Base-Mediated [2+4] Cycloadditions of in situ formed azaoxyallyl cations with *N*-(2-Chloromethyl)aryl Amides

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1. General information

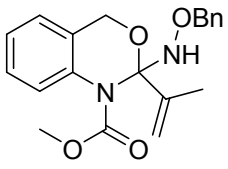
All reactions were performed in anhydrous solvents under an argon atmosphere and were monitored by thin-layer chromatography carried out on silica gel aluminum sheets (60F-254) and spots were visualized with UV light. All solvents were purchased from commercial suppliers and were purified according to standard procedures. *α*-halohydroxamates **1**[1] and *N*-(2-chloromethyl)aryl amides **2**[2] can be prepared according to known procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on BRUKER Avance 400 spectrometers. Chemical shifts were reported in parts per million (ppm, δ units), and tetramethylsilane (TMS) was used as an internal reference. Coupling constants (J) were expressed in hertz. High-resolution mass spectra (HRMS) were recorded on TOF perimer for ESI^{+}.

2. General procedure for the [2+4] Cycloadditions of in situ formed azaoxyallyl cations with *N*-(2-Chloromethyl)aryl Amides

To the solution of *α*-halohydroxamates **1** (0.2 mmol) and *N*-(2-chloromethyl)aryl amides **2** (0.25 mmol) in DMF (2 mL), Cs_2CO_3 (2.0 equiv) was added. The resulting mixture was stirred at room temperature under argon atmosphere for the required period of time. After completion of the reaction as monitored by TLC, the reaction mixture was diluted with 8 mL EA, which was washed with water and brine successively, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (PE/EtOAc, 4:1) to afford the product **3**.

3. Characterization Data

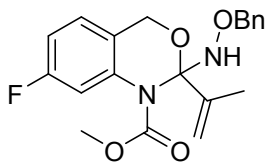
Methyl 2-((benzyloxy)amino)-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (**3a**)



Yellow oil (50 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.44-7.31 (m, 6H), 7.25-7.23 (m, 1H), 7.10-7.03 (m, 1H), 5.46 (s, 1H), 5.35 (s, 1H), 4.79 (s, 2H), 4.69 (s, 2H), 3.78 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 154.9, 139.2, 137.3, 133.7, 131.4, 129.6, 129.3, 129.3, 129.0, 128.7, 128.6, 128.6, 123.2, 121.5,

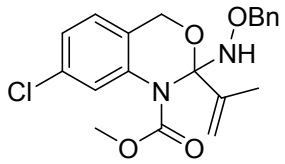
119.2, 78.1, 52.2, 48.8, 19.7. HRMS calcd for $C_{20}H_{22}N_2O_4Na$ $[M+Na]^+$ 377.1477, found 377.1483.

Methyl 2-((benzyloxy)amino)-7-fluoro-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3b)



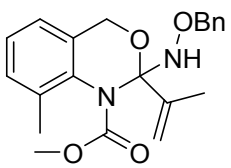
Colorless oil (48 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.96 (dd, *J* = 11.5, 2.1 Hz, 1H), 7.44-7.39 (m, 3H), 7.32-7.27 (m, 3H), 6.80-6.75 (m, 1H), 5.52 (s, 1H), 5.41 (s, 1H), 4.78 (s, 2H), 4.73 (s, 2H), 3.83 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ172.2, 164.5, 162.1, 154.6, 139.2, 139.0 (d, *J* = 8.0 Hz), 133.6, 132.6 (d, *J* = 40.0 Hz), 129.3, 129.1, 128.7, 120.0 (d, *J* = 12.0 Hz), 119.4, 109.6(d, *J* = 88.0 Hz), 108.2 (d, *J* = 108.0 Hz), 78.15, 52.4, 48.2, 19.7. HRMS calcd for $C_{20}H_{21}N_2O_4FNa$ $[M+Na]^+$ 395.1383, found 395.1386.

Methyl 2-((benzyloxy)amino)-7-chloro-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3c)



Colorless oil (60 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.20 (s, 1H), 7.49-7.37 (m, 4H), 7.32-7.27 (m, 2H), 7.06 (dd, *J* = 8.1, 2.1 Hz, 1H), 5.51 (s, 1H), 5.42 (s, 1H), 4.77 (s, 2H), 4.75 (s, 2H), 3.84 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 154.6, 139.0, 138.5, 135.4, 133.6, 132.3, 129.3, 129.2, 128.8, 128.7, 128.6, 123.1, 122.9, 121.1, 119.5, 78.1, 52.4, 48.3, 19.7. HRMS calcd for $C_{20}H_{21}N_2O_4ClNa$ $[M+Na]^+$ 411.1088, found 411.1096.

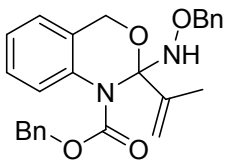
Methyl 2-((benzyloxy)amino)-8-methyl-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3d)



Colorless oil (73 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.40-7.34 (m, 3H), 7.25-7.21 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 1H), 7.10 (s, 1H), 5.45 (s, 1H), 5.35 (s, 1H), 4.75 (s, 2H), 4.69 (s, 2H), 3.77 (s, 3H), 2.30 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 154.9, 139.3, 134.6, 133.8, 131.9, 130.1, 129.3, 129.3, 129.0, 128.6, 128.6, 128.5, 119.1, 78.0, 52.2, 48.7, 20.6, 19.7. HRMS calcd for $C_{21}H_{24}N_2O_4Na$

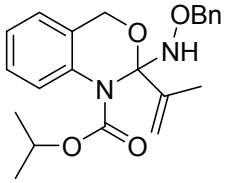
[M+Na]$^+$ 391.1634, found 391.1638.

Benzyl 2-((benzyloxy)amino)-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3e)



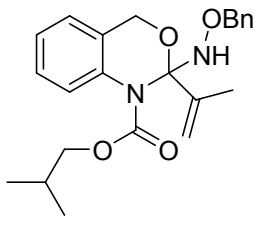
Colorless oil (78 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.45-7.43 (m, 2H), 7.39-7.29 (m, 8H), 7.23-7.21 (m, 2H), 7.06 (dd, *J* = 7.4, 6.5 Hz, 1H), 5.44 (s, 1H), 5.33 (s, 1H), 5.24 (s, 2H), 4.79 (s, 2H), 4.66 (s, 2H), 1.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 154.2, 139.2, 137.2, 136.6, 133.7, 131.3, 129.5, 129.3, 129.0, 128.6, 128.4, 128.0, 127.9, 125.0, 123.3, 121.5, 119.2, 78.1, 66.5, 48.9, 19.7. HRMS calcd for $C_{26}H_{26}N_2O_4Na$ [M+Na]$^+$ 453.1790, found 453.1794.

Isopropyl 2-((benzyloxy)amino)-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3g)



Yellow oil (66 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.34-7.26 (m, 5H), 7.23-7.15 (m, 2H), 7.02-6.98 (m, 1H), 5.40 (s, 1H), 5.34-5.26 (m, 1H), 5.00-4.97 (m, 1H), 4.74 (s, 2H), 4.63 (s, 2H), 1.90 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 154.1, 139.5, 137.4, 133.8, 131.3, 129.4, 129.4, 129.0, 128.6, 125.0, 123.2, 121.7, 118.9, 78.0, 68.4, 48.8, 22.0, 19.7. HRMS calcd for $C_{22}H_{26}N_2O_4Na$ [M+Na]$^+$ 405.1790, found 405.1778.

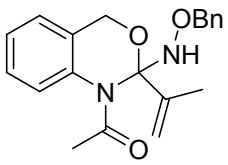
Isobutyl 2-((benzyloxy)amino)-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3h)



Yellow oil (35 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.39-7.31 (m, 5H), 7.25-7.20 (m, 2H), 7.07-7.03 (m, 1H), 5.47 (s, 1H), 5.36 (s, 1H), 4.80 (s, 2H), 4.65 (s, 2H), 3.98-3.95 (m, 2H), 1.95 (s, 3H), 1.70-1.65 (m, 1H), 0.99 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 154.6, 139.4, 137.4, 133.8, 132.8, 131.3, 129.5, 129.4, 129.0, 128.6, 128.4, 127.3, 123.1, 119.2, 78.1, 71.1, 49.0, 28.0, 19.7, 19.1. HRMS calcd for $C_{23}H_{28}N_2O_4Na$ [M+Na]$^+$ 419.1947, found

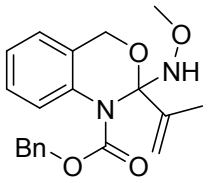
419.1951.

1-(2-((benzyloxy)amino)-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazin-1(4*H*)-yl)ethan-1-one (3i)



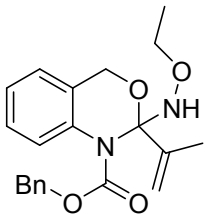
Colorless oil (24 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.49-7.30 (m, 6H), 7.16-7.12 (m, 1H), 7.10-7.01 (m, 1H), 5.55 (s, 1H), 5.30 (s, 1H), 5.13 (s, 2H), 4.99 (s, 2H), 1.93 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 155.8, 138.2, 136.7, 134.6, 129.9, 129.7, 128.7, 128.5, 128.4, 125.4, 123.8, 122.5, 118.9, 71.5, 24.2, 18.5. HRMS calcd for $C_{20}H_{22}N_2O_3Na$ $[M+Na]^+$ 361.1528, found 361.1534.

Benzyl 2-(methoxyamino)-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3k)



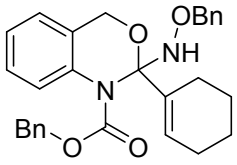
Colorless oil (61 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.46-7.44 (m, 2H), 7.36-7.28 (m, 5H), 7.07-7.03 (m, 1H), 5.40 (s, 1H), 5.29 (s, 1H), 5.24 (s, 2H), 4.76 (s, 2H), 3.58 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.3, 139.1, 137.1, 136.7, 131.3, 129.4, 128.4, 128.0, 127.9, 123.4, 119.0, 98.2, 66.5, 47.7, 36.8, 19.7. HRMS calcd for $C_{20}H_{22}N_2O_4Na$ $[M+Na]^+$ 377.1477, found 377.1485.

Benzyl 2-(ethoxyamino)-2-(prop-1-en-2-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3l)



Colorless oil (60 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.1 Hz, 2H), 7.38-7.29 (m, 5H), 7.07-7.03 (m, 1H), 5.41 (s, 1H), 5.29-5.27 (m, 1H), 5.24 (s, 2H), 4.76 (s, 2H), 3.77 (q, *J* = 7.1 Hz, 2H), 1.95 (s, 3H), 1.13 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 154.2, 139.1, 137.1, 136.6, 131.3, 129.4, 128.6, 128.5, 128.4, 127.9, 127.9, 125.1, 123.3, 121.5, 119.0, 71.5, 66.5, 48.3, 19.7, 13.2. HRMS calcd for $C_{21}H_{24}N_2O_4Na$ $[M+Na]^+$ 391.1634, found 391.1637.

Benzyl 2-((benzyloxy)amino)-2-(cyclohex-1-en-1-yl)-2*H*-benzo[*d*][1,3]oxazine-1(4*H*)-carboxylate (3m)



Colorless oil (72 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s,

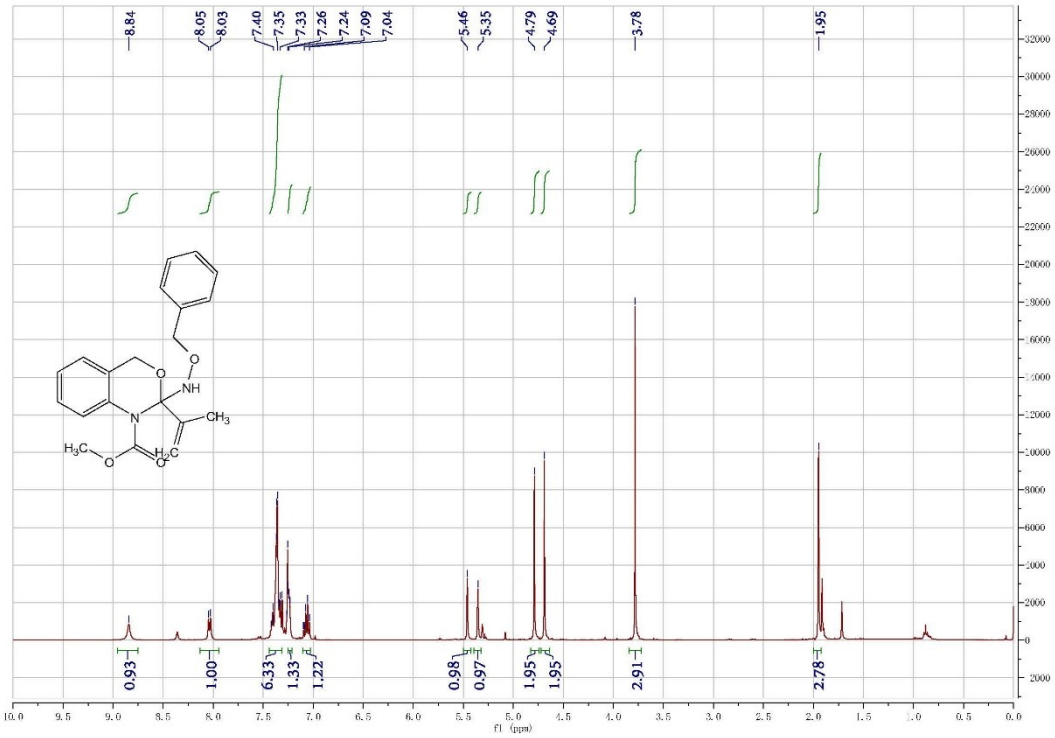
1H), 7.98 (d, J = 8.1 Hz, 1H), 7.40-7.33 (m, 2H), 7.31-7.19 (m, 8H), 7.14-7.11 (m, 2H), 7.02-6.91 (m, 1H), 6.24-6.11 (m, 1H), 5.16 (s, 2H), 4.71 (s, 2H), 4.53 (s, 2H), 2.13-2.07 (m, 2H), 2.06-1.97 (m, 2H), 1.58-1.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 154.2, 137.3, 136.7, 133.9, 133.0, 132.8, 131.3, 129.4, 129.0, 128.6, 128.4, 128.0, 127.9, 125.1, 123.2, 121.3, 78.1, 66.5, 49.2, 25.3, 25.1, 22.0, 21.5. HRMS calcd for $C_{29}H_{30}N_2O_4Na$ $[M+Na]^+$ 493.2103, found 493.2113.

4. References

1. C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff and C. R. Carson, *J. Am. Chem. Soc.* 2011, **133**, 7688.
2. A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra and K. A. Scheidt, *J. Am. Chem. Soc.* 2014, **136**, 10589.

5. Copies of NMR spectra for products 3

3a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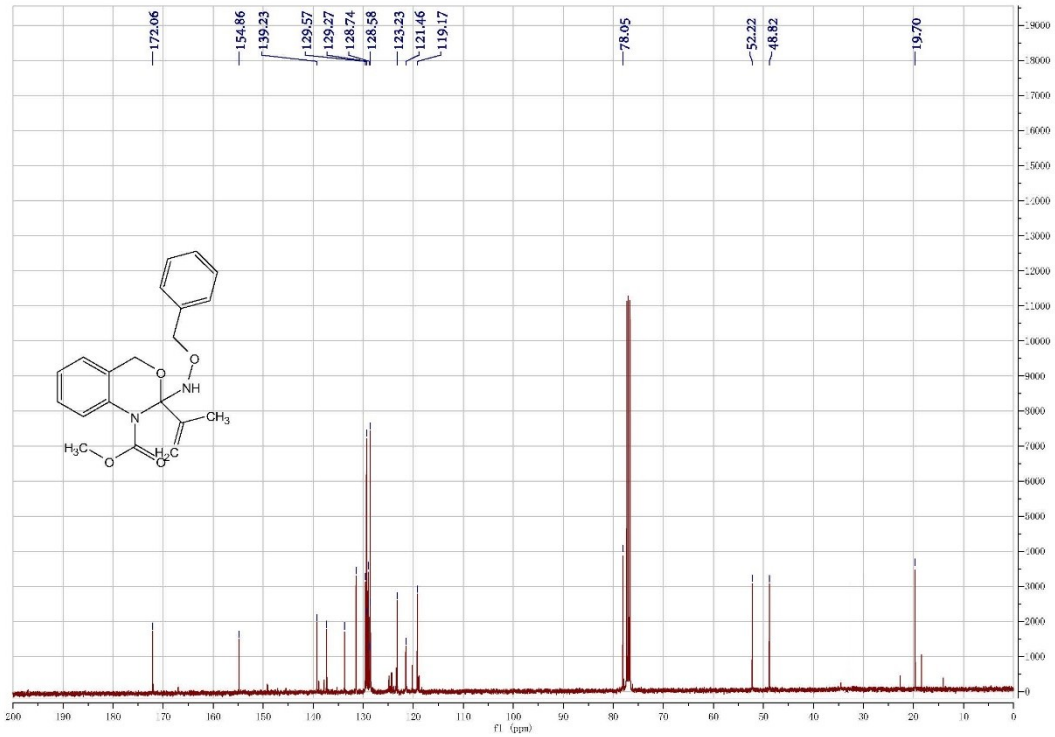
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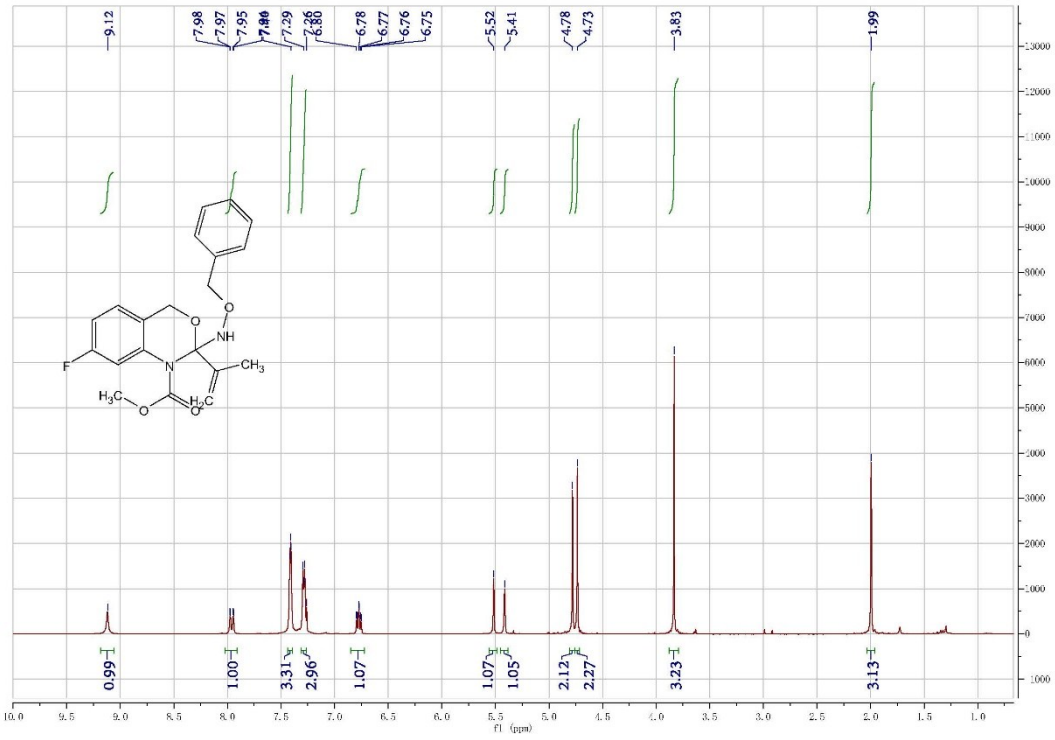
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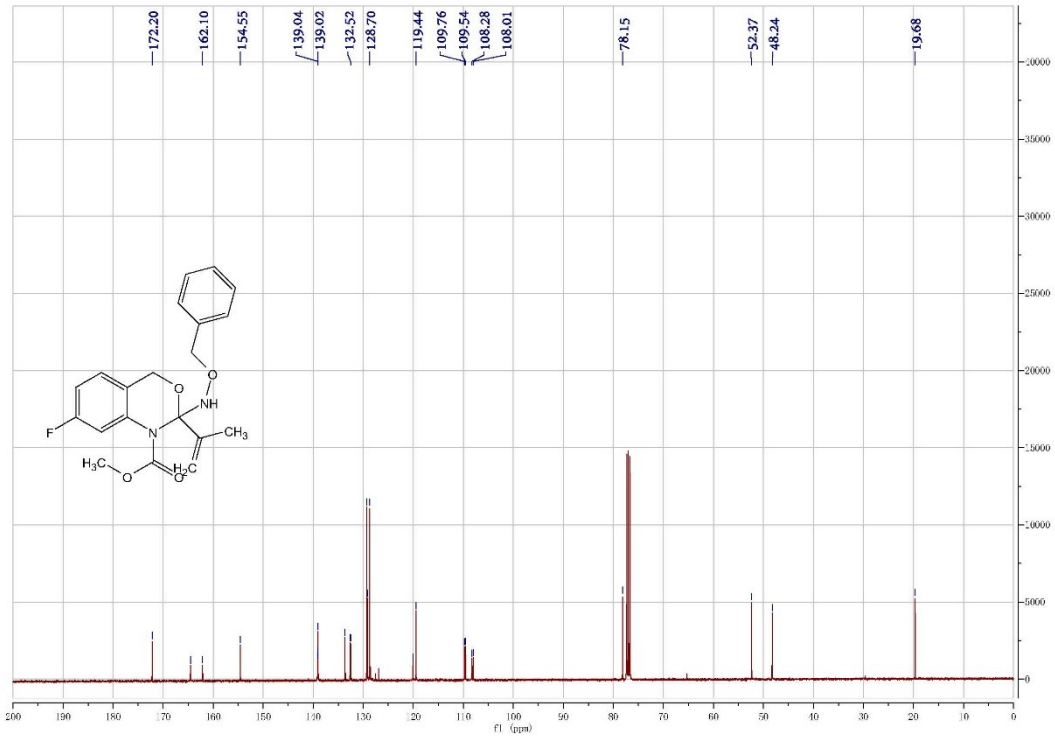
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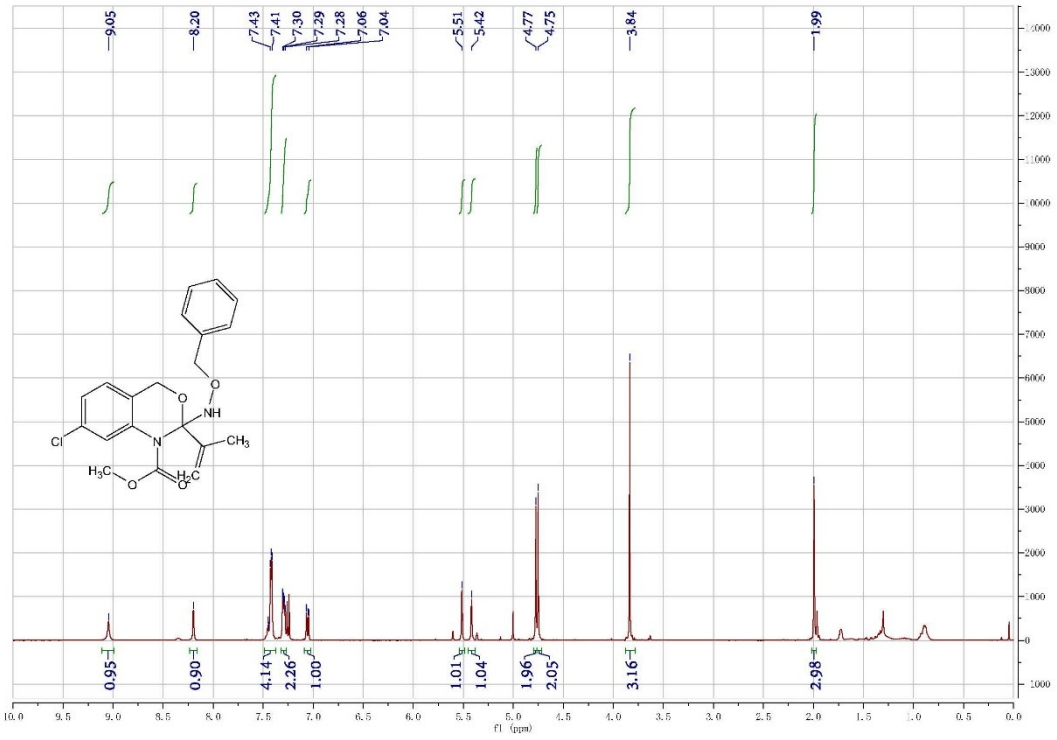
3c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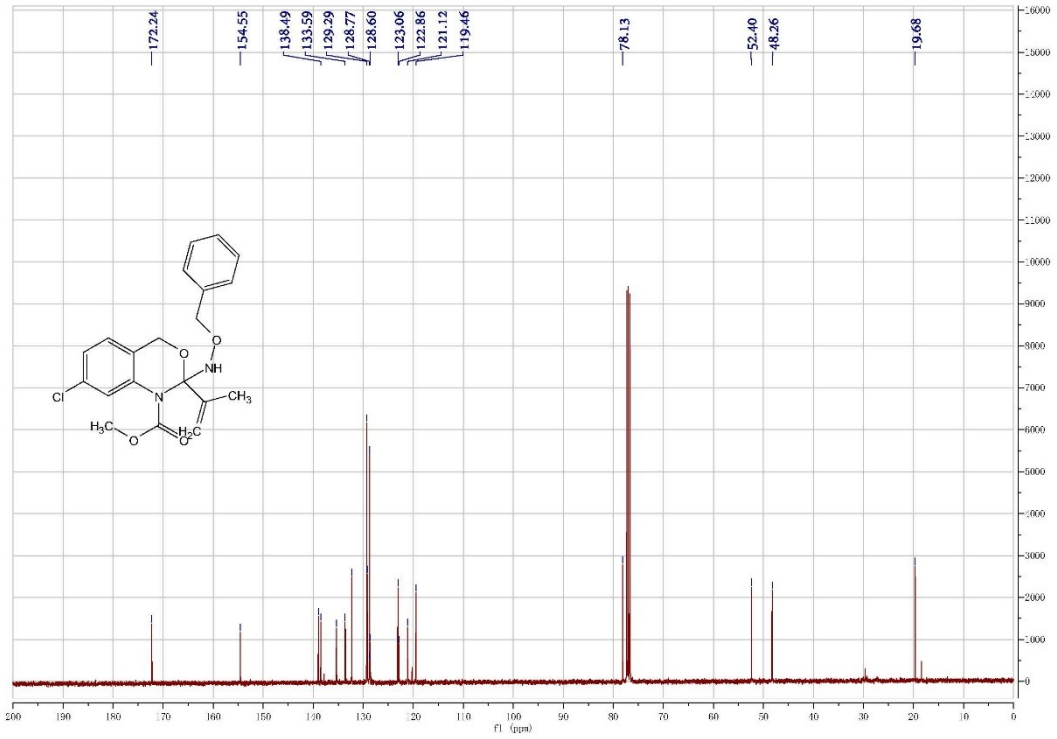
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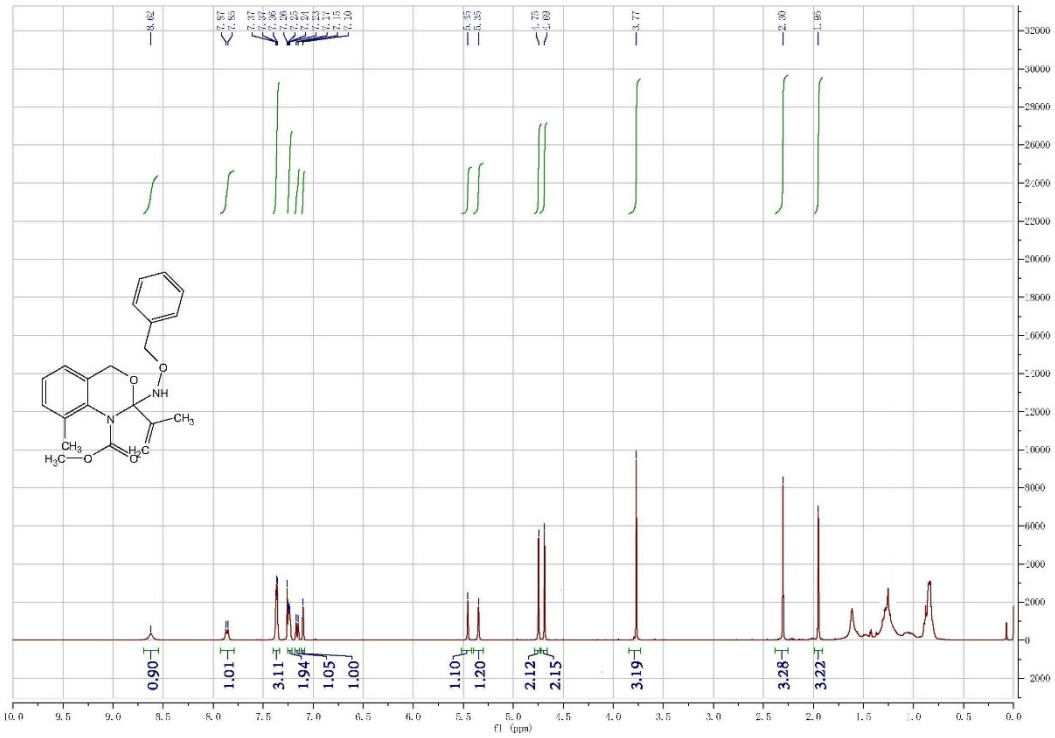
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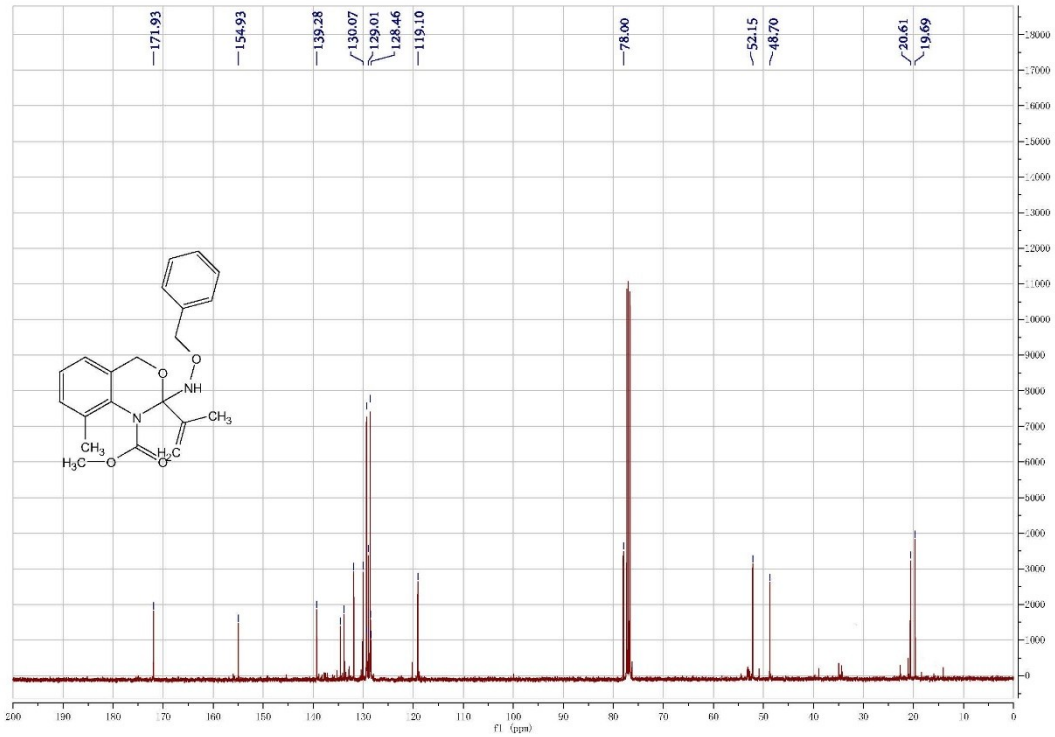
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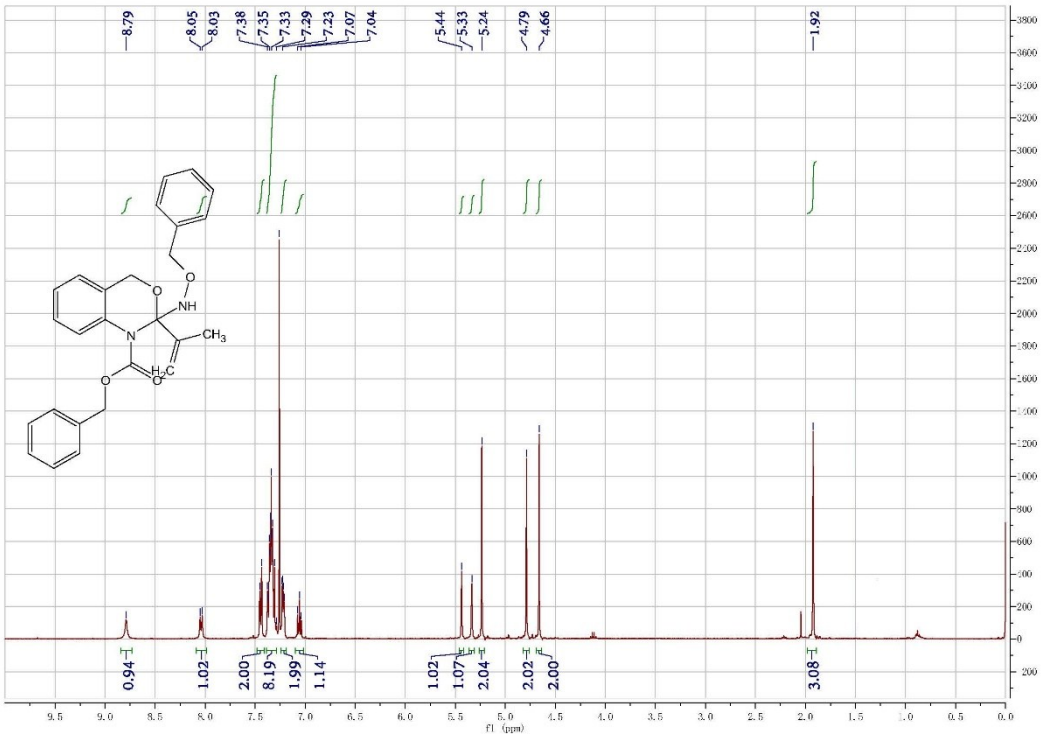
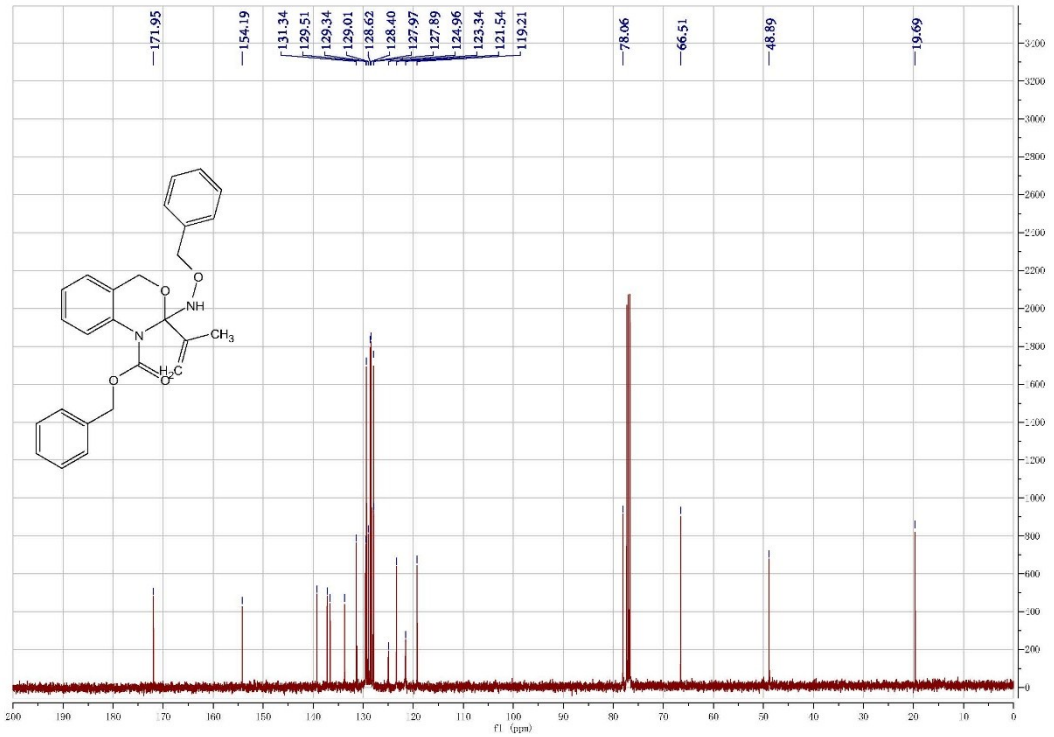
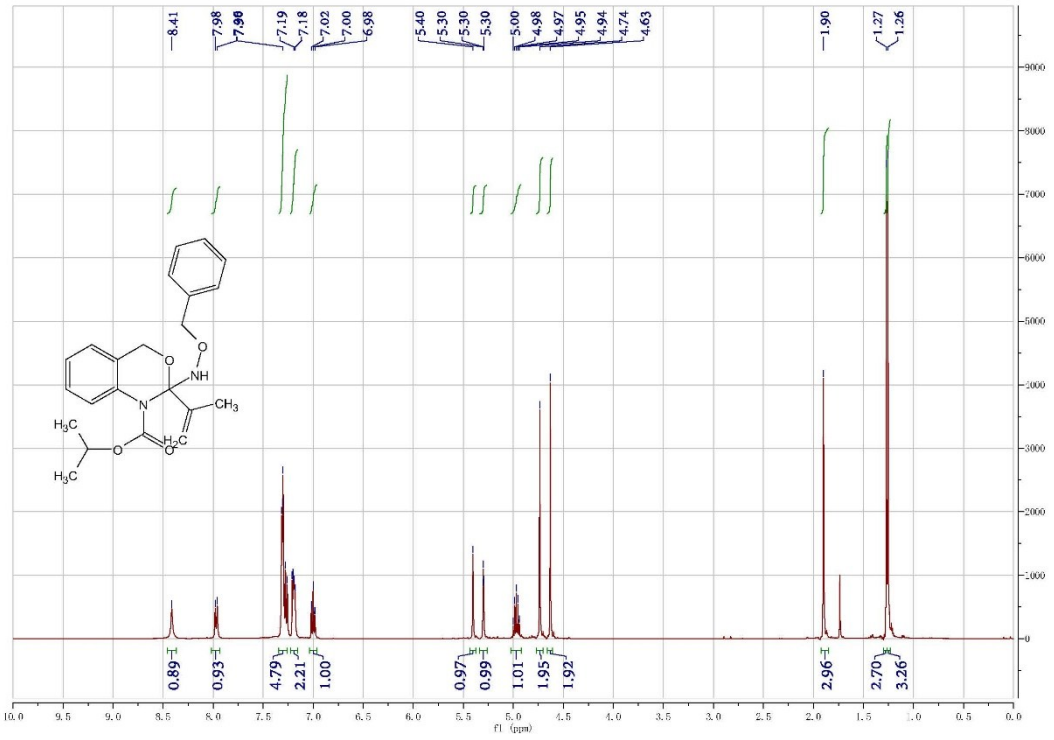
f1 (ppm)

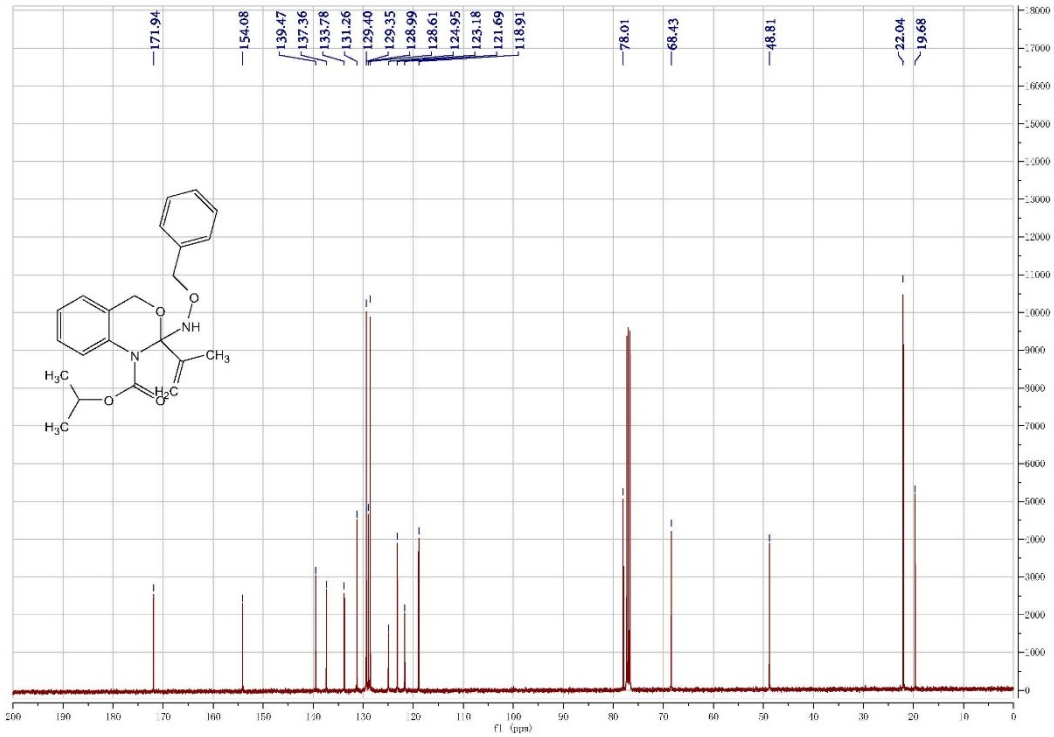
3e


8.79
8.05
8.03
7.38
7.35
7.33
7.29
7.23
7.07
7.04
5.44
5.33
5.24
4.79
4.66
1.92
0.94
1.02
2.00
8.19
1.99
1.14
1.02
1.07
2.04
2.02
2.00
3.08
O
NH
N
CH3
H2C
O
O
f1 (ppm)

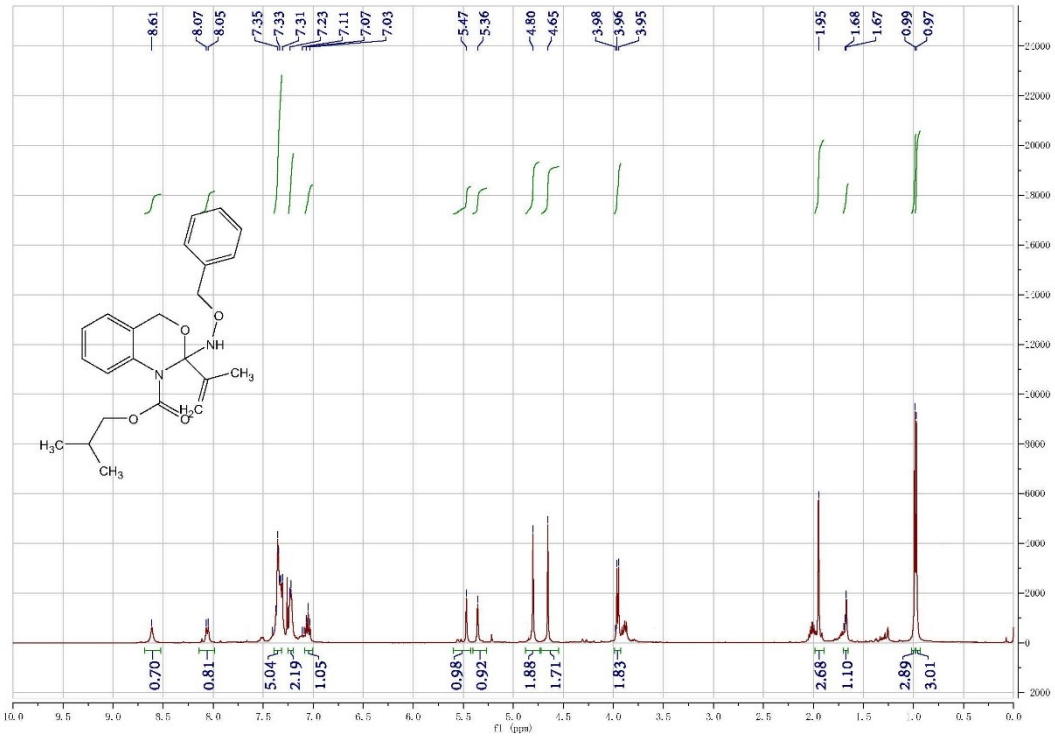

171.95
154.19
131.34
129.51
129.34
129.01
128.62
128.40
127.97
127.89
124.96
123.34
121.54
119.21
78.06
66.51
48.89
19.69
O
NH
N
CH3
H2C
O
O
f1 (ppm)

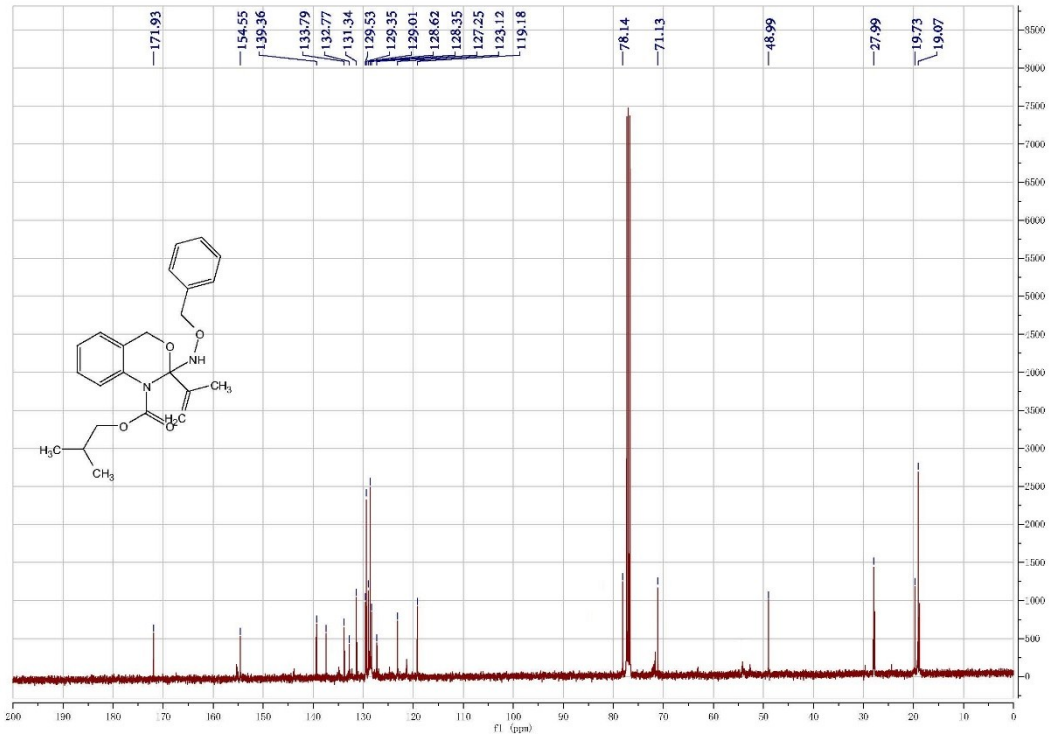
3g


8.41
7.98
7.96
7.19
7.18
7.02
7.00
6.98
5.40
5.30
5.30
5.30
5.00
4.98
4.97
4.95
4.94
4.74
4.63
1.90
1.27
1.26
0.89
0.93
4.79
2.21
1.00
0.97
0.99
1.01
1.95
1.92
2.96
2.70
3.26
f1 (ppm)

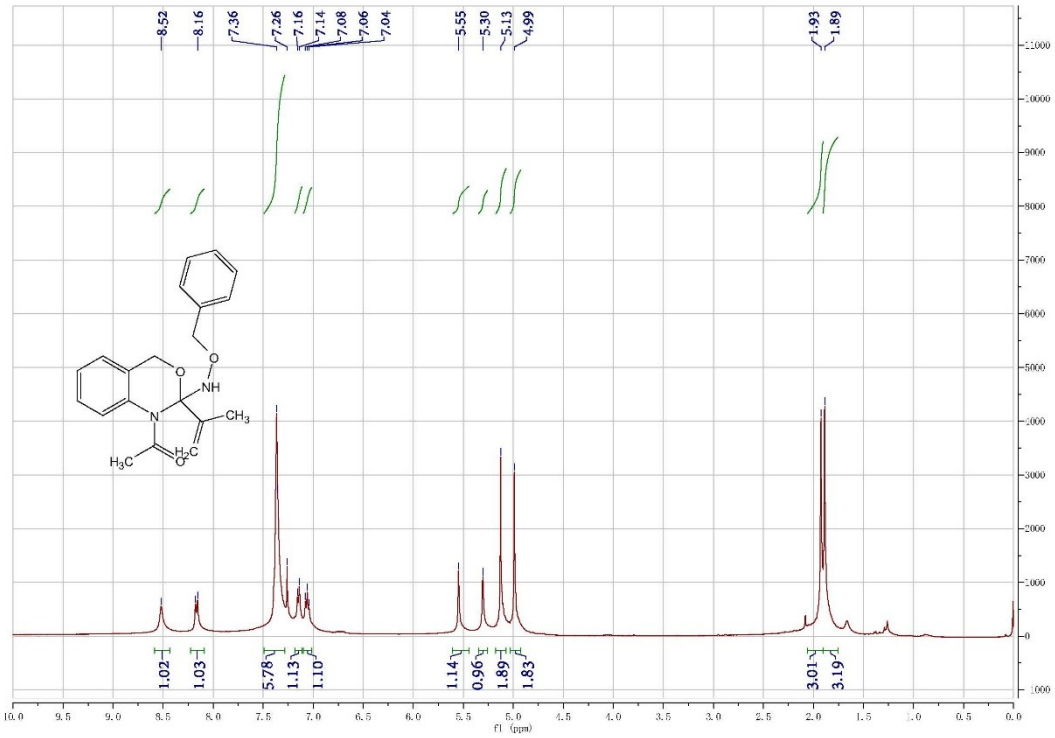

171.94
154.08
139.47
137.36
133.78
131.26
129.40
129.35
128.99
128.61
124.95
123.18
121.69
118.91
78.01
68.43
48.81
22.04
19.68
f1 (ppm)

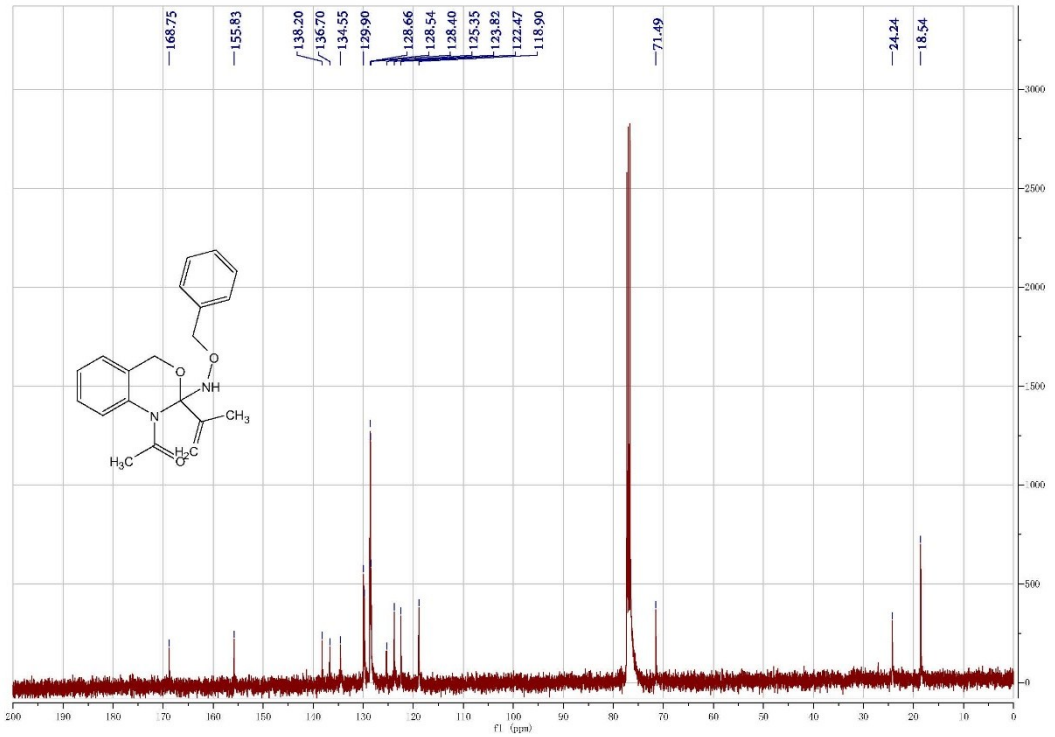
3h


8.61
8.07
8.05
7.35
7.33
7.31
7.23
7.11
7.07
7.03
5.47
5.36
4.80
4.65
3.98
3.96
3.95
1.95
1.68
1.67
0.99
0.97
0.70
0.81
5.04
2.19
1.05
0.98
0.92
1.88
1.71
1.83
2.68
1.10
2.89
3.01
f1 (ppm)

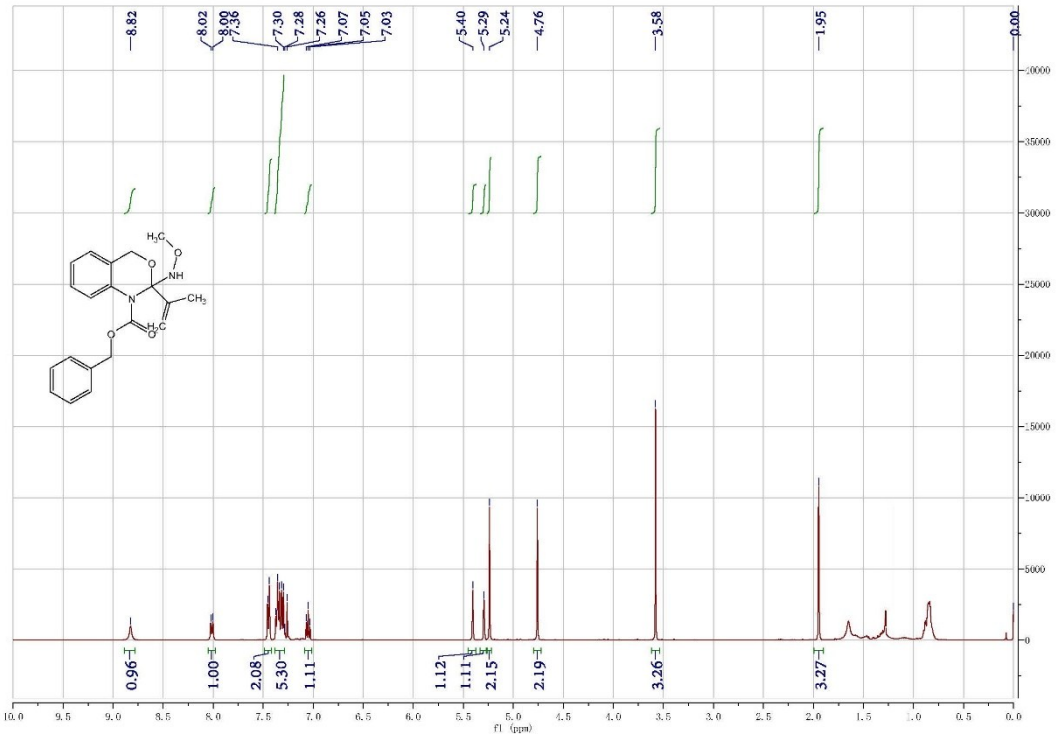

171.93
154.55
139.36
133.79
132.77
131.34
129.53
129.35
129.01
128.62
128.35
127.25
123.12
119.18
78.14
71.13
48.99
27.99
19.73
19.07
f1 (ppm)

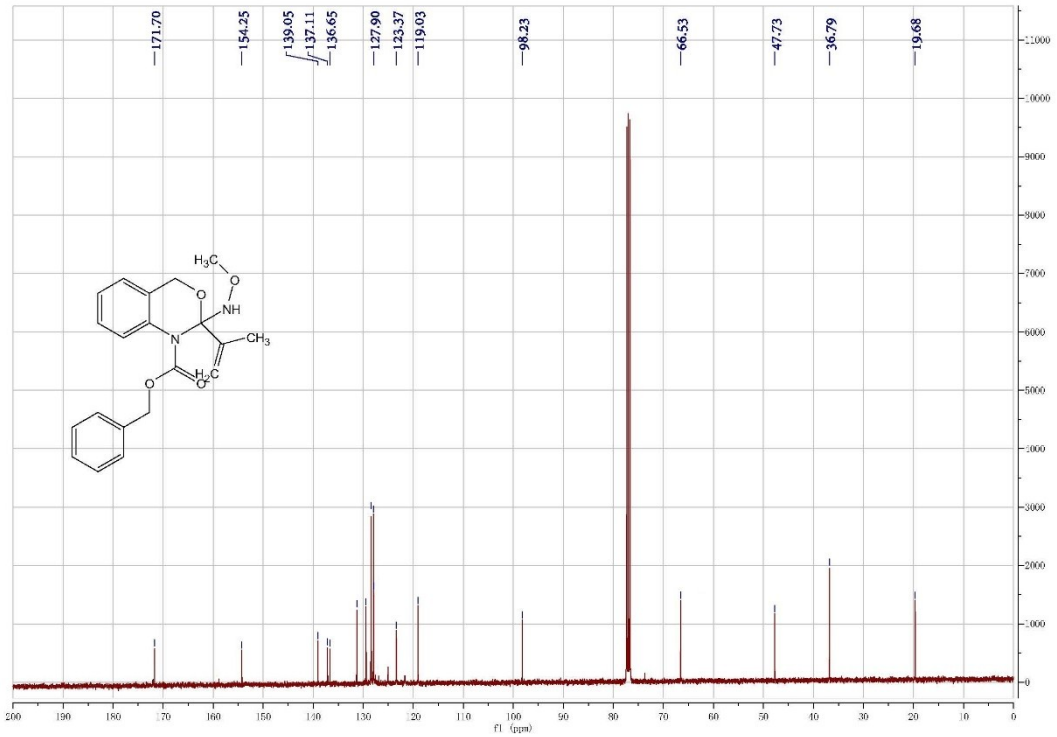
3i


8.52
8.16
7.36
7.26
7.16
7.14
7.08
7.06
7.04
5.55
5.30
5.13
4.99
1.93
1.89
1.02
1.03
5.78
1.13
1.10
1.14
0.96
1.89
1.83
3.01
3.19
f1 (ppm)

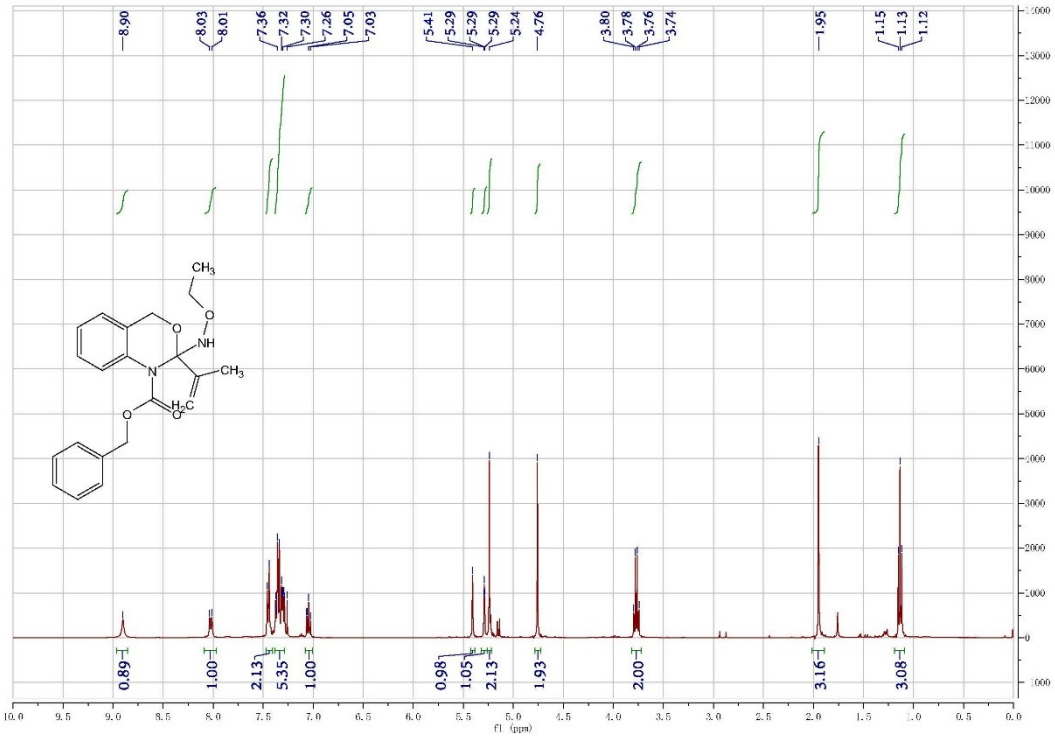

168.75
155.83
138.20
136.70
134.55
129.90
128.66
128.54
128.40
125.35
123.82
122.47
118.90
71.49
24.24
18.54
f1 (ppm)

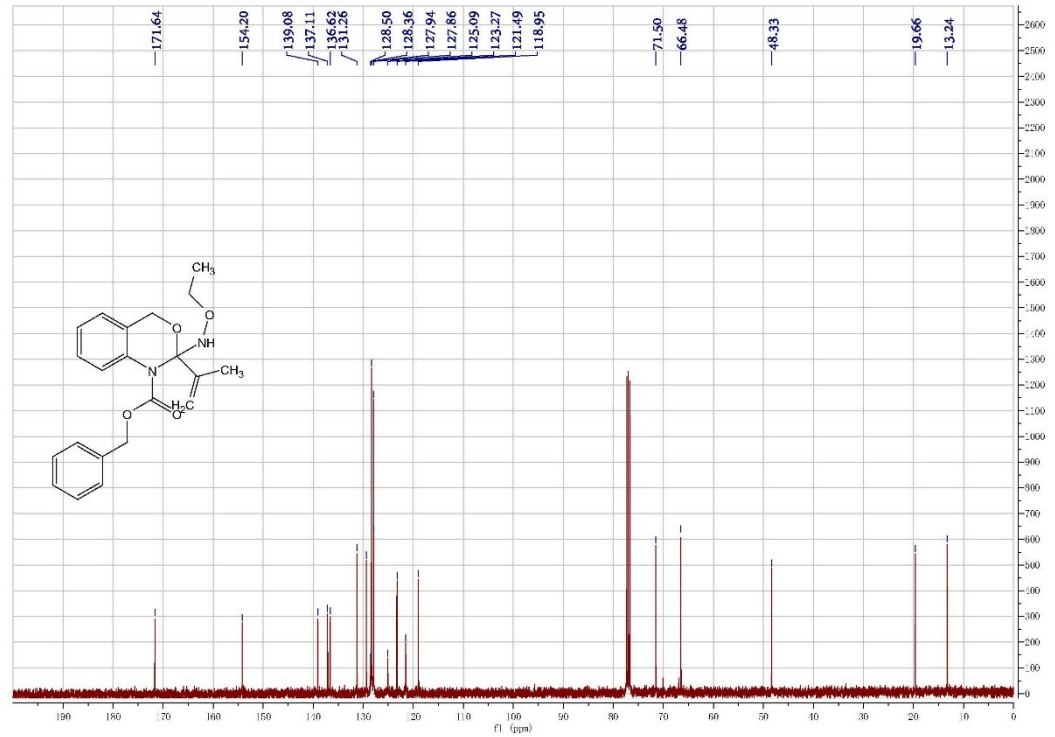
3k


8.82
8.02
8.00
7.36
7.30
7.28
7.26
7.07
7.05
7.03
5.40
5.29
5.24
4.76
3.58
1.95
0.00
0.96
1.00
2.08
5.30
1.11
1.12
1.11
2.15
2.19
3.26
3.27
f1 (ppm)

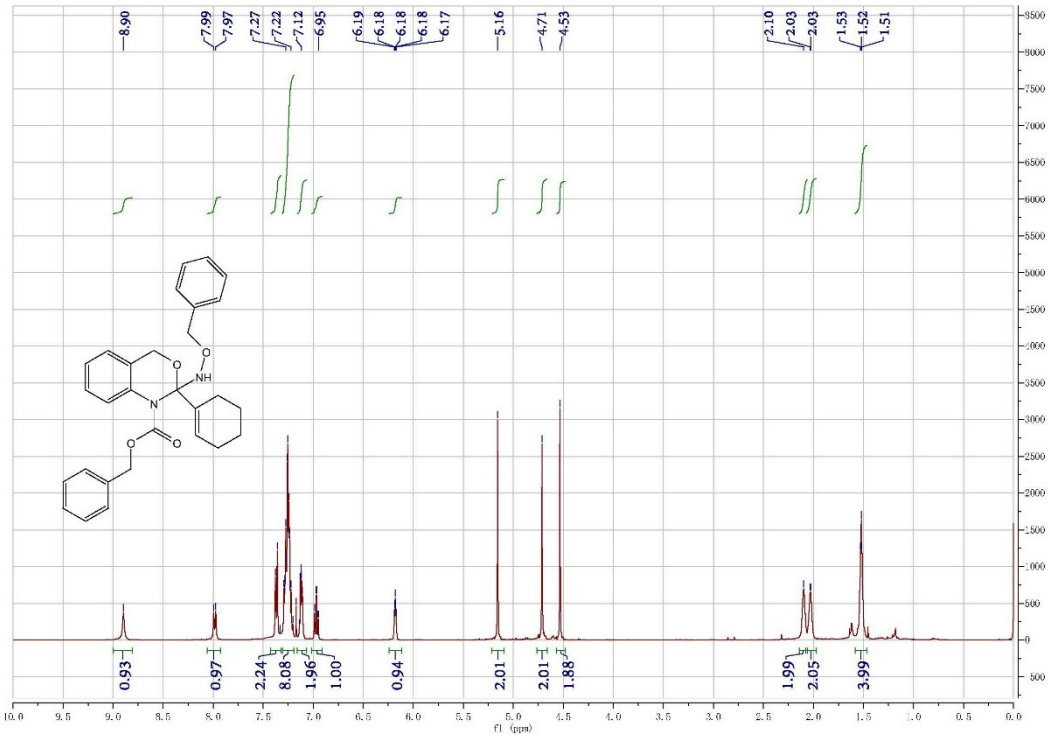

171.70
154.25
139.05
137.11
136.65
127.90
123.37
119.03
98.23
66.53
47.73
36.79
19.68
f1 (ppm)

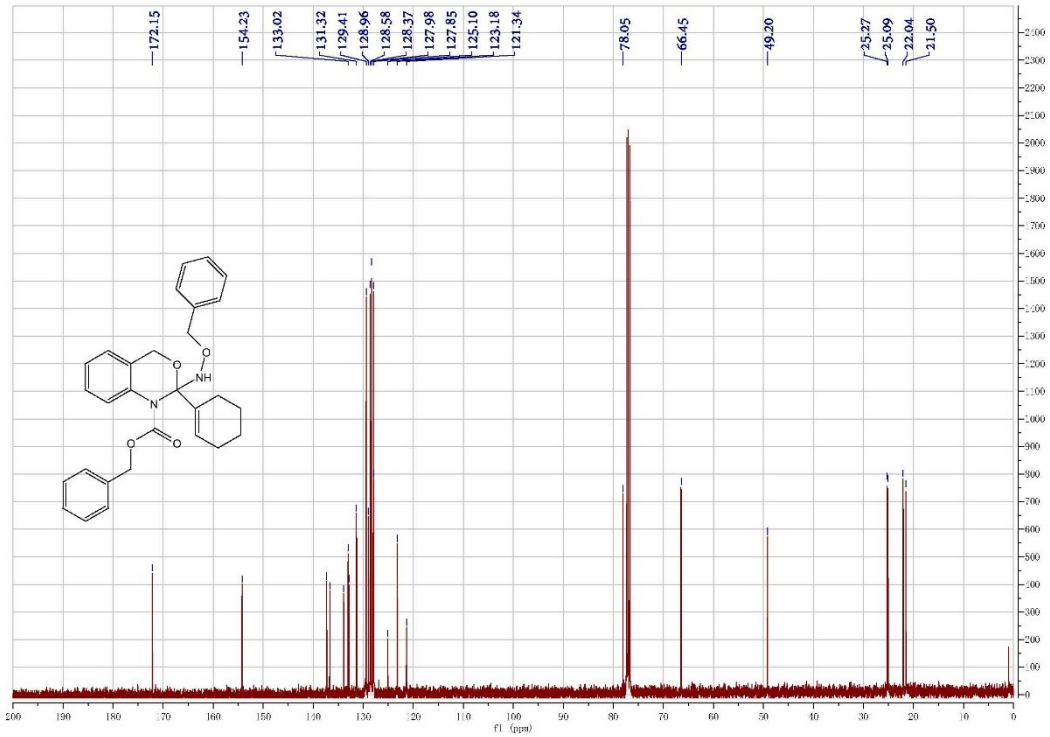
3l


8.90
8.03
8.01
7.36
7.32
7.30
7.26
7.05
7.03
5.41
5.29
5.29
5.29
5.24
4.76
3.80
3.78
3.76
3.74
1.95
1.15
1.13
1.12
0.89
1.00
2.13
5.35
1.00
0.98
1.05
2.13
1.93
2.00
3.16
3.08
f1 (ppm)


171.64
154.20
139.08
137.11
136.62
131.26
128.50
128.36
127.94
127.86
125.09
123.27
121.49
118.95
71.50
66.48
48.33
19.66
13.24
f1 (ppm)

3m


8.90
7.99
7.97
7.27
7.22
7.12
6.95
6.19
6.18
6.18
6.18
6.17
5.16
4.71
4.53
2.10
2.03
2.03
1.53
1.52
1.51
0.93
0.97
2.24
8.08
1.96
1.00
0.94
2.01
2.01
1.88
1.99
2.05
3.99
f1 (ppm)


172.15
154.23
133.02
131.32
129.41
128.96
128.58
128.37
127.98
127.85
125.10
123.18
121.34
78.05
66.45
49.20
25.27
25.09
22.04
21.50
f1 (ppm)