Supporting Information

For

Electrolysis promoted reductive amination of electron-deficient aldehydes/ketones: green route to the racemic Clopidogrel

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Experimental

General Unless stated otherwise, reactions were conducted in dried glassware. Commercially available reagents and solvents were used as received. Acetonitrile was refluxed with CaH_2 and distilled before use. 300–400 mesh silica gel was used for flash column chromatography. Visualization on TLC was achieved by the use of UV light (254 nm). 400 MHz and 100 MHz spectrometers were used for recording ^1H NMR and ^{13}C NMR spectra. Chemical shifts (δ ppm) were reported in parts per million referring to either the internal standard of TMS or the residue of the deuterated solvents.

Nickel net (50 mesh) was activated by treatment of 6 N HCl for 15 min and washed by anhydrous acetonitrile. Electrolysis experiments were performed using a cylindrical glass container with a cap and a magnetic stir bar, a DC power supply, a zinc bar anode (length 15 cm and diameter 0.8 cm) and a nickel net cathode (50 mesh, 15 x 12 cm).

General procedure for the synthesis of compound 3:

An oven-dried, undivided electrochemical cell was equipped with a magnetic stir bar, a zinc bar anode (length 15 cm and diameter 0.8 cm) and a Nickel net cathode (50 mesh, 15 x 12 cm). To this setup was added a solution of **1** (5 mmol), **2** or its hydrochloride (7.5 mmol) and $Zn(OAc)_2$ (5 mmol) in 50 mL of HOAc-MeCN (1:10, v/v). Electrolysis was initiated at a constant current of 8 mA at room temperature and the reaction was monitored by TLC. After the substrate **1** was completely consumed, the solvent was removed in vacuum. The residue of reaction mixture was quenched with ammonia water and extracted with methyl *tert*-butyl ether (MTBE). The organic layer was washed with water and purified by column chromatography to afford the desired product **3**. For the large scale cases, the organic layer was added MsCl in DCM and stirring for 1 h, then charged anhydrous HCl in MeOH to pH < 2. After removal of the solvent, the solid was washed by DCM and diethyl ether; recrystallization with MeOH gave the racemic Clopidogrel hydrochloride.

Characterization data of the products:

Methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)acetate (3a): [1] 1.321 g, 82% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 4.0 Hz, 1H), 7.42-7.40 (m, 1H), 7.32-7.27 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 4.0 Hz, 1H), 4.96 (s, 1H), 3.80 (d, *J* = 12.0 Hz, 1H), 3.73(s, 3H), 3.68 (d, *J* = 12.0 Hz, 1H), 2.91 (d, *J* = 8.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 134.7, 133.8, 133.2, 130.0, 129.8, 129.4, 127.2, 125.2, 122.8, 67.8, 52.2, 50.7, 48.3, 25.5; IR (neat): 2983, 1732 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{16}{}^{35}ClNO_2S$ 321.0590, found 321.0592.

Methyl 2-(2-chlorophenyl)-2-(diethylamino)acetate (3b): 0.956 g, 75% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 7.34 (dd, *J* = 4.0 Hz, 8.0 Hz, 1H), 7.25-7.17 (m, 2H), 4.93 (s, 1H), 3.66 (s, 3H), 2.70-2.59 (m, 4H), 0.99 (t, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 135.1, 134.5, 130.0, 129.6, 128.9, 126.7, 65.1, 51.7, 43.9, 12.3; HRMS (EI) calcd for $C_{13}H_{18}{}^{35}ClNO_2$ 255.1026, found 255.1029.

Methyl 2-(2-chlorophenyl)-2-morpholinoacetate (3c): [2] 1.062 g, 79% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 4.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.28-7.20 (m, 2H), 4.65 (s, 1H), 3.70 (t, *J* = 4.0 Hz, 4H), 3.67(s, 3H), 2.58-2.55 (m, 2H), 2.47-2.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 134.8, 133.1, 130.0, 129.7, 129.4, 127.1, 68.8, 66.8, 52.1, 51.2; HRMS (EI) calcd for $C_{13}H_{16}{}^{35}ClNO_3$ 269.0819, found 269.0823.

Methyl 2-(2-chlorophenyl)-2-(dimethylamino)acetate (3d): 0.919 g, 81% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.28-7.20 (m, 2H), 4.58 (s, 1H), 3.68 (s, 3H), 2.29 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 134.8, 133.1, 130.0, 129.7, 129.4, 127.1, 68.8, 66.8, 52.1, 51.2; IR (neat): 2974, 1738 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}{}^{35}ClNO_2$ 227.0713, found 227.0718.

Methyl 2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)-2-phenylacetate (3e): [3] 1.148 g, 80% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.39-7.33 (m, 3H), 7.06 (d, *J* = 4.0 Hz, 1H), 6.66 (d, *J* = 4.0 Hz, 1H), 4.31 (s, 1H), 3.72(s, 3H), 3.63 (d, *J* = 8.0 Hz, 2H), 2.90-2.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

172.0, 135.9, 133.3, 133.2, 128.8, 128.7, 128.5, 125.3, 122.7, 72.9, 52.1, 51.0, 48.3, 25.3; HRMS (EI) calcd for $C_{16}H_{17}NO_2S$ 287.0980, found 287.0983.

Methyl 2-(diethylamino)-2-phenylacetate (3f): [4] 0.785 g, 71% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.35-7.26 (m, 3H), 4.49 (s, 1H), 3.69 (s, 3H), 2.66-2.57 (m, 4H), 0.99 (t, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 137.0, 128.7, 128.3, 127.9, 69.3, 51.7, 43.6, 11.8; HRMS (EI) calcd for $C_{13}H_{19}NO_2$ 221.1416, found 221.1418.

Methyl 2-morpholino-2-phenylacetate (3g): [5] 0.893 g, 76% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 2H), 7.36-7.31 (m, 3H), 3.98 (s, 1H), 3.77 (t, *J* = 4.0 Hz, 4H), 3.67(s, 3H), 2.45 (t, *J* = 4.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 135.2, 128.9, 128.6, 128.5, 74.4, 66.8, 52.1, 51.6; HRMS (EI) calcd for $C_{13}H_{17}NO_3$ 235.1208, found 235.1211.

Methyl 2-(dimethylamino)-2-phenylacetate (3h): [6] 0.676 g, 70% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.31-7.26 (m, 3H), 3.83 (s, 1H), 3.64 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 136.3, 128.6, 128.5, 128.4, 75.2, 52.0, 43.4; HRMS (EI) calcd for $C_{11}H_{15}NO_2$ 193.1103, found 193.1108.

2-(6,7-Dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)-1-phenylethanone (3i): 0.925 g, 72% yield; amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 4.0 Hz, 1H), 6.72 (d, *J* = 4.0 Hz, 1H), 4.06 (s, 2H), 3.80 (s, 2H), 3.02-2.99 (m, 2H), 2.96-2.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 135.9, 133.4, 133.1, 133.1, 128.6, 128.2, 125.2, 122.7, 63.1, 52.9, 50.8, 24.9; IR (neat): 2948, 1693 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}NOS$ 257.0874, found 257.0879.

***tert*-Butyl 2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)acetate (3j):** 1.113 g, 88% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 4.0 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 2H), 3.29 (s, 2H), 2.89 (d, *J* = 4.0 Hz, 2H), 2.86 (d, *J* = 4.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 133.4, 133.0, 125.1, 122.5, 81.0, 59.0, 52.3, 50.4, 28.2, 25.3; IR (neat): 2956, 1746 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{19}NO_2S$ 253.1136, found 253.1132.

Methyl 2-(2-chlorophenyl)-2-hydroxyacetate (4a): [7] 0.824 g, 82% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.28-7.24 (m, 2H), 5.56 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 136.0, 129.9, 129.9, 129.8, 128.8, 127.2, 70.3, 53.2; HRMS (EI) calcd for $C_9H_9{}^{35}ClO_3$ 200.0240, found 200.0245.

Methyl 2-hydroxy-2-phenylacetate (4b): [8] 0.647 g, 78% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.39-7.33 (m, 3H), 5.18 (s, 1H), 3.76 (d, J = 4.0 Hz, 3H), 2.82 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 138.3, 128.6, 128.5, 126.6, 72.9, 53.0; HRMS (EI) calcd for $C_9H_{10}O_3$ 166.0630, found 166.0633.

methyl 2-(methylamino)-2-phenylacetate (5): [9] 36 mg, 4% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.21 (m, 5H), 4.22 (s, 1H), 3.62(s, 3H), 2.39 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 137.9, 128.6, 128.1, 127.4, 67.2, 52.1, 34.2; HRMS (EI) calcd for $C_{10}H_{13}NO_2$ 179.0946, found 179.0948.

References

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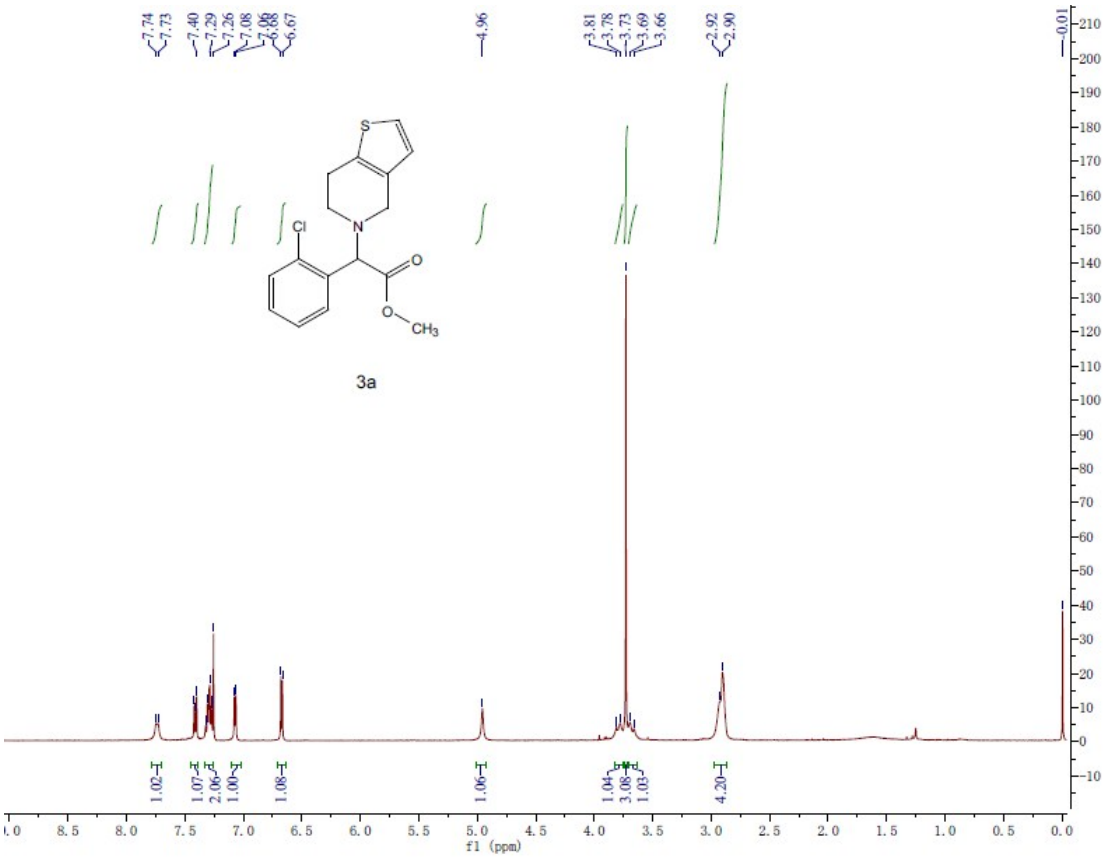
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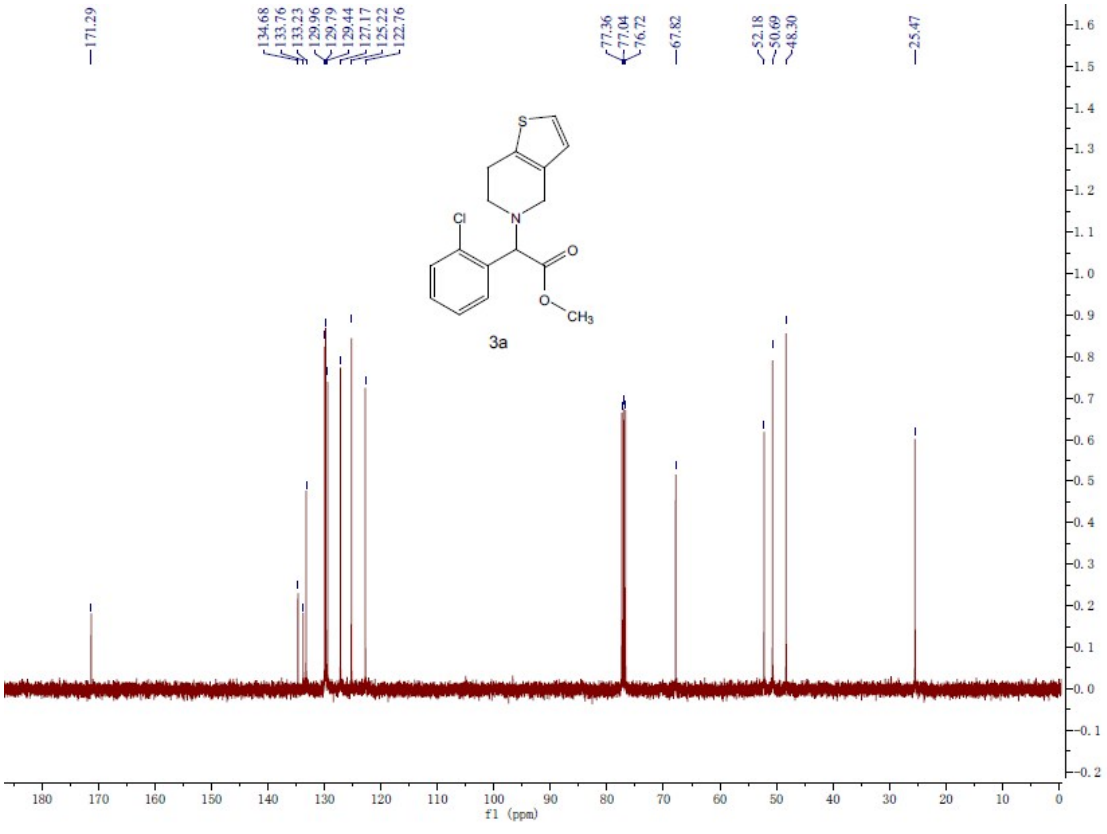
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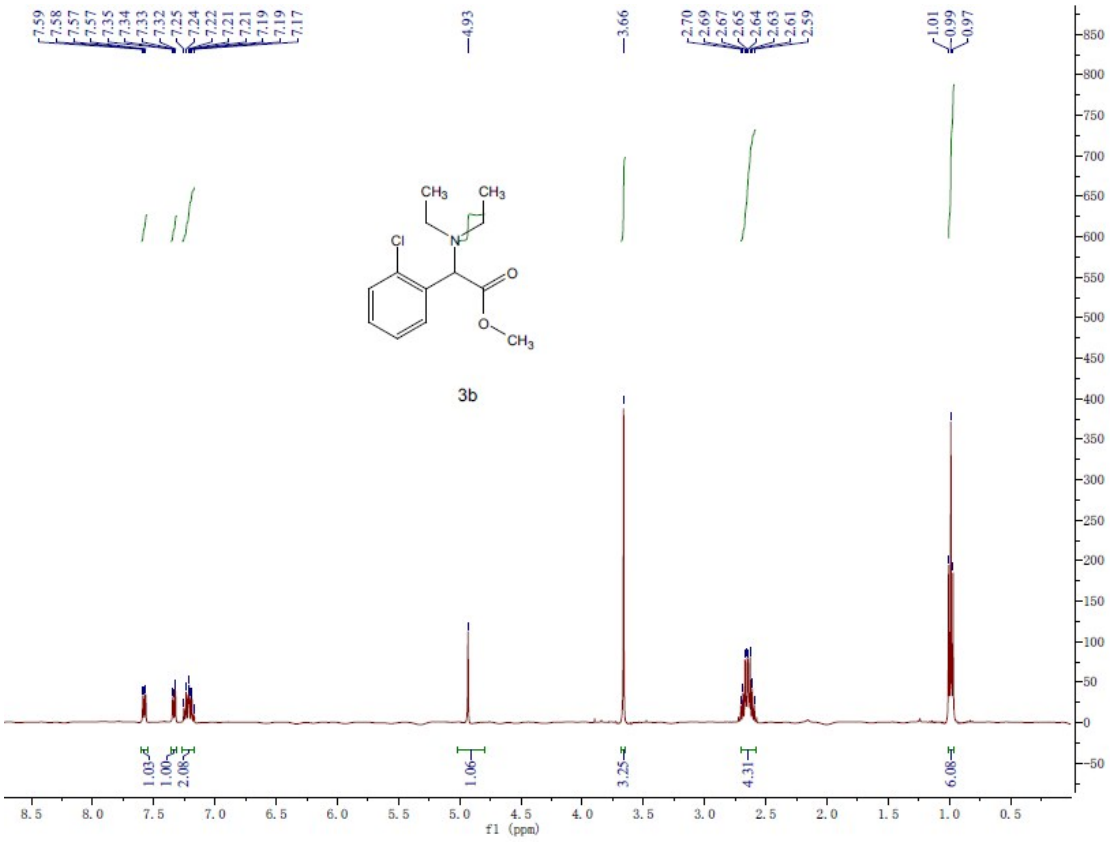
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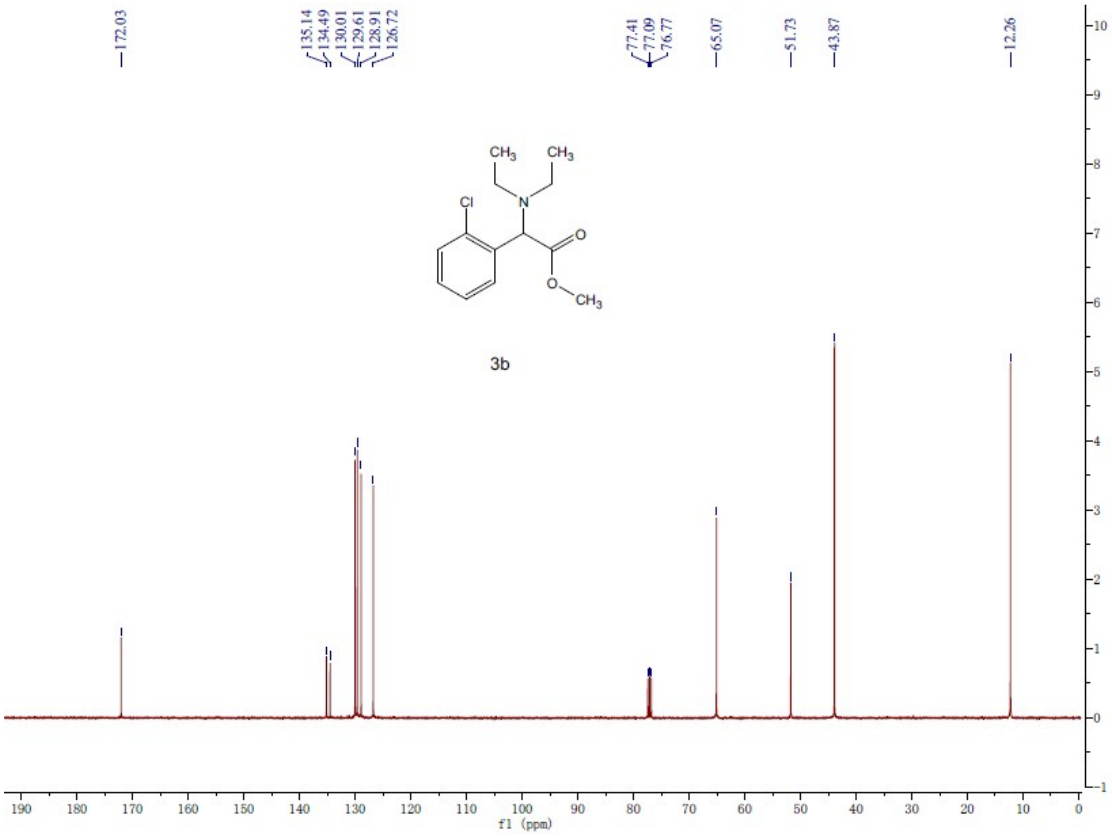
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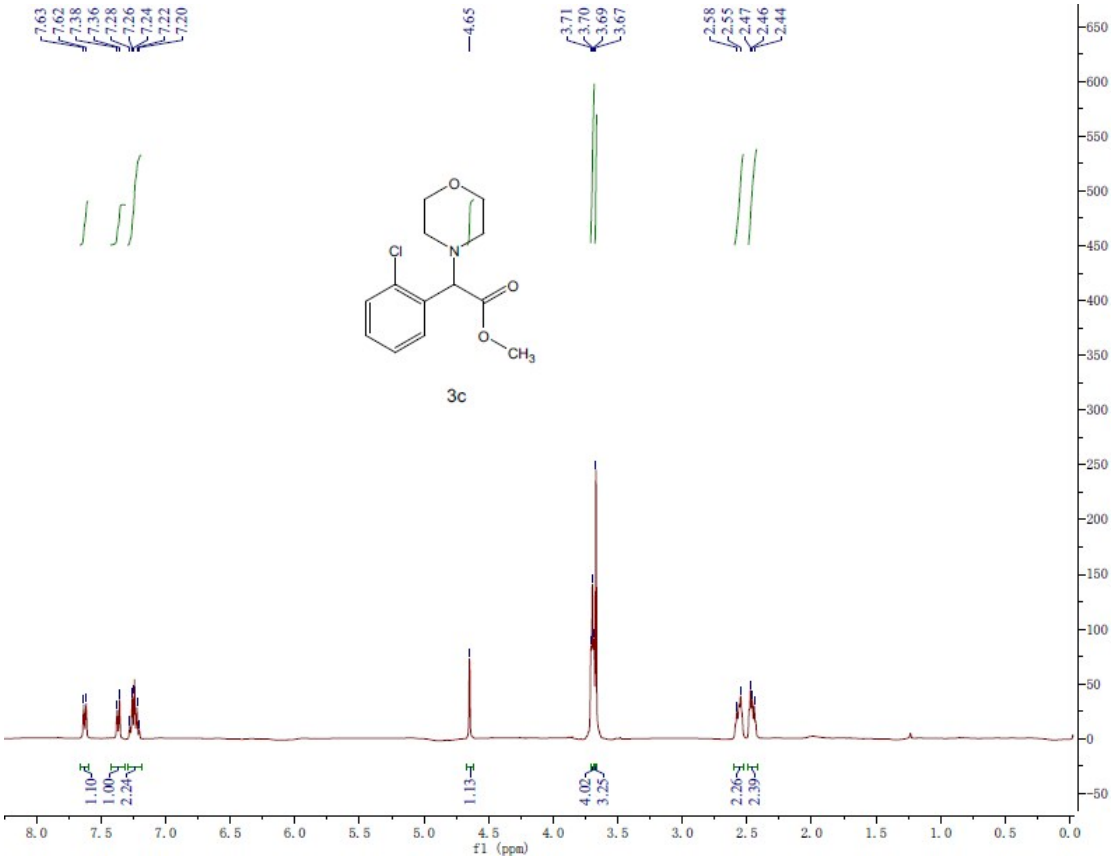
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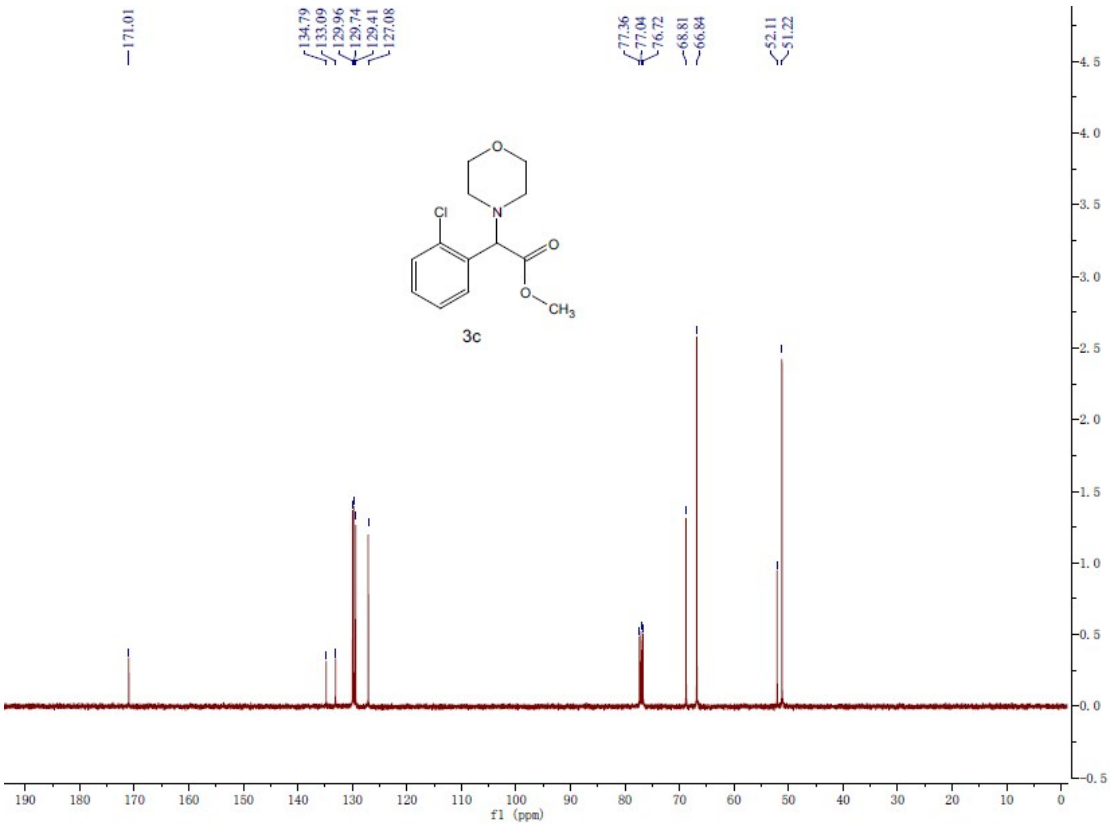
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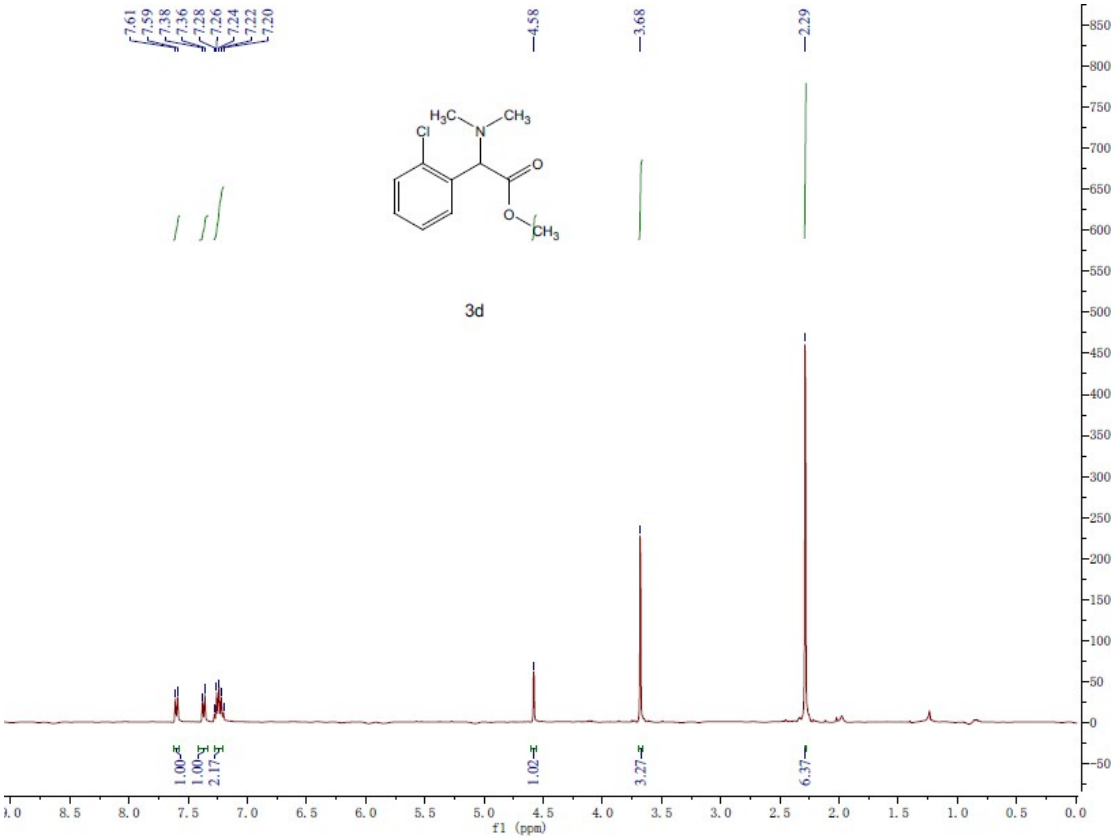
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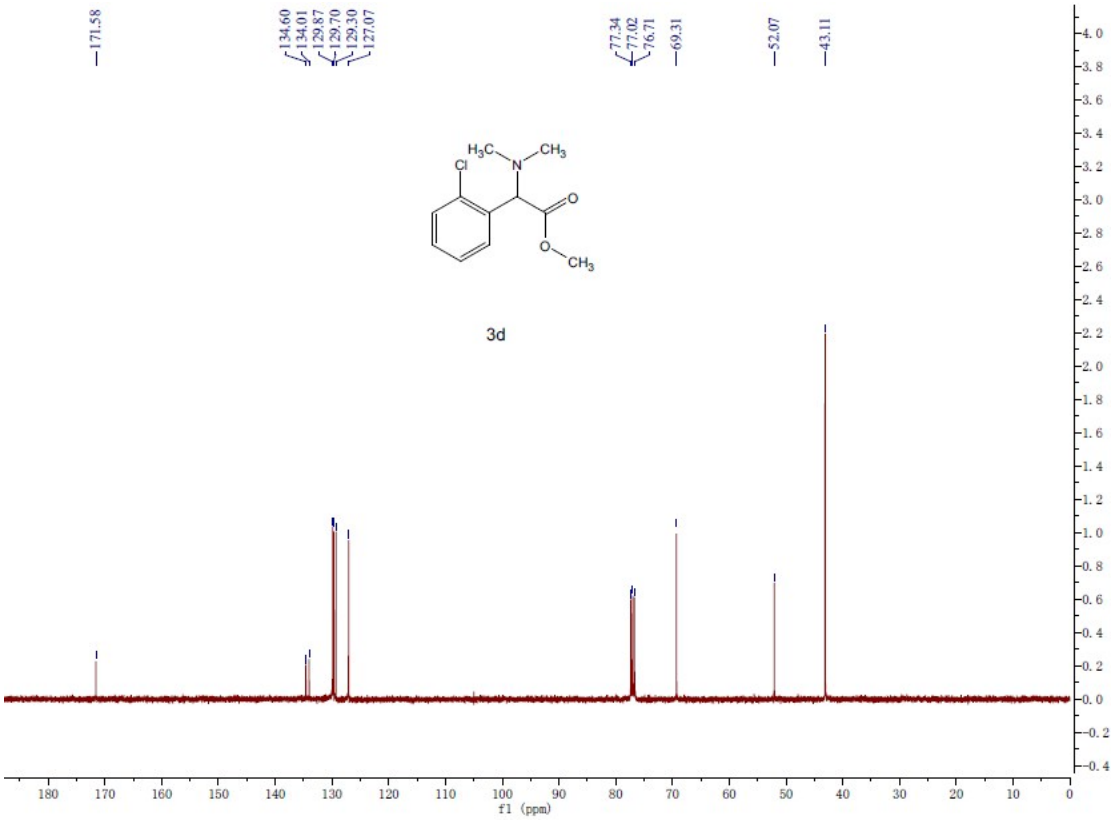
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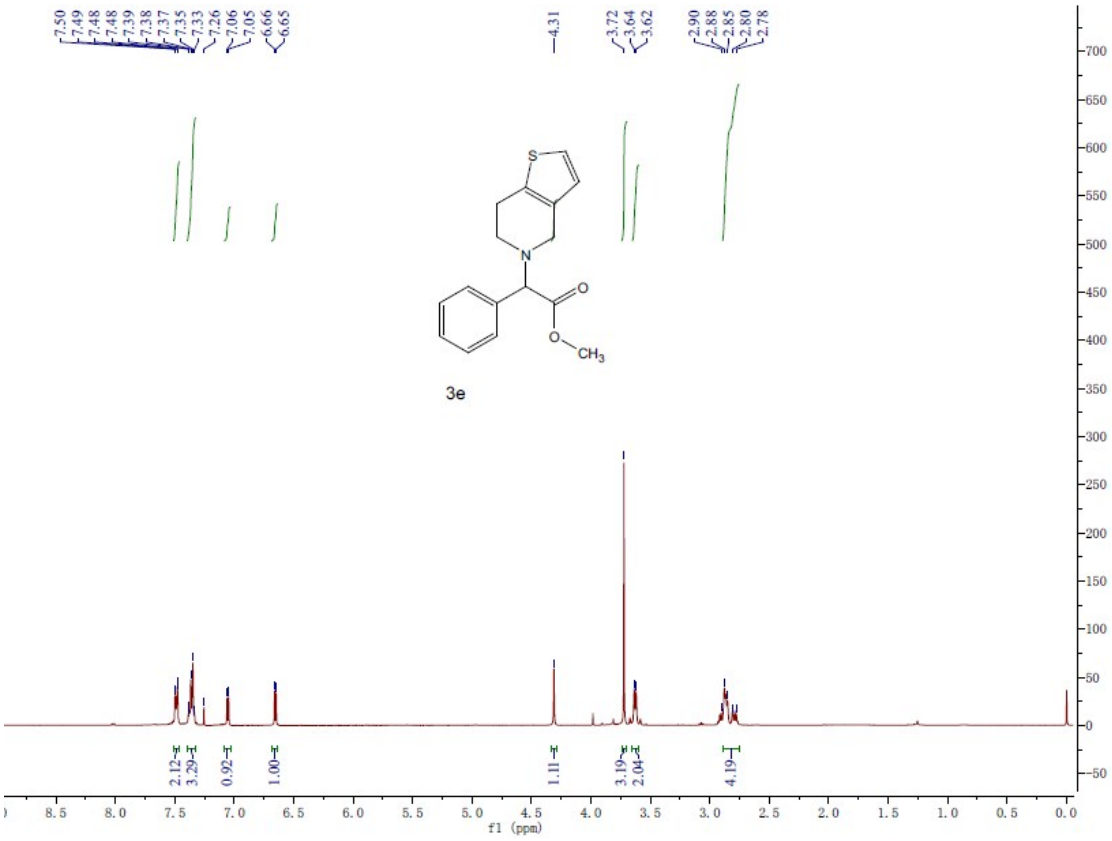
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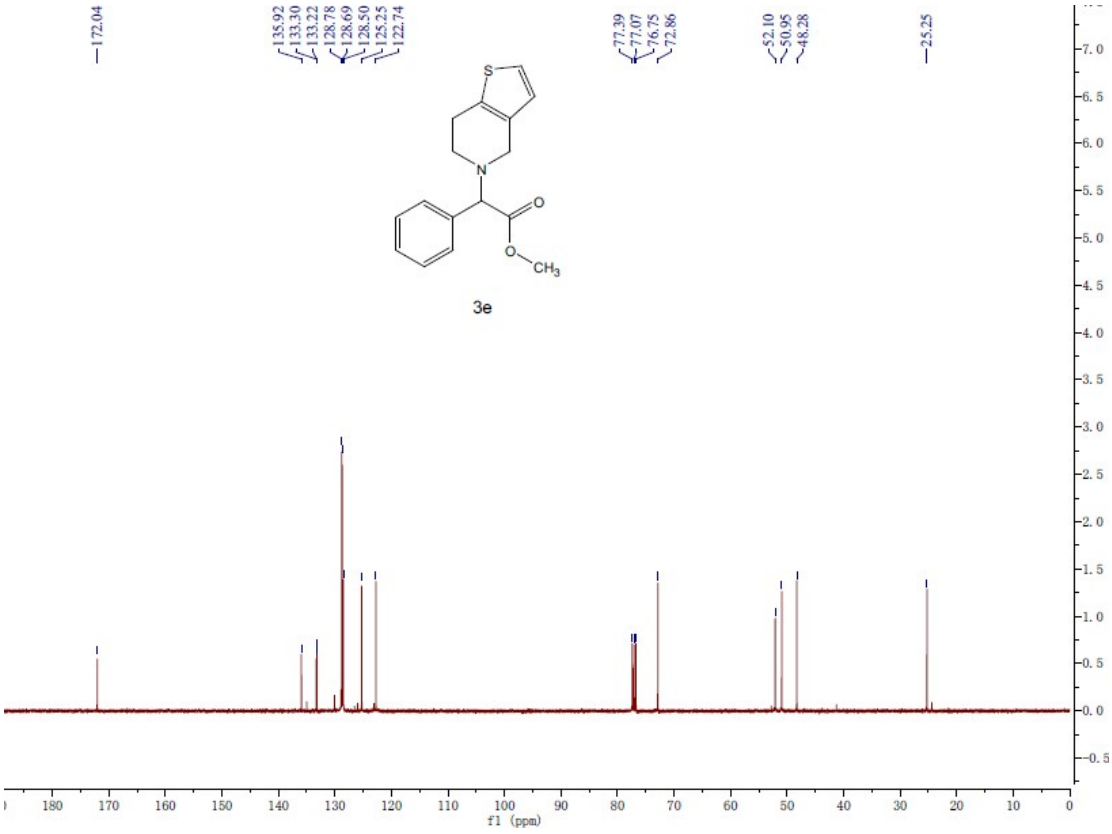
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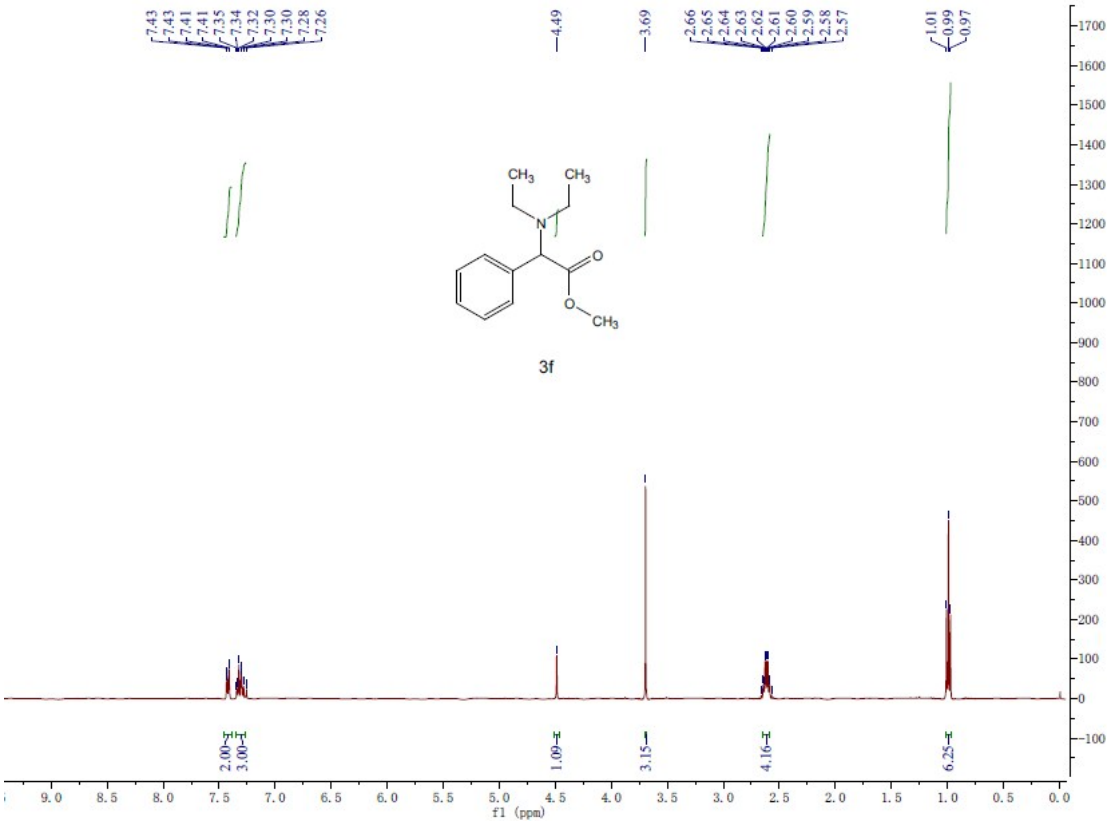
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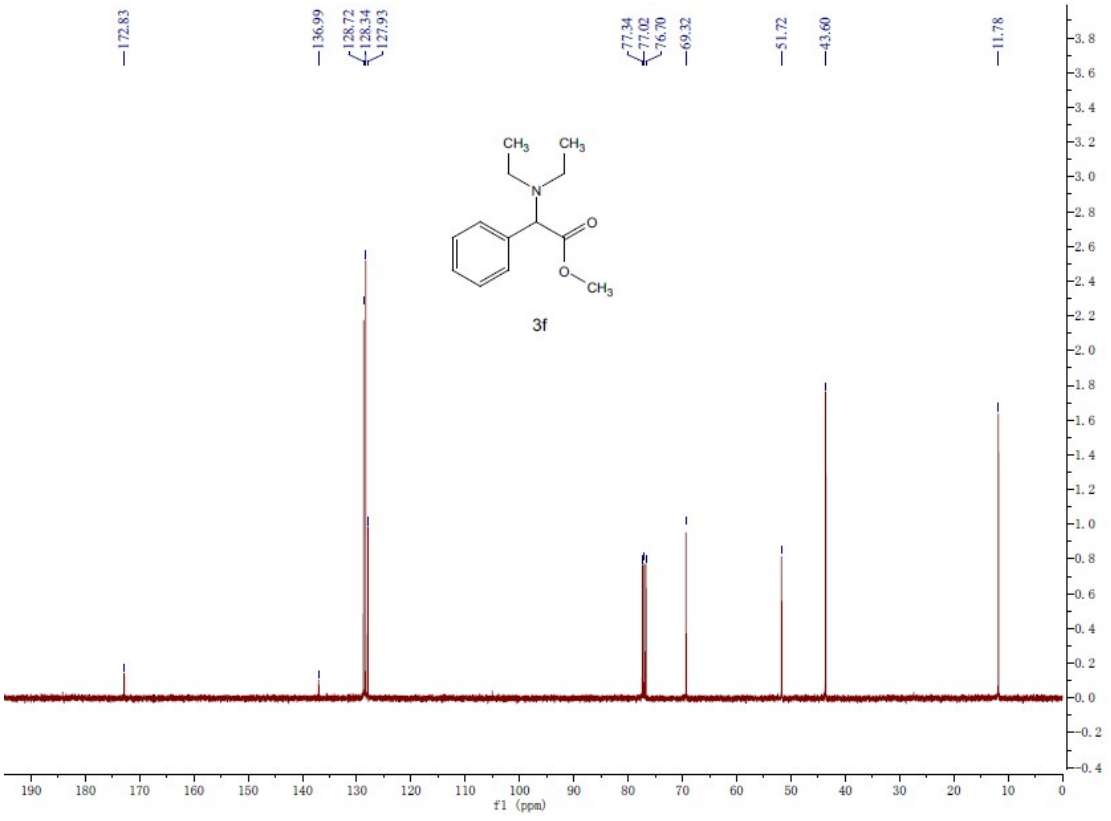
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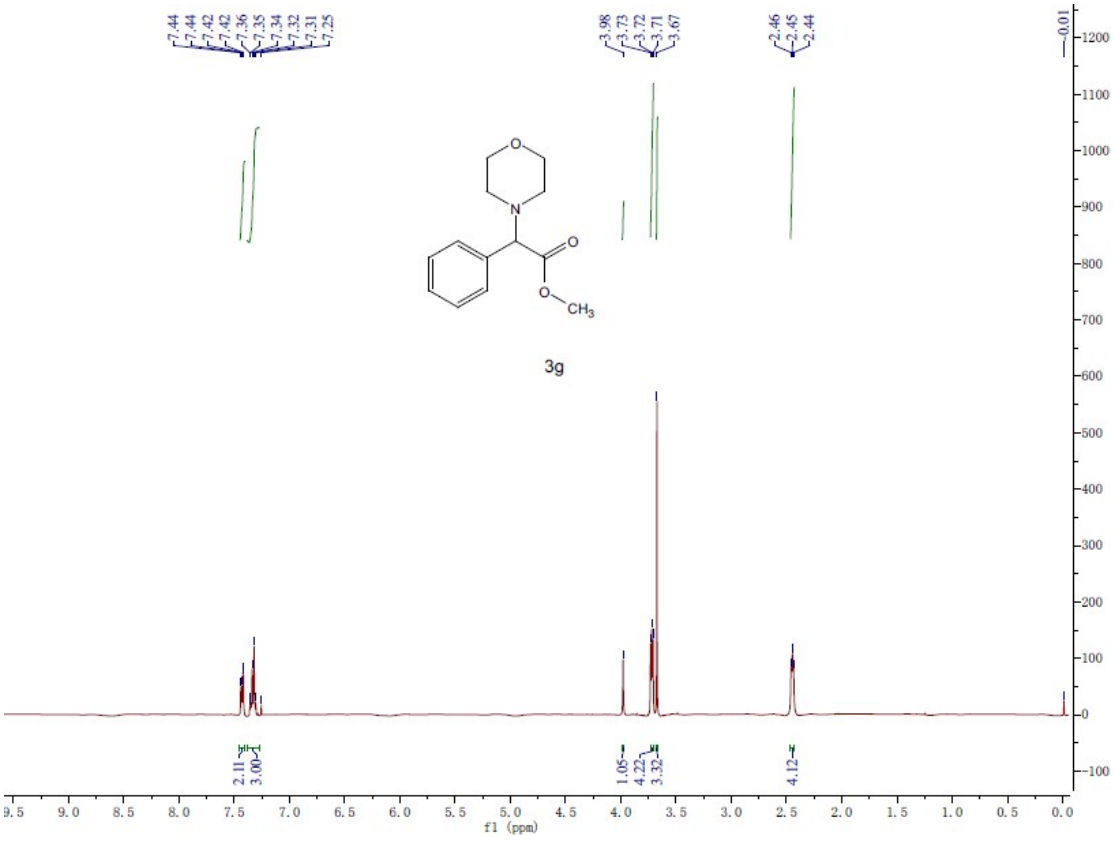
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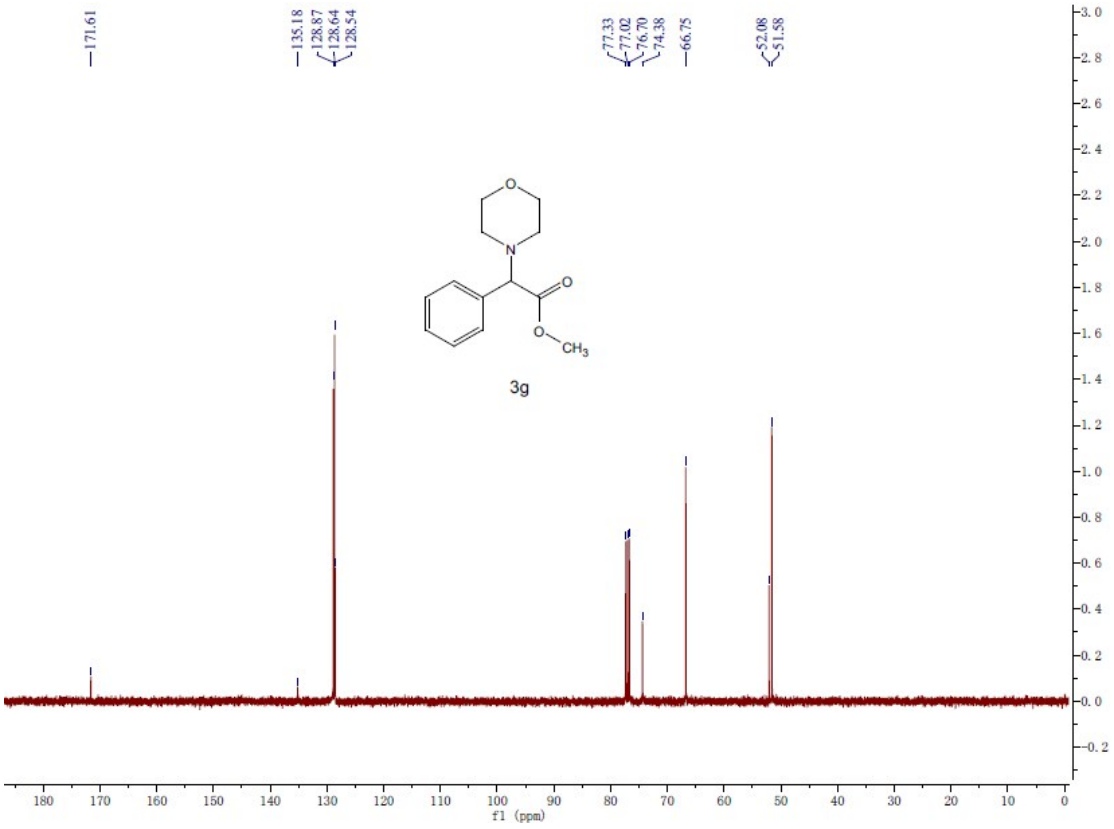
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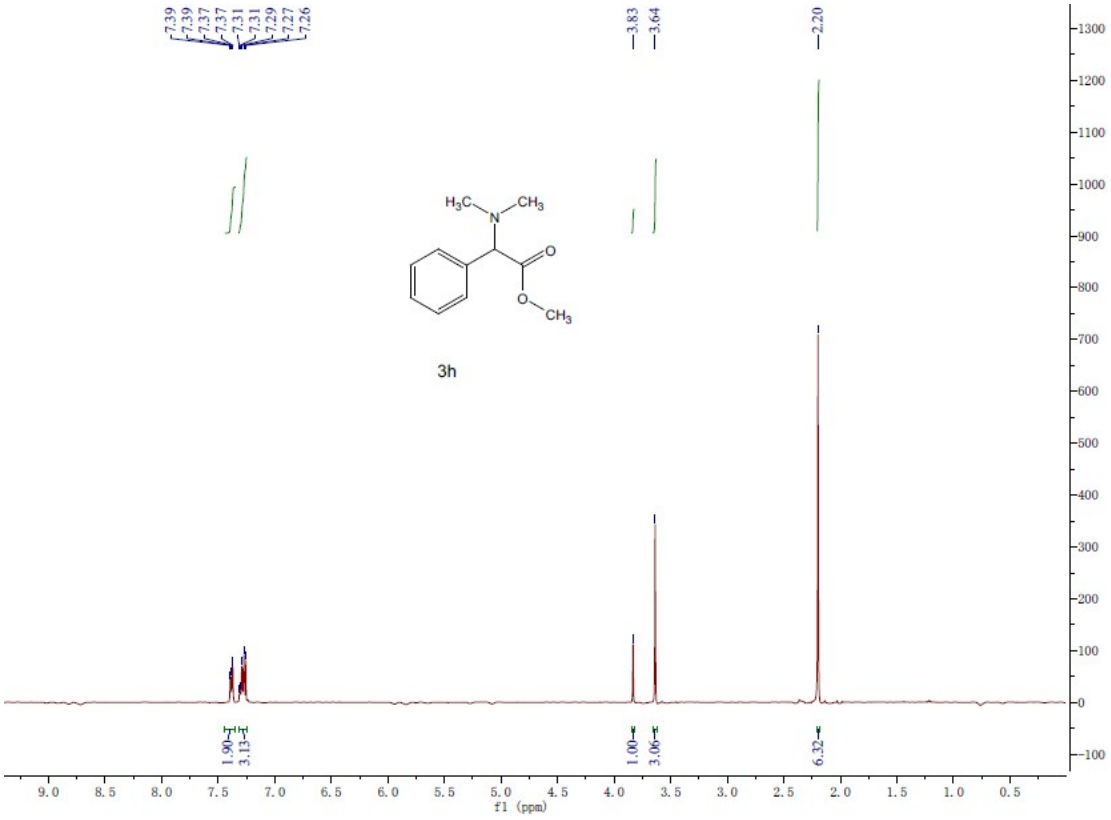
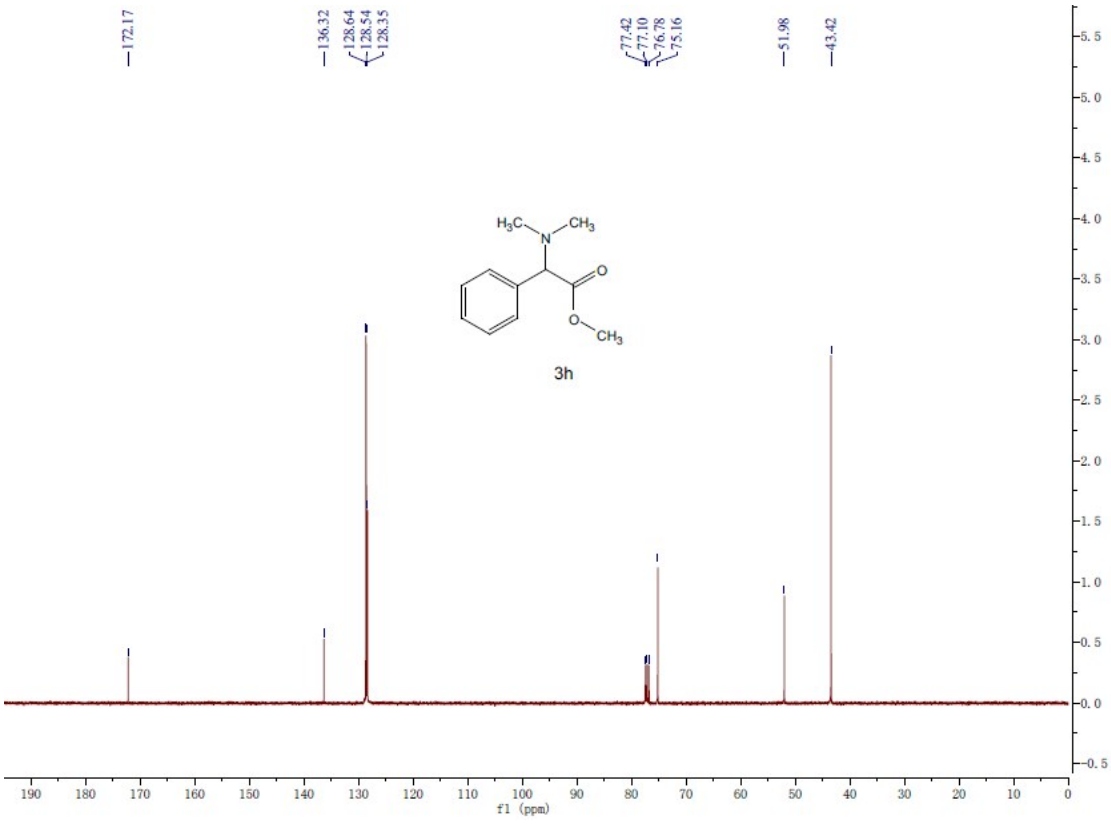
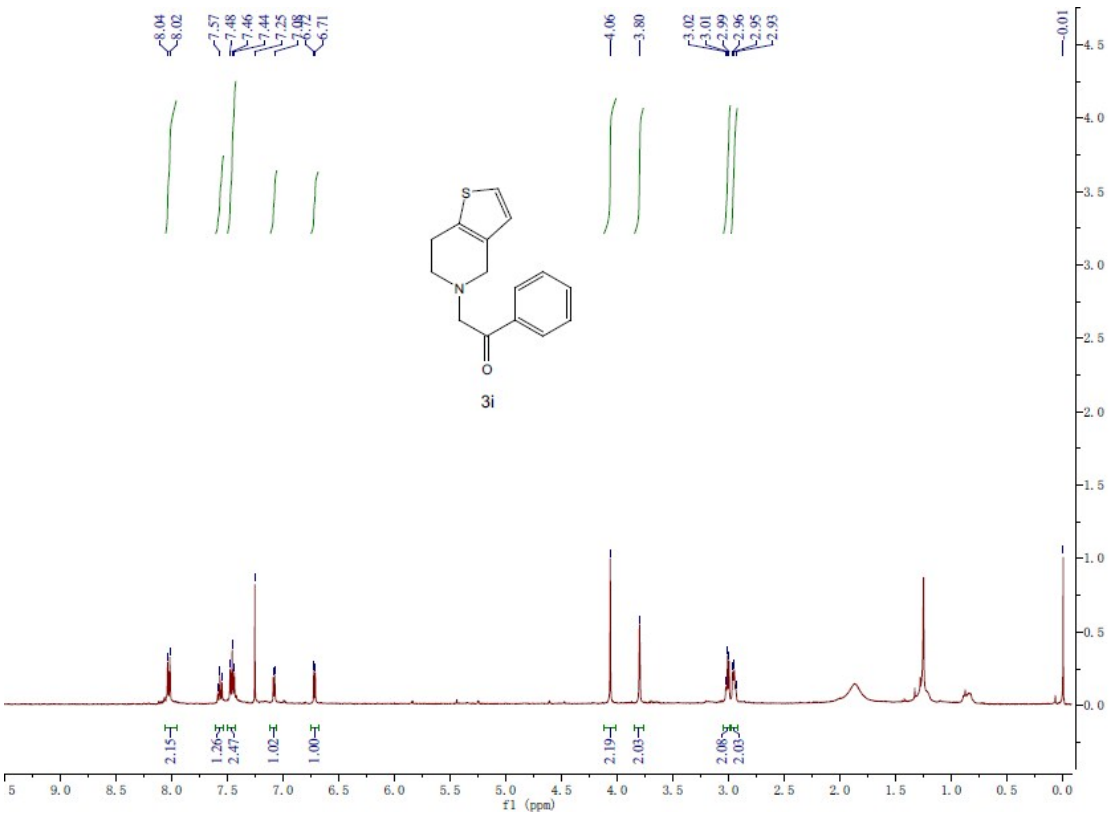
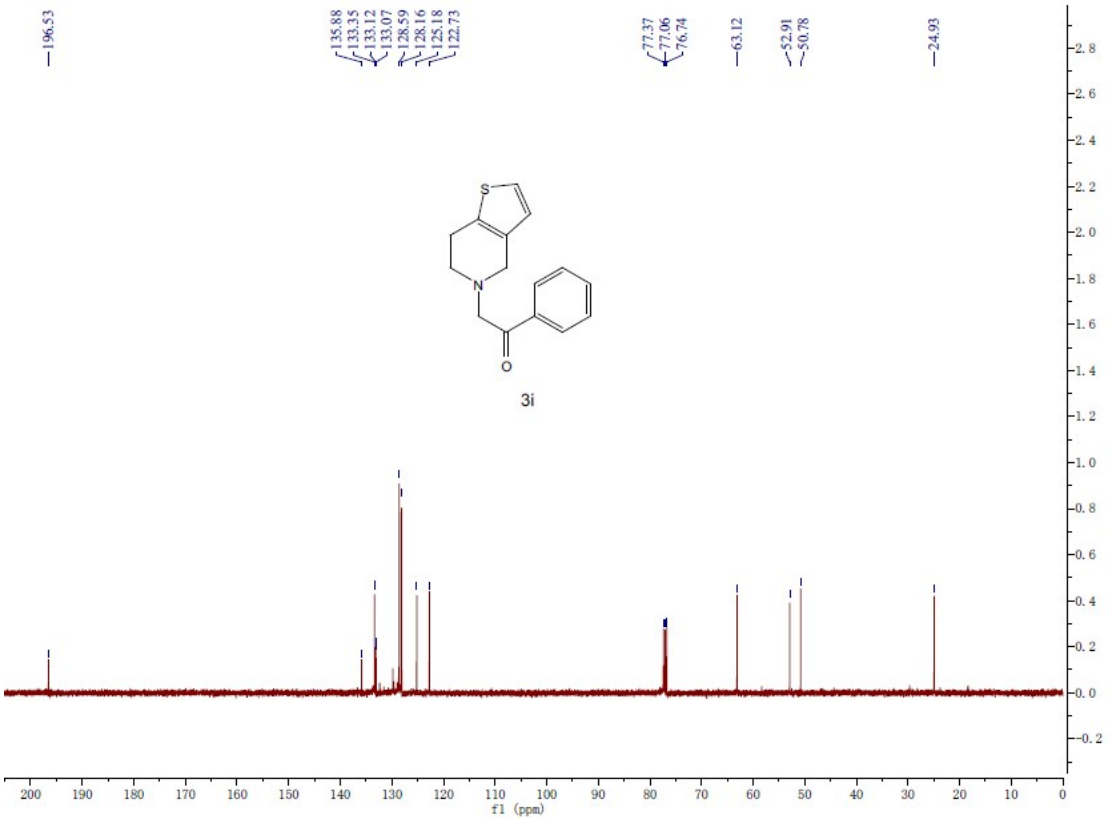
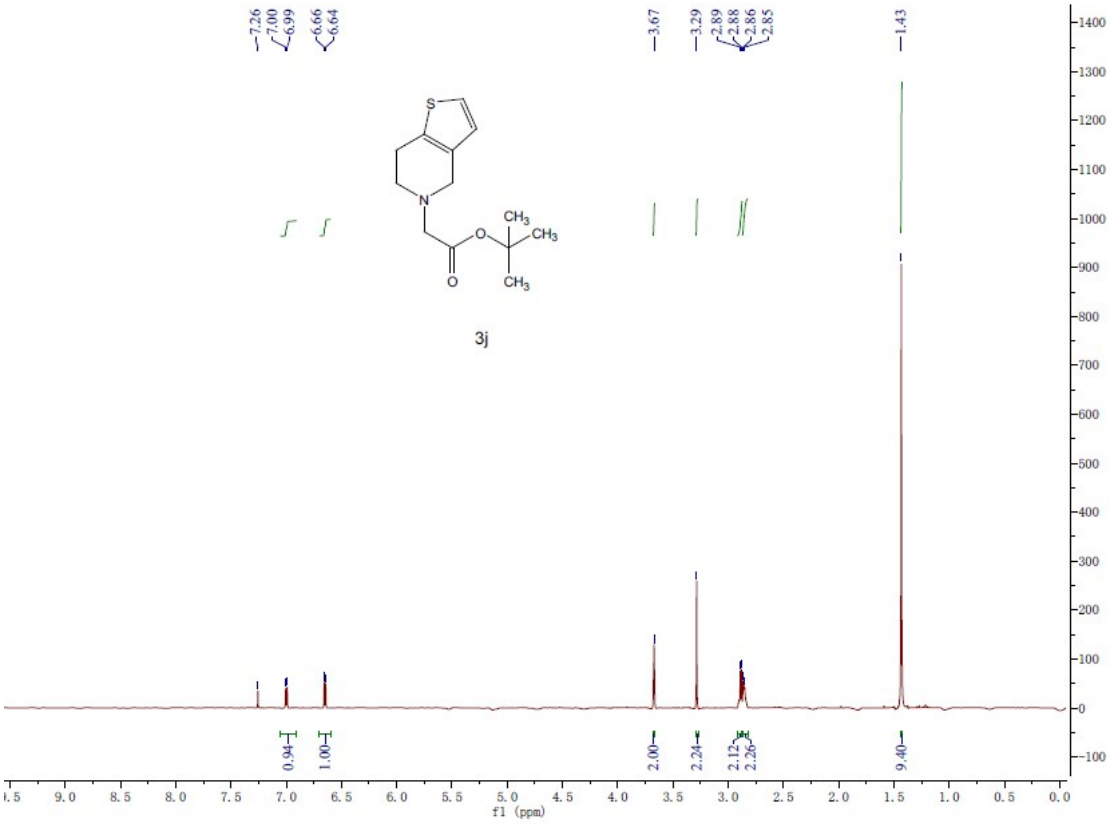
f1 (ppm)

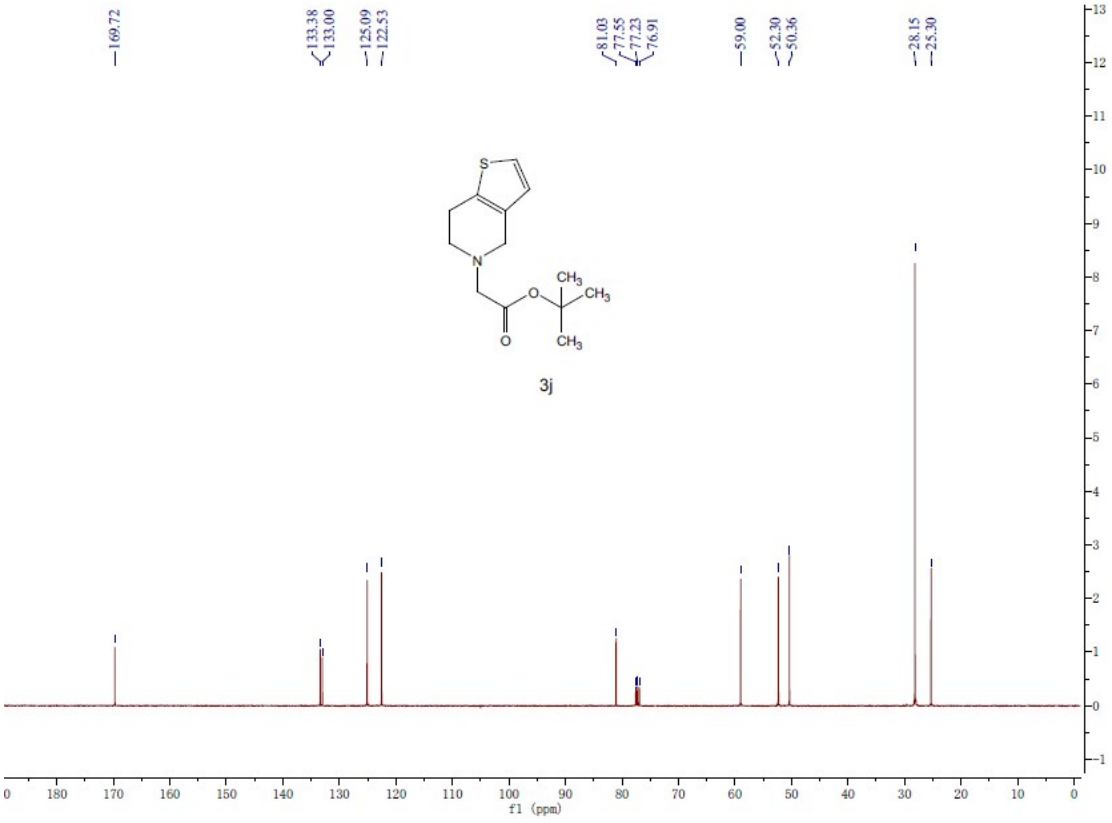

7.39
7.39
7.37
7.37
7.31
7.31
7.29
7.27
7.26
3.83
3.64
2.20
H3C
N
CH3
O
O
CH3
3h
1.90
3.13
1.00
3.06
6.32
f1 (ppm)

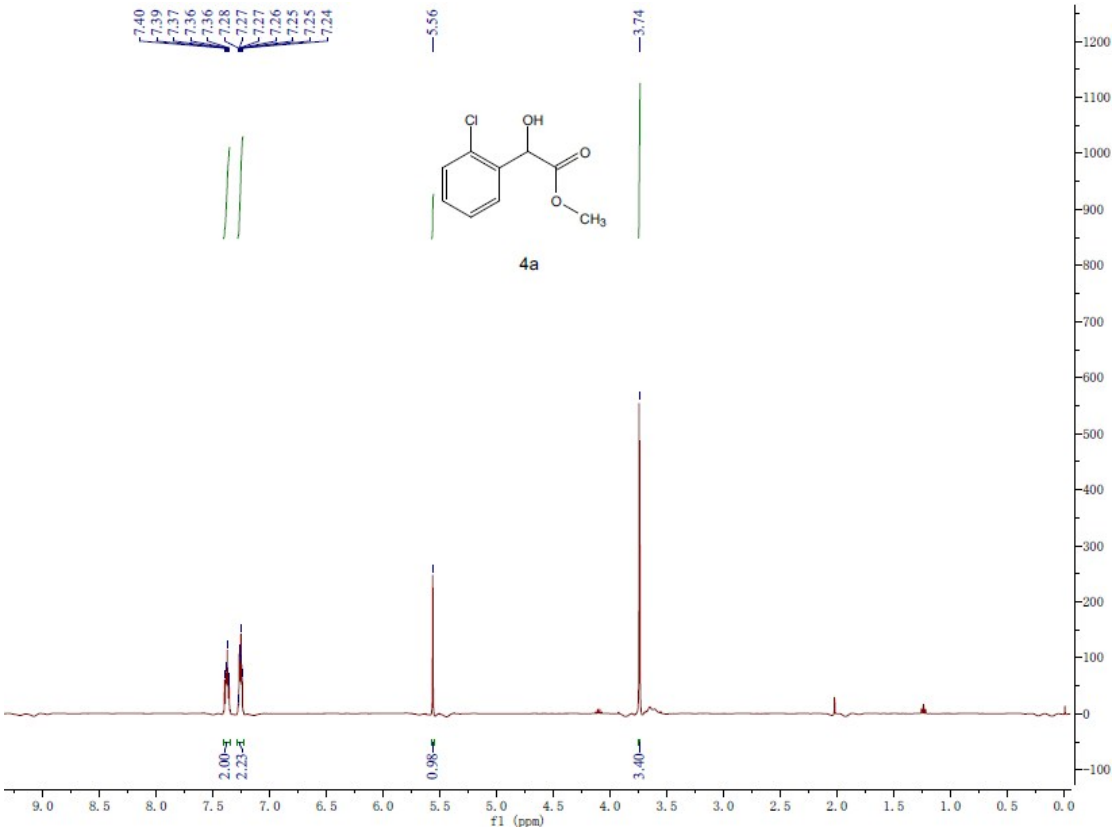

172.17
136.32
128.64
128.54
128.35
77.42
77.10
76.78
75.16
51.98
43.42
H3C
N
CH3
O
O
CH3
3h
f1 (ppm)

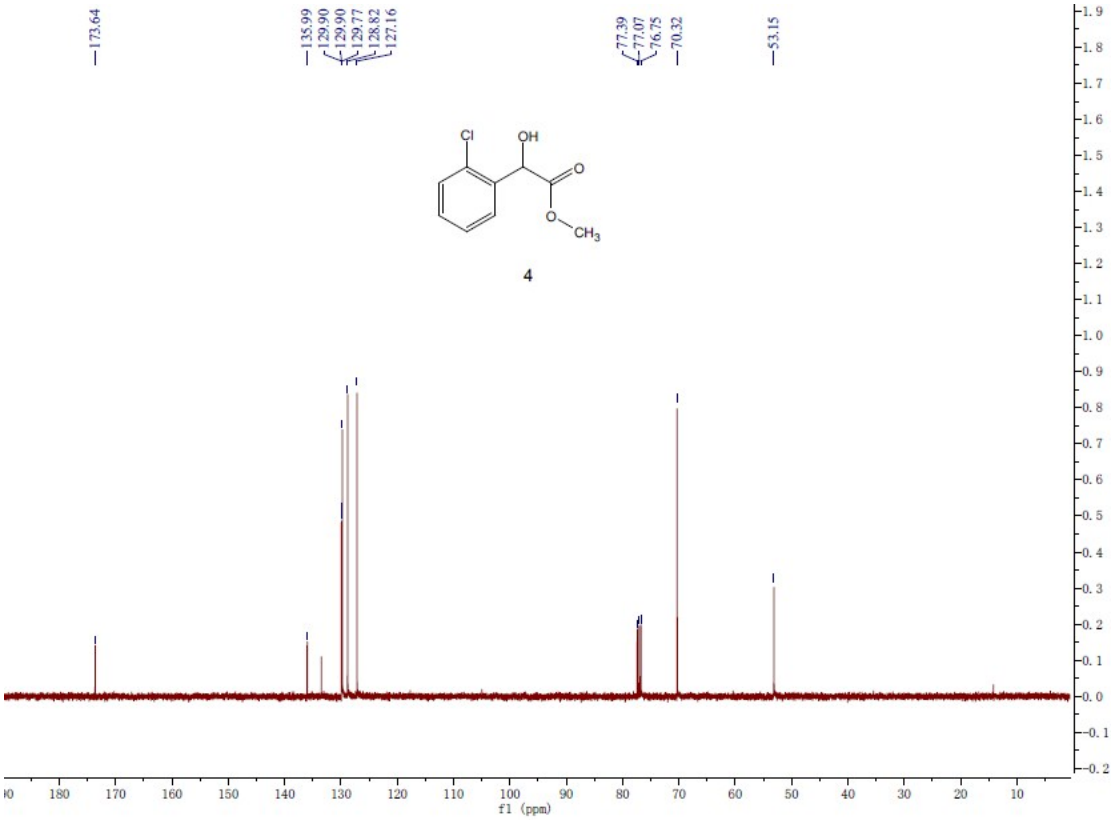

8.04
8.02
7.57
7.48
7.46
7.44
7.25
6.71
4.06
3.80
3.02
3.01
2.99
2.96
2.95
2.93
0.01
2.15
1.26
2.47
1.02
1.00
2.19
2.03
2.08
2.03
f1 (ppm)
3i

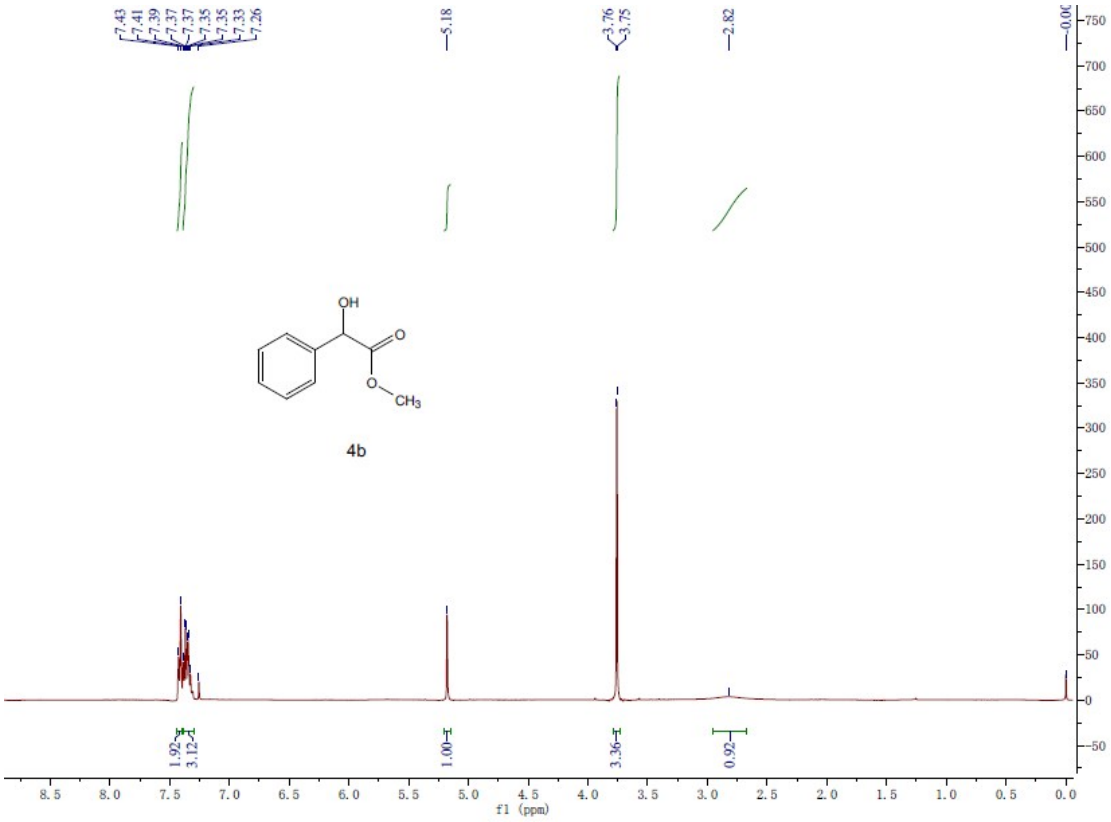

196.53
135.88
133.35
133.12
133.07
128.59
128.16
125.18
122.73
77.37
77.06
76.74
63.12
52.91
50.78
24.93
f1 (ppm)
3i

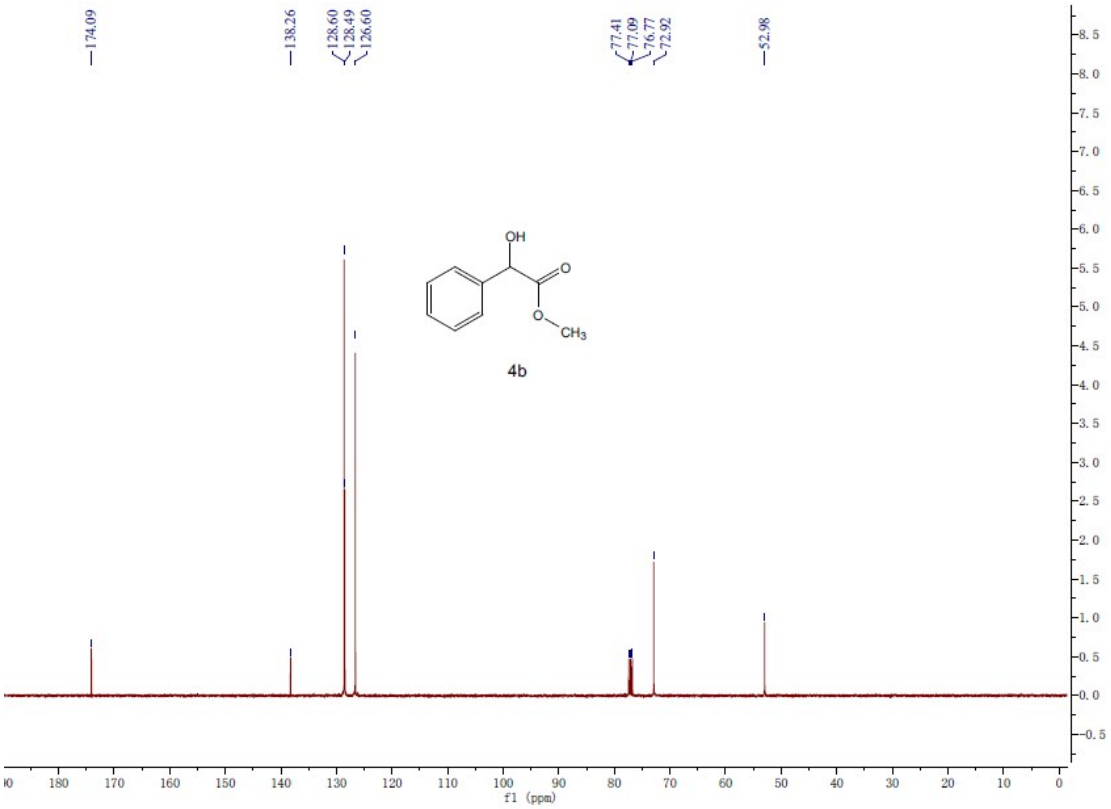

7.26
7.00
6.99
6.66
6.64
3.67
3.29
2.89
2.88
2.86
2.85
1.43
S
N
O
O
CH3
CH3
CH3
3j
0.94
1.00
2.00
2.24
2.12
2.26
9.40
f1 (ppm)

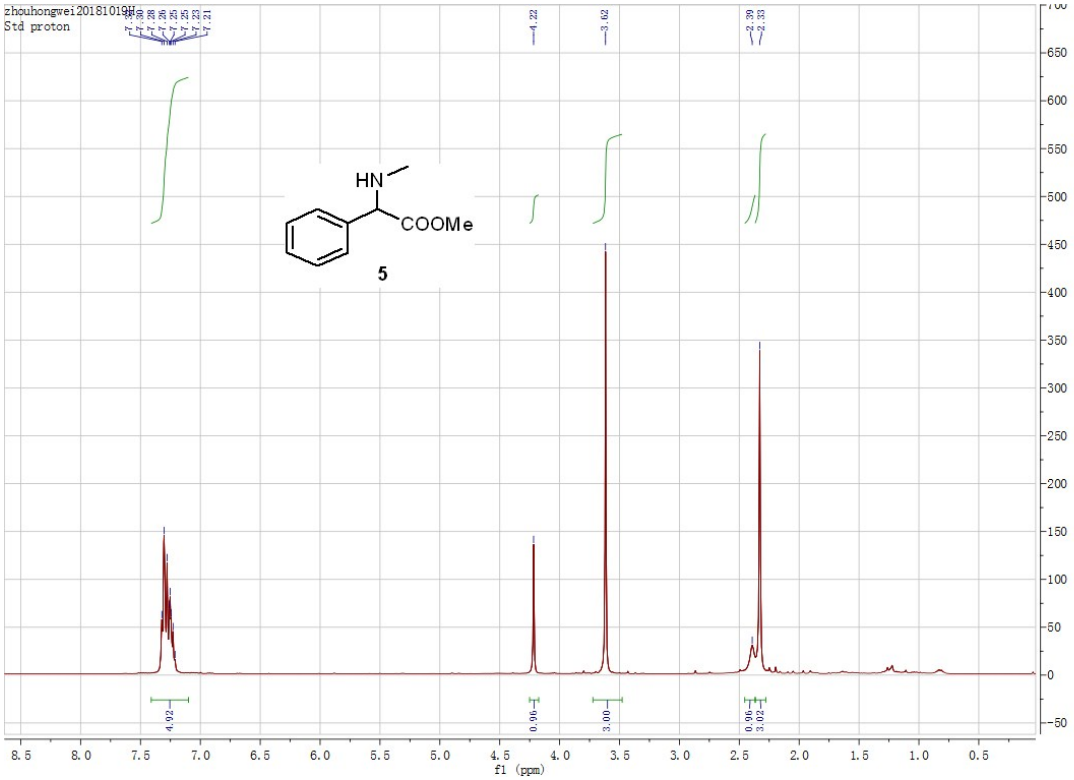

169.72
133.38
133.00
125.09
122.53
81.03
77.55
77.23
76.91
59.00
52.30
50.36
28.15
25.30
S
N
O
O
CH3
CH3
CH3
3j
f1 (ppm)

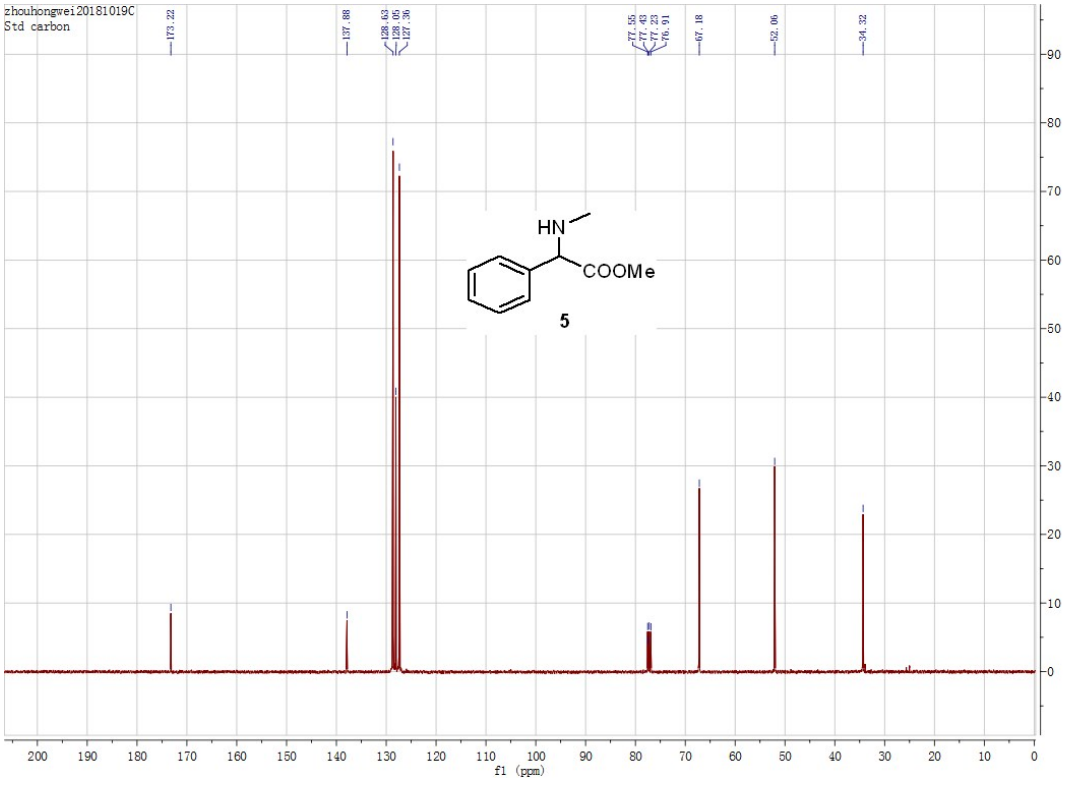

7.40
7.39
7.37
7.36
7.36
7.28
7.27
7.27
7.26
7.25
7.25
7.24
5.56
3.74
Cl
OH
O
O
CH3
4a
2.00
2.23
0.98
3.40
f1 (ppm)


173.64
135.99
129.90
129.90
129.77
128.82
127.16
77.39
77.07
76.75
70.32
53.15
Cl
OH
O
O
CH3
4
f1 (ppm)


7.43
7.41
7.39
7.37
7.37
7.35
7.35
7.33
7.26
5.18
3.76
3.75
2.82
0.00
OH
O
O
CH3
4b
1.92
3.12
1.00
3.36
0.92
f1 (ppm)


174.09
138.26
128.60
128.49
126.60
77.41
77.09
76.77
72.92
52.98
OH
O
O
CH3
4b
f1 (ppm)


zhouhongwei20181019H
Std proton
HN
COOMe
5
fl (ppm)


zhouhongwei20181019C
Std carbon
HN
COOMe
5
fl (ppm)