Electronic Supplementary Information

Chloride-Incorporating Cascade Dearomatization of Isoquinolines with Chloroformate and DMAD Achieving 100% Atom Economy

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1. General Information

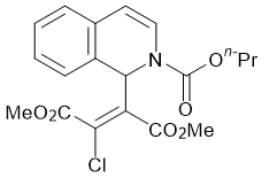
All commercially available reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with a fluorescentindicator. Flash chromatography was performed on silica gel (300-400) with Petroleum/EtOAc or DCM/MeOH as eluent. HRMS was measured on an LTQ-Orbitrap-XL apparatus. Infrared (IR) spectra were recorded in the attenuated total reflection (ATR) mode over the wavenumber range of 500–4000 cm^{-1}. ^{1}H NMR (400 MHz) chemical shifts were reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard and ^{13}C NMR (100 MHz) chemical shifts were reported in ppm (δ) from tetramethylsilane (TMS) with the solvent resonance as the internal standard.

2. Experimental Details

2.1 General Procedure for Synthesis of **4**

Isoquinoline **1** (1 mmol) was dissolved in dry acetonitrile (10 mL). Subsequently, chloroformate **2** (1.1 mmol) and alkyne **3** (1.1 mmol) were added simultaneously to the reaction mixture at room temperature. After stirring at room temperature for 2 hours, the mixture was concentrated under reduced pressure and purified via column chromatography (PE/EA = 3:1) to afford the target product **4**.

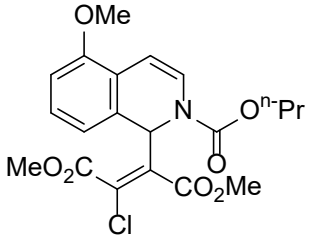
Dimethyl 2-chloro-3-(2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4a)



Following the above procedure, the product **4a** was obtained in 76% yield (300 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2955, 1718, 1637, 1234, 1119, 1022, 767; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.54-7.52 (m, 1H), 7.29-7.24 (m, 1H), 7.20-7.18 (m, 2H), 6.98-6.97 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 0.5H), 6.74 (d, *J* = 8.0 Hz, 0.5H), 5.71

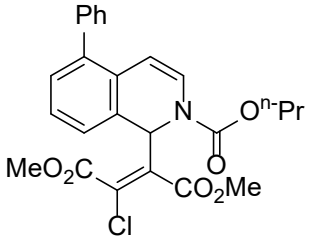
(d, J = 8.0 Hz, 0.5H), 5.62 (d, J = 8.0 Hz, 0.5H), 4.18-4.15 (m, 2H), 3.95 (s, 1.5H), 3.92 (s, 1.5H), 3.64 (s, 1.5H), 3.60 (s, 1.5H), 1.69-1.65 (m, 2H), 0.3 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 164.7, 164.4, 162.3, 162.1, 153.0, 152.5, 142.6, 140.6, 130.2, 130.0, 128.7, 128.6, 127.6, 127.5, 126.9, 126.7, 125.0, 124.8, 124.7, 124.6, 121.6, 120.4, 107.1, 106.6, 68.3, 68.1, 53.6, 53.4, 52.7, 52.5, 22.0, 21.9, 10.1, 10.0. HRMS (ESI) m/z: calcd for $C_{19}H_{20}ClNO_6$ $(M+H)^+$ 394.1052, found 394.1054.

Dimethyl 2-chloro-3-(5-methoxy-2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4b)



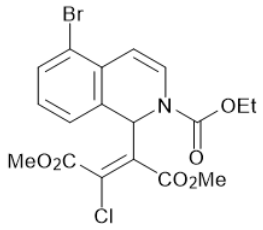
Following the above procedure, the product **4b** was obtained in 73% yield (310 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2962, 1730, 1719, 1323, 1241, 1220, 1113, 1078, 759; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.25-7.23 (m, 1H), 7.16-7.14 (m, 2H), 6.82 (d, J=8.0 Hz, 0.45H), 6.78-6.75 (m, 1H), 6.71 (d, J=8.0 Hz, 0.55H), 6.12 (d, J = 8.0 Hz, 0.45H), 6.03 (d, J = 8.0 Hz, 0.55 Hz), 4.19-4.13 (m, 2H), 3.98 (s, 1.65H), 3.96 (s, 1.35H), 3.82 (s, 3H), 3.69 (s, 1.35H), 3.65 (s, 1.65H), 1.72-1.64 (m, 2H), 0.97-0.93 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.2, 164.8, 162.7, 162.5, 154.0, 153.9, 153.5, 153.0, 142.7, 140.7, 129.1, 129.1, 128.6, 128.5, 124.4, 124.1, 122.1, 120.8, 119.9, 119.6, 119.5, 119.3, 110.8, 110.6, 102.0, 101.5, 68.6, 68.4, 55.7, 53.7, 53.6, 53.4, 53.2, 52.9, 29.9, 22.3, 22.2, 10.4, 10.4. HRMS (ESI) m/z: calcd for $C_{20}H_{22}ClNO_7$ $(M+H)^+$ 424.1158, found 424.1153.

Dimethyl 2-chloro-3-(5-phenyl-2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4c)



Following the above procedure, the product **4c** was obtained in 67% yield (314 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2955, 1718, 1323, 1237, 1221, 1118, 1025, 761; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.59-7.55 (m, 1H), 7.43-7.36 (m, 3H), 7.35-7.31 (m, 3H), 7.26-7,19 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 0.45H), 6.68 (d, *J* = 8.0 Hz, 0.55H), 5.79 (d, *J* = 8.0 Hz, 0.45H), 5.70 (d, *J* = 8.0 Hz, 0.55H), 4.19-4.16 (m, 2H), 4.00 (s, 1.65H), 3.98 (s, 1.35H), 3.67 (s, 1.35H), 3.63 (s, 1.65H), 1.72-1.66 (m, 2H), 0.98-0.93 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.2, 162.6, 153.4, 152.9, 142.9, 140.9, 140.1, 138.1, 130.5, 130.4, 129.8, 129.7, 128.6, 128.4, 128.3, 127.6, 127.4, 126.6, 126.3, 125.4, 125.1, 122.2, 120.9, 105.8, 105.2, 100.1, 68.7, 68.5, 54.0, 53.8, 53.2, 52.9, 22.3, 10.4. HRMS (ESI) m/z: calcd for $C_{25}H_{24}ClNO_6$ $(M+H)^+$ 470.1365, found 470.1358.

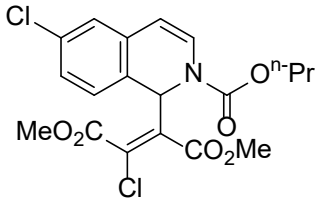
Dimethyl 2-chloro-3-(2-(ethoxycarbonyl)-1,2-dihydroisoquinolin-1 -yl)fumarate (4d)



Following the above procedure, the product **4d** was obtained in 51% yield (233 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2952, 1734, 1715, 1627, 1326, 1240, 1020, 762; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.50-7.49 (m, 0.44H), 7.49-7.47 (m, 0.56H), 7.46-7.44 (m, 0.44H), 7.44-7.42 (m, 0.56H), 7.26-7.24 (m, 0.56H), 7.22-7.19 (m, 0.44H), 7.05-7.00 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 0.44H), 6.83 (d, *J* = 8.4 Hz, 0.56H), 6.08 (d, *J* = 8.4 Hz, 0.44H), 6.00 (d, *J* = 8.4 Hz, 0.56H), 4.29-4.23 (m, 2H), 3.98 (s, 1.68H), 3.96 (s, 1.32H), 3.68 (s, 1.32H), 3.64 (s, 1.68H), 1.31-1.27 (m, 3H). ^{13}C{^{1}H}

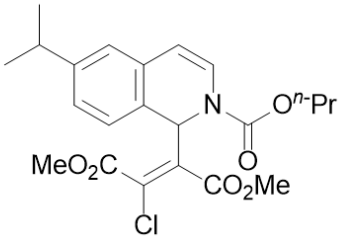
NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 164.8, 164.4, 162.4, 162.3, 152.8, 152.4, 141.7, 140.1, 133.0, 132.8, 130.1, 129.9, 129.7, 129.7, 128.6, 128.5, 127.0, 126.7, 126.5, 126.3, 122.5, 121.3, 120.3, 120.2, 105.6, 105.1, 63.1, 53.7, 53.6, 53.3, 53.0, 52.8, 14.5, 14.2. HRMS (ESI) m/z: calcd for $C_{18}H_{17}BrClNO_6$ $(M+H)^+$ 458.0001, 459.9981 found 458.0000, 459.9980.

Propyl(Z)-6-chloro-1-(3-chloro-4-methoxy-1-(methylperoxy)-4-oxobut-2-en-2-yl)isoquinoline-2 (1H)-carboxylate (4e)



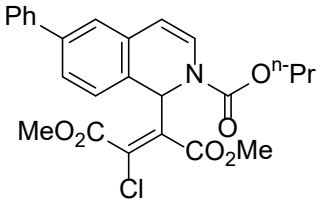
Following the above procedure, the product **4e** was obtained in 68% yield (291 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2970, 1717, 1638, 1433, 1230, 1122, 1027, 761; ^1H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.44-7.41 (m, 1H), 7.19-7.16 (m, 1H), 7.10-7.07 (m, 1H), 6.93-6.92 (m, 1H), 6.85 (d, J = 8.0 Hz, 0.45H), 6.73 (d, J = 8.0 Hz, 0.55H), 5.59 (d, J = 8.0 Hz, 0.45H), 5.50 (d, J = 8.0 Hz, 0.55H), 4.17-4.09 (m, 2H), 3.92 (s, 1.65H), 3.90 (s, 1.35H), 3.63 (s, 1.35H), 3.59 (s, 1.65H), 1.67-1.58 (m, 2H), 0.92-0.87 (m, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.1, 164.8, 162.7, 162.6, 153.3, 152.7, 142.7, 140.6, 134.9, 134.7, 132.3, 132.1, 128.7, 128.5, 127.8, 127.7, 126.6, 126.3, 126.2, 124.9, 124.7, 122.4, 121.2, 106.4, 105.7, 68.9, 68.7, 53.9, 53.7, 53.6, 53.3, 53.0, 22.3, 22.2, 10.4, 10.4. HRMS (ESI) m/z: calcd for $C_{19}H_{21}Cl_2NO_6$ $(M+H)^+$ 428.0662, found 428.0667.

Dimethyl 2-chloro-3-(6-isopropyl-2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4f)



Following the above procedure, the product **4f** was obtained in 71% yield (309 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2962, 1718, 1397, 1231, 1117, 1027, 761; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.47-7.44 (m, 1H), 7.26-7.23 (m, 1H), 7.09-7.05 (m, 1H), 6.87-6.85 (m, 1.5H), 6.74 (d, *J* = 8.0 Hz, 0.5H), 5.73 (d, *J* = 8.0 Hz, 0.5H), 5.64 (d, *J* = 8.0 Hz, 0.5H), 4.21-4.13 (m, 2H), 3.98 (s, 1.5H), 3.96 (s, 1.5H), 3.69 (s, 1.5H), 3.64 (s, 1.5H), 2.89-2.82 (m, 1H), 1.71-1.64 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 0.98-0.93 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.2, 164.9, 162.7, 162.6, 153.5, 152.9, 149.8, 149.7, 143.1, 141.1, 130.4, 130.1, 127.2, 127.0, 126.2, 126.1, 125.4, 125.1, 124.8, 123.3, 123.1, 121.8, 120.6, 108.0, 107.4, 68.6, 68.4, 53.9, 53.7, 53.6, 53.6, 53.2, 52.9 34.0, 24.0, 22.3, 22.2, 10.4, 10.4. HRMS (ESI) m/z: calcd for $C_{22}H_{26}ClNO_6$ $(M+H)^+$ 436.1522, found 436.1512.

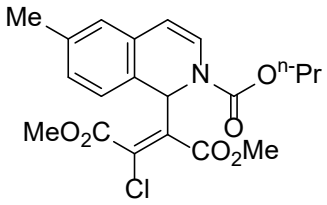
Dimethyl 2-chloro-3-(6-phenyl-2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4g)



Following the above procedure, the product **4g** was obtained in 78% yield (366 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2995, 1718, 1637, 1325, 1239, 1220, 1117, 1027, 762; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.66-7.63 (m, 1H), 7.61-7.60 (m, 1H), 7.59-7.57 (m, 1H), 7.47-7.43 (m, 3H), 7.38-7.37 (m, 2H), 7.27-7.24 (m, 1H), 6.95 (d, *J* = 8.0 Hz, 0.47H), 6.83 (d, *J* = 8.0 Hz, 0.53H), 5.83 (d, *J* = 8.0 Hz, 0.47H), 5.74 (d, *J* = 8.0 Hz, 0.53H), 4.27-4.14 (m, 2H), 4.02 (s, 1.59H), 4.00 (s, 1.41H), 3.73 (s, 1.41H), 3.69 (s, 1.59H), 1.75-1.69 (m, 2H), 1.01-0.98 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.2, 164.9, 162.7, 162.6, 153.4, 152.9, 143.0, 142.0, 141.8, 141.0, 140.6, 140.6, 131.0, 130.7, 128.9, 127.8, 127.7, 127.5, 127.2, 126.9, 126.9, 126.7, 126.6, 125.6, 125.3, 123.8, 123.6, 122.2, 120.9, 107.6, 107.0, 68.8, 68.6, 53.9, 53.8, 53.7, 53.6, 53.2, 53.0, 22.3, 22.2, 10.5, 10.4. HRMS (ESI) m/z: calcd for

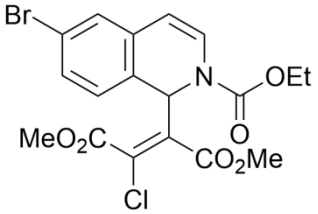
$C_{25}H_{24}ClNO_6$ $(M+H)^+$ 470.1365, found 470.1355.

Dimethyl 2-chloro-3-(6-methyl-2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl) fumarate (4h)



Following the above procedure, the product **4h** was obtained in 75% yield (306 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2962, 1716, 1640, 1433, 1399, 1230, 1027, 862, 761; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.43-7.40 (m, 1H), 7.25-7.21 (m, 1H), 7.02-6.99 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 0.5H), 6.83-6.80 (m, 1H), 6.73 (d, *J* = 8.0 Hz, 0.5H), 5.69 (d, *J* = 8.0 Hz, 0.5H), 5.60 (d, *J* = 8.0 Hz, 0.5H), 4.19-4.13 (m, 2H), 3.98 (s, 1.5H), 3.96 (s, 1.5H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 2.30 (s, 3H), 1.73-1.63 (m, 2H), 0.98-0.93 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.3, 164.9, 162.7, 162.6, 153.5, 152.9, 143.1, 141.2, 138.9, 138.7, 130.4, 130.1, 128.8, 128.7, 127.2, 126.9, 125.9, 125.7, 125.2, 125.0, 124.9, 121.8, 120.6, 107.7, 107.1, 68.7, 68.5, 53.8, 53.8, 53.6, 53.6, 53.2, 52.9, 22.3, 22.2, 21.4, 10.5, 10.4. HRMS (ESI) m/z: calcd for $C_{20}H_{22}ClNO_6$ $(M+H)^+$ 408.1209, found 408.1205.

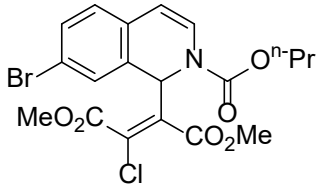
Dimethyl 2-(6-bromo-2-(ethoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)-3-chlorofumarate (4i)



Following the above procedure, the product **4i** was obtained in 64% yield (293 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2955, 1720, 1431, 1230, 1022, 759; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.45-7.41 (m, 0.5H), 7.41-7.40 (m, 0.5H), 7.33-7.28 (m, 1H), 7.24-7.21 (m, 0.5H), 7.19-7.16 (m, 0.5H), 7.15-7.13 (m, 1H), 6.91 (d, *J*

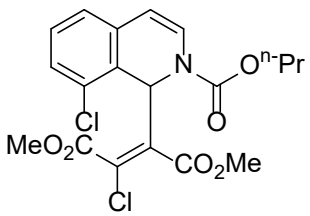
= 8.0H, 0.5H), 6.79 (d, *J* = 8.0 Hz, 0.5H), 5.65 (d, *J* = 8.0 Hz, 0.5H), 5.56 (d, *J* = 8.0 Hz, 0.5H), 4.31-4.18 (m, 2H), 3.98 (s, 1.5H), 3.96 (s, 1.5H), 3.69 (s, 1.5H), 3.66 (s, 1.5H), 1.33-1.25 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.0, 164.6, 162.6, 153.0, 152.6, 142.0, 140.5, 132.5, 132.3, 130.6, 130.5, 128.9, 128.7, 127.7, 127.5, 126.7, 126.6, 126.4, 126.2, 123.0, 122.8, 122.4, 121.3, 106.0, 105.5, 63.1, 53.8, 53.7, 53.6, 53.2, 53.2, 52.9, 14.6, 14.3. HRMS (ESI) m/z: calcd for $C_{18}H_{17}BrClNO_6$ $(M+H)^+$ 458.0001, 459.9981 found 457.9996, 459.9968.

Dimethyl 2-(7-bromo-2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)-3-chlorofumarate (4j)



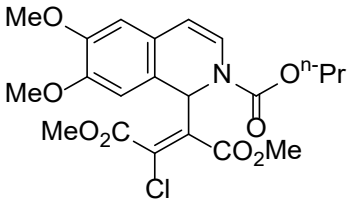
Following the above procedure, the product **4j** was obtained in 54% yield (254 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2955, 1717, 1636, 1333, 1227, 1095, 1030, 834, 706; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.74-7.68 (m, 1H), 7.38-7.33 (m, 1H), 7.27-7.24 (m, 1H), 6.91-6.86 (m, 1.45H), 6.77 (d, *J* = 8.0 Hz, 0.55H), 5.69 (d, *J*=8.0 Hz, 0.55H), 5.59 (d, *J*=8.0 Hz, 0.45H), 4.23- 4.13 (m, 2H), 4.00 (s, 1.65H), 3.98 (s, 1.35H), 3.69 (s, 1.65H), 3.65 (s, 1.35H), 1.73-1.61 (m, 2H), 0.98-0.96 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 152.7, 142.4, 140.5, 132.2, 132.1, 130.4, 130.2, 129.8, 126.5, 126.3, 125.8, 125.5, 106.8, 106.1, 68.9, 68.7, 53.9, 53.8, 53.4, 53.3, 53.1, 53.0, 22.3, 22.2, 10.5. HRMS (ESI) m/z: calcd for $C_{19}H_{19}BrClNO_6$ $(M+H)^+$ 472.0158, 474.0137 found 472.0148, 474.0129.

Dimethyl 2-chloro-3-(8-chloro-2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4k)



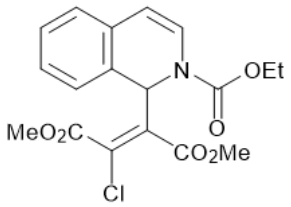
Following the above procedure, the product **4k** was obtained in 59% yield (252 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2959, 1734, 1322, 1259, 1223, 1110, 1025, 971, 767; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.40-7.36 (m, 1H), 7.24-7.14 (m, 3H), 6.92-6.91 (m, 0.5H), 6.91-6.90 (m, 0.5H), 6.87-6.80 (m, 1H), 5.76-5.65 (m, 1H), 4.18-4.15 (m, 2H), 3.91 (s, 3H), 3.56 (s, 3H), 1.72-1.67 (m, 2H), 0.96-0.92 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 130.0, 128.8, 125.0, 123.6, 107.4, 68.8, 53.5, 52.9, 51.4, 22.3, 10.5. HRMS (ESI) m/z: calcd for $C_{19}H_{19}Cl_2NO_6$ $(M+H)^+$ 428.0662, found 428.0667.

Dimethyl 2-chloro-3-(6,7-dimethoxy-2-(propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl) fumarate (4l)



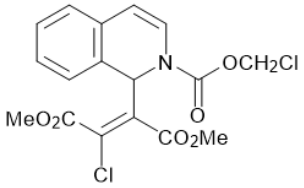
Following the above procedure, the product **4l** was obtained in 79% yield (358 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2962, 1736, 1629, 1403, 1272, 1222, 1110, 1023, 966, 759; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.19-7.18 (m, 0.47H), 7.15-7.14 (m, 0.53H), 7.10-7.09 (m, 0.53H), 7.09-7.08 (m, 0.47H), 6.77 (d, *J*=8.0 Hz, 0.47H), 6.65(d, *J*=8.0 Hz, 0.53H), 6.54-6.52 (m, 1H), 5.67 (d, *J* = 8.0 Hz, 0.47H), 5.58 (d, *J* = 8.0 Hz, 0.53H), 4.21-4.10 (m, 2H), 3.98 (s, 1.59H), 3.96 (s, 1.41H), 3.88-3.87 (m, 3H), 3.87 (s, 3H), 3.71 (s, 1.41H), 3.67 (s, 1.59H), 1.73-1.63 (m, 2H), 0.98-0.94 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ165.2, 164.9, 162.9, 162.8, 153.5, 153.0, 149.4, 149.3, 148.9, 148.8, 142.7 140.8, 123.8, 123.7, 123.5, 123.3, 121.7, 120.4, 120.1, 119.9, 110.5, 110.4, 108.2, 108.1, 107.7, 107.1, 68.7, 68.5, 56.1, 56.1, 56.1, 53.9, 53.8, 53.6, 53.2, 53.0, 22.4, 22.3, 10.5, 10.4. HRMS (ESI) m/z: calcd for $C_{21}H_{24}ClNO_8$ $(M+H)^+$ 454.1263, found 454.1264.

Dimethyl 2-chloro-3-(2-(ethoxycarbonyl)-1,2-dihydroisoquinolin-1-yl) fumarate (4m)



Following the above procedure, the product **4m** was obtained in 71% yield (269 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2951, 1741, 1716, 1304, 1232, 1117, 774; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.54-7.52 (m, 0.5H), 7.52-7.49 (m, 0.5H), 7.27-7.15 (m, 3H), 6.99-6.97 (m, 0.5H), 6.97-6.93 (m, 0.5H), 6.86 (d, *J* = 8.0 Hz, 0.5H), 6.74 (d, *J* = 8.0 Hz, 0.5H), 5.70 (d, *J* = 8.0 Hz, 0.5H), 5.62 (d, *J* = 8.0 Hz, 0.5H), 4.28-4.16 (m, 2H), 3.94 (s, 1.5H), 3.92 (s, 1.5H), 3.63 (s, 1.5H), 3.60 (s, 1.5H), 1.30-1.22 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 164.7, 164.4, 162.2, 162.2, 152.8, 152.4, 142.0, 140.6, 130.2, 130.0, 128.7, 128.6, 127.5, 127.4, 126.9, 126.7, 124.9, 124.8, 124.7, 124.6, 121.6, 120.6, 107.0, 106.5, 62.6, 53.6, 53.5, 53.3, 52.7, 52.5, 14.3, 14.0. HRMS (ESI) m/z: calcd for $C_{18}H_{18}ClNO_6$ $(M+H)^+$ 380.0896, found 380.0890.

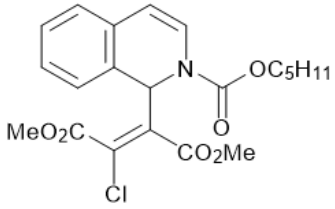
Dimethyl 2-chloro-3-(2-((chloromethoxy)carbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4n)



Following the above procedure, the product **4n** was obtained in 77% yield (308 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2955, 1738, 1714, 1233, 1118, 1092, 1022, 765; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.53-7.51 (m, 0.6H), 7.47-7.44 (m, 0.4H), 7.26-7.25 (s, 0.6H), 7.22-7.21 (m, 2H), 7.14-7.11 (m, 0.4H), 7.02-7.00 (m, 0.6H), 6.99-6.98 (m, 0.4H), 6.80 (d, *J* = 8.0 Hz, 0.4H), 6.69 (d, *J* = 8.0 Hz, 0.6H), 5.89 (d, *J* = 6.0 Hz, 0.6 H), 5.86 (d, *J* = 6.0 Hz, 0.4H), 5.81 (d, *J* = 8.0 Hz, 0.4H), 5.74-5.73 (m, 0.4H), 5.72-5.71 (m, 0.6H), 5.70-5.68 (m, 0.6H), 3.98 (s, 1.2H), 3.96 (s, 1.8H), 3.63 (s, 1.2H),

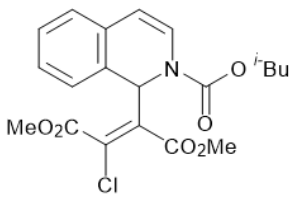
3.61 (s, 1.8H). $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 164.5, 164.2, 162.4, 162.2, 150.7, 150.2, 140.4, 140.0, 129.5, 129.3, 129.0, 128.9, 128.1, 127.9, 127.3, 127.2, 126.9, 126.8, 125.2, 125.1, 124.1, 123.3, 122.3, 121.7, 108.9, 108.4, 70.9, 70.7, 53.7, 53.6, 52.9, 52.7. HRMS (ESI) m/z: calcd for $C_{17}H_{15}Cl_2NO_6$ $(M+H)^+$ 400.0349, found 400.0345.

Dimethyl 2-chloro-3-(2-((pentyloxy)carbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4o)



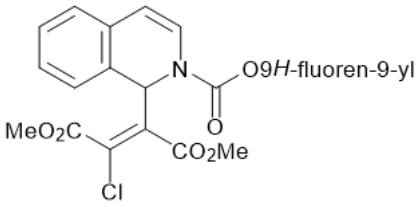
Following the above procedure, the product **4o** was obtained in 71% yield (299 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2954, 1708, 1309, 1238, 1116, 1020, 965, 767; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.54-7.52 (m, 0.5H), 7.52-7.50 (m, 0.5H), 7.26-7.24 (m, 1H), 7.19-7.15 (m, 2H), 6.98-6.97 (m, 0.5H), 6.96-6.95 (m, 0.5H), 6.86 (d, *J* = 8.0 Hz, 0.5H), 6.73 (d, *J* = 8.0 Hz, 0.5H), 5.70 (d, *J* = 8.0 Hz, 0.5H), 5.62 (d, *J* = 8.0 Hz, 0.5H), 4.23-4.12 (m, 2H), 3.94 (s, 1.5H), 3.92 (s, 1.5H), 3.64 (s, 1.5H), 3.60 (s, 1.5H), 1.67-1.60 (m, 2H), 1.36-1.28 (m, 4H), 0.92-0.89 (m, 1.5H), 0.89-0.86 (m, 1.5H). $^{13}C\{^{1}H\}$ NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 164.7, 164.4, 162.3, 162.2, 153.0, 152.5, 142.8, 140.6, 130.3, 130.0, 128.7, 128.6, 127.7, 127.6, 127.5, 127.0, 126.7, 125.0, 124.8, 124.7, 124.6, 121.7, 120.3, 107.1, 106.6, 66.8, 66.7, 53.6, 53.3, 53.3, 52.7, 52.5, 28.3, 27.8, 27.6, 22.2, 22.1, 13.8, 13.8. HRMS (ESI) m/z: calcd for $C_{21}H_{24}ClNO_6$ $(M+H)^+$ 422.1365, found 422.1358.

Dimethyl 2-chloro-3-(2-(isobutoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4p)



Following the above procedure, the product **4p** was obtained in 69% yield (281 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2959, 1719, 1313, 1228, 1119, 1027, 769; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.59-7.55 (m, 0.44H), 7.55-7.51 (m, 0.56H), 7.34-7.31 (m, 0.44H), 7.28-7.25 (m, 0.56H), 7.22-7.14 (m, 2H), 7.00-6.97 (m, 0.56H), 6.97-6.94 (m, 0.44H), 6.87 (d, *J* = 8.0 Hz, 0.44H), 6.76 (d, *J* = 8.0 Hz, 0.56H), 5.73 (d, *J* = 8.0 Hz, 0.44H), 5.64 (d, *J* = 8.0 Hz, 0.56H), 4.10-3.96 (m, 2H), 3.95 (s, 1.68H), 3.91 (s, 1.32H), 3.65 (s, 1.32H), 3.61 (s, 1.68H), 2.01-1.91 (m, 1H), 0.97-0.91 (m, 6H). ^{13}C{1H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 164.6, 164.4, 162.2, 162.1, 153.0, 152.4, 143.2, 140.6, 130.2, 129.9, 128.7, 128.6, 127.7, 127.6, 127.5, 126.9, 126.7, 125.1, 124.8, 124.7, 124.5, 121.6, 120.2, 107.3, 106.6, 72.9, 72.5, 53.4, 52.7, 52.5, 27.7, 18.7. HRMS (ESI) m/z: calcd for $C_{20}H_{22}ClNO_6$ $(M+H)^+$ 408.1209, found 408.1200.

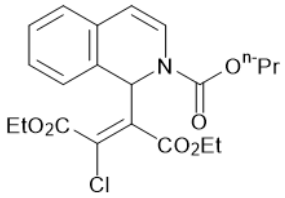
Dimethyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-1,2-dihydroisoquinolin-1-yl)-3-chlorofumarate (4q)



Following the above procedure, the product **4q** was obtained in 57% yield (302 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2951, 1718, 1386, 1234, 1123, 1021, 736; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.58-7.57 (m, 1H), 7.56-7.55 (m, 1H), 7.44-7.35 (m, 3H), 7.23-7.19 (m, 2H), 7.18-7.11 (m, 3H), 7.07-7.03 (m, 2H), 6.87-6.83 (m, 1H), 6.75 (d, *J* = 8.0 Hz, 0.3H), 6.59 (d, *J* = 8.0 Hz, 0.7H), 5.64 (d, *J* = 8.0 Hz, 0.3H), 5.52 (d, *J* = 8.0 Hz, 0.7H), 4.37-4.24 (m, 2H), 4.12-4.09 (m, 1H), 3.78 (s, 2H), 3.53 (s, 1H), 3.45 (s, 2H), 3.33 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.1, 164.8, 162.7, 162.5, 153.4, 152.6, 143.7, 143.6, 143.5, 142.4, 141.5, 141.4, 141.3, 140.6, 130.4, 130.1, 129.3, 129.0, 128.1, 128.0, 128.0, 127.9, 127.6, 127.5, 127.4, 127.3, 127.3, 127.2, 125.5, 125.4, 125.3, 125.2, 125.1,

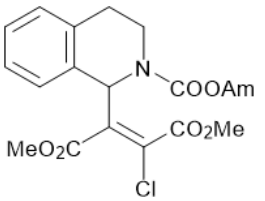
125.1, 124.5, 122.3, 120.2, 108.3, 107.6, 69.8, 68.8, 54.1, 53.8, 53.7, 53.5, 53.2, 52.9, 47.1, 47.0. HRMS (ESI) m/z: calcd for $C_{30}H_{24}ClNO_6$ $(M+H)^+$ 530.1365, found 530.1372.

Diethyl 2-chloro-3- (2- (propoxycarbonyl)-1,2-dihydroisoquinolin-1-yl)fumarate (4r)



Following the above procedure, the product **4r** was obtained in 78% yield (329 mg) as a white foam after column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v); IR (ATR): ν_{max}/cm^{-1} 2952, 1716, 1266, 1237, 1220, 1118, 1024, 769; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.58-7.52 (m, 1H), 7.29-7.27 (m, 1H), 7.24-7.16 (m, 2H), 7.02-6.98 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 0.46H), 6.77 (d, *J* = 8.0 Hz, 0.54H), 5.72 (d, *J* = 8.0 Hz, 0.46H), 5.63 (d, *J* = 8.0 Hz, 0.54H), 4.50-4.37 (m, 2H), 4.25-4.06 (m, 4H), 1.74-1.65 (m, 2H), 1.48-1.42 (m, 3H), 1.21-1.11 (m, 3H), 0.99-0.94 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 164.7, 164.4, 162.3, 162.2, 153.5, 152.8, 142.8, 140.6, 130.6, 130.3, 129.0, 128.8, 128.1, 127.9, 127.8, 127.4, 127.1, 125.4, 125.1, 125.0, 124.9, 122.3, 121.0, 107.5, 107.0, 68.6, 68.4, 63.1, 62.4, 62.1, 54.0, 53.6, 53.6, 22.3, 22.3, 14.2, 13.8, 10.5, 10.3, . HRMS (ESI) m/z: calcd for $C_{21}H_{24}ClNO_6$ $(M+H)^+$ 422.1365 found 422.1357.

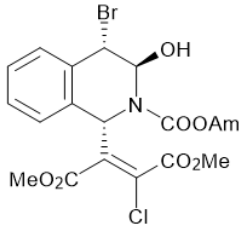
Dimethyl 2-chloro-3-(2-((pentyloxy)carbonyl)-1,2-dihydroisoquinolin-1-yl)succinate (5)



To a solution of **5** (210 mg, 0.5mmol) in DCM (2 ml) was added TFA (2ml) and Et_3SiH (0.5ml), and the mixture was stirred at rt for 8 h. The reaction was quenched with saturated $NaHCO_3$ solution, and the aqueous phase was extracted with DCM (2 × 10

mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (eluent = Petroleum ether/EtOAc 3:1 v/v) to afford the target product **5** in 90% (190 mg) yield as colorless oil. IR (ATR): ν_{max}/cm^{-1} 2955, 1735, 1703, 1405, 1267, 1234, 1025, 767; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.42-7.38 (m, 1H), 7.27-7.20 (m, 2H), 7.16-7.11 (m, 1H), 6.66 (s, 1H), 4.29-4.04 (m, 3H), 3.90 (s, 3H), 3.68(s, 3H), 3.27-2.94 (m, 1H), 2.89-2.69 (m, 2H), 1.67-1.56 (m, 2H), 1.36-1.26 (m, 4H), 0.94-0.89 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.4, 163.0, 155.8, 143.7, 134.9, 130.7, 129.0, 127.6, 126.8, 114.9, 66.3, 53.8, 53.6, 52.9, 39.2, 29.2, 28.8, 28.0, 22.5, 14.1. HRMS (ESI) m/z: calcd for $C_{21}H_{28}ClNO_6$ $(M+H)^+$ 424.1522, found 424.1518.

Dimethyl 2-(4-bromo-3-hydroxy-2-((pentyloxy)carbonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-3-chlorofumarate (6)



To a solution of **6** (210 mg, 0.5 mmol) in DMSO/H_2O mixture (7:1, 2 mL) was added NBS (178 mg, 1 mmol) and the mixture was stirred at rt for 5 h. The reaction was quenched with saturated $NaHCO_3$ solution and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic layers wased with water (30 ml) and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (eluent = Petroleum ether/EtOAc 2:1 v/v) to afford the target product **6** in 72% (186 mg) yield as white foam. IR (ATR): ν_{max}/cm^{-1} 2955, 1718, 1313, 1231, 1030, 755; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers) δ 7.58-7.53 (m, 1H), 7.40-7.29 (m, 3H), 6.8 (s, 1H), 6.26-6.18 (m, 1H), 5.2-5.1 (m, 1H), 4.26-4.06 (m, 2H), 3.93 (s, 3H), 3.63 (s, 3H), 1.71-1.57 (m, 2H), 1.39-1.29 (m, 4H), 0.95-0.88 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*, mixture of rotamers) δ 165.0, 162.7, 162.5, 162.4, 156.2, 152.5, 152.0, 143.9, 142.5, 140.3, 131.3, 129.6, 129.3, 128.3, 124.0, 122.7, 121.3, 103.3, 102.6, 67.6, 53.8, 53.2, 52.8, 47.9, 28.5, 27.9, 22.5,

14.1. HRMS (ESI) m/z: calcd for $C_{21}H_{25}BrClNO_7$ $(M+H)^+$ 518.0576, 520.0556 found 518.0574, 520.0058.

3. X-Ray Structure for compound 4o

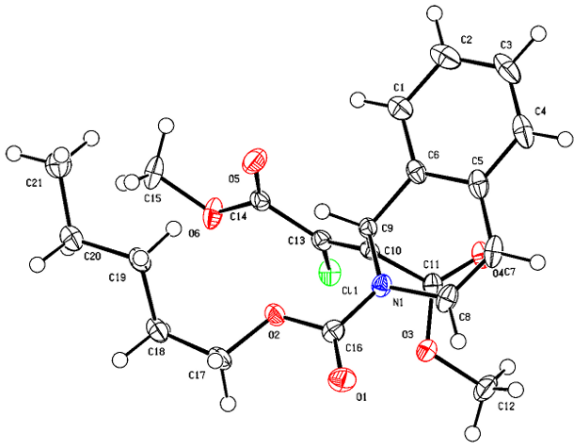


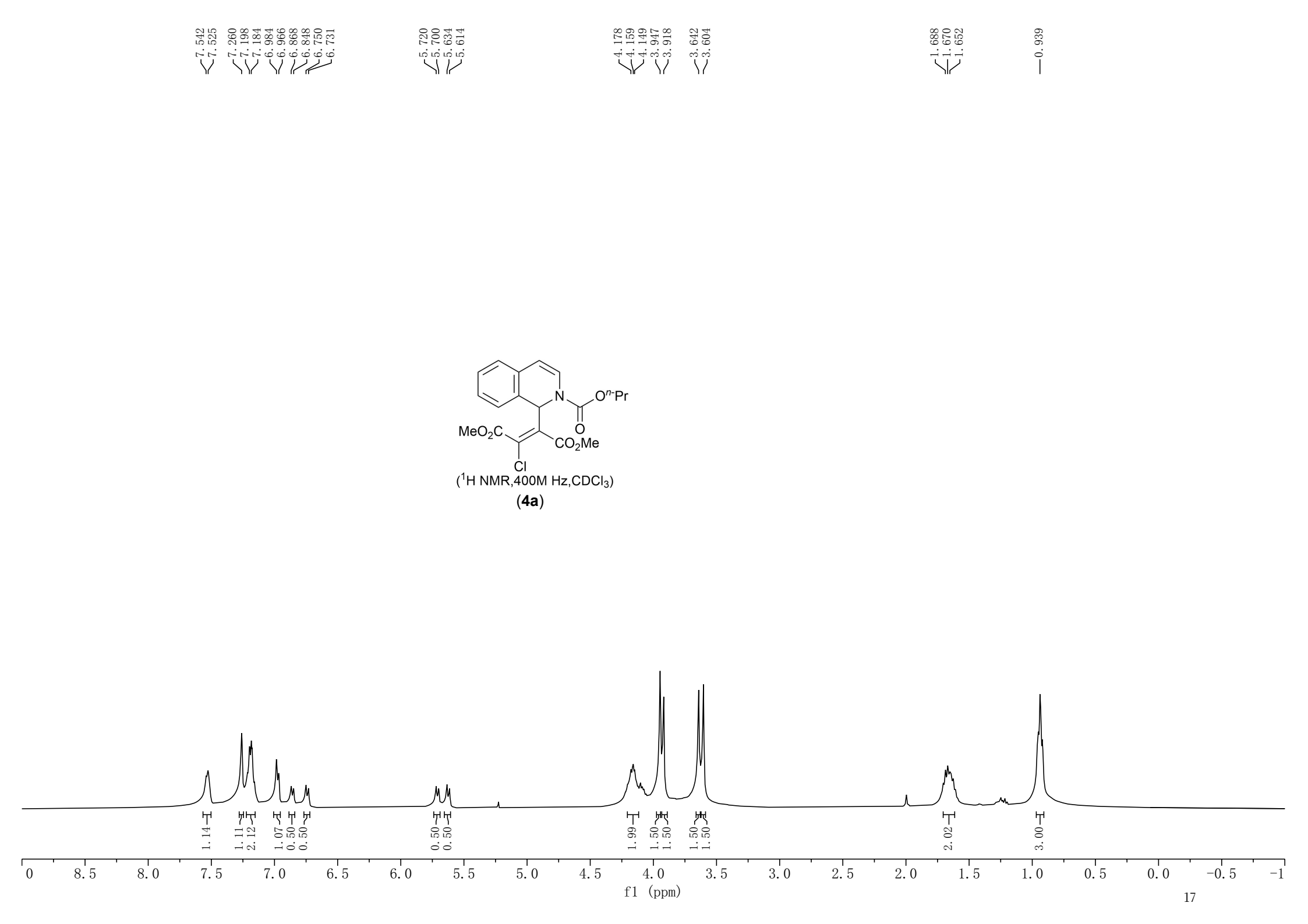
Table S1 Crystal data and structure refinement for 4o-100K_auto.

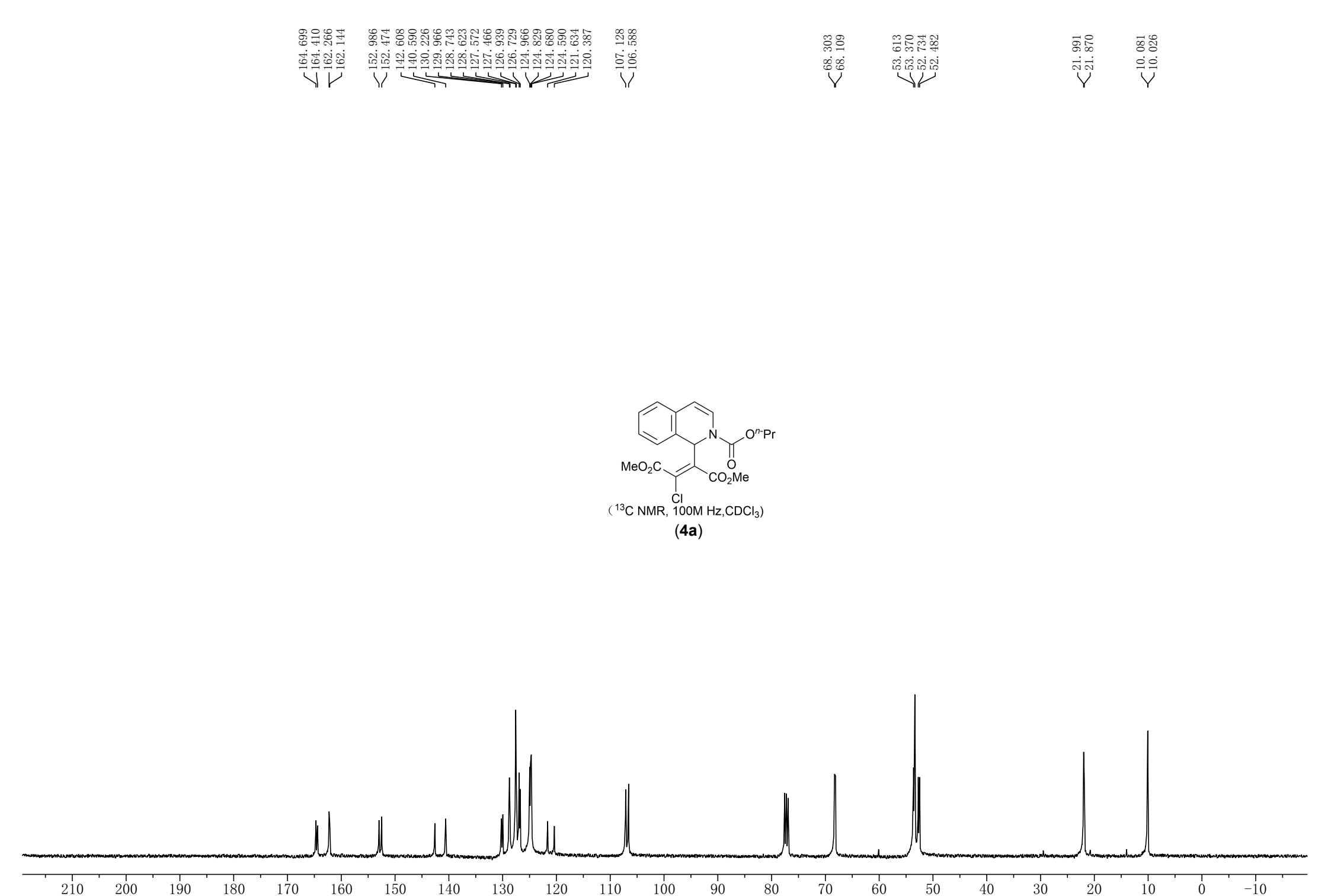
Identification code	4o-100K_auto
Empirical formula	$C_{21}H_{24}ClNO_6$
Formula weight	421.86
Temperature/K	99.99(10)
Crystal system	monoclinic
Space group	C2/c
a/Å	20.5201(5)
b/Å	8.6569(2)
c/Å	22.7664(6)
α/°	90
β/°	90.366(2)
γ/°	90
Volume/Å^3	4044.15(17)
Z	8
ρ_{calc}g/cm^3	1.386
μ/mm^{-1}	0.227

Table S1 Crystal data and structure refinement for 4o-100K_auto.

F(000)	1776.0
Crystal size/mm^3	0.53 × 0.33 × 0.23
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	3.578 to 58.952
Index ranges	-25 ≤ h ≤ 27, -11 ≤ k ≤ 10, -25 ≤ l ≤ 27
Reflections collected	16369
Independent reflections	4621 [R_{int} = 0.0310, R_{sigma} = 0.0327]
Data/restraints/parameters	4621/0/265
Goodness-of-fit on F^2	1.060
Final R indexes [I>=2σ (I)]	R_1 = 0.0368, wR_2 = 0.0873
Final R indexes [all data]	R_1 = 0.0456, wR_2 = 0.0917
Largest diff. peak/hole / e Å^{-3}	0.25/-0.30

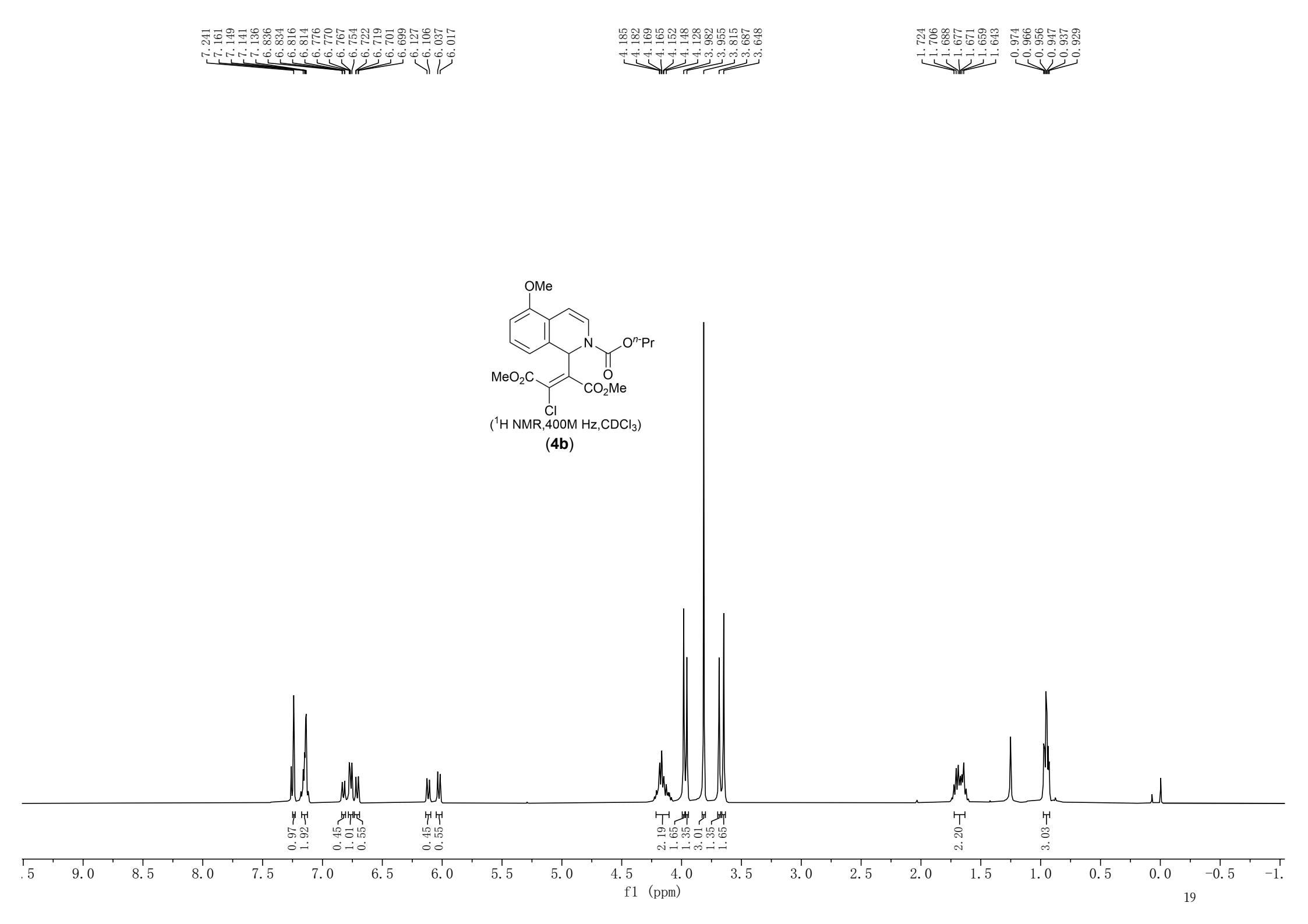
4. NMR Spectra of New Compounds

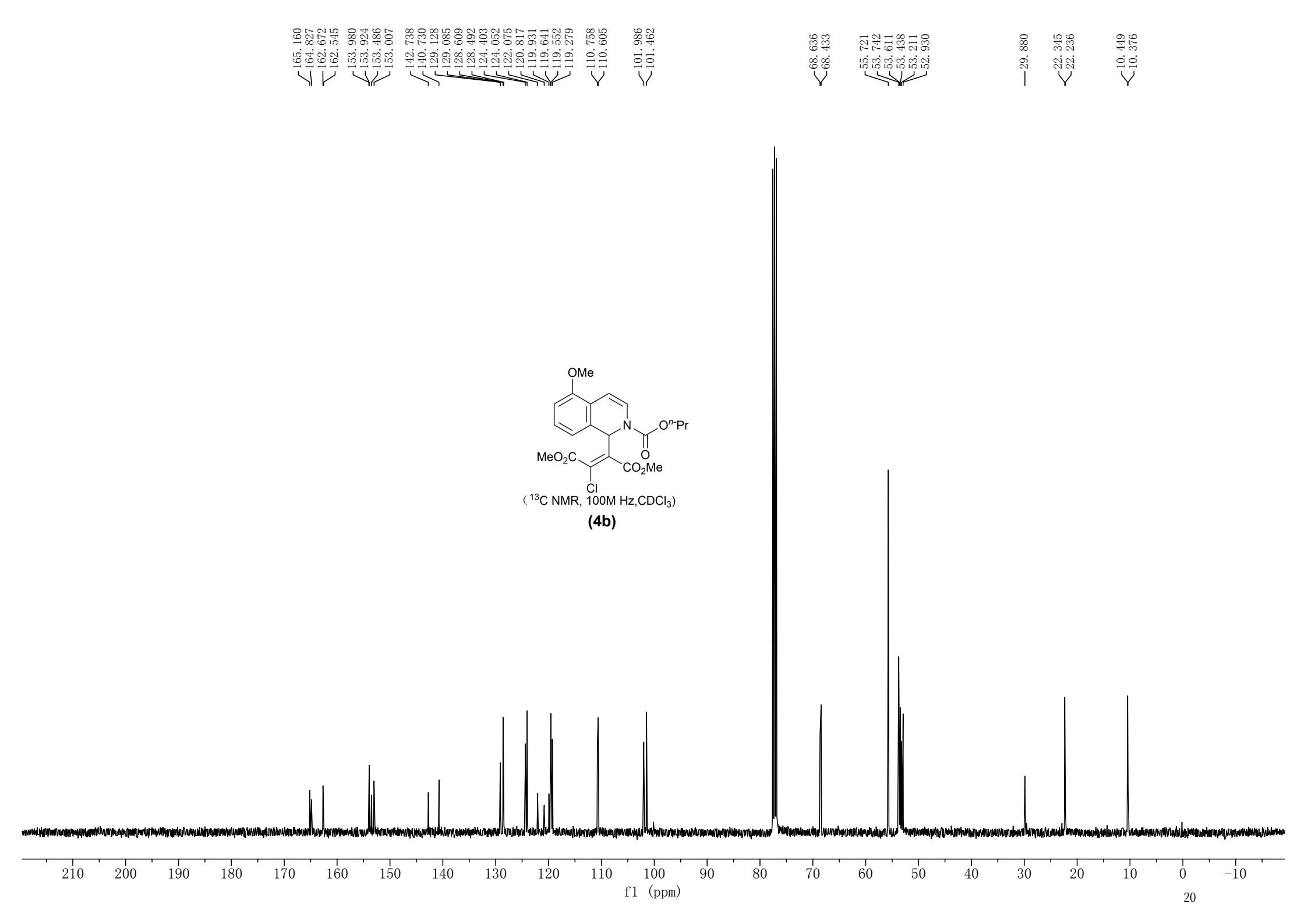

7.542
7.525
7.260
7.198
7.184
6.984
6.966
6.868
6.848
6.750
6.731
5.720
5.700
5.634
5.614
4.178
4.159
4.149
3.947
3.918
3.642
3.604
1.688
1.670
1.652
0.939
N
O^{n}Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4a)
1.14
1.11
2.12
1.07
0.50
0.50
0.50
0.50
1.99
1.50
1.50
1.50
1.50
2.02
3.00
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)

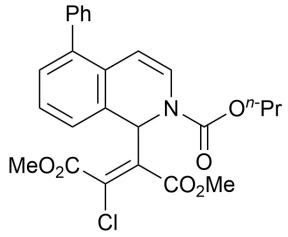


(^{13}C NMR, 100M Hz,CDCl$_3$)

(4a)

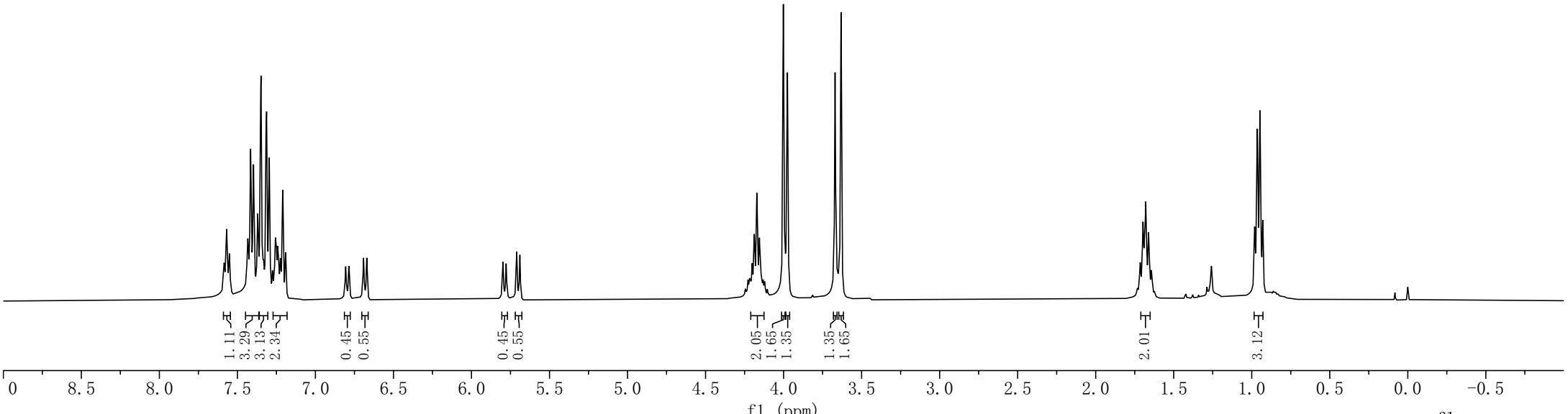

7.241
7.161
7.149
7.141
7.136
6.836
6.834
6.816
6.814
6.776
6.770
6.767
6.754
6.722
6.719
6.701
6.699
6.127
6.106
6.037
6.017
4.185
4.182
4.169
4.165
4.152
4.148
4.128
3.982
3.955
3.815
3.687
3.648
1.724
1.706
1.688
1.677
1.671
1.659
1.643
0.974
0.966
0.956
0.947
0.937
0.929
OMe
N
O^{n}-Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4b)
0.97
1.92
0.45
1.01
0.55
0.45
0.55
2.19
1.65
1.35
3.01
1.35
1.65
2.20
3.03
f1 (ppm)

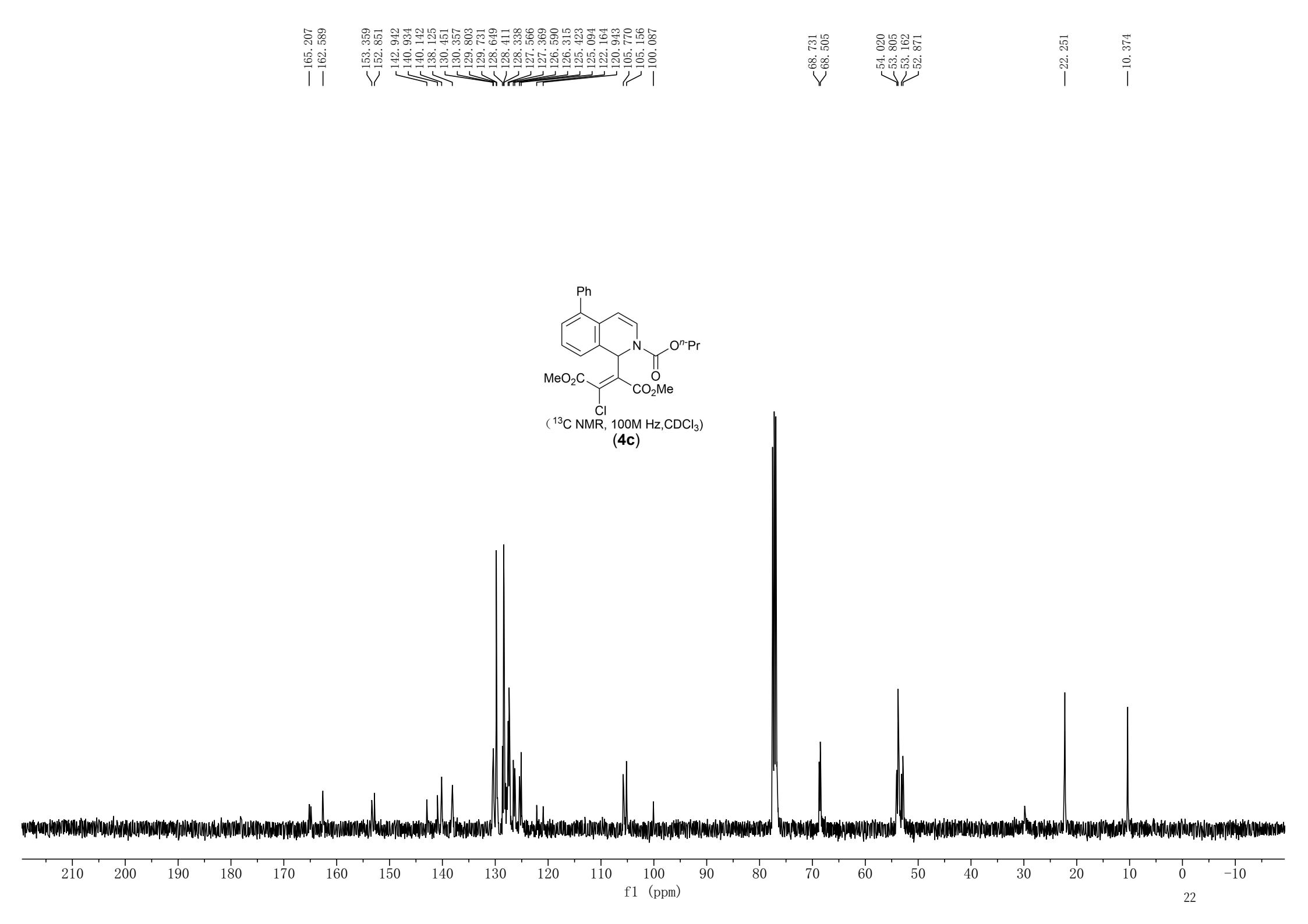

165.160
164.827
162.672
162.545
153.980
153.924
153.486
153.007
142.738
140.730
129.128
129.085
128.609
128.492
124.403
124.052
122.075
120.817
119.931
119.641
119.552
119.279
110.758
110.605
101.986
101.462
68.636
68.433
55.721
53.742
53.611
53.438
53.211
52.930
29.880
22.345
22.236
10.449
10.376
OMe
N
O^{n}-Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4b)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

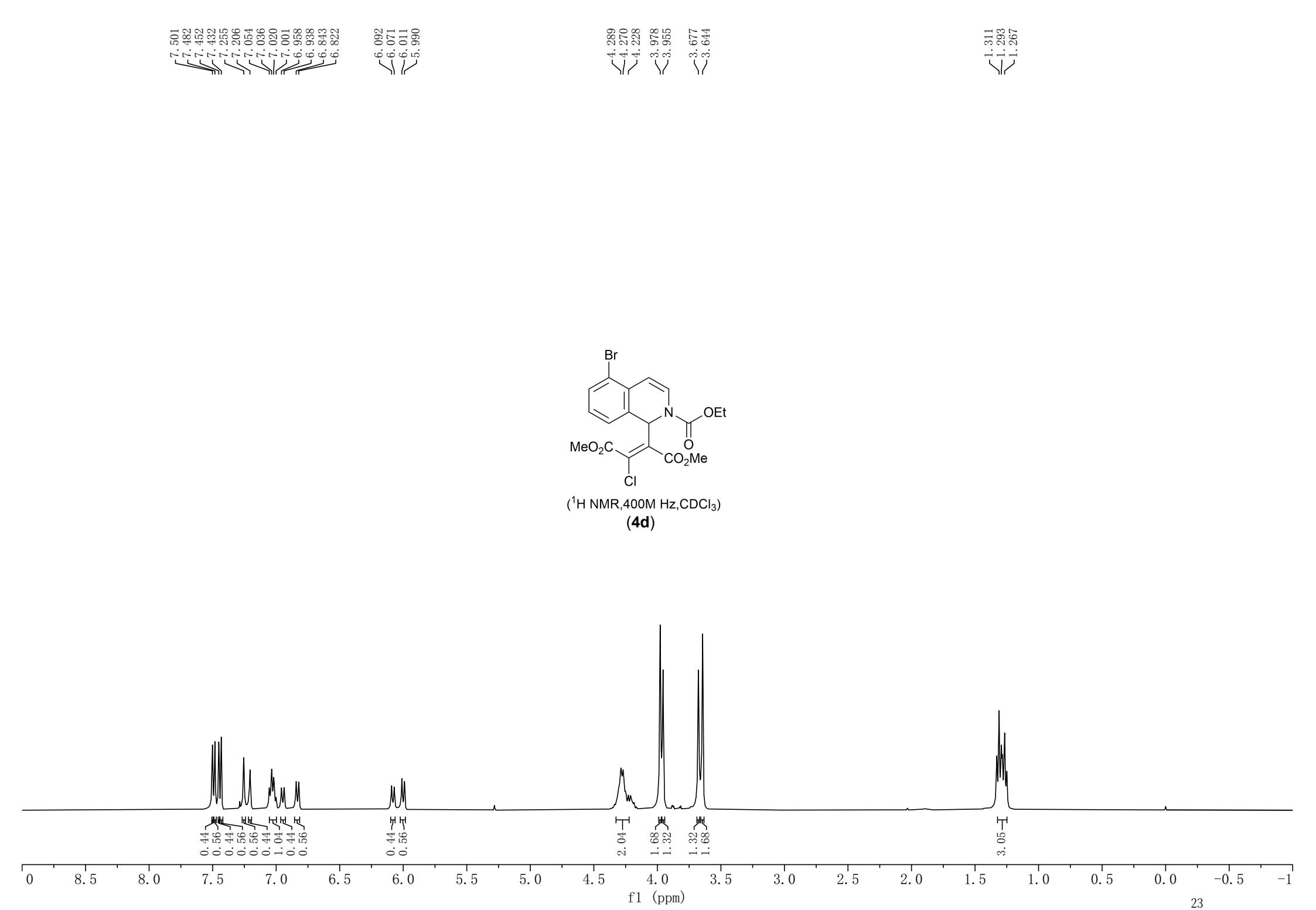


(^{1}H NMR,400M Hz,CDCl$_3$)

(4c)

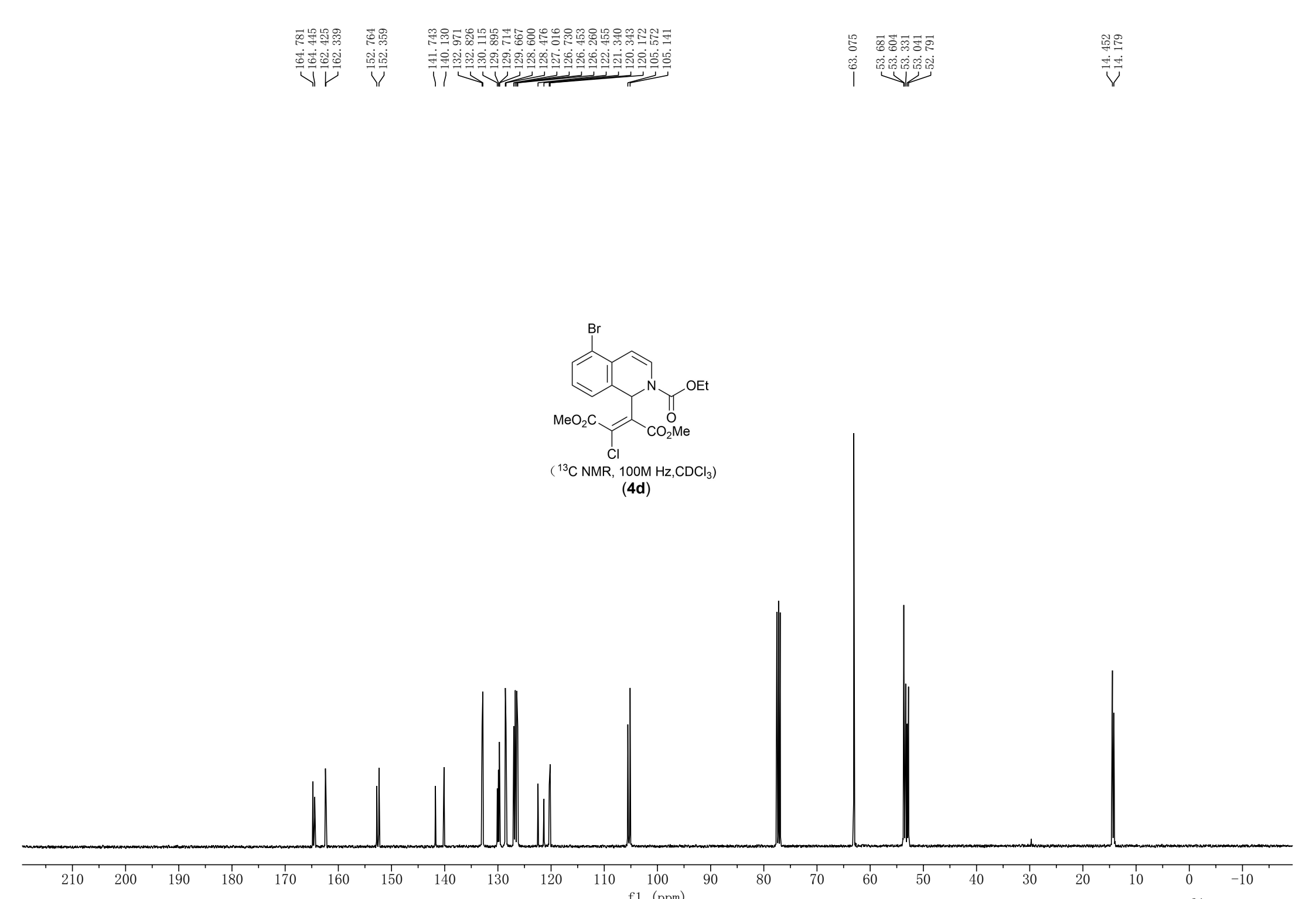



165.207
162.589
153.359
152.851
142.942
140.934
140.142
138.125
130.451
130.357
129.803
129.731
128.649
128.411
128.338
127.566
127.369
126.590
126.315
125.423
125.094
122.164
120.943
105.770
105.156
100.087
68.731
68.505
54.020
53.805
53.162
52.871
22.251
10.374
Ph
N
O^{n}Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4c)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



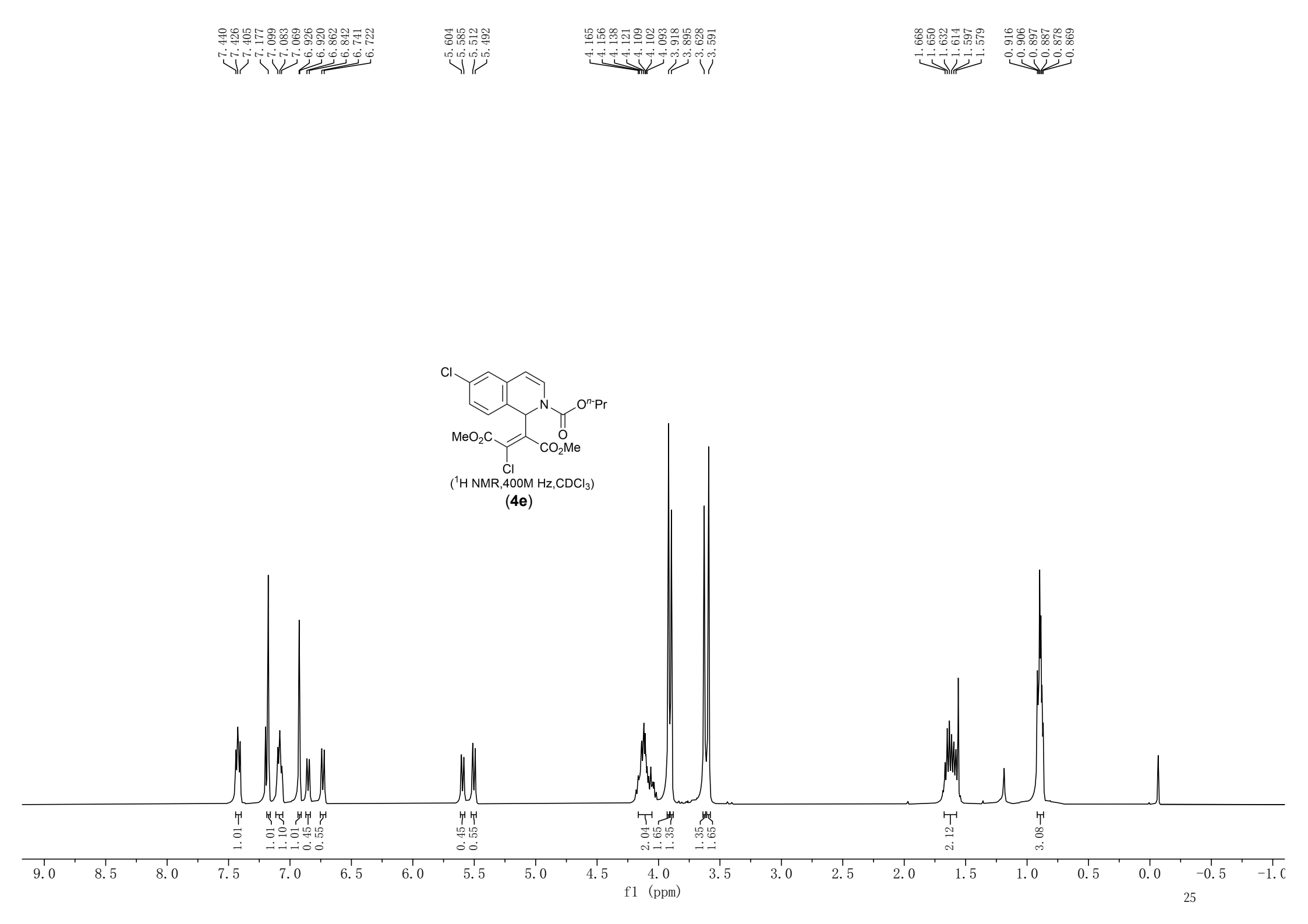
(^{1}H NMR,400M Hz,$CDCl_3$)

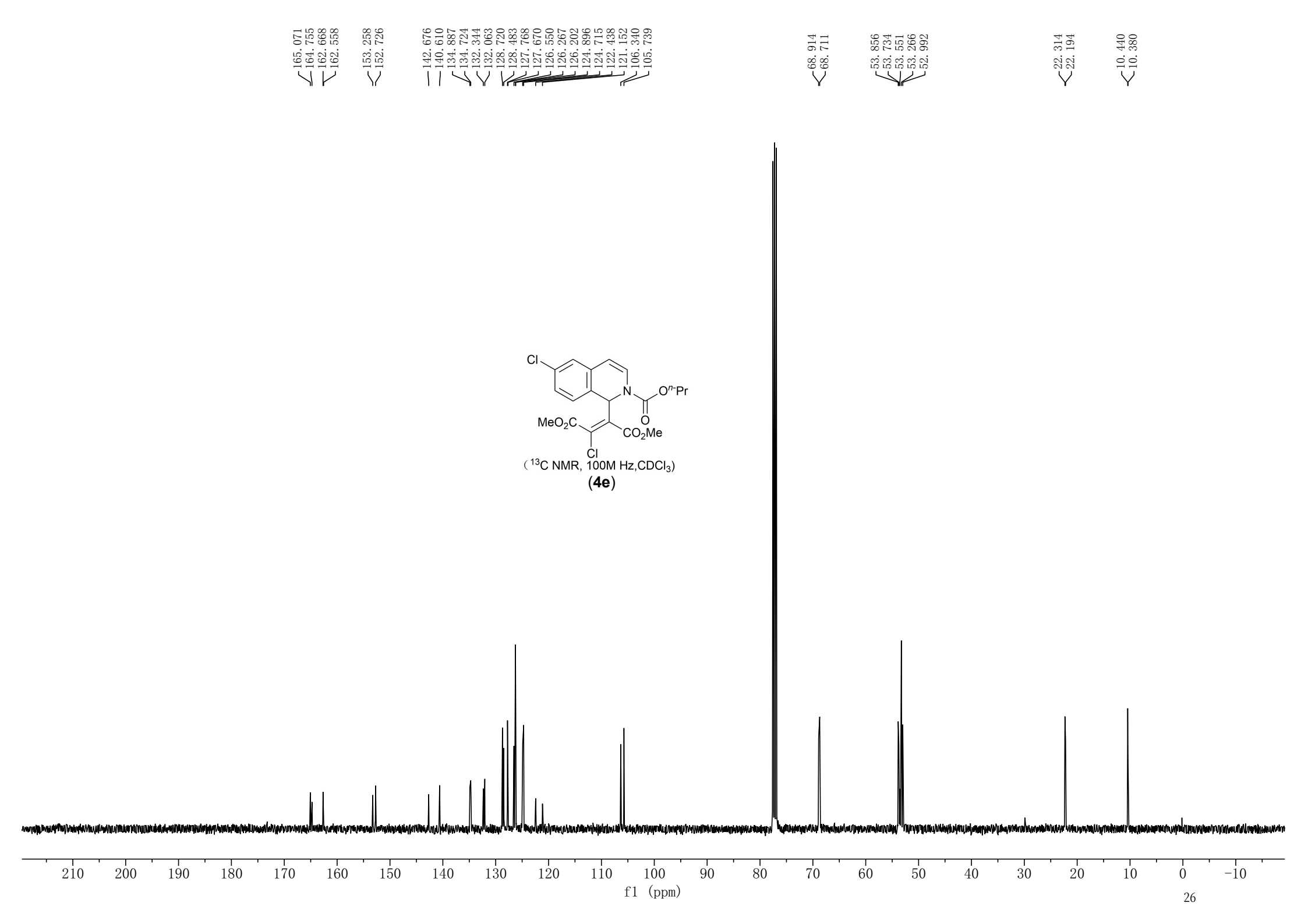
(**4d**)

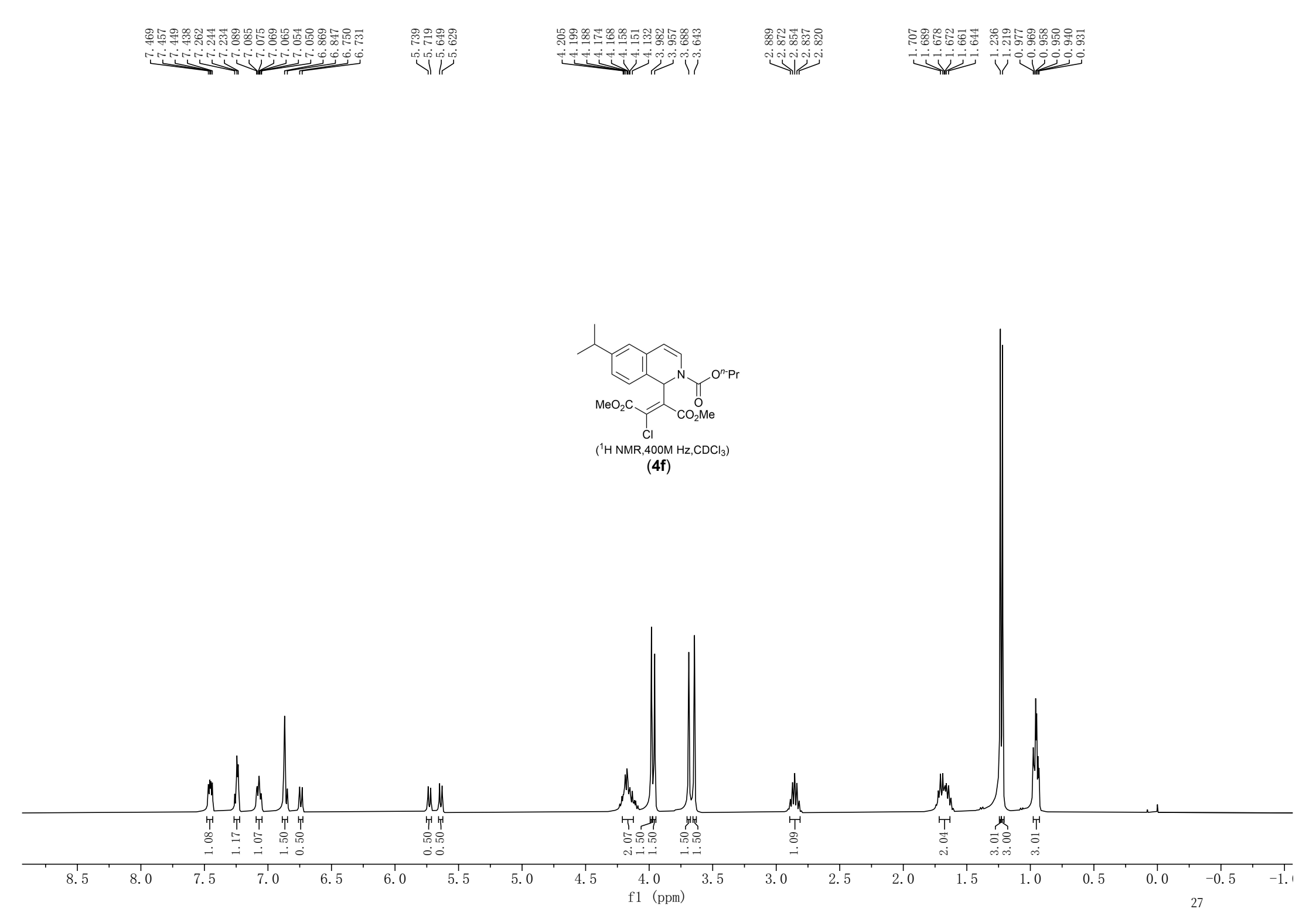


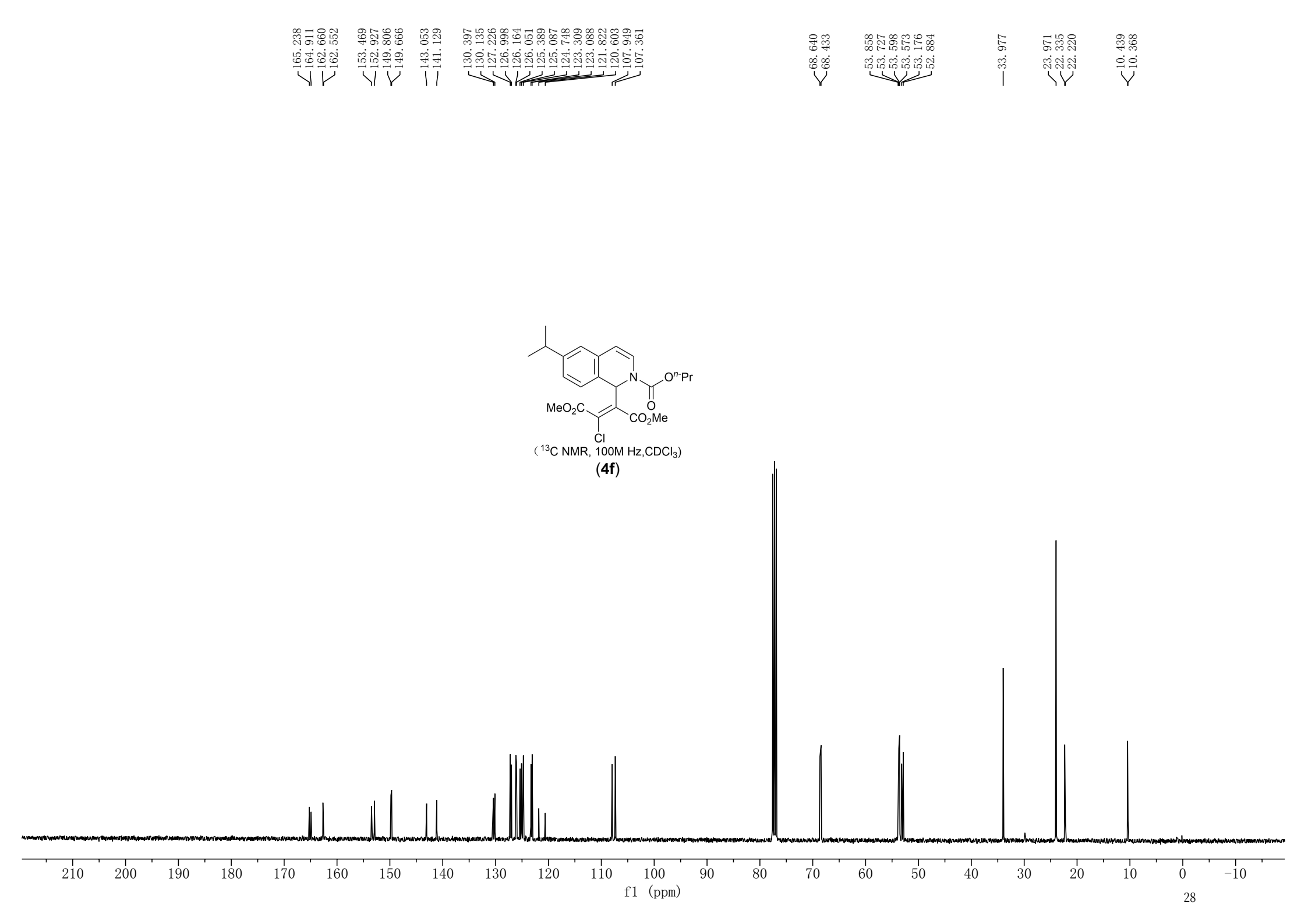
(^{13}C NMR, 100M Hz,$CDCl_3$)

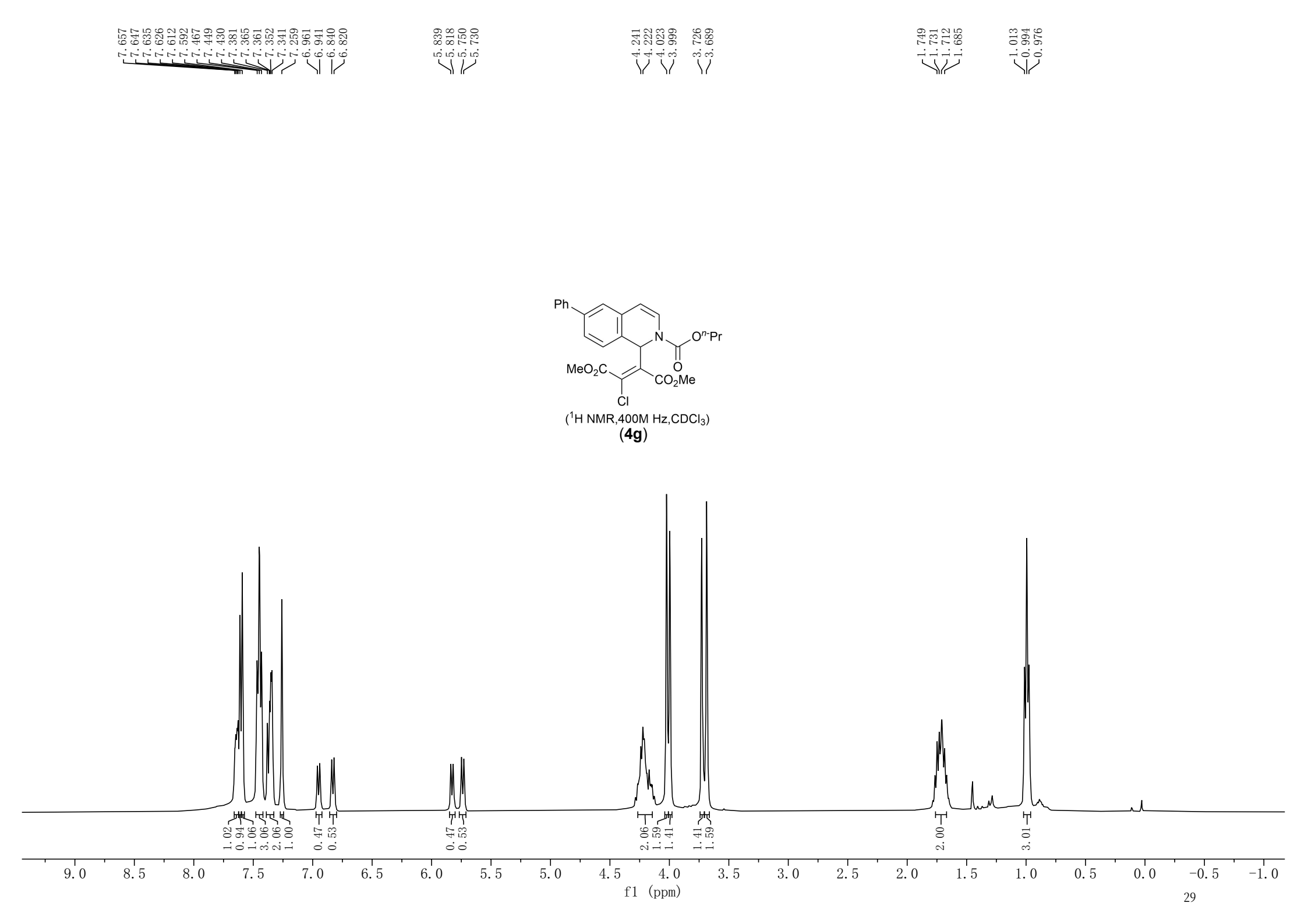
(4d)

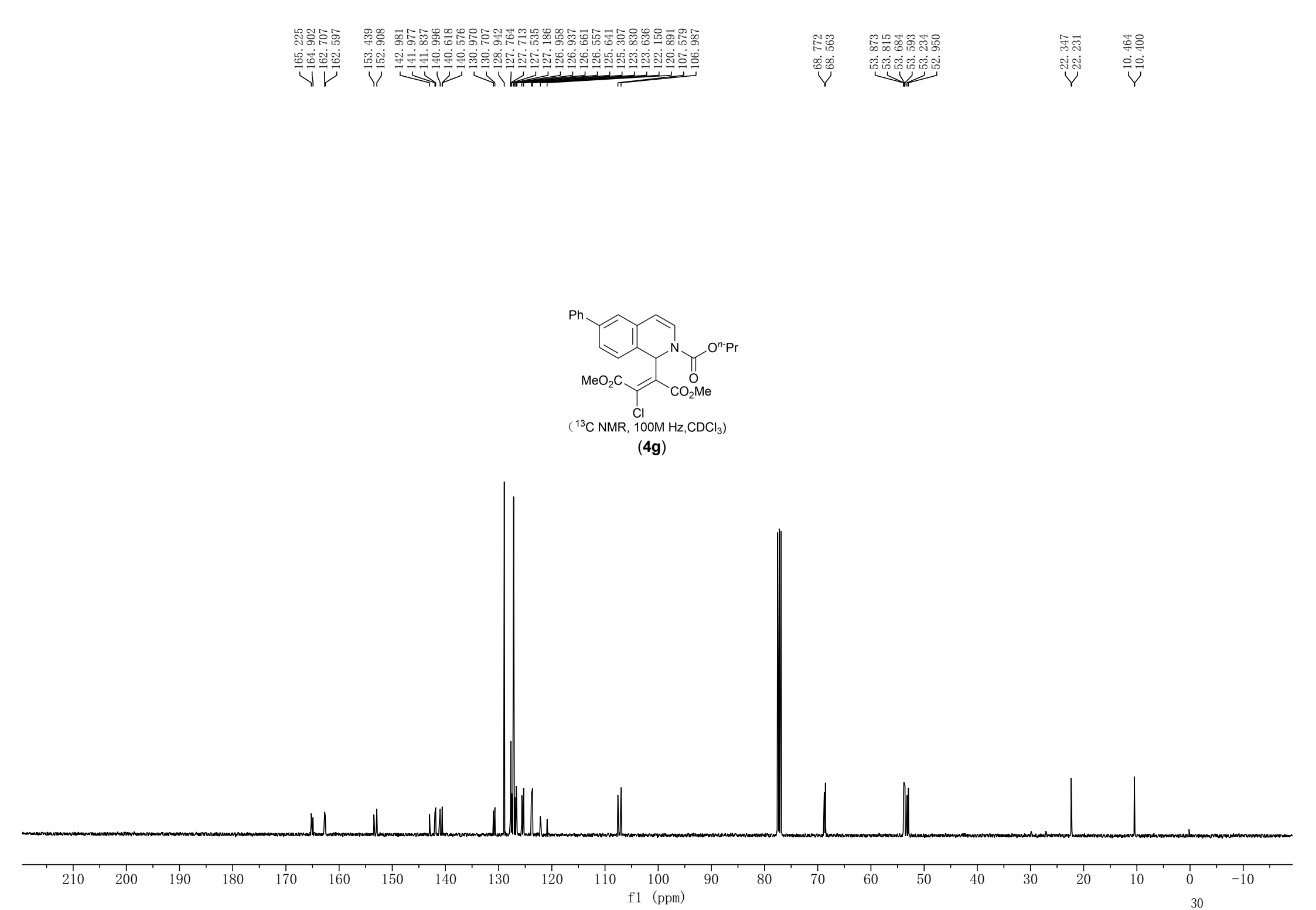

7.440
7.426
7.405
7.177
7.099
7.083
7.069
6.926
6.920
6.862
6.842
6.741
6.722
5.604
5.585
5.512
5.492
4.165
4.156
4.138
4.121
4.109
4.102
4.093
3.918
3.895
3.628
3.591
1.668
1.650
1.632
1.614
1.597
1.579
0.916
0.906
0.897
0.887
0.878
0.869
Cl
N
O^{n}-Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4e)
1.01
1.01
1.10
1.01
0.45
0.55
0.45
0.55
2.04
1.65
1.35
1.35
1.65
2.12
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

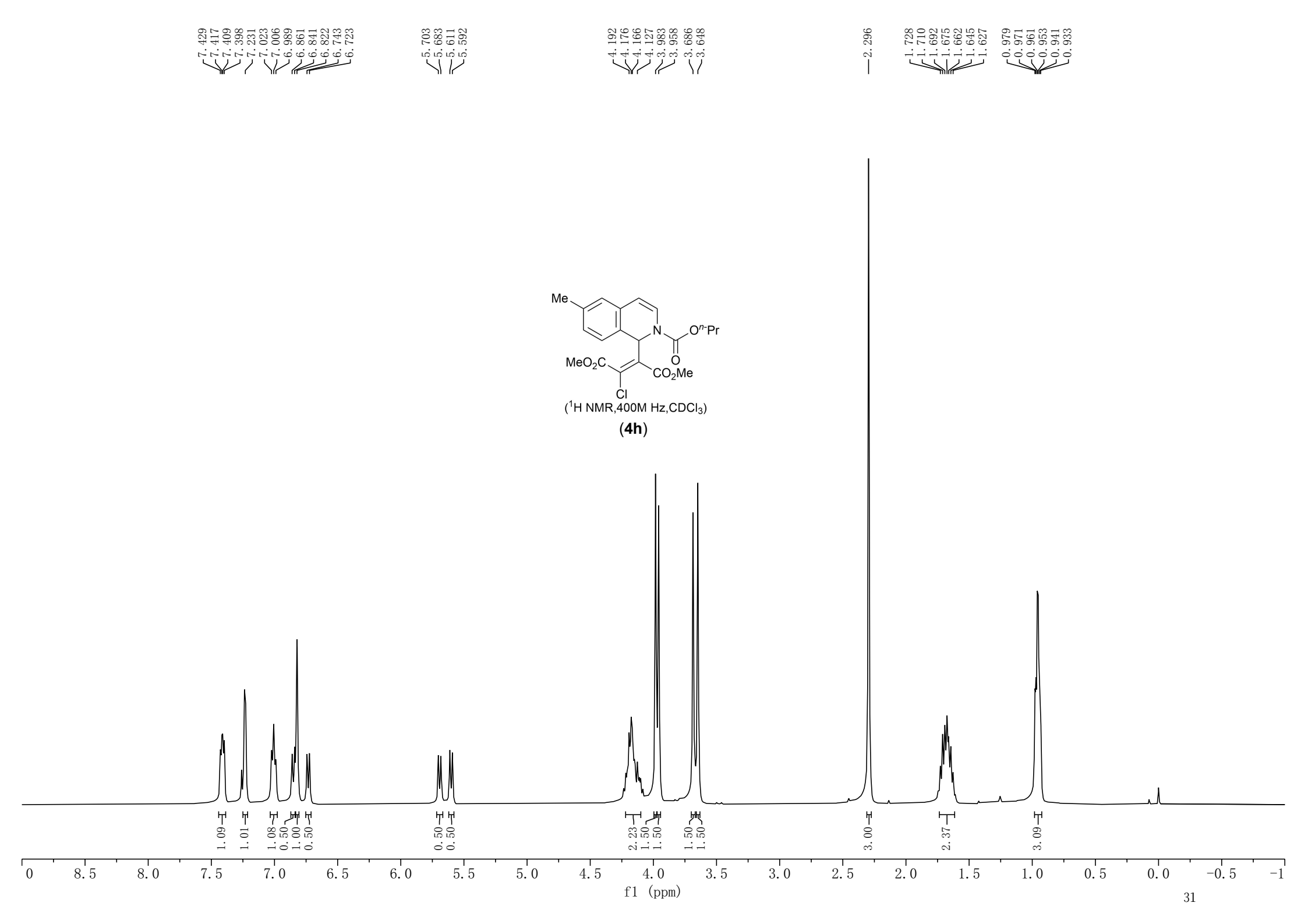

165.071
164.755
162.668
162.558
153.258
152.726
142.676
140.610
134.887
134.724
132.344
132.063
128.720
128.483
127.768
127.670
126.550
126.267
126.202
124.896
124.715
122.438
121.152
106.340
105.739
68.914
68.711
53.856
53.734
53.551
53.266
52.992
22.314
22.194
10.440
10.380
Cl
N
O
O^{n}-Pr
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4e)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

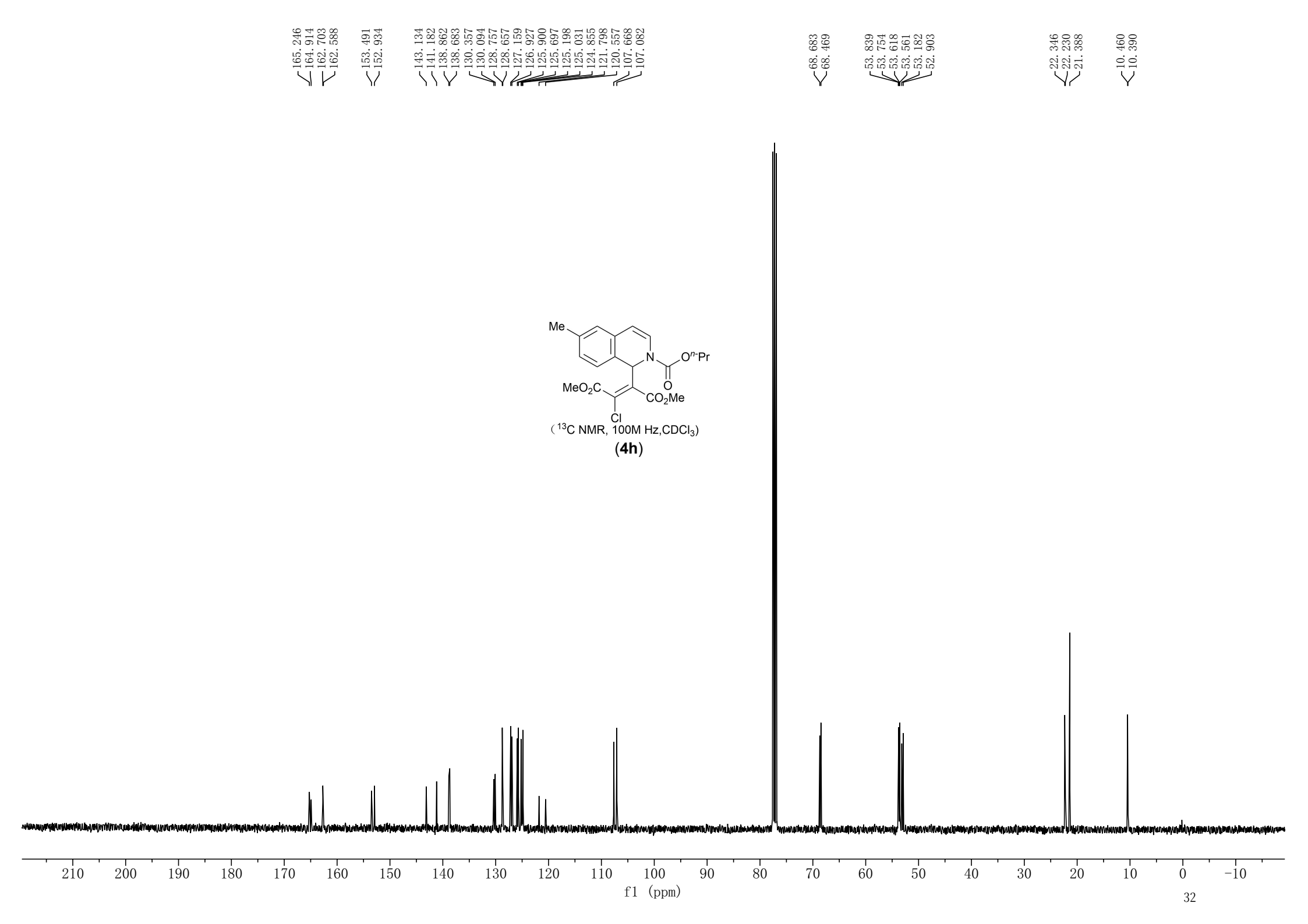

7.469
7.457
7.449
7.438
7.262
7.244
7.234
7.089
7.085
7.075
7.069
7.065
7.054
7.050
6.869
6.847
6.750
6.731
5.739
5.719
5.649
5.629
4.205
4.199
4.188
4.174
4.168
4.158
4.151
4.132
3.982
3.957
3.688
3.643
2.889
2.872
2.854
2.837
2.820
1.707
1.689
1.678
1.672
1.661
1.644
1.236
1.219
0.977
0.969
0.958
0.950
0.940
0.931
N
O^{n}Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4f)
1.08
1.17
1.07
1.50
0.50
0.50
0.50
2.07
1.50
1.50
1.50
1.50
1.09
2.04
3.01
3.00
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

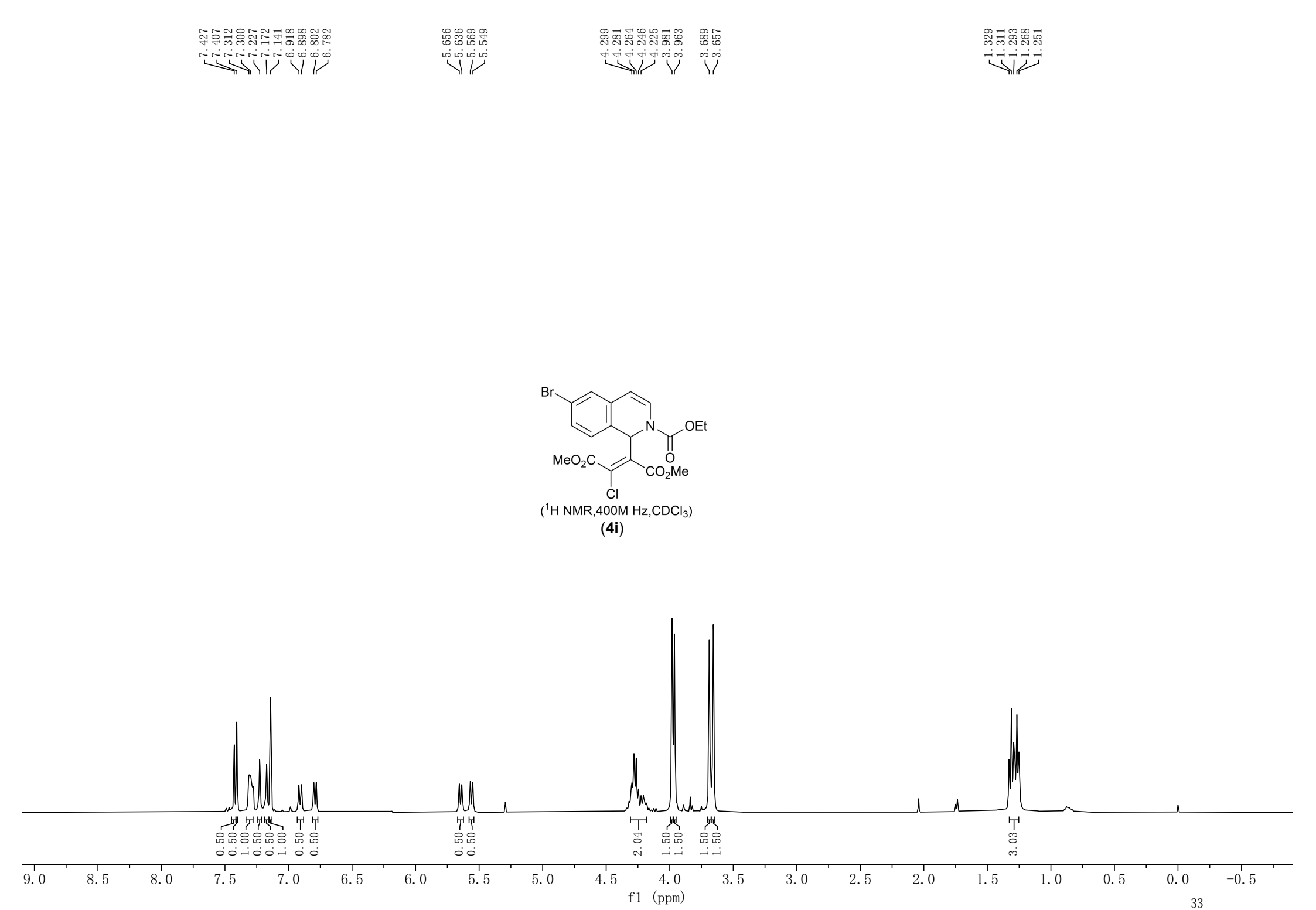

165.238
164.911
162.660
162.552
153.469
152.927
149.806
149.666
143.053
141.129
130.397
130.135
127.226
126.998
126.164
126.051
125.389
125.087
124.748
123.309
123.088
121.822
120.603
107.949
107.361
68.640
68.433
53.858
53.727
53.598
53.573
53.176
52.884
33.977
23.971
22.335
22.220
10.439
10.368
N
O
O^{n}-Pr
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4f)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

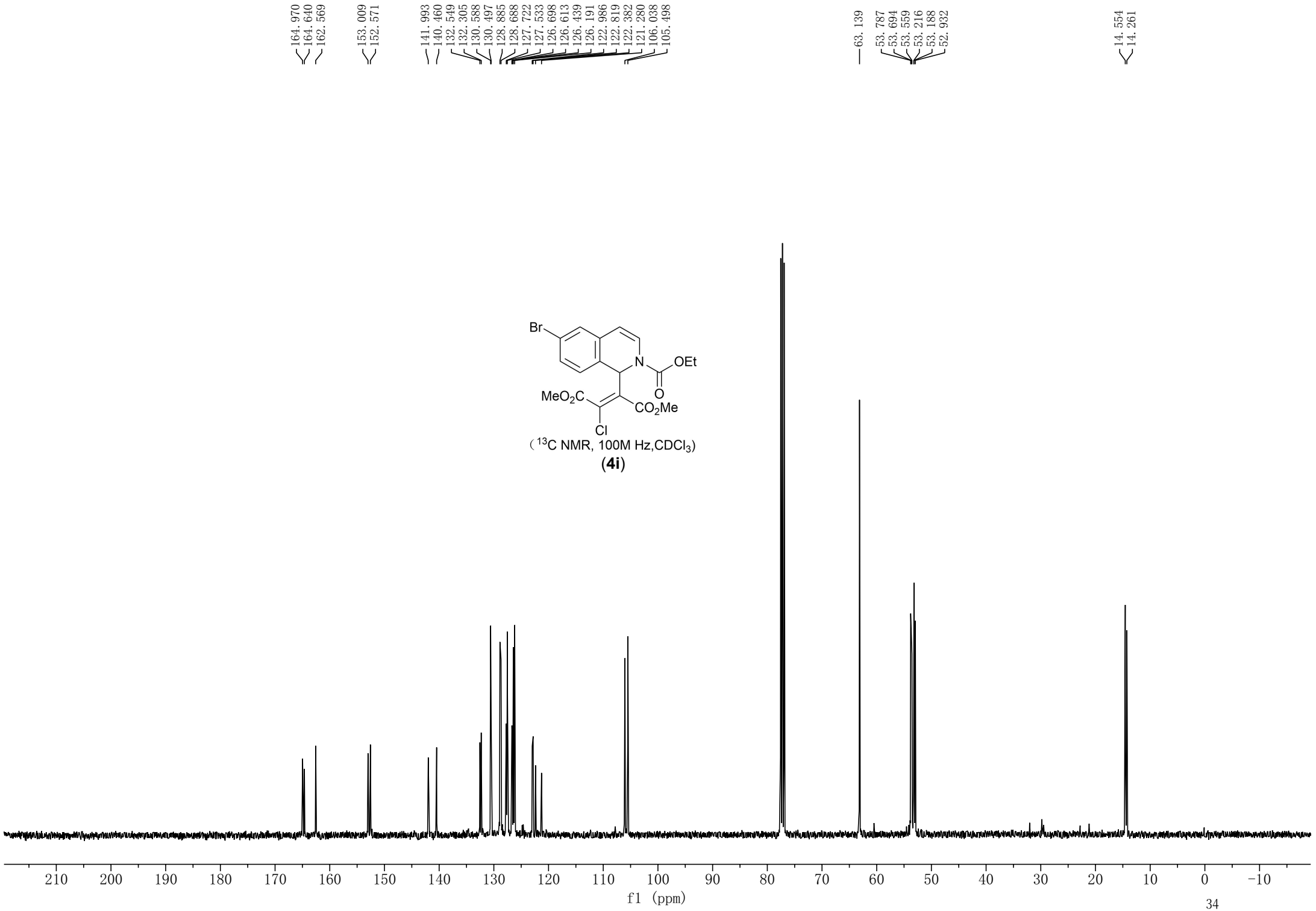

7.657
7.647
7.635
7.626
7.612
7.592
7.467
7.449
7.430
7.381
7.365
7.361
7.352
7.341
7.259
6.961
6.941
6.840
6.820
5.839
5.818
5.750
5.730
4.241
4.222
4.023
3.999
3.726
3.689
1.749
1.731
1.712
1.685
1.013
0.994
0.976
Ph
N
O^{n}-Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4g)
1.02
0.94
1.06
3.06
2.06
1.00
0.47
0.53
0.47
0.53
2.06
1.59
1.41
1.41
1.59
2.00
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

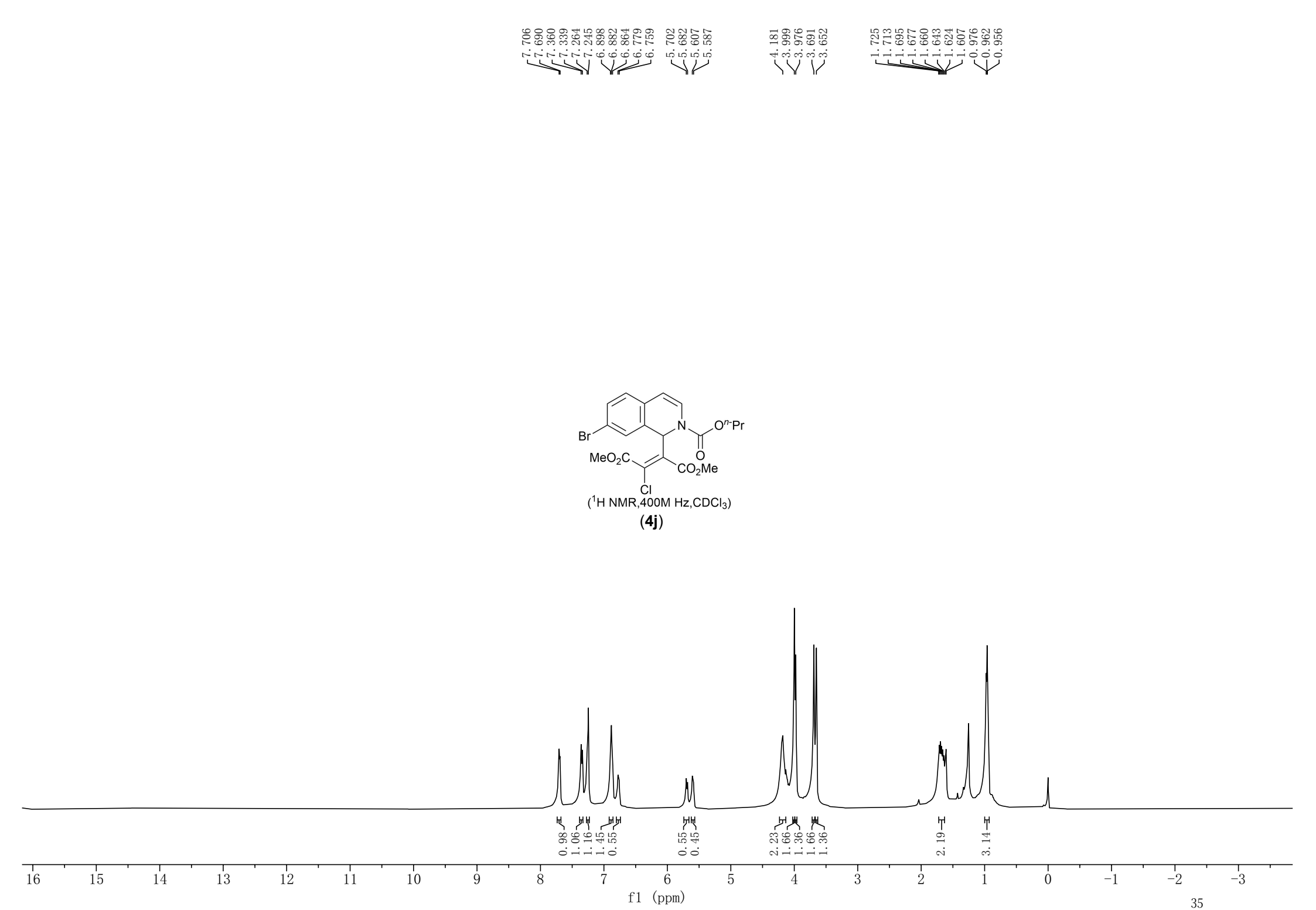

165.225
164.902
162.707
162.597
153.439
152.908
142.981
141.977
141.837
140.996
140.618
140.576
130.970
130.707
128.942
127.764
127.713
127.535
127.186
126.958
126.937
126.661
126.557
125.641
125.307
123.830
123.636
122.150
120.891
107.579
106.987
68.772
68.563
53.873
53.815
53.684
53.593
53.234
52.950
22.347
22.231
10.464
10.400
Ph
N
O^{n}Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4g)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

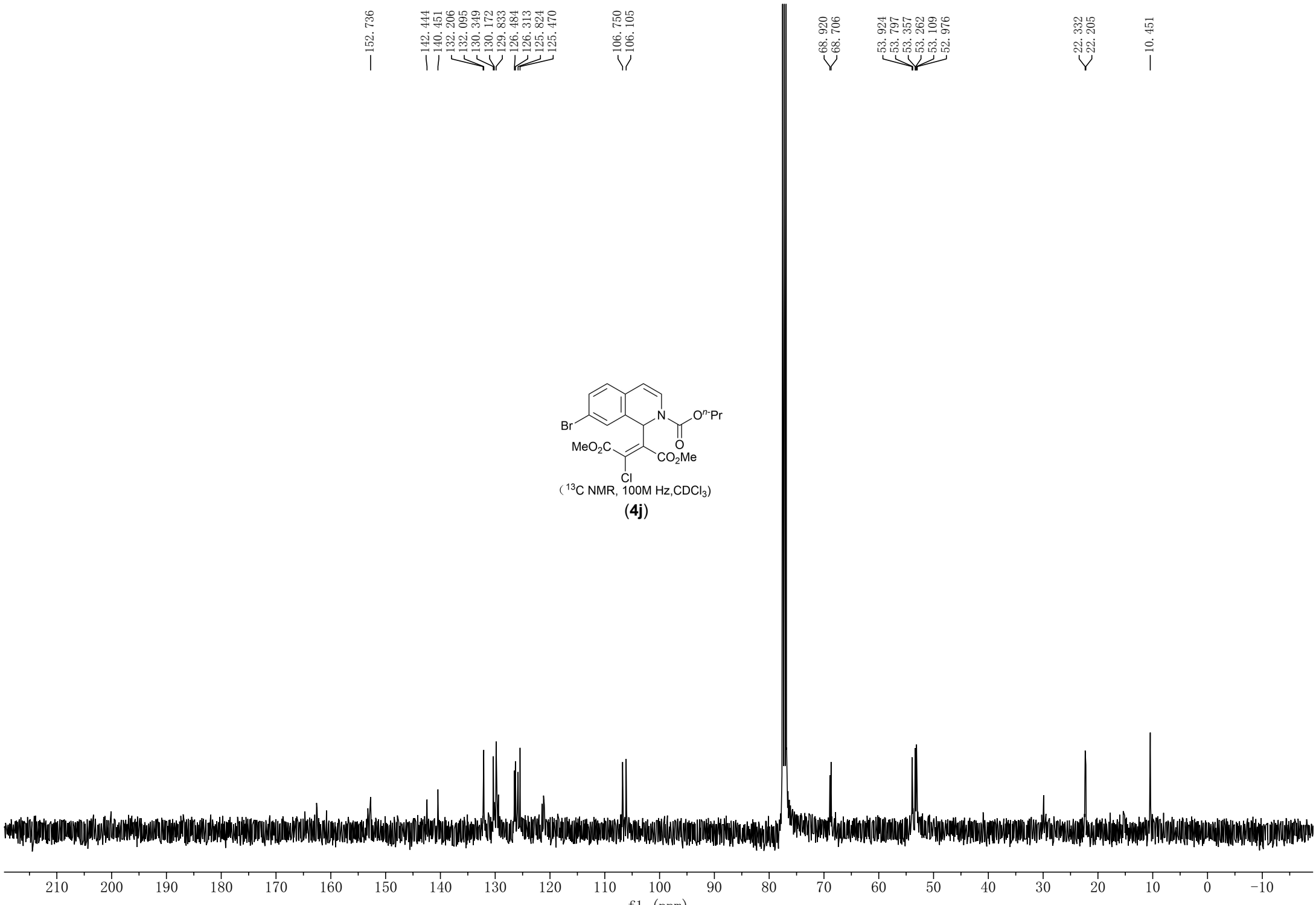

7.429
7.417
7.409
7.398
7.231
7.023
7.006
6.989
6.861
6.841
6.822
6.743
6.723
5.703
5.683
5.611
5.592
4.192
4.176
4.166
4.127
3.983
3.958
3.686
3.648
2.296
1.728
1.710
1.692
1.675
1.662
1.645
1.627
0.979
0.971
0.961
0.953
0.941
0.933
Me
N
O^{n}-Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4h)
1.09
1.01
1.08
0.50
1.00
0.50
0.50
0.50
2.23
1.50
1.50
1.50
1.50
3.00
2.37
3.09
f1 (ppm)

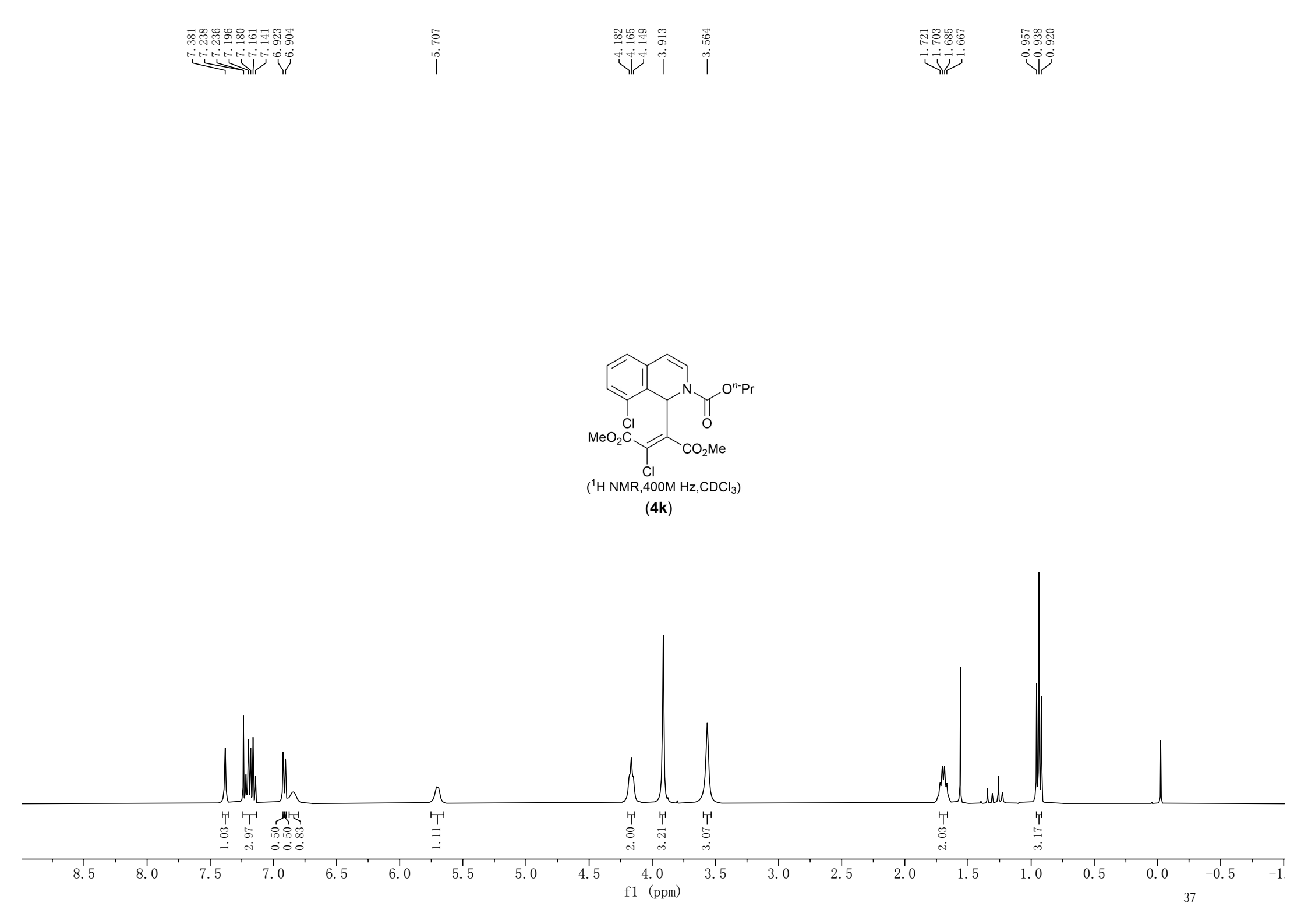

165.246
164.914
162.703
162.588
153.491
152.934
143.134
141.182
138.862
138.683
130.357
130.094
128.757
128.657
127.159
126.927
125.900
125.697
125.198
125.031
124.855
121.798
120.557
107.668
107.082
68.683
68.469
53.839
53.754
53.618
53.561
53.182
52.903
22.346
22.230
21.388
10.460
10.390
Me
N
O
O^{n}-Pr
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4h)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

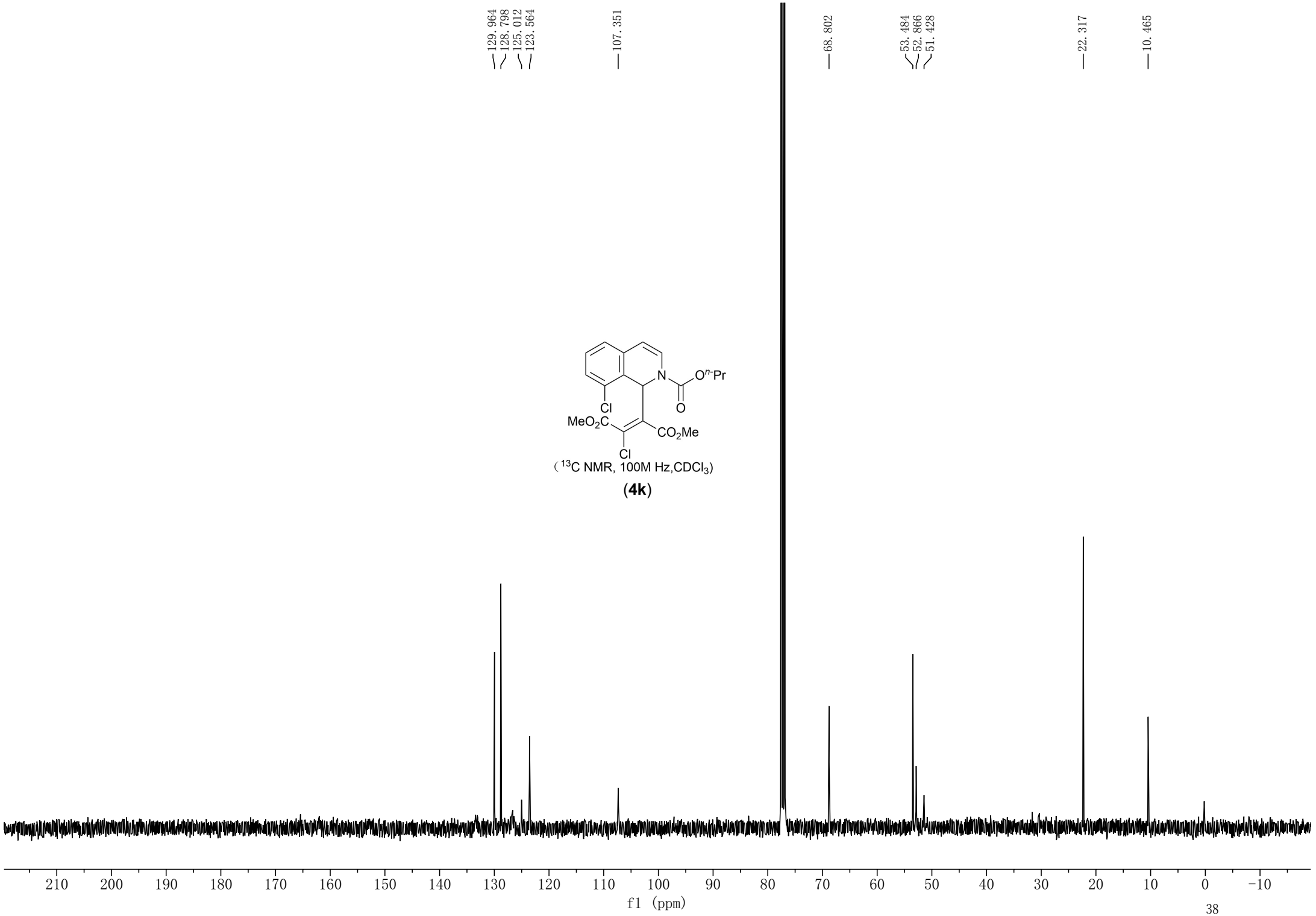

7.427
7.407
7.312
7.300
7.227
7.172
7.141
6.918
6.898
6.802
6.782
5.656
5.636
5.569
5.549
4.299
4.281
4.264
4.246
4.225
3.981
3.963
3.689
3.657
1.329
1.311
1.293
1.268
1.251
Br
N
OEt
O
MeO2C
CO2Me
Cl
(1H NMR,400M Hz,CDCl3)
(4i)
0.50
0.50
1.00
0.50
0.50
1.00
0.50
0.50
0.50
0.50
2.04
1.50
1.50
1.50
1.50
3.03
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

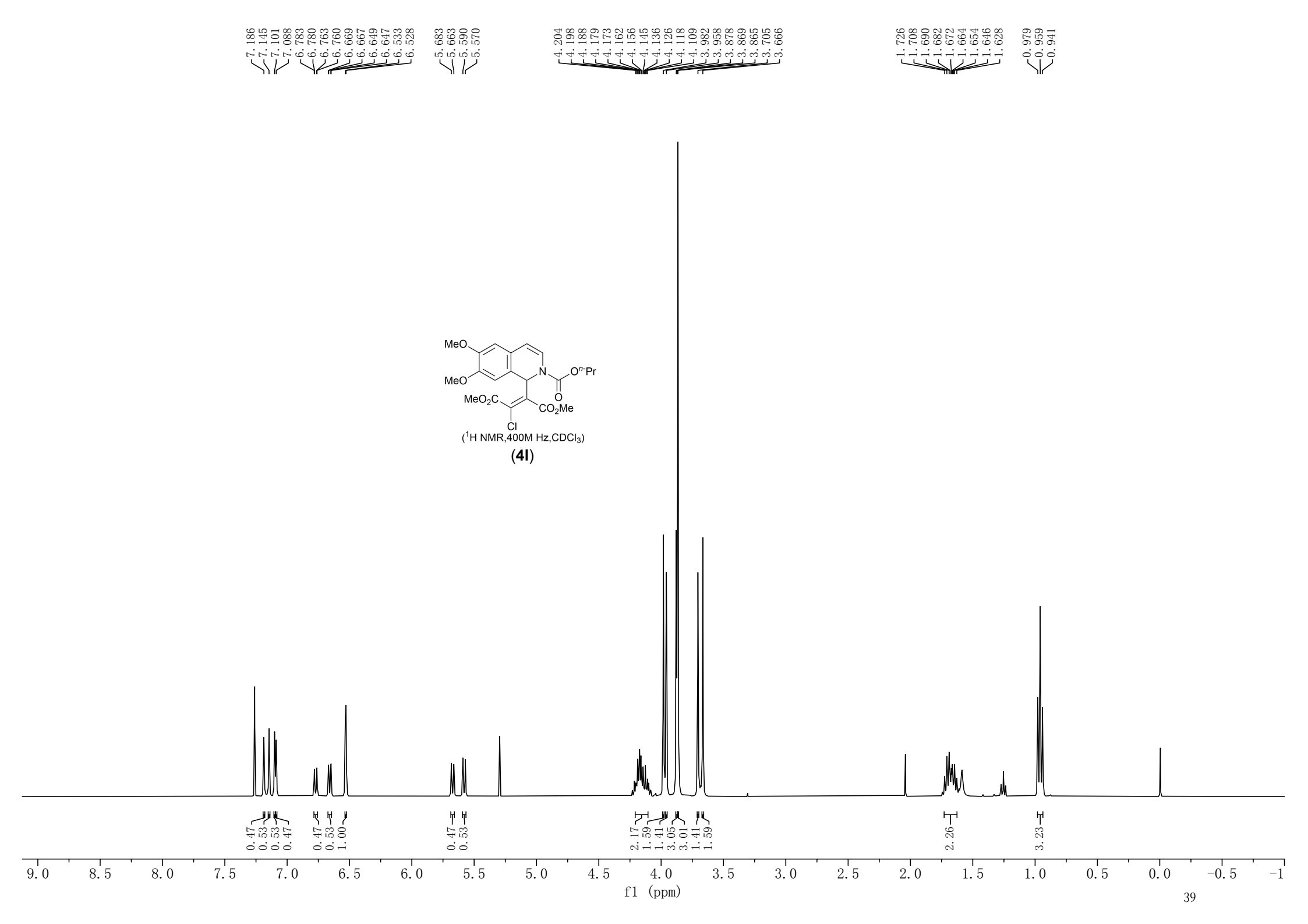

164.970
164.640
162.569
153.009
152.571
141.993
140.460
132.549
132.305
130.588
130.497
128.885
128.688
127.722
127.533
126.698
126.613
126.439
126.191
122.986
122.819
122.382
121.280
106.038
105.498
63.139
53.787
53.694
53.559
53.216
53.188
52.932
14.554
14.261
Br
N
OEt
O
MeO2C
CO2Me
Cl
(13C NMR, 100M Hz,CDCl3)
(4i)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

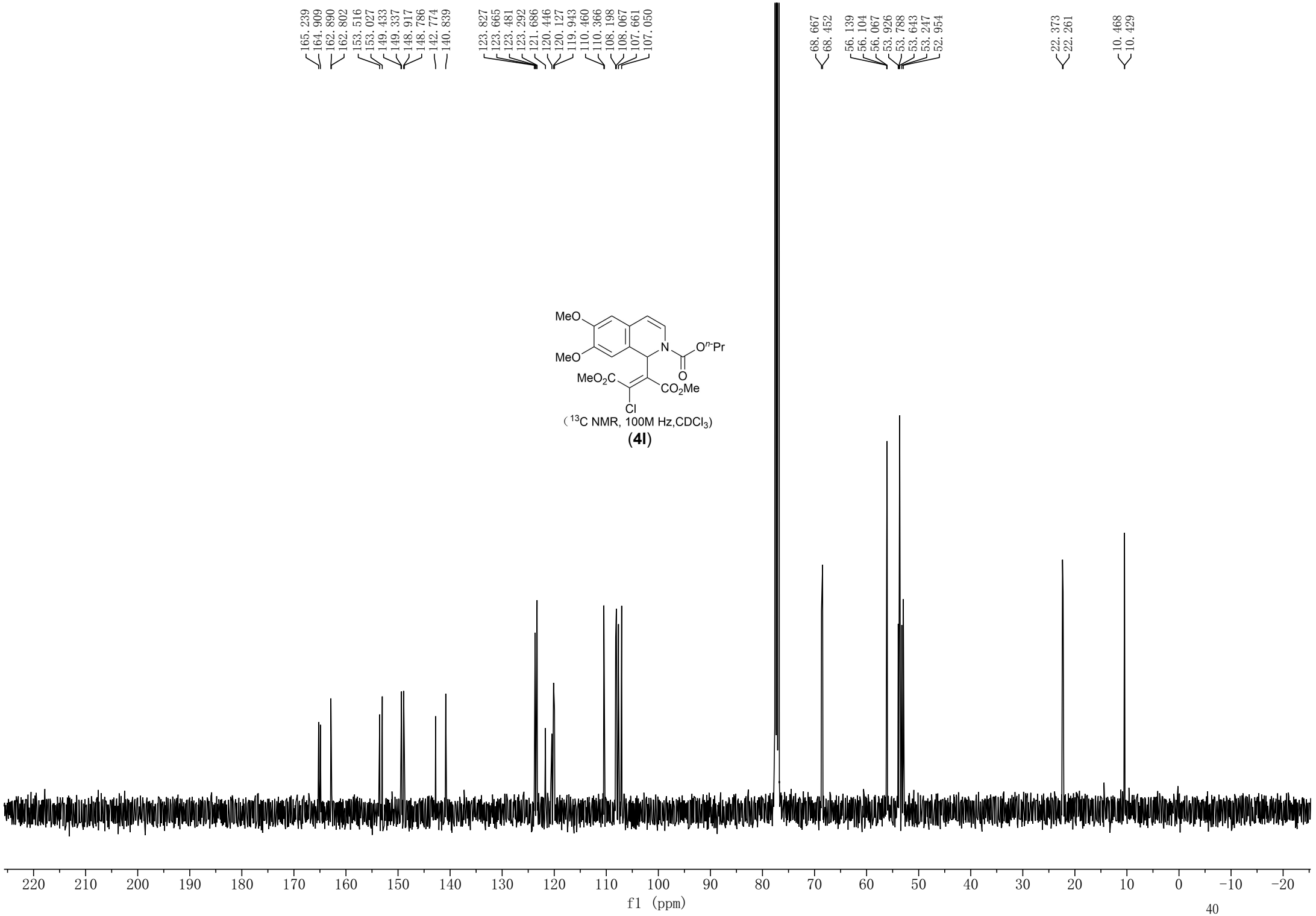

7.706
7.690
7.360
7.339
7.264
7.245
6.898
6.882
6.864
6.779
6.759
5.702
5.682
5.607
5.587
4.181
3.999
3.976
3.691
3.652
1.725
1.713
1.695
1.677
1.660
1.643
1.624
1.607
0.976
0.962
0.956
Br
N
O^{n}-Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4j)
0.98
1.06
1.16
1.45
0.55
0.55
0.45
2.23
1.66
1.36
1.66
1.36
2.19
3.14
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
−3
f1 (ppm)

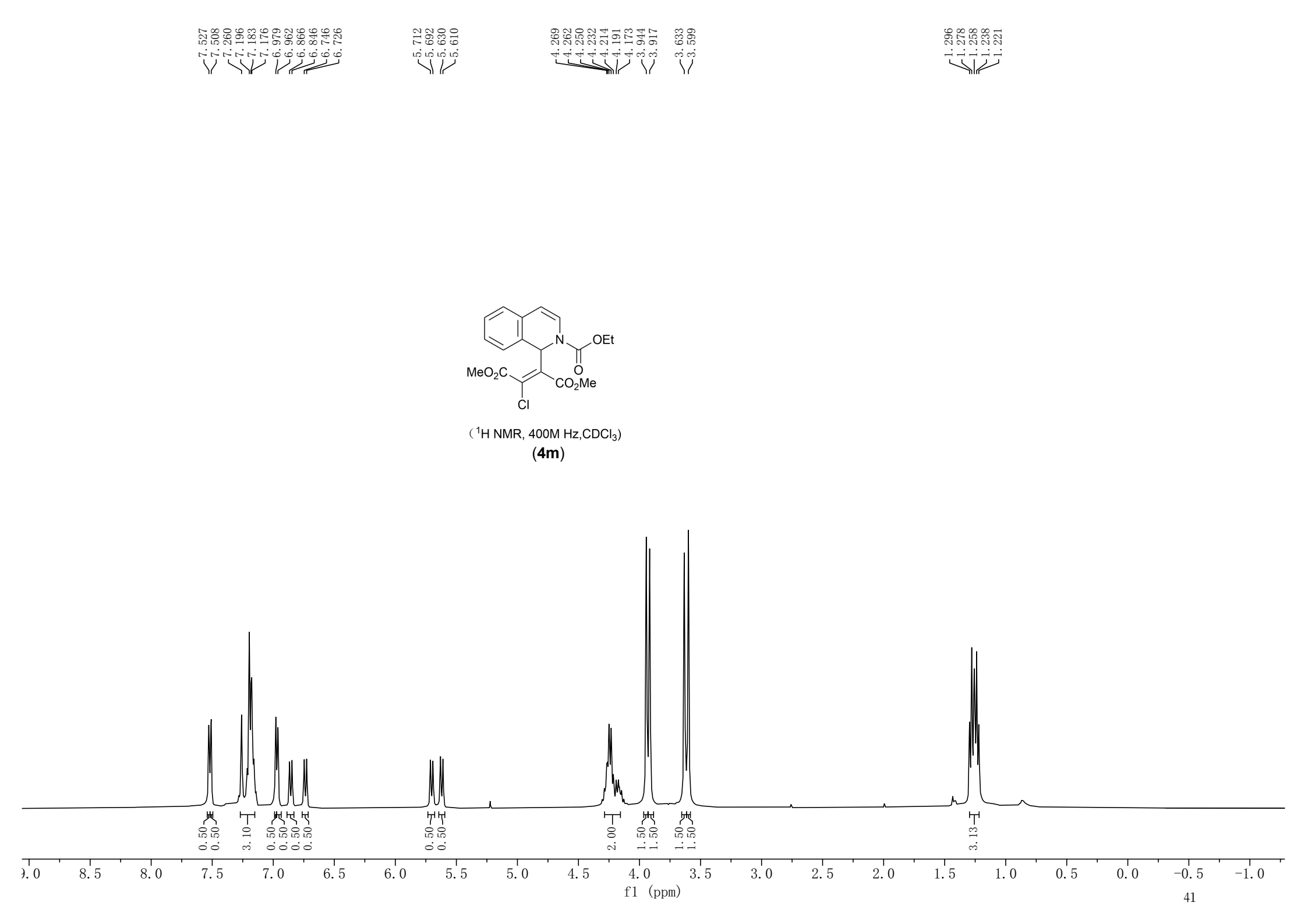

152.736
142.444
140.451
132.206
132.095
130.349
130.172
129.833
126.484
126.313
125.824
125.470
106.750
106.105
68.920
68.706
53.924
53.797
53.357
53.262
53.109
52.976
22.332
22.205
10.451
Br
N
O^{n}-Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4j)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

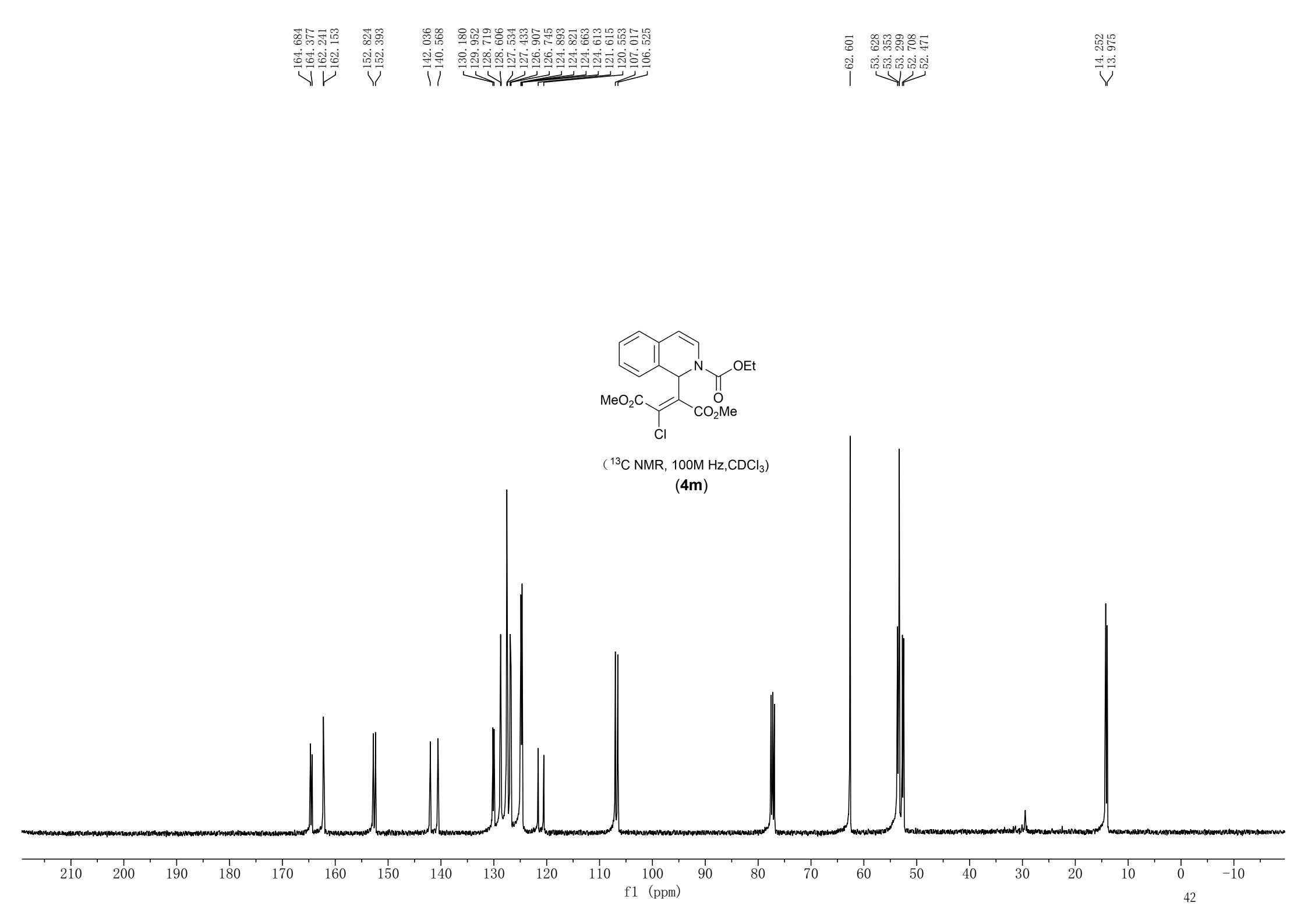

7.381
7.238
7.236
7.196
7.180
7.161
7.141
6.923
6.904
5.707
4.182
4.165
4.149
3.913
3.564
1.721
1.703
1.685
1.667
0.957
0.938
0.920
N
O^{n}-Pr
O
Cl
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4k)
1.03
2.97
0.50
0.50
0.83
1.11
2.00
3.21
3.07
2.03
3.17
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

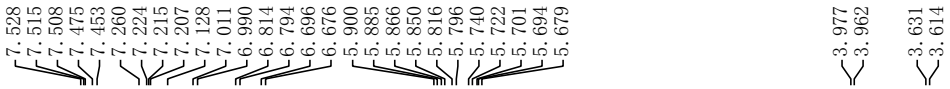

129.964
128.798
125.012
123.564
107.351
68.802
53.484
52.866
51.428
22.317
10.465
N
O^{n}-Pr
O
Cl
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4k)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

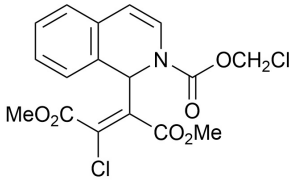

7.186
7.145
7.101
7.088
6.783
6.780
6.763
6.760
6.669
6.667
6.649
6.647
6.533
6.528
5.683
5.663
5.590
5.570
4.204
4.198
4.188
4.179
4.173
4.162
4.156
4.145
4.136
4.126
4.118
4.109
3.982
3.958
3.878
3.869
3.865
3.705
3.666
1.726
1.708
1.690
1.682
1.672
1.664
1.654
1.646
1.628
0.979
0.959
0.941
MeO
MeO
N
O^{n}Pr
O
MeO$_2$C
CO$_2$Me
Cl
(^{1}H NMR,400M Hz,CDCl$_3$)
(4l)
0.47
0.53
0.53
0.47
0.47
0.53
1.00
0.47
0.53
2.17
1.59
1.41
3.05
3.01
1.41
1.59
2.26
3.23
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


165.239
164.909
162.890
162.802
153.516
153.027
149.433
149.337
148.917
148.786
142.774
140.839
123.827
123.665
123.481
123.292
121.686
120.446
120.127
119.943
110.460
110.366
108.198
108.067
107.661
107.050
68.667
68.452
56.139
56.104
56.067
53.926
53.788
53.643
53.247
52.954
22.373
22.261
10.468
10.429
MeO
MeO
N
O^{n}-Pr
O
MeO$_2$C
CO$_2$Me
Cl
(13C NMR, 100M Hz,CDCl3)
(4l)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)


7.527
7.508
7.260
7.196
7.183
7.176
6.979
6.962
6.866
6.846
6.746
6.726
5.712
5.692
5.630
5.610
4.269
4.262
4.250
4.232
4.214
4.191
4.173
3.944
3.917
3.633
3.599
1.296
1.278
1.258
1.238
1.221
N
OEt
O
MeO2C
CO2Me
Cl
(1H NMR, 400M Hz,CDCl3)
(4m)
0.50
0.50
3.10
0.50
0.50
0.50
0.50
0.50
0.50
2.00
1.50
1.50
1.50
1.50
3.13
f1 (ppm)

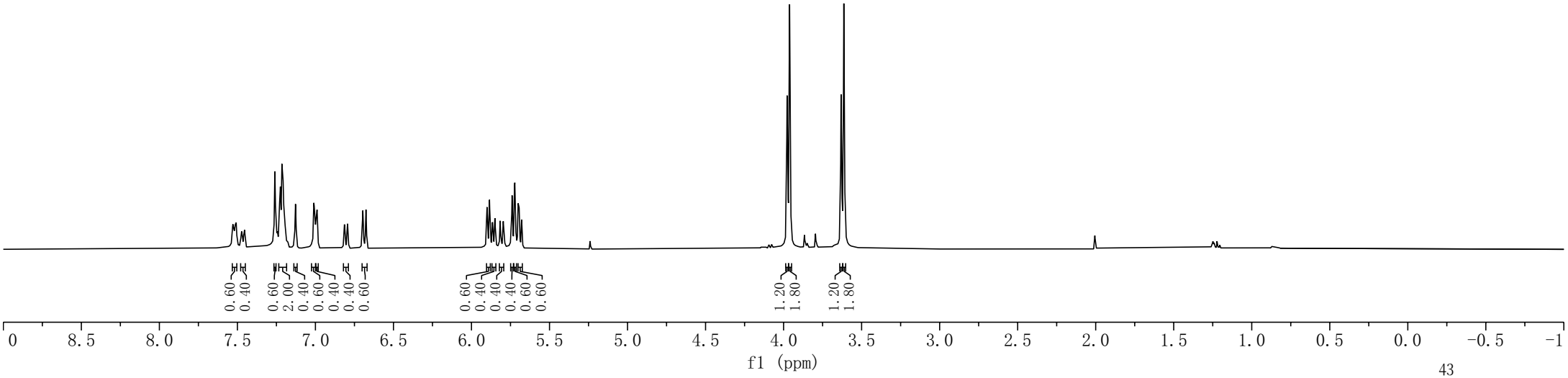

164.684
164.377
162.241
162.153
152.824
152.393
142.036
140.568
130.180
129.952
128.719
128.606
127.534
127.433
126.907
126.745
124.893
124.821
124.663
124.613
121.615
120.553
107.017
106.525
62.601
53.628
53.353
53.299
52.708
52.471
14.252
13.975
N
OEt
O
MeO2C
CO2Me
Cl
(13C NMR, 100M Hz,CDCl3)
(4m)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

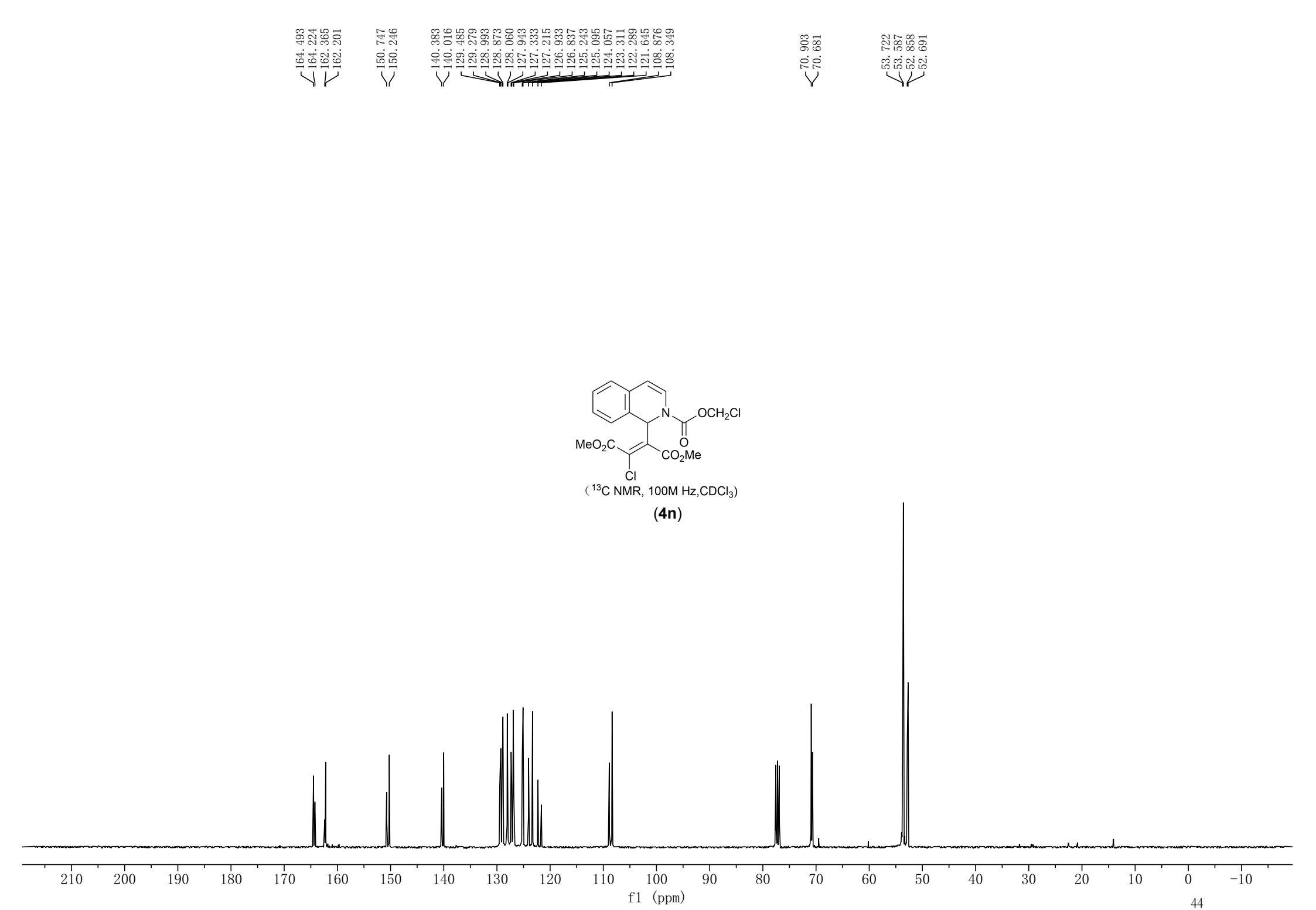


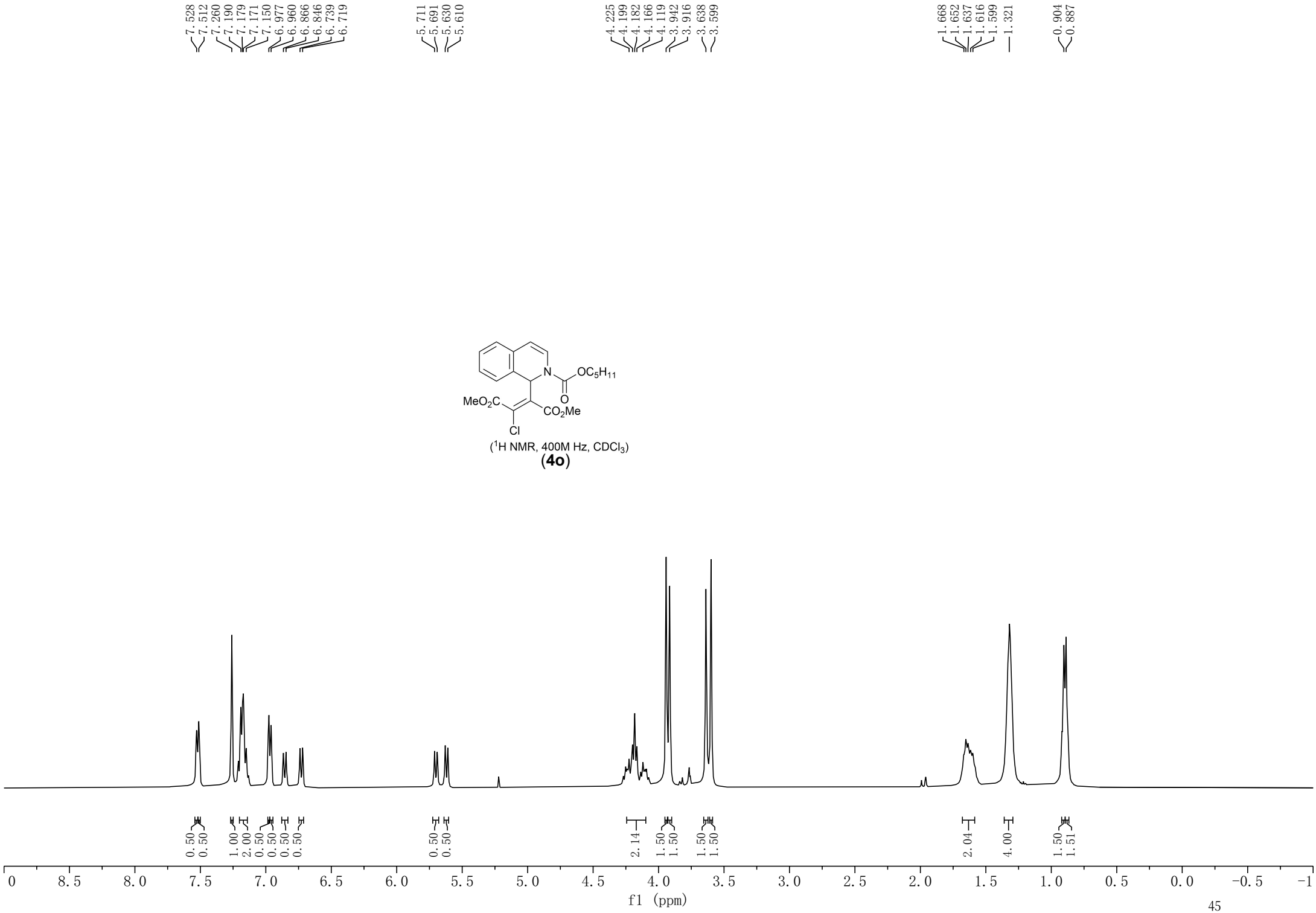


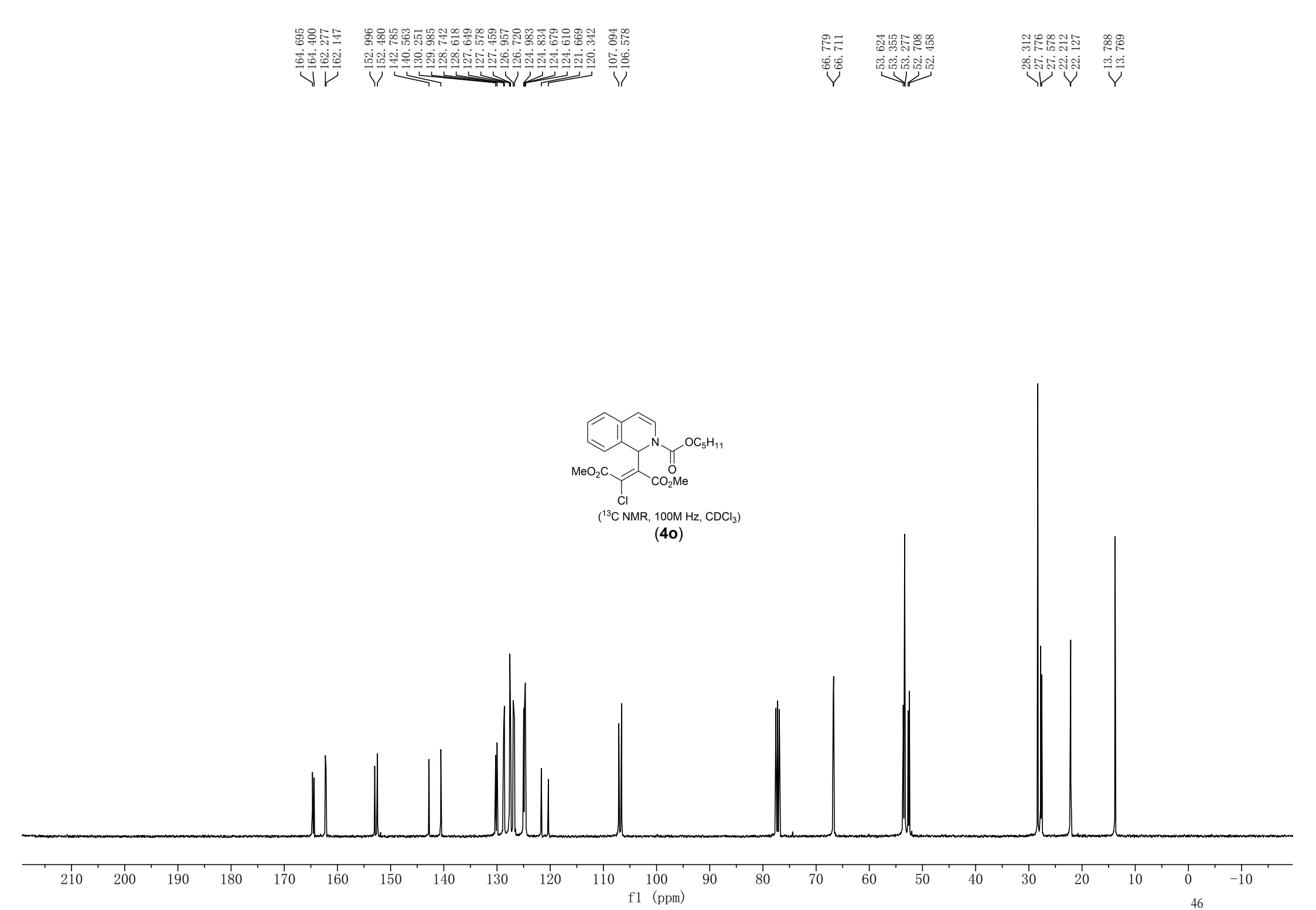
(^{1}H NMR,400M Hz,$CDCl_3$)

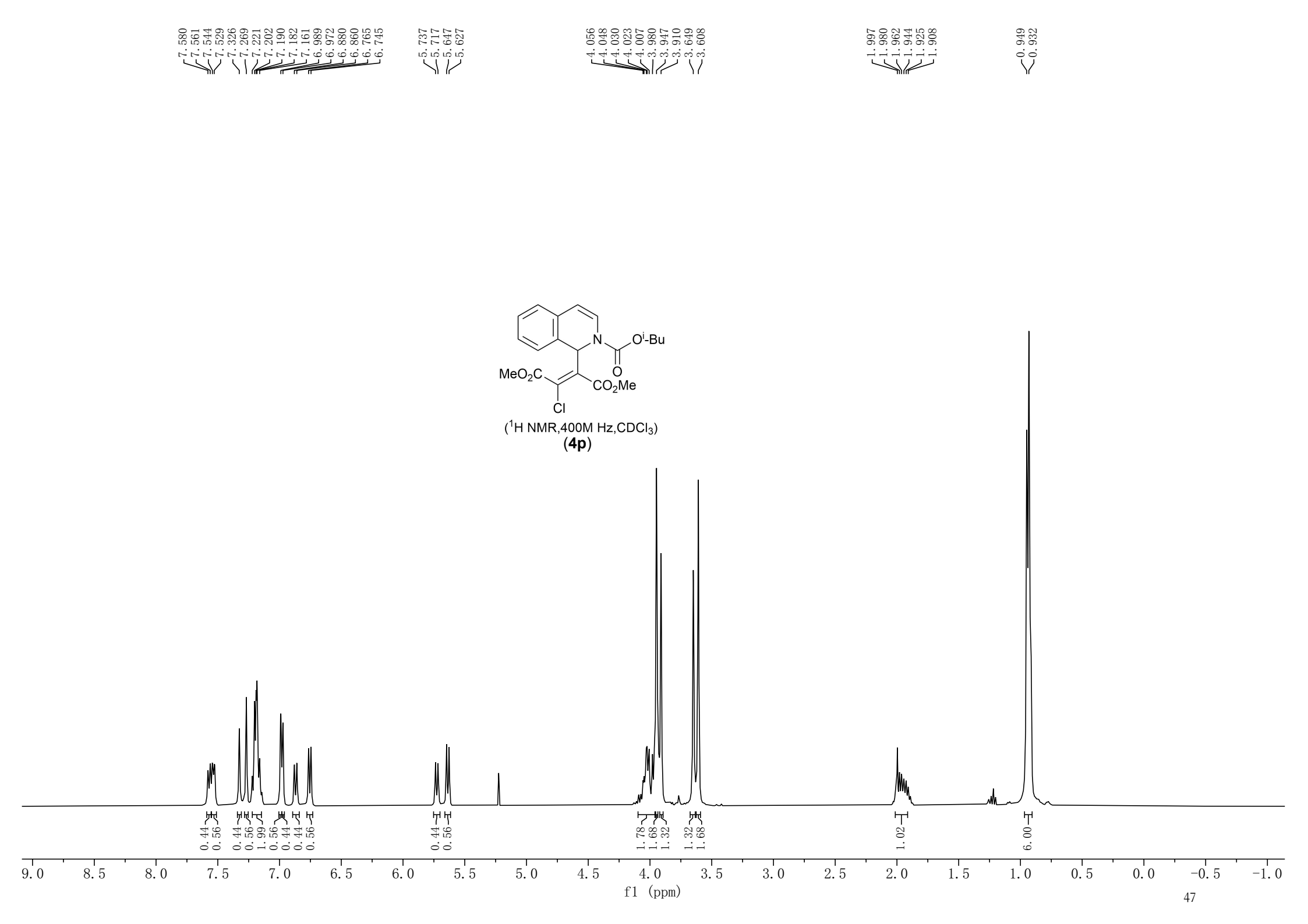
(4n)

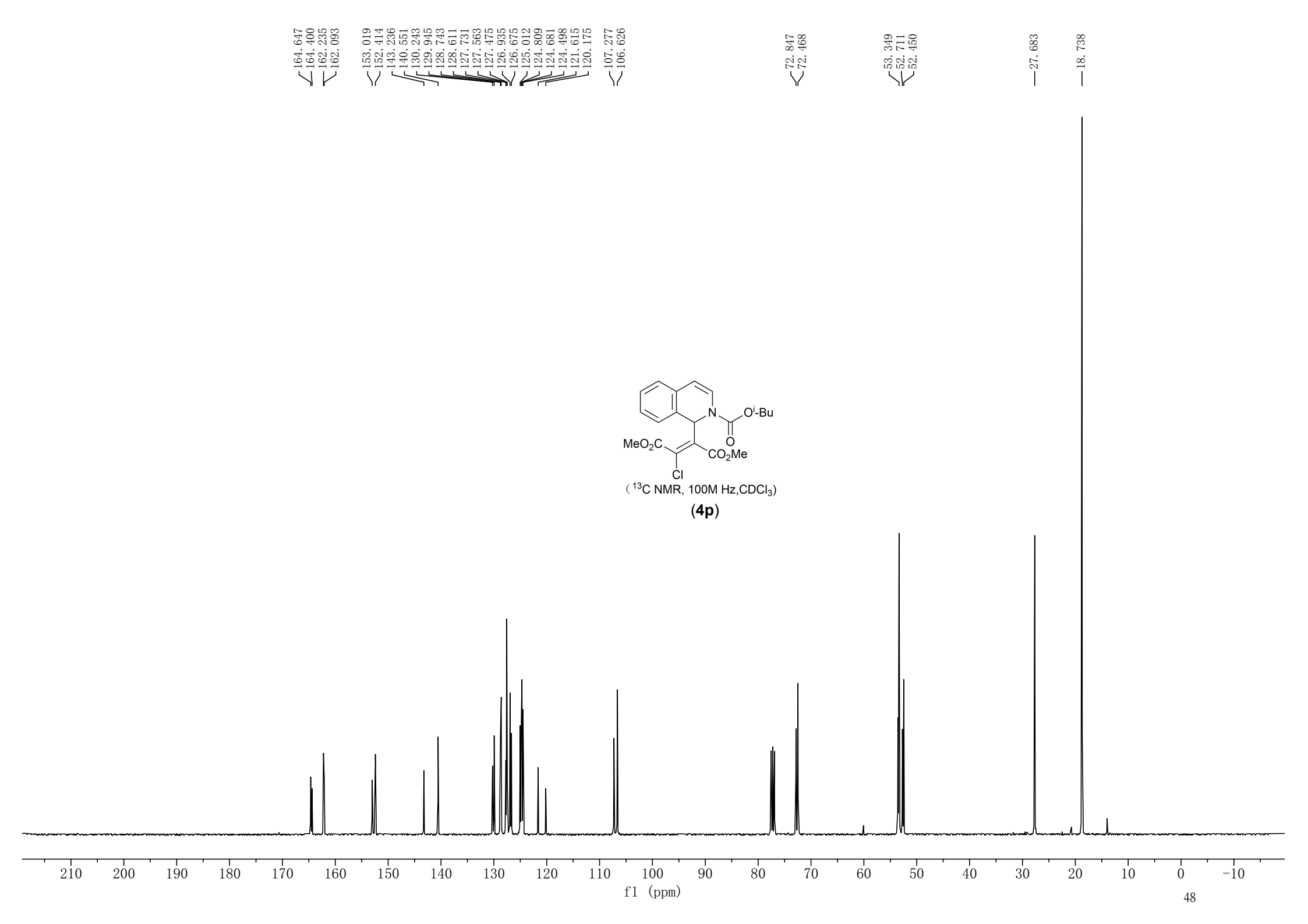



164.493
164.224
162.365
162.201
150.747
150.246
140.383
140.016
129.485
129.279
128.993
128.873
128.060
127.943
127.333
127.215
126.933
126.837
125.243
125.095
124.057
123.311
122.289
121.645
108.876
108.349
70.903
70.681
53.722
53.587
52.858
52.691
N
OCH2Cl
O
MeO2C
CO2Me
Cl
(13C NMR, 100M Hz,CDCl3)
(4n)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.528
7.512
7.260
7.190
7.179
7.171
7.150
6.977
6.960
6.866
6.846
6.739
6.719
5.711
5.691
5.630
5.610
4.225
4.199
4.182
4.166
4.119
3.942
3.916
3.638
3.599
1.668
1.652
1.637
1.616
1.599
1.321
0.904
0.887
N
OC5H11
O
MeO2C
CO2Me
Cl
(1H NMR, 400M Hz, CDCl3)
(4o)
0.50
0.50
1.00
2.00
0.50
0.50
0.50
0.50
0.50
2.14
1.50
1.50
1.50
1.50
2.04
4.00
1.50
1.51
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


164.695
164.400
162.277
162.147
152.996
152.480
142.785
140.563
130.251
129.985
128.742
128.618
127.649
127.578
127.459
126.957
126.720
124.983
124.834
124.679
124.610
121.669
120.342
107.094
106.578
66.779
66.711
53.624
53.355
53.277
52.708
52.458
28.312
27.776
27.578
22.212
22.127
13.788
13.769
N
OC5H11
O
MeO2C
CO2Me
Cl
(13C NMR, 100M Hz, CDCl3)
(4o)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.580
7.561
7.544
7.529
7.326
7.269
7.221
7.202
7.190
7.182
7.161
6.989
6.972
6.880
6.860
6.765
6.745
5.737
5.717
5.647
5.627
4.056
4.048
4.030
4.023
4.007
3.980
3.947
3.910
3.649
3.608
1.997
1.980
1.962
1.944
1.925
1.908
0.949
0.932
N
O
O
i
-Bu
MeO2C
CO2Me
Cl
(1H NMR,400M Hz,CDCl3)
(4p)
0.44
0.56
0.44
0.56
1.99
0.56
0.44
0.44
0.56
0.44
0.56
1.78
1.68
1.32
1.32
1.68
1.02
6.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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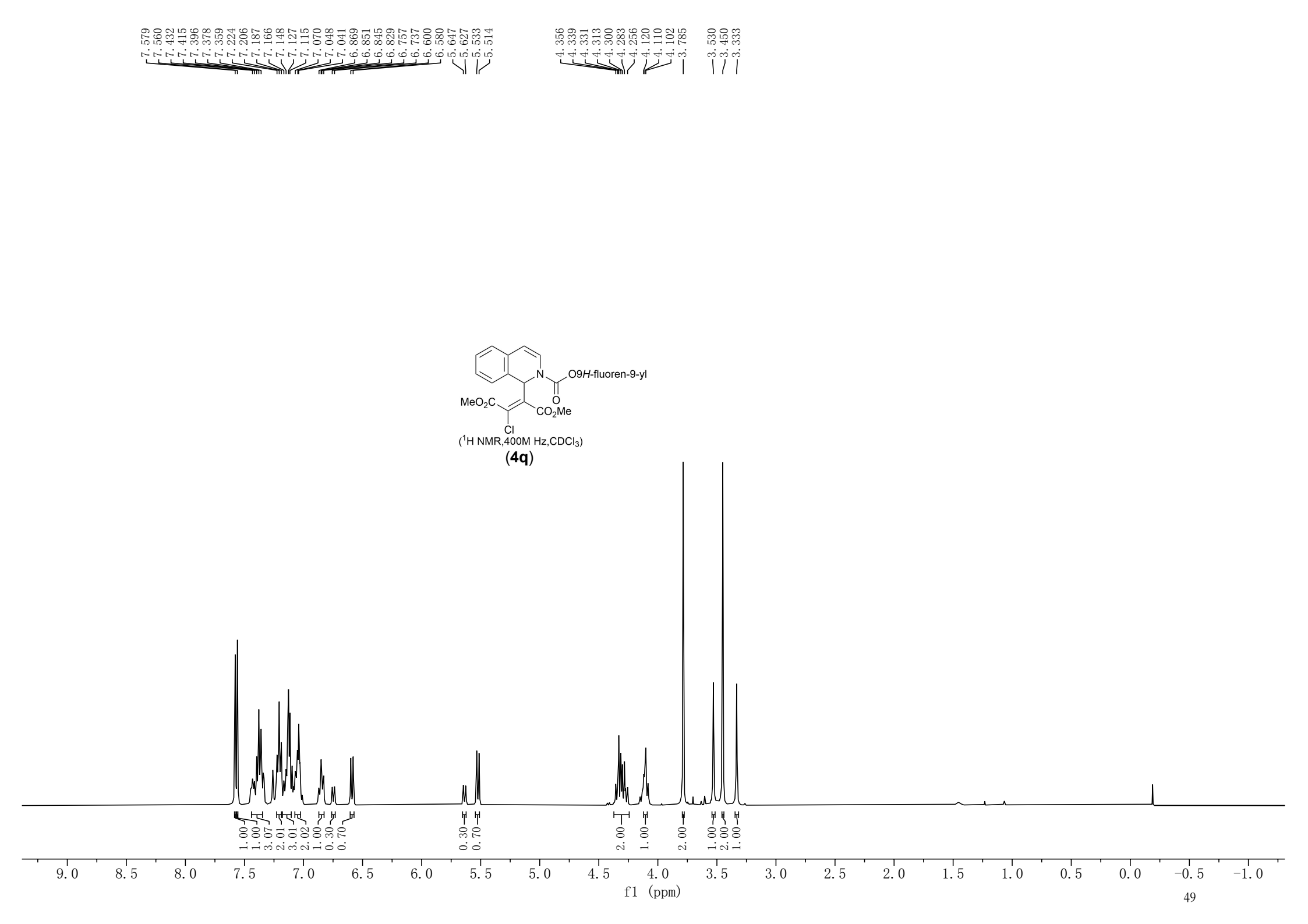
164.400
162.235
162.093
153.019
152.414
143.236
140.551
130.243
129.945
128.743
128.611
127.731
127.563
127.475
126.935
126.675
125.012
124.809
124.681
124.498
121.615
120.175
107.277
106.626
72.847
72.468
53.349
52.711
52.450
27.683
18.738
N
O^{i}-Bu
O
MeO$_2$C
CO$_2$Me
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4p)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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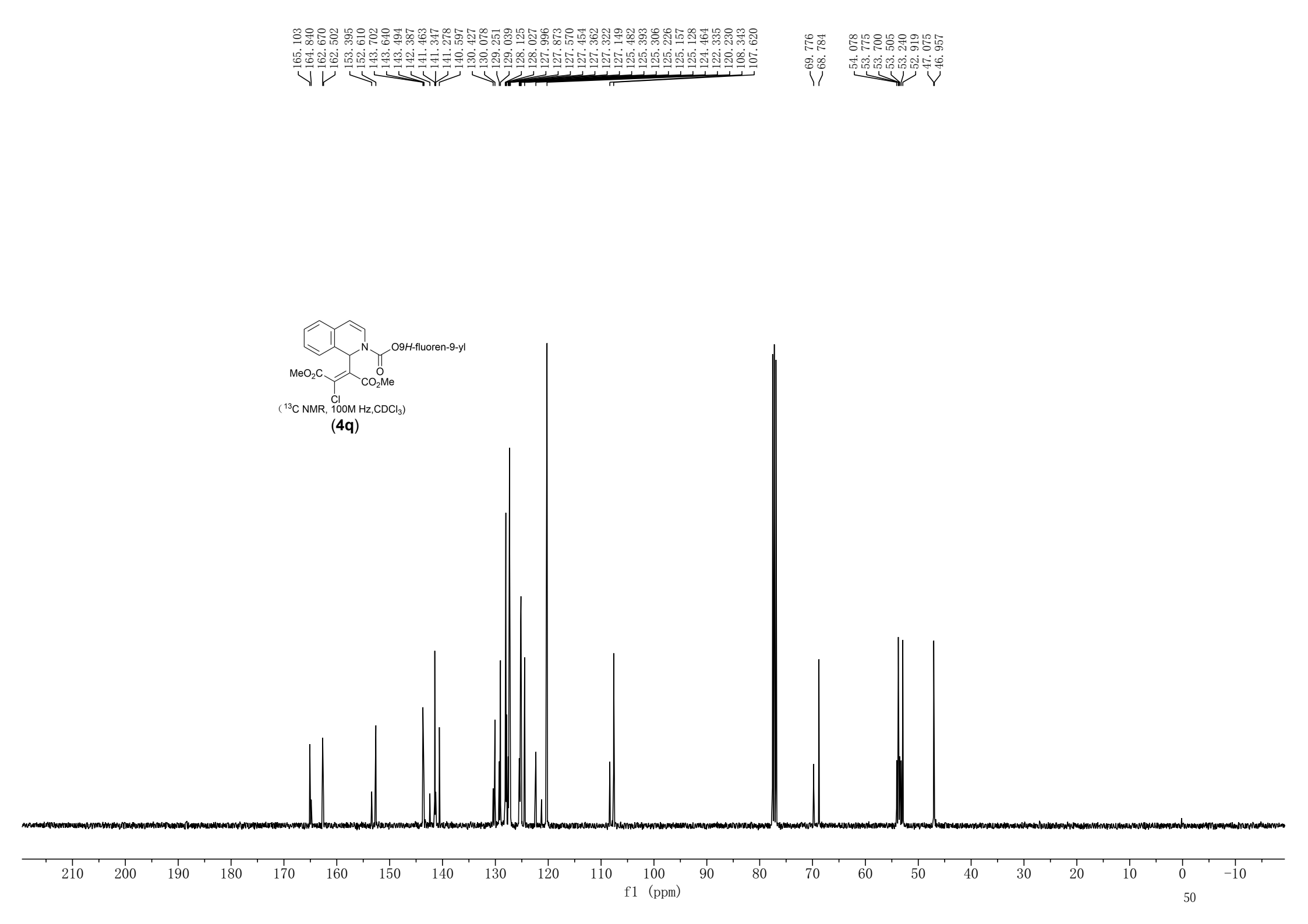
7.560
7.432
7.415
7.396
7.378
7.359
7.224
7.206
7.187
7.166
7.148
7.127
7.115
7.070
7.048
7.041
6.869
6.851
6.845
6.829
6.757
6.737
6.600
6.580
5.647
5.627
5.533
5.514
4.356
4.339
4.331
4.313
4.300
4.283
4.256
4.120
4.110
4.102
3.785
3.530
3.450
3.333
O9H-fluoren-9-yl
MeO2C
CO2Me
Cl
(1H NMR,400M Hz,CDCl3)
(4q)
1.00
1.00
3.07
2.01
3.01
2.02
1.00
0.30
0.70
0.30
0.70
2.00
1.00
2.00
1.00
2.00
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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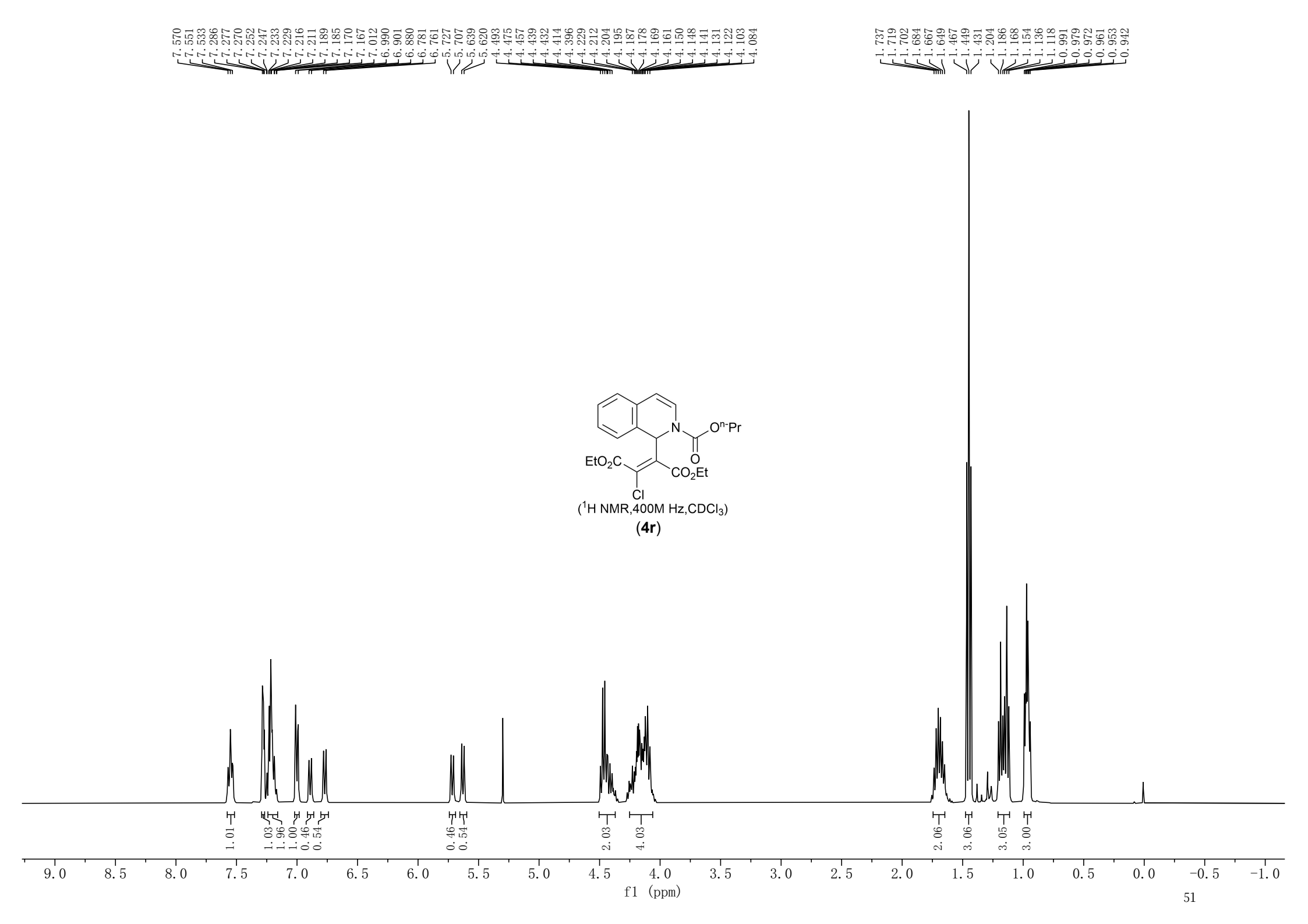
162.502
153.395
152.610
143.702
143.640
143.494
142.387
141.463
141.347
141.278
140.597
130.427
130.078
129.251
129.039
128.125
128.027
127.996
127.873
127.570
127.454
127.362
127.322
127.149
125.482
125.393
125.306
125.226
125.157
125.128
124.464
122.335
120.230
108.343
107.620
69.776
68.784
54.078
53.775
53.700
53.505
53.240
52.919
47.075
46.957
O9H-fluoren-9-yl
MeO2C
CO2Me
Cl
(13C NMR, 100M Hz,CDCl3)
(4q)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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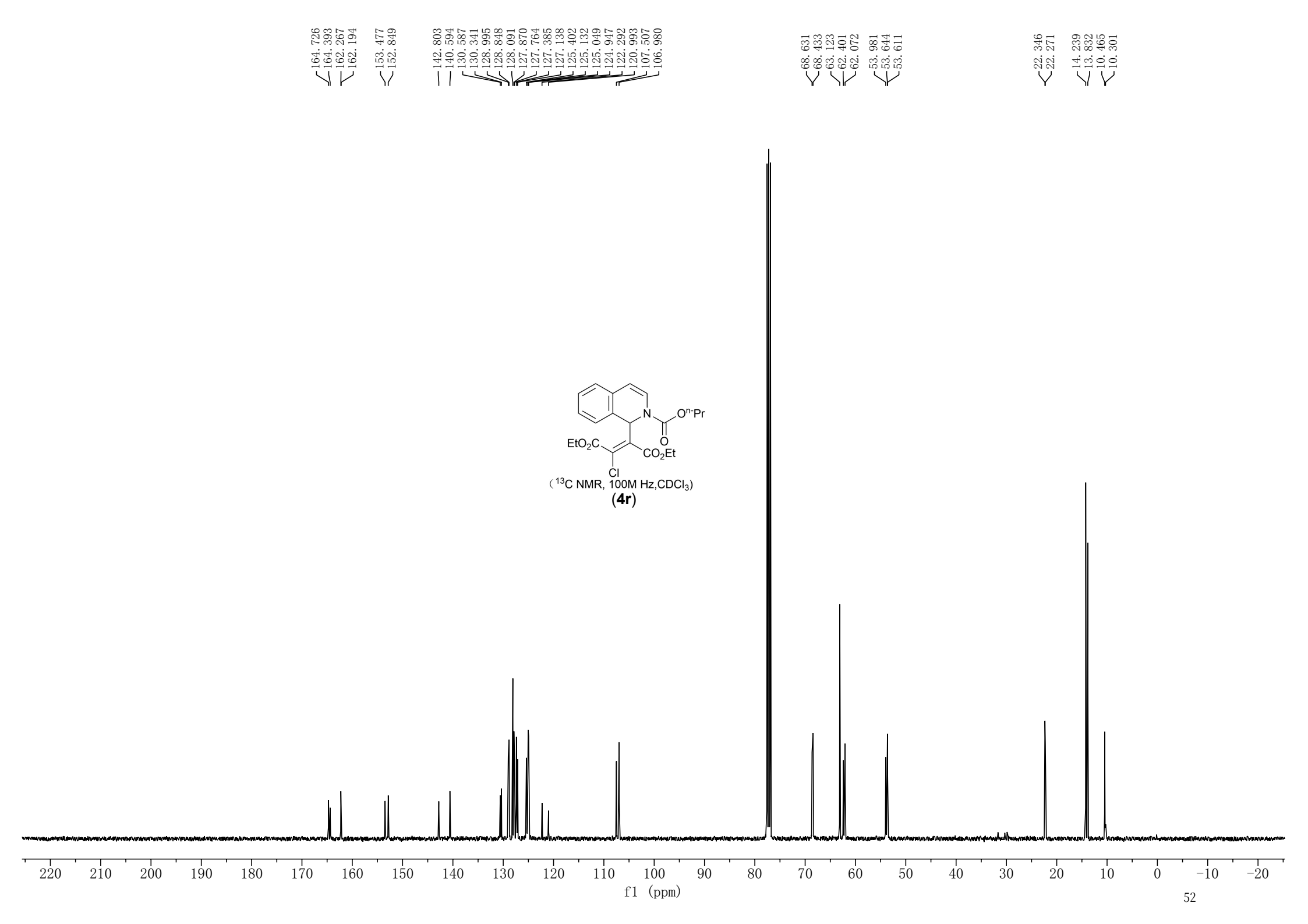
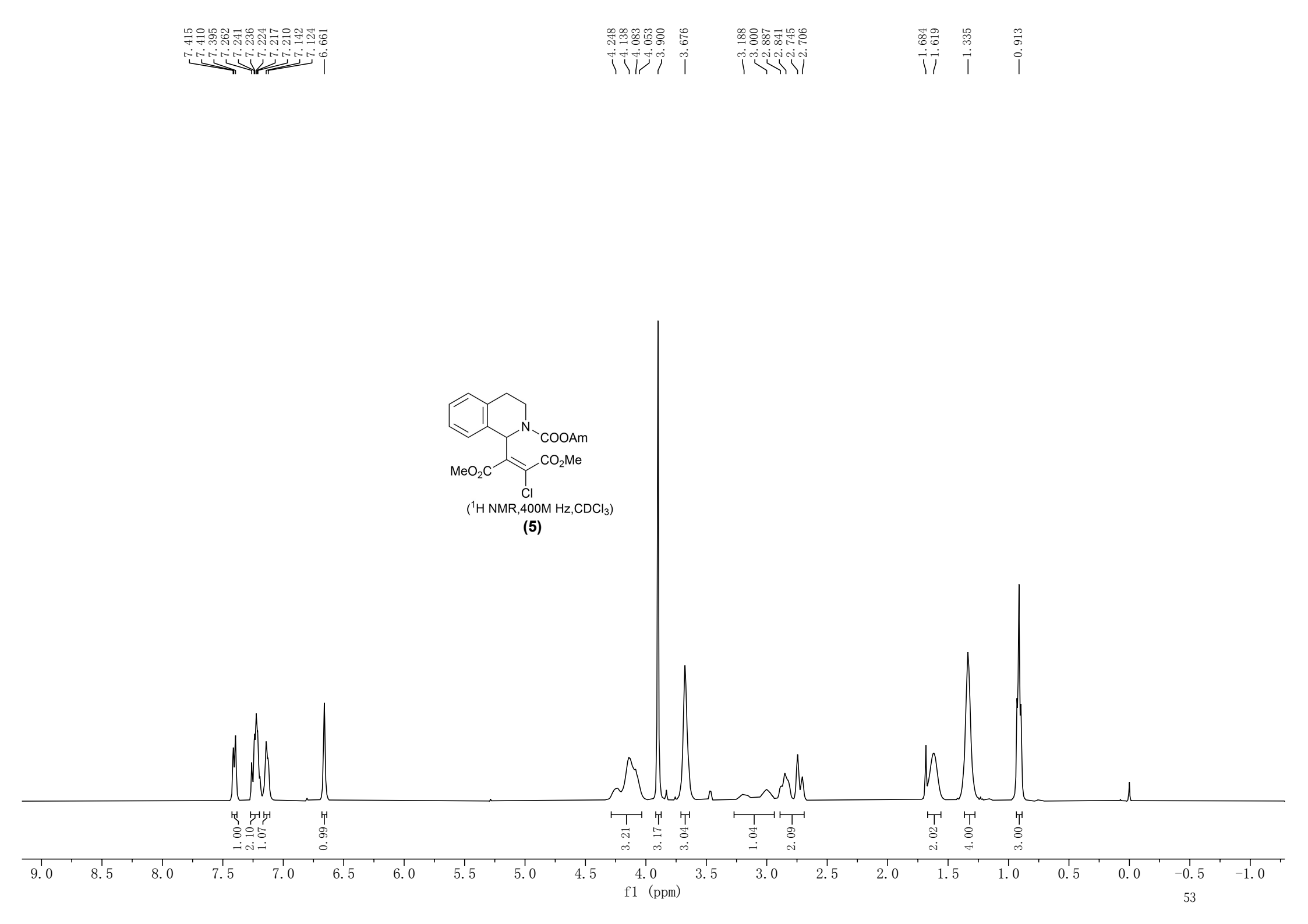
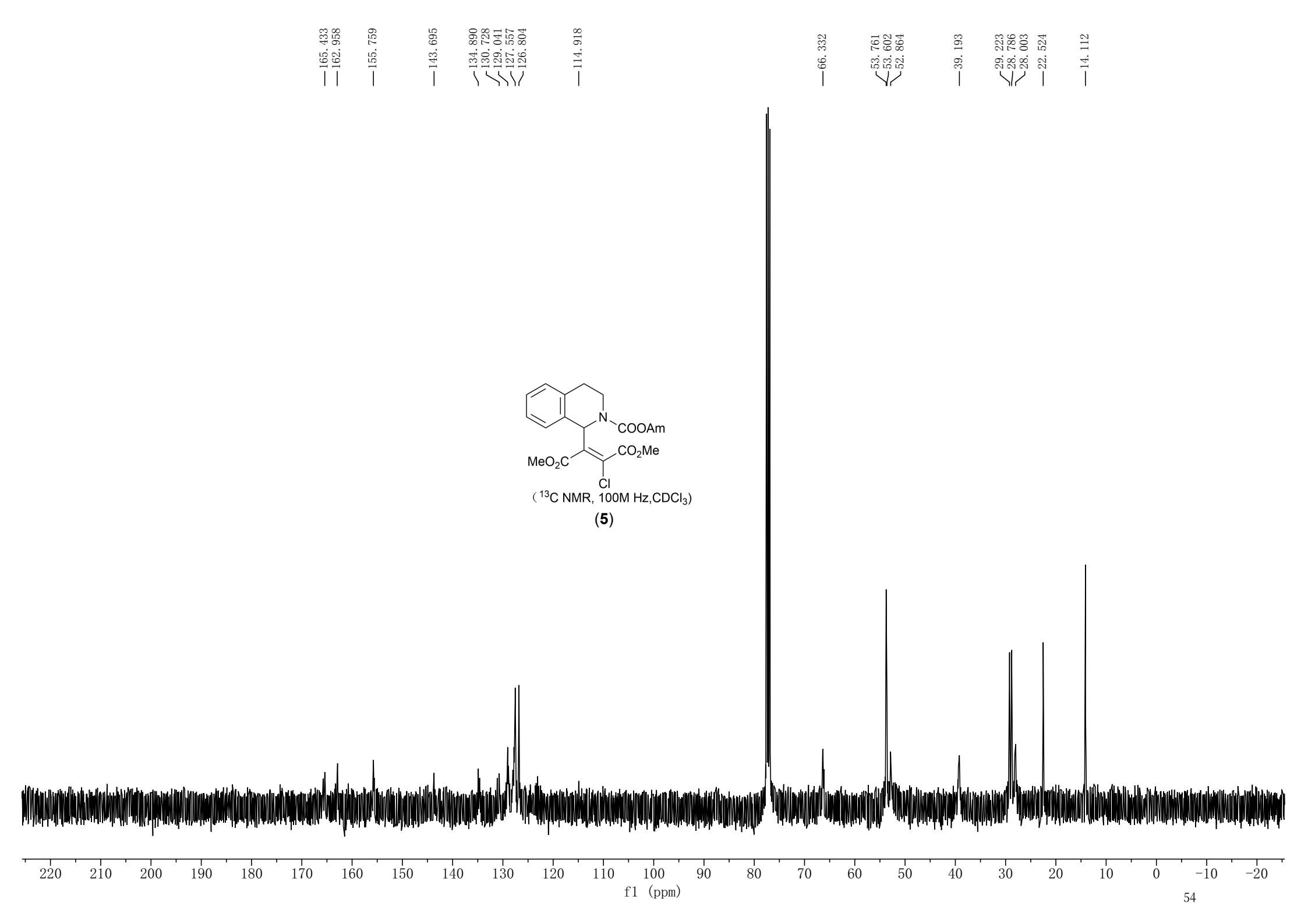
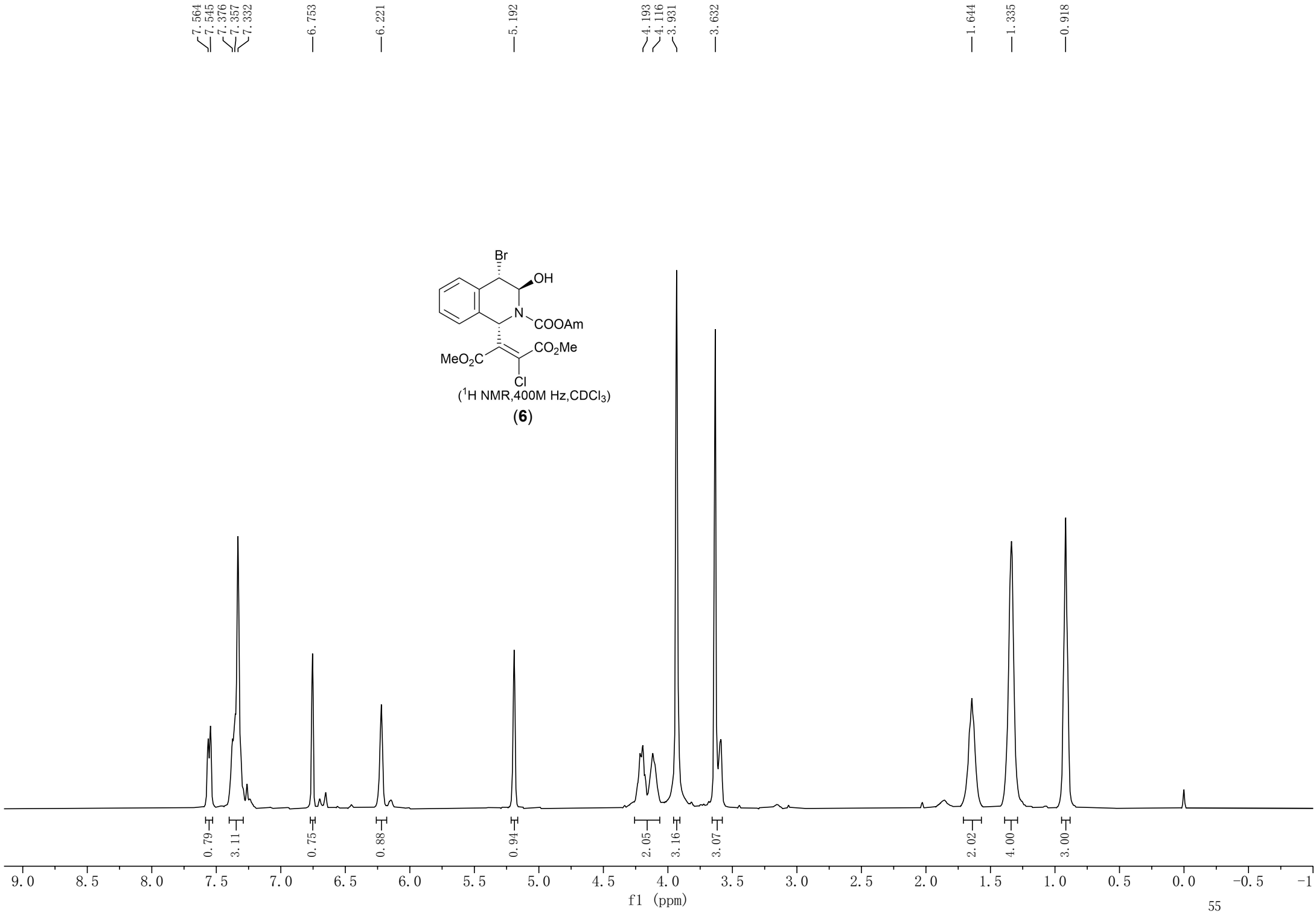
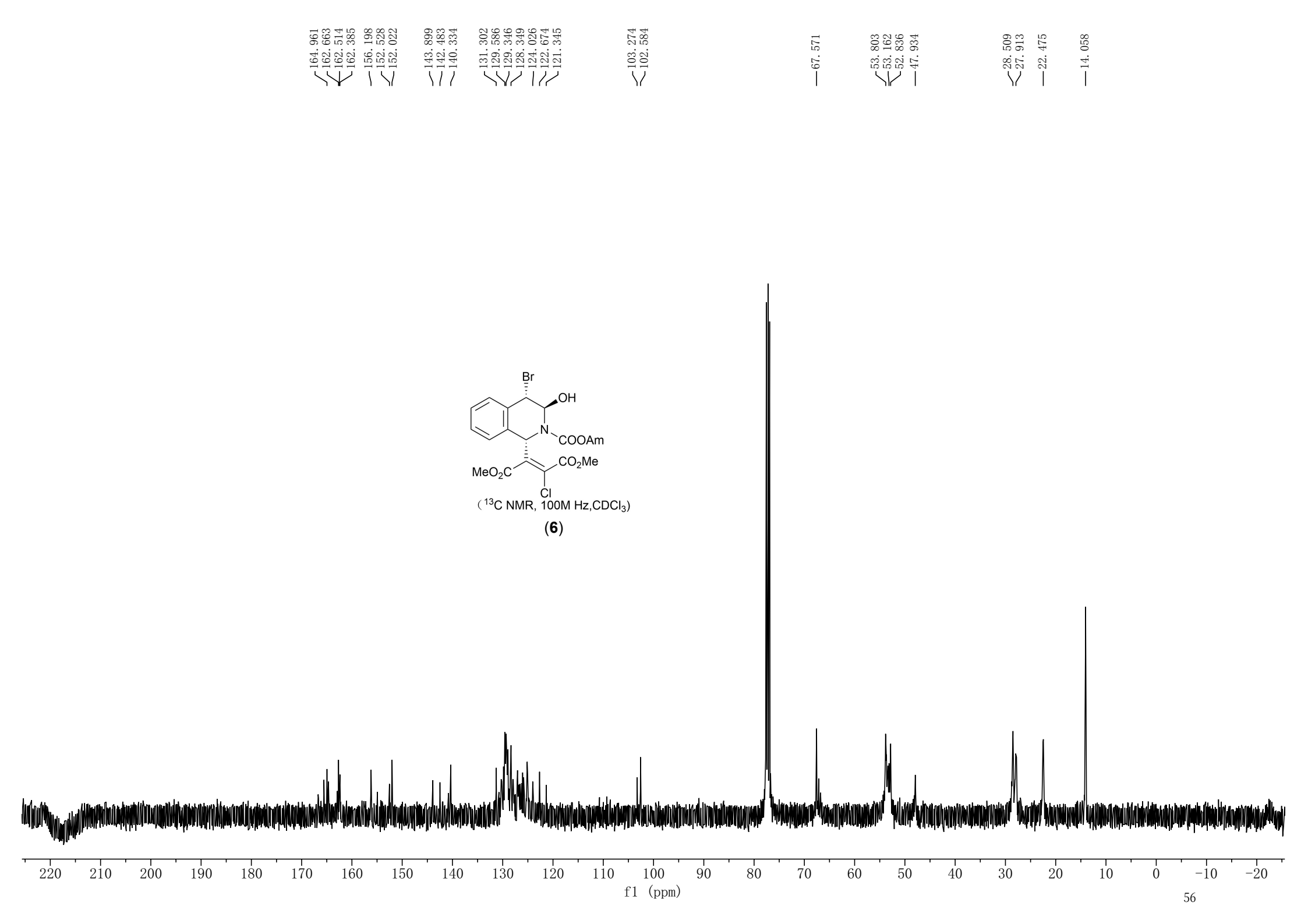
7.551
7.533
7.286
7.277
7.270
7.252
7.247
7.233
7.229
7.216
7.211
7.189
7.185
7.170
7.167
7.012
6.990
6.901
6.880
6.781
6.761
5.727
5.707
5.639
5.620
4.493
4.475
4.457
4.439
4.432
4.414
4.396
4.229
4.212
4.204
4.195
4.187
4.178
4.169
4.161
4.150
4.148
4.141
4.131
4.122
4.103
4.084
1.737
1.719
1.702
1.684
1.667
1.649
1.467
1.449
1.431
1.204
1.186
1.168
1.154
1.136
1.118
0.991
0.979
0.972
0.961
0.953
0.942
N
O
O^n-Pr
EtO2C
CO2Et
Cl
(1H NMR,400M Hz,CDCl3)
(4r)
1.01
1.03
1.96
1.00
0.46
0.54
0.46
0.54
2.03
4.03
2.06
3.06
3.05
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


164.726
164.393
162.267
162.194
153.477
152.849
142.803
140.594
130.587
130.341
128.995
128.848
128.091
127.870
127.764
127.385
127.138
125.402
125.132
125.049
124.947
122.292
120.993
107.507
106.980
68.631
68.433
63.123
62.401
62.072
53.981
53.644
53.611
22.346
22.271
14.239
13.832
10.465
10.301
N
O^{n}-Pr
O
EtO$_2$C
CO$_2$Et
Cl
(^{13}C NMR, 100M Hz,CDCl$_3$)
(4r)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)


7.415
7.410
7.395
7.262
7.241
7.236
7.224
7.217
7.210
7.142
7.124
6.661
4.248
4.138
4.083
4.053
3.900
3.676
3.188
3.000
2.887
2.841
2.745
2.706
1.684
1.619
1.335
0.913
N
COOAm
CO2Me
MeO2C
Cl
(1H NMR,400M Hz,CDCl3)
(5)
1.00
2.10
1.07
0.99
3.21
3.17
3.04
1.04
2.09
2.02
4.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


165.433
162.958
155.759
143.695
134.890
130.728
129.041
127.557
126.804
114.918
66.332
53.761
53.602
52.864
39.193
29.223
28.786
28.003
22.524
14.112
N
COOAm
CO2Me
MeO2C
Cl
(13C NMR, 100M Hz,CDCl3)
(5)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)

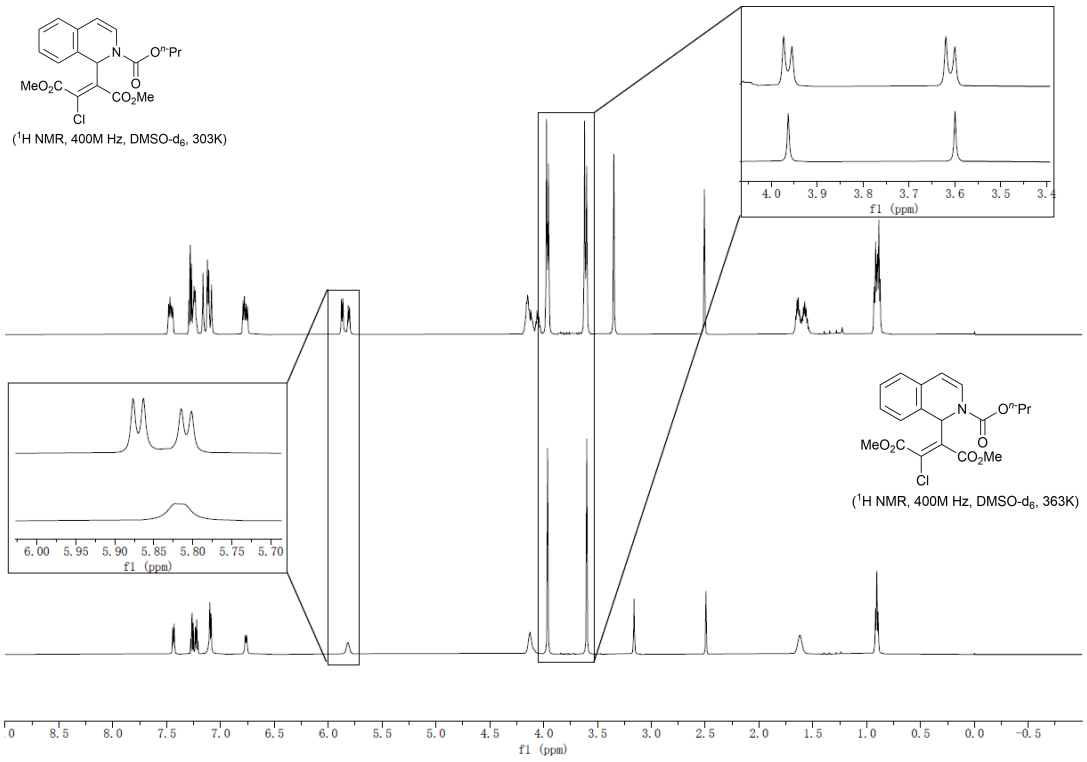

7.564
7.545
7.376
7.357
7.332
6.753
6.221
5.192
4.193
4.116
3.931
3.632
1.644
1.335
0.918
Br
OH
N
COOAm
CO2Me
MeO2C
Cl
(1H NMR,400M Hz,CDCl3)
(6)
0.79
3.11
0.75
0.88
0.94
2.05
3.16
3.07
2.02
4.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)


164.961
162.663
162.514
162.385
156.198
152.528
152.022
143.899
142.483
140.334
131.302
129.586
129.346
128.349
124.026
122.674
121.345
103.274
102.584
67.571
53.803
53.162
52.836
47.934
28.509
27.913
22.475
14.058
Br
OH
N
COOAm
CO2Me
MeO2C
Cl
(13C NMR, 100M Hz,CDCl3)
(6)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
−20
f1 (ppm)

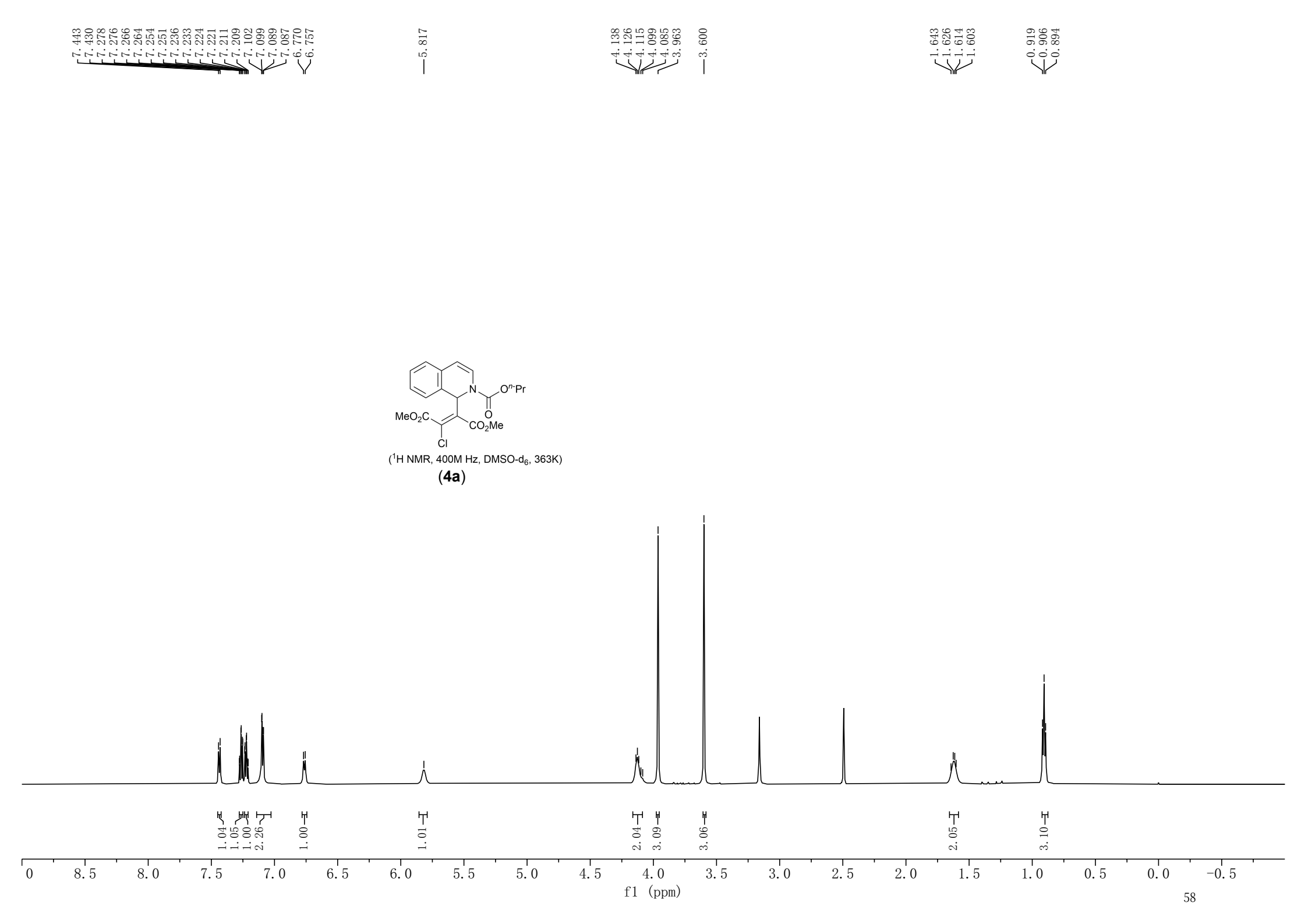
5.variable-temperature NMR of 4a

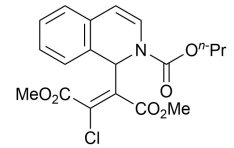
^{1}H NMR (400 MHz,DMSO-d_6, mixture of rotamers, 303K) δ 7.49-7.44 (m, 1H), 7.29-7.22 (m, 2H), 7.16-7.08 (m, 2H), 6.78 (d, *J*=5.2 Hz, 0.55H), 6.75 (d, *J*=5.2 Hz, 0.45H), 5.87 (d, *J*=5.2 Hz, 0.55H), 5.81 (d, *J*=5.2 Hz, 0.45H), 4.18- 4.03 (m, 2H), 3.96 (s, 1.55H), 3.96 (s, 1.45H), 3.62 (s, 1.55H), 3.60 (s, 1.45H), 1.68-1.52 (m, 2H), 0.97- 0.83 (m, 3H).

^{1}H NMR (400 MHz,DMSO-d_6, 363K) δ 7.45-7.42 (m, 1H), 7.28-7.25 (m, 1H), 7.24-7,21 (m, 1H), 7.10-7.09 (m, 2H), 6.76 (d, *J*=5.2 Hz, 1H), 5.85-5.79 (m, 1H), 4.14-4.09 (m, 2H), 3.96 (s, 3H), 3.60 (s, 3H), 1.63-1.60 (m, 2H), 0.92-0.89 (m, 3H).



Stacked ^{1}H NMR of compound **4a** (303K) and compound **4a** (363K)


7.443
7.430
7.278
7.276
7.266
7.264
7.254
7.251
7.236
7.233
7.224
7.221
7.211
7.209
7.102
7.099
7.089
7.087
6.770
6.757
5.817
4.138
4.126
4.115
4.099
4.085
3.963
3.600
1.643
1.626
1.614
1.603
0.919
0.906
0.894
N
O^{n}Pr
O
MeO$_2$C
CO$_2$Me
Cl
(1H NMR, 400M Hz, DMSO-d6, 363K)
(4a)
1.04
1.05
1.00
2.26
1.00
1.01
2.04
3.09
3.06
2.05
3.10
0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



(^{1}H NMR, 400M Hz, DMSO-d_6, 303K)

(**4a**)