Supporting Information

Experimental Procedures

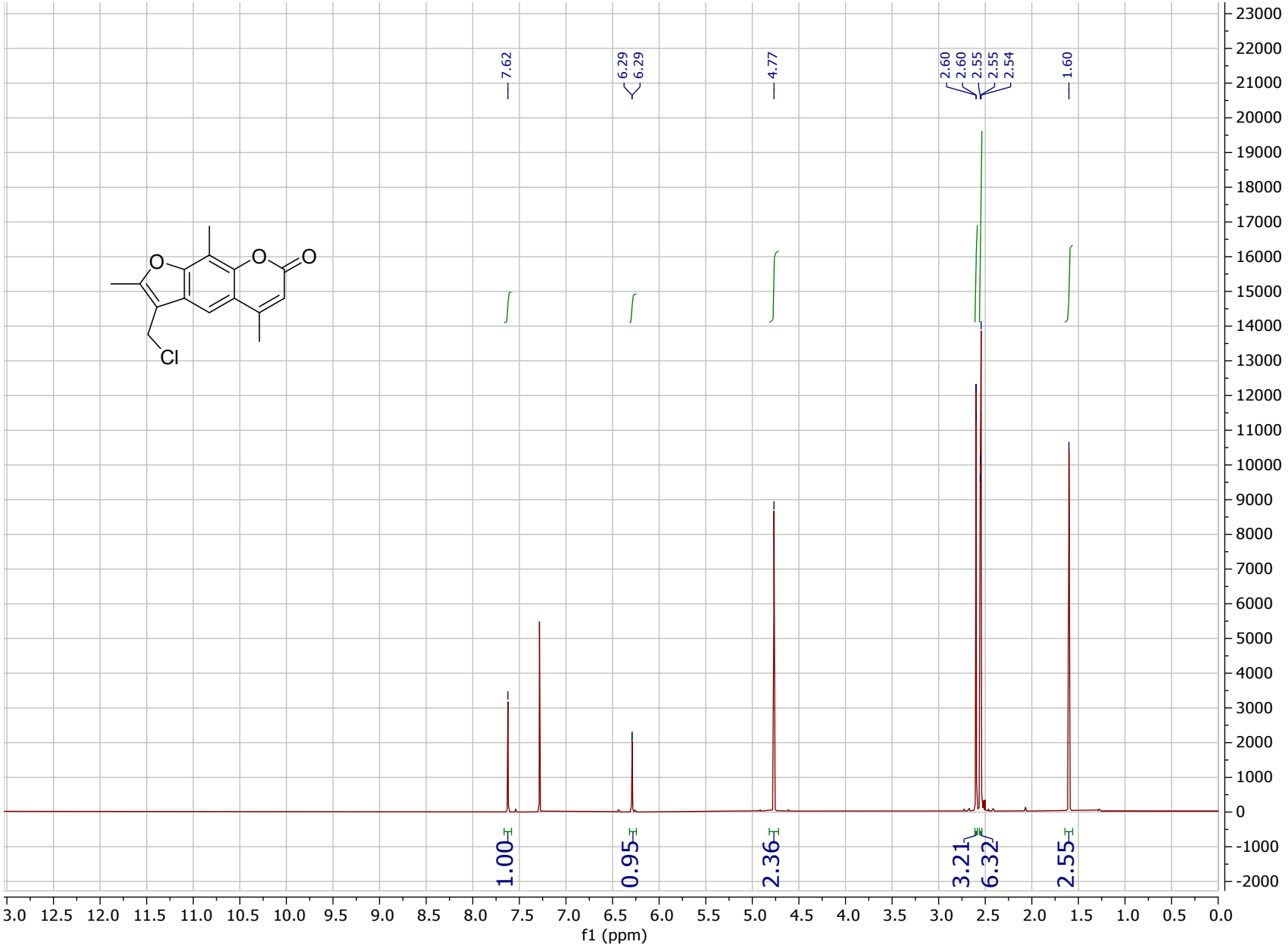
In-cell fluoresces assay. Hela cells were plated on 35 mm imaging petri dishes in DMEM supplemented with 10% FBS and grown for 24 h at 37 ^{o}C with 5% CO_2. The next day the media was removed followed by a PBS wash (1 mL). Cells were then incubated at 37 ^{o}C with 1 mL of blocking solution (1X PBS, 5% BSA, 0.1% Saponin) for 30 min. PP3B, AP3B, or vehicle (10 μL DMSO) was added and incubated for 10 min at 37 ^{o}C. The solution was removed, and the cells were washed once with PBS to remove excess compound. The dishes that needed to be exposed to UV light were placed on ice and exposed to 368 nm light (5 1.2 W bulbs) at a distance of 6 cm for 30 min using a UV oven during which time cell death occurred. The unexposed samples were kept under ambient light for 30 min. All dishes were then washed with 40% formamide, PBS, and blocking solution to remove unreacted molecules at which point cell death occurred for the non-UV exposed cells. The cells were then incubated with a streptavidin-rhodamine conjugate (TheremoFisher Scientific, catalog number 21724) solution (1 μg/mL in blocking solution) at 4 ^{o}C for 1 h. Unbound conjugate was removed by 3 washes with blocking solution (1 mL each). Anti-fade reagent containing DAPI (30 μL) was added to each dish and the fluorescent intensities of the DAPI and rhodamine signals were quantified using a Cytation 5 microscope. Integrals of nuclear rhodamine intensity were calculated by taking the integral of the rhodamine signal that overlapped with DAPI signals.

DNA electrophoretic mobility shift assay. A DNA fragment (~500bp) was purified after PCR amplification for this experiment. A denaturing agarose gel (2% agarose, 30 mM NaOH, 2 mM EDTA, pH 8) was prepared. Reaction solutions were prepared by mixing 20μL of purified DNA (30 ng/μL), 1 μL of the crosslinker solutions (prepared at different concentrations in DMSO) or (DMSO (control without crosslinker). The reaction solutions were placed on ice and exposed to a 368 nm light source (5 1.2 W bulbs) 6 cm away for 30 min using a UV oven. Then 10x running buffer was added to make the samples a 1x solution. The samples heated to 95 ^{o}C for 3 min prior to loading onto the gel. The gel was run for 180 min at 45 V then stained with a solution of 1X SYBR Gold in 0.5 M Tris at pH 7.5 for 18 h prior to imaging.

Synthesis of 4'-Chloromethyl-4,5',8-trimethylpsoralen (2). To a solution of 1,3,5 Trioxane (0.71g, 7.9 mmol) in concentrated HCl (45 mL) was added **1** (2.05g 9.0 mmol). The reaction mixture was stirred at room temperature for 16 h then diluted with water (50 mL) and extracted three times with chloroform (100 mL each). The organic layers were combined, washed with brine (100 mL), dried with Na_2SO_4, then concentrated with a rotary evaporator. The crude product was recrystallized from ethyl acetate to yield the final compound (1.19g, 4.3 mmol, 54%).^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.59 (s, 1H), 6.26 (s, 1H), 4.74 (s, *2*H), 2.57 (s, 3H), 2.52 (s, 6H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 161.3, 155.2, 154.6, 153.12, 149.5, 123.9, 116.4, 113.2, 112.2, 111.2, 109.6, 36.2, 19.4, 12.3, 8.5.

Synthesis of AMT-alkyne (3). 2 (0.90g, 0.36 mmol) and propargylamine (0.23 mL, 36 mmol) were combined in toluene (50 mL). The reaction mixture was refluxed for 16 h after which the solution was cooled to room temperature and concentrated with a rotary evaporator. The crude residue was then purified by column chromatography (Hexane: EtOAc 1:1 → 1:2) to give the final product (0.80g 76%). ^{1}H NMR (500 MHz, DMSO): δ 7.79 (s, 1H), 6.31 (s, 1H), 3.87 (s, 2H), 3.27 (s, 2H), 3.14 (s, 1H) 2.47 (s, 6H) 2.44 (s,3H); ^{13}C NMR (126 MHz, DMSO) δ 160.1, 154.1, 153.9, 153.7, 148.3, 125.3, 115.5, 112.8, 112.5, 112.0, 107.5, 82.9, 73.8, 36.2, 18.7, 11.9, 8.2;

Synthesis of AP3B. 3 (0.16g, .54 mmol) and Biotin-PEG3-Azide (0.24g, 0.54 mmol) were dissolved in a solution of methanol and water (1:1, 14 mL). $NaHCO_3$ (64 mg, 0.76 mmol), $Cu_2SO_4 \cdot 5H_2O$ (14 mg, .054 mmol) and sodium ascorbate (21 mg, 0.11 mmol) were added to the reaction vessel. This solution was stirred at room temperature for 16h. The solution was extracted three times with DCM (14 mL). The pooled organic layers were washed with brine (30 mL), dried with Na_2SO_4, and then the solvent was removed with a rotary evaporator. The crude was purified by column chromatography (DCM: MeOH 10:1, 8:1, and then 6:1) to give the final product (0.37g, 0.50 mmol, 93%) 1H NMR (500 MHz, Methanol-d4) δ 7.98 (s, 1H), 7.82 (s, 1H), 6.28 – 6.22 (m, 1H), 4.60 (t, J = 5.0 Hz, 2H), 4.49 (dd, J = 7.9, 4.9 Hz, 1H), 4.29 (dd, J = 7.9, 4.5 Hz, 1H), 3.97 (s, 4H), 3.91 (t, J = 5.1 Hz, 2H), 3.65 – 3.58 (m, 4H), 3.58 – 3.52 (m, 4H), 3.49 (t, J = 5.5 Hz, 2H), 3.22 – 3.14 (m, 1H), 2.92 (dd, J = 12.8, 4.9 Hz, 1H), 2.70 (d, J = 12.8 Hz, 1H), 2.56 (s, 3H), 2.49 (d, J = 13.7 Hz, 6H), 2.18 (t, J = 7.4 Hz, 2H), 1.78 – 1.51 (m, 4H), 1.41 (p, J = 8.7, 8.1 Hz, 2H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 174.6, 164.7, 162.1, 155.3, 155.2, 154.5, 148.7, 145.1, 125.4, 123.8, 115.9, 112.2, 112.0, 111.5, 108.2, 70.13, 70.08, 70.02, 69.8, 69.2, 69.0, 62.0, 60.2, 55.6, 50.0, 42.7, 40.7, 39.6, 38.9, 35.3, 28.3, 28.1, 25.4, 18.1, 10.8, 7.0. HRMS (ESI) m/z: calculated for $C_{36}H_{49}O_8N_7S$ $[M+H]^+$: 740.3436, found 740.3413.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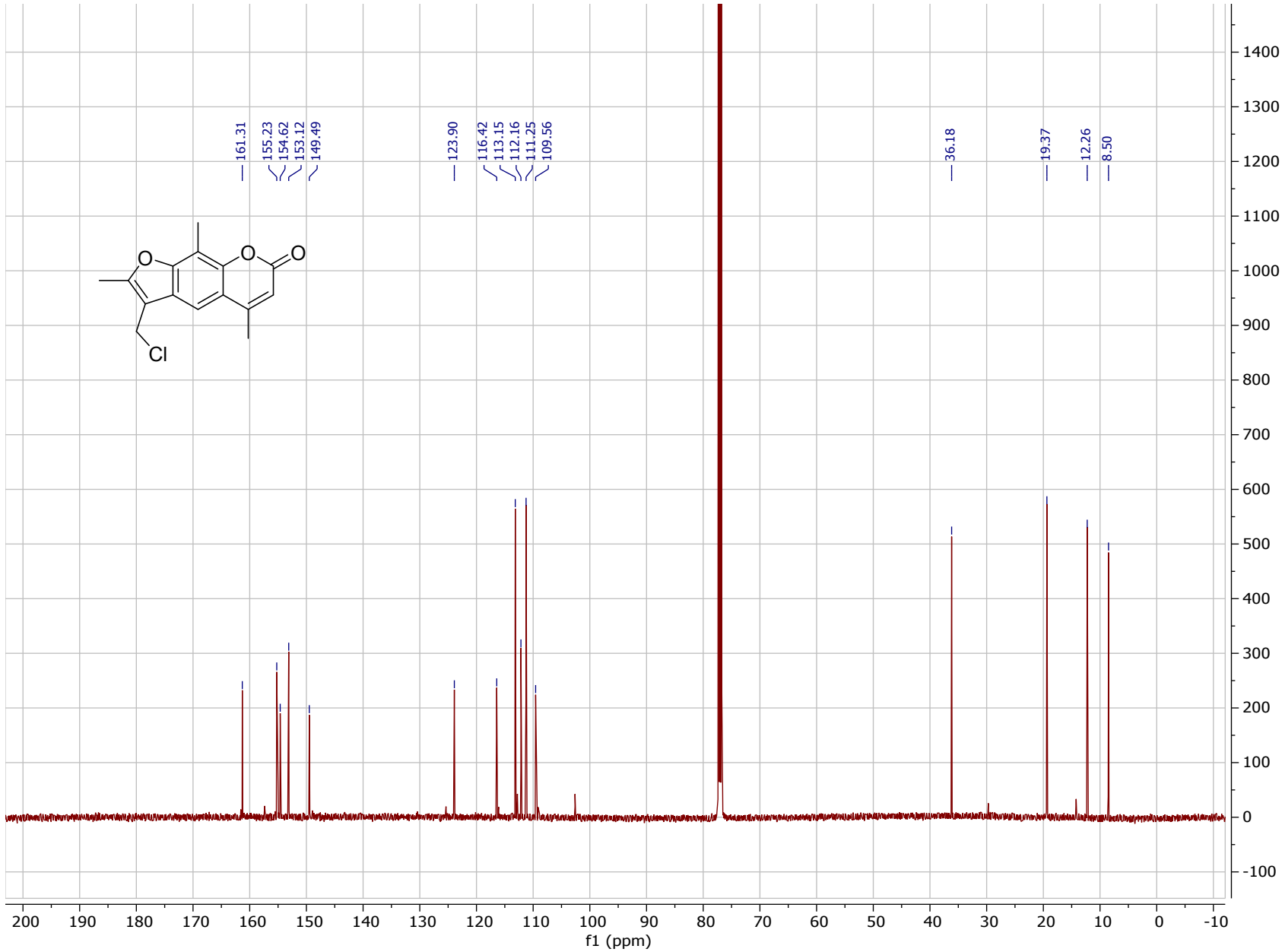
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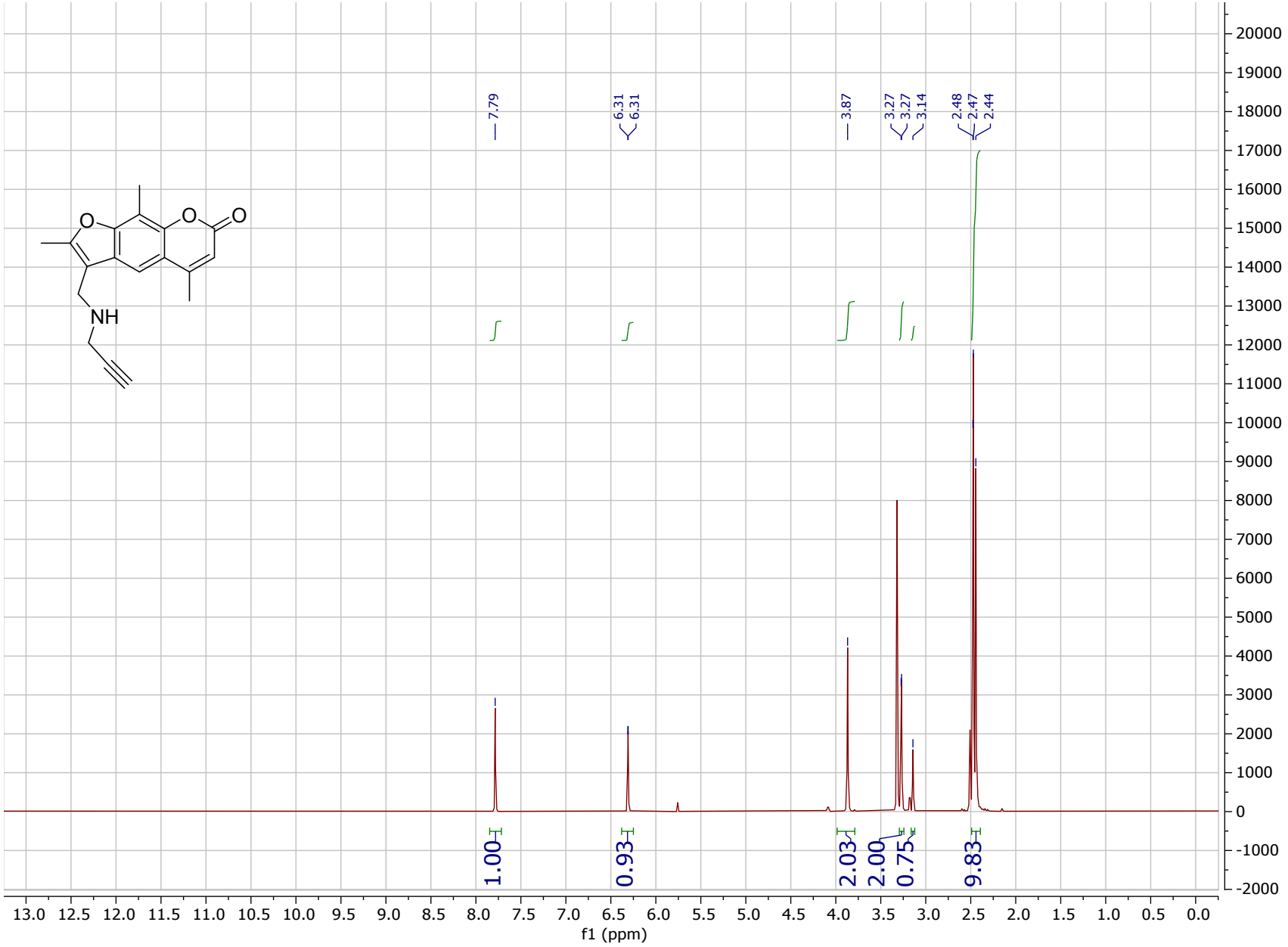
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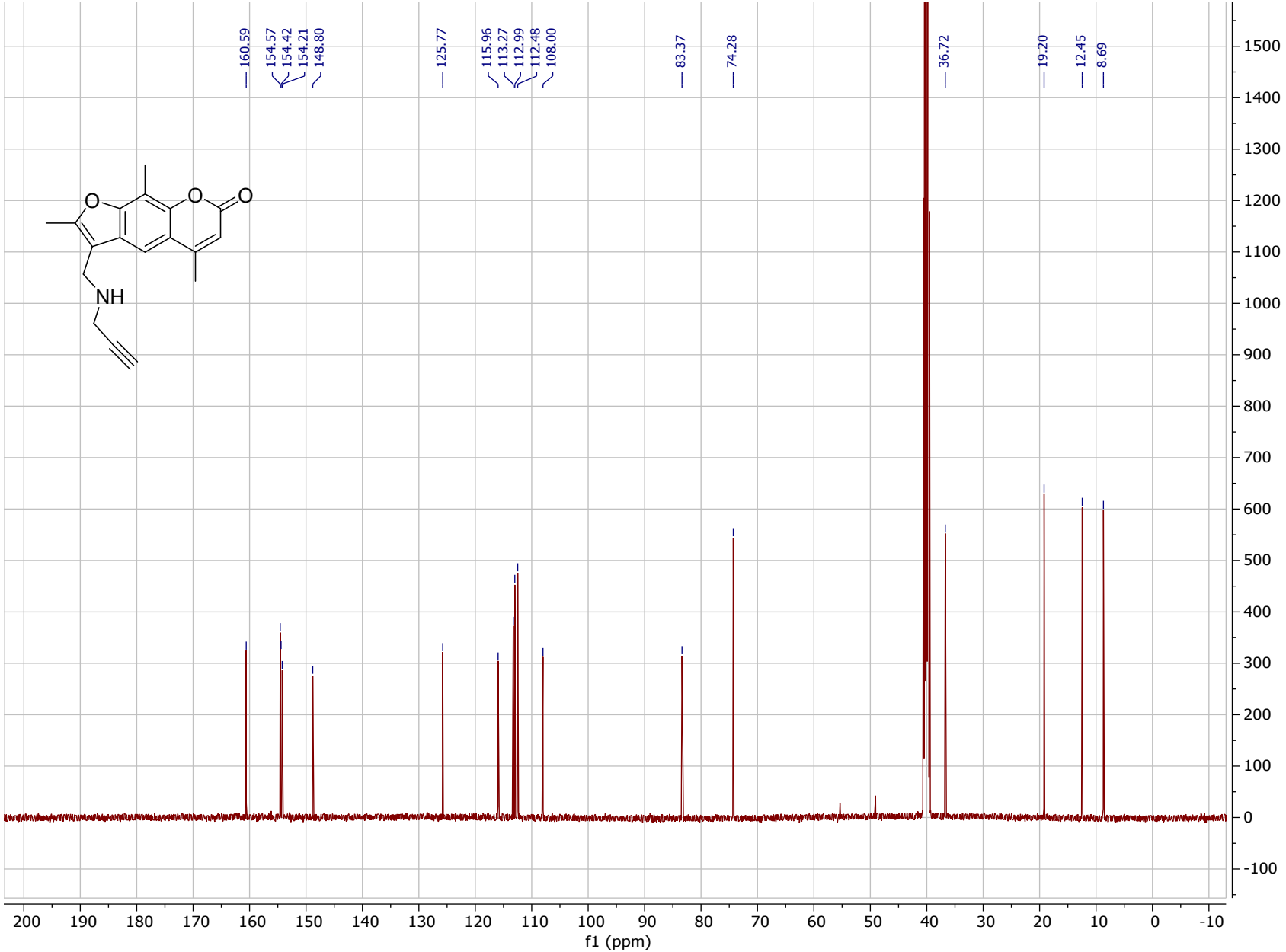
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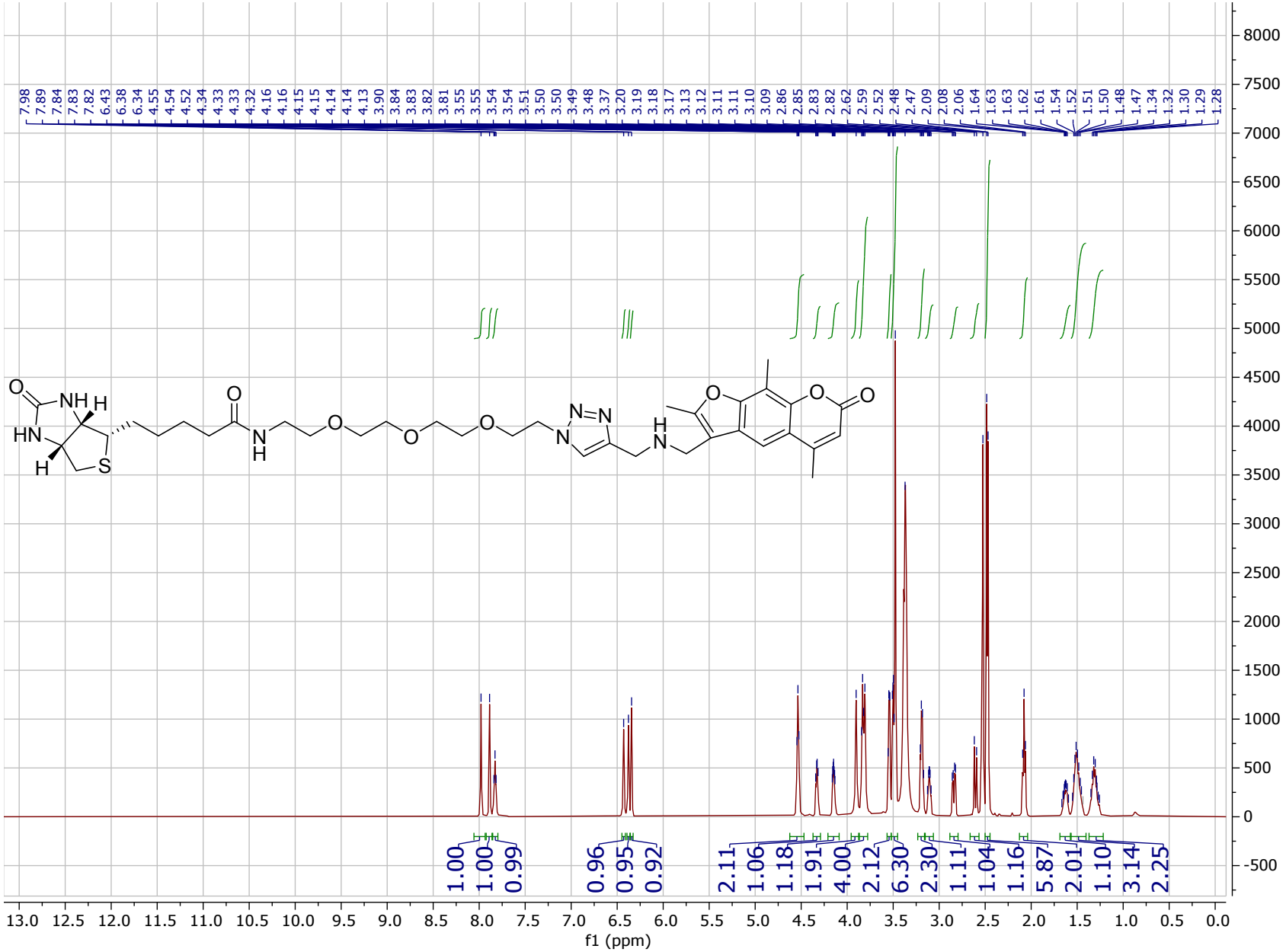
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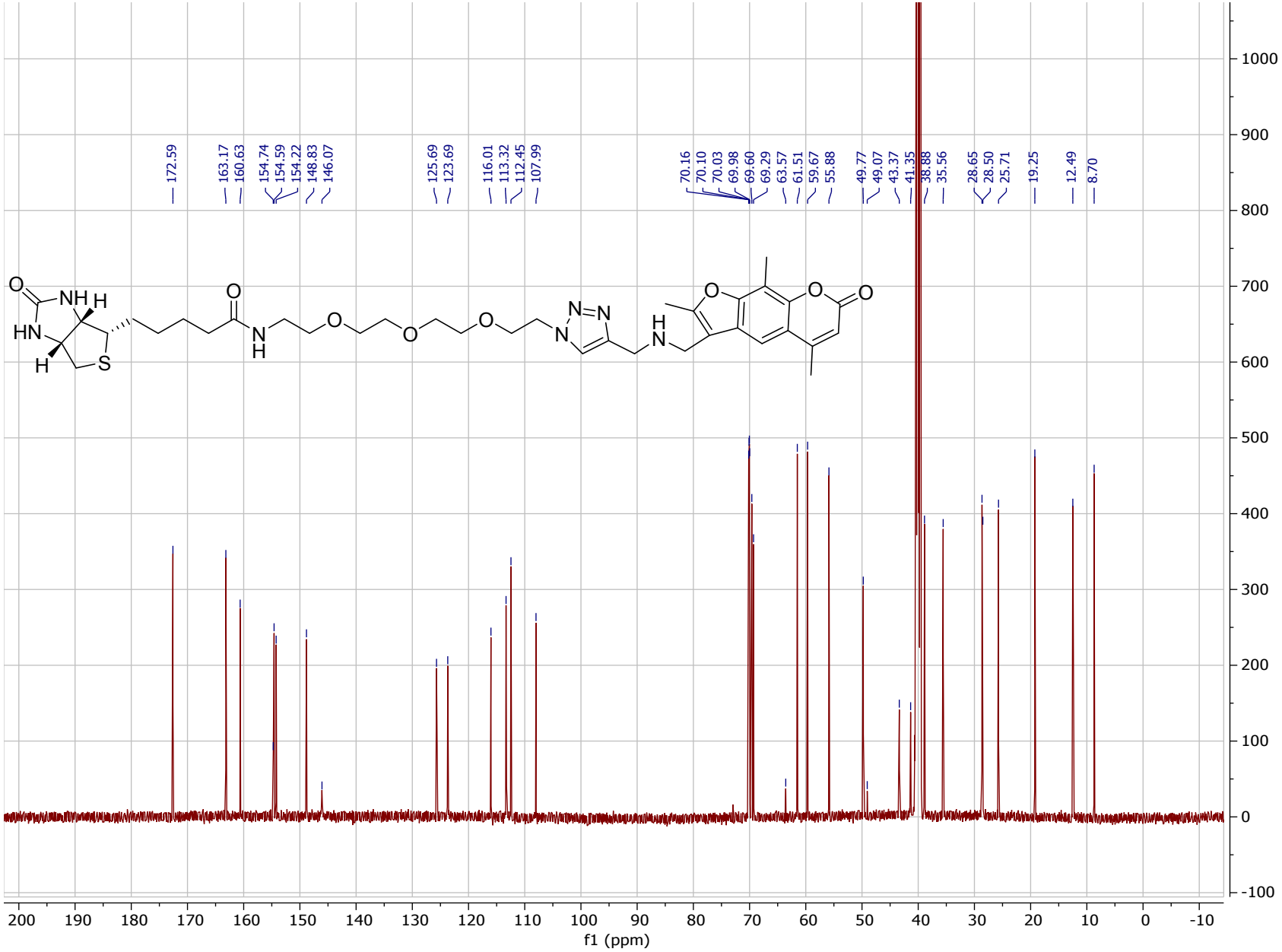
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