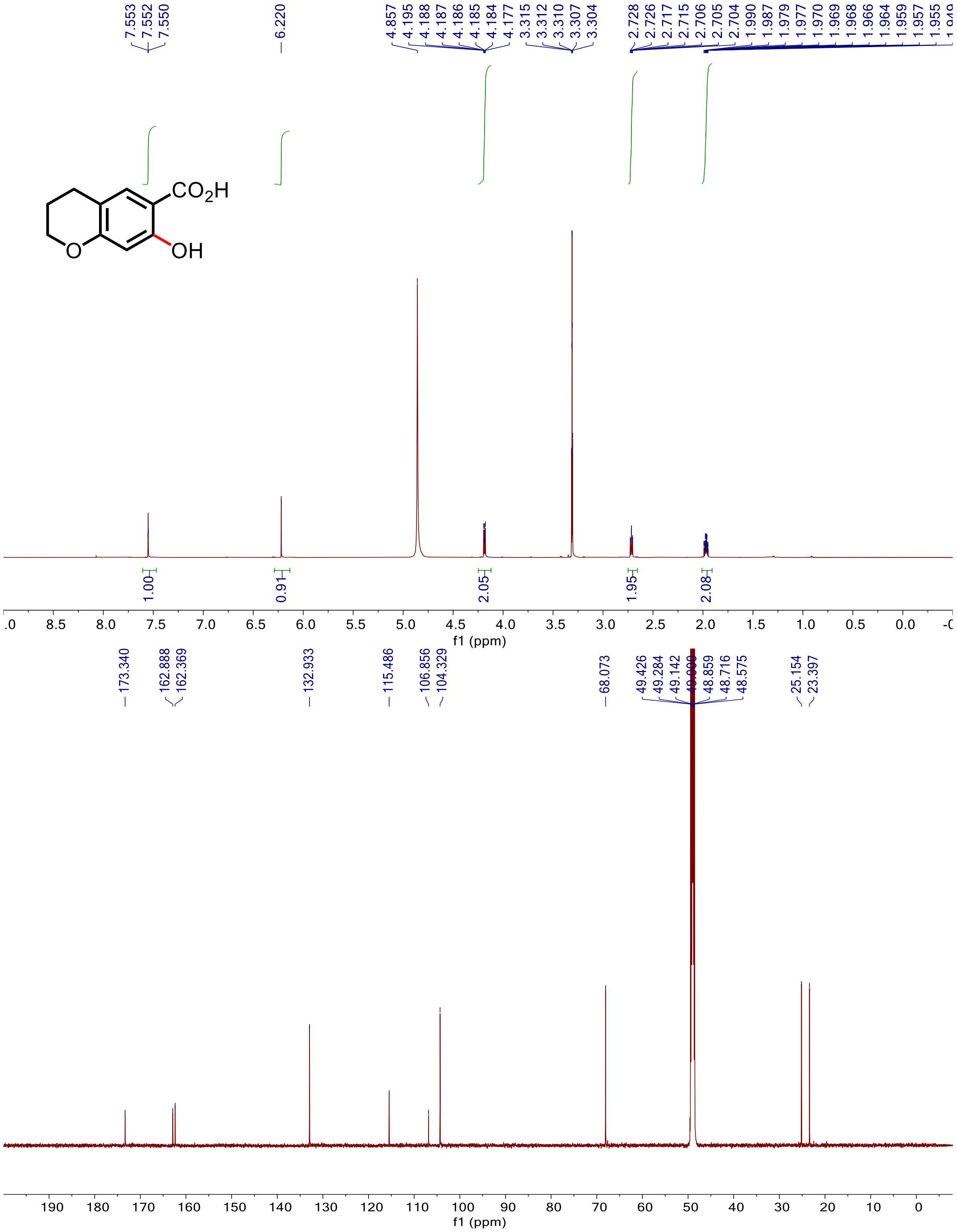
f1 (ppm)



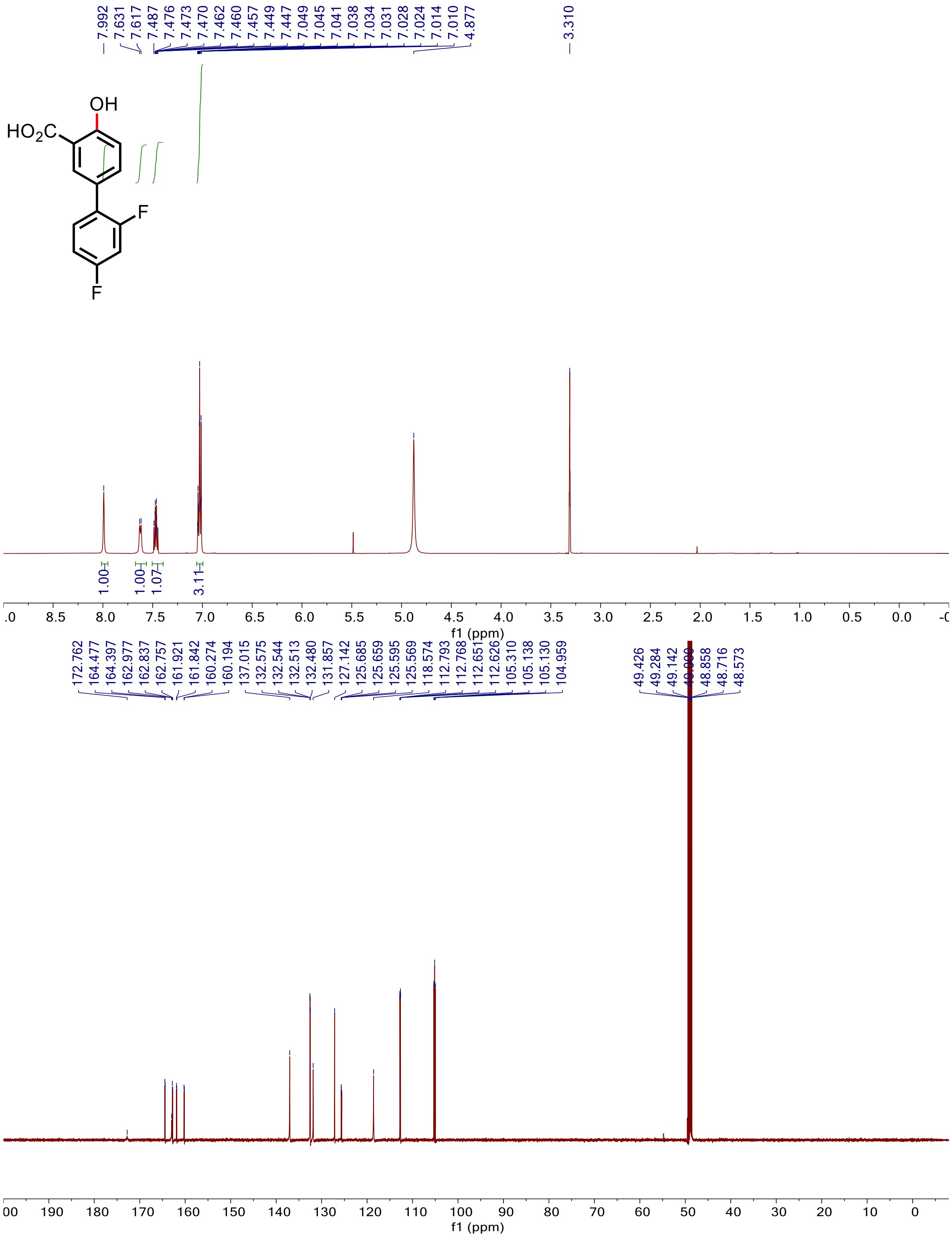
NMR Spectra of **4i**



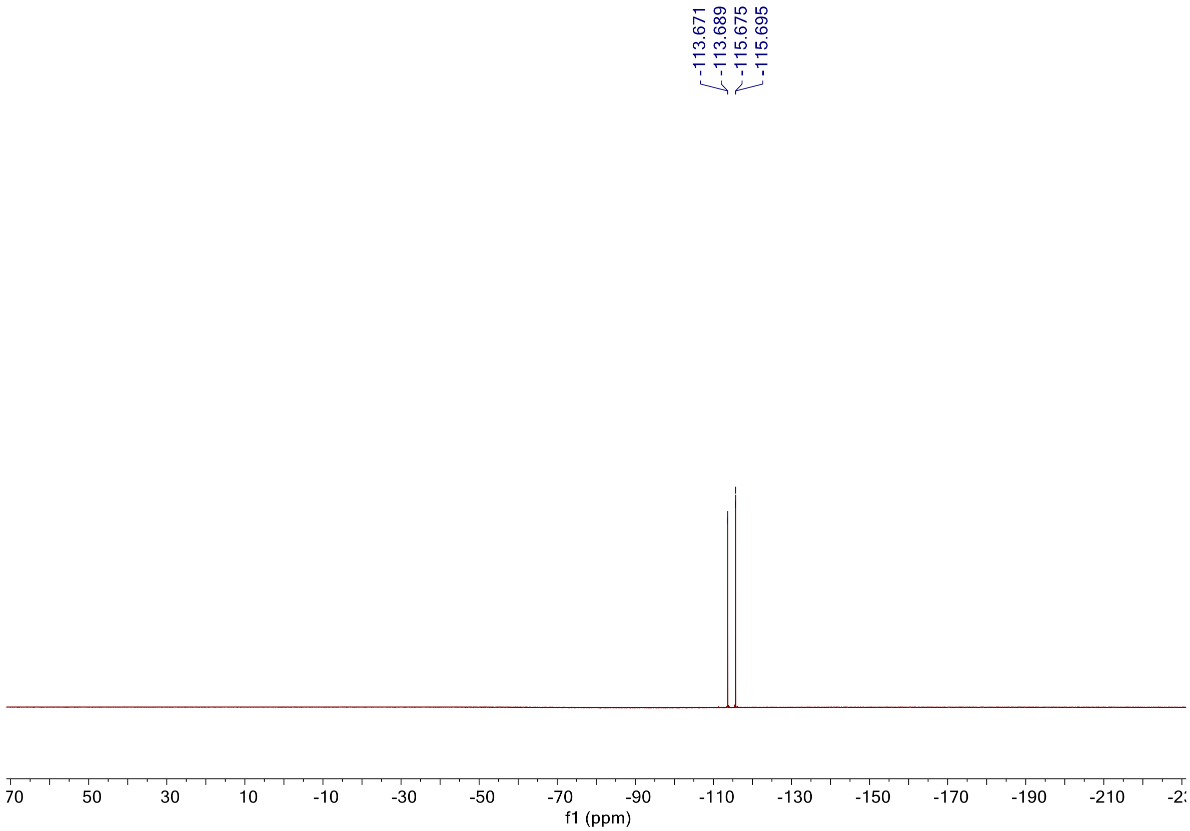
NMR Spectra of **4j and 4j'**



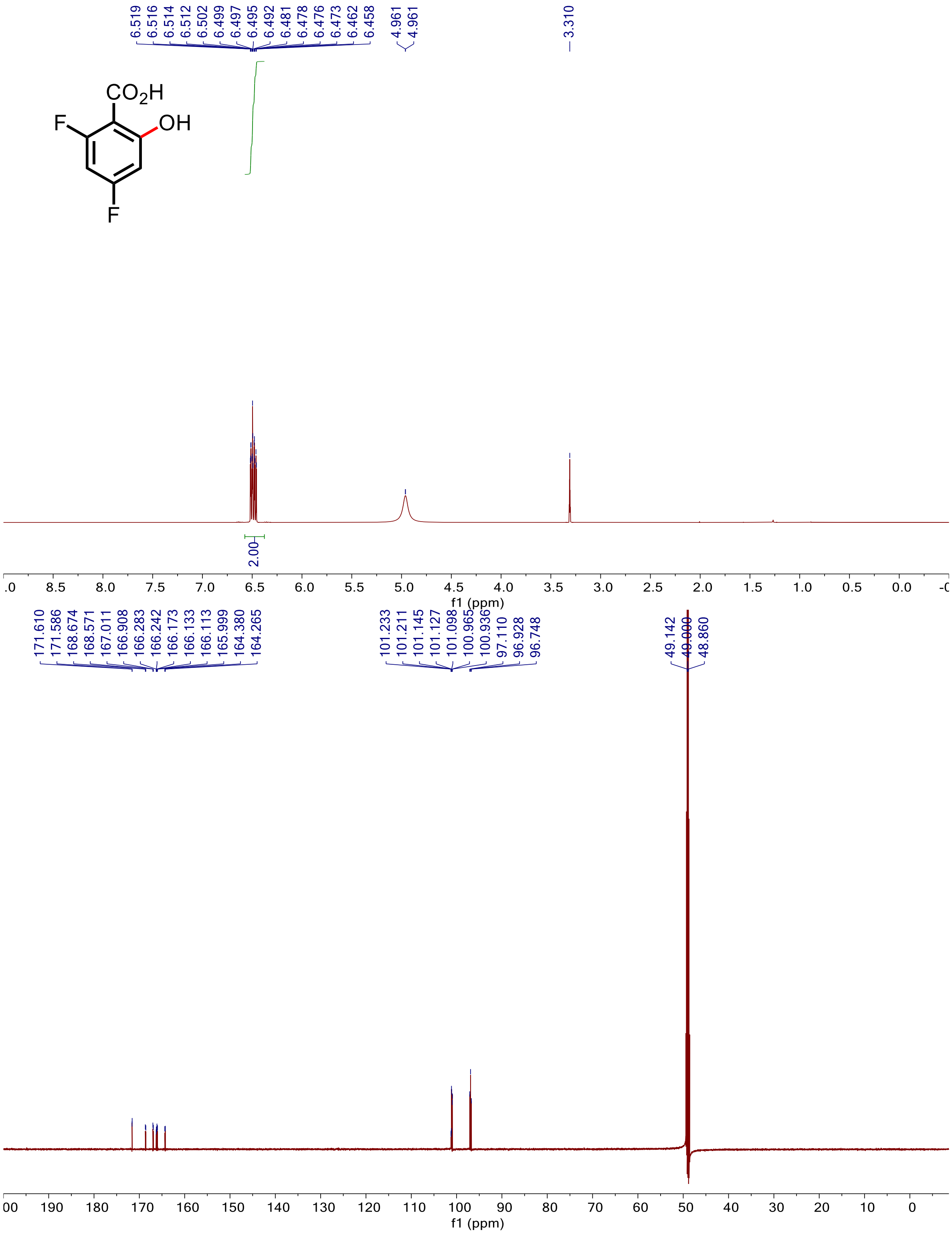
NMR Spectra of **4k**



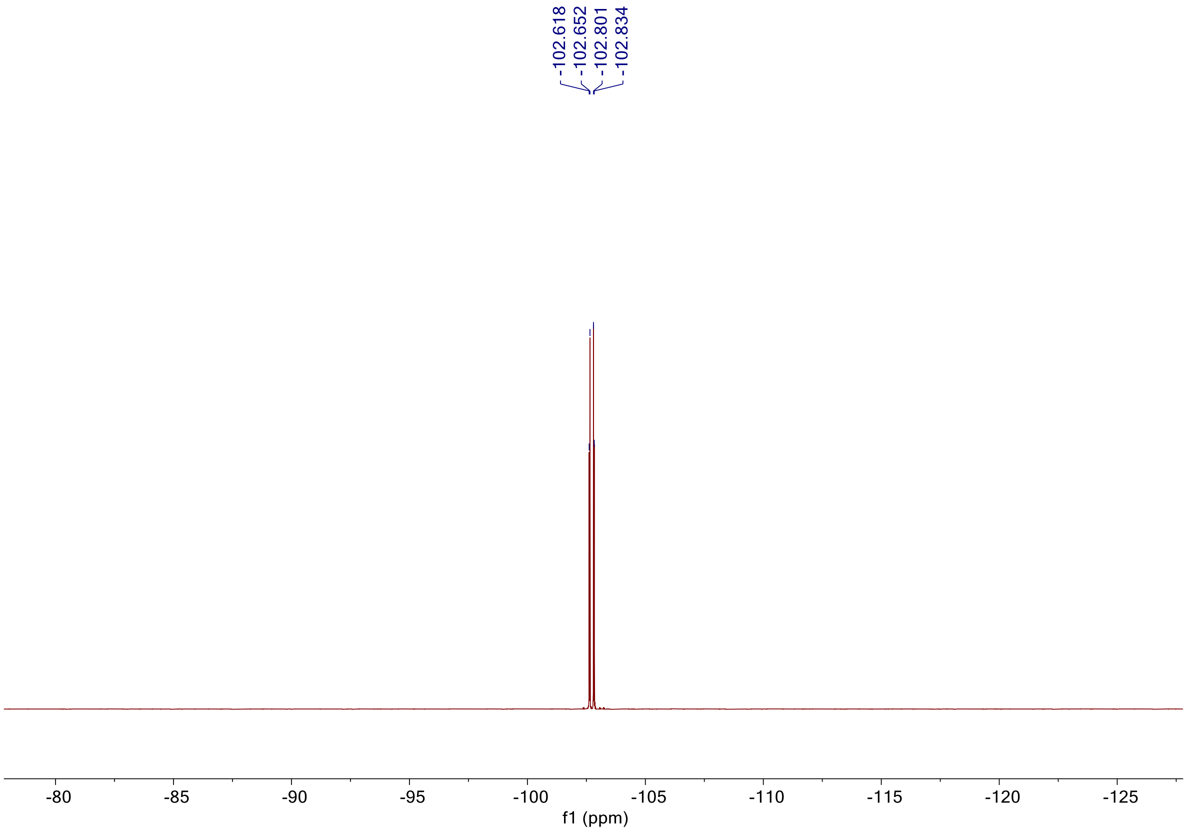
NMR Spectra of **4l**



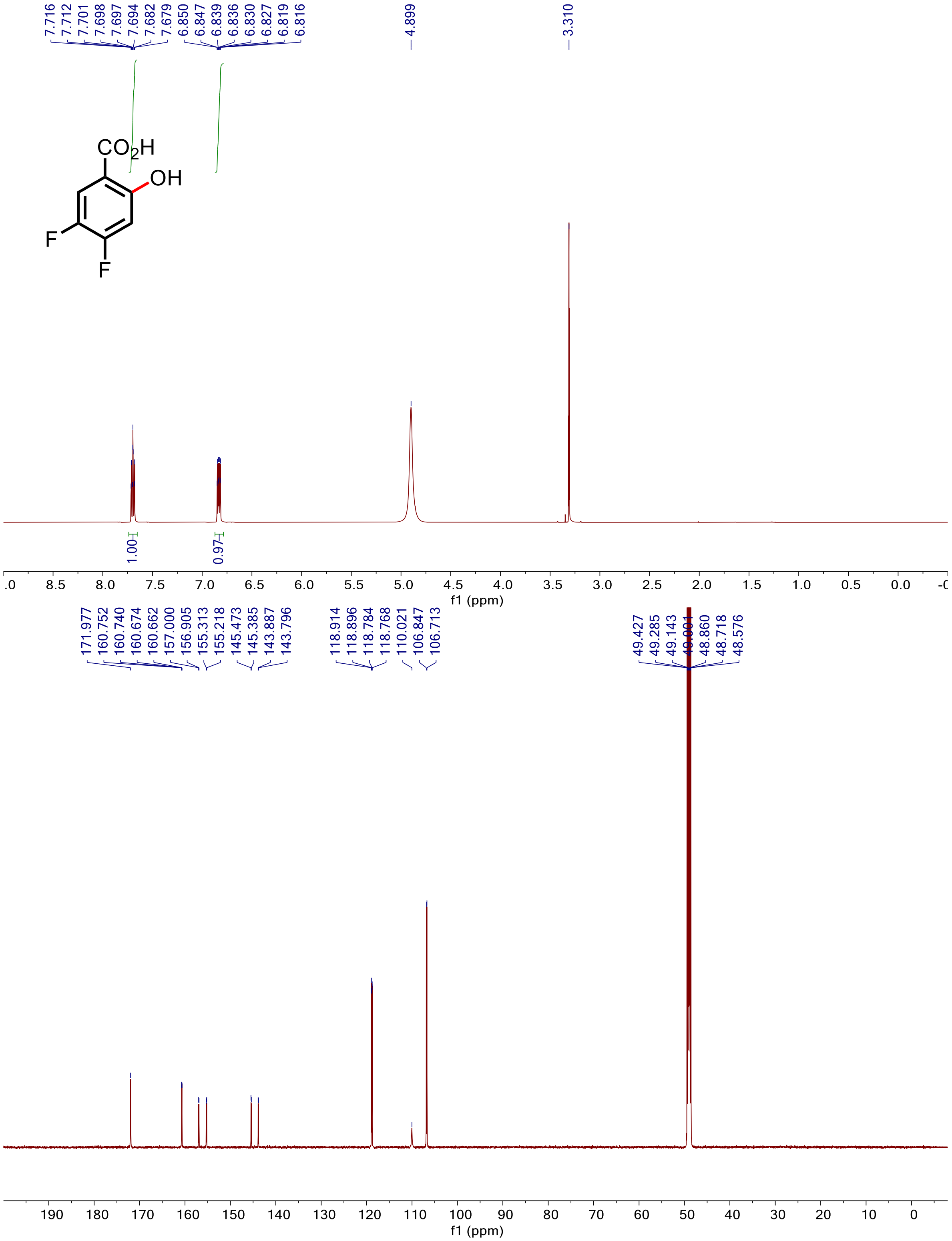
NMR Spectra of **4l**



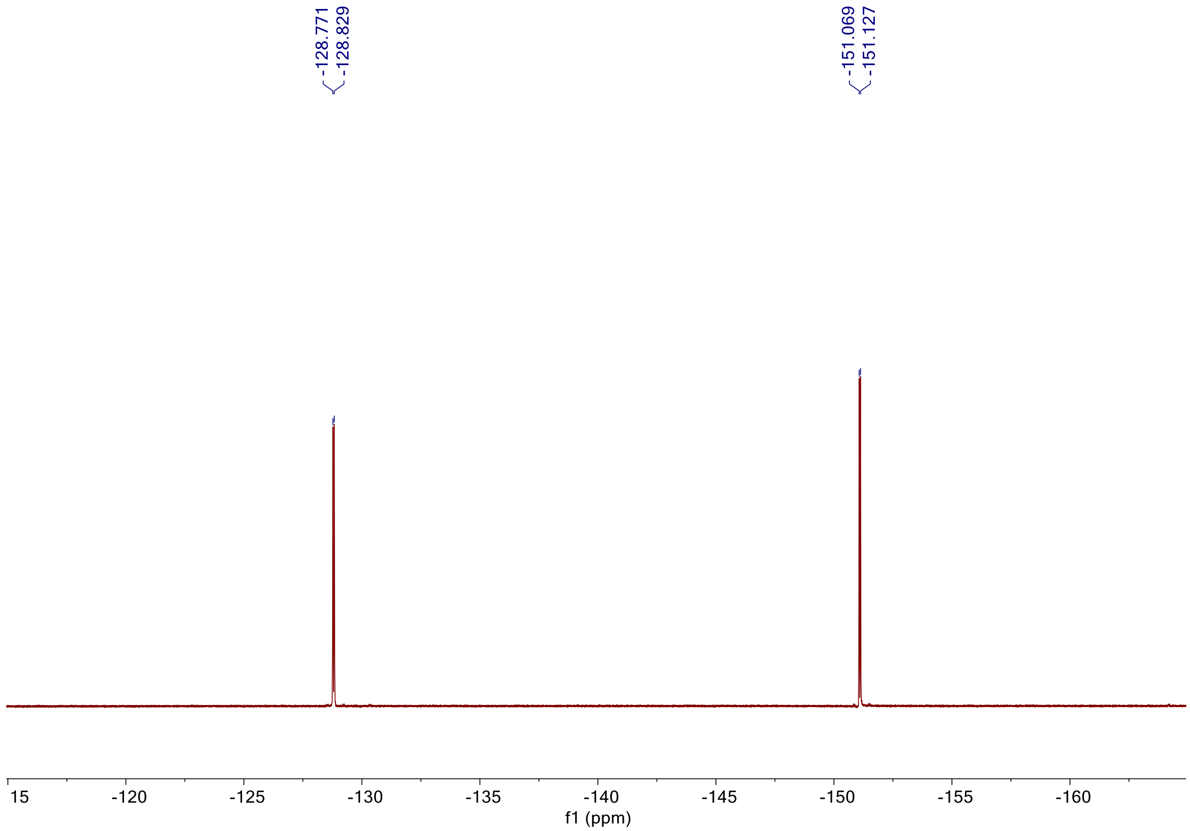
NMR Spectra of **4m**



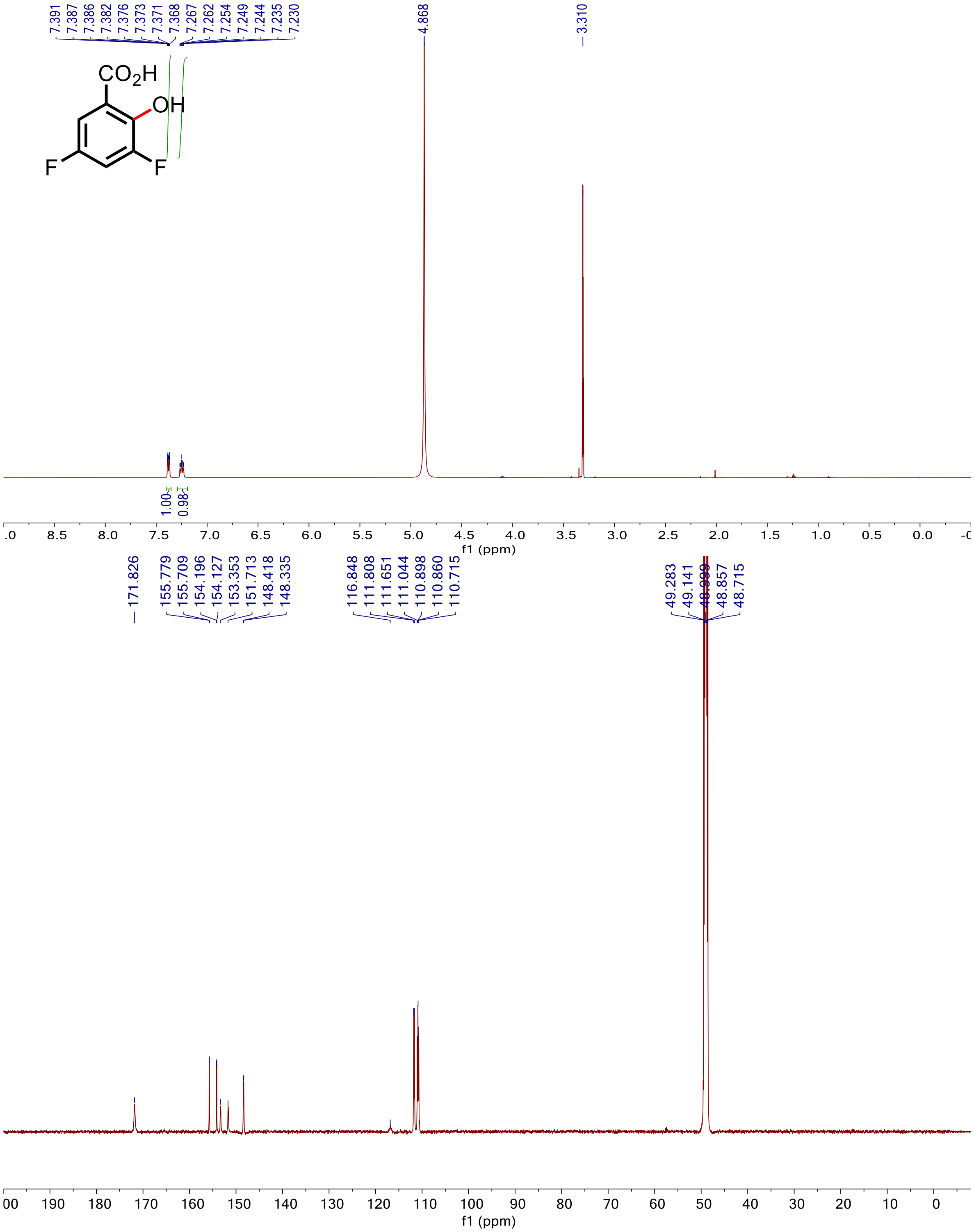
NMR Spectra of **4m**



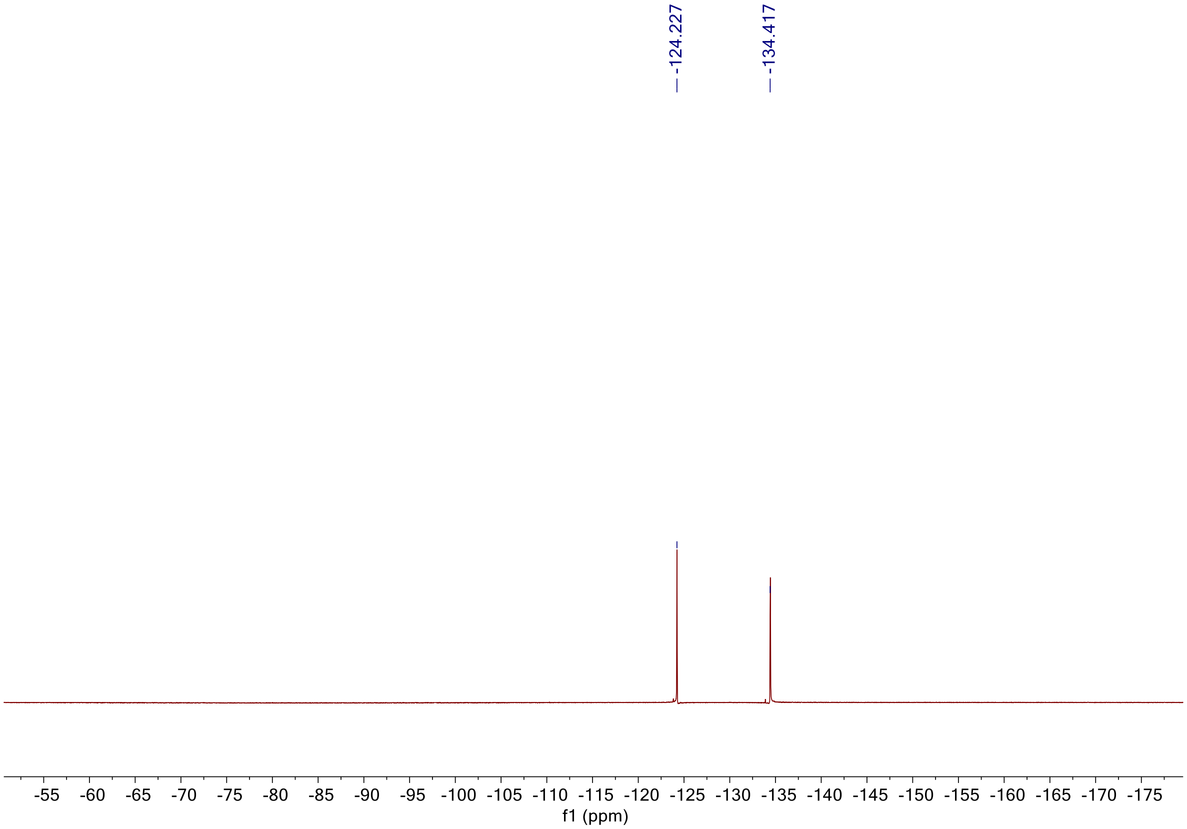
NMR Spectra of **4n**



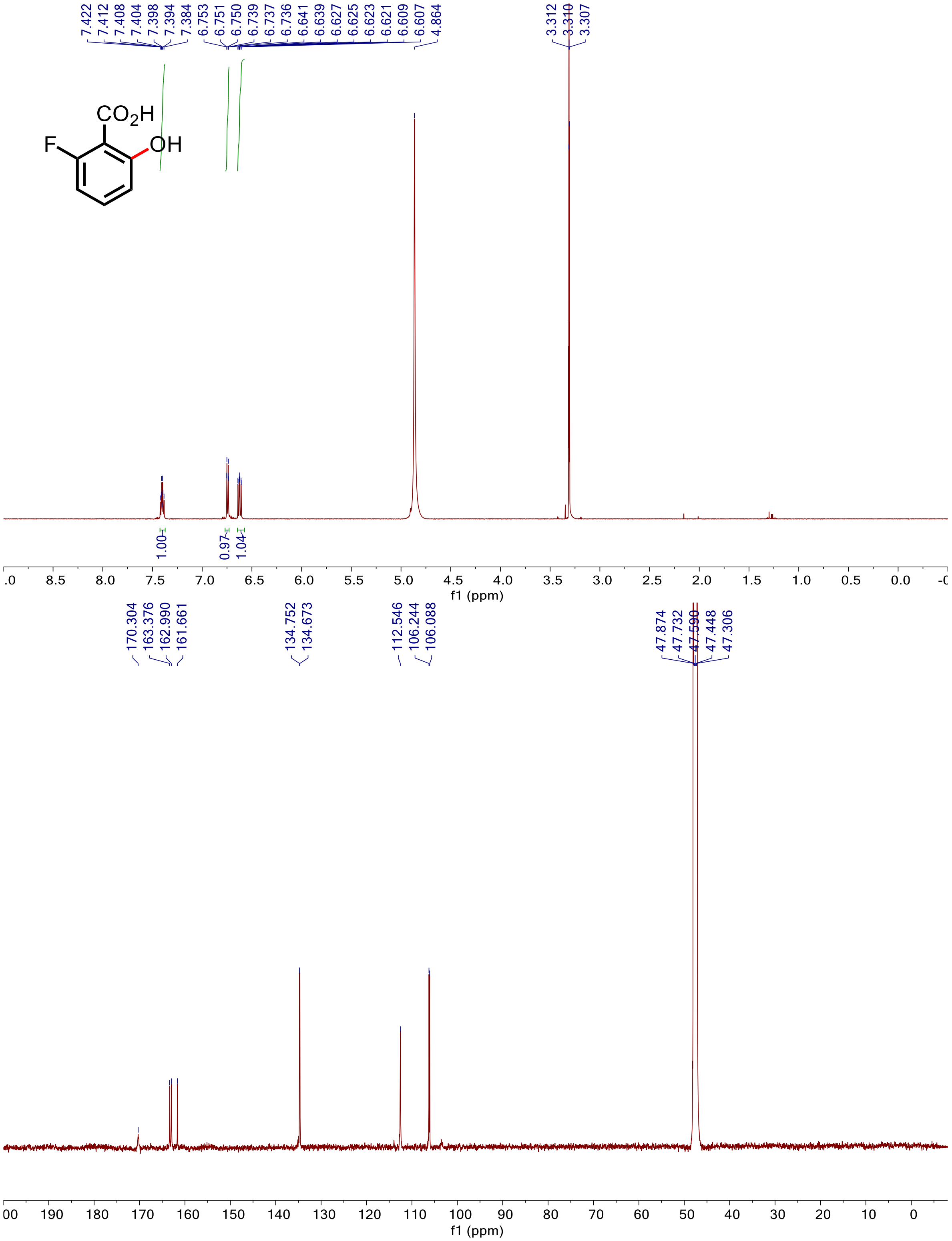
NMR Spectra of **4n**



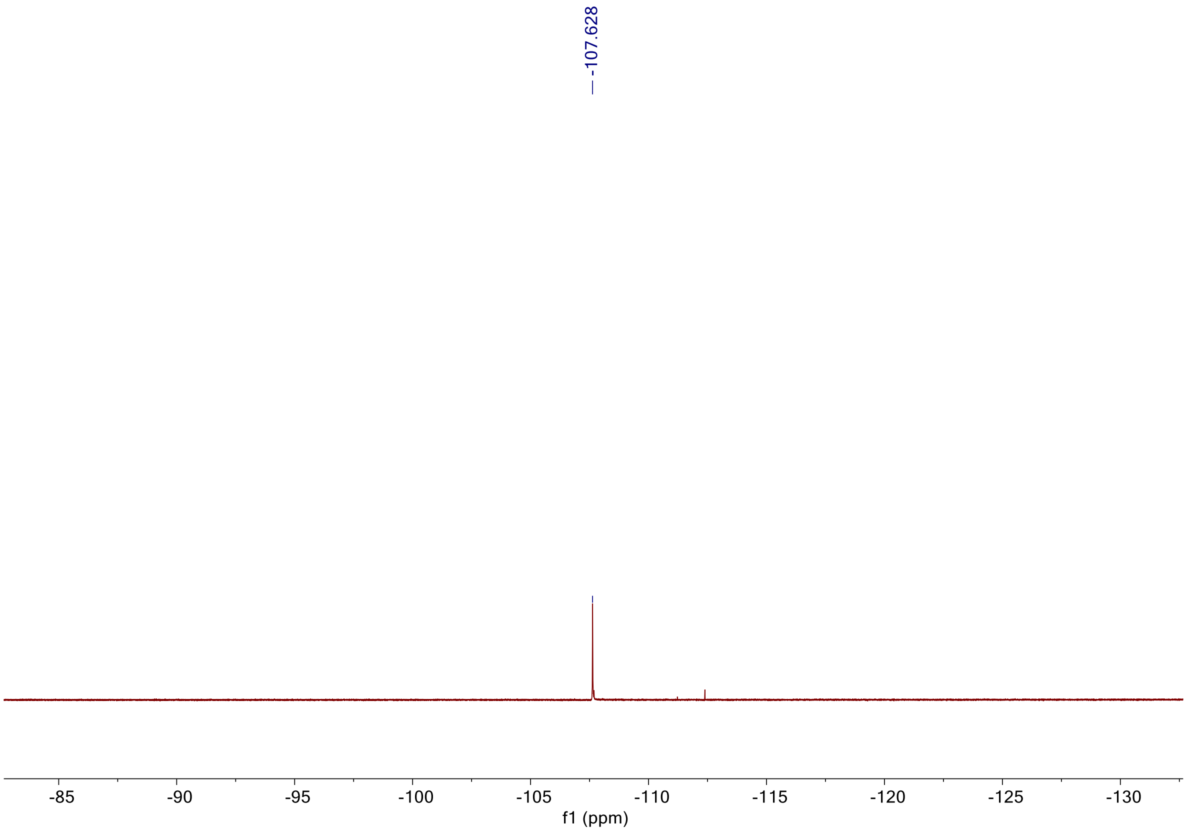
NMR Spectra of **4o**



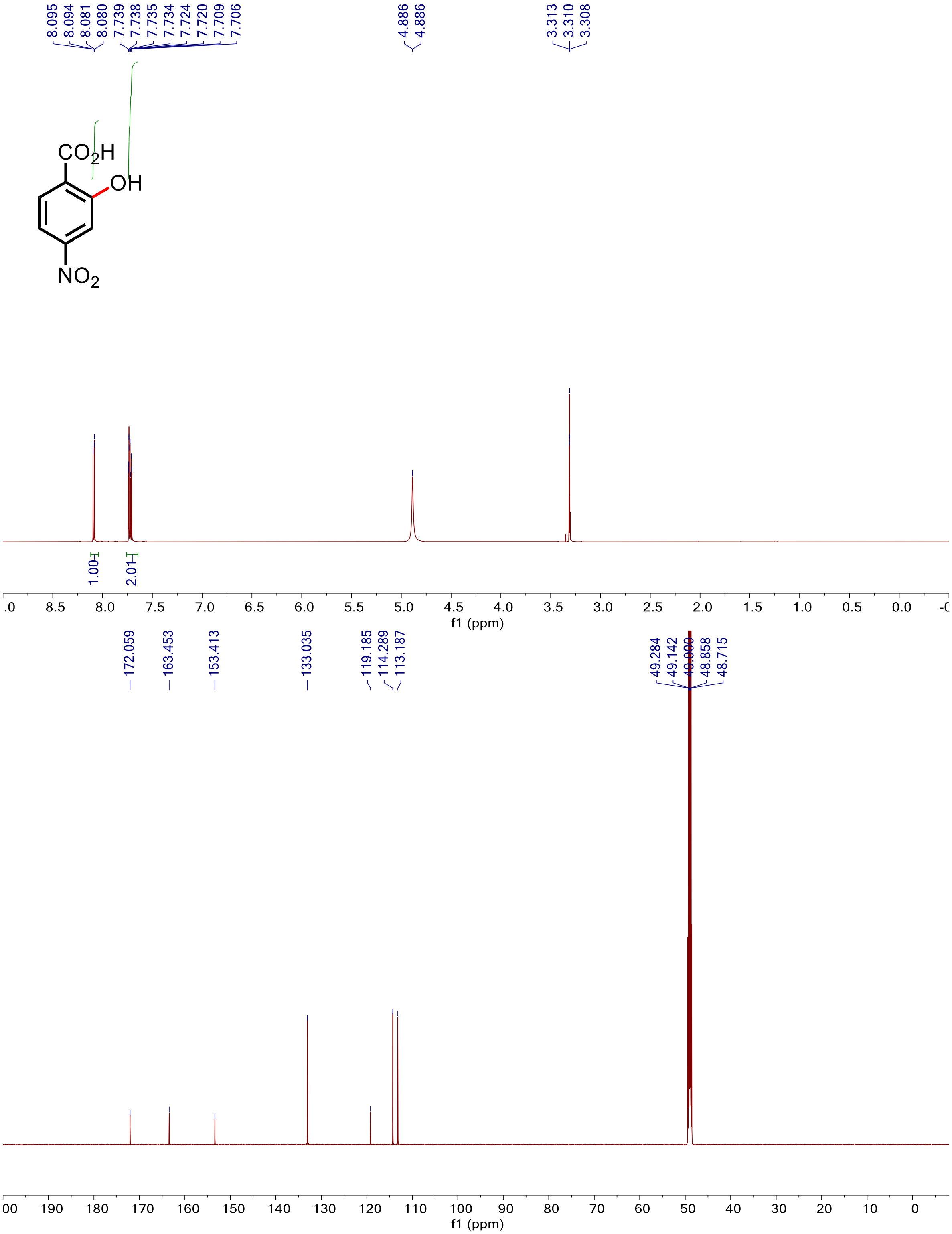
NMR Spectra of **4o**



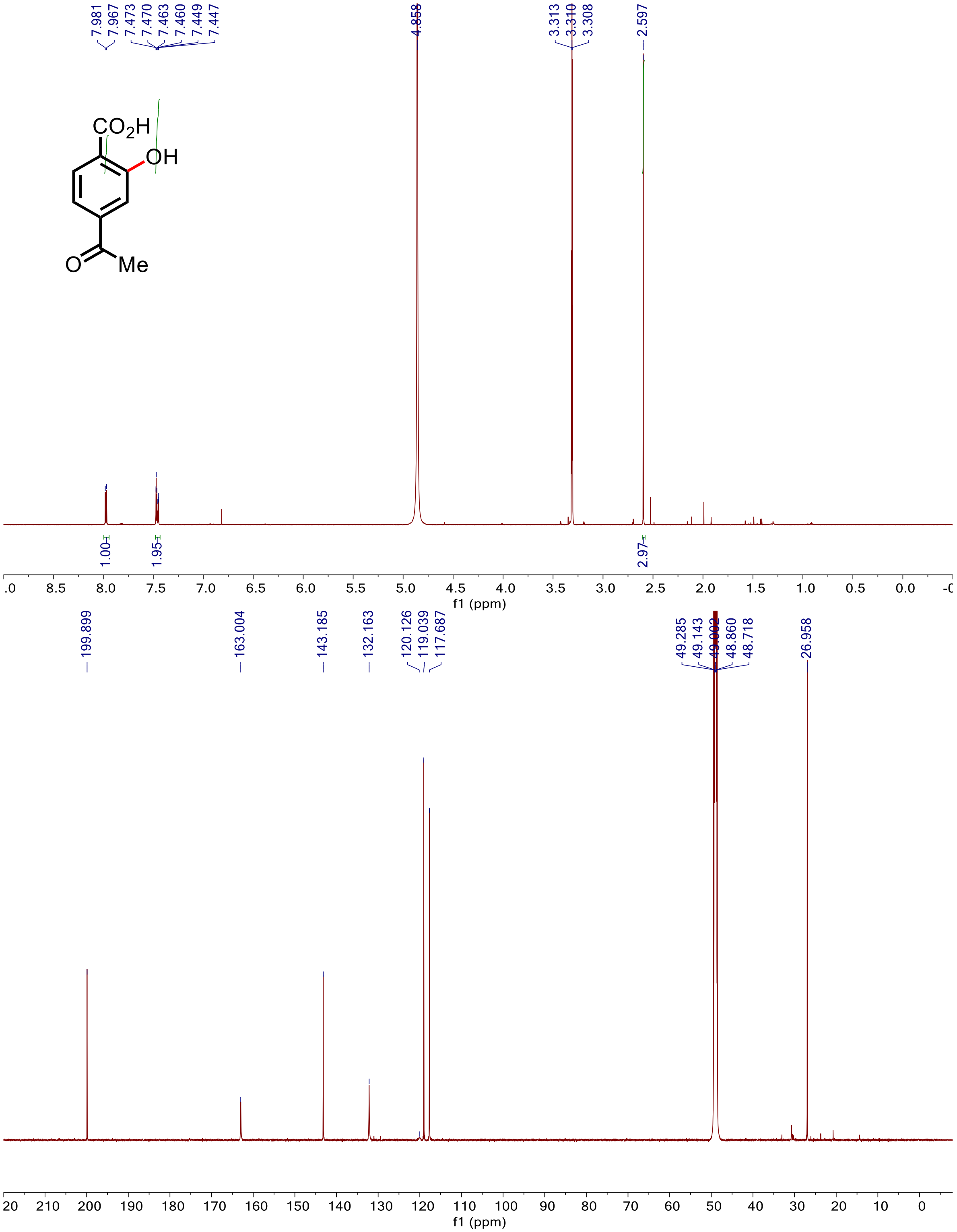
NMR Spectra of **4p**



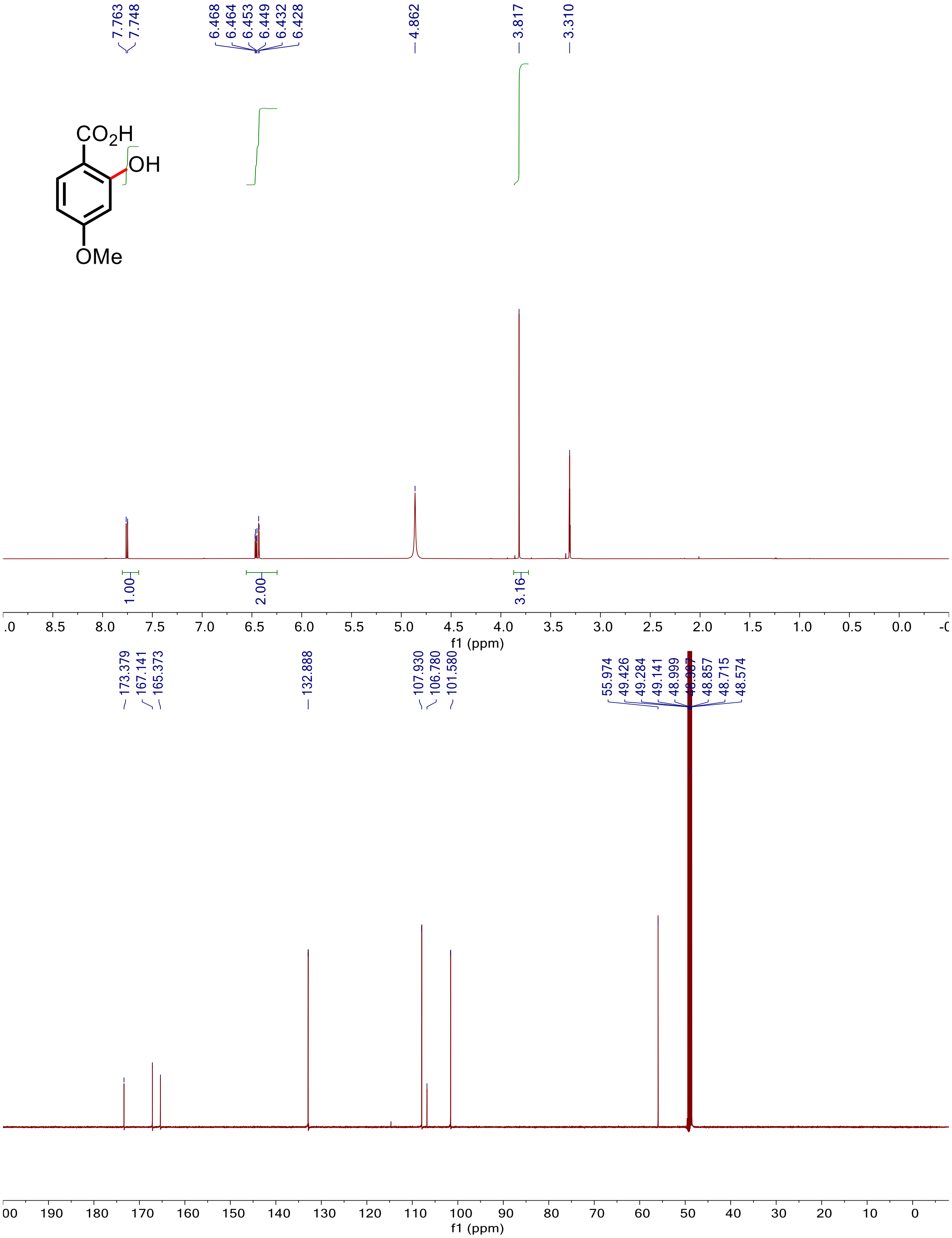
NMR Spectra of **4p**



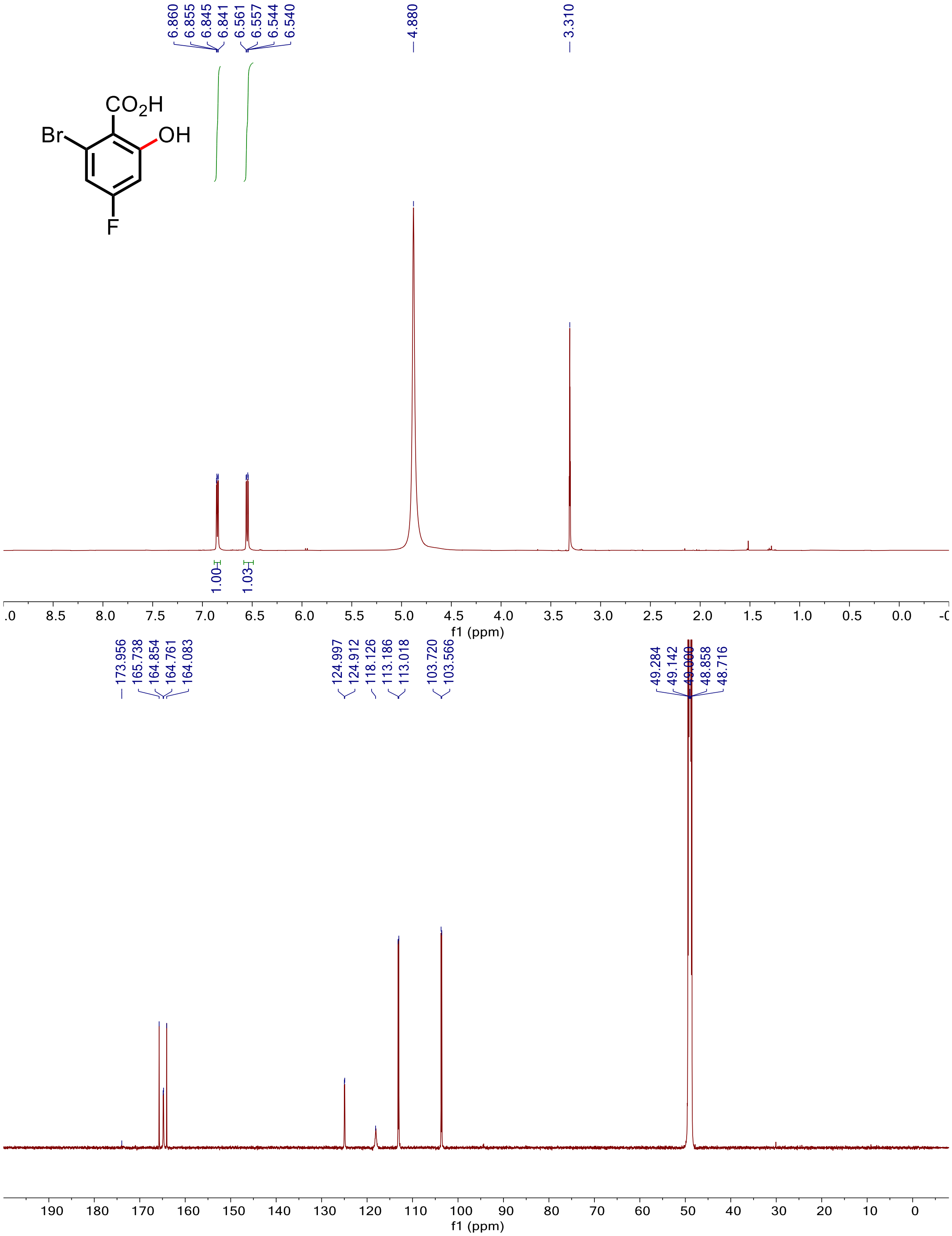
NMR Spectra of **4q**



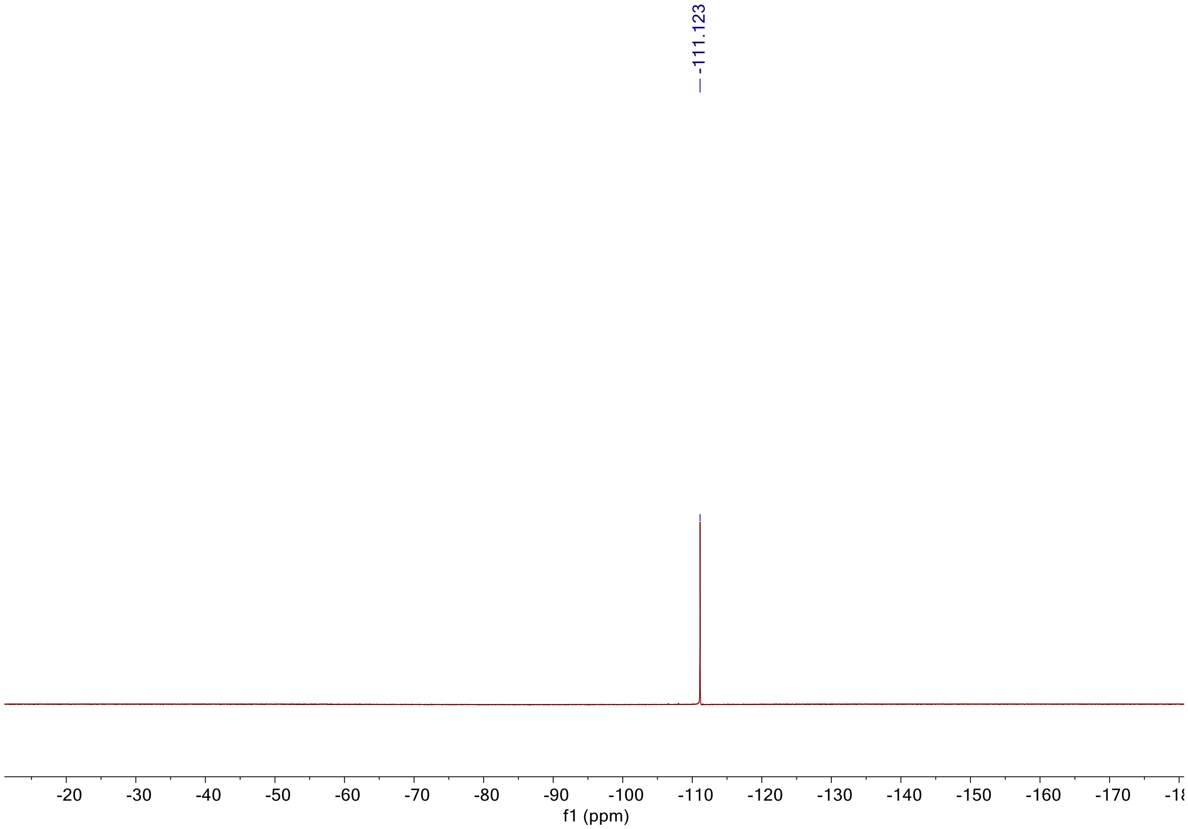
NMR Spectra of **4r**



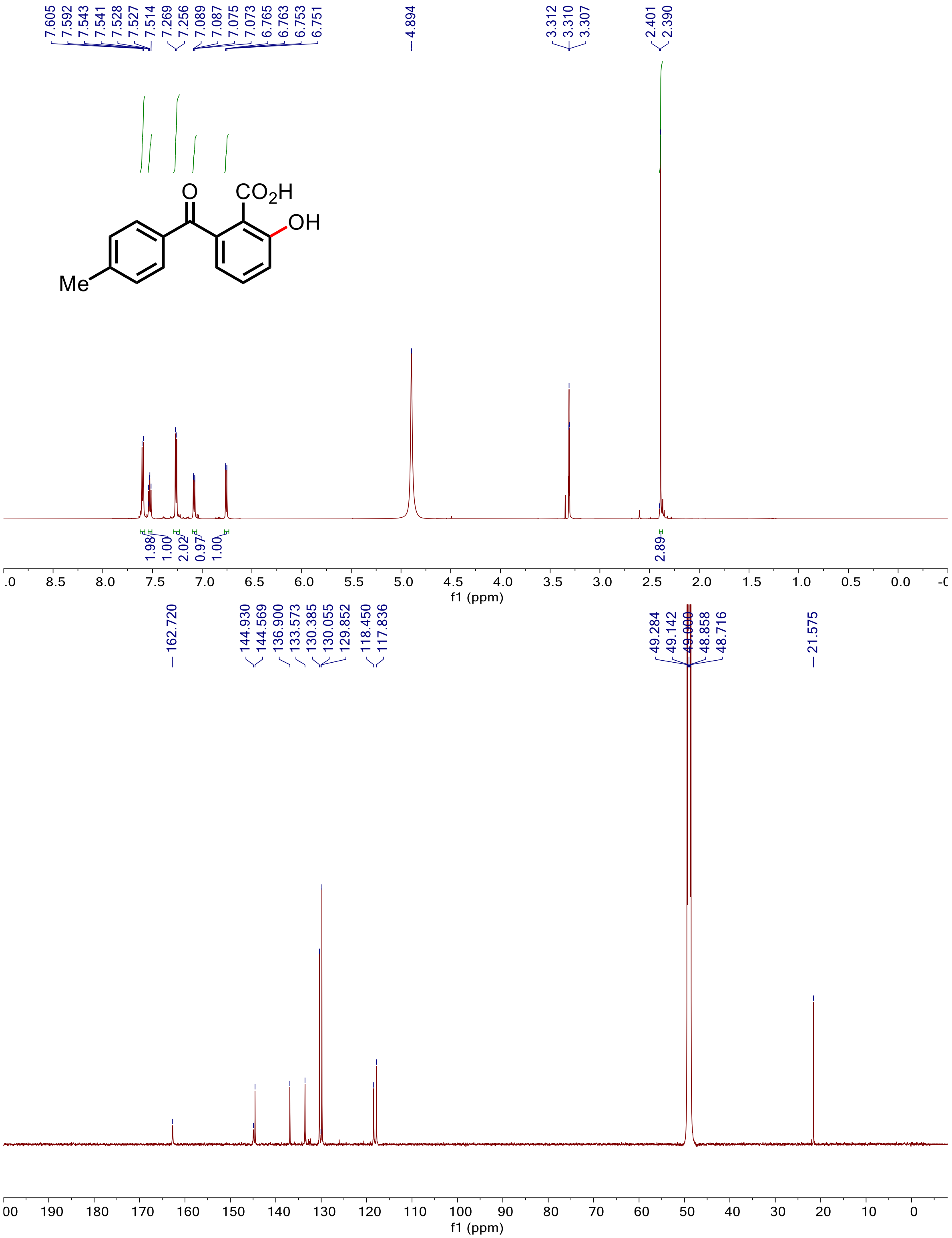
NMR Spectra of **4s**



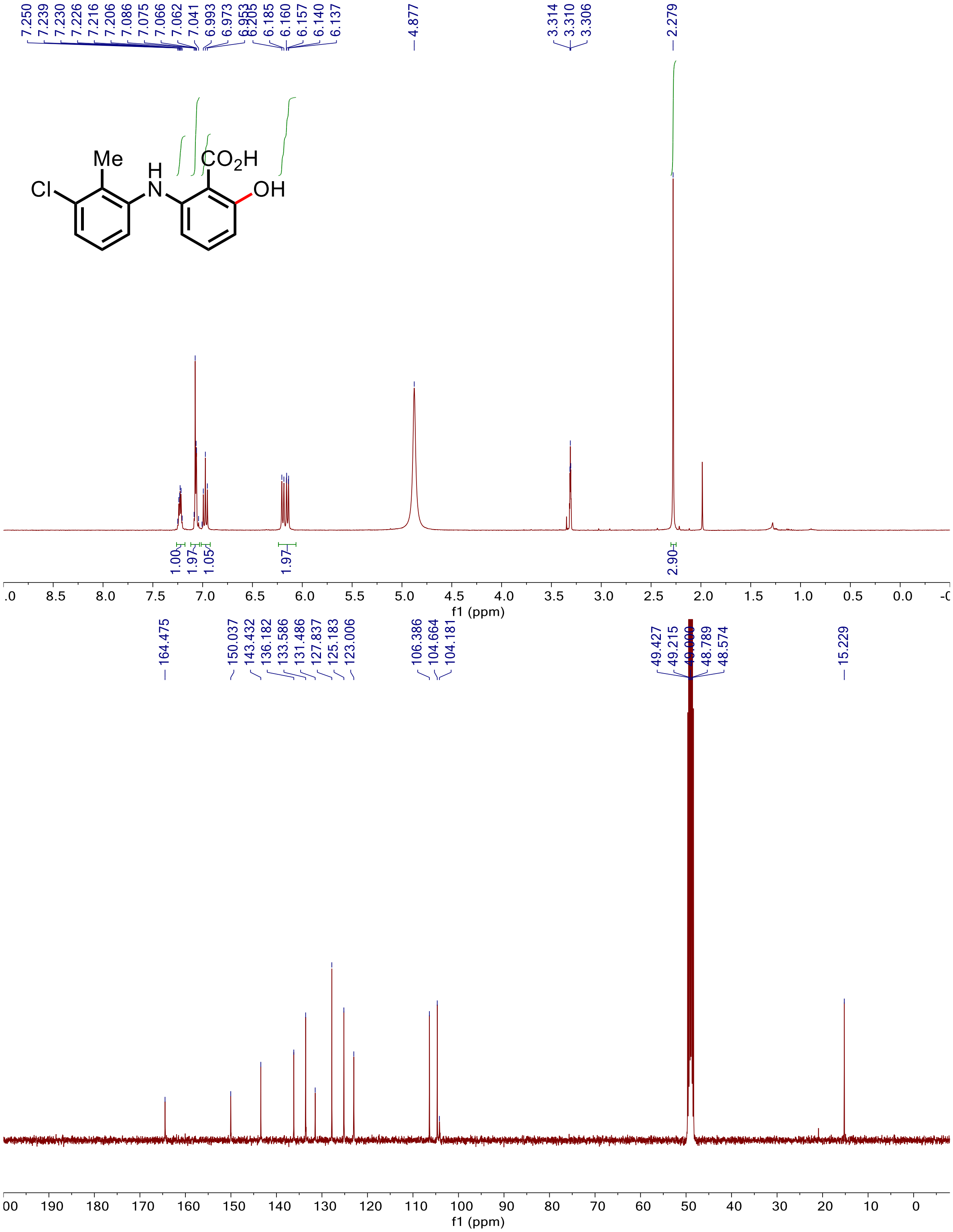
NMR Spectra of **4t**



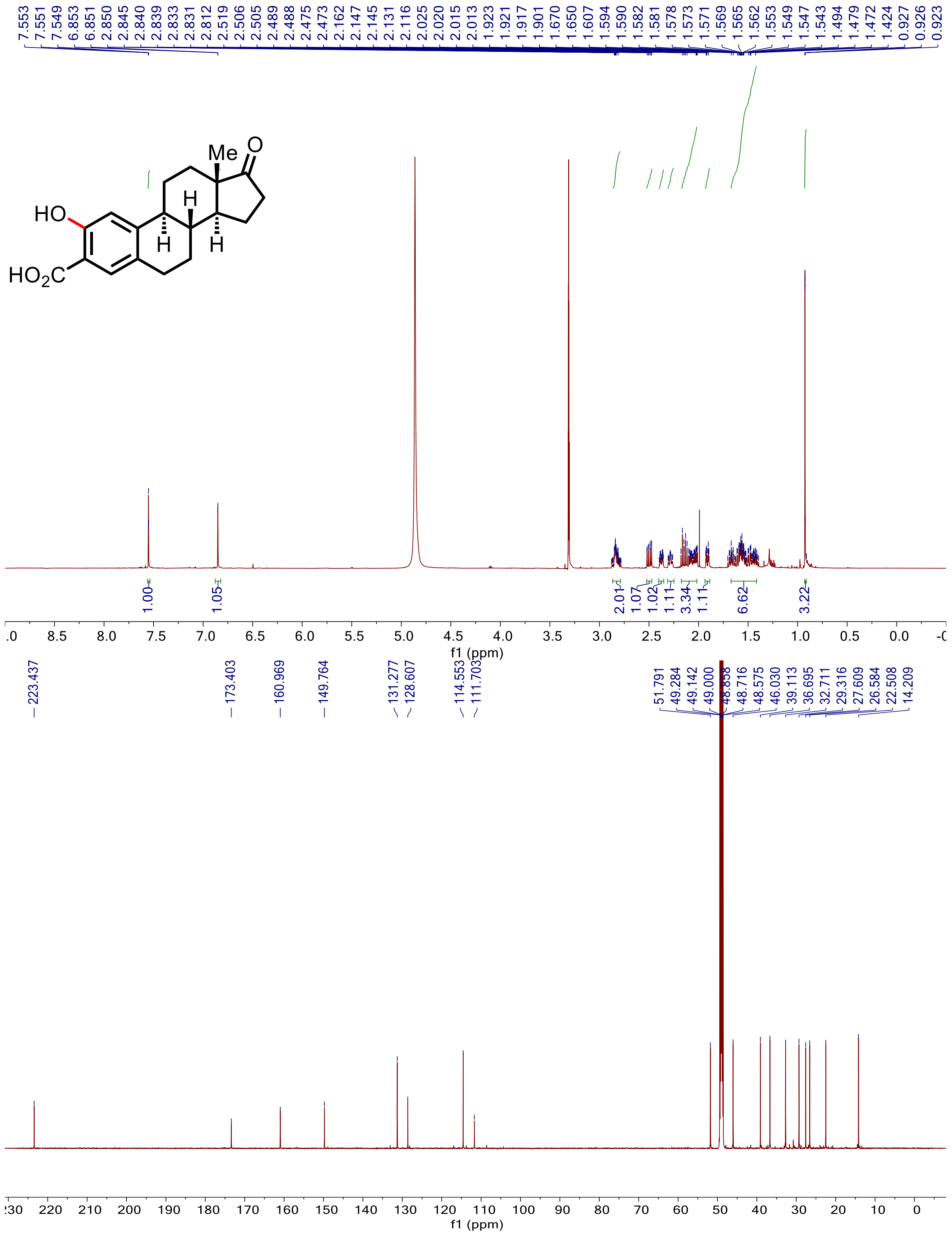
NMR Spectra of **4t**



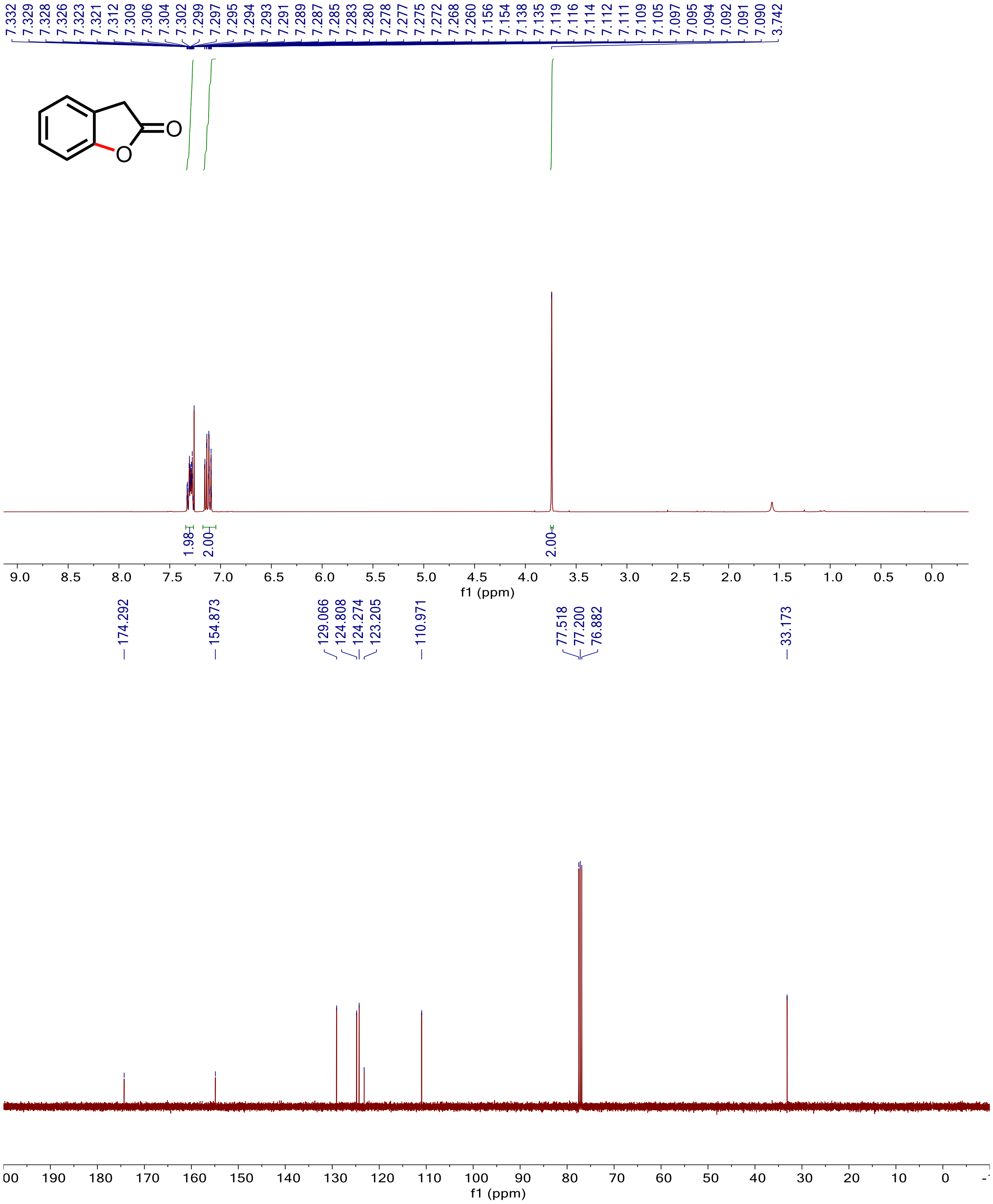
NMR Spectra of **4u**



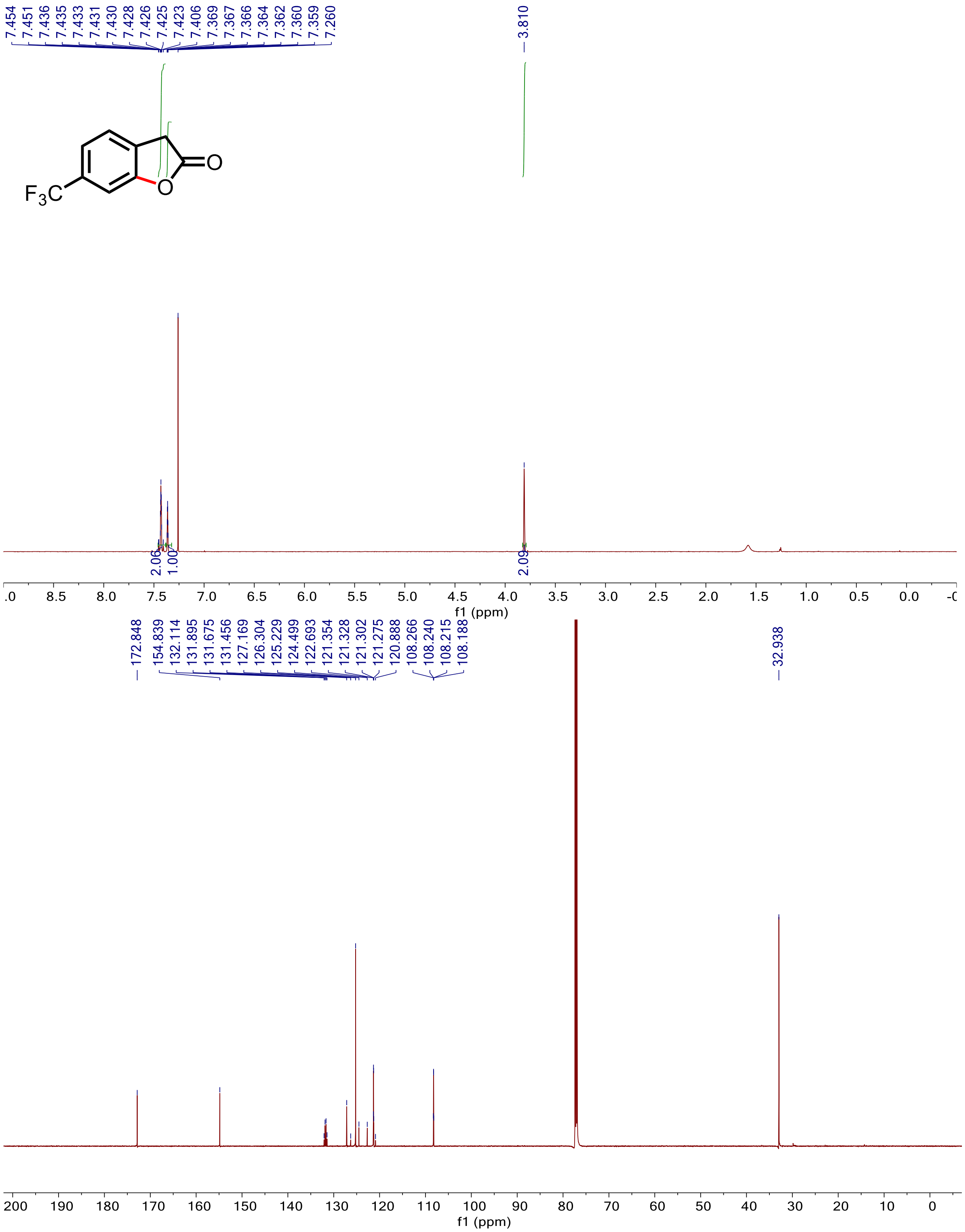
NMR Spectra of **4v**



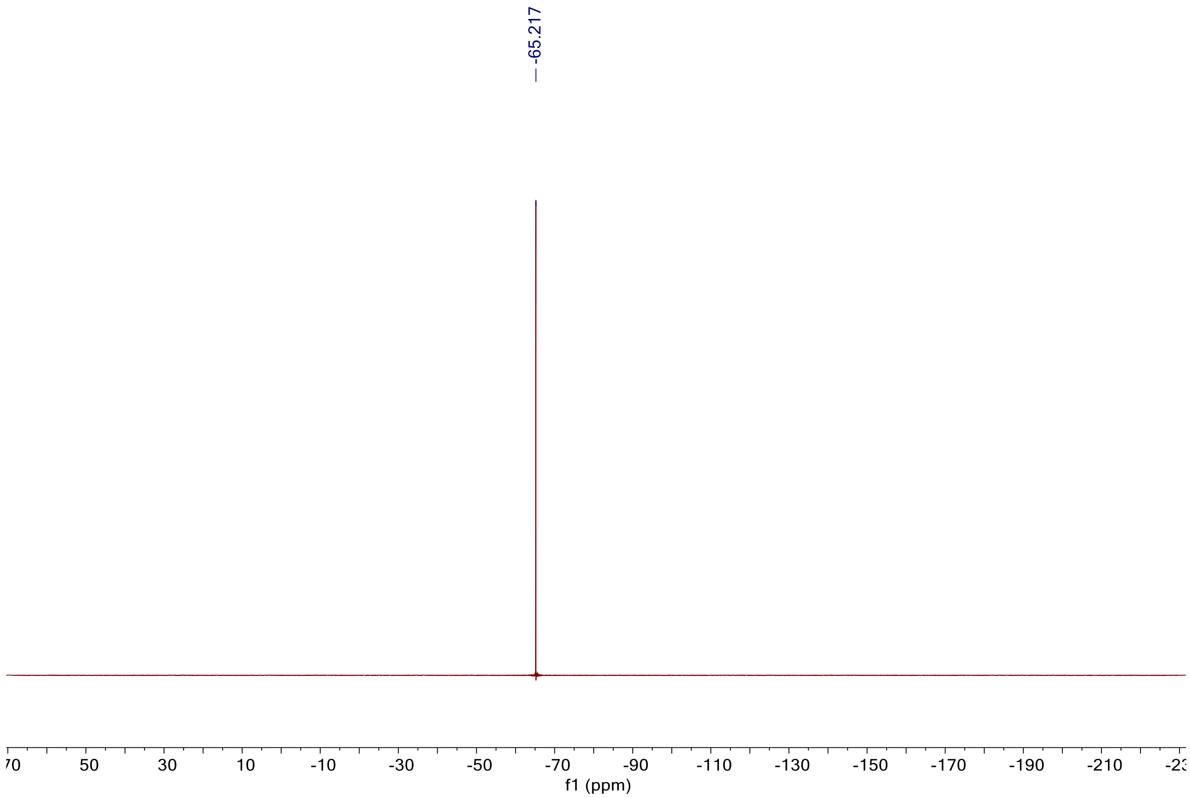
NMR Spectra of **4w**



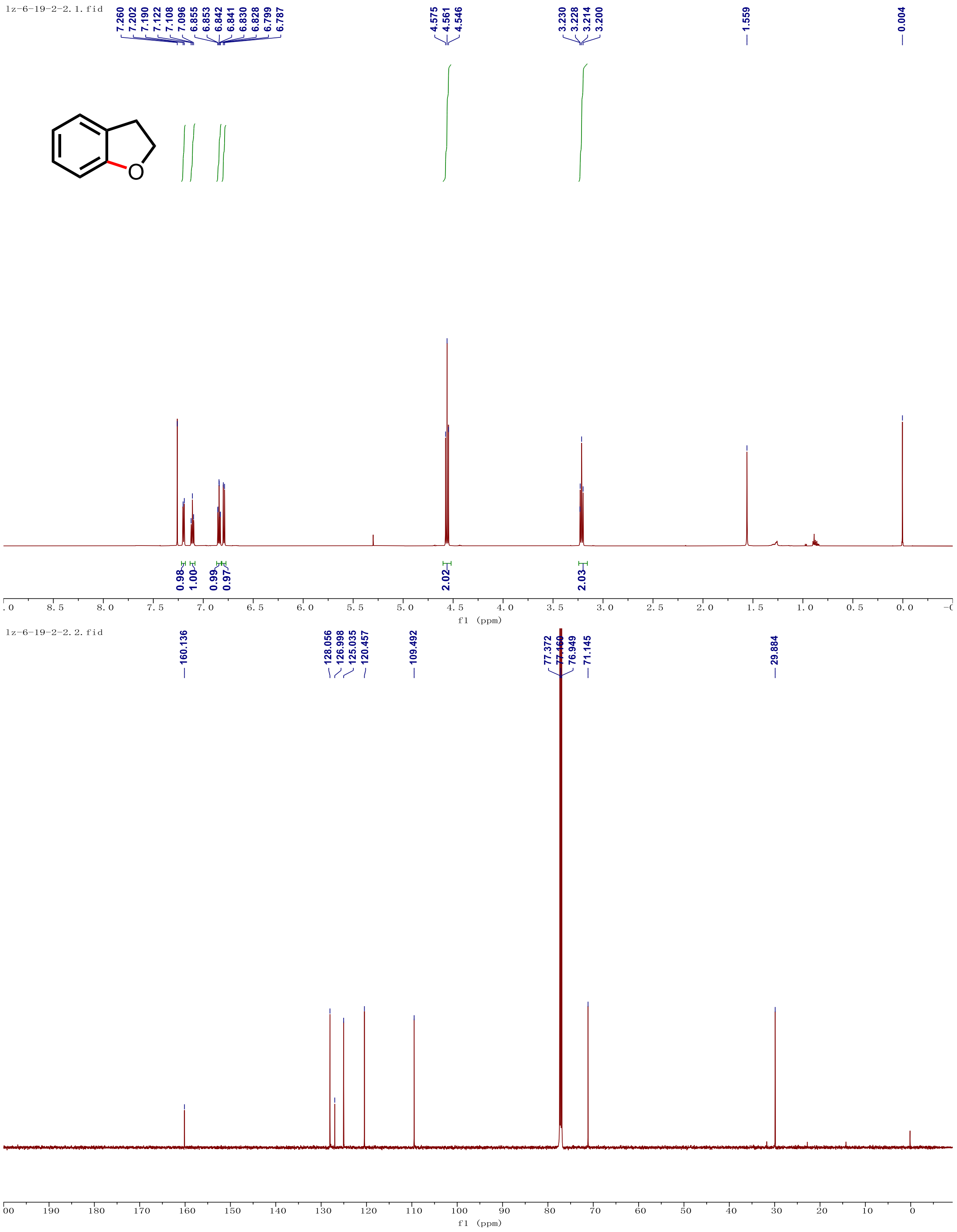
NMR Spectra of **5a**



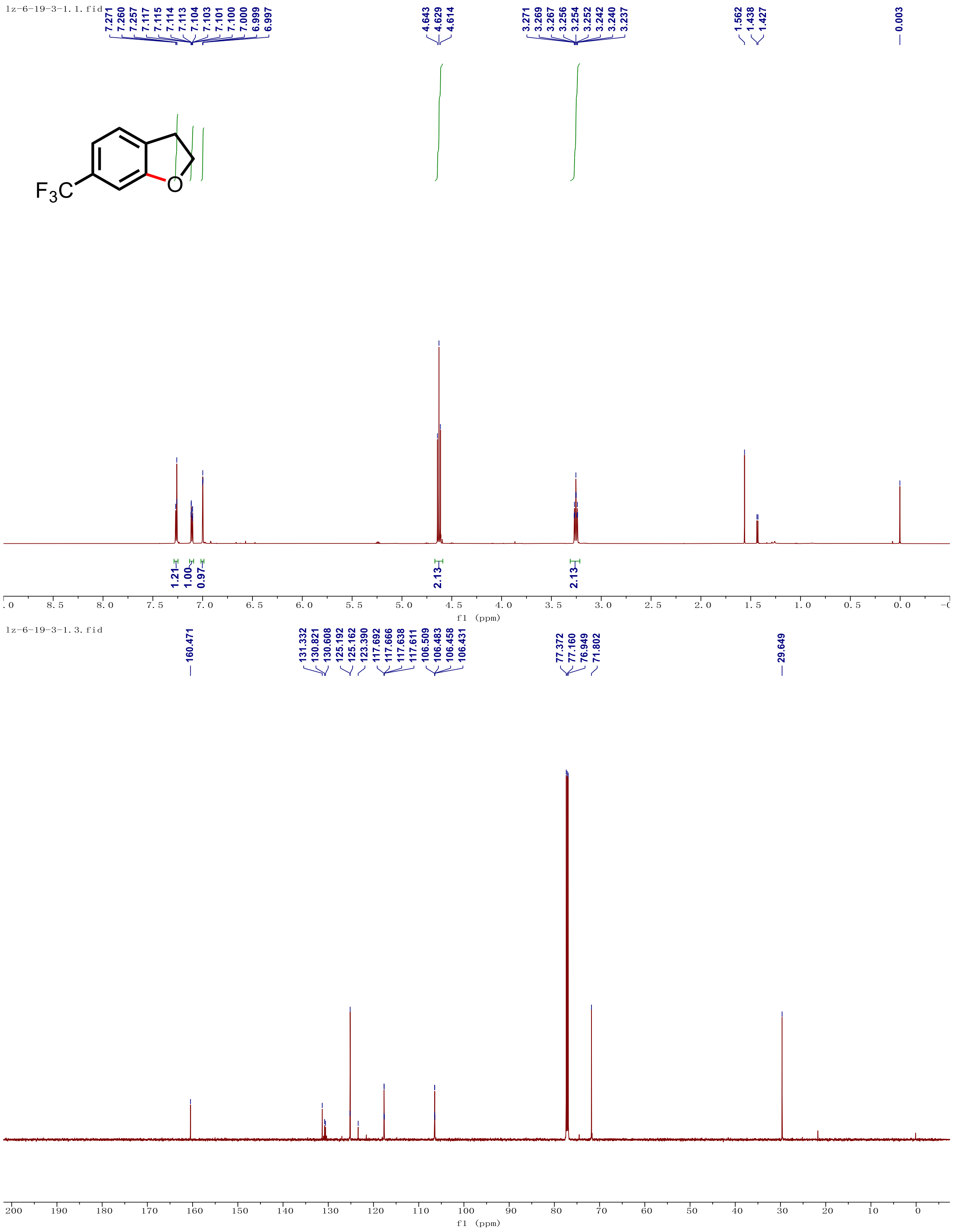
NMR Spectra of **5b**



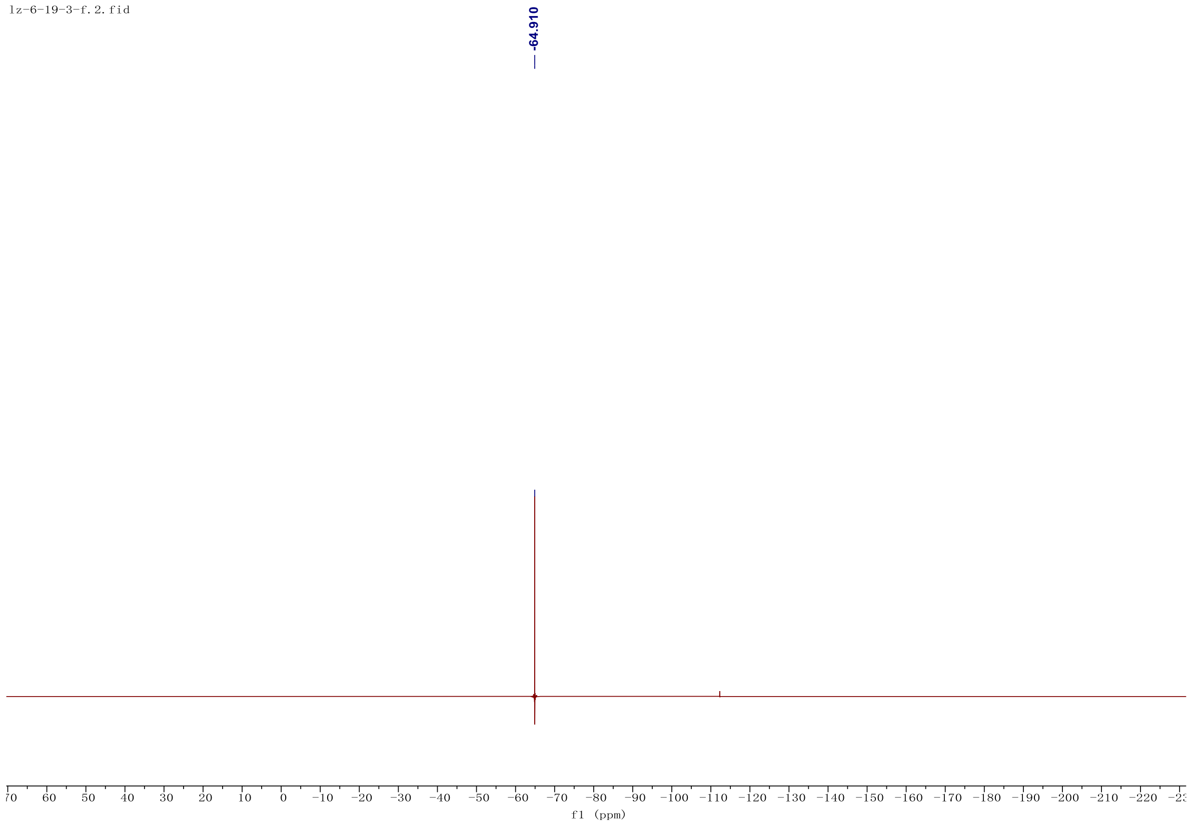
NMR Spectra of **5b**



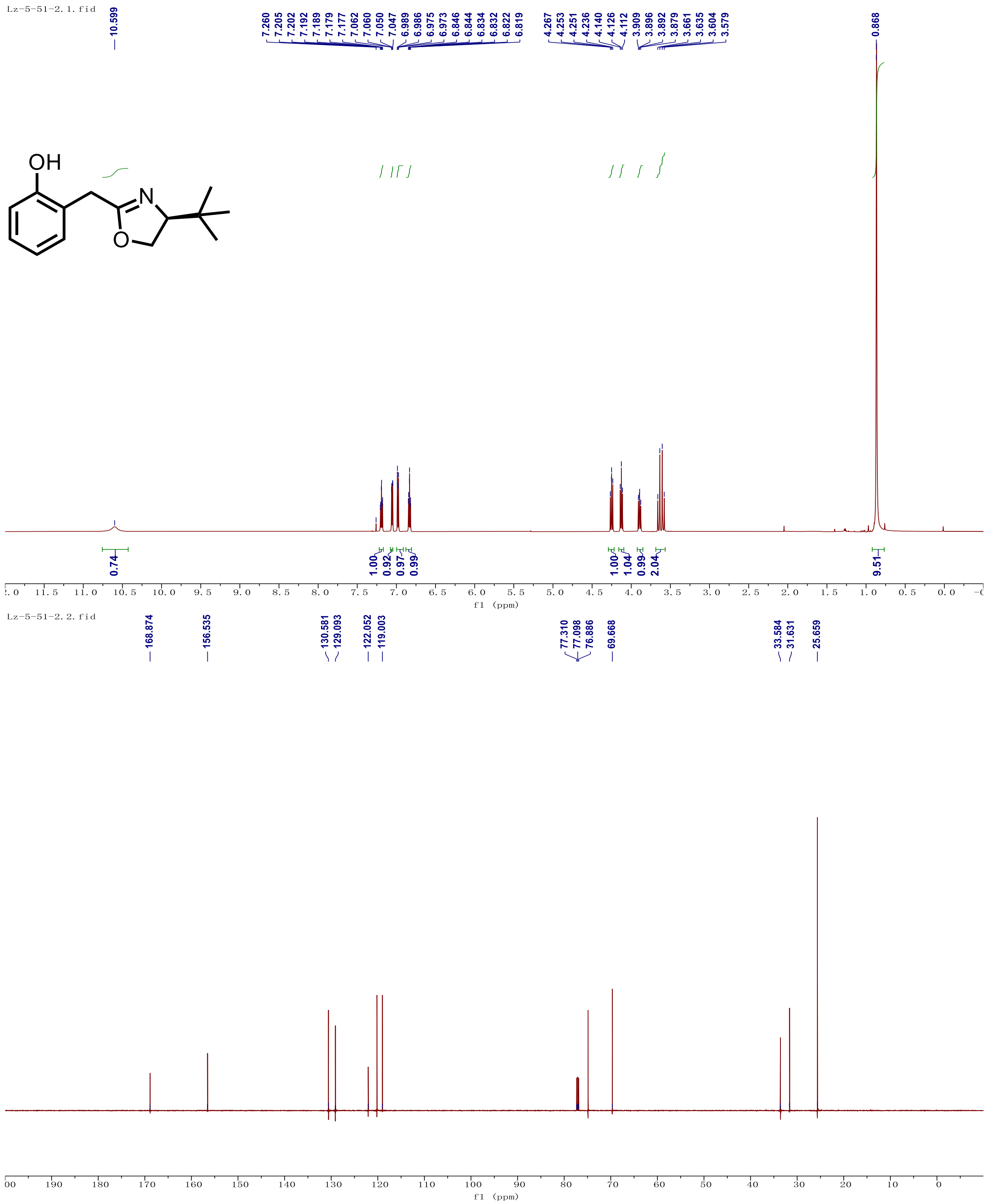
NMR Spectra of **5c**



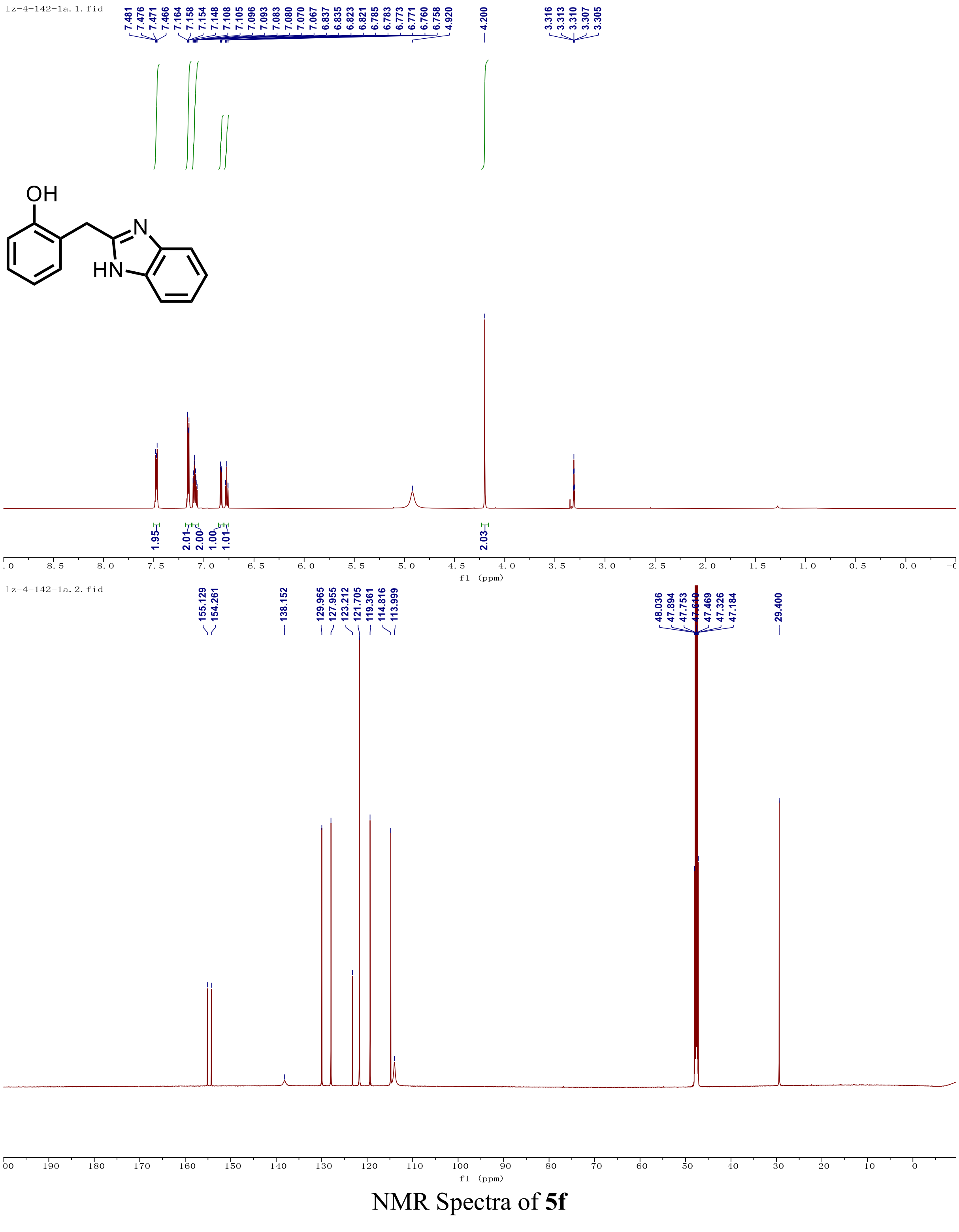
NMR Spectra of **5d**



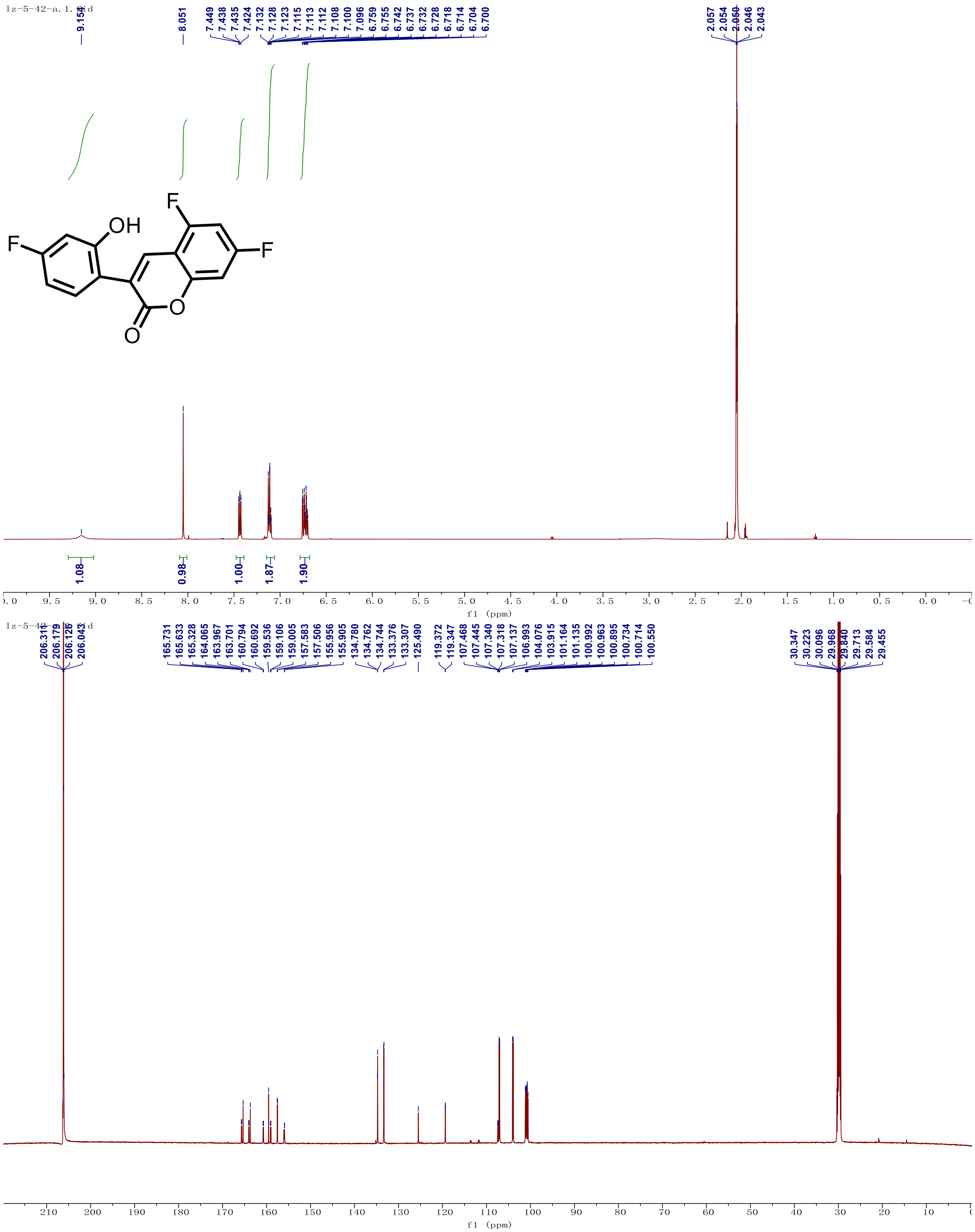
NMR Spectra of **5d**



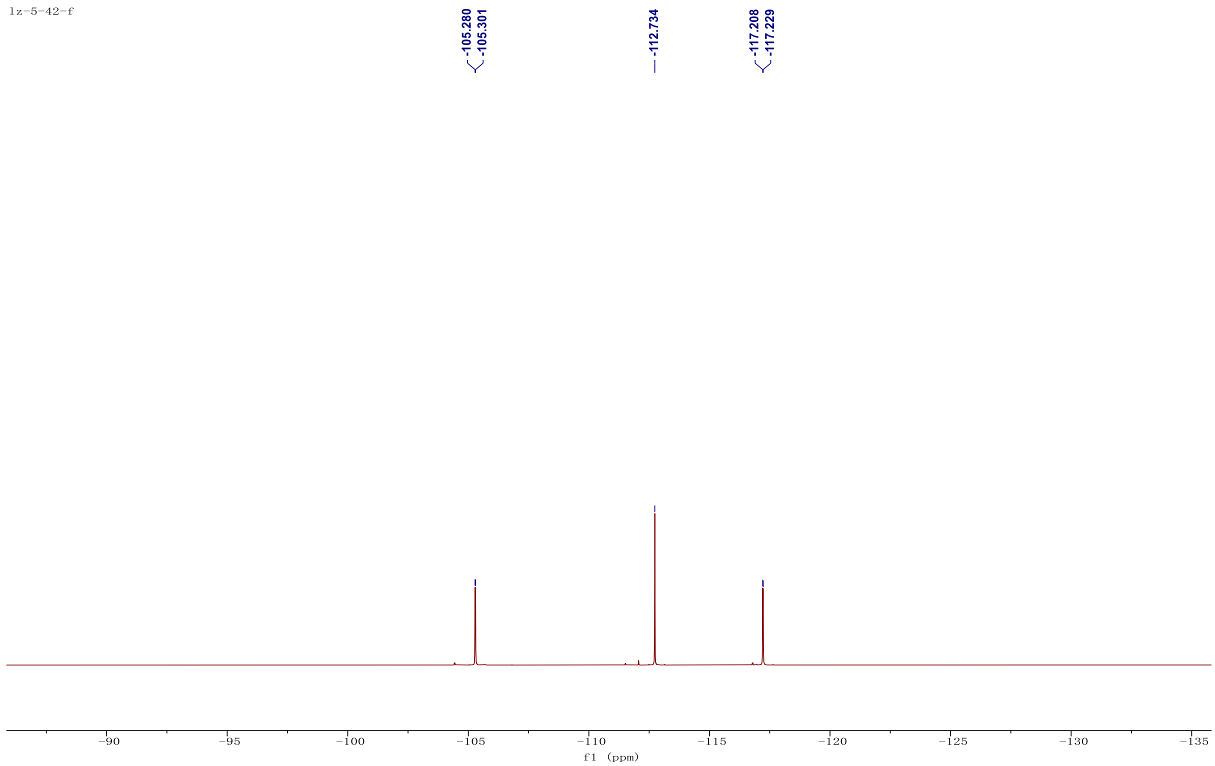
NMR Spectra of **5e**



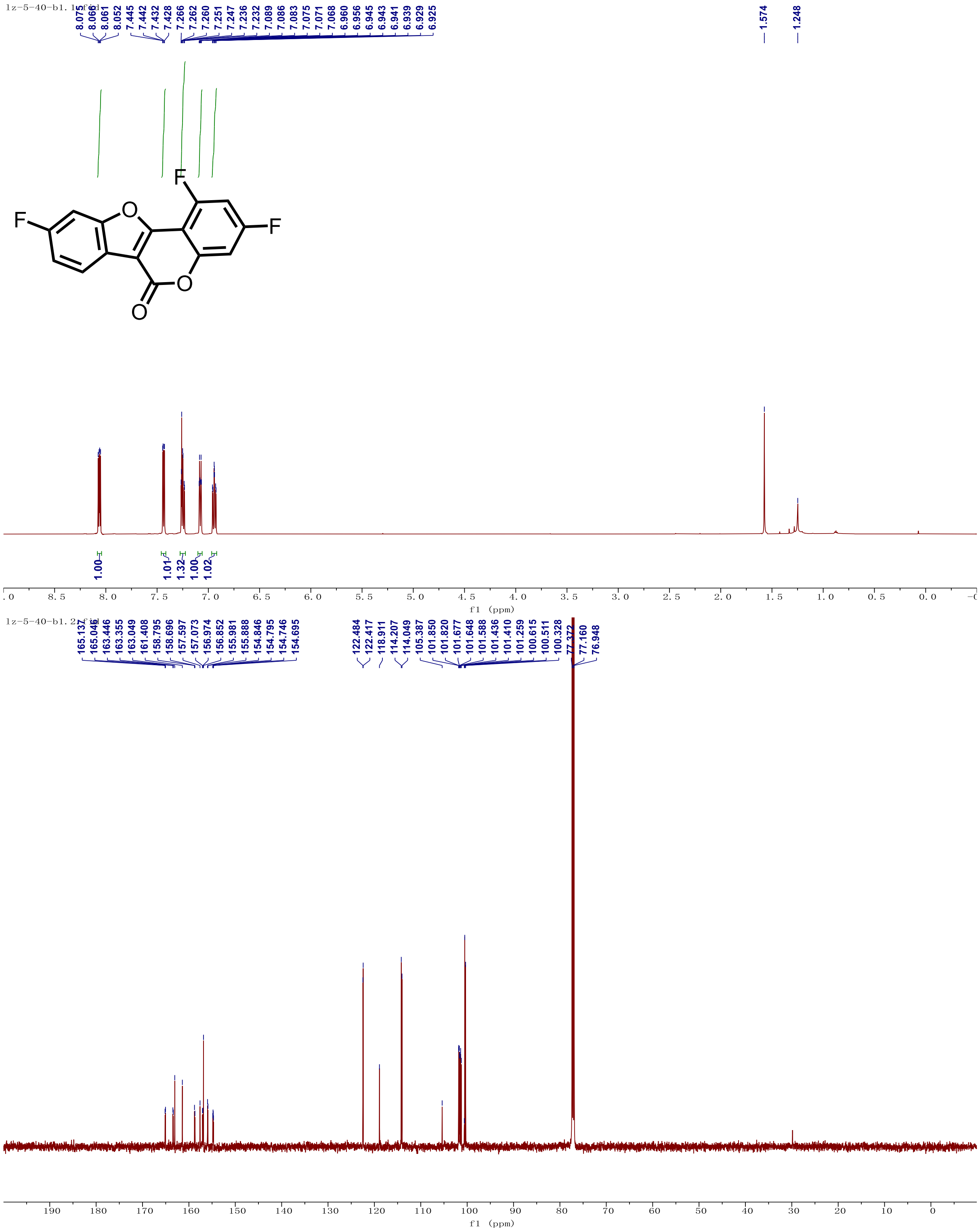
NMR Spectra of **5f**



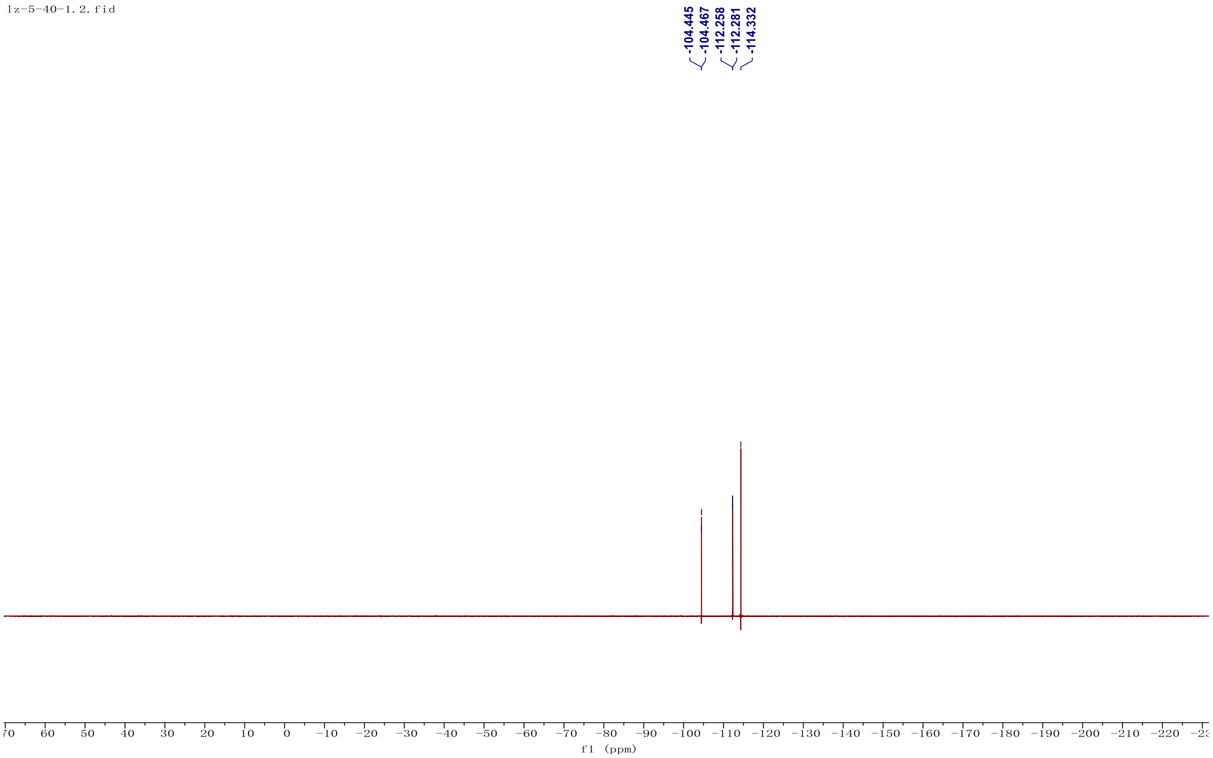
NMR Spectra of **7a**



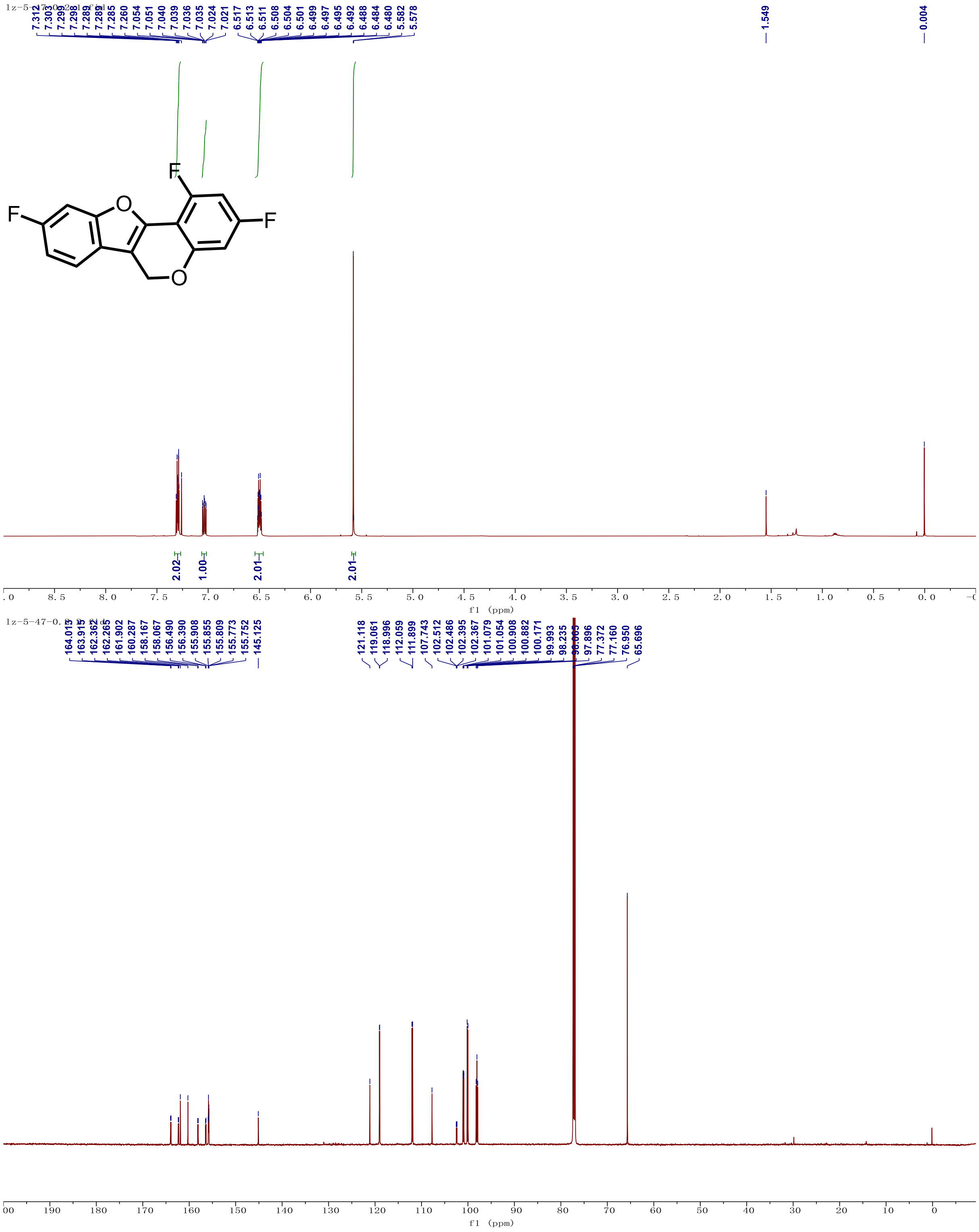
NMR Spectra of **7a**



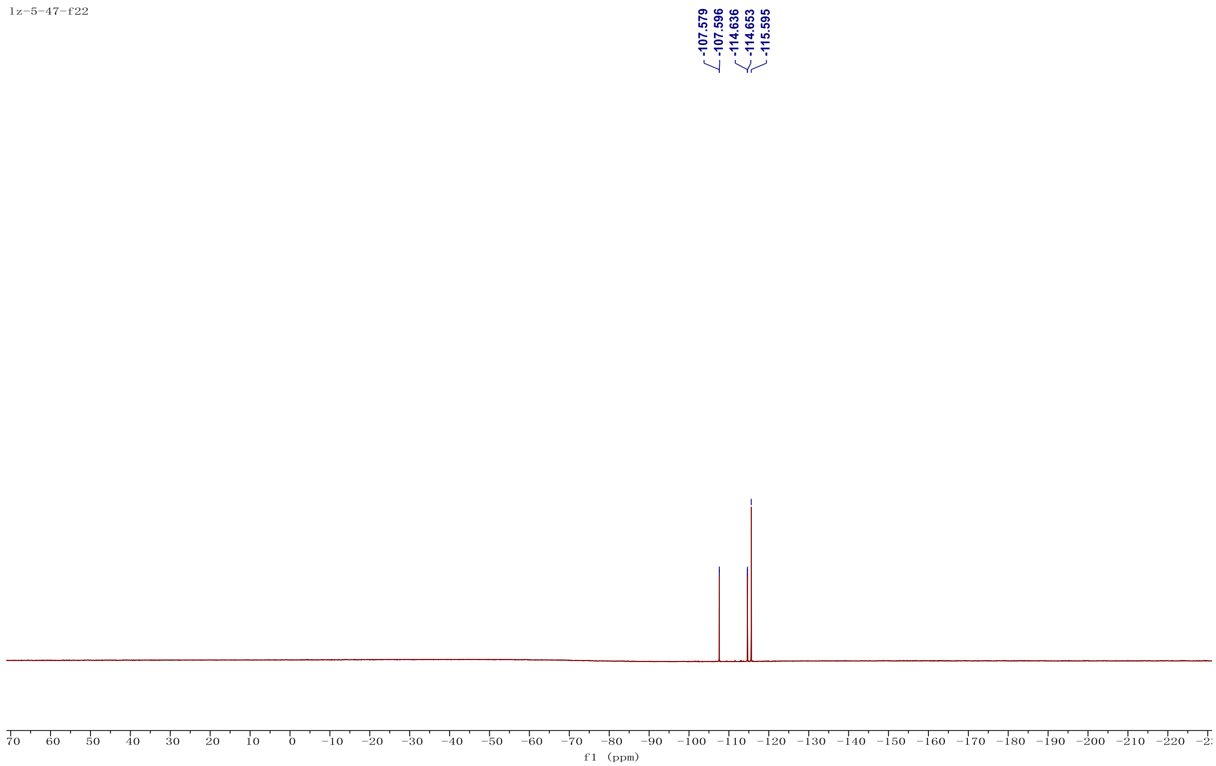
NMR Spectra of **7**



NMR Spectra of **7**



NMR Spectra of **8**



NMR Spectra of **8**