Ionic liquid catalyzed synthesis of (1,4-benzoxazin-3-yl)malonate Derivatives via c ross-dehydrogenative-coupling reactions

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Typical [omim]$FeCl_4$ catalyzed synthesis of 3

DDQ (110 mg, 0.5 mmol) was added to a mixture of dimethyl malonate (**2a**, 264 mg, 2.0 mmol), 3,4-dihydro-2H-benzo[b][1,4]oxazin-2-one (**1a**, 239 mg, 1.0 mmol) in [omim]$FeCl_4$ (0.4 g, 1.0 mmol), and the mixture was stirred at 60 °C for 1 h. The mixture was extracted with EtOAc (10 mL) and the extract was washed with H_2O (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was fractionated by column chromatography on silica gel using acetone/hexanes (1:10) as the eluent to afford **3a** (355 mg, 96%).

Dimethyl 2-(4-benzyl-2-oxo-3,4-dihydro-2*H*-benzo[b][1,4]oxazin-3-yl)malonate (**3a**) [1]. White solid in 96% yield: mp 98 – 100 (reported 95– 96) °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 3H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.02 – 7.00 (m, 1H), 6.90 – 6.85 (m, 1H), 6.80 (d, *J* =7.5 Hz, 1H), 4.90 (d, *J* = 6.5 Hz, 1H), 4.60 (d, *J* = 15.5 Hz, 1H), 4.45 (d, *J* = 15.5 Hz, 1H), 3.70 (d, *J* = 6.5 Hz, 1H), 3.65 (s, 3H), 3.60 (s, 3H).

Diethyl 2-(4-benzyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-methylmalonate (**3b**). White solid in 80% yield: mp 77 – 79 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 3H), 7.13 (d, *J* = 6.6 Hz, 2H), 7.02 (3, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* =7.6 Hz, 1H), 5.0 (s, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.53 (d, *J* = 15.6 Hz, 1H), 4.11 (m, 1H), 4.08 – 3.99 (m, 3H), 1.45 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 169.2, 163.0, 143.4, 139.5, 132.0, 128.8, 127.9, 127.8, 125.1, 121.3, 118.5, 116.5, 63.9, 62.1, 62.0, 59.2, 58.3, 18.5, 13.8, 13.7; MS (70 eV) m/z (%) 411, 320, 239, 146, 90, 65;

IR (KBr, cm^{-1}) 3447, 2984, 1732, 1504, 1248, 1104, 746. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.25; H, 6.20; N, 3.55.

Diethyl 2-(4-benzyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-ethylmalonate (**3c**). White solid in 75% yield: mp 93–95 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 3H), 7.13 (d, *J* = 6.5 Hz, 2H), 7.0 (t, *J* = 7.7 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.86 (t, *J* =7.7 Hz, 1H), 4.92 (s, 1H), 4.78 (d, *J* = 15.5 Hz, 1H), 4.56 (d, *J* = 15.5 Hz, 1H), 4.09 – 4.02 (m, 1H), 3.99 – 3.91 (m, 1H), 3.86 – 3.79 (m, 1H), 3.77 – 3.70 (m, 1H), 2.18 – 2.09 (m, 1H), 1.99 – 1.90 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 168.8, 162.6, 143.5, 136.6, 131.6, 128.7, 127.6, 127.5, 124.9, 121.4, 119.0, 116.4, 63.6, 62.3, 61.8, 61.6, 58.3, 26.9, 13.77, 13.74, 9.3; MS (70 eV) m/z (%) 425, 239, 209, 160, 119, 90, 65, 41; IR (KBr, cm^{-1}) 2982, 1730, 1504, 1233, 1026, 748. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.66; H, 6.53; N, 3.41.

Dimethyl 2-(4-benzyl-6-methyl-2-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)malonate (**3d**) [1]. White solid in 88% yield: mp 119 – 121 (reported 119 – 120) °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 3H), 7.20 – 7.15 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.70 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.60 (s, 1H), 4.85 (d, *J* = 6.5 Hz, 1H), 4.61 (d, *J* = 15.5 Hz, 1H), 4.45 (d, *J* = 15.5 Hz, 1H), 3.70 – 3.62 (m, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 2.25 (s, 3H).

Diethyl 2-(4-benzyl-6-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-methylmalonate (**3e**). White solid in 88% yield: mp 58–60 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 3H), 7.13 (d, *J* = 6.7 Hz, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.77 (s, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.96 (s, 1H), 4.78 (d, *J* = 15.5 Hz, 1H), 4.50 (d, *J* = 15.5 Hz, 1H), 4.18 – 4.0 (m, 4H), 2.27 (s, 3H), 1.44 (s, 3H), 1.26 – 1.21 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 169.2, 163.1, 141.5, 136.7, 134.8, 131.7, 128.7, 127.8, 127.5, 122.1, 119.0, 116.2, 63.6, 62.1, 62.0, 59.2, 58.4, 21.1, 18.4, 13.8, 13.7; MS (70 eV) m/z (%) 425, 356, 302, 300, 91; IR (KBr, cm^{-1}) 2979, 1775, 1726, 1505, 1446, 1249, 1107, 850, 736. Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.34; H, 4.44; N, 3.39.

Diethyl 2-(4-benzyl-6-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-ethylmalonate (**3f**). White solid in 83% yield: mp 71–73 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 3H), 7.14 (d, *J* = 6.8 Hz, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.75 (s, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.87 (s, 1H), 4.78 (d, *J* = 15.4 Hz, 1H), 4.52 (d, *J* = 15.4 Hz, 1H), 4.09 – 4.04 (m, 1H), 3.97 – 3.91 (m, 1H), 3.89 – 3.84 (m, 1H), 3.78 – 3.73 (m, 1H), 2.26 (s, 3H), 2.17 – 2.09 (m, 1H), 1.99 – 1.91 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 168.9, 162.8, 141.5, 136.7, 134.6, 131.3, 128.7, 127.8, 127.6, 122.1, 119.5, 116.0, 63.4, 62.3, 61.7, 61.6, 58.4, 26.9, 21.1, 13.75, 13.72, 9.2; MS (70 eV) m/z (%) 439, 348, 252, 174, 132, 91, 65, 43; IR (KBr, cm^{-1}) 2983, 1756, 1721, 1201, 1028, 805, 731. Anal. Calcd for $C_{25}H_{29}O_6$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.40; H, 6.70; N, 3.32.

Dimethyl 2-(4-benzyl-6-chloro-2-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)malonate (**3g**) [1]. White solid in 95% yield: mp 124 – 126 (reported 125-127) °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 3H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.00 (dd, *J* = 8.5, 5.5 Hz,

1H), 6.82 – 6.79 (m, 1H), 6.70 (s, 1H), 4.87 (d, *J* = 6.0 Hz, 1H), 4.60 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 3.75 (d, *J* = 6.0 Hz, 1H), 3.65 (s, 3H), 3.62 (s, 3H).

Diethyl 2-(4-benzyl-6-chloro-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-methylmalonate (**3h**). White solid in 90% yield: mp 113 – 114 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 3H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.89 (s, 1H), 6.82 (dd, *J* = 8.6, 2.2 Hz, 1H), 4.97 (s, 1H), 4.75 (d, *J* = 15.7 Hz, 1H), 4.55 (d, *J* = 15.7 Hz, 1H), 4.19 – 4.11 (m, 1H), 4.10 – 3.98 (m, 3H), (d, *J* = 15.9 Hz, 1H), 4.5 (d, *J* = 15.9 Hz, 1H), 4.25 – 4.17 (m, 1H), 4.17 – 4.07 (m, 3H), 1.46 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 169.1, 162.2, 141.8, 136.0, 133.2, 130.1, 128.9, 128.0, 127.3, 120.9, 117.9, 117.4, 63.4, 62.3, 62.2, 59.2, 57.8, 18.6, 13.8, 13.7; MS (70 eV) m/z (%) 445, 272, 149, 91; IR (KBr, cm^{-1}) 2981, 1775, 1724, 1502, 1161, 846, 801. Anal. Calcd for $C_{23}H_{24}ClNO_6$: C, 61.95; H, 5.43; N, 3.14. Found: C, 62.11; H, 5.32; N, 3.02.

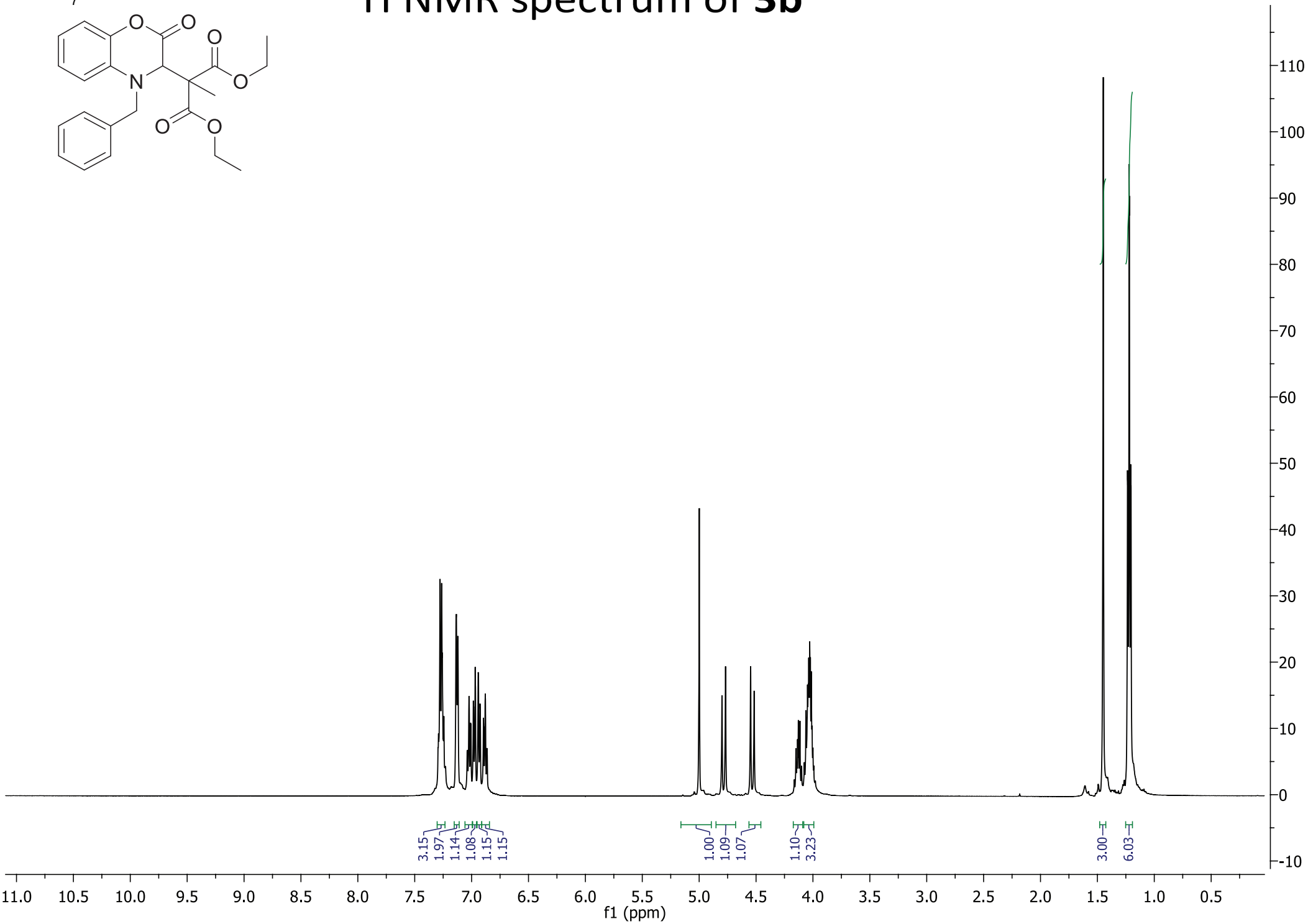
4,4'-Dibenzyl-3,3',4,4'-tetrahydro-2*H*,2'*H*-[3,3'-bibenzo[*b*][1,4]oxazine]-2,2'-dione. (**11**) [2]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 5.49 (s, 1H), 4.82 (d, *J* = 15.1 Hz, 1H), 4.61 (d, *J* = 15.1 Hz, 1H).

Reference

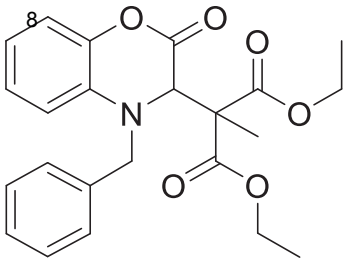
[1] Dong, J.; Min, W.; Li, H.; Quan, Z.; Yang, C.; Huo, C. Iron-Catalyzed C(sp^3)–C(sp^3) Bond Formation in 3,4-Dihydro-1,4-benzoxazin-2-ones. *Adv. Synth. Catal*. **2017**, *359*, 3940–3944. DOI: 10.1002/adsc.201700816.

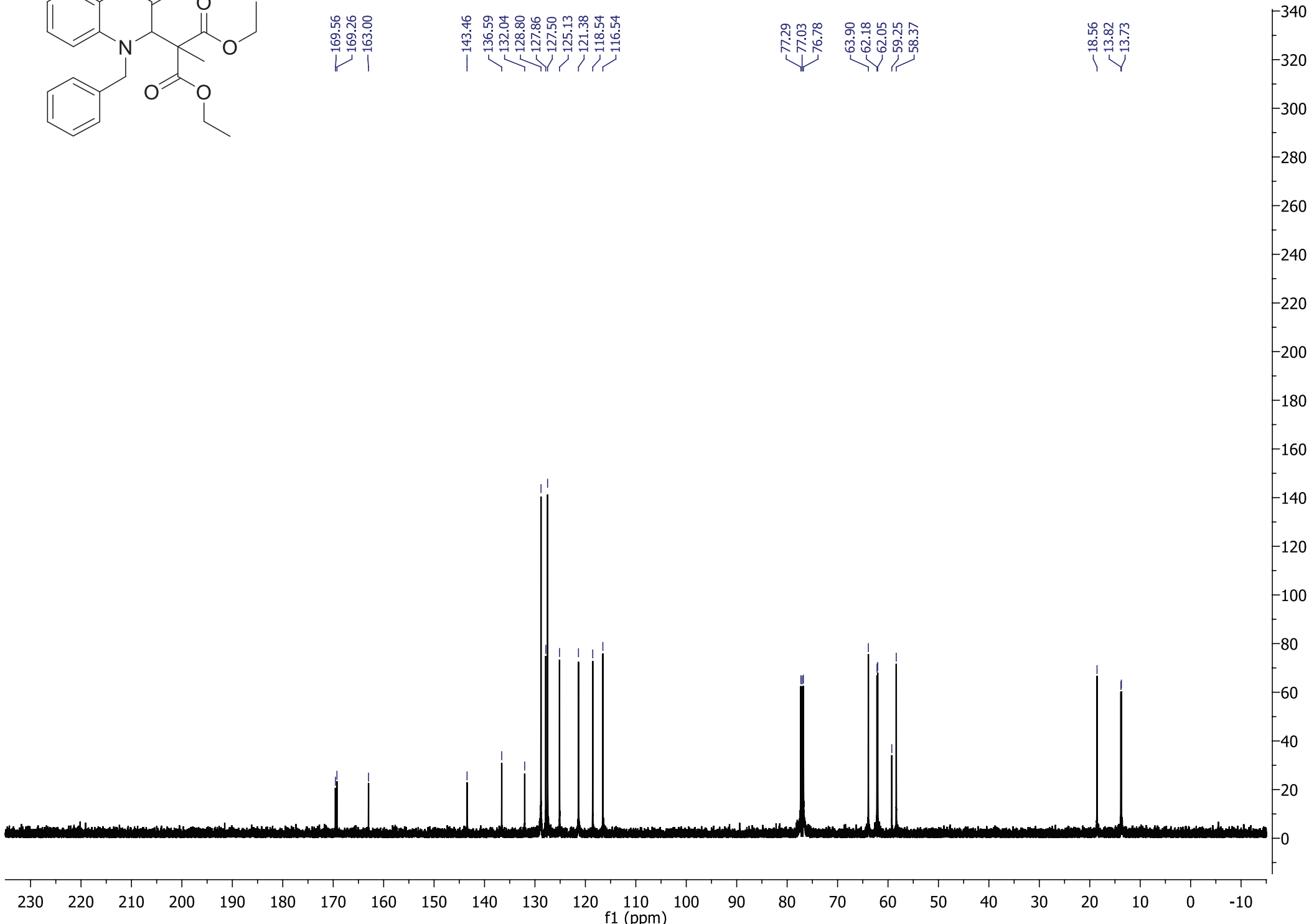
[2] Zhang, G.-Y.; Yu, K.-X.; Zhang, C.; Guan, Z.; He, Y. H. Oxidative Cross-Dehydrogenative-Coupling Reaction of 3,4-Dihydro-1,4-benzoxazin-2-ones through Visible-Light Photoredox Catalysis. *Eur. J. Org. Chem*. **2018**, *2018*, 525–531. DOI: 10.1002/ejoc.201701683.

^{1}H NMR spectrum of **3b**

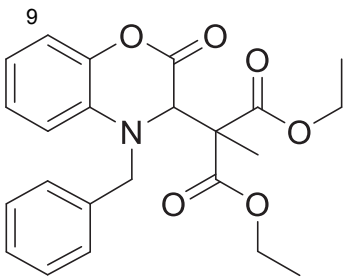


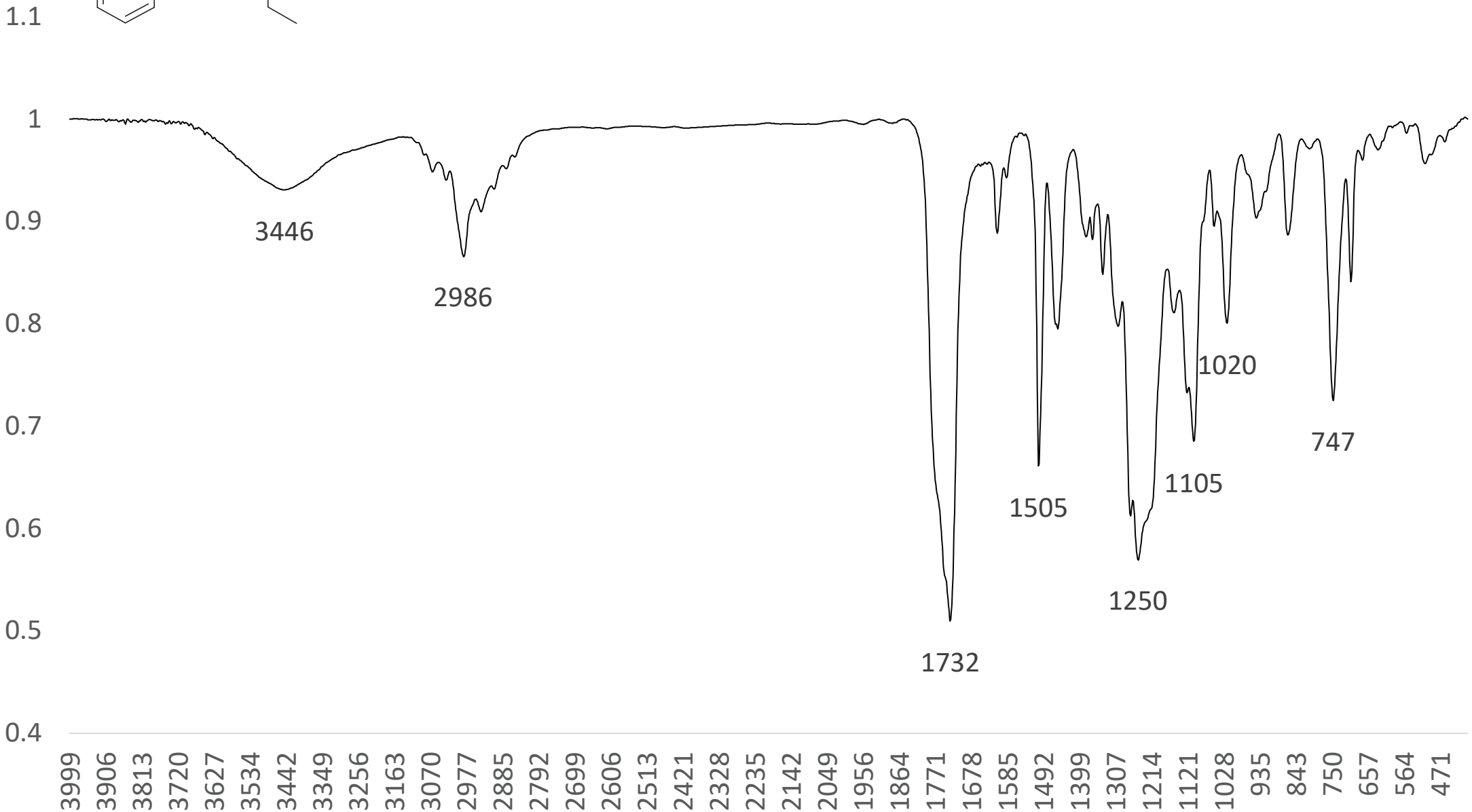
^{13}C NMR spectrum of **3b**

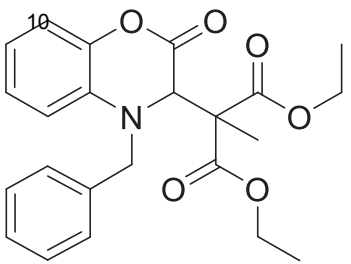




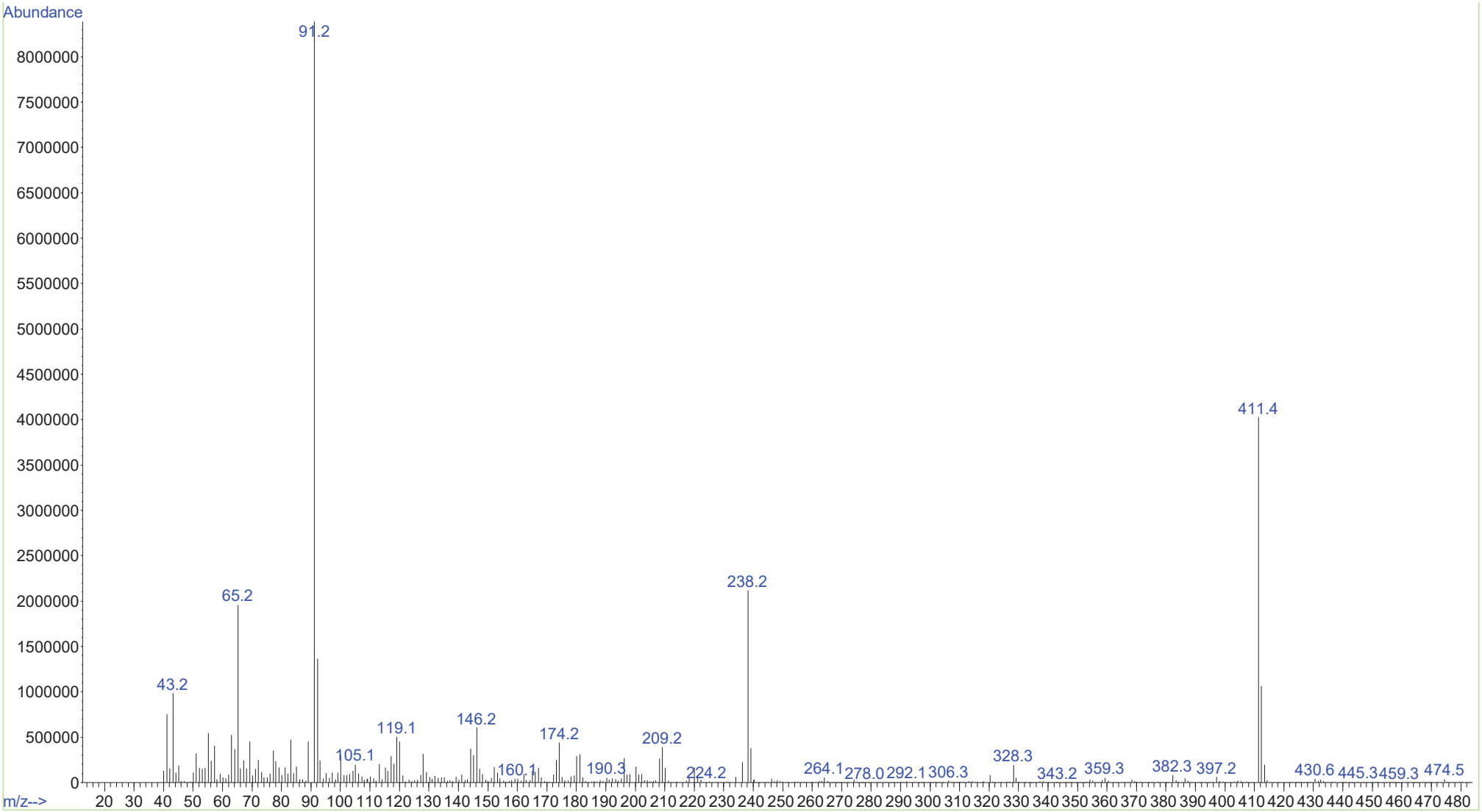
IR spectrum of **3b**



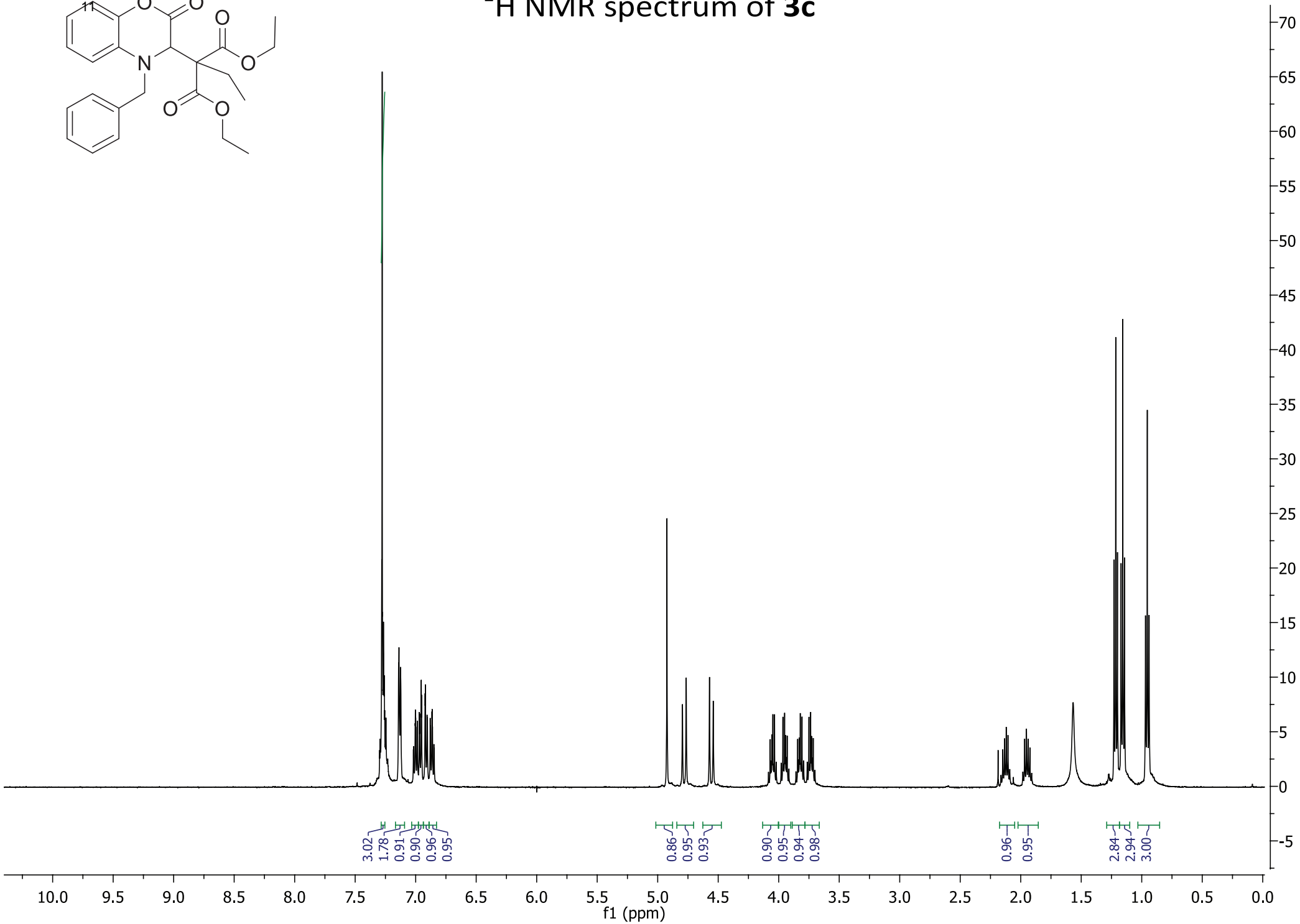




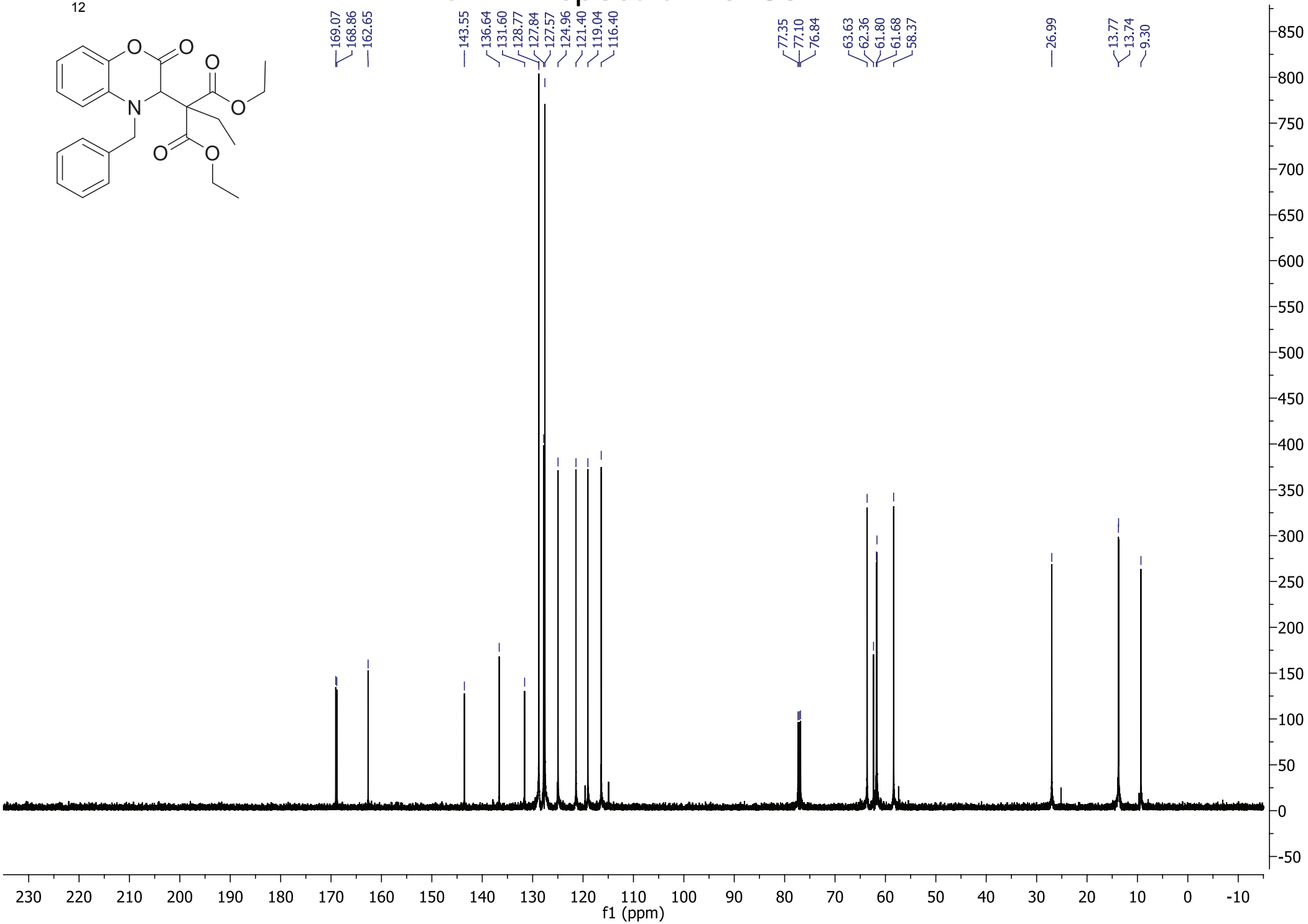
Mass spectrum of **3b**



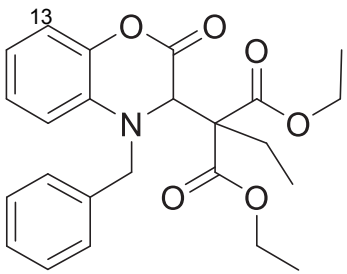
^{1}H NMR spectrum of **3c**

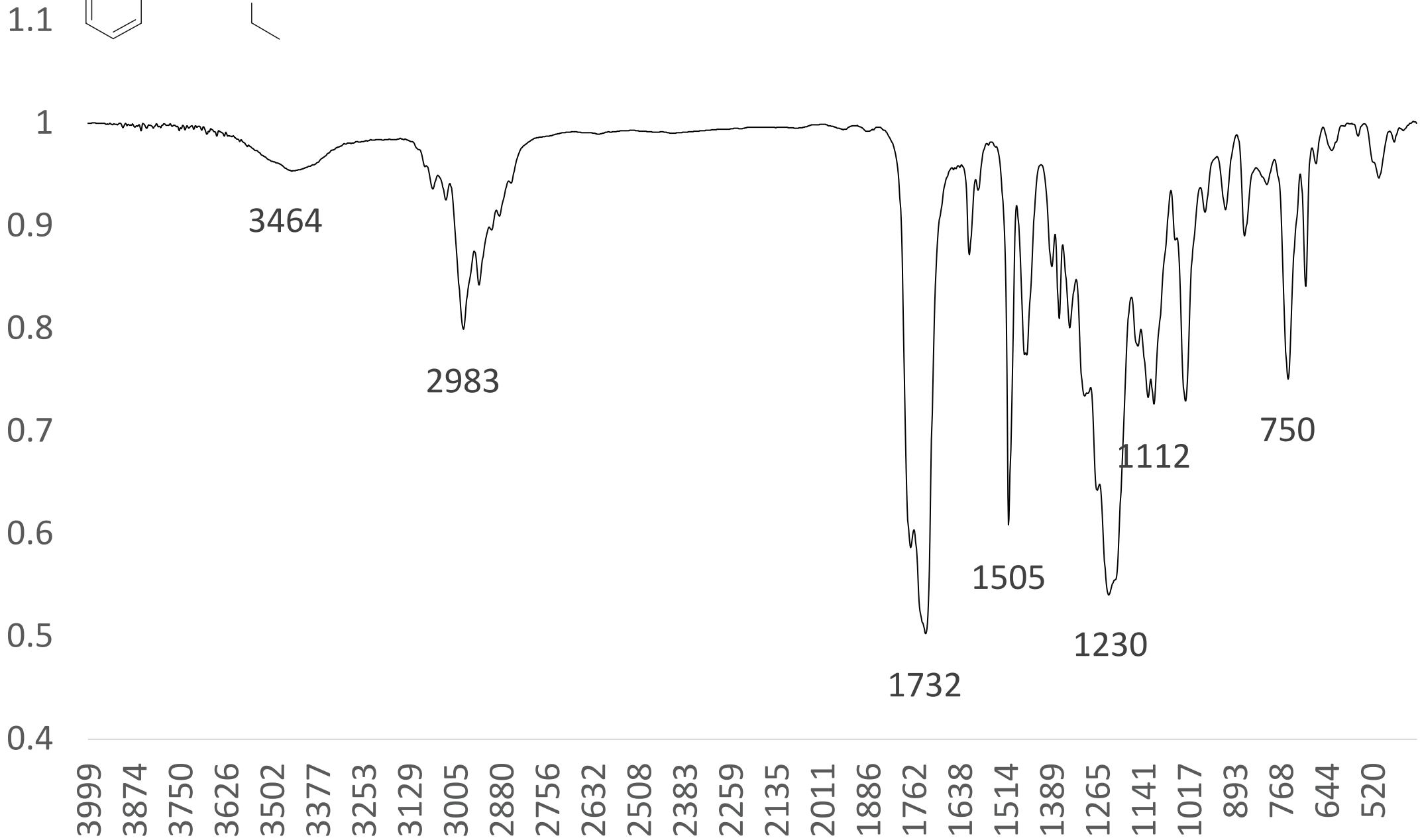


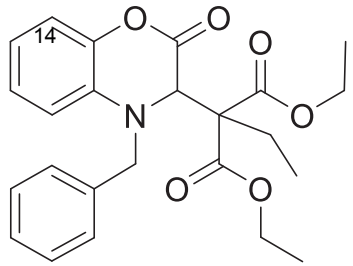
^{13}C NMR spectrum of **3c**



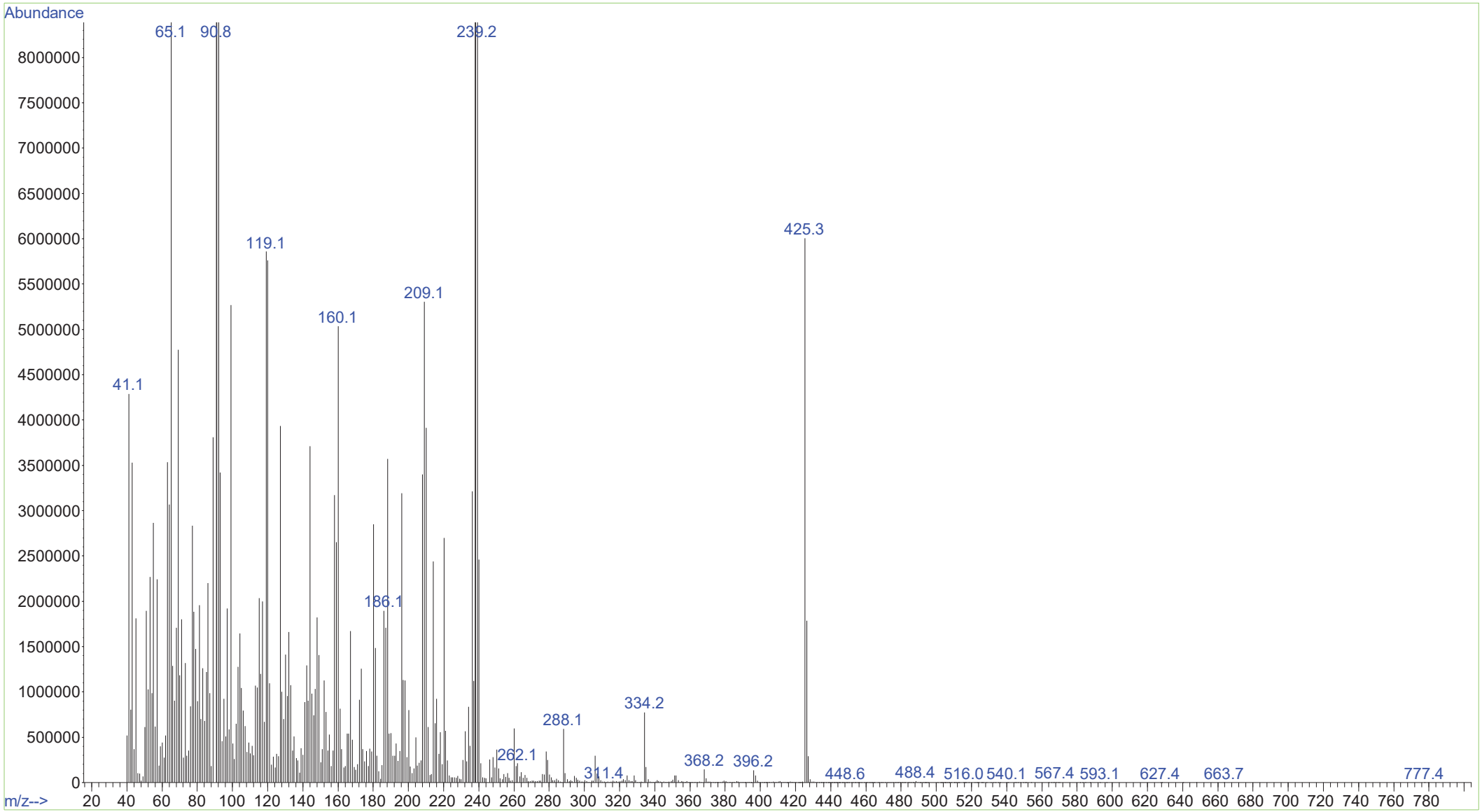
IR spectrum of **3c**



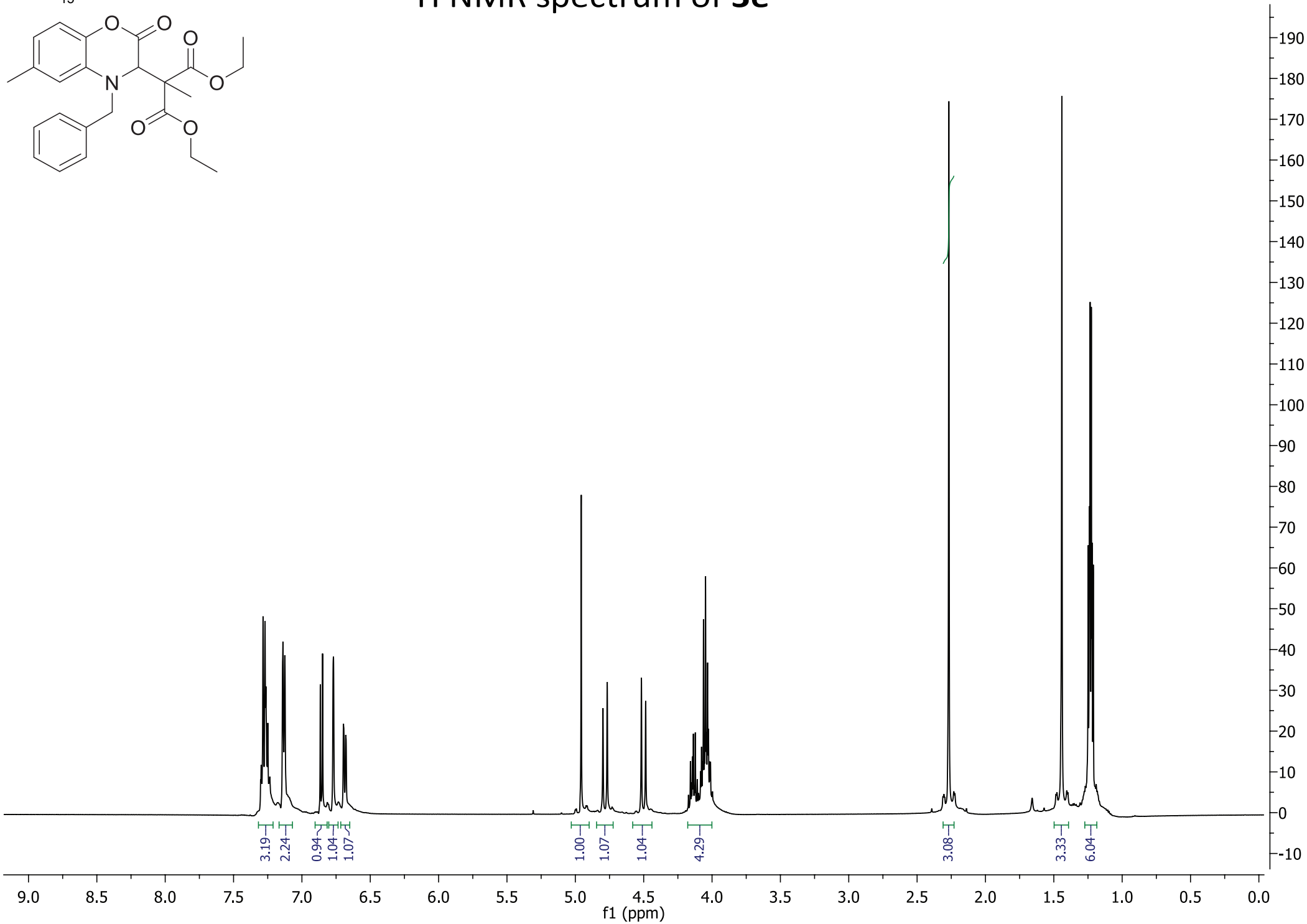




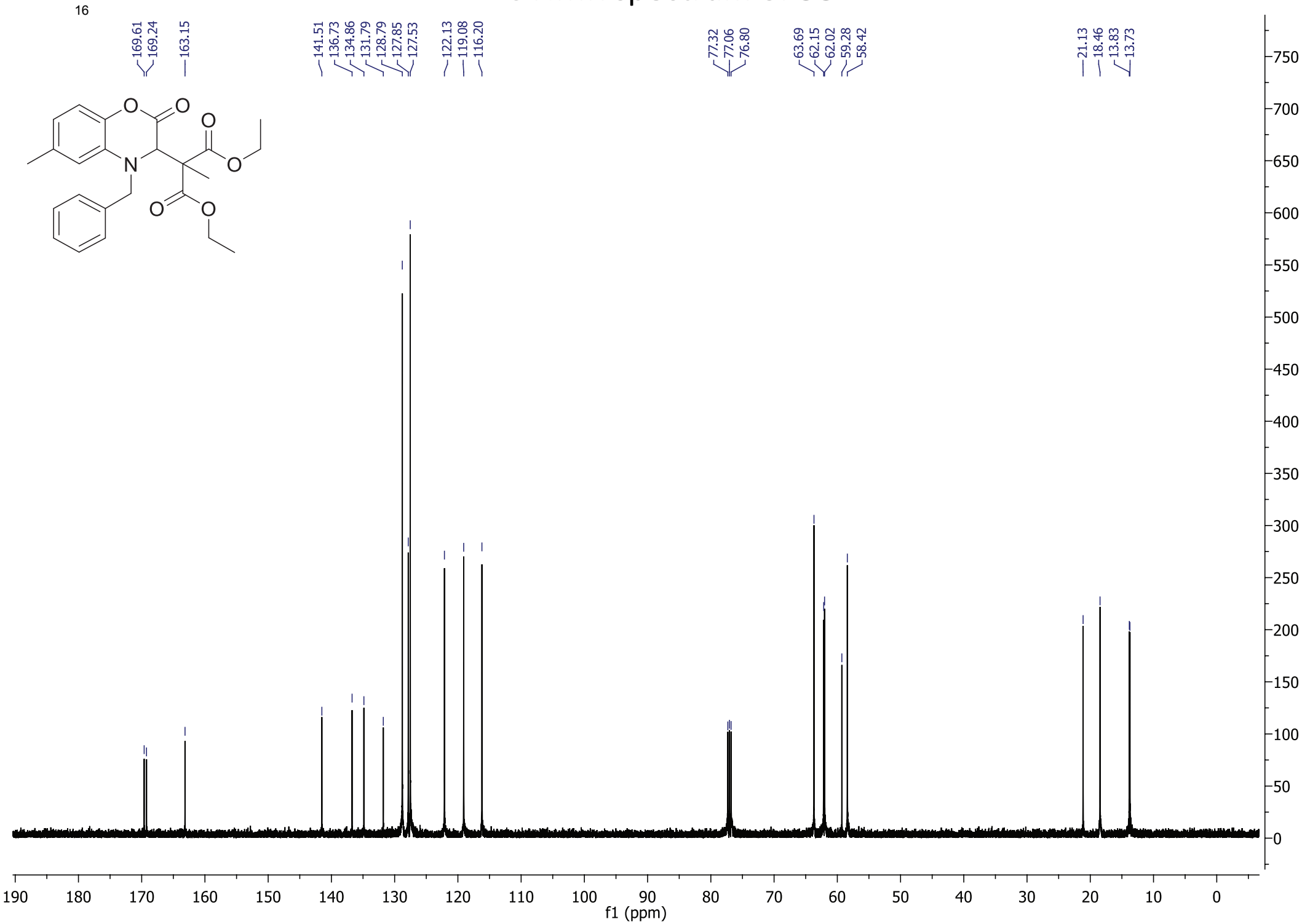
Mass spectrum of **3c**



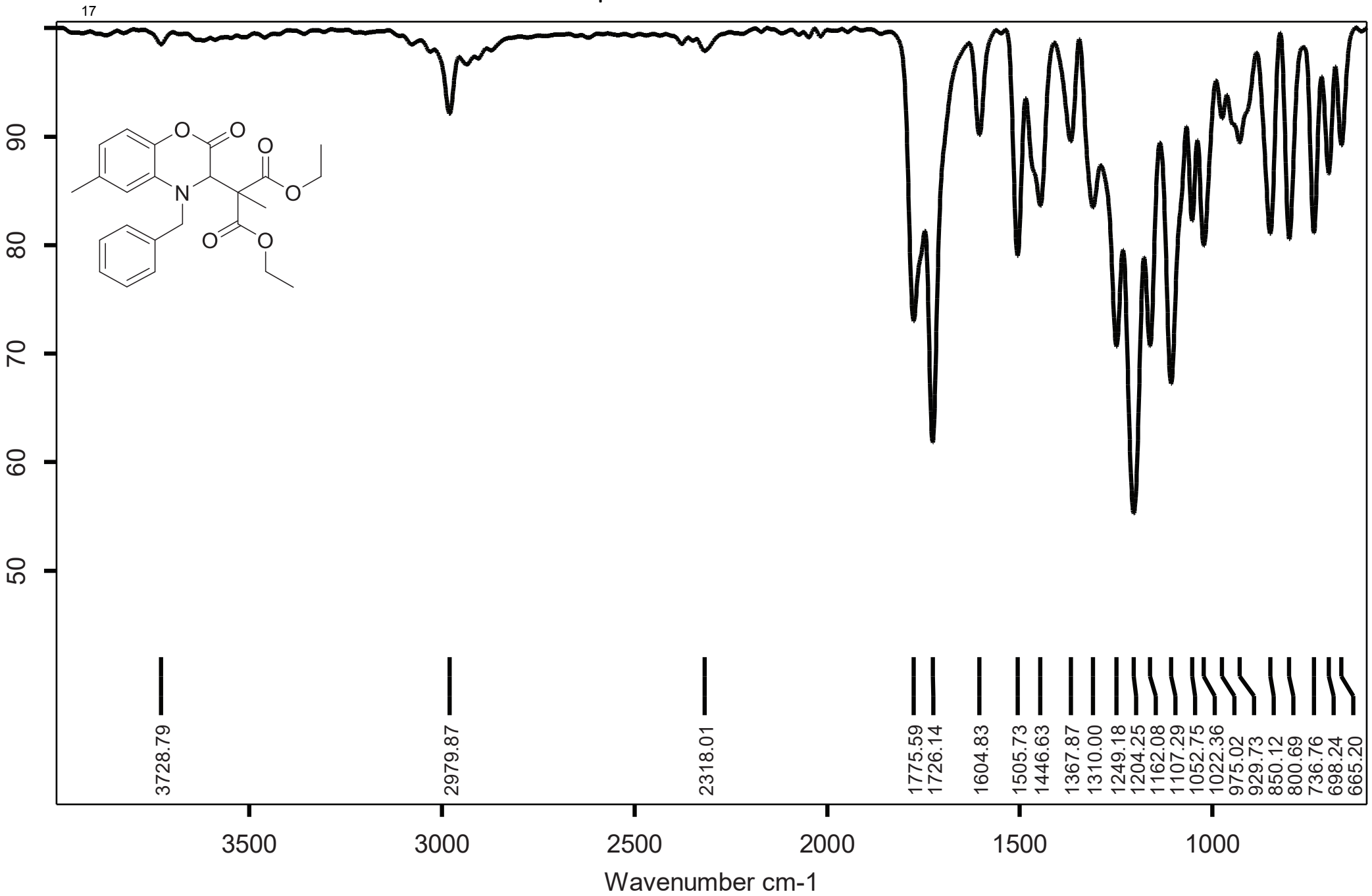
^{1}H NMR spectrum of **3e**



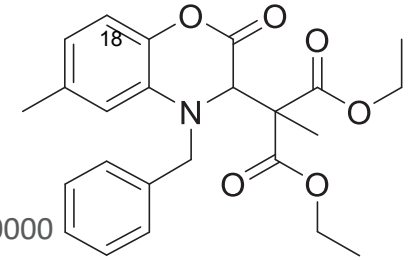
^{13}C NMR spectrum of **3e**

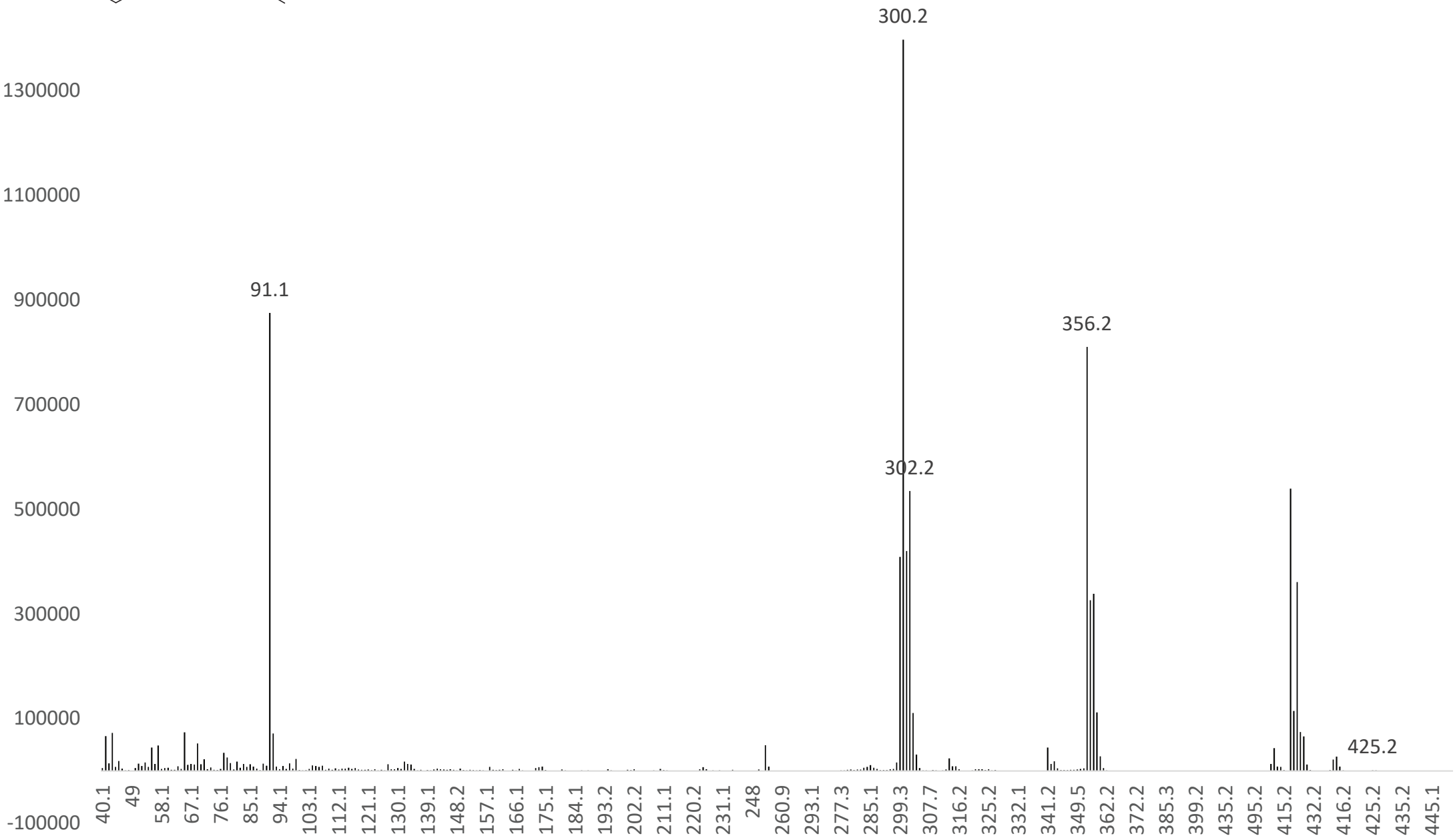


IR spectrum of **3e**

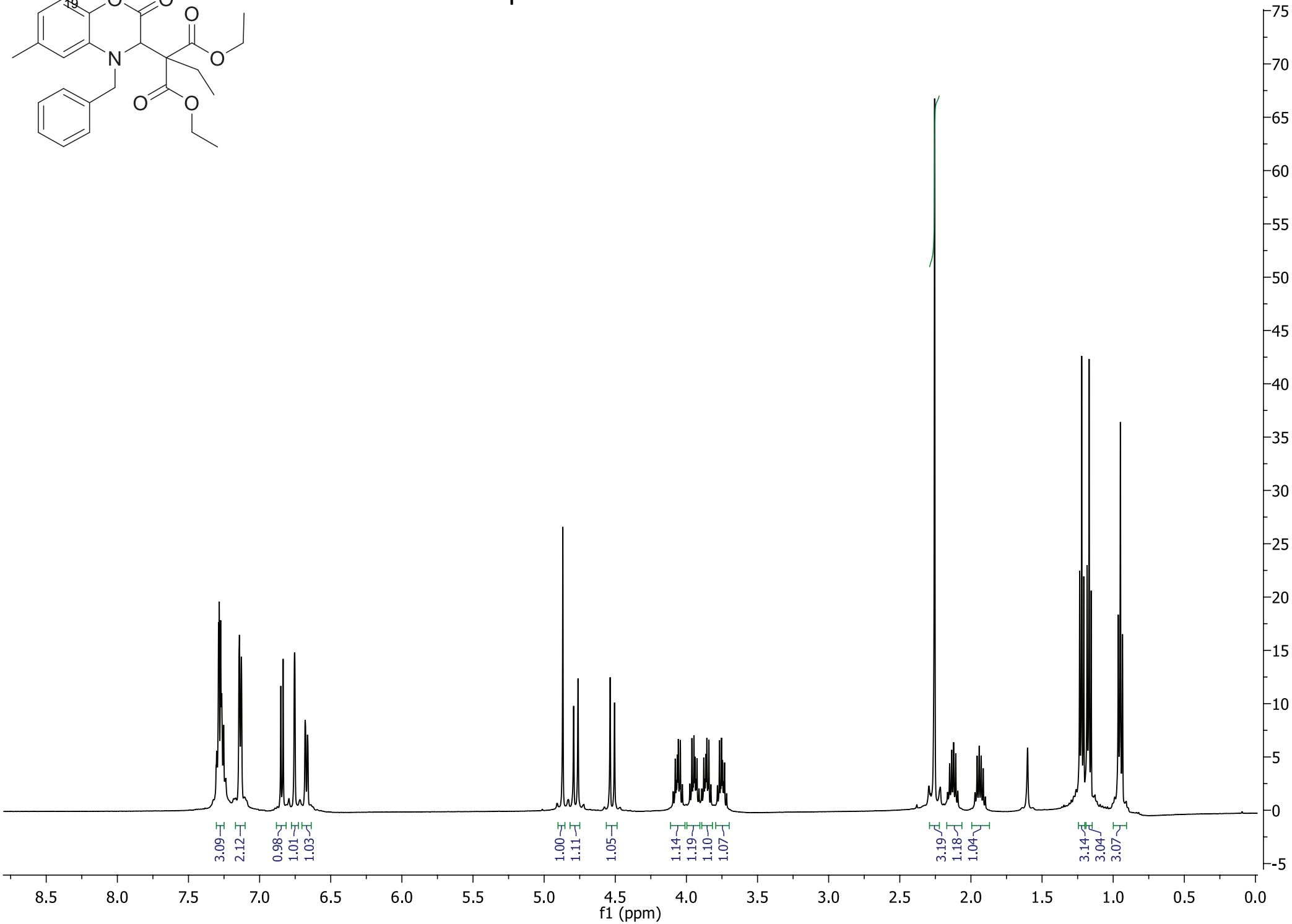


Mass spectrum of **3e**

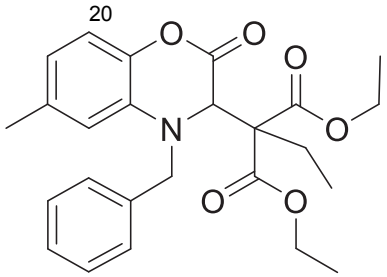


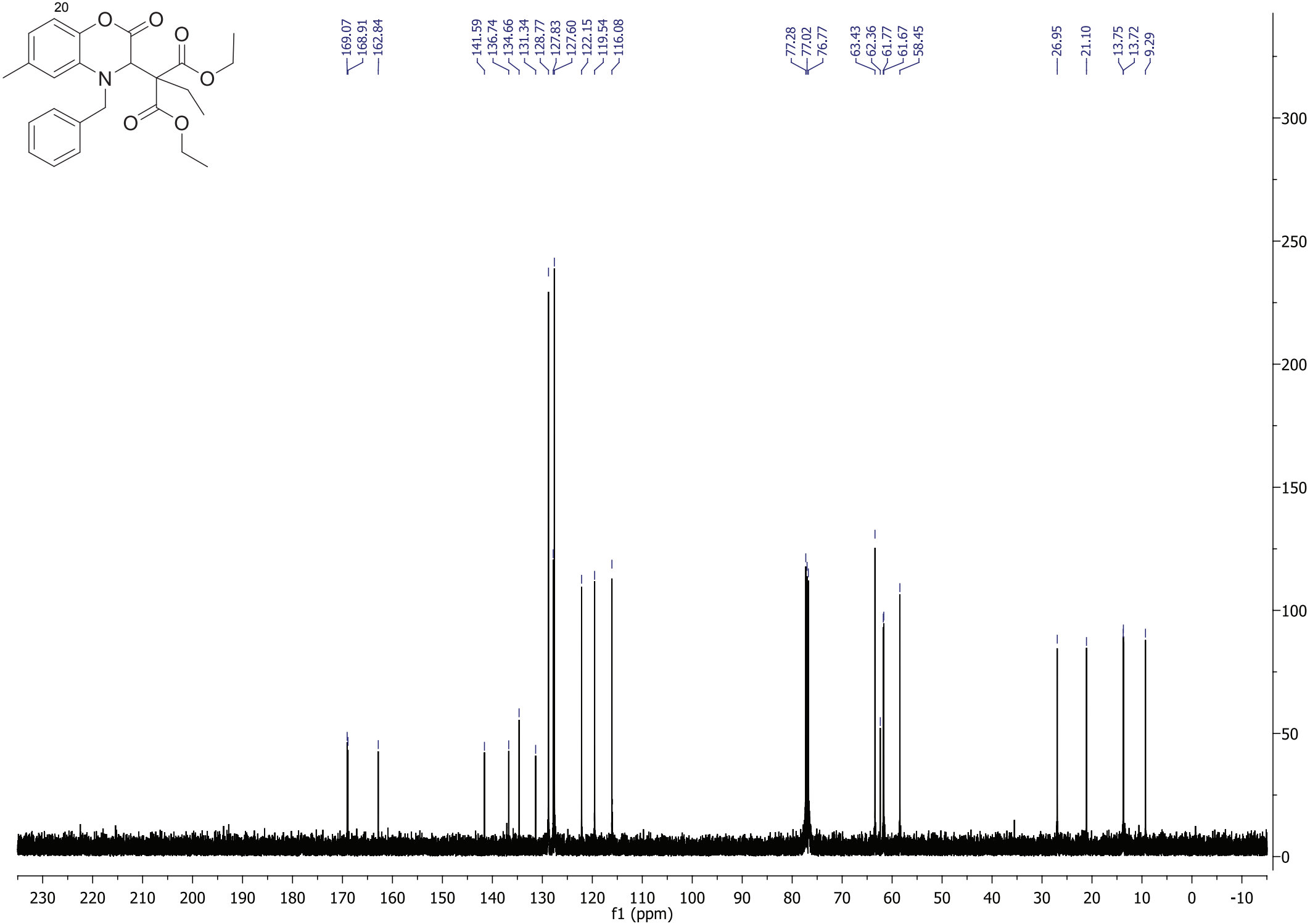


^{1}H NMR spectrum of **3f**

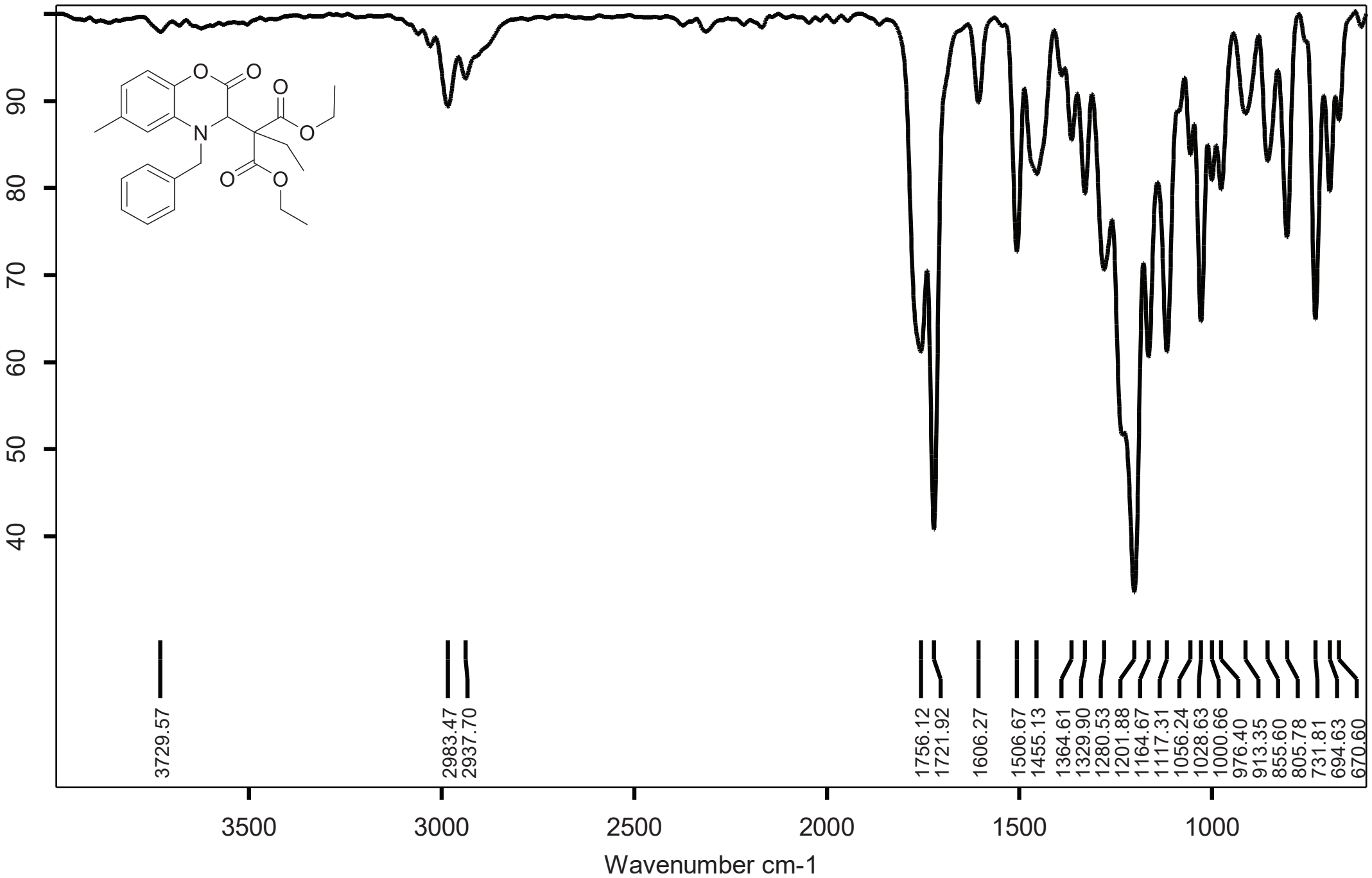


^{13}C NMR spectrum of **3f**

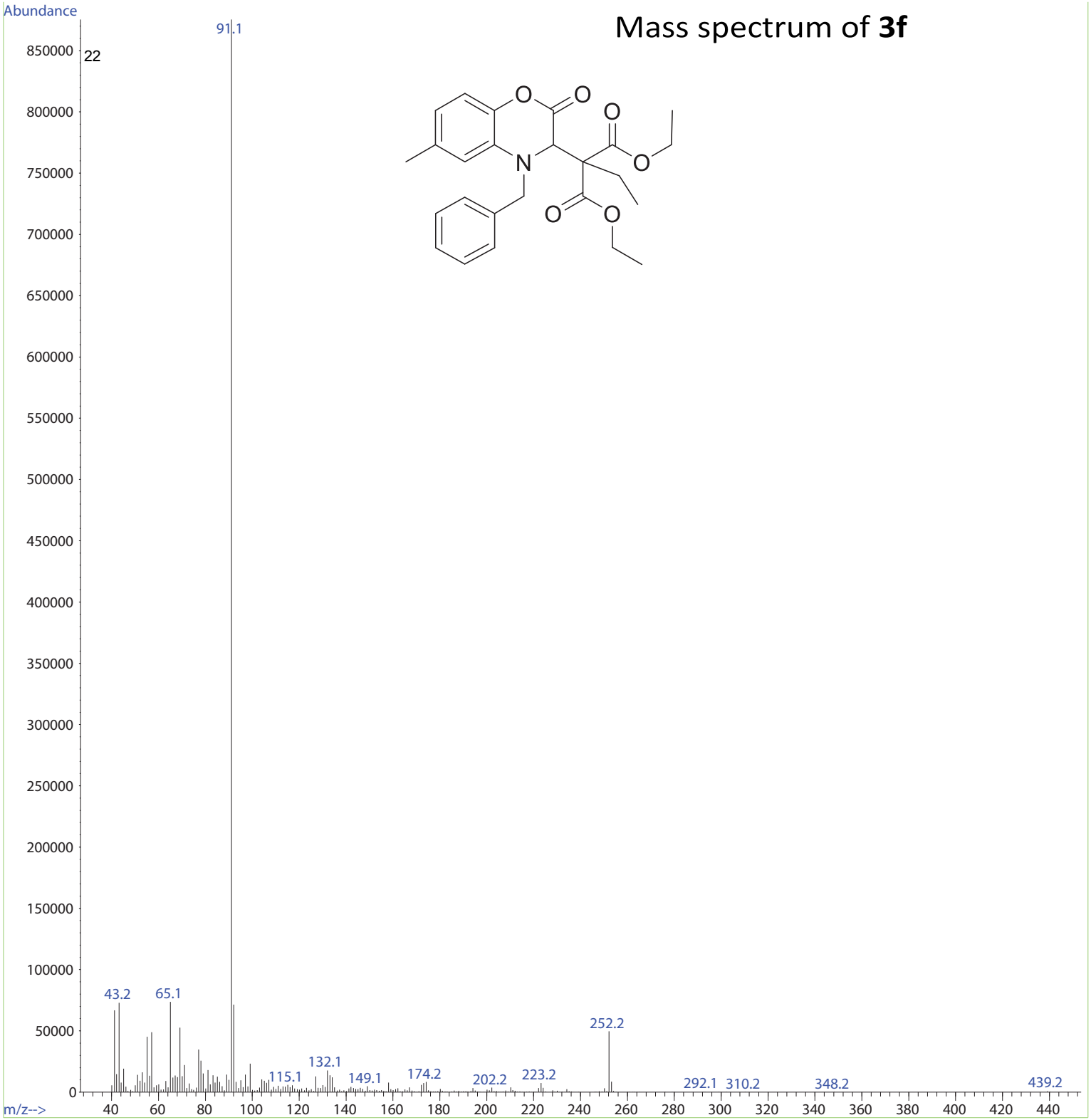




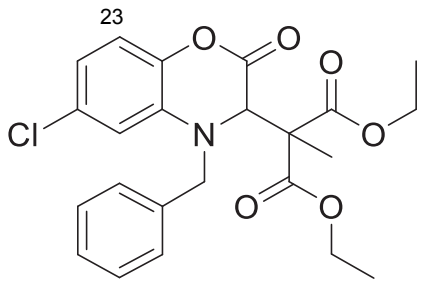
IR spectrum of **3f**

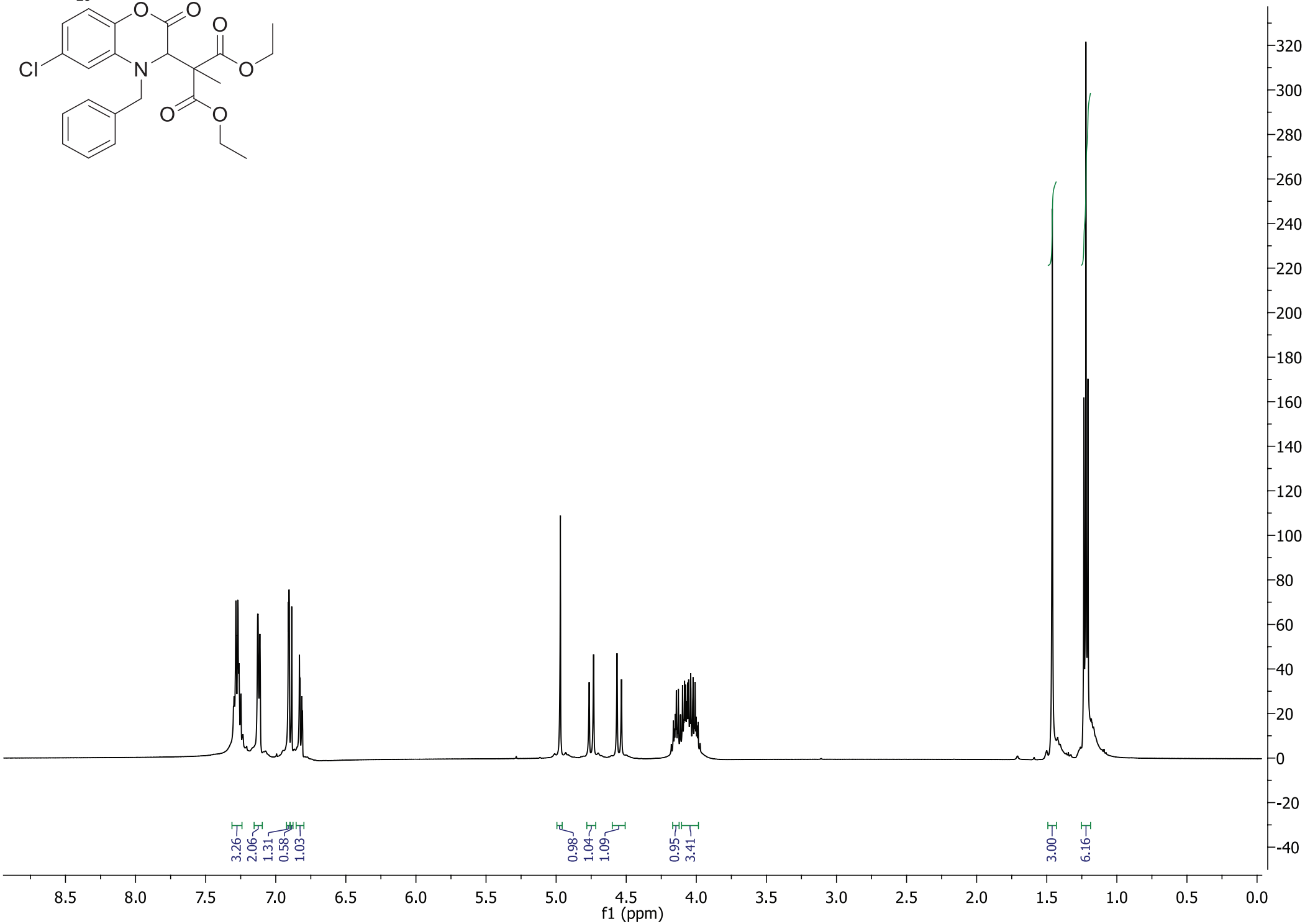


Mass spectrum of **3f**



^{1}H NMR spectrum of **3h**

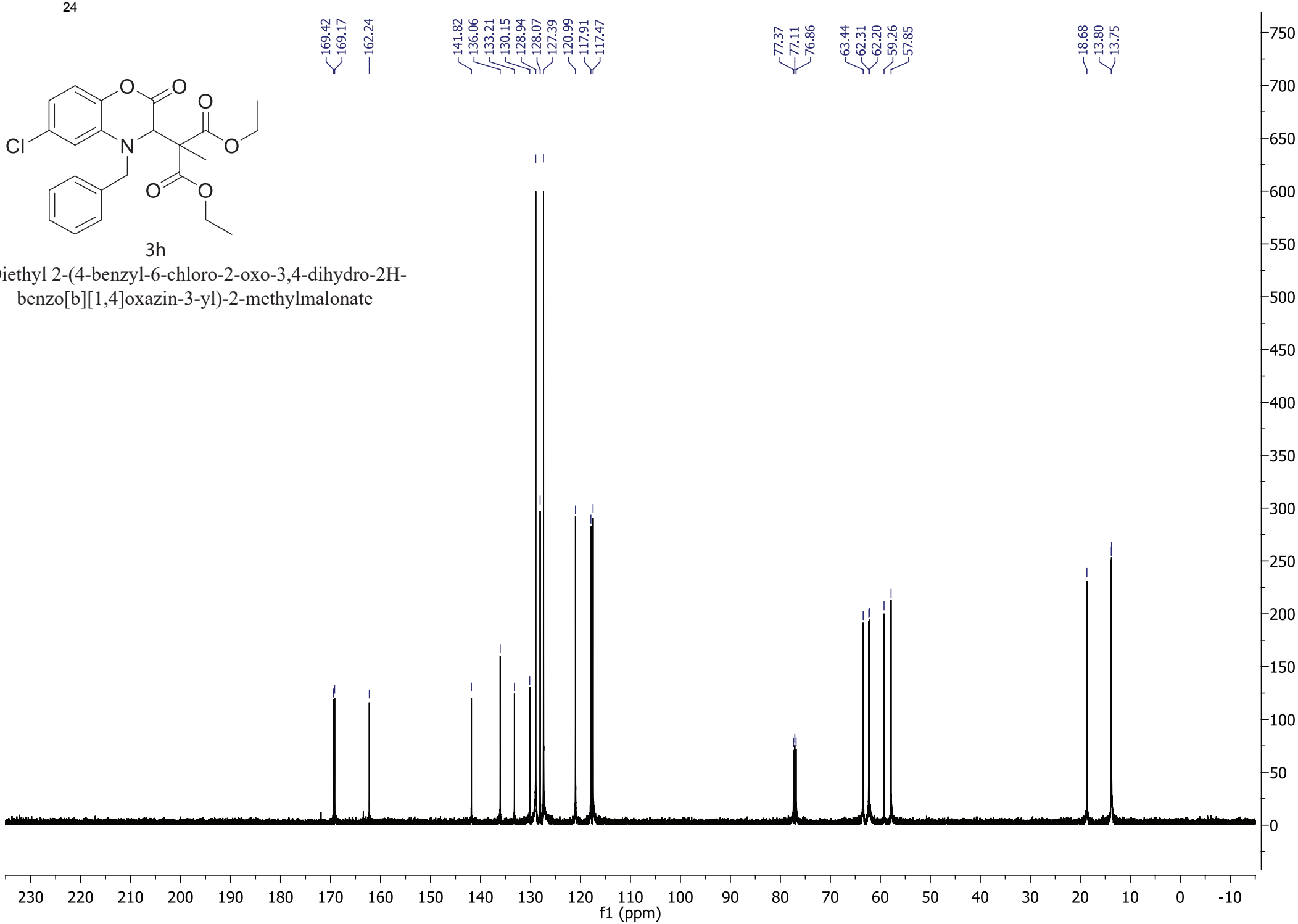




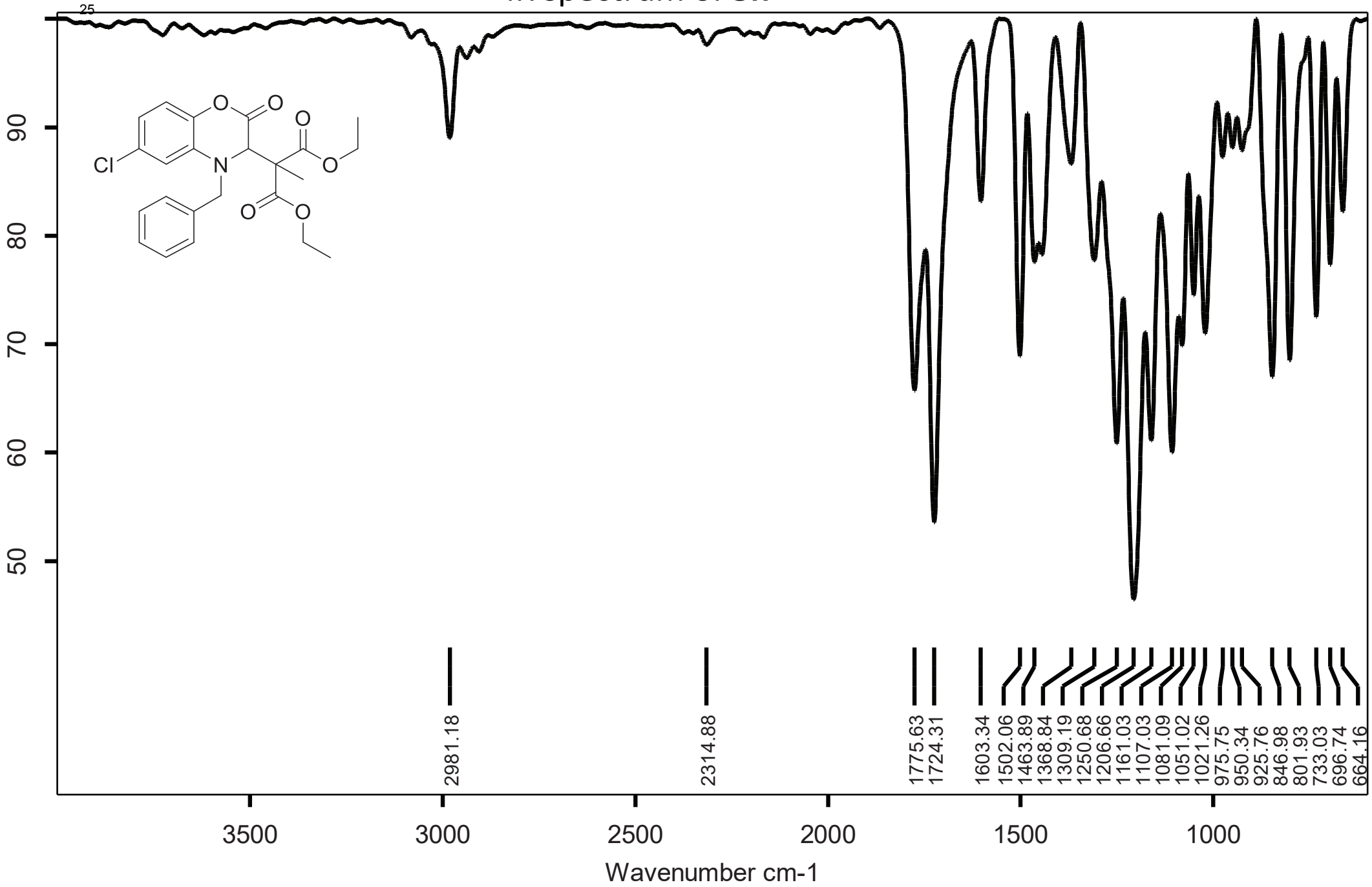
^{13}C NMR spectrum of **3h**

3h

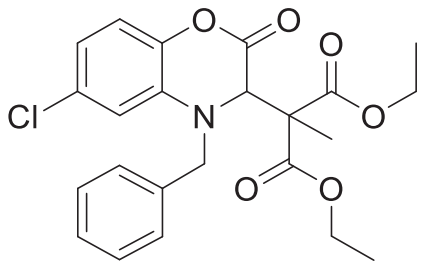
Diethyl 2-(4-benzyl-6-chloro-2-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-3-yl)-2-methylmalonate

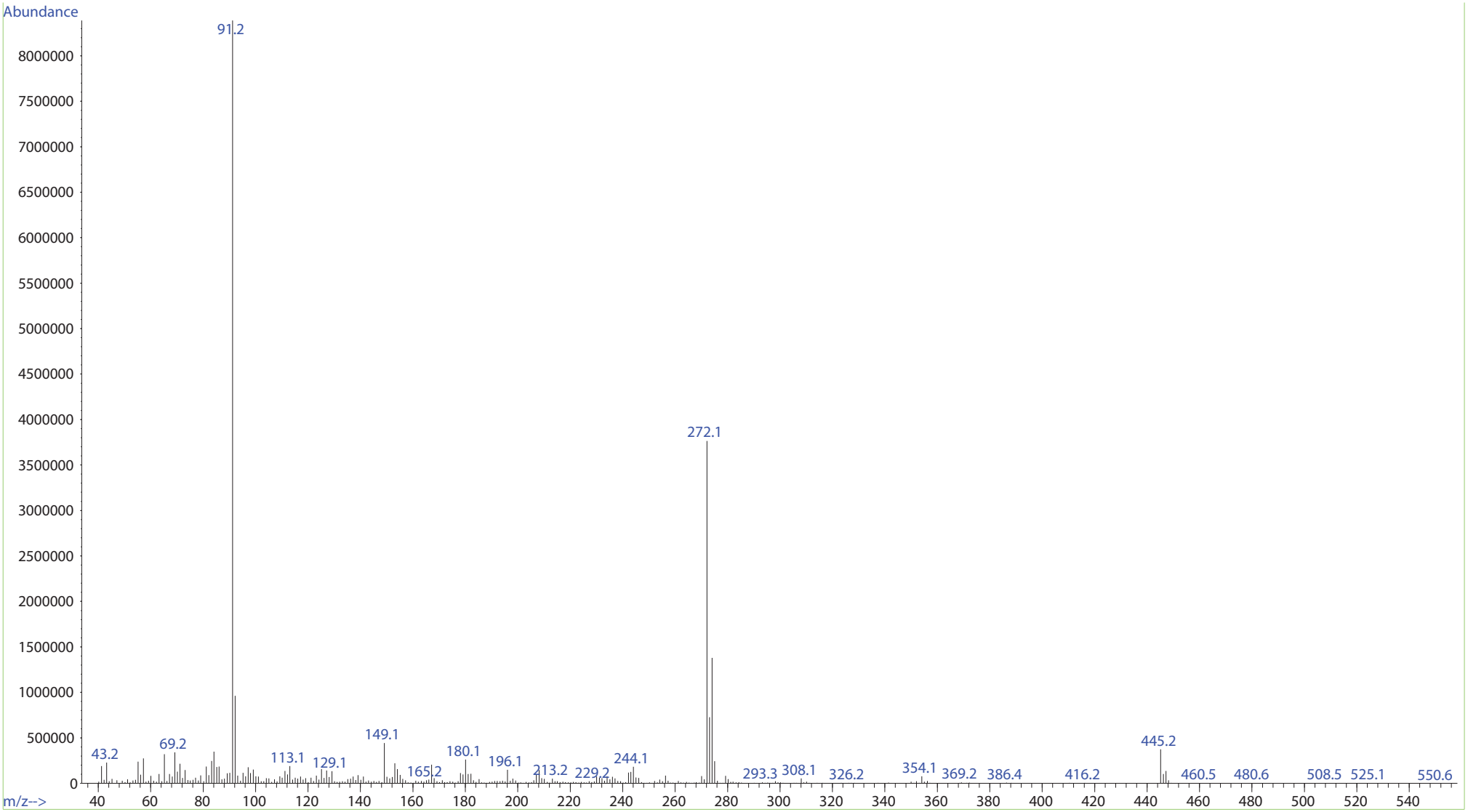


IR spectrum of **3h**



Mass spectrum of **3h**





^{1}H NMR spectrum of **11**

dimer