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Metal-Free Oxidative Functionalization of C(sp^3)−H of Ketones and Alcohols for the Synthesis of Isoquinolinonediones

Su-Li Zhu,[a] Ping-Xin Zhou [b] and Xiao-Feng Xia [a*]

[a] The Key Laboratory of Food Colloids and Biotechnology, Ministry of Education, School of Chemical and Material Engineering, Jiangnan University, Wuxi, Jiangsu, 214122, China. E-mail: xiaxf@jiangnan.edu.cn.

[b] School of Basic Medical Sciences, Xinxiang Medical University, Xinxiang, Henan, 453003, China.

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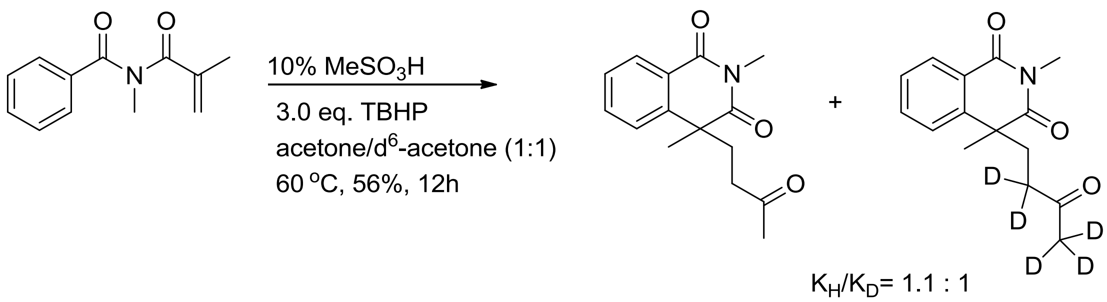
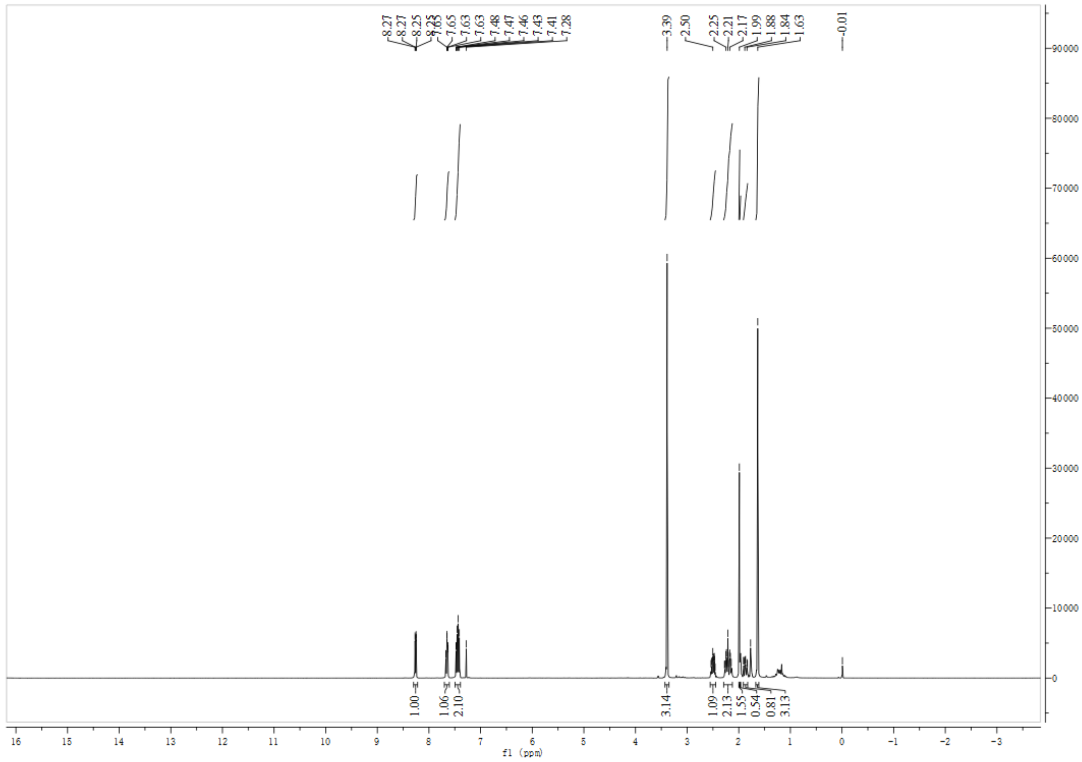
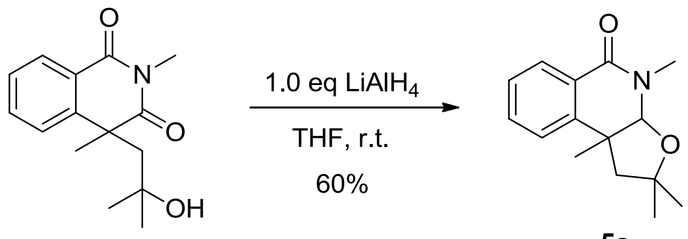
General Remarks: Column chromatography was carried out on silica gel. Unless noted ^{1}H NMR spectra were recorded on 400 MHz in $CDCl_3$, ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and were uncorrected. All new products were further characterized by HRMS (high resolution mass spectra), high resolution mass spectrometry (HRMS) spectra was obtained on a Thermo Scientific LTQ Orbitrap XL instrument equipped with an ESI source; copies of their ^{1}H NMR and ^{13}C NMR spectra are provided.

Kinetic Isotope Effect (KIE) Experiment





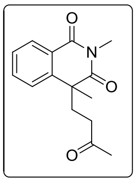
Preparation of Tetrahydrofuro[2,3-c]isoquinolin-5(2H)-one 5a from 4a.



0.4 mmol, **4a** **5a**

An oven-dried Schlenk tube (10 mL) was equipped with a magnetic stir bar, **4a** (0.4 mmol), dry THF (5.0 mL). The reaction mixture was then stirred at 0 °C, and 1.0 equiv. $LiAlH_4$ (28 mg) was slowly added. After the reaction was completed, 6 mL water was added to quench the reaction at 0 °C, and the resulting mixture was extracted twice with EtOAc (2×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the crude product by flash column chromatography afforded the product **5a** (petroleum ether/ethyl acetate as eluent (4:1)).

5a, m.p.=100-102 °C, 2,2,4,9b-tetramethyl-1,3a,4,9b-tetrahydrofuro[2,3-c]isoquinolin-5(2H)-one, ^{1}H NMR (400 MHz): 8.17-8.19 (m, 1 H), 7.49-7.53 (m, 1 H), 7.29-7.36 (m, 2 H), 4.94 (s, 1 H), 3.24 (s, 3 H), 2.55-2.58 (m, 1 H), 2.07-2.10 (m, 1 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 0.86 (s, 3 H);
^{13}C NMR (100 MHz): 163.6, 143.7, 132.2, 128.6, 126.8, 126.5, 125.5, 95.9, 78.2, 52.3, 44.9, 34.4, 30.3, 28.9, 26.9;
IR (cm^{-1}): 2969, 2929, 2871, 1656, 1474, 1338, 1021, 765, 703;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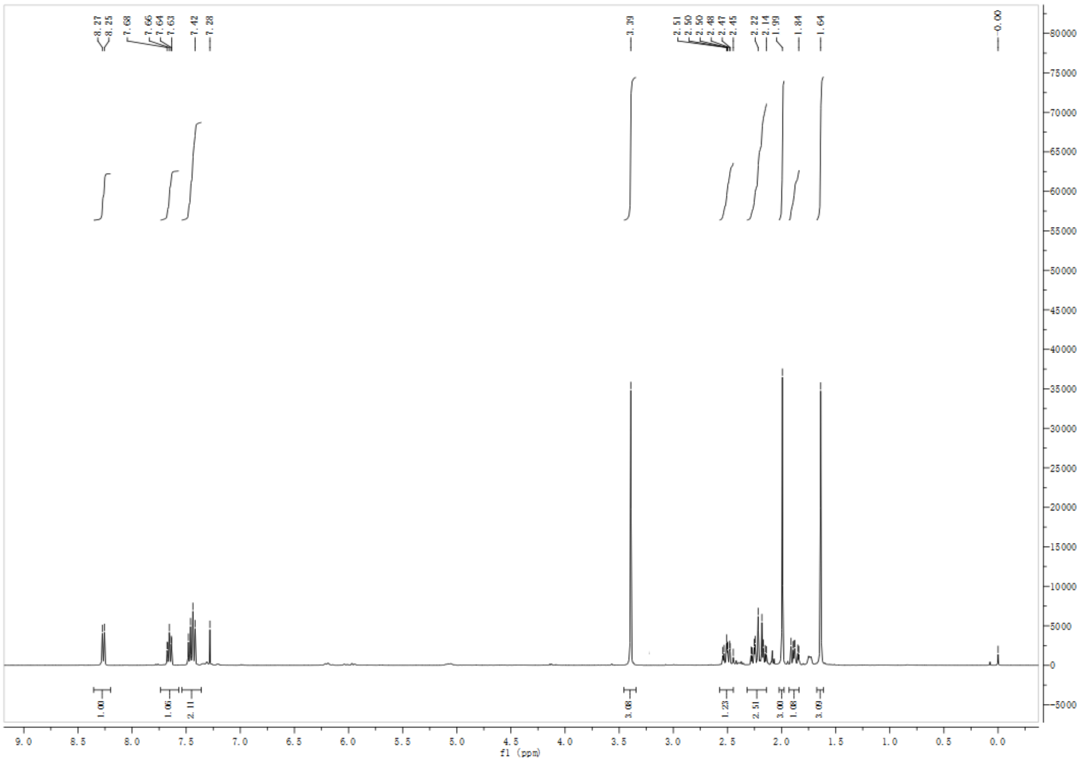

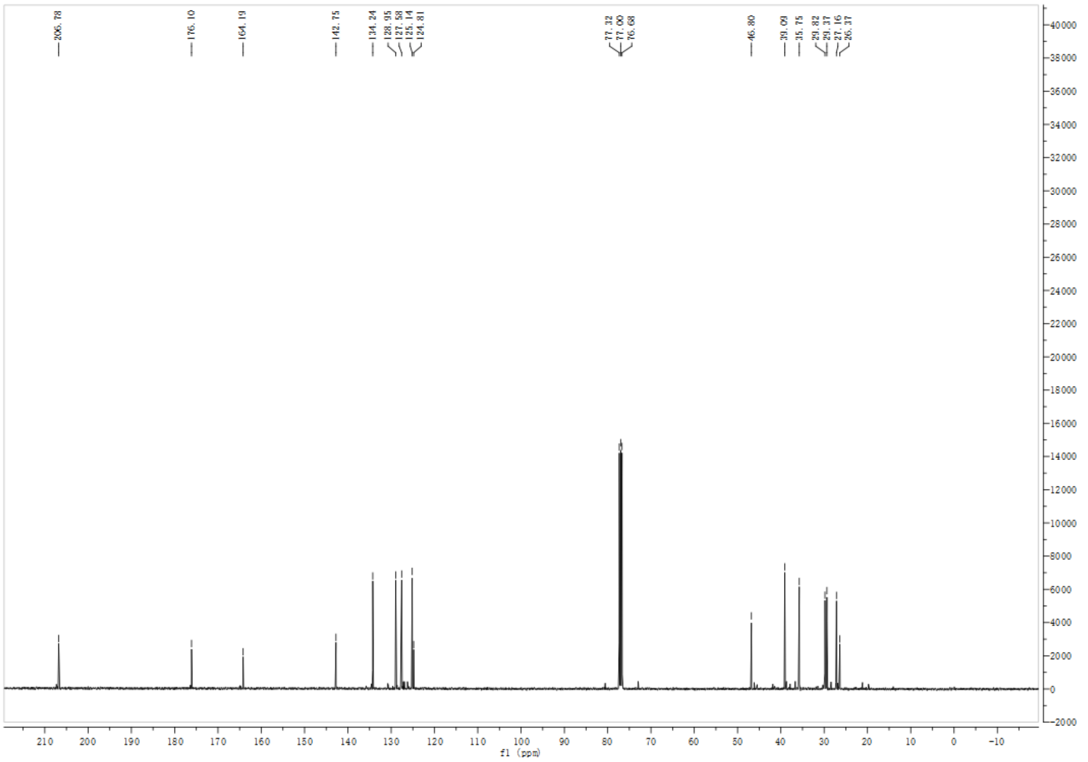

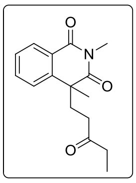

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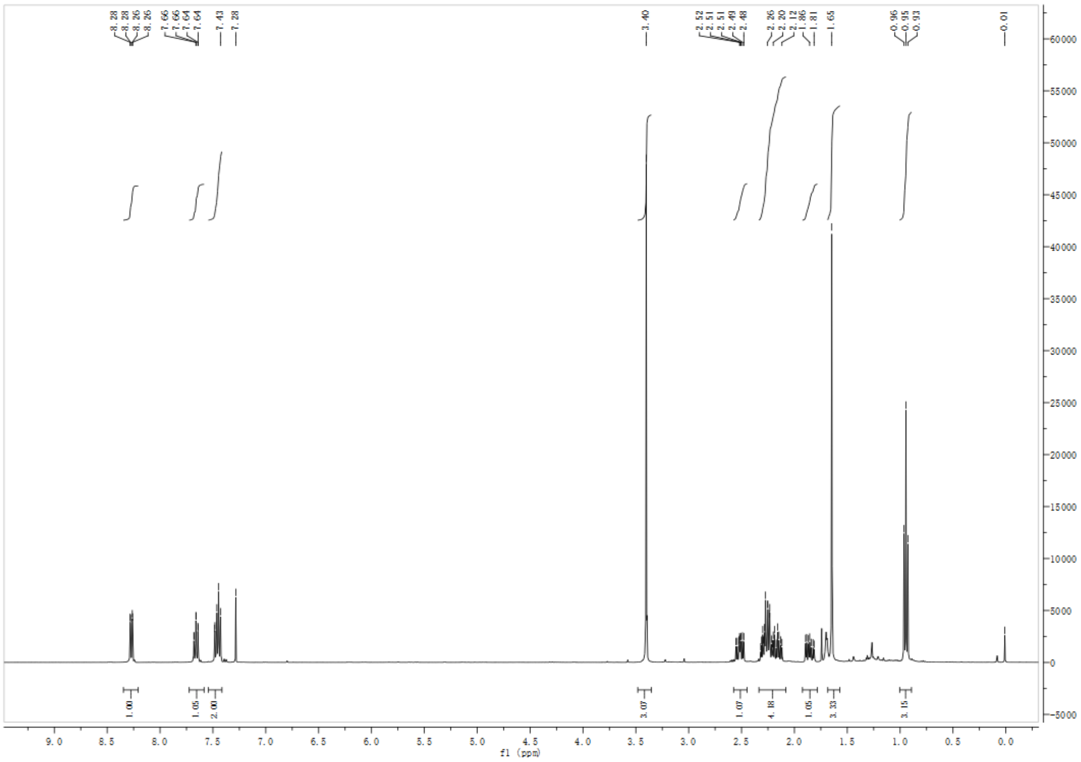
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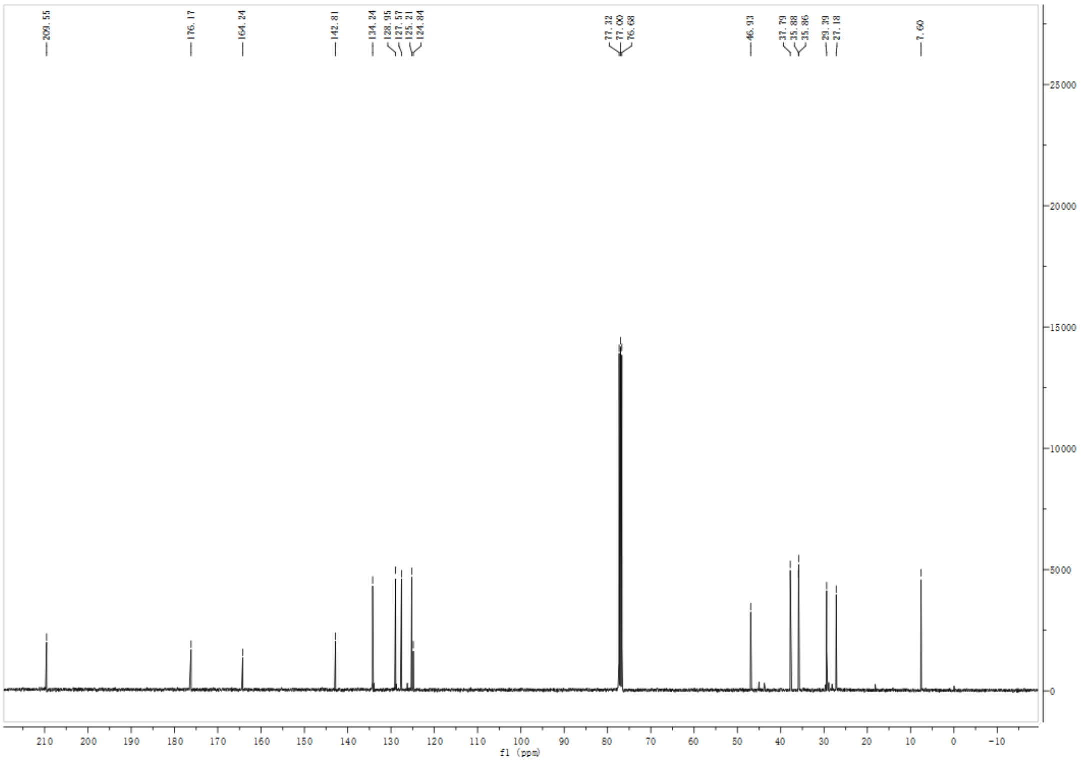
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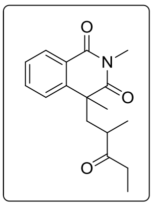

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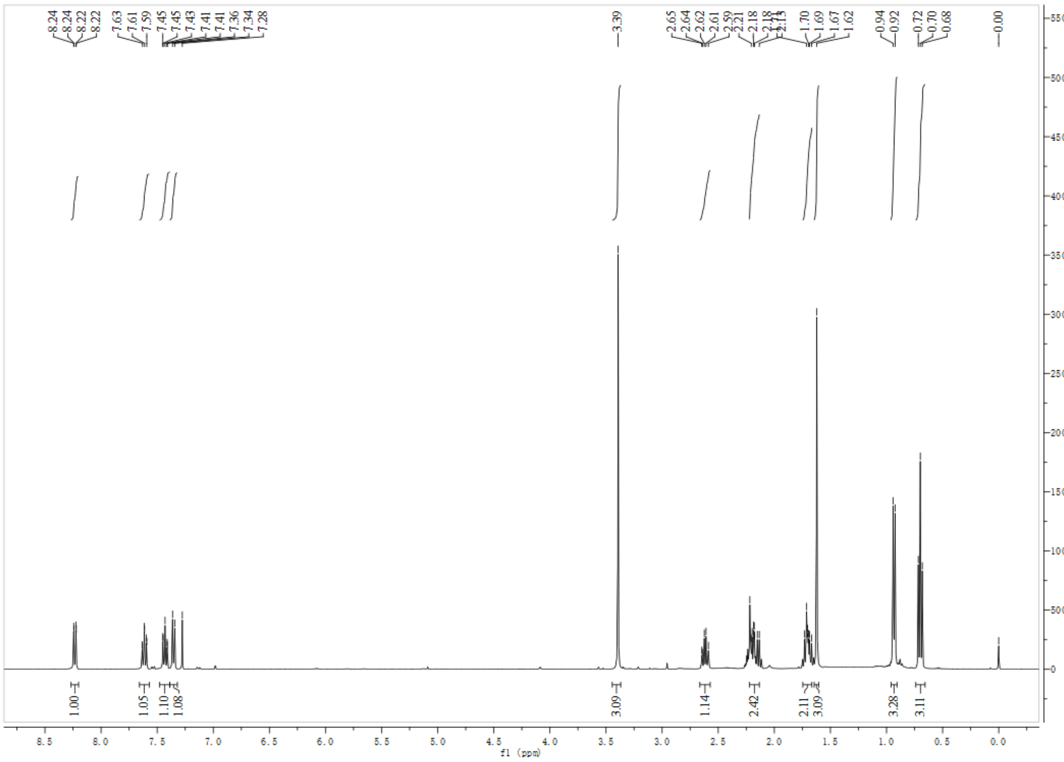

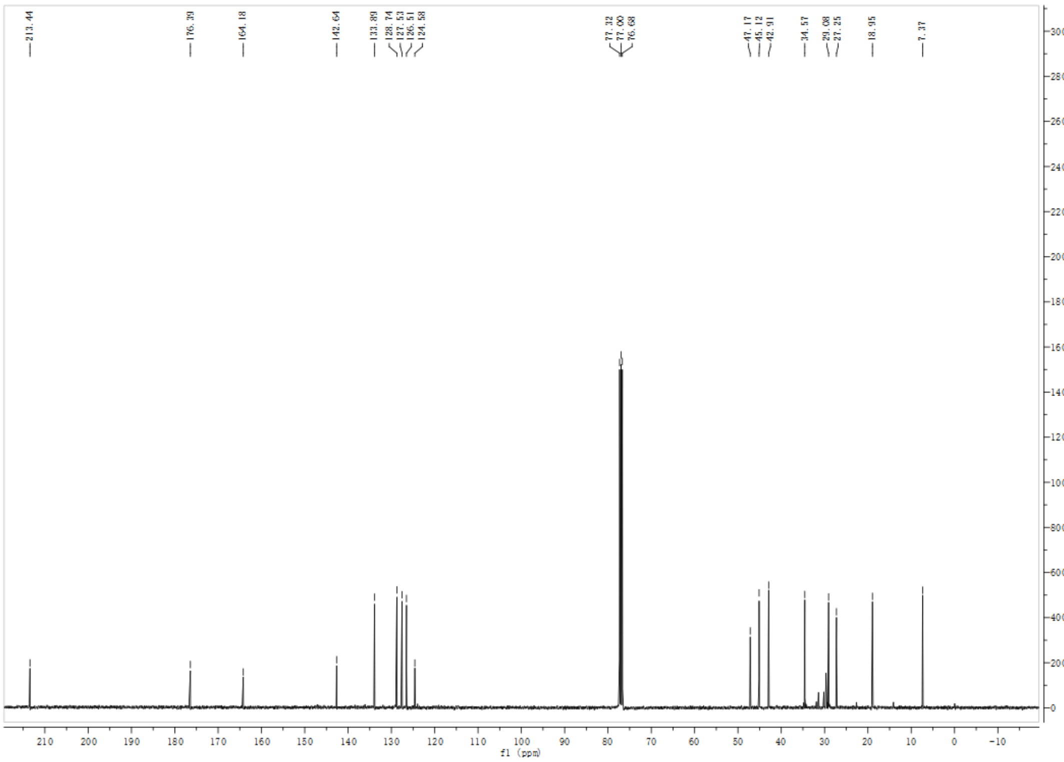

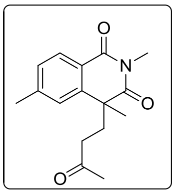
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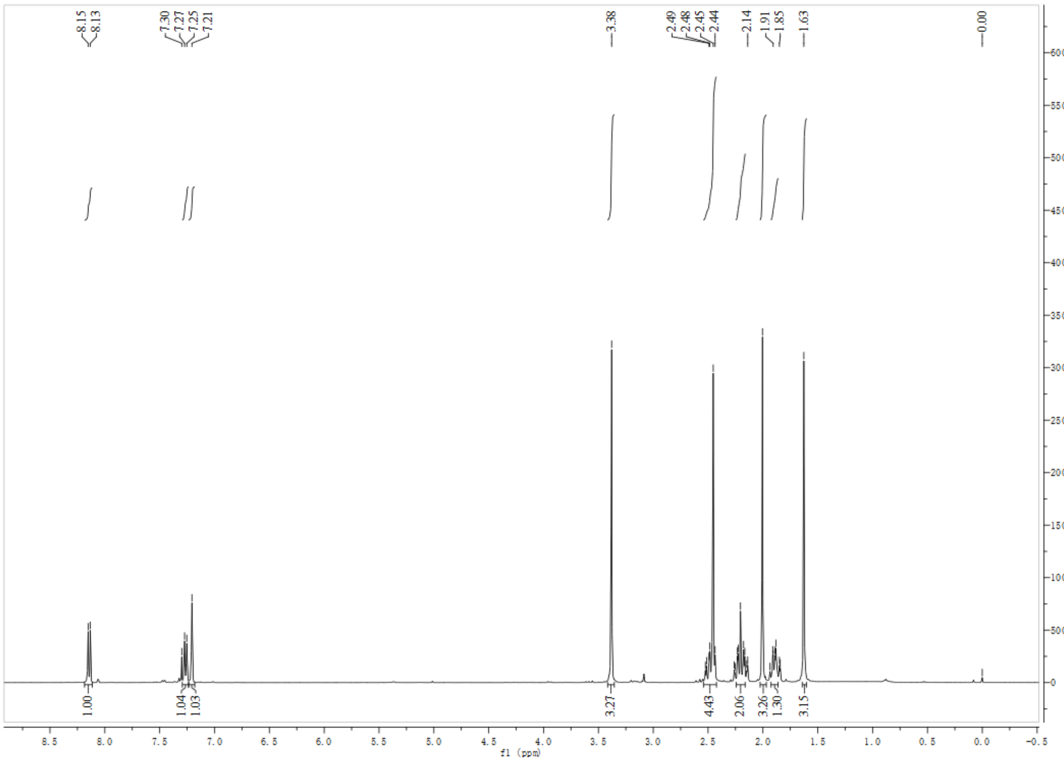
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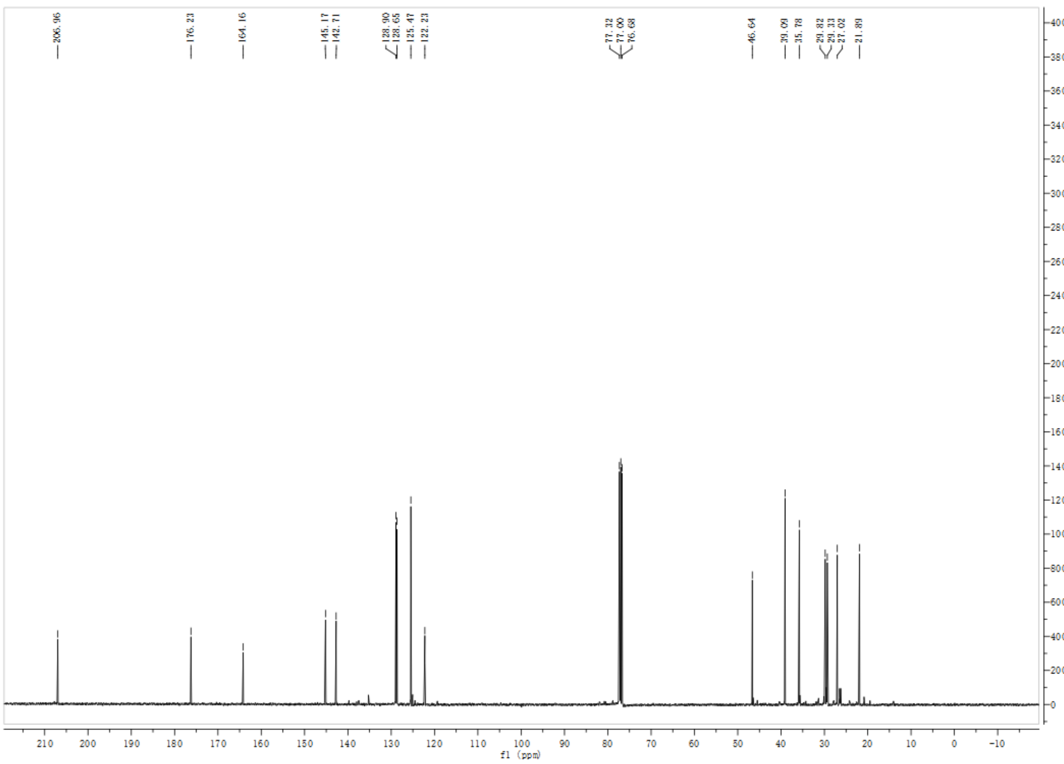
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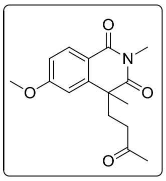
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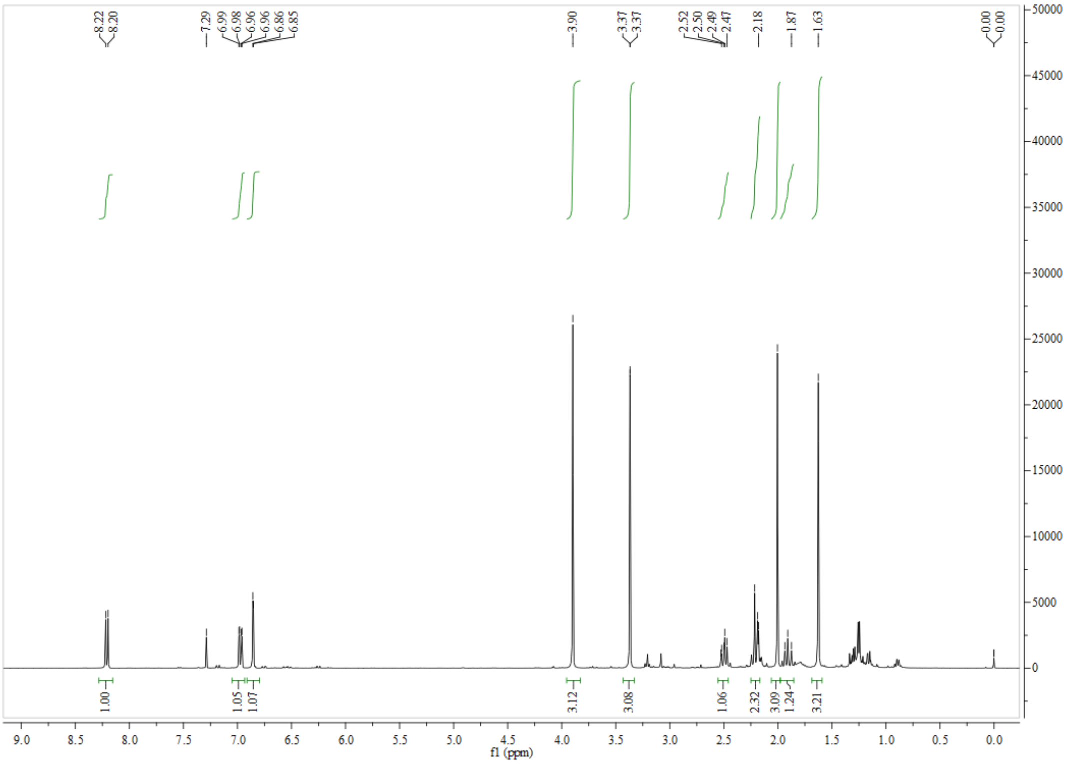
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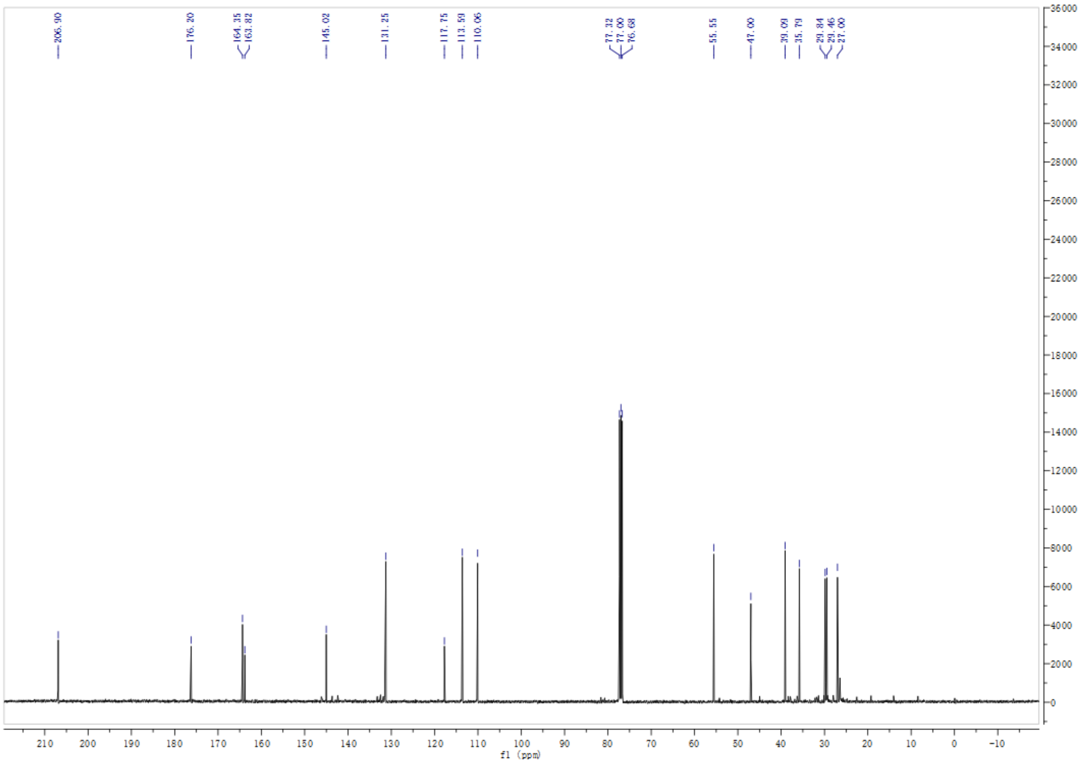
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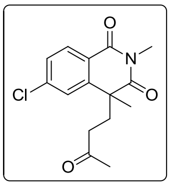
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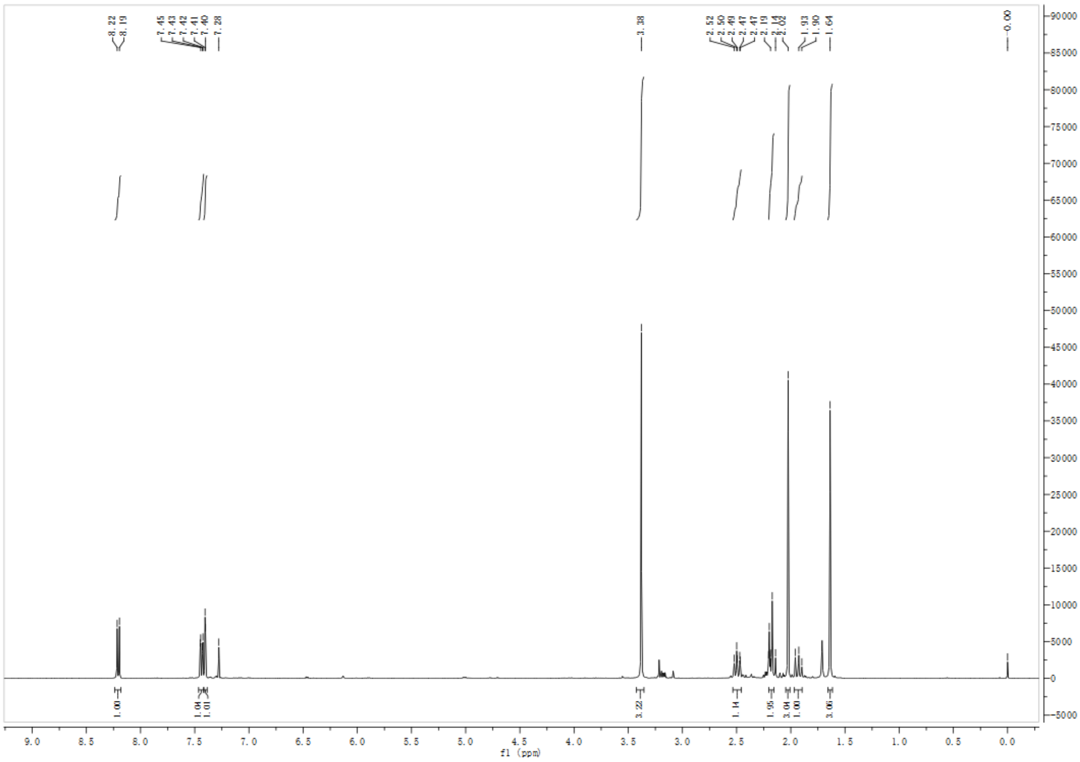
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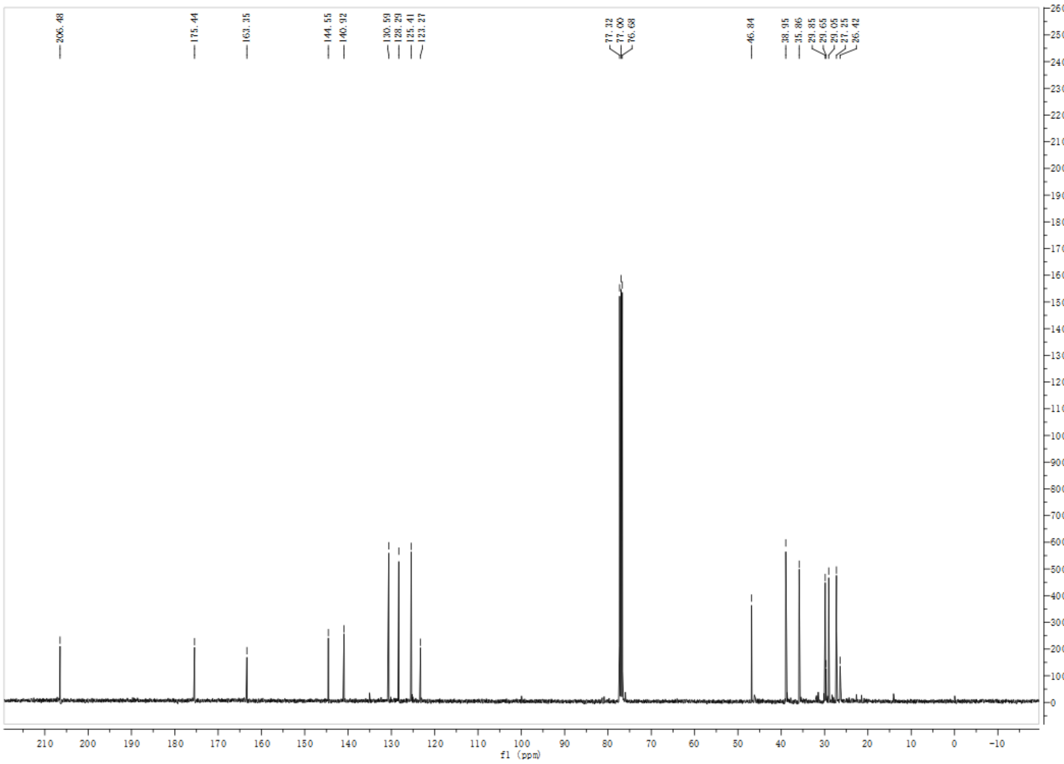
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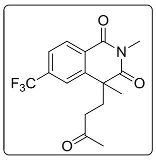
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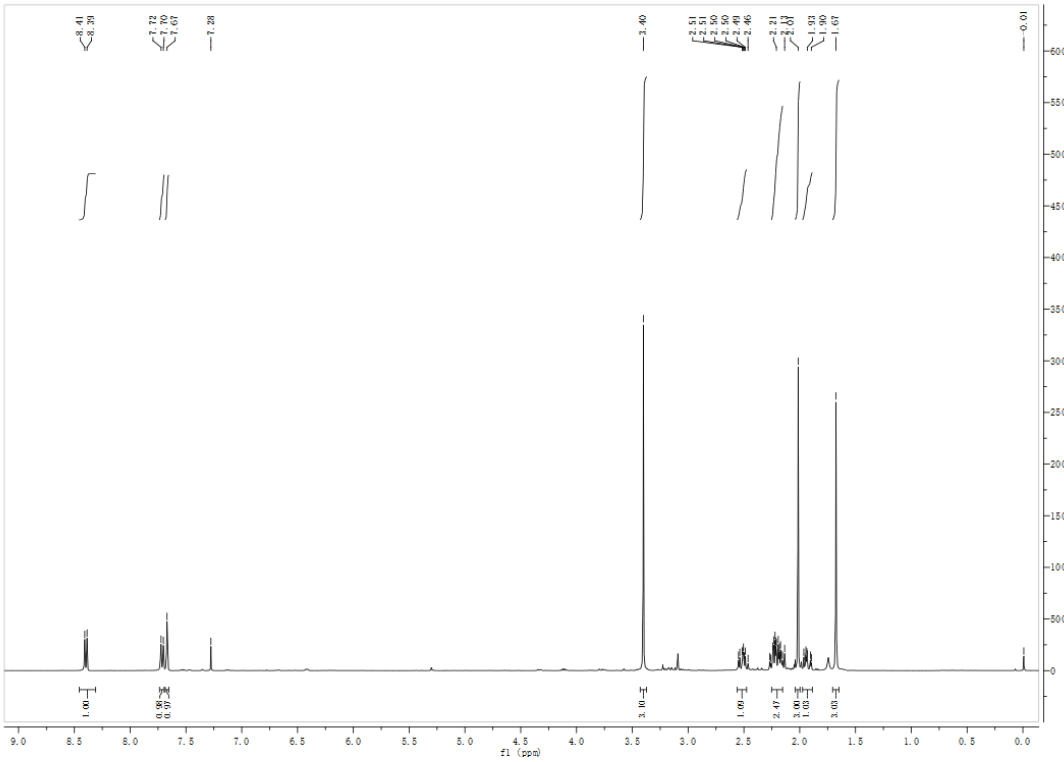
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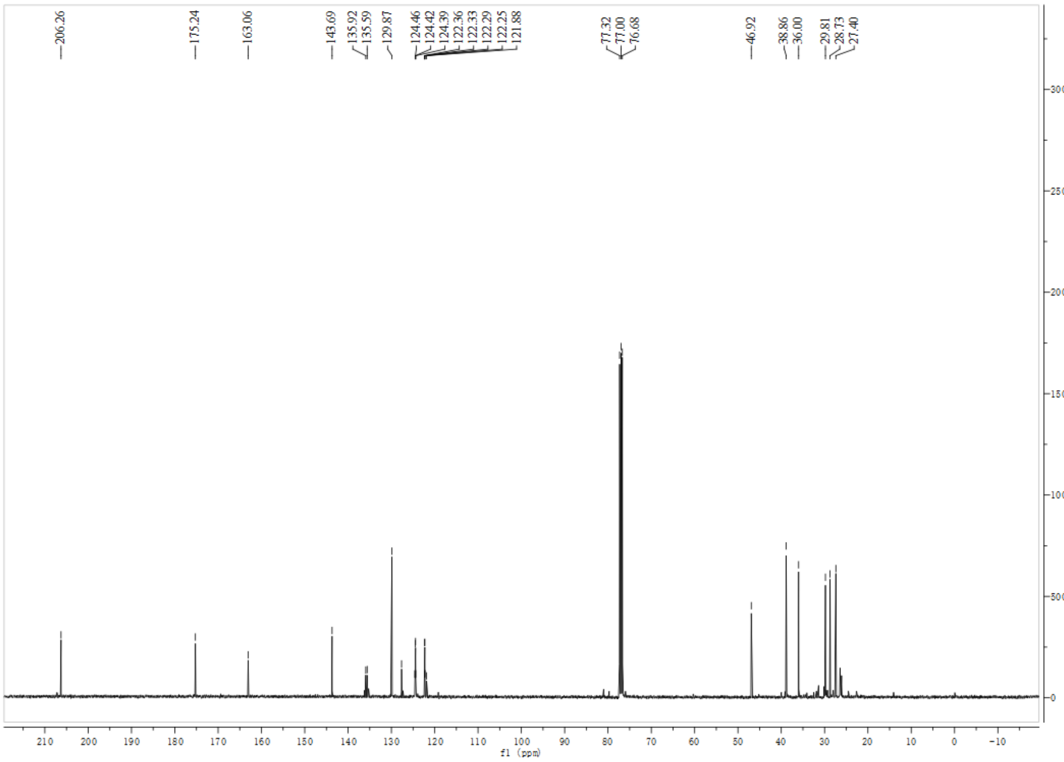
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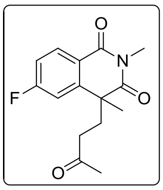

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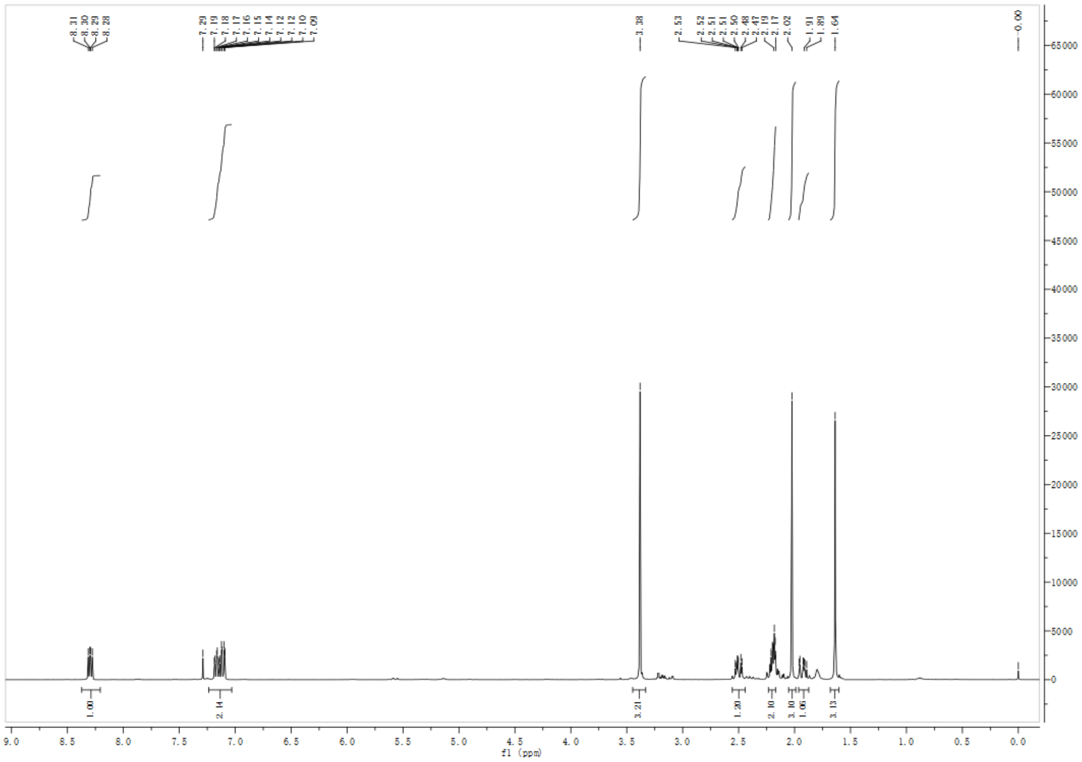

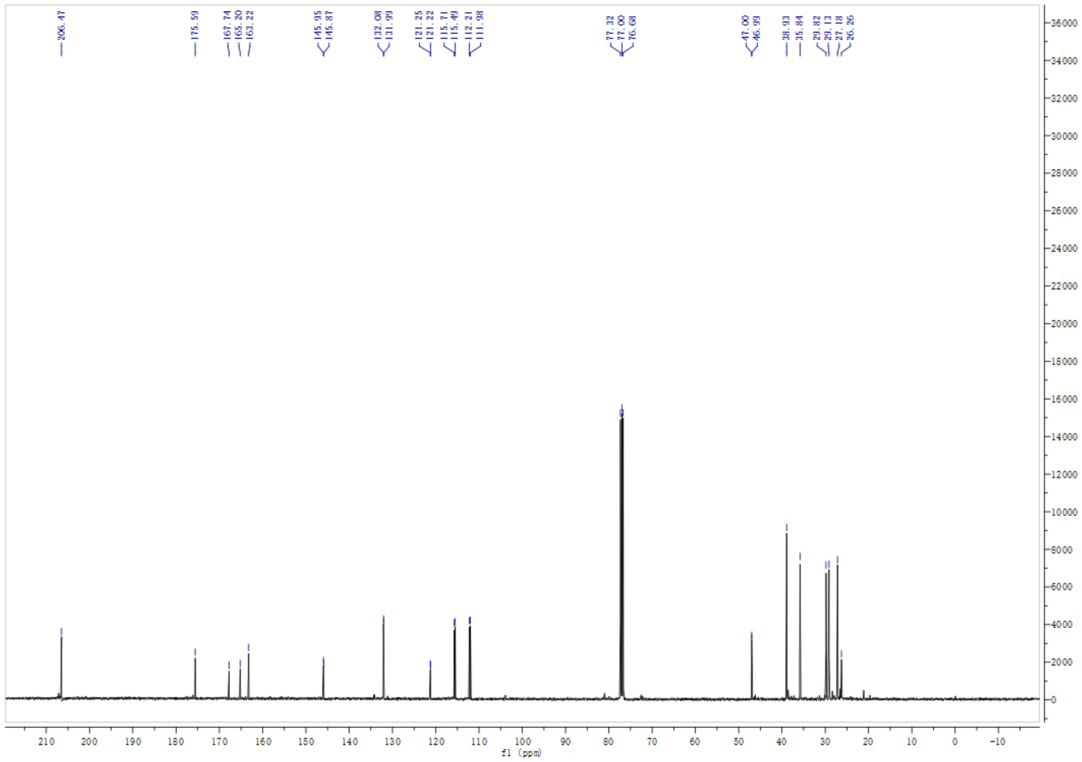

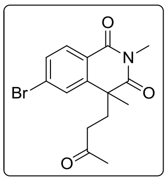
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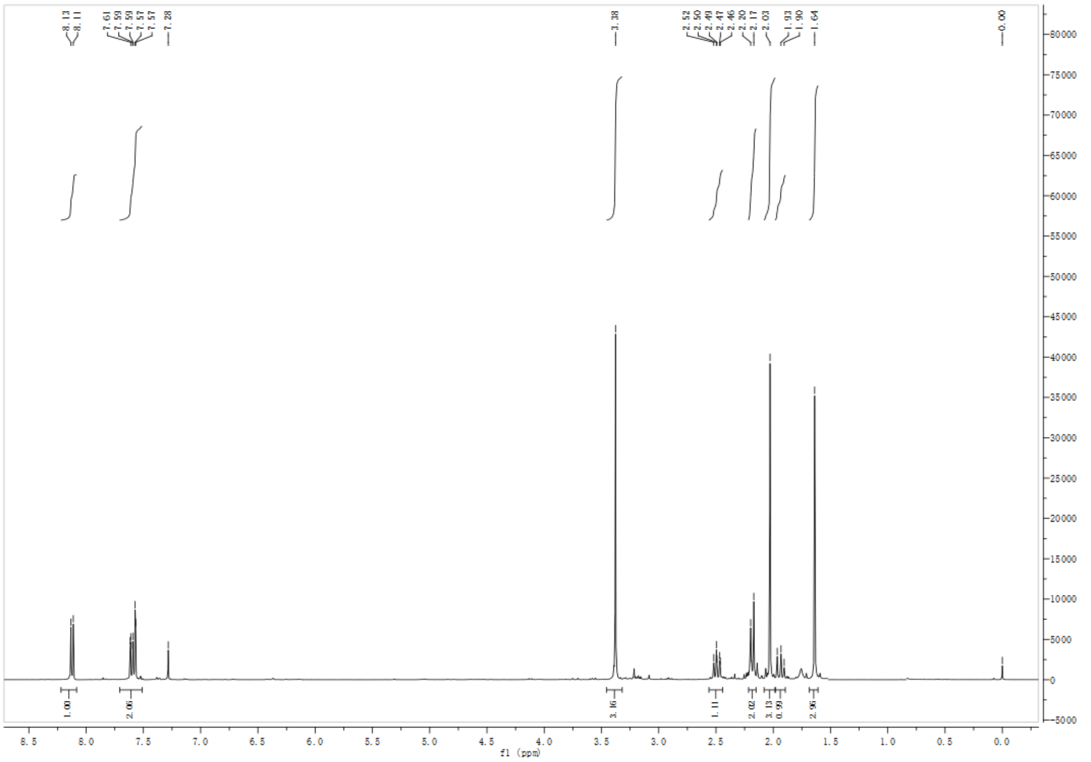

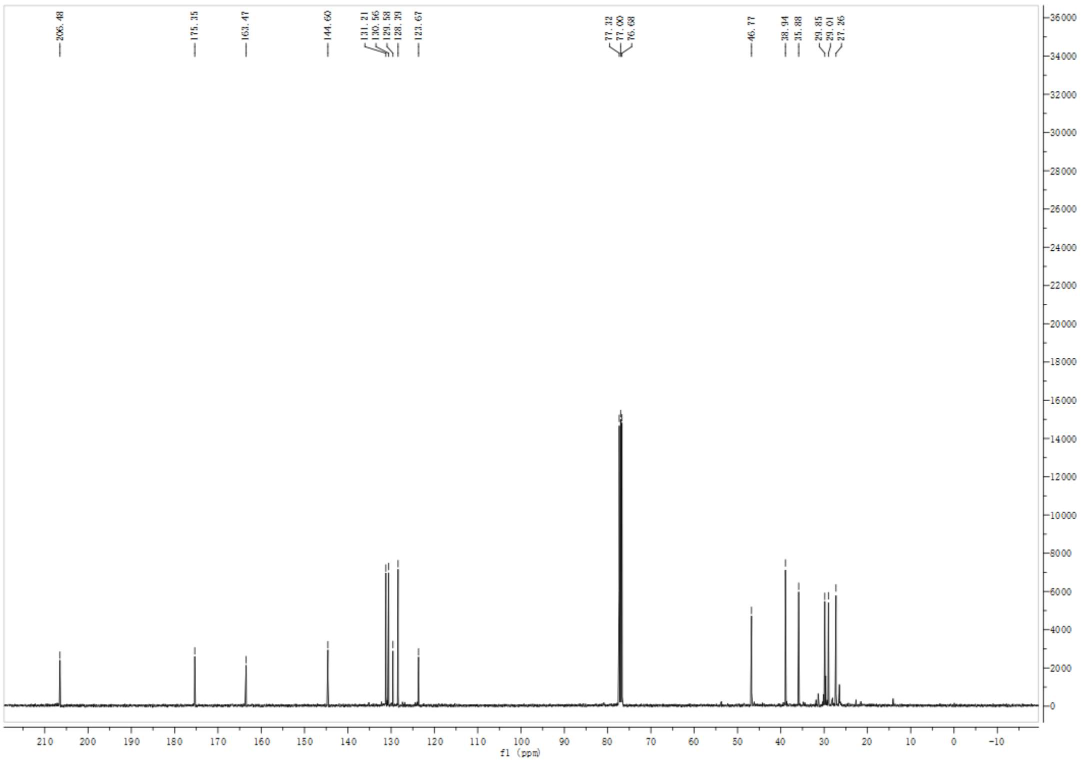

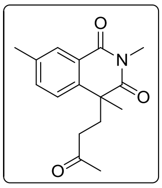
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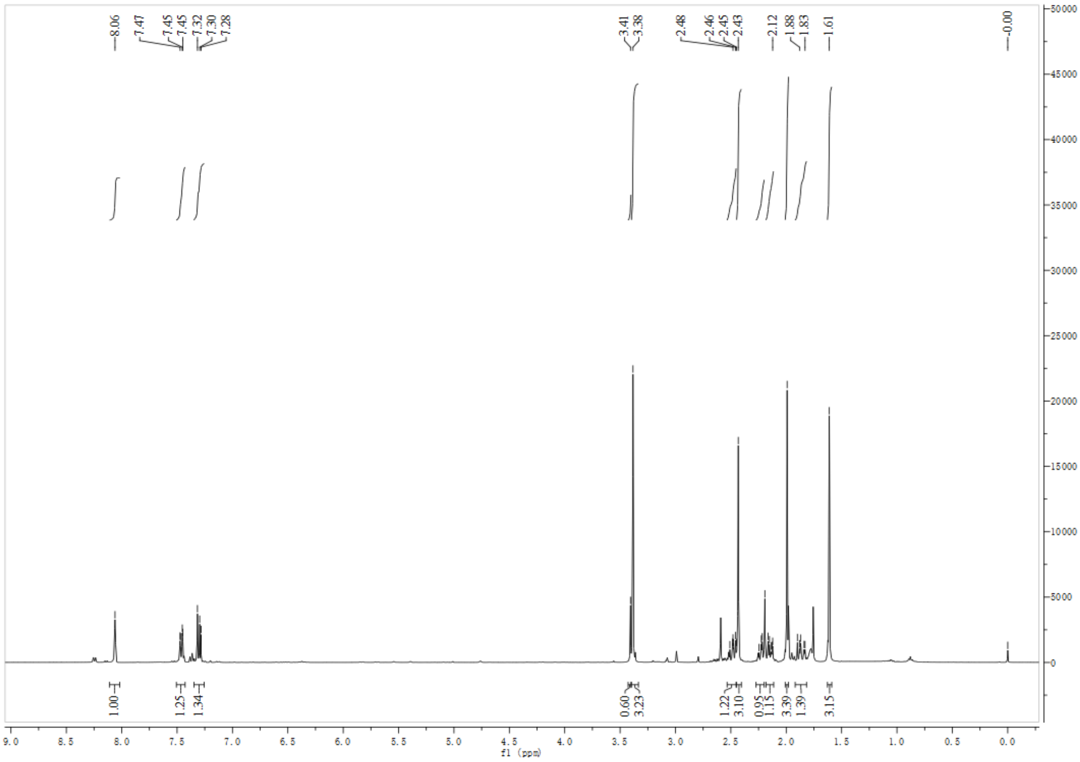
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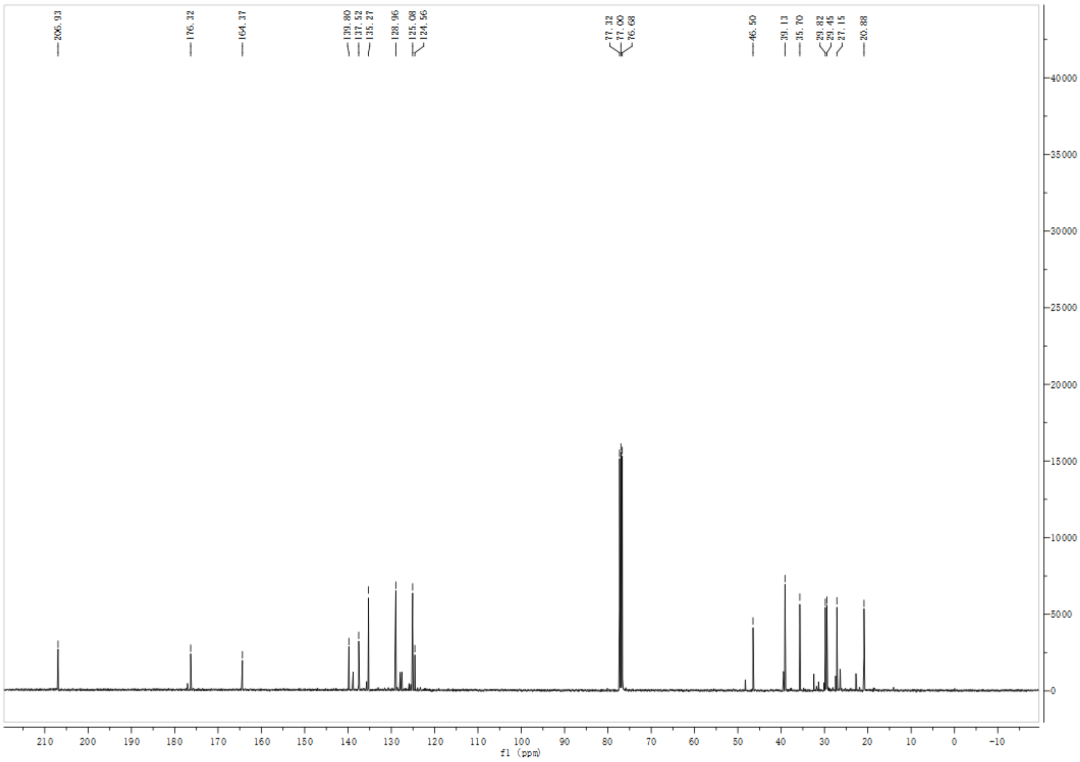
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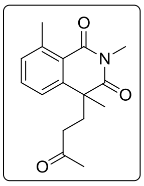

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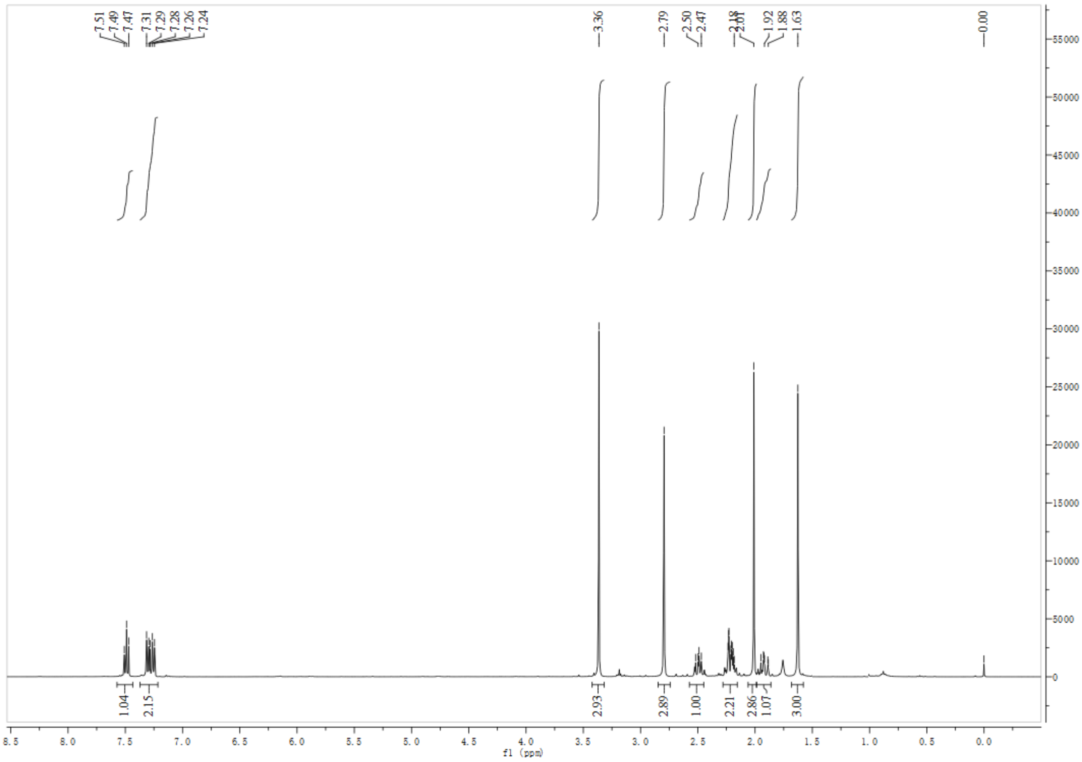

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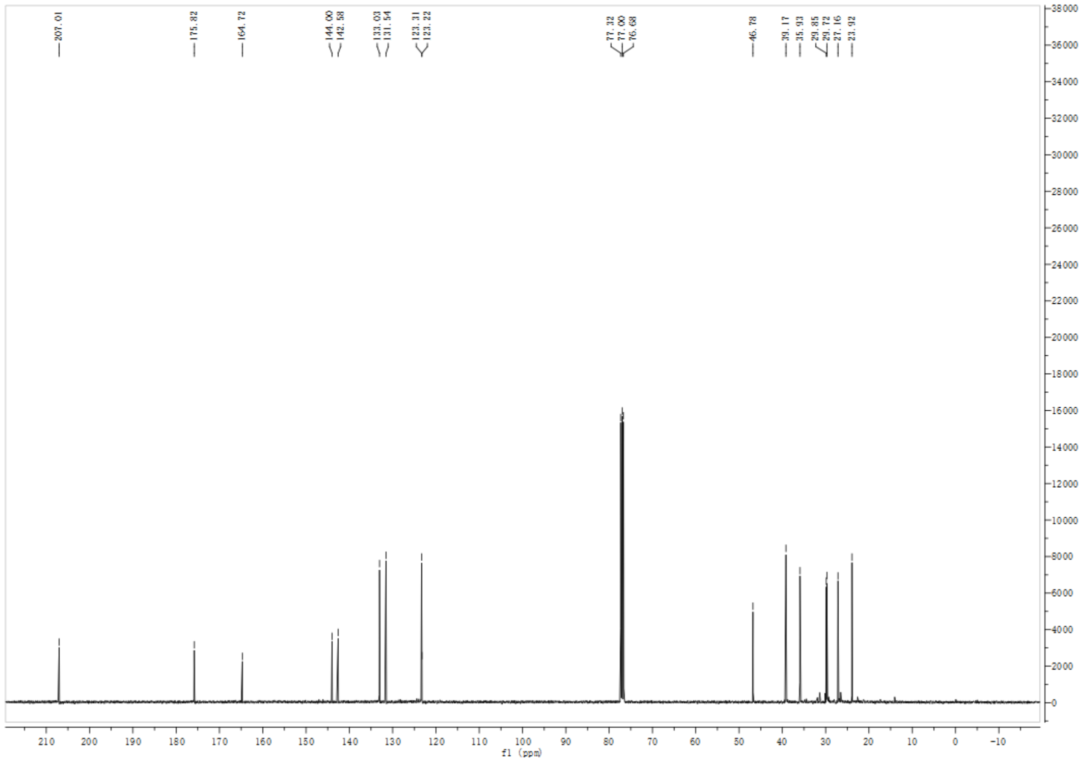

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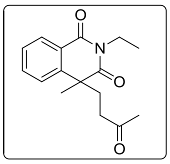
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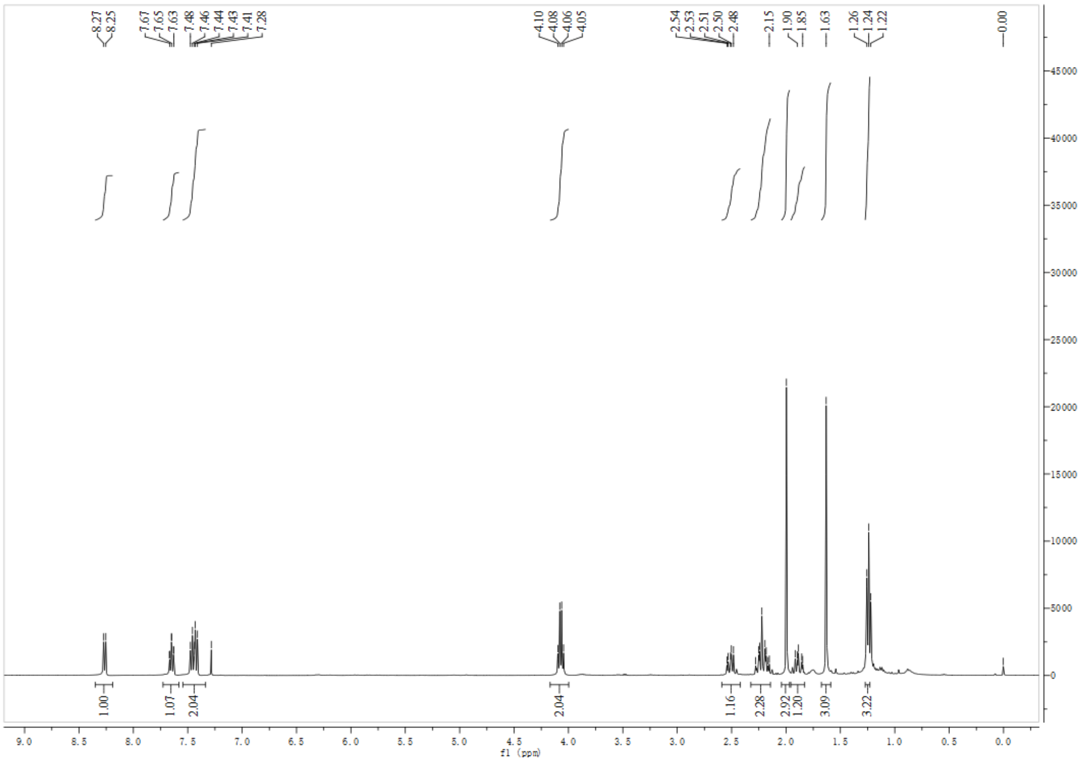
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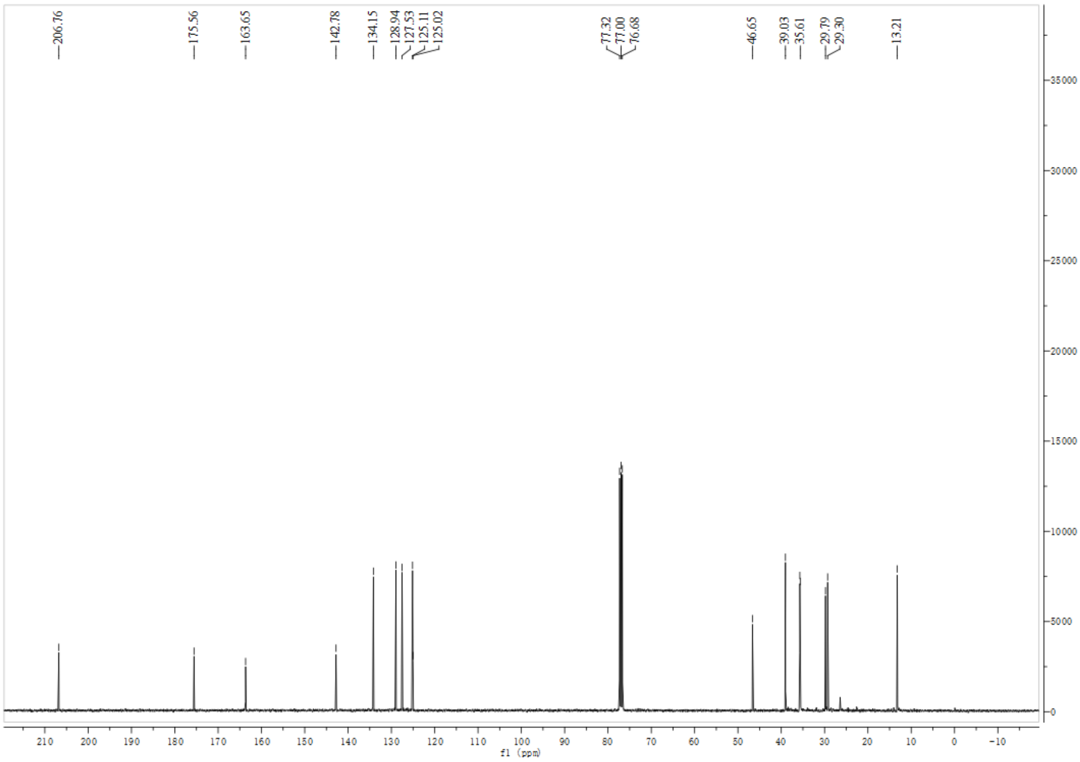
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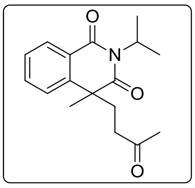
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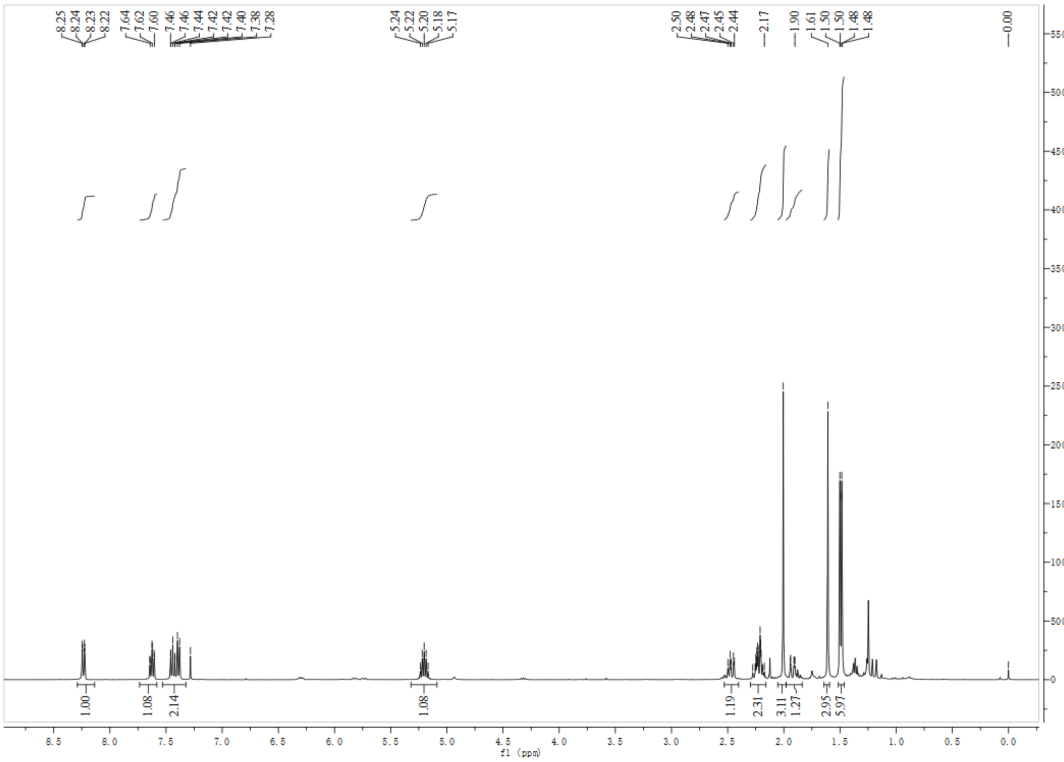
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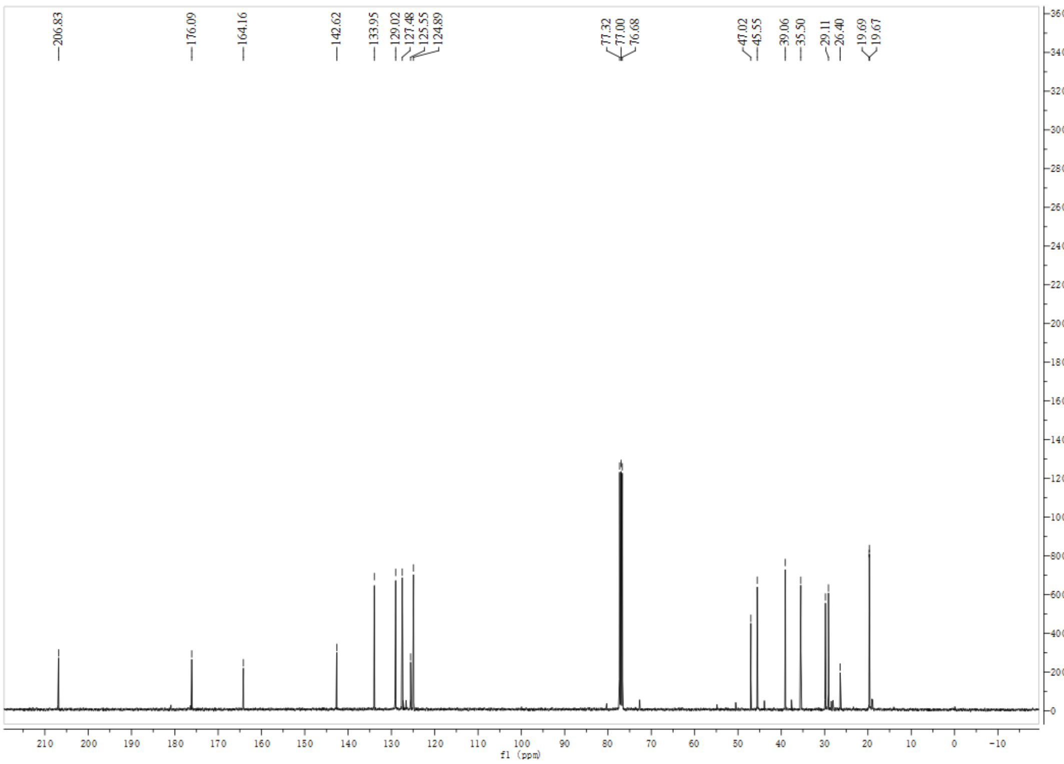
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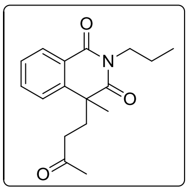
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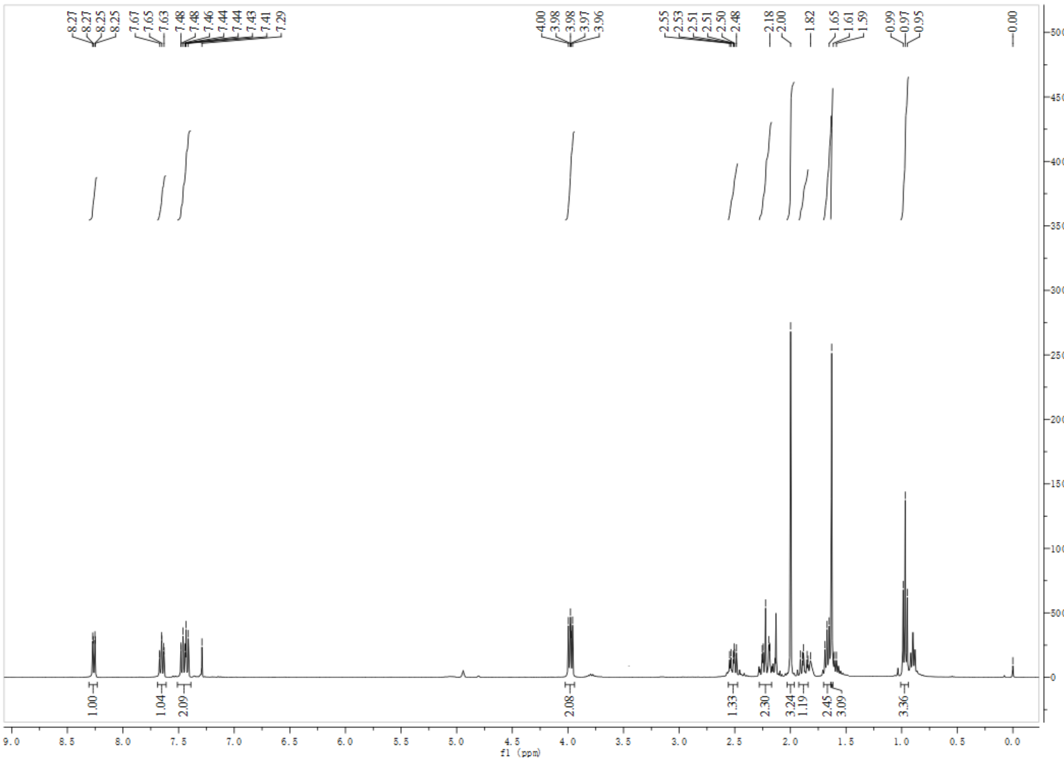
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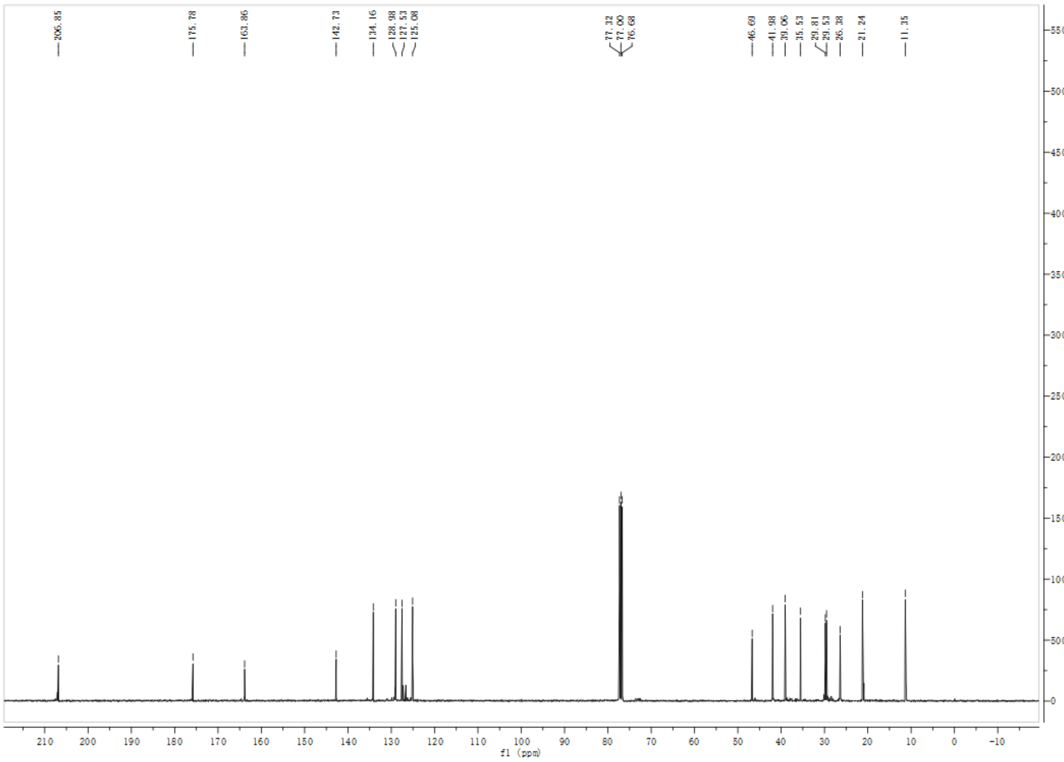
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142.73
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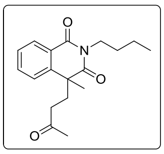
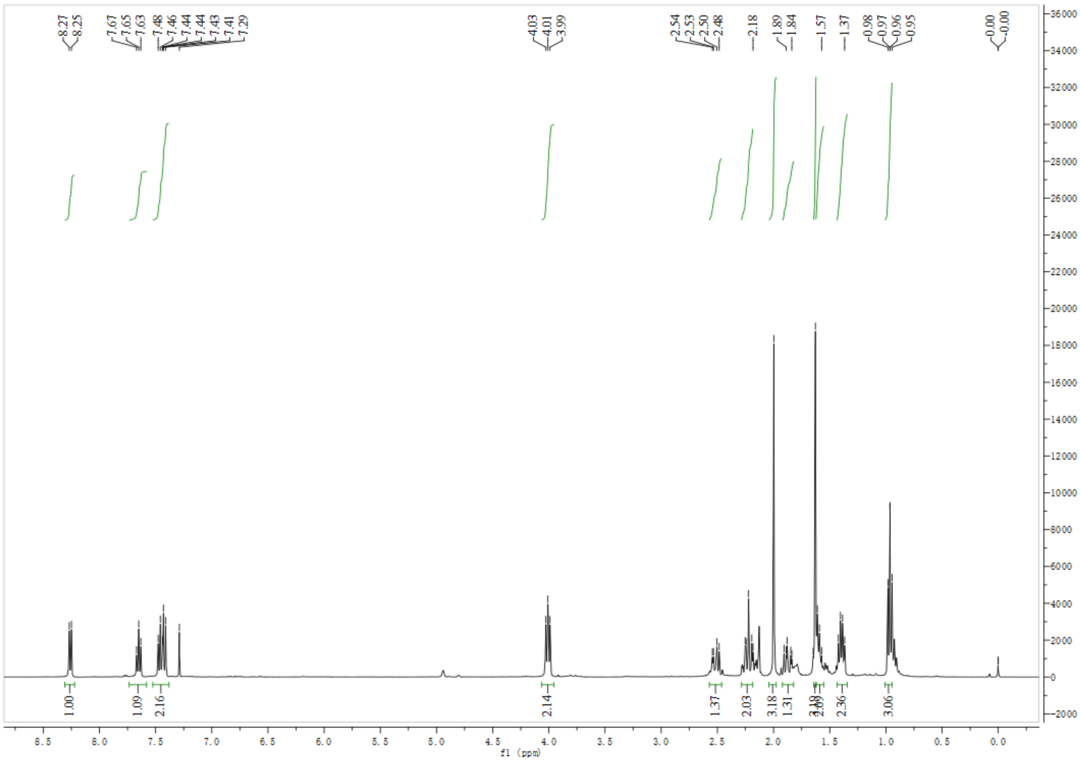
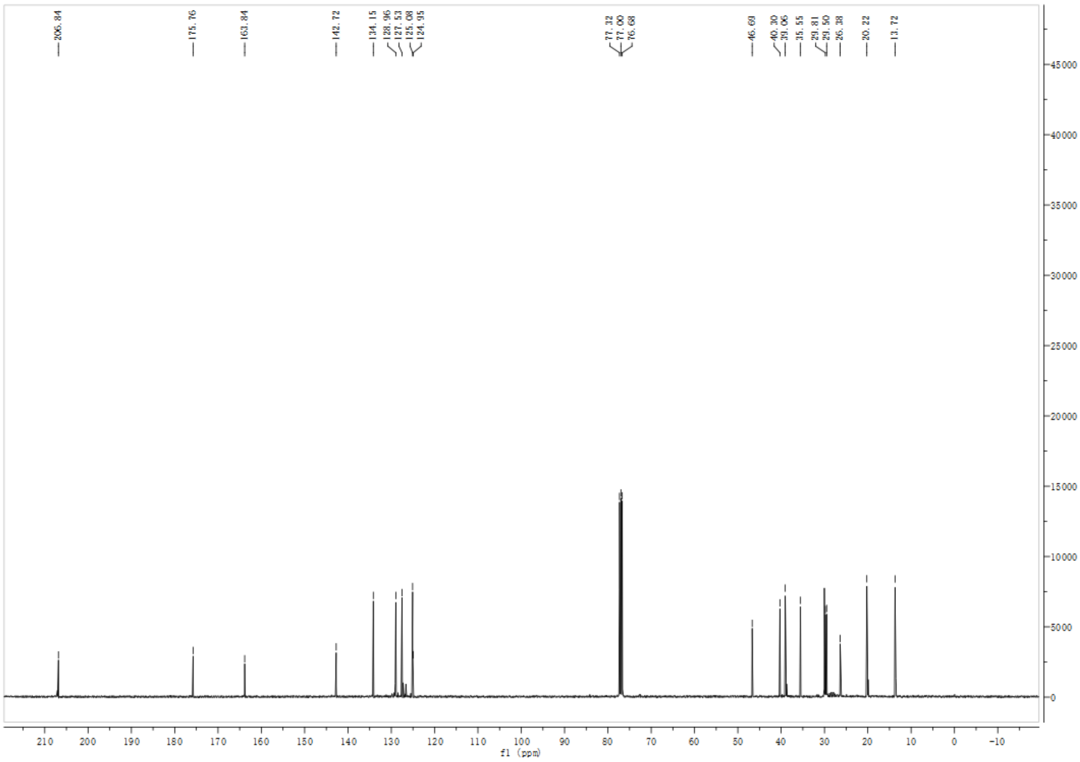
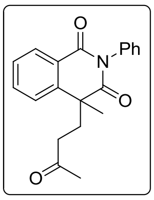
77.32 77.00 76.68
46.69 41.98 39.06 35.53 29.81 29.53 26.38 21.24 11.35
f1 (ppm)



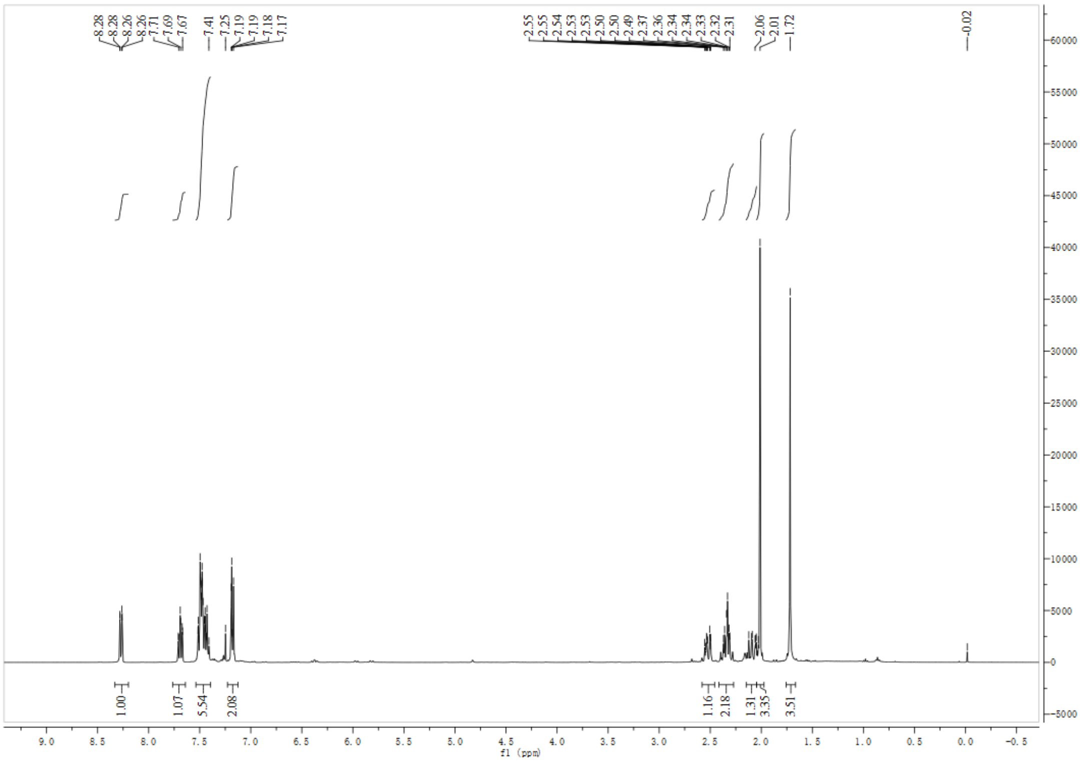
3o

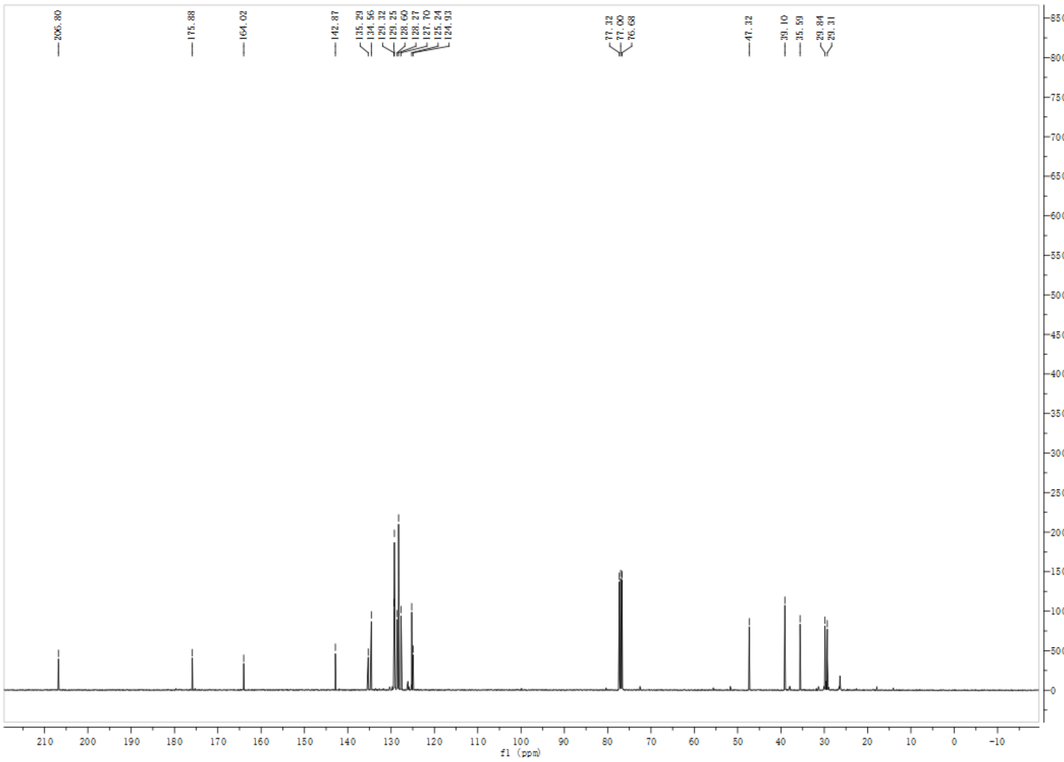


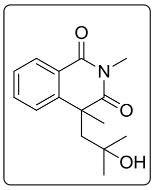


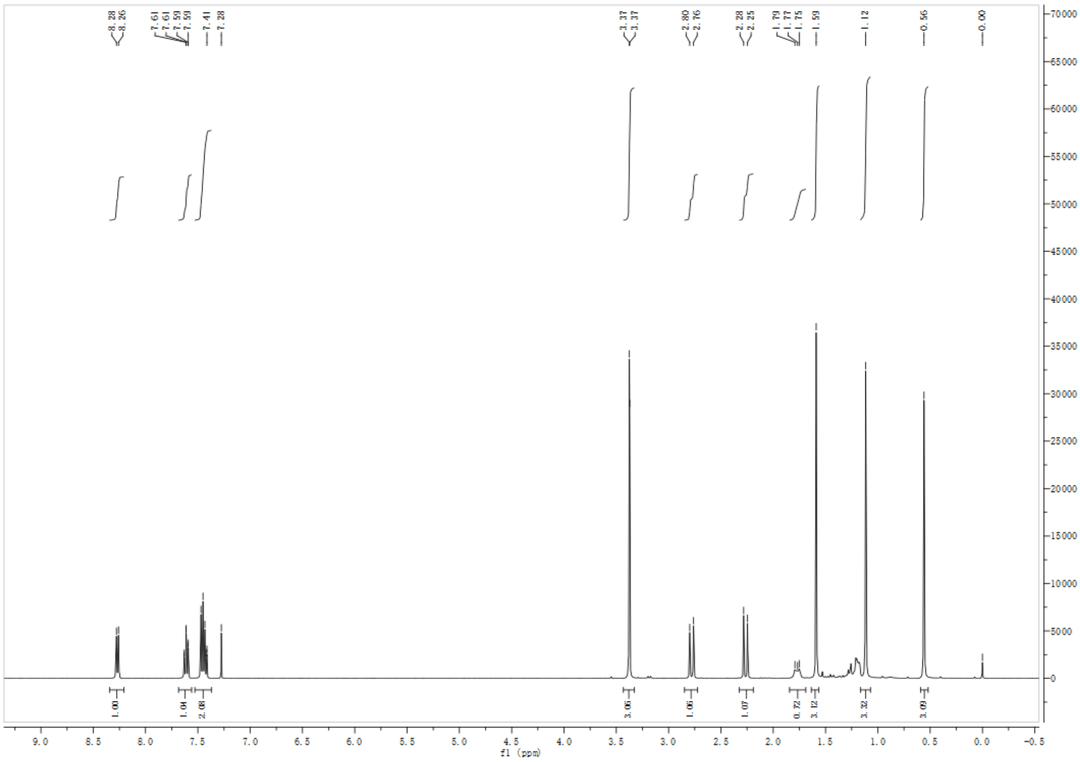

O
N
Ph
O
O

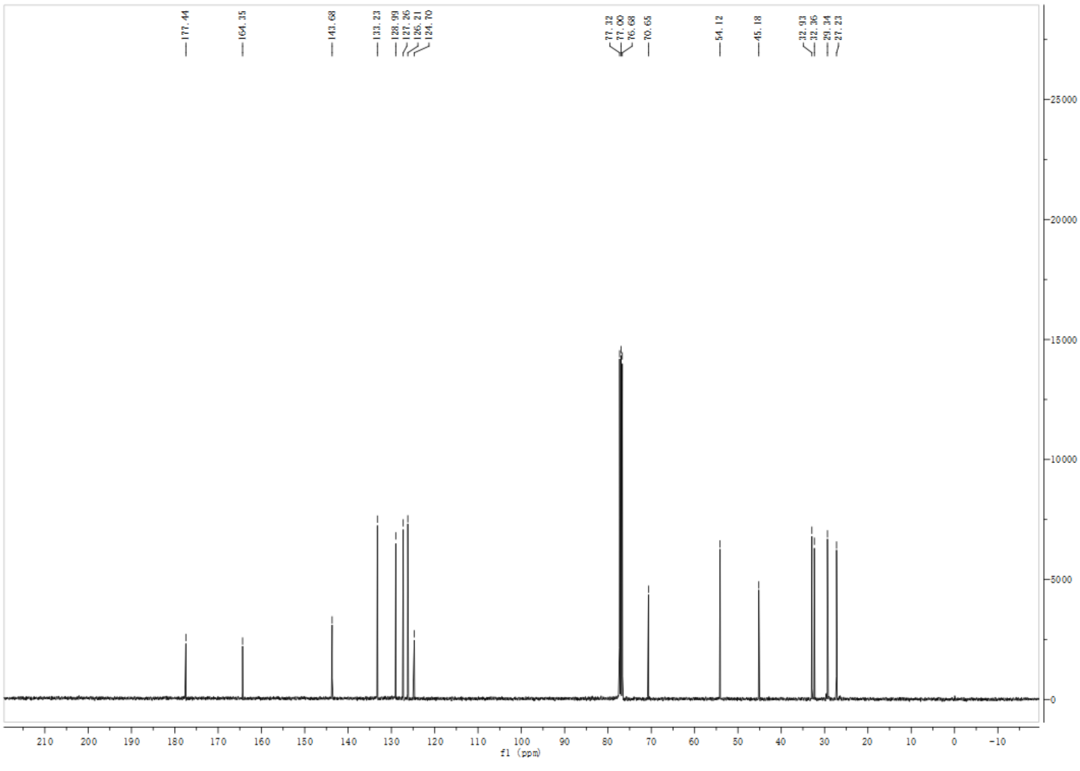
3p

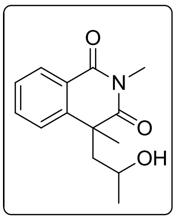

8.28
8.28
8.26
8.26
7.71
7.69
7.67
7.41
7.25
7.19
7.19
7.18
7.17
2.55
2.55
2.54
2.53
2.53
2.50
2.50
2.49
2.37
2.36
2.34
2.34
2.33
2.32
2.31
2.06
2.01
1.72
-0.02
1.00
1.07
5.54
2.08
1.16
2.18
1.31
3.35
3.51
f1 (ppm)


206.80
175.88
164.02
142.87
135.29
134.56
129.32
129.25
128.60
128.27
127.70
125.24
124.93
77.32
77.00
76.68
47.32
39.10
35.59
29.84
29.31
f1 (ppm)

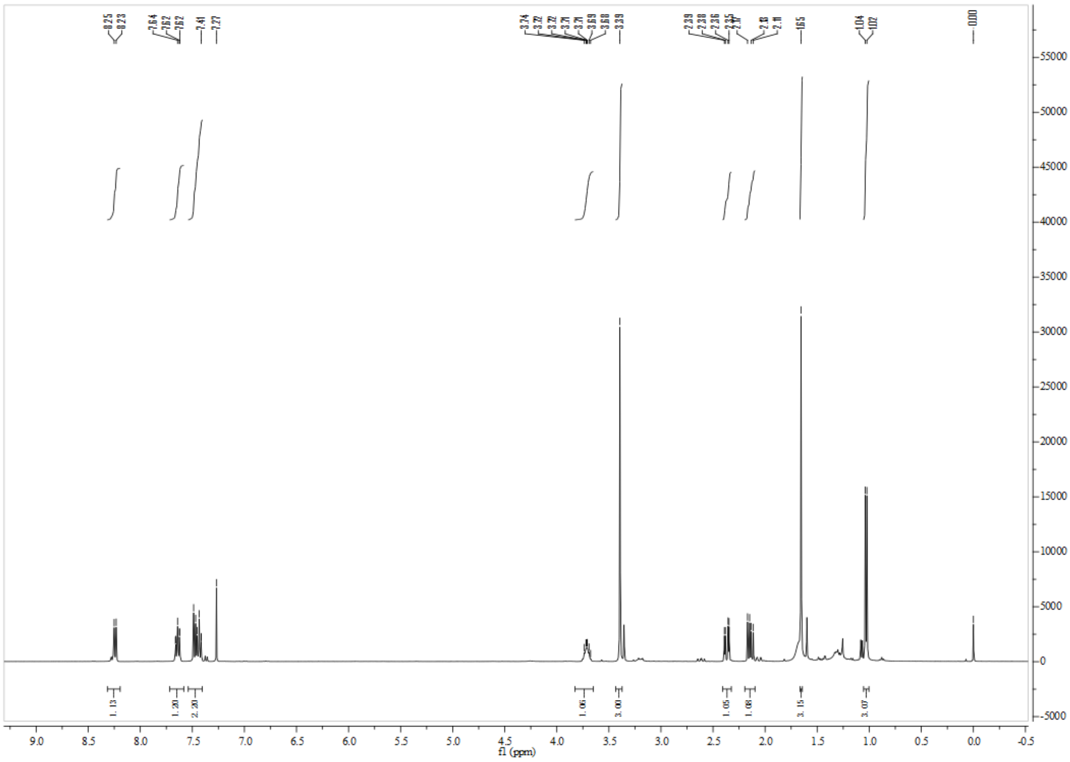

4a

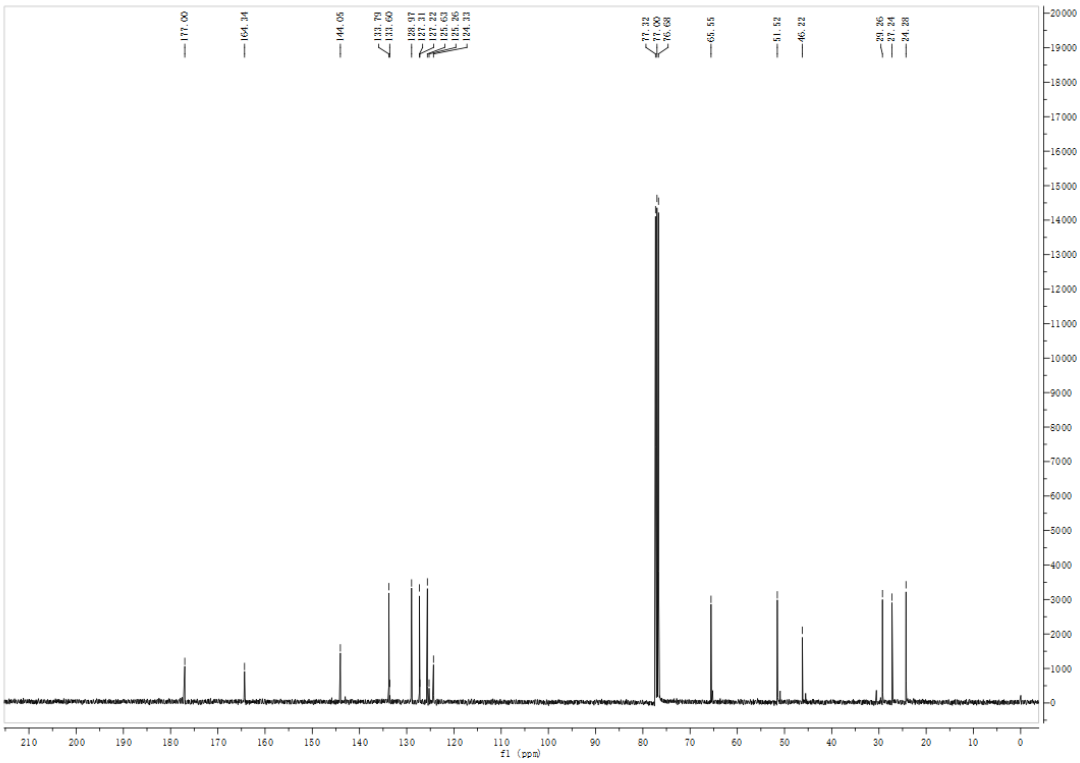


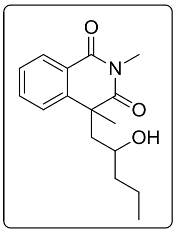




4b







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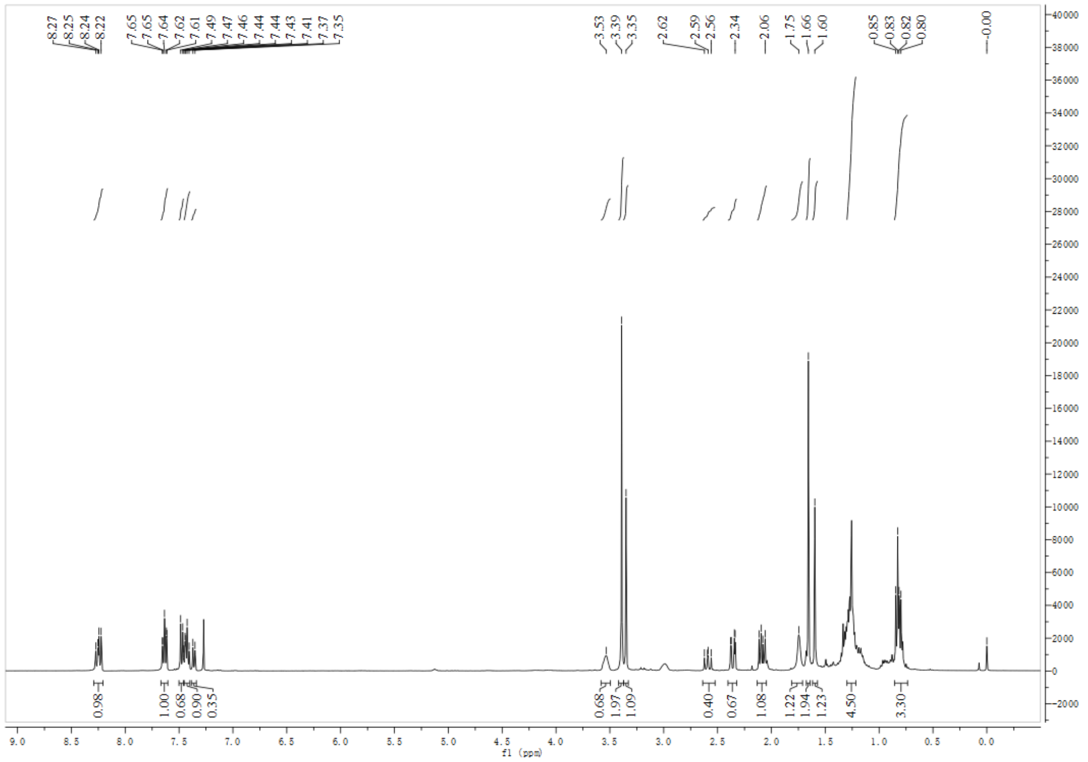
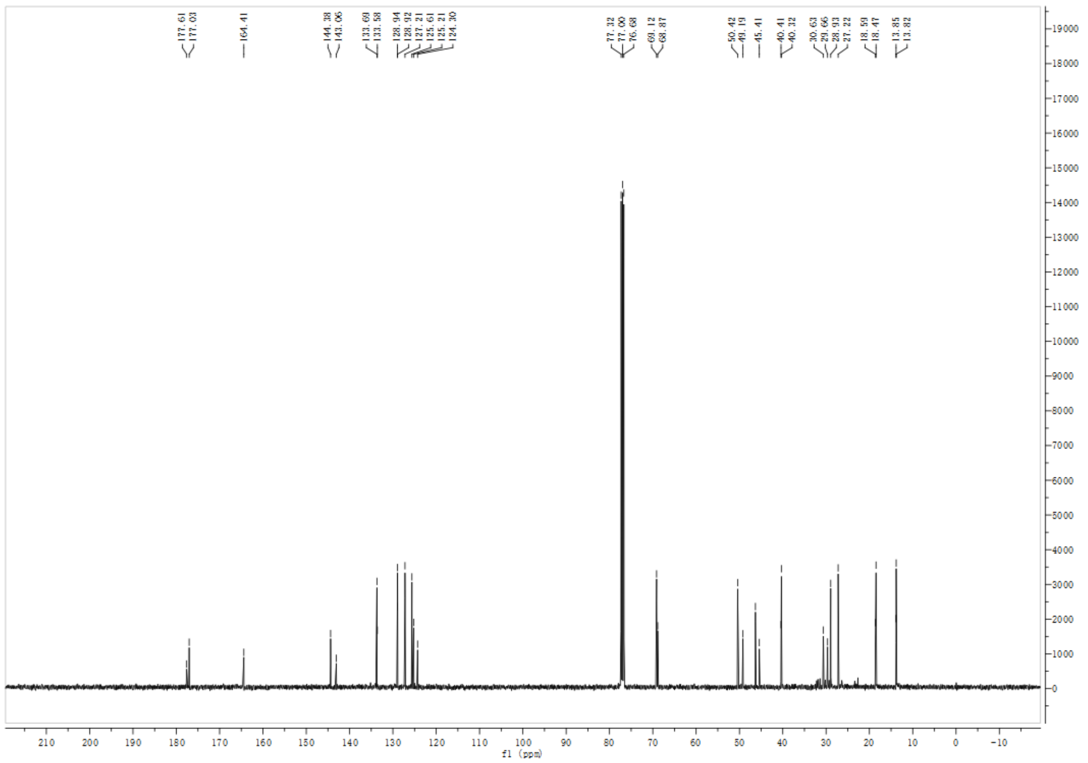
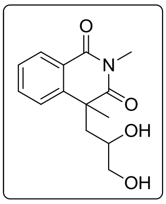
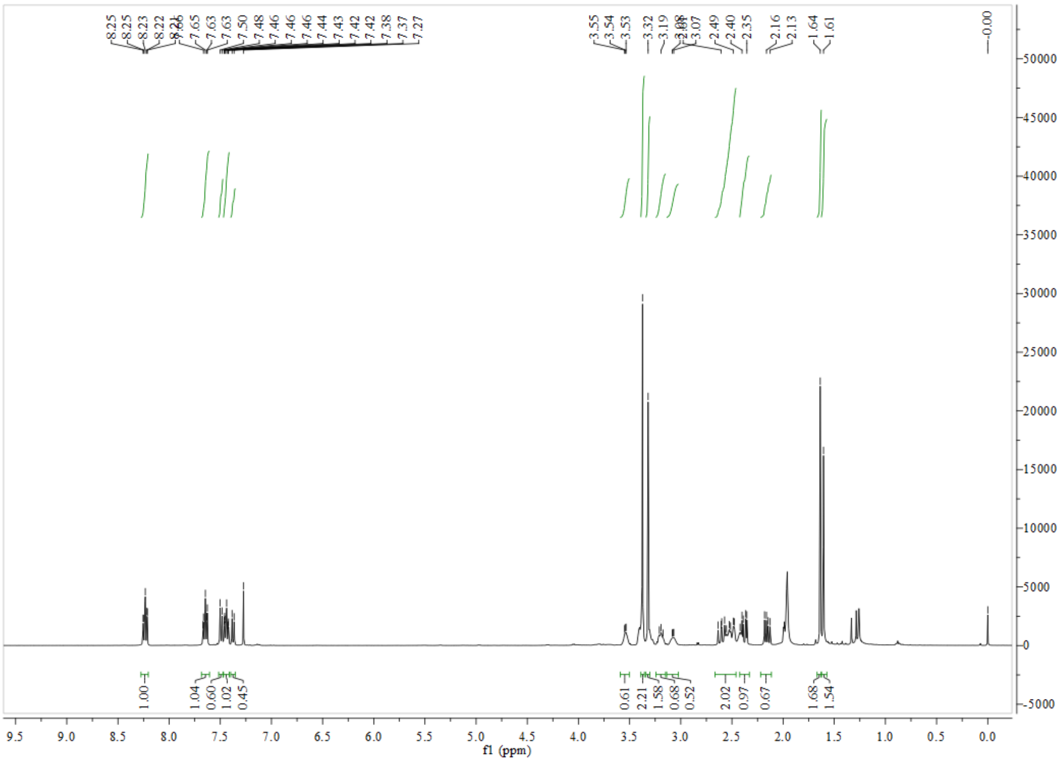




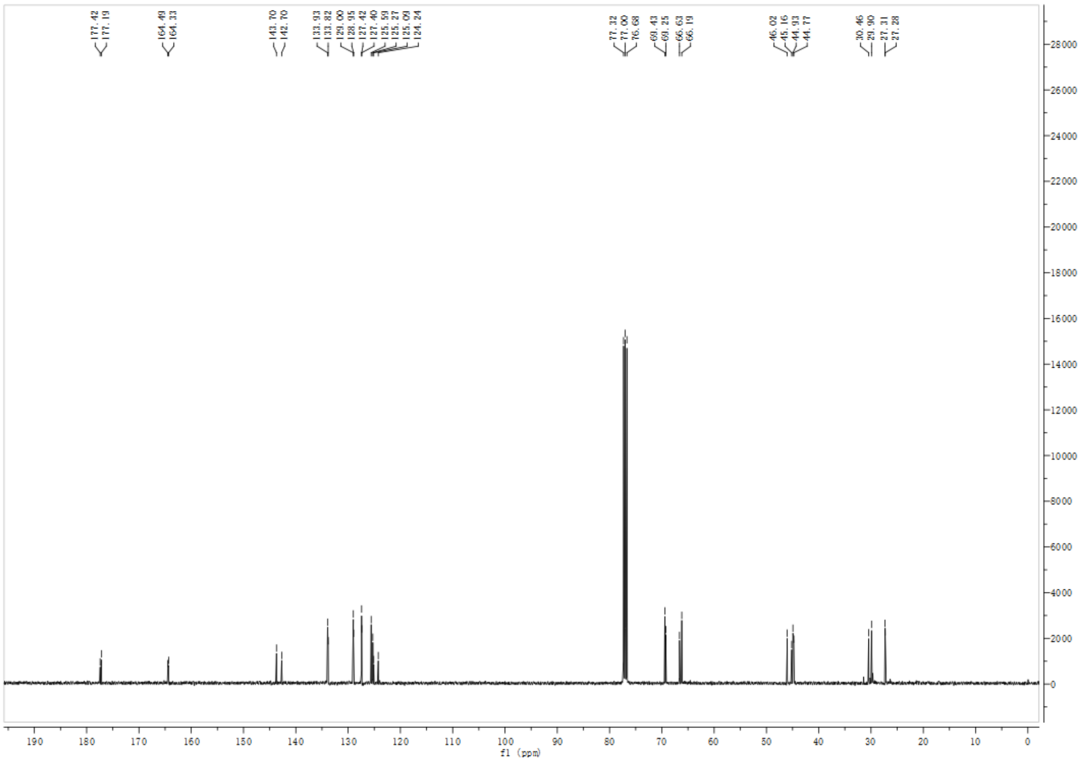


O
N
O
OH
OH

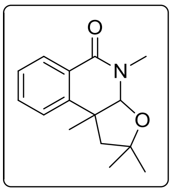
4d



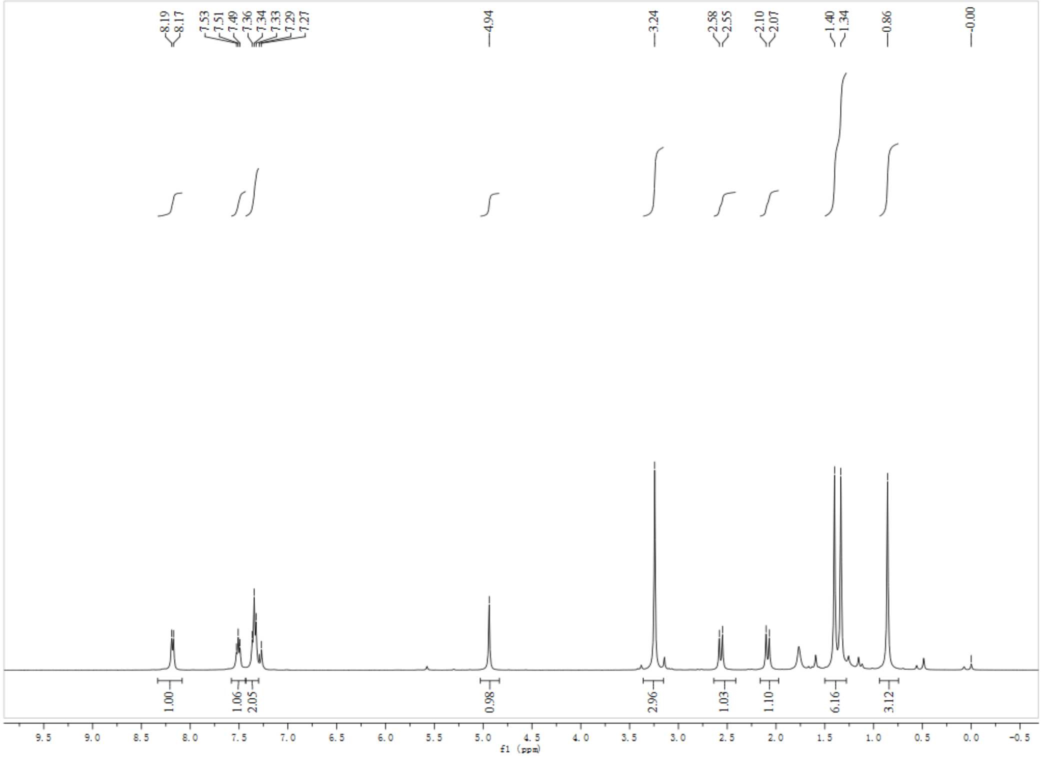
8.25
8.25
8.23
8.22
7.65
7.63
7.63
7.50
7.48
7.46
7.46
7.46
7.44
7.43
7.42
7.42
7.38
7.37
7.27
3.55
3.54
3.53
3.32
3.19
3.07
2.49
2.40
2.35
2.16
2.13
1.64
1.61
0.00
1.00
1.04
0.60
1.02
0.45
0.61
2.21
1.58
0.68
0.52
2.02
0.97
0.67
1.68
1.54
f1 (ppm)

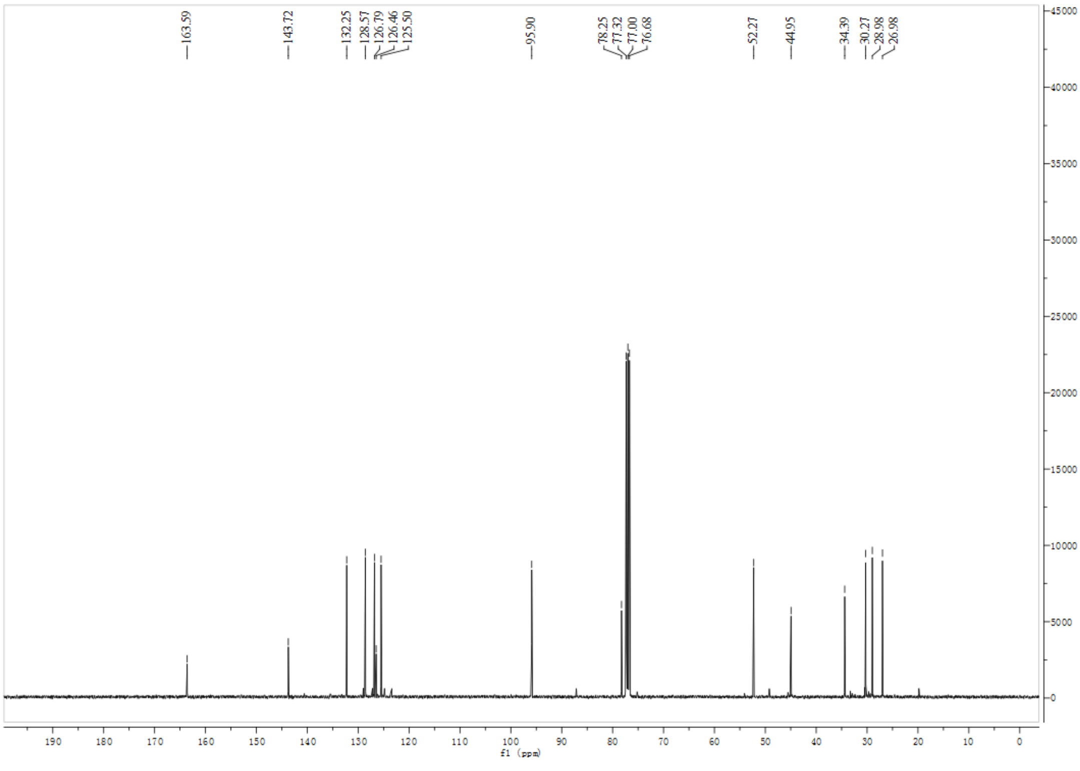


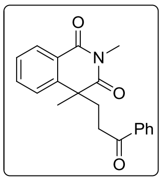
177.42
177.19
164.49
164.33
143.70
142.70
133.93
133.82
129.00
128.95
127.42
127.40
125.59
125.27
125.09
124.24
77.32
77.00
76.68
69.43
69.25
66.63
66.19
46.02
45.16
44.93
44.77
30.46
29.90
27.31
27.28
f1 (ppm)


O
N
O

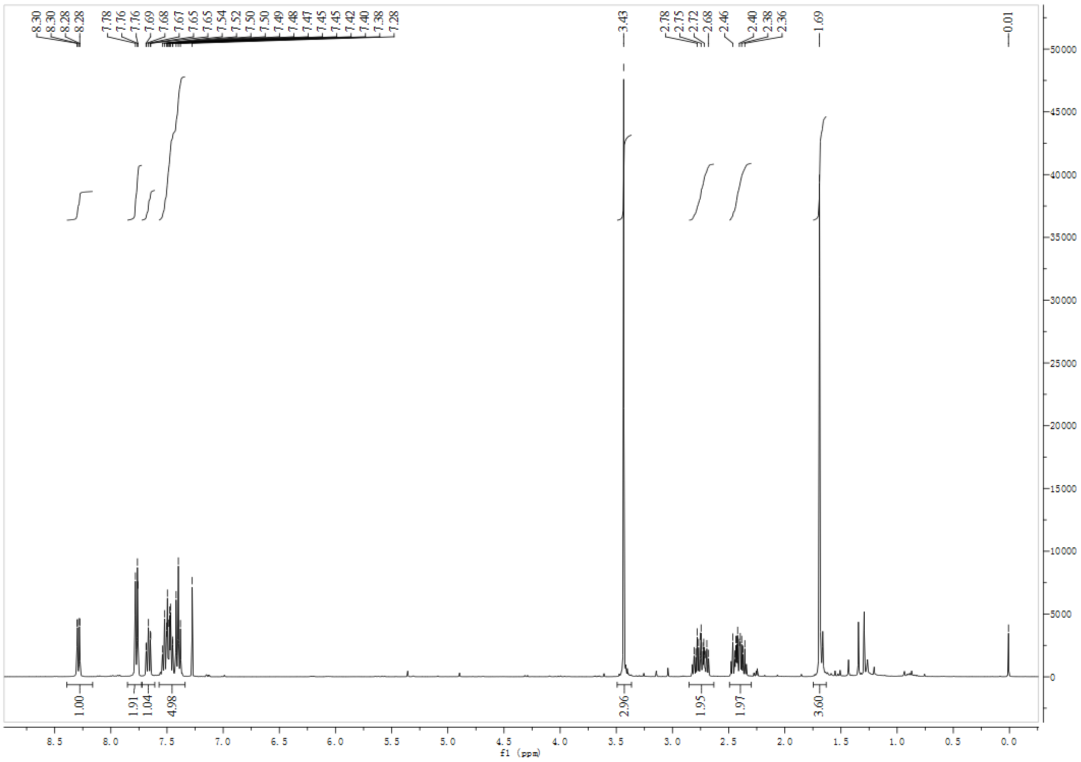
6a


8.19
8.17
7.53
7.51
7.49
7.36
7.34
7.33
7.29
7.27
4.94
3.24
2.58
2.55
2.10
2.07
1.40
1.34
0.86
0.00
1.00
1.06
2.05
0.98
2.96
1.03
1.10
6.16
3.12
f1 (ppm)


163.59
143.72
132.25
128.57
126.79
126.46
125.50
95.90
78.25
77.32
77.00
76.68
52.27
44.95
34.39
30.27
28.98
26.98
f1 (ppm)


O
N
O
Ph
O

3q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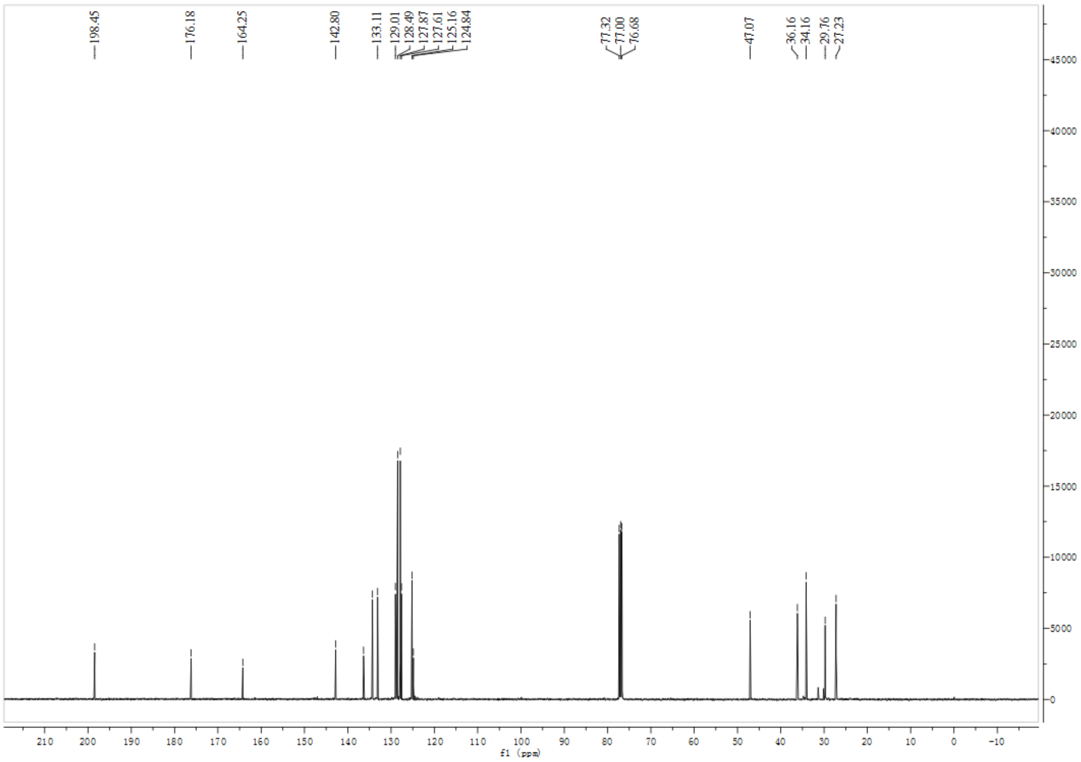
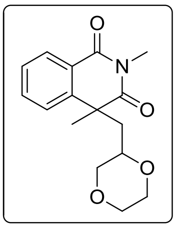
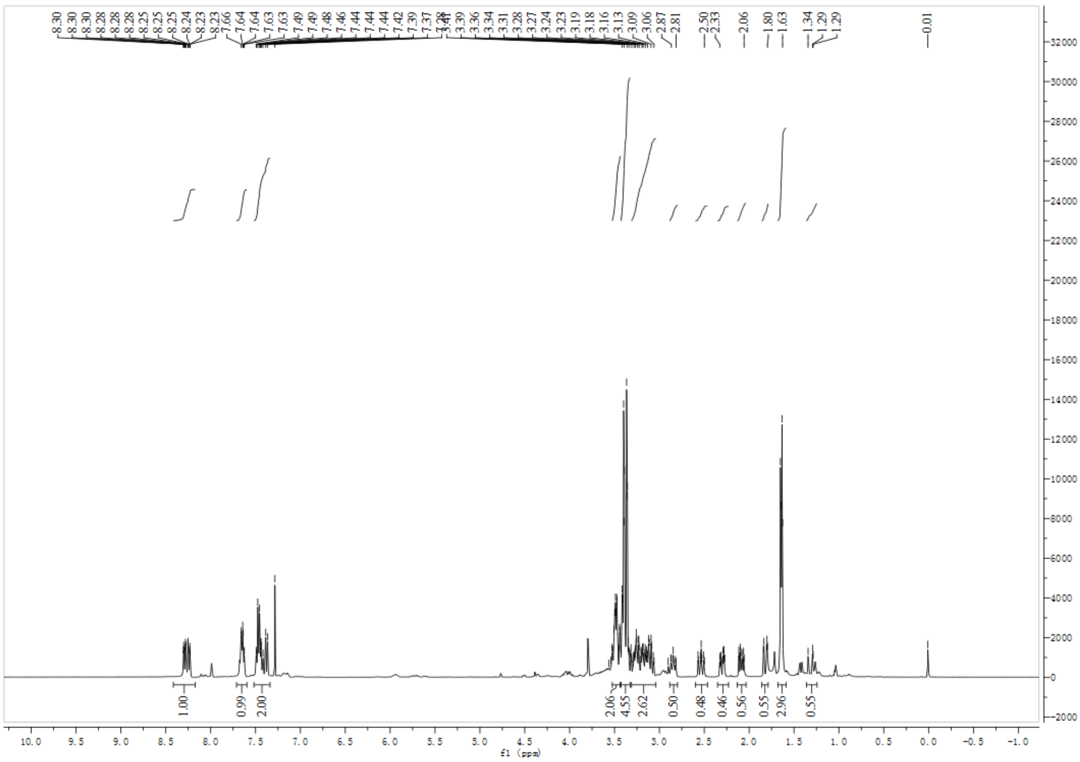
3.43
2.78 2.75 2.72 2.68 2.46 2.40 2.38 2.36
1.69
0.01
1.00 1.91 1.04 4.98 2.96 1.95 1.97 3.60
f1 (ppm)


198.45
176.18
164.25
142.80
133.11 129.01 128.49 127.87 127.61 125.16 124.84
77.32 77.00 76.68
47.07
36.16 34.16 29.76 27.23
f1 (ppm)


O
N
O
O
O

5a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8.30
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8.28
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8.28
8.25
8.25
8.25
8.24
8.23
8.23
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7.63
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7.42
7.39
7.37
3.48
3.41
3.39
3.36
3.34
3.31
3.28
3.27
3.24
3.23
3.19
3.18
3.16
3.13
3.09
3.06
2.87
2.81
2.50
2.33
2.06
1.80
1.63
1.34
1.29
1.29
0.01
1.00
0.99
2.00
2.06
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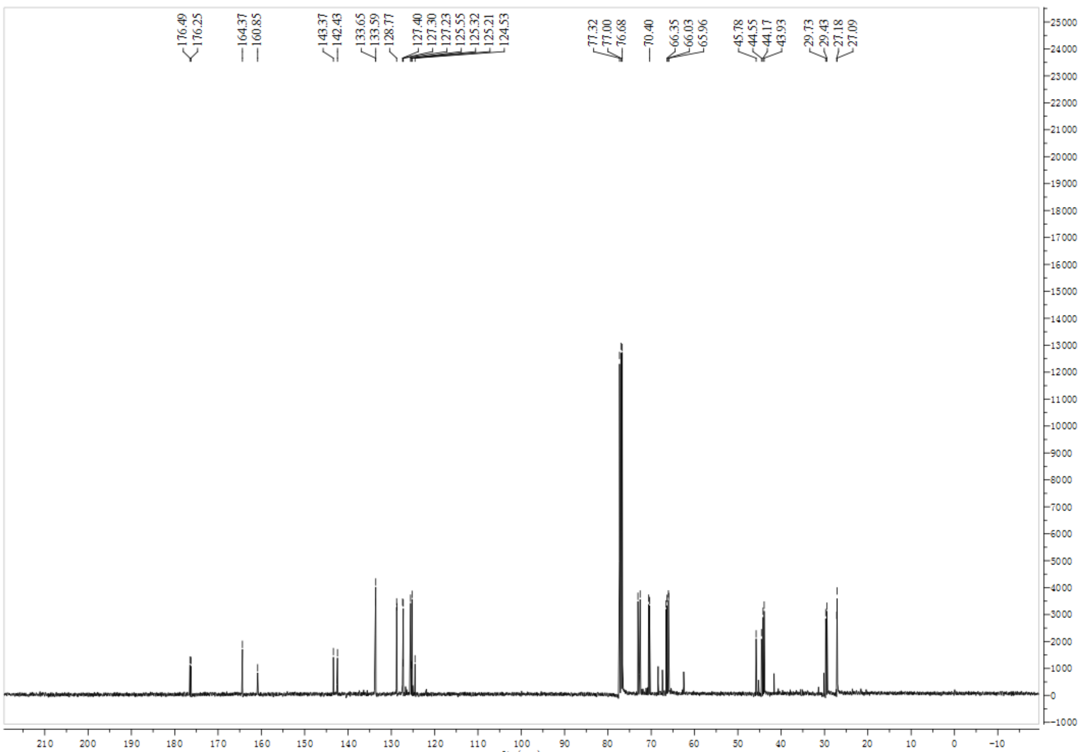
2.62
0.50
0.48
0.46
0.56
0.55
2.96
0.55
f1 (ppm)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176.25
164.37
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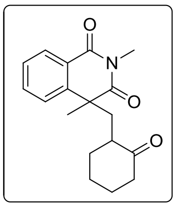
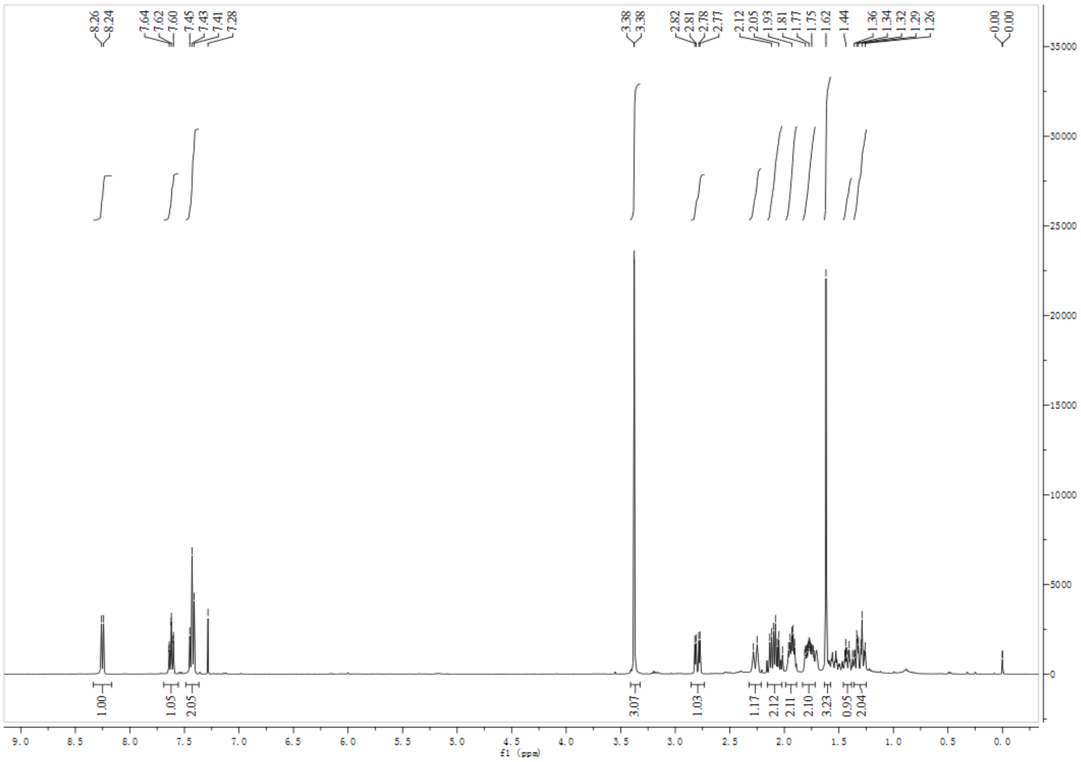
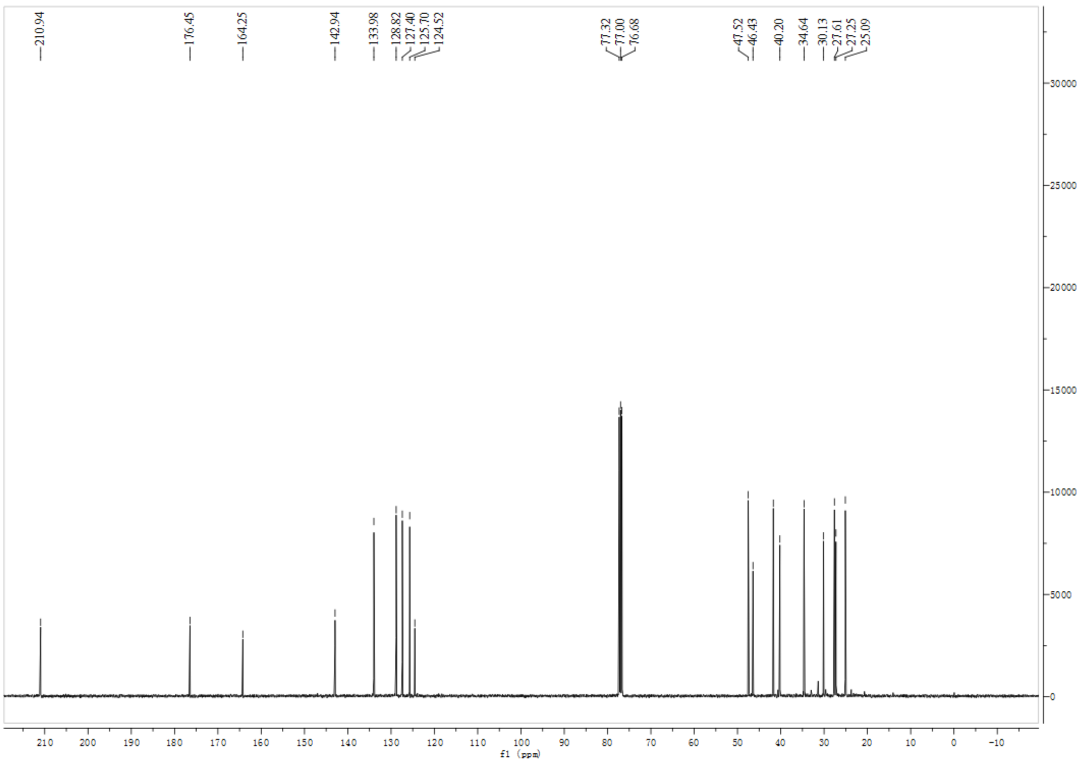
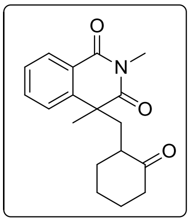
143.37
142.43
133.65
133.59
128.77
127.40
127.30
127.23
125.55
125.32
125.21
124.53
77.32
77.00
76.68
70.40
66.35
66.03
65.96
45.78
44.55
44.17
43.93
29.73
29.43
27.18
27.09
f1 (ppm)



3r, isomer-1, low polarity







3r, isomer-2, high polarity