Supporting Information

Productive Exchange of Thiols and Thioesters to Form Dynamic Polythioester-Based Polymers

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Table of contents

Figures

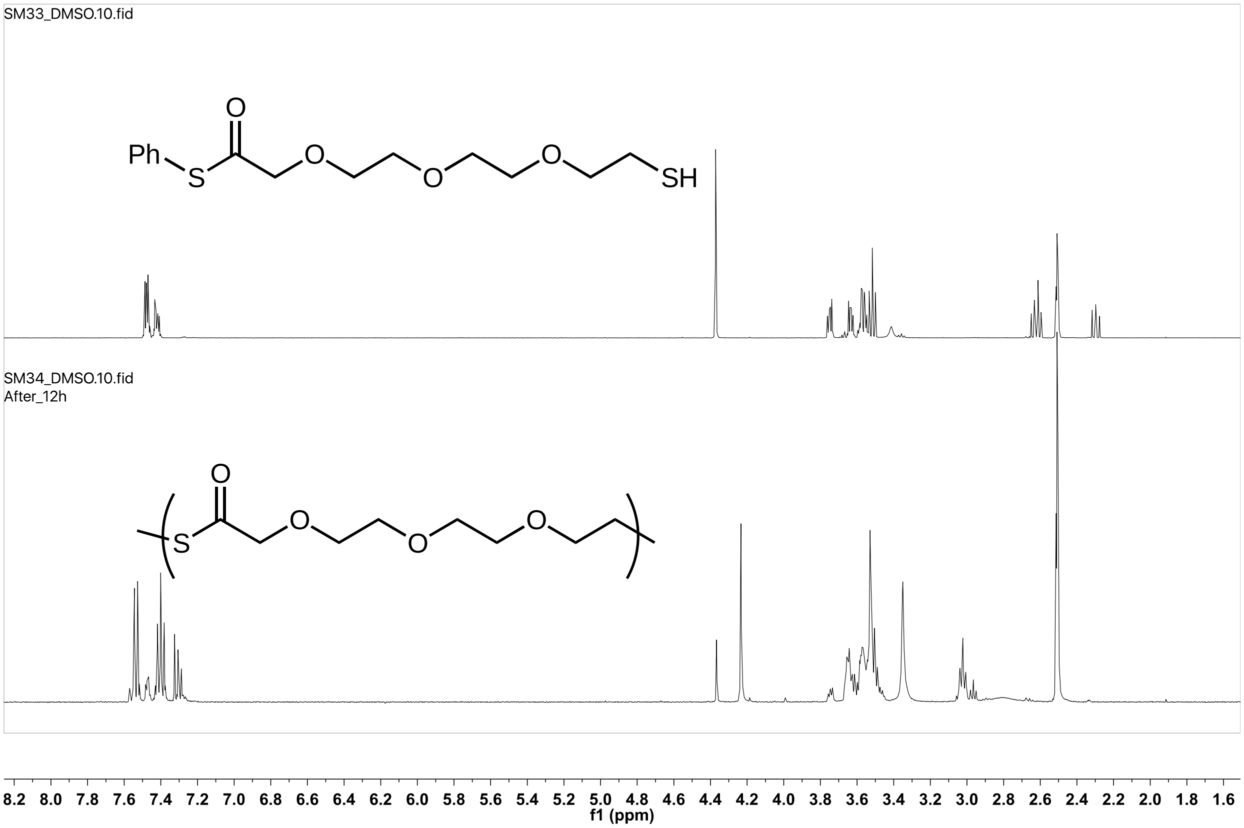


Figure S1. The ^{1}H NMR spectra of monomer **1a** and its polymer in D^6-DMSO. Reaction conditions: 1.0 mol/L, 10 mol% of TEA, 2 h.

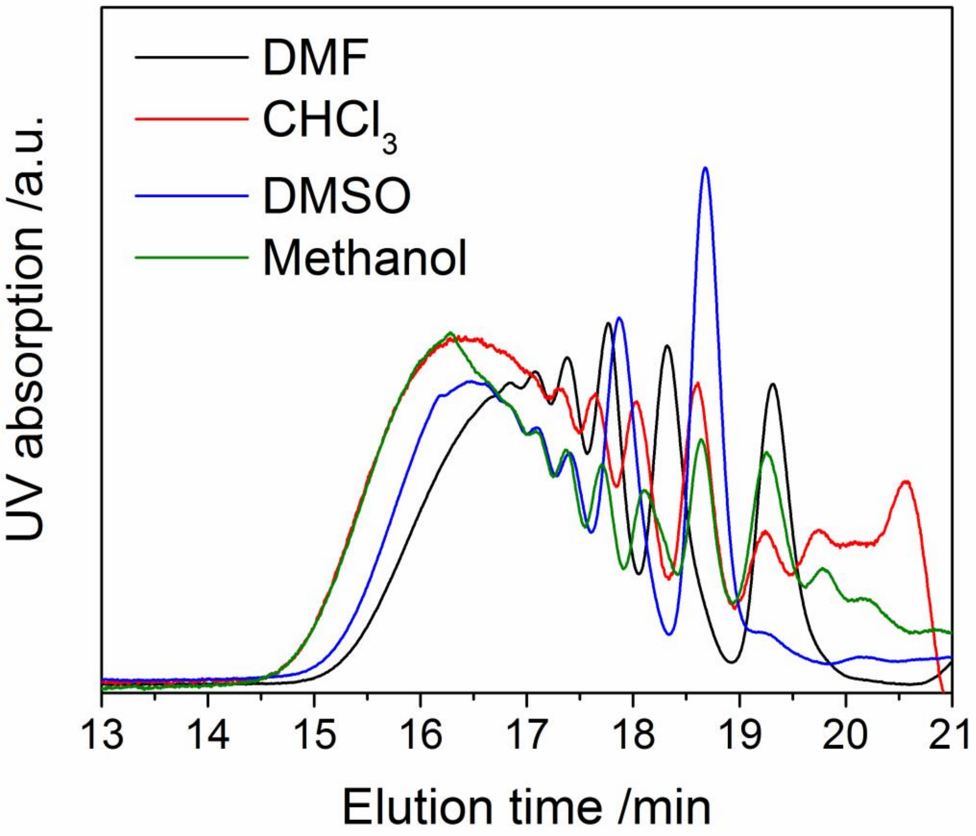


Figure S2. The GPC profiles of polymerizations in various solvents from monomer **1a**. Reaction conditions: 1.0 mol/L in chloroform, DMF, DMSO and methanol, 10 mol% of TEA, 2 h, ambient.

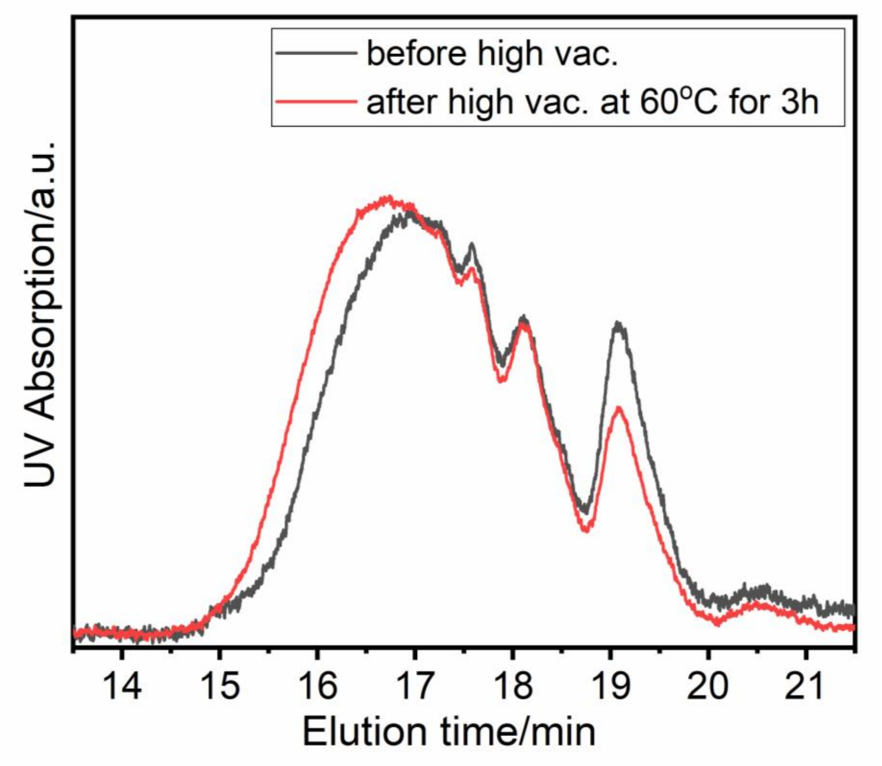


Figure S3. GPC overlay obtained for the polymerization of **1a** applying high vacuum to remove the thiophenol released during polymerization: before applying vacuum (back) and after applying vaccum at 60°C for 3 hrs. General reaction conditions: monomer **1a** (1.0 equiv) and PMDETA (10 mol%) in DMSO (1.0 M), at ambient (~25ºC) for 2 hrs.

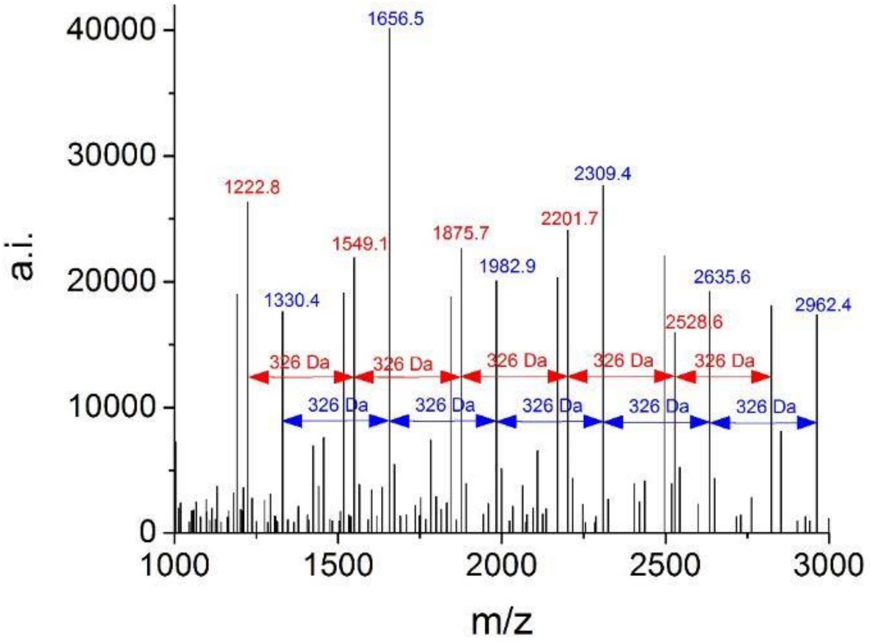


Figure S4. The MALDI-TOF spectra of poly **2d**, poly(N-Fmoc-Cys-SPh), with a m/z spacing series of 326 Da. Reaction conditions: 0.3 mol/L in dry DMSO, 10 mol% of TEA, 2 h, overnight.

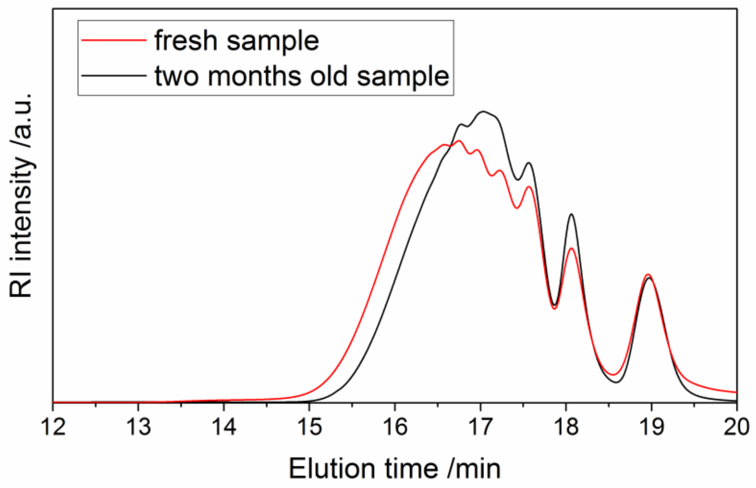
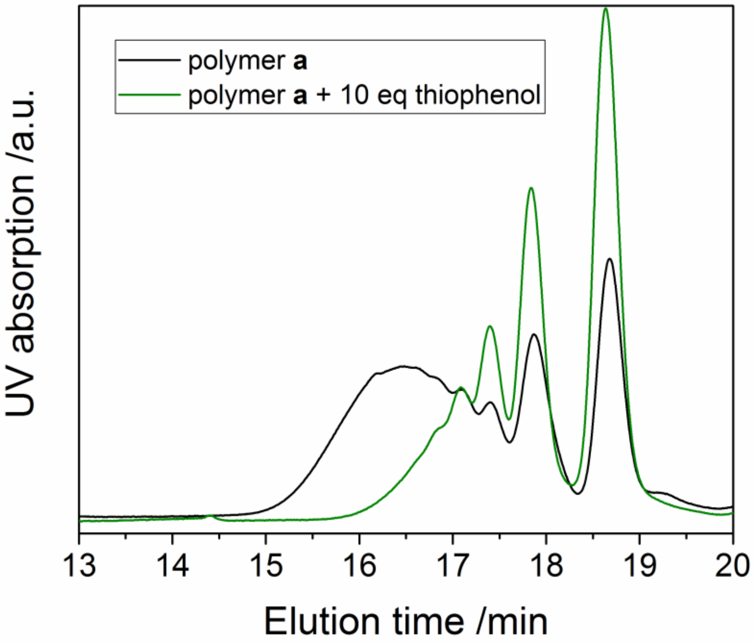


Figure S5. The GPC profiles of both fresh poly **2d**, poly(N-Fmoc-Cys-SPh) and its two months old sample. Reaction conditions: 0.3 mol/L in dry DMSO, 10 mol% of TEA, 2 h, overnight. The two months old sample was stored in a 2 mL drum vial with GPC analysis concentration (10 mg/mL in dry DMSO) with closed cap.



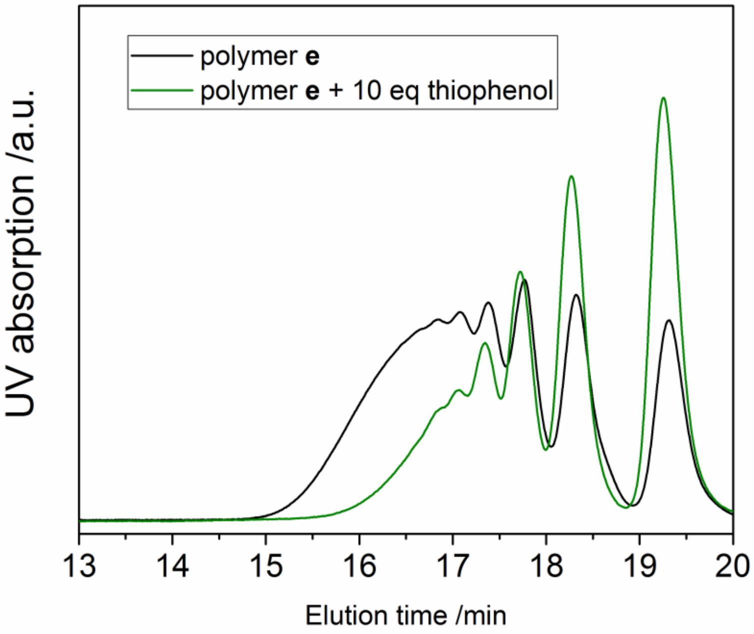


Figure S6. GPC profile of polythioesters from monomer **1a** and **1e** before and after equilibrating with 10 equivalent thiophenol in DMSO for overnight.

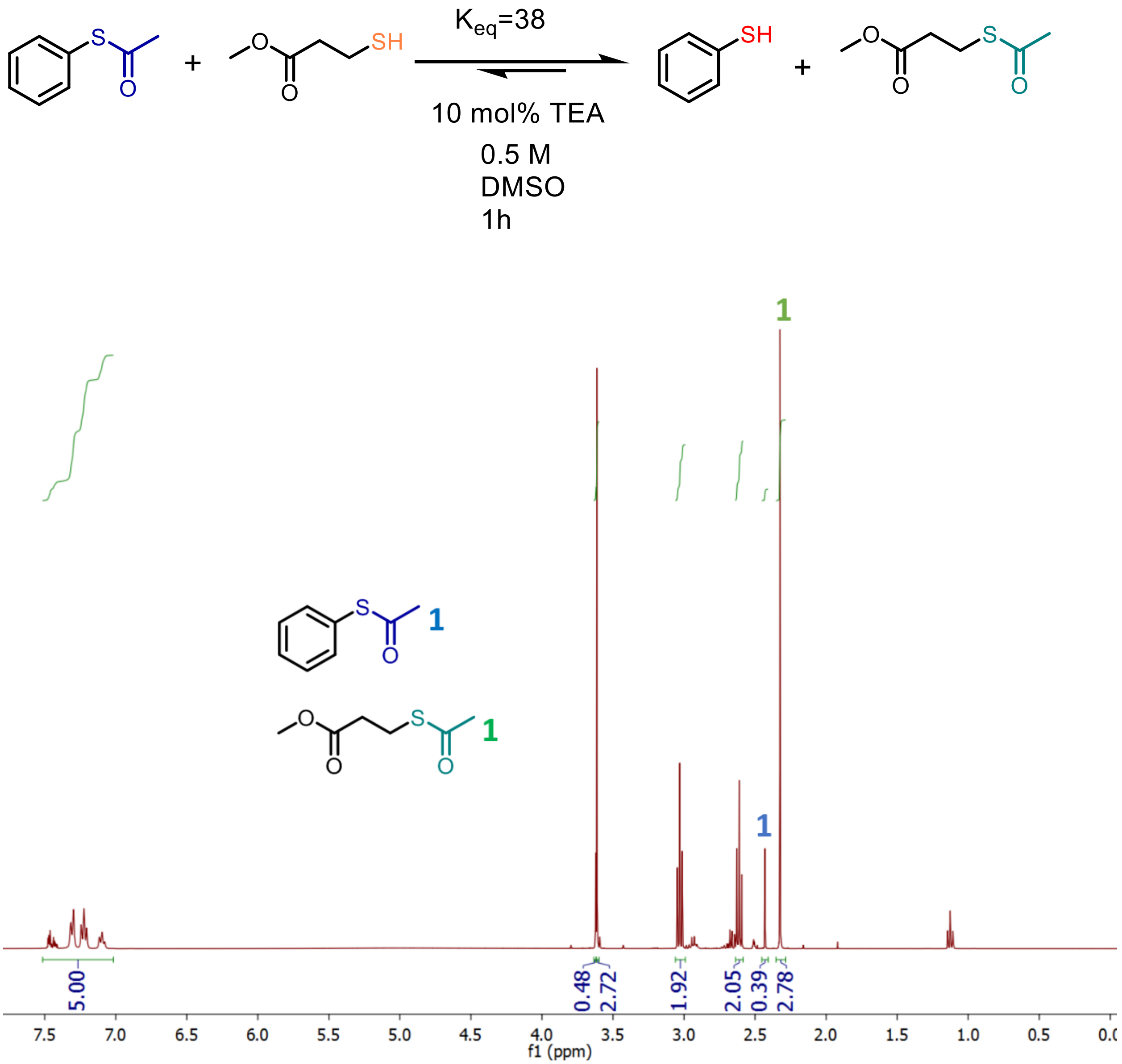


Figure S7. Equilibrium reaction scheme and ^{1}H NMR spectrum starting with equal molar S-phenol thioacetate and methyl mercaptopropionate (0.5 mol/L) in DMSO. The equilibrium constant and reaction conversion were calculated from the concentrations of thiophenol, S-methyl propionate thioacetate, S-phenol thioacetate and methyl mercaptopropionate, determined by ^{1}H NMR in D$_6$-DMSO.

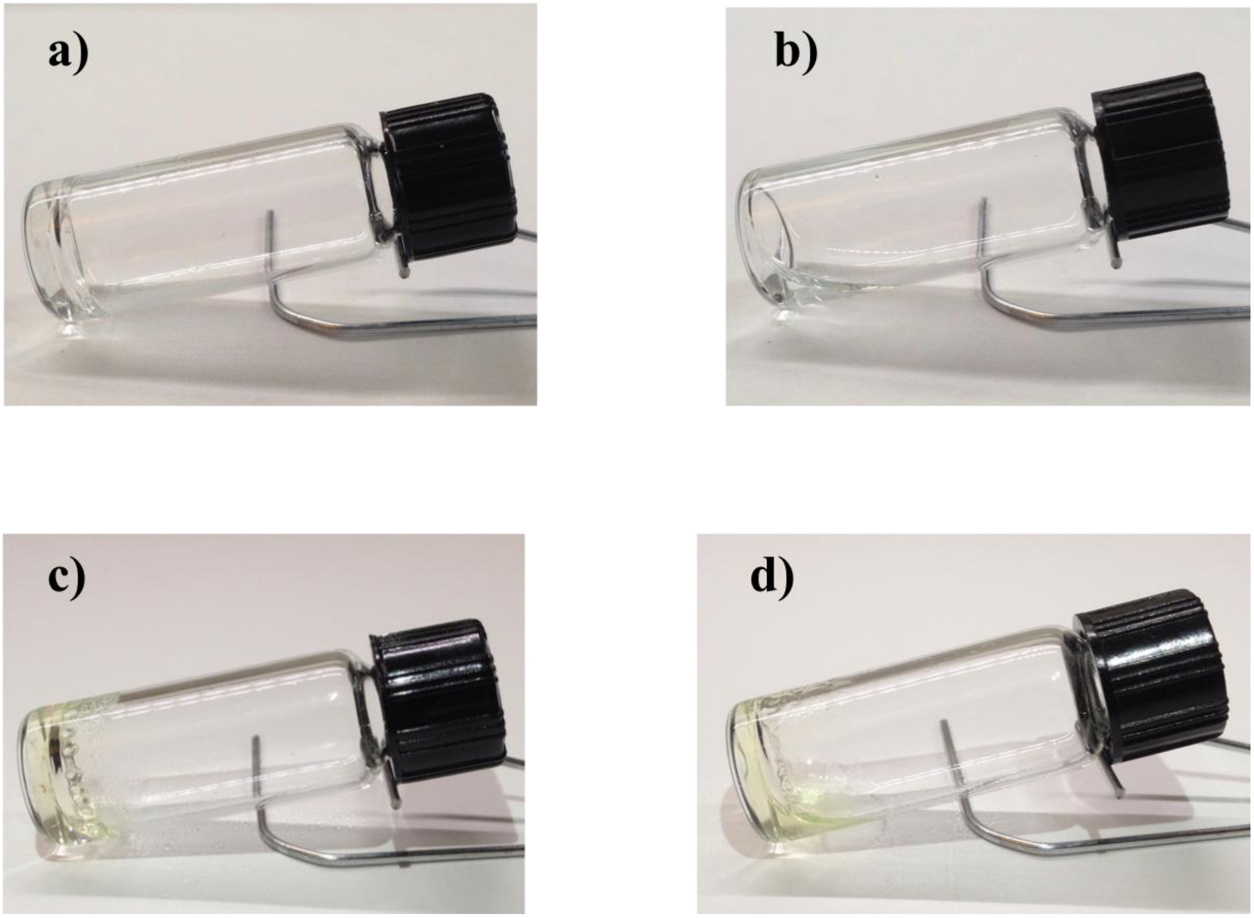


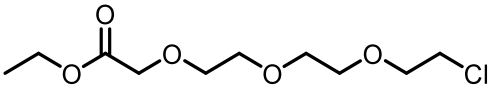
Figure S8. Control experiments for the formation of a dynamic hydrogel via transthioesterification reactions **a)** in neutral aqueous media, **b)** in acetate buffer at pH = 4, **c)** hydrogel after the treatment with excess thiol (linear PEG-thiol 800, 10 equiv.) dissolved in acetate buffer (25 μL) at pH = 4 for 12 hr. **d)** degradation of hydrogel after the treatment with excess thiol (linear PEG-thiol 800, 10 equiv.) dissolved in neutral aqueous media (25 μL) for 12 hr. Reaction conditions: monomer **3a** (1.0 equiv, 0.5 μmol), PEG-thiol 10’000 (2.0 equiv, 1.0 μmol), in 75 μL of aqueous media (20 wt% solid content), at ambient (~25^{o}C) for 12 hr.

Experimental details

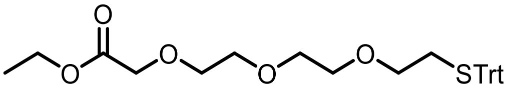
Materials

Thiophenol, methyl thioglycolate, methyl thiomercaptopropionate, thioglycolic acid, 3-mercaptopropionic acid, pentaerythritol tetrakis(3-mercaptopropionate) (PETMP), triphenylmethyl chloride, hexanedioyl dichloride, dodecanedioyl dichloride, 4-dimethylaminopyridine (DMAP), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), 4-pentenoyl chloride, triethylsilane (TES), N,N-diisopropylethylamine (DIPEA), N,N,N',N'',N''-pentamethyldiethylenetriamine (PMDETA), triethylamine (TEA), and poly(ethylene glycol) methyl ether thiol (PEG-thiol, average Mn 800) were purchased from Sigma Aldrich. S-phenyl thioacetate was purchased from Alfa Aesar. Trifluoroacetic acid (TFA) was purchased from Protein Technologies Inc. 2,2-Dimethoxy-2-phenyl acetophenone (DMPA) was purchased from Ciba. 4-Arm polyethylene glycol 10'000 tetrathiol was purchased from JenKem Technology. Glycol di-mercaptopropionate (GDMP) was purchased from Wako. N-Fmoc-Cys(Trt)-OH was purchased from Chem-Impex Int'l. Inc. All chemicals and solvents are used as received.

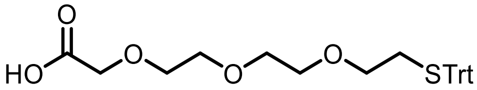
Monomer synthesis procedures



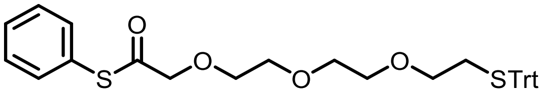
Ethyl-11-chloro-3,6,9-trioxaundecanoate (**1**). Sodium hydride (60% in mineral oil) (2.9 g, 71.17 mmol) was added portion-wise to a solution of 2-[2-chloroethoxy) ethoxy]ethanol (10 g, 59.31 mmol) dissolved in anhydrous THF (100 mL) at 0 °C under N_2 atmosphere. After stirring 30 min at room temperature, ethyl bromoacetate (12.87 g, 77.10 mmol) was added drop-wise at 0 °C. The reaction mixture was then stirred at room temperature overnight. Quenched by the addition of water and THF was removed by under reduced pressure. The residue obtained was diluted with ethyl acetate (250 mL) and washed with (100 mL), brine (50 mL) and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography using 30% ethyl acetate in hexane as eluent to afford **1** (9.1 g, 60%) as colorless liquid. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.21 (q, J = 7.1 Hz, 2H), 4.14 (s, 2H), 3.78 – 3.59 (m, 12H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5, 71.4, 70.9, 70.7, 70.6, 70.6, 68.7, 60.8, 42.7, 14.2



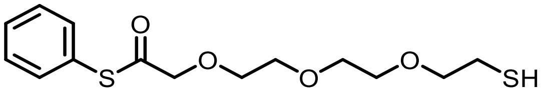
Ethyl-*S*-triphenylmethyl-11-mercapto-3,6,9-trioxaundecanoate (**2**). Sodium hydride (60% in mineral oil) (1.32 g, 32.97 mmol) was added portion-wise to a solution of triphenylmethanethiol (7.0 g, 27.48 mmol) dissolved in anhydrous DMF (100 mL) at 0 °C under N_2 atmosphere. After stirring 30 min at room temperature, **1** (7.60 g, 27.48 mmol) was added drop-wise over 15 min at 0 °C. The reaction mixture was then stirred at room temperature overnight. Quenched by the addition of water and DMF was removed by under reduced pressure. The residue obtained was dissolved in ethyl acetate (250 mL) and washed with water (100 mL), brine (50 mL) and then dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography using 20% ethyl acetate in hexane as eluent to afford the product **2** (11.0 g, 82 %) as colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 – 7.39 (m, 6H), 7.30-7.25 (m, 6H), 7.23 – 7.18 (m, 3H), 4.20 (q, 2H), 4.12 (s, 2H), 3.73 – 3.69 (m, 2H), 3.67 – 3.64 (m, 2H), 3.58 – 3.56 (m, 2H), 3.48 – 3.43 (m, 2H), 3.29 (t, 2H), 2.43 (t, 2H), 1.27 (t, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 170.5, 144.8, 129.6, 127.9, 126.7, 70.9, 70.6, 70.5, 70.1, 69.6, 68.7, 66.6. 60.8, 31.6, 14.2.



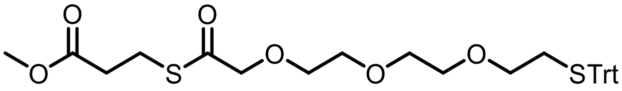
***S*-triphenylmethyl-11-mercapto-3,6,9-trioxaundecanoic acid** (**3**)**.** To a solution of **2** (5.0 g, 10.11 mmol) dissolved in 30 mL of ethanol was added 4 mL of 10 M NaOH (1.62 g, 40.44 mmol) , and the mixture was stirred for 3 h at room temperature. Ethanol was evaporated and the residue was dissolved in 20 mL of water. Acidified to a pH of 2 by the addition of 1N HCl and extracted with EtOAc (3 × 50 mL). Combined EtOAc extracts were dried over Na_2SO_4, filtered and evaporated to give **3** (4.5.0 g, 96 %) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 – 7.43 (m, 6H), 7.33-7.28 (m, 6H), 7.25 – 7.21 (m, 3H), 4.16 (s, 2H), 3.76 – 3.74 (m, 2H), 3.70 – 3.67 (m, 2H), 3.65 – 3.63 (m, 2H), 3.50 – 3.47 (m, 2H), 3.32 (t, 2H), 2.46 (t, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 172.4, 144.8, 129.6, 127.9, 126.7, 71.5, 70.6, 70.1, 69.9, 69.7, 68.8, 66.6, 31.6.



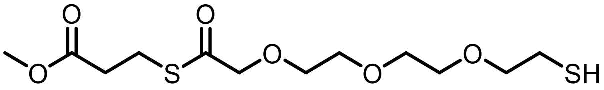
***S*-phenyl-*S*-triphenylmethyl-11-mercapto-3,6,9-trioxaundecanethioate (4).** Triphenylphosphine (562.1mg, 2.14 mmol) was added to a mixture of **3** (1.0 g, 2.14 mmol) and diphenyl disulfide (468.0 mg, 2.14 mmol) dissolved in 30 mL of acetonitrile. The mixture was refluxed for 16 h under N2 atmosphere. Cooled to room temperature and the solvent was evaporated completely under reduced pressure. The crude product was purified by silica-gel column chromatography using 40 % EtOAc in hexane as eluent o give **4** (1.05g, 88 %) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 – 7.43 (m, 10H), 7.33-7.28 (m, 7H), 7.25 – 7.20 (m, 3H), 4.32 (s, 2H), 3.85 – 3.83 (m, 2H), 3.76 – 3.74 (m, 2H), 3.66 – 3.64 (m, 2H), 3.51 – 3.49 (m, 2H), 3.34 (t, 2H), 2.46 (t, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 198.5, 144.8, 34.8, 129.6, 129.5, 129.3, 127.9, 127.9, 127.9, 126.7, 76.4, 71.9, 70.7, 70.2, 69.7, 66.6, 31.6.



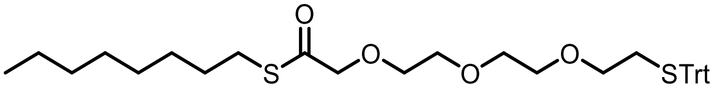
***S*-phenyl-11-mercapto-3,6,9-trioxaundecanethioate** (**5** or **1a**). To a solution of **4** (480.0 mg, 0.89 mmol) dissolved in 5 mL of CH_2Cl_2 was added triethylsilane (0.715 mL, 4.48 mmol) and trifluoroacetic acid (343 mL, 4.48 mmol). The mixture was stirred overnight at room temperature. All the volatiles were evaporated *in vaccuo* and the residue was co-evaporated twice with toluene. The crude was purified using silica-gel column chromatography using 20% EtOAc in hexane as eluent to give **5** (180 mg, 64 %) as colorless viscous liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (m, 3H) 4.35 (s, 2H), 3.88 – 3.85 (m, 2H), 3.82 – 3.78 (m, 2H), 3.75 – 3.72 (m, 2H), 3.70 – 3.67 (m, 4H), 3.65 (t, 2H), 2.75- 2.70 (m, 2H), 1.61 (t, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 198.5, 134.8, 129.5, 129.3, 126.7, 76.3, 72.9, 72.9, 71.9, 70.7, 70.7, 70.6, 70.2, 24.2.



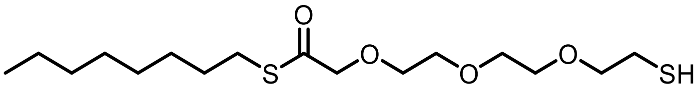
_S_-methyl mercaptopropionate-_S_-triphenylmethyl-11-mercapto-3,6,9-trioxaundecanethioate (6). To a 20 mL scintillation vial equipped with a magnetic stir bar was added 1.00 grams (2.15 mmol, 1.00 equiv) of **3** and this was diluted with 10.0 mLs (0.22 M) of reagent grade DCM. To this clear solution was added 13.0 mgs (0.11 mmol, 10.0 mol%, 0.10 equiv) of DMAP, followed by 263 μLs (285 mgs, 2.37 mmol, 1.10 equiv) of methyl 3-mercaptopropionate, and this was stirred at room temperature for ~5 minutes to form a clear solution. To this stirring solution was added 367 μLs (299 mgs, 2.37 mmol, 1.10 equiv) of diisopropylcarbodiimide (DIC) dropwise via syringe. After stirring for ~10 minutes a fine white precipitate was noted to have formed (likely diisopropylurea, DIU) and this suspension was allowed to stir at room temperature overnight. After this period the suspension was vacuum filtered, the filter cake was washed with additional small portions of reagent grade DCM (~10 mLs, 3X), and the combined organics were concentrated *in vacuo*. This crude residue was taken up in a small amount of reagent grade EtOAc (~20 mLs), resulting in the formation of additional precipitate, which was again vacuum filtered and washed with additional portions of EtOAc (~5 mLs, 3X). The combined organics were concentrated *in vacuo* and the resultant crude residue was directly submitted to column chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 30% EtOAc/hexanes) and concentration of fractions containing the desired product (R_f = 0.43, 40% EtOAc/hexanes) yielded 1.06 grams (87% yield) of the title compound as a viscous liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 – 7.39 (m, 6H), 7.30 – 7.25 (m, 6H), 7.22 – 7.18 (m, 3H), 4.18 (s, 2H), 3.73 – 3.70 (m, 2H), 3.69 (s, 3H), 3.68 – 3.65 (m, 2H), 3.59 – 3.57 (m, 2H), 3.46 – 3.44 (m, 2H), 3.30 (t, *J* = 6.93 Hz, 2H), 3.12 (t, *J* = 7.12 Hz, 2H), 2.62 (t, *J* = 7.06 Hz, 2H), 2.43 (t, *J* = 6.97 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 200.10, 174.56, 172.18, 144.93, 129.75, 128.01, 126.78, 76.40, 71.87, 70.74, 70.29, 69.77, 66.72, 52.03, 34.22, 31.75, 22.99.



***S*-methyl mercaptopropionate-11-mercapto-3,6,9-trioxaundecanethioate** (**7** or **1b**). To a solution of **6** (568 mg, 1.0 mmol) dissolved in 3.0 mL of CH_2Cl_2 was added triethylsilane (0.32 mL, 2.0 mmol) and trifluoroacetic acid (0.76 mL, 10.0 mmol). The mixture was stirred overnight at ambient. The crude was purified using silica-gel column chromatography using 10% EtOAc in hexane as eluent to give **7** (210 mg, 65 %) as colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.19 (s, 2H), 3.75 – 3.59 (m, 13H), 3.12 (t, 2H), 2.68 (q, 2H), 2.63 (t, 2H), 1.58 (t, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 200.38, 172.50, 77.83, 76.72, 73.35, 72.17, 72.14, 71.11, 71.09, 71.02, 70.66, 69.00, 52.35, 34.51, 24.71, 23.30.

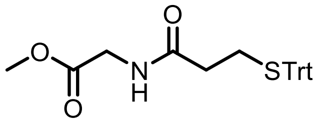


***S*-methyl mercaptopropionate-*S*-triphenylmethyl-11-mercapto-3,6,9-trioxaundecanethioate (8).** To a 20 mL scintillation vial equipped with a magnetic stir bar was added 1.00 grams (2.15 mmol, 1.00 equiv) of **3** and this was diluted with 10.0 mLs (0.22 M) of reagent grade DCM. To this clear solution was added 13.0 mgs (0.11 mmol, 10.0 mol%, 0.10 equiv) of DMAP, followed by 411 μLs (347 mgs, 2.37 mmol, 1.10 equiv) of 1-octanethiol, and this was stirred at room temperature for ~5 minutes to form a clear solution. To this stirring solution was added 367 μLs (299 mgs, 2.37 mmol, 1.10 equiv) of diisopropylcarbodiimide (DIC) dropwise via syringe. After stirring for ~10 minutes a fine white precipitate was noted to have formed (likely diisopropylurea, DIU) and this suspension was allowed to stir at room temperature overnight. After this period the suspension was vacuum filtered, the filter cake was washed with additional small portions of reagent grade DCM (~10 mLs, 3X), and the combined organics were concentrated *in vacuo*. This crude residue was taken up in a small amount of reagent grade EtOAc (~20 mLs), resulting in the formation of additional precipitate, which was again vacuum filtered and washed with additional portions of EtOAc (~5 mLs, 3X). The combined organics were concentrated *in vacuo* and the resultant crude residue was directly submitted to column chromatography (5% EtOAc/hexanes → 10% EtOAc/hexanes → 15% EtOAc/hexanes) and concentration of fractions containing the desired product (R_f = 0.35, 20% EtOAc/hexanes) yielded 942 mgs (74% yield) of the title compound as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 – 7.42 (m, 6H), 7.33-7.29 (m, 6H), 7.24 – 7.21 (m, 3H), 4.19 (s, 2H), 3.76 – 3.74 (m, 2H), 3.71 – 3.69 (m, 2H), 3.61 – 3.60 (m, 2H), 3.49 – 3.48 (m, 2H), 3.33 (t, 2H), 2.44 (t, 2H), 1.58 – 1.55 (m, 2H), 1.36 – 1.28 (m, 10H), 0.90 (t, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 200.39, 144.97, 129.78, 128.10, 128.08, 128.05, 127.43, 126.81, 76.88, 76.55, 71.80, 70.76, 70.34, 70.17, 69.81, 66.75, 31.96, 31.79, 29.58, 29.32, 29.26, 29.07, 28.00, 22.82, 14.29.

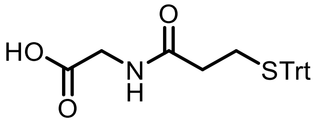


***S*-methyl mercaptopropionate-11-mercapto-3,6,9-trioxaundecanethioate** (**9** or **1c**). To a solution of compound **7** (594 mg, 1.0 mmol) in 3.00 mL (0.33 M) of reagent grade DCM was added triethylsilane (0.32 mL, 2.0 mmol), trifluoroacetic acid (0.76 mL, 10.0 mmol), and the mixture was stirred for at room temperature. Following this period the volatiles were removed *in vacuo*, the crude residue was directly submitted to silica-gel column chromatography (10% EtOAc/hexanes → 20% EtOAc/hexanes → 30% EtOAc/hexanes), and concentration of fractions containing the desired product (R_f = 0.45, 30% EtOAc/hexanes) yielded 180 mgs (64% yield) of the title compound as a colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.20 (s, 2H), 3.76 – 3.60 (m, 10H), 2.90 – 2.85 (m, 2H), 2.73 – 2.66 (m, 2H), 1.60 – 1.54 (m, 3H), 1.40 – 1.21 (bm, 10H), 0.88 – 0.85 (m, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 200.25, 76.58, 73.09, 71.81, 70.84, 70.42, 31.93, 29.56, 29.28, 29.23, 29.04, 28.00, 22.77, 14.23.

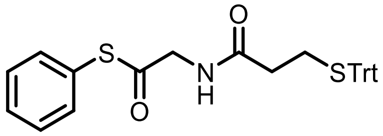
Glycinemethylester hydrochloride[1] and 3-(triphenylmethylthio)propionic acid[2] were prepared according to the published procedure.



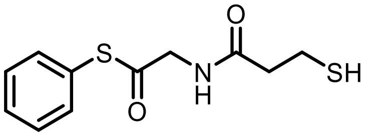
Methyl 2-(3-(triphenylmathylthio)propanamido)acetate (10). N,N-Di-*iso*-propylethylamine (3.09 g, 23.9 mmol) was added to the glycinemethylester hydrochloride (1.0 g, 8.0 mmol) in 40 mL of CH_2Cl_2. After stirring the reaction mixture for 10 min at room temperature, 1-hydroxybenzotriazole (1.18 g, 8.76 mmol) was added, followed by the addition of 3-(triphenylmethylthio)propionic acid (2.80 g, 7.96 mmol) and EDC. HCl (1.68 g, 8.76 mmol). The reaction mixture was then stirred at room temperature overnight. Diluted with CH_2Cl_2 (200 mL) and washed with 10 % aqueous citric acid (25 mL), saturated Na_2HCO_3 (25 mL), water (50 mL) and brine (25 mL). The EtOAc extract was dried over Na_2SO_4 and then evaporated in vaccuo. The residue was purified by silica-gel column chromatography using 40% EtOAc in hexane as eluent to give **10** (3.20 g, 95%) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 – 7.44 (m, 6H), 7.34-7.28 (m, 6H), 7.26 – 7.22 (m, 3H), 5.84 (s, 2H), 4.01-3.99 (m, 2H), 3.77 (s, 3H), 2.57 – 2.53 (m, 2H), 2.07 – 2.03 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.0, 170.3, 144.6, 129.6, 128.0, 126.7, 66.9, 52.4, 41.2, 35.3, 27.5.



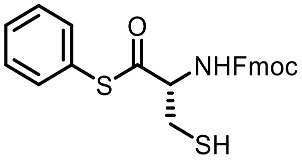
2-(3-(triphenylmethylthio)propanamido)acetic acid (11). To a solution of **10** (3.0 g, 7.15 mmol) dissolved in 20 mL of methanol was added 3 mL of 10 M NaOH (1.20 g, 28.60 mmol), and the mixture was stirred at room temperature overnight. Methanol was evaporated and the residue was diluted with 20 mL of water. Acidified to a pH of 2 by the addition of 1N HCl and extracted with EtOAc (3 × 50 mL). Combined EtOAc extracts were dried over Na_2SO_4, filtered and evaporated to give **11** (2.8 g, 96 %) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.54 (s, 1H), 8.19 (t, 1H), 7.37 – 7.29 (m, 12H), 7.28-7.23 (m, 3H), 3.70 (d, 2H), 2.24-2.22 (m, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 171.7, 170.9, 144.9, 129.5, 128.5, 127.2, 66.4, 41.0, 34.1, 27.7.



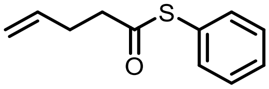
***S*-phenyl-2-(3-(triphenylmethylthio)propanamido)ethanethioate (12).** Triphenylphosphine (656.0 mg, 2.47 mmol) was added to a mixture of **11** (1.0 g, 2.47 mmol) and diphenyl disulfide (546.0 mg, 2.47 mmol) dissolved in 30 mL of acetonitrile. The mixture was refluxed for 16 h under N_2 atmosphere. Cooled to room temperature and the solvent was evaporated completely under reduced pressure. The crude product was purified by silica-gel column chromatography using 40 % EtOAc in hexane as eluent to give **12** (1.15g, 93 %) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48 – 7.40 (m, 11H), 7.34-7.28 (m, 6H), 7.26-7.21 (m, 3H), 5.95-5.93 (m, 1H), 4.25 (d, 2H), 2.58 (t, 2H), 2.07 (t, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 195.3, 171.1, 144.6, 134.7, 129.8, 129.6, 129.4, 128.0, 126.8, 126.1, 66.9, 48.9, 35.4, 27.4.



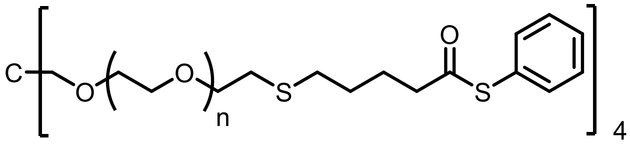
***S*-phenyl-2-(3-mercaptopropanamido)ethanethioate** (**13** or **1d**)**.** To a solution of **12** (300.0 mg, 0.060 mmol) dissolved in 5 mL of CH_2Cl_2 was added triethylsilane (0.482 mL, 3.015 mmol) and trifluoroacetic acid (0.231 mL, 3.015 mmol). The mixture was stirred overnight at room temperature. All the volatiles were evaporated *in vaccuo* and the residue was co-evaporated twice with toluene. The crude was purified using silica-gel column chromatography using 20% EtOAc in hexane as eluent to give **13** (109 mg, 71 %) as pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46 – 7.44 (m, 5H), 6.34 (m, 1H), 4.36 (d, 2H), 2.89-2.83 (m, 2H), 2.62 (m, 2H), 1.73 (t, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 195.3, 171.1, 134.8, 129.9, 129.5, 126.0, 49.0, 40.2, 20.2.



N-Fmoc-Cys-SPh (**14** or **1e**). *N*-Fmoc-Cys(Trt)-SPh was synthesized from *N*-Fmoc-Cys(Trt)-OH as previously reported.[17] Deprotection was carried out with 10 equivalent TFA, 2 equivalent TES in DCM overnight. Column chromatography (hexane: ethyl acetate 4:1) gave **14** as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.81 (d, *J* = 7.6 Hz, 2H), 7.67 (dd, *J* = 7.7, 2.9 Hz, 2H), 7.55 – 7.39 (m, 7H), 7.36 (td, *J* = 7.5, 1.2 Hz, 2H), 5.80 (d, *J* = 9.2 Hz, 1H), 4.85 (dt, *J* = 9.3, 4.6 Hz, 1H), 4.62 (dd, *J* = 10.6, 6.8 Hz, 1H), 4.50 (dd, *J* = 10.7, 6.9 Hz, 2H), 4.31 (t, *J* = 6.7 Hz, 1H), 3.23 (m, 1H), 2.89 (m, 1H), 1.48 (dd, *J* = 10.4, 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 197.85, 155.89, 143.84, 143.71, 141.54, 141.53, 134.78, 129.99, 129.56, 128.00, 127.32, 127.30, 126.73, 125.24, 120.24, 77.41, 67.54, 61.36, 47.36, 27.43.



S-phenyl pent-4-enethioate (15). 4-Pentenoyl chloride (0.118 g, 1.0 mmol) was added dropwise into a solution of thiophenol (0.110 g, 1.0 mmol) and TEA (139 µL, 1.0 mmol) in 3.0 mL DCM under icebath. The reaction was allowed stirring overnight and subsequently column chromatography gave the product **15** as a colorless liquid (127 mg, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (ppm): 7.44 (s, 5H), 5.91 – 5.81 (m, 1H), 5.17 – 5.03 (m, 2H), 2.79 (dd, *J* = 8.4, 6.6 Hz, 2H), 2.54 – 2.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 196.98, 136.21, 134.66, 129.56, 129.46, 129.36, 127.85, 116.19, 42.92, 29.53.



4-arm PEG-S-phenol thioester-10’000 (16 or **2b)**. 4-Arm PEG-SH-10’000 (100 mg, 0.01 mmol) and **15** (15.4 mg, 0.08 mmol) and DMPA (1 mg) was dissolved in 0.1 mL of chloroform. The mixture was irradiated with 365 nm centered UV light (~8 mW/cm^2) for 15 min. The product **16** was purified by dissolving in chloroform and precipitating in cold diethyl ether twice, subsequently dried under vacuum and stored at -20 °C before use. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 (ppm): 7.39 (s, 4H), 3.76 – 3.61 (m, 248H), 2.68 (m, 4H), 2.56 (m, 2H), 1.80 (m, 2H), 1.65 (m, 2H), 1.19 (t, 2H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 197.2, 134.6, 129.5, 129.3, 70.7, 43.2, 32.2, 31.5, 29.0, 24.7.

Characterizations methods

Gel permeation chromatography (GPC)

The molecular weights of oligomer/polymer were obtained from a Tosoh EcoSEC GPC system (HLC-8320). Dimethyl sulfoxide was used as eluent at 0.350 mL/min under 50 ^{0}C. Column sets: two TSKgel SuperHM-H, 3 μm, 6.0 mm ID × 15 cm columns. Molecular weights from both RI and UV detectors were calibrated by narrow polydispersity poly(methyl methacrylate) standards.

Rheology

The modulus of hydrogels was monitored by oscillatory rheology on a TA ARES. The hydrogel was formed between two parallel quartz plates with a diameter of 8 cm and a gap of 50 µm, sealed with pump oil to prevent dehydration. The strain scan was performed at a frequency of 1 rad/s, while frequency scan was performed at 100 % oscillatory strain. All measurements were performed 24 h after the hydrogel was formed.

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS)

Measurements were performed with a Voyager DE-RP mass spectrometer (Applied Biosystems, Framingham, MA). Dithranol was selected as matrix. Solution of polymer (10 mg/mL in DMSO) and dithranol (25mg/mL in THF) were mixed in a 1/20 volumetric ratio. Then 0.5 µL portions of the mixture were deposited onto 100 wells of the sample plate and dried in air at room temperature.

Polymerization procedures

AB-type polymerization by biased equilibrium.

Compound **1a-e** were dissolved in 1.0 mol/L DMSO solutions with the presence of 10 mol% TEA (with respect to thiol/thioester groups). The samples were kept sitting on bench for 2 hours before directly diluted to 10 mg/mL GPC samples in DMSO, which were analyzed immediately.

A_2-B_2 type polymerizations. Linear polymer formation.

Di-*S*-phenol thioadipate (**2a**, 33.0 mg, 0.1 mmol) and glycol dimercaptopropionate (GDMP, 23.8 mg, 0.1 mmol) were dissolved in 0.12 mL of chloroform with 1.4 µL of TEA (10 mol% to both monomers). The mixture was allowed to react for overnight, then was directly diluted to 10 mg/mL DMSO solution and analyzed by GPC immediately.

A_2-B_2 type polymerizations. Organogel formation.

Di-*S*-phenol thioadipate (**2a**, 66.0 mg, 0.2 mmol) and PETMP (48.8 mg, 0.1 mmol) were dissolved in 0.4 mL of DMSO with 2.8 µL of TEA. Gelation was observed within 3h.

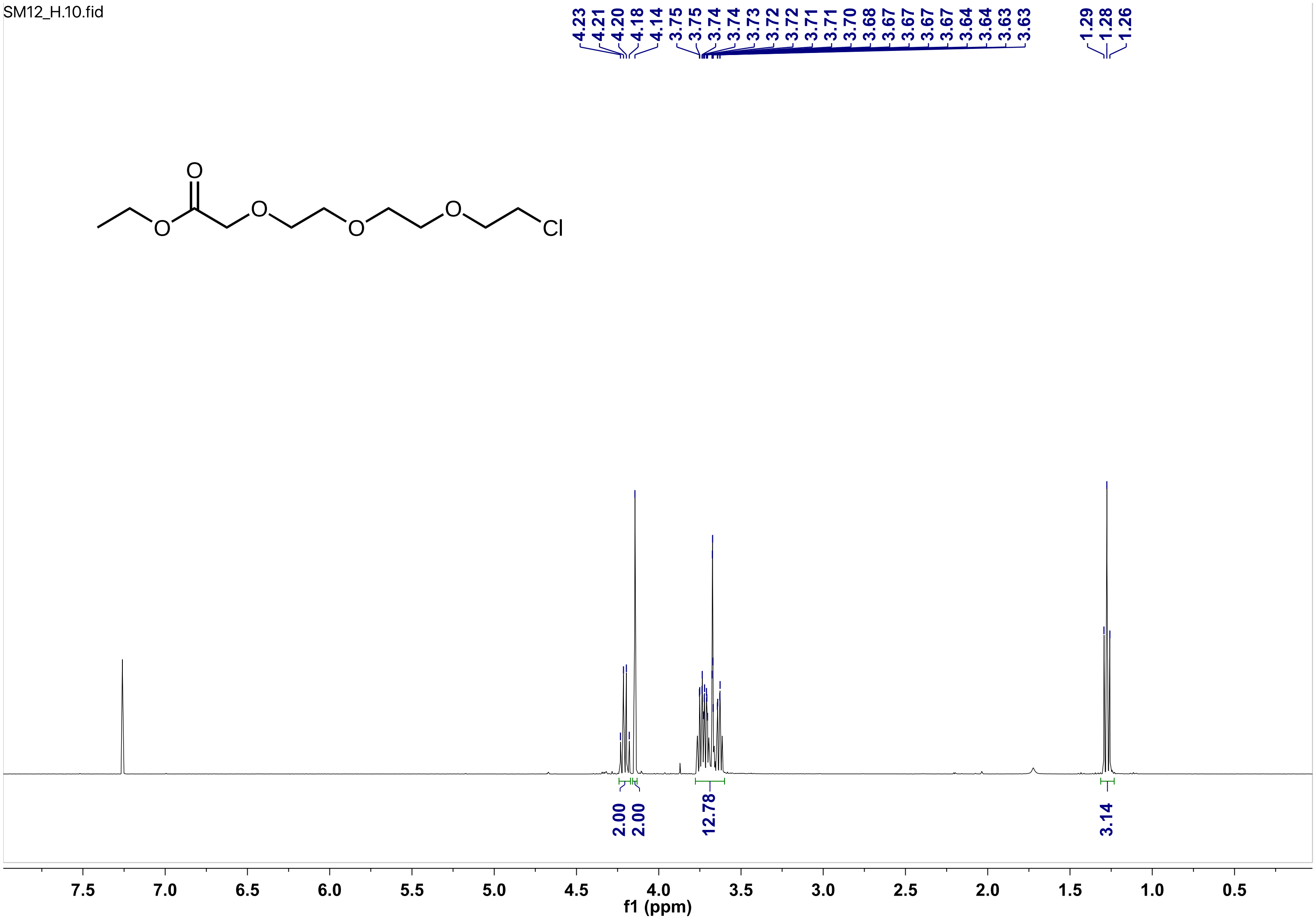
Hydrogel formation.

4-arm PEG-S-phenol thioester-10’000 (**2b**, 5.0 mg) and 4-arm PEG-SH-10’000 (10 mg) were added to 135 µL of deionized water. The mixture formed a gel within an hour. The rheology of such hydrogel was performed 24 h after the sample preparation.

References

1. G. Coban, F. A. Kose, P. B. Kirmizibayrak and V. Pabuccuoglu. Synthesis, biological activity screening and molecular modeling study of acylaminoacetamide derivatives. *Med. Chem. Res.*, 2015, 24, 3710-3729.
2. C. J. Benjamin, K. J. Wright, S.-H. Hyun, K. Krynski, G. Yu, R. Bajaj, F. Guo, C. V. Stauffacher, W. Jiang and D. H. Thompson. Nonfouling NTA-PEG-based TEM grid coatings for selective capture of histidine-tagged protein targets from cell lysates. *Langmuir*, 2016, 32, 551-559.

NMR Spectra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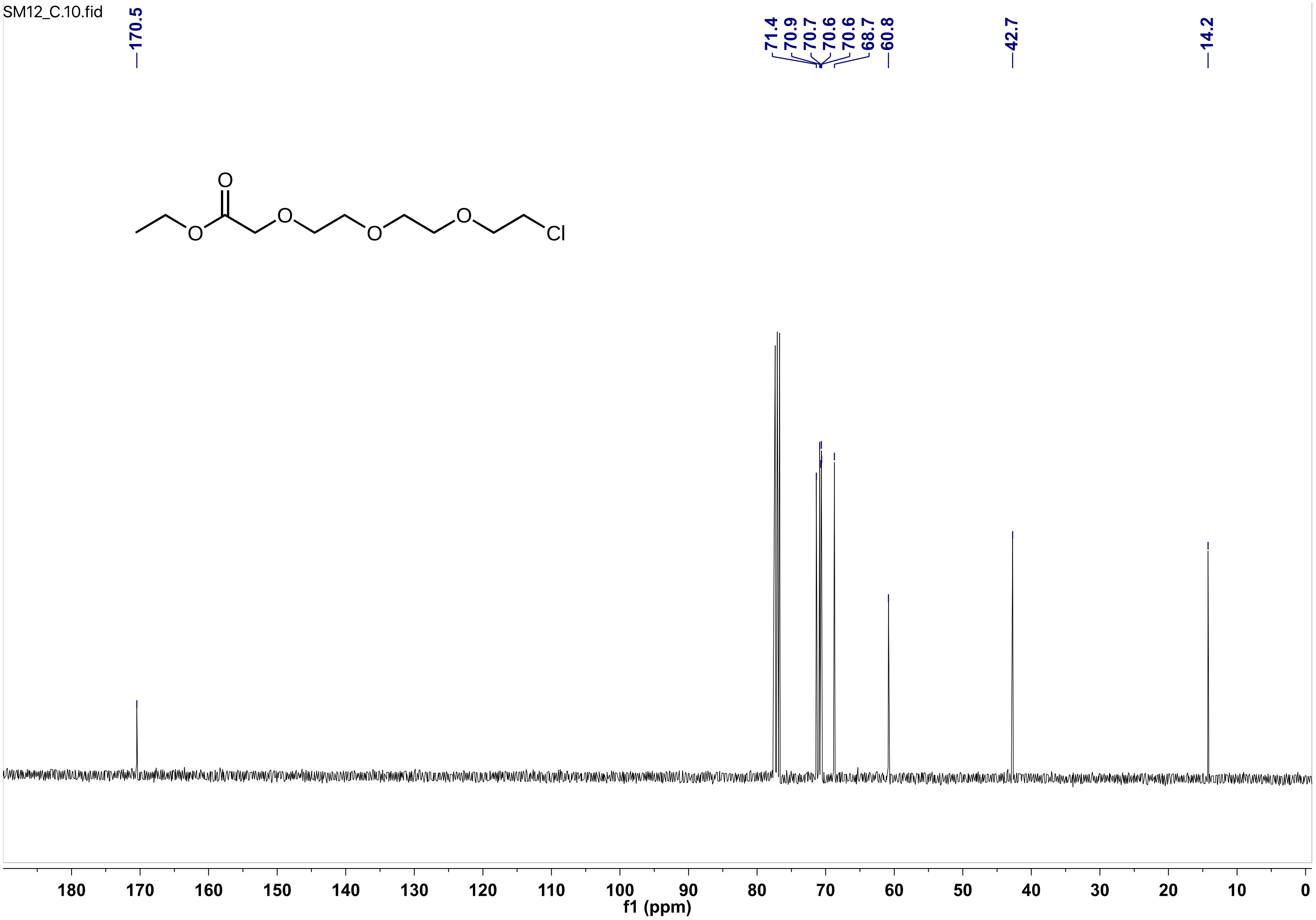
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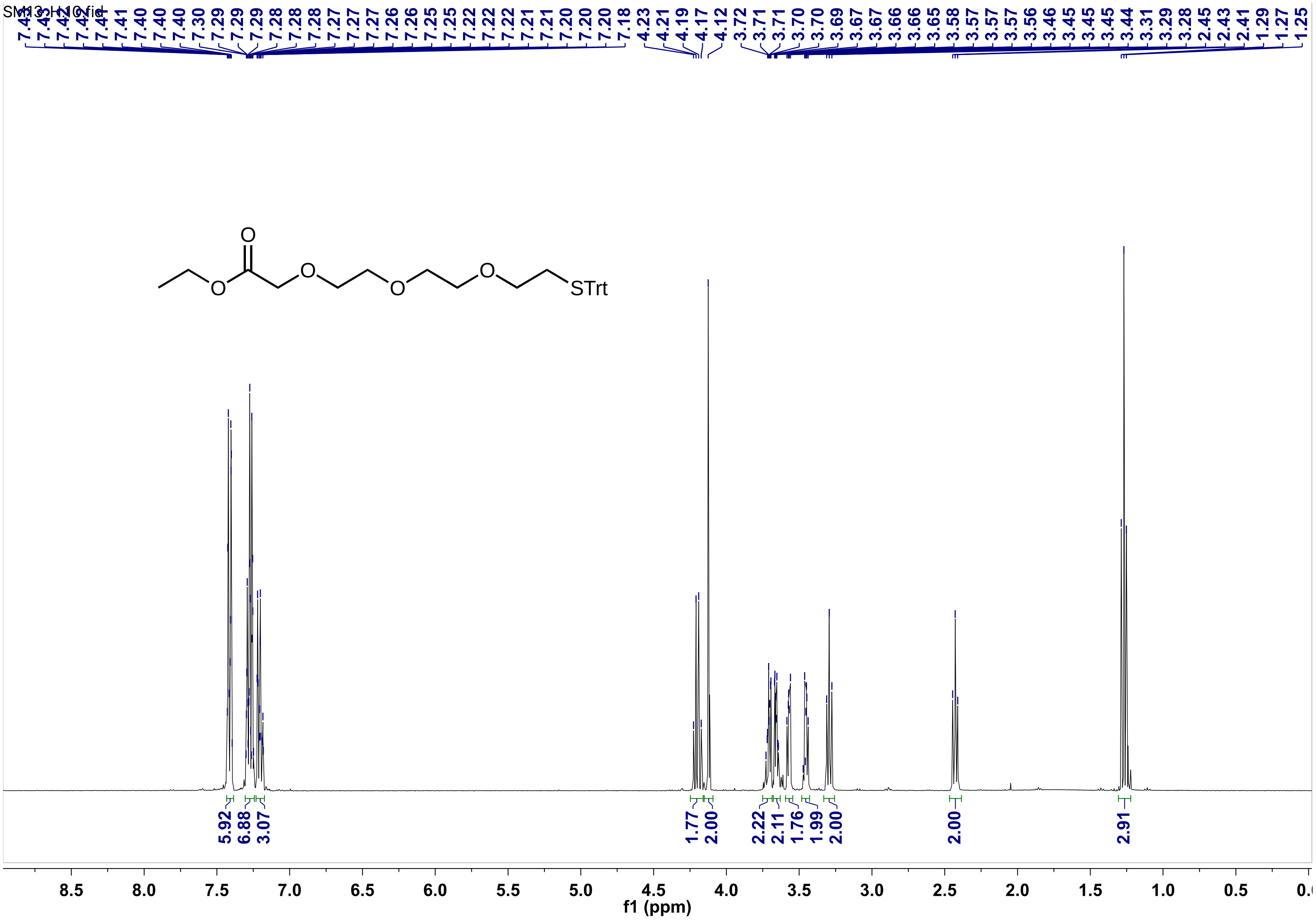
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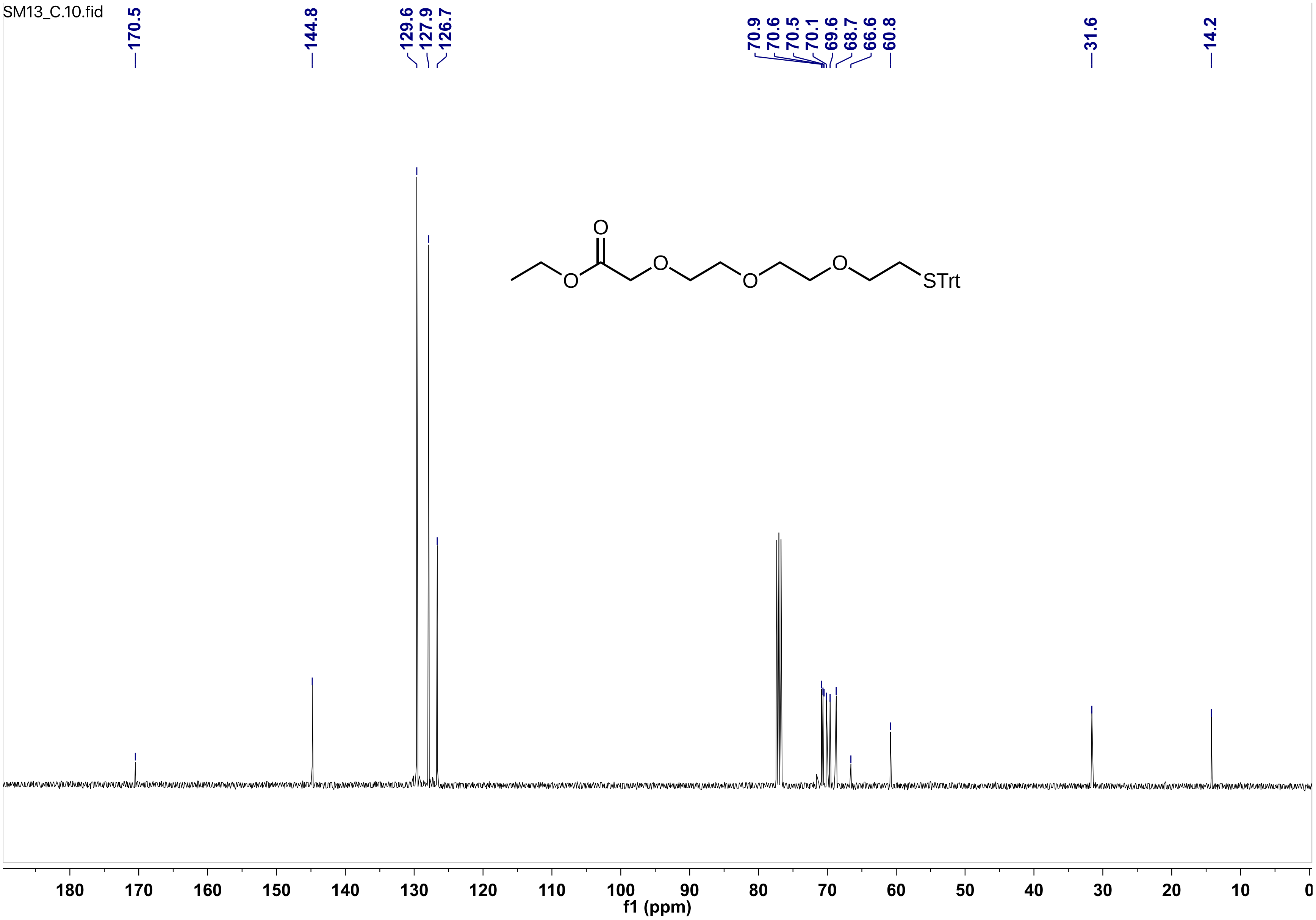
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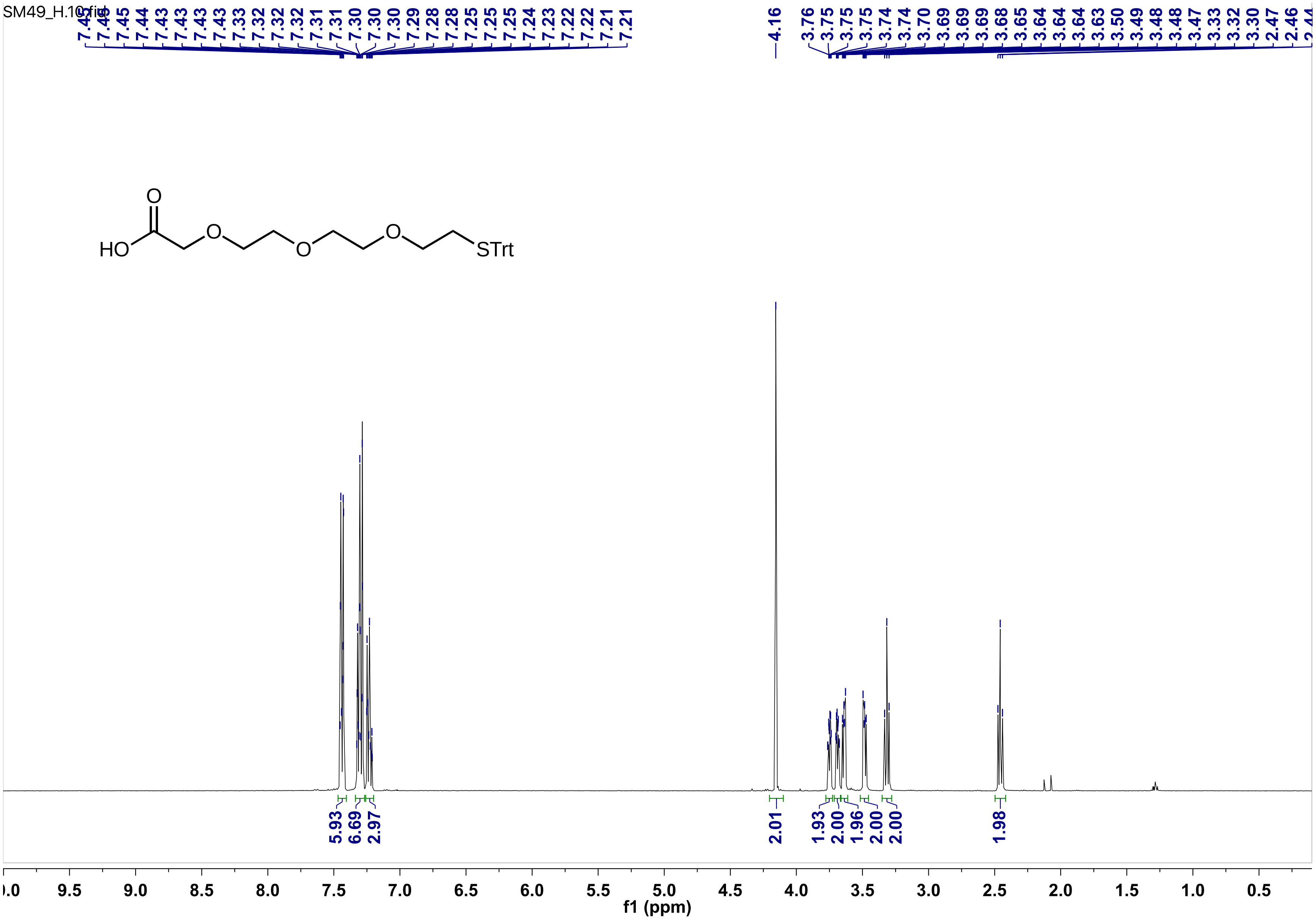
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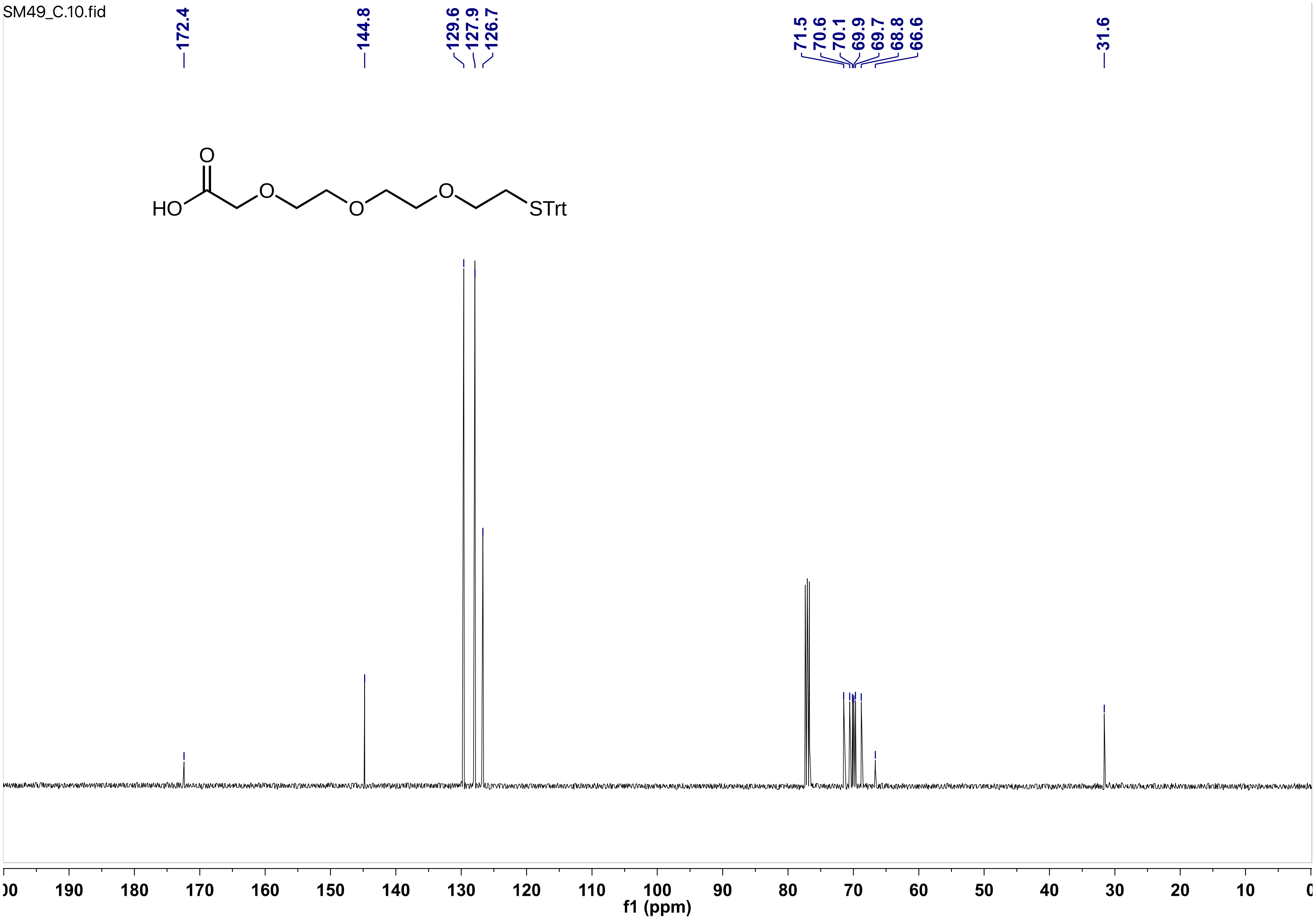
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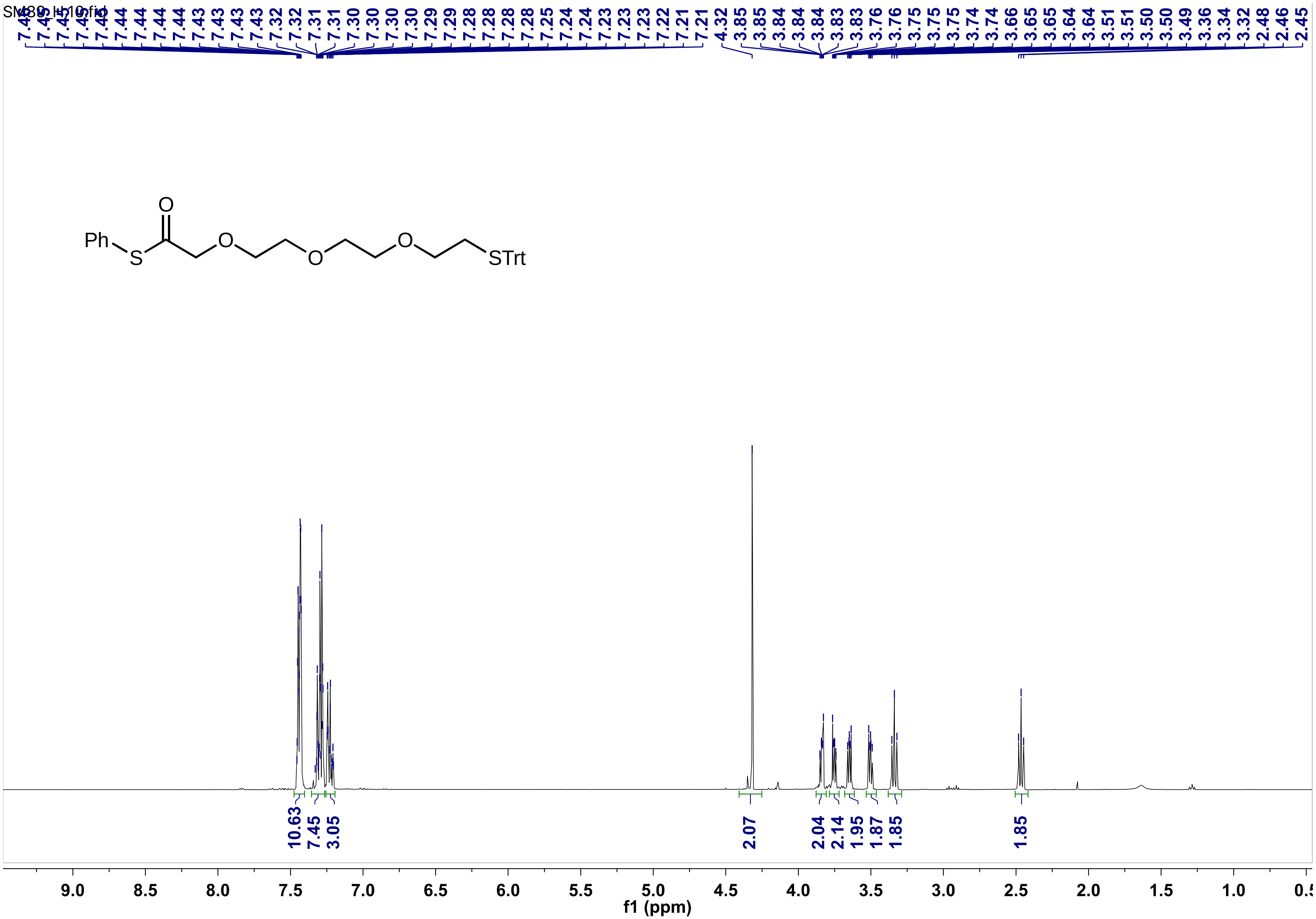
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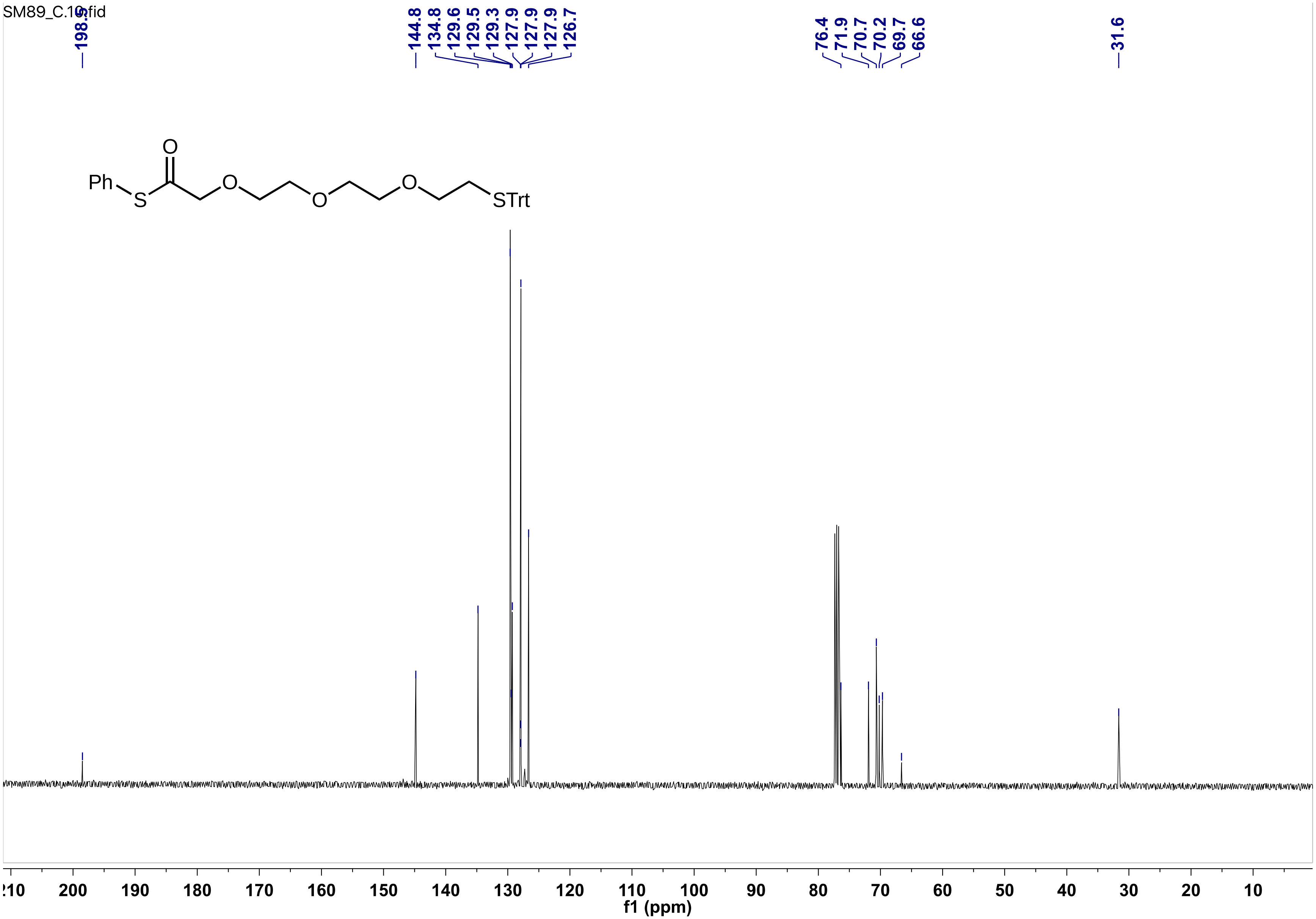
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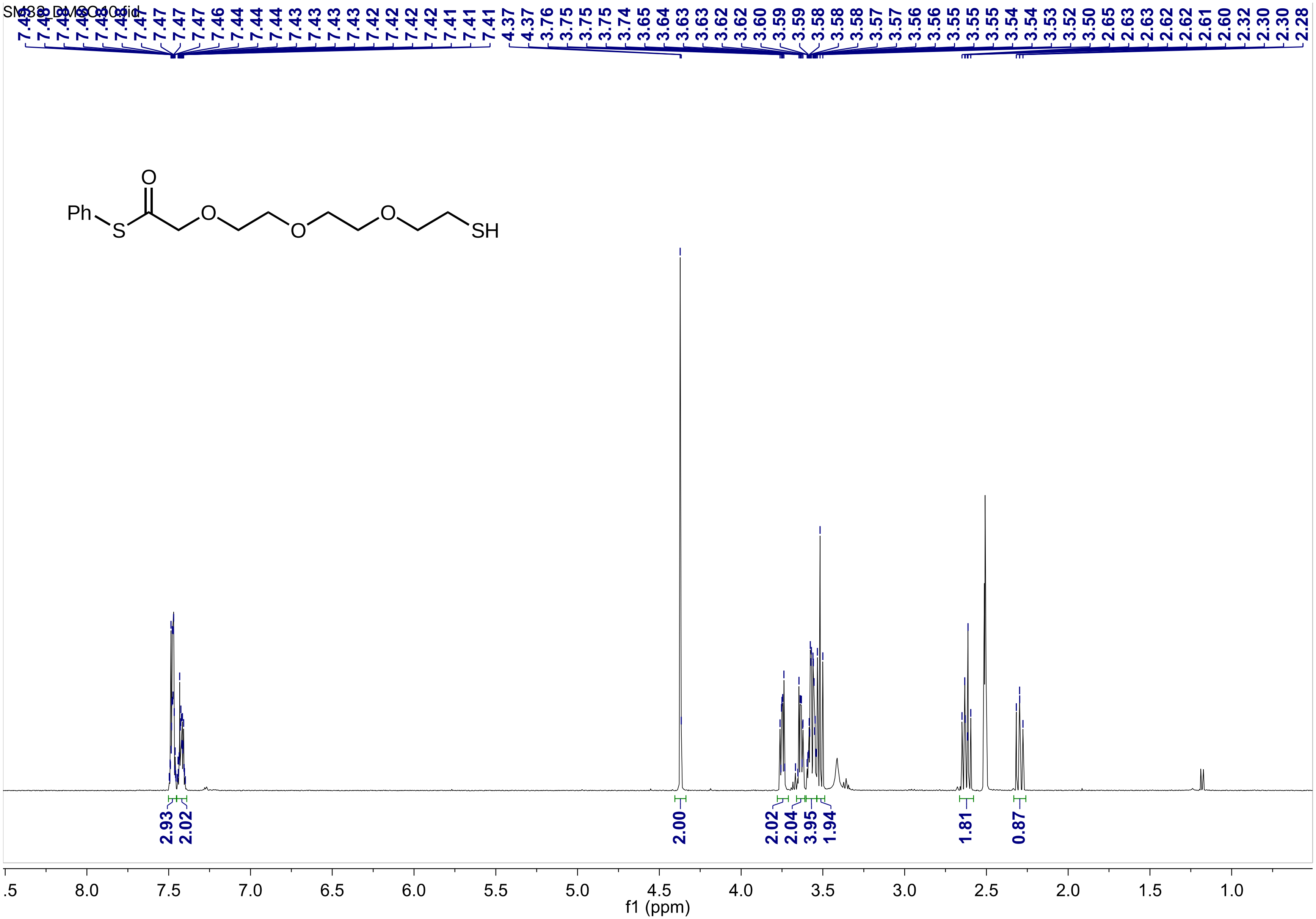
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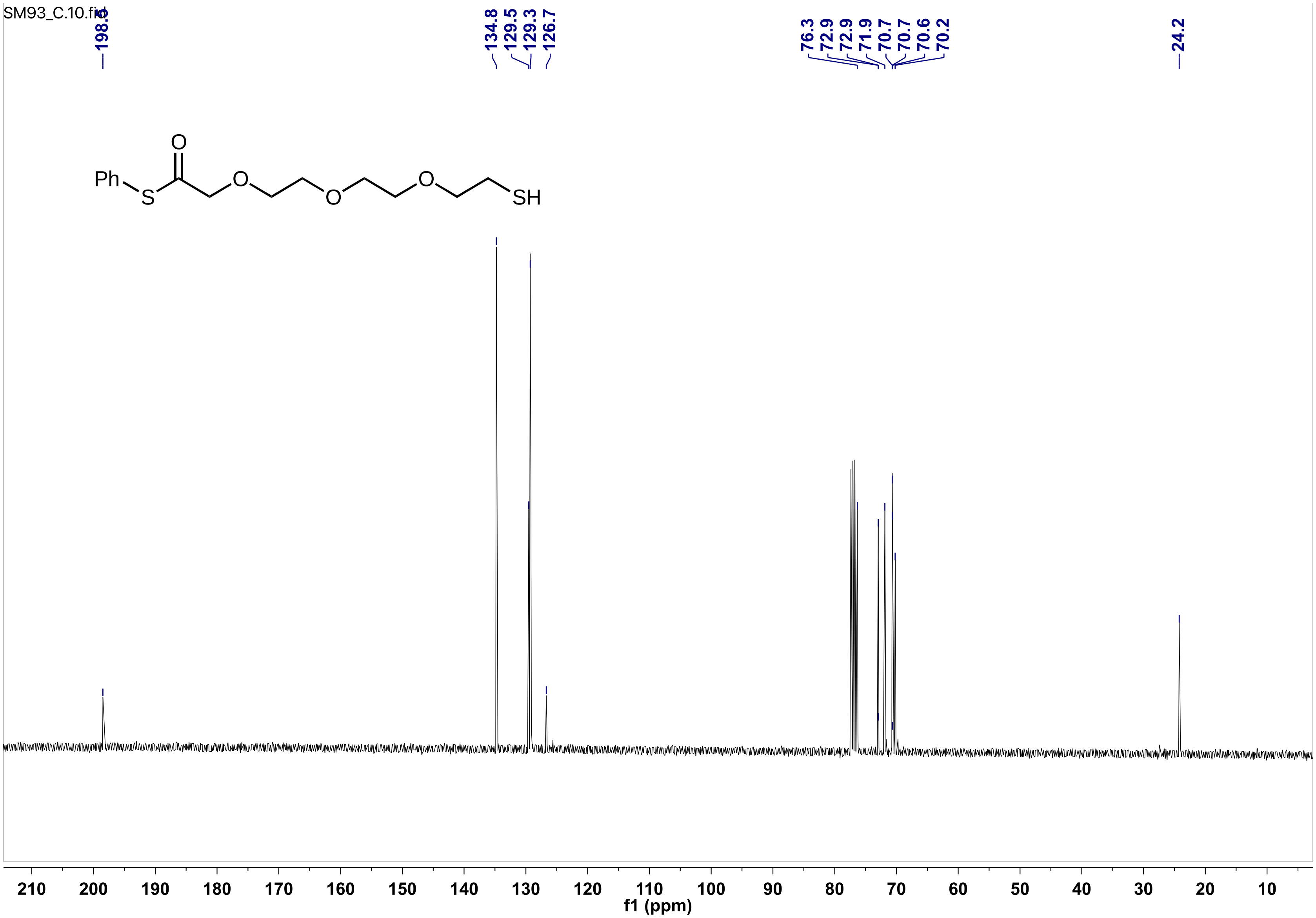
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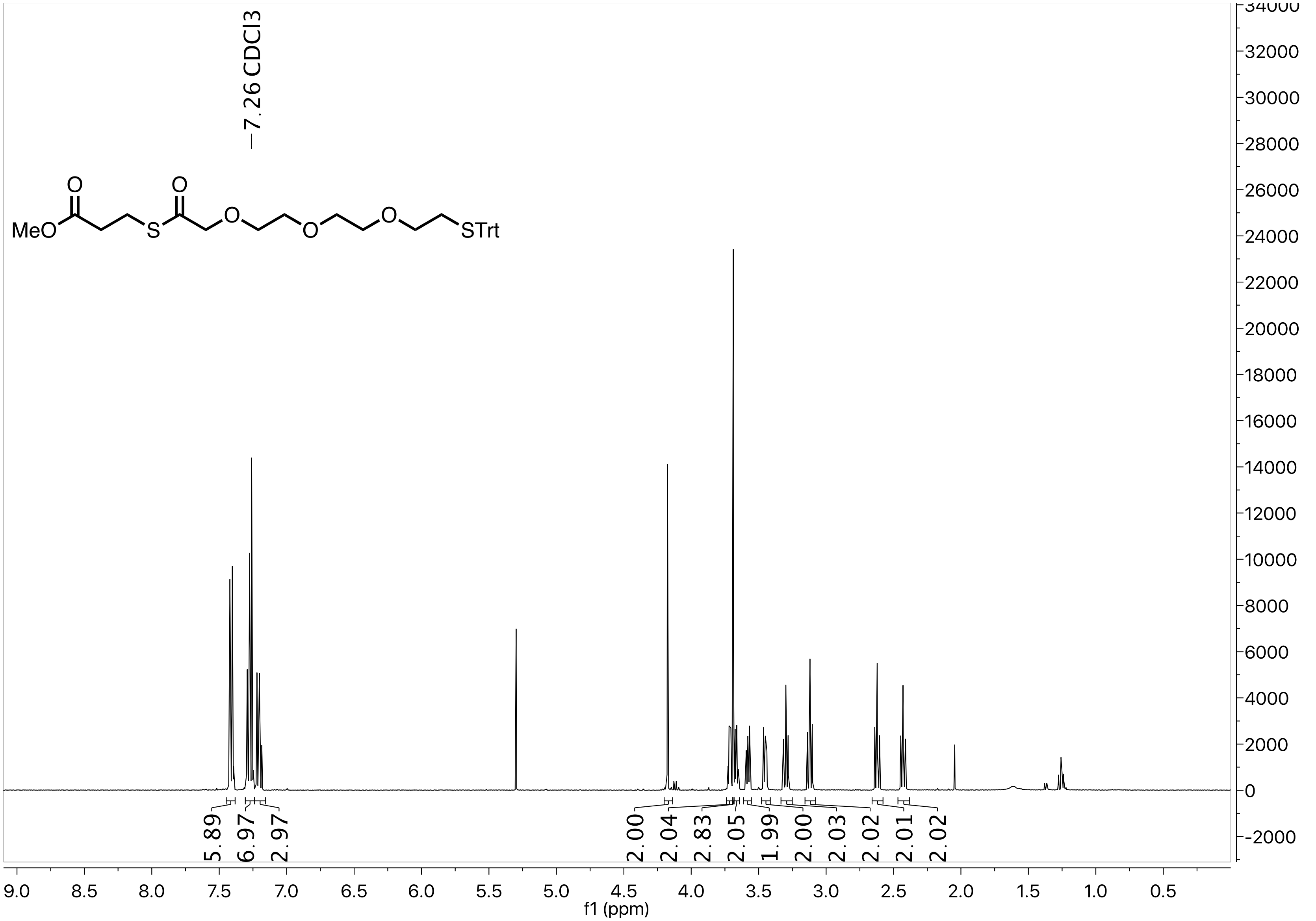
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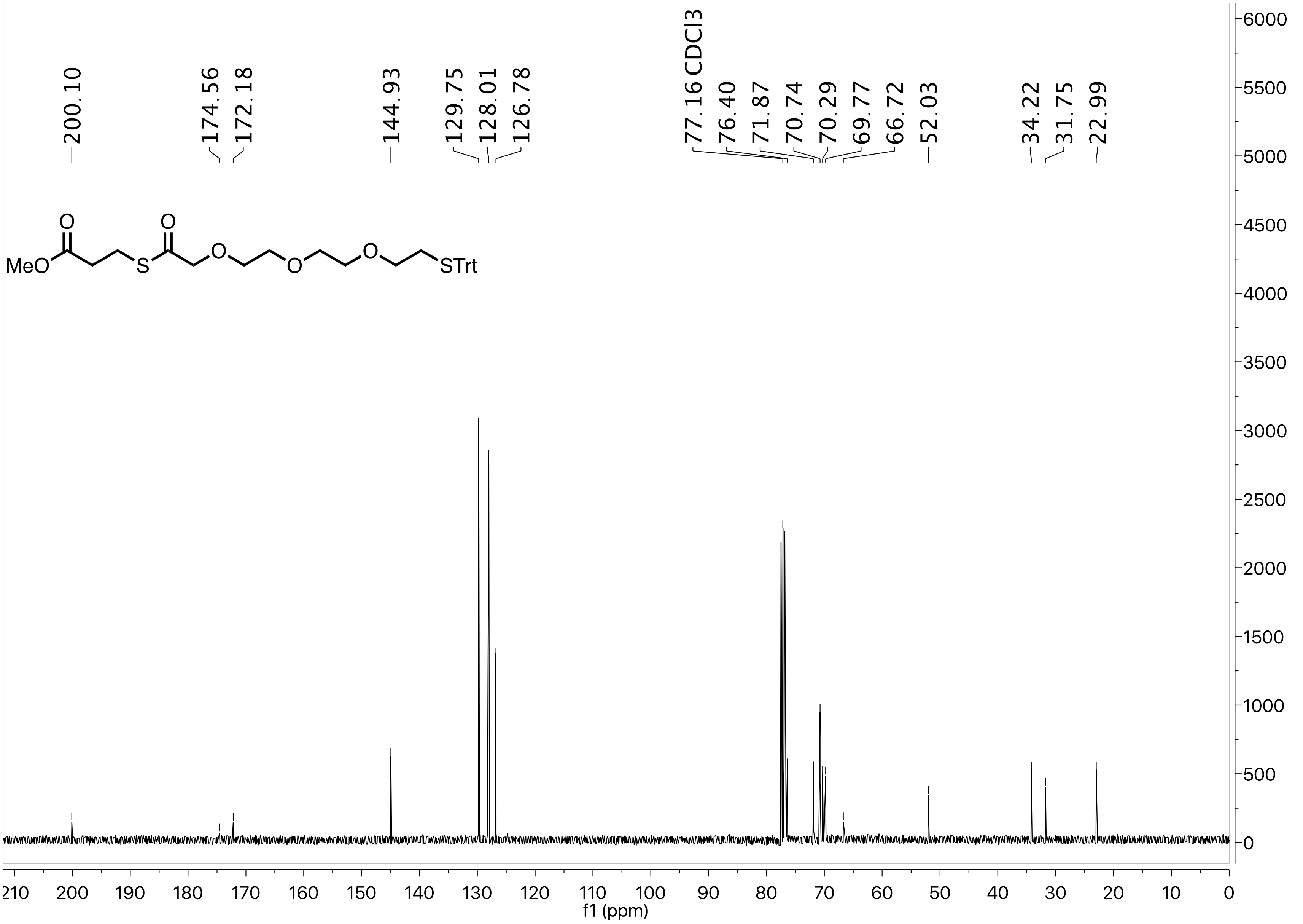
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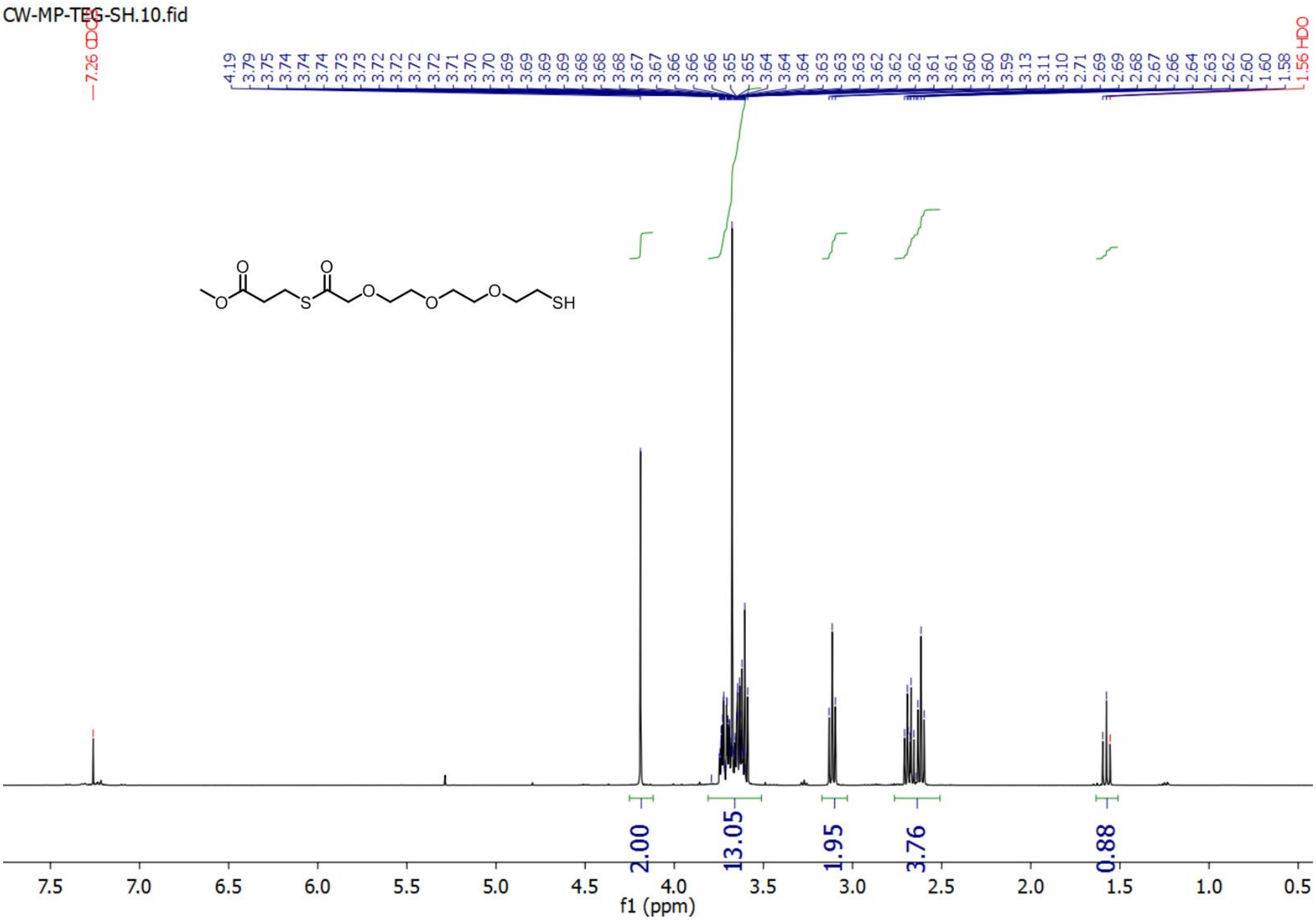
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3.69
3.69
3.69
3.68
3.68
3.68
3.67
3.67
3.66
3.66
3.66
3.65
3.65
3.64
3.64
3.64
3.63
3.63
3.63
3.62
3.62
3.62
3.61
3.61
3.60
3.60
3.59
3.13
3.11
3.10
2.71
2.69
2.69
2.68
2.67
2.66
2.64
2.63
2.62
2.60
1.60
1.58
1.56 HDO
O
O
O
S
O
O
O
SH
2.00
13.05
1.95
3.76
0.88
7.5
7.0
6.5
6.0
5.5
5.0
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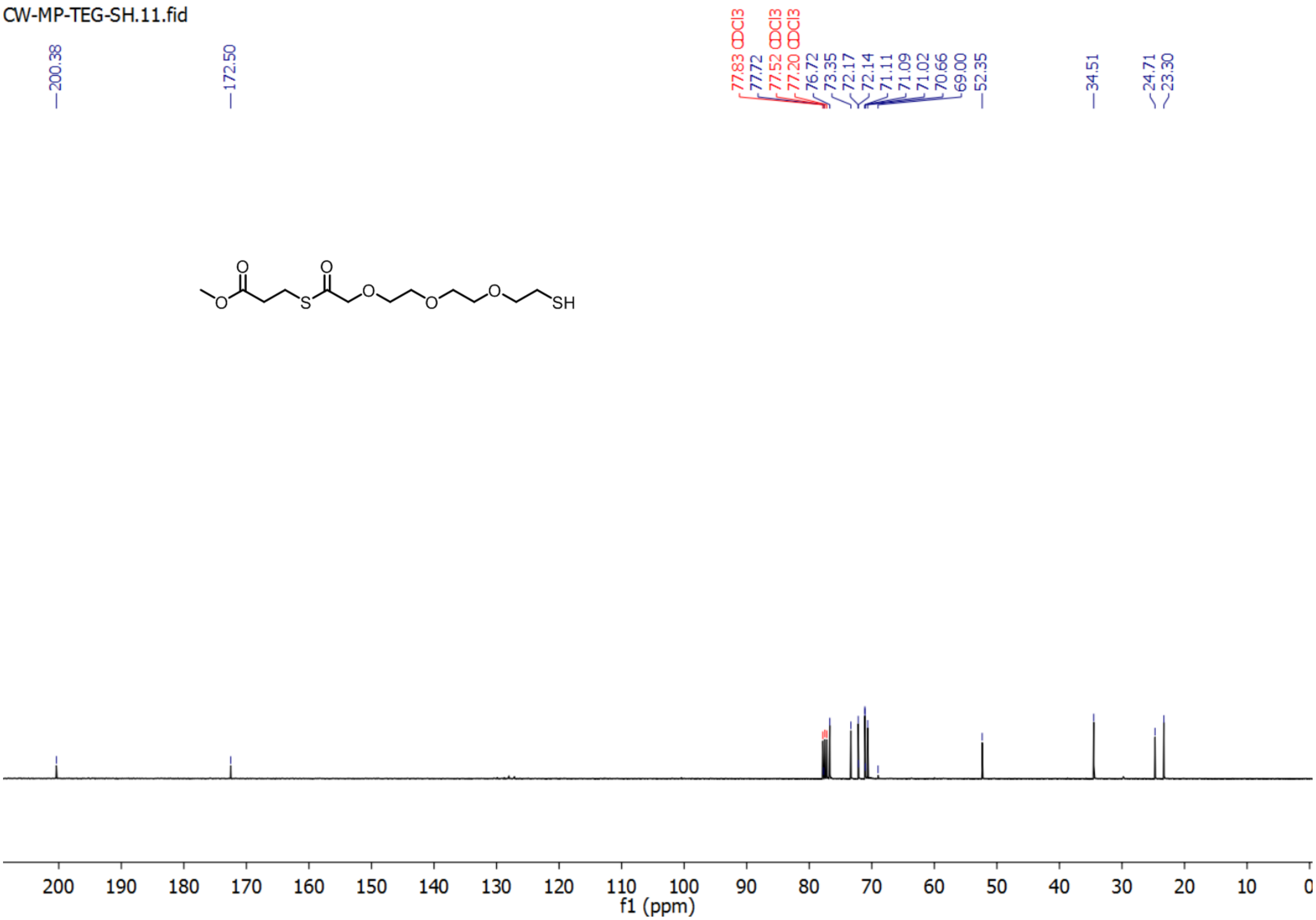
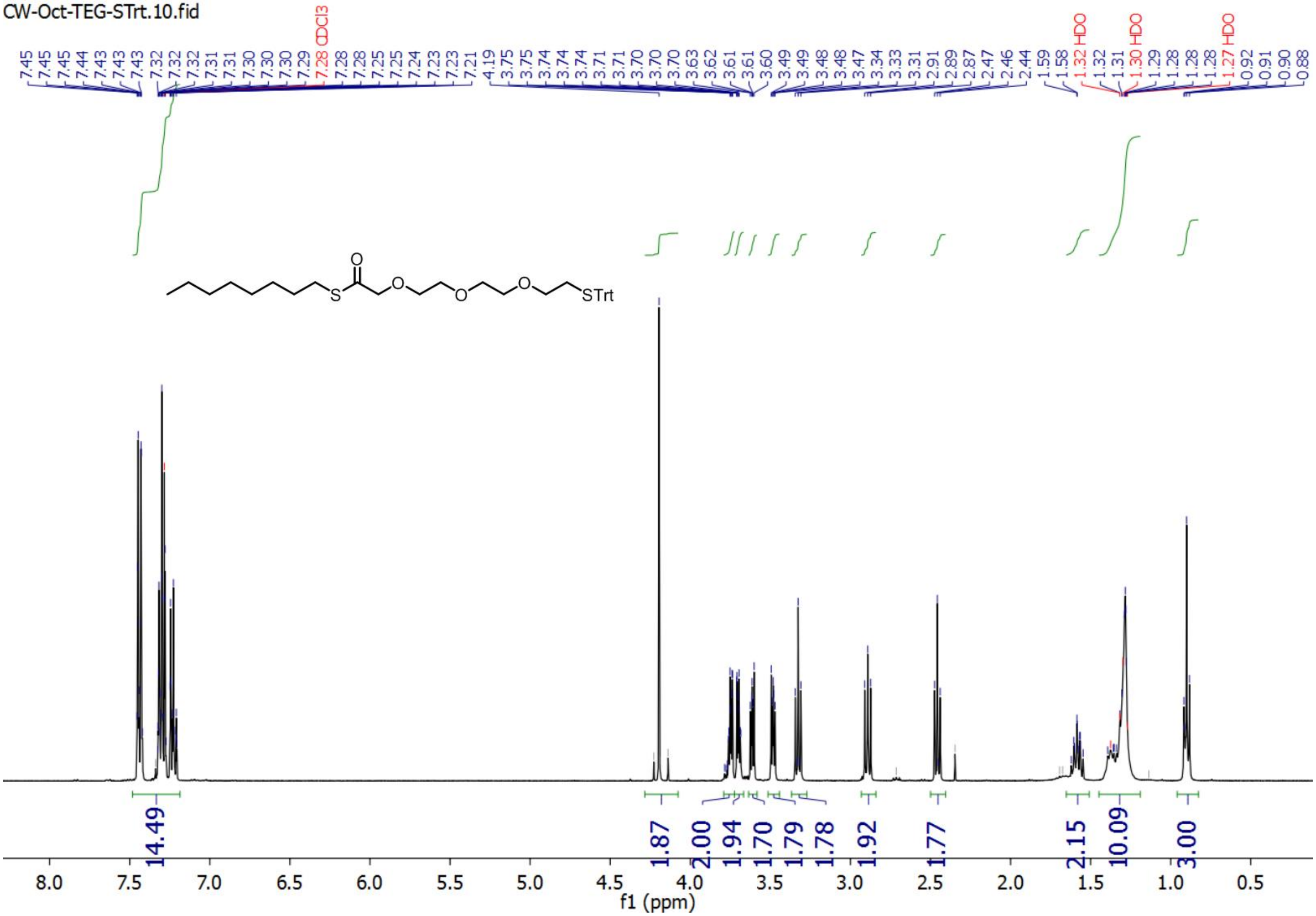
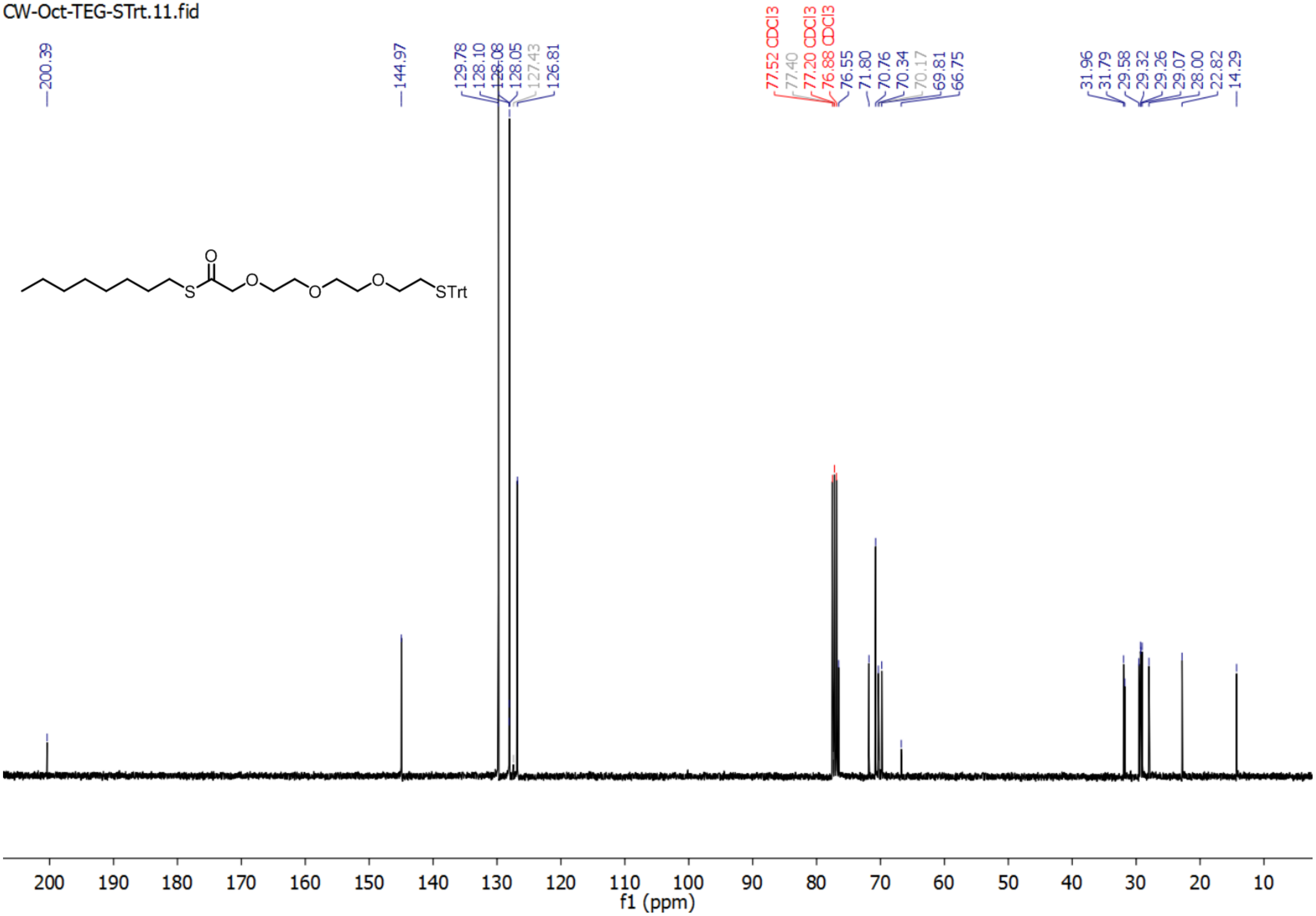
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CW-MP-TEG-SH.11.fid
200.38
172.50
77.83 CDCl3
77.72
77.52 CDCl3
77.20 CDCl3
76.72
73.35
72.17
72.14
71.11
71.09
71.02
70.66
69.00
52.35
34.51
24.71
23.30
O
O
O
S
O
O
O
SH
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CW-Oct-TEG-STrt.10.fid
7.45
7.45
7.45
7.44
7.43
7.43
7.43
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.30
7.29
7.28 CDCl3
7.28
7.28
7.25
7.25
7.24
7.23
7.23
7.21
4.19
3.75
3.75
3.74
3.74
3.71
3.71
3.70
3.70
3.70
3.63
3.62
3.61
3.61
3.60
3.49
3.49
3.48
3.48
3.47
3.34
3.33
3.31
2.91
2.89
2.87
2.47
2.46
2.44
1.59
1.58
1.32 HDO
1.32
1.31
1.30 HDO
1.29
1.28
1.28
1.28
1.27 HDO
0.92
0.91
0.90
0.88
O
S
O
O
O
STrt
14.49
1.87
2.00
1.94
1.70
1.79
1.78
1.92
1.77
2.15
10.09
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


CW-Oct-TEG-STrt.11.fid
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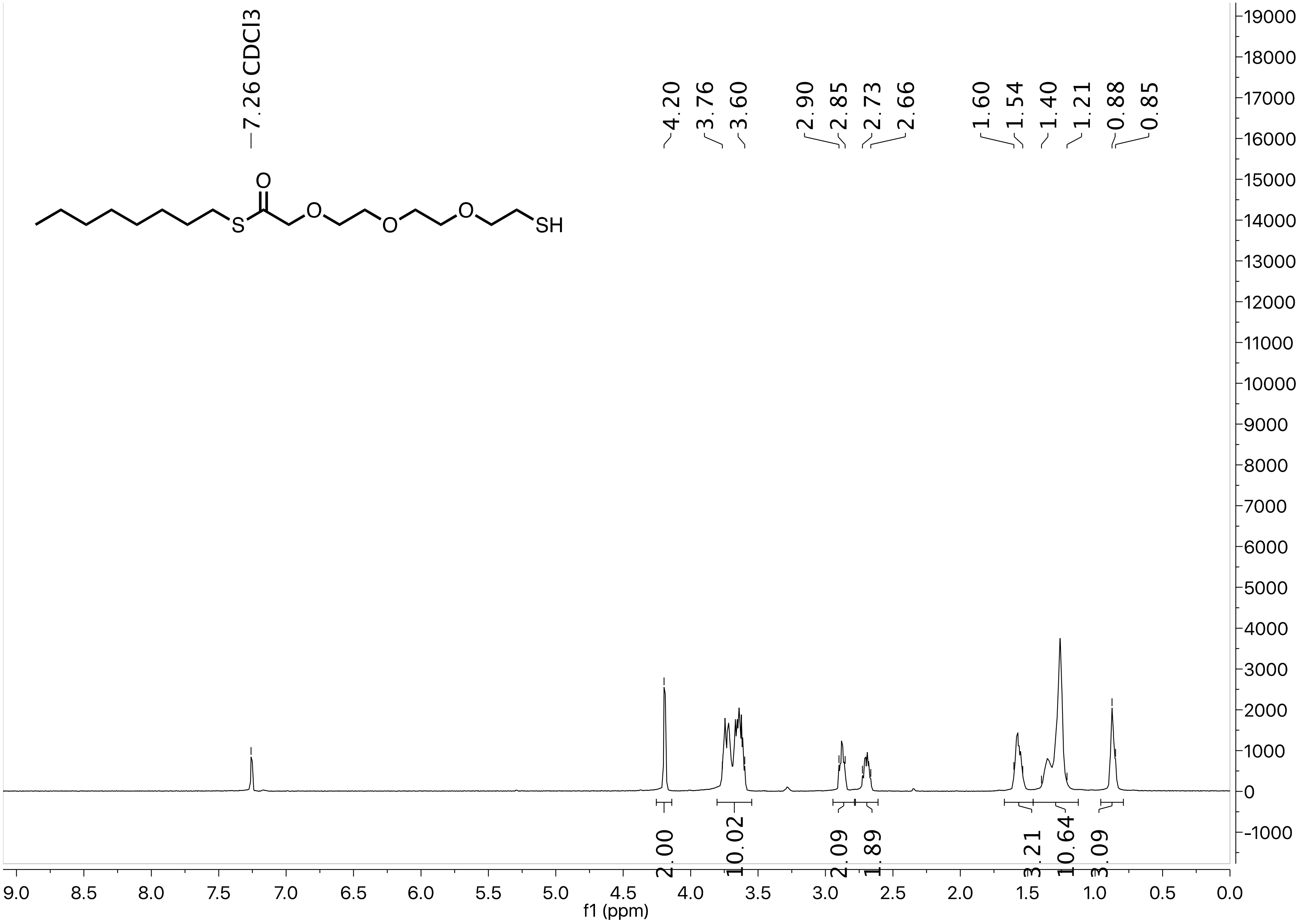
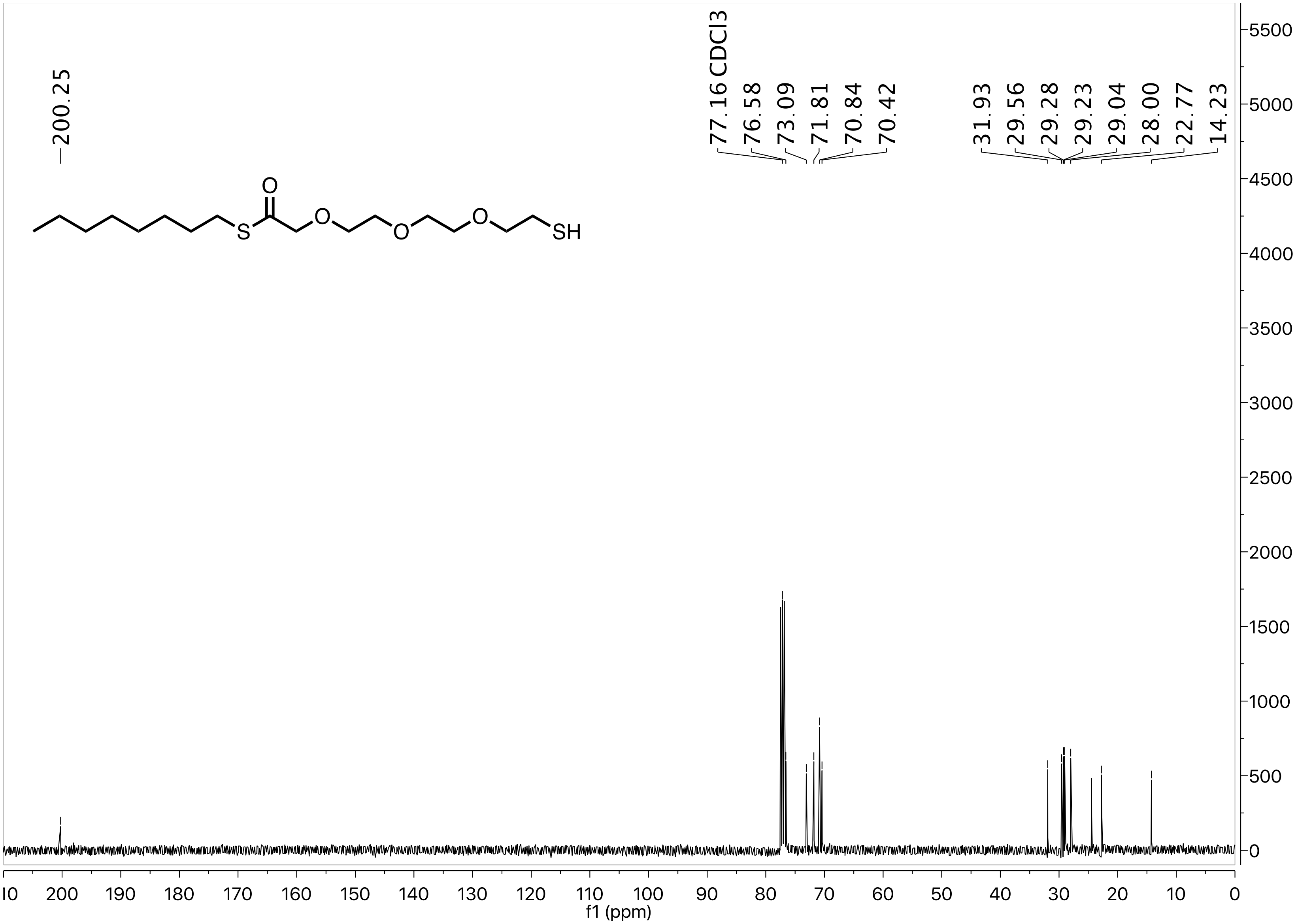
144.97
129.78
128.10
128.08
128.05
127.43
126.81
77.52 CDCl3
77.40
77.20 CDCl3
76.88 CDCl3
76.55
71.80
70.76
70.34
70.17
69.81
66.75
31.96
31.79
29.58
29.32
29.26
29.07
28.00
22.82
14.29
O
S
O
O
O
STrt
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.26 CDCl3
4.20
3.76
3.60
2.90
2.85
2.73
2.66
1.60
1.54
1.40
1.21
0.88
0.85
O
S
O
O
O
SH
2.00
10.02
2.09
1.89
3.21
10.64
3.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000


200.25
77.16 CDCl3
76.58
73.09
71.81
70.84
70.42
31.93
29.56
29.28
29.23
29.04
28.00
22.77
14.23
O
S
O
O
O
SH
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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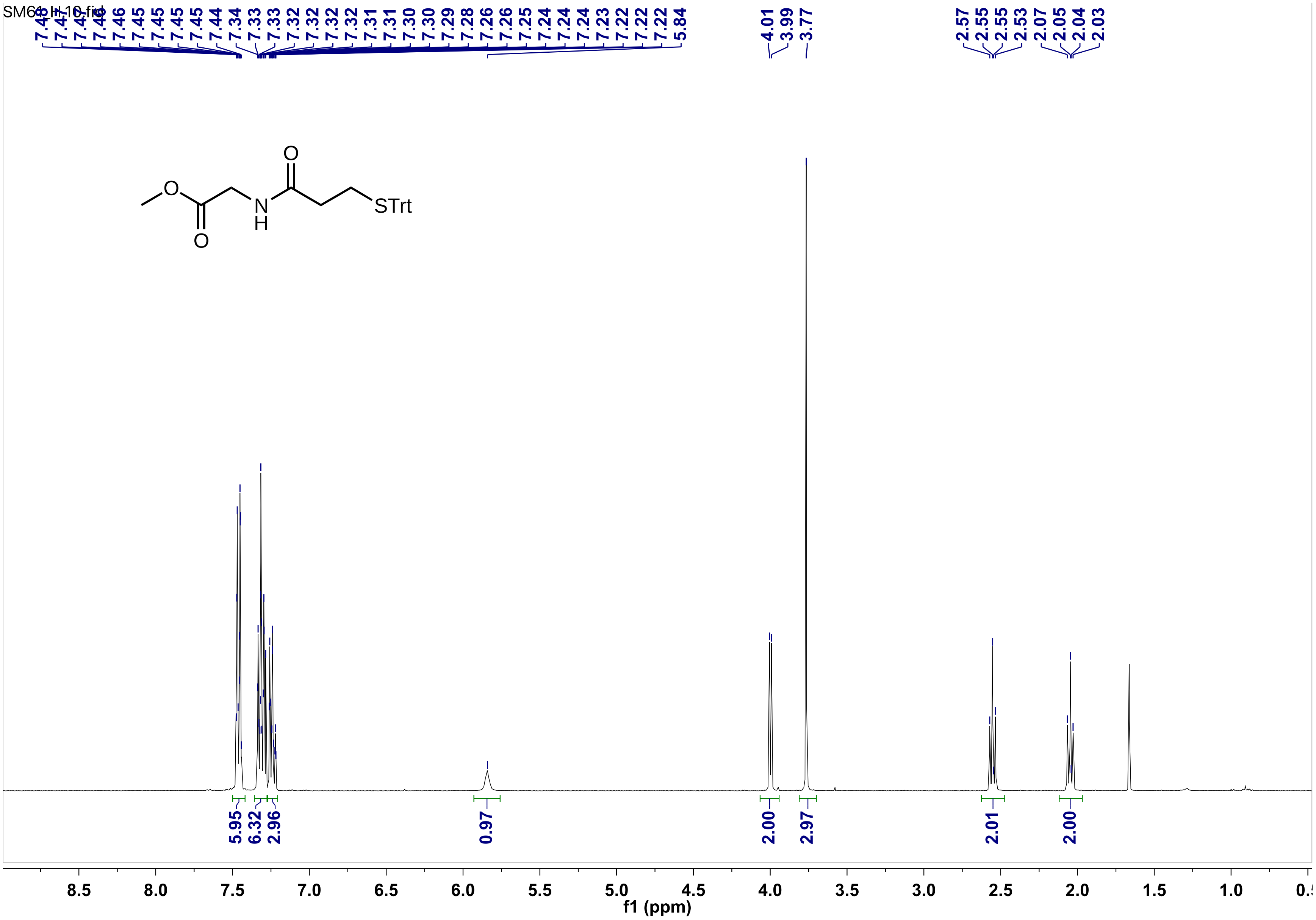
50
40
30
20
10
0
f1 (ppm)


SM61_H.10.fid
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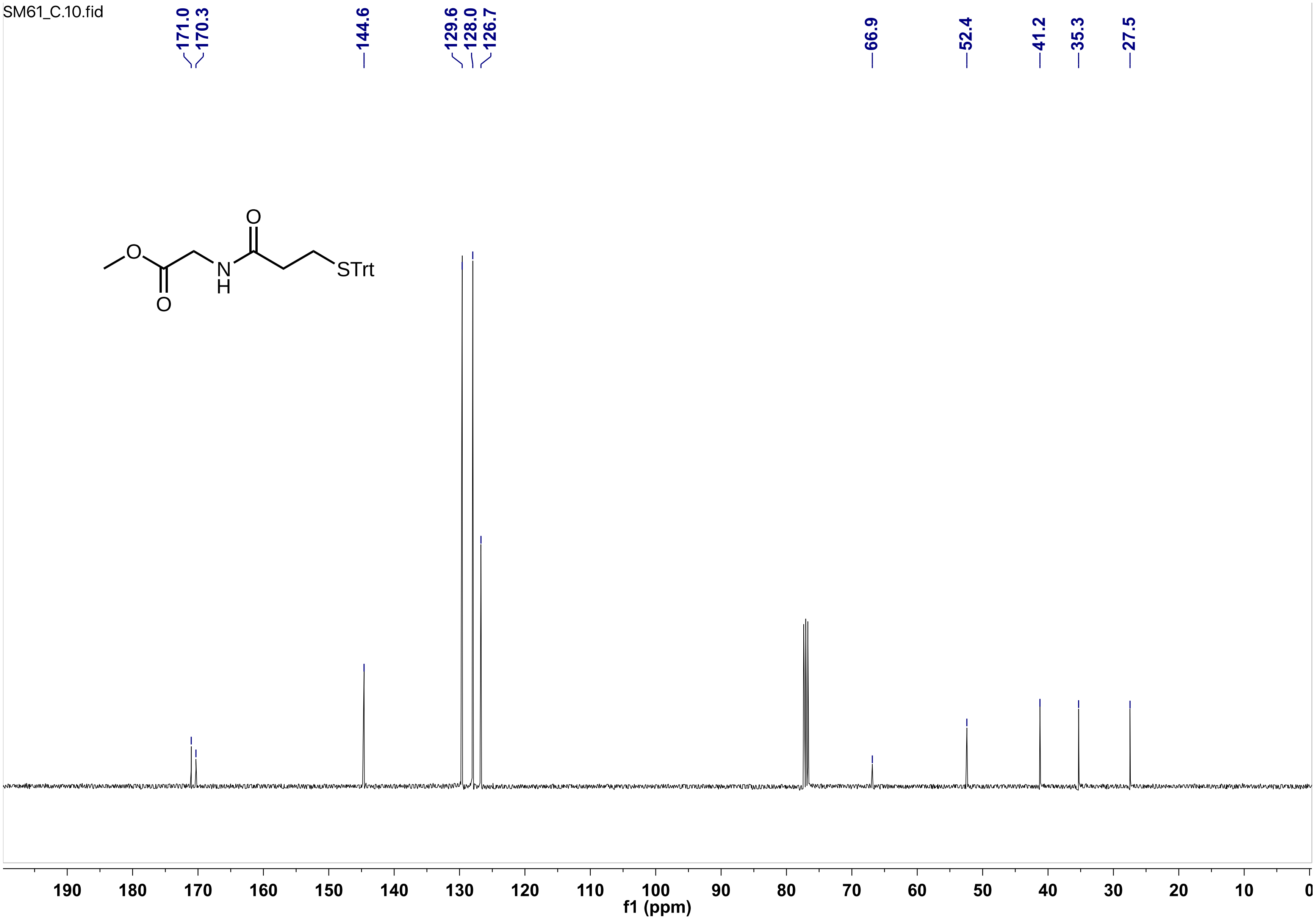
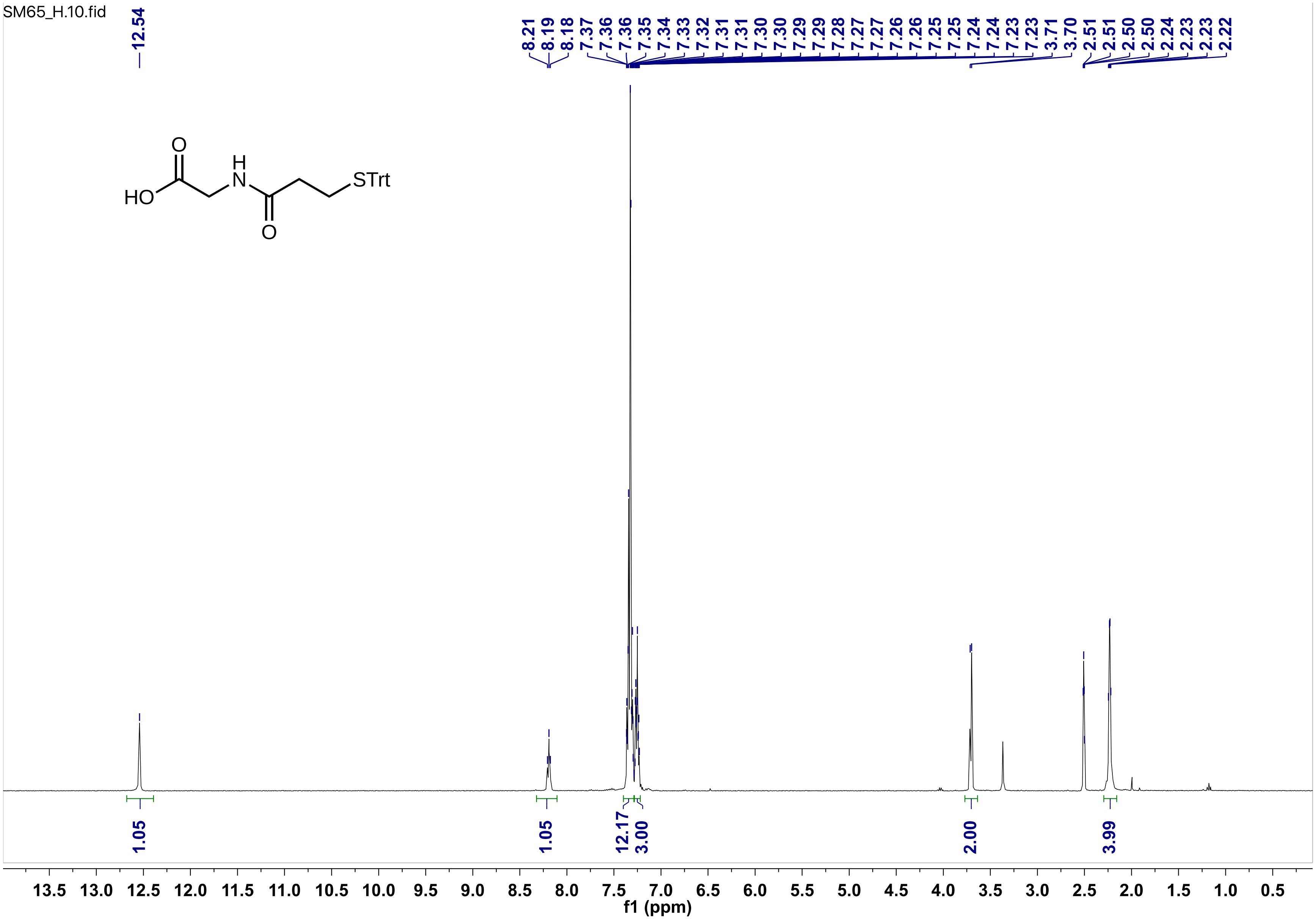
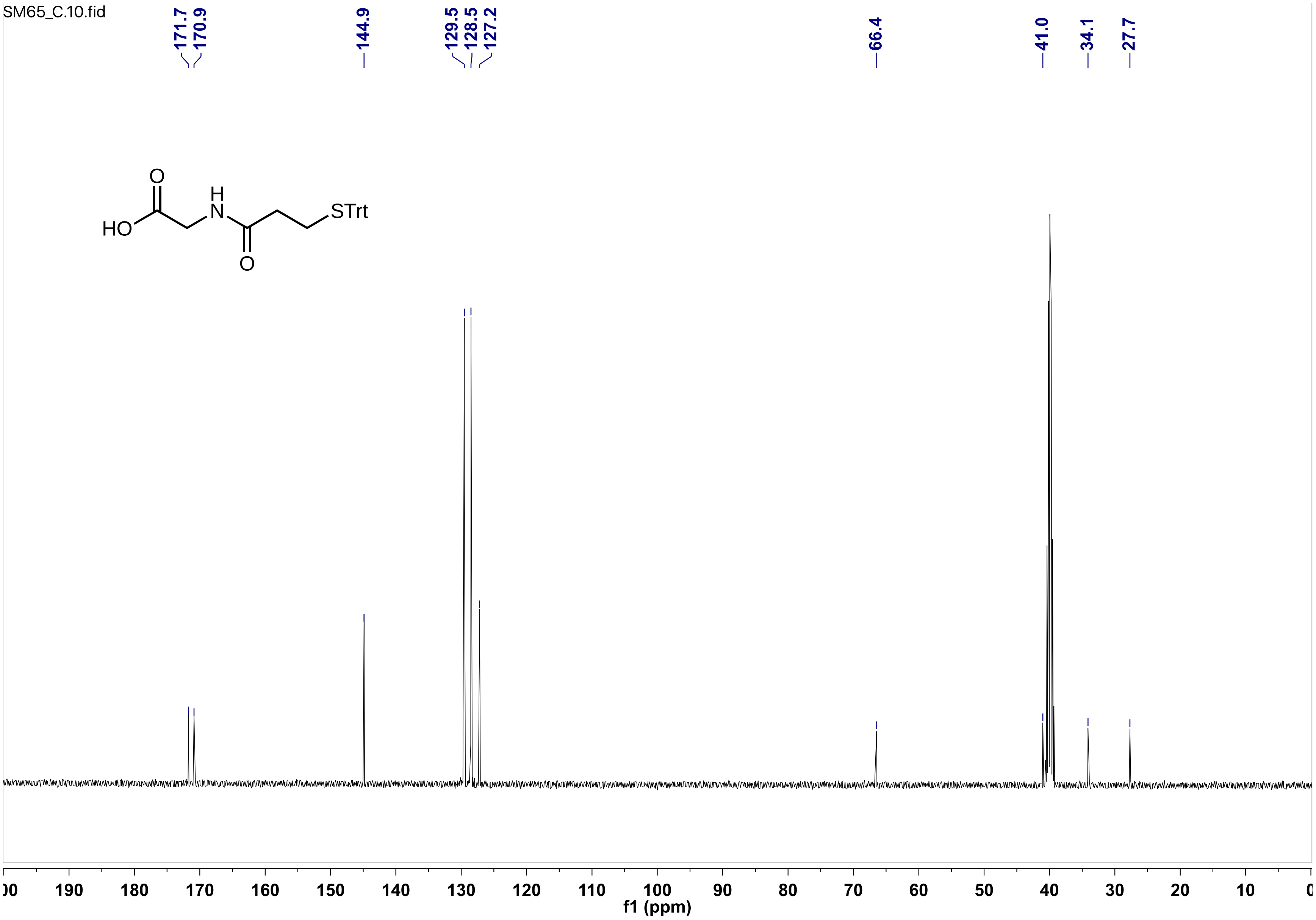
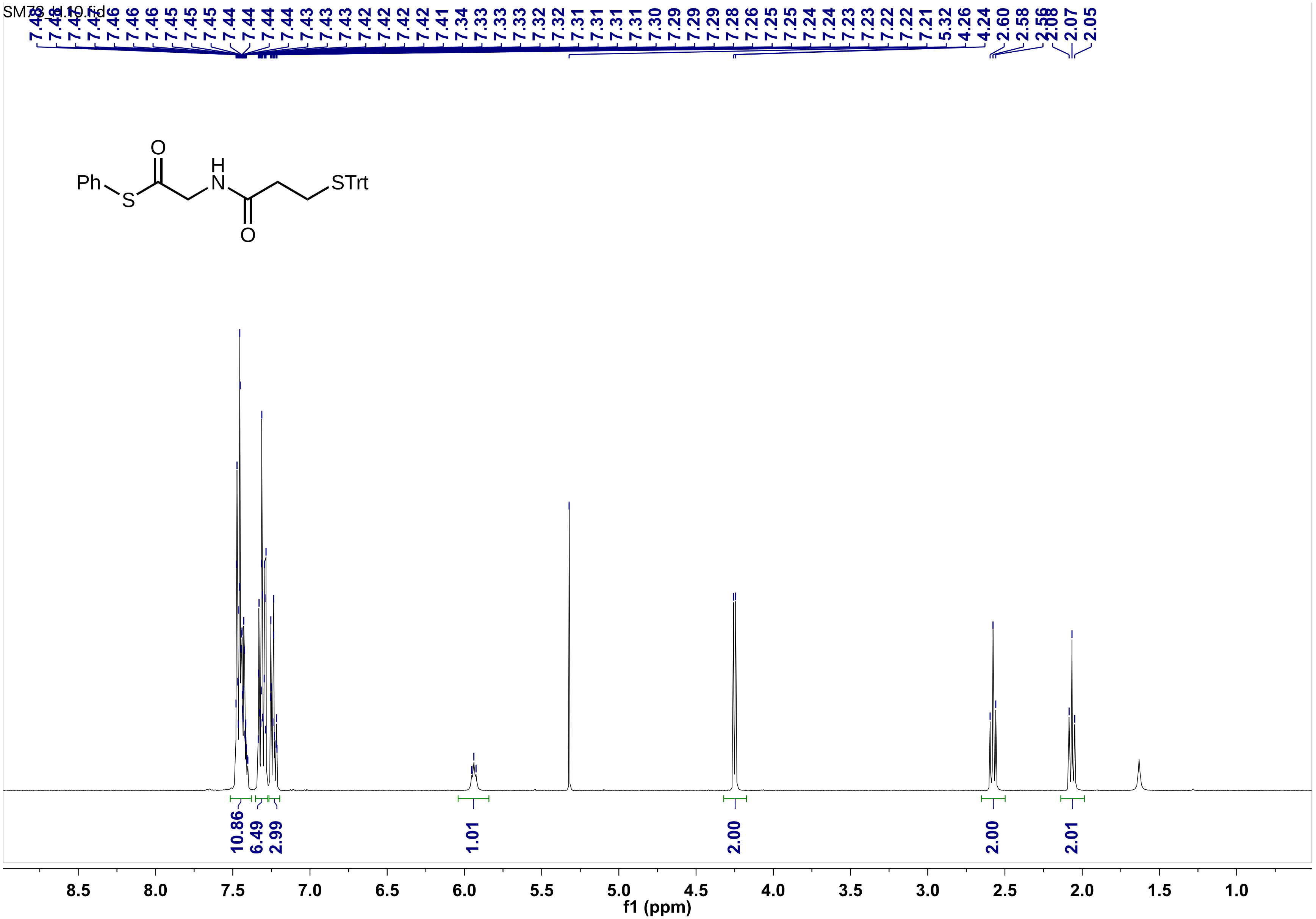
7.47
7.47
7.46
7.46
7.45
7.45
7.45
7.45
7.44
7.34
7.33
7.33
7.32
7.32
7.32
7.32
7.31
7.31
7.30
7.29
7.28
7.26
7.26
7.25
7.24
7.24
7.24
7.23
7.22
7.22
7.22
5.84
4.01
3.99
3.77
2.57
2.55
2.55
2.53
2.07
2.05
2.04
2.03
O
O
N
H
O
STrt
5.95
6.32
2.96
0.97
2.00
2.97
2.01
2.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


SM61_C.10.fid
171.0
170.3
144.6
129.6
128.0
126.7
66.9
52.4
41.2
35.3
27.5
O
O
N
H
O
STrt
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


SM65_H.10.fid
12.54
8.21
8.19
8.18
7.37
7.36
7.36
7.35
7.34
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.24
7.24
7.23
7.23
3.71
3.70
2.51
2.51
2.50
2.50
2.24
2.23
2.23
2.22
HO
O
H
N
O
STrt
1.05
1.05
12.17
3.00
2.00
3.99
13.5
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


SM65_C.10.fid
171.7
170.9
144.9
129.5
128.5
127.2
66.4
41.0
34.1
27.7
HO
O
H
N
O
STrt
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.46
7.46
7.45
7.45
7.45
7.44
7.44
7.44
7.44
7.43
7.43
7.43
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7.42
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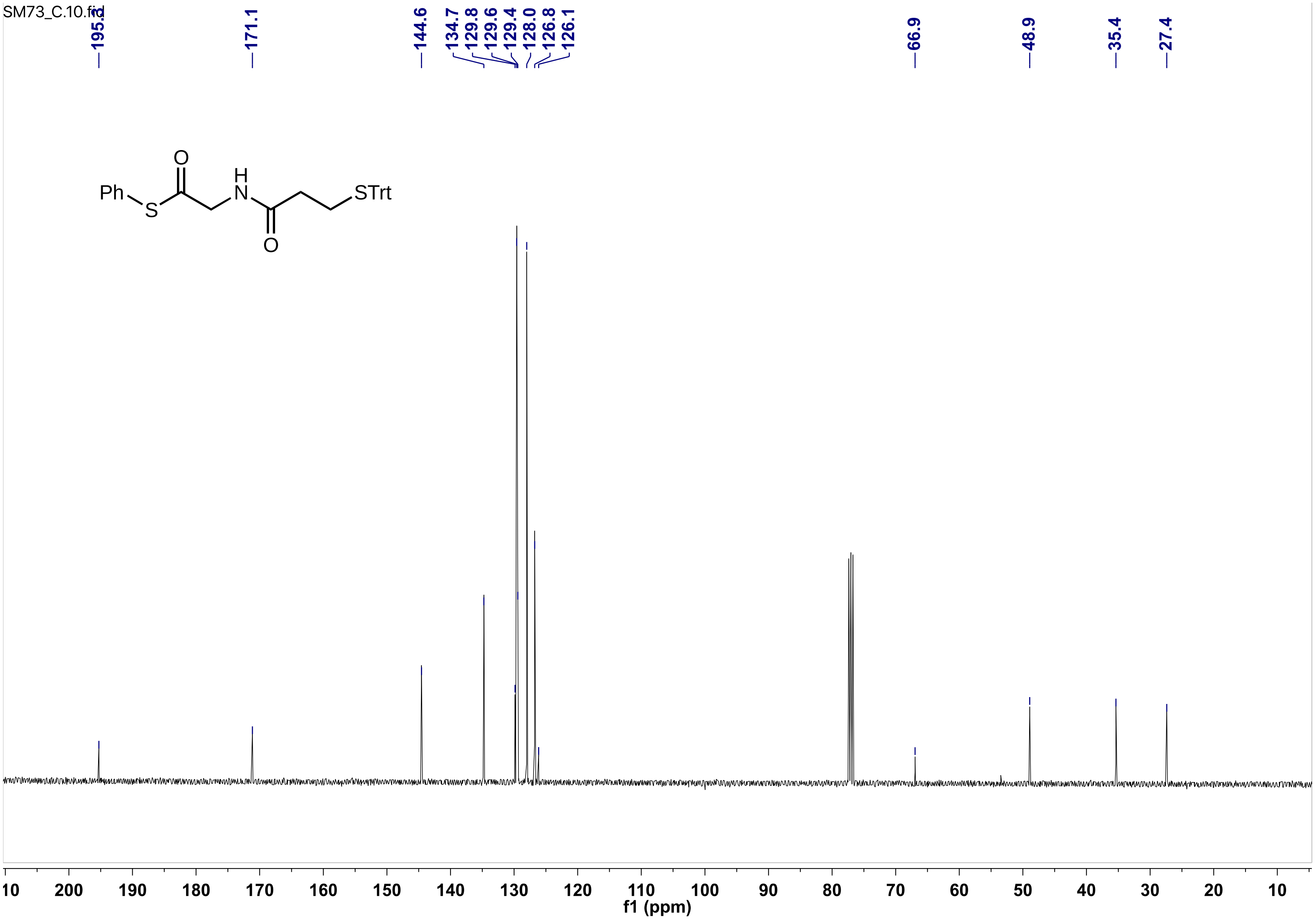
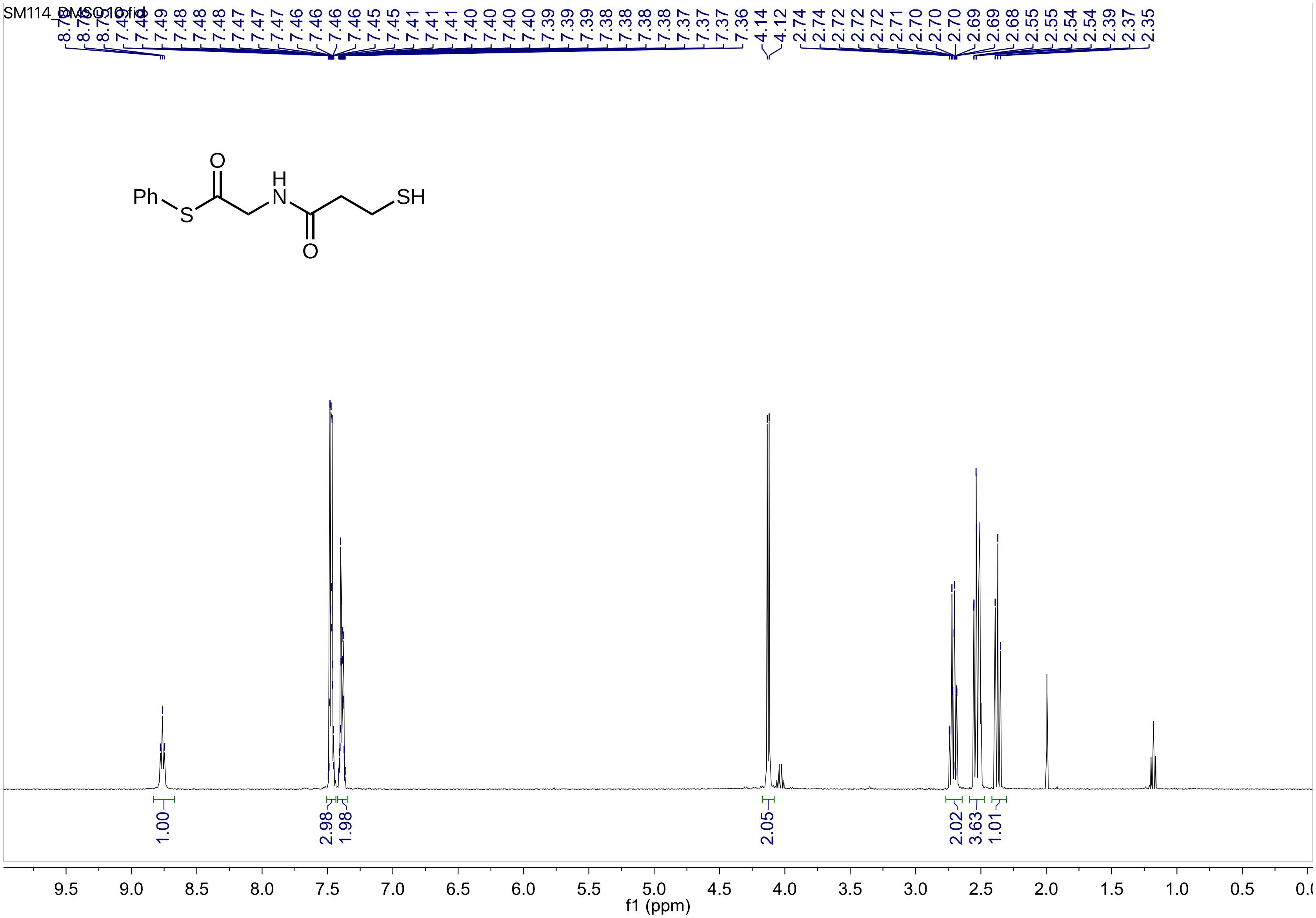
7.41
7.34
7.33
7.33
7.33
7.32
7.32
7.31
7.31
7.31
7.31
7.30
7.29
7.29
7.29
7.28
7.26
7.25
7.25
7.24
7.24
7.23
7.23
7.22
7.22
7.21
5.32
4.26
4.24
2.60
2.58
2.56
2.08
2.07
2.05
Ph
S
O
H
N
O
STrt
10.86
6.49
2.99
1.01
2.00
2.00
2.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


SM73_C.10.fid
195.2
171.1
144.6
134.7
129.8
129.6
129.4
128.0
126.8
126.1
66.9
48.9
35.4
27.4
O
H
Ph
S
N
STrt
O
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


SM114_DMSO.10.fid
8.76
8.75
8.73
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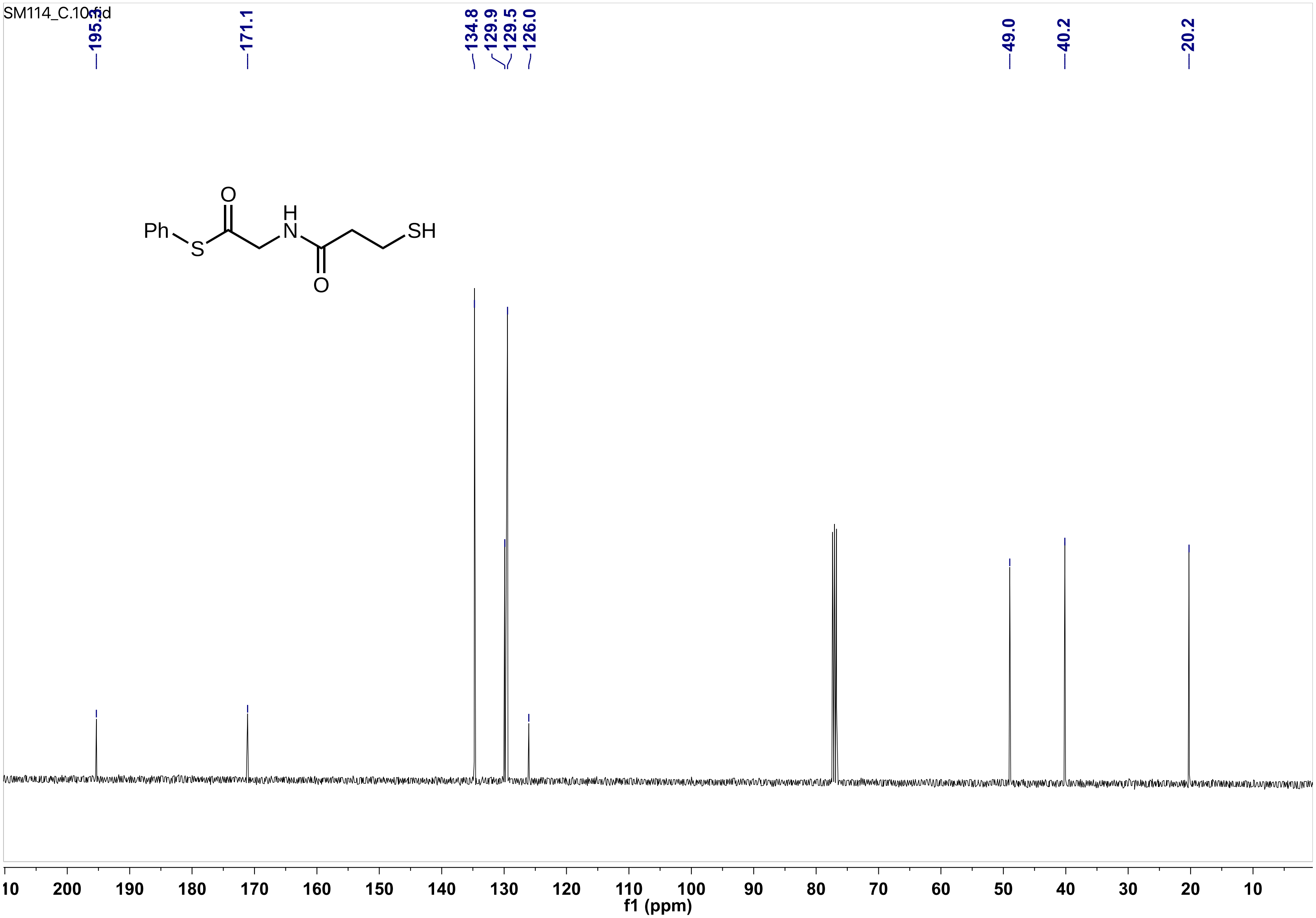
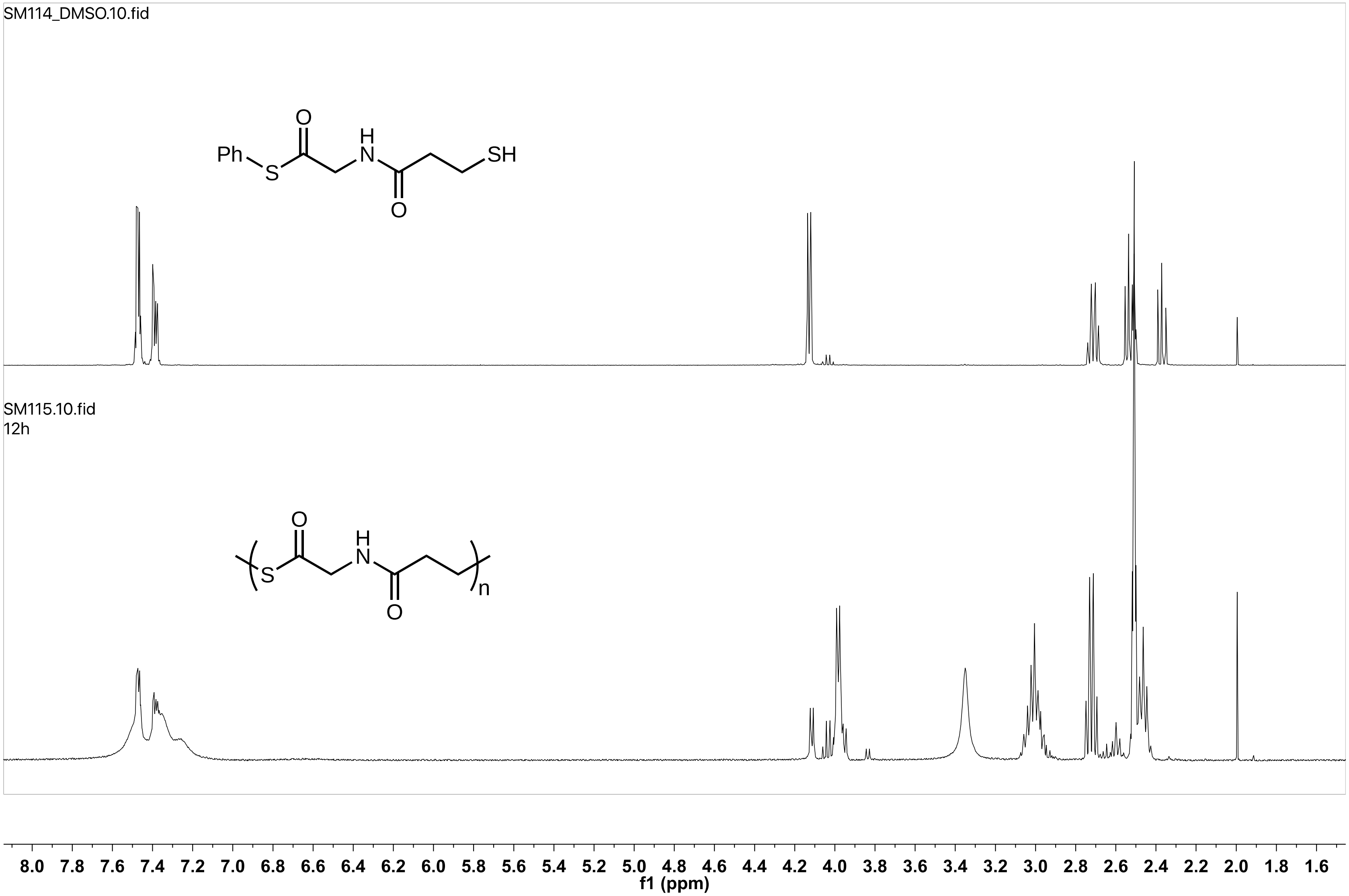
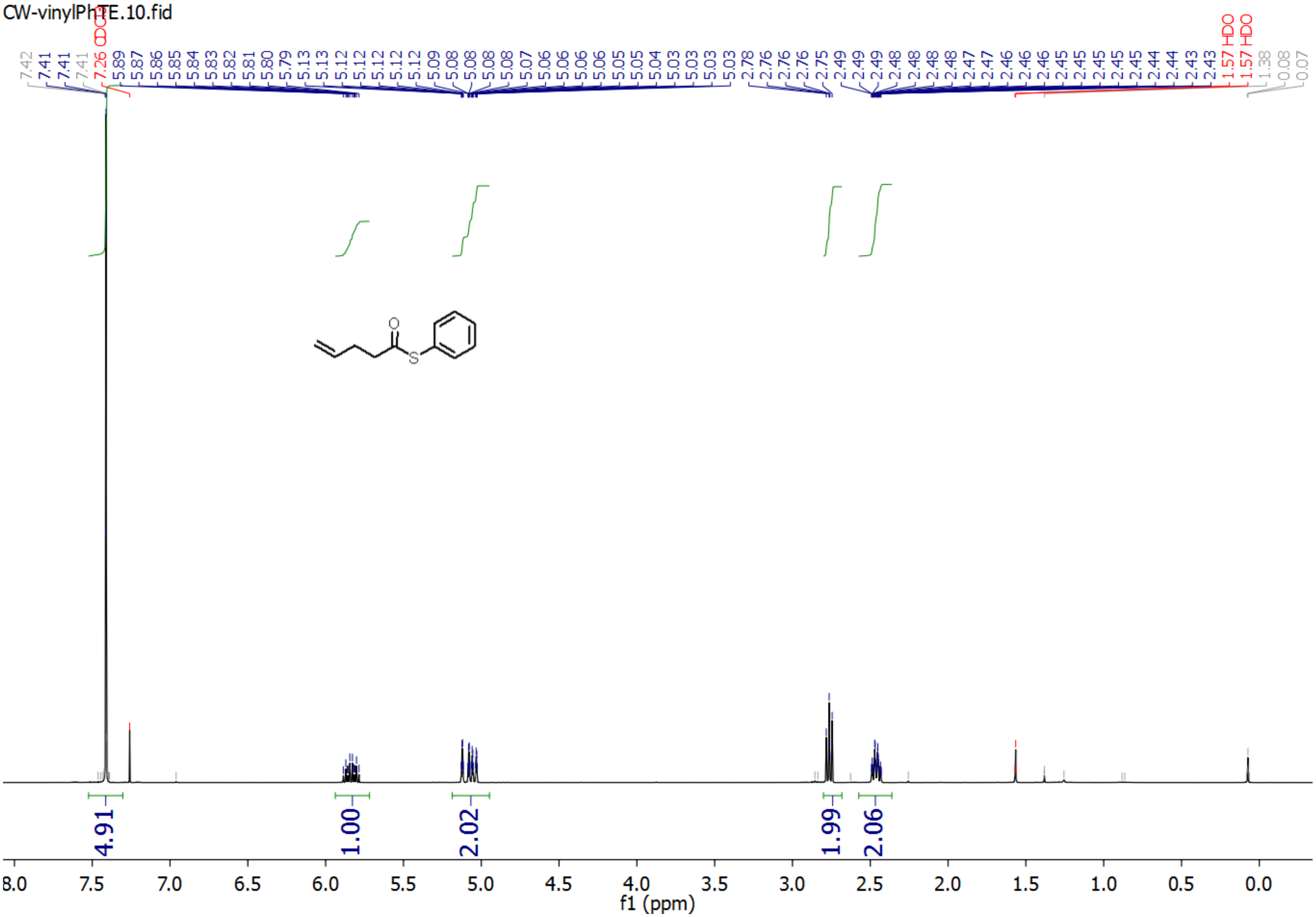
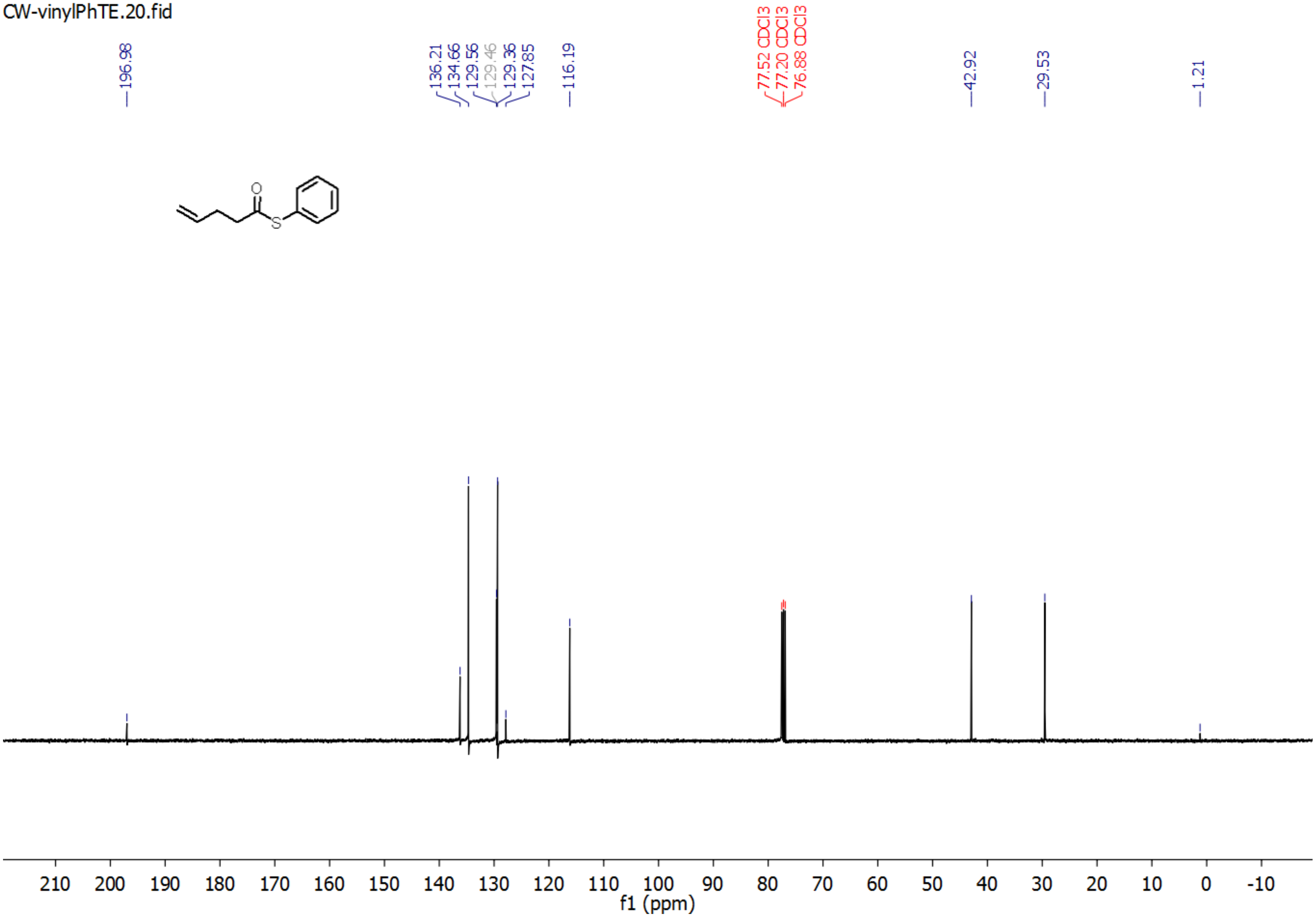
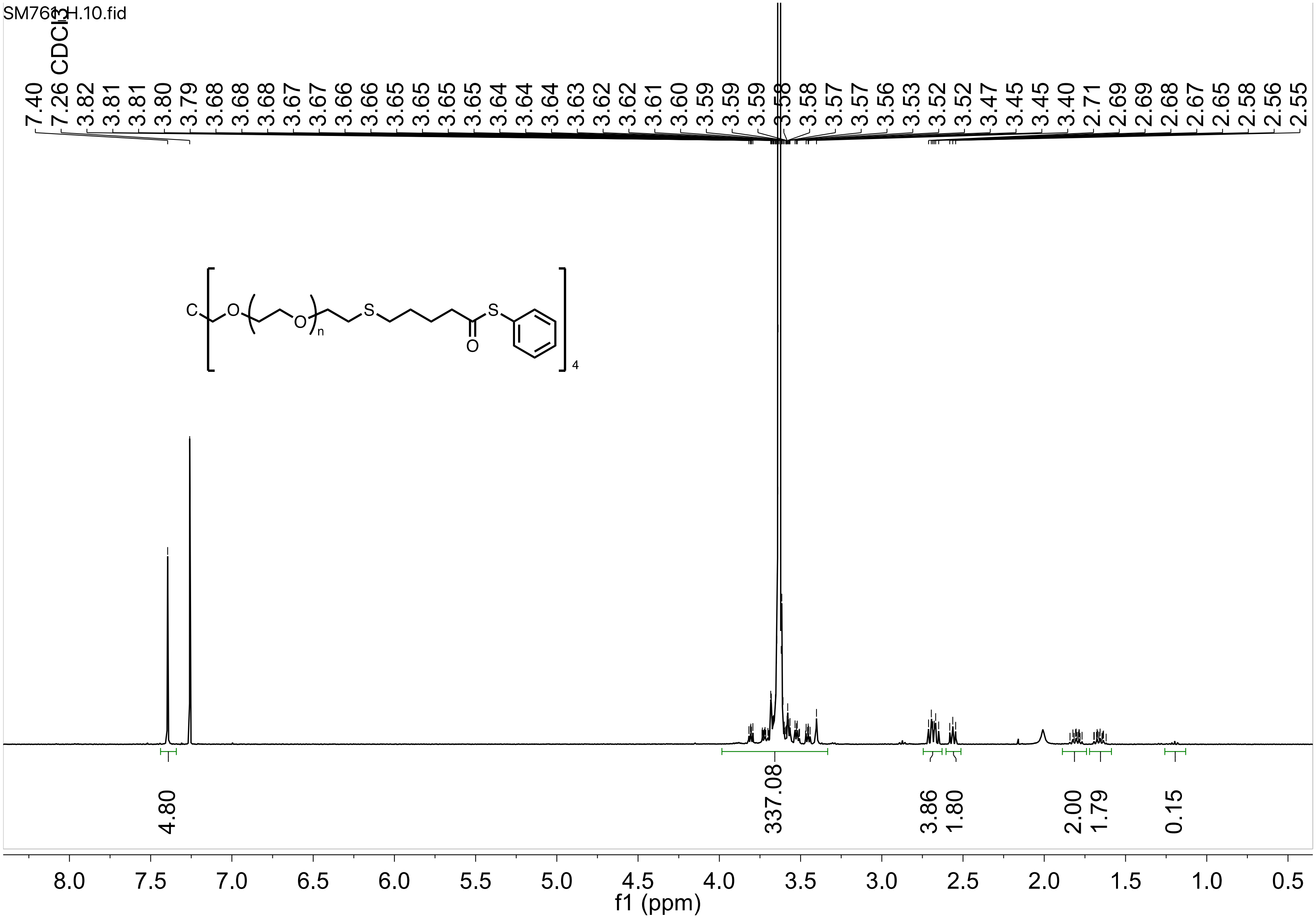
7.49
7.49
7.48
7.48
7.48
7.47
7.47
7.47
7.46
7.46
7.46
7.46
7.45
7.45
7.41
7.41
7.41
7.40
7.40
7.40
7.40
7.39
7.39
7.39
7.38
7.38
7.38
7.38
7.37
7.37
7.37
7.36
4.14
4.12
2.74
2.74
2.72
2.72
2.72
2.71
2.70
2.70
2.70
2.69
2.69
2.68
2.55
2.55
2.54
2.54
2.39
2.37
2.35
Ph
S
O
H
N
O
SH
1.00
2.98
1.98
2.05
2.02
3.63
1.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


SM114_C.10.fid
195.3
171.1
134.8
129.9
129.5
126.0
49.0
40.2
20.2
Ph
S
O
H
N
O
SH
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


SM114_DMSO.10.fid
Ph
S
O
H
N
O
SH
SM115.10.fid
12h
S
O
H
N
O
n
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6
f1 (ppm)


CW-vinylPhTE.10.fid
7.42
7.41
7.41
7.41
7.26 CDCl3
5.89
5.87
5.86
5.85
5.84
5.83
5.82
5.81
5.80
5.79
5.13
5.13
5.12
5.12
5.12
5.12
5.12
5.09
5.08
5.08
5.08
5.08
5.07
5.06
5.06
5.06
5.06
5.05
5.05
5.04
5.03
5.03
5.03
5.03
2.78
2.76
2.76
2.76
2.75
2.49
2.49
2.49
2.48
2.48
2.48
2.47
2.47
2.46
2.46
2.46
2.45
2.45
2.45
2.45
2.45
2.44
2.44
2.43
2.43
1.57 HDO
1.57 HDO
1.38
0.08
0.07
O
S
4.91
1.00
2.02
1.99
2.06
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CW-vinylPhTE.20.fid
196.98
136.21
134.66
129.56
129.46
129.36
127.85
116.19
77.52 CDCl3
77.20 CDCl3
76.88 CDCl3
42.92
29.53
1.21
O
S
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


SM761_1H.10.fid
7.40
7.26 CDCl3
3.82
3.81
3.81
3.80
3.79
3.68
3.68
3.68
3.67
3.67
3.66
3.66
3.65
3.65
3.65
3.65
3.64
3.64
3.64
3.63
3.62
3.62
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3.60
3.59
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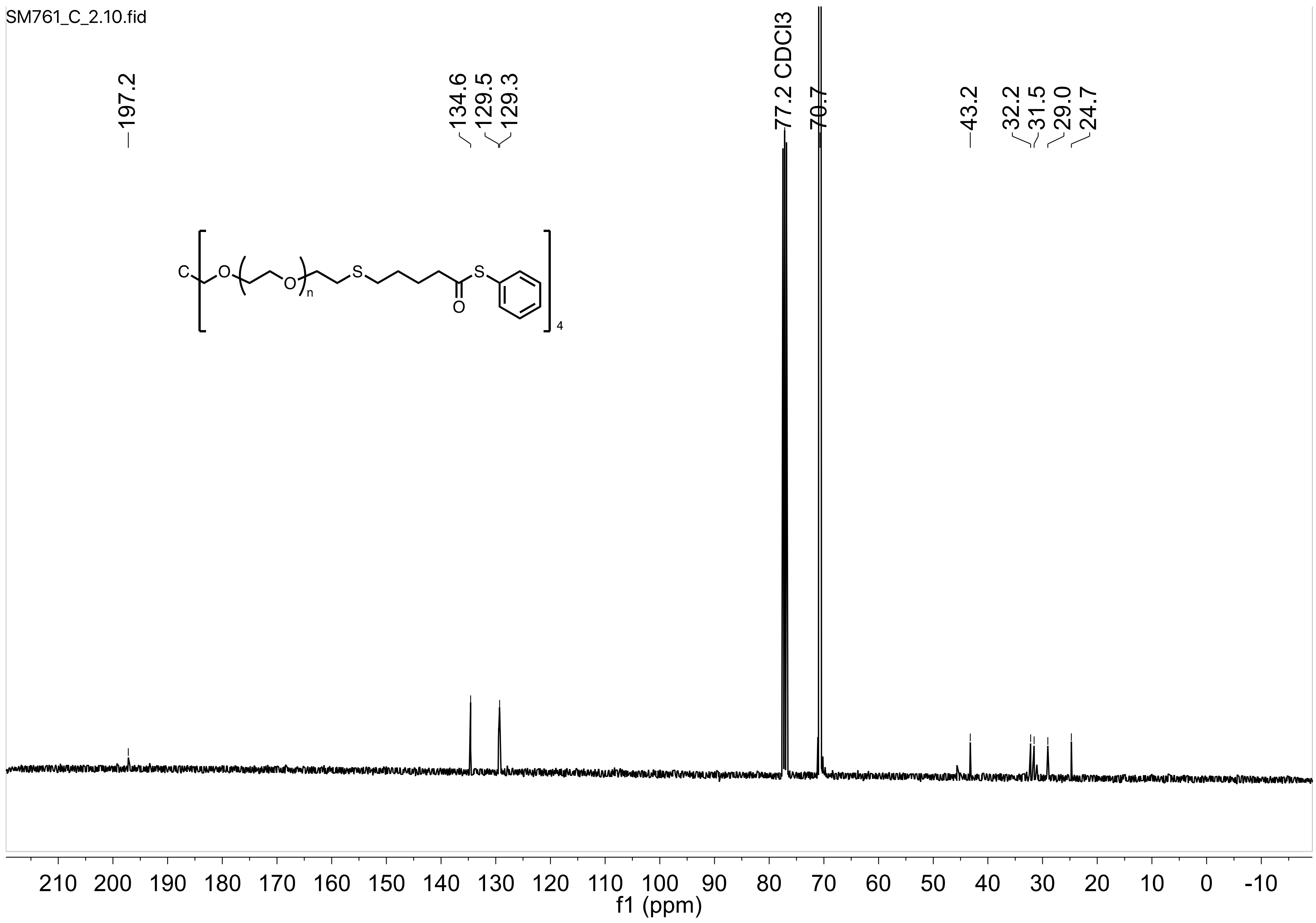
3.59
3.58
3.58
3.57
3.57
3.56
3.53
3.52
3.52
3.47
3.45
3.45
3.40
2.71
2.69
2.69
2.68
2.67
2.65
2.58
2.56
2.55
C
O
O
n
S
S
O
4
4.80
337.08
3.86
1.80
2.00
1.79
0.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


SM761_C_2.10.fid
197.2
134.6
129.5
129.3
77.2 CDCl3
70.7
43.2
32.2
31.5
29.0
24.7
C
O
O
n
S
S
O
4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)