1,3-Dipolar cycloadditions from tricyclic hemiaminals. Synthesis of the quinocarcin core through catalyst-free generation of azomethine ylides

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1.- Synthesis and Characterization Data

One-pot synthesis of compounds 1.

To a stirred solution of 1-acetyl-3-(2,5-dimethoxybenzyl)-piperazine-2,5-dione (3.26 mmol) in dry DCM (50 mL) were added TMSCl (4.9 mmol) and triethylamine (4.9 mmol) and the mixture was stirred under an argon atmosphere at room temperature for 1 h. Then, the corresponding dimethyl acetal (6.52 mmol) and TMSOTf (9.78 mmol) were added and this mixture was stirred for 12 h at room temperature or for additional 48 h at reflux conditions (for compound **1b**). The reaction was quenched with a 10% aqueous solution of $NaHCO_3$ (50 mL) and extracted with DCM (30 mL x 3). The combined extracts were washed with H_2O (20 mL) and with a saturated aqueous solution of NaCl (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, to give a residue that was purified by flash column chromatography on silica gel.

(6*S,11a*S**) Methyl 7,10-dimethoxy-1,4-dioxo-1,2,3,4,11, 11a-hexahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-6-carboxylate (1b).**
Purification by flash chromatography on silica gel with methanol/dichloromethane (1:9) as eluent give **1b** (54%) as a yellow solid. Mp 160-161 ºC; IR ν_{max} (film): 1661, 1628 and 1563 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 6.74 (d, *J* = 8.8 Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 1H), 6.45 (s, 1H), 6.08 (ws, 1H), 4.43 (dd, *J* = 11.7 and 4.6 Hz, 1H), 4.17 (d, *J* = 16.5 Hz, 1H), 4.07 (d, *J* = 16.5 Hz, 1H), 3.76 (s, 6H), 3.72 (s, 3H), 3.42 (dd, *J* = 17.5 and 4.6 Hz, 1H), 2.80 (dd, *J* = 17.5 and 11.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 169.5, 167.2, 161.9, 150.9, 150.4, 122.6, 120.1, 109.6, 108.4, 55.8, 55.7, 53.0, 52.9, 51.3, 44.8, 27.4. HRMS (negative ESI), m/z: Calcd for $C_{16}H_{18}N_2O_6$: 334.11649 (M^+). Found: 333.10921 (M^+ - 1). Anal. calcd. for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.05; H, 5.12; N, 7.98.

(6*R,11a*S**)-6-Benzyloxymethyl-7,10-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (1c).**
Purification by flash chromatography on silica gel with methanol/ethyl acetate (1:9) as eluent give **1c** (77%) as a brown oil. IR ν_{max} (film): 3630, 2980, 1698 and 1491 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.30-7.10 (m, 5H), 6.64 (d, *J* = 8.9 Hz, 1H), 6.59 (d, *J* = 8.9 Hz, 1H), 6.46 (s, 1H), 6.07 (dd, *J* = 7.2 and 3.6 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.52 (dd, *J* = 12.5 and 4.6 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.02 (s, 2H), 3.79 (m, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 3.40 (dd, *J* = 17.4 and 4.6 Hz, 1H), 2.61 (dd, *J* = 17.4 and 12.5 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.7, 161.5, 151.0, 150.0, 138.0, 128.3, 127.8, 127.6, 123.0, 122.0, 108.6, 108.0, 72.6, 68.9, 55.6, 55.4, 51.5, 48.3, 44.8, 28.2. HRMS (negative ESI), m/z: Calcd for $C_{22}H_{24}N_2O_5$: 396.16852 (M^+). Found: 395.16125 (M^+ - 1). Anal. calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.39; H, 5.88; N, 6.83.

General procedure for the synthesis of compounds 2b-c

A solution of compounds **1** (9.1 mmol), triethylamine (54 mmol) and 4-dimethylaminopyridine (27 mmol) in dry DCM (140 mL) was cooled in ice water, and isopropyl chloroformate (18 mmol) was added dropwise. The solution was stirred under argon atmosphere for 16h at room temperature and then, water (50 mL) was added. After extraction with DCM (20 mL x 3), the extracts were washed with HCl (25 mL x 3), H_2O (30 mL) and with saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue that was purified by flash column chromatography on silica gel.

(6*S,11a*S**) Methyl 2-isopropoxycarbonyl-7,10-dimethoxy-1,4-dioxo-1,2,3,4,11,11a-hexahydro-6*H*-pyrazino[1,2-*b*] isoquinoline-6-carboxylate (2b).** The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluent to give **2b** (95%) as a white solid. Mp 164-165 ºC; IR ν_{max} (film): 2981, 1921, 1628 and 1501 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 6.82 (d, *J* = 9.0 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.48 (s, 1H), 5.13 (sept, *J* = 6.2 Hz, 1H), 4.64 (dd, *J* = 7.9 and 6.3 Hz, 1H), 4.52 (d, *J* = 17.2 Hz, 1H), 4.50 (d, *J* = 17.2 Hz, 1H), 3.86 (s, 6H), 3.76 (s, 3H), 3.32 (dd, *J* = 17.0 and 7.9 Hz, 1H), 3.20 (dd, *J* = 17.0 and 6.3 Hz, 1H), 1.37 (d, *J* =

6.2 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 169.5, 165.7, 163.4, 150.7, 150.1, 122.4, 120.6, 110.2, 108.9, 72.5, 55.9, 54.8, 52.9, 50.6, 47.8, 24.5, 21.6. HRMS (negative ESI), m/z: Calcd for $C_{20}H_{24}N_2O_8$: 420.15327 (M^+). Found: 419.14599 (M^+ - 1). Anal. calcd. for $C_{20}H_{24}N_2O_8$: C, 57.14; H, 5.75; N, 6.66. Found: C, 56.85; H, 5.48; N, 6.21.

(6*R,11a*S**)-6-Benzyloxymethyl-2-isopropoxycarbonyl-7,10-dimethoxy-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (2c)**. The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (8:2) as eluent to give **2c** (77%) as a brown oil. IR ν_{max} (film): 3439, 2982, 1779, 1670 and 1494 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.30-7.10 (m, 5H), 6.73 (d, *J* = 9.0 Hz, 1H), 6.71 (d, *J* = 9.0 Hz, 1H), 6.10 (dd, *J* = 7.8 and 3.4 Hz, 1H), 5.16 (sept, *J* = 6.3 Hz, 1H), 4.69 (dd, *J* = 11.5 and 5.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 17.7 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.27 (d, *J* = 17.7 Hz, 1H), 3.84 (m, 1H), 3.73 (m, 3H), 3.69 (s, 3H), 3.64 (dd, *J* = 11.0 and 7.8 Hz, 1H), 3.38 (dd, *J* = 17.2 and 5.1 Hz, 1H), 2.85 (dd, *J* = 17.2 and 11.5 Hz, 1H), 1.40 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 166.2, 162.0, 151.2, 150.8, 149.7, 137.9, 128.2, 127.7, 127.6, 122.8, 121.8, 108.7, 108.1, 72.5, 72.9, 68.9, 55.6, 55.3, 53.4, 48.4, 47.6, 27.4, 21.6. HRMS (negative ESI), m/z: Calcd for $C_{26}H_{30}N_2O_7$: 482.21201 (M^+). Found: 481.19802 (M^+ - 1). Anal. calcd. for $C_{26}H_{30}N_2O_7$: C, 64.72; H, 6.27; N, 5.81. Found: C, 64.41; H, 5.96; N, 5.61.

(6*R,11a*S**)-2-isopropoxycarbonyl-7,10-dimethoxy-6-naphtycarbonyloxymethyl-2,3,11,11a-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (2d)**. To a solution of **2c** (400 mg, 0.83 mmol) and Pd/C (66 mg) in ethanol (4 mL) was stirred under hidrogen atmosphere (3 atm.), at 70 ºC, for 3.5 h. Then, was filtered through celite and the solvent was concentrated in vacuo to give an oil residue. The unpurified crude was used in the next step. A solution of this crude, EDC (2.3 mmol), 4-dimethylaminopyridine (1.21 mmol) and naphthoic acid (1.2 mmol) in dry DCM (20 mL) was stirred under argon atmosphere for 20 h at room temperature. Then the solvent was evaporated and the residue was dissolved in AcOEt (150 mL), the organic solution was washed with HCl 0.1 N (50 mL), $NaHCO_3$ (50 mL),

H_2O (30 mL) and a saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give a residue that was purified by flash column chromatography on silica gel with hexane/ethyl acetate mixture (8:2) as eluent to give **2d** as a brown oil (265 mg, 44%). IR ν_{max} (film): 2981, 1780, 1509 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 8.82 (d, *J* = 7.9 Hz, 1H), 8.19 (dd, *J* = 7.3 and 1.1 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.90 (dd, *J* = 7.3 and 1.7 Hz, 1H), 7.54 (m, 3H), 6.79 (m, 2H), 6.34 (dd, *J* = 9.0 and 3.3 Hz, 1H), 5.07 (sept, *J* = 6.2 Hz, 1H), 4.91 (dd, *J* = 11.6 and 9.0 Hz, 1H), 4.80 (dd, *J* = 11.4 and 5.0 Hz, 1H), 4.69 (dd, *J* = 11.6 and 3.3 Hz, 1H), 4.41 (d, *J* = 17.8 Hz, 1H), 4.29 (d, *J* = 17.8 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.52 (dd, *J* = 17.3 and 5.0 Hz, 1H), 2.95 (dd, *J* = 17.3 and 11.4 Hz, 1H), 1.33 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.2, 166.2, 165.8, 151.1, 151.0, 149.9, 133.7, 133.6, 131.3, 130.6, 128.5, 127.8, 126.4, 126.2, 125.6, 124.6, 122.9, 120.6, 109.4, 108.4, 72.4, 63.1, 55.7, 55.6, 53.5, 48.4, 47.6, 27.2, 21.6. HRMS (negative ESI), m/z: Calcd for $C_{30}H_{30}N_2O_8$: 546.20022 (M^+). Found: 545.19305 (M^+ - 1). Anal. calcd. for $C_{30}H_{30}N_2O_8$ C, 65.92; H, 5.53; N, 5.13; Found: C, 65.50; H, 5.46; N, 5.22.

General procedure for the synthesis of hemiaminals 3 and 8.

To a stirred solution of lithium tri-*tert*-buthoxide aluminum hydride (8.12 mmol) in dry THF (50 mL) cooled in ice water was added a solution of compounds **2** or **7** (2.7 mmol) in dry THF, and the mixture was stirred under an argon atmosphere at room temperature for 16 h. The reaction mixture was quenched by addition of ice, filtered over celite, and extracted with ethyl acetate. The organic phases were washed with H_2O and with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*.

(1*R,6*R**,11a*S** and 1*S**,6*R**,11a*S**)-1-Hydroxy-2-isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,6,11,11a-hexahydropyrazino[1,2-*b*]isoquinolin-4-one (3a).**

According to the general procedure compound **3a** (86%) was obtained as a crude product in a 7/3 diasteroisomer mixture. IR ν_{max} (film): 3325, 2979, 1704 and 1634 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 6.67 (s, 2H), 5.93 (q, *J* = 6.4 Hz, 1H), 5.84 (ws, 1H), 4.93 (sept, *J* = 6.1

Hz, 1H), 4.34 (m, 1H), 4.30 (d, *J* = 17.5 Hz, 0.3H), 4.02 (m, 2H), 3.78 (s, 4.2H), 3.76 (s, 1.8 H), 3.20 (dd, *J* = 17.2 and 8.0 Hz, 0.3H), 2.96 (dd, *J* = 17.2 and 7.5 Hz, 1H), 2.49 (m, 1H), 1.52 (d, *J* = 7.2, 2.1H), 1.40 (d, *J* = 6.5, 1.3H), 1.31 (d, *J* = 6.5, 6H), 1.27 (m, 6H), 1.20 (d, *J* = 6.0, 1.3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 176.8, 165.2, 163.0, 150.8, 150.3, 149.8, 149.2, 127.7, 126.5, 122.3, 121.5, 107.8, 107.7, 107.6, 76.3, 76.2, 70.1, 70.0, 55.5, 55.4, 52.6, 50.8, 44.8, 44.1, 43.9, 43.4, 23.8, 21.8, 18.9, 18.3. HRMS (negative ESI), m/z: Calcd for $C_{19}H_{26}N_2O_6$: 378.17909 (M^+). Found: 377.17181 (M^+ - 1).

(1*R,6*R**,11a*S** and 1*S**,6*R**,11a*S**)-6-Benzyloxymethyl-1-hydroxy-2-isopropoxycarbonyl-7,10-dimethoxy-1,2,3,6,11,11a-hexahydropyrazino[1,2-*b*] isoquinolin-4-one (3c).**

Compound **3c** was unstable and could not be purified, being stored at - 5 ºC. This crude product was used to obtain compouds **5** and **6** (see below).

2-Isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,6-tetrahydropyrazino[1,2-*b*] isoquinolin-4-one (4).

Compound **3a** (0.26 mmol) was dissolved in toluene (5 mL) and acrilonitrile (5 eq) was added. The reaction was carried out in a sealed tube for 48 h at 120 ºC. Then the solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluent to give the compound **4** (32%) as a yellow oil. IR ν_{max} (film): 2979, 1702 and 1648 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.71 (s, 2H), 6.23 (ws, 1H), 6.05 (q, *J* = 6.5 Hz, 1H), 4.95 (sept, *J* = 6.4 Hz, 1H), 4.71 (m, 1H), 4.54 (d, *J* = 18.4 Hz, 1H), 4.11 (d, *J* = 18.4 Hz, 1H), 3.96 (m, 1H), 3.81 (s, 6H), 1.28 (m, 3H), 1.27 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 163.4, 154.0, 148.8, 148.2, 128.8, 123.1, 119.1, 109.7, 109.5, 101.3, 69.7, 55.9, 55.6, 48.3, 44.4, 22.1, 18.8. HRMS (negative ESI), m/z: Calcd for $C_{19}H_{24}N_2O_5$: 360.16852 (M^+). Found: 383.15774 (M^+ + Na). Anal. calcd. for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.03; H, 6.42; N, 7.35.

Synthesis of 5 and 6

To a solution of compound **3c** (140 mg, 0.3 mmol) in anhydrous DCM (3 mL) was added TFA (1.16 mL, 15 mmol). The reaction was stirred for 3.5 h at room temperature and, then the reaction was concentrated to dryness in vacuo. The residue was dissolved in anhydrous DCM (3 mL) and cooled in ice water. After addition of acrolein (0.4 mL, 6 mmol) and Et_3N (0.42 mL, 3 mmol) the mixture was stirred at room temperature for 3.5 h and extracted with AcOEt (20 mL x 2). The extracts were washed with NH_4Cl (30 mL), H_2O (30 mL) and a saturated aqueous solution of NaCl (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue, that was purified by flash column chromatography on silica gel with hexane/ethyl acetate (7:3) as eluent to give **5** as an orange solid (25%) and **6** as a yellow solid (43%).

6-Benzyloxymethyl-2-isopropoxycarbonyl-7,10-dimethoxy-2,3,6,11-tetrahydropyrazino[1,2-*b*]isoquinoline-4-one (5). Mp 64-65 °C; IR ν_{max}(film): 2980, 1649 and 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.19 (m, 5H), 6.63 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.31 (dd, *J* = 7.0 and 3.0 1H), 6.12 (br s, 1H), 4.84 (sept, *J* = 6.5 Hz , 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.45 (m, 2H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.06 (d, *J* = 18.6 Hz, 1H), 3.83 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.38 (dd, *J* = 10.8 and 3.3 Hz, 1H), 1.28 (m, 6H). ^{13}C NMR (85 MHz, $CDCl_3$) δ: 164.2, 154.1, 149.3, 148.4, 138.4, 128.3, 127.7, 127.5, 120.9, 120.8, 118.7, 110.3, 109.7, 72.6, 69.7, 69.1, 56.0, 55.6, 48.2, 47.0, 35.9, 22.2. HRMS (negative ESI), m/z: Calcd for $C_{26}H_{30}N_2O_6$: 466.21039 (M^+). Found: 489.19961 (M^+ + Na). Anal. calcd. for $C_{26}H_{30}N_2O_6$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.71; H, 6.23; N, 5.84.

6-Benzyloxymethyl-2-isopropoxycarbonyl-7,10-dimethoxy-1,2,3,6-tetrahydropyrazino[1,2-*b*]isoquinolin-4-one (6). Mp 64-65 ºC; IR ν_{max} (film): 2934, 1649 and 1452 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.00–7.20 (m, 7H), 6.51 (s, 1H), 6.38 (dd, *J* = 8.9 and 3.8 Hz, 1H), 4.98 (sept, *J* = 5.2 Hz , 1H), 4.78 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 12.3 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 4.21 (d, *J* = 12.3 Hz, 1H), 3.69

(s, 3H), 3.65 (s, 3H), 3.61 (dd, *J* = 10.8 and 8.9 Hz, 1H), 3.44 (dd, *J* = 10.8 and 3.8 Hz, 1H), 4.00 (m, 2H), 1.29 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 164.3, 154.1, 150.5, 148.4, 140.5, 138.2, 133.7, 128.8, 128.5, 128.3, 127.8, 127.7, 127.6, 126.2, 119.2, 112.5, 72.8, 69.7, 69.5, 62.1, 55.8, 48.2, 47.2, 35.9, 22.2. Anal. calcd. for $C_{26}H_{30}N_2O_6$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.61; H, 6.19; N, 5.79.

General procedure for compounds 7

A solution of **2a**, **2b** or **2d** (6.9 mmol), AIBN (0.69 mmol) and NBS (8.3 mmol) in CCl_4 (70 mL) was refluxed under an argon atmosphere for 16 h. The unreacted NBS was filtered from the cooled reaction, the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel.

Methyl 2-isopropoxycarbonyl-7,10-dimethoxy-1,4-dioxo-1,2,3,4-tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-6-carboxylate (7b). The residue was purified by flash column chromatography on silica gel with ethyl acetate/hexane (7:3) as eluent, to give compound **7b** (85%) as a brown oil. IR ν_{max} (film): 2983, 2358 and 1698 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.64 (s, 1H), 6.97 (d, *J* = 9.1 Hz, 1H), 6.86 (d, *J* = 9.1 Hz, 1H), 6.83 (s, 1H), 5.18 (sept, *J* = 6.2 Hz, 1H), 4.88 (d, *J* = 17.2 Hz, 1H), 4.21 (d, *J* = 17.2 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.68 (s, 3H), 1.33 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 168.4, 162.3, 158.7, 152.3, 150.2, 150.0, 126.2, 119.2, 117.8, 114.7, 113.7, 111.3, 72.5, 56.3, 56.0, 53.2, 49.6, 47.4, 21.7. Anal. calcd. for $C_{20}H_{22}N_2O_8$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.23; H, 5.11; N, 6.55.

2-Isopropoxycarbonyl-7,10-dimethoxy-6-naphtycarbonyloxymethyl-2,3-dihydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (7d). IR ν_{max} (film): 2360, 1717, 1489cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.88 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 7.2, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 7.4, 1H), 7.69 (s, 1H), 7.57 (m, 3H), 6.93 (d, *J* = 8.9, 1H), 6.84 (d, *J* = 8.9, 1H), 6.65 (dd, *J* = 7.8 and 3.5 Hz, 1H), 5.10 (sept, *J* = 6.2 Hz, 1H), 4.76 (d, *J* = 17.3 Hz, 1H), 4.58 (dd, *J* = 11.4 and 7.8 Hz, 1H), 4.41 (dd, *J* = 11.4 and 3.5 Hz, 1H), 4.16 (d, *J* = 17.3 Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 1.33 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 166.9, 162.8, 158.9, 151.6, 150.2, 149.3, 133.7, 133.6,

133.5, 131.4, 130.8, 128.4, 127.7, 126.1, 125.8, 125.7, 124.6, 119.7, 119.0, 114.5, 112.9, 111.0, 72.3, 63.6, 56.0, 55.8, 47.6, 47.5, 21.6. HRMS (negative ESI), m/z: Calcd for $C_{30}H_{28}N_2O_8$: 544.18457 (M^+). Found: 543.17958 (M^+ - 1). Anal. calcd. for $C_{30}H_{28}N_2O_8$: C, 66.17; H, 5.18; N, 5.14. Found: C, 66.50; H, 5.46; N, 5.24.

(1*R,6*S**)1-Hydroxy-2-isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,6-tetrahydropyrazino[1,2-*b*]isoquinolin-4-one (8a).**

Compound **8a** was unstable by flash column chromatography on silica gel, and was purified by precipitation from a mixture of hexane/ethyl acetate (1:1) to yield **8a** (98%) as a pale yellow solid. Mp 94-95 ºC; IR ν_{max} (film): 3351, 2980, 1713 and 1682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 6.72 (s, 2H), 6.39 (s, 1H), 6.22 (ws, 1H), 6.07 (q, *J* = 6.5 Hz, 1H), 4.96 (sept, *J* = 6.1 Hz, 1H), 4.42 (d, *J* = 18.3 Hz, 1H), 4.08 (d, *J* = 18.3 Hz, 1H), 3.97 (s, 6H), 1.30 (m, 3H), 1.30 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 171.2, 162.7, 148.7, 128.4, 123.8, 118.9, 110.2, 109.5, 70.3, 55.8, 55.6, 44.9, 44.3, 22.0. Anal. calcd. for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44. Found: C, 60.57; H, 6.36; N, 7.28.

Methyl 1-hydroxy-2-isopropoxycarbonyl-7,10-dimethoxy-4-oxo-1,2,3,6-tetrahydro-1*H*-pyrazino[1,2-*b*]isoquinoline-6-carboxylate (8b).

Compound **8b** was unstable and could not be purified. It was stored at -5 ºC and this crude product was used for the synthesis of compounds **17,18** and **25** (see below).

1-Hydroxy-2-isopropoxycarbonyl-7,10-dimethoxy-6-naphtycarbonyloxymethyl-1,2,3,6-tetrahydropyrazino[1,2-*b*]isoquinolin-4-one (8d).

Compound **8d** was unstable and could not be purified. It was stored at -5 ºC and this crude product was used for the synthesis of

compounds **19** and **20** (see below).

7,10-Dimethoxy-6-methyl-3,6-dihydropyrazino[1,2-*b*]isoquinolin-4-one (9)

A solution of compound **8a** (100 mg, 0.26 mmol) in 5 mL of a mixture of TFA/H_2SO_4 (20:1) was stirred at room temperature for 16 h. Then the mixture was dropped over a saturated aqueous solution of $NaHCO_3$. The aqueous residue was extracted with dichloromethane (20 mL x 3) and the organic extracts were washed with H_2O and with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give the unstable imine **9** (60 mg, 85%) as a brown oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.99 (bs, 1H), 6.80 (d, *J* = 8.9 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 1H), 6.48 (s, 1H), 6.10 (q, *J* = 6.5 Hz, 1H), 4.69 (d, *J* = 23.2 Hz, 1H), 4.40 (d, *J* = 23.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 1.28 (d, *J* = 6.5Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 164.8, 155.6, 149.6, 149.3, 127.9, 124.8, 119.2, 112.2, 110.0, 108.6, 56.3, 56.2, 56.1, 44.5, 19.7.

7,10-Dimethoxy-2,6-dimethyl-4-oxo-3,4-dihydro-6*H*-pyrazino[1,2-*b*]isoquinolinium iodide (10). To a solution of unpurifed compound **9** in anhydrous methanol (5 mL), methyl iodide (0.03 mL, 0.44 mmol) was added and the mixture was stirred at reflux for 2 h. Then the solvent was removed in vacuo to give **10** (50 mg, 94%) as a green oil. IR ν_{max} (film): 2933, 1575, 1489 and 1261 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.06 (s, 1H), 7.40 (s, 1H), 6.82 (d, *J* = 10.5 Hz, 1H), 6.77 (d, *J* = 10.5 Hz, 1H), 6.35 (q, *J* = 6.7 Hz , 1H), 4.33 (d, *J* = 19.2 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.63 (d, *J* = 19.2 Hz, 1H), 1.50 (d, *J* = 6.7 Hz, 3H), 1.32 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 156.1, 149.7, 149.1, 145.6, 136.8, 126.2, 122.4, 120.0, 109.5, 108.9, 55.8, 55.7, 46.6, 32.1, 24.1, 18.5. Anal. Calcd for $C_{16}H_{19}IN_2O_3$: C, 46.39; H, 4.62; N, 6.76. Found: C, 46.23; H, 4.26; N, 6.45.

General procedure for the 1,3-DPC reactions with hemiaminals 8.

Compounds **8a** or **8b** (0.26 mmol) were dissolved in toluene (5 mL) and the corresponding dipolarophile (alkene or alkyne) (5eq) was added. The reaction was carried out in a closed tube or, alternatively, refluxed for 48 h at 120 ºC or under microwave heating at 140 ºC for 2 h. Then the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel.

Synthesis of compounds 12 and 13.

The reaction of compound **8a** (100 mg, 0.26 mmol) and acrylonitrile (0.037 mL, 1.3 mmol) as described earlier, gave a mixture that was purified by column chromatography on silica gel with hexane/ethyl acetate (8:2) as eluent to give compounds **12** (42%) and **13** (18%) as brown oils.

(1*S,3*R**,12*S**,6*S**) 13-Isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carbonitrile (12).** IR ν_{max} (film): 3369, 2981, 1713 and 1692 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 6.72 (s, 2H), 6.21 (s, 1H), 5.98 (q, *J* = 6.4 Hz, 1H), 5.23 (s, 1H), 5.00 (sept, *J* = 6.1 Hz, 1H), 4.81 (d, *J* = 5.0 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.09 (dd, *J* = 9.2 and 4.0, 1H), 2.59 (m, 1H), 2.43 (m, 1H), 1.29 (d, *J* = 6.1 Hz, 6H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 167.6, 154.2, 148.8, 148.1, 132.4, 122.6, 120.1, 119.0, 109.9, 109.6, 100.4, 70.6, 61.2, 59.4, 55.9, 55.6, 44.5, 35.3, 34.0, 21.9, 19.1. HRMS (negative ESI), m/z: Calcd for $C_{22}H_{25}N_3O_5$: 411.17942 (M^+). Found: 410.17214 (M^+ -1). Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21. Found: C, 64.18; H, 6.06; N, 10.15.

(1*S,3*S**,12*R**,6*S**)-13-Isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carbonitrile (13).** IR ν_{max} (film): 3279, 1713 and 1489 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ: 6.72 (s, 2H), 6.25 (s, 1H), 5.88 (q, *J* = 6.3 Hz, 1H), 5.19 (s, 1H), 4.95 (sept, *J* = 6.3 Hz, 1H), 4.84 (d, *J* = 2.0, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.20 (t, *J* = 8.2 Hz, 1H), 2.63 (m, 2H),

1.28 (m, 6H), 1.23 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 165.3, 148.8, 148.5, 130.8, 122.6, 119.9, 118.4, 110.2, 109.7, 100.8, 77.1, 70.5, 59.9, 55.9, 55.6, 44.2, 37.1, 32.5, 21.9, 18.5. HRMS (negative ESI), m/z: Calcd for $C_{22}H_{25}N_3O_5$: 411.17942 (M^+). Found: 410.17214 (M^+ -1). Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.12; N, 10.21. Found: C, 64.02; H, 5.87; N, 9.96.

Synthesis of compounds 14 and 15.

The reaction of compound **8a** (100 mg, 0.26 mmol) and acrolein (1.3 mmol, 0.1 mL), as described earlier, gave a mixture which was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (7:3) to give compounds **14** (32%) as a yellow solid and **15** (22%) as a brown oil.

(1*S,3*R**,12*S**,6*S**)-13-isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carbaldehyde (14).** Mp 100-101 ºC; IR ν_{max} (film): 2933, 1694 and 1488 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 6.71 (s, 2H), 6.22 (s, 1H), 6.04 (q, *J* = 6.4 Hz, 1H), 5.29 (s, 1H), 4.93 (sept, *J* = 6.3 Hz, 1H), 4.73 (d, *J* = 18.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.97 (dd, *J* = 9.6 and 4.3 Hz, 1H), 2.69 (m, 1H), 2.23 (m, 1H), 1.27 (d, *J* = 6.3 Hz, 6H), 1.20 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 198.2, 168.7, 154.6, 149.0, 148.0, 127.8, 122.7, 119.6, 118.7, 109.6, 109.4, 70.2, 60.0, 57.7, 55.9, 55.6, 44.5, 28.4, 21.9, 19.2. HRMS (negative ESI), m/z: Calcd for $C_{22}H_{26}N_2O_6$: 414.17909 (M^+). Found: 413.17181 (M^+ -1). Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.54; H, 6.26; N, 6.45.

(1*S,3*S**,12*R**,6*S**)-13-Isopropoxycarbonyl-7,10-dimethoxy-6-methyl-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carbaldehyde (15).** IR ν_{max} (film): 3448, 2936, 1684 and 1488 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 6.69 (s, 2H), 6.22 (s, 1H), 5.92 (q, *J* = 6.3 Hz, 1H), 5.18 (bs, 1H), 4.89 (sept, *J* = 6.3 Hz, 1H), 4.81 (d, *J* = 14.0, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.16 (m, 1H),

2.70 (m, 1H), 2.38 (m, 1H), 1.25 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 197.8, 166.5, 148.8, 148.4, 132.5, 122.6, 118.9, 109.8, 109.6, 99.5, 69.9, 60.3, 57.7, 56.0, 55.6, 54.4, 44.1, 29.7, 21.9, 18.4. HRMS (negative ESI), m/z: Calcd for $C_{22}H_{26}N_2O_6$: 414.17909 (M^+). Found: 413.17181 (M^+ -1). Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.27; H, 6.05; N, 6.33.

(1*S,2*S**,3*R**,6*S**,12*S**) Ethyl 13-isopropoxycarbonyl-7,10-dimethoxy-2,6-dimethyl-4-oxo-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carboxylate (16).**

The reaction of compound **8a** (100 mg, 0.26 mmol) and ethyl crotonate (0.15 mL, 1.3 mmol), as described earlier, gave a a crude product which was purified by column chromatography on silica gel with dichloromethane as eluent to give compound **16** as a brown solid (72 mg, 70%). Mp 60-61 ºC; IR ν_{max} (film): 3056, 1628 and 1591 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.72 (d, *J* = 8.9 Hz, 1H), 6.68 (d, *J* = 8.9 Hz, 1H), 6.13 (s, 1H), 6.07 (q, *J* = 6.5 Hz, 1H), 5.13 (s, 1H), 4.92 (sept, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.4 Hz, 1H), 4.24 (dd, *J* = 11.1 and 7.1 Hz, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 2.88 (m, 1H), 2.48 (d, *J* = 5.7 Hz, 1H), 1.35-1.36 (m, 15H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 172.1, 167.3, 154.5, 148.9, 147.9, 135.2, 122.7, 119.8, 109.4, 109.1, 69.8, 65.2, 61.4, 59.7, 56.0, 55.9, 44.5, 40.3, 21.9, 19.2, 15.9, 14.5. HRMS (negative ESI), m/z: Calcd for $C_{25}H_{32}N_2O_7$: 472.22095 (M^+). Found: 471.21367 (M^+ -1). Anal. Calcd for $C_{25}H_{32}N_2O_7$: C, 63.54; H, 6.83; N, 5.93. Found: C, 63.21; H, 6.55; N, 5.72.

Synthesis of compounds 17 and 18

The reaction of compound **8b** (100 mg, 0.26 mmol) and *tert*-butyl acrilate (0.1 mL, 1.3 mmol) as described earlier, gave a mixture which was purified by column chromatography on silica gel eluting with hexane/dichloromethane (8/2) to give compounds **17** (52 mg, 20%) and **18** (54 mg, 23%) as yellow oils.

(1*S,3*S**,6*R**,12*R**)-13-Isopropoxycarbonyl-7,10-dimethoxy-4-oxo-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-**

carboxylic acid *tert*-butyl ester 6-caboxylic acid methyl ester (17). IR ν_{max} (film): 3438, 2094, 1649 and 1491 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.77 (s, 2H), 6.55 (s, 1H), 6.11 (s, 0.7H), 6.05 (s, 0.3H), 5.17 (s, 0.7H), 5.09 (s, 0.3H), 4.88 (m, 1H), 4.86 (m, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 3.44 (m, 1H), 2.53 (m, 2H), 1.49 (s, 9H), 1.22 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 171.7, 169.9, 167.8, 166.6, 150.4, 148.2, 135.0, 120.4, 115.2, 111.0, 110.4, 99.0, 81.6, 69.5, 60.5, 60.3, 56.2, 56.0, 52.8, 49.4, 47.9, 34.6, 28.0, 21.9. HRMS (negative ESI), m/z: Calcd for $C_{27}H_{34}N_2O_9$: 530.22643 (M^+). Found: 529.21601 (M^+ -1). Anal. Calcd for $C_{27}H_{34}N_2O_9$: C, 61.12; H, 6.46; N, 5.28. Found: C, 60.86; H, 6.11; N, 5.03.

(1*S,3*R**,6*R**,12*S**)-13-Isopropoxycarbonyl-7,10-dimethoxy-4-oxo-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carboxylic acid *tert*-butyl ester 6-caboxylic acid methyl ester (18).** IR ν_{max} (film): 3433, 2979, 1702 and 1490 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 6.64 (s, 2H), 6.52 (s, 1H), 6.02 (s, 1H), 5.18 (s, 1H), 4.91 (sept, J = 6.2 Hz, 1H), 4.72 (m, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.45 (s, 3H), 2.76 (dd, J = 9.4 and 5.0 Hz, 1H), 2.48 (m, 1H), 2.01 (m, 2H), 1.36 (s, 9H), 1.14 (d, J = 6.2 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 171.0, 169.8, 168.9, 153.9, 150.5, 147.8, 136.4, 121.0, 115.7, 111.0, 110.1, 98.6, 81.9, 69.6, 60.0, 59.4, 56.2, 56.0, 51.0, 49.4, 47.2, 31.7, 27.9, 22.2. HRMS (negative ESI), m/z: Calcd for $C_{27}H_{34}N_2O_9$: 530.22643 (M^+). Found: 529.21915 (M^+ -1). Anal. Calcd for $C_{27}H_{34}N_2O_9$: C, 61.12; H, 6.46; N, 5.28. Found: C, 60.77; H, 6.21; N, 5.10.

Synthesis of compounds 19 and 20

The reaction of compound **8d** (100 mg, 0.26 mmol) and *tert*-butyl acrilate (0.1 mL, 1.3 mmol) as described earlier, gave a mixture which was purified by column chromatography on silica gel eluting with hexane/dichloromethane (8/2) to give an inseparable mixture containing **19** and **20** (55%) as a yellow oil.

(1*S,3*S**,6*R**,12*R**) and (1*R**,3*R**,6*R**,12*R**) *tert*-Butyl 13-isopropoxycarbonyl-7,10-dimethoxy-6-naphtycarbonyloxymethyl-4-oxo-1,2,3,4,6,12-hexahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carboxylate (19 and 20).**

IR ν_{max} (film): 2978, 1713, 1593cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 8.89 (m, 1.3H), 8.18 (m, 1.3H), 8.02 (m, 1.3H), 7.85 (m, 1.3H), 7.54 (m, 3.9H), 6.75 (m, 2.6H), 6.50 (m, 1H), 6.39 (m, 0.3H), 6.18 (m, 1.3H), 5.32 (s, 1.3H), 4.88 (m, 1.3H), 4.66 (sept, *J* = 6.2 Hz, 1.3H), 4.35 (dd, *J* = 10.9 and 3.7 Hz, 1.3H), 4.55 (m, 1.3H), 3.82 (m, 8H), 3.03 (m, 0.3H), 2.94 (q, *J* = 12.5 Hz, 1H), 2.58 (m, 1H), 2.34 (m, 0.3H), 2.21 (m, 1.3H), 2.07 (m, 0.3H), 1.52-1.20 (m, 19 H). ^{13}C NMR (63 MHz, $CDCl_3$) δ:171.3, 171.1, 167.5, 167.0, 166.9,153.6, 149.6, 149.3, 148.5, 147.9, 135.9, 134.2, 133.7, 133.6, 133.3, 131.5, 131.3, 130.8, 128.4, 128.3, 127.8, 127.5, 126.0, 125.8, 124.7, 124.5, 121.3, 120.7, 117.0, 116.8, 110.7, 109.6, 109.2, 99.3, 97.7, 81.9, 81.5, 69.6, 69.5, 64.3, 60.7, 60.6, 59.9, 56.0, 55.6, 47.7, 47.1, 46.8, 31.9, 29.6, 27.9, 27.8, 21.9, 21.7. HRMS (negative ESI), m/z: Calcd for $C_{37}H_{40}N_2O_9$: 656.27338 (M^+). Found: 701.27158 (M^+ -1 + 2 Na). Anal. calcd. for $C_{37}H_{40}N_2O_9$: C, 67.67; H, 6.14; N, 4.27. Found: C, 67.20; H, 6.30; N, 4.11.

Synthesis of compounds 21 and 22

The reaction of compound **8a** (100 mg, 0.26 mmol) and diethyl acetylenedicarboxylate (0.2 mL, 1.3 mmol), as described earlier, gave a mixture which was purified by column chromatography on silica gel eluting with hexane/dichloromethane (8:2) to give compounds **21** (56%) and **22** (14%) as brown oils.

(3*R,6*S**,12*S**) Diethyl 13-isopropoxycarbonyl-7,10-dimethoxy-6-methyl-4-oxo-3,4,6,12-tetrahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1,2-dicarboxylate (21).** IR ν_{max} (film): 2982, 1726, 1489 and 1370 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.70 (s, 2H), 6.35 (s, 1H), 5.95 (q, *J* = 6.4 Hz, 1H), 5.59 (s, 1H), 5.28 (s, 1H), 4.92 (sept, *J* = 6.2 Hz, 1H), 4.34 (m, 4H), 3.82 (s, 3H), 3.80 (s, 3H), 1.34 (m,

6H), 1.24 (m, 6H), 1.10 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 161.4, 161.2, 148.8, 148.7, 142.5, 140.7, 137.4, 127.5, 123.9, 110.2, 109.5, 102.8, 70.3, 66.3, 63.7, 62.1, 61.8, 55.9, 55.7, 44.5, 22.0, 21.9, 17.3, 14.0. HRMS (negative ESI), m/z: Calcd for $C_{27}H_{32}N_2O_9$: 528.21078 (M^+). Found: 551.19843 (M^+ + Na). Anal. Calcd for $C_{27}H_{32}N_2O_9$: C, 61.35; H, 6.10; N, 5.30. Found: C, 61.03; H, 5.86; N, 5.03.

(3*S,6*S**,12*R**) Diethyl 13-isopropoxycarbonyl-7,10-dimethoxy-6-methyl-4-oxo-3,4,6,12-tetrahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1,2-dicarboxylate (22).** IR ν_{max} (film): 2922, 1721, 1488 and 1373 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.71 (s, 2H), 6.27 (s, 1H), 5.97 (q, J = 6.5 Hz, 1H), 5.53 (s, 1H), 5.20 (s, 1H), 5.02 (sept, J = 6.2 Hz, 1H), 4.33 (m, 4H), 3.80 (s, 6H), 1.42-1.23 (m, 15H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 161.5, 160.8, 160.3, 148.9, 148.5, 139.4, 138.8, 128.5, 123.8, 119.3, 110.2, 109.9, 101.6, 70.5, 66.8, 62.1, 61.8, 55.9, 55.7, 44.6, 21.9, 19.4, 14.0. HRMS (negative ESI), m/z: Calcd for $C_{27}H_{32}N_2O_9$: 528.21078 (M^+). Found: 551.19825 (M^+ + Na). Anal. Calcd for $C_{27}H_{32}N_2O_9$: C, 61.35; H, 6.10; N, 5.30. Found: C, 60.92; H, 5.73; N, 4.97.

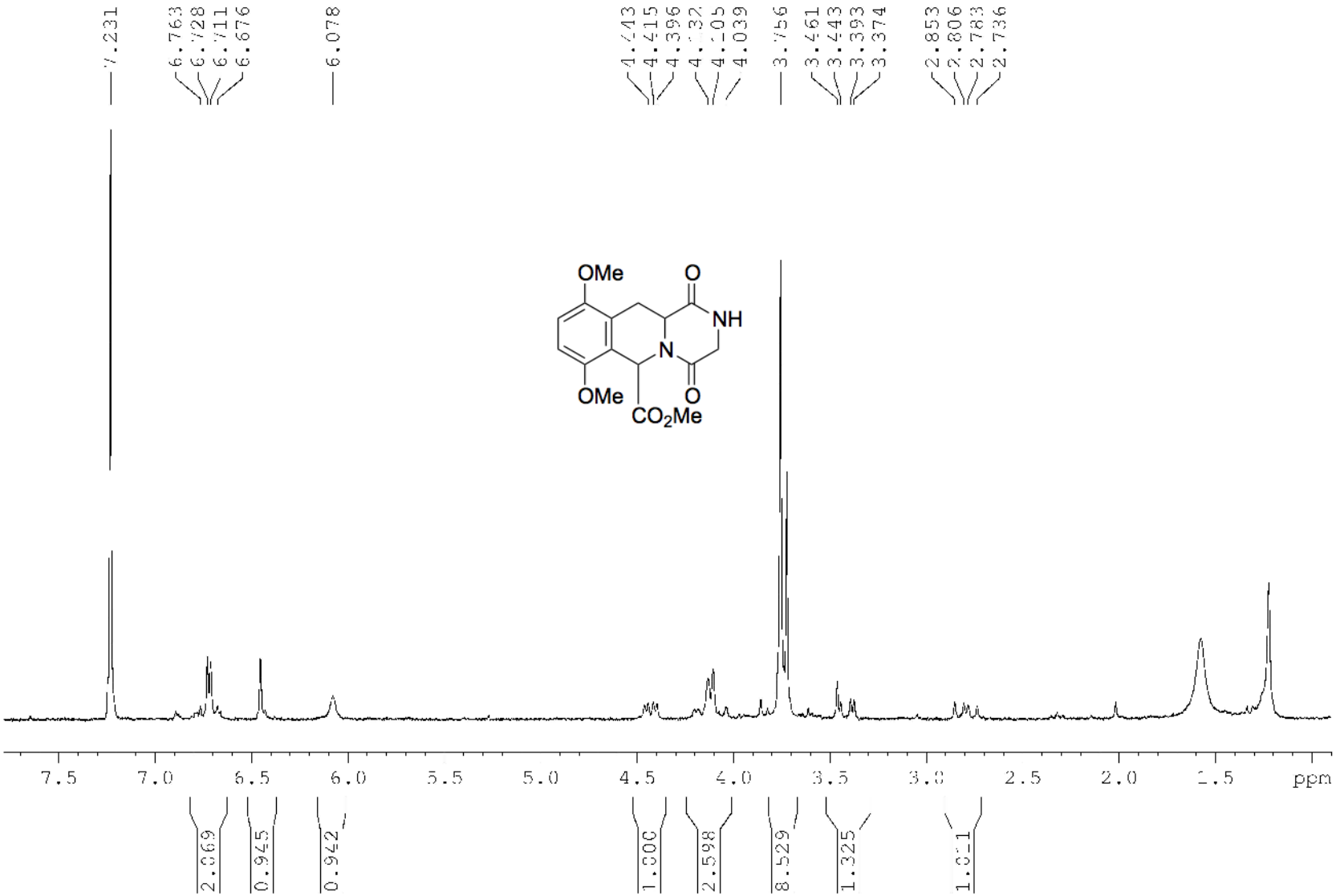
(3*R,6*S**,12*S**) and (3*S**,6*S**,12*R**) Methyl 13-isopropoxycarbonyl-7,10-dimethoxy-6-methyl-4-oxo-3,4,6,12-tetrahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1-carboxylate (23 and 24).** The reaction of compound **8** (100 mg, 0.26 mmol) and methyl propiolate (0.1 mL, 1.3 mmol) as described earlier, gave a crude product which was purified by column chromatography on silica gel eluting with hexane/dichloromethane (8:2) to give an inseparable mixture containing **23** and **24**. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (d, J = 2.9 Hz, 1H), 7.06 (d, J = 3.0 Hz, 1H), 6.67 (s, 4H), 6.37 (s, 1H), 6.26 (s, 1H), 6.00 (q, J = 6.5 Hz, 1H), 5.88 (q, J = 6.3 Hz, 1H), 5.48 (m, 2H), 5.12 (d, J = 3.9 Hz, 1H), 5.05 (m, 1H), 4.87 (sept, J = 6.3 Hz, 1H), 4.92 (sept, J = 6.2 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 1.35-1.15 (m, 18H), 1.04 (d, J = 6.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ: 162.1, 161.5, 148.8, 148.7, 148.6, 148.4, 140.2, 138.9, 138.2, 128.4, 127.7, 123.7, 123.5, 119.4, 119.0, 109.9, 109.6, 109.4, 102.2, 70.2, 69.9, 66.0, 65.5, 60.9, 56.1, 55.9, 55.6, 55.5, 52.3, 52.1, 44.5, 44.3, 21.8, 20.7, 17.4, 17.2. HRMS (negative ESI), m/z: Calcd for $C_{23}H_{26}N_2O_7$: 442.17400 (M^+). Found: 465.16322 (M^+ + Na). Anal. Calcd

for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.99; H, 6.22; N, 5.93.

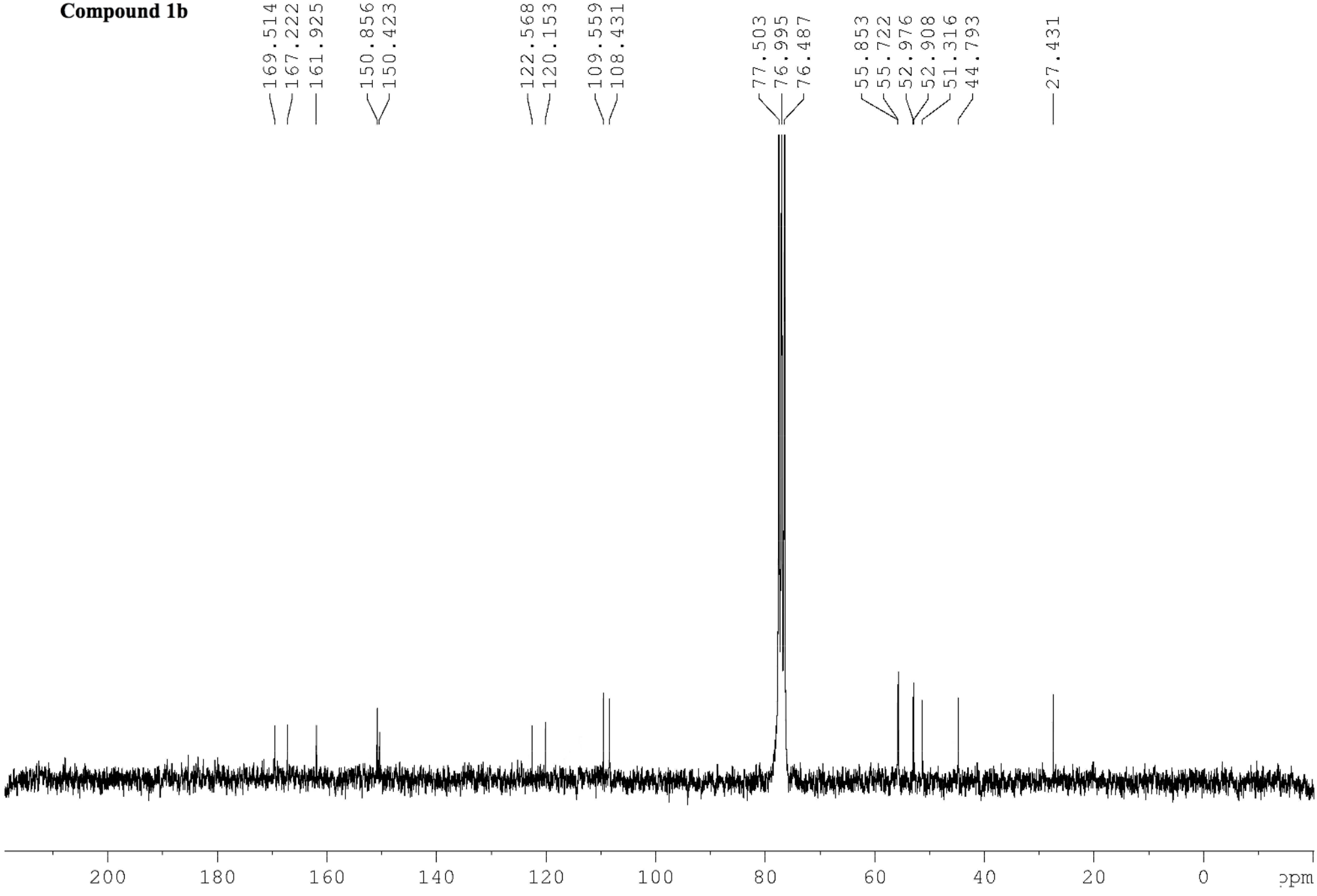
(3*R,6*R**,12*S**) Diethyl 13-isopropoxycarbonyl-7,10-dimethoxy-6-methoxycarbonyl-4-oxo-3,4,6,12-tetrahydro-3,12-iminoazepino[1,2-*b*]isoquinoline-1,2-dicarboxylate (25)**

The reaction of compound **8b** (100 mg, 0.26 mmol) and diethyl acetylenedicarboxylate (0.2 mL, 1.3 mmol), as described earlier, gave a mixture which was purified by column chromatography on silica gel eluting with hexane/dichloromethane (7:3) to give compound **25** (23%) as a brown oil. IR ν_{max} (film): 3424, 1698 and 1490 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.78 (s, 2H), 6.61 (s, 1H), 6.30 (s, 1H), 5.62 (bs, 1H), 5.29 (s, 1H), 5.11 (sept, J = 6.2 Hz, 1H), 4.27 (m, 4H), 4.21 (s, 3H), 4.16 (s, 3H), 3.62 (s, 3H), 1.33 (m, 6H), 1.32 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.9, 161.5, 160.8, 160.3, 153.1, 151.1, 148.5, 144.8, 139.4, 129.8, 117.1, 116.6, 111.1, 110.7, 101.7, 67.4, 62.5, 62.2, 61.8, 56.3, 56.0, 52.7, 49.4, 27.2, 21.9, 13.9, 13.7. HRMS (negative ESI), m/z: Calcd for $C_{28}H_{32}N_2O_{11}$: 572.20061 (M^+). Found: 595.18983 (M^+ + Na). Anal. Calcd for $C_{28}H_{32}N_2O_{11}$: C, 58.74; H, 5.63; N, 4.89. Found: C, 58.45; H, 5.34; N, 4.43.

Compound 1b



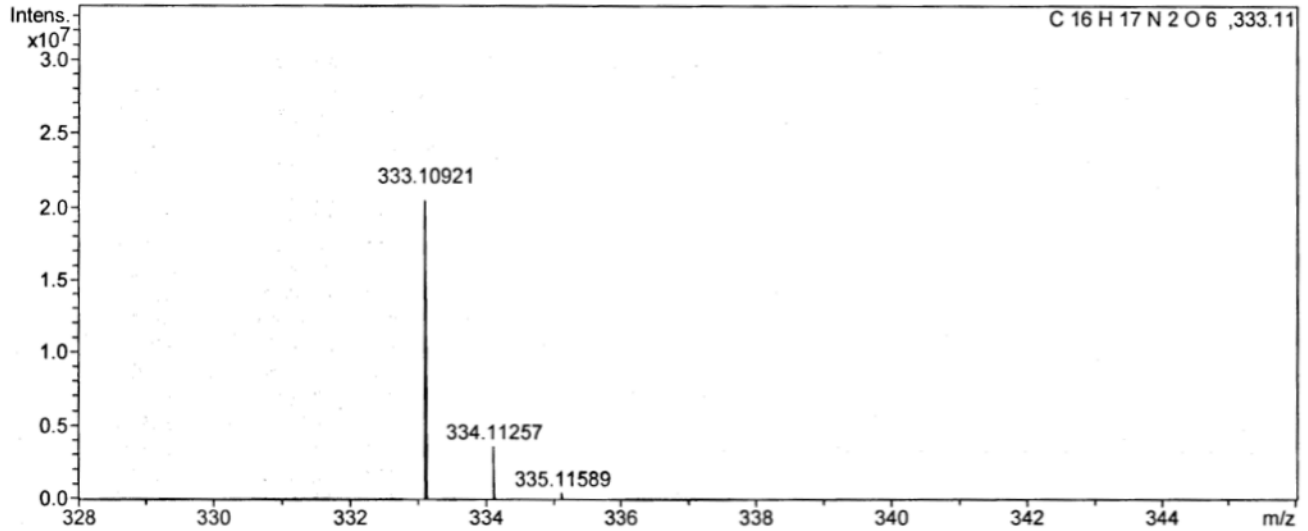
Compound 1b



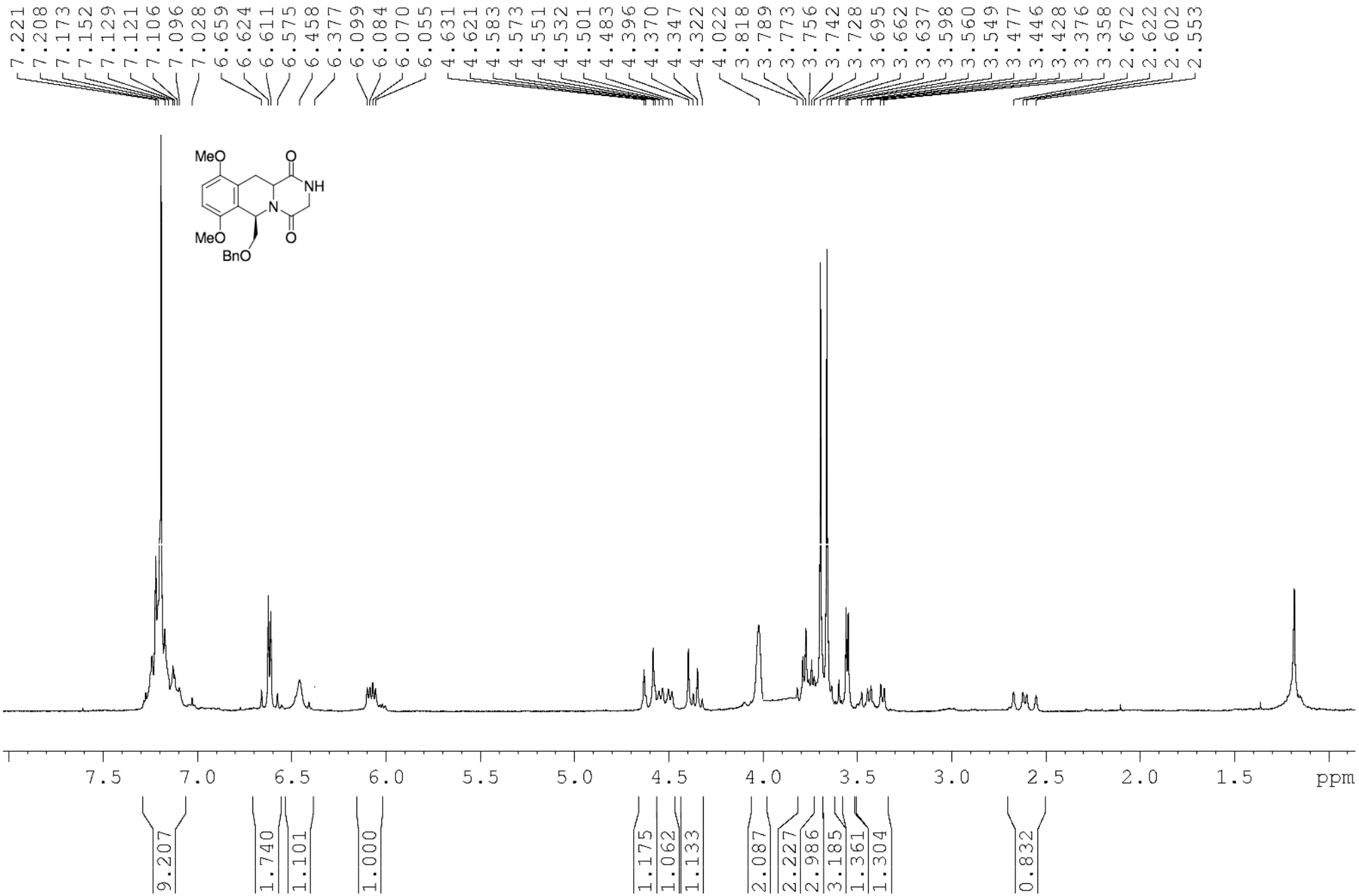
Compound 1b

HRMS

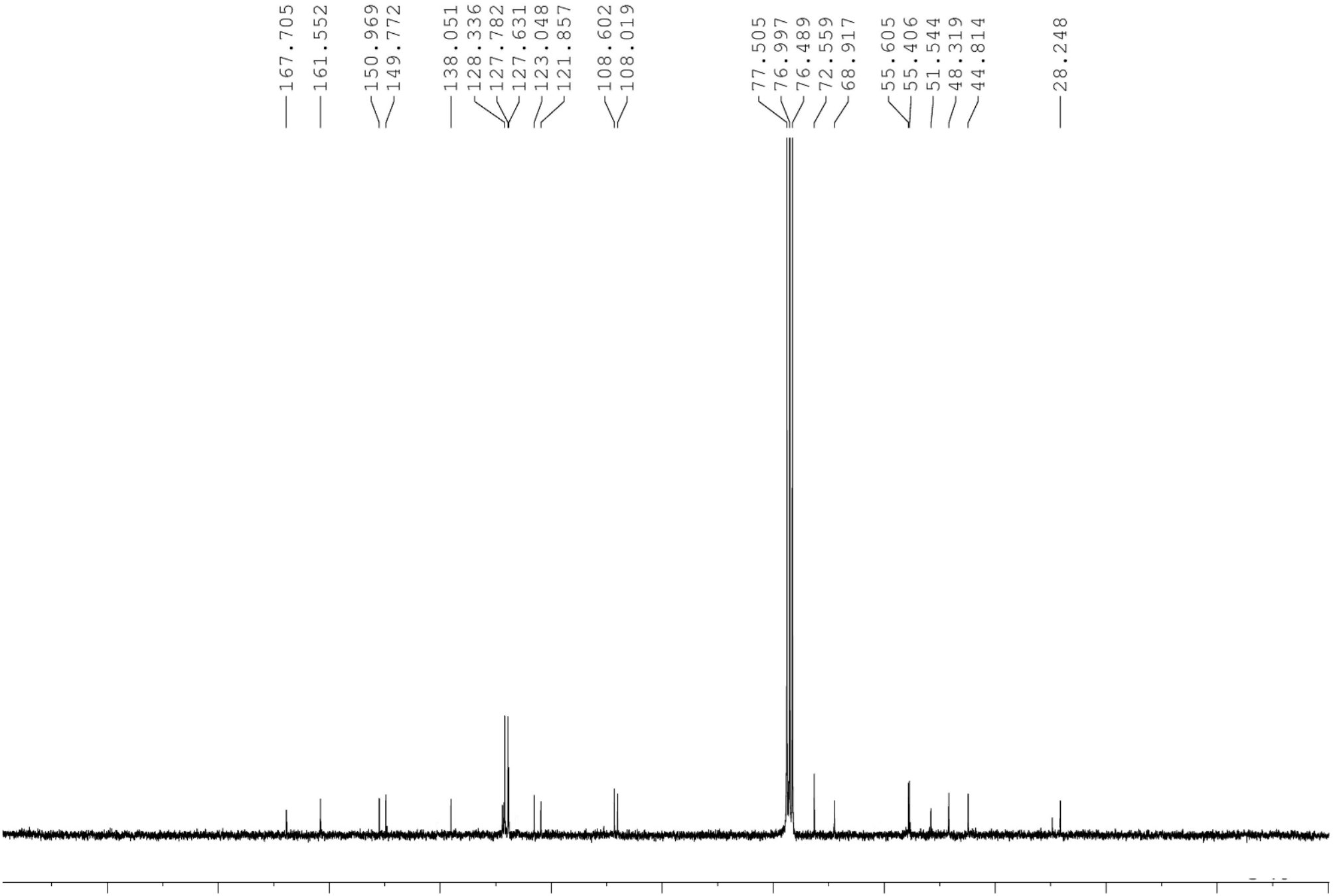
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e¯ Conf
C 16 H 17 N 2 O 6	333.10921	3.1	2.9	1.0	32.35	9.5	even



Compound 1c



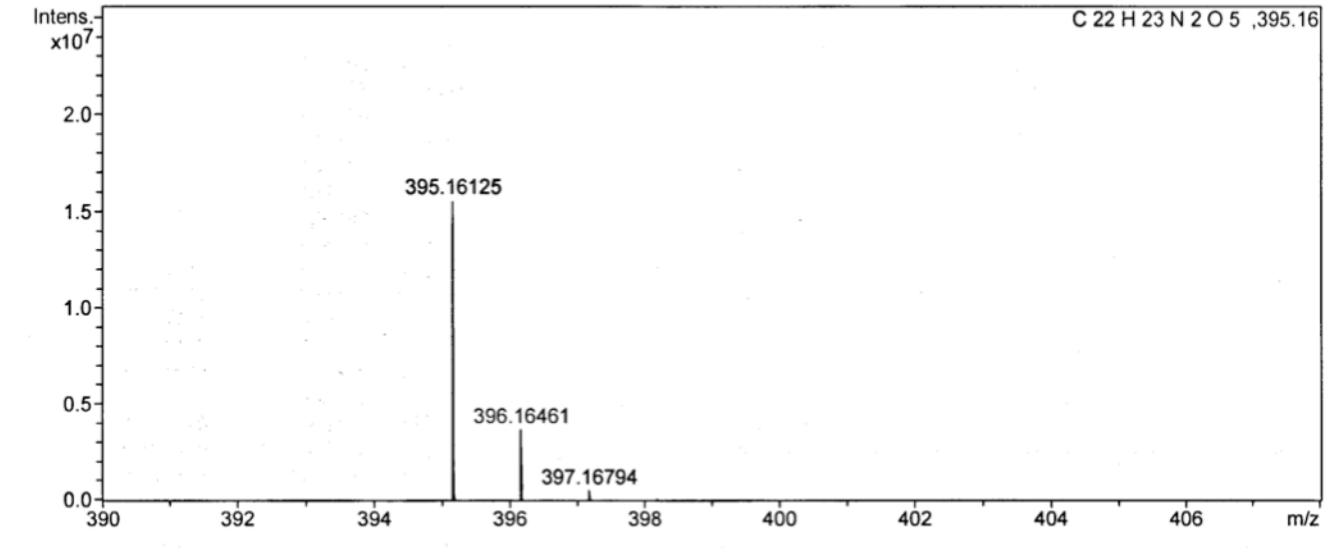
Compound 1c



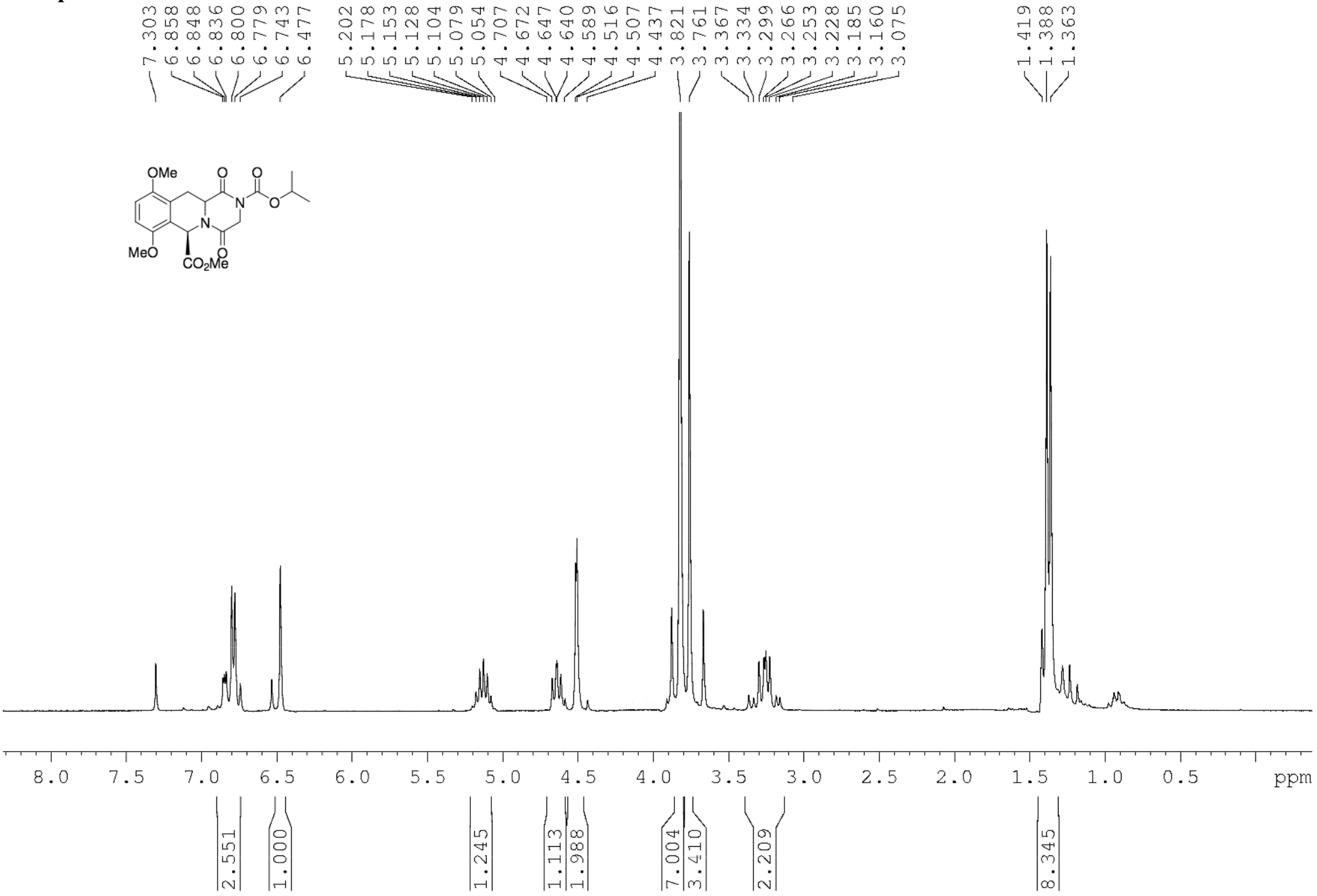
Compound 1c

HRMS

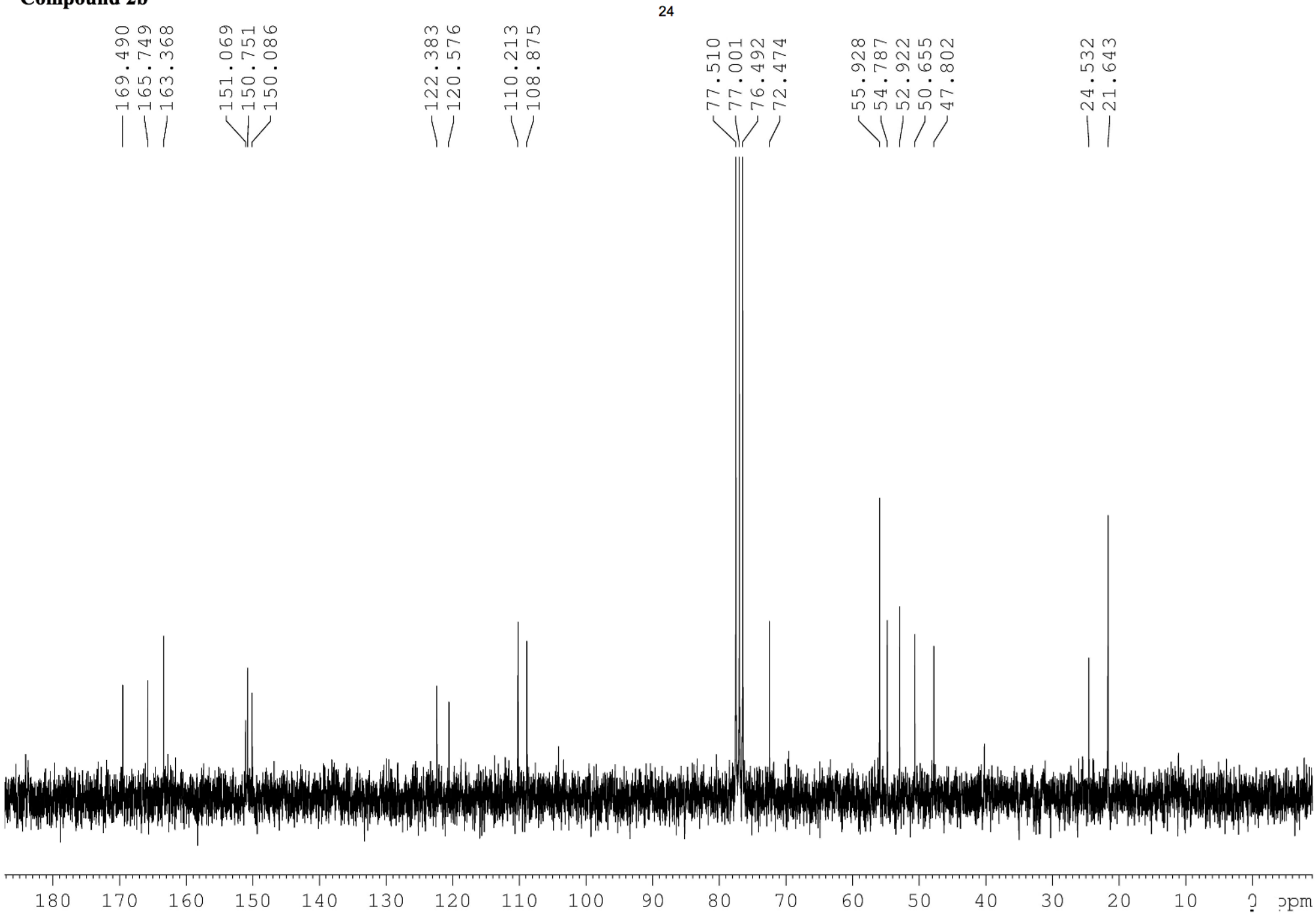
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e⁻ Conf
C 22 H 23 N 2 O 5	395.16125	3.2	3.0	1.3	35.56	12.5	even



Compound 2b



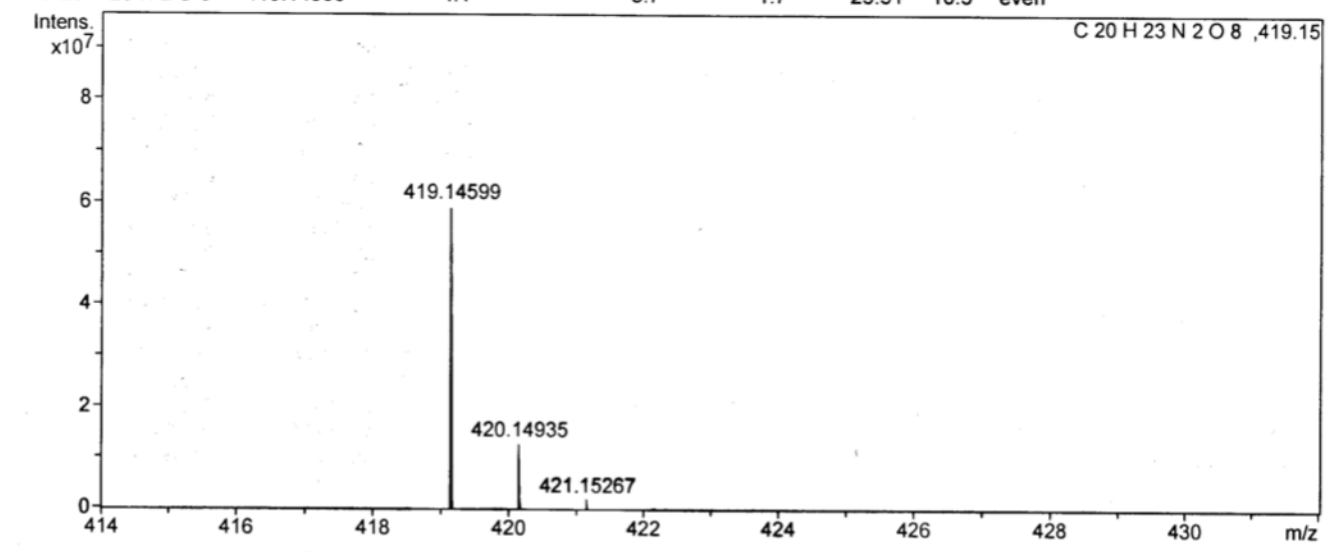
Compound 2b



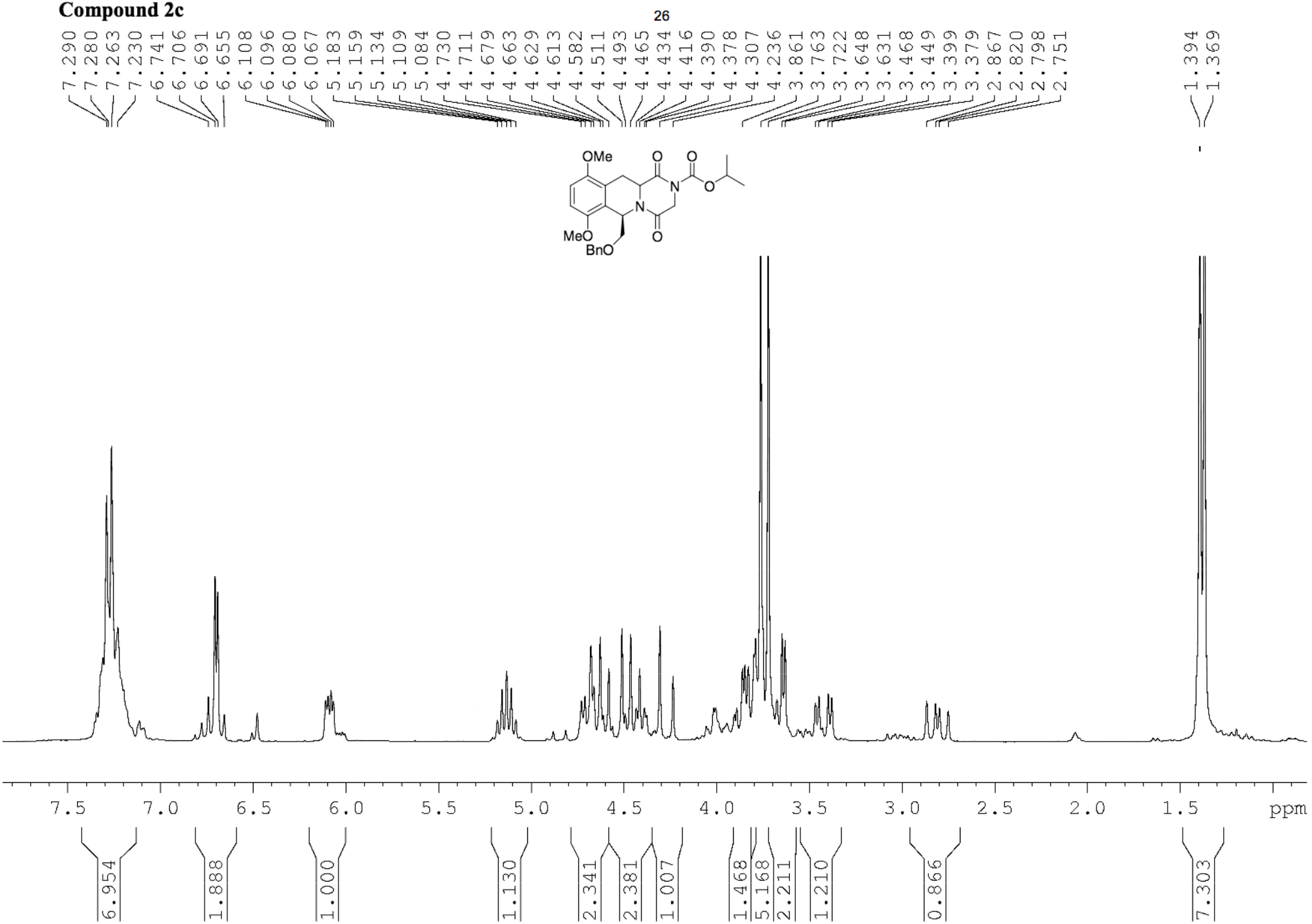
Compound 2b

HRMS

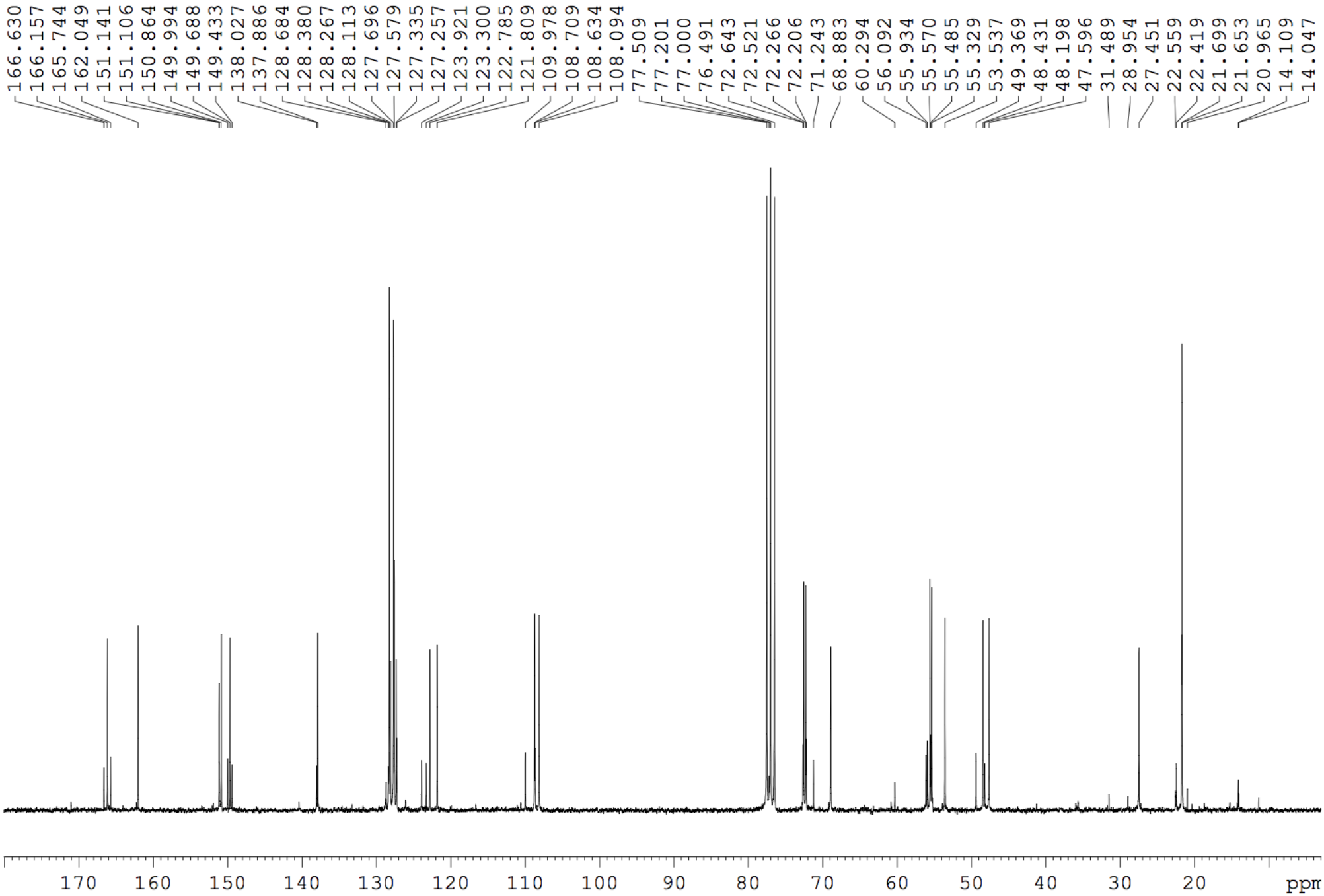
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e^- Conf
C 20 H 23 N 2 O 8	419.14599	4.1	3.7	1.7	25.31	10.5	even



Compound 2c



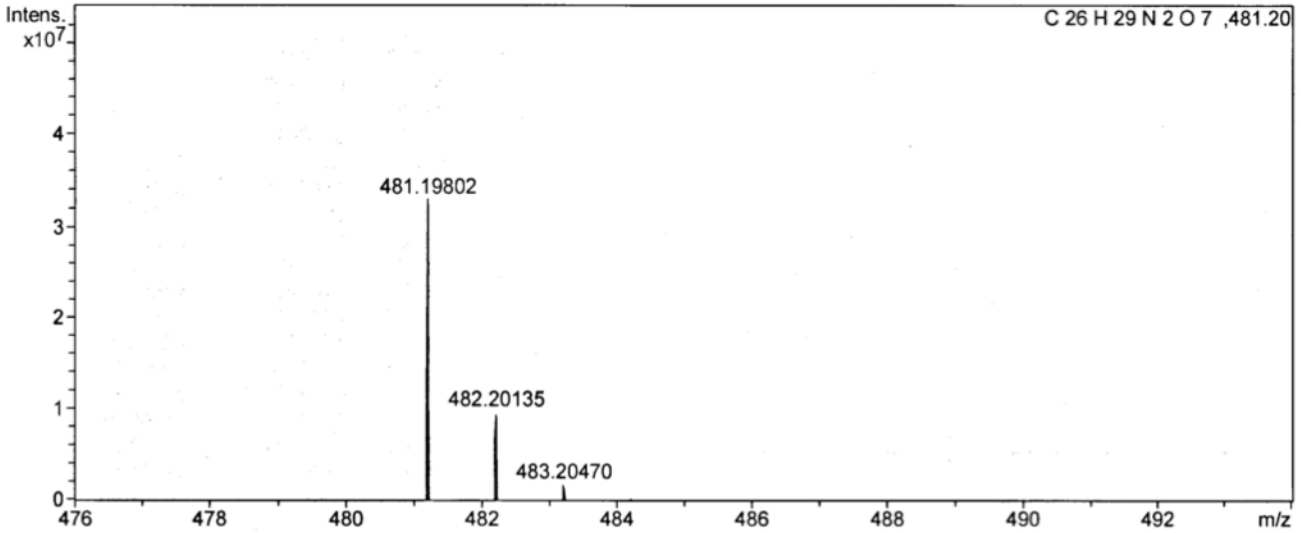
Compound 2c



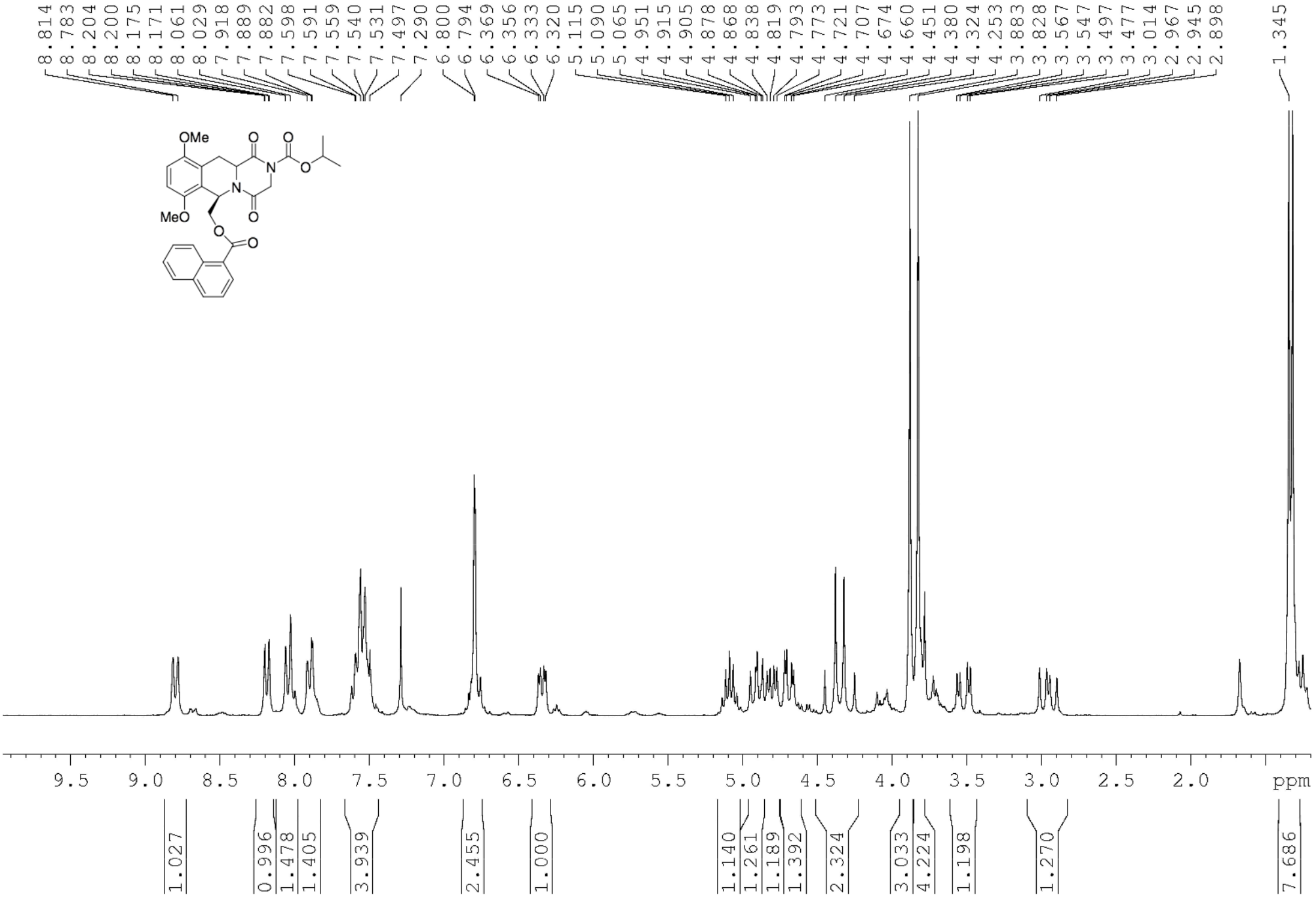
Compound 2c

HRMS

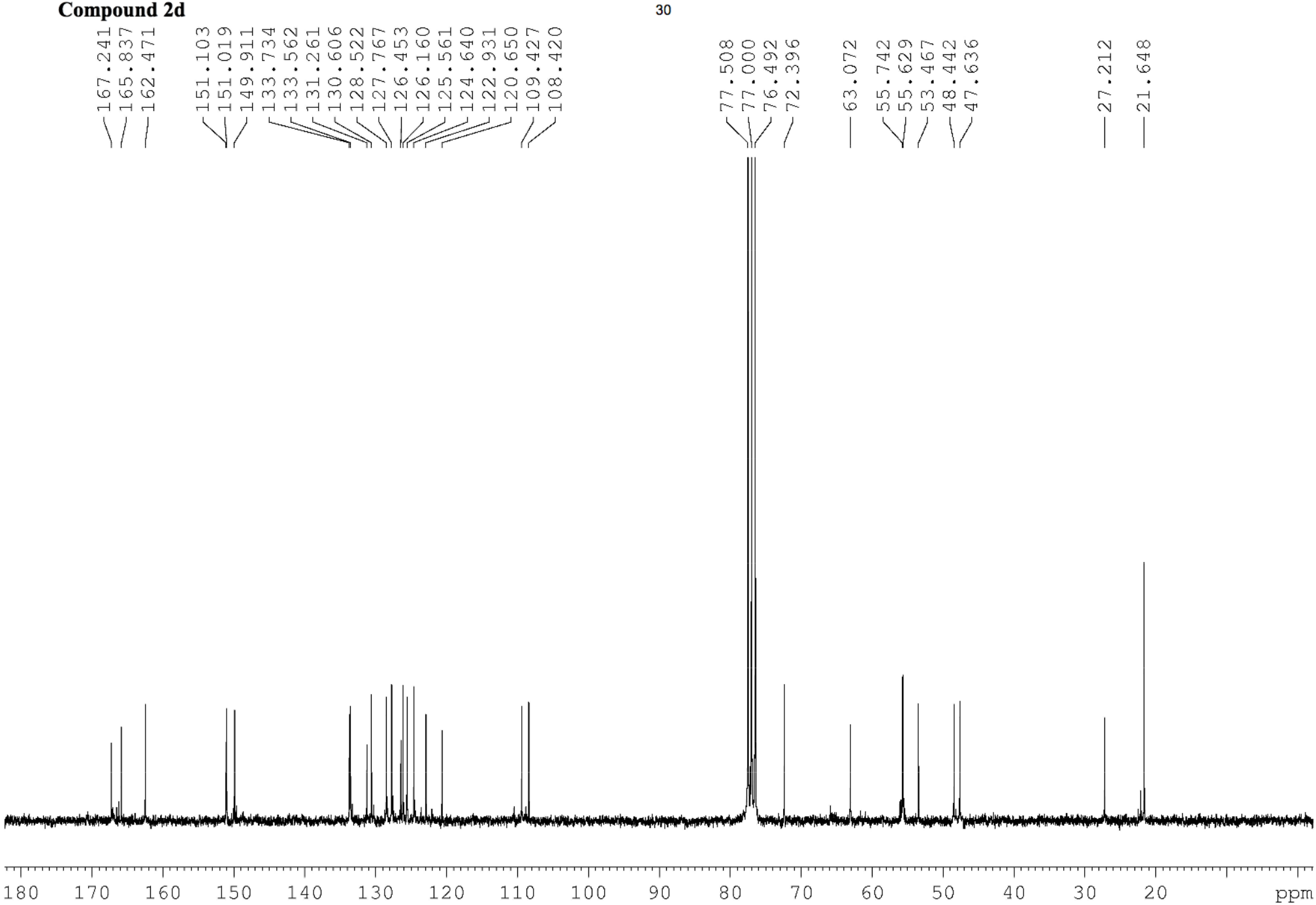
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e^- Conf
C 26 H 29 N 2 O 7	481.19802	-2.2	-2.4	-1.0	26.12	13.5	even



Compound 2d

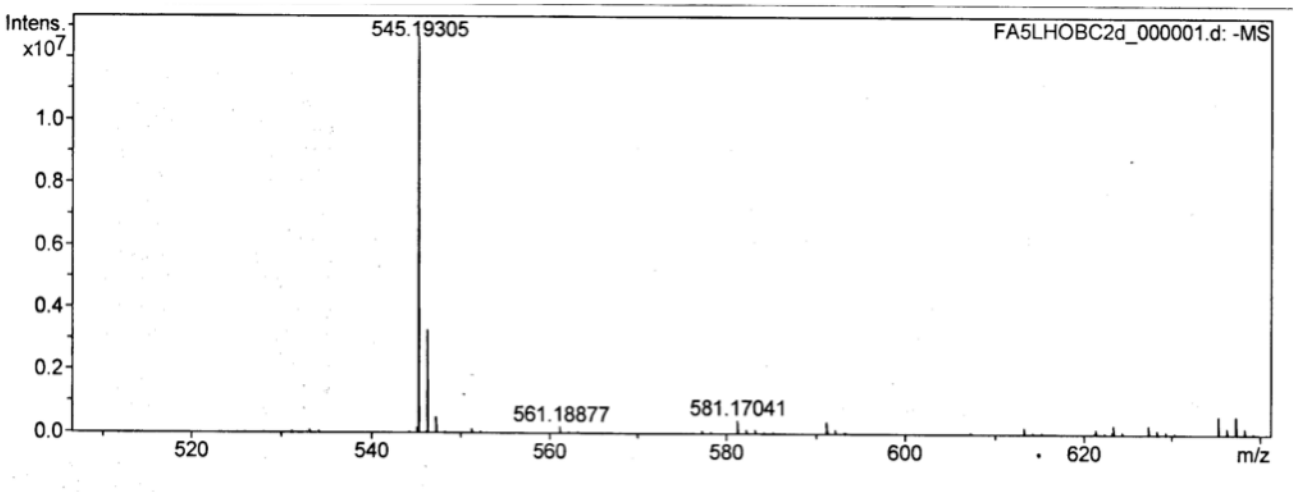


Compound 2d

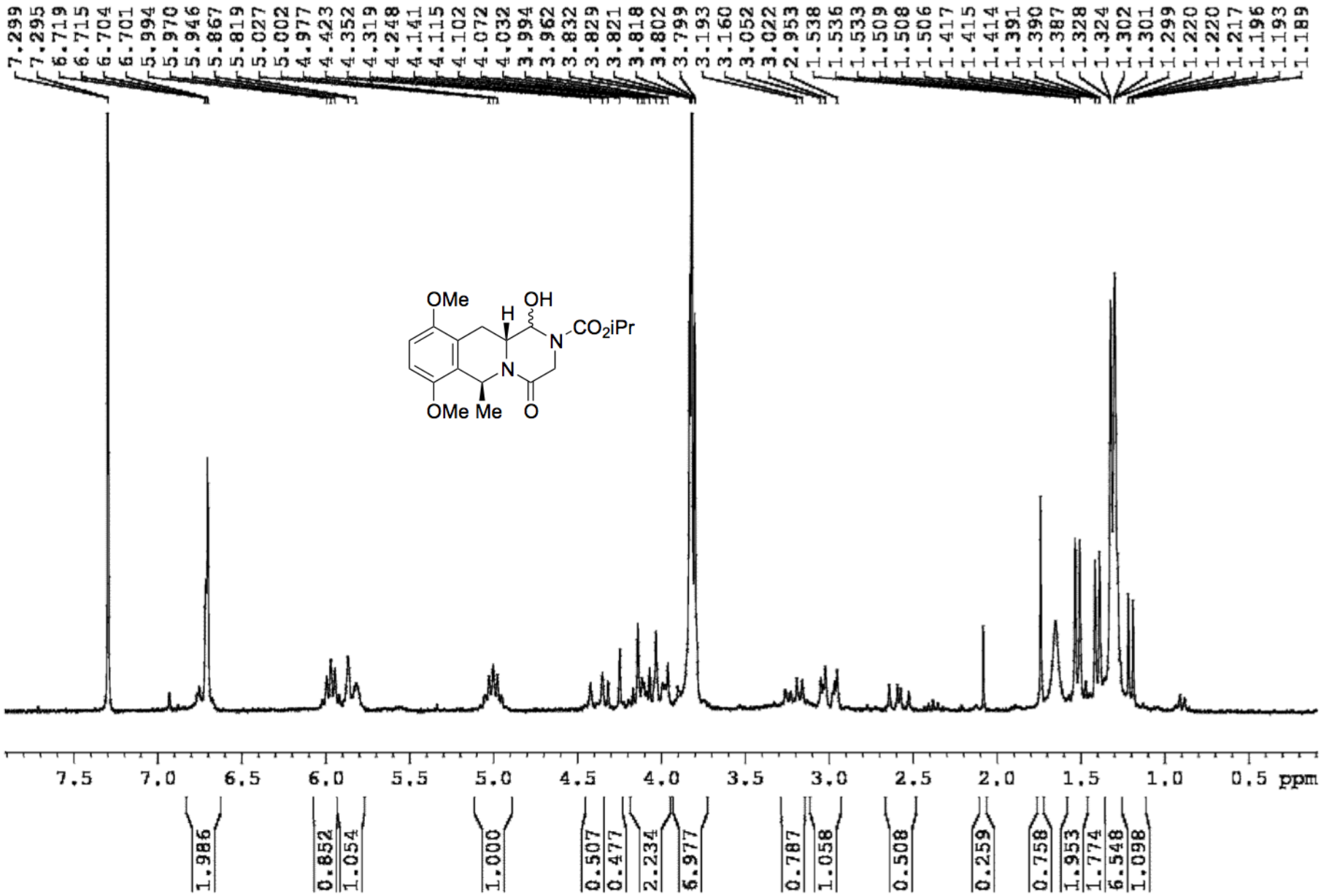


Compound 2d

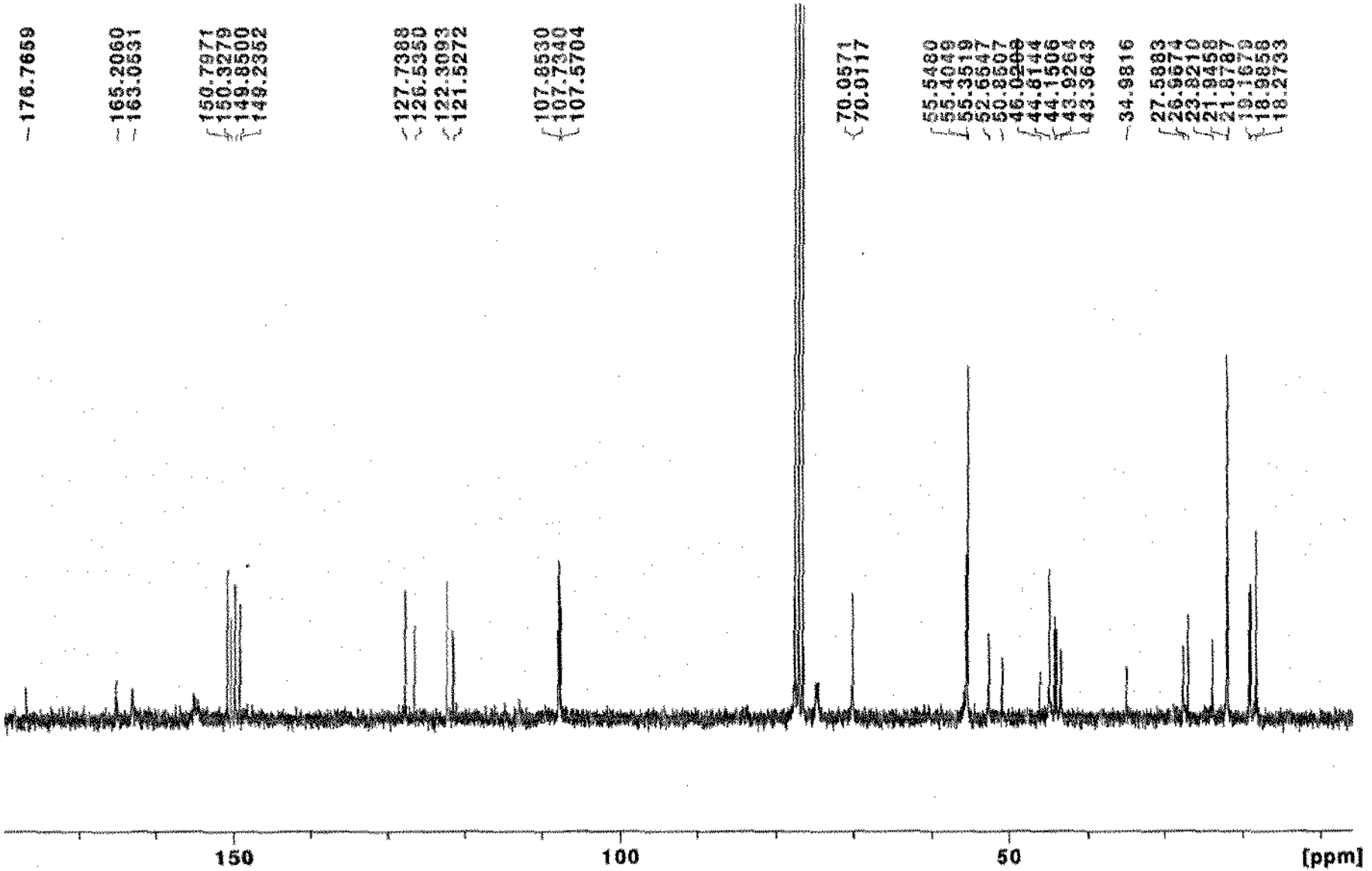
HRMS



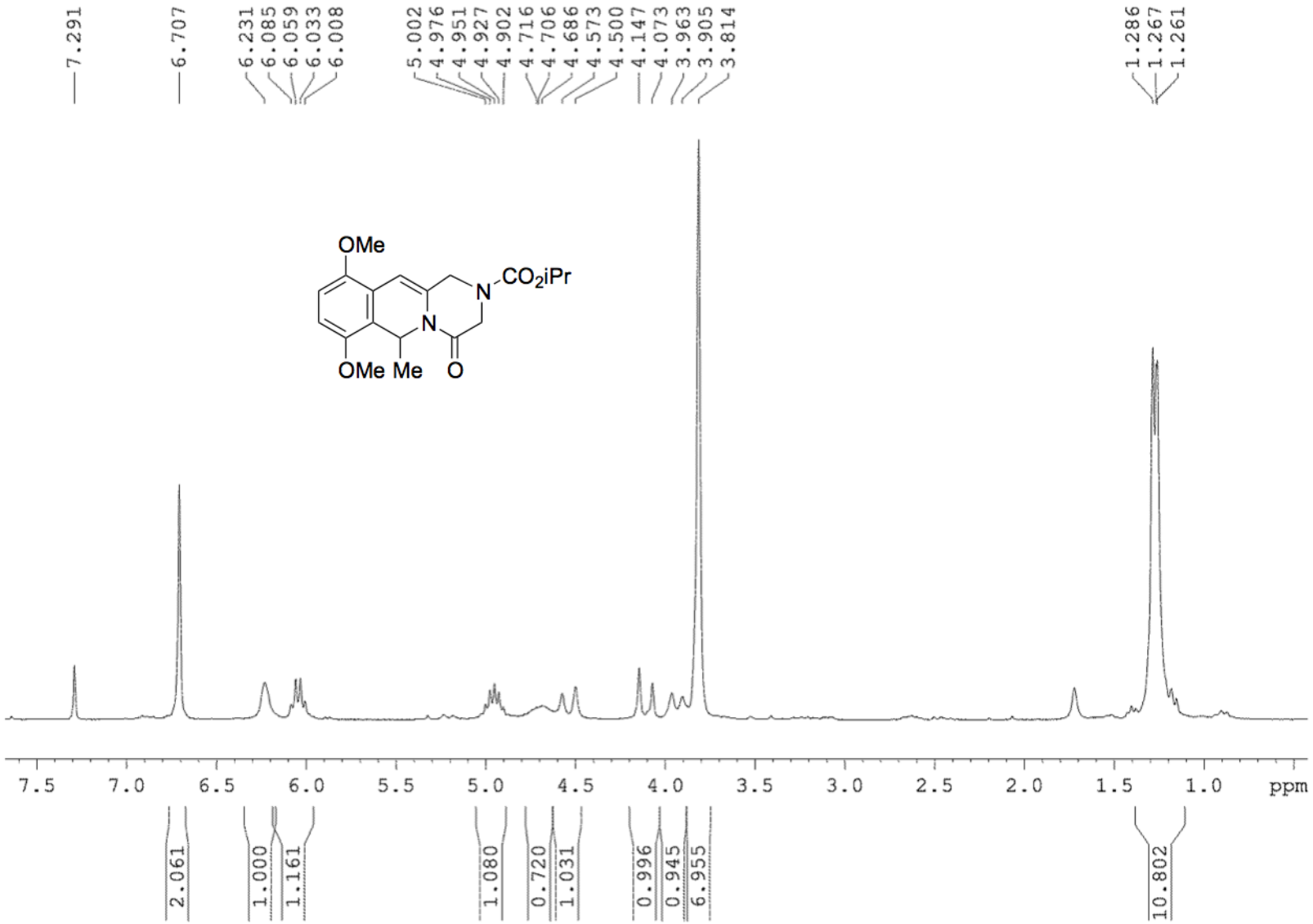
Compound 3a



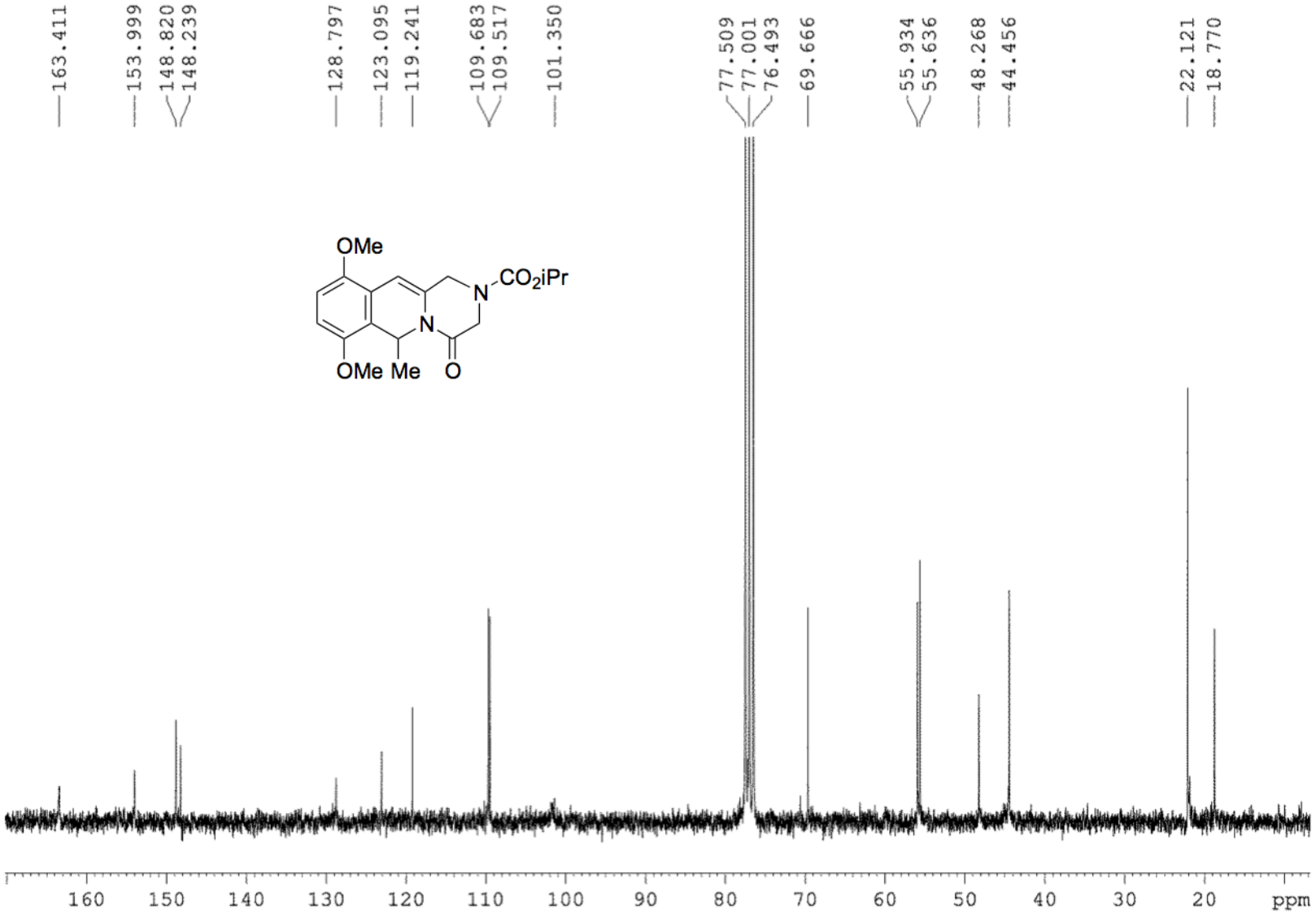
Compound 3a



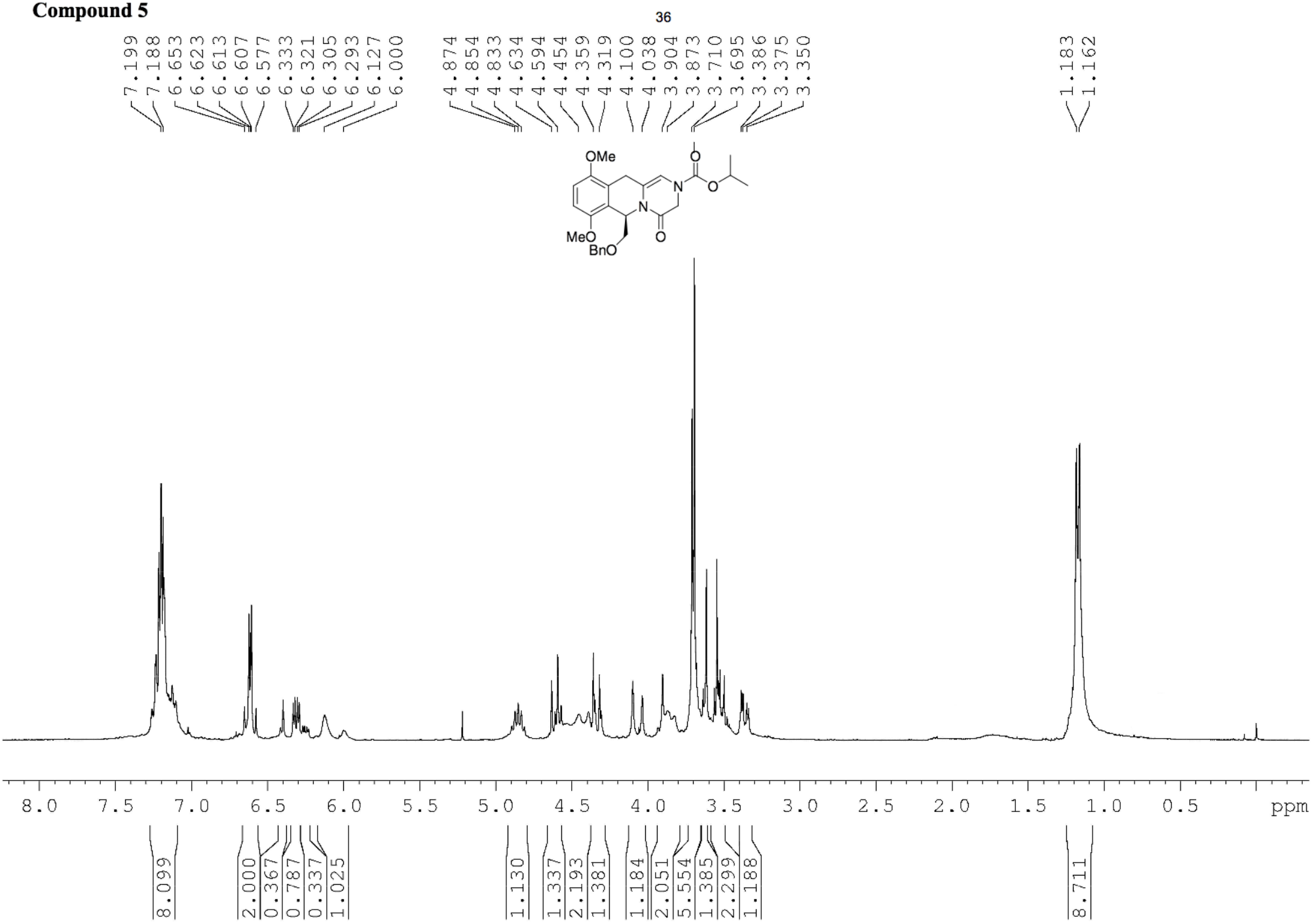
Compound 4



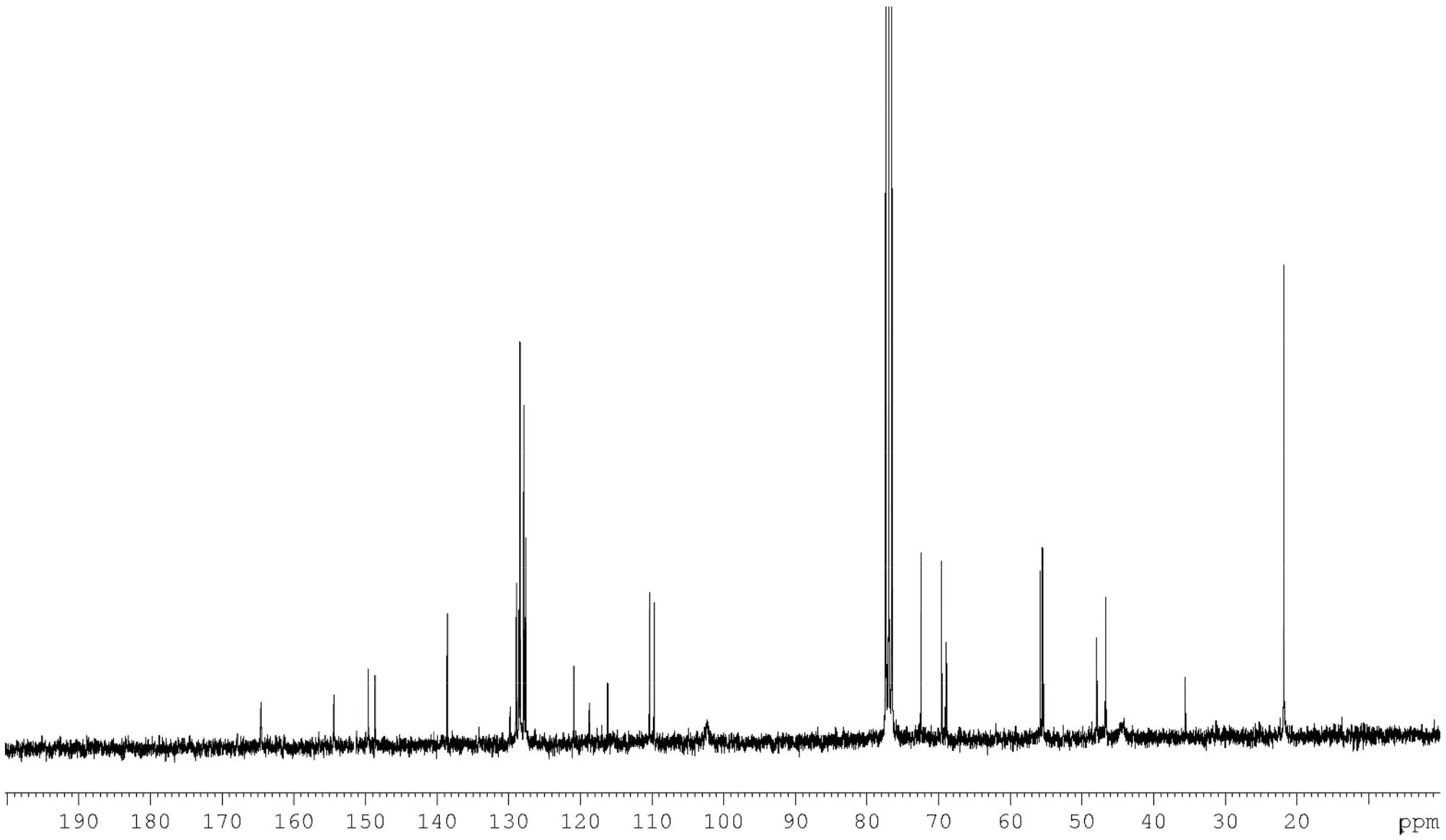
Compound 4



Compound 5



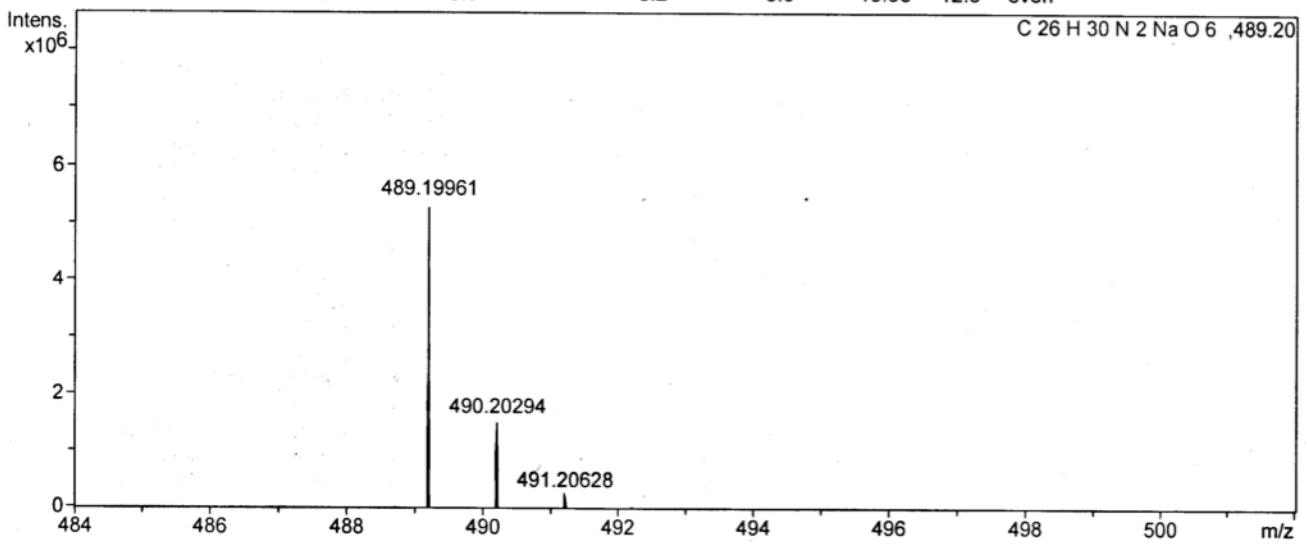
Compound 5



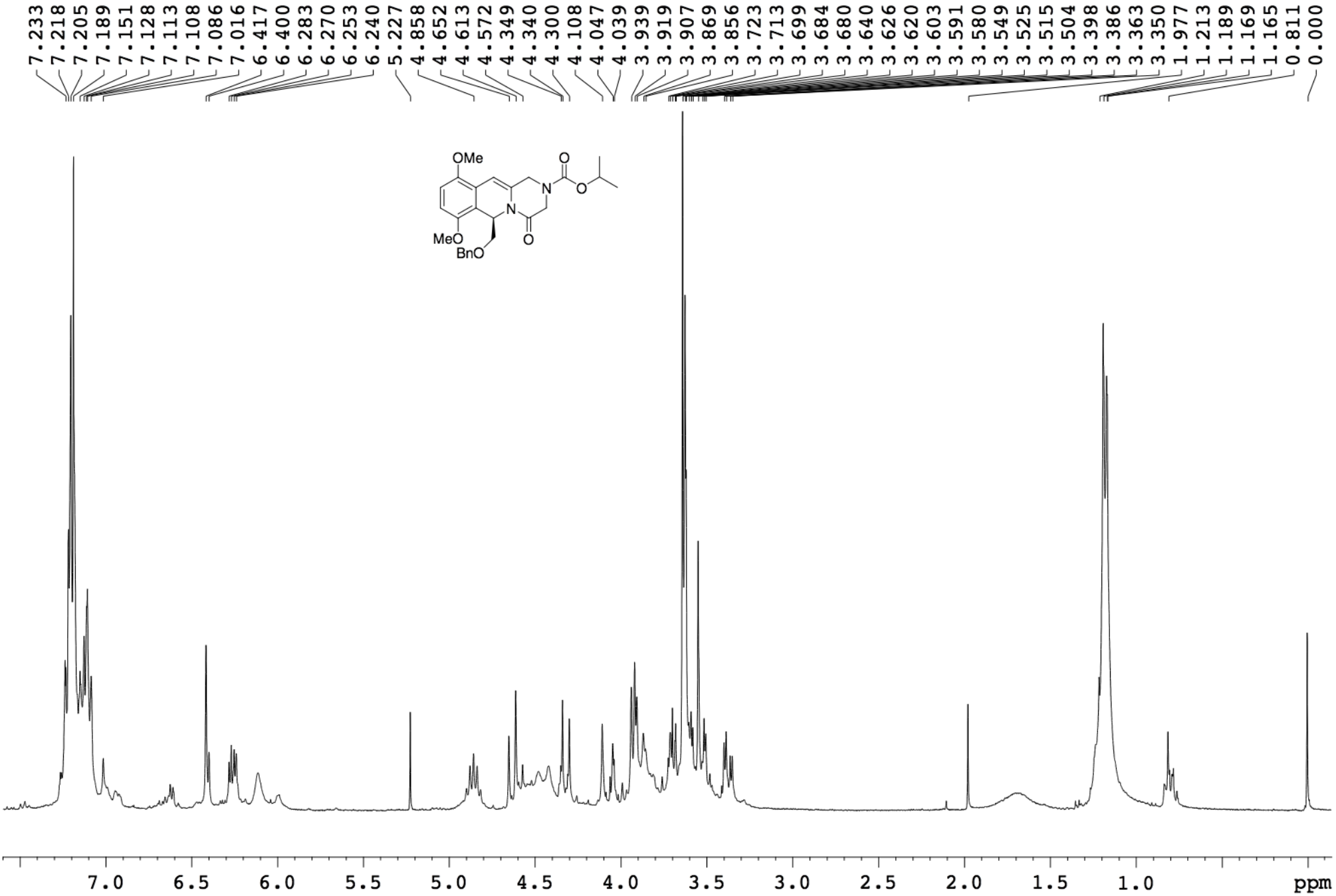
Compound 5

HRMS

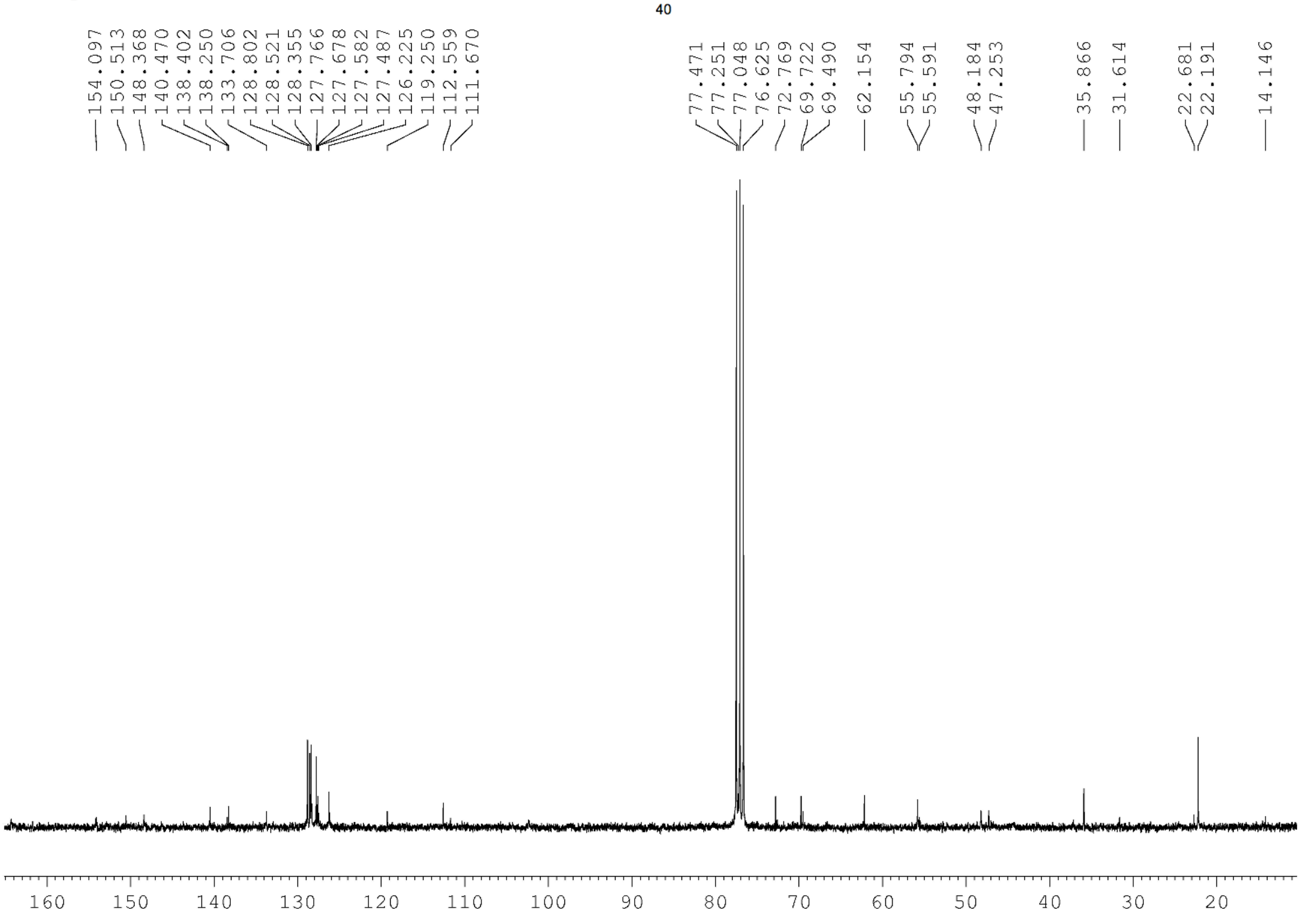
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e^- Conf
C 26 H 30 N 2 Na O 6	489.19961	-8.0	-8.2	-3.9	19.93	12.5	even



Compound 6

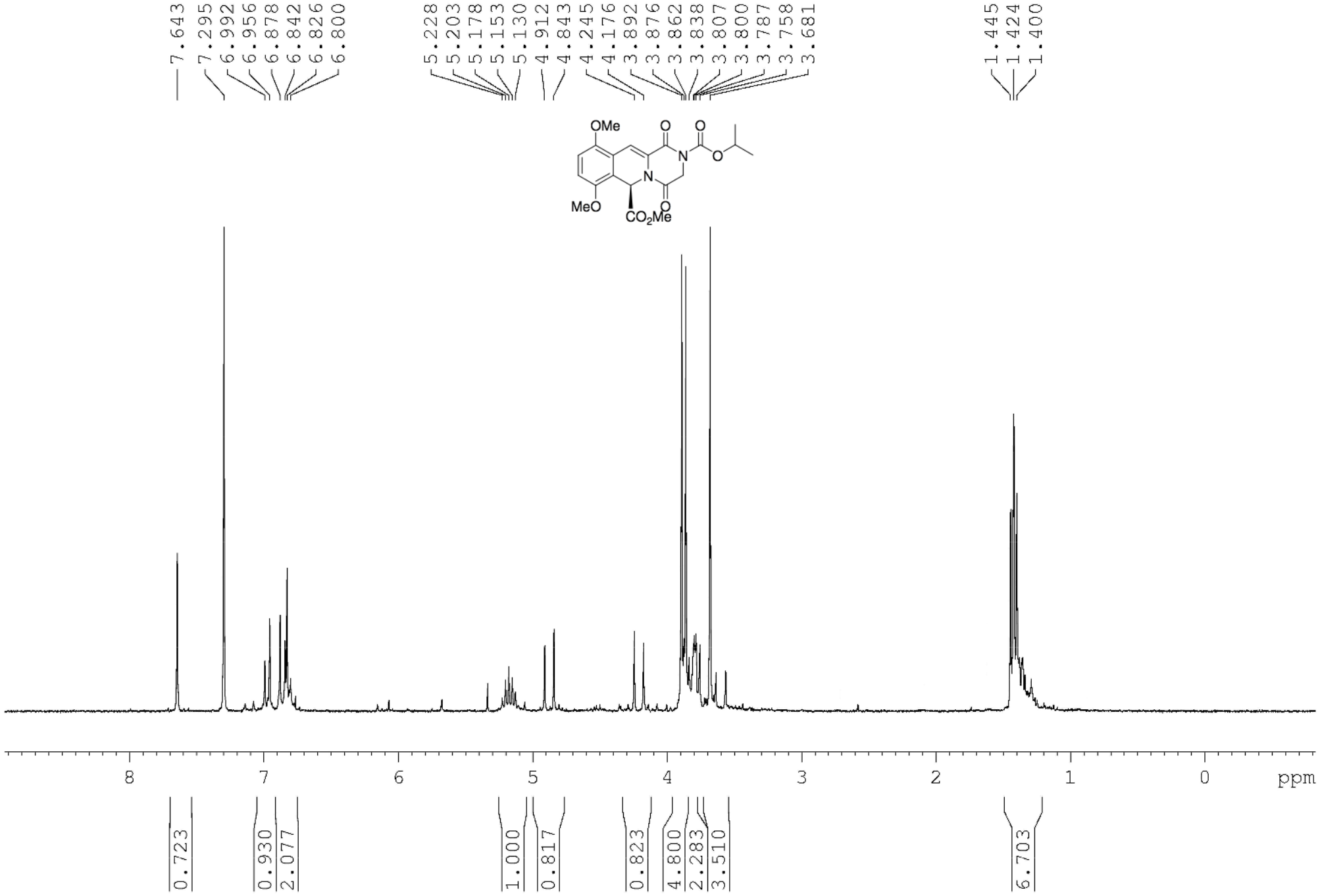


Compound 6

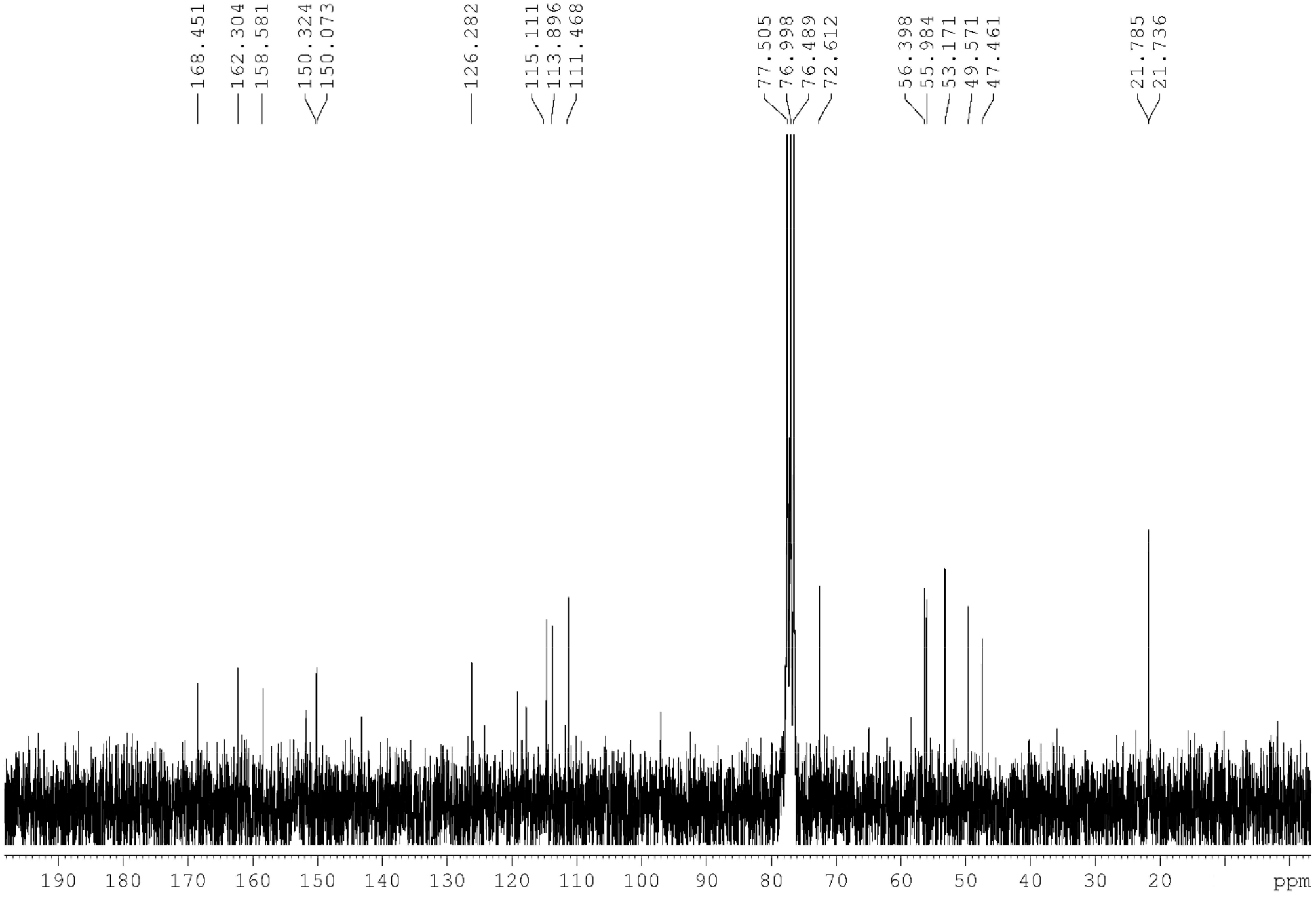


Compound 7b

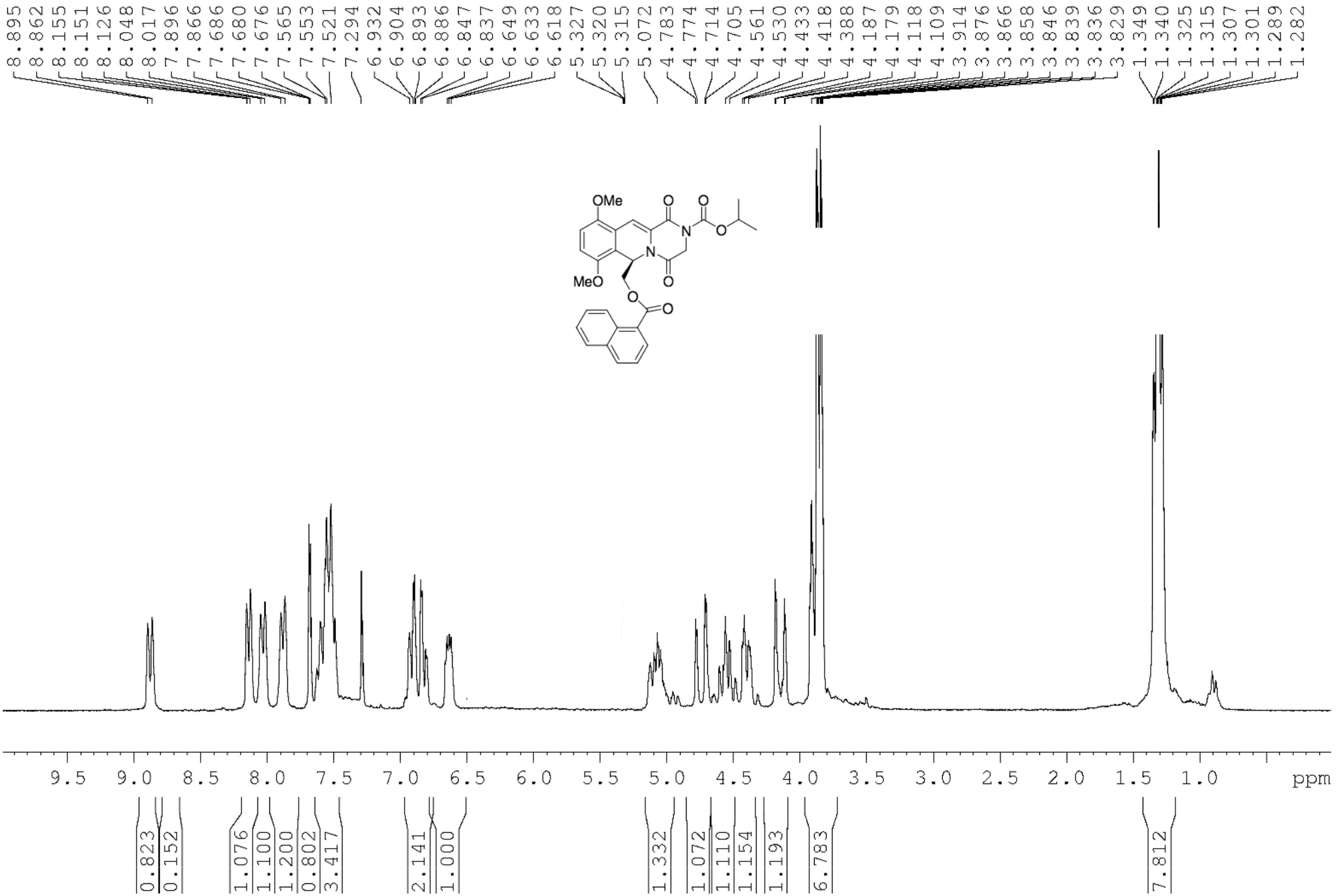
41



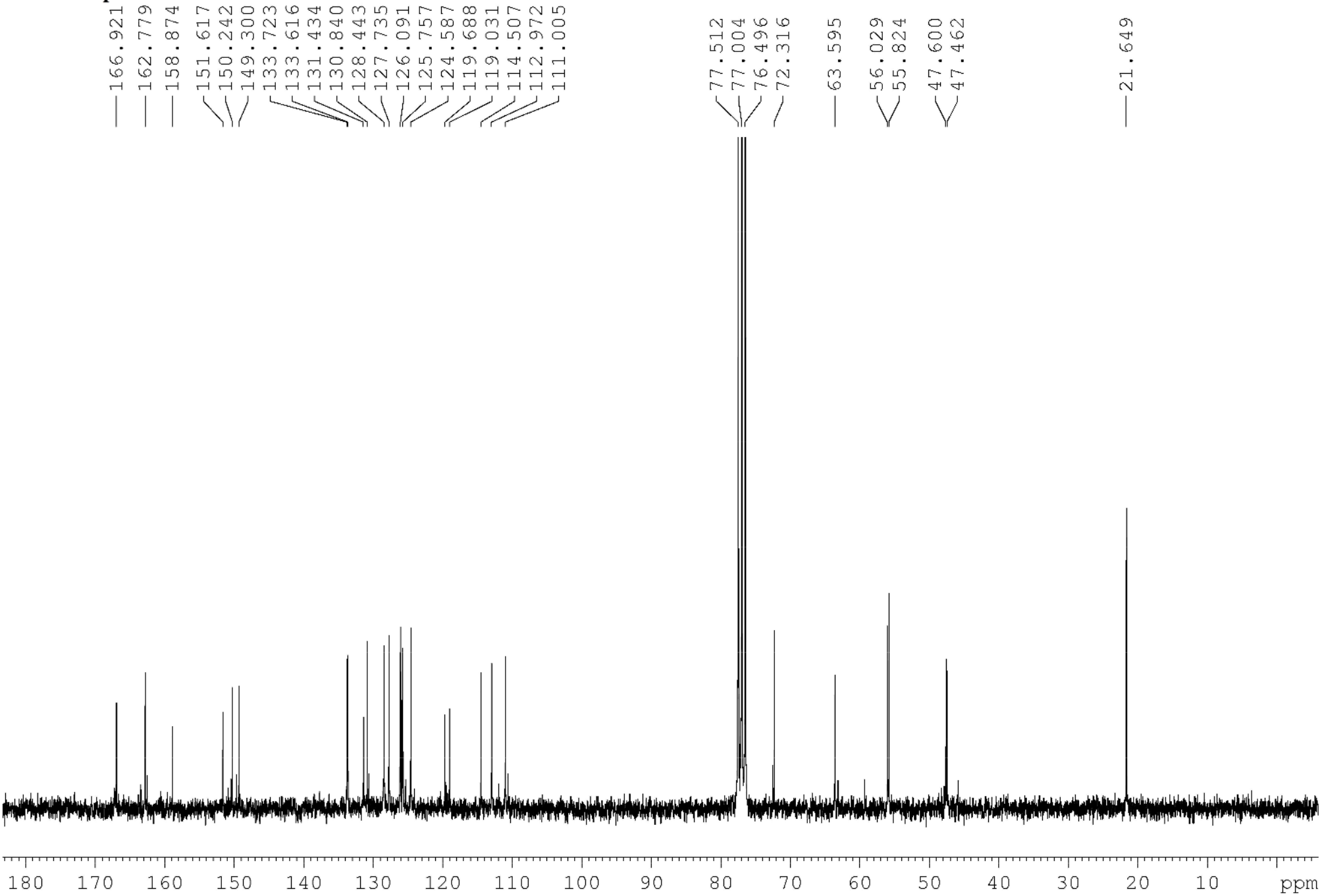
Compound 7b

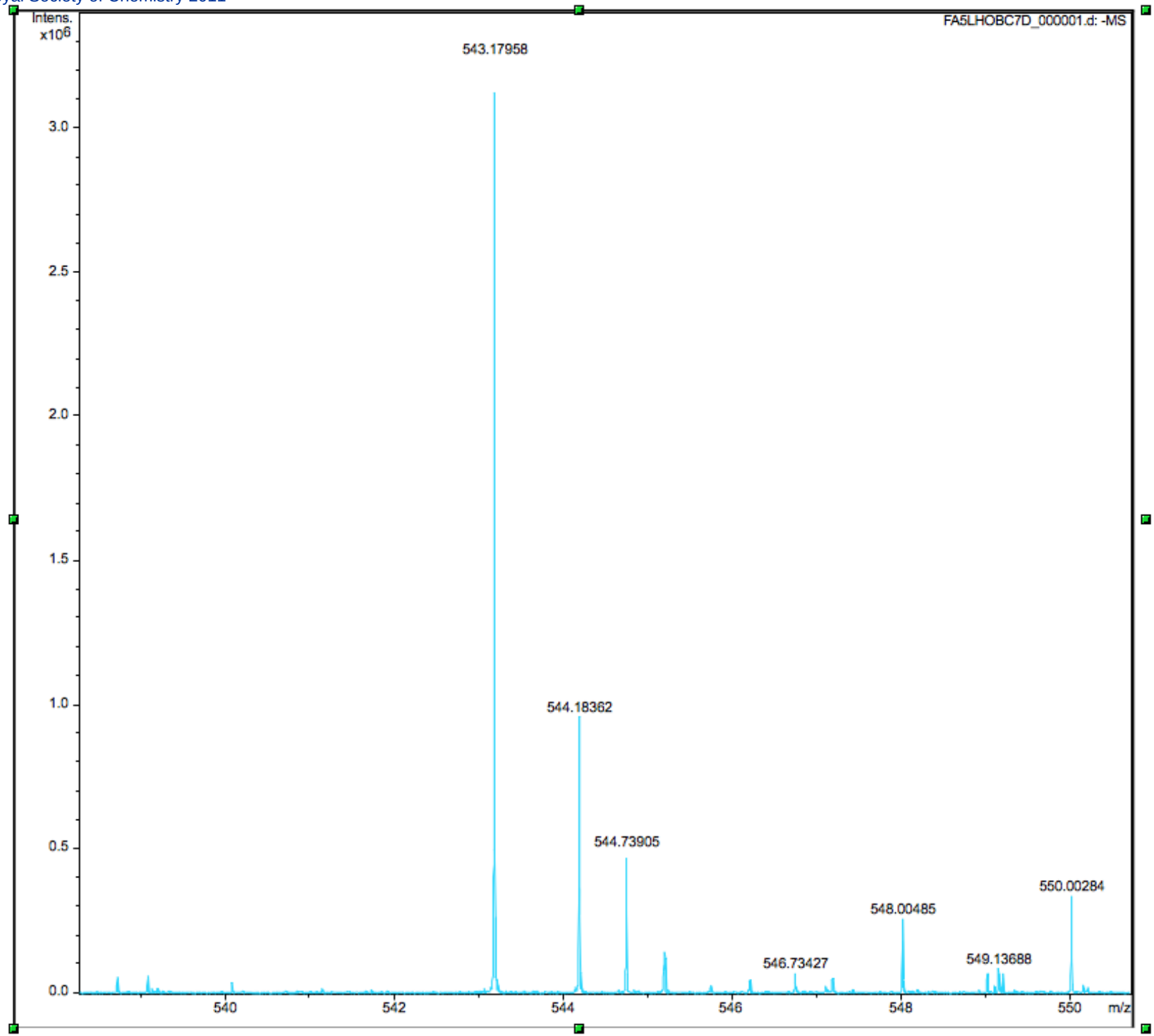


Compound 7d

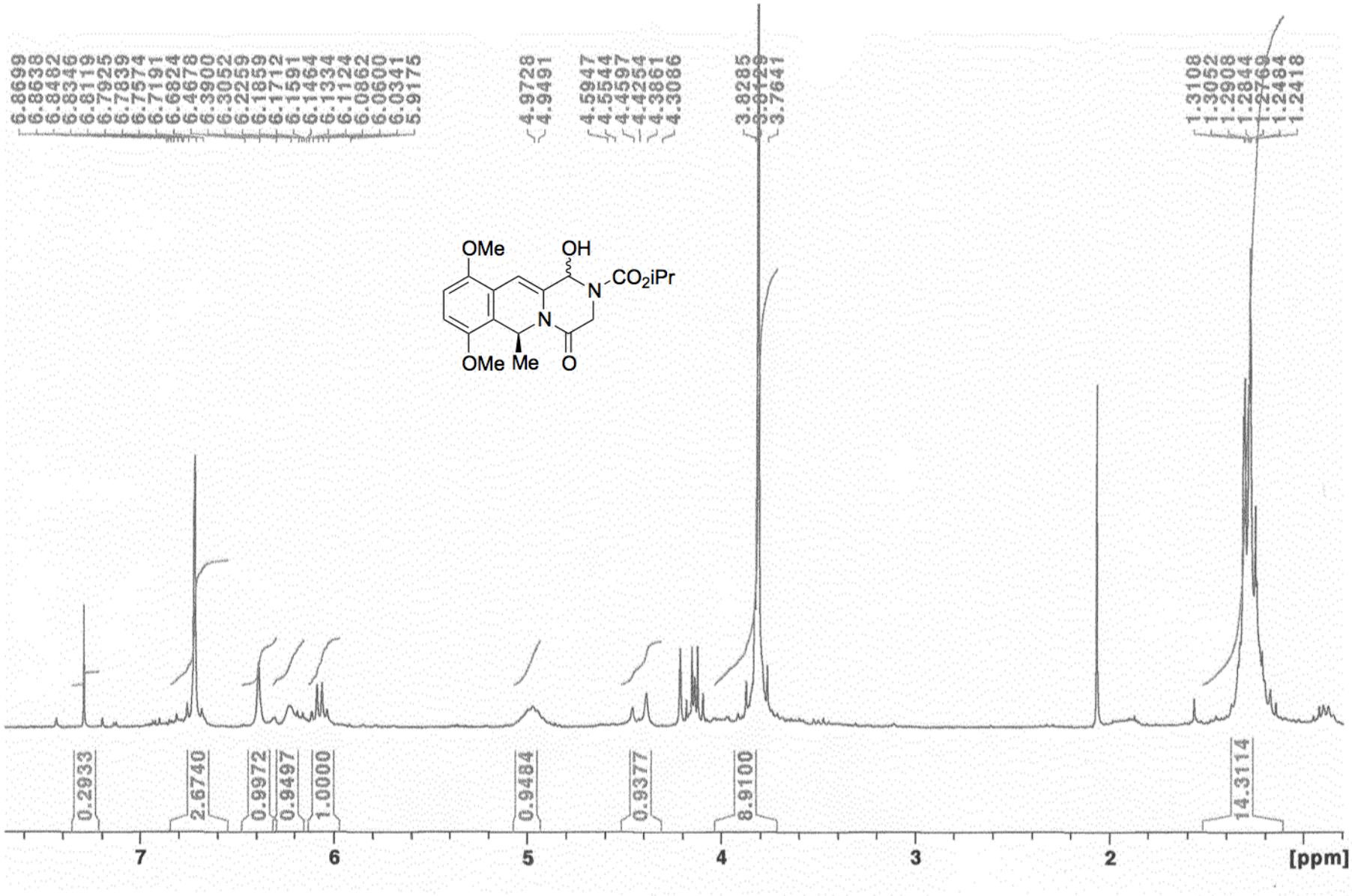


Compound 7d

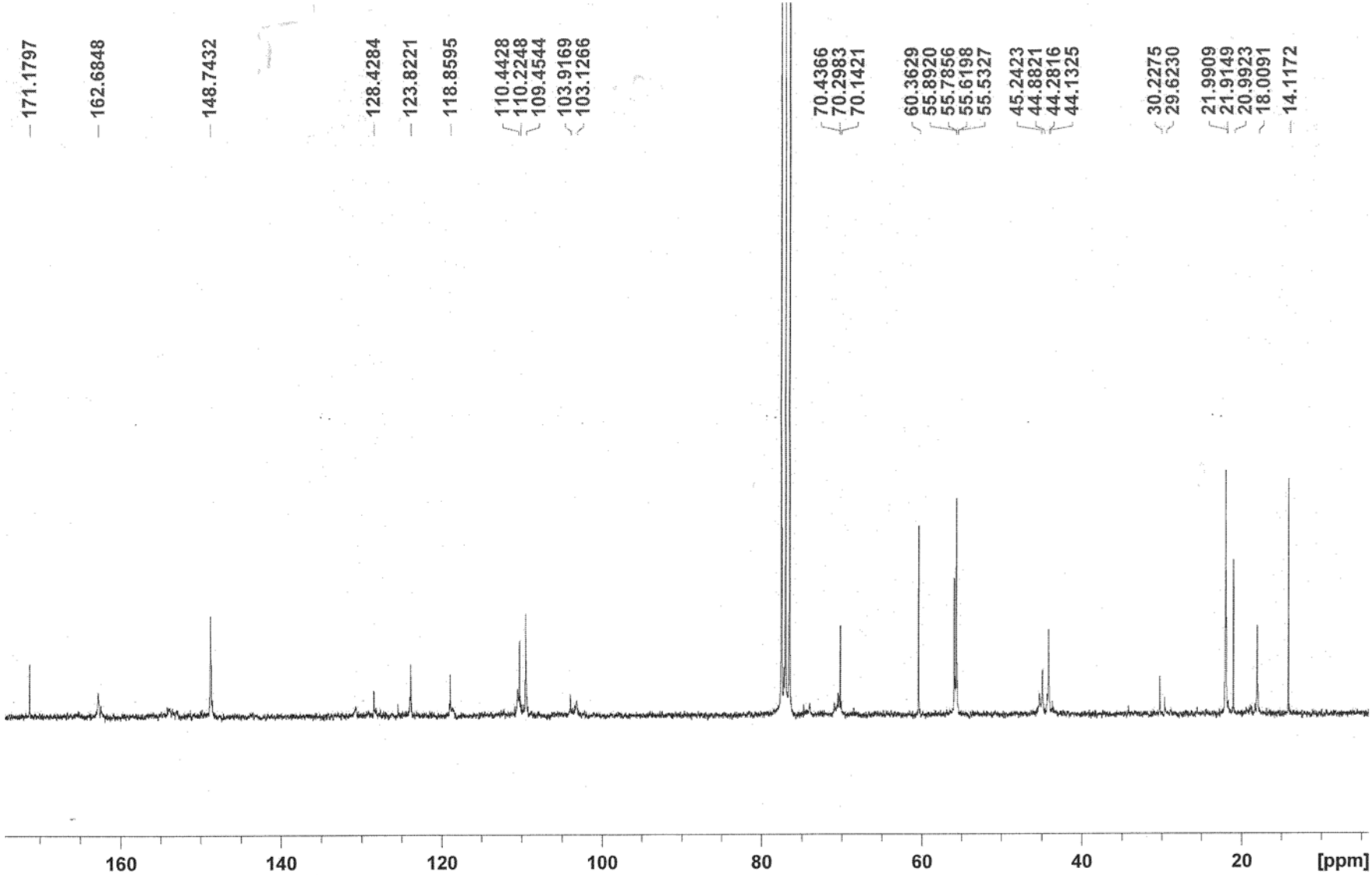




Compound 8a



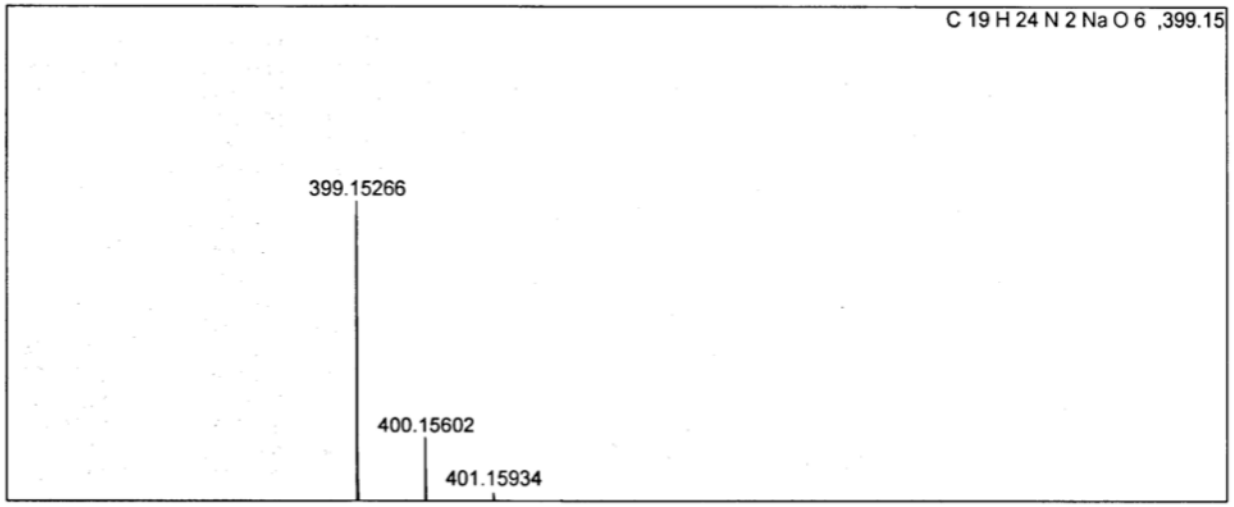
Compound 8a



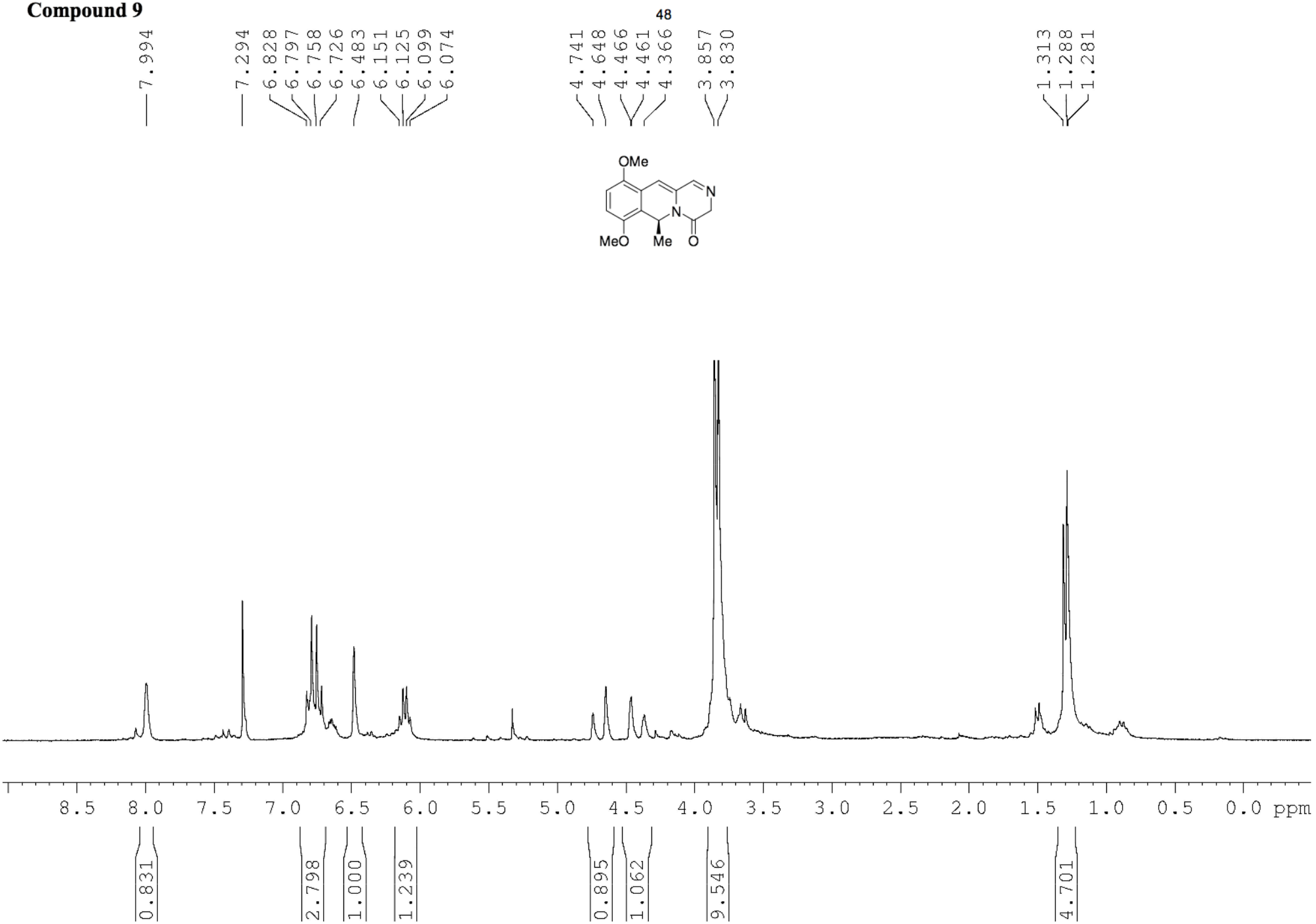
Compound 8a

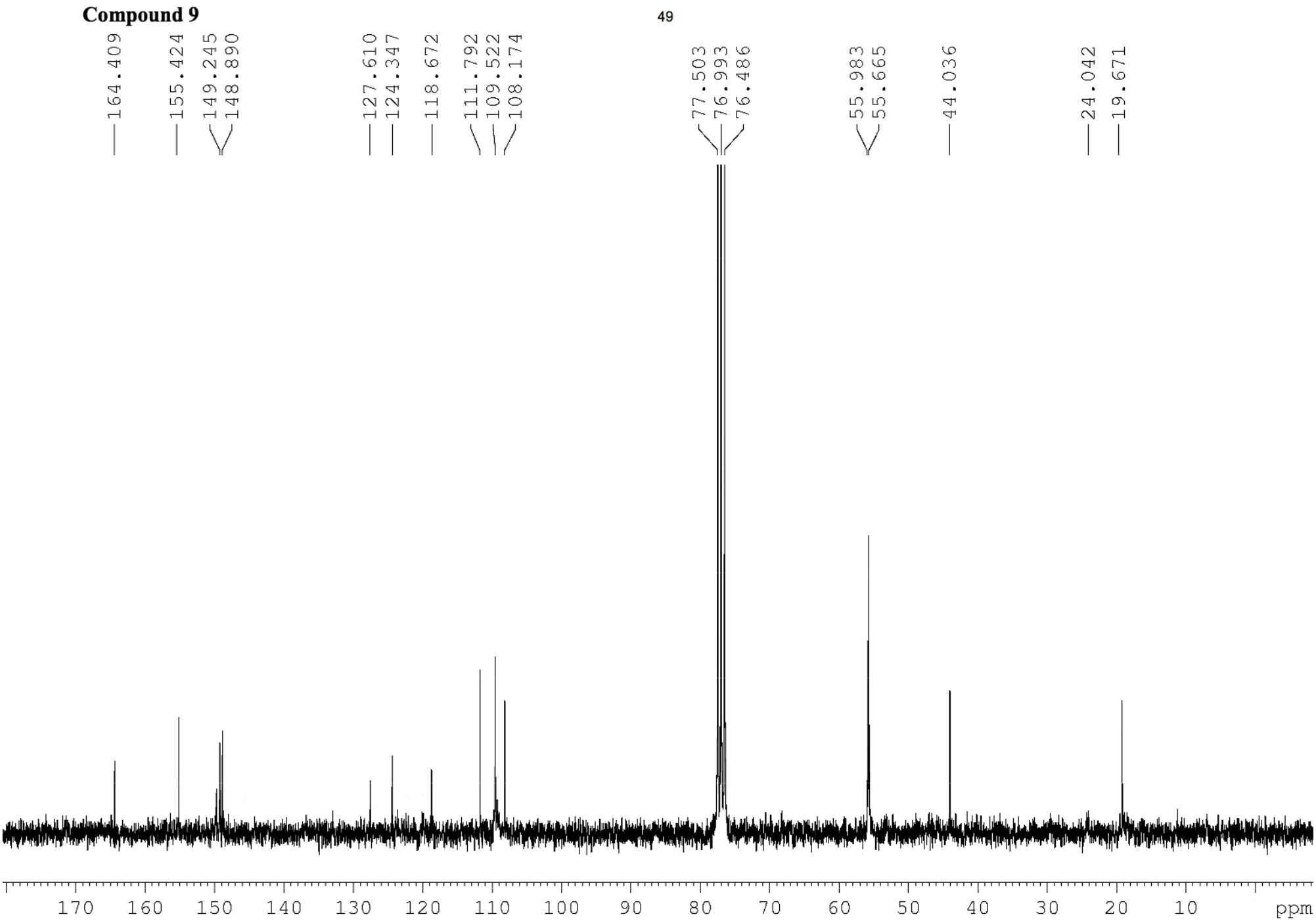
HRMS

Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e¯ Conf
C 19 H 24 N 2 Na O 6	399.15266	-2.7	-3.0	-1.1	31.77	8.5	even

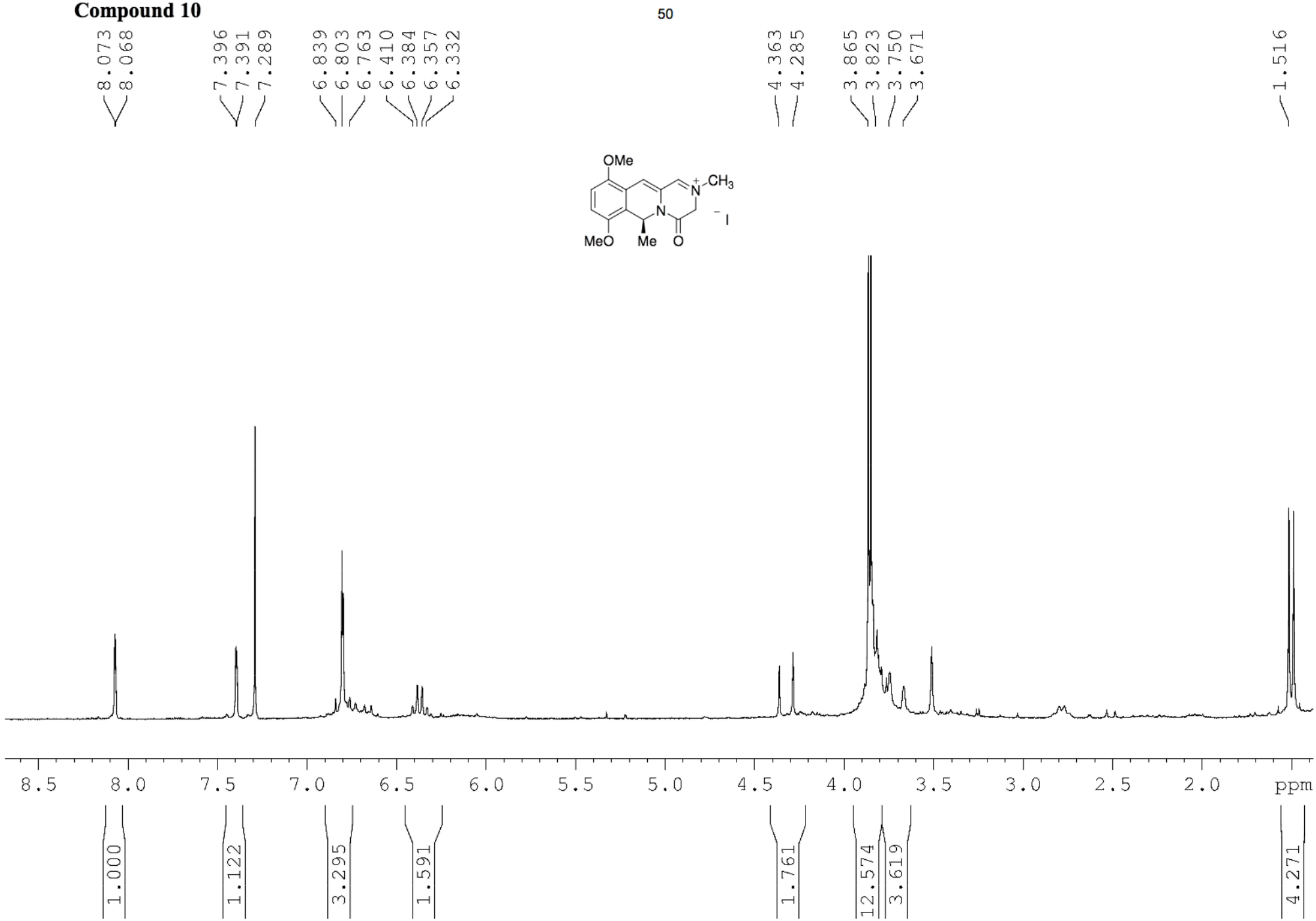


Compound 9

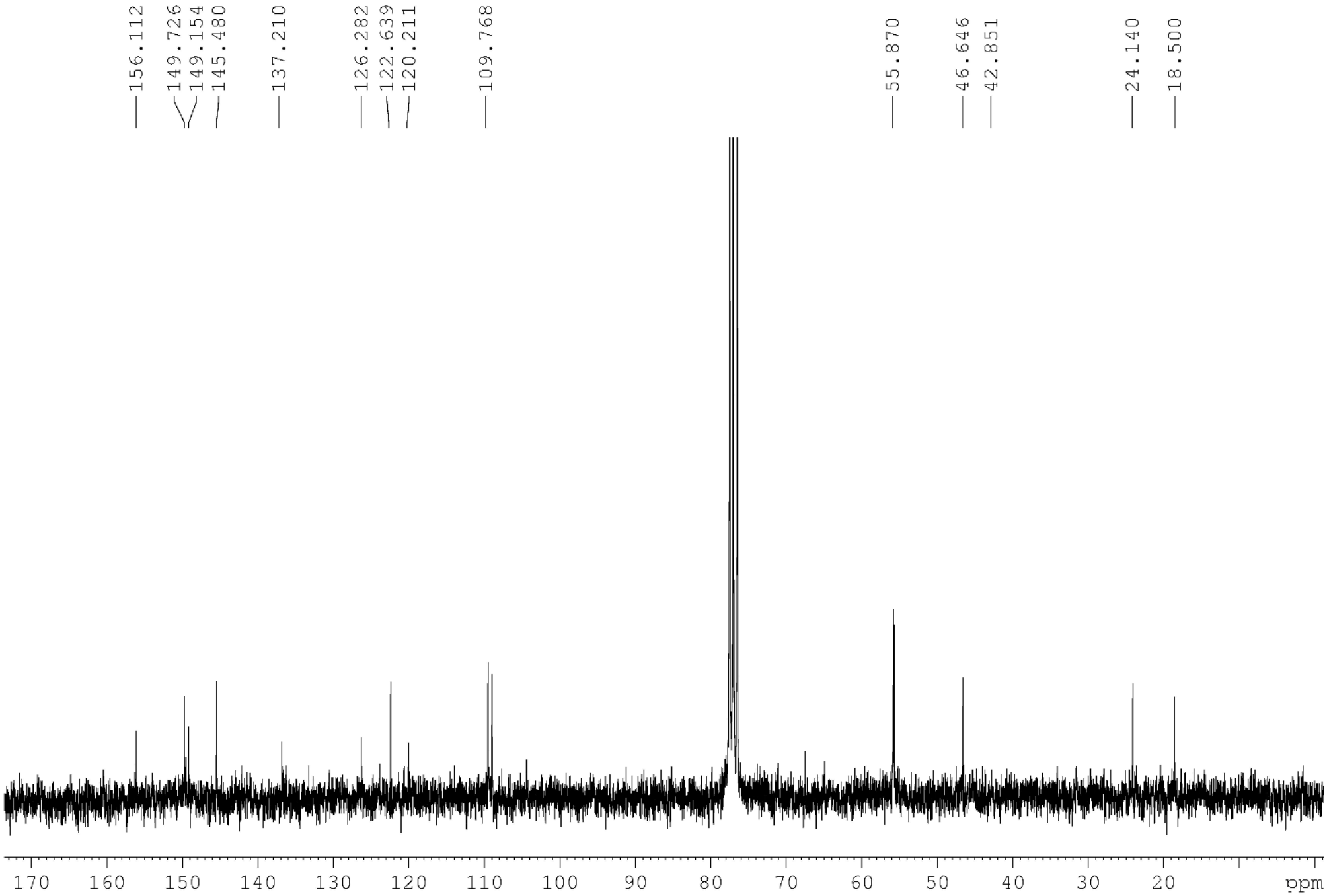




Compound 10

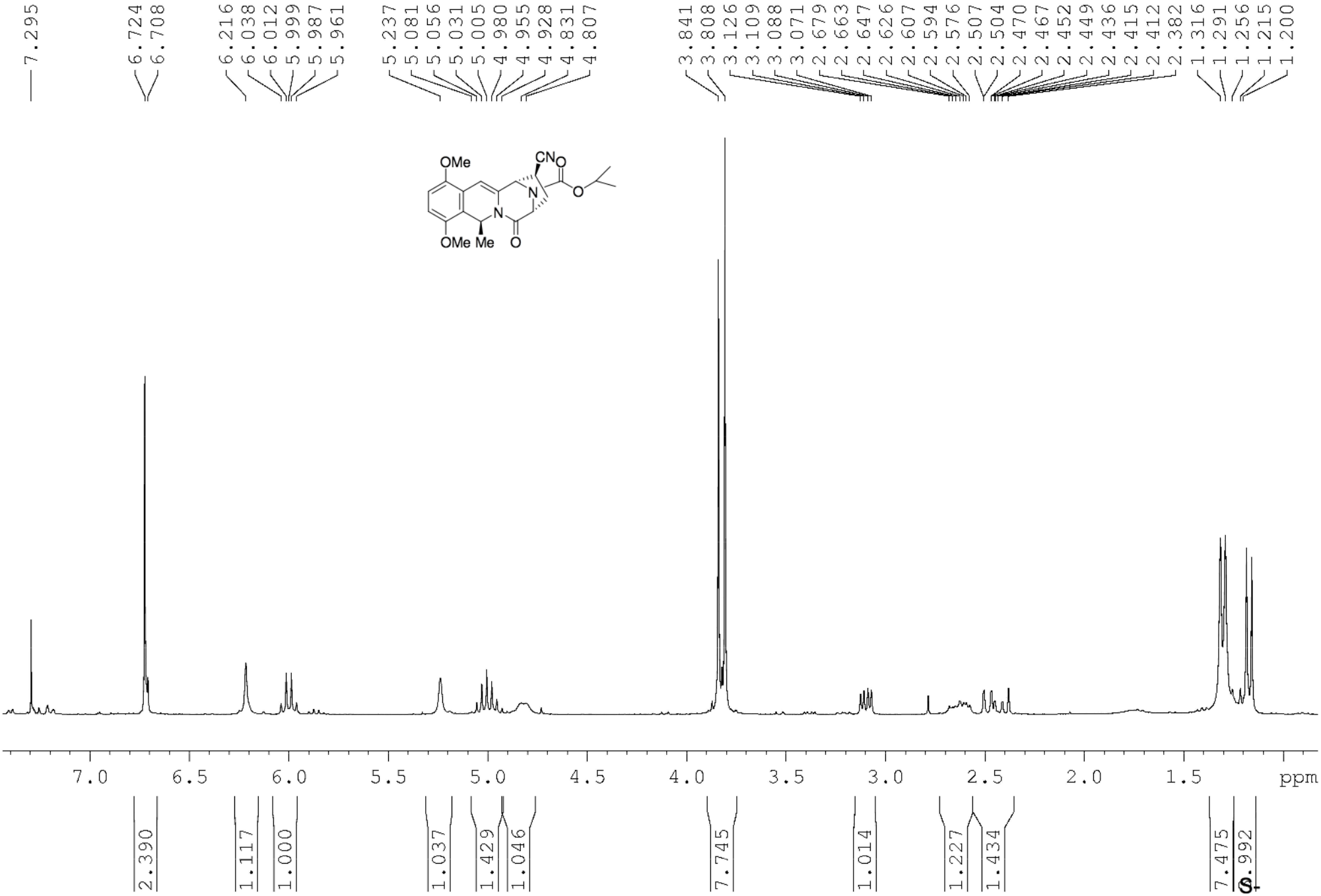


Compound 10

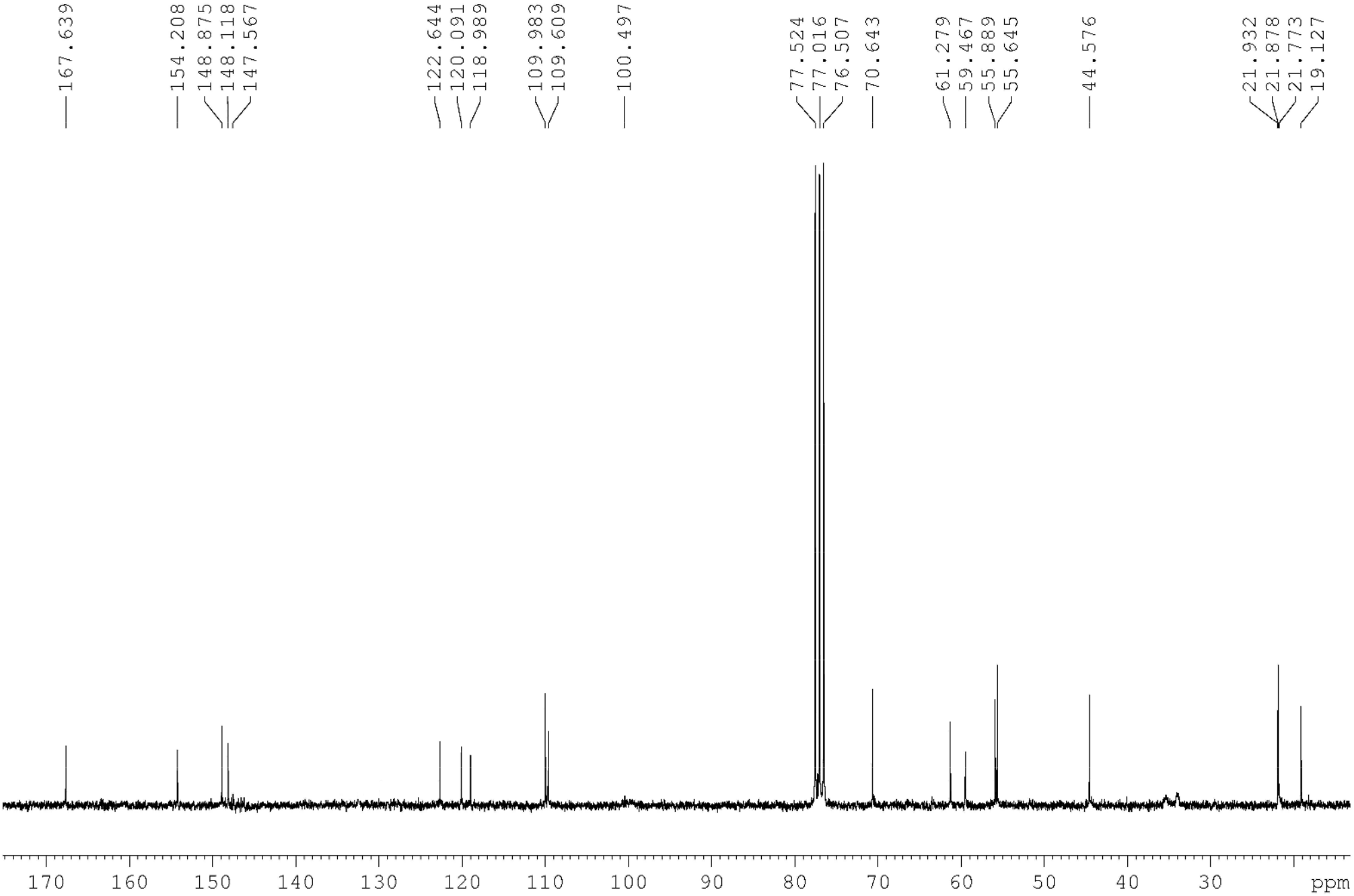


Compound 12

52



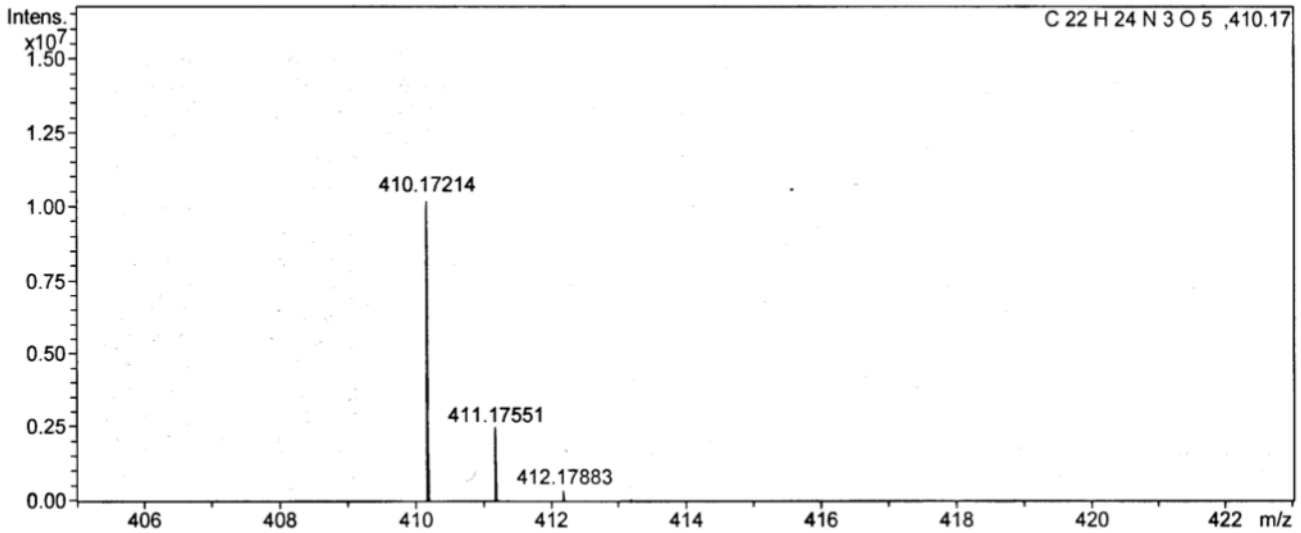
Compound 12



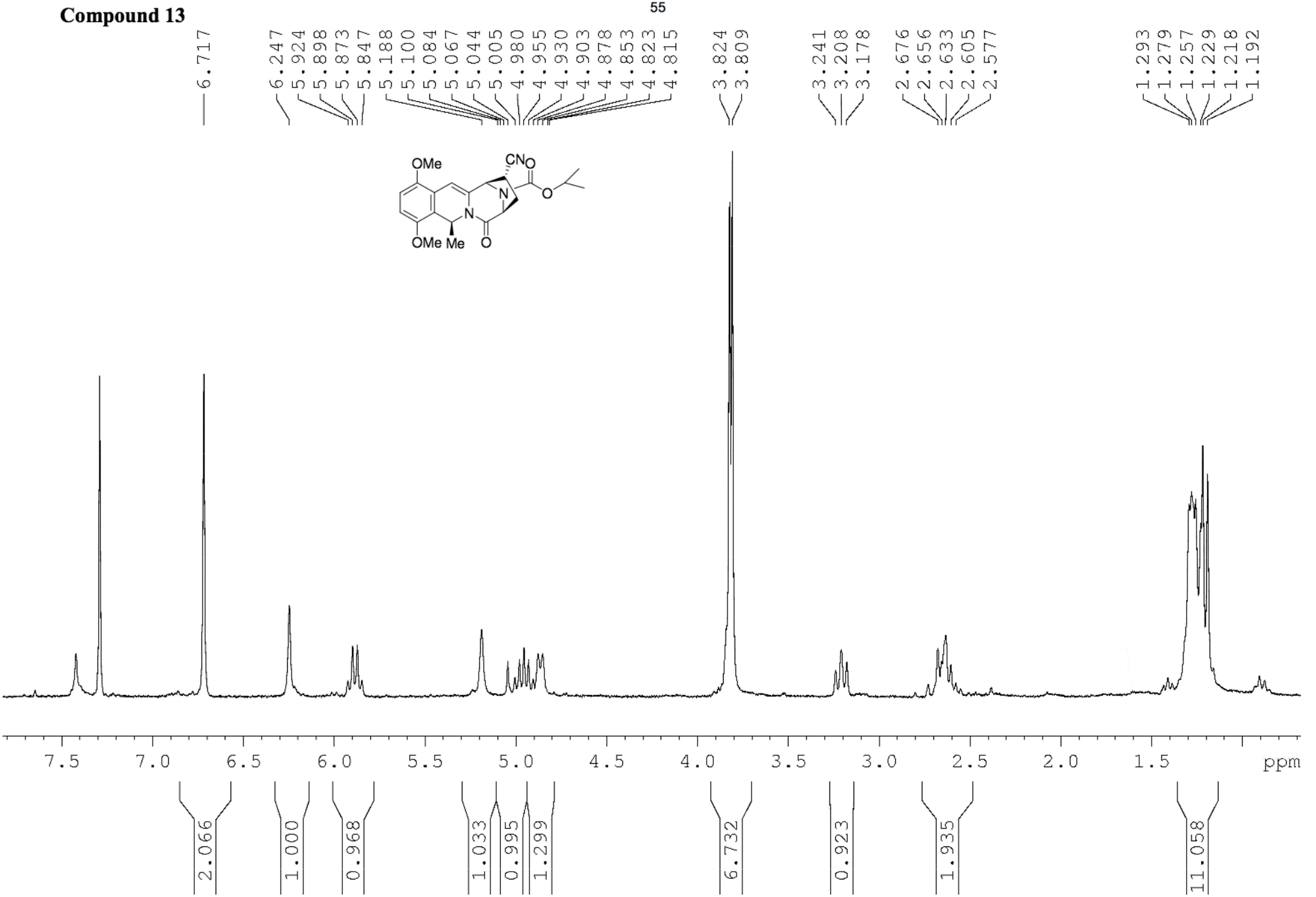
Compound 12

HRMS

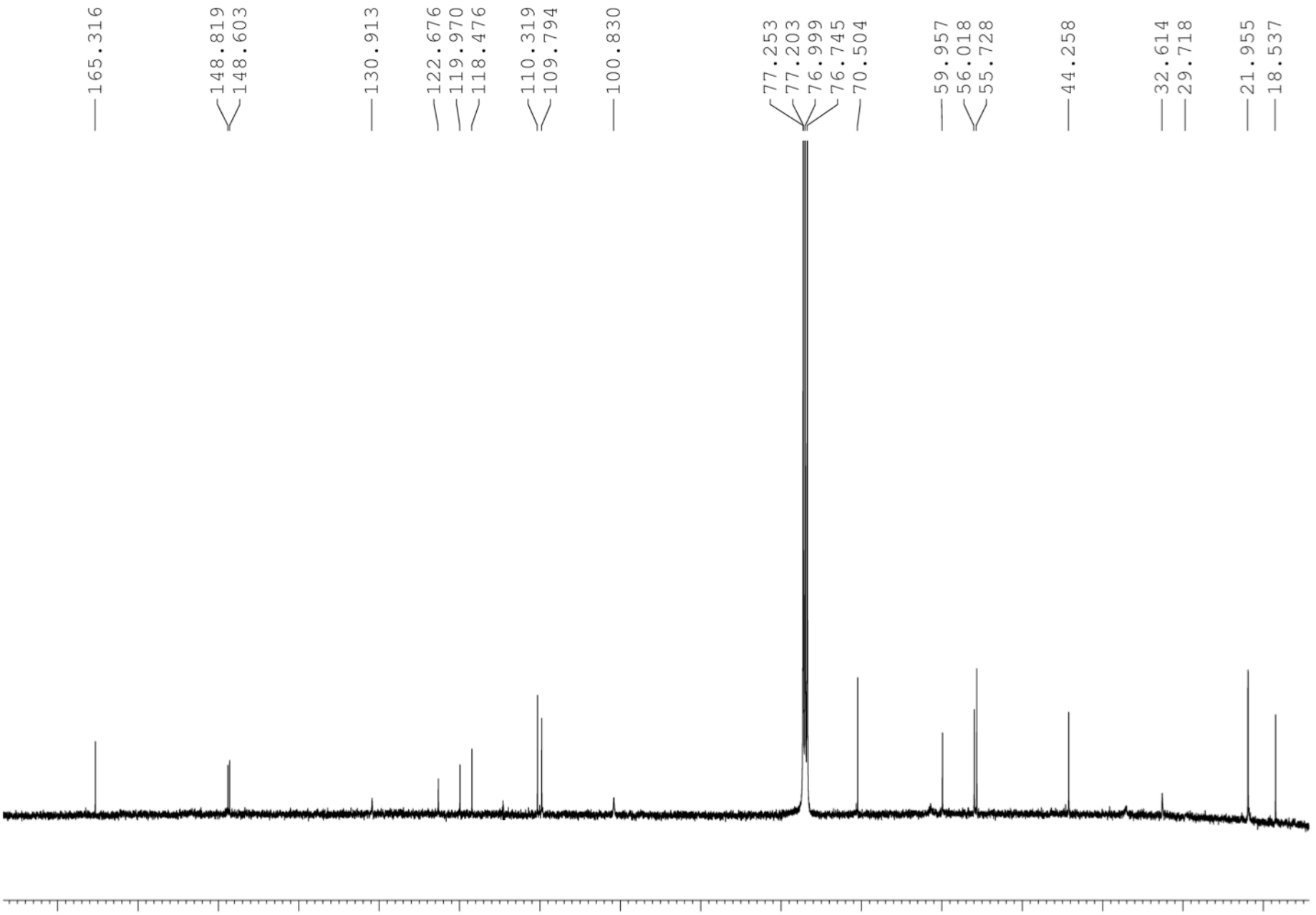
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e^- Conf
C 22 H 24 N 3 O 5	410.17214	-4.1	-4.5	-1.7	32.22	12.5	even



Compound 13



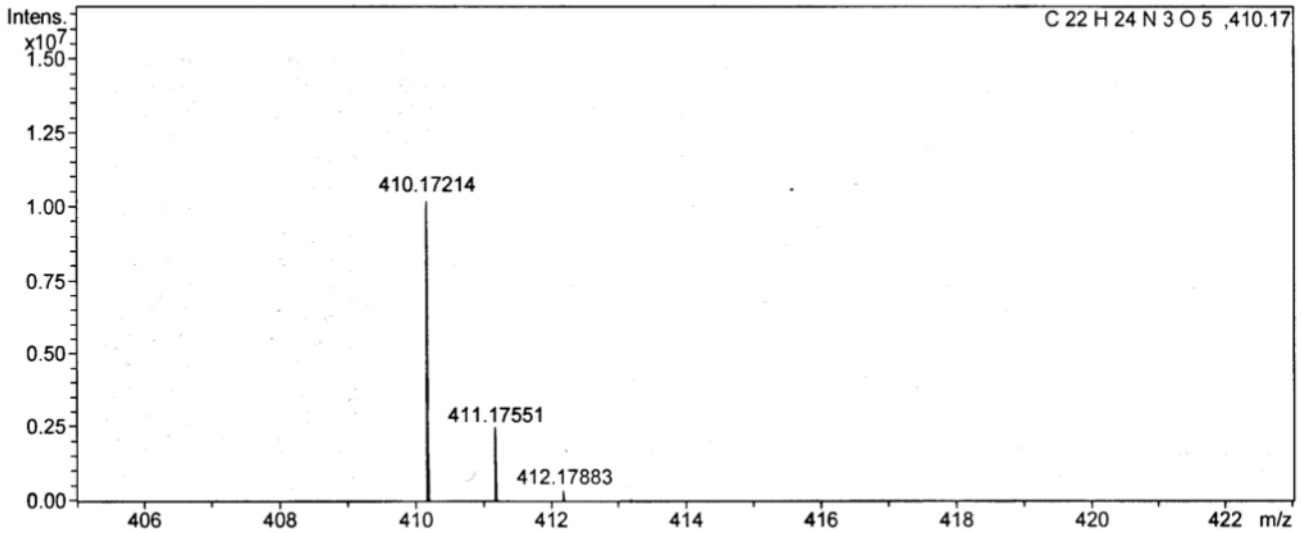
Compound 13

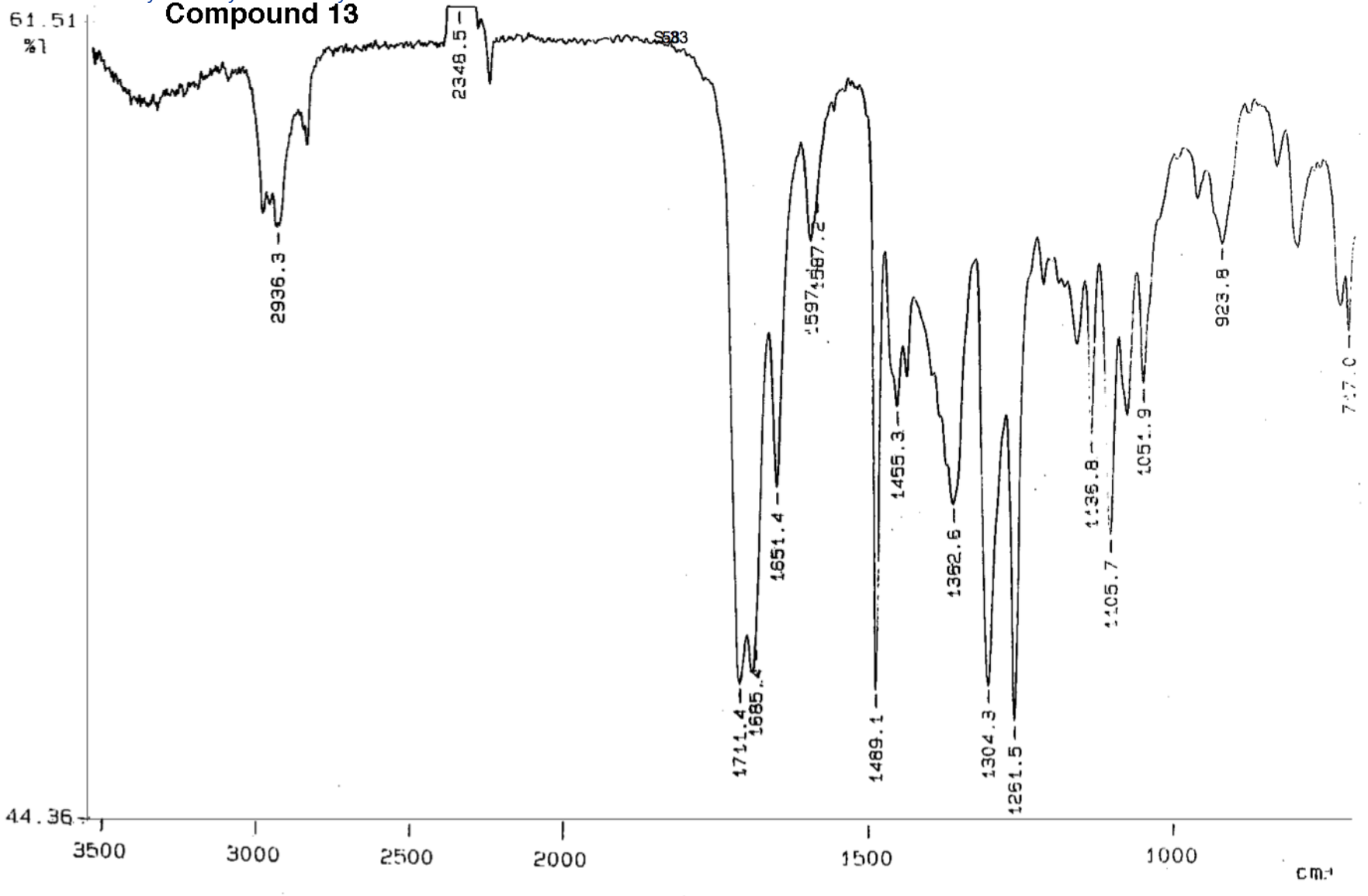


Compound 12

HRMS

Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e⁻ Conf
C 22 H 24 N 3 O 5	410.17214	-4.1	-4.5	-1.7	32.22	12.5	even

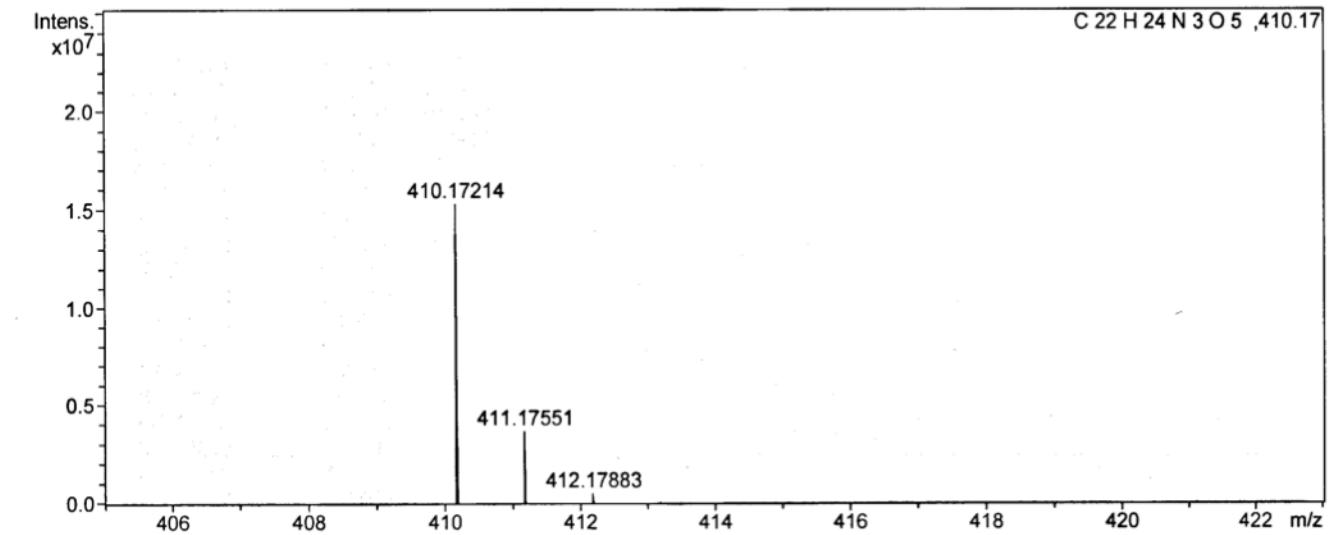


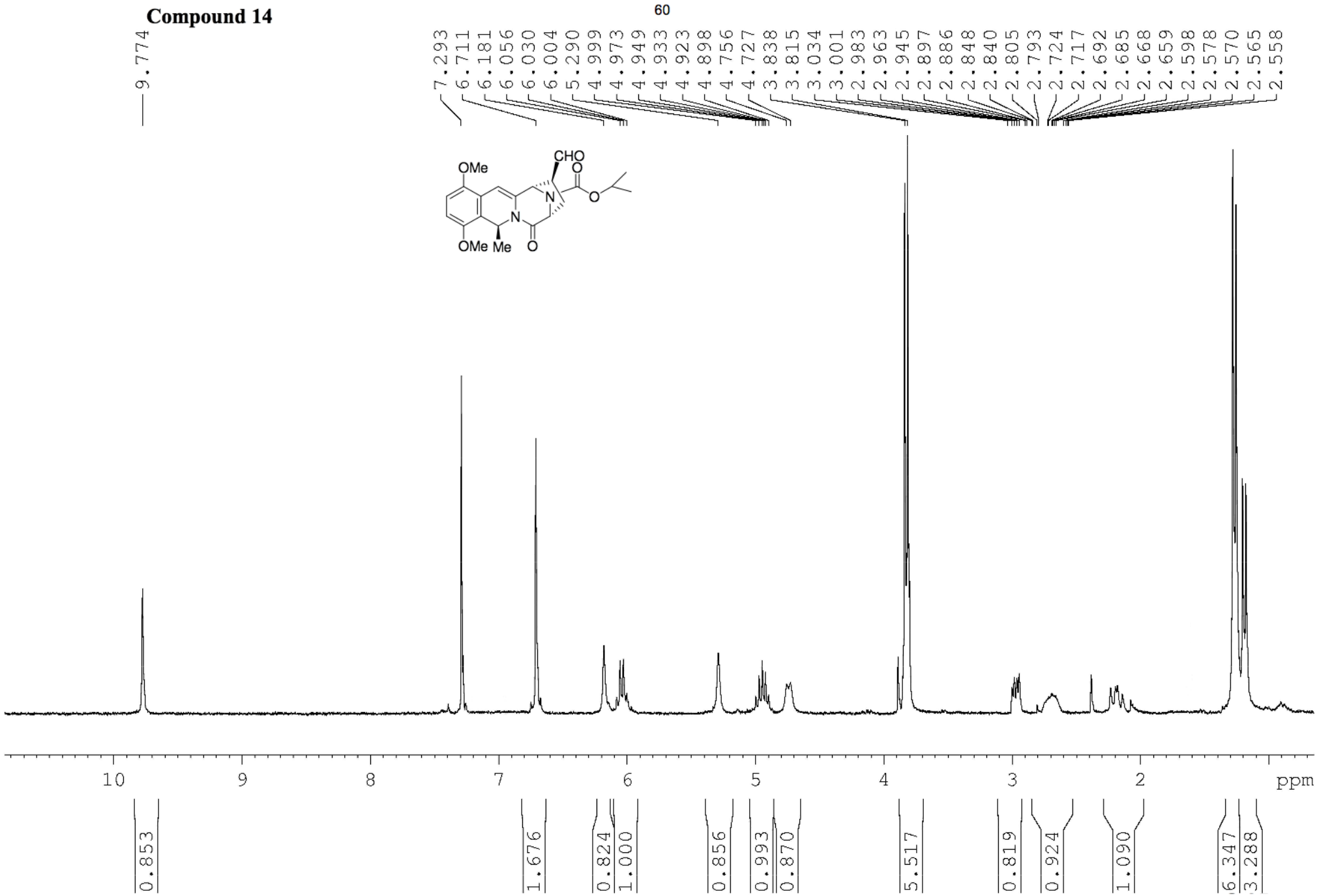


Compound 13

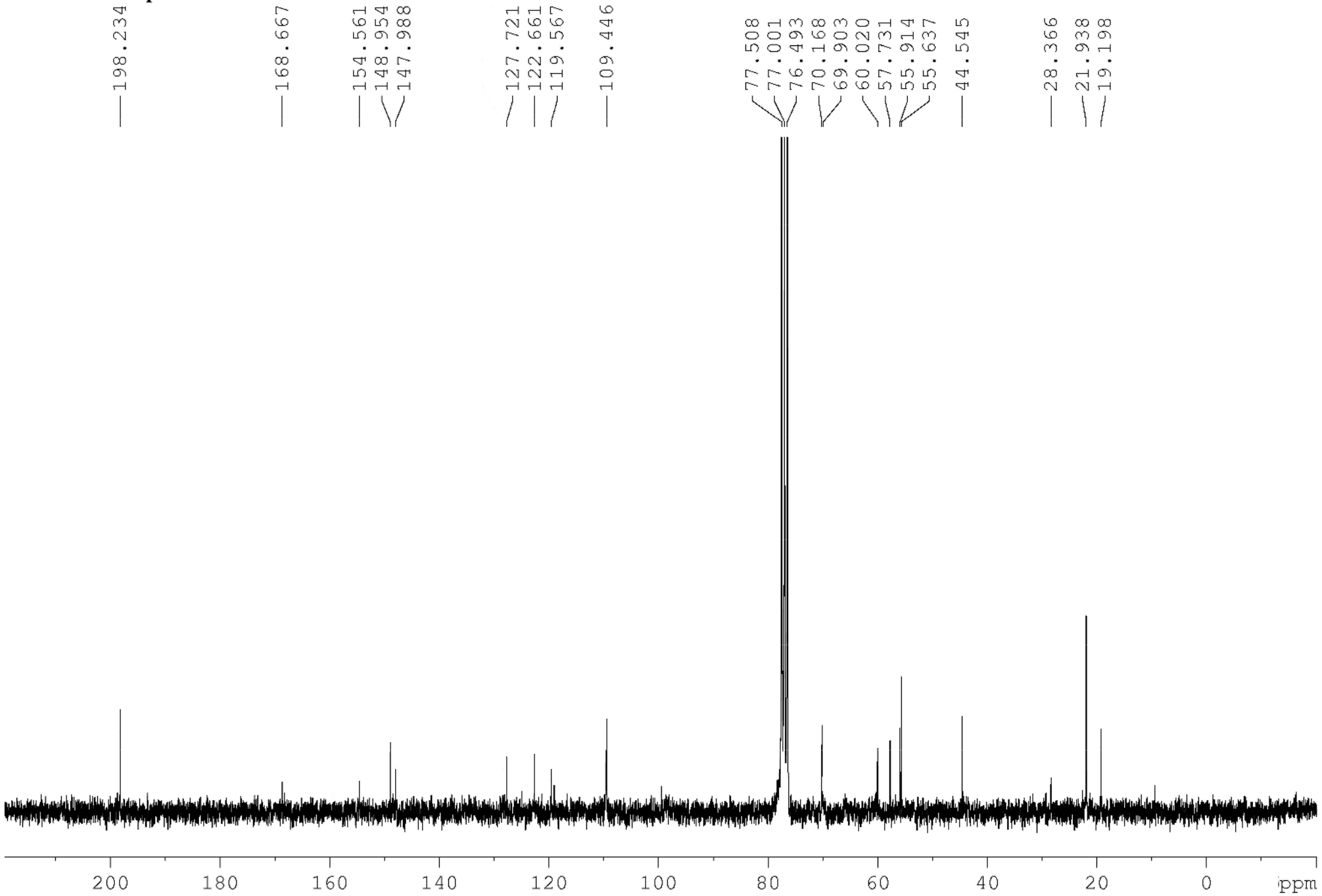
HRMS

Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e⁻ Conf
C 22 H 24 N 3 O 5	410.17214	-3.3	-3.7	-1.4	26.20	12.5	even





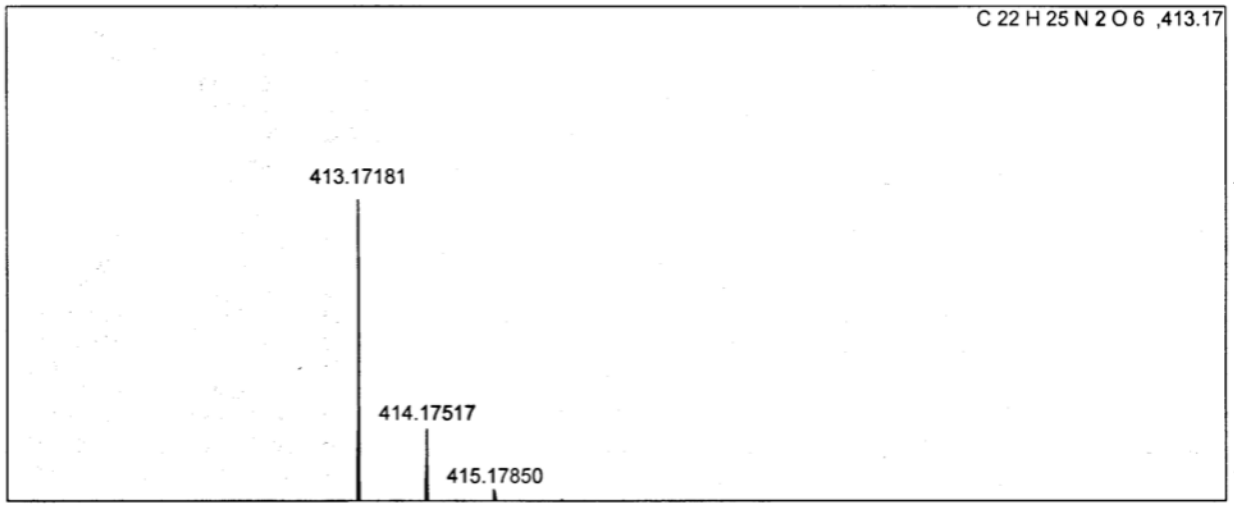
Compound 14



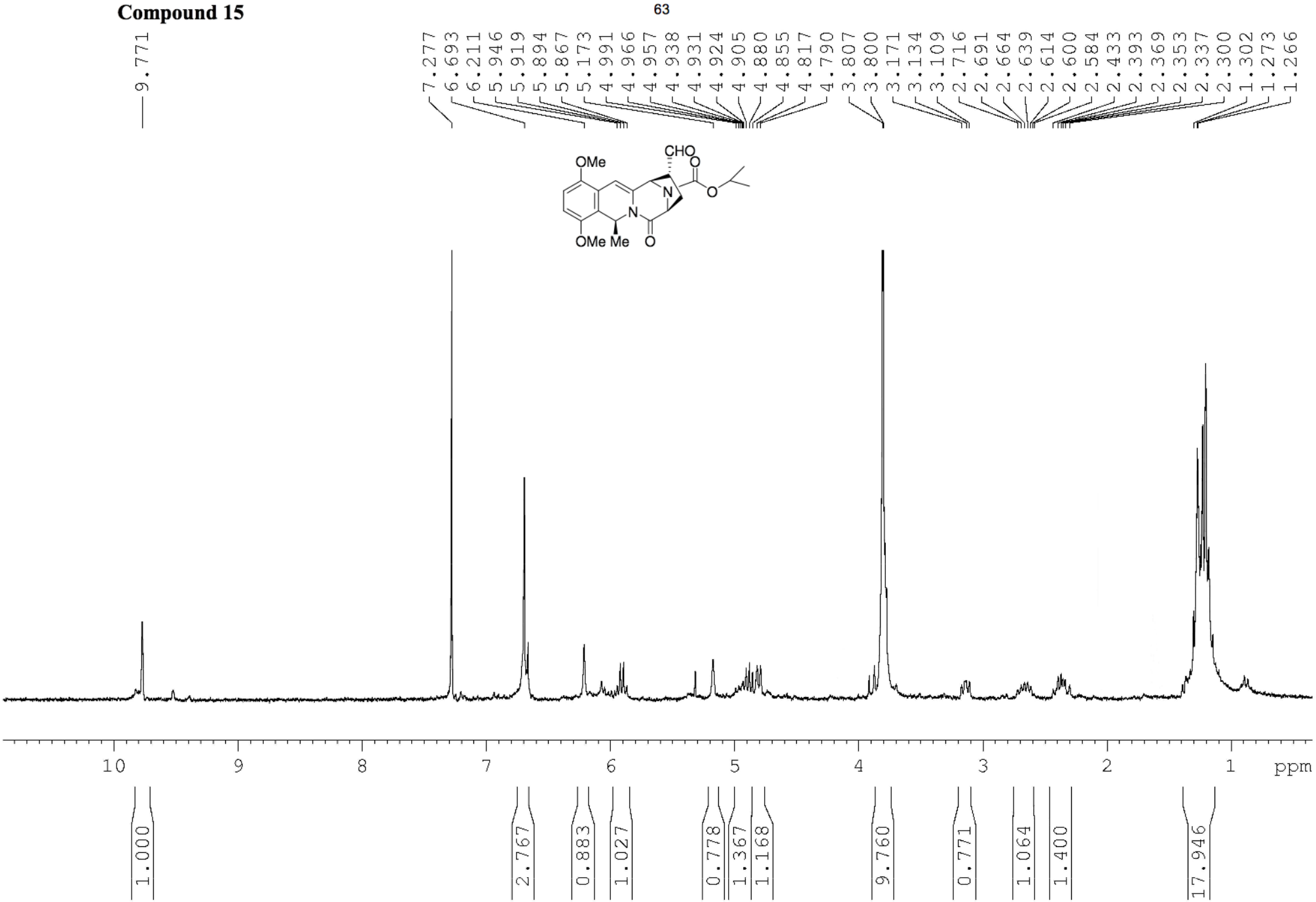
Compound 14

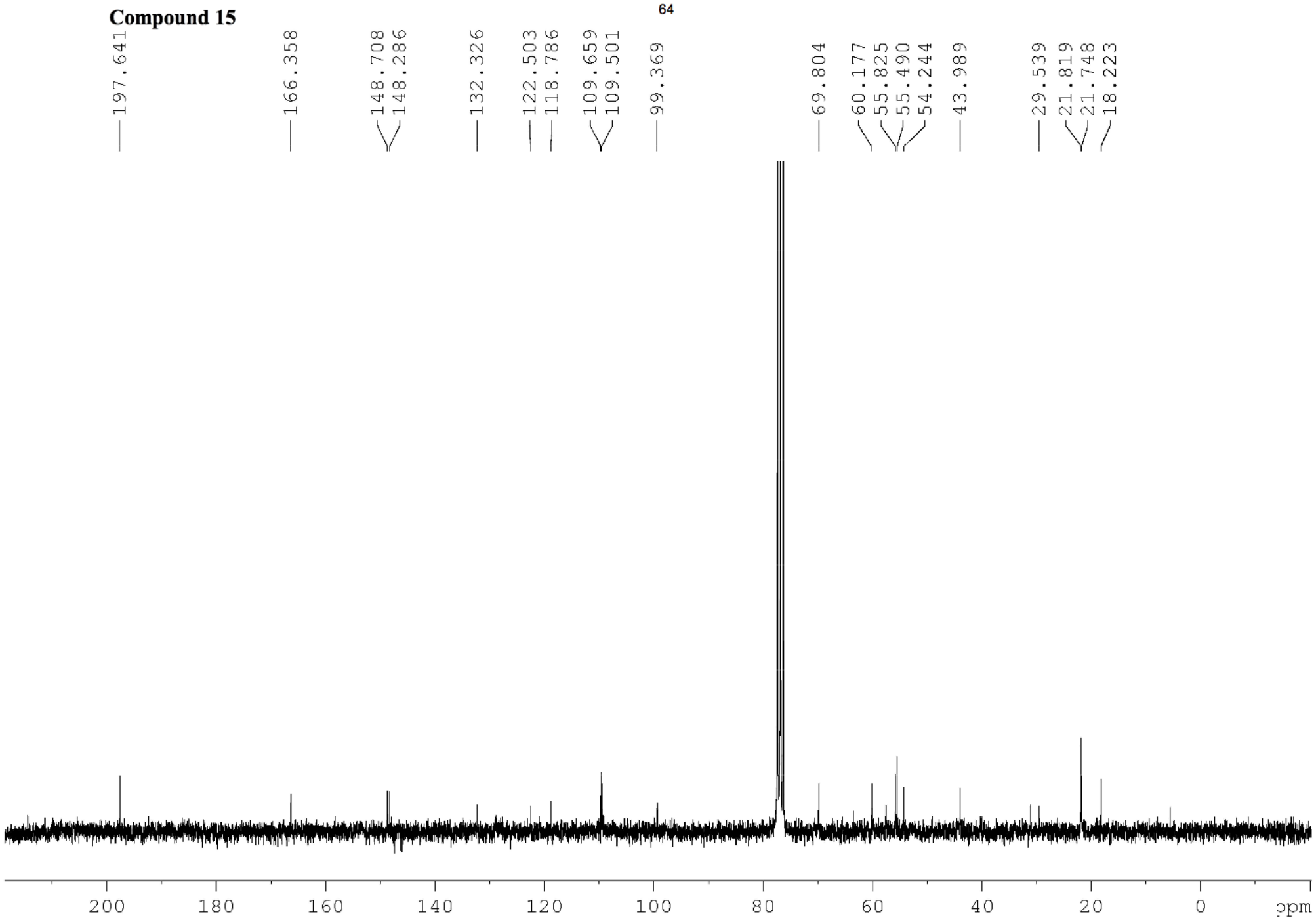
HRMS

Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e^- Conf
C 22 H 25 N 2 O 6	413.17181	-3.1	-3.6	-1.3	27.60	11.5	even



Compound 15

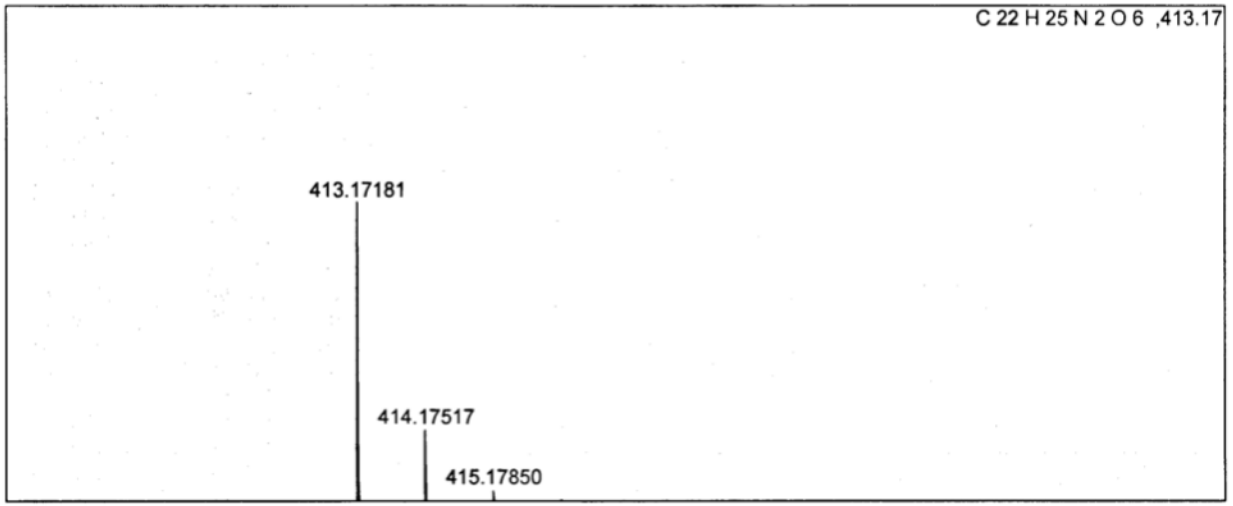




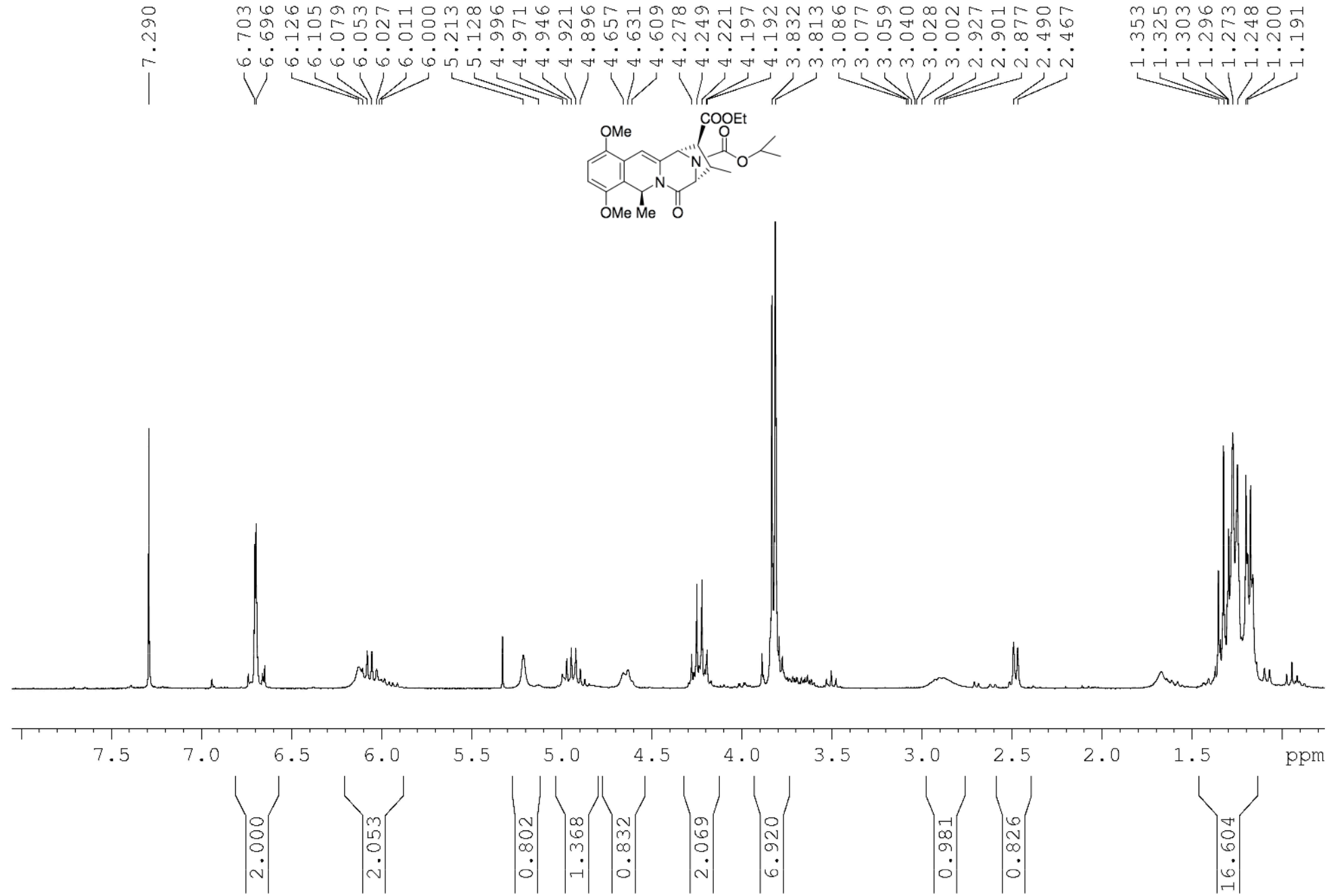
Compound 15

HRMS

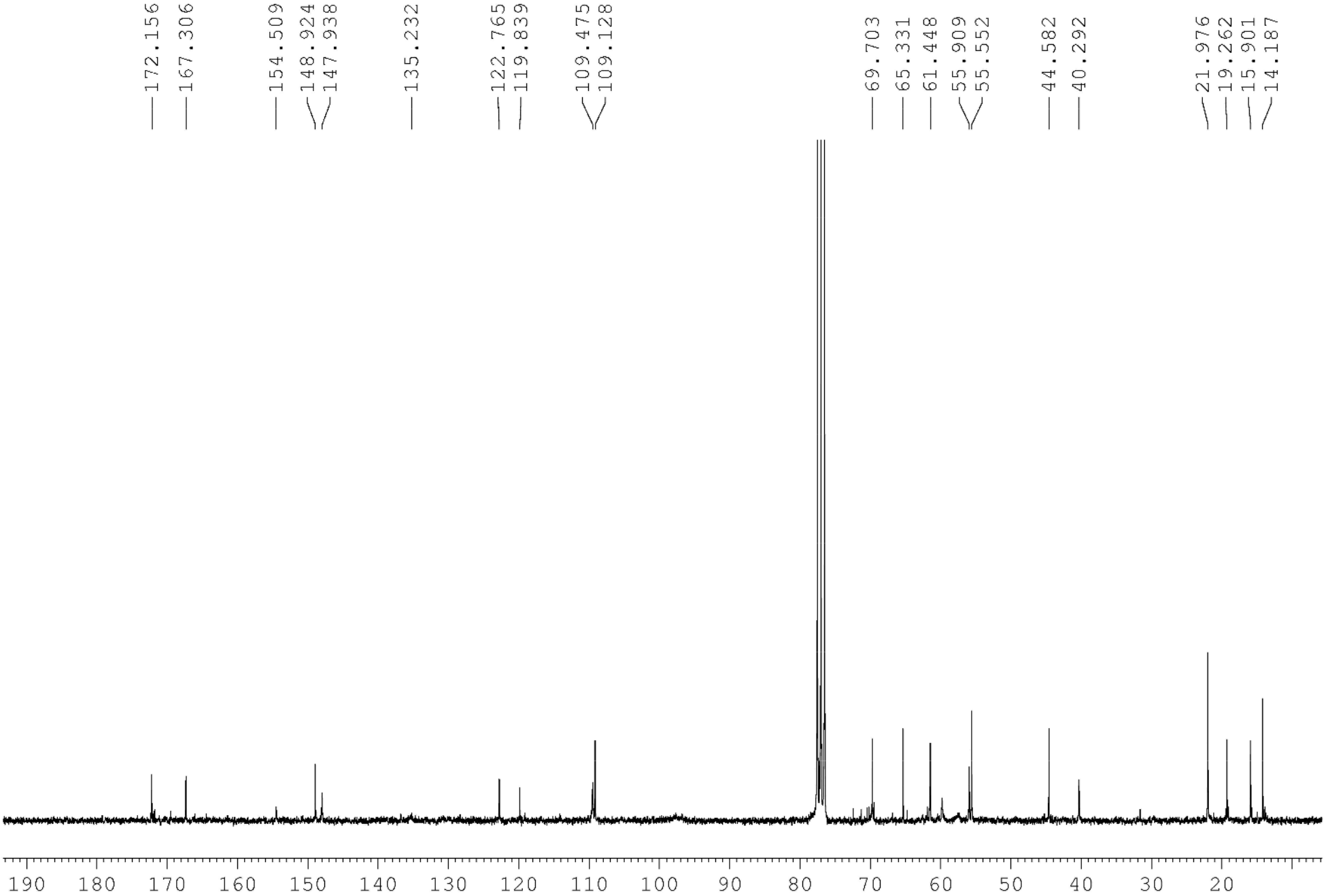
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e⁻ Conf
C 22 H 25 N 2 O 6	413.17181	-0.8	-1.3	-0.3	22.83	11.5	even



Compound 16



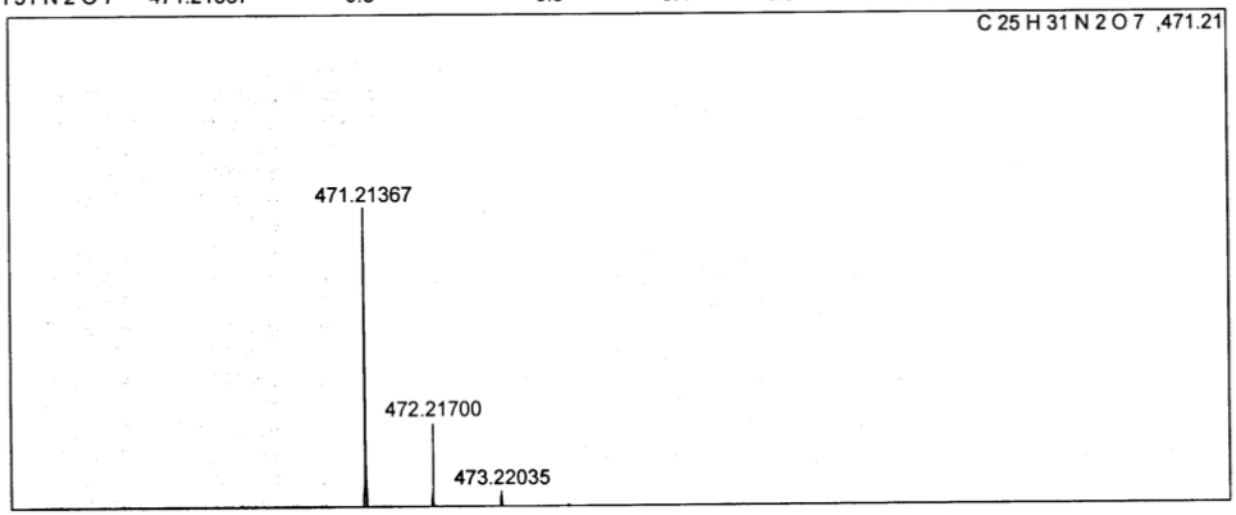
Compound 16



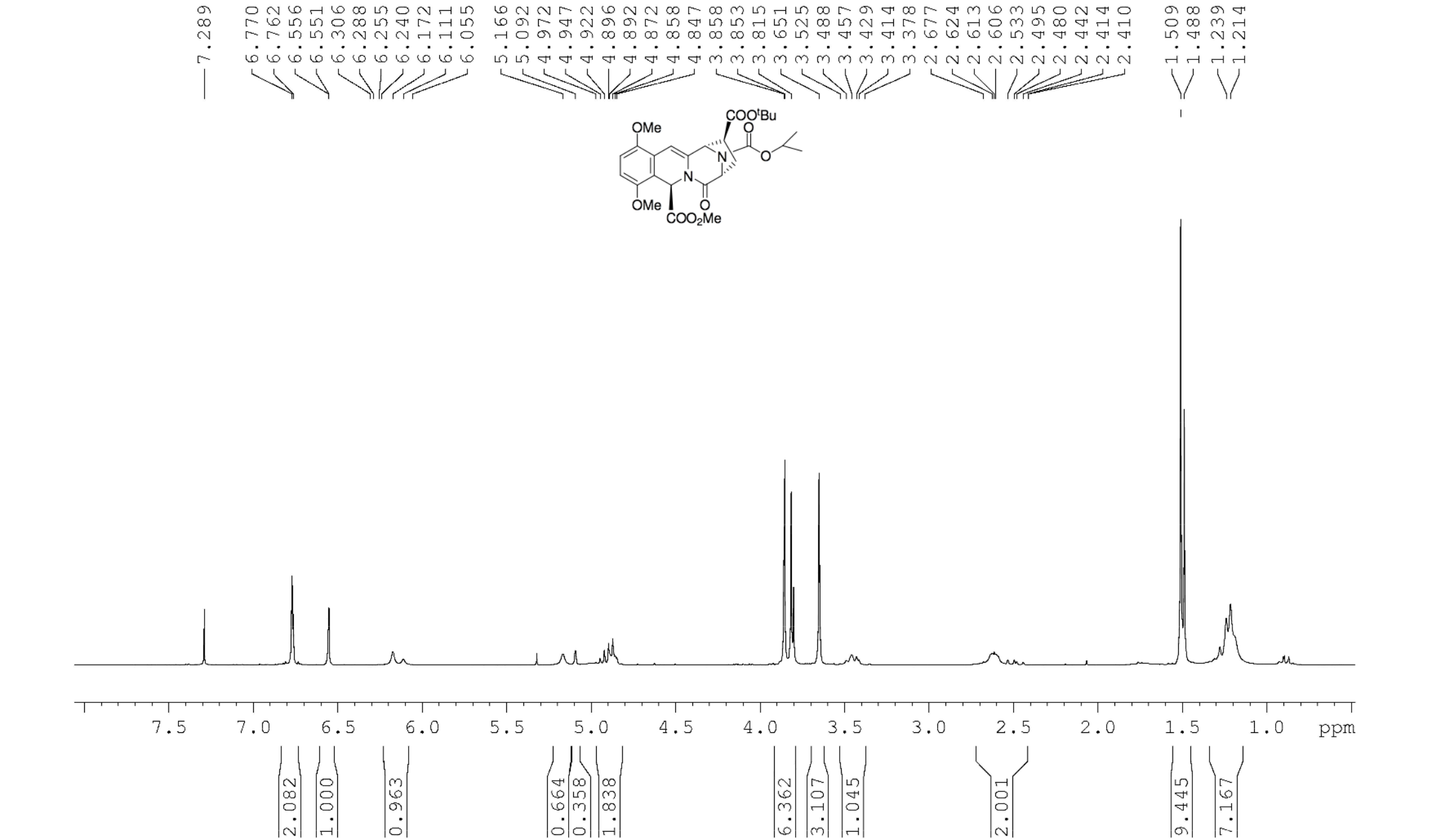
Compound 16

HRMS

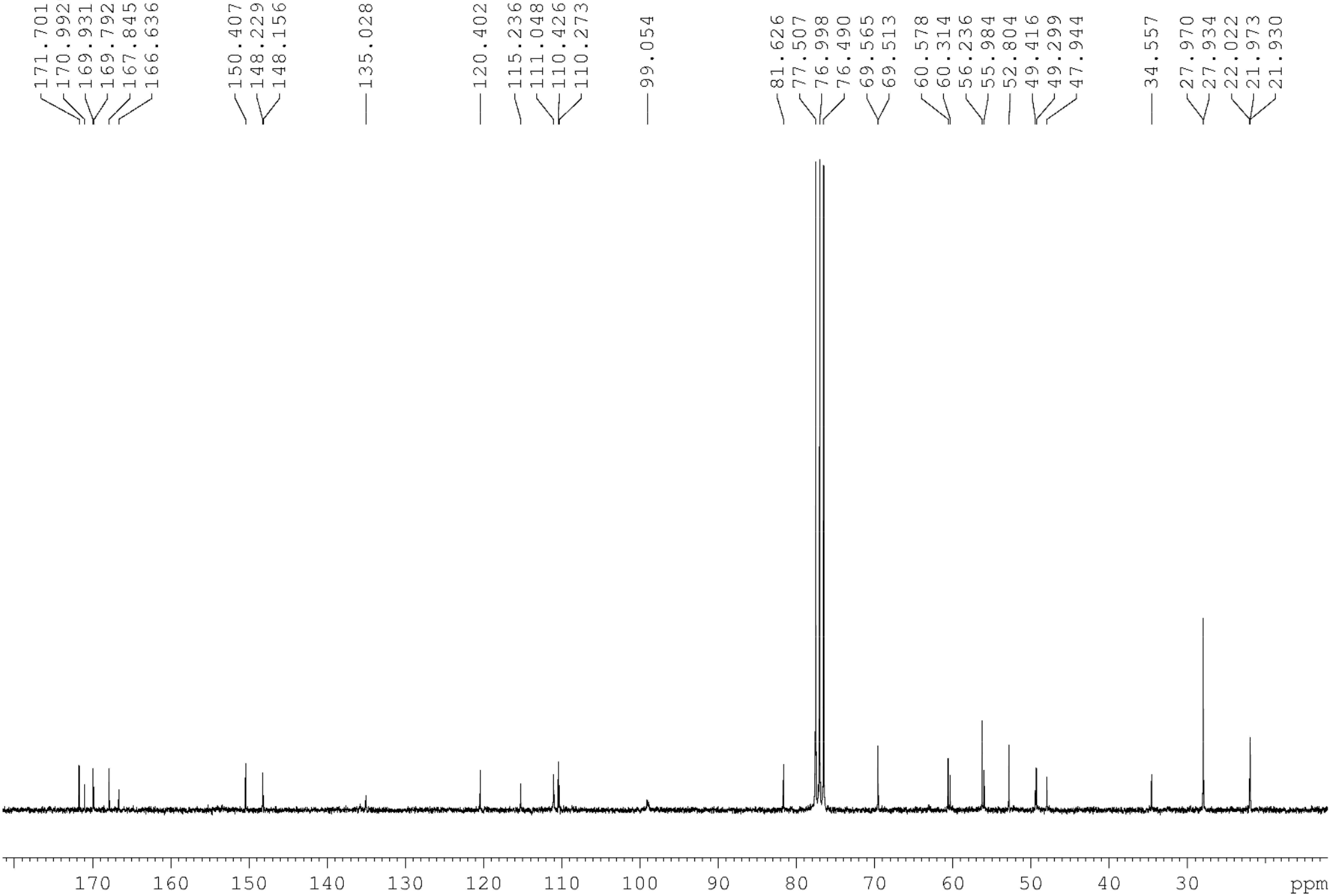
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e⁻ Conf
C 25 H 31 N 2 O 7	471.21367	-0.8	-0.8	-0.4	9.54	11.5	even



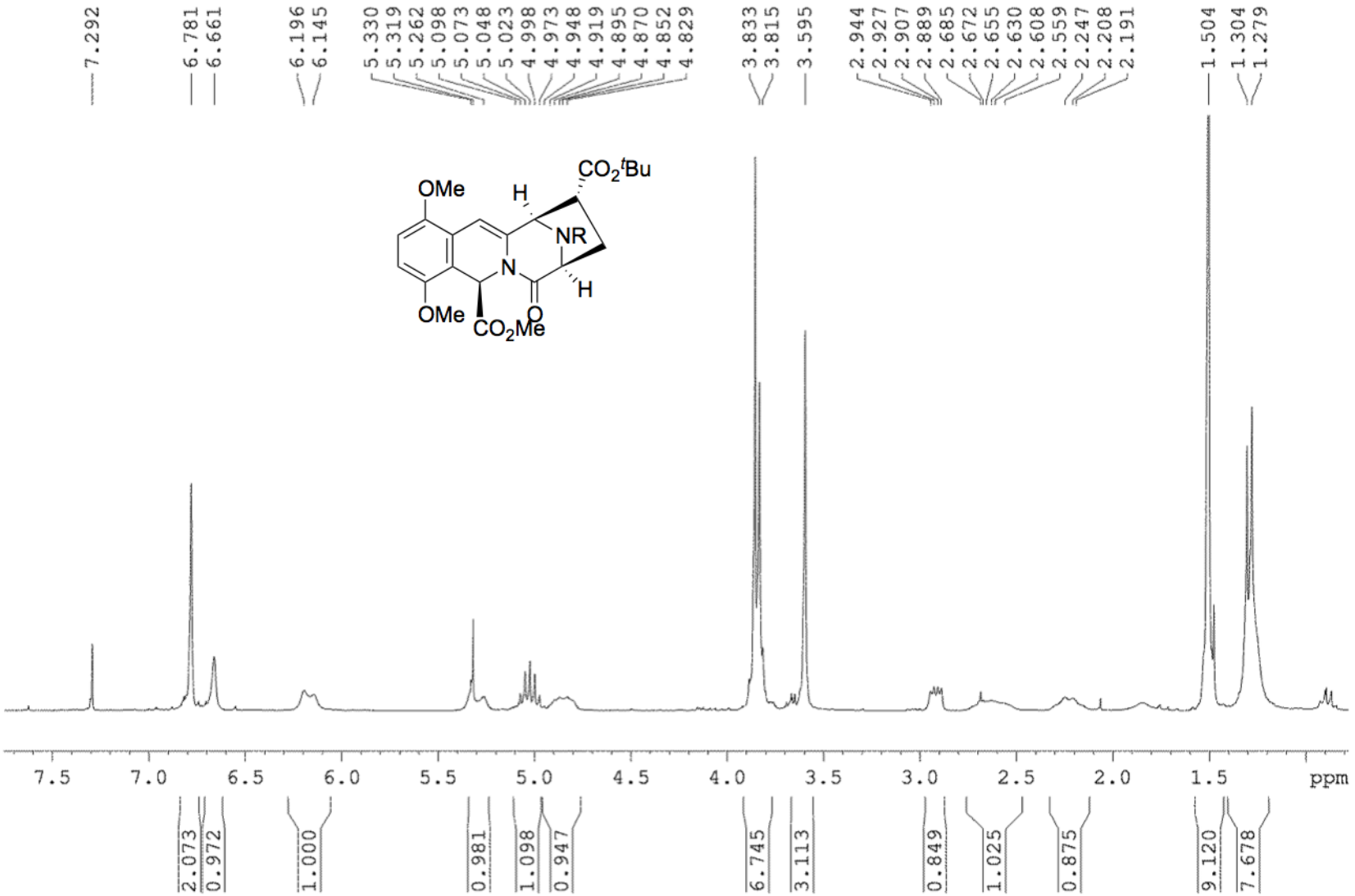
Compound 17



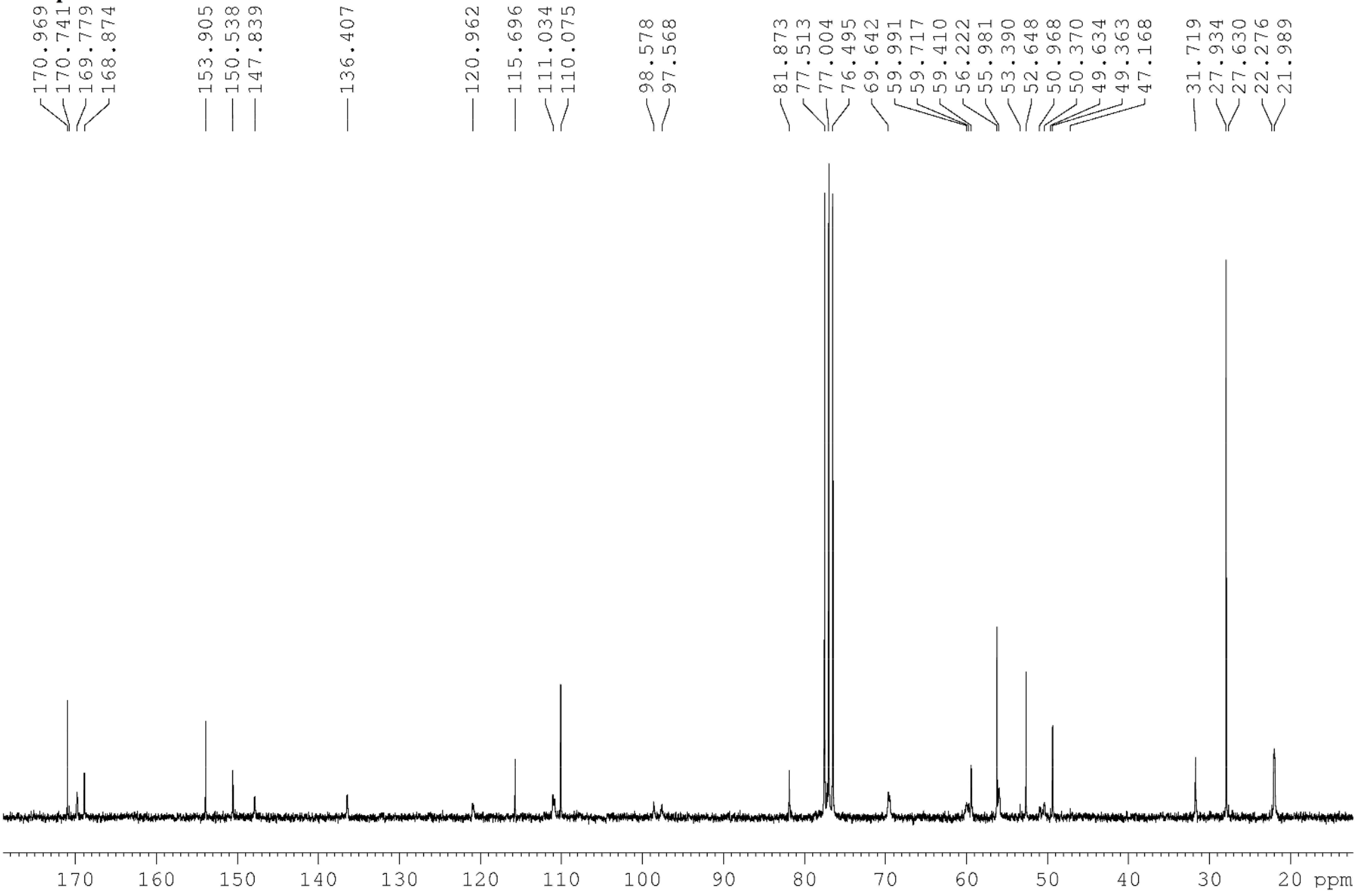
Compound 17



Compound 18



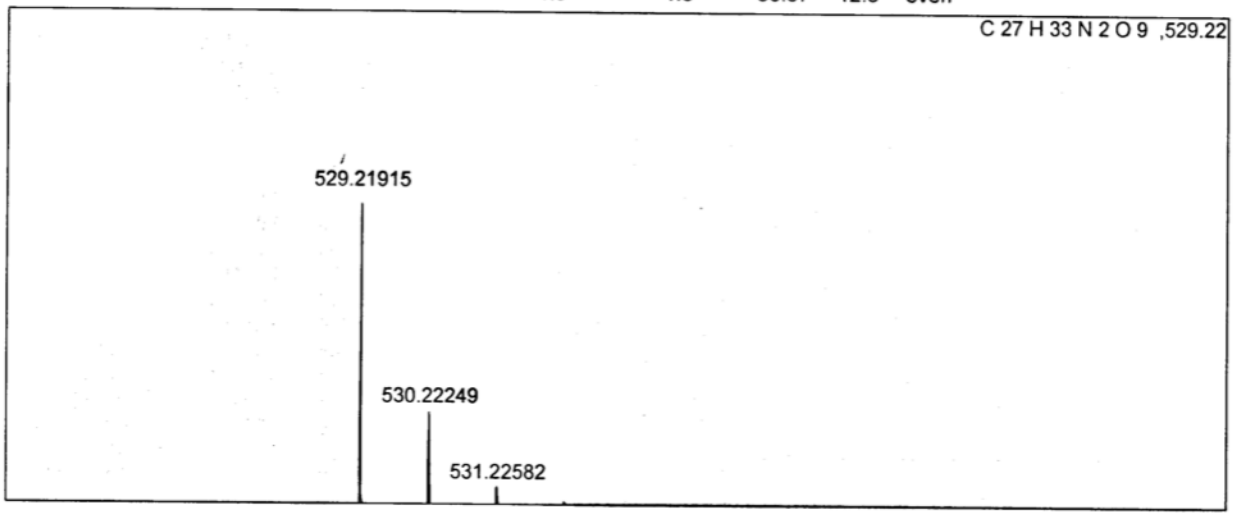
Compound 18



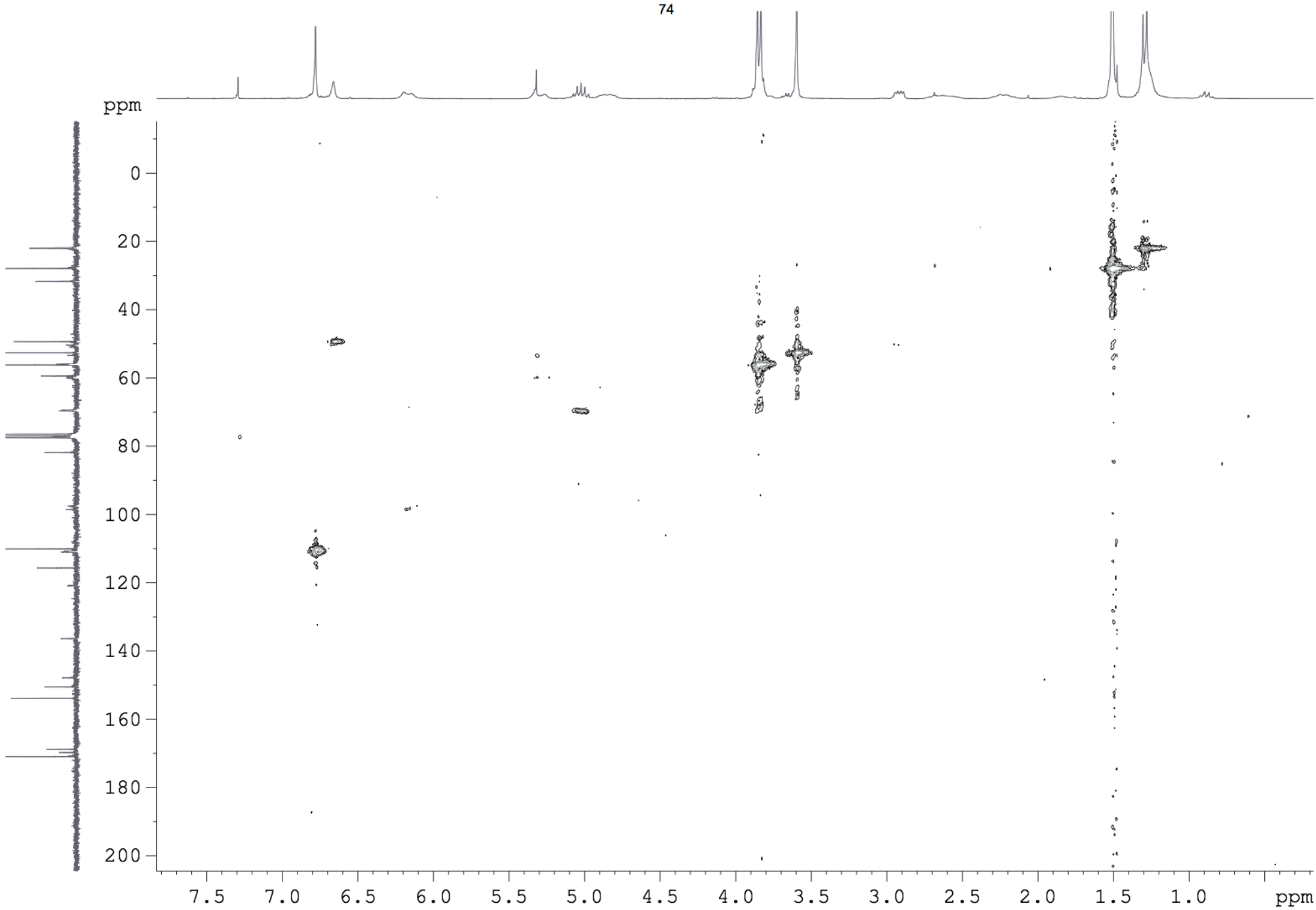
Compound 18

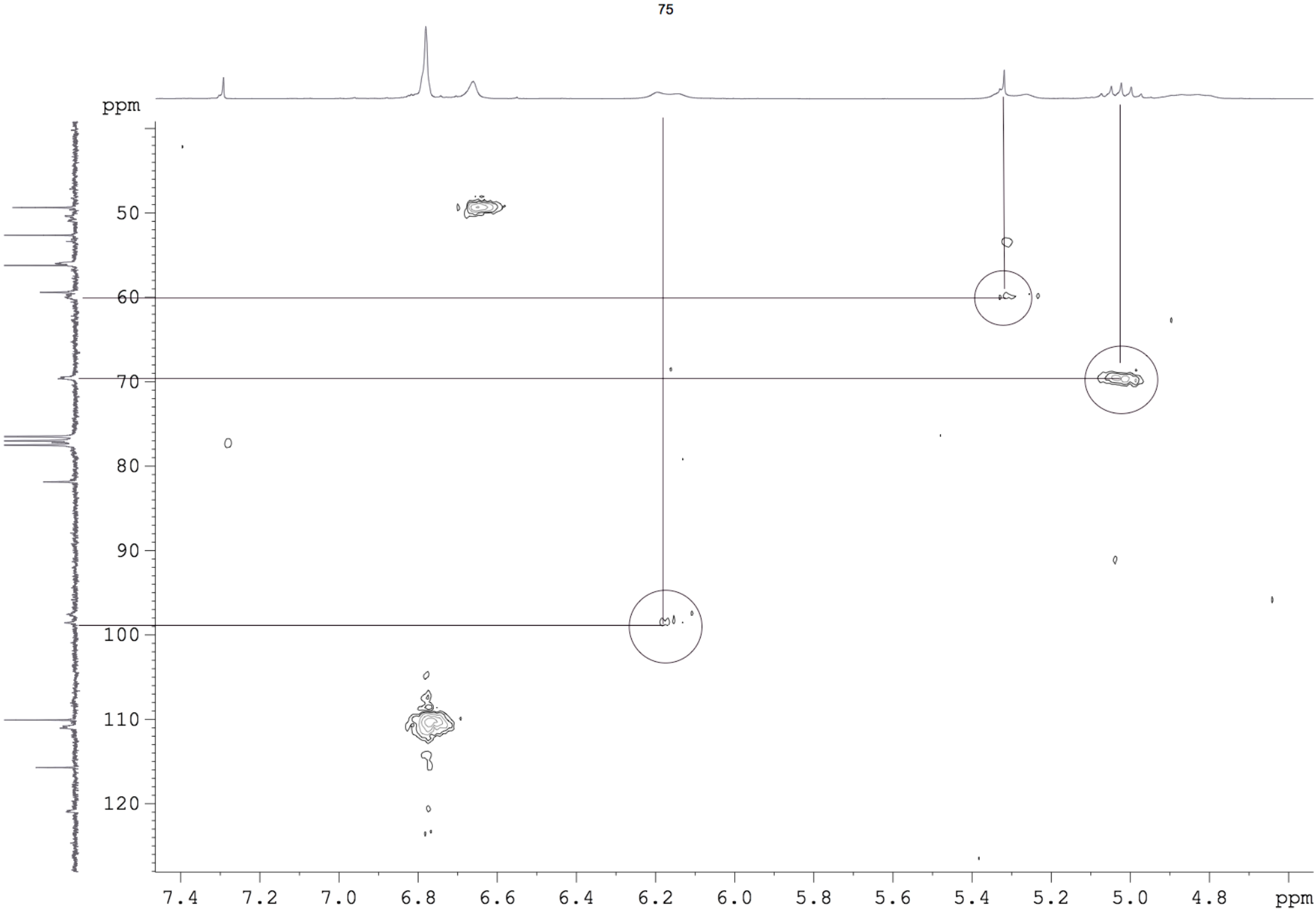
HRMS

Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e¯ Conf
C 27 H 33 N 2 O 9	529.21915	2.4	1.9	1.3	30.37	12.5	even

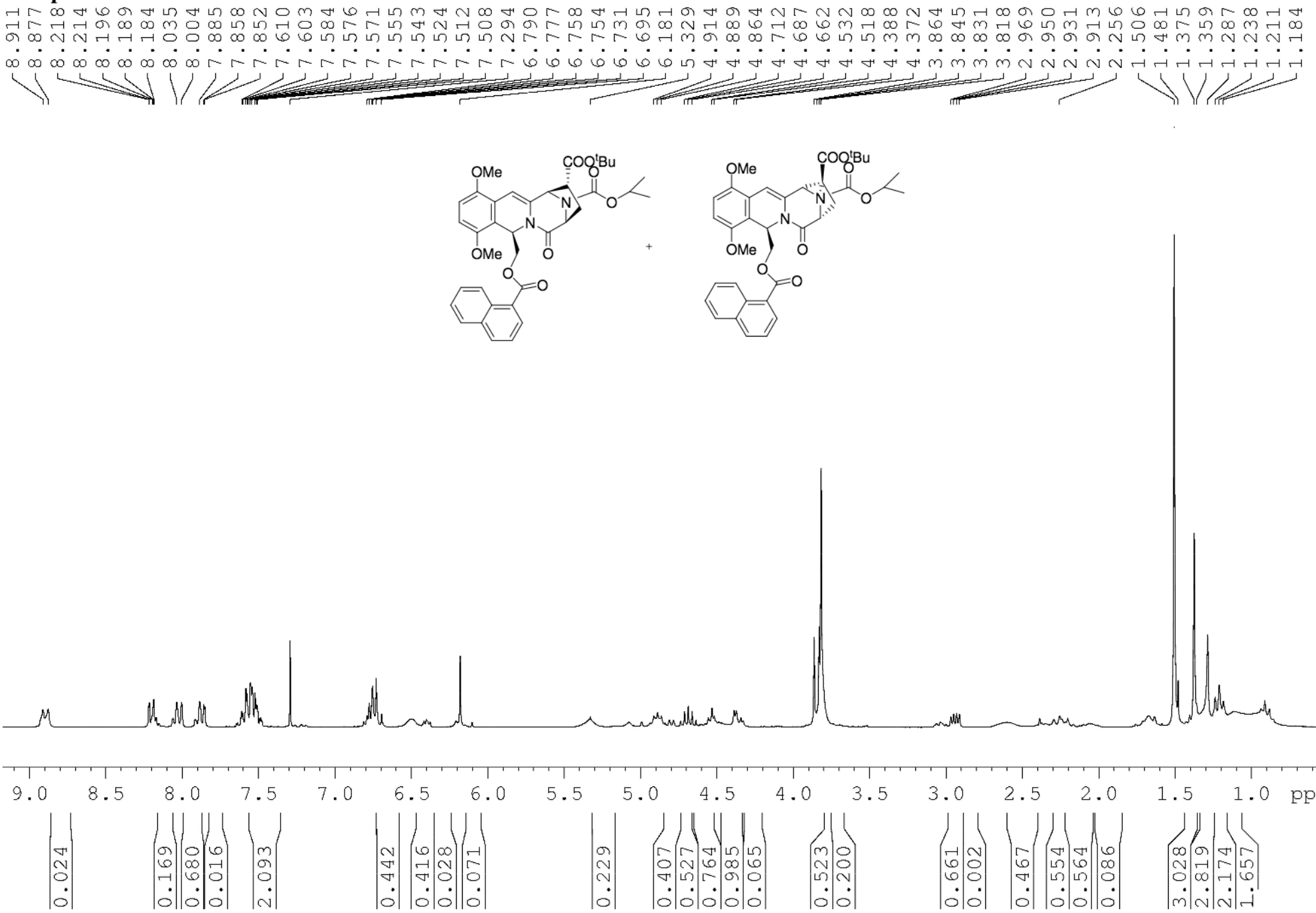


HMBC experiment of compound 18

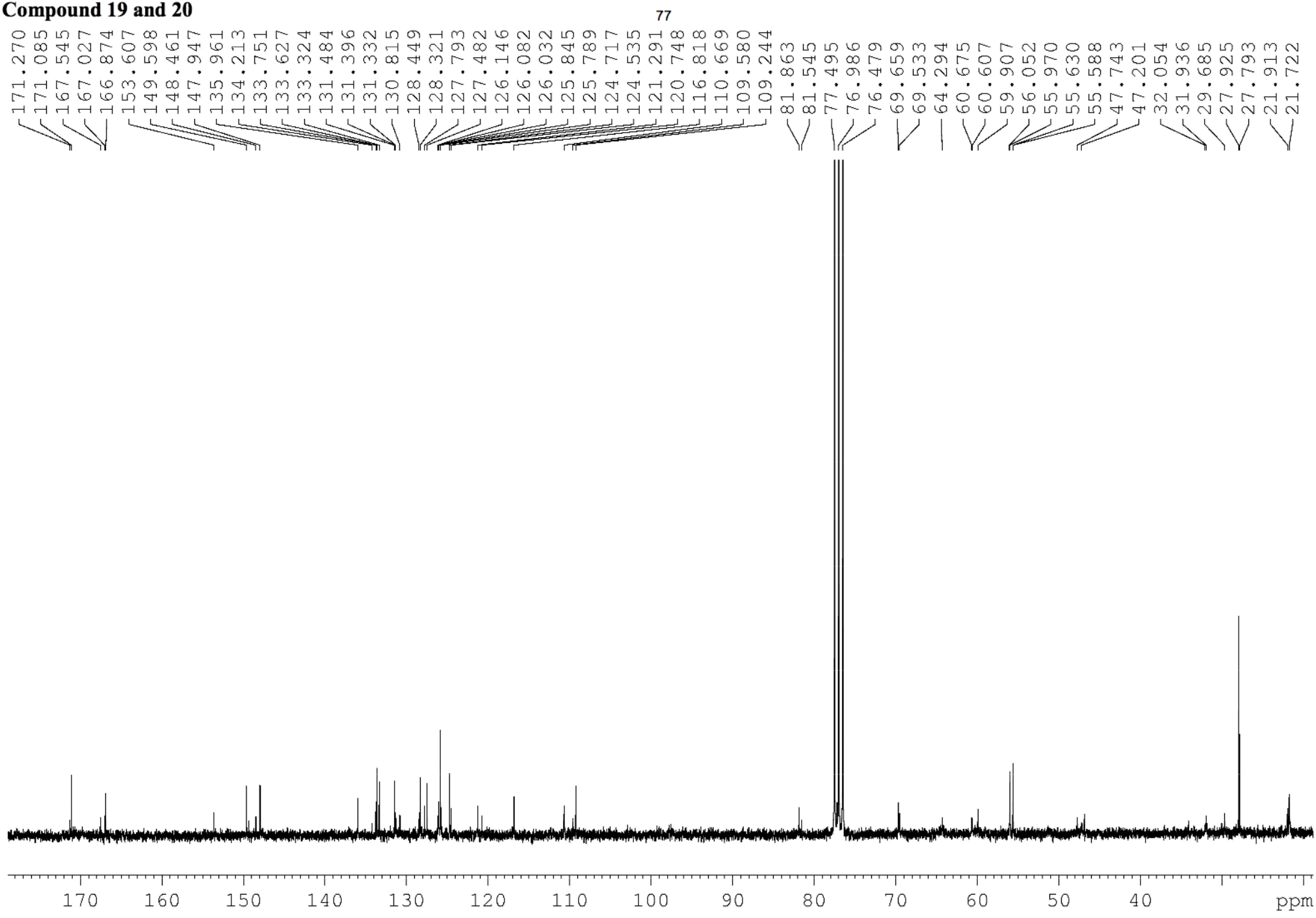




Compound 19 and 20



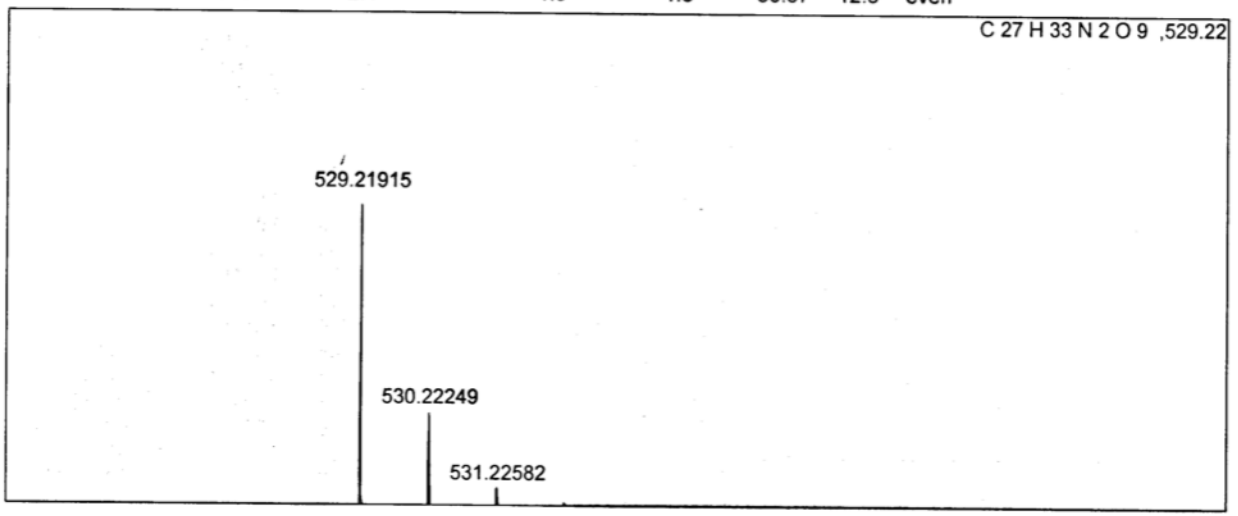
Compound 19 and 20



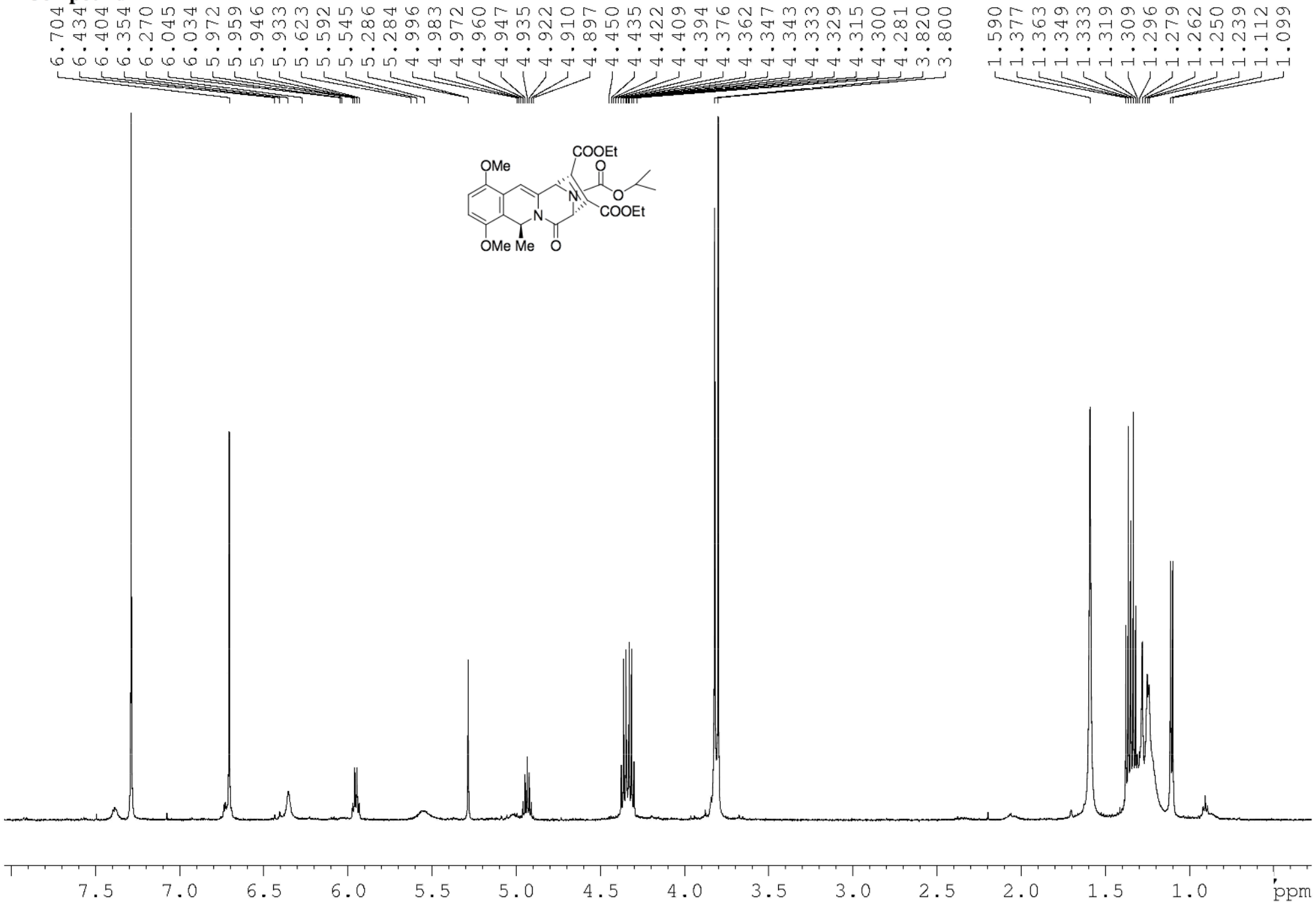
Compound 19 + 20

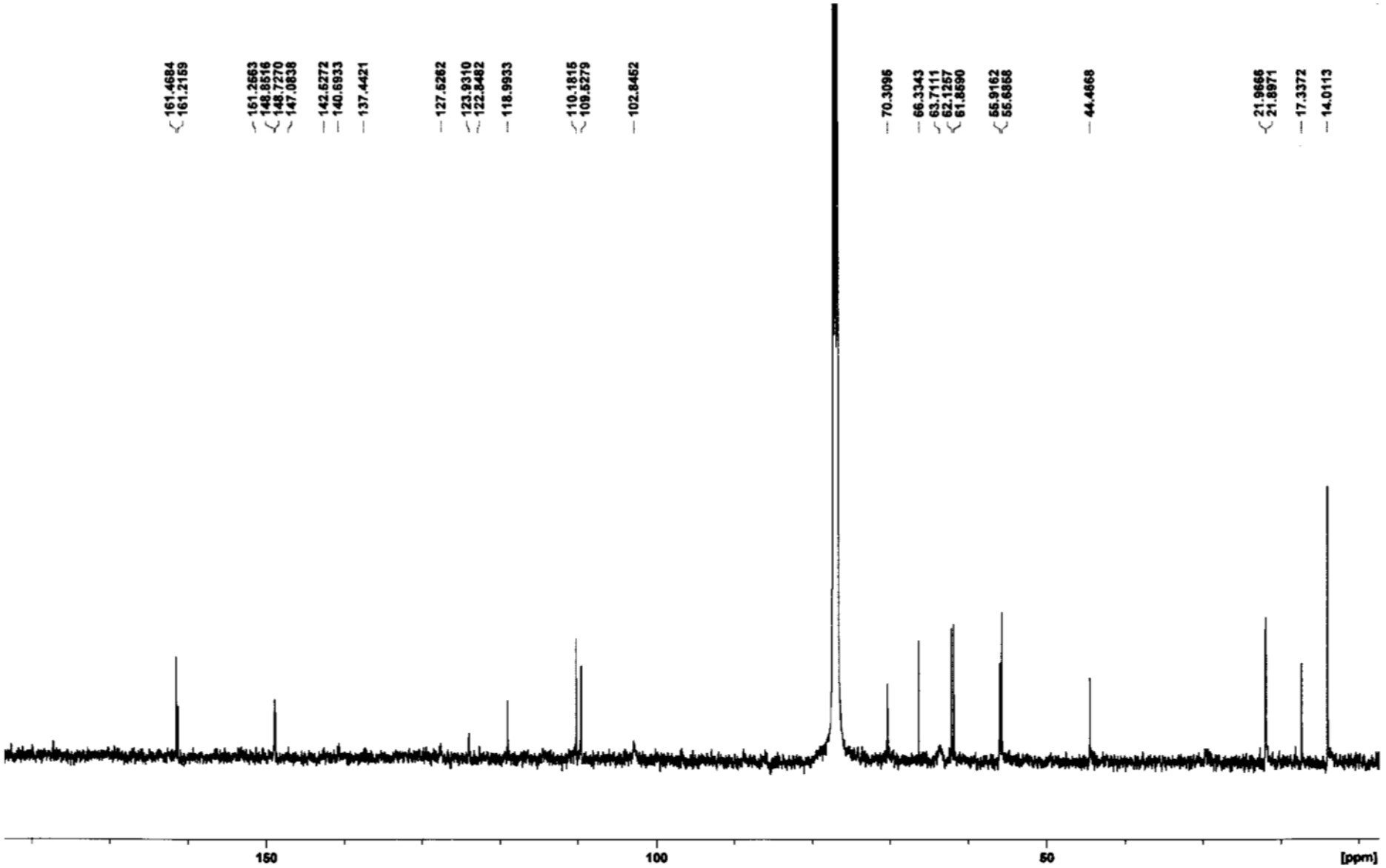
HRMS

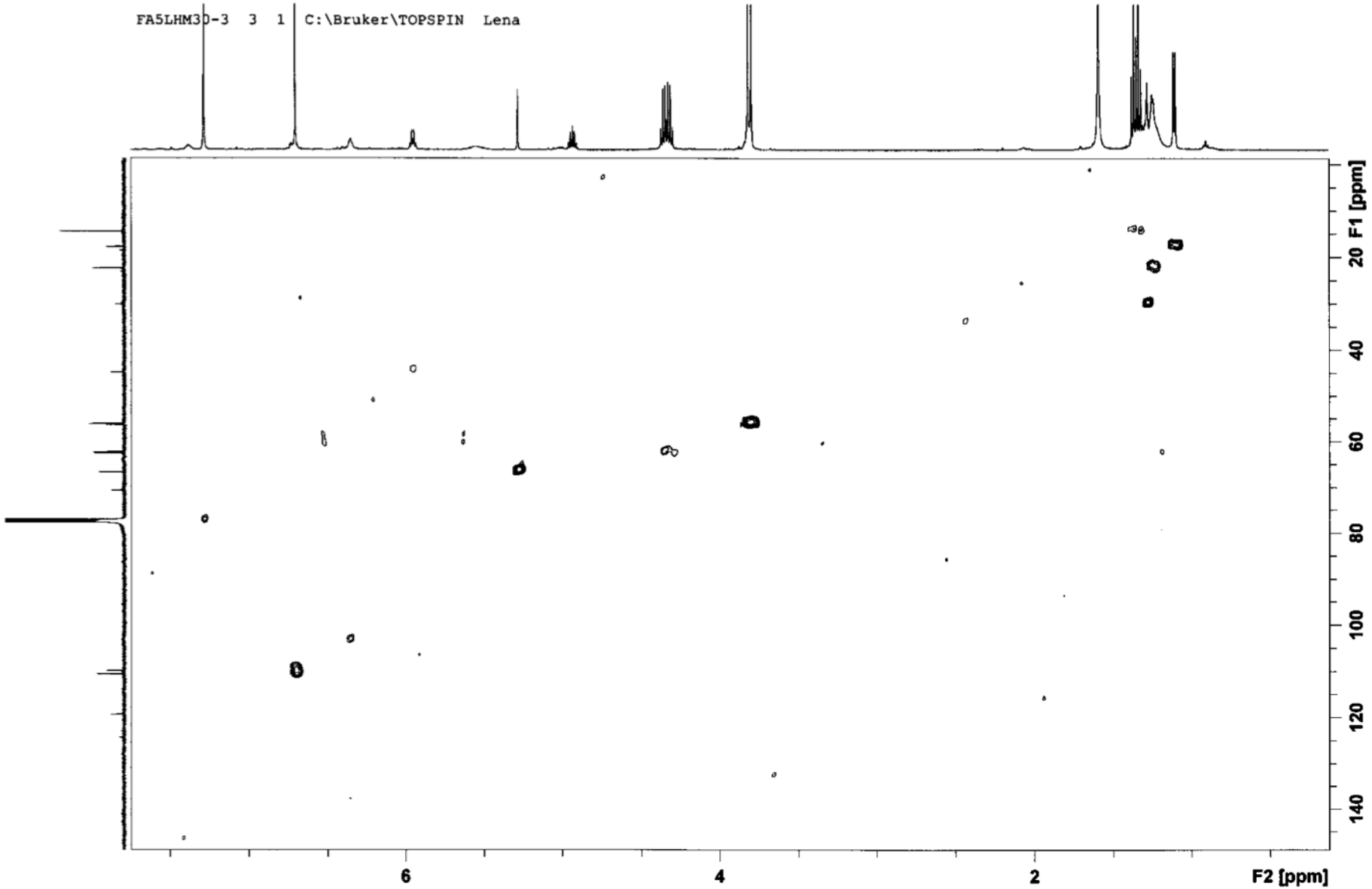
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e¯ Conf
C 27 H 33 N 2 O 9	529.21915	2.4	1.9	1.3	30.37	12.5	even



Compound 21

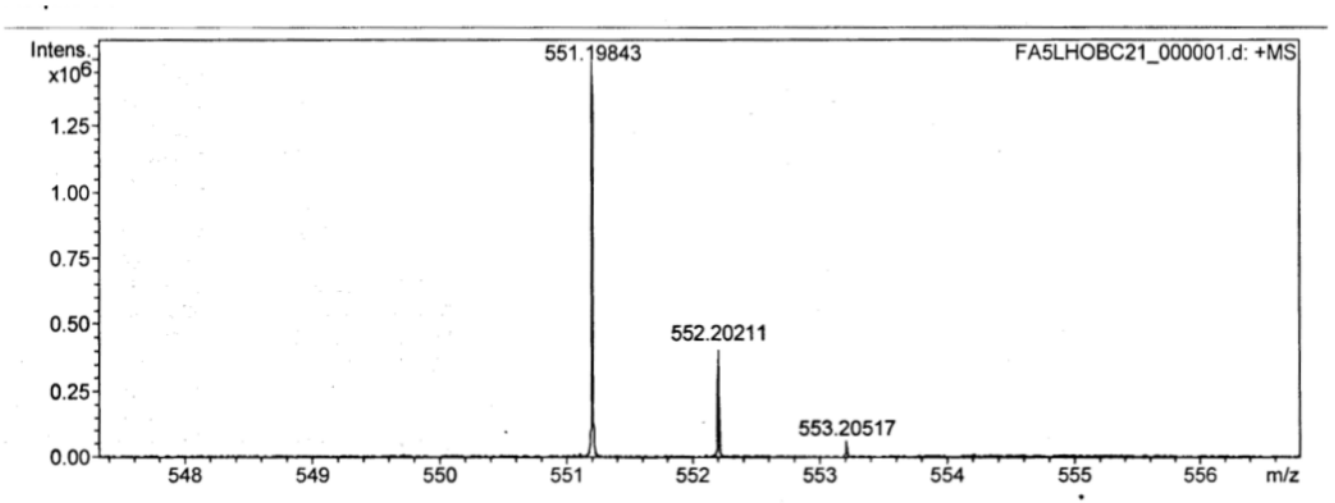




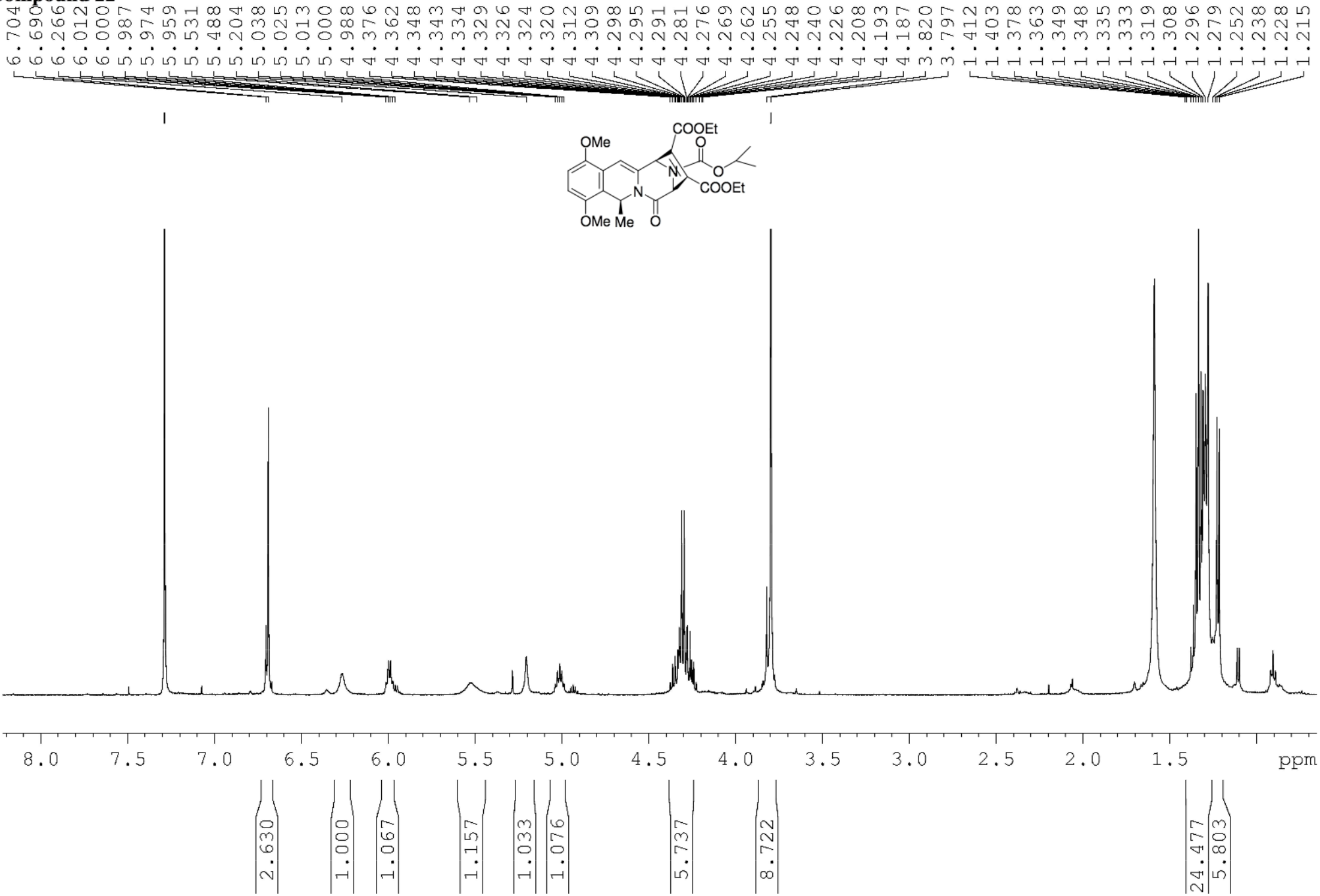


Compound 21

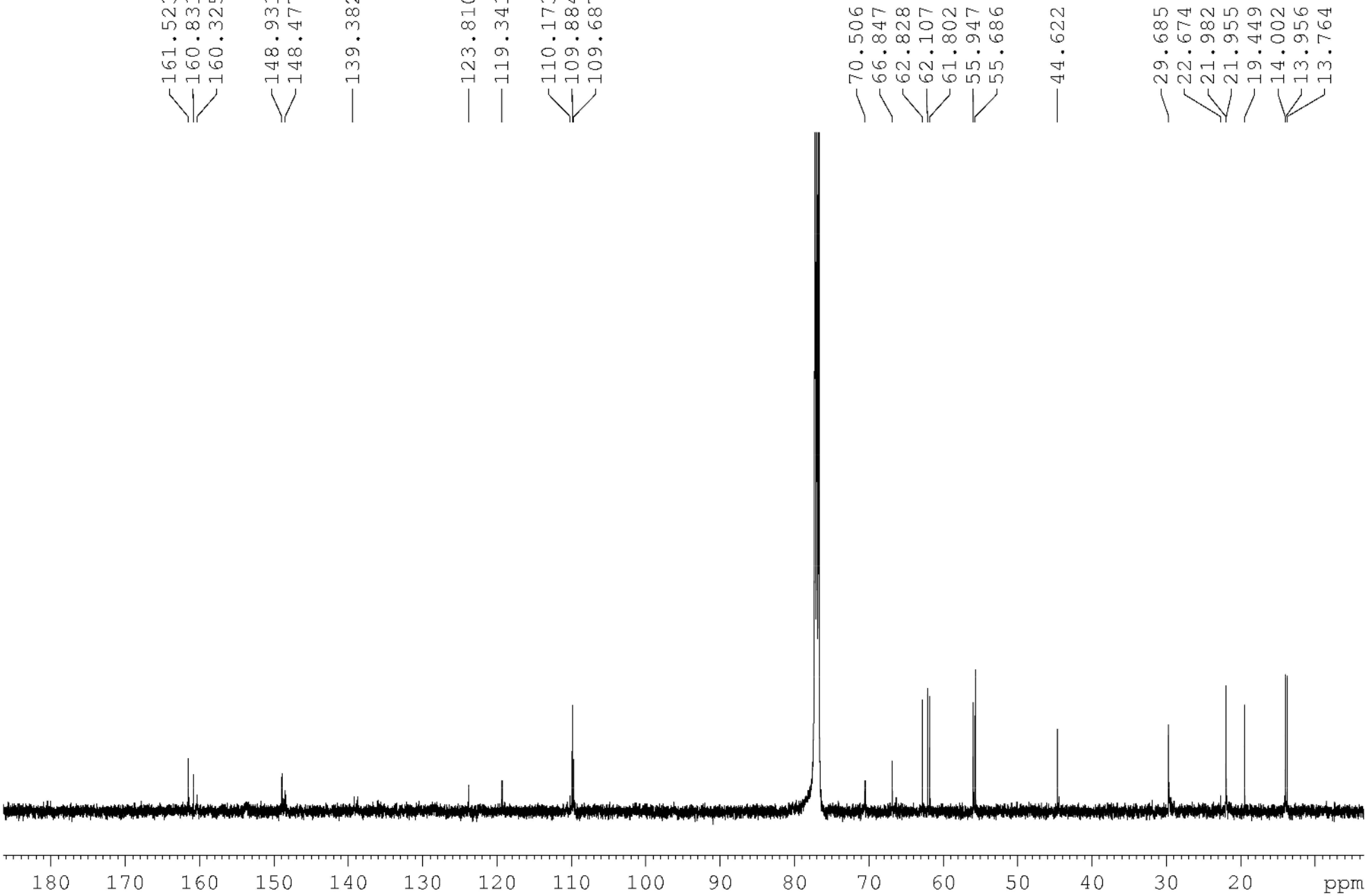
HRMS



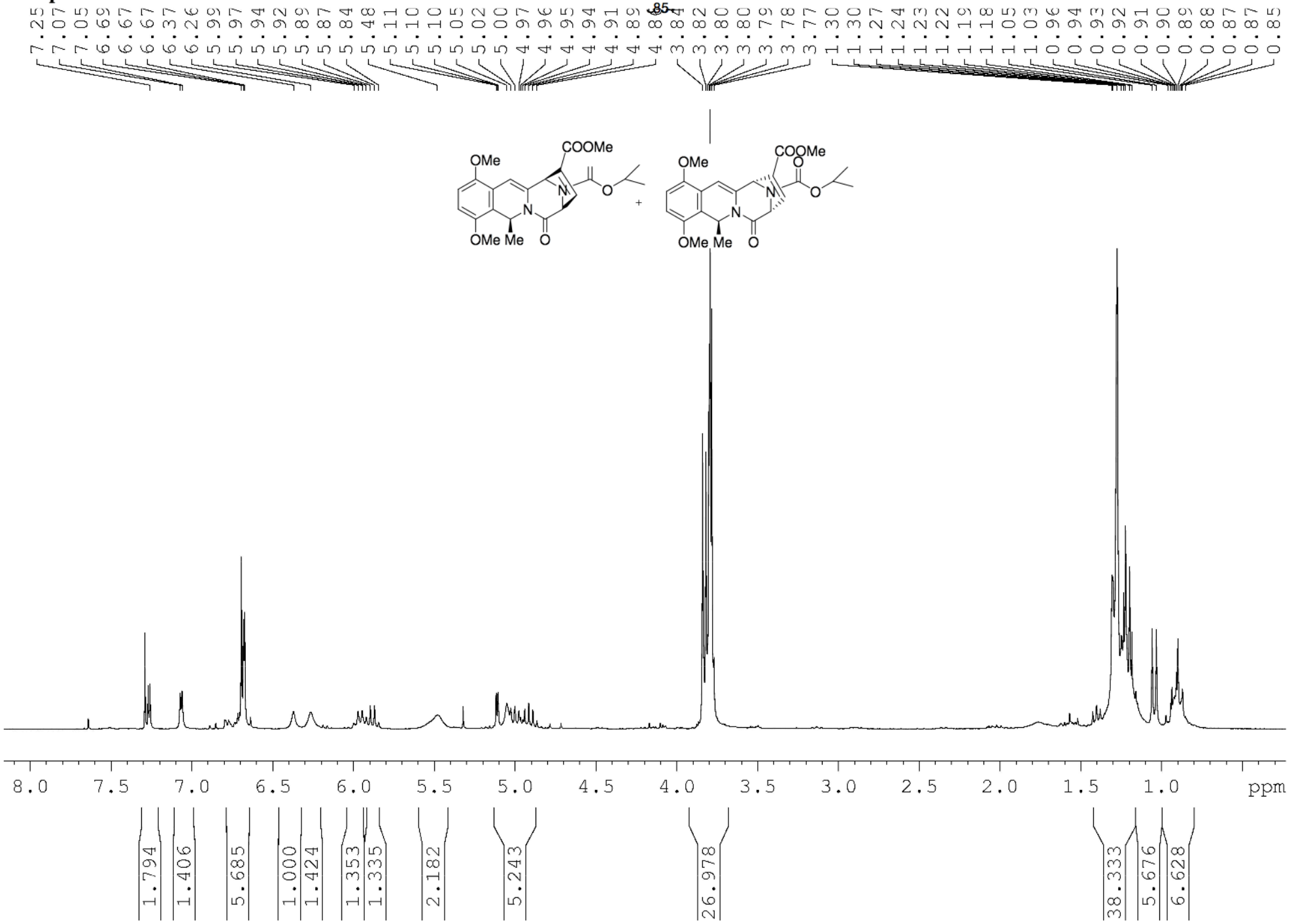
Compound 22



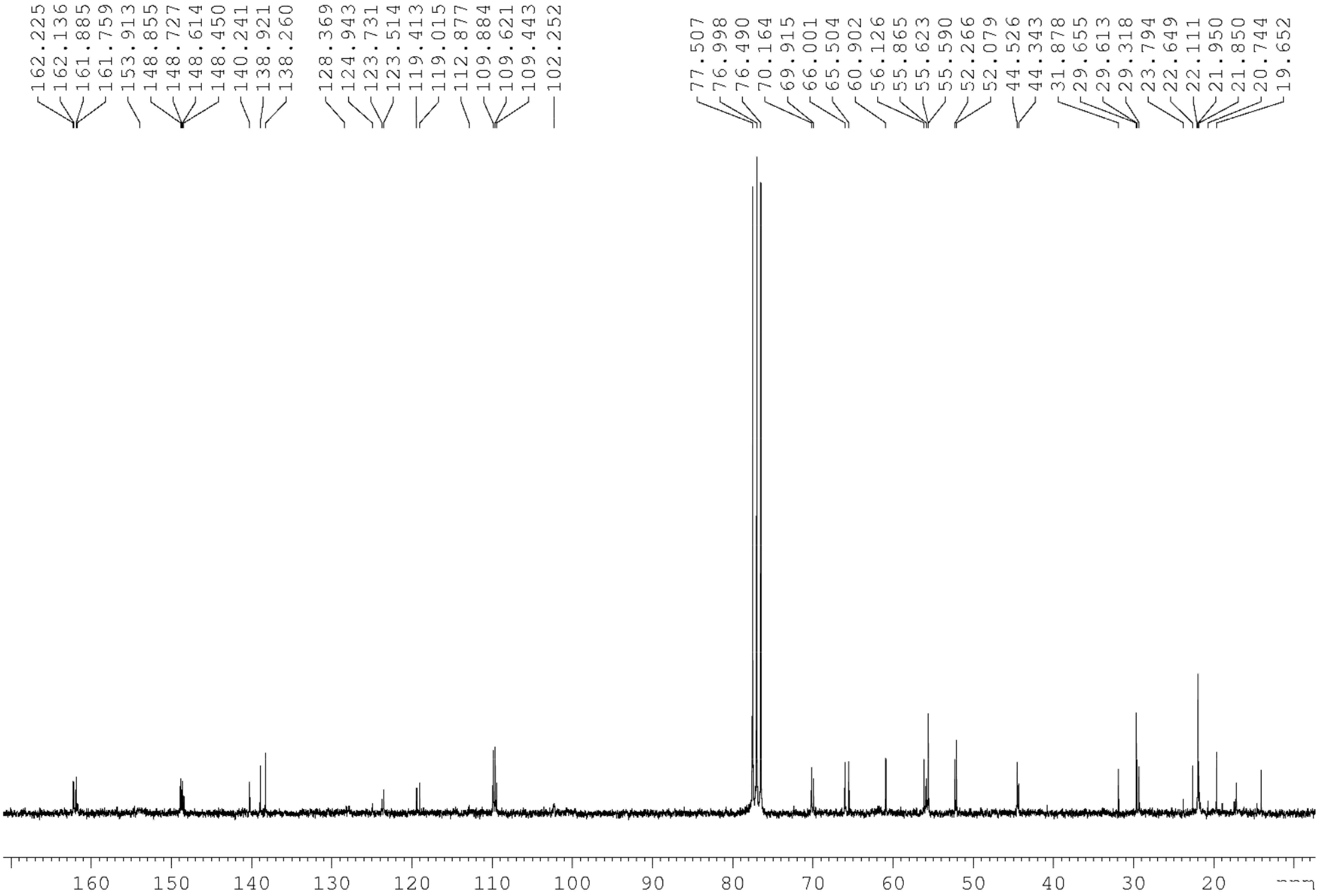
Compound 22



Compound 23 and 24



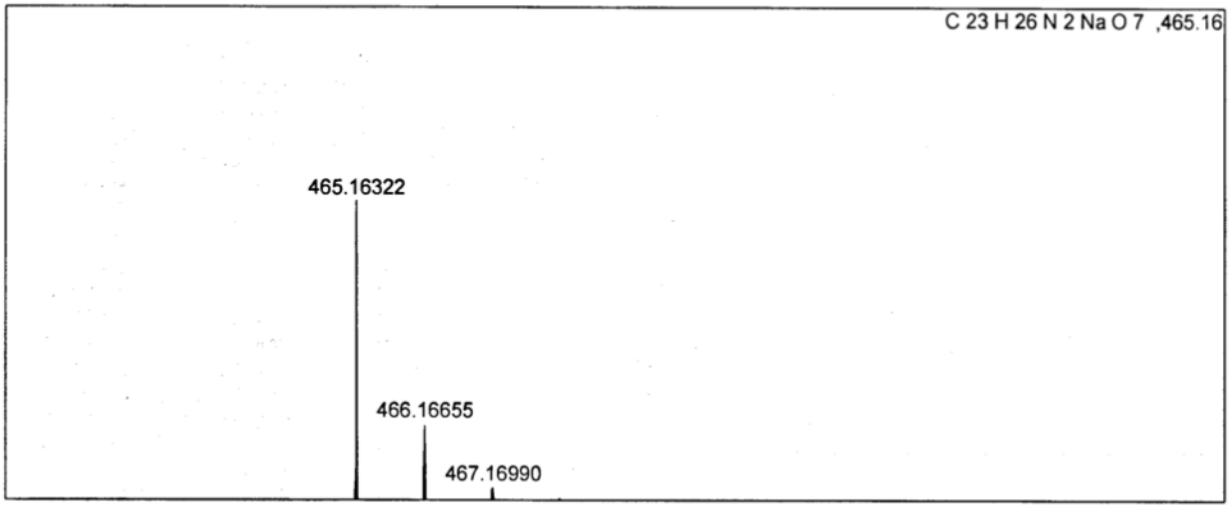
Compound 23 and 24



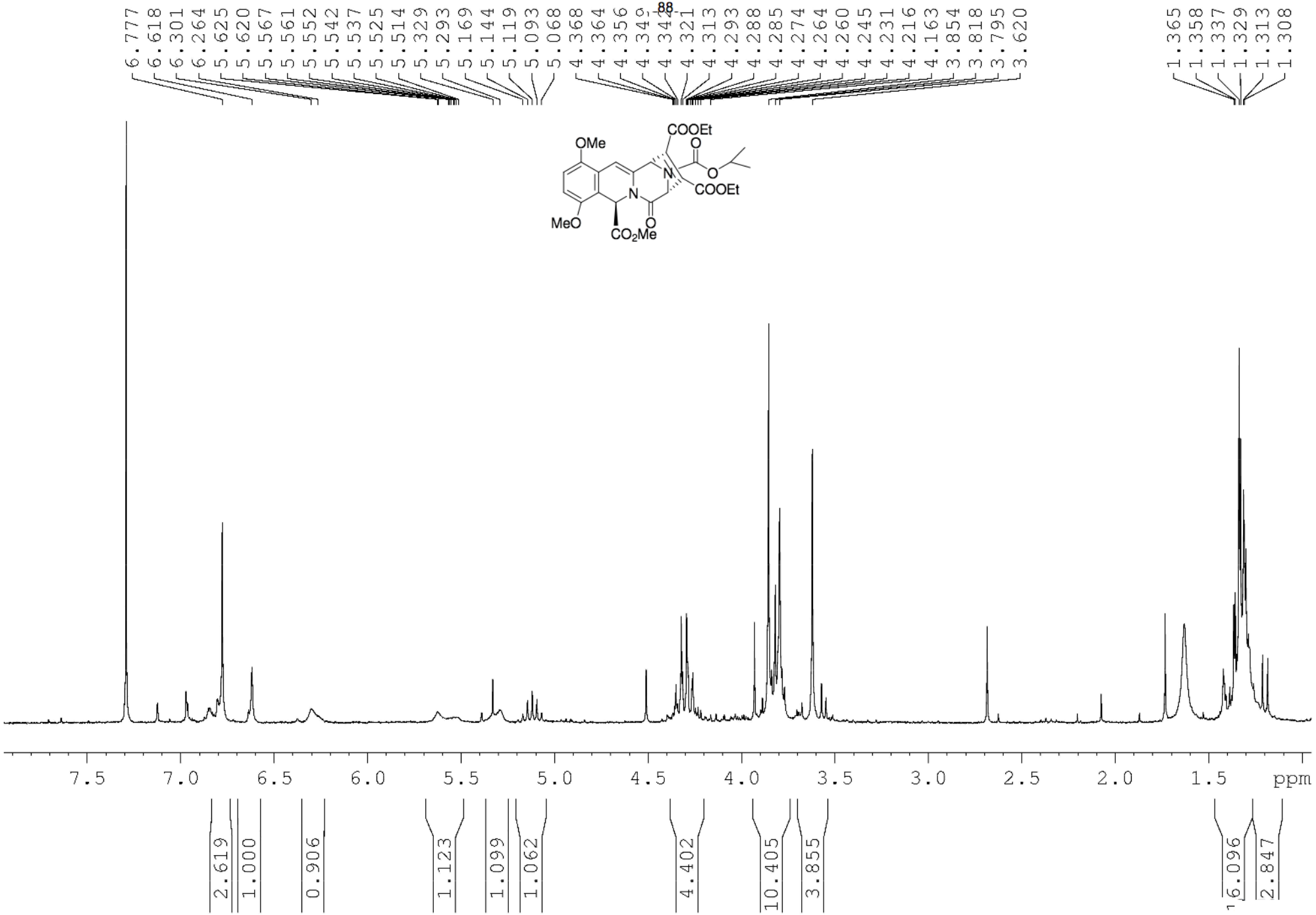
Compound 23 + 24

HRMS

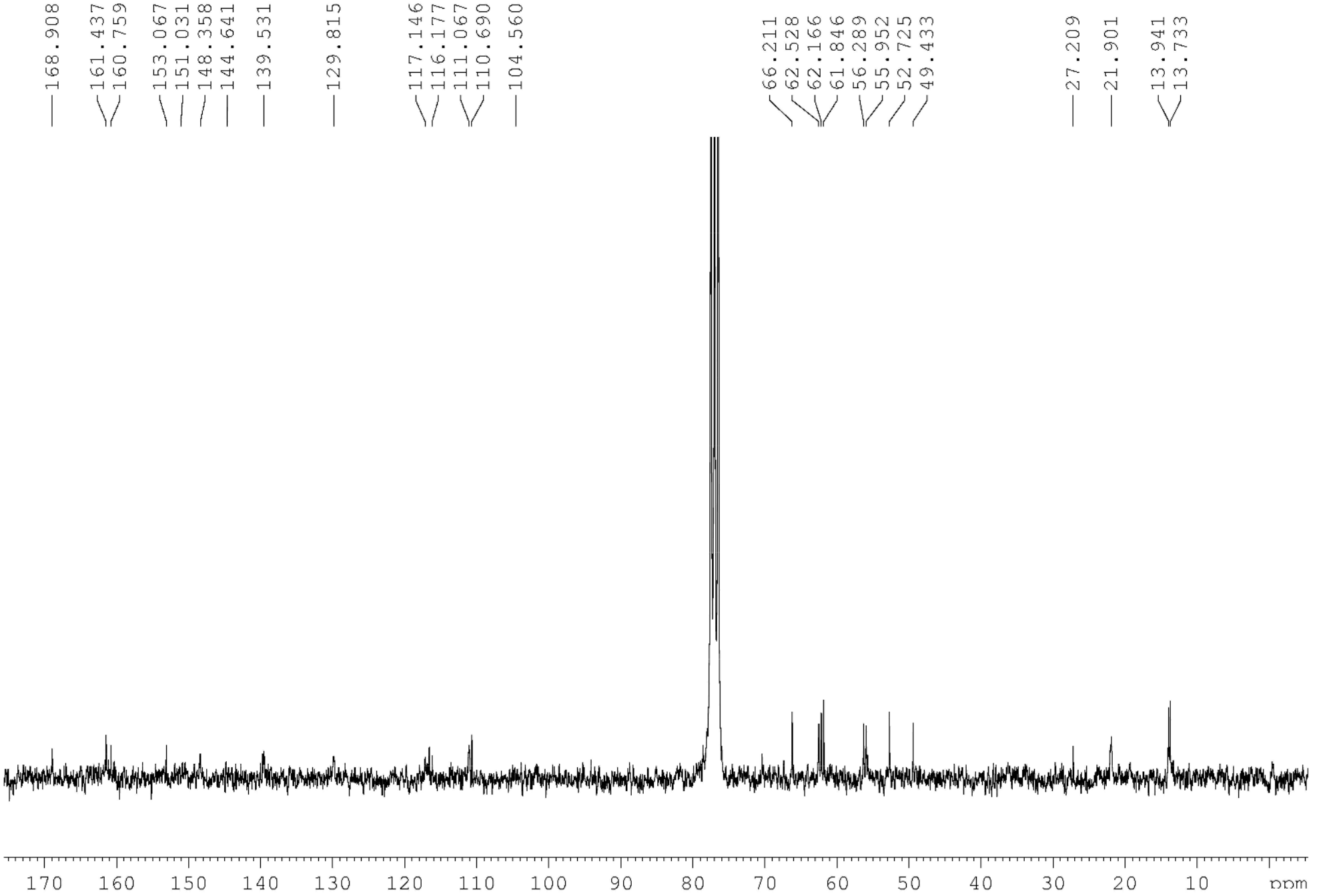
Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e^- Conf
C 23 H 26 N 2 Na O 7	465.16322	1.8	1.5	0.8	19.99	11.5	even



Compound 25



Compound 25



Compound 25

HRMS

Formula	m/z	err [ppm]	Mean err [ppm]	err [mDa]	mSigma	rdb	e^- Conf
C 28 H 32 N 2 Na O 11	595.18983	2.1	1.9	1.3	30.48	13.5	even