Lewis base-Catalyzed Cascade [4+2]-Annulation Reaction of *N*-alkoxy Acrylamides and Acyl Isothiocyanates: Facile Access to 2-imino-1, 3-thiazinone Derivatives

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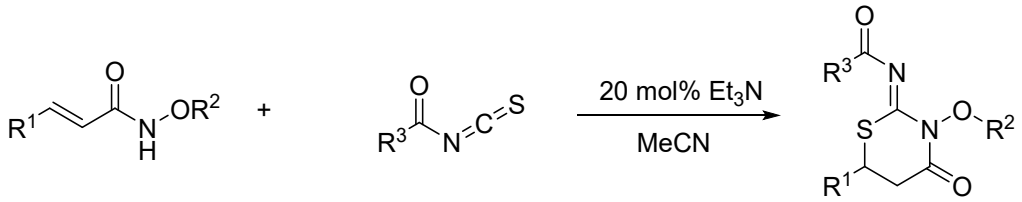
Contents

1. General information

All reactions were carried out under an atmosphere of air in oven dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Organic solutions were concentrated under reduced pressure on a rotary evaporator or an oil pump. Flash column chromatography was performed using Qingdao Haiyang flash silica gel (100–200 mesh). NMR spectra were recorded with a Bruker Avance DPX400 spectrometer with tetramethylsilane as the internal standard. Mass spectra were acquired with an Agilent 6520 Q-TOF MS system equipped with an Electrospray ionization (ESI) source. Melting points were determined on a Stuard SMP3 melting point apparatus. X-raycrystallographic data were collected using a Bruker APEX-II CCD. The *N*-alkoxy acrylamides **1** were prepared by the reported procedure.[1] The acyl isothiocyanates **2** were synthesized according to the known literature procedure.[2]

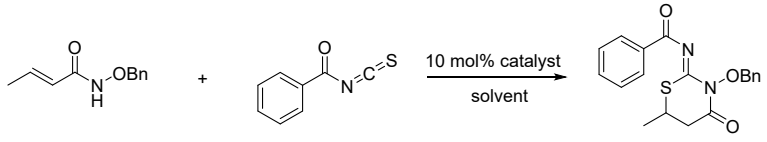
2. General procedure for the cascade [4+2]-cycloaddition reaction of N-alkoxy acrylamides 1 and acyl isothiocyanates 2



1 **2** **3**

To a stirred solution of *N*-alkoxy acrylamides **1** (0.20 mmol) and acyl isothiocyanates **2** (0.24 mmol) in anhydrous MeCN (2.0 mL), Et_3N (0.2 equiv.) was added. Then the reaction mixture was stirred at room temperature and monitored by TLC. After the reaction was complete, solvent was removed under reduced pressure, the mixture was subjected to flash column chromatography (PE/EtOAc = 5:1) to furnish the corresponding product **3**.

3. Optimization of reaction conditions for the organocatalytic asymmetric [4+2]-cycloaddition reaction of *N*-alkoxy acrylamide 1a and benzoyl isothiocyanate 2a[a, b]



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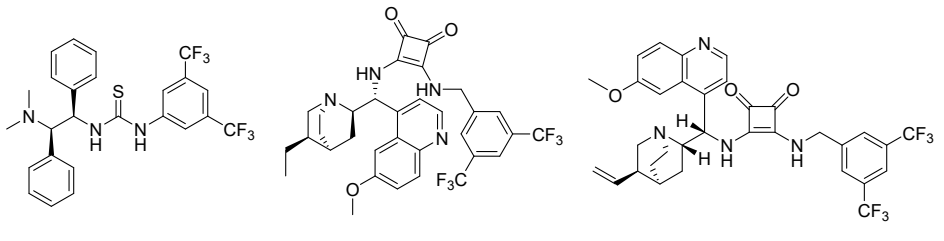

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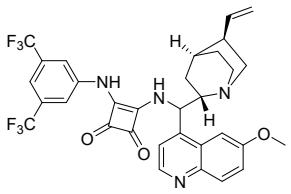

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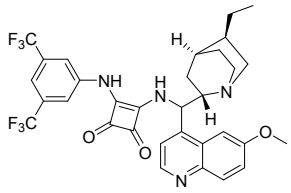

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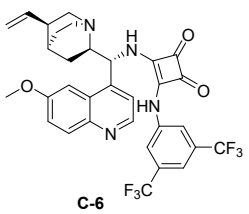

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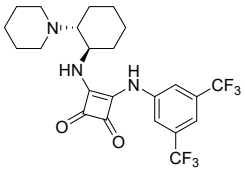

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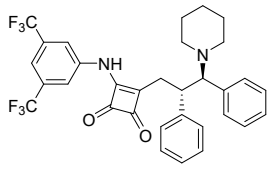

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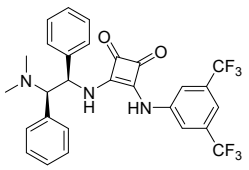

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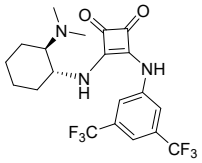

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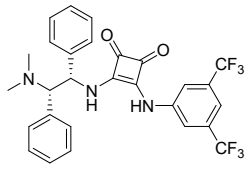


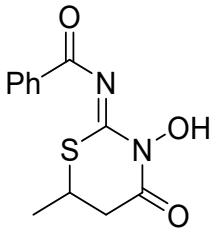
C-11

Entry	Cat.	Solvent	Time(h)	Yield(%)[b]	ee(%)[c]
1	**C-1**	CH_2Cl_2	24	30	-30
2	**C-2**	CH_2Cl_2	24	42	-53
3	**C-3**	CH_2Cl_2	24	40	68
4	**C-4**	CH_2Cl_2	24	Trace	n.d.[d]
5	**C-5**	CH_2Cl_2	24	38	60
6	**C-6**	CH_2Cl_2	24	30	-41
7	**C-7**	CH_2Cl_2	24	Trace	n.d.[d]
8	**C-8**	CH_2Cl_2	24	Trace	n.d.[d]
12	**C-9**	CH_2Cl_2	24	35	-25
13	**C-10**	CH_2Cl_2	24	30	-31
14	**C-11**	CH_2Cl_2	24	Trace	n.d.[d]
15	**C-3**	$CHCl_3$	24	35	53
16	**C-3**	CH_3CN	24	Trace	n.d.
17	**C-3**	toluene	24	28	40
18	**C-3**	DCE	24	38	67
19	**C-3**	EtOAc	24	Trace	n.d.[d]

[a] Reactions were carried out with **1a** (0.20 mmol), **2a** (0.20 mmol), and 10 mol% catalyst in 2 mL of solvent at rt. [b] Isolated yields. [c] Determined by HPLC analysis. [d] Not detected.

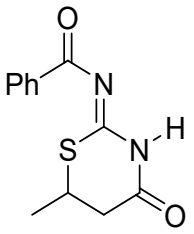
4. Chemoselective deprotection of product 3aa

***N*-(3-hydroxy-6-methyl-4-oxo-1,3-thiazinan-2-ylidene)benzamide (4)**



Under a nitrogen atmosphere, $TiCl_4$ (289mg 1.0mmol) was added dropwise to a solution of **3aa** (71 mg, 0.2 mmol) in 2mL of DCM in an ice bath, After stirring for 30 minutes at room temperature, the reaction mixture was quenched by saturated $NaHCO_3$ and extracted with DCM, The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (Petroleum ether/EtOAc 1:1) to give the compound **4**.

***N*-(6-methyl-4-oxo-1,3-thiazinan-2-ylidene)benzamide (5)**



To a solution of **3aa** (71 mg, 0.2 mmol) in MeOH (1.5 mL) and EtOAc (1.5 mL) added 10% Pd/C (28 mg). The reaction mixture was stirred at room temperature for 6 hours. After filtration through a plug of Celite, the volatiles were removed under reduced pressure and the residue was purified via flash column chromatography (PE/EA = 3/1) to afford compound **5**.

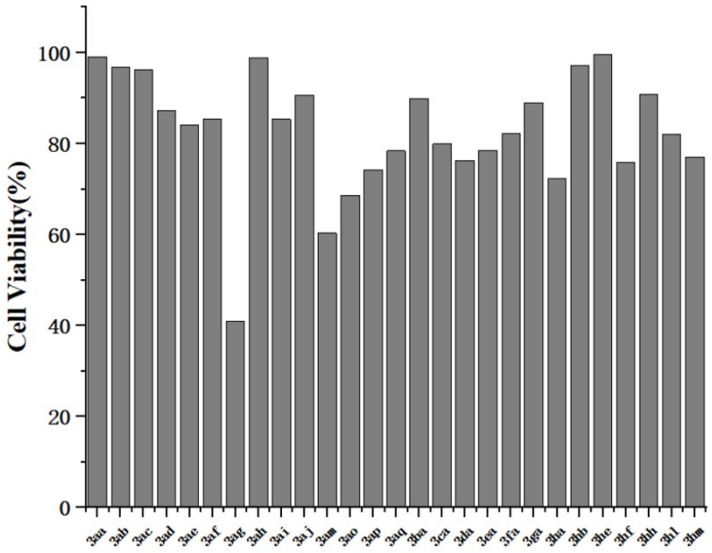
5. Antitumor activity investigation towards human lung adenocarcinoma cell line

5.1 Cell Lines and Cell Culture

Human cancerous cell line: A549 (human lung adenocarcinoma cell line) used in this study. The cell was cultivated in RPMI 1640 medium, supplemented with 10% fetal bovine serum containing L-glutamine and 1% penicillin-streptomycin (HyClone) and maintained in a humidified atmosphere of 95% air, 5% CO_2 at 37 ℃.

5.2 Vitro anticancer activities of the synthesized 2-imino-1, 3-thiazinone derivatives against cancerous A549.

The in vitro anticancer activity of the synthesized 2-imino-1, 3-thiazinone derivatives against human lung adenocarcinoma cell line A549 was investigated. Using oxaliplatin as a positive control, most of these compounds exhibited the anticancer activity. Among them, the inhibition rates of eight compounds measured at a concentration of 250 μM exceeded 90%, and the highest inhibition rate was up to 99.67%. Subsequently, five compounds (**3aa, 3ah, 3ai, 3hb, 3h**e) were selected to test the IC50 value. Unfortunately, high concentrations of lead compounds are required to inhibit the cell viability of cancerous A549. Although **3ah** exhibits optimal antitumor activity, but further modification was still needed.



Compound	Inhibition rate against cancerous A549 (average)
3aa	99.03664383
3ab	96.76821289
3ac	96.14657586
3ad	87.30551129
3ae	84.08826565
3af	85.32426952
3ag	40.8717471
3ah	98.83306703
3ai	85.30245785
3aj	90.63908653
3am	60.29518862
3ao	68.64912043
3ap	74.16387941
3aq	78.44021148
3ba	89.89021434
3ca	79.93311087
3da	76.25175737
3ea	78.54442319
3fa	82.16518868
3ga	89.01046946
3ha	72.40439181
3hb	97.08448446
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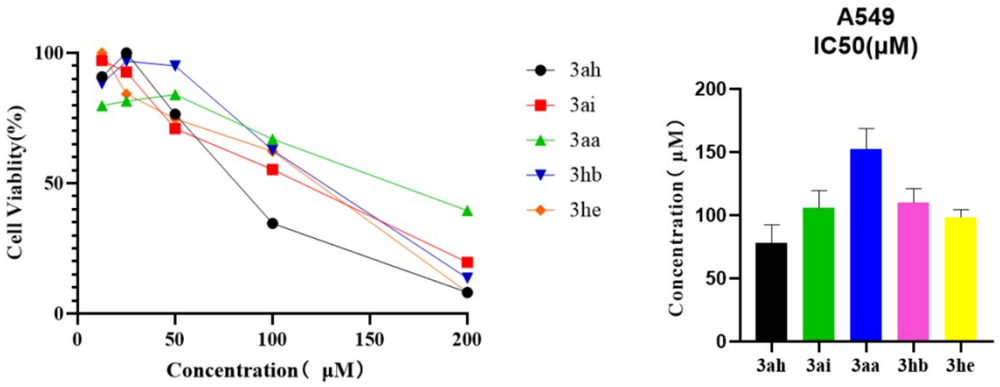
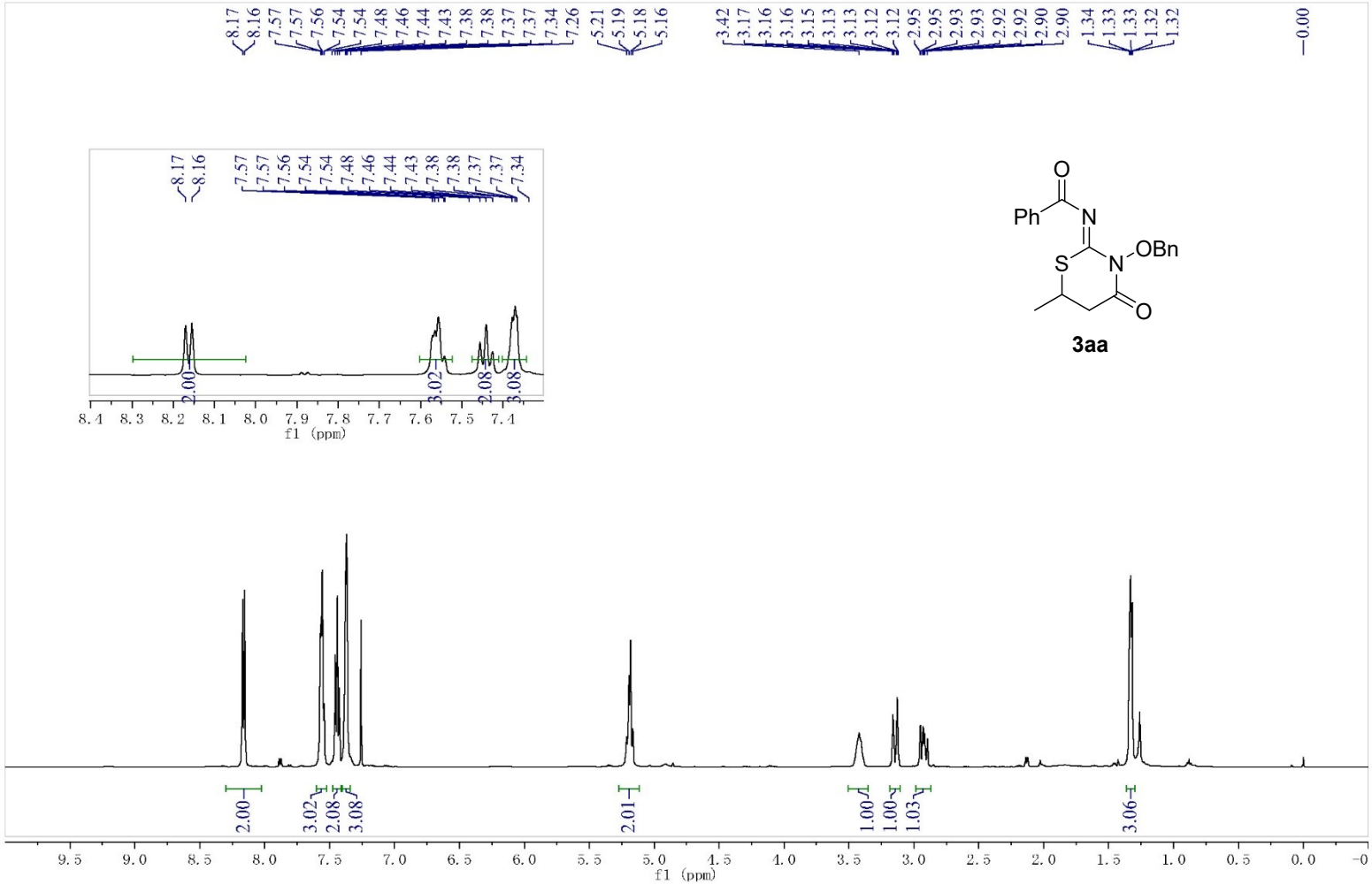


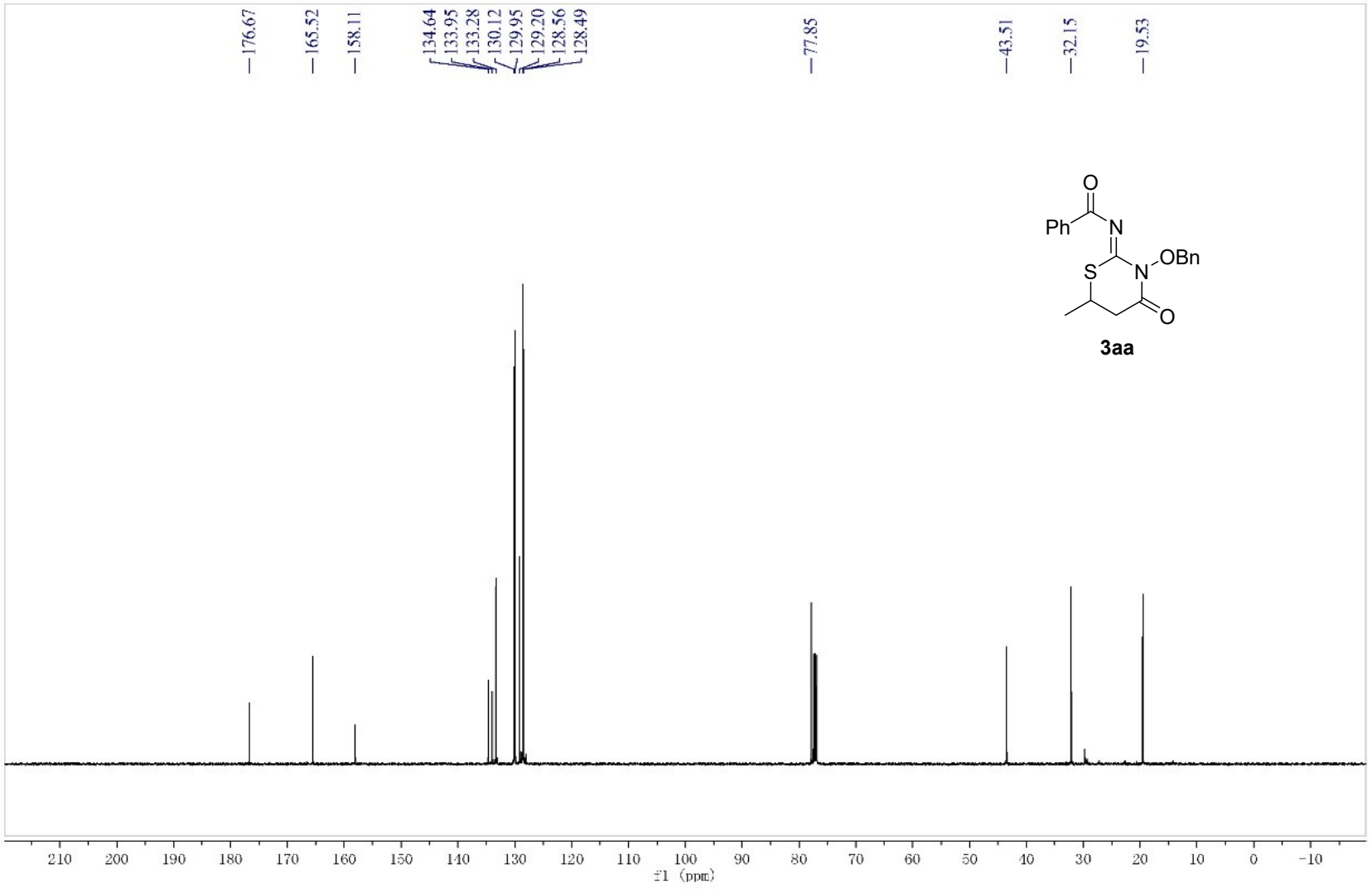
6. Reference

1. Tang, Q. G., Cai, S. L., Wang, C. C., Lin, G. Q., Sun, X. W. Organocatalytic Aza-Michael/Michael Cyclization Cascade Reaction: Enantioselective Synthesis of Spiro-oxindole Piperidin-2-one Derivatives. *Org. Lett.*, **2020**, *22*(9), 3351-3355.

2. Dahiya, A., Ali, W., Alam, T., Patel, B. K. A cascade synthesis of S-allyl benzoylcarbamothioates via Mumm-type rearrangement. *Org. Biomol. Chem.*, 2018, *16*(42), 7787-7791.

7. ^{1}H and ^{13}C NMR spectra of all products

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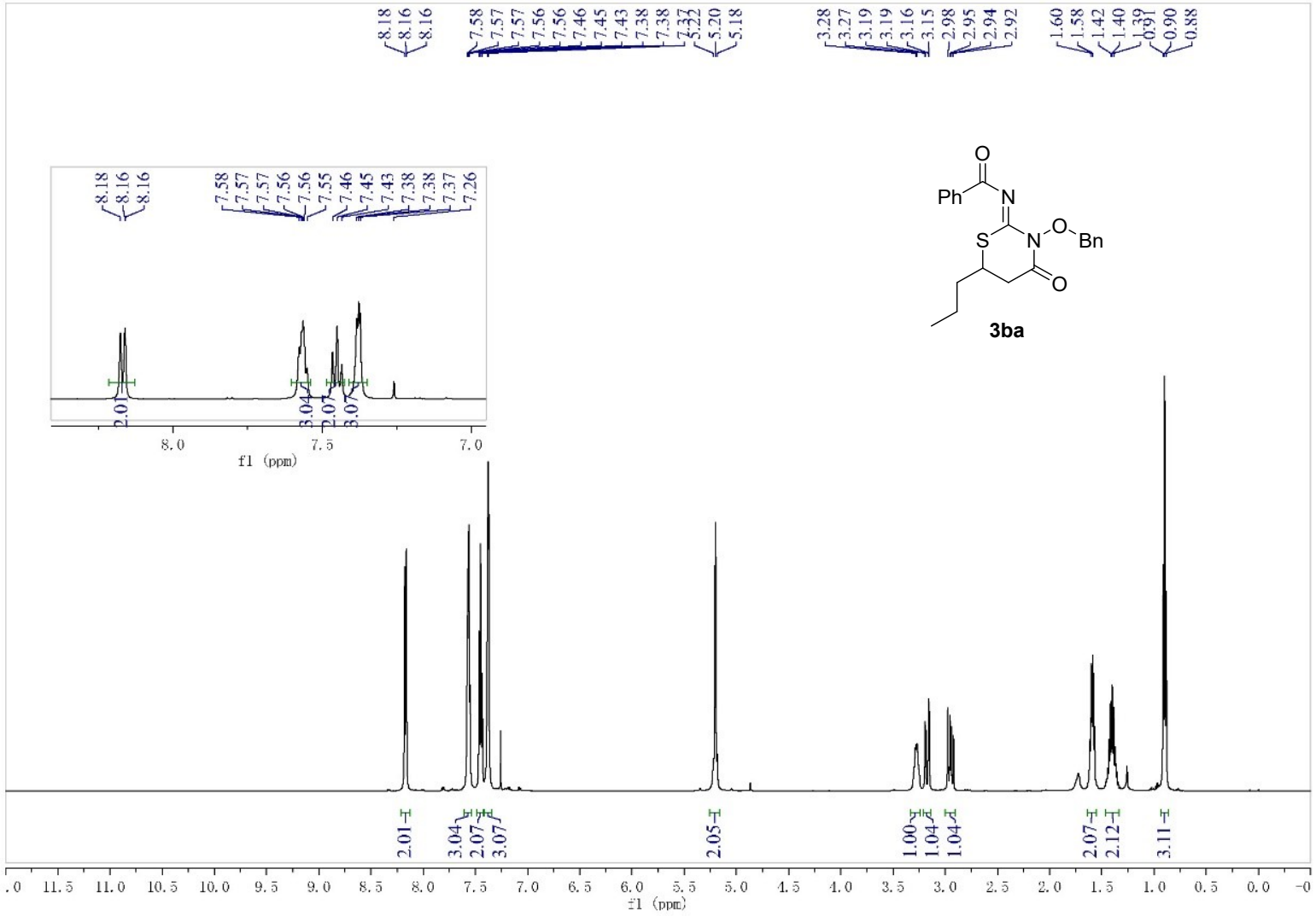
f1 (ppm)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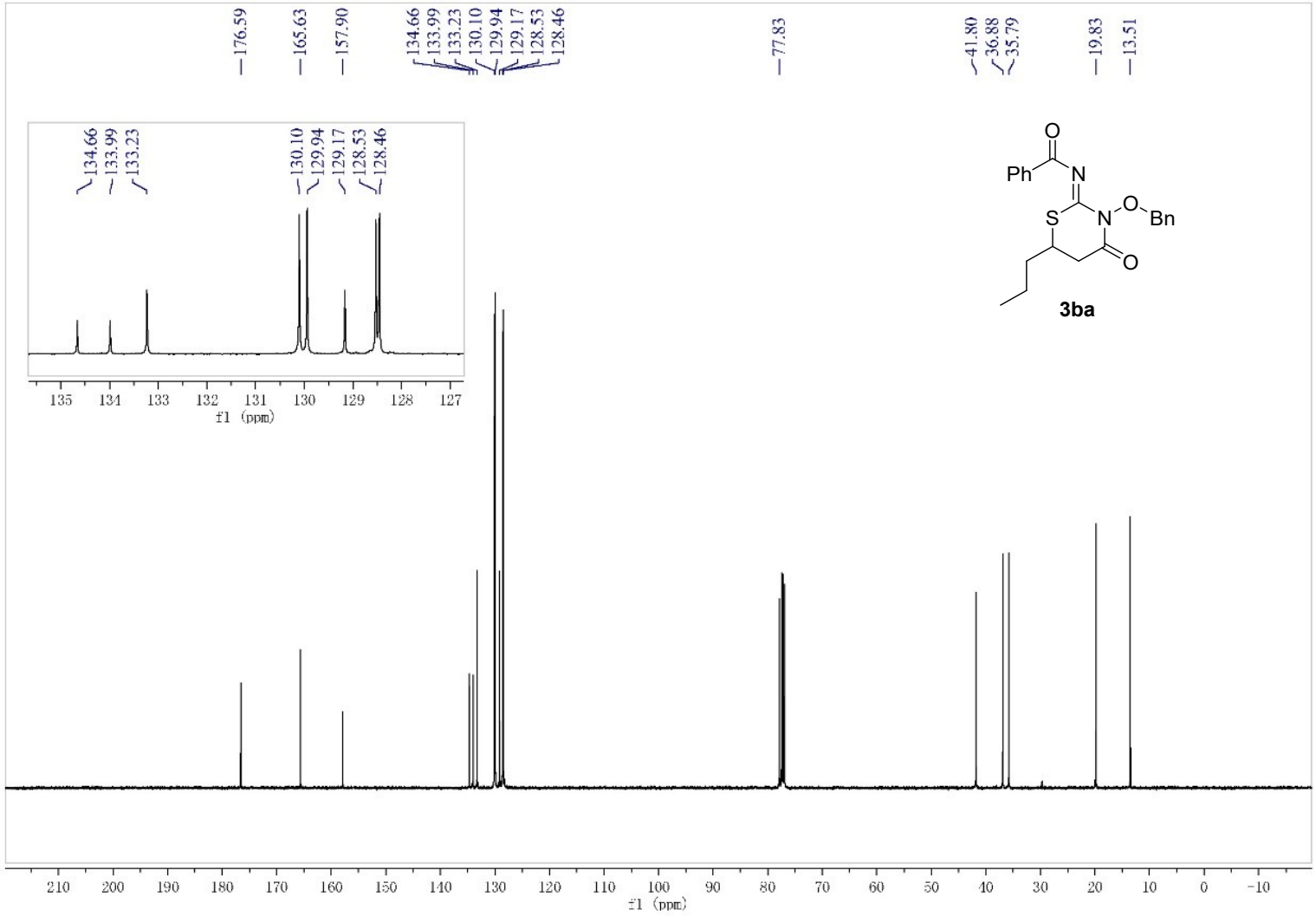
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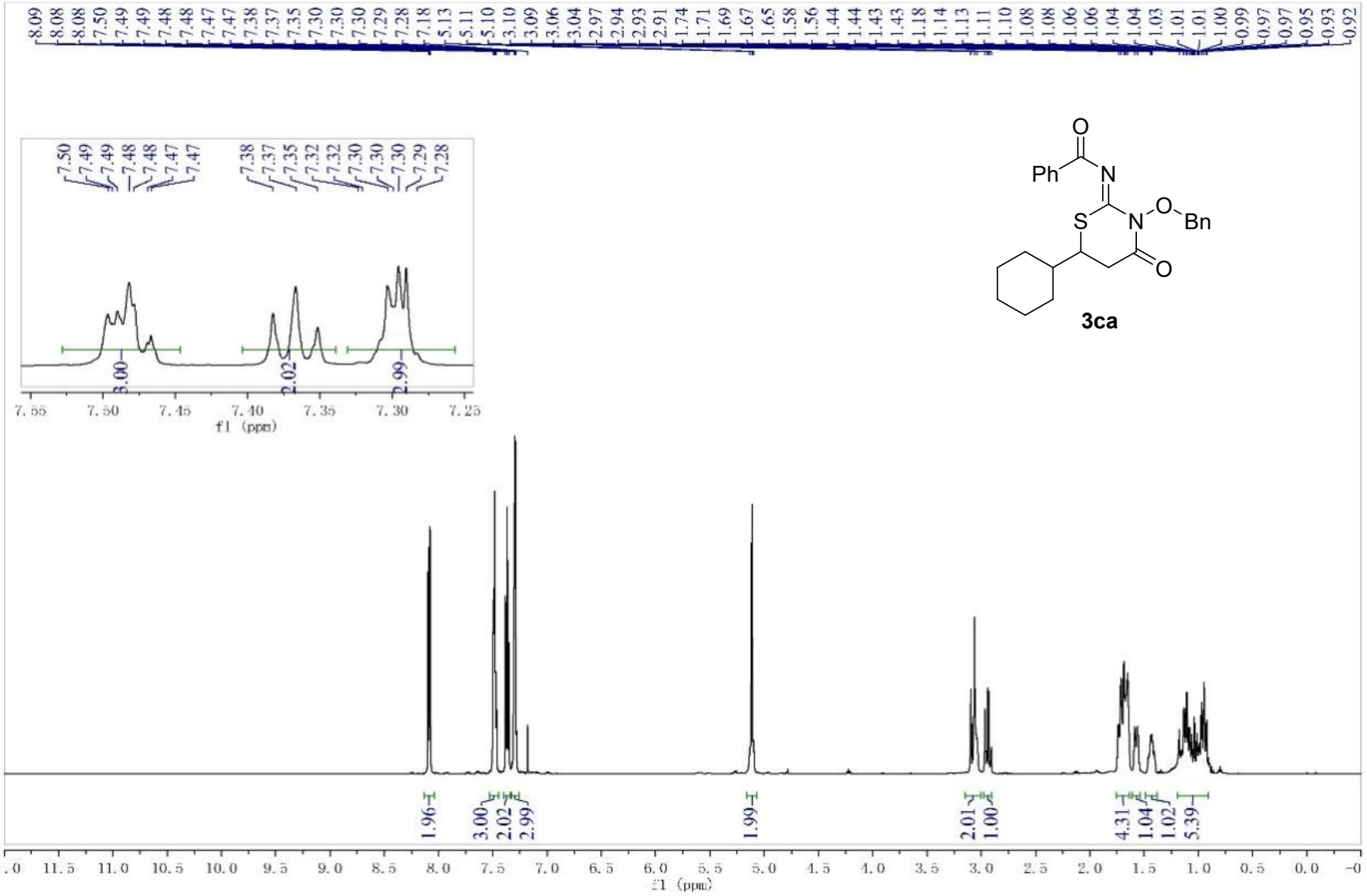
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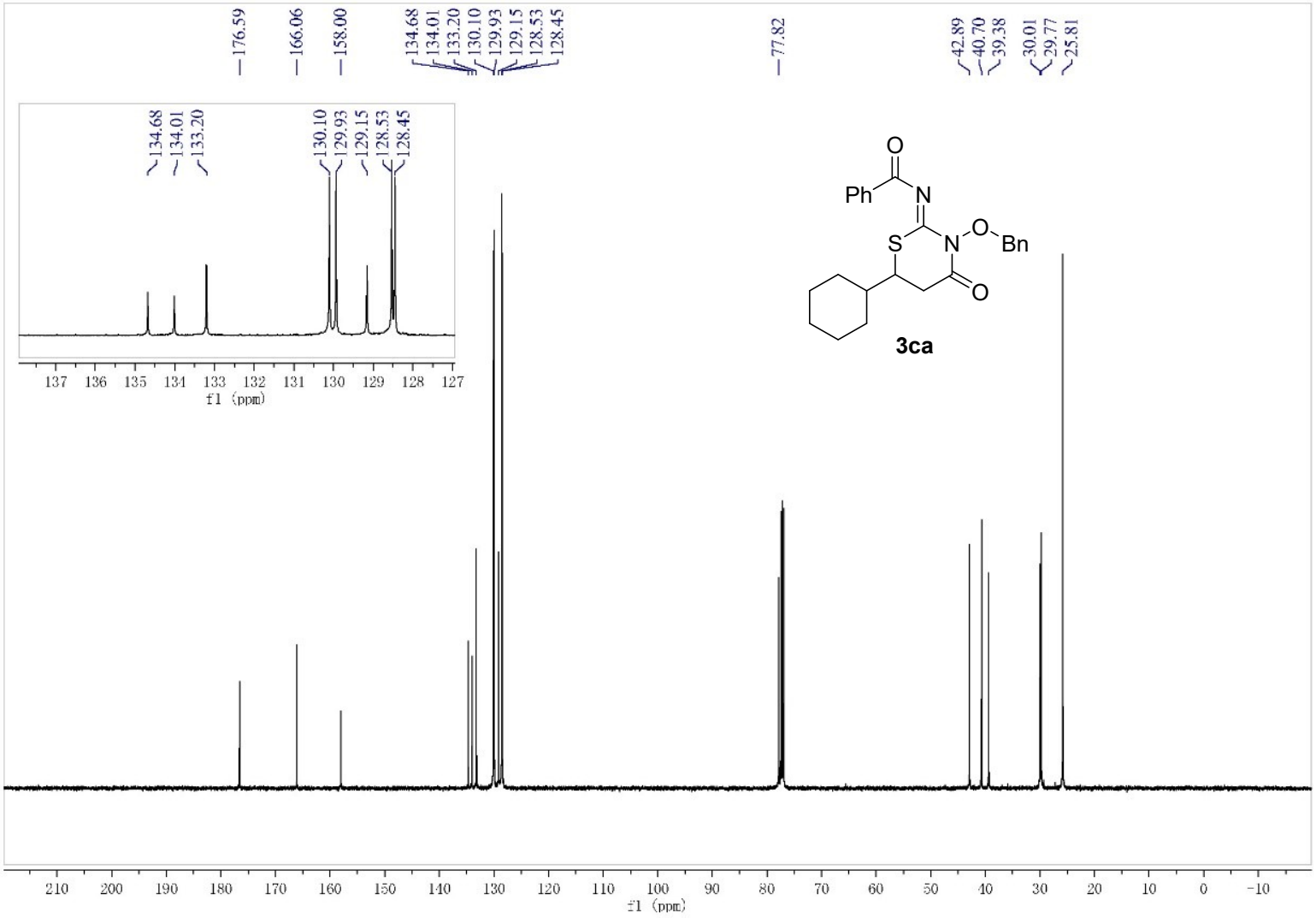
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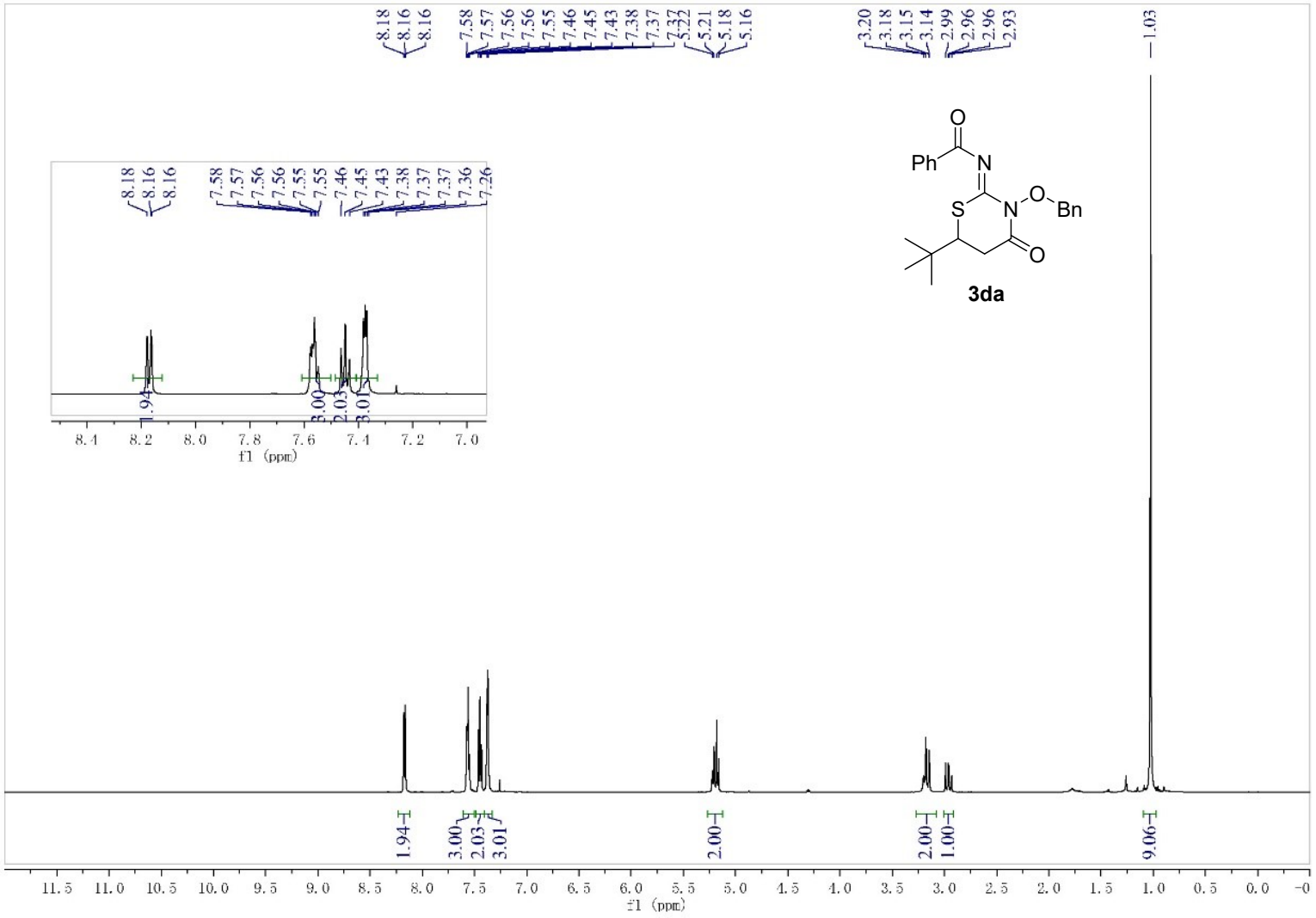
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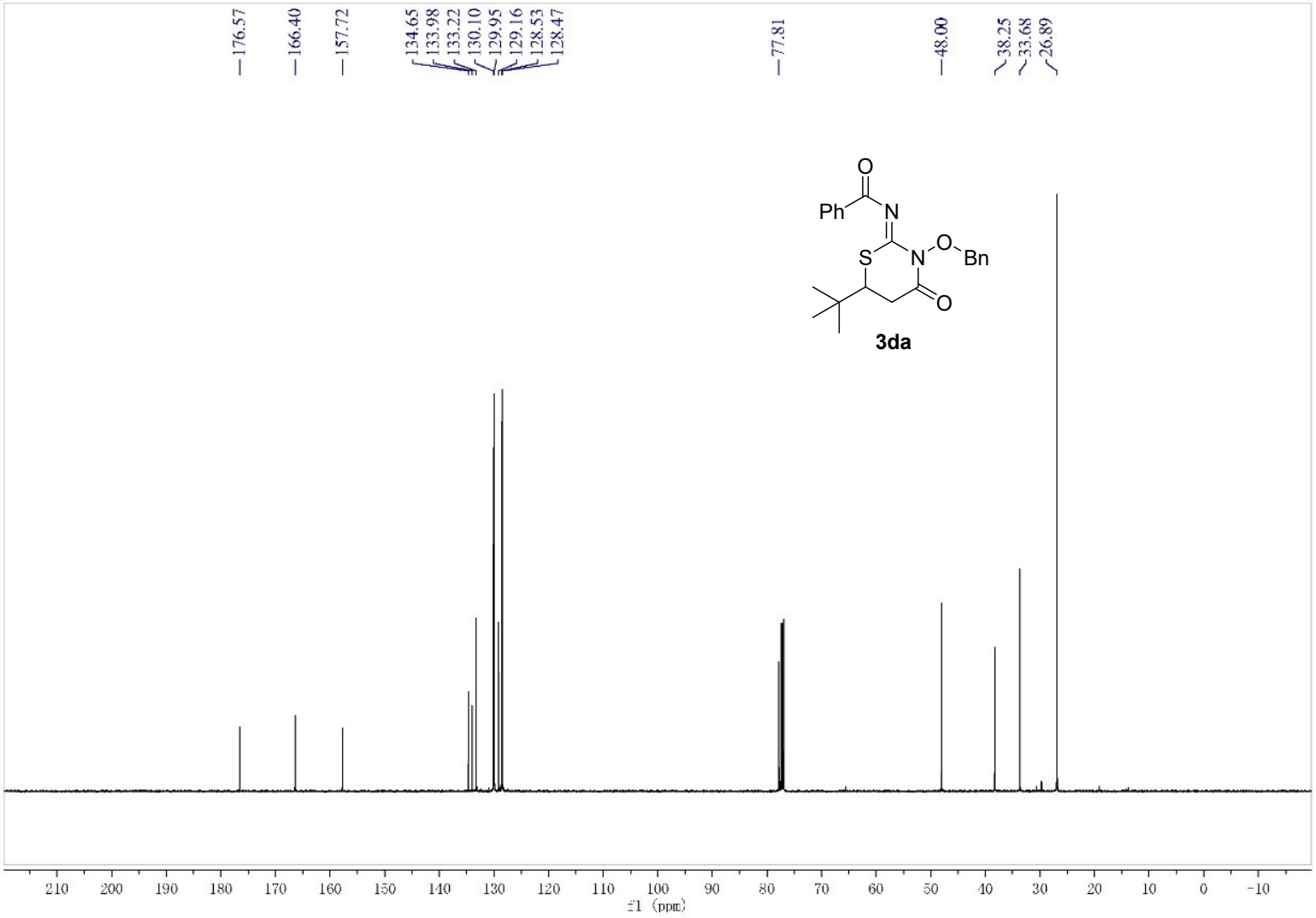
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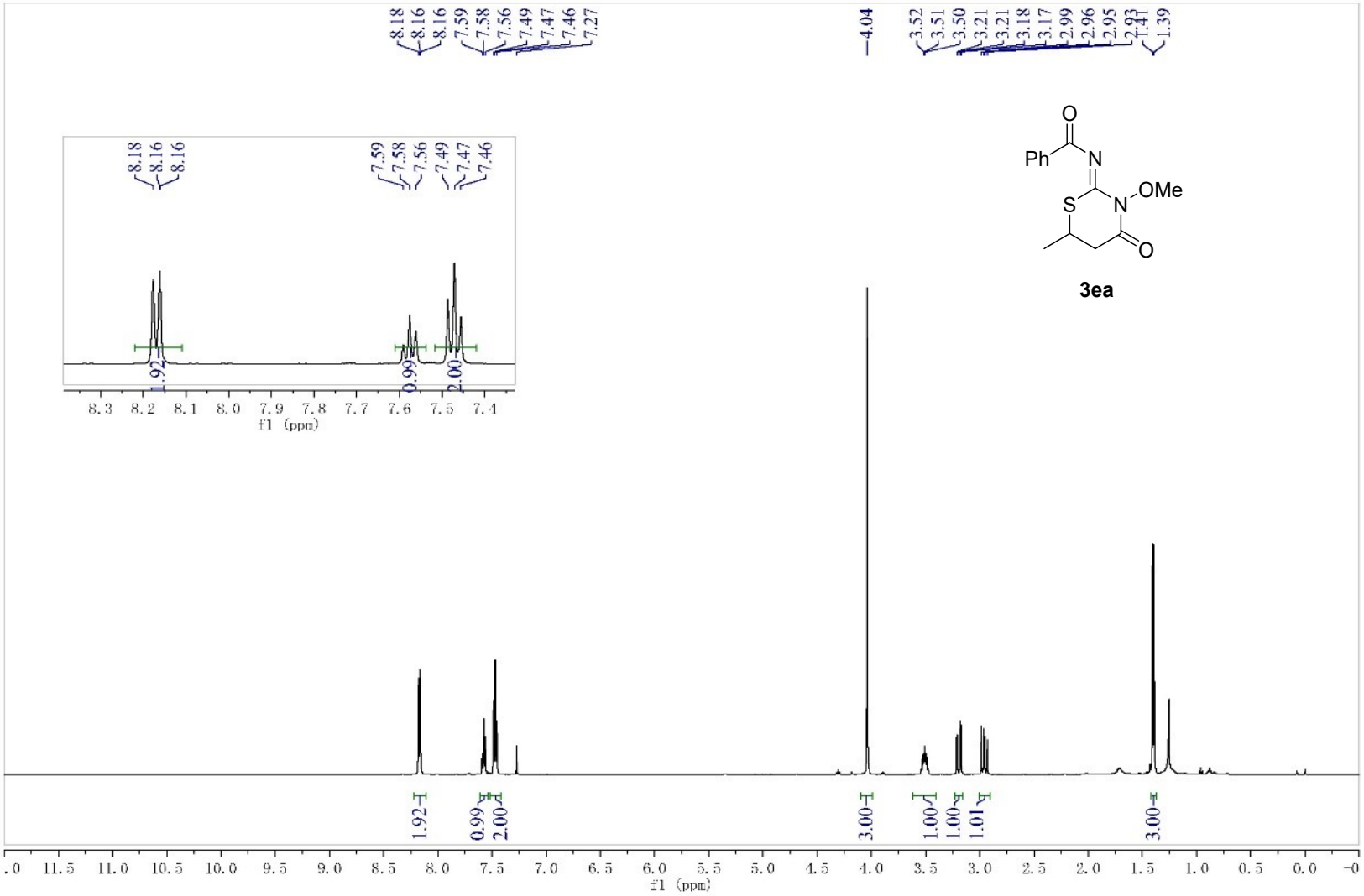
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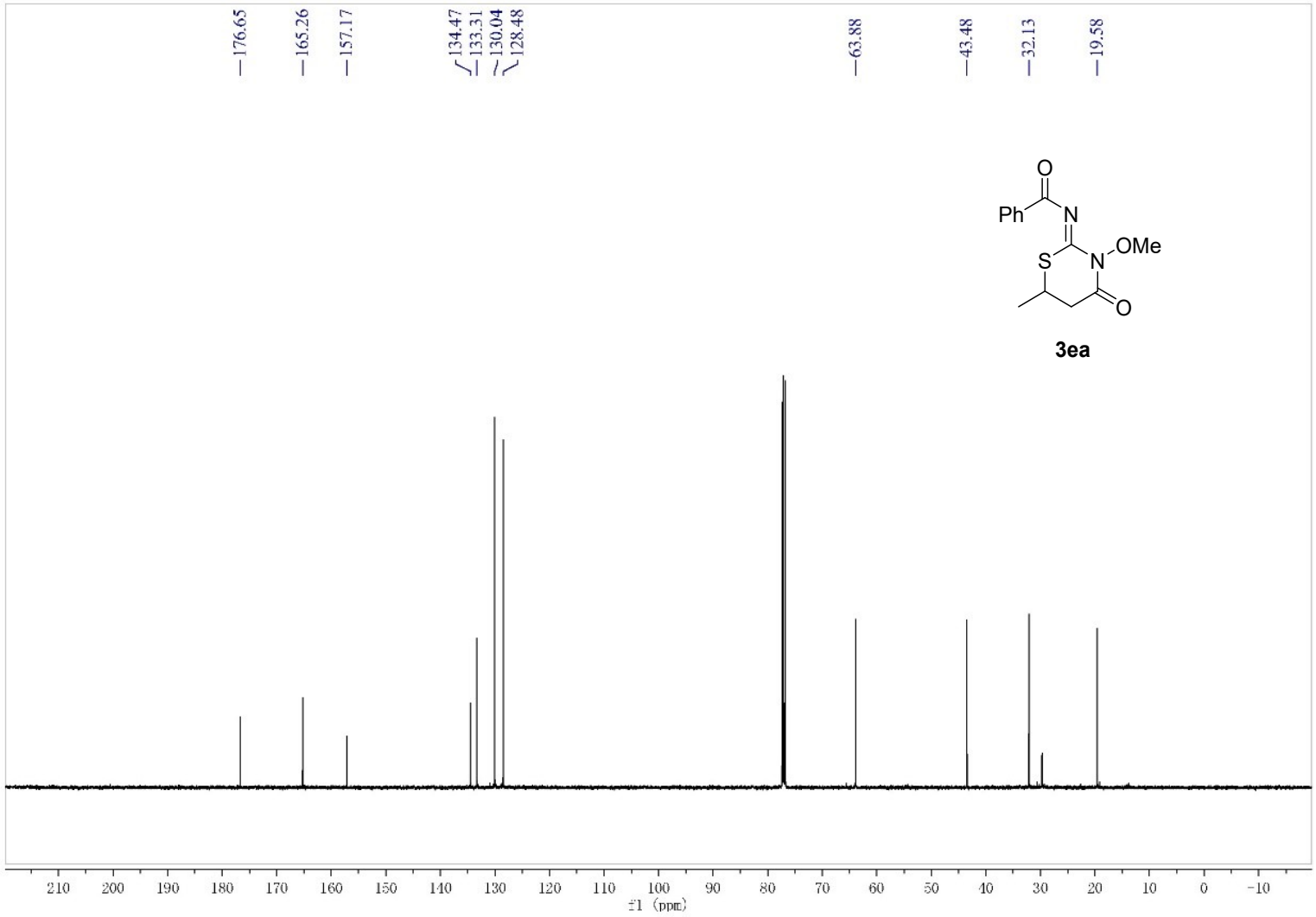
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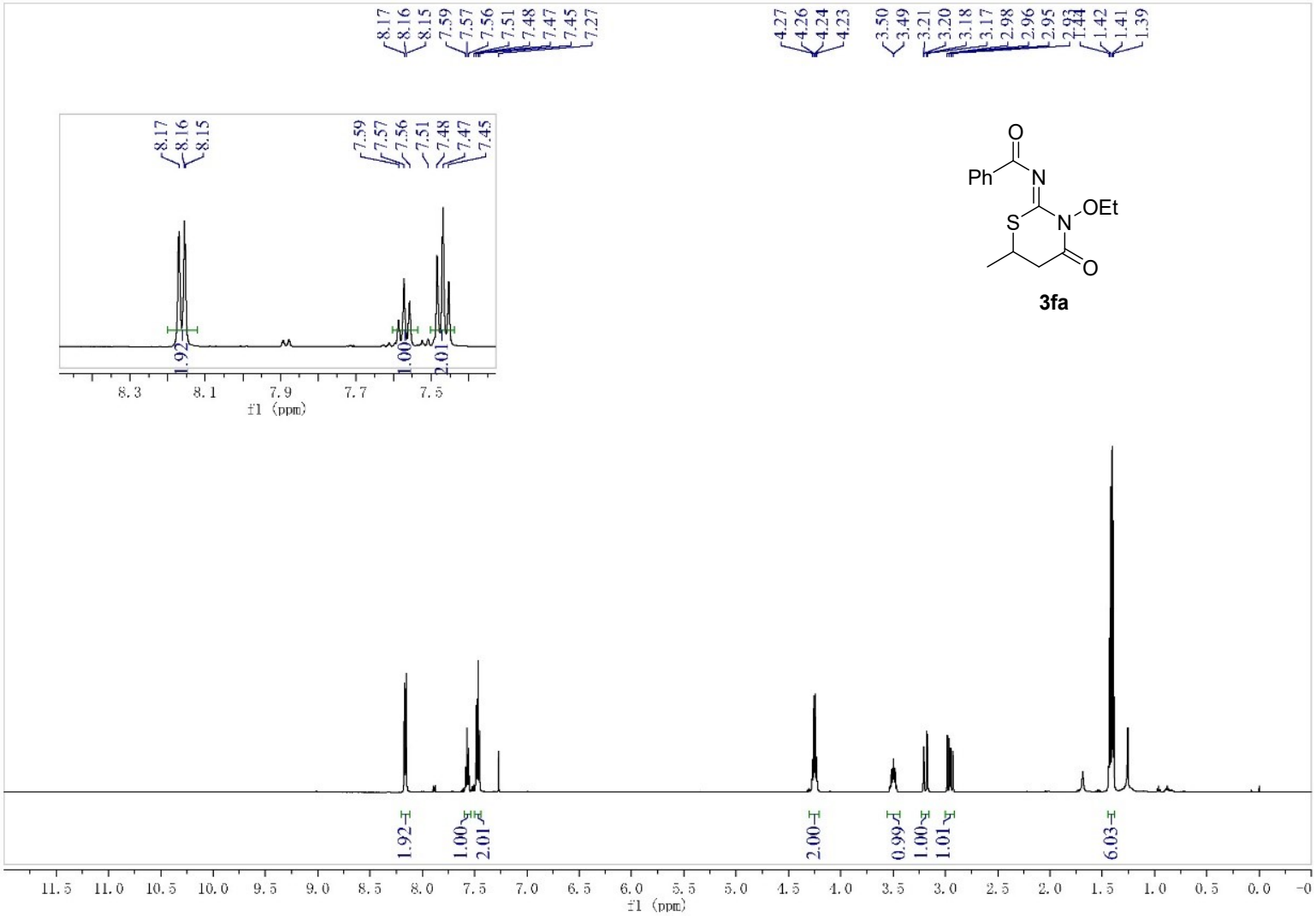
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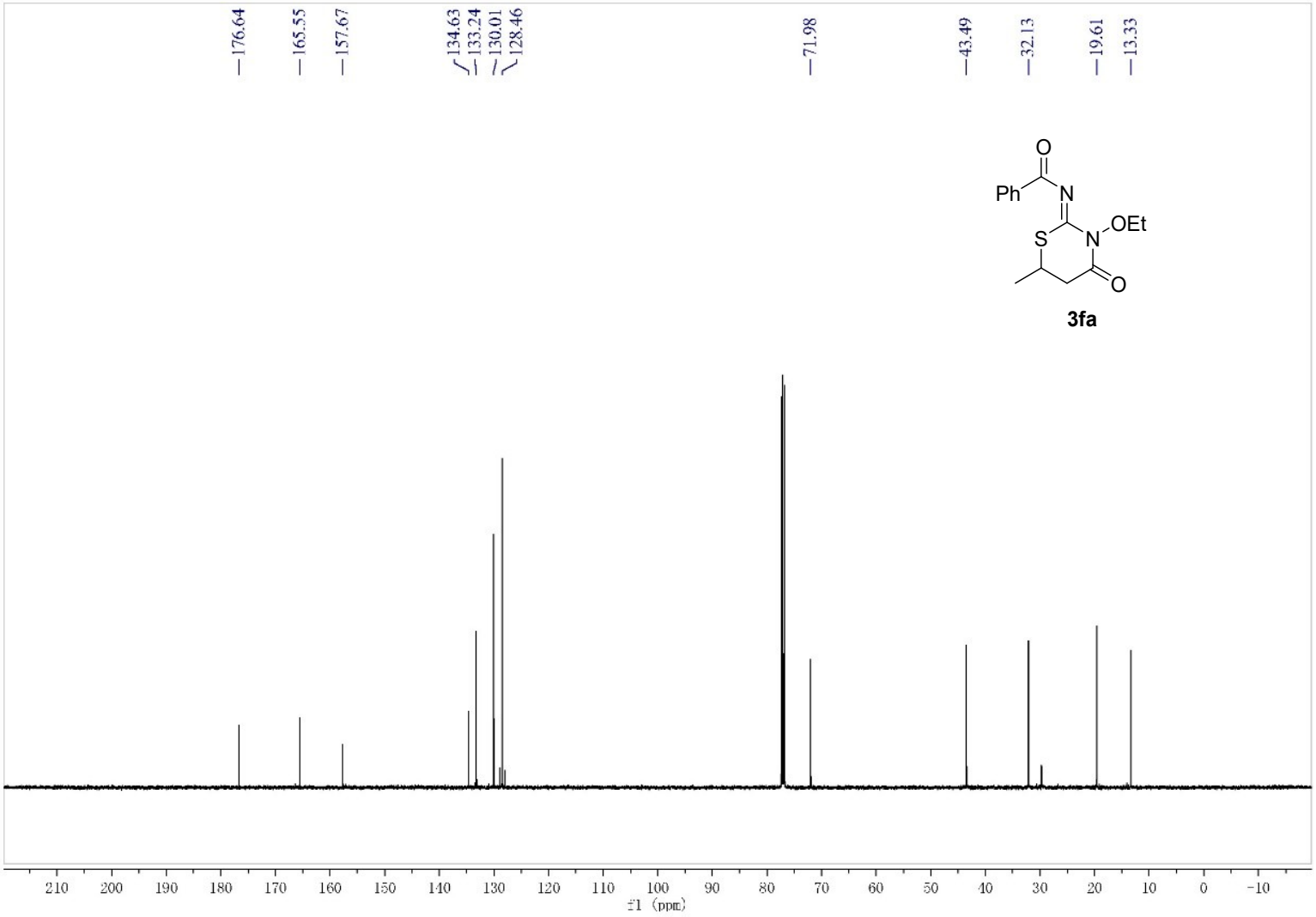
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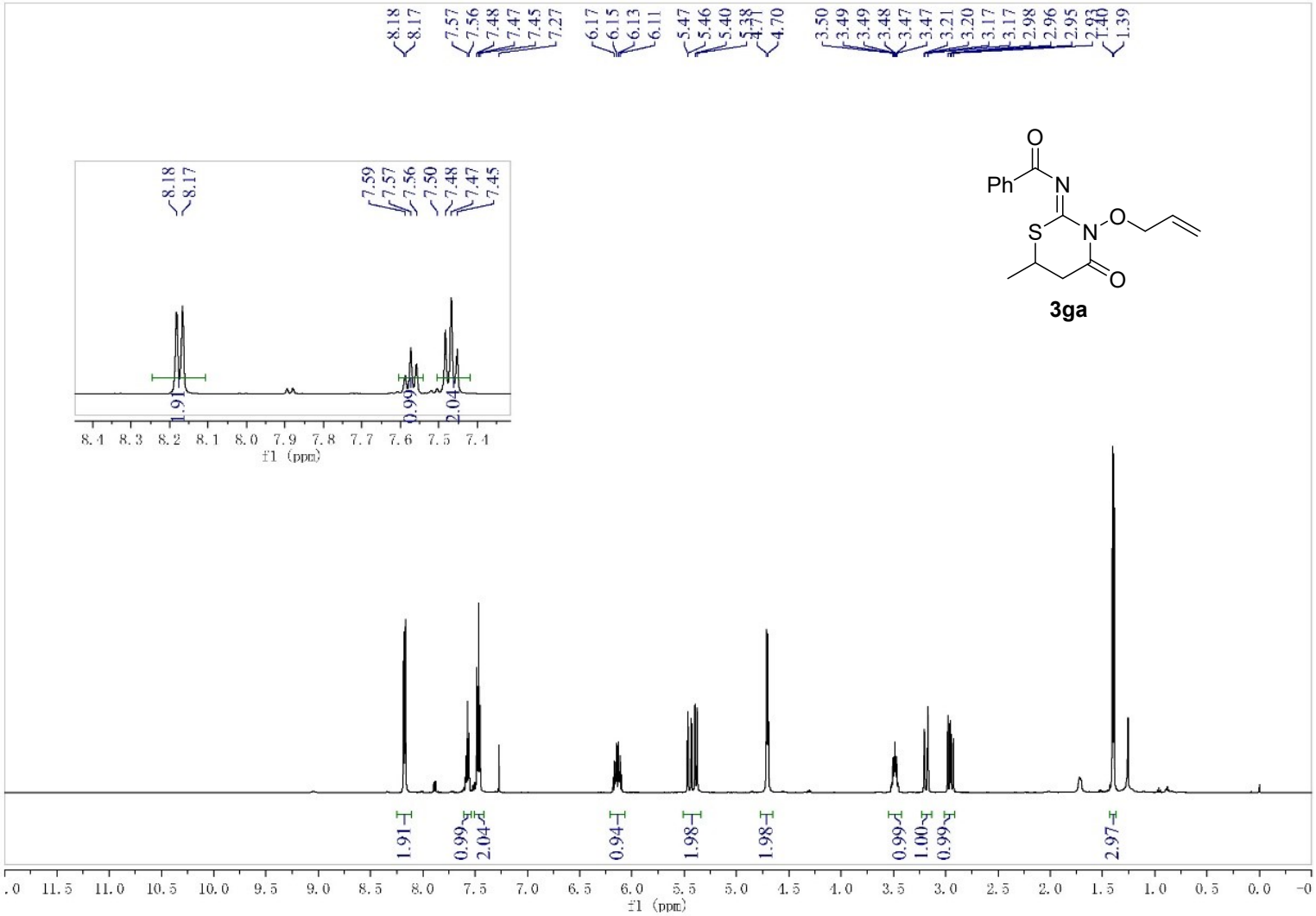
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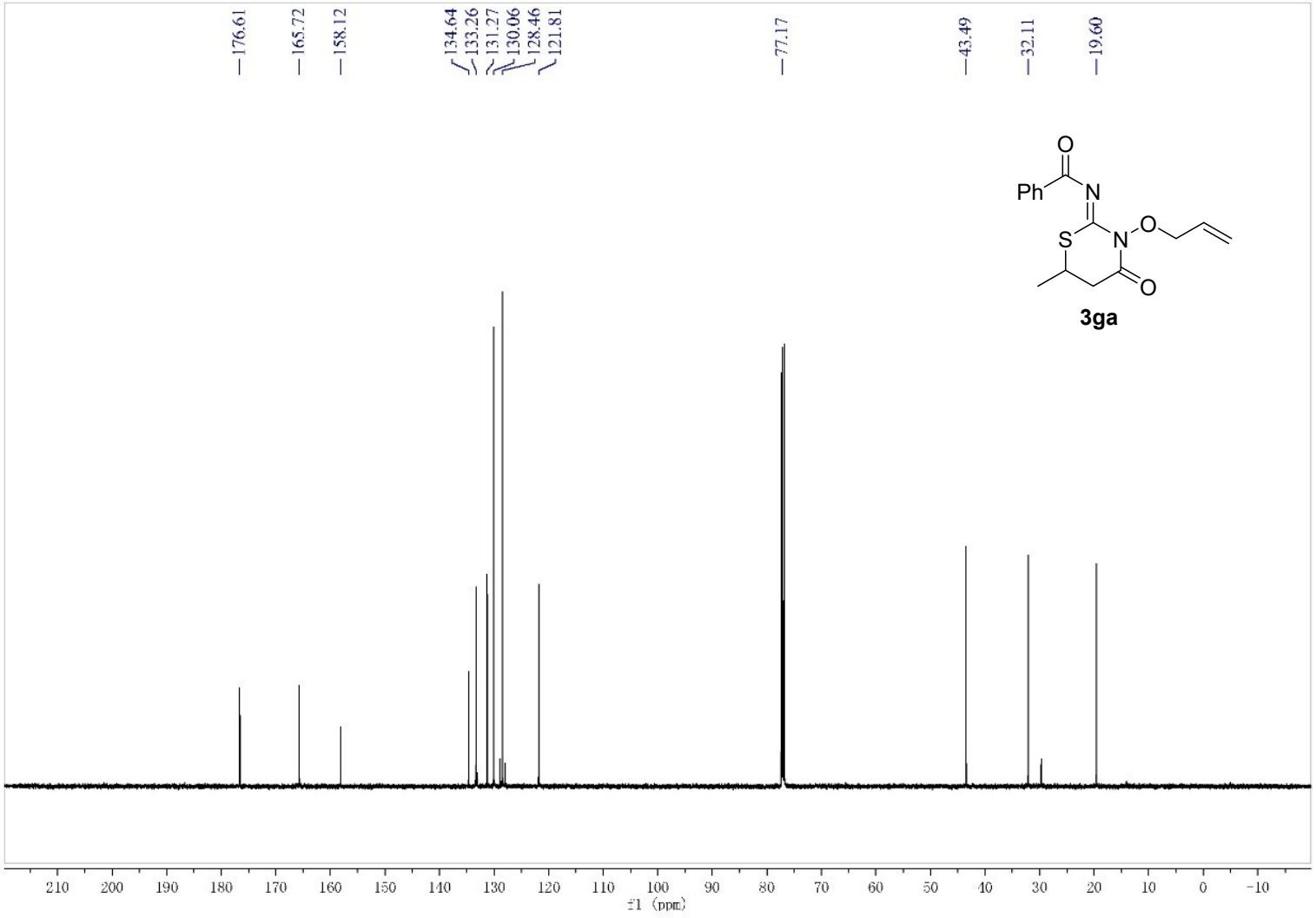
1.98
1.98
0.99
1.00
0.99
2.97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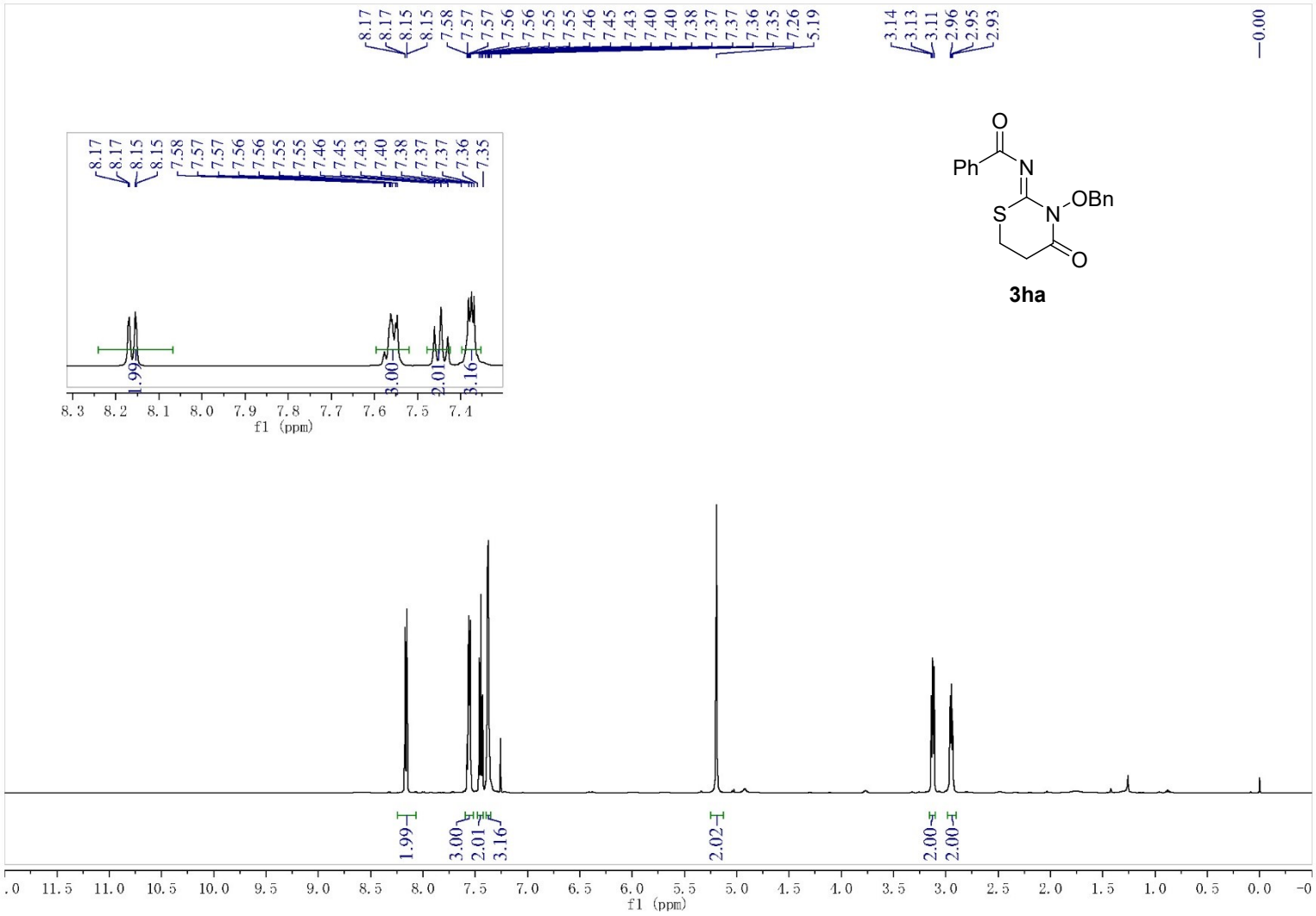
165.72
158.12
134.64
133.26
131.27
130.06
128.46
121.81
77.17
43.49
32.11
19.60
O
Ph
N
S
N
O
O
3ga
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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8.17
8.15
8.15
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7.57
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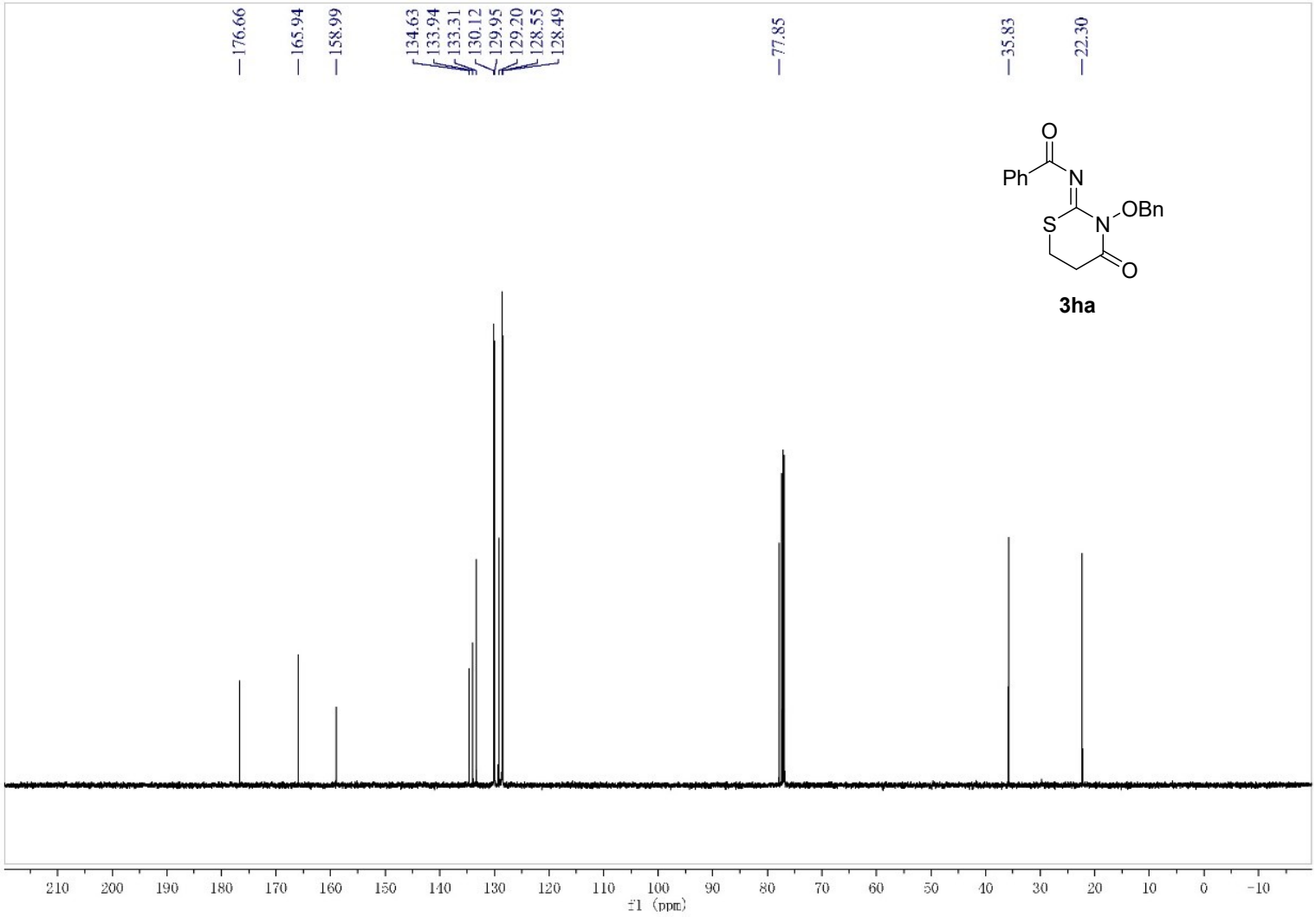
7.56
7.56
7.55
7.55
7.46
7.45
7.43
7.40
7.40
7.38
7.37
7.37
7.36
7.35
7.26
5.19
3.14
3.13
3.11
2.96
2.95
2.93
0.00
1.99
3.00
2.01
3.16
f1 (ppm)
Ph
N
O
S
N
OBn
O
3ha
2.02
2.00
2.00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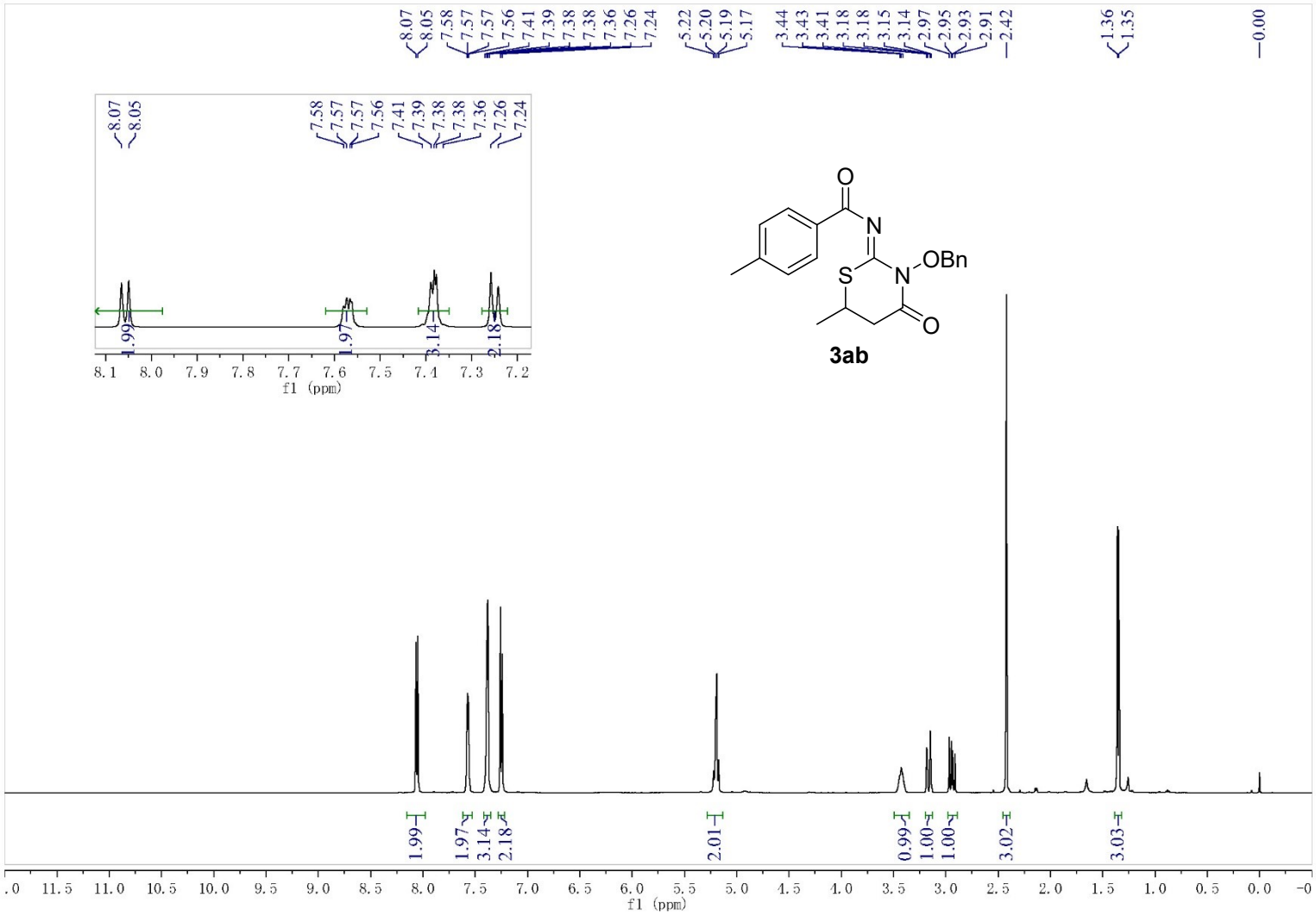
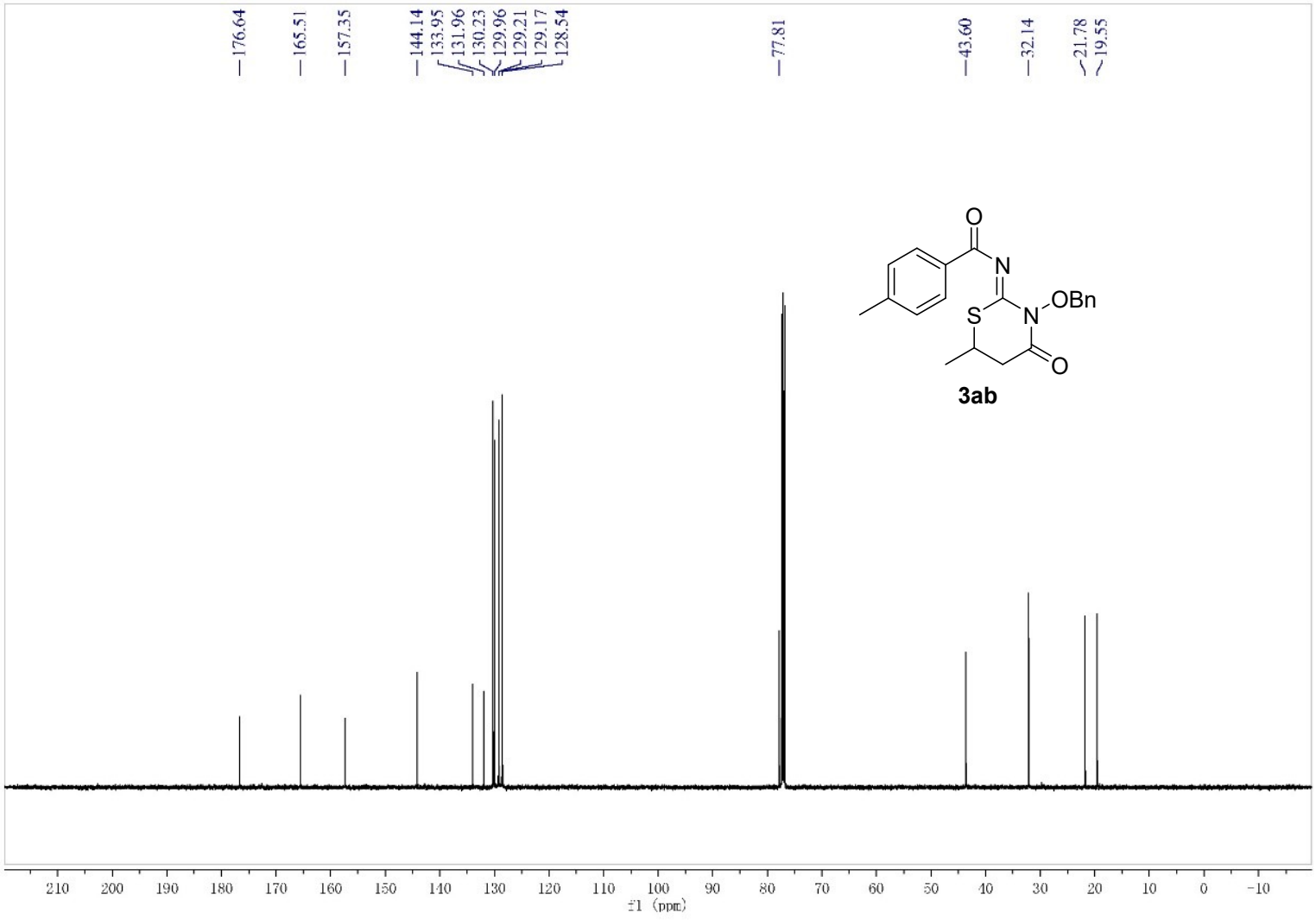
165.94
158.99
134.63
133.94
133.31
130.12
129.95
129.20
128.55
128.49
77.85
35.83
22.30
O
Ph
N
S
N
OBn
O
3ha
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.07
8.05
7.58
7.57
7.57
7.56
7.41
7.39
7.38
7.38
7.36
7.26
7.24
5.22
5.20
5.19
5.17
3.44
3.43
3.41
3.18
3.18
3.15
3.14
2.97
2.95
2.93
2.91
2.42
1.36
1.35
0.00
1.99
1.97
3.14
2.18
f1 (ppm)
O
N
S
N
OBn
O
3ab
2.01
0.99
1.00
1.00
3.02
3.03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157.35
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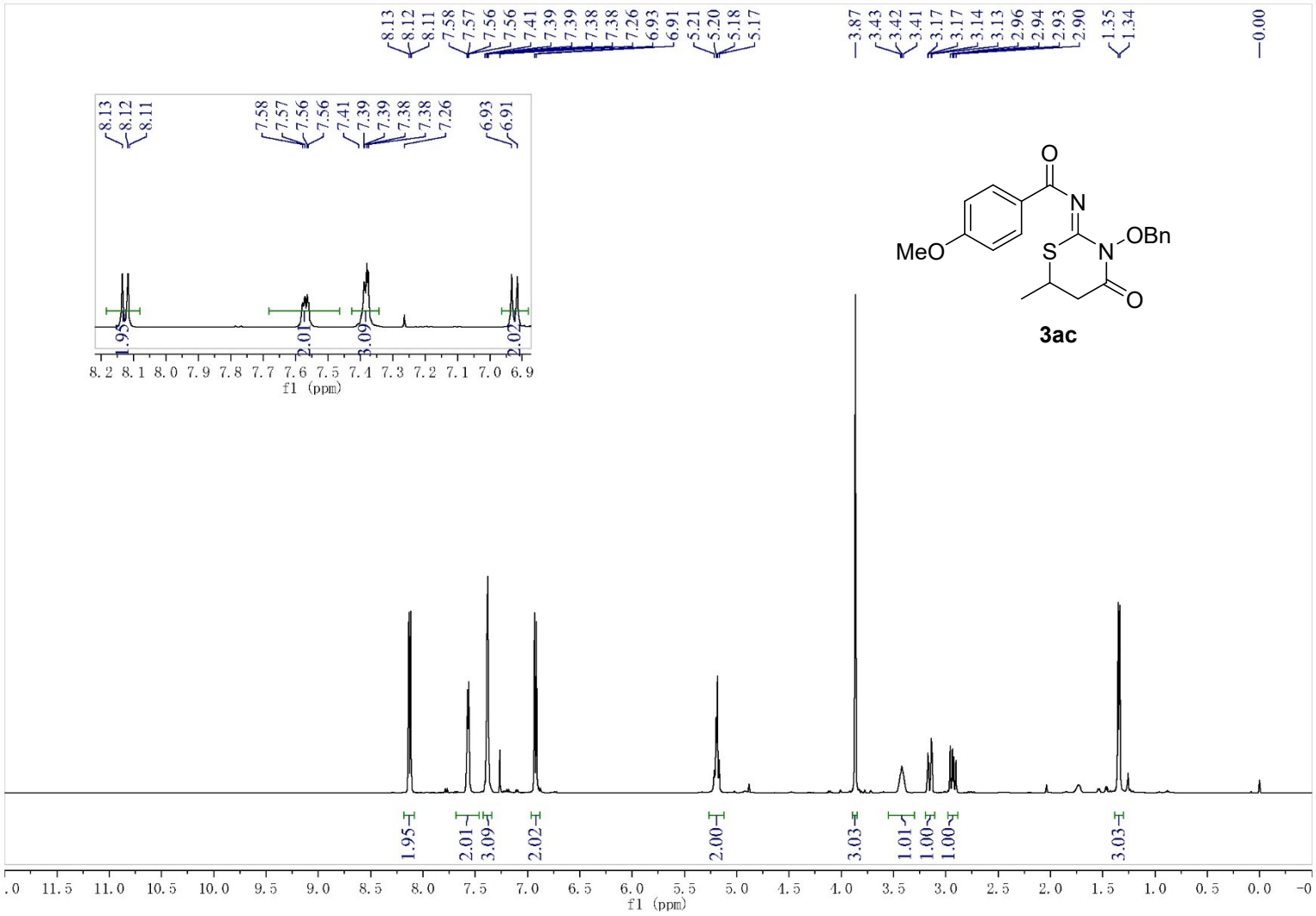
131.96
130.23
129.96
129.21
129.17
128.54
77.81
43.60
32.14
21.78
19.55
O
N
OBn
S
N
O
3ab
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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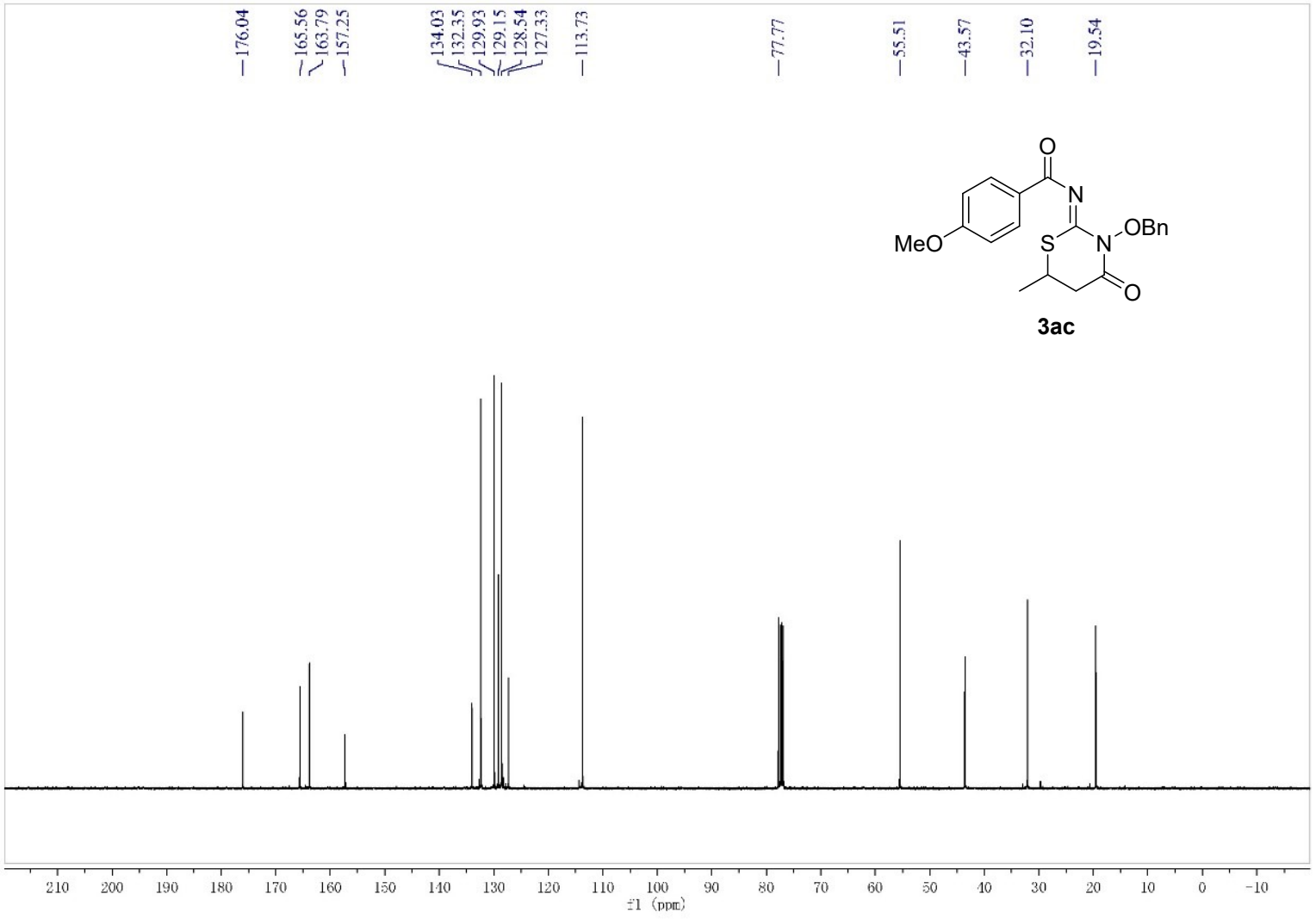
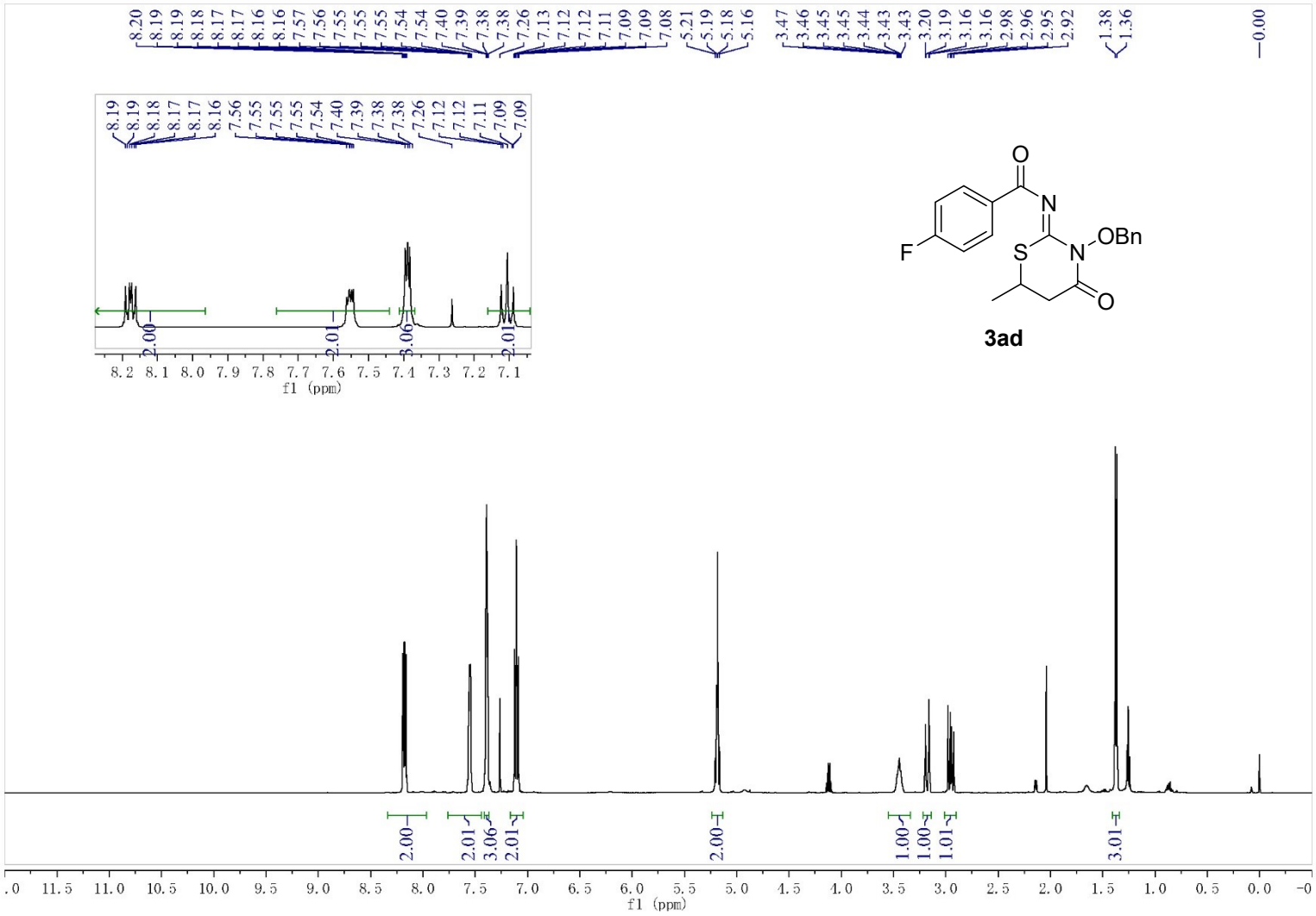
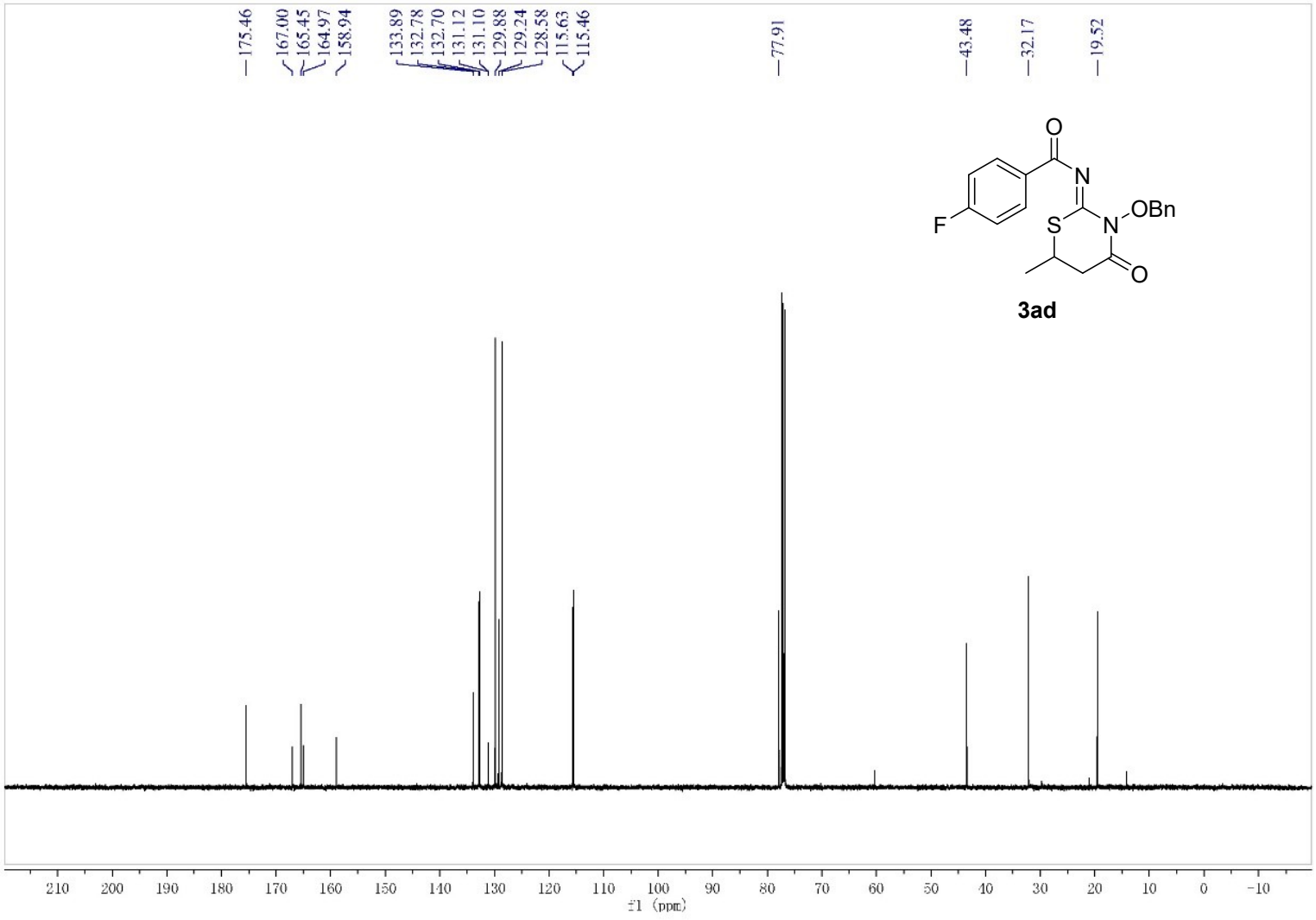
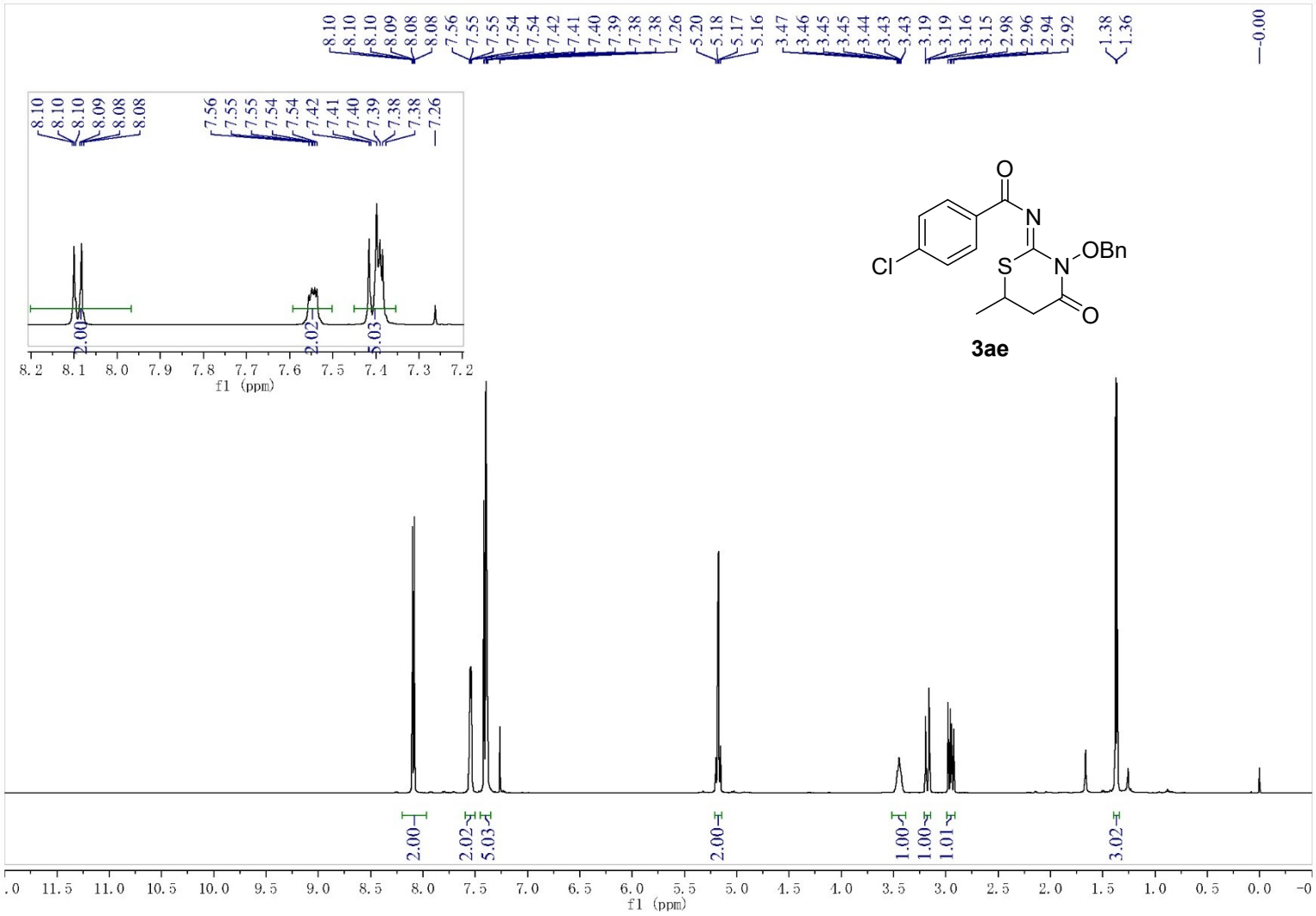
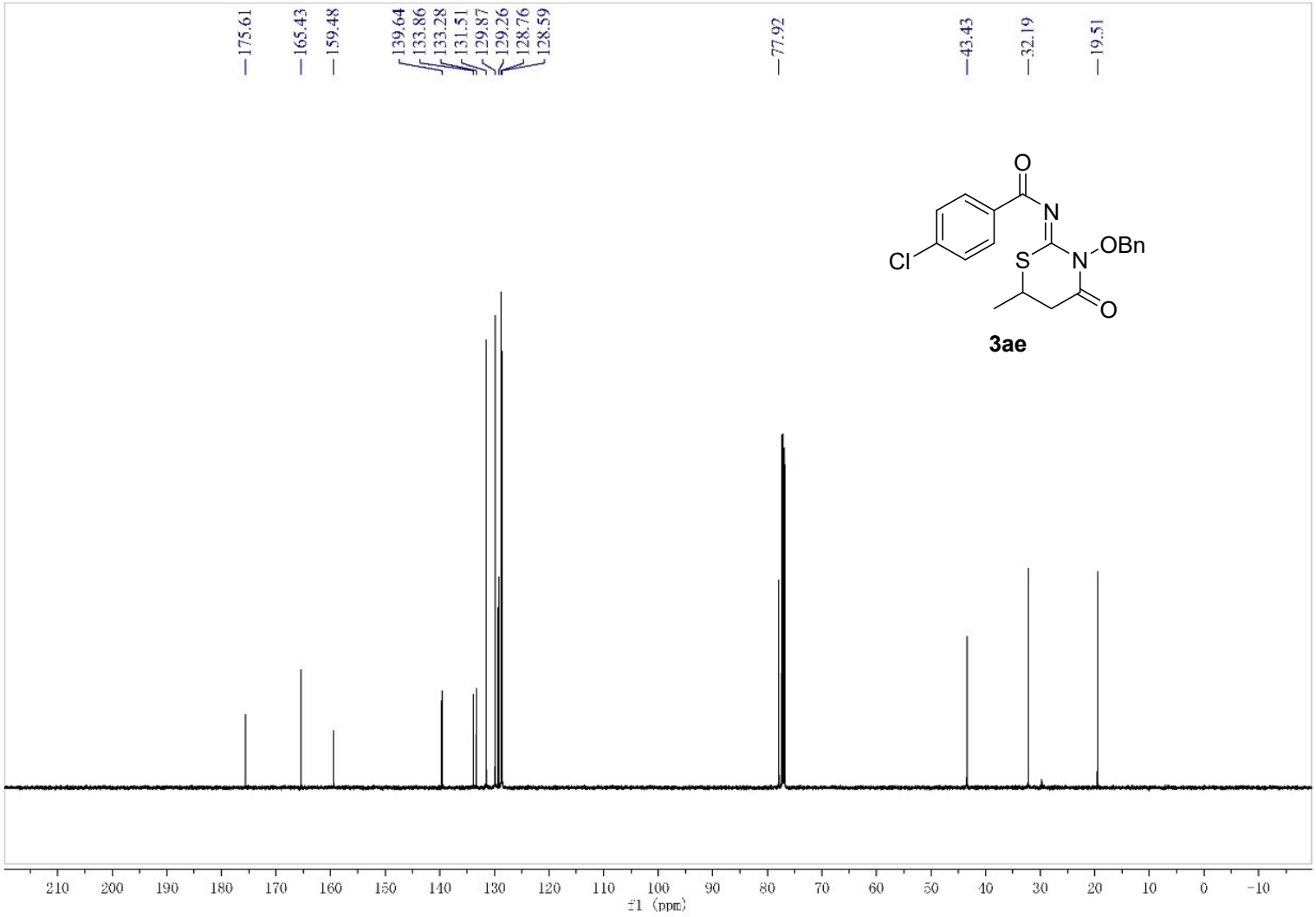
8.12
8.11
7.58
7.57
7.56
7.56
7.41
7.39
7.39
7.38
7.38
7.26
6.93
6.91
5.21
5.20
5.18
5.17
3.87
3.43
3.42
3.41
3.17
3.17
3.14
3.13
2.96
2.94
2.93
2.90
1.35
1.34
0.00
1.95
2.01
3.09
2.02
2.00
3.03
1.01
1.00
1.00
3.03
f1 (ppm)
O
N
MeO
S
N
OBn
O
3ac

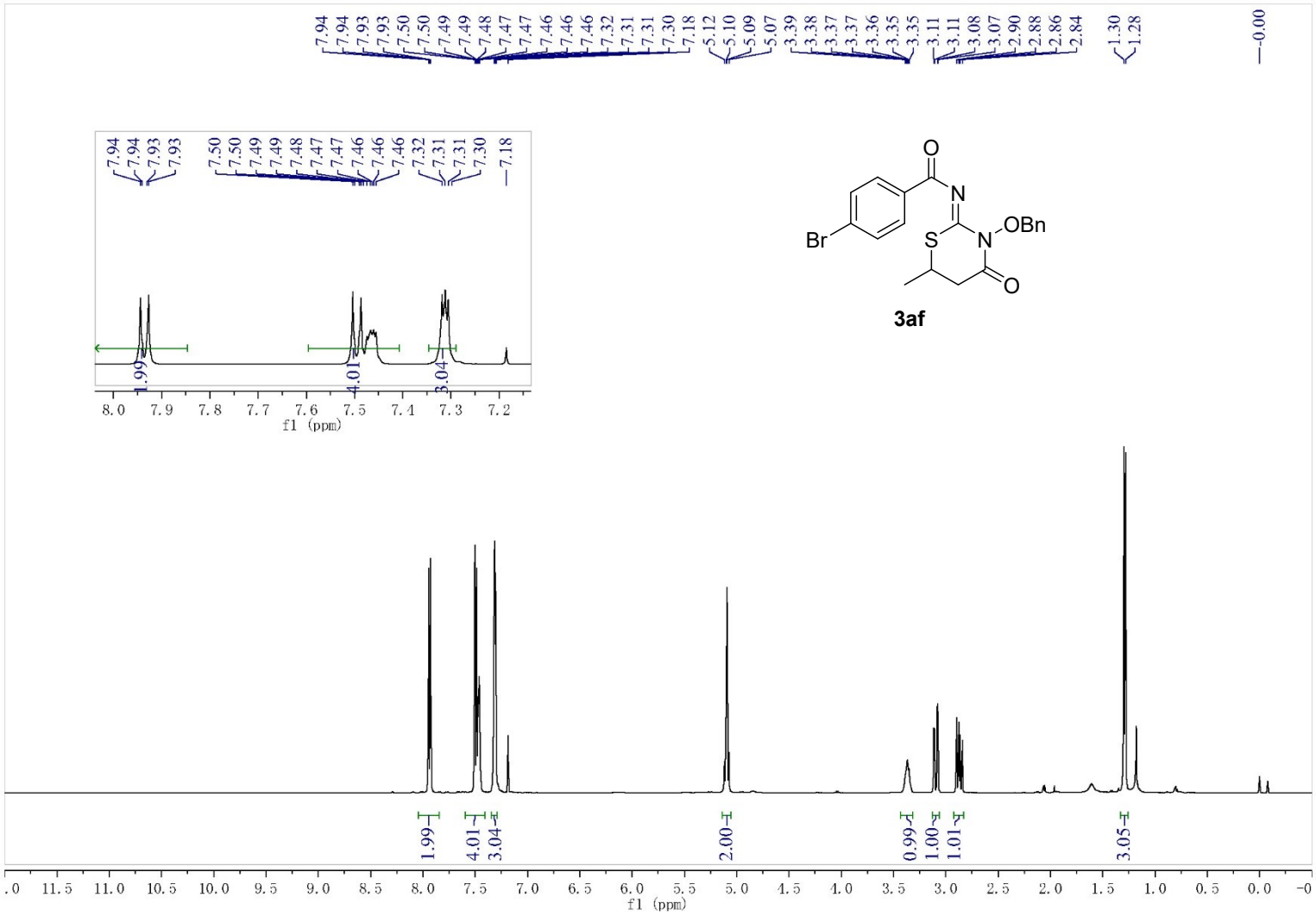

176.04
165.56
163.79
157.25
134.03
132.35
129.93
129.15
128.54
127.33
113.73
77.77
55.51
43.57
32.10
19.54
O
N
MeO
S
N
OBn
O
3ac
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

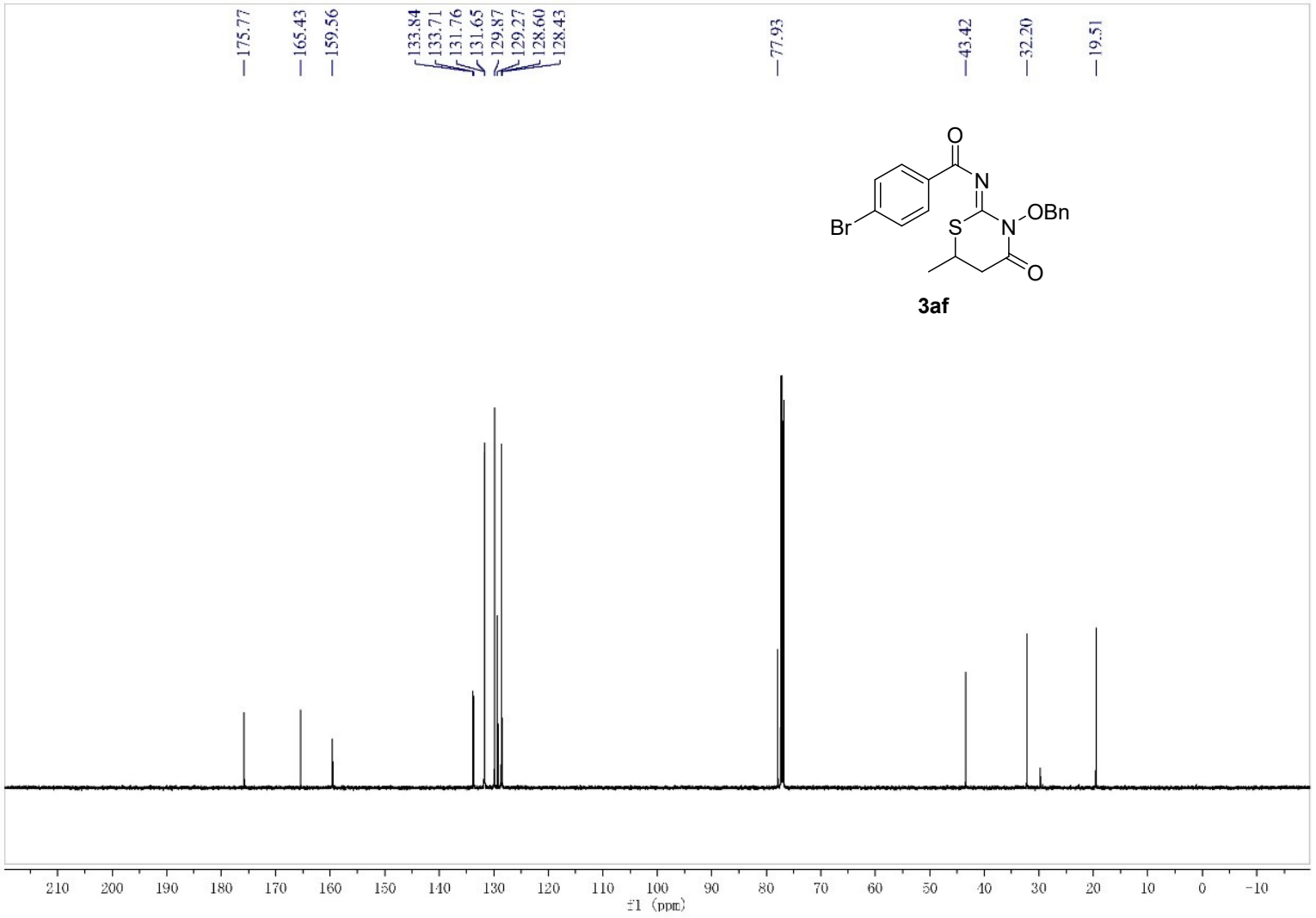

8.20 8.19 8.19 8.18 8.17 8.17 8.16 8.16 7.57 7.56 7.55 7.55 7.55 7.54 7.54 7.40 7.39 7.38 7.38 7.26 7.13 7.12 7.12 7.11 7.09 7.09 7.08 5.21 5.19 5.18 5.16 3.47 3.46 3.45 3.45 3.44 3.43 3.43 3.20 3.19 3.16 3.16 2.98 2.96 2.95 2.92 1.38 1.36 0.00
2.00 2.01 3.06 2.01
f1 (ppm)
O N S N OBn F O
3ad
2.00 2.01 3.06 2.01 2.00 1.00 1.00 1.01 3.01
f1 (ppm)


175.46
167.00
165.45
164.97
158.94
133.89
132.78
132.70
131.12
131.10
129.88
129.24
128.58
115.63
115.46
77.91
43.48
32.17
19.52
O
N
F
S
N
OBn
O
3ad
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.10
8.10
8.10
8.09
8.08
8.08
7.56
7.55
7.55
7.54
7.54
7.42
7.41
7.40
7.39
7.38
7.38
7.26
5.20
5.18
5.17
5.16
3.47
3.46
3.45
3.45
3.44
3.43
3.43
3.19
3.19
3.16
3.15
2.98
2.96
2.94
2.92
1.38
1.36
-0.00
2.00
2.02
5.03
f1 (ppm)
O
N
OBn
Cl
S
N
O
3ae
2.00
2.02
5.03
2.00
1.00
1.00
1.01
3.02
f1 (ppm)


175.61
165.43
159.48
139.64
133.86
133.28
131.51
129.87
129.26
128.76
128.59
77.92
43.43
32.19
19.51
O
N
OBn
Cl
S
N
O
3ae
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.94
7.94
7.93
7.93
7.50
7.50
7.49
7.49
7.48
7.47
7.47
7.46
7.46
7.46
7.32
7.31
7.31
7.30
7.18
5.12
5.10
5.09
5.07
3.39
3.38
3.37
3.37
3.36
3.35
3.35
3.11
3.11
3.08
3.07
2.90
2.88
2.86
2.84
1.30
1.28
-0.00
1.99
4.01
3.04
f1 (ppm)
O
N
OBn
Br
S
N
O
3af
2.00
0.99
1.00
1.01
3.05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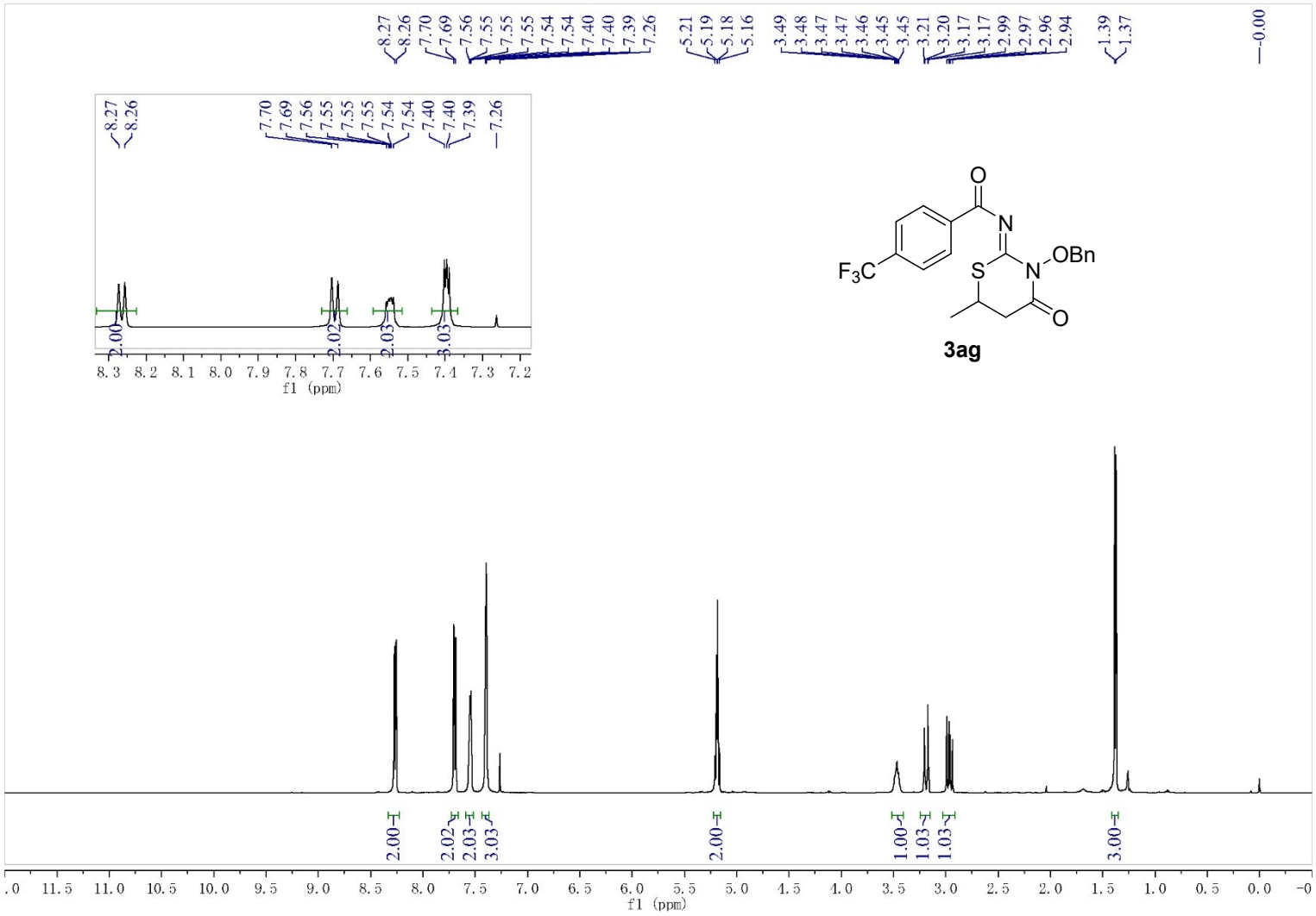
165.43
159.56
133.84
133.71
131.76
131.65
129.87
129.27
128.60
128.43
77.93
43.42
32.20
19.51
O
N
Br
S
N
OBn
O
3af
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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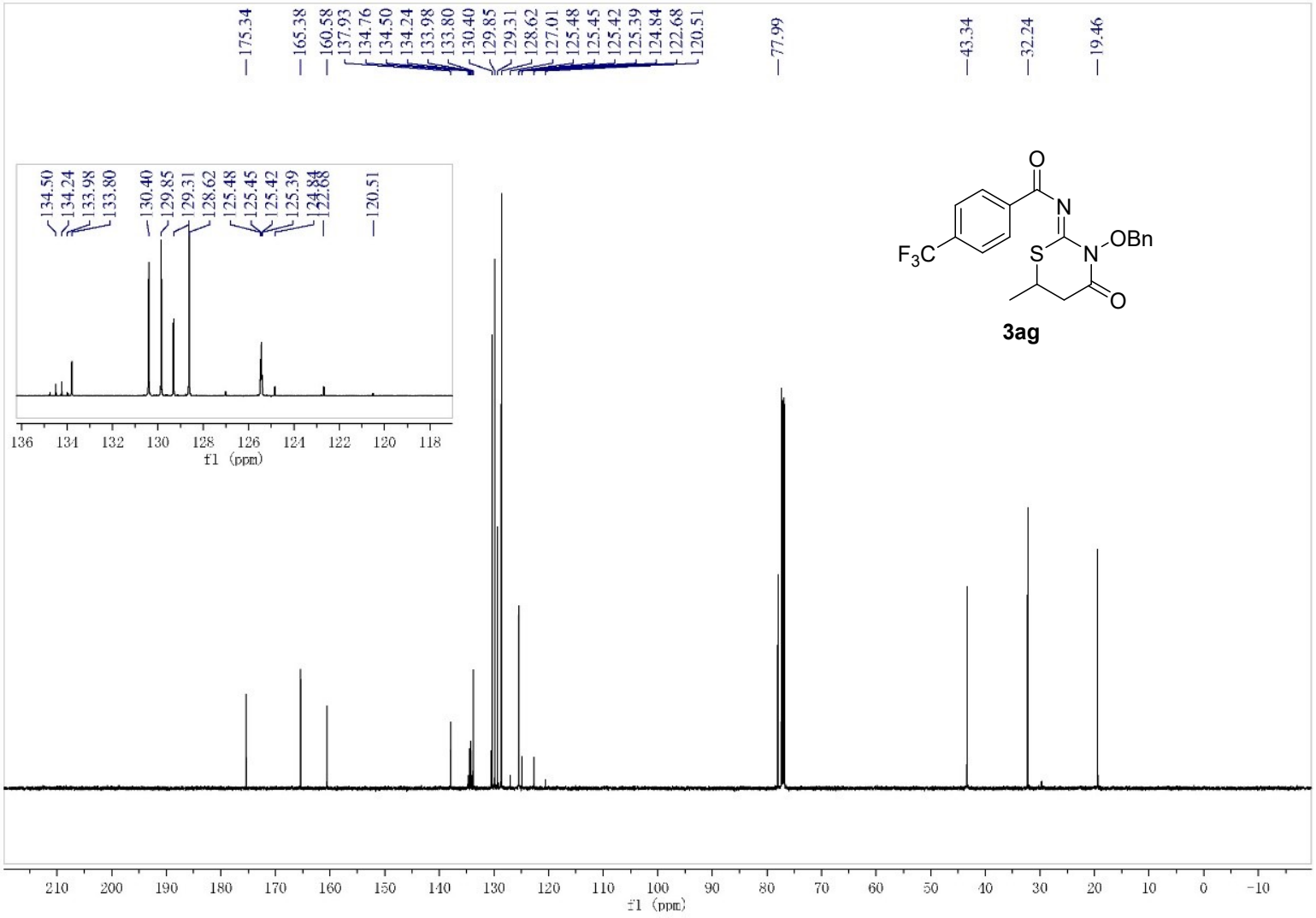
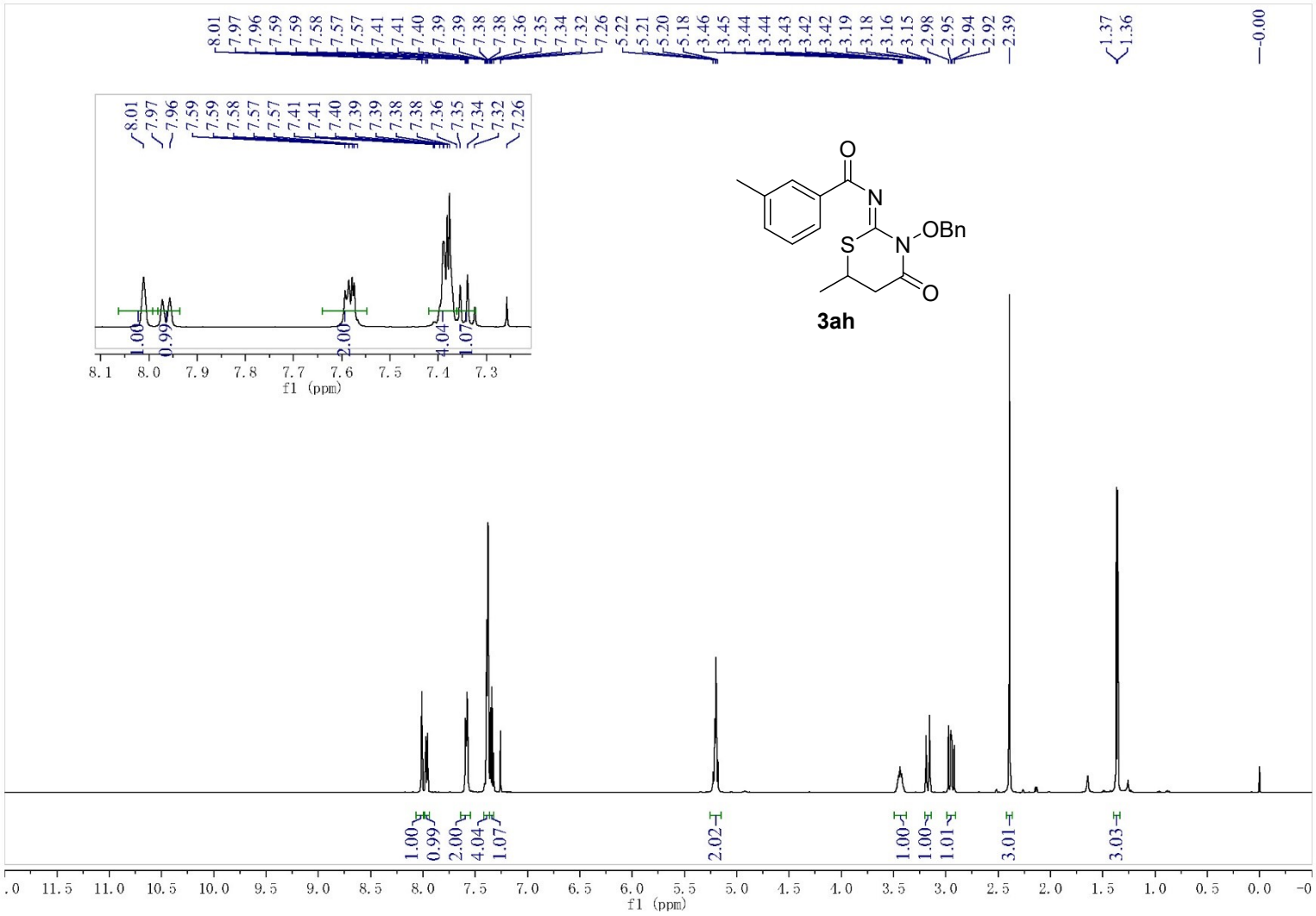
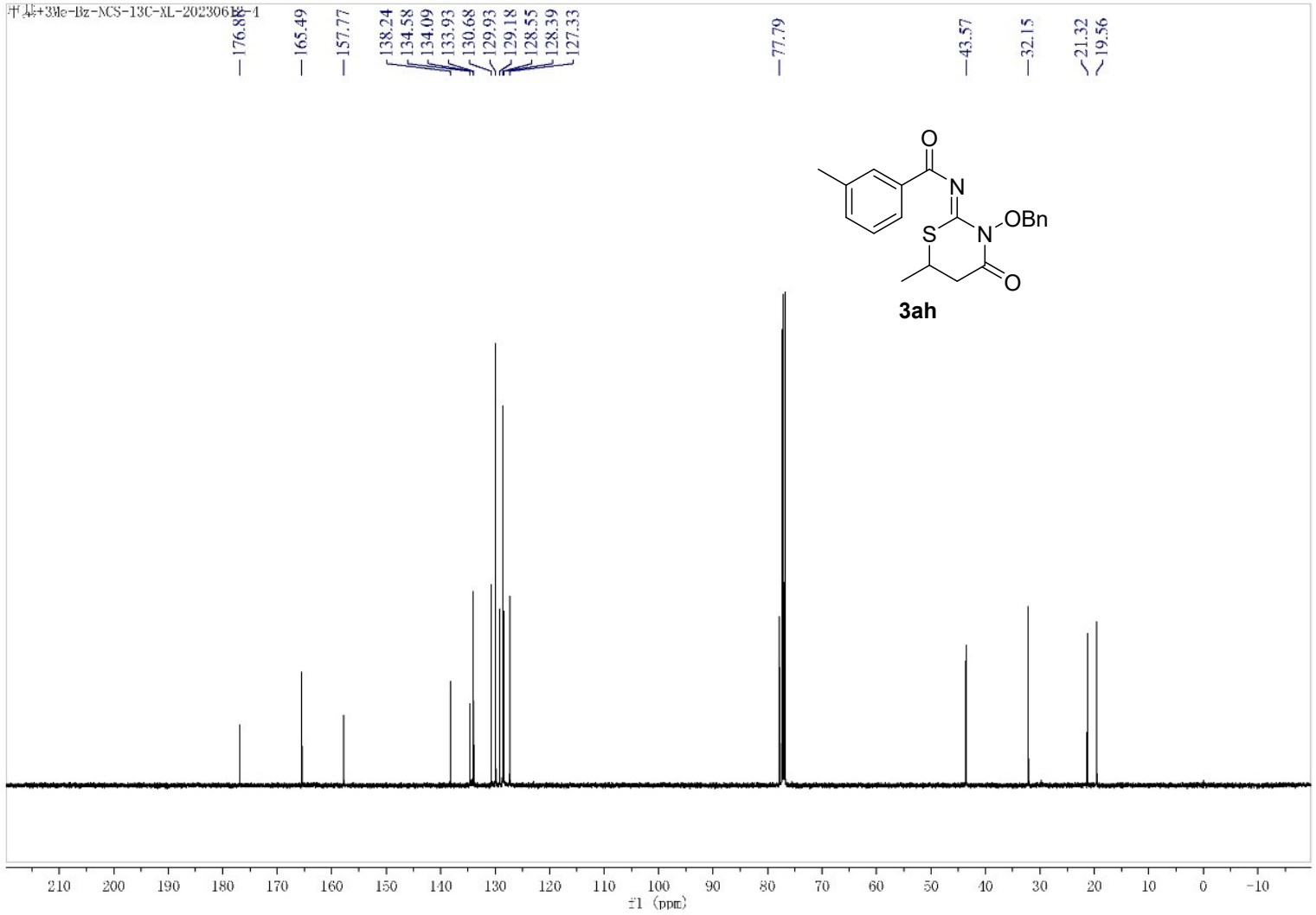
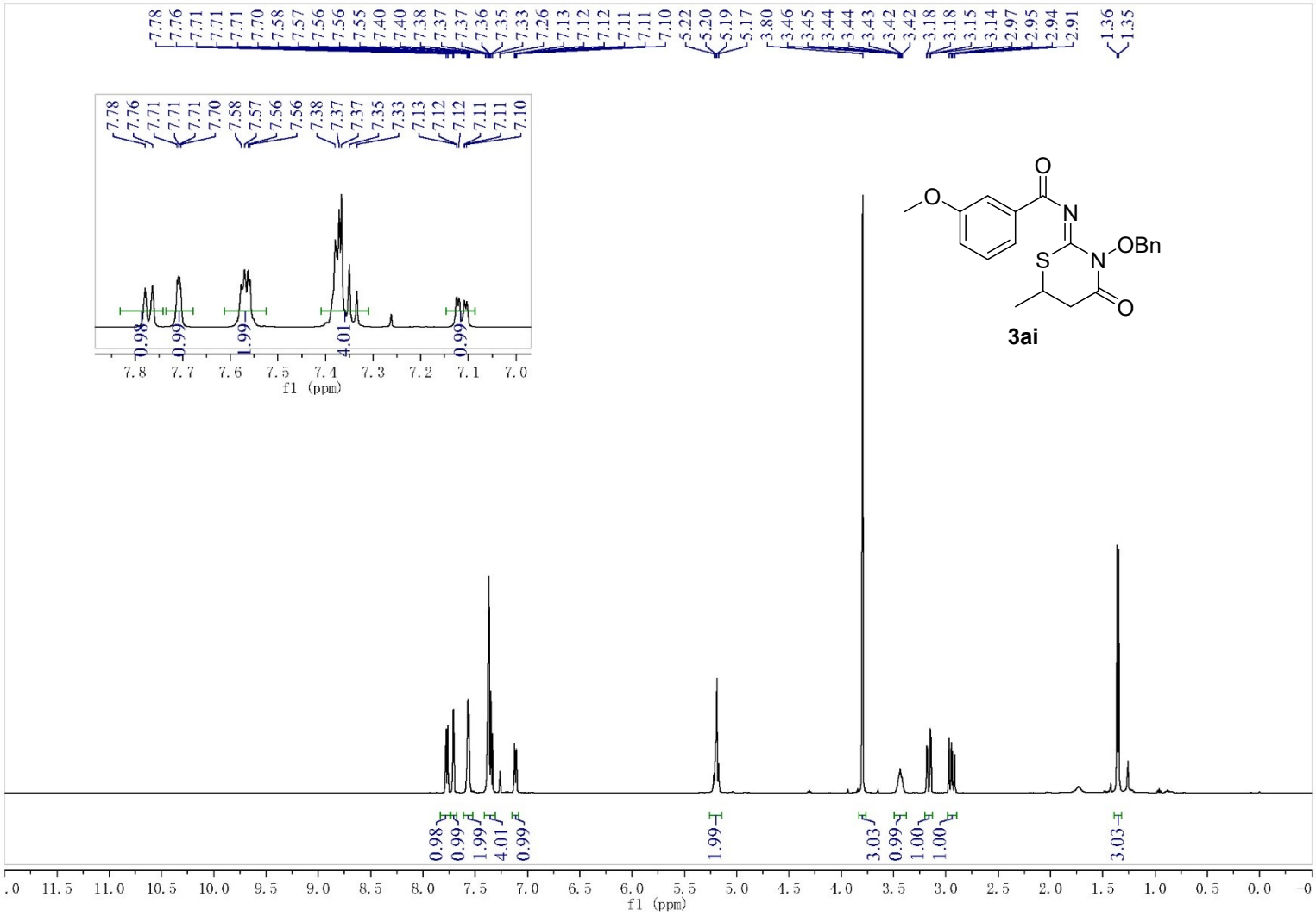
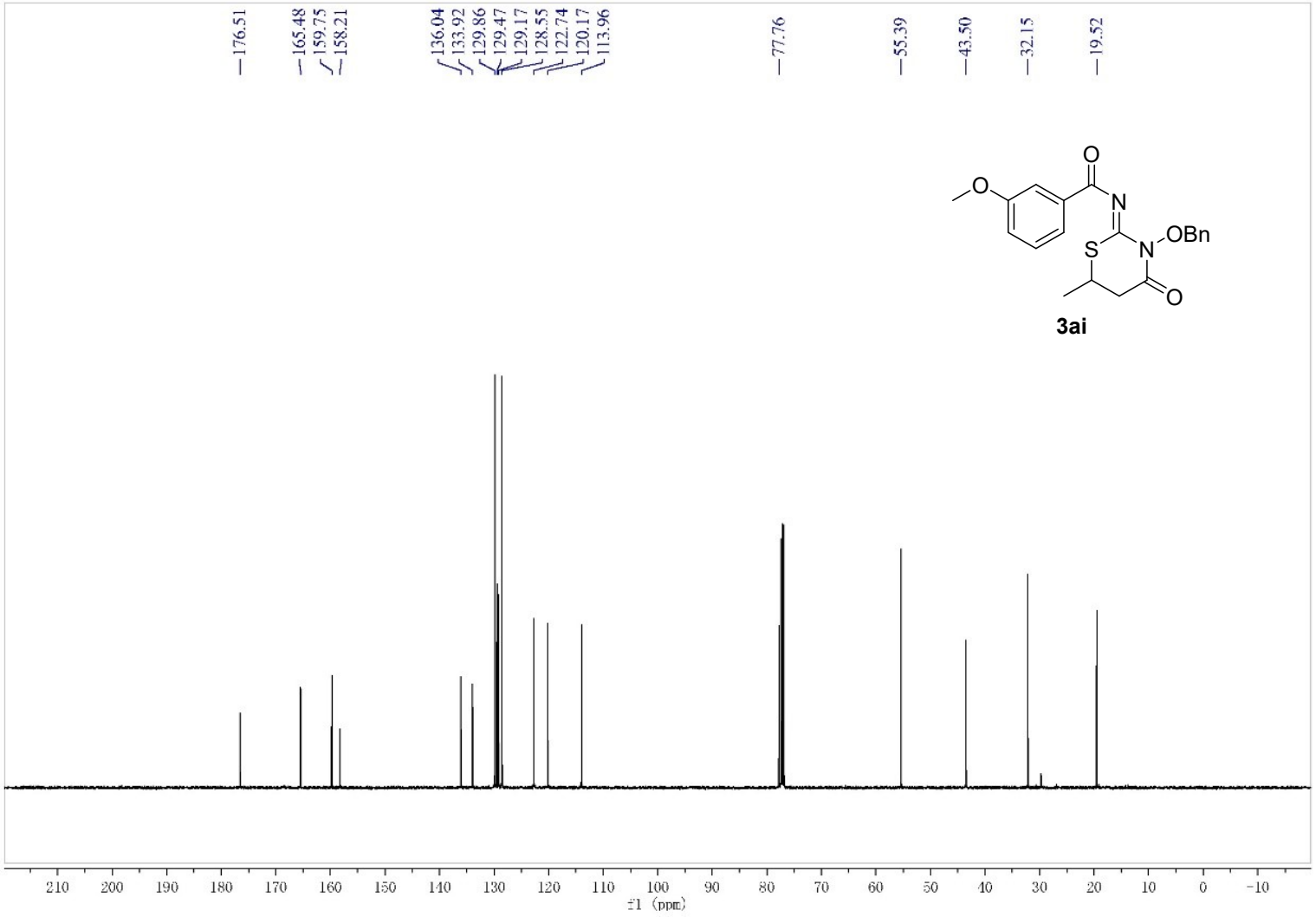
8.26
7.70
7.69
7.56
7.55
7.55
7.55
7.54
7.54
7.40
7.40
7.39
7.26
5.21
5.19
5.18
5.16
3.49
3.48
3.47
3.47
3.46
3.45
3.45
3.21
3.20
3.17
3.17
2.99
2.97
2.96
2.94
1.39
1.37
-0.00
2.00
2.02
2.03
3.03
f1 (ppm)
F3C
S
N
OBn
O
3ag
2.00
2.02
2.03
3.03
2.00
1.00
1.03
1.03
3.00
f1 (ppm)

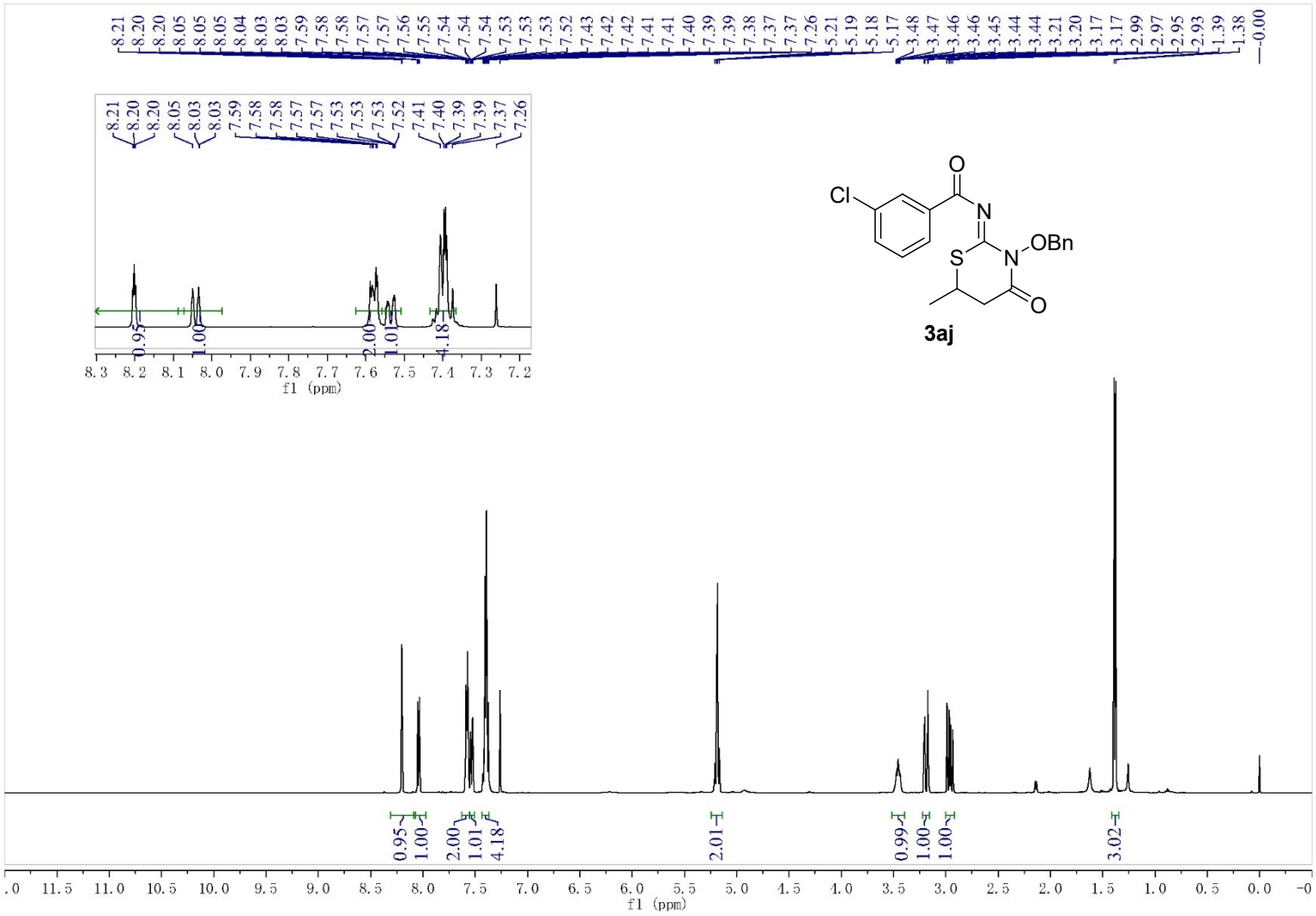

175.34
165.38
160.58
137.93
134.76
134.50
134.24
133.98
133.80
130.40
129.85
129.31
128.62
127.01
125.48
125.45
125.42
125.39
124.84
122.68
120.51
77.99
43.34
32.24
19.46
f1 (ppm)
O
N
OBn
S
N
O
F3C
3ag

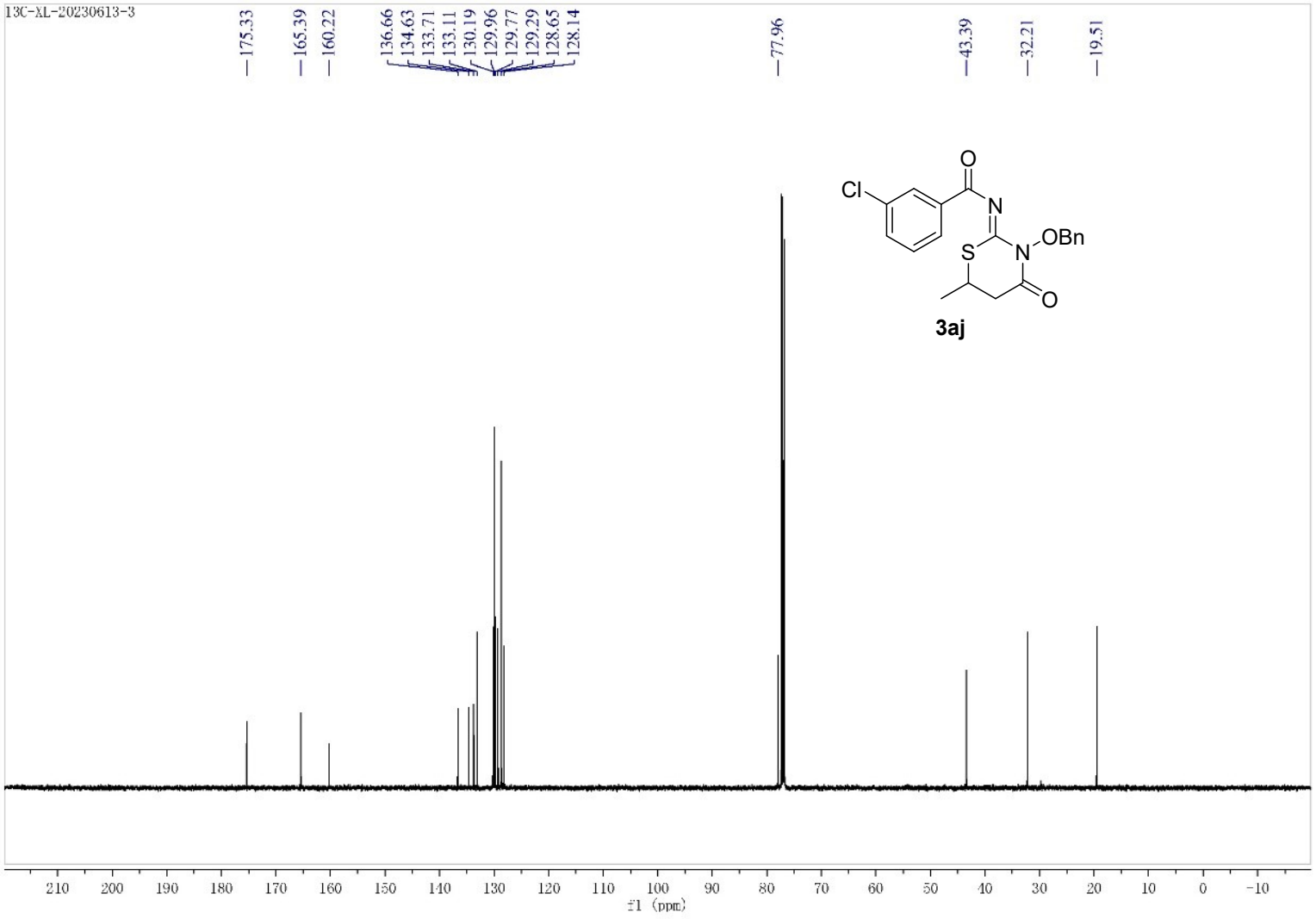

8.01
7.97
7.96
7.59
7.59
7.58
7.57
7.57
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.36
7.35
7.34
7.32
7.26
5.22
5.21
5.20
5.18
3.46
3.45
3.44
3.44
3.43
3.42
3.42
3.19
3.18
3.16
3.15
2.98
2.95
2.94
2.92
2.39
1.37
1.36
0.00
1.00
0.99
2.00
4.04
1.07
2.02
1.00
1.00
1.01
3.01
3.03
f1 (ppm)
O
N
S
N
OBn
O
3ah

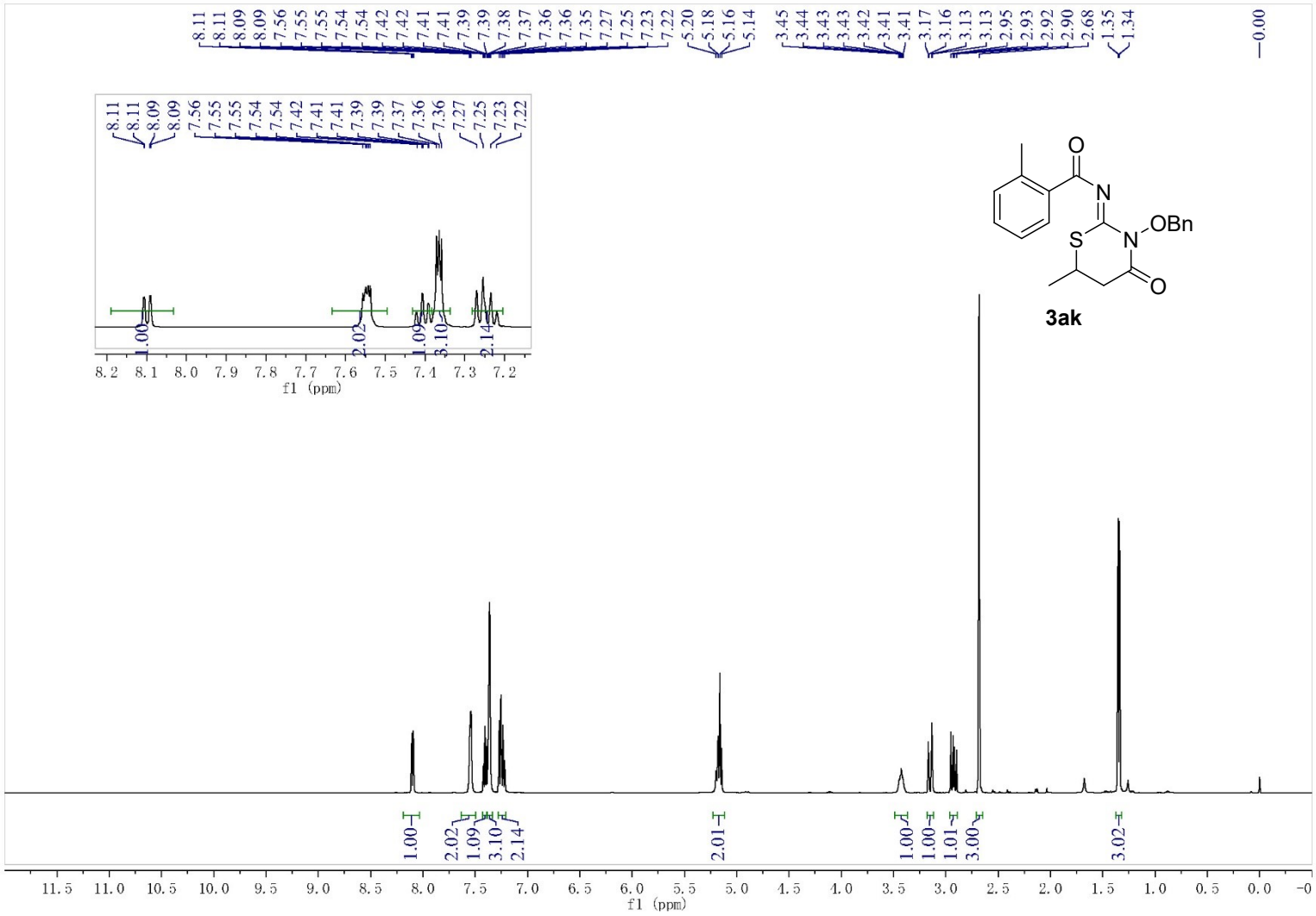

176.88
165.49
157.77
138.24
134.58
134.09
133.93
130.68
129.93
129.18
128.55
128.39
127.33
77.79
43.57
32.15
21.32
19.56
O
N
OBn
S
N
O
3ah
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

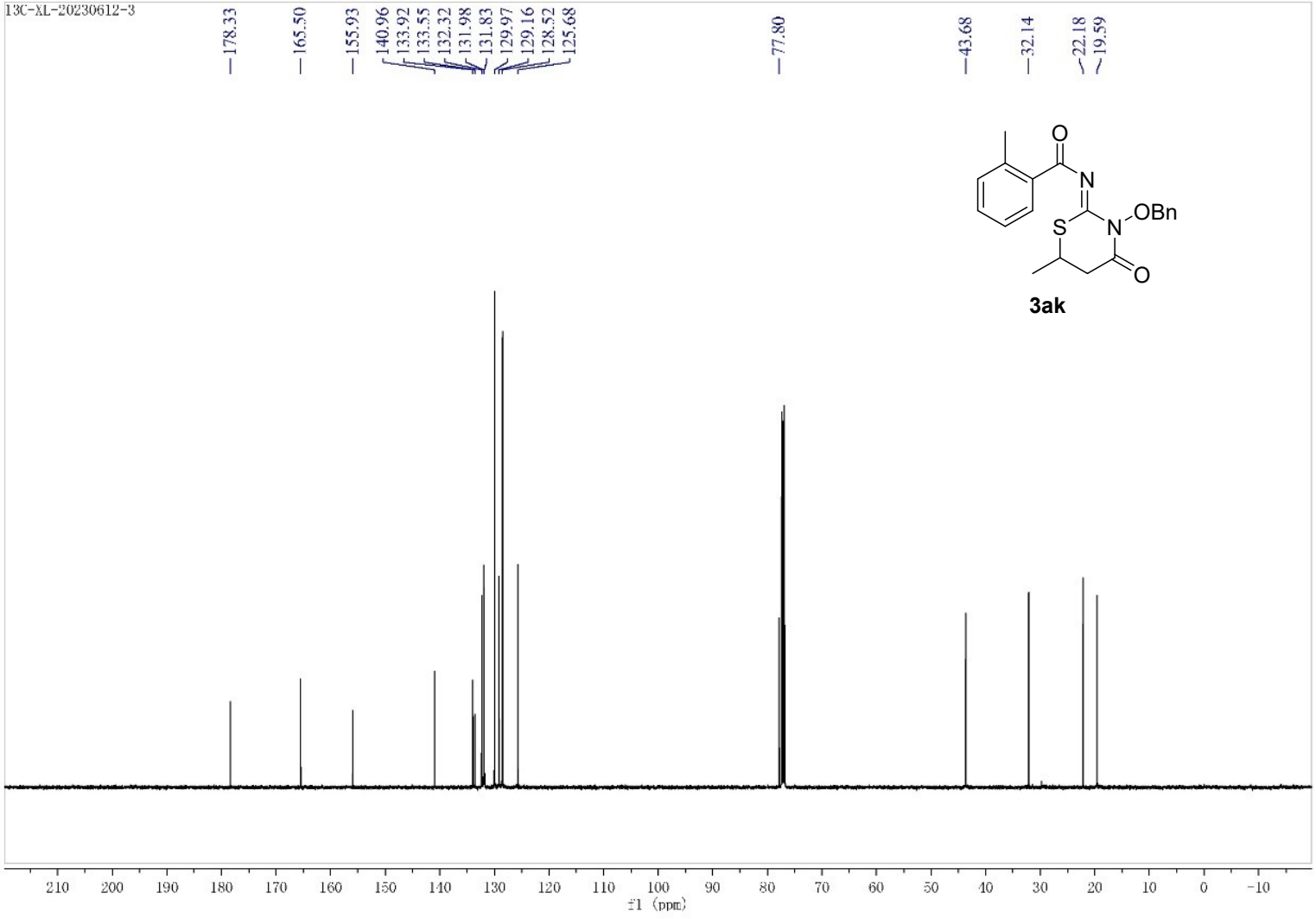

7.78 7.76 7.71 7.71 7.71 7.70 7.58 7.57 7.56 7.56 7.55 7.40 7.40 7.38 7.37 7.37 7.36 7.35 7.33 7.26 7.13 7.12 7.12 7.11 7.11 7.10 5.22 5.20 5.19 5.17 3.80 3.46 3.45 3.44 3.44 3.43 3.42 3.42 3.18 3.18 3.15 3.14 2.97 2.95 2.94 2.91 1.36 1.35
0.98 0.99 1.99 4.01 0.99
f1 (ppm)
O
O
N
S
N
OBn
O
3ai
0.98 0.99 1.99 4.01 0.99 1.99 3.03 0.99 1.00 1.00 3.03
f1 (ppm)

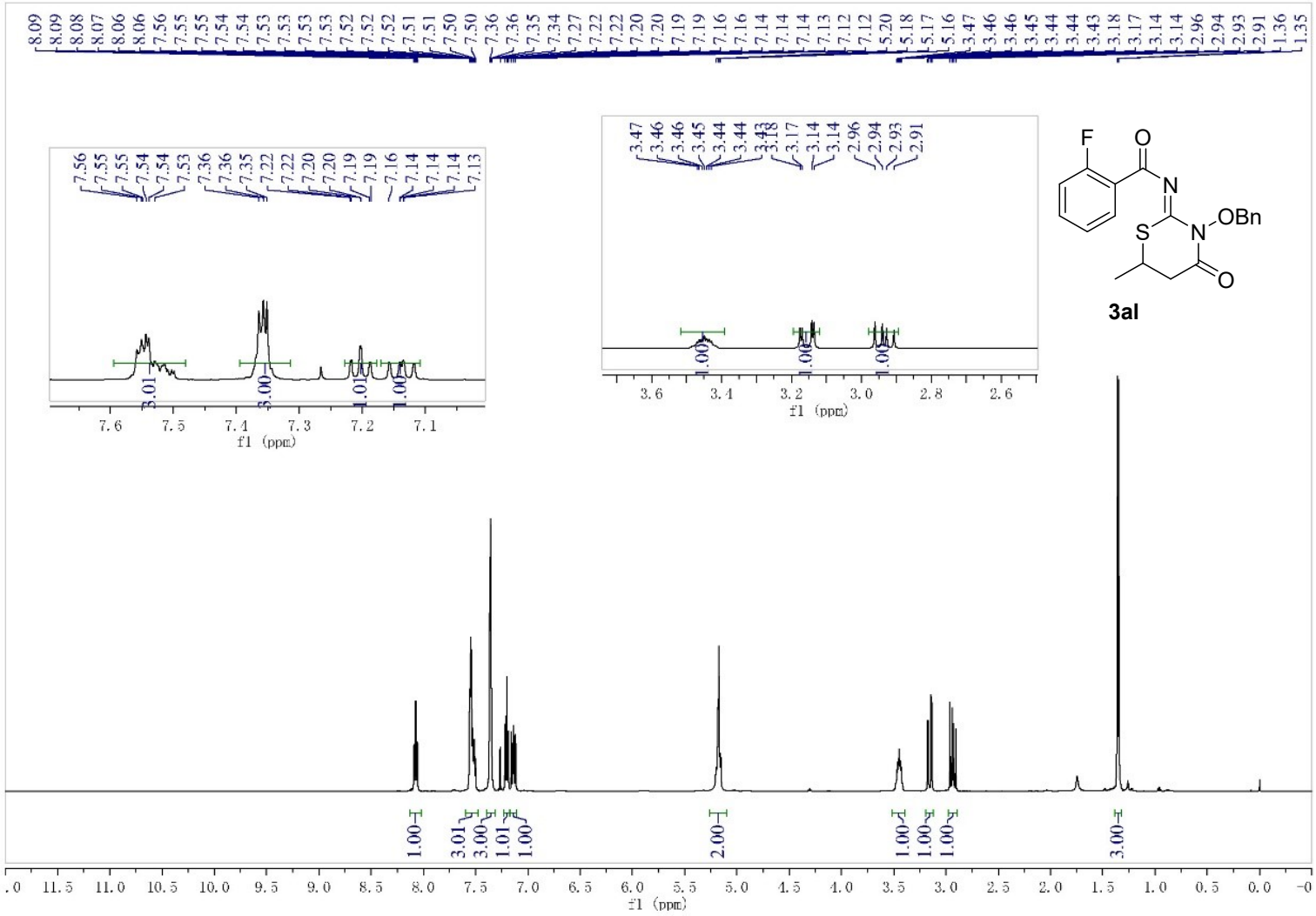

176.51
165.48
159.75
158.21
136.04
133.92
129.86
129.47
129.17
128.55
122.74
120.17
113.96
77.76
55.39
43.50
32.15
19.52
O
O
N
S
N
OBn
O
3ai
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

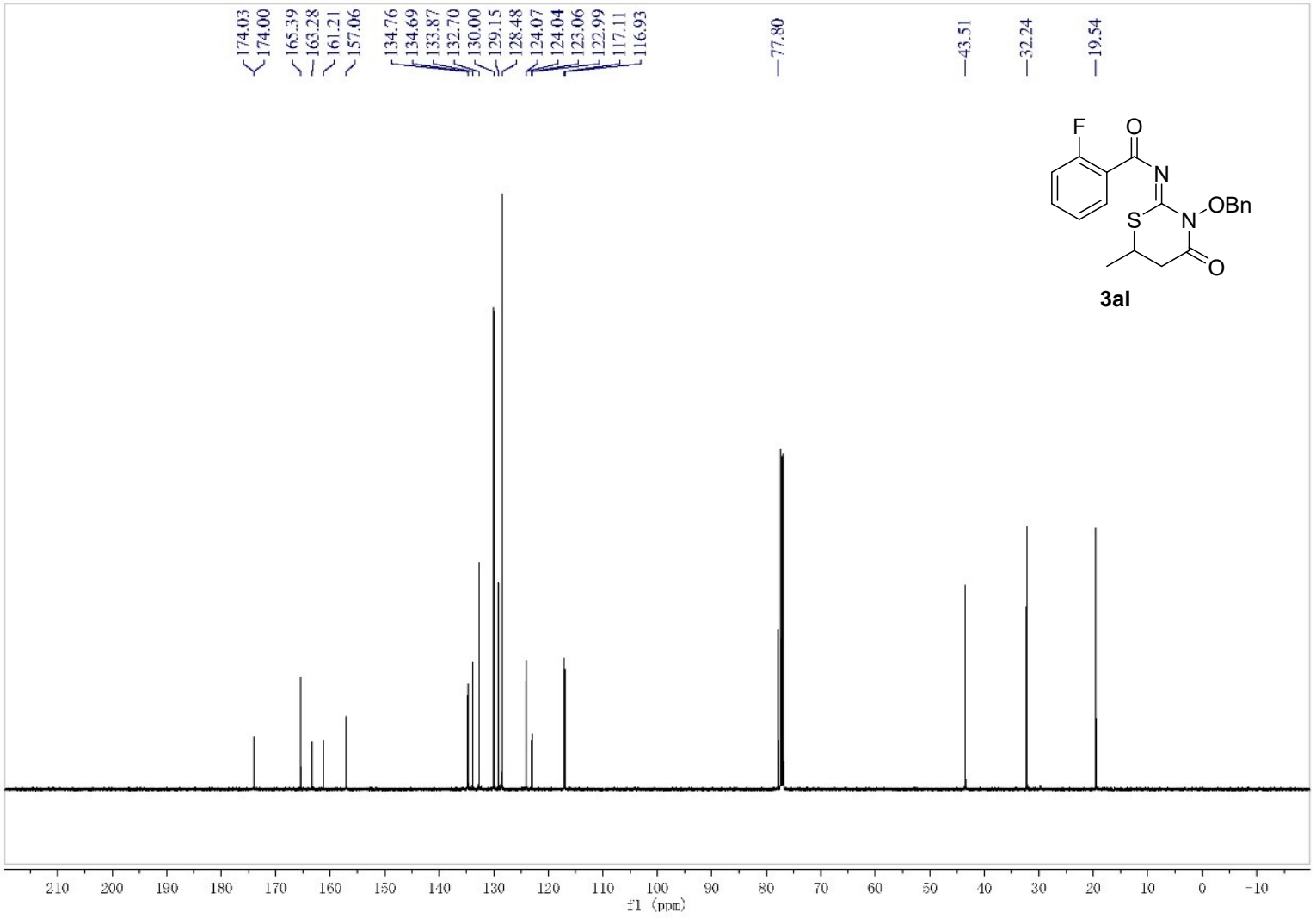

8.21 8.20 8.20 8.05 8.05 8.05 8.04 8.03 8.03 7.59 7.58 7.58 7.57 7.57 7.56 7.55 7.54 7.54 7.54 7.53 7.53 7.53 7.52 7.43 7.42 7.42 7.41 7.41 7.40 7.39 7.39 7.38 7.37 7.37 7.26 5.21 5.19 5.18 5.17 3.48 3.47 3.46 3.46 3.45 3.44 3.44 3.21 3.20 3.17 3.17 2.99 2.97 2.95 2.93 1.39 1.38 -0.00
0.95 1.00 2.00 1.01 4.18
f1 (ppm)
Cl
O
N
S
N
OBn
O
3aj
0.95 1.00 2.00 1.01 4.18 2.01 0.99 1.00 1.00 3.02
f1 (ppm)

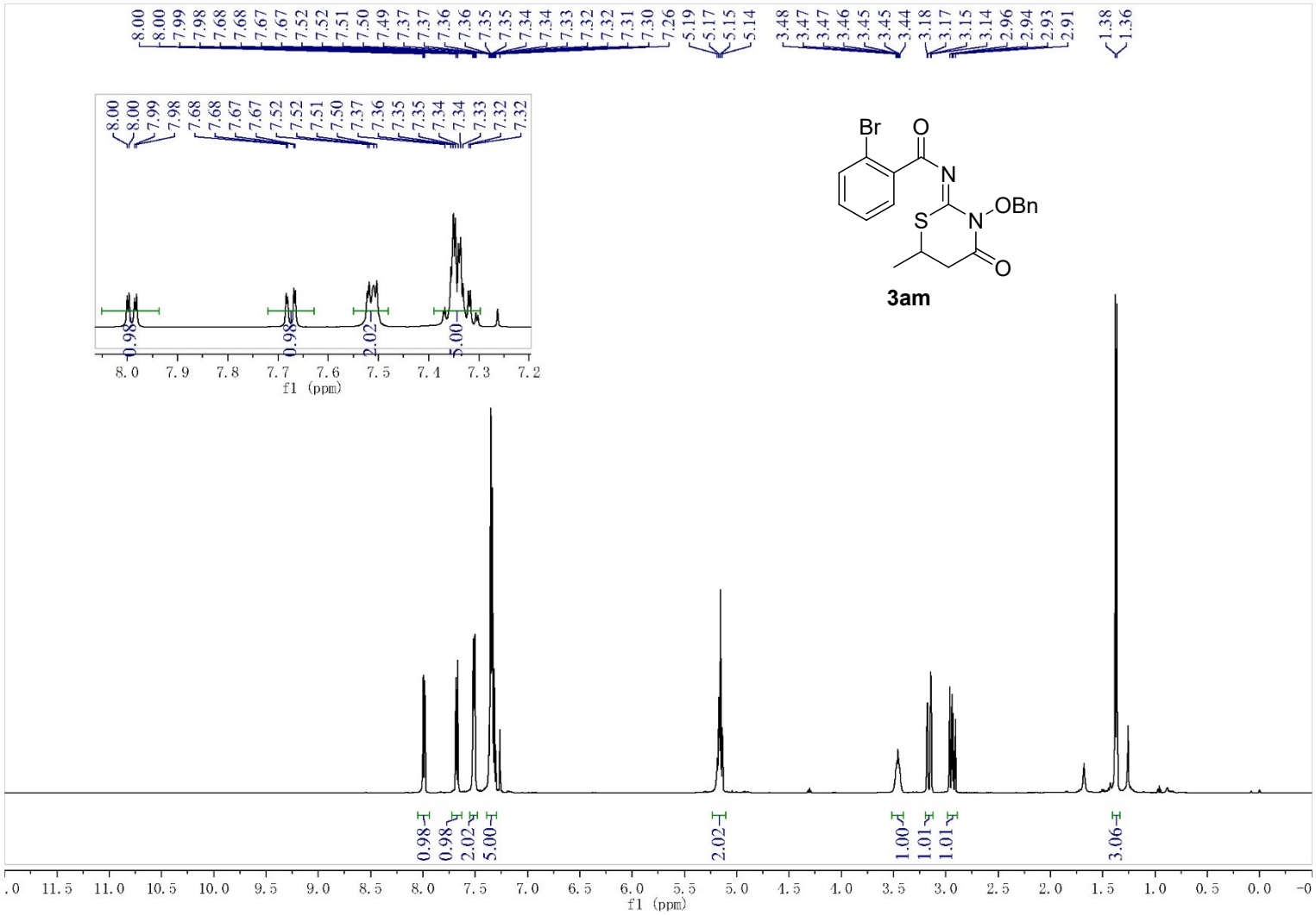

13C-XL-20230613-3
175.33
165.39
160.22
136.66
134.63
133.71
133.11
130.19
129.96
129.77
129.29
128.65
128.14
77.96
43.39
32.21
19.51
Cl
O
N
S
N
OBn
O
3aj
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

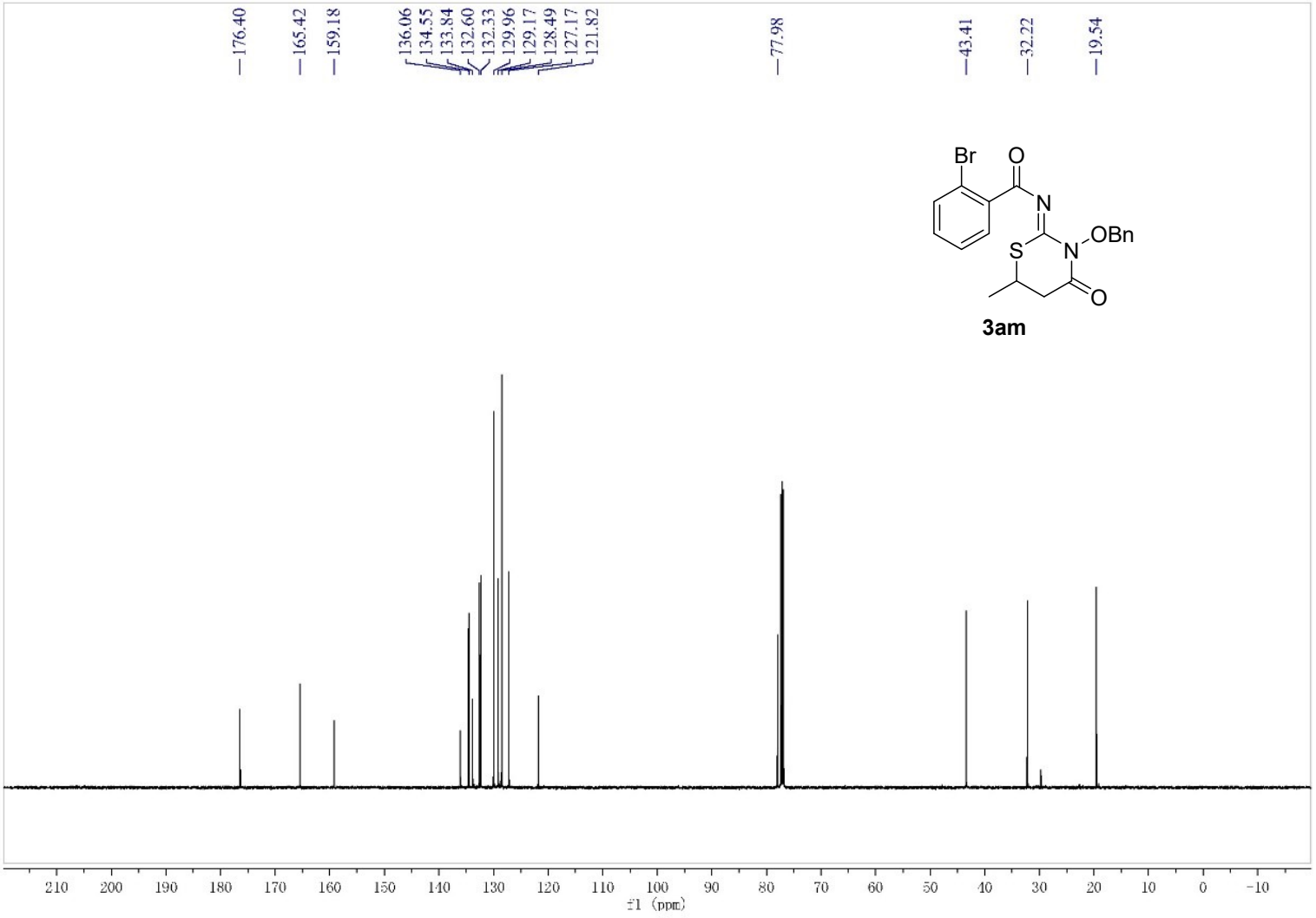

8.11 8.11 8.09 8.09 7.56 7.55 7.55 7.54 7.54 7.42 7.42 7.41 7.41 7.39 7.39 7.38 7.37 7.36 7.36 7.35 7.27 7.25 7.23 7.22 5.20 5.18 5.16 5.14 3.45 3.44 3.43 3.43 3.42 3.41 3.41 3.17 3.16 3.13 3.13 2.95 2.93 2.92 2.90 2.68 1.35 1.34 0.00
1.00 2.02 1.09 3.10 2.14
f1 (ppm)
O N OBn S N O
3ak
1.00 2.02 1.09 3.10 2.14 2.01 1.00 1.00 1.01 3.00 3.02
f1 (ppm)


13C-XL-20230612-3
178.33
165.50
155.93
140.96
133.92
133.55
132.32
131.98
131.83
129.97
129.16
128.52
125.68
77.80
43.68
32.14
22.18
19.59
O
N
OBn
S
N
O
3ak
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


F
O
N
S
N
OBn
O
3al
f1 (ppm)


174.03
174.00
165.39
163.28
161.21
157.06
134.76
134.69
133.87
132.70
130.00
129.15
128.48
124.07
124.04
123.06
122.99
117.11
116.93
77.80
43.51
32.24
19.54
F
O
N
OBn
S
N
O
3al
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Br
O
N
S
N
OBn
O
3am
f1 (ppm)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132.33
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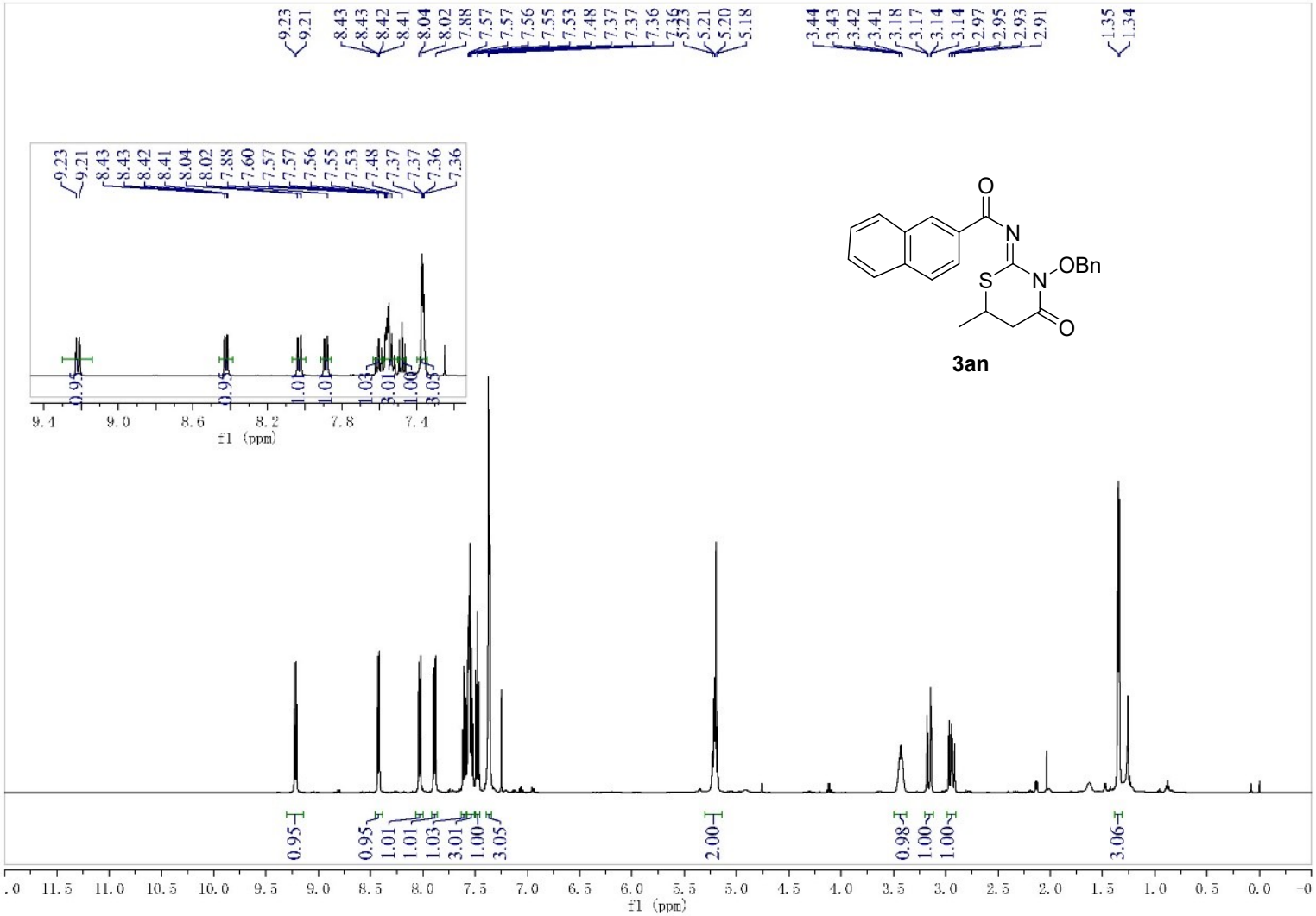
129.17
128.49
127.17
121.82
77.98
43.41
32.22
19.54
Br
O
N
OBn
S
N
O
3am
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.02
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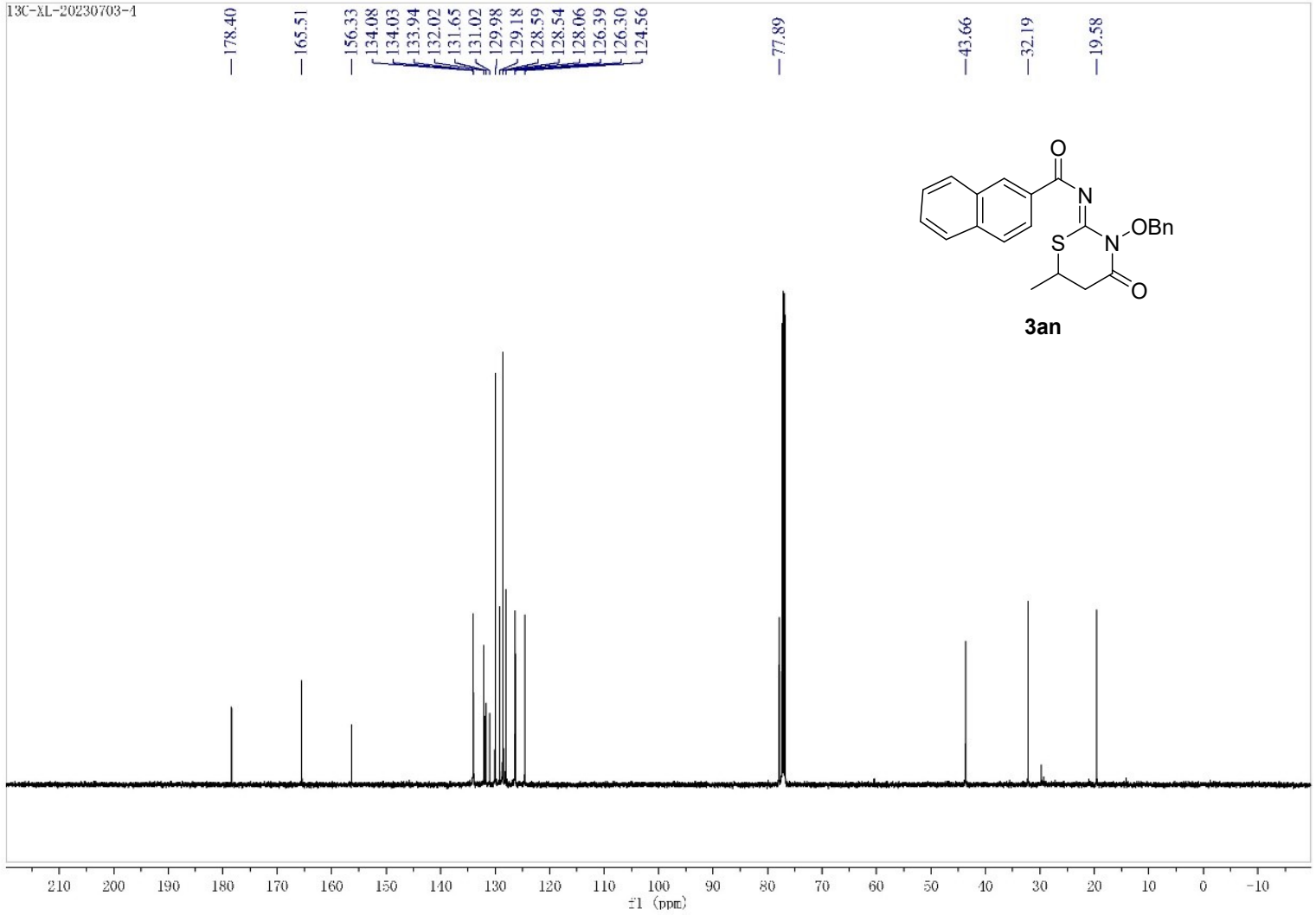
7.57
7.57
7.56
7.55
7.53
7.48
7.37
7.37
7.36
5.23
5.21
5.20
5.18
3.44
3.43
3.42
3.41
3.18
3.17
3.14
3.14
2.97
2.95
2.93
2.91
1.35
1.34
0.95
0.95
1.01
1.01
1.03
3.01
1.00
3.05
2.00
0.98
1.00
1.00
3.06
f1 (ppm)
O
N
OBn
S
N
O
3an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133.94
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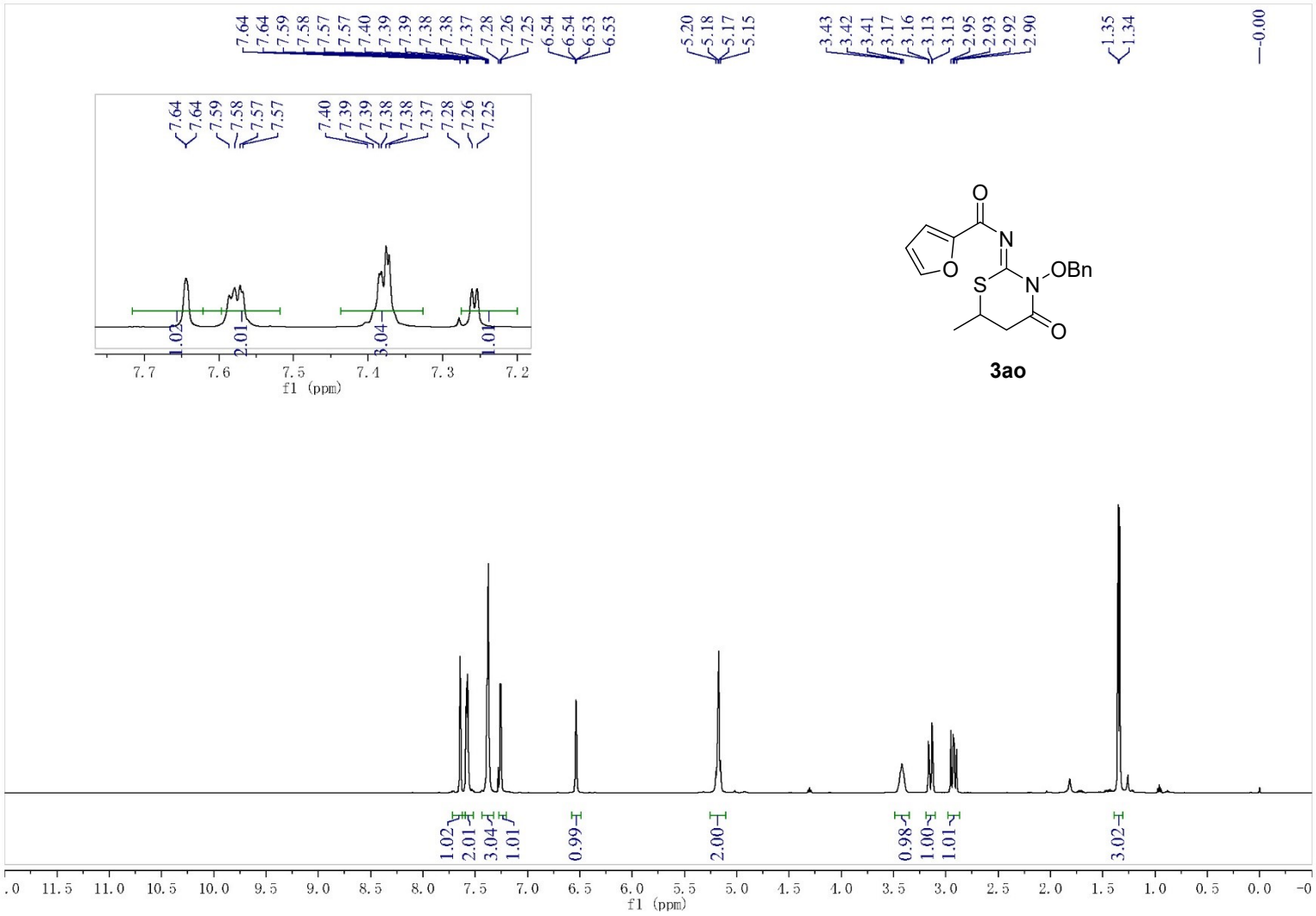
131.02
129.98
129.18
128.59
128.54
128.06
126.39
126.30
124.56
77.89
43.66
32.19
19.58
O
N
S
N
OBn
O
3an
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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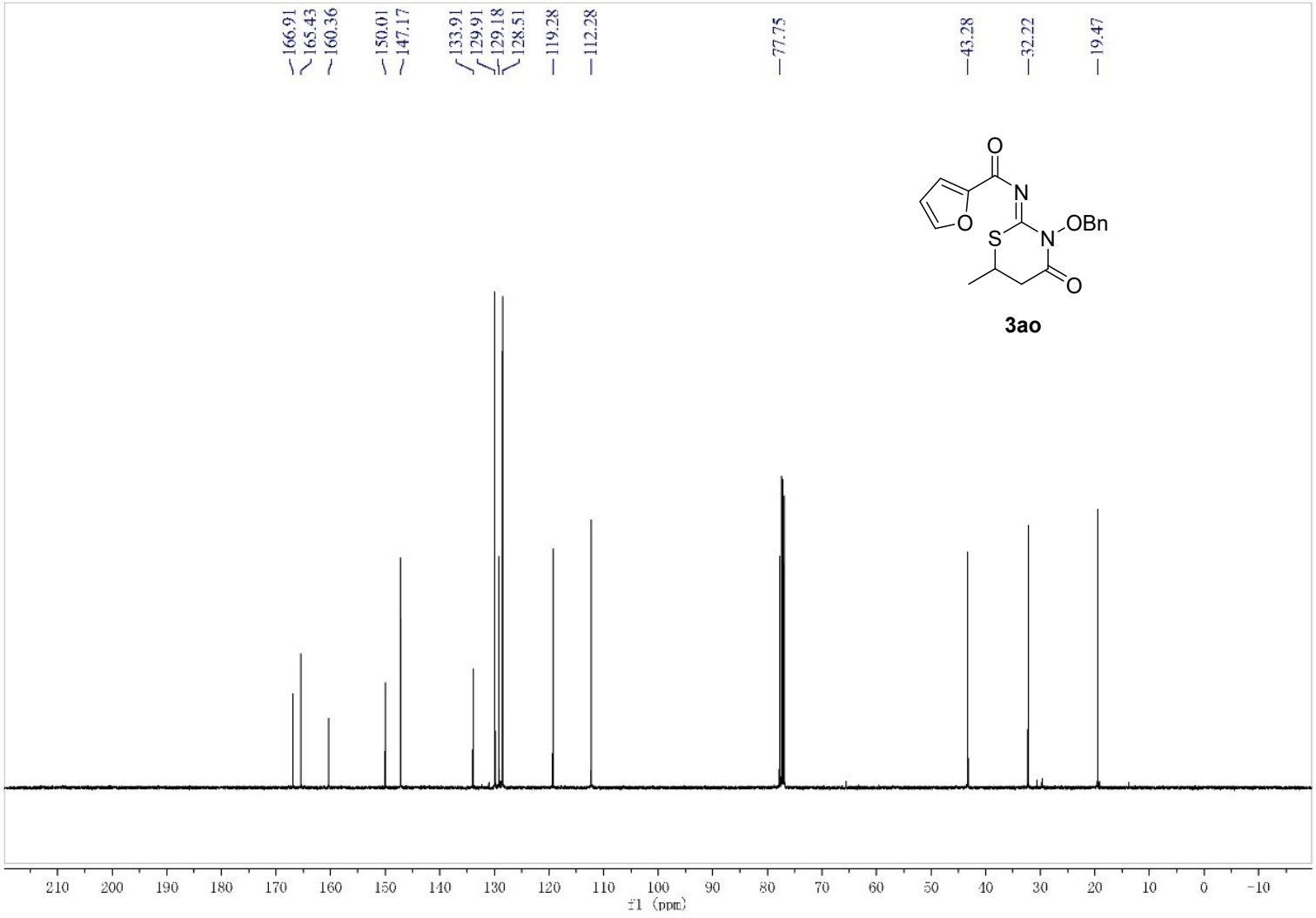
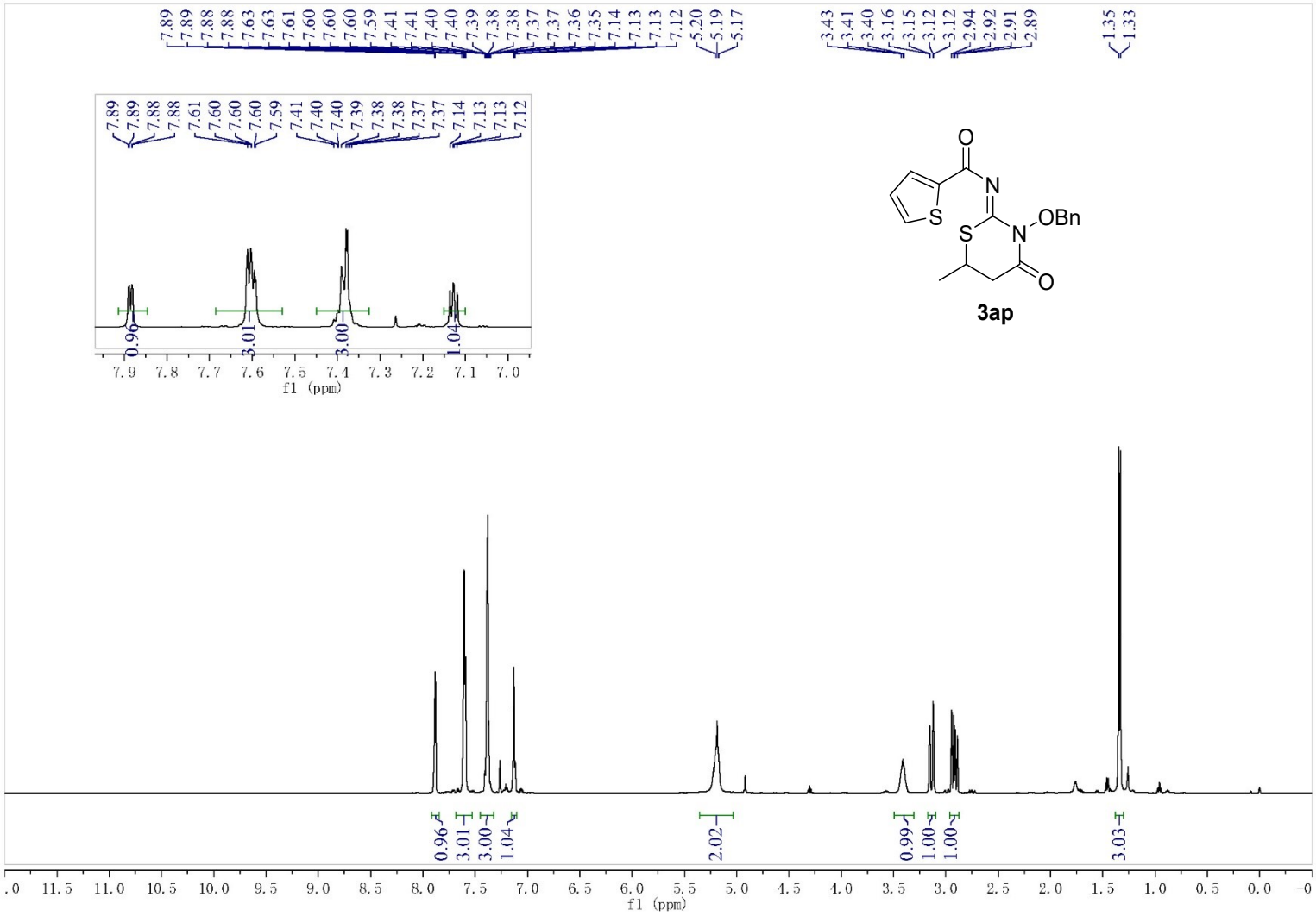
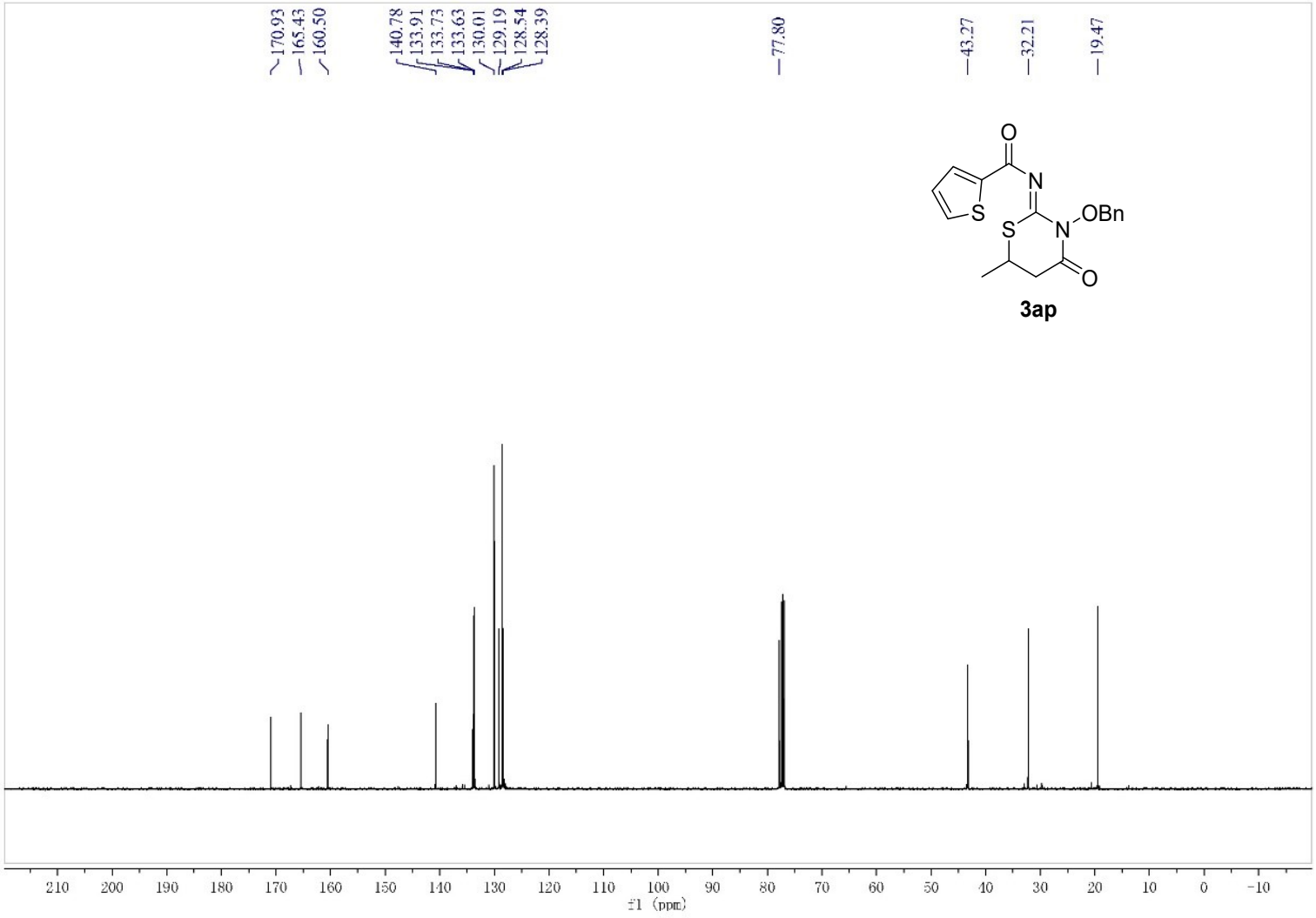
7.57
7.40
7.39
7.39
7.38
7.38
7.37
7.28
7.26
7.25
6.54
6.54
6.53
6.53
5.20
5.18
5.17
5.15
3.43
3.42
3.41
3.17
3.16
3.13
3.13
2.95
2.93
2.92
2.90
1.35
1.34
-0.00
1.02
2.01
3.04
1.01
f1 (ppm)
O
N
O
S
N
OBn
O
3ao
1.02
2.01
3.04
1.01
0.99
2.00
0.98
1.00
1.01
3.02
f1 (ppm)


166.91
165.43
160.36
150.01
147.17
133.91
129.91
129.18
128.51
119.28
112.28
77.75
43.28
32.22
19.47
O
N
O
S
N
OBn
O
3ao
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.89 7.89 7.88 7.88 7.63 7.63 7.61 7.60 7.60 7.60 7.59 7.41 7.41 7.40 7.40 7.39 7.38 7.38 7.37 7.37 7.36 7.35 7.14 7.13 7.13 7.12 5.20 5.19 5.17
3.43 3.41 3.40 3.16 3.15 3.12 3.12 2.94 2.92 2.91 2.89
1.35 1.33
0.96 3.01 3.00 1.04
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)
O
N
S
S
N
OBn
O
3ap
0.96 3.01 3.00 1.04 2.02 0.99 1.00 1.00 3.03
f1 (ppm)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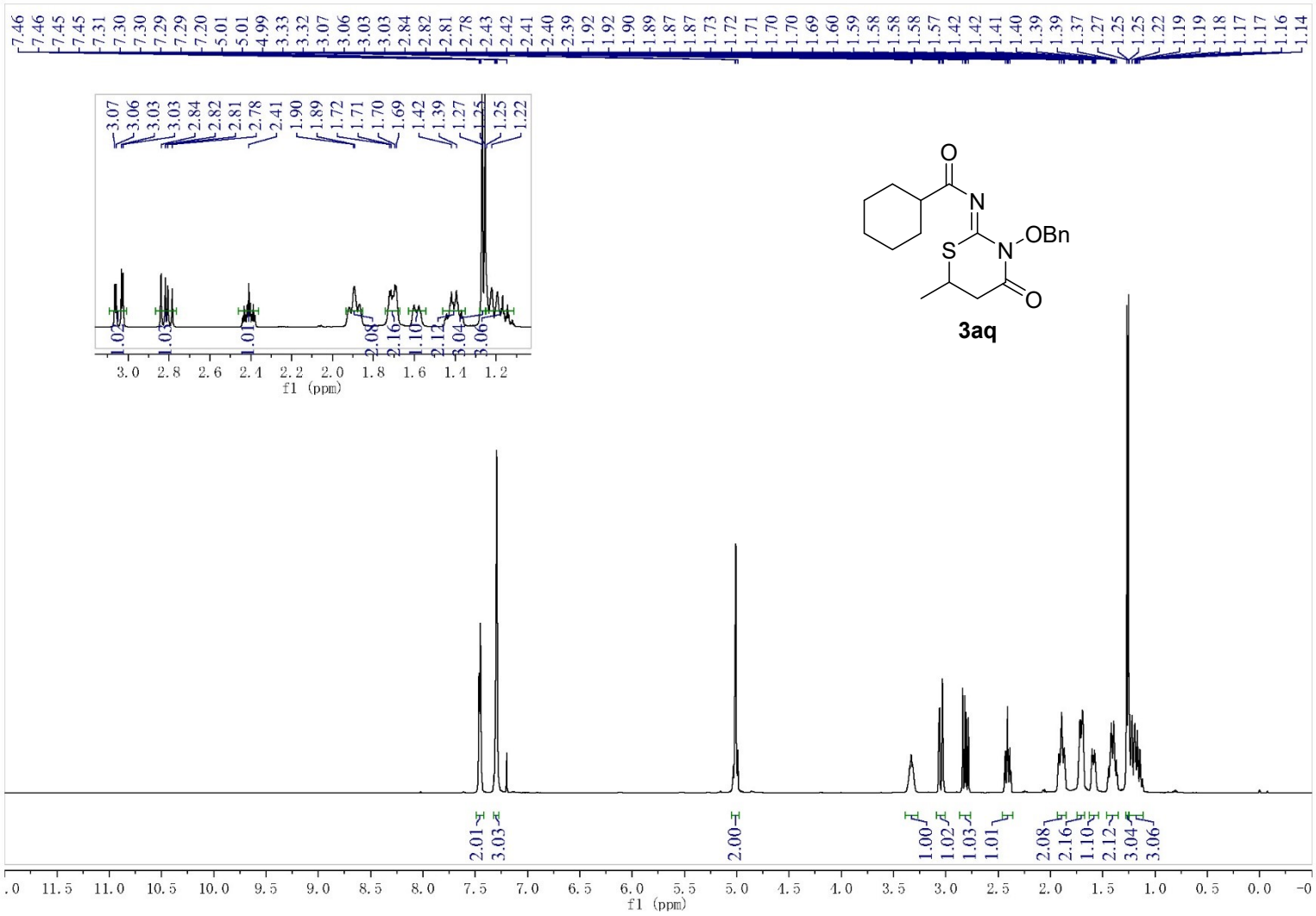
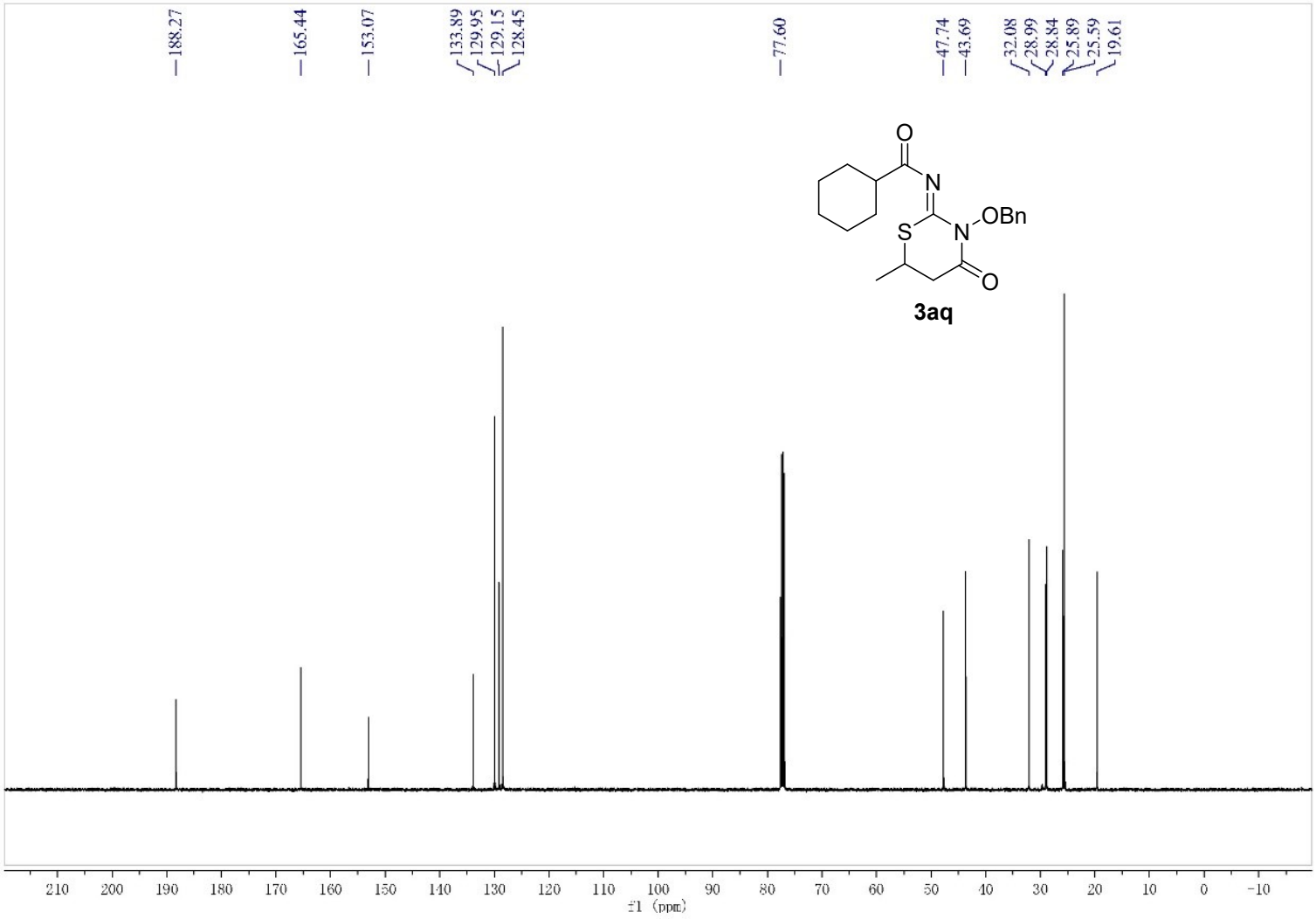
165.43
160.50
140.78
133.91
133.73
133.63
130.01
129.19
128.54
128.39
77.80
43.27
32.21
19.47
O
N
S
S
N
OBn
O
3ap
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


3aq
f1 (ppm)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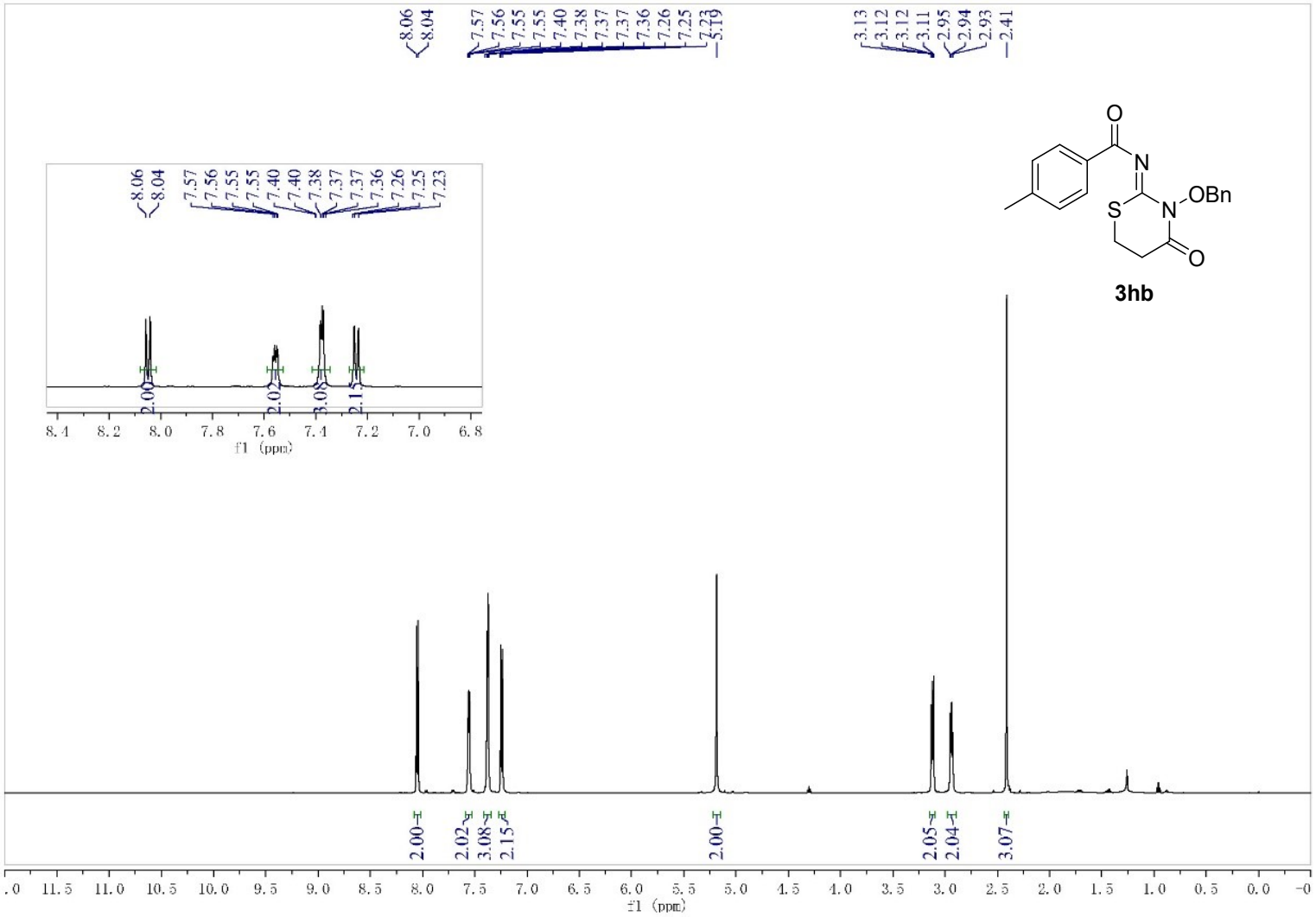
129.15
128.45
77.60
47.74
43.69
32.08
28.99
28.84
25.89
25.59
19.61
O
N
OBn
S
N
O
3aq
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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8.04
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7.55
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7.38
7.37
7.37
7.36
7.26
7.25
7.23
5.19
3.13
3.12
3.12
3.11
2.95
2.94
2.93
2.41
O
N
OBn
S
N
O
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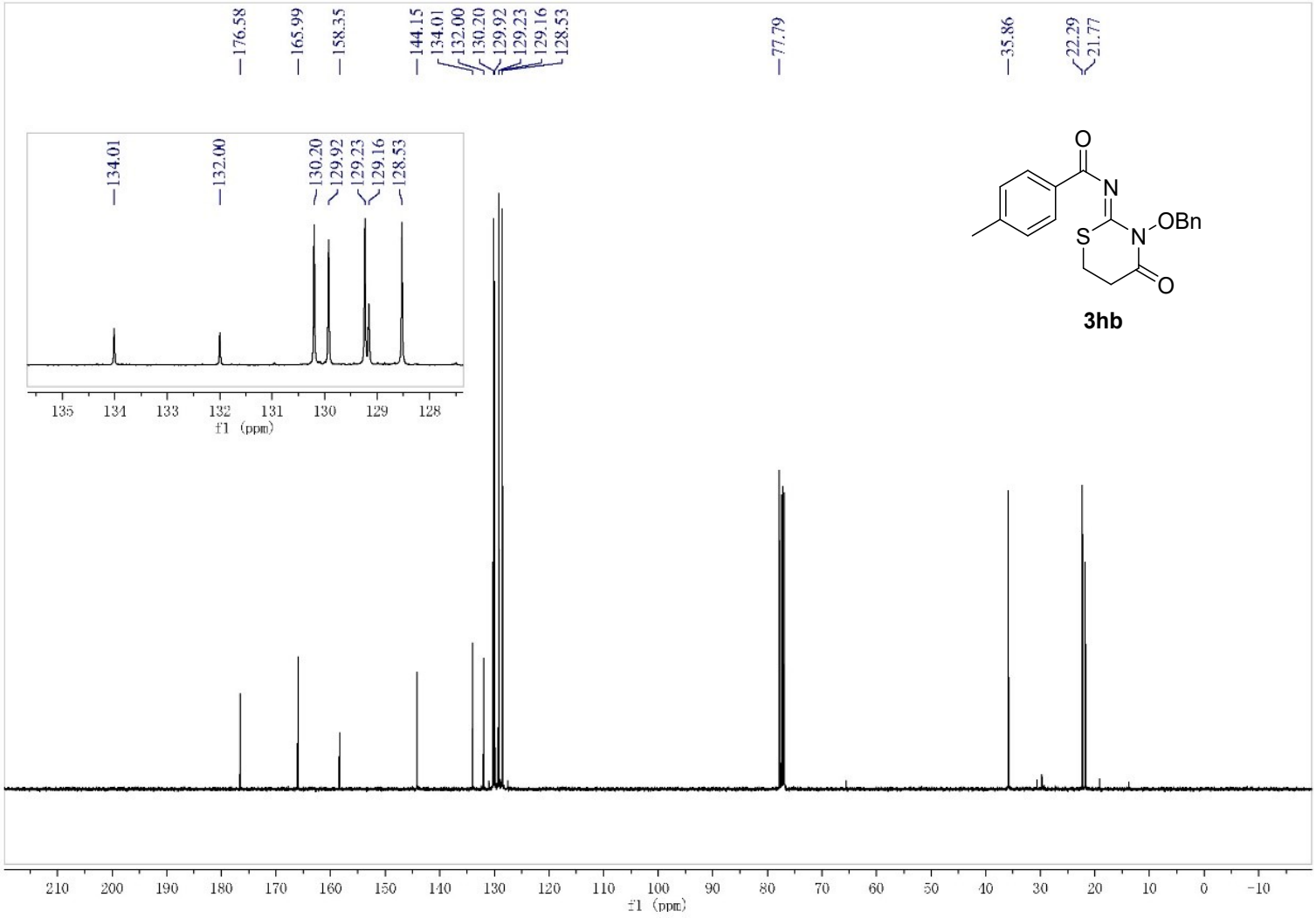
2.00
2.05
2.04
3.07
f1 (ppm)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134.01
132.00
130.20
129.92
129.23
129.16
128.53
77.79
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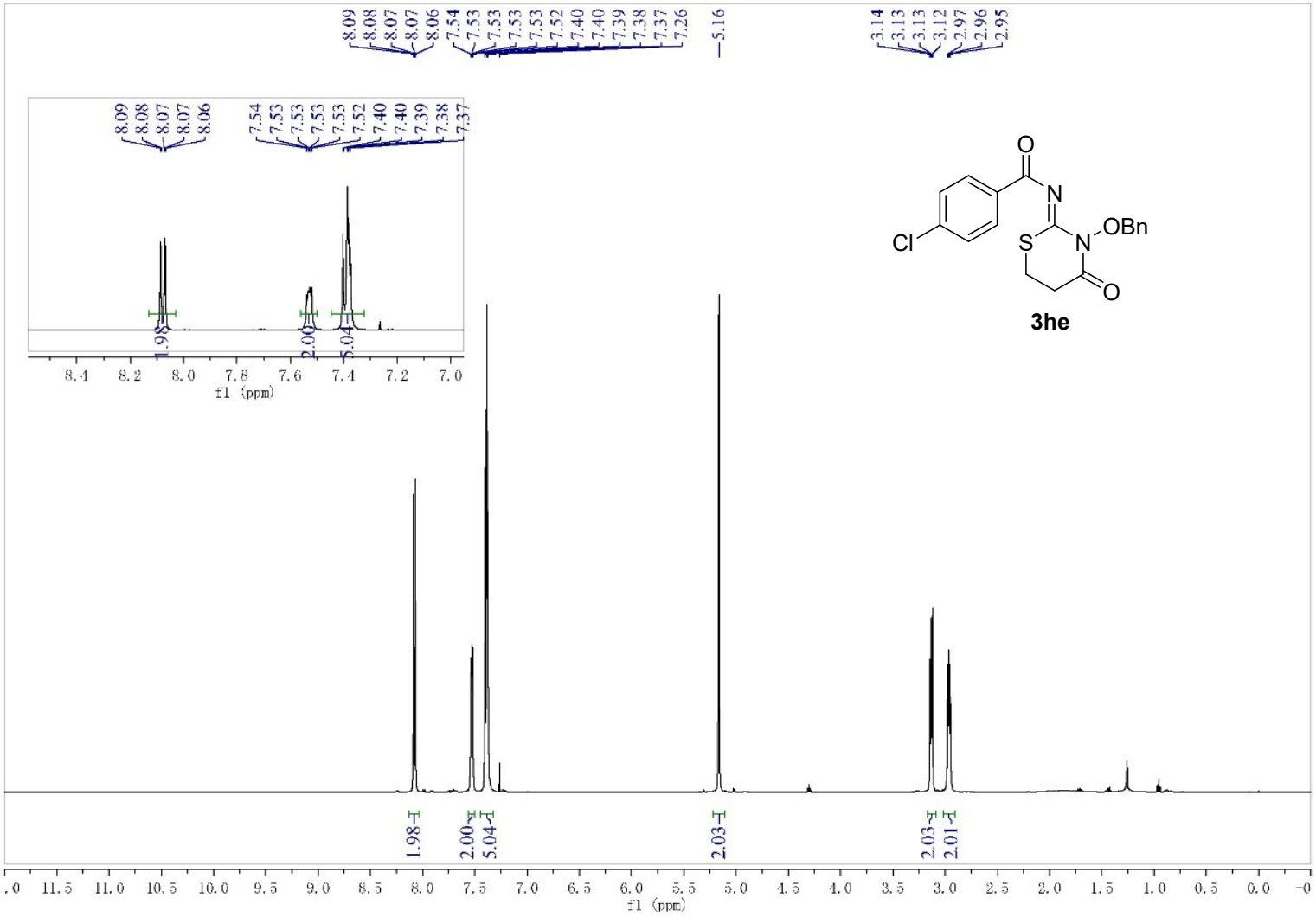
S
N
O
3hb
f1 (ppm)
f1 (ppm)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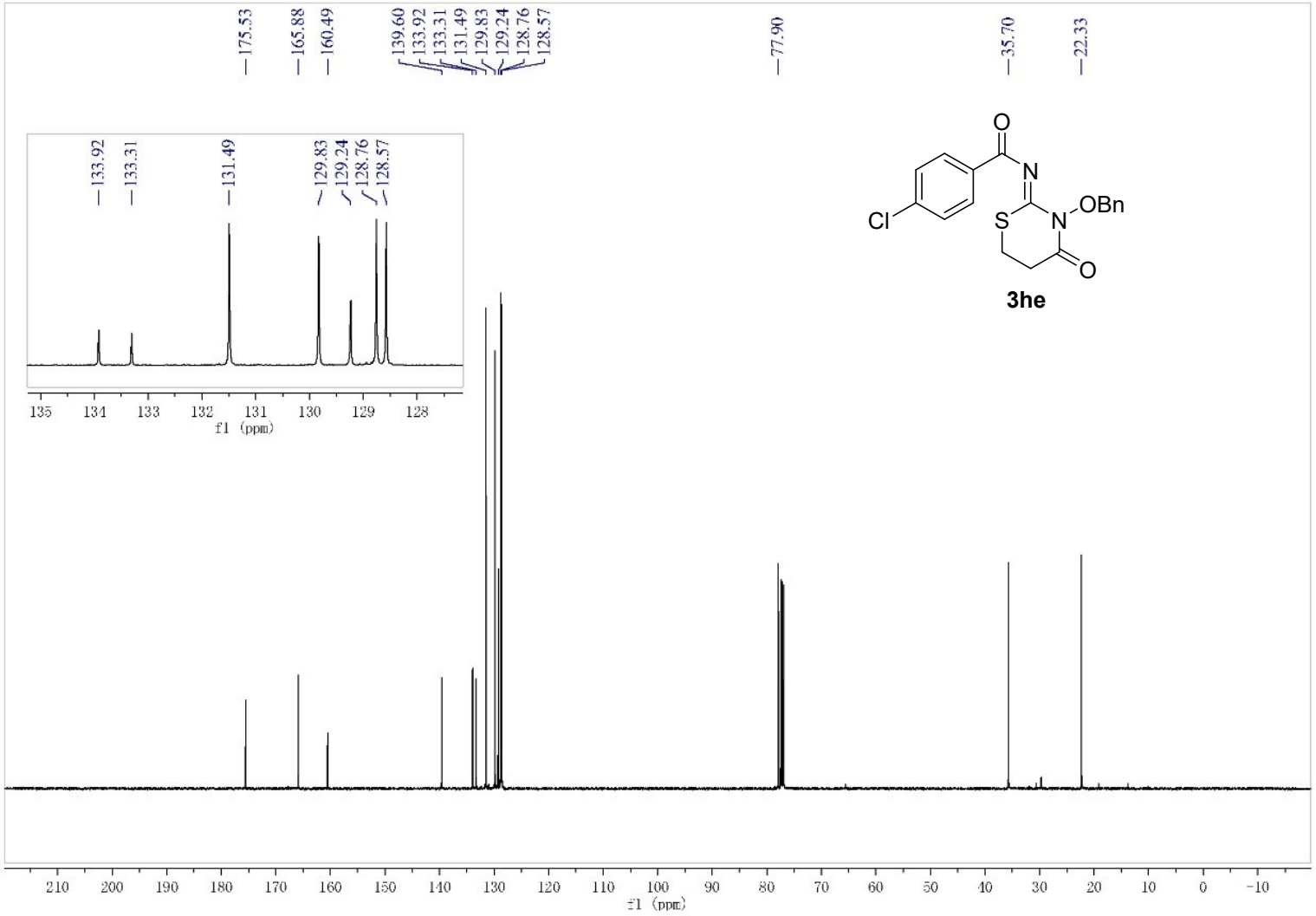
8.08
8.07
8.07
8.06
7.54
7.53
7.53
7.53
7.53
7.52
7.40
7.40
7.39
7.38
7.37
7.26
5.16
3.14
3.13
3.13
3.12
2.97
2.96
2.95
1.98
2.00
5.04
f1 (ppm)
O
N
OBn
Cl
S
N
O
3he
1.98
2.00
5.04
2.03
2.03
2.01
f1 (ppm)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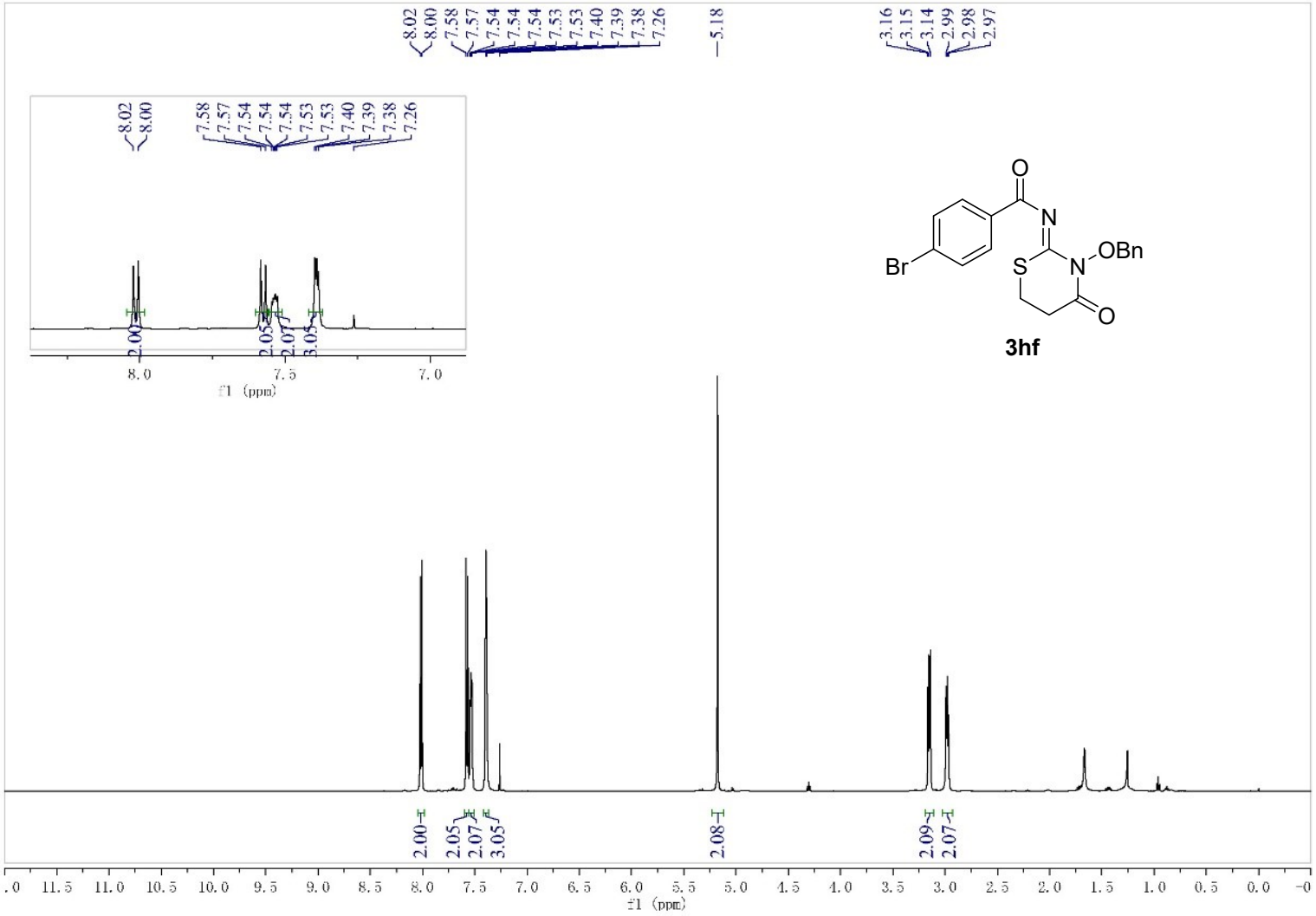
129.83
129.24
128.76
128.57
77.90
35.70
22.33
133.92
133.31
131.49
129.83
129.24
128.76
128.57
135
134
133
132
131
130
129
128
f1 (ppm)
O
N
Cl
S
N
OBn
O
3he
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.57
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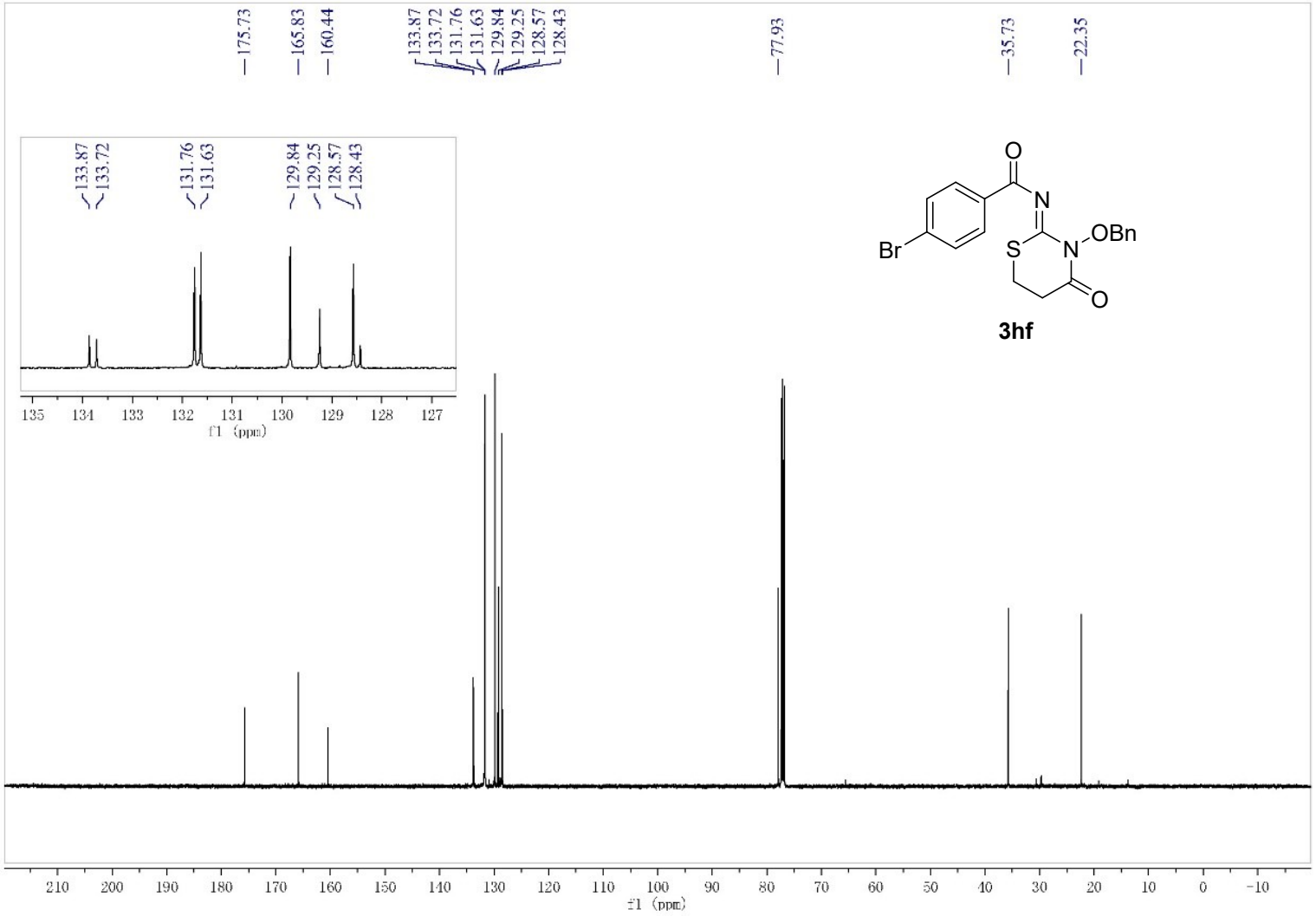
7.54
7.54
7.53
7.53
7.40
7.39
7.38
7.26
5.18
3.16
3.15
3.14
2.99
2.98
2.97
Br
O
N
S
N
OBn
O
3hf
2.00
2.05
2.07
3.05
2.08
2.09
2.07
f1 (ppm)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133.72
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131.63
129.84
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128.57
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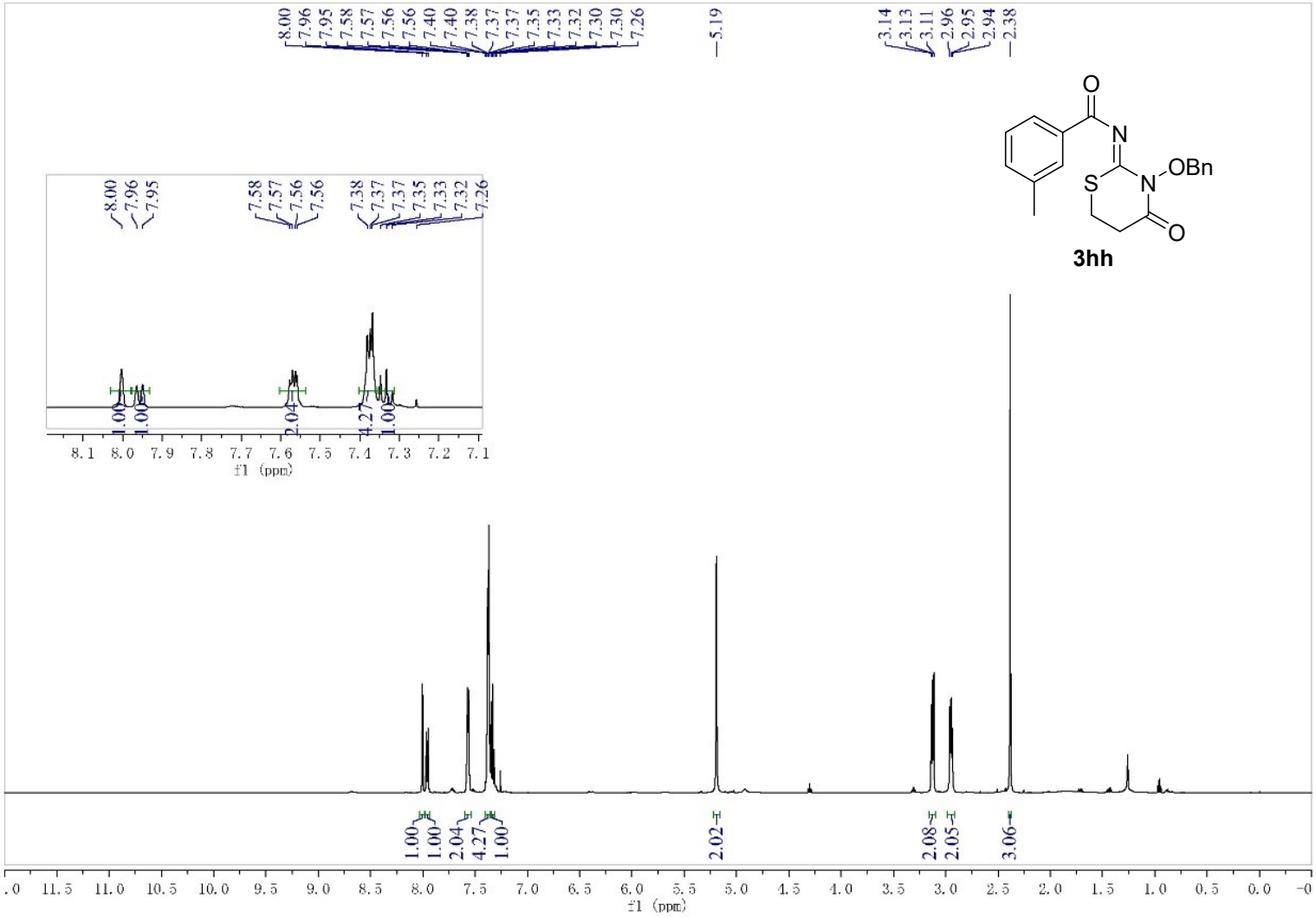
77.93
35.73
22.35
O
N
Br
S
N
OBn
O
3hf
f1 (ppm)
f1 (ppm)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7.96
7.95
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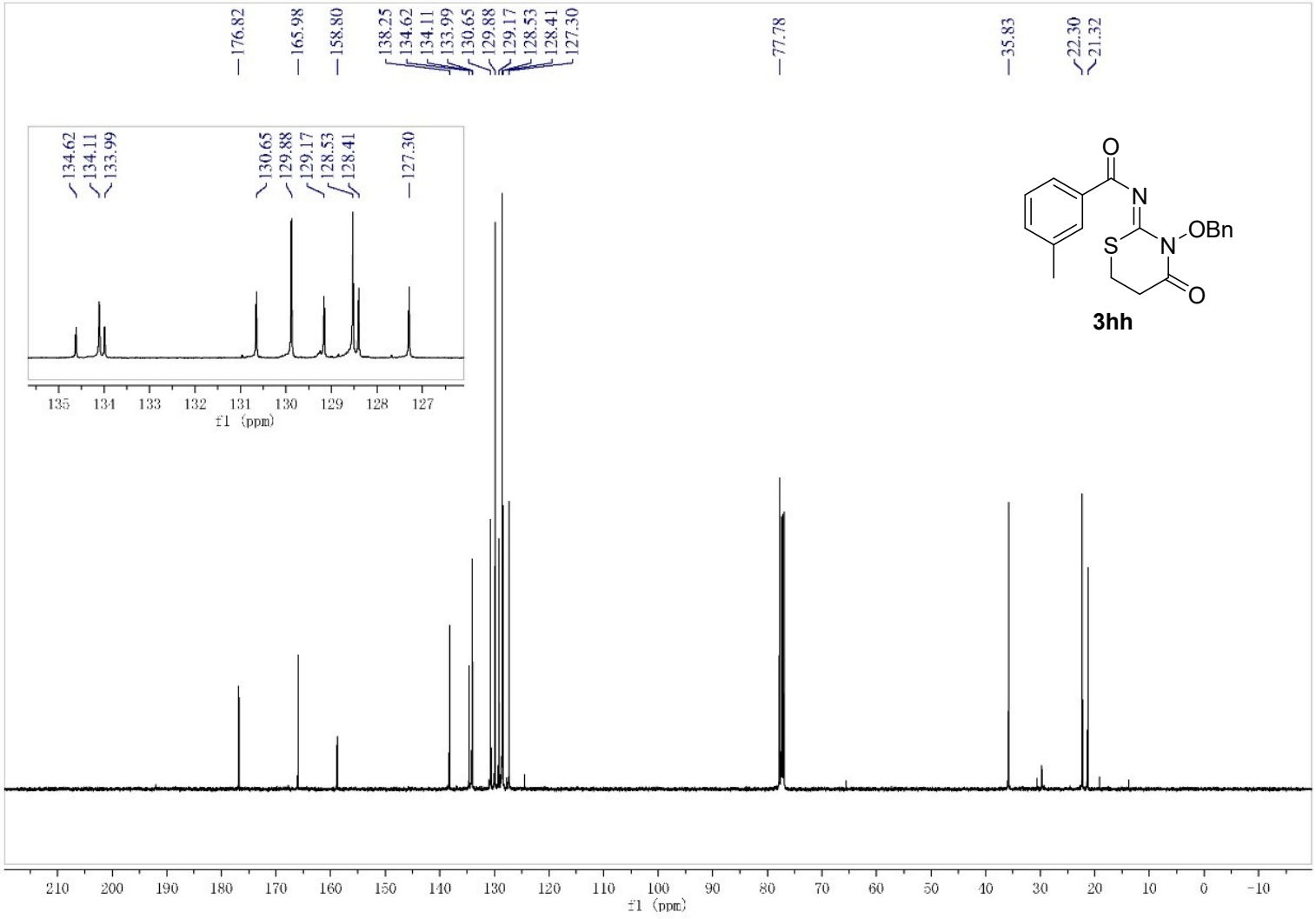
7.57
7.56
7.56
7.40
7.40
7.38
7.37
7.37
7.35
7.33
7.32
7.30
7.30
7.26
5.19
3.14
3.13
3.11
2.96
2.95
2.94
2.38
O
N
OBn
S
N
O
3hh
1.00
1.00
2.04
4.27
1.00
2.02
2.08
2.05
3.06
f1 (ppm)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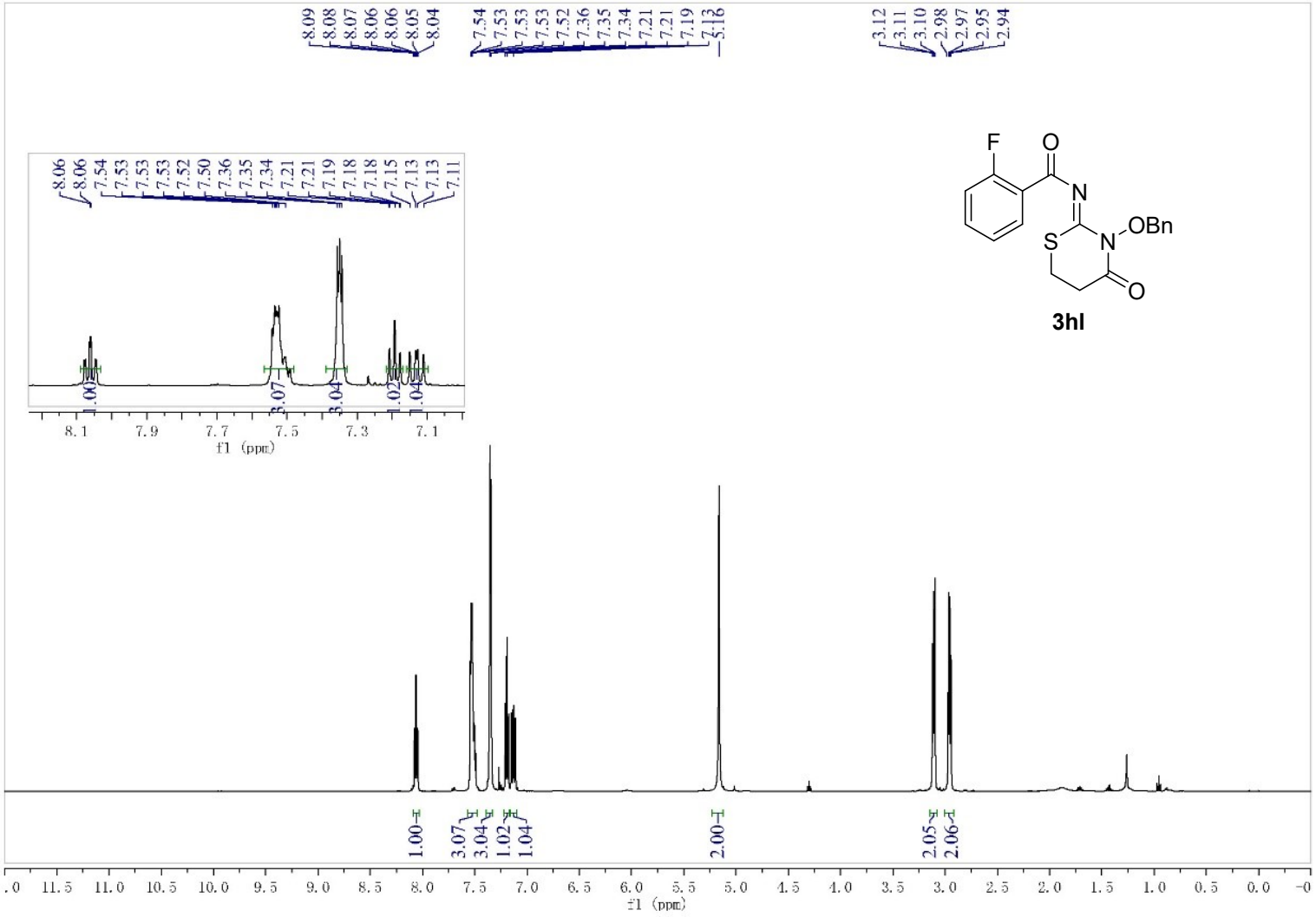
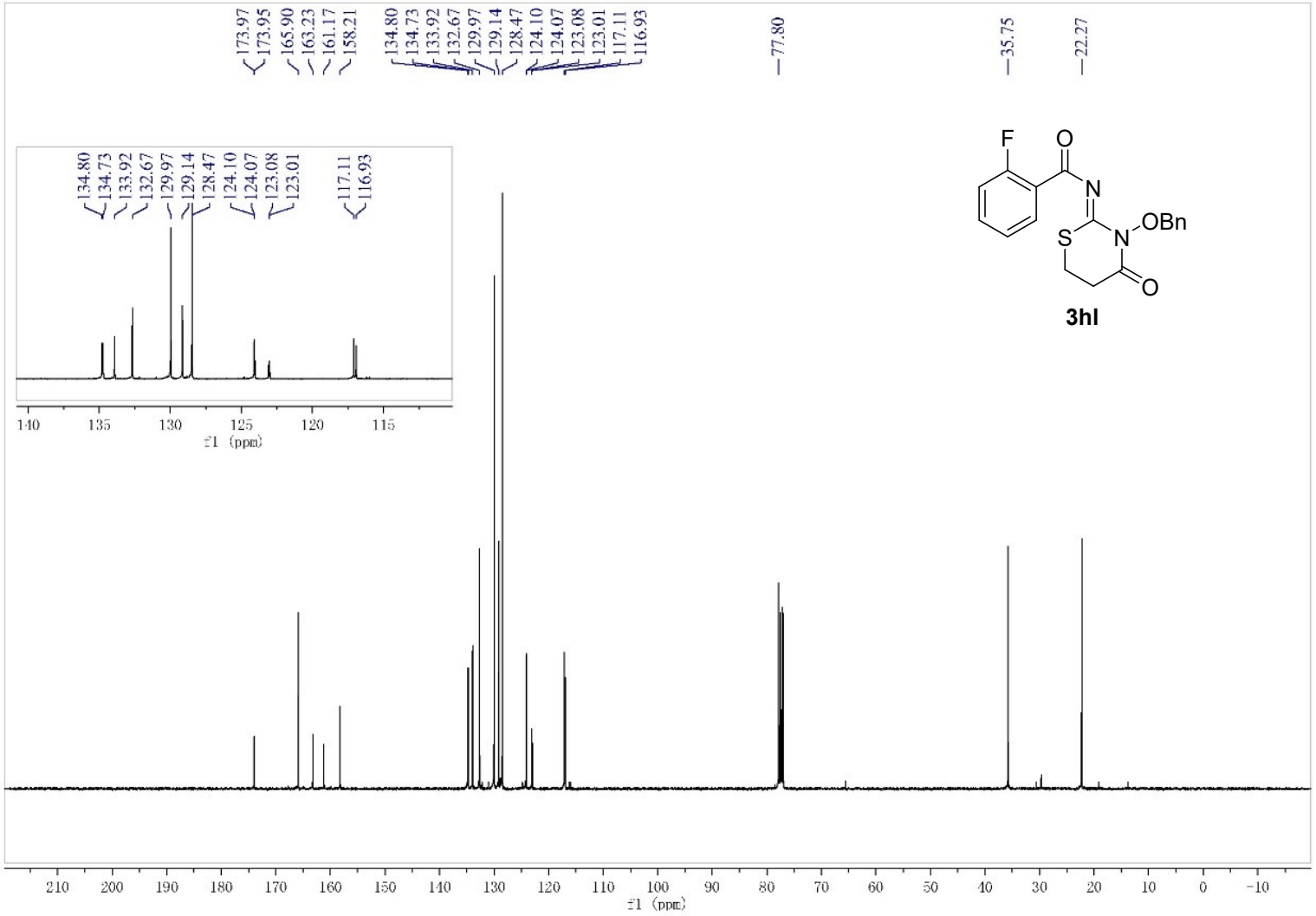
129.88
129.17
128.53
128.41
127.30
77.78
35.83
22.30
21.32
O
N
S
N
OBn
O
3hh
f1 (ppm)
f1 (ppm)


F
O
N
S
N
OBn
O
3hl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158.21
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134.73
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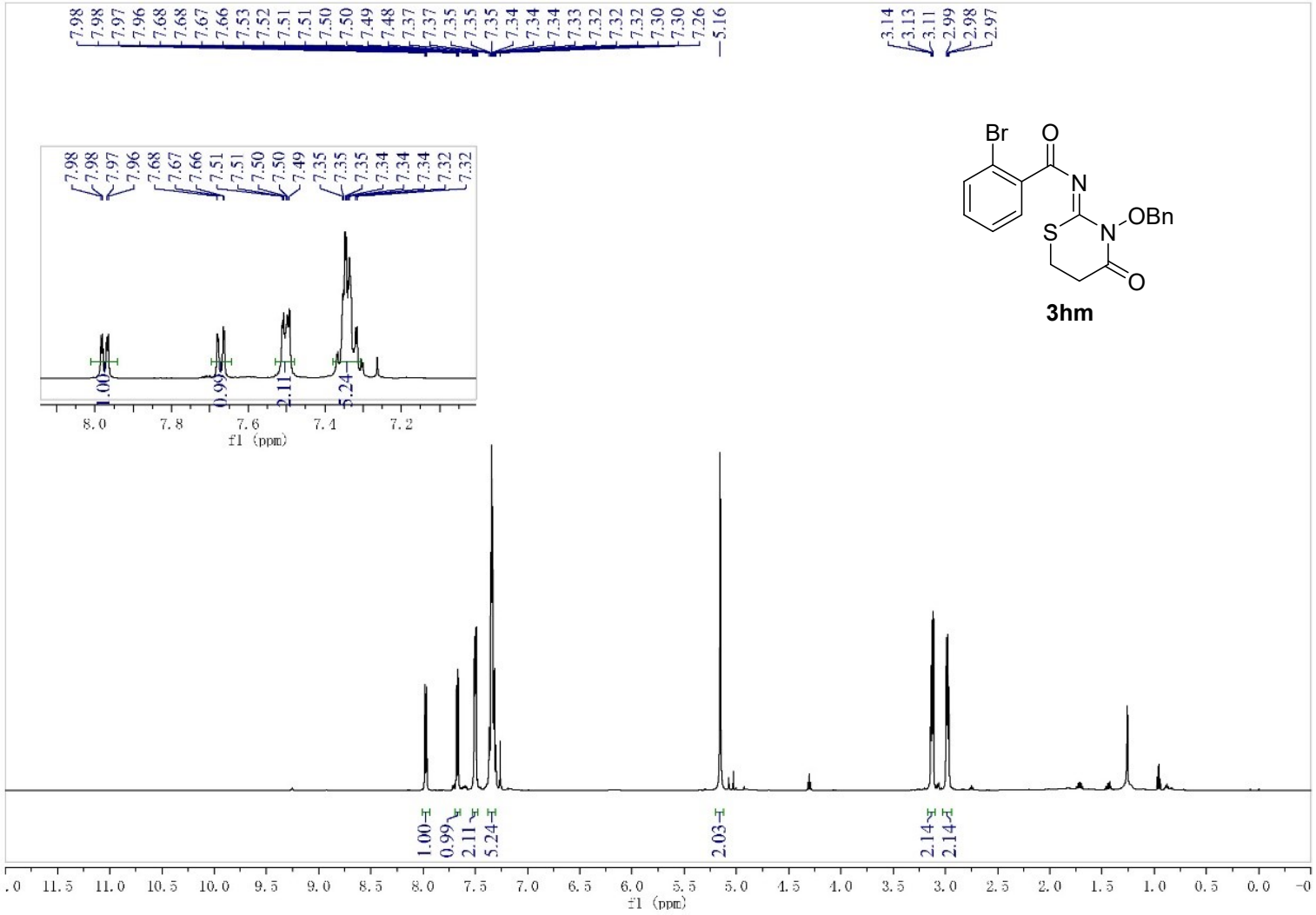
132.67
129.97
129.14
128.47
124.10
124.07
123.08
123.01
117.11
116.93
77.80
35.75
22.27
F
O
N
S
N
OBn
O
3hl
f1 (ppm)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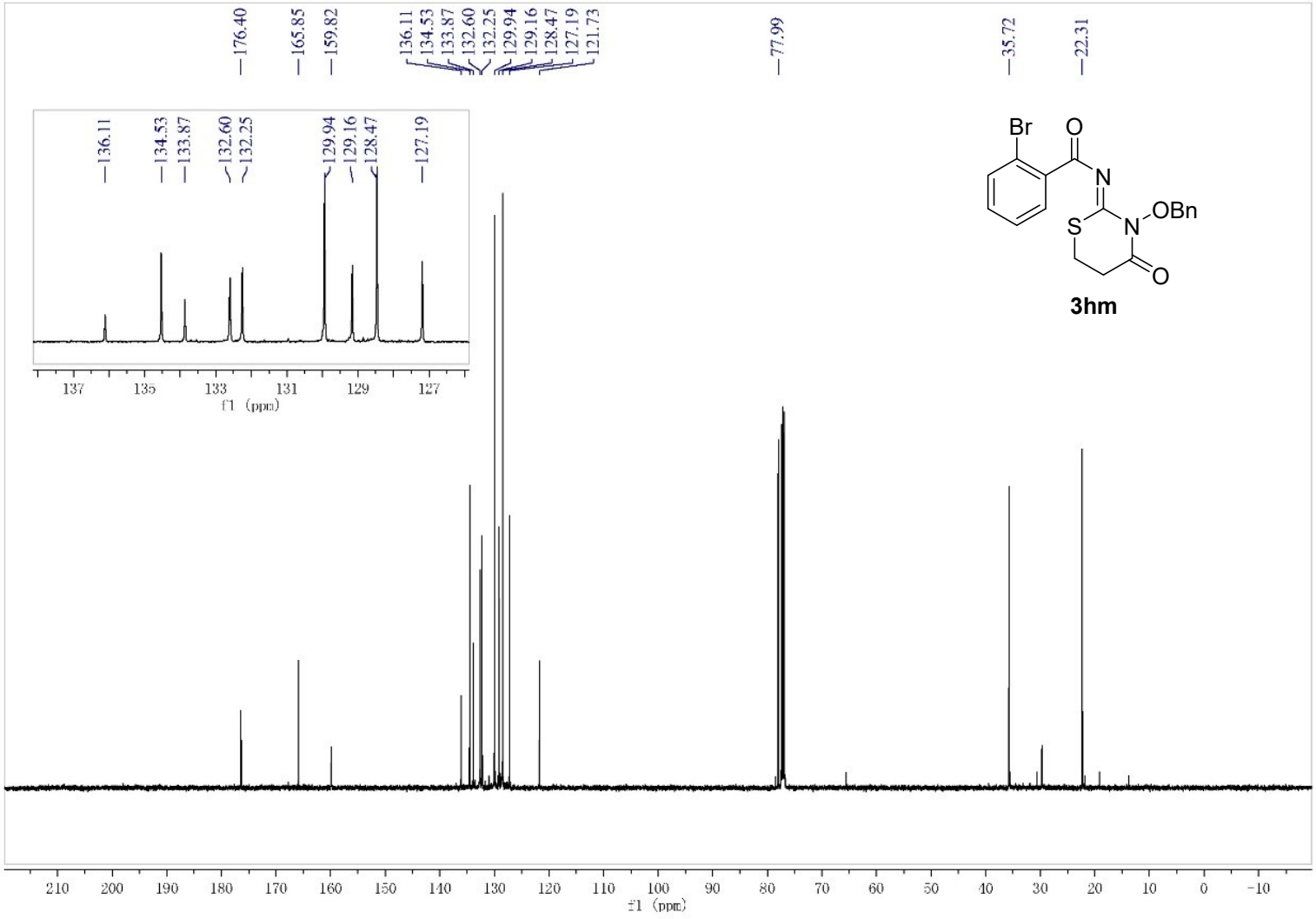
3.14 3.13 3.11 2.99 2.98 2.97
Br O N S N OBn O
3hm
1.00 0.99 2.11 5.24
8.0 7.8 7.6 7.4 7.2
f1 (ppm)
1.00 0.99 2.11 5.24 2.03 2.14 2.14
f1 (ppm)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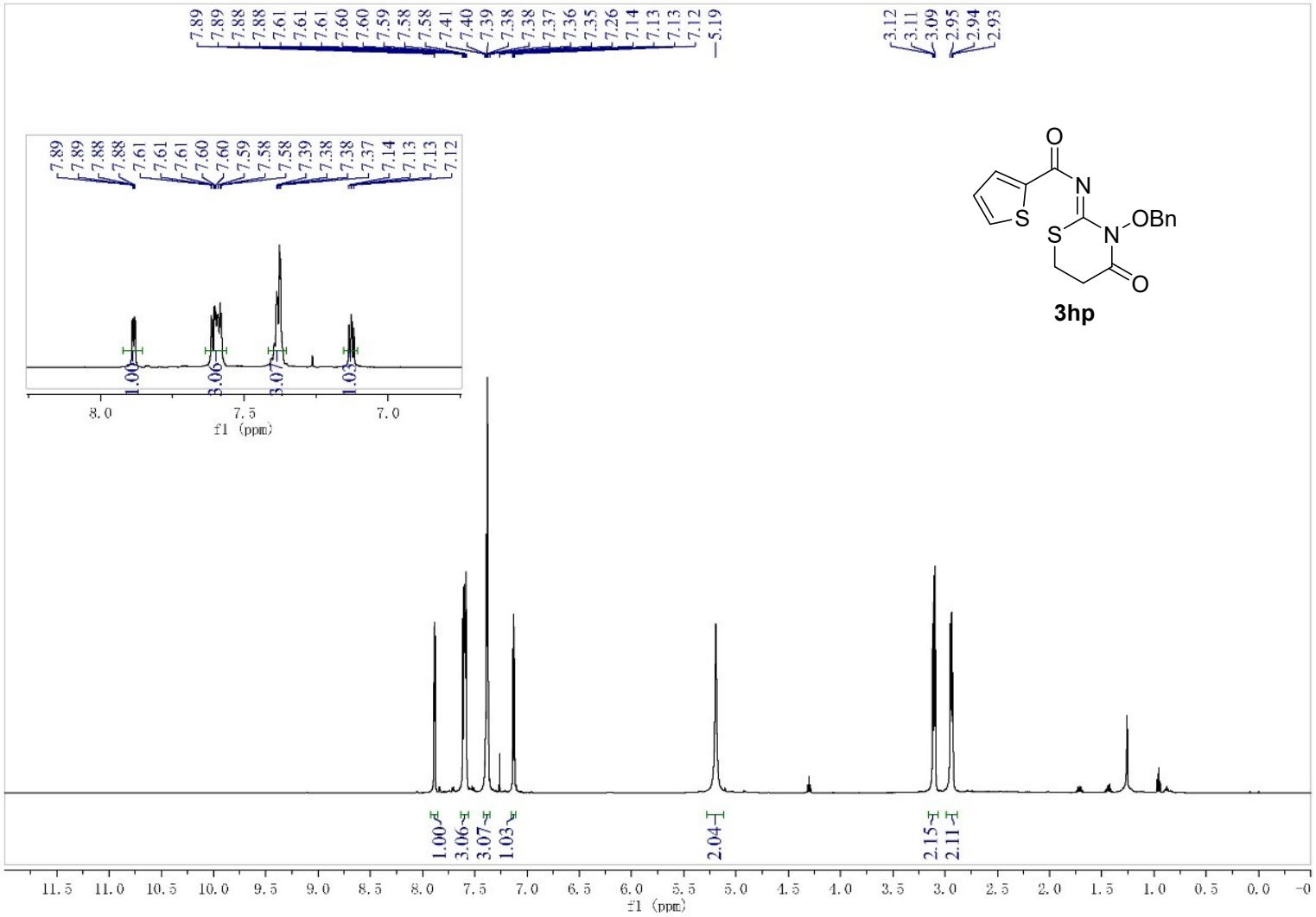
136.11
134.53
133.87
132.60
132.25
129.94
129.16
128.47
127.19
121.73
77.99
35.72
22.31
f1 (ppm)
Br
O
N
S
N
OBn
O
3hm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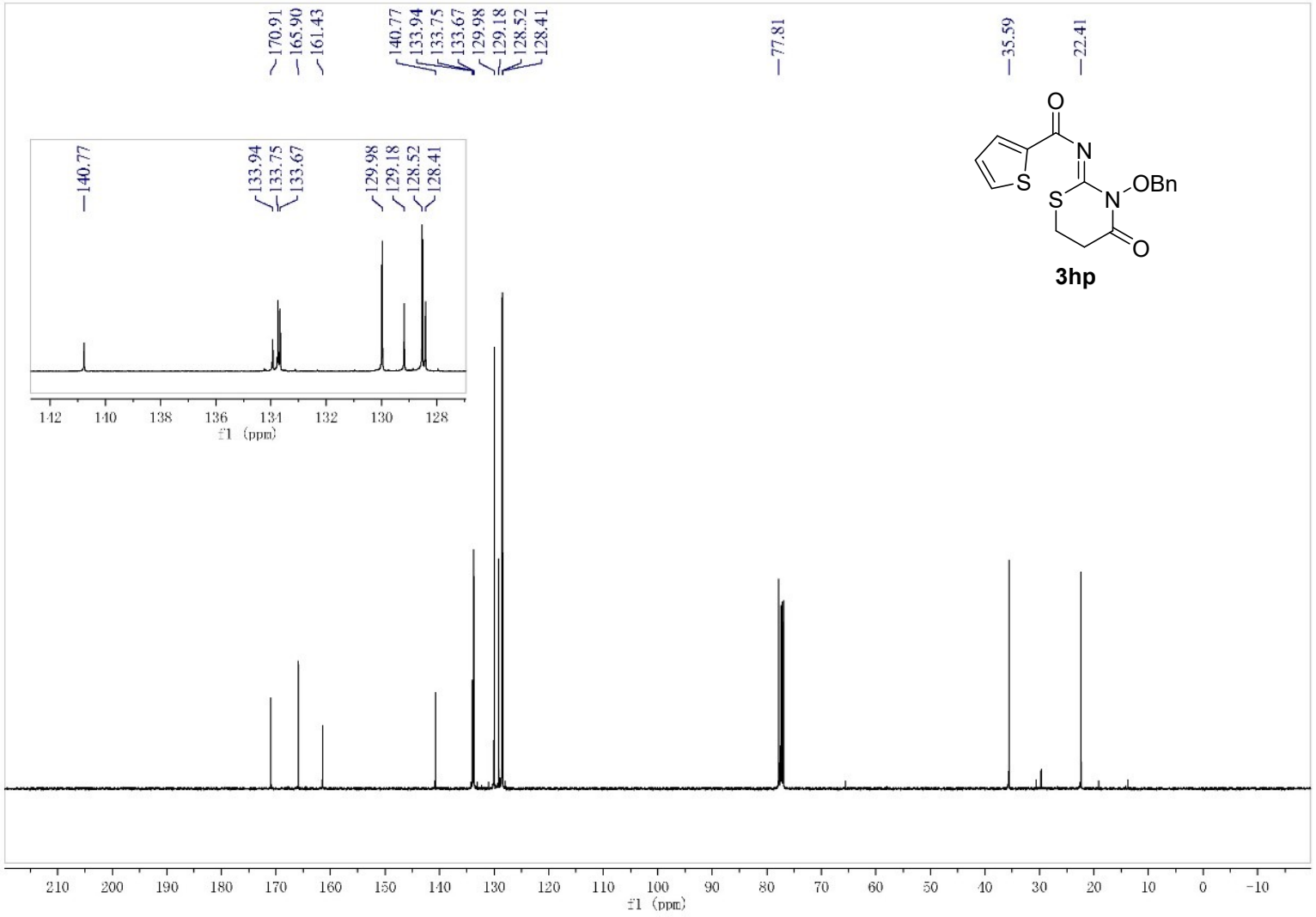
7.58
7.58
7.41
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.26
7.14
7.13
7.13
7.12
5.19
3.12
3.11
3.09
2.95
2.94
2.93
1.00
3.06
3.07
1.03
2.04
2.15
2.11
f1 (ppm)
O
N
S
S
N
OBn
O
3hp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133.75
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129.98
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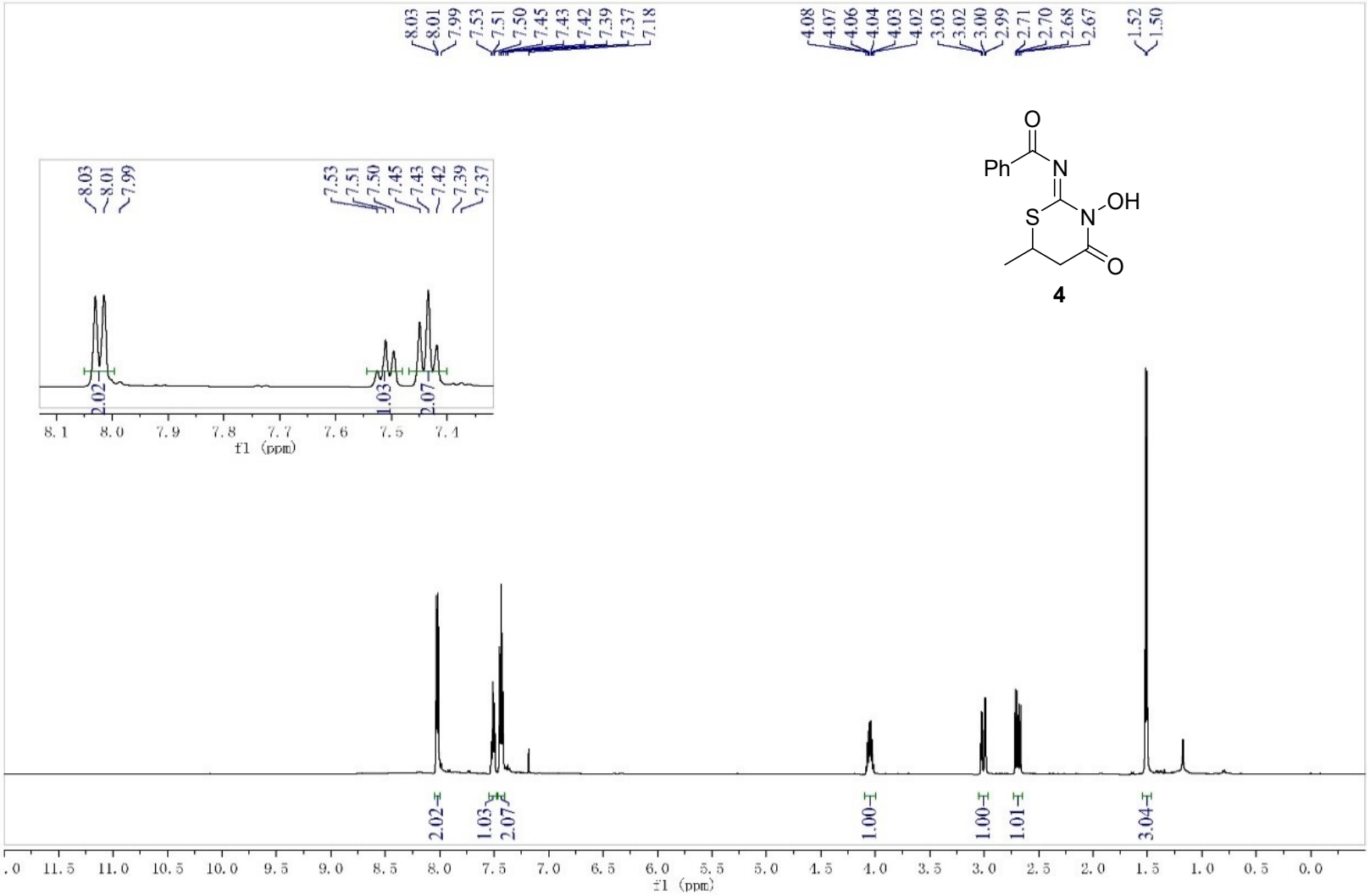
128.52
128.41
77.81
35.59
22.41
O
N
S
S
N
OBn
O
3hp
f1 (ppm)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7.53
7.51
7.50
7.45
7.43
7.42
7.39
7.37
7.18
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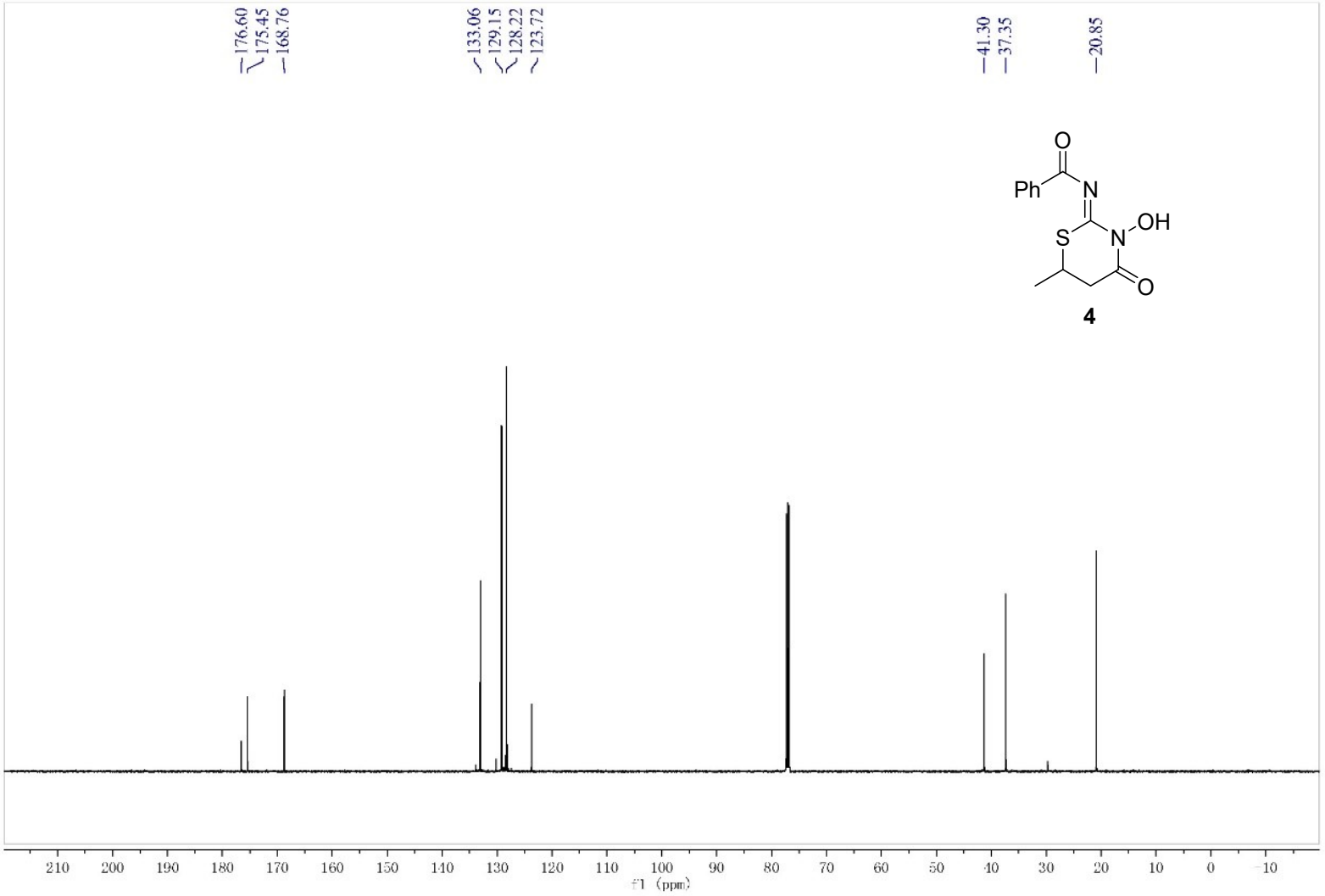
4.07
4.06
4.04
4.03
4.02
3.03
3.02
3.00
2.99
2.71
2.70
2.68
2.67
1.52
1.50
Ph
N
O
S
N
OH
O
4
2.02
1.03
2.07
1.00
1.00
1.01
3.04
f1 (ppm)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133.06
129.15
128.22
123.72
41.30
37.35
20.85
O
Ph
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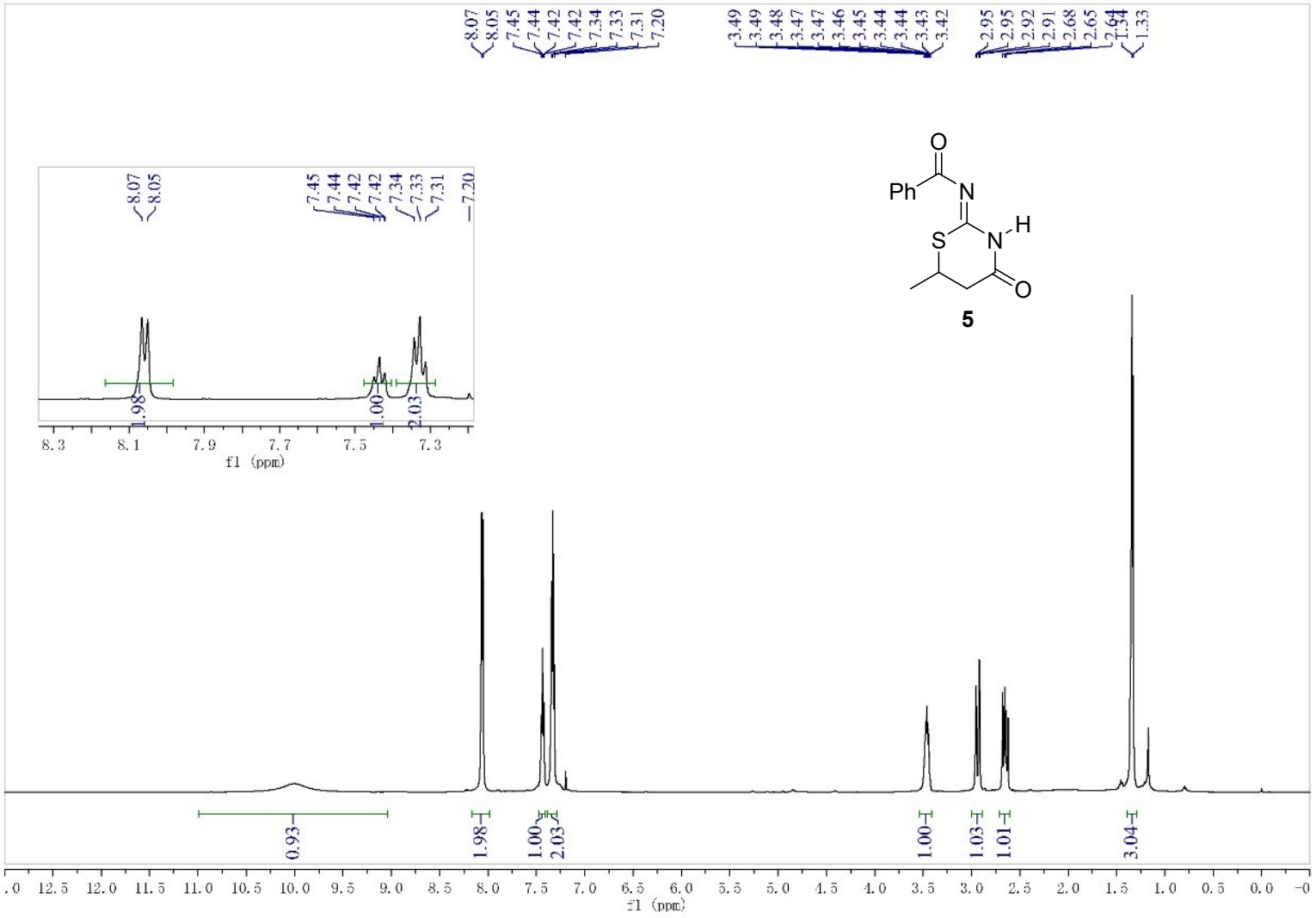
S
N
OH
O
4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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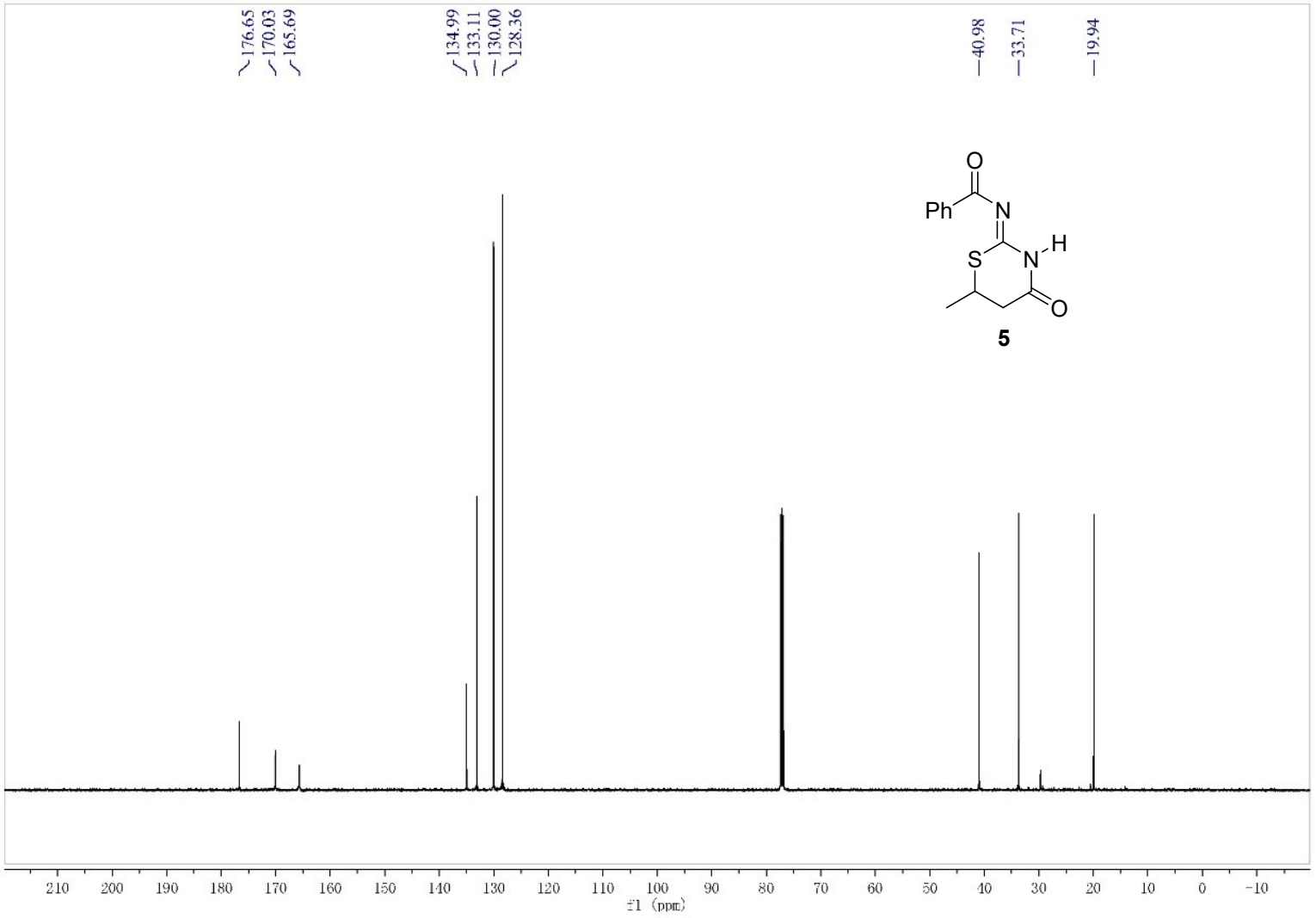
7.42
7.42
7.34
7.33
7.31
7.20
3.49
3.49
3.48
3.47
3.47
3.46
3.45
3.44
3.44
3.43
3.42
2.95
2.95
2.92
2.91
2.68
2.65
2.64
1.34
1.33
O
Ph
N
H
S
N
O
5
1.98
1.00
2.03
8.3
8.1
7.9
7.7
7.5
7.3
f1 (ppm)
0.93
1.98
1.00
2.03
1.00
1.03
1.01
3.04
f1 (ppm)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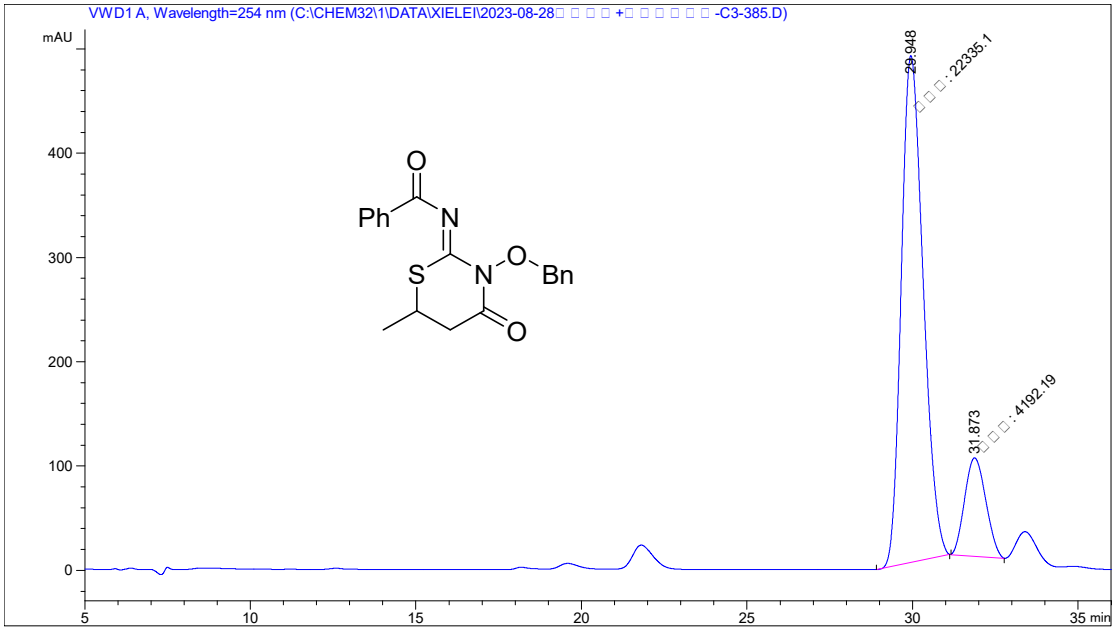
170.03
165.69
134.99
133.11
130.00
128.36
40.98
33.71
19.94
O
Ph
N
S
N
H
O
5
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

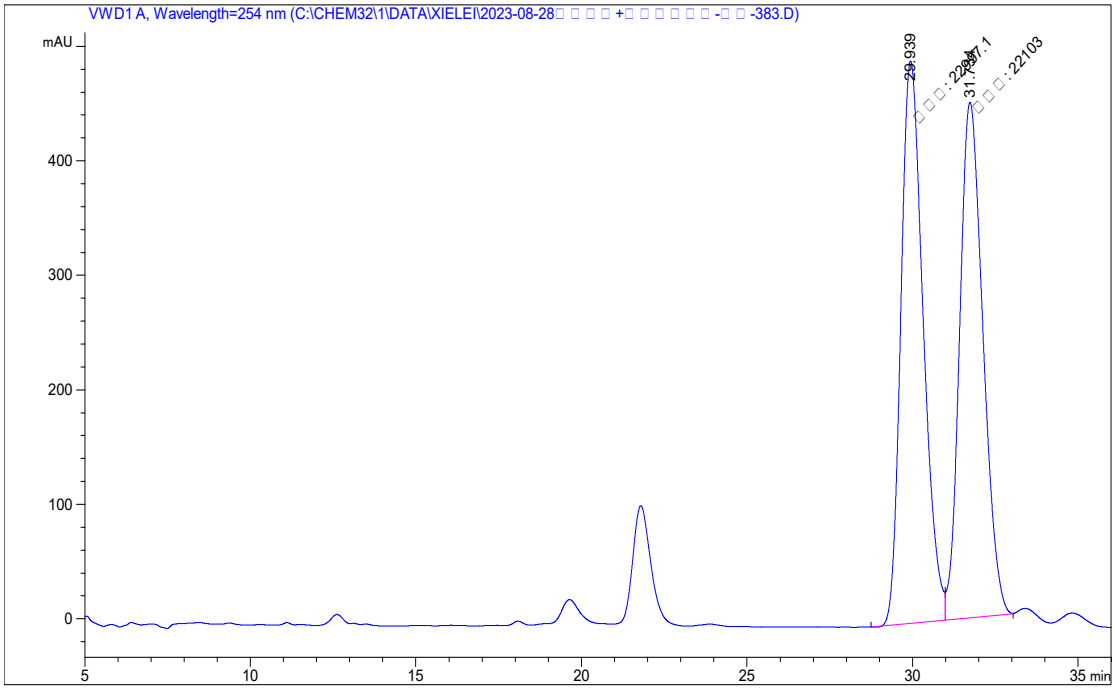
8. HPLC Chromatograms for the product

HPLC Chromatograms for the product for 3aa

Daicel Chiralcel-IC, n-hexane/i-PrOH = 85:15, 1.0 mL/min, 254 nm; t_R (major) = 29.948 min, t_R (minor) = 31.873 min; 68% ee.



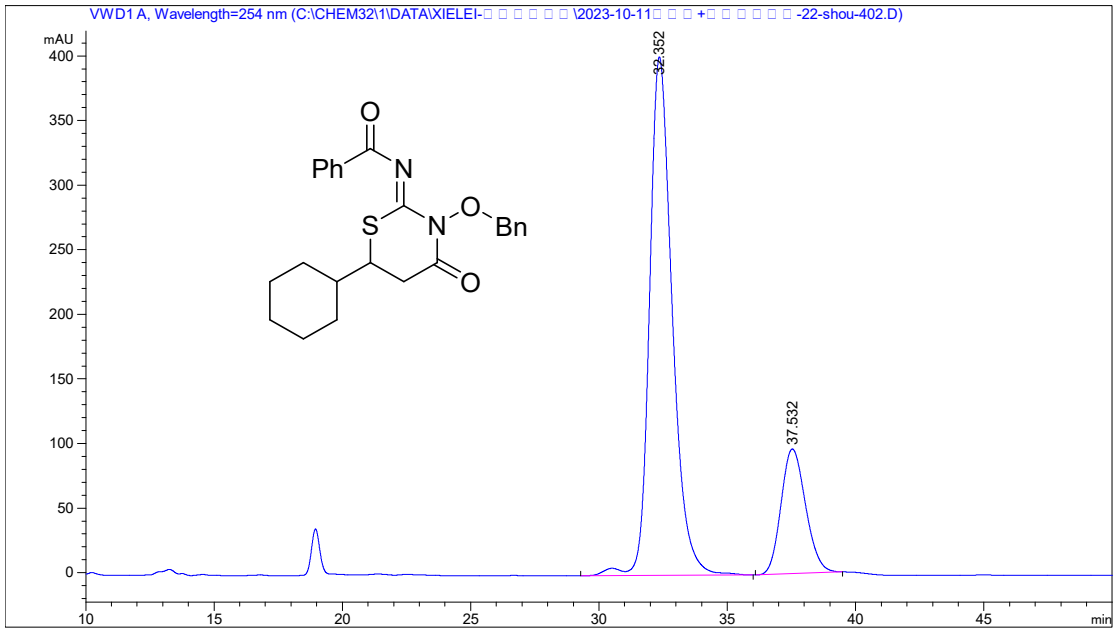
#	Time	Area	Height	Width	Symmetry	Area%
1	29.948	22335.1	486.1	0.7659	0.751	84.197
2	31.873	4192.2	94.5	0.7396	0.855	15.803



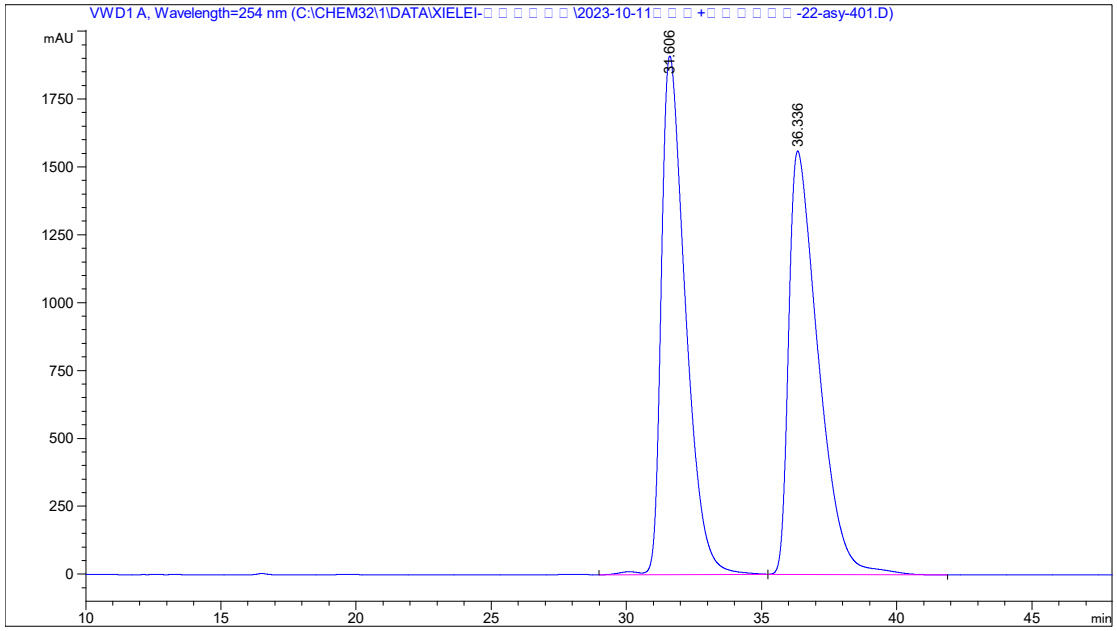
#	Time	Area	Height	Width	Symmetry	Area%
1	29.939	22997.1	491.4	0.7801	0.732	50.991
2	31.734	22103	450.5	0.8177	0.771	49.009

HPLC Chromatograms for the product for 3ca

Daicel Chiralcel-IC, n-hexane/i-PrOH = 85:15, 1.0 mL/min, 254 nm; t_R (major) = 32.352 min, t_R (minor) = 37.532 min; 59% ee.



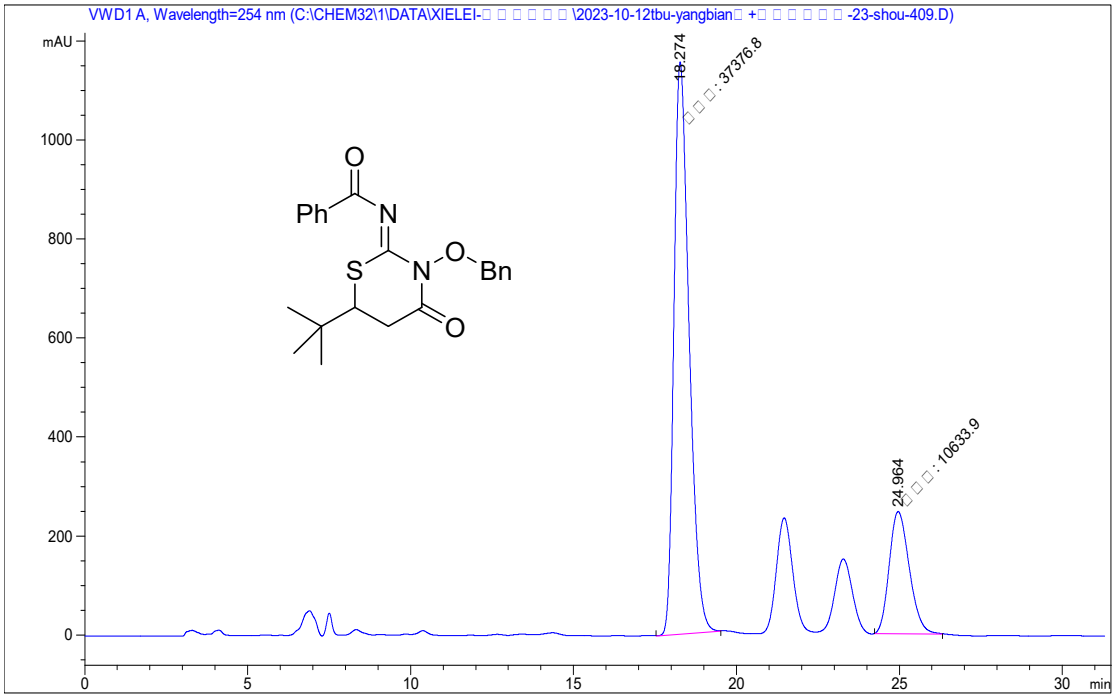
#	Time	Area	Height	Width	Symmetry	Area%
1	32.352	24769.4	401.5	0.9372	0.755	79.409
2	37.532	6422.6	96.5	1.0301	0.821	20.591



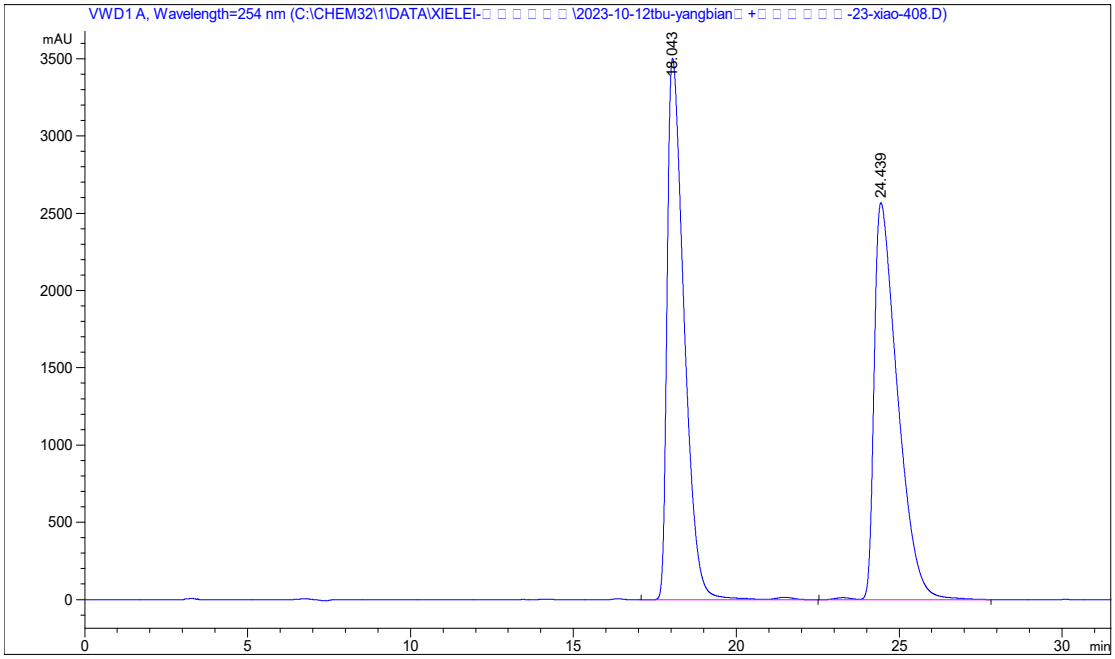
#	Time	Area	Height	Width	Symmetry	Area%
1	31.606	118837.8	1910.5	0.9503	0.511	50.079
2	36.336	118463.8	1559.3	1.1513	0.4	49.921

HPLC Chromatograms for the product for 3da

Daicel Chiralcel-IC, n-hexane/i-PrOH = 85:15, 1.0 mL/min, 254 nm; t_R (major) = 18.274 min, t_R (minor) = 24.964 min; 56% ee.



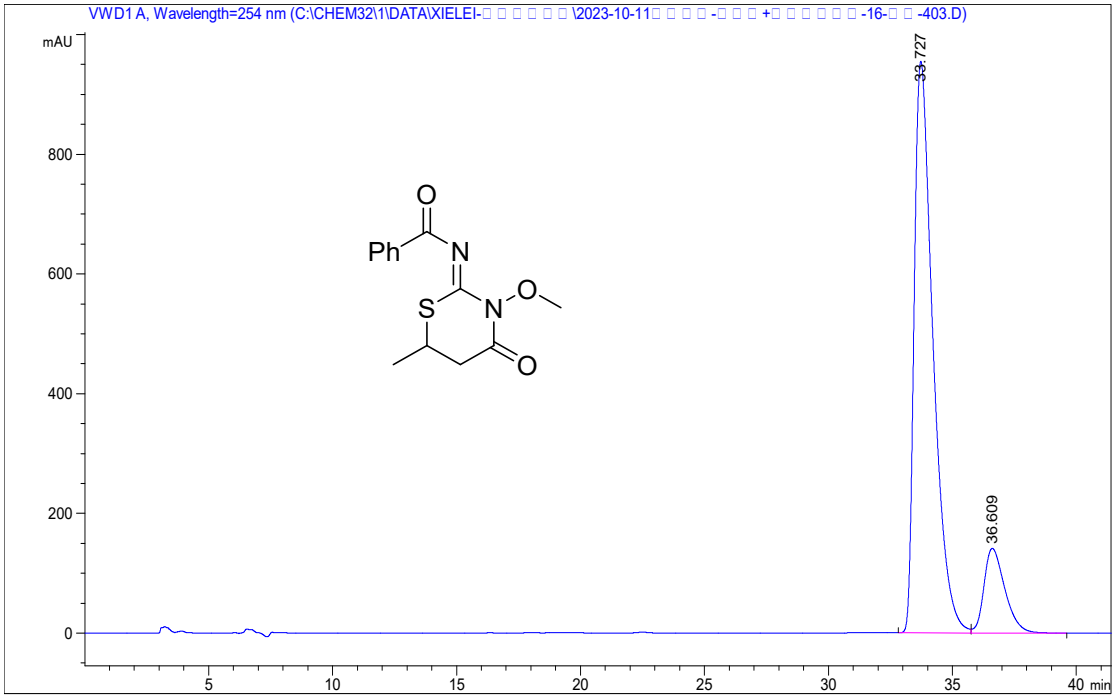
#	Time	Area	Height	Width	Symmetry	Area%
1	18.274	37376.8	1156.8	0.5385	0.663	77.851
2	24.964	10633.9	247.2	0.7169	0.773	22.149



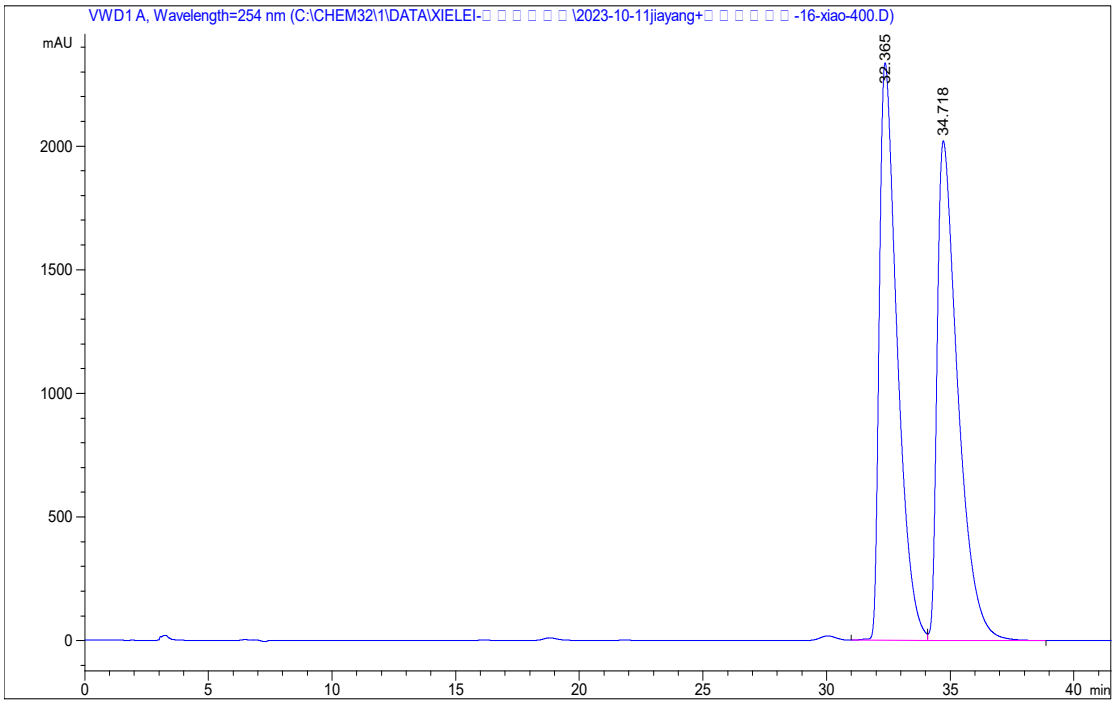
#	Time	Area	Height	Width	Symmetry	Area%
1	18.043	127382.8	3505.7	0.5549	0.434	49.829
2	24.439	128258.8	2569.2	0.7422	0.384	50.171

HPLC Chromatograms for the product for 3ea

Daicel Chiralcel-IC, n-hexane/i-PrOH = 85:15, 1.0 mL/min, 254 nm; t_R (major) = 33.727 min, t_R (minor) = 36.609 min; 72% ee.



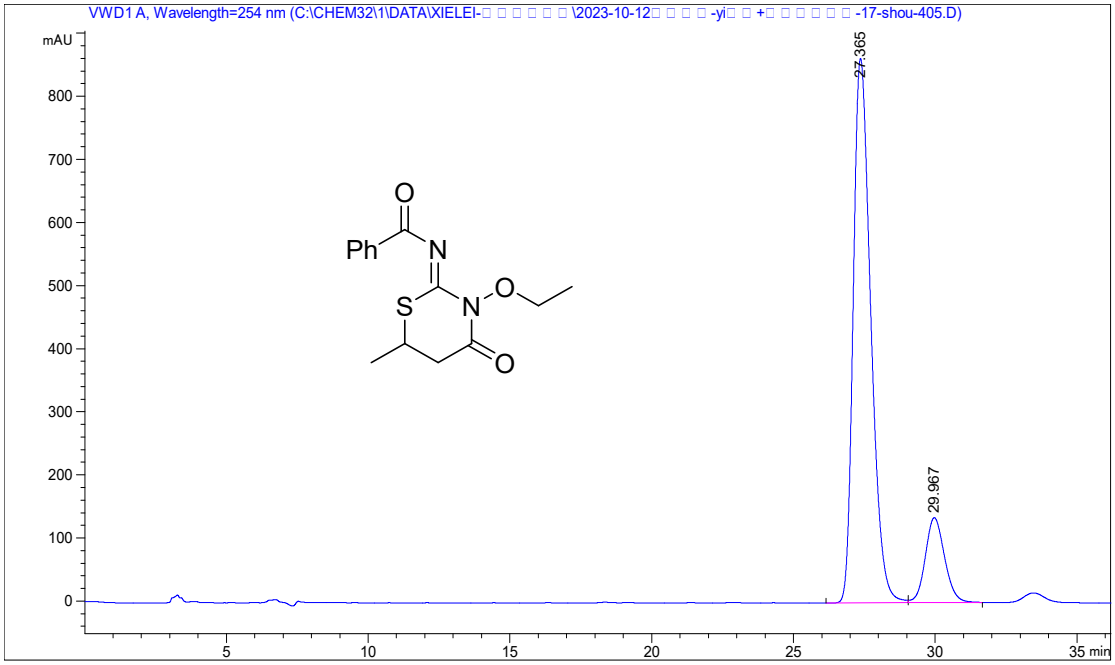
#	Time	Area	Height	Width	Symmetry	Area%
1	33.727	50328.6	955.3	0.7946	0.502	85.853
2	36.609	8293	141.5	0.896	0.63	14.147



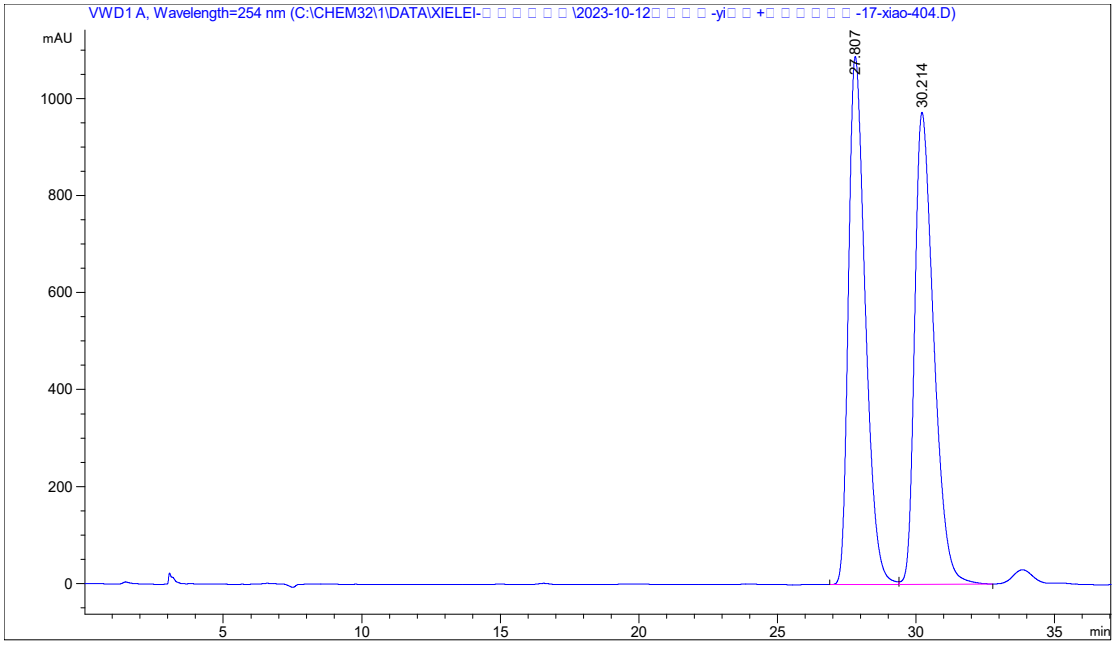
#	Time	Area	Height	Width	Symmetry	Area%
1	32.365	117459.4	2335.3	0.7558	0.44	49.970
2	34.718	117599.1	2020	0.8602	0.39	50.030

HPLC Chromatograms for the product for 3fa

Daicel Chiralcel-IC, n-hexane/i-PrOH = 85:15, 1.0 mL/min, 254 nm; t_R (major) = 27.365 min, t_R (minor) = 29.967 min; 71% ee.



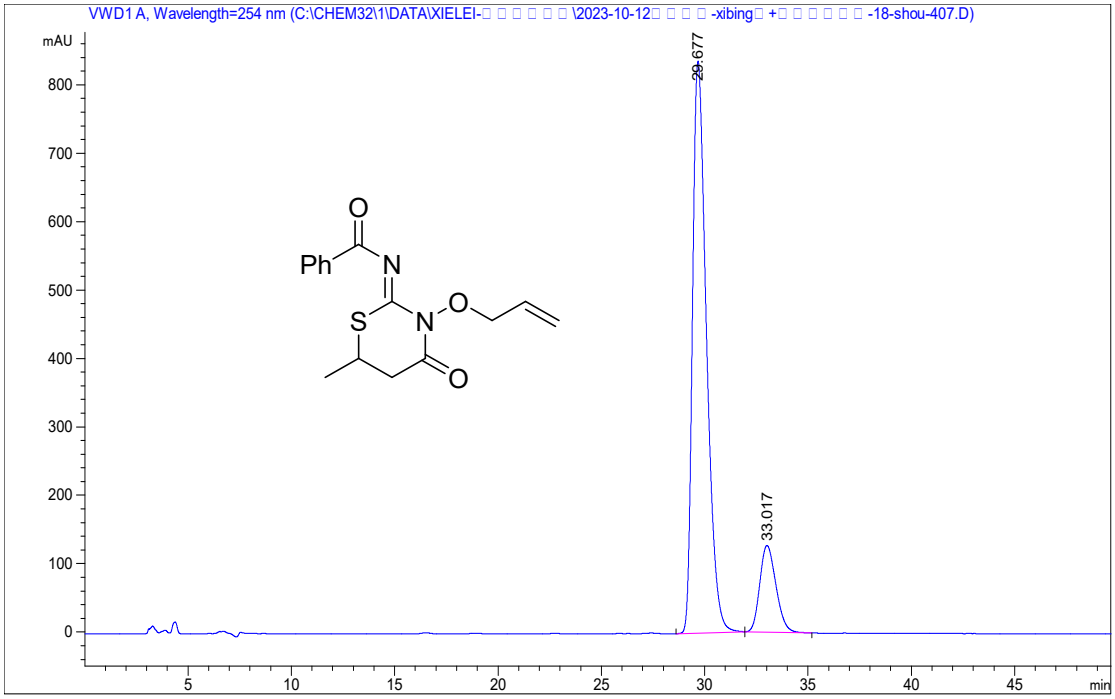
#	Time	Area	Height	Width	Symmetry	Area%
1	27.365	36983.5	863	0.659	0.66	85.326
2	29.967	6360.4	134.5	0.7268	0.84	14.674



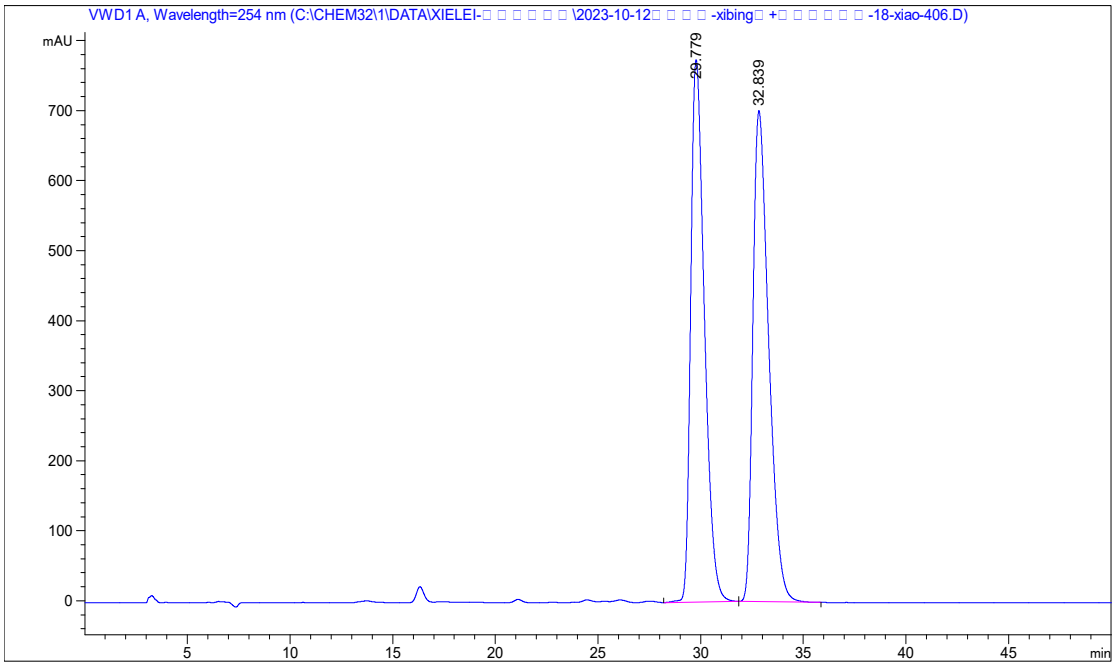
#	Time	Area	Height	Width	Symmetry	Area%
1	27.807	46042.8	1089.6	0.651	0.634	49.814
2	30.214	46387.1	973.4	0.732	0.579	50.186

HPLC Chromatograms for the product for 3ga

Daicel Chiralcel-IC, n-hexane/i-PrOH = 85:15, 1.0 mL/min, 254 nm; t_R (major) = 29.677 min, t_R (minor) = 33.017 min; 70% ee.



#	Time	Area	Height	Width	Symmetry	Area%
1	29.677	39160.8	836.5	0.7202	0.602	85.024
2	33.017	6897.8	126.6	0.8458	0.766	14.976



#	Time	Area	Height	Width	Symmetry	Area%
1	29.779	35859.9	774.8	0.71	0.612	48.892
2	32.839	37485.6	701	0.8069	0.578	51.108

9. X-Ray Crystallographic Data of 3aa

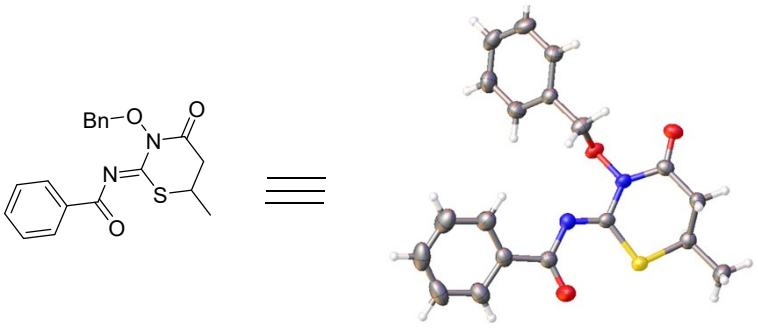


Table 1 Crystal data and structure refinement for 3aa.

Empirical formula	$C_{19}H_{18}N_2O_3S$
Formula weight	354.41
Temperature/K	296.15
Crystal system	monoclinic
Space group	C2/c
a/Å	32.264(3)
b/Å	6.0091(5)
c/Å	19.0987(17)
α/°	90
β/°	110.3890(10)
γ/°	90
Volume/Å^3	3470.9(5)
Z	8
ρ_{calc}g/cm^3	1.356
μ/mm^{-1}	0.207
F(000)	1488.0
Crystal size/mm^3	? × ? × ?
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.714 to 54.728
Index ranges	-30 ≤ h ≤ 41, -7 ≤ k ≤ 7, -24 ≤ l ≤ 24
Reflections collected	9891
Independent reflections	3885 [R_{int} = 0.0153, R_{sigma} = 0.0183]
Data/restraints/parameters	3885/0/227
Goodness-of-fit on F^2	1.032
Final R indexes [I>=2σ (I)]	R_1 = 0.0337, wR_2 = 0.0831
Final R indexes [all data]	R_1 = 0.0407, wR_2 = 0.0876
Largest diff. peak/hole / e Å^{-3}	0.23/-0.20