

Supporting Information:

Part I. Experimental Data

Structure-Activity Relationships in Toll-like Receptor 2-Agonists Leading to Simplified Monoacyl Lipopeptides

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Synthesis of Compound 2: Isopropyl 2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)propanamido)acetate. To a solution of **1** (1 g, 2.98 mmol) in anhydrous DMF were added glycine isopropyl ester hydrochloride (548 mg, 5.96 mmol), HOBr (805 mg, 5.96 mmol), and triethylamine (830 μ L, 5.96 mmol). The reaction mixture was stirred at 0 °C for 30 min, followed by addition of EDCI (1.14 g, 3.58 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, followed by evaporation of the solvent under reduced pressure. The residue was then dissolved in ethyl acetate and washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (30% EtOAc/hexanes) to obtain compound **2** (931 mg, 72 %). 1 H NMR (500 MHz, CDCl₃) δ 6.96 (s, 1H), 5.55 (d, *J* = 6.6 Hz, 1H), 5.04 (hept, *J* = 6.3 Hz, 1H), 4.34 (d, *J* = 5.7 Hz, 1H), 4.30–4.21 (m, 1H), 4.10–4.05 (m, 1H), 3.98 (qd, *J* = 18.3, 5.2 Hz, 2H), 3.66 (dd, *J* = 8.3, 6.5 Hz, 1H), 3.06 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.89 (dd, *J* = 14.0, 6.3 Hz, 1H), 2.73 (ddd, *J* = 31.5, 13.6, 6.2 Hz, 2H), 1.47–1.39 (m, 12H), 1.34 (d, *J* = 4.5 Hz, 3H), 1.24 (dd, *J* = 6.8, 2.0 Hz, 6H). 13 C NMR (126 MHz, CDCl₃) δ 170.82, 169.03, 155.59, 109.80, 80.57, 75.65, 69.48, 68.80, 60.49, 54.20, 41.74, 35.75, 35.02, 28.40, 26.95, 25.60, 21.85. MS (ESI) calculated for C₁₉H₃₄N₂O₇S, m/z 434.20, found 457.22 (M + Na)⁺.

Synthesis of Compound 3: Isopropyl 2-((*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((*R*)-2,3-dihydroxypropyl)thio)propanamido)acetate. The solution of **2** (1 g, 2.30 mmol) in trifluoroacetic acid was stirred for 10 min, followed by removal of the solvent by purging nitrogen and drying under vacuum to obtain the trifluoroacetate salt. To the solution of

trifluoroacetate salt in acetonitrile, aqueous solution of sodium bicarbonate (580 mg, 6.90 mmol) was added at 10 °C. The reaction mixture was stirred at room temperature for 30 min, followed by the addition of Fmoc.OSu (931 mg, 2.76 mmol) solution in acetonitrile. The reaction mixture was stirred at room temperature for 16 h, followed by removal of the solvent under reduced pressure. The residue was dissolved in ethyl acetate and washed with water. The ethyl acetate was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (5% MeOH/CH₂Cl₂) to obtain compound **3** (1.05 g, 89 %). ¹H NMR (500 MHz, MeOD) δ 7.70 (d, *J* = 7.54 Hz, 2H), 7.59 (d, *J* = 7.35 Hz, 2H), 7.29 (t, *J* = 7.47 Hz, 2H), 7.22 (t, *J* = 7.43 Hz, 2H), 4.91 (dt, *J* = 6.16, 12.24 Hz, 1H), 4.33 (dd, *J* = 7.24, 10.16 Hz, 1H), 4.30–4.18 (m, 2H), 4.15 (t, *J* = 6.81 Hz, 1H), 3.85–3.76 (m, 2H), 3.68–3.63 (m, 1H), 3.46 (qd, *J* = 5.33, 11.17 Hz, 2H), 2.96 (dd, *J* = 4.79, 13.89 Hz, 1H), 2.76–2.64 (m, 2H), 2.52 (dd, *J* = 6.99, 13.56 Hz, 1H), 1.14 (d, *J* = 6.15 Hz, 6H). ¹³C NMR (126 MHz, MeOD) δ 173.81, 170.59, 158.55, 145.29, 145.24, 142.61, 128.82, 128.22, 126.36, 126.31, 120.94, 72.73, 70.26, 68.21, 65.90, 56.25, 42.39, 36.69, 21.99. MS (ESI) calculated for C₂₆H₃₂N₂O₇S, m/z 516.19, found 539.21 (M + Na)⁺.

Synthesis of Compound 4: (*R*)-3-((*R*)-2-(((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-((2-isopropoxy-2-oxoethyl)amino)-3-oxopropylthio)propane-1,2-diyl dipalmitate. To a solution of **3** (130 mg, 0.25 mmol) in anhydrous dichloromethane were added triethylamine (104 μL, 0.75 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 30 min. Palmitoyl chloride (181 μL, 0.6 mmol) was then added at 0 °C, followed by stirring of the reaction mixture at room temperature for 6h. After completion of the reaction, the

reaction mixture was sequentially washed with water, saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (30% EtOAc/hexanes) to obtain compound **3** (202 mg, 81 %).

¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, *J* = 7.54 Hz, 2H), 7.64–7.56 (m, 2H), 7.40 (t, *J* = 7.44 Hz, 2H), 7.32 (t, *J* = 7.44 Hz, 2H), 6.91 (s, 1H), 5.78 (d, *J* = 5.70 Hz, 1H), 5.23 (s, 1H), 5.06 (dq, *J* = 6.26, 12.52 Hz, 1H), 4.49–4.35 (m, 3H), 4.31 (dd, *J* = 2.54, 11.71 Hz, 1H), 4.23 (t, *J* = 7.04 Hz, 1H), 4.17 (dd, *J* = 5.59, 11.41 Hz, 1H), 4.00 (d, *J* = 4.63 Hz, 2H), 3.07–2.90 (m, 2H), 2.88–2.75 (m, 2H), 2.31 (dt, *J* = 7.59, 11.59 Hz, 4H), 1.65–1.55 (m, 4H), 1.37–1.16 (m, 54H), 0.88 (t, *J* = 6.97 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 173.48, 173.41, 170.15, 168.74, 155.98, 143.71, 143.69, 141.30, 127.75, 127.10, 125.13, 125.10, 120.02, 70.33, 69.45, 67.31, 63.60, 54.38, 47.09, 41.71, 35.34, 34.32, 34.08, 33.46, 31.93, 29.71, 29.67, 29.67, 29.65, 29.65, 29.51, 29.50, 29.37, 29.31, 29.30, 29.14, 29.12, 24.91, 24.86, 22.70, 21.76, 14.13. MS (ESI) calculated for C₅₈H₉₂N₂O₉S, m/z 992.65, found 1015.61 (M + Na)⁺.

Synthesis of Compound 5: (9Z,9'Z,12Z,12'Z)-(R)-3-(((R)-2-(((9*H*-Fluoren-9-yl)methoxy) carbonyl)amino)-3-((2-isopropoxy-2-oxoethyl)amino)-3-oxopropyl)thio)propane-1,2-diyil bis(octadeca-9,12-dienoate). To a solution of **3** (130 mg, 0.25 mmol) in anhydrous dichloromethane were added triethylamine (104 μL, 0.75 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 30 min. Linoleoyl chloride (192 μL, 0.6 mmol) was then added at 0 °C, followed by stirring of the reaction mixture at room temperature for 3h. After completion of the reaction, the reaction mixture was sequentially washed with water, saturated sodium bicarbonate

solution. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (35% EtOAc/hexanes) to obtain compound **4** (187 mg, 72 %).

¹H NMR (500 MHz, CDCl₃) δ 7.77 (d, *J* = 7.54 Hz, 2H), 7.63–7.57 (m, 2H), 7.40 (t, *J* = 7.45 Hz, 2H), 7.32 (t, *J* = 7.41 Hz, 2H), 6.90 (s, 1H), 5.78 (d, *J* = 5.84 Hz, 1H), 5.42–5.29 (m, 7H), 5.27–5.17 (m, 1H), 5.07 (dp, *J* = 6.25, 12.49 Hz, 1H), 4.50–4.34 (m, 3H), 4.31 (dd, *J* = 2.80, 11.77 Hz, 1H), 4.23 (t, *J* = 7.04 Hz, 1H), 4.17 (dd, *J* = 5.48, 11.34 Hz, 1H), 4.00 (d, *J* = 4.67 Hz, 2H), 2.98 (dd, *J* = 5.78, 19.66 Hz, 2H), 2.81–2.75 (m, 6H), 2.31 (dt, *J* = 7.74, 11.37 Hz, 4H), 2.08–2.00 (m, 7H), 1.65–1.52 (m, 5H), 1.41–1.19 (m, 35H), 0.89 (t, *J* = 6.91 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 173.43, 173.37, 170.15, 168.75, 155.99, 143.69, 141.30, 130.23, 130.02, 130.00, 128.05, 127.88, 127.76, 127.10, 125.10, 120.02, 70.33, 69.46, 67.32, 63.61, 54.37, 47.09, 41.71, 35.33, 34.29, 34.04, 33.45, 31.52, 29.62, 29.34, 29.22, 29.20, 29.15, 29.14, 29.10, 29.08, 27.20, 25.62, 24.89, 24.83, 22.58, 21.76, 14.09. MS (ESI) calculated for C₆₂H₉₂N₂O₉S, m/z 1040.65 found 1063.42 (M + Na)⁺.

Synthesis of Compound 6: (9Z,9'Z,12Z,12'Z,15Z,15'Z)-(R)-3-(((R)-2-(((9H-fluoren-9-yl) methoxy)carbonyl)amino)-3-((2-isopropoxy-2-oxoethyl)amino)-3-oxopropyl)thio)propane-1,2-diyil bis(octadeca-9,12,15-trienoate). To a solution of **3** (130 mg, 0.25 mmol) in anhydrous dichloromethane were added triethylamine (104 μL, 0.75 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 30 min. Linolenoyl chloride (189 μL, 0.6 mmol) was then added at 0 °C, followed by stirring of the reaction mixture at room temperature for 1.5h. After completion of the reaction, the reaction mixture was sequentially washed with water, saturated sodium

bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (30% EtOAc/hexanes) to obtain compound **4** (238 mg, 93 %). ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, *J* = 7.51 Hz, 2H), 7.59 (d, *J* = 3.72 Hz, 2H), 7.40 (t, *J* = 7.43 Hz, 2H), 7.31 (t, *J* = 7.42 Hz, 2H), 5.46–5.27 (m, 7H), 5.14–4.96 (m, 1H), 4.42–4.34 (m, 3H), 4.25–4.14 (m, 2H), 4.00 (d, *J* = 4.61 Hz, 1H), 3.07–2.88 (m, 1H), 2.83–2.72 (m, 5H), 2.36–2.27 (m, 4H), 2.10–2.02 (ddd, *J* = 2.65, 9.59, 15.86 Hz, 6H), 1.65–1.54 (m, 5H), 1.44–1.08 (m, 38H), 0.97 (t, *J* = 7.54 Hz, 3H), 0.90–0.86 (m, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 173.44, 173.38, 170.19, 168.77, 143.69, 141.30, 131.96, 130.24, 130.02, 128.30, 128.23, 128.05, 127.88, 127.73, 127.10, 125.10, 120.02, 70.33, 69.46, 67.32, 63.62, 47.09, 41.71, 35.32, 34.29, 34.04, 33.96, 33.43, 31.52, 29.70, 29.60, 29.34, 29.20, 29.13, 29.10, 29.08, 29.04, 28.28, 27.20, 25.61, 25.52, 24.88, 24.83, 22.58, 21.76, 20.55, 14.29, 14.09. MS (ESI) calculated for C₆₂H₈₈N₂O₉S, m/z 1036.62 found 1059.60 (M + Na)⁺.

Synthesis of Compound 7: (*R*)-3-((*R*)-2-amino-3-((2-isopropoxy-2-oxoethyl)amino)-3-oxopropyl)thio)propane-1,2-diyl dipalmitate. Compound **4** (50 mg, 0.05 mmol) was dissolved in 10 mL of dichloromethane, followed by the addition of 3 mL of piperidine. The reaction mixture was stirred for 30 min, followed by removal of the solvent under reduced pressure. The crude was dissolved in ethyl acetate washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (50% EtOAc/CH₂Cl₂) to obtain compound **2** (35 mg, 90 %). ¹H NMR (500 MHz, CDCl₃) δ 7.87 (t, *J* = 5.33 Hz, 1H), 5.16 (qd, *J* = 3.59, 6.31 Hz, 1H),

5.07 (dt, $J = 6.27, 12.53$ Hz, 1H), 4.34 (ddd, $J = 3.51, 8.22, 11.69$ Hz, 1H), 4.15 (dd, $J = 6.05, 11.90$ Hz, 1H), 4.05–3.94 (m, 2H), 3.55 (dd, $J = 3.80, 8.73$ Hz, 1H), 3.12 (dd, $J = 3.81, 13.58$ Hz, 1H), 2.81–2.70 (m, 3H), 2.32 (q, $J = 7.35$ Hz, 4H), 1.74–1.65 (m, 3H), 1.65–1.57 (m, 4H), 1.35–1.19 (m, 53H), 0.88 (t, $J = 6.94$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.79, 173.75, 173.51, 169.65, 70.69, 69.64, 63.99, 54.49, 41.67, 38.80, 34.68, 34.50, 33.11, 32.33, 30.11, 30.08, 30.07, 30.05, 29.91, 29.90, 29.77, 29.71, 29.70, 29.54, 29.51, 25.32, 25.28, 23.10, 22.17, 14.53. MS (ESI) calculated for $\text{C}_{43}\text{H}_{82}\text{N}_2\text{O}_7\text{S}$, m/z 770.58, found 771.54 ($\text{M} + \text{H}$) $^+$.

Synthesis of Compound 8: (9Z,9'Z,12Z,12'Z)-(R)-3-((R)-2-amino-3-((2-isopropoxy-2-oxoethyl)amino)-3-oxopropyl)thio)propane-1,2-diyi bis(octadeca-9,12-dienoate). Compound **8** (92%) was synthesized from compound **5** using the procedure as described earlier for compound **7**. ^1H NMR (500 MHz, CDCl_3) δ 7.87 (s, 1H), 5.45–5.25 (m, 8H), 5.16 (qd, $J = 3.70, 6.26$ Hz, 1H), 5.07 (dt, $J = 6.27, 12.54$ Hz, 1H), 4.35 (dd, $J = 3.58, 11.88$ Hz, 1H), 4.15 (dd, $J = 5.99, 11.89$ Hz, 1H), 4.10–3.88 (m, 2H), 3.56 (dd, $J = 3.45, 8.48$ Hz, 1H), 3.12 (dd, $J = 3.83, 13.60$ Hz, 1H), 2.81–2.73 (m, 6H), 2.32 (dd, $J = 7.19, 14.89$ Hz, 4H), 2.05 (q, $J = 6.87$ Hz, 8H), 1.67–1.55 (m, 4H), 1.41–1.18 (m, 37H), 0.89 (t, $J = 6.91$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.35, 173.07, 169.25, 130.24, 130.03, 128.06, 127.89, 70.29, 69.25, 63.60, 54.06, 41.28, 38.35, 34.25, 34.06, 32.71, 31.53, 29.63, 29.35, 29.21, 29.15, 29.10, 29.08, 27.20, 25.63, 24.89, 24.85, 22.58, 21.78, 14.09. MS (ESI) calculated for $\text{C}_{47}\text{H}_{82}\text{N}_2\text{O}_7\text{S}$, m/z 818.58, found 841.54 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 9: (9Z,9'Z,12Z,12'Z,15Z,15'Z)-(R)-3-((R)-2-amino-3-((2-isopropoxy-2-oxoethyl)amino)-3-oxopropyl)thio)propane-1,2-diyi bis(octadeca-9,12,15-trienoate). Compound **9** (87%) was synthesized from compound **6** using the

procedure described earlier for compound **7**. ^1H NMR (500 MHz, CDCl_3) δ 7.87 (t, J = 5.25 Hz, 1H), 5.44–5.28 (m, 10H), 5.16 (ddd, J = 3.69, 6.28, 12.49 Hz, 1H), 5.07 (dt, J = 6.26, 12.53 Hz, 1H), 4.35 (dd, J = 3.58, 11.89 Hz, 1H), 4.15 (dd, J = 5.99, 11.89 Hz, 1H), 4.06–3.94 (m, 2H), 3.55 (dd, J = 3.73, 8.70 Hz, 1H), 3.12 (dd, J = 3.80, 13.58 Hz, 1H), 2.84–2.71 (m, 9H), 2.32 (dd, J = 7.28, 14.93 Hz, 4H), 2.15–1.94 (m, 8H), 1.89–1.66 (m, 3H), 1.61 (d, J = 4.70 Hz, 4H), 1.40–1.21 (m, 25H), 0.98 (t, J = 7.53 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.35, 173.07, 169.25, 131.97, 130.25, 130.03, 128.30, 128.24, 128.06, 127.89, 127.74, 127.11, 70.30, 69.25, 63.60, 54.08, 41.28, 38.39, 34.25, 34.06, 32.72, 31.53, 29.61, 29.35, 29.20, 29.14, 29.10, 29.08, 27.22, 27.21, 25.62, 25.53, 24.89, 24.85, 21.78, 20.56, 14.30, 14.10. MS (ESI) calculated for $\text{C}_{47}\text{H}_{78}\text{N}_2\text{O}_7\text{S}$, m/z 814.55, found 837.52 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 10: (6*S*,11*R*,15*R*)-6-(*tert*-Butoxycarbonyl)-11-((2-isopropoxy-2-oxoethyl)carbamoyl)-2,2-dimethyl-4,9-dioxo-3-oxa-13-thia-5,10-diazahexadecane-15,16-diyl dipalmitate. To a solution of **7** (120 mg, 0.15 mmol) in anhydrous DMF were added *N*-Boc-L-glutamic acid 1-*tert*-butyl ester (52 mg, 0.17 mmol), HOBt (40 mg, 0.30 mmol), and triethylamine (42 μL , 0.30 mmol). The reaction mixture was stirred at 0 °C for 30 min, followed by addition of EDCI (57 mg, 0.30 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, followed by evaporation of the solvent under reduced pressure. The residue was then dissolved in ethyl acetate and washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (5% MeOH/ CH_2Cl_2) to obtain compound **10** (102 mg, 65 %). ^1H NMR (500 MHz, CDCl_3) δ 7.09 (t, J = 5.33 Hz, 1H),

6.91 (d, $J = 7.05$ Hz, 1H), 5.23 (ddd, $J = 2.83, 7.14, 9.48$ Hz, 2H), 5.06 (dt, $J = 6.27, 12.53$ Hz, 1H), 4.63 (dd, $J = 6.64, 13.67$ Hz, 1H), 4.33 (dd, $J = 3.42, 11.92$ Hz, 1H), 4.26–4.20 (m, 1H), 4.16 (dd, $J = 6.07, 11.93$ Hz, 1H), 3.99 (qd, $J = 5.42, 18.12$ Hz, 2H), 3.04–2.92 (m, 2H), 2.81 (qd, $J = 6.51, 14.20$ Hz, 2H), 2.41–2.25 (m, 6H), 2.23–2.13 (m, 1H), 1.93–1.86 (m, 1H), 1.79–1.66 (m, 3H), 1.65–1.56 (m, 4H), 1.48–1.42 (m, 17H), 1.39–1.17 (m, 52H), 0.88 (t, $J = 6.96$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.49, 173.44, 172.39, 171.45, 170.32, 168.85, 155.79, 82.31, 79.99, 70.38, 69.31, 63.69, 53.31, 52.63, 41.65, 34.58, 34.35, 34.09, 33.32, 32.30, 31.93, 29.71, 29.68, 29.67, 29.65, 29.53, 29.51, 29.37, 29.32, 29.31, 29.15, 29.13, 29.04, 28.32, 27.99, 24.94, 24.87, 22.70, 21.76, 14.13. MS (ESI) calculated for $\text{C}_{57}\text{H}_{105}\text{N}_3\text{O}_{12}\text{S}$, m/z 1055.74, found 1078.73 ($\text{M} + \text{Na}^+$).

General Procedure for One-Step Deprotection of *N*-Boc and *O*-*tert*-Butyl Group. Synthesis of Compound 11: (S)-2-amino-5-(((8*R*,12*R*)-2-methyl-4,7,15-trioxo-12-(palmitoyloxy)-3,14-dioxa-10-thia-6-azatriacontan-8-yl)amino)-5-oxopentanoic acid, trifluoroacetate. The solution of **10** (50 mg, 0.047 mmol) in anhydrous trifluoroacetic acid was stirred for 10 min, followed by removal of the solvent by purging nitrogen and drying under vacuum to obtain the trifluoroacetate salt of compound **11** (47 mg, quantitative yield). ^1H NMR (500 MHz, CDCl_3) δ 8.26–7.80 (m, 5H), 5.16 (d, $J = 2.59$ Hz, 1H), 5.00 (dt, $J = 6.00, 12.21$ Hz, 1H), 4.64 (d, $J = 3.37$ Hz, 1H), 4.34 (d, $J = 10.10$ Hz, 1H), 4.13 (dd, $J = 6.01, 11.55$ Hz, 1H), 4.04–4.01 (m, 1H), 3.87–3.82 (m, 2H), 2.99–2.95 (m, 1H), 2.91–2.82 (m, 1H), 2.82–2.66 (m, 3H), 2.65–2.36 (m, 6H), 2.30 (dd, $J = 8.08, 15.52$ Hz, 4H), 2.17–2.08 (m, 2H), 1.62–1.54 (m, 4H), 1.34–1.16 (m, 48H), 0.88 (t, $J = 6.92$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.62, 173.57, 173.53, 70.21, 69.59, 63.73, 41.53, 34.34, 34.10, 31.94, 29.75, 29.72, 29.69, 29.62, 29.59,

29.39, 29.21, 29.18, 24.95, 24.88, 22.70, 21.62, 14.13. MS (ESI) calculated for C₄₈H₈₉N₃O₁₀S, m/z 899.62, found 900.65 (M + H)⁺.

Synthesis of Compound 12: (S)-tert-butyl 3-(tert-butoxy)-2-((R)-2-((tert-butoxy carbonyl)amino)-3-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)propanamido)propanoate. To a solution of **1** (500 mg, 1.49 mmol) in anhydrous DMF were added H-Ser(tBu)-OtBu.HCl (416 mg, 1.64 mmol), HOBr (402 mg, 2.98 mmol), and triethylamine (415 µL, 2.98 mmol). The reaction mixture was stirred at 0 °C for 30 min, followed by addition of EDCI (571 mg, 2.98 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, followed by evaporation of the solvent under reduced pressure. The residue was then dissolved in ethyl acetate and washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (35% EtOAc/hexanes) to obtain compound **12** (572 mg, 72 %). ¹H NMR (400 MHz, CDCl₃) δ 7.06 (d, *J* = 7.98 Hz, 1H), 5.51 (d, *J* = 4.12 Hz, 1H), 4.55 (d, *J* = 8.07 Hz, 1H), 4.45–4.18 (m, 2H), 4.10 (dd, *J* = 6.09, 8.28 Hz, 1H), 3.79 (dd, *J* = 2.90, 8.77 Hz, 1H), 3.70 (dd, *J* = 6.57, 8.28 Hz, 1H), 3.54 (dd, *J* = 3.01, 8.80 Hz, 1H), 3.05 (dd, *J* = 5.95, 13.92 Hz, 1H), 2.94 (dd, *J* = 6.28, 13.92 Hz, 1H), 2.83 (dd, *J* = 6.23, 13.53 Hz, 1H), 2.72 (dd, *J* = 6.13, 13.53 Hz, 1H), 1.51–1.41 (m, 21H), 1.37 (d, *J* = 5.63 Hz, 3H), 1.15 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 170.17, 168.90, 109.66, 81.92, 75.60, 73.11, 68.74, 61.99, 53.50, 35.57, 35.32, 28.31, 28.01, 27.35, 26.86, 25.56. MS (ESI) calculated for C₂₅H₄₆N₂O₈S, m/z 534.29, found 557.26 (M + Na)⁺.

Synthesis of Compound 13: (R)-3-((R)-2-((tert-butoxycarbonyl)amino)-3-(((S)-1,3-di-tert-butoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)thio)propane-1,2-diyl

didodecanoate. Compound **12** (500 mg, 0.93 mmol) was dissolved in 70% acetic acid and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude was purified using column chromatography (5% MeOH/CH₂Cl₂) to obtain compound **13** (430 mg, 93 %). ¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J* = 7.90 Hz, 1H), 5.62 (s, 1H), 4.59 (d, *J* = 8.05 Hz, 1H), 4.42 (s, 1H), 3.88 (d, *J* = 10.62 Hz, 1H), 3.82 (dd, *J* = 2.67, 8.76 Hz, 1H), 3.71 (dd, *J* = 3.69, 11.22 Hz, 1H), 3.62 (dd, *J* = 6.21, 11.35 Hz, 1H), 3.57 (dd, *J* = 2.78, 8.80 Hz, 1H), 3.04 (dd, *J* = 5.34, 14.19 Hz, 1H), 2.97–2.89 (m, 1H), 2.84–2.74 (m, 2H), 1.48 (d, *J* = 5.15 Hz, 18H), 1.18 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 170.19, 82.28, 65.24, 62.00, 53.52, 35.89, 28.32, 28.04, 27.36. MS (ESI) calculated for C₂₂H₄₂N₂O₈S, m/z 494.26, found 517.25 (M + Na)⁺.

Synthesis of Compound 14: (*R*)-3-(((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1,3-di-*tert*-butoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)thio)propane-1,2-diyldidodecanoate. To a solution of **13** (100 mg, 0.2 mmol) in anhydrous dichloromethane were added triethylamine (84 µL, 0.6 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 30 min. Lauroyl chloride (113 µL, 0.48 mmol) was then added at 0 °C, followed by stirring of the reaction mixture at room temperature for 4h. After completion of the reaction, the reaction mixture was sequentially washed with water, saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (20% EtOAc/hexanes) to obtain compound **14** (160 mg, 93 %). ¹H NMR (500 MHz, CDCl₃) δ 7.12 – 7.00 (m, 1H), 5.41 (d, *J* = 5.55 Hz, 1H), 5.18 (dd, *J* = 5.97, 9.57 Hz, 1H), 4.58–4.50 (m, 1H), 4.34

(dd, $J = 3.53$, 11.89 Hz, 2H), 4.17 (dd, $J = 5.90$, 11.94 Hz, 1H), 3.79 (dt, $J = 3.10$, 8.76 Hz, 1H), 3.53 (dd, $J = 3.04$, 8.79 Hz, 1H), 2.96 (d, $J = 6.24$ Hz, 2H), 2.82 (d, $J = 5.83$ Hz, 2H), 2.32 (dq, $J = 5.90$, 7.57 Hz, 4H), 1.62 (dt, $J = 7.16$, 14.04 Hz, 4H), 1.49–1.40 (m, 17H), 1.40–1.18 (m, 33H), 1.17–1.11 (m, 9H), 0.88 (t, $J = 6.96$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.37, 173.10, 170.09, 170.07, 168.89, 81.94, 73.14, 70.31, 63.62, 63.50, 62.02, 61.95, 53.98, 53.50, 53.25, 35.62, 34.30, 34.09, 33.14, 31.92, 29.65, 29.63, 29.62, 29.50, 29.35, 29.31, 29.30, 29.14, 29.13, 28.29, 28.01, 27.34, 24.90, 24.88, 24.78, 22.69, 14.13. MS (ESI) calculated for $\text{C}_{46}\text{H}_{86}\text{N}_2\text{O}_{10}\text{S}$, m/z 858.60, found 881.59 ($\text{M} + \text{Na}^+$).

Synthesis of Compound 15: (*R*)-3-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1,3-di-*tert*-butoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)thio)propane-1,2-diylditetradecanoate. To a solution of **13** (100 mg, 0.2 mmol) in anhydrous dichloromethane were added triethylamine (84 μL , 0.6 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 30 min. Myristoyl chloride (130 μL , 0.48 mmol) was then added at 0 °C, followed by stirring of the reaction mixture at room temperature for 4h. After completion of the reaction, the reaction mixture was sequentially washed with water, saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (15% EtOAc/hexanes) to obtain compound **15** (155 mg, 85 %). ^1H NMR (500 MHz, CDCl_3) δ 7.06 (d, $J = 7.91$ Hz, 1H), 5.51–5.38 (m, 1H), 5.24–5.08 (m, 1H), 4.53 (dt, $J = 2.91$, 8.08 Hz, 1H), 4.33 (dd, $J = 3.52$, 11.89 Hz, 1H), 4.16 (dd, $J = 5.91$, 11.95 Hz, 1H), 3.78 (dd, $J = 2.99$, 8.79 Hz, 1H), 3.61–3.45 (m, 1H), 2.95–2.80 (m, 3H), 2.35–2.27 (m, 4H), 1.65–1.56 (m, 4H),

1.45 (d, $J = 3.56$ Hz, 16H), 1.36–1.18 (m, 44H), 1.17–1.09 (m, 9H), 0.87 (t, $J = 6.95$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.51, 173.24, 170.27, 169.04, 82.08, 73.28, 70.45, 70.11, 63.64, 62.15, 62.09, 54.12, 53.64, 53.39, 42.14, 40.20, 35.73, 34.43, 34.23, 34.01, 33.32, 33.25, 32.06, 29.83, 29.81, 29.79, 29.78, 29.74, 29.64, 29.64, 29.59, 29.50, 29.45, 29.44, 29.40, 29.28, 29.27, 29.23, 28.42, 28.14, 27.46, 25.68, 25.03, 25.01, 24.87, 22.83, 14.26. MS (ESI) calculated for $\text{C}_{50}\text{H}_{94}\text{N}_2\text{O}_{10}\text{S}$, m/z 914.66, found 937.67 ($\text{M} + \text{Na}^+$).

Synthesis of Compound 16: (*R*)-3-((*(R*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1,3-di-*tert*-butoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)thio)propane-1,2-diyI distearate. To a solution of **13** (100 mg, 0.2 mmol) in anhydrous dichloromethane were added triethylamine (84 μL , 0.6 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 30 min. Stearoyl chloride (162 μL , 0.48 mmol) was then added at 0 °C, followed by stirring of the reaction mixture at room temperature for 4h. After completion of the reaction, the reaction mixture was sequentially washed with water and saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (15% EtOAc/hexanes) to obtain compound **16** (168 mg, 82 %). ^1H NMR (500 MHz, CDCl_3) δ 7.11–6.99 (m, 1H), 5.47–5.36 (m, 1H), 5.17 (dt, $J = 6.01, 12.40$ Hz, 1H), 4.55 (ddt, $J = 2.89, 8.06, 11.01$ Hz, 1H), 4.34 (dd, $J = 3.51, 11.88$ Hz, 2H), 4.20–4.09 (m, 2H), 3.79 (dt, $J = 3.06, 8.76$ Hz, 1H), 3.53 (dd, $J = 3.03, 8.80$ Hz, 1H), 2.96 (d, $J = 6.24$ Hz, 1H), 2.81 (d, $J = 5.84$ Hz, 2H), 2.37–2.27 (m, 4H), 1.65–1.59 (m, 5H), 1.46–1.45 (m, 16H), 1.37–1.23 (m, 57H), 1.15 (d, $J = 3.42$ Hz, 9H), 0.88 (t, $J = 6.95$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.51, 173.24, 170.23, 170.21, 169.04, 82.08, 73.28, 70.45, 63.64, 62.10, 60.55, 54.13,

53.64, 53.39, 35.76, 34.44, 34.24, 33.28, 32.07, 29.86, 29.83, 29.81, 29.66, 29.66, 29.52, 29.47, 29.45, 29.29, 29.28, 28.44, 28.15, 27.48, 25.04, 25.02, 22.84, 21.21, 14.34, 14.28.

MS (ESI) calculated for $C_{58}H_{110}N_2O_{10}S$, m/z 1026.78, found 1049.80 ($M + Na$)⁺.

Syntheses of Compounds 17-19: Compounds **14-16** were deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O-tert*-Butyl (see synthesis of Compound **11**).

(S)-2-((R)-2-amino-3-(((R)-2,3-bis(dodecanoyloxy)propyl)thio)propanamido)-3-hydroxy propanoic acid, trifluoroacetate (17). 1H NMR (500 MHz, $CDCl_3$) δ 8.57–8.49 (m, 1H), 5.17–5.12 (m, 2H), 4.39–4.32 (m, 3H), 4.23–3.67 (m, 5H), 3.27–2.87 (m, 3H), 2.86–2.65 (m, 2H), 2.40–2.20 (m, 4H), 1.58 (d, $J = 4.69$ Hz, 4H), 1.45–0.99 (m, 31H), 0.88 (t, $J = 6.94$ Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.20, 174.05, 70.05, 64.02, 52.80, 34.51, 34.24, 32.09, 29.89, 29.86, 29.79, 29.76, 29.63, 29.54, 29.37, 29.34, 25.11, 25.01, 22.85, 14.26. MS (ESI) calculated for $C_{33}H_{62}N_2O_8S$, m/z 646.42, found 647.43 ($M + H$)⁺.

(S)-2-((R)-2-amino-3-(((R)-2,3-bis(tetradecanoyloxy)propyl)thio)propanamido)-3-hydroxypropanoic acid, trifluoroacetate (18). 1H NMR (500 MHz, $CDCl_3$) δ 8.92–8.54 (m, 2H), 5.16 (d, $J = 0.94$ Hz, 1H), 4.35–4.27 (m, 3H), 4.06 (d, $J = 2.01$ Hz, 2H), 3.90–3.79 (m, 2H), 3.24–3.15 (m, 2H), 3.03–2.57 (m, 5H), 2.30–2.26 (m, 5H), 1.57 (d, $J = 5.33$ Hz, 4H), 1.38–1.14 (m, 38H), 0.88 (t, $J = 6.93$ Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.10, 173.06, 161.63, 161.36, 33.34, 33.07, 30.93, 28.78, 28.76, 28.72, 28.70, 28.65, 28.63, 28.48, 28.40, 28.39, 28.37, 28.21, 28.17, 23.91, 23.81, 21.68, 13.09. MS (ESI) calculated for $C_{37}H_{70}N_2O_8S$, m/z 702.48, found 725.48 ($M + Na$)⁺.

(S)-2-((R)-2-amino-3-(((R)-2,3-bis(stearoyloxy)propyl)thio)propanamido)-3-hydroxypropanoic acid, trifluoroacetate (19). ^1H NMR (500 MHz, 5% MeOD in CDCl_3) δ 5.31–5.16 (m, 2H), 4.54–4.50 (s, 3H), 4.11–4.06 (dd, J = 6.86, 14.45 Hz, 2H), 3.94–3.84 (m, 2H), 3.17–3.09 (m, 1H), 2.99–2.66 (m, 4H), 2.29 (d, J = 6.01 Hz, 4H), 1.57 (s, 4H), 1.42–1.10 (s, 53H), 0.84 (d, J = 5.61 Hz, 6H). ^{13}C NMR (126 MHz, 5% MeOD in CDCl_3) δ 173.87, 173.76, 167.37, 167.35, 69.85, 63.64, 61.43, 54.97, 52.08, 34.02, 33.83, 32.90, 32.03, 31.69, 29.46, 29.41, 29.30, 29.27, 29.12, 29.09, 29.07, 28.88, 28.87, 24.67, 24.62, 22.42, 13.69, 13.67. MS (ESI) calculated for $\text{C}_{45}\text{H}_{86}\text{N}_2\text{O}_8\text{S}$, m/z 814.61, found 815.68 ($\text{M} + \text{H}$) $^+$.

General Procedure for Syntheses of Compounds 21a-c: To a solution of **20a** (600 mg, 3.13 mmol) in anhydrous dichloromethane was added triethylamine (872 μL , 6.26 mmol) and the reaction mixture was stirred at 0 °C for 30 min. Methyl bromoacetate (296 μL , 3.13 mmol) was added dropwise at 0 °C, followed by stirring of the reaction mixture at room temperature for 14h. After completion of the reaction, Di-*tert*-butyl dicarbonate (751 mg, 3.43 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2h, followed by evaporation of the solvent to obtain the crude product which was purified using column chromatography (30% EtOAc/hexanes) to obtain compound **21a** (738 mg, 65 %).

Methyl 13-(*tert*-butoxycarbonyl)-3,6,9-trioxa-13-azapentadecan-15-oate (21a). ^1H NMR (400 MHz, CDCl_3) δ 3.96 (s, 1H), 3.88 (s, 1H), 3.72 (s, 3H), 3.63 (dd, J = 3.80, 5.46 Hz, 4H), 3.57 (dt, J = 3.08, 6.20 Hz, 4H), 3.54–3.44 (m, 4H), 3.39–3.29 (m, 2H), 1.85–1.76 (m, 2H), 1.43 (d, J = 21.52 Hz, 9H), 1.20 (t, J = 7.01 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 170.92, 170.81, 155.99, 155.29, 80.29, 80.21, 70.82, 70.76, 70.67,

70.66, 70.30, 69.94, 68.70, 68.54, 66.77, 52.09, 52.03, 49.90, 49.22, 45.95, 28.86, 28.52, 28.49, 28.36, 15.28. MS (ESI) calculated for C₁₇H₃₃NO₇, m/z 363.22, found 386.23 (M + Na)⁺.

Methyl 19-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-oxo-3,9,12,15-tetraoxa-5,19-diazahenicosan-21-oate (21b). ¹H NMR (500 MHz, CDCl₃) δ 5.08–4.93 (m, 1H), 3.95 (s, 1H), 3.86 (s, 1H), 3.70 (d, *J* = 2.75 Hz, 3H), 3.61 (d, *J* = 2.83 Hz, 4H), 3.56 (dd, *J* = 2.43, 5.70 Hz, 4H), 3.51 (t, *J* = 5.96 Hz, 2H), 3.47 (dd, *J* = 6.39, 13.57 Hz, 2H), 3.33 (dt, *J* = 7.00, 19.00 Hz, 2H), 3.20 (dd, *J* = 5.94, 12.02 Hz, 2H), 1.76 (dp, *J* = 6.29, 28.66 Hz, 4H), 1.49–1.35 (m, 18H). ¹³C NMR (126 MHz, CDCl₃) δ 170.63, 170.53, 155.89, 155.70, 155.00, 80.01, 79.94, 78.71, 70.42, 70.40, 70.38, 70.05, 69.47, 68.43, 68.27, 51.82, 51.76, 49.59, 48.94, 45.65, 38.41, 29.45, 28.57, 28.30, 28.21, 28.07. MS (ESI) calculated for C₂₃H₄₄N₂O₉, m/z 492.30, found 515.31 (M + Na)⁺.

Methyl 9,14,18-tris(*tert*-butoxycarbonyl)-2,2-dimethyl-4-oxo-3-oxa-5,9,14,18-tetraazaicosan-20-oate (21c). ¹H NMR (500 MHz, CDCl₃) δ 5.38–5.26 (m, 1H), 3.95 (s, 1H), 3.87 (s, 1H), 3.72 (s, 3H), 3.29–3.09 (m, 12H), 1.73 (s, 2H), 1.65–1.60 (m, 4H), 1.47–1.41 (m, 38H). ¹³C NMR (126 MHz, CDCl₃) δ 155.80, 155.64, 155.28, 80.47, 80.42, 79.60, 79.55, 79.45, 52.16, 52.10, 49.42, 46.99, 46.97, 46.64, 46.60, 46.25, 44.86, 37.42, 28.61, 28.59, 28.53, 28.36, 26.18, 26.11. MS (ESI) calculated for C₃₃H₆₂N₄O₁₀, m/z 674.44, found 697.45 (M + Na)⁺.

General Procedure for Syntheses of Compounds 22a-c: The compound **21a** (500 mg, 1.37 mmol) was dissolved in THF, followed by the addition of aqueous solution of lithium hydroxide (65 mg, 2.75 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the solvent was evaporated under

reduced pressure to obtain the residue. The residue was dissolved in ethyl acetate and water, and the solution was acidified using 10% HCl until pH was ~4. The aqueous layer was washed with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (5% MeOH/CH₂Cl₂) to obtain compound **22a** (454 mg, 95 %).

22a 13-(*tert*-butoxycarbonyl)-3,6,9-trioxa-13-azapentadecan-15-oic acid. ¹H NMR (400 MHz, CDCl₃) δ 9.82 (s, 1H), 3.97 (d, *J* = 32.72 Hz, 2H), 3.67–3.46 (m, 12H), 3.42–3.31 (m, 2H), 1.82 (dd, *J* = 5.87, 11.83 Hz, 2H), 1.44 (d, *J* = 16.07 Hz, 9H), 1.21 (t, *J* = 7.02 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 174.11, 173.75, 156.26, 155.37, 80.60, 80.46, 70.63, 70.56, 70.47, 70.25, 69.86, 68.92, 68.50, 66.77, 49.89, 49.33, 46.00, 28.72, 28.44, 28.39, 28.30, 15.12. MS (ESI) calculated for C₁₆H₃₁NO₇, m/z 349.21, found 348.23 (M - H)⁺.

22b 19-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-oxo-3,9,12,15-tetraoxa-5,19-diazahenicosan-21-oic acid. ¹H NMR (400 MHz, CDCl₃) δ 4.04 (s, 1H), 3.95 (s, 1H), 3.60 (ddd, *J* = 5.44, 11.66, 23.18 Hz, 12H), 3.46–3.35 (m, 2H), 3.29–3.19 (s, 2H), 1.89–1.72 (m, 4H), 1.47 (d, *J* = 11.66 Hz, 18H). ¹³C NMR (126 MHz, CDCl₃) δ 172.77, 172.55, 156.44, 155.45, 80.67, 80.48, 79.47, 70.67, 70.54, 70.43, 70.33, 69.48, 69.09, 68.81, 68.53, 50.14, 49.69, 46.23, 46.15, 39.01, 38.51, 29.80, 29.55, 28.87, 28.57, 28.53, 28.37. MS (ESI) calculated for C₂₂H₄₂N₂O₉, m/z 478.28, found 501.30 (M + Na)⁺.

22c 9,14,18-tris(*tert*-butoxycarbonyl)-2,2-dimethyl-4-oxo-3-oxa-5,9,14,18-tetraazaicosan-20-oic acid. ¹H NMR (500 MHz, CDCl₃) δ 4.00–3.81 (m, 2H), 3.36–3.03

(m, 12H), 1.71 (d, $J = 37.06$ Hz, 4H), 1.44 (t, $J = 12.24$ Hz, 40H). MS (ESI) calculated for $C_{32}H_{60}N_4O_{10}$, m/z 660.43, found 683.43 ($M + Na$)⁺.

Synthesis of Compound 23: (*R*)-3-(((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*S*)-1,3-di-*tert*-butoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)thio)propane-1,2-diyil bis(13-(*tert*-butoxycarbonyl)-3,6,9-trioxa-13-azapentadecan-15-oate). To a solution of **13** (30 mg, 0.06 mmol) in anhydrous DMF were added **22a** (52 mg, 0.15 mmol), HOBr (25 mg, 0.18 mmol), and triethylamine (25 μ L, 0.18 mmol). The reaction mixture was stirred at 0 °C for 30 min, followed by addition of EDCI (35 mg, 0.18 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, followed by evaporation of the solvent under reduced pressure. The residue was then dissolved in ethyl acetate and washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (50% EtOAc/hexanes) to obtain compound **23** (47 mg, 67 %). ¹H NMR (500 MHz, CDCl₃) δ 7.18–6.93 (m, 1H), 5.19 (d, $J = 3.20$ Hz, 1H), 4.59–4.47 (m, 1H), 4.39 (ddd, $J = 3.39, 12.13, 16.06$ Hz, 1H), 4.33–4.23 (m, 1H), 4.06–3.93 (m, 2H), 3.93–3.83 (m, 2H), 3.80–3.75 (m, 1H), 3.69–3.62 (m, 8H), 3.59 (dd, $J = 3.34, 5.39$ Hz, 8H), 3.56–3.44 (m, 9H), 3.41–3.27 (m, 4H), 3.00–2.78 (m, 3H), 1.91–1.72 (m, 7H), 1.45 (d, $J = 3.43$ Hz, 27H), 1.42 (d, $J = 3.92$ Hz, 9H), 1.21 (t, $J = 7.01$ Hz, 6H), 1.14 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 170.08, 170.05, 169.48, 168.91, 155.76, 155.70, 155.12, 155.08, 81.90, 81.84, 80.21, 80.15, 80.12, 73.12, 71.20, 70.70, 70.63, 70.57, 70.53, 70.17, 70.16, 69.82, 68.70, 68.68, 68.56, 68.52, 66.63, 63.93, 63.72, 61.94, 54.00, 53.49, 49.46, 49.09, 49.00, 45.85, 45.77, 45.73, 45.70, 35.35, 32.80, 32.73, 28.75, 28.39,

28.30, 28.27, 28.21, 28.02, 27.35, 15.17. MS (ESI) calculated for C₅₄H₁₀₀N₄O₂₀S, m/z 1156.66, found 1179.64 (M + Na)⁺.

Synthesis of Compound 24: (18*R*,22*R*,25*S*)-18-(3,6,9-trioxa-13-azapentadecan-15-oyloxy)-22-amino-25-(hydroxymethyl)-15,23-dioxo-3,6,9,16-tetraoxa-20-thia-13,24-diazahexacosan-26-oic acid, trifluoroacetate. Compound **23** (30 mg, 0.02 mmol) was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O*-*tert*-Butyl (see synthesis of compound **11**) to obtain compound **24** as trifluoroacetate salt (28 mg, quantitative yield). ¹H NMR (500 MHz, MeOD) δ 5.45–5.37 (m, 1H), 4.59 (dd, *J* = 3.47, 12.11 Hz, 1H), 4.54 (dd, *J* = 3.71, 4.33 Hz, 1H), 4.43 (dd, *J* = 5.75, 12.11 Hz, 1H), 4.18 (dd, *J* = 4.90, 8.16 Hz, 1H), 4.14–4.02 (m, 4H), 3.98 (dd, *J* = 4.59, 11.17 Hz, 1H), 3.85 (dd, *J* = 3.53, 11.15 Hz, 1H), 3.67–3.60 (m, 16H), 3.57 (dt, *J* = 2.53, 4.10 Hz, 4H), 3.52 (qd, *J* = 1.75, 7.02 Hz, 4H), 3.28–3.17 (m, 5H), 3.06 (dd, *J* = 5.00, 14.71 Hz, 1H), 2.99–2.88 (m, 2H), 2.02–1.95 (m, 4H), 1.18 (td, *J* = 1.07, 7.01 Hz, 6H). ¹³C NMR (126 MHz, MeOD) δ 172.95, 168.92, 167.88, 73.78, 71.50, 71.49, 71.22, 71.19, 71.16, 70.73, 70.11, 70.06, 67.56, 66.02, 62.72, 56.25, 53.37, 48.29, 48.19, 48.11, 34.45, 32.47, 26.99, 26.97, 15.46, 15.45. MS (ESI) calculated for C₃₁H₆₀N₄O₁₄S m/z 744.38, found 745.39 (M + H)⁺.

General Procedure for Syntheses of Compounds 25–27: To a solution of **13** (150 mg, 0.30 mmol) in anhydrous DMF were added **22a** (104 mg, 0.30 mmol), HOEt (60 mg, 0.45 mmol), and triethylamine (62 μL, 0.45 mmol). The reaction mixture was stirred at 0 °C for 30 min, followed by addition of EDCI (86 mg, 0.45 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, followed by evaporation of the solvent under reduced pressure. The residue was then dissolved in ethyl acetate and

washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (50% EtOAc/hexanes) to obtain monoacyl compound **25** with diacyl derivative. For synthesis of compounds **28** and **29**, this mixture of monoacyl and diacyl derivatives was used as starting material.

(R)-3-(((R)-2-((tert-butoxycarbonyl)amino)-3-(((S)-1,3-di-tert-butoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)thio)-2-hydroxypropyl 9,14,18-tris(tert-butoxycarbonyl)-2,2-dimethyl-4-oxo-3-oxa-5,9,14,18-tetraazaicosan-20-oate (27). ^1H NMR (500 MHz, CDCl_3) δ 7.13 (s, 1H), 5.60 (s, 1H), 5.34 (ddd, $J = 6.93, 9.85, 17.96$ Hz, 1H), 4.57 (ddd, $J = 2.79, 7.25, 10.45$ Hz, 1H), 4.38 (s, 1H), 4.26–4.14 (m, 2H), 4.05–3.89 (m, 3H), 3.88–3.72 (m, 2H), 3.53 (td, $J = 3.05, 8.34$ Hz, 1H), 3.34–2.98 (m, 13H), 2.94 (dd, $J = 6.54, 14.17$ Hz, 1H), 2.74 (dd, $J = 13.79, 17.78$ Hz, 2H), 1.74–1.65 (m, 8H), 1.56–1.39 (m, 54H), 1.15 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 170.36, 170.31, 169.20, 156.27, 156.07, 155.89, 155.67, 155.29, 82.30, 82.24, 80.65, 80.60, 80.49, 80.47, 80.39, 79.69, 79.67, 79.65, 79.57, 79.48, 73.41, 69.21, 69.14, 67.54, 62.09, 53.97, 53.92, 53.88, 53.87, 53.82, 53.79, 53.64, 53.40, 47.00, 46.98, 46.93, 46.84, 46.82, 46.76, 46.69, 46.66, 46.61, 46.54, 46.27, 37.50, 37.46, 37.43, 36.28, 36.08, 36.02, 35.96, 35.90, 35.84, 28.62, 28.59, 28.54, 28.45, 28.39, 28.16, 27.49. MS (ESI) calculated for $\text{C}_{54}\text{H}_{100}\text{N}_6\text{O}_{17}\text{S}$, m/z 1136.68, found 1159.72 ($\text{M} + \text{Na}^+$).

General Procedure for syntheses of compounds 28-30 (General procedure for Palmitoylation). To a solution of **25** (150 mg, 0.18 mmol) in anhydrous dichloromethane were added triethylamine (38 μL , 0.27 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 30 min. Palmitoyl chloride (66 μL , 0.21 mmol)

was then added at 0 °C, followed by stirring of the reaction mixture at room temperature for 4 h. After completion of the reaction, the reaction mixture was sequentially washed with water, saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (35% EtOAc/hexanes) to obtain compound **28** (170 mg, 53% in two step).

(R)-3-(((R)-2-((tert-butoxycarbonyl)amino)-3-((S)-1,3-di-tert-butoxy-1-oxopropan-2-yl)amino)-3-oxopropylthio)-2-(palmitoyloxy)propyl 13-(tert-butoxycarbonyl)-3,6,9-trioxa-13-azapentadecan-15-oate (28). ^1H NMR (500 MHz, CDCl₃) δ 7.04 (dd, *J* = 7.53, 16.27 Hz, 2H), 5.45–5.37 (m, 1H), 5.18 (s, 1H), 4.53 (dt, *J* = 2.88, 7.98 Hz, 1H), 4.36 (ddd, *J* = 2.90, 10.19, 11.95 Hz, 2H), 4.28–4.20 (m, 1H), 3.97 (dd, *J* = 7.01, 13.70 Hz, 1H), 3.93–3.88 (m, 1H), 3.78 (d, *J* = 8.56 Hz, 1H), 3.66–3.46 (m, 12H), 3.39–3.30 (m, 2H), 2.94 (d, *J* = 5.11 Hz, 2H), 2.81 (d, *J* = 4.64 Hz, 2H), 2.32 (t, *J* = 7.66 Hz, 2H), 1.80 (dq, *J* = 6.29, 12.63 Hz, 2H), 1.74–1.54 (m, 5H), 1.52–1.38 (m, 25H), 1.37–1.07 (m, 35H), 0.88 (t, *J* = 6.93 Hz, 3H). ^{13}C NMR (126 MHz, CDCl₃) δ 173.09, 173.04, 170.10, 170.03, 169.89, 169.80, 168.89, 155.76, 155.22, 155.06, 81.93, 81.88, 80.18, 80.15, 73.11, 70.71, 70.65, 70.57, 70.54, 70.19, 70.17, 69.83, 68.63, 68.50, 66.64, 64.15, 64.01, 61.96, 53.49, 49.57, 49.03, 45.85, 45.77, 34.22, 32.99, 32.93, 31.93, 29.71, 29.68, 29.67, 29.52, 29.37, 29.32, 29.16, 28.75, 28.39, 28.30, 28.26, 28.02, 27.34, 24.84, 22.70, 15.17, 14.13. MS (ESI) calculated for C₅₄H₁₀₁N₃O₁₅S, m/z 1063.69, found 1086.63 (M + Na)⁺.

(R)-3-(((R)-2-((tert-butoxycarbonyl)amino)-3-((S)-1,3-di-tert-butoxy-1-oxopropan-2-yl)amino)-3-oxopropylthio)-2-(palmitoyloxy)propyl 19-(tert-

butoxycarbonyl)-2,2-dimethyl-4-oxo-3,9,12,15-tetraoxa-5,19-diazahenicosan-21-oate

(29). ^1H NMR (500 MHz, CDCl_3) δ 7.11–6.99 (m, 1H), 5.42 (dd, J = 5.55, 13.09 Hz, 1H), 5.18 (s, 1H), 5.01 (dd, J = 4.32, 8.80 Hz, 1H), 4.53 (dt, J = 2.91, 8.01 Hz, 1H), 4.42–4.29 (m, 2H), 4.27–4.19 (m, 1H), 3.99 (dd, J = 12.38, 18.29 Hz, 1H), 3.94–3.88 (m, 1H), 3.81–3.75 (m, 1H), 3.69–3.43 (m, 13H), 3.40–3.30 (m, 2H), 3.23 (d, J = 5.94 Hz, 2H), 3.00–2.88 (m, 2H), 2.81 (d, J = 4.76 Hz, 2H), 2.32 (dd, J = 7.05, 14.66 Hz, 2H), 1.90–1.66 (m, 7H), 1.65–1.36 (m, 35H), 1.36–1.17 (m, 24H), 1.15 (s, 9H), 0.88 (t, J = 6.95 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.10, 173.05, 170.12, 170.05, 169.88, 169.80, 168.91, 156.06, 155.75, 155.06, 81.94, 81.89, 80.19, 80.18, 78.90, 73.13, 73.12, 70.59, 70.57, 70.54, 70.22, 69.64, 68.65, 68.51, 64.17, 64.03, 61.97, 61.95, 54.07, 53.49, 49.53, 49.03, 45.84, 45.76, 38.59, 35.63, 35.61, 35.51, 34.22, 32.99, 32.93, 31.93, 29.71, 29.68, 29.66, 29.61, 29.52, 29.37, 29.32, 29.16, 28.74, 28.46, 28.39, 28.30, 28.25, 28.01, 27.34, 24.84, 22.70, 14.13. MS (ESI) calculated for $\text{C}_{60}\text{H}_{112}\text{N}_4\text{O}_{17}\text{S}$, m/z Exact Mass: 1192.77, found 1215.75 ($\text{M} + \text{Na}$)⁺.

(30). ^1H NMR (500 MHz, CDCl_3) δ 7.05 (t, J = 9.44 Hz, 1H), 5.47–5.29 (m, 2H), 5.22–5.15 (m, 1H), 4.53 (dt, J = 2.90, 8.00 Hz, 1H), 4.42–4.31 (m, 2H), 4.27–4.19 (m, 1H), 3.91 (d, J = 23.64 Hz, 2H), 3.78 (dd, J = 2.41, 8.65 Hz, 1H), 3.53 (d, J = 7.87 Hz, 1H), 3.32–3.01 (m, 12H), 2.95 (t, J = 5.66 Hz, 2H), 2.81 (d, J = 5.15 Hz, 2H), 2.32 (t, J = 7.67 Hz, 2H), 1.83–1.54 (m, 12H), 1.54–1.35 (m, 51H), 1.34–1.21 (m, 25H), 1.15 (s, 9H), 0.88 (t, J = 6.94 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.04, 170.11, 170.05, 168.90, 156.11, 155.49, 155.45, 155.07, 99.98, 81.94, 81.90, 80.28, 80.24, 80.22, 79.51, 79.46, 79.44, 79.34, 79.29, 79.27, 73.13, 70.18, 70.13, 61.95, 54.04, 53.49, 49.10, 46.83, 46.77, 46.53, 46.47, 46.38, 46.04, 35.62, 35.51, 34.22, 32.98, 32.93, 31.92, 29.71, 29.66, 29.52,

29.36, 29.32, 29.16, 28.48, 28.45, 28.40, 28.30, 28.23, 28.01, 27.34, 24.84, 22.69, 14.13.

MS (ESI) calculated for C₇₀H₁₃₀N₆O₁₈S, m/z 1374.91, found 1397.93 (M + Na)⁺.

General Procedure for syntheses of compounds 31-33. Compound **28** (50 mg, 0.04 mmol) was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O*-*tert*-Butyl (see synthesis of compound **11**) to obtain compound **31** as trifluoroacetate salt (46 mg, quantitative yield).

(18*R*,22*R*,25*S*)-22-amino-25-(hydroxymethyl)-15,23-dioxo-18-(palmitoyloxy)-3,6,9,16-tetraoxa-20-thia-13,24-diazahexacosan-26-oic acid, trifluoroacetate (31). ¹H NMR (500 MHz, CDCl₃) δ 8.98 (t, *J* = 52.61 Hz, 2H), 8.17 (t, *J* = 62.78 Hz, 3H), 5.64–4.90 (m, 6H), 4.57 (s, 1H), 4.42 (dd, *J* = 14.77, 37.99 Hz, 2H), 4.31 (d, *J* = 8.17 Hz, 1H), 4.11–3.84 (m, 4H), 3.75–3.55 (m, 9H), 3.52 (q, *J* = 7.01 Hz, 2H), 3.27 (s, 2H), 3.21–3.13 (m, 1H), 3.07–2.98 (m, 1H), 2.93–2.85 (m, 1H), 2.78 (dd, *J* = 5.16, 12.20 Hz, 1H), 2.35–2.23 (m, 2H), 2.01 (s, 2H), 1.63–1.51 (m, 2H), 1.36–1.22 (m, 21H), 1.19 (t, *J* = 7.01 Hz, 3H), 0.88 (t, *J* = 6.94 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 173.38, 172.66, 168.01, 166.41, 70.28, 69.94, 69.80, 69.40, 66.62, 65.10, 61.69, 55.54, 52.79, 47.54, 34.00, 31.93, 29.73, 29.68, 29.56, 29.37, 29.31, 29.13, 25.27, 24.74, 22.69, 14.89, 14.12. MS (ESI) calculated for C₃₆H₆₉N₃O₁₁S, m/z 751.46, found 752.49 (M + H)⁺.

(2*S*,5*R*,9*R*)-5,27-diamino-2-(hydroxymethyl)-4,12-dioxo-9-(palmitoyloxy)-11,18,21,24-tetraoxa-7-thia-3,14-diazahexacosan-1-oic acid, trifluoroacetate (32). ¹H NMR (500 MHz, MeOD) δ 5.16–5.04 (m, 2H), 4.46–4.30 (m, 3H), 4.06–3.94 (m, 2H), 3.94–3.74 (m, 4H), 3.64–3.45 (m, 11H), 3.15–3.06 (m, 3H), 2.96 (dt, *J* = 7.03, 10.13 Hz, 3H), 2.85–2.79 (m, 3H), 2.31–2.23 (m, 2H), 1.91 (dt, *J* = 6.44, 12.58 Hz, 2H), 1.87–1.80 (m, 2H), 1.57–1.48 (m, 2H), 1.29–1.12 (m, 22H), 0.80 (t, *J* = 6.95 Hz, 3H). ¹³C NMR

(126 MHz, MeOD) δ 174.77, 168.74, 167.96, 71.54, 71.28, 71.26, 71.13, 70.03, 69.94, 69.85, 66.57, 63.20, 57.22, 53.70, 53.62, 49.64, 49.47, 47.80, 47.50, 39.65, 35.16, 35.01, 34.78, 33.55, 33.09, 30.81, 30.67, 30.49, 30.23, 28.28, 27.11, 25.98, 23.75, 14.46. MS (ESI) calculated for C₃₇H₇₂N₄O₁₁S, m/z 780.49, found 781.51 (M + H)⁺.

(2*S*,5*R*,9*R*)-5,26-diamino-2-(hydroxymethyl)-4,12-dioxo-9-(palmitoyloxy)-11-oxa-7-thia-3,14,18,23-tetraazahexacosan-1-oic acid, trifluoroacetate (33). ¹H NMR (500 MHz, MeOD) δ 5.32–5.20 (m, 2H), 4.58 (dt, *J* = 3.73, 7.12 Hz, 2H), 4.45 (dd, *J* = 5.18, 11.90 Hz, 1H), 4.25 (dd, *J* = 4.95, 8.46 Hz, 1H), 4.17–4.07 (m, 2H), 3.97 (ddd, *J* = 4.20, 11.31, 14.85 Hz, 3H), 3.34–3.24 (m, 3H), 3.17 (ddt, *J* = 7.63, 20.38, 32.39 Hz, 9H), 3.07–2.89 (m, 3H), 2.40 (t, *J* = 7.39 Hz, 2H), 2.19 (ddt, *J* = 7.71, 15.37, 40.61 Hz, 5H), 1.90 (s, 4H), 1.65 (dd, *J* = 7.26, 14.55 Hz, 3H), 1.44–1.23 (m, 21H), 0.92 (t, *J* = 6.94 Hz, 3H). ¹³C NMR (126 MHz, MeOD) δ 174.83, 168.81, 71.34, 66.45, 63.00, 56.62, 53.72, 49.92, 49.75, 49.58, 48.52, 48.27, 48.23, 45.94, 45.84, 37.93, 35.16, 34.66, 33.14, 30.87, 30.84, 30.72, 30.54, 30.32, 26.03, 25.37, 24.25, 23.98, 23.82, 14.71. MS (ESI) calculated for C₃₇H₇₄N₆O₈S, m/z 762.52, found 763.55 (M + H)⁺.

Synthesis of Compound 34: (*R*)-3-(((*R*)-2-((tert-butoxycarbonyl)amino)-3-((*S*)-1,3-di-tert-butoxy-1-oxopropan-2-yl)amino)-3-oxopropylthio)-2-hydroxypropyl palmitate. To a solution of **13** (50 mg, 0.10 mmol) in anhydrous dichloromethane were added triethylamine (21 μL, 0.15 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at 0 °C for 30 min. Palmitoyl chloride (27 μL, 0.09 mmol) was then added at 0 °C, followed by stirring of the reaction mixture at room temperature for 2h. After completion of the reaction, the reaction mixture was sequentially washed with water, saturated sodium bicarbonate solution. The organic layer

was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (35% EtOAc/hexanes) to obtain compound **34** (55 mg, 76%). ¹H NMR (500 MHz, CDCl₃) δ 7.11 (d, *J* = 8.10 Hz, 1H), 5.59 (d, *J* = 6.67 Hz, 1H), 4.55 (dt, *J* = 2.88, 8.11 Hz, 1H), 4.38 (d, *J* = 5.22 Hz, 1H), 4.13 (qd, *J* = 5.29, 11.38 Hz, 2H), 4.00 (ddd, *J* = 3.86, 7.70, 13.58 Hz, 1H), 3.80 (dd, *J* = 2.88, 8.81 Hz, 1H), 3.54 (dd, *J* = 3.02, 8.82 Hz, 1H), 3.05 (dd, *J* = 5.30, 14.07 Hz, 1H), 2.92 (dd, *J* = 6.80, 14.07 Hz, 1H), 2.85–2.68 (m, 2H), 2.39–2.29 (m, 2H), 1.73–1.52 (m, 5H), 1.52–1.38 (m, 18H), 1.34–1.22 (m, 22H), 1.15 (s, 9H), 0.88 (t, *J* = 6.95 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 173.82, 170.15, 169.07, 82.18, 80.32, 73.29, 69.30, 66.79, 61.95, 53.71, 53.50, 36.21, 35.78, 34.15, 31.93, 29.70, 29.69, 29.66, 29.62, 29.47, 29.37, 29.28, 29.16, 28.30, 28.02, 27.35, 24.90, 22.70, 14.14. MS (ESI) calculated for C₃₈H₇₂N₂O₉S, m/z 732.49, found 755.50 (M + Na)⁺.

Synthesis of Compound 35: (S)-2-((R)-2-amino-3-((R)-2-hydroxy-3-(palmitoyloxy)propyl)thio)propanamido-3-hydroxypropanoic acid, trifluoroacetate.

Compound **34** (40 mg, 0.05 mmol) was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O*-*tert*-Butyl (see synthesis of compound **11**) to obtain compound **35** as trifluoroacetate salt (34 mg, quantitative yield). ¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H), 4.69–4.62 m, 1H), 4.57 (s, 1H), 4.15–4.11 (m, 4H), 3.36–3.19 (m, 1H), 3.09–2.80 (m, 2H), 2.68–2.65 (m, 1H), 2.37 (t, *J* = 7.46 Hz, 2H), 1.66–1.53 (m, 2H), 1.29–1.20 (m, 28H), 0.87 (t, *J* = 6.66 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 174.48, 162.34, 34.06, 31.95, 29.78, 29.77, 29.71, 29.64, 29.41, 29.24, 24.85, 22.71, 14.12. MS (ESI) calculated for C₂₅H₄₈N₂O₇S, m/z 520.31, found 521.37 (M + H)⁺.

Synthesis of Compound 36: (6*R*,10*R*,13*S*)-*tert*-butyl 10-((*tert*-butoxycarbonyl)amino)-13-(*tert*-butoxymethyl)-6-hydroxy-2,2,3,3-tetramethyl-11-oxo-4-oxa-8-thia-12-aza-3-silatetradecan-14-oate. To a solution of **13** (100 mg, 0.20 mmol) in anhydrous DMF were added Imidazole (27 mg, 0.40 mmol) and *tert*-Butyldimethylsilyl chloride (34 mg, 0.22 mmol). The reaction mixture was stirred at room temperature for 16 h, followed by evaporation of the solvent under reduced pressure. The residue was then dissolved in ethyl acetate and washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (35% EtOAc/hexanes) to obtain compound **36** (96 mg, 79%). ¹H NMR (500 MHz, CDCl₃) δ 7.19 (d, *J* = 7.70 Hz, 1H), 5.61 (t, *J* = 12.51 Hz, 1H), 4.59–4.52 (m, 1H), 4.42–4.37 (m, 1H), 3.80 (ddd, *J* = 4.46, 10.04, 11.69 Hz, 2H), 3.70–3.55 (m, 2H), 3.52 (ddd, *J* = 3.55, 6.69, 13.10 Hz, 1H), 3.03 (dd, *J* = 5.74, 13.99 Hz, 1H), 2.91 (dd, *J* = 6.50, 13.98 Hz, 1H), 2.86–2.60 (m, 2H), 1.89–1.75 (m, 1H), 1.45 (d, *J* = 4.59 Hz, 18H), 1.14 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 170.28, 169.03, 155.45, 81.97, 80.10, 73.17, 71.62, 65.81, 62.02, 53.84, 53.49, 53.26, 35.79, 35.68, 35.48, 28.31, 28.02, 27.35, 25.88, 18.29, -5.38. MS (ESI) calculated for C₂₈H₅₆N₂O₈SSi, m/z 608.35, found 631.35 (M + Na)⁺.

Synthesis of Compound 37: (6*R*,10*R*,13*S*)-*tert*-butyl 10-((*tert*-butoxycarbonyl)amino)-13-(*tert*-butoxymethyl)-2,2,3,3-tetramethyl-11-oxo-6-(palmitoyloxy)-4-oxa-8-thia-12-aza-3-silatetradecan-14-oate. Compound **36** (50 mg, 0.08 mmol) was palmitoylated using the general procedure for palmitoylation (see synthesis of compound **28**) to obtain compound **37** (64 mg, 93%). ¹H NMR (500 MHz,

CDCl_3) δ 7.08 (d, J = 7.89 Hz, 1H), 5.42 (d, J = 4.23 Hz, 1H), 4.97 (dt, J = 5.35, 10.55 Hz, 1H), 4.52 (dt, J = 2.92, 7.98 Hz, 1H), 4.32 (d, J = 5.23 Hz, 1H), 3.81–3.70 (m, 3H), 3.53 (dd, J = 3.04, 8.77 Hz, 1H), 3.02–2.83 (m, 3H), 2.80–2.73 (m, 1H), 2.35–2.27 (m, 2H), 1.65–1.57 (m, 2H), 1.45 (d, J = 3.07 Hz, 18H), 1.33–1.22 (m, 24H), 1.19–1.10 (m, 9H), 0.98–0.77 (m, 12H), 0.05 (d, J = 1.78 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.37, 170.20, 168.91, 81.87, 73.18, 73.10, 62.76, 61.99, 53.51, 35.57, 34.42, 32.96, 31.93, 29.70, 29.66, 29.64, 29.48, 29.37, 29.31, 29.17, 28.30, 28.01, 27.34, 25.81, 24.93, 22.70, 18.24, 14.13, -5.39, -5.40. MS (ESI) calculated for $\text{C}_{44}\text{H}_{86}\text{N}_2\text{O}_9\text{SSi}$, m/z 846.58, found 869.54 ($\text{M} + \text{Na}^+$).

Synthesis of Compound 38: (S)-2-((R)-2-amino-3-((R)-3-hydroxy-2-(palmitoyloxy)propyl)thio)propanamido-3-hydroxypropanoic acid, trifluoroacetate.

Compound **37** (60 mg, 0.06 mmol) was dissolved in acetic acid/THF/H₂O (6:2:2) and the reaction mixture was stirred at room temperature for 14 h. After completion of the reaction, the solvent was evaporated, followed by coevaporation with toluene under reduced pressure to obtain the crude. The crude residue was purified using column chromatography (40% EtOAc/hexanes) to obtain pure compound, which was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O*-*tert*-Butyl (see synthesis of compound **11**) to obtain compound **38** as trifluoroacetate salt (30 mg, quantitative yield). ^1H NMR (500 MHz, 10 % MeOD in CDCl_3) δ 4.83 (dd, J = 2.80, 6.39 Hz, 1H), 4.25–4.14 (m, 2H), 3.82–3.68 (m, 3H), 3.58–3.55 (m, 2H), 3.11–2.87 (m, 2H), 2.74 (ddd, J = 4.01, 9.05, 11.01 Hz, 1H), 2.69–2.52 (m, 2H), 2.19 (t, J = 7.42 Hz, 2H), 2.12–1.95 (m, 1H), 1.85 (d, J = 5.30 Hz, 1H), 1.46 (d, J = 6.71 Hz, 2H), 1.27–0.94 (m, 20H), 0.72 (t, J = 6.86 Hz, 3H). ^{13}C NMR

(126 MHz, 10 % MeOD in CDCl₃) δ 174.40, 73.28, 66.79, 62.60, 62.57, 62.12, 53.28, 49.46, 49.29, 34.50, 34.29, 32.09, 32.02, 29.86, 29.82, 29.67, 29.53, 29.47, 29.32, 25.08, 25.04, 22.84, 14.15. MS (ESI) calculated for C₂₅H₄₈N₂O₇S, m/z 520.31, found 521.33 (M + H)⁺.

Synthesis of Compound 56: (S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)-3-methylbutanoate. To a solution of compound **54** (200 mg, 0.82 mmol) in DMF were added triethylamine (153 μL, 1.1 mmol) and **55** (144 mg, 0.55 mmol). The reaction mixture was stirred at 90 °C for 10h. After completion of the reaction, the solvent was removed under reduced pressure to obtain the crude product which was purified using column chromatography (35% EtOAc/hexanes) to obtain compound **56** (134 mg, 65%). ¹H NMR (500 MHz, CDCl₃) δ 5.37 (d, *J* = 8.89 Hz, 1H), 4.31 (d, *J* = 9.14 Hz, 1H), 4.19 (dq, *J* = 6.06, 12.12 Hz, 1H), 4.08 (dd, *J* = 6.04, 8.33 Hz, 1H), 3.75 (s, 3H), 3.69 (dd, *J* = 6.26, 8.34 Hz, 1H), 2.84 (dd, *J* = 5.82, 11.82 Hz, 1H), 2.65 (dd, *J* = 7.33, 11.70 Hz, 1H), 1.44 (d, *J* = 5.26 Hz, 12H), 1.38–1.33 (m, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 171.19, 155.34, 109.58, 80.16, 74.96, 68.88, 60.32, 52.08, 47.48, 31.70, 28.29, 26.88, 26.41, 25.71, 25.52. MS (ESI) calculated for C₁₇H₃₁NO₆S, m/z 377.18, found 400.18 (M + Na)⁺.

Synthesis of Compound 57 (General Procedure for Deesterification and Subsequent Amide-coupling): (S)-methyl 3-(tert-butoxy)-2-((S)-2-((tert-butoxycarbonyl)amino)-3-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)-3-methylbutanamido)propanoate. Compound **56** (100 mg, 0.26 mmol) was dissolved in THF, followed by the addition of aqueous solution of lithium hydroxide (13 mg, 0.53 mmol). The reaction mixture was stirred at room temperature for 16 h. After completion

of the reaction, the solvent was evaporated under reduced pressure to obtain the residue. The residue was dissolved in ethyl acetate and water, and the solution was acidified using 10% HCl until pH was ~4. The aqueous layer was washed with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtain the carboxylic acid derivative. To a solution of carboxylic acid (0.26 mmol) in anhydrous DMF were added H-Ser(*t*Bu)-OMe.HCl (67 mg, 0.31 mmol), HOtB (71 mg, 0.53 mmol), and triethylamine (73 µL, 0.53 mmol). The reaction mixture was stirred at 0 °C for 30 min, followed by addition of EDCI (101 mg, 0.53 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, followed by evaporation of the solvent under reduced pressure. The residue was then dissolved in ethyl acetate and washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (25% EtOAc/hexanes) to obtain compound **57** (87 mg, 65%). ¹H NMR (500 MHz, CDCl₃) δ 7.30 (d, *J* = 7.85 Hz, 1H), 5.57 (d, *J* = 6.25 Hz, 1H), 4.66 (dt, *J* = 3.04, 7.89 Hz, 1H), 4.27–4.19 (m, 2H), 4.11–4.06 (m, 1H), 3.81 (dd, *J* = 2.98, 9.11 Hz, 1H), 3.73 (s, 3H), 3.68 (dd, *J* = 6.55, 8.29 Hz, 1H), 3.56 (dd, *J* = 3.22, 9.10 Hz, 1H), 2.87 (dd, *J* = 6.59, 12.14 Hz, 1H), 2.73 (dd, *J* = 6.39, 12.40 Hz, 1H), 1.42 (t, *J* = 7.49 Hz, 15H), 1.34 (d, *J* = 3.24 Hz, 6H), 1.12 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 170.61, 169.63, 155.79, 109.78, 79.96, 75.46, 73.65, 69.11, 61.79, 60.30, 53.39, 52.41, 48.19, 32.18, 28.41, 27.41, 26.95, 25.91, 25.67, 25.63. MS (ESI) calculated for C₂₄H₄₄N₂O₈S, m/z 520.28, found 543.26 (M + Na)⁺.

General Procedure for Acetonide Deprotection and Subsequent Palmitoylation (Synthesis of Compound 58): (*R*)-3-(((*S*)-4-(((*S*)-3-(*tert*-butoxy)-1-

methoxy-1-oxopropan-2-yl)amino)-3-((*tert*-butoxycarbonyl)amino)-2-methyl-4-oxobutan-2-yl)thio)propane-1,2-diyil dipalmitate. Compound **57** (70 mg, 0.13 mmol) was dissolved in 70% acetic acid (AcOH:H₂O) and the reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the solvent was evaporated, followed by coevaporation with toluene under reduced pressure. After complete removal of the solvent, *O*-palmitoylation was carried out as discussed in the general procedure for palmitoylation (see synthesis of compound **28**) to afford compound **58** (110 mg, 88%).

¹H NMR (500 MHz, CDCl₃) δ 7.10 (d, *J* = 8.07 Hz, 1H), 5.56 (d, *J* = 5.78 Hz, 1H), 5.14 (qd, *J* = 3.63, 6.46 Hz, 1H), 4.64 (dt, *J* = 2.97, 7.99 Hz, 1H), 4.34 (dd, *J* = 3.55, 11.89 Hz, 1H), 4.17 (dd, *J* = 6.35, 7.87 Hz, 1H), 4.13 (dd, *J* = 6.05, 11.92 Hz, 1H), 3.82 (dd, *J* = 2.89, 9.09 Hz, 1H), 3.73 (s, 3H), 3.56 (dd, *J* = 3.22, 9.11 Hz, 1H), 2.84 (d, *J* = 6.35 Hz, 2H), 2.29 (t, *J* = 7.56 Hz, 4H), 1.64–1.55 (m, 4H), 1.46–1.34 (m, 15H), 1.31–1.21 (m, 48H), 1.13 (s, 9H), 0.87 (t, *J* = 6.96 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 173.46, 173.13, 170.62, 169.49, 80.08, 73.68, 70.96, 63.78, 61.69, 60.37, 53.30, 52.46, 48.66, 34.41, 34.21, 32.06, 29.81, 29.79, 29.77, 29.64, 29.50, 29.45, 29.44, 29.28, 29.26, 28.89, 28.41, 27.40, 25.98, 25.72, 25.02, 25.00, 22.83, 14.26. MS (ESI) calculated for C₅₃H₁₀₀N₂O₁₀S, m/z 956.71, found 979.74 (M + Na)⁺.

Synthesis of Compound 59: (*R*)-3-((*S*)-3-amino-4-((*S*)-3-hydroxy-1-methoxy-1-oxopropan-2-yl)amino)-2-methyl-4-oxobutan-2-yl)thio)propane-1,2-diyil dipalmitate, trifluoroacetate. Compound **58** (50 mg, 0.05 mmol) was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O*-*tert*-Butyl (see synthesis of compound **11**) to obtain compound **59** as trifluoroacetate salt (47 mg, quantitative yield). ¹H NMR (500 MHz, CDCl₃) δ 8.60 (d, *J*

= 7.24 Hz, 1H), 5.23–5.08 (m, 1H), 4.76–4.62 (m, 1H), 4.35 (s, 1H), 4.30 (dd, J = 2.86, 12.00 Hz, 1H), 4.09 (dd, J = 6.36, 12.02 Hz, 1H), 3.99 (dd, J = 4.72, 11.74 Hz, 1H), 3.90 (d, J = 9.00 Hz, 1H), 3.76 (s, 3H), 2.87–2.75 (m, 2H), 2.31 (dt, J = 7.42, 14.97 Hz, 4H), 1.77–1.54 (m, 6H), 1.37–1.13 (m, 54H), 0.88 (t, J = 6.94 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.24, 173.78, 170.14, 70.68, 63.94, 61.65, 58.72, 55.58, 52.85, 47.76, 34.43, 34.15, 32.08, 29.87, 29.85, 29.82, 29.69, 29.68, 29.53, 29.47, 29.45, 29.28, 28.80, 26.58, 24.99, 24.98, 23.07, 22.85, 14.28. MS (ESI) calculated for $\text{C}_{44}\text{H}_{84}\text{N}_2\text{O}_8\text{S}$, m/z 800.59, found 801.63 ($\text{M} + \text{H}$) $^+$.

Synthesis of Compound 61: (*R*)-methyl 2-((*tert*-butoxycarbonyl)amino)-3-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)-3-methylbutanoate. Compound **60** (144 mg, 0.55 mmol) was *S*-alkylated with **54** (200 mg, 0.82 mmol) as discussed for the synthesis of compound **56** to obtain compound **61** (132 mg, 64%). ^1H NMR (500 MHz, CDCl_3) δ 5.37 (d, J = 8.79 Hz, 1H), 4.29 (d, J = 9.10 Hz, 1H), 4.21–4.15 (m, 1H), 4.06 (dd, J = 6.05, 8.33 Hz, 1H), 3.73 (s, 3H), 3.67 (dd, J = 6.21, 8.34 Hz, 1H), 2.78 (dd, J = 5.70, 11.91 Hz, 1H), 2.65 (dd, J = 7.34, 11.87 Hz, 1H), 1.42 (d, J = 7.20 Hz, 12H), 1.37 (s, 3H), 1.33 (d, J = 5.41 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 171.32, 155.45, 109.70, 80.27, 75.06, 68.95, 60.57, 52.18, 47.48, 31.76, 28.40, 27.01, 26.55, 25.95, 25.60. MS (ESI) calculated for $\text{C}_{17}\text{H}_{31}\text{NO}_6\text{S}$, m/z 377.18, found 400.18 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 62: (*S*)-*tert*-butyl 3-(*tert*-butoxy)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)-3-methylbutanamido) propanoate. Compound **61** (100 mg, 0.26 mmol) was deesterified and coupled with serine derivative using the general procedure (see synthesis of compound **57**) to obtain compound **62** (107 mg, 72%). ^1H NMR (500 MHz, CDCl_3) δ

7.09 (d, $J = 7.87$ Hz, 1H), 5.62 (d, $J = 5.13$ Hz, 1H), 4.56 (dt, $J = 2.94, 7.92$ Hz, 1H), 4.25 (p, $J = 6.34$ Hz, 1H), 4.15 (dd, $J = 6.89, 13.67$ Hz, 1H), 4.10 (dt, $J = 5.36, 8.30$ Hz, 1H), 3.77 (dd, $J = 2.93, 8.74$ Hz, 1H), 3.68 (dd, $J = 6.48, 8.31$ Hz, 1H), 3.54 (dd, $J = 3.04, 8.75$ Hz, 1H), 2.88–2.73 (m, 2H), 1.46 (s, 9H), 1.44 (d, $J = 3.74$ Hz, 15H), 1.38 (s, 3H), 1.35 (s, 3H), 1.15 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 169.23, 169.06, 155.82, 109.70, 82.03, 80.03, 75.22, 73.24, 69.12, 62.11, 60.85, 53.67, 48.04, 31.86, 28.40, 28.17, 27.46, 27.01, 26.30, 25.77, 25.67. MS (ESI) calculated for $\text{C}_{27}\text{H}_{50}\text{N}_2\text{O}_8\text{S}$, m/z 562.32, found 585.33 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 63: (*R*)-3-((*R*)-3-((*tert*-butoxycarbonyl)amino)-4-((*S*)-1,3-di-*tert*-butoxy-1-oxopropan-2-yl)amino)-2-methyl-4-oxobutan-2-yl)thio)propane-1,2-diyil dipalmitate. Acetonide deprotection followed by palmitoylation of compound **62** (90 mg, 0.16 mmol) was carried out as per the general procedure reported earlier (see synthesis of compound **58**) to obtain compound **63** (143 mg, 90%). ^1H NMR (500 MHz, CDCl_3) δ 7.01 (d, $J = 7.91$ Hz, 1H), 5.56 (d, $J = 5.96$ Hz, 1H), 5.16 (dd, $J = 2.98, 5.08$ Hz, 1H), 4.54 (dt, $J = 2.90, 7.80$ Hz, 1H), 4.35 (dd, $J = 3.32, 11.95$ Hz, 1H), 4.16 (dd, $J = 5.89, 11.97$ Hz, 2H), 3.77 (dd, $J = 2.91, 8.77$ Hz, 1H), 3.53 (dd, $J = 3.04, 8.77$ Hz, 1H), 2.84 (d, $J = 6.29$ Hz, 2H), 2.37–2.23 (m, 4H), 1.61 (dd, $J = 6.61, 13.32$ Hz, 4H), 1.46–1.42 (m, 24H), 1.32–1.22 (m, 48H), 1.14 (s, 9H), 0.88 (t, $J = 6.95$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.45, 173.08, 169.23, 169.06, 155.77, 82.05, 80.05, 73.26, 70.83, 63.72, 62.08, 60.84, 53.68, 48.52, 34.40, 34.22, 33.79, 32.06, 29.84, 29.81, 29.80, 29.78, 29.64, 29.50, 29.45, 29.44, 29.28, 29.26, 28.79, 28.40, 28.18, 27.45, 26.34, 25.64, 25.01, 22.83, 14.26. MS (ESI) calculated for $\text{C}_{56}\text{H}_{106}\text{N}_2\text{O}_{10}\text{S}$, m/z 998.75, found 1021.77 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 64: (S)-2-((R)-2-amino-3-(((R)-2,3-bis(palmitoyloxy)propyl)thio)-3-methylbutanamido)-3-hydroxypropanoic acid, trifluoroacetate. Compound **63** (50 mg, 0.05 mmol) was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O*-*tert*-Butyl (see synthesis of compound **11**) to obtain compound **64** as trifluoroacetate salt (45 mg, quantitative yield). ^1H NMR (500 MHz, CDCl_3) δ 5.17 (d, J = 1.46 Hz, 1H), 4.53–4.23 (m, 2H), 4.23–3.96 (m, 2H), 3.95–3.60 (m, 2H), 2.79 (ddd, J = 24.93, 27.75, 53.40 Hz, 2H), 2.27 (dd, J = 13.42, 18.12 Hz, 4H), 1.58 (s, 6H), 1.46–1.08 (m, 54H), 0.88 (t, J = 6.93 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.01, 173.40, 70.98, 64.30, 45.99, 34.41, 34.23, 32.10, 29.92, 29.86, 29.79, 29.77, 29.55, 29.37, 29.35, 25.09, 24.99, 22.85, 14.27. MS (ESI) calculated for $\text{C}_{43}\text{H}_{82}\text{N}_2\text{O}_8\text{S}$, m/z 786.57, found 787.60 ($\text{M} + \text{H}$) $^+$.

Synthesis of Compound 66: (S)-methyl 2-((*tert*-butoxycarbonyl)amino)-4-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)butanoate. To a solution of **65** (170 mg, 0.68 mmol) in DMF at 0 °C was added **54** (193 mg, 0.82 mmol) and K_2CO_3 (113 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 16 h, followed by removal of solvent to obtain the residue. The residue was then dissolved in ethyl acetate and washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (30% EtOAc/hexanes) to obtain compound **65** (160 mg, 65%). ^1H NMR (500 MHz, CDCl_3) δ 5.16 (d, J = 7.83 Hz, 1H), 4.36 (dd, J = 7.28, 12.17 Hz, 1H), 4.24–4.17 (m, 1H), 4.06 (dd, J = 6.06, 8.32 Hz, 1H), 3.71 (s, 3H), 3.66 (dd, J = 6.40, 8.32 Hz, 1H), 2.71 (dd, J = 5.79, 13.50 Hz, 1H), 2.65–2.53 (m, 3H), 2.15–2.03 (m, 1H), 1.88 (dtd, J = 6.01, 8.42, 14.08 Hz, 1H), 1.39 (d, J = 7.01 Hz, 12H),

1.32 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 172.79, 155.40, 109.66, 80.10, 75.79, 68.91, 52.72, 52.49, 35.19, 32.81, 28.57, 28.35, 26.96, 25.60. MS (ESI) calculated for $\text{C}_{16}\text{H}_{29}\text{NO}_6\text{S}$, m/z 363.17, found 386.17 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 67: (*S*)-*tert*-butyl 3-(*tert*-butoxy)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-4-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)butanamido)propanoate. Compound **66** (100 mg, 0.27 mmol) was deesterified and coupled with serine derivative using the general procedure (see synthesis of compound **57**) to obtain compound **67** (114 mg, 77%). ^1H NMR (500 MHz, CDCl_3) δ 6.70 (d, $J = 8.03$ Hz, 1H), 5.25 (d, $J = 7.82$ Hz, 1H), 4.56 (dt, $J = 2.63, 8.14$ Hz, 1H), 4.29 (qt, $J = 6.85, 13.52$ Hz, 2H), 4.11 (dd, $J = 6.05, 8.31$ Hz, 1H), 3.80 (dd, $J = 2.80, 8.73$ Hz, 1H), 3.71 (dd, $J = 6.45, 8.31$ Hz, 1H), 3.52 (dd, $J = 2.95, 8.73$ Hz, 1H), 2.79 (dd, $J = 5.74, 13.45$ Hz, 1H), 2.76–2.68 (m, 2H), 2.64 (dd, $J = 7.00, 13.47$ Hz, 1H), 2.10 (td, $J = 6.47, 14.04$ Hz, 1H), 1.99–1.92 (m, 1H), 1.52–1.39 (m, 21H), 1.36 (s, 3H), 1.15 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 171.06, 169.10, 155.41, 109.69, 82.08, 80.09, 75.70, 73.34, 69.08, 62.07, 53.37, 53.32, 35.07, 33.17, 28.64, 28.46, 28.16, 27.48, 27.05, 25.74. MS (ESI) calculated for $\text{C}_{26}\text{H}_{48}\text{N}_2\text{O}_8\text{S}$, m/z 548.31, found 571.31 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 68: (*R*)-3-((*S*)-3-((*tert*-butoxycarbonyl)amino)-4-((*S*)-1,3-di-*tert*-butoxy-1-oxopropan-2-yl)amino)-4-oxobutyl)thio)propane-1,2-diyil dipalmitate. Acetonide deprotection followed by palmitoylation of compound **67** (100 mg, 0.18 mmol) was carried out as per the general procedure reported earlier (see synthesis of compound **58**) to obtain compound **68** (156 mg, 88%). ^1H NMR (500 MHz, CDCl_3) δ 6.77 (d, $J = 8.30$ Hz, 1H), 5.27 (d, $J = 8.01$ Hz, 1H), 5.16 (qd, $J = 3.30, 6.44$ Hz, 1H), 4.56 (dt, $J = 2.74, 8.23$ Hz, 1H), 4.36 (dd, $J = 3.23, 11.93$ Hz, 2H), 4.18 (dd, $J =$

6.02, 11.94 Hz, 1H), 3.80 (dd, $J = 2.84, 8.74$ Hz, 1H), 3.52 (dd, $J = 2.97, 8.74$ Hz, 1H), 2.73 (dd, $J = 7.01, 14.94$ Hz, 4H), 2.34–2.28 (m, 4H), 2.08 (dq, $J = 6.77, 13.44$ Hz, 1H), 1.95 (td, $J = 7.39, 14.63$ Hz, 1H), 1.66–1.57 (m, 4H), 1.45 (d, $J = 7.59$ Hz, 18H), 1.32–1.22 (m, 48H), 1.15 (s, 9H), 0.88 (t, $J = 6.96$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.53, 173.20, 171.06, 169.12, 155.44, 82.03, 80.02, 73.31, 70.34, 63.74, 62.09, 53.34, 53.21, 34.45, 34.25, 32.84, 32.06, 31.95, 29.84, 29.81, 29.80, 29.78, 29.65, 29.64, 29.50, 29.45, 29.44, 29.28, 29.27, 28.48, 28.44, 28.15, 27.47, 25.05, 25.03, 22.83, 14.26. MS (ESI) calculated for $\text{C}_{55}\text{H}_{104}\text{N}_2\text{O}_{10}\text{S}$, m/z 984.74, found 1007.75 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 69: (S)-2-((S)-2-amino-4-((R)-2,3-bis(palmitoyloxy)propyl) thio)butanamido)-3-hydroxypropanoic acid, trifluoroacetate. Compound **68** (50 mg, 0.05 mmol) was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O*-*tert*-Butyl (see synthesis of compound **11**) to obtain compound **69** as trifluoroacetate salt (45 mg, quantitative yield). ^1H NMR (500 MHz, CDCl_3) δ 8.42 (d, $J = 0.82$ Hz, 1H), 8.32–8.03 (m, 2H), 5.09 (s, 1H), 4.52 (s, 1H), 4.35 (d, $J = 10.23$ Hz, 1H), 4.25 (s, 1H), 4.13 (d, $J = 5.69$ Hz, 1H), 3.90 (d, $J = 1.13$ Hz, 2H), 2.67 (s, 4H), 2.38–2.24 (m, 4H), 2.14 (dd, $J = 19.76, 25.04$ Hz, 2H), 1.57 (d, $J = 6.26$ Hz, 4H), 1.35–1.16 (m, 50H), 0.88 (t, $J = 6.95$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.60, 174.31, 70.25, 63.89, 55.55, 53.07, 34.59, 34.27, 32.10, 29.93, 29.87, 29.86, 29.81, 29.78, 29.56, 29.56, 29.53, 29.50, 29.36, 29.32, 25.07, 25.01, 22.85, 14.27. MS (ESI) calculated for $\text{C}_{42}\text{H}_{80}\text{N}_2\text{O}_8\text{S}$, m/z 772.56, found 773.59 ($\text{M} + \text{H}$) $^+$.

Synthesis of Compound 71: (R)-methyl 3-(((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)propanoate. Compound **70** (150 mg, 1.24 mmol) was S-alkylated with

54 (352 mg, 1.49 mmol) as discussed for the synthesis of compound **66** to obtain the compound **71** (244 mg, 84%). ^1H NMR (500 MHz, CDCl_3) δ 4.25 (dt, $J = 6.11, 12.56$ Hz, 1H), 4.10 (dd, $J = 6.06, 8.33$ Hz, 1H), 3.77–3.63 (m, 4H), 2.90–2.80 (m, 2H), 2.77 (dd, $J = 5.68, 13.46$ Hz, 1H), 2.68–2.57 (m, 3H), 1.42 (s, 3H), 1.37–1.32 (m, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 172.39, 109.76, 75.61, 68.97, 51.98, 35.43, 34.77, 27.75, 27.05, 25.67. MS (ESI) calculated for $\text{C}_{10}\text{H}_{18}\text{O}_4\text{S}$, m/z 234.09, found 257.08 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 72: (S)-methyl 3-(*tert*-butoxy)-2-(3-(((R)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)propanamido)propanoate. Compound **71** (200 mg, 0.85 mmol) was deesterified and coupled with serine derivative using the general procedure (see synthesis of compound **57**) to obtain compound **72** (228 mg, 71%). ^1H NMR (500 MHz, CDCl_3) δ 6.53 (d, $J = 8.26$ Hz, 1H), 4.74 (dt, $J = 2.91, 8.40$ Hz, 1H), 4.27 (p, $J = 6.20$ Hz, 1H), 4.12 (dd, $J = 6.07, 8.34$ Hz, 1H), 3.82 (dd, $J = 2.83, 9.09$ Hz, 1H), 3.75 (s, 3H), 3.71 (dd, $J = 1.85, 6.45$ Hz, 1H), 3.57 (dd, $J = 3.07, 9.10$ Hz, 1H), 2.91 (ddd, $J = 3.19, 7.78, 14.27$ Hz, 2H), 2.78 (dd, $J = 5.90, 13.51$ Hz, 1H), 2.66 (dd, $J = 6.83, 13.51$ Hz, 1H), 2.57 (t, $J = 7.33$ Hz, 2H), 1.44 (s, 3H), 1.36 (s, 3H), 1.14 (s, 9H). ^{13}C NMR (126 MHz, CDCl_3) δ 170.99, 170.87, 109.65, 75.51, 73.53, 68.89, 62.00, 52.87, 52.47, 36.64, 35.45, 28.19, 27.34, 26.96, 25.58. MS (ESI) calculated for $\text{C}_{17}\text{H}_{31}\text{NO}_6\text{S}$, m/z 377.18, found 400.18 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 73: (R)-3-((3-((S)-3-(*tert*-butoxy)-1-methoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)thio)propane-1,2-diyl dipalmitate. Acetonide deprotection followed by palmitoylation of compound **72** (120 mg, 0.31 mmol) was carried out as per the general procedure reported earlier (see synthesis of compound **58**) to obtain compound **73** (214 mg, 83%). ^1H NMR (500 MHz, CDCl_3) δ 5.14 (qd, $J = 3.40,$

6.43 Hz, 1H), 4.72 (dt, J = 2.95, 8.33 Hz, 1H), 4.36 (dd, J = 3.36, 11.92 Hz, 1H), 4.16 (dd, J = 6.05, 11.93 Hz, 1H), 3.80 (dd, J = 2.86, 9.09 Hz, 1H), 3.73 (s, 3H), 3.55 (dd, J = 3.12, 9.09 Hz, 1H), 2.88 (t, J = 7.22 Hz, 2H), 2.73 (d, J = 6.61 Hz, 2H), 2.55 (t, J = 7.28 Hz, 2H), 2.30 (td, J = 4.64, 7.55 Hz, 4H), 1.65–1.56 (m, 4H), 1.35–1.20 (m, 49H), 1.13 (s, 9H), 0.87 (t, J = 6.94 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.39, 173.13, 170.91, 170.63, 73.46, 70.38, 63.55, 61.93, 52.88, 52.38, 36.50, 34.32, 34.12, 32.50, 31.93, 29.71, 29.68, 29.67, 29.66, 29.65, 29.51, 29.51, 29.37, 29.31, 29.30, 29.14, 29.12, 28.10, 27.29, 24.92, 24.89, 22.70, 14.13. MS (ESI) calculated for $\text{C}_{46}\text{H}_{87}\text{NO}_8\text{S}$, m/z 813.61, found 836.62 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 74: (*R*)-3-((*(3-((S)-3-hydroxy-1-methoxy-1-oxopropan-2-yl)amino)-3-oxopropyl)thio)propane-1,2-diyI dipalmitate, trifluoroacetate.* Compound **73** (50 mg, 0.06 mmol) was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O-tert-Butyl* (see synthesis of compound **11**) to obtain compound **74** (46 mg, quantitative yield). ^1H NMR (500 MHz, CDCl_3) δ 6.67 (d, J = 7.19 Hz, 1H), 5.14 (qd, J = 3.25, 6.53 Hz, 1H), 4.68 (dt, J = 3.42, 7.13 Hz, 1H), 4.39 (dd, J = 3.22, 11.94 Hz, 1H), 4.15 (dd, J = 6.41, 11.96 Hz, 1H), 3.97 (qd, J = 3.45, 11.37 Hz, 2H), 3.79 (s, 3H), 2.98–2.91 (m, 1H), 2.86 (dt, J = 6.70, 13.40 Hz, 1H), 2.72 (d, J = 6.54 Hz, 2H), 2.63–2.52 (m, 2H), 2.31 (dd, J = 7.28, 14.91 Hz, 4H), 1.65–1.56 (m, 4H), 1.43–1.10 (m, 49H), 0.87 (t, J = 6.95 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.78, 173.75, 171.27, 170.97, 70.74, 63.75, 63.35, 54.93, 52.92, 36.73, 34.49, 34.26, 32.71, 32.07, 29.84, 29.81, 29.80, 29.79, 29.65, 29.64, 29.51, 29.43, 29.27, 29.25, 28.46, 25.04, 25.00, 22.83, 14.27. MS (ESI) calculated for $\text{C}_{42}\text{H}_{79}\text{NO}_8\text{S}$, m/z 757.55, found 780.55 ($\text{M} + \text{Na}$) $^+$.

Synthesis of Compound 76: (2*S*,2'*S*)-dimethyl 2,2'-(((2*R*,2'*R*)-3,3'-diselanediylbis(2-((*tert*-butoxycarbonyl)amino)propanoyl))bis(azanediyl))bis(3-(*tert*-butoxy)propanoate). To a solution of L-selenocystine (**75**, 500 mg, 1.49 mmol) in water were added triethylamine (624 μ L, 4.48 mmol) and Di-*tert*-butyl-dicarbonate (1.0 g, 4.48 mmol). The reaction mixture was stirred at room temperature for 2h. After completion of the reaction, the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 10% HCl. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (15% MeOH/CH₂Cl₂) to obtain compound *N*_α,*N*_α'-di-Boc-L-selenocystine (870 mg, 95%). To a solution of di-Boc-L-selenocystine (400 mg, 0.74 mmol) in anhydrous DMF were added H-Ser(*t*Bu)-OMe.HCl (348 mg, 1.64 mmol), HOEt (300 mg, 2.22 mmol), and triethylamine (309 μ L, 2.22 mmol). The reaction mixture was stirred at 0 °C for 30 min, followed by addition of EDCI (425 mg, 2.22 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h, followed by evaporation of the solvent under reduced pressure. The residue was then dissolved in ethyl acetate and washed with water. The organic solvent was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was purified using column chromatography (40% EtOAc/hexanes) to obtain compound **76** (450 mg, 73%). ¹H NMR (500 MHz, CDCl₃) δ 7.39 (d, *J* = 5.79 Hz, 2H), 5.69 (d, *J* = 6.98 Hz, 2H), 4.67 (dt, *J* = 4.45, 13.24 Hz, 4H), 3.78 (dd, *J* = 3.57, 9.12 Hz, 2H), 3.71 (s, 6H), 3.57 (dd, *J* = 3.74, 9.19 Hz, 2H), 3.37 (dd, *J* = 7.36, 12.93 Hz, 2H), 3.29 (dd, *J* = 4.51, 12.38 Hz, 2H), 1.44 (s, 18H), 1.11 (d, *J* = 3.40 Hz, 18H). ¹³C NMR (126 MHz, CDCl₃) δ 170.65, 170.55, 155.47, 80.27, 73.63,

61.82, 54.70, 53.25, 52.46, 34.34, 28.49, 27.40. MS (ESI) calculated for C₃₂H₅₈N₄O₁₂Se₂, m/z 850.23, found 873.24 (M + Na)⁺.

Synthesis of Compound 77: (S)-methyl 3-(*tert*-butoxy)-2-((*R*)-2-((*tert*-butoxycarbonyl)amino)-3-(((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)selanyl)propanamido)propanoate To a solution of compound **76** (270 mg, 0.31 mmol) in ethanol at 0 °C was added sodium borohydride (25 mg, 0.68 mmol). The reaction mixture was stirred at 0 °C for 15 min, followed by addition of compound **54** (373 mg, 1.58 mmol). The reaction mixture was stirred at room temperature for 18h. After completion of the reaction, the reaction was quenched with 1N HCl, followed by washing of the reaction mixture with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered and, evaporated under reduced pressure to obtain the crude product which was column purified (50%EtOAc/hexanes) to obtain pure compound **77** (274 mg, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.06 (d, *J* = 7.90 Hz, 1H), 5.59 (d, *J* = 5.00 Hz, 1H), 4.65 (dt, *J* = 3.01, 8.12 Hz, 1H), 4.40 (d, *J* = 4.72 Hz, 1H), 4.32 (p, *J* = 6.33 Hz, 1H), 4.10 (dd, *J* = 6.05, 8.26 Hz, 1H), 3.81 (dd, *J* = 2.96, 9.09 Hz, 1H), 3.73 (s, 3H), 3.65 (dd, *J* = 6.69, 8.24 Hz, 1H), 3.55 (dd, *J* = 3.21, 9.10 Hz, 1H), 3.12 (dd, *J* = 5.69, 12.94 Hz, 1H), 2.90 (dd, *J* = 6.12, 12.95 Hz, 1H), 2.82 (dd, *J* = 6.52, 12.70 Hz, 1H), 2.73 (dd, *J* = 6.08, 12.72 Hz, 1H), 1.46–1.43 (m, 12H), 1.35 (s, 3H), 1.13 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 170.67, 170.60, 155.42, 109.80, 80.39, 76.34, 73.63, 69.51, 61.84, 54.54, 53.24, 52.53, 28.44, 27.62, 27.42, 27.02, 26.95, 25.72. MS (ESI) calculated for C₂₂H₄₀N₂O₈Se, m/z 540.19, found 563.19 (M + Na)⁺.

Synthesis of Compound 78: (*R*)-3-((*R*)-3-((*S*)-3-(*tert*-butoxy)-1-methoxy-1-oxopropan-2-yl)amino)-2-((*tert*-butoxycarbonyl)amino)-3-

oxopropylselanyl)propane-1,2-diyI dipalmitate. Acetonide deprotection followed by palmitoylation of compound **77** (180 mg, 0.33 mmol) was carried out as per the general procedure reported earlier (see synthesis of compound **58**) to obtain compound **78** (260 mg, 80%). ¹H NMR (500 MHz, CDCl₃) δ 7.02 (d, *J* = 8.12 Hz, 1H), 5.41 (d, *J* = 6.27 Hz, 1H), 5.20 (s, 1H), 4.65 (dt, *J* = 3.04, 8.14 Hz, 1H), 4.43 (d, *J* = 5.08 Hz, 1H), 4.33 (dd, *J* = 3.52, 11.86 Hz, 1H), 4.18 (dd, *J* = 5.97, 11.87 Hz, 1H), 3.82 (dd, *J* = 2.97, 9.10 Hz, 1H), 3.73 (s, 3H), 3.56 (dd, *J* = 3.24, 9.11 Hz, 1H), 2.98 (ddd, *J* = 6.16, 12.94, 33.73 Hz, 2H), 2.82 (d, *J* = 6.34 Hz, 2H), 2.31 (ddd, *J* = 2.44, 7.34, 9.56 Hz, 4H), 1.65–1.56 (m, 4H), 1.46 (d, *J* = 11.54 Hz, 9H), 1.34–1.20 (m, 48H), 1.14 (s, 9H), 0.87 (t, *J* = 6.96 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 173.51, 173.24, 170.58, 170.52, 155.28, 80.34, 73.65, 71.04, 64.07, 61.80, 54.40, 53.26, 52.54, 34.46, 34.23, 32.06, 29.84, 29.81, 29.80, 29.78, 29.65, 29.64, 29.51, 29.46, 29.44, 29.28, 29.28, 28.43, 27.56, 27.42, 25.05, 25.01, 24.96, 22.83, 14.27. MS (ESI) calculated for C₅₁H₉₆N₂O₁₀Se, m/z 976.62, found 999.63 (M + Na)⁺.

Synthesis of Compound 79: (R)-3-((R)-2-amino-3-((S)-3-hydroxy-1-methoxy-1-oxopropan-2-yl)amino)-3-oxopropylselanyl)propane-1,2-diyI dipalmitate, trifluoroacetate. Compound **78** (50 mg, 0.05 mmol) was deprotected with trifluoroacetic acid as described earlier in the general procedure for one step deprotection of *N*-Boc and *O*-*tert*-Butyl (see synthesis of compound **11**) to obtain compound **79** as trifluoroacetate salt (48 mg, quantitative yield). ¹H NMR (500 MHz, CDCl₃) δ 8.23 (d, *J* = 7.59 Hz, 1H), 5.18 (dt, *J* = 6.51, 9.53 Hz, 1H), 4.70–4.65 (m, 1H), 4.39–4.31 (m, 2H), 4.12 (dd, *J* = 6.44, 11.90 Hz, 1H), 3.97 (d, *J* = 9.20 Hz, 1H), 3.87 (dd, *J* = 4.91, 11.65 Hz, 1H), 3.77 (s, 3H), 3.15 (dd, *J* = 6.21, 13.52 Hz, 1H), 3.08 (dd, *J* = 6.21, 13.46 Hz, 1H),

2.86–2.76 (m, 2H), 2.31 (dt, $J = 7.56, 12.73$ Hz, 4H), 1.65–1.54 (m, 4H), 1.33–1.20 (m, 48H), 0.88 (t, $J = 6.93$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 174.24, 173.89, 170.24, 71.06, 64.15, 61.98, 55.48, 53.39, 52.97, 34.52, 34.22, 32.08, 29.88, 29.83, 29.72, 29.70, 29.53, 29.48, 29.32, 29.29, 25.13, 25.04, 25.00, 22.85, 14.28. MS (ESI) calculated for $\text{C}_{42}\text{H}_{80}\text{N}_2\text{O}_8\text{Se}$, m/z 820.50, found 821.53 ($\text{M} + \text{H}$) $^+$.

Supporting Information: Part II.

^1H , ^{13}C NMR, and Mass Spectral Characterization

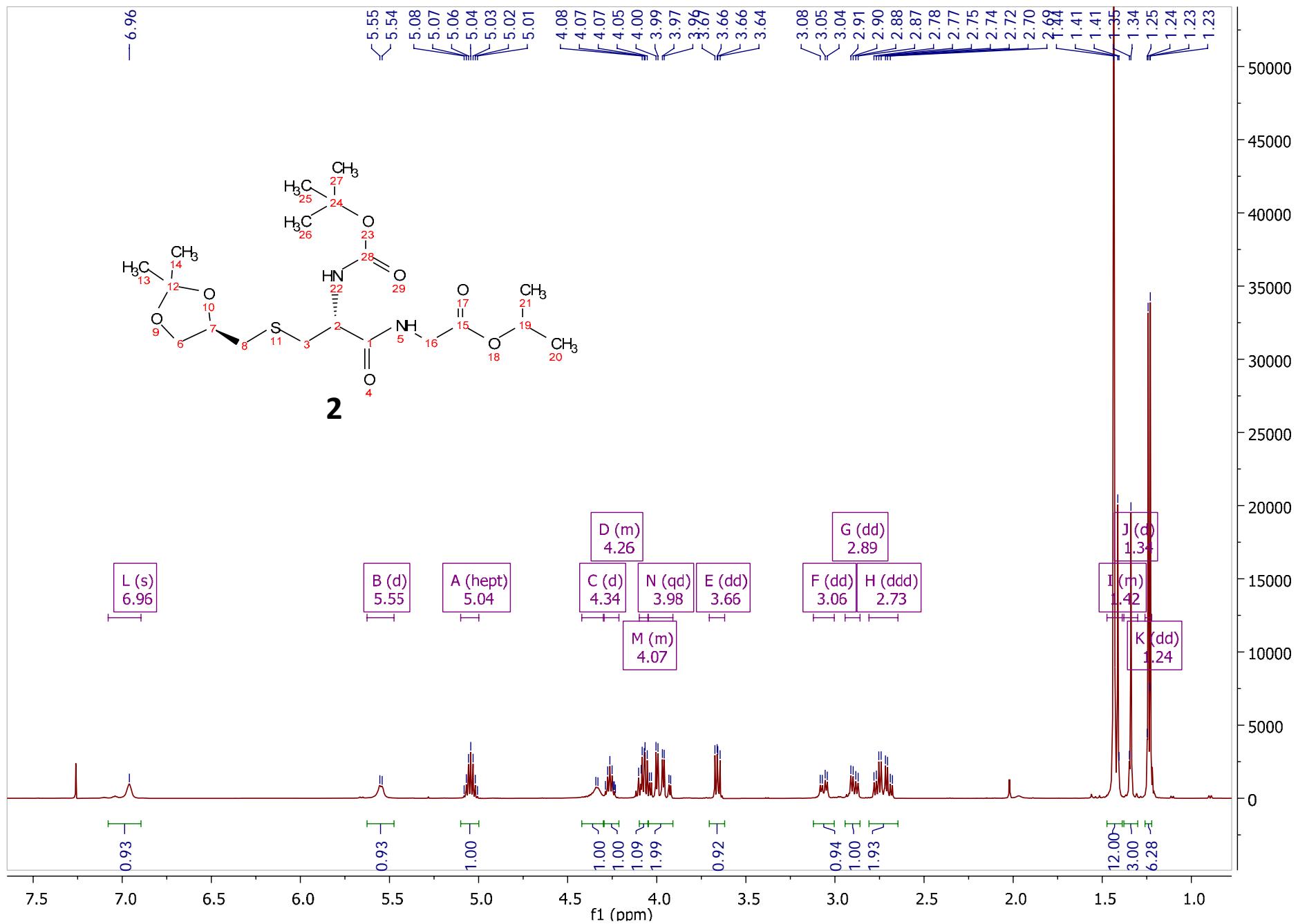
Structure-Activity Relationships in Toll-like Receptor 2-Agonists Leading to Simplified Monoacyl Lipopeptides

Geetanjali Agnihotri, Breanna M. Crall, Tyler C. Lewis,
Timothy P. Day, Rajalakshmi Balakrishna, Hemamali J.
Warshakoon, Subbalakshmi S. Malladi,
and Sunil A. David*

Department of Medicinal Chemistry, University of Kansas.

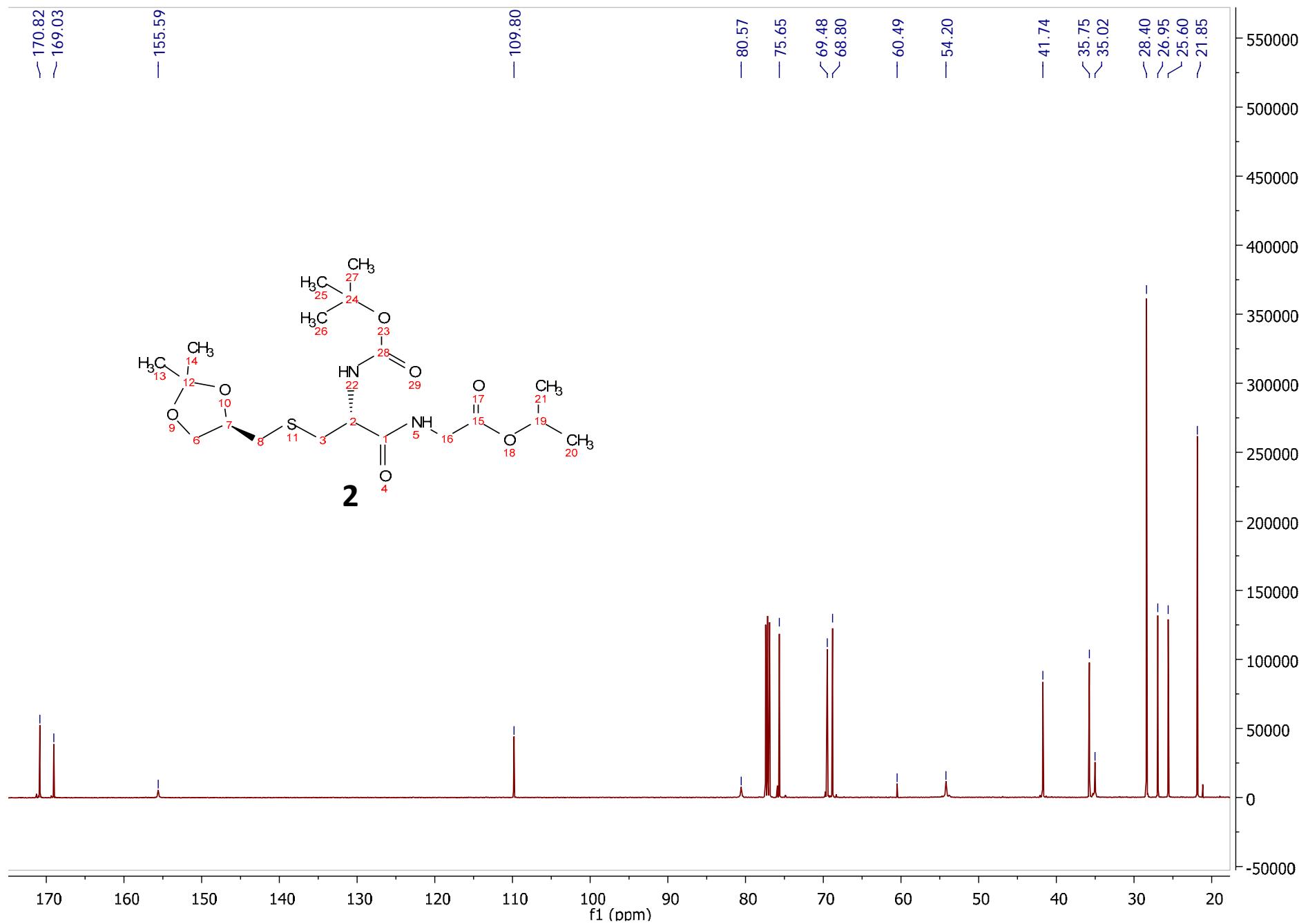
¹H Spectrum

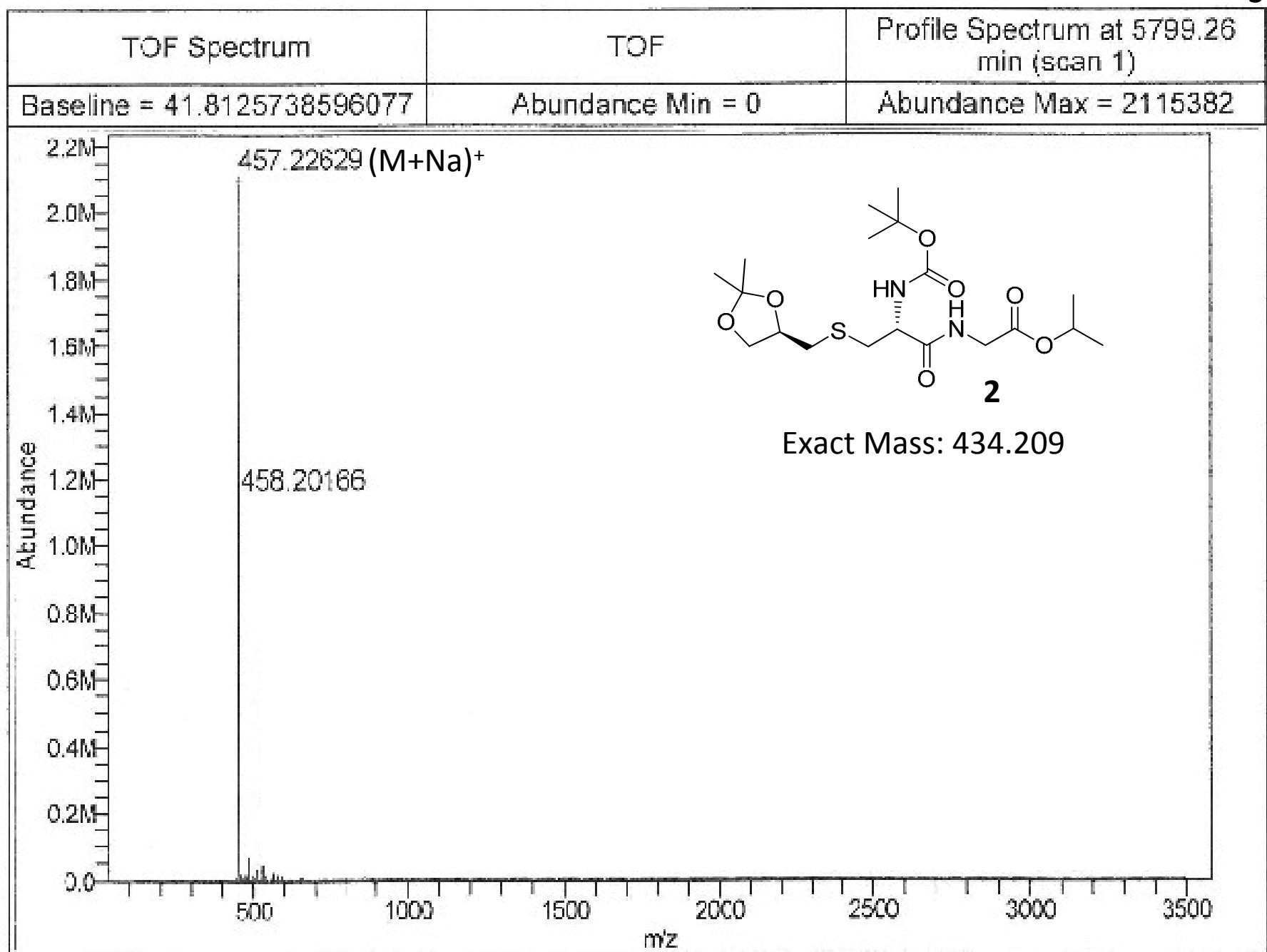
S43



¹³C Spectrum

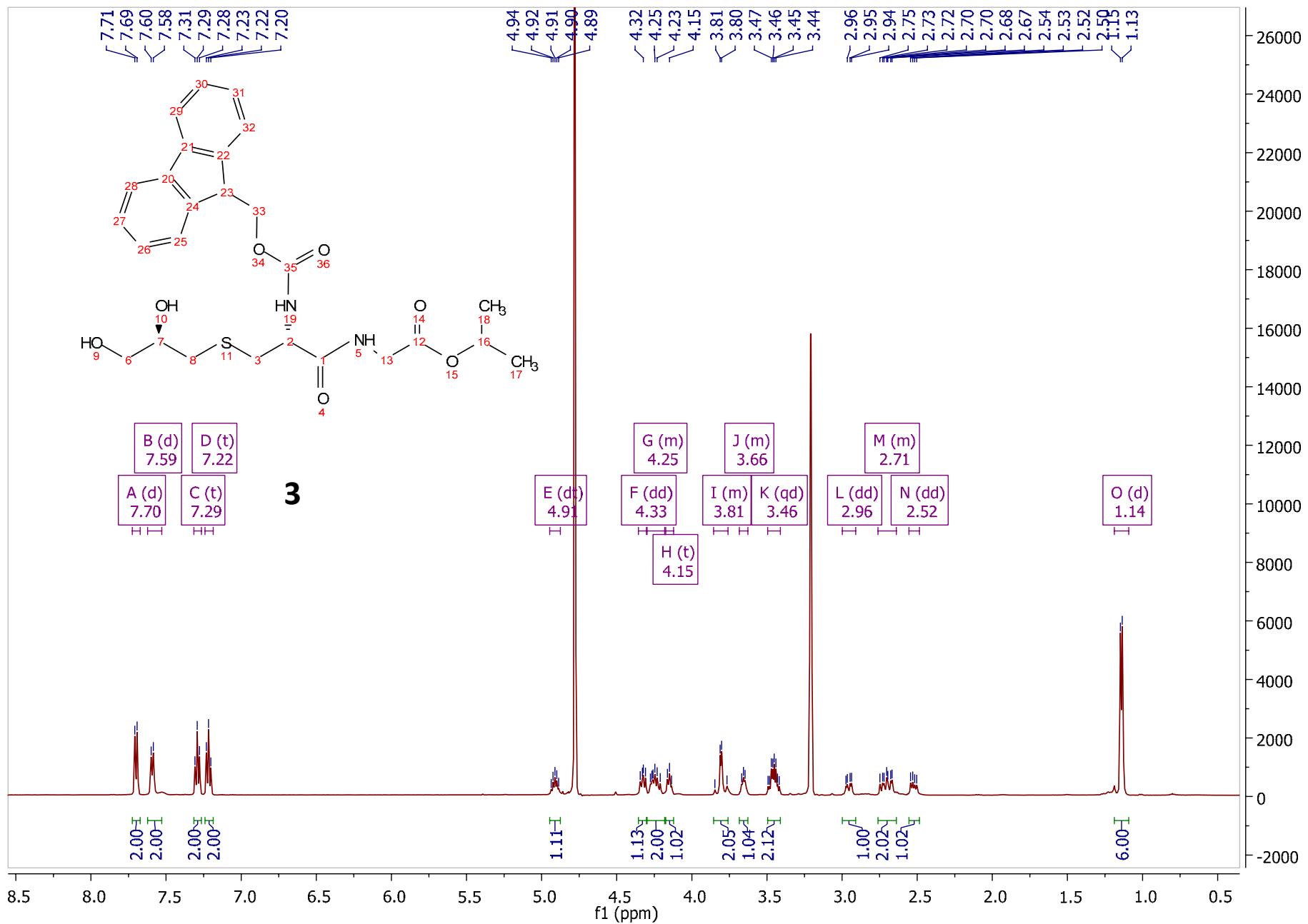
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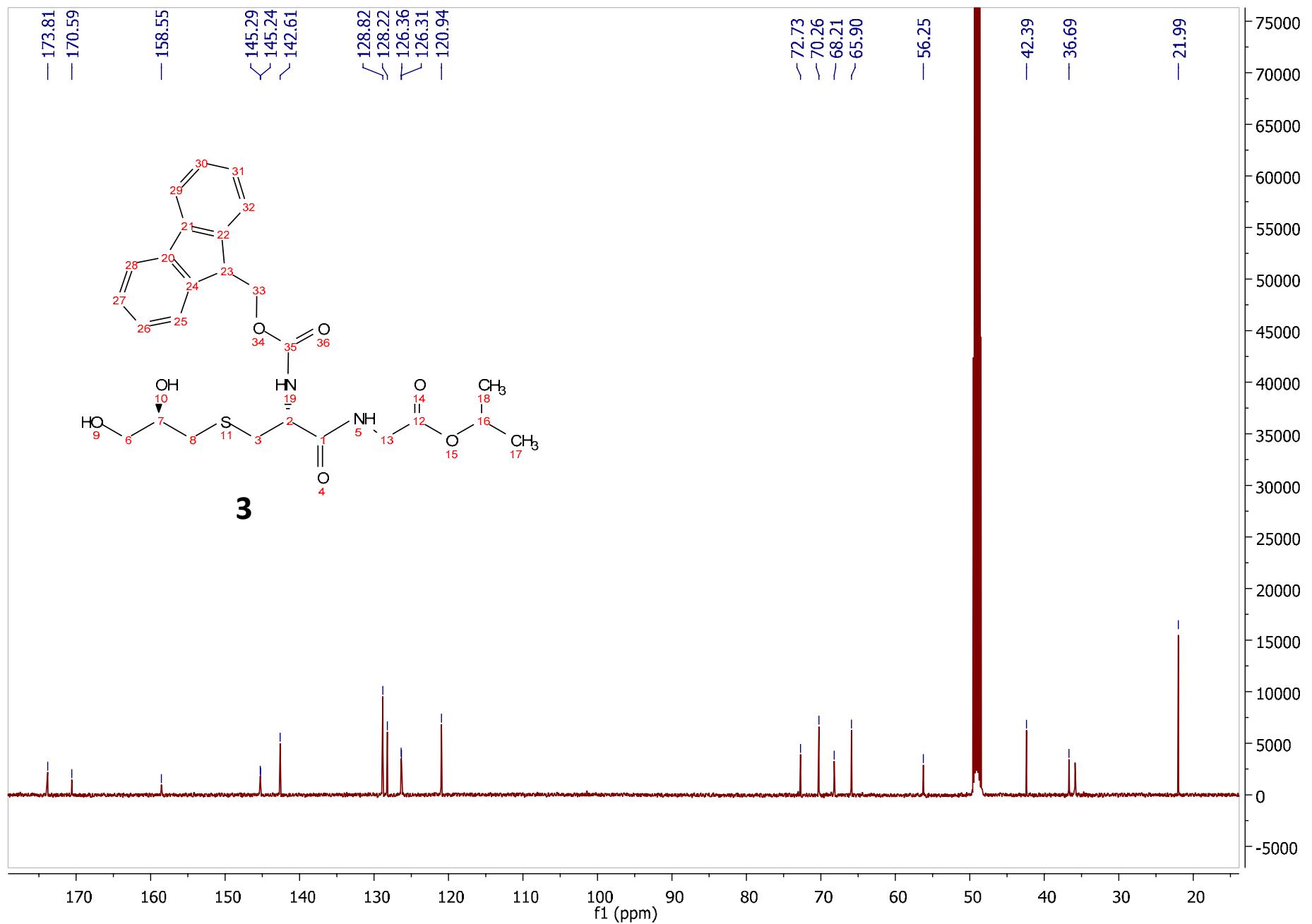
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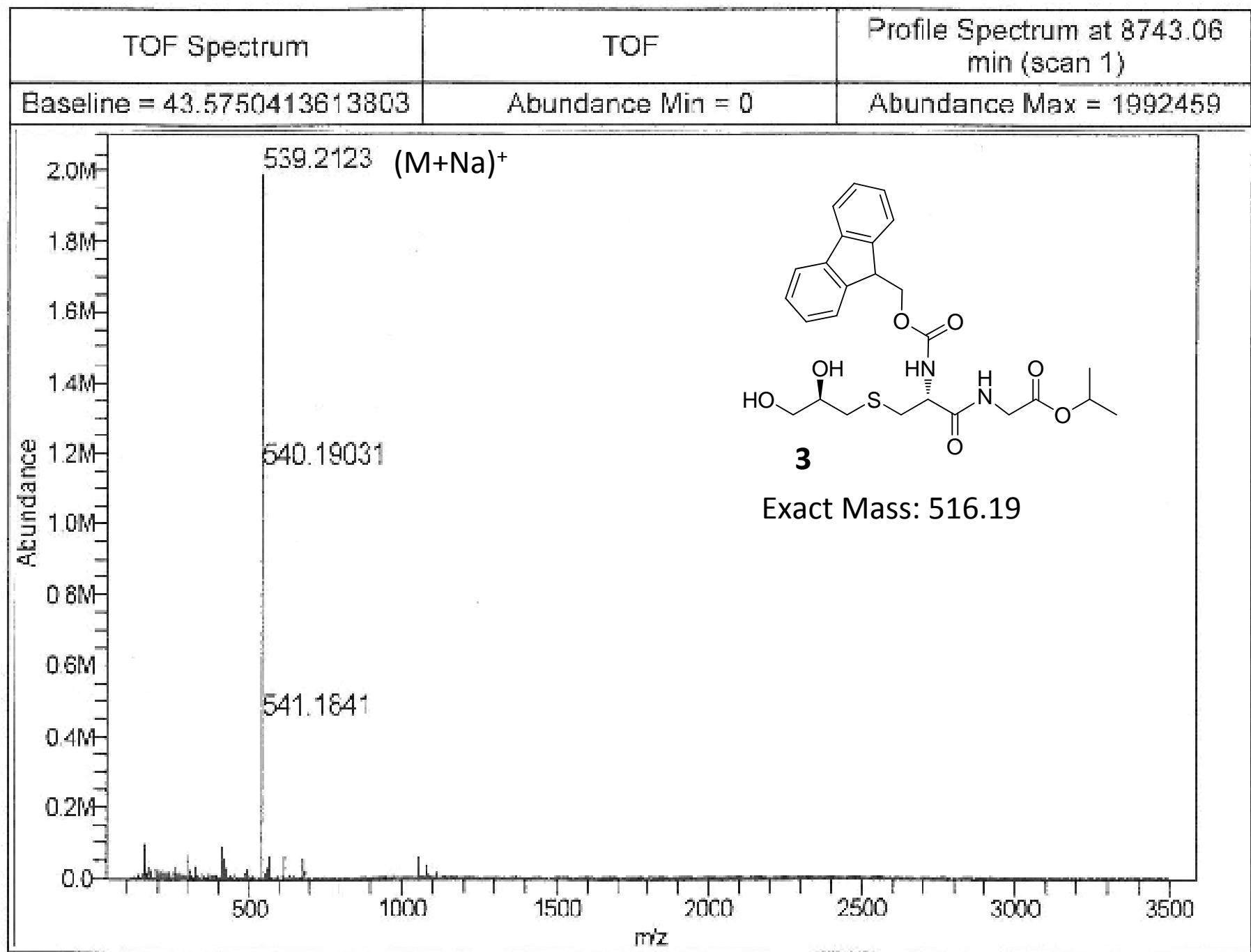
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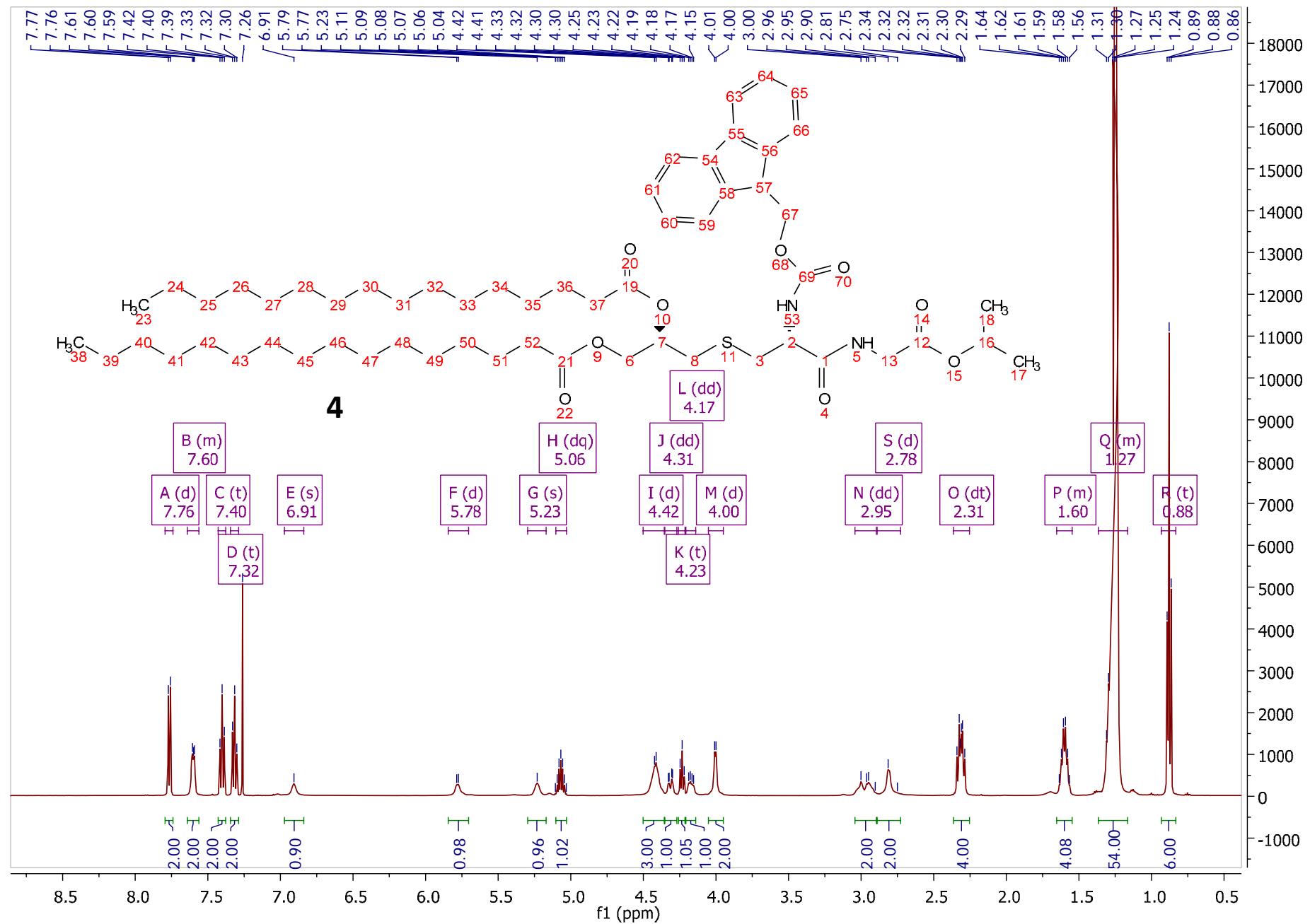
S47





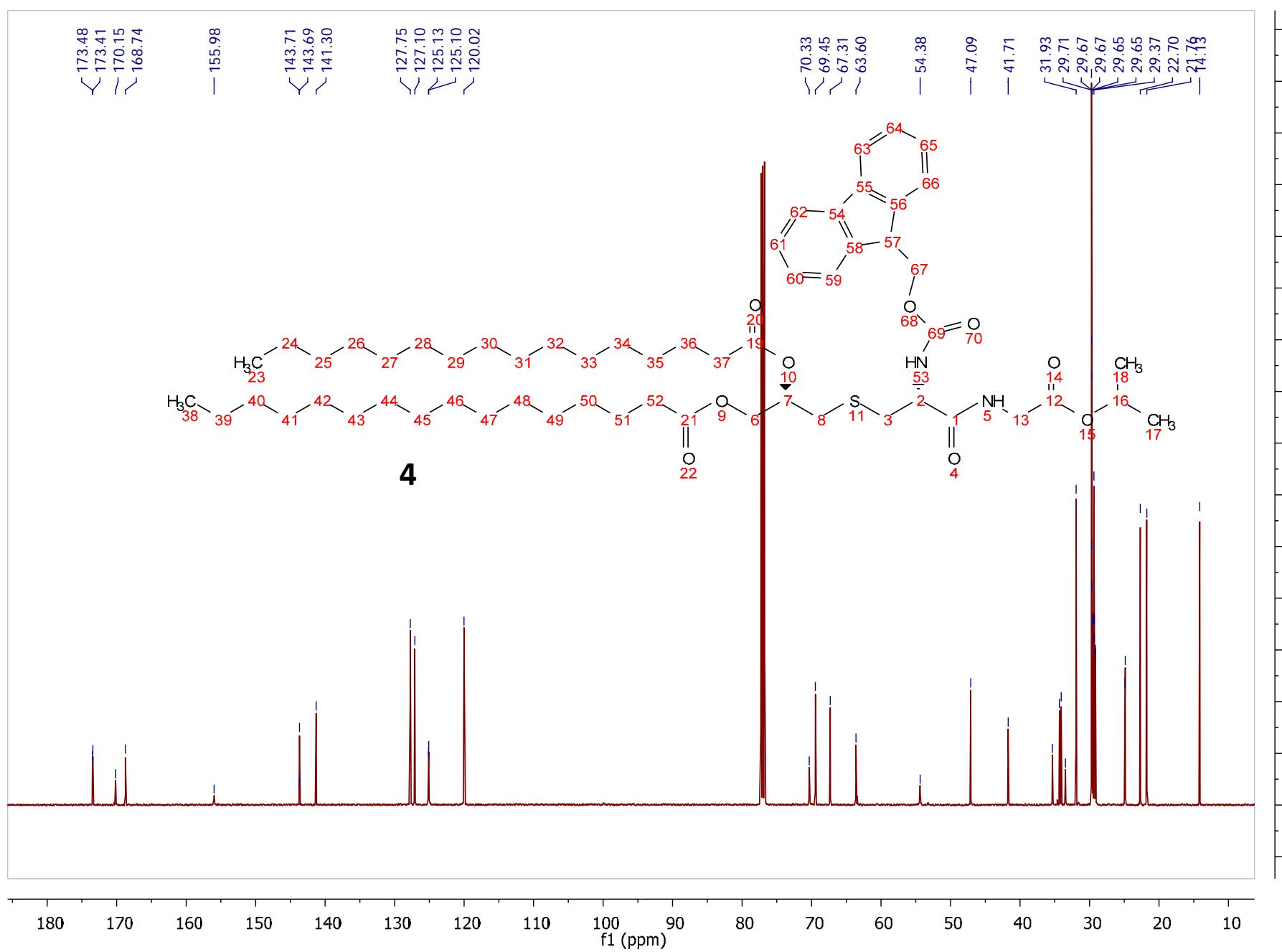
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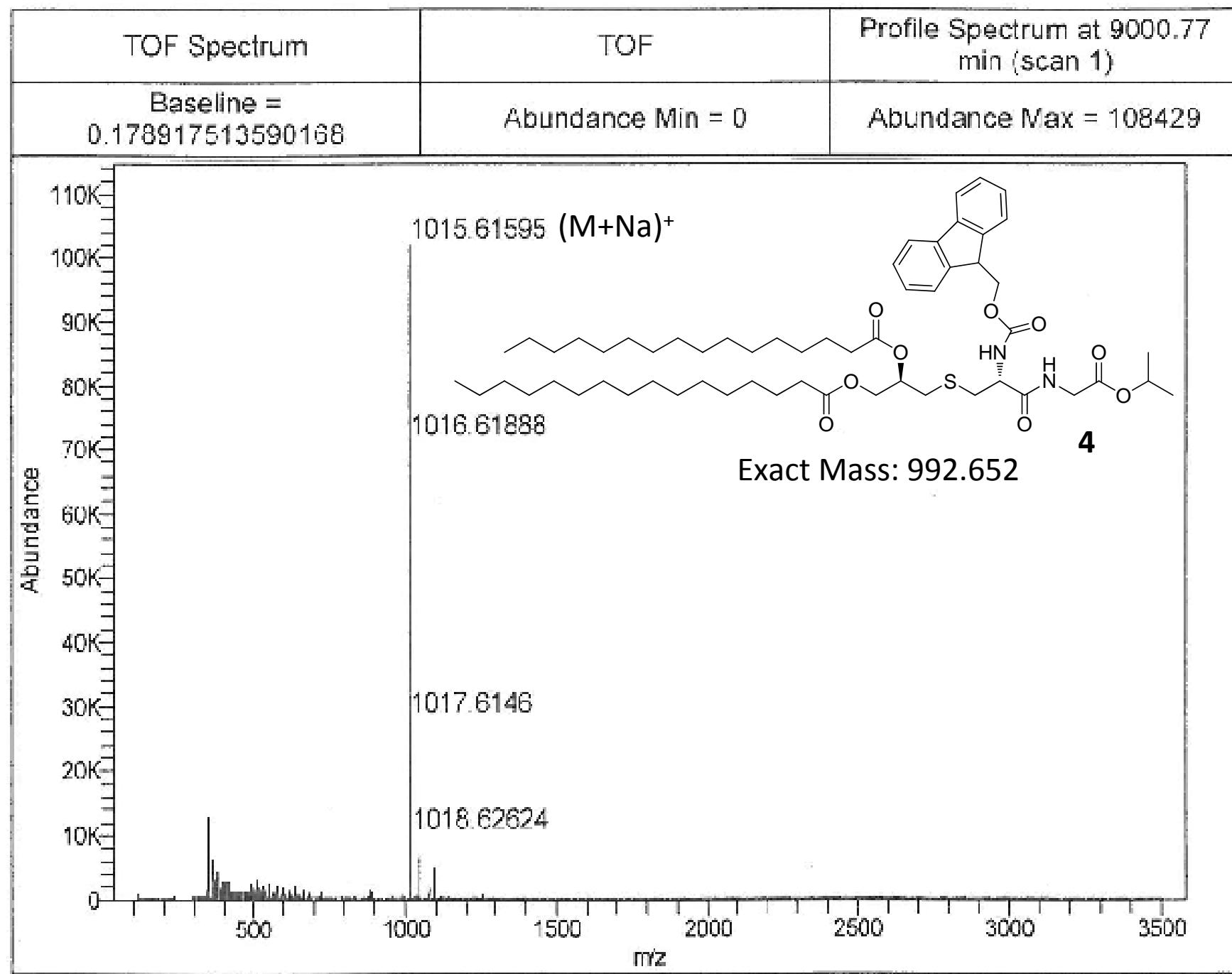
S49



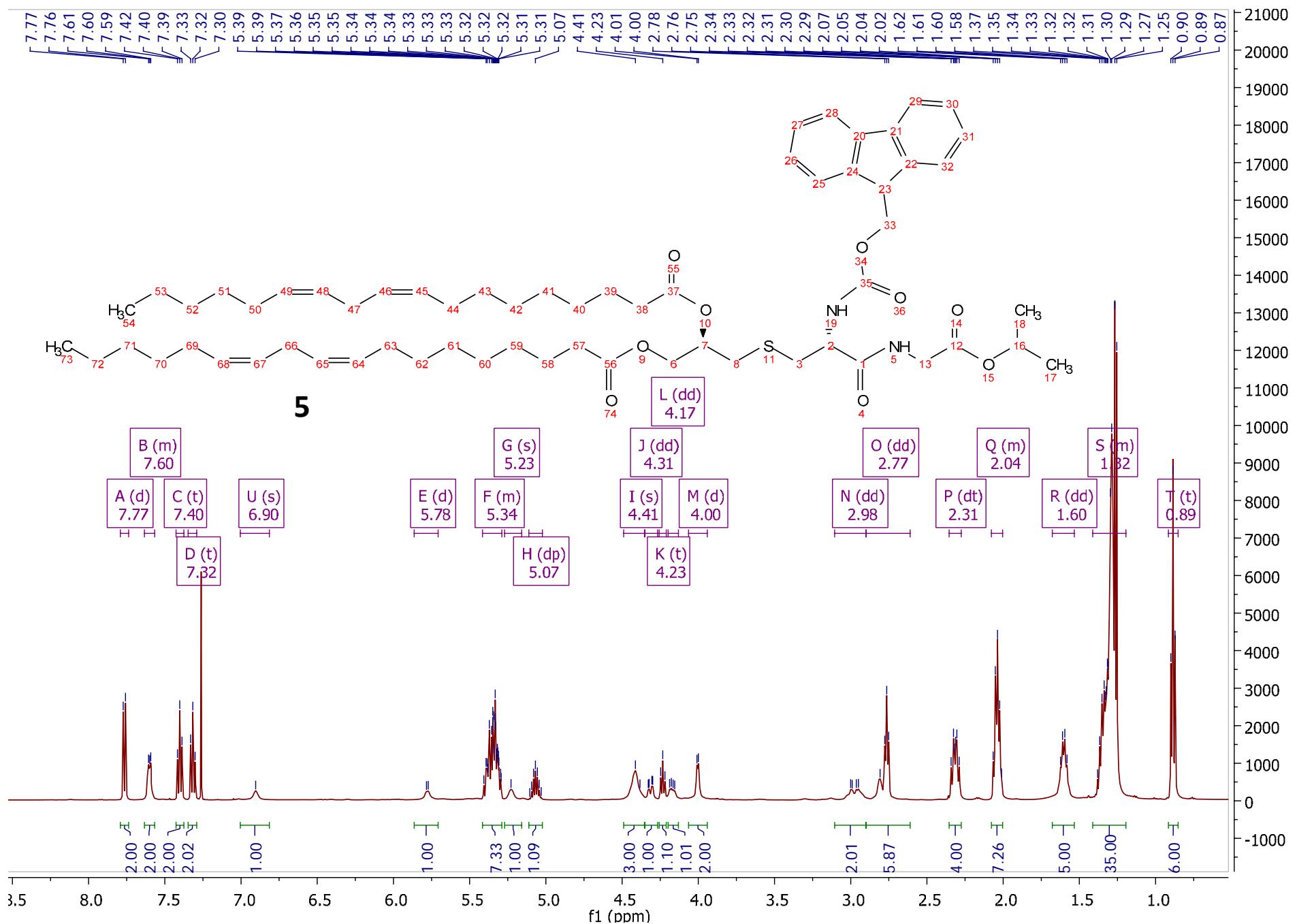
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S50



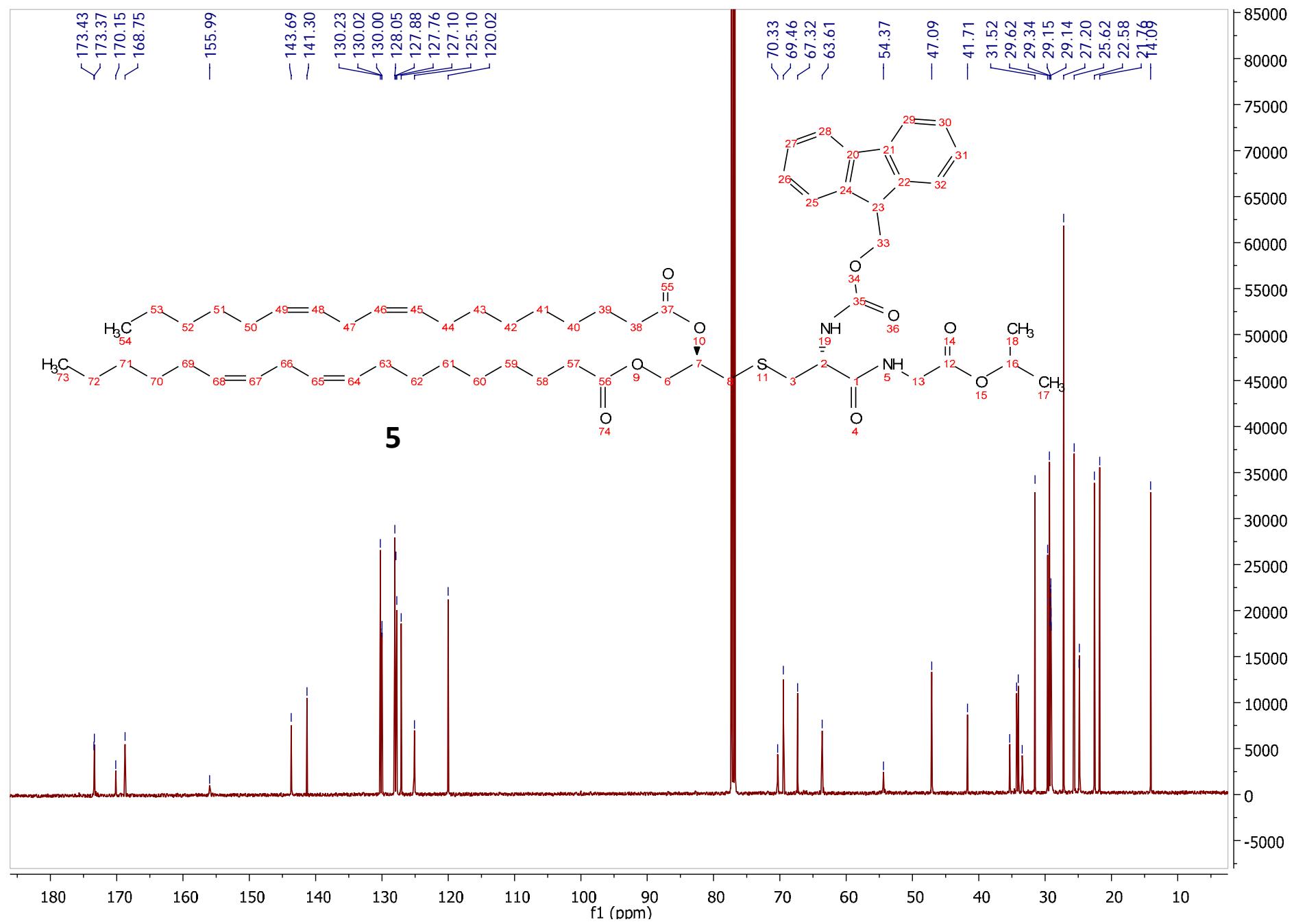


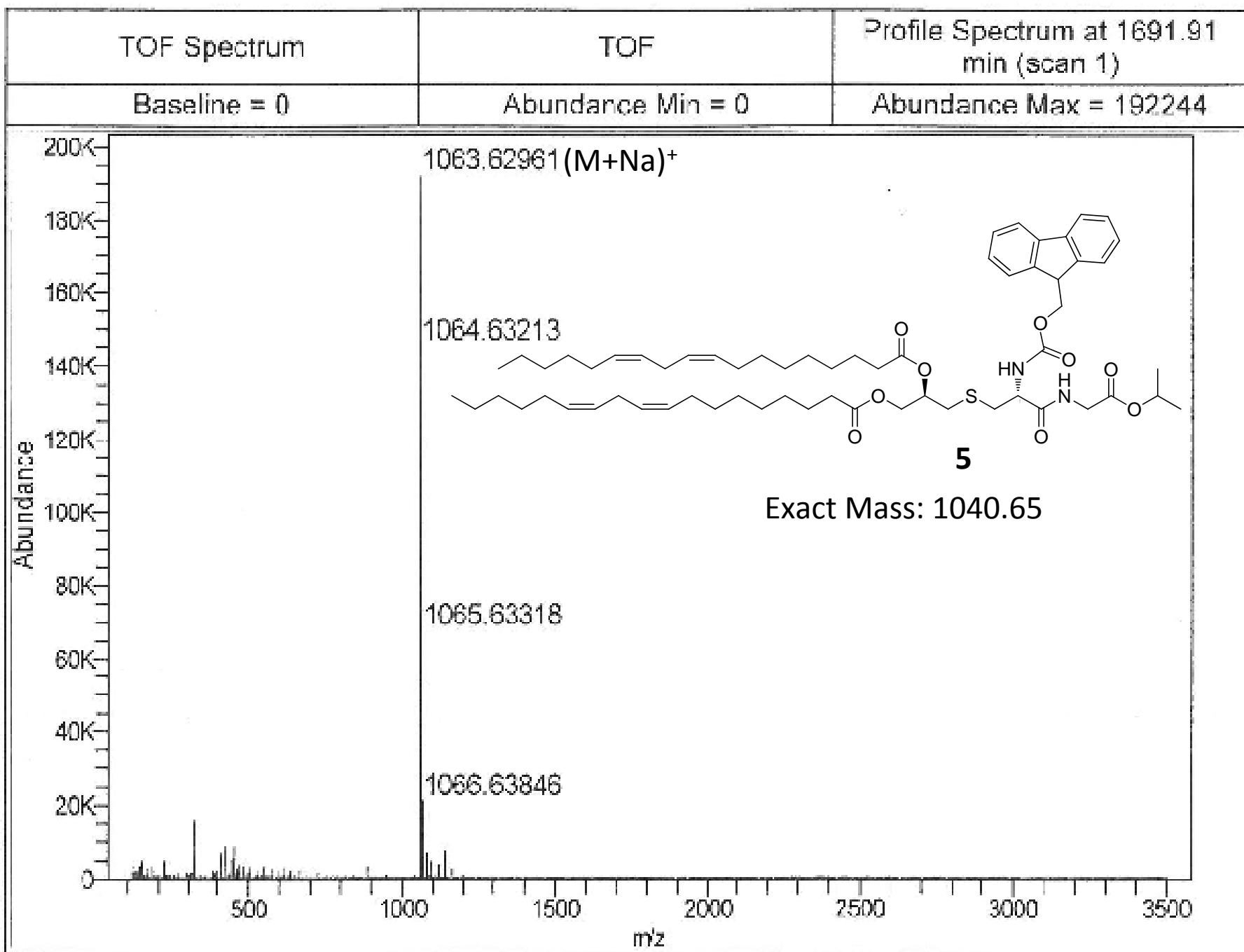
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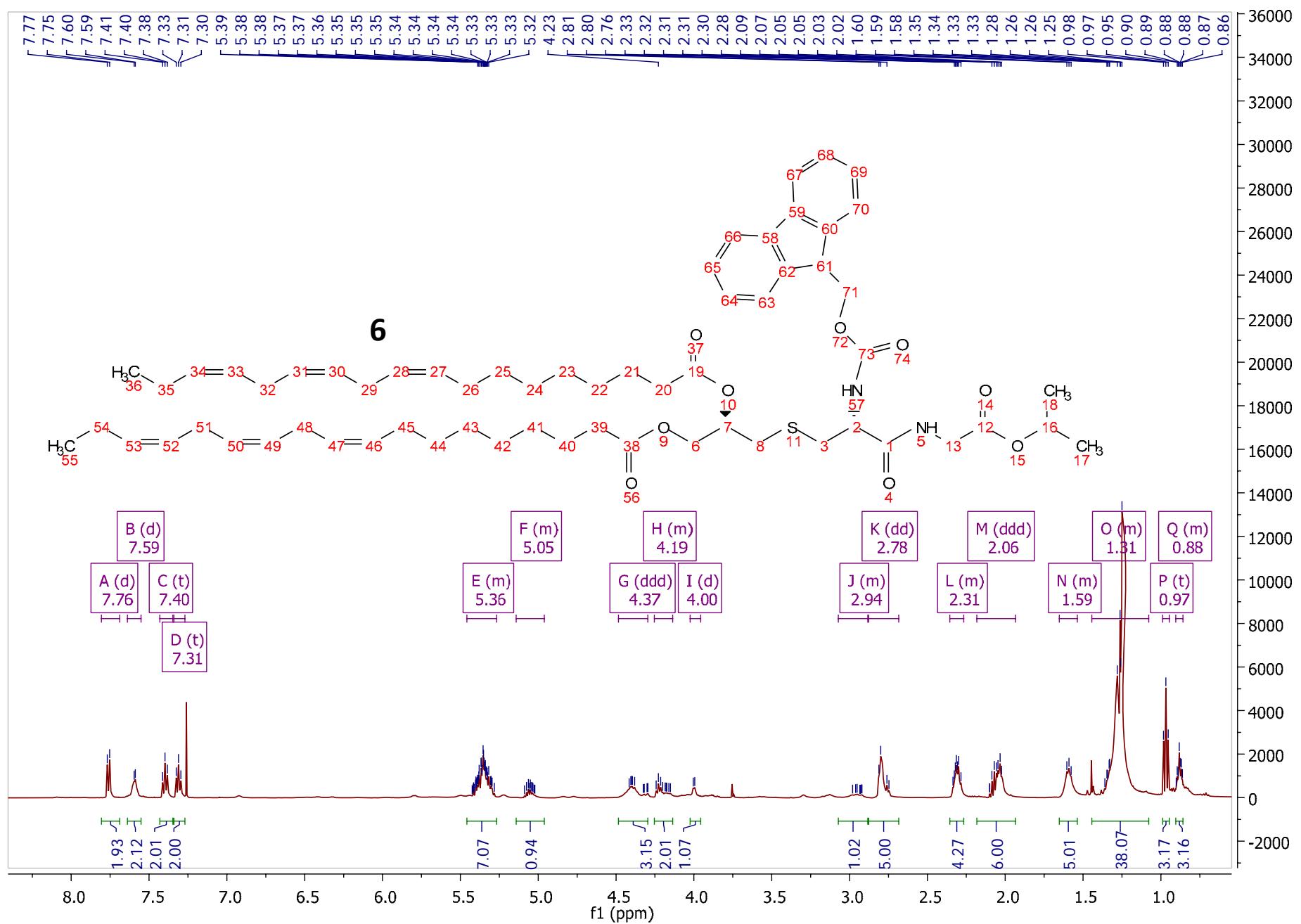
S53





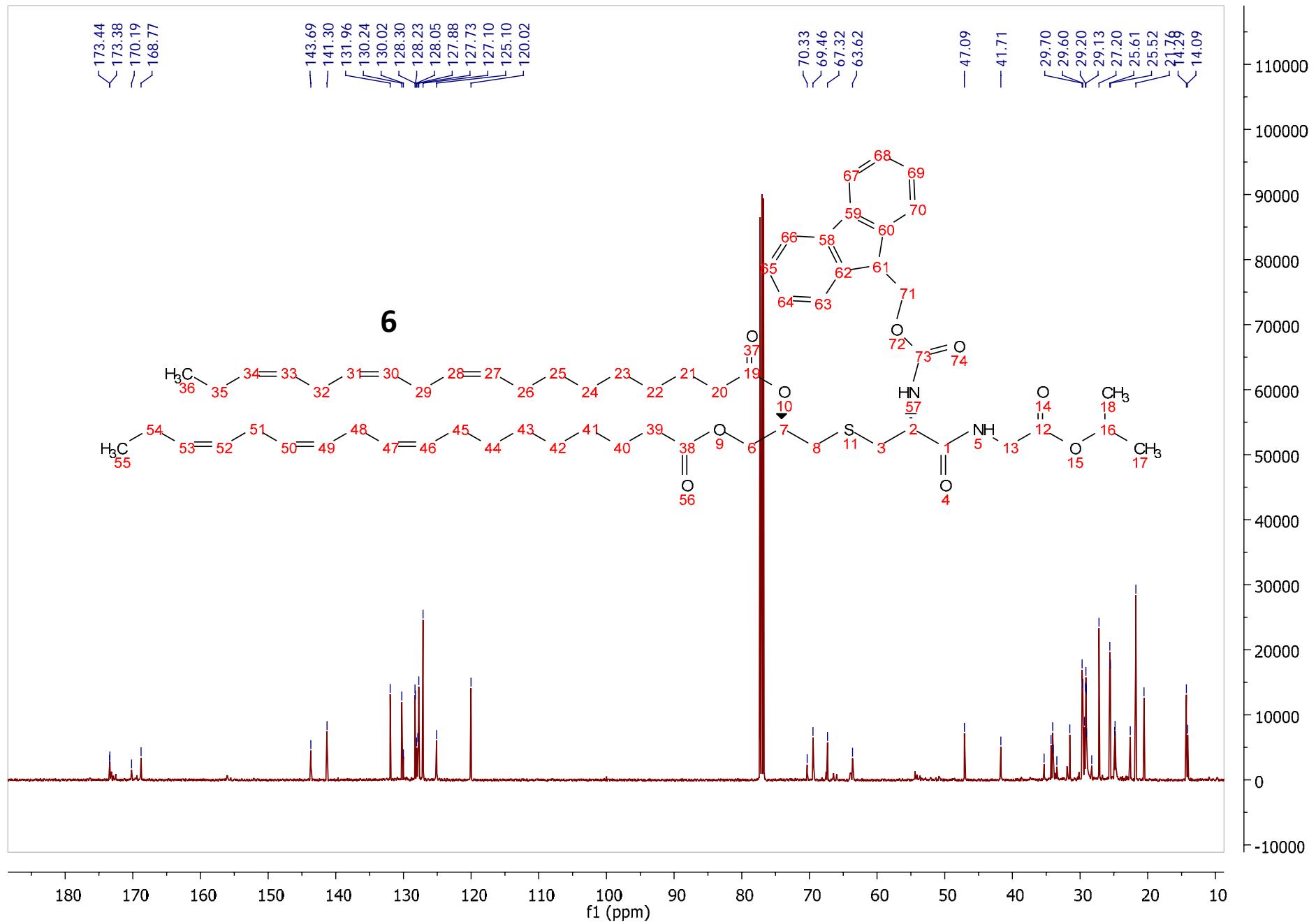
¹H Spectrum

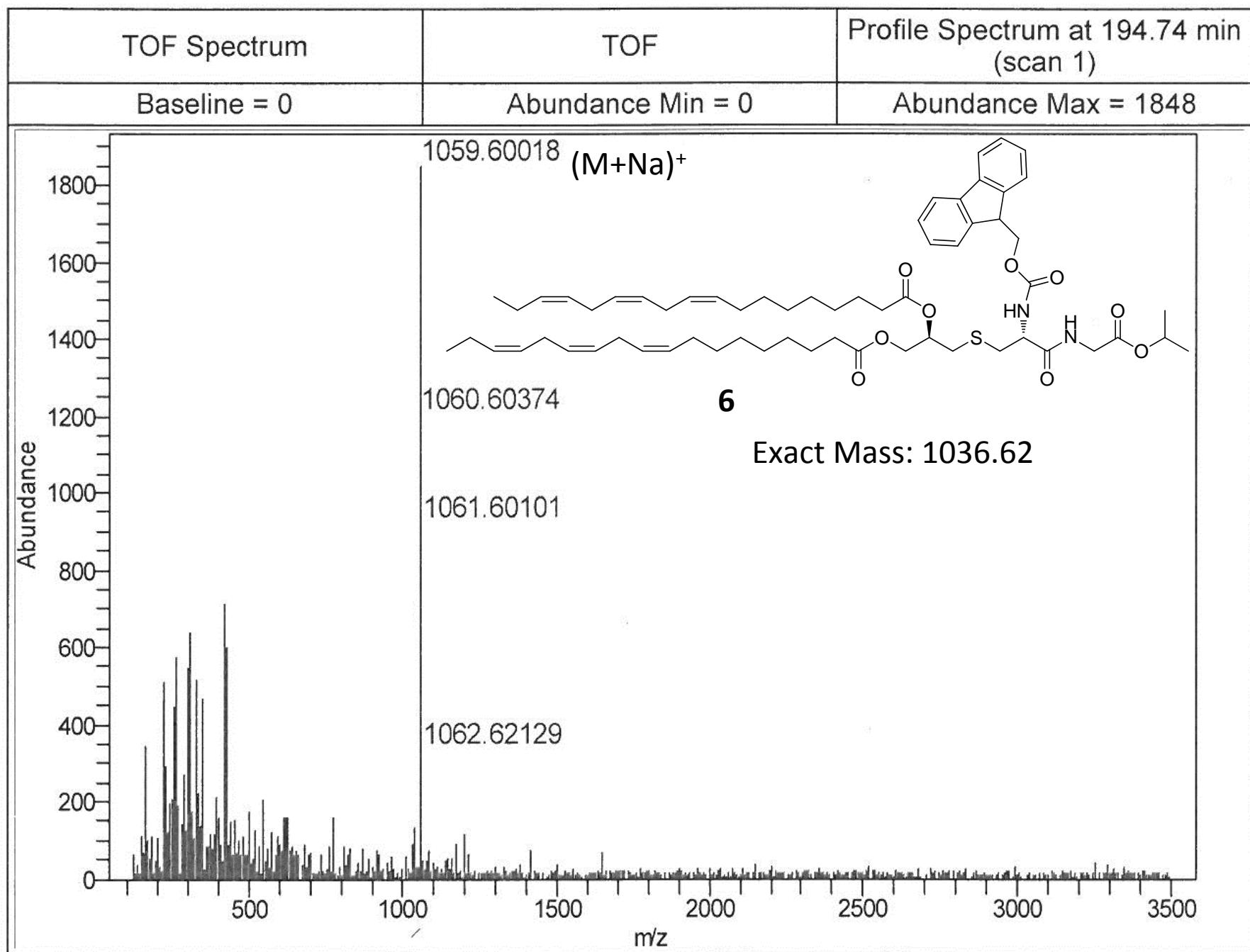
S55



¹³C Spectrum

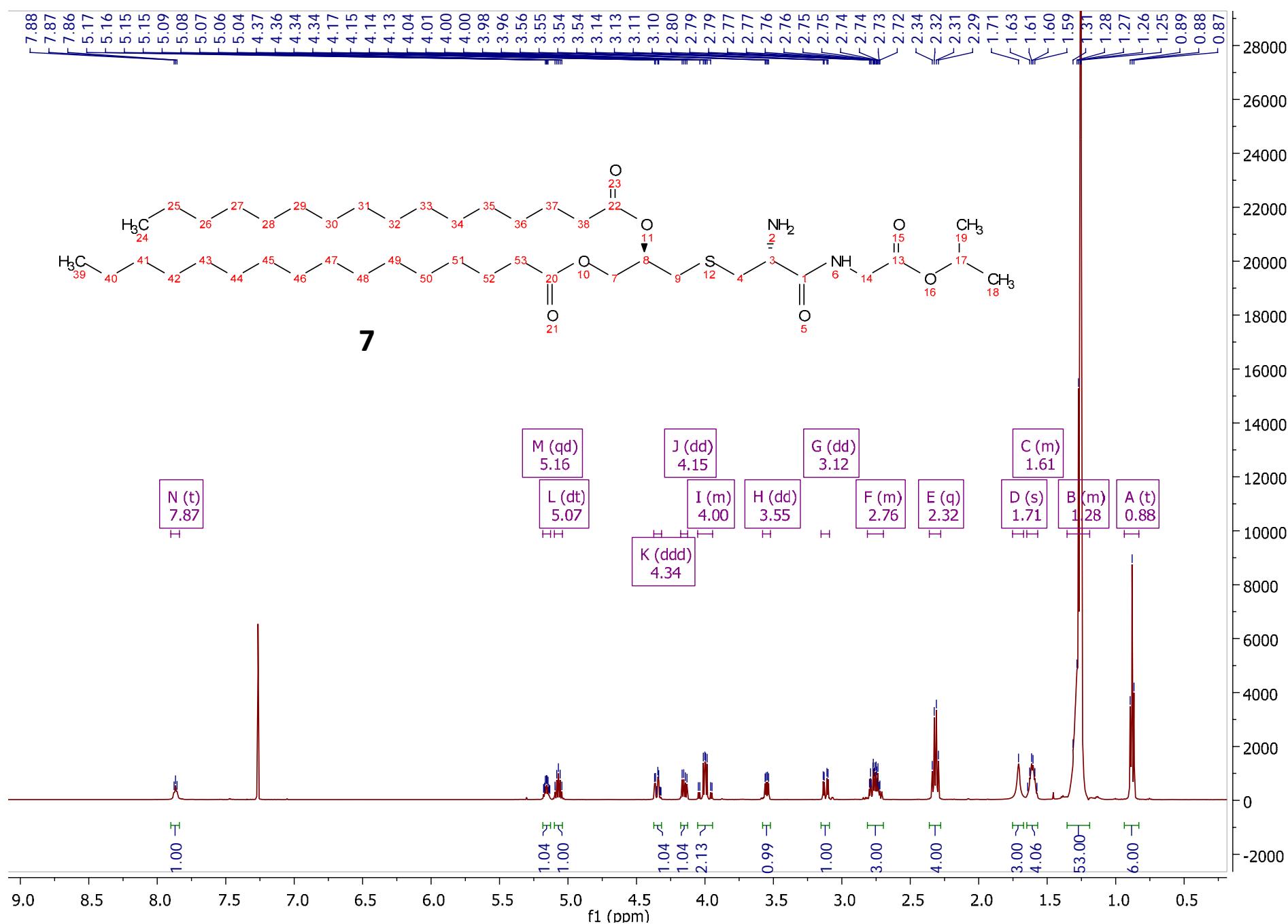
S56





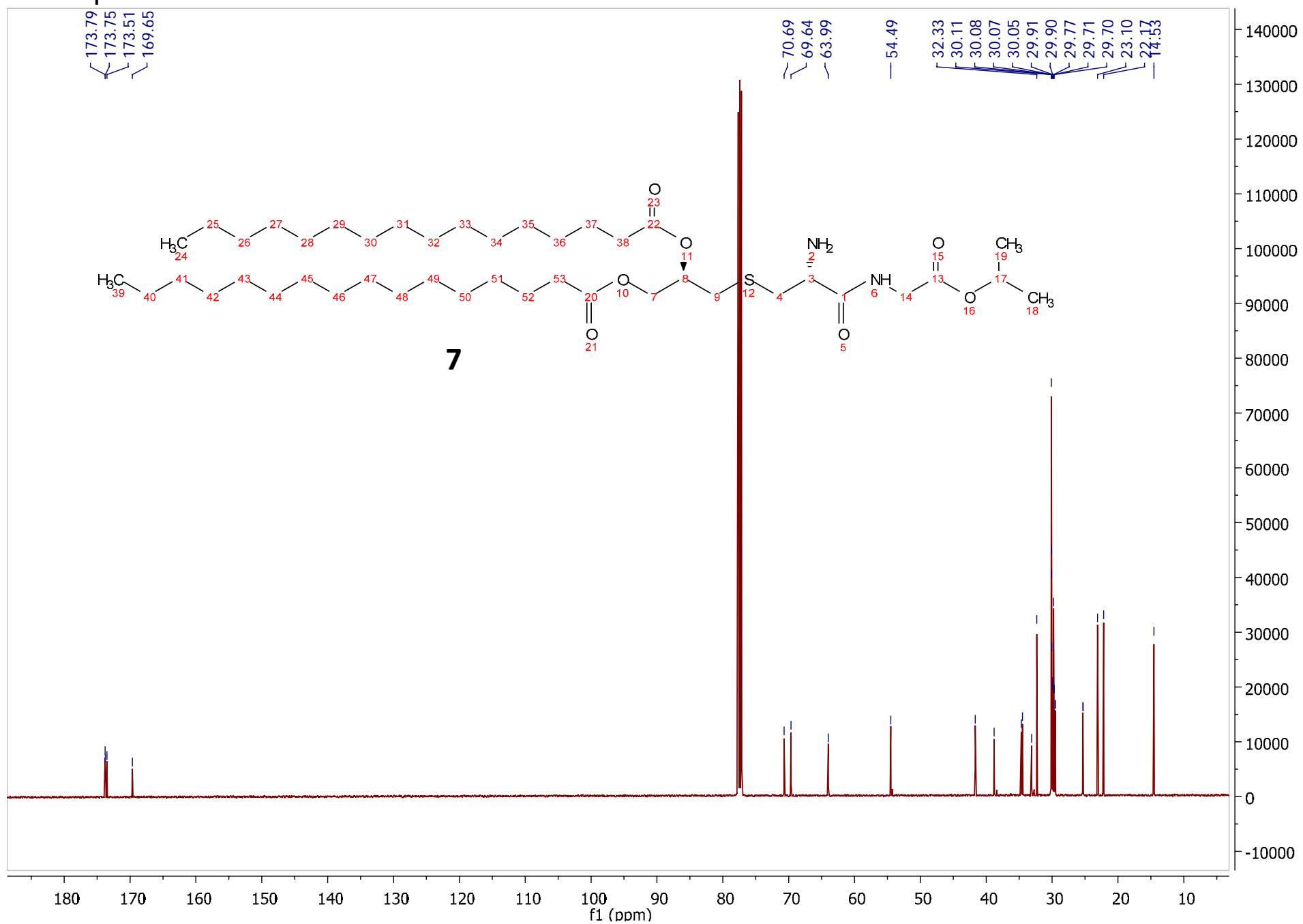
¹H Spectrum

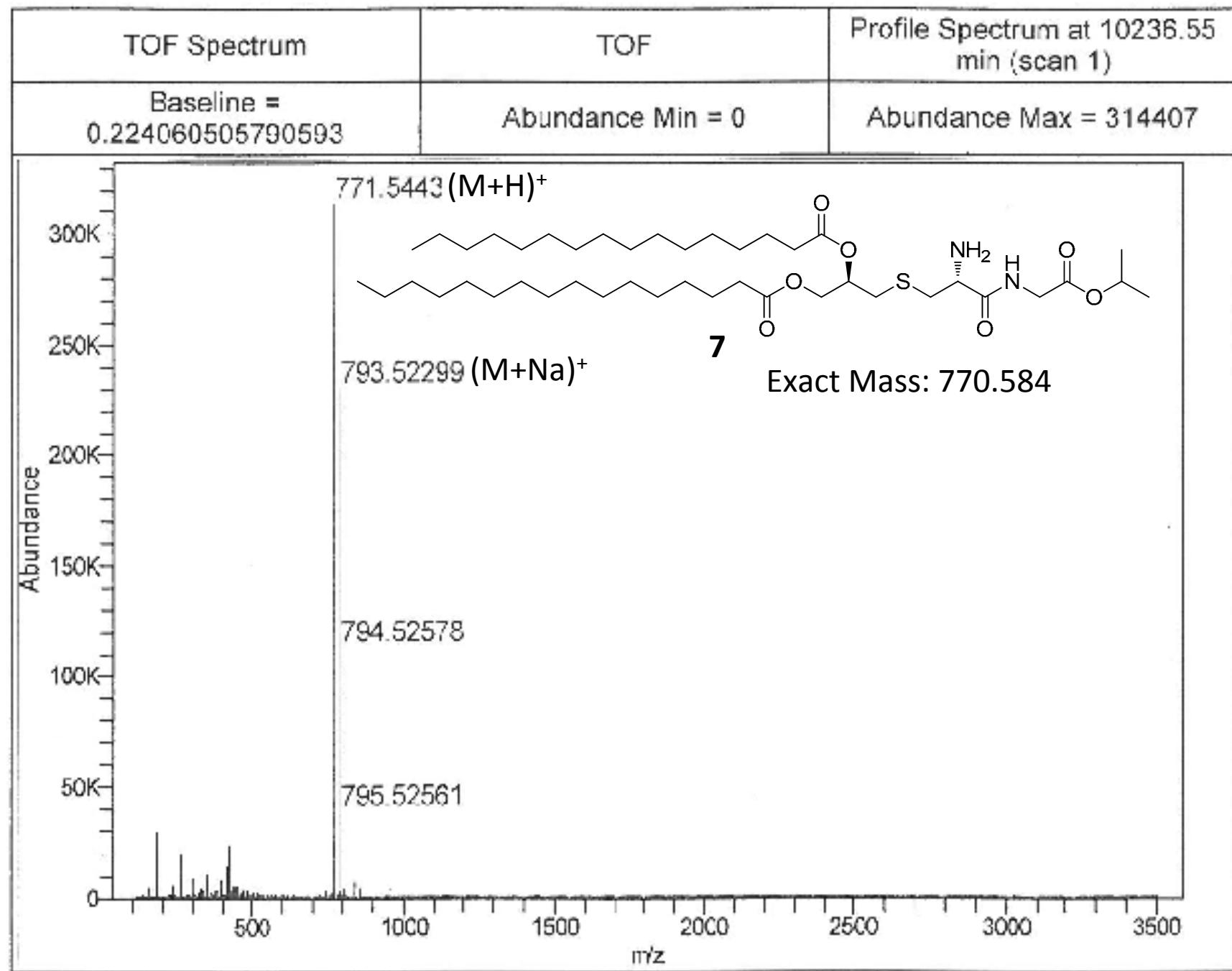
S58



¹³C Spectrum

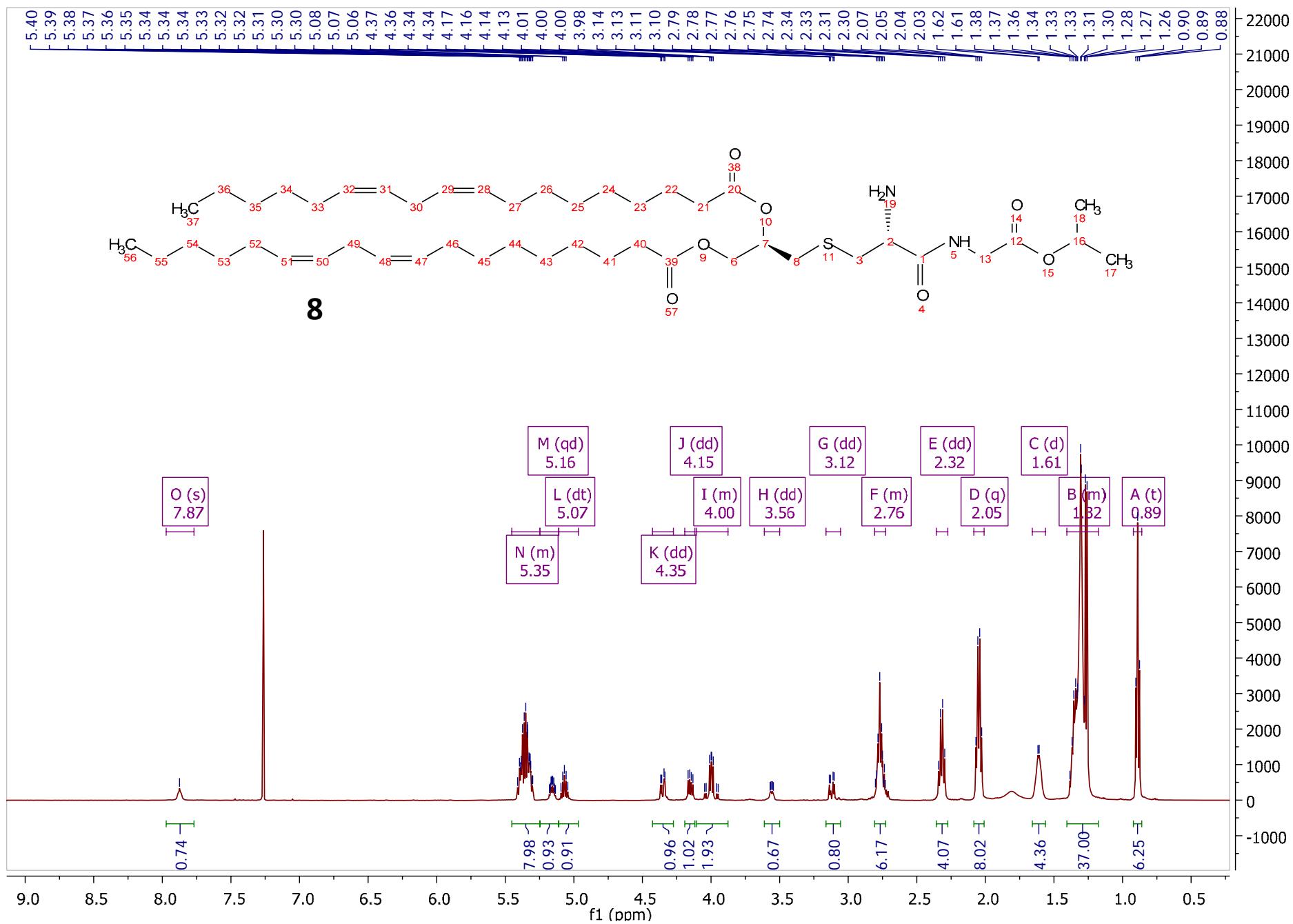
S59





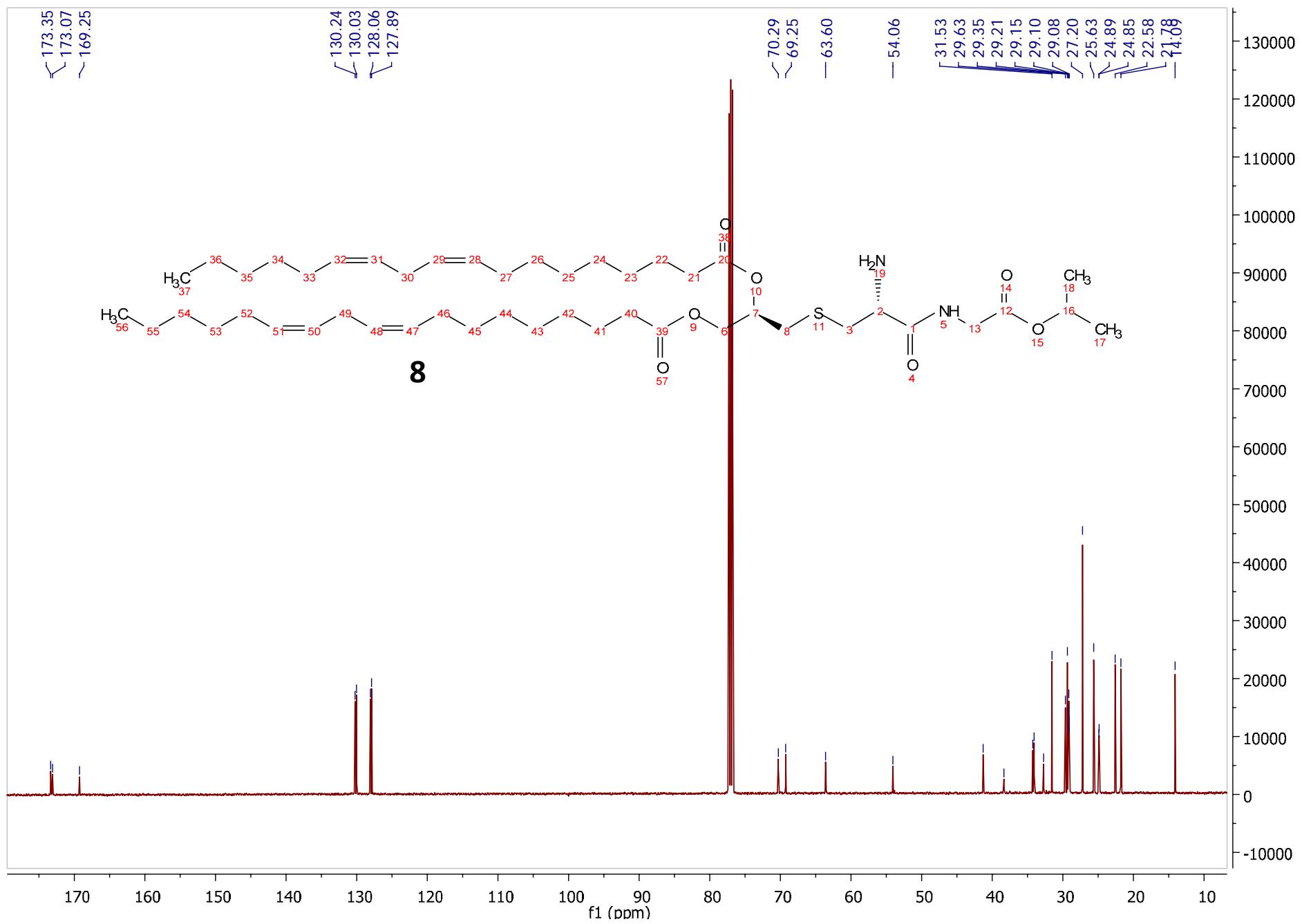
¹H Spectrum

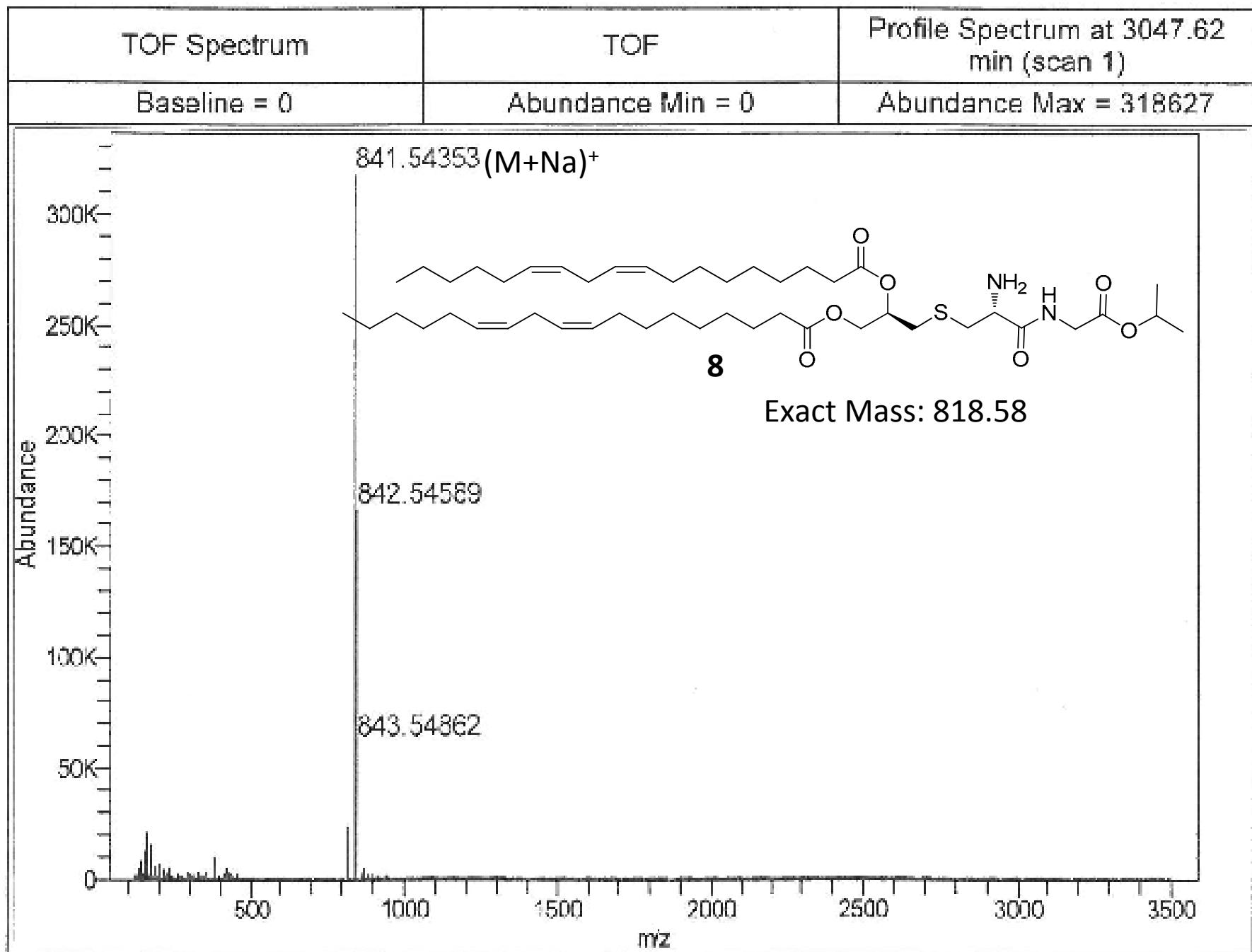
S61

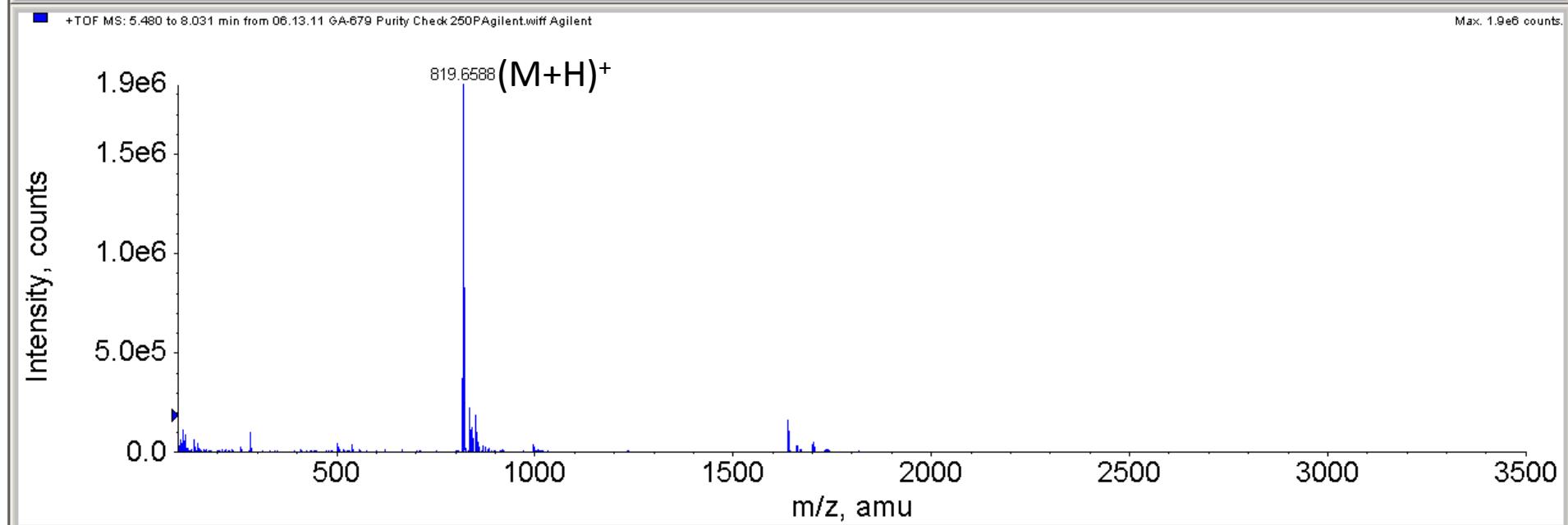
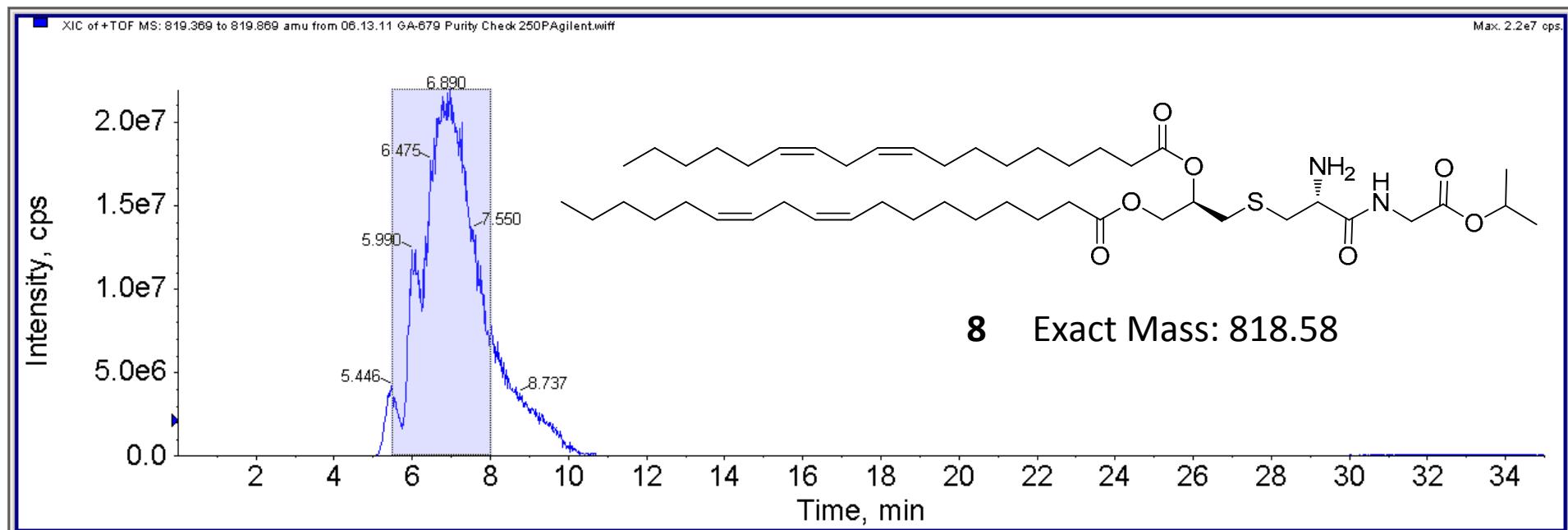


¹³C Spectrum

S62

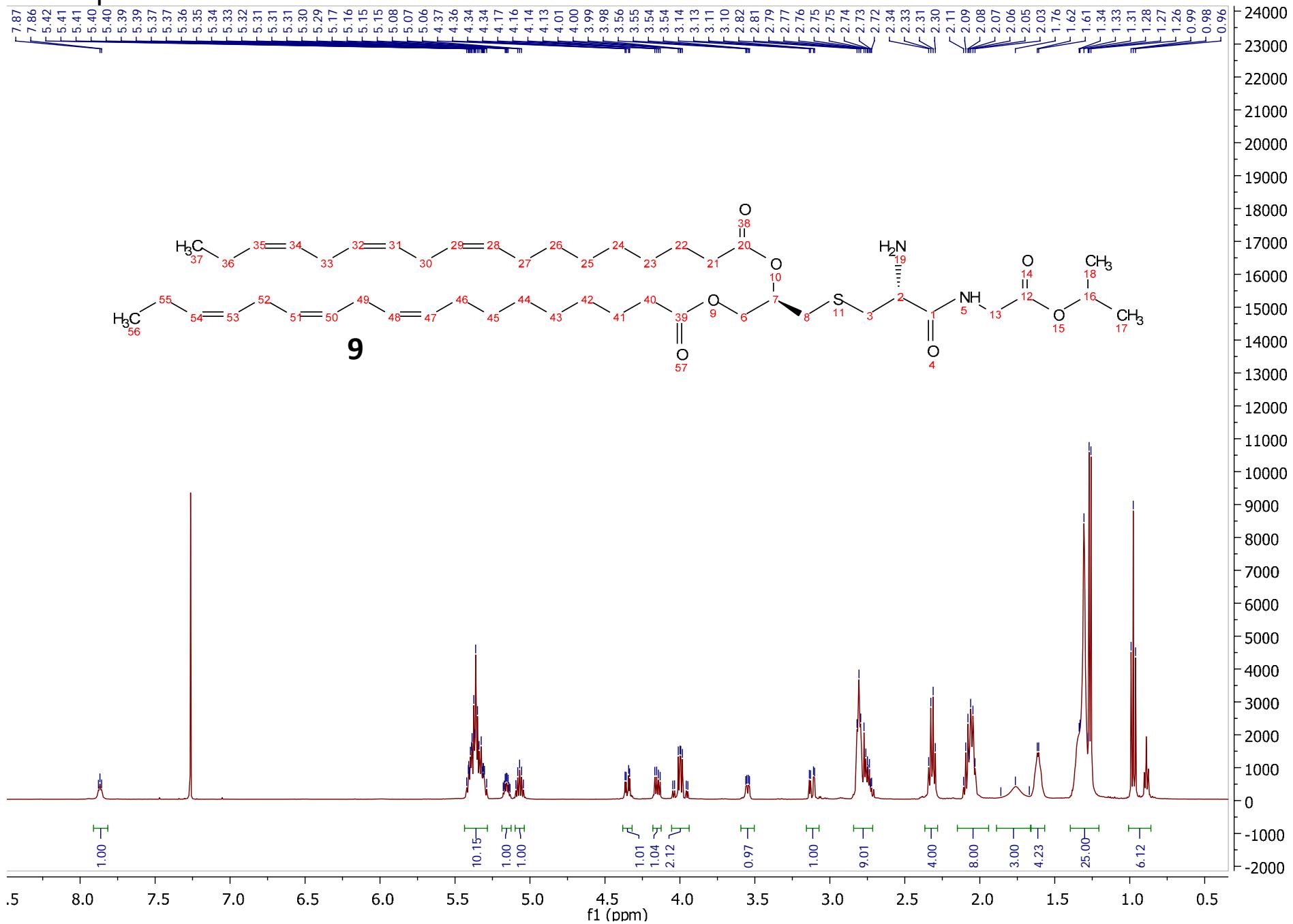






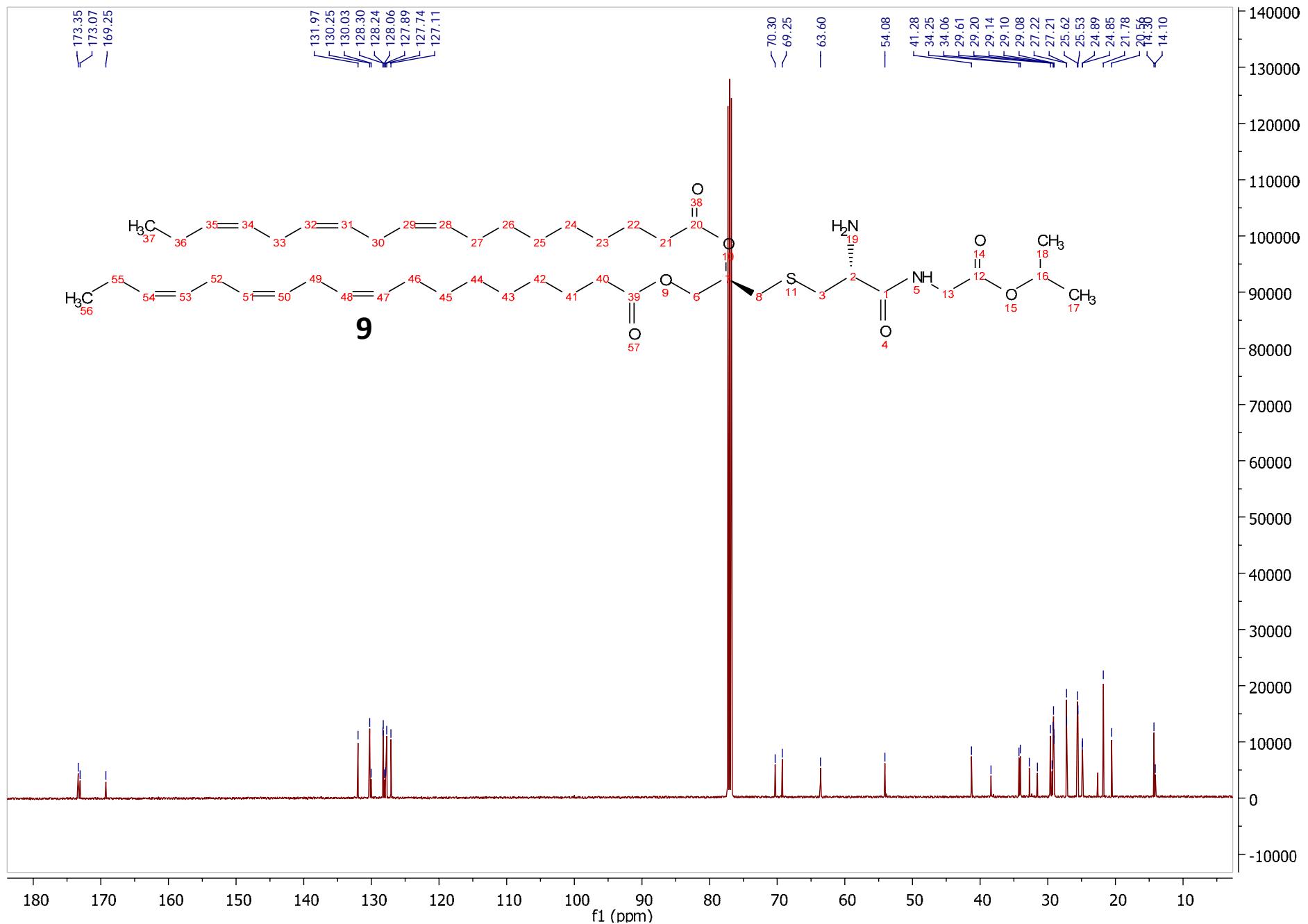
¹H Spectrum

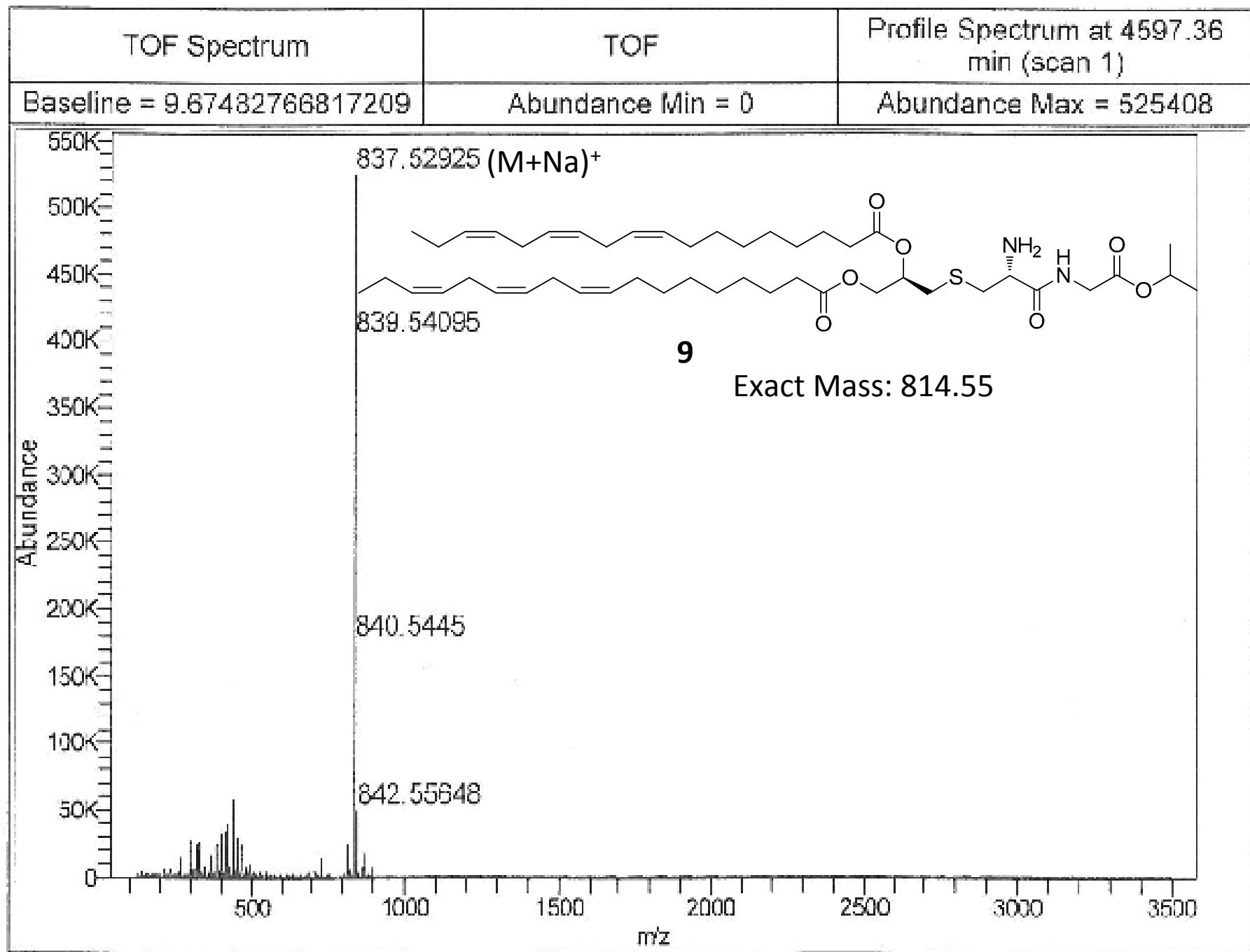
S65

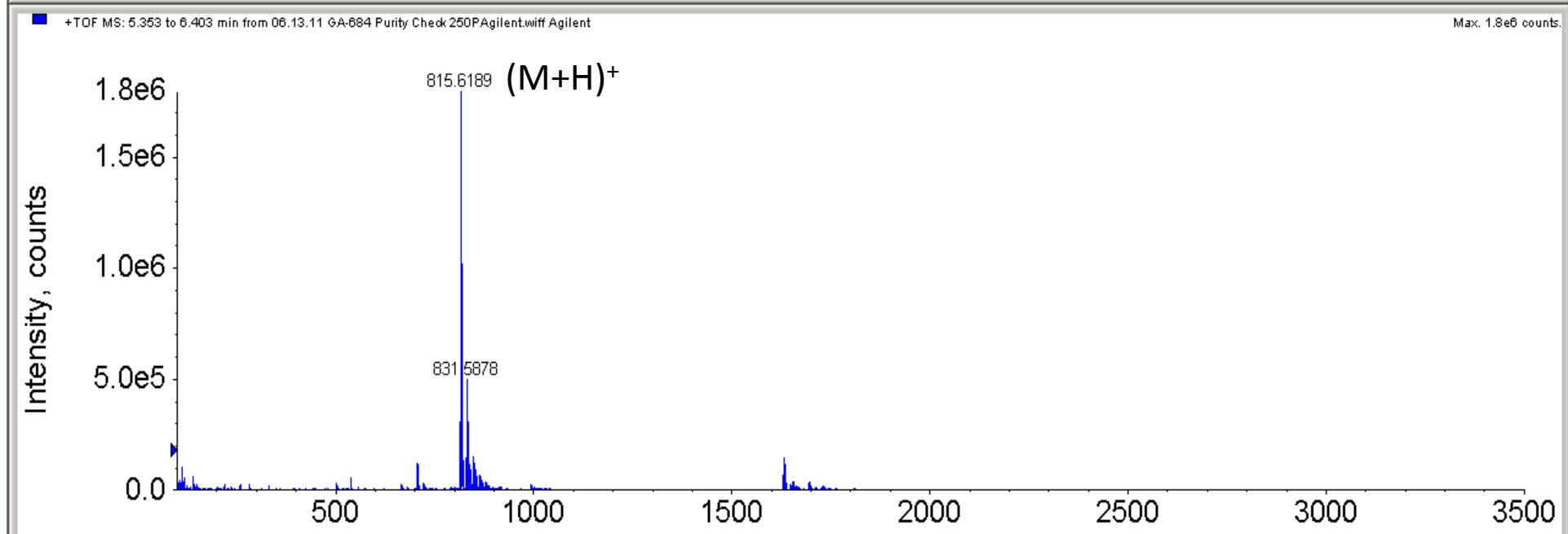
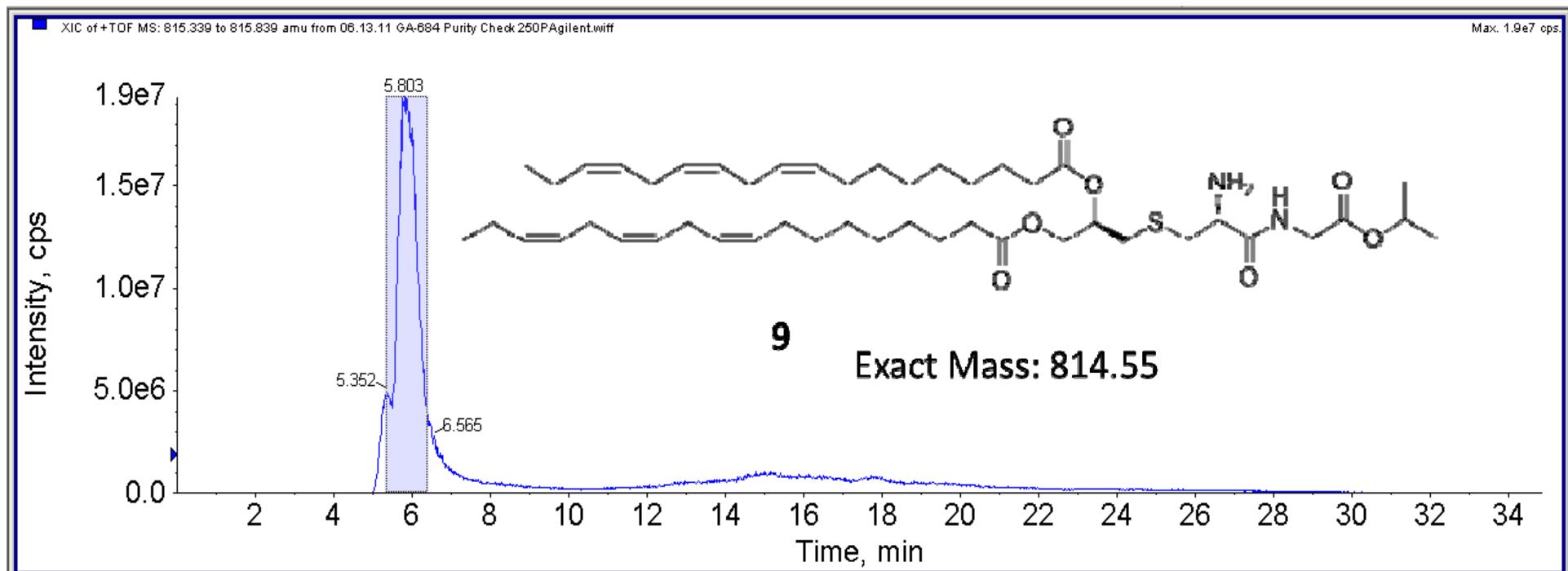


¹³C Spectrum

S66

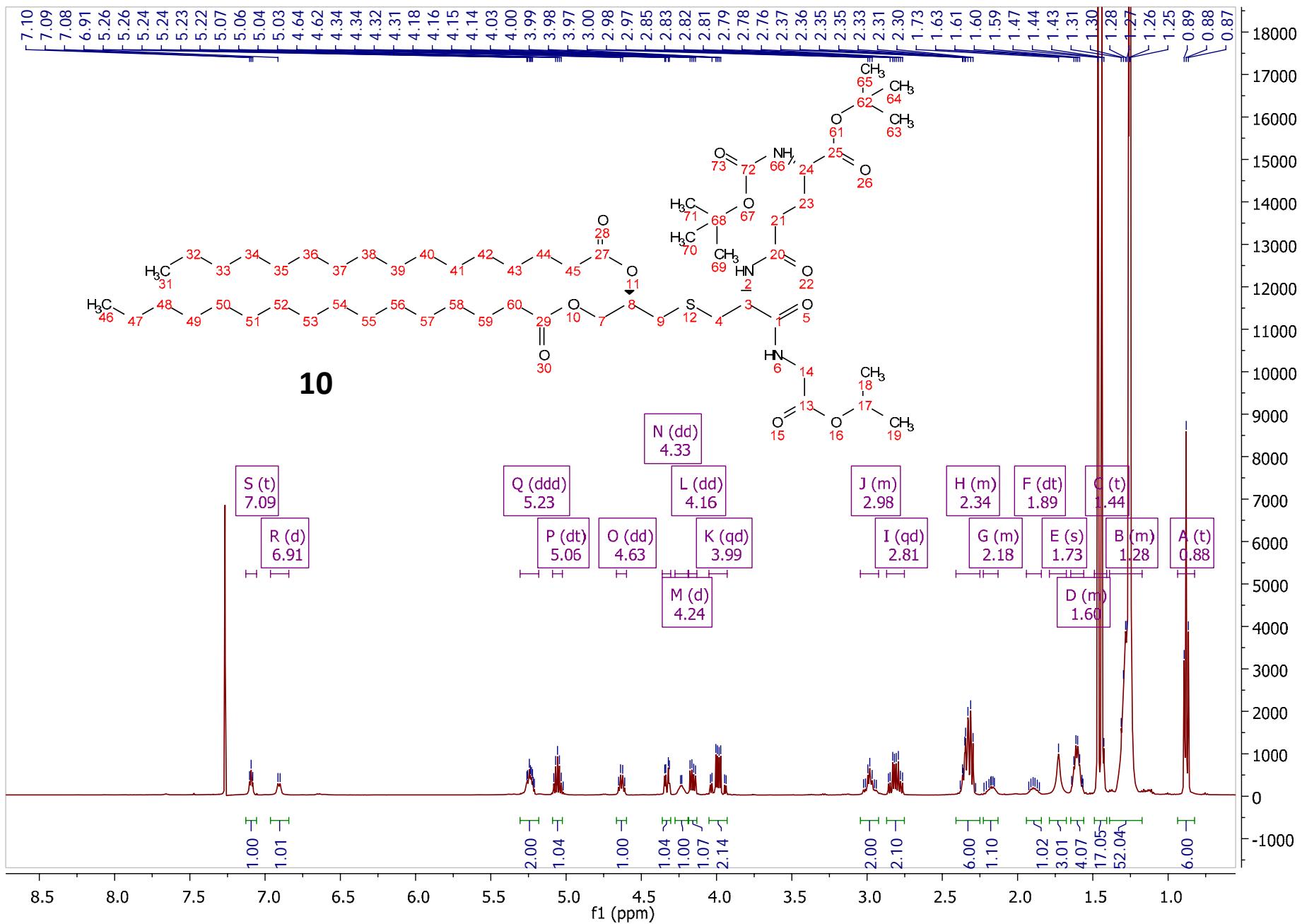






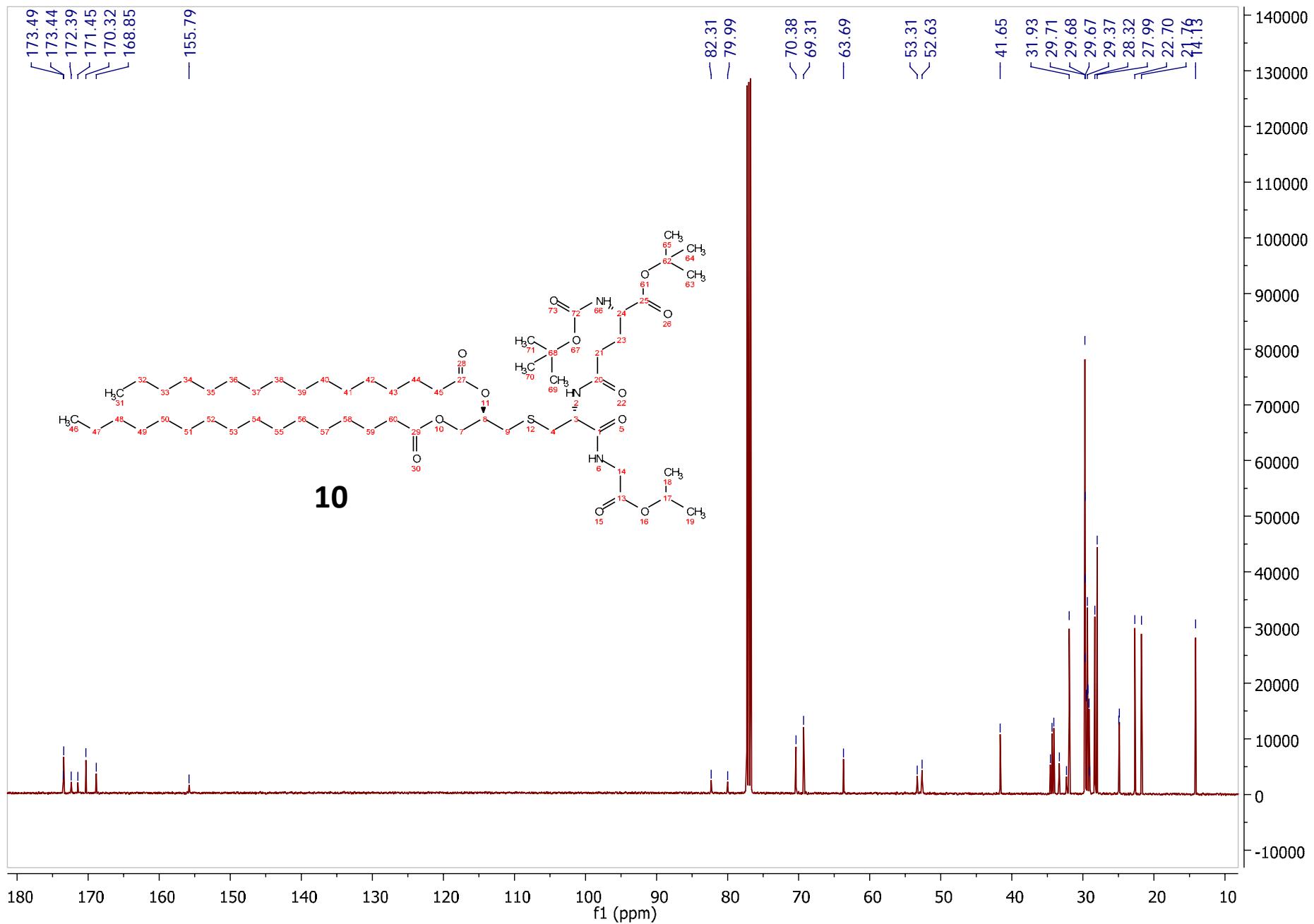
¹H Spectrum

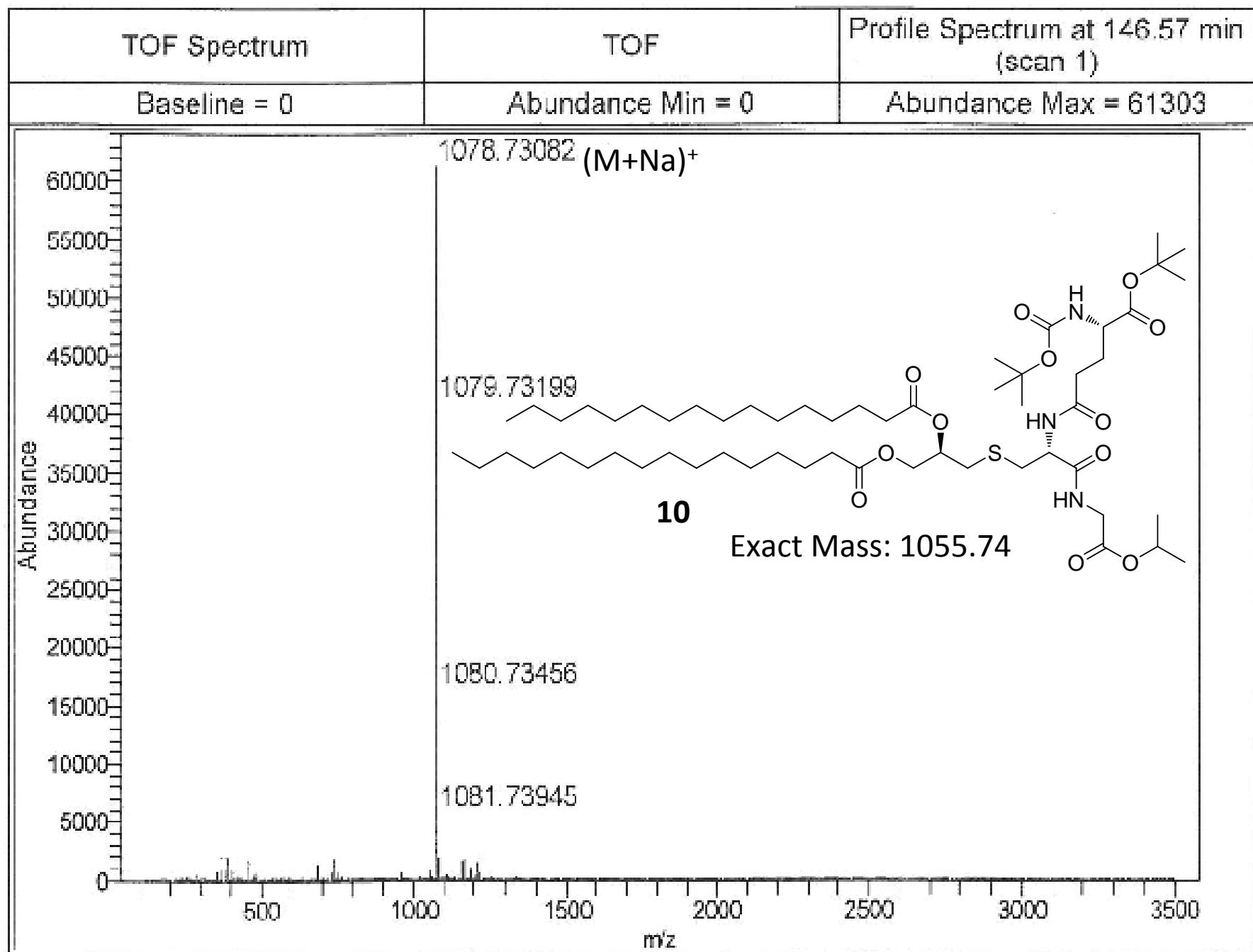
S69



¹³C Spectrum

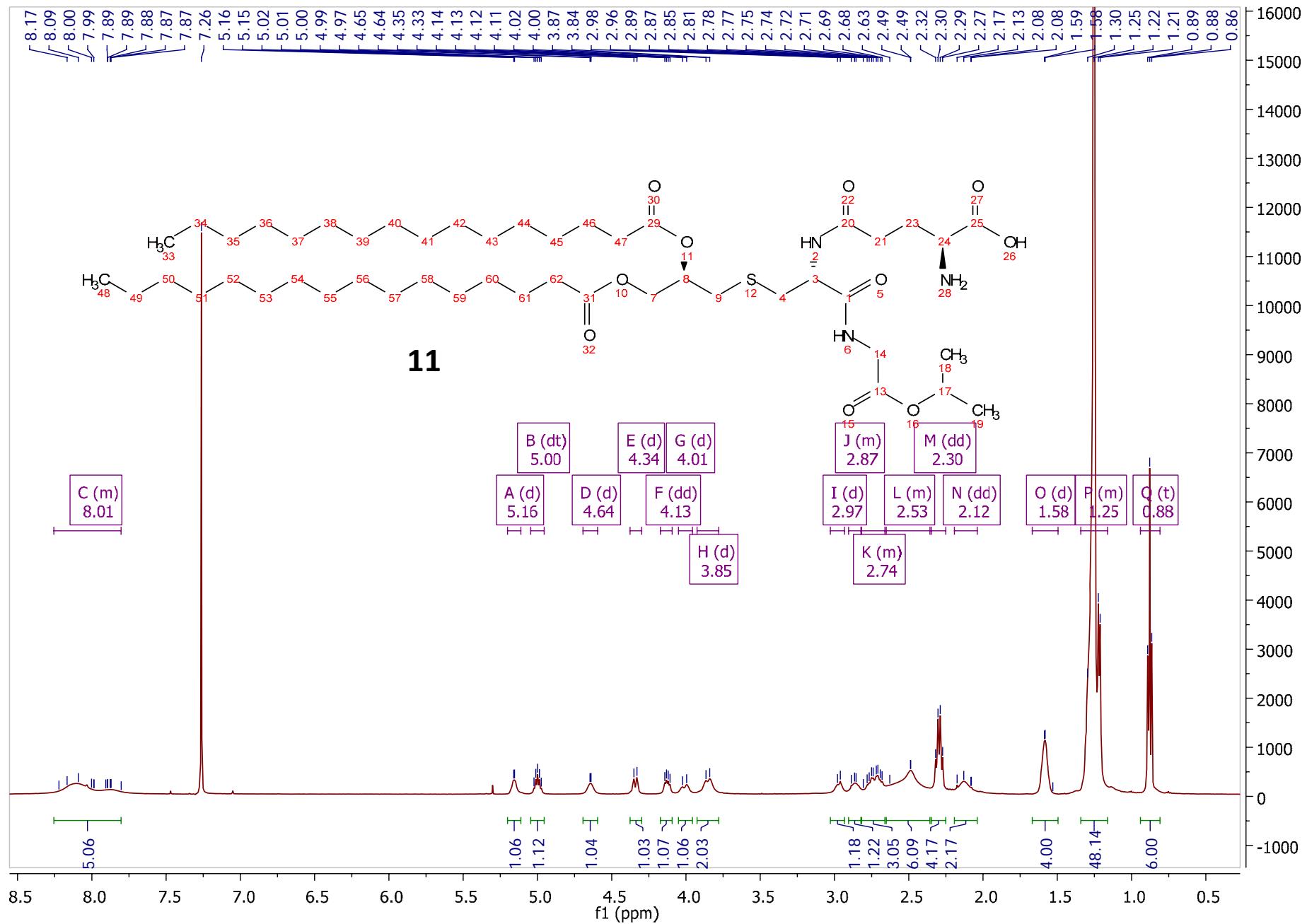
S70





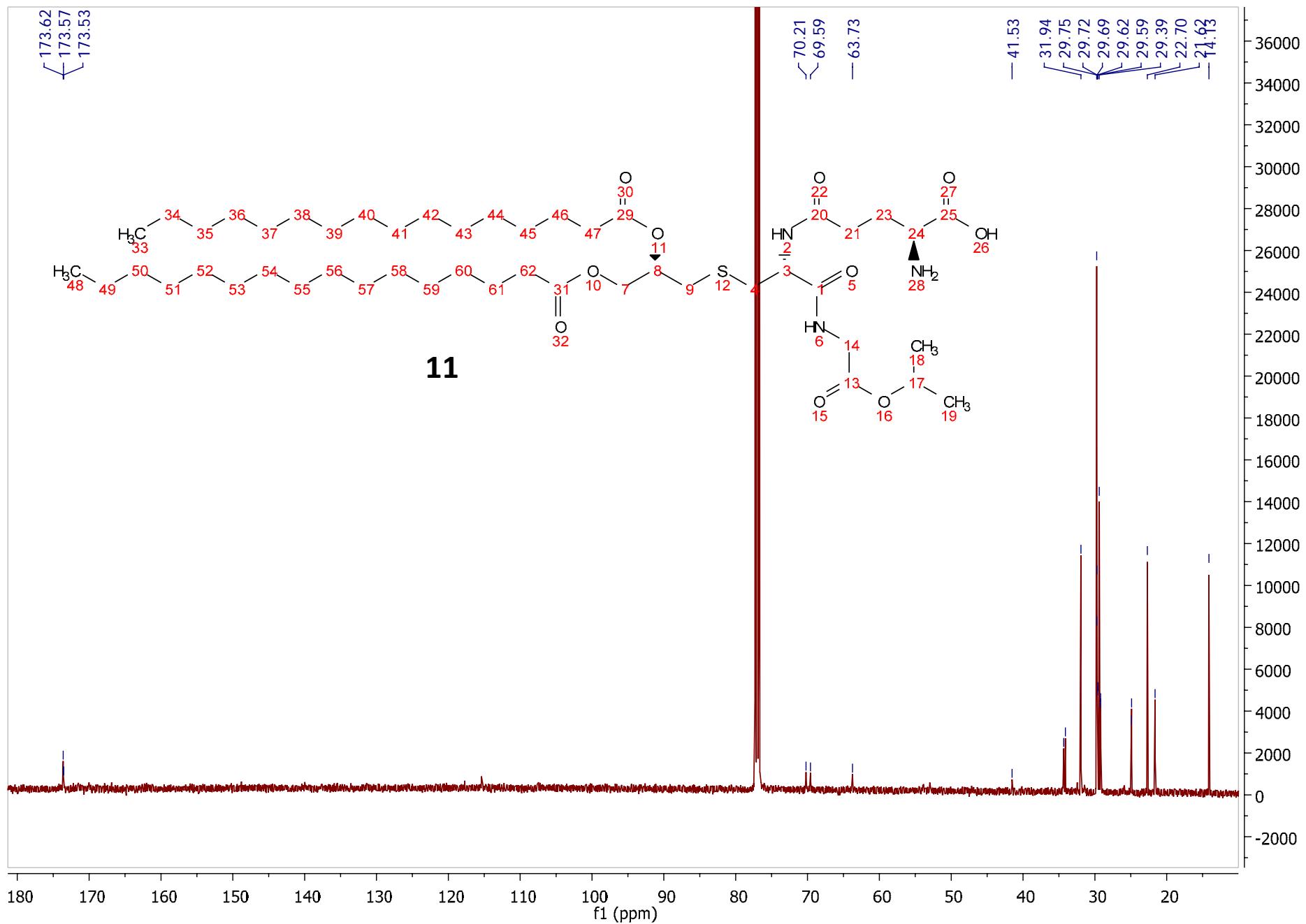
¹H Spectrum

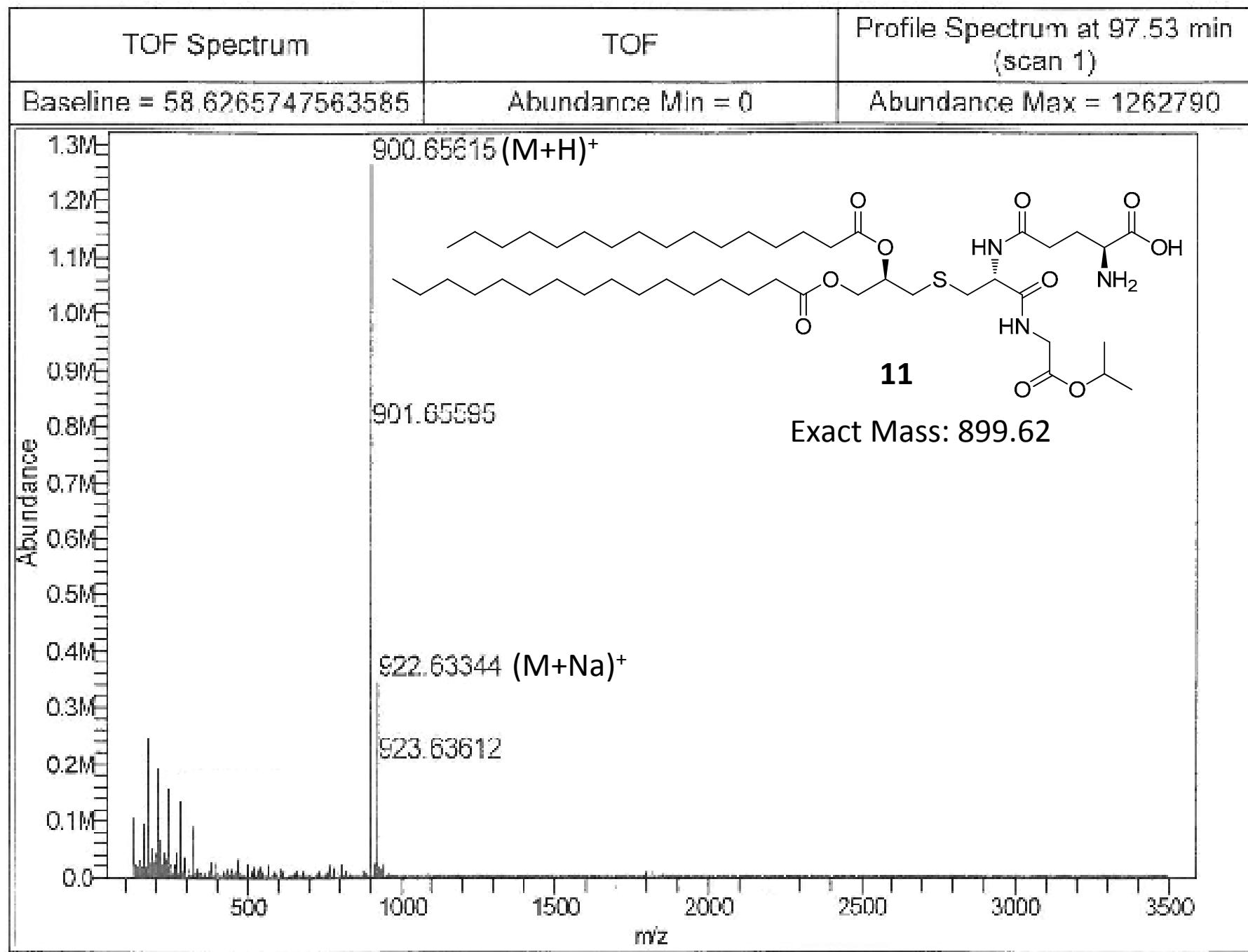
S72

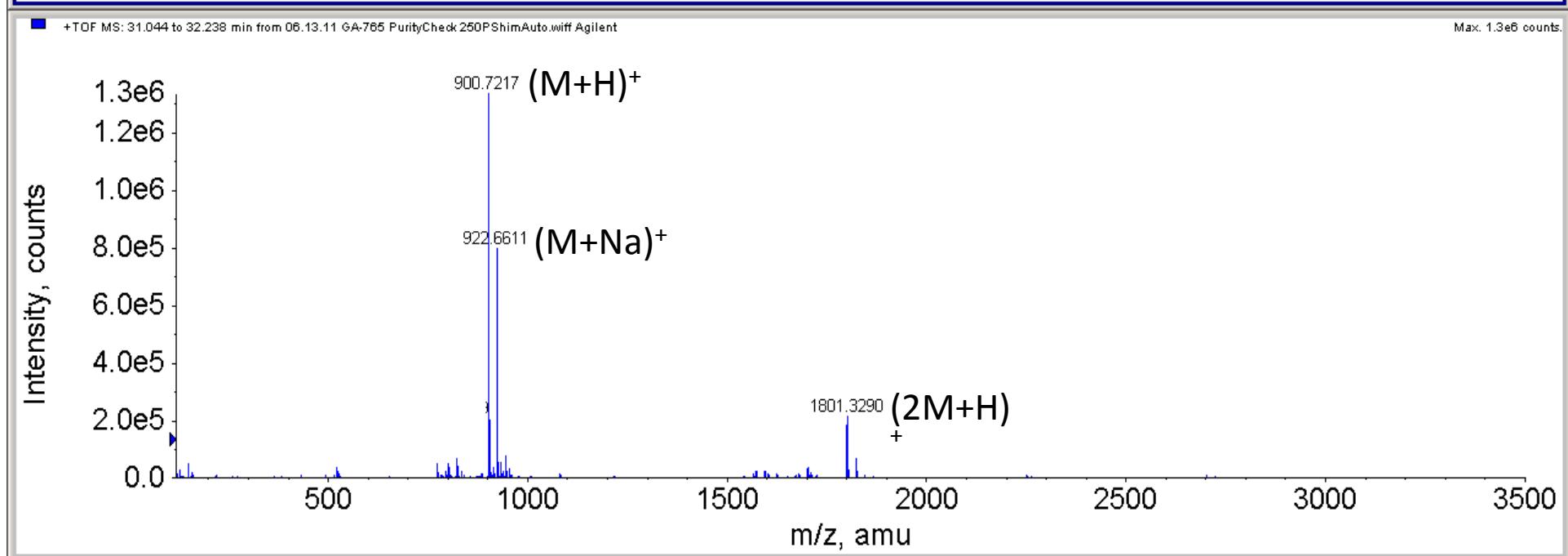
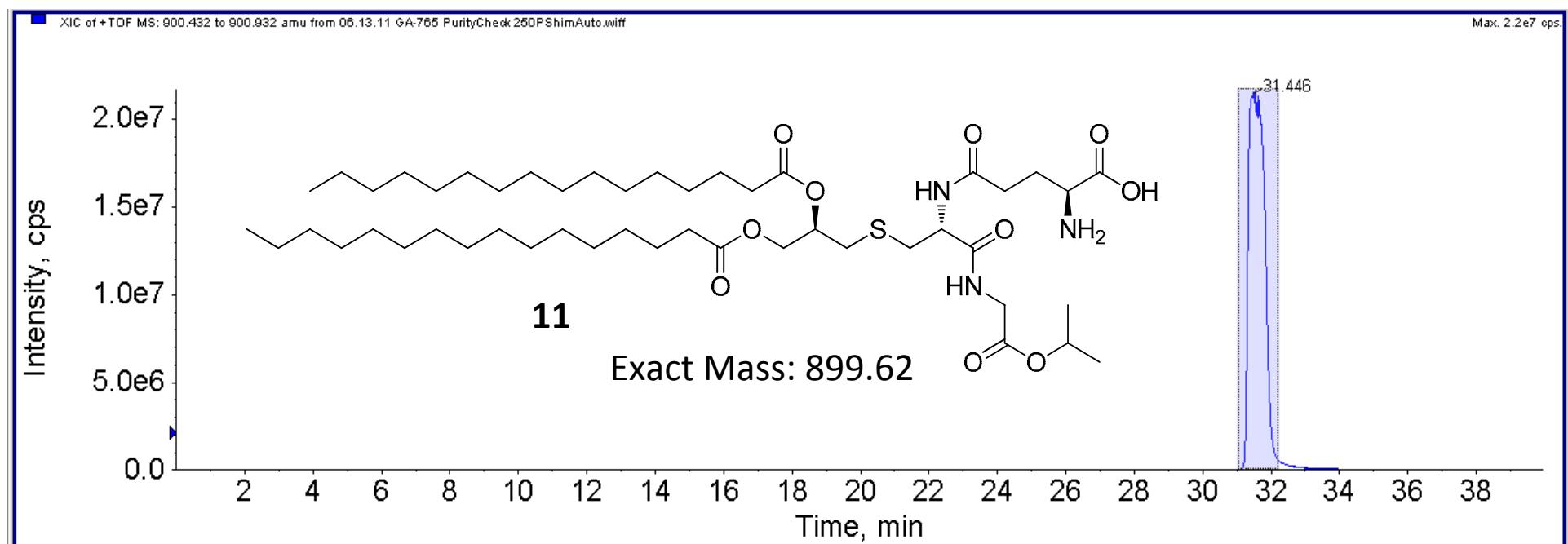


¹³C Spectrum

S73

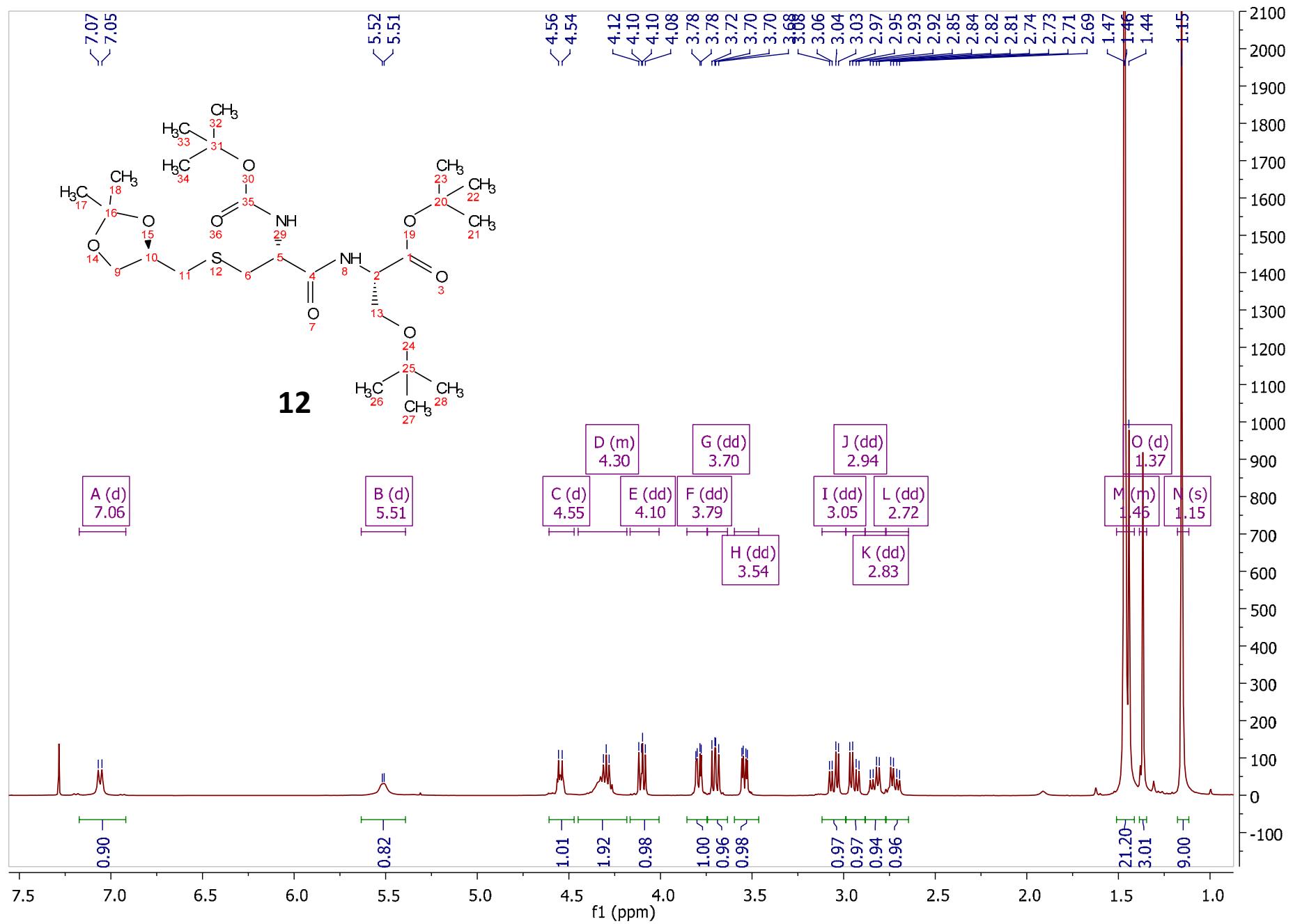






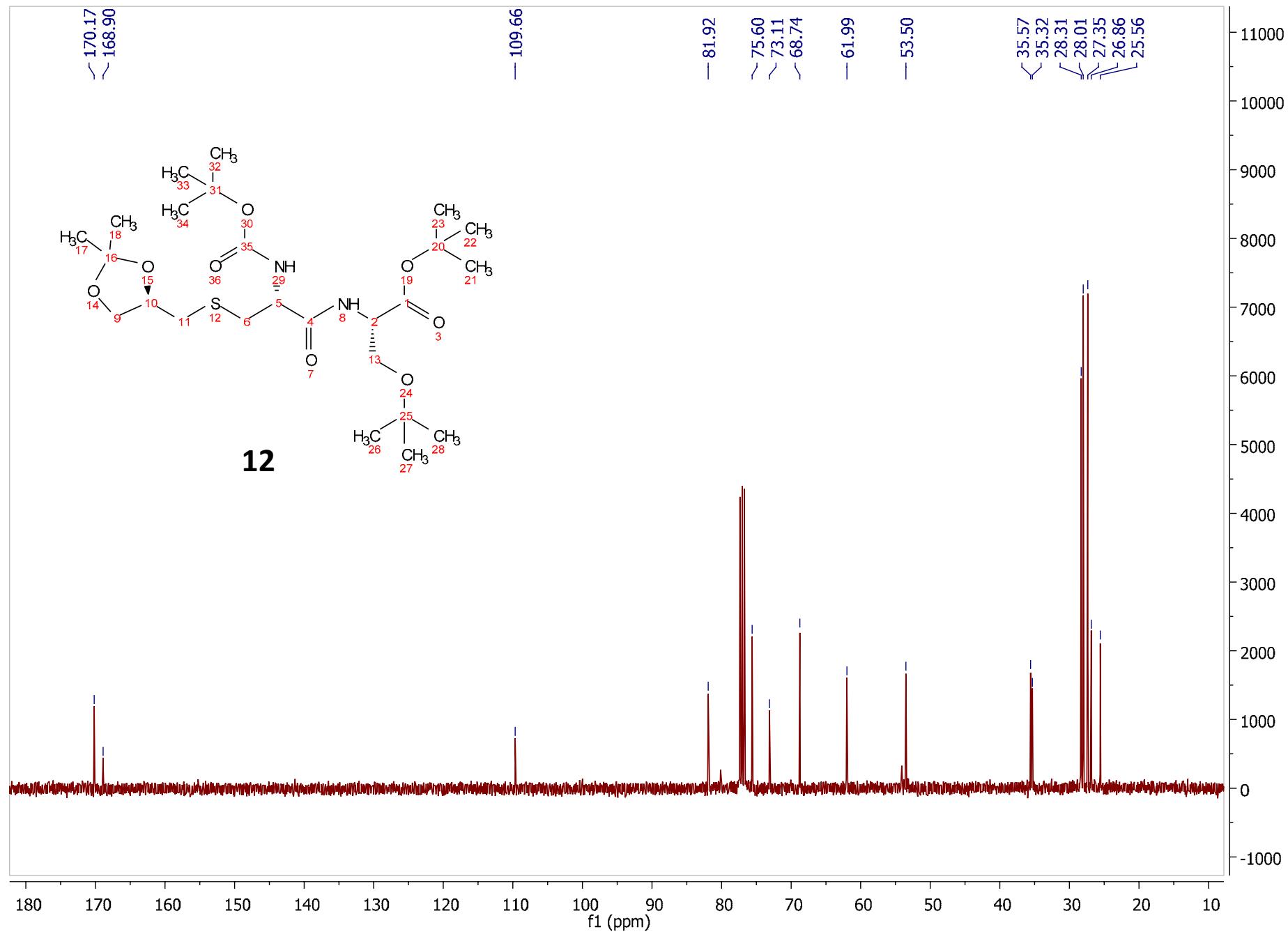
¹H Spectrum

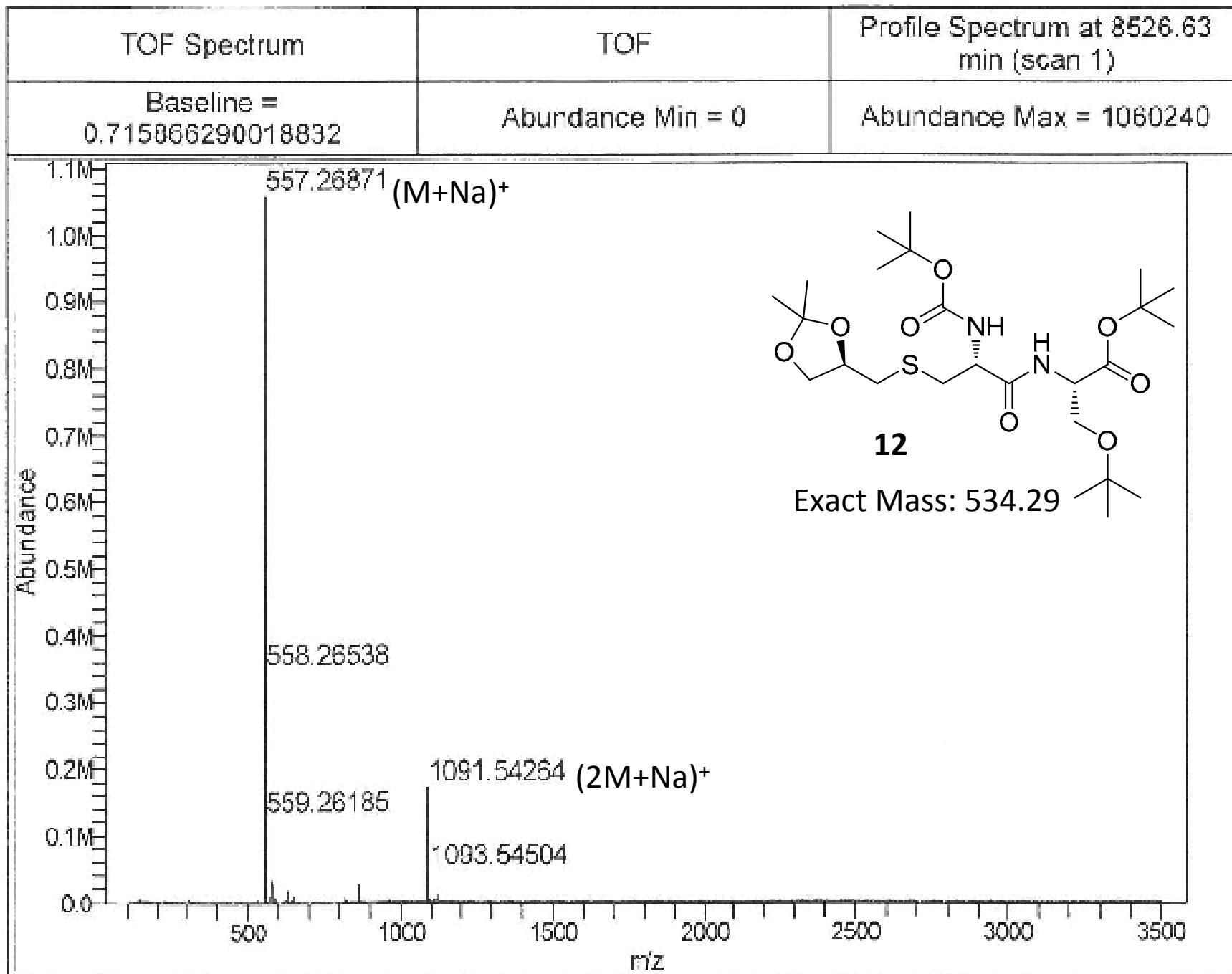
S76



¹³C Spectrum

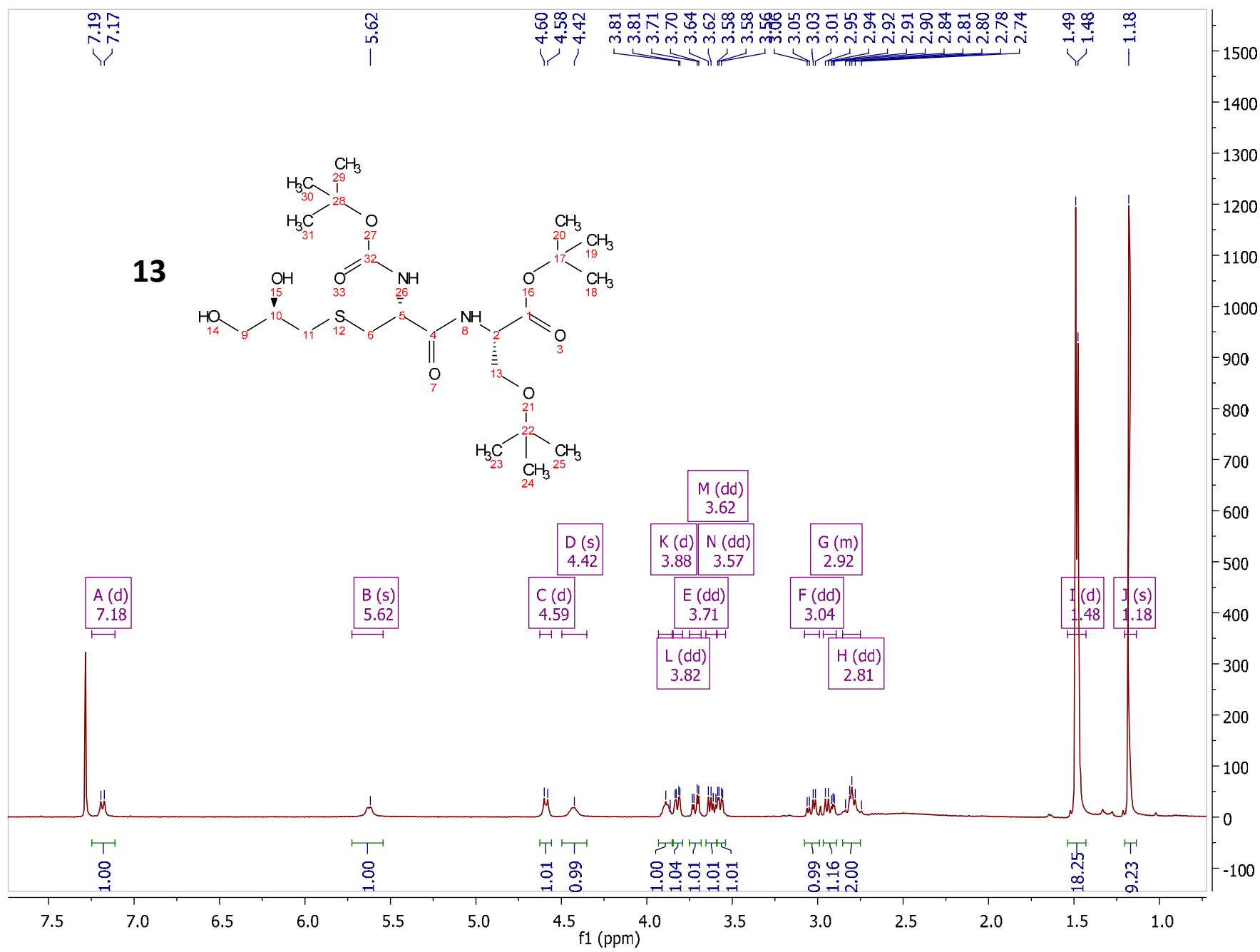
S77





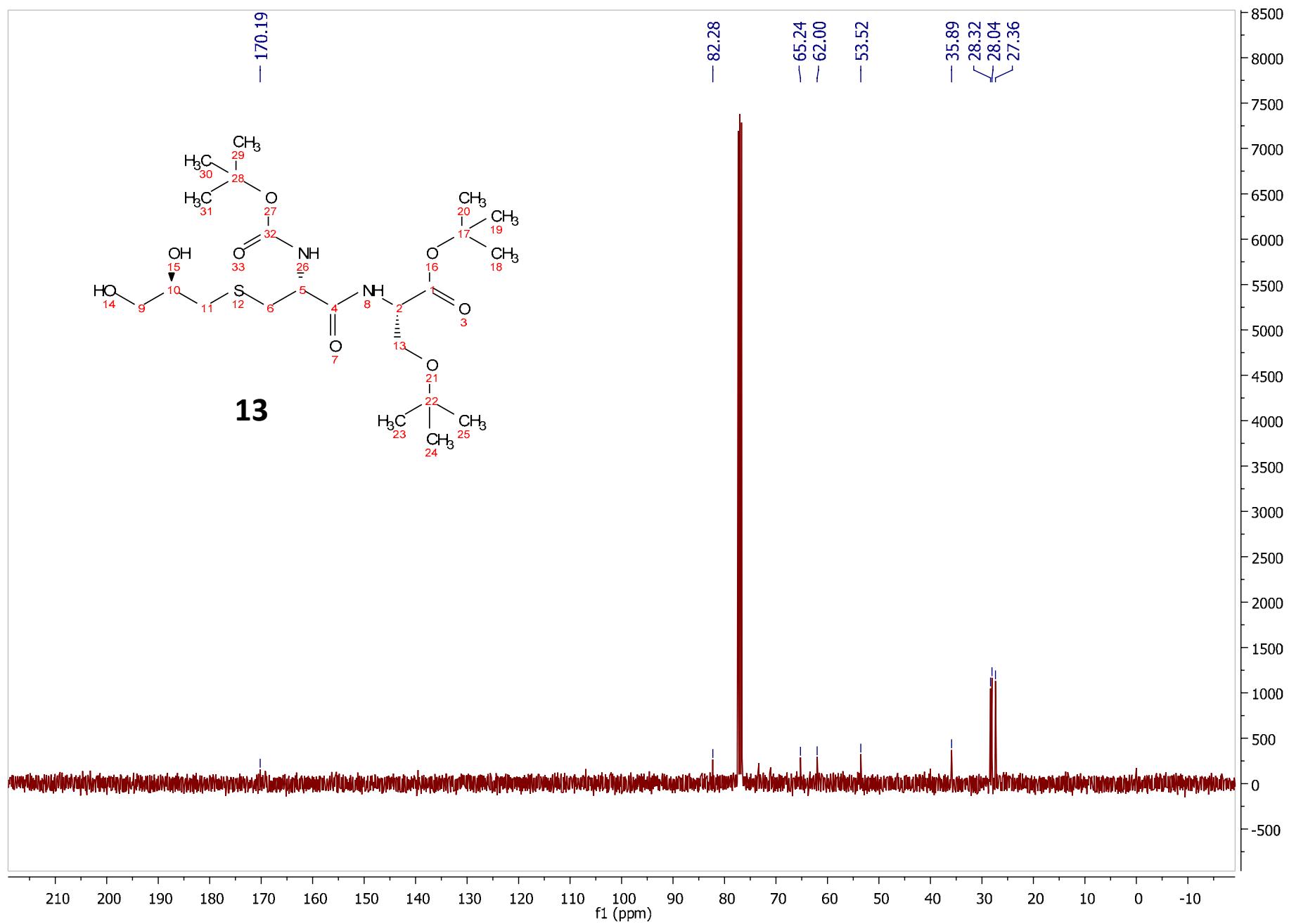
¹H Spectrum

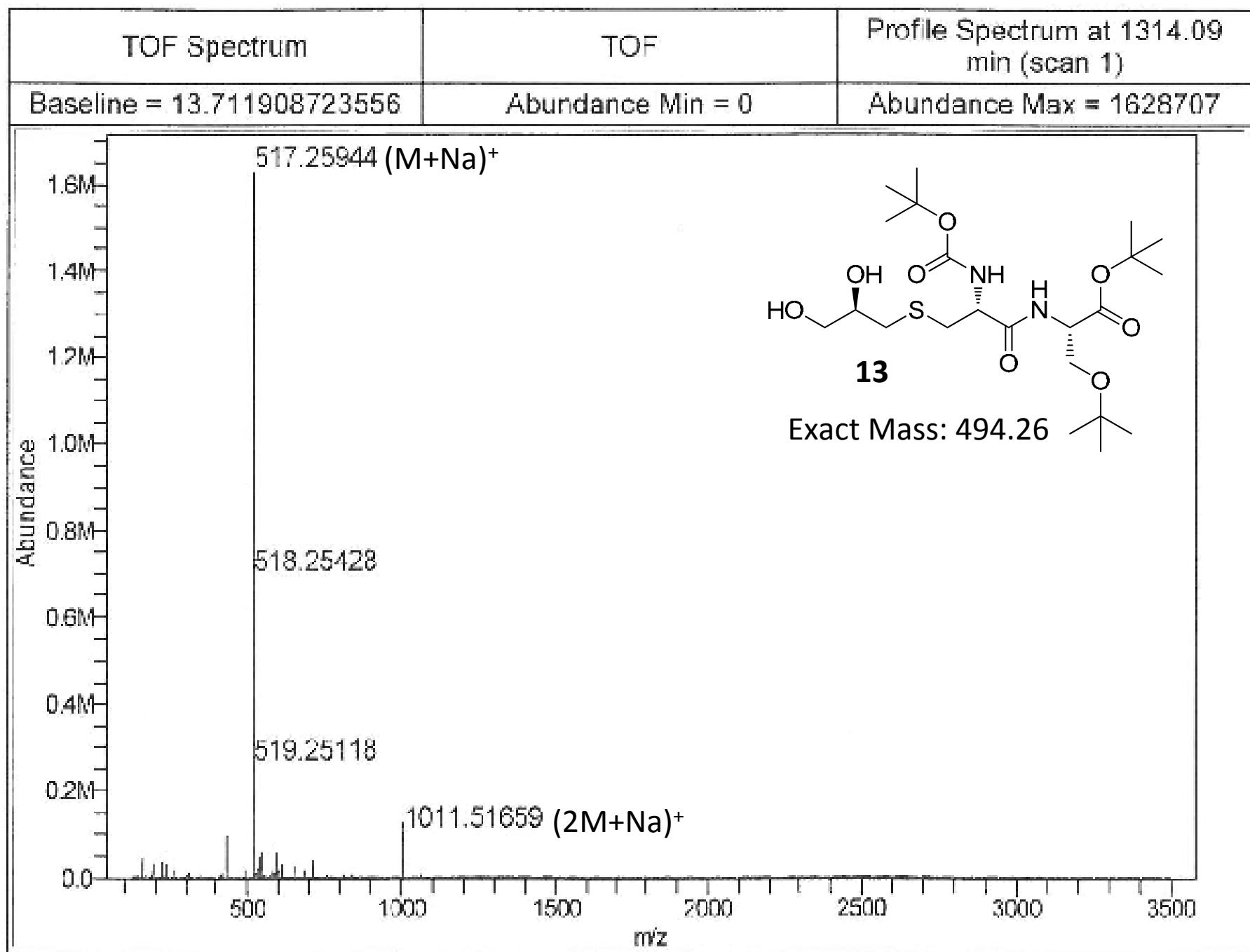
S79



¹³C Spectrum

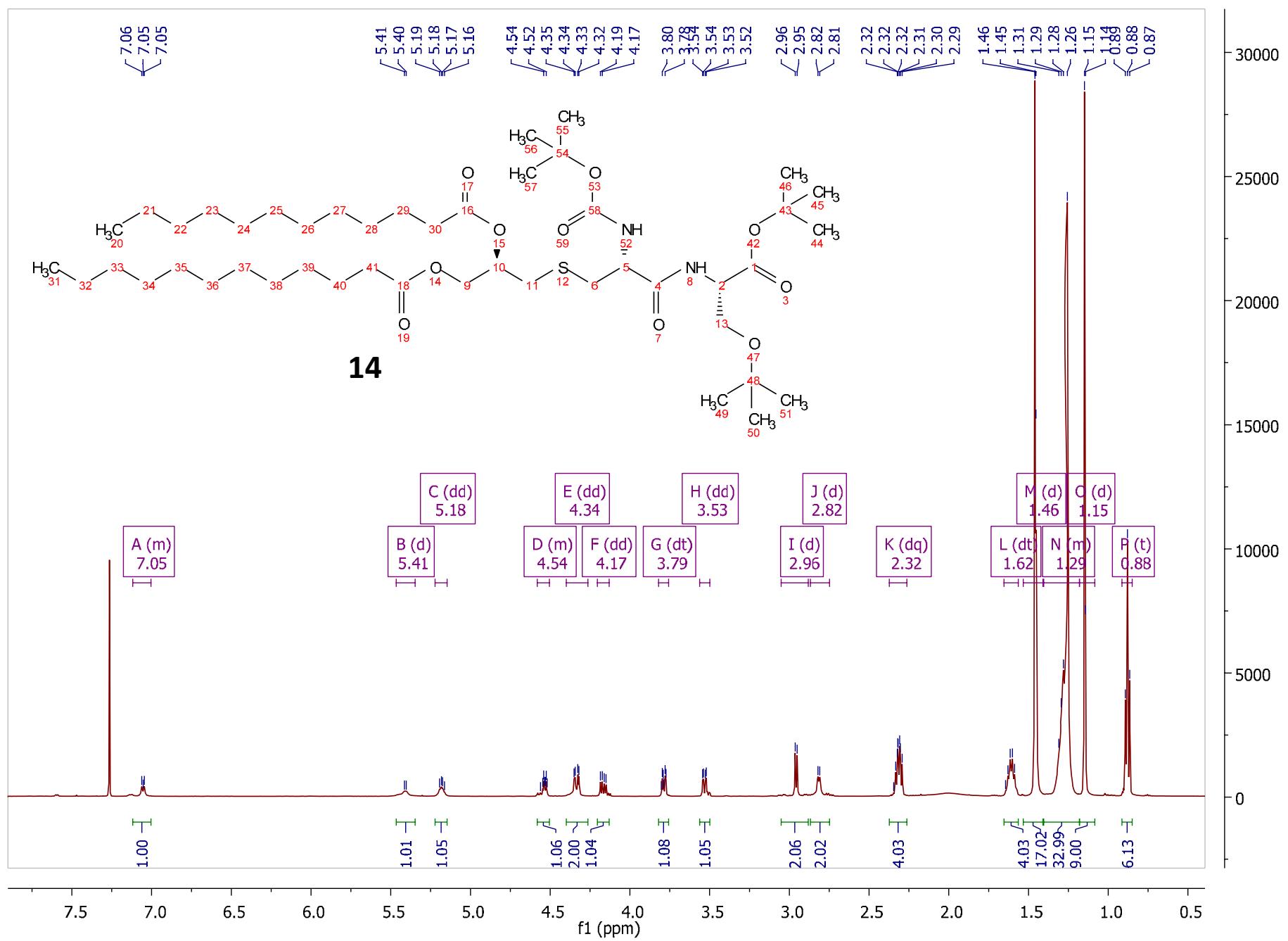
S80





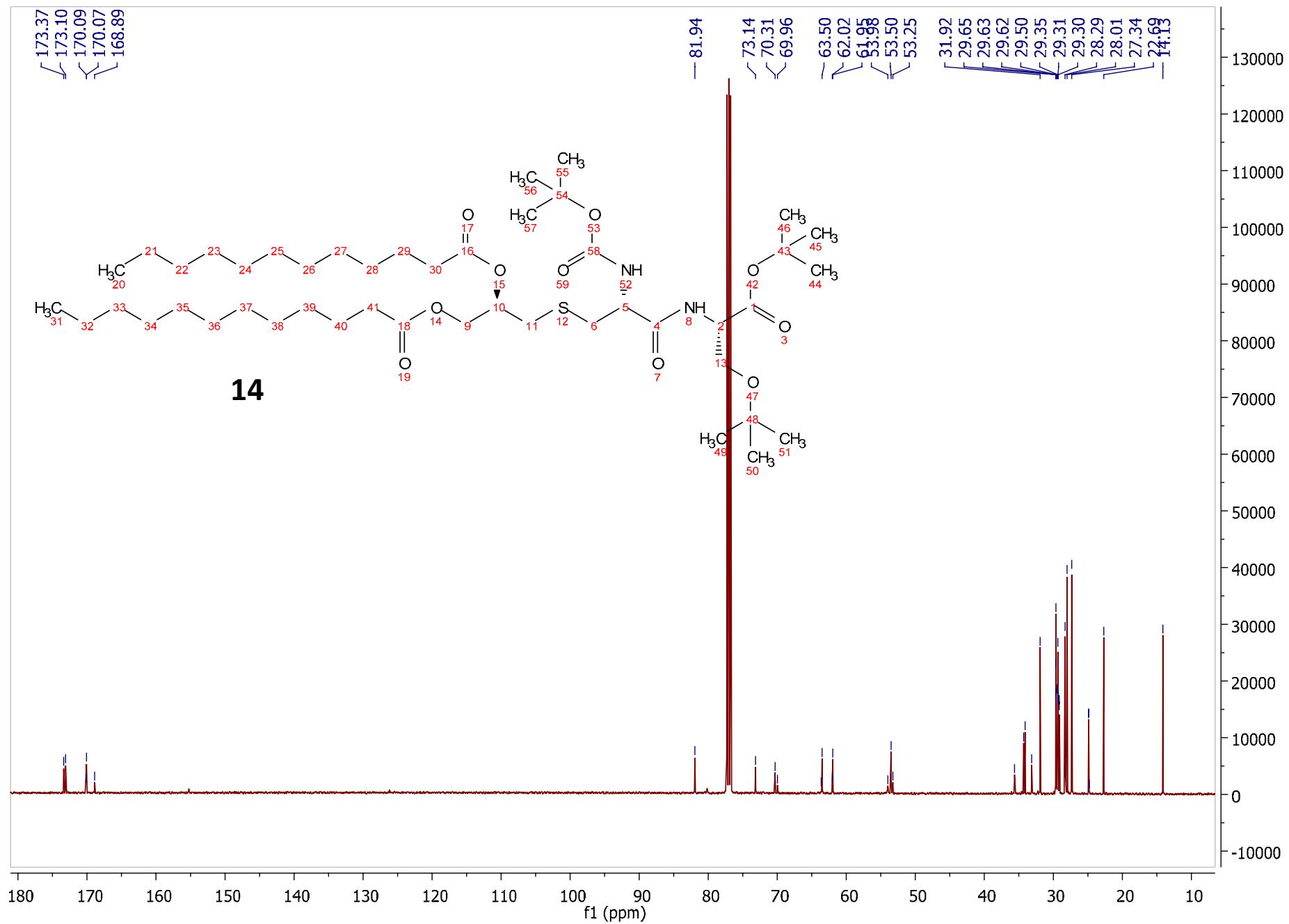
¹H Spectrum

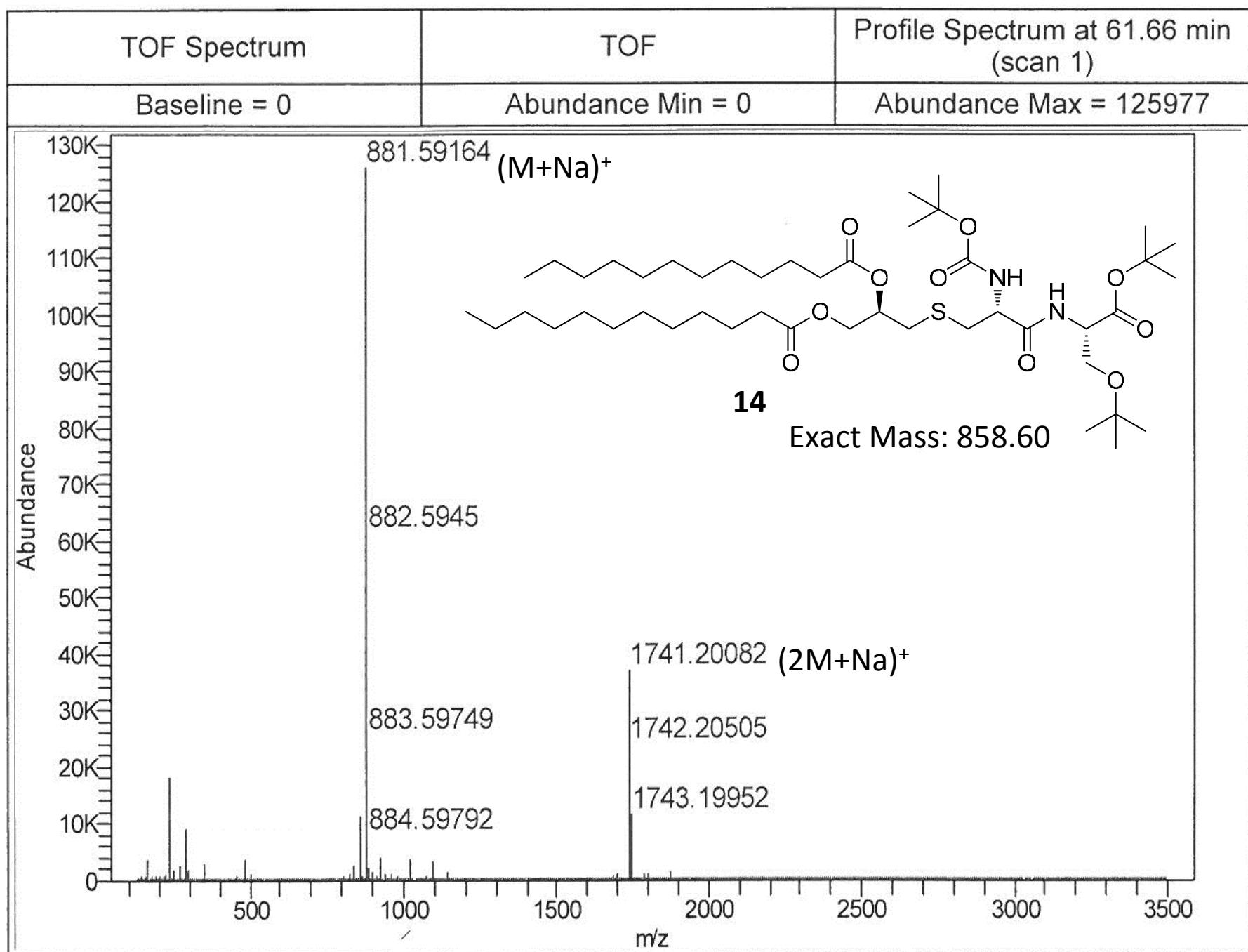
S82



¹³C Spectrum

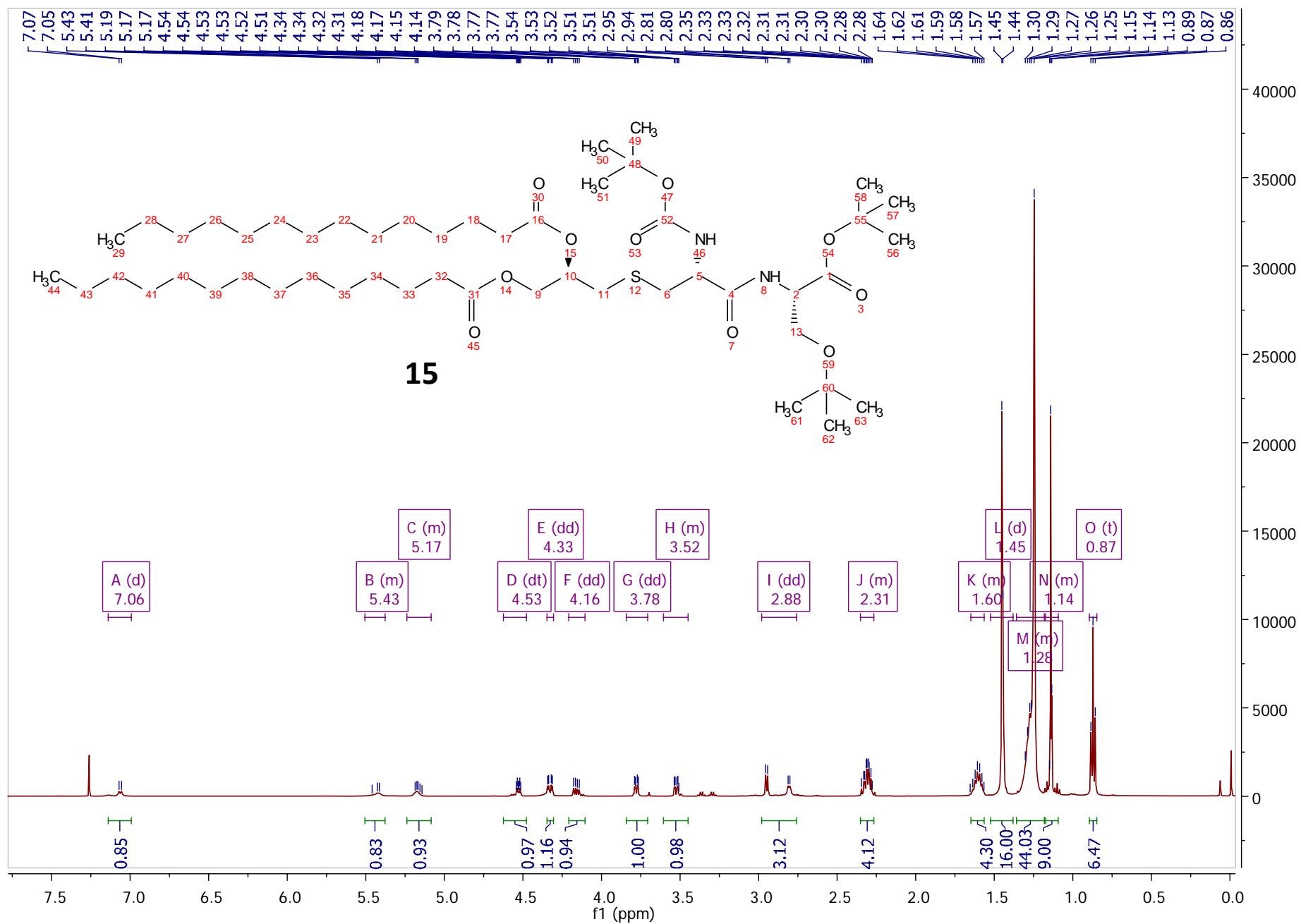
S83





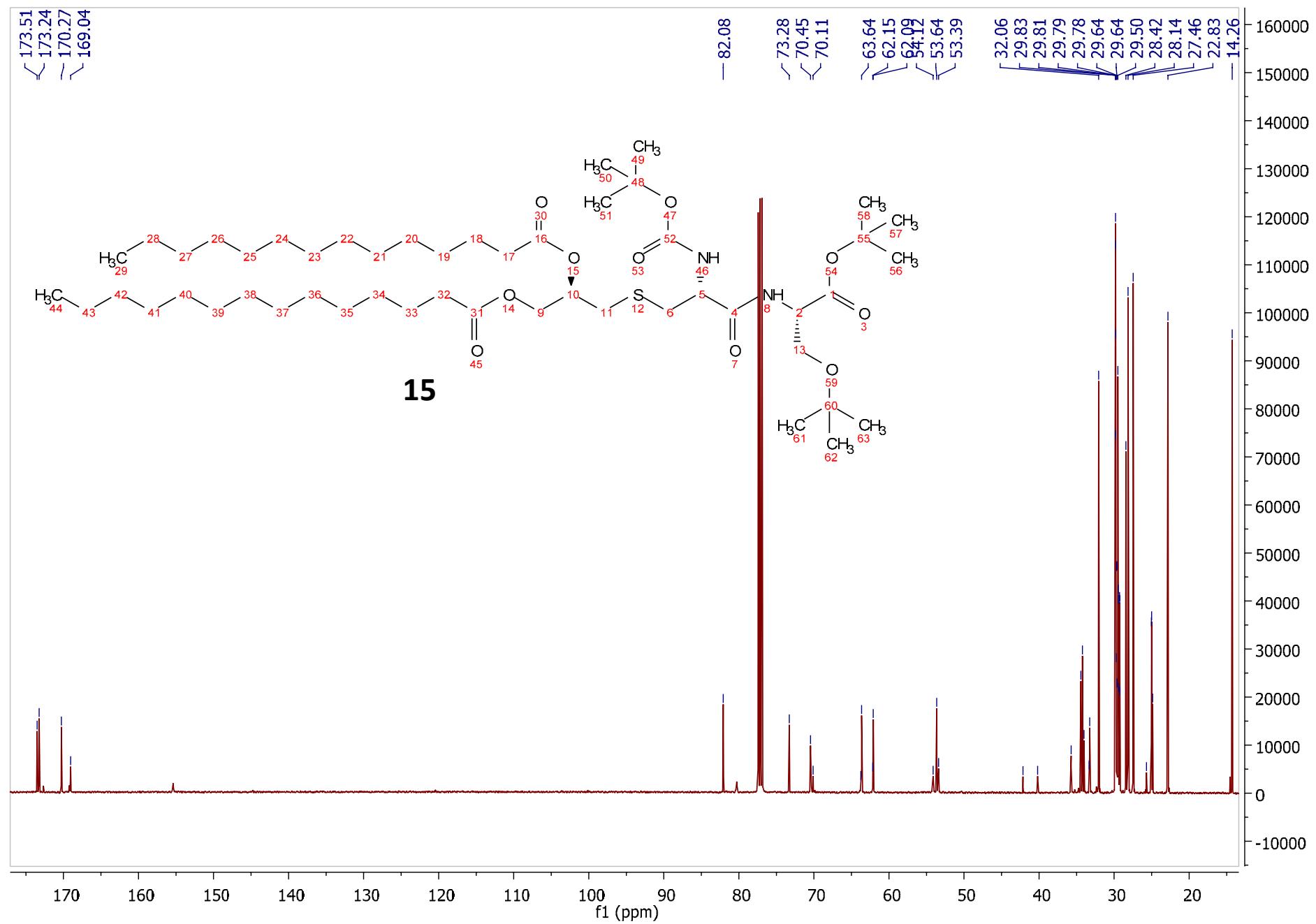
¹H Spectrum

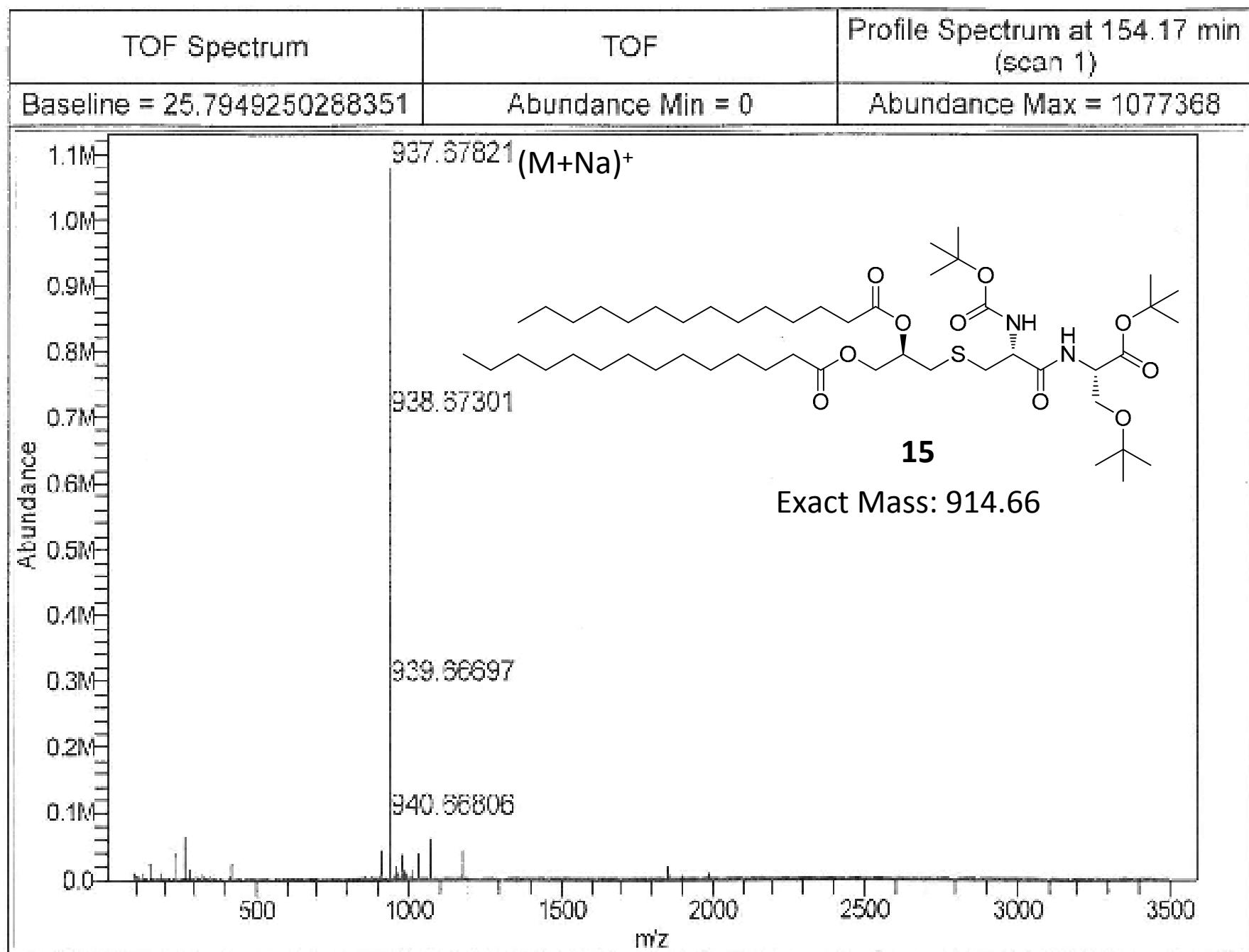
S85



¹³C Spectrum

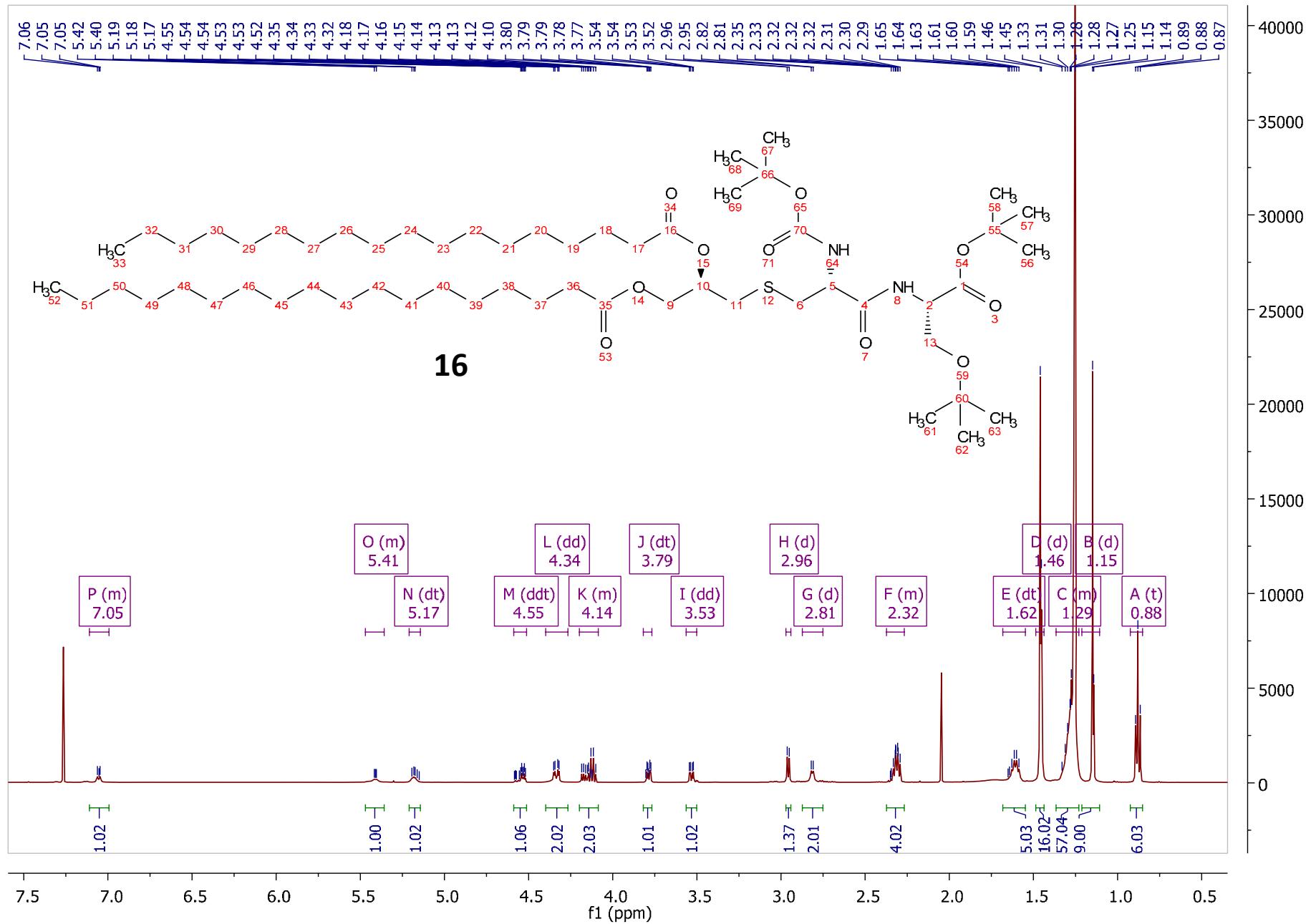
S86





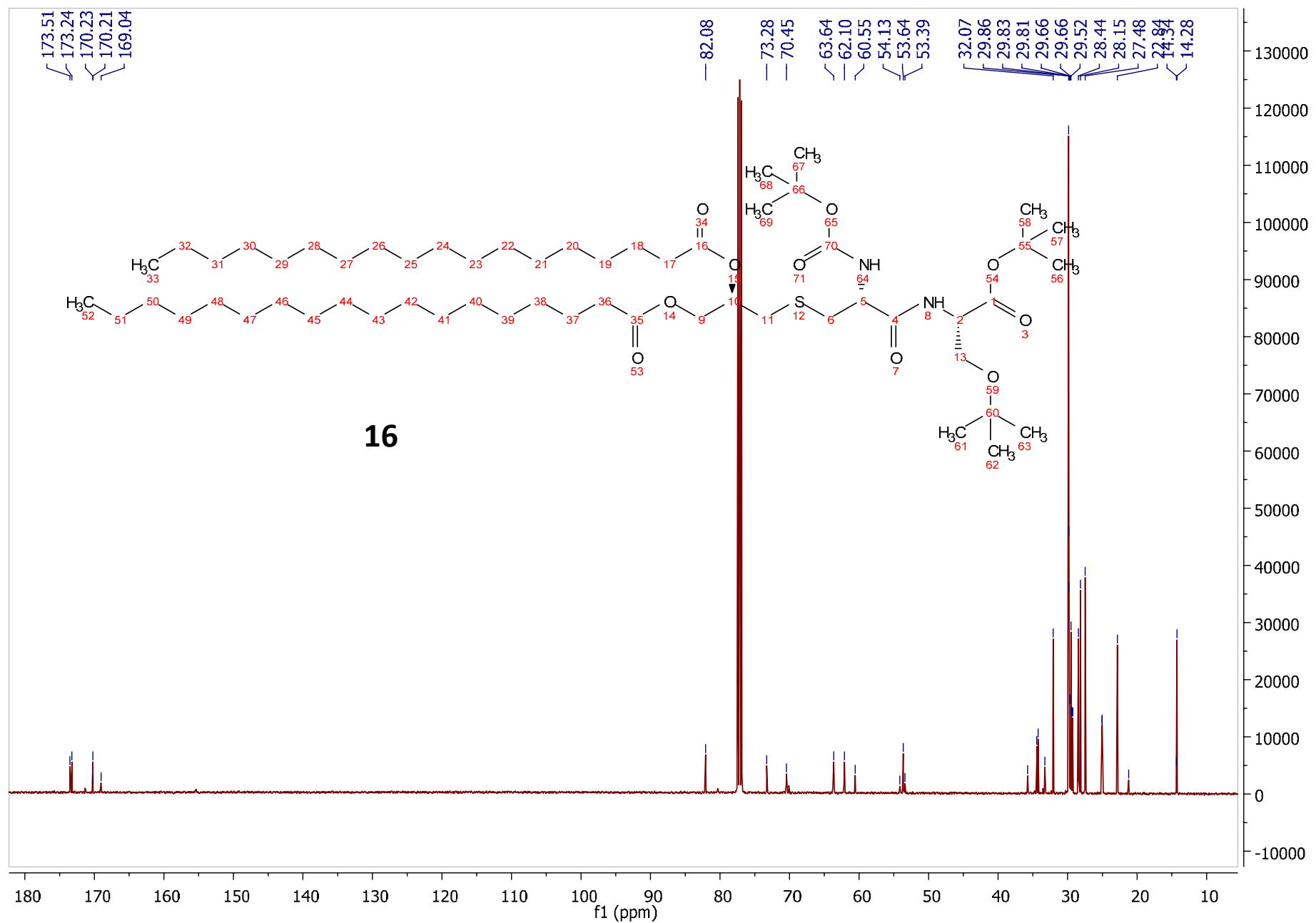
¹H Spectrum

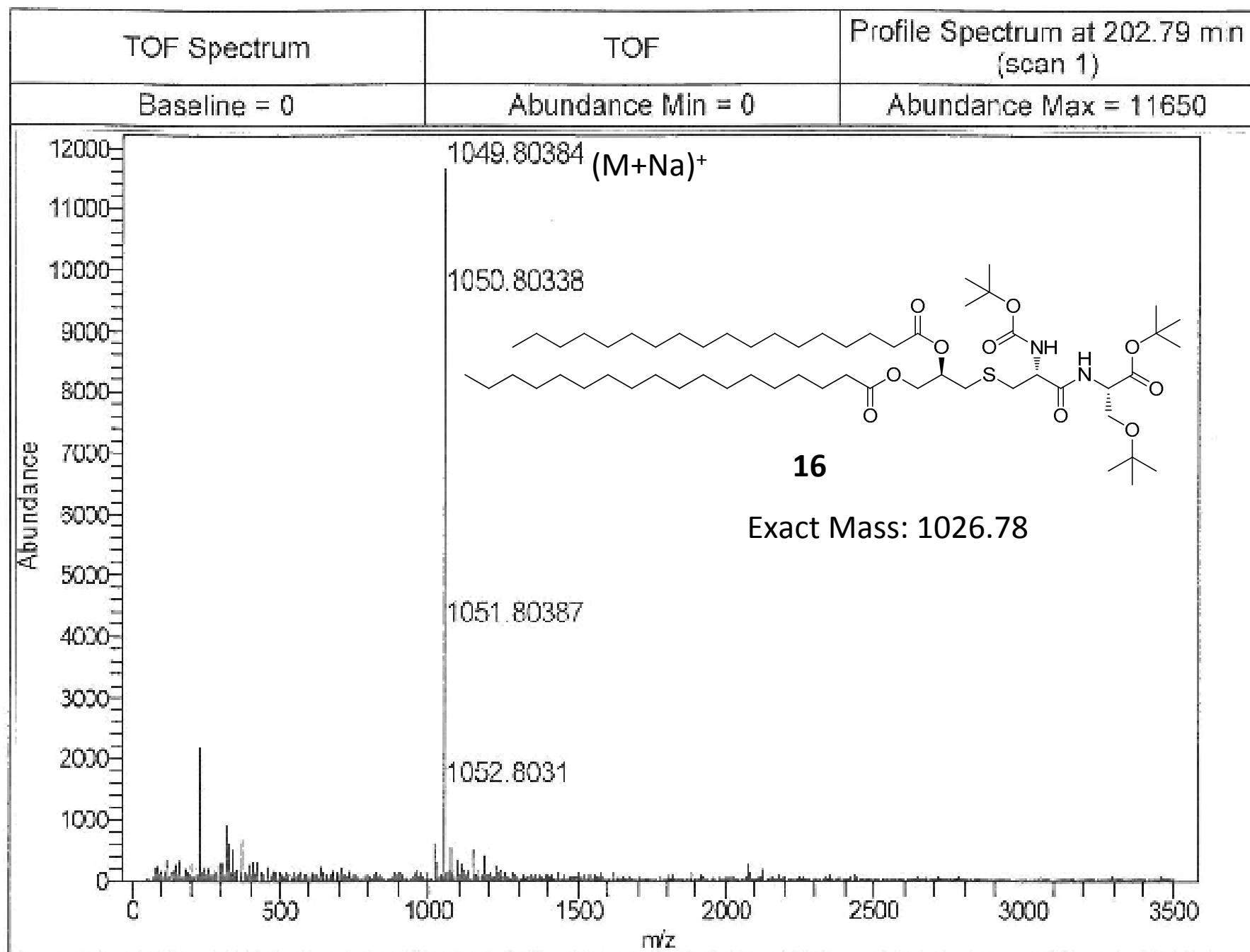
S88



¹³C Spectrum

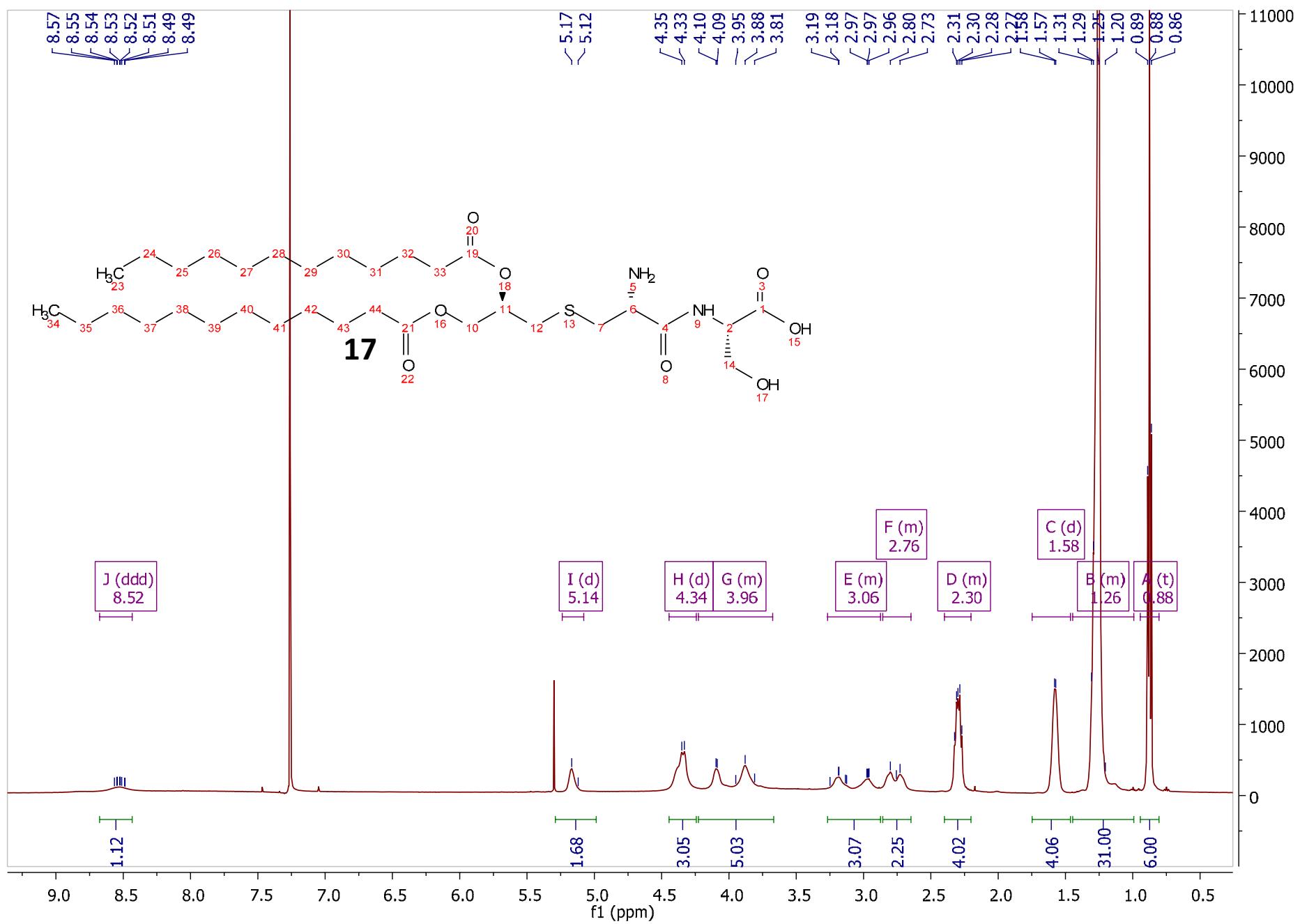
S89





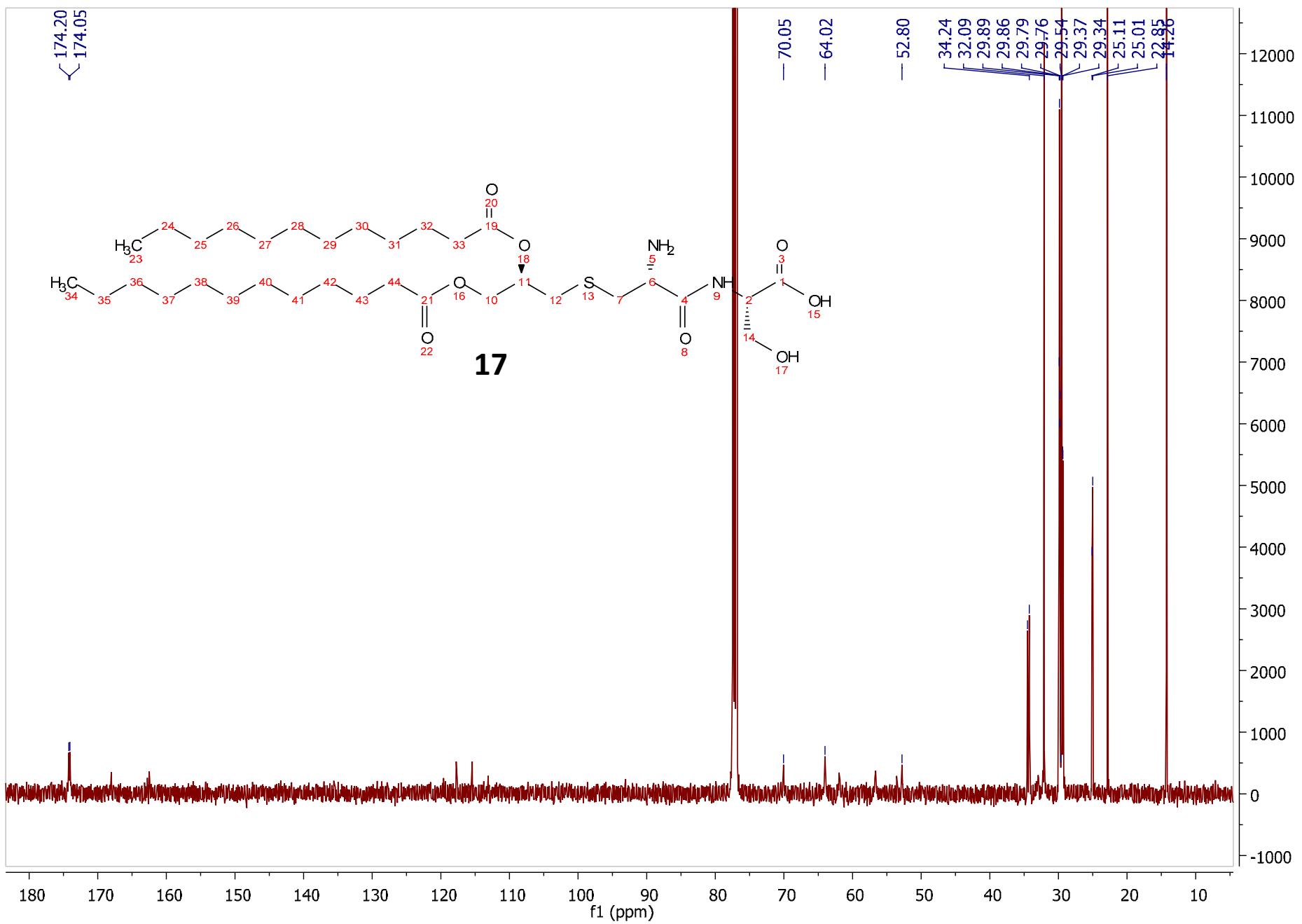
¹H Spectrum

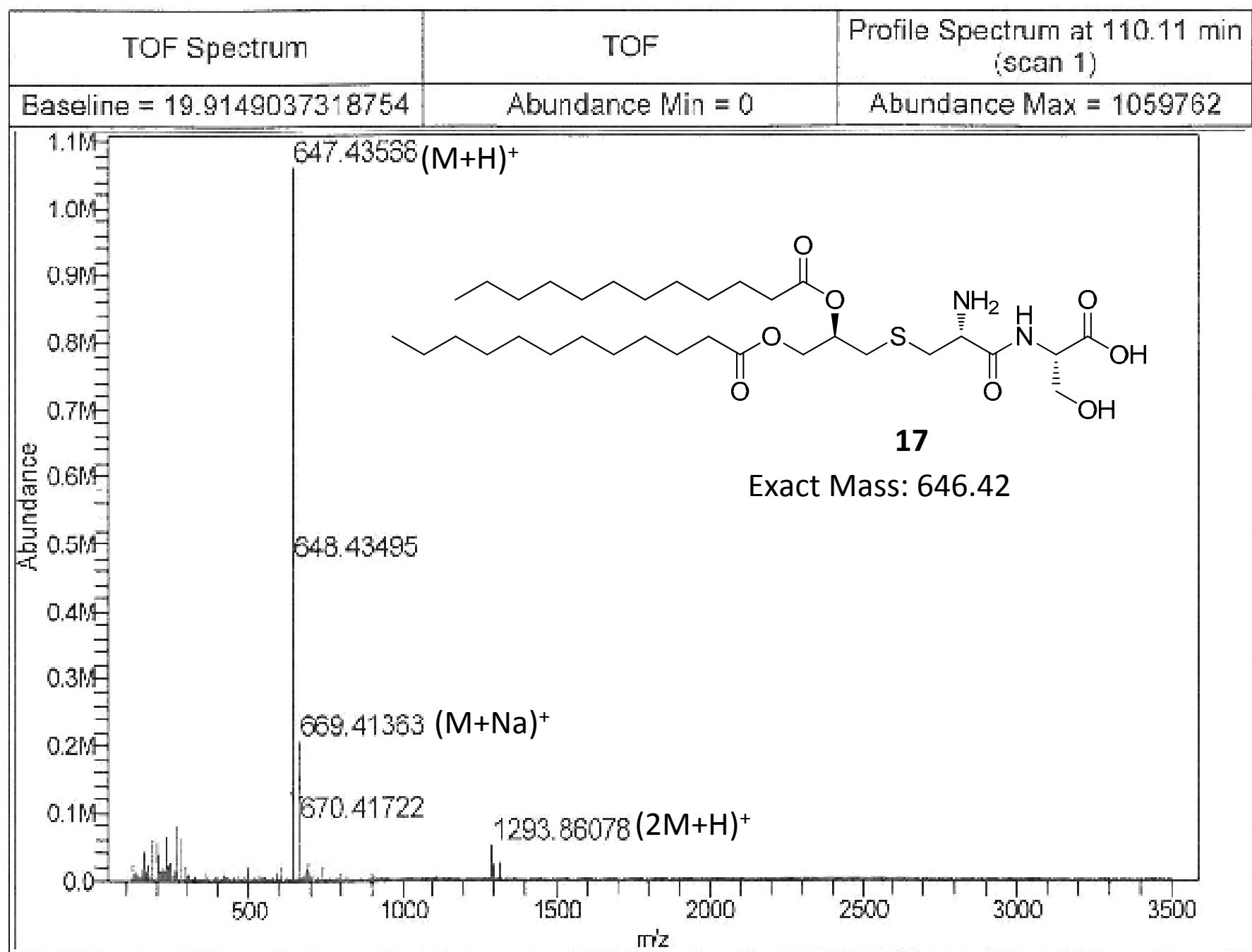
S91

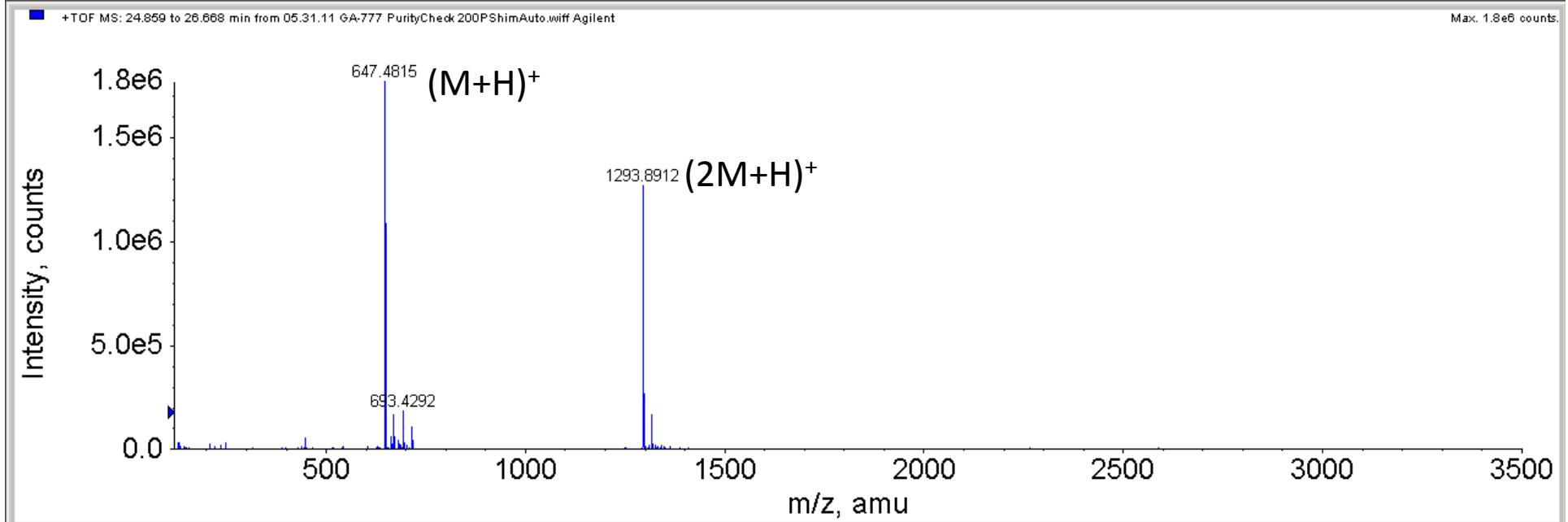
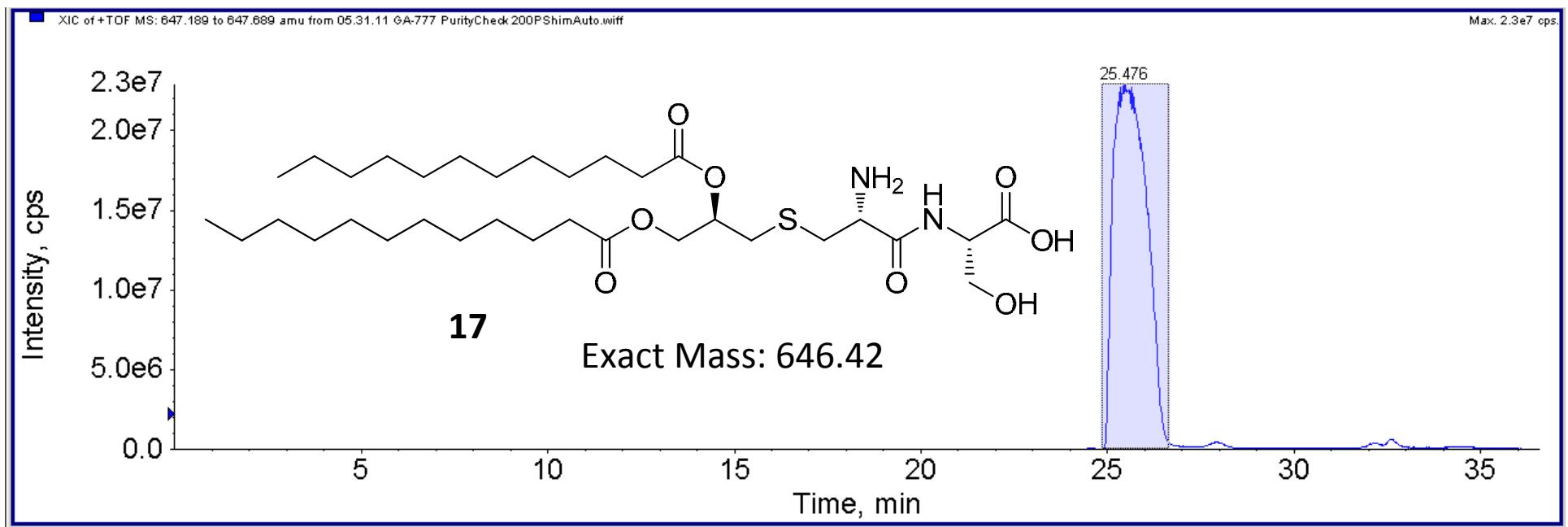


¹³C Spectrum

S92

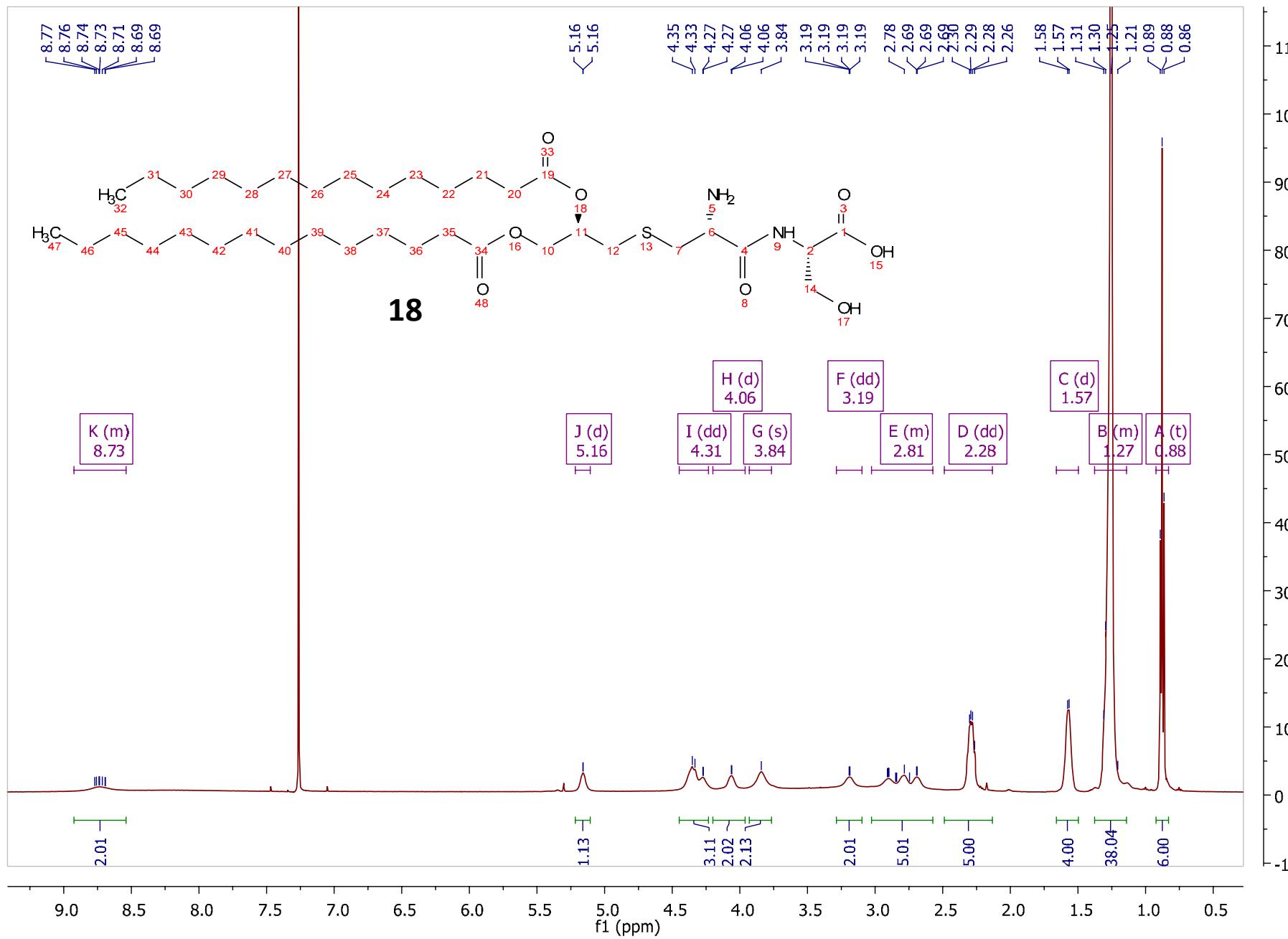






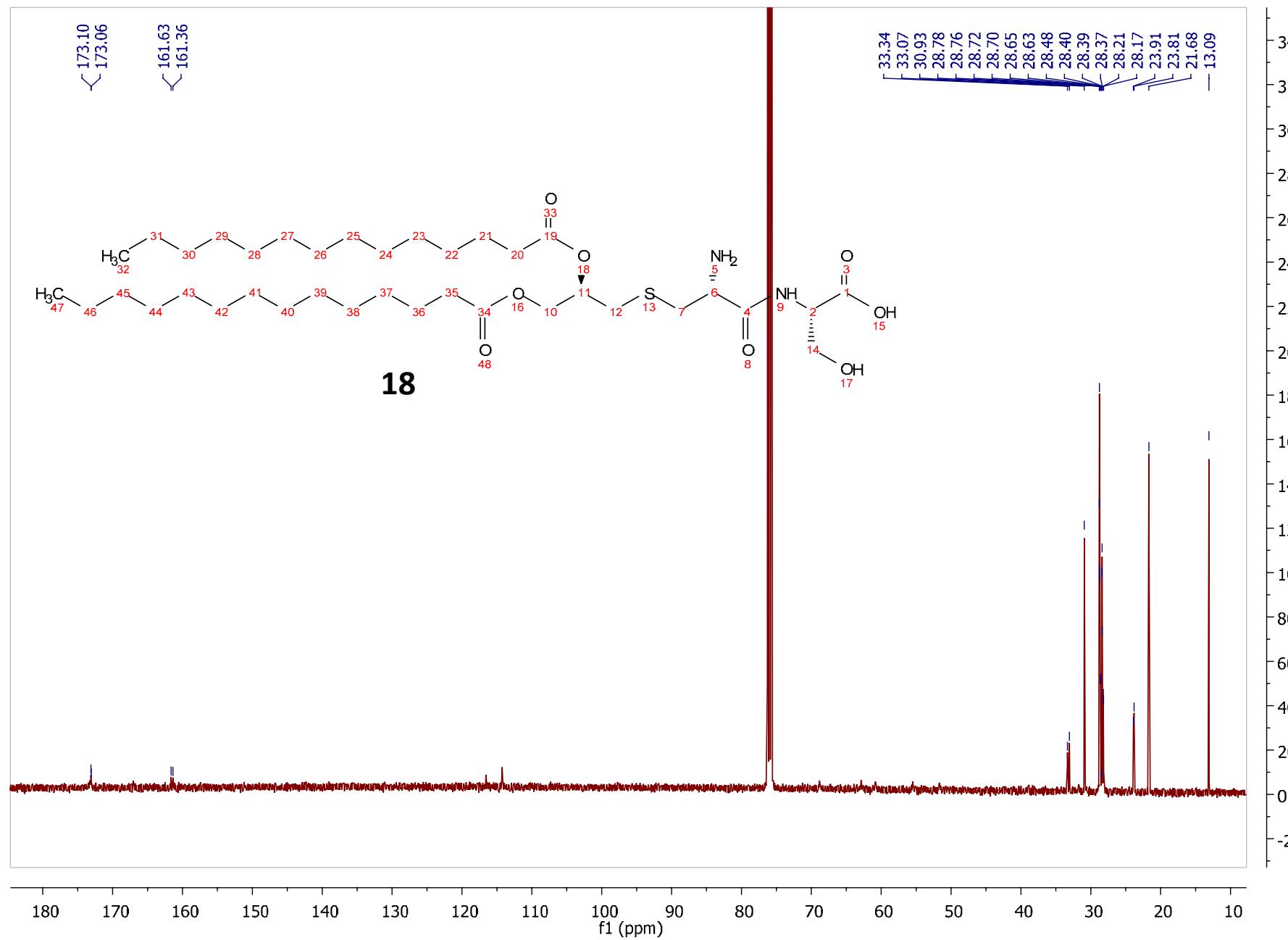
¹H Spectrum

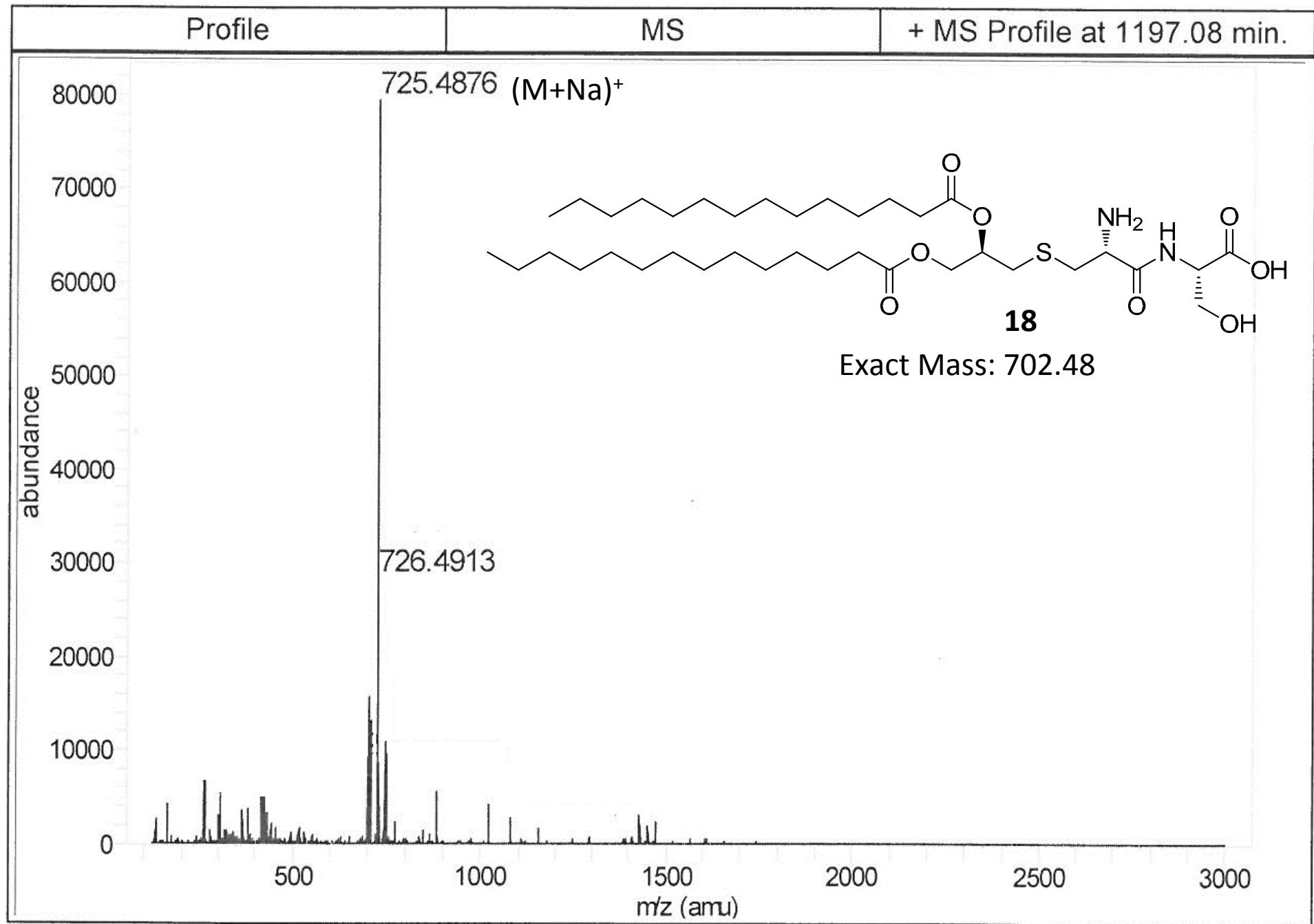
S95

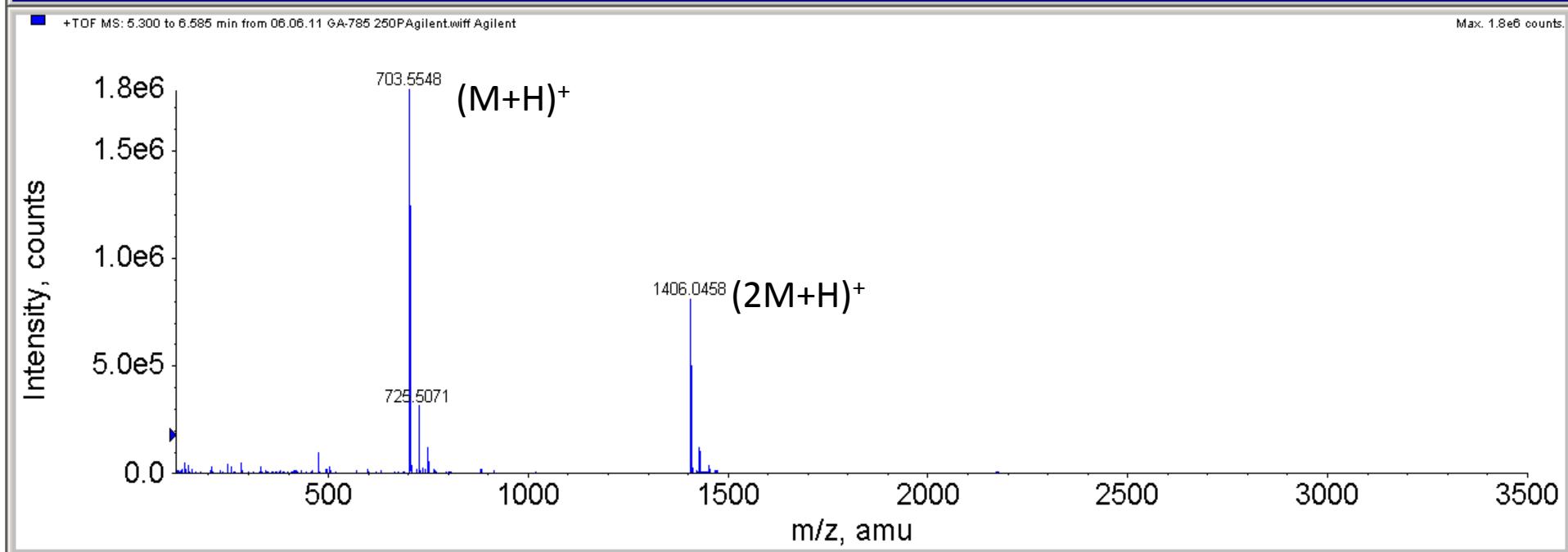
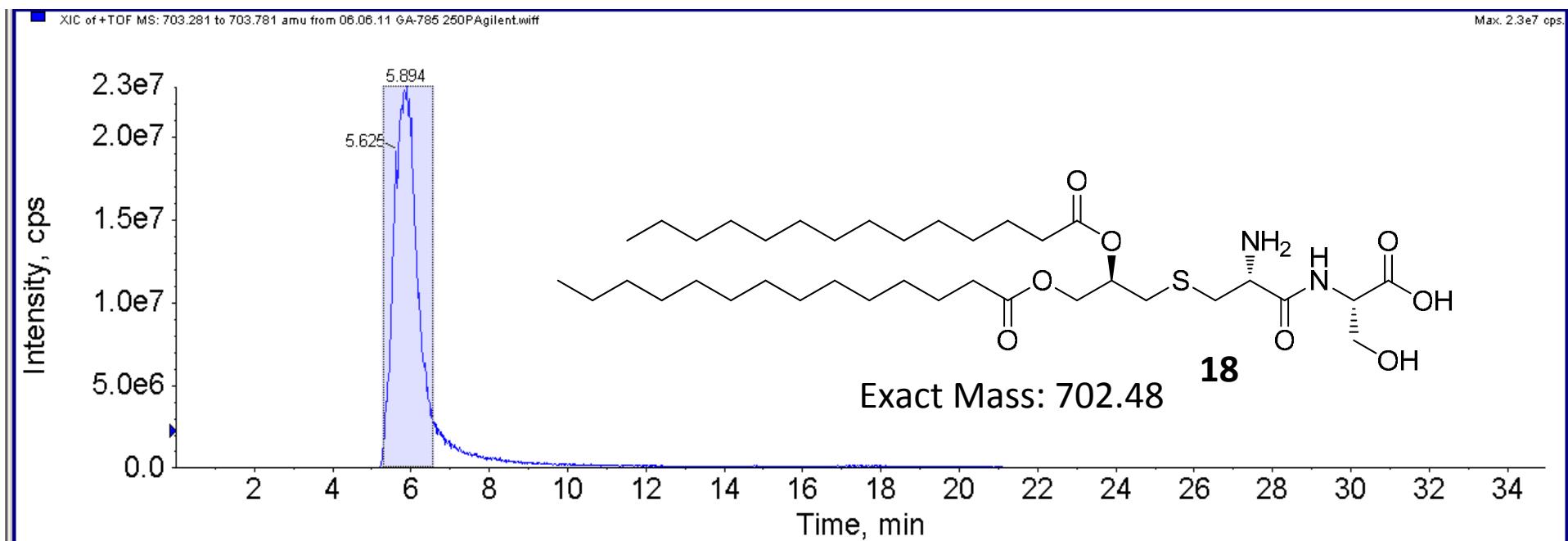


¹³C Spectrum

S96

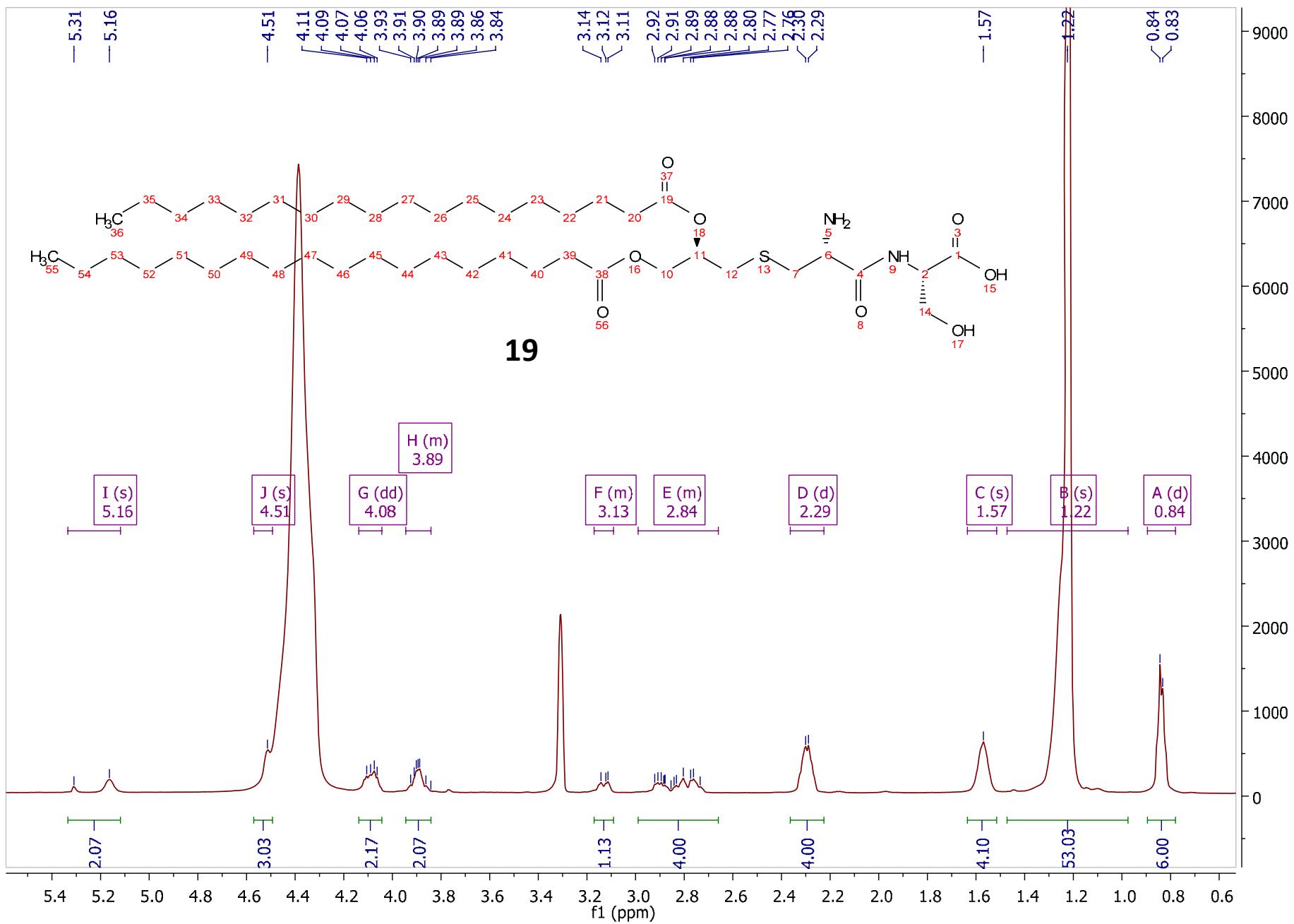






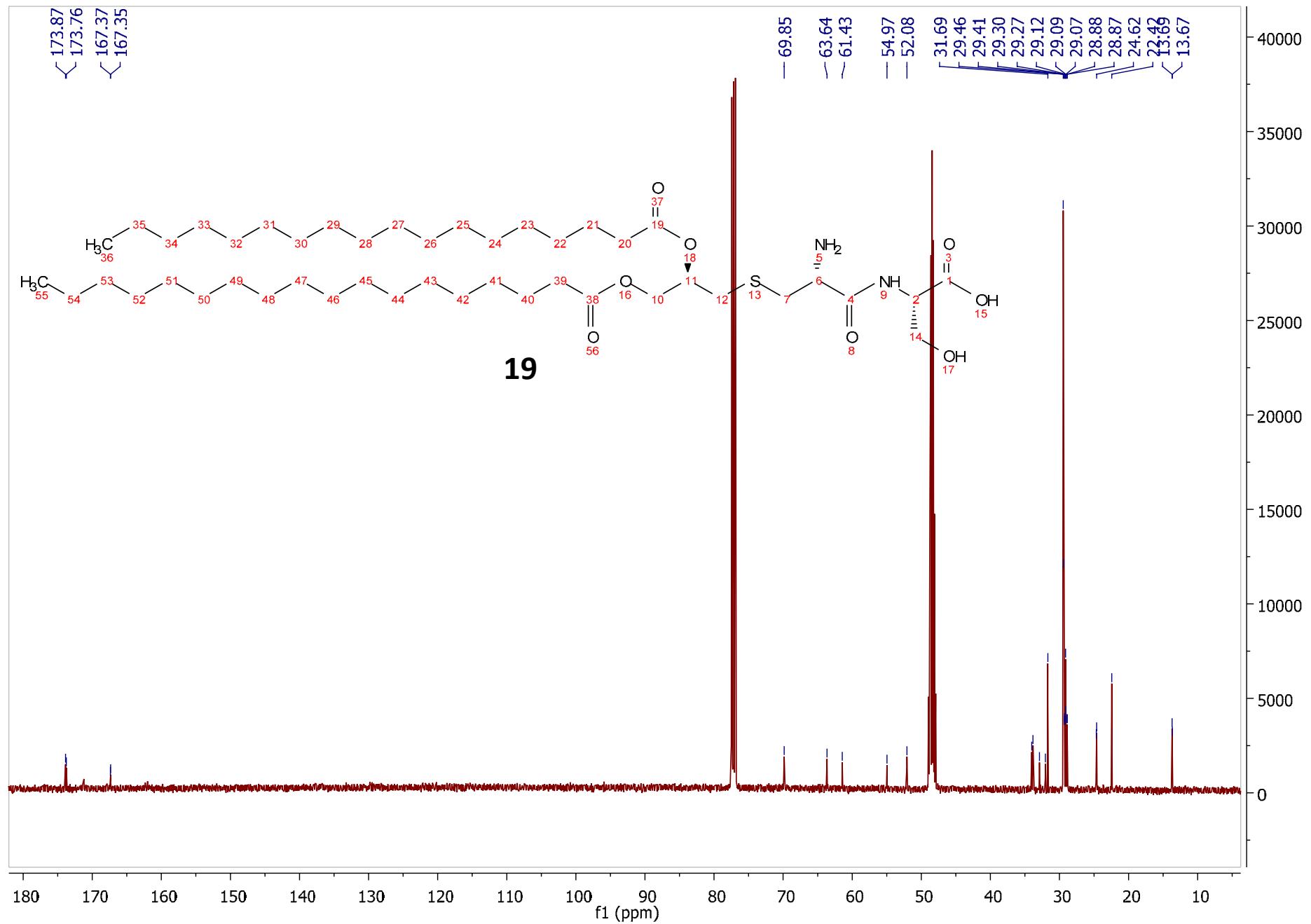
¹H Spectrum

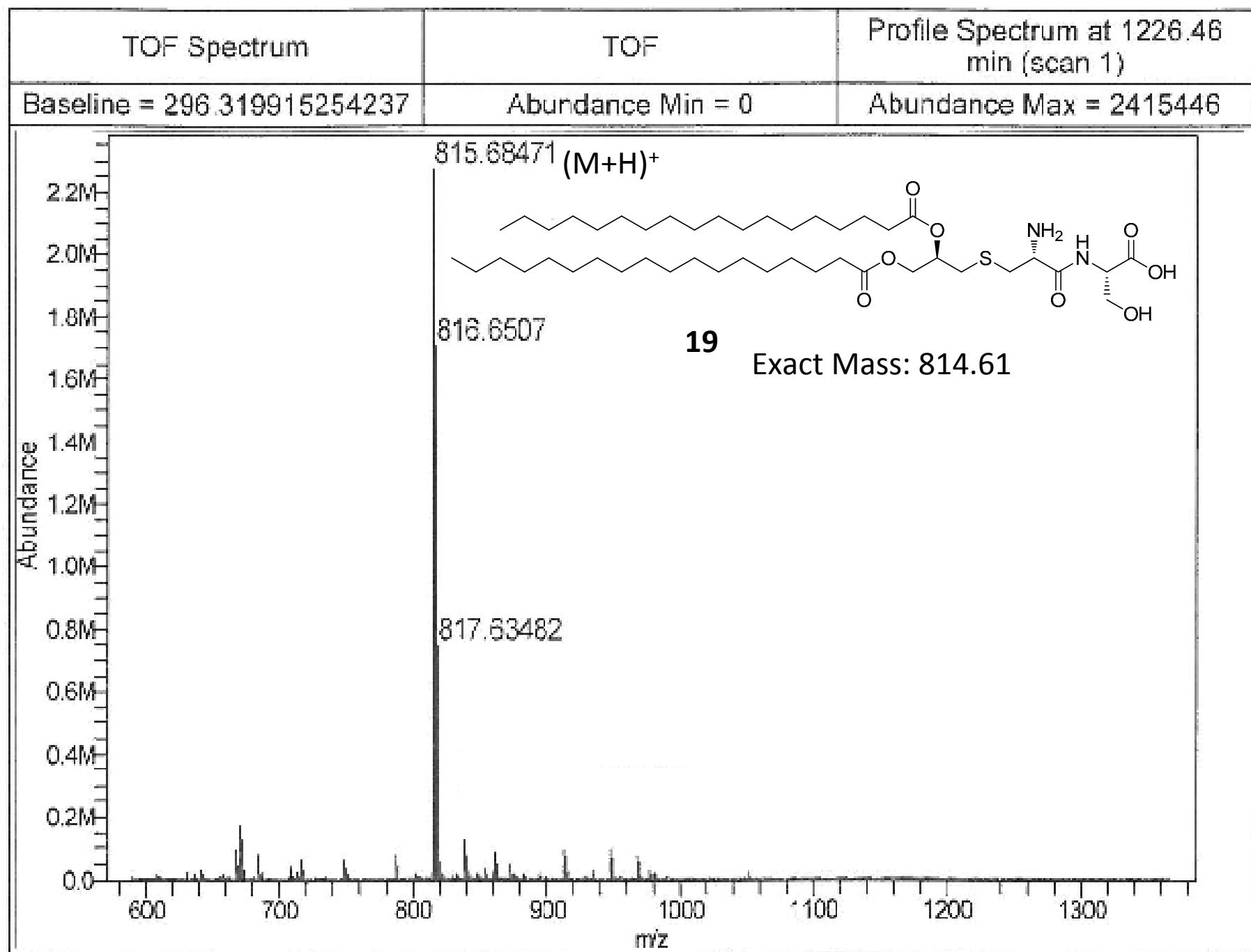
S99

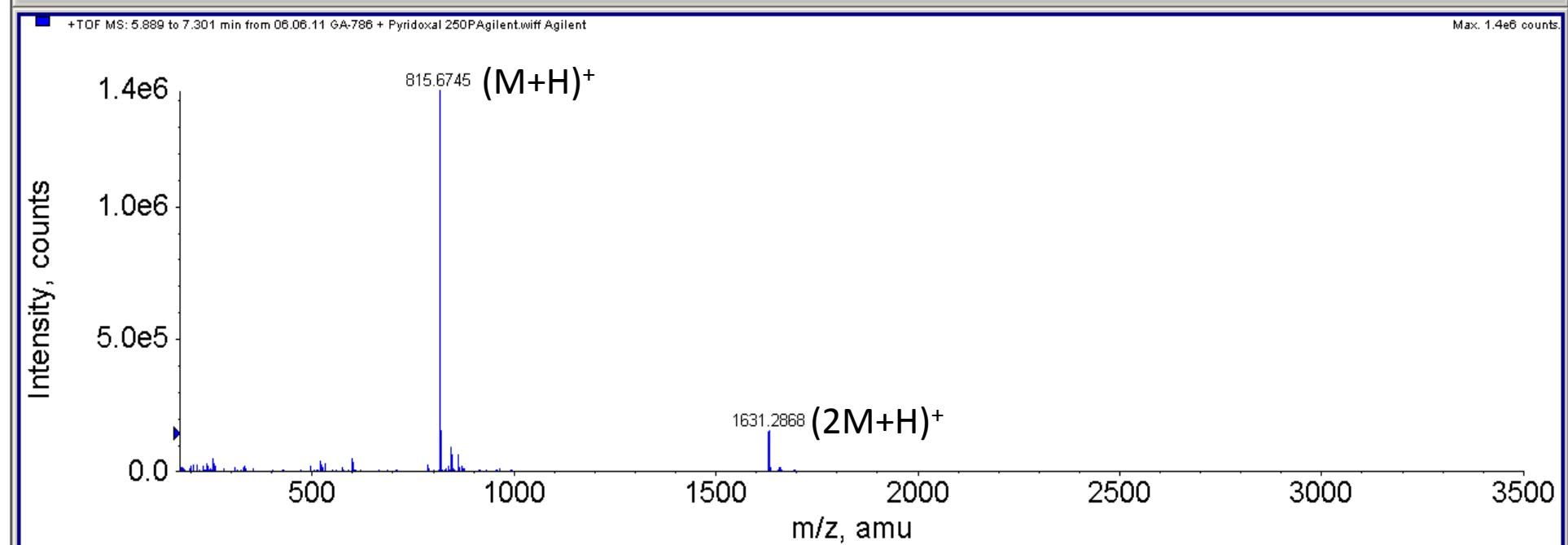
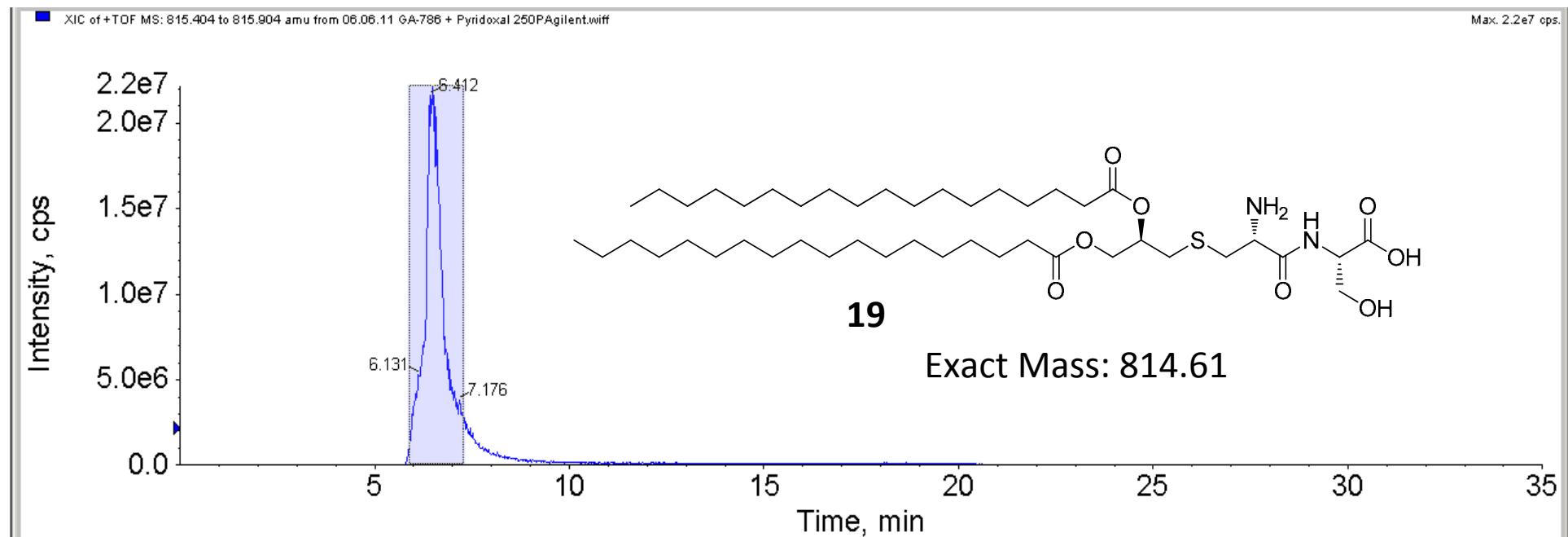


¹³C Spectrum

S100

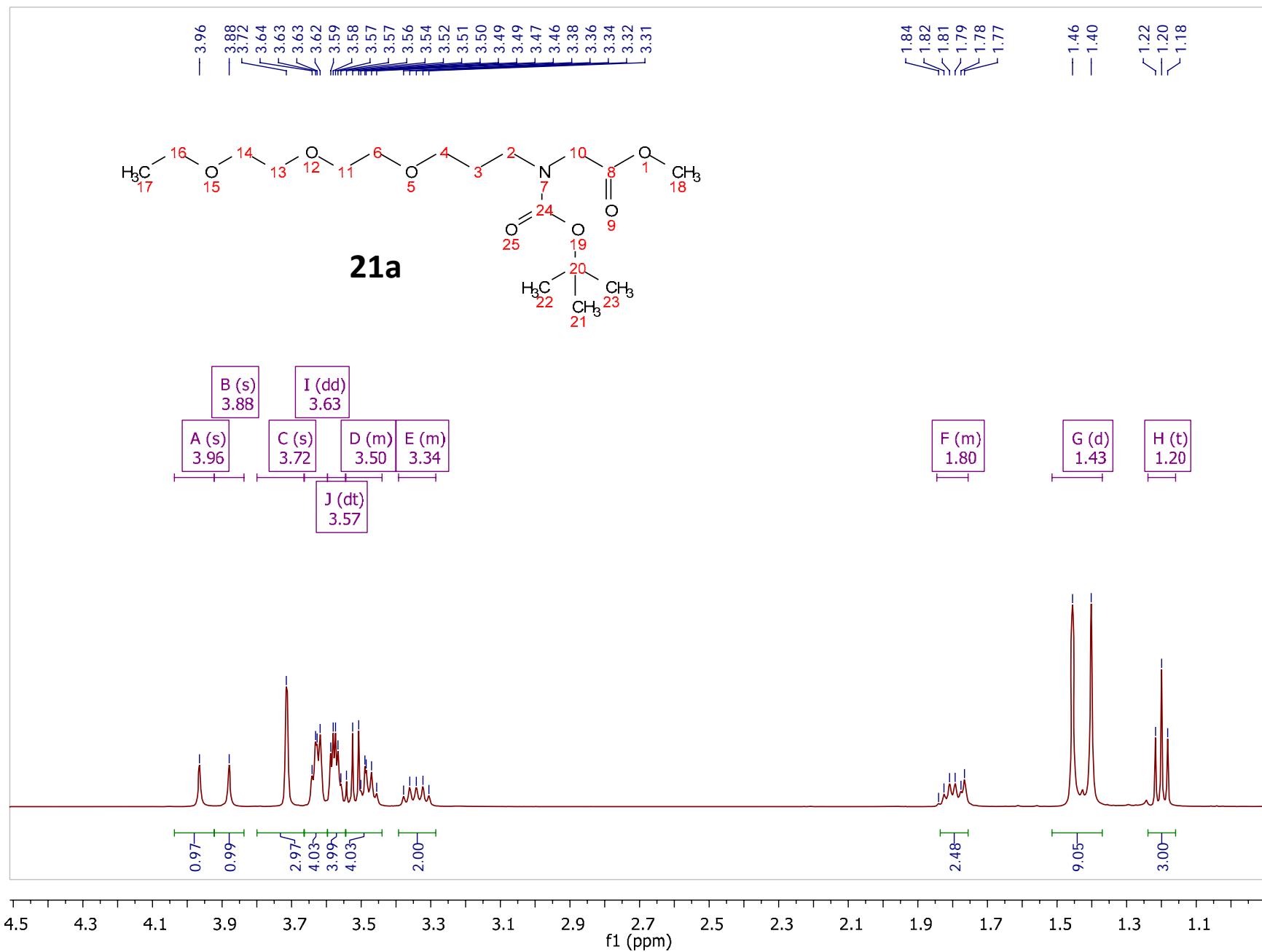






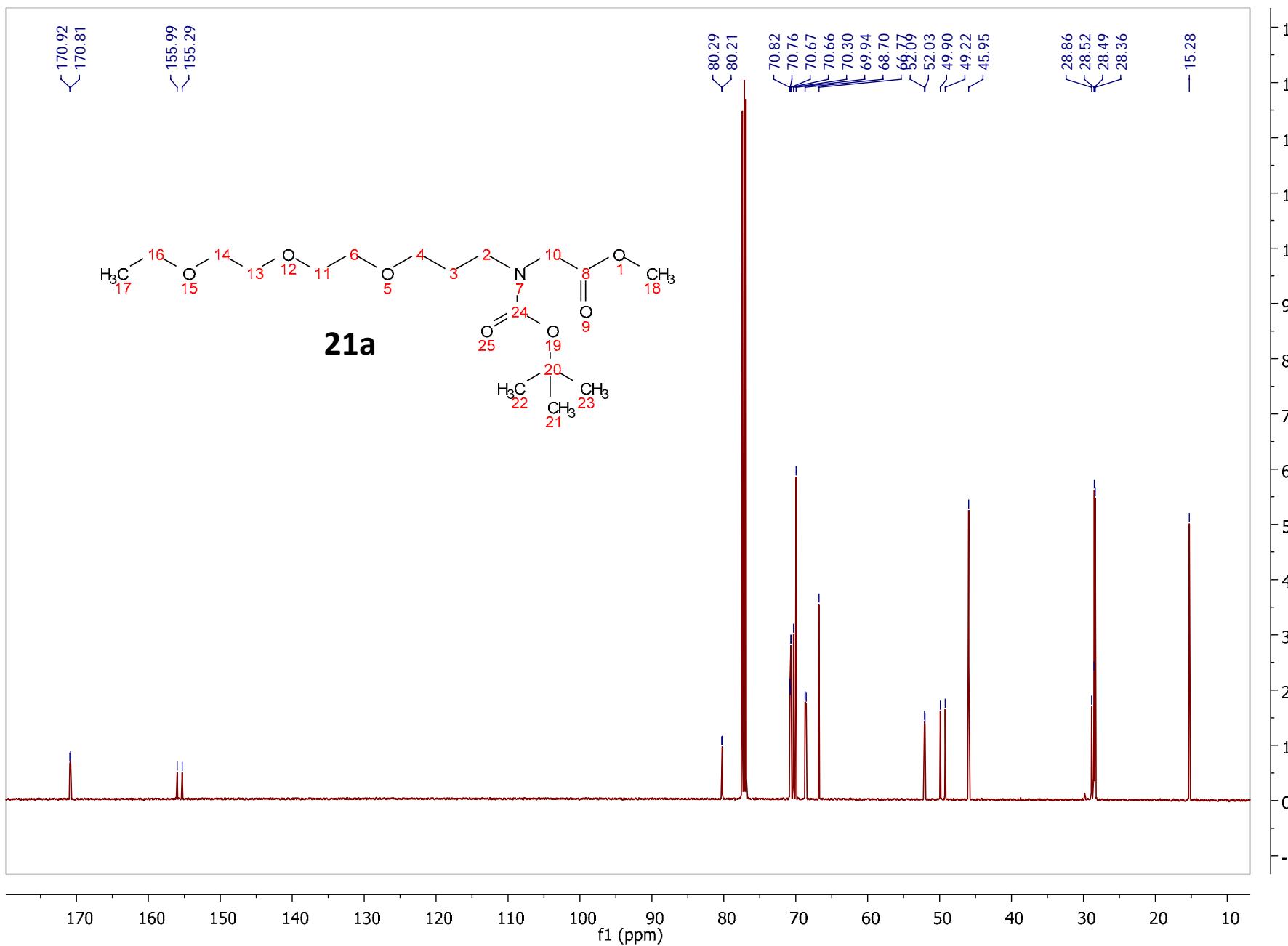
¹H Spectrum

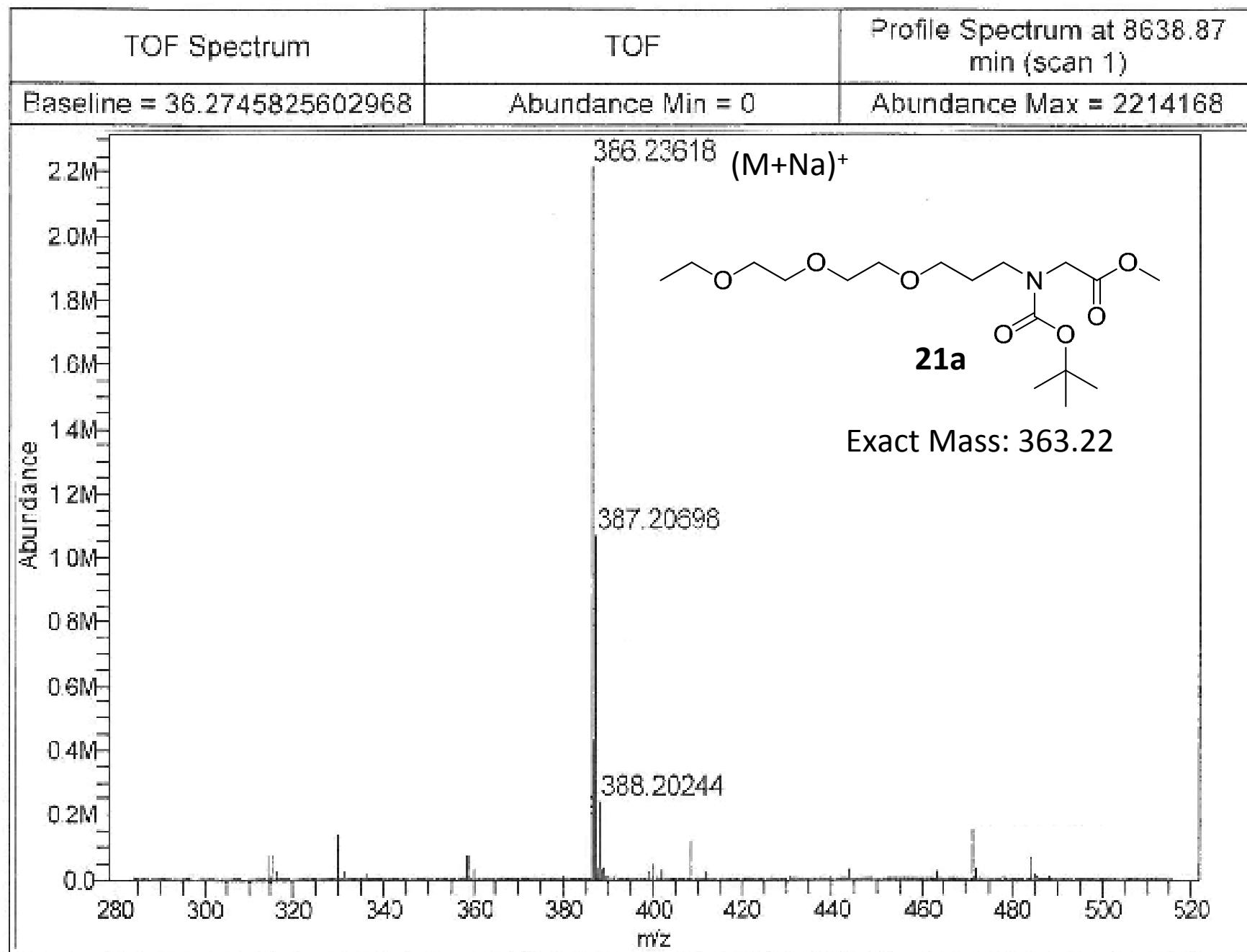
S103



¹³C Spectrum

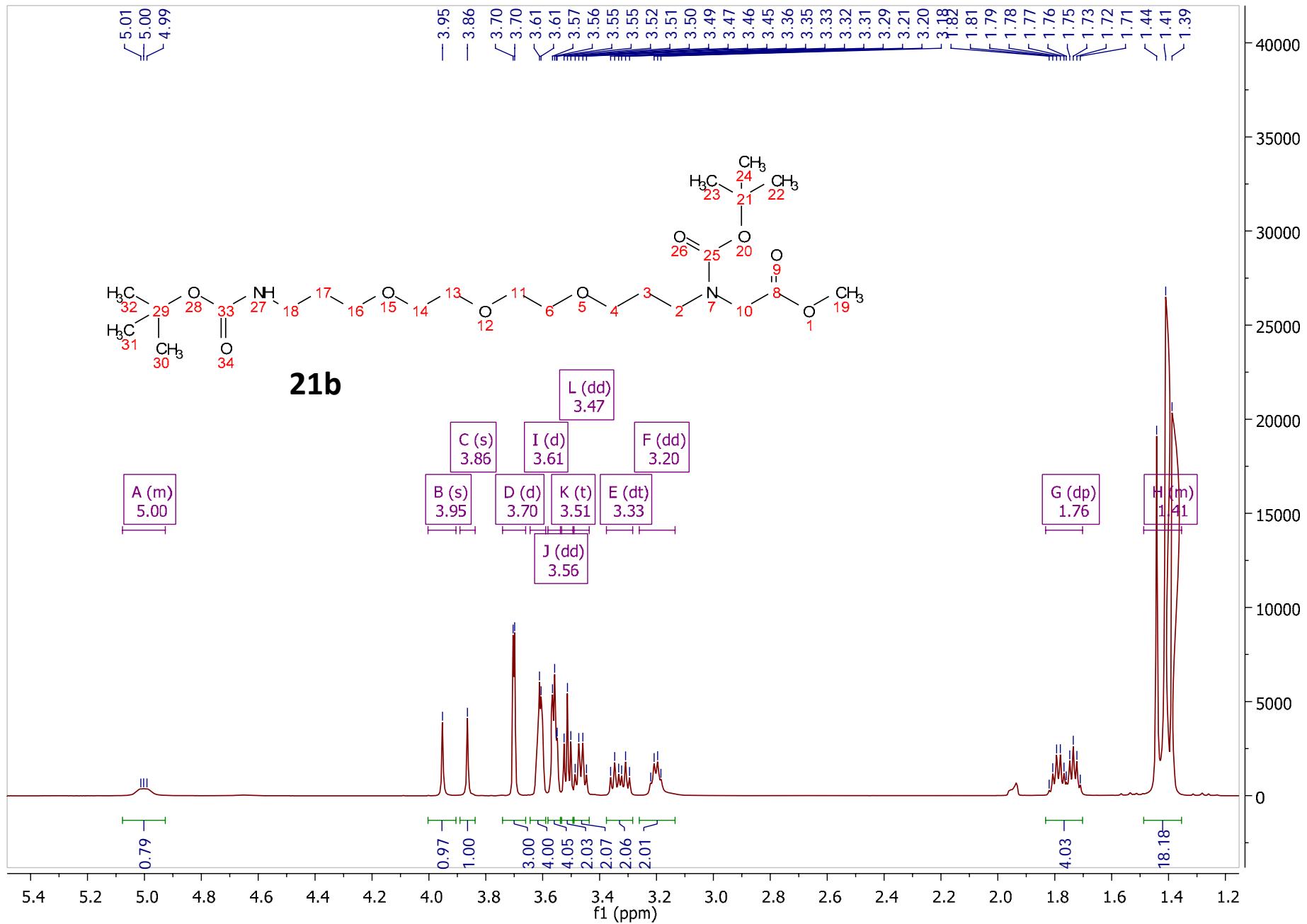
S104

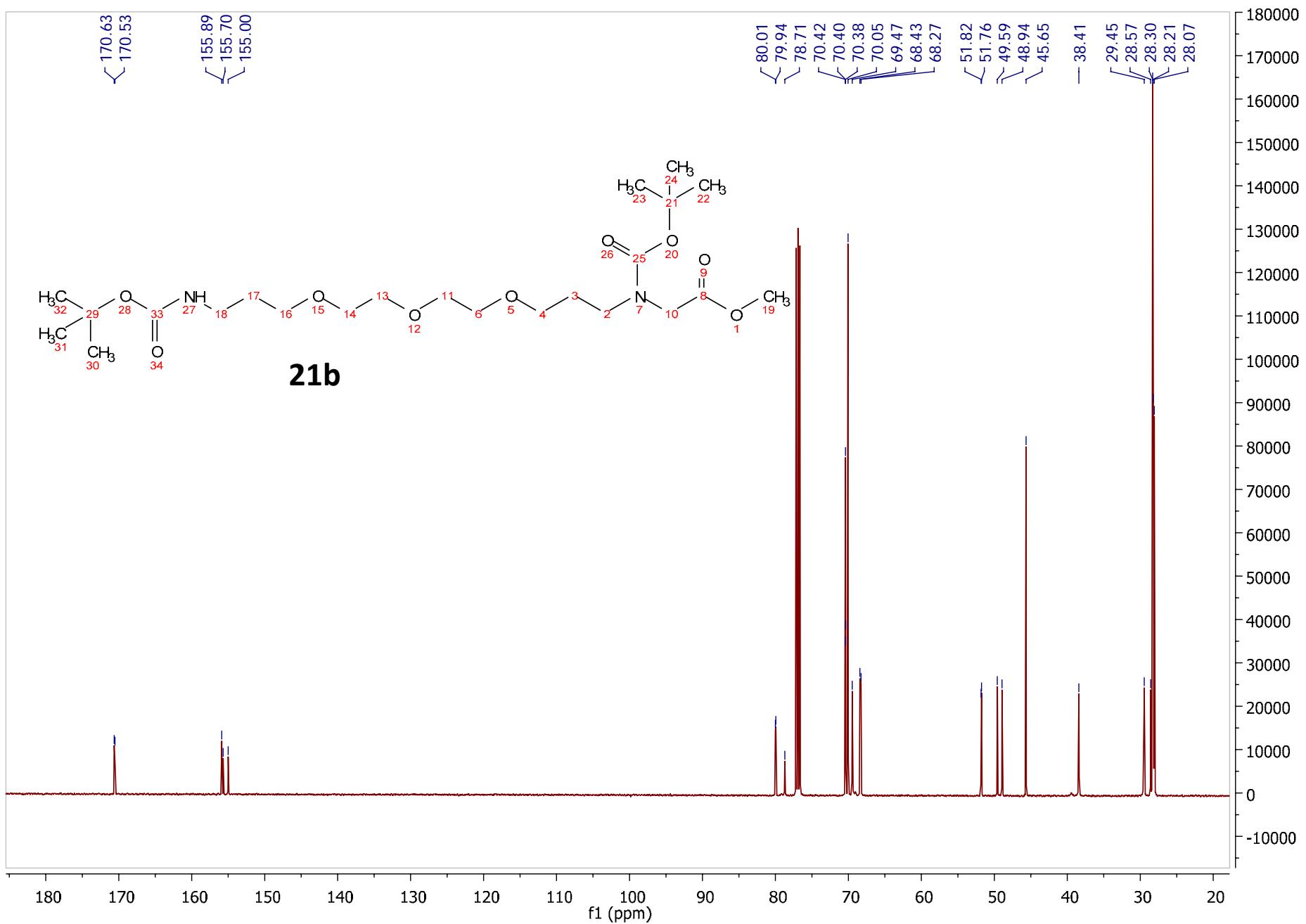


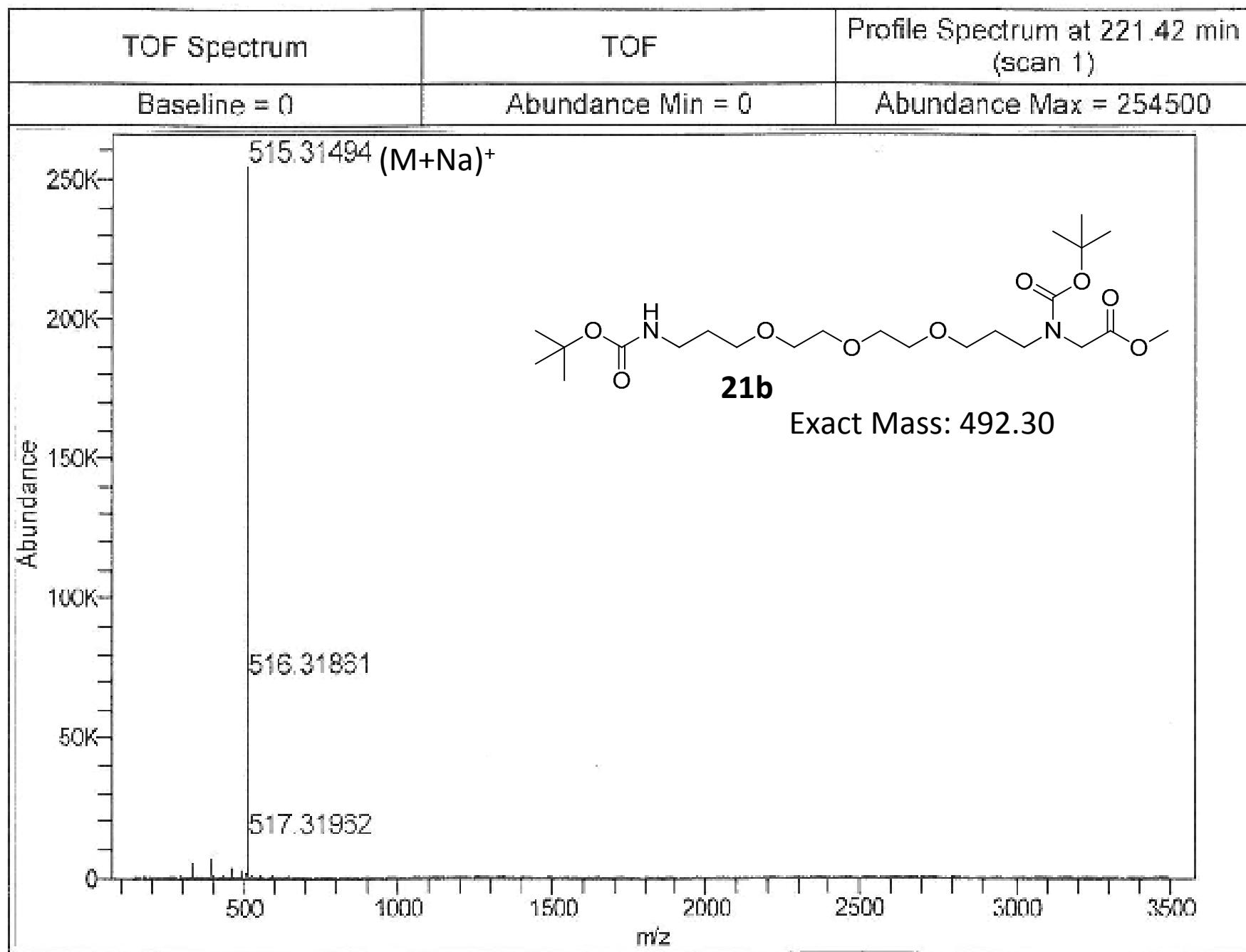


¹H Spectrum

S106

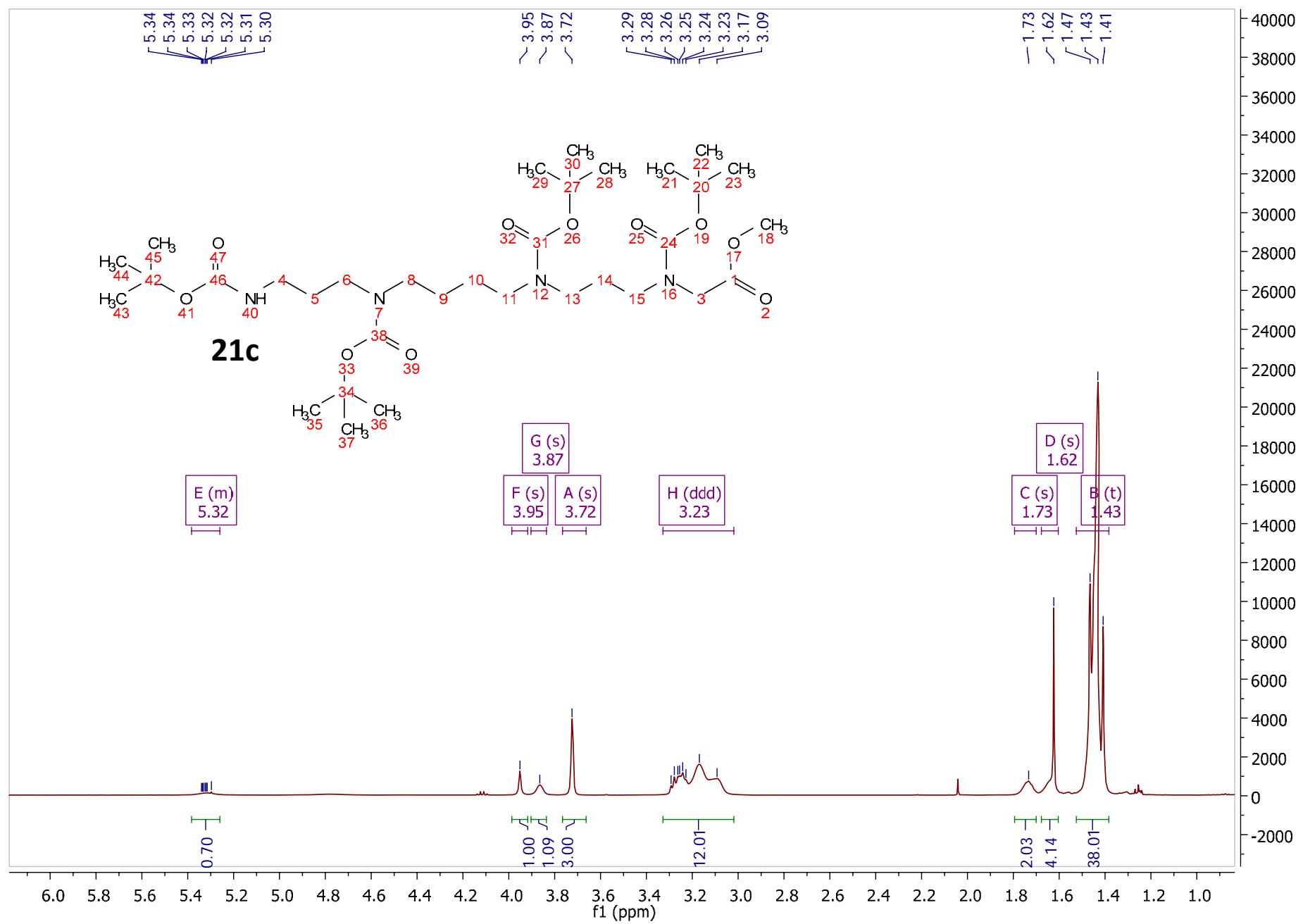






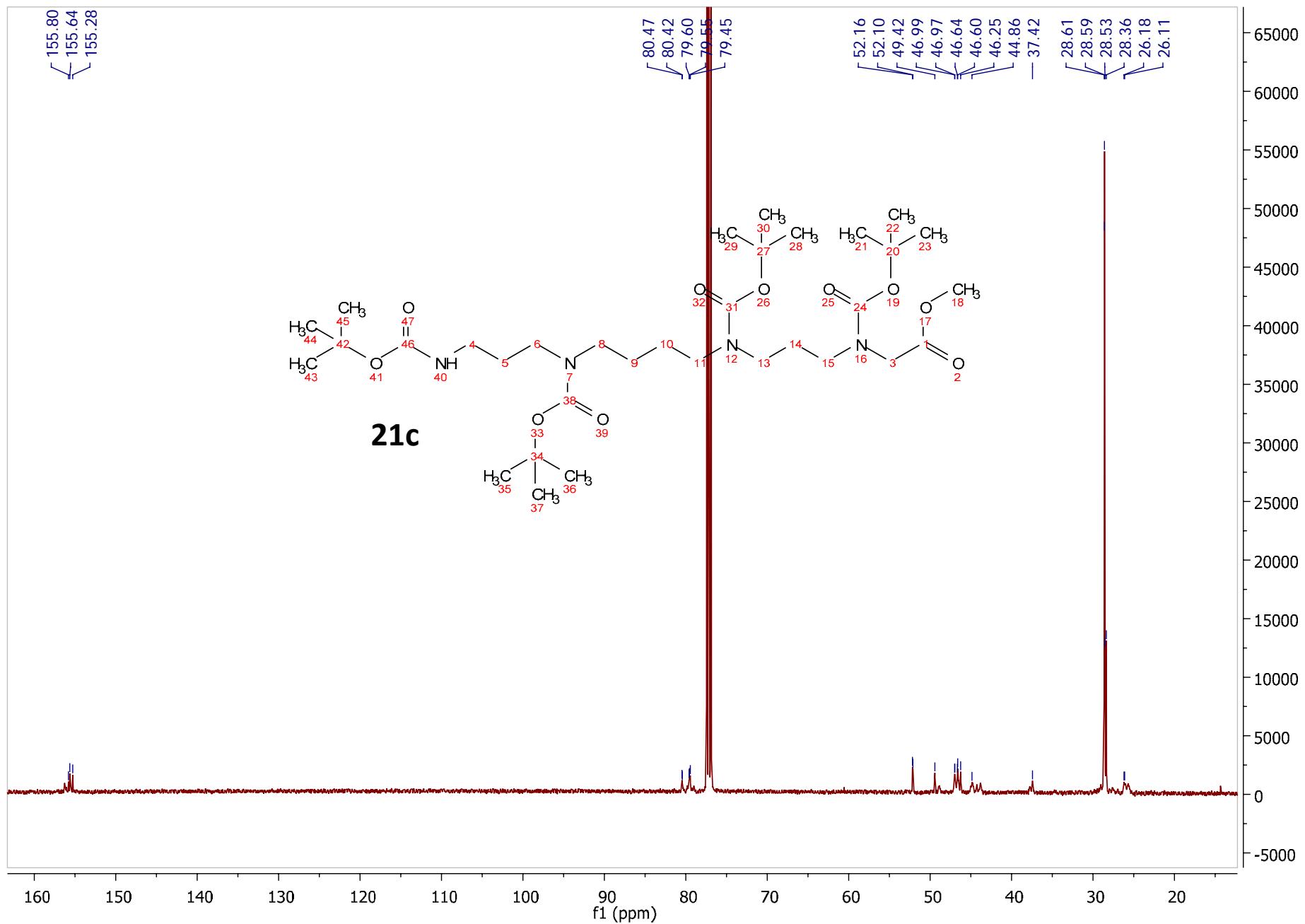
¹H Spectrum

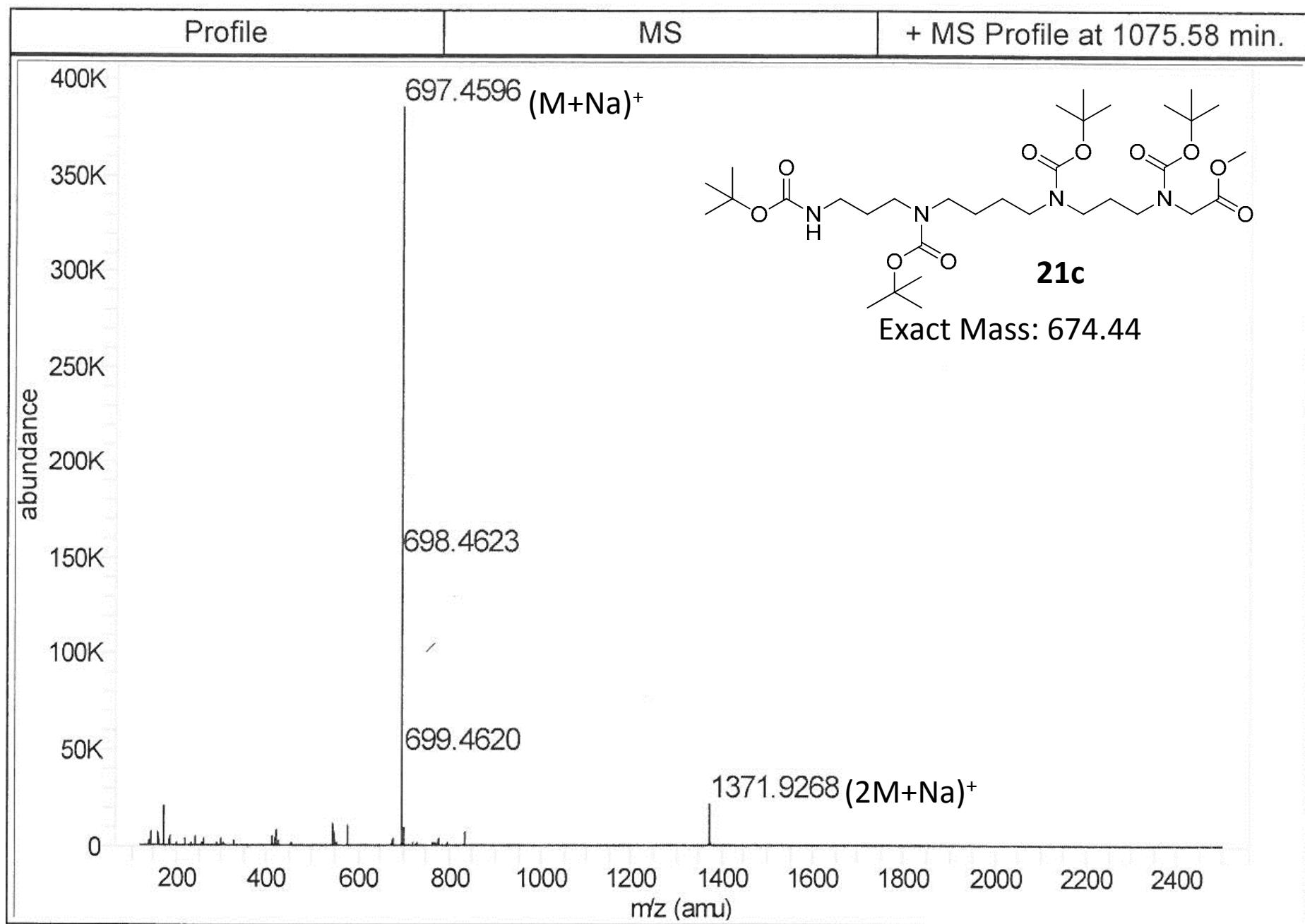
S109



¹³C Spectrum

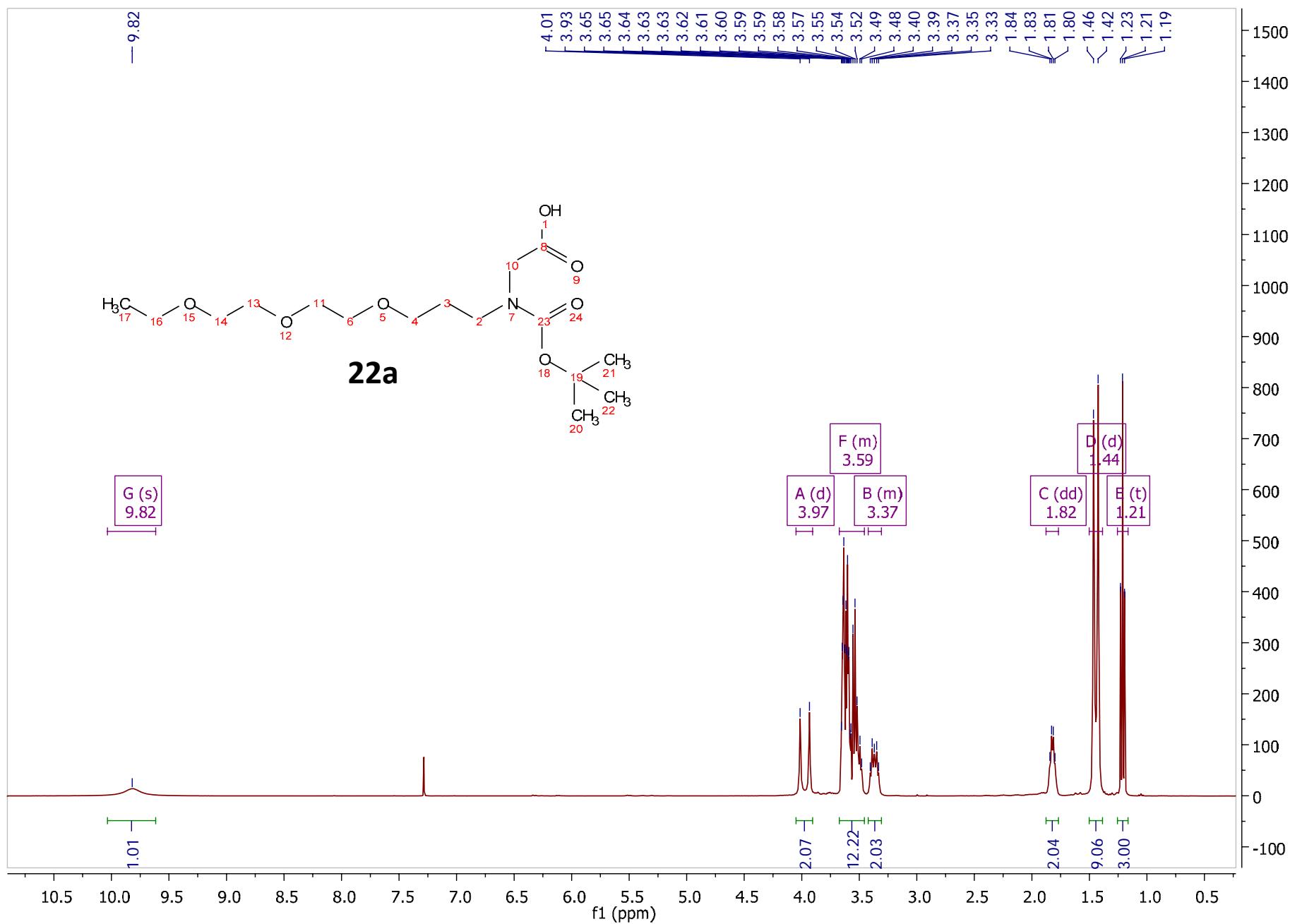
S110





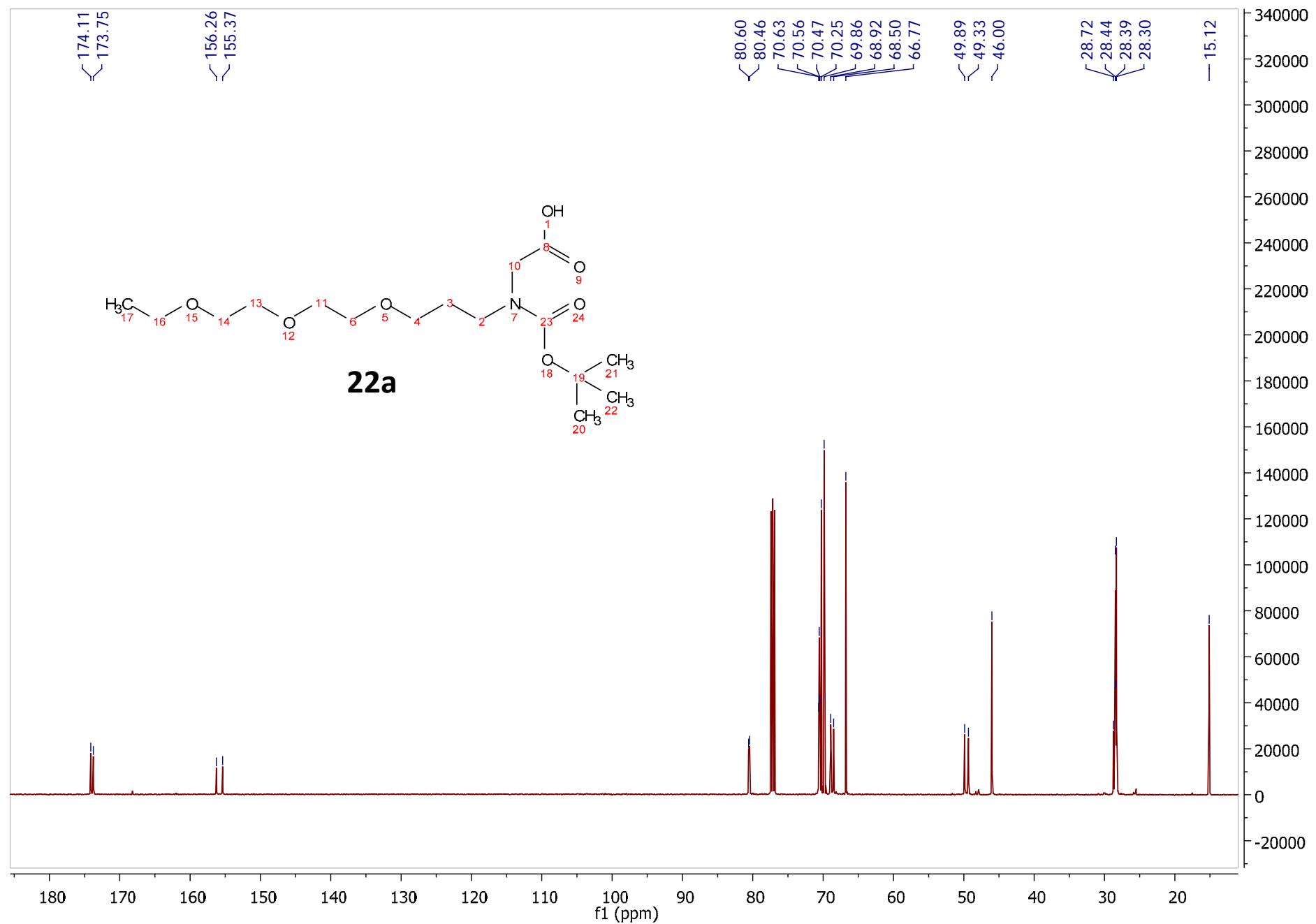
¹H Spectrum

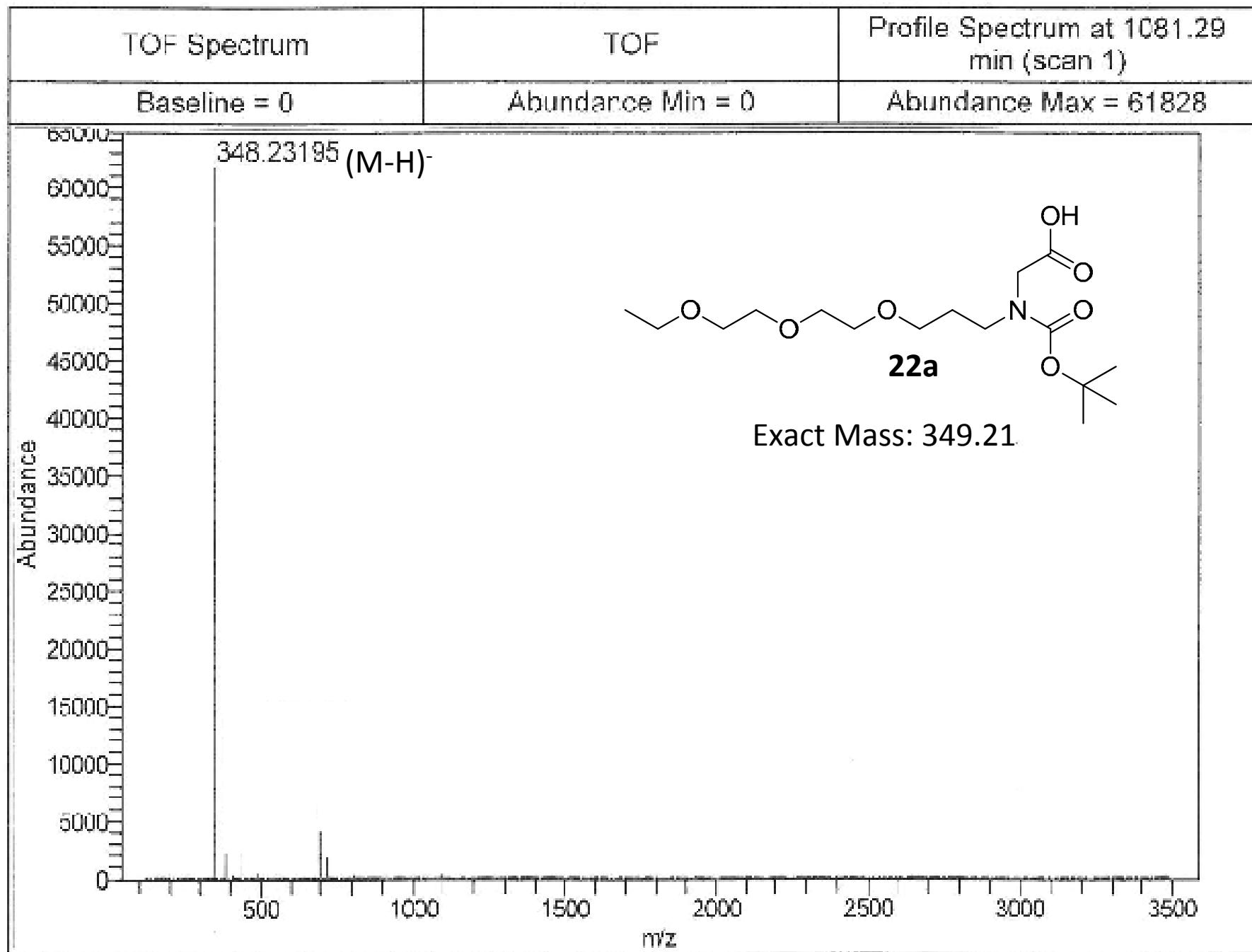
S112



¹³C Spectrum

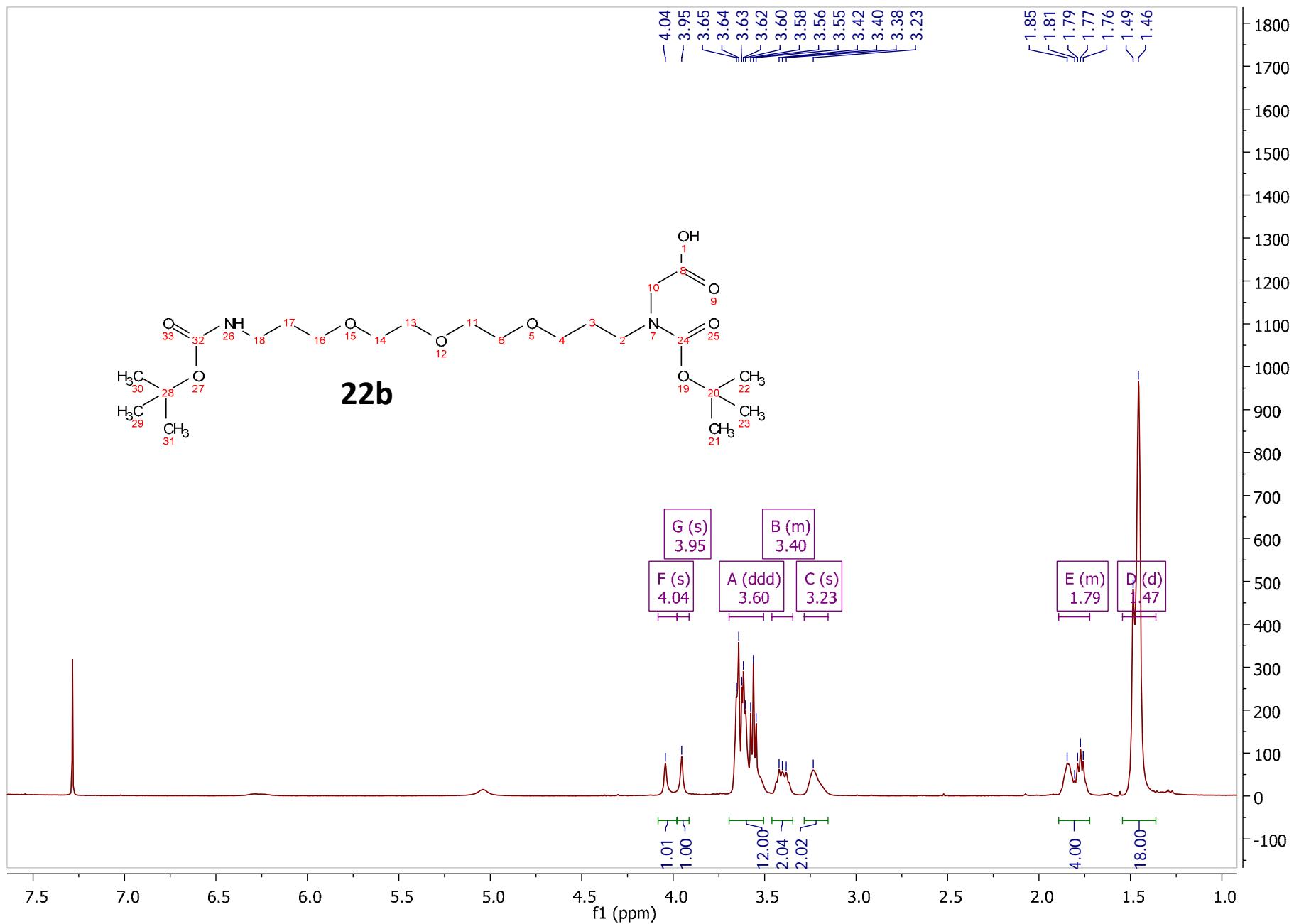
S113





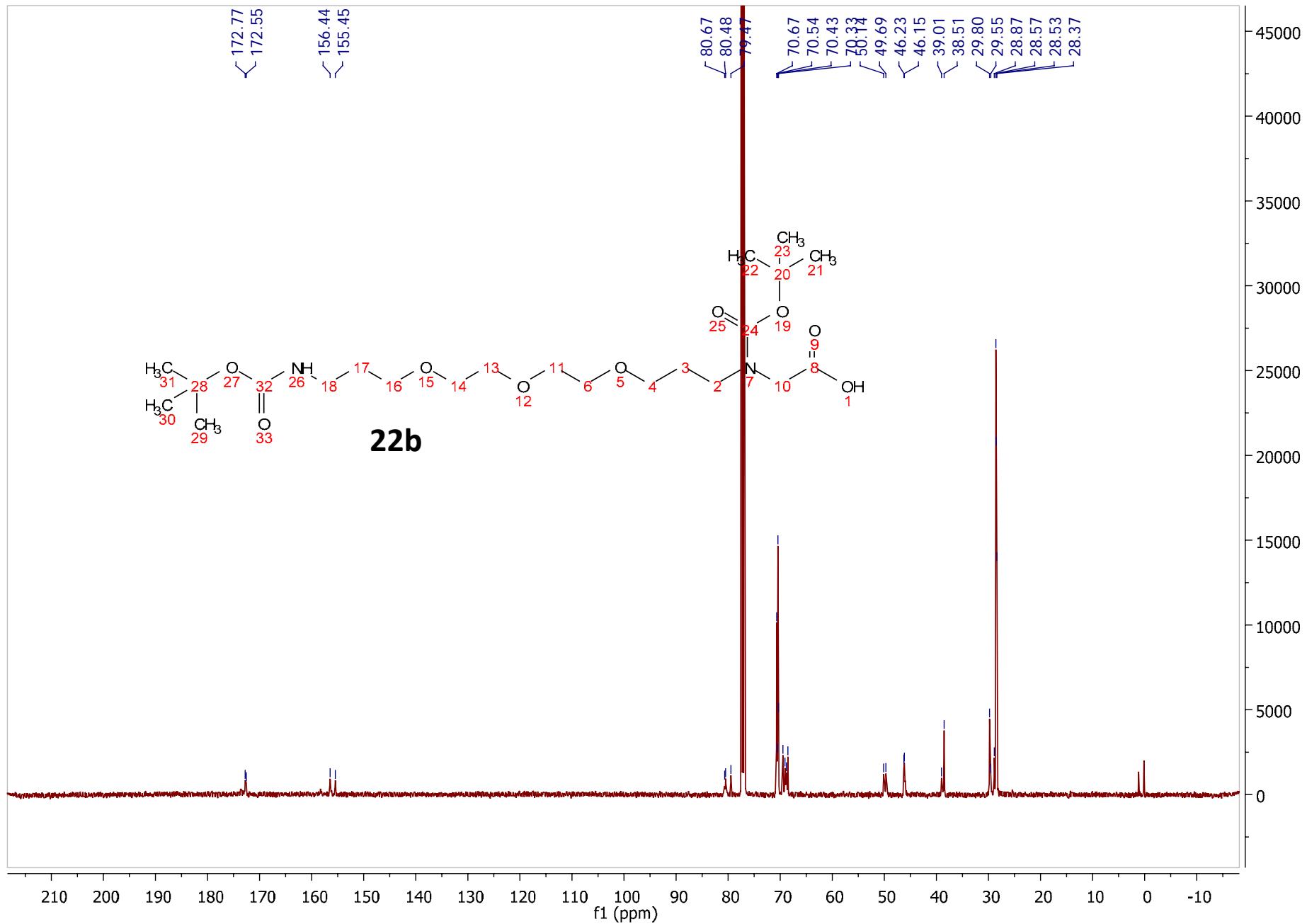
¹H Spectrum

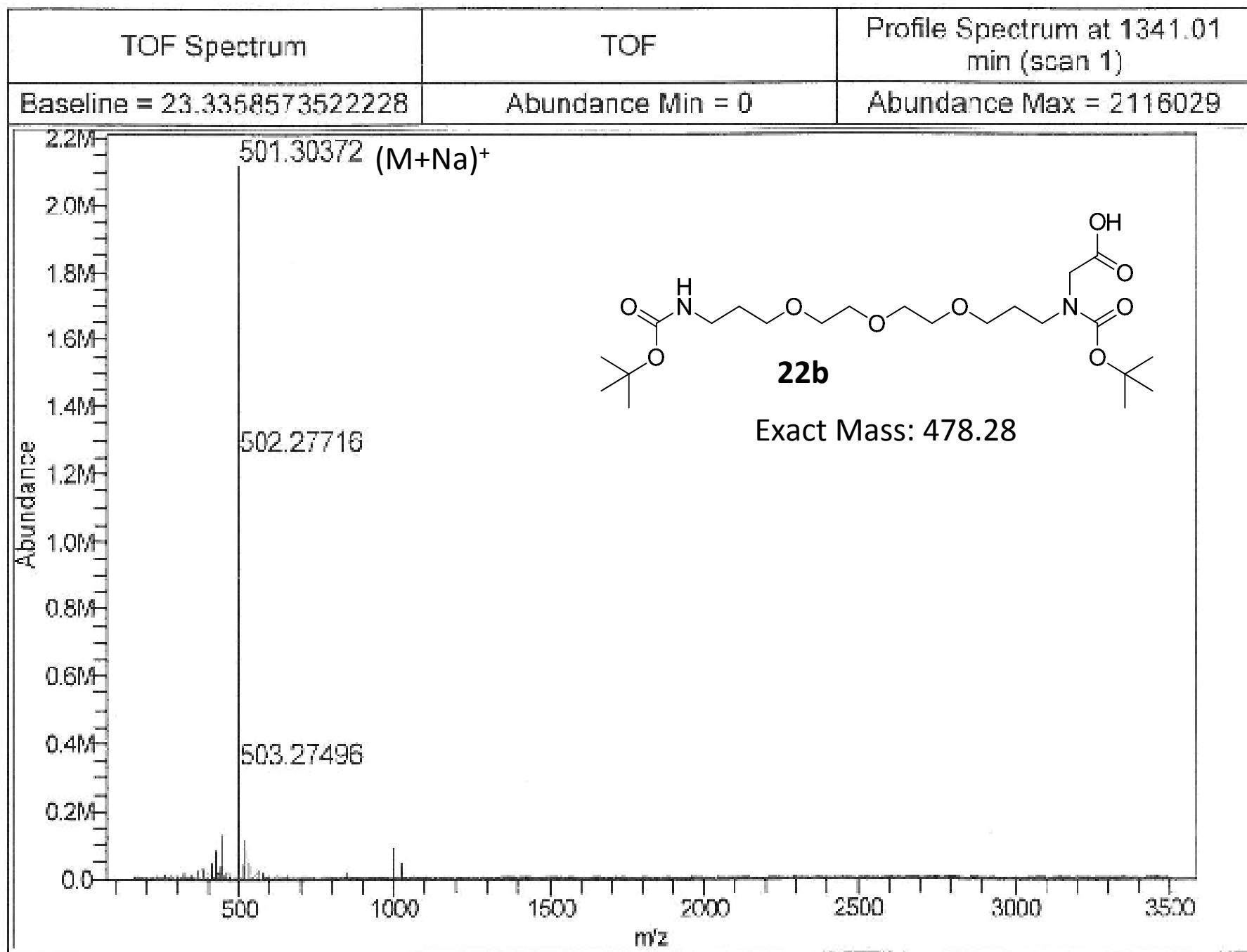
S115



¹³C Spectrum

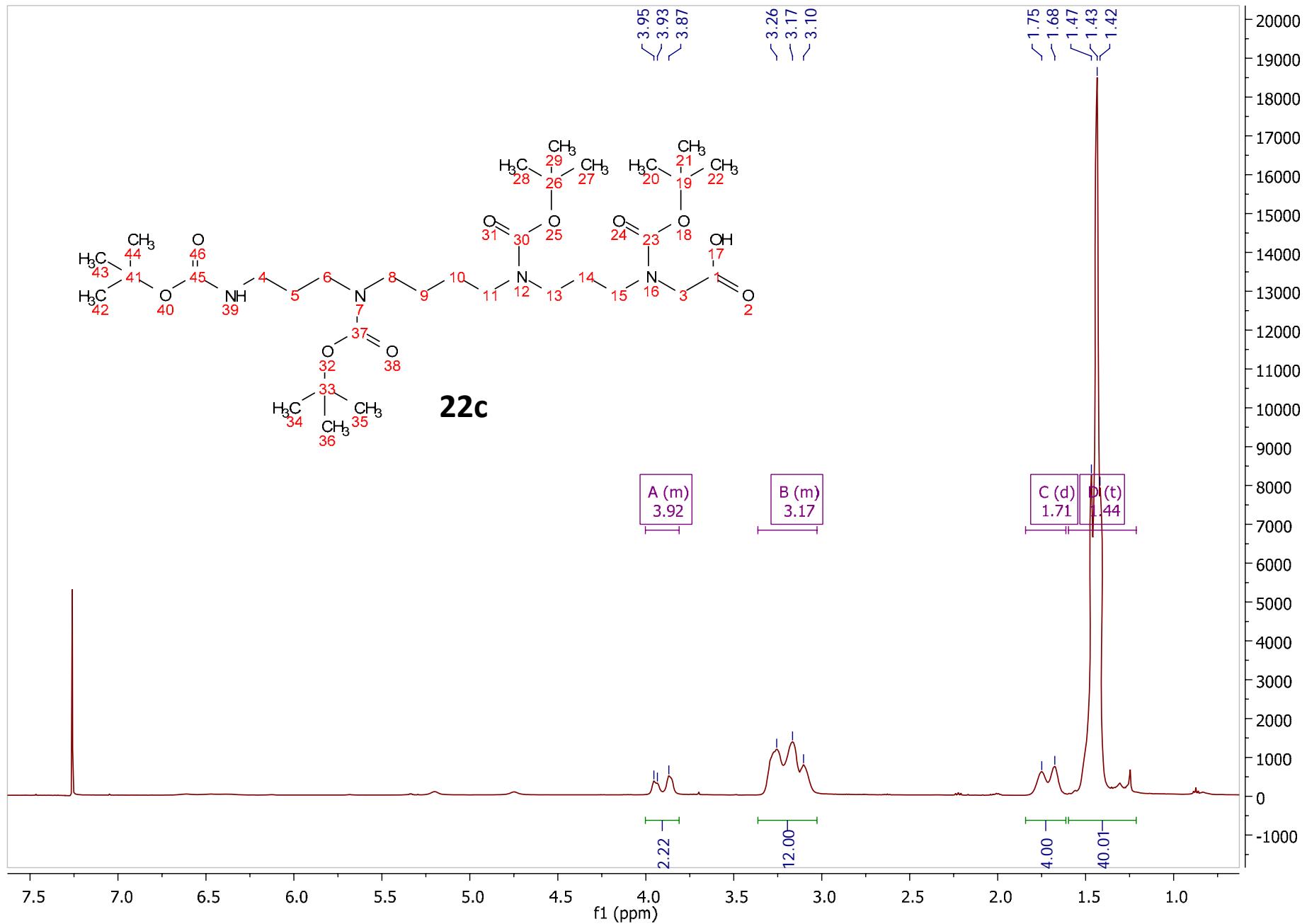
S116

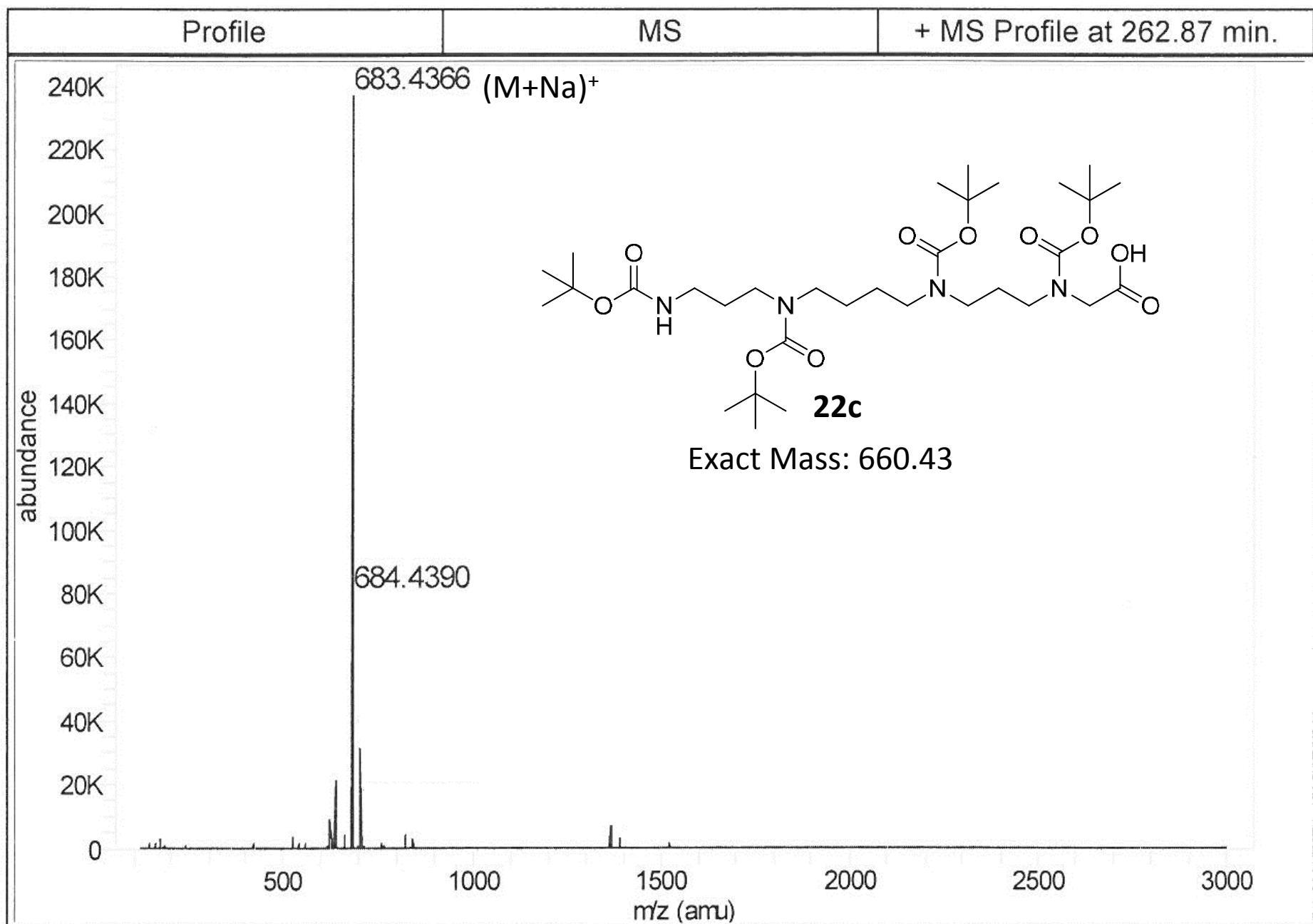




¹H Spectrum

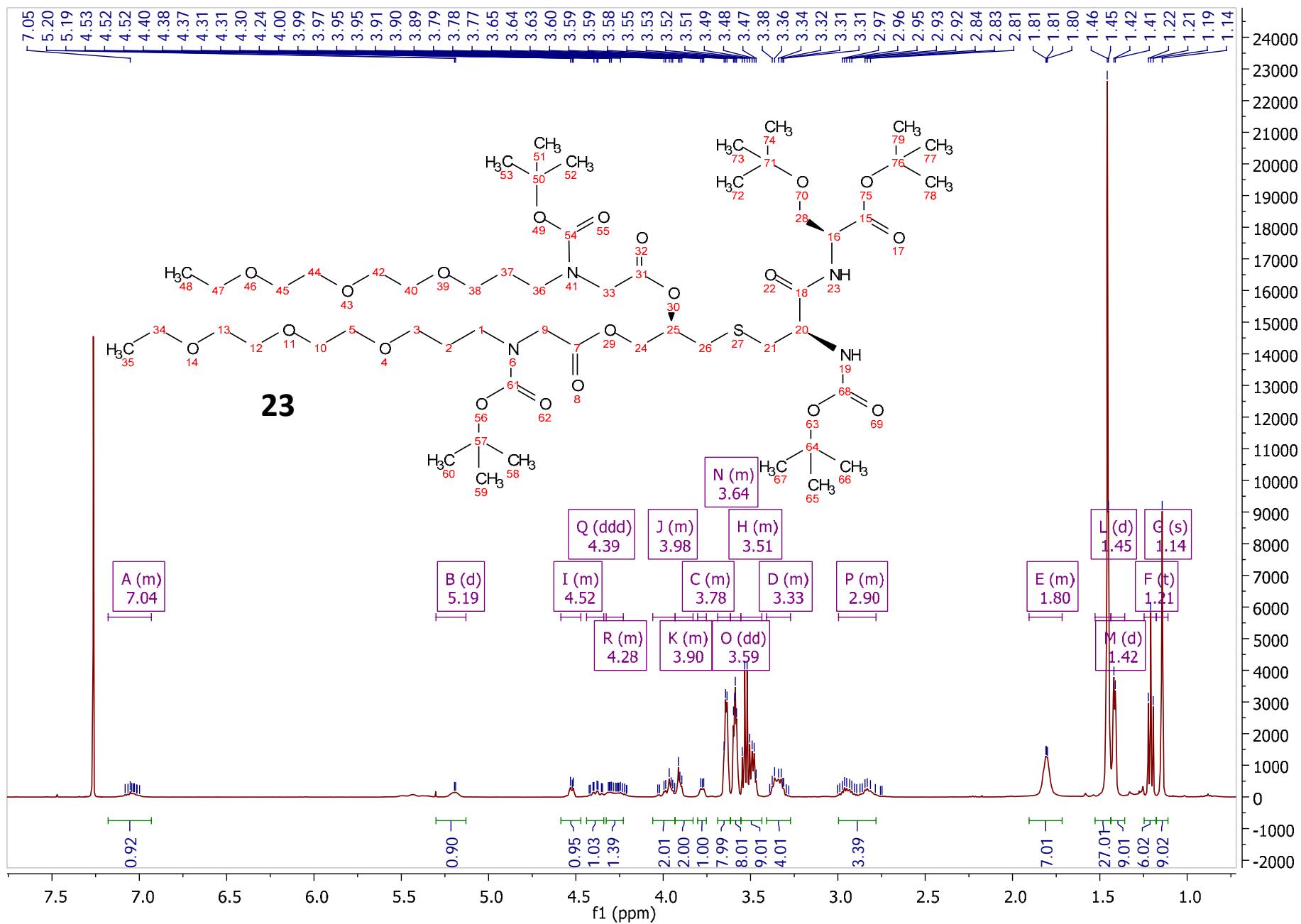
S118





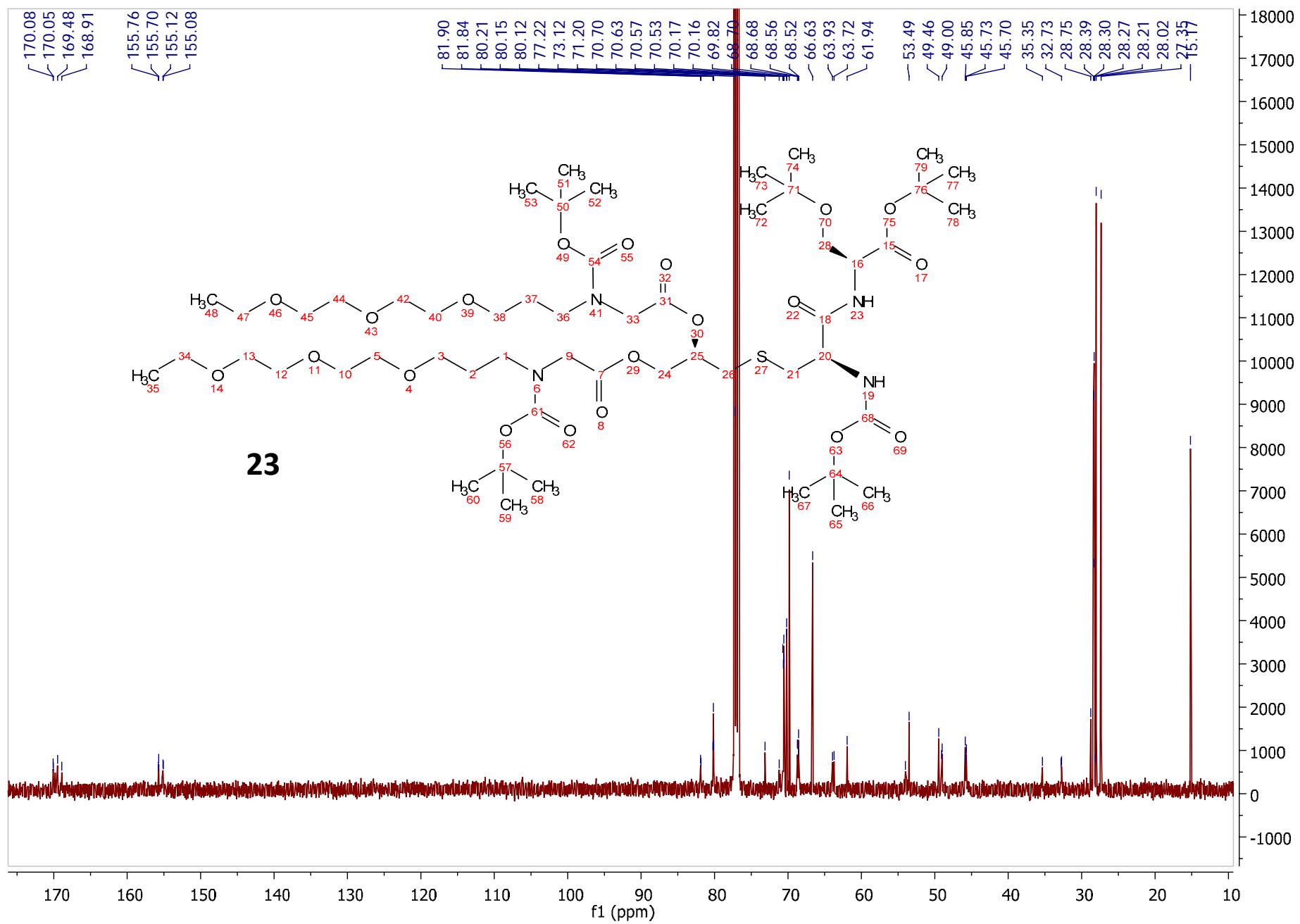
¹H Spectrum

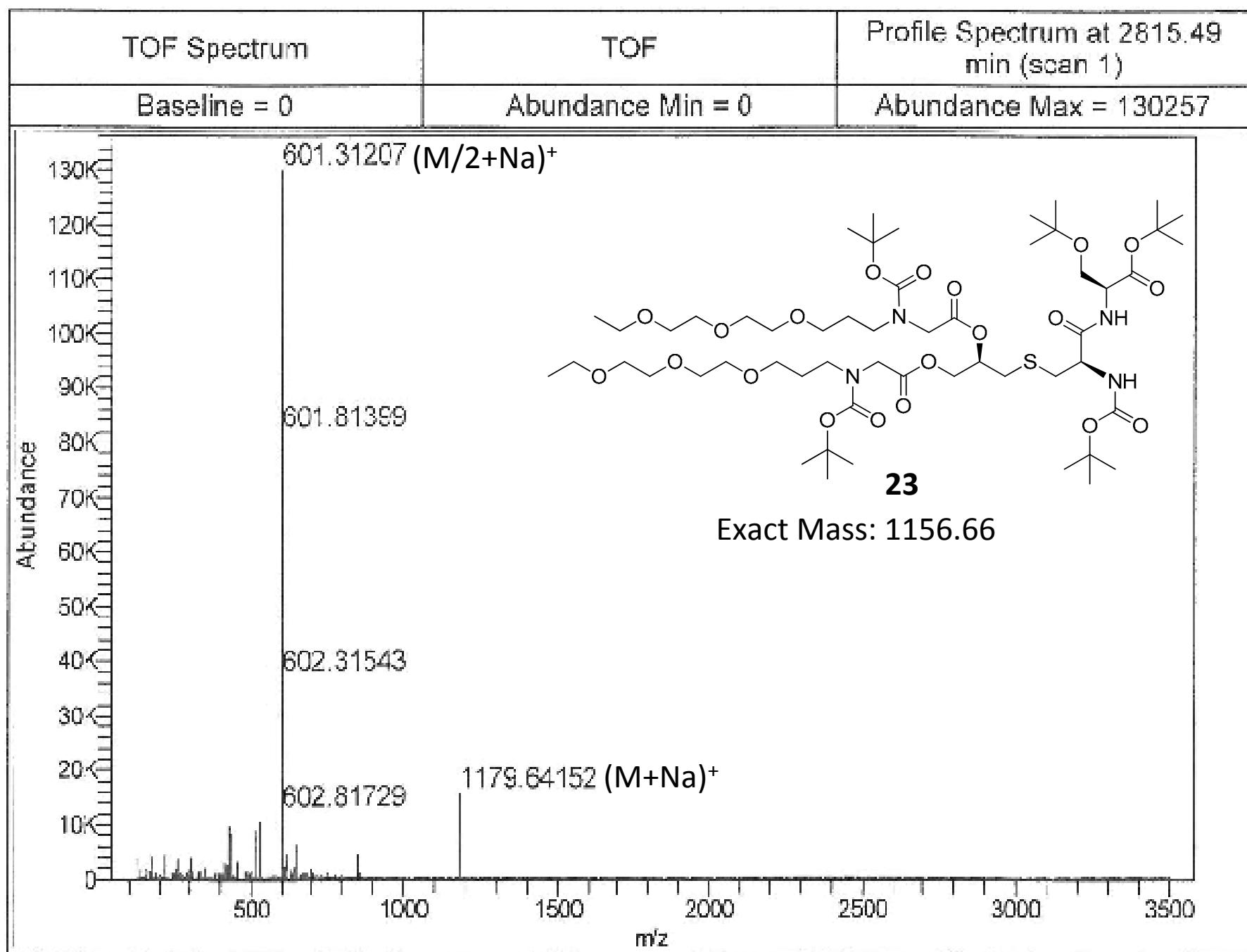
S120



¹³C Spectrum

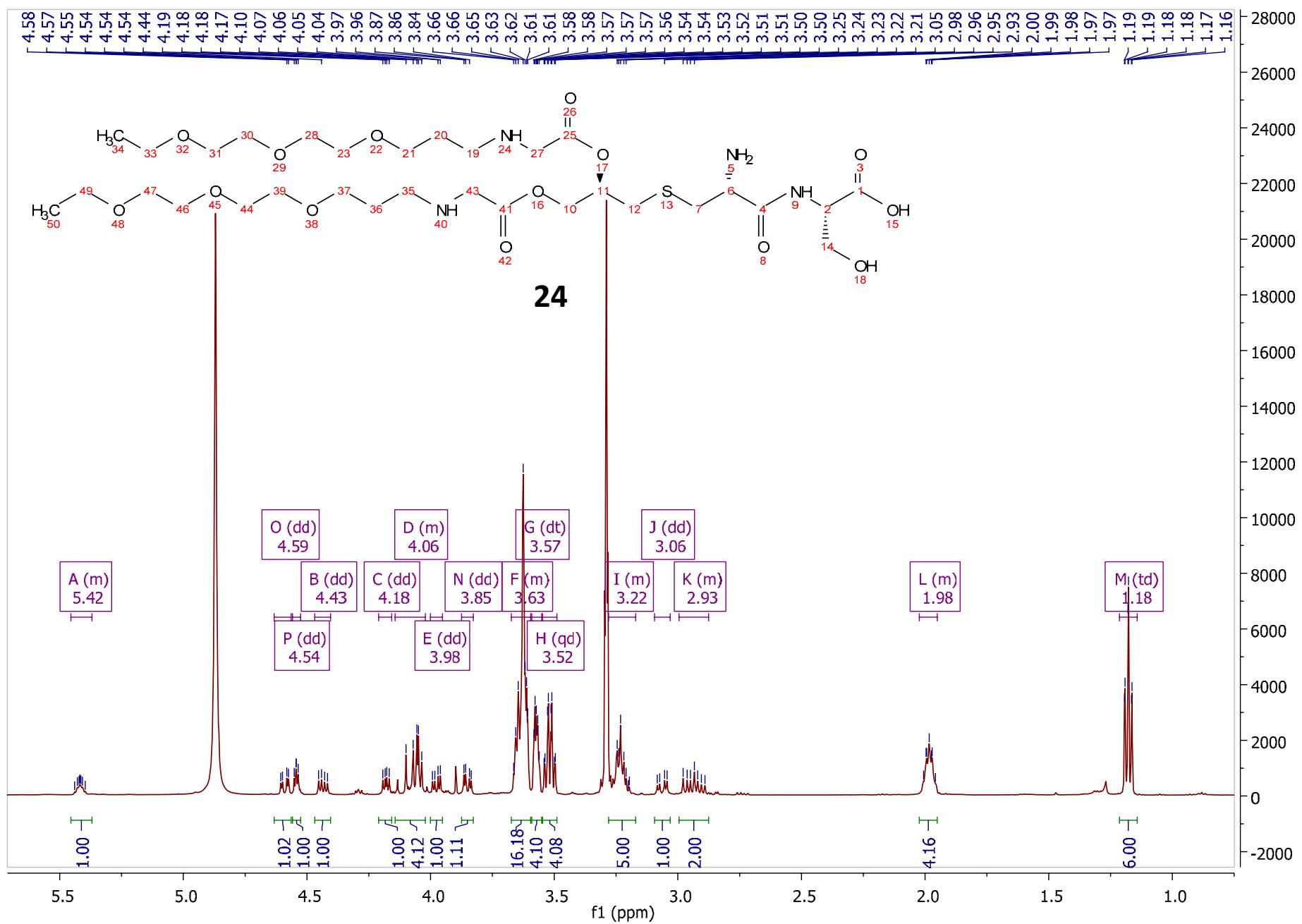
S121





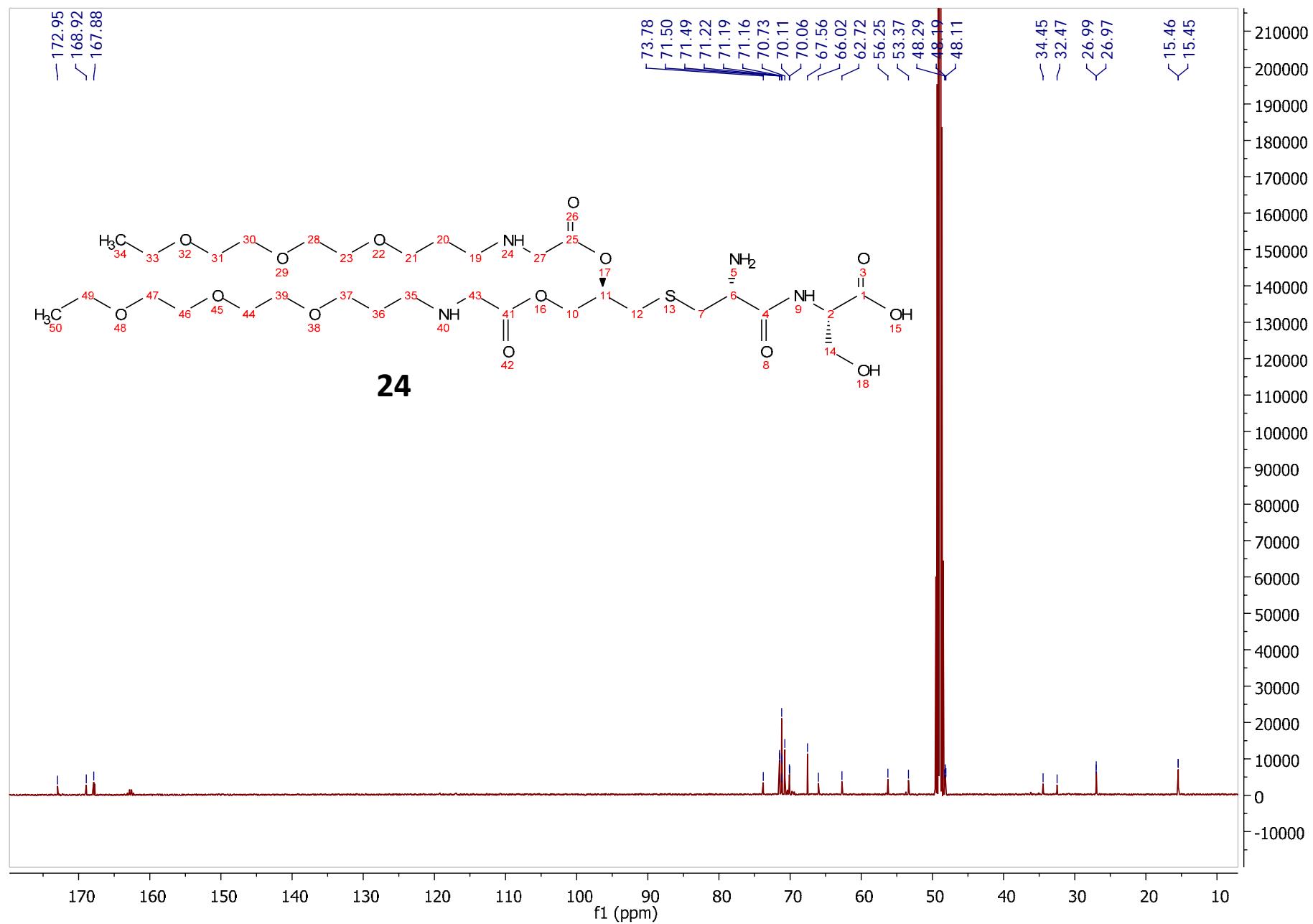
¹H Spectrum

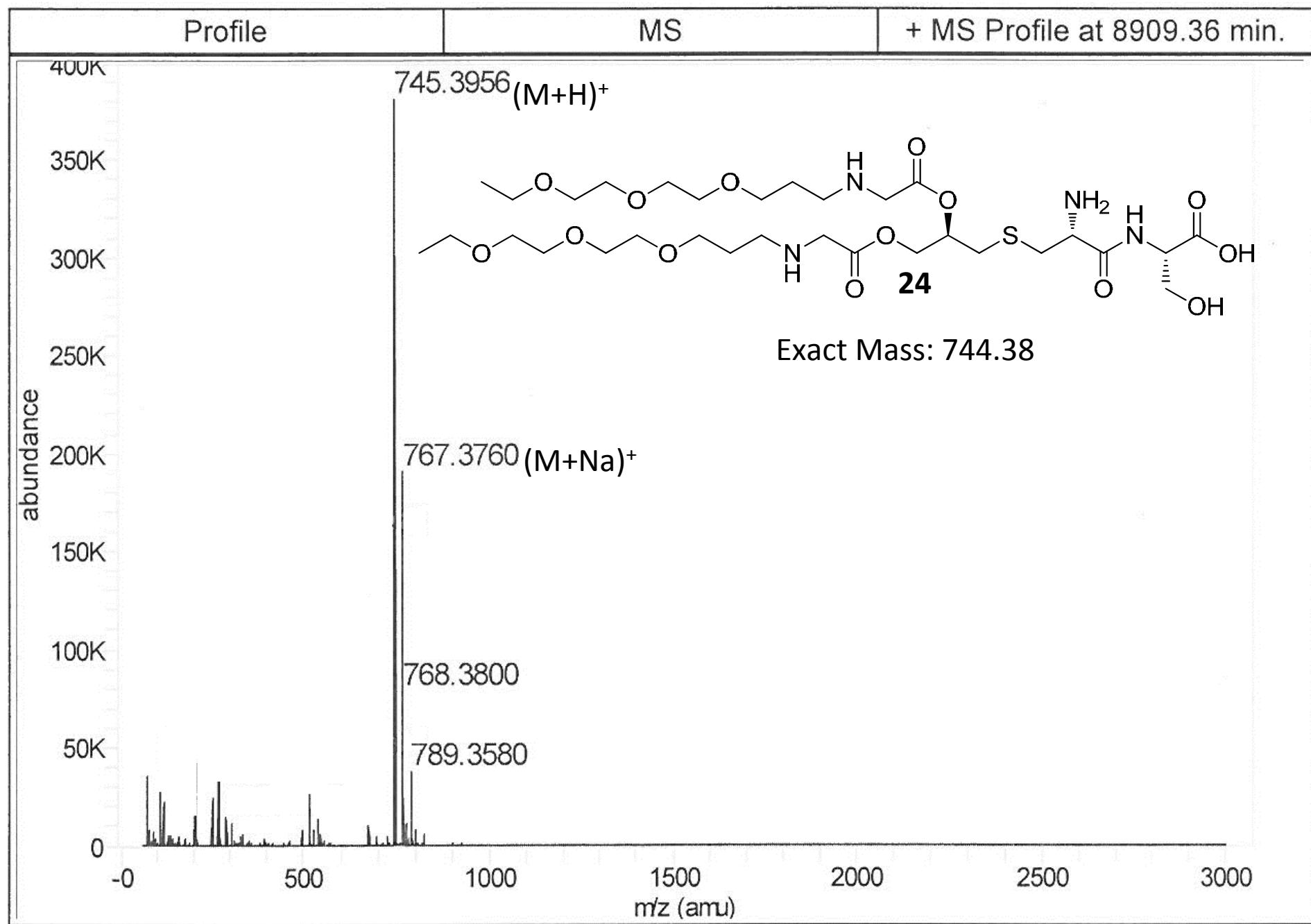
S123

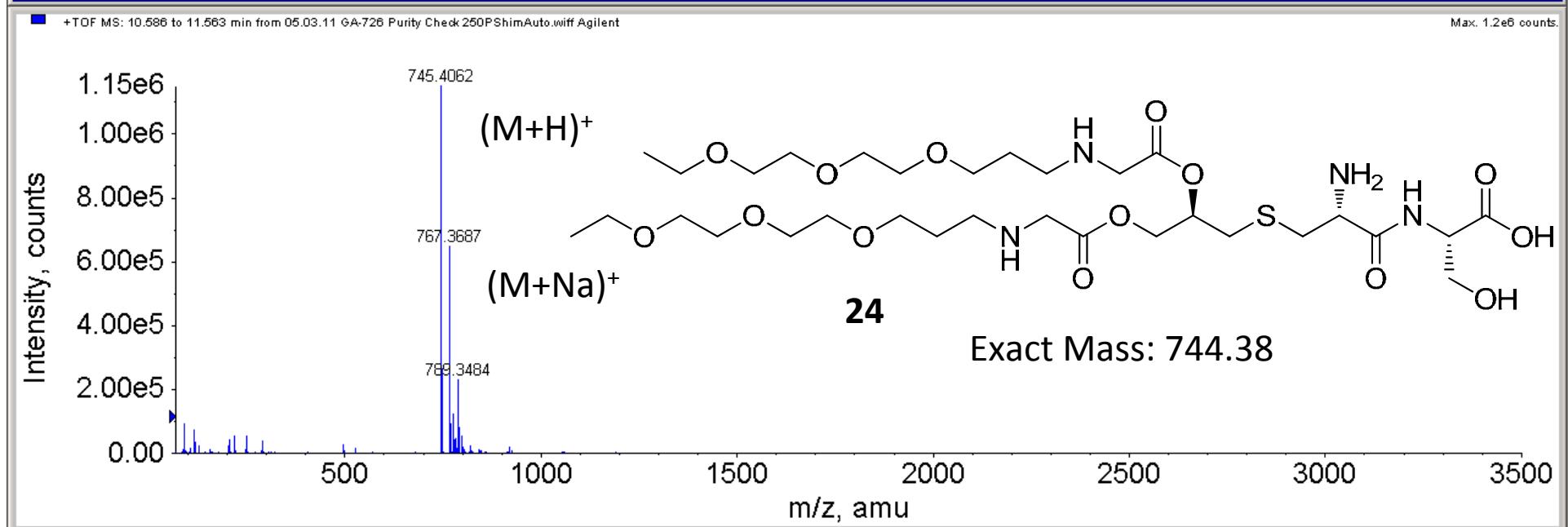
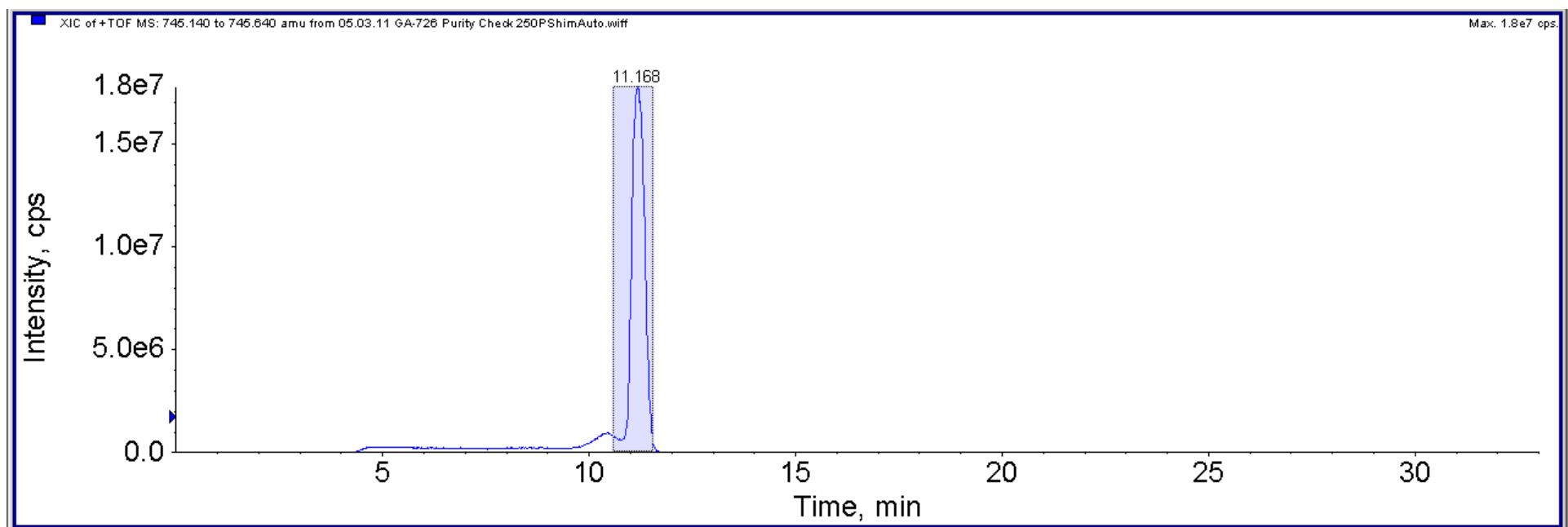


¹³C Spectrum

S124

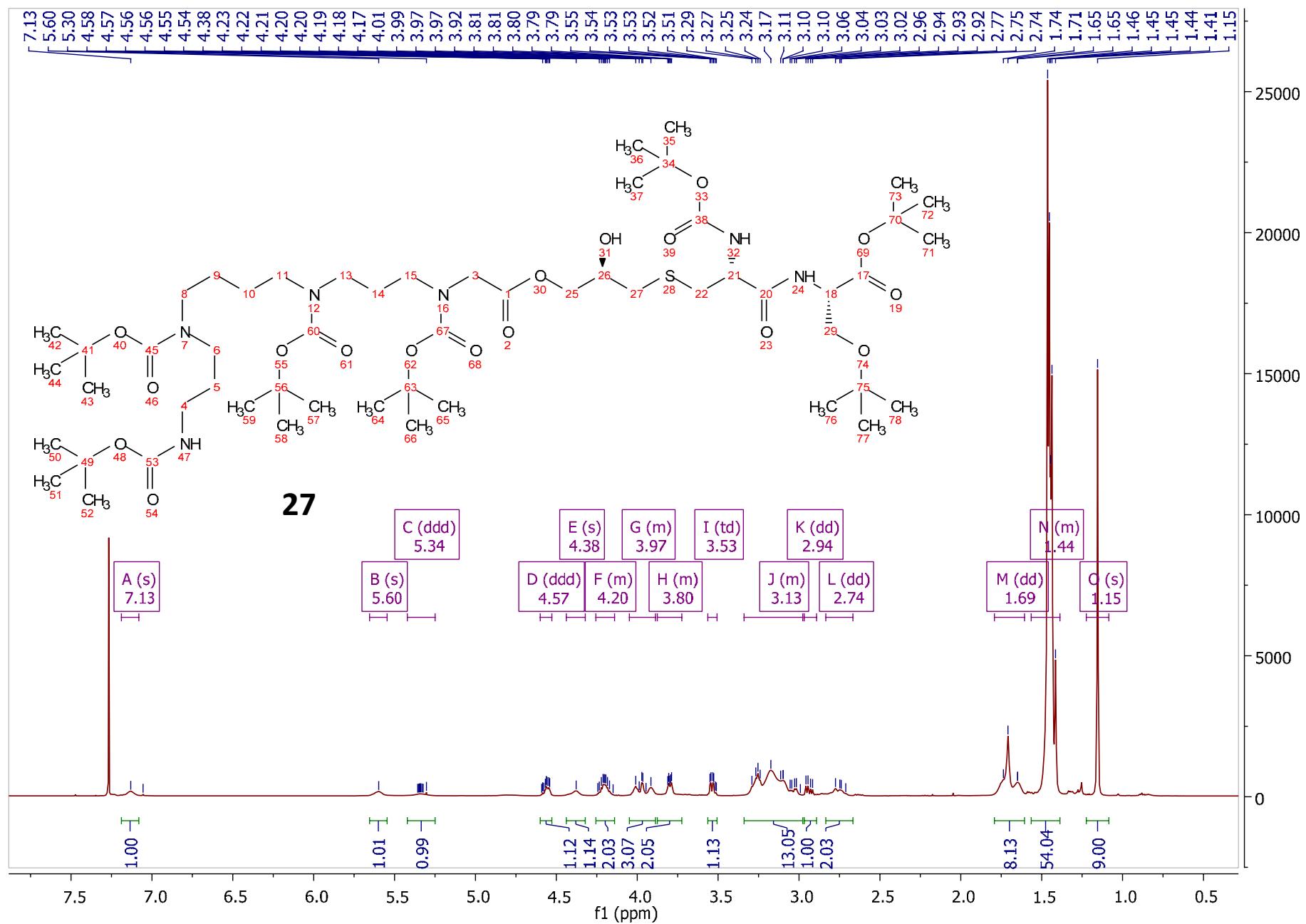






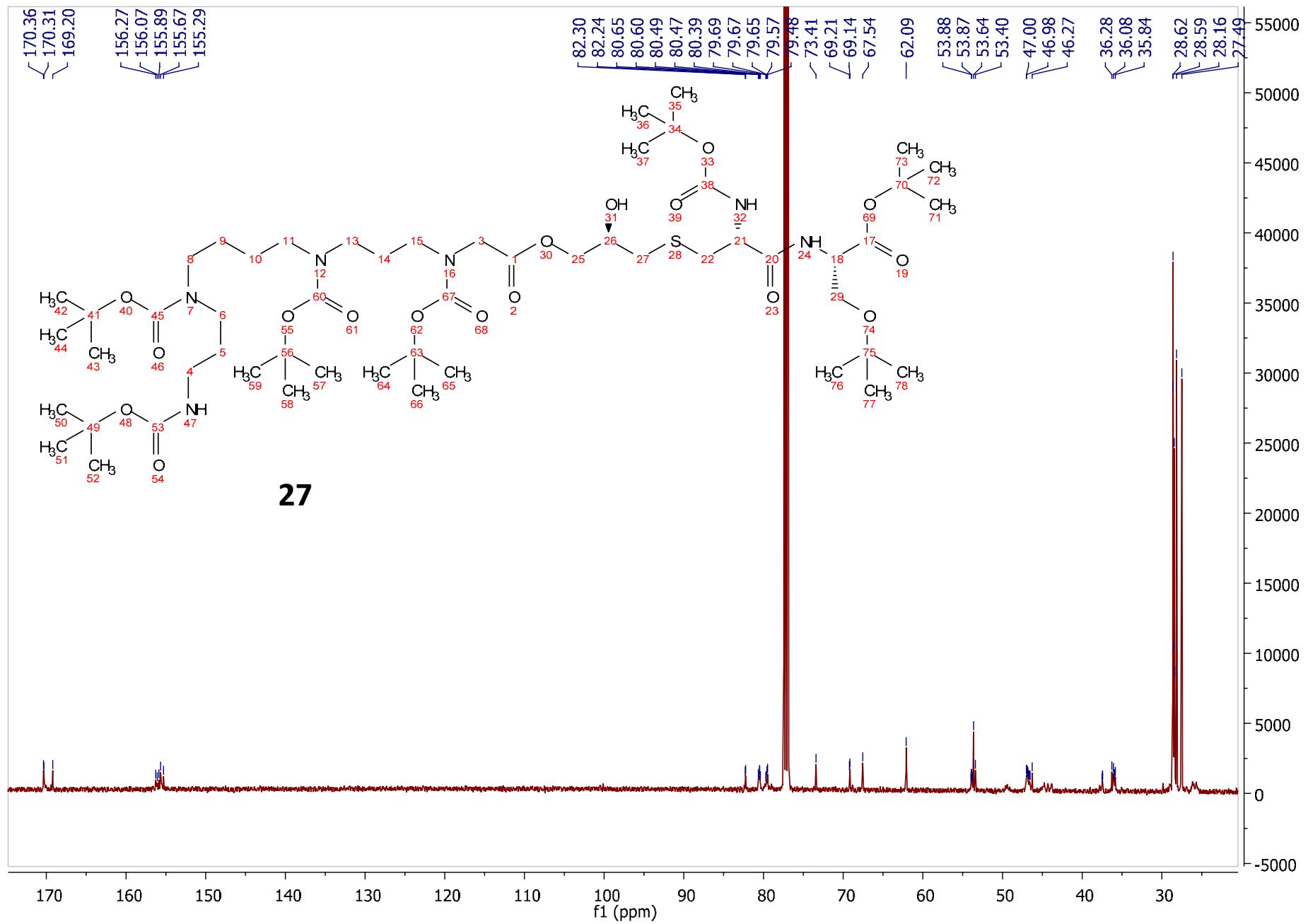
¹H Spectrum

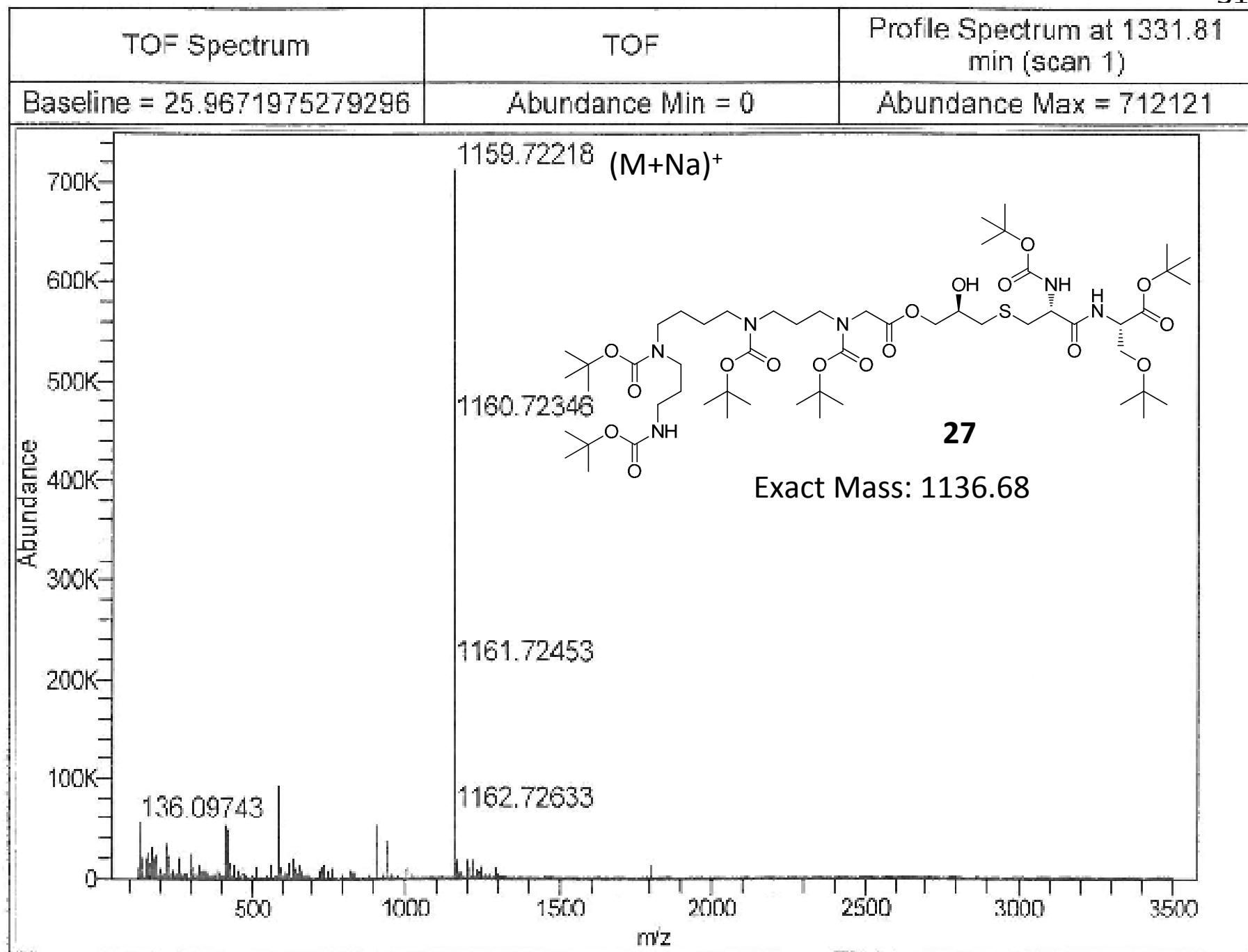
S127



¹³C Spectrum

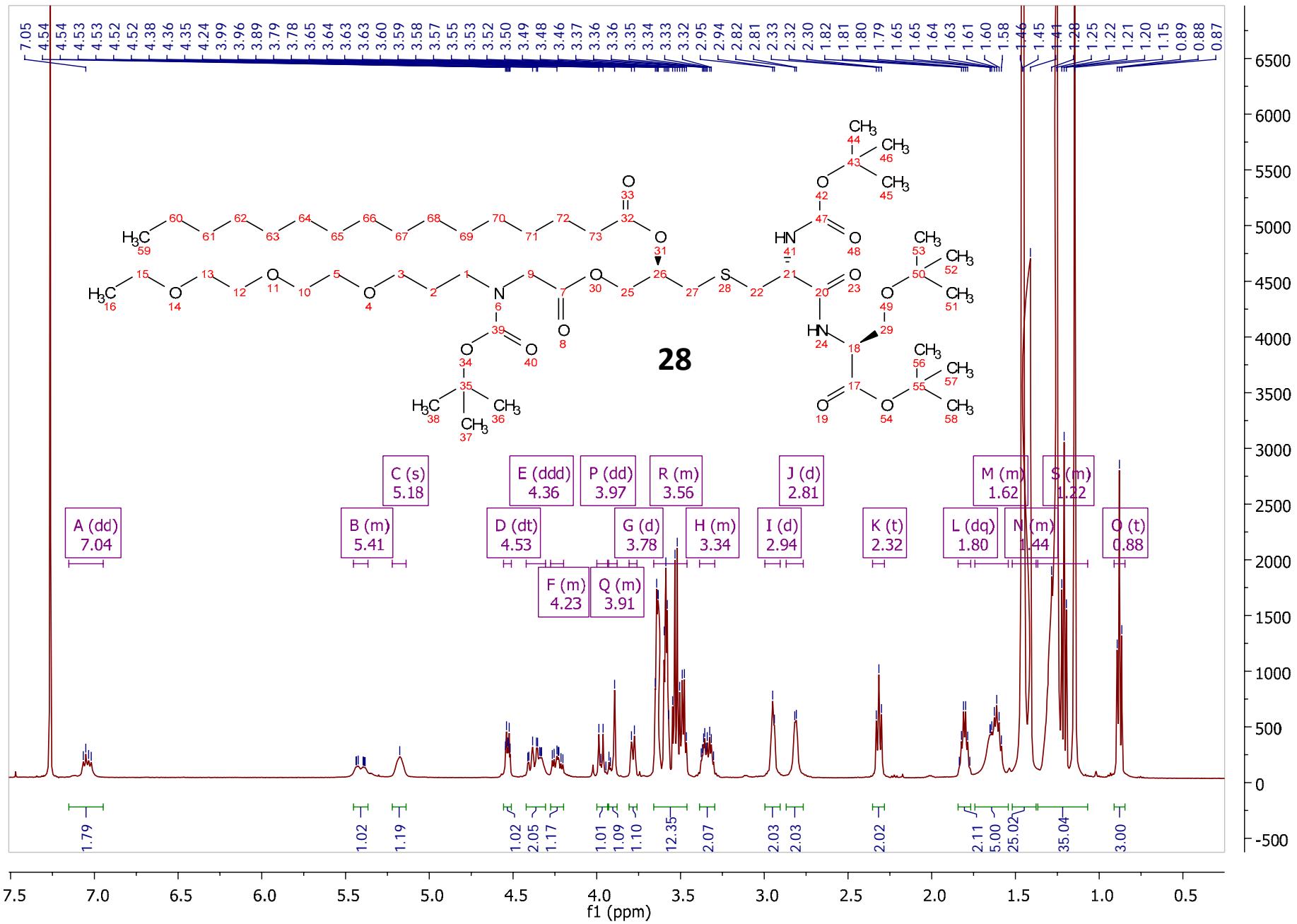
S128





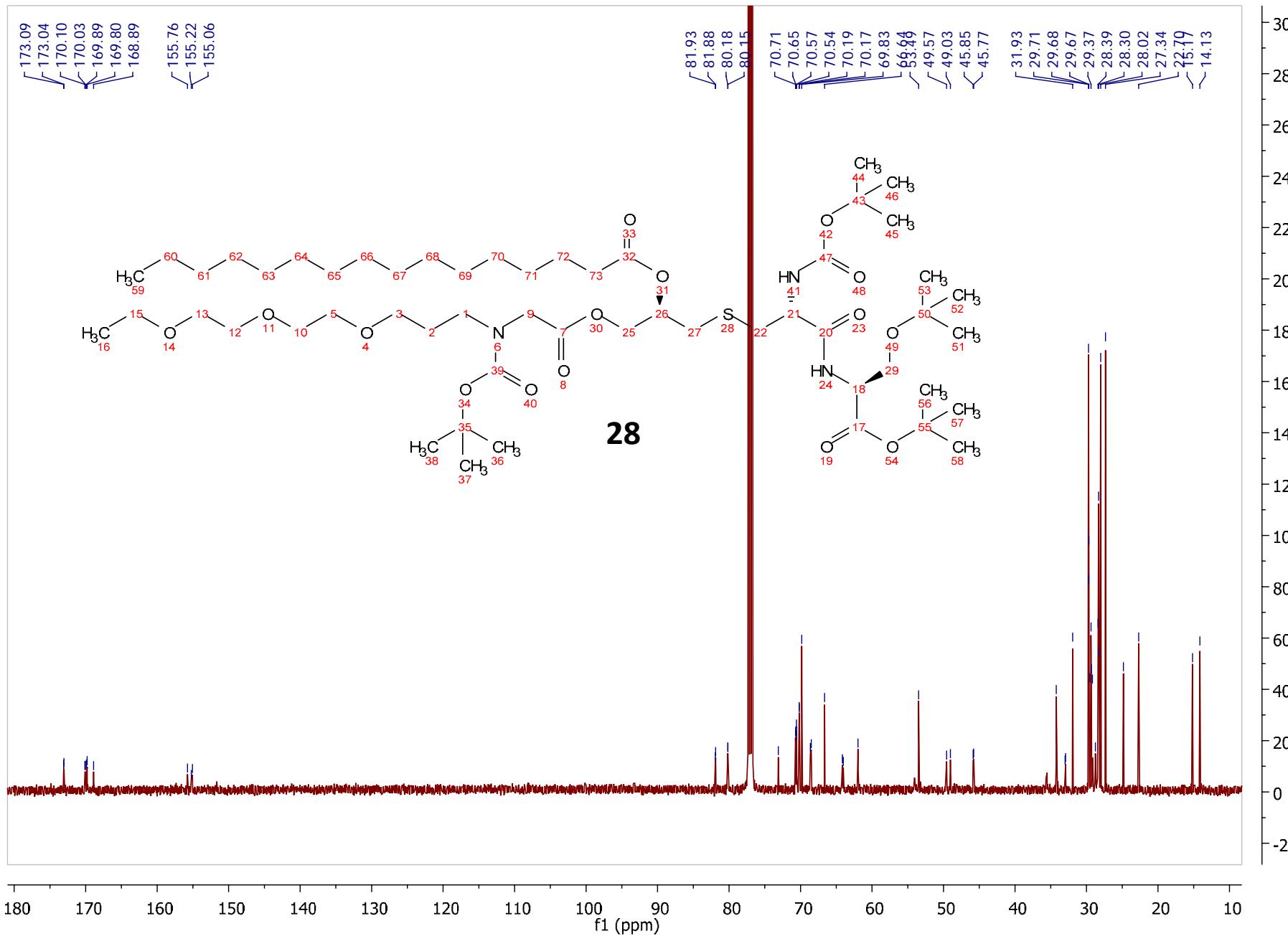
¹H Spectrum

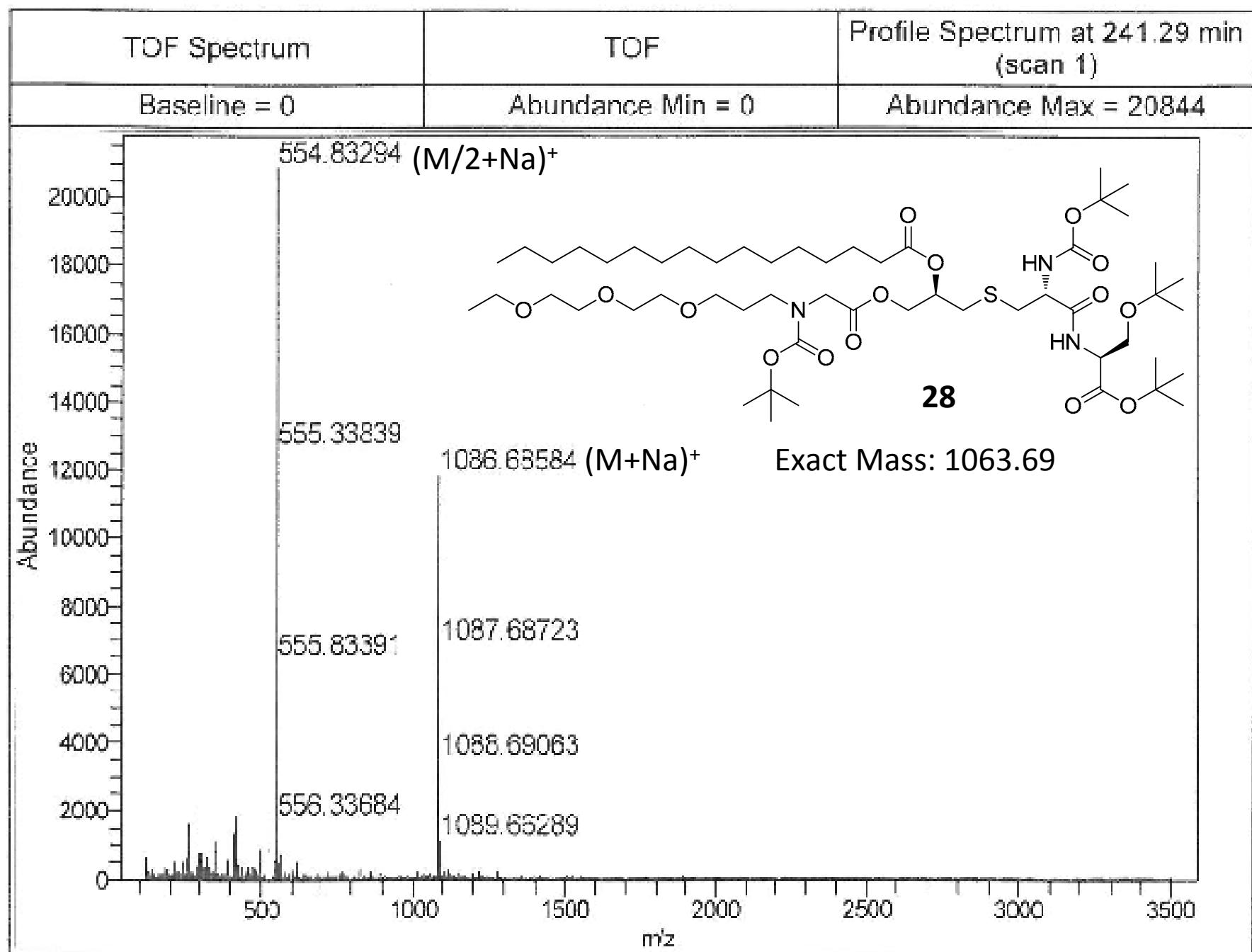
S130



¹³C Spectrum

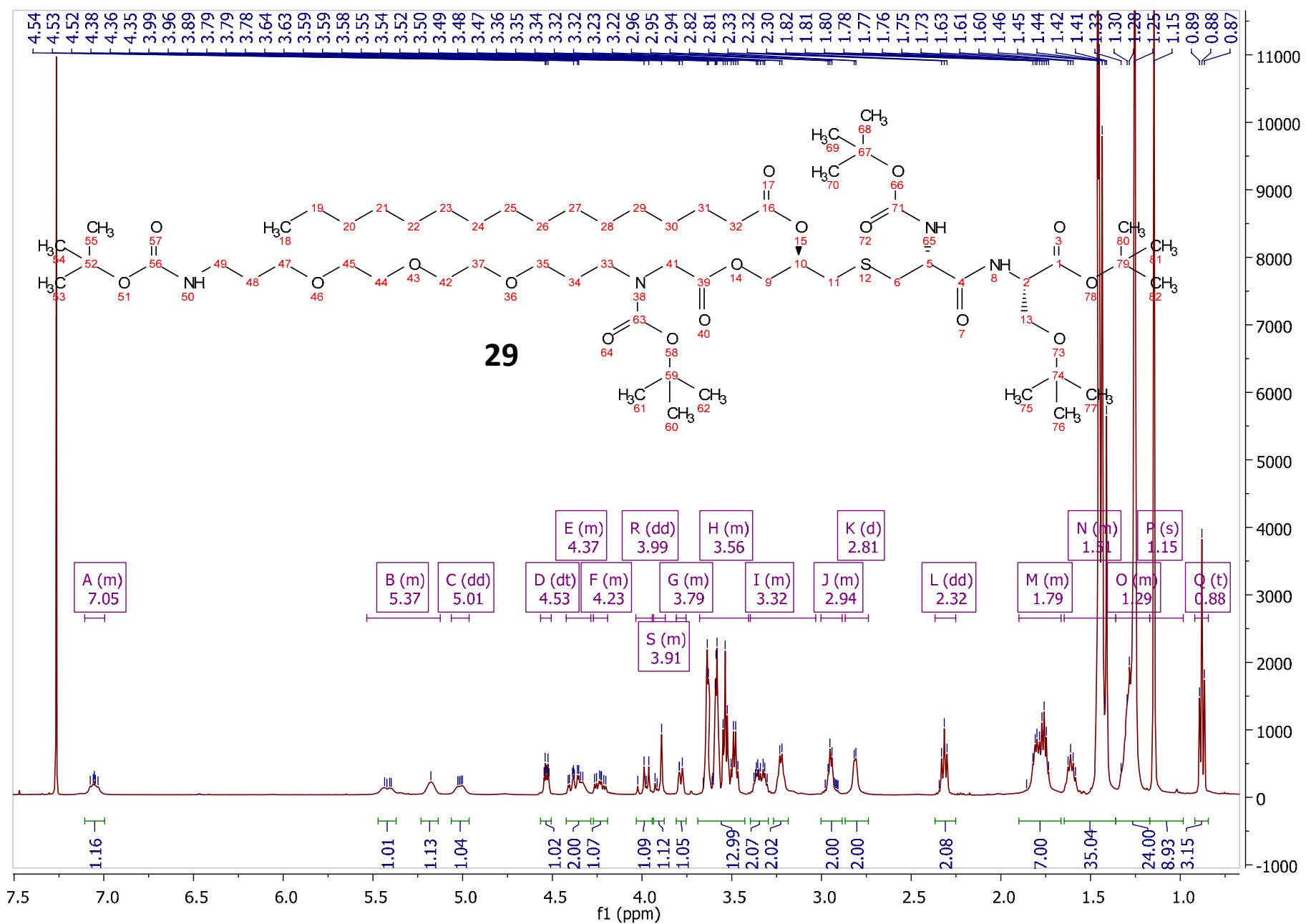
S131





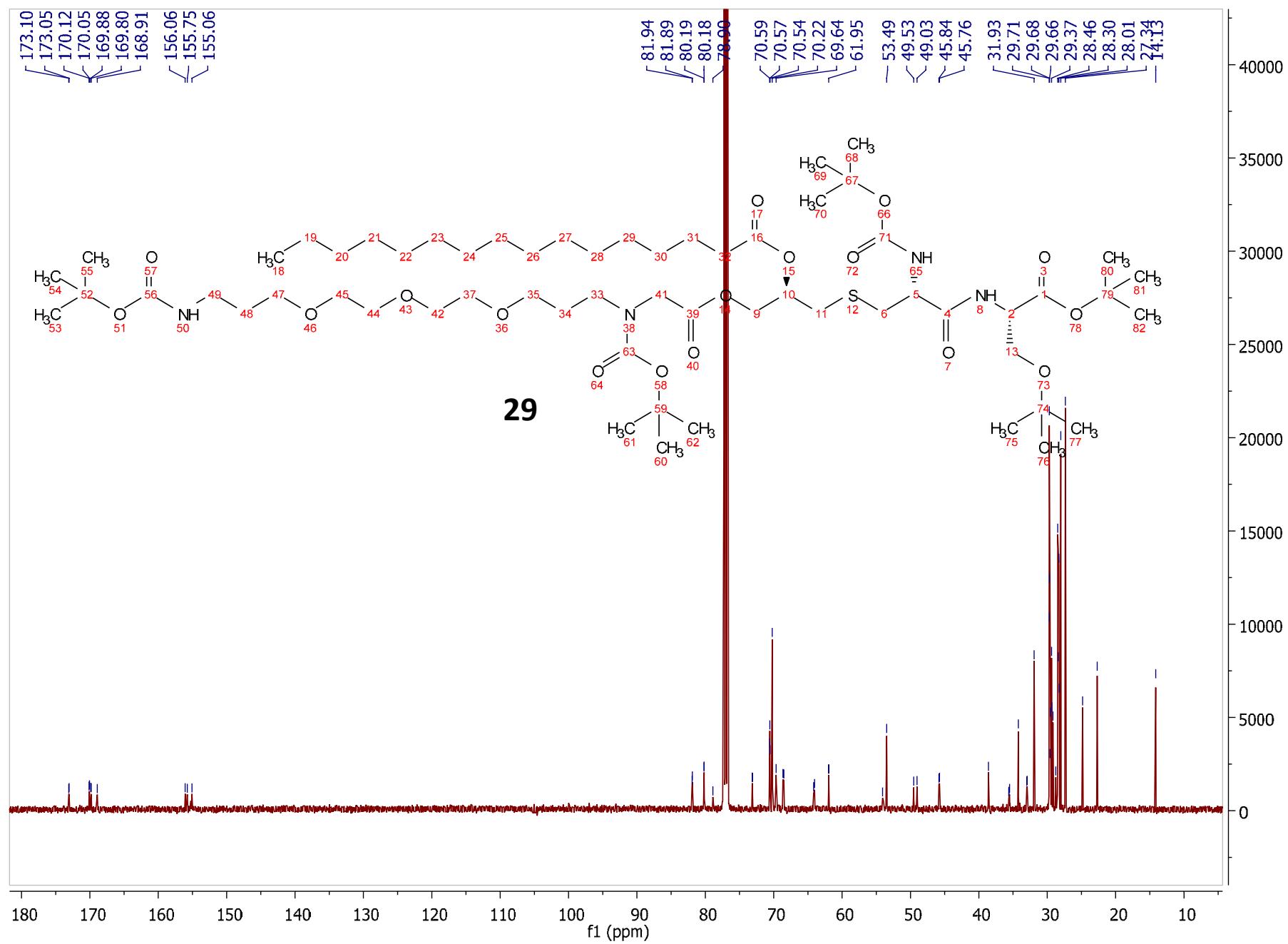
¹H Spectrum

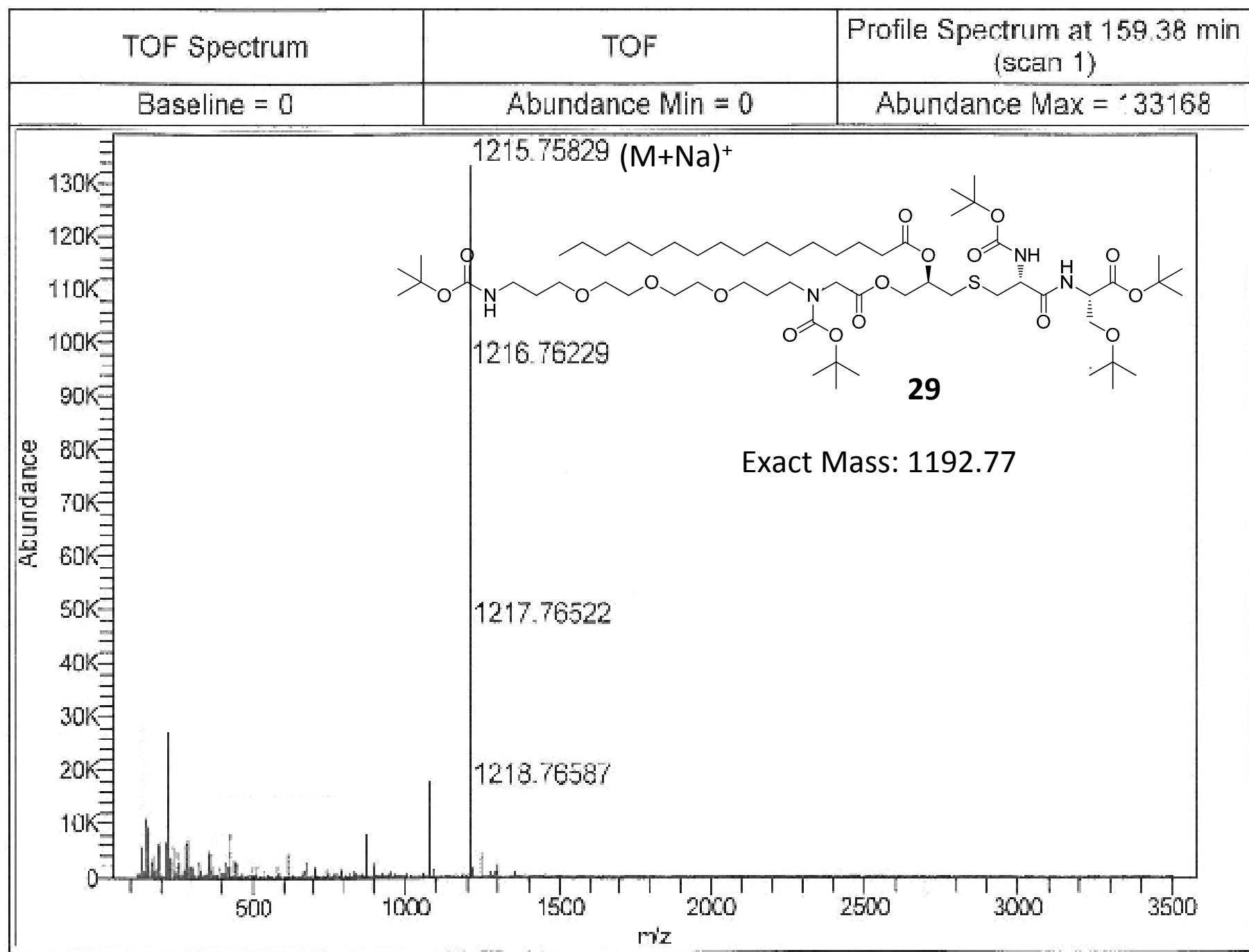
S133



¹³C Spectrum

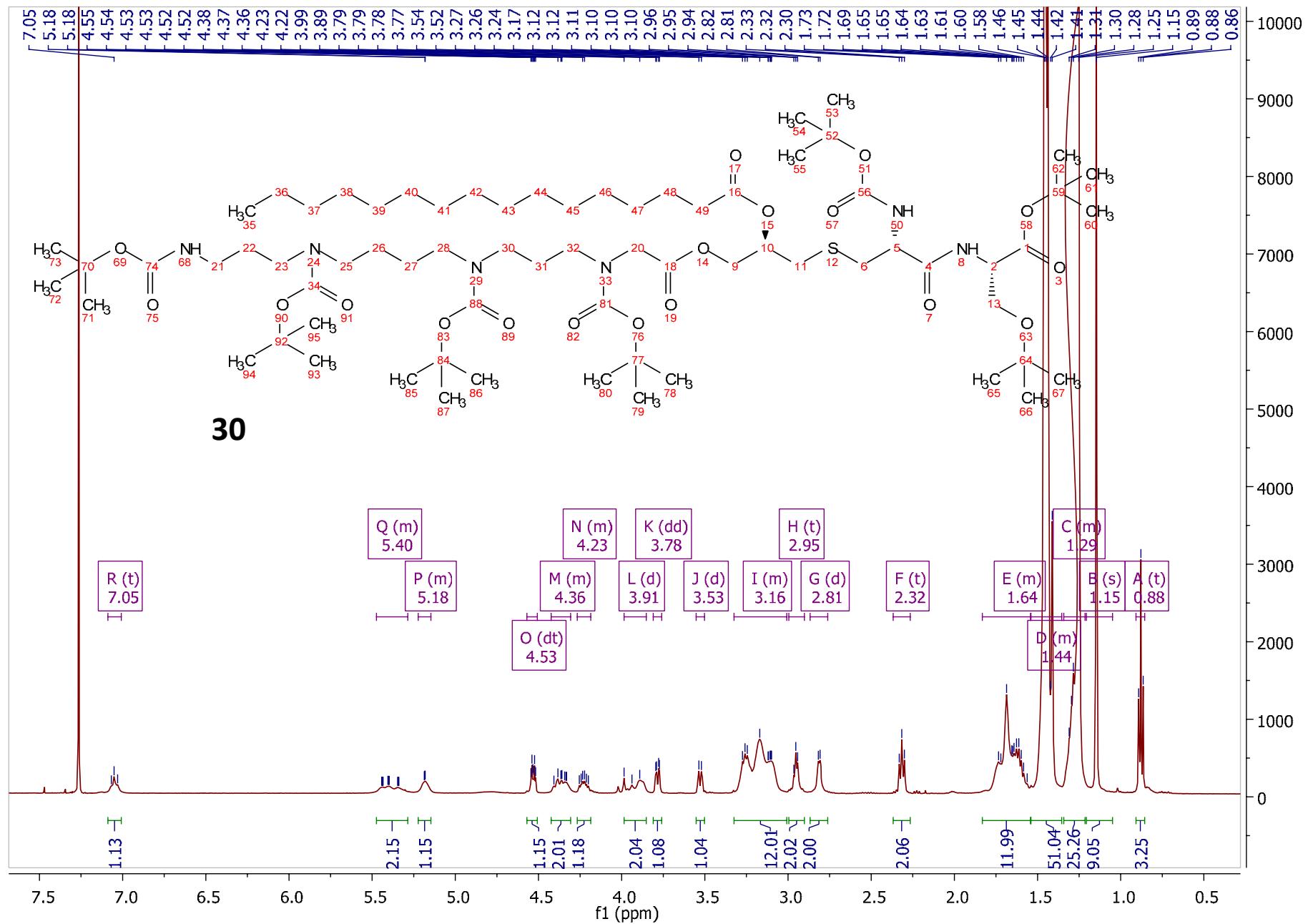
S134





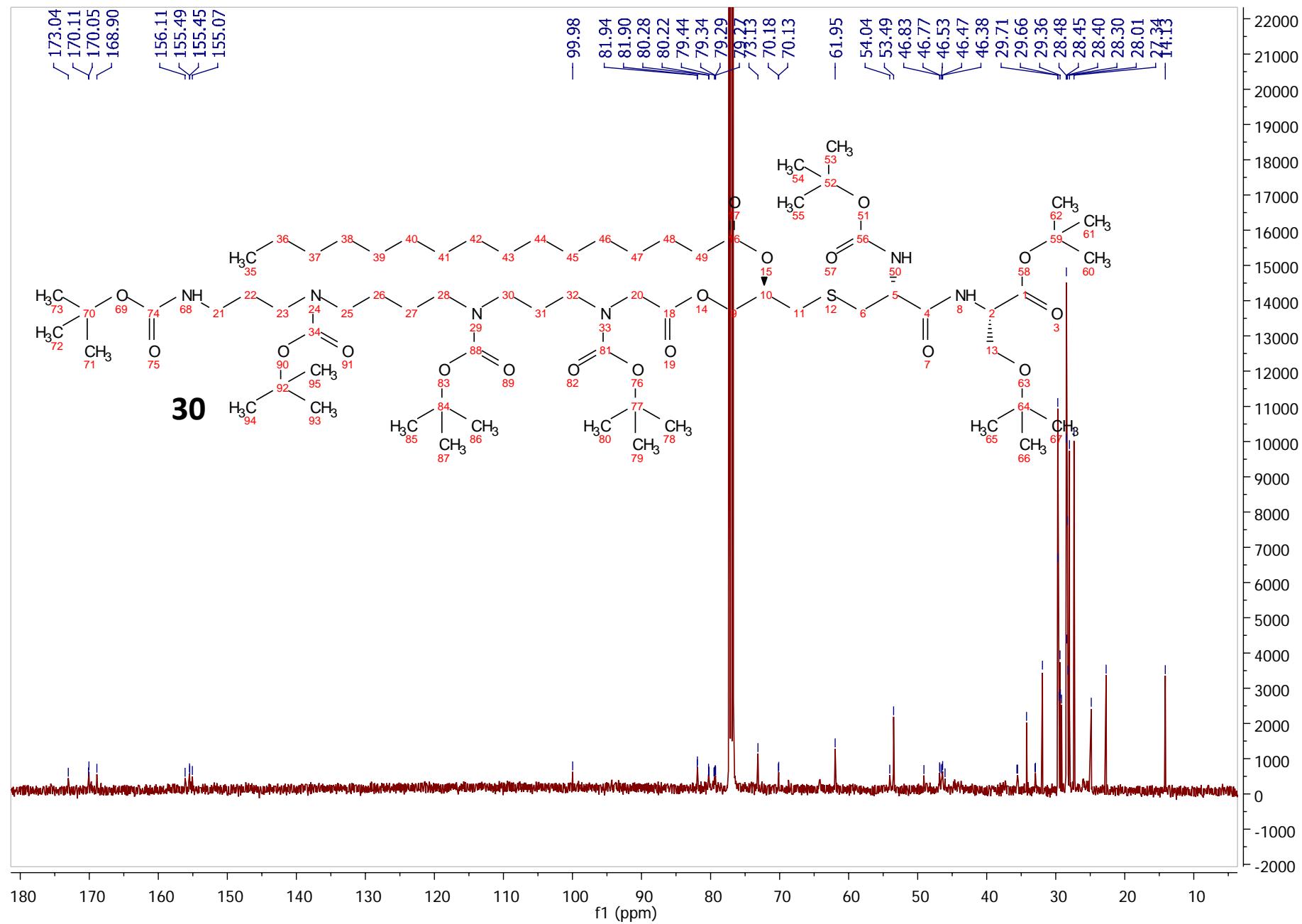
¹H Spectrum

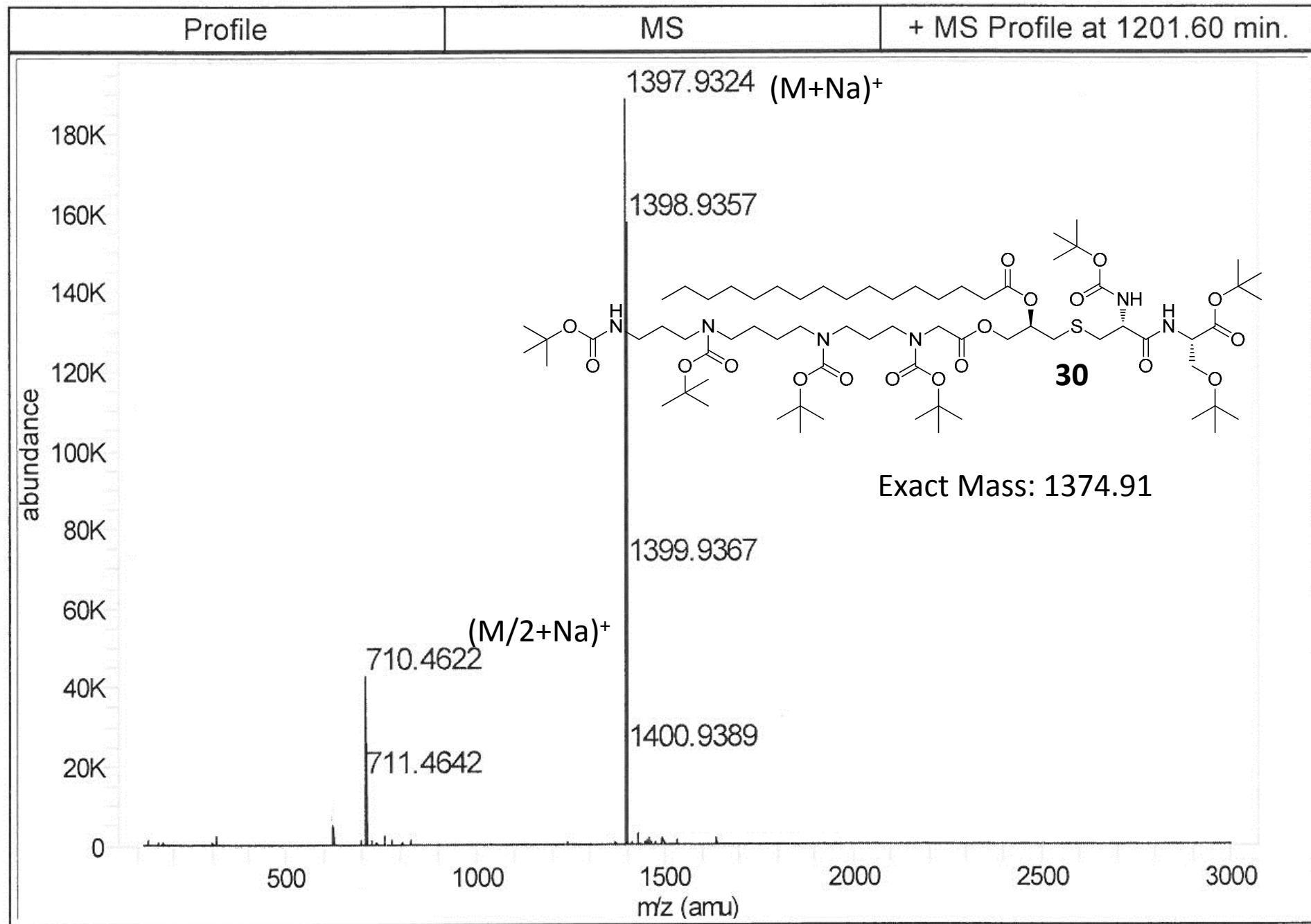
S136



¹³C Spectrum

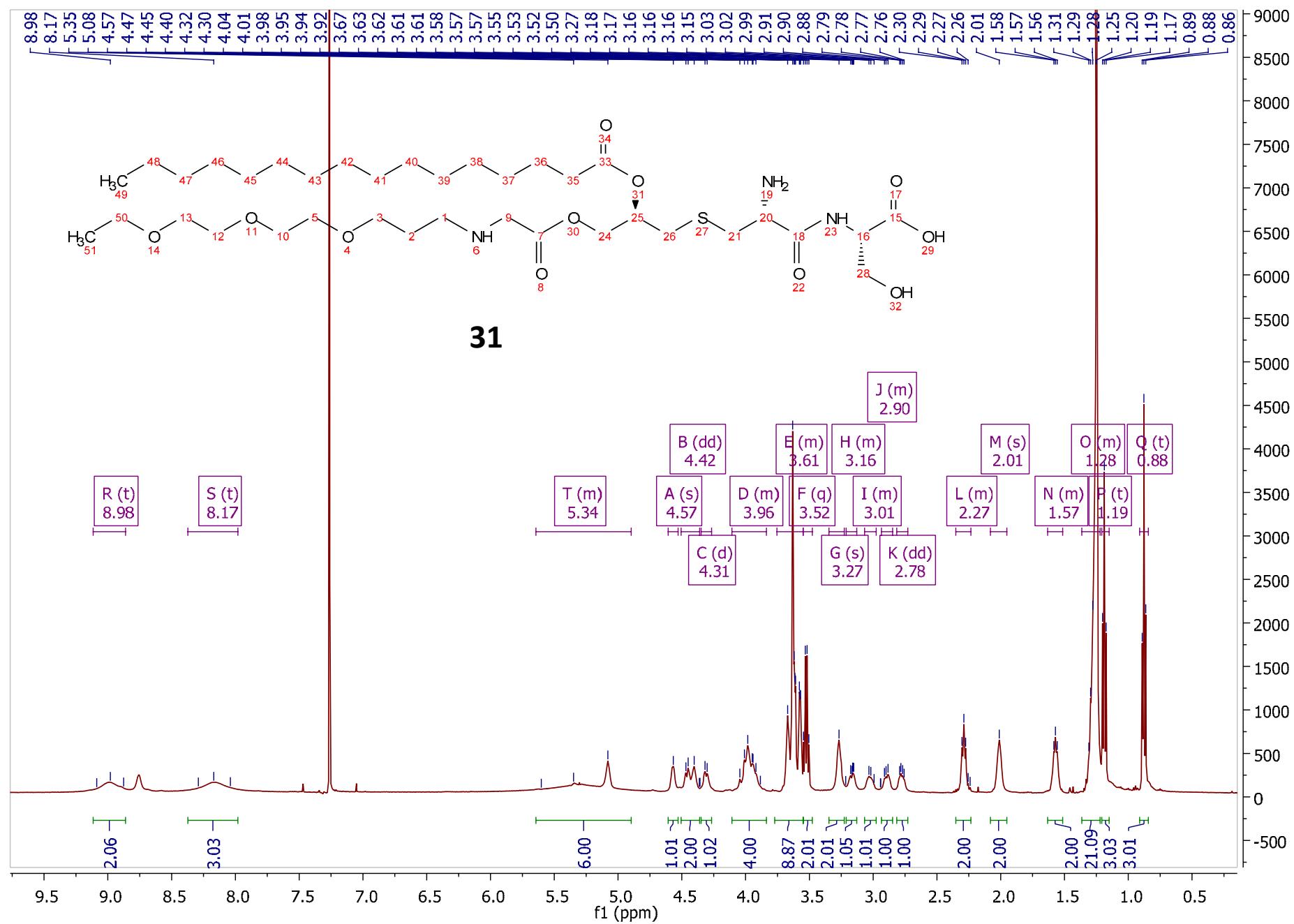
S137





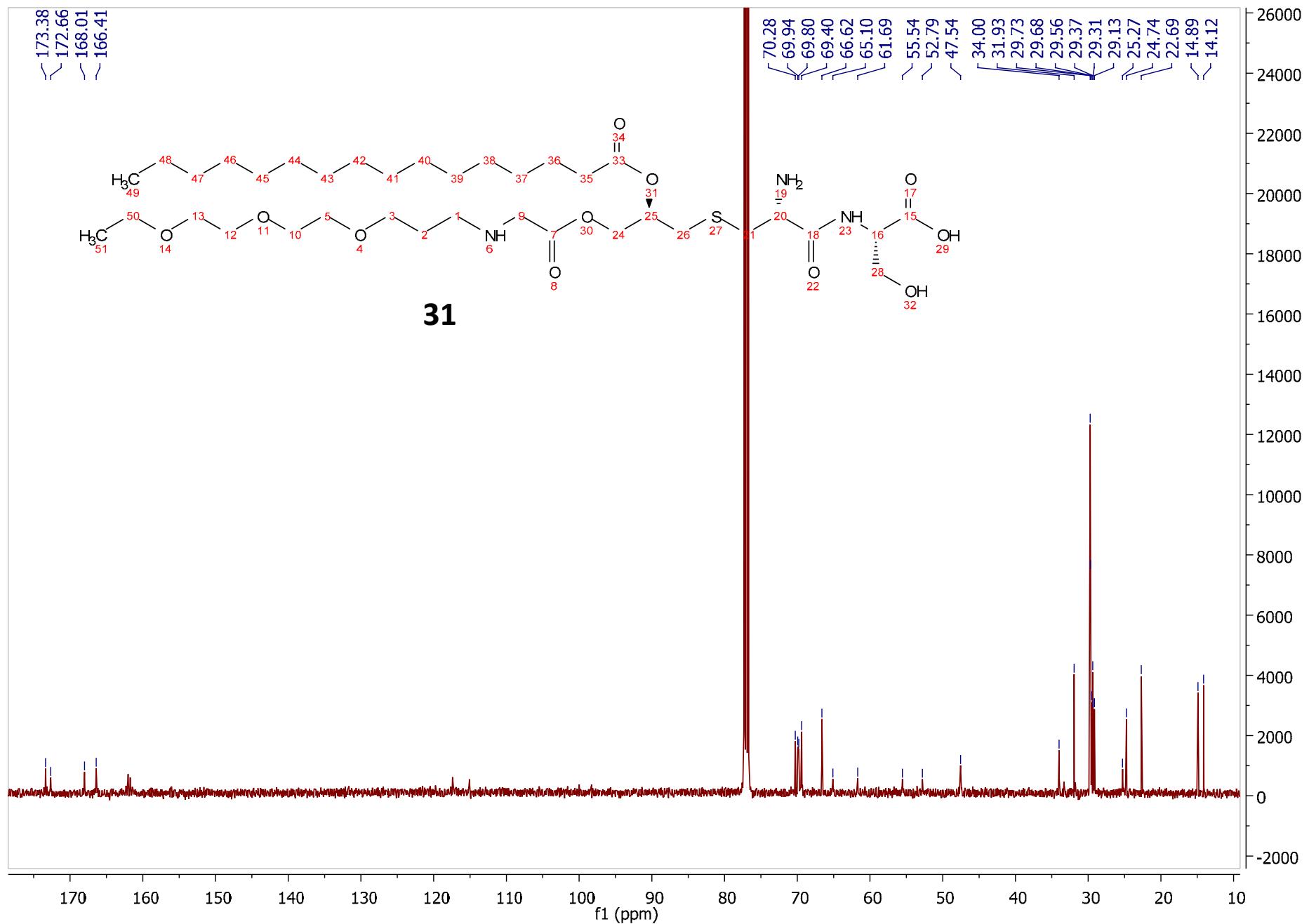
¹H Spectrum

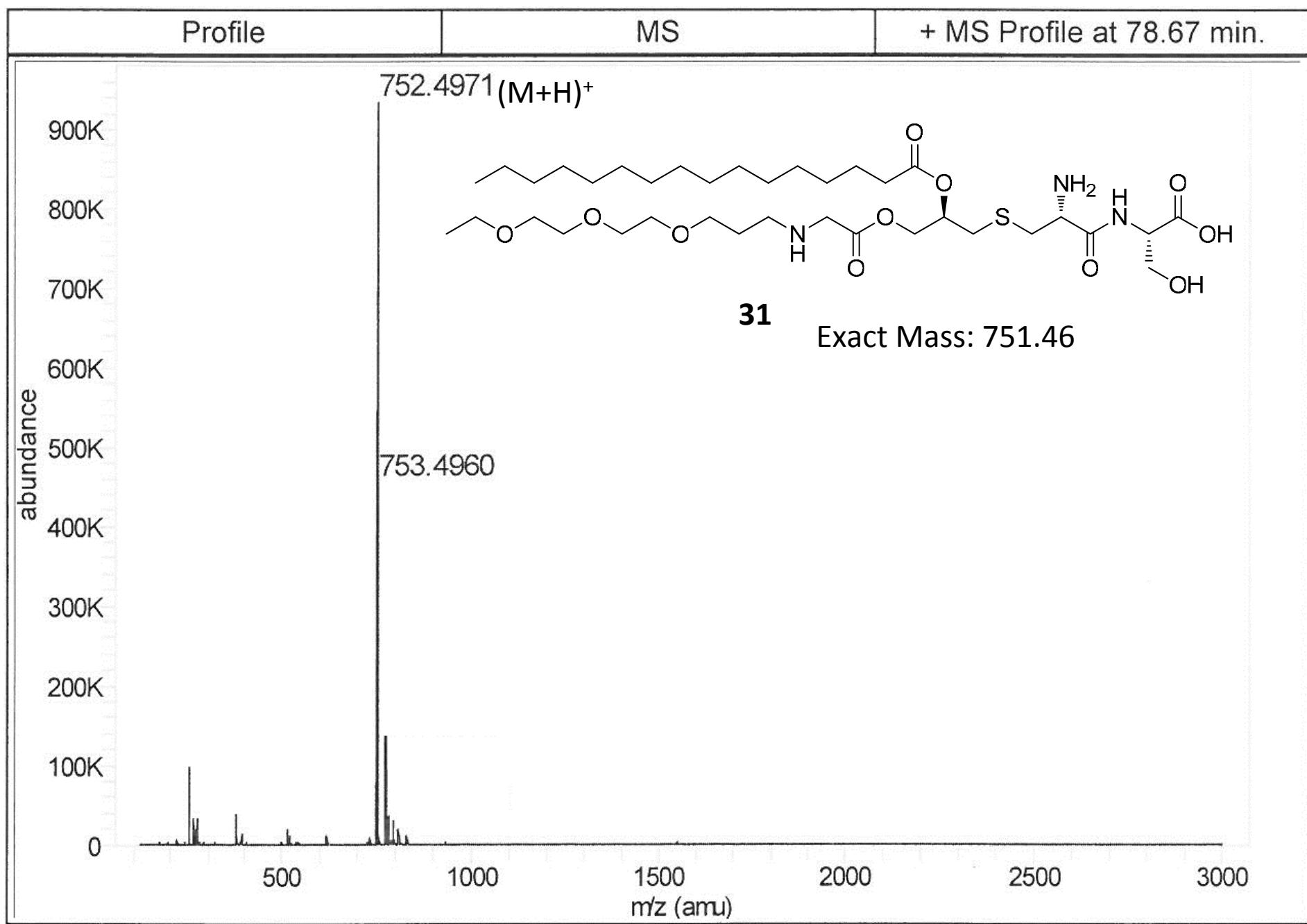
S139

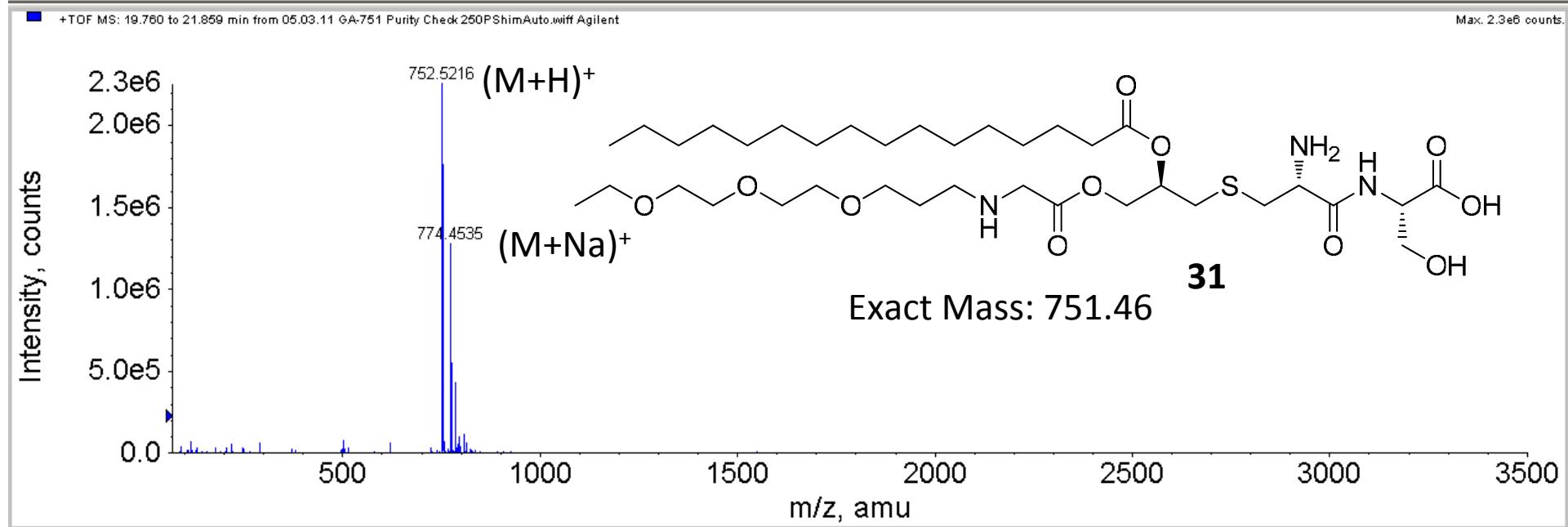
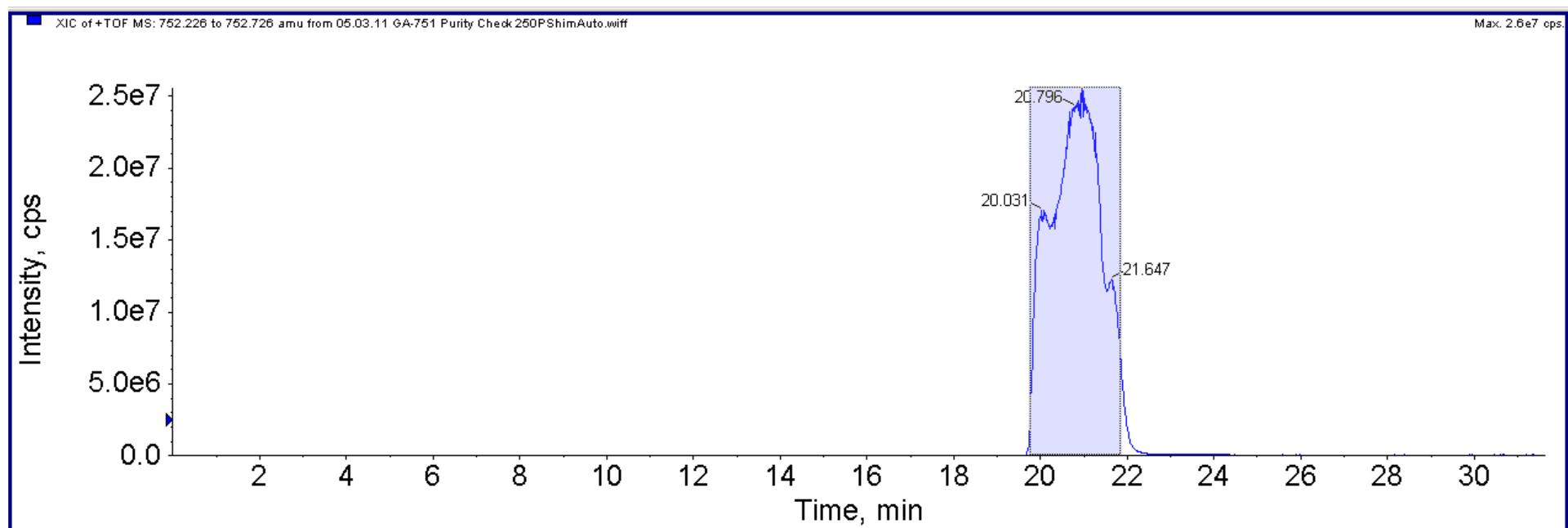


¹³C Spectrum

S140

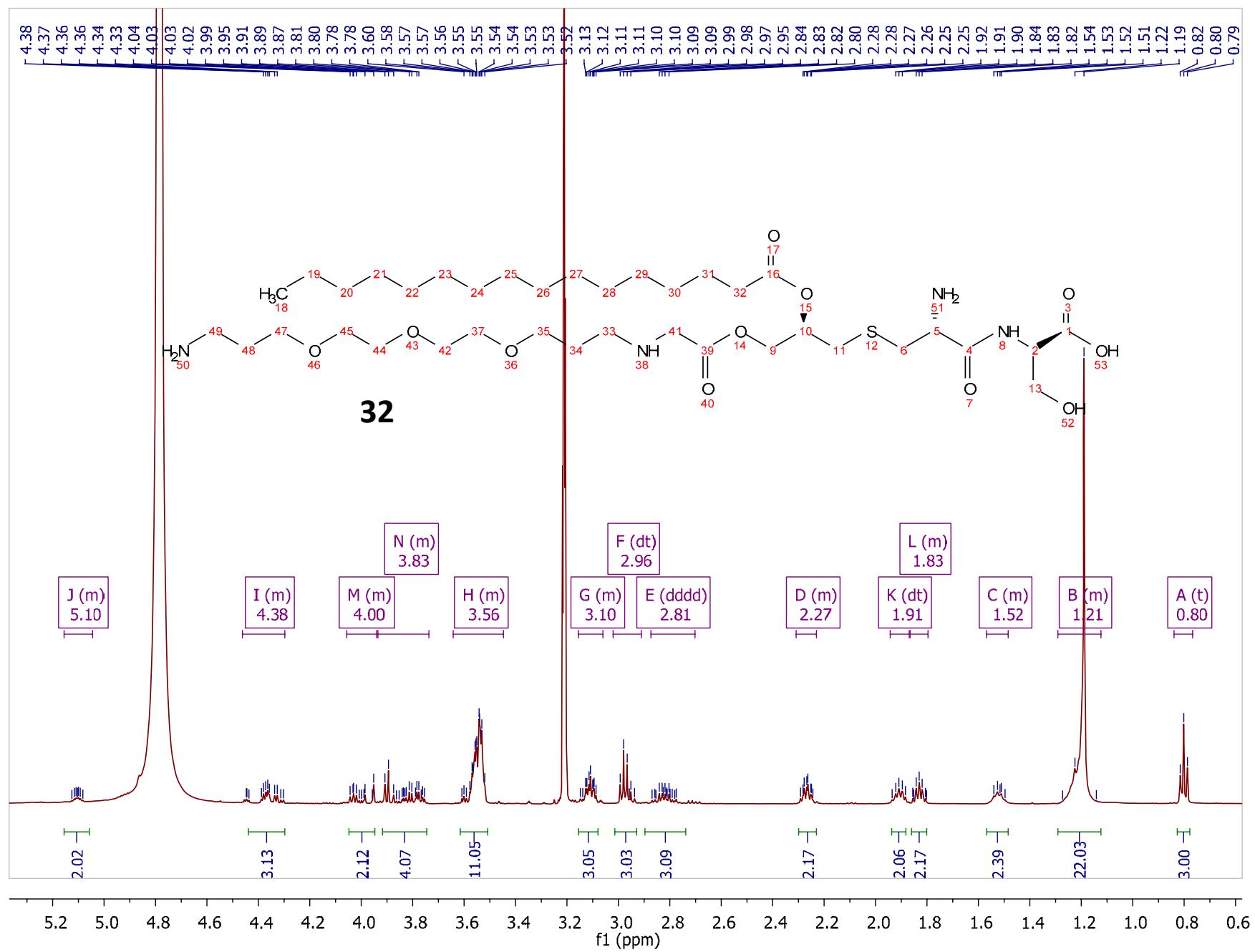






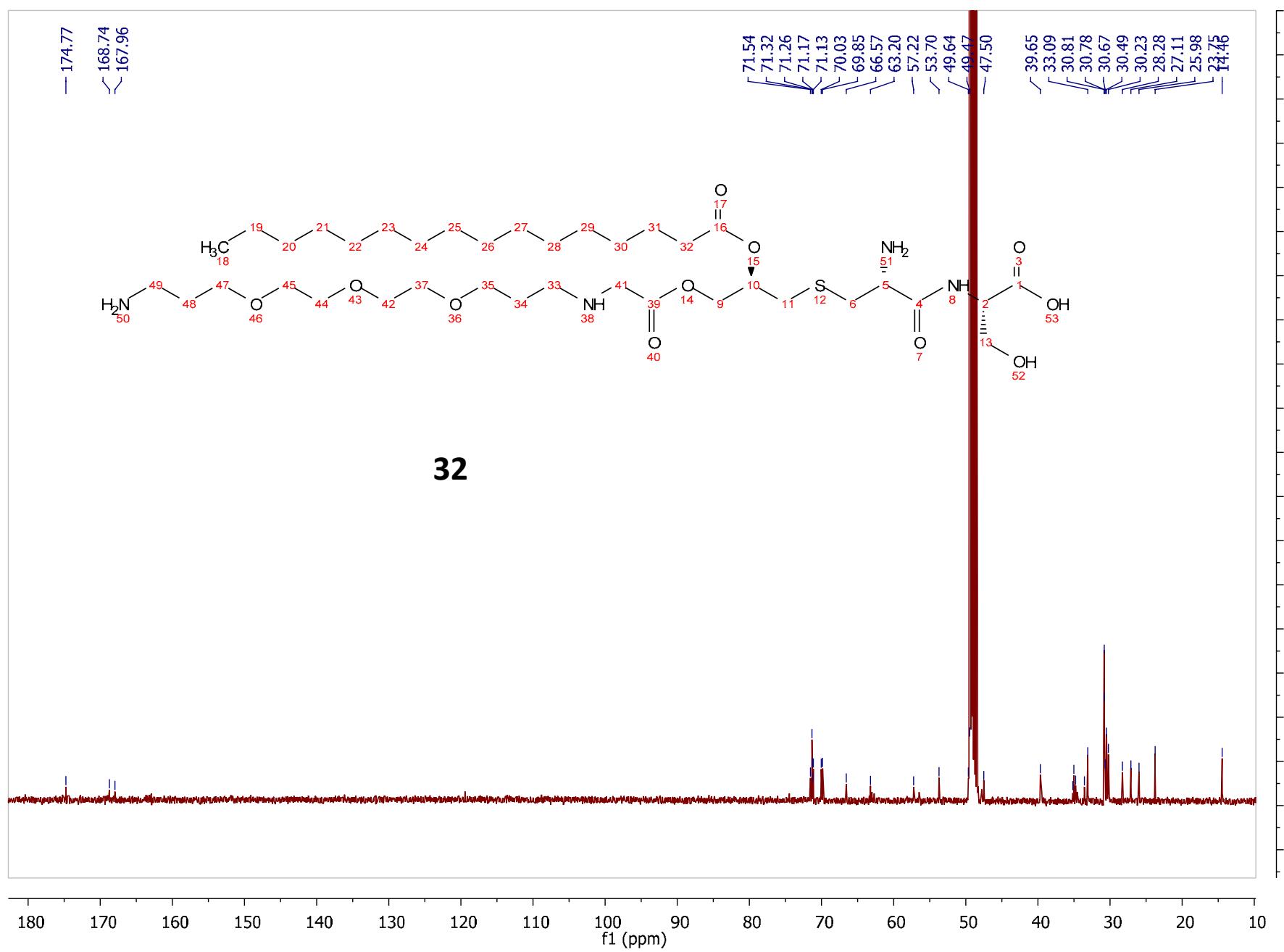
¹H Spectrum

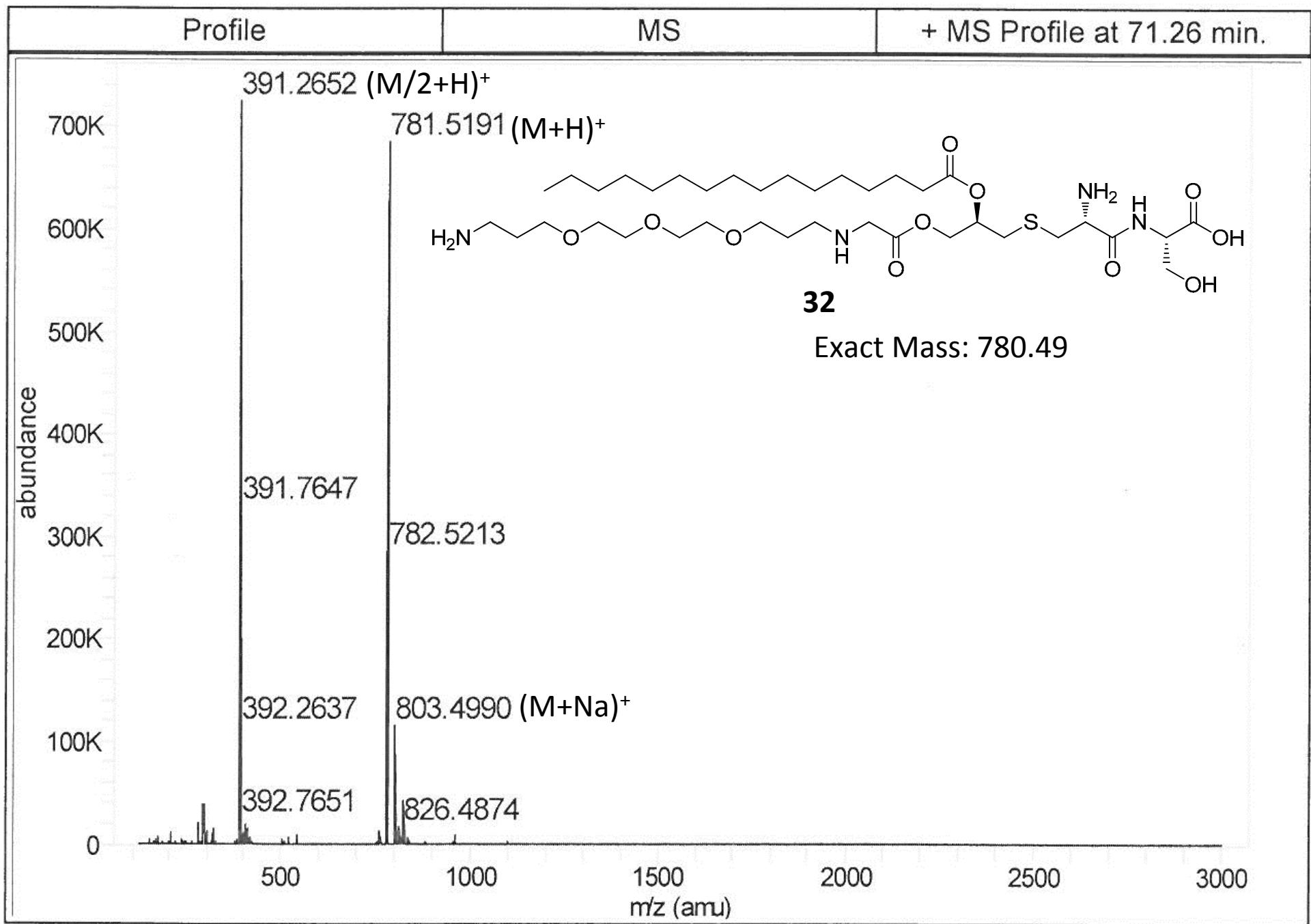
S143

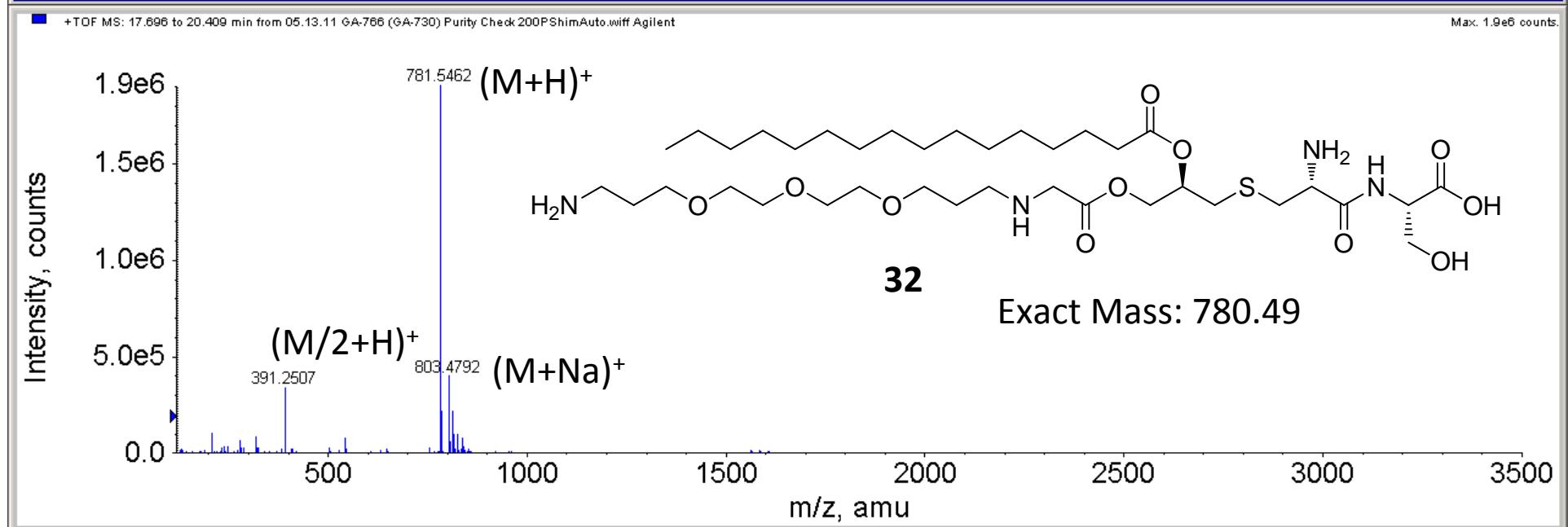
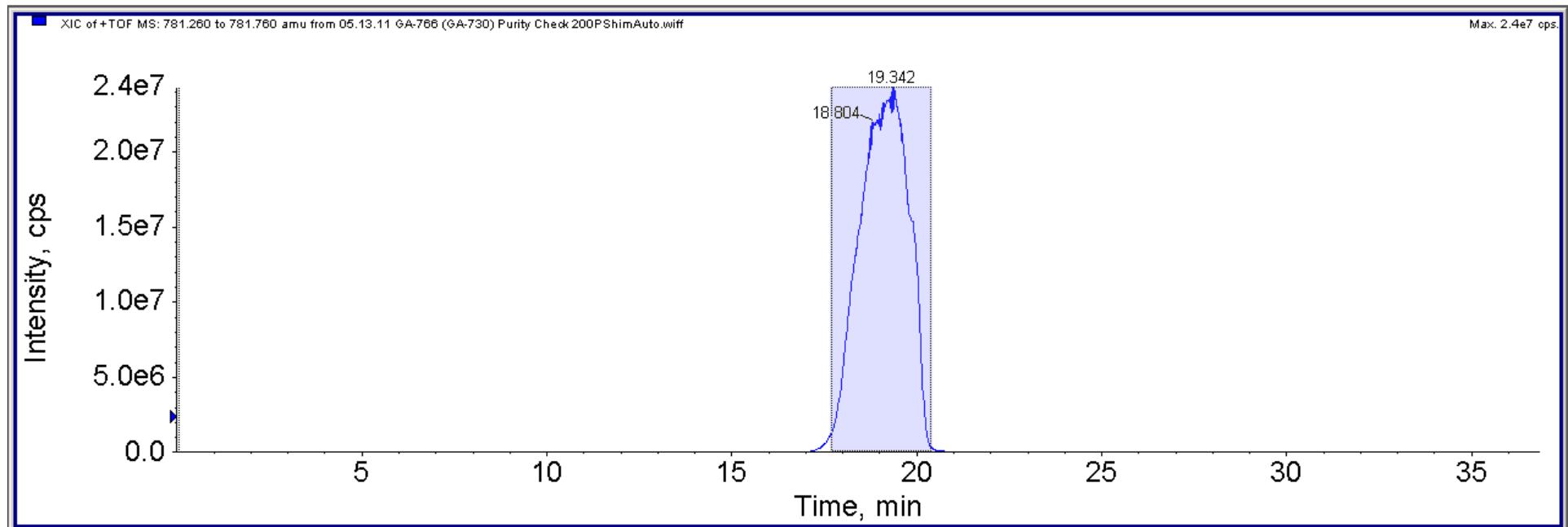


¹³C Spectrum

S144

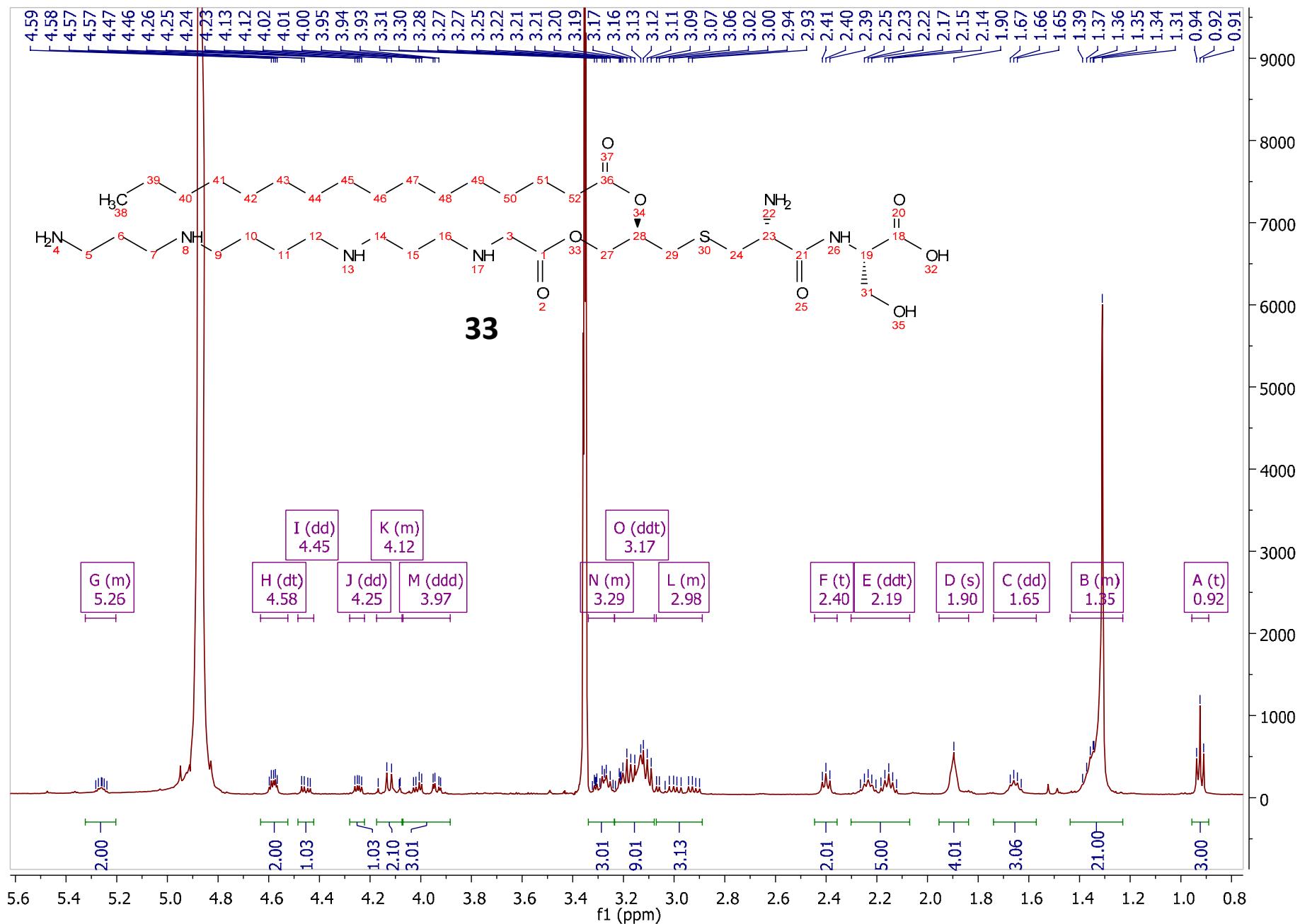






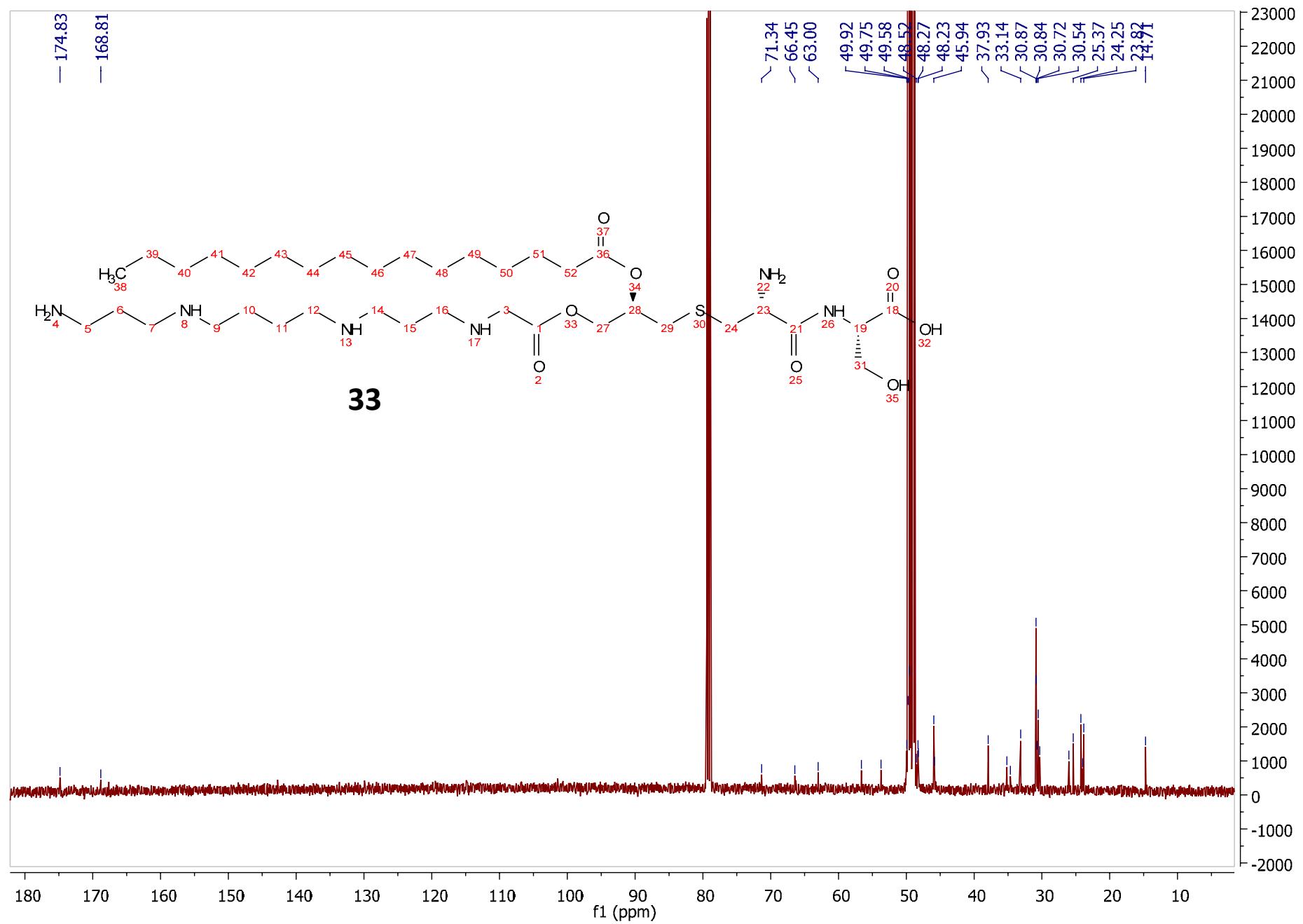
¹H Spectrum

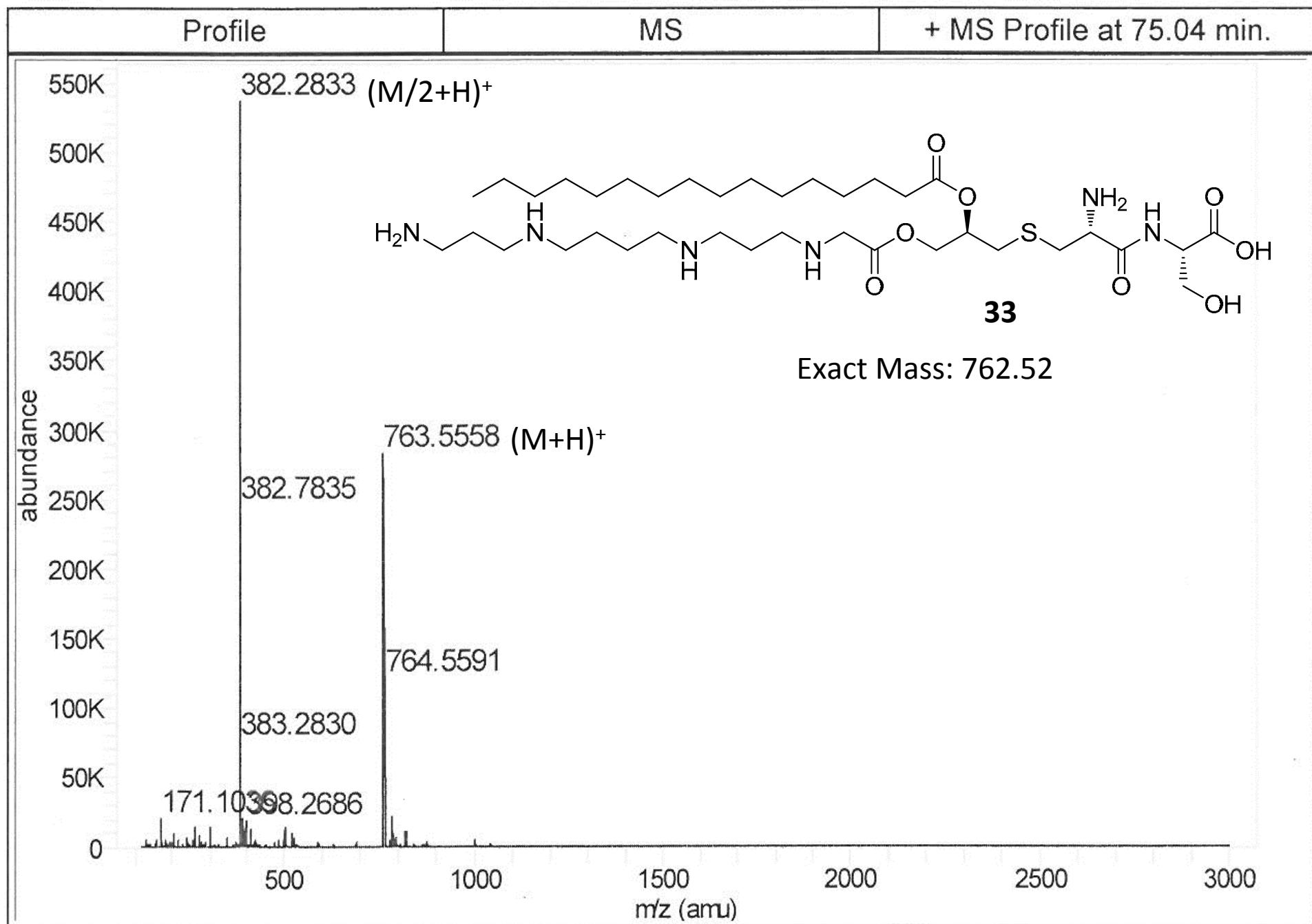
S147

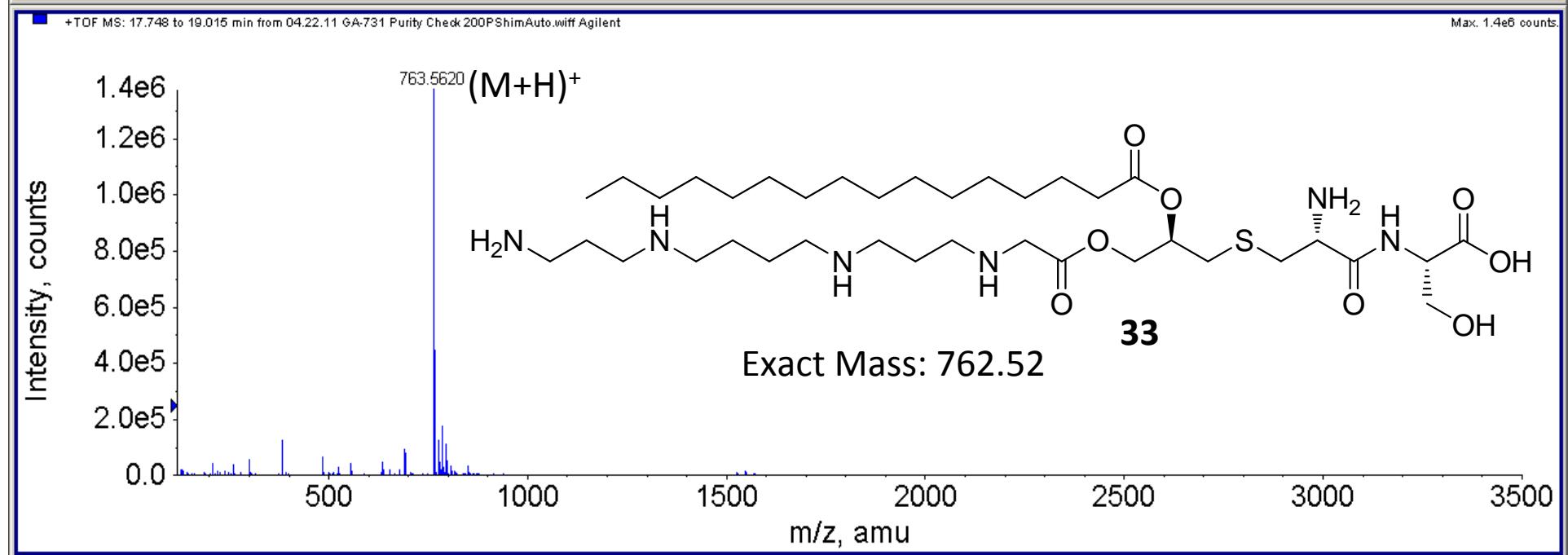
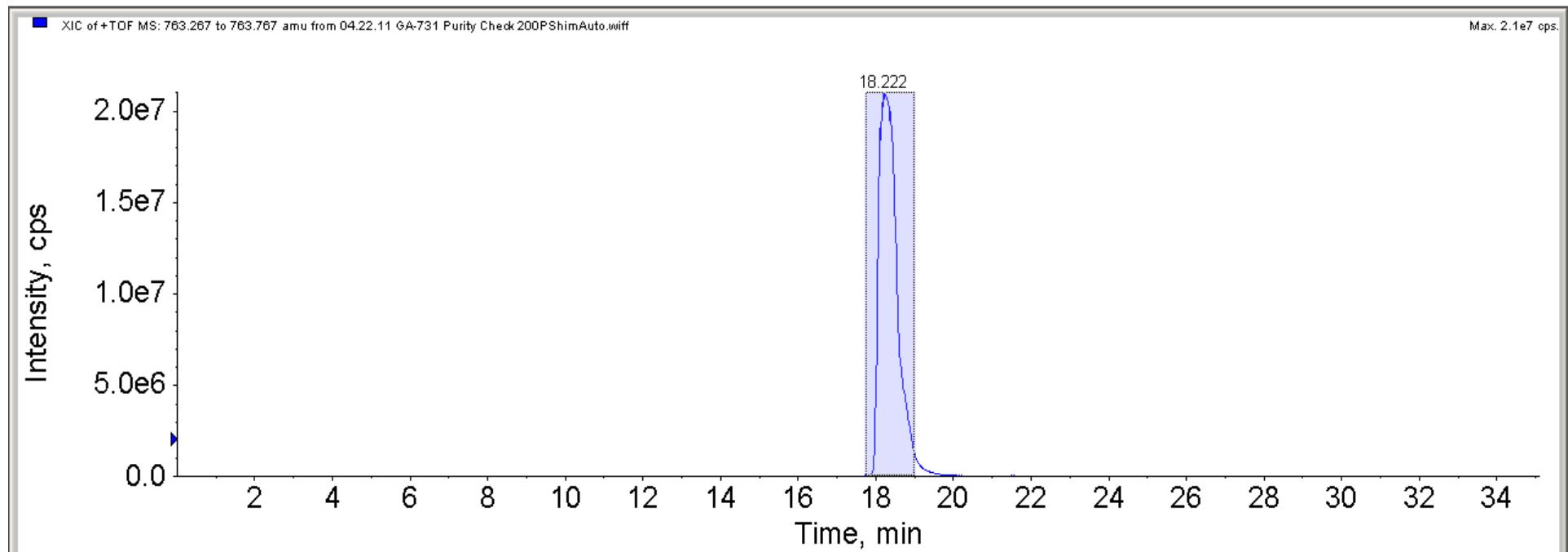


¹³C Spectrum

S148

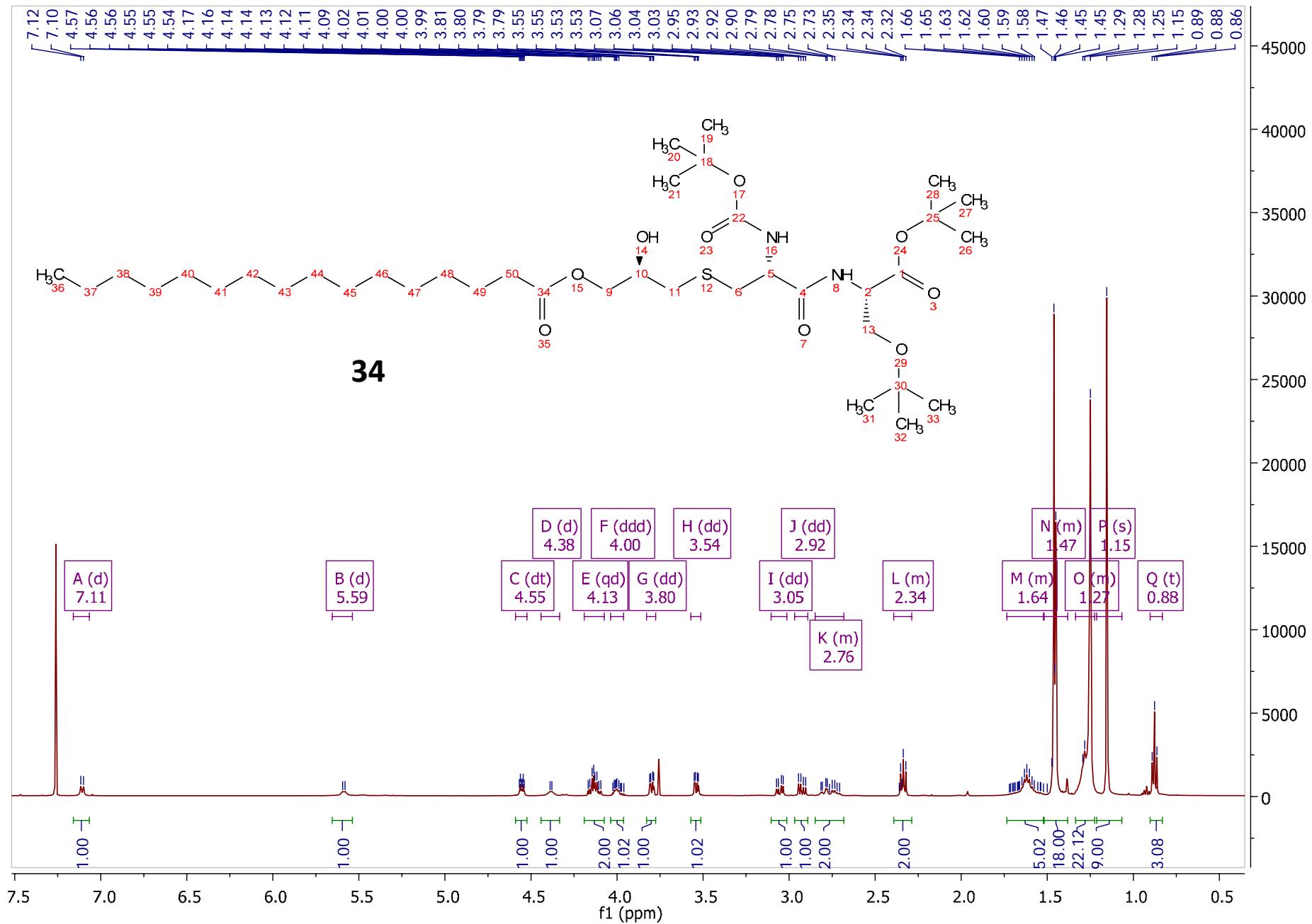






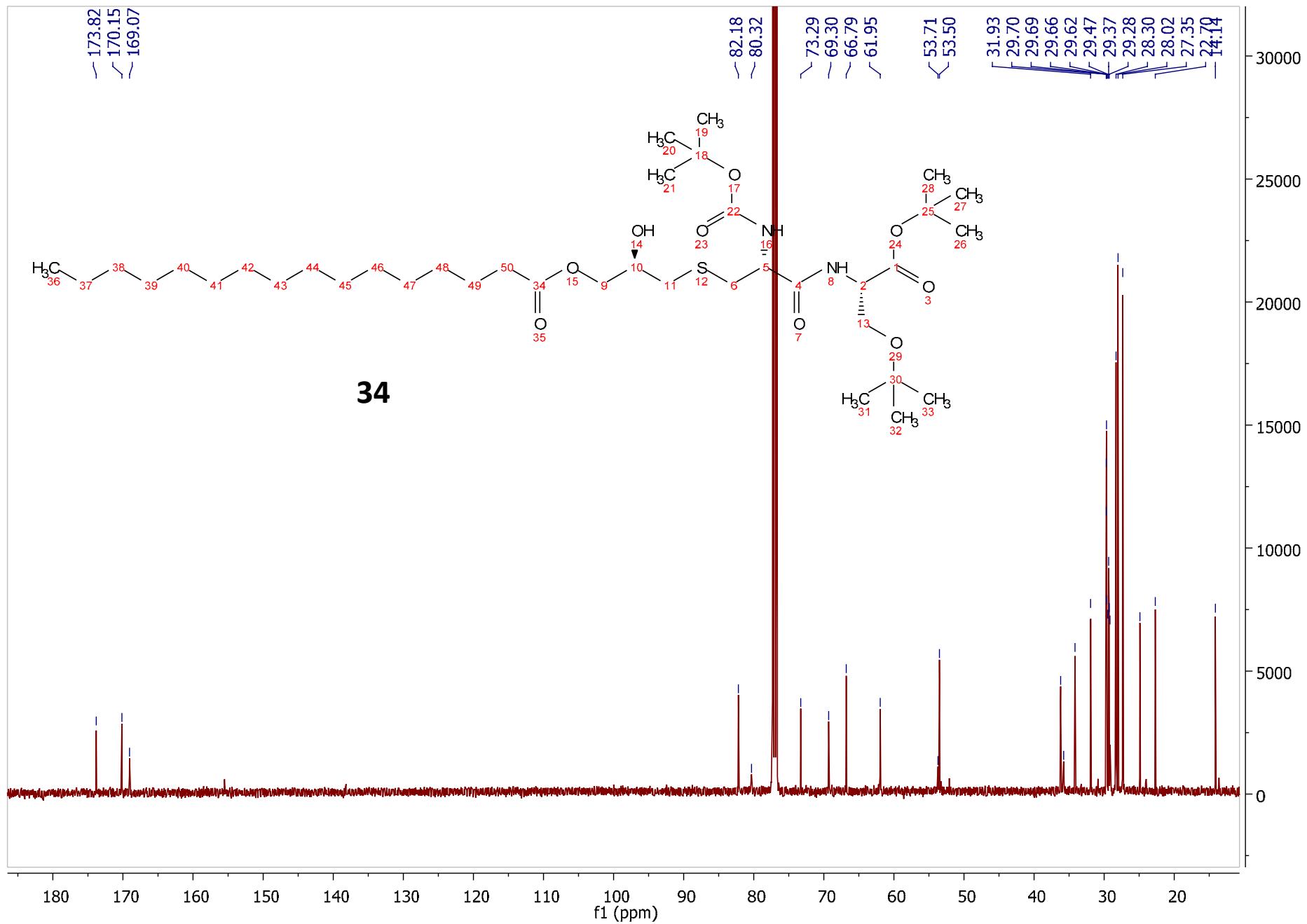
¹H Spectrum

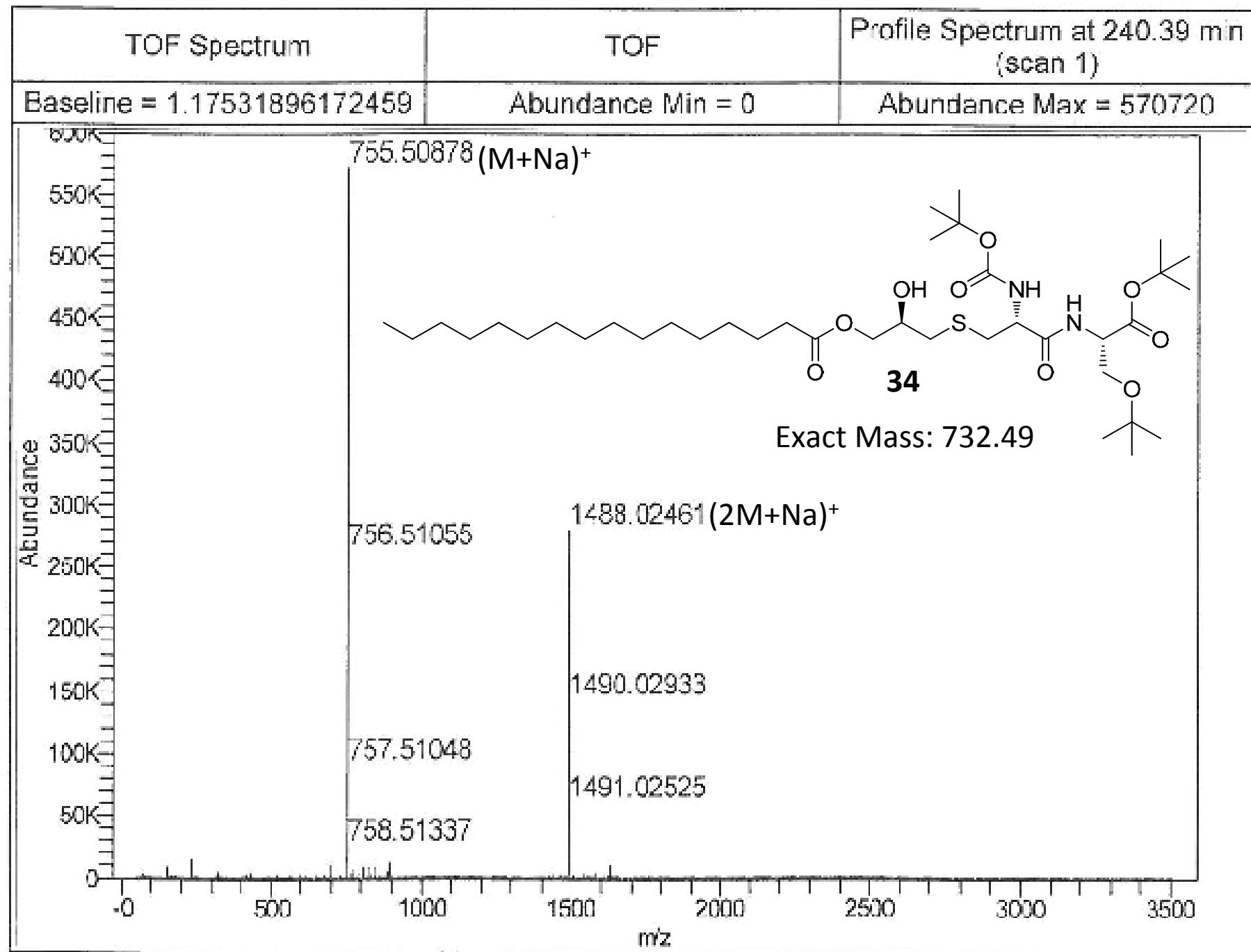
S151



¹³C Spectrum

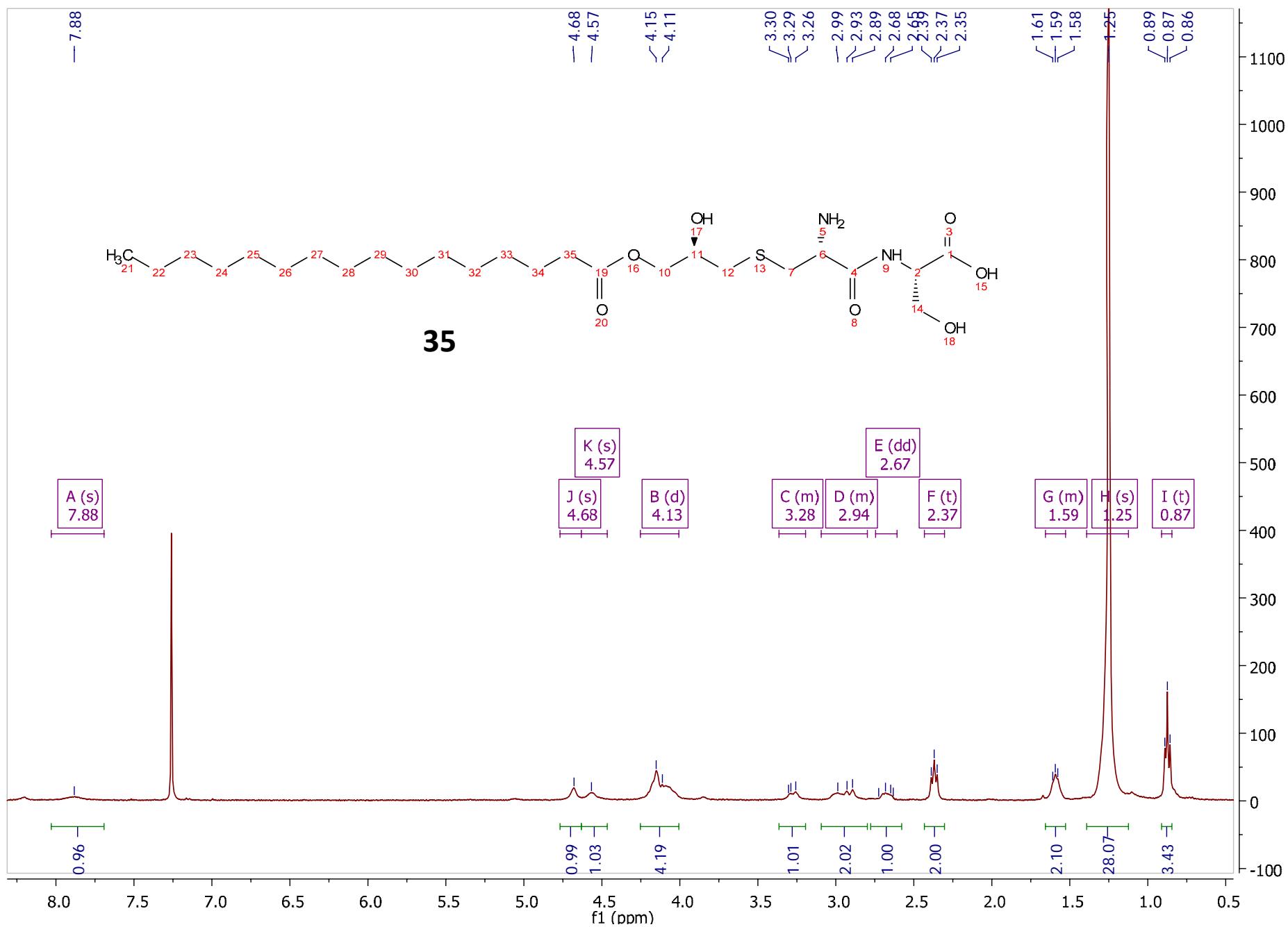
S152





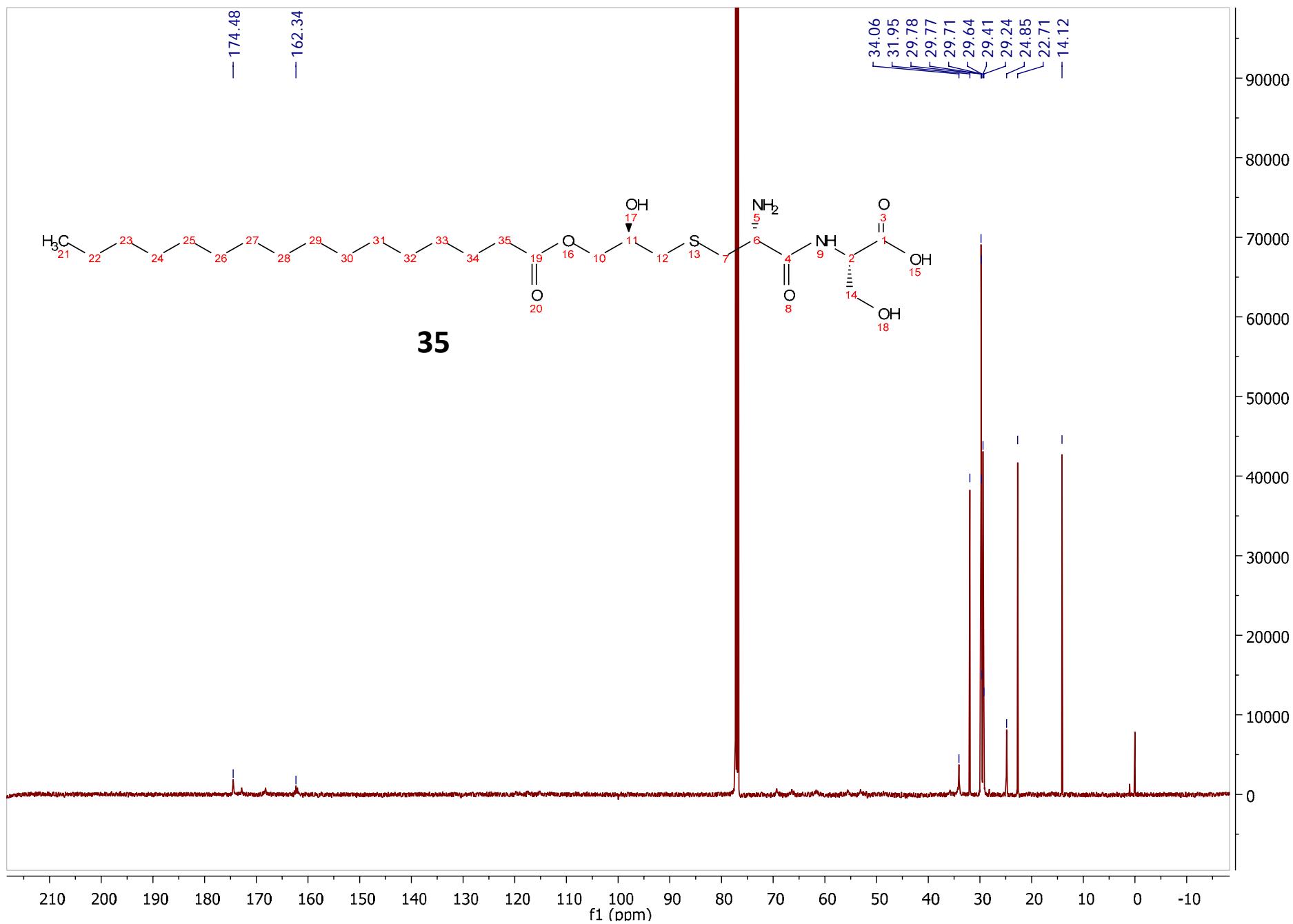
¹H Spectrum

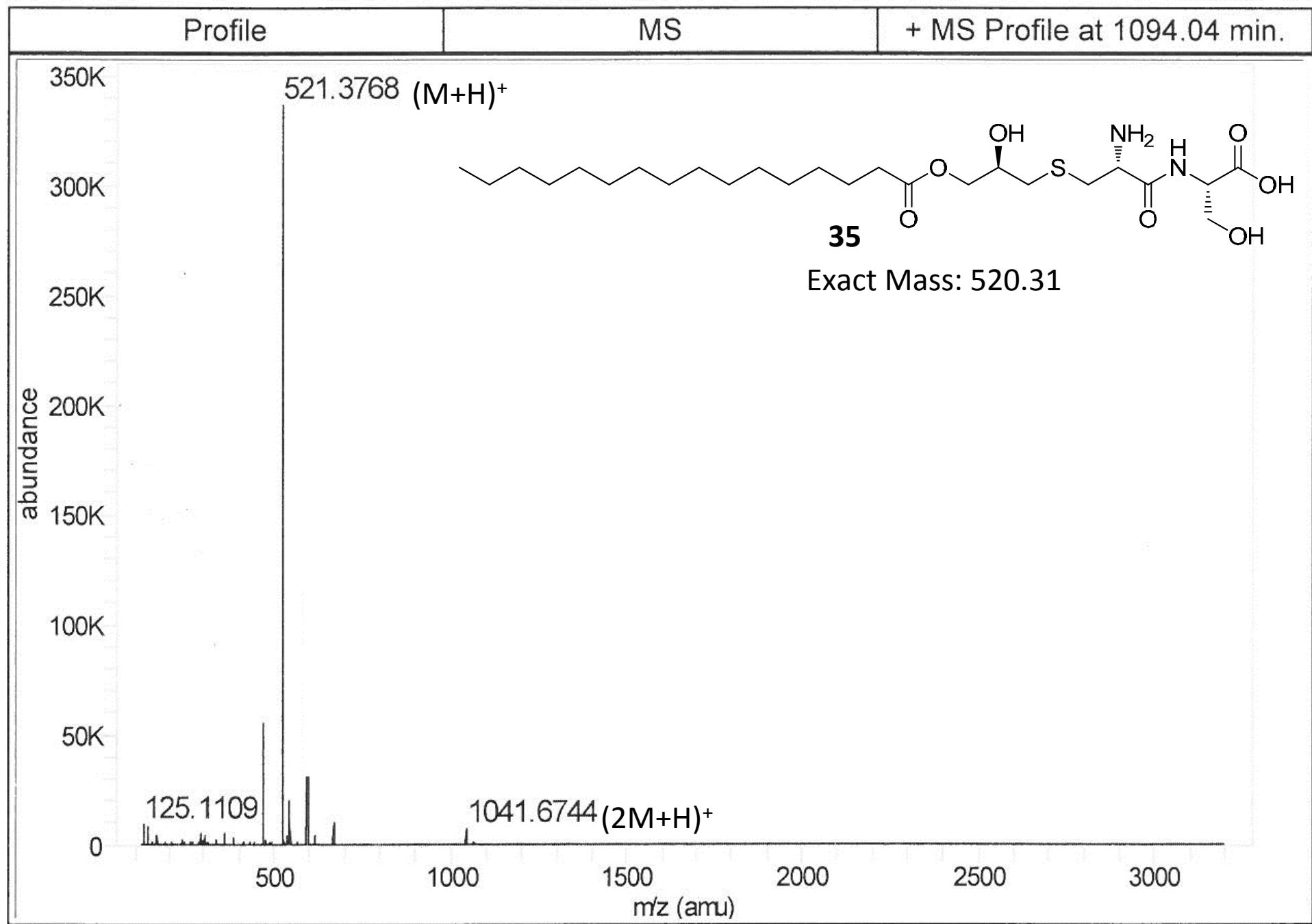
S154

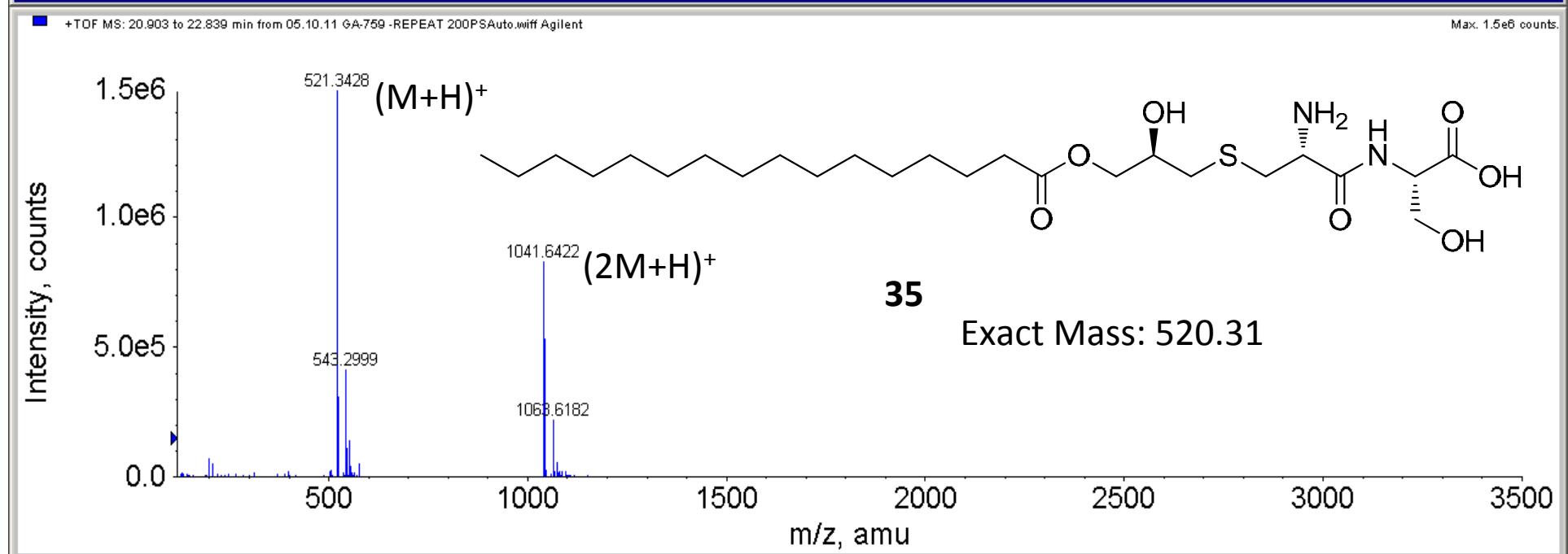
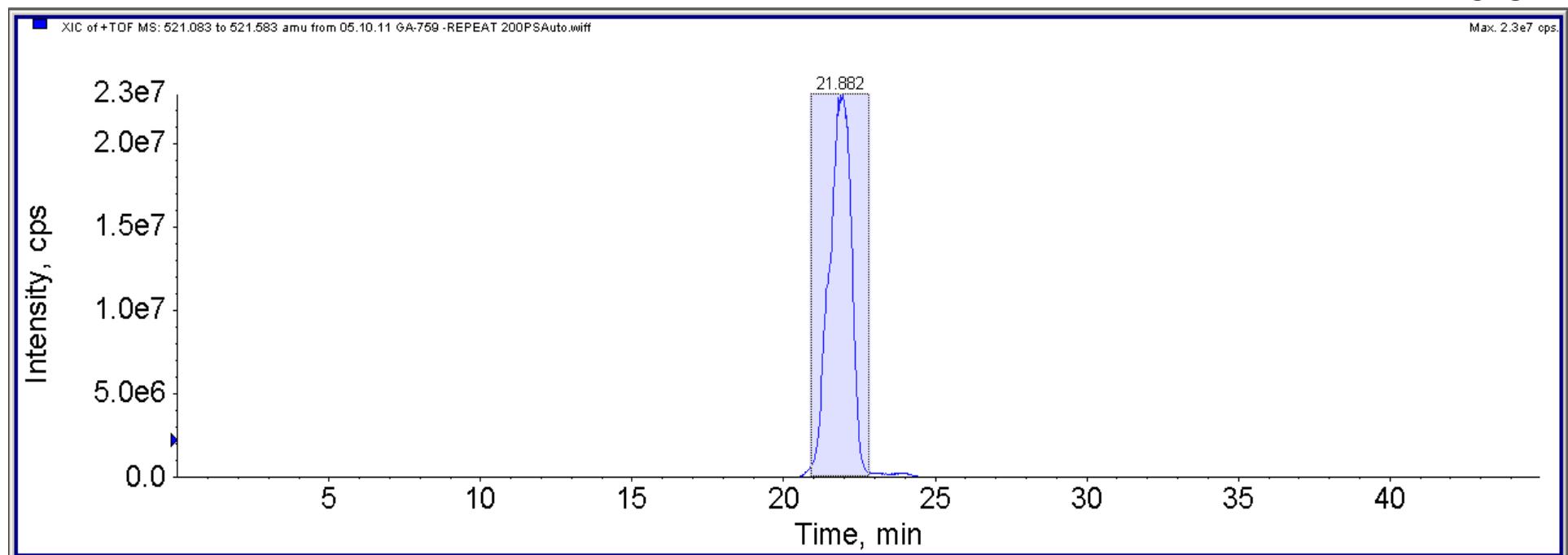


¹³C Spectrum

S155

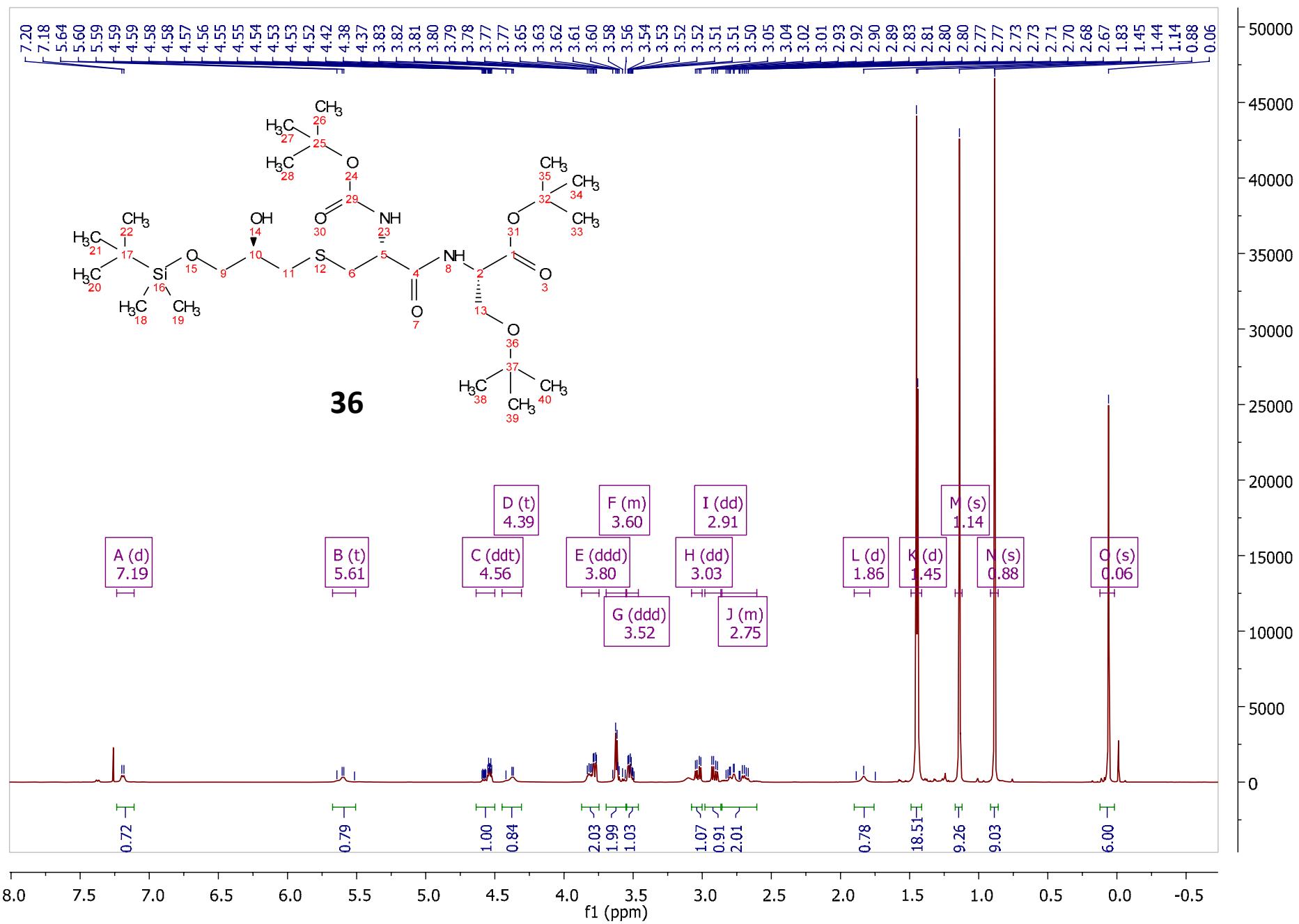






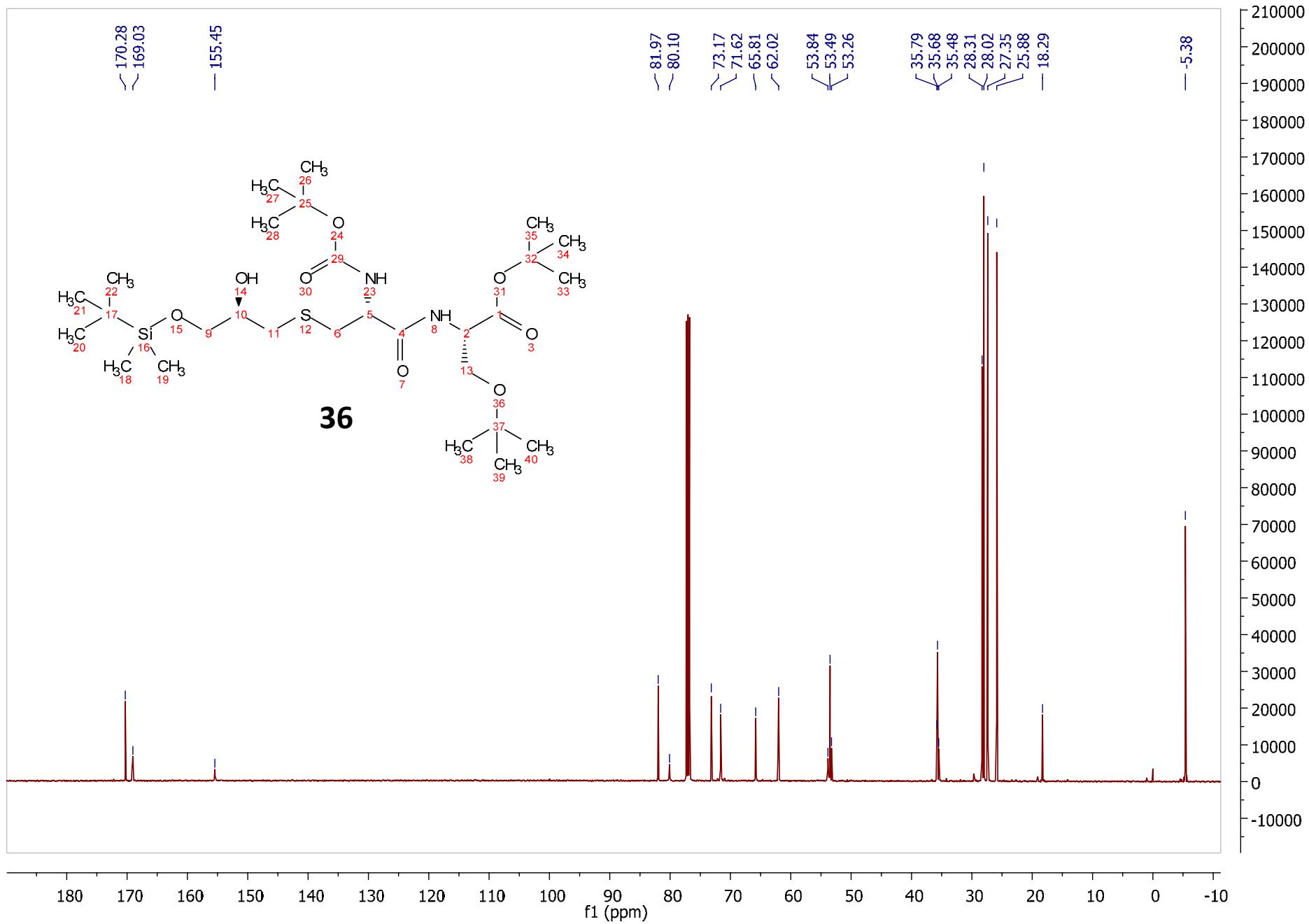
¹H Spectrum

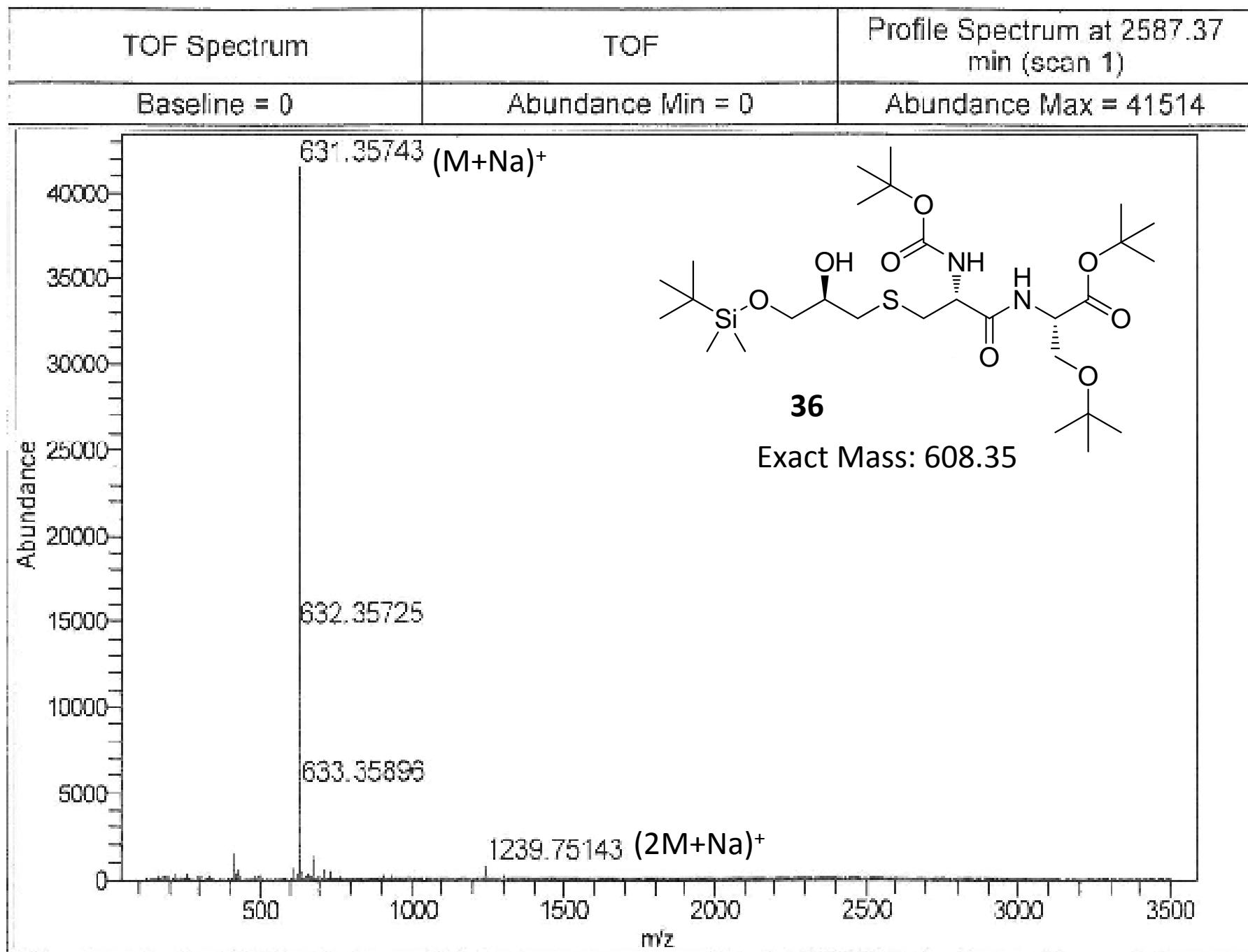
S158



¹³C Spectrum

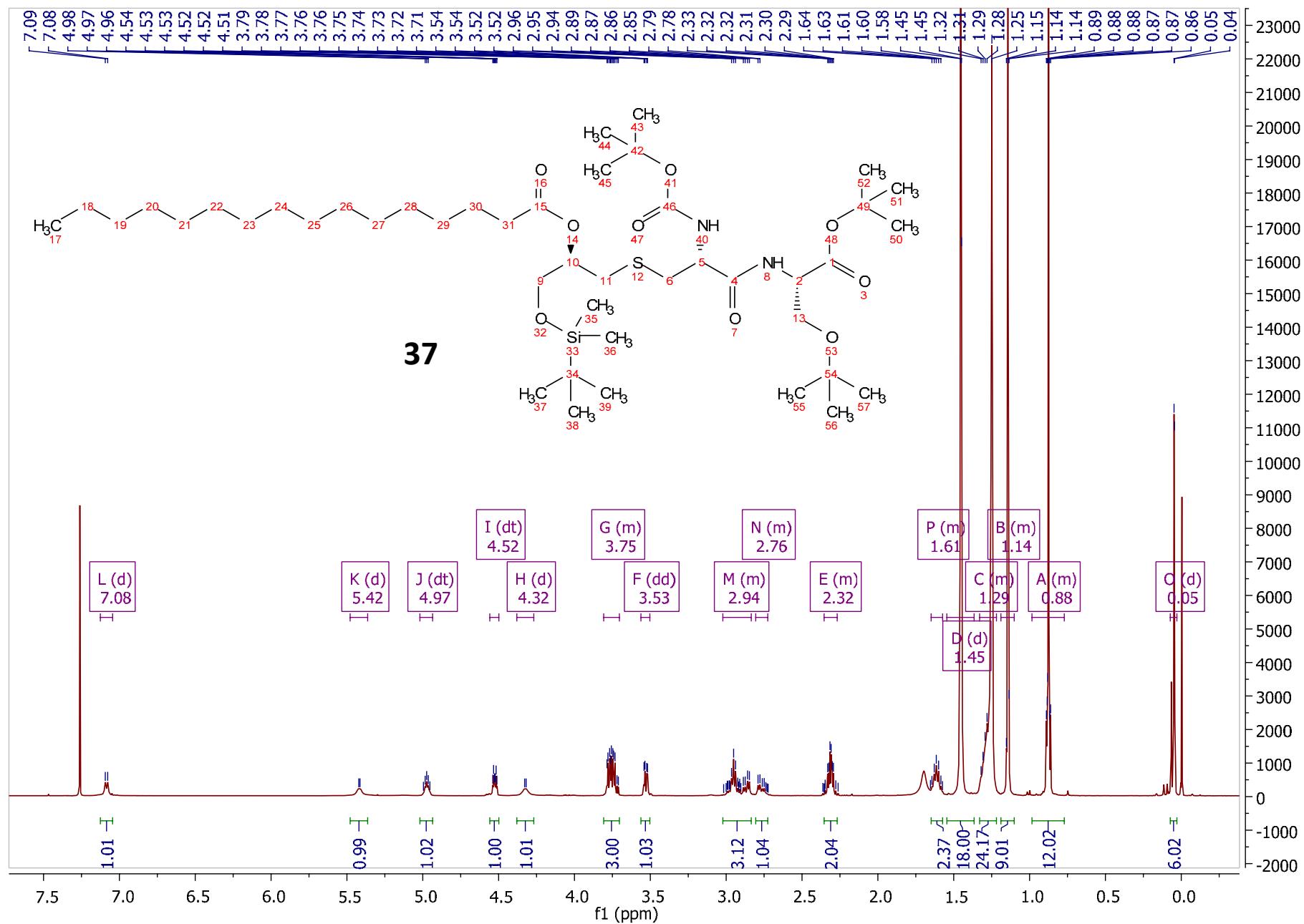
S159

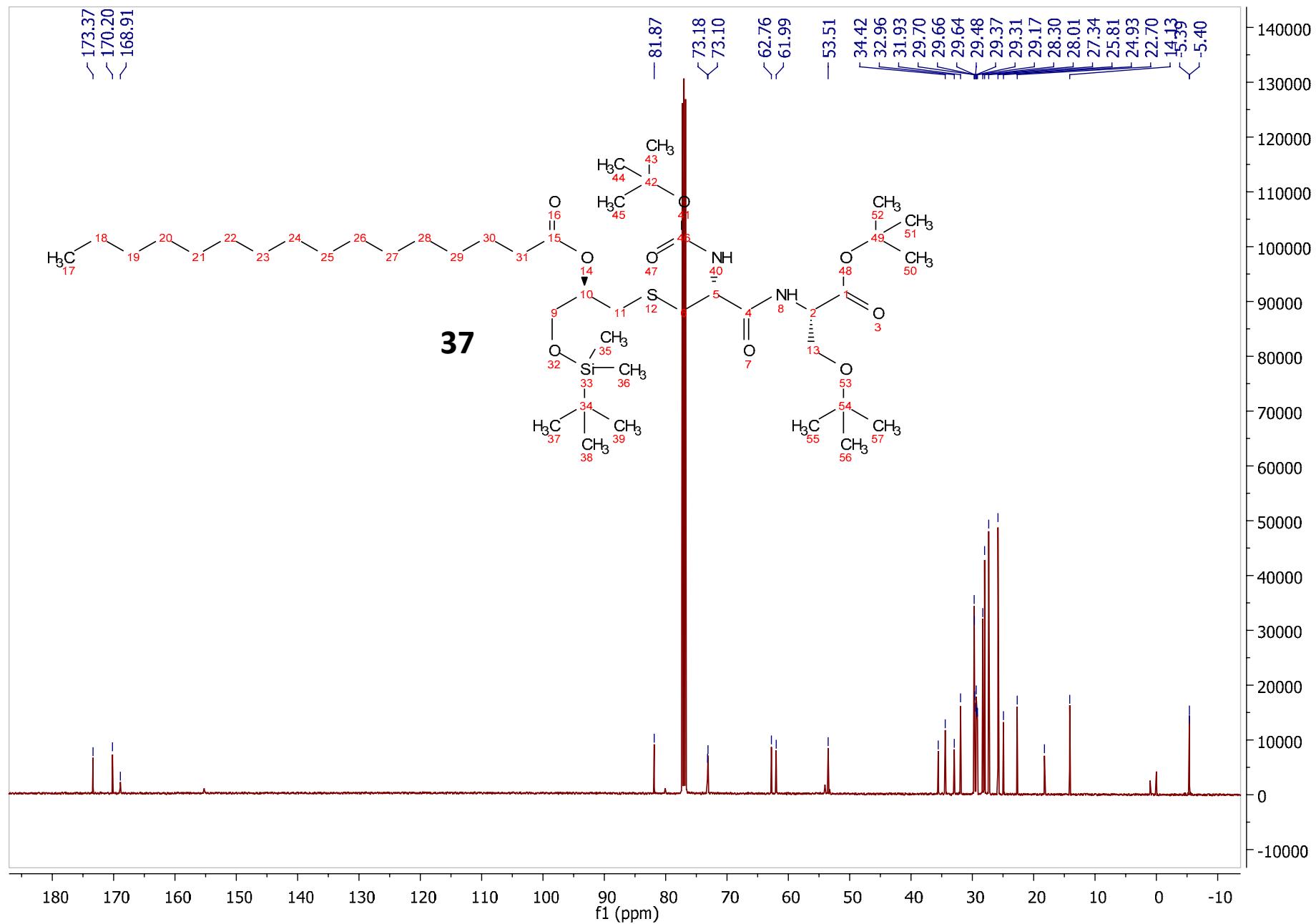


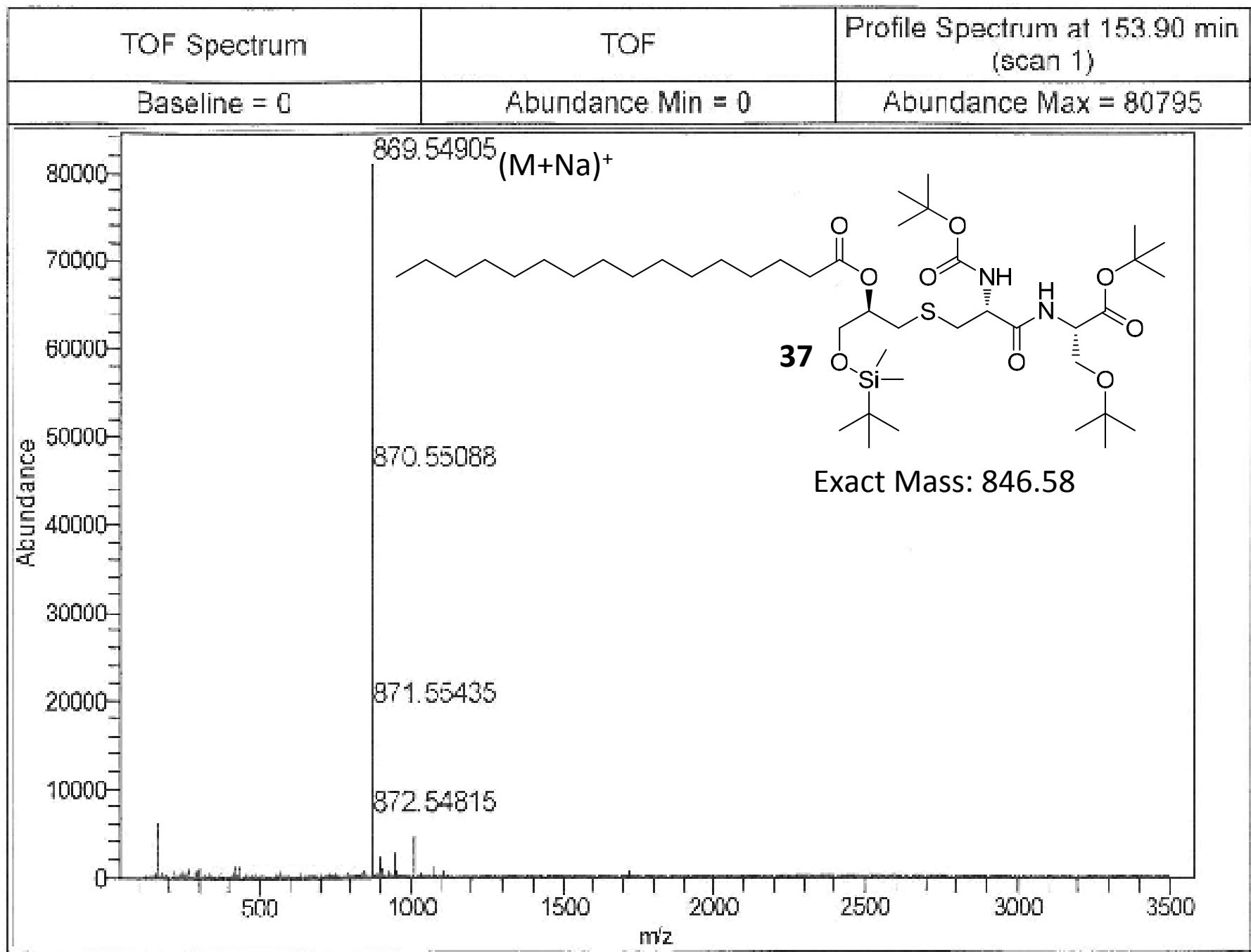


¹H Spectrum

S161

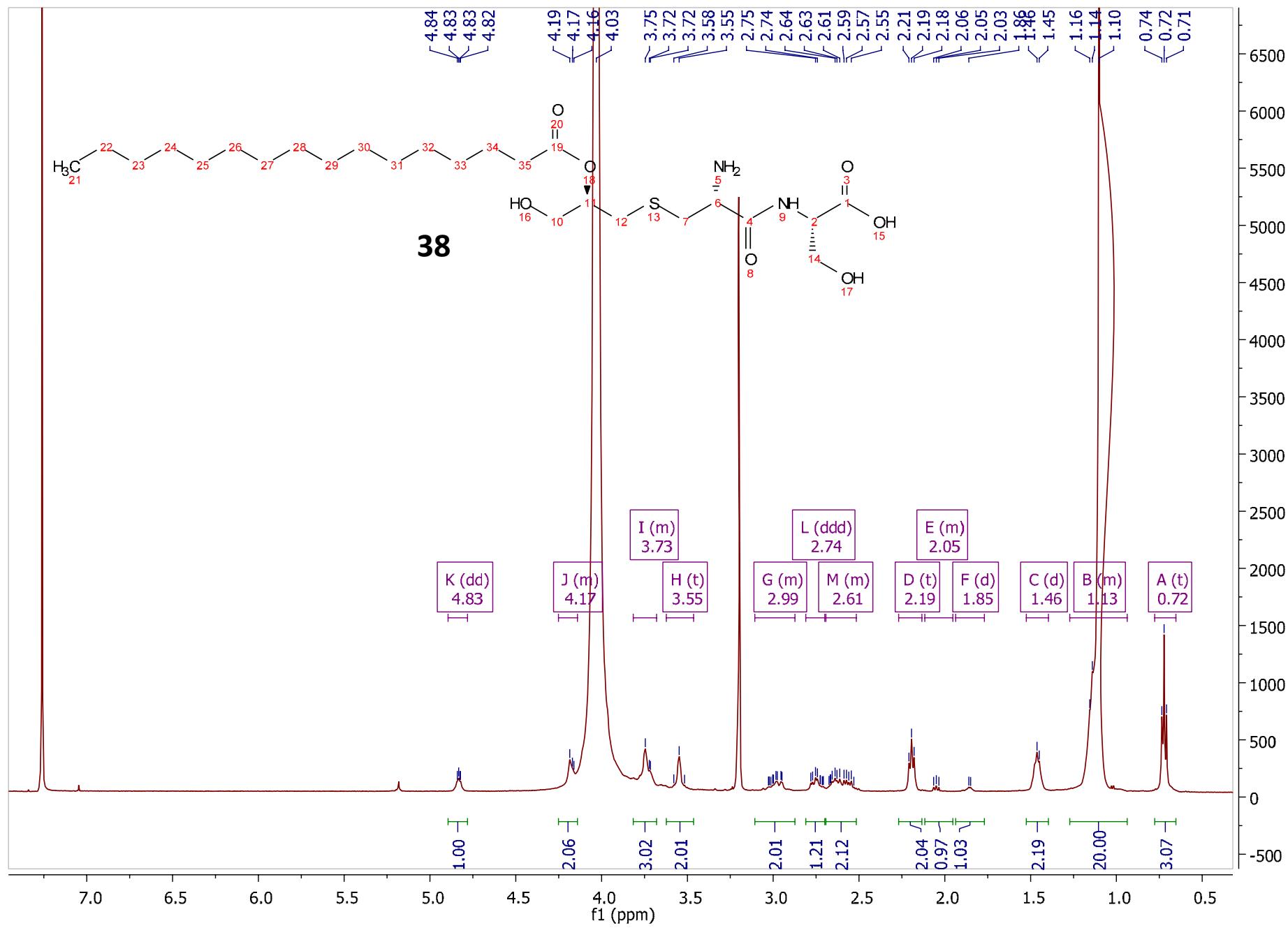






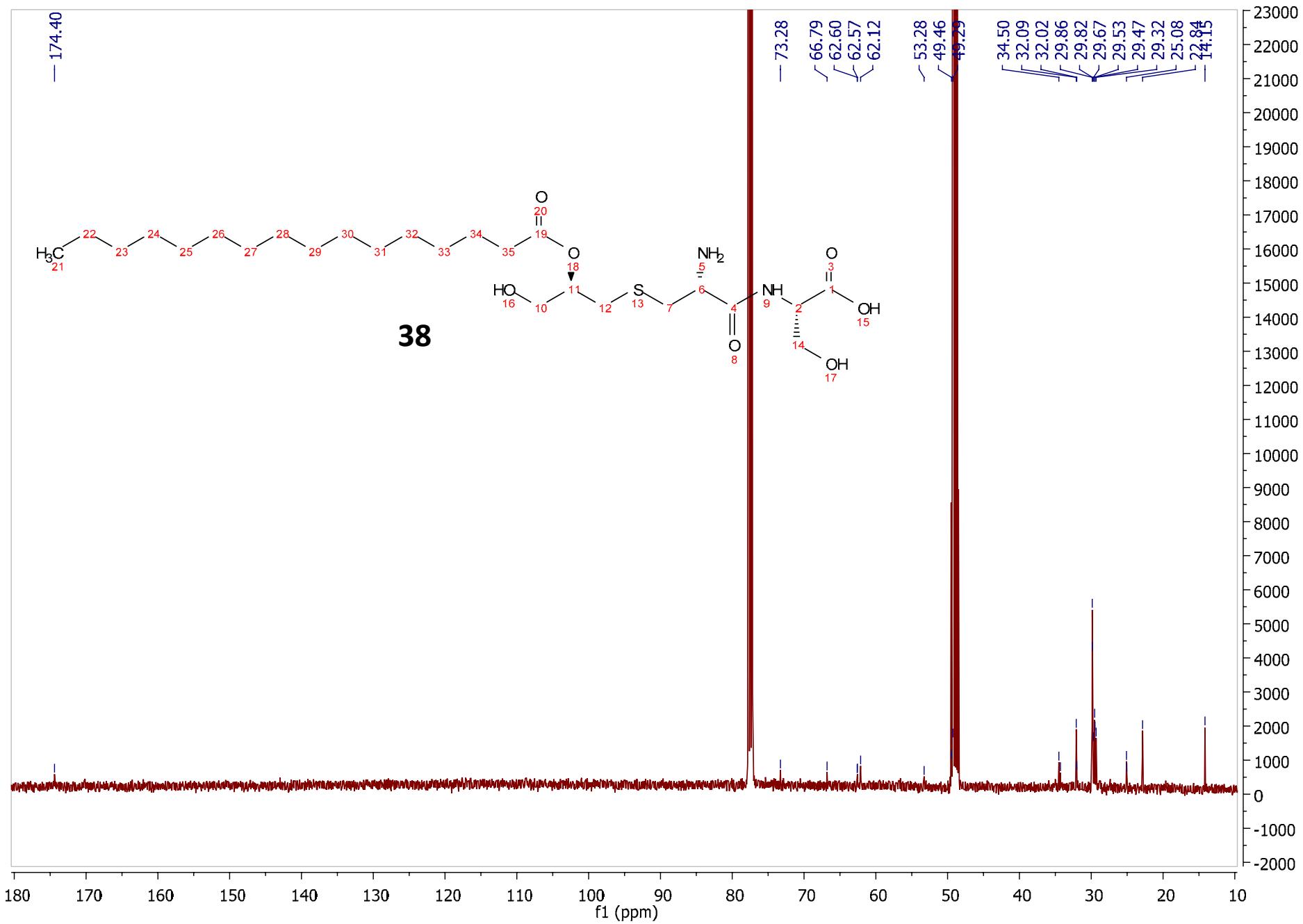
¹H Spectrum

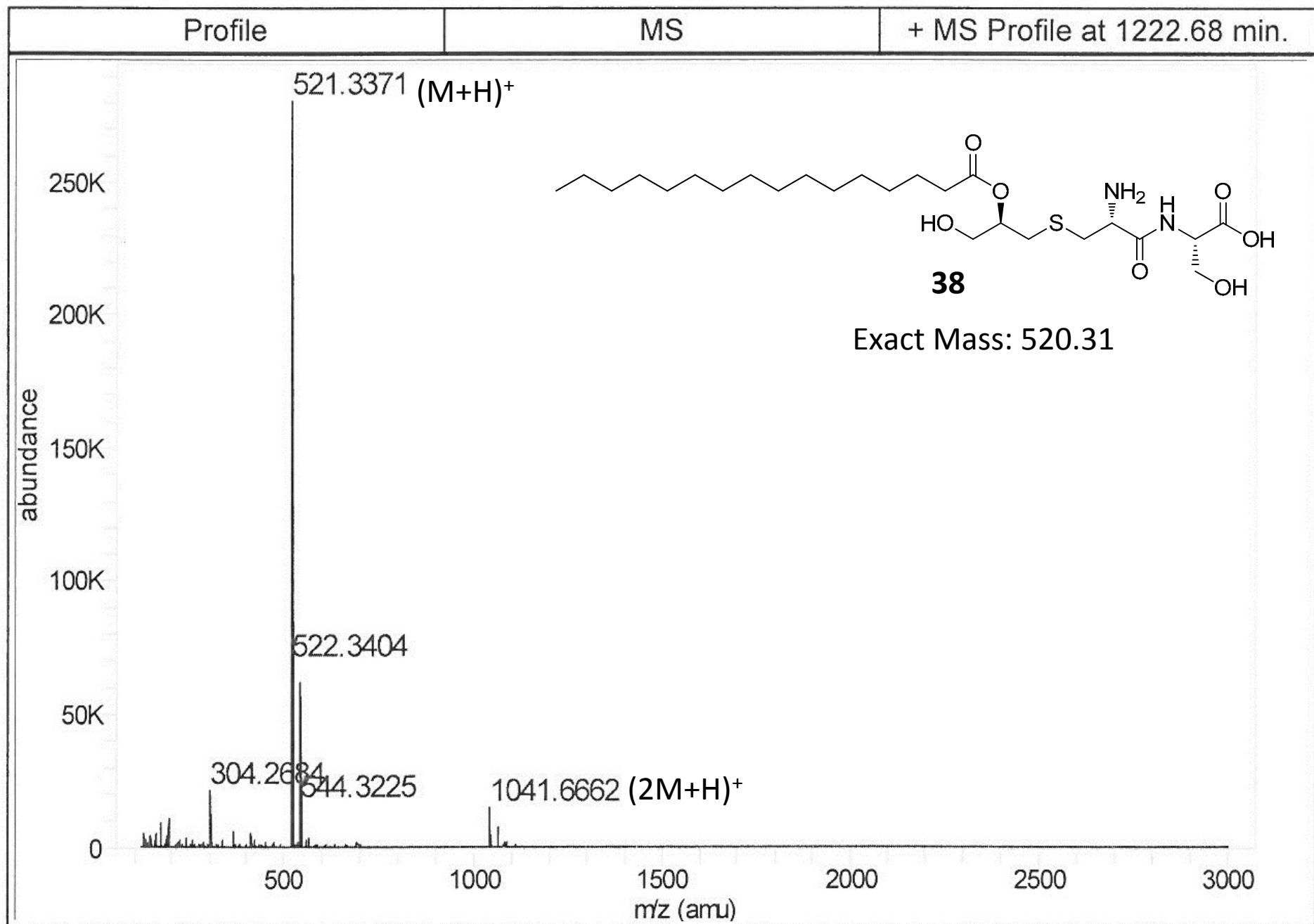
S164

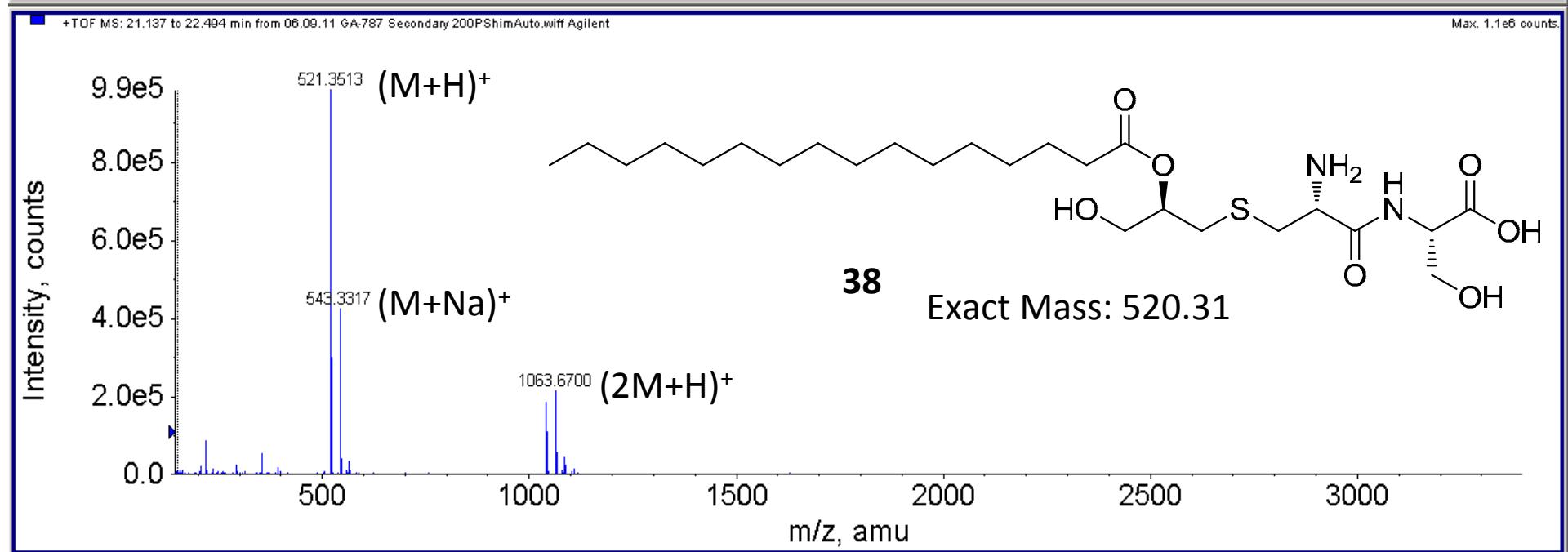
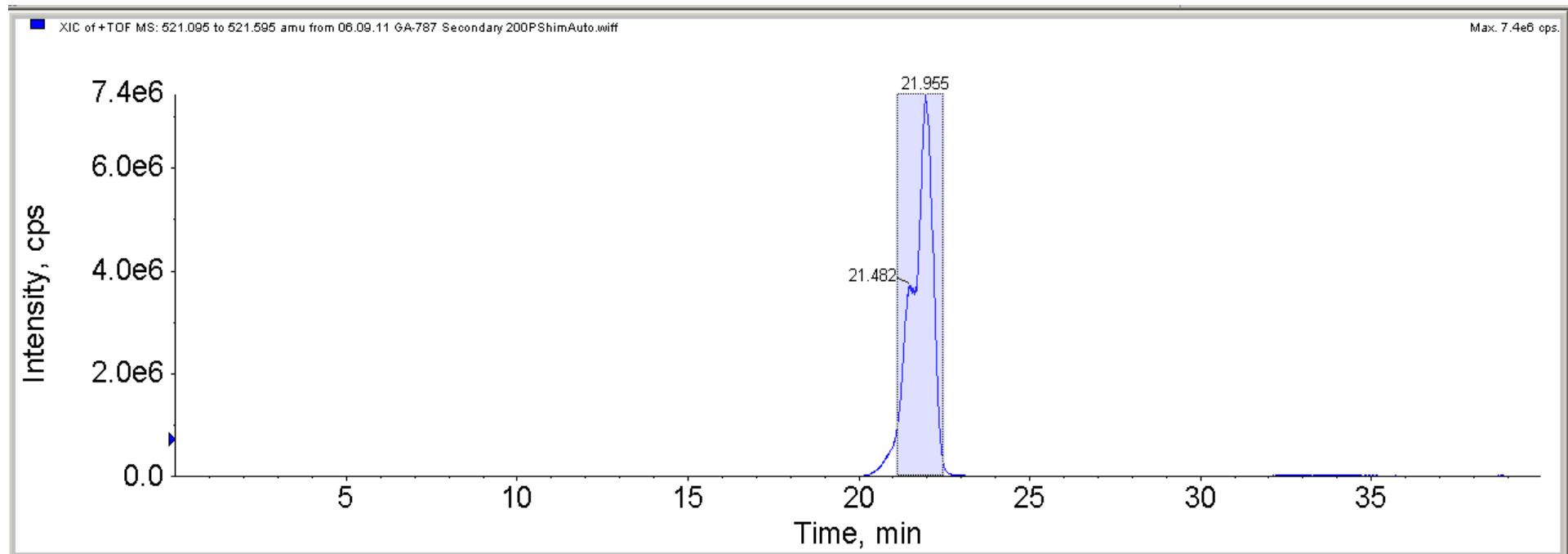


¹³C Spectrum

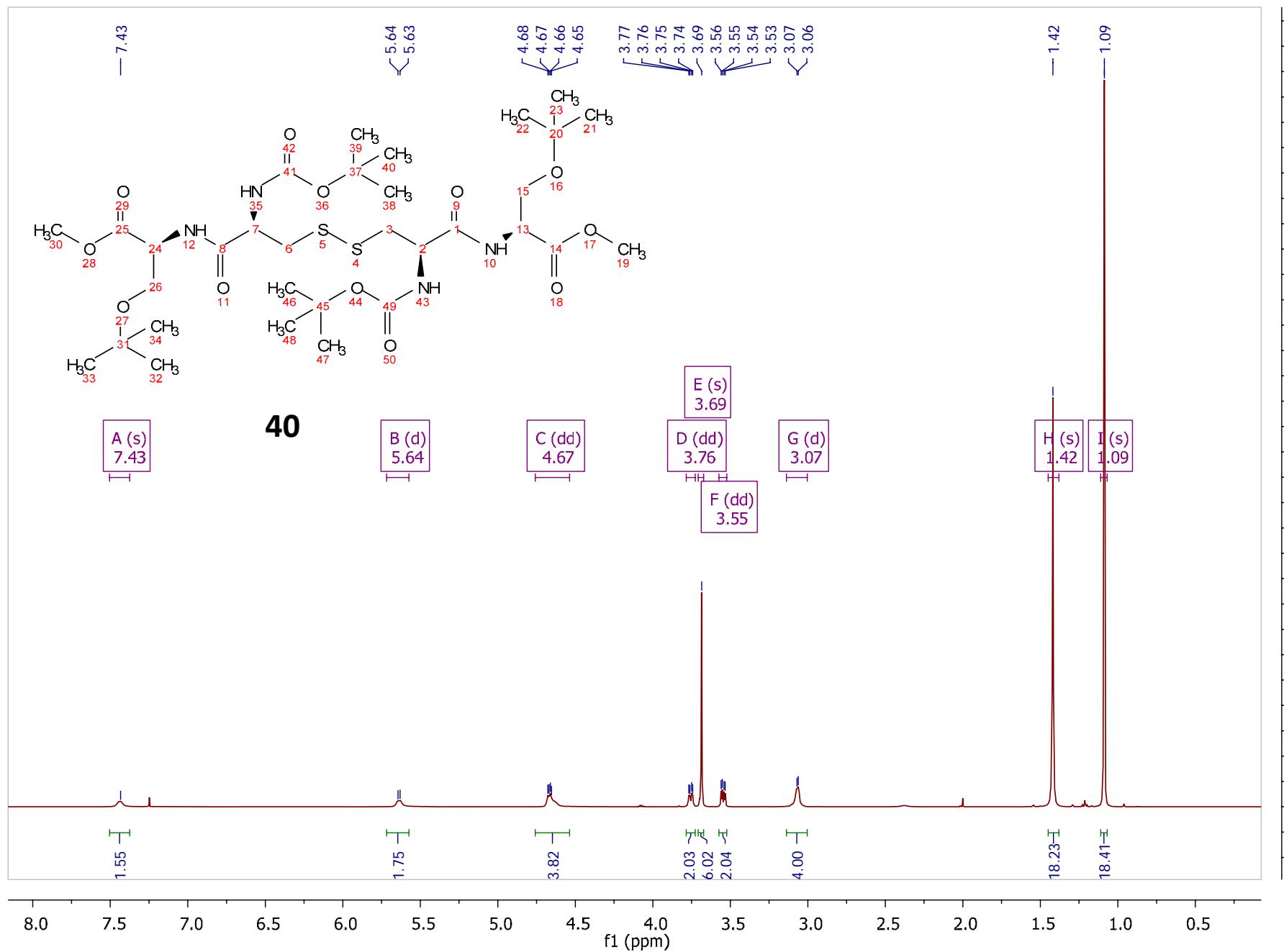
S165





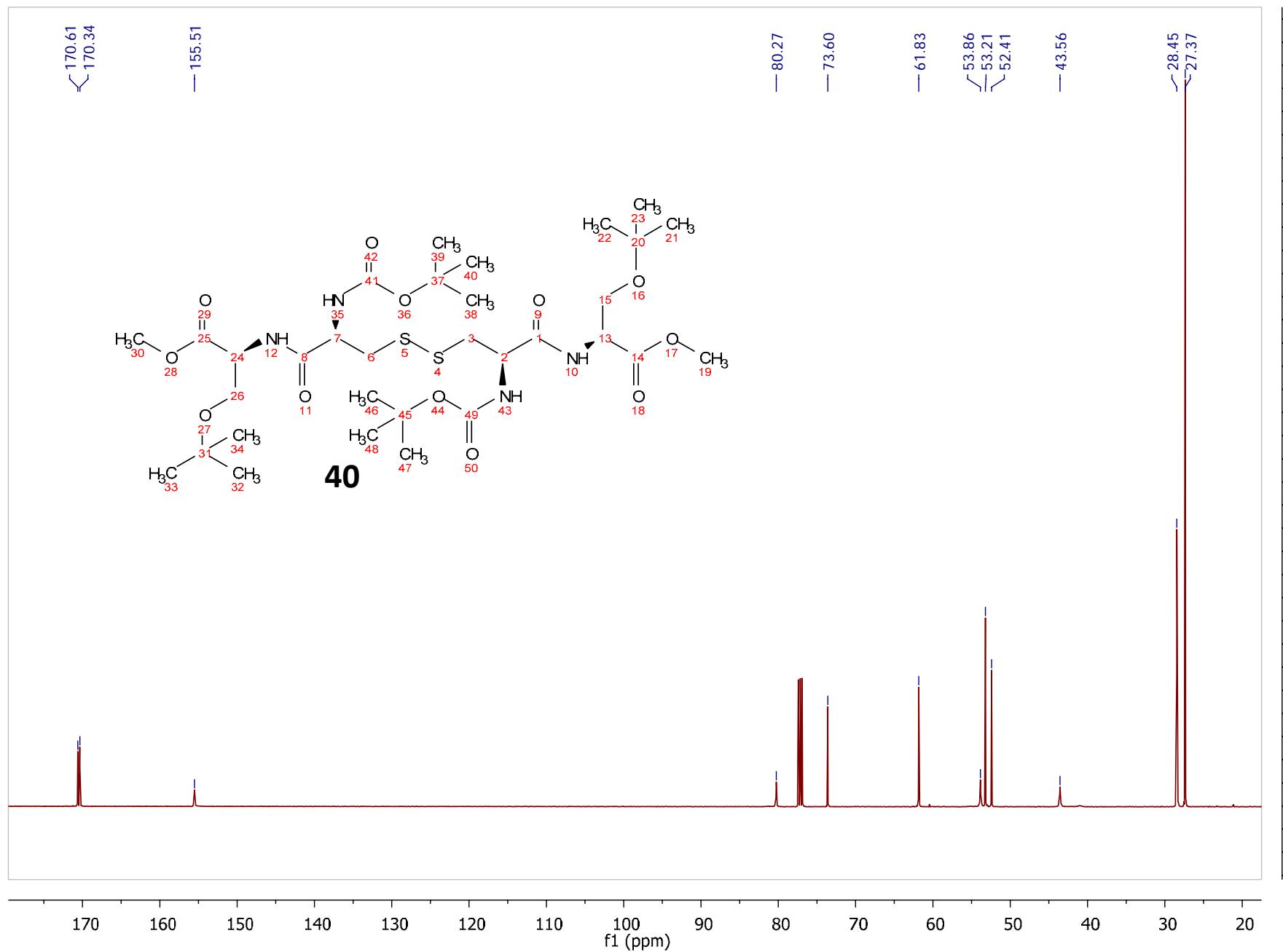


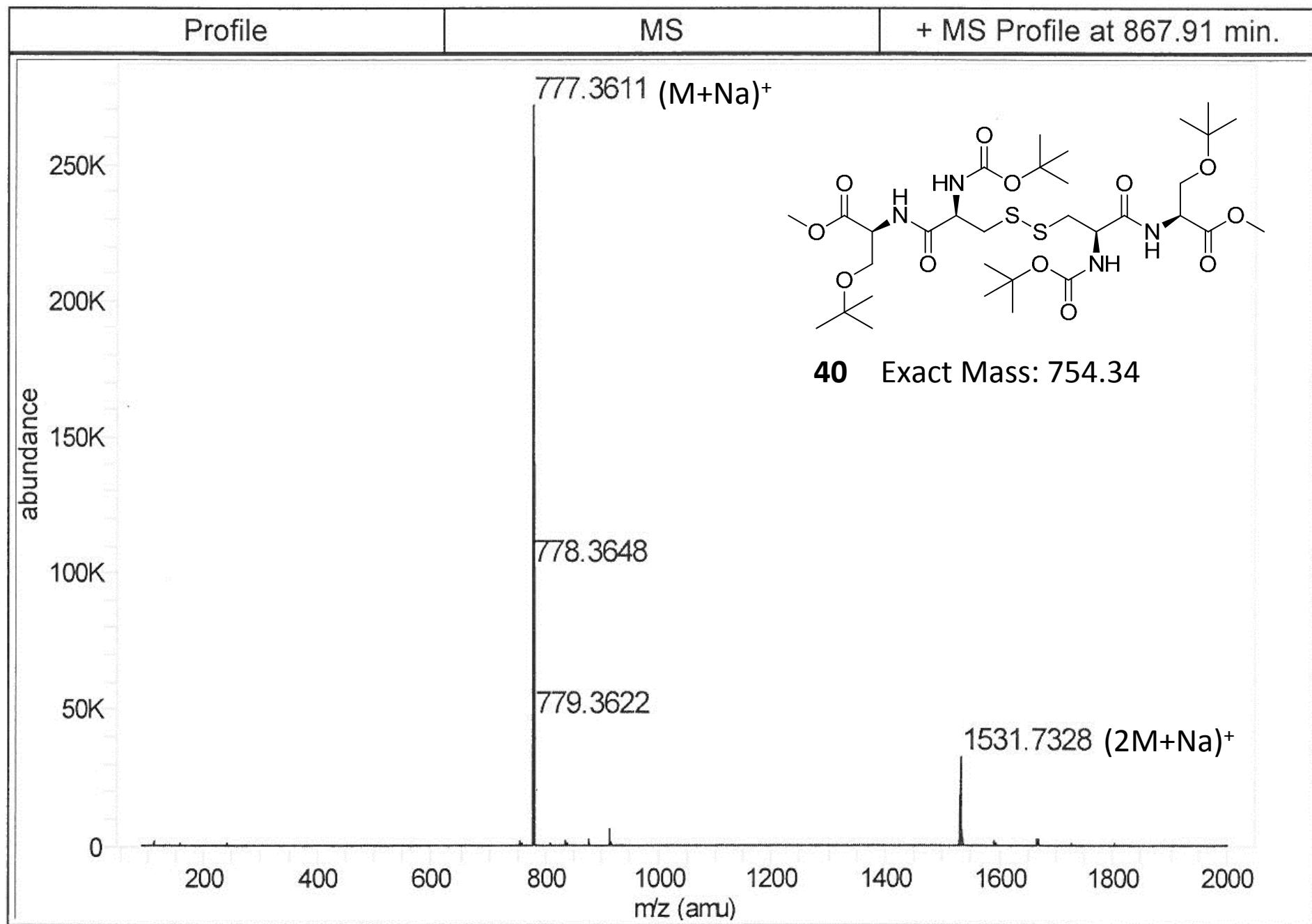
¹H Spectrum



¹³C Spectrum

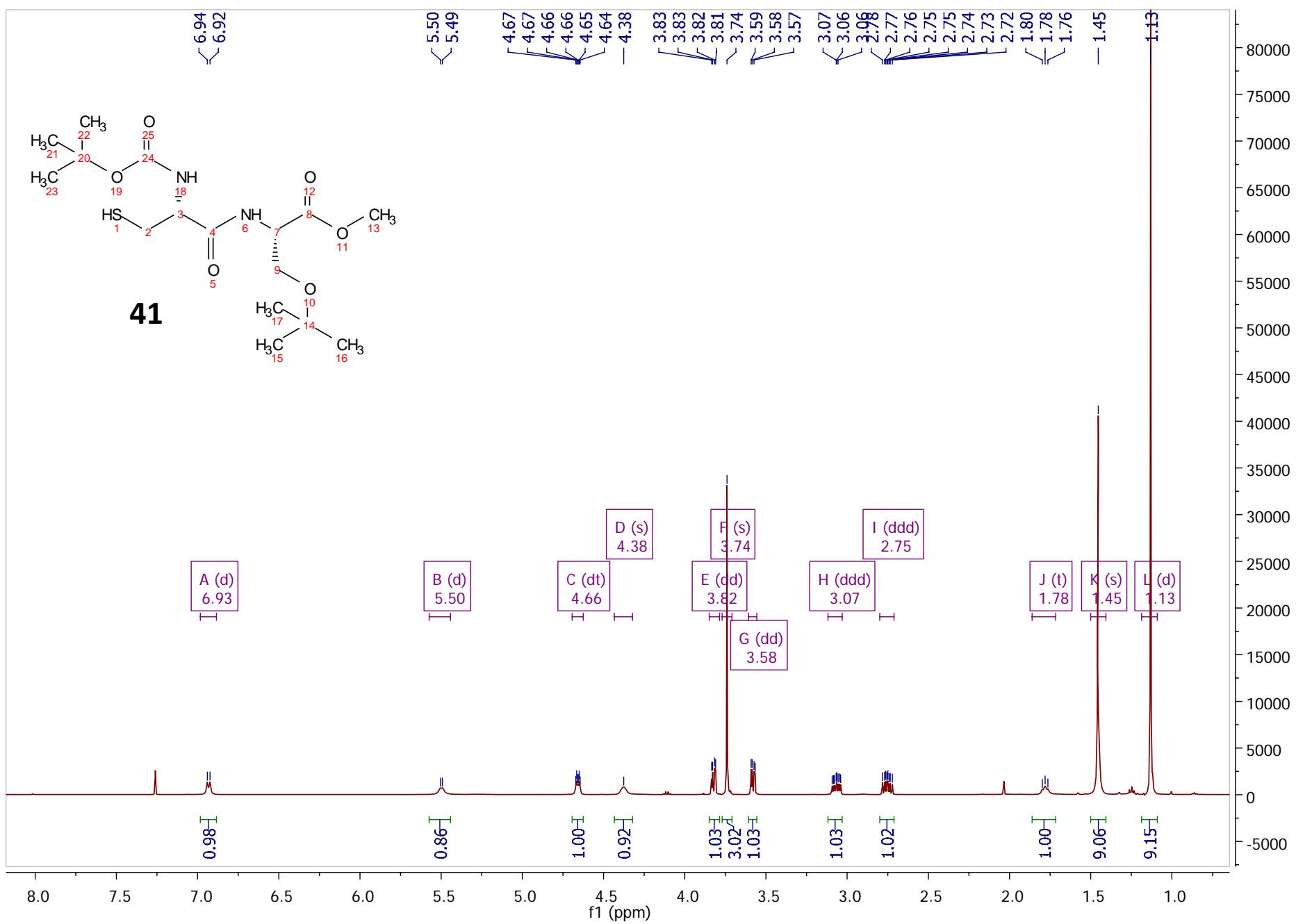
S169

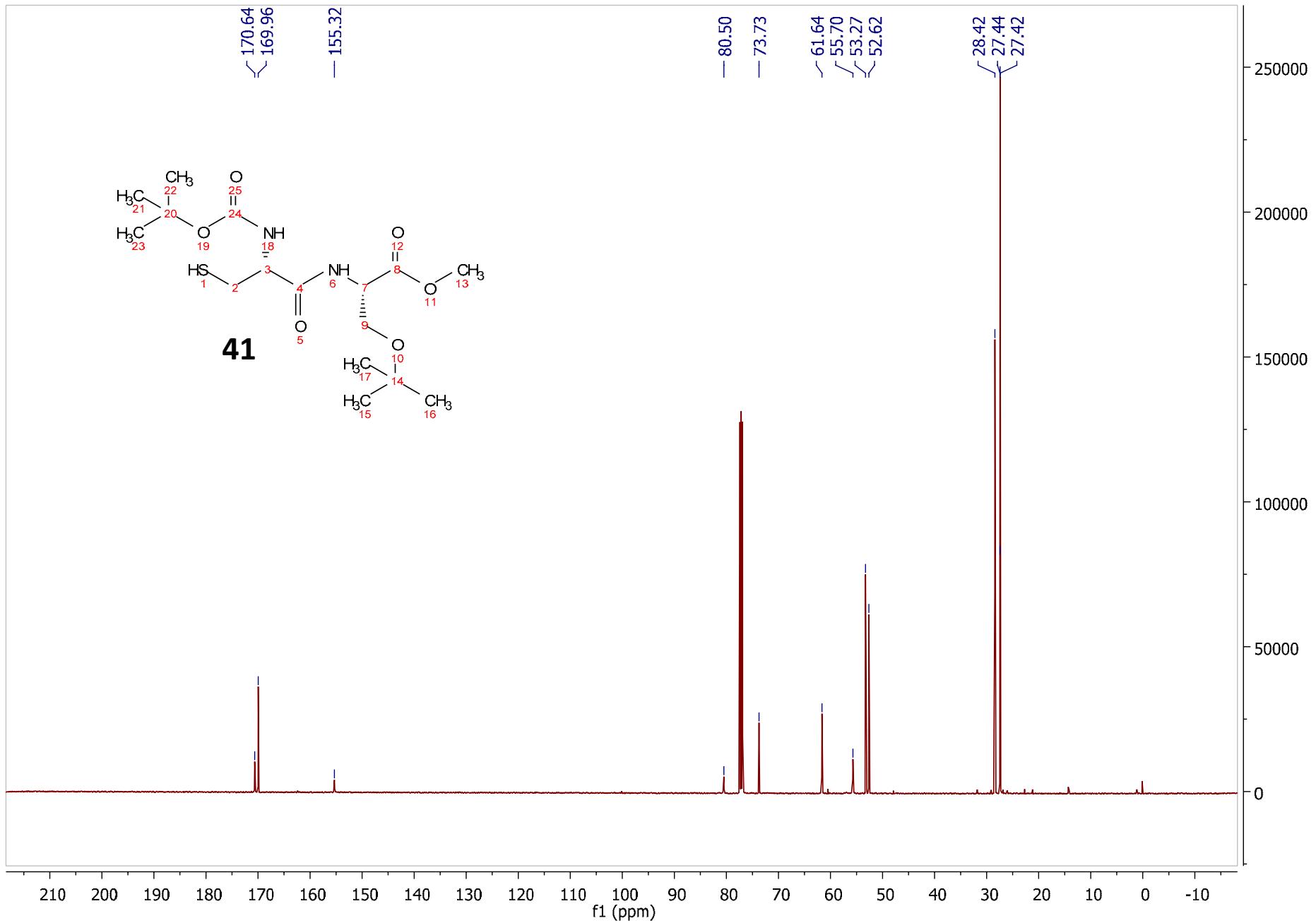


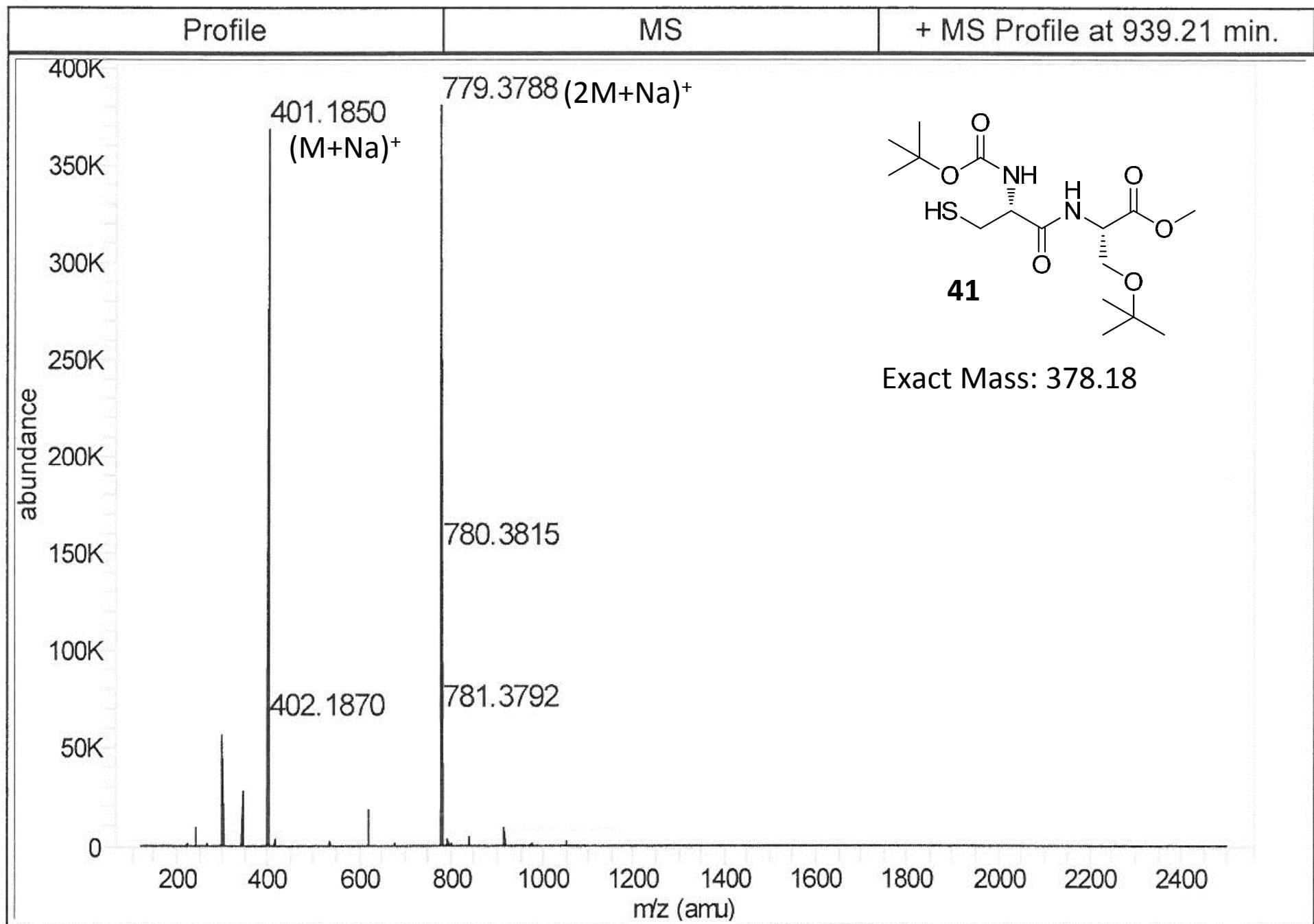


¹H Spectrum

S171

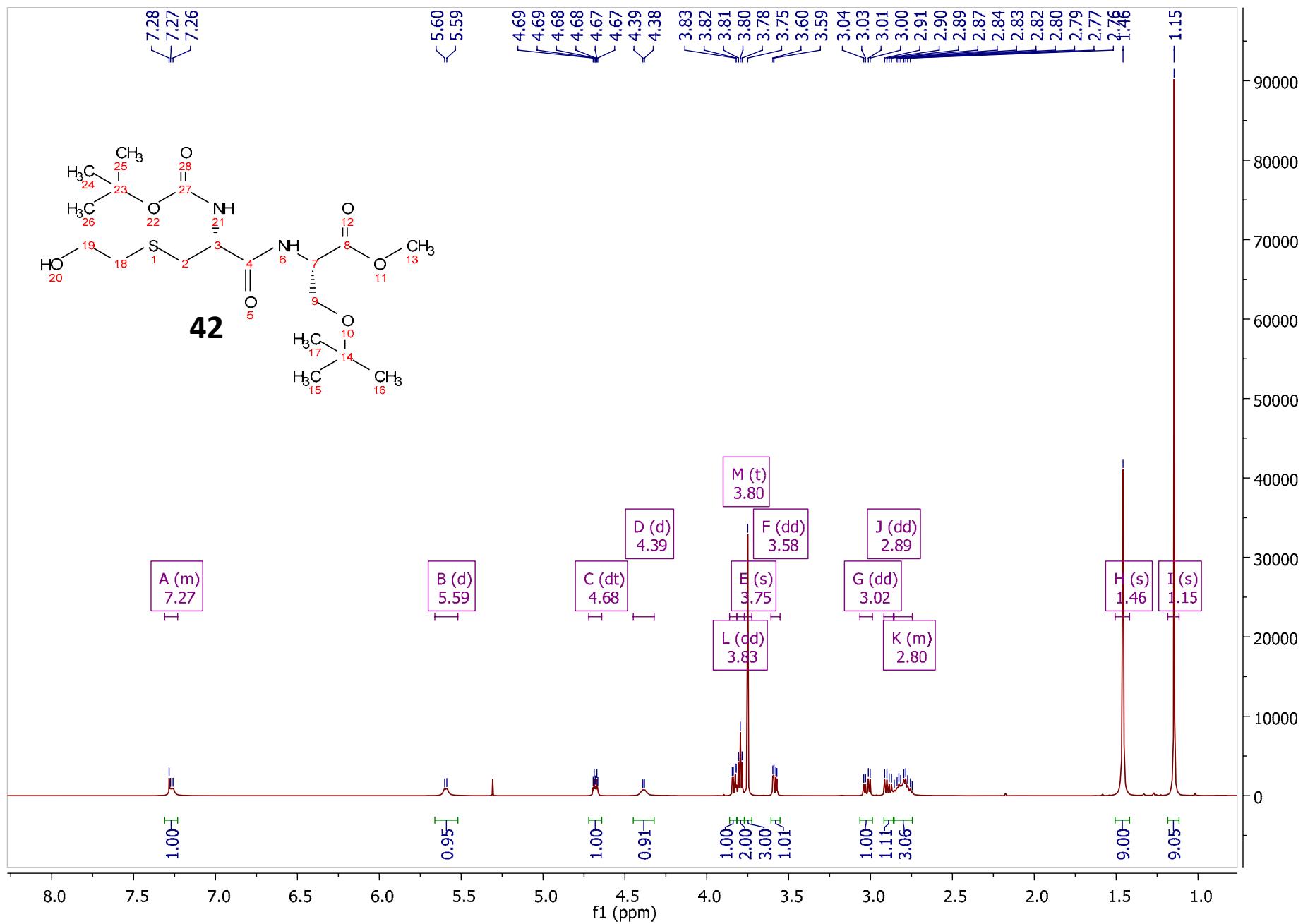






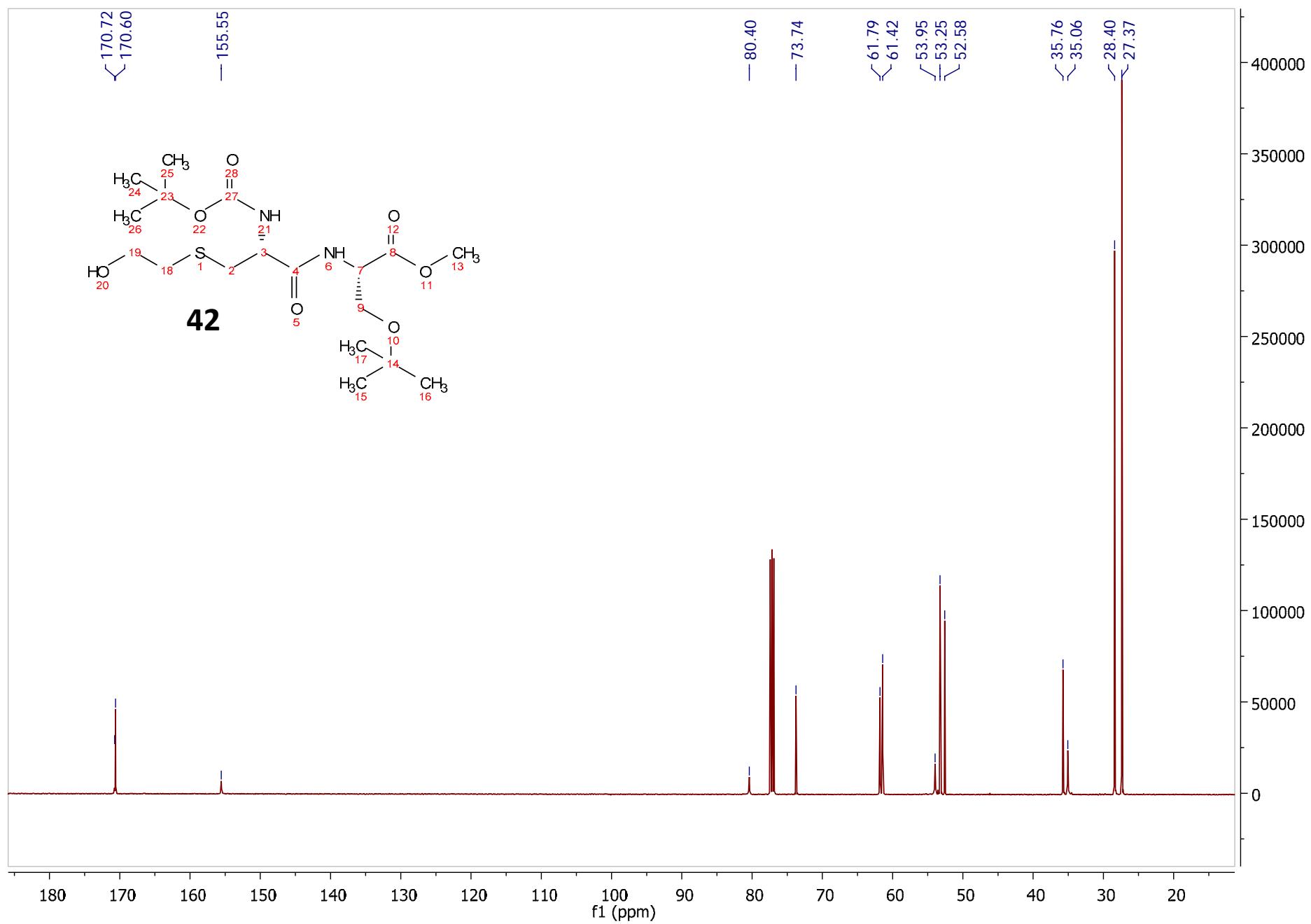
¹H Spectrum

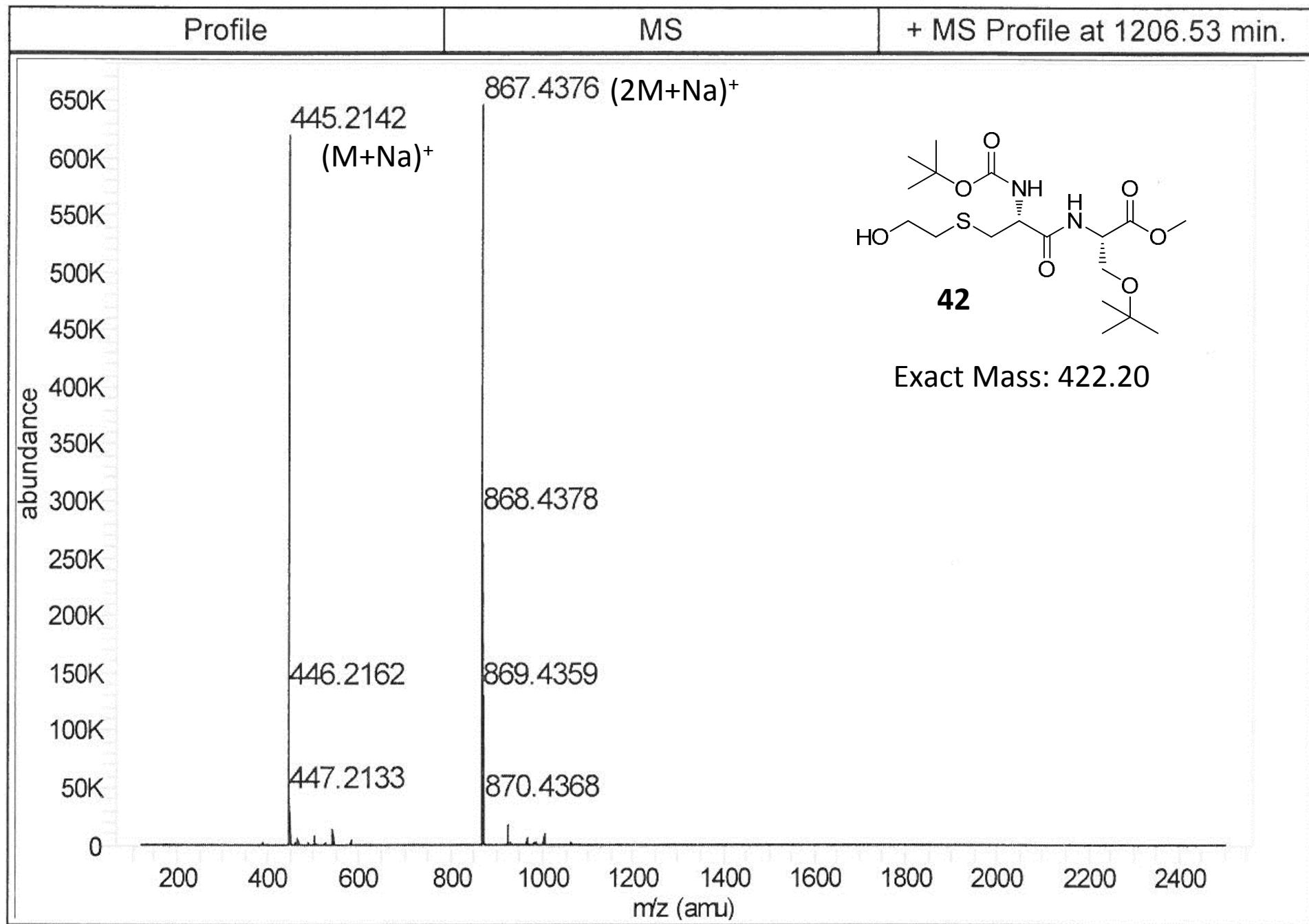
S174

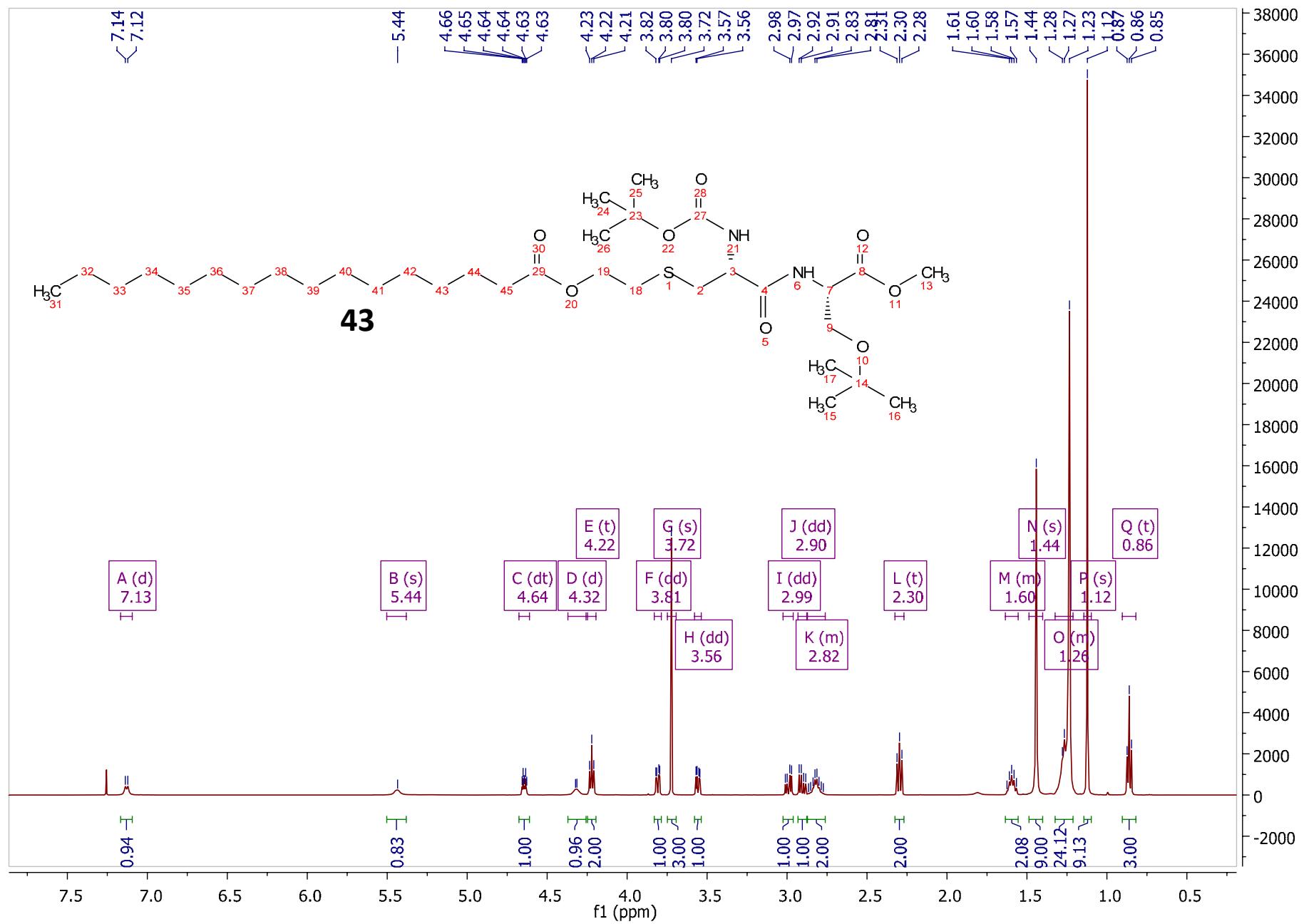


¹³C Spectrum

S175

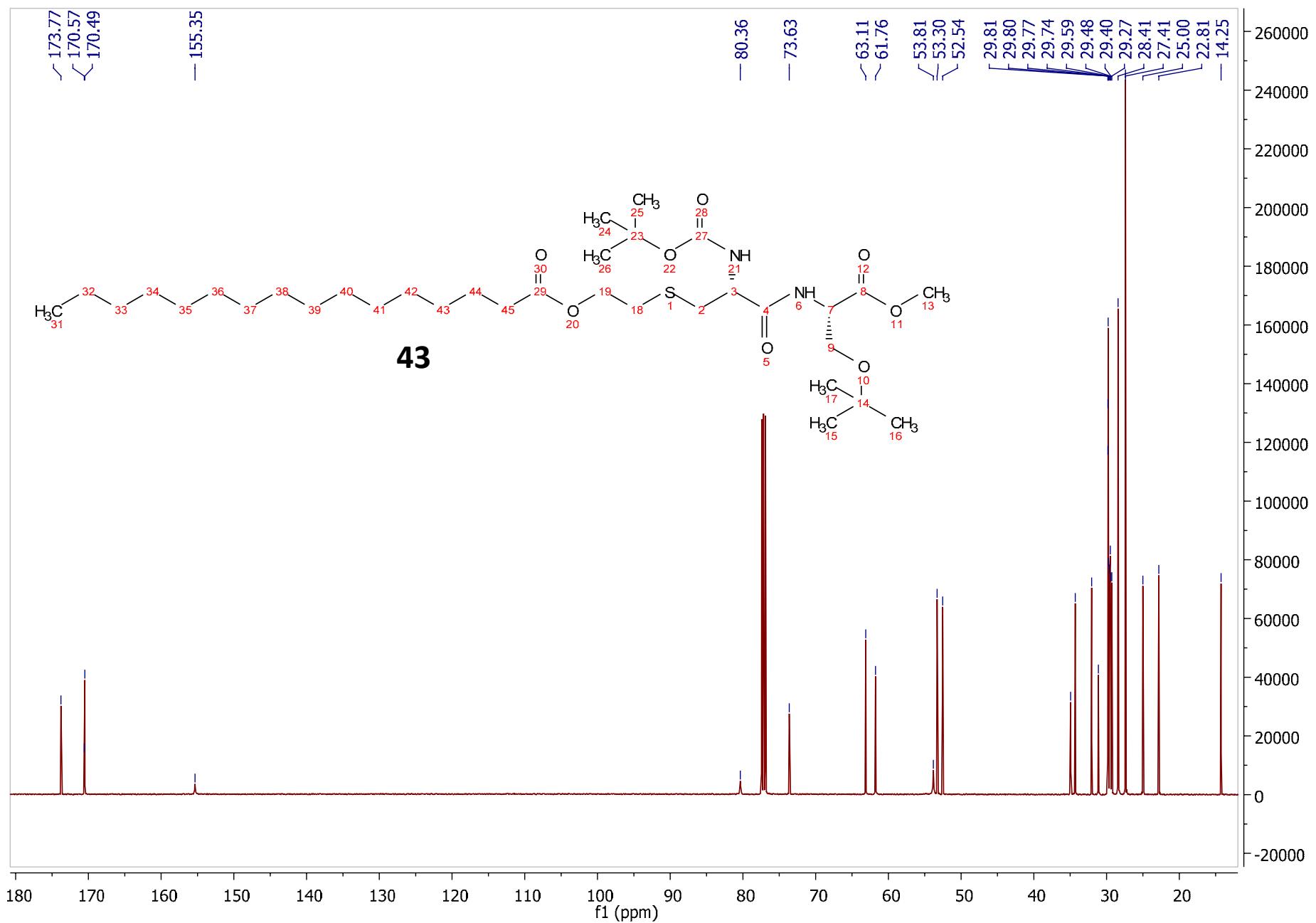


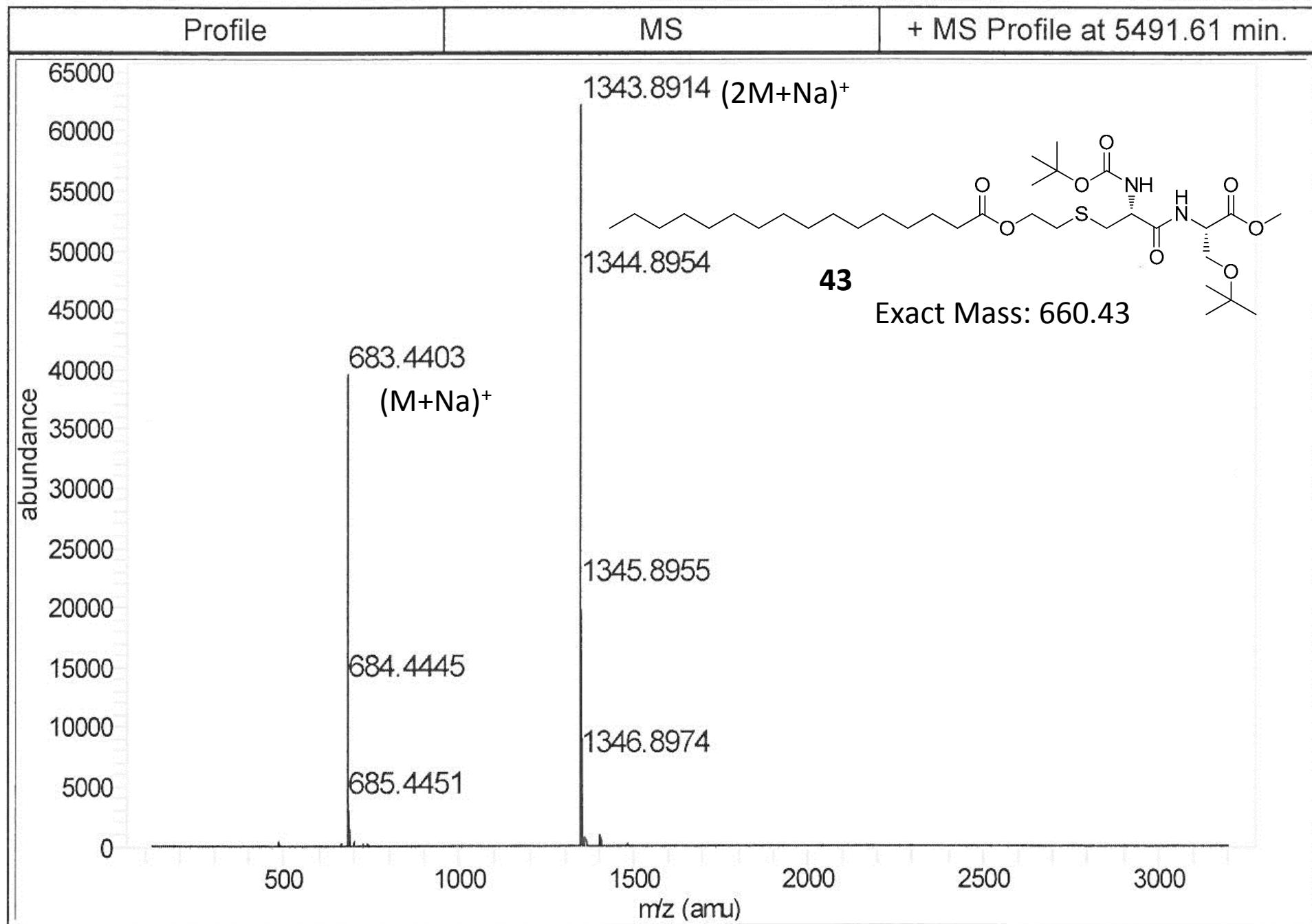




¹³C Spectrum

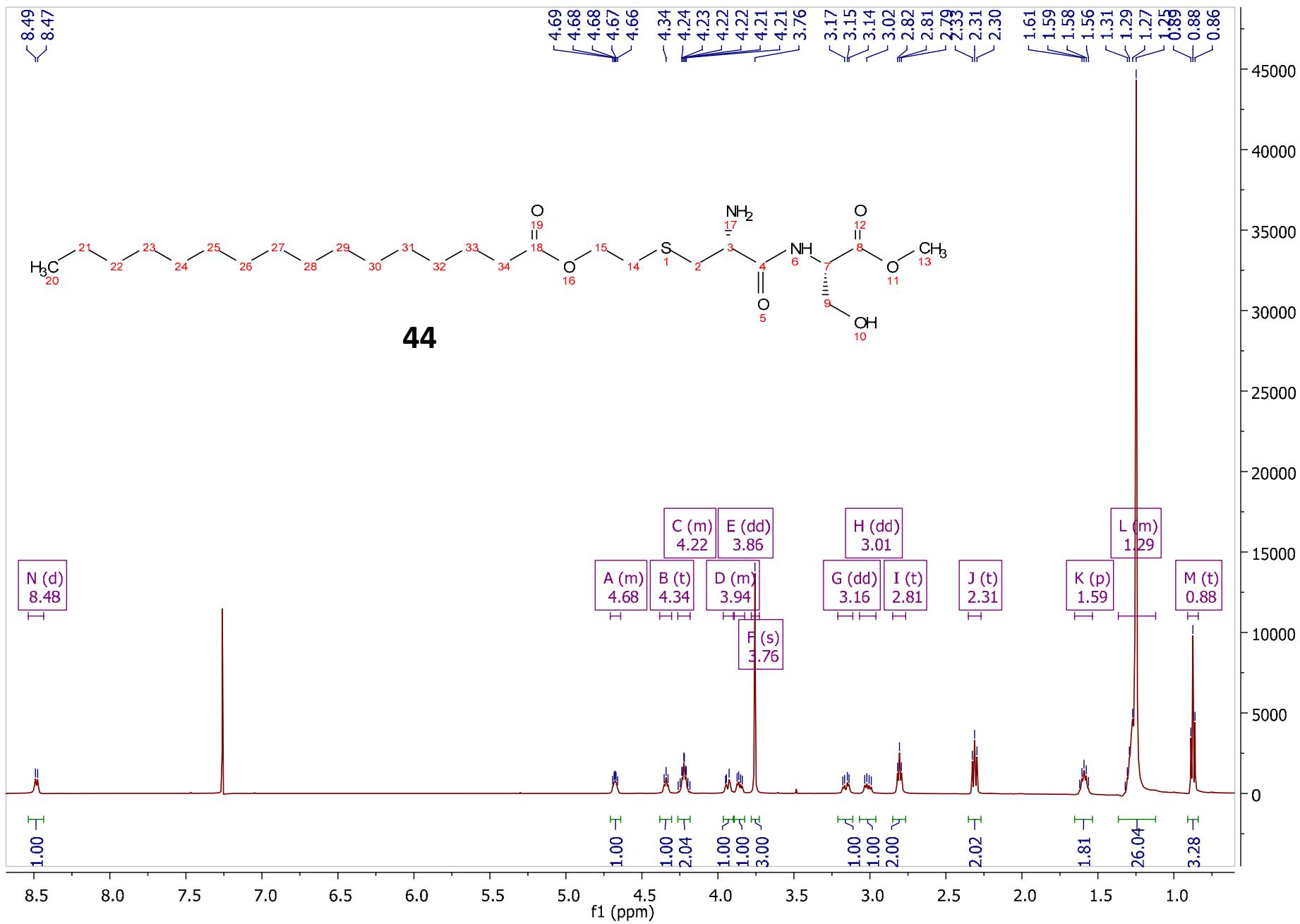
S178





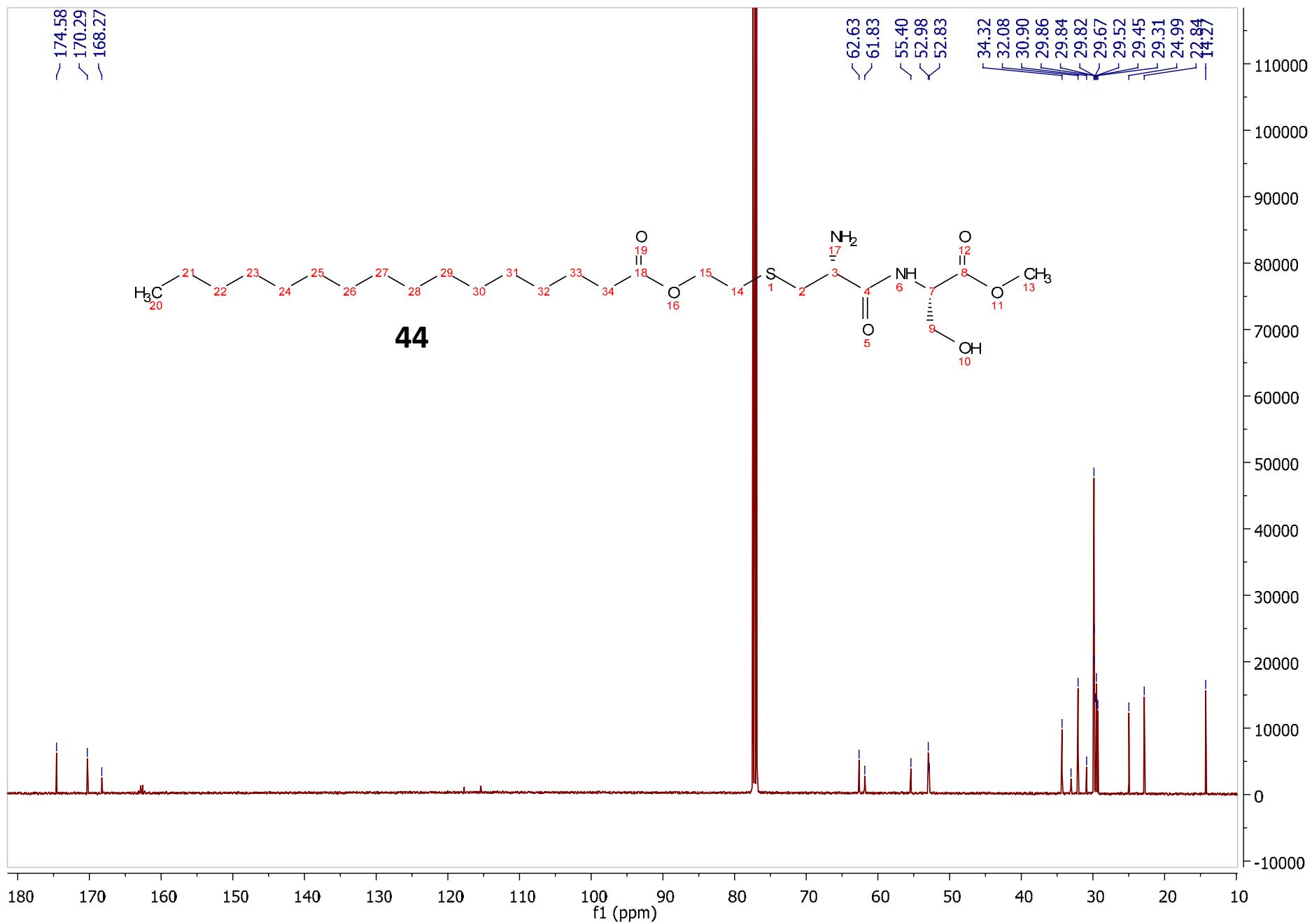
¹H Spectrum

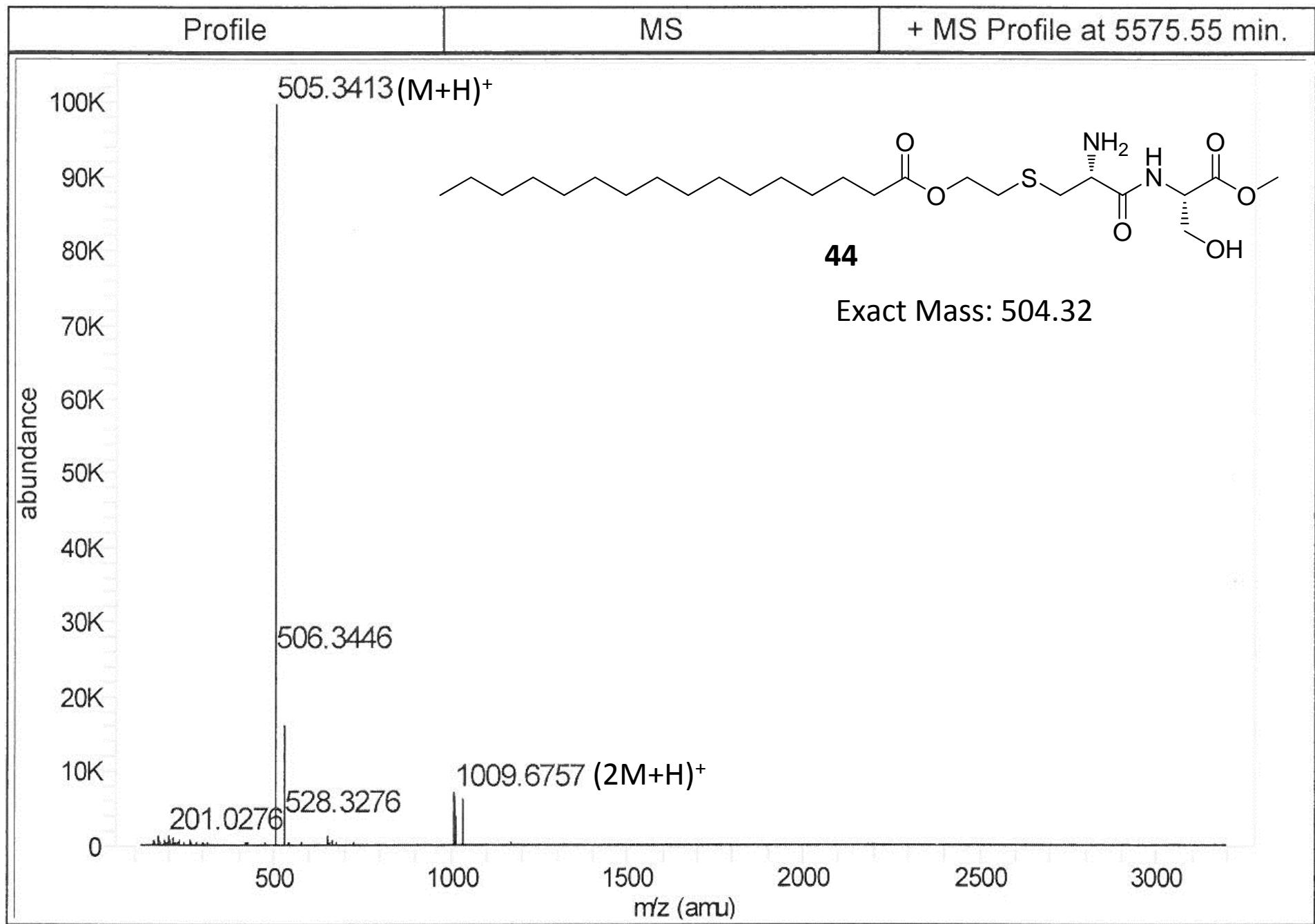
S180

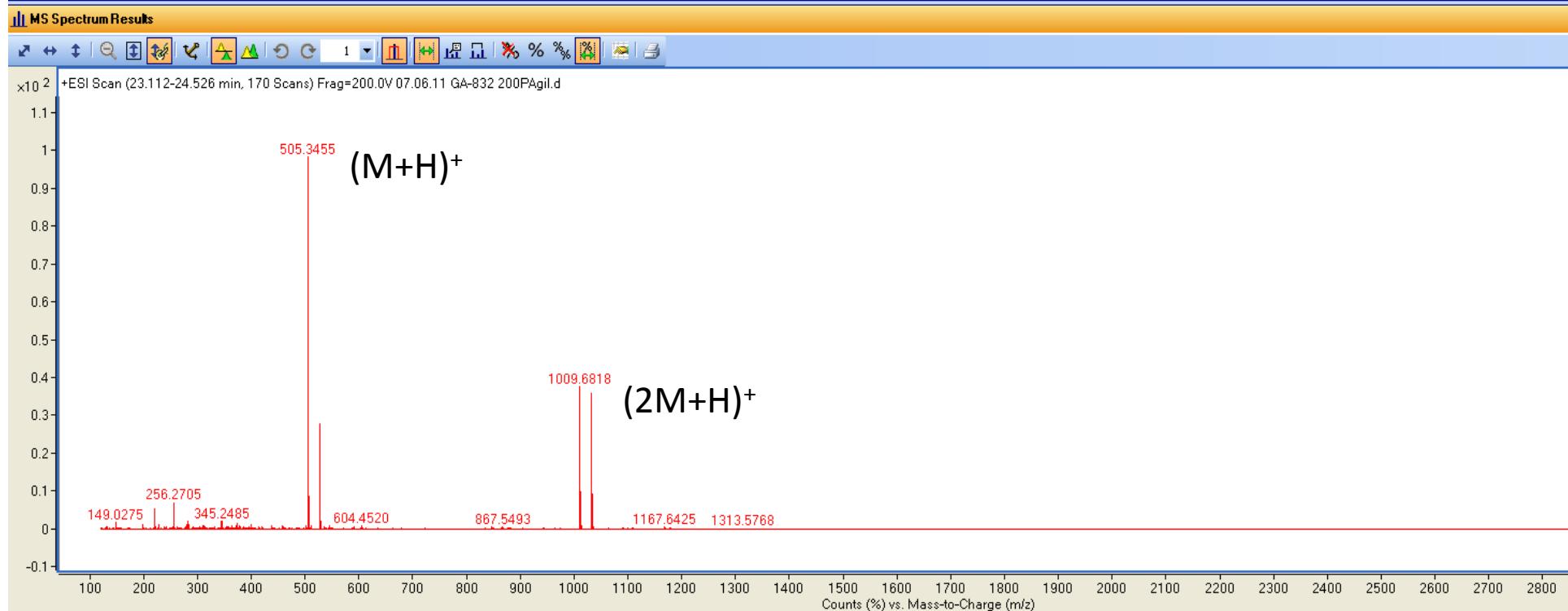
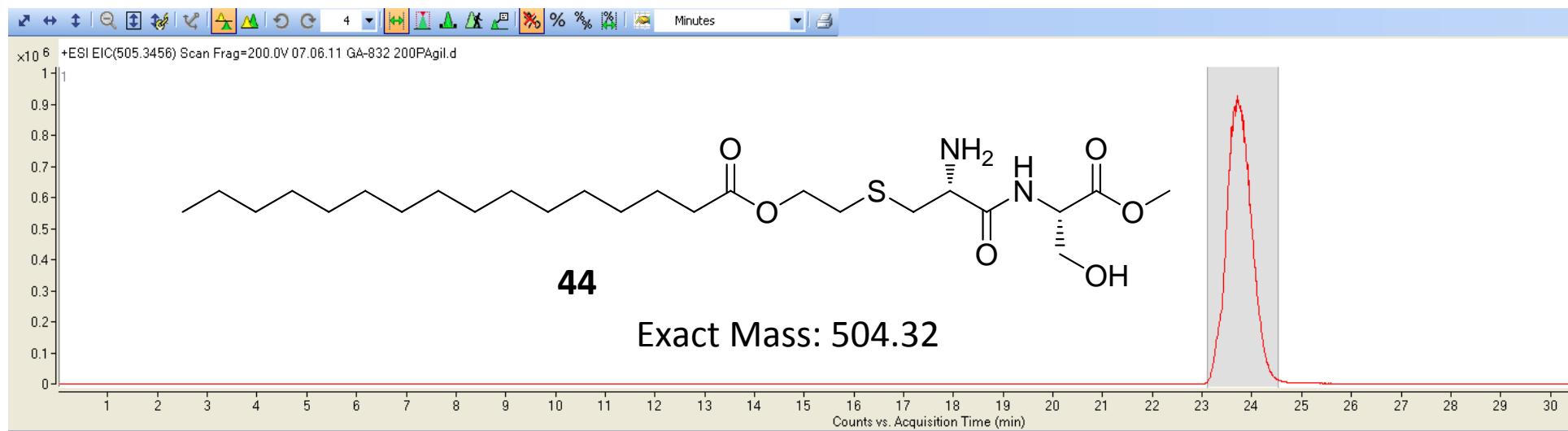


¹³C Spectrum

S181

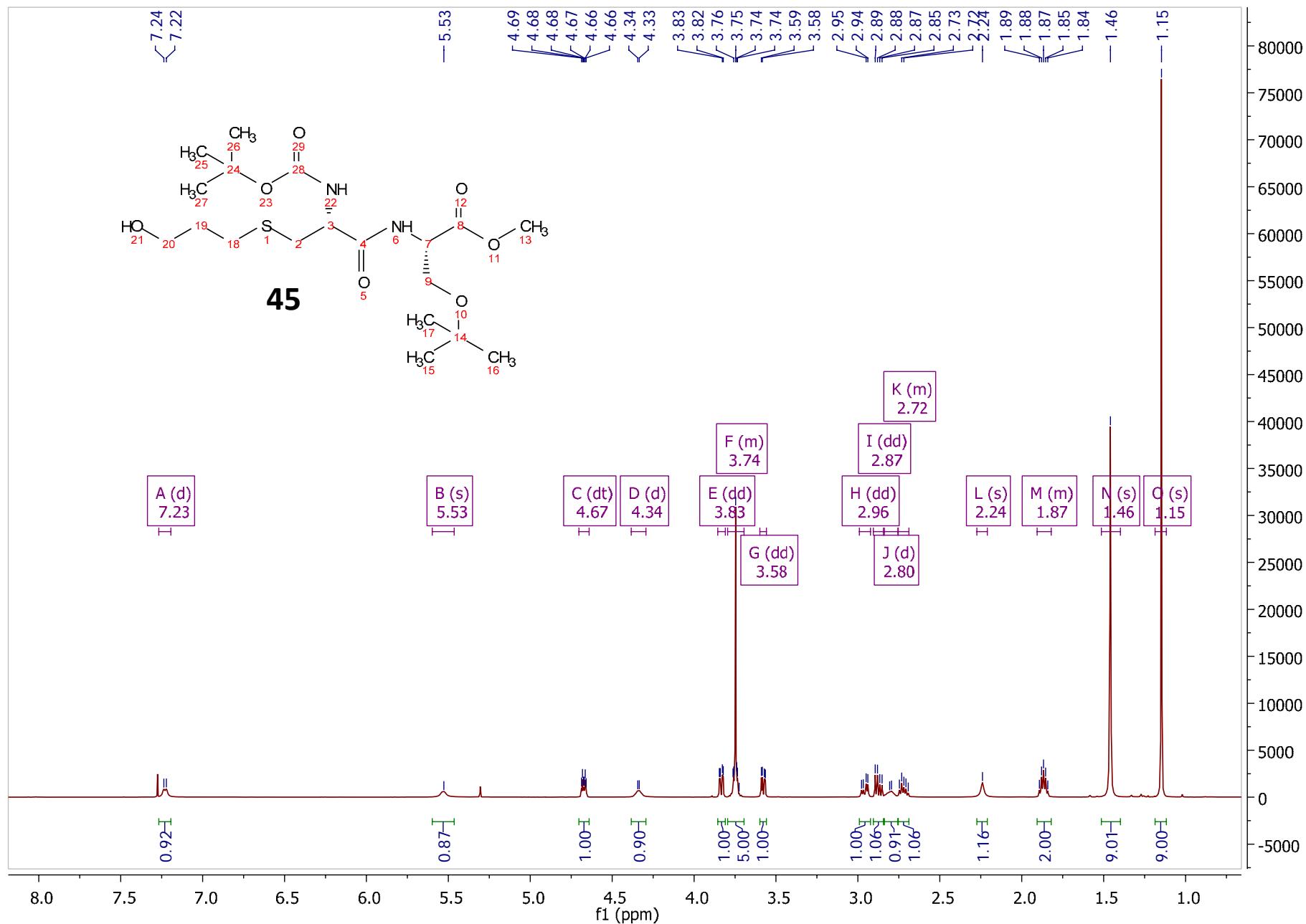






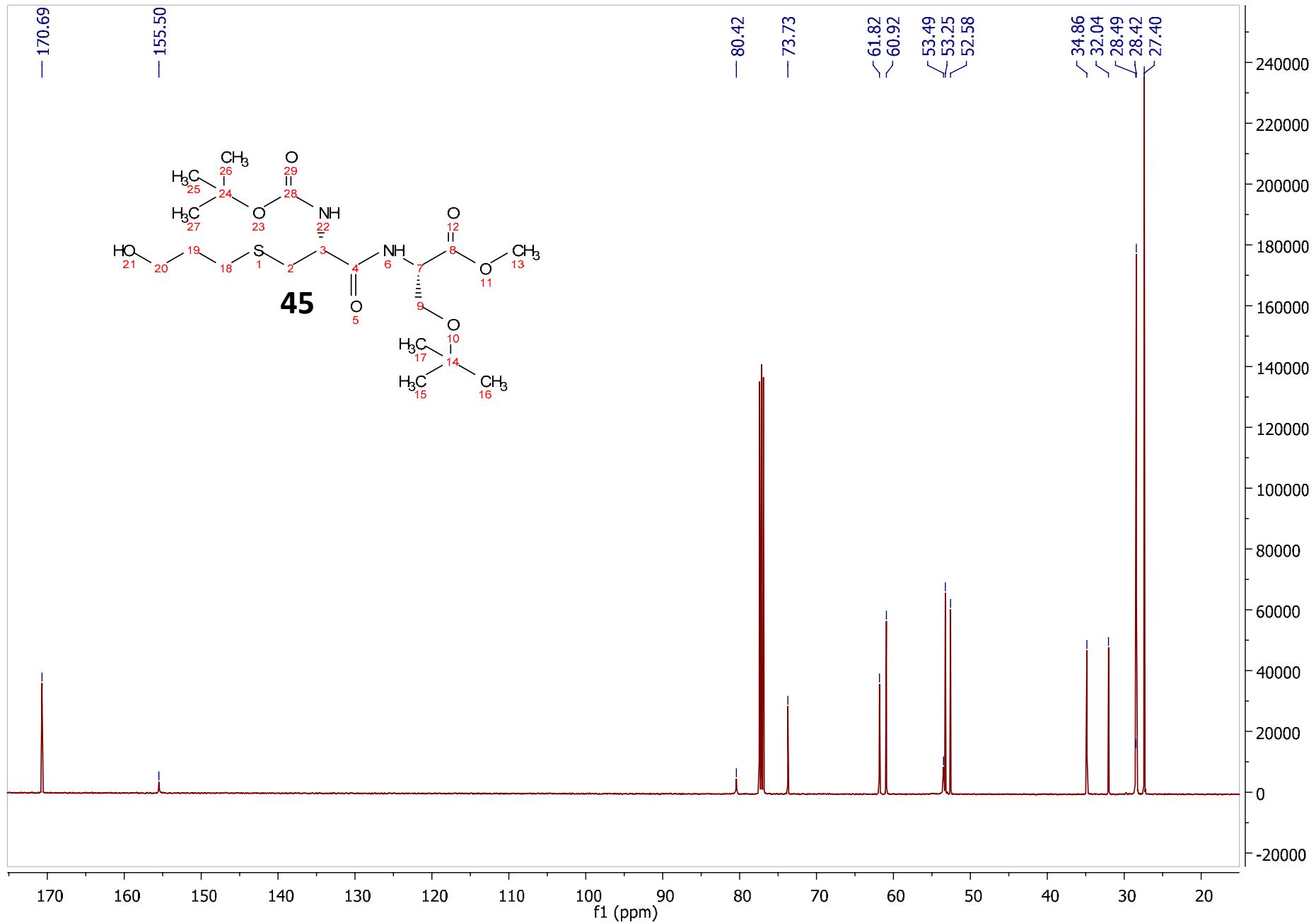
¹H Spectrum

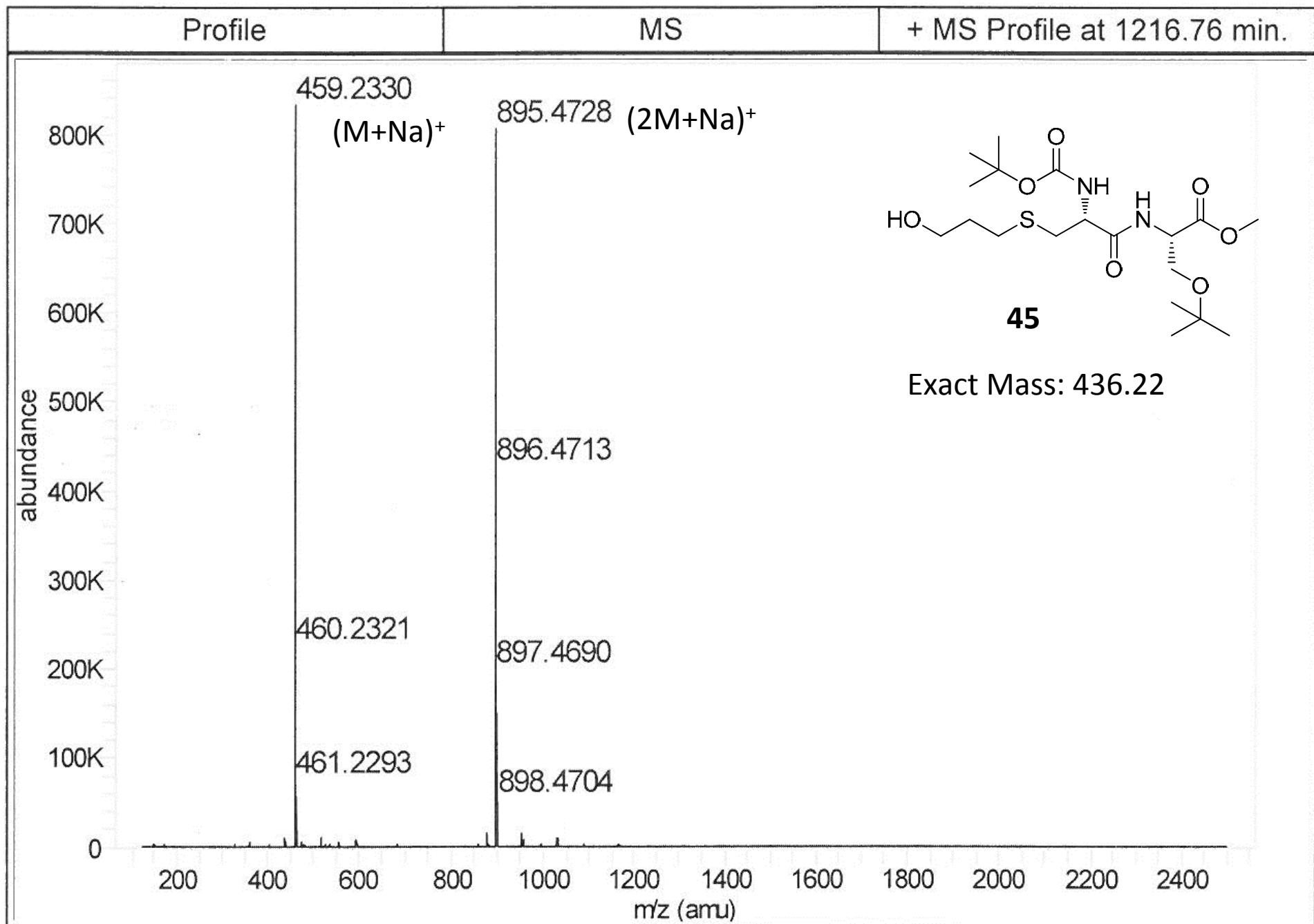
S184



¹³C Spectrum

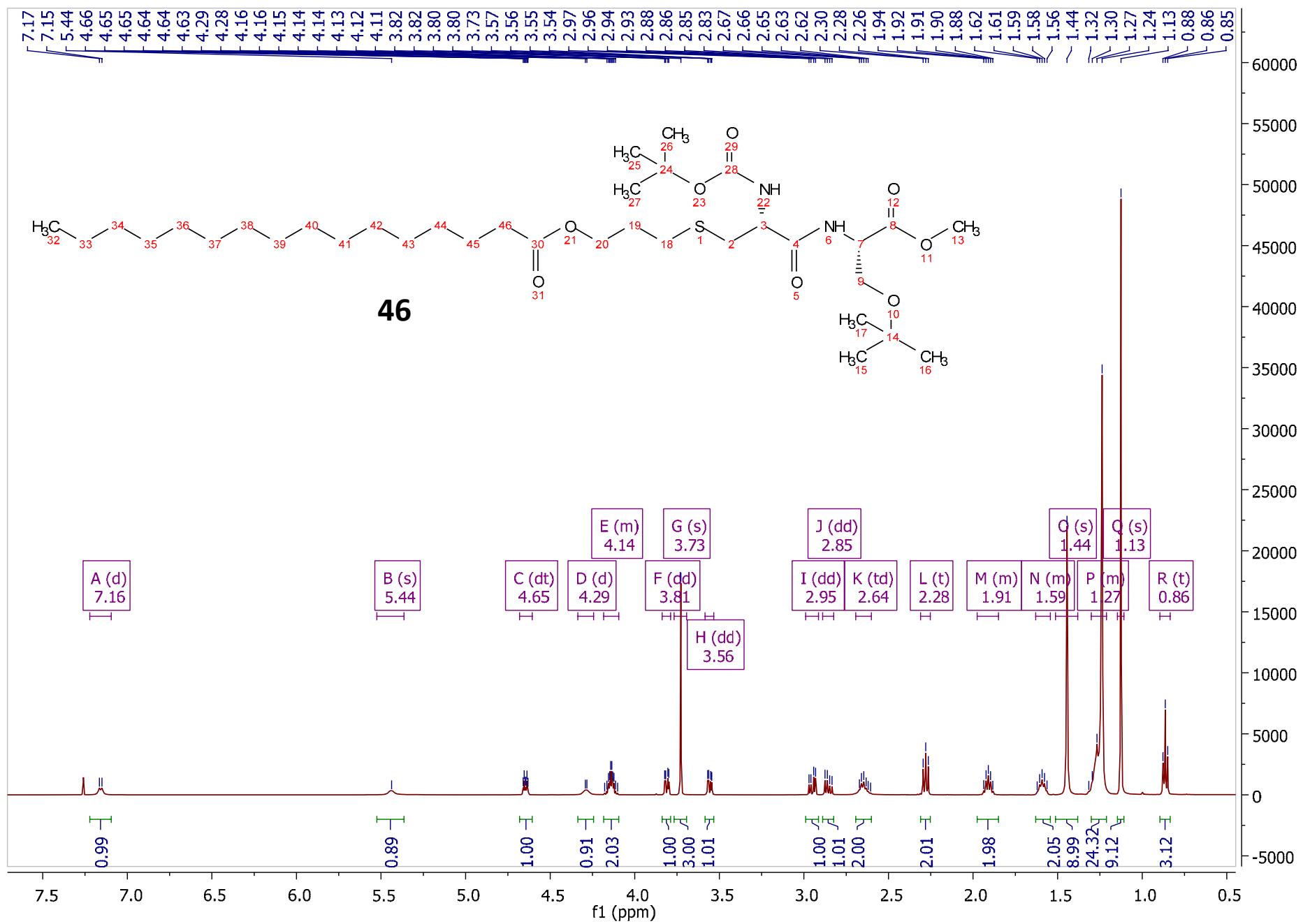
S185





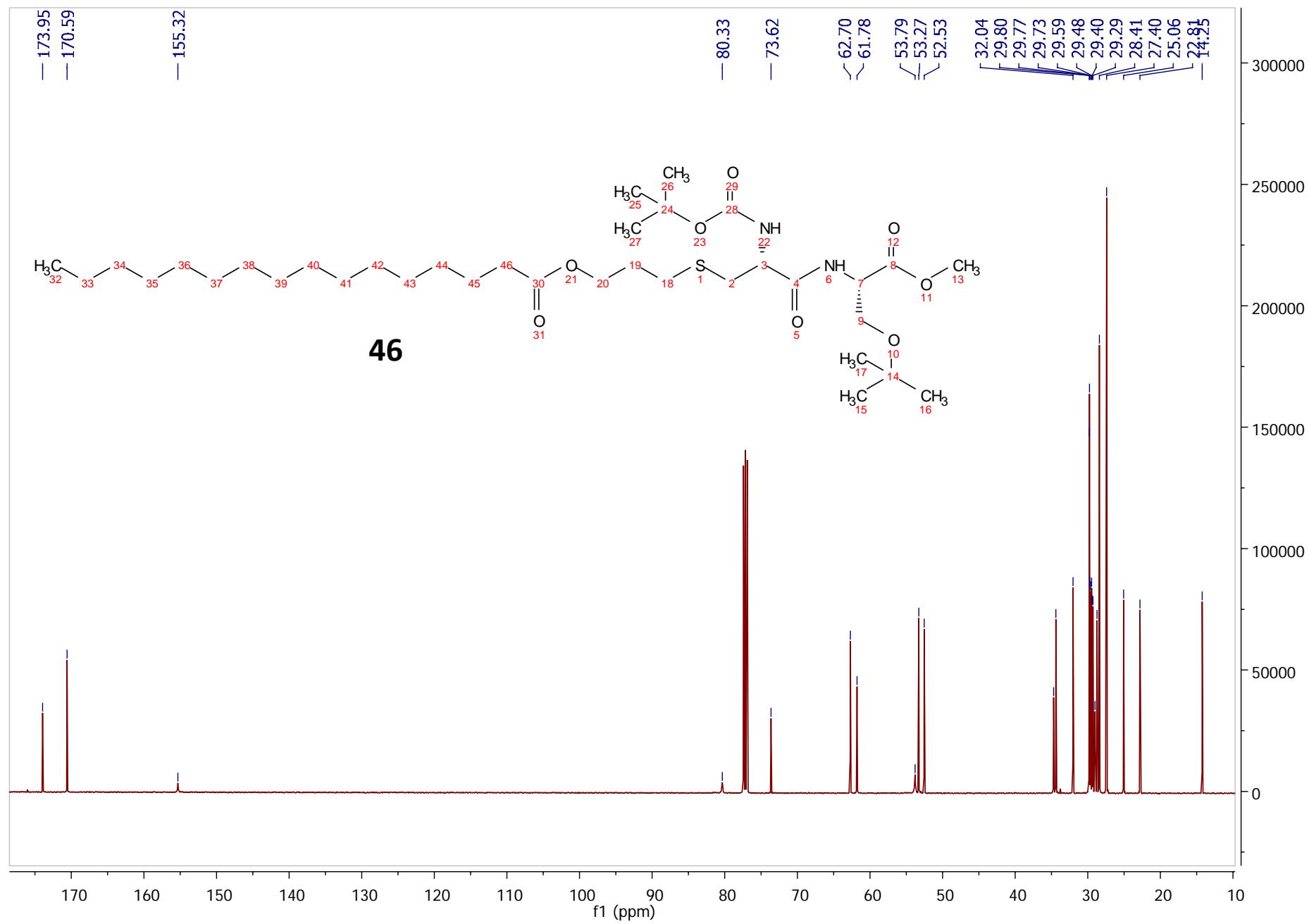
¹H Spectrum

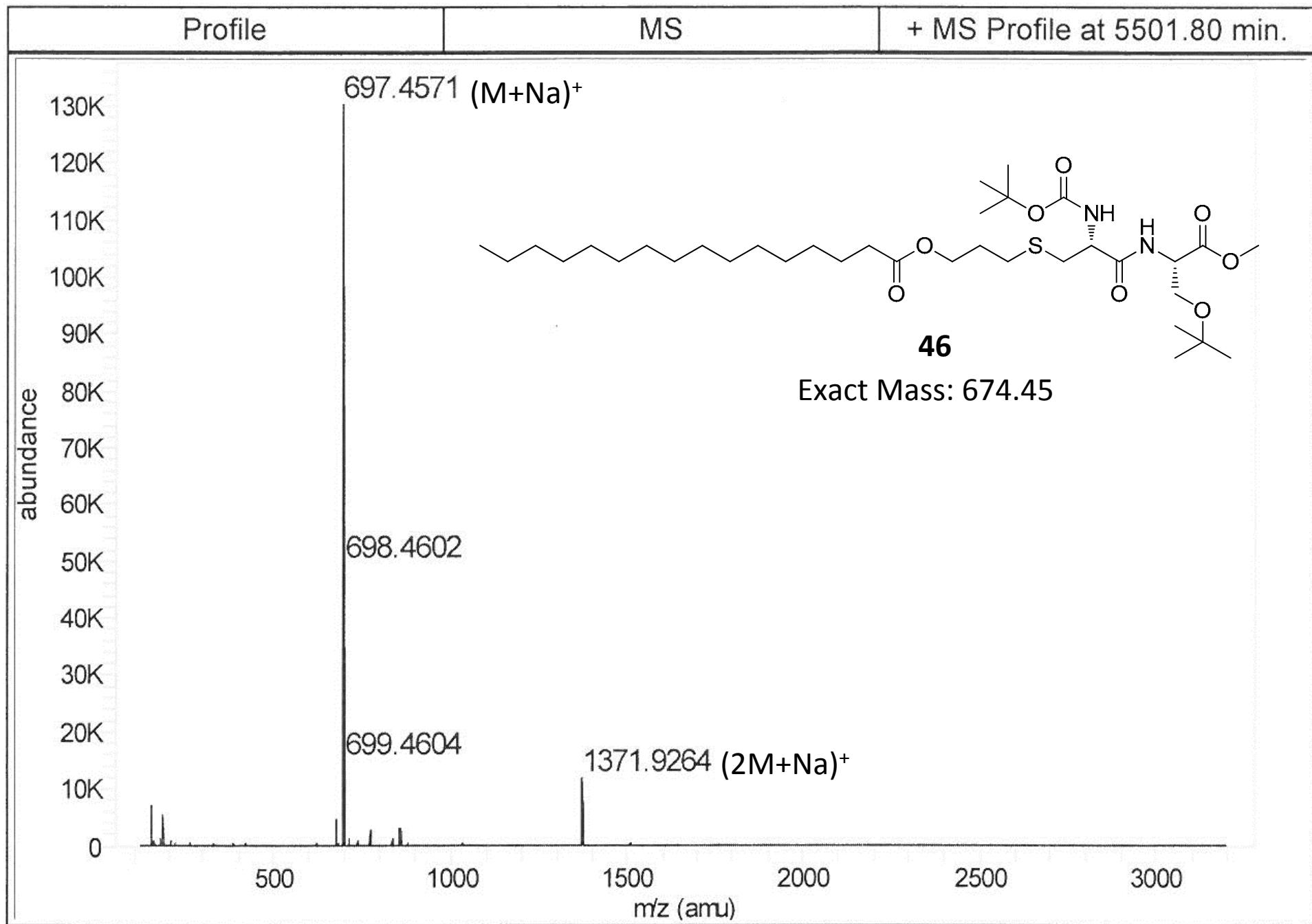
S187



¹³C Spectrum

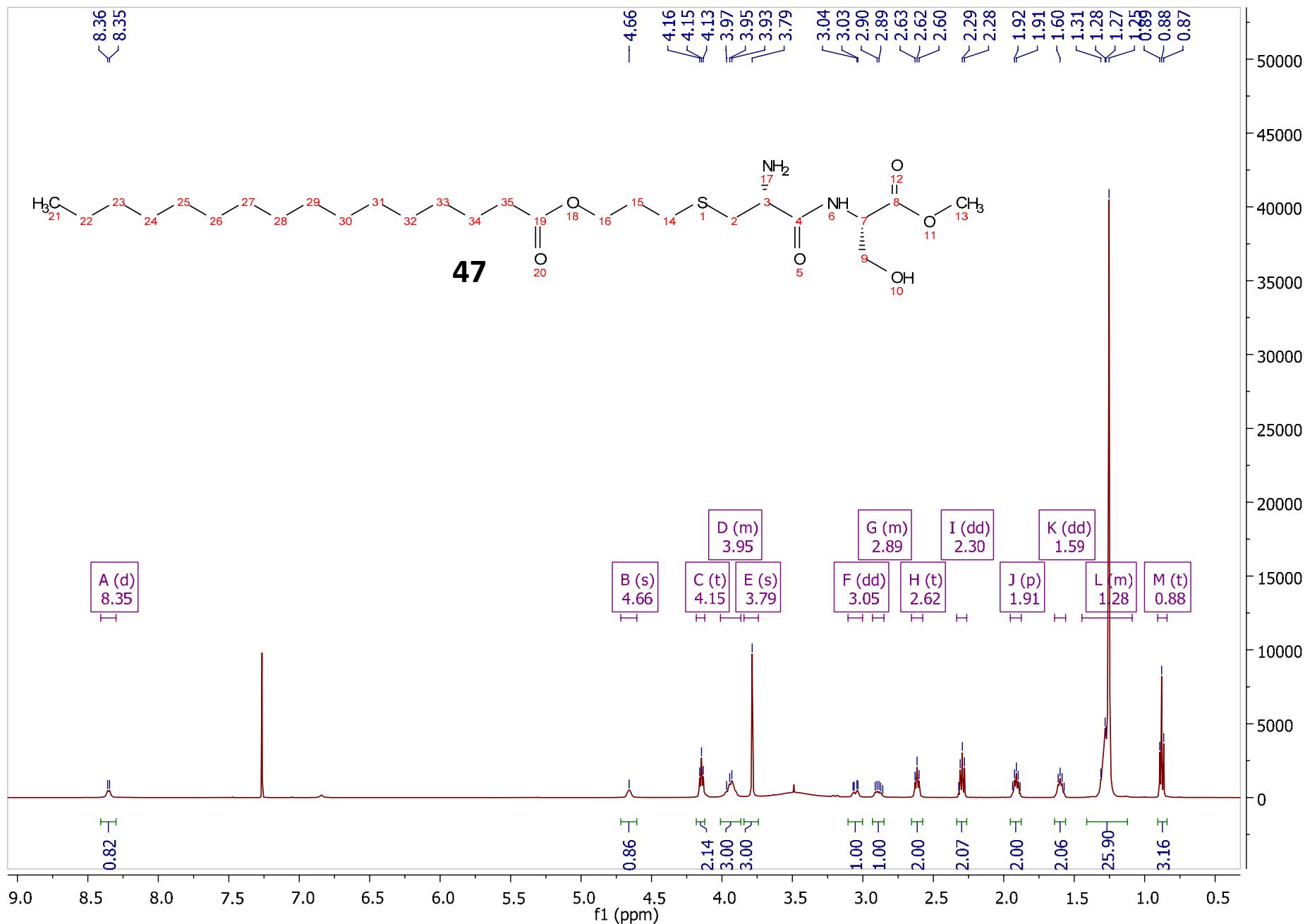
S188





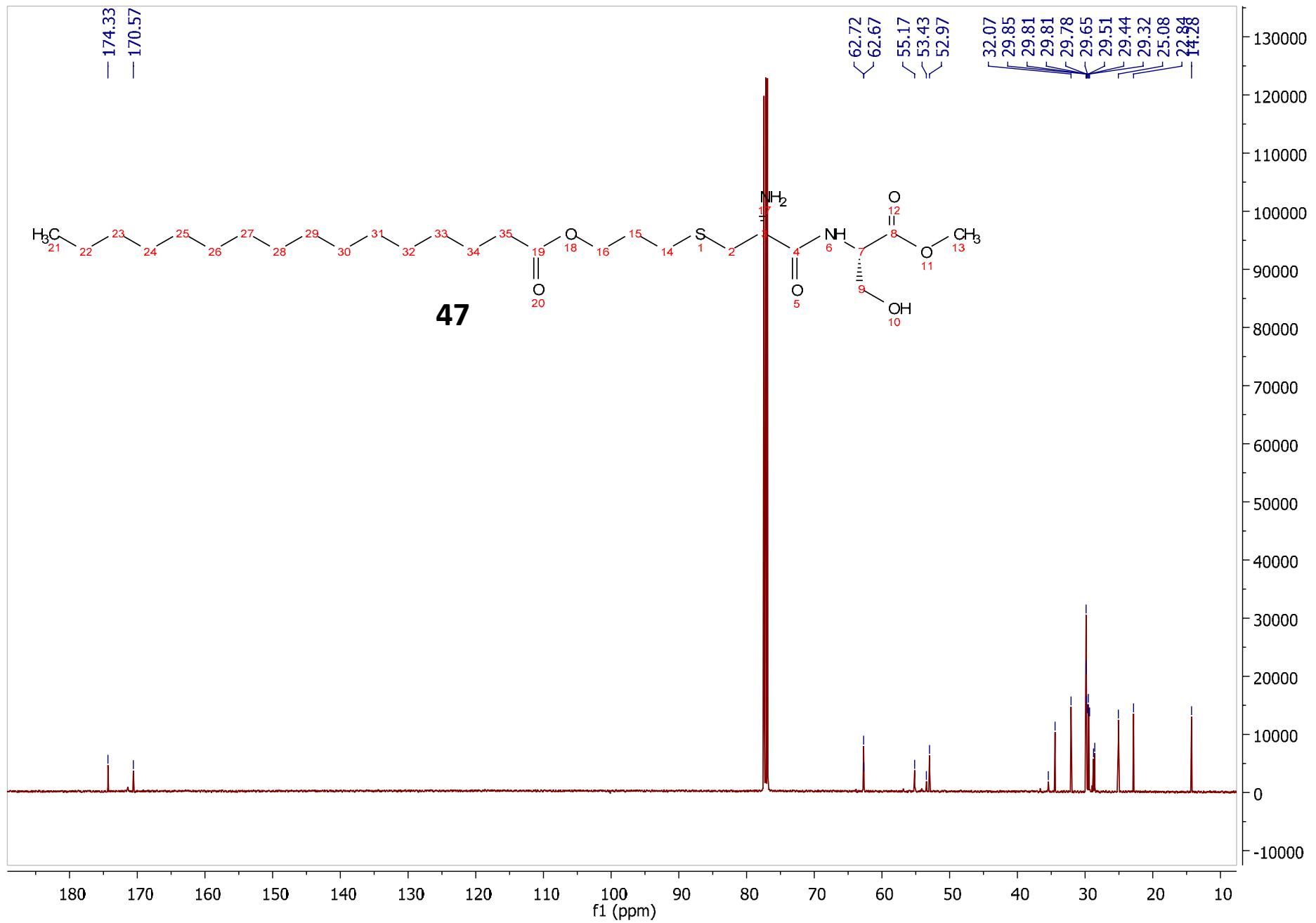
¹H Spectrum

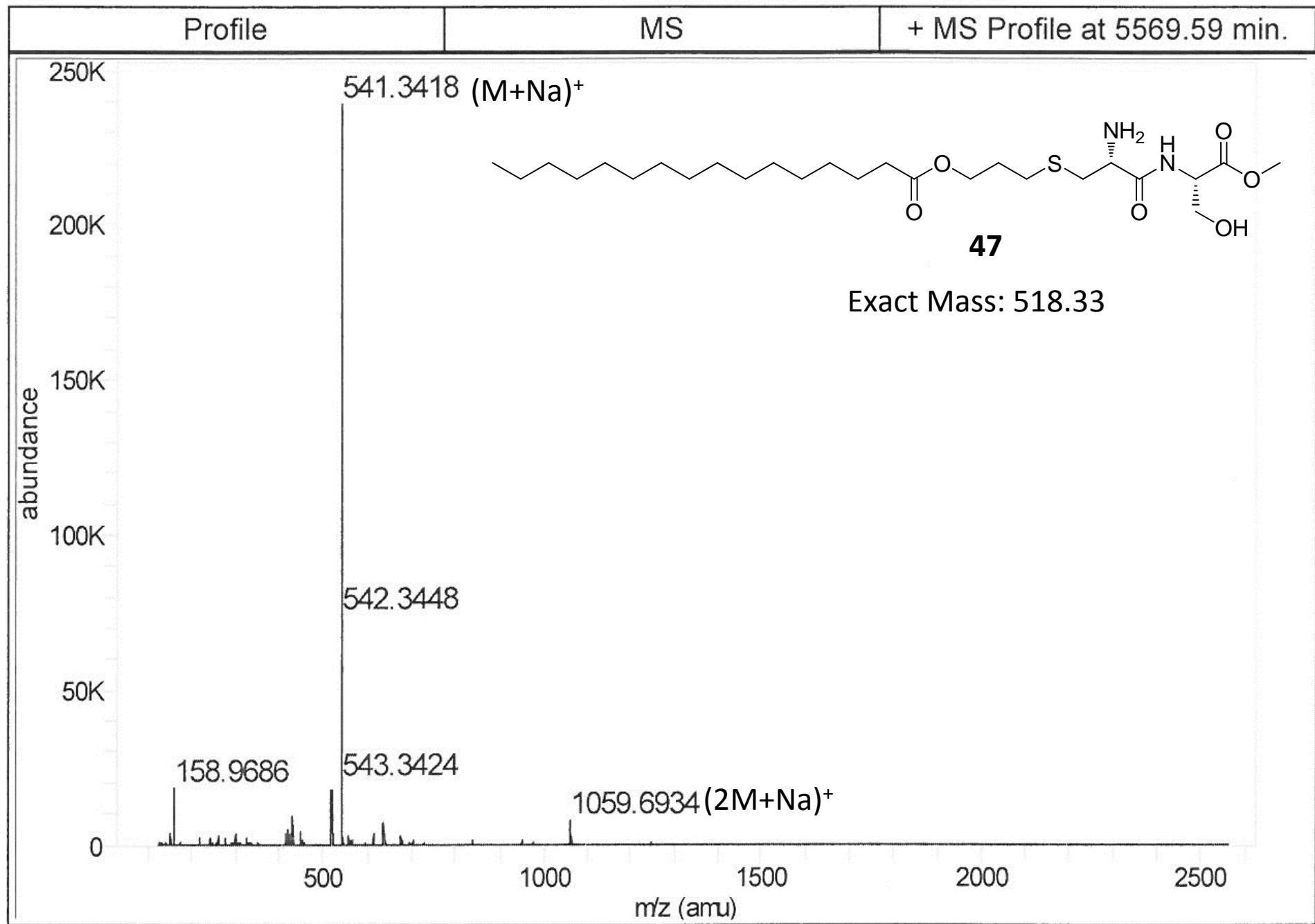
S190

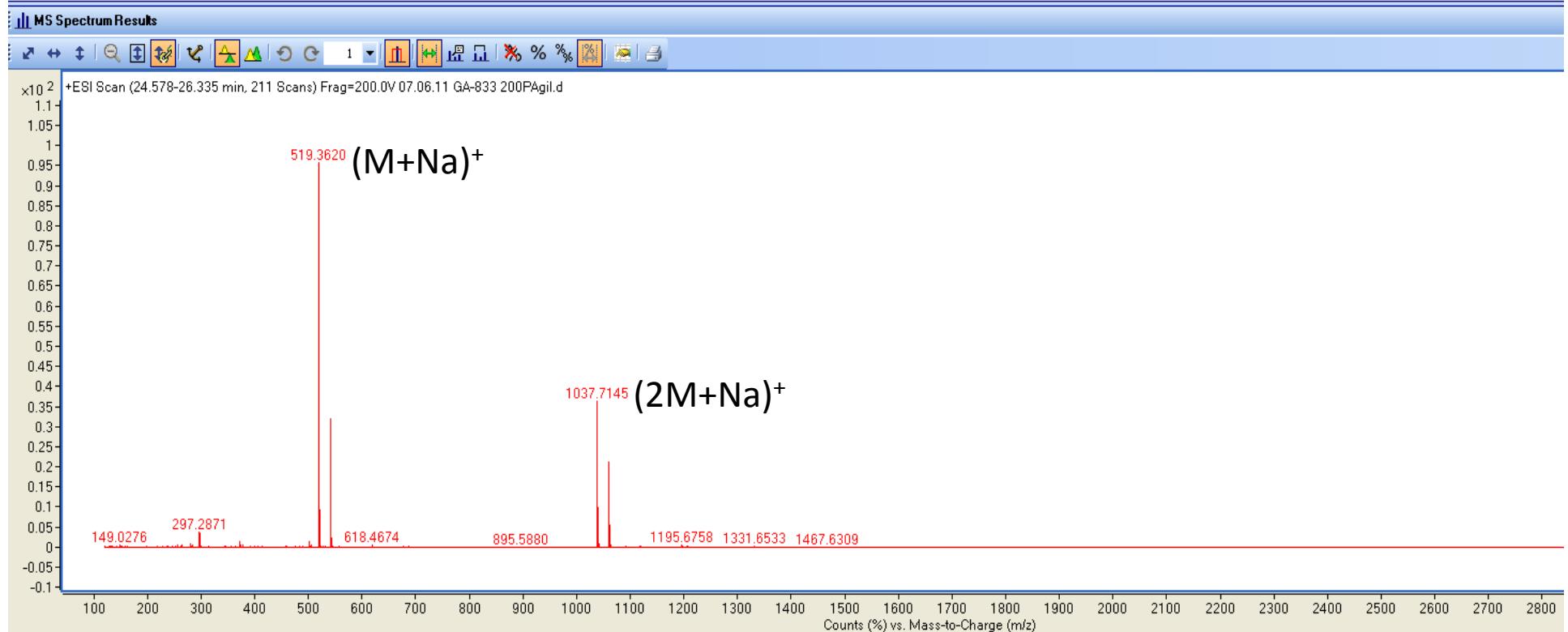
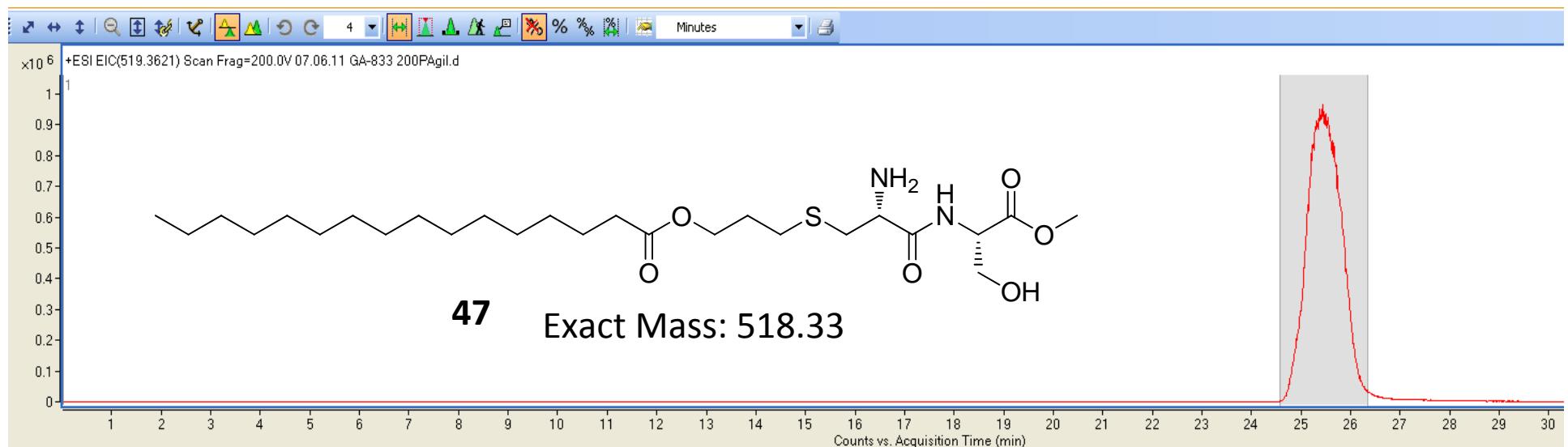


¹³C Spectrum

S191

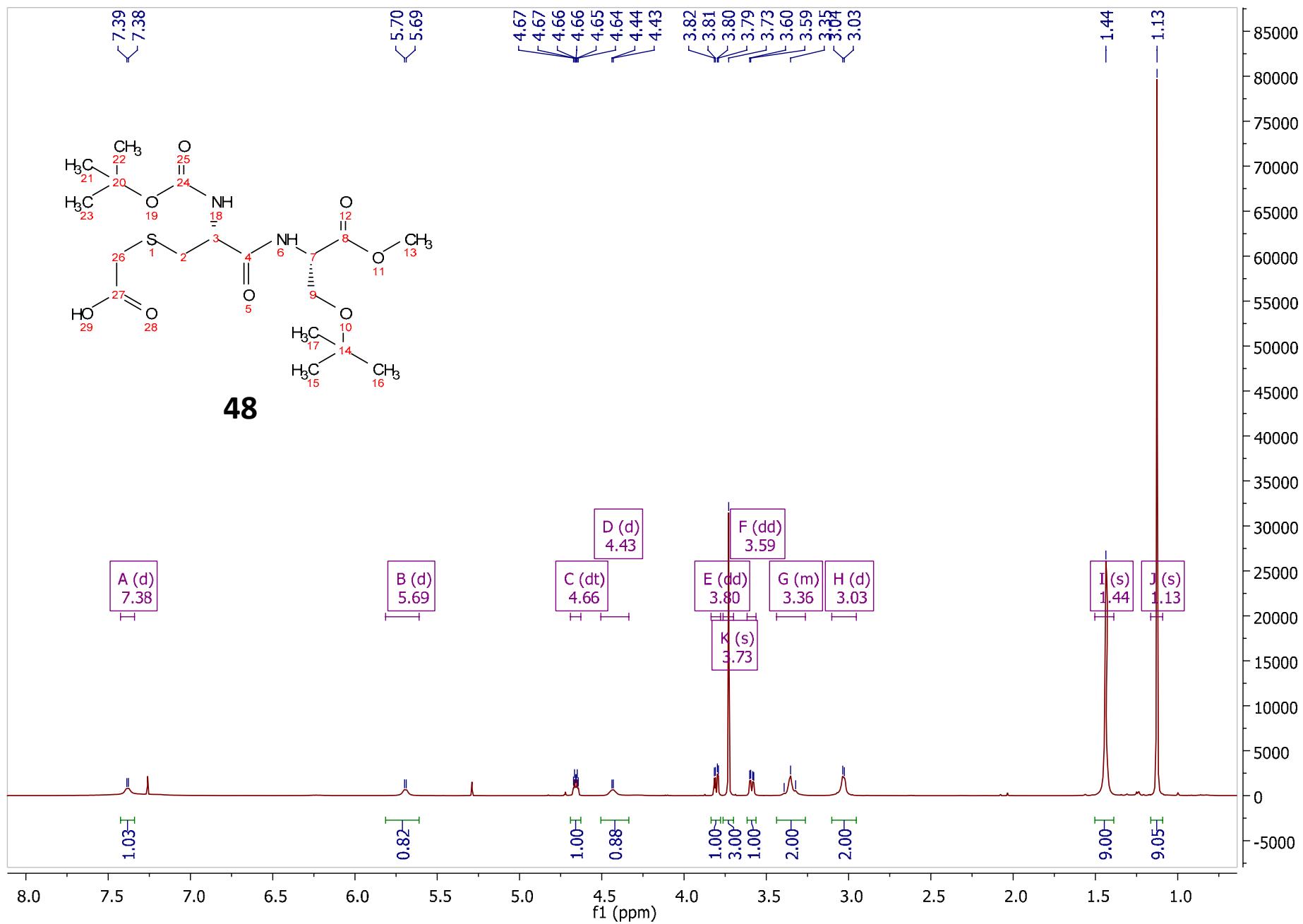


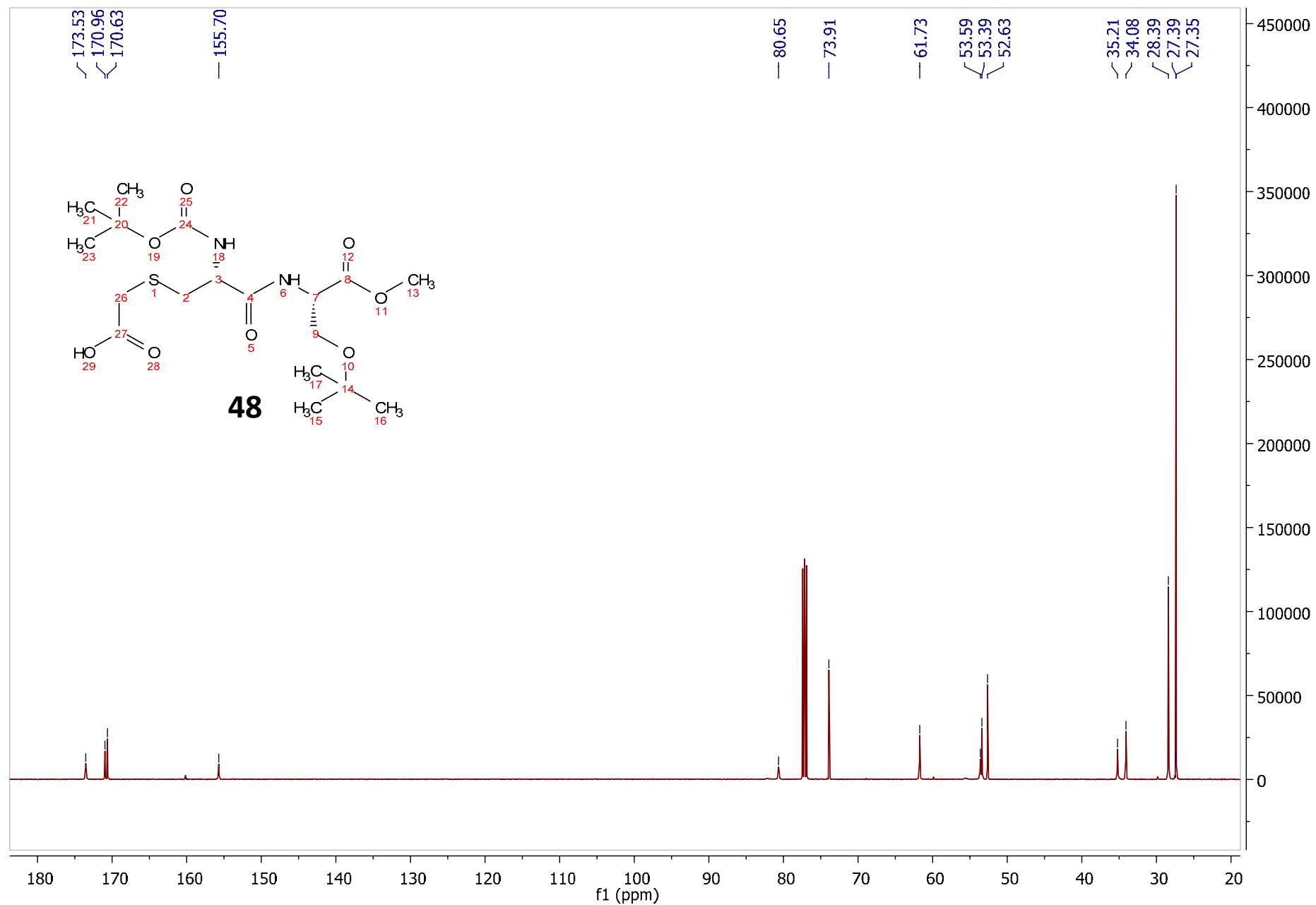


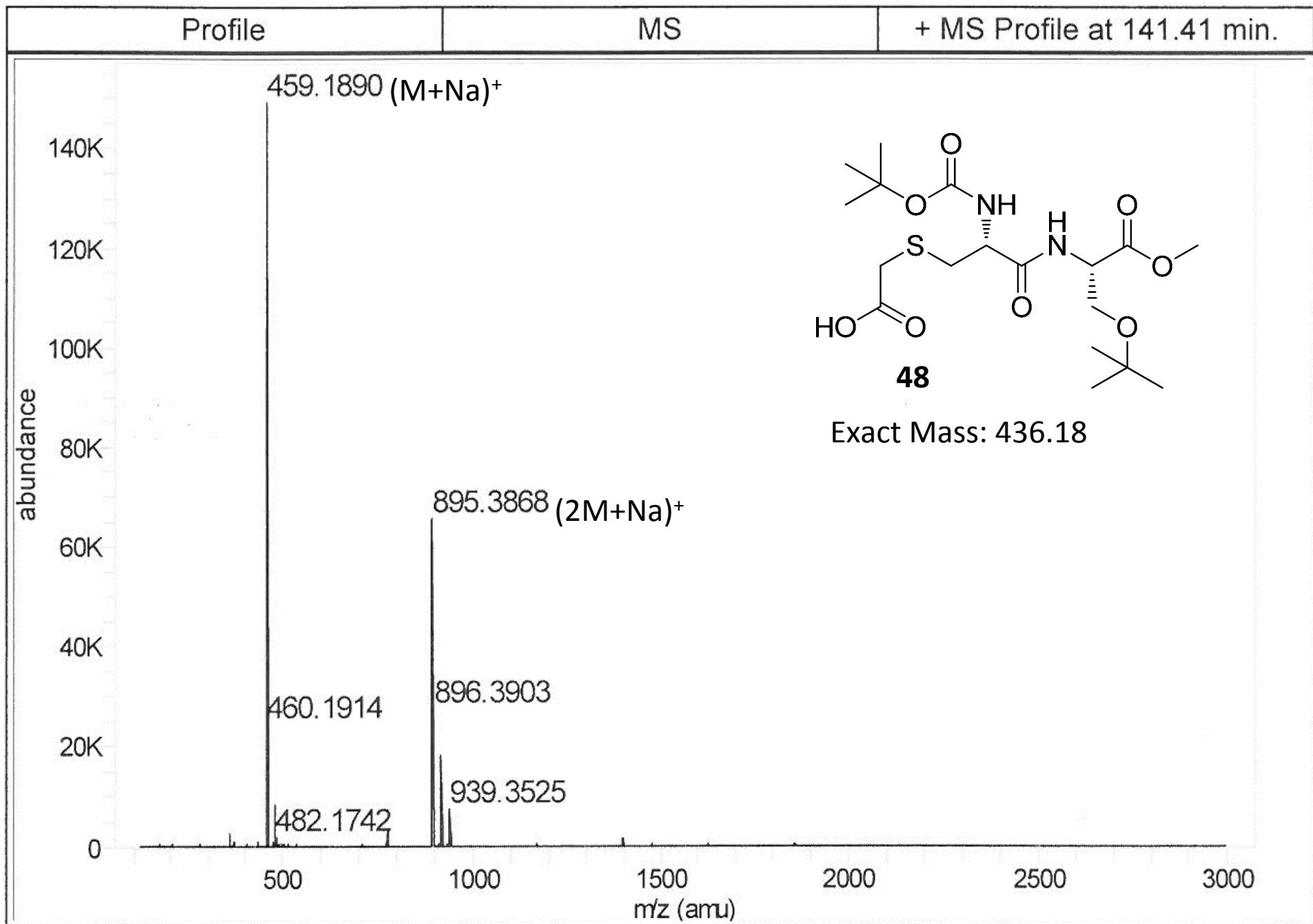


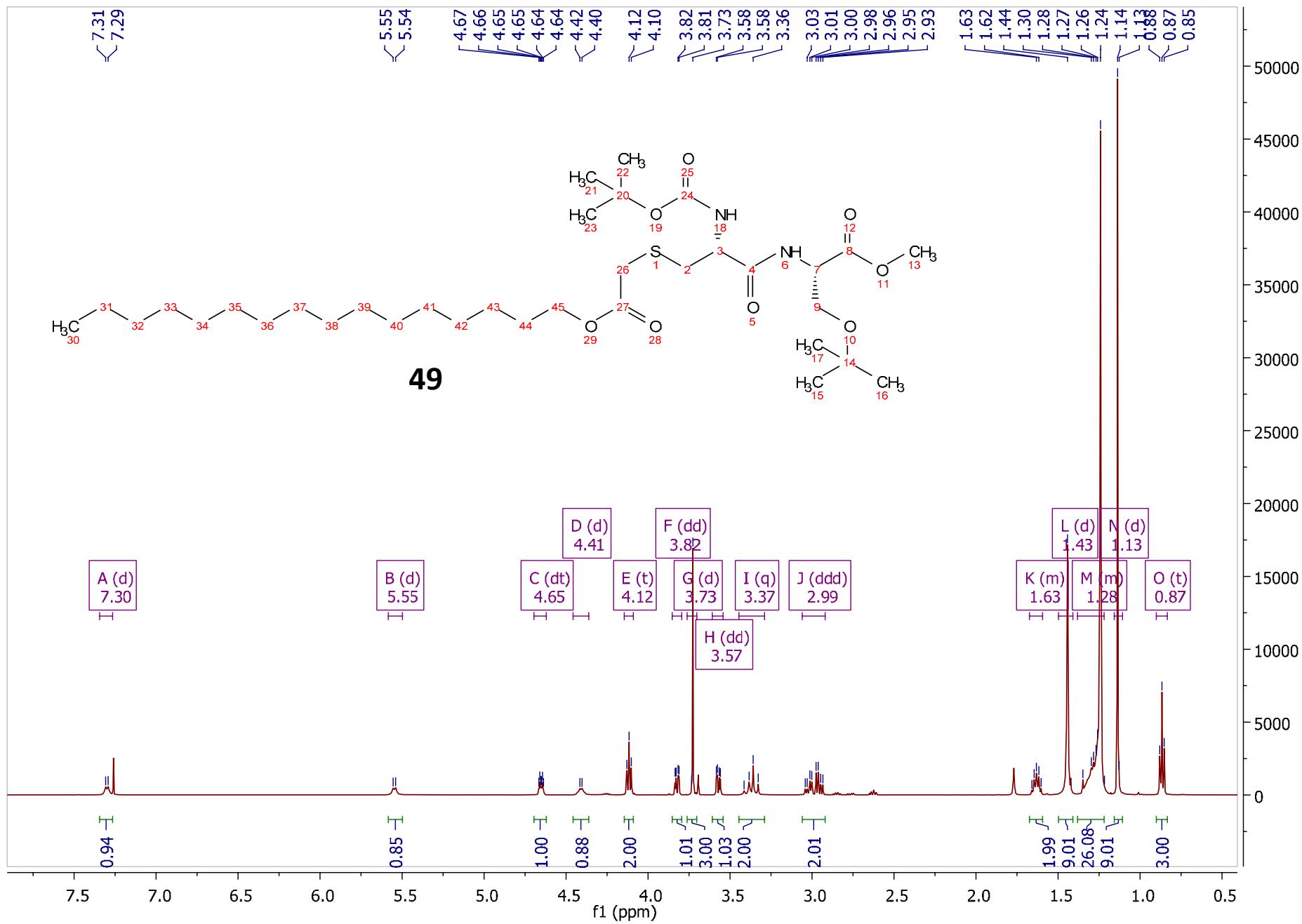
¹H Spectrum

S194



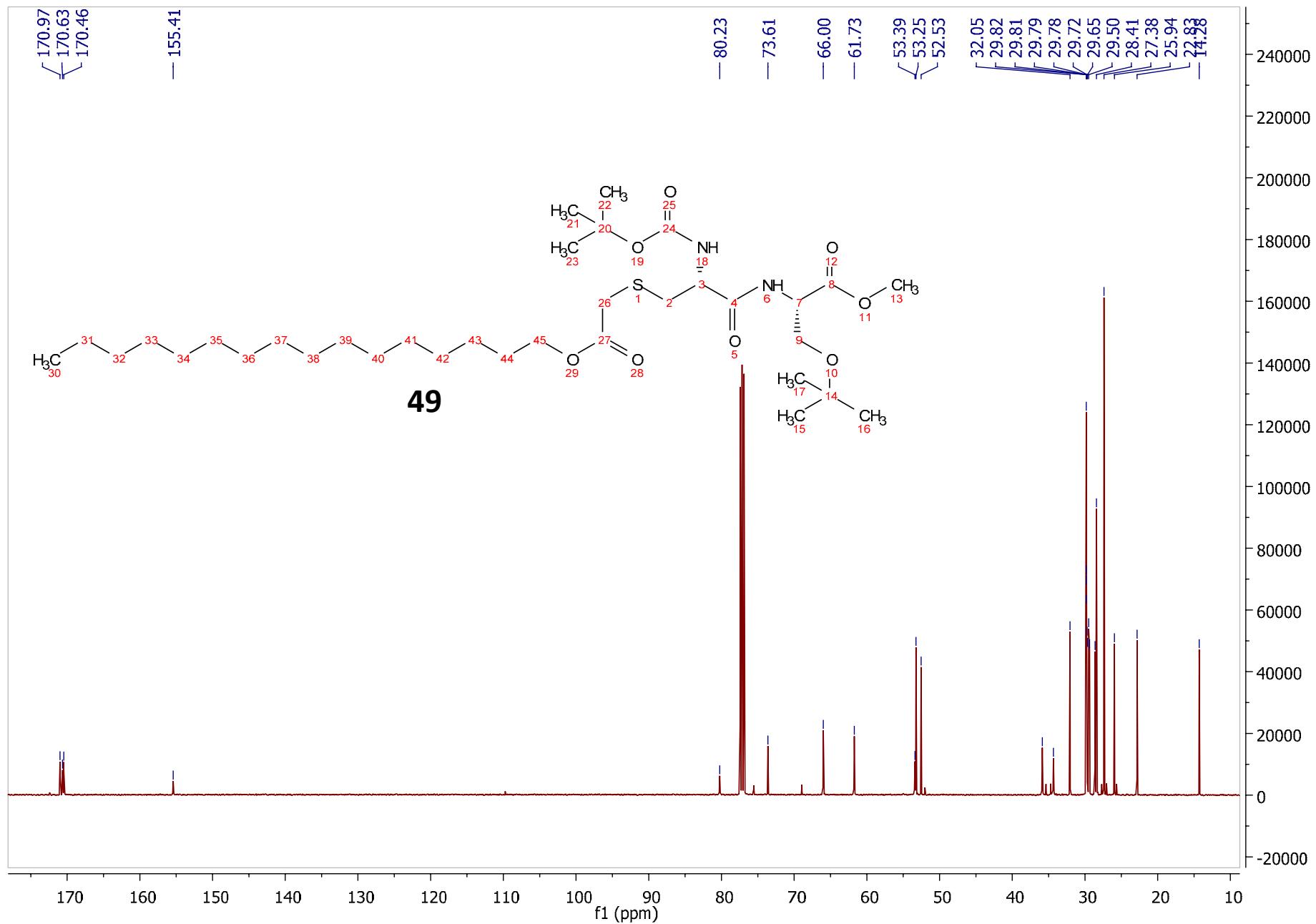
¹³C Spectrum

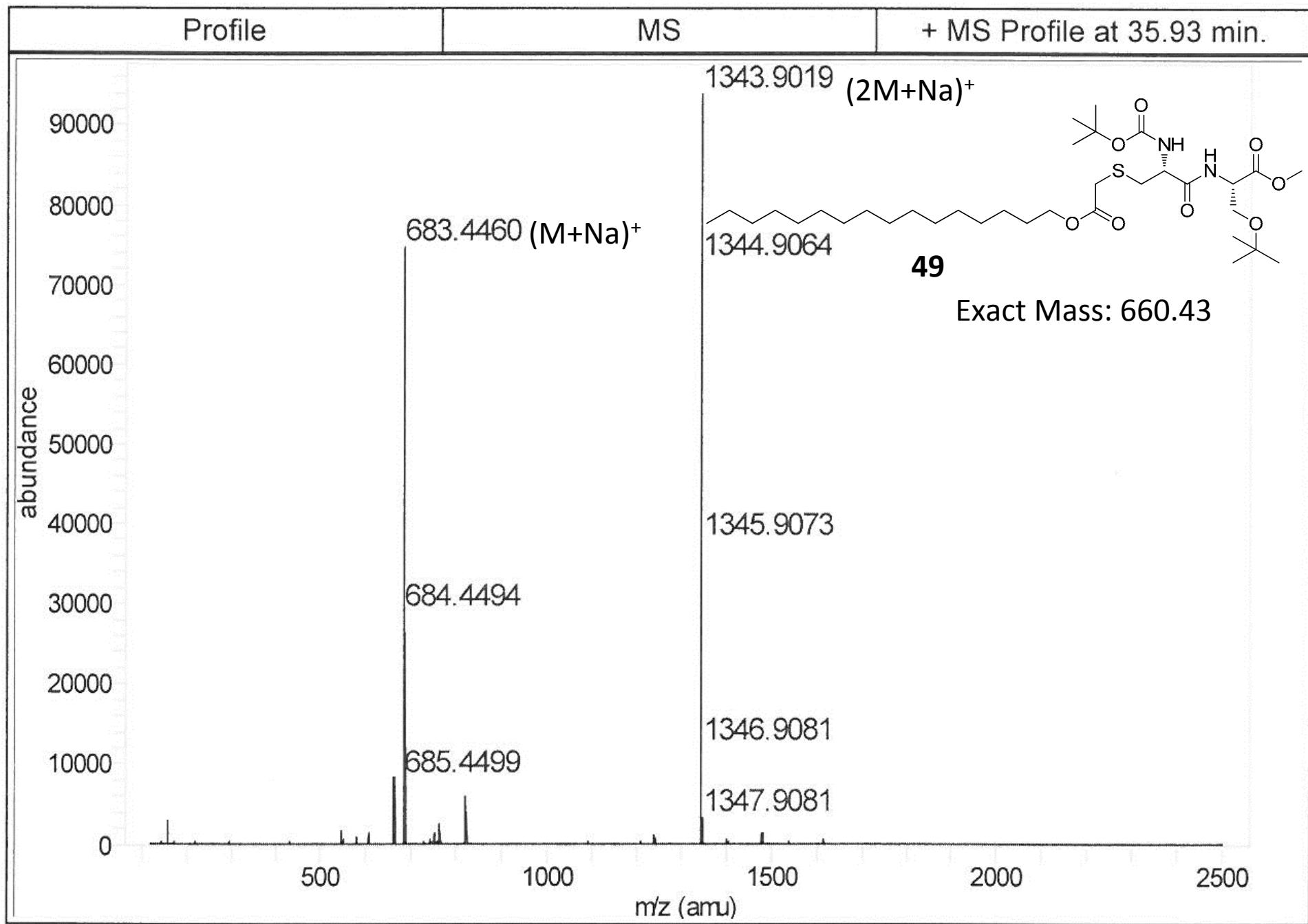




¹³C Spectrum

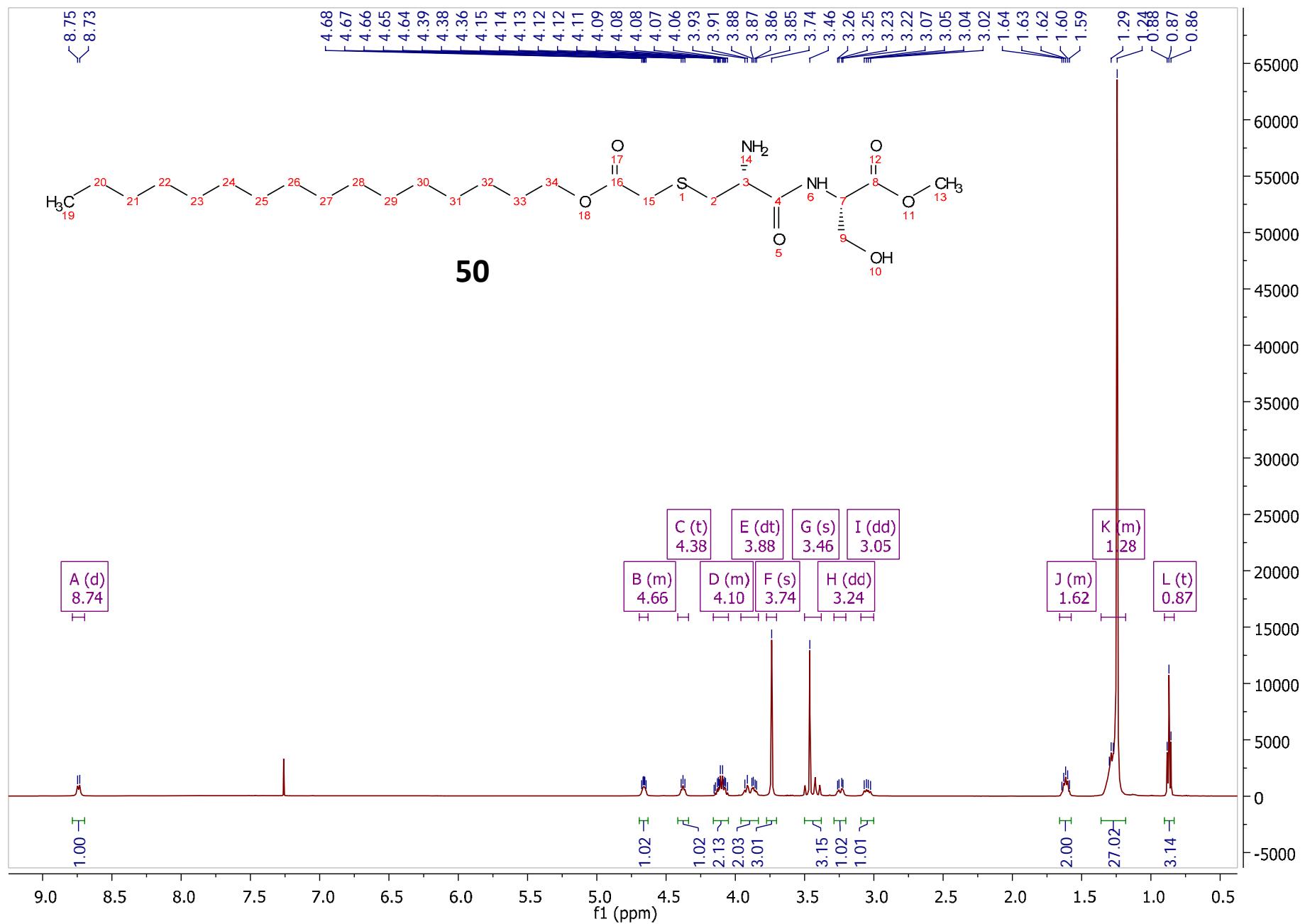
S198





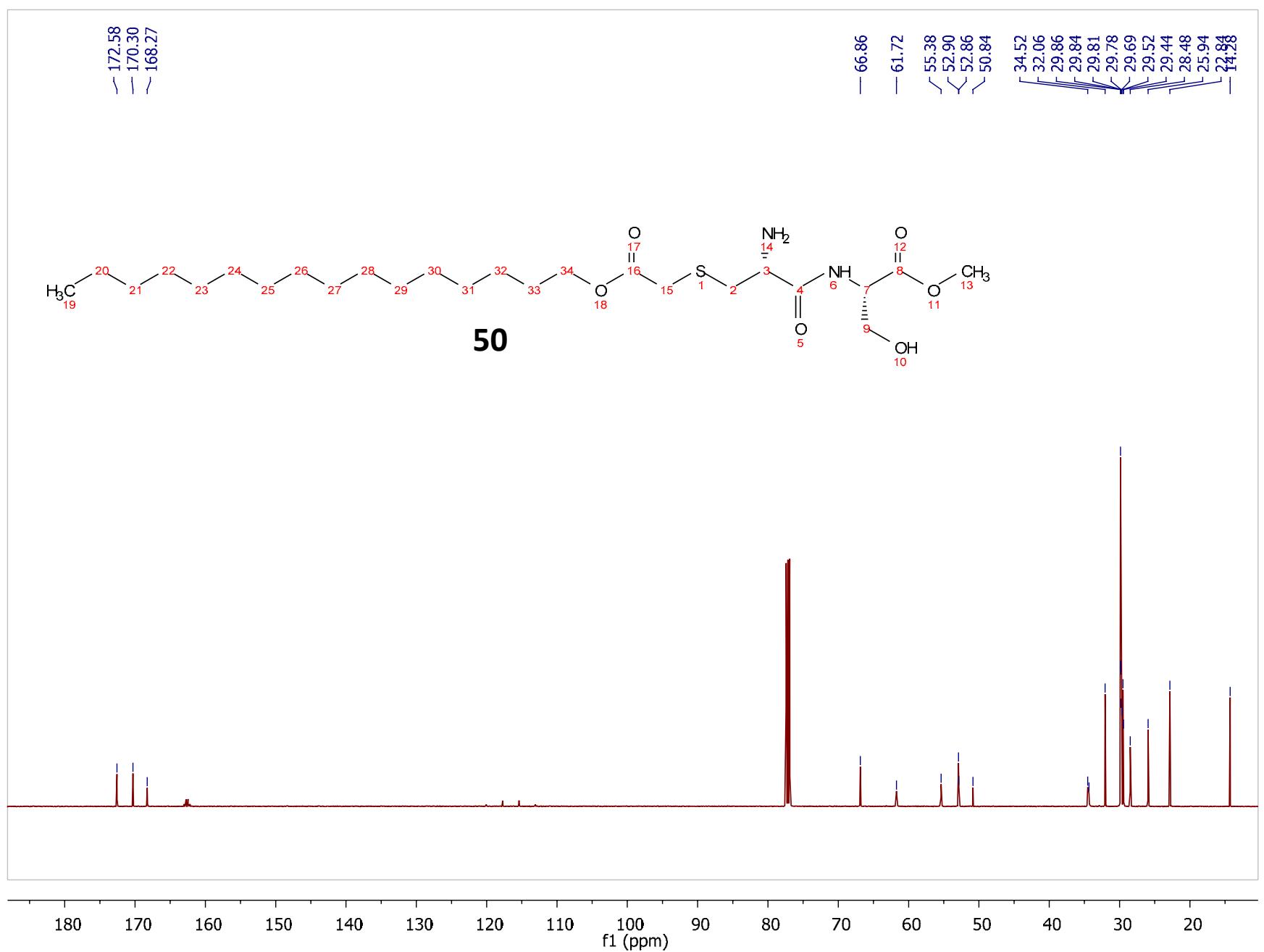
¹H Spectrum

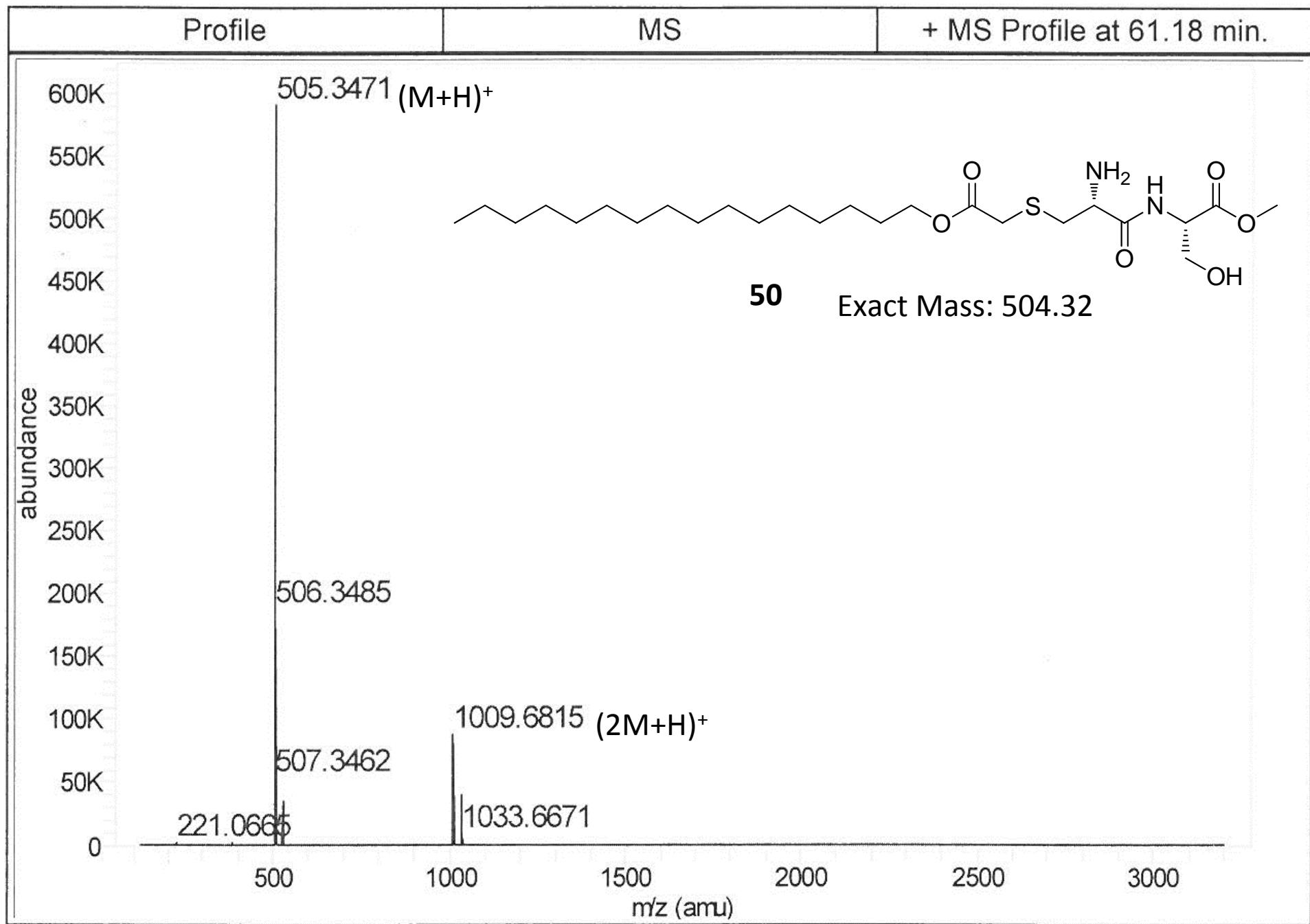
S200

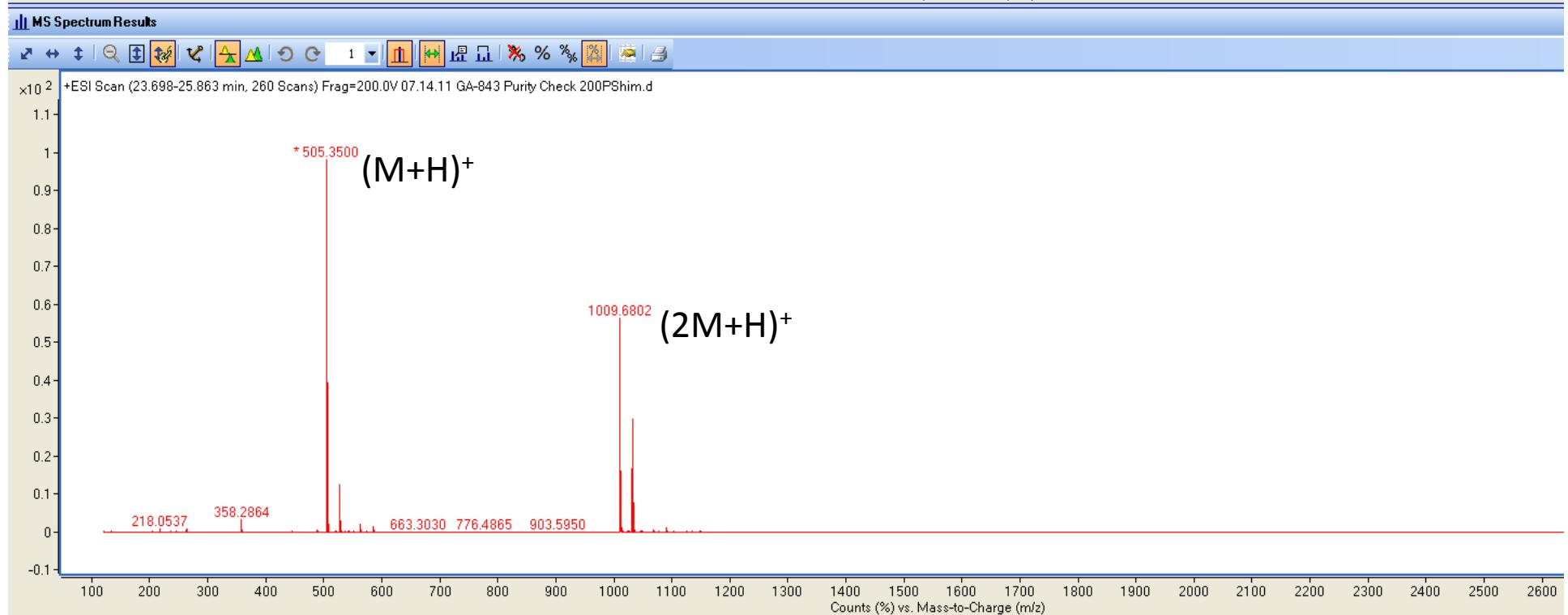
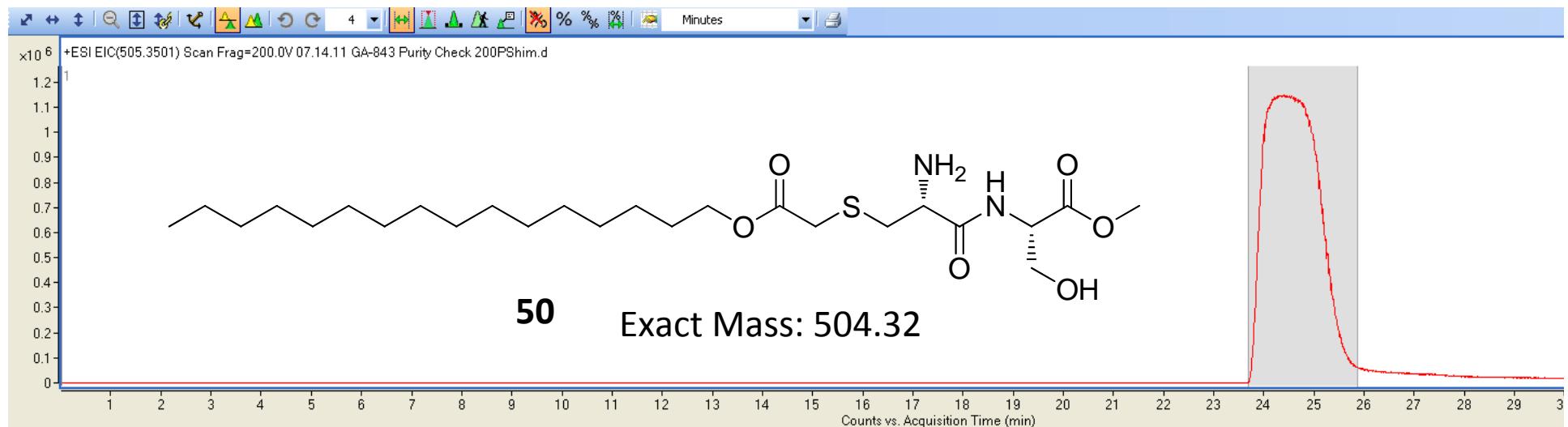


¹³C Spectrum

S201

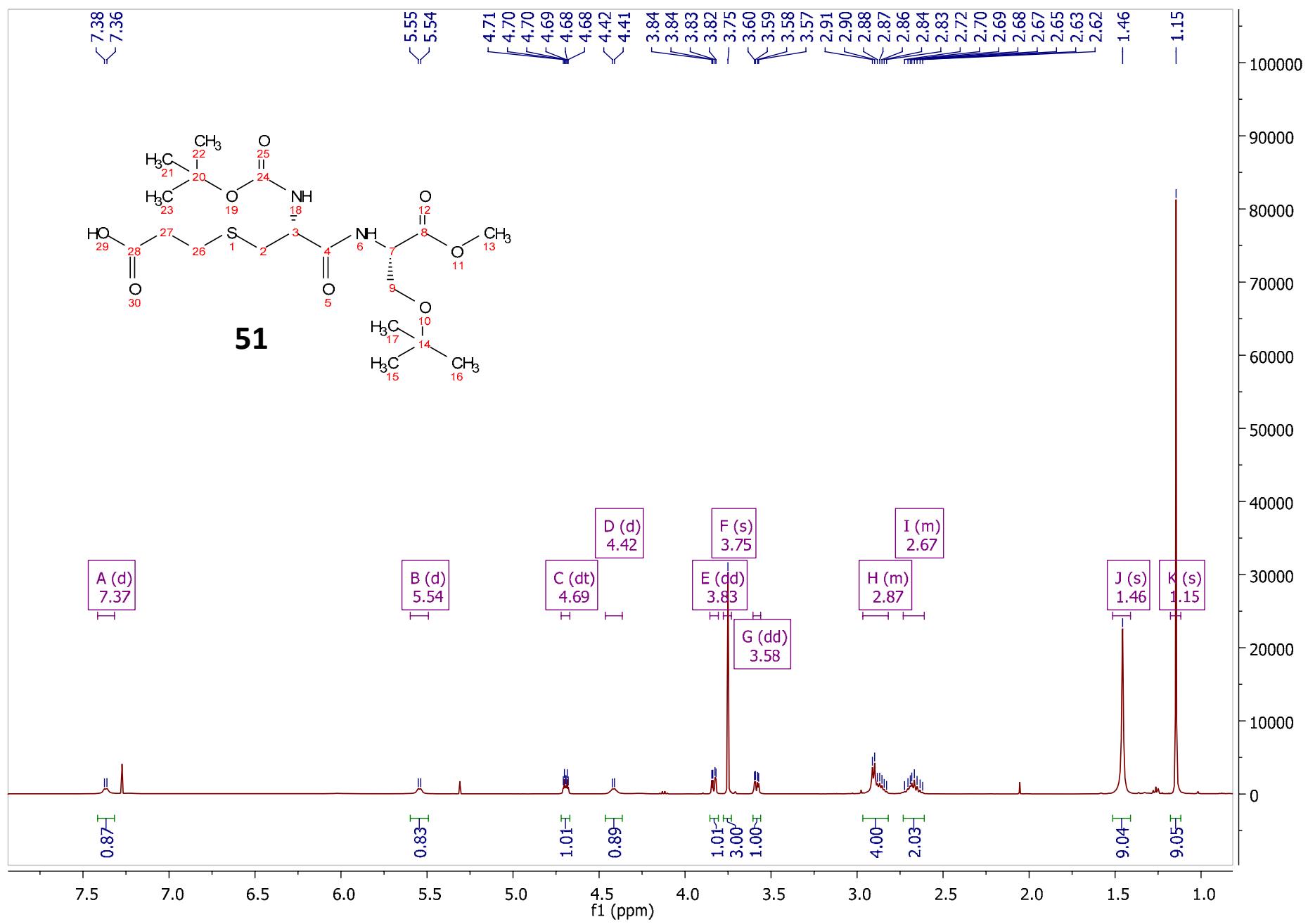






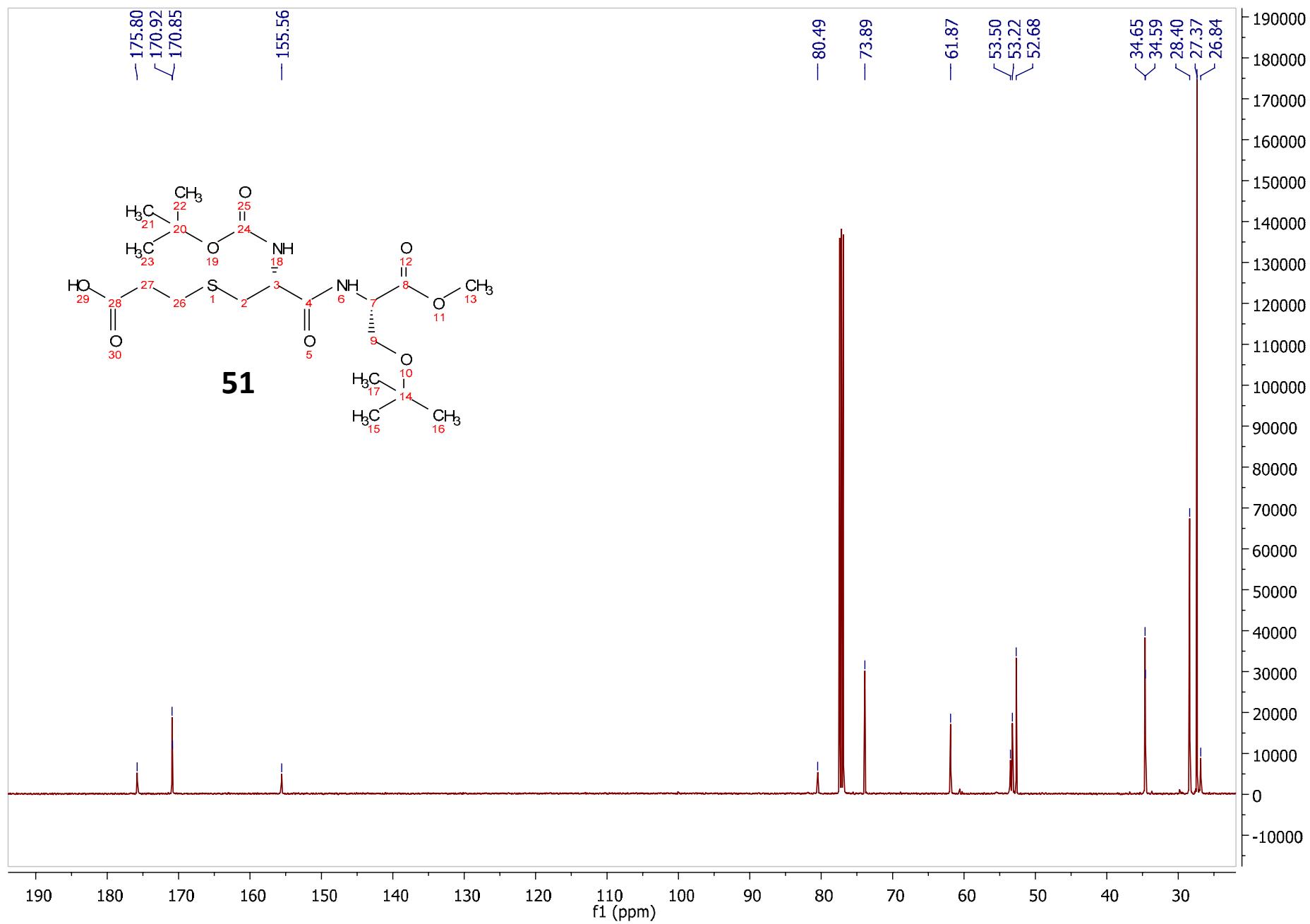
¹H Spectrum

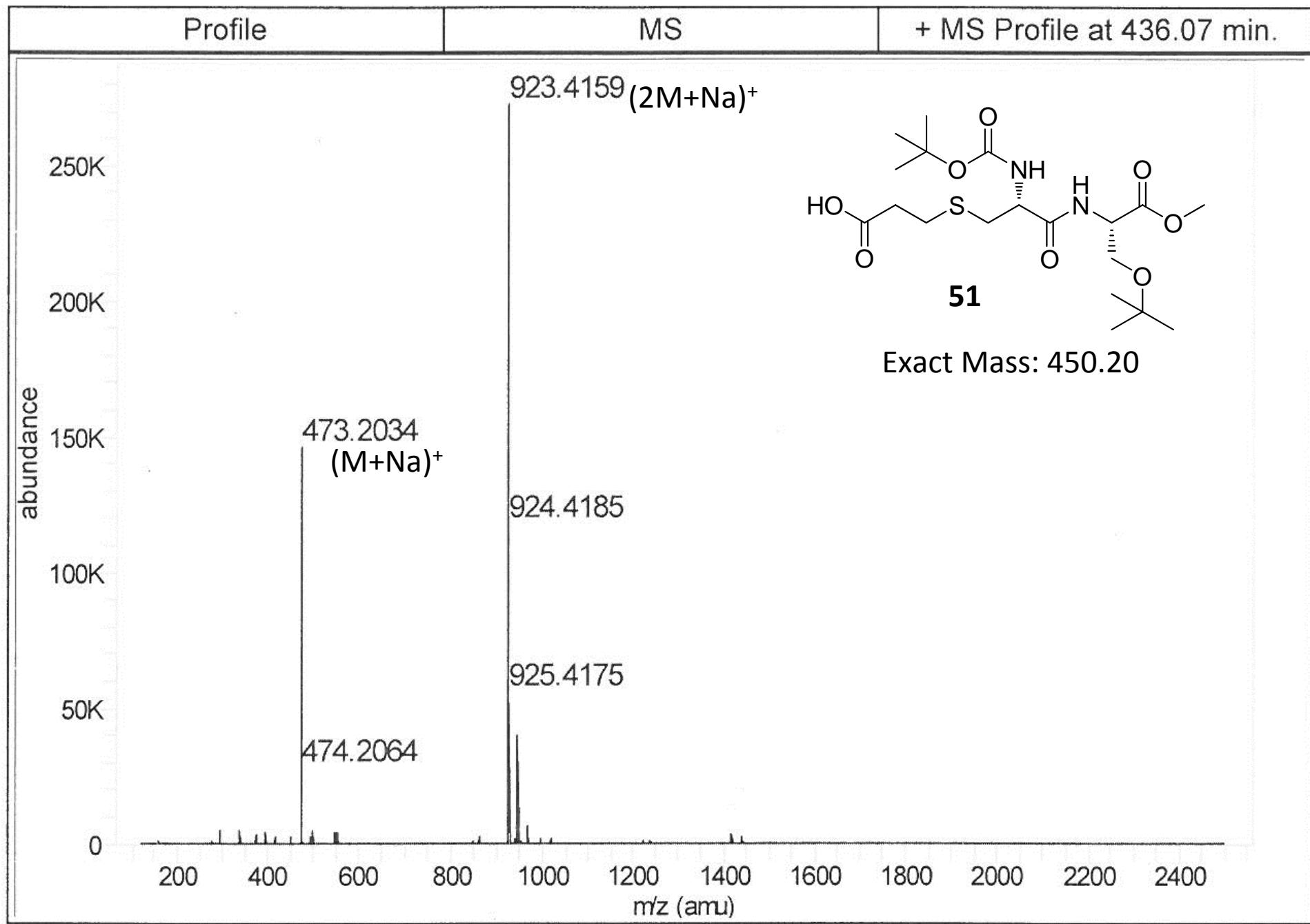
S204

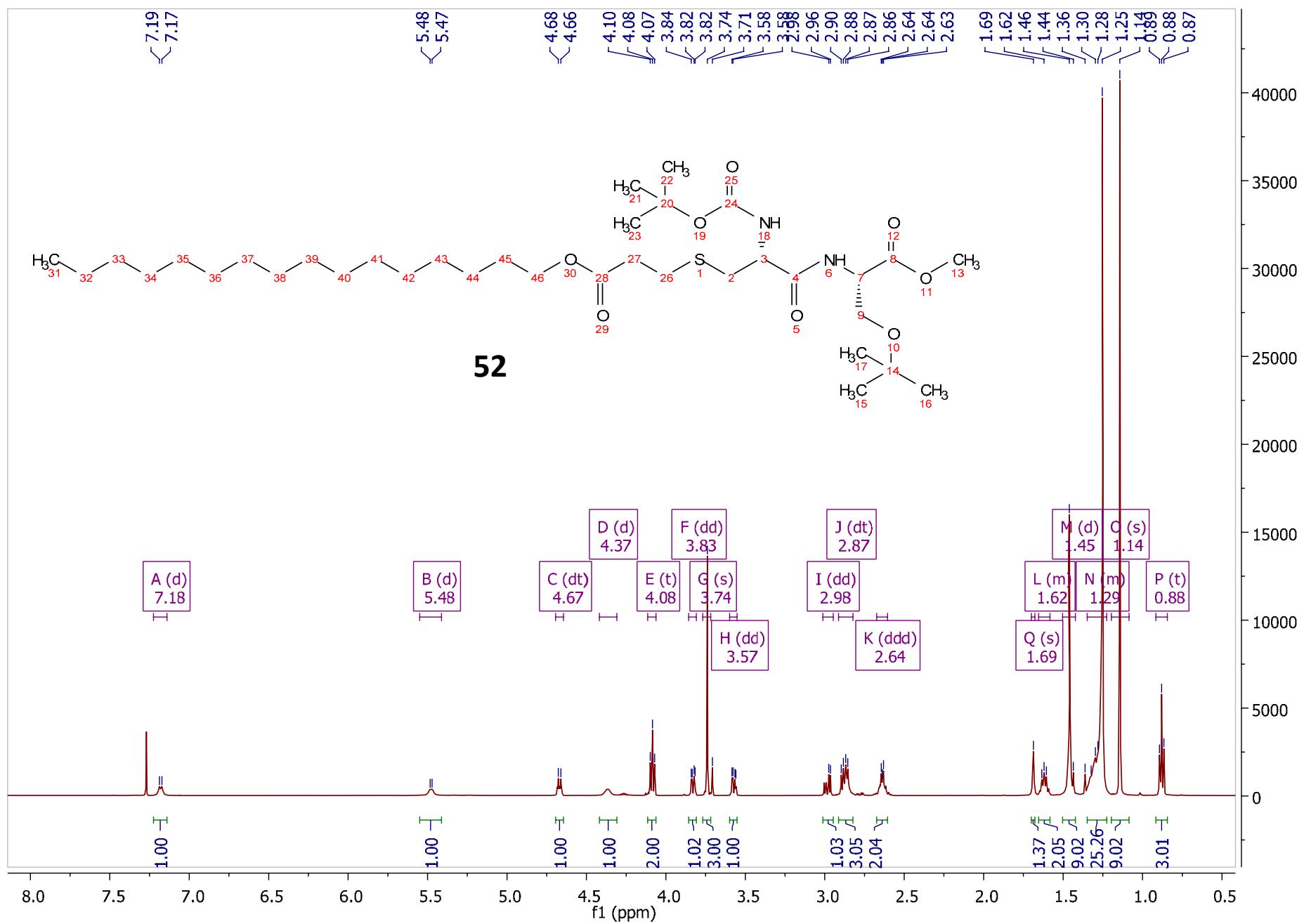


¹³C Spectrum

S205

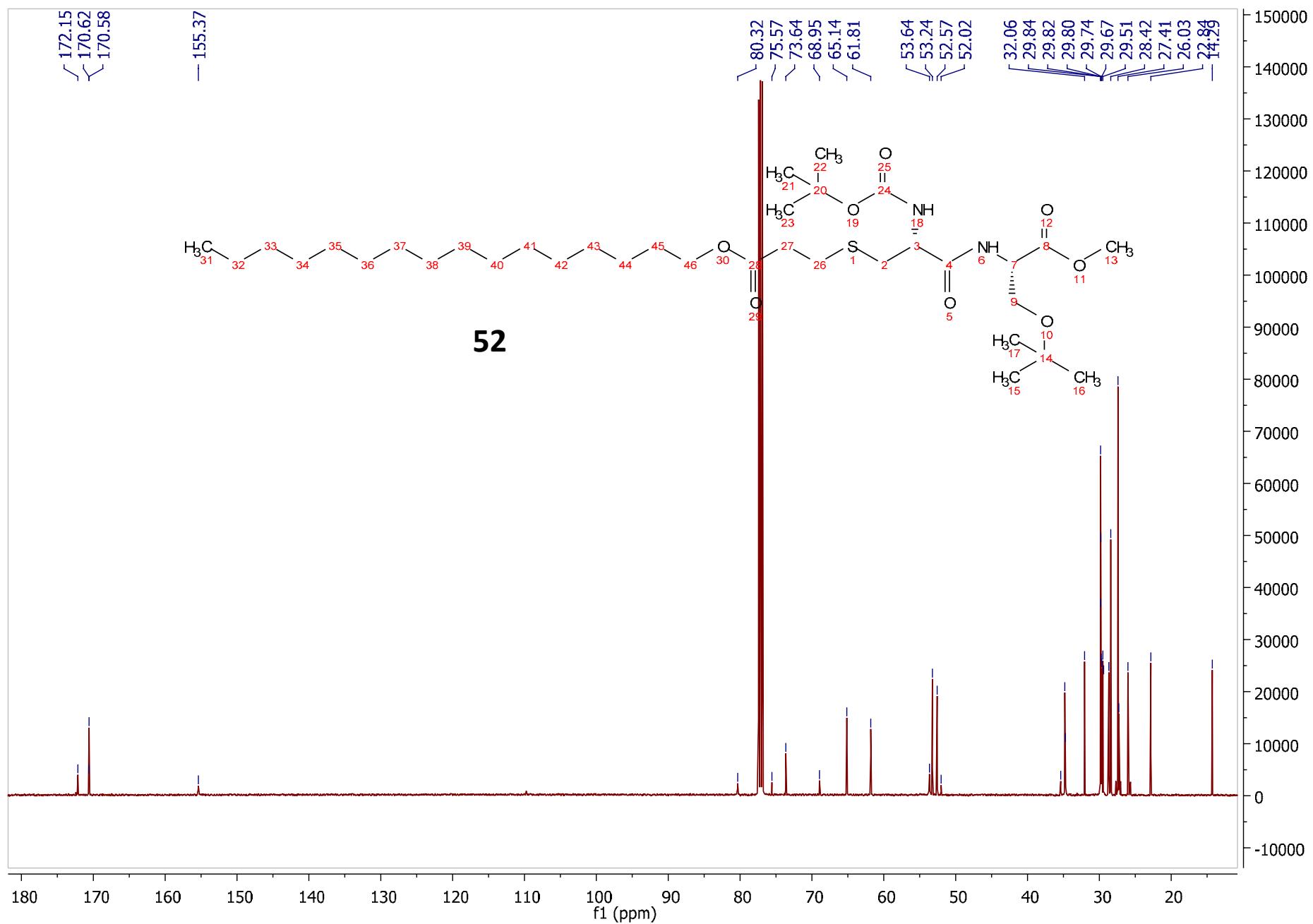


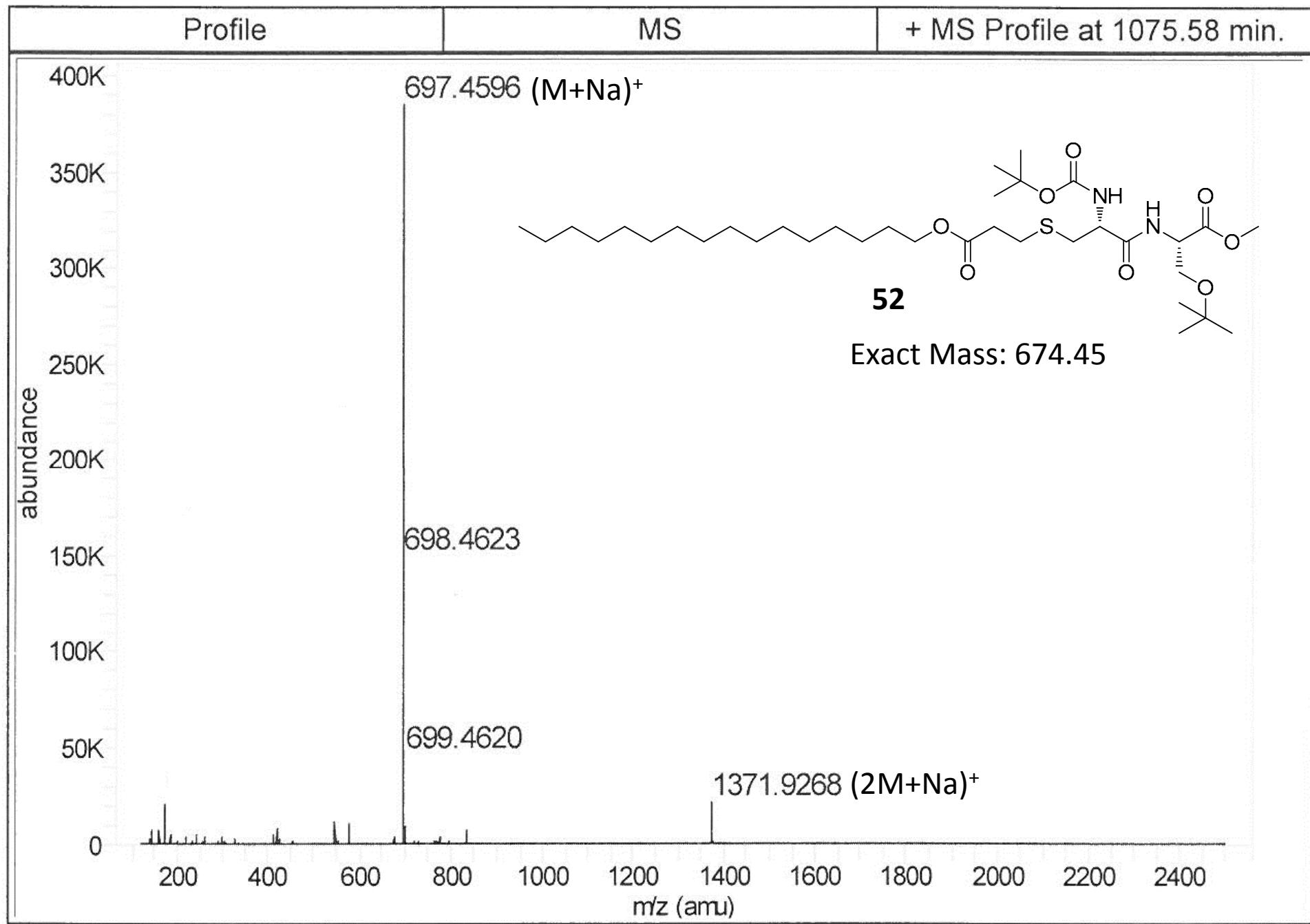




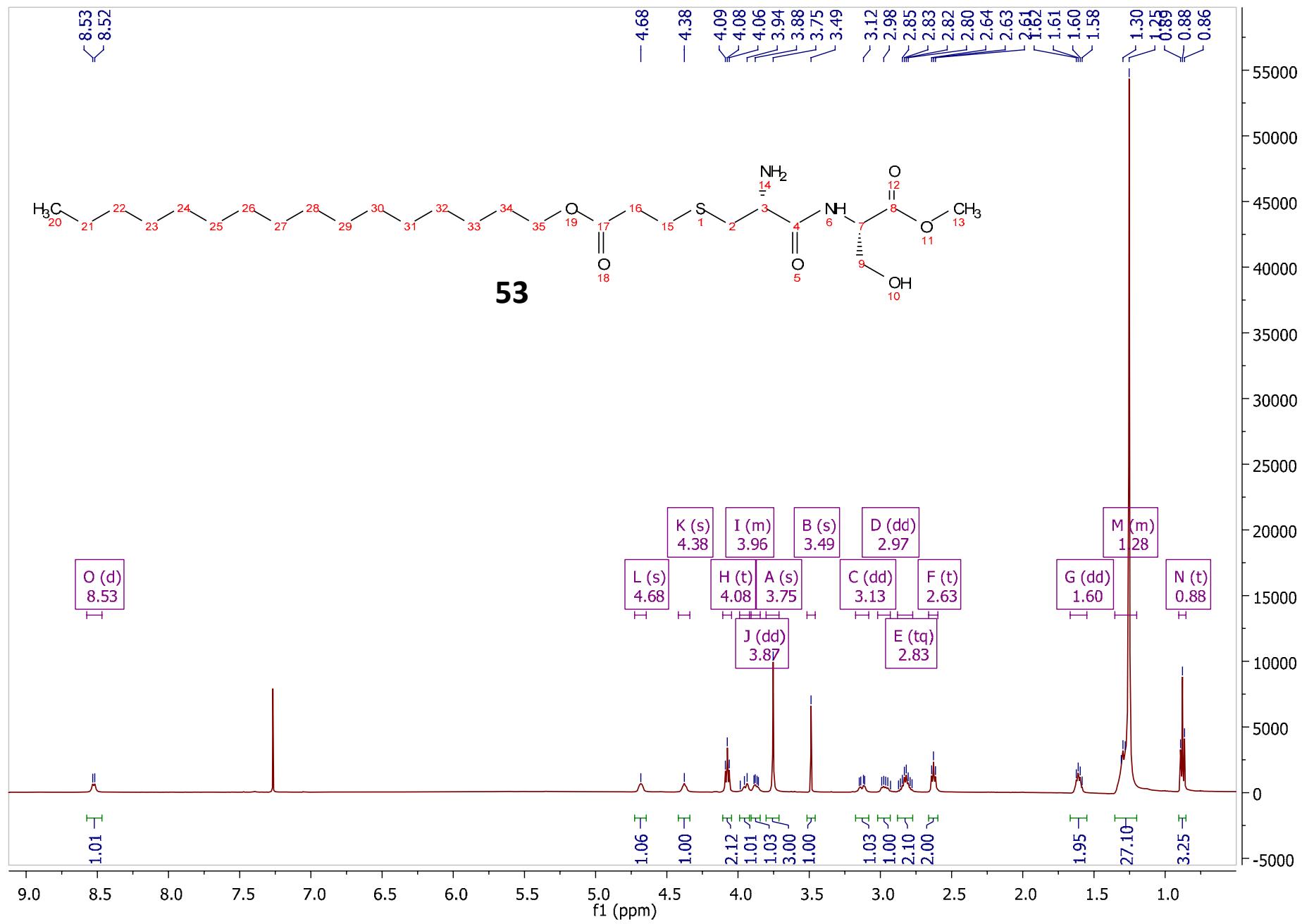
¹³C Spectrum

S208



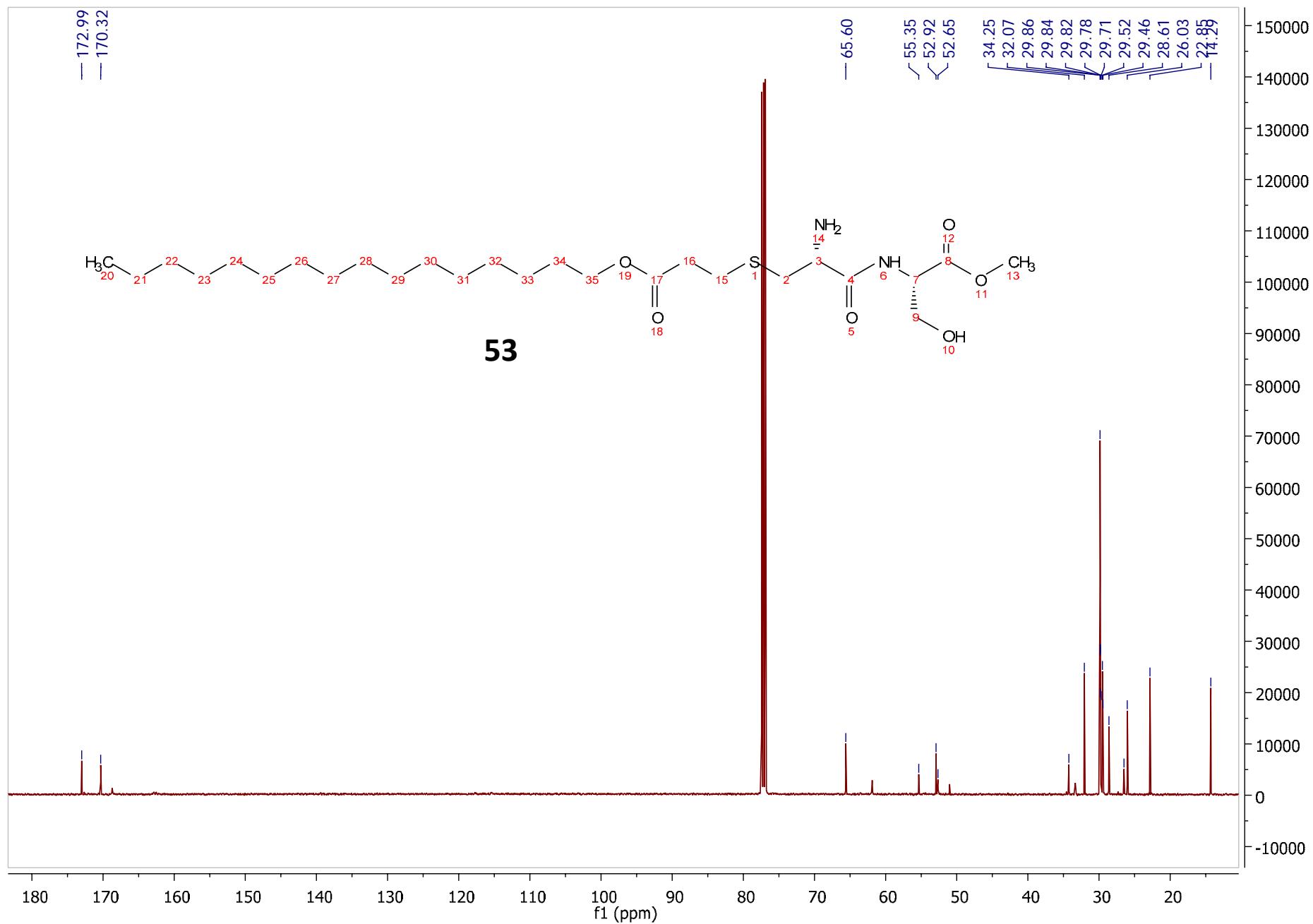


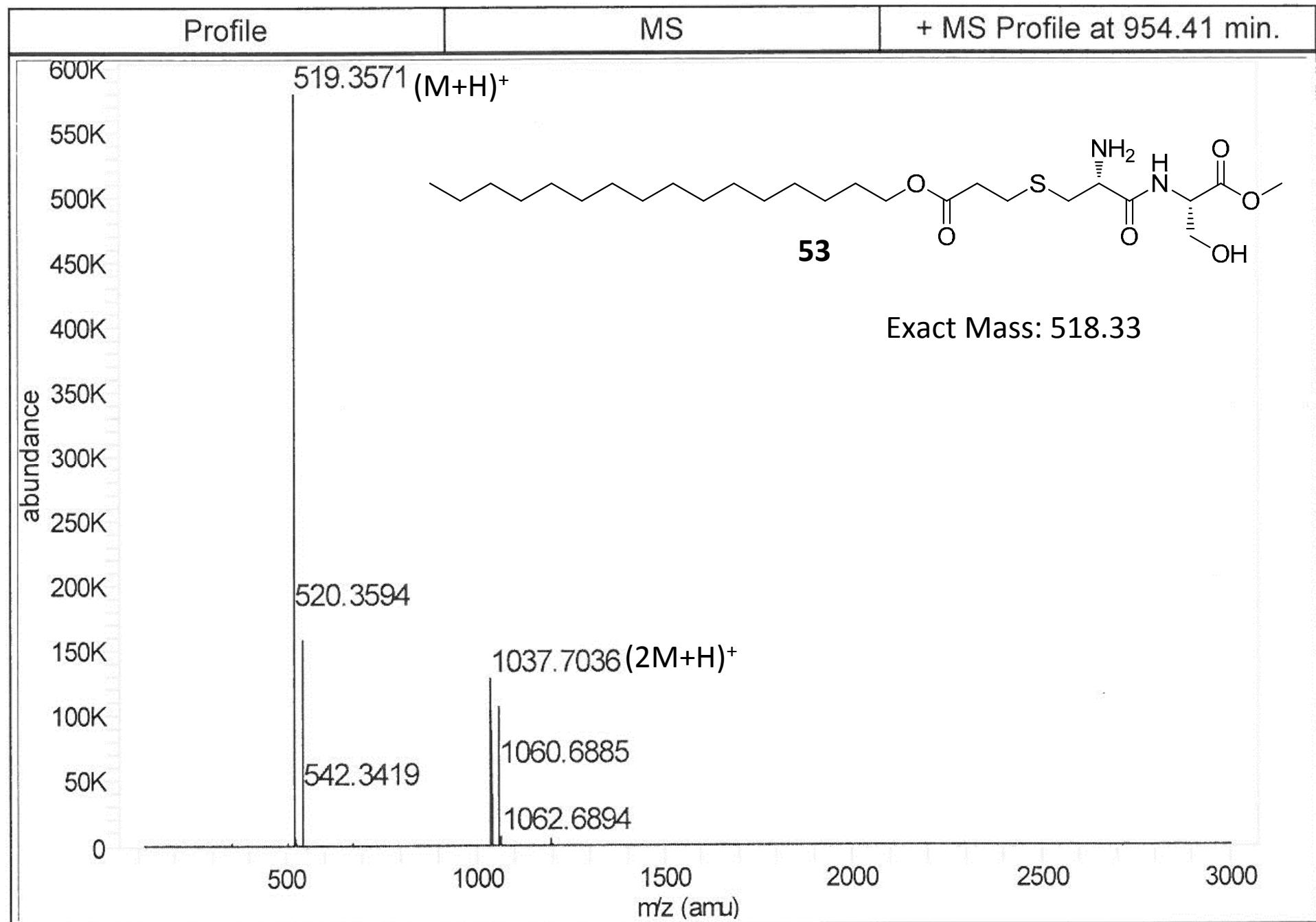
¹H Spectrum

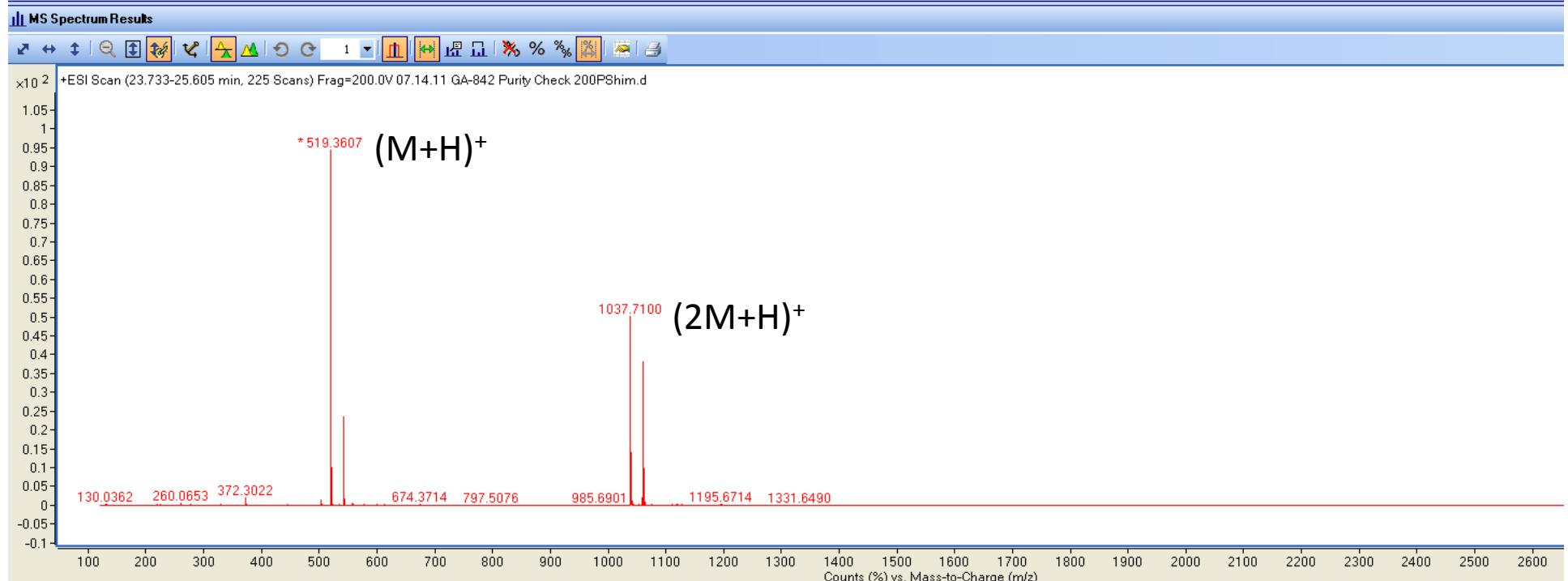
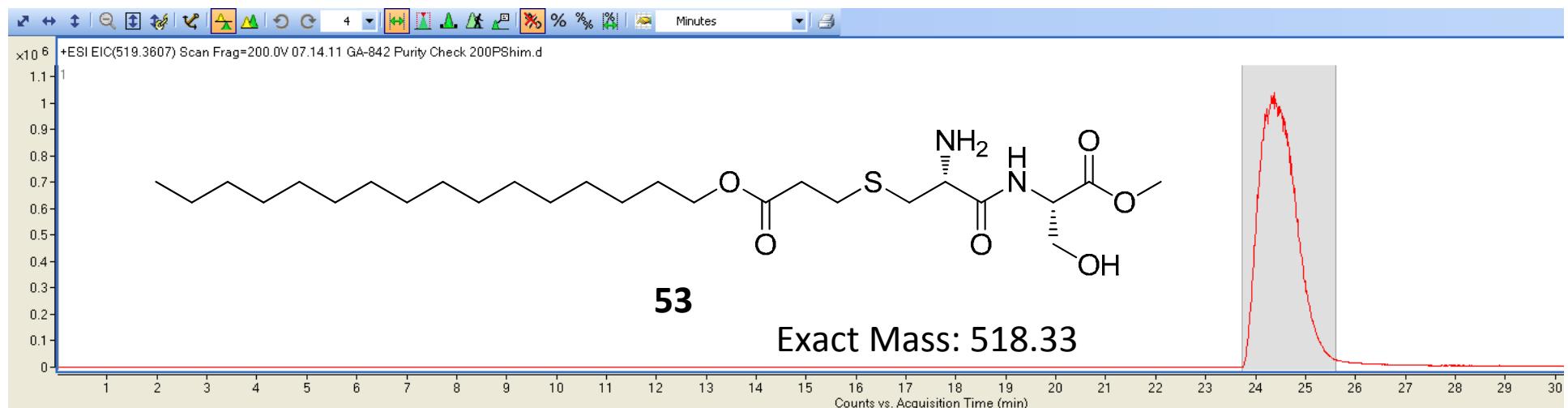


¹³C Spectrum

S211

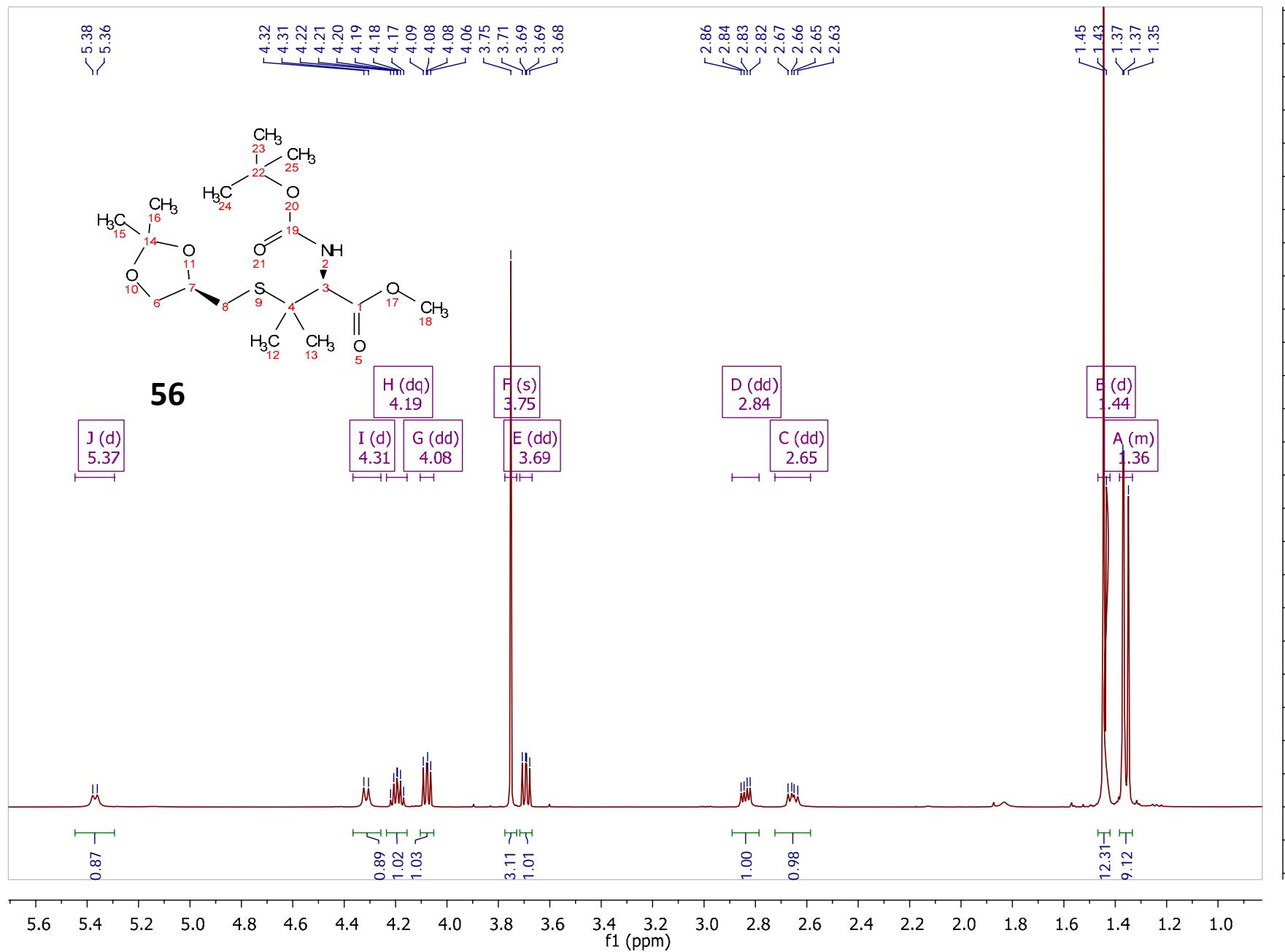






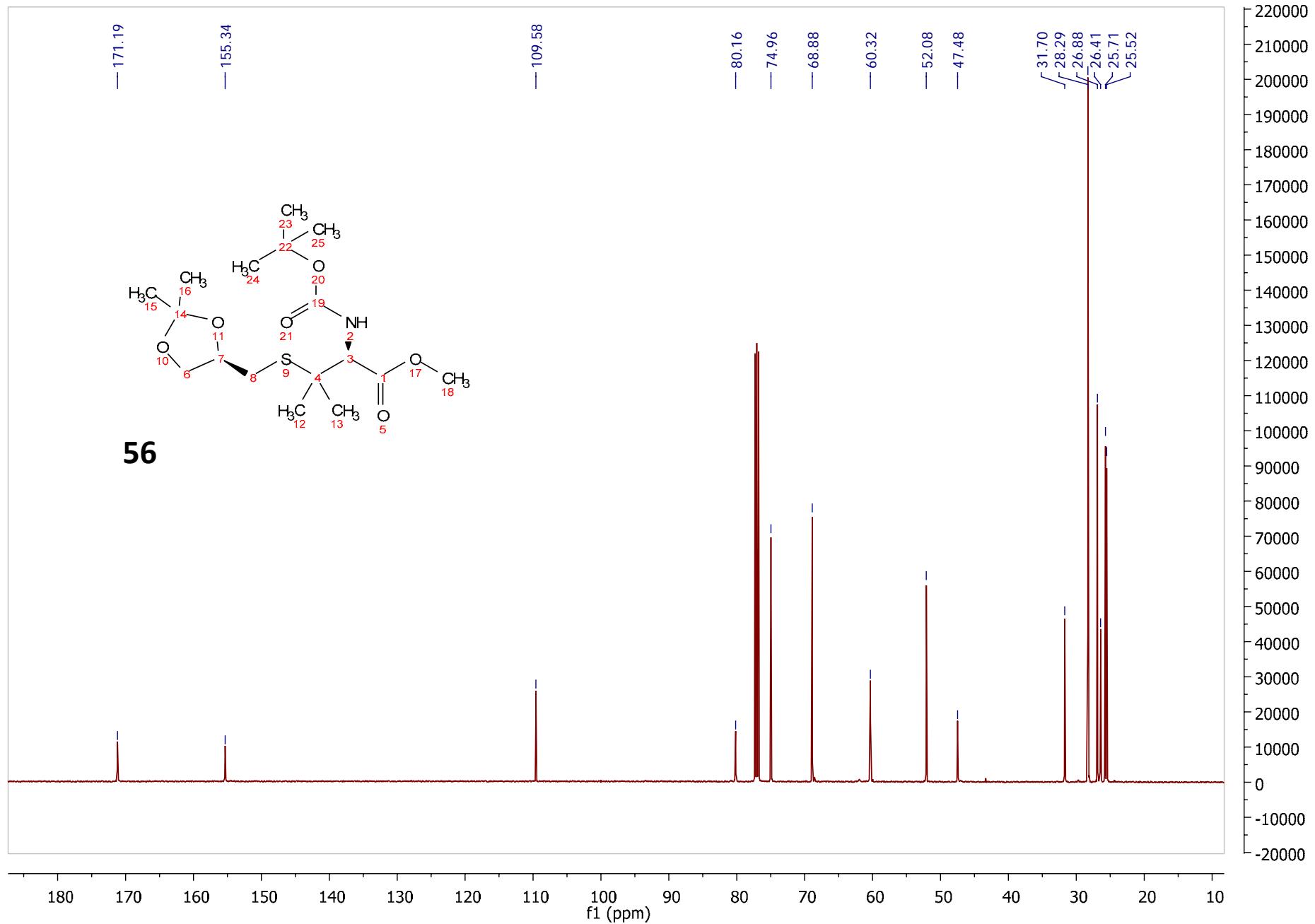
¹H Spectrum

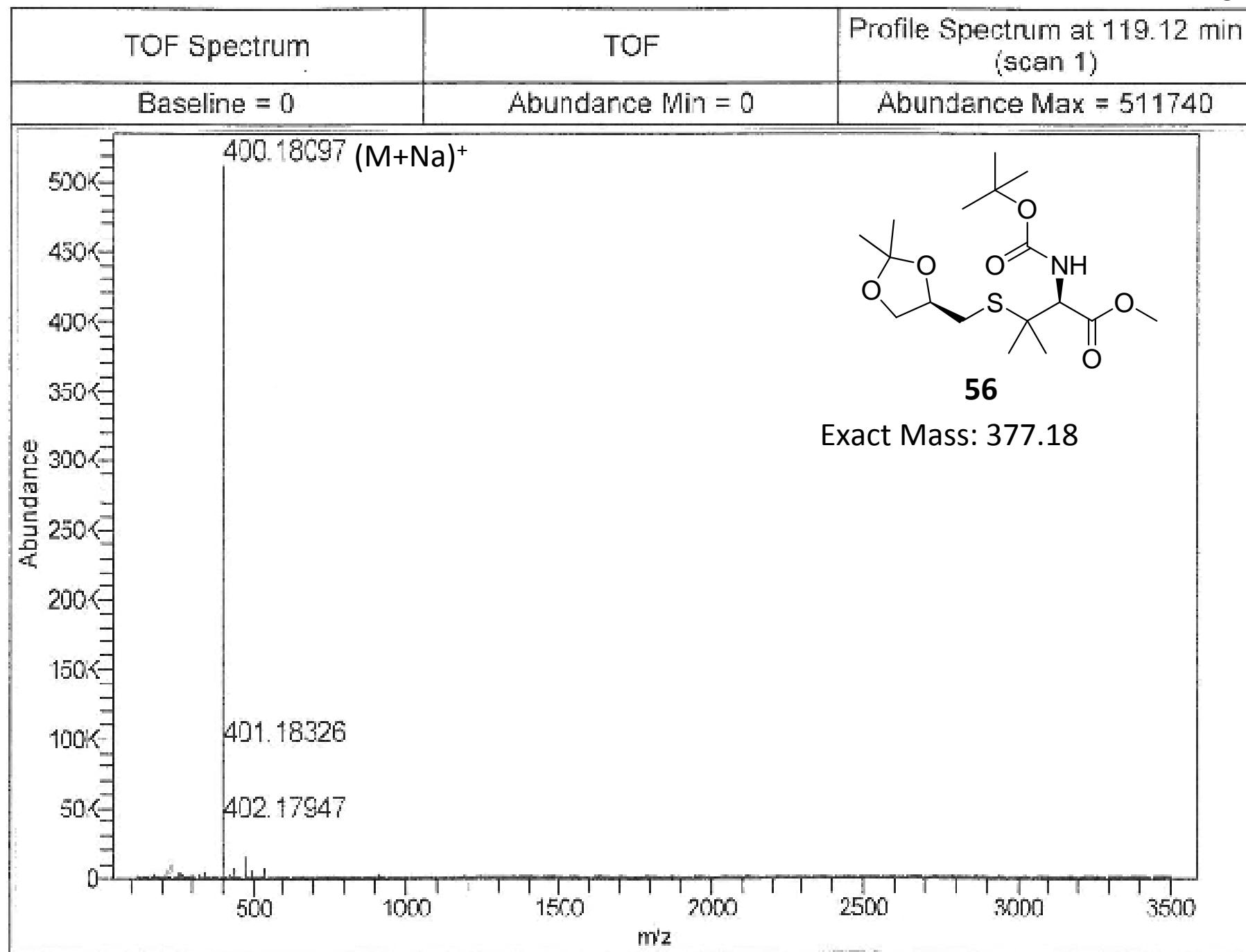
S214



¹³C Spectrum

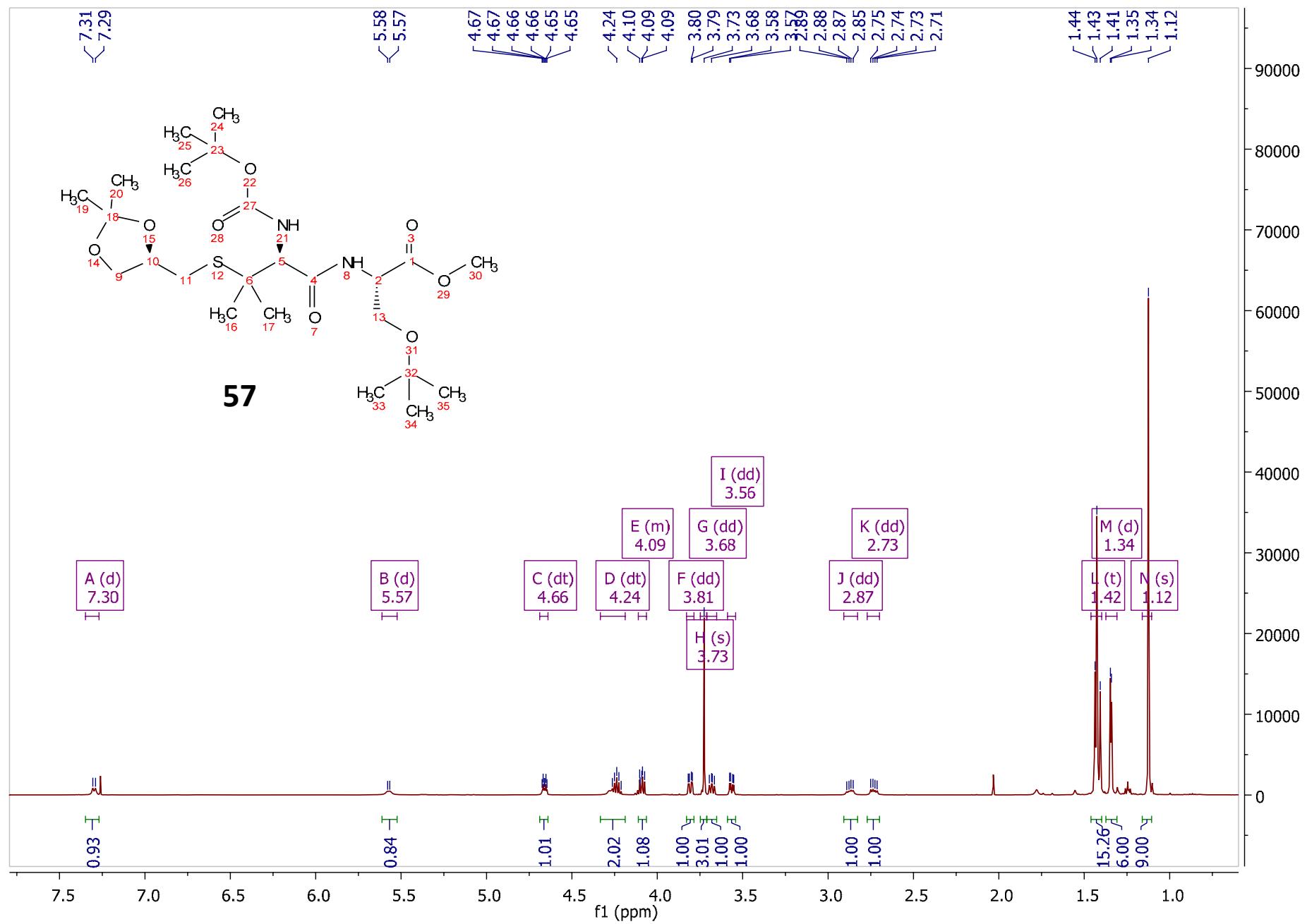
S215





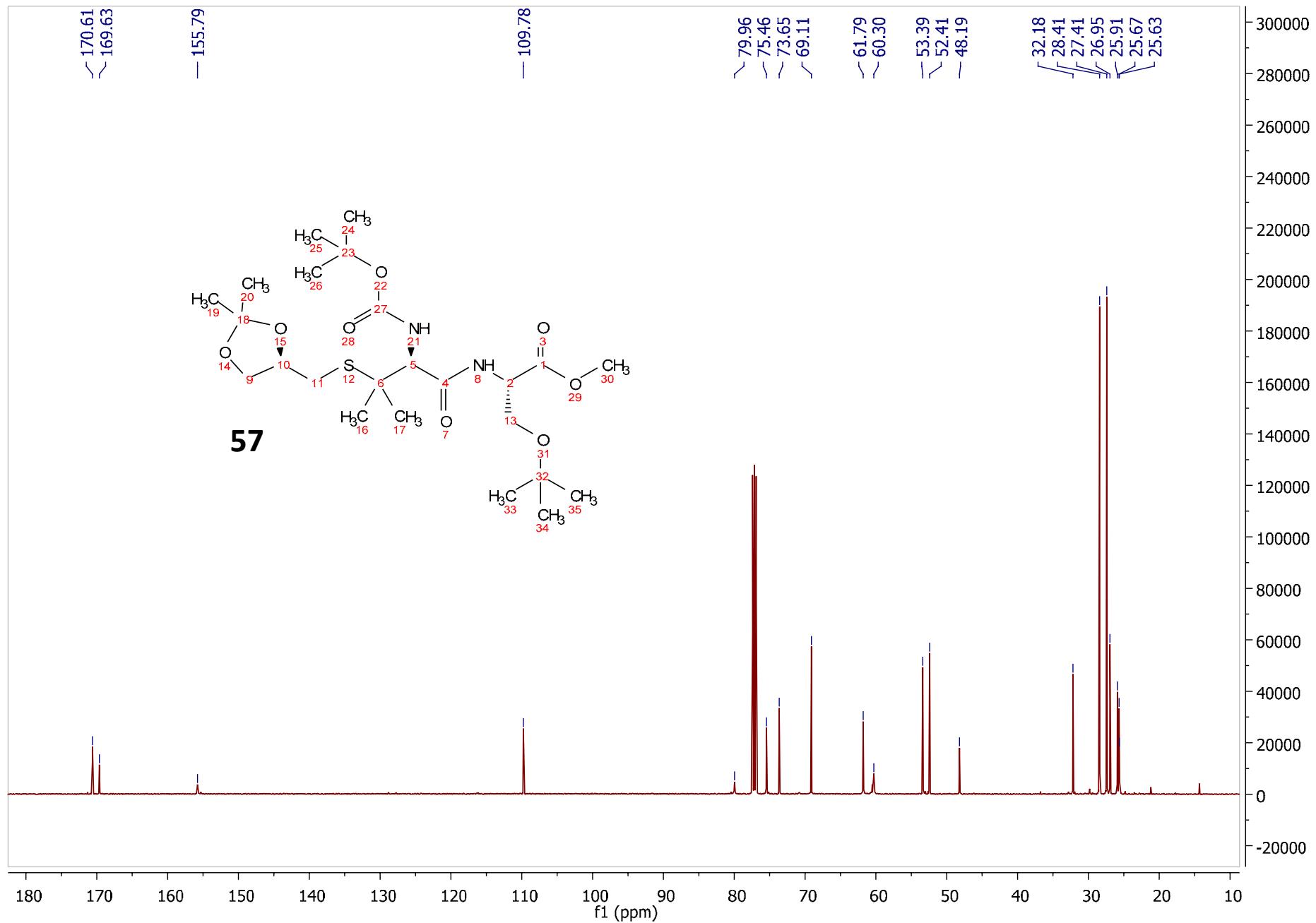
¹H Spectrum

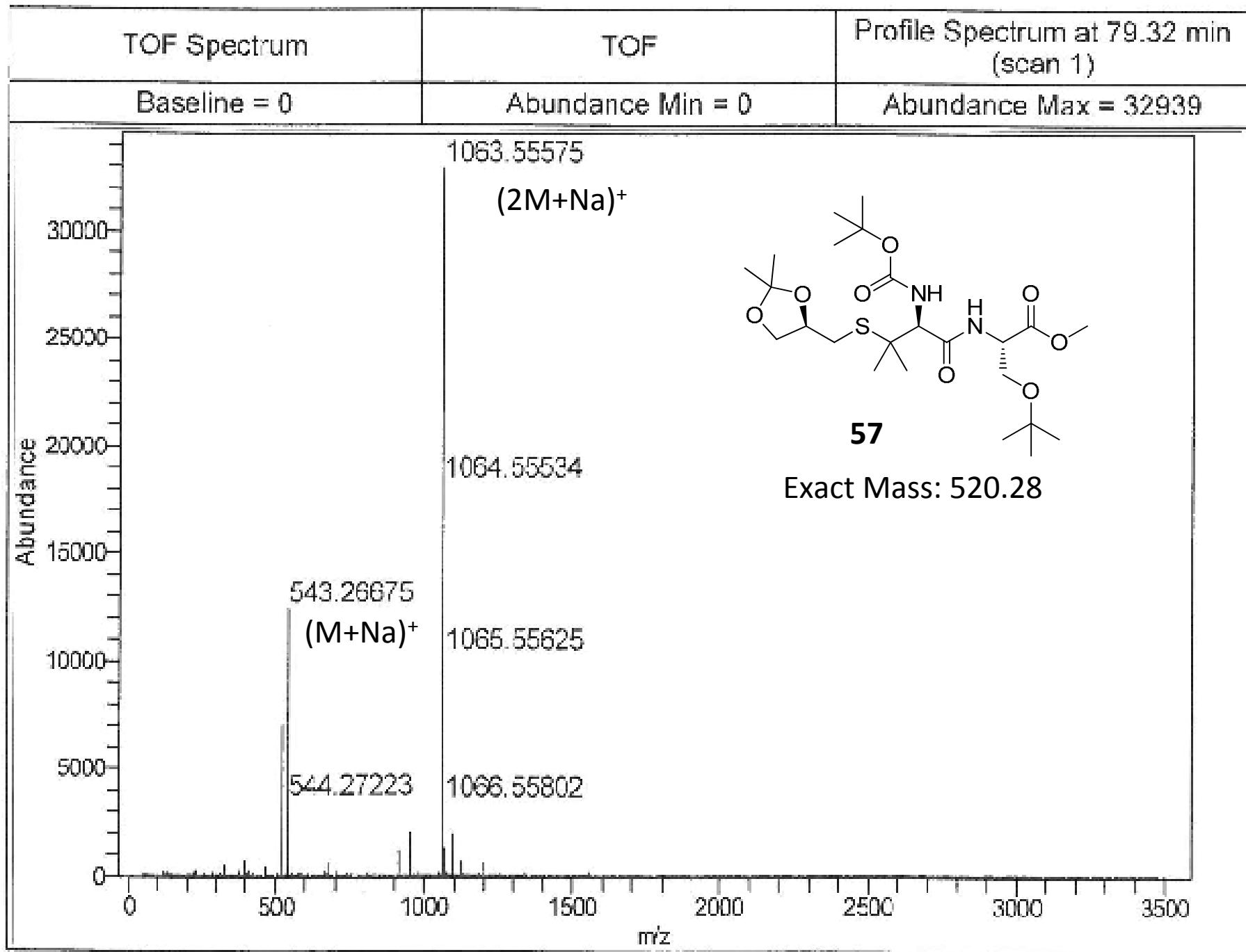
S217



¹³C Spectrum

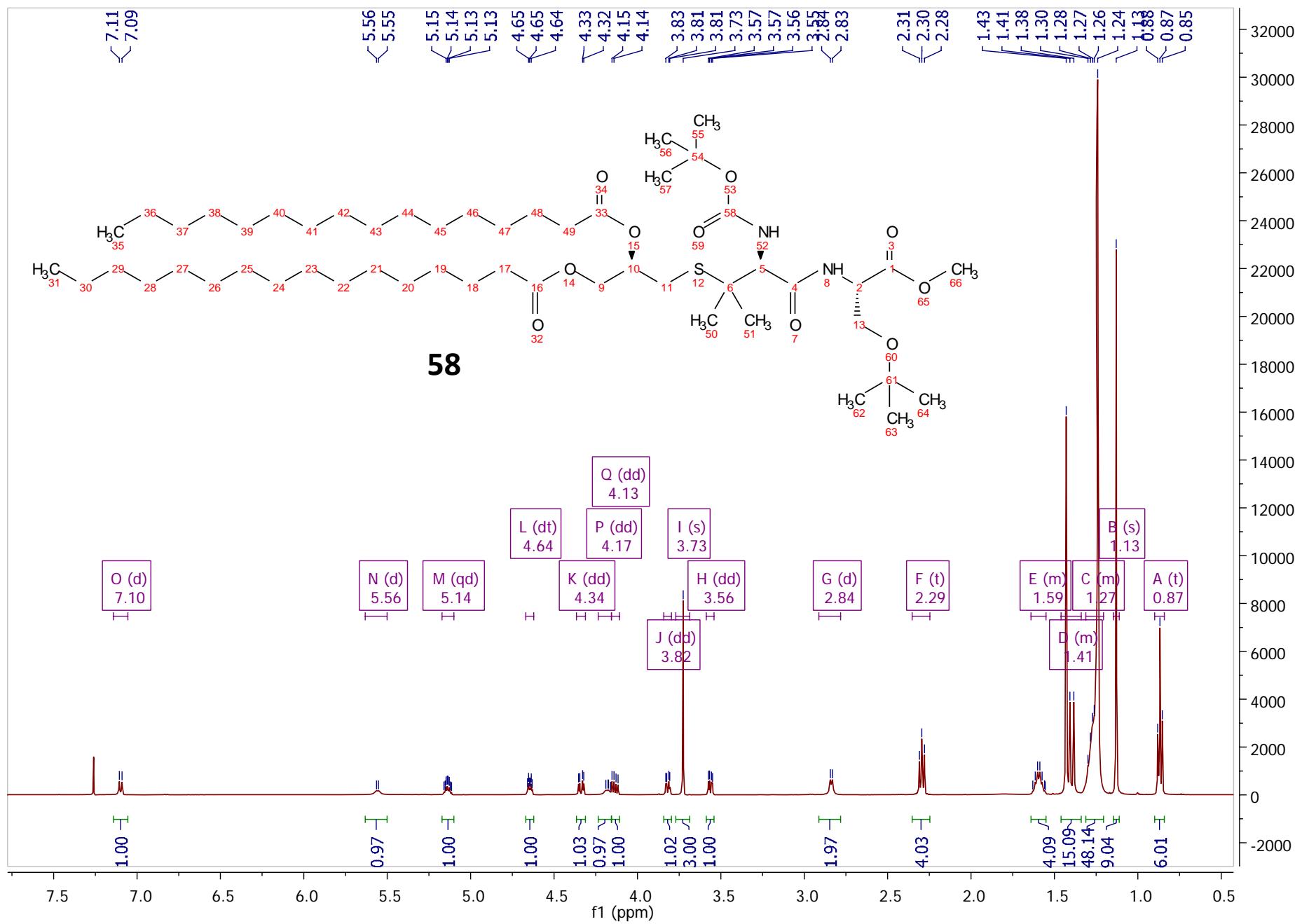
S218

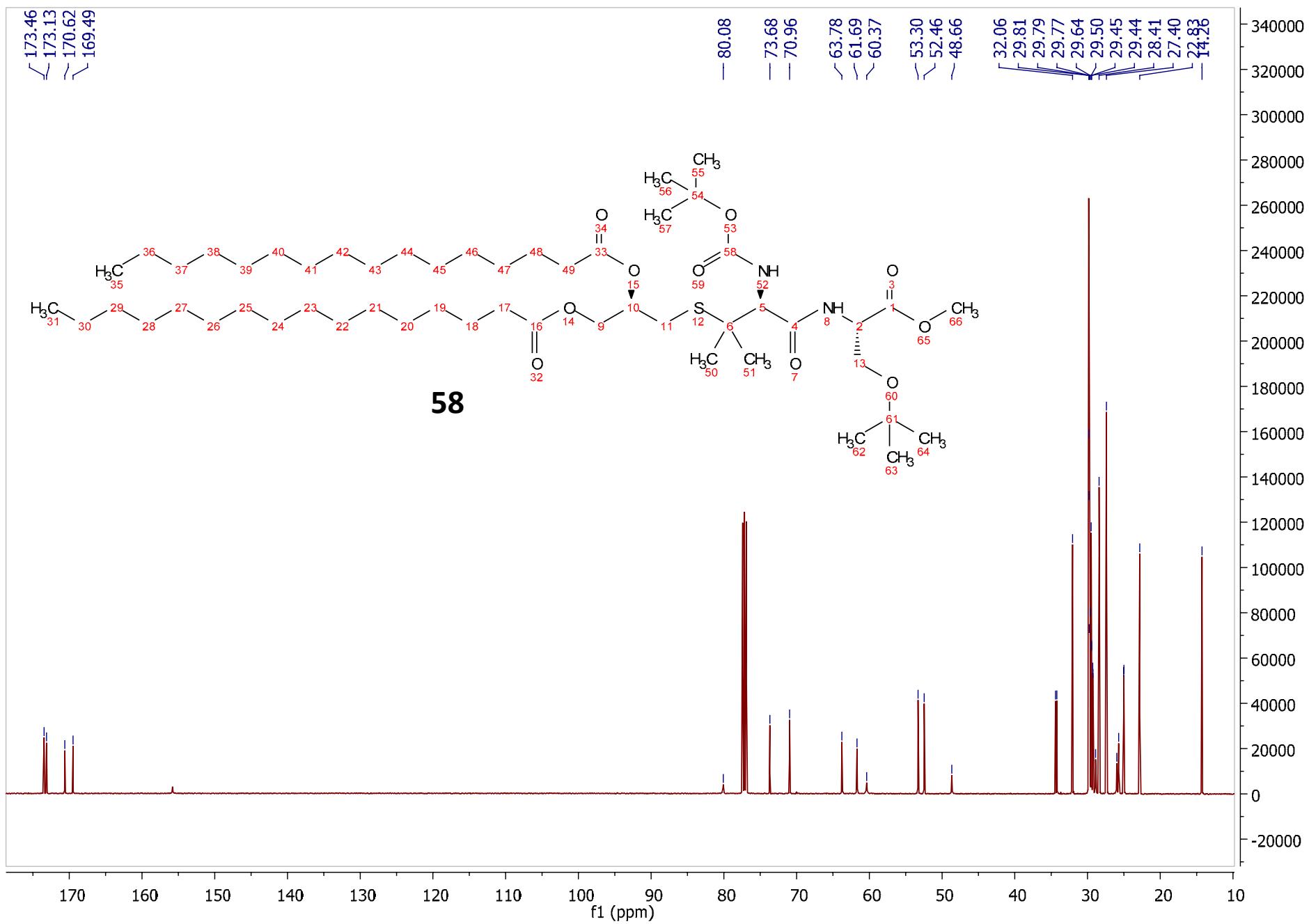


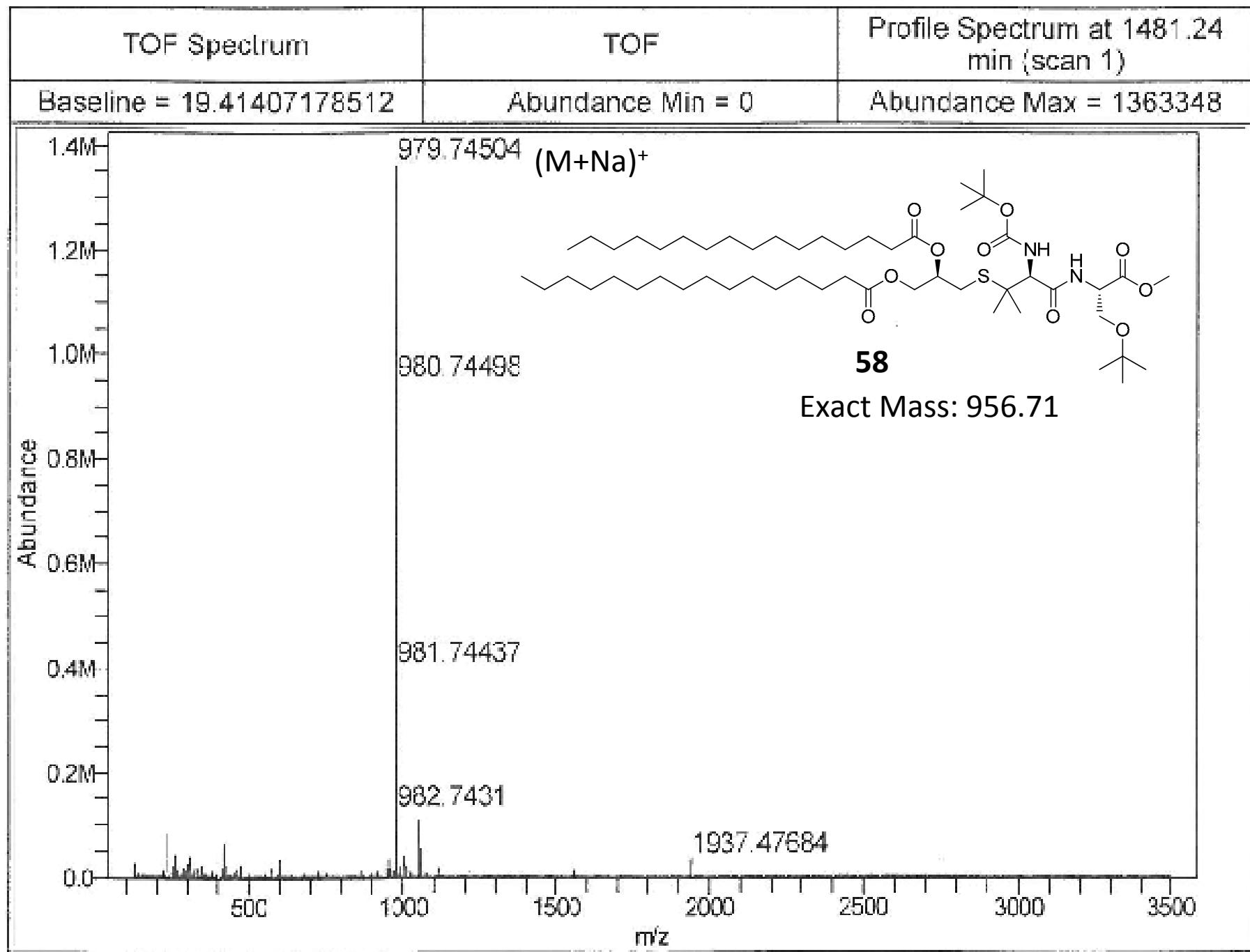


¹H Spectrum

S220

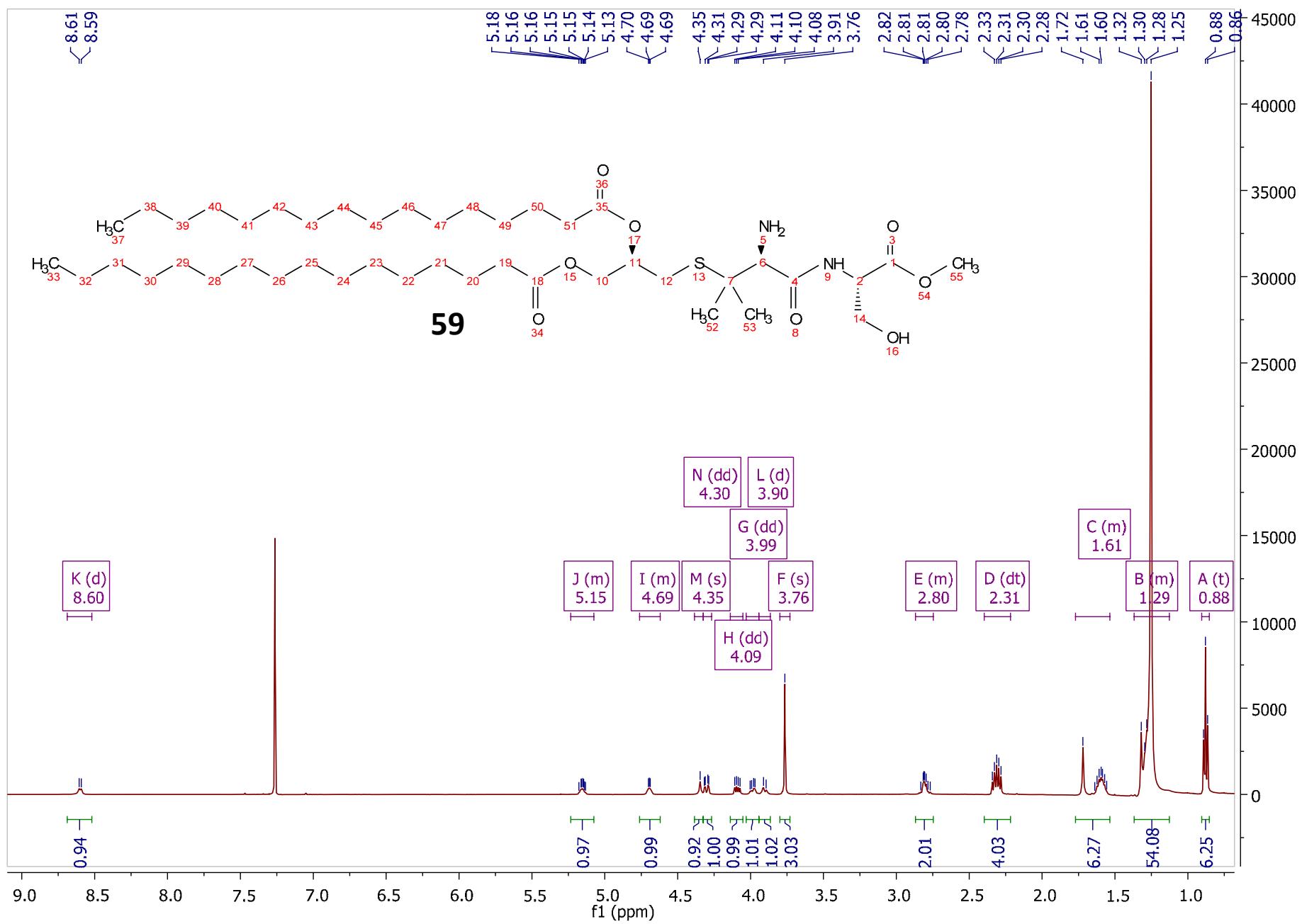


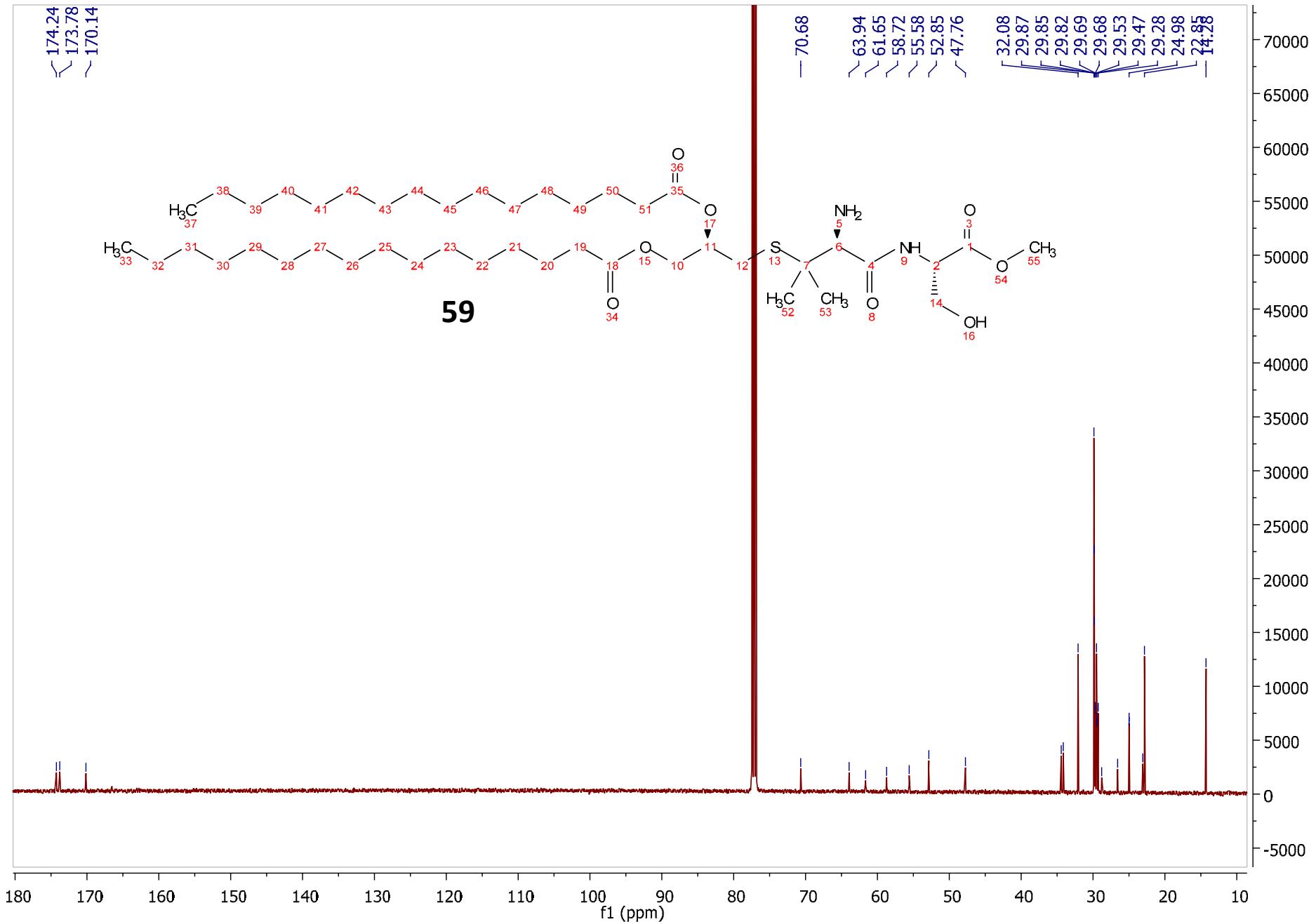


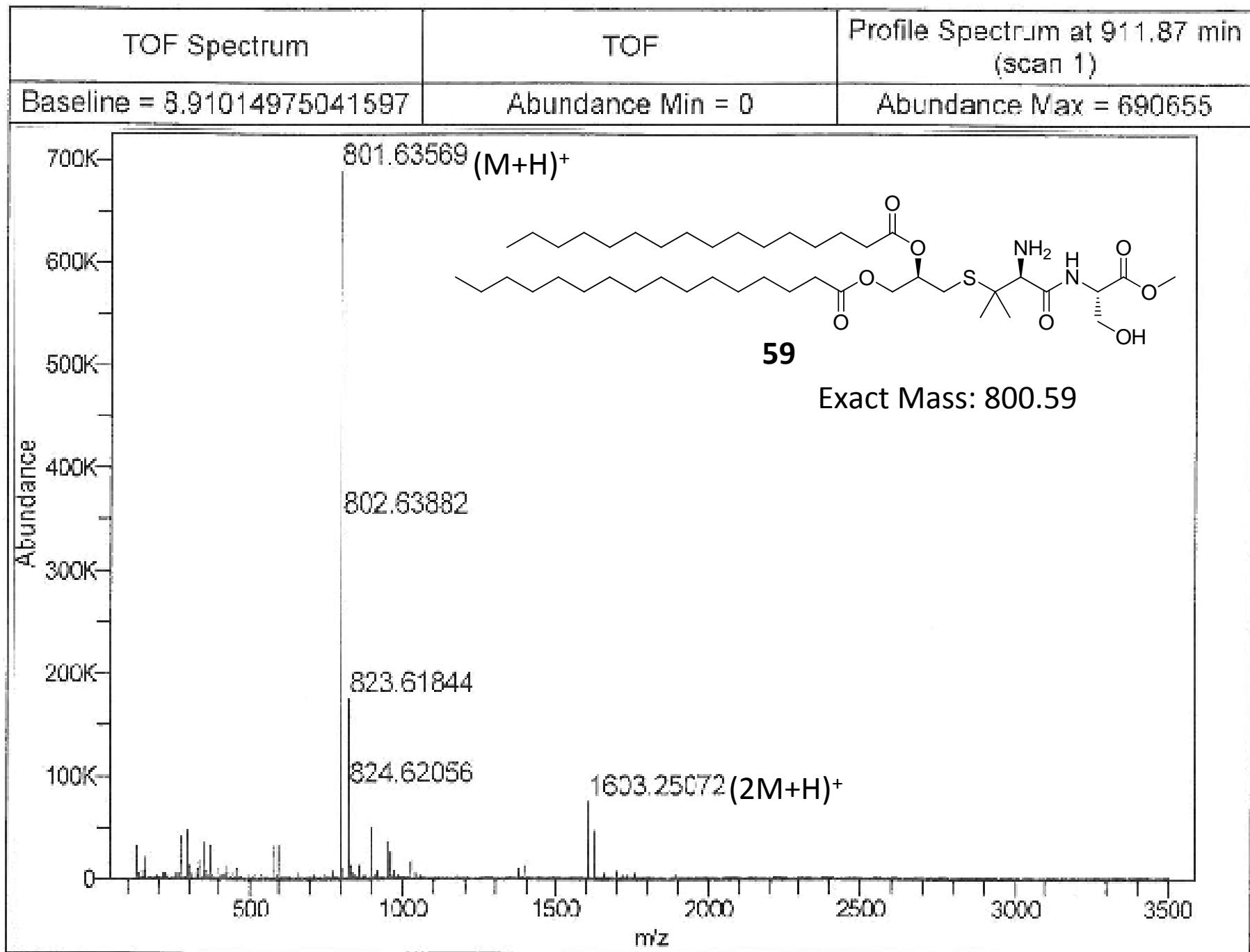


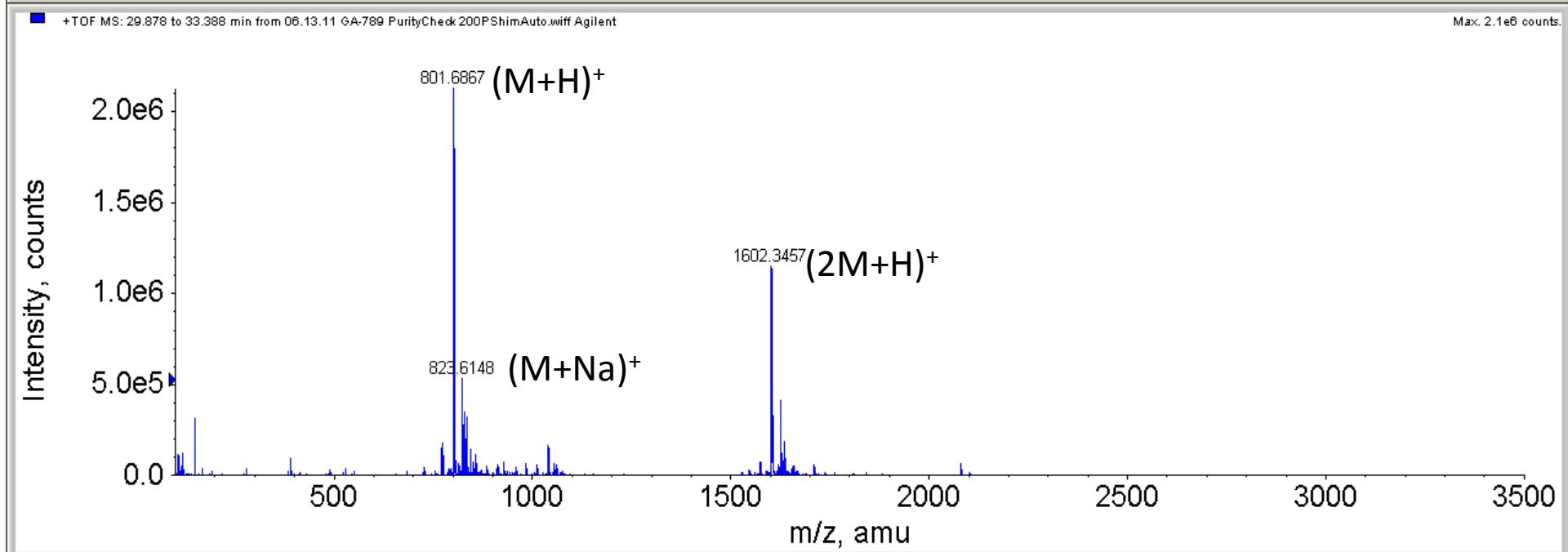
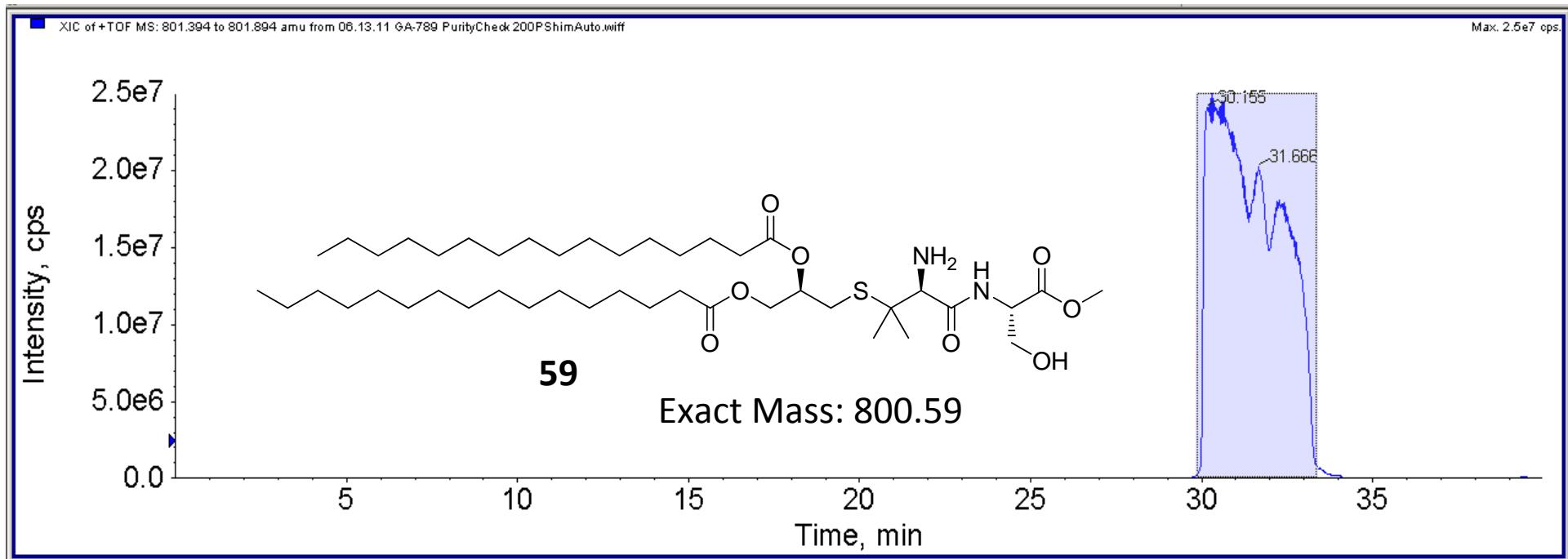
¹H Spectrum

S223



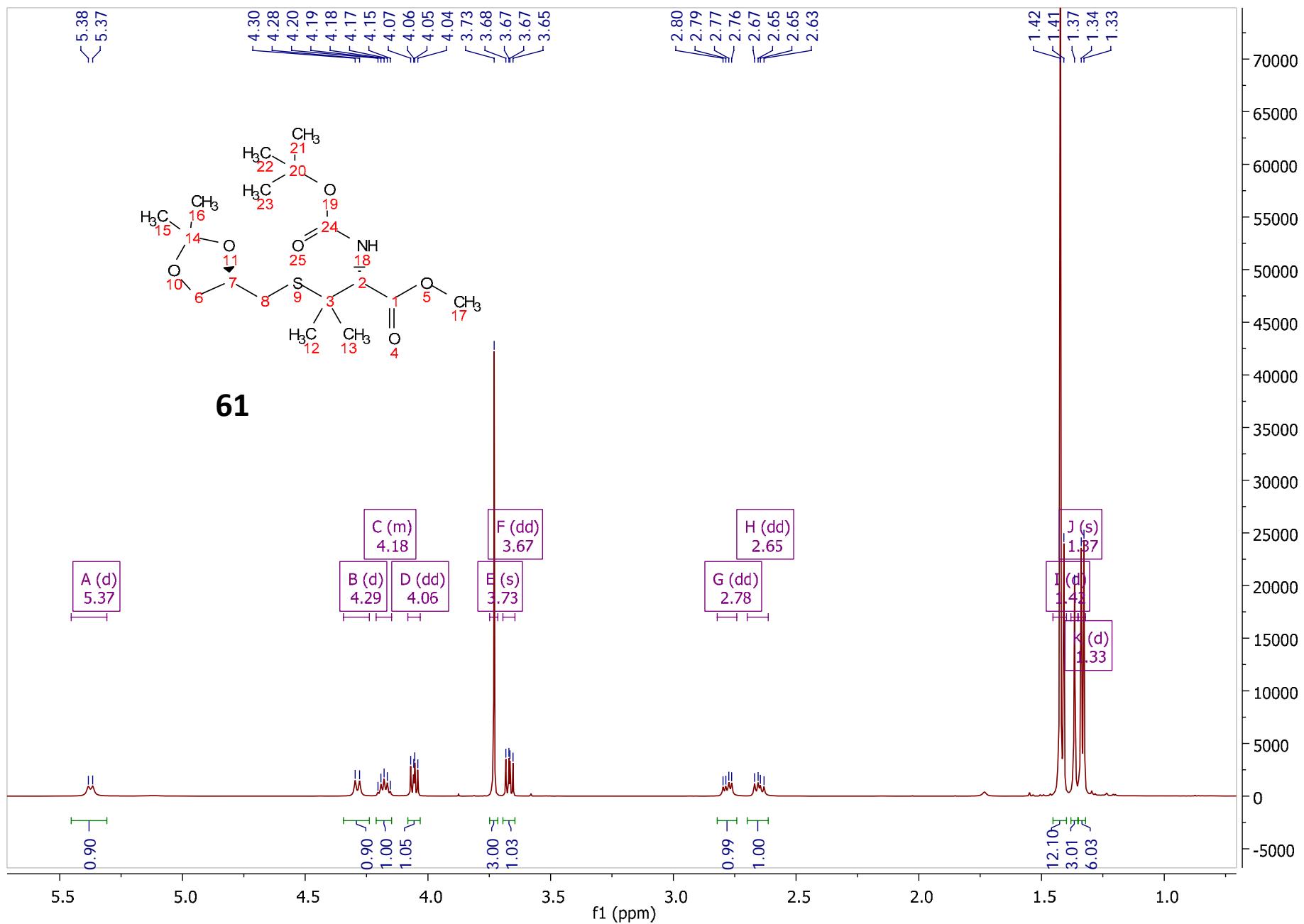






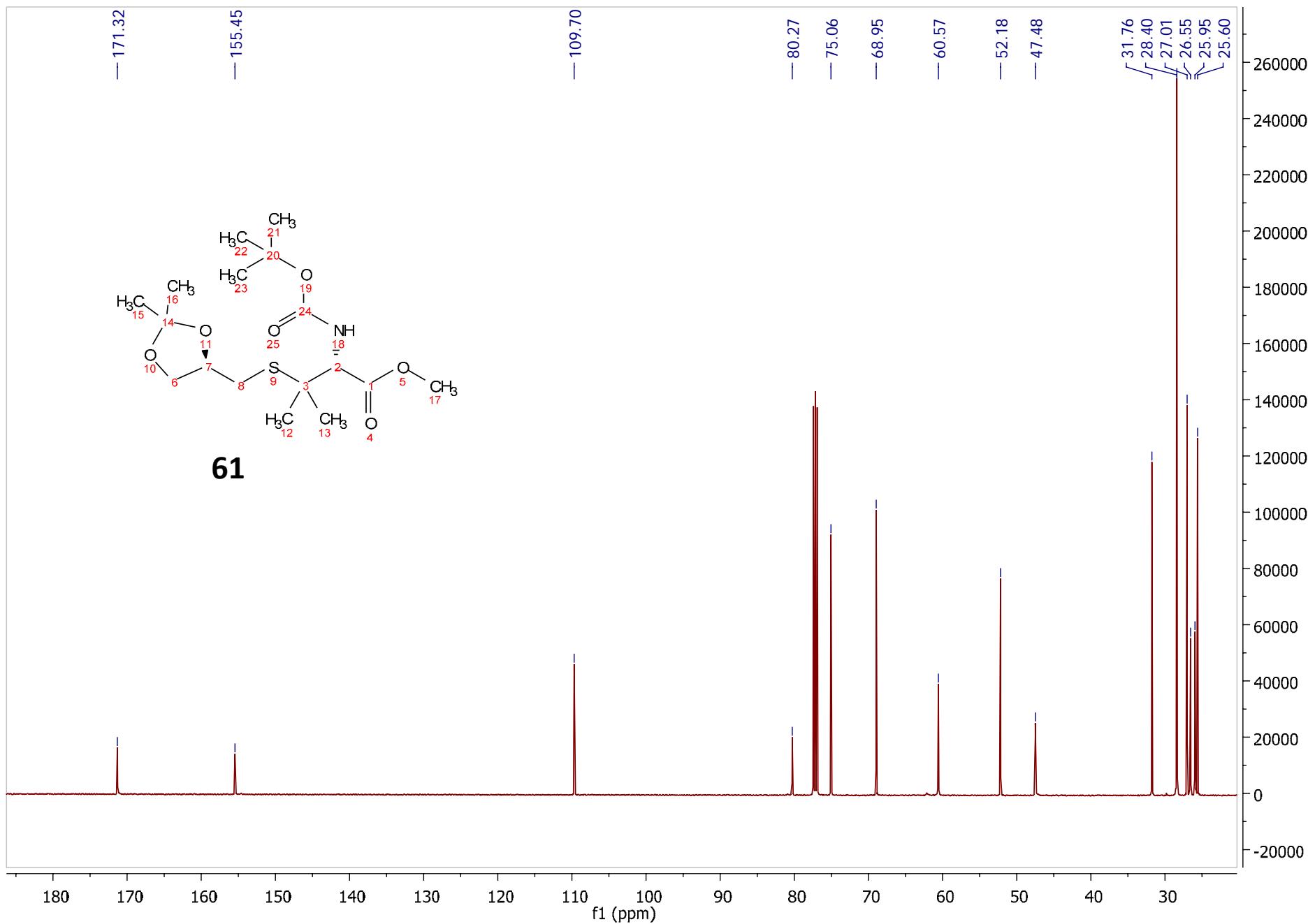
¹H Spectrum

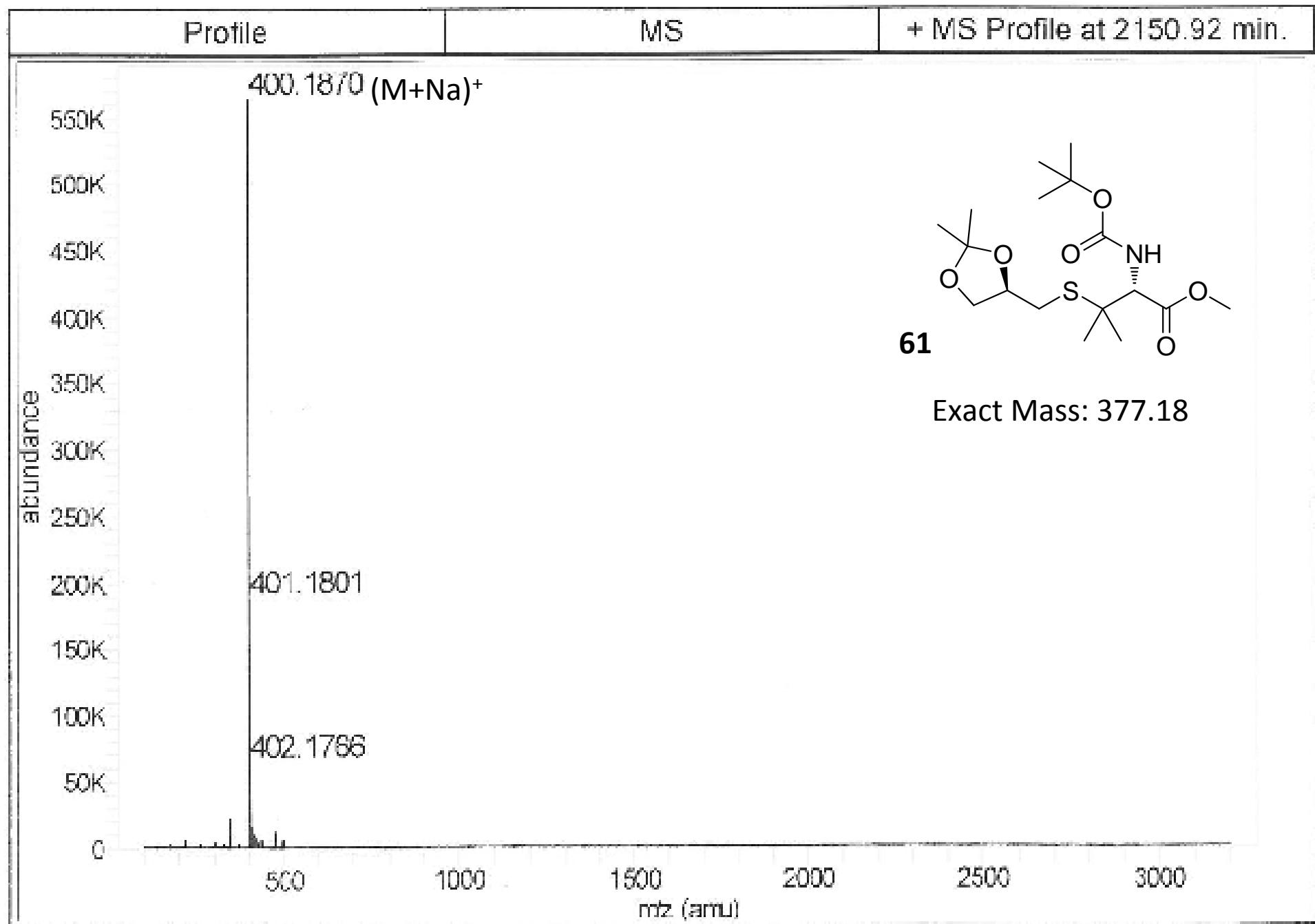
S227



¹³C Spectrum

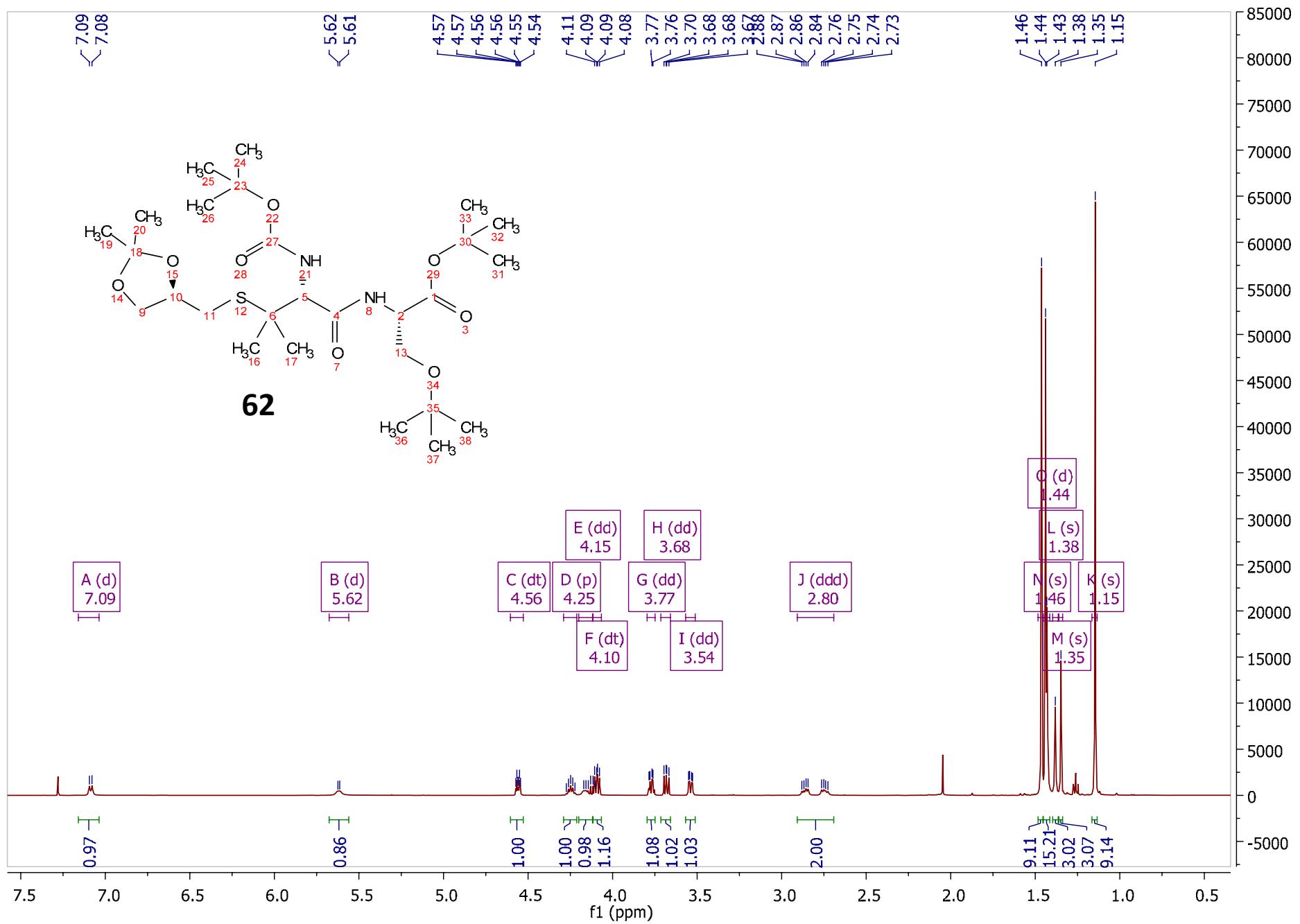
S228





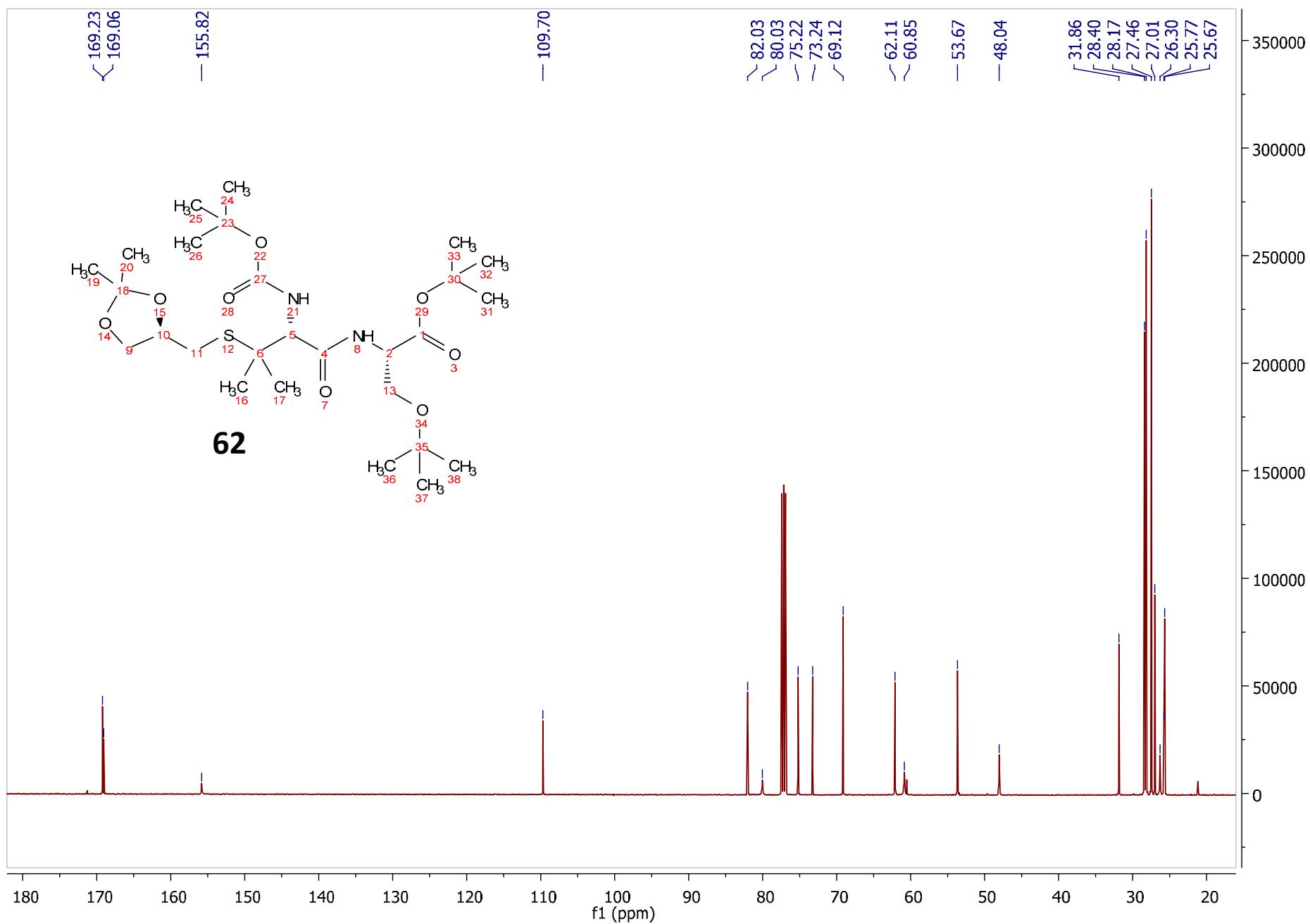
¹H Spectrum

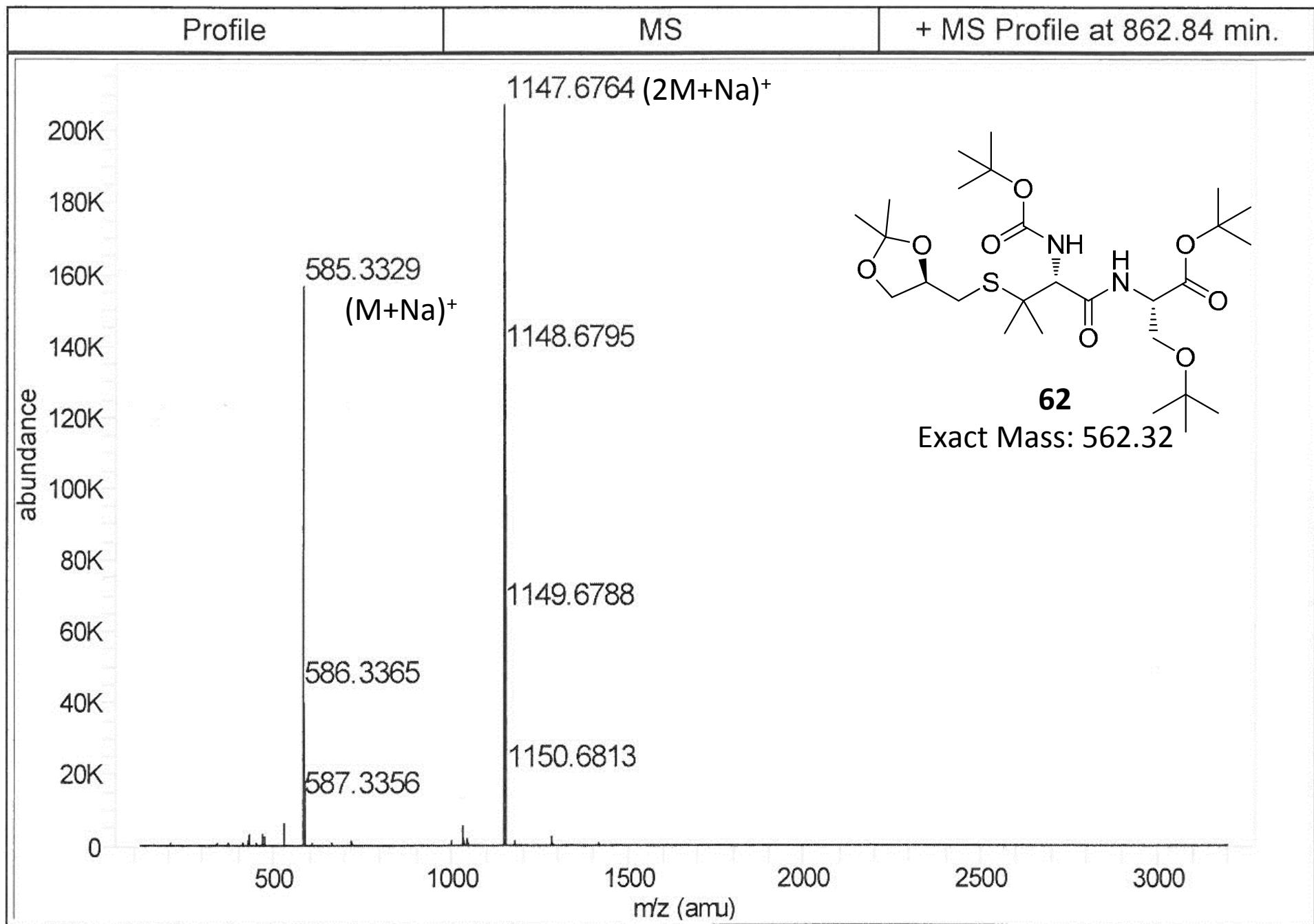
S230



¹³C Spectrum

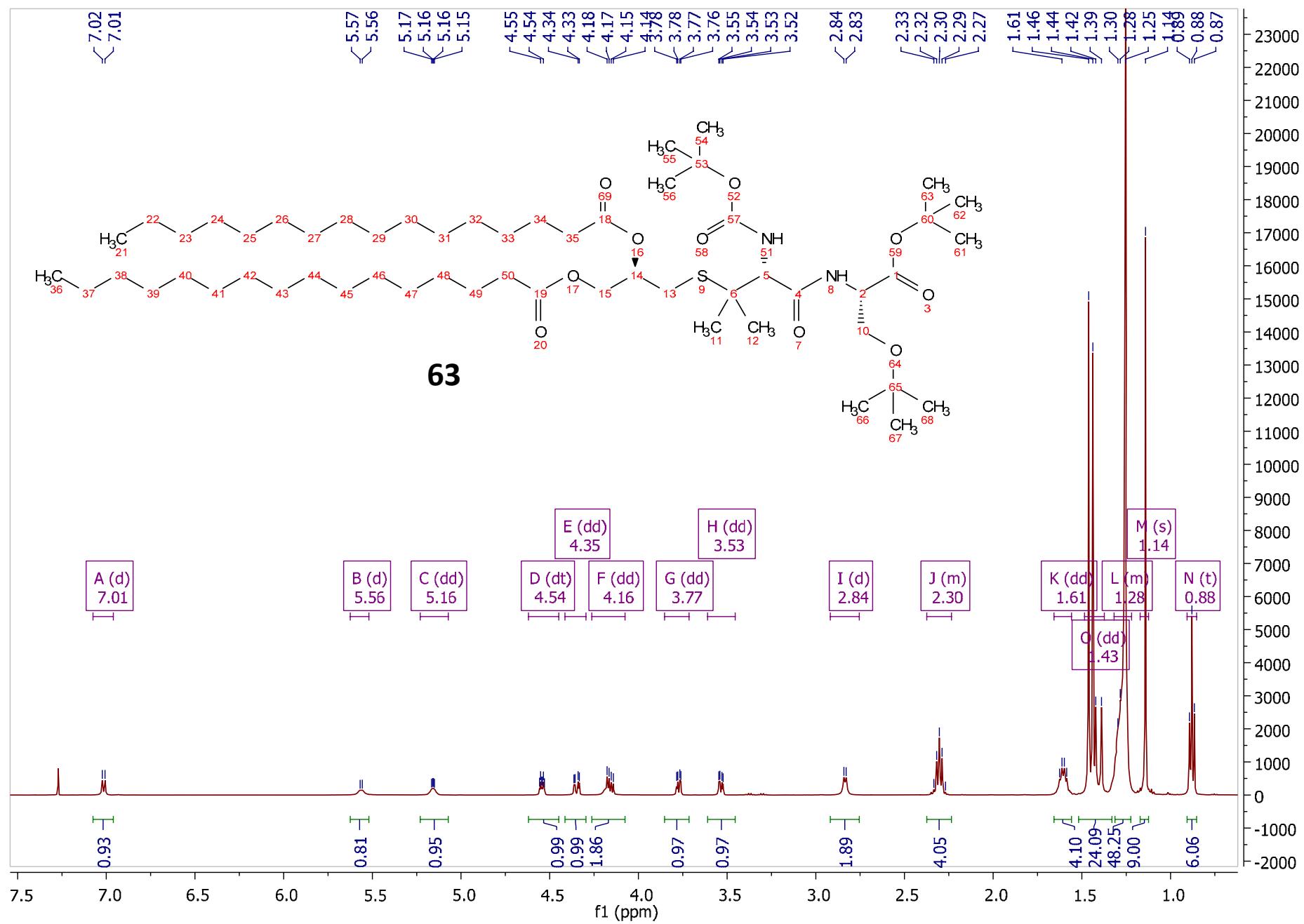
S231





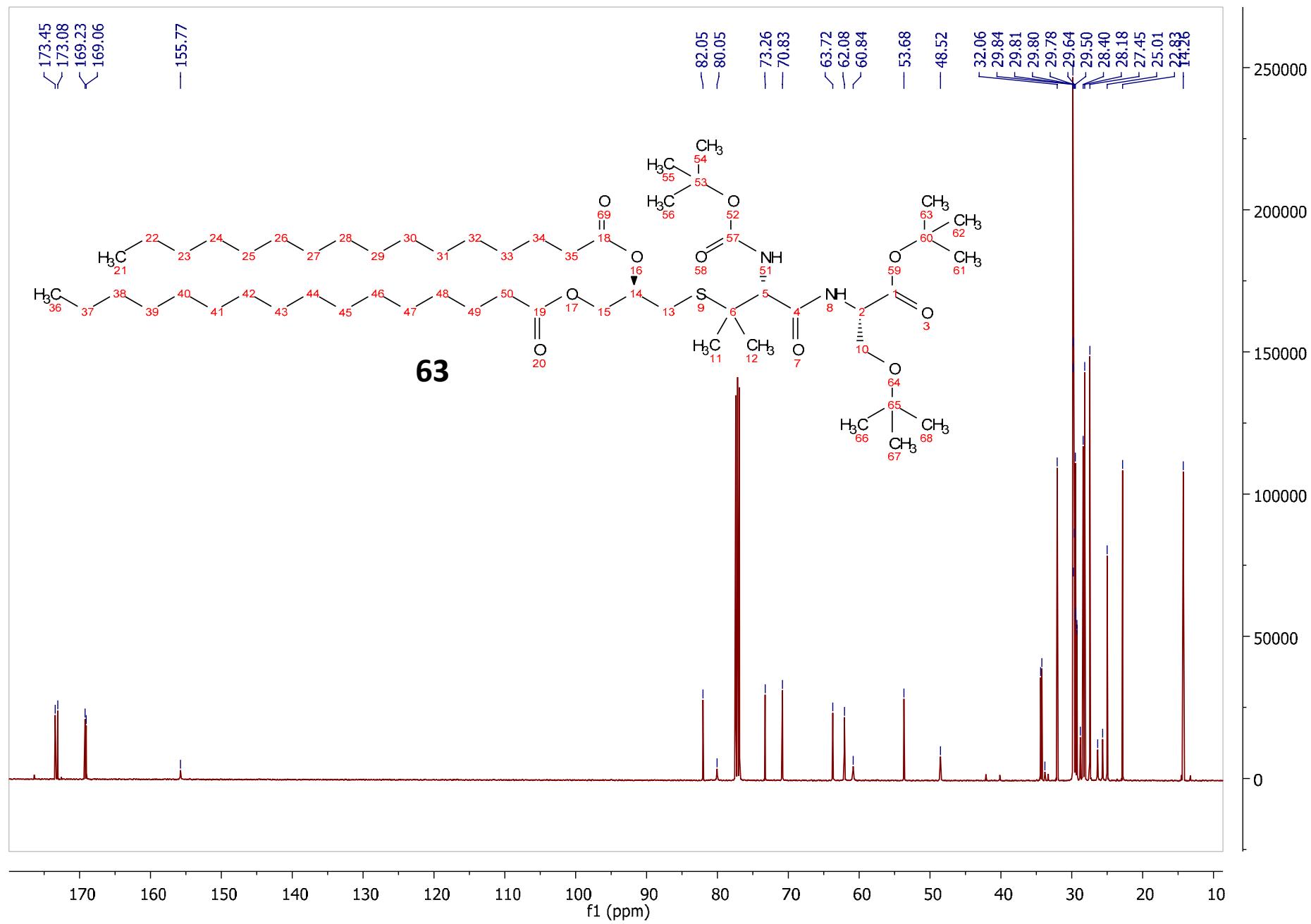
¹H Spectrum

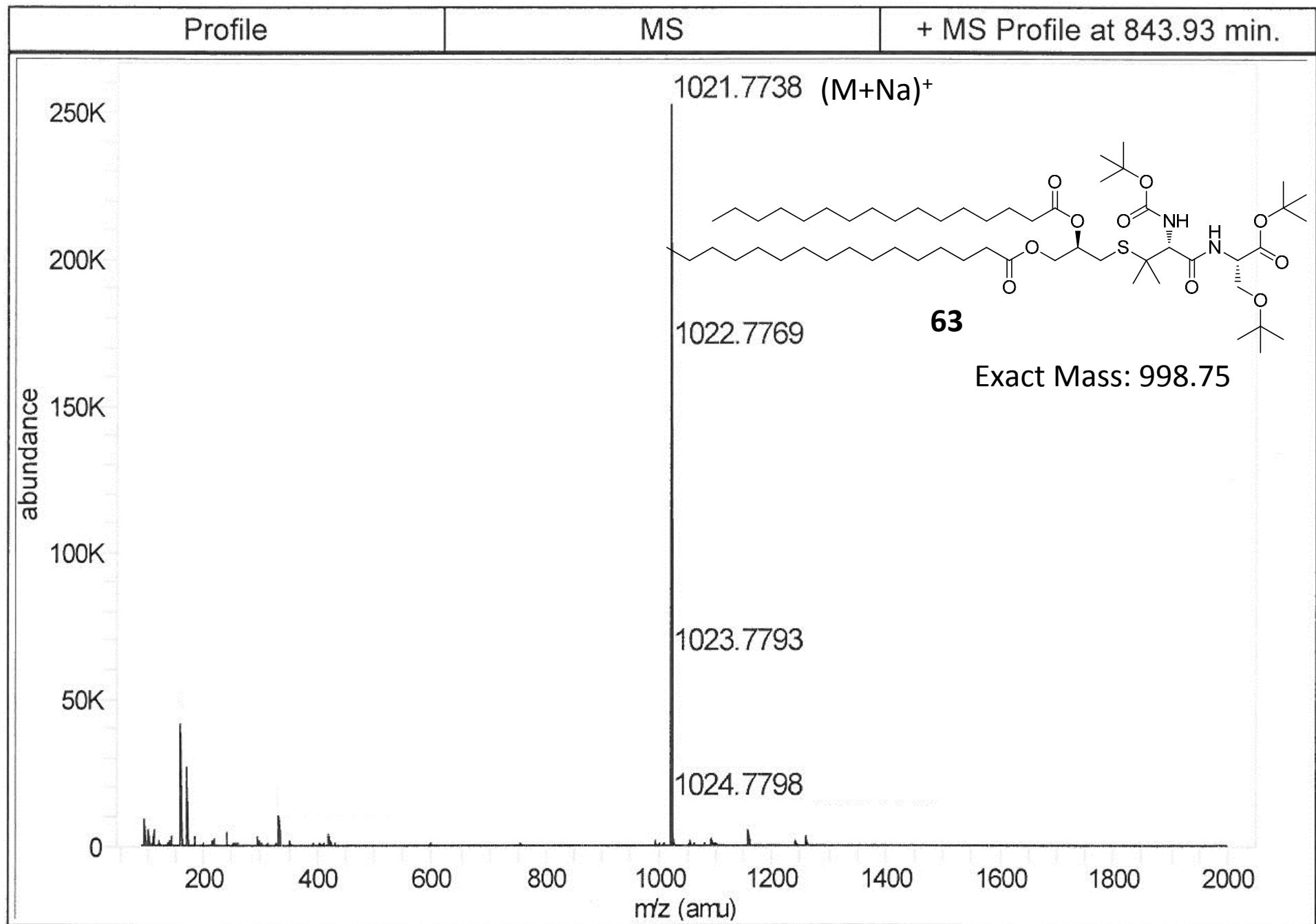
S233



¹³C Spectrum

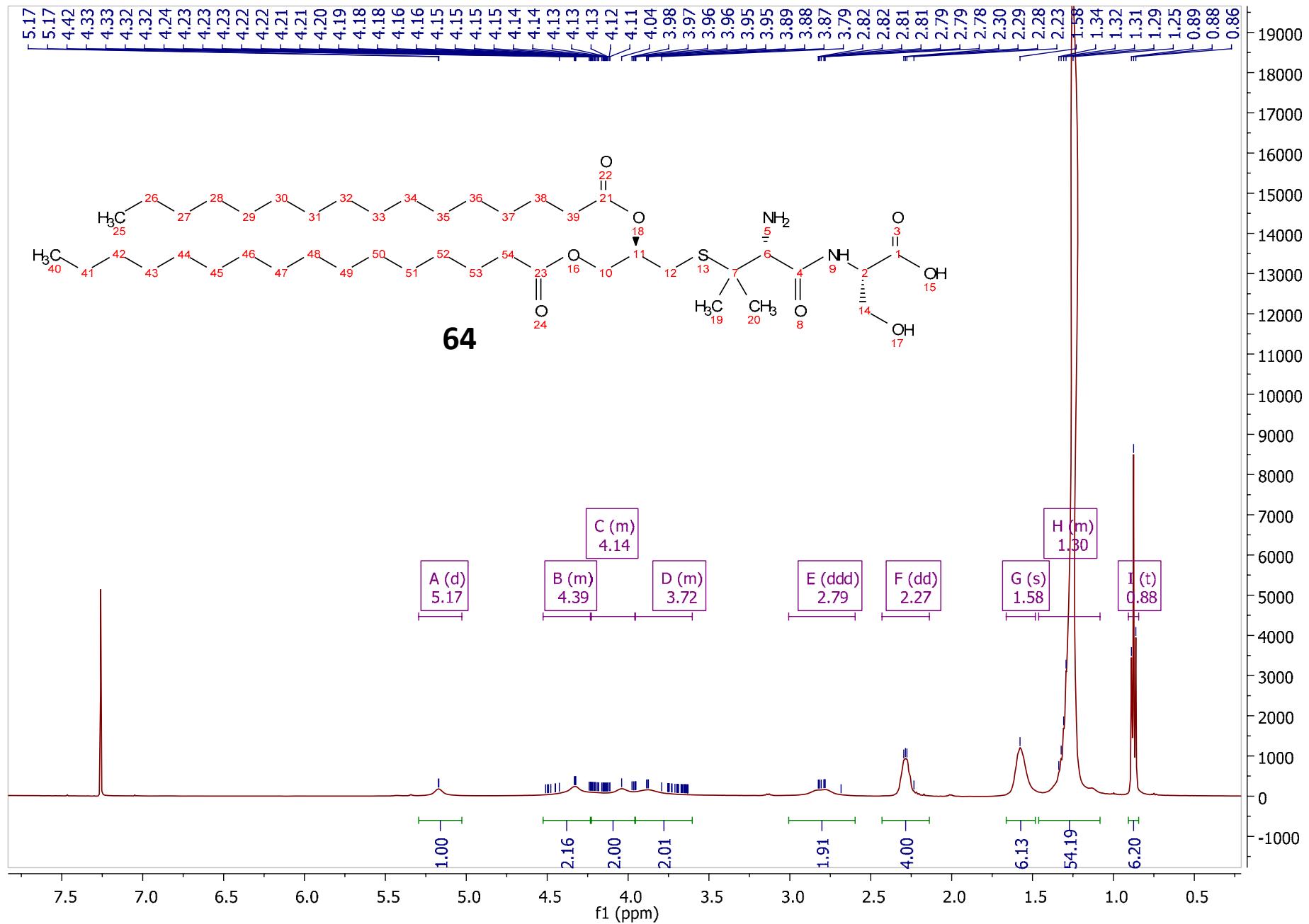
S234

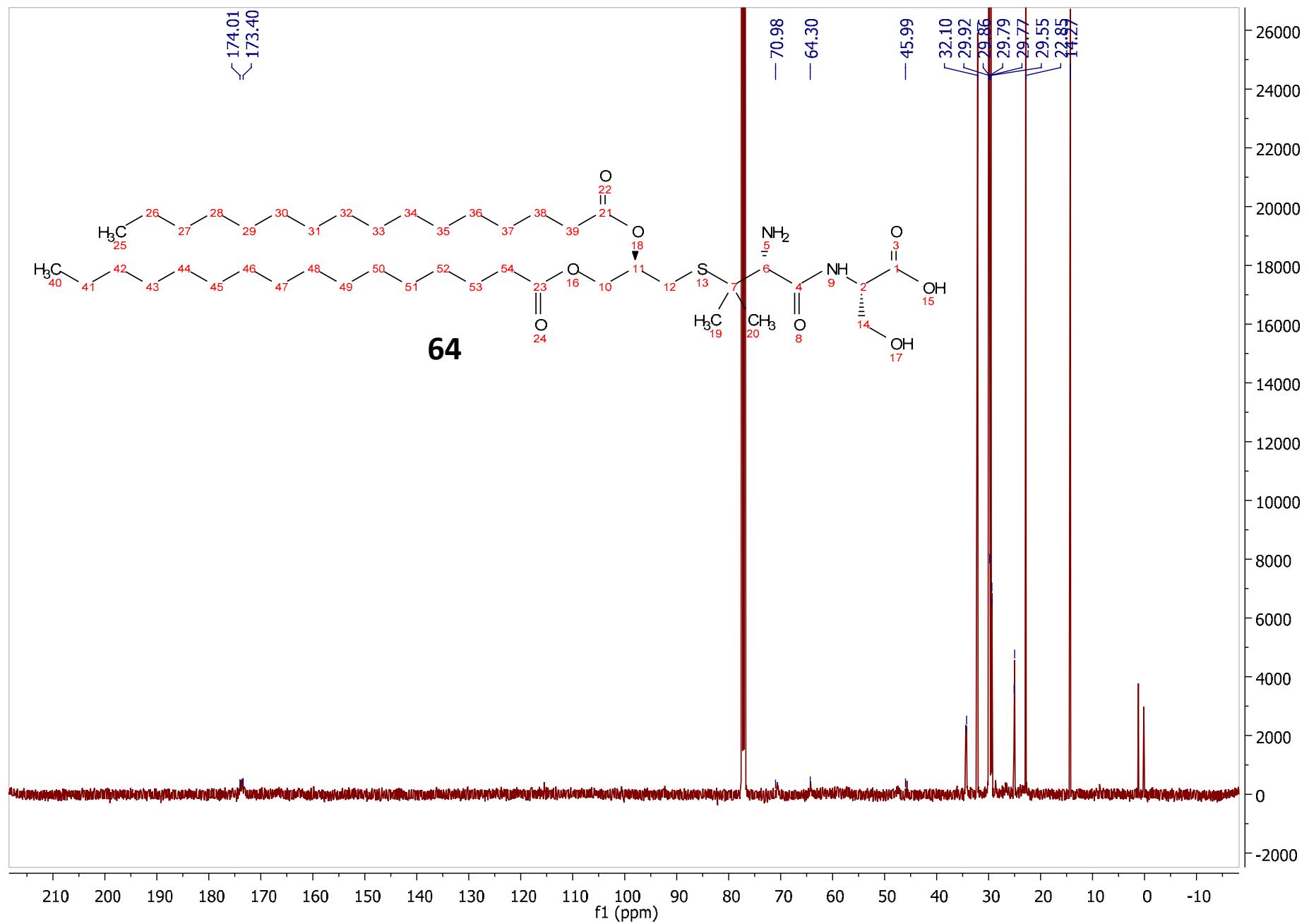


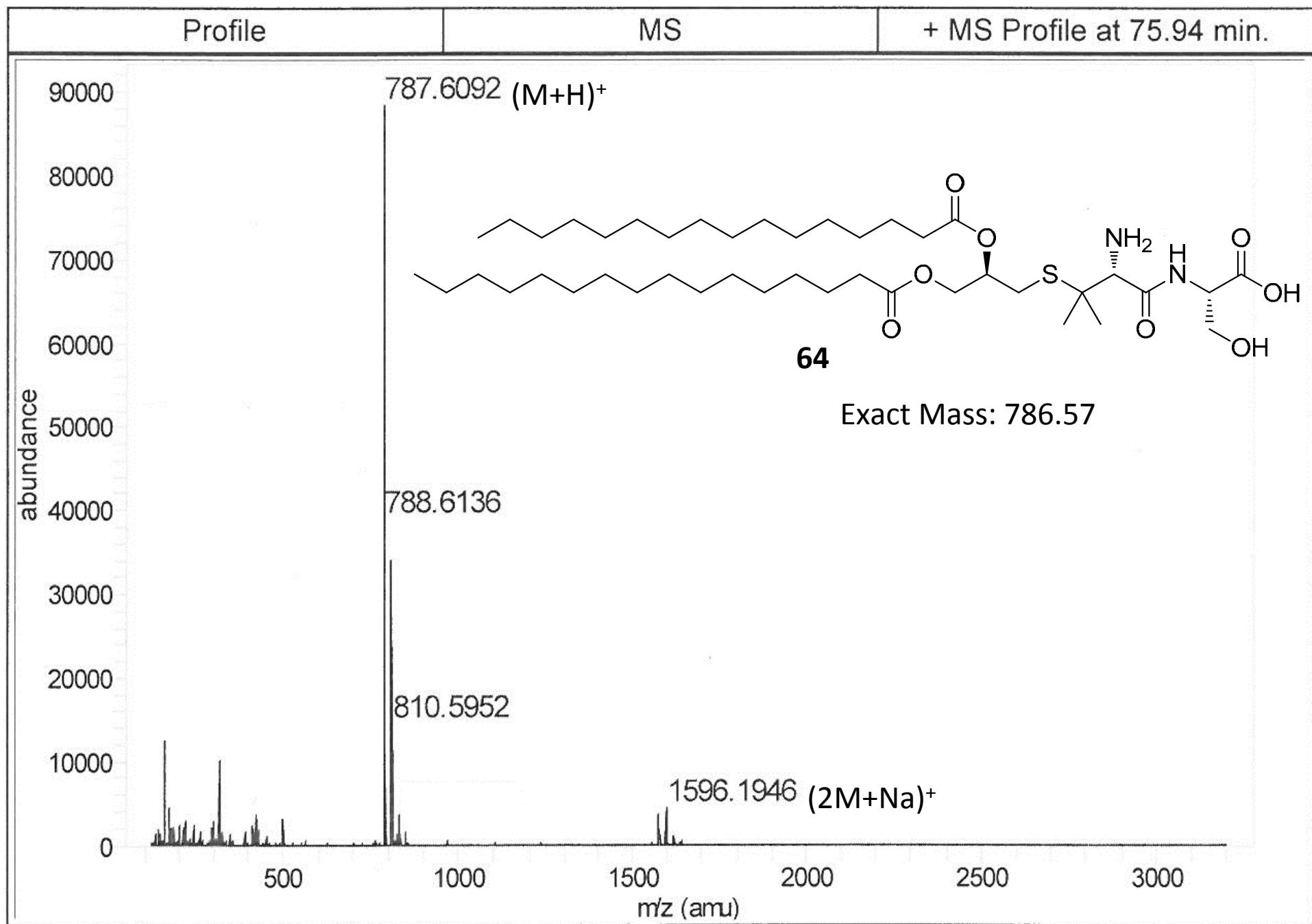


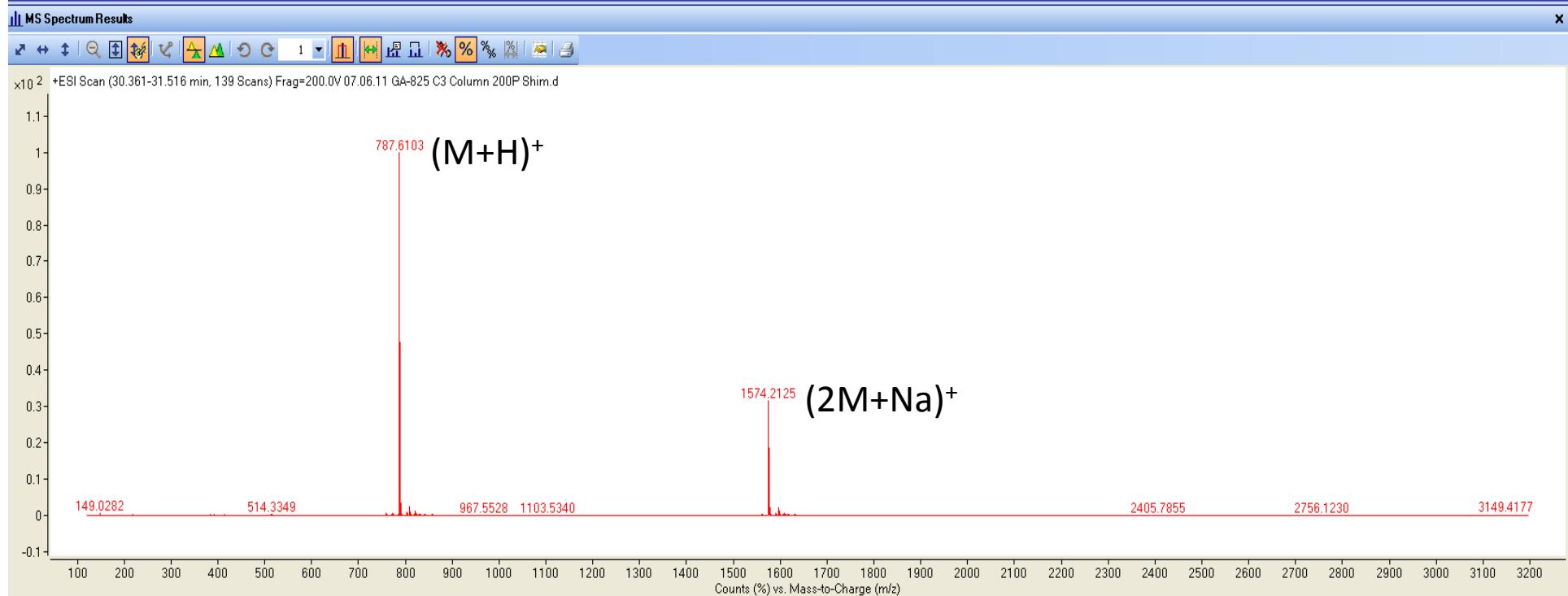
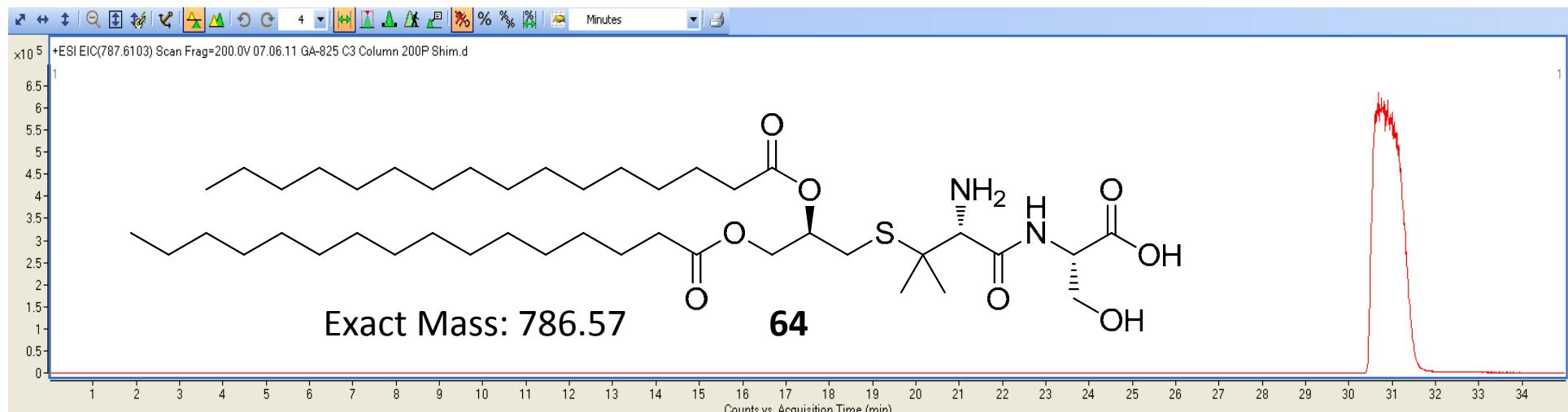
¹H Spectrum

S236



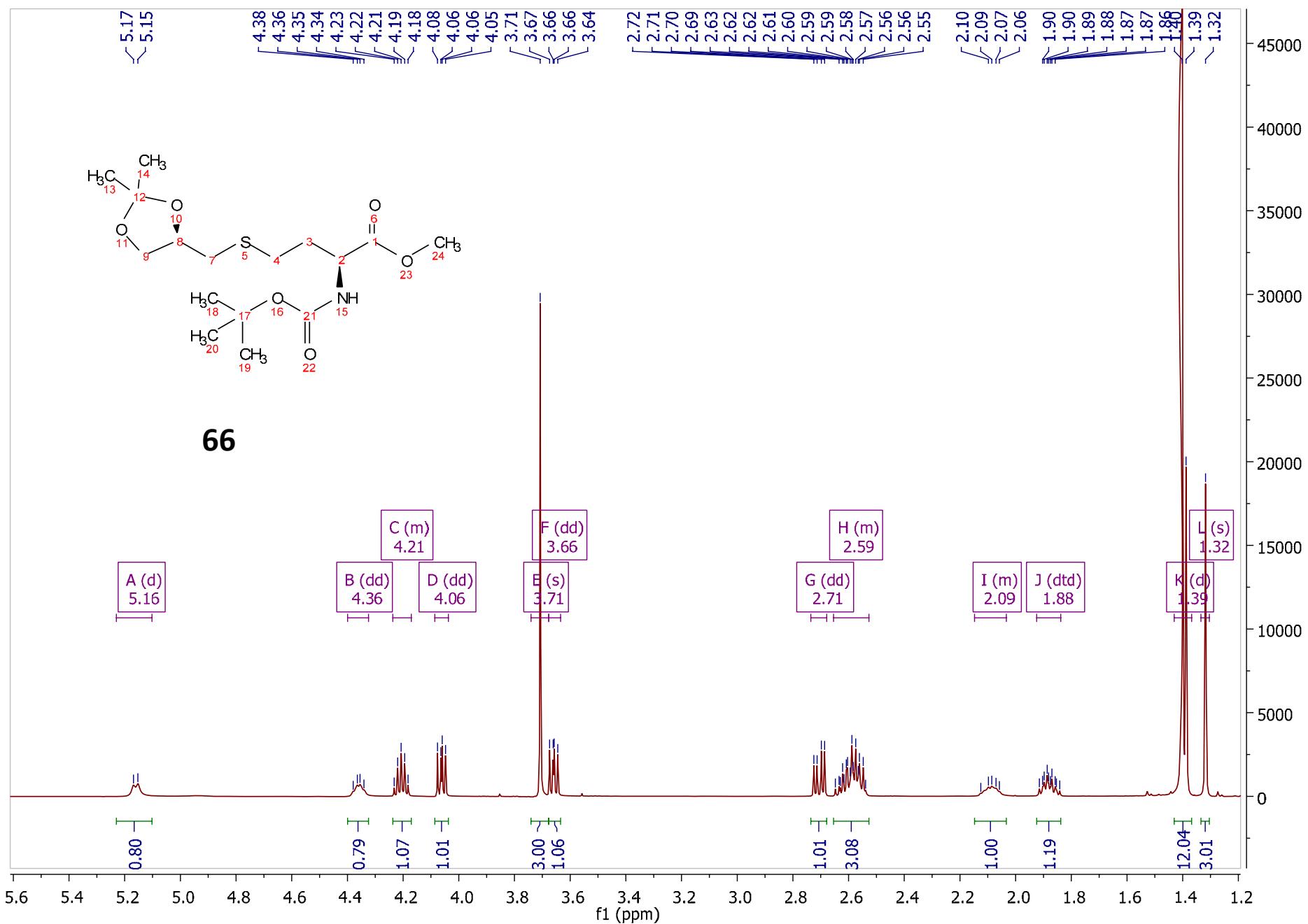






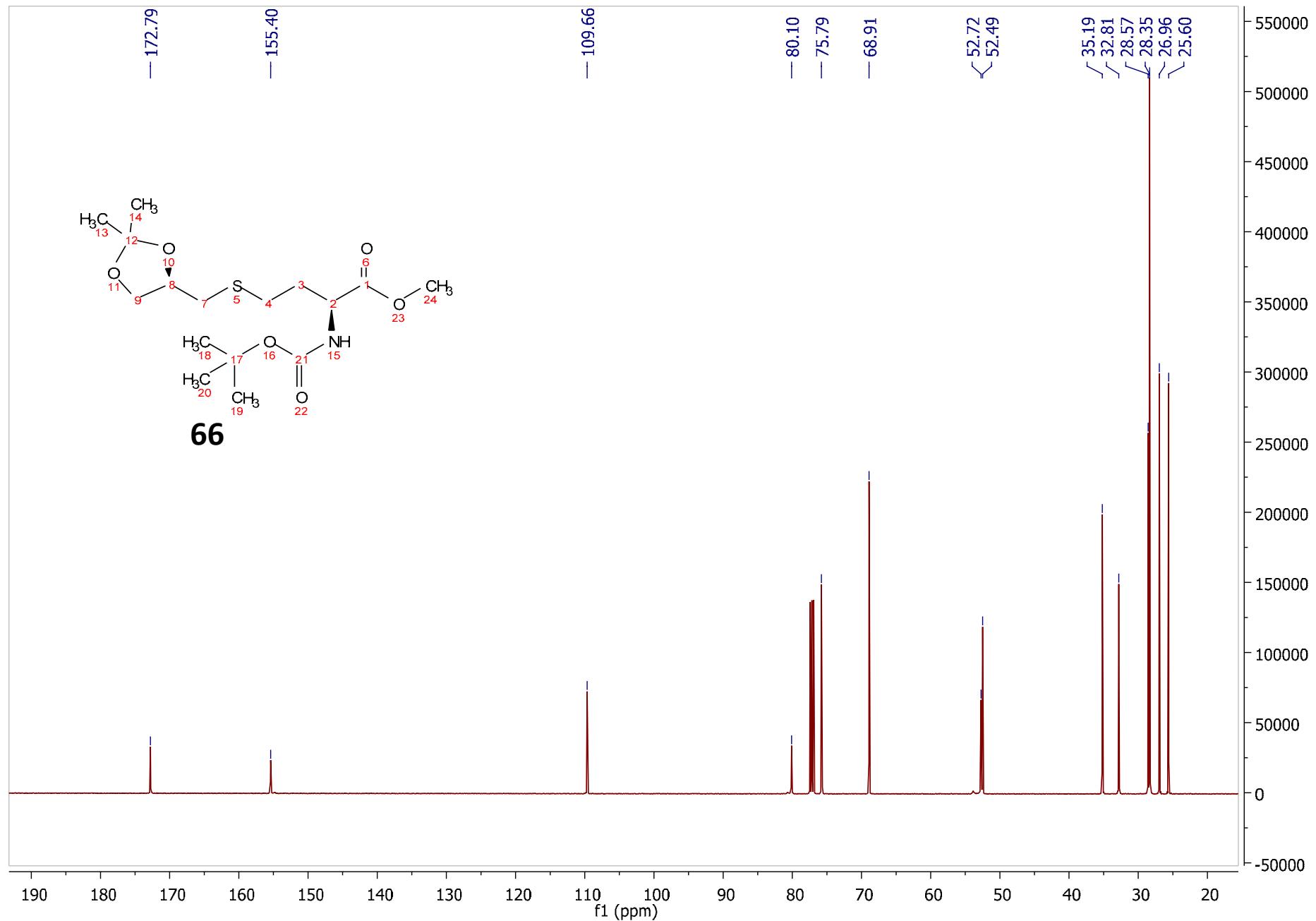
¹H Spectrum

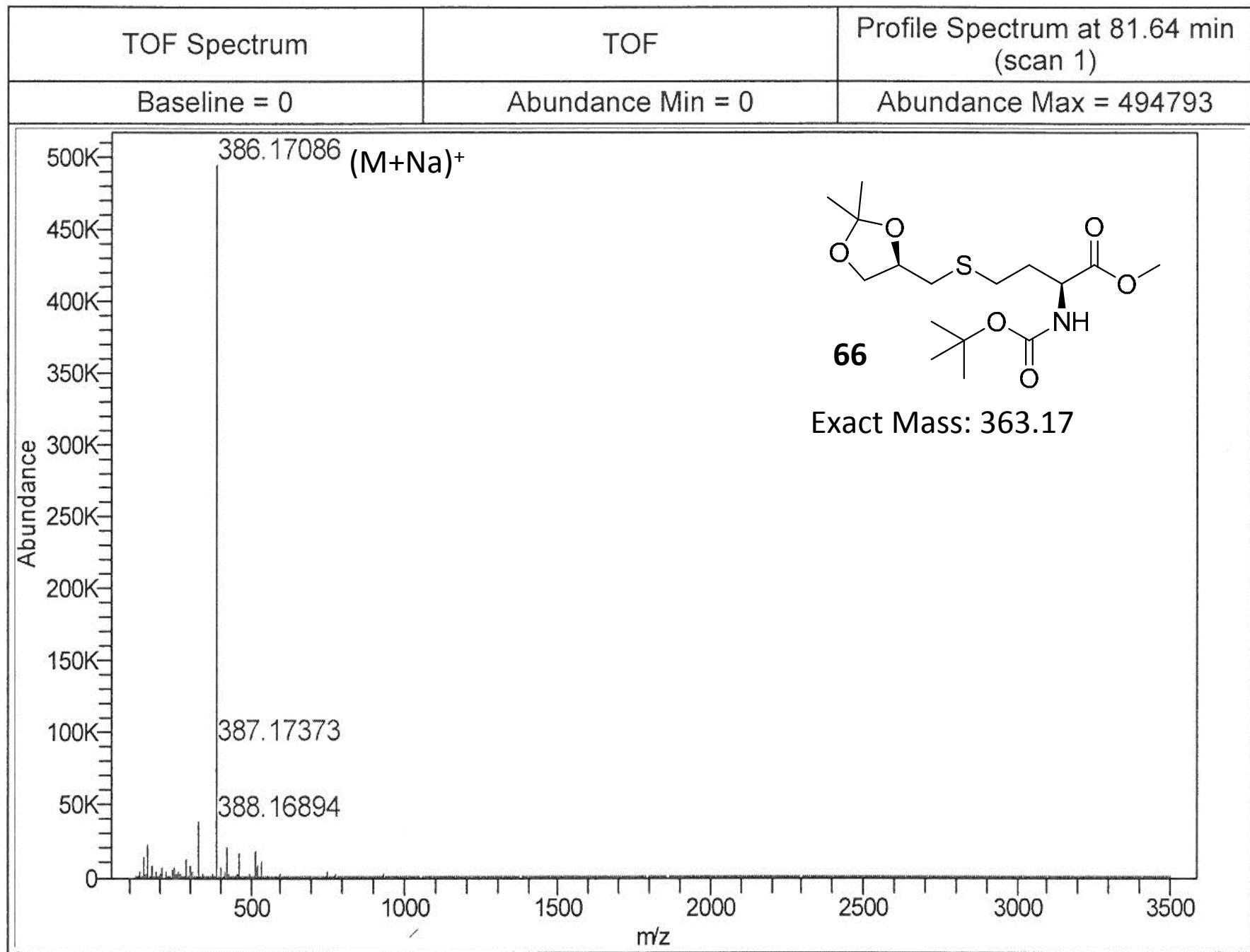
S240



¹³C Spectrum

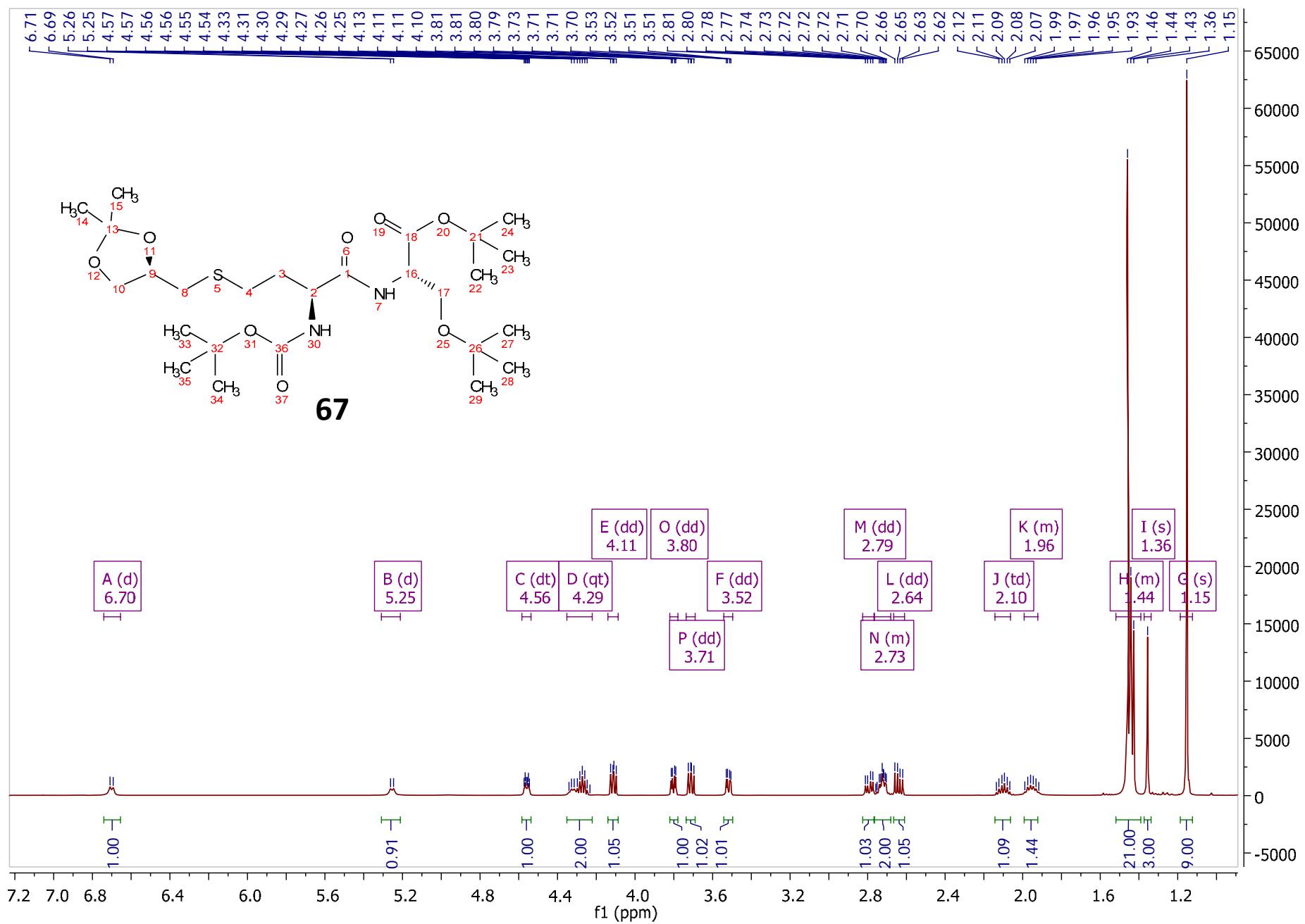
S241





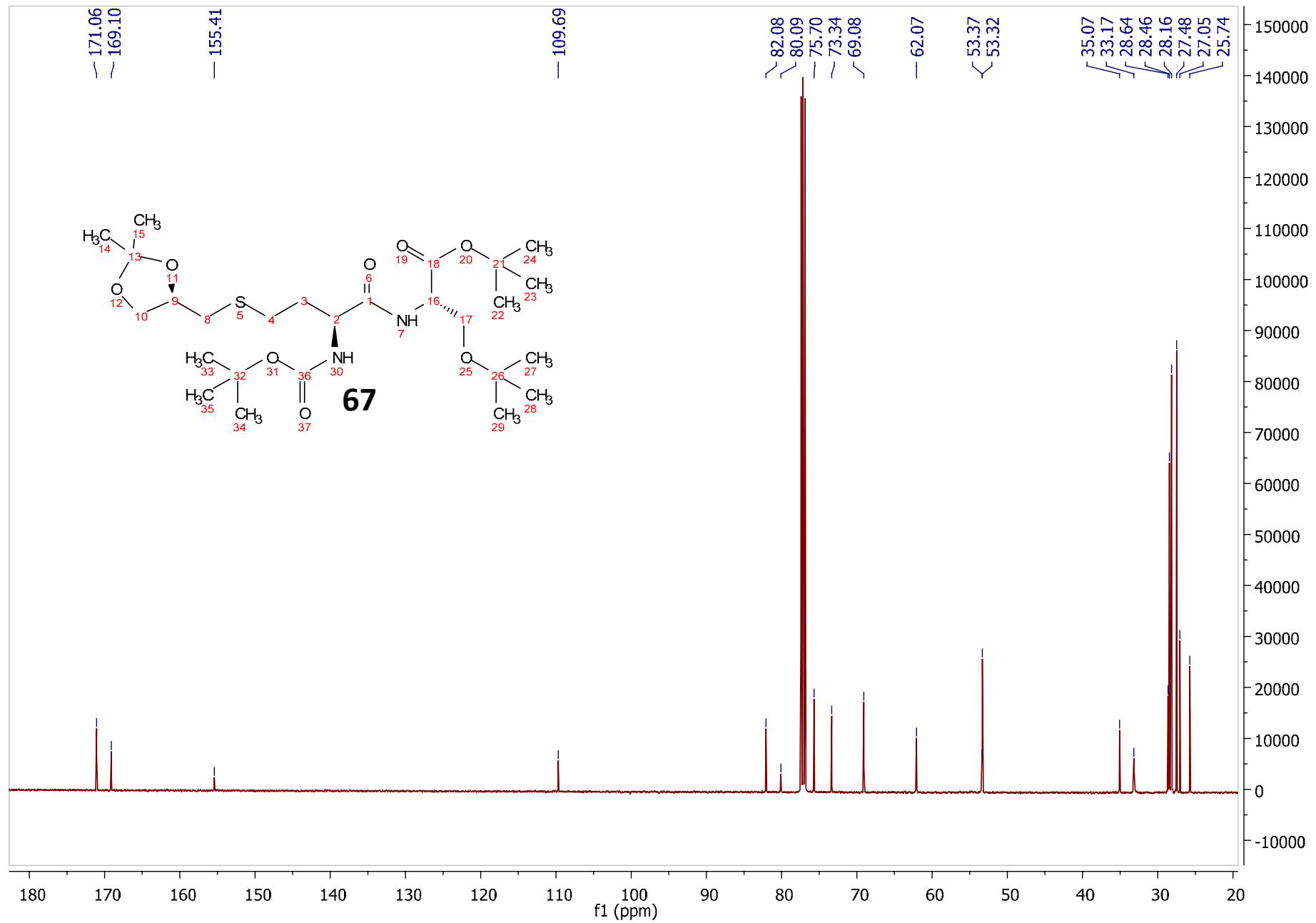
¹H Spectrum

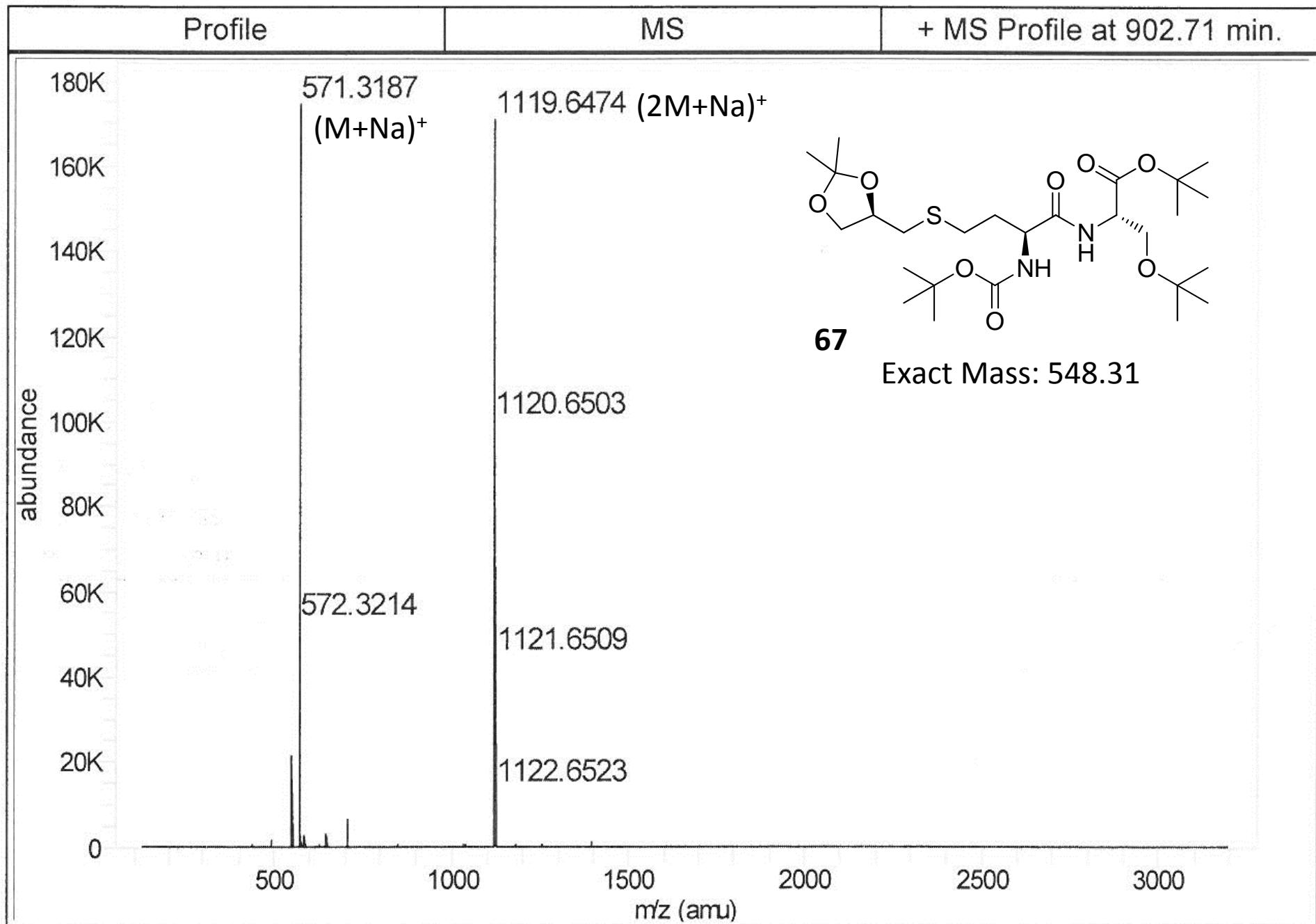
S243



¹³C Spectrum

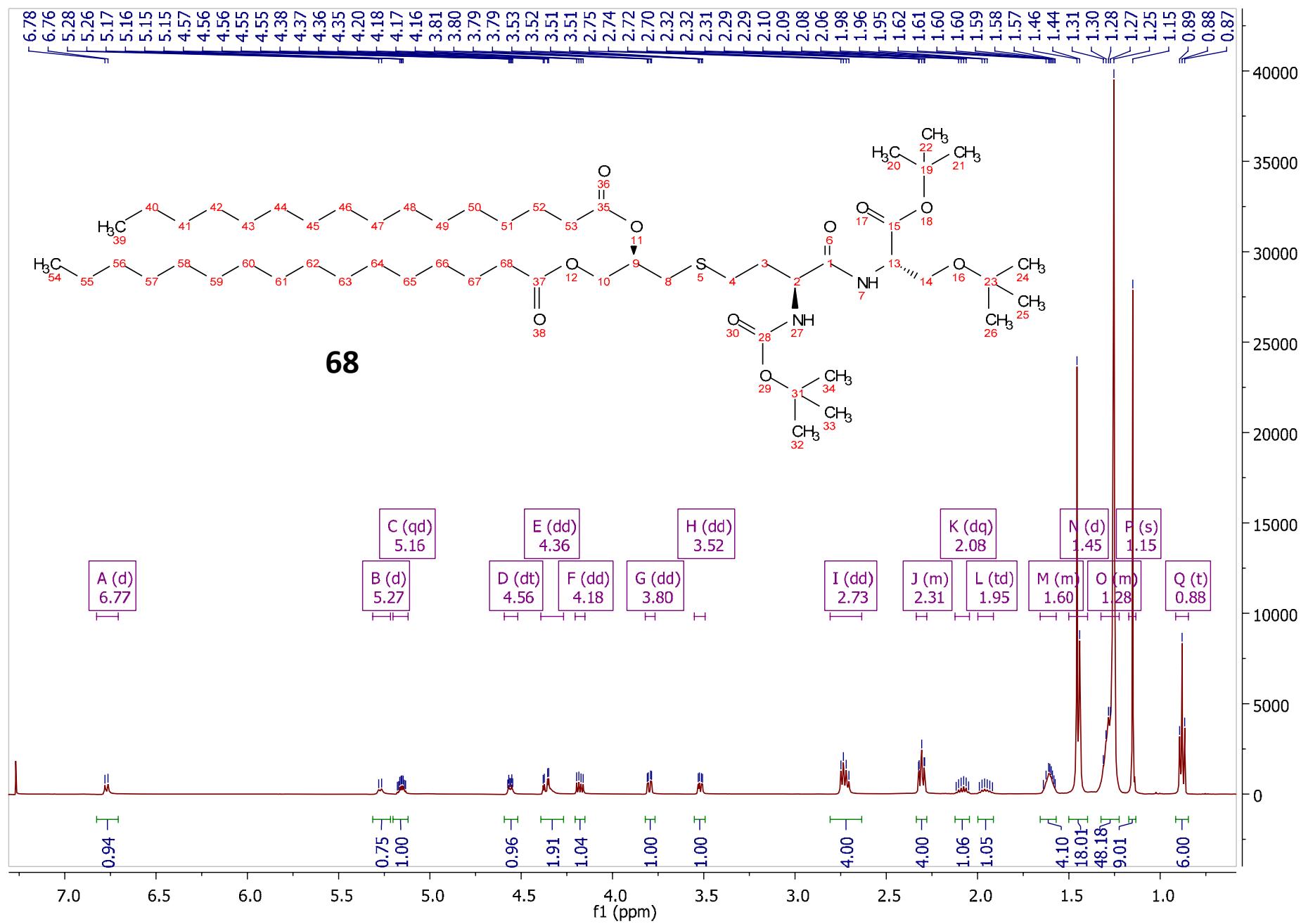
S244

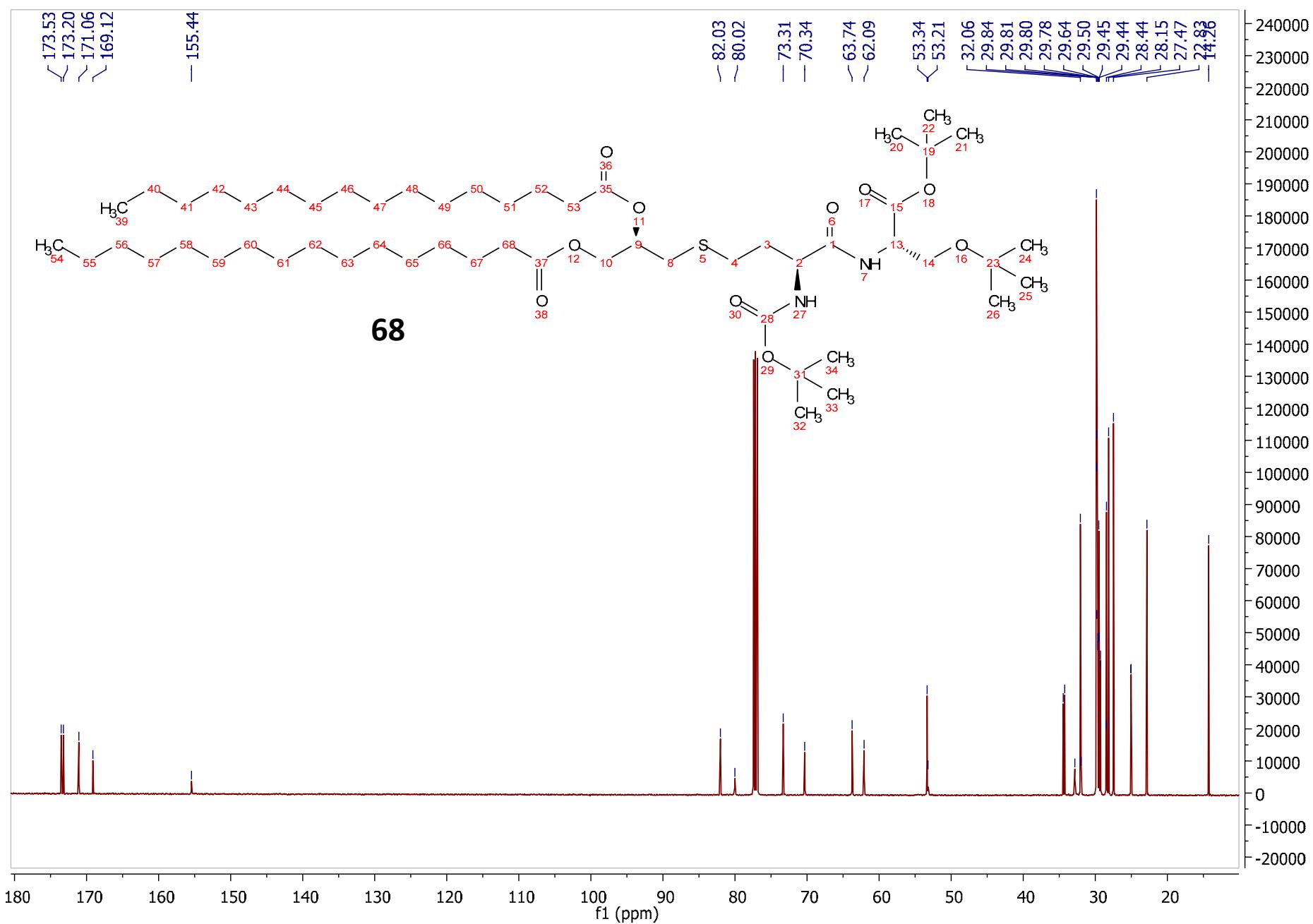


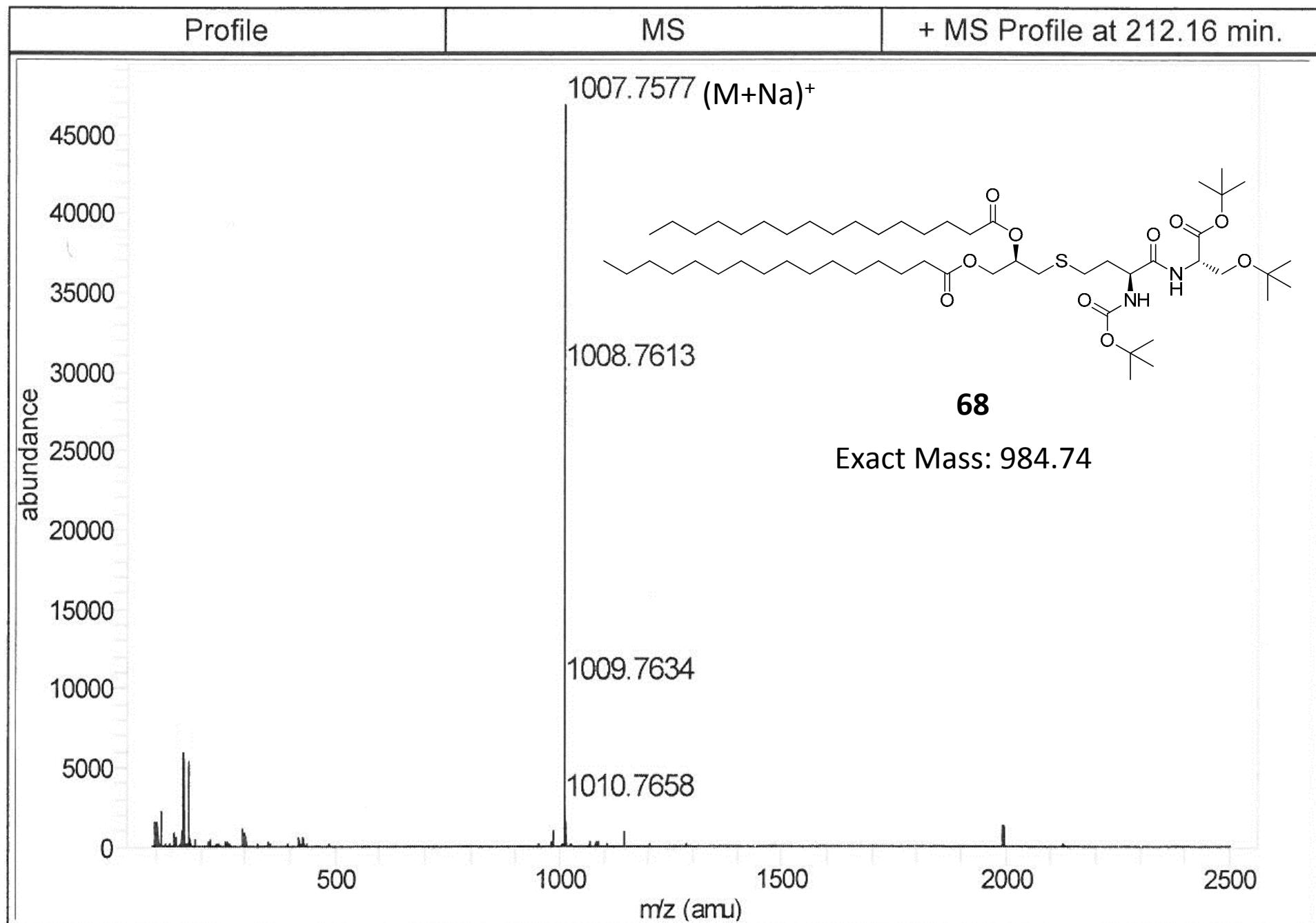


¹H Spectrum

S246

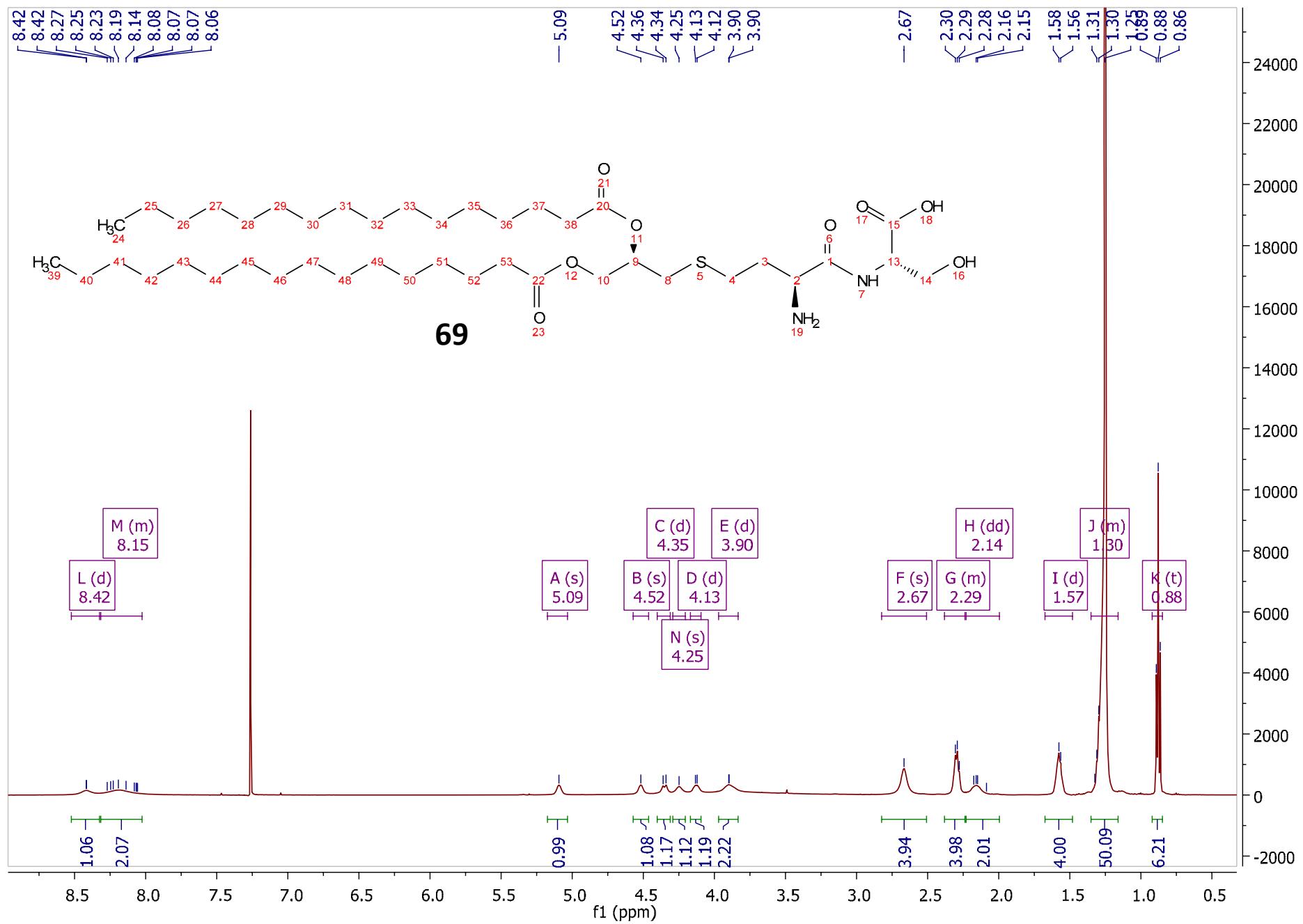






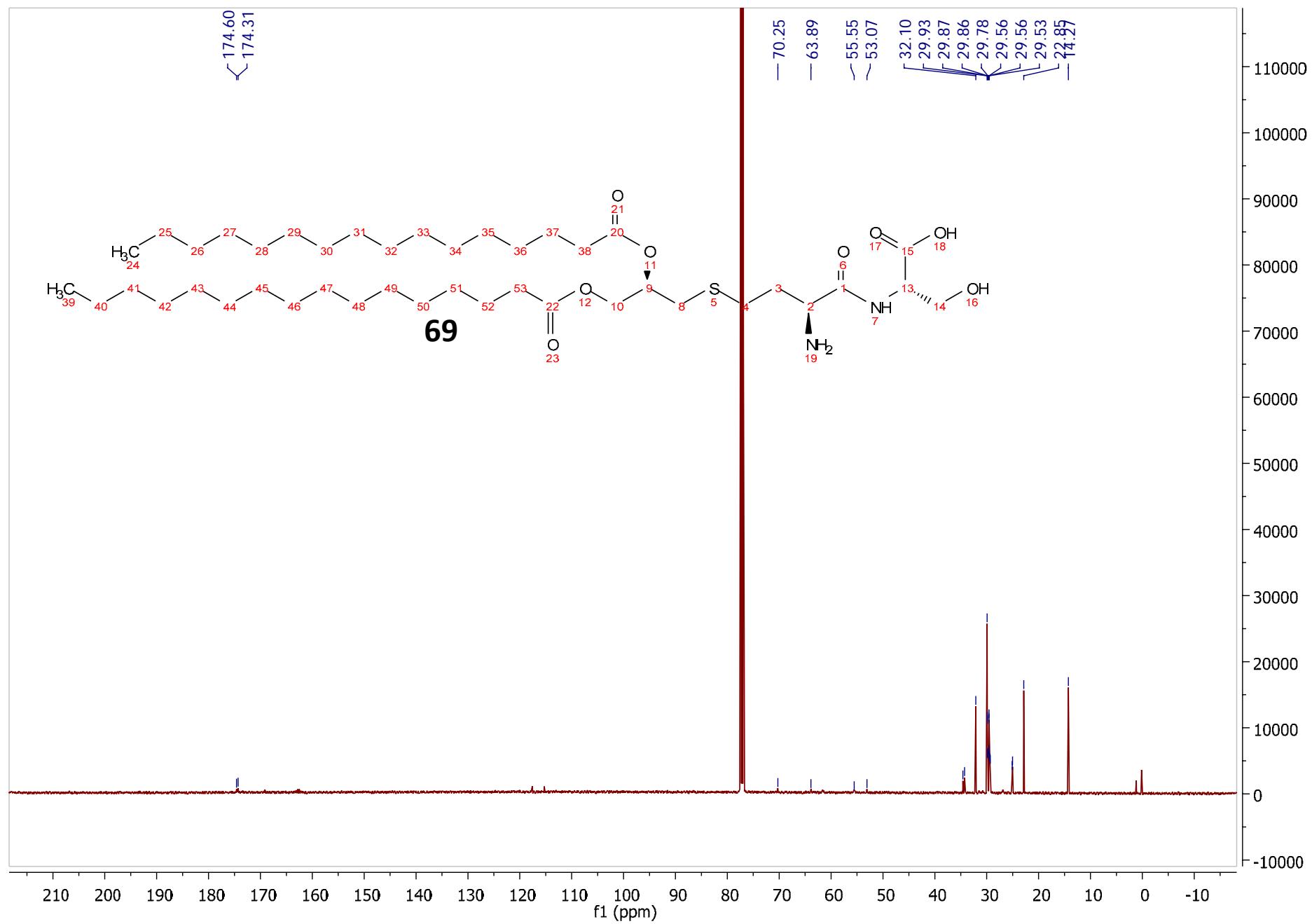
¹H Spectrum

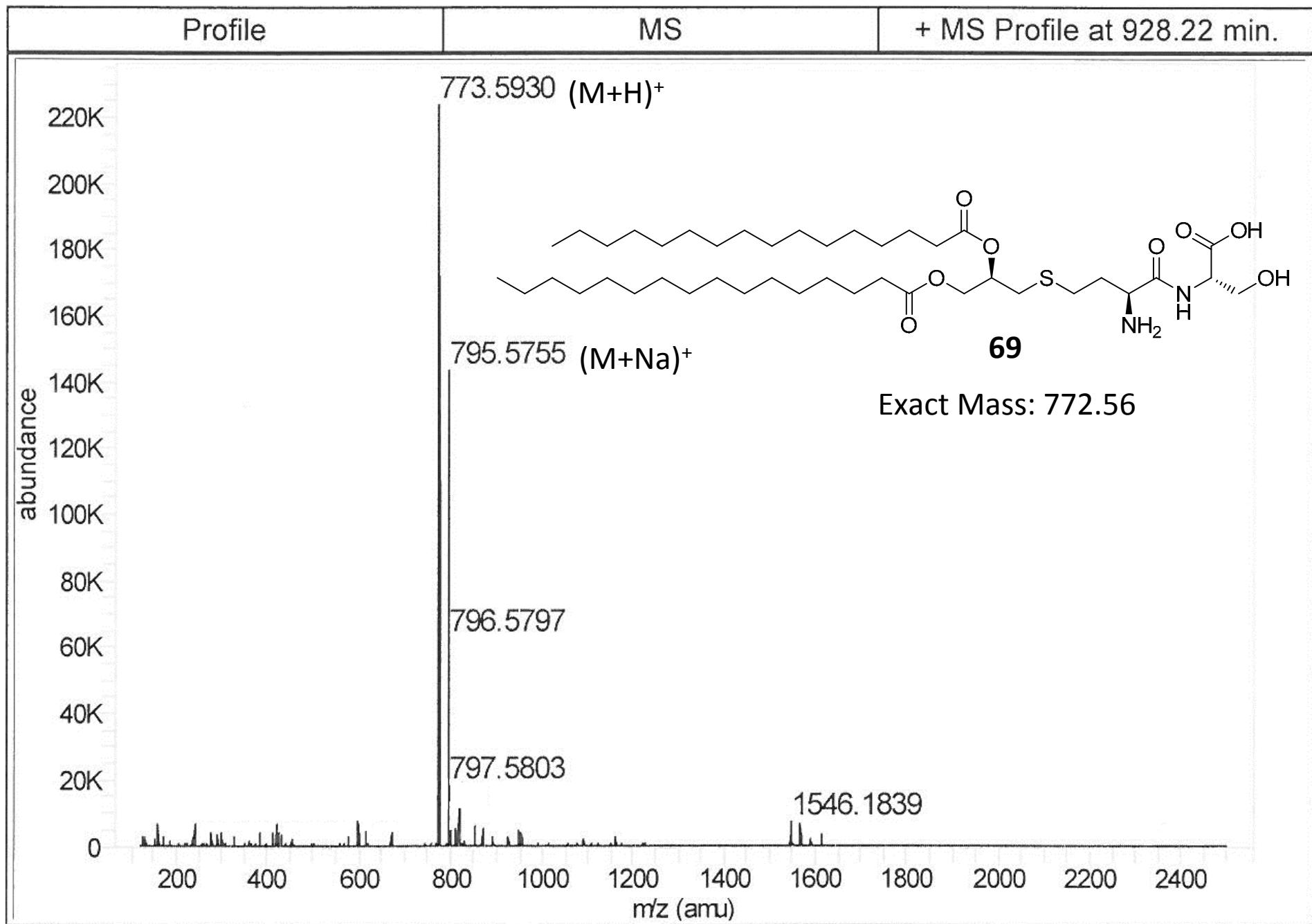
S249

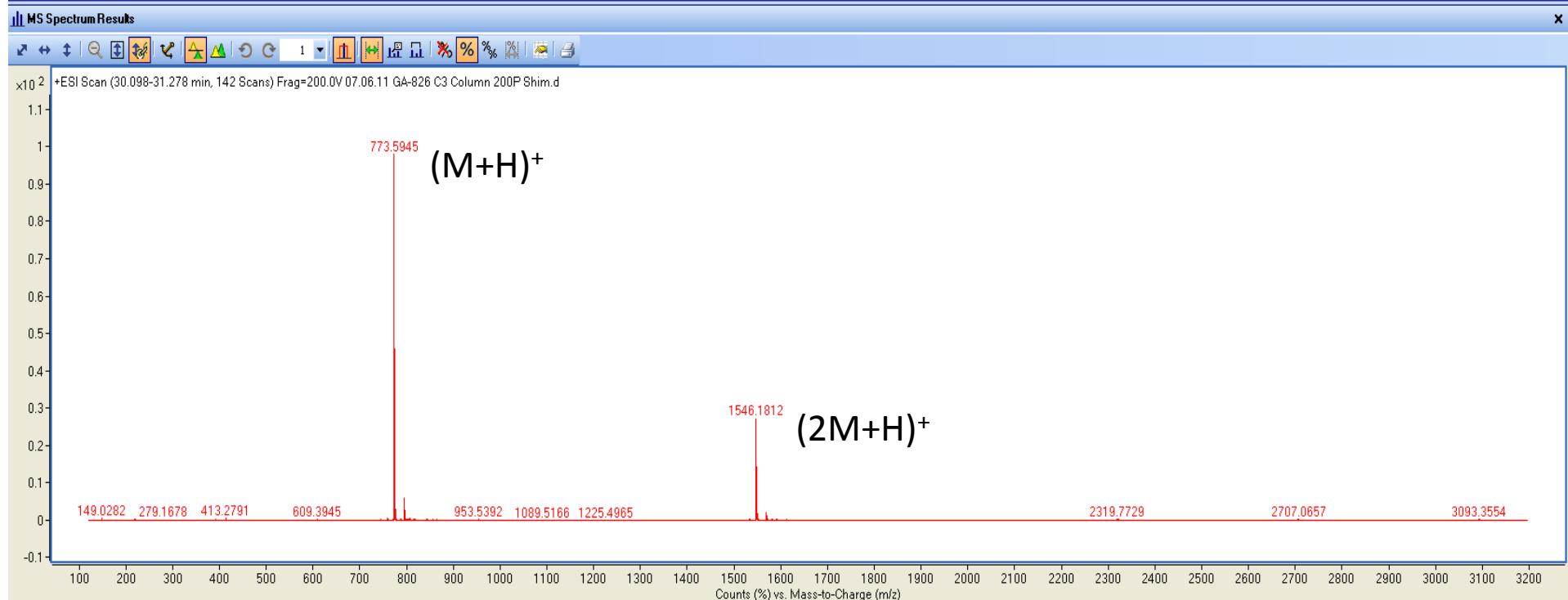
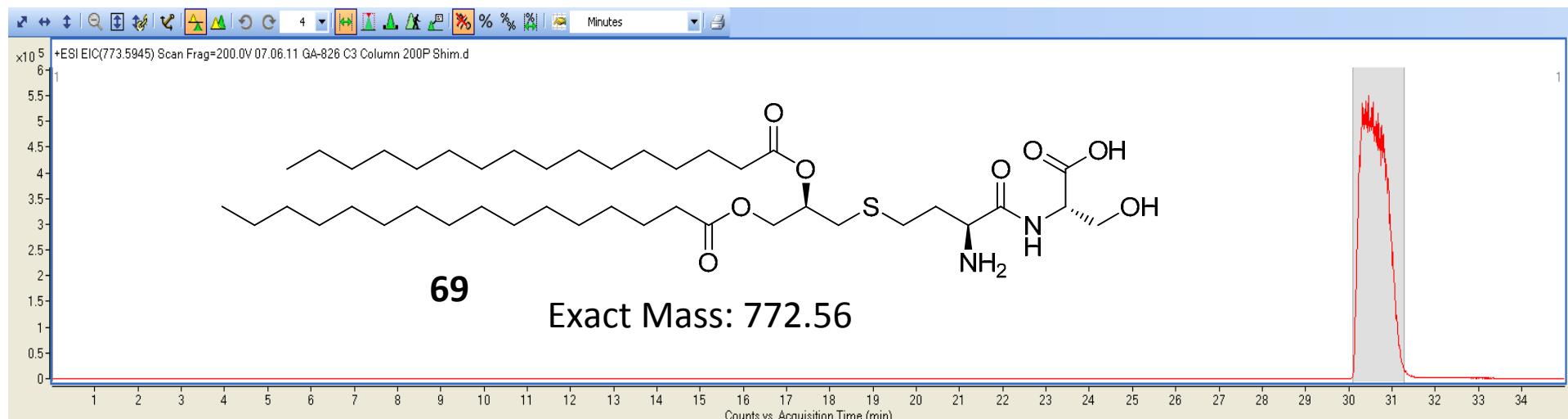


¹³C Spectrum

S250

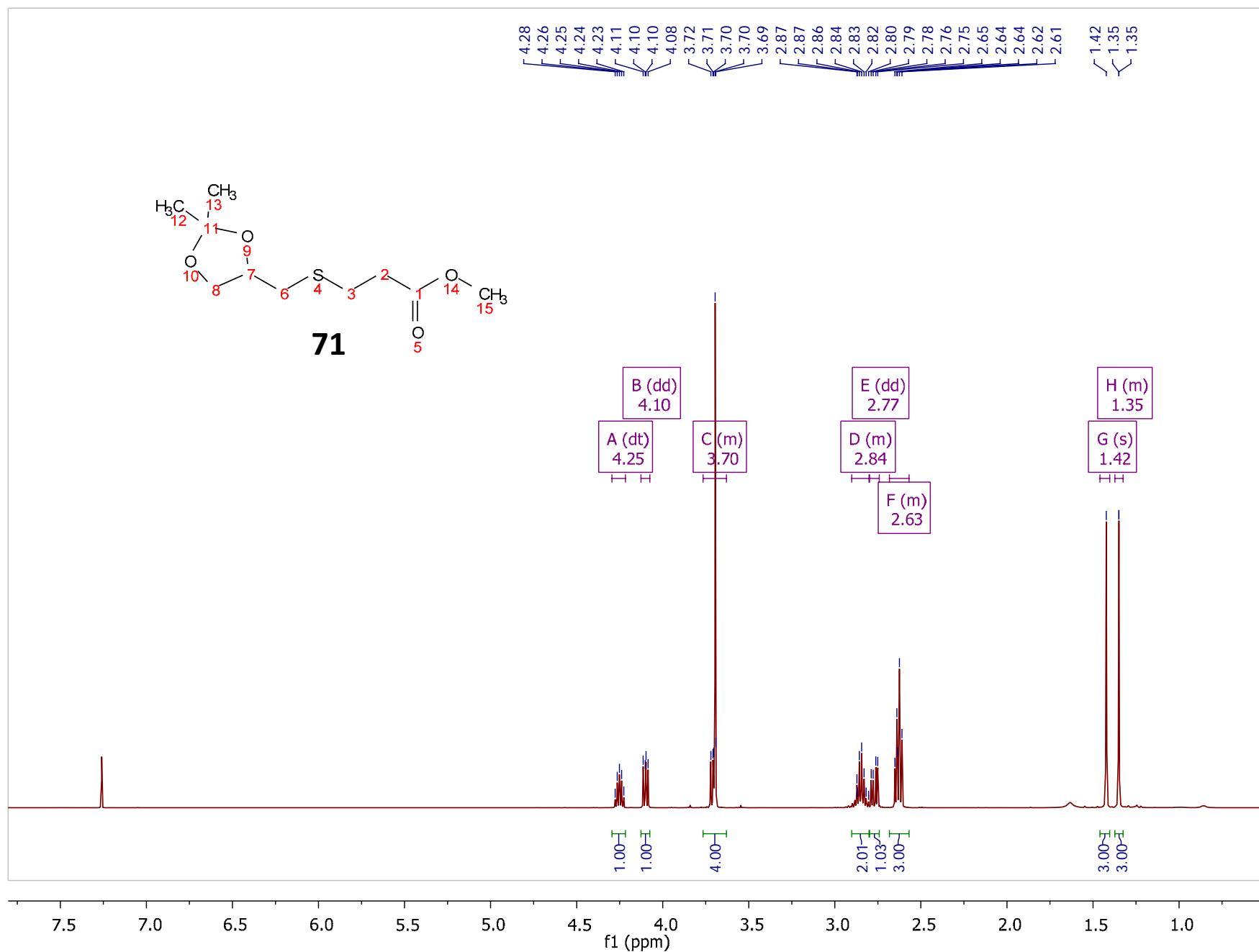






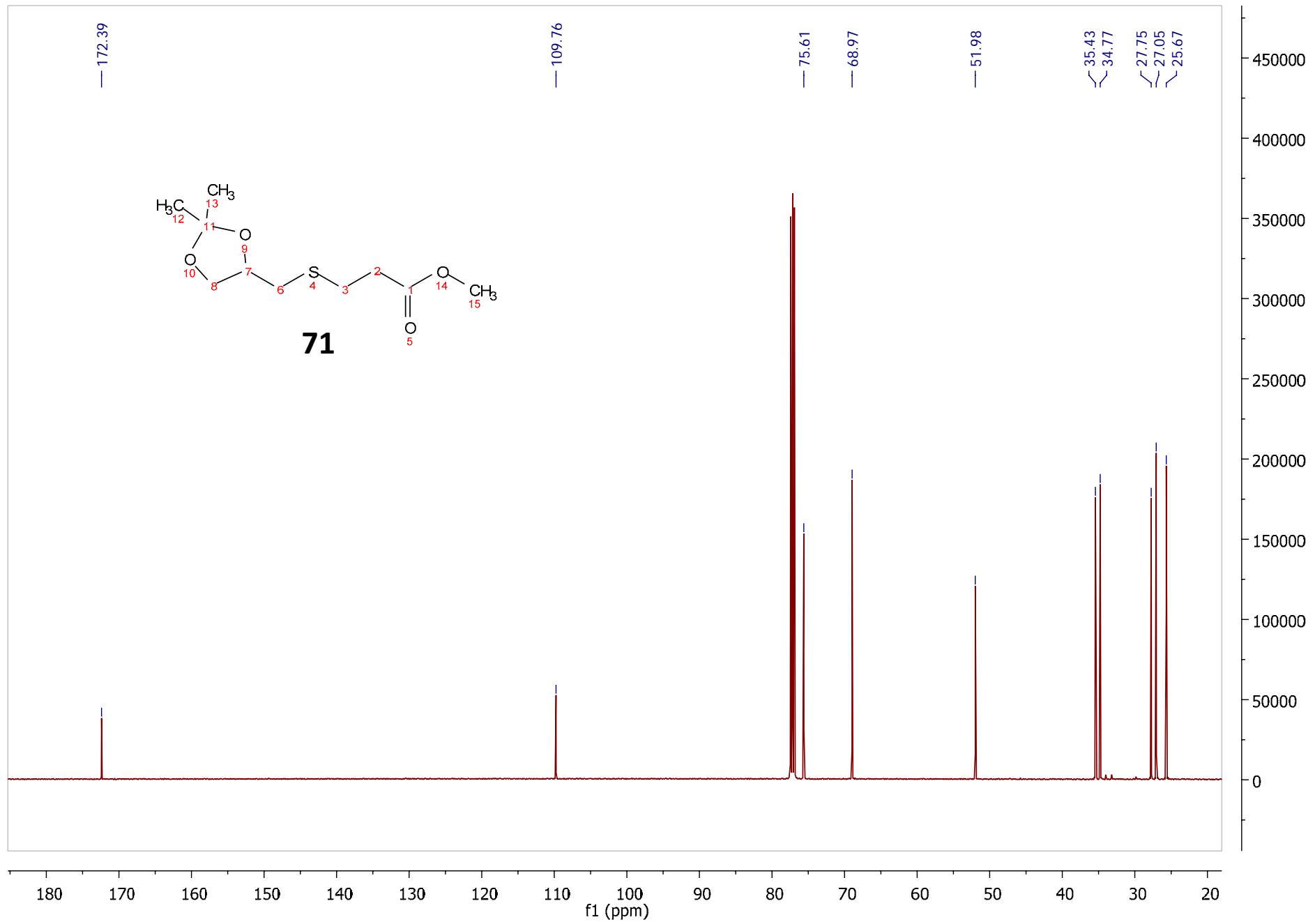
¹H Spectrum

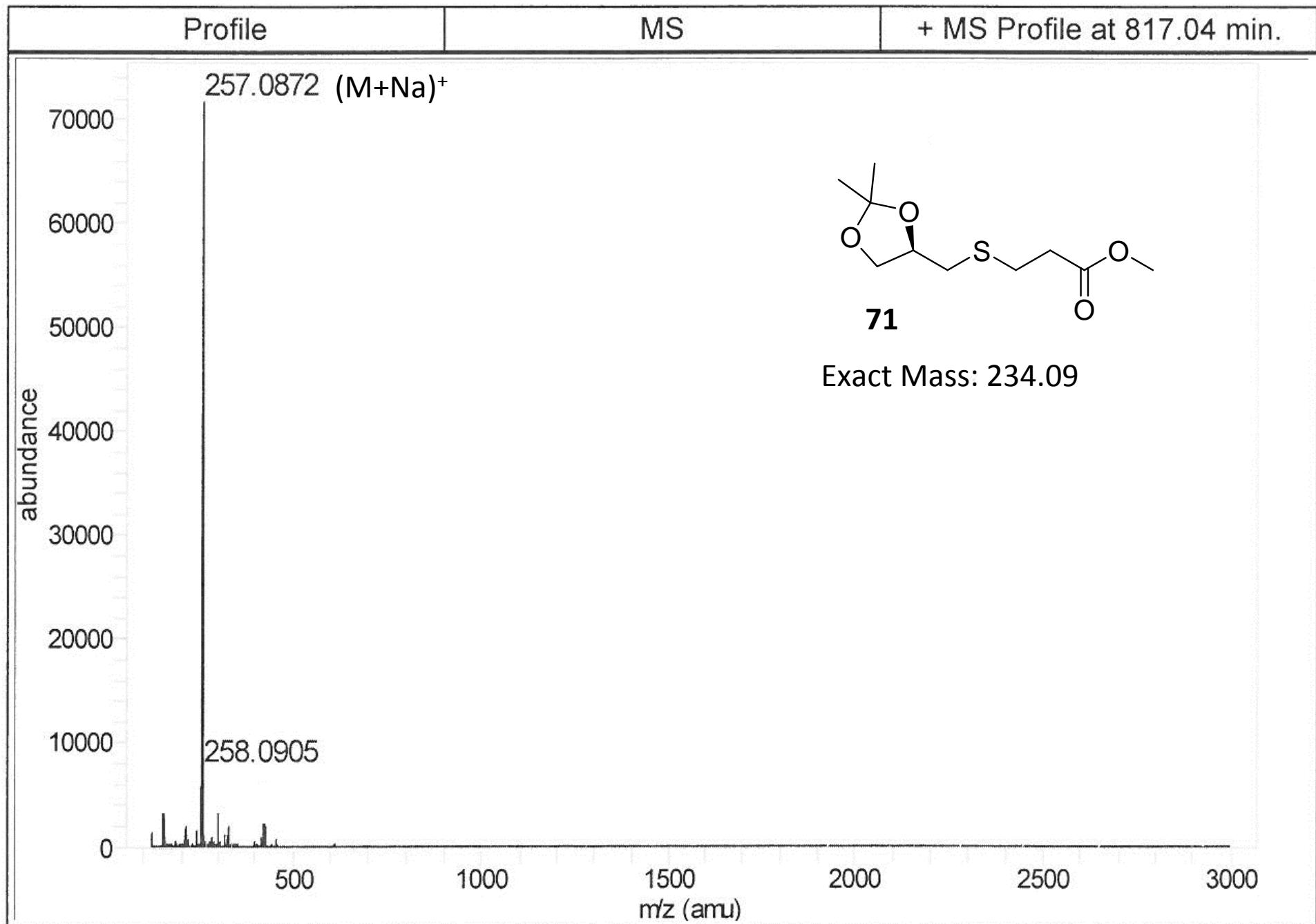
S253



¹³C Spectrum

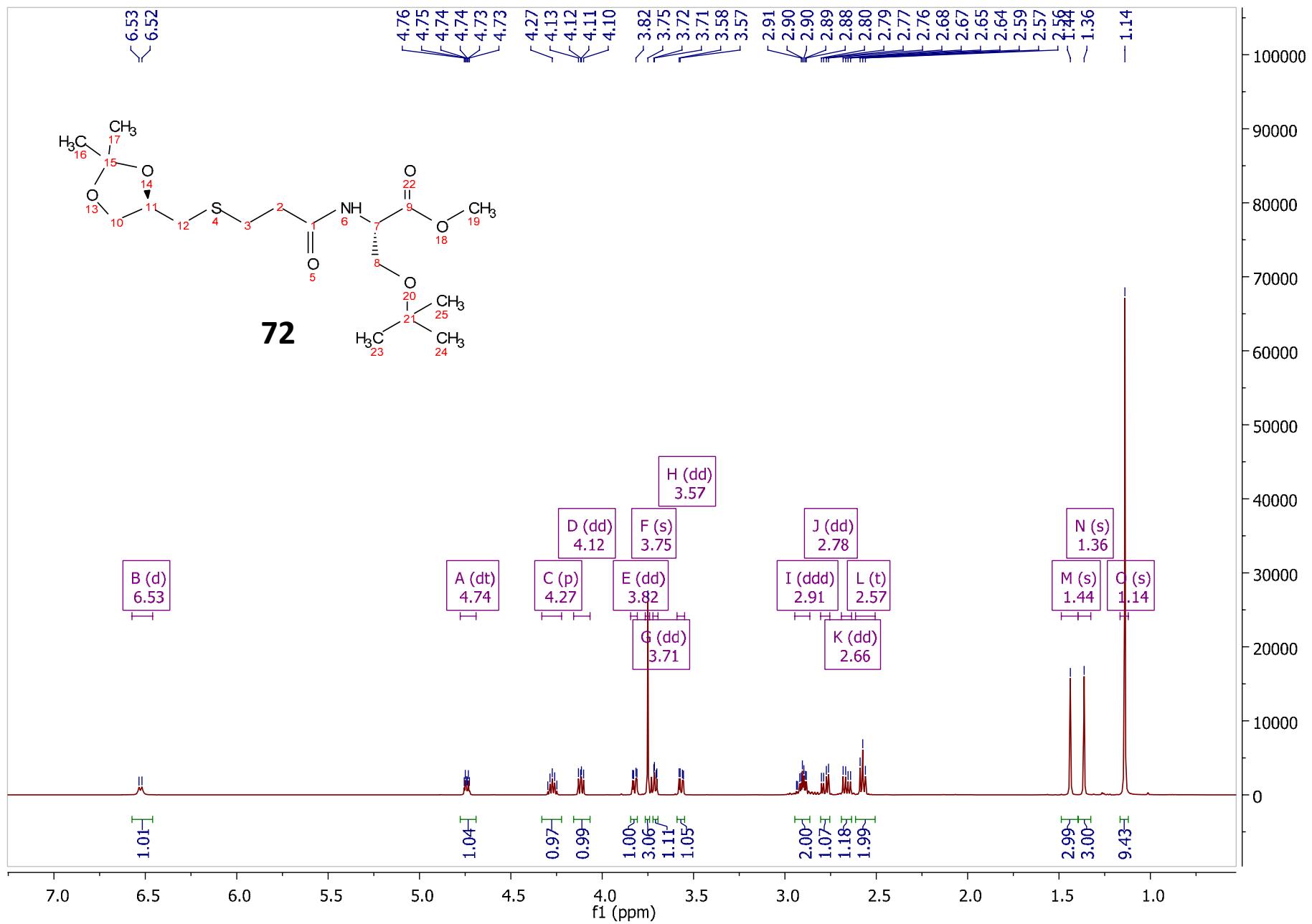
S254

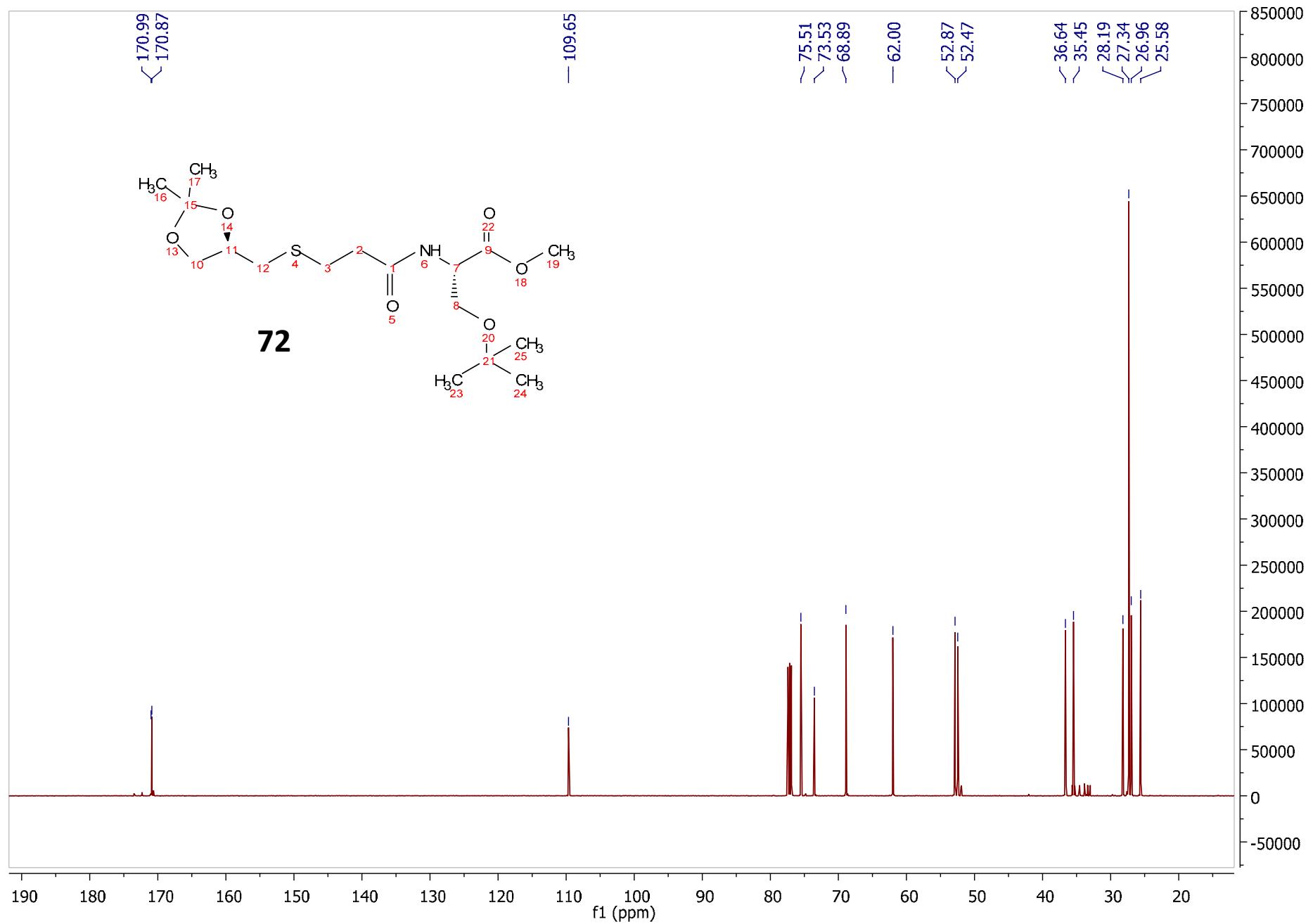


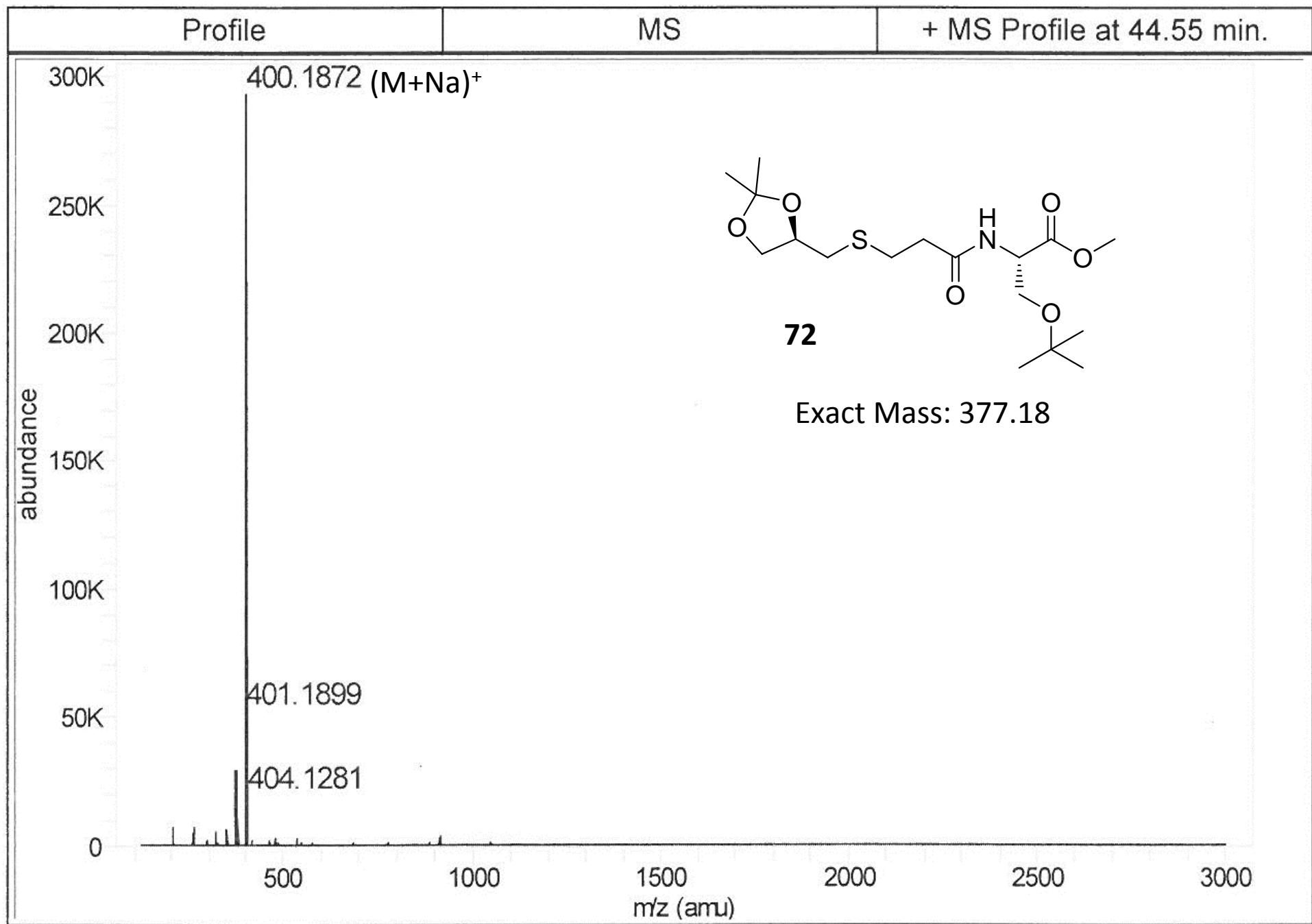


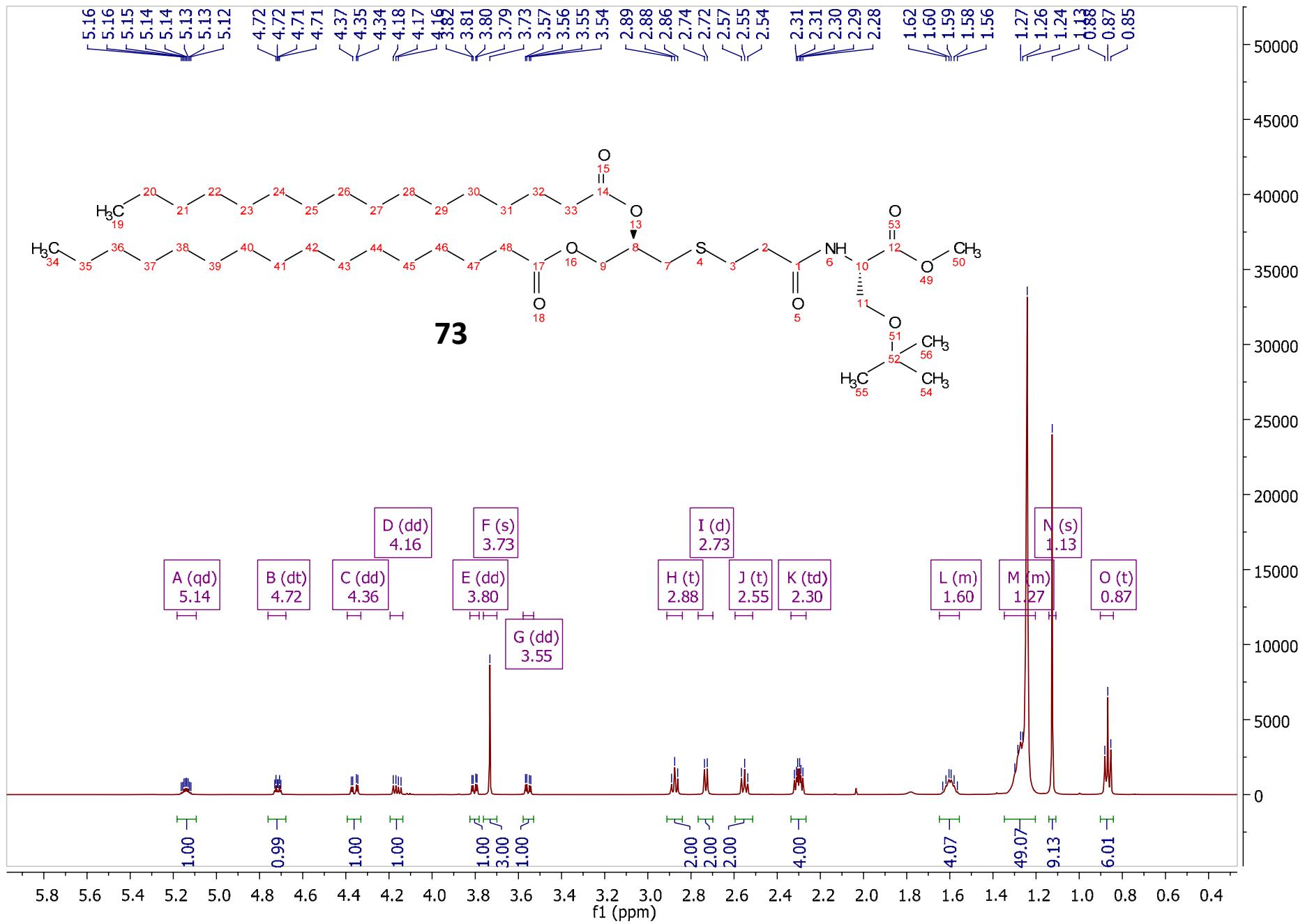
¹H Spectrum

S256



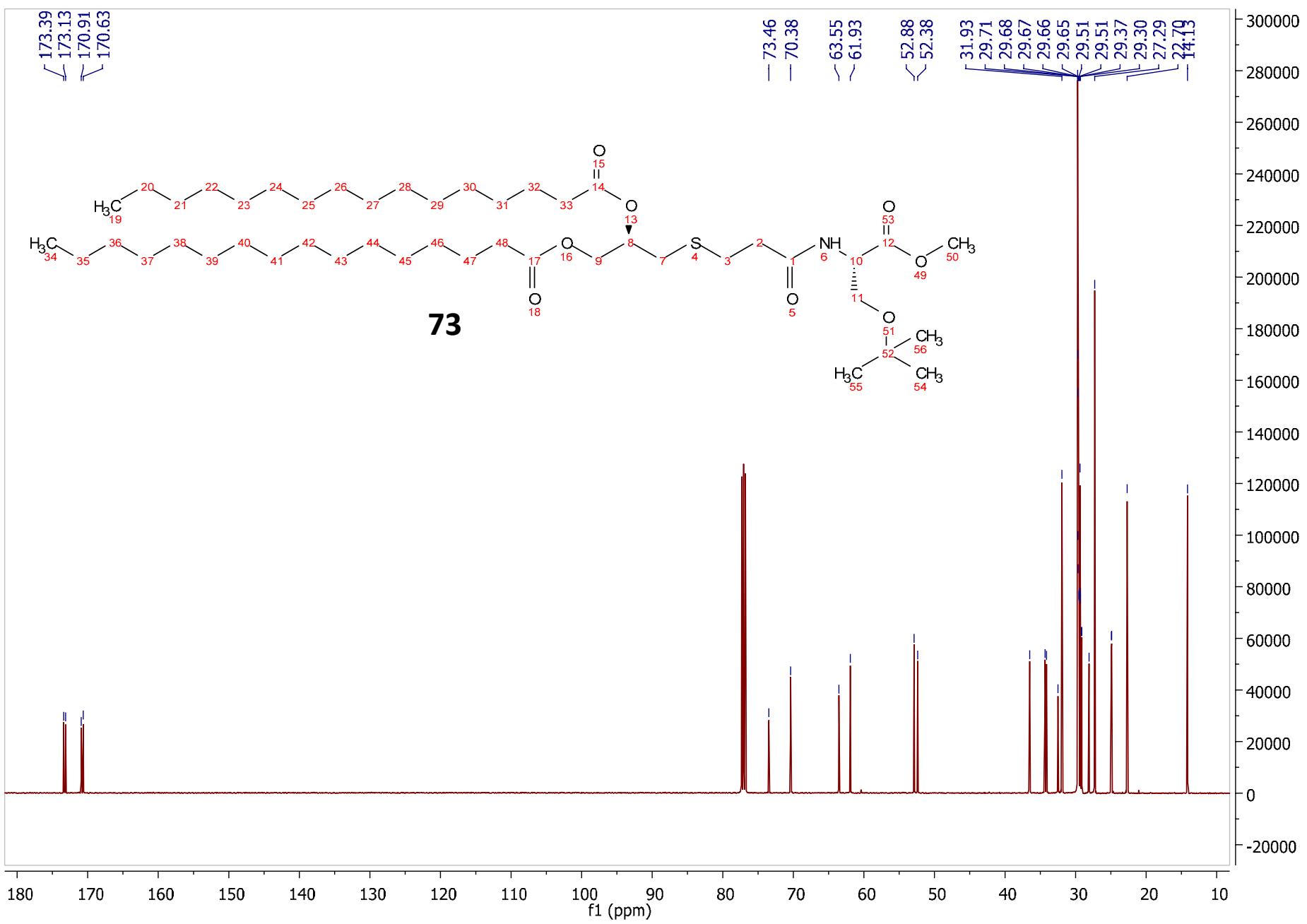


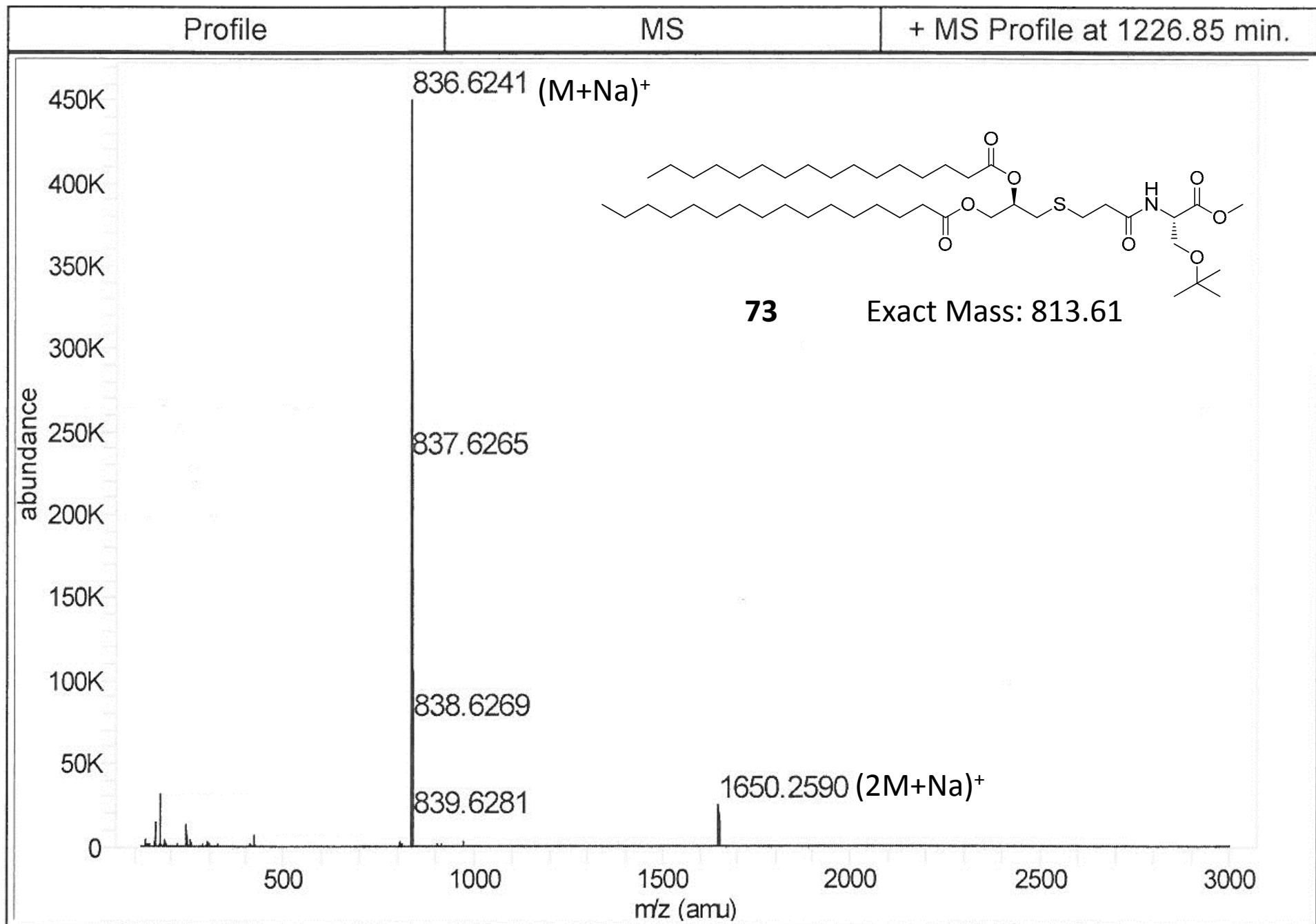


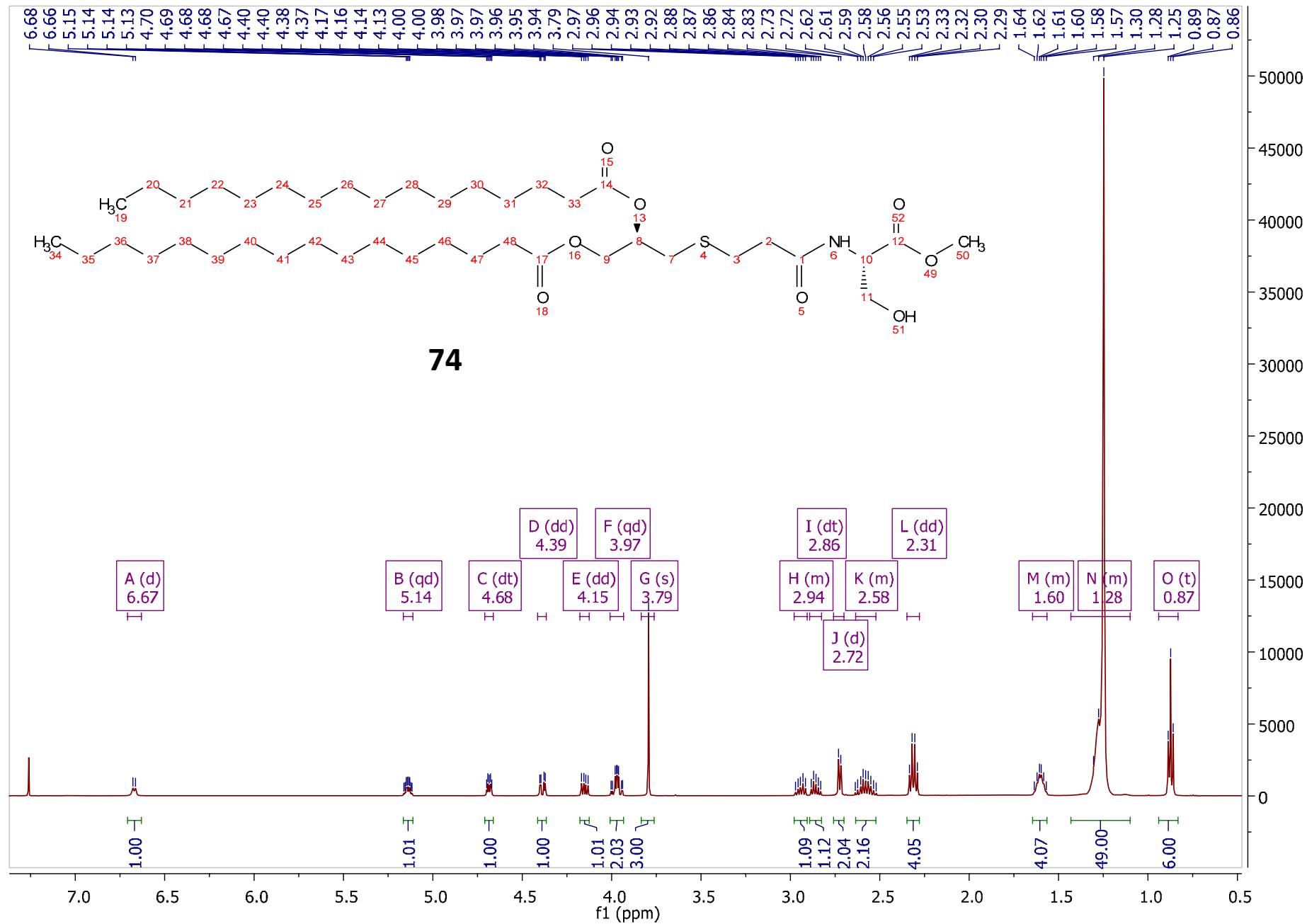


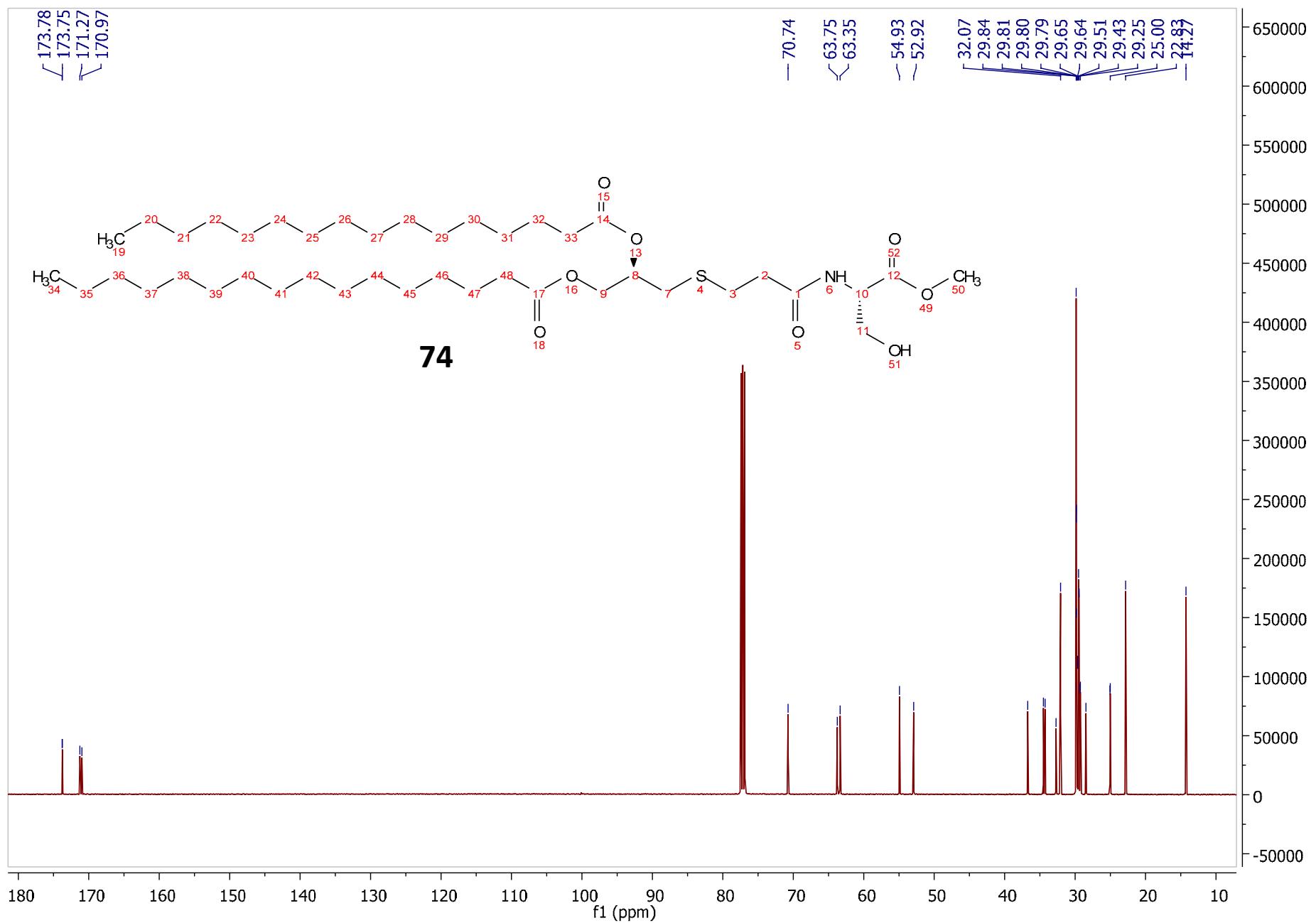
¹³C Spectrum

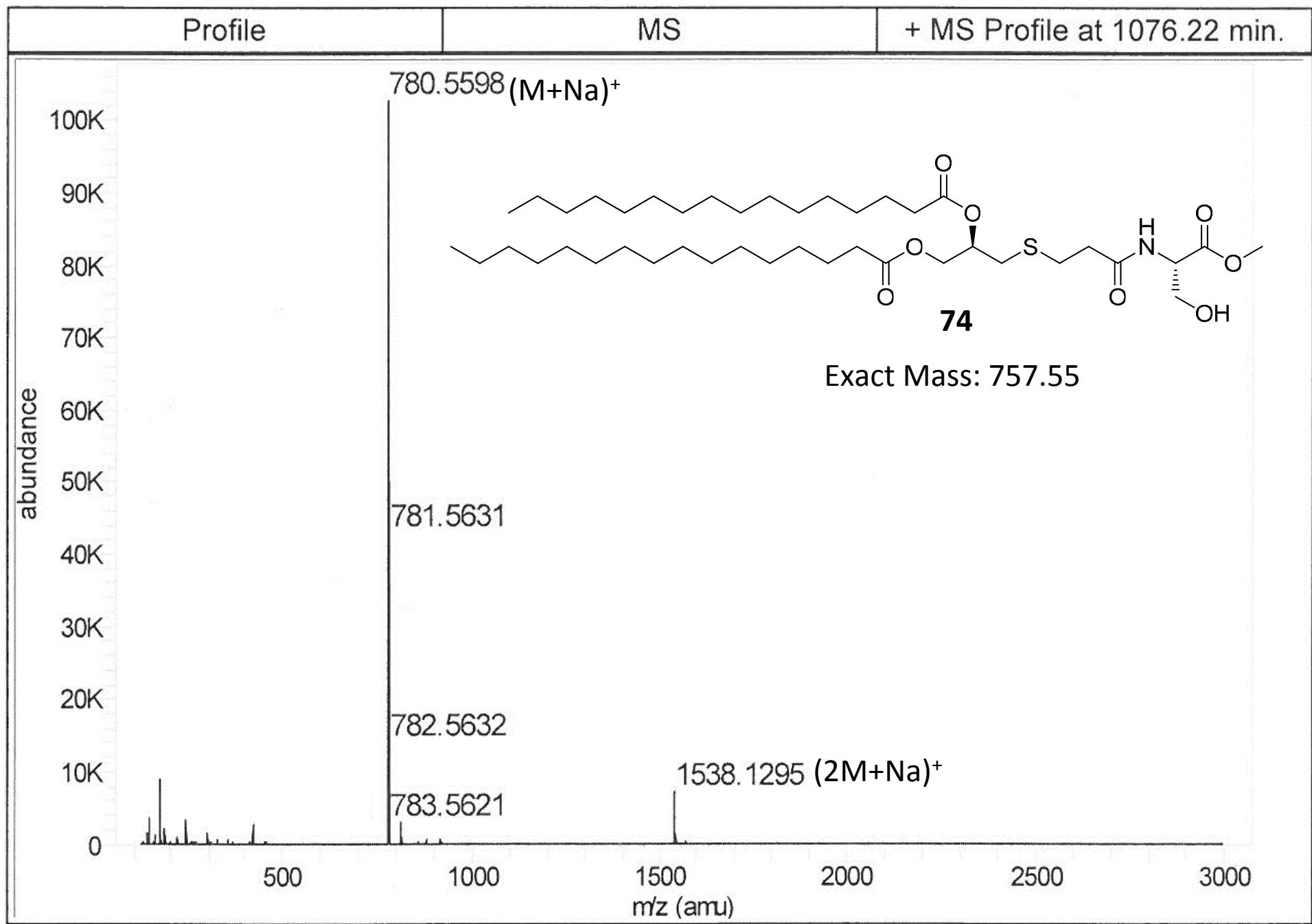
S260





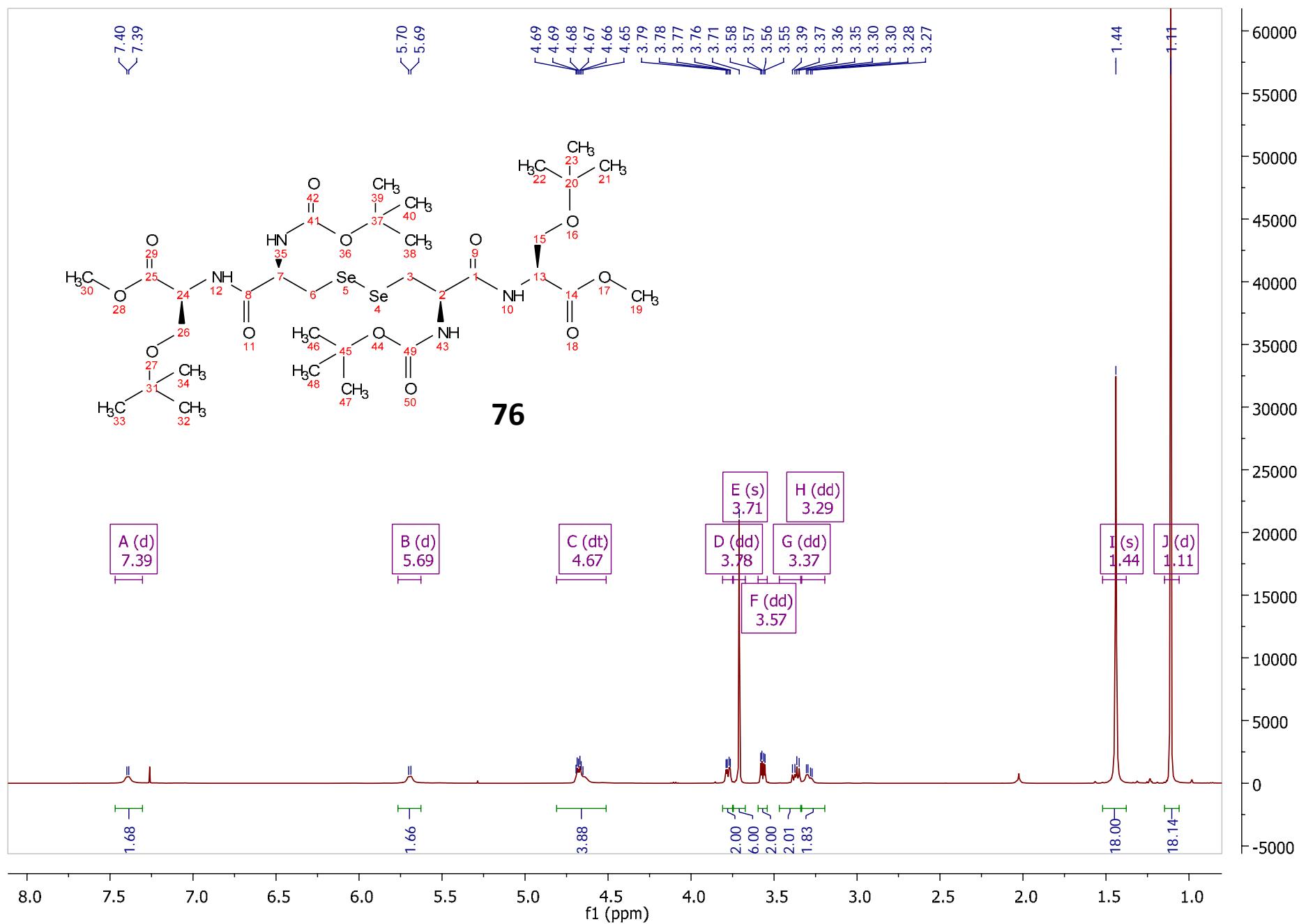






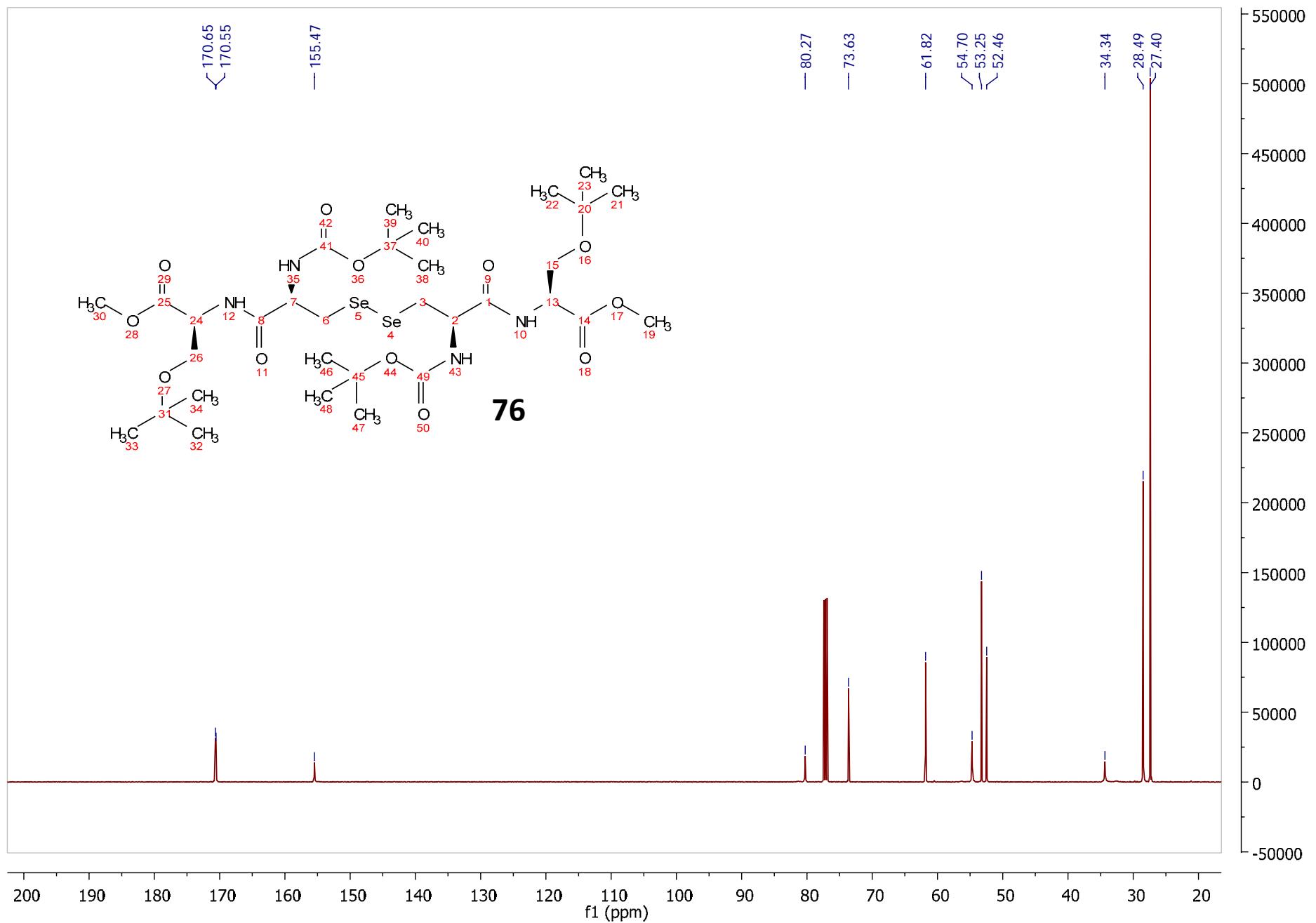
¹H Spectrum

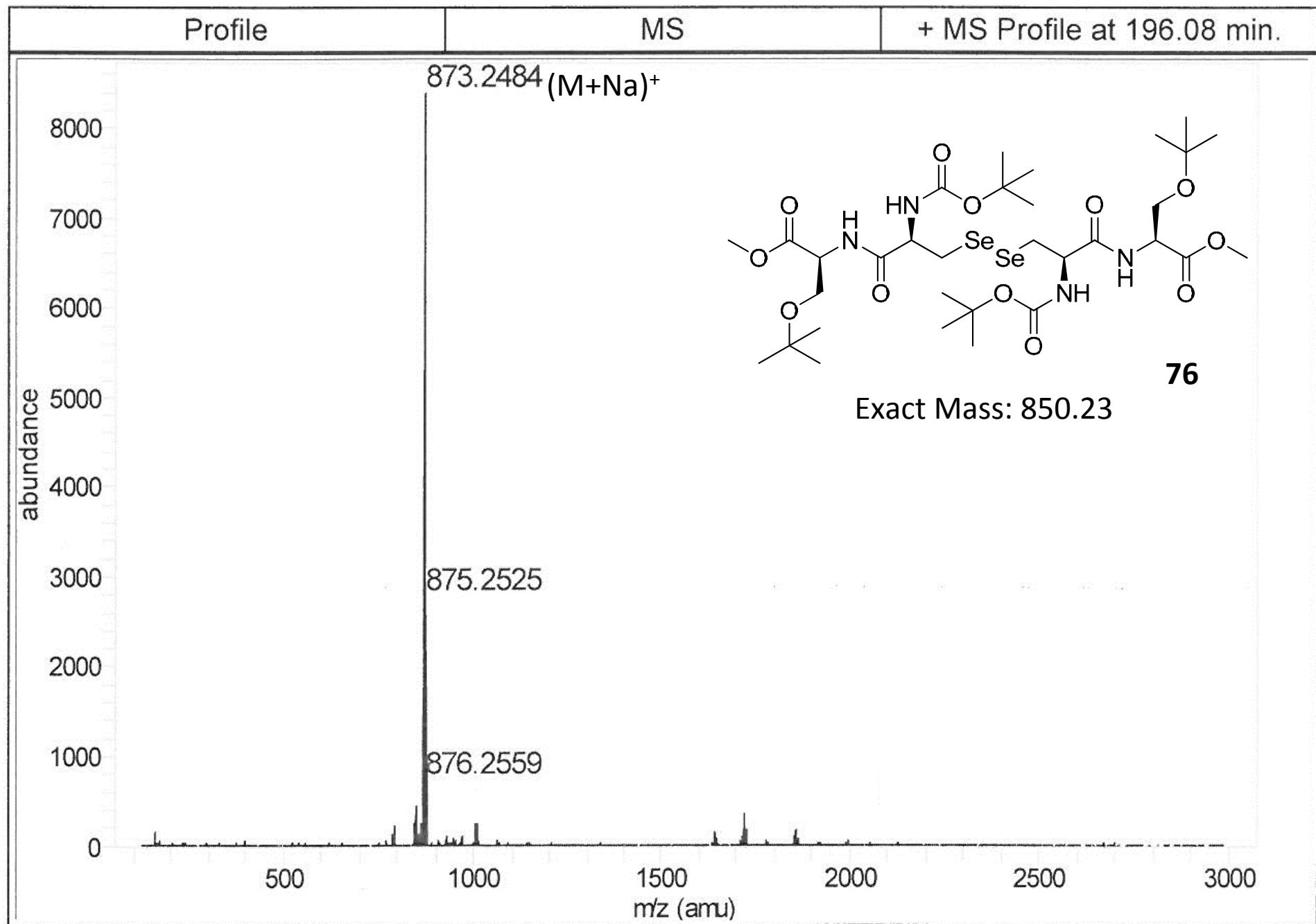
S265



¹³C Spectrum

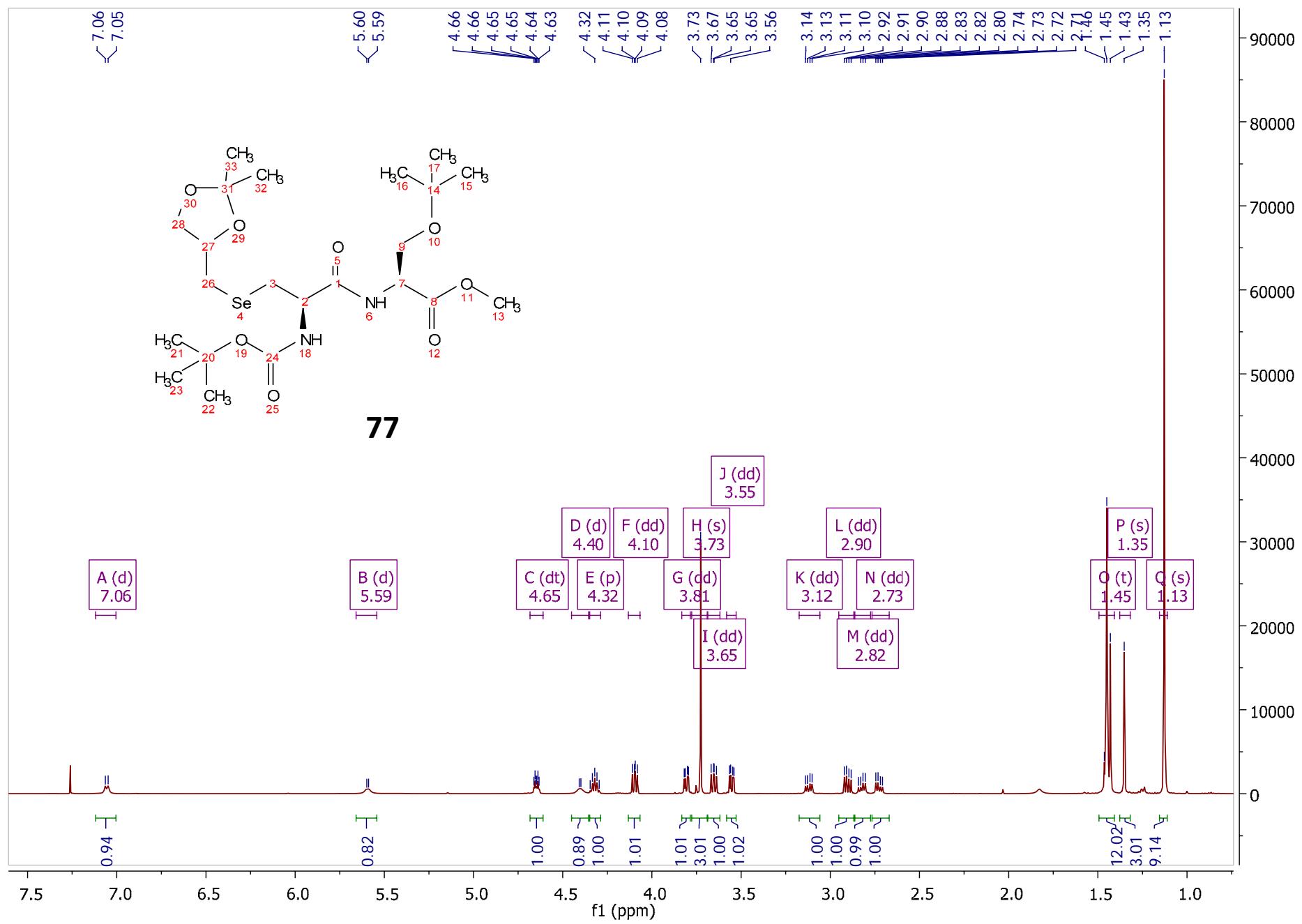
S266





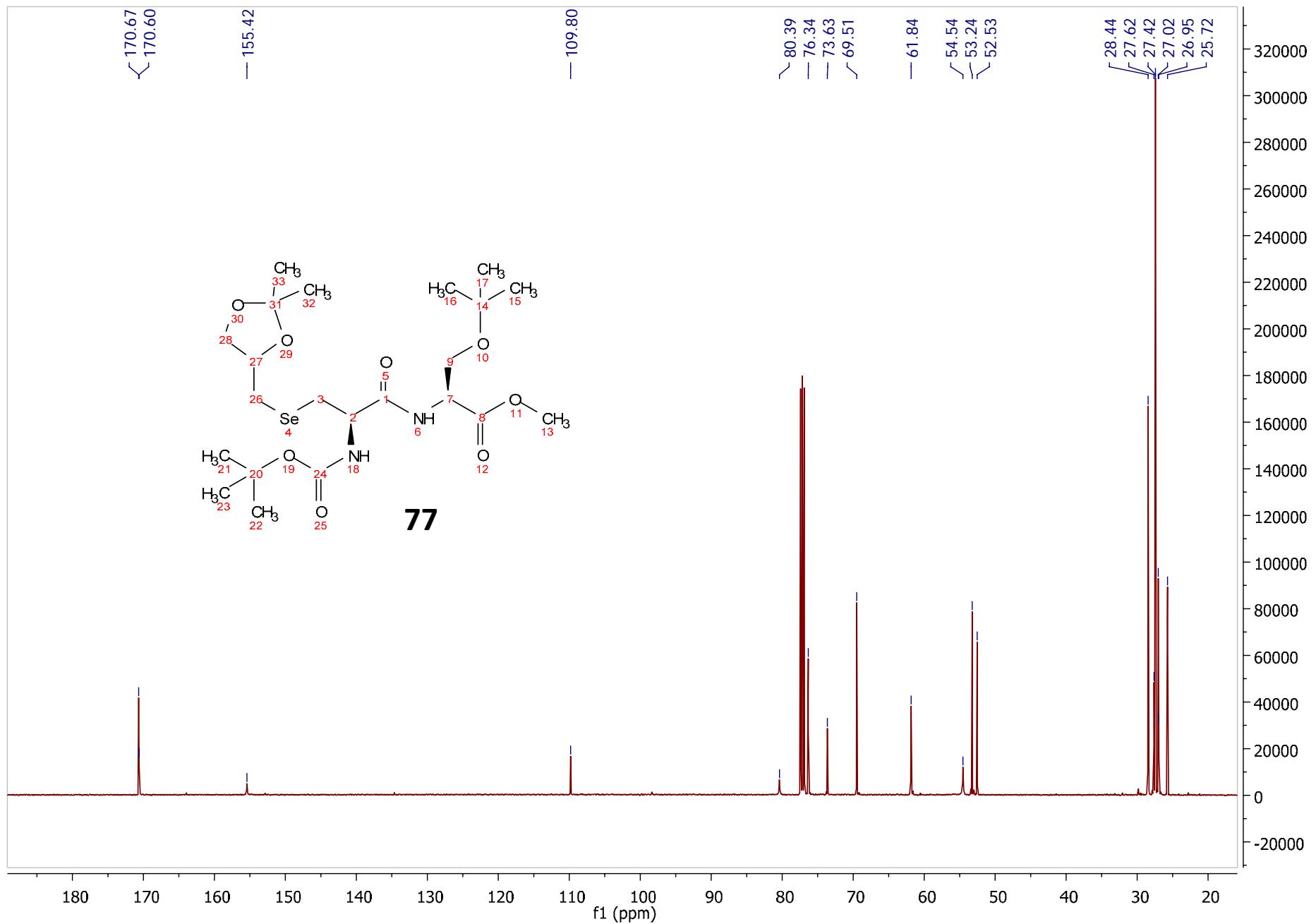
¹H Spectrum

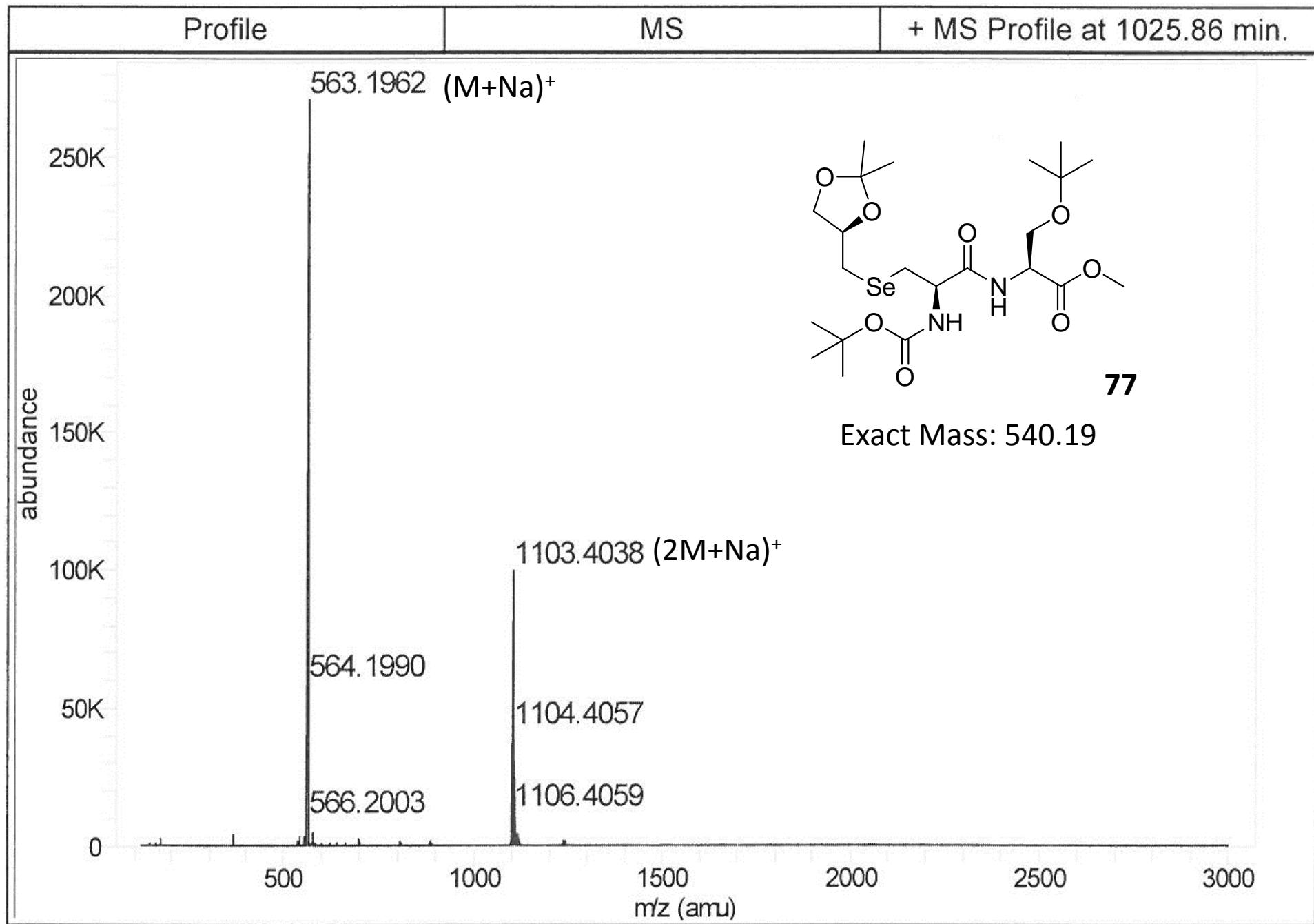
S268

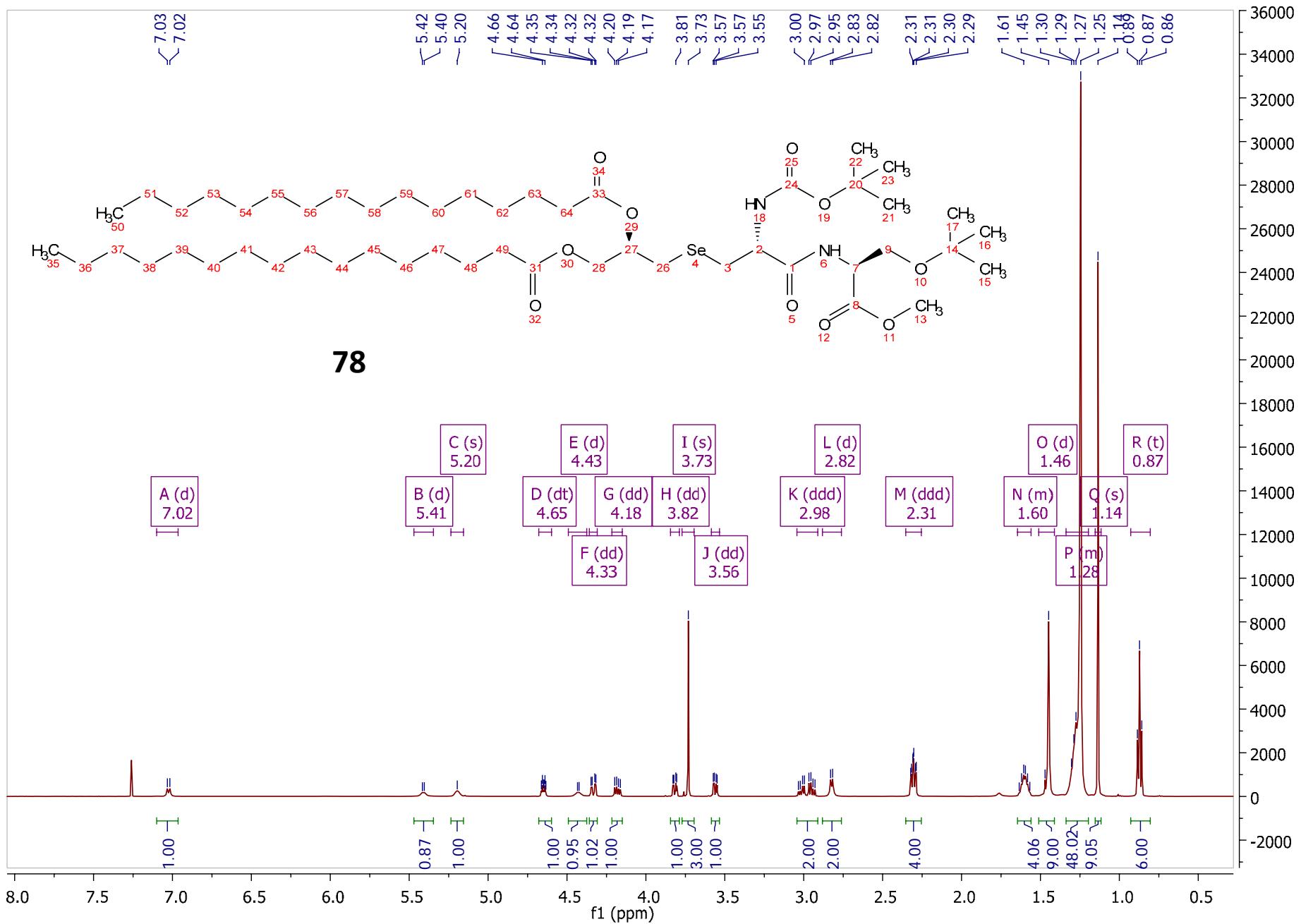


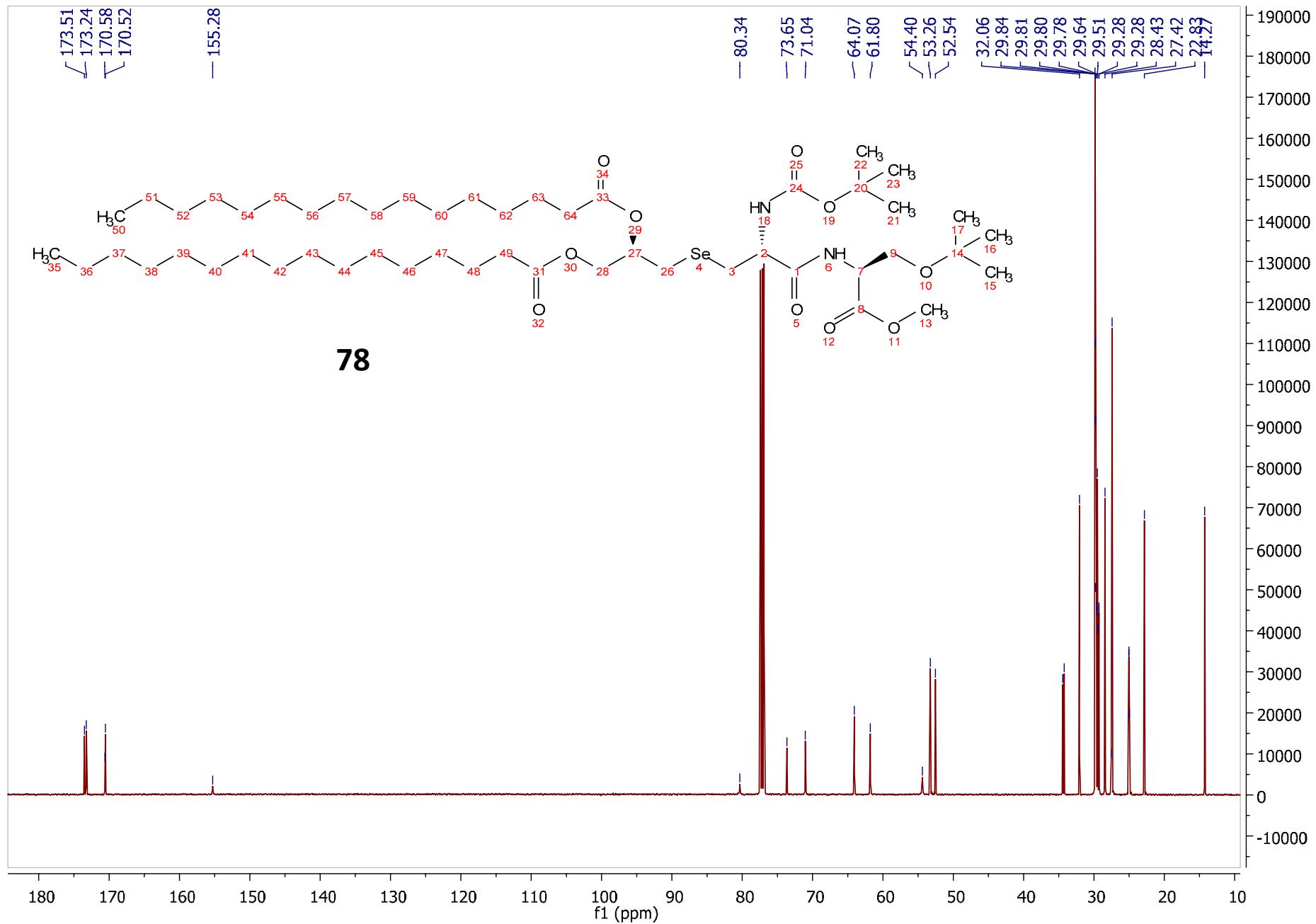
¹³C Spectrum

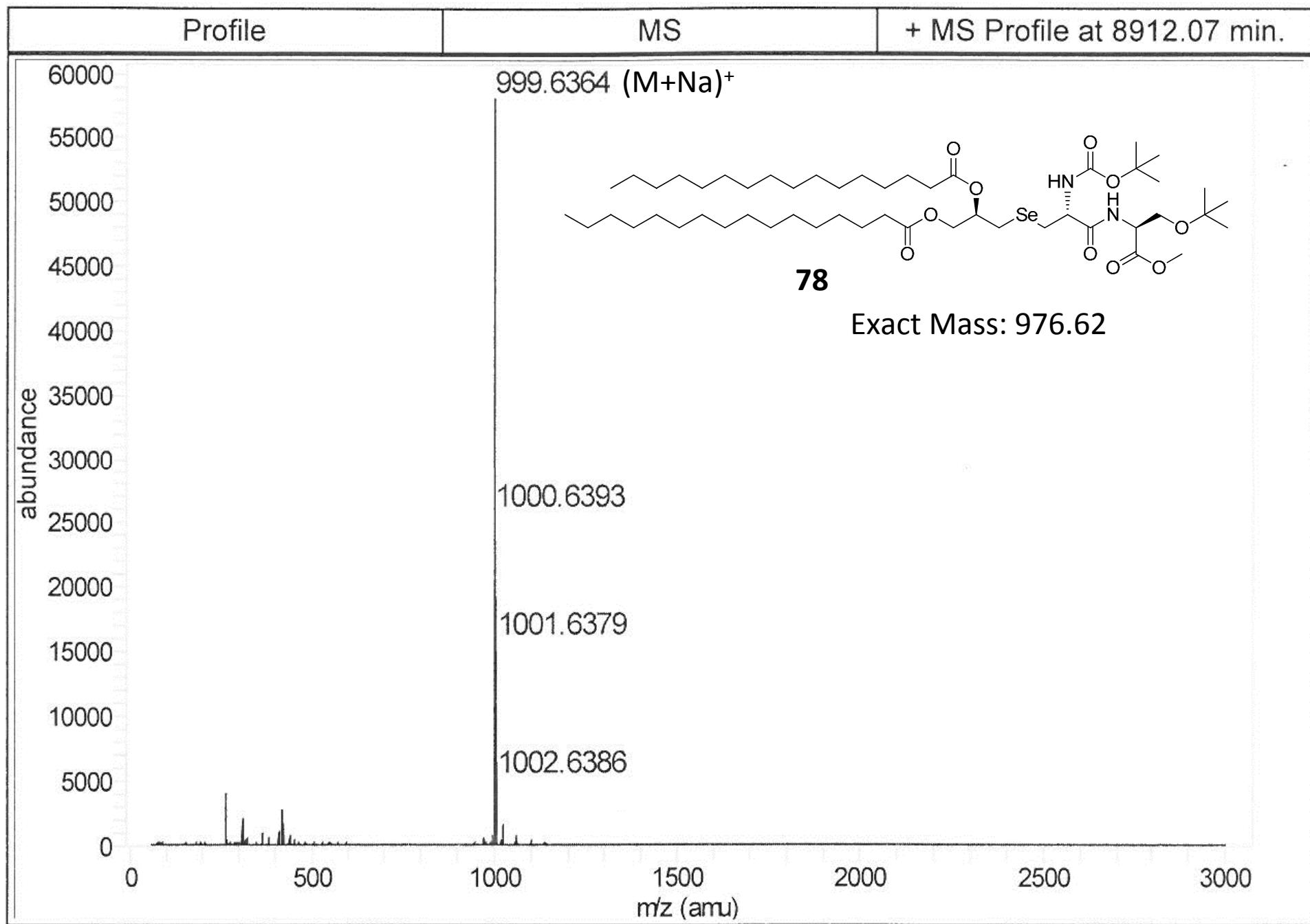
S269





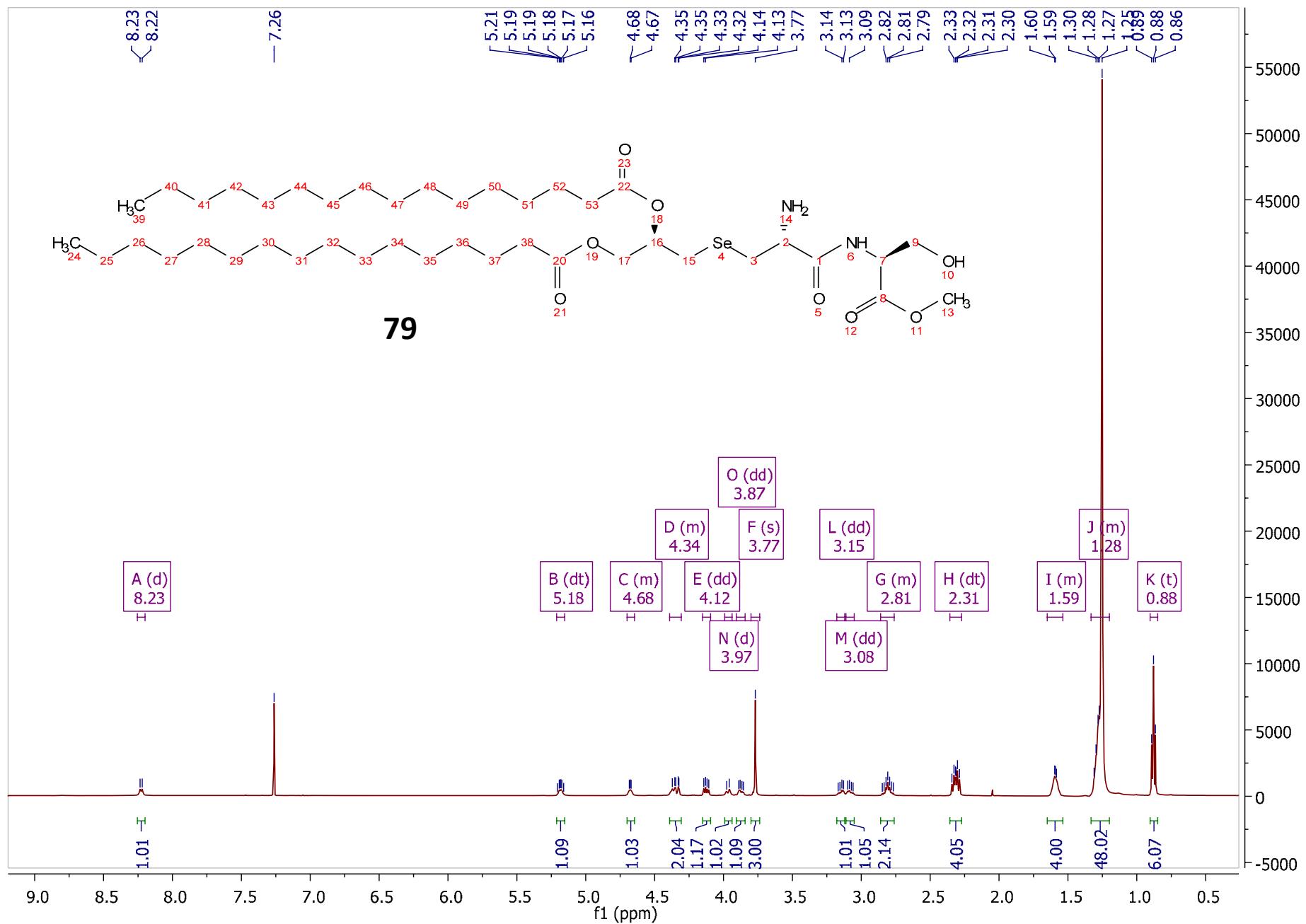






¹H Spectrum

S274



¹³C Spectrum

S275

