A Cascade Dehydrogenative Cross-Coupling / Annulation Reaction of Benzamides with *β*-Keto Esters for Synthesis of Isoquinolinone Derivatives

Guo-Dong Xu[a], Zhi-Zhen Huang*[,a]

[a]Department of Chemistry, Zhejiang University, Hangzhou 310028, P. R. China

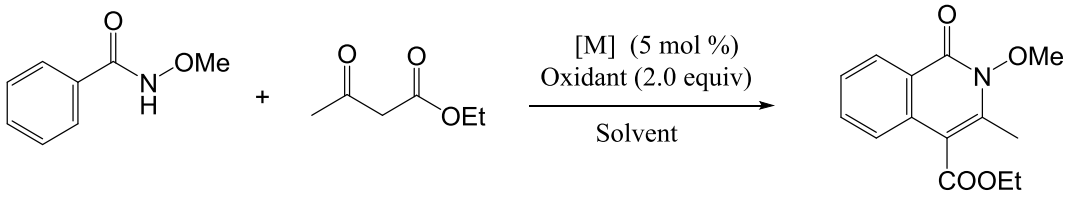
Supporting Information

Contents

1. General Information

Unless otherwise indicated, all reagents were purchased from commercial distributors and used without further purification. ^{1}H NMR and ^{13}C NMR were recorded at 400 MHz and 100 MHz respectively, using tetramethylsilane as an internal reference. Mass spectroscopy data were collected on HRMS-EI instrument. Column chromatography was performed over silica gel 200-300. *N*-Alkoxybenzamides **1** were prepared according to previous literatures.[1]

2. Optimization of the DCC Reaction Conditions



1a **2a** **3aa**

Table S1. Screening of Reaction Conditions.[a]

entry	[M]	oxidant	solvent	yield (%)[b]
1	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH	43
2	$Pd(TFA)_2$	$K_2S_2O_8$	AcOH	56
3	$PdCl_2$	$K_2S_2O_8$	AcOH	trace
4	$Pd(PPh_3)_4$	$K_2S_2O_8$	AcOH	0
5	$[Cp^*RhCl_2]_2$	$K_2S_2O_8$	AcOH	0
6	$[Cp^*IrCl_2]_2$	$K_2S_2O_8$	AcOH	0
7	-	$K_2S_2O_8$	AcOH	0
8	$Pd(TFA)_2$	-	AcOH	0
9	$Pd(TFA)_2$	TBHP	AcOH	50
10	$Pd(TFA)_2$	DTBP	AcOH	trace
11	$Pd(TFA)_2$	DDQ	AcOH	trace
12	$Pd(TFA)_2$	Ag_2O	AcOH	0
13	$Pd(TFA)_2$	$K_2S_2O_8$	THF	42

14	$Pd(TFA)_2$	$K_2S_2O_8$	GDE	30
15	$Pd(TFA)_2$	$K_2S_2O_8$	DCE	19
16	$Pd(TFA)_2$	$K_2S_2O_8$	toluene	8.3
17	$Pd(TFA)_2$	$K_2S_2O_8$	DMF	0
18[c]	$Pd(TFA)_2$	$K_2S_2O_8$	AcOH	68
19[cd]	$Pd(TFA)_2$	$K_2S_2O_8$	AcOH	61
20[ce]	$Pd(TFA)_2$	$K_2S_2O_8$	AcOH	41
21[cf]	$Pd(TFA)_2$	$K_2S_2O_8$	AcOH	76
22[cfg]	$Pd(TFA)_2$	$K_2S_2O_8$	AcOH	84

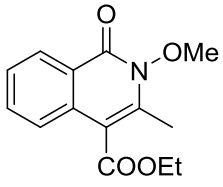
a) Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [M] (5 mol %), oxidant (2.0 equiv), solvent (2.5 mL), 80 ºC, for 12 h. b) Isolated yields. c) 24 h. d) 40 ºC. e) 100 ºC. f) 60 ºC. g) air.

3. Experimental Procedure

General procedure for the cascade DCC / annulation reaction of *N*-alkoxybenzamides **1** with *β*-keto esters **2** for isoquinolone derivatives **3**: The mixture of *N*-methoxybenzamides **1** (0.20 mmol), *β*-keto esters **2** (0.40 mmol), $Pd(TFA)_2$ (3.3 mg, 0.01 mmol, 5 mol %), $K_2S_2O_8$ (108.1mg, 0.40 mmol) in AcOH (2.5 mL) was stirred at 60 ^oC for 24 h. Then, the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether = 1/2 as eluent) to give desired isoquinolone derivatives **3**.

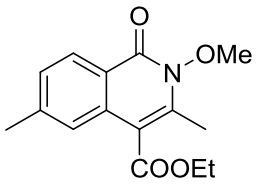
4. Characterization of Isoquinolone Derivatives 3

Ethyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3aa**[2]



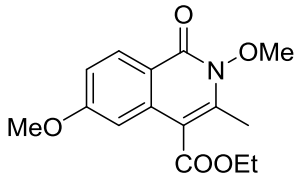
Yield: 84% (43.8 mg); Light yellow oil; ^1H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.31 (d, J = 8.0 Hz, 1 H), 7.58-7.52 (m, 2 H), 7.37-7.33 (m, 1 H), 4.36 (q, J = 7.0 Hz, 2 H), 3.98 (s, 3 H), 2.44 (s, 3 H), 1.32 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.7, 158.1, 140.7, 133.0, 132.8, 127.7, 126.5, 125.3, 123.9, 109.6, 63.8, 61.6, 14.9, 14.2.

Ethyl 2-methoxy-3,6-dimethyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ba**[2]



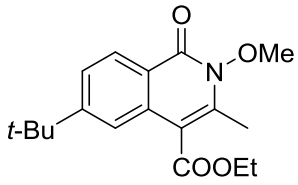
Yield: 87% (47.9 mg); Light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.23 (s, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 7.48 (dd, J = 8.0, 4.0 Hz, 1 H), 4.46 (q, J = 8.0 Hz, 2 H), 4.08 (s, 3 H), 2.45 (s, 3 H), 2.47 (s, 3 H), 1.43 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.9, 158.2, 139.8, 136.8, 134.4, 130.8, 127.3, 125.3, 123.9, 109.6, 63.8, 61.6, 21.2, 14.9, 14.3.

Ethyl 2,6-dimethoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ca**[2]



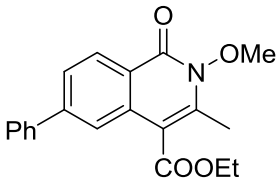
Yield: 78% (45.4 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.25 (d, J = 8.0 Hz, 1 H), 7.01 (d, J = 2.4 Hz, 1 H), 6.96 (dd, J = 8.8, 2.4 Hz, 1 H), 4.39 (q, J = 7.2 Hz, 2 H), 4.00 (s, 3 H), 3.81 (s, 3 H), 2.46 (s, 3 H), 1.36 (t, J =7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.9, 163.2, 157.9, 141.7, 135.1, 129.8, 119.0, 115.9, 109.0, 105.5, 63.9, 61.6, 55.4, 15.1, 14.3.

Ethyl 6-(tert-butyl)-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3da**[2]



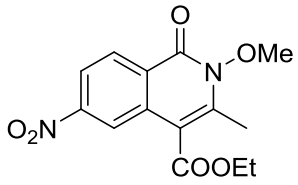
Yield: 70% (44.4 mg); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.27 (d, J = 8.4 Hz, 1 H), 7.56 (d, J = 2 Hz, 1 H), 7.46 (dd, J = 8.6, 1.8 Hz, 1 H), 4.40 (q, J = 7.2 Hz, 2 H), 4.00 (s, 3 H), 2.47 (s, 3 H), 1.38(t, J = 6.6 Hz, 3 H), 1.28 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.0, 157.1, 155.3, 139.6, 131.9, 126.5, 123.8, 122.0, 118.9, 108.8, 62.8, 60.5, 34.3, 30.0, 13.9, 13.3.

Ethyl 2-methoxy-3-methyl-1-oxo-6-phenyl-1,2-dihydroisoquinoline-4-carboxylate **3ea**



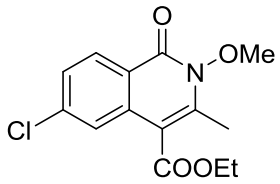
Yield: 66% (44.5 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.39 (d, J = 8.4 Hz, 1 H), 7.79 (d, J = 1.2 Hz, 1 H), 7.61 (dd, J = 8.4, 1.6 Hz, 1 H), 7.56-7.54 (m, 2 H), 7.41-7.37 (m, 2 H), 7.34-7.30 (m, 1 H)，4.40 (q, J = 7.0 Hz, 2 H), 4.02 (s, 3 H), 2.48 (s, 3 H), 1.36 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.8, 158.1, 145.6, 141.3, 140.1, 133.5, 129.0, 128.4, 128.3, 127.5, 125.9, 124.2, 122.3, 109.7, 63.9, 61.7, 15.1, 14.4; HR-MS (EI-TOF) (M^+) calculated for $C_{20}H_{19}NO_4$ 337.1314, found 337.1312.

Ethyl 6-fluoro-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3fa**[2]



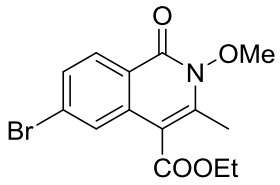
Yield: 84% (51.4 mg); Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.62 (d, J = 2.0 Hz, 1 H), 8.51 (d, J = 4.8 Hz, 1 H), 8.14 (dd, J = 8.8, 5.0 Hz, 1 H), 4.45 (q, J = 7.1 Hz, 2 H), 4.05 (s, 3 H), 2.57 (s, 3 H), 1.41 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 165.7, 157.0, 150.5, 144.6, 133.9, 129.9, 128.7, 120.3, 120.1, 109.0, 64.1, 62.2, 15.3, 14.3.

Ethyl 6-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ga**[2]



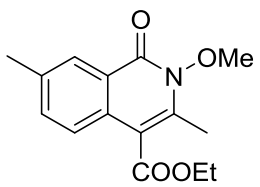
Yield: 76% (44.8 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.35 (d, J = 8.4 Hz, 1 H), 7.72 (d, J = 1.6 Hz, 1 H), 7.42 (dd, J = 8.6, 1.8 Hz, 1 H), 4.48 (q, J = 7.2 Hz, 2 H), 4.09 (s, 3 H), 2.57 (s, 3 H), 1.45 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.2, 157.6, 142.7, 139.6, 134.3, 129.51, 127.2, 123.61, 123.57, 108.5, 64.0, 61.9, 15.2, 14.3.

Ethyl 6-bromo-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ha**[2]



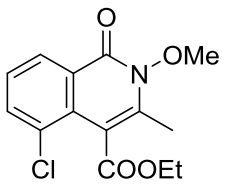
Yield: 67% (45.4 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.20 (d, J = 8.4 Hz, 1 H), 7.82 (d, J = 6.4 Hz, 1 H), 7.49 (dd, J = 8.6, 1.8 Hz, 1 H), 4.40 (q, J = 7.2 Hz, 2 H), 4.01 (s, 3 H), 2.49 (s, 3 H), 1.37 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.2, 157.8, 142.7, 134.5, 130.0, 129.5, 128.3, 126.7, 123.9, 108.4, 64.0, 61.9, 15.2, 14.3.

Ethyl 2-methoxy-3,7-dimethyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ia**[2]



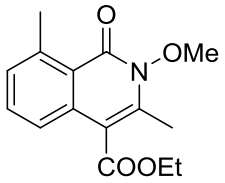
Yield: 80% (44.0 mg); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.14 (s, 1 H), 7.05 (d, J = 8.4 Hz, 1 H), 7.40 (dd, J = 8.4, 2.0 Hz, 1 H), 4.38 (q, J = 7.1 Hz, 2 H), 4.00 (s, 3 H), 2.46 (s, 3 H), 2.39 (s, 3 H), 1.35 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.9, 158.2, 139.8, 136.8, 134.4, 130.8, 127.3, 125.3, 123.9, 109.6, 63.8, 61.6, 21.2, 14.9, 14.3.

Ethyl 5-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ja**



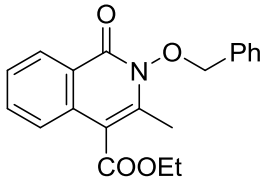
Yield: 64% (37.8 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.40 (d, J = 2.4 Hz, 1 H), 7.67 (d, J = 8.8 Hz, 1 H), 7.60 (dd, J = 8.8, 2.4 Hz, 1 H), 4.47 (q, J = 7.2 Hz, 2 H), 4.09 (s, 3 H), 2.56 (s, 3 H), 1.44 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.5, 157.2, 141.5, 133.3, 132.8, 131.6, 127.2, 126.5, 125.8, 109.1, 64.0, 61.9, 15.1, 14.3; HR-MS (EI-TOF) (M^+) calculated for $C_{14}H_{14}ClNO_4$ 295.0611, found 295.0612.

Ethyl 2-methoxy-3,8-dimethyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ka**[2]



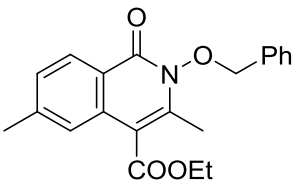
Yield: 87% (47.9 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 7.40 (t, J = 7.8 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.14 (d, J = 7.2 Hz, 1 H), 4.37 (q, J = 7.2 Hz, 2 H), 3.98 (s, 3 H), 2.85 (s, 3 H), 2.41 (s, 3 H), 1.35 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.3, 157.9, 141.2, 138.7, 133.6, 130.9, 128.7, 122.7, 120.8, 108.8, 62.7, 60.6, 22.8, 13.9, 13.2.

Ethyl 2-(benzyloxy)-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3la**



Yield: 62% (41.8 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.49-8.46 (m, 1 H), 7.71-7.66 (m, 2 H), 7.57-7.54 (m, 2 H), 7.53-7.48 (m, 1 H), 7.45-7.40 (m, 3 H), 5.26 (s, 2 H), 4.46 (q, J = 7.2 Hz, 2 H), 2.48 (s, 3 H), 1.43 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.9, 158.5, 141.2, 133.7, 133.2, 132.9, 129.9, 129.4, 128.8, 127.8, 126.7, 125.4, 123.9, 109.5, 78.1, 61.7, 15.5, 14.3; HR-MS (EI-TOF) (M^+) calculated for $C_{20}H_{19}NO_4$ 337.1314, found 337.1312.

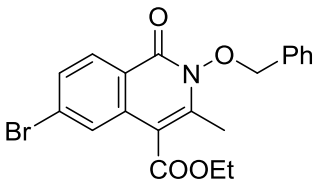
Ethyl 2-(benzyloxy)-3,6-dimethyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ma**



Yield: 79% (55.5 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.36 (d, J = 8.0 Hz, 1 H), 7.56-7.54 (m, 2 H), 7.45 (s, 1 H), 7.43-7.40 (m, 3 H), 7.32 (dd, J = 8.0, 1.6 Hz, 1 H), 5.26 (s, 2 H), 4.46 (q, J = 7.2 Hz, 2 H), 2.48 (s, 3 H), 2.45 (s, 3 H), 1.43 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 167.0, 158.5, 143.6, 141.0, 133.8, 133.3, 129.9, 129.4, 128.8, 128.3, 127.8, 123.6,

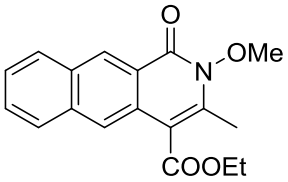
123.2, 109.3, 78.1, 61.6, 22.2, 15.5, 14.3; HR-MS (EI-TOF) (M^+) calculated for $C_{21}H_{21}NO_4$ 351.1471, found 351.1470.

Ethyl 2-(benzyloxy)-6-bromo-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3na**



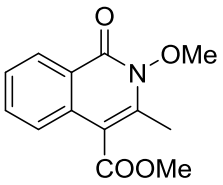
Yield: 62% (51.5 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.30 (d, J = 8.4 Hz, 1 H), 7.91 (d, J = 2.0 Hz, 1 H), 7.58 (dd, J = 8.6, 1.8 Hz, 1 H), 7.54-7.52 (m, 2 H), 7.42-7.40 (m, 3 H), 5.25 (s, 2 H), 4.45 (q, J = 7.2 Hz, 2 H), 2.47 (s, 3 H), 1.43 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.3, 158.1, 143.2, 134.6, 133.5, 130.0, 129.9, 129.5, 128.8, 128.4, 126.8, 124.0, 108.3, 78.2, 61.9, 15.7, 14.3; HR-MS (EI-TOF) (M^+) calculated for $C_{20}H_{18}BrNO_4$ 415.0419, found 415.0419.

Ethyl 2-methoxy-3-methyl-1-oxo-1,2-dihydrobenzo[g]isoquinoline-4-carboxylate **3oa**



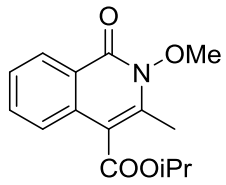
Yield: 46% (28.6 mg); Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.95 (s, 1 H), 8.05 (s, 1 H), 7.95 (d, J = 8.4 Hz, 1 H), 7.83 (d, J = 8.4 Hz, 1 H), 7.53-7.42 (m, 2 H), 4.46 (q, J = 7.2 Hz, 2 H), 4.0 3(s, 3 H), 2.49 (s, 3 H), 1.40 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 167.1, 158.8, 139.7, 135.4, 131.2, 129.22, 129.17, 128.8, 128.5, 128.1, 126.5, 123.5, 122.7, 109.6, 64.0, 61.7, 15.2, 14.4; HR-MS (EI-TOF) (M^+) calculated for $C_{18}H_{17}NO_4$ 311.1158, found 311.1155.

Methyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ab**[2]



Yield: 83% (41.0 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.44 (d, J = 8.0 Hz, 1 H), 7.69-7.65 (m, 2 H), 7.52-7.45 (m, 1 H), 4.09 (s, 3 H), 3.99 (s, 3 H), 2.55 (s, 3 H); ^{13}C NMR (100 MHz $CDCl_3$) δ (ppm) 167.3, 158.3, 141.1, 133.1, 132.9, 127.9, 126.7, 125.3, 124.0, 109.3, 63.9, 52.5, 15.1.

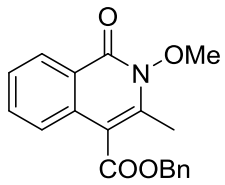
Isopropyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ac**



Yield: 80% (44.0 mg); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.35 (d, J = 8.0 Hz, 1 H), 7.59-7.58 (m, 2 H),

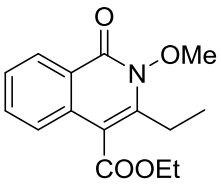
7.41-7.37 (m, 1 H), 5.31-5.25 (m, 1 H), 4.01 (s, 3 H), 2.46 (s, 3 H), 1.35 (d, *J* = 6.4 Hz, 6 H); ^{13}C NMR (100 MHz, CDCl3), δ (ppm): 166.3, 158.2, 140.2, 133.1, 132.8, 127.8, 126.6, 125.4, 123.7, 110.0, 69.6, 63.9, 21.9, 14.9; HR-MS (EI-TOF) (M^+) calculated for $C_{15}H_{17}NO_4$ 275.1158, found 275.1162.

Benzyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylat **3ad**



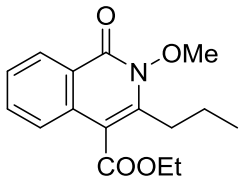
Yield: 70% (45.2 mg); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), *δ* (ppm): 8.41 (d, *J* = 8.0 Hz, 1 H), 7.64-7.59 (m, 2 H), 7.47-7.36 (m, 6 H), 5.43 (s, 2 H), 4.06 (s, 3 H), 2.49 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), *δ* (ppm): 166.7, 158.2, 141.0, 135.2, 133.1, 132.9, 128.8, 128.72, 128.70, 127.8, 126.7, 125.3, 123.9, 109.1, 67.5, 63.9, 15.0; HR-MS (EI-TOF) (M^+) calculated for $C_{19}H_{17}NO_4$ 323.1158, found 323.1159.

Ethyl 3-ethyl-2-methoxy-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ae**[2]



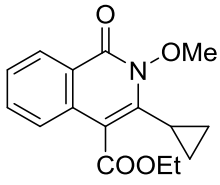
Yield: 60% (33.0 mg); Light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$), *δ* (ppm): 8.3 (d, *J* = 8.0 Hz, 1 H), 7.69-7.64 (m, 2 H), 7.50-7.46 (m, 1 H), 4.47 (q, *J* = 7.2 Hz, 2 H), 4.12 (s, 3 H), 2.83 (q, *J* = 7.3 Hz, 2 H), 1.44 (t, *J* = 7.2 Hz, 3 H), 1.37 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), *δ* (ppm): 166.8, 158.4, 145.3, 133.2, 132.8, 127.8, 126.6, 125.5, 123.9, 109.4, 64.3, 61.7, 23.2, 14.3, 14.0.

Ethyl 2-methoxy-1-oxo-3-propyl-1,2-dihydroisoquinoline-4-carboxylate **3af**



Yield: 59% (34.1 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), *δ* (ppm): 8.46 (d, *J* = 8.0 Hz, 1 H), 7.71-7.65 (m, 2 H), 7.52-7.48 (m, 1 H), 4.49 (q, *J* = 7.2 Hz, 2 H), 4.14 (s, 3 H), 2.82-2.78 (m, 2 H), 1.86-1.77 (m, 2 H), 1.46 (t, *J* = 7.2 Hz, 3 H), 1.06 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), *δ* (ppm): 166.9, 158.3, 144.0, 133.2, 132.8, 127.8, 126.6, 125.5, 124.0, 109.8, 64.2, 61.7, 31.4, 22.9, 14.3, 14.2; HR-MS (EI-TOF) (M^+) calculated for $C_{16}H_{19}NO_4$ 289.1314, found 289.1315.

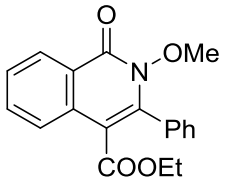
Ethyl 3-cyclopropyl-2-methoxy-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ag**



Yield: 50% (28.7 mg); Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$), *δ* (ppm): 8.45-8.43 (m, 1 H), 7.69-7.62 (m, 2 H), 7.51-7.47 (m, 1 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 4.16 (s, 3 H), 2.13-2.05 (m, 1 H),

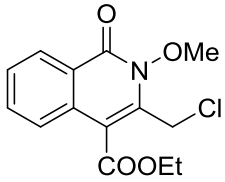
1.44 (t, *J* = 7.0 Hz, 3 H), 1.12-1.07 (m, 2 H), 0.86-0.81 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.9, 158.4, 143.7, 132.83, 132.78, 127.9, 126.9, 125.7, 123.5, 111.4, 64.2, 61.7, 14.2, 11.3, 7.0; HR-MS (EI-TOF) (M^+) calculated for $C_{16}H_{17}NO_4$ 287.1158, found 287.1157.

Ethyl 2-methoxy-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carboxylate **3ah**



Yield: 46% (29.7 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.56 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.77 (t, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.55-7.49 (m, 5 H), 4.01 (q, J = 7.2 Hz, 2 H), 3.73 (s, 3 H), 0.88 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 166.2, 158.1, 142.8, 133.132.9, 131.2, 129.6, 129.5, 128.05, 127.4, 126.1, 124.5, 111.48, 63.7, 61.4, 13.5; HR-MS (EI-TOF) (M^+) calculated for $C_{19}H_{17}NO_4$ 323.1158, found 323.1156.

Ethyl 3-(chloromethyl)-2-methoxy-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ai**[2]



Yield: 41% (24.2 mg); White solid; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 8.39 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.64(td, *J* = 7.6, 1.3 Hz, 1 H), 7.49 (td, *J* = 7.6, 1.1 Hz, 1 H), 4.78 (s, 2 H), 4.45 (q, *J* = 7.1 Hz, 2 H), 4.21 (s, 3 H), 1.40 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 165.6, 158.1, 139.0, 133.1, 132.4, 128.1, 127.9, 126.7, 125.1, 112.1, 65.3, 62.3, 40.0, 14.2.

5. Preparation of Isoquinolone Derivative 3ca at One mmol Scale

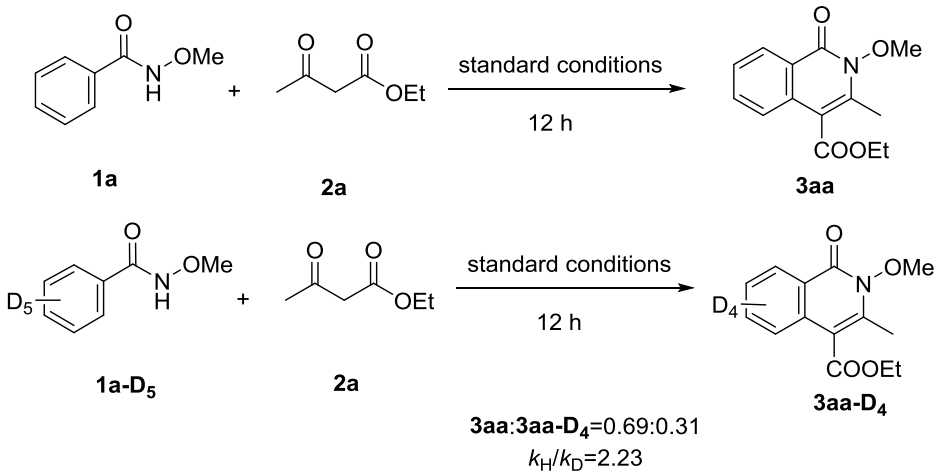
N,4-dimethoxybenzamide **1c** (1.0 mmol, 181.1 mg), ethyl acetoacetate **2a** (2.0 mmol, 260.1 mg), $Pd(TFA)_2$ (0.05 mmol, 16.5 mg, 5 mol %), and $K_2S_2O_8$ (2.0 mmol, 540.5 mg) were added in 100mL round-bottom flask, and then AcOH (10 mL) was added as a solvent. The reaction mixture was stirred at 60 ºC for 24 h under nitrogen. Then, the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether = 1/2 as eluent) to give desired isoquinolone derivative **3ca** in 69% (186.2 mg) yield.

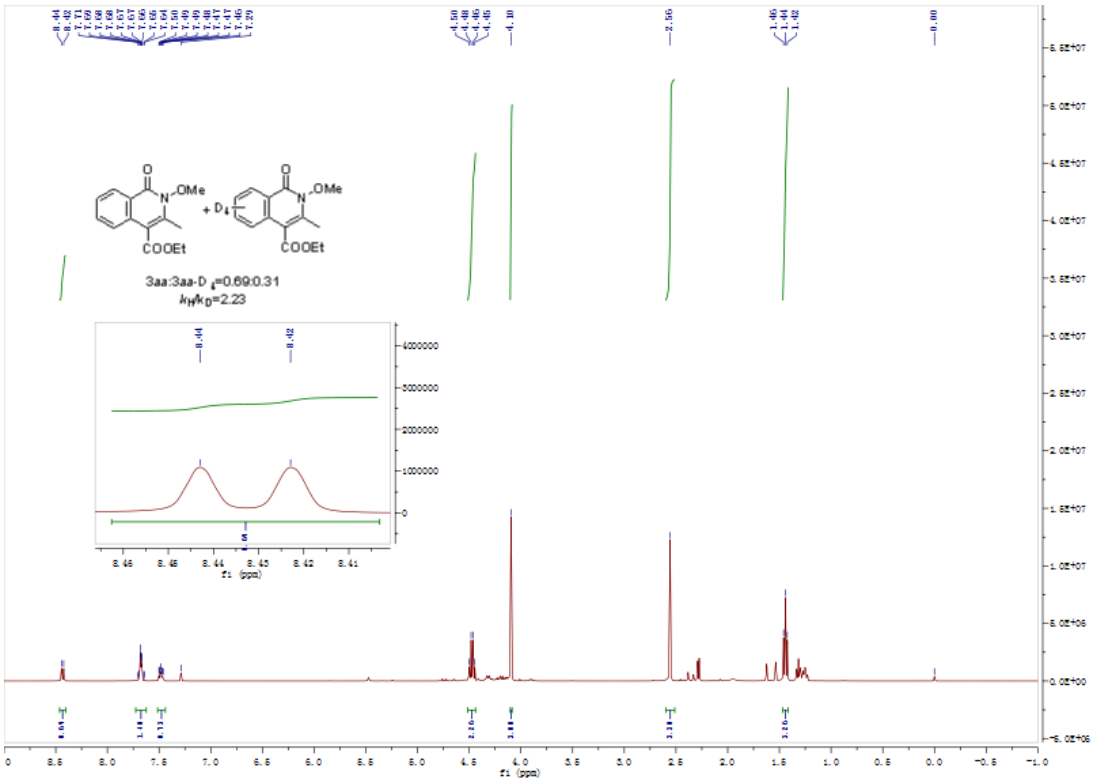
6. Primary Mechanistic Study.

(1) Two parallel reactions for KIE value

N-Methoxybenzamide **1a** (0.1 mmol, 15.1 mg) or deuterated

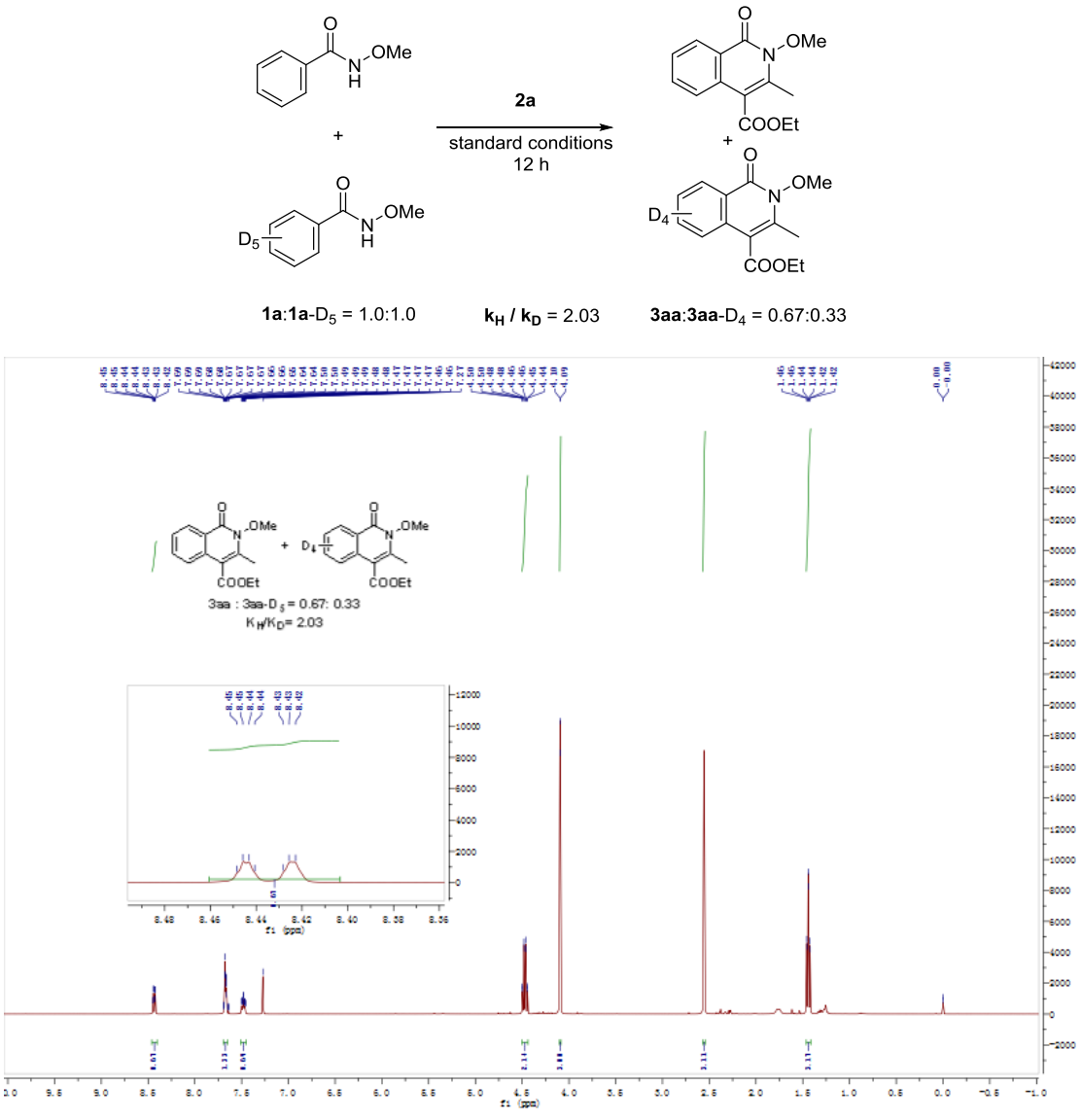
N-methoxybenzamide **1a**-D_5 (0.1 mmol, 15.6 mg), ethyl acetoacetate **2a** (0.2 mmol, 26.0 mg), $Pd(TFA)_2$ (0.01 mmol, 1.7 mg, 5 mol %), $K_2S_2O_8$ (0.2 mmol, 54.1 mg) and AcOH (2.5 mL) were added in two separated tubes. The reaction mixtures were stirred at 60 ºC for 12 h independently. Then the two mixtures were combined and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether = 1/2 as eluent) to afford the mixture of isoquinolone derivative **3aa** and deuterated isoquinolone derivative **3aa**-D_4. The ratio of **3aa** to **3aa**-D_4 was determined to be 2.23:1 by ^{1}H NMR.



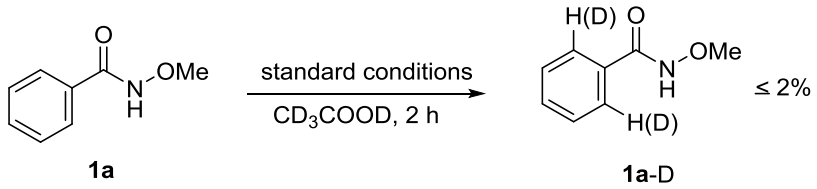


(2) An intermolecular competition reaction for KIE value

The mixture of *N*-methoxybenzamide **1a** (0.1 mmol, 15.1 mg) and deuterated *N*-methoxybenzamide **1a**-D_5 (0.1 mmol, 15.6 mg), ethyl acetoacetate **2a** (0.2 mmol, 26.0 mg), $Pd(TFA)_2$ (0.01 mmol, 1.7 mg, 5 mol %), $K_2S_2O_8$ (0.2 mmol, 54.1 mg) and AcOH (2.5 mL) was stirred at 60 ºC for 12 h. Then, the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether = 1/2 as eluent) to afford isoquinolone derivative **3aa** and deuterated isoquinolone derivative **3aa**-D_4. The ratio of **3aa** to **3aa**-D_4 was determined to be 2.03:1 by ^{1}H NMR.

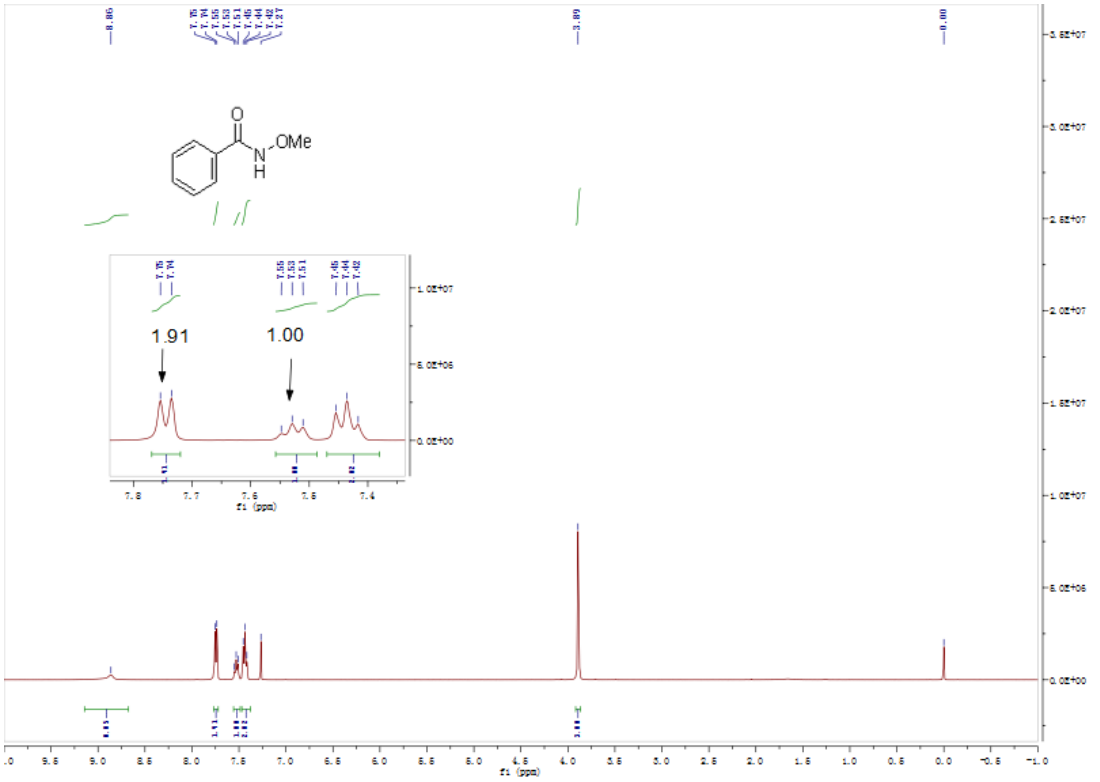


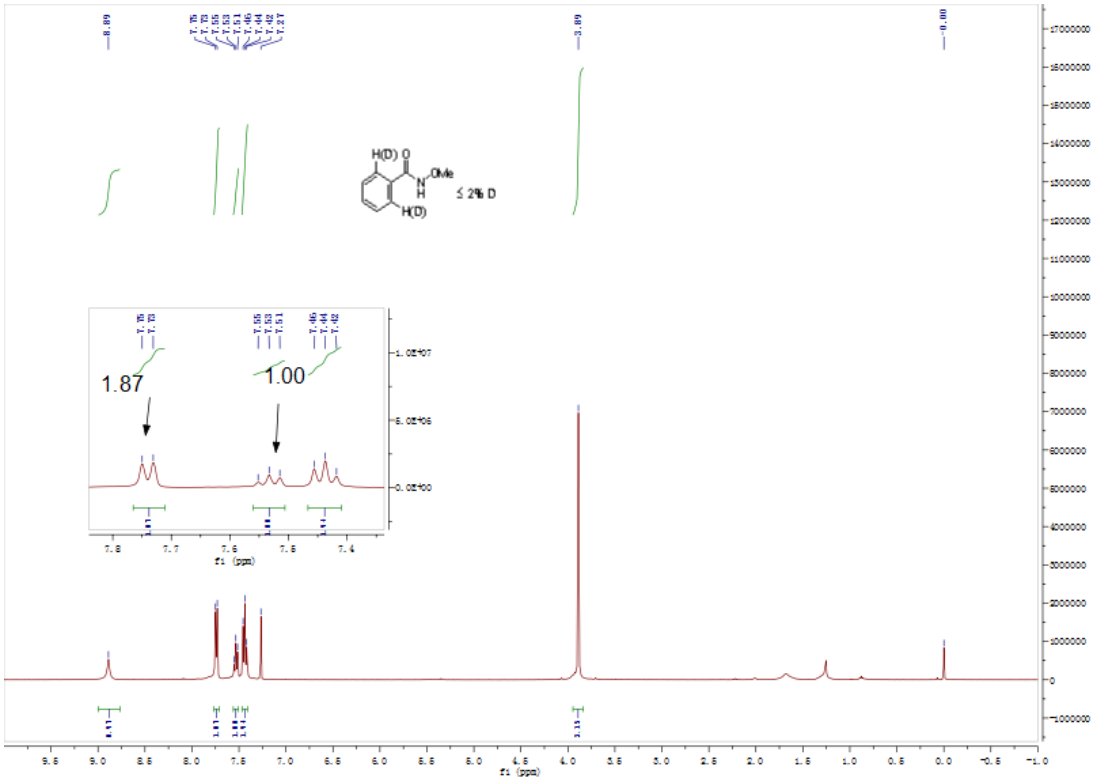
(2) H/D exchange experiment



1a **1a**-D

The mixture of *N*-methoxybenzamide **1a** (0.1 mmol, 15.1 mg), $Pd(TFA)_2$ (0.01 mmol, 1.7 mg, 5 mol %), $K_2S_2O_8$ (0.2 mmol, 54.1 mg) and deuterated AcOH (2.5 mL) was stirred at 60 ºC for 2 h. Then, the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/ petroleum ether = 1/2 as eluent) to recover *N*-methoxybenzamide **1a** without a significant amount of deuterated *N*-methoxybenzamide **1a**-D found by ^{1}HNMR analysis.





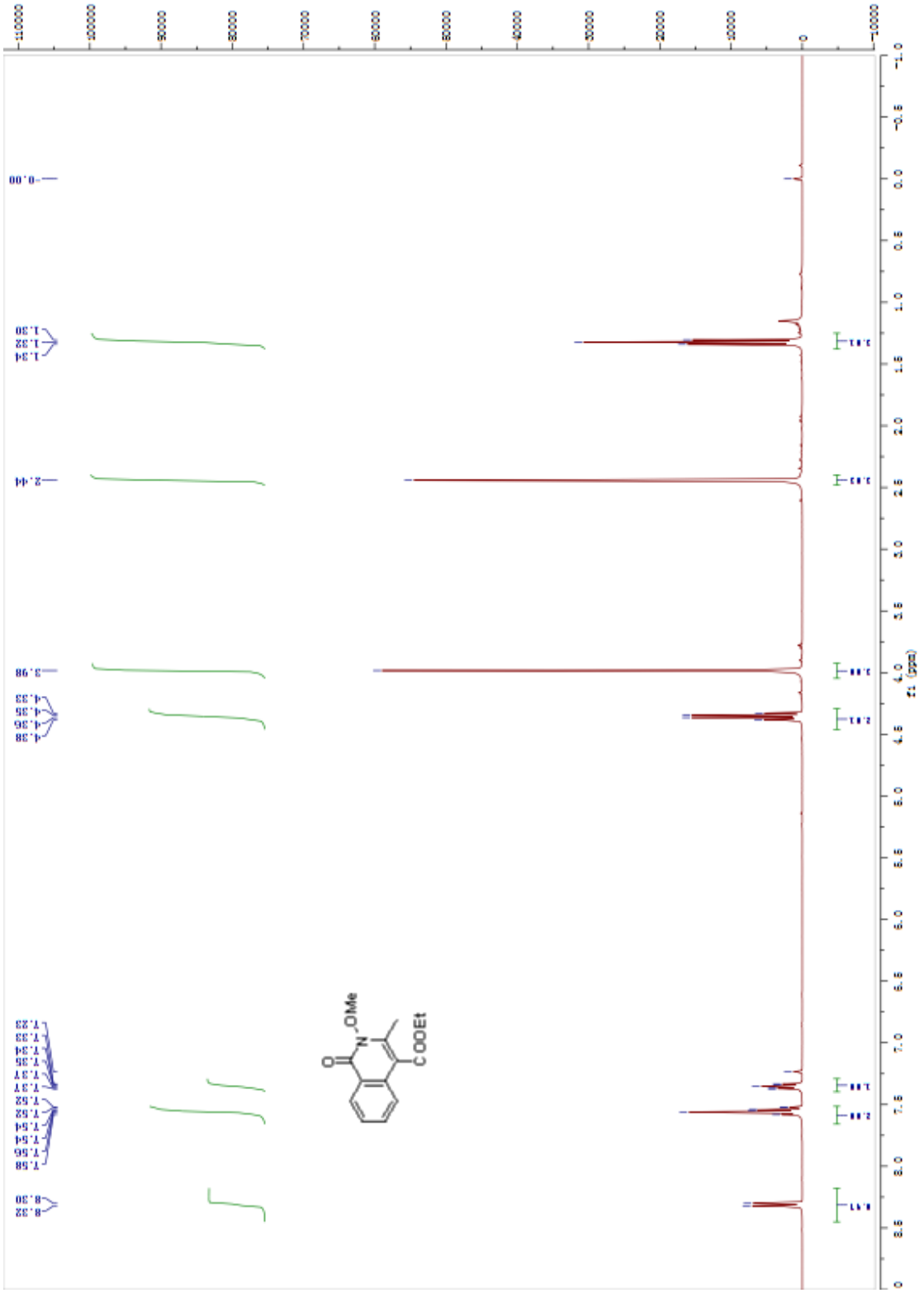
7. References

[1] Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350.

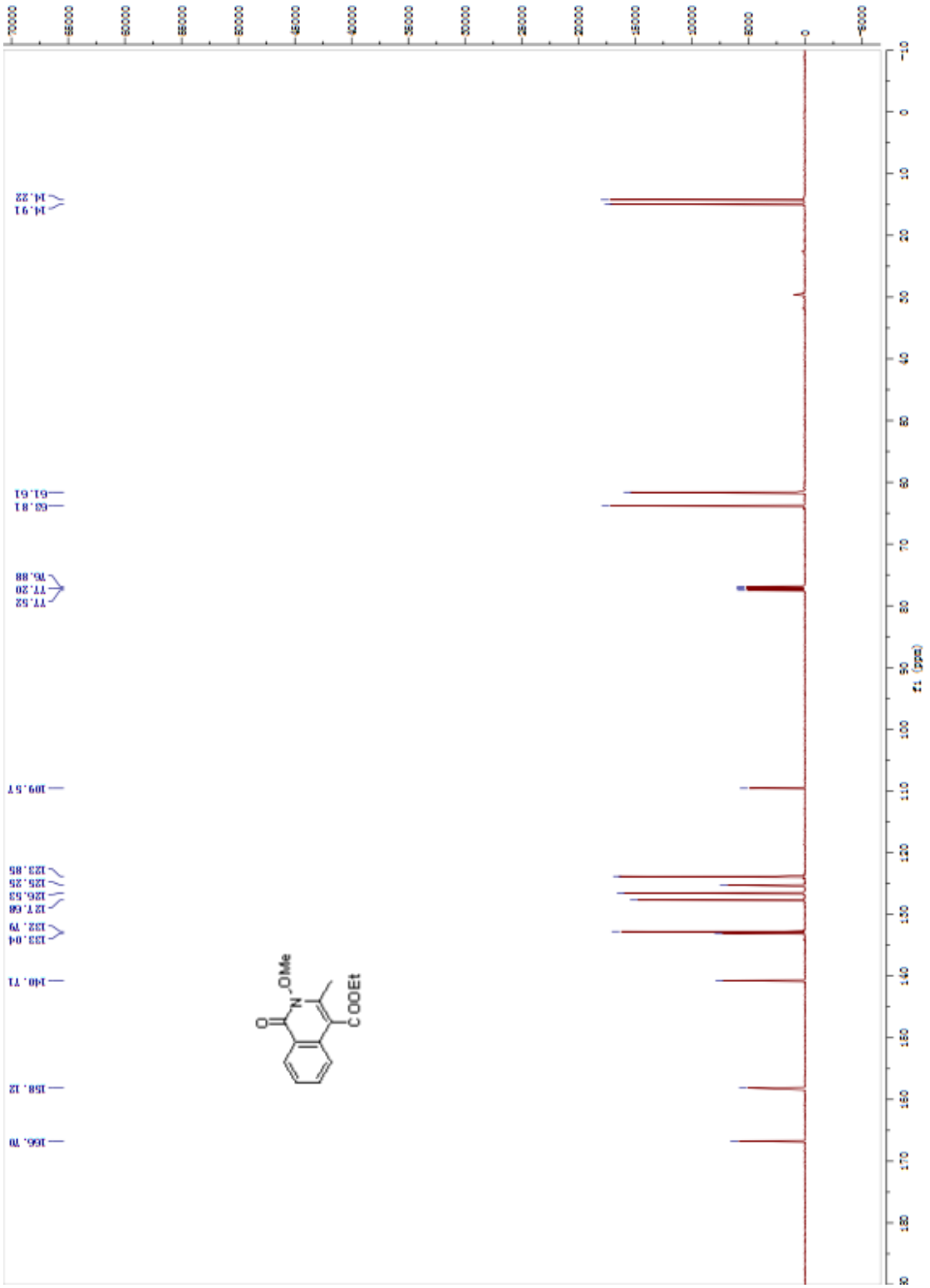
[2] Shi, L.-L.; Yu, K.; Wang, B.-Q. *Chem. Commun.* **2015**, *51*, 17277.

8. ^{1}H NMR, ^{13}C NMR and HR-MS Spectra of Isoquinolone Derivatives 3

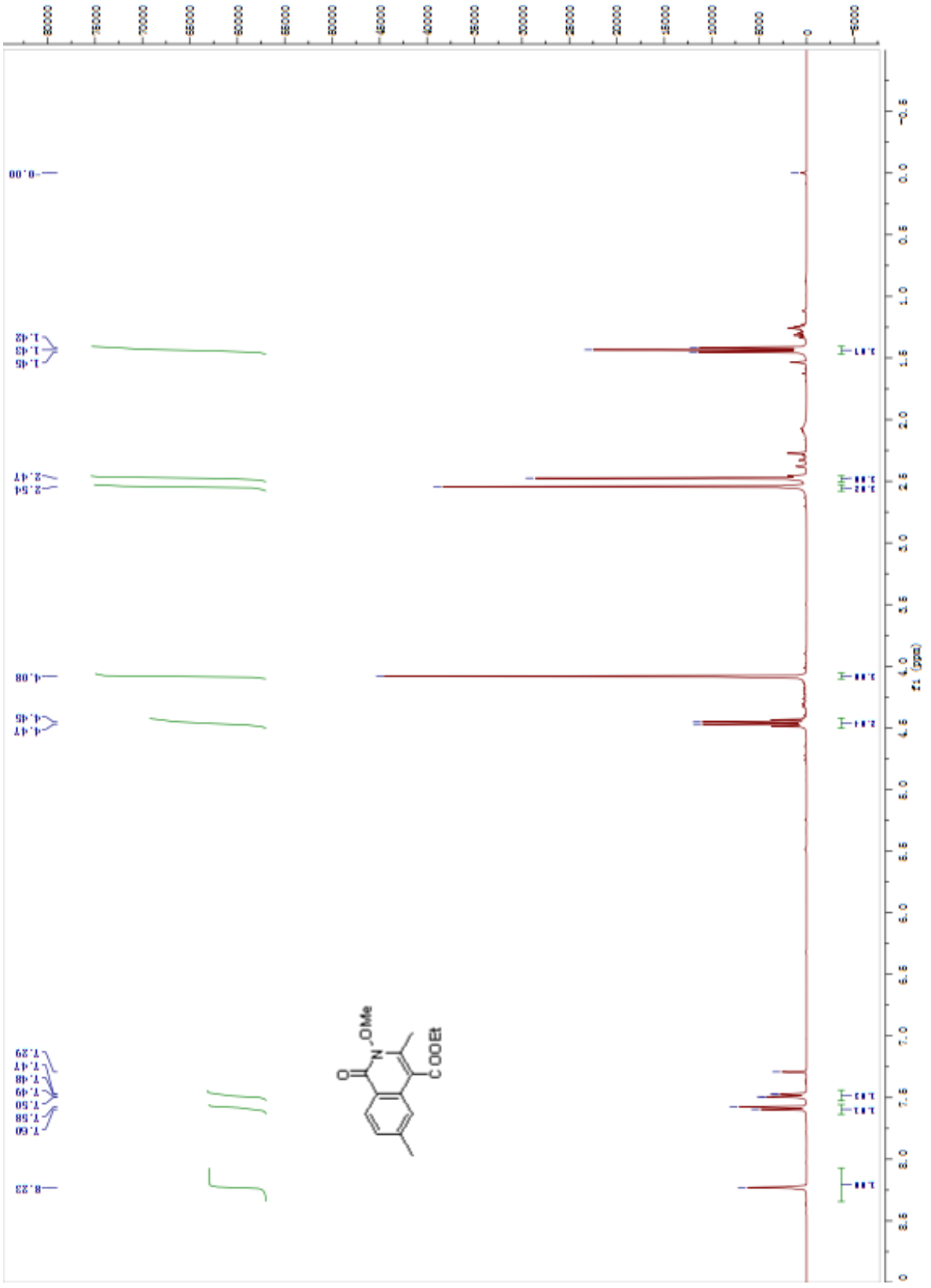
^{1}H NMR Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3aa**



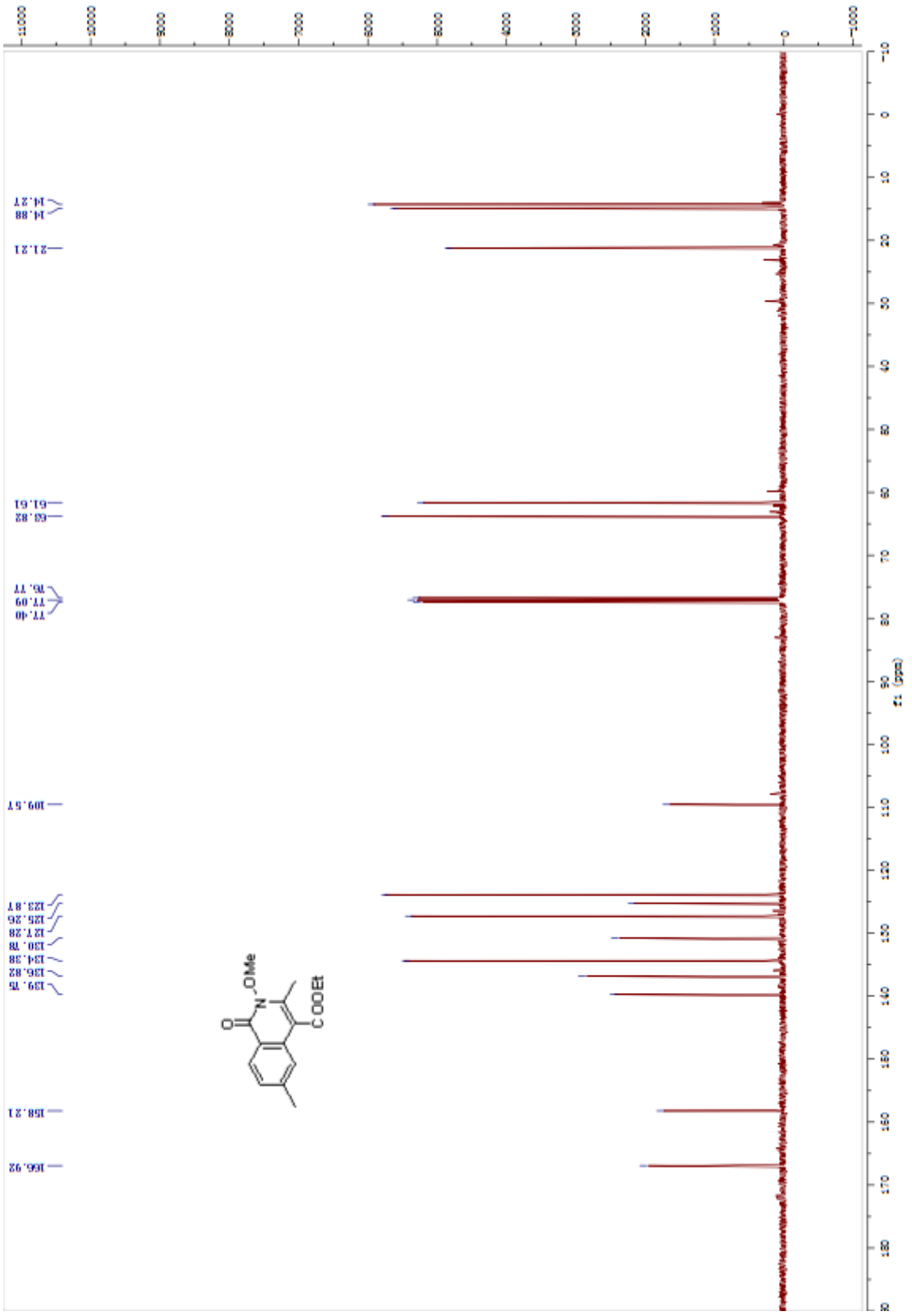
^{13}C NMR Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquino line-4-carboxylate **3aa**



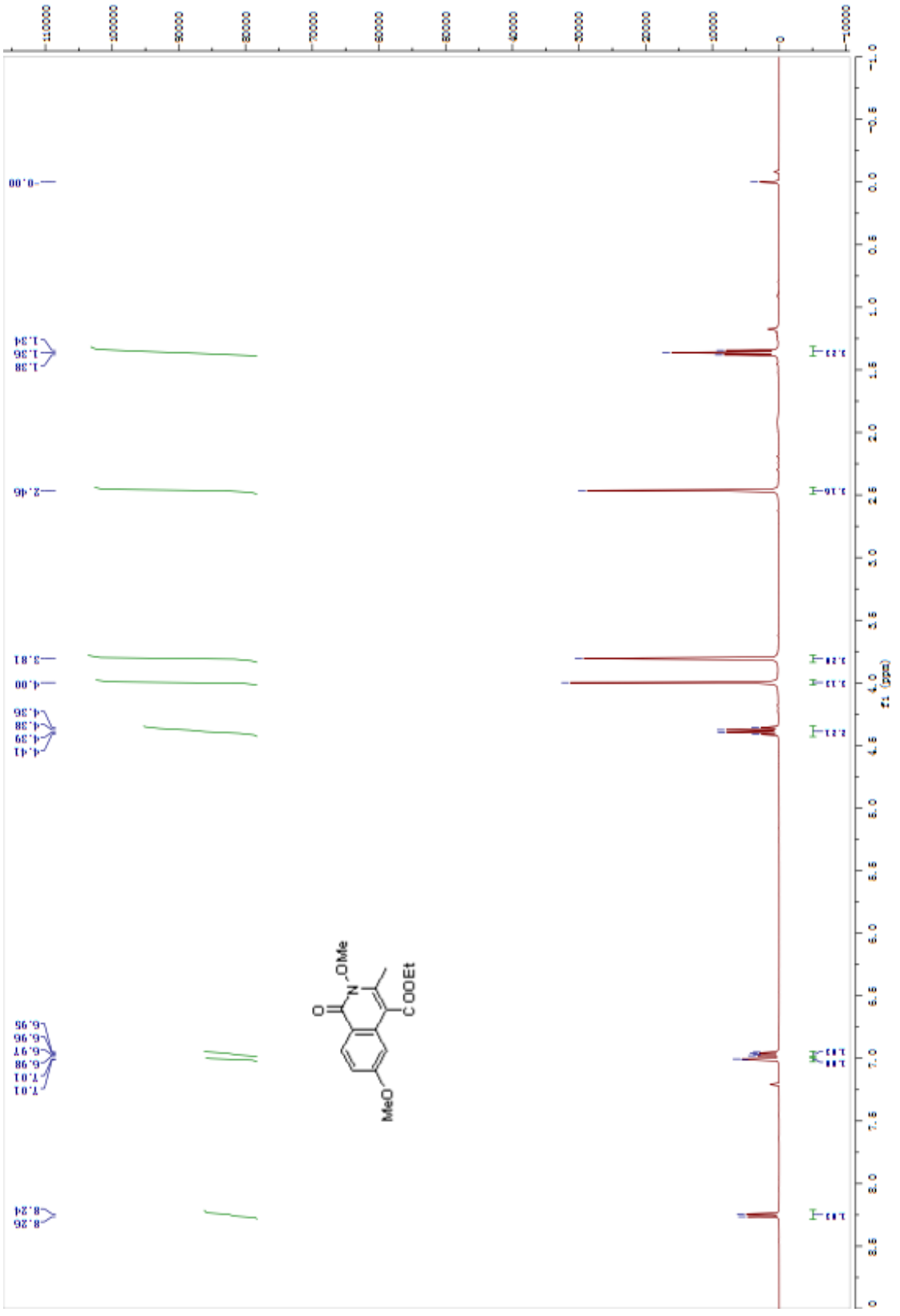
^{1}H NMR Spectrum of ethyl 2-methoxy-3,6-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ba**



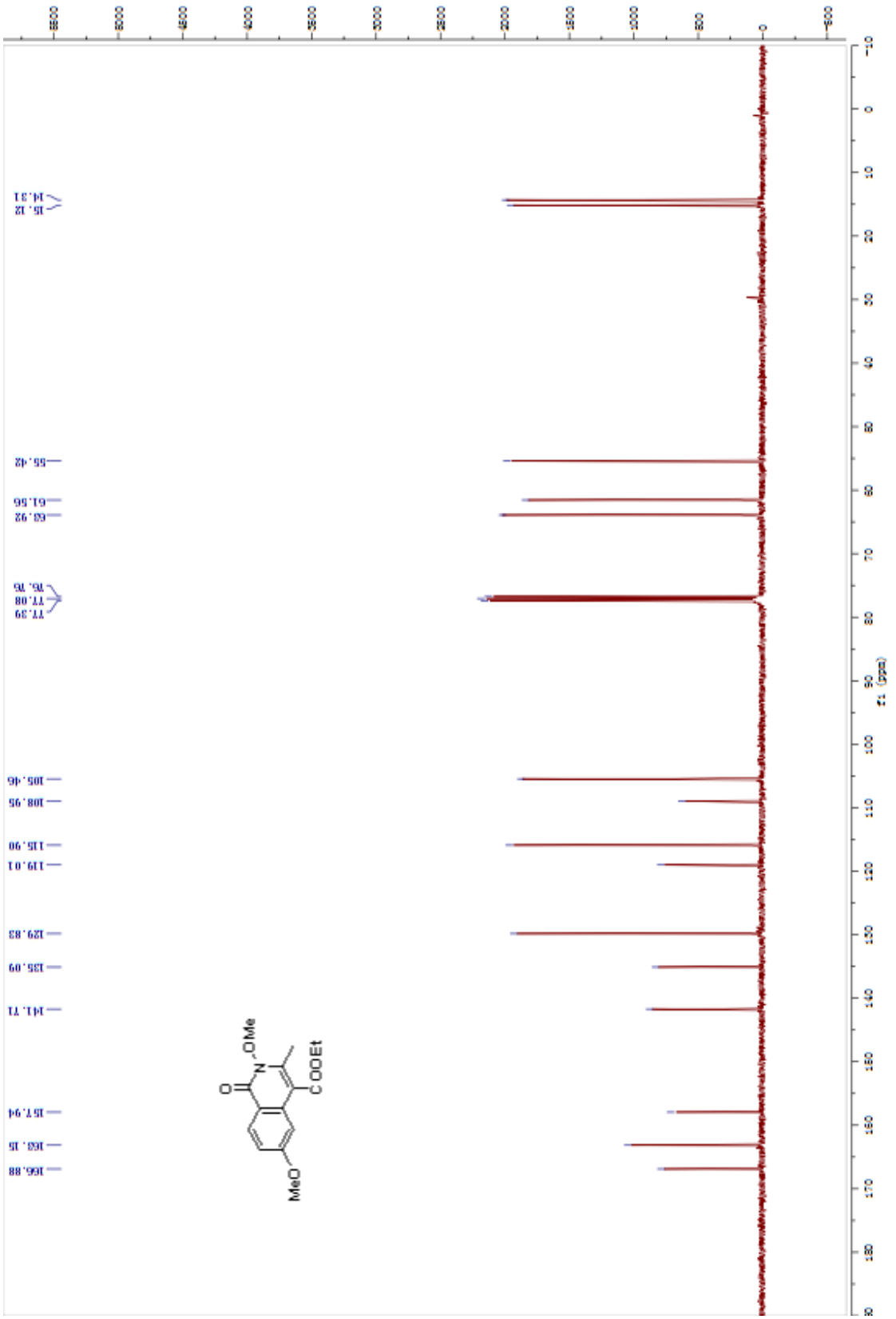
^{13}C NMR Spectrum of ethyl 2-methoxy-3,6-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxy late **3ba**



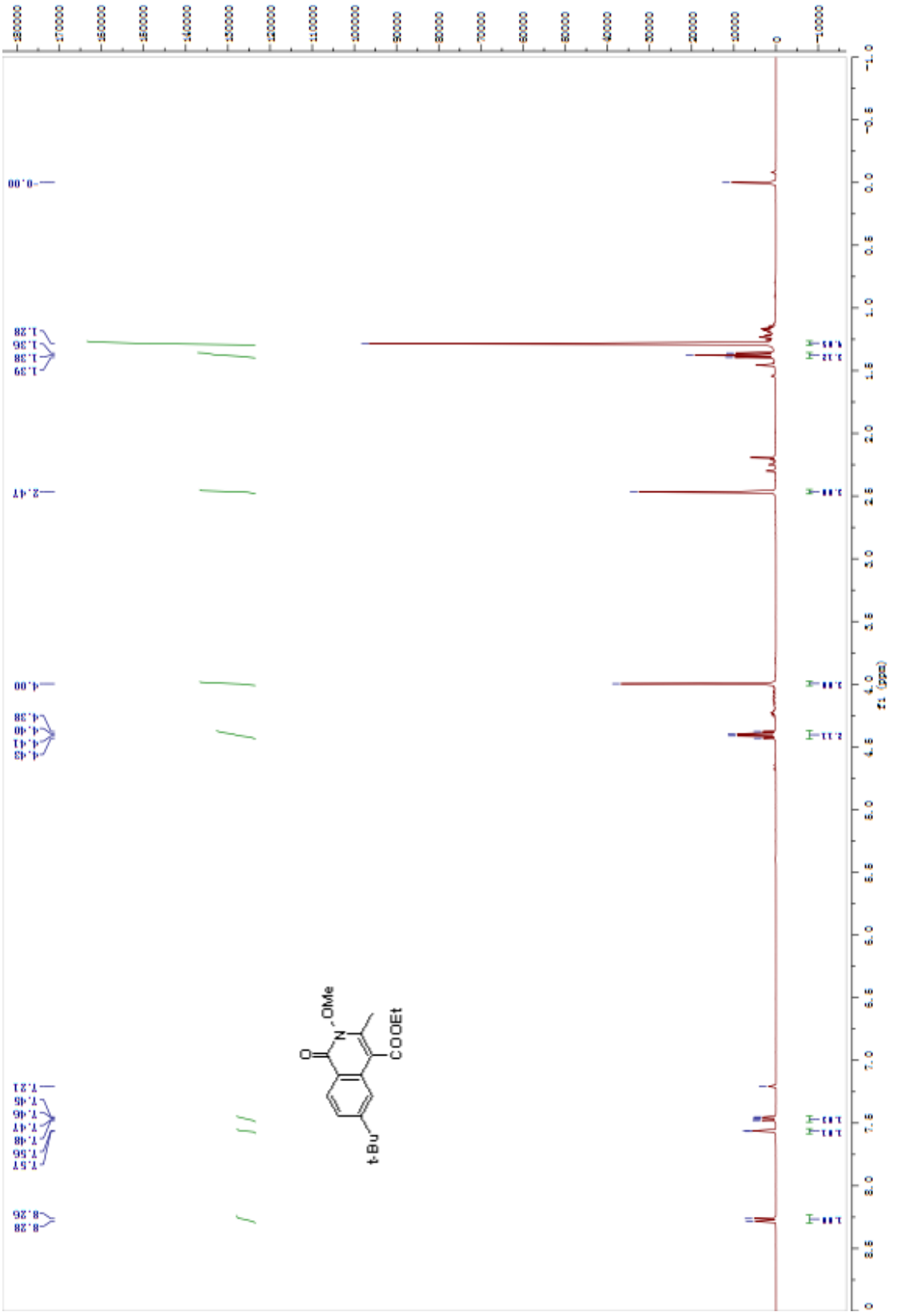
^{1}H NMR of Spectrum ethyl 2,6-dimethoxy-3-methyl-1-oxo-1,2-dihydroiso quinoline-4-carboxy late **3ca**



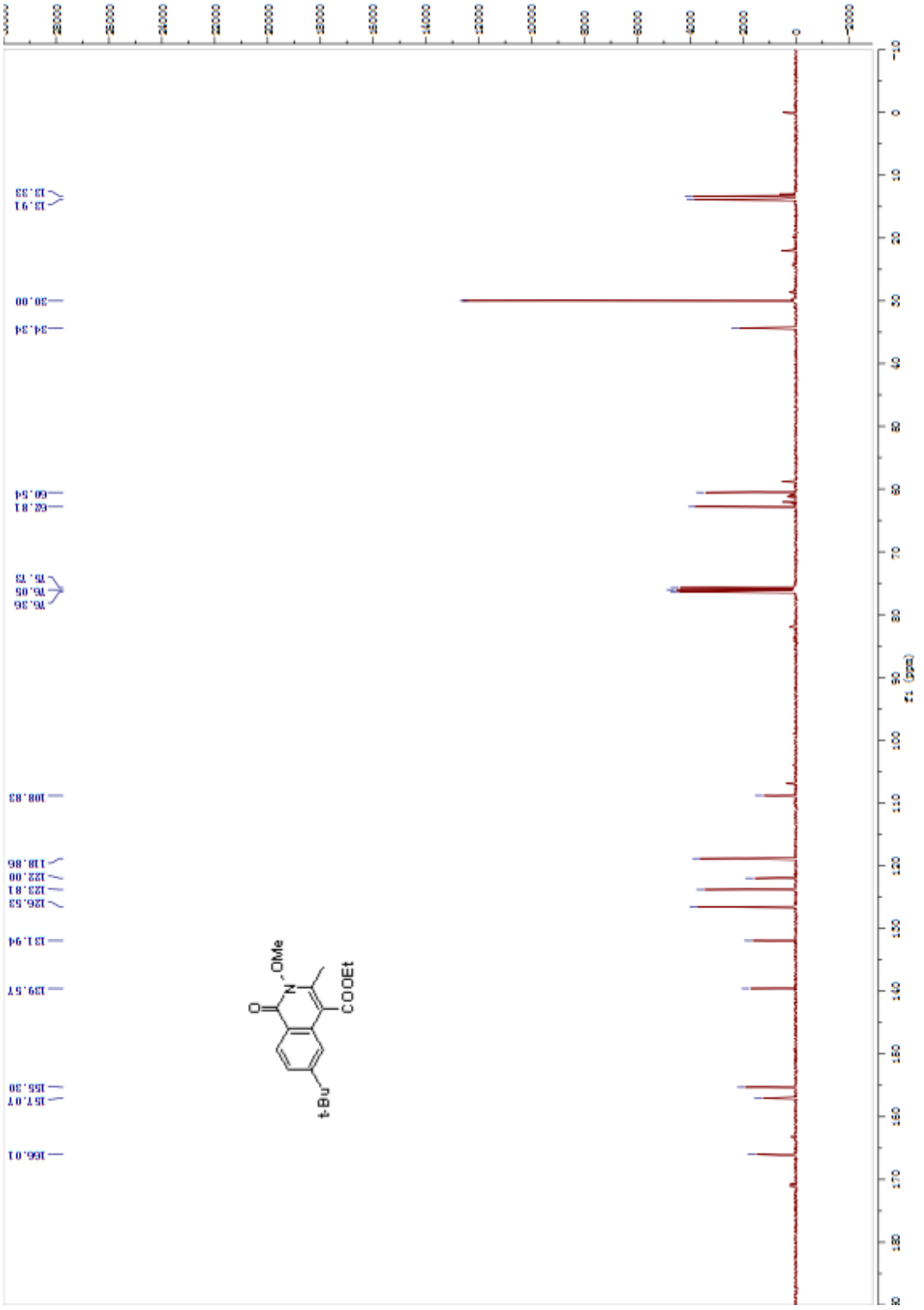
^{13}C NMR Spectrum of ethyl 2,6-dimethoxy-3-methyl-1-oxo-1,2-dihydroiso quinoline-4-carboxy late **3ca**



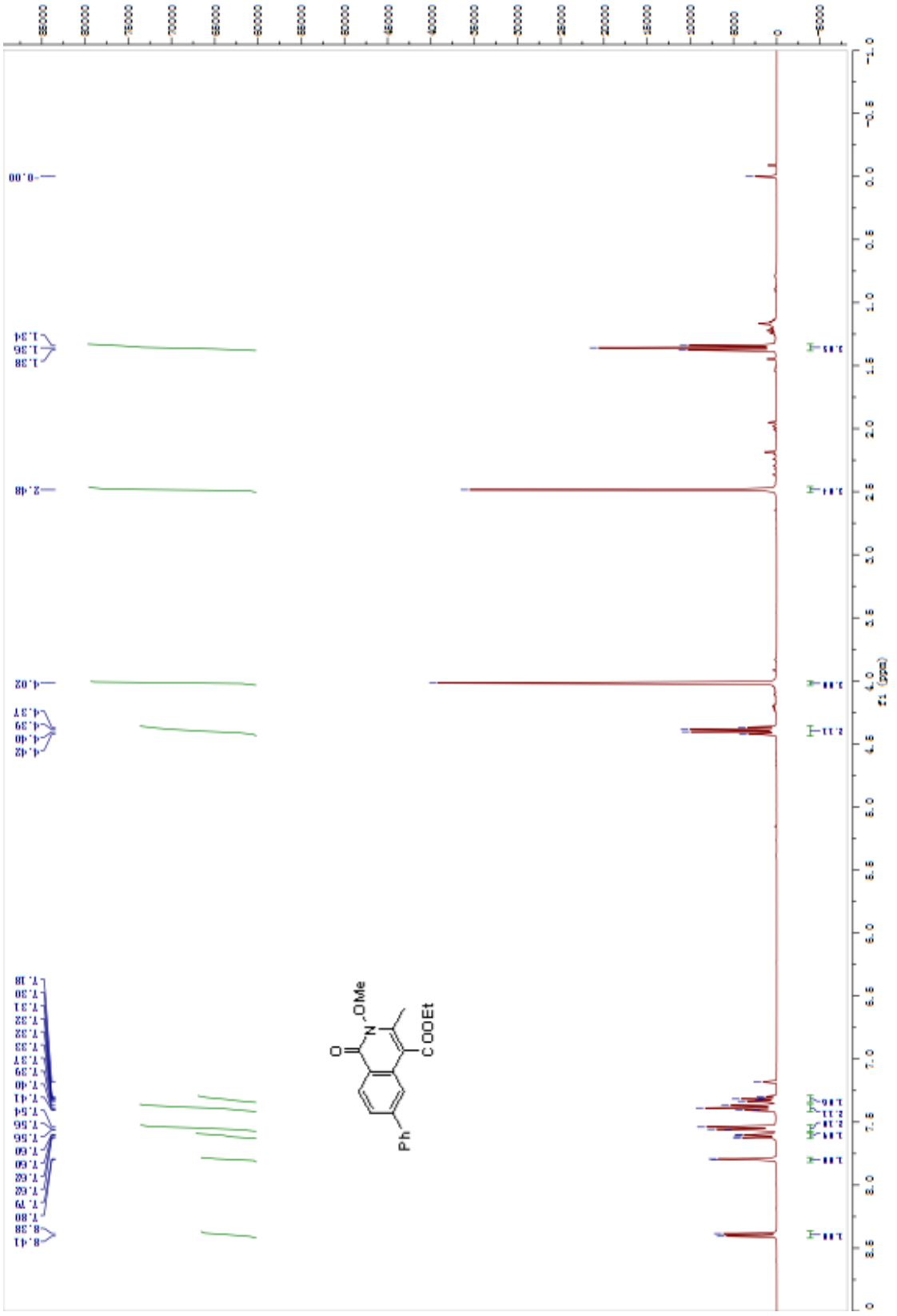
^{1}H NMR of Spectrum ethyl 6-(*tert*-butyl)-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3da**



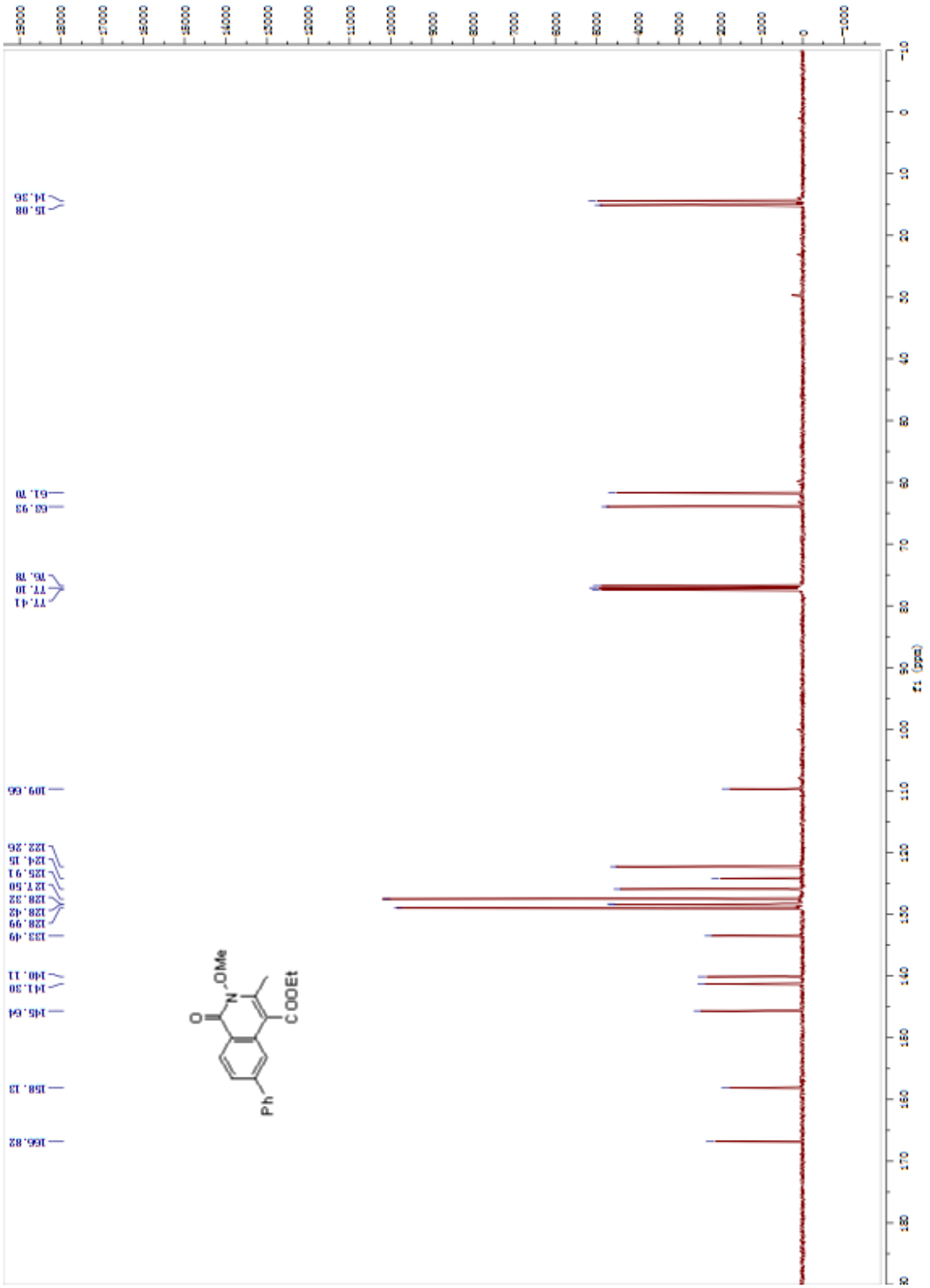
^{13}C NMR Spectrum of ethyl 6-(*tert*-butyl)-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3da**



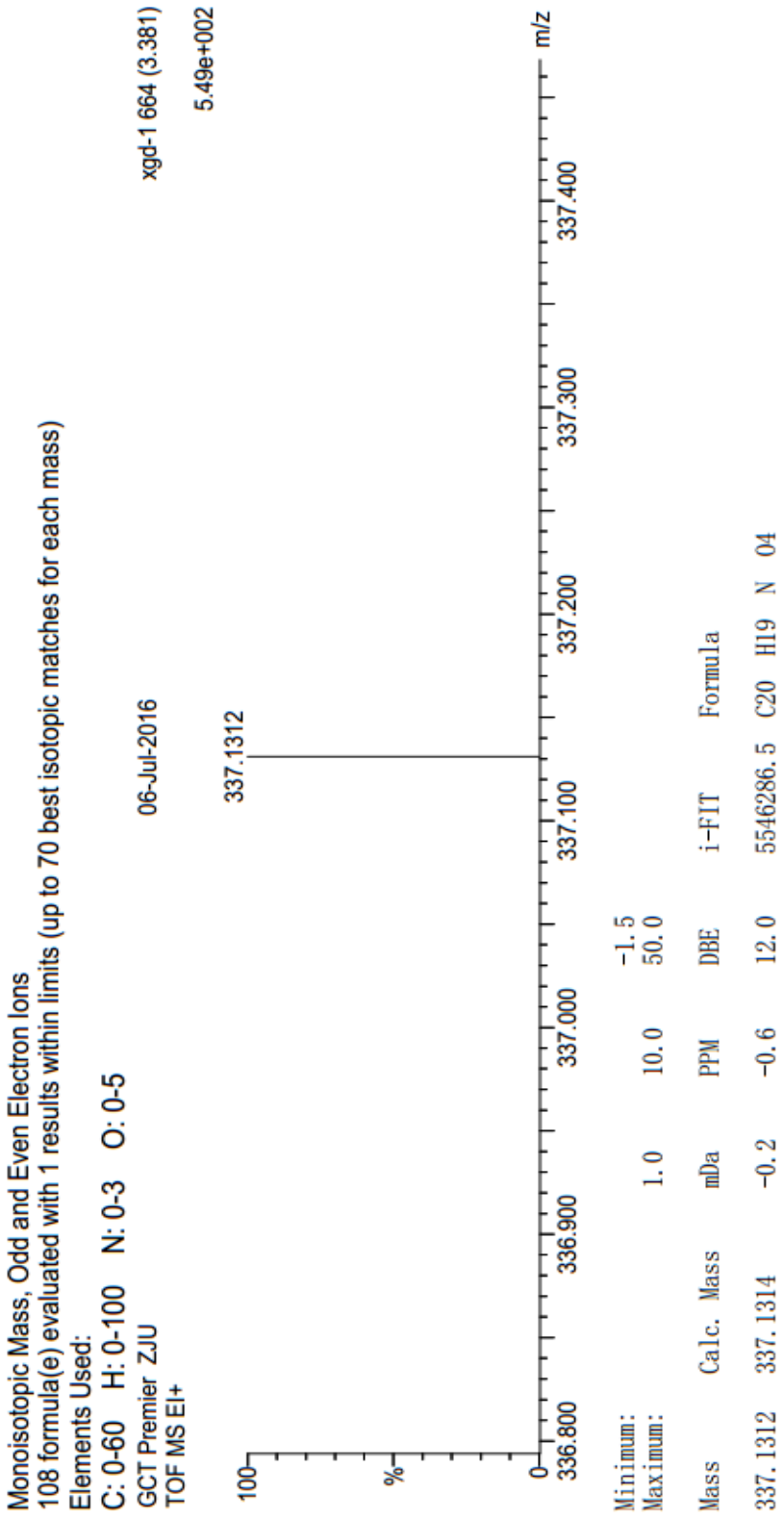
^{1}H NMR Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-6-phenyl-1,2-dihydro isoquinoline-4-carboxylate **3ea**



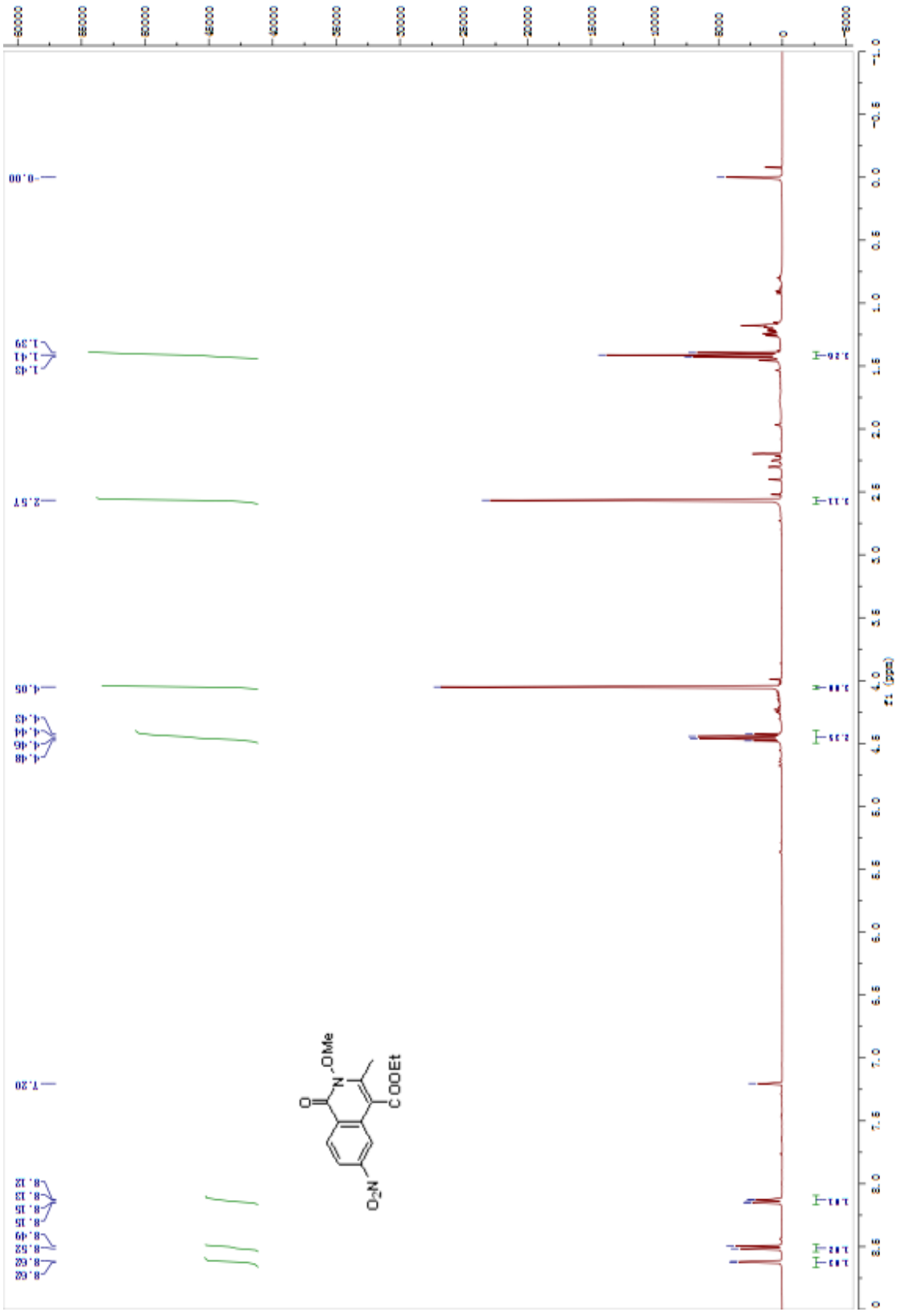
^{13}C NMR Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-6-phenyl-1,2-dihydro isoquinoline-4-carboxylate **3ea**



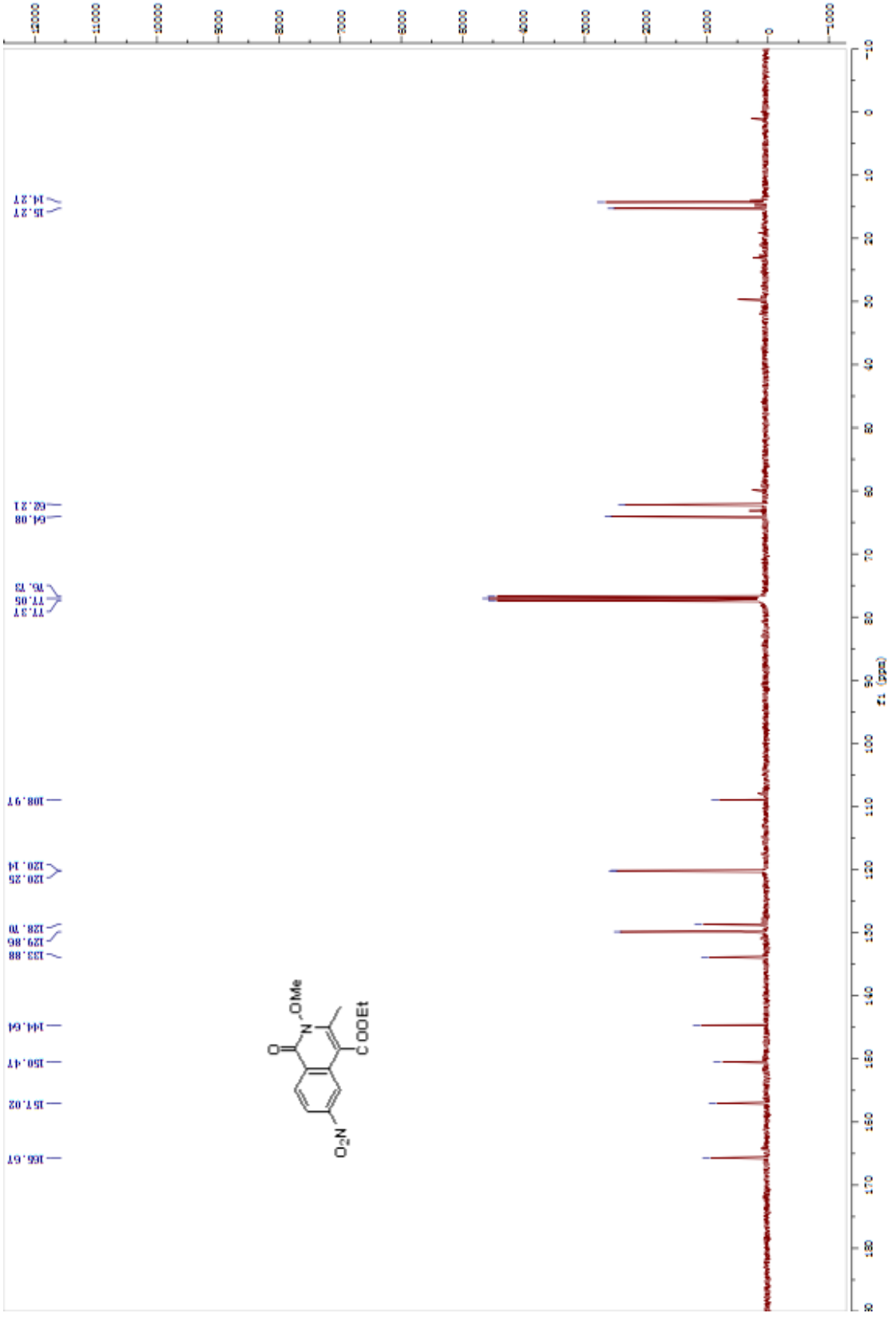
HR-MS Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-6-phenyl-1,2-dihydroiso quinoline-4-carboxylate **3ea**



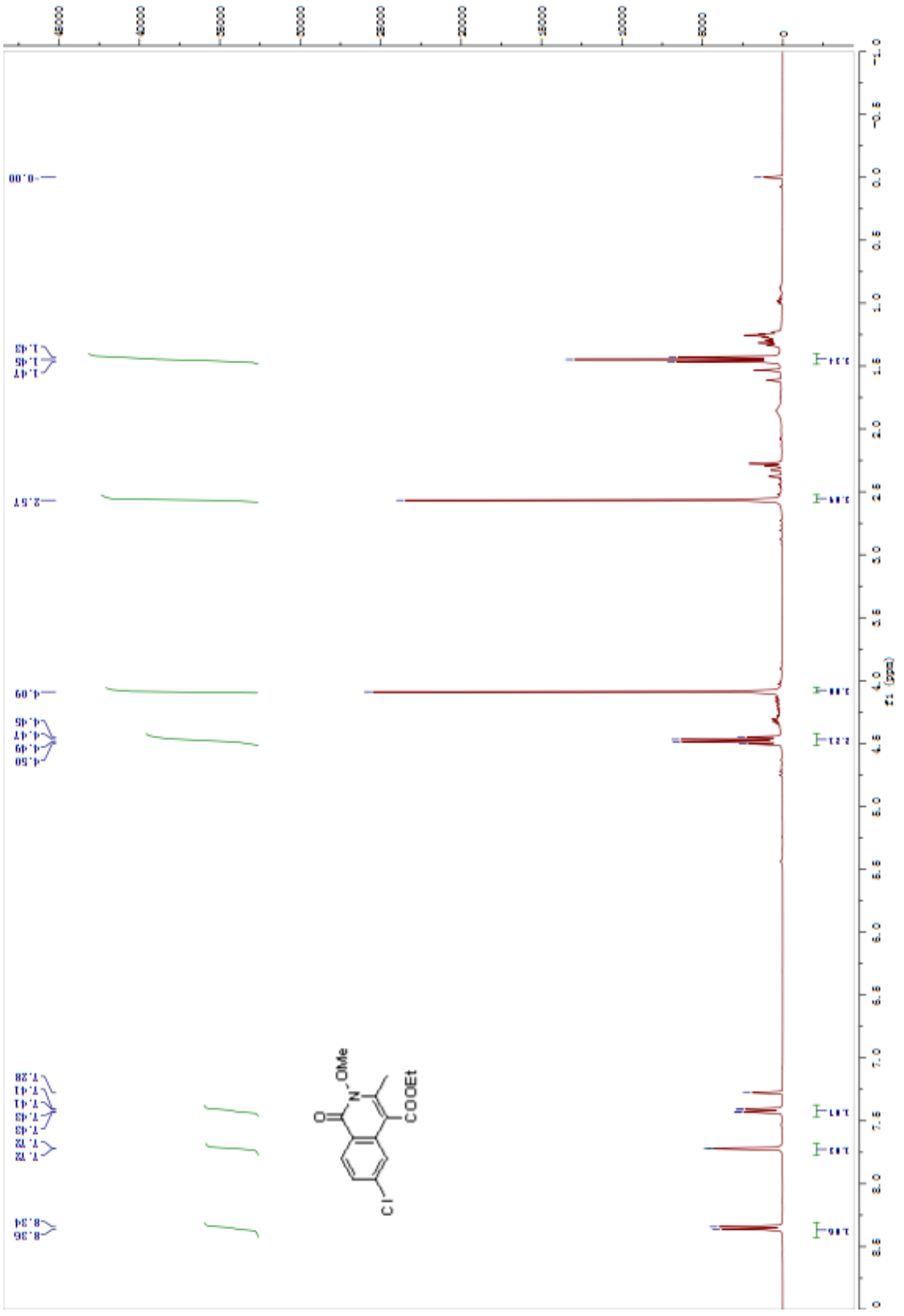
^{1}H NMR Spectrum of ethyl 2-methoxy-3-methyl-6-nitro-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3fa**



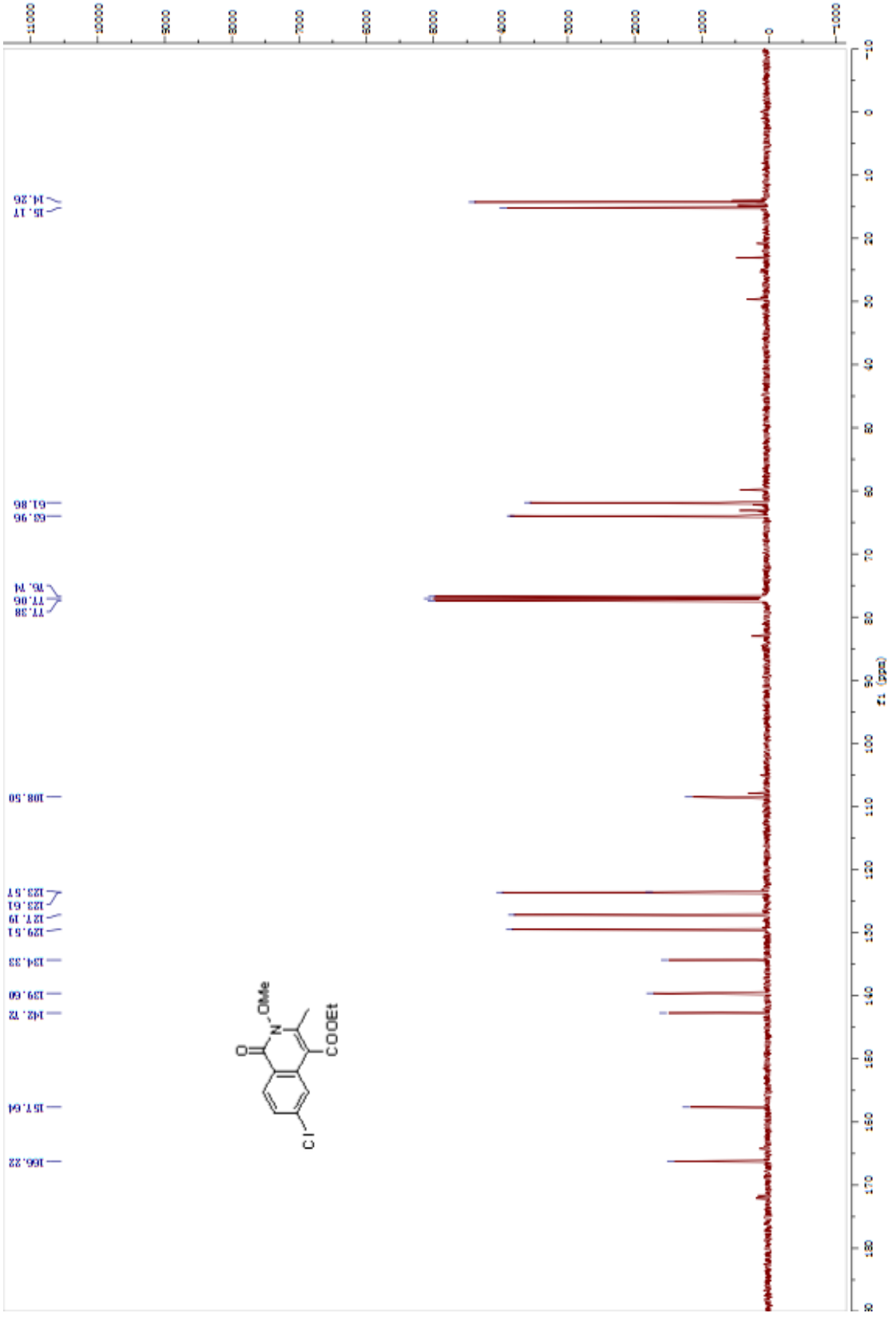
^{13}C NMR Spectrum of ethyl 2-methoxy-3-methyl-6-nitro-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3fa**



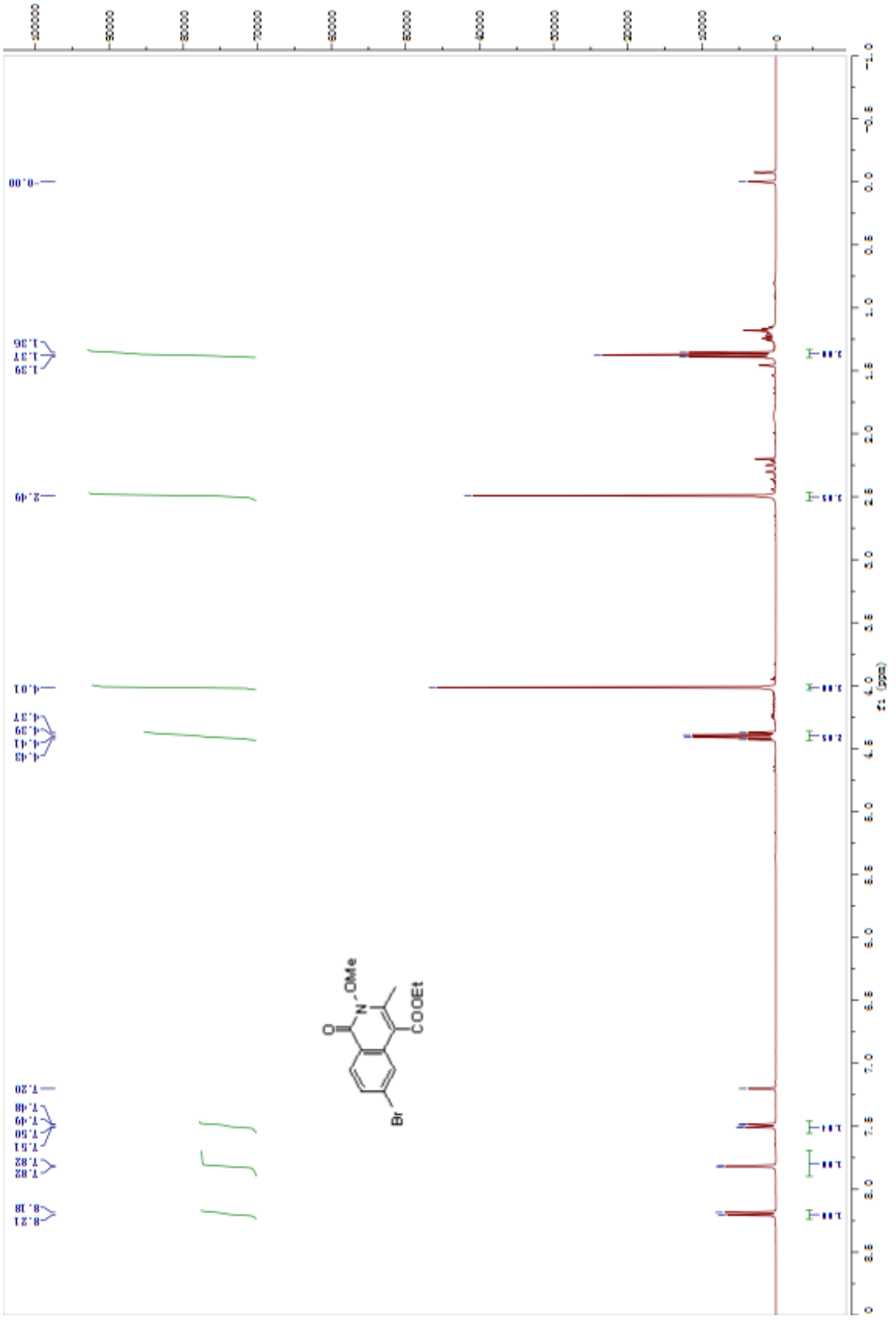
^{1}H NMR Spectrum of ethyl 6-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydro isoquinoline-4-carboxylate **3ga**



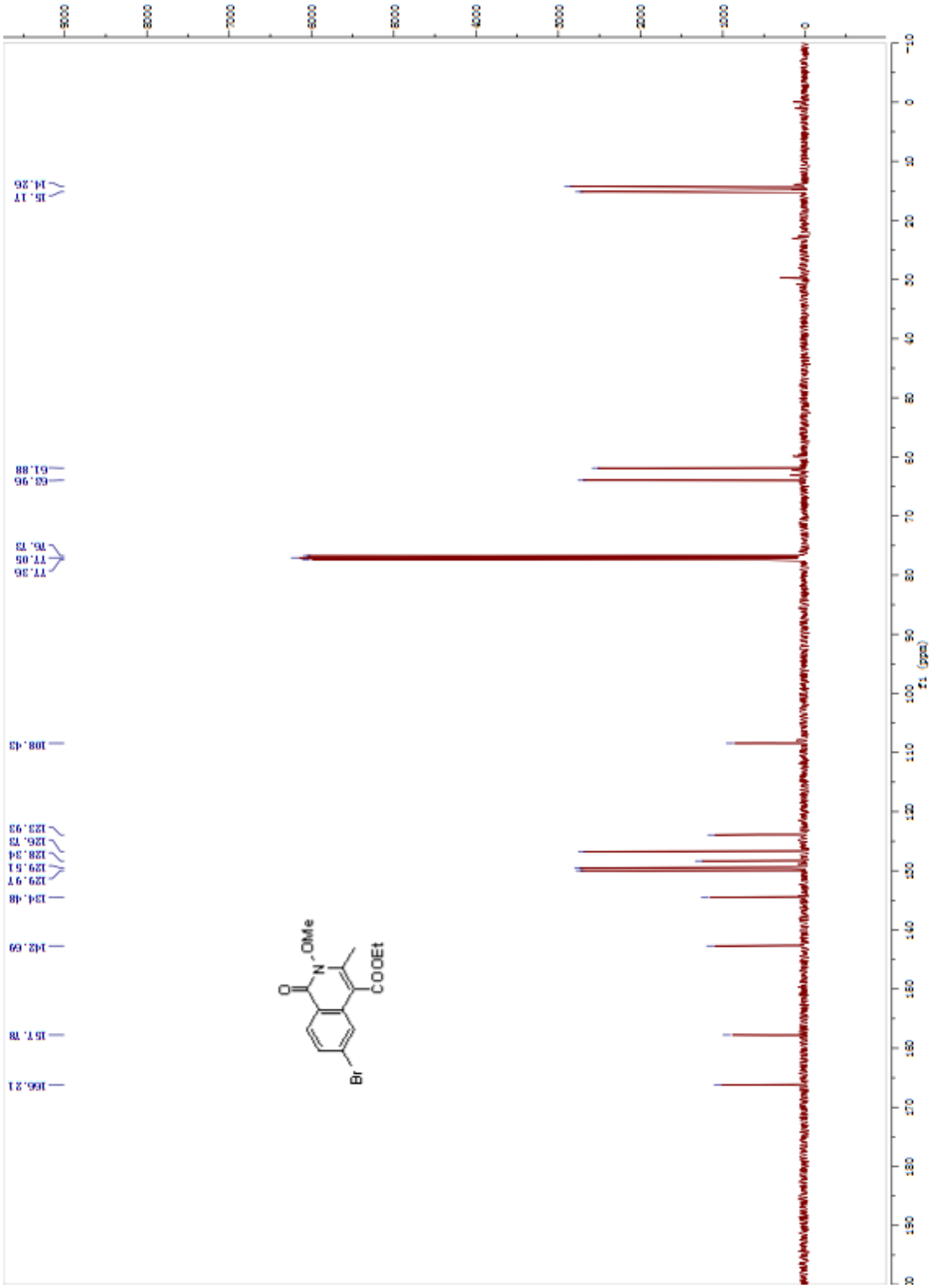
^{13}C NMR Spectrum of ethyl 6-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydro isoquinoline-4-carboxylate **3ga**



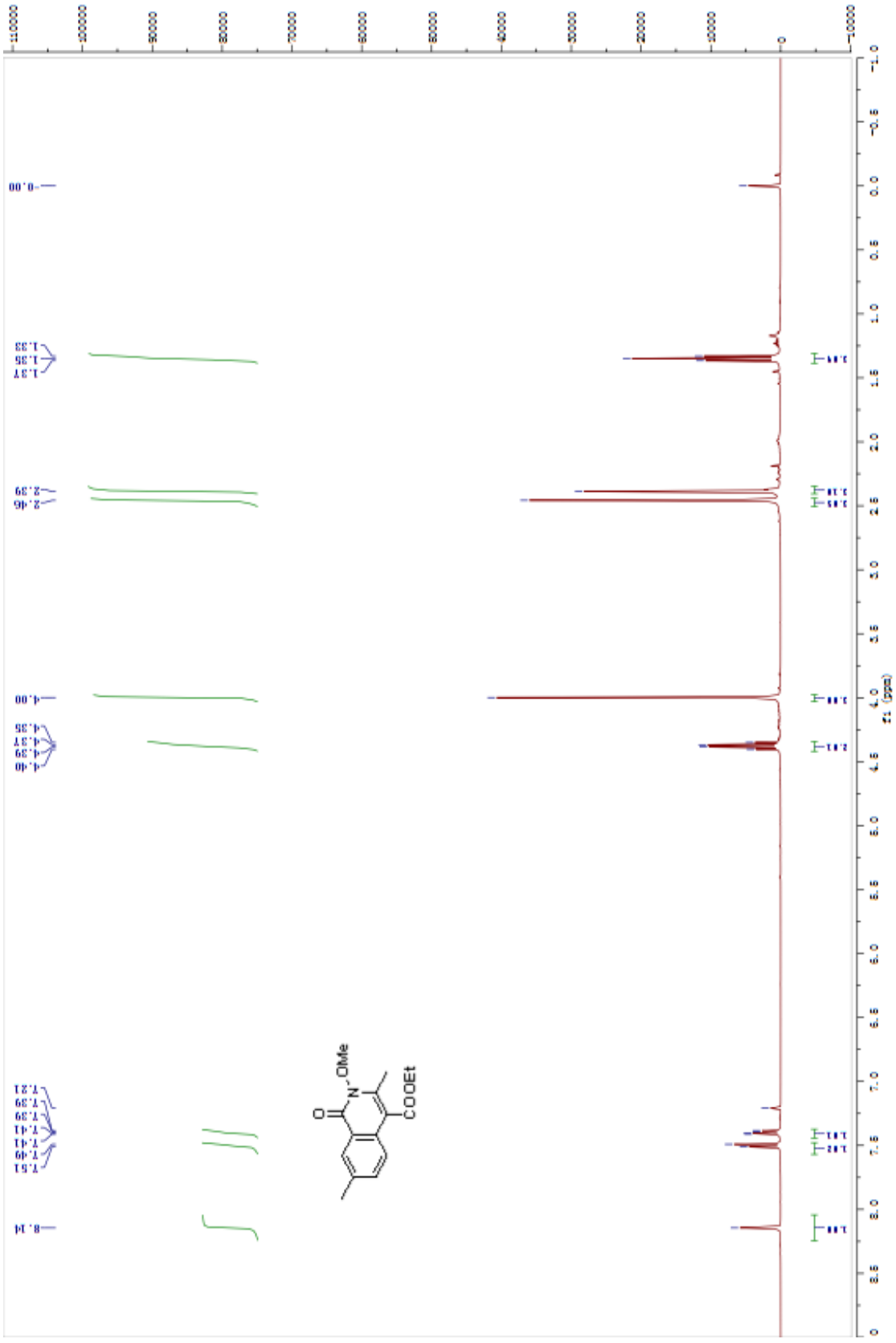
^{1}H NMR Spectrum of ethyl 6-bromo-2-methoxy-3-methyl-1-oxo-1,2-dihydro isoquinoline-4-carboxylate **3ha**



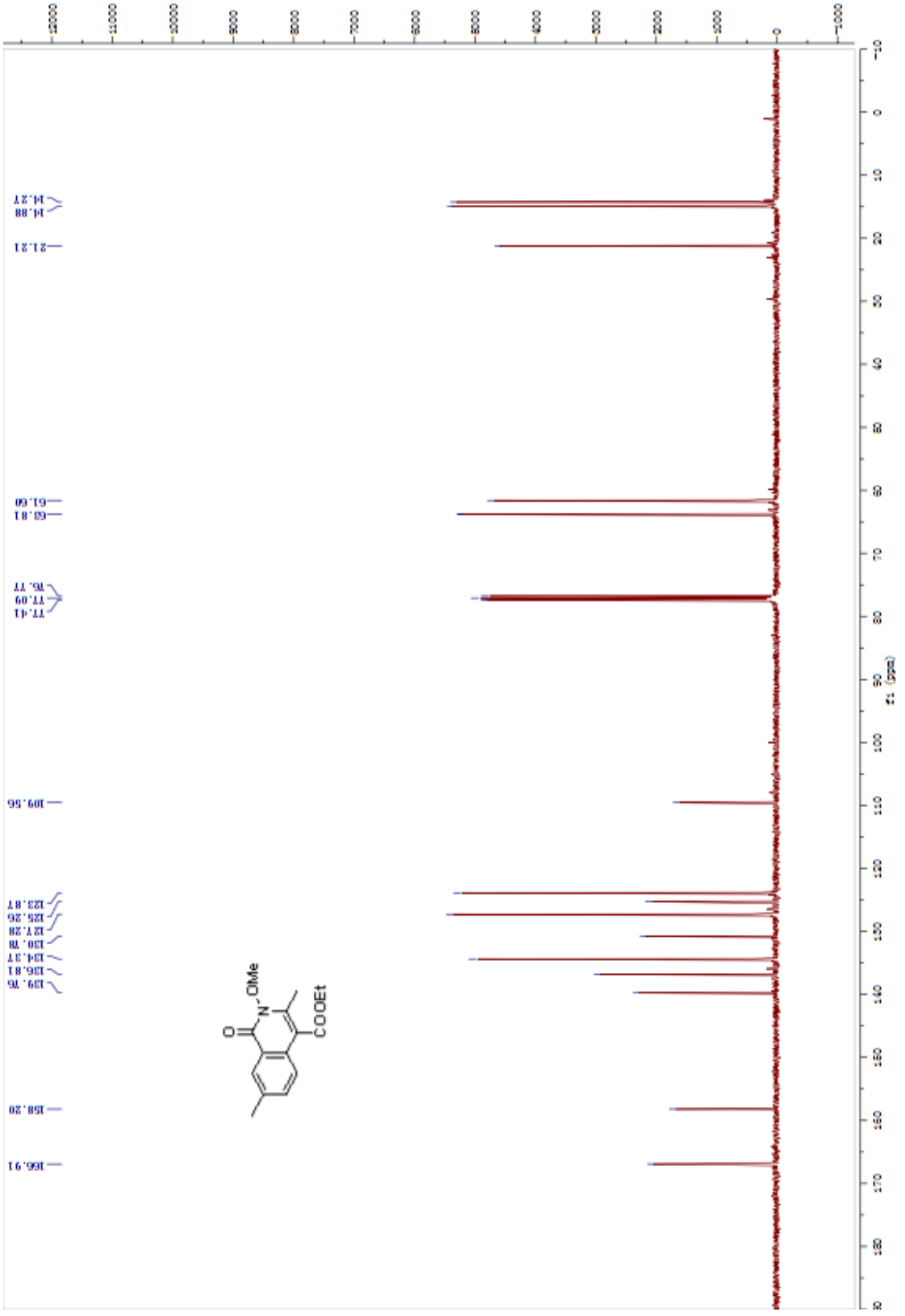
^{13}C NMR Spectrum of ethyl 6-bromo-2-methoxy-3-methyl-1-oxo-1,2-dihydro isoquinoline-4-carboxylate **3ha**



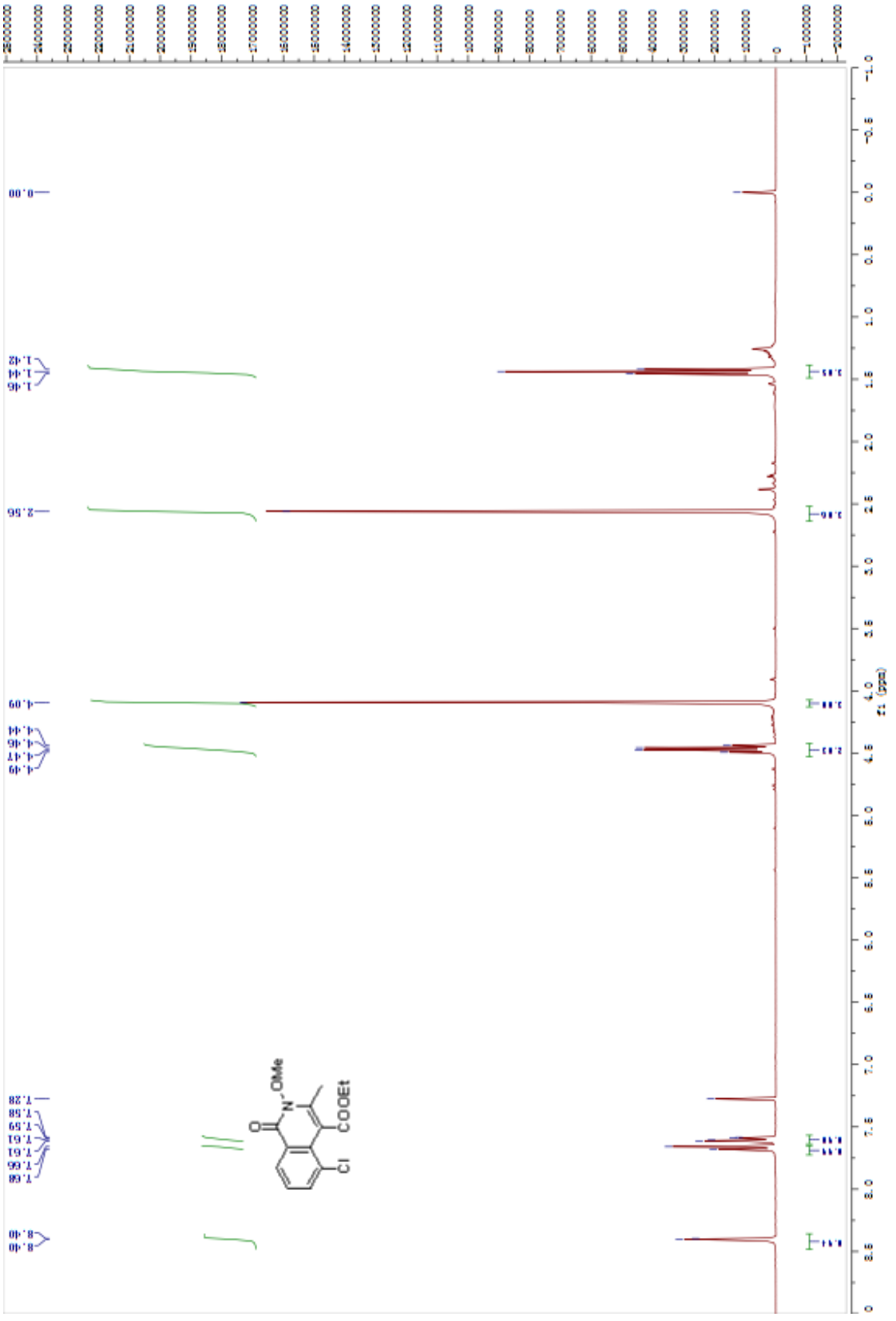
^{1}H NMR Spectrum of ethyl 2-methoxy-3,7-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ia**



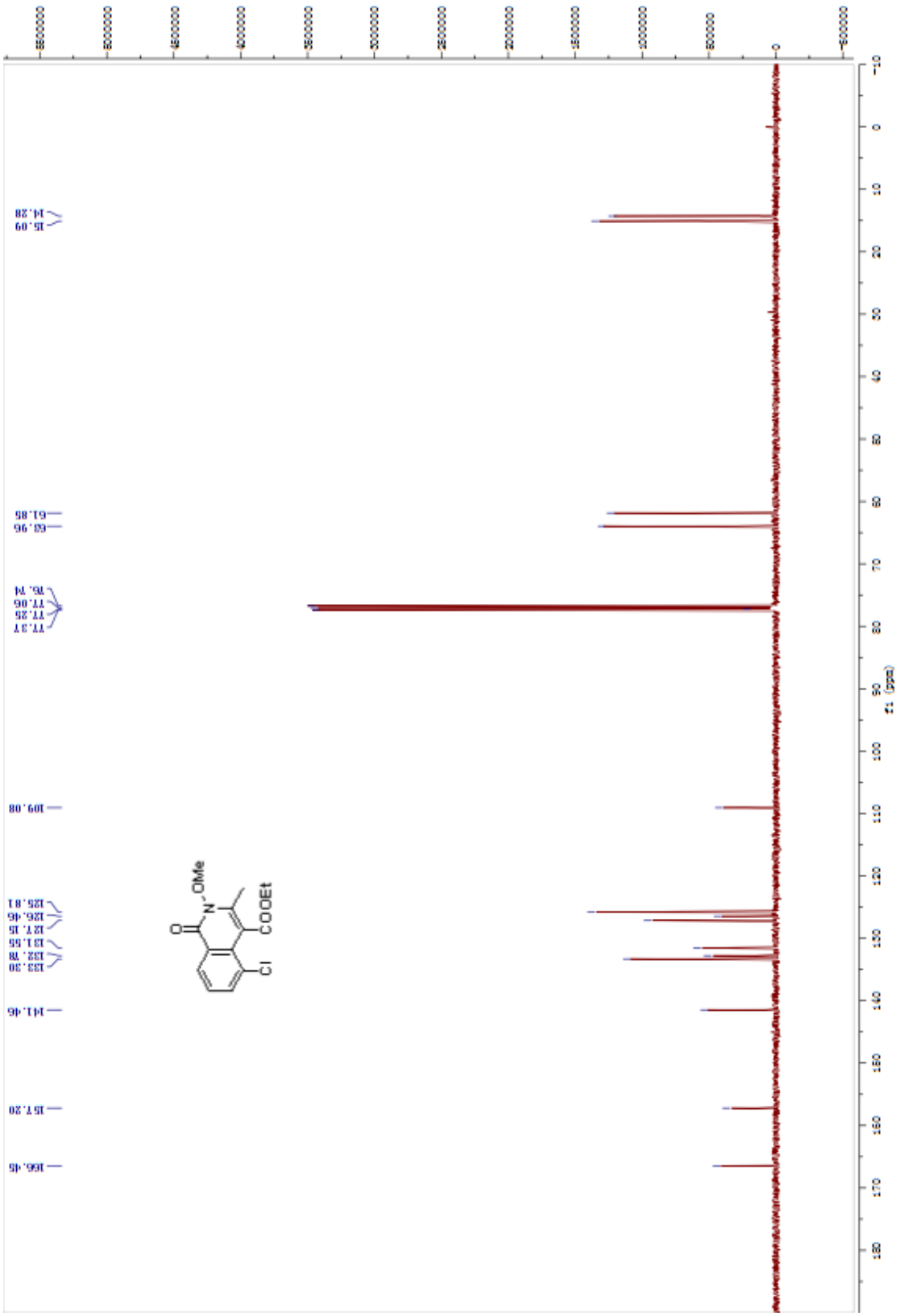
^{13}C NMR Spectrum of ethyl 2-methoxy-3,7-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ia**



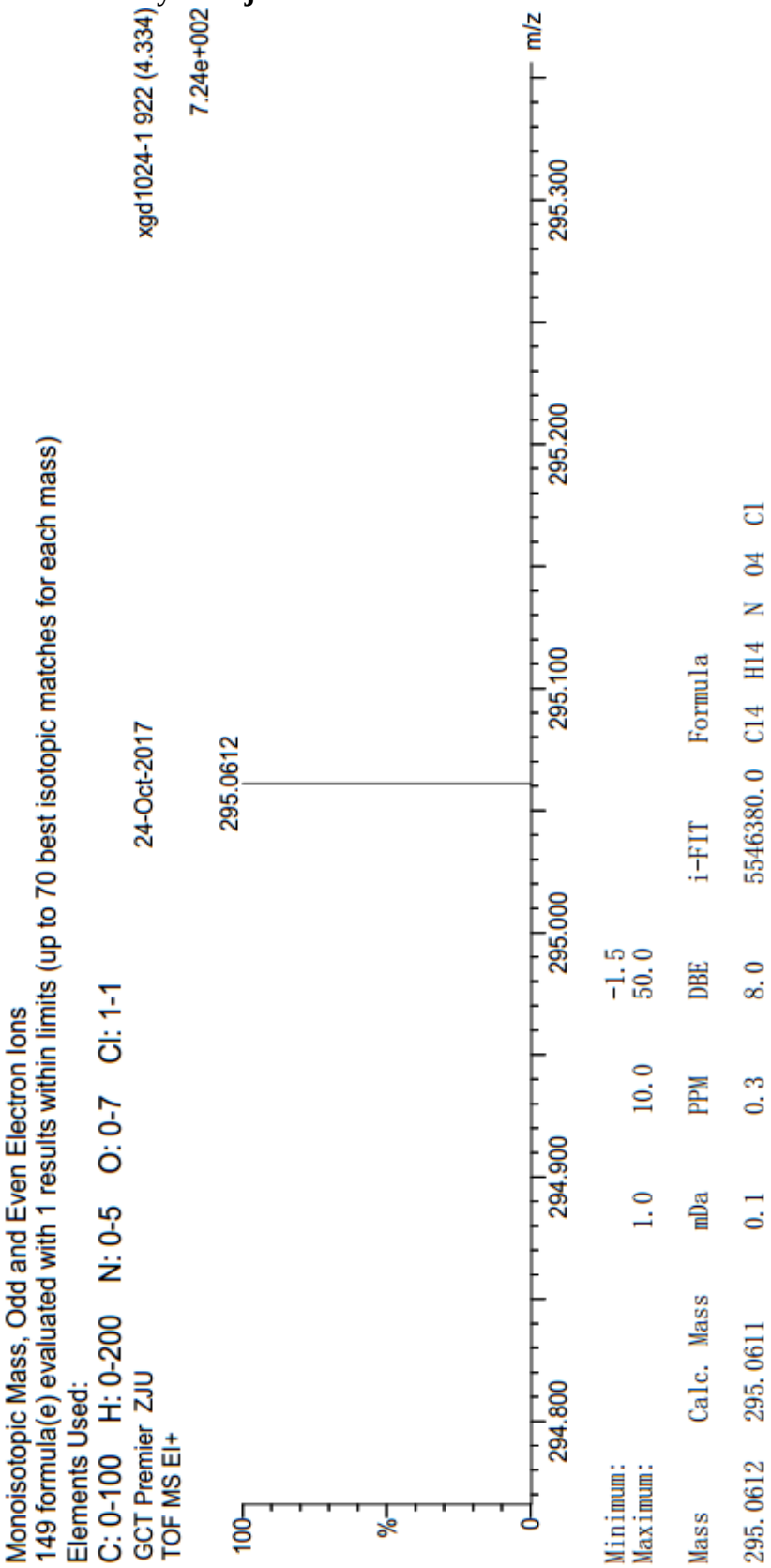
^{1}H NMR Spectrum of ethyl 5-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydro isoquinoline-4-carboxylate **3ja**



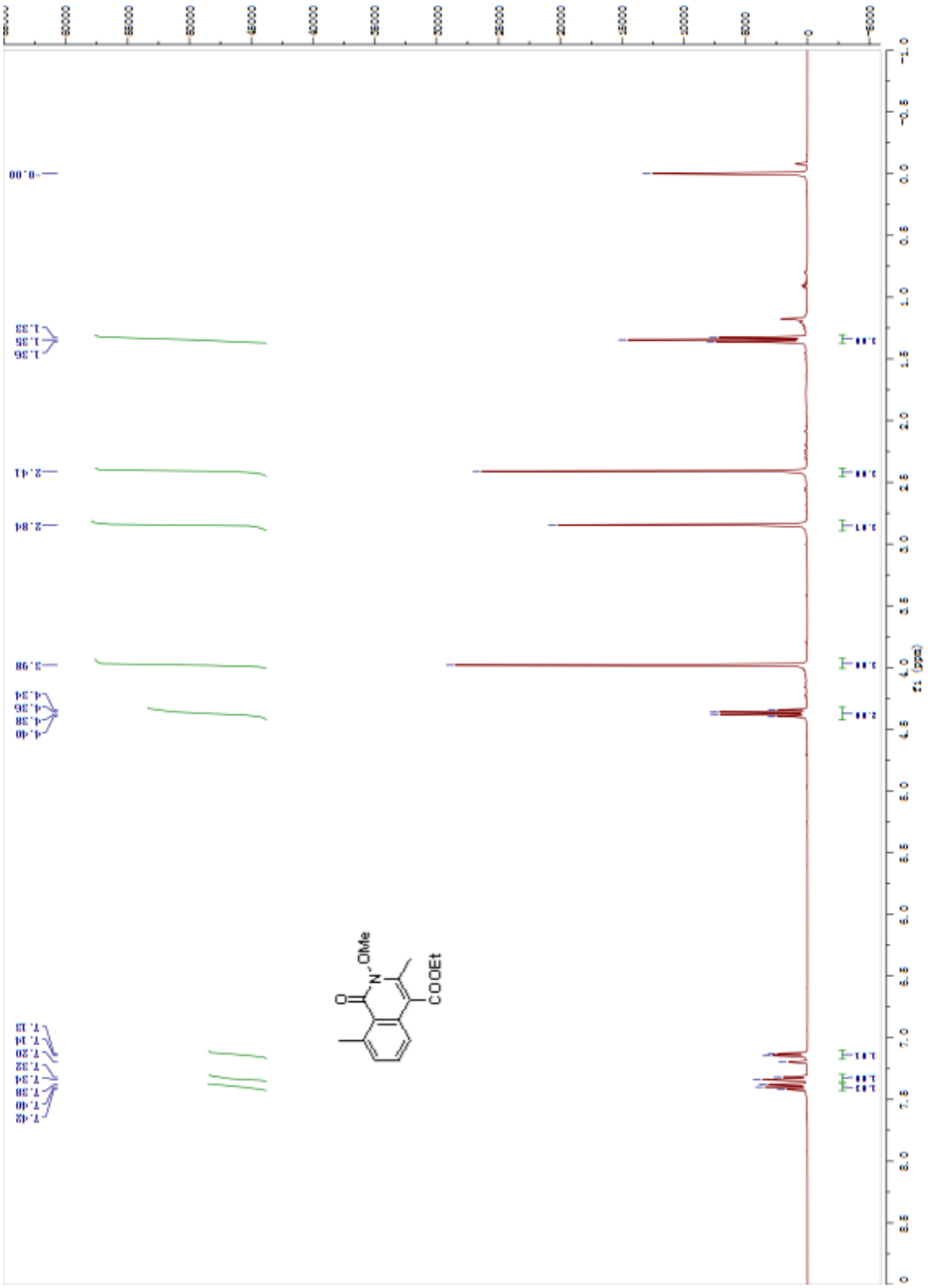
^{13}C NMR Spectrum of ethyl 5-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydro isoquinoline-4-carboxylate **3ja**



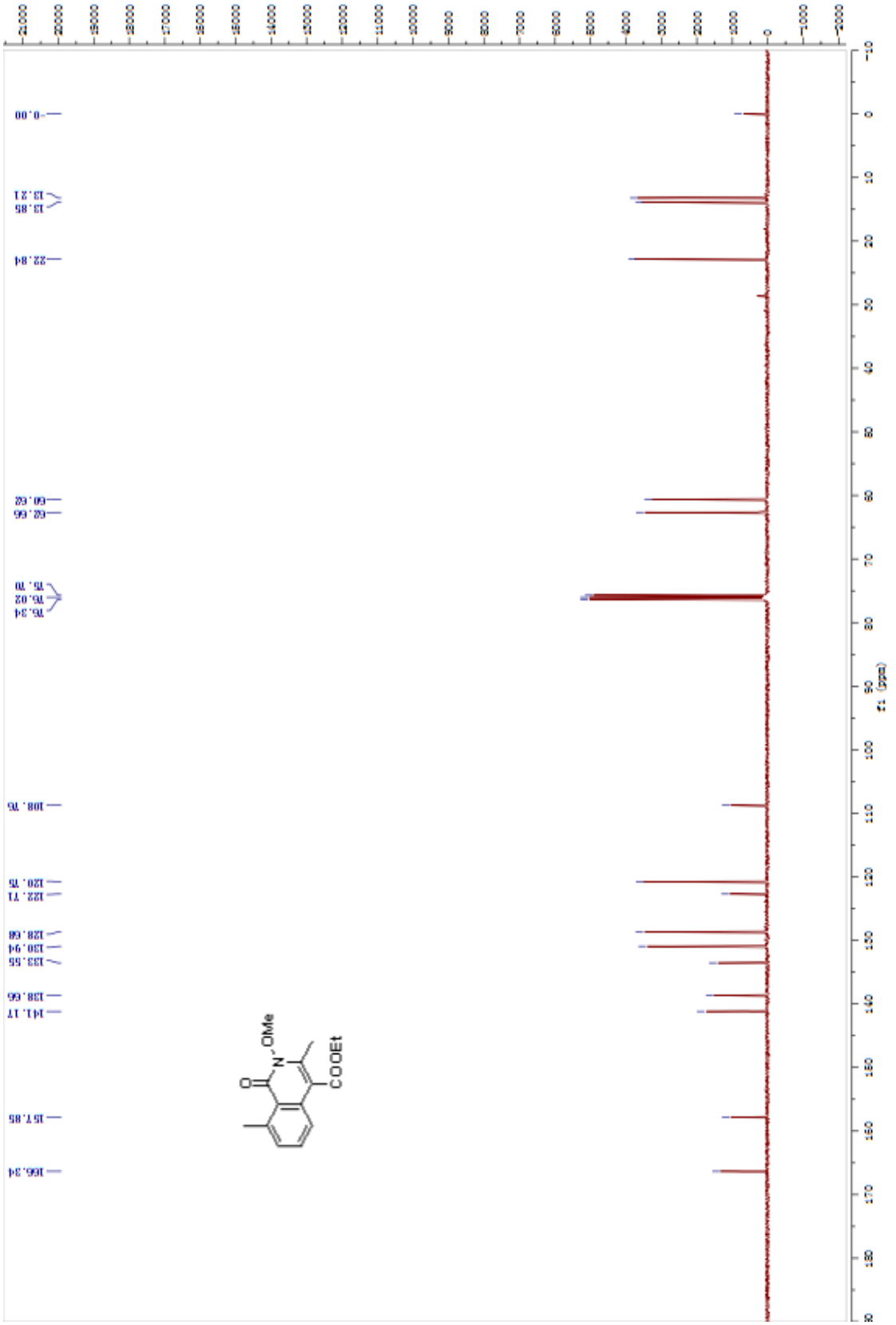
HR-MS Spectrum of ethyl 5-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydro isoquinoline-4-carboxylate **3ja**



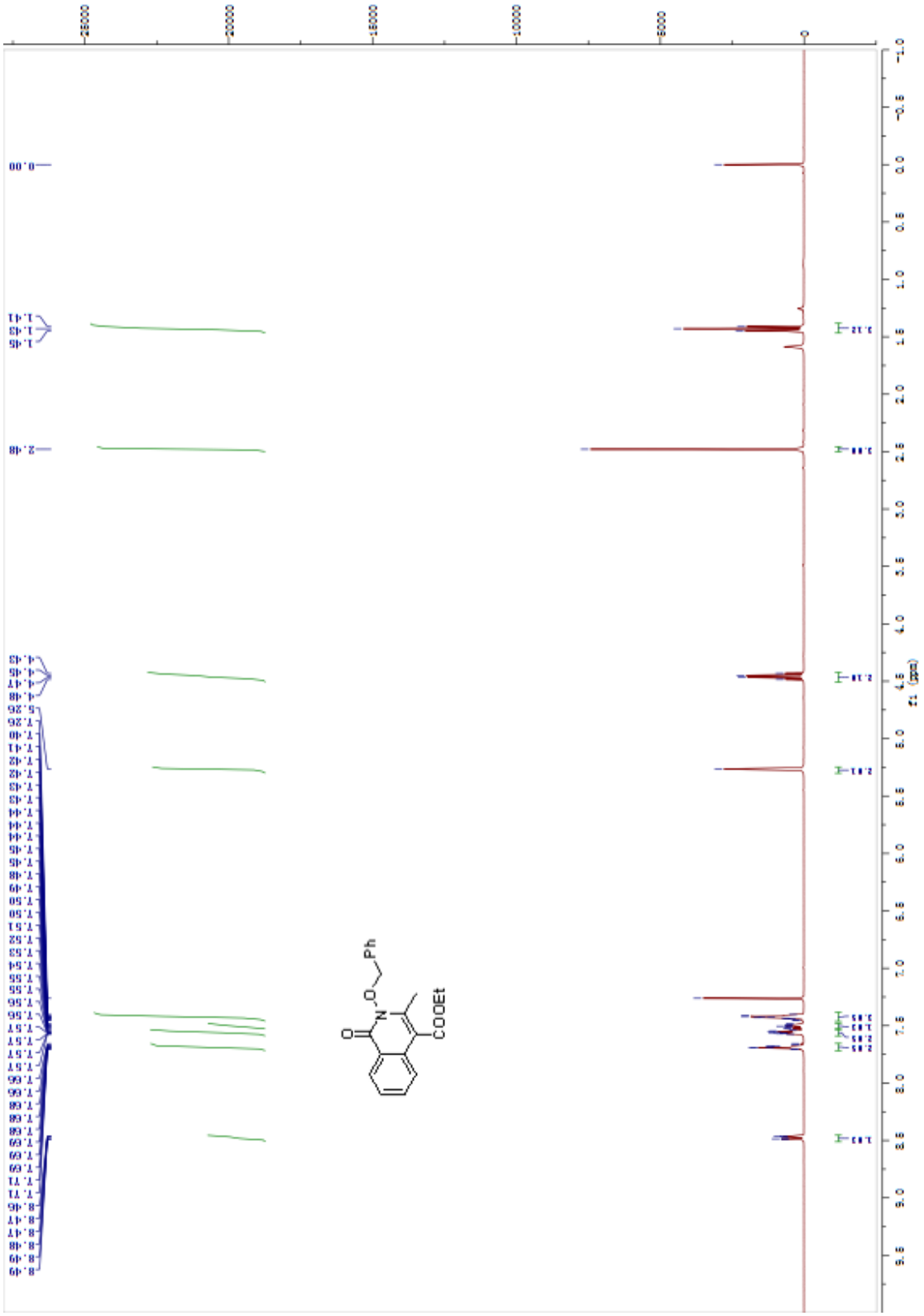
^{1}H NMR Spectrum of ethyl 2-methoxy-3,8-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ka**



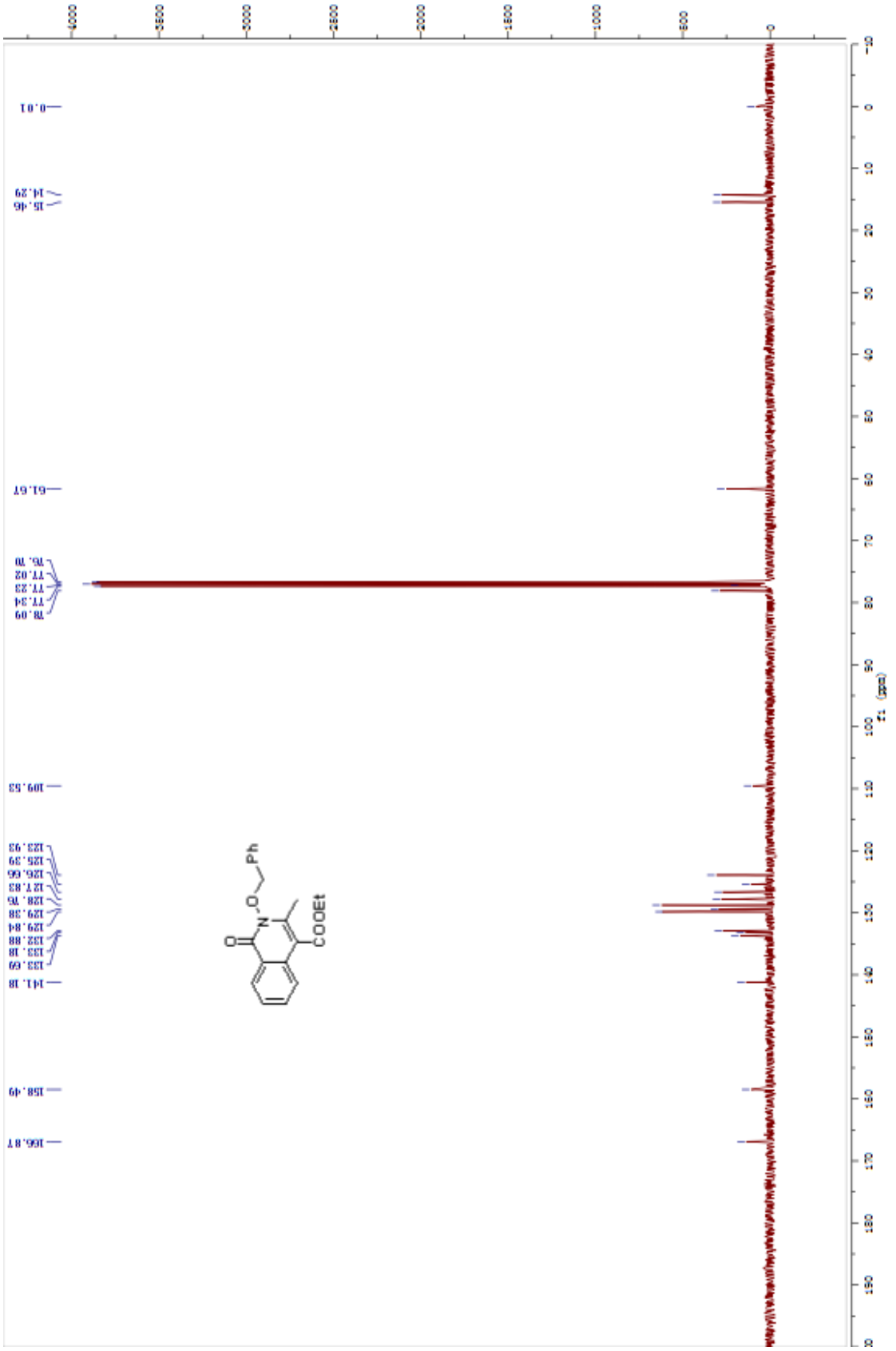
^{13}C NMR Spectrum of ethyl 2-methoxy-3,8-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ka**



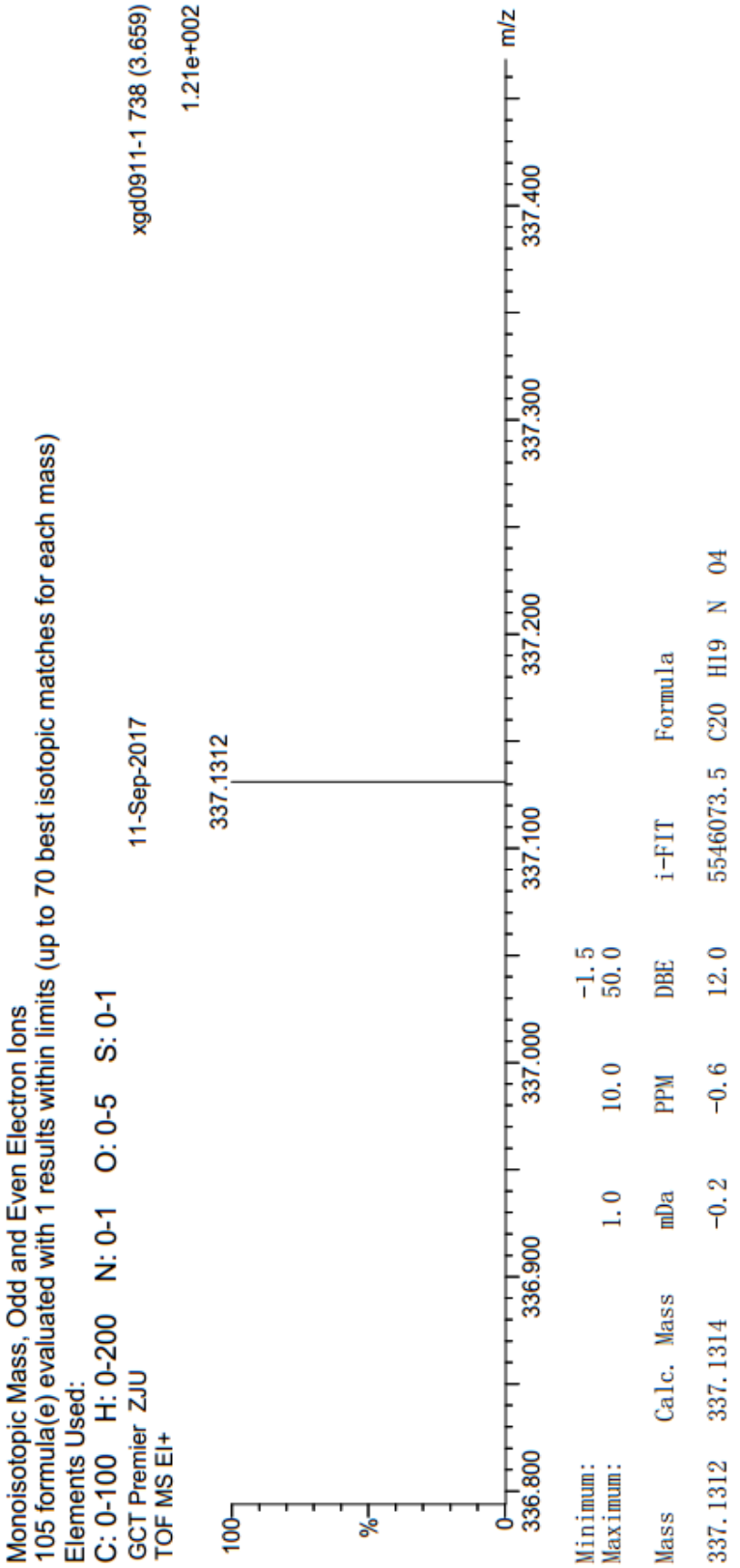
^{1}H NMR Spectrum of ethyl 2-(benzyloxy)-3-methyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3la**



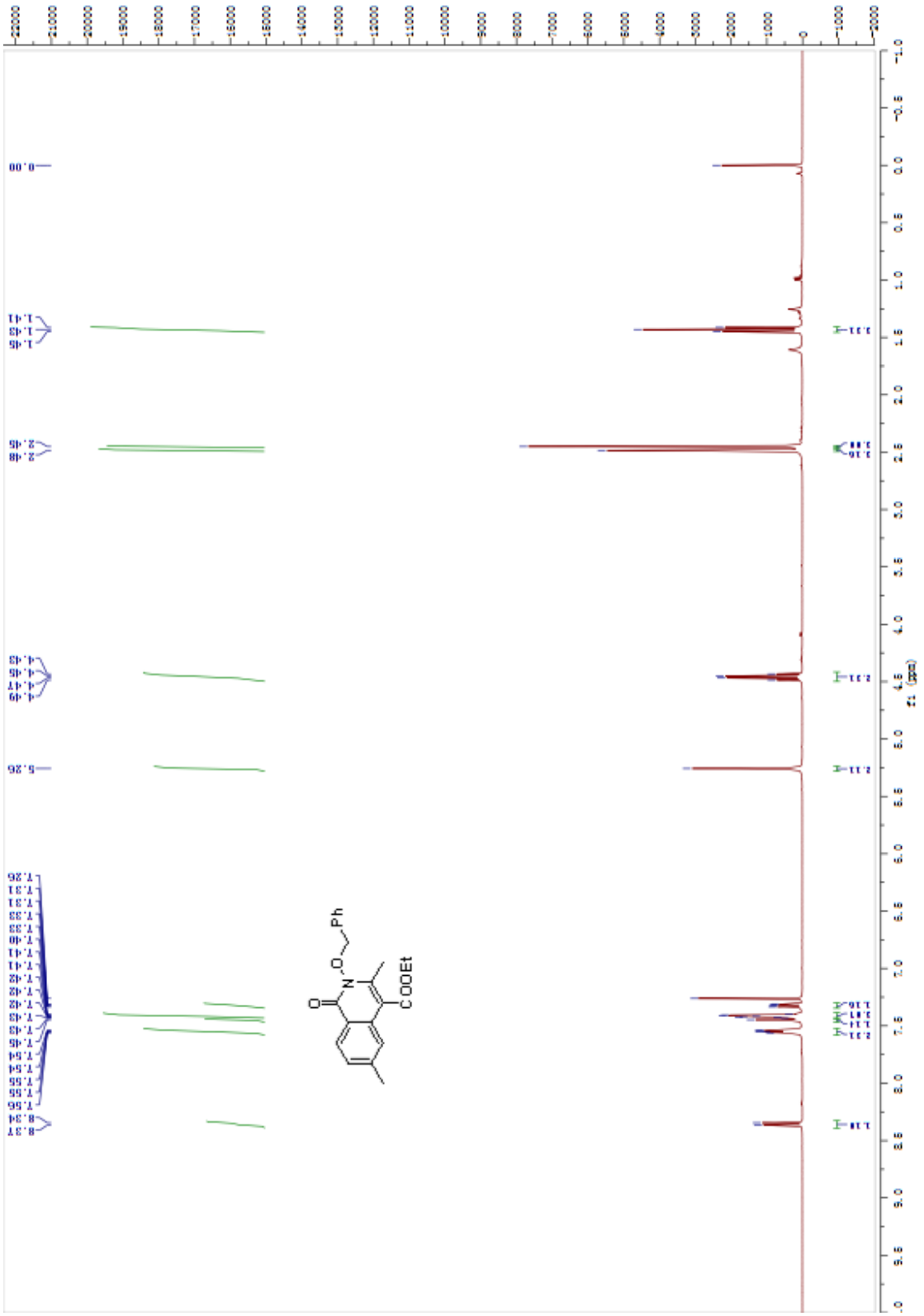
^{13}C NMR Spectrum of ethyl 2-(benzyloxy)-3-methyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3la**



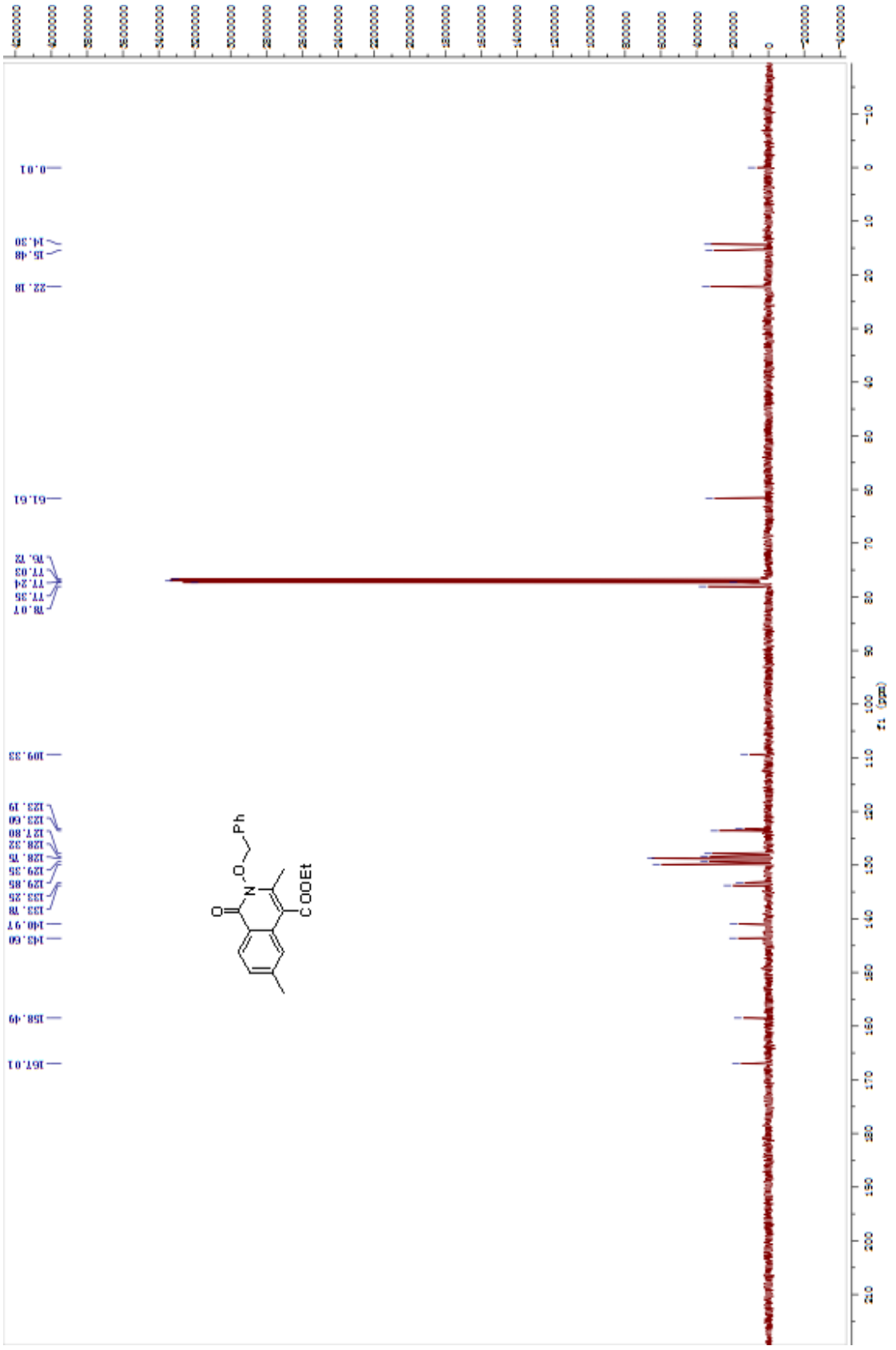
HR-MS Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-6-phenyl-1,2-dihydroiso quinoline-4-carboxylate **3la**



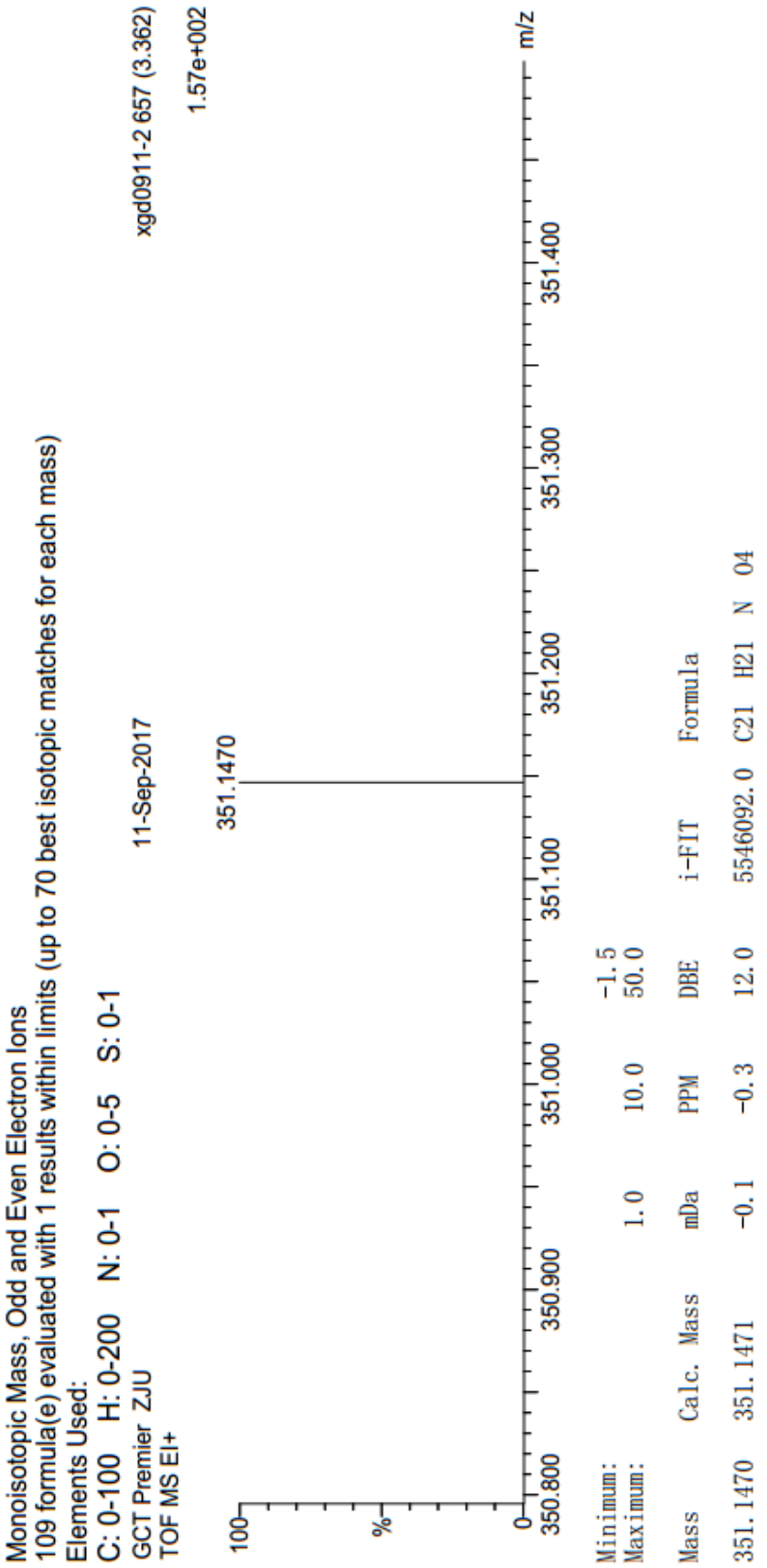
^{1}H NMR Spectrum of ethyl 2-(benzyloxy)-3,6-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ma**



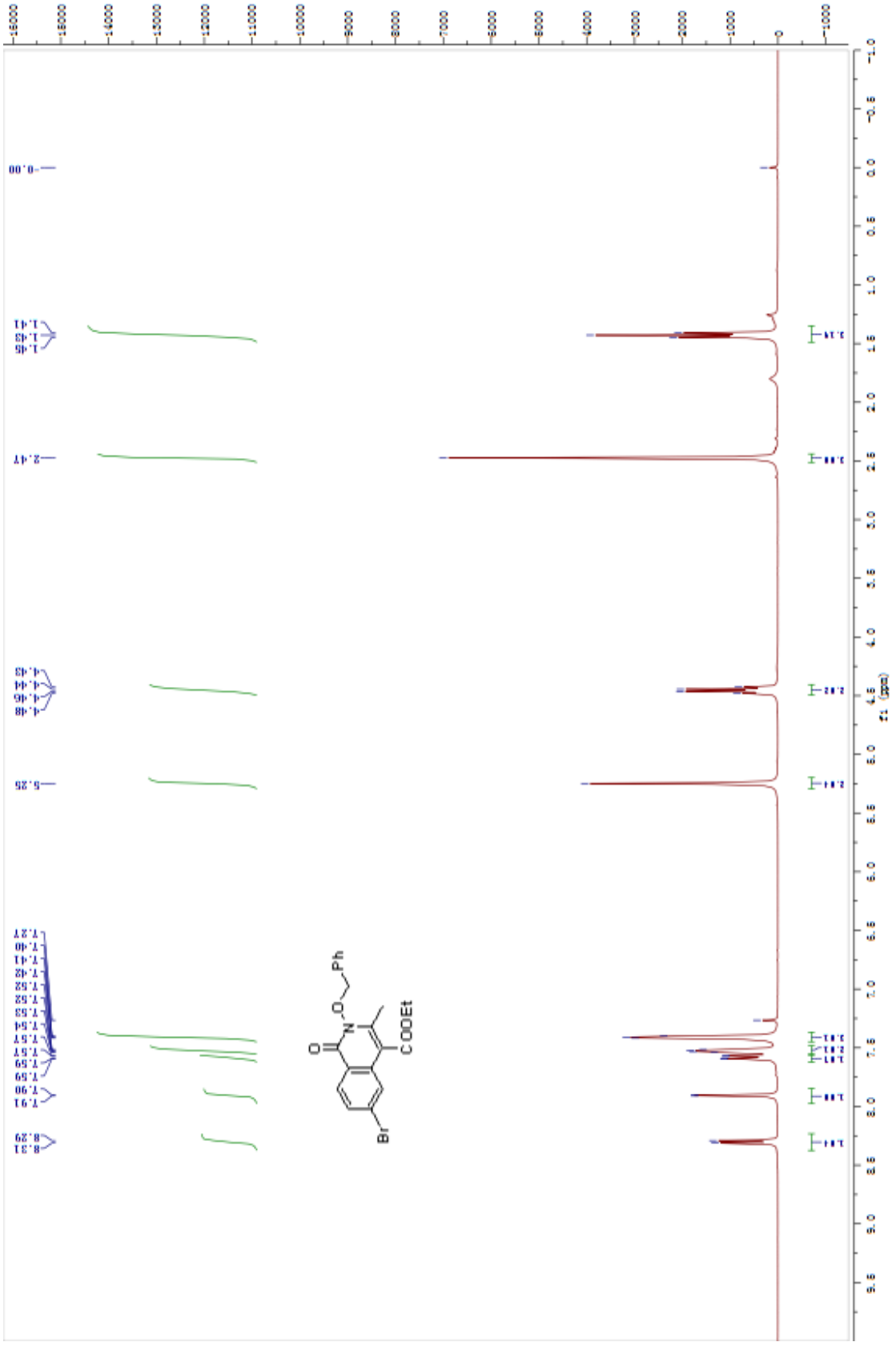
^{13}C NMR Spectrum of ethyl 2-(benzyloxy)-3,6-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ma**



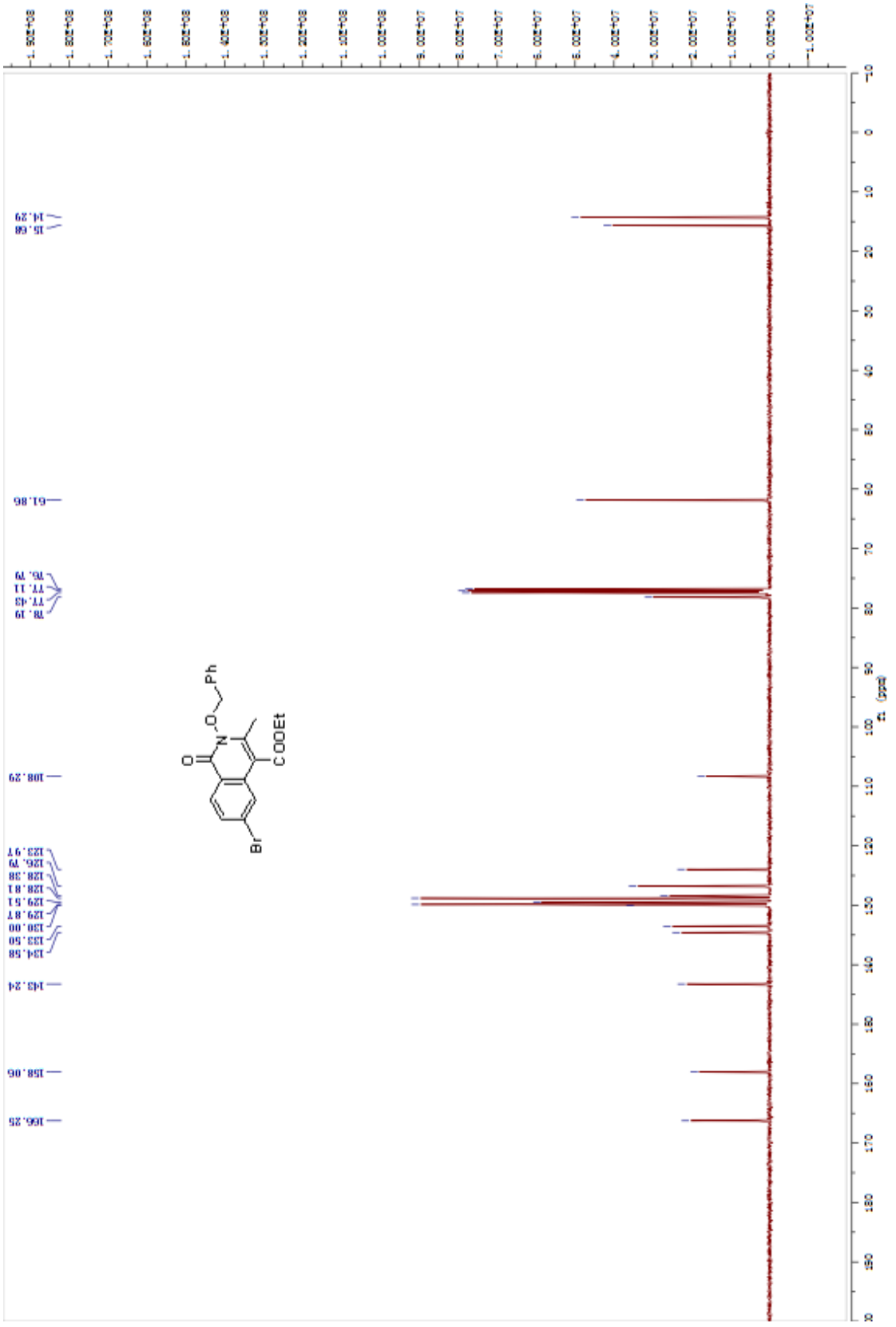
HR-MS Spectrum of ethyl 2-(benzyloxy)-3,6-dimethyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ma**



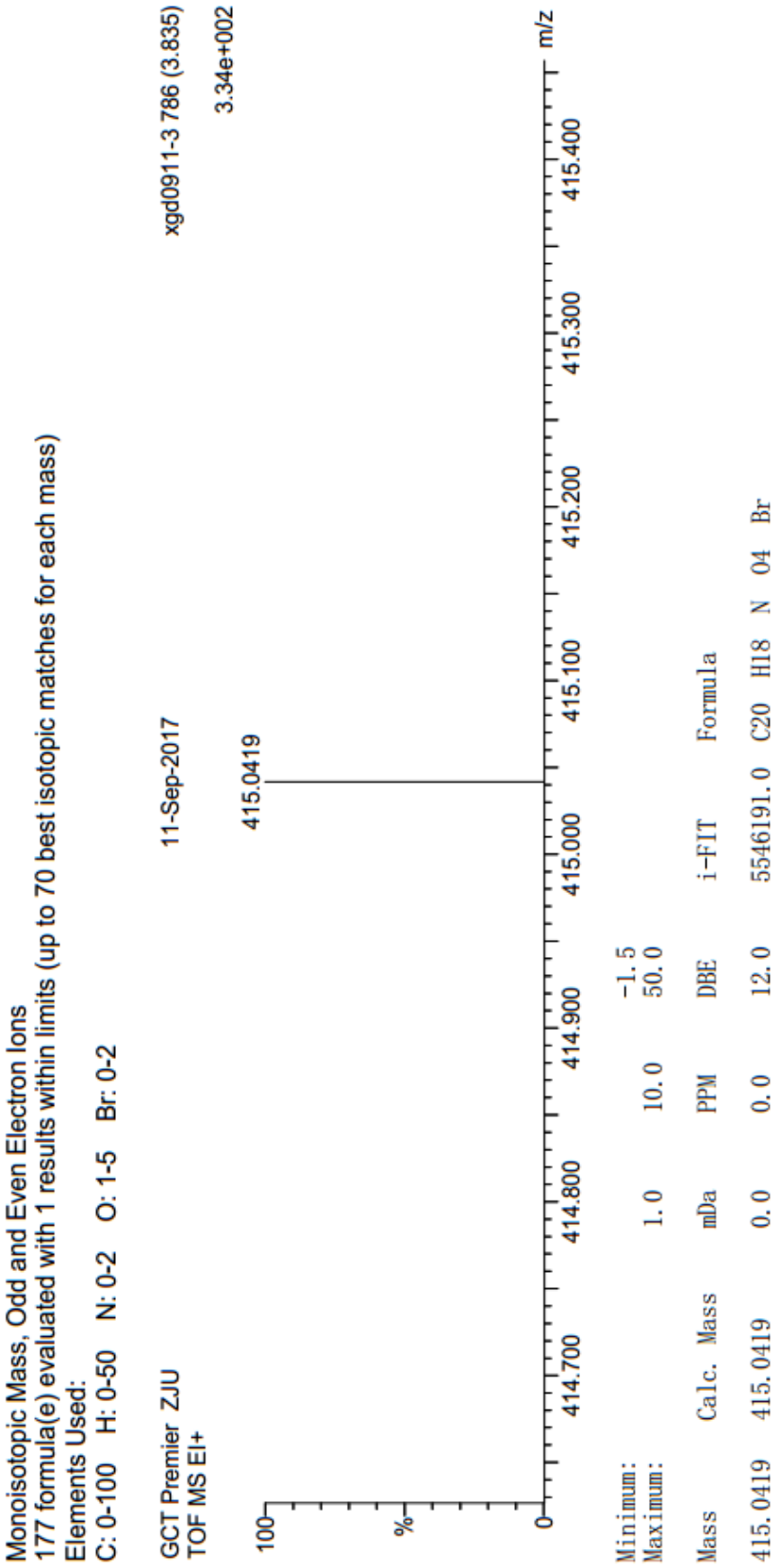
^{1}H NMR Spectrum of ethyl 2-(benzyloxy)-6-bromo-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3na**



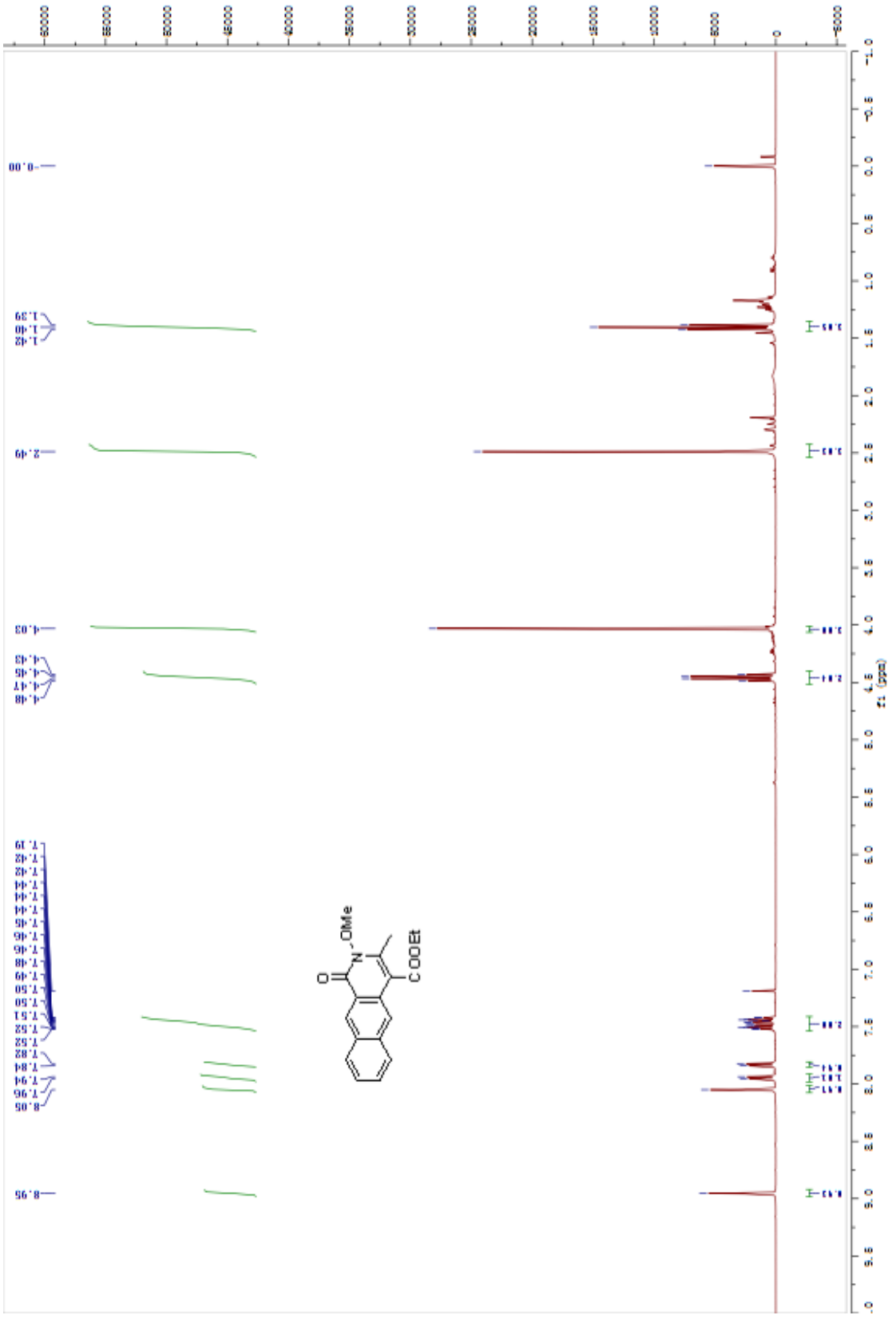
^{13}C NMR Spectrum of ethyl 2-(benzyloxy)-6-bromo-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3na**



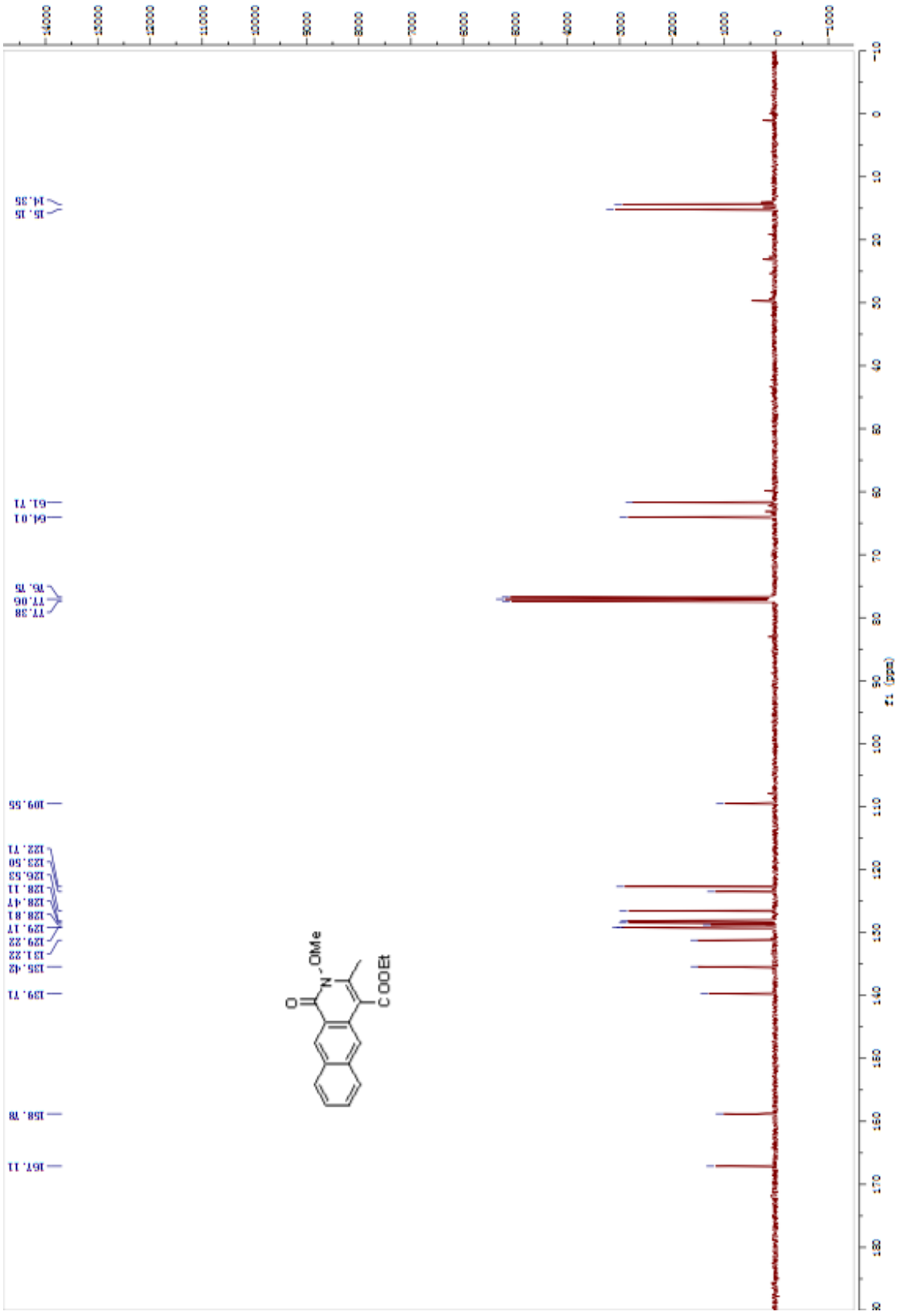
HR-MS Spectrum of ethyl 2-(benzyloxy)-6-bromo-3-methyl-1-oxo-1,2-dihydro isoquinoline-4 -carboxylate **3na**



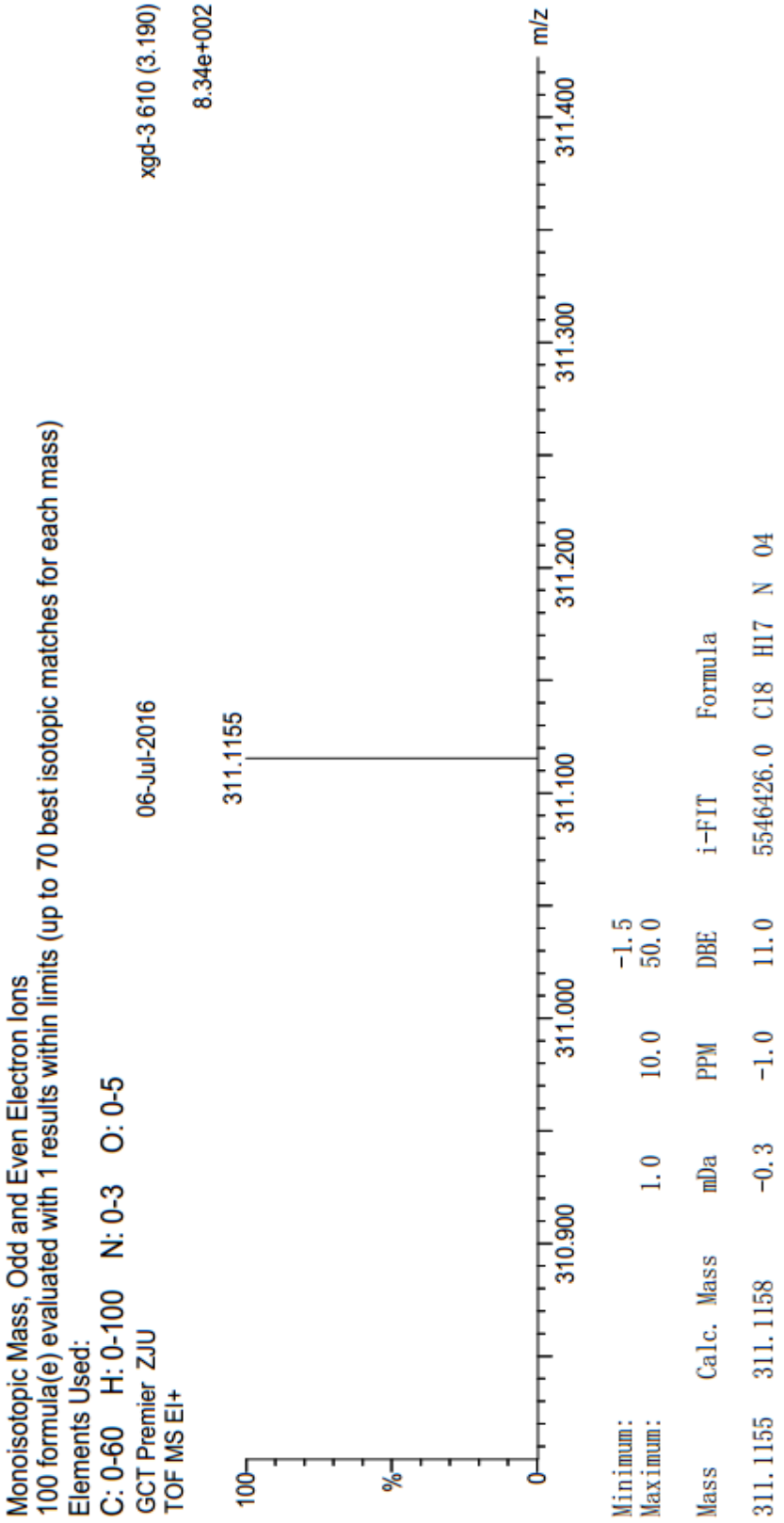
^{1}H NMR Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-1,2-dihydrobenzo[g] isoquinoline-4-carboxylate **3oa**



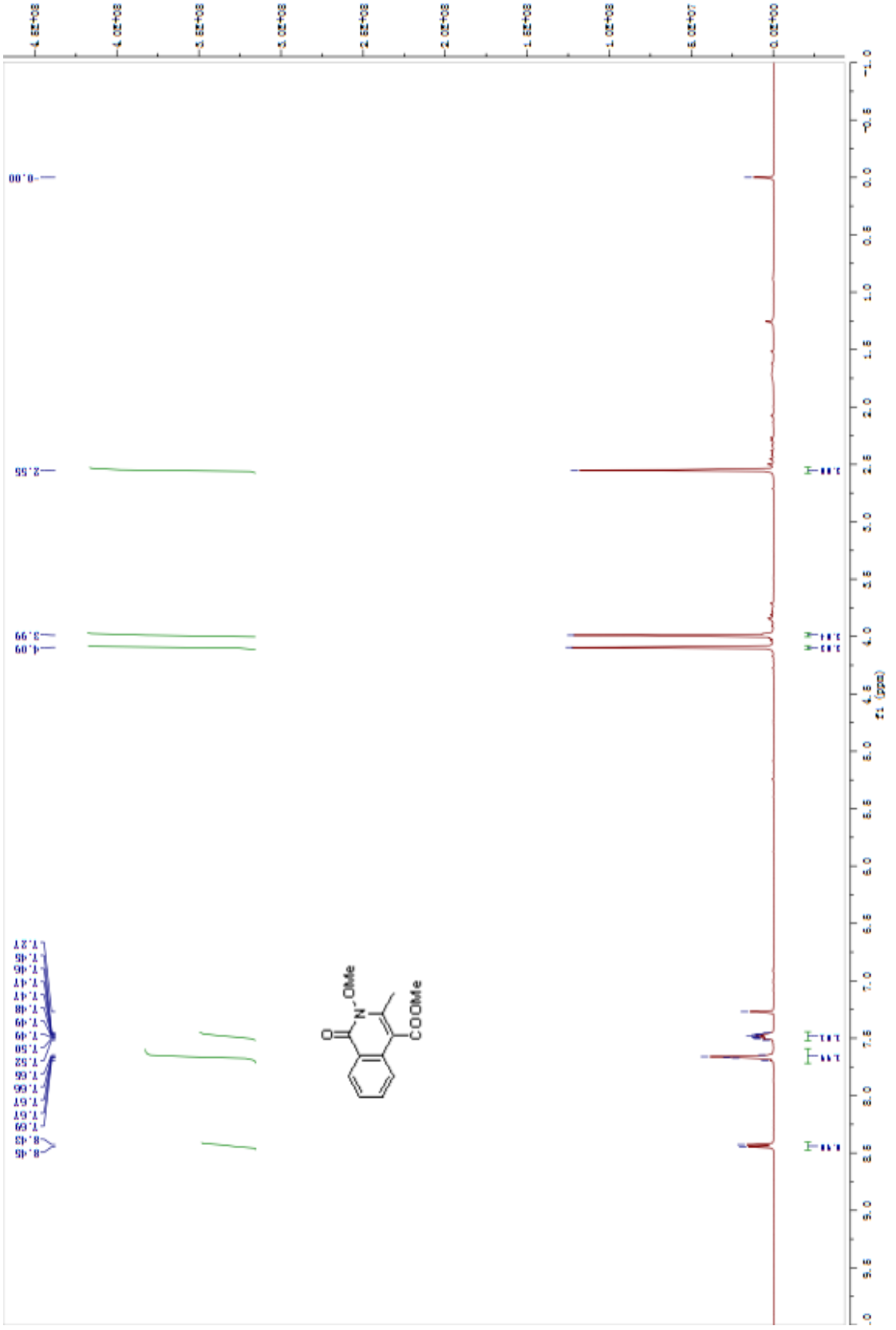
^{13}C NMR Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-1,2-dihydrobenzo[g] isoquinoline-4-carboxylate **3oa**



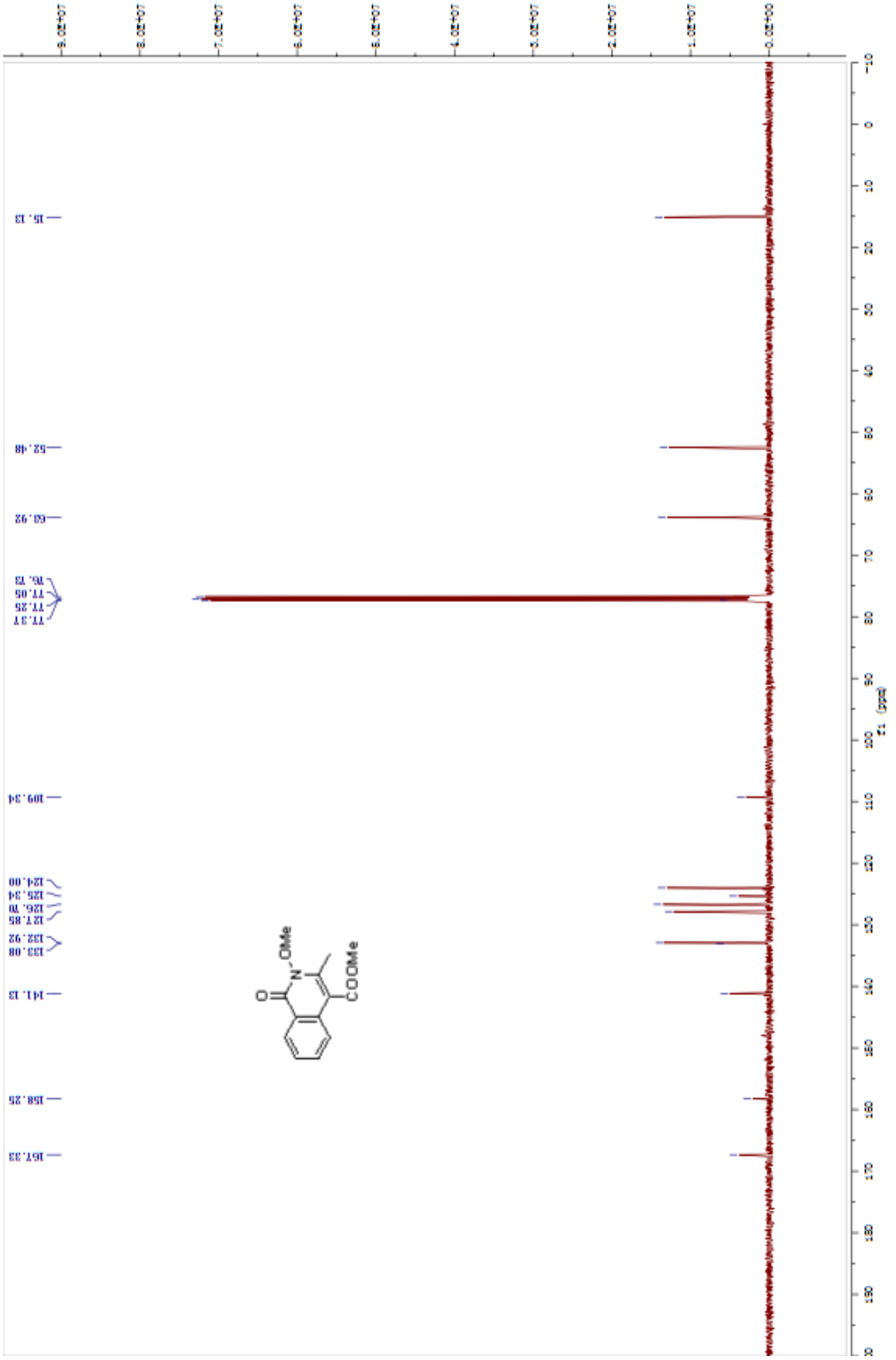
HR-MS Spectrum of ethyl 2-methoxy-3-methyl-1-oxo-1,2-dihydrobenzo[g]iso quinoline-4-carboxylate **3oa**



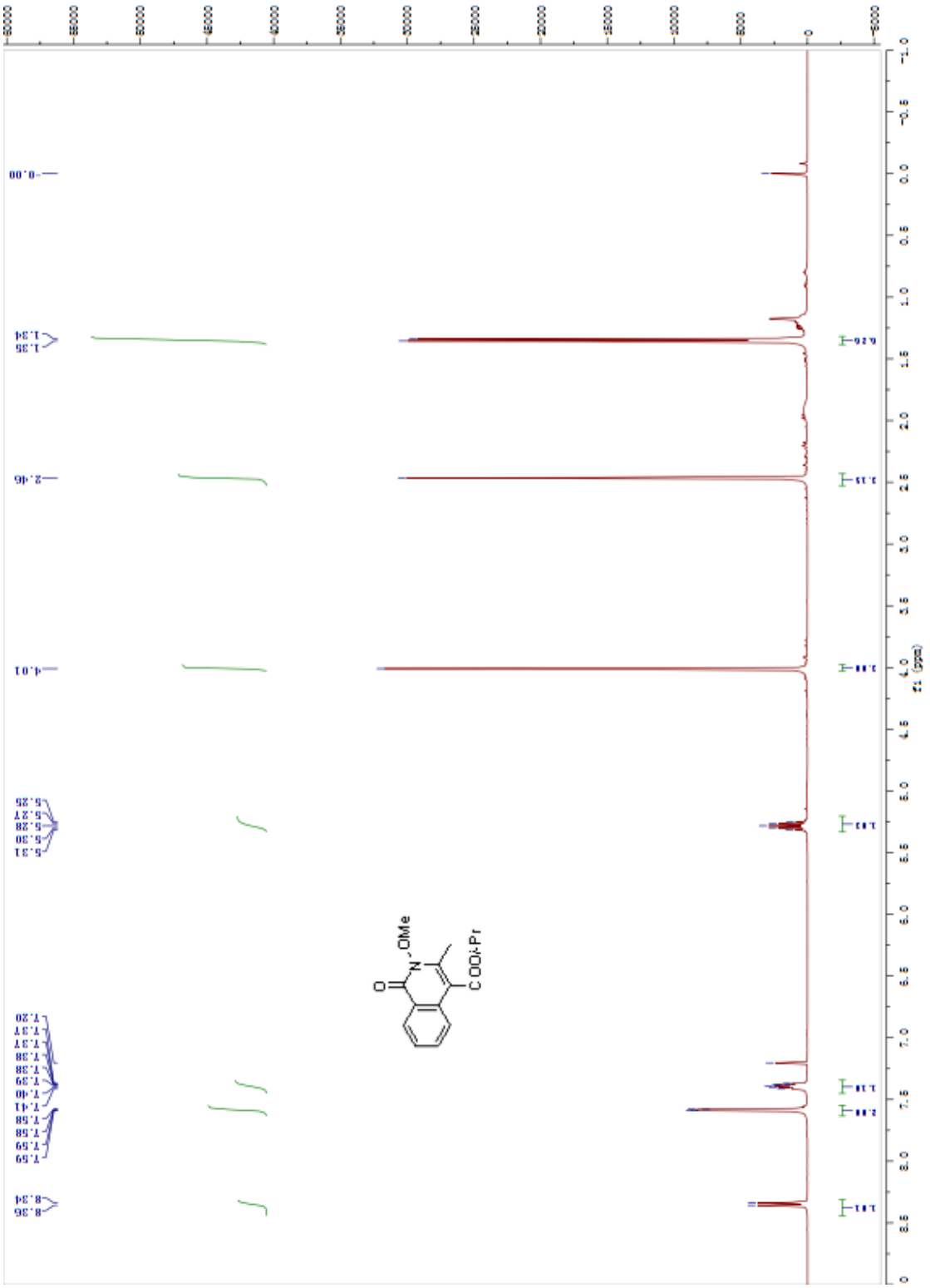
^{1}H NMR of methyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ab**



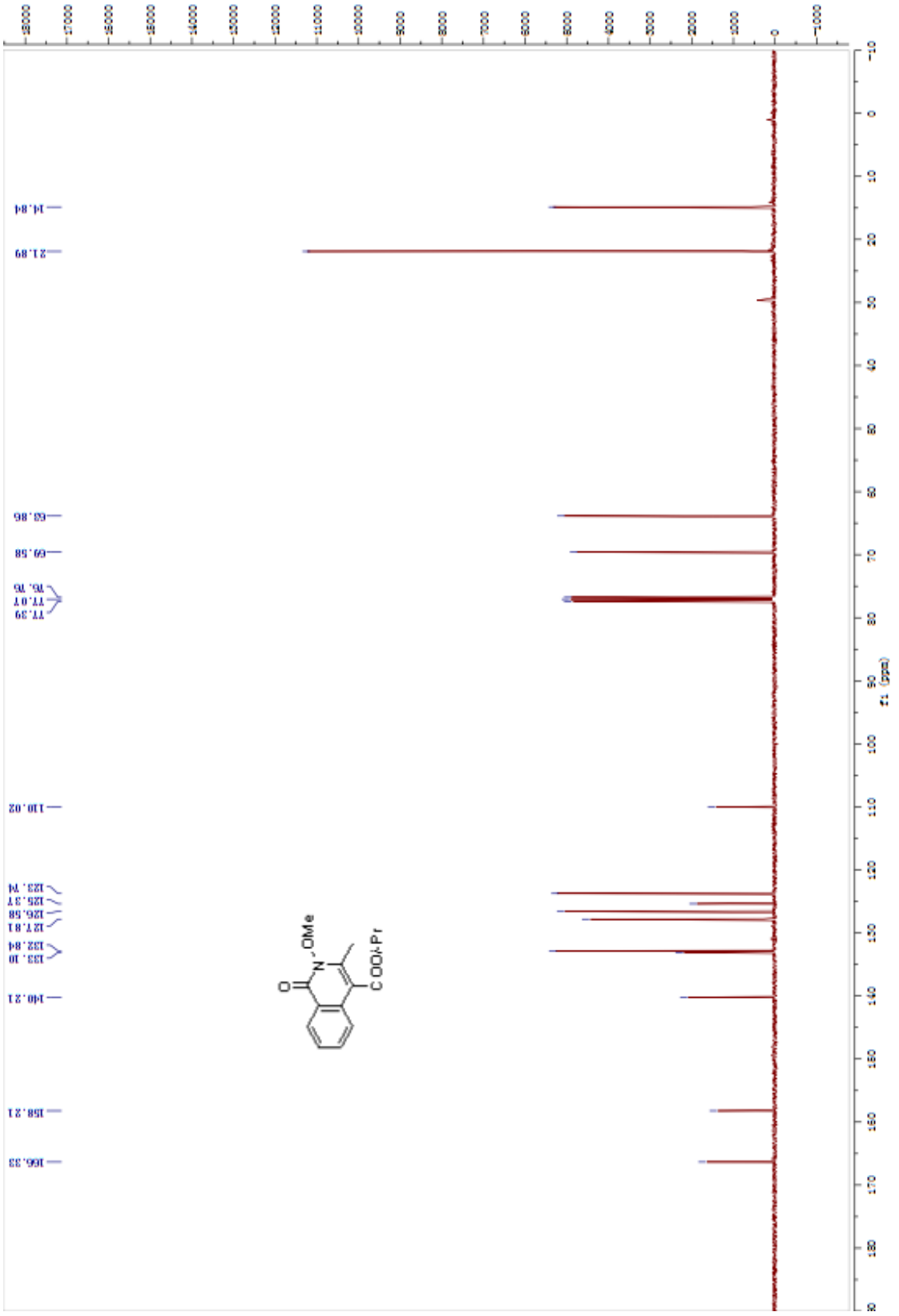
^{13}C NMR of methyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ab**



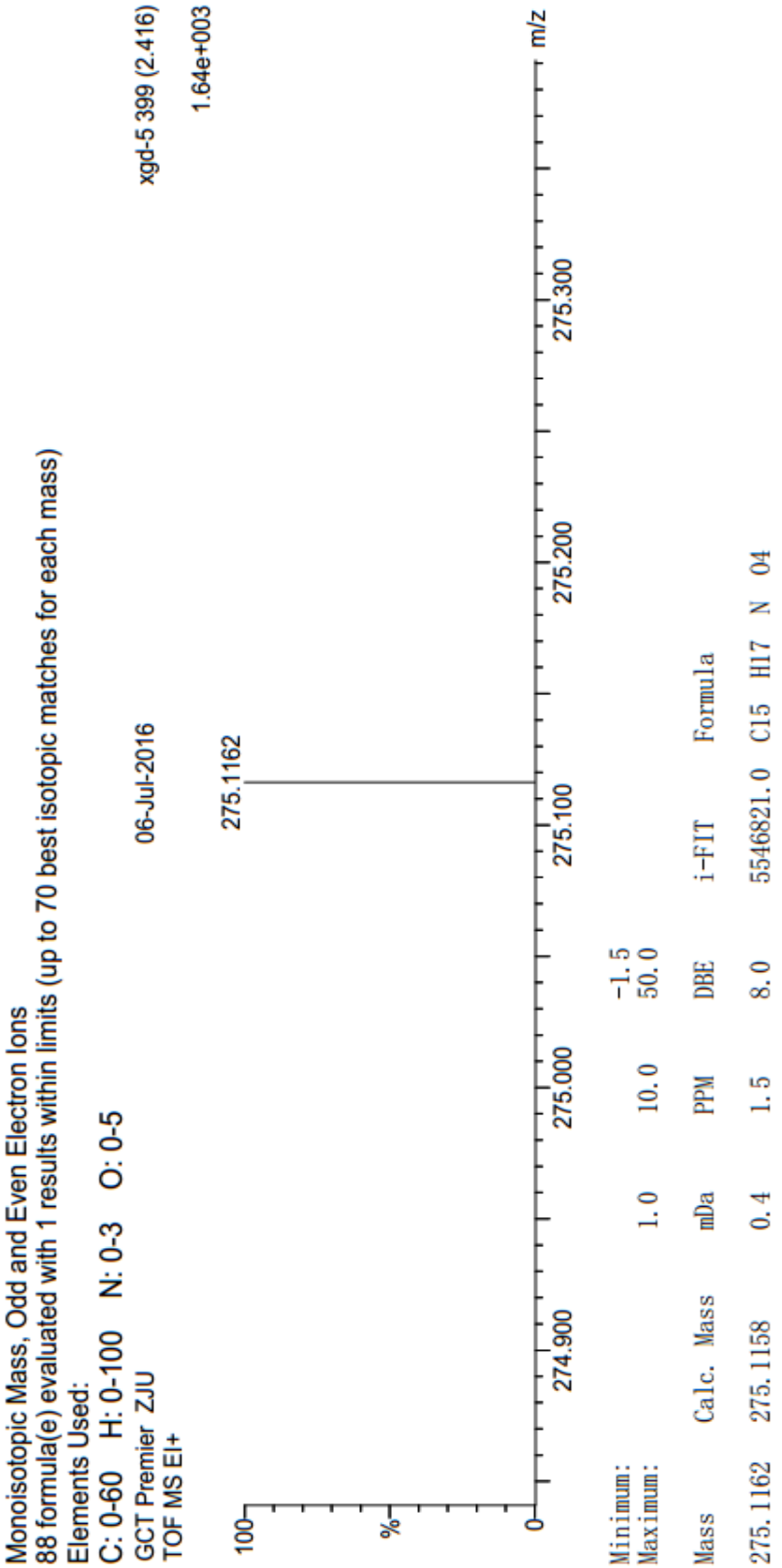
^{1}H NMR Spectrum of isopropyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ac**



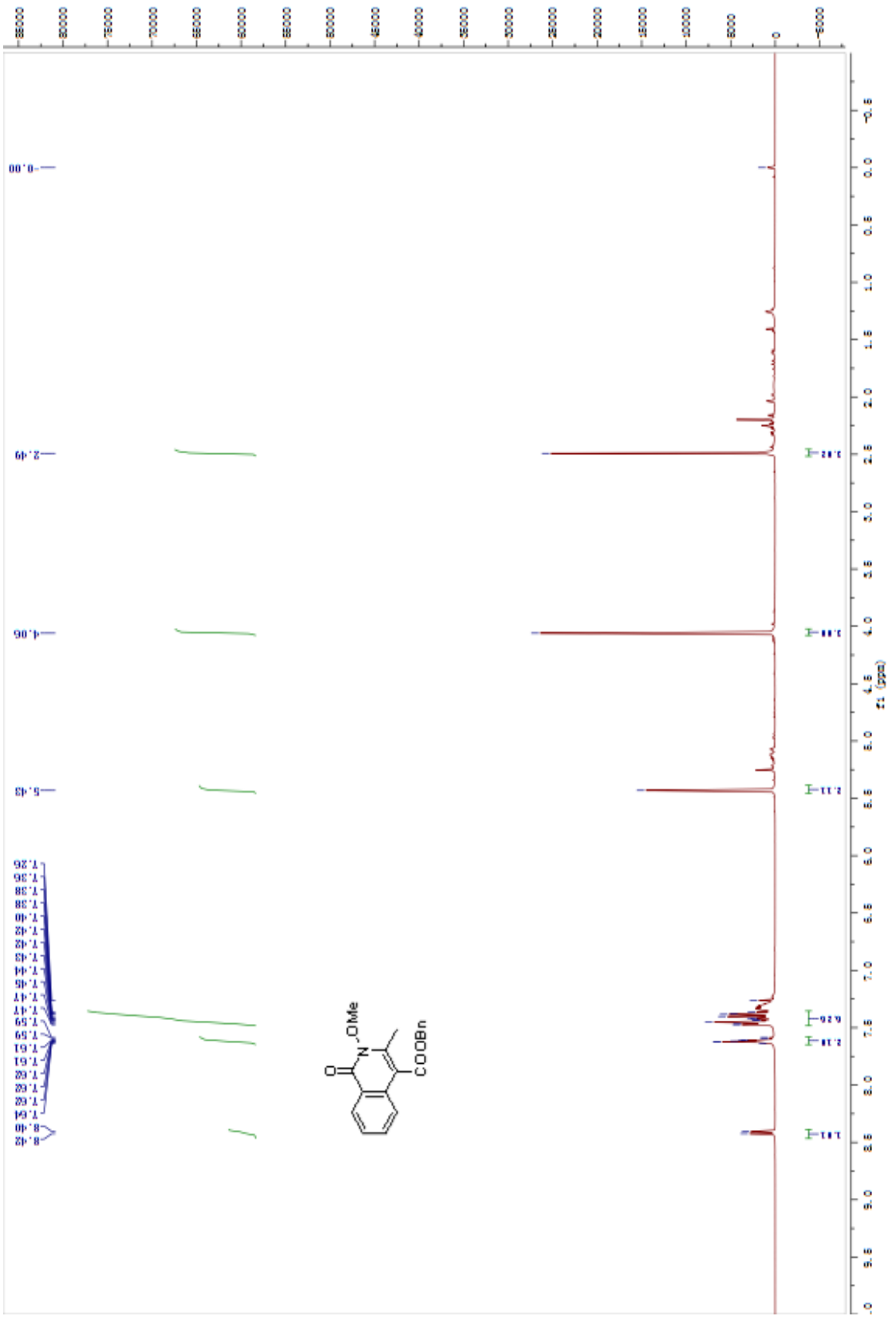
^{13}C NMR Spectrum of isopropyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ac**



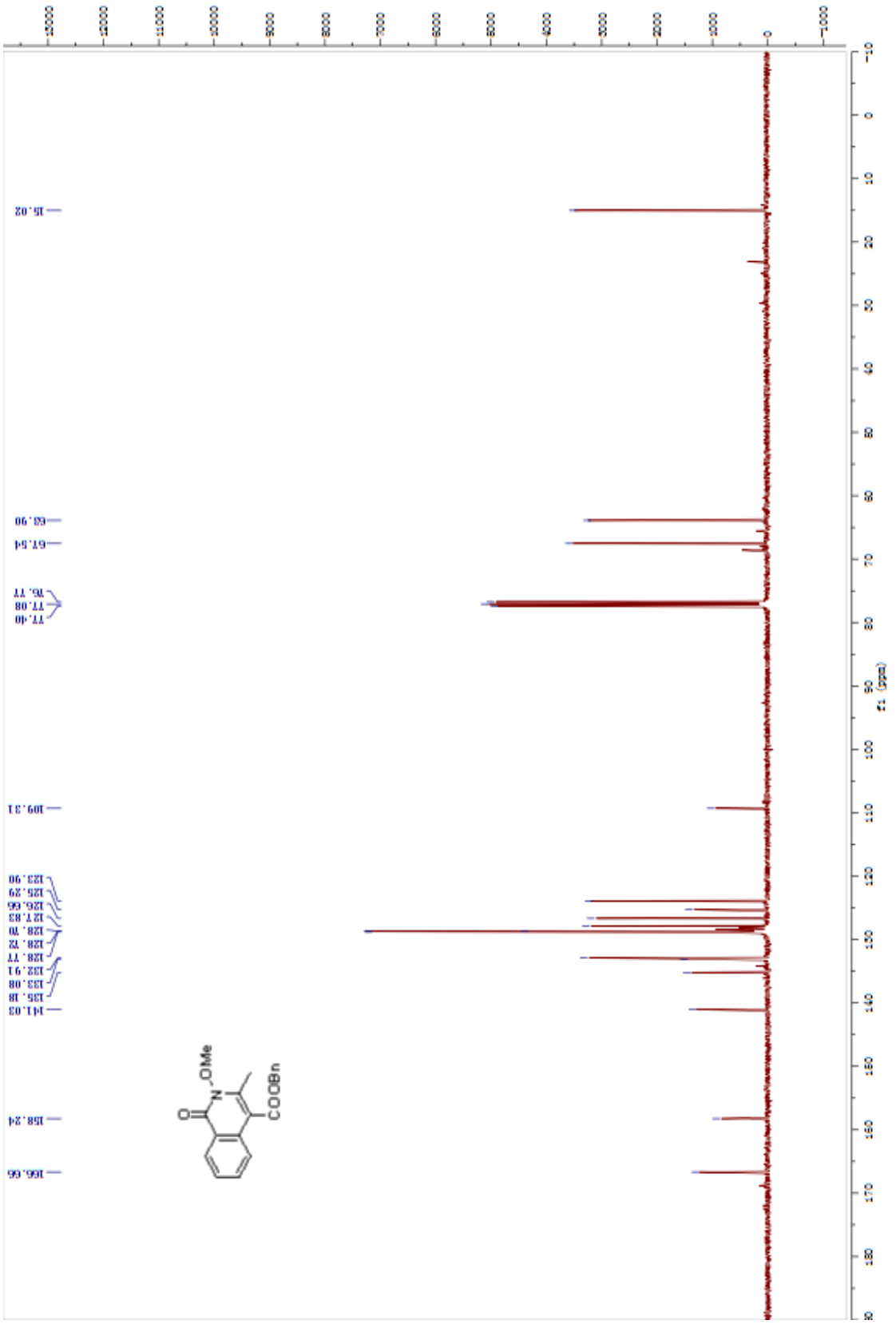
HR-MS Spectrum of isopropyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ac**



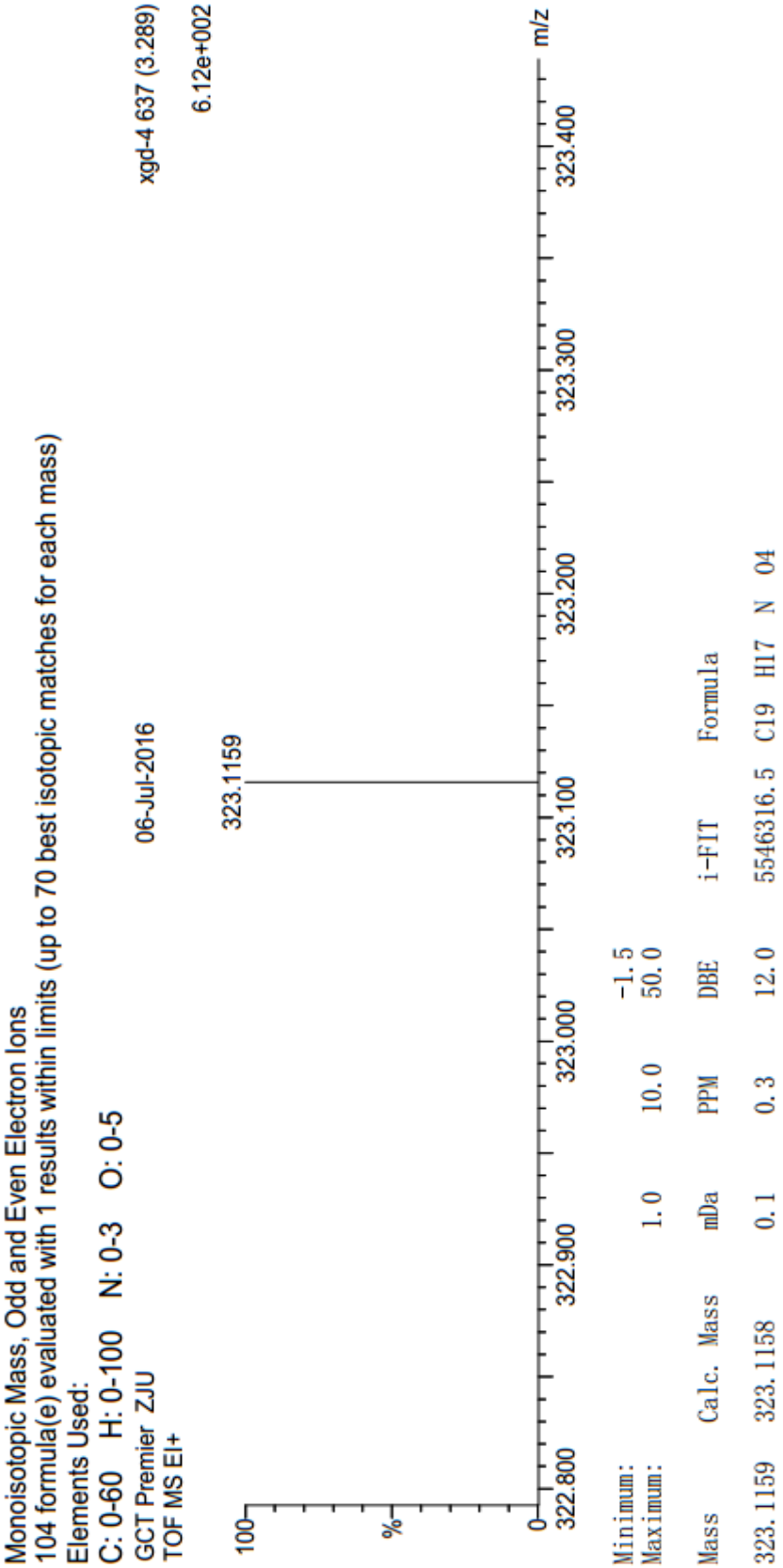
^{1}H NMR Spectrum of benzyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ad**



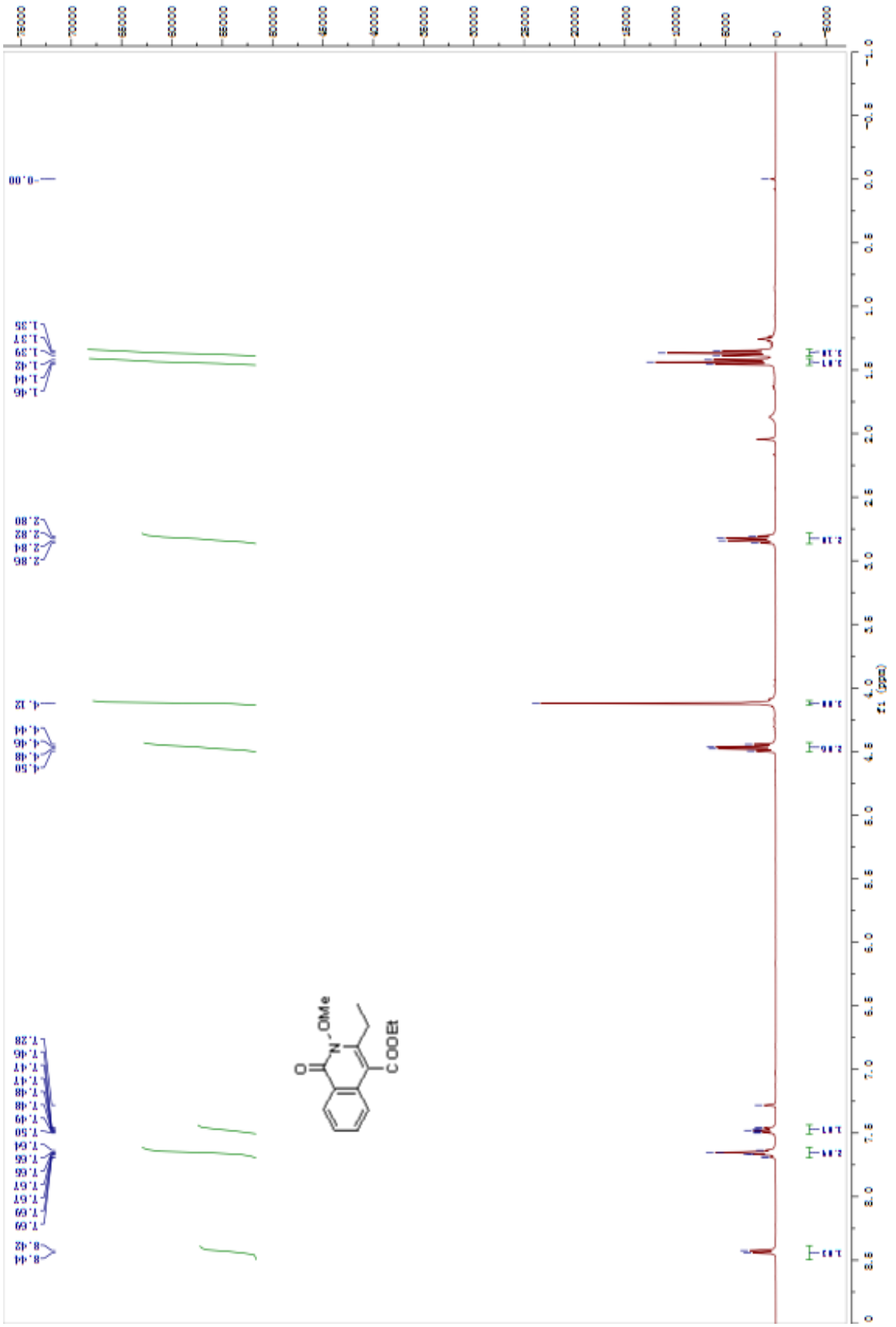
^{13}C NMR Spectrum of benzyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ad**



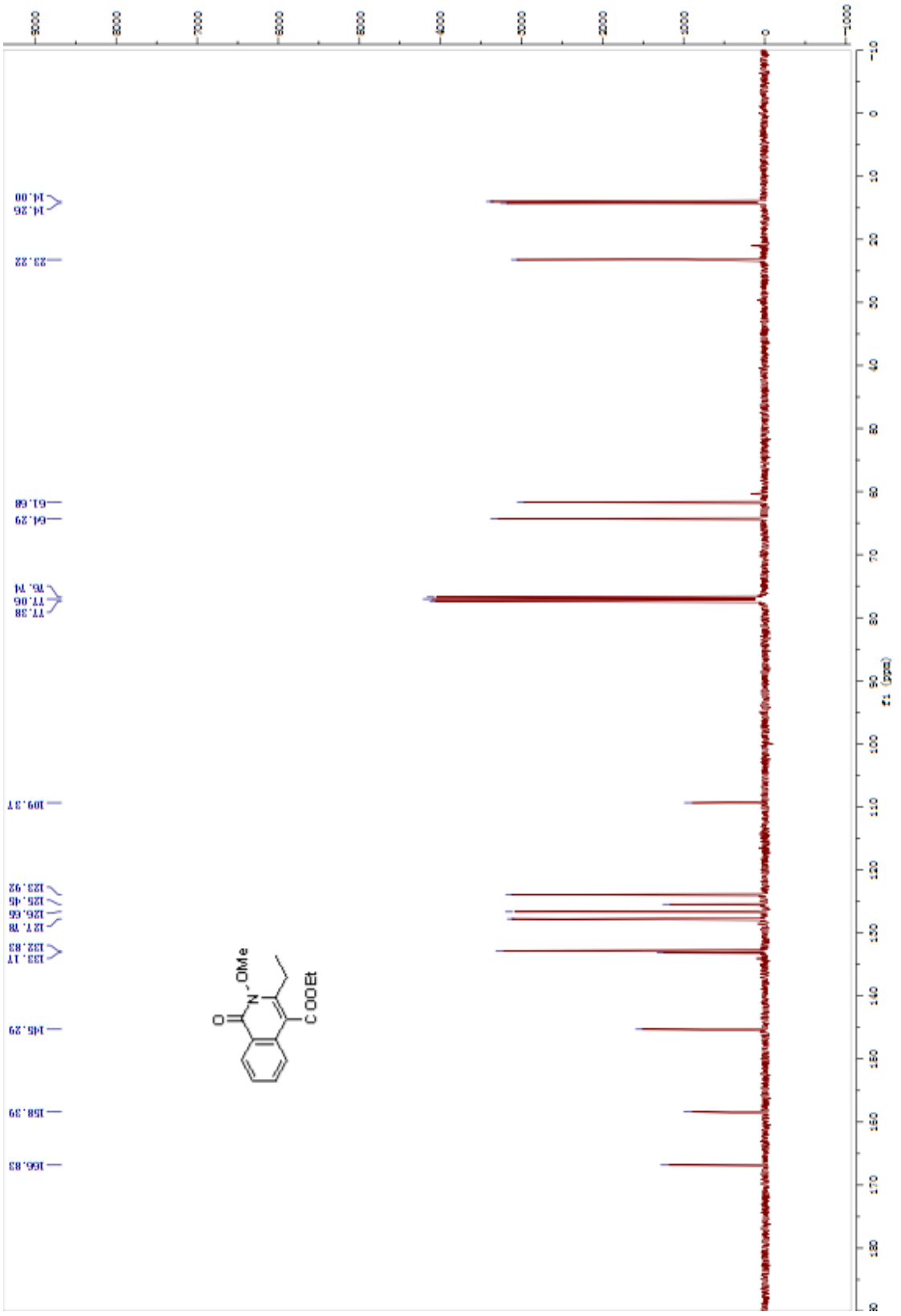
HR-MS Spectrum of benzyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquino line-4-carboxylate **3ad**



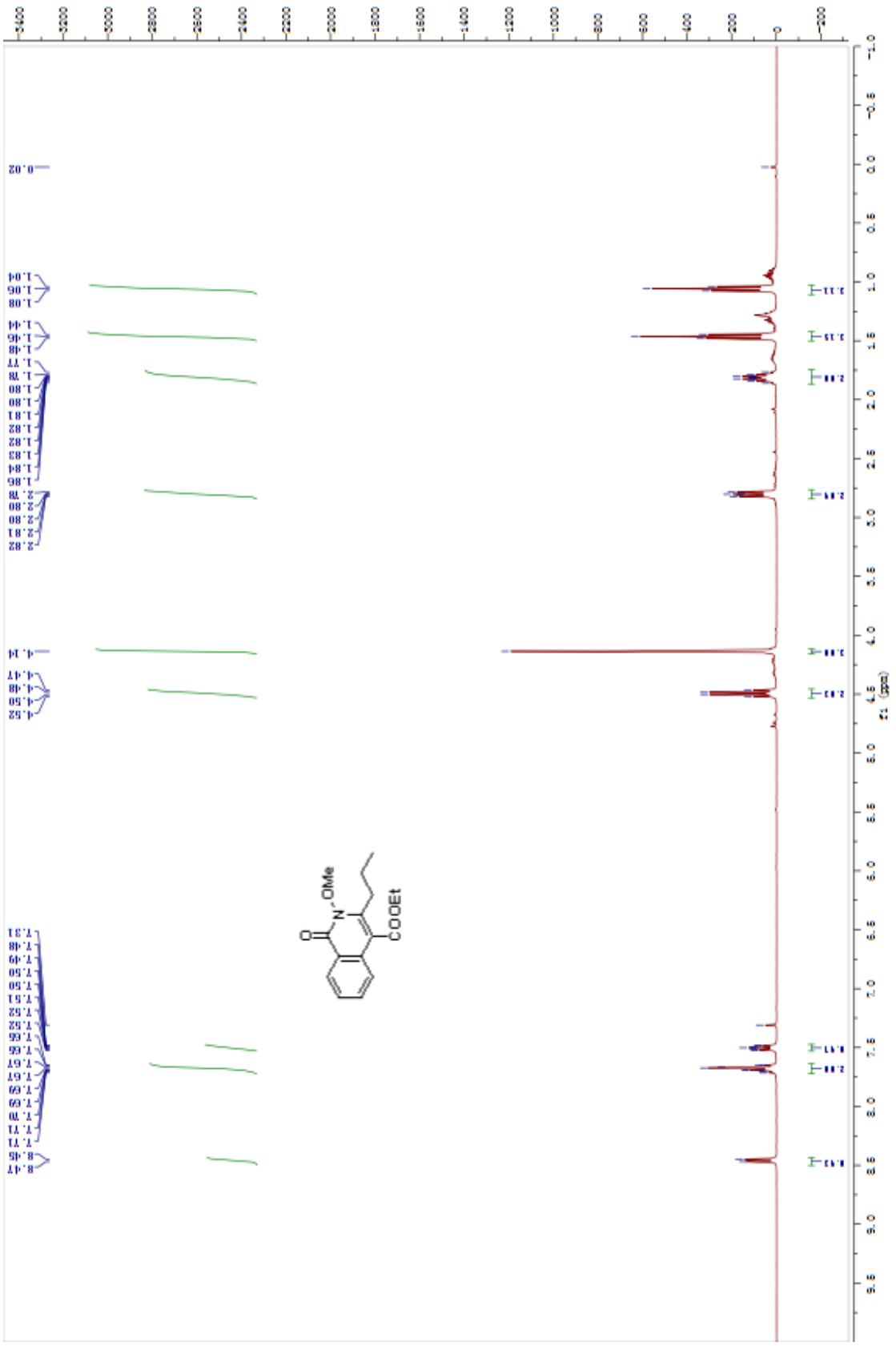
^{1}H NMR Spectrum of ethyl 3-ethyl-2-methoxy-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3ae**



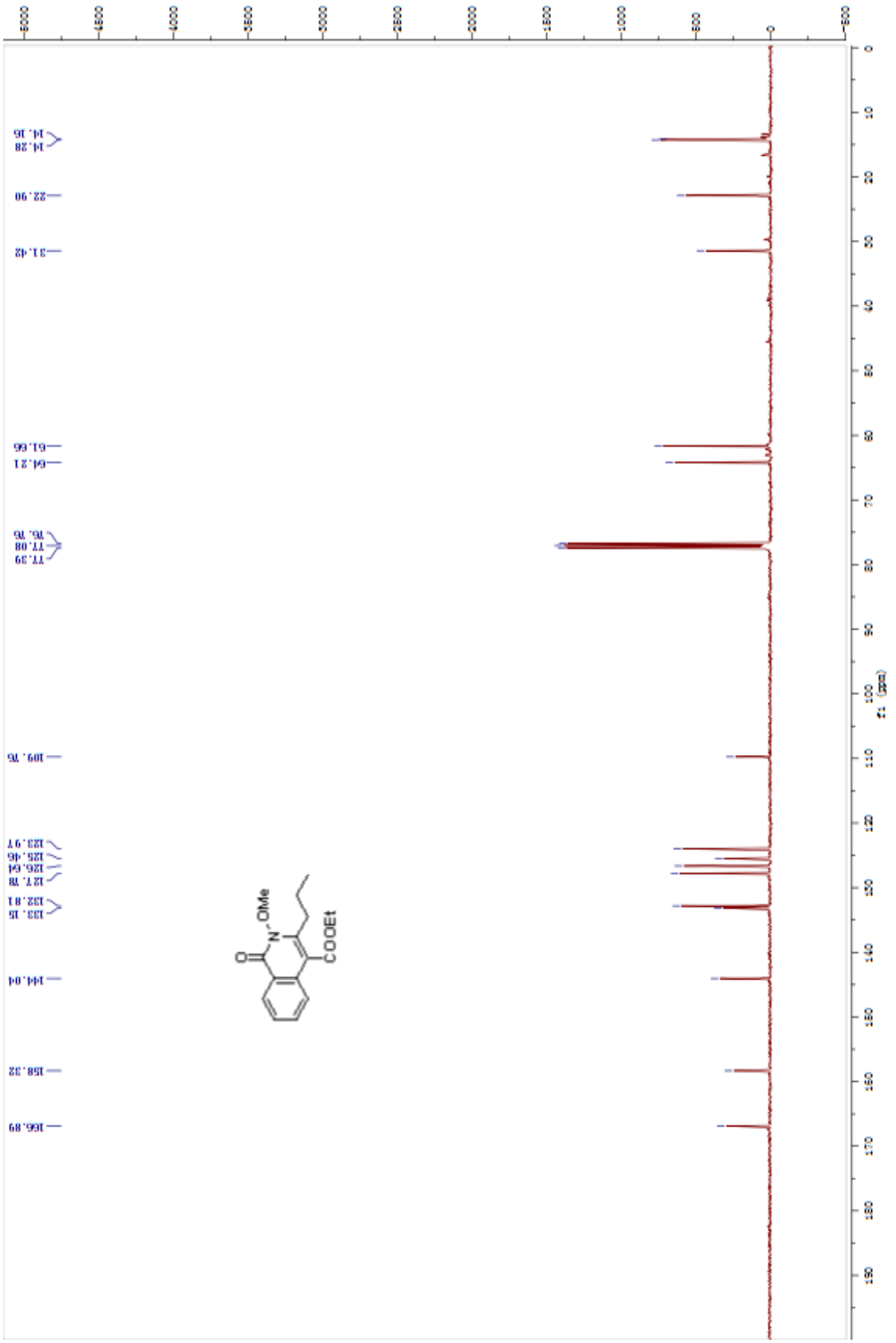
^{13}C NMR Spectrum of ethyl 3-ethyl-2-methoxy-1-oxo-1,2-dihydroisoquino line-4-carboxylate **3ae**



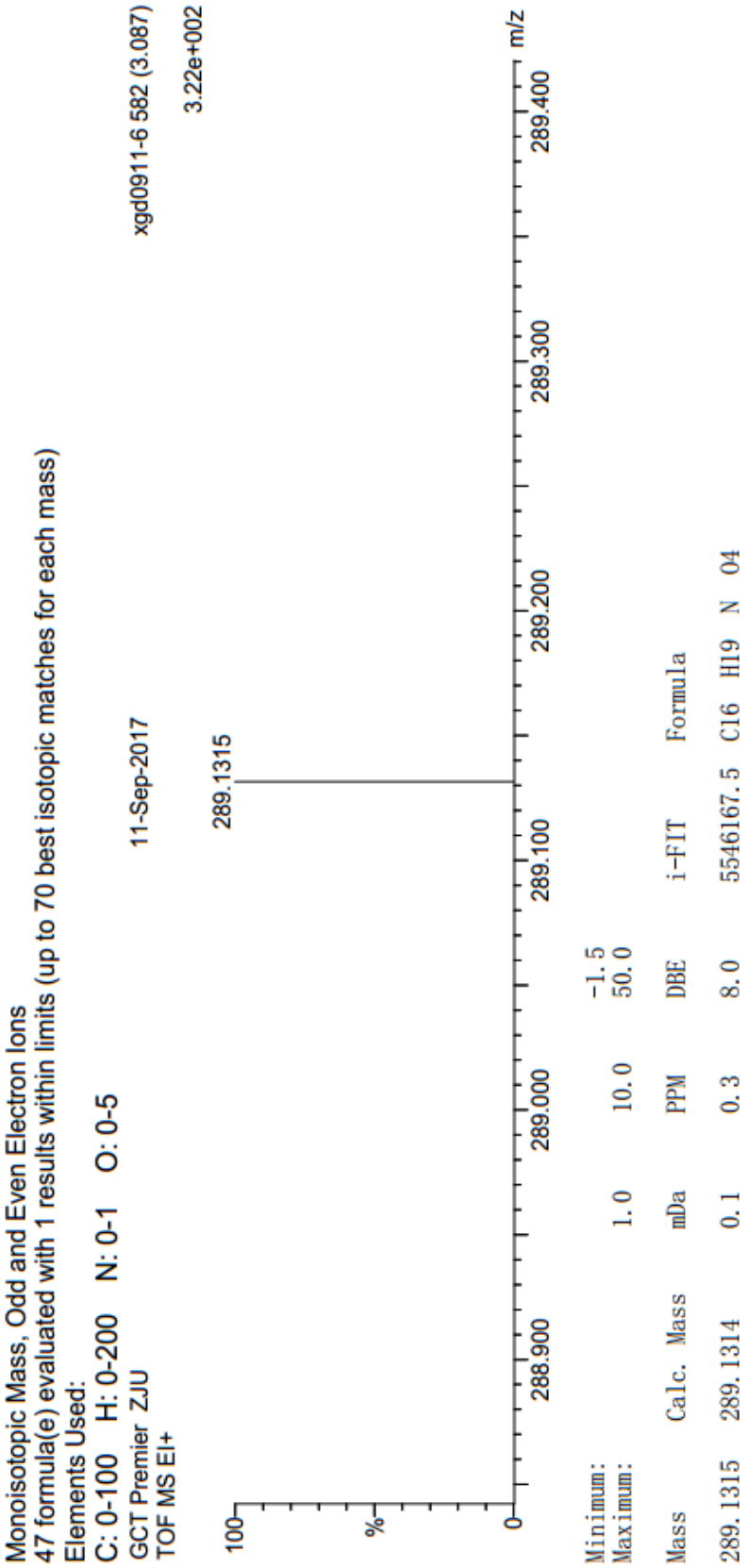
^{1}H NMR of Spectrum ethyl 2-methoxy-1-oxo-3-propyl-1,2-dihydroisoquinoline-4-carboxylate **3af**



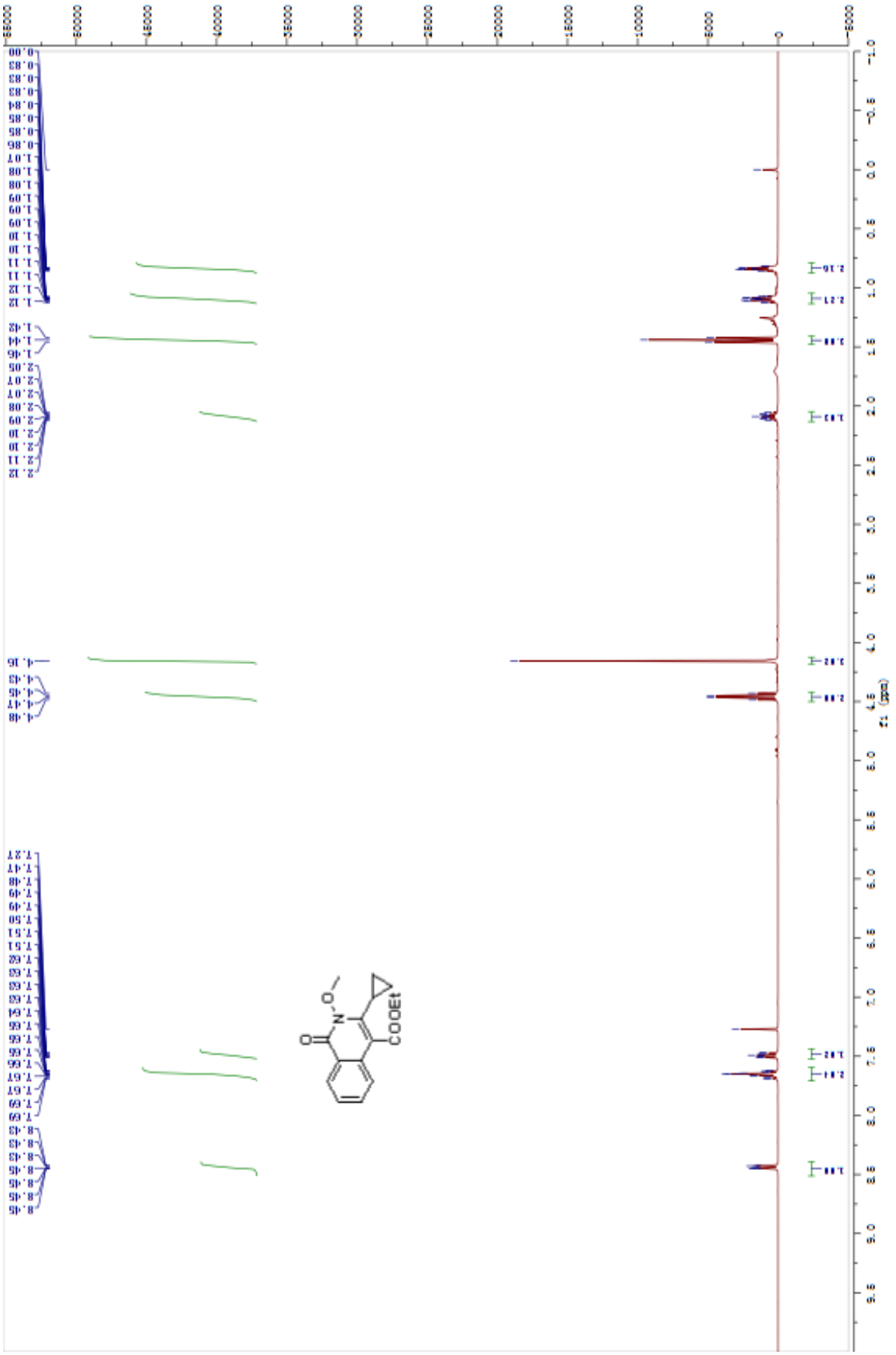
^{13}C NMR Spectrum of ethyl 2-methoxy-1-oxo-3-propyl-1,2-dihydroisoquinoline-4-carboxylate **3af**



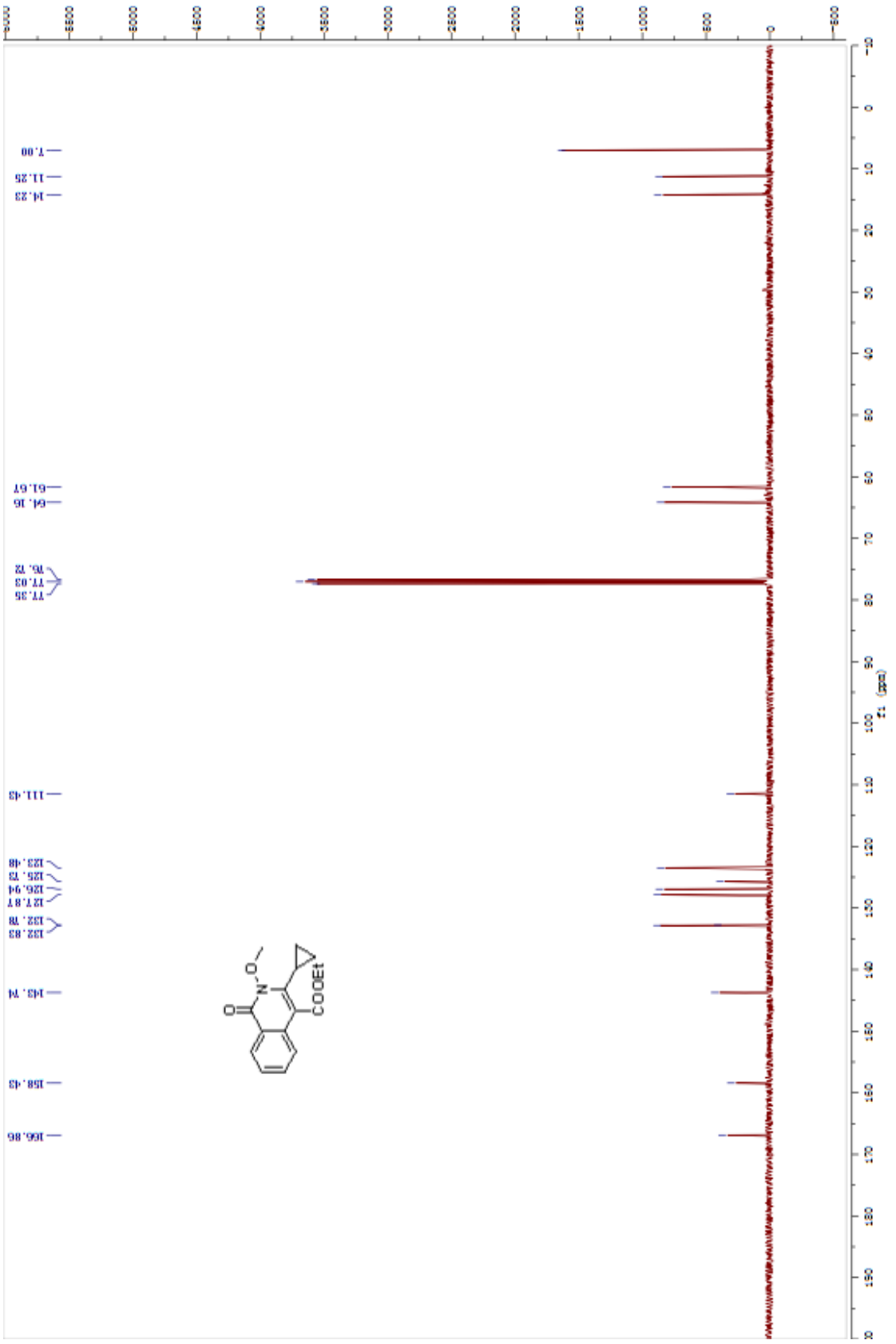
HR-MS Spectrum of ethyl 2-methoxy-1-oxo-3-propyl-1,2-dihydroisoquinoline-4-carboxylate **3af**



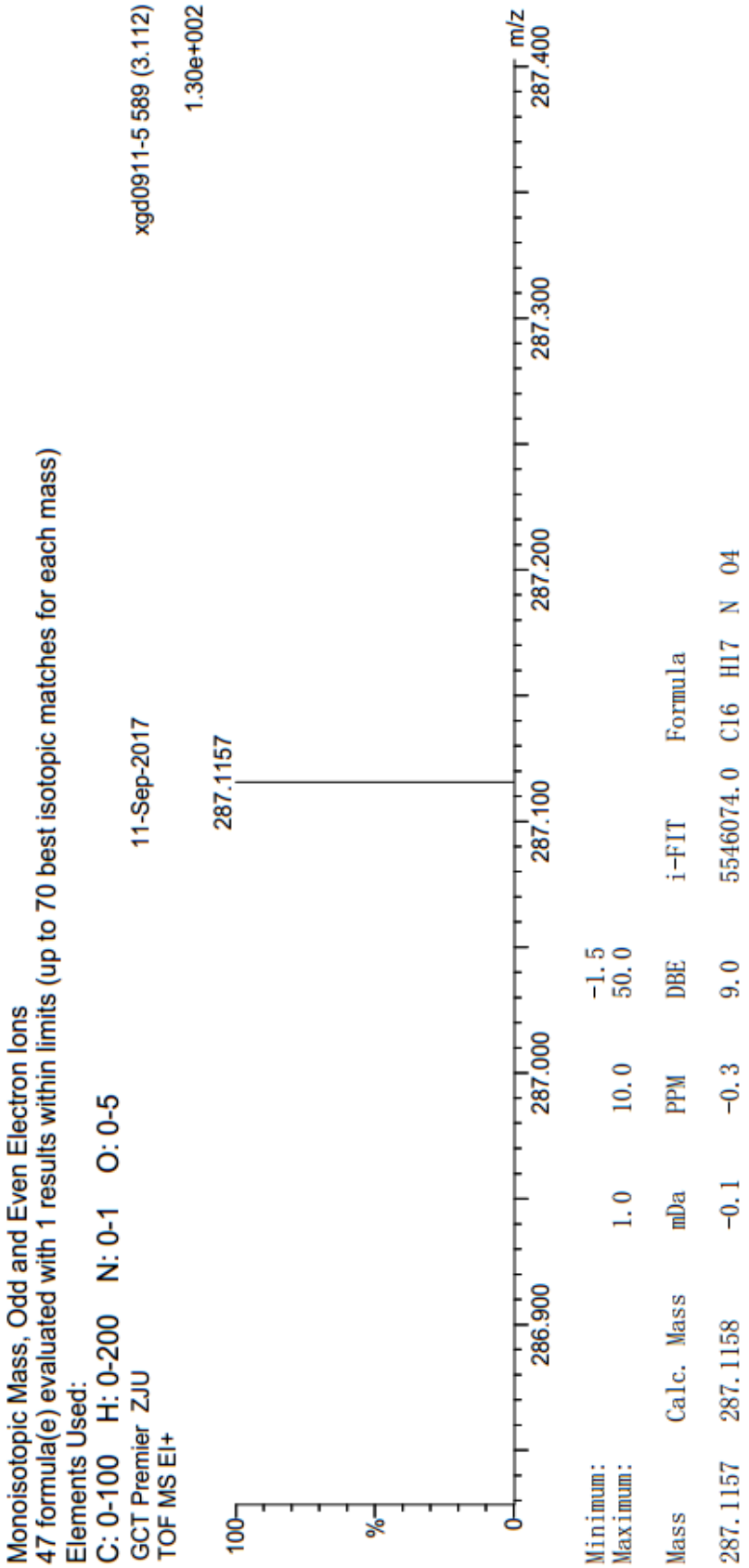
^{1}H NMR Spectrum of ethyl 3-cyclopropyl-2-methoxy-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ag**



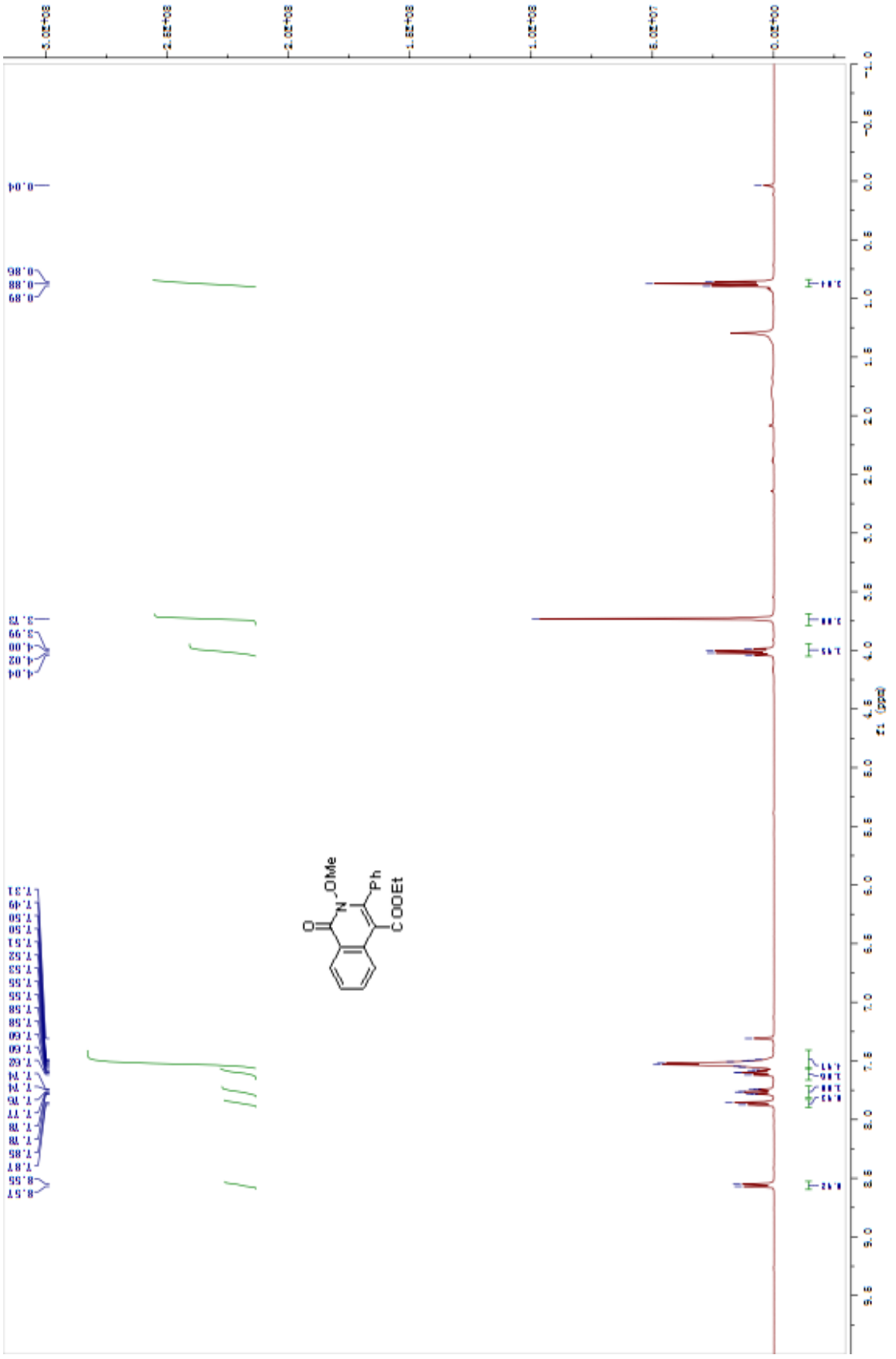
^{13}C NMR Spectrum of ethyl 3-cyclopropyl-2-methoxy-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ag**



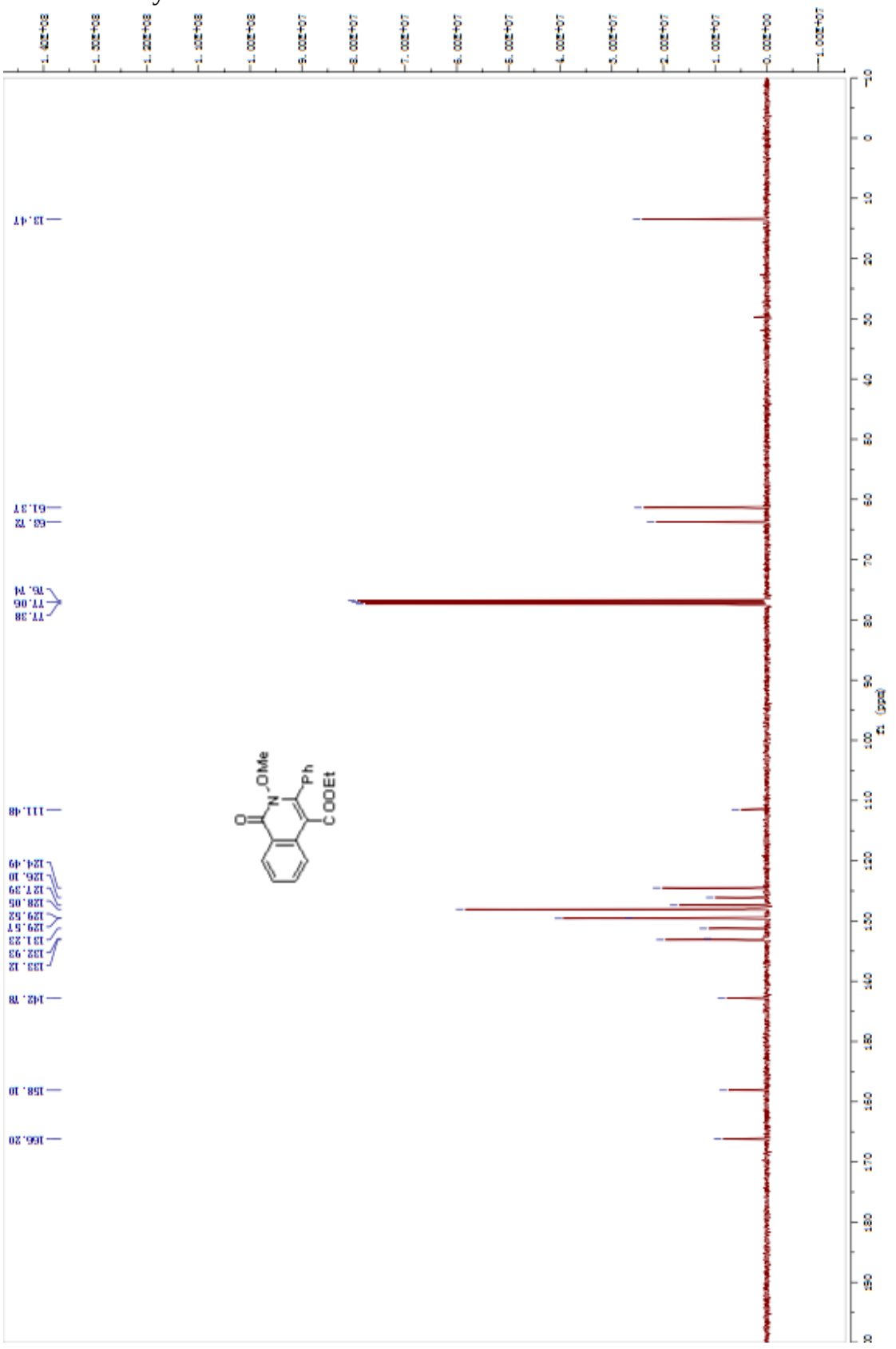
HR-MS Spectrum of ethyl 3-cyclopropyl-2-methoxy-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ag**



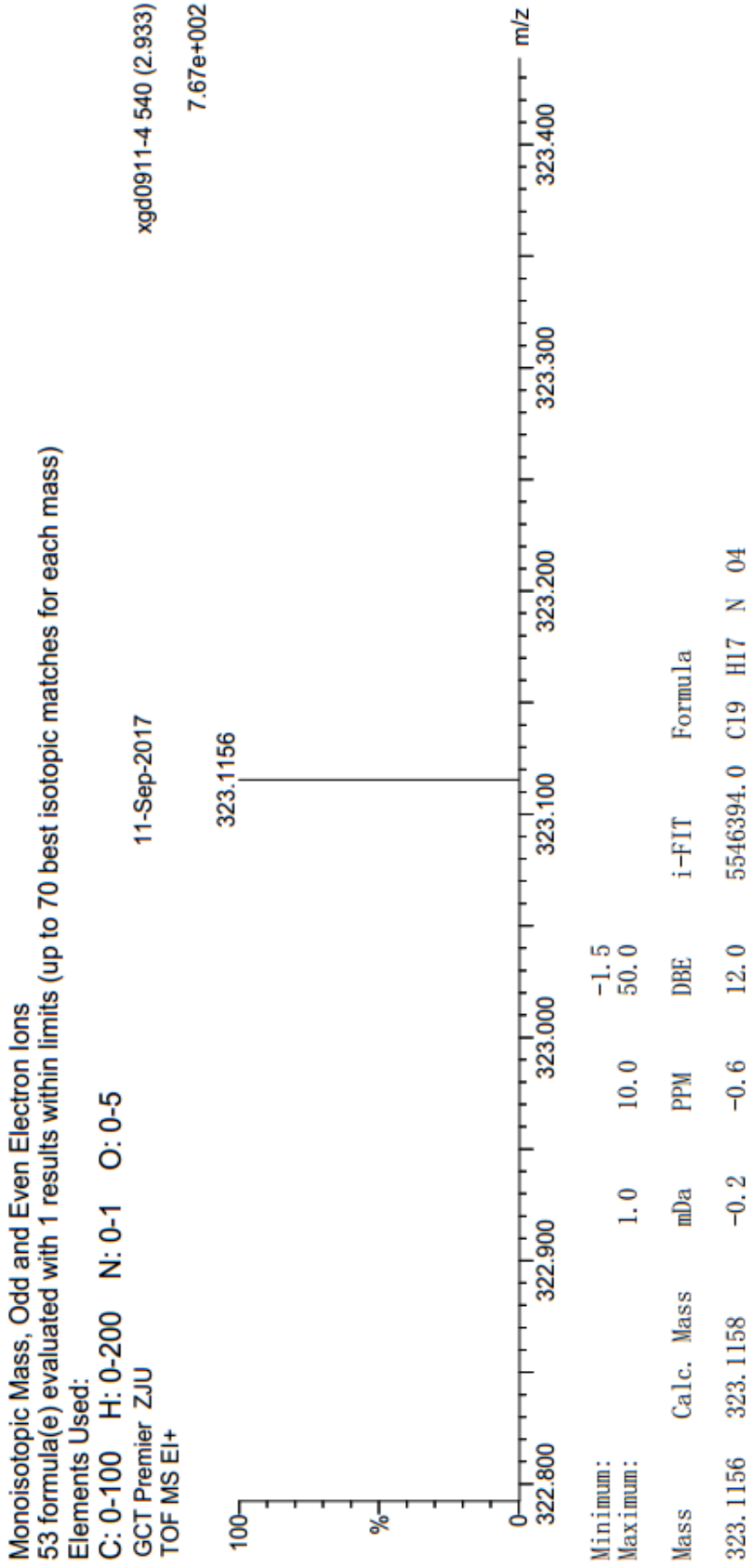
^{1}H NMR Spectrum of ethyl 2-methoxy-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carboxylate **3ah**



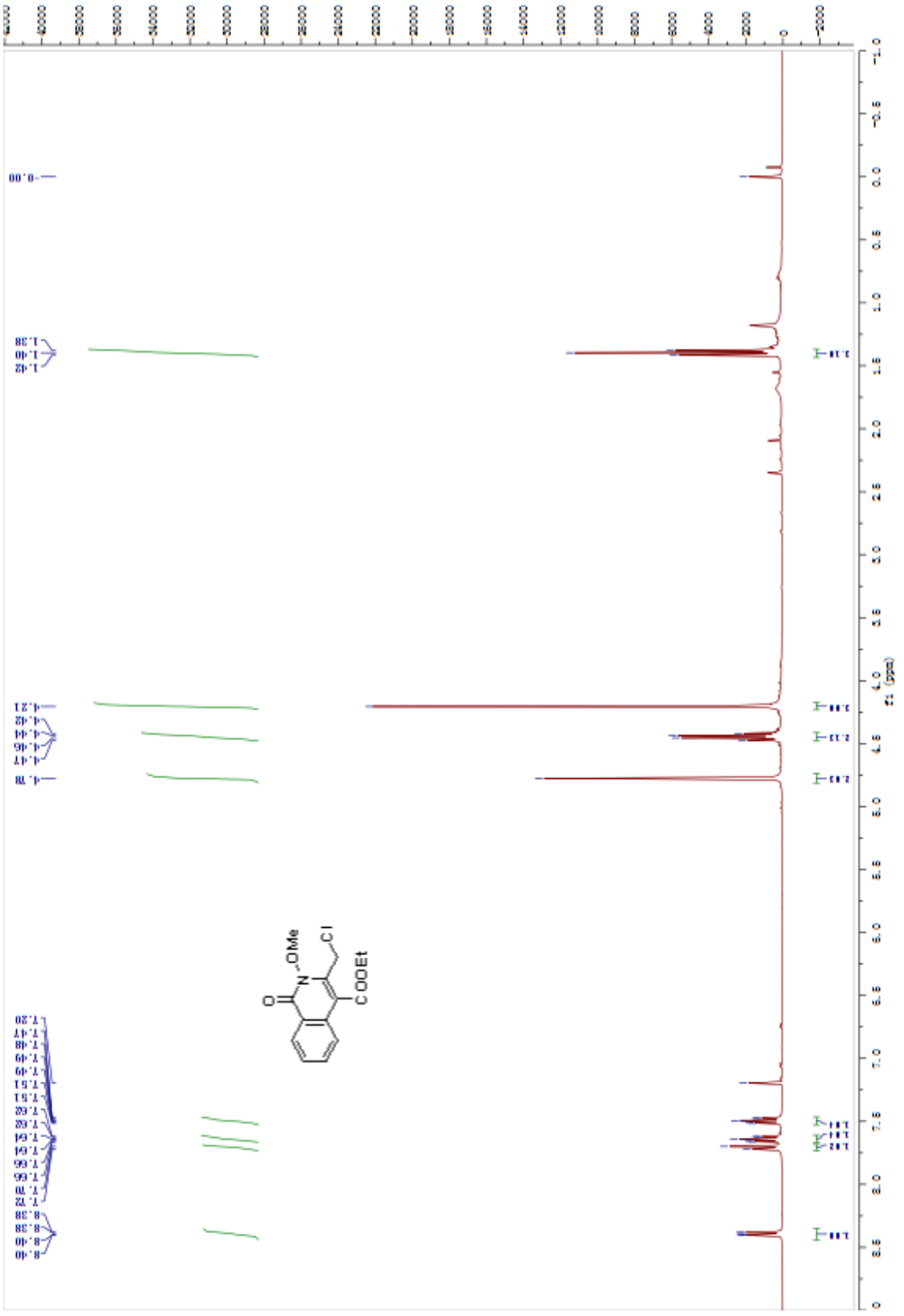
^{13}C NMR Spectrum of ethyl 2-methoxy-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carboxylate **3ah**



HR-MS Spectrum of ethyl 2-methoxy-1-oxo-3-phenyl-1,2-dihydroisoquinoline-4-carboxylate **3ah**



^{1}H NMR Spectrum of ethyl 3-(chloromethyl)-2-methoxy-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ai**



^{13}C NMR Spectrum of ethyl 3-(chloromethyl)-2-methoxy-1-oxo-1,2-dihydroiso quinoline-4-carboxylate **3ai**