Supporting Information

C-H Bond Cleavage-Enabled Aerobic Ring-Opening Reaction of in Situ Formed 2-Aminobenzofuran-3(2H)-ones

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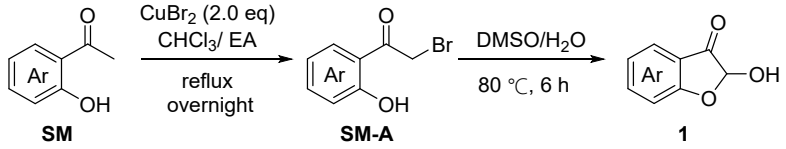
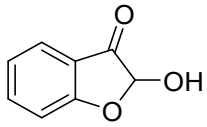
1. Synthesis and characterization of substrates 1a-1g



The intermediates **SM-A** were synthesized according the published methods[1] and this final material was used without further purification.

To a solution of **SM-A** in DMSO (1 M) was added H_2O (1 M) at room temperature. After stirring 6 hours at 80 ℃，the reaction mixture was allowed to cooled to room temperature and subsequently diluted with saturated aqueous $NaHCO_3$. The crude products were extracted with EtOAc and the organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography to afford **1a~1g**.



2-hydroxybenzofuran-3(2H)-one (**1a**) [2]

R_f: 0.27 (petroleum ether/EtOAc = 2:1)

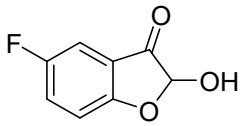
Light yellow solid.

Yield: 72% (from 2'-hydroxyacetophenone)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64-7.67 (m, 2H), 7.09-7.12 (m, 2H), 5.58 (s, 1H), 4.03 (br, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 197.72, 171.35, 139.29, 125.04, 122.61, 119.11, 113.54, 96.73.

HRMS (ESI) m/z calcd for $C_8H_7O_3$ $(M + H)^+$: 151.0390; found: 151.0314.



5-fluoro-2-hydroxybenzofuran-3(2H)-one (**1b**) [2]

R_f: 0.29 (petroleum ether/EtOAc = 2:1)

Light white solid.

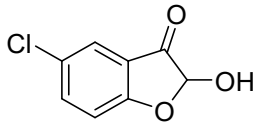
Yield: 75% (from 1-(5-fluoro-2-hydroxyphenyl)ethan-1-one)

^{1}H NMR (600 MHz, DMSO) δ 8.12 (d, J = 9.4 Hz, 1H), 7.61-7.64 (m, 1H), 7.45 (m, 1H), 7.23 (m, 1H), 5.64 (d, J = 9.4 Hz, 1H).

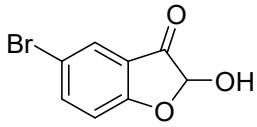
^{13}C NMR (151 MHz, DMSO) δ 198.78 (d, J_{CF} = 2.8 Hz), 167.47, 157.45 (d, J_{CF} = 240.1 Hz), 126.91 (d, J_{CF} = 25.7 Hz), 120.30 (d, J_{CF} = 7.8 Hz), 115.36, 109.93 (d, J_{CF} = 23.7 Hz), 99.21.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -119.67.

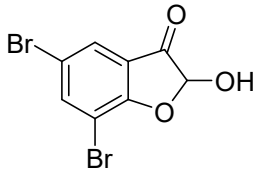
HRMS (ESI) m/z calcd for $C_8H_6FO_3$ $(M + H)^+$: 169.0230; found: 169.0291.



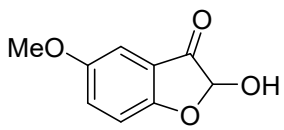
1-(5-chloro-2-hydroxyphenyl)ethan-1-one (**1c**)
m.p. 185 ℃
R_f: 0.32 (petroleum ether/EtOAc = 2:1)
Light white solid.
Yield: 68% (from 1-(5-chloro-2-hydroxyphenyl)ethan-1-one.
^{1}H NMR (600 MHz, DMSO) δ 8.18 (d, *J* = 9.5 Hz, 1H), 7.75-7.77 (m, 1H), 7.67 (d, *J* = 2.3 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 5.66 (d, *J* = 9.4 Hz, 1H).
^{13}C NMR (151 MHz, DMSO) δ 197.97, 169.58, 138.99, 126.43, 123.91, 121.21, 115.76, 99.15.
HRMS (ESI) m/z calcd for $C_8H_6ClO_3$ $(M + H)^+$: 185.0000; found: 184.9996.



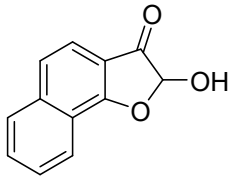
5-bromo-2-hydroxybenzofuran-3(2H)-one (**1d**) [2]
R_f: 0.33 (petroleum ether/EtOAc = 2:1)
White solid.
Yield: 57% (from 1-(5-bromo-2-hydroxyphenyl)ethan-1-one).
^{1}H NMR (600 MHz, DMSO) δ8.18 (d, *J* = 9.4 Hz, 1H), 7.86-7.88 (m, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 5.65 (d, *J* = 9.4 Hz, 1H).
^{13}C NMR (151 MHz, DMSO) δ 197.29, 169.46, 141.19, 126.44, 121.33, 115.72, 113.42, 98.53.
HRMS (ESI) m/z calcd for $C_8H_4BrO_3$ $(M - H)^-$: 228.9323; found: 228.9353.



5,7-dibromo-2-hydroxybenzofuran-3(2H)-one (**1e**)
m.p. 174 ℃
R_f: 0.44 (petroleum ether/EtOAc = 2:1)
Yellow solid.
Yield: 63%.
^{1}H NMR (600 MHz, DMSO) δ 8.40 (d, *J* = 8.1 Hz, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 5.79 (d, *J* = 8.0 Hz, 1H).
^{13}C NMR (151 MHz, DMSO) δ 196.64, 166.20, 142.29, 125.94, 122.47, 113.73, 107.11, 99.59.
HRMS (ESI) m/z calcd for $C_8H_3Br_2O_3$ $(M - H)^-$: 306.8449; found: 306.8417.



2-hydroxy-5-methoxybenzofuran-3(2H)-one (**1f**) [2]
R_f: 0.21 (petroleum ether/EtOAc = 2:1)
Yellow solid.
Yield: 69%.
^{1}H NMR (600 MHz, DMSO) δ 7.99 (d, *J* = 9.3 Hz, 1H), 7.34-7.36 (m, 1H), 7.12 (d, *J* = 9.0 Hz, 1H), 7.06 (d, *J* = 2.9 Hz, 1H), 5.56 (d, *J* = 9.3 Hz, 1H).
^{13}C NMR (151 MHz, DMSO) δ 198.65, 165.74, 154.38, 127.99, 119.26, 114.31, 104.91, 98.29, 55.84.
HRMS (ESI) m/z calcd for $C_9H_9O_4$ $(M + H)^+$: 181.0495; found: 181.0491.

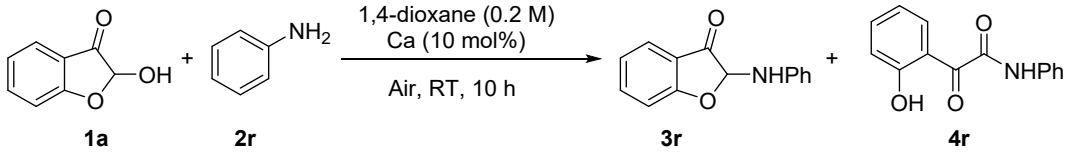


2-hydroxynaphtho[1,2-b]furan-3(2H)-one (**1g**) [2]
R_f: 0.27 (petroleum ether/EtOAc = 2:1)
Yellow solid.
Yield: 42%.
^{1}H NMR (600 MHz, DMSO) δ 8.29 (d, *J* = 9.6 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 5.84 (d, *J* = 9.6 Hz, 1H).
^{13}C NMR (151 MHz, DMSO) δ 197.38, 171.06, 138.53, 131.15, 128.70, 127.23, 122.14, 121.96, 120.79, 118.67, 113.94, 99.43.
HRMS (ESI) m/z calcd for $C_{12}H_9O_3$ $(M + H)^+$: 201.0546; found: 201.0549.

2. Optimization studies for the reaction of 1 with arylamines

To smoothly promote conversion of **1** with arylamines into *o*-hydroxyaryl glyoxylamides, the step-wise screening of reaction conditions was operated. For condensation reaction to access *N,O*-acetals, reactions of **1a** with aniline **2r** were performed in the presence of a catalytic amount of a Lewis or Brφnsted acid (10 mol%) at room temperature in 1,4-dioxane under open air (Table S1). Among a few acid catalysts tested (Table S1, Entries 2-5), DPP (diphenyl phosphate) was found to be the most effective (Table S1, Entry 4), and the *N,O*-acetal **3r** was obtained in 93% yield, but the ring-opening product **4r** did not be observed.

Table S1. Condition optimization for condensation reactions. [a]



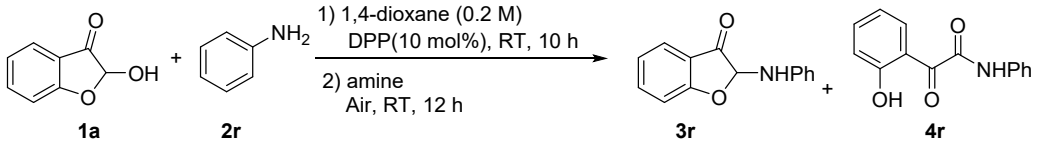
Entry	Ca.	Yield[b] of **3r** (%)	Yield[b] of **4r** (%)
1[c]	None	21	ND[e]

2	TfOH	72	ND
3	$TsOH.H_2O$	87	ND
4	DPP[d]	**93**	ND
5	$BF_3.Et_2O$	85	ND

[a] Reaction conditions: **1a** (30 mg, 0.2 mmol), **2r** (19 mg, 0.2 mmol) , catalyst (0.02 mmol), and 1,4-dioxane (1 mL) were stirred at room temperature (RT) for 10 h under open air. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture with dibromomethane as an internal standard. [c] Incomplete conversion was observed. [d] DPP: Diphenyl phosphate. [e] Not detected.

With the optimized catalyst for condensation reactions at hand, various amines, including primary alkylamines, secondary alkylamines and arylamine, were allowed to direct the ring-opening reaction of *N,O*-acetal **3r**. As summarized in Table S2, alkylamines rather than arylamines facilitated the transformation, in which the desired product **4r** was obtained in the highest yield when diethylamine was used as the promoter (Table S2, Entry 2). Furthermore, the yield of **4r** decreased to 30% with the amount of diethylamine reduced to 0.5 equivalent (Table S2, Entry 6).

Table S2. Condition optimization for ring-opening reactions. [a]

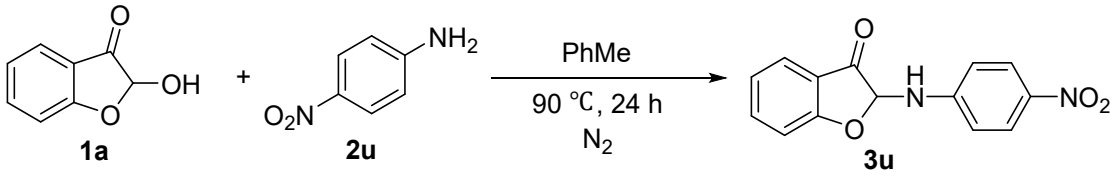


Entry	Amines	Yield[b] of **3r**	Yield[b] of **4r**
1	$PhNH_2$	37%	ND[c]
2	Diethylamine	ND	**76**(73[d])
3	Pyrrolidine	ND	60
4	*tert*-Butylamine	ND	73
5	Propylamine	ND	47
6[e]	Diethylamine	ND	30

[a] Reaction conditions: **1a** (30 mg, 0.2 mmol), **2r** (19mg, 0.2 mmol), DPP (5 mg, 0.02 mmol) and 1,4-dioxane (1 mL) at RT for 10 h followed by the addition of amine (0.2 mmol), stirring continued under open air at RT for 12 h. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture with dibromomethane as an internal standard. [c] Not detected. [d] Isolated yield. [e] 0.5 equivalents of diethylamine were used.

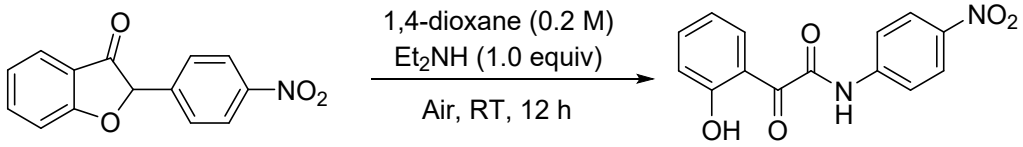
3. Mechanistic studies

1) The control experiment of semicyclic *N,O*-acetal **3u**
Synthesis of **3u**:



A reaction tube was charged with the 2-hydroxybenzofuran-3(2H)-one **1a** (75 mg, 0.5 mmol, 1.0 eq.), *p*-nitroaniline **2u** (69 mg, 0.5 mmol, 1.0eq) and PhMe (3 mL). The mixture was heated to 90 ℃ oil bath temperature for 24 hours while stirring under nitrogen atmosphere. After cooling the precipitate was filtered and rinsed with a minimum amount of cold PhMe. The yellow solid was dried under vacuum to afford semicyclic *N,O*-acetal **3u** (121 mg, 90%). m.p. 154 ℃. R_f: 0.38 (petroleum ether/EtOAc = 4:1). ^{1}H NMR (600 MHz, DMSO) δ 8.38 (d, *J* = 9.5 Hz, 1H), 8.15 (d, *J* = 9.1 Hz, 2H), 7.79-7.82 (m, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.26 (d, *J* = 8.3 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 9.1 Hz, 2H), 6.31 (d, *J* = 9.5 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 196.05, 170.91, 152.02, 139.44, 139.10, 125.97, 124.33, 122.27, 119.76, 113.71, 113.16, 86.67. HRMS (ESI) m/z calcd for $C_{14}H_{10}N_2O_4$ $(M + H)^+$: 271.0713; found: 271.0716.

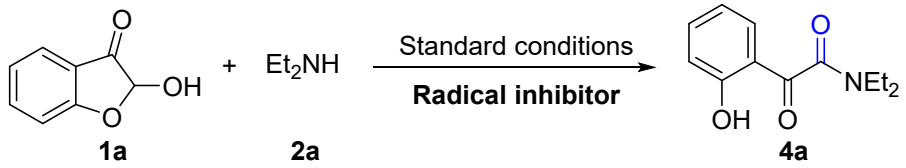
The control experiment of **3u**:



3u **4u**

To a solution of **3u** (54 mg, 0.2 mmol) in 1,4-dioxane (1 mL) was diethylamine (15 mg, 0.2 mmol) at RT, then the reaction mixture was stirred at RT under open air. After 12 hours, the mixture was diluted with HCl aqueous solution (0.2 N, 5 mL) and extracted with ethyl acetate (2×5 mL). The combined organic extracts were washed with brine (5 ml), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel using petroleum ether/EtOAc (4:1) as the eluent to give the desired product **4u** in 57% yield.

2) Radical-trapping experiments



1a **2a** **4a**

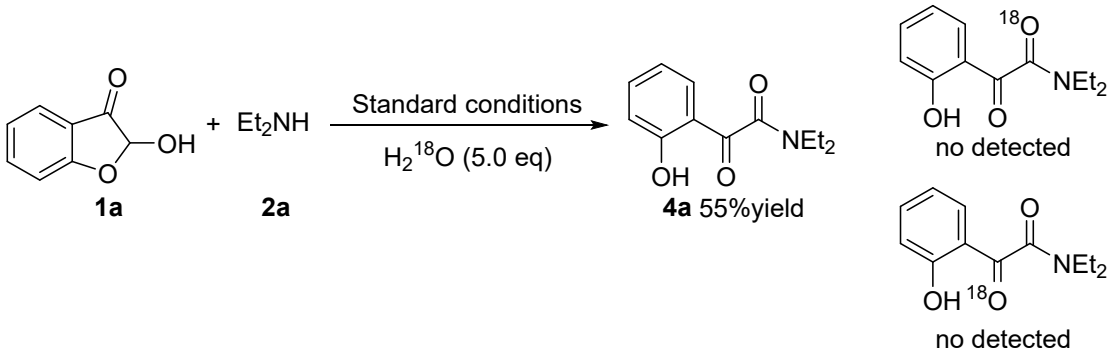
Radical inhibitor	Yield of **4a** (%)
None	96
TEMPO	98
BHT	95
TRION	94

Reaction conditions: **1a** (30 mg, 0.2 mmol), **2a** (29 mg, 0.4 mmol), Radical inhibitor (0.4 mmol), in 1,4-dioxane (1.0 mL), at RT, under open air, for 14 h. Isolated yields.

The reactions performed well in the TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (2,6-di-tert-butyl-4-methylphenol) producing the desired product **4a** in 98% and 95% yields, respectively, which indicate that a radical process might not be involved in the present reaction

system. The superoxide radical anion scavenger TIRON (sodium 4,5-dihydroxybenzene-1,3-disulfonate)[3] was added to the model reaction. However, the reaction did not be inhibited and 4a was obtained in 94% isolated yield, which may exclude reactive oxygen species in this transformation.

3) Control experiment of ^{18}O-labeled water



Reaction conditions: **1a** (30 mg, 0.2 mmol), **2a** (29 mg, 0.4 mmol), $H^{18}O$ (20 mg, 1.0 mmol), in 1,4-dioxane (1.0 mL), at RT, under open air, for 14 h. Isolated yield. The ^{18}O in product **4a** was determined by HRMS and no ^{18}O incorporation was observed.

4) The consumption of Et_2NH detected by ^1H NMR.

At the end of model reaction of **1a** with Et_2NH, the solvent was concentrated in vacuo under room temperature and appropriate amount of residue was dissolved $CDCl_3$ for ^1H NMR analysis, as shown in Figure S1a. By comparing the ^1H NMR spectra of the reaction mixture with that of **4a** (Figure S1b) and diethylamine (Figure S1c), we found excessive diethylamine was consumed completely.

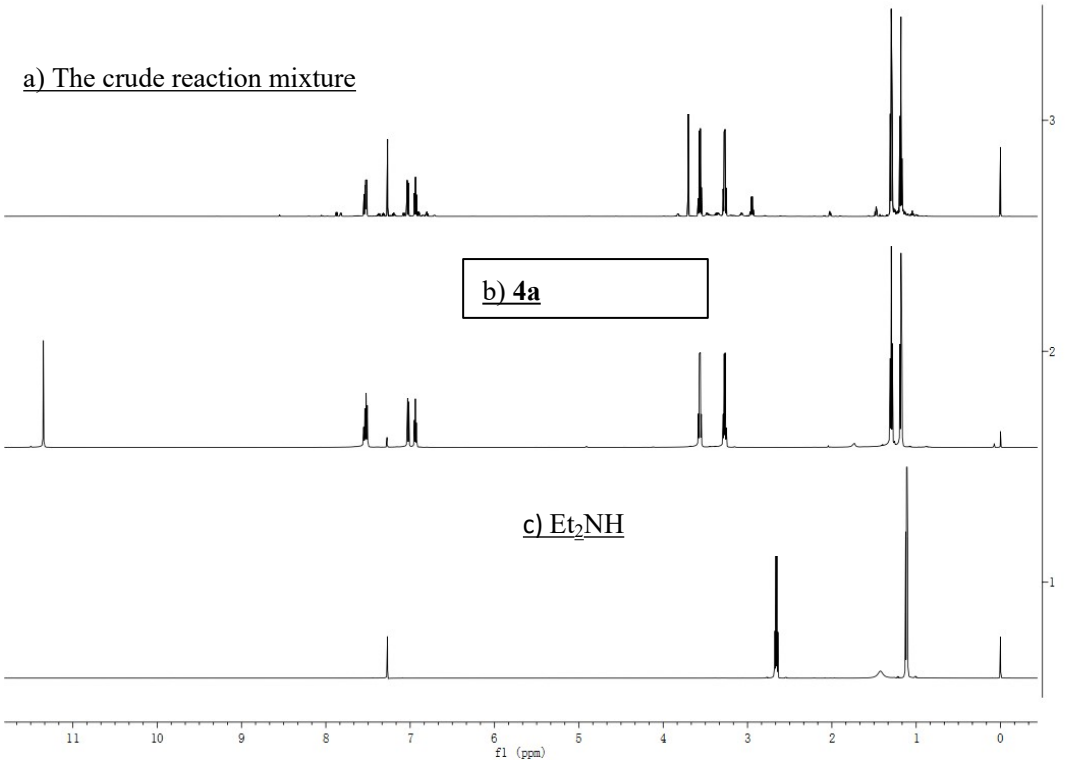
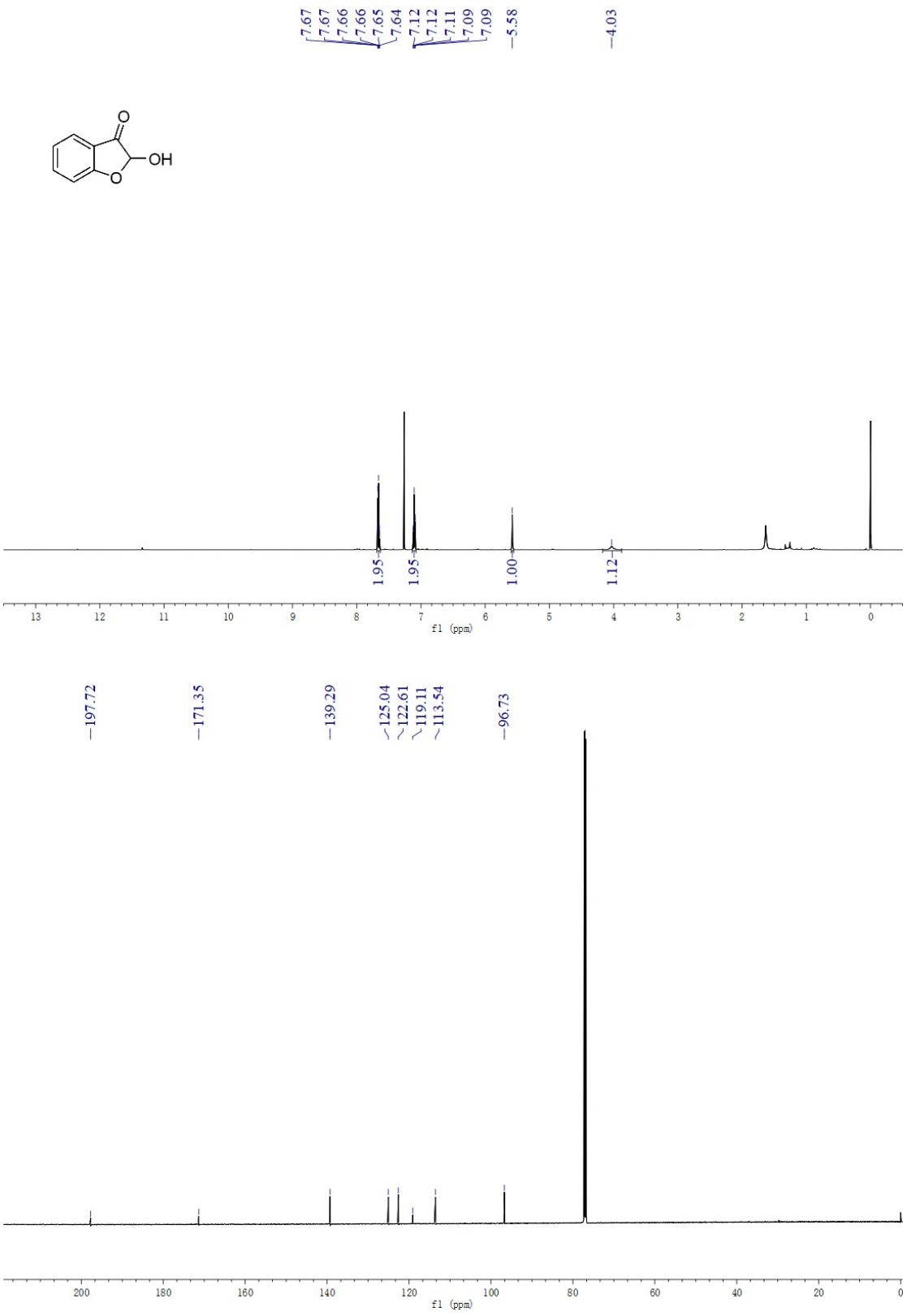


Figure S1. ^{1}H NMR spectra of a) reaction mixture, b) **4a** and c) **2a**

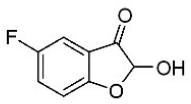
4. References

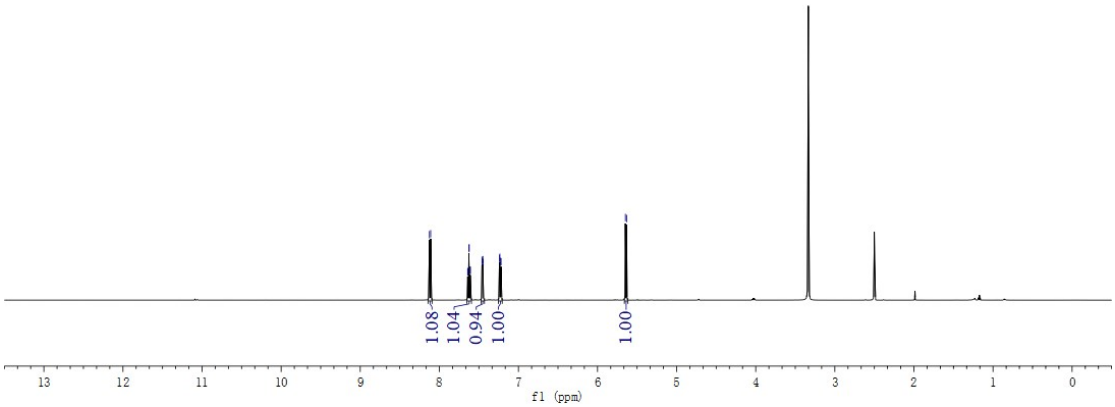
[1] D. S. Black, N. Kumar, D. B. McConnell, *Tetrahedron* **2001**, *57*, 2203.
[2] F. F. Gao, W. J. Xue, J. G. Wang, A. X. Wu, *Tetrahedron* **2014**, *70*, 4331.
[3] W. D. Castro-Godoy, L. C. Schmidt, J. E. Arguello, *Eur. J. Org. Chem.* **2019**, *2019*, 3035.

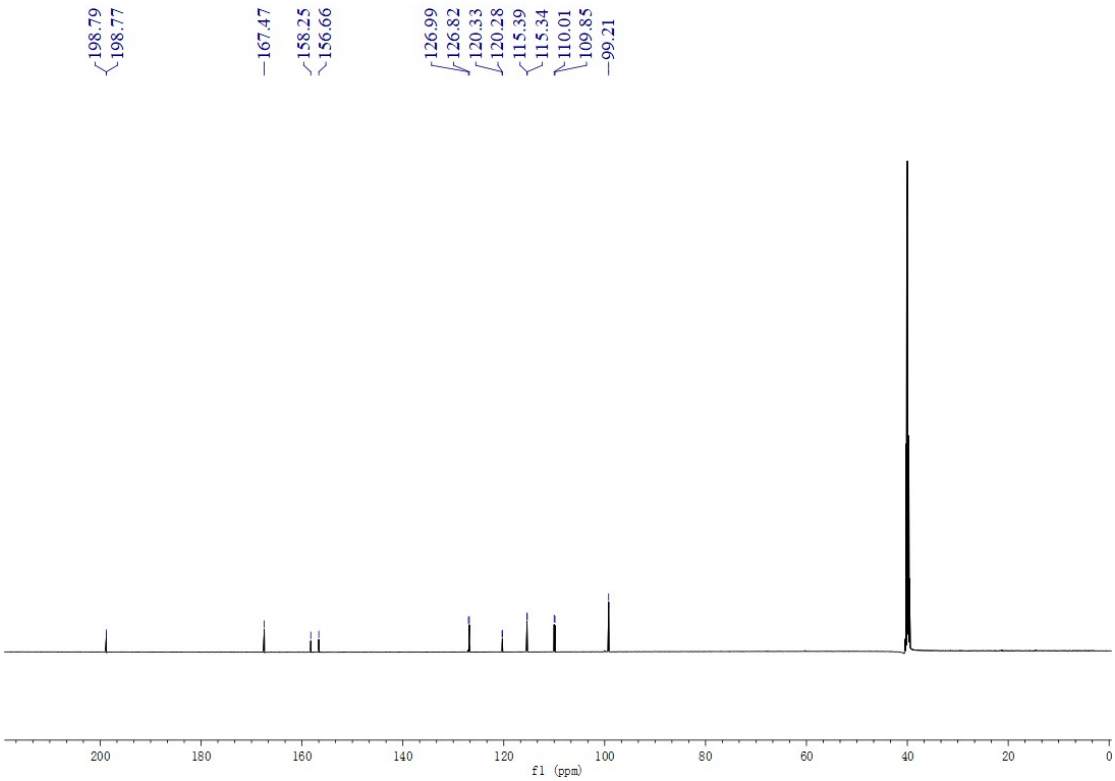
^{1}H and ^{13}C NMR Spectra for **1a**

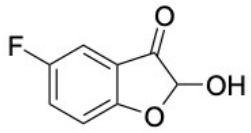


^{1}H, ^{13}C and ^{19}F NMR Spectra for **1b**

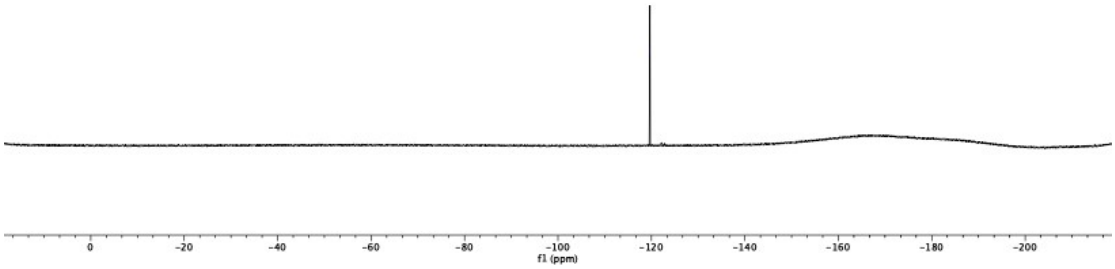




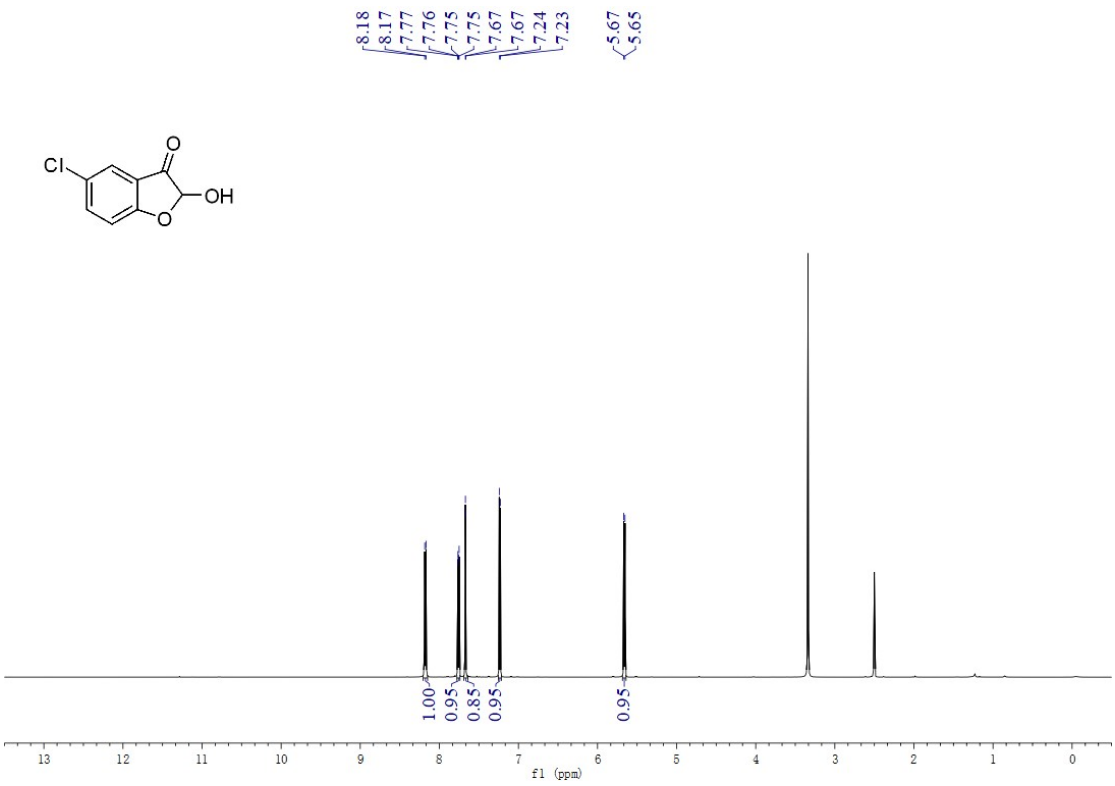


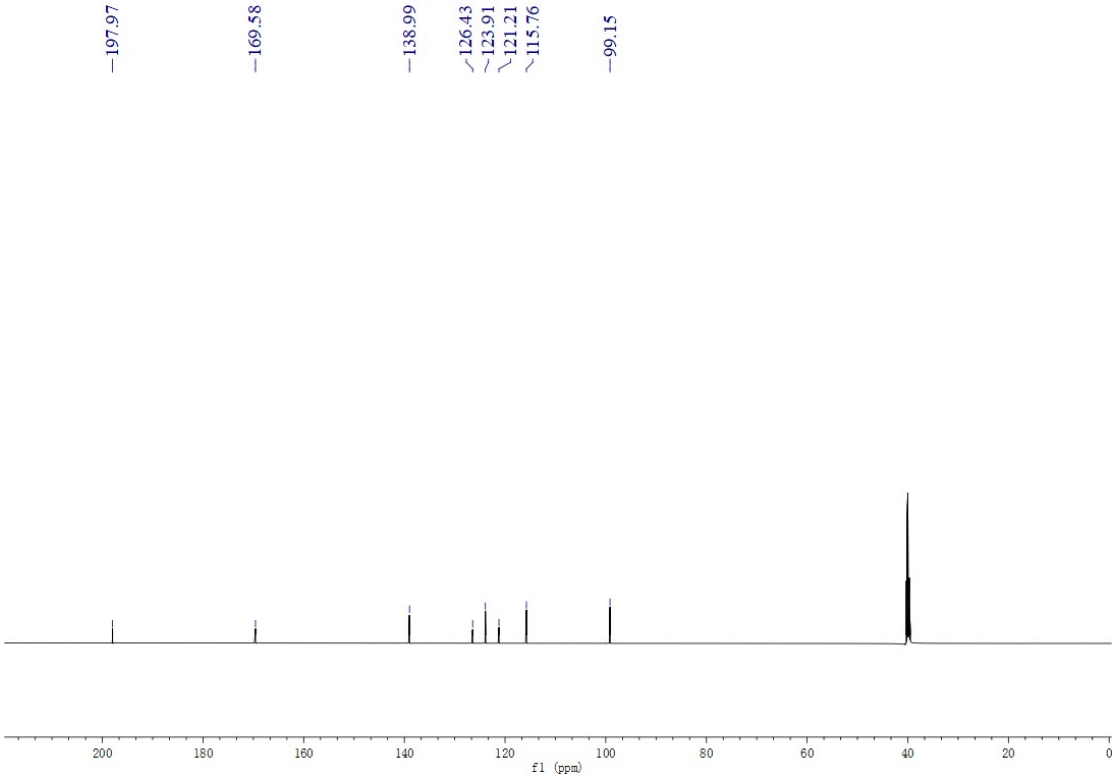


−119.67

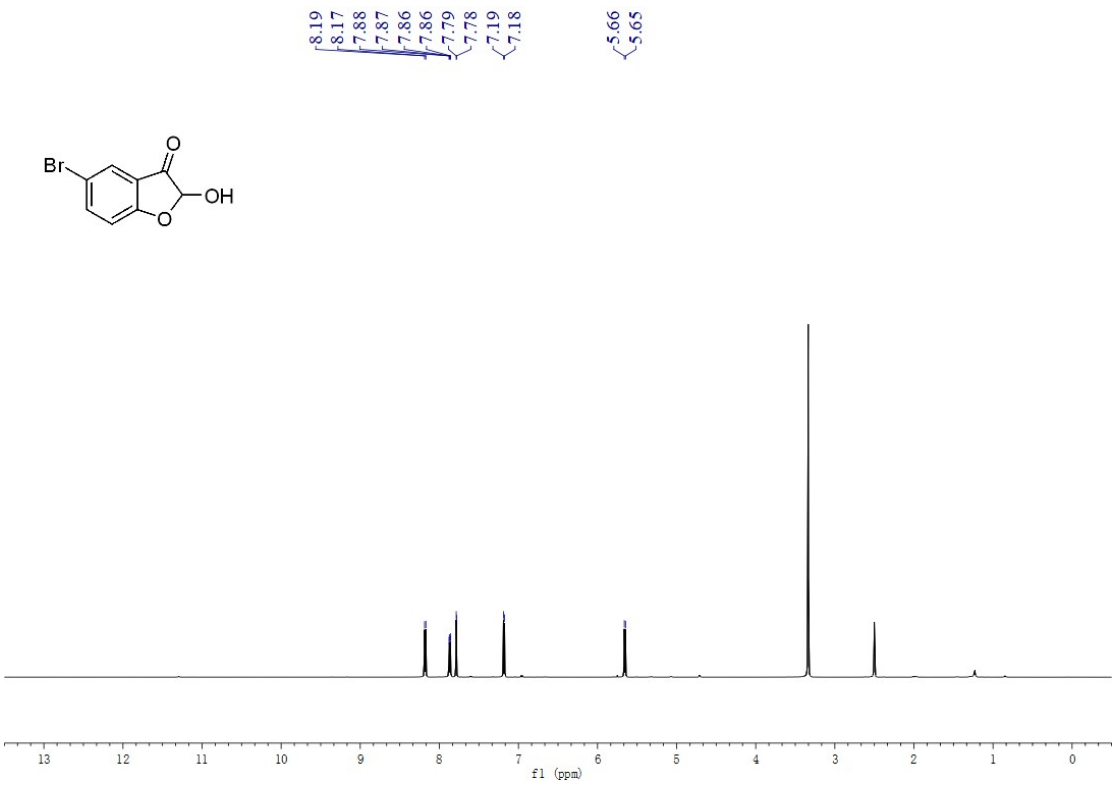


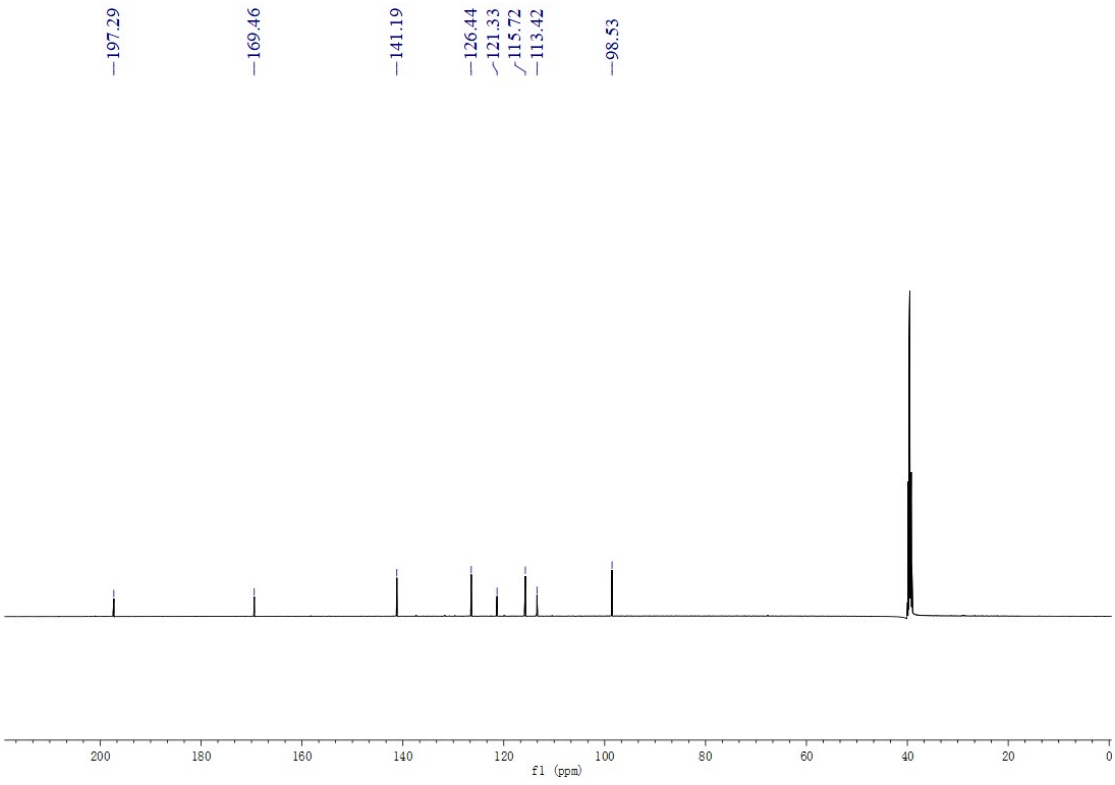
^{1}H and ^{13}C NMR Spectra for **1c**



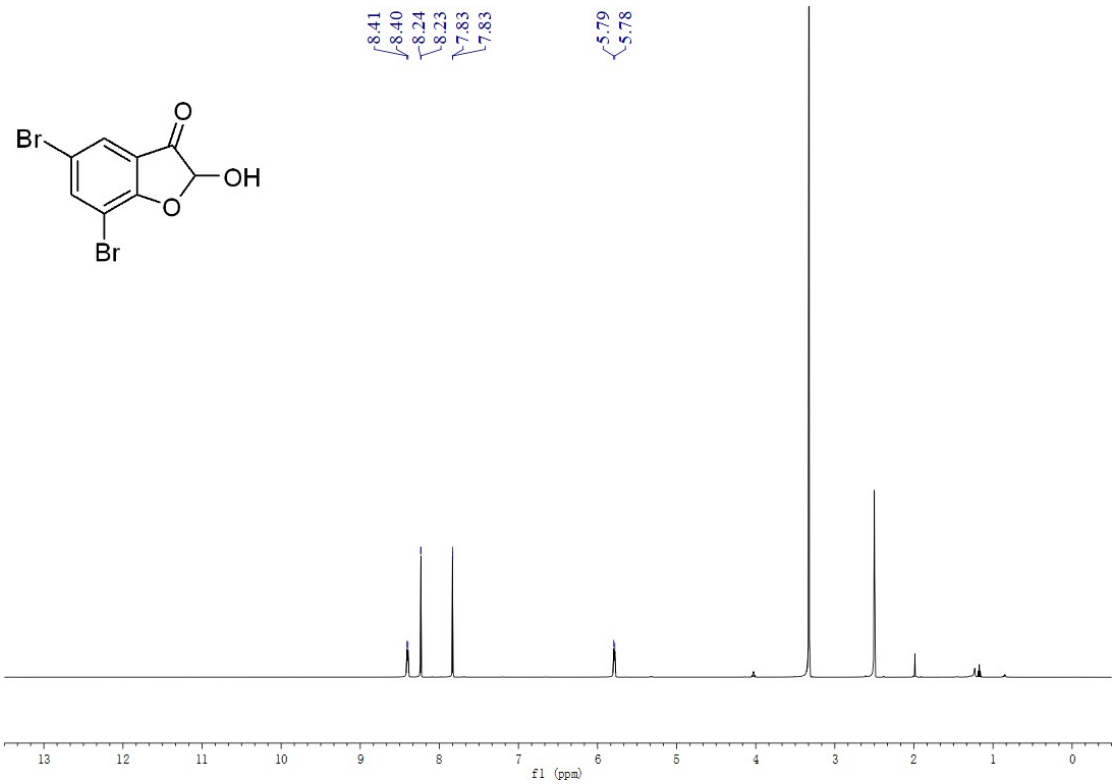


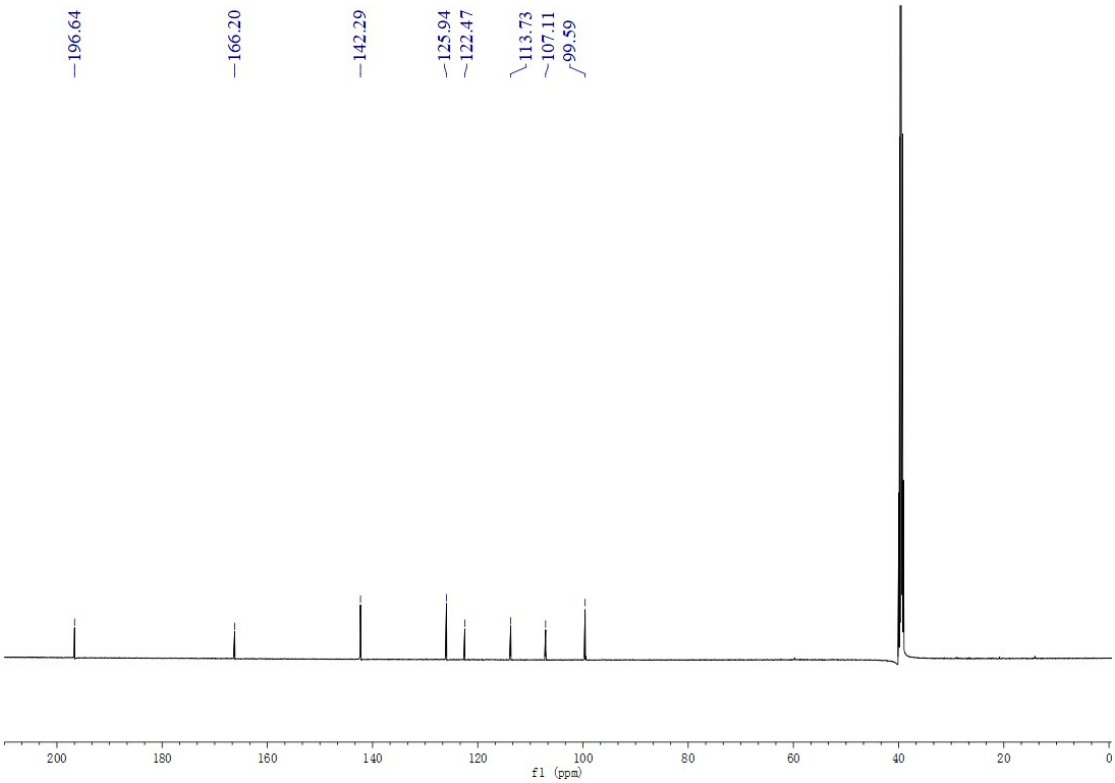
^{1}H and ^{13}C NMR Spectra for **1d**



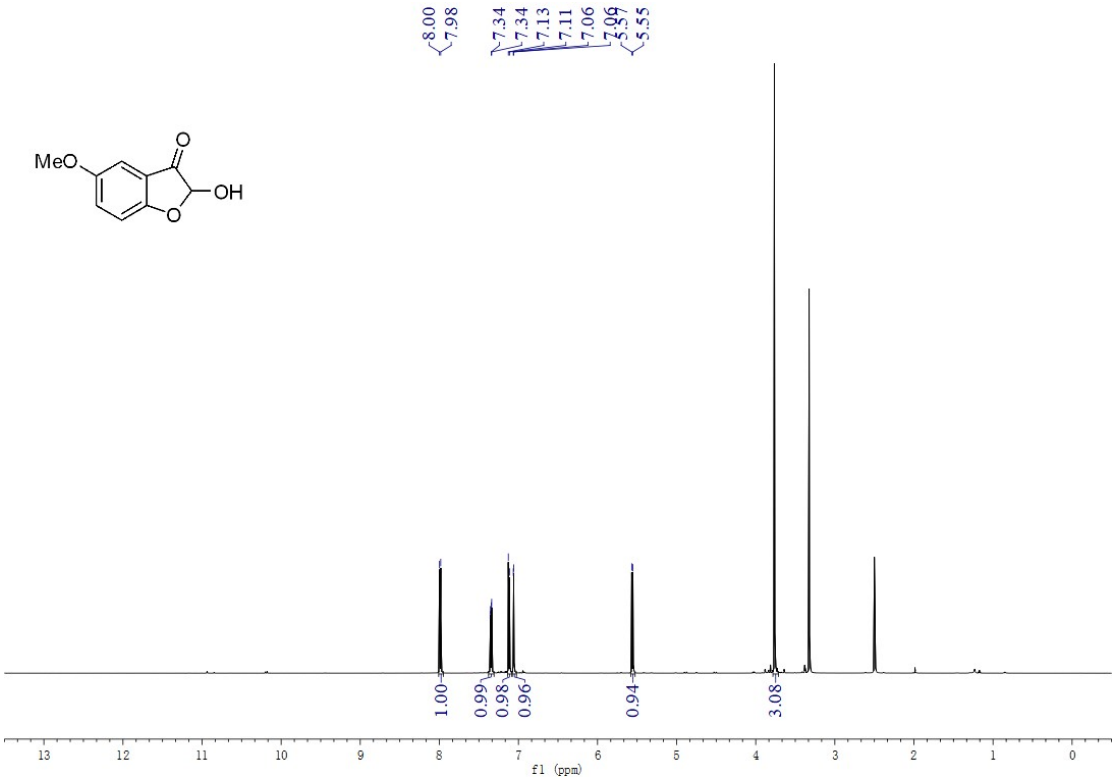


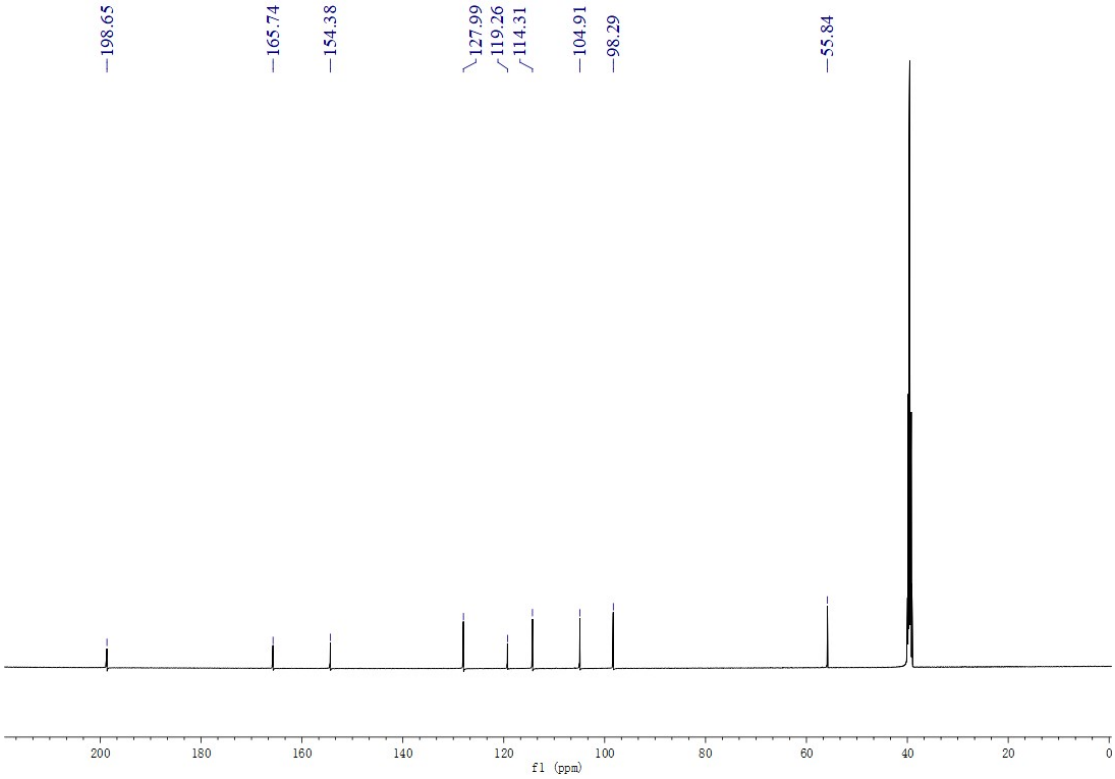
^{1}H and ^{13}C NMR Spectra for **1e**



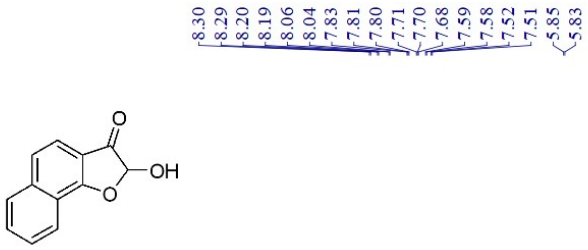


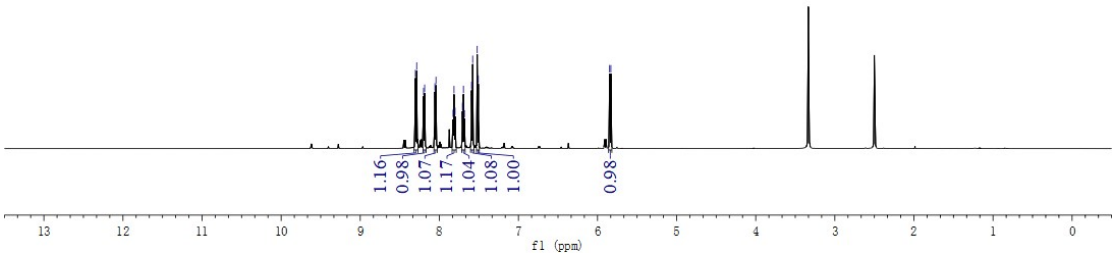
^{1}H and ^{13}C NMR Spectra for **1f**

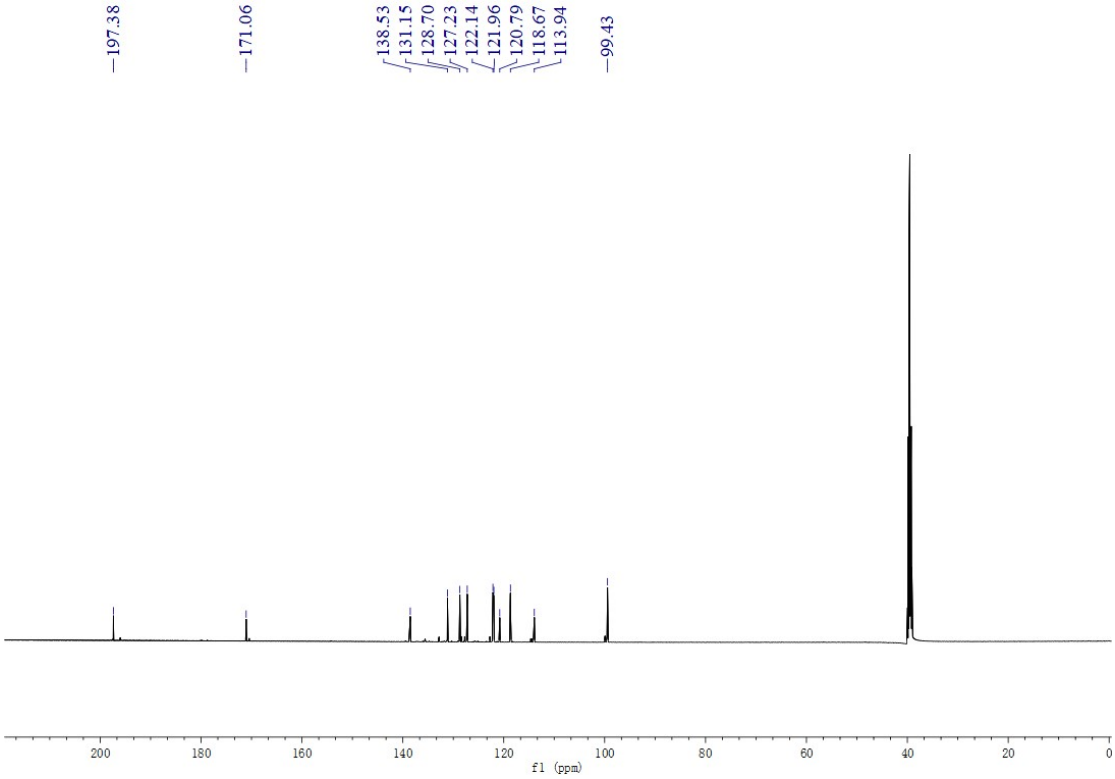




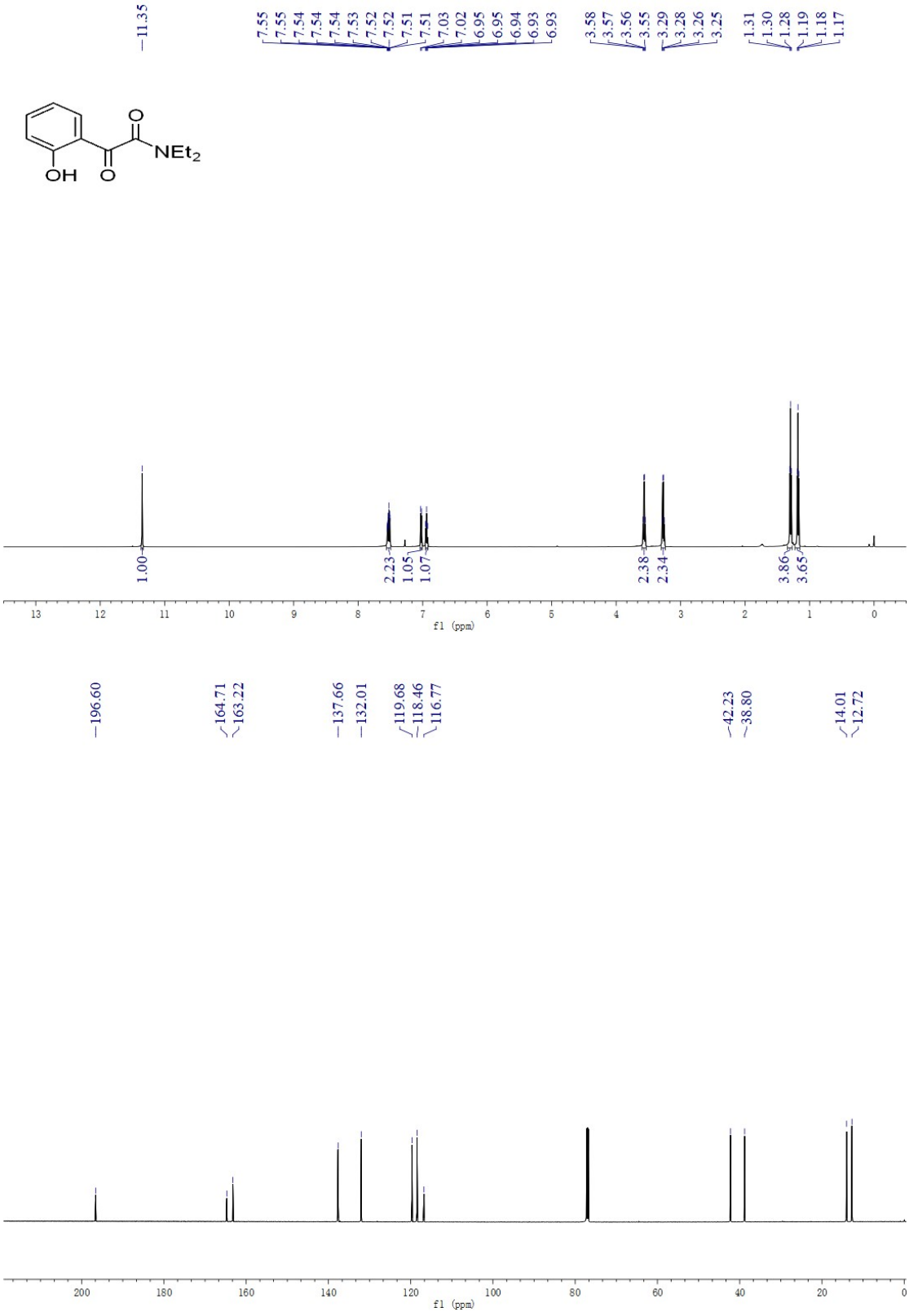
^{1}H and ^{13}C NMR Spectra for **1g**



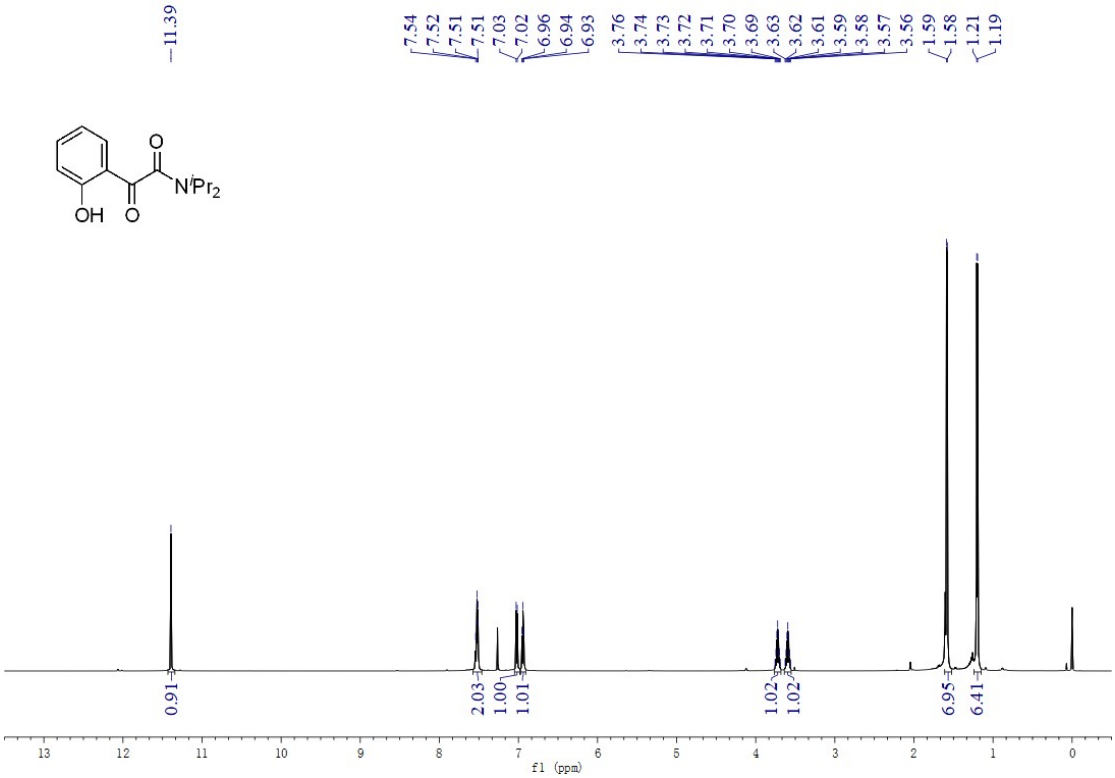


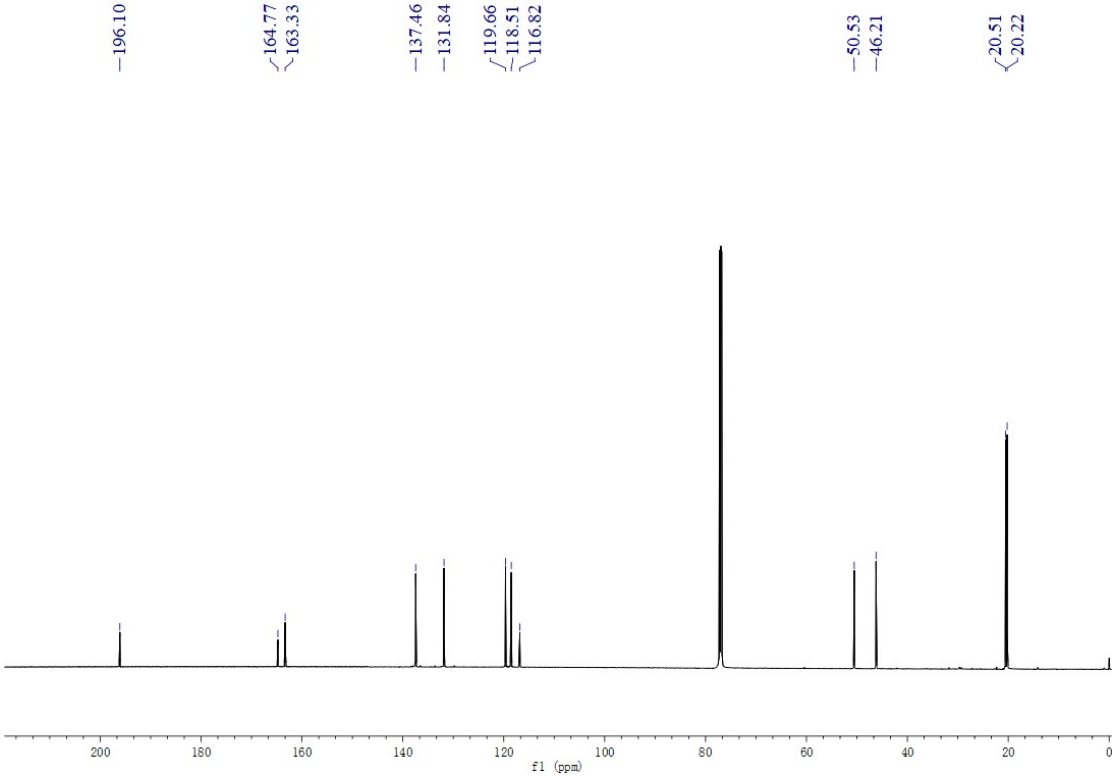


^{1}H and ^{13}C NMR Spectra for **4a**

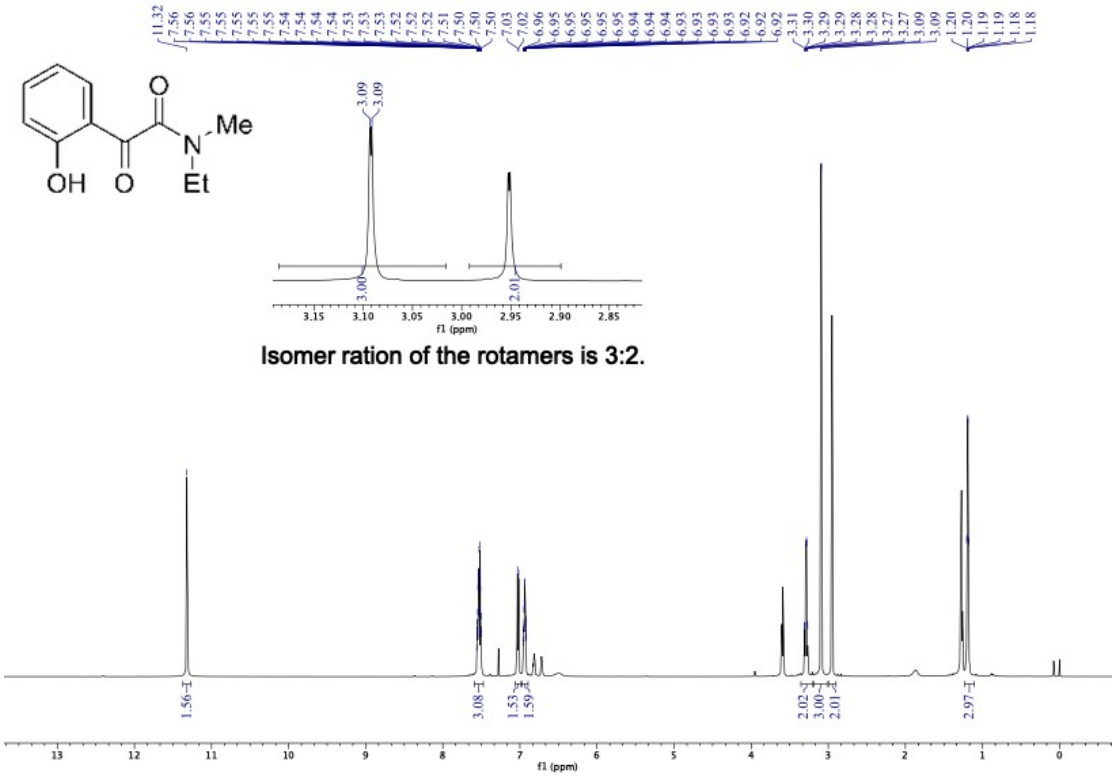


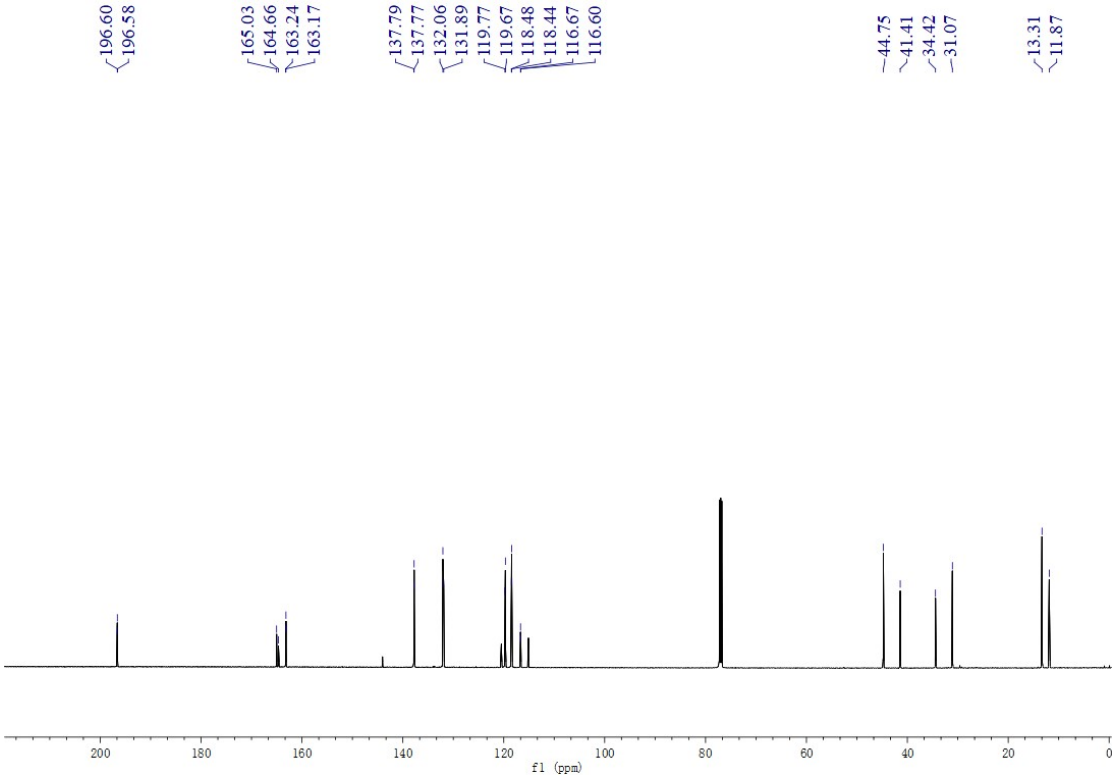
^{1}H and ^{13}C NMR Spectra for **4b**



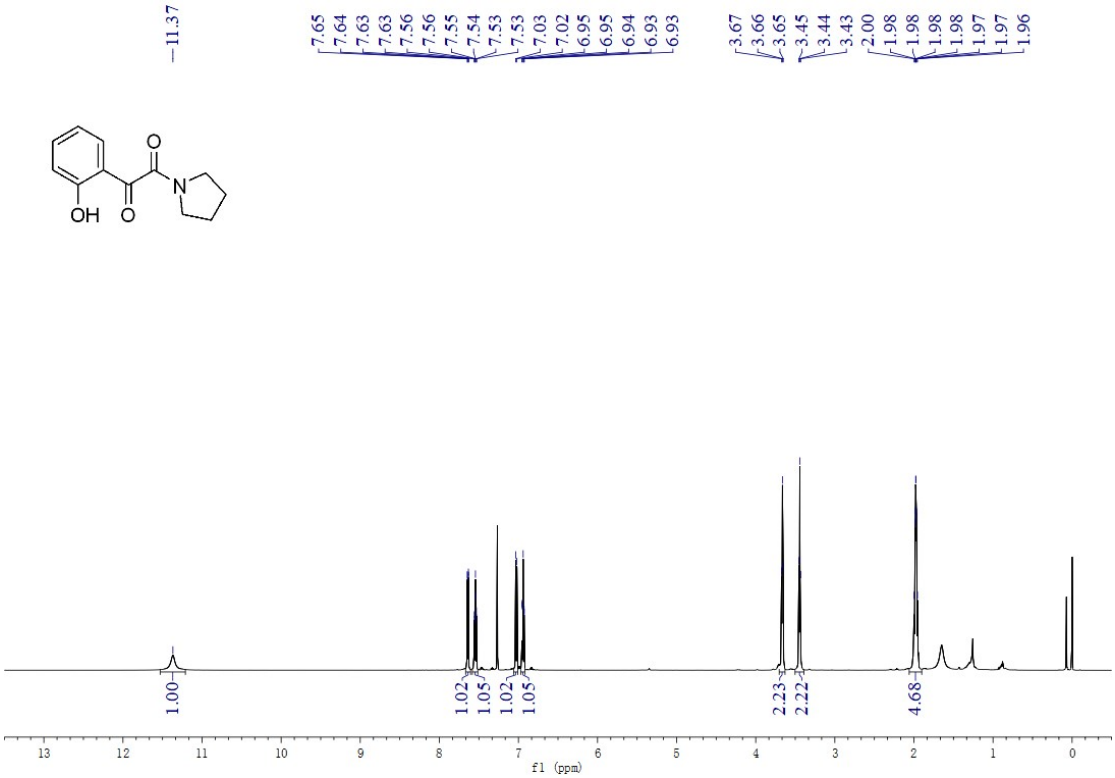


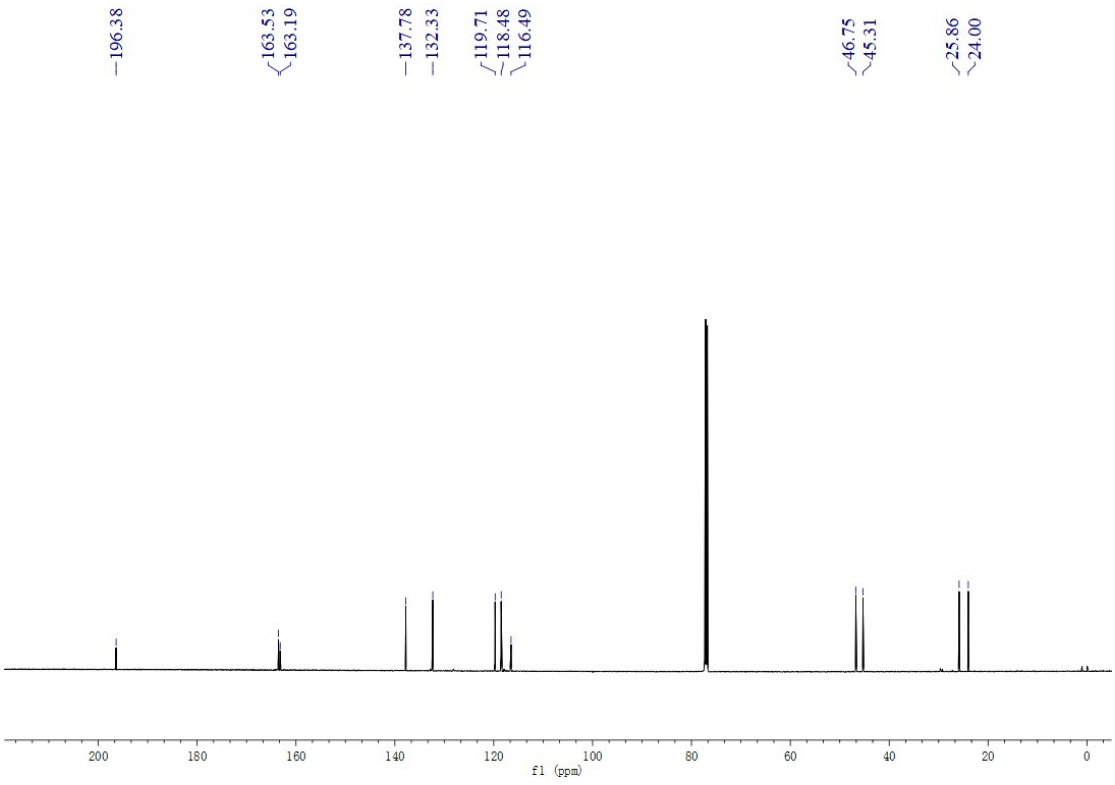
^{1}H and ^{13}C NMR Spectra for **4c**



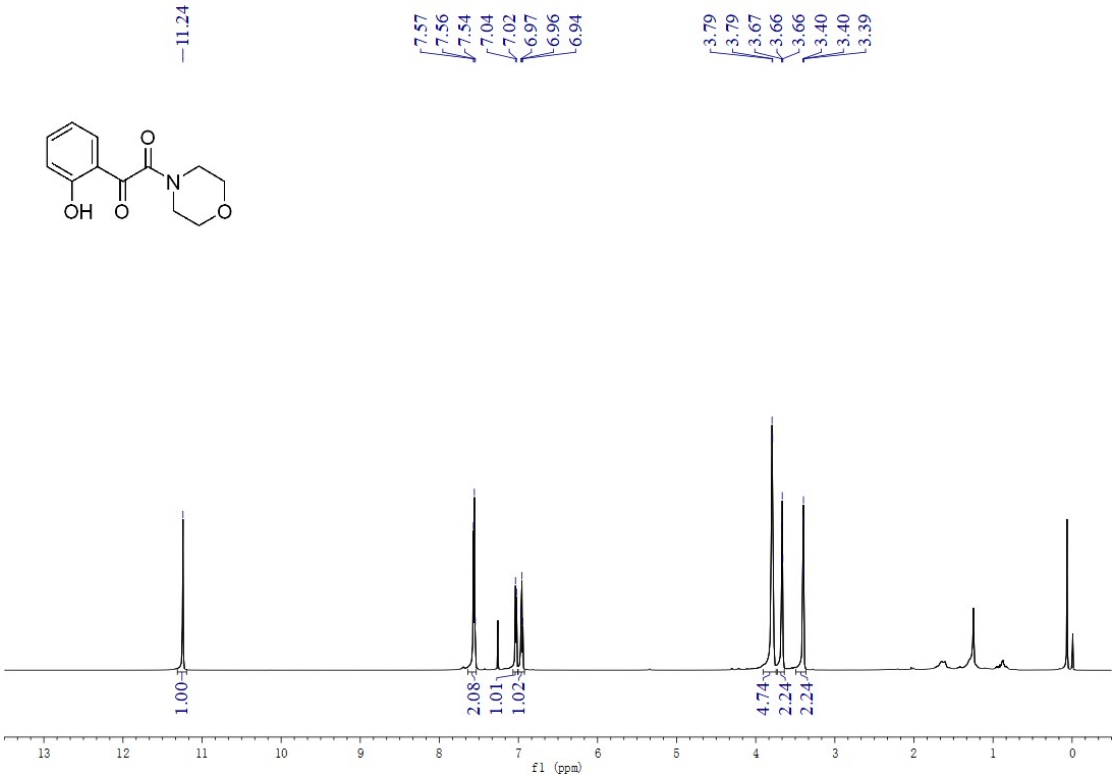


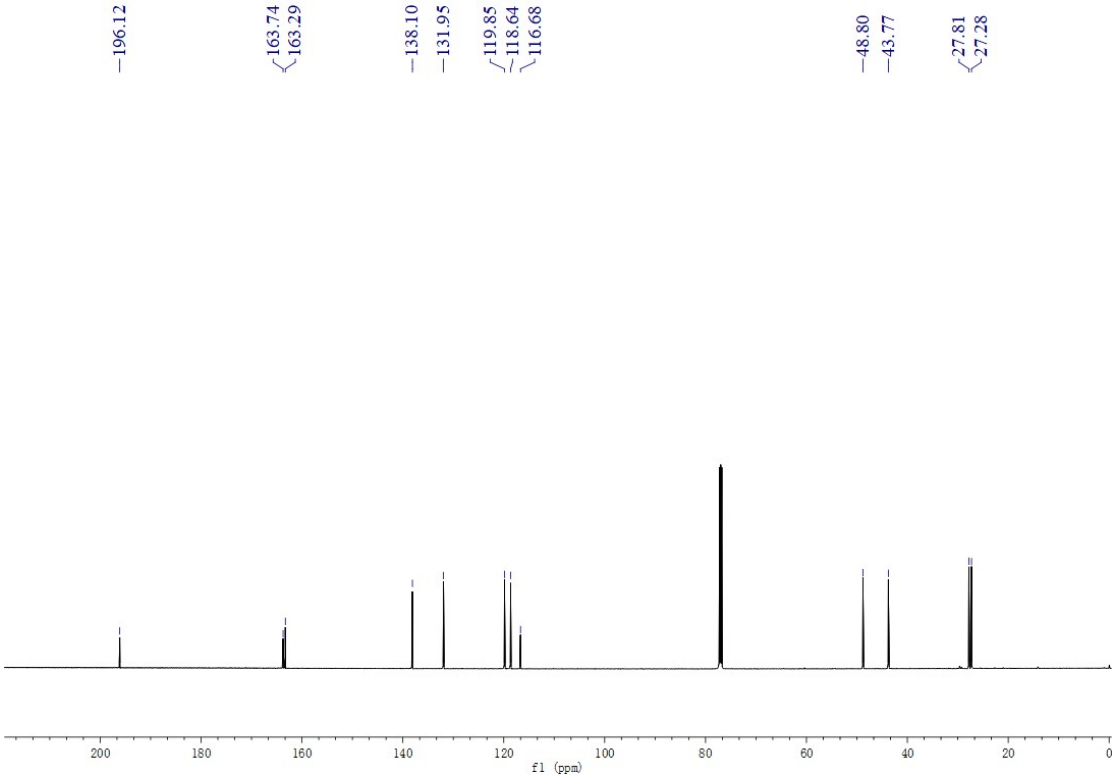
^{1}H and ^{13}C NMR Spectra for **4d**



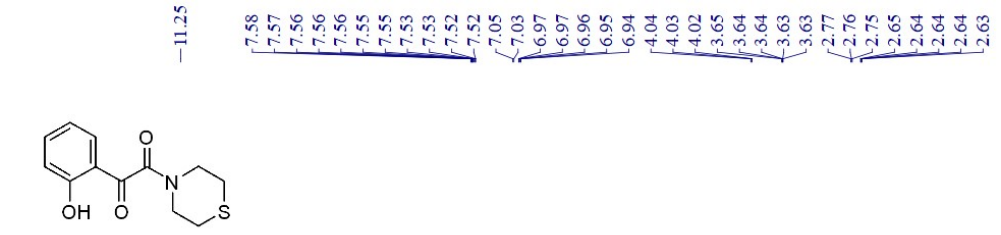


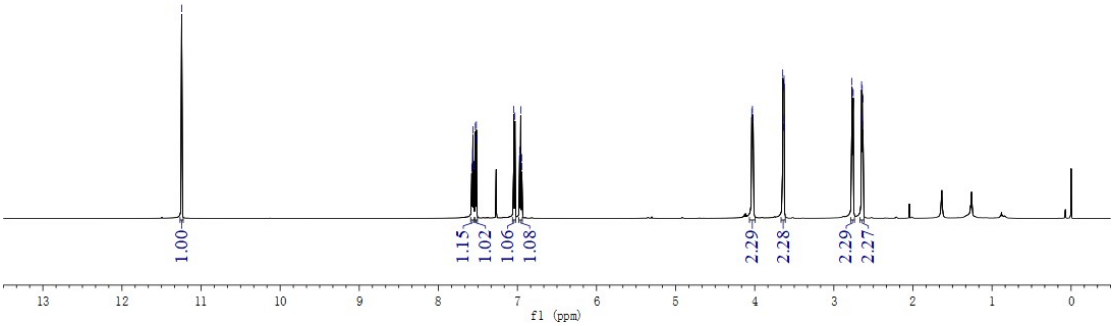
^{1}H and ^{13}C NMR Spectra for **4e**



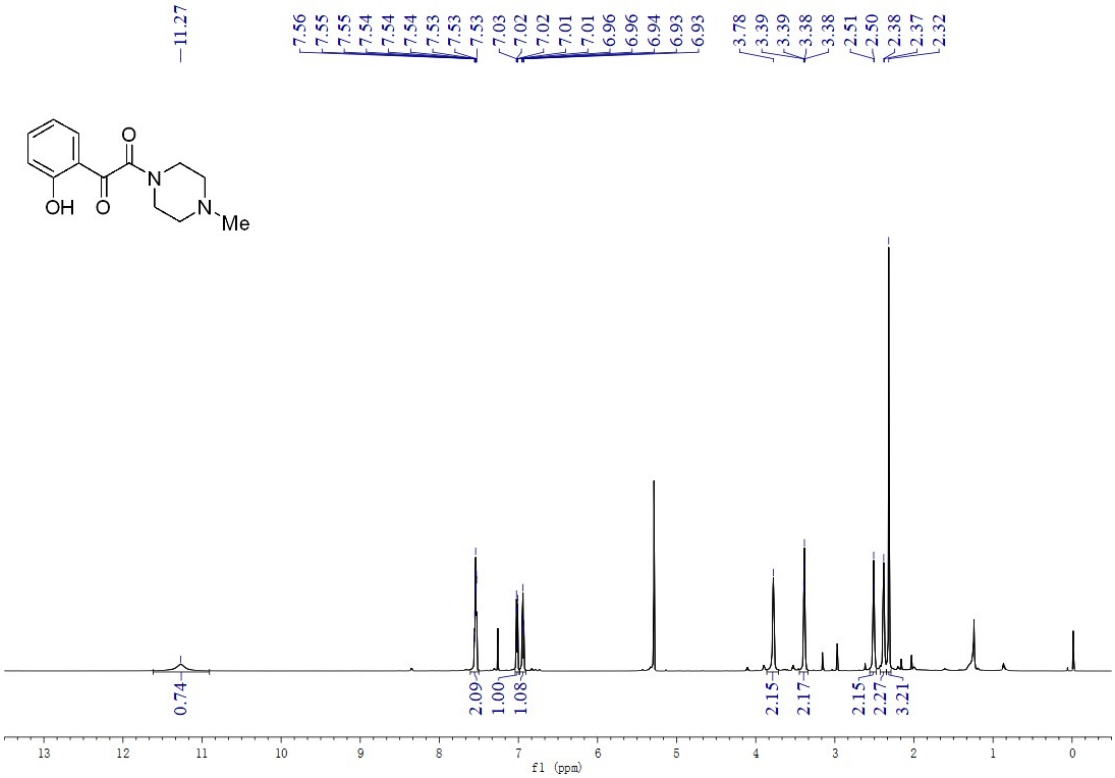


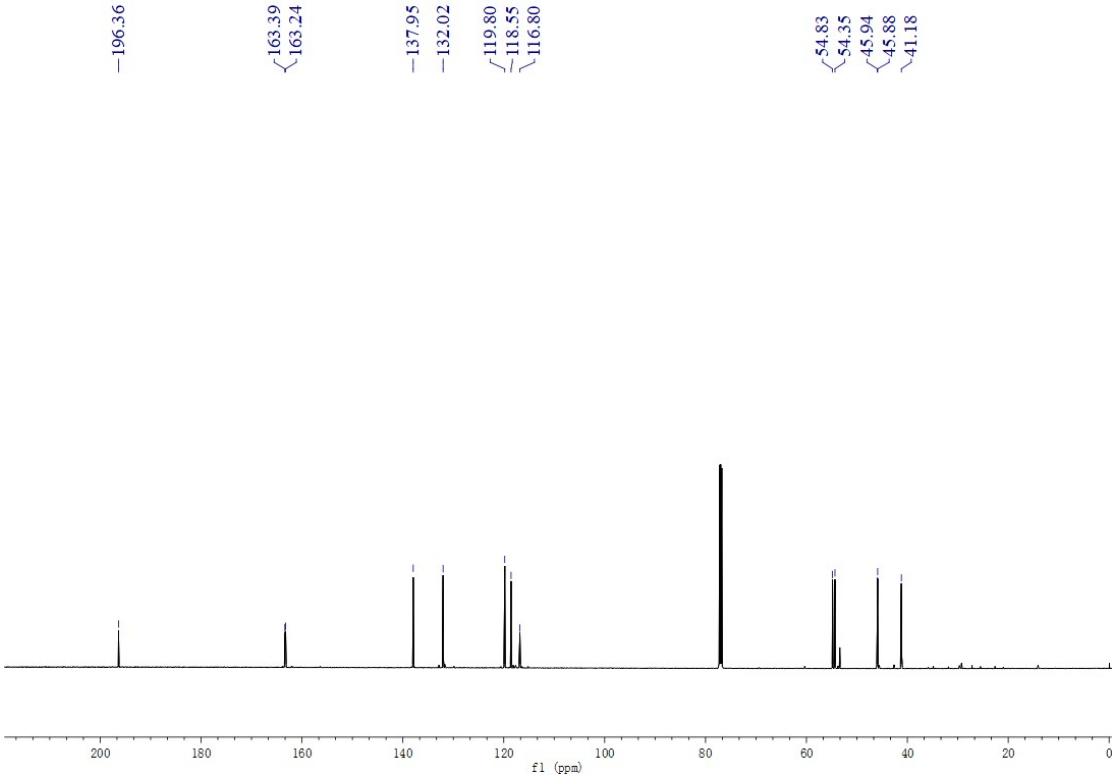
^{1}H and ^{13}C NMR Spectra for **4f**



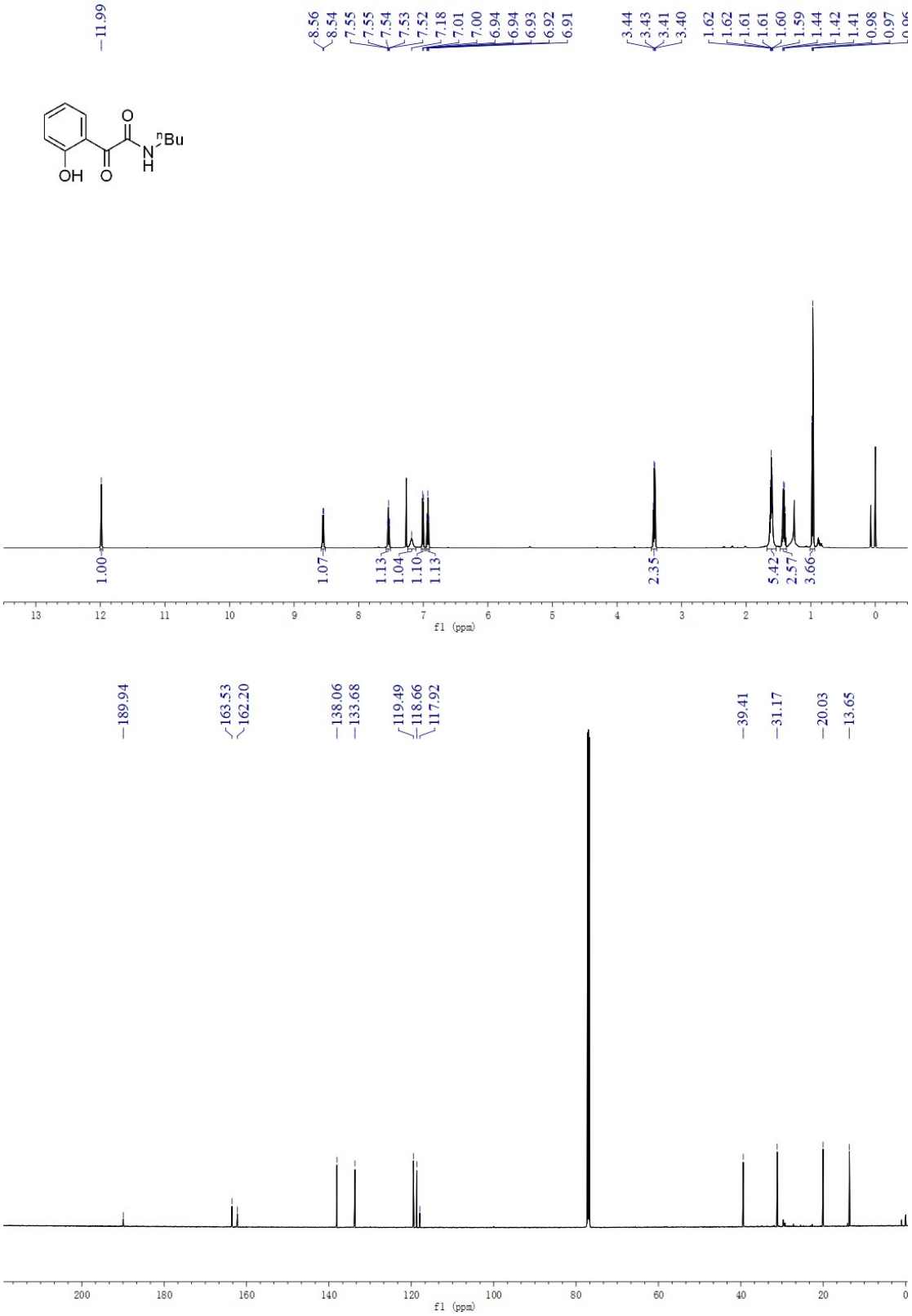


^{1}H and ^{13}C NMR Spectra for **4g**

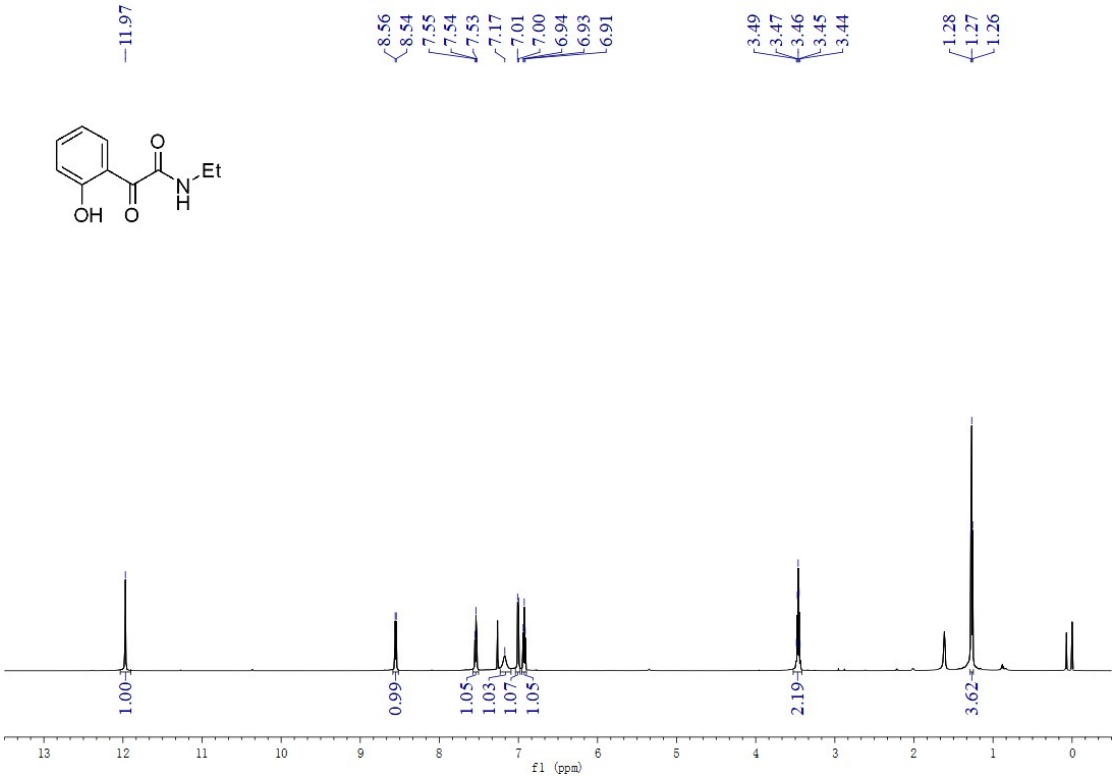


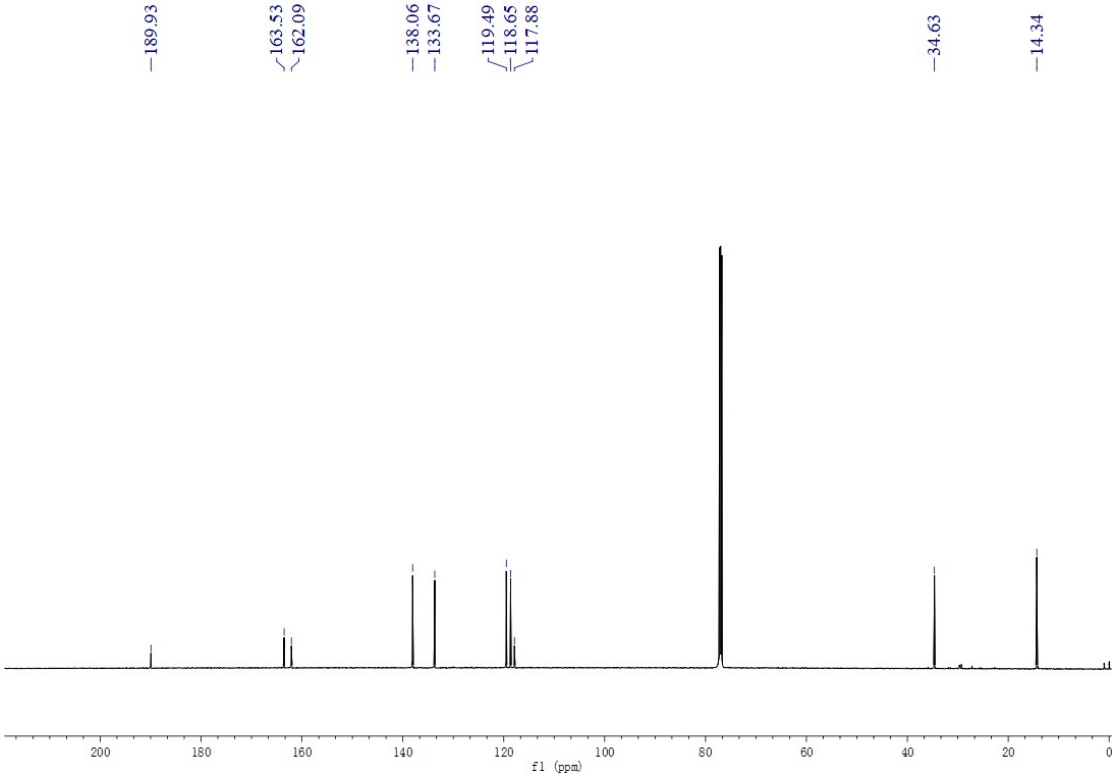


^{1}H and ^{13}C NMR Spectra for **4h**

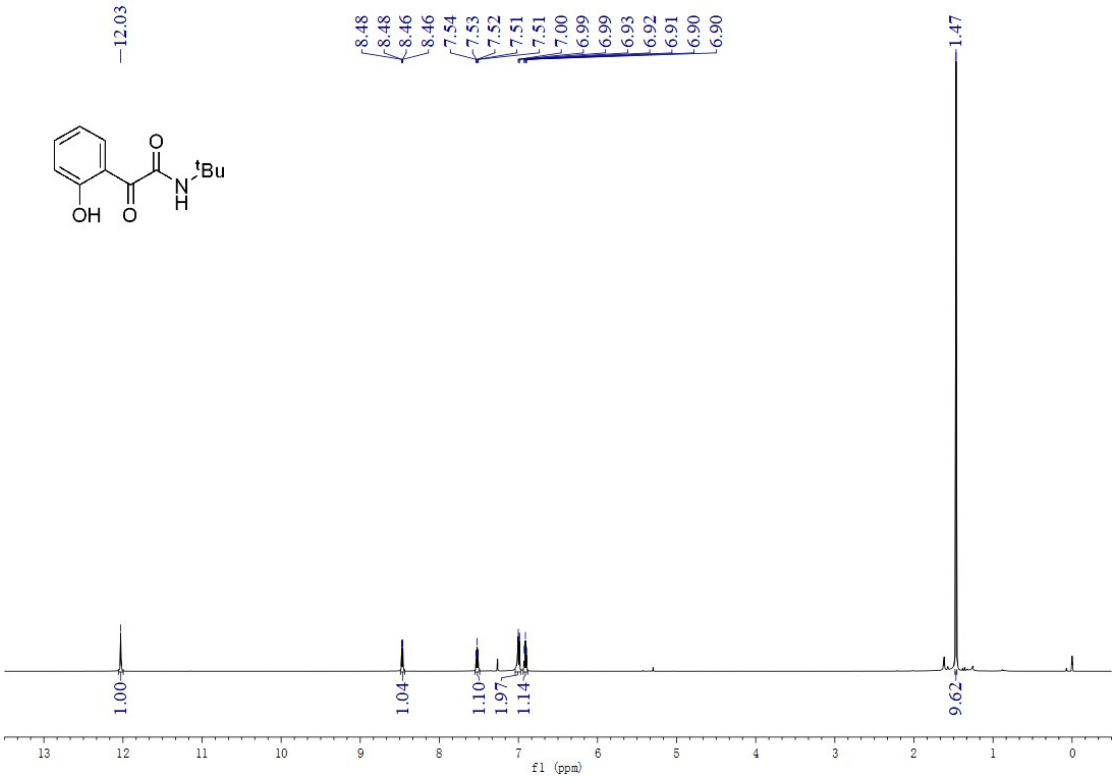


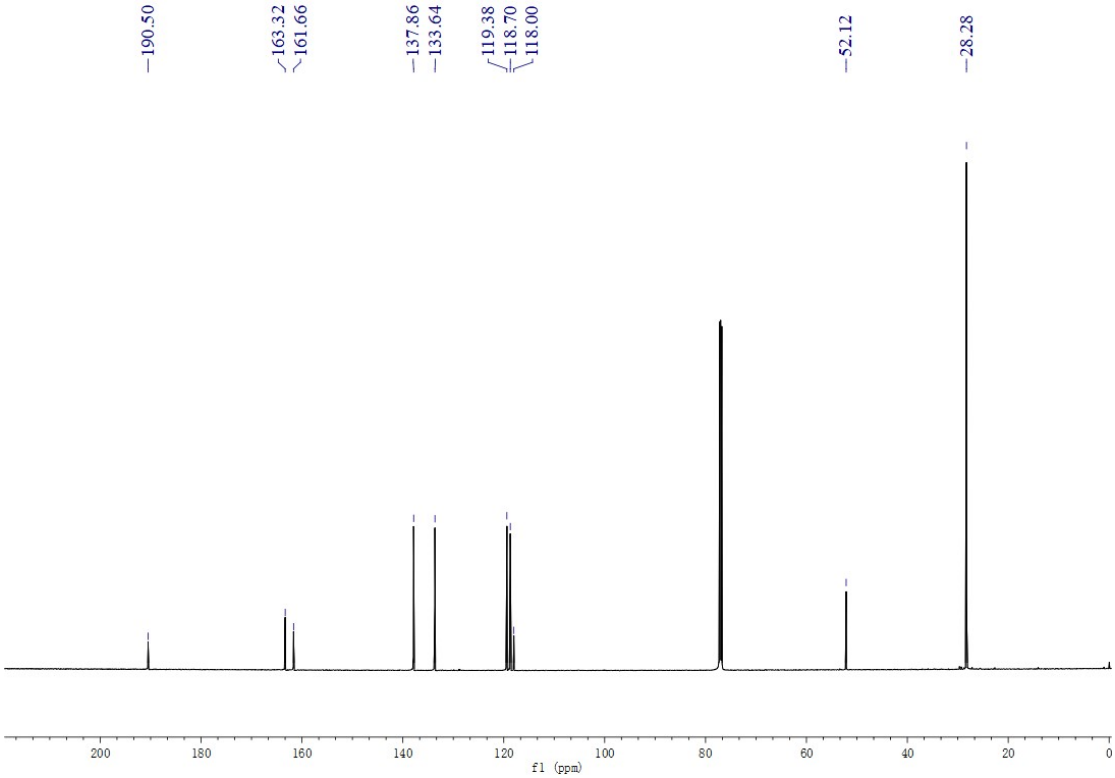
^{1}H and ^{13}C NMR Spectra for **4i**



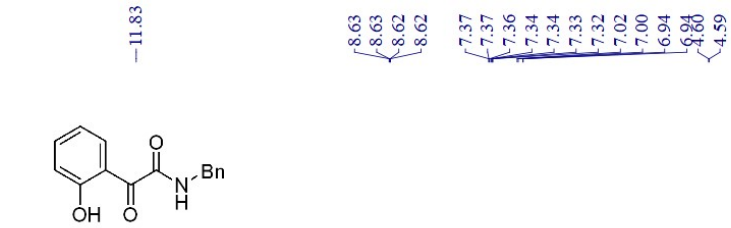


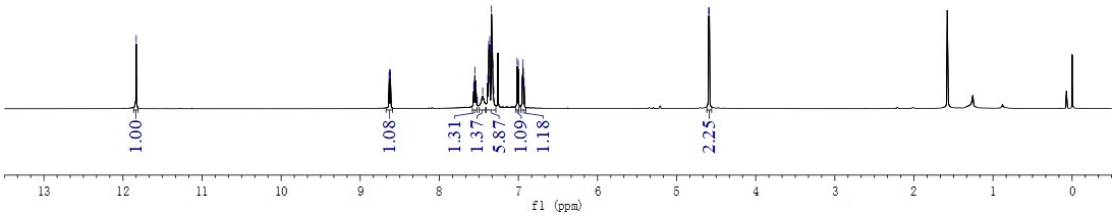
^{1}H and ^{13}C NMR Spectra for **4j**

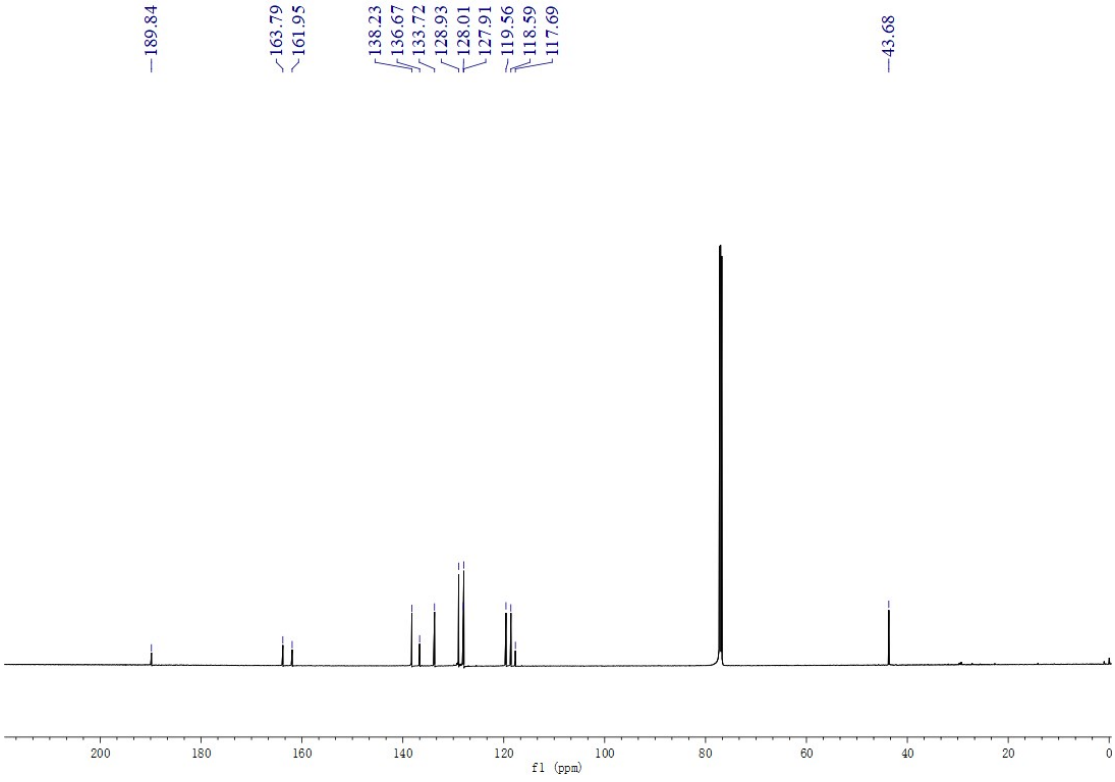




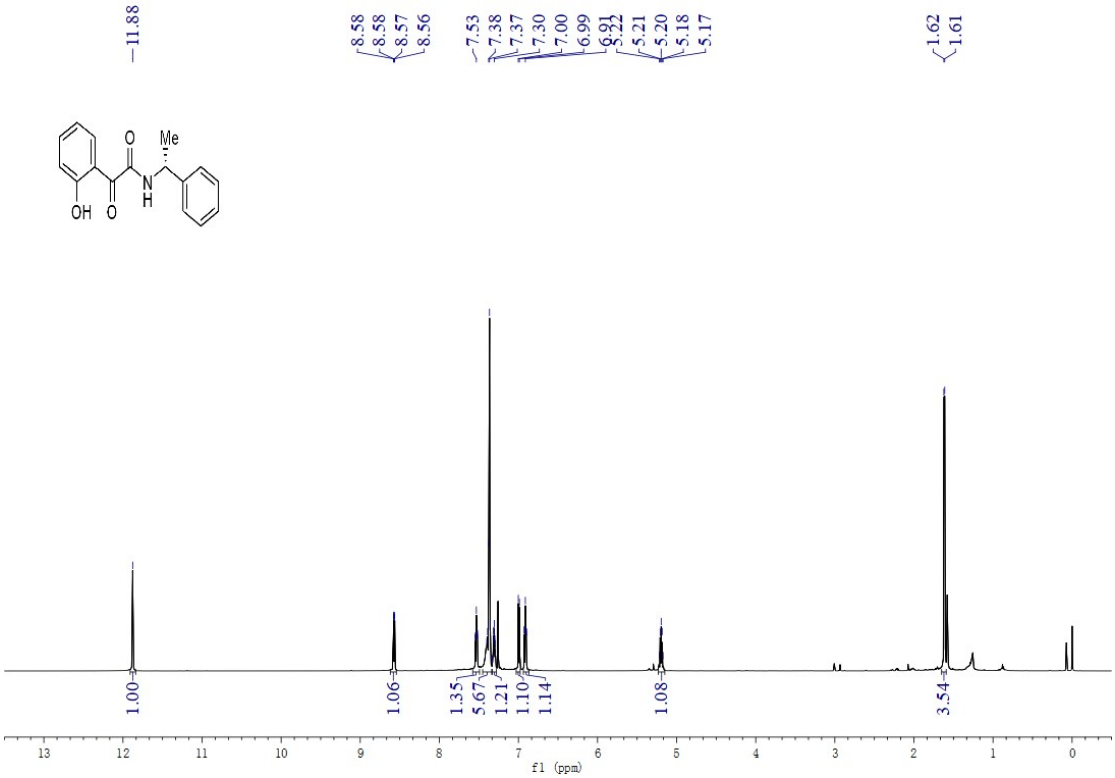
^{1}H and ^{13}C NMR Spectra for **4k**

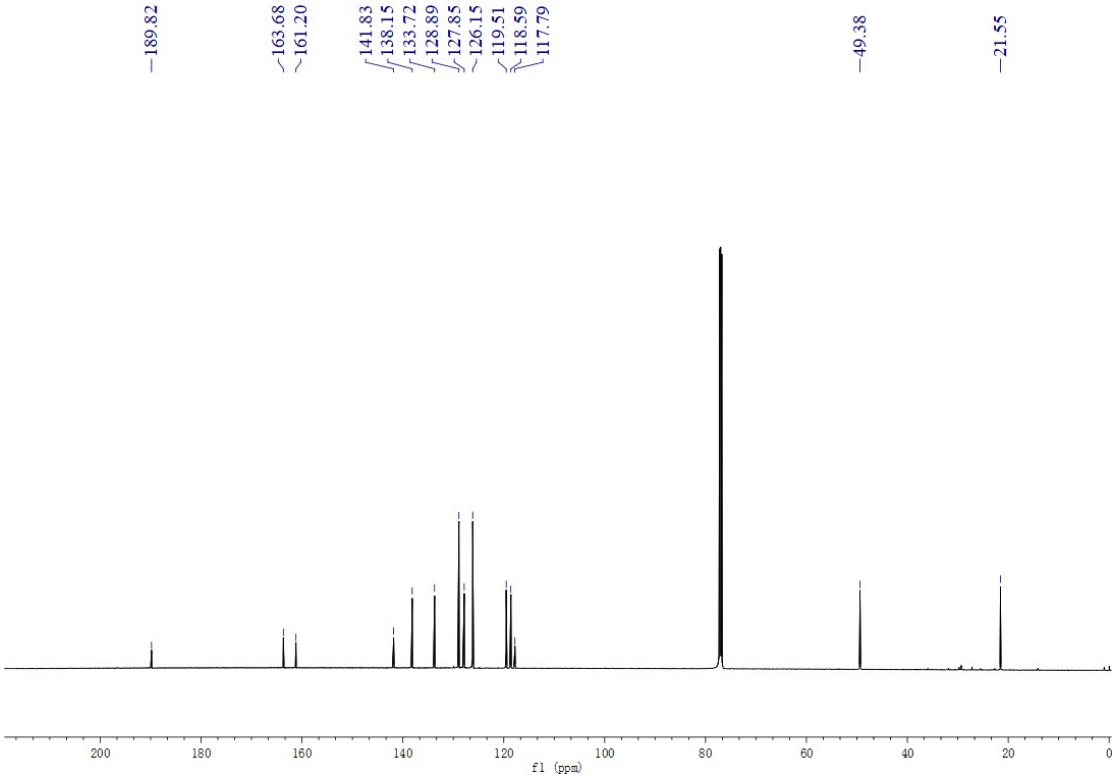




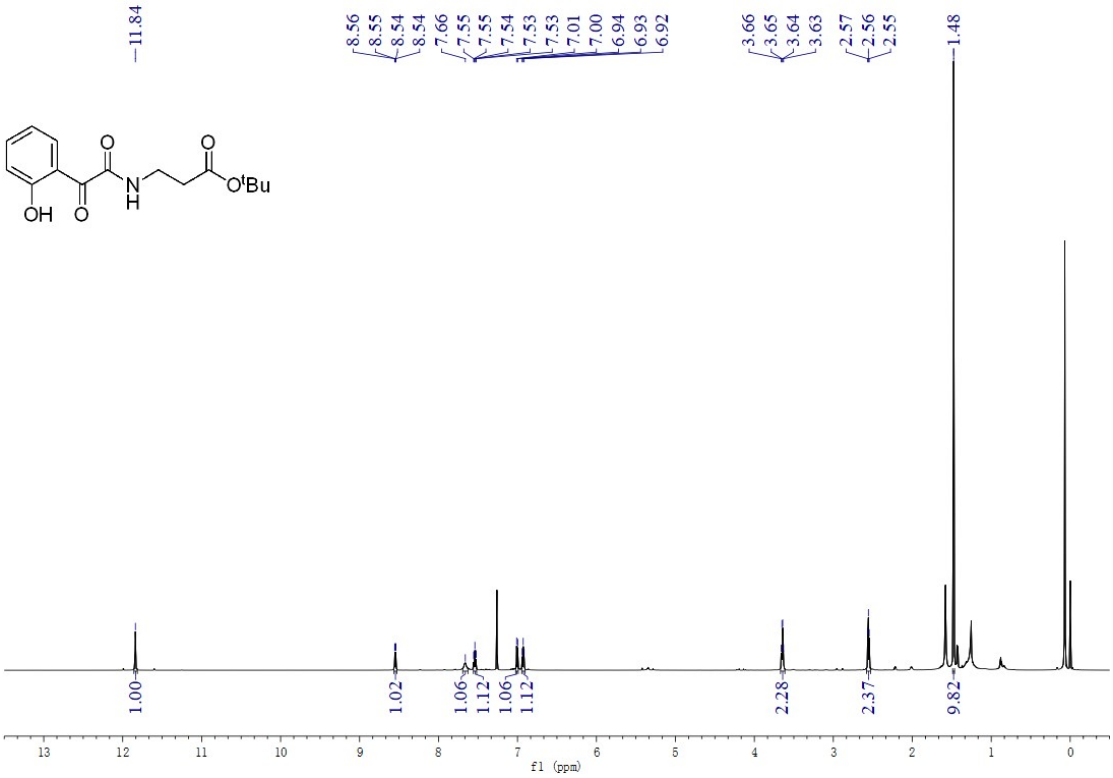


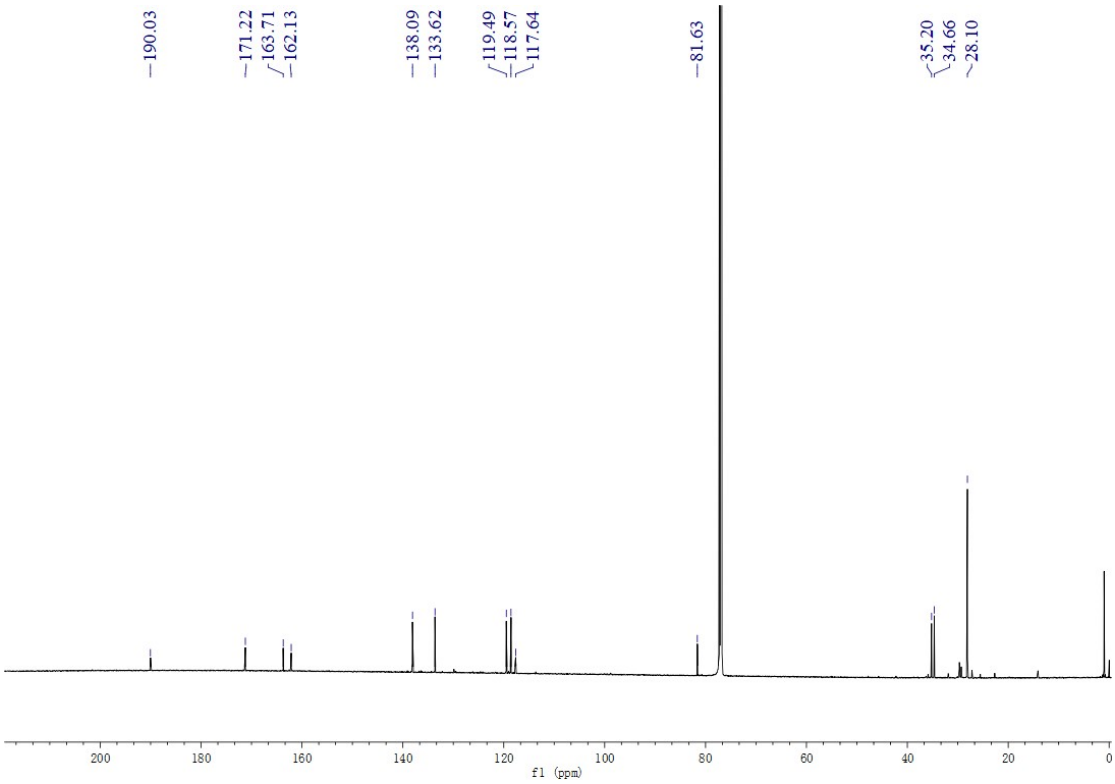
^{1}H and ^{13}C NMR Spectra for **4l**



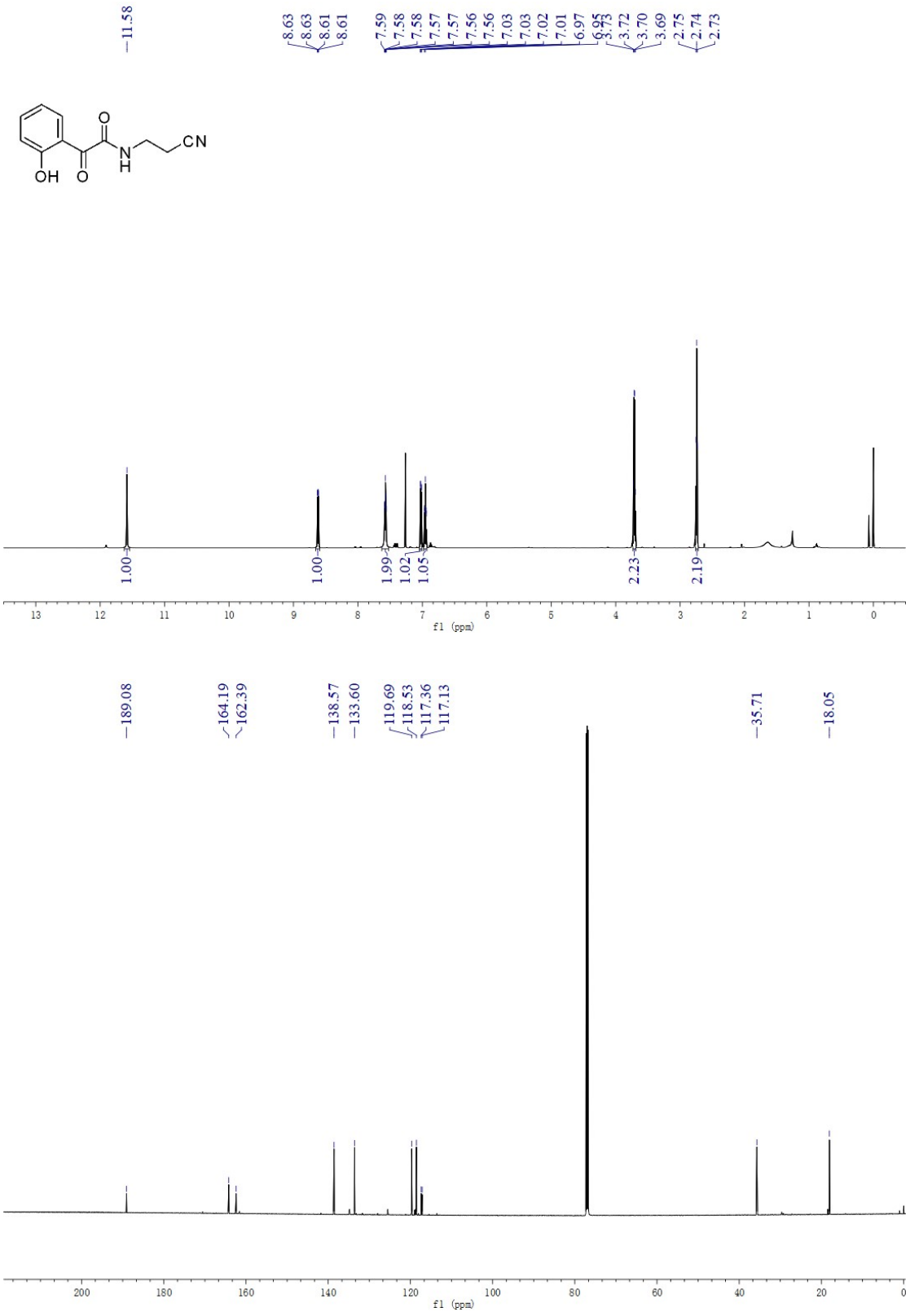


^{1}H and ^{13}C NMR Spectra for **4m**

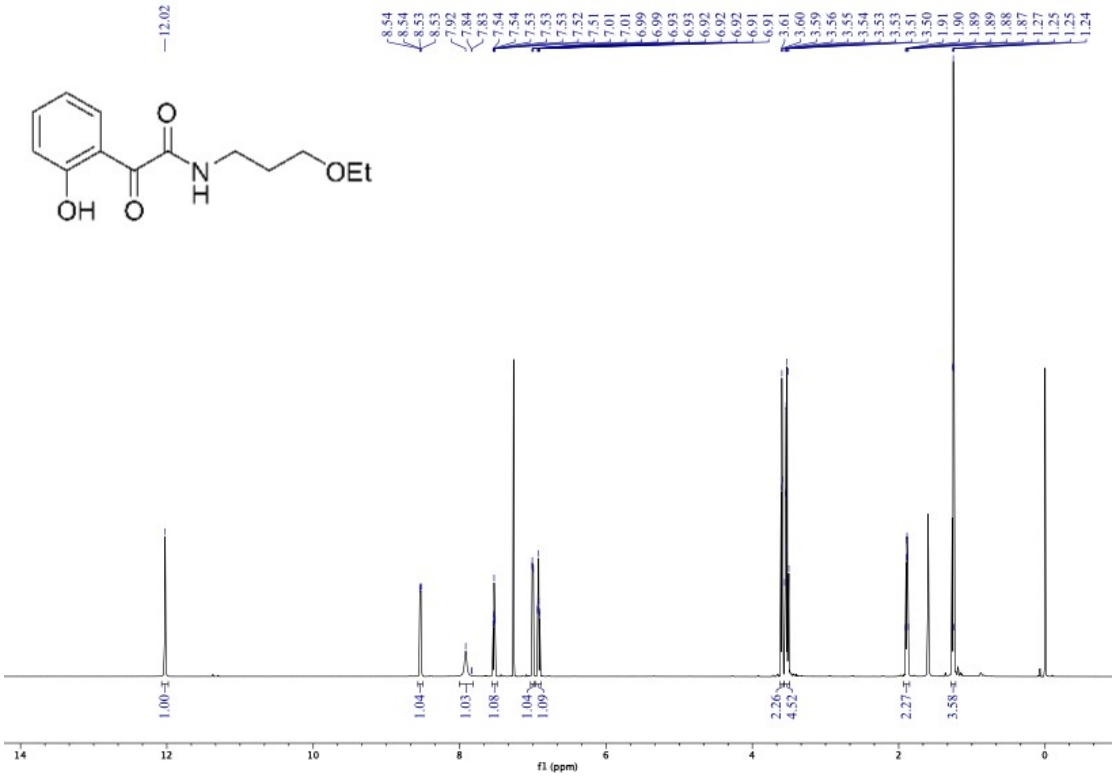


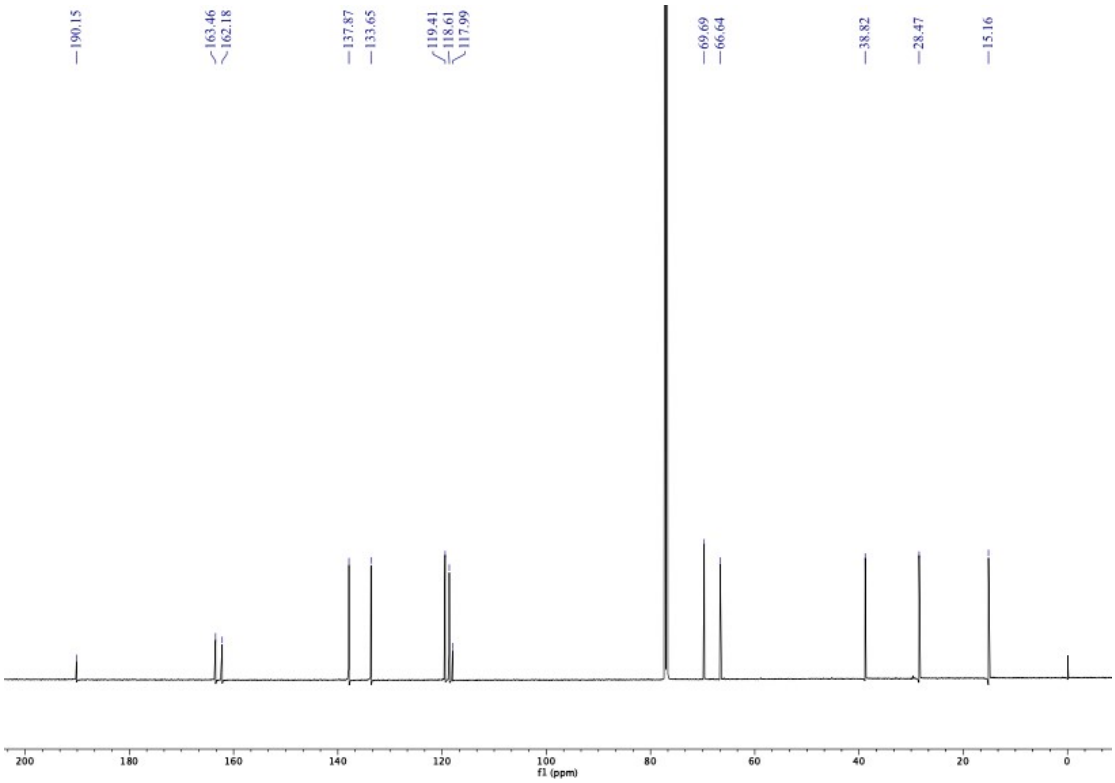


^{1}H and ^{13}C NMR Spectra for **4n**

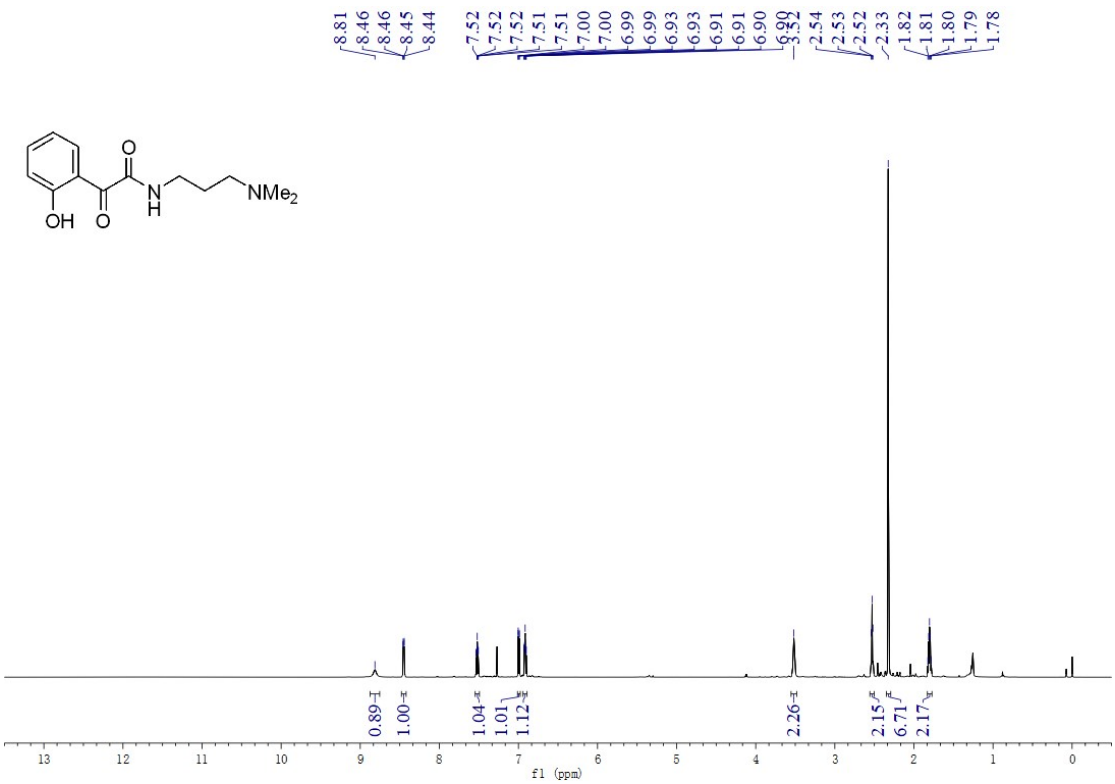


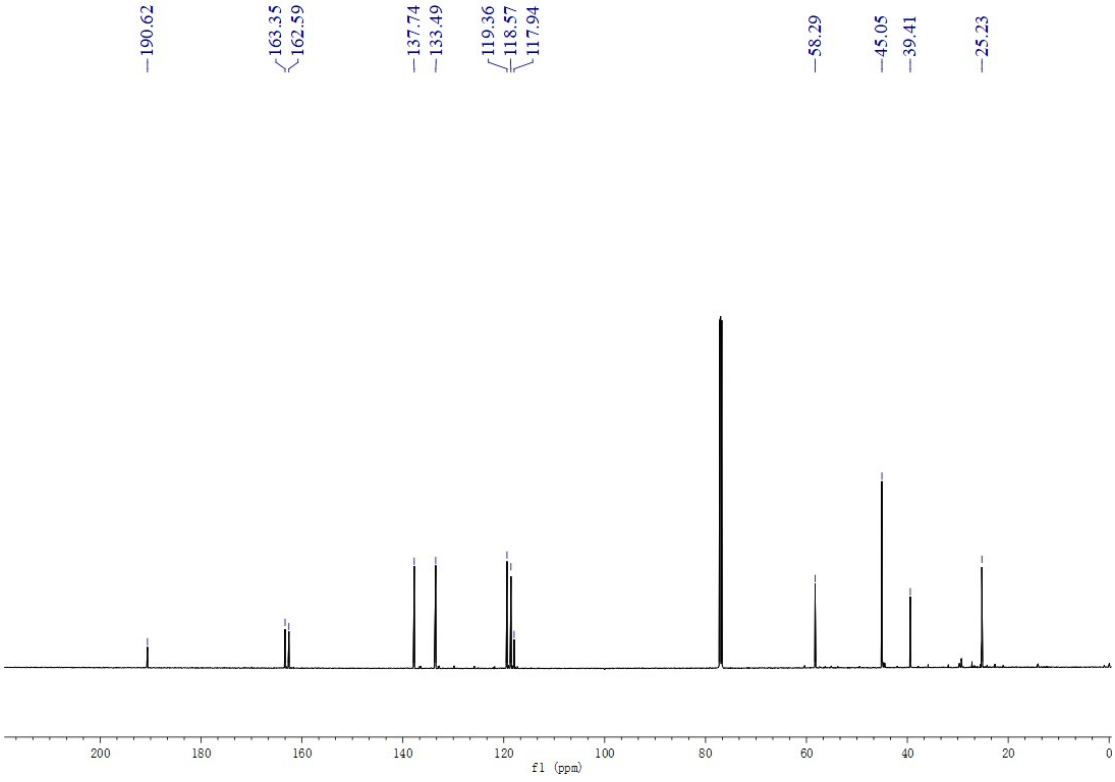
^{1}H and ^{13}C NMR Spectra for **4o**



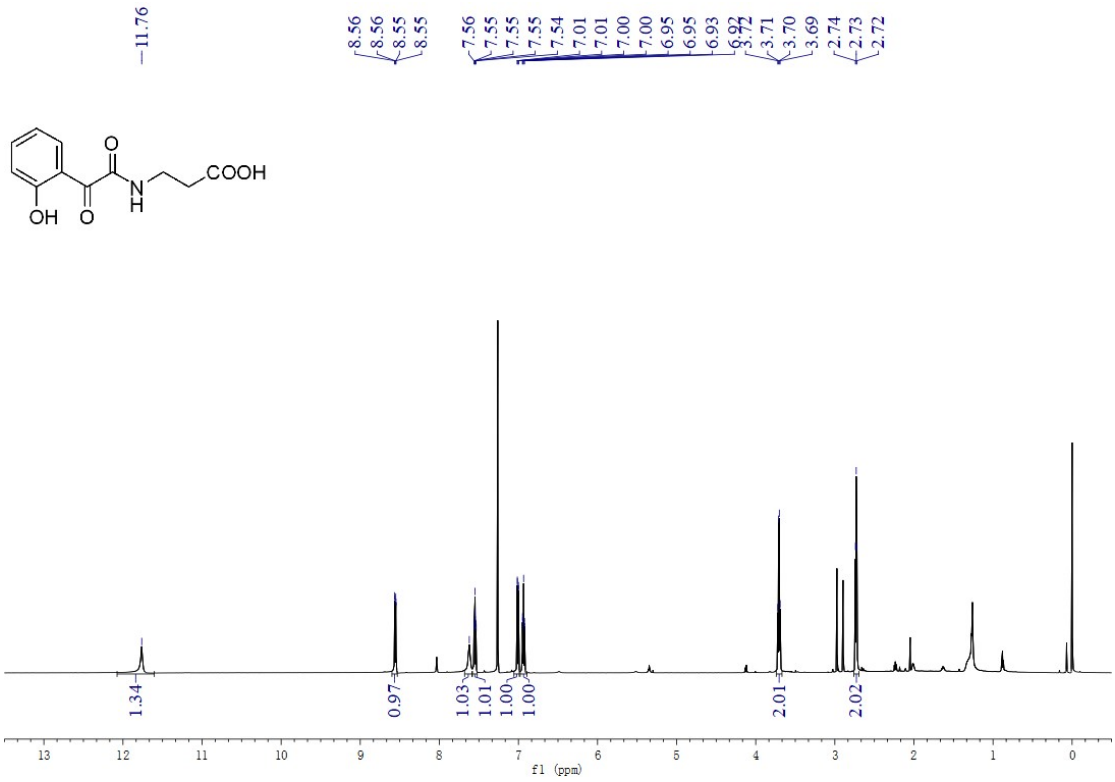


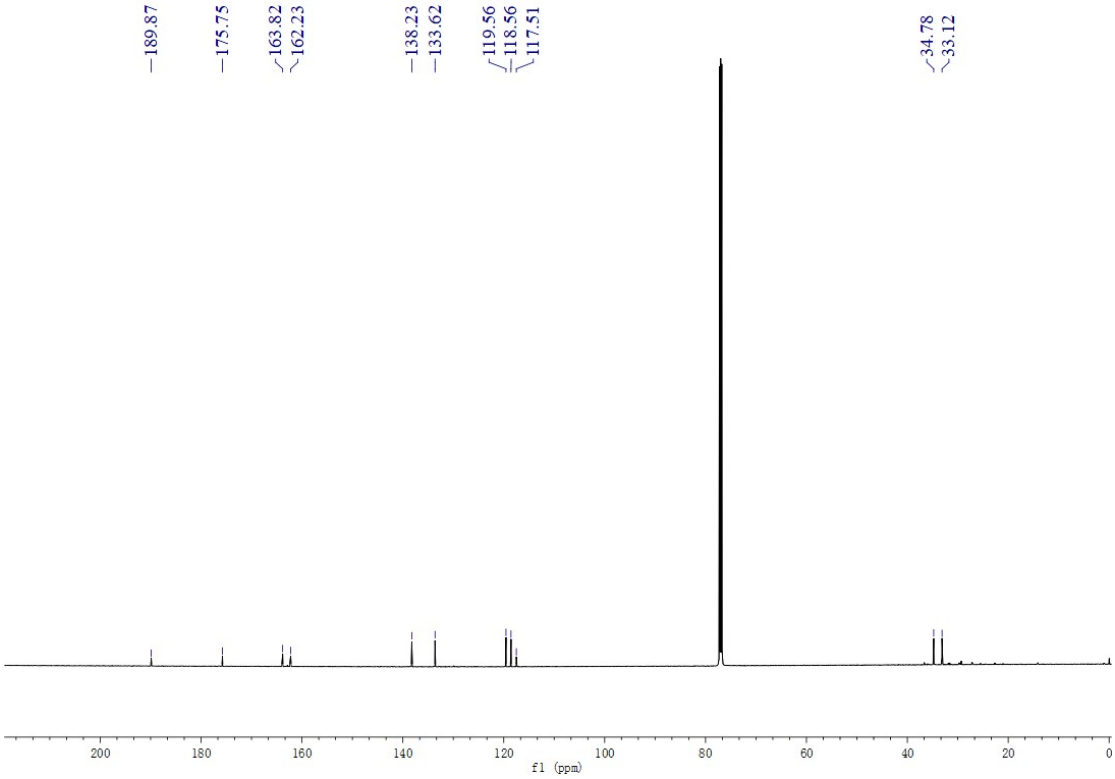
^{1}H and ^{13}C NMR Spectra for **4p**



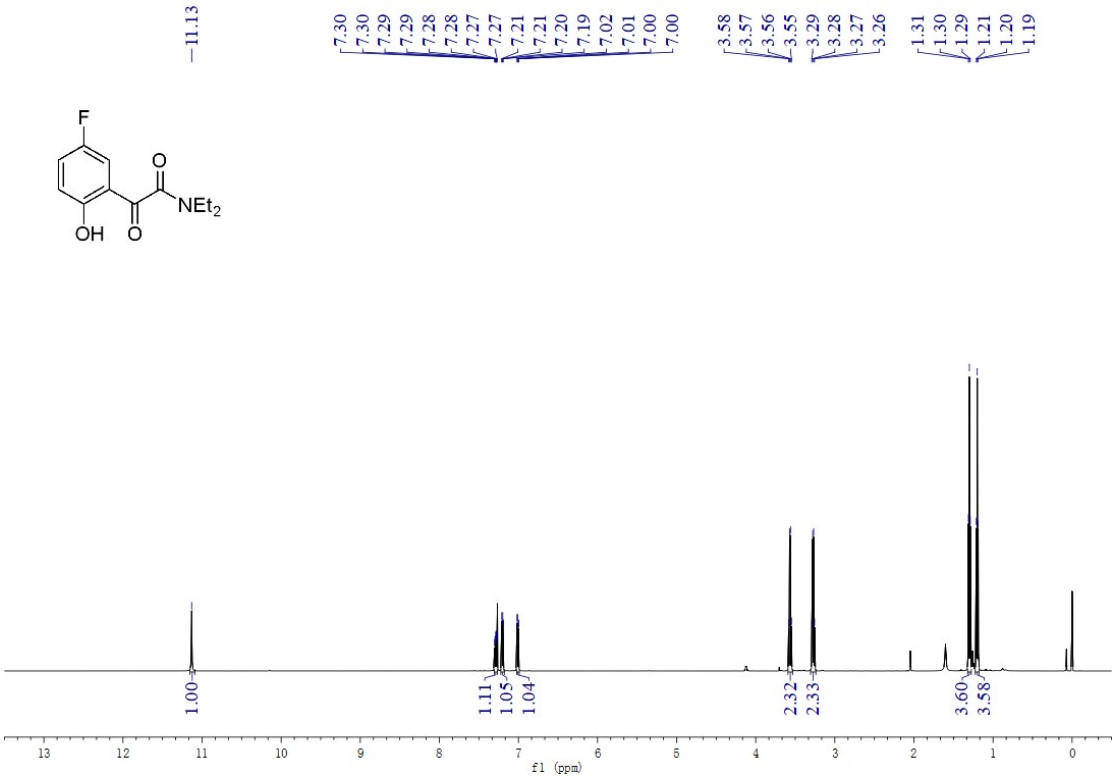


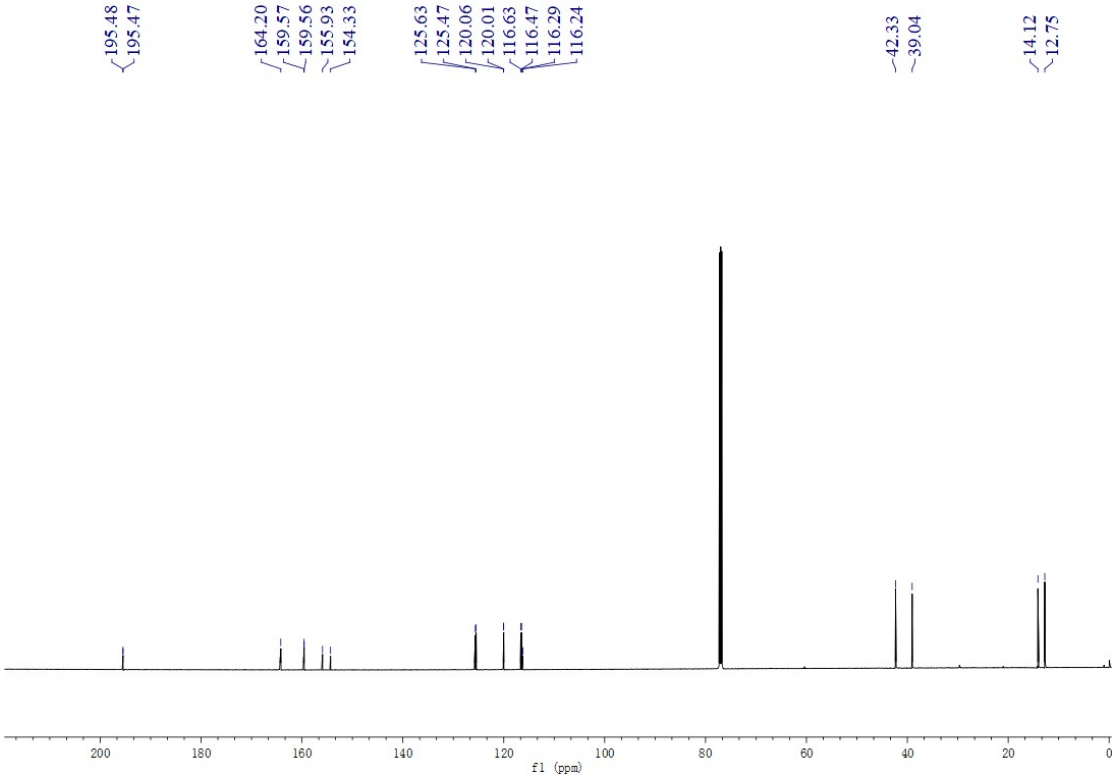
^{1}H and ^{13}C NMR Spectra for **4q**

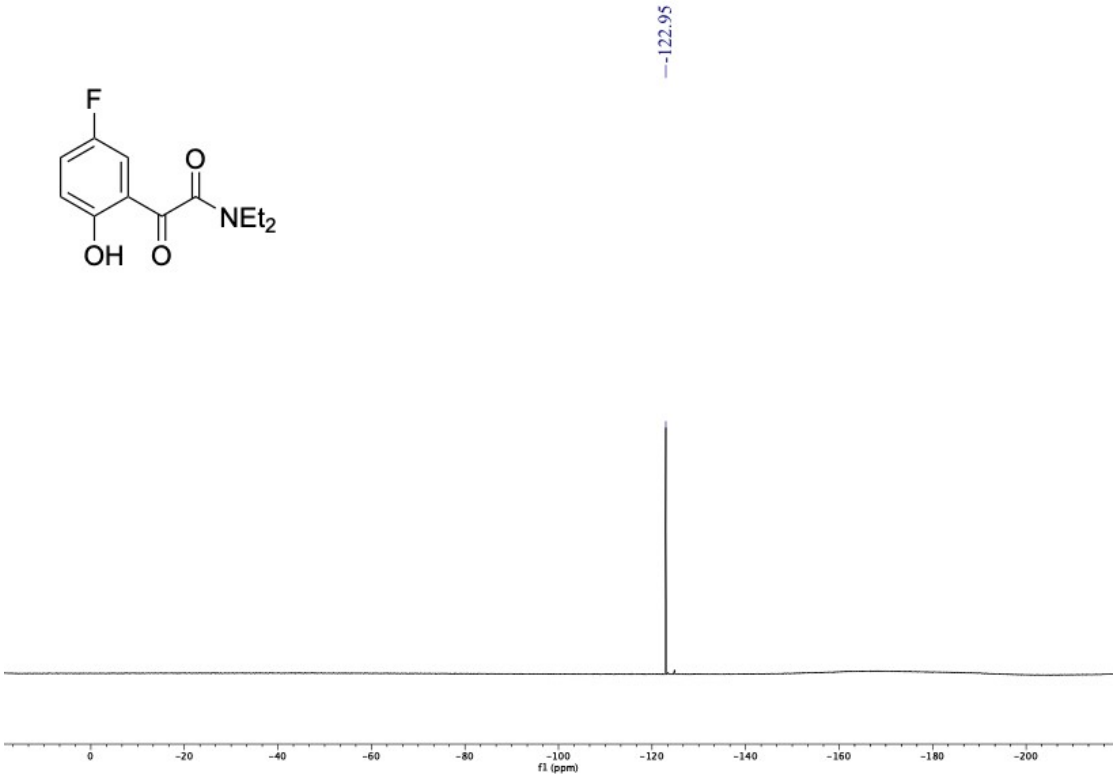




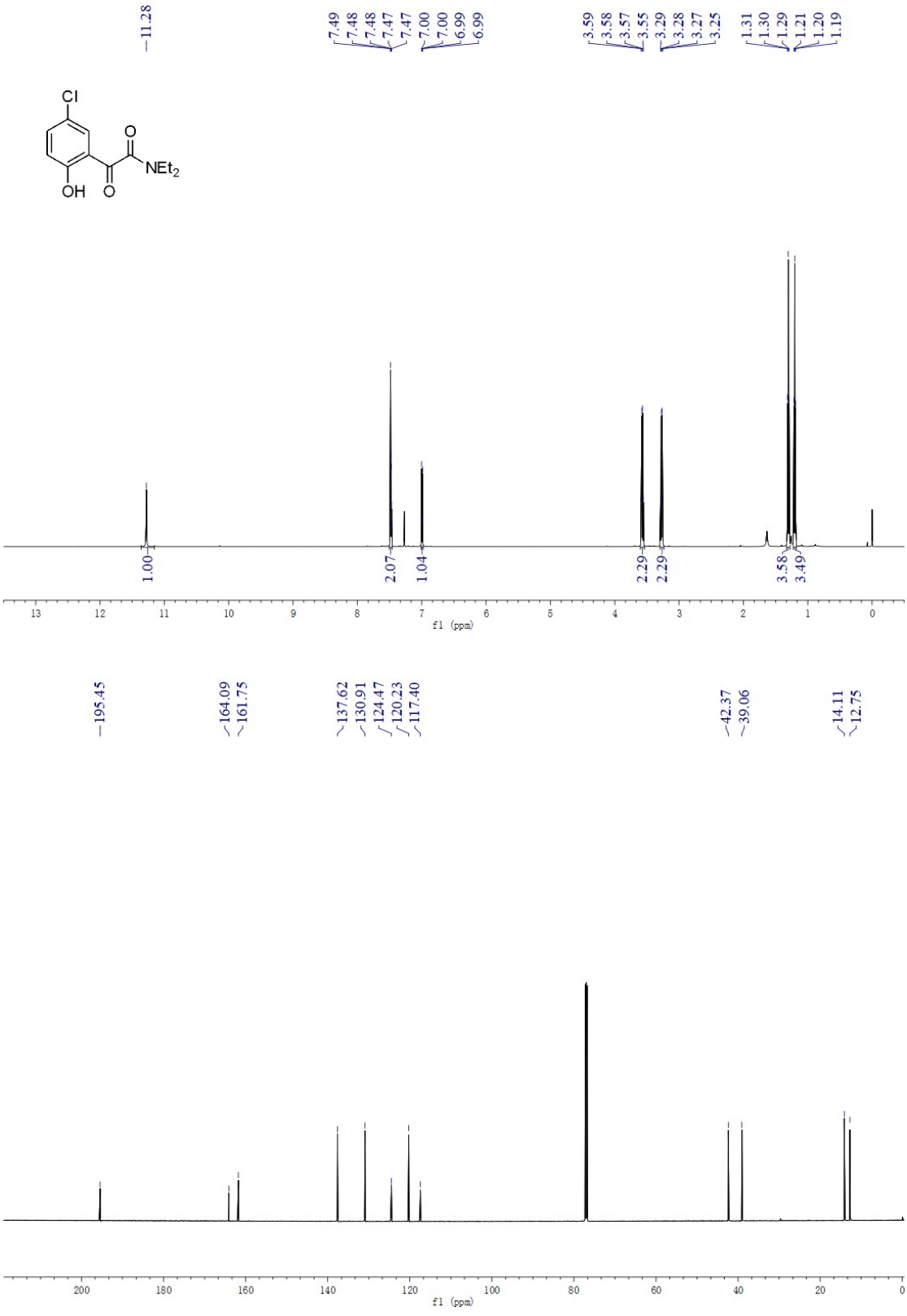
^{1}H, ^{13}C and ^{19}F NMR Spectra for **4ab**



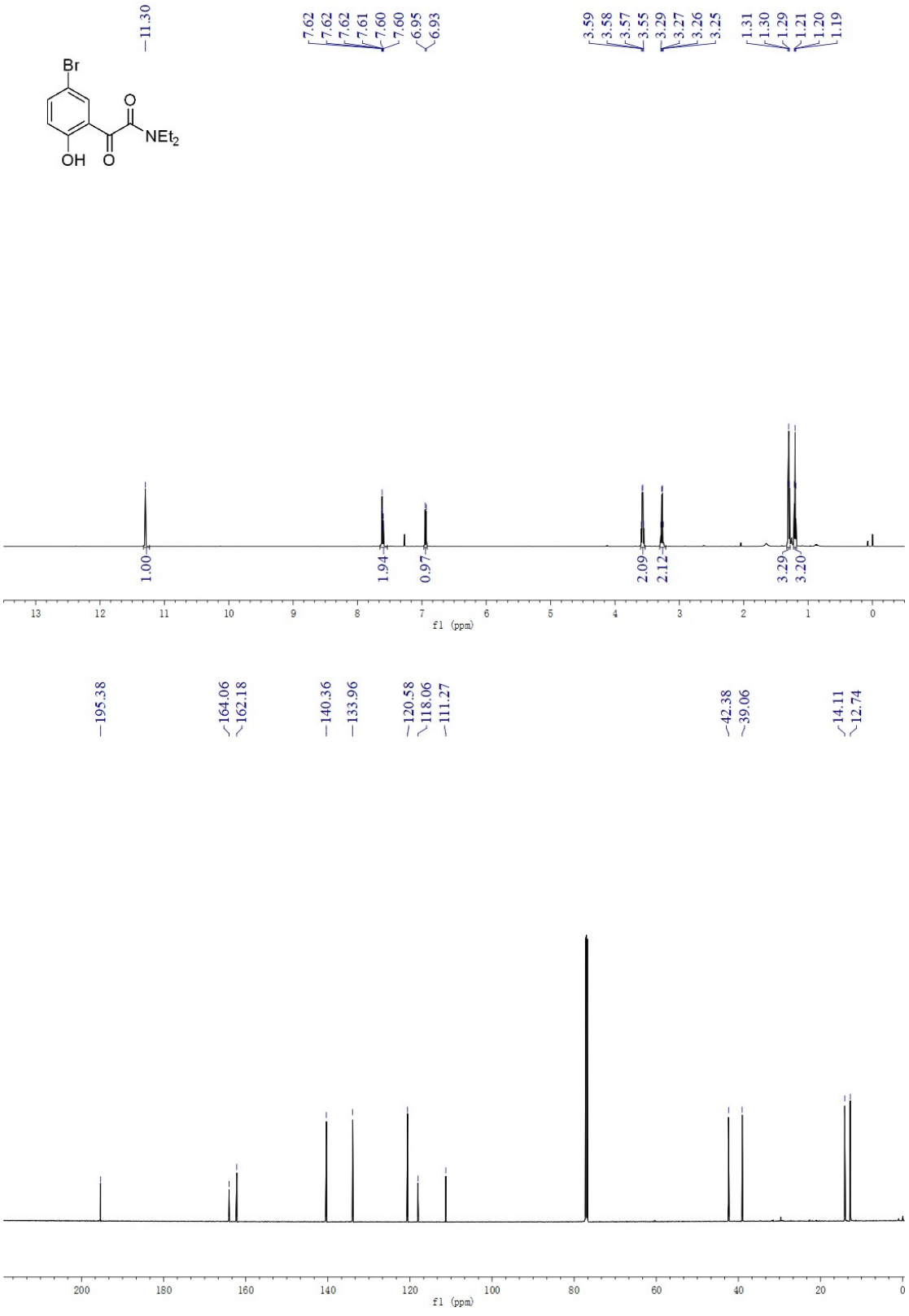




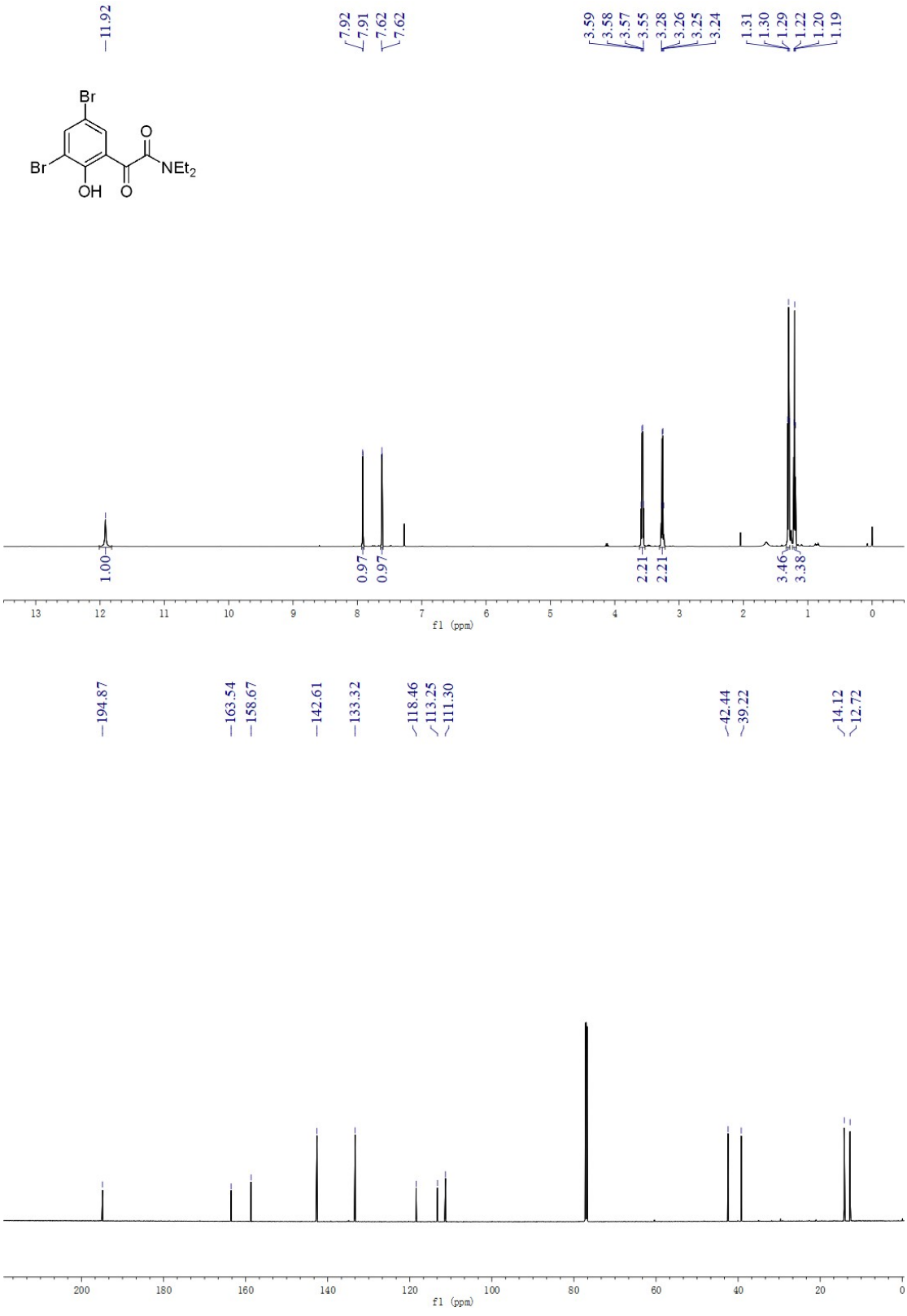
^{1}H and ^{13}C NMR Spectra for **4ac**



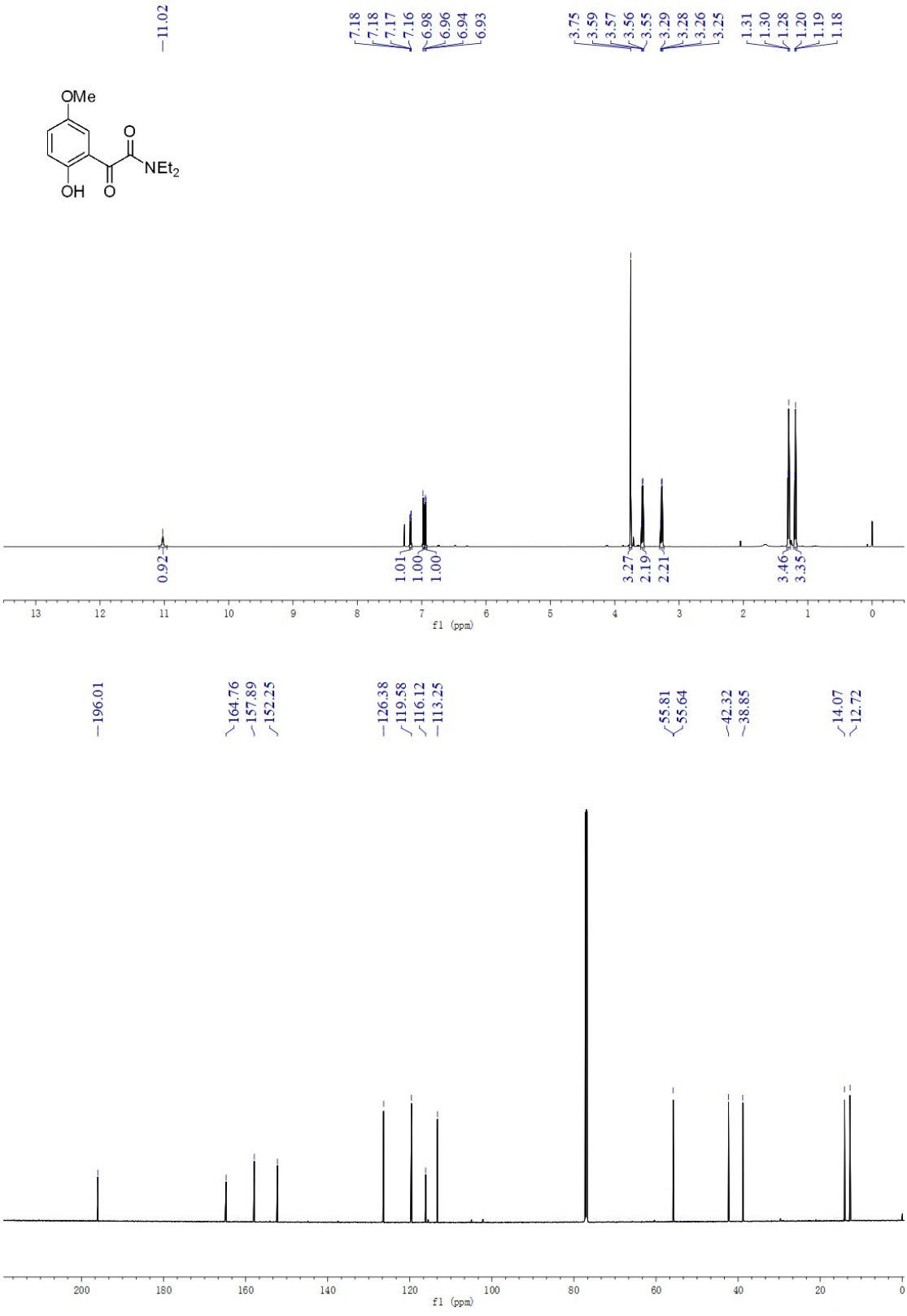
^{1}H and ^{13}C NMR Spectra for **4ad**



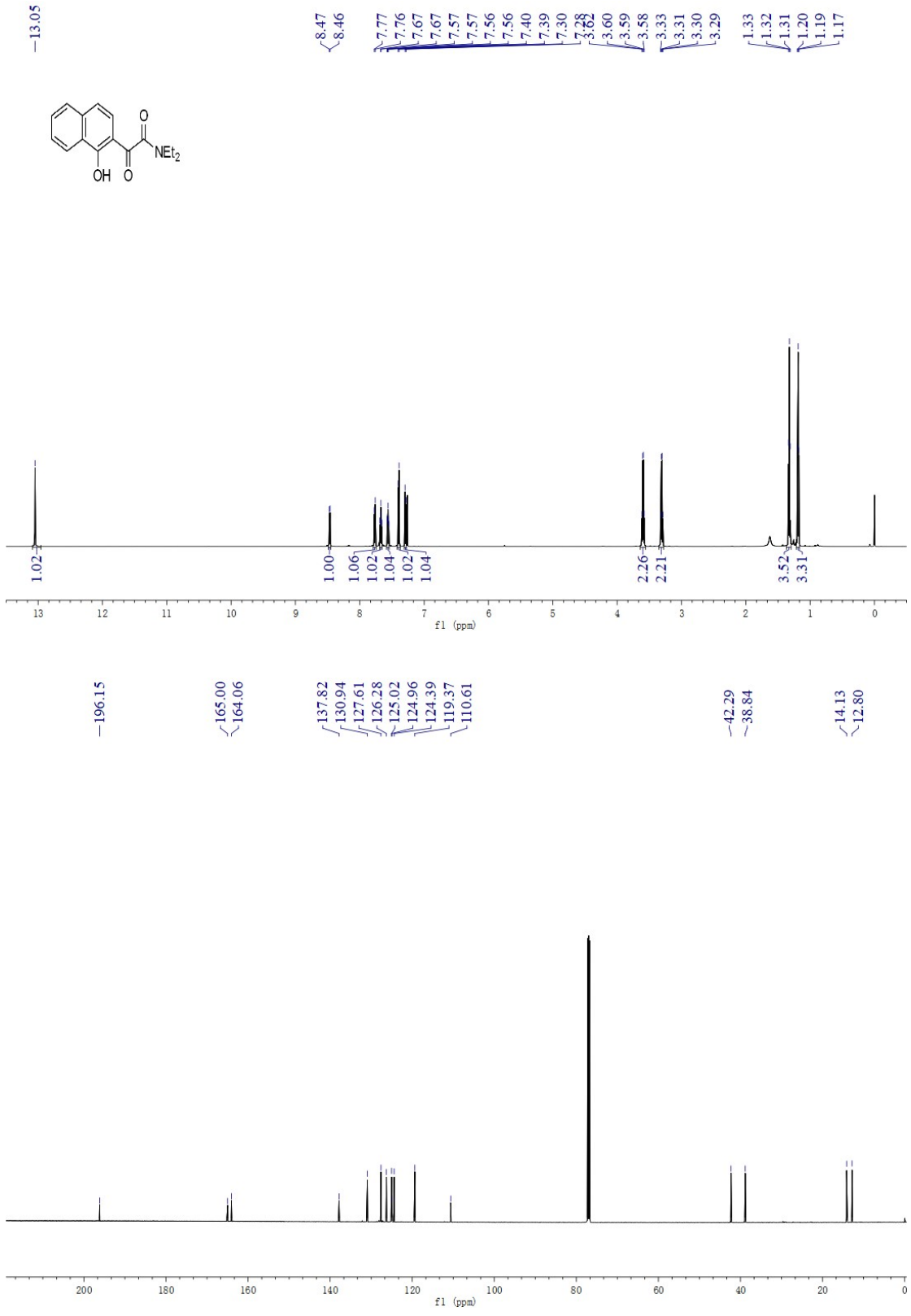
^{1}H and ^{13}C NMR Spectra for **4ae**



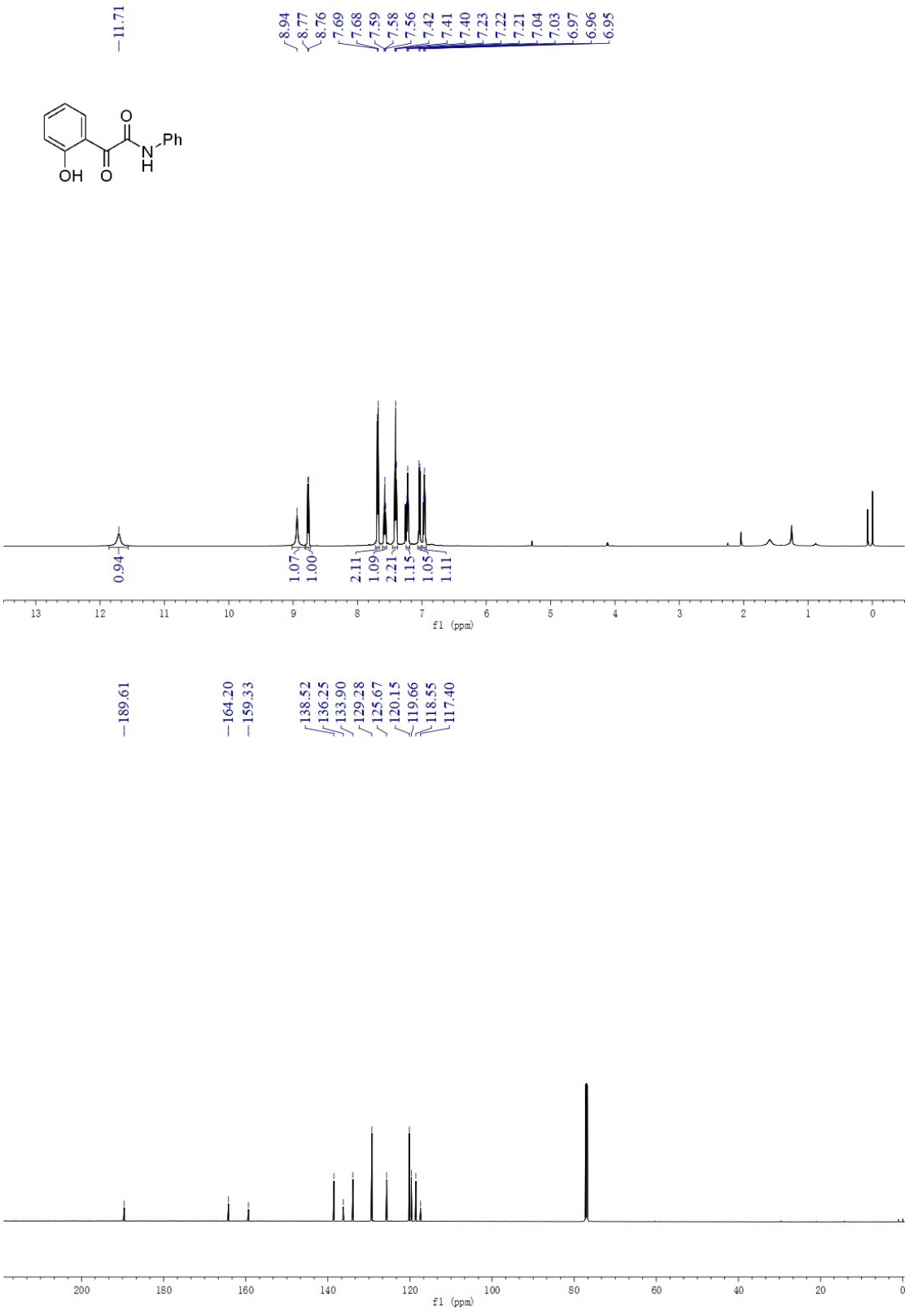
^{1}H and ^{13}C NMR Spectra for **4af**



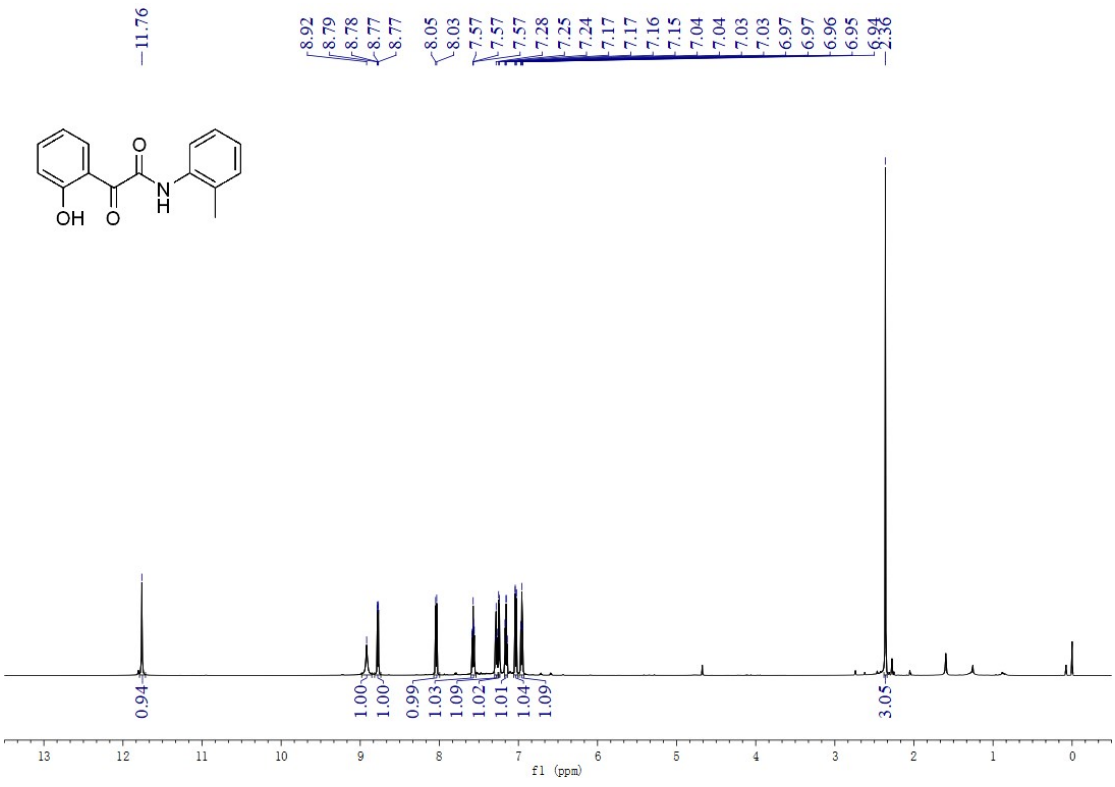
^{1}H and ^{13}C NMR Spectra for **4ag**

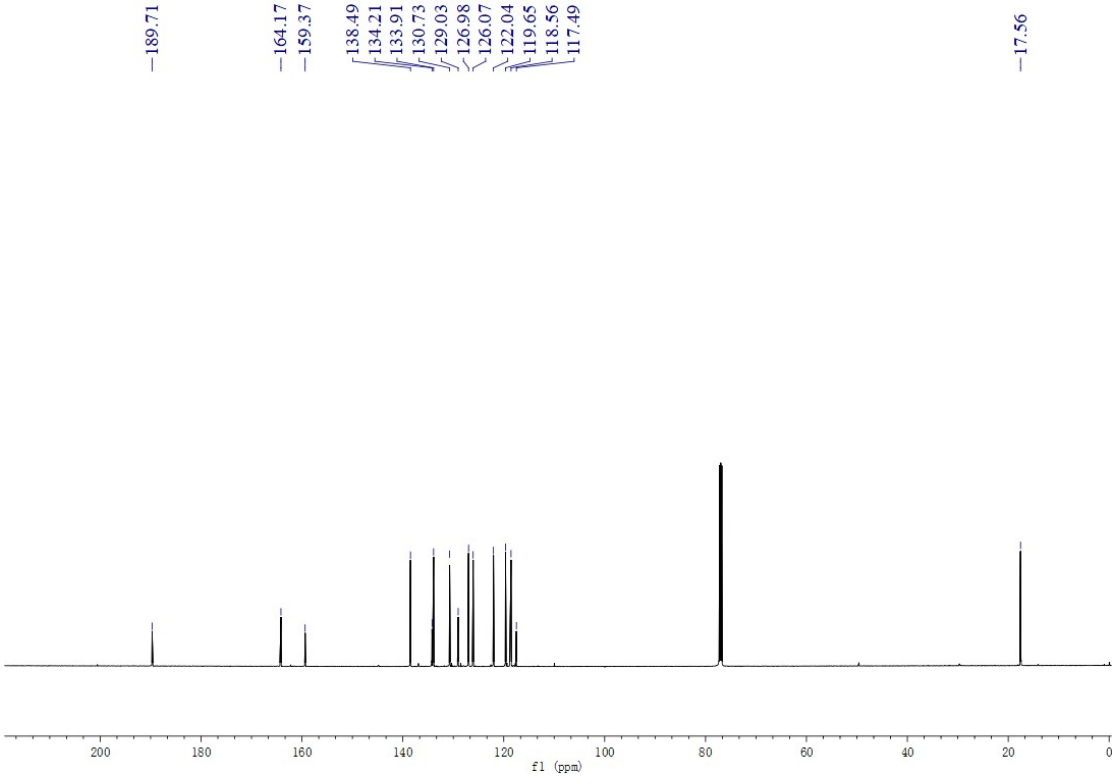


^{1}H and ^{13}C NMR Spectra for **4r**

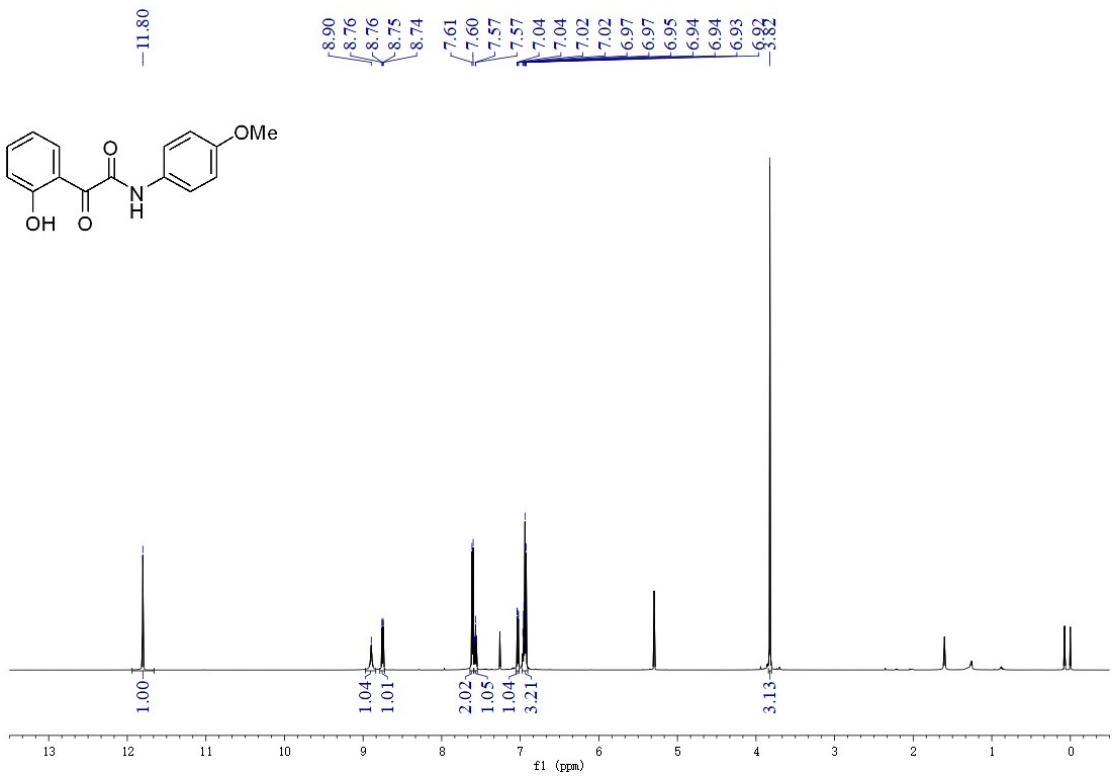


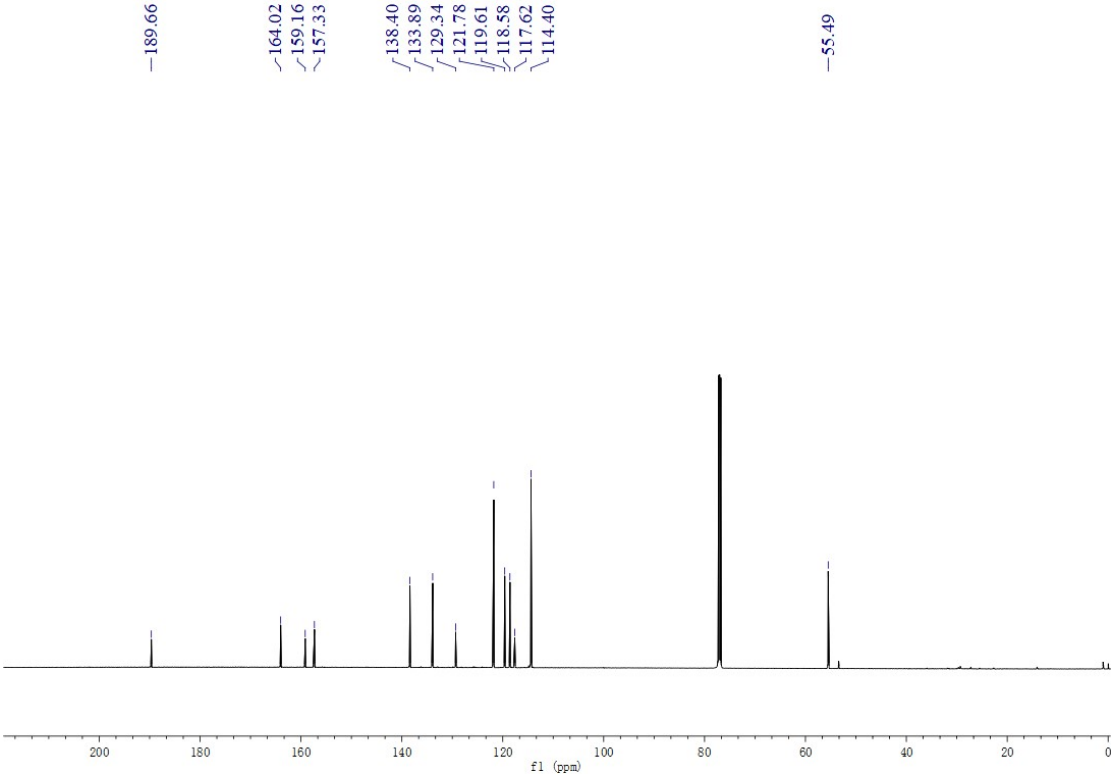
^{1}H and ^{13}C NMR Spectra for **4s**



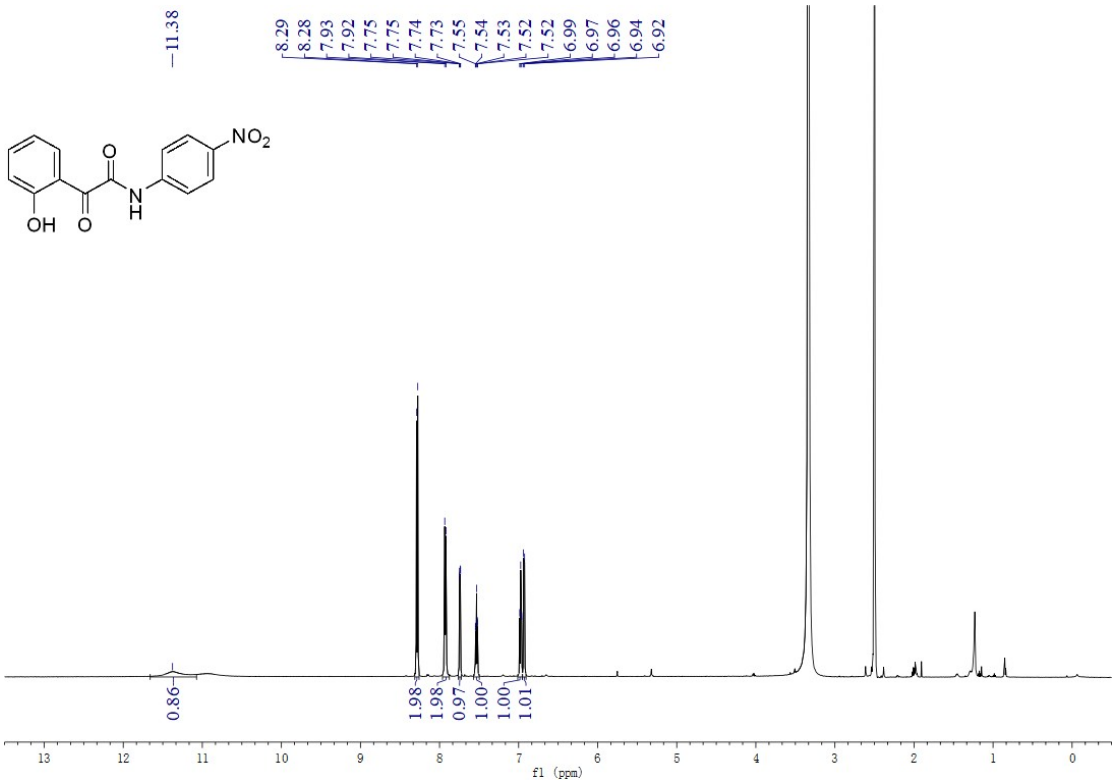


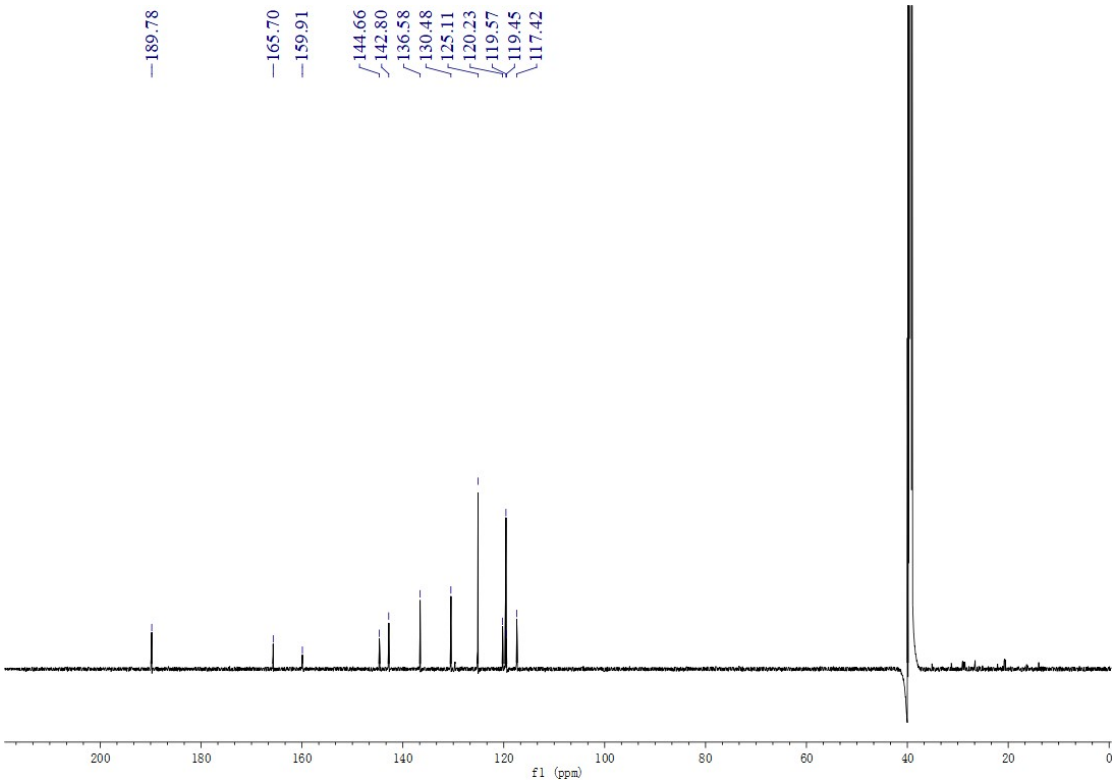
^{1}H and ^{13}C NMR Spectra for **4t**



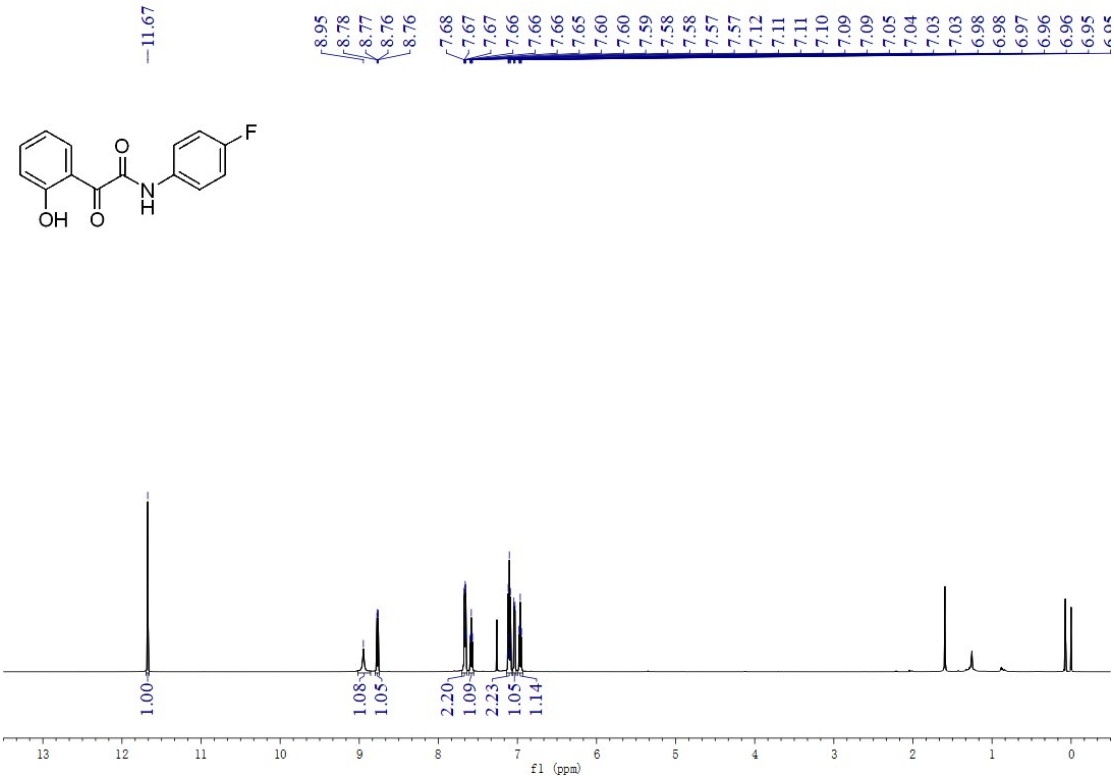


^{1}H and ^{13}C NMR Spectra for **4u**





^{1}H ^{13}C and ^{19}F NMR Spectra for **4v**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7.05
7.04
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6.98
6.97
6.96
6.96
6.95
F
O
N
H
OH
O
1.00
1.08
1.05
2.20
1.09
2.23
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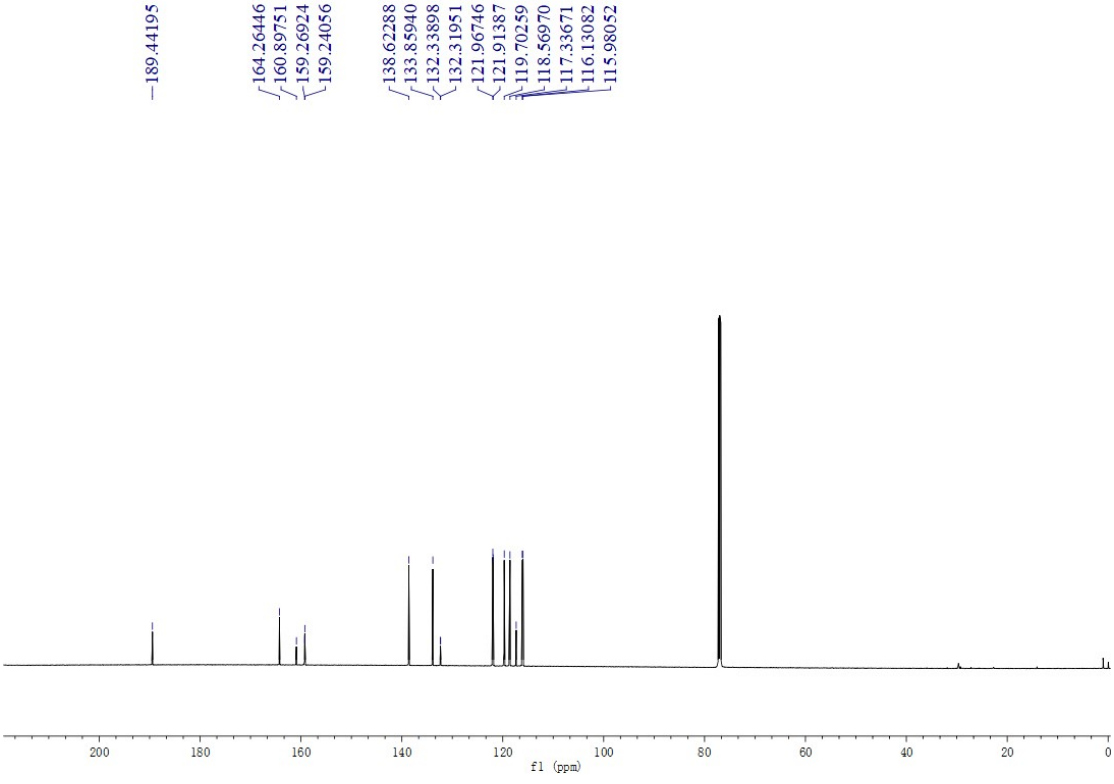
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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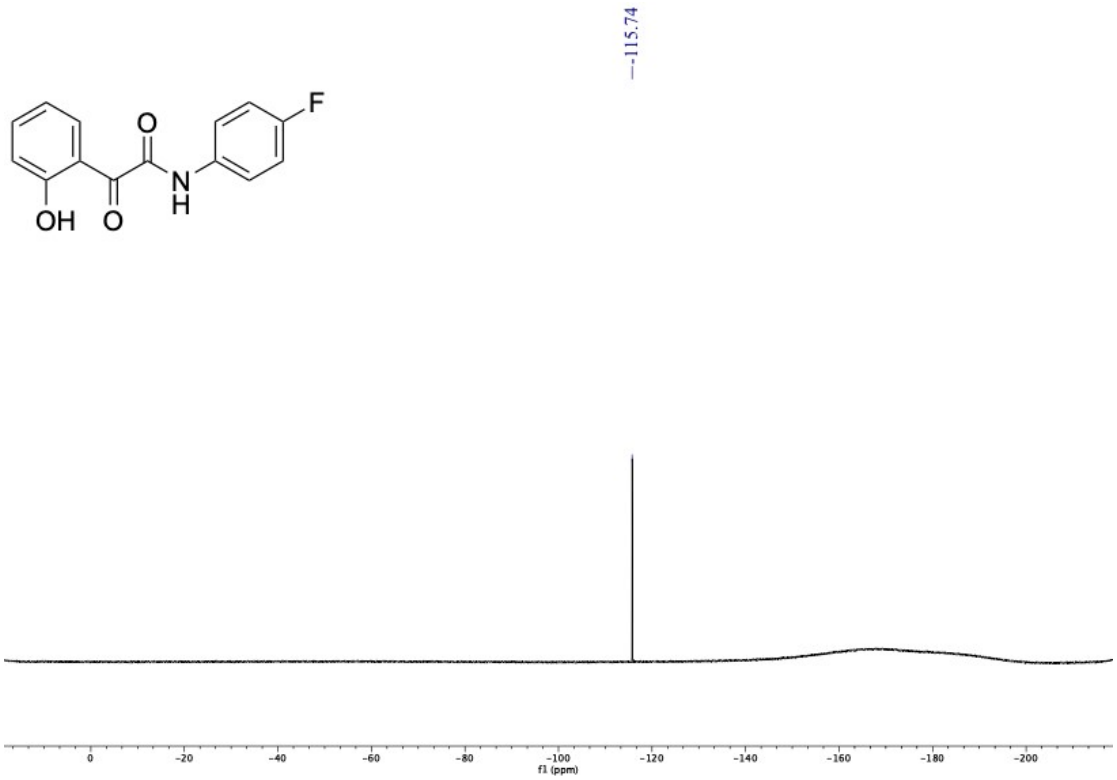
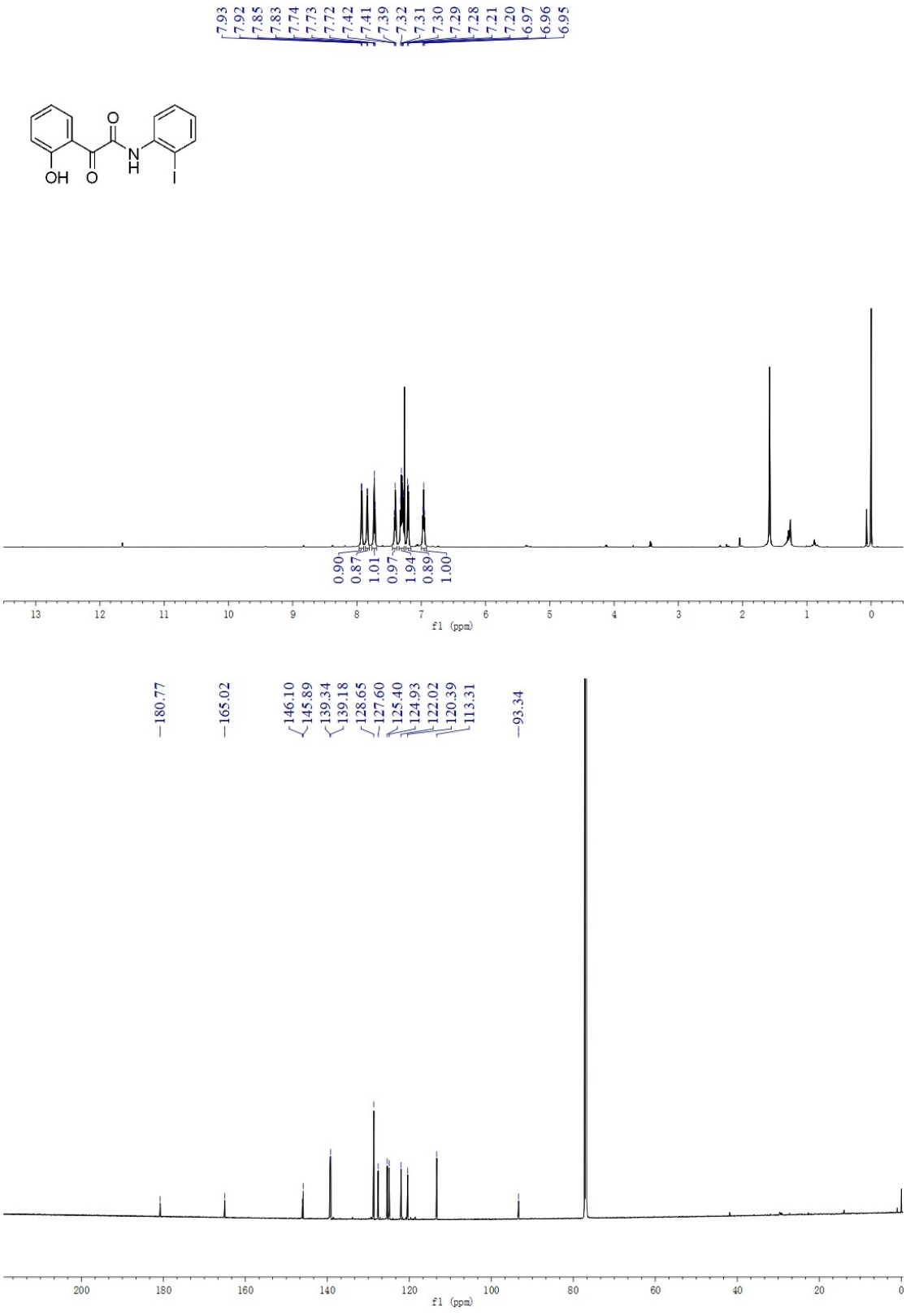
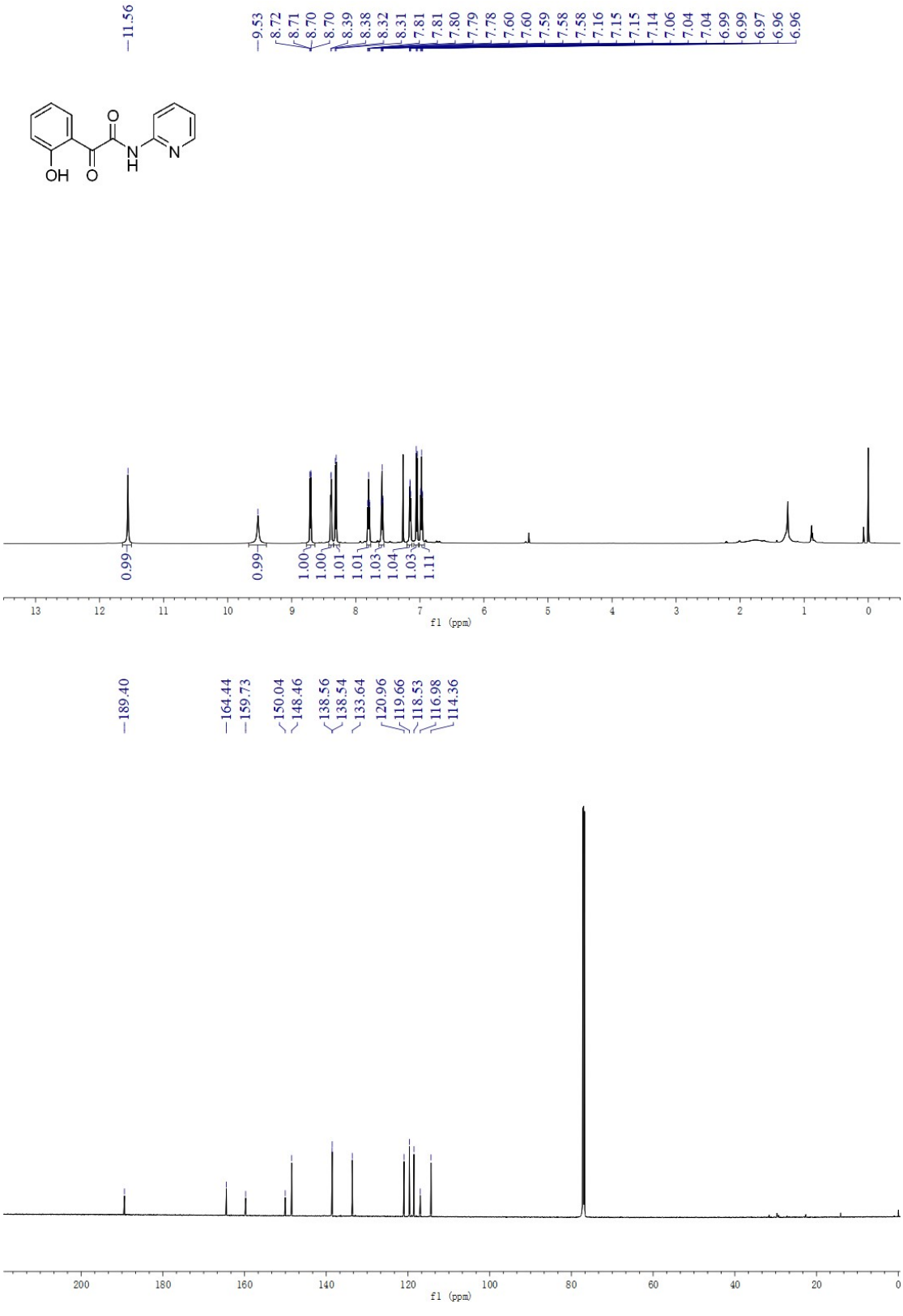


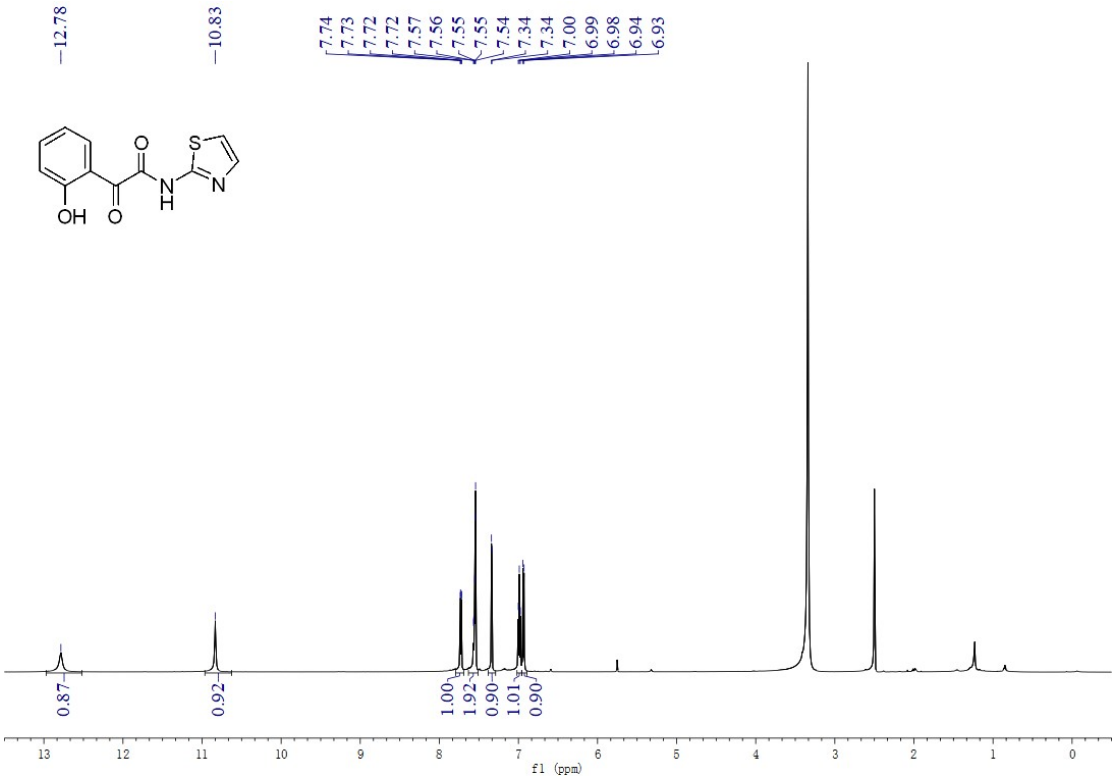
^{1}H and ^{13}C NMR Spectra for **4w**

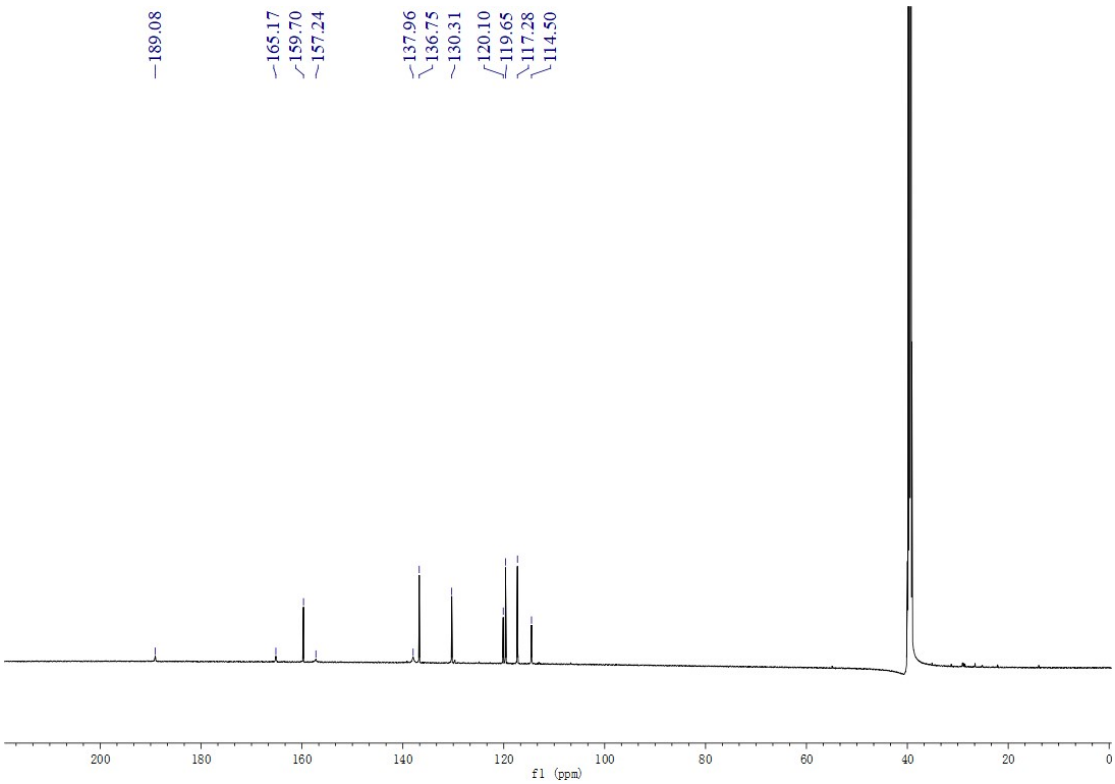


^{1}H and ^{13}C NMR Spectra for **4x**

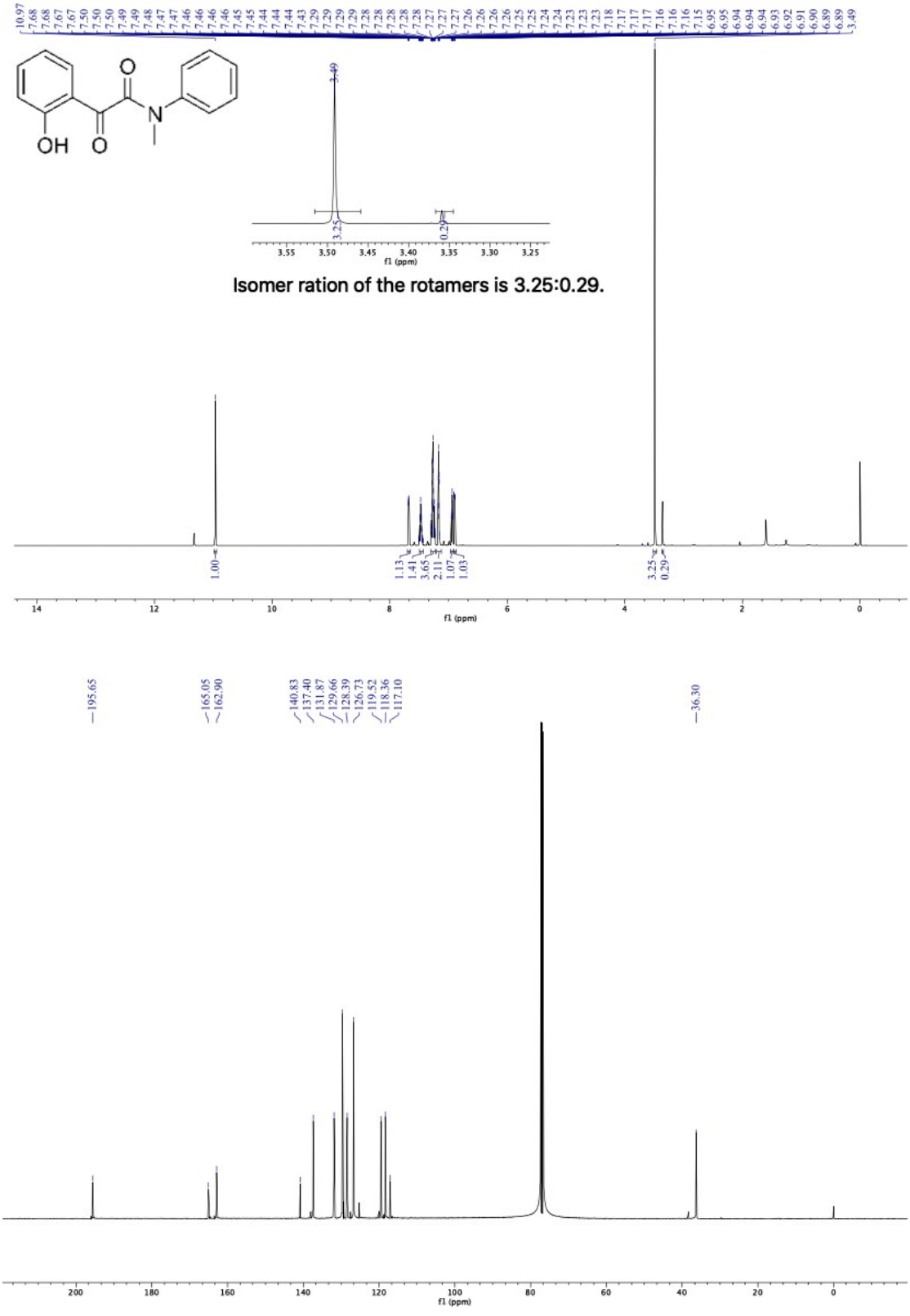


^{1}H and ^{13}C NMR Spectra for **4y**

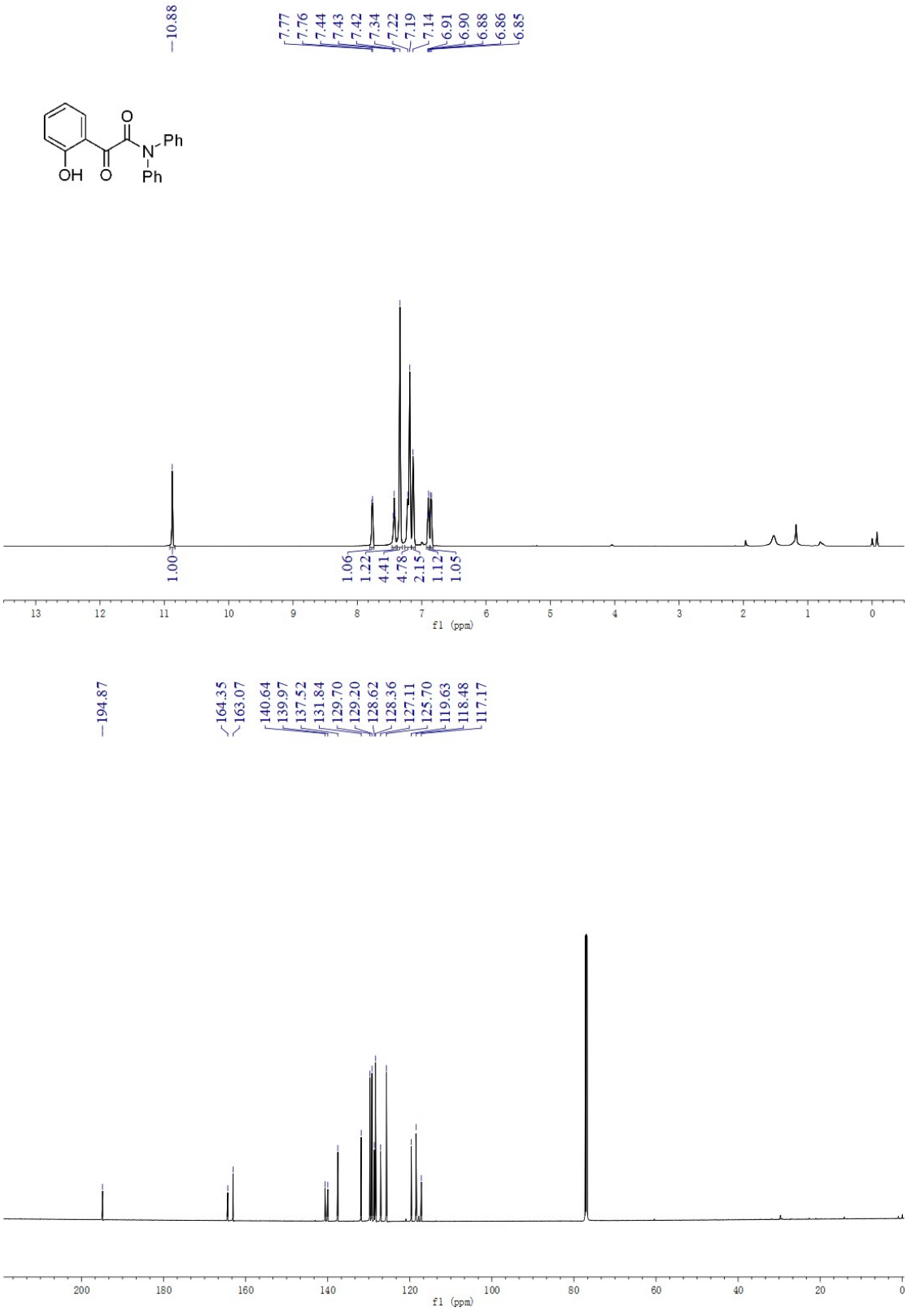




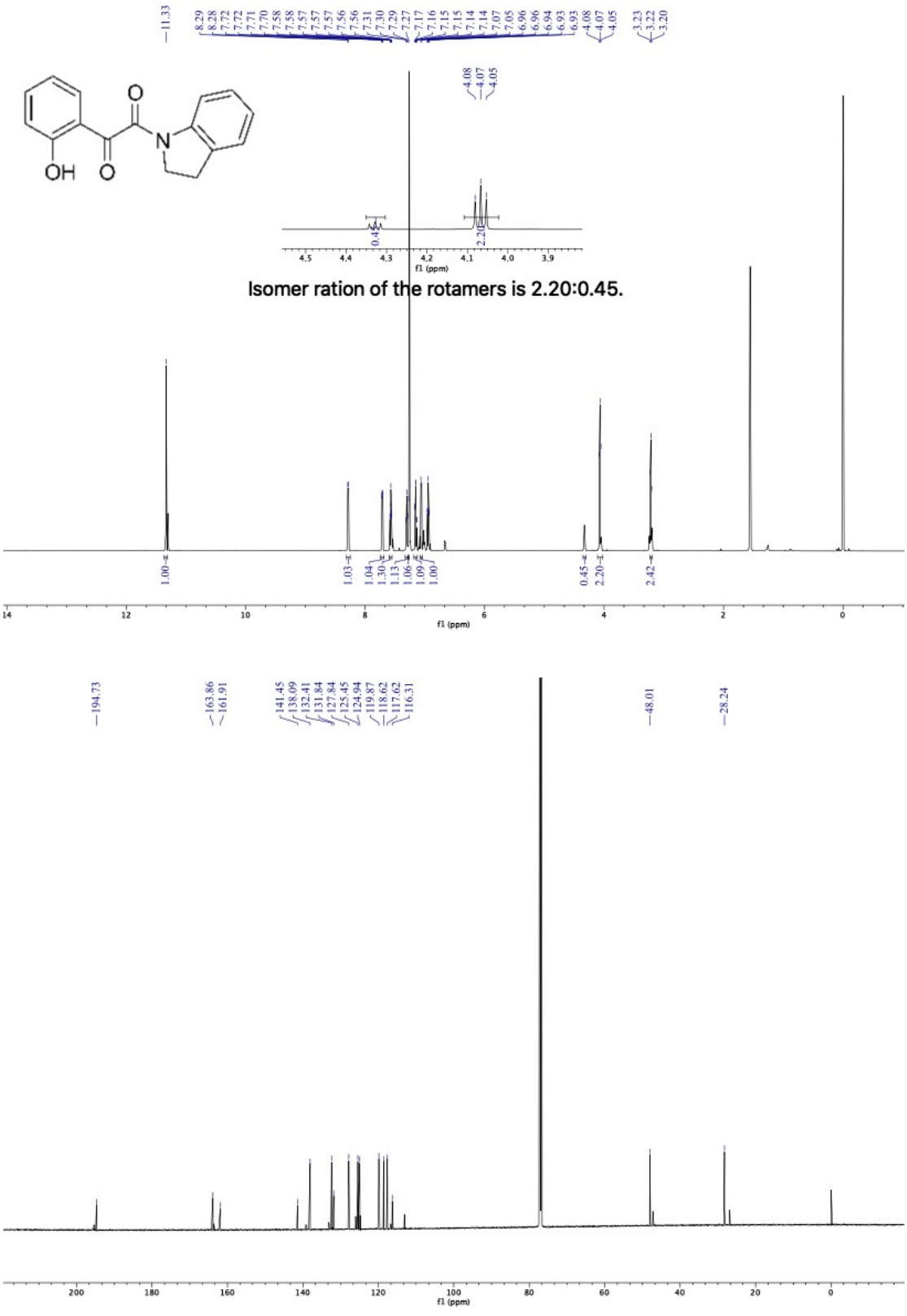
^{1}H and ^{13}C NMR Spectra for **4z**



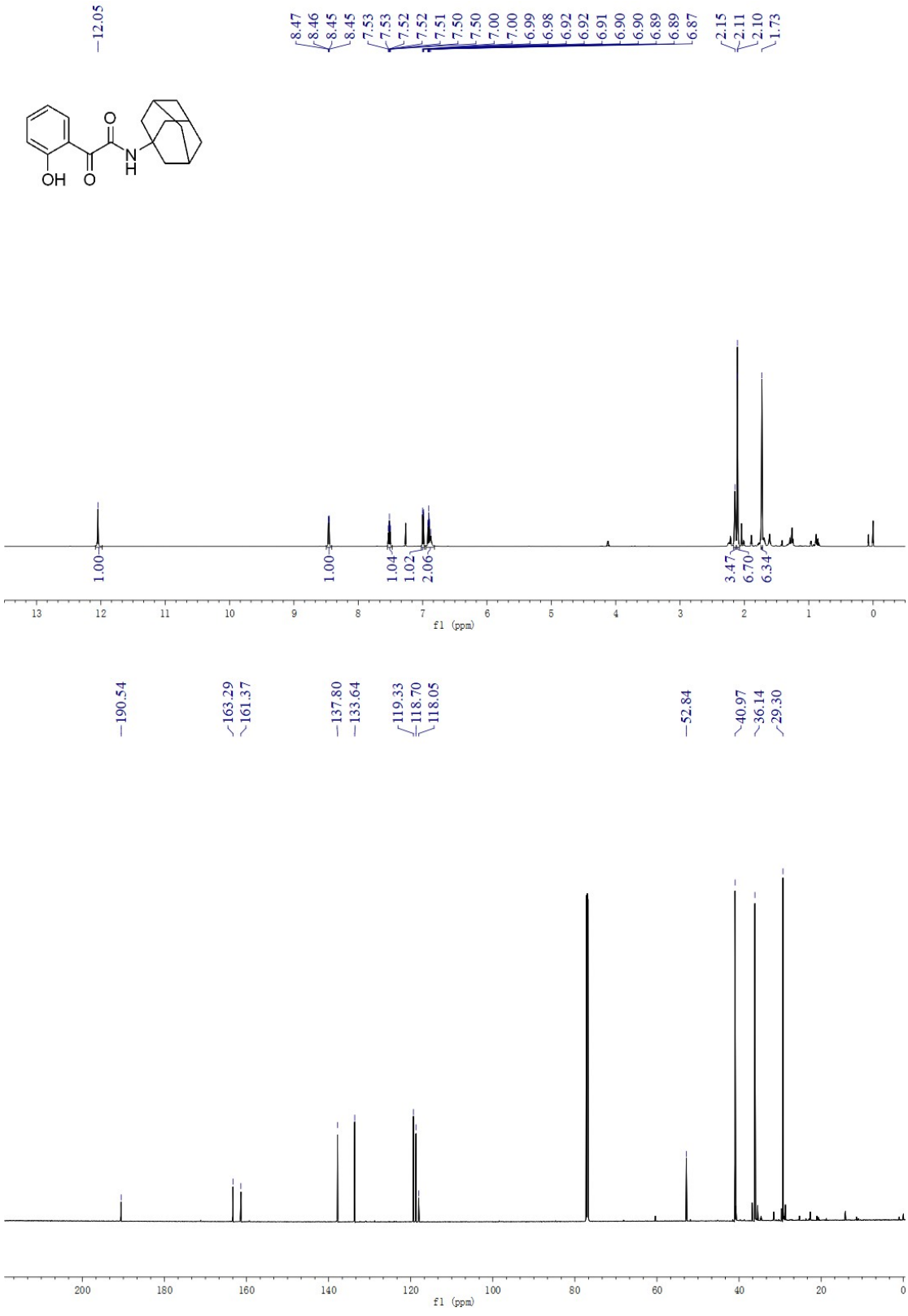
^{1}H and ^{13}C NMR Spectra for **4za**



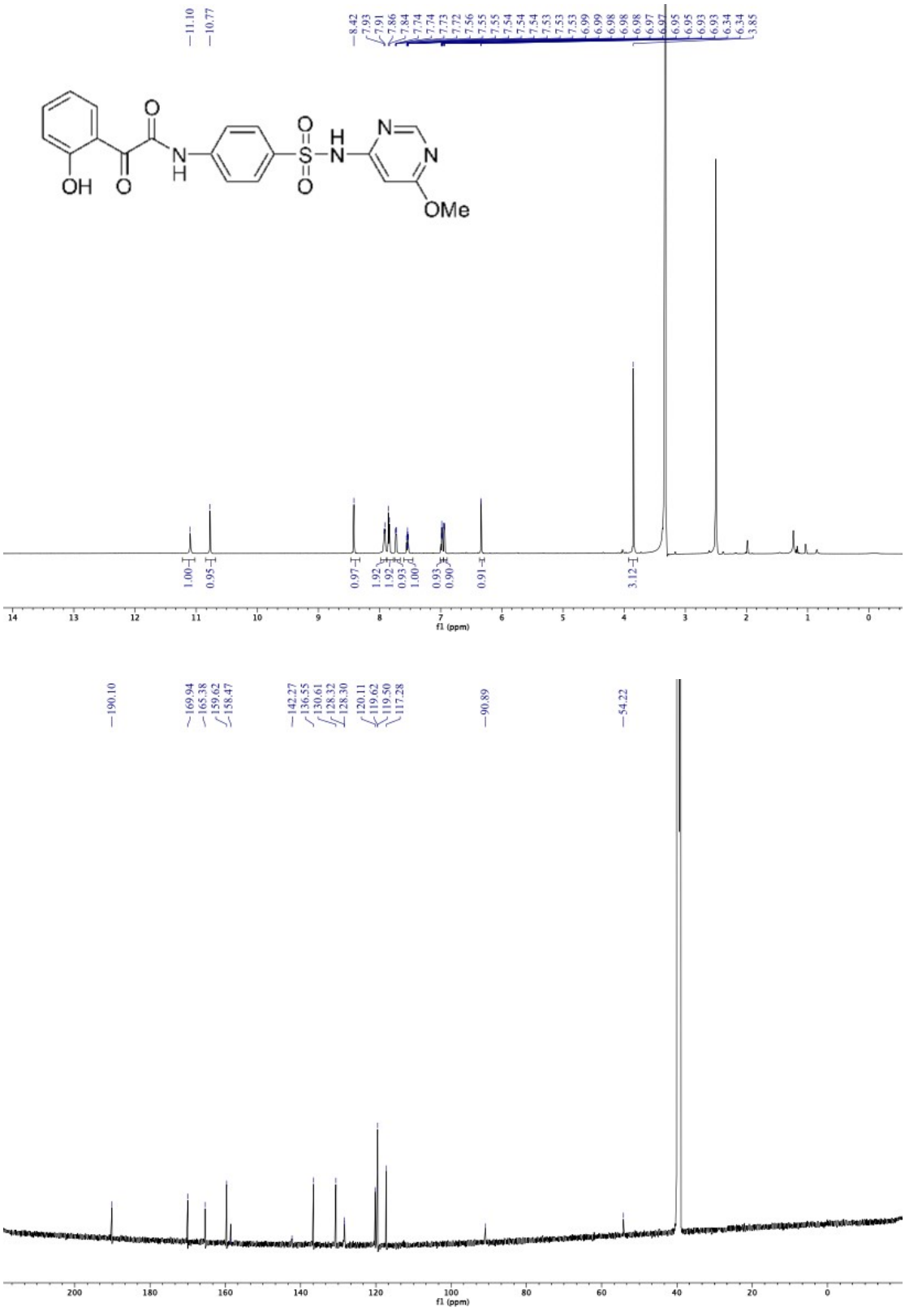
^{1}H and ^{13}C NMR Spectra for **4zb**



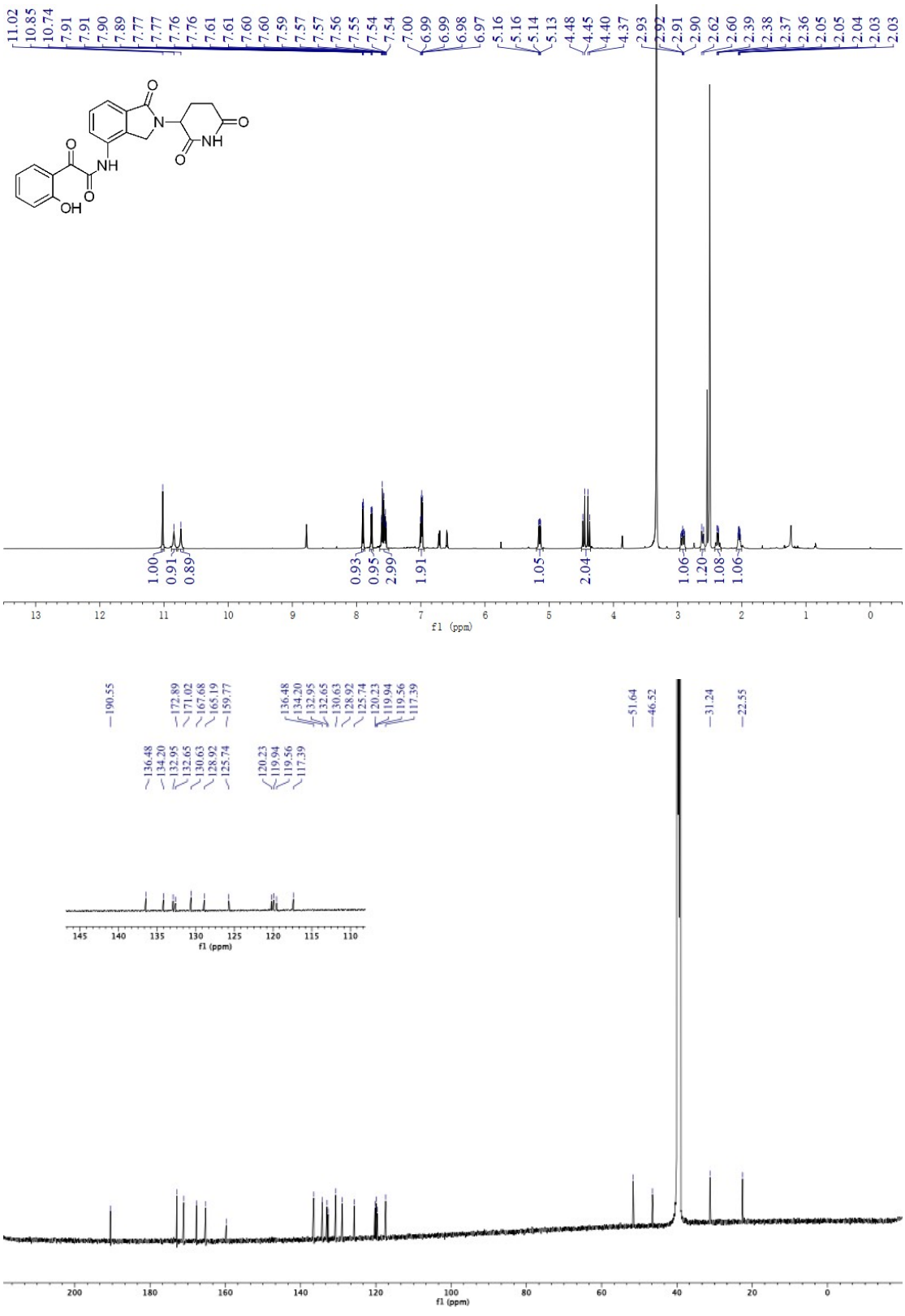
^{1}H and ^{13}C NMR Spectra for **5a**



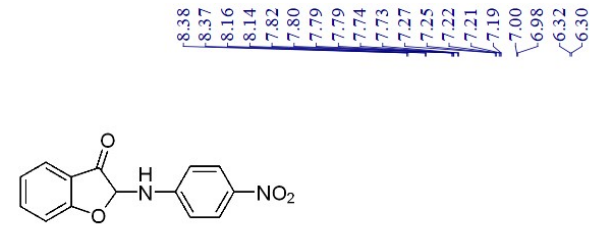
^{1}H and ^{13}C NMR Spectra for **5b**

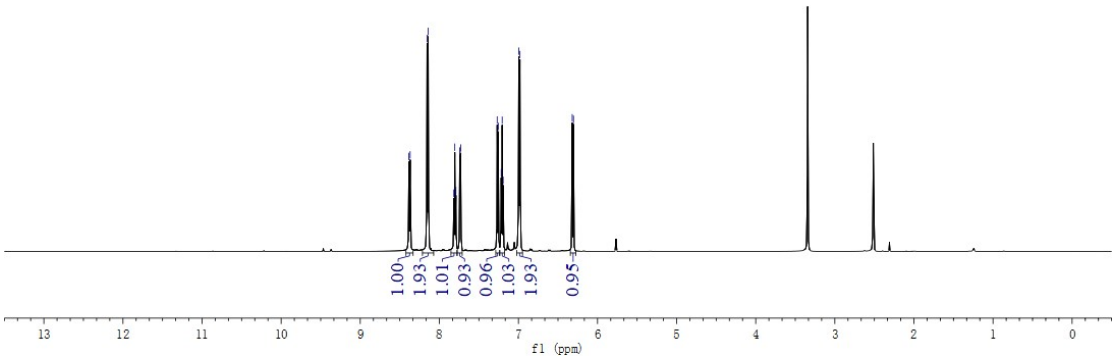


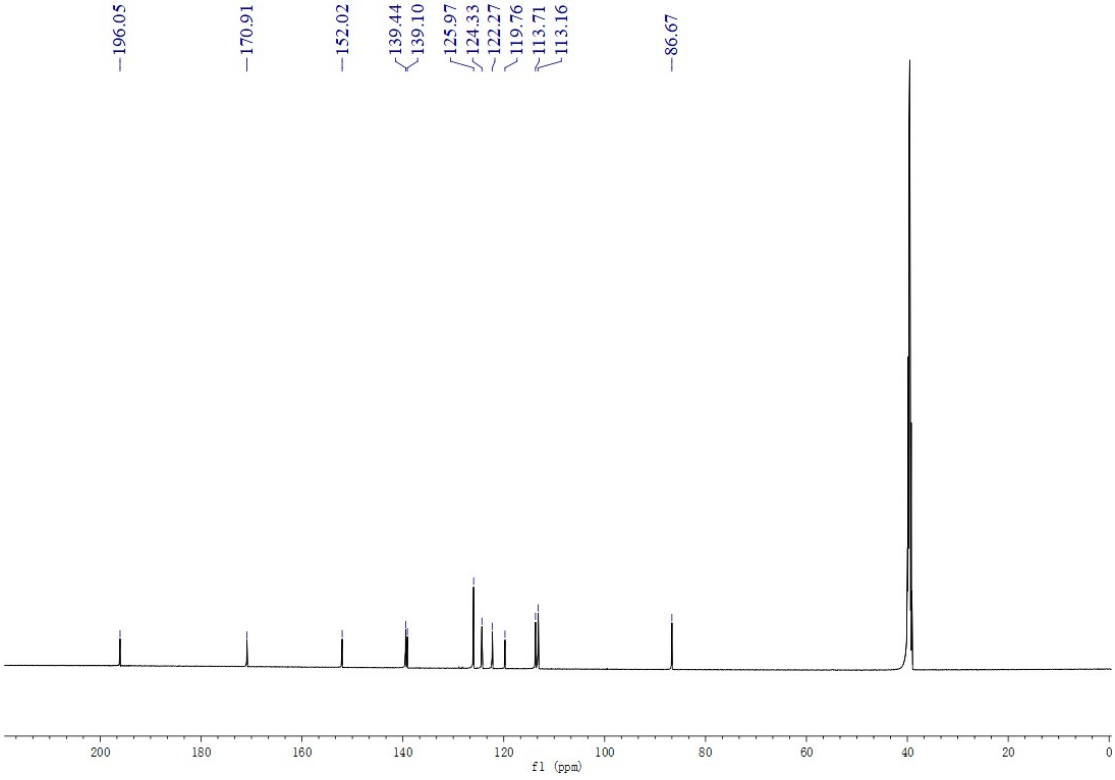
^{1}H and ^{13}C NMR Spectra for **5c**



^{1}H and ^{13}C NMR Spectra for **3u**


8.38
8.37
8.16
8.14
7.82
7.80
7.79
7.79
7.74
7.73
7.27
7.25
7.22
7.21
7.19
7.00
6.98
6.32
6.30
O
H
N
O
NO2


1.00
1.93
1.01
0.93
0.96
1.03
1.93
0.95
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


196.05
170.91
152.02
139.44
139.10
125.97
124.33
122.27
119.76
113.71
113.16
86.67
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)