SUPPORTING INFORMATION

Alkaloid inspired spirocyclic oxindoles from 1,3-dipolar cycloaddition of pyridinium ylides

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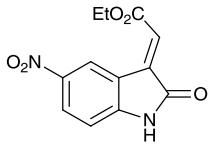
1. General Procedure for 2-oxoindolin-3-ylidenes by Wittig reaction:

To a stirred solution of the substituted isatin (1.0 equiv.) in anhydrous THF was added ethyl 2-(triphenylphosphoranylidene) acetate (1.2 equiv.) at 0 °C. The mixture was stirred at room temperature until the reaction was completed by TLC analysis. Water was added and the mixture extracted into ethyl acetate (3 x) and washed with sat. $NH_4Cl_{(aq)}$, water, brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (EtOAc/Petrol; 1/1).

(*E*)-ethyl 2-(5-nitro-2-oxoindolin-3-ylidene)acetate 1c



Yellow solid; 545 mg (80 %); m.p. 176-178 °C (ethanol); IR (ν_{max}/cm^{-1}, $CHCl_3$) 3436, 3012, 1745, 1717, 1623, 1529, 1467, 1343, 1289, 1192; NMR δ_H (400 MHz, d^6-acetone) 10.31 (1H, br s, N*H*), 9.45 (1H, d, *J*= 2.4 Hz, Ar*H*), 8.32 (1H, dd, *J*= 8.7, 2.4 Hz, Ar*H*), 7.17 (1H, d, *J*= 8.7 Hz, Ar*H*), 6.83 (1H, s, C=C*H*), 4.38 (2H, q, *J*= 7.1 Hz, C*H*$_2$CH$_3$), 1.39 (3H, t, *J*= 7.1 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz, d^6-DMSO) 168.4 (C), 165.2 (C), 151.0 (C), 142.5 (C), 136.9 (C), 129.5 (CH), 124.1 (CH), 123.9 (CH), 120.1 (C), 111.0 (CH), 62.0 (CH_2), 14.4 (CH_3); *m/z* (HRMS-ESI+) 285.0470 (M+Na $C_{12}H_{10}N_2NaO_5$ requires 285.0482).

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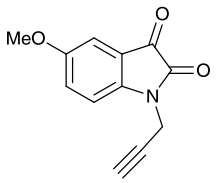
5-methoxy-1-(prop-2-yn-1-yl)indoline-2,3-dione



Propargyl bromide (0.61 mL, 6.77 mmol; 80 % solution in toluene), 5-methoxy isatin (1.0 g, 5.64 mmol) and K_2CO_3 (1.09 g, 7.90 mmol) were stirred in acetonitrile (20 mL) at 65 °C for 4 h, followed by stirring at room temperature for 16 h. Solvent was removed *in vacuo* and the residue purified by column chromatography on silica gel (EtOAc/Petrol; 1/1) to give the product as a red solid (430 mg, 36%); m.p. 130-132 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 3307, 2962, 1737, 1623, 1602, 1492, 1437, 1332, 1274, 1180, 1021; NMR δ_H (400 MHz, d^6-DMSO) 7.33 (1H, dd, *J*= 8.8, 2.8 Hz, Ar*H*), 7.19 (1H, d, *J*= 2.8 Hz, Ar*H*), 7.18 (1H, d, *J*= 8.8 Hz, Ar*H*), 4.53 (2H, d, *J*= 2.5 Hz, CH_2), 3.34 (1H, t, *J*= 2.5 Hz, CC*H*), 3.32 (3H, s, OCH_3); NMR δ_C (100 MHz, d^6-DMSO) 183.2 (C), 157.9 (C), 156.5 (C), 143.7 (C), 124.4 (CH), 118.6 (C), 112.7 (CH), 109.7 (CH), 77.9 (C), 75.4 (CH), 56.4 (CH_3), 29.5 (CH_2); *m/z* (HRMS-ESI+) 238.0476 (M+Na $C_{12}H_9NO_3Na$ requires 238.0475).

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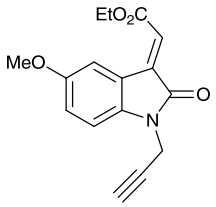
(*E*)-ethyl 2-(5-methoxy-2-oxo-1-(prop-2-yn-1-yl)indolin-3-ylidene)acetate 1d



5-Methoxy, *N*-propagyl isatin was converted to **1d** using the general procedure described above and the product was obtained as dark red solid, 171 mg (65%); m.p. 128-130 °C (ethanol); IR (ν_{max}/cm^{-1}, $CHCl_3$) 3306, 3011, 1708, 1596, 1482, 1437, 1371, 1291, 1192; NMR δ_H (400 MHz, *d*^{6}-DMSO) 8.07 (1H, d, *J*= 2.4 Hz, Ar*H*), 7.12 (1H, dd, *J*= 8.6, 2.4 Hz, Ar*H*), 7.08 (1H, d, *J*= 8.6 Hz, Ar*H*), 6.71 (1H, s, C=C*H*), 4.55 (2H, d, *J*= 2.5 Hz, CH_2), 4.28 (2H, q, *J*= 7.1 Hz, CH_2CH$_3$), 3.76 (3H, s, OCH_3), 3.29 (1H, t, *J*= 2.5 Hz, C≡C*H*), 1.30 (3H, t, *J*= 7.1 Hz, CH$_2$CH_3); NMR δ_C (100 MHz, *d*^{6}-DMSO) 166.1 (C), 165.3 (C), 155.8 (C), 138.2 (C), 137.5 (C), 122.9 (CH), 120.2 (C), 118.4 (CH), 114.7 (CH), 110.8 (CH), 78.2 (C), 75.0 (CH), 61.7 (CH$_2$), 56.1 (CH$_3$), 29.5 (CH$_2$), 14.5 (CH$_3$); *m/z* (HRMS-ESI+) 308.0876 (M+Na $C_{16}H_{15}NNaO_4$ requires 308.0893).

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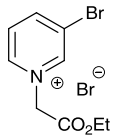
2. General Procedure A or B for the preparation of pyridinium salts:

An α-halocarbonyl (1 equiv.) and substituted pyridine (1 equiv.) in dry ethyl acetate were stirred overnight under argon at room temperature (A) or at reflux (B). Diethyl ether was added and the resulting precipitates filtered, washed with diethyl ether and recrystallised from ethanol.

3-bromo-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide 2a



Procedure A. White solid; 4.10 g (80 %); m.p. 177-179 °C; IR_{Solid} (ν_{max}/cm^{-1}) 2955, 1748, 1485, 1348, 1300, 1240; NMR δ_H (400 MHz, D_2O) 9.11 (1H, s, Ar*H*), 8.81 (2H, m, Ar*H*), 8.01 (1H, dd, *J*= 8.4, 6.2 Hz, Ar*H*), 5.51 (2H, s, CH_2), 4.26 (2H, q, *J*= 7.2 Hz, CH_2CH_3), 1.22 (3H, t, *J*= 7.2 Hz, CH_2CH_3); NMR δ_C (100 MHz, D_2O) 166.7 (C), 149.7 (CH), 147.0 (CH), 144.7 (CH), 128.6 (CH), 122.8 (C), 64.2 (CH_2), 61.0 (CH_2), 13.2 (CH_3); *m/z* (HRMS-ESI+) 243.9961 (M^+ $C_9H_{11}NO_2{}^{79}Br^+$ requires 243.9968), 245.9939 (M^+ $C_9H_{11}NO_2{}^{81}Br^+$ requires 245.9948).

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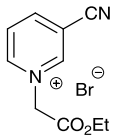
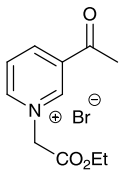
3-Cyano-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide 2g



Procedure B. Dark yellow solid; 6.10 g (78 %); m.p. 152-154 °C; IR_{Solid} (ν_{max}/cm^{-1}) 3002, 2922, 2257, 1748, 1642, 1510, 1467, 1365, 1228, 1205, 1026; NMR δ_H (300 MHz, D_2O) 9.48 (1H, s, Ar*H*), 9.23 (1H, dt, *J*= 6.5, 1.3 Hz, Ar*H*), 9.11 (1H, dt, *J*= 8.3, 1.3 Hz, Ar*H*), 8.34 (1H, dd, *J*= 8.3 Hz, 6.5 Hz, Ar*H*), 5.66 (2H, s, CH_2), 4.30 (2H, q, *J*= 7.2 Hz, C*H*$_2$CH$_3$), 1.26 (3H, t, *J*= 7.2 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz, D_2O) 166.3 (C), 150.3 (CH), 149.8 (CH), 149.7 (CH), 129.1 (CH), 114.0 (C), 113.2 (C), 63.5 (CH_2), 61.7 (CH_2), 13.4 (CH_3); *m/z* (HRMS-ESI+) 191.0828 (M^+ $C_{10}H_{11}N_2O_2^+$ requires 191.0815).

3-Acetyl-1-(2-ethoxy-2-oxoethyl)pyridin-1-ium bromide 2i



Procedure B. Red brown solid (11.5 g, 99 %); m.p. 123-125 °C (acetone); IR (ν_{max}/cm^{-1}, $CHCl_3$) 2954, 1747, 1711, 1637, 1585, 1467, 1397, 1376, 1277, 1240, 1020; NMR δ_H (400 MHz, D_2O) 9.40 (1H, s, Ar*H*), 9.10-8.98 (2H, m, Ar*H*), 8.28-8.24 (1H, m, Ar*H*), 5.63 (2H, s, C*H*$_2$), 4.28 (2H, q, *J*= 7.0 Hz, C*H*$_2$CH$_3$), 2.73 (3H, s, COC*H*$_3$), 1.28 (3H, t, *J*= 7.0 Hz, CH$_2$C*H*$_3$); NMR δ_C (100 MHz, D_2O) 196.0 (C), 166.8 (C), 148.6 (CH), 146.5 (CH), 145.9 (CH), 145.3 (CH), 135.8 (C), 64.2 (CH_2), 26.6 (CH_3), 13.2 (CH_3); *m/z* (HRMS-ESI+) 208.0985 (M+H $C_{11}H_{14}NO_3$ requires 208.0986).

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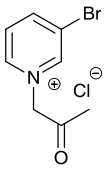
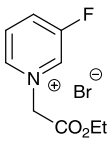
3-Bromo-1-(2-oxopropyl)pyridin-1-ium chloride 2j



Procedure B. Brown solid; 3.40 g (72%); m.p. 188-190 °C (ethanol); IR_{Solid} (ν_{max}/cm^{-1}) 3004, 1730, 1629, 1496, 1430, 1355, 1318, 1204, 1174; NMR δ_H (300 MHz, D_2O) 8.93 (1H, t, *J*= 1.2 Hz, Ar*H*), 7.77 (1H, dt, *J*= 8.5, 1.2 Hz, Ar*H*), 8.64 (1H, dt, *J*= 6.2, 1.2 Hz, Ar*H*), 7.99 (1H, dd, *J*= 8.5, 6.2 Hz, Ar*H*), 5.72 (2H, s, CH_2), 2.36 (3H, s, COCH_3); NMR δ_C (100 MHz, D_2O) 201.1 (C), 149.2 (CH), 146.8 (CH), 144.5 (CH), 128.5 (CH), 122.6 (C), 68.4 (CH_2), 26.7 (CH_3); *m/z* (HRMS-ESI+) 213.9867 (M^+ $C_8H_9{}^{79}BrNO^+$ requires 213.9863), 215.9845 (M^+ $C_8H_9{}^{81}BrNO$ requires 215.9843).

1-(2-ethoxy-2-oxoethyl)-3-fluoropyridin-1-ium bromide 2k



Procedure B. Brown solid; 110 mg (36%); m.p. 90-92 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 2952, 1749, 1595, 1506, 1397, 1350, 1240, 1167; NMR δ_H (400 MHz, D_2O) 9.04 (1H, s, Ar*H*), 8.79 (1H, d, *J*= 6.0 Hz, Ar*H*), 8.56 (1H, t, *J*= 6.0 Hz, Ar*H*), 8.24-8.19 (1H, m, Ar*H*), 5.62 (2H, s, CH_2), 4.32 (2H, q, *J*= 7.1 Hz, C$H_2$$CH_3$), 1.28 (3H, t, *J*= 7.1 Hz, CH_2CH_3); NMR δ_C (100 MHz, D_2O) 213.5 (C), 162.0 (C), 143.1 (CH), 134.8 (CH, d, *J*= 50 Hz), 129.6 (CH, d, *J*= 10 Hz), 122.6 (C), 68.4 (CH_2), 26.7 (CH_3); *m/z* (HRMS-ESI+) 184.0793 (M^+ $C_9H_{11}FNO_2{}^+$ requires 184.0768).

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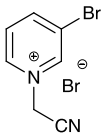
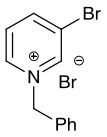
3-bromo-1-(cyanomethyl)pyridin-1-ium bromide 2m



Procedure A. Brown solid; 2.35 g (80 %); m.p. 171-173 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 3054, 2260, 1601, 1239, 944; NMR δ_H (400 MHz, DMSO) 9.90 (1H, s, Ar*H*), 9.44 (1H, d, *J*= 6.1 Hz, Ar*H*), 9.02 (1H, app d, *J*= 8.5 Hz, Ar*H*), 8.24 (1H, dd, *J*= 8.5, 6.1 Hz, Ar*H*), 6.28 (2H, s, C*H*$_2$); NMR δ_C (100 MHz, DMSO) 149.7 (CH), 146.9 (CH), 144.5 (CH), 129.1 (CH), 122.1 (C), 114.0 (C), 47.2 (CH_2), 61.0 (CH_2), 13.2 (CH_3); *m/z* (HRMS-ESI+) 198.9713 (M^+ $C_7H_6N_2{}^{79}Br^+$ requires 198.9689), 196.9724 (M^+ $C_7H_6N_2{}^{81}Br^+$ requires 245.9948).

1-benzyl-3-bromopyridin-1-ium bromide 2n



Procedure A. white solid; 5.21 g (84 %); m.p. 150-152 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 3071, 3048, 2948, 1602, 1483, 1240, 1156, 1029; NMR δ_H (400 MHz, DMSO) 9.76 (1H, s, Ar*H*), 9.26 (1H, d, *J*= 6.1 Hz, Ar*H*), 8.93-8.89 (1H, m, Ar*H*), 8.13 (1H, dd, J= 8.4, 6.1, Ar*H*), 7.64-7.59 (2H, m, Ar*H*), 7.48-7.41 (3H, m, Ar*H*), 5.88 (2H, s, C*H*$_2$); NMR δ_C (100 MHz, DMSO) 148.3 (CH), 145.9 (CH), 143.7 (CH), 133.8 (C), 129.4 (CH), 129.5 (CH), 129.1 (CH), 129.0 (CH), 122.3 (C), 63.2 (CH_2); *m/z* (HRMS-ESI+) 248.0074 (M^+ $C_{12}H_{11}N^{79}Br^+$ requires 248.0070), 250.0052 (M^+ $C_{12}H_{11}N^{81}Br^+$ requires 250.0049).

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3. General Procedure for preparation of cycloadducts:

Base (2 equiv.) was added to substituted pyridinium salt (2 equiv.) in dry solvent, under argon and the mixture stirred at room temperature for 5 mins, followed by the addition of oxindole (1 equiv.). The reaction mixture was stirred at room temperature until reaction was complete by TLC analysis. Water was added and the organic layer separated, washed with water (2x), brine, dried over Na_2SO_4, filtered and evaporated. The crude products were purified *via* column chromatography ($MeOH/CH_2Cl_2$; 1/10 or EtOAc/Petrol; 1/1) or recrystallised with ethanol.

References for previously described compounds:

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1b: Malhotra, S., Balwani, S., Dhawan. A., Singh. B. K. et. al. *Med. Chem. Commun*., **2011**, *2*, 743-751

1e: Long, D. R.; *J. Het. Chem.*, **1978**, *15*, 633-6.

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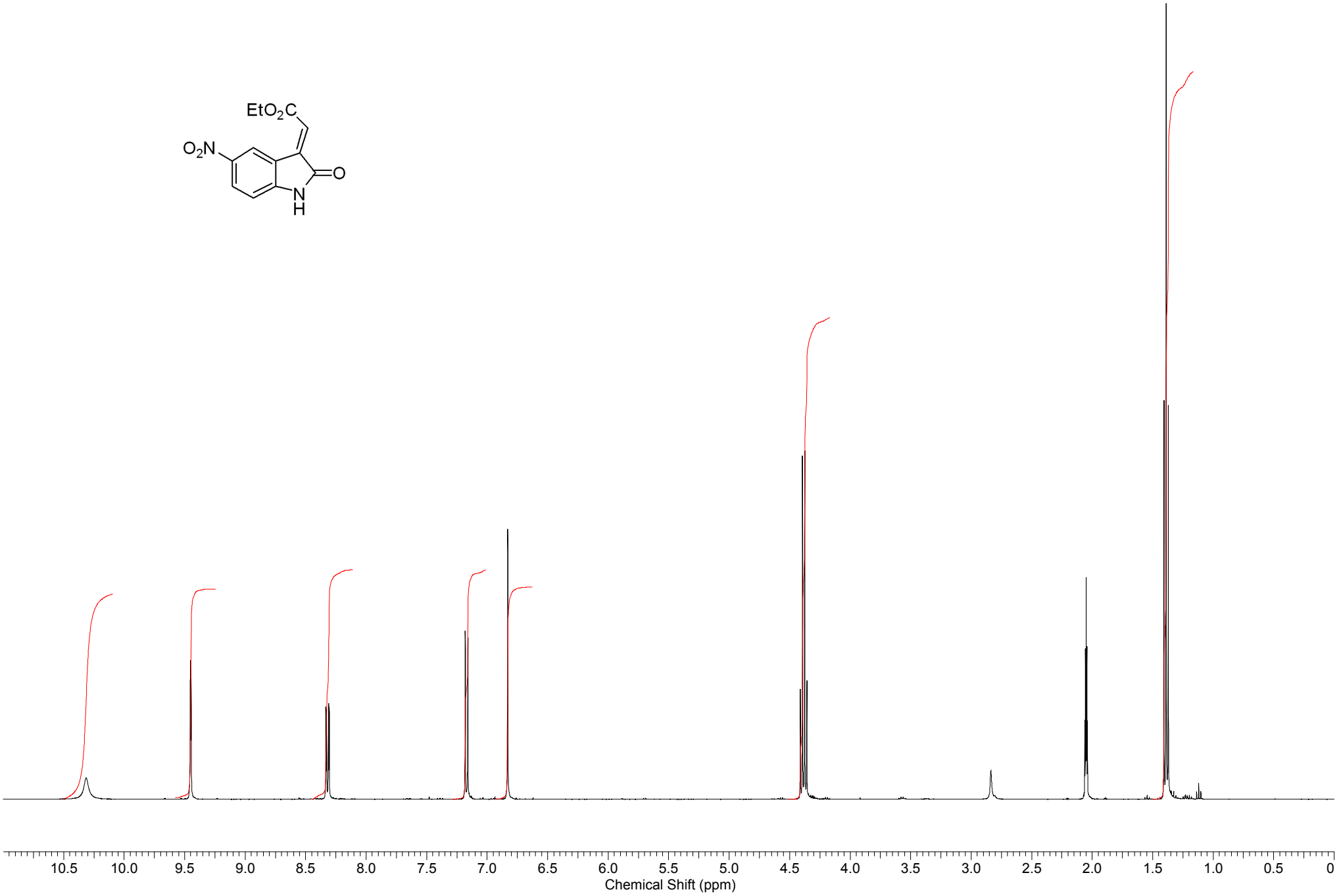
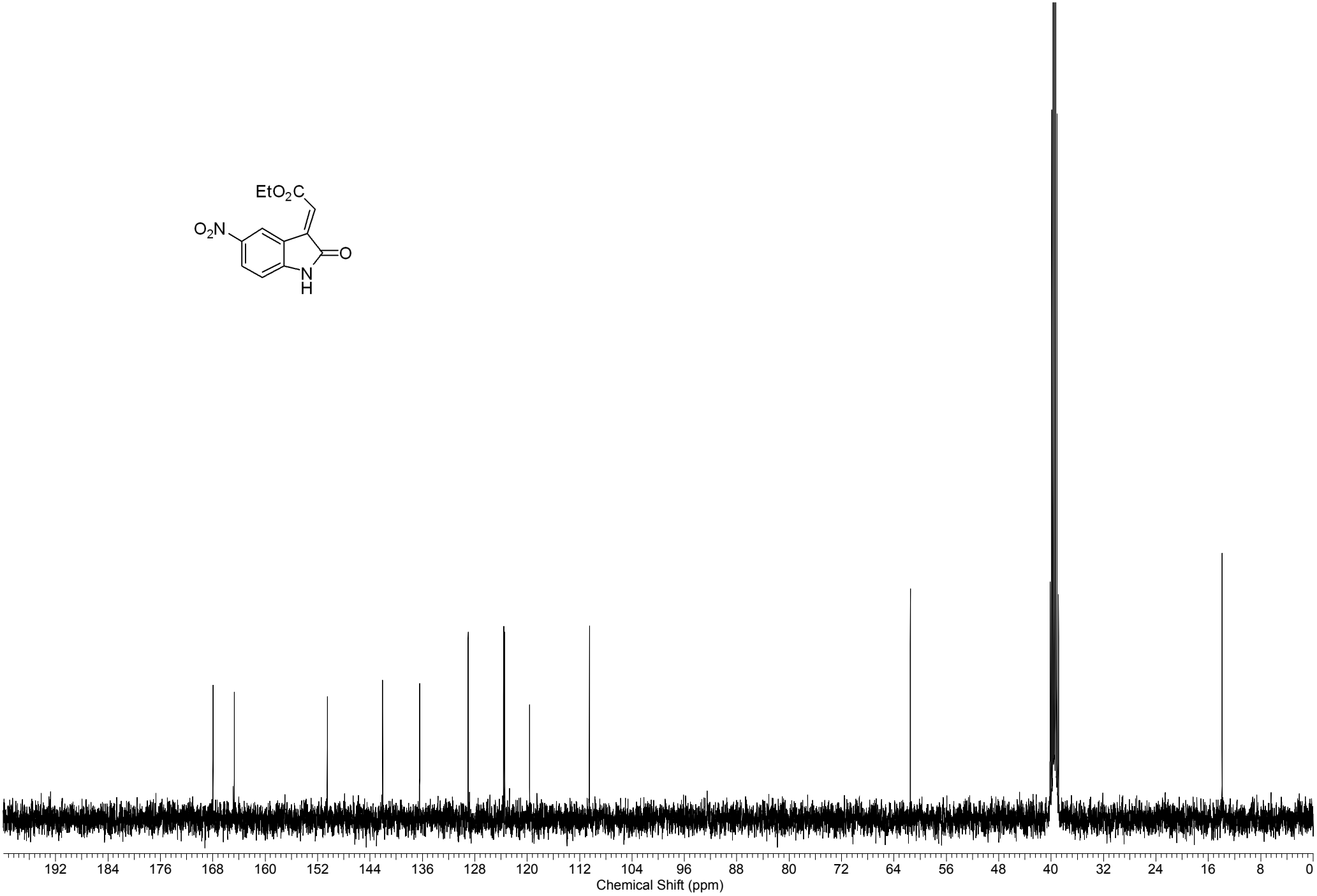
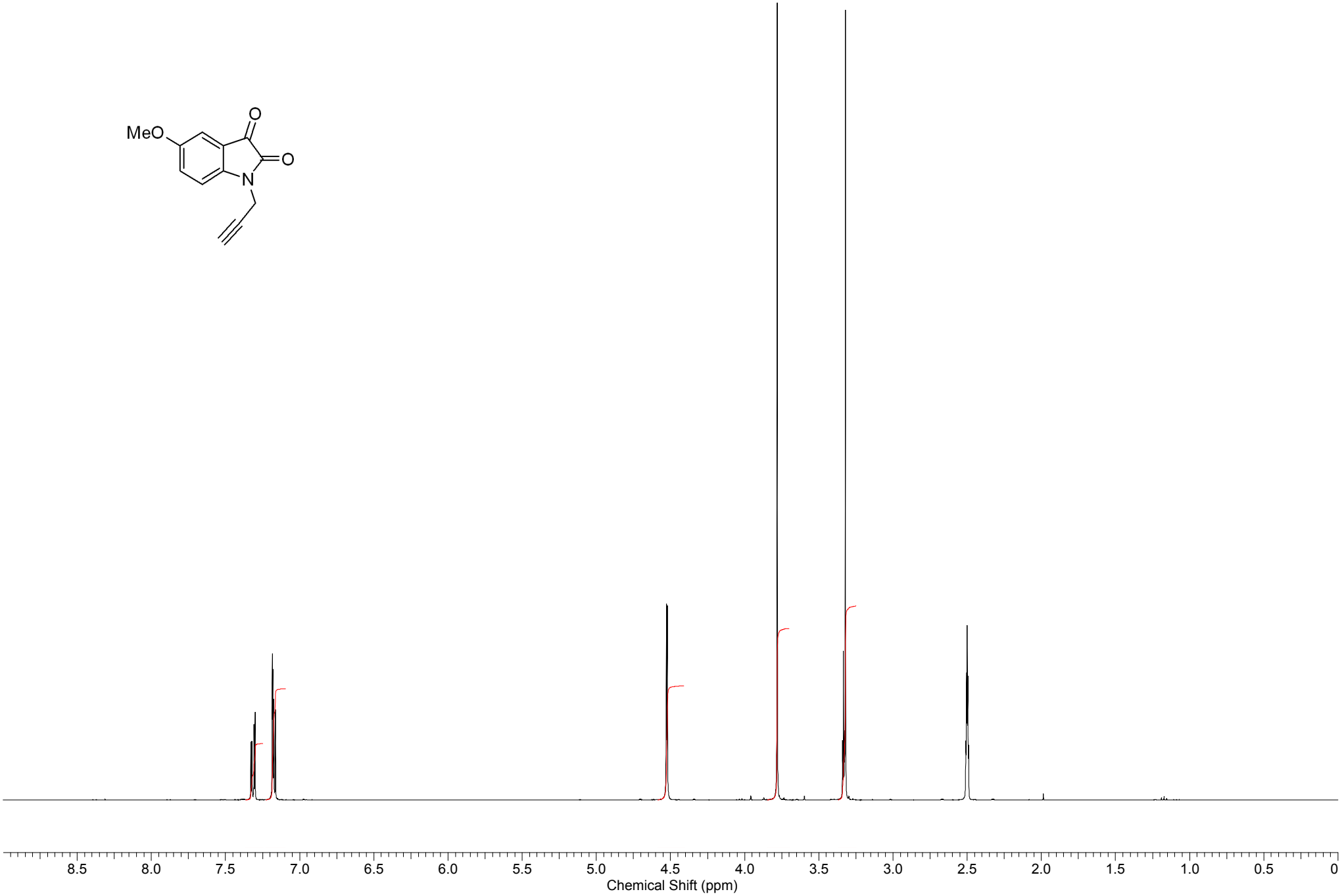
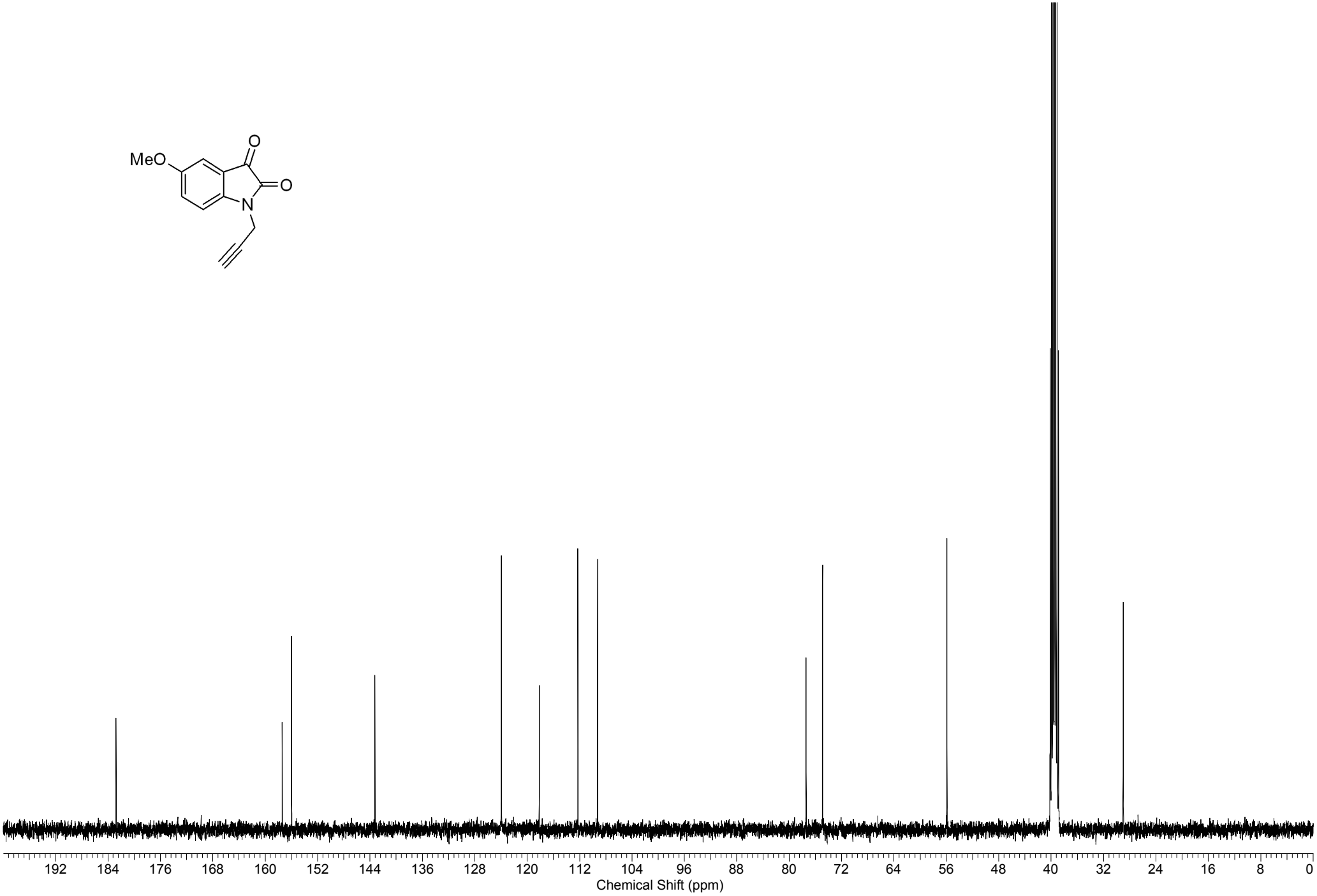
2h: Delaine, T.; Bernardes-Genisson, V.; Meunier, B.; Bernadou, J. *J. Org. Chem.* **2007**, *72*, 675-678.

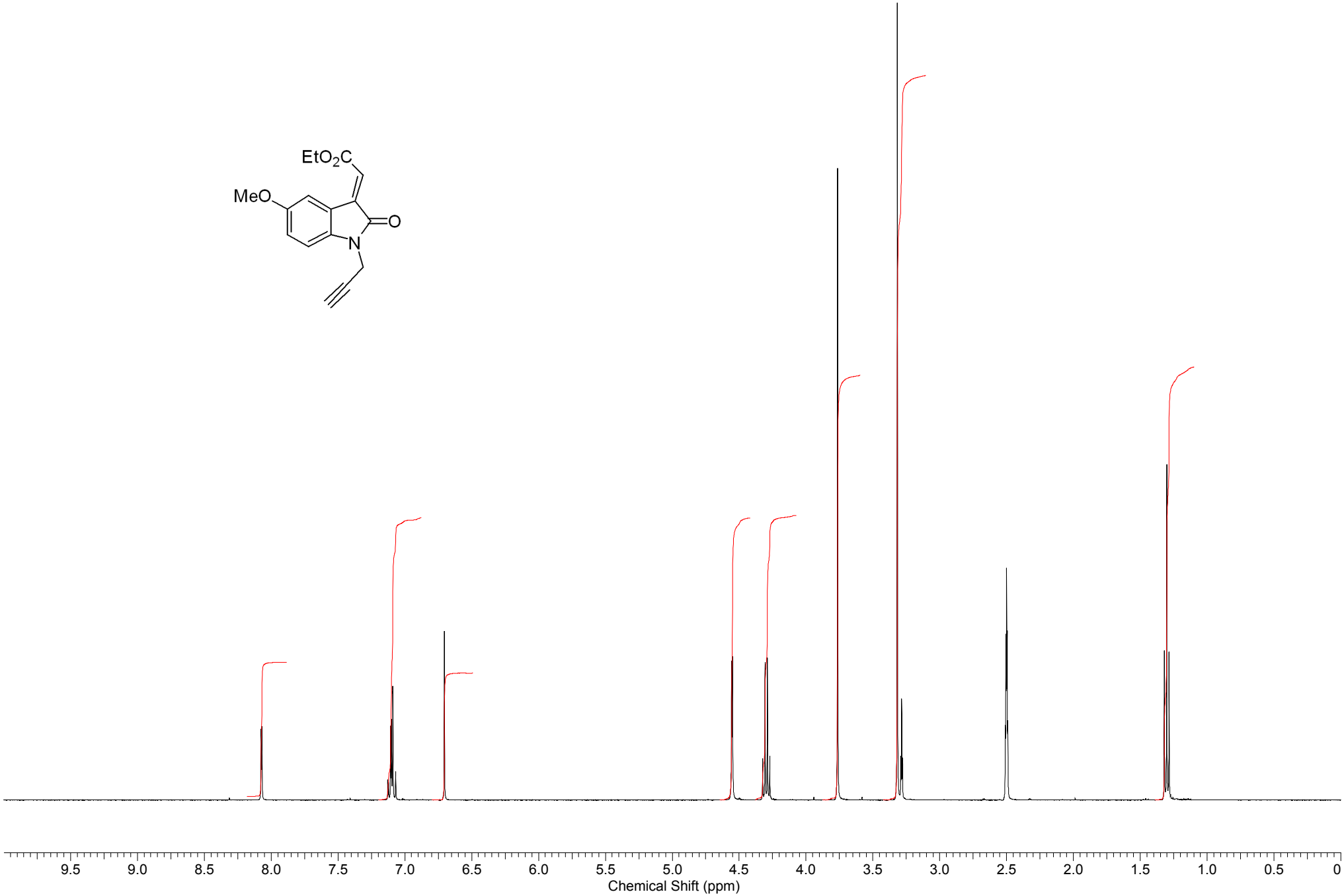
2l: Katritzky, A. R.; Grzeskowiak, N. E.; Alvarezbuilla, J. *J. Chem. Soc.-Perkin Trans. 1* **1981**, 1180-1185.

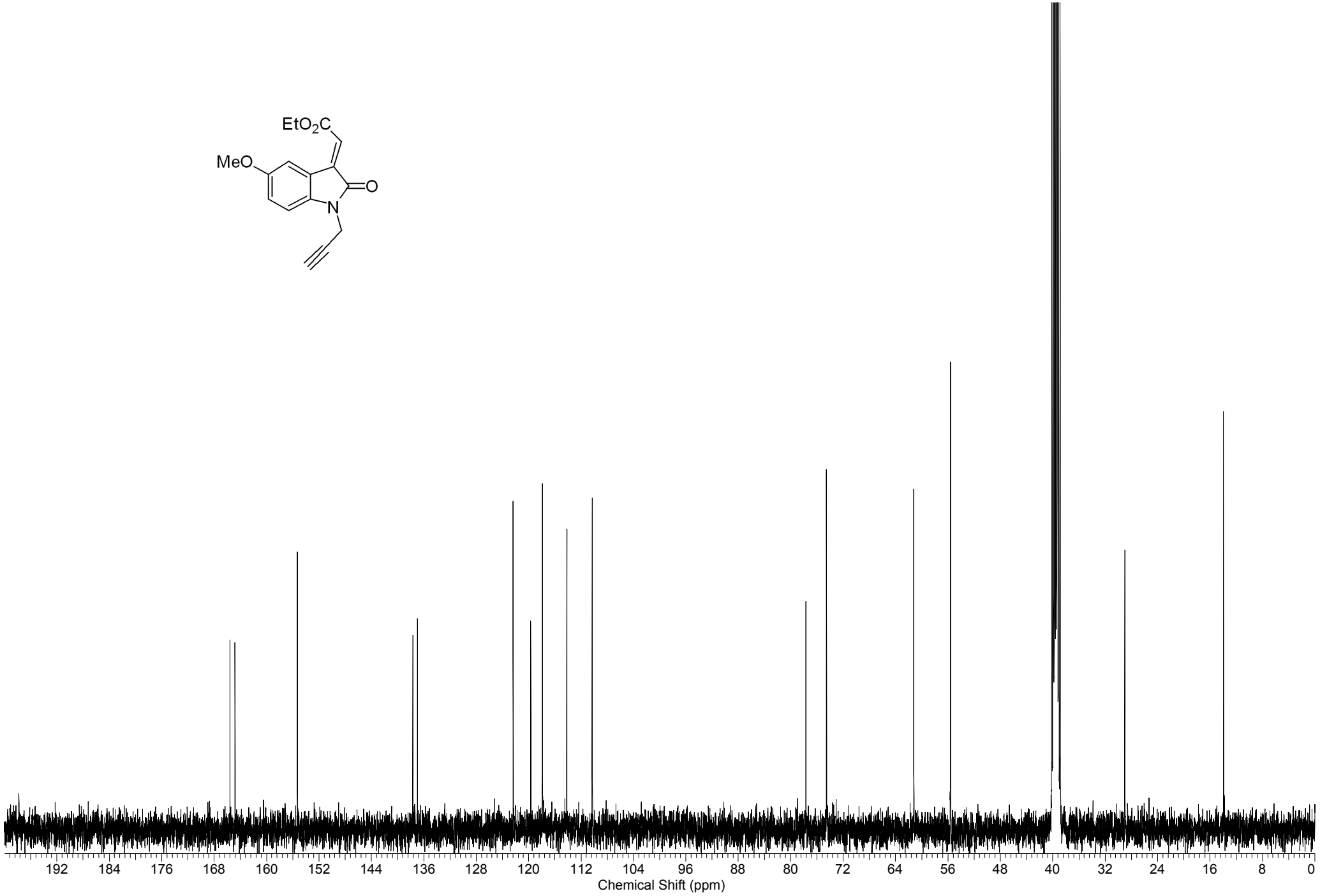


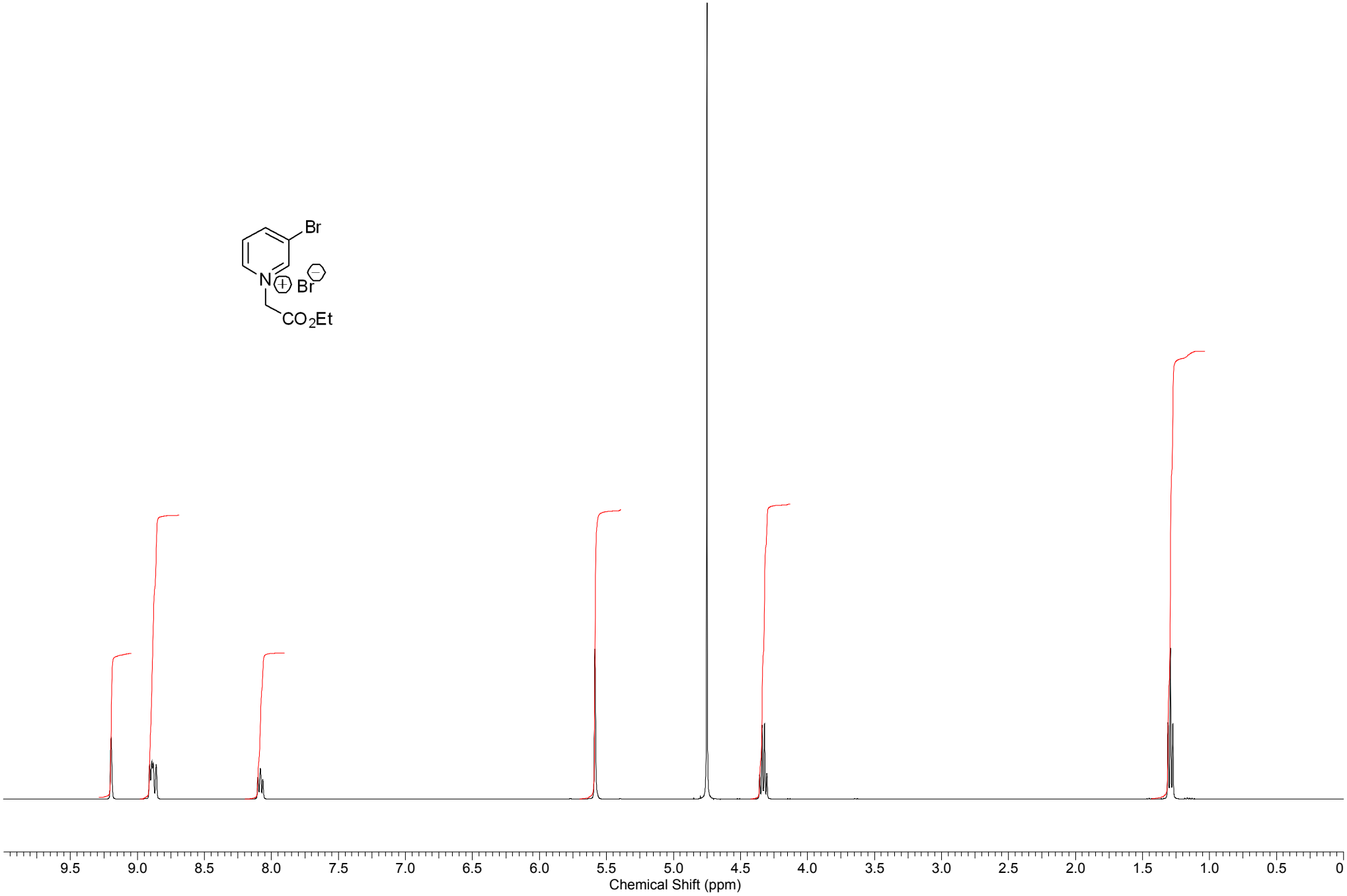


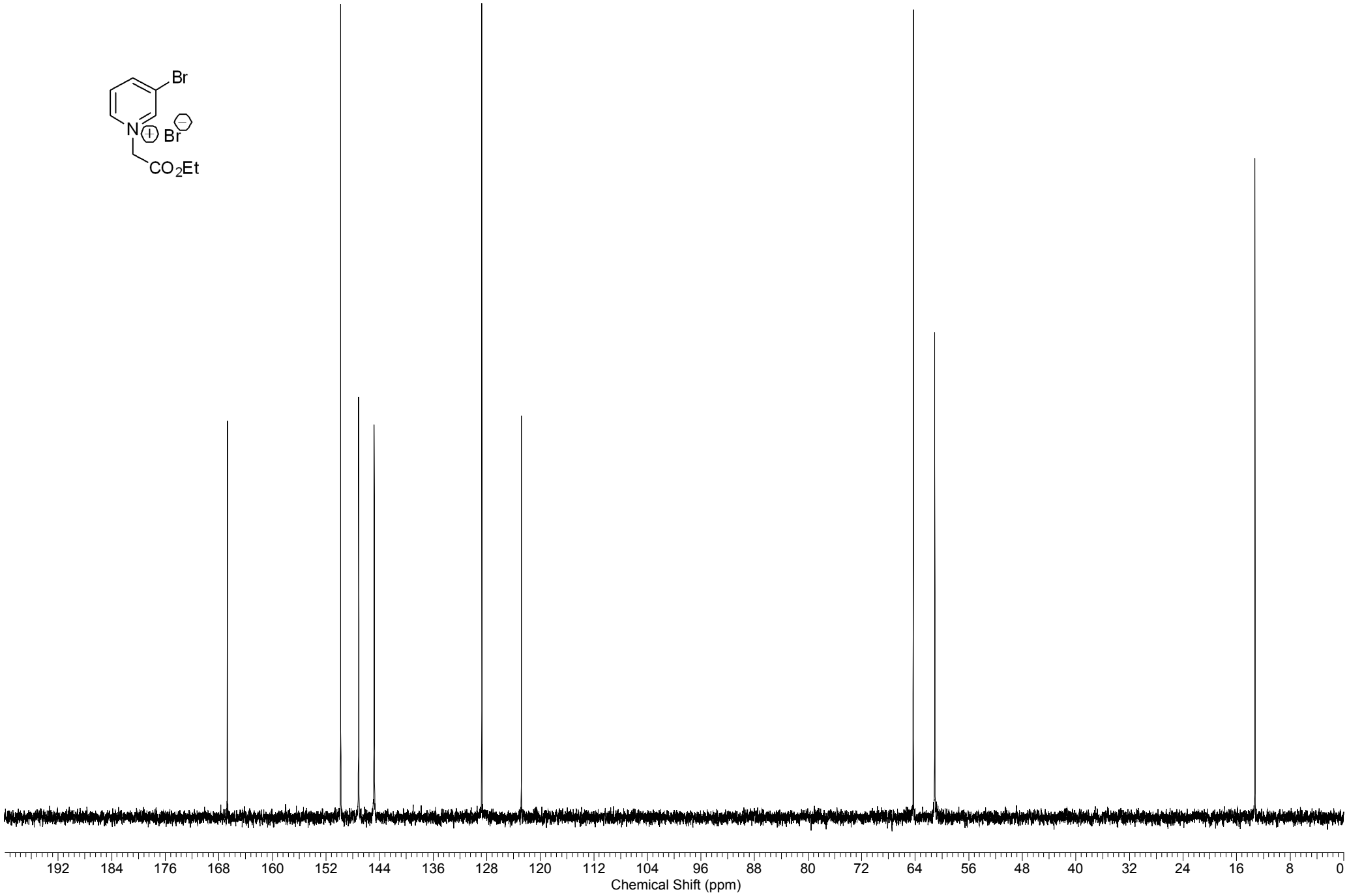


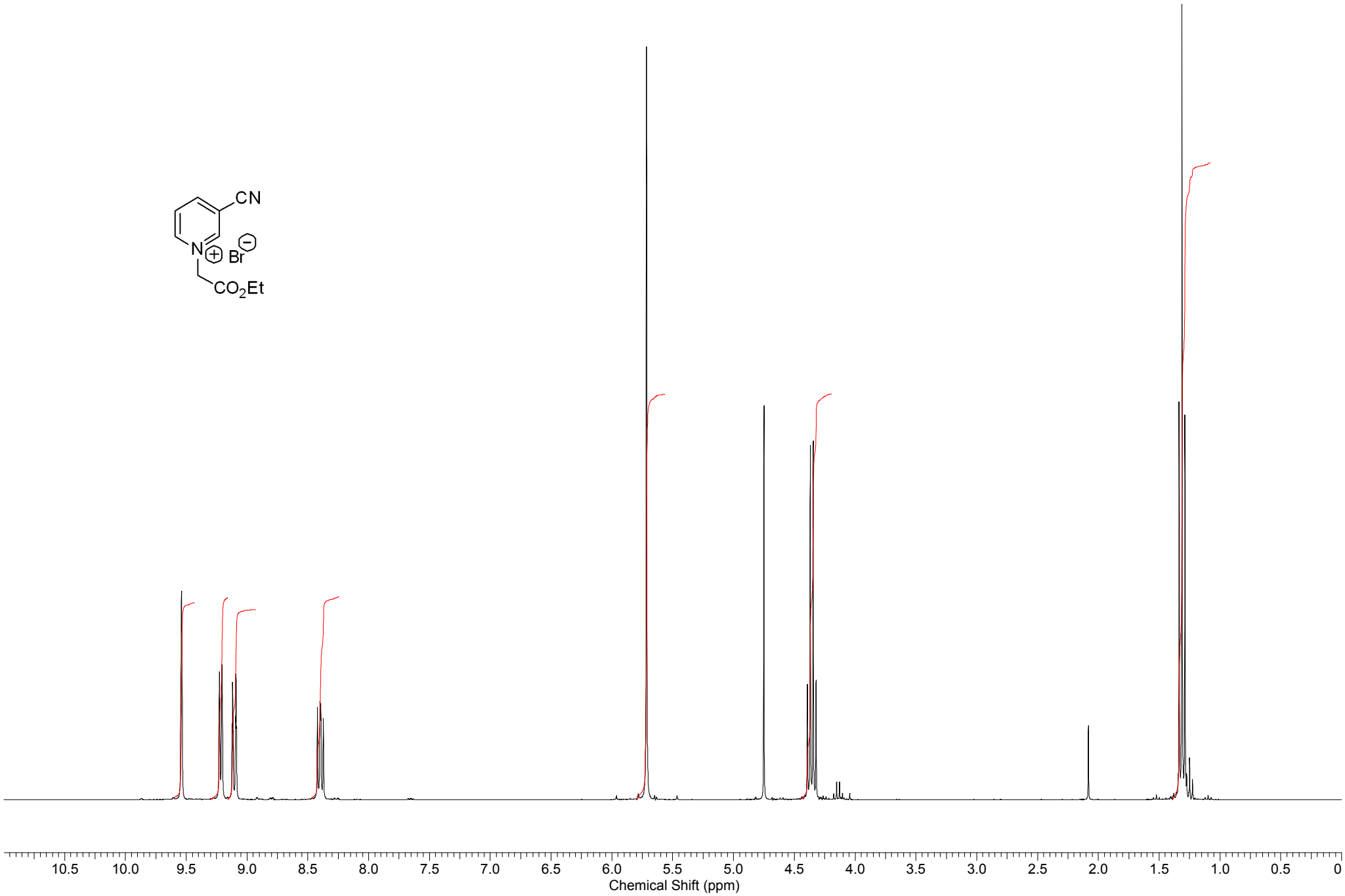


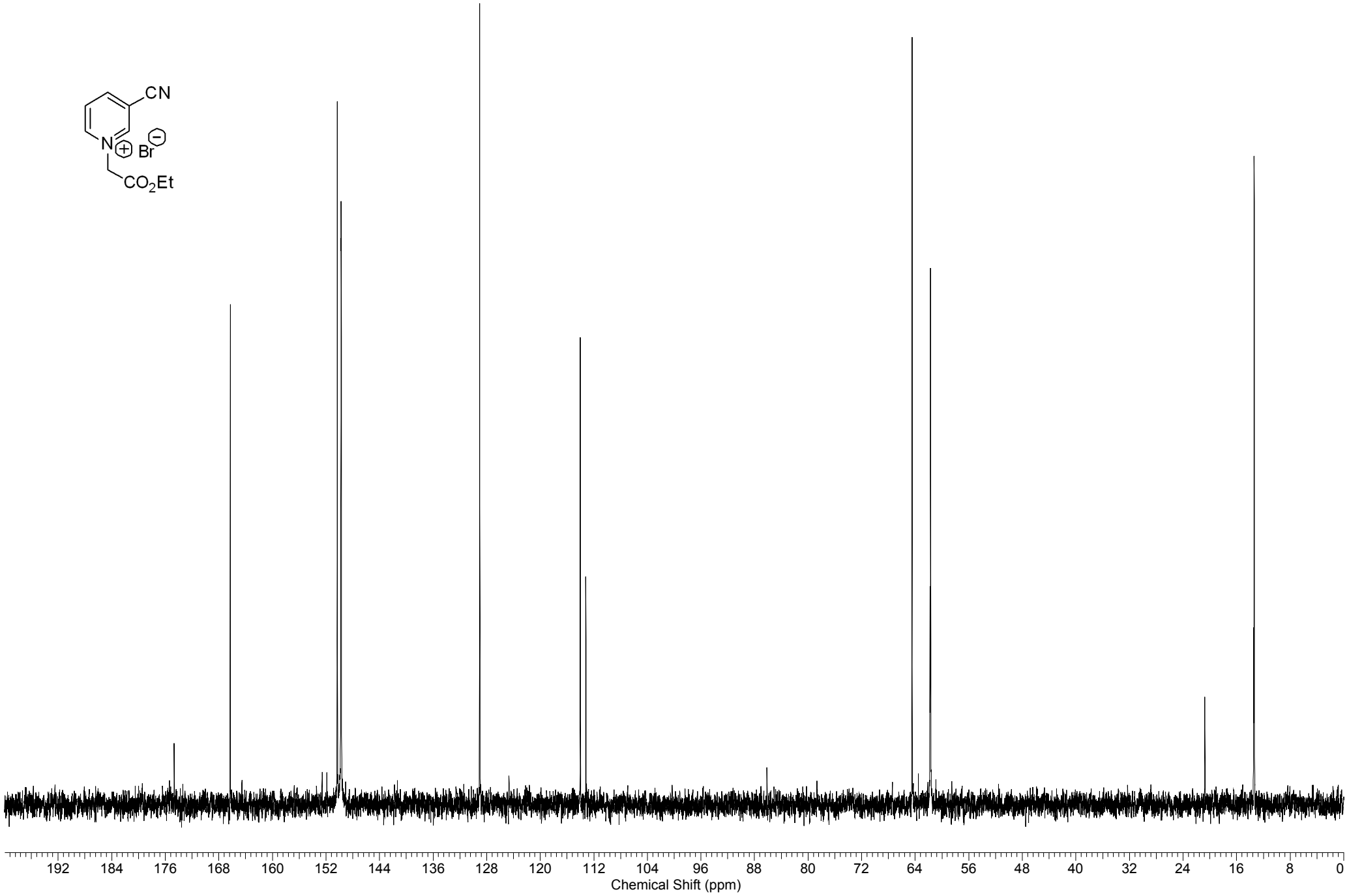


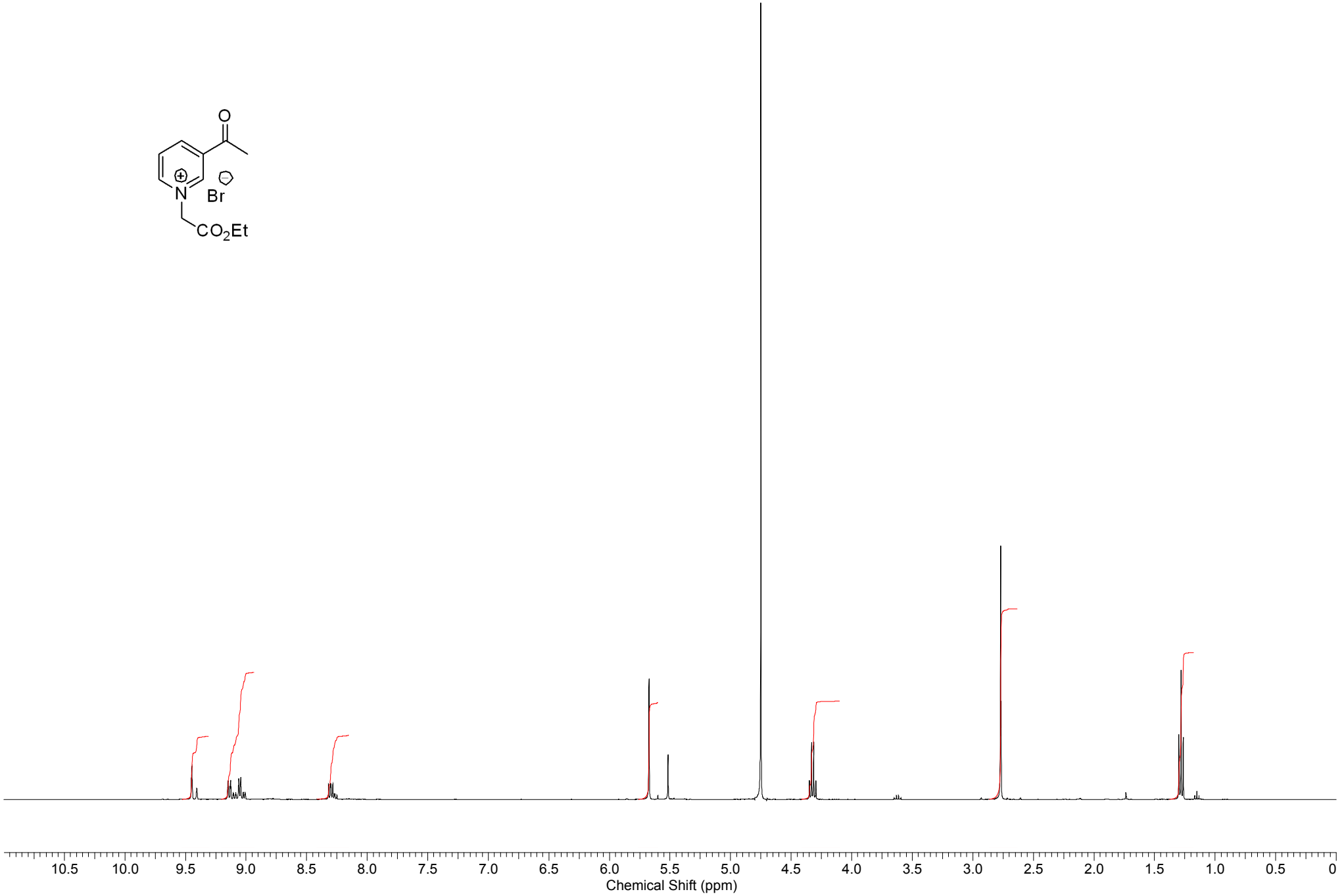


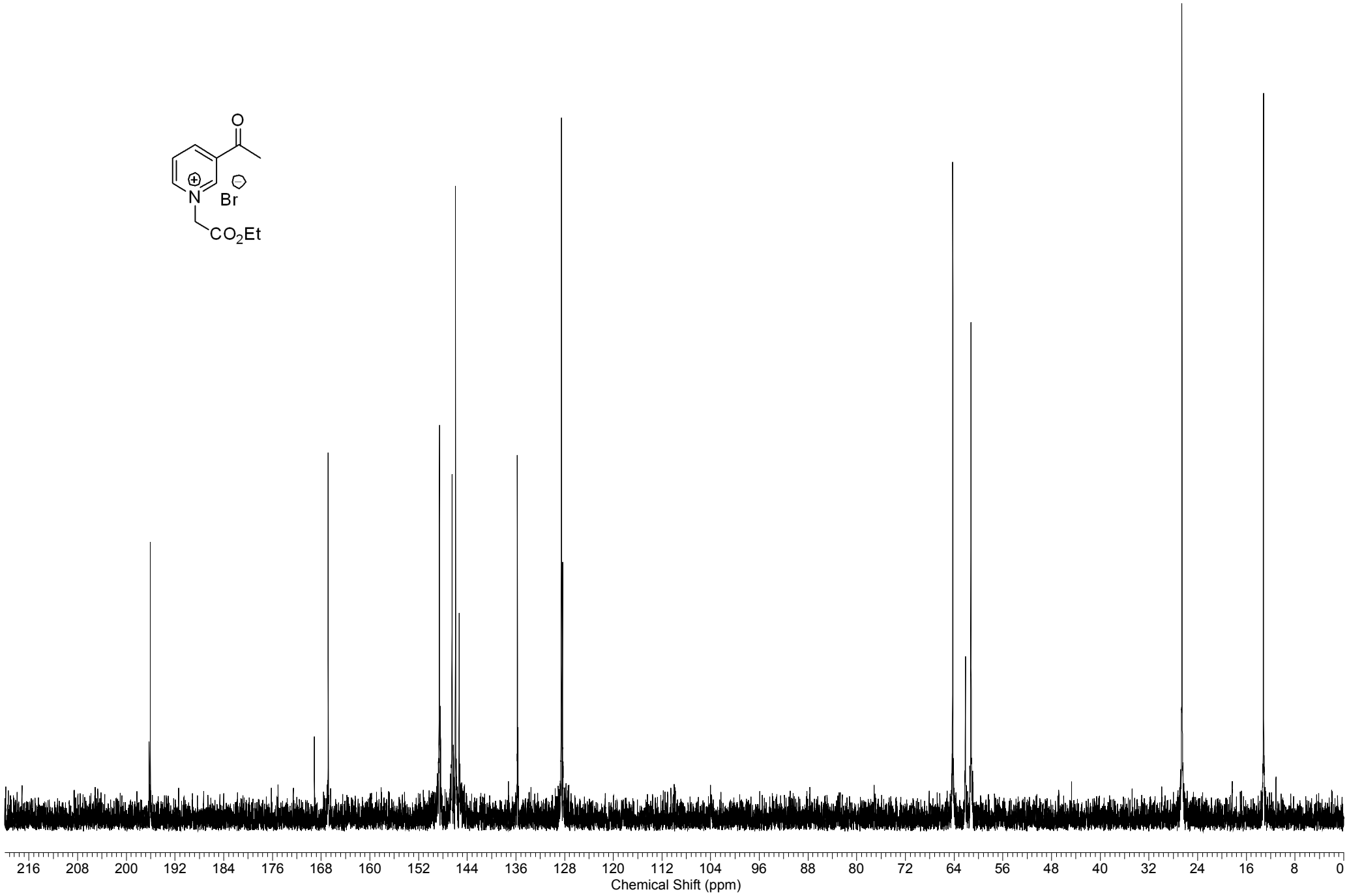


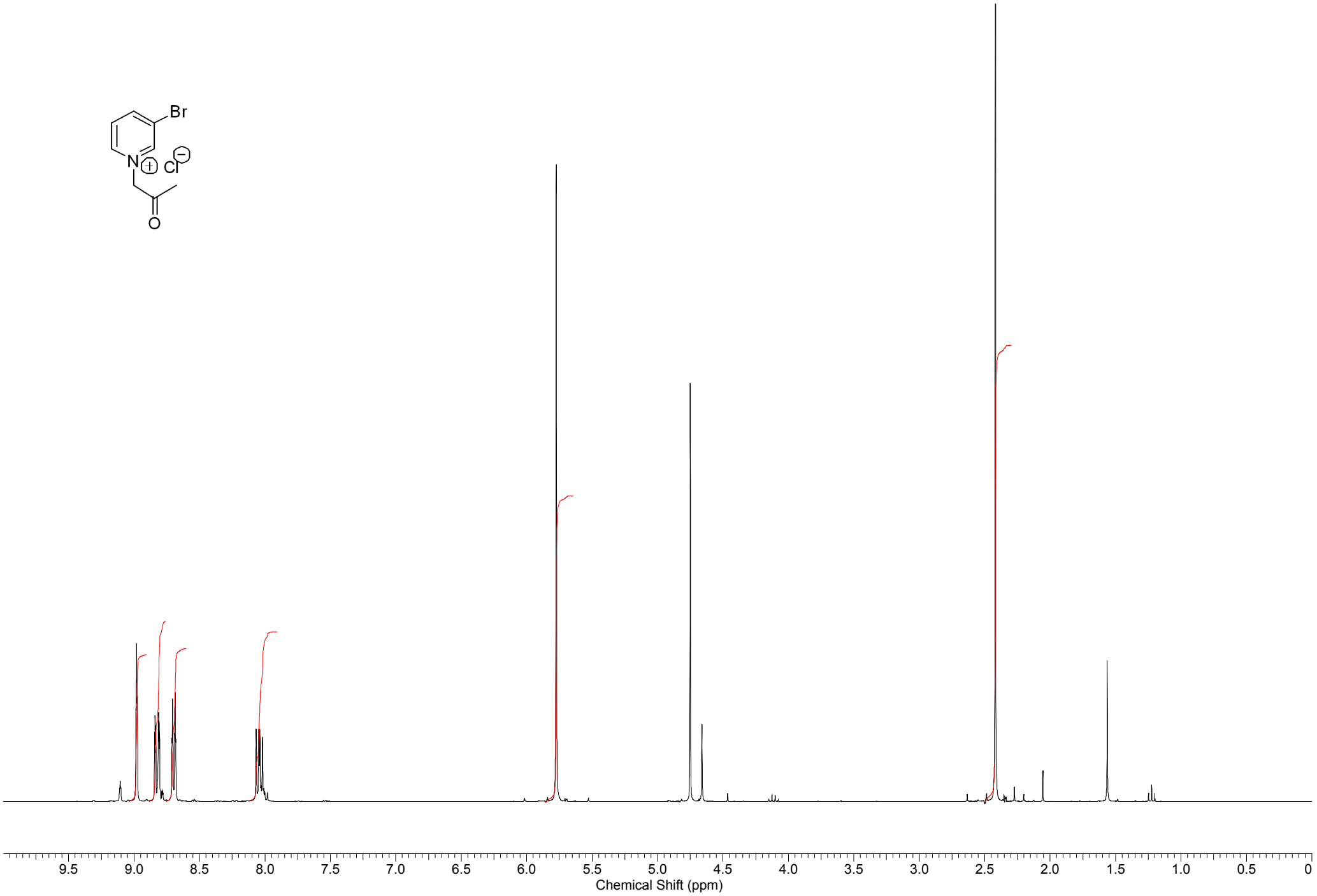


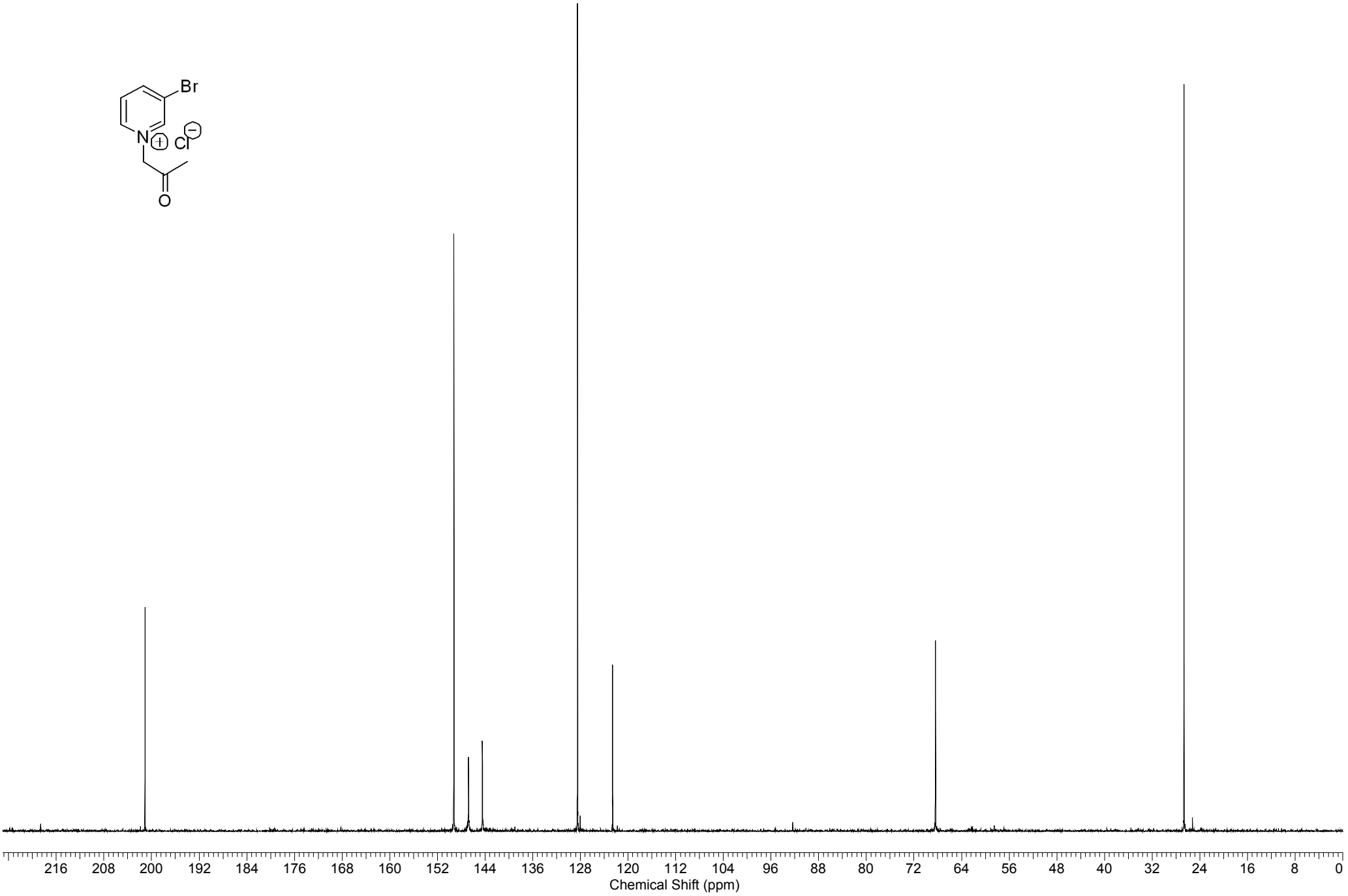


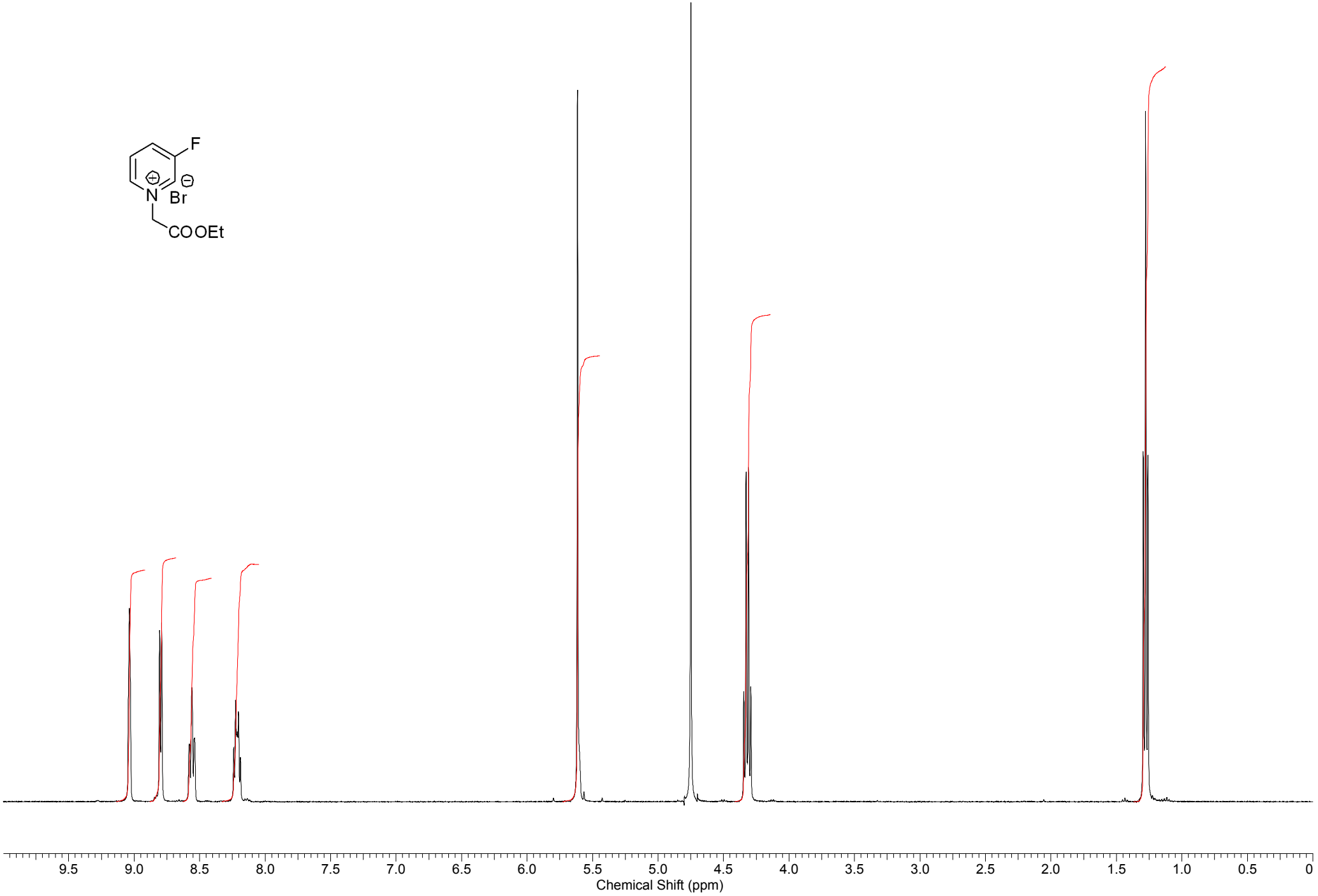


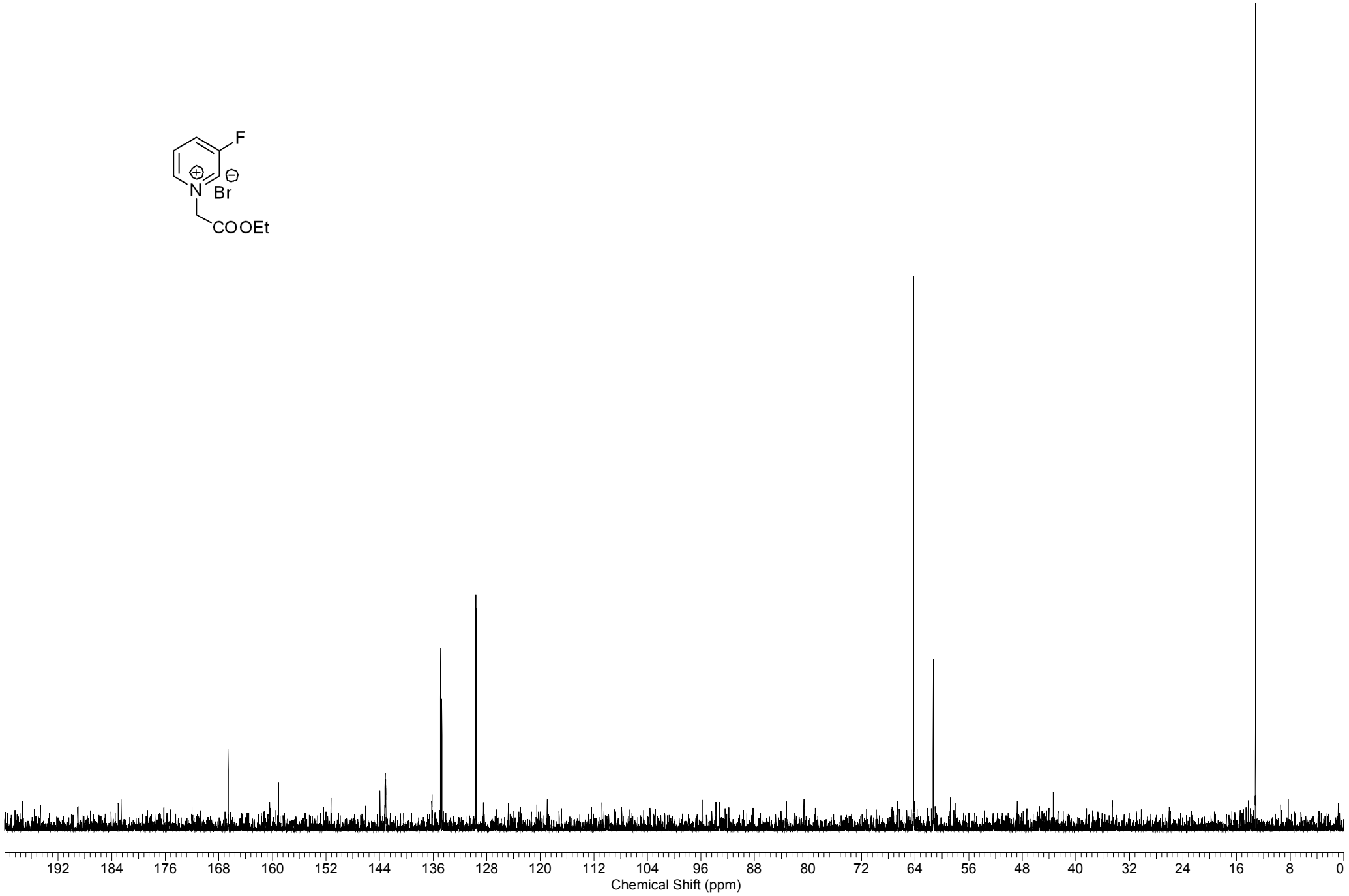


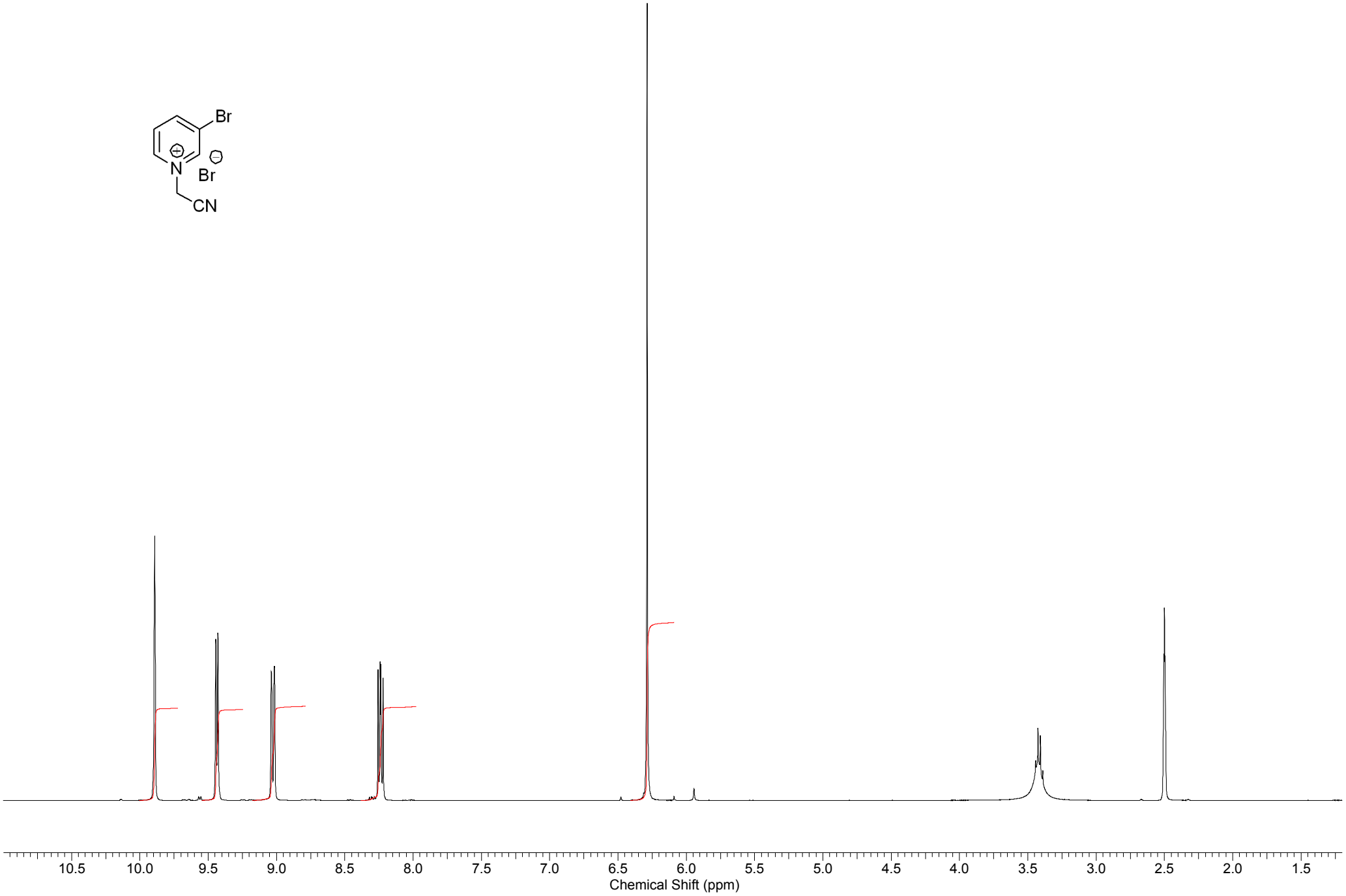


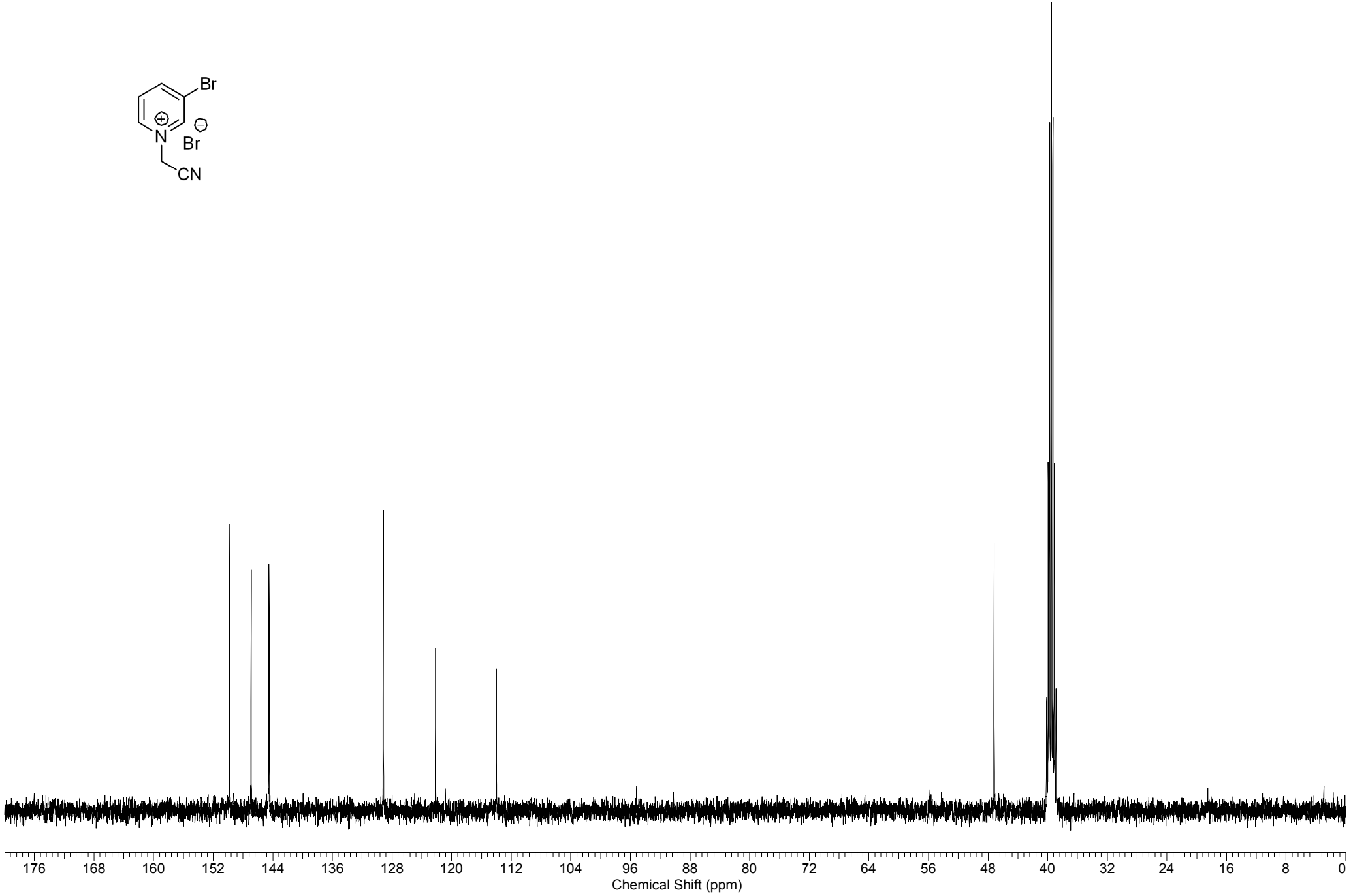


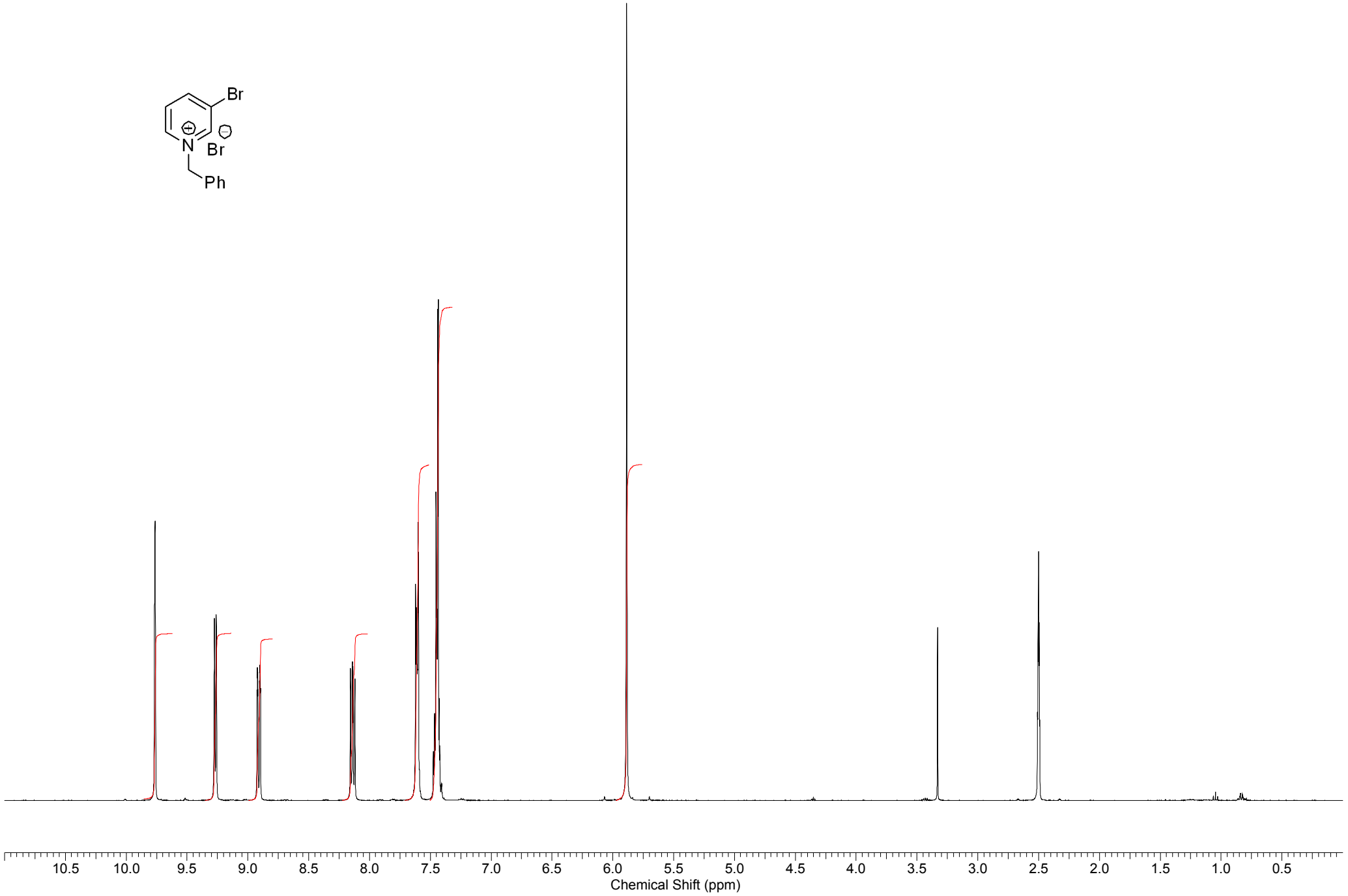


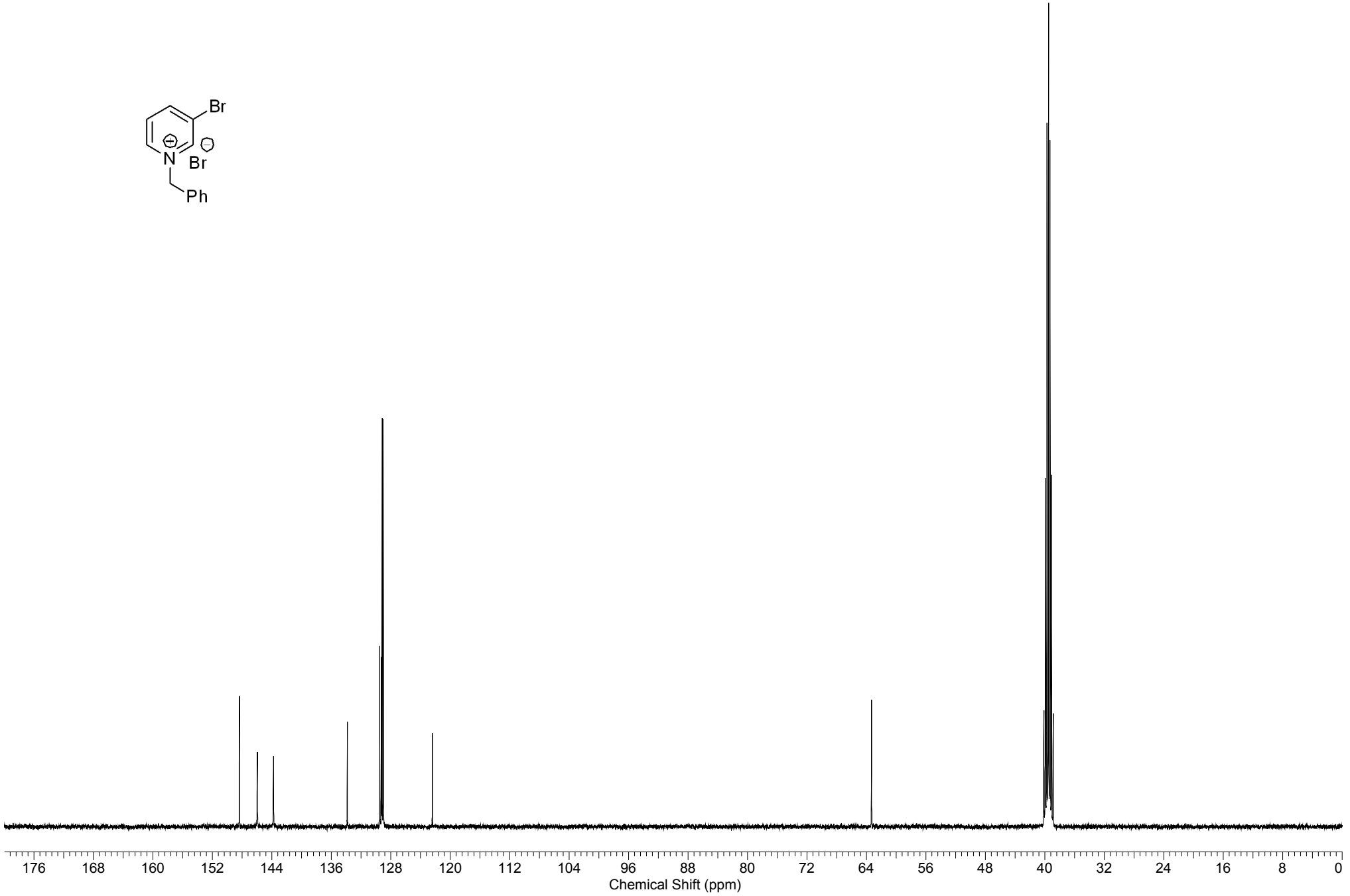


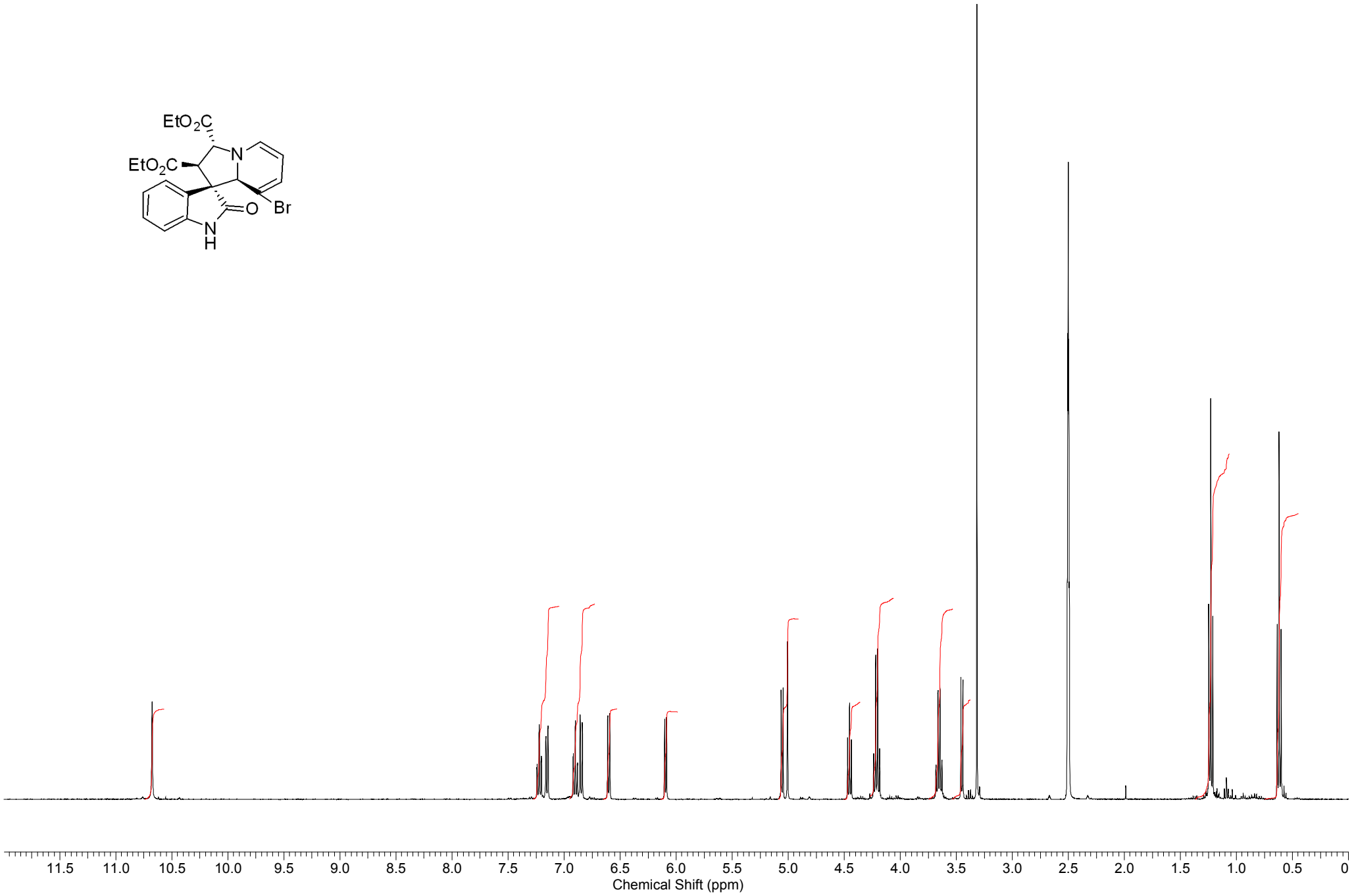


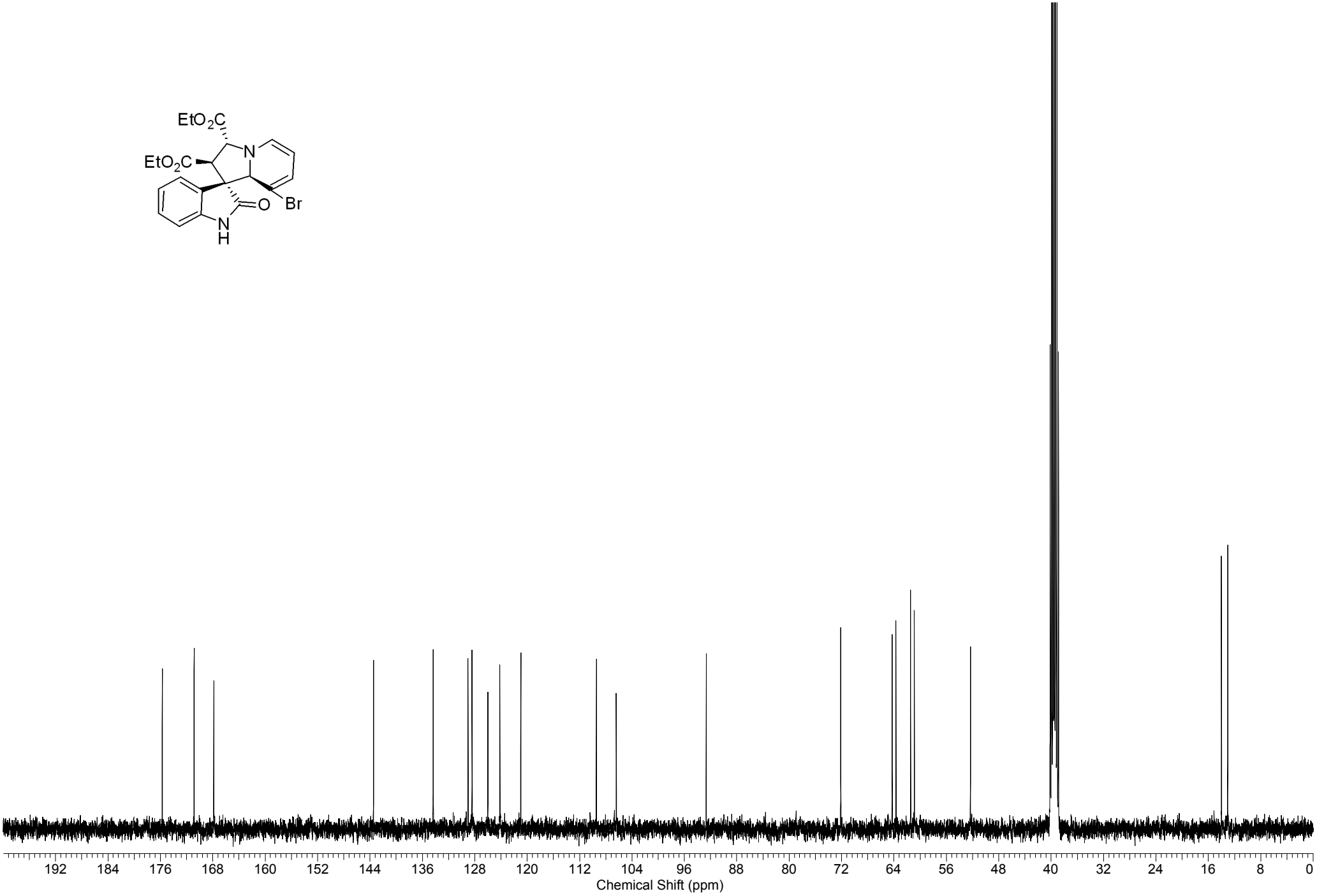


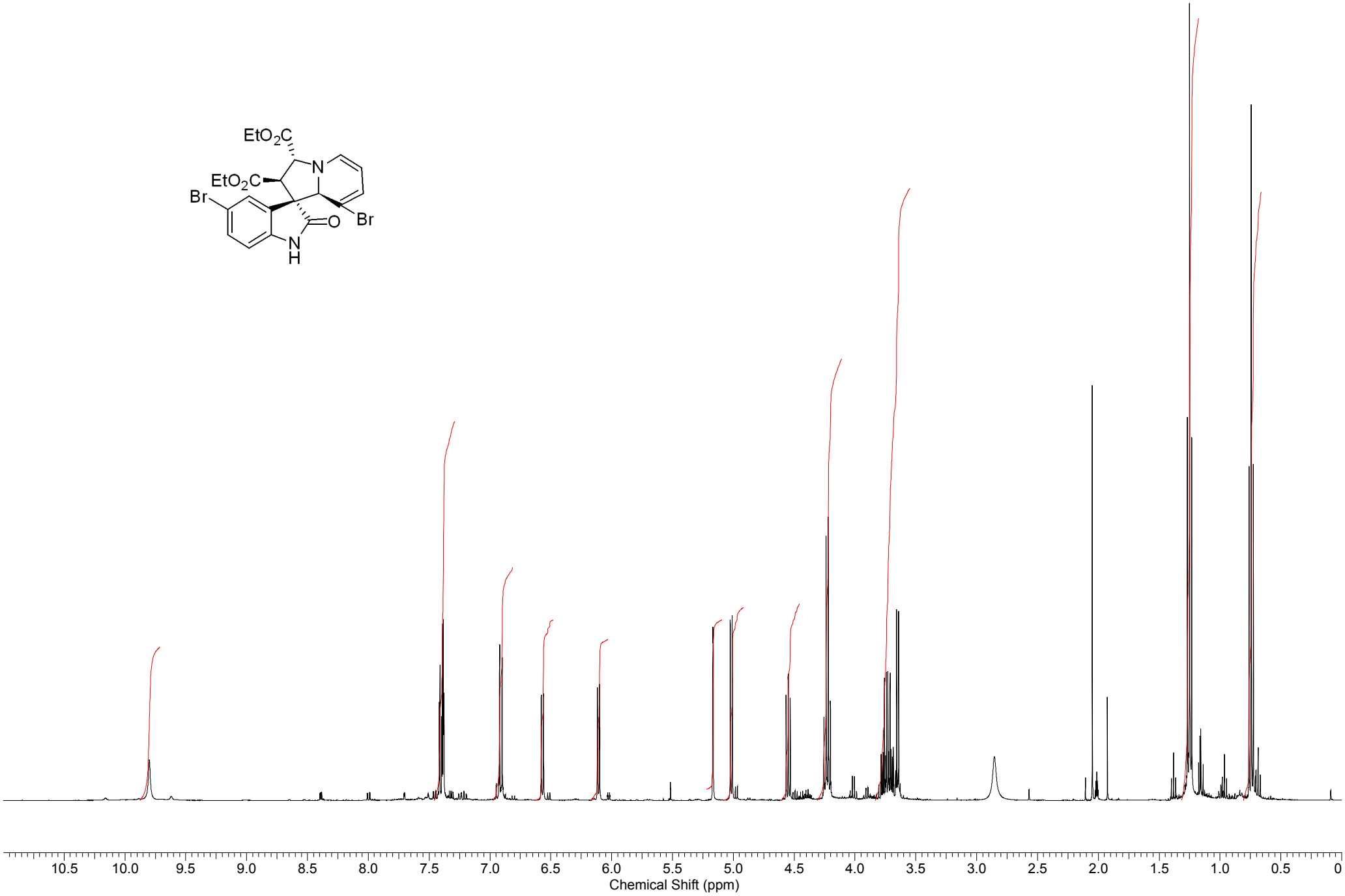


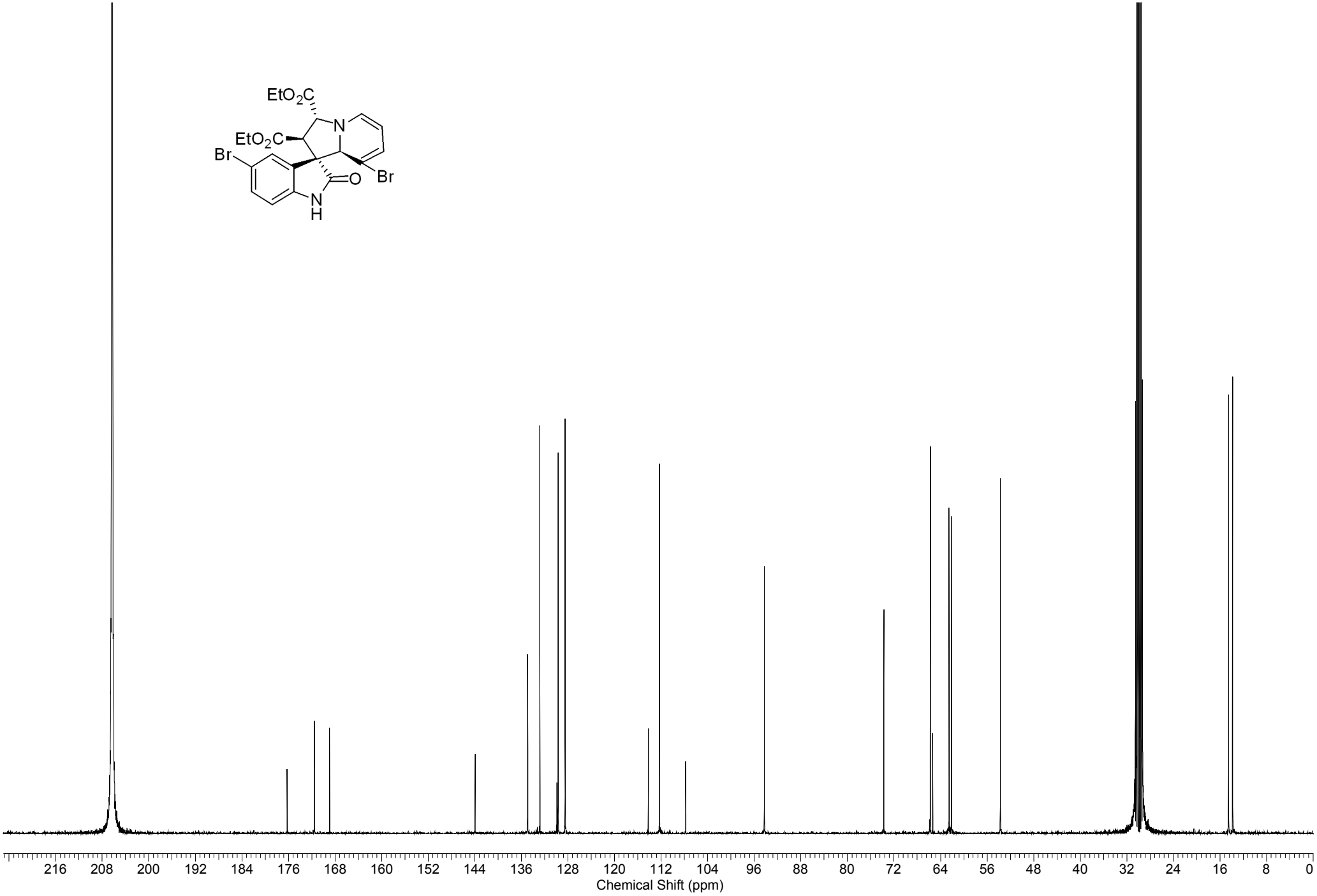


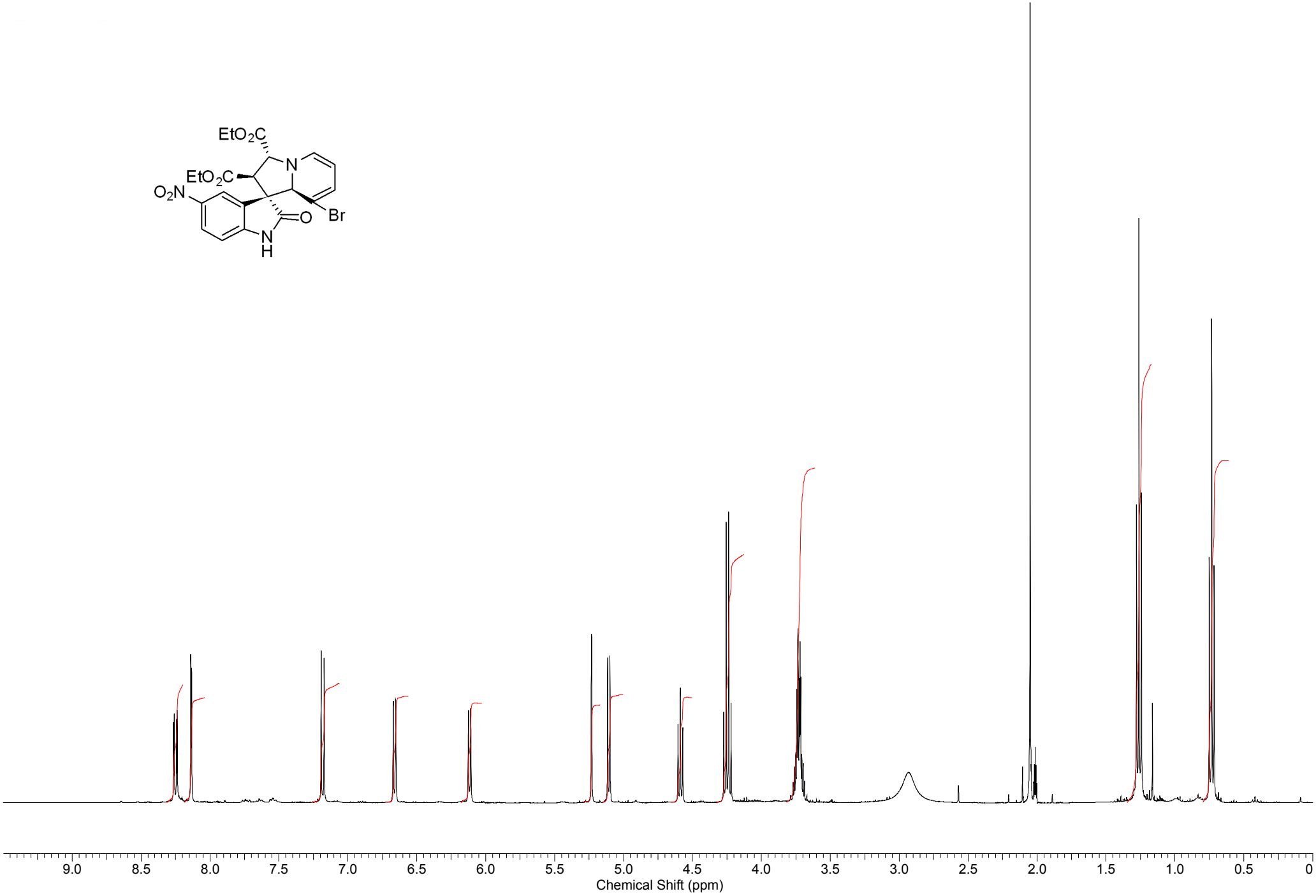


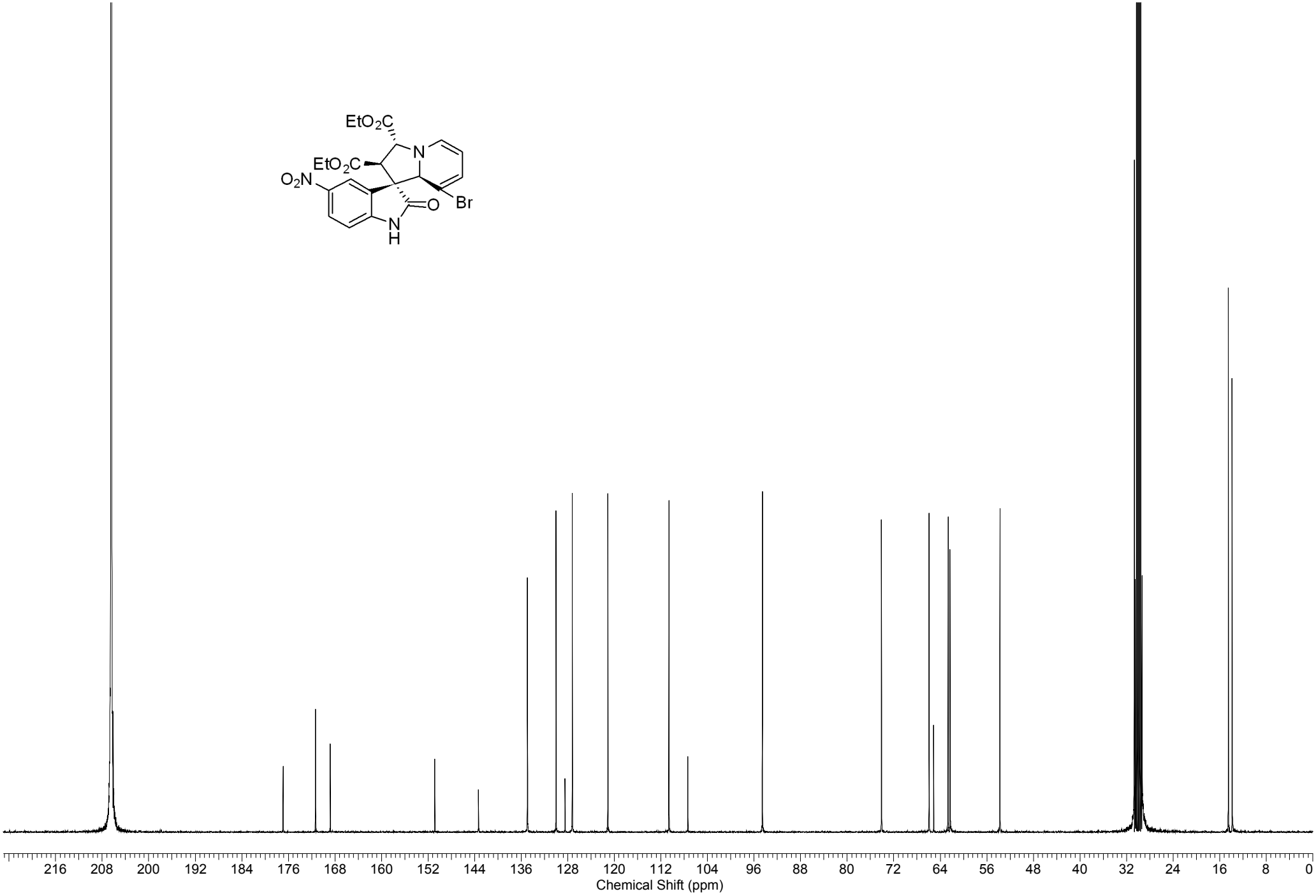


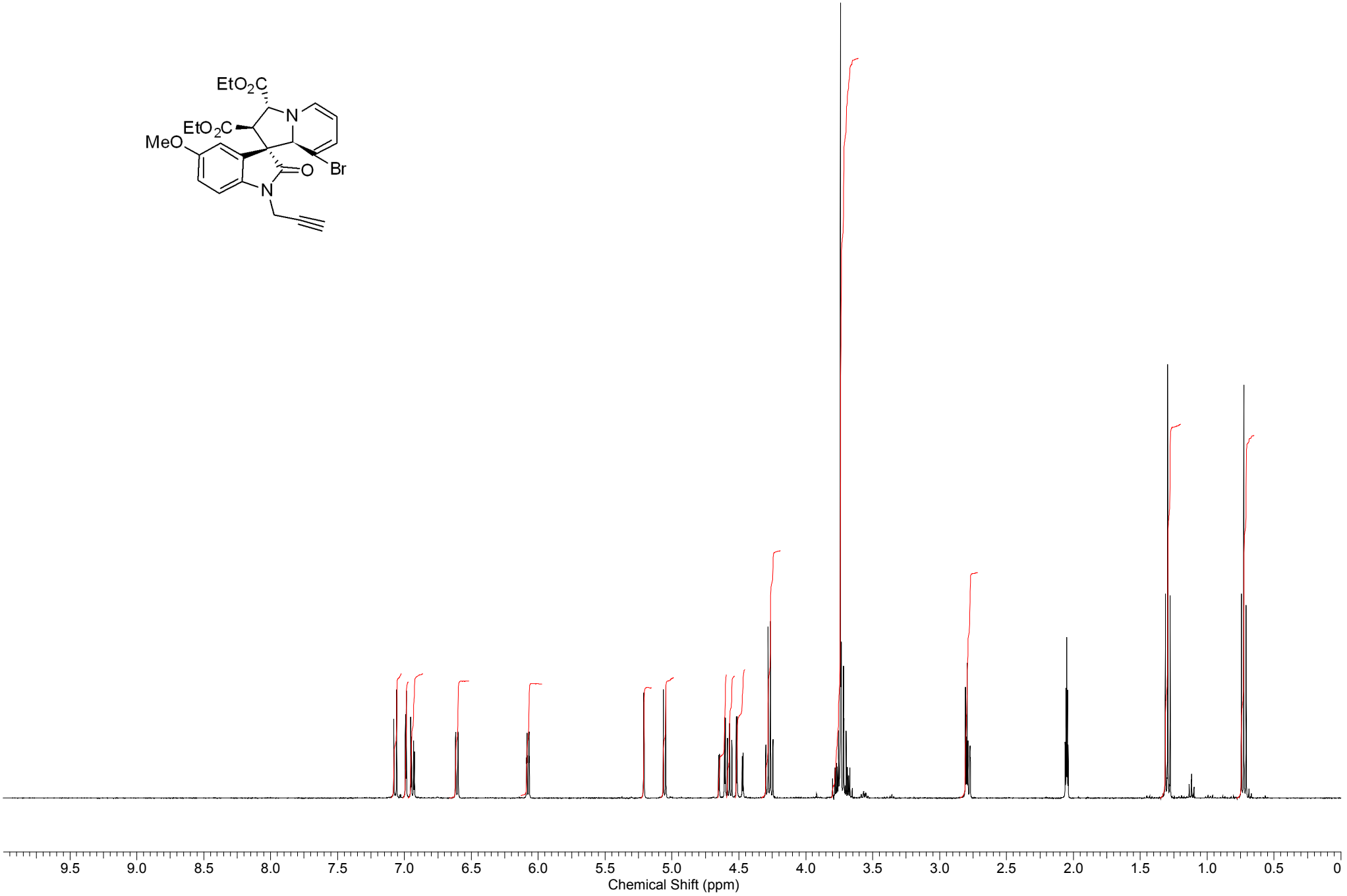


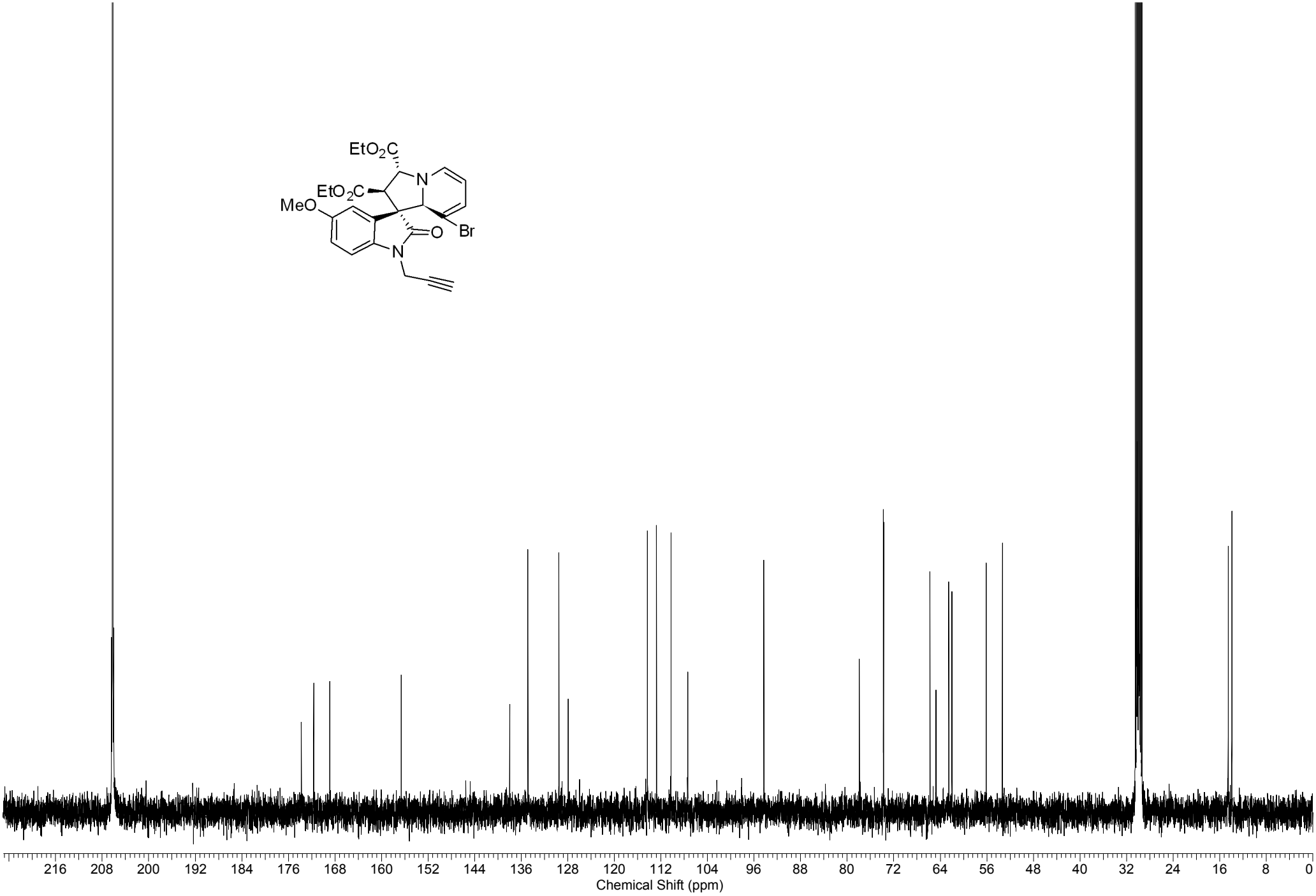


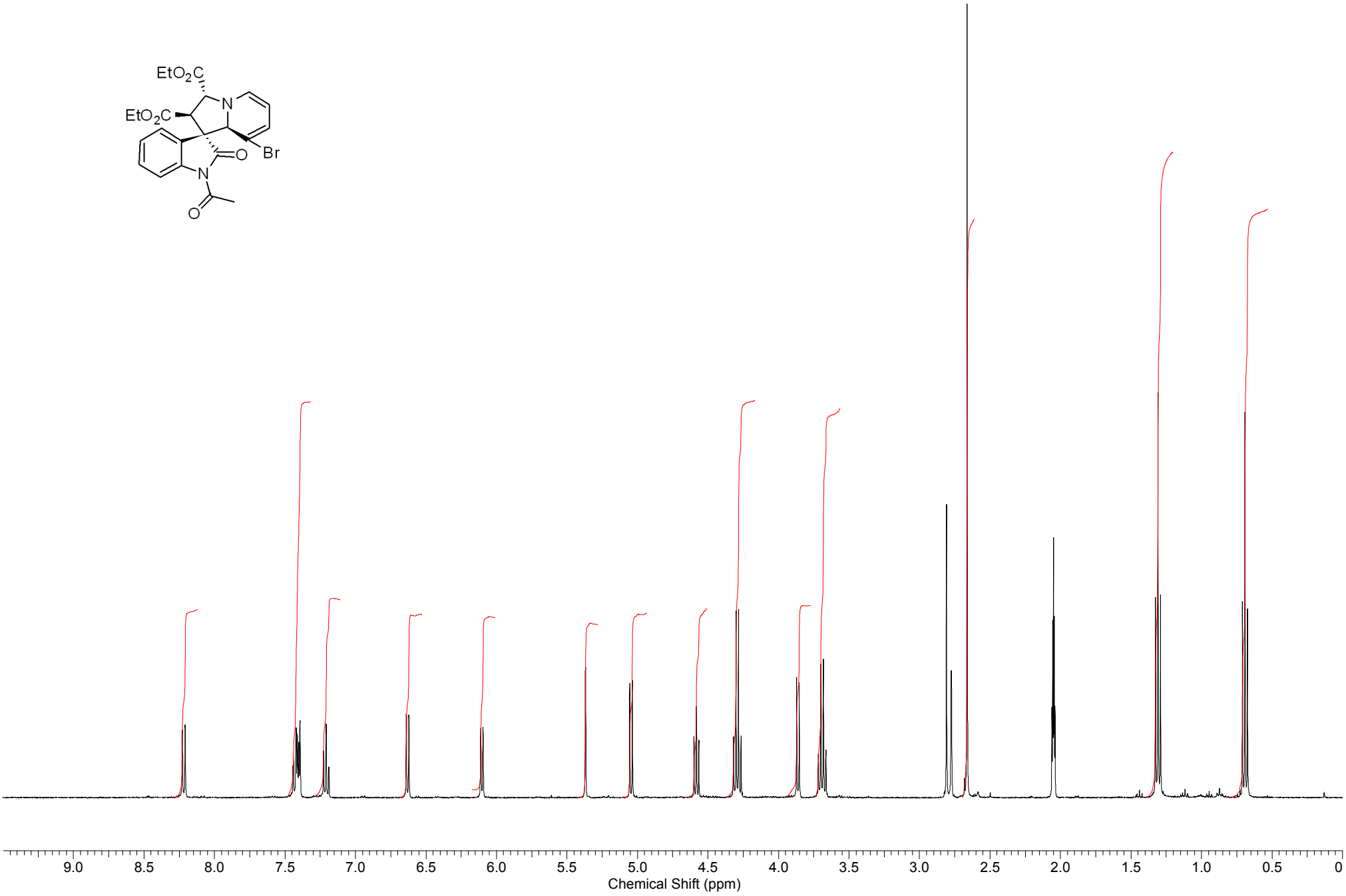


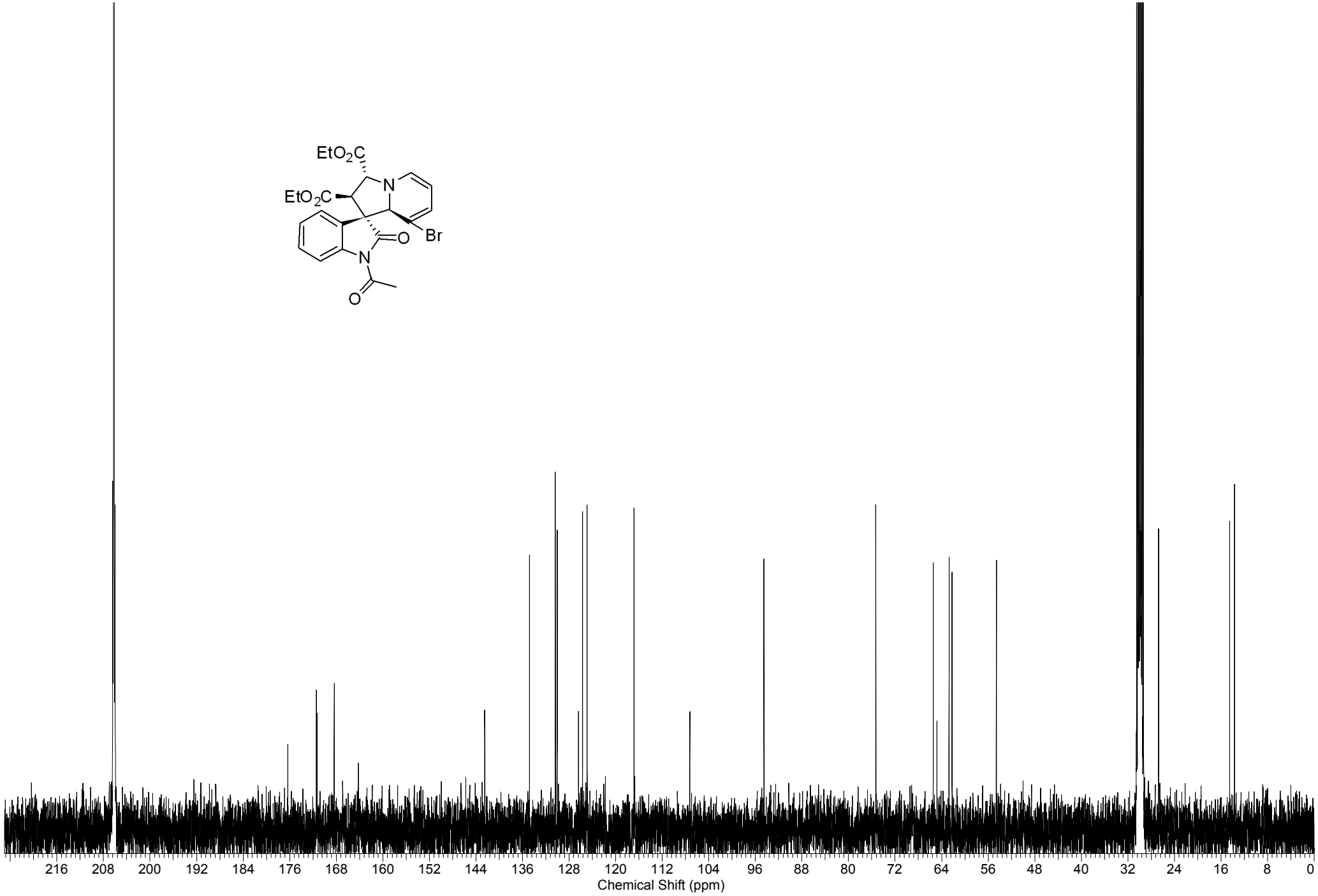


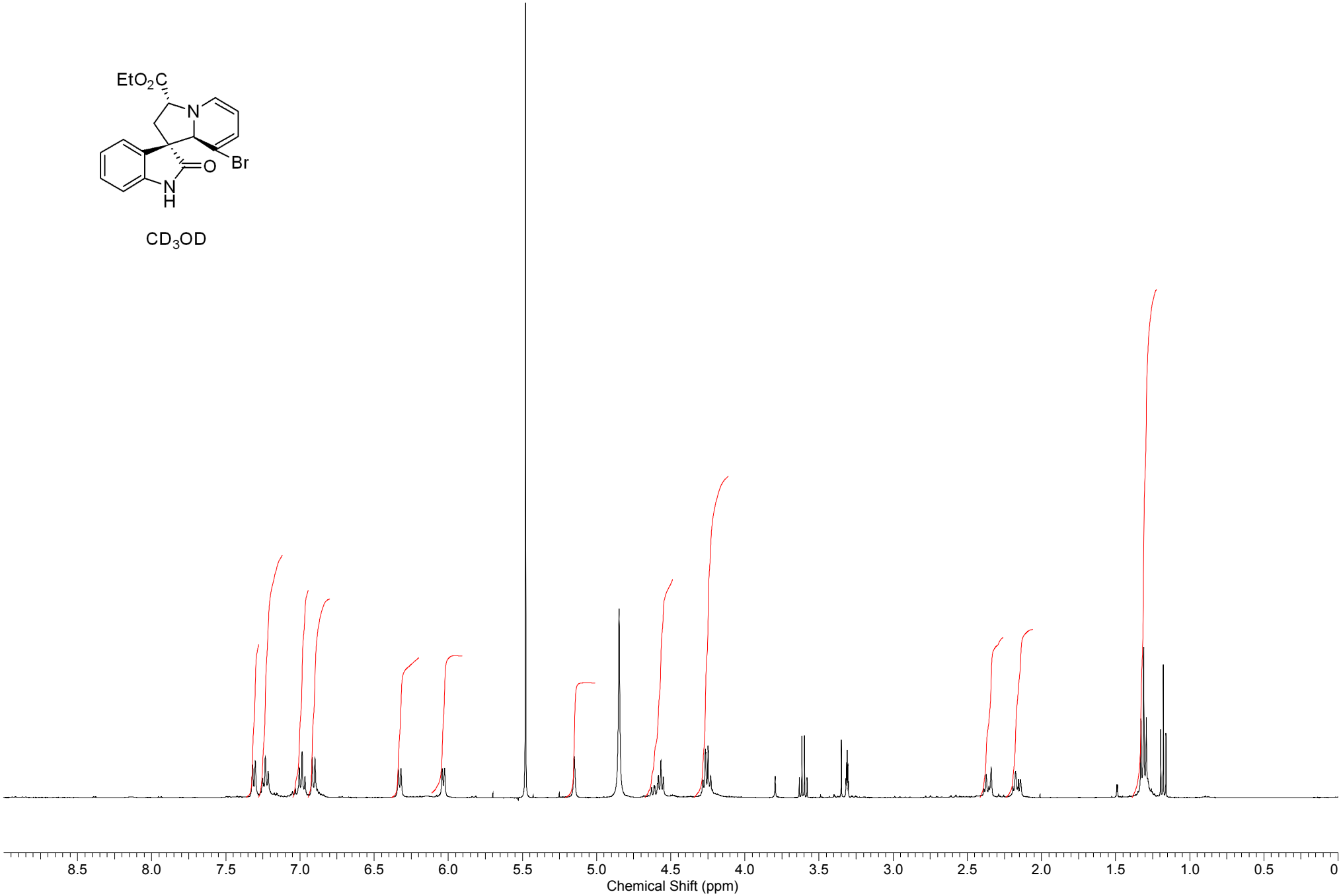












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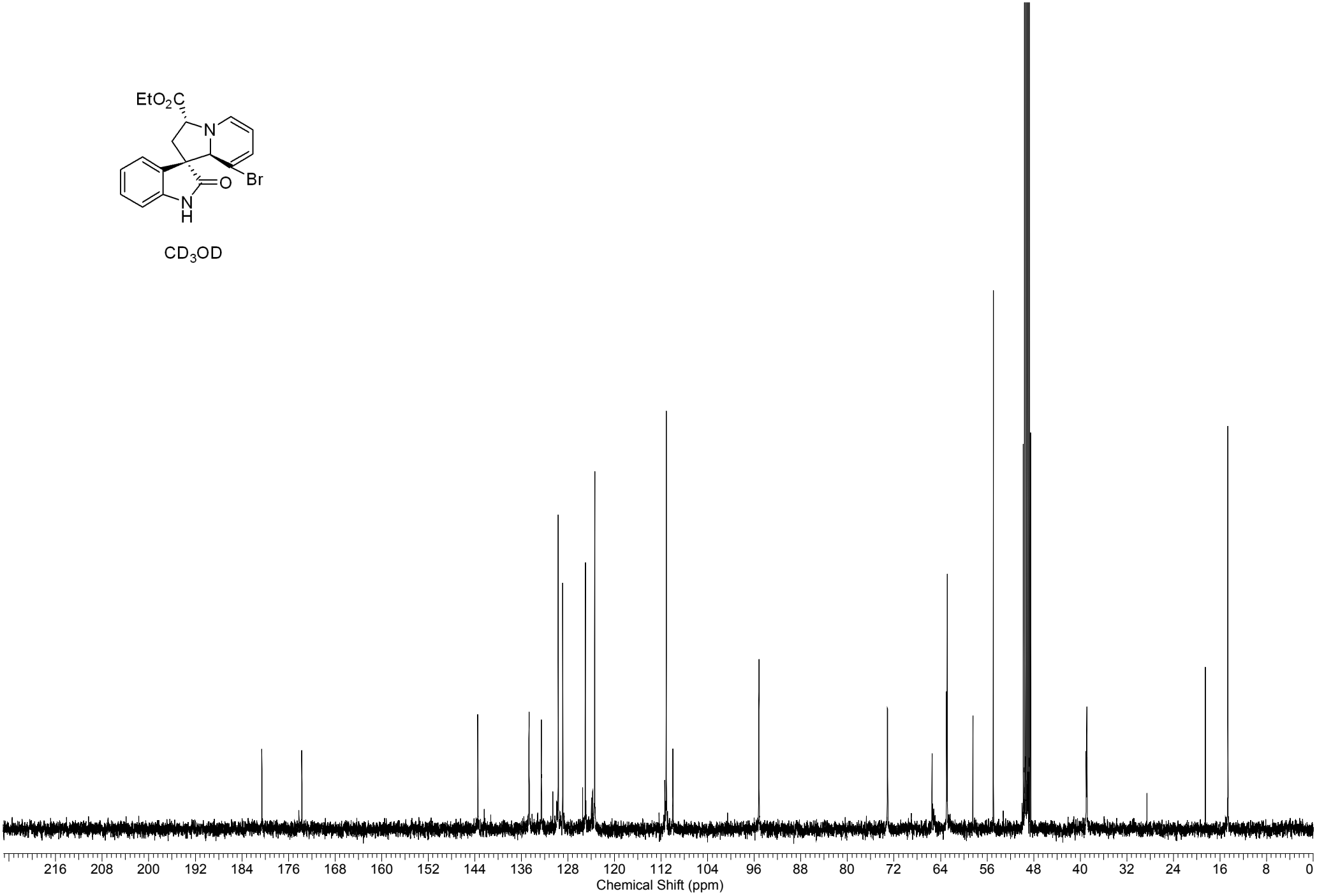
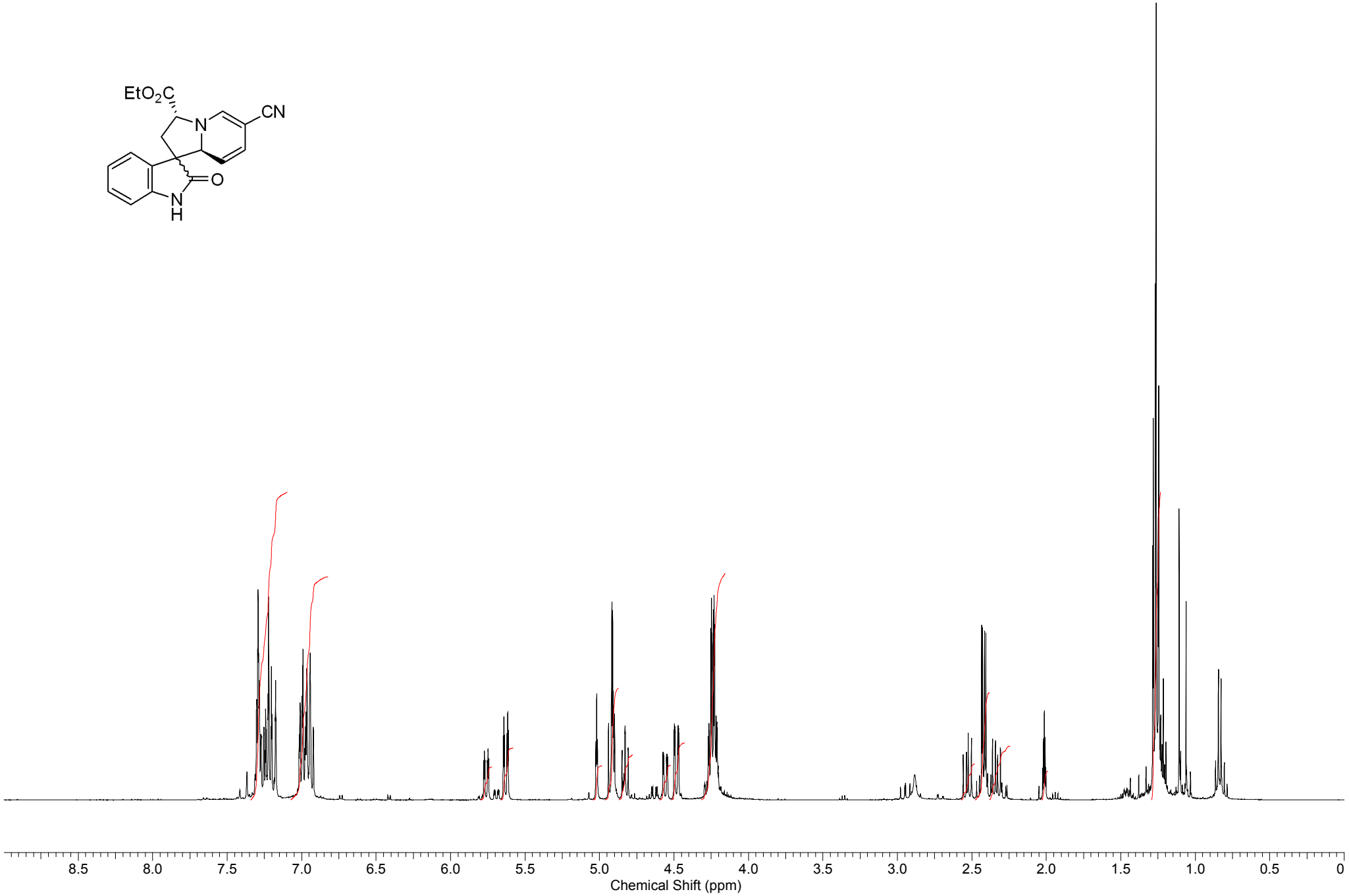
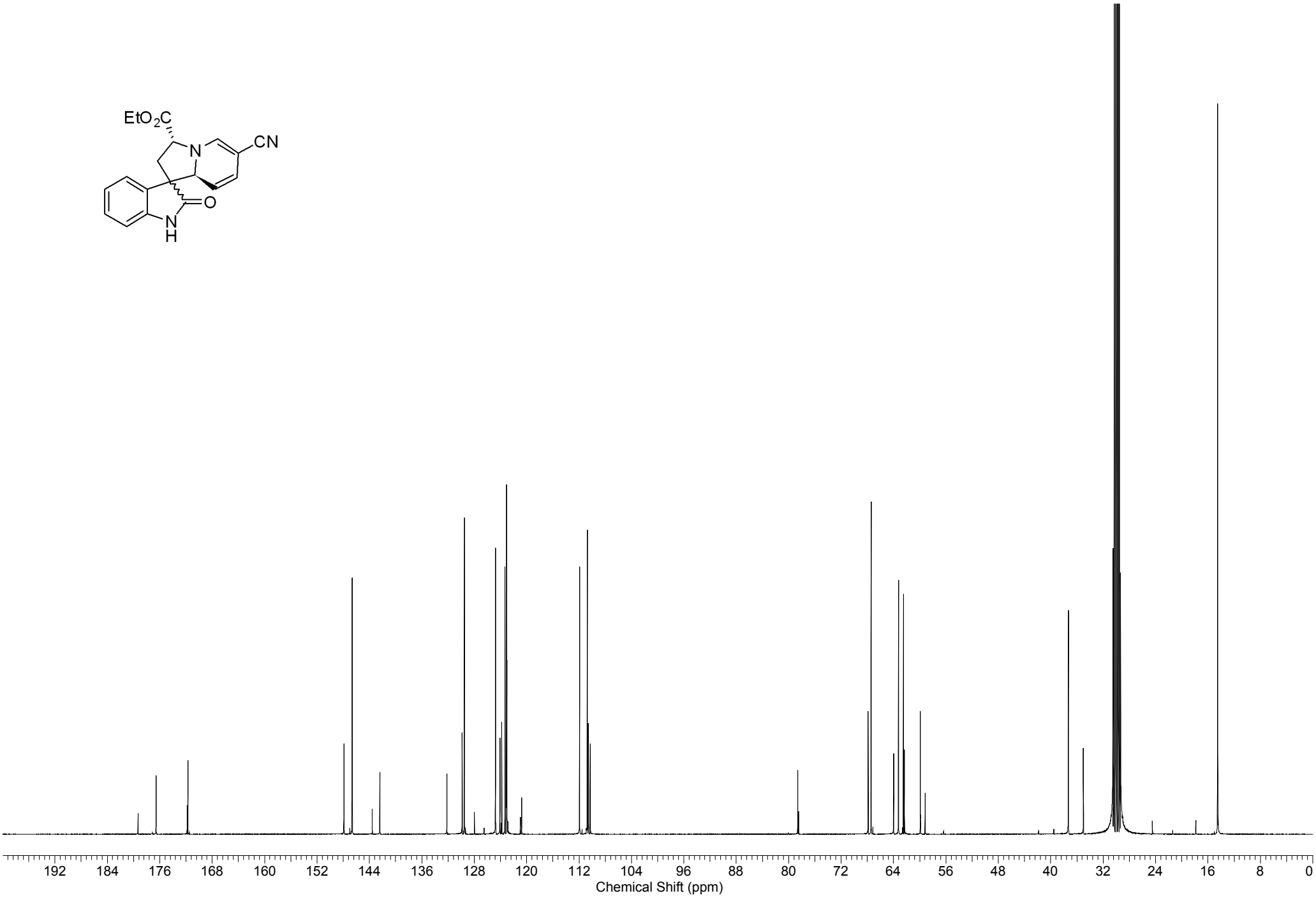
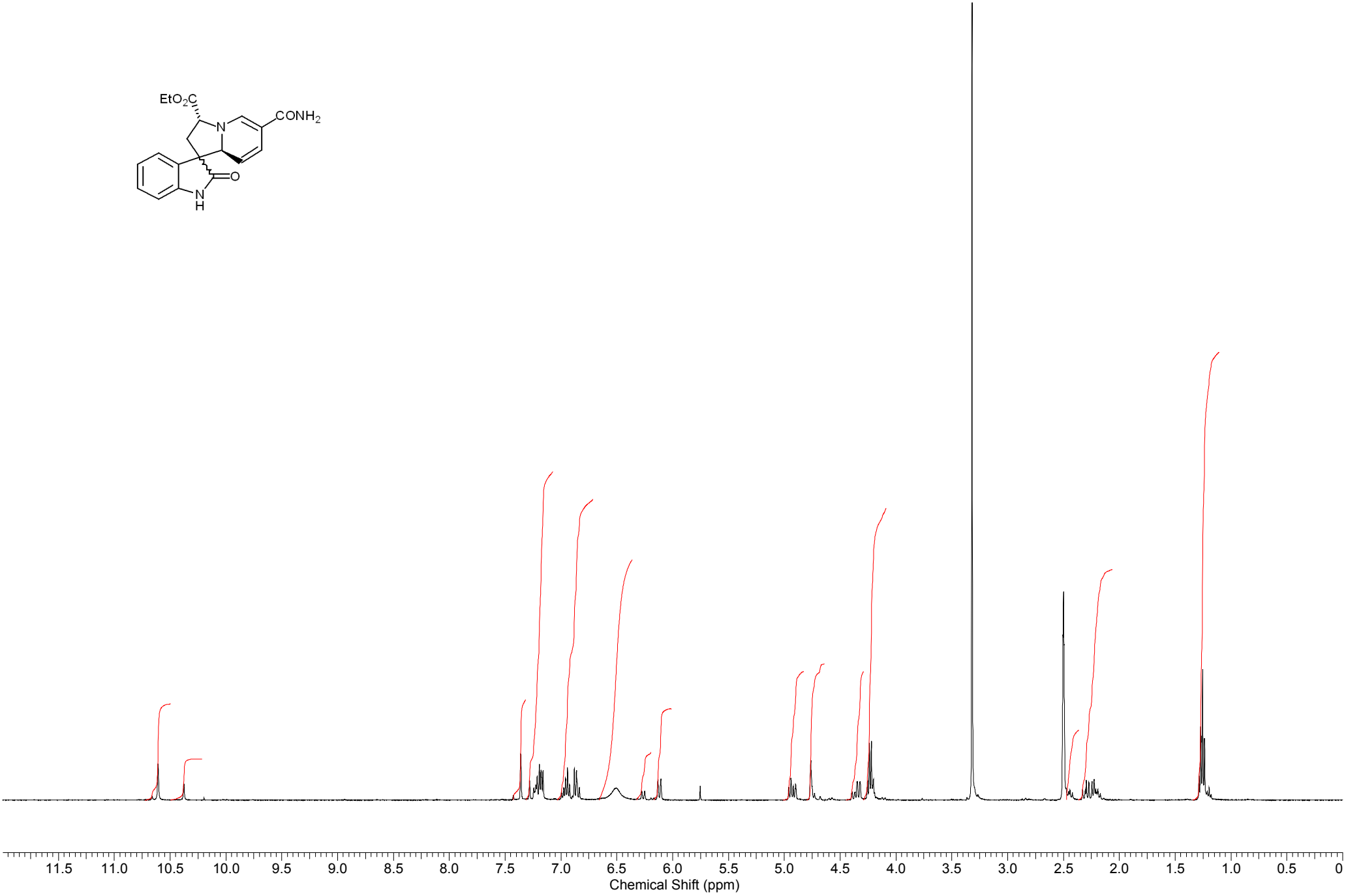
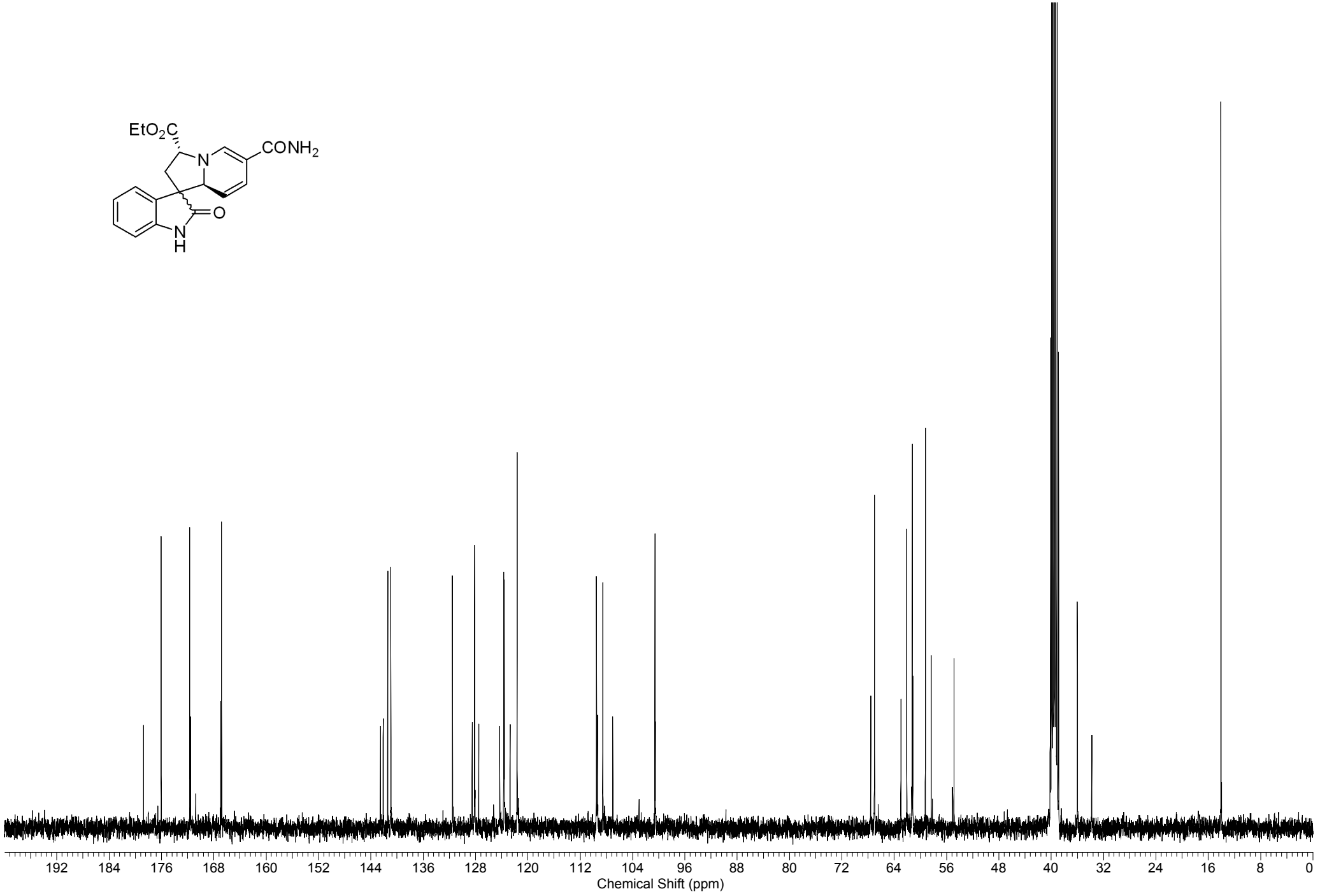
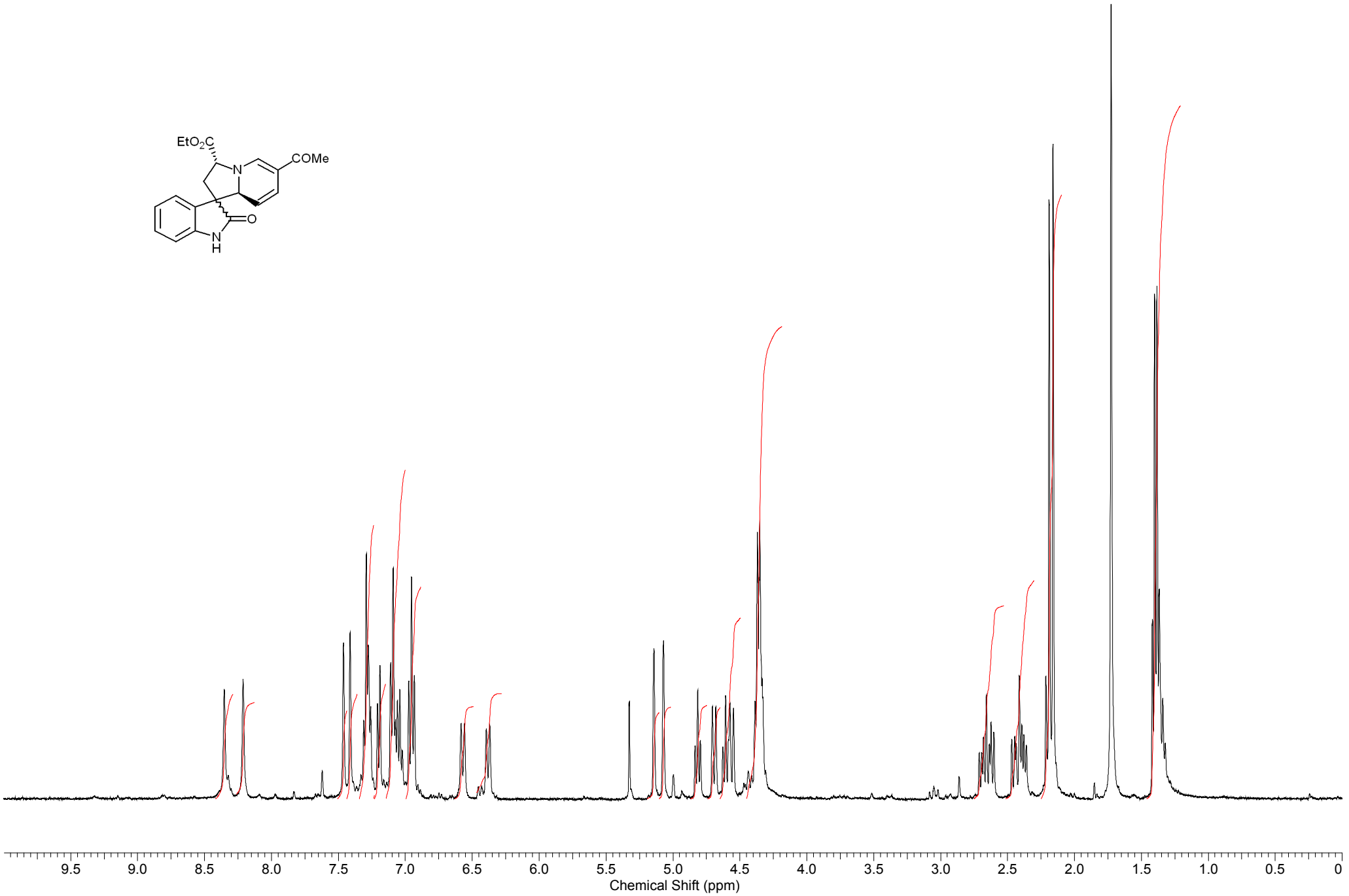


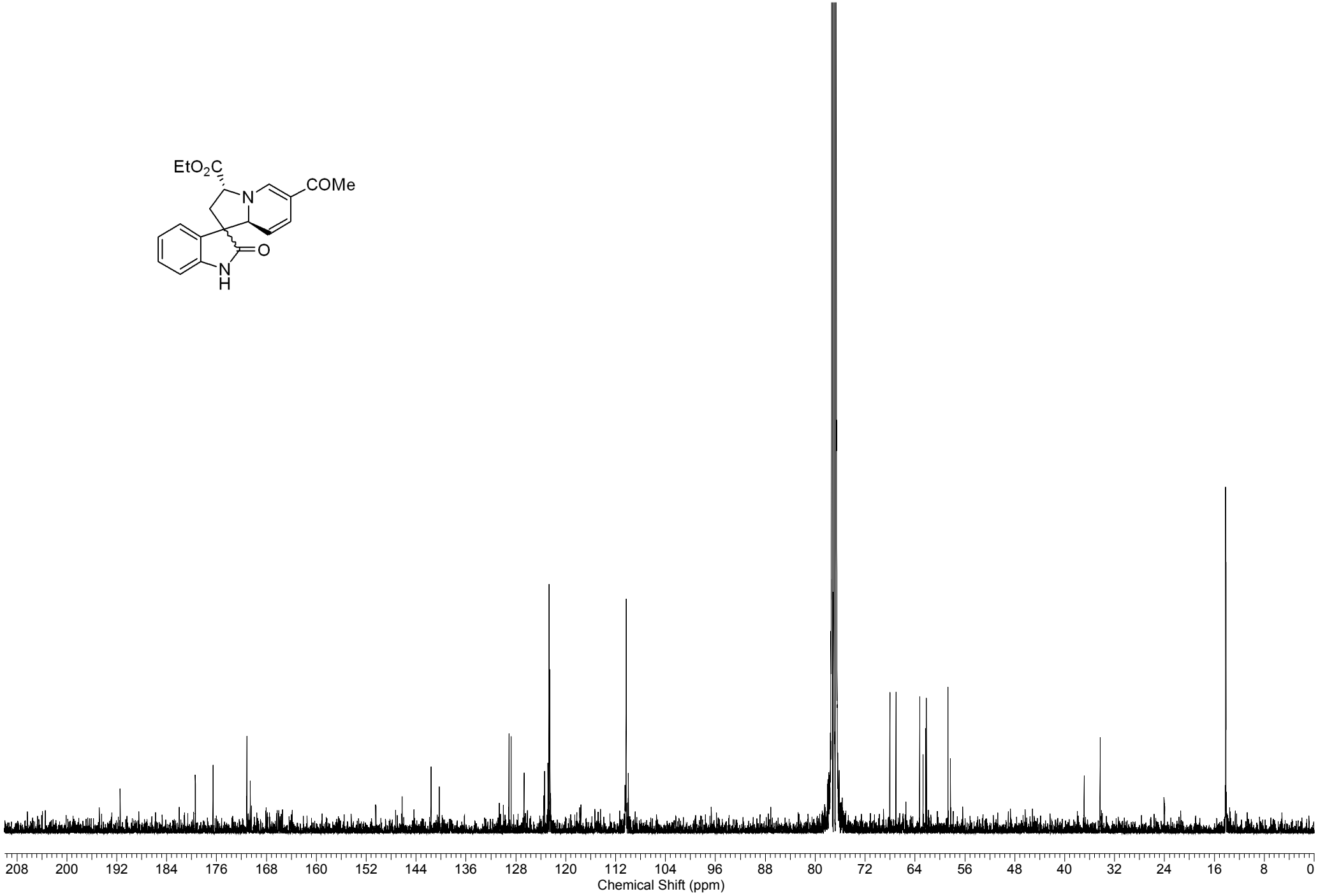








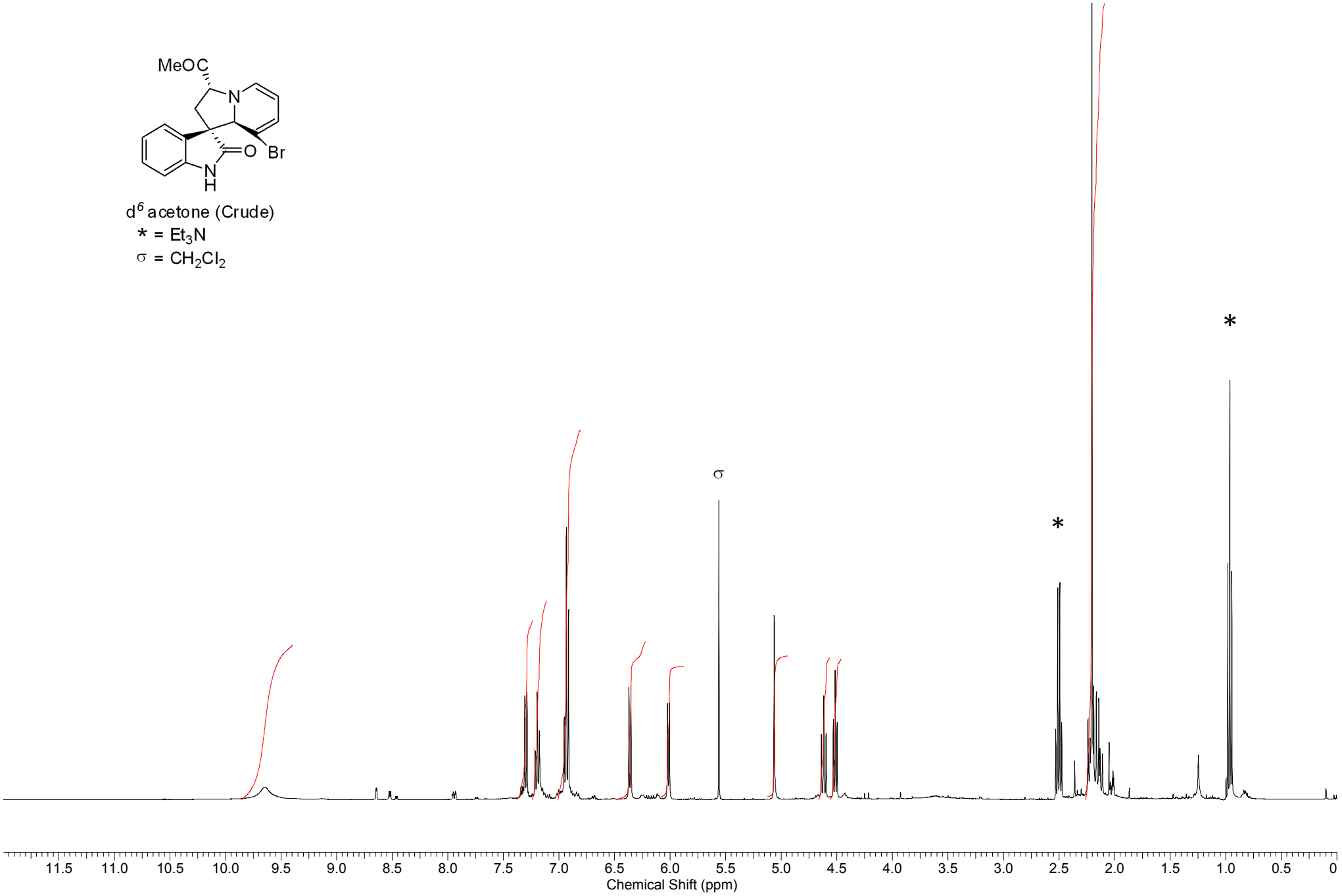




d^6 acetone (Crude)

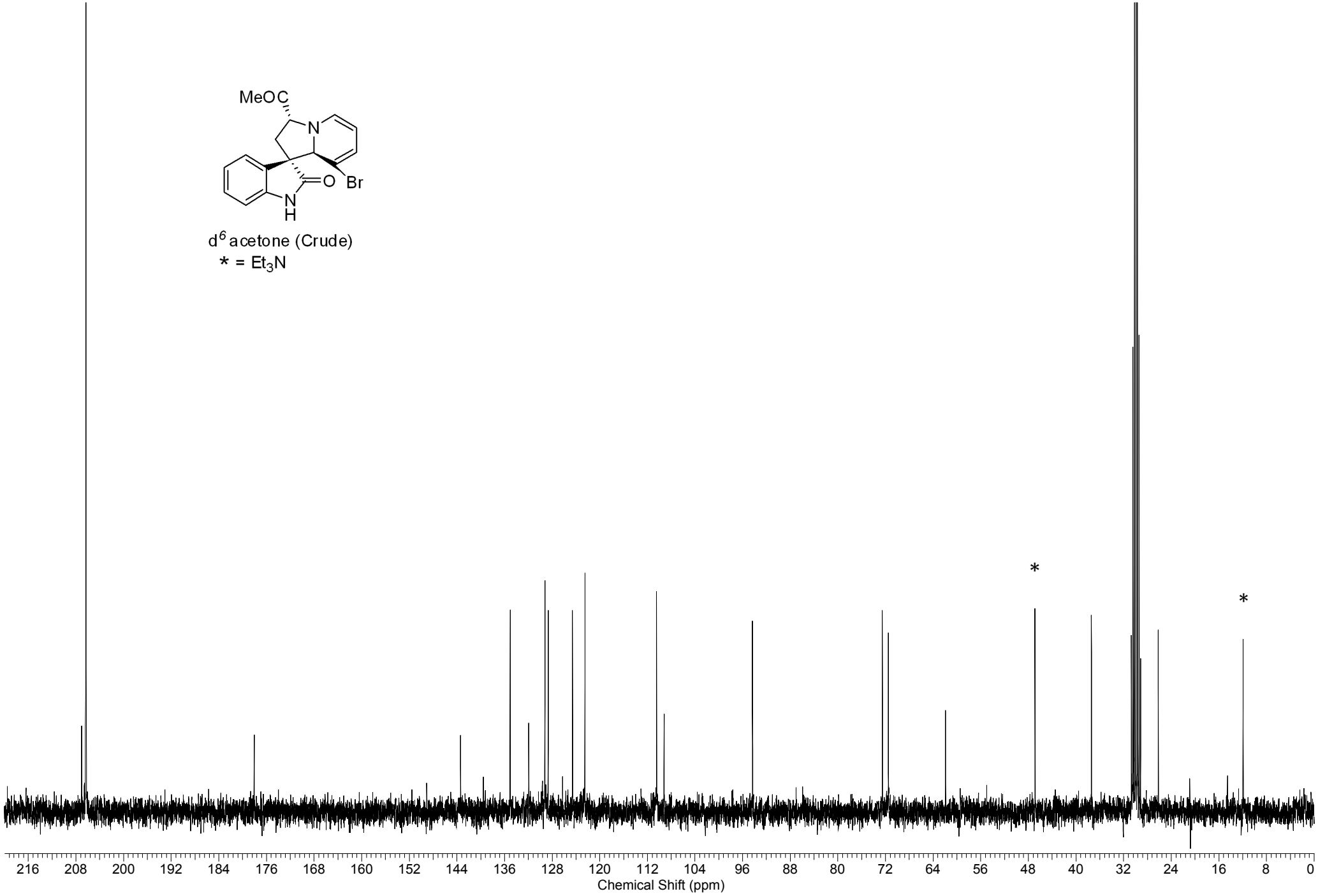
* = Et_3N

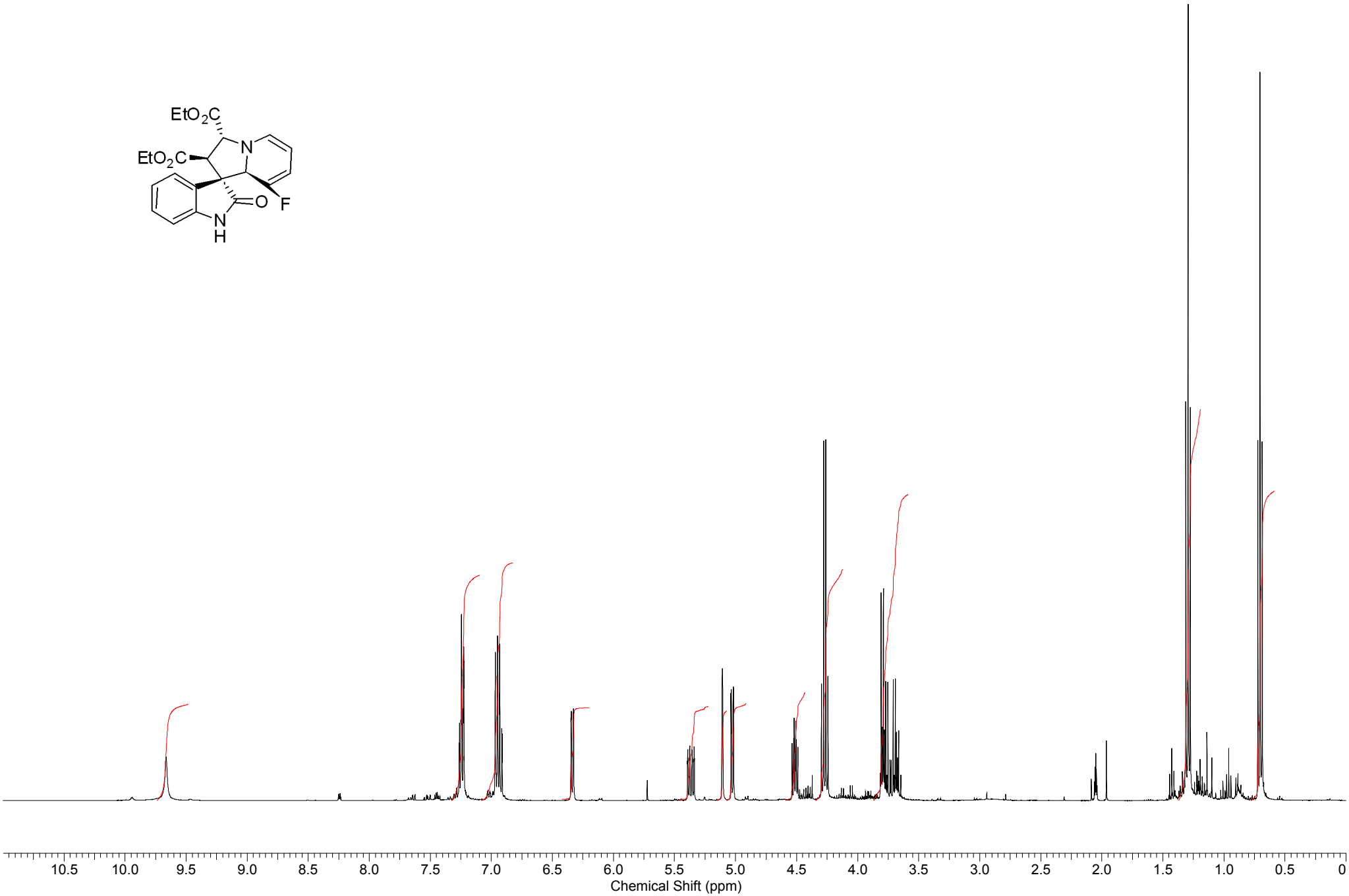
σ = CH_2Cl_2

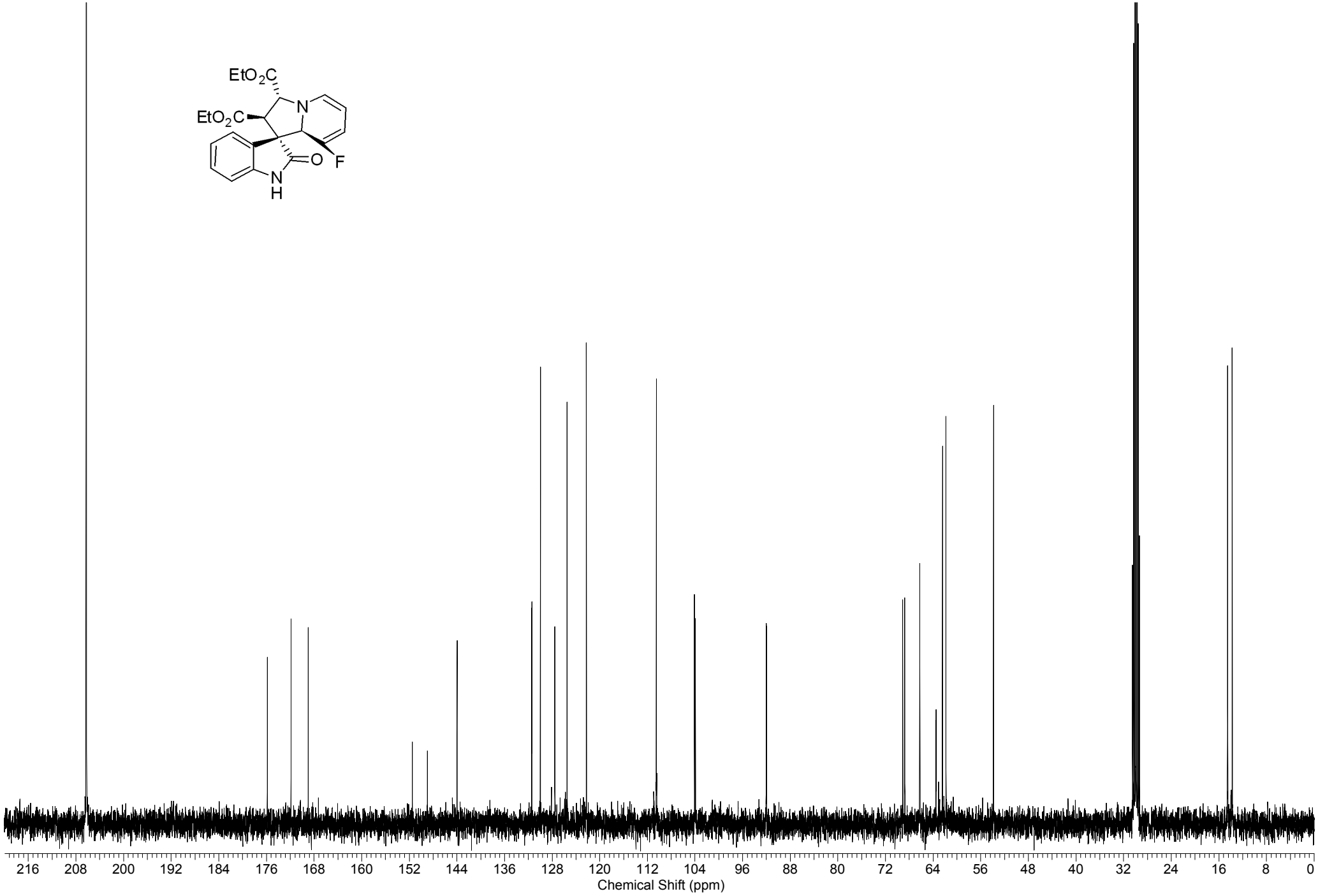


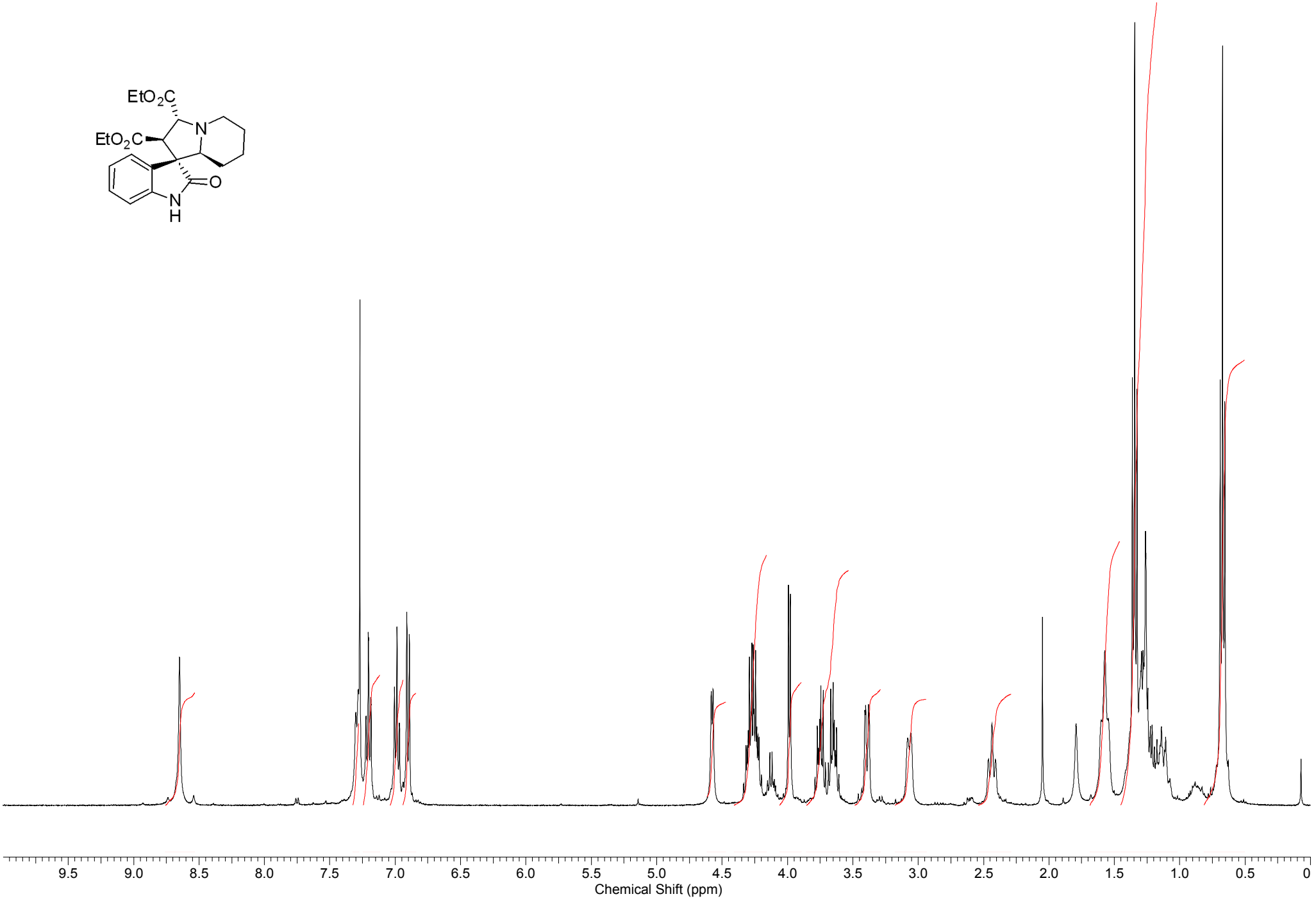
d^6 acetone (Crude)

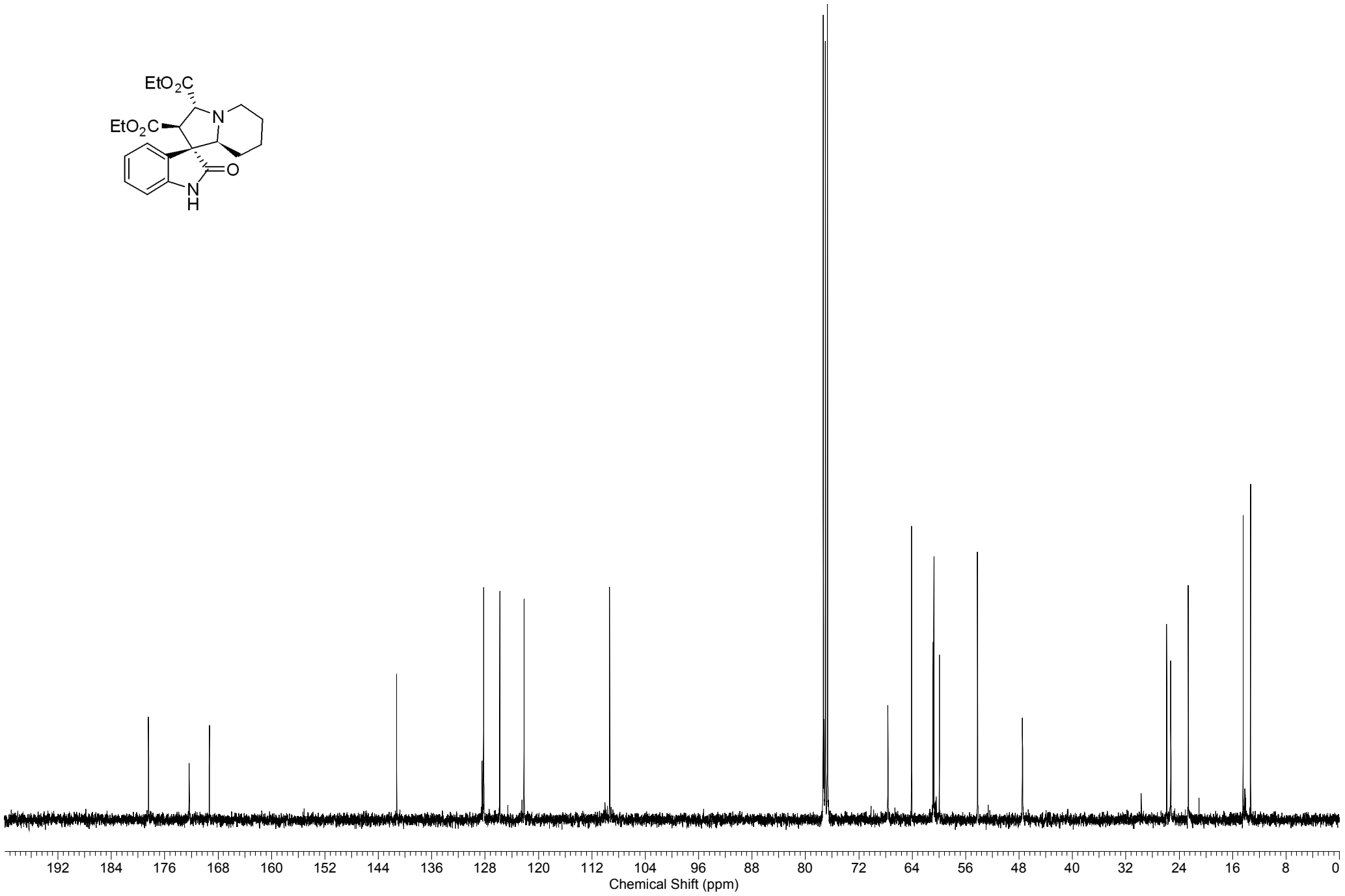
* = Et_3N

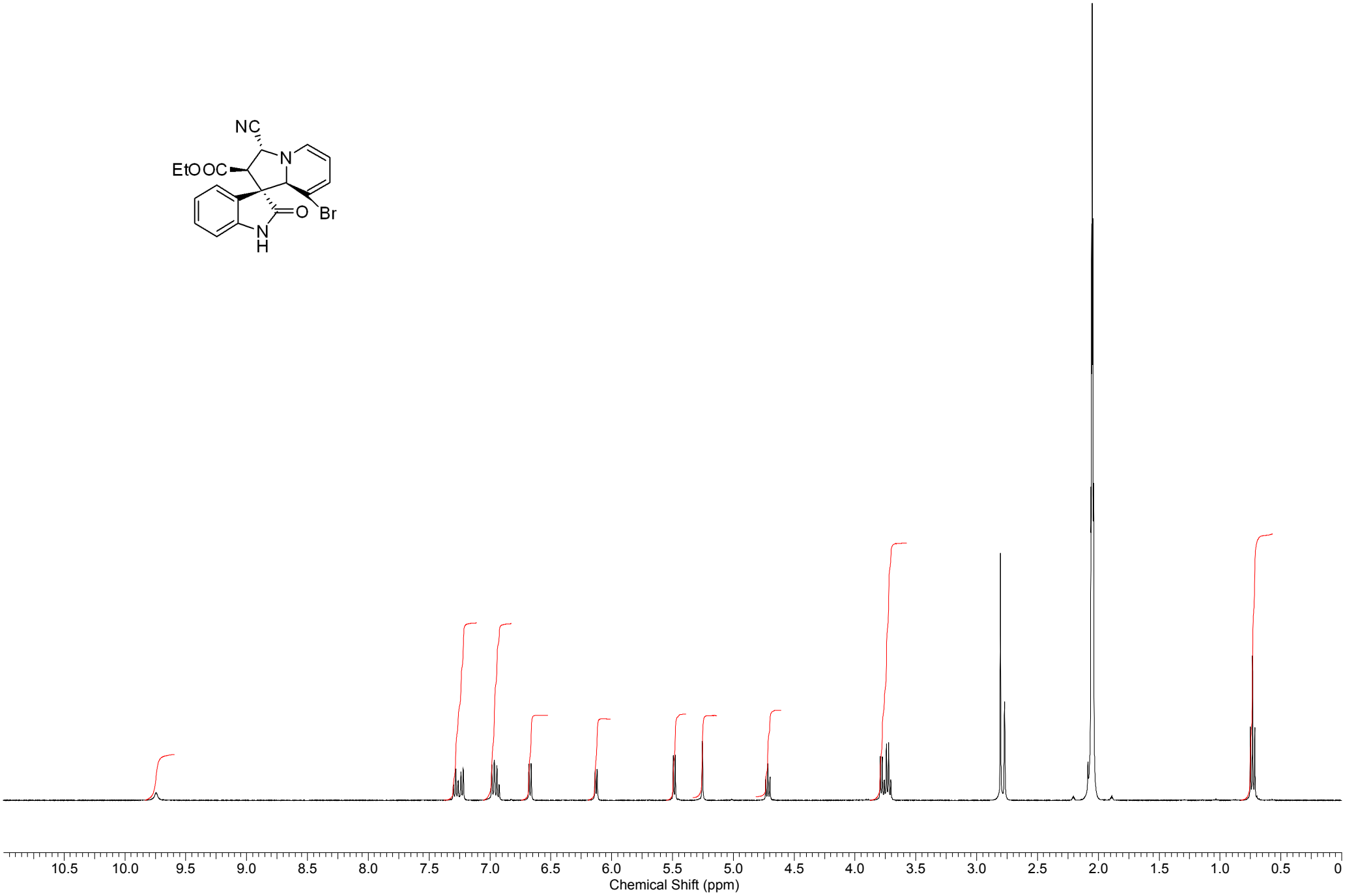


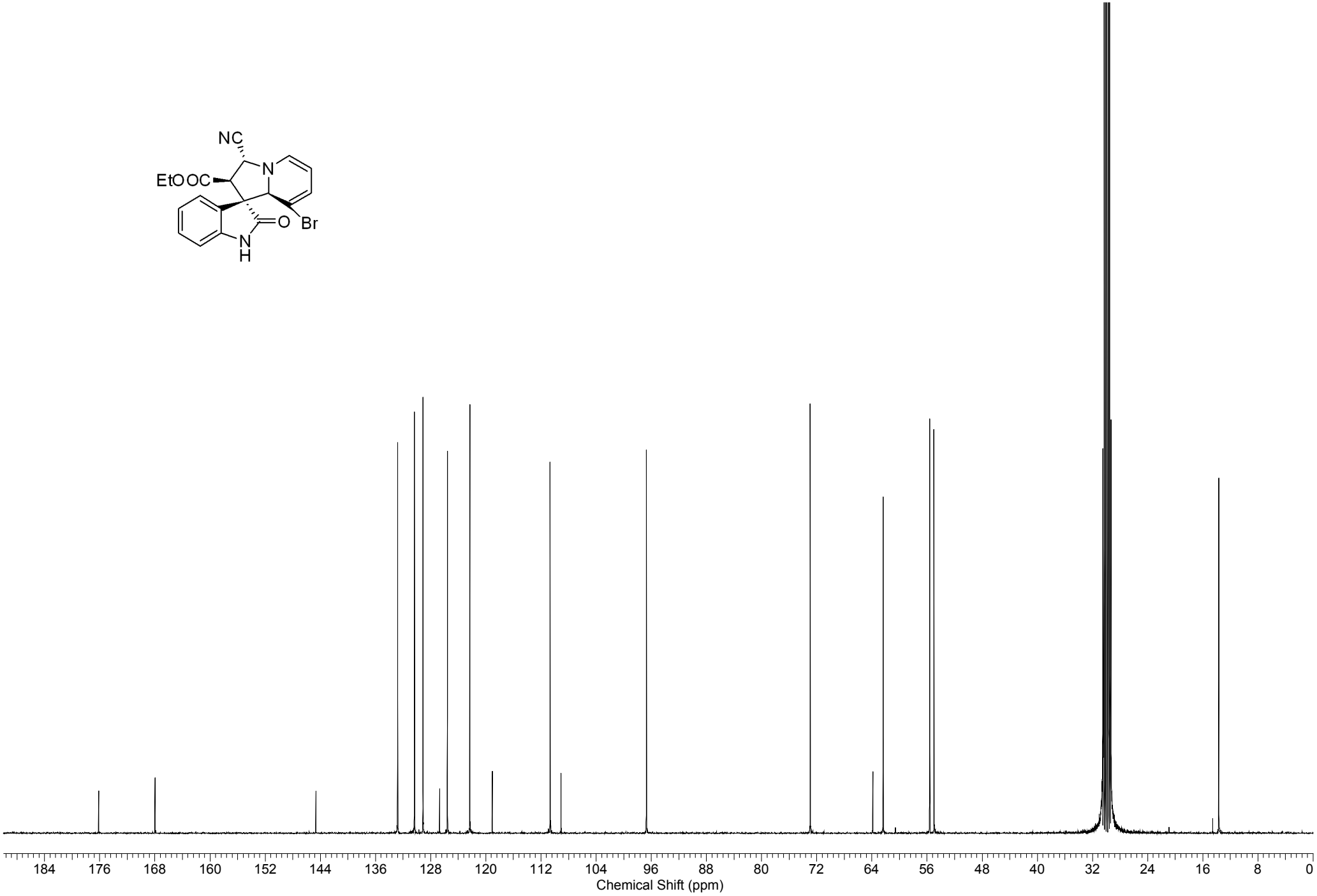


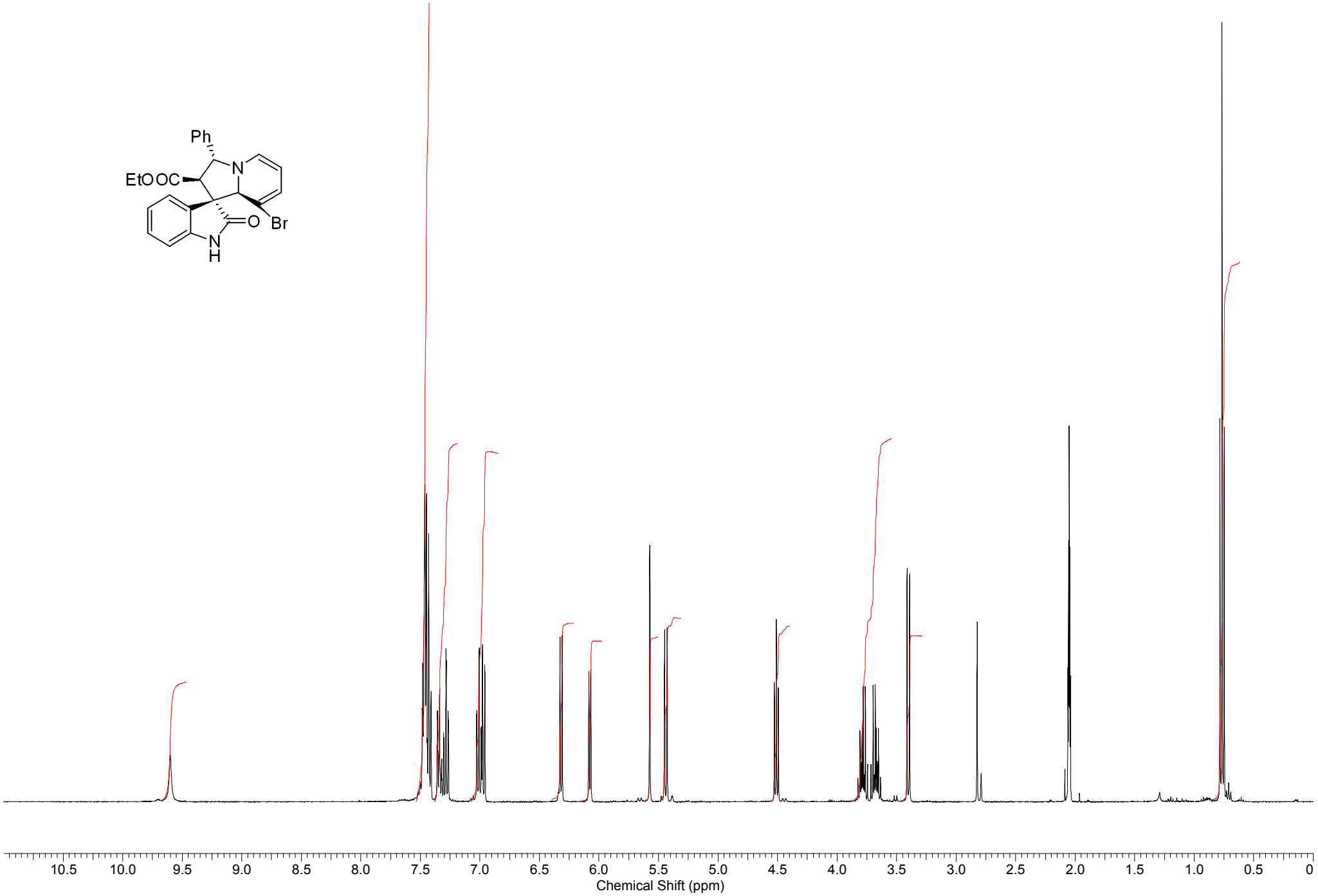


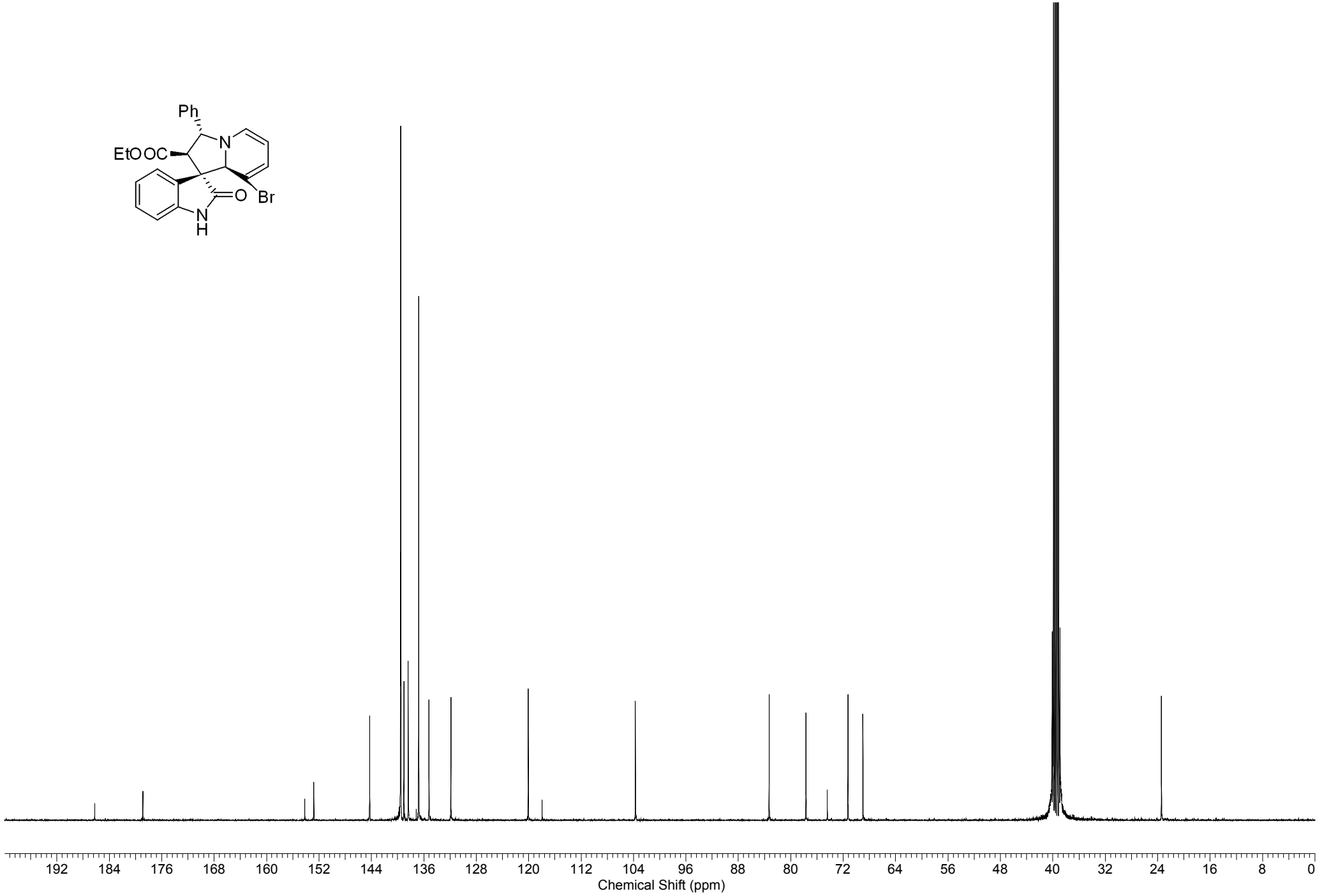


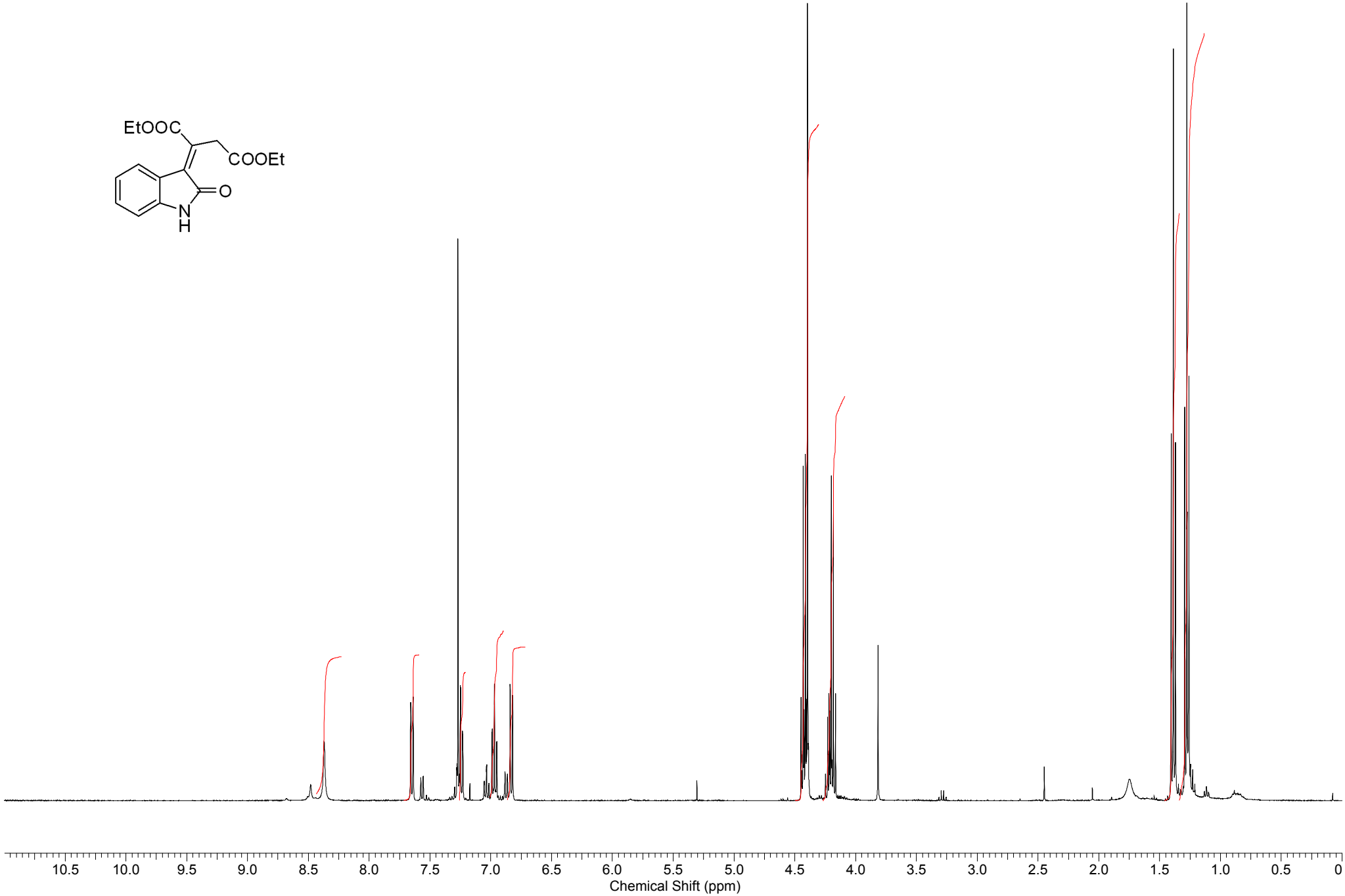


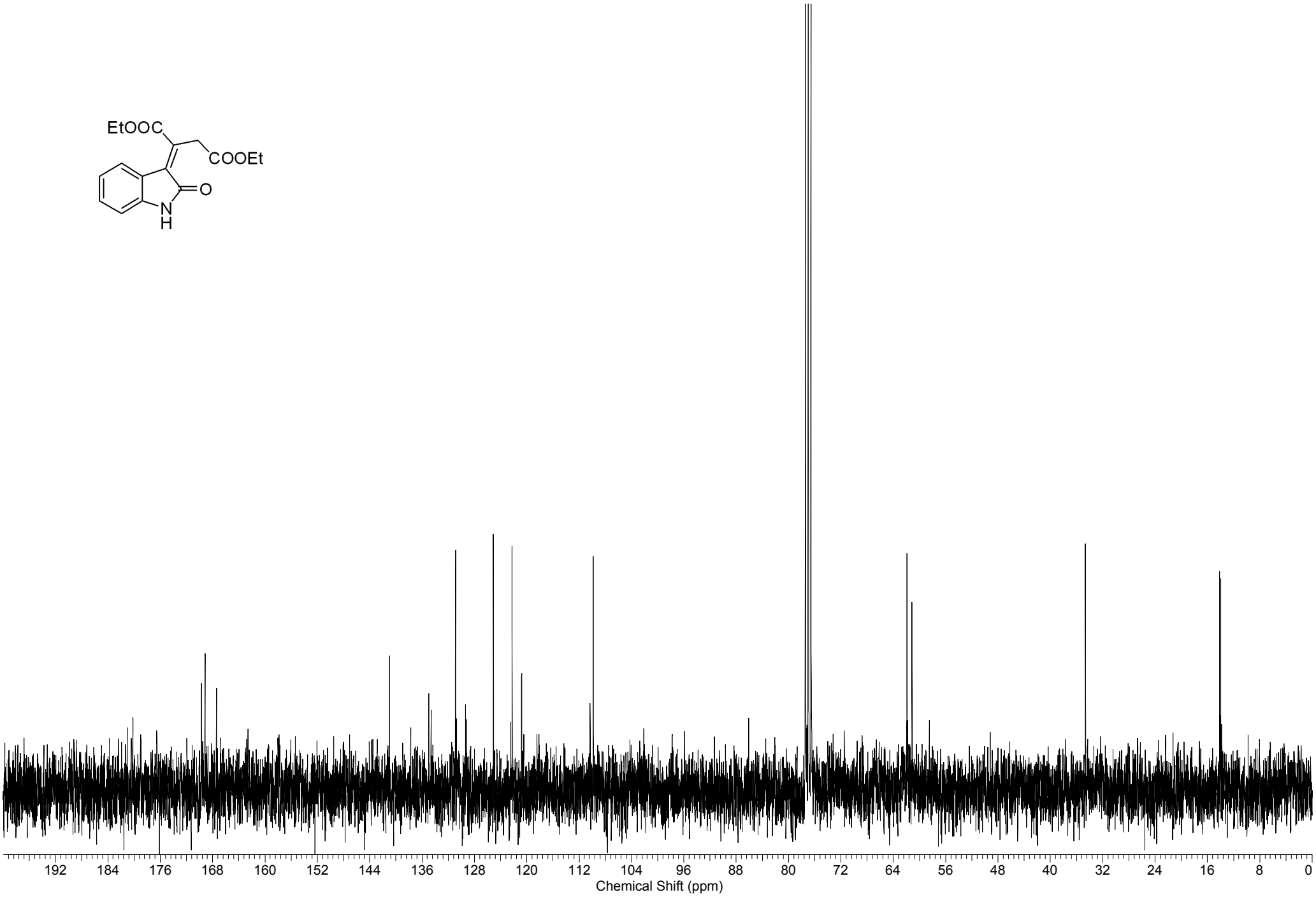








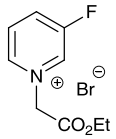




Correction added in proof:

The ^{13}C data originally provided for pyridinium salt was incorrect and should have read:

1-(2-ethoxy-2-oxoethyl)-3-fluoropyridin-1-ium bromide 2k



Procedure B. Brown solid; 110 mg (36%); m.p. 90-92 °C; IR (ν_{max}/cm^{-1}, $CHCl_3$) 2952, 1749, 1595, 1506, 1397, 1350, 1240, 1167; NMR δ_H (400 MHz, D_2O) 9.04 (1H, s, Ar*H*), 8.79 (1H, d, *J*= 6.0 Hz, Ar*H*), 8.56 (1H, t, *J*= 6.0 Hz, Ar*H*), 8.24-8.19 (1H, m, Ar*H*), 5.62 (2H, s, CH_2), 4.32 (2H, q, *J*= 7.1 Hz, CH_2CH_3), 1.28 (3H, t, *J*= 7.1 Hz, CH_2CH_3); NMR δ_C (100 MHz, D_2O) 166.6 (C), 159.3 (C, d, J^{C-F} = 340 Hz), 143.2 (CH, d, J^{C-F} = 4 Hz), 136.0 (CH, d, J^{C-F}= 50 Hz), 134.8 (CH, d, J^{C-F} = 50 Hz), 129.6 (CH, d, J^{C-F} = 10 Hz), 64.2 (CH_2), 61.4 (CH_2), 13.23 (CH_3); *m/z* (HRMS-ESI+) 184.0793 (M^+ $C_9H_{11}FNO_2^+$ requires 184.0768).