Supporting Information

A Ratiometric Acoustogenic Probe for *In Vivo* Imaging of Endogenous Nitric Oxide

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Materials. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), dichloromethane, isoamyl nitrite, propargyl bromide (80 % w/w in toluene), and triethylamine were purchased from Acros Organic. Hydrogen was purchased from Airgas. 1,3-Dimethylbarbituric acid, 4'-hydroxyacetophenone, 4'methoxyacetophenone, and ninhydrin were purchased from AK Scientific. Allyl bromide, nitromethane, sodium hypochlorite (14.5 % available chlorine in water), and tetraethyleneglycol were purchased from Alfa Aesar. Ammonium acetate and sodium nitrate were purchased from Amersco. All deuterated solvents were purchased from Cambridge Isotope Laboratories. Methylamine hexamethylene methylamine NONOate (MAHMA-NONOate) and sodium α-oxyhyponitrite (Angeli's salt) were purchased from Cayman Chemicals. Tris(3-hydroxypropyltriazolylmethyl)amine was purchased from Click Chemistry Tools. 4'-Hydroxy-3'-nitroacetophenone was purchased from Combi-Blocks. Anhydrous ethanol (Decon Lab), ammonium chloride, chloroform, copper sulfate pentahydrate, Cremophor EL (Fluka), diethyl ether, ethyl acetate, glacial acetic acid, *n*-butanol, phosphate saline buffer (Corning), *o*-phosphoric acid, potassium phosphate dibasic, potassium phosphate monobasic, sodium bicarbonate, sodium chloride, and toluene were purchased from Fisher Scientific. Agarose LE (Molecular Biology Grade) was purchased from Gold Biotechnology. ER-Tracker™ Green, LysoTracker® Green DND-26, MitoTracker® Green FM were purchased from Life Technologies. Acetonitrile, anhydrous methanol, concentrated hydrochloric acid, hydrogen peroxide (30 % v/v) and sodium hydroxide were purchased from Macron Fine Chemicals. 2-Aminophenol, 4'-fluoro-3'-nitroacetophenone, 4-dimethylaminopyridine, 4-methoxyacetophenone, aluminum trichloride, carbonyldiimidazole, di-tert-butyl dicarbonate, diisopropylethylamine, methanesulfonyl chloride, methyl iodide, potassium carbonate, potassium hydroxide, potassium iodide, sodium azide, sodium sulfate

(anhydrous), tetrakis(triphenylphosphine)palladium(0), and triphenylphosphine were purchased from Oakwood Chemicals. 1,4-Dioxane, acetyl chloride, ammonia (7 M in methanol), ammonium iron sulfate (Mohr's salt), anhydrous acetonitrile, anhydrous dichloromethane, anhydrous dimethylformamide, anhydrous dimethysulfoxide, anhydrous tetrahydrofuran, benzaldehyde, boric acid, boron trifluoride dietherate, celite 545, copper(II) chloride, dimethylamine (40 % w/w in water), formaldehyde (37 % w/w in water), glyoxal (40 % w/w in water), HEPES, hexanes, indocynanine green, iron(II) sulfate heptahydrate, iron(III) chloride (anhydrous), iron powder, L-ascorbic acid, L-dehydroascorbic acid, lipopolysaccharides from Escherichia coli O111:B4 (purified by phenol extraction), manganese(II) chloride, nitric oxide, palladium on carbon (10 % w/w), potassium permanganate, potassium superoxide, rat liver microsomes (pooled, male), sodium hydride (60 % dispersion in mineral oil), sodium ascorbate, sodium nitrite, tosyl chloride, trifluoroacetic acid, and trypan blue powder were purchased from Sigma Aldrich. Fluorinated ethylene propylene (FEP) tubing (wall thickness 0.01", inner diameters 0.08" and 0.12") was purchased from McMaster-Carr.

Cell Culture. 264.7 RAW macrophage cells were acquired from Prof. Elvira de Mejia (Food Science and Human Nutrition, UIUC). Cells were cultured in phenol-red free Dulbecco's modified eagle medium (DMEM, Corning) supplemented with 10 % fetal bovine serum (FBS, Sigma Aldrich), and 1 % penicillin/streptomycin (Corning). Cells were incubated at 37 °C with 5 % CO_2. Experiments were performed in 4-well chambered cover glasses (Lab-Tek, Thermo Scientific), 6-well plates (Nunclon Delta Surface, Thermo Scientific), or 96-well plates (Nunclon Delta Surface Flat Bottom, Thermo Scientific).

Trypan Blue Cytotoxicity Assay. 6-well plates were seeded with 300,000 cells per well (3 mL of 100,000 cells/mL) and incubated at 37 °C with 5 % CO_2 for 48 h (~60 % confluent). Media

was removed and fresh DMEM with 10 % FBS (3 mL) was applied followed by addition of 7.5 μL vehicle control (DMSO) or APNO-5 for a final concentration of 1 or 5 μM. After 3, 6, and 24 h, cells were suspended by scraping, pelleted via centrifugation at 1000 × g for 5 min and the supernatant was discarded. The cell pellet was re-suspended in PBS (300 μL) and mixed 1:1 with trypan blue (0.4 % w/v stock in PBS). The mixture was allowed to incubate for 1-3 min at room temperature and then unstained (viable) and stained (nonviable) cells were counted using a hemocytometer. Viability was calculated as the percent viable cells for the experimental condition relative to the vehicle control.

MTT Cytotoxicity Assay. 96-well plate was seeded with 20,000 cells per well (200 μL of 100,000 cells/mL) and incubated at 37 ℃ with 5 % CO_2 for 24 h (~60 % confluent). Media was removed and fresh serum-free DMEM media (199 μL) was applied followed by addition of 1 μL vehicle control (DMSO) or APNO-5 for a final concentration of 1 or 5 μM. After 3, 6, and 24 h the media was removed and replaced with 200 μL 20∶1 mixture of FBS-free DMEM and (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT, 5 mg/mL stock in PBS). The cells were incubated for 4 h under the same conditions and then the medium was removed and replaced with DMSO (100 μL/well). The absorbance of each well was recorded at 555 nm on a microplate reader. Viability was calculated by the absorbance relative to the vehicle control.

Saline Preparation and *in vivo* Injection Formulation. Sterile saline was prepared by dissolving sodium chloride (90 mg) in Milli-Q water (10 mL) and filtering the resulting solution through a Millex-GS 0.22 μm sterile filter. For all *in vivo* injections, a 3.4 mM solution of APNO-5 in DMF was prepared and diluted into sterile saline for a final concentration of 17 μM (0.5 % DMF).

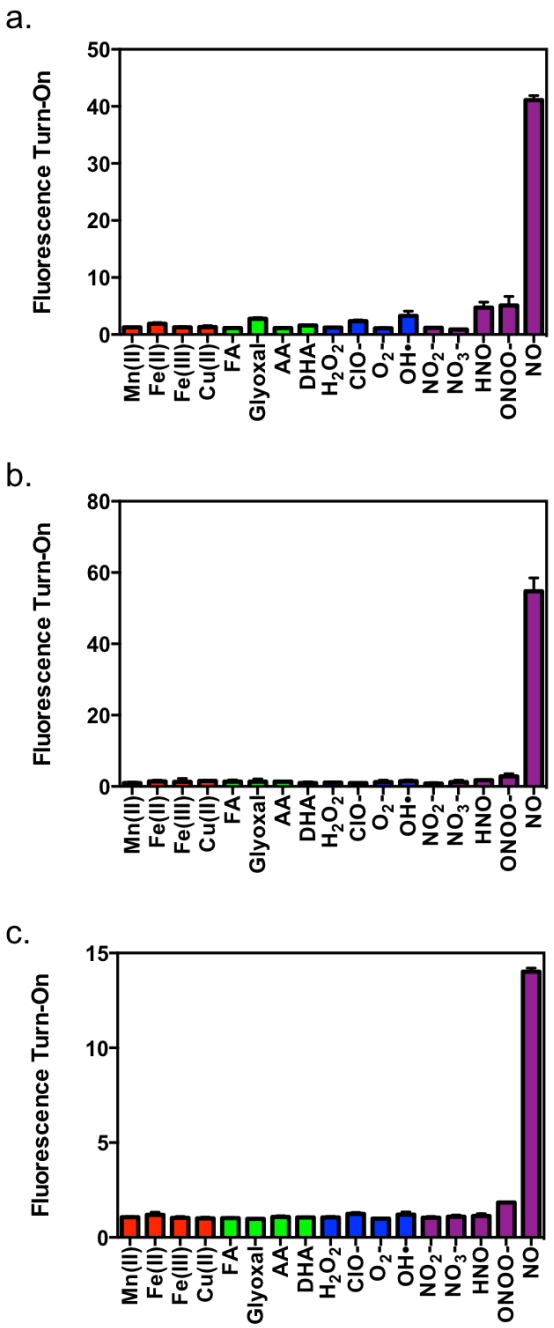


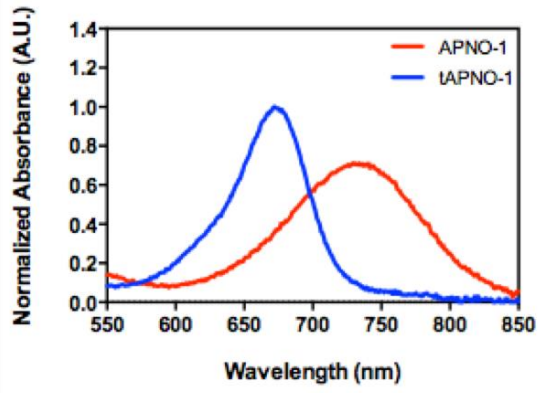
Figure S1. Selectivity studies for (a) APNO-1, (b) ANPO-2, and (c) APNO-3. 2 μM dye was treated with excess (100 equiv) reactive metal (red), carbonyl (green), oxygen (blue), or nitrogen (purple) species. Fluorescence turn-on was determined after 1 h incubation 37 °C. Data represented as mean ± standard deviation (n = 3).

Table S1. Photophysical characterization of APNO in chloroform.

APNO	λ_{max} (nm)	ε ($M^{-1}cm^{-1}$)	ϕ^a
1	720	4.7E+04	0.02
2	735	8.7E+04	0.0071
3	684	3.5E+04	0.0024
4	755	6.8E+04	0.0008
5	755	3.4E+04	0.0003

[a] Measured relative to ICG.

a.



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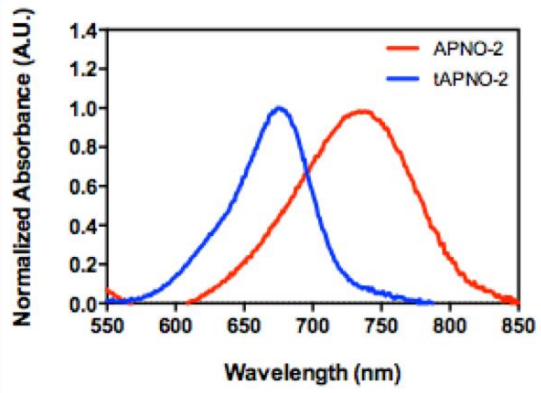


c.

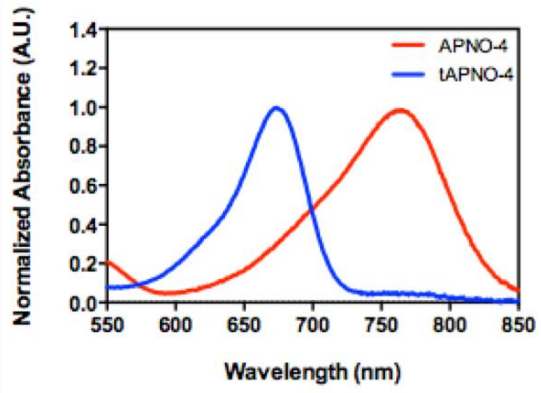


Figure S2. UV-vis absorbance profiles for (a) APNO-1, (b) APNO-2, (c) APNO-3, and (d) APNO-4 (2 μM) in ethanolic 20 mM potassium phosphate buffer (pH = 7.4, 50 % v/v).

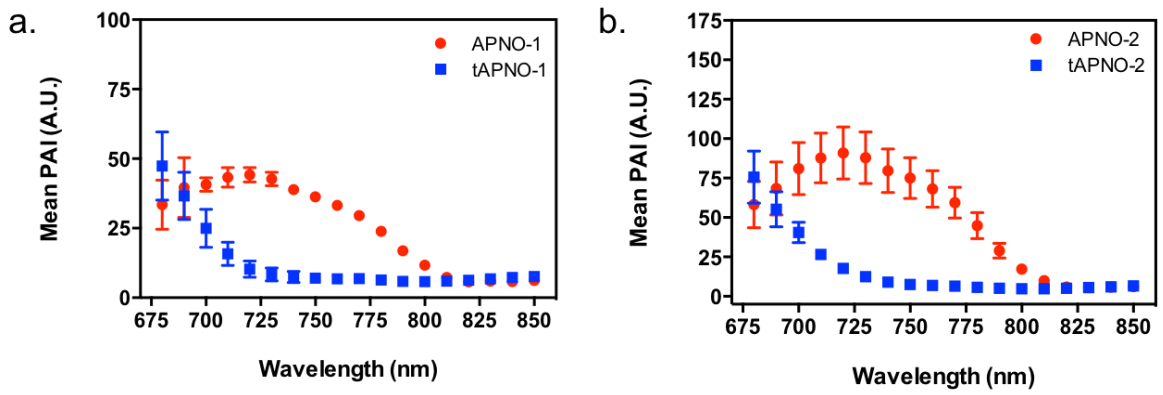


Figure S3. PA spectra for 10 μM (a) APNO-1, (b) APNO-2 and their corresponding products in ethanolic 20 mM potassium phosphate buffer (pH = 7.4, 50 % v/v). Data represented as mean ± standard deviation (n = 3).

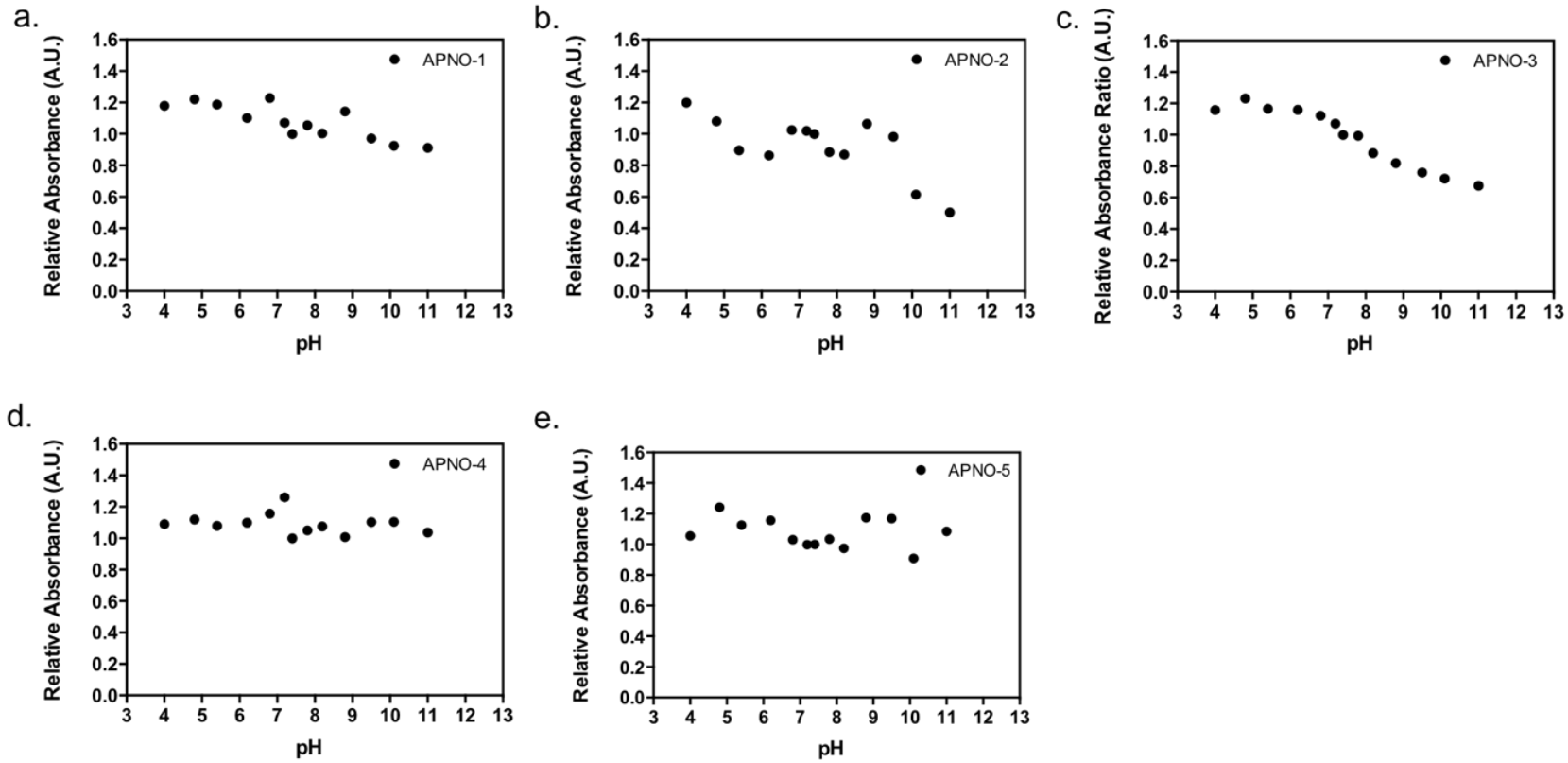


Figure S4. pH profiles of 2 μM APNO in ethanolic 20 mM Britton-Robinson buffer (50 % v/v).[2,3]

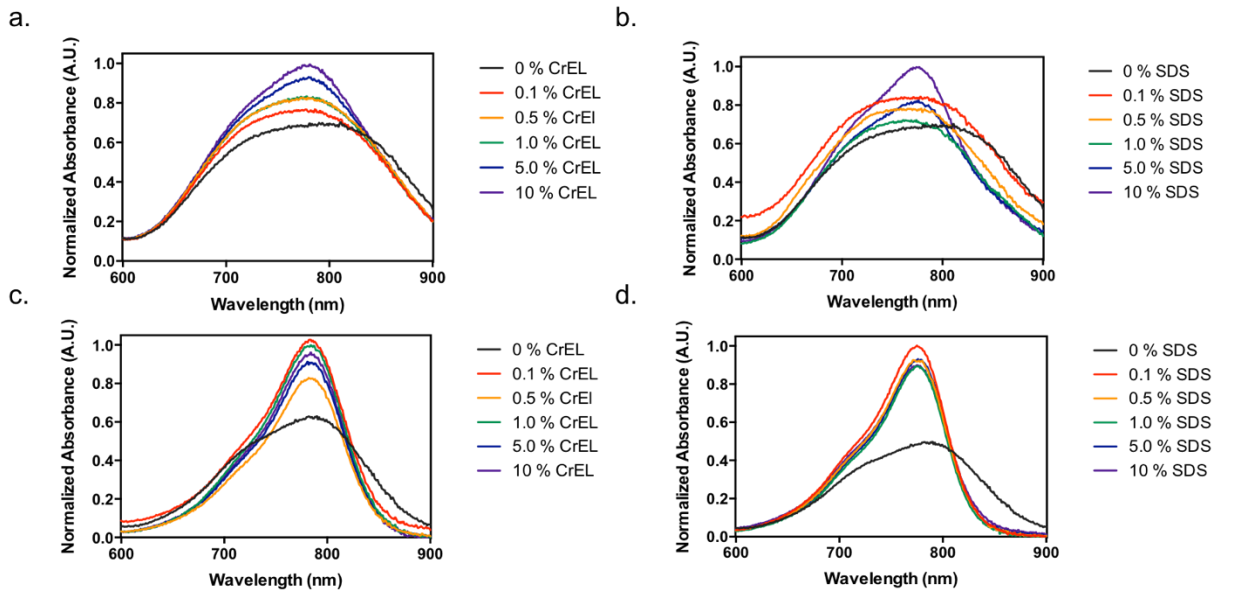


Figure S5. Effect of surfactant concentration on (a-b) APNO-4 and (c-d) APNO-5 aggregation/nanoparticle formation. UV-visible spectra were recorded of 2 μM dye solutions in variable (a, c) Cremophor EL (CrEL) and (b, d) sodium dodecyl sulfate (SDS) solutions of phosphate buffer saline solution (pH = 7.4).

Table S2. Tabulation of calculated partition coefficients (clogP) for APNO and tAPNO. Structures were draw in Avagadro[4] and ChemDraw (version 15.0) for ALOGPS[5] and ChemDraw predictions (Chemical Properties Tool), respectively.

APNO	ALOGPS	ChemDraw	tAPNO	ALOGPS	ChemDraw
1	4.88	7	1	6.68	8.32
2	5.05	7.53	2	7.38	8.38
3	5.07	7.53	3	5.41	8.34
4	7.6	8.66	4	7.26	8.66
5	3.8	3.95	5	3.77	3.96

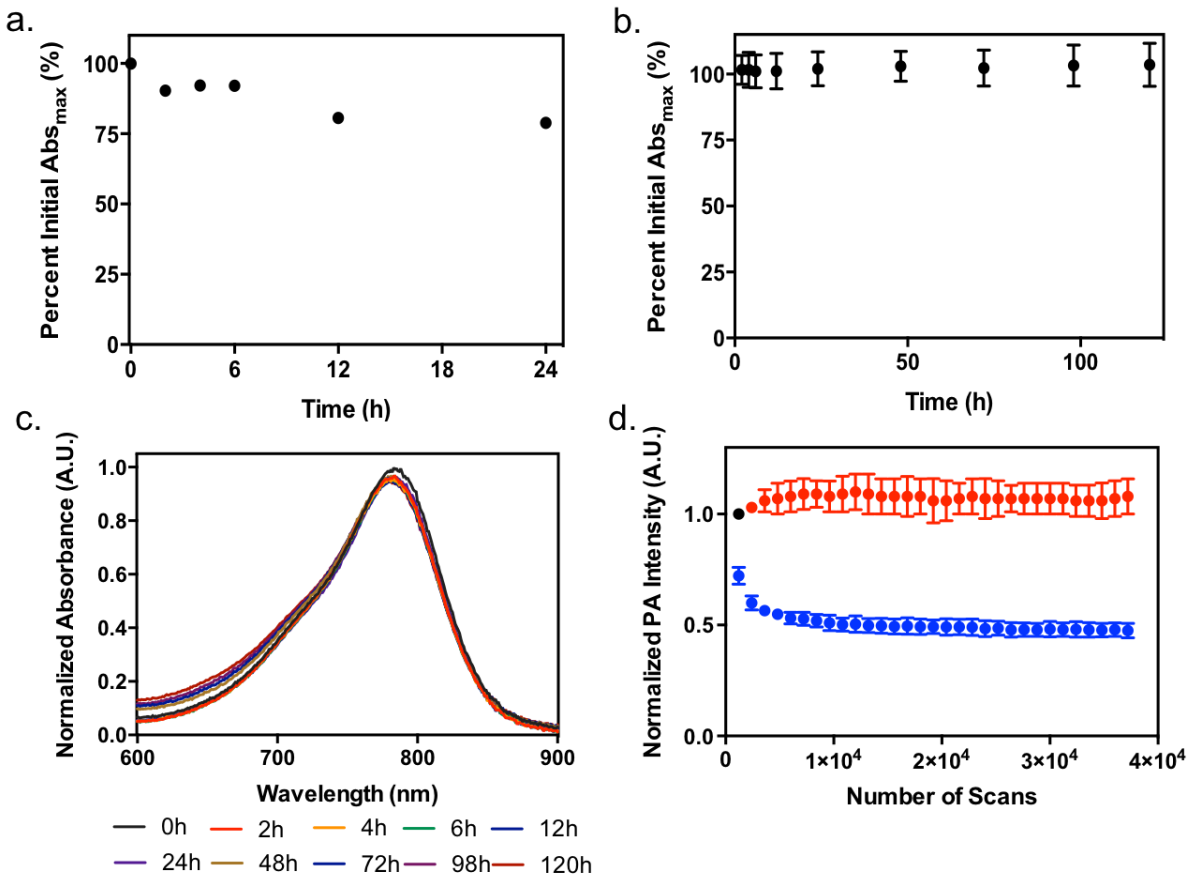


Figure S6. (a) Stability of 2 mM APNO-5 in DMSO stock under ambient light and at room temperature. Measurements were acquired by preparing 2 μM solutions of the sample in ethanolic 20 mM potassium phosphate buffer (pH = 7.4, 50 % v/v). (b) Stability of 2 μM solution of APNO-5 in 0.1 % CrEL phosphate buffer saline (pH = 7.4) at 37 °C as measured by the maximal absorbance. (c) UV-vis spectra of 2 μM solution of APNO-5 in 0.1 % CrEL phosphate buffer saline (pH = 7.4) at 37 °C. (d) Photostability of APNO-5 (red) and tAPNO-5 (blue) in 0.1 % CrEL phosphate buffer saline (pH = 7.4). Data represented as mean ± standard deviation (n = 3).

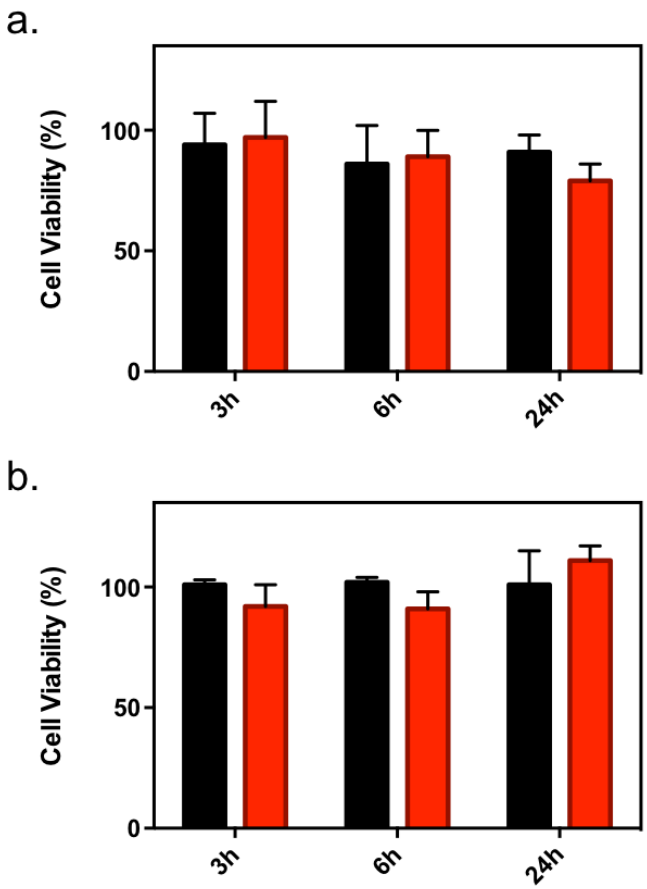


Figure S7. APNO-5 (1 μM, black; 5 μM, red) biocompatibility according to (a) trypan blue dye exclusion assay and (b) MTT cell viability assay in RAW 264.7 macrophage cells. Data represented as mean ± standard deviation (n = 3).

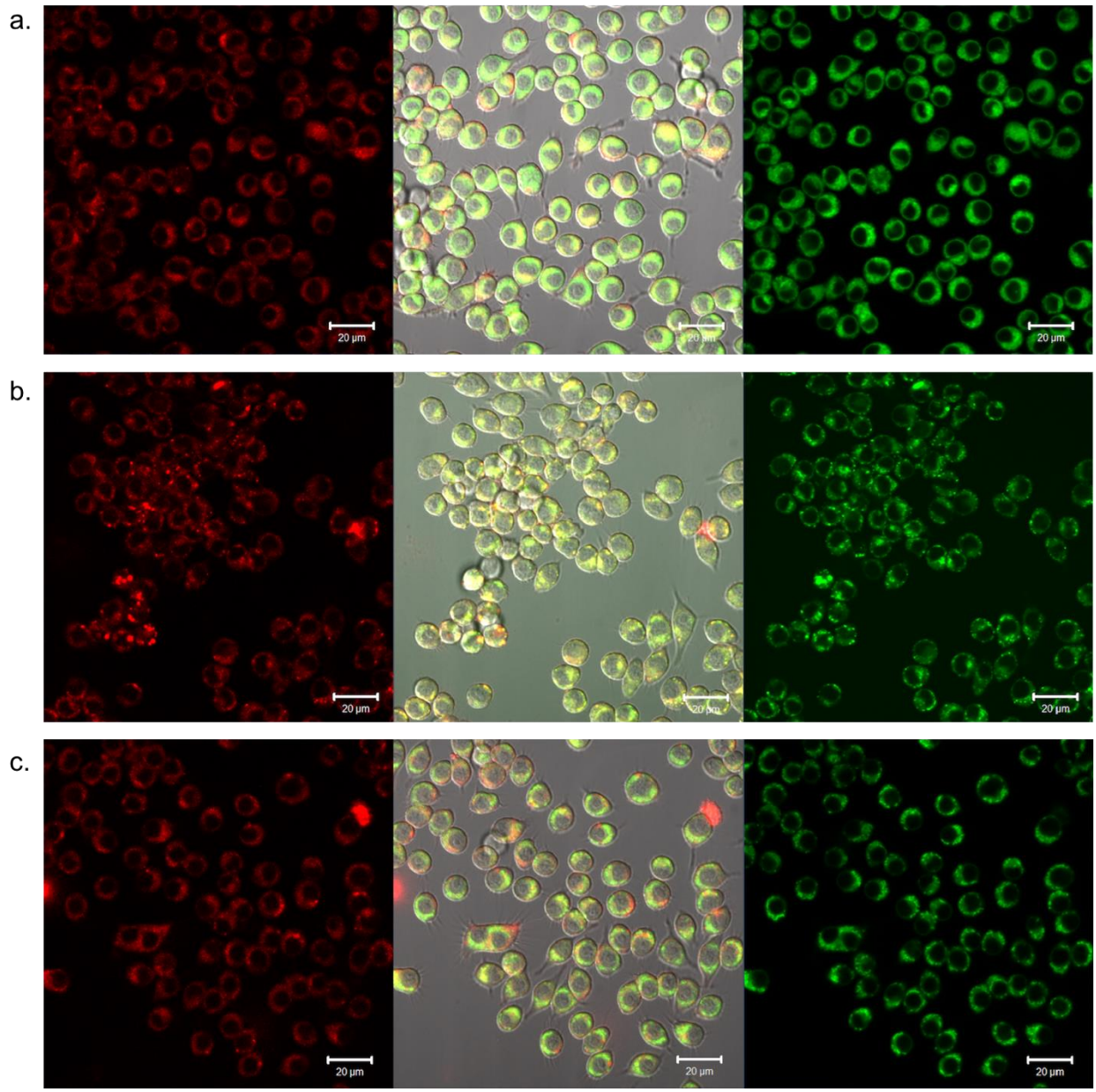


Figure S8. Colocalization studies of APNO-5 with (a) ER-Tracker™ Green, (b) LysoTracker® Green DND-26, and (c) MitoTracker® Green FM in RAW 264.7 macrophage cells. Pearson coefficients were calculated for as 0.6, 0.8, and 0.7, respectively.

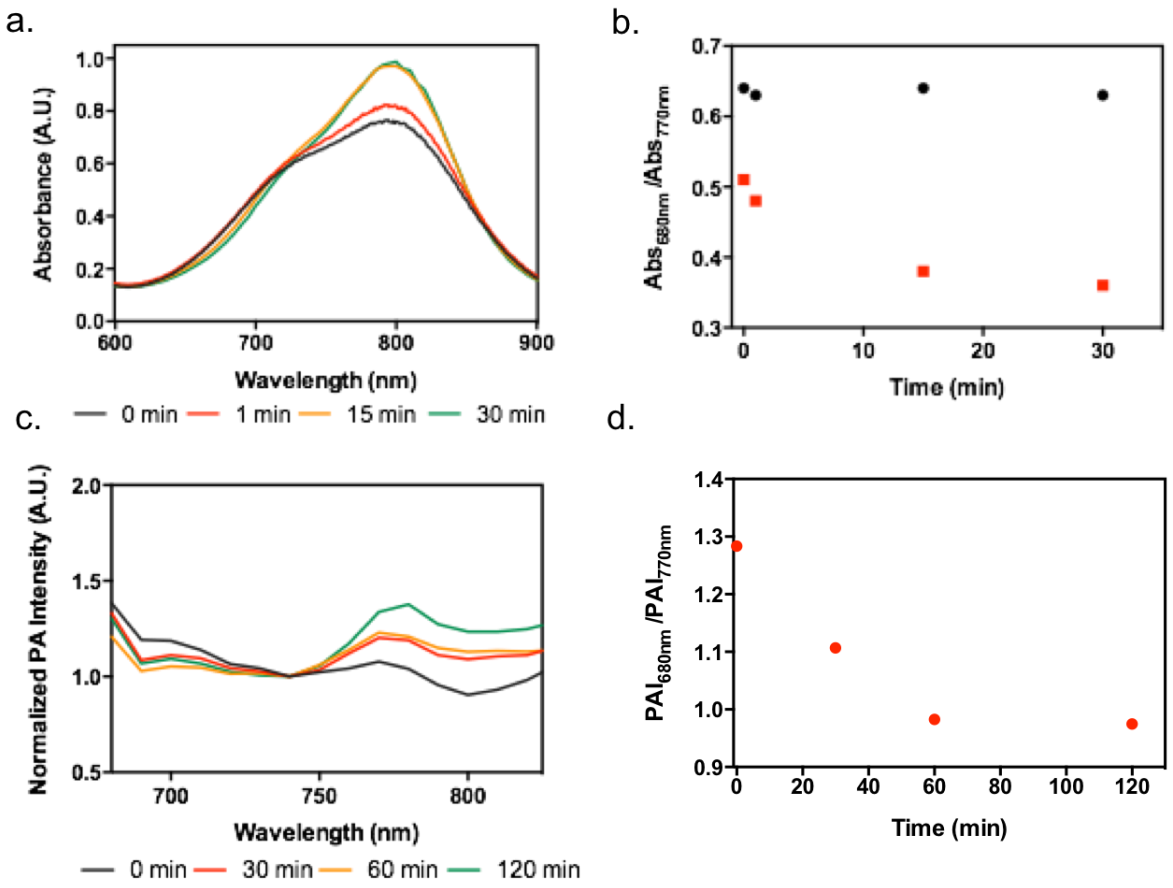


Figure S9. (a) Time dependent UV-vis absorbance profile of APNO-5 (50 μM) in saline with rat liver microsomes (10 μL). (b) Ratio of absorbance at 680 nm and 770 nm for APNO-5 (50 μM) either in the presence or absence of rat liver microsomes (10 μL) as a function of time. (c) Time dependent, normalized PA spectrum of APNO-5 (68 μg/kg) following s.c. injection into the flank of a mouse. (d) Ratio of PAI_{680nm}/PAI_{770nm} for APNO-5 (68 μg/kg) following s.c. injection into the flank of the mouse. Note that all *in vitro* experiments were incubated at 37 °C throughout the experiment and the mouse was allowed to wake up in between *in vivo* time points.

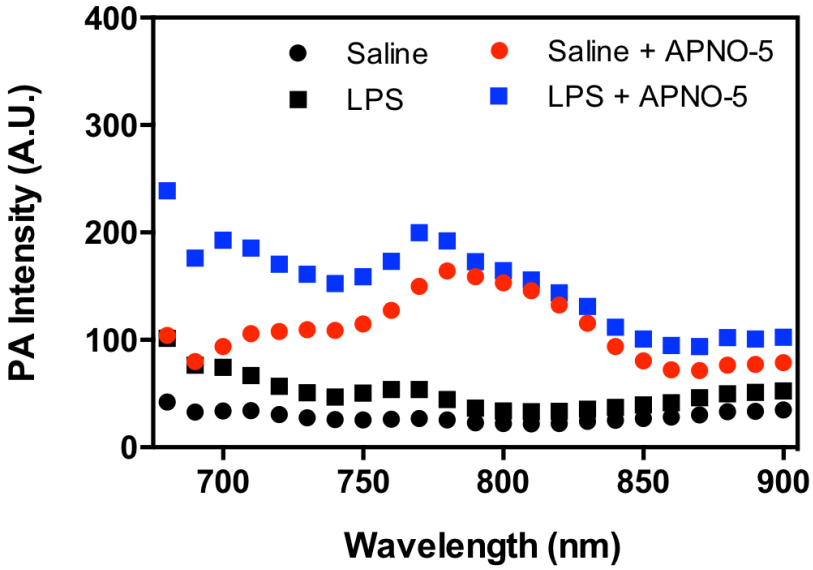


Figure S10. *In vivo* PA spectra of mice treated with LPS (4 mg/kg) or saline (equal volume) both in the presence and absence of APNO-5 (68 μg/kg). Contrast-free images were acquired 9 h after the administration of LPS or saline. APNO-5 spectra were acquired 5 h after the administration of dye (9 h after the administration of LPS or saline). Note that background signals were comparable for all of the mice before treatment.

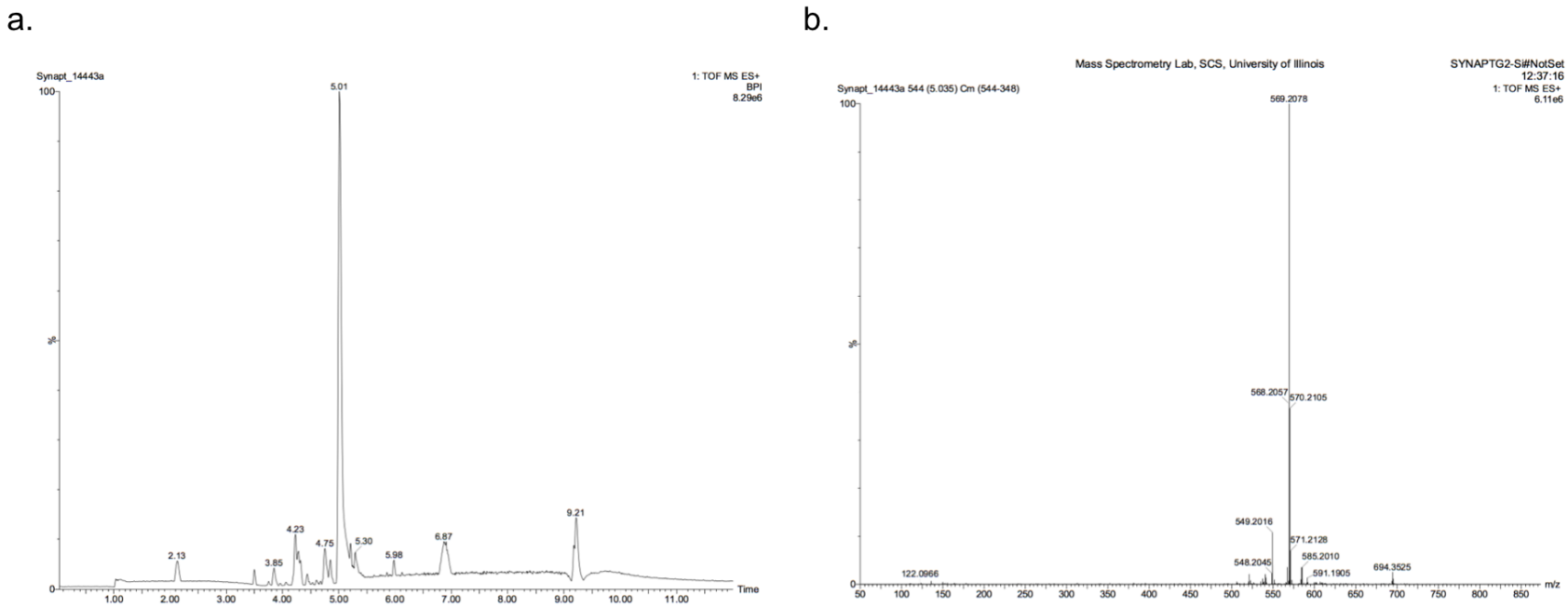


Fig. S11. (a) Chromatograph and (b) HR-MS of tAPNO-1 ESI-LC/MS analysis. tAPNO-1 was prepared by treating APNO-1 (20 μM) in ethanolic water (50 % v/v) with NO (*g*).

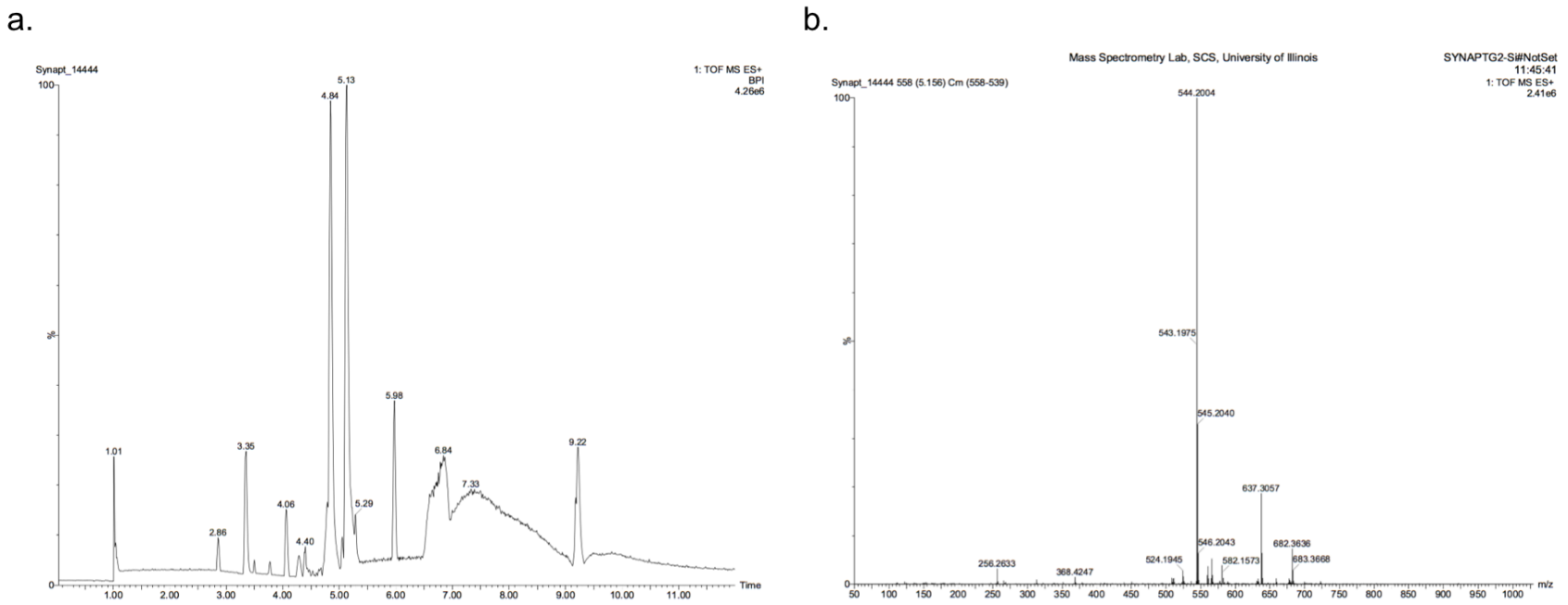


Fig. S12. (a) Chromatograph and (b) HR-MS of tAPNO-2 ESI-LC/MS analysis. tAPNO-2 was prepared by treating APNO-2 (20 μM) in ethanolic water (50 % v/v) with NO (*g*).

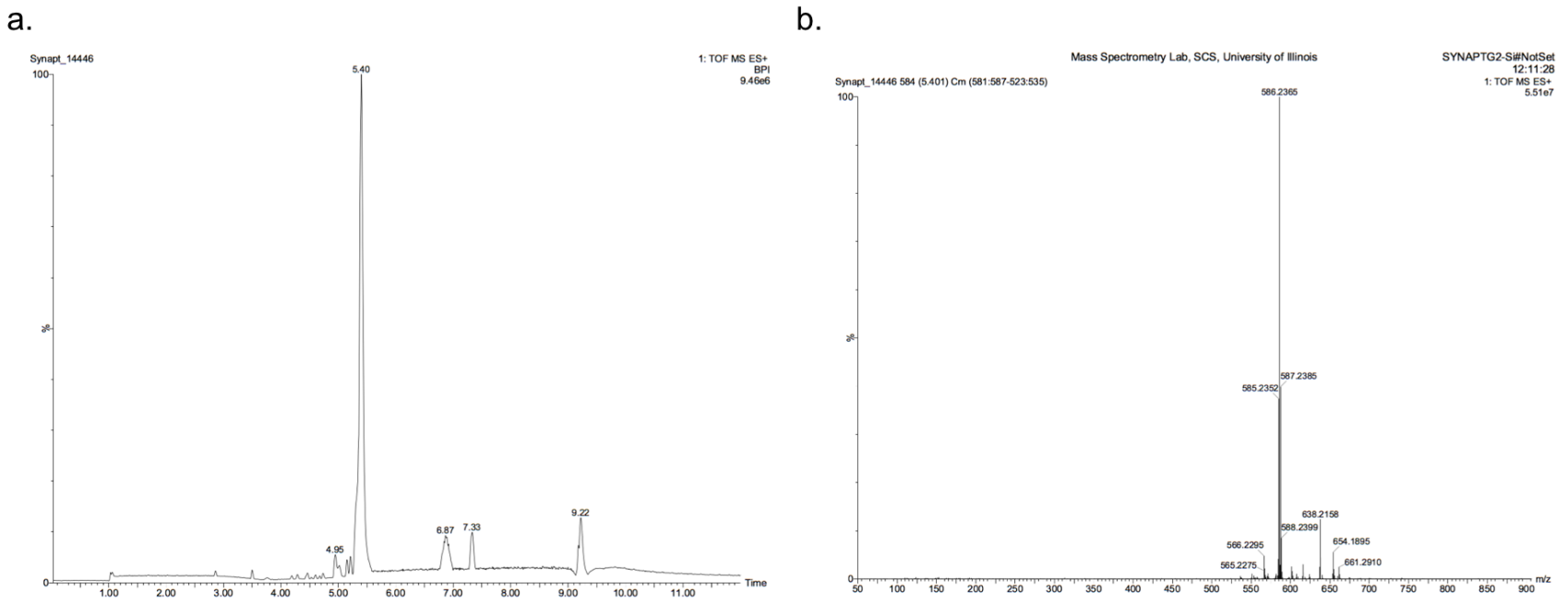


Fig. S13. (a) Chromatograph and (b) HR-MS of tAPNO-4 ESI-LC/MS analysis. tAPNO-4 was prepared by treating APNO-4 (20 μM) in ethanolic water (50 % v/v) with NO (*g*).

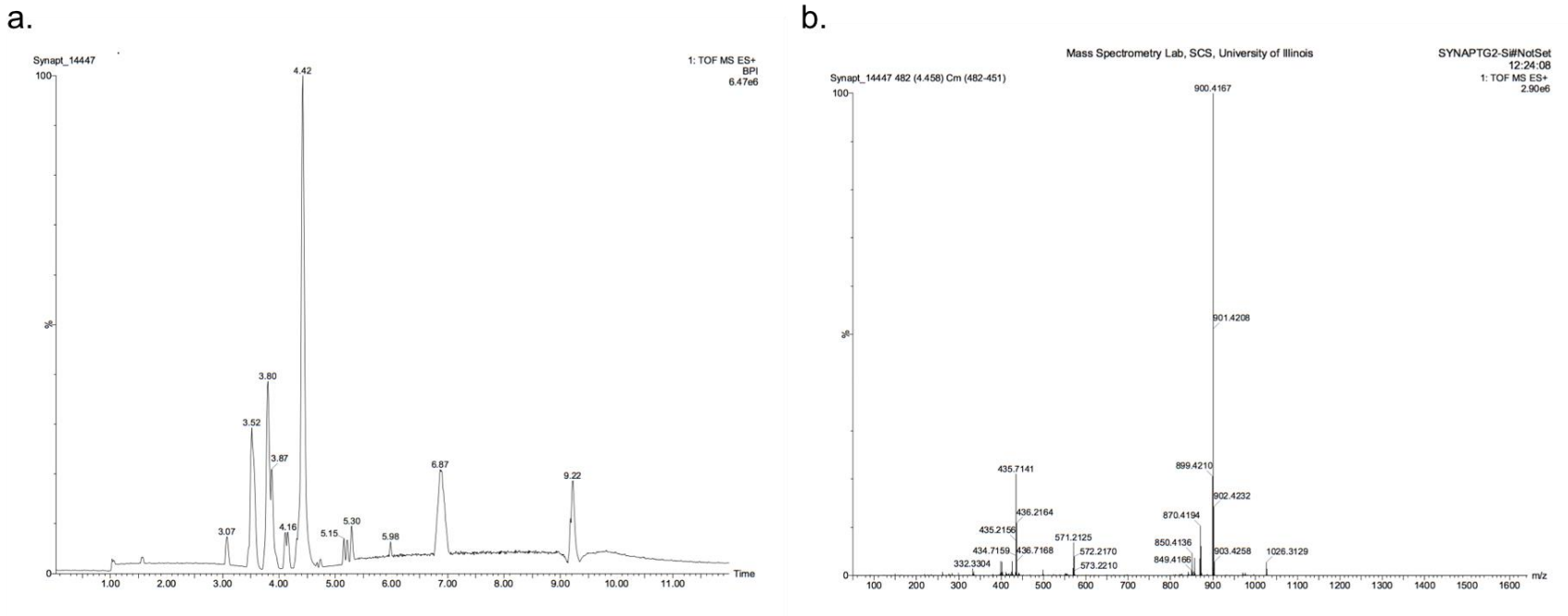
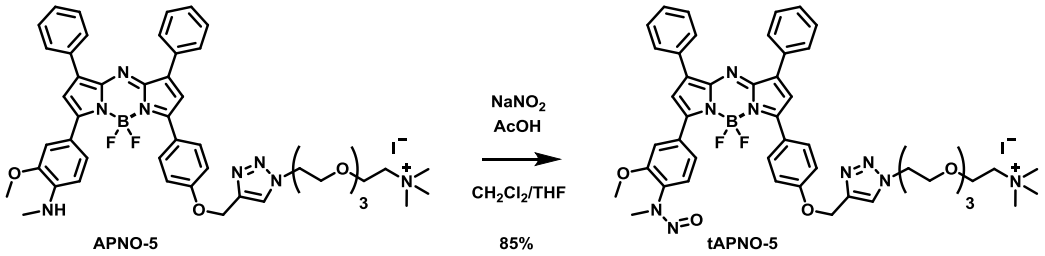


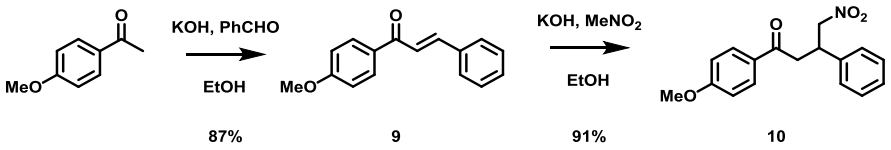
Fig. S14. (a) Chromatograph and (b) HR-MS of tAPNO-5 ESI-LC/MS analysis. tAPNO-5 was prepared by treating APNO-5 (20 μM) in ethanolic water (50 % v/v) with NO (*g*).

Synthetic Procedures.



Scheme 1. Synthesis of **tAPNO-5**.

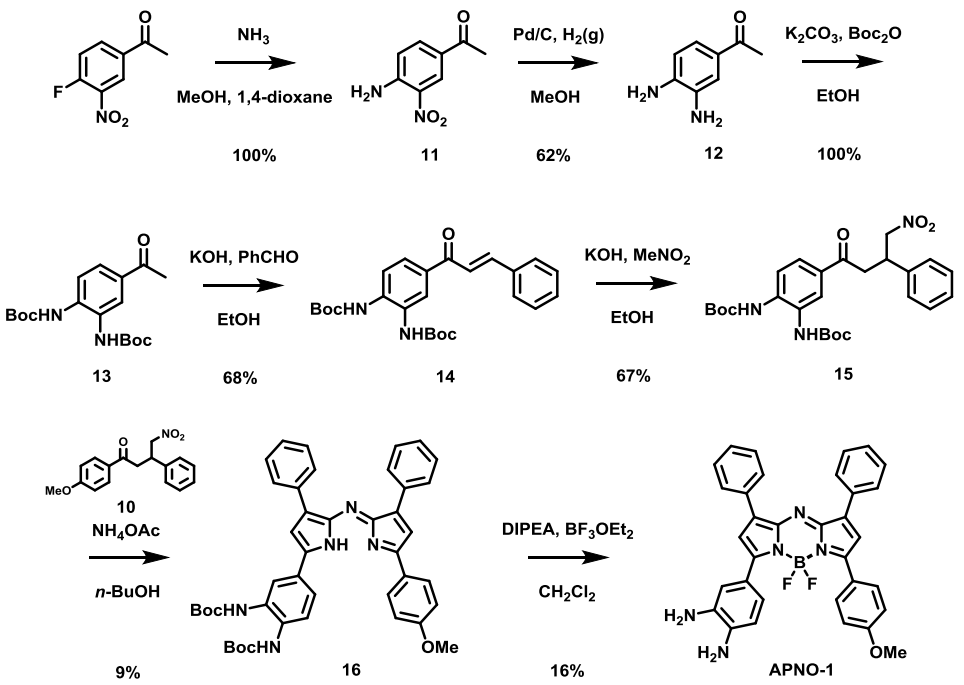
tAPNO-5. To a solution of APNO-5 (15.6 mg, 15.6 μmol, 1 equiv) in THF (3.2 mL), acetic acid (0.4 mL), and CH_2Cl_2 (0.8 mL) at 0 °C was added sodium nitrite (5.6 mg, 81.5 μmol, 5.2 equiv) and the reaction was allowed to stir at the same temperature for 30 minutes. The reaction was warmed to room temperature, additional acetic acid (0.4 mL) and sodium nitrite (2.6 mg, 37.8 μmol, 2.4 equiv) were added and allowed to stir for 2.5 h. The reaction was diluted in CH_2Cl_2 and washed with sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4 and concentrated to a green solid. The product was purified via alumina column chromatography (1:19 v/v MeOH/CH_2Cl_2) to afford a green solid (22.6 mg, 13.2 μmol, 85%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.33 (d, J = 8.8 Hz, 2H), 8.27 (s, 1H), 8.22 (d, J = 7.5 Hz, 2H), 8.17 (d, J = 7.8 Hz, 2H), 7.93 (s, 1H), 7.87 (s, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.64 – 7.46 (m, 8H), 7.31 (d, J = 8.9 Hz, 2H), 5.33 (s, 2H), 4.56 (t, J = 5.2 Hz, 2H), 3.98 (s, 3H), 3.83 (t, J = 5.2 Hz, 2H), 3.80 (m, 2H), 3.53 (m, 4H), 3.50 – 3.46 (m, 6H), 3.36 (s, 3H), 3.07 (s, 9H). ^{19}F NMR (470 MHz, DMSO-d_6) δ -130.14 (dd, J = 64.2, 31.4 Hz). HR-MS calcd for $[M]^+$ 900.8153, found 900.4191.



Scheme 2. Synthesis of Compound **10**.

[(E)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one] (9). To a solution of 4'methoxyacetophenone (10 g, 66.9 mmol, 1 equiv) and benzaldehyde (6.83 mL, 61.9 mmol, 0.9 equiv), in EtOH (130 mL) at 0 °C was added a 10 M solution of aq. KOH (20.7 mL, 207 mmol, 3.1 equiv). The reaction was allowed to warm to room temperature and stir for 1.5 h. The resulting white precipitate was collected via filtration to afford the product (13.9 g, 58.33 mmol, 87 %). R_f = 0.42 (3:14 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 8.02 (m, 2H), 7.81 (d, *J* = 15.7 Hz, 1H), 7.67 – 7.62 (m, 2H), 7.55 (d, *J* = 15.6 Hz, 1H), 7.41 (tdd, *J* = 4.8, 3.5, 1.4 Hz, 3H), 7.01 – 6.96 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.83, 163.56, 144.08, 135.23, 131.24, 130.95, 130.45, 129.05, 128.49, 122.03, 113.98, 55.63.

[1-(4-methoxyphenyl)-4-nitro-3-phenylbutan-1-one] (10). To a suspension of **9** (4.8 g, 20.1 mmol, 1 equiv) and nitromethane (13.6 mL, 254 mmol, 13 equiv) in EtOH (35 mL) was added a 10 M solution of aq. KOH (0.34 mL, 3.4 mmol, 0.2 equiv) and the was stirred at room temperature for 3 h. The reaction was monitored via TLC. When complete, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc (3×). The combined organic fractions were dried over Na_2SO_4. The compound was concentrated to afford a white solid (5.48 g, 18.3 mmol, 91 %), which was used without further purification. Note that the compound decomposes on silica. R_f = 0.37 (1:3 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) 7.96 – 7.89 (m, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.26 (m, 3H), 6.99 – 6.91 (m, 2H), 4.86 (dd, *J* = 12.5, 6.4 Hz, 1H), 4.71 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.24 (tt, *J* = 7.9, 6.4 Hz, 1H), 3.89 (s, 3H), 3.44 (dd, *J* = 17.4, 6.3 Hz, 1H), 3.39 (dd, *J* = 17.4, 7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.43, 163.97, 139.42, 130.49, 129.61, 129.18, 127.95, 127.59, 114.02, 79.76, 55.66, 41.31, 39.58.



Scheme 3. Synthesis of **APNO-1**.

4'-Amino-3'-nitroacetophenone (11). A solution of 4'-fluoro-3'-nitroacetophenone (11.5 g, 63.0 mmol, 1.0 equiv) and 7 M solution of ammonia in methanol (90.0 mL, 15.0 equiv) in 1,4-dioxane (85.0 mL) was stirred under nitrogen in a sealed pressure flask at 100 °C for 2 h. Reaction progress was monitored by TLC. When judged to be complete, the reaction was cooled to room temperature and sparged with nitrogen to remove excess ammonia. The solution was concentrated to afford a solid, suspended in sat. $NaHCO_3$, and extracted with EtOAc (3×). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated to afford an orange solid (11.4 g, 63.0 mmol, 100 %), which was used without purification. R_f = 0.17 (1:3 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.1 Hz, 1H), 8.00 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.67 – 6.39 (bs, 2H), 2.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.11, 147.73, 134.65, 128.47, 126.84, 119.00, 26.15.

3',4'-Diaminoacetophenone (12). A suspension of **11** (2.5 g, 13.6 mmol, 1 equiv) and 10 wt. % Pd/C (0.25 g, 10 % w/w) in MeOH (70.0 mL) was stirred under a H_2 (g) atmosphere maintained using a balloon at room temperature for 12 h. When the reaction was judged to be complete by TLC, it was filtered through a pad of celite and washed with MeOH. The filtrate was concentrated and purified via silica gel column chromatography (1:9 v/v MeOH/CH_2Cl_2 with 0.1 % TEA) to afford the product as a brown solid (1.26 g, 8.4 mmol, 62 %). R_f = 0.45 (3:97 v/v MeOH/CH_2Cl_2 with 0.1 % TEA). ^{1}H NMR (500 MHz, MeOD) δ 7.36 – 7.31 (m, 2H), 6.68 – 6.61 (m, 1H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, MeOD) δ 199.74, 143.70, 134.25, 128.36, 123.75, 117.30, 114.66, 25.97.

Di-*tert*-butyl (4-acetyl-1,2-phenylene)dicarbamate (13). A suspension of **12** (1.4 g, 9 mmol, 1 equiv), K_2CO_3 (7.8 g, 36.0 mmol, 4 equiv), and di-*tert*-butyl-dicarbonate (3.8 g, 27.0 mmol, 3 equiv) in EtOH (9 mL) was stirred at 45 °C for 18 h. When judged to be complete by TLC the reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc (3×). The combined organic fractions were concentrated and purified via silica gel column chromatography (2:3 v/v EtOAc/Hexanes) to afford a white hygroscopic foam (3.2 g, 9.0 mmol, 100 %). R_f = 0.20 (3:17 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.73 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.20 (bs, 1H), 6.67 (bs, 1H), 2.55 (s, 3H), 1.513 (s, 9H), 1.509 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.90, 154.21, 152.99, 136.57, 132.97, 128.04, 126.67, 125.59, 121.84, 81.63, 28.36, 28.34, 26.59.

Di-*tert*-butyl (4-cinnamoyl-1,2-phenylene) dicarbamate (14). A solution of **13** (2.7 g, 7.6 mmol, 1 equiv) and benzaldehyde (0.78 mL, 7.6 mmol, 1 equiv) in EtOH (25.0 mL) was cooled to 0 °C in an ice bath and treated with a 10 M aq. solution of KOH (2.3 mL, 22.8 mmol, 3 equiv). The reaction was allowed to stand in the refrigerator at 4 °C for 20 h. The reaction was

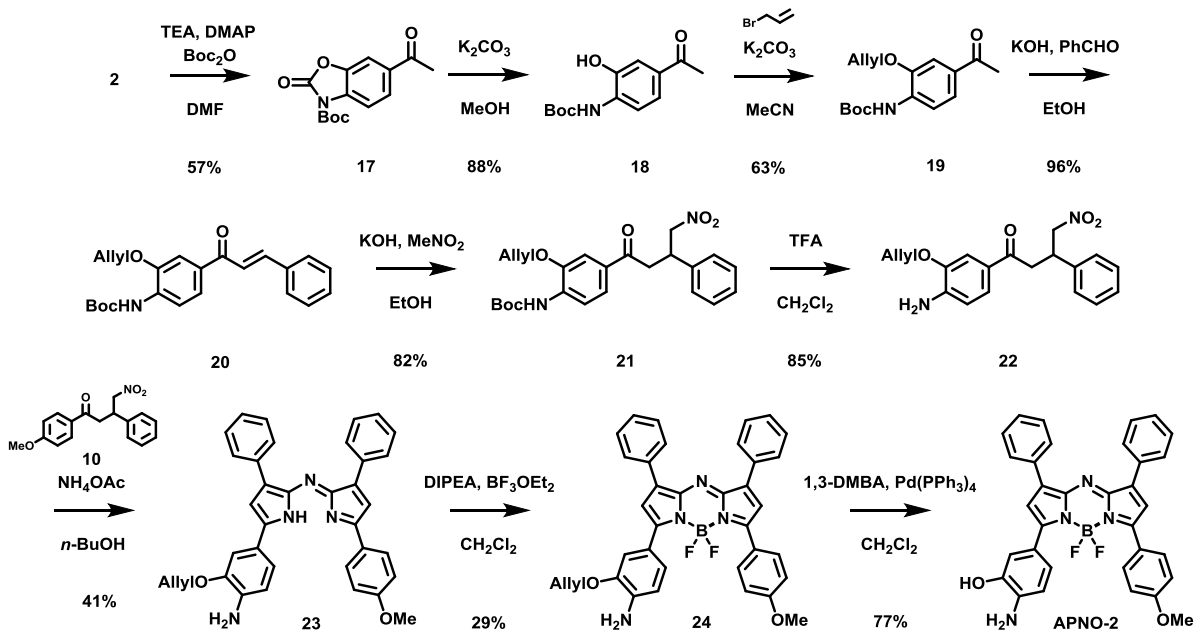
quenched with sat. NH_4Cl and extracted with EtOAc (3×). The combined organic fractions were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (3:17 v/v EtOAc/Hexanes) to afford the product as an off-white solid (2.3 g, 5.3 mmol, 68 %). R_f = 0.55 (3:7 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.93 – 7.86 (m, 1H), 7.82 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.78 (d, *J* = 15.7 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.48 (d, *J* = 15.7 Hz, 1H), 7.40 (dd, *J* = 4.9, 1.9 Hz, 3H), 7.33 (bs, 1H), 6.78 (bs, 1H), 1.524 (s, 9H), 1.520 (s, 9H). ^{13}C NMR δ 188.87, 154.30, 153.00, 144.81, 134.99, 133.79, 130.60, 129.03, 128.61, 126.89, 126.02, 125.99, 125.93, 121.75, 81.62, 81.39, 77.36, 28.36, 28.34.

Di-*tert*-butyl (4-(4-nitro-3-phenylbutanoyl)-1,2-phenylene)dicarbamate (15). A solution of **14** (2.2 g, 5.0 mmol, 1 equiv) and nitromethane (0.6 g, 10.1 mmol, 2 equiv) in EtOH (10.0 mL) was cooled to 0 °C in an ice bath and treated with a 10 M aq. solution of KOH (0.1 mL, 1.0 mmol, 0.2 equiv). The reaction was stirred at 40 °C for 20 h, diluted with brine, and extracted with EtOAc (3×). The combined organic fractions were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (1:3 v/v EtOAc/Hexanes) to afford the product as an off-white solid (1.7 g, 3.4 mmol, 67 %). R_f = 0.38 (1:3 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.84 – 7.79 (m, 1H), 7.66 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.40 – 7.22 (m, 6H), 6.72 (s, 1H), 4.84 (dd, *J* = 12.6, 6.4 Hz, 1H), 4.70 (dd, *J* = 12.6, 8.3 Hz, 1H), 4.22 (quint, *J* = 7.0 Hz, 1H), 3.39 (qd, *J* = 17.6, 7.0 Hz, 2H), 1.55 (s, 9H), 1.54 (s, 9H).^{13}C NMR (125 MHz, $CDCl_3$) δ 195.46, 154.17, 152.92, 139.28, 137.02, 132.02, 129.12, 128.32, 128.12, 127.91, 127.59, 126.23, 125.39, 125.27, 121.81, 81.71, 81.58, 79.62, 41.44, 39.40, 28.33, 28.31.

***tert*-Butyl (Z)-(2-((tert-butoxycarbonyl)amino)-4-(5-((5-(4-methoxyphenyl)-3-phenyl-2H-pyrrol-2-ylidene)amino)-4-phenyl-1H-pyrrol-2-yl)phenyl)carbamate (16).** A solution of **15** (0.4 g, 0.8 mmol, 1 equiv) and **10** (0.5 g, 1.6 mmol, 2 equiv) in *n*-butanol (16.0 mL) was heated

to 90 °C to ensure all reactants were dissolved. NH_4OAc (1.0 g, 12.3 mmol, 15 equiv) was added and the reaction was stirred at 90 °C for 8 h. The reaction was concentrated under reduced pressure, suspended in brine, and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (1:1 v/v CH_2Cl_2/Hexanes to CH_2Cl_2, step gradient). All fractions containing product were pooled and concentrated to afford a dark blue solid (0.05 g, 0.075 mmol, 9.2 %), which was used without further purification. R_f = 0.57 (3:7 v/v EtOAc/Hexanes).

APNO-1. A solution of **16** (0.05 g, 0.75 mmol, 1 equiv) and *N*,*N*-diisopropylethylamine (0.1 g, 0.8 mmol, 10 equiv) in anhydrous CH_2Cl_2 was cooled to 0 °C in an ice bath and treated dropwise with boron trifluoride diethyl etherate (0.13 mL, 1.15 mmol, 15 equiv). The reaction was stirred at room temperature for 18 h under a nitrogen atmosphere, quenched with H_2O (5.0 mL), and extracted with CH_2Cl_2 (3×). The combined organic layers were concentrated and purified via silica gel column chromatography (1:99 v/v MeOH/CH_2Cl_2 with 0.1 % TEA) to afford the product as a green solid (6.6 mg, 0.01 mmol, 16 %). R_f = 0.35 (1:99 v/v MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 8.02 (m, 7H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.61 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.48 – 7.37 (m, 7H), 7.10 (d, *J* = 1.0 Hz, 1H), 7.03 – 6.99 (m, 2H), 6.98 (s, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 3.89 (s, 3H). ^{11}B NMR (161 MHz, $CDCl_3$) δ 1.16 (t, *J* = 32.8 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -131.75 (dd, *J* = 64.1, 32.1 Hz). HR-MS calcd for $[M+H]^+$ 558.2277, found 558.2268.



Scheme 4. Synthesis of **APNO-2**.

***tert*-Butyl 6-acetyl-2-oxobenzo[d]oxazole-3(2H)-carboxylate (17).** Di-*tert*-butyl-dicarbonate (38.5 g, 175.9 mmol, 2 equiv) was added to a solution of **2** (15.6 g, 88.0 mmol, 1 equiv), TEA (8.8 g, 88.0 mmol, 1 equiv) and DMAP (10.7 g, 88.0 mmol, 1 equiv) in THF (250.0 mL). The reaction was stirred at room temperature for 1 h, poured into sat. $NaHCO_3$, and extracted with EtOAc (3×). The combined organic fractions were dried over Na_2SO_4, concentrated under reduced pressure and purified via silica gel column chromatography (1:1 v/v EtOAc/Hexanes) to afford the product as a white solid (13.9 g, 50.1 mmol, 57 %). R_f = 0.31 (3:17 v/v EtOAc/Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 1H), 7.80 – 7.74 (m, 2H), 2.60 (s, 3H), 1.66 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ196.25, 149.20, 147.38, 141.99, 134.26, 131.56, 125.78, 114.48, 109.74, 87.16, 28.13, 26.83.

***tert*-Butyl (4-acetyl-2-hydroxyphenyl)carbamate (18).** A suspension of **17** (13.9 g, 50.1 mmol, 1 equiv) and K_2CO_3 (6.96 g, 50.4 mmol, 1 equiv) in MeOH (250 mL) was stirred at room temperature for 9 h under a nitrogen atmosphere. The volatiles were removed under reduced

pressure and the resulting residue was dissolved in EtOAc, treated with sat. NH_4Cl, and the product was extracted with EtOAc (3×). The combined organic fractions were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (2:3 v/v EtOAc/Hexanes) to afford the product as an orange solid (11.1 g, 44.0 mmol, 88 %). R_f = 0.35 (3:7 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 7.84 – 7.79 (m, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.48 (dd, *J* = 8.5, 1.9 Hz, 1H), 2.56 (s, 1H), 1.53 (s, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.83, 153.35, 145.42, 132.23, 132.03, 122.79, 118.28, 115.42, 81.84, 28.40, 26.55.

***tert*-Butyl (4-acetyl-2-(allyloxy)phenyl)carbamate (19).** A suspension of **18** (3.6 g, 14.3 mmol, 1 equiv), allyl bromide (3.1 mL, 35.8 mmol, 2.5 equiv) and K_2CO_3 (3.95 g, 28.6 mmol, 2 equiv) in anhydrous MeCN (30.0 mL) was stirred at 45 °C for 3 h. The reaction was quenched with H_2O and extracted with EtOAc (3×). The combined organic fractions were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (3:17 v/v EtOAc/Hexanes) to afford the product as a white solid (2.6 g, 9.0 mmol, 63 %). R_f = 0.39 (3:17 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.31 (bs, 1H), 6.08 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1H), 5.42 (dq, *J* = 17.3, 1.5 Hz, 1H), 5.34 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.66 (dt, *J* = 5.5, 1.5 Hz, 2H), 2.55 (s, 3H), 1.54 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.04, 152.41, 146.24, 133.32, 132.58, 131.35, 123.52, 118.75, 116.72, 109.99, 81.26, 69.75, 28.43, 26.40.

***tert*-Butyl (2-(allyloxy)-4-cinnamoylphenyl)(methyl)carbamate (20).** A 10 M aq. solution of KOH (0.44 mL, 4.4 mmol, 1.2 equiv) was added dropwise to a solution of **19** (1.1 g, 3.65 mmol, 1 equiv) and benzaldehyde (0.41 mL, 4.0 mmol, 1.1 equiv) in EtOH (8.0 mL). After stirring at room temperature for 12 h, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc

(3×). The organic layers were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (3:17 v/v EtOAc/Hexanes) to afford the product as a yellow solid (1.3 g, 3.43 mmol, 96 %). R_f = 0.41 (1:9 v/v EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.67 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.59 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 15.6 Hz, 1H), 7.43 – 7.38 (m, 3H), 7.36 (s, 1H), 6.09 (ddt, *J* = 17.3, 10.7, 5.5 Hz, 1H), 5.43 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.34 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.68 (dt, *J* = 5.6, 1.5 Hz, 2H), 1.54 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.58, 152.30, 146.39, 144.06, 135.08, 133.17, 132.53, 132.09, 130.40, 128.95, 128.45, 123.11, 121.68, 118.70, 116.59, 110.67, 81.15, 69.68, 28.35.

***tert*-Butyl (2-(allyloxy)-4-(4-nitro-3-phenylbutanoyl)phenyl)carbamate (21).** A solution of **20** (1.8 g, 4.63 mmol, 1 equiv) and nitromethane (0.5 mL, 9.26 mmol, 2 equiv) in EtOH (15 mL) was treated with a 10 M aq. solution of KOH (0.09 mL, 0.9 mmol, 0.2 equiv). The reaction was stirred at room temperature for 14 h and then quenched with sat. NH_4Cl. The reaction mixture was extracted with EtOAc (3×). The combined organic fractions were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (3:17 v/v EtOAc/Hexanes) to afford the product as a yellow foam (1.4 g, 3.18 mmol, 82 %). R_f = 0.25 (1:9 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.5 Hz, 1H), 7.51 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.44 (d, *J* = 1.9 Hz, 1H), 7.37 – 7.27 (m, 6H), 6.07 (ddt, *J* = 17.3, 10.7, 5.5 Hz, 1H), 5.41 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.34 (dq, *J* = 10.5, 1.2 Hz, 1H), 4.83 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.70 – 4.65 (m, 1H), 4.64 (dt, *J* = 5.5, 1.5 Hz, 2H), 4.21 (ddd, *J* = 14.4, 7.9, 6.5 Hz, 1H), 3.43 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.35 (dd, *J* = 17.4, 7.6 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.60, 152.34, 146.33, 139.38, 133.80, 132.45, 130.44, 129.19, 127.96, 127.59, 122.90, 118.86, 116.72, 110.03, 81.42, 79.76, 69.78, 41.28, 39.68, 28.43.

1-(3-(Allyloxy)-4-aminophenyl)-4-nitro-3-phenylbutan-1-one (22). A solution of **21** (2.4 g, 6.4 mmol, 1 equiv) in CH_2Cl_2 (24.0 mL) was cooled to 0 °C in an ice bath and treated with dropwise addition of TFA (6.0 mL). After stirring at room temperature for 2 h, the reaction was cooled to 0 °C in an ice bath and quenched by dropwise addition of sat. $NaHCO_3$. The reaction was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4 and concentrated to afford the product as a yellow oil (1.9 g, 5.58 mmol, 85 %), which was used without further purification. R_f = 0.25 (3:17 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.36 – 7.29 (m, 2H), 7.31 – 7.25 (m, 3H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.06 (ddt, *J* = 17.2, 10.6, 5.4 Hz, 1H), 5.41 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.30 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.84 (dd, *J* = 12.5, 6.4 Hz, 1H), 4.67 (dd, *J* = 12.5, 8.4 Hz, 1H), 4.60 (dt, *J* = 5.4, 1.5 Hz, 2H), 4.20 (tt, *J* = 8.2, 6.2 Hz, 1H), 3.36 (dd, *J* = 17.1, 6.2 Hz, 1H), 3.30 (dd, *J* = 17.1, 7.9 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 194.95, 145.49, 142.45, 139.63, 132.97, 129.14, 127.87, 127.59, 126.91, 123.89, 118.20, 112.83, 110.80, 79.84, 69.38, 40.96, 39.85.

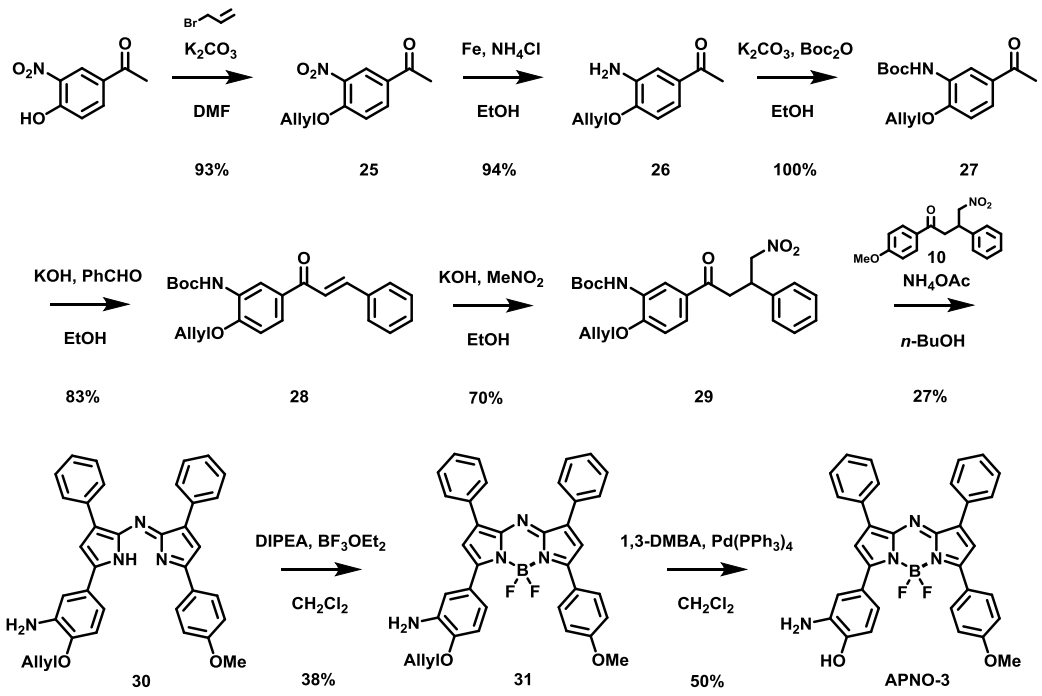
(Z)-2-(Allyloxy)-4-(5-((5-(4-methoxyphenyl)-3-phenyl-2H-pyrrol-2-ylidene)amino)-4-phenyl-1H-pyrrol-2-yl)aniline (23). A suspension of **22** (0.96 g, 2.8 mmol, 1 equiv) and **10** (1.7 g, 5.6 mmol, 2 equiv) in *n*-butanol (50 mL) was heated to 110 °C to dissolve all solids. NH_4OAc (3.3 g, 43.5 mmol, 15 equiv) was added in one portion and the reaction was stirred at the same temperature for 4 h. Volatiles were removed under reduced pressure, suspended in brine, and extracted with EtOAc (3×). The combined organic layers were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (step gradient from 1:1 v/v CH_2Cl_2/Hexanes with 0.1 % TEA to 4:1 CH_2Cl_2/Hexanes with 0.1 % TEA) to afford the product as a blue solid (0.65 g, 1.18 mmol, 41 %). R_f = 0.42 (3:7 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.09 (dd, *J* = 13.1, 7.7 Hz, 4H), 7.82 (d, *J* = 7.9 Hz, 2H), 7.76 (s, 1H), 7.69 – 7.63 (m, 2H),

7.48 – 7.37 (m, 5H), 7.36 – 7.27 (m, 2H), 7.26 (s, 1H), 7.04 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.20 (ddt, *J* = 16.0, 10.7, 5.4 Hz, 1H), 6.03 (s, 2H), 5.56 (d, *J* = 17.8 Hz, 1H), 5.36 (d, *J* = 10.6 Hz, 1H), 4.78 (d, *J* = 5.3 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.43, 159.82, 156.82, 145.28, 145.07, 143.99, 143.95, 143.45, 141.35, 141.15, 134.14, 133.91, 133.68, 133.55, 133.15, 129.01, 128.72, 128.40, 128.22, 128.16, 127.78, 127.11, 126.52, 124.51, 123.59, 121.07, 119.44, 118.21, 117.09, 114.77, 113.18, 109.53, 109.22, 79.80, 79.17, 68.33, 55.38.

2-(Allyloxy)-4-(5,5-difluoro-7-(4-methoxyphenyl)-1,9-diphenyl-5H-5l4,6l4-dipyrrolo[1,2-c:2',1'-f][1,3,5,2]triazaborinin-3-yl)aniline (24) A solution of **23** (0.40 g, 0.72 mmol, 1 equiv) and *N*,*N*-diisopropylethylamine (1.4 g, 10.8 mmol, 15 equiv) in anhydrous CH_2Cl_2 (30.0 mL) was treated with the portion-wise addition of boron trifluoride diethyl etherate (2.6 mL, 21.6 mmol, 30 equiv) at 0 °C. The reaction was stirred at room temperature for 24 h under a nitrogen atmosphere. The reaction progress was monitored via UV-Vis at 724 nm in chloroform indicating formation of the product. Upon completion the reaction was quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated, purified twice by silica gel column chromatography (1:19 v/v MeOH/ CH_2Cl_2 and 4:1 CH_2Cl_2/Hexanes) to afford the product as a red solid (0.12 g, 0.2 mmol, 29 %). R_f = 0.17 (1:9 v/v MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 – 8.19 (m, 2H), 8.14 – 8.11 (m, 2H), 8.10 – 8.07 (m, 2H), 8.02 (d, *J* = 1.9 Hz, 1H), 7.99 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.98 (s, 1H), 7.59 – 7.52 (m, 2H), 7.53 – 7.46 (m, 3H), 7.42 – 7.36 (m, 1H), 7.28 (s, 1H), 7.09 – 7.03 (m, 2H), 6.83 (s, 2H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.91 – 6.73 (m, 3H), 6.18 (ddt, *J* = 17.4, 10.6, 5.3 Hz, 1H), 5.54 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.34 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.70 (dt, *J* = 5.3, 1.5 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.29, 159.76, 149.29, 146.58, 145.81, 144.45, 142.15, 141.57, 135.80, 133.24, 133.17, 133.06, 131.58, 130.57, 130.53, 130.49, 129.58, 129.05, 128.88,

128.58, 128.51, 128.45, 128.19, 128.13, 127.77, 125.30, 124.76, 121.95, 117.90, 116.32, 116.09, 113.90, 113.68, 113.52, 68.85, 55.33. ^{11}B NMR (161 MHz, DMSO-d_6) δ 1.29 (t, J = 30.8 Hz). ^{19}F NMR (471 MHz, DMSO-d_6) δ -130.11 (dd, J = 67.0, 30.8 Hz).

APNO-2. A suspension of **24** (0.047 g, 0.078 mmol, 1 equiv), 1,3-dimethylbarbituric acid (1,3-DMBA) (0.015 g, 0.12 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (0.009 g, 0.008 mmol, 0.1 equiv), in anhydrous CH_2Cl_2 (10 mL) was stirred under nitrogen atmosphere at room temperature for 12 h. The reaction was treated with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (1:99 v/v MeOH/CH_2Cl_2) to afford the product as a red solid (0.033 g, 0.060 mmol, 77 %) R_f = 0.32 (1:99 v/v MeOH/CH_2Cl_2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.20 (dt, J = 6.4, 1.4 Hz, 2H), 8.14 – 8.09 (m, 2H), 8.07 – 8.04 (m, 2H), 7.90 – 7.81 (m, 3H), 7.59 – 7.53 (m, 2H), 7.52 – 7.46 (m, 3H), 7.41 – 7.36 (m, 1H), 7.23 (s, 1H), 7.12 – 7.03 (m, 2H), 6.77 (d, J = 8.4 Hz, 1H), 6.69 (s, 2H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.14, 148.95, 146.76, 145.83, 143.62, 141.92, 141.47, 135.21, 133.19, 131.58, 130.57, 129.52, 129.02, 128.59, 128.49, 128.40, 127.99, 124.96, 122.32, 116.91, 115.98, 115.73, 113.98, 113.51, 55.35. ^{11}B NMR (161 MHz, DMSO-d_6) δ 1.21 (t, J = 33.7 Hz). ^{19}F NMR (471 MHz, DMSO-d_6) δ -130.00 (dd, J = 66.2, 31.3 Hz). HR-MS calcd $[M+H]^+$ 559.2117, found 559.2125.



Scheme 5. Synthesis of **APNO-3**.

1-(4-(Allyloxy)-3-nitrophenyl)ethan-1-one (25). A suspension of 1-(4-hydroxy-3-nitrophenyl)ethan-1-one (0.9 g, 5.0 mmol, 1 equiv) and K_2CO_3 (1.0 g, 7.5 mmol, 1.5 equiv) in anhydrous DMF (10 mL) was cooled to 0 °C in an ice bath. Allyl bromide (0.65 mL, 7.5 mmol, 1.5 equiv) was added dropwise and the mixture was stirred at 55 °C for 16 h. Completion was observed via TLC. After cooling to room temperature, the reaction was diluted with brine and extracted with a 2:1 v/v mixture of CH_2Cl_2/isopropanol. The combined organic fractions were dried over Na_2SO_4 and concentrated to afford the product as an oil that crystallized to a yellow solid (1.03 g, 4.66 mmol, 93 %). The product was used without further purification. R_f = 0.40 (3:7 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.3 Hz, 1H), 8.04 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.3, 4.9 Hz, 1H), 5.43 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.28 (d, *J* = 10.6, 1H), 4.70 (d, *J* = 2.0 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (125

MHz, $CDCl_3$) δ 194.77, 154.97, 139.29, 133.86, 130.89, 129.46, 125.89, 118.70, 114.38, 77.41, 77.16, 76.90, 70.15, 26.24.

1-(4-(Allyloxy)-3-aminophenyl)ethan-1-one (26). A flask was charged with **25** (220 mg, 1.0 mmol, 1.0 equiv), NH_4Cl (54.5 mg, 1.0 mmol, 1.0 equiv), H_2O (2 mL) and EtOH (8 mL). Iron powder (560 mg, 10.0 mmol, 10 equiv) was added to the rapidly stirred reaction mixture which was then heated to 80 °C for 4 h. The mixture was diluted with brine and sequentially extracted with EtOAc and a 2:1 v/v mixture of CH_2Cl_2:isopropanol. The combined organic layers were dried over Na_2SO_4 and concentrated to an oil, which crystallized to a beige solid (179 mg, 0.935 mmol, 94 %). The product was used without further purification. R_f = 0.40 (1:3 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CHCl_3$) δ 7.36 – 7.30 (m, 2H), 6.77 (d, *J* = 8.6 Hz, 1H), 6.05 (ddt, *J* = 16.2, 10.5, 5.3 Hz, 1H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 5.3 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.43, 150.17, 136.42, 132.73, 130.78, 120.36, 118.17, 114.19, 110.54, 69.22, 26.39.

***tert*-Butyl (5-acetyl-2-(allyloxy)phenyl)carbamate (27).** A suspension of **26** (179 mg, 0.935 mmol, 1.0 equiv), di-*tert*-butyl-dicarbonate (408 mg, 1.87 mmol, 2.0 equiv), K_2CO_3 (194 mg, 1.4 mmol, 1.5 equiv), and EtOH (2 mL) was stirred at 45 °C for 8 h, diluted with brine and extracted with EtOAc (3×). The organic layers were dried over Na_2SO_4 and concentrated to a thick yellow oil which solidified overnight (272.4 mg, 0.935 mmol, 100 %). R_f = 0.31 (1:9 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.64 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.08 (s, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.07 (ddt, *J* = 17.2, 10.8, 5.4 Hz, 1H), 5.41 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.36 (dd, *J* = 10.5, 1.3 Hz, 1H), 4.67 (dd, *J* = 5.3, 1.5 Hz, 2H), 2.58 (d, *J* = 0.7 Hz, 3H), 1.55 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.41, 152.73, 150.13, 132.34, 130.83, 128.26, 123.27, 118.92, 118.85, 110.83, 69.78, 28.51, 26.74.

***tert*-Butyl (2-(allyloxy)-5-cinnamoylphenyl)carbamate (28).** A solution of **27** (217 mg, 0.73 mmol, 1.0 equiv), EtOH (1.6 mL), benzaldehyde (82 μL, 0.8 mmol, 1.1 equiv), and a 10 M aq. solution of KOH (219 μL, 2.19 mmol, 3 equiv) was stirred at room temperature for 3.5 h. Upon consumption of **25**, the reaction was concentrated and the residue was taken up in brine and EtOAc. The aqueous layer was extracted with EtOAc; the organic layers were dried and concentrated to a pale yellow solid (230 mg, 0.60 mmol, 83 %). Used without further purification. R_f = 0.20 (1:9 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 15.6 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.64 (dd, *J* = 7.3, 2.2 Hz, 2H), 7.56 (d, *J* = 15.6 Hz, 1H), 7.42 – 7.36 (m, 3H), 7.13 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.06 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.40 (d, *J* = 17.4 Hz, 1H), 5.34 (d, *J* = 10.4 1H), 4.65 (dd, *J* = 5.4, 1.6 Hz, 2H), 1.56 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ215.81, 188.97, 152.59, 150.03, 144.02, 143.99, 135.11, 132.22, 132.19, 131.51, 130.29, 128.88, 128.50, 128.26, 123.83, 122.01, 118.77, 118.50, 110.85, 69.65, 28.39.

***tert*-Butyl (2-(allyloxy)-5-(4-nitro-3-phenylbutanoyl)phenyl)carbamate (29).** To a round bottom flask was added **28** (458 mg, 1.21 mmol, 1.0 equiv), EtOH (2.5 mL), nitromethane (0.2 mL), and a 10 M aq. solution of KOH (0.12 mL, 1.20 mmol, 1.0 equiv). The reaction mixture was stirred 45 °C for 5 h. The reaction mixture was diluted in brine and extracted with EtOAc. The organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography (3:17 v/v EtOAc/Hexanes to 1:4 v/v EtOAc/Hexanes) to afford the product as a clear oil (370 mg, 0.84 mmol, 70 %). R_f = 0.28 (1:9 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.72 (s, 1H), 7.60 (d, *J* = 8.55, 1H), 7.33 (m, 4 h), 7.19 (s, 1H), 6.91 (d, *J* = 8.63, 1H), 6.09 (ddt, *J* = 16.53, 10.83, 5.43, 1H), 5.40 (d, *J* = 13.94, 1H), 5.36 (d, *J* = 13.94, 1H), 4.88 (dd, *J* = 12.65, 6.01, 1H), 4.72 (dd, *J* = 12.65, 6.01), 4.68 (d, *J* = 5.42, 2H), 4.23 (p, *J* = 6.82, 1H), 3.41

(m, 2H), 3.36 (ddd, *J* = 17.63, 7.69, 1.59), 1.57 (s, 9H). ^{13}C NMR (125 MHz, CD_2Cl_2) δ 196.00, 152.96, 150.96, 140.25, 132.78, 130.20, 129.37, 128.97, 128.10, 123.66, 119.011, 118.22, 118.02, 111.20, 81.16, 80.20, 70.22, 41.82, 40.01, 28.57.

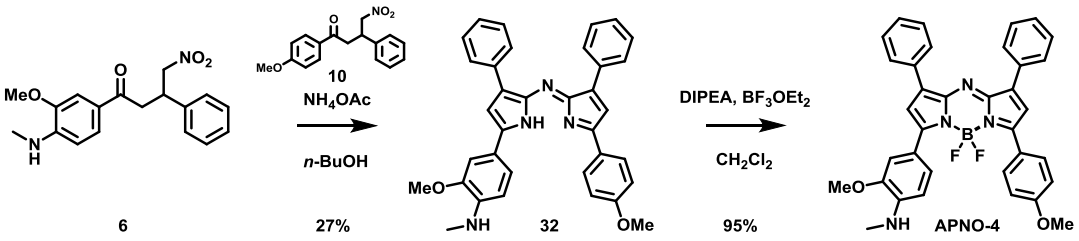
***tert*-Butyl (Z)-(2-(allyloxy)-5-(5-((5-(4-methoxyphenyl)-3-phenyl-2H-pyrrol-2-ylidene)amino)-4-phenyl-1H-pyrrol-2-yl)phenyl)carbamate (30).** A suspension of **29** (207 mg, 0.47 mmol, 1.0 equiv) and **10** (281 mg, 0.94 mmol, 2.0 equiv) in *n*-butanol (9 mL) was heated to 70 °C until the solids were dissolved. NH_4OAc (543 mg, 7.05 mmol, 15 equiv) was added in one portion and the reaction mixture stirred at 120 °C for 5 h. Then, the reaction was cooled, concentrated via rotary evaporation, and taken up in CH_2Cl_2. The organic layer was washed with brine (5×), dried, concentrated, and purified by silica gel column chromatography (1:1 v/v CH_2Cl_2/Hexanes) to obtain a blue solid with a reddish shine (81.5 mg, 0.125 mmol, 27 %). R_f = 0.71 (8:2 v/v CH_2Cl_2/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (ddd, *J* = 8.3, 3.3, 1.3 Hz, 4H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.50 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.41 (td, *J* = 7.6, 2.5 Hz, 4H), 7.34 (ddd, *J* = 7.2, 4.4, 1.7 Hz, 2H), 7.17 (s, 1H), 7.14 (d, *J* = 2.3 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.10 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.44 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.37 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.66 (dt, *J* = 5.4, 1.5 Hz, 2H), 3.86 (s, 3H), 1.59 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ161.37, 155.69, 153.52, 152.61, 150.22, 148.53, 147.92, 142.65, 141.38, 134.16, 134.08, 132.69, 129.23, 129.21, 129.17, 128.52, 128.28, 128.24, 127.86, 127.73, 125.68, 125.22, 120.95, 118.64, 115.97, 115.02, 114.80, 114.49, 111.67, 80.59, 69.81, 55.57, 28.59.

2-(Allyloxy)-5-(5,5-difluoro-7-(4-methoxyphenyl)-1,9-diphenyl-5H-5l4,6l4-dipyrrolo[1,2-c:2',1'-f][1,3,5,2]triazaborinin-3-yl)aniline (**31**)**.** A solution of **30** (48.5 mg, 0.075 mmol, 1.0 equiv) and *N*,*N*-diisopropylethylamine (0.195 mL, 1.12 mmol, 15 equiv) in anhydrous CH_2Cl_2

was treated with boron trifluoride diethyl etherate (0.142 mL, 1.12 mmol, 15 equiv). The reaction mixture was stirred under a nitrogen atmosphere at room temperature for 1 h. Upon consumption of **30,** as judged by TLC (2:1 v/v CH_2Cl_2/Hexanes), the reaction mixture was diluted in CH_2Cl_2 and washed with sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography (2:1 v/v CH_2Cl_2/toluene) to afford the product as a blue-green solid (17 mg, 0.028 mmol, 38 %). R_f = 0.35 (8:2 v/v CH_2Cl_2/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 8.2, 2.8, 1.3 Hz, 4H), 7.83 (d, *J* = 8.9 Hz, 2H), 7.34 (td, *J* = 7.6, 1.6 Hz, 4H), 7.27 (dd, *J* = 7.3, 1.6 Hz, 2H), 7.24 (tt, *J* = 4.1, 2.0 Hz, 2H), 7.06 (s, 1H), 7.01 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 1H), 6.05 (ddt, *J* = 17.3, 10.6, 5.3 Hz, 1H), 5.39 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.28 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.60 (dt, *J* = 5.4, 1.5 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.40, 154.90, 154.07, 149.97, 148.92, 148.30, 142.44, 141.81, 137.10, 134.12, 134.09, 133.11, 129.17, 129.15, 128.33, 127.91, 127.87, 125.58, 125.40, 118.15, 117.87, 114.75, 114.65, 114.27, 112.81, 112.09, 69.49, 55.66, 29.86. ^{19}F NMR (471 MHz, $CDCl_3$) δ -131.69 (dd, *J* = 63.7, 31.6 Hz).

APNO-3. To a round bottom flask was added **31** (17 mg, 28.0 μmol, 1.0 equiv), 1,3-dimethylbarbituric acid (6.6 mg, 43.0 μmol, 1.5 equiv), and $Pd(PPh_3)_4$ (3.3 mg, 3 μmol, 0.1 equiv) under nitrogen, followed by anhydrous CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature for 11 h. Upon consumption of **31** as judged by TLC, the reaction mixture was diluted in CH_2Cl_2 and washed with brine and sat. $NaHCO_3$. The organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography (1:99 v/v MeOH/ CH_2Cl_2) to afford the product as a green solid (7.9 mg, 0.014 mmol, 50 %). R_f = 0.21 (1:1 v/v CH_2Cl_2/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 – 7.99 (m, 6H), 7.53 (s, 1H), 7.49 – 7.36 (m, 7H), 7.05 – 6.95 (m, 4H), 6.77 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 3H). ^{11}B NMR (161 MHz,

$CDCl_3$) 1.05 (t, J = 32.00). ^{19}F NMR (471 MHz, $CDCl_3$) δ -131.49 (dd, J = 63.04, 32). HR-MS calcd $[M+H]^+$ 559.2117, found 559.2112.

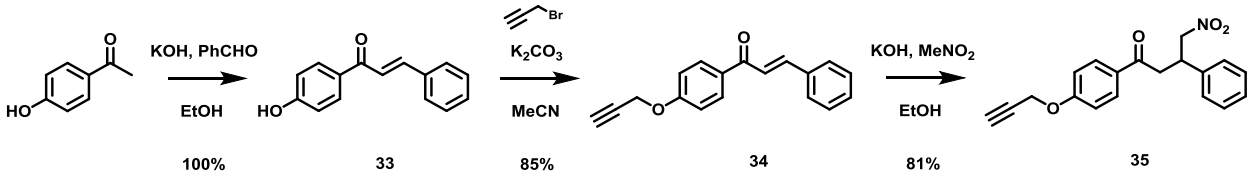


Scheme 6. Synthesis of **APNO-4**.

1-(3-Methoxy-4-(methylamino)phenyl)-4-nitro-3-phenylbutan-1-one (32). A suspension of **6** (0.211 g, 0.641 mmol, 1 equiv) and **10** (0.387 g, 1.29 mmol, 2 equiv) in *n*-butanol (15 mL) was heated to 110 °C until all of the solids dissolved. NH_4OAc (0.749 g, 9.71 mmol, 15 equiv) was added to the reaction in one portion. The reaction was stirred at 110 °C for 4 h. After complete, the solution was concentered as an azeotrope with toluene to afford a blue-green solid. The crude residue was diluted with brine and extracted with CH_2Cl_2 (3×). The combined organic fractions were dried over Na_2SO_4 and purified via silica gel column chromatography (13:7 v/v CH_2Cl_2/Hexanes). The fractions containing product were collected, precipitated from CH_2Cl_2/Hexanes at 0 °C (3×), filtered, and collected. The filtrate was re-purified via silica gel column chromatography (3:7 v/v EtOAc/Hexanes) to afford the product as a dark red solid (0.196 g, 0.184 mmol, 29 %). R_f = 0.39 (3:7 v/v EtOAc/Hexanes). ^1H NMR (500 MHz, DMSO-d_6) δ 12.84 (s, 1H), 8.12 (dd, J = 16.9, 7.6 Hz, 4H), 7.89 – 7.78 (m, 4H), 7.68 (d, J = 1.8 Hz, 1H), 7.52 – 7.38 (m, 5H), 7.35 – 7.29 (m, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.3 Hz, 1H), 6.41 (q, J = 5.1 Hz, 1H), 4.07 (s, 3H), 3.86 (s, 3H), 2.88 (d, J = 4.9 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 165.90, 159.80, 157.31, 146.55, 145.46, 143.80, 140.84, 140.62, 134.20,

133.46, 133.15, 128.72, 128.28, 128.23, 128.10, 127.07, 126.40, 125.04, 123.59, 121.37, 118.81, 117.04, 114.75, 108.86, 108.17, 107.09, 55.40, 55.18, 29.37.

APNO-4. Boron trifluoride diethyl etherate (0.15 mL, 1.2 mmol, 15 equiv) was added to a solution of **32** (0.043 g, 0.079 mmol, 1 equiv) and *N*,*N*-diisopropylethylamine (0.21 mL, 1.2 mmol, 15 equiv) in anhydrous CH_2Cl_2 (3.2 mL). The reaction was stirred at room temperature for 14 h under a nitrogen atmosphere, quenched with sat. $NaHCO_3$, and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography (step gradient, 3:7 v/v EtOAc/Hexanes then 13:7 v/v CH_2Cl_2/Hexanes) to afford the product as a red solid (0.044 g, 0.075 mmol, 95 %). R_f = 0.22 (1:1 v/v CH_2Cl_2/Hexanes). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, *J* = 8.7 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 7.7 Hz, 2H), 8.08 (d, *J* = 8.7 Hz, 2H), 8.04 (s, 1H), 7.98 – 7.95 (m, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.52 – 7.45 (m, 3H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.26 (s, 1H), 7.20 – 7.14 (m, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 2.93 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.70, 160.22, 149.36, 147.20, 146.51, 145.87, 142.52, 141.96, 135.88, 133.62, 132.09, 130.97, 130.93, 130.89, 130.03, 129.54, 129.04, 128.97, 128.89, 128.52, 125.32, 122.62, 116.45, 116.41, 114.40, 109.49, 56.07, 55.83, 29.79. ^{11}B NMR (161 MHz, DMSO-d_6) δ 1.40 (t, *J* = 34.5 Hz). ^{19}F NMR (471 MHz, DMSO-d_6) δ -130.04 (dd, *J* = 67.0, 30.6 Hz). HR-MS calcd for $[M+H]^+$ 587.2430, found 587.2440.

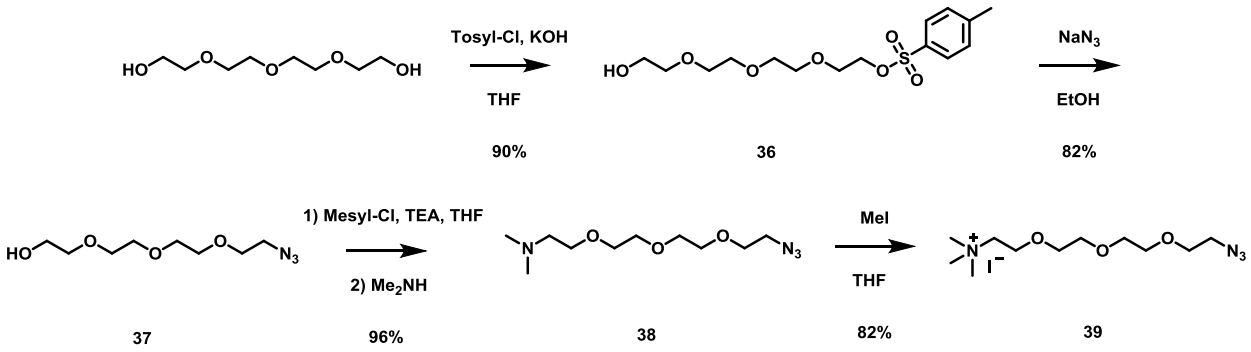


Scheme 7. Synthesis of Compound **35**.

(E)-1-(4-Hydroxyphenyl)-3-phenylprop-2-en-1-one (33). A solution of 1-(4-hydroxyphenyl)ethan-1-one (10.0 g, 73.8 mmol, 1 equiv) and benzaldehyde (7.8 g, 73.8 mmol, 1 equiv) in EtOH (140 mL) was cooled to 0 °C in an ice bath and treated with dropwise addition of a 10 M aq. solution of KOH (22.1 mL, 221 mmol, 3 equiv). The reaction was stirred at room temperature for 24 h. The reaction was quenched with conc. HCl to a pH of approximately 1. The mixture was stirred at 0 °C for 30 min then filtered to afford the product as a light yellow solid (18.7g, 73.8 mmol, 100 %). R_f = 0.39 (3:7 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 15.6 Hz, 1H), 7.88 – 7.84 (m, 2H), 7.68 (d, *J* = 15.6 Hz, 1H), 7.48 – 7.38 (m, 3H), 6.92 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 187.12, 162.31, 142.70, 134.89, 131.18, 130.32, 129.03, 128.89, 128.72, 122.12, 115.42.

(E)-3-Phenyl-1-(4-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one (34). A flame-dried round bottom flask was charged with **33** (3.1 g, 13.7 mmol, 1 equiv), K_2CO_3 (2.4 g, 17.1 mmol, 1.25 equiv), and DMF (30 mL) under nitrogen. Propargyl bromide (3.2 mL, 17.2 mmol, 1.25 equiv) was added and the reaction was stirred at room temperature for 24 h. The reaction was quenched in sat. $NaHCO_3$, extracted with EtOAc, and washed with sat. $NaHCO_3$ (3×). The combined organic layers were collected, dried over Na_2SO_4, concentrated, and purified via silica gel column chromatography (gradient from 1:9 v/v EtOAc/Hexanes to 1:3 v/v EtOAc/Hexanes) to afford the product as a white solid (3.0 g, 11.7 mmol, 85 %). R_f = 0.24 (1:9 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 8.01 (m, 2H), 7.81 (d, *J* = 15.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.54 (d, *J* = 15.7 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.13 – 7.04 (m, 2H), 4.78 (d, *J* = 2.4 Hz, 2H), 2.57 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.84, 161.32, 144.31, 135.15, 131.98, 130.85, 130.52, 129.06, 128.50, 121.94, 114.85, 77.93, 77.91, 76.34, 76.28, 56.00.

4-Nitro-3-phenyl-1-(4-(prop-2-yn-1-yloxy)phenyl)butan-1-one (35). A mixture of **34** (1.18 g, 4.5 mmol, 1 equiv) and nitromethane (3.6 mL, 66.8 mmol, 15 equiv) in EtOH (9.0 mL) was dropwise treated with 10 M aq. solution of KOH (0.090 mL, 0.2 equiv). The resulting mixture was stirred at room temperature for 24 h. After complete, the reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc (3×). The organic fraction was washed with sat. $NaHCO_3$ (3×), concentrated, and purified via silica gel column chromatography (1:3 v/v EtOAc/Hexanes) to afford the product as an off-white solid (1.18 g, 3.63 mmol, 81 %). R_f = 0.39 (3:7 v/v EtOAc/Hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 2H), 7.39 – 7.33 (m, 2H), 7.32 – 7.27 (m, 3H), 7.06 – 7.00 (m, 2H), 4.86 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.78 (d, *J* = 2.4 Hz, 2H), 4.71 (dd, *J* = 12.5, 8.1 Hz, 1H), 4.24 (tt, *J* = 7.9, 6.4 Hz, 1H), 3.45 (dd, *J* = 17.5, 6.4 Hz, 1H), 3.39 (dd, *J* = 17.5, 7.6 Hz, 1H), 2.58 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.41, 161.73, 139.35, 130.40, 130.31, 129.18, 127.96, 127.57, 114.89, 79.73, 77.74, 76.41, 56.01, 41.34, 39.52.



Scheme 8. Synthesis of Compound **39**.

[2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate] (36). The product was synthesized according to previously reported protocols.[1] Briefly, tetraethyleneglycol (8.67 g, 44.6 mmol, 8.4 equiv) was dissolved in tetrahydrofuran (2.1 mL) followed by the addition of a 4

M aq. solution of sodium hydroxide (2.13 mL, 8.52 mmol, 1.6 equiv). The reaction was cooled to 0 °C and tosyl chloride (1.01 g, 5.31 mmol, 1 equiv) in tetrahydrofuran (6 mL) was added dropwise. The reaction was allowed to stir for 3 h at the same temperature. The product was extracted with CH_2Cl_2 (3×) from cold water. The combined organic fractions were washed with water (2×) and dried over Na_2SO_4. The organic fractions were concentrated to afford a clear oil (1.66 g, 4.76 mmol, 90 %), which was used without further purification. R_f = 0.25 (3:97 v/v MeOH/CH_2Cl_2).

[2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-ol] (37). The product was synthesized according to previously reported protocols.[1] Briefly, a solution of **36** (3.96 g, 11.38 mmol, 1 equiv) and sodium azide (1.85g, 28.5 mmol, 2.5 equiv) in EtOH (45 mL) was refluxed at 80 °C under a nitrogen atmosphere for 14 h. The reaction was cooled to room temperature, diluted with water, and volatiles were removed. The product was extracted with EtOAc (3×) from the water. The organic fractions were dried over Na_2SO_4 and concentrated to afford a yellow oil (2.05 g, 9.36 mmol, 82 %), which was used without further purification. R_f (1:9 v/v MeOH/$CHCl_3$) 0.70. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (dd, *J* = 5.3, 3.7 Hz, 2H), 3.67 (d, *J* = 1.5 Hz, 10H), 3.63 – 3.59 (m, 2H), 3.40 (t, *J* = 5.1 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 72.63, 70.81, 70.78, 70.70, 70.44, 70.16, 61.87, 50.80.

[2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-N,N-dimethylethan-1-amine] (38). A solution of **37** (0.75 g, 3.42 mmol, 1 equiv), and triethylamine (1.4 mL, 10.3 mmol, 3 equiv) in anhydrous THF (17.1 mL) was cooled to 0 °C in an ice bath. Methanesulfonyl chloride (0.54 mL, 2 equiv) was added dropwise under a nitrogen atmosphere and stirred at 0 °C for 1 h. 40 % w/w aq. dimethylamine (4.3 mL, 34.2 mmol, 10 equiv) was added dropwise and stirred for an additional 24 h at room temperature. The product was purified by silica gel column chromatography (1:4

v/v MeOH/$CHCl_3$) to afford a brown oil (0.807 g, 3.28 mmol, 96 %). R_f (1:4 v/v MeOH/$CHCl_3$) 0.52. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.61 – 3.59 (m, 2H), 3.58 – 3.45 (m, 10H), 3.39 (dd, *J* = 5.6, 4.4 Hz, 2H), 2.41 – 2.37 (m, 2H), 2.15 (s, 6H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 69.81, 69.80, 69.70, 69.64, 69.62, 69.25, 68.60, 58.29, 49.99, 45.53.

[2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)-N,N,N-trimethylethan-1-aminium iodide] (39) - A pressure vial was charged with **38** (0.51 g, 2 mmol, 1 equiv), anhydrous acetonitrile (4 mL), and methyl iodide (0.64 mL, 10.2 mmol, 5 equiv) under nitrogen. The reaction was heated to 60 °C for 72 h. When complete according to TLC, the product was loaded onto celite and purified by silica gel chromatography (1:4 v/v MeOH/$CHCl_3$) to afford a pale yellow solid (0.81 g, 1.7 mmol, 82 %). R_f (1:4 v/v MeOH/$CHCl_3$) 0.40. ^{1}H NMR (500 MHz, CD_3CN) δ 3.88 (m, 2H), 3.65 – 3.57 (m, 10H), 3.54 – 3.51 (m, 2H), 3.37 (t, J = 4.9 Hz, 2H), 3.15 (s, 9H). ^{13}C NMR (125 MHz, CD_3CN) δ 71.08, 71.05, 70.96, 70.78, 70.42, 66.50, 66.48, 66.45, 65.41, 55.01, 54.97, 54.94, 51.44.

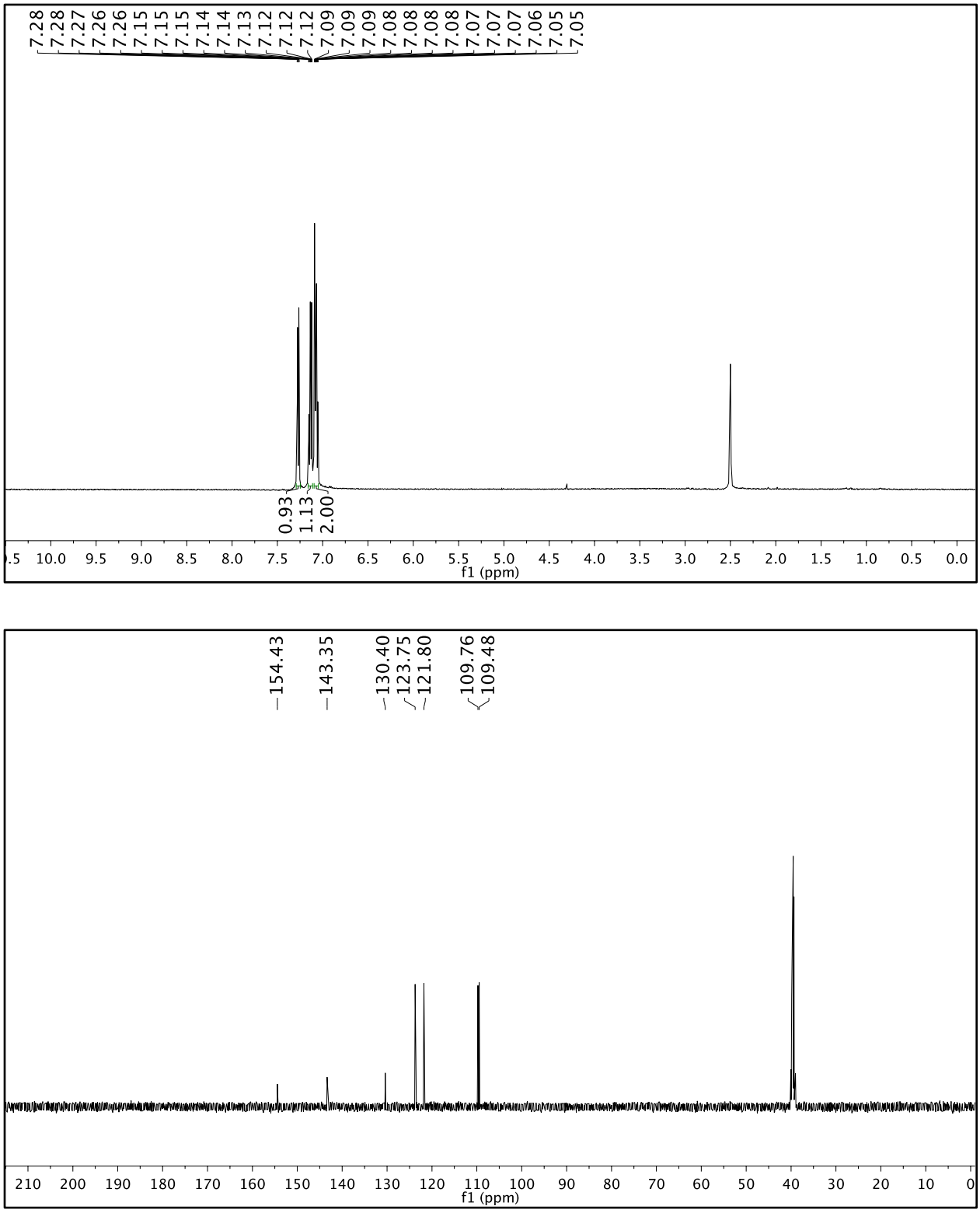


Fig. S15: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) NMR spectra of **1**.

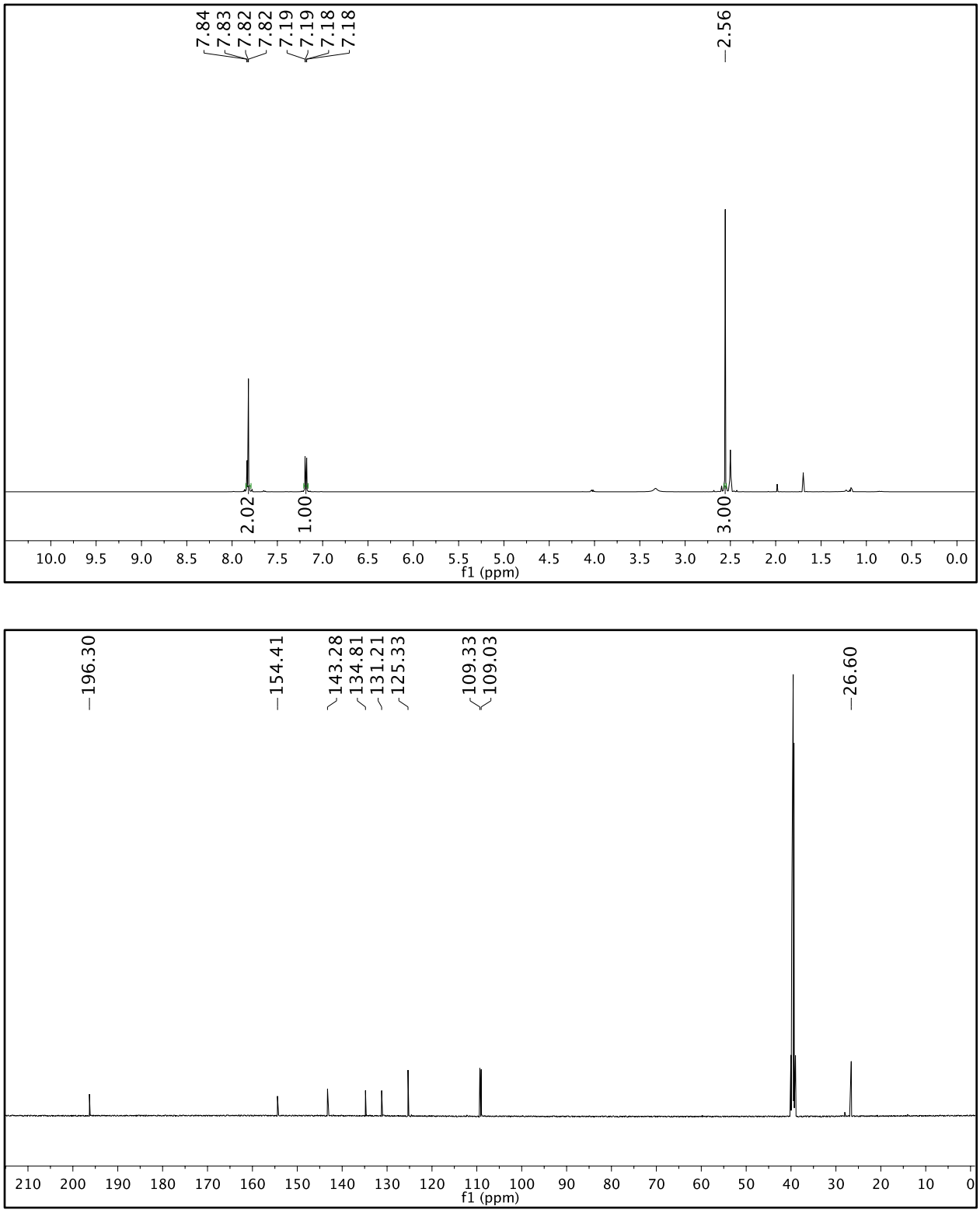


Fig. S16: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) NMR spectra of **2**.

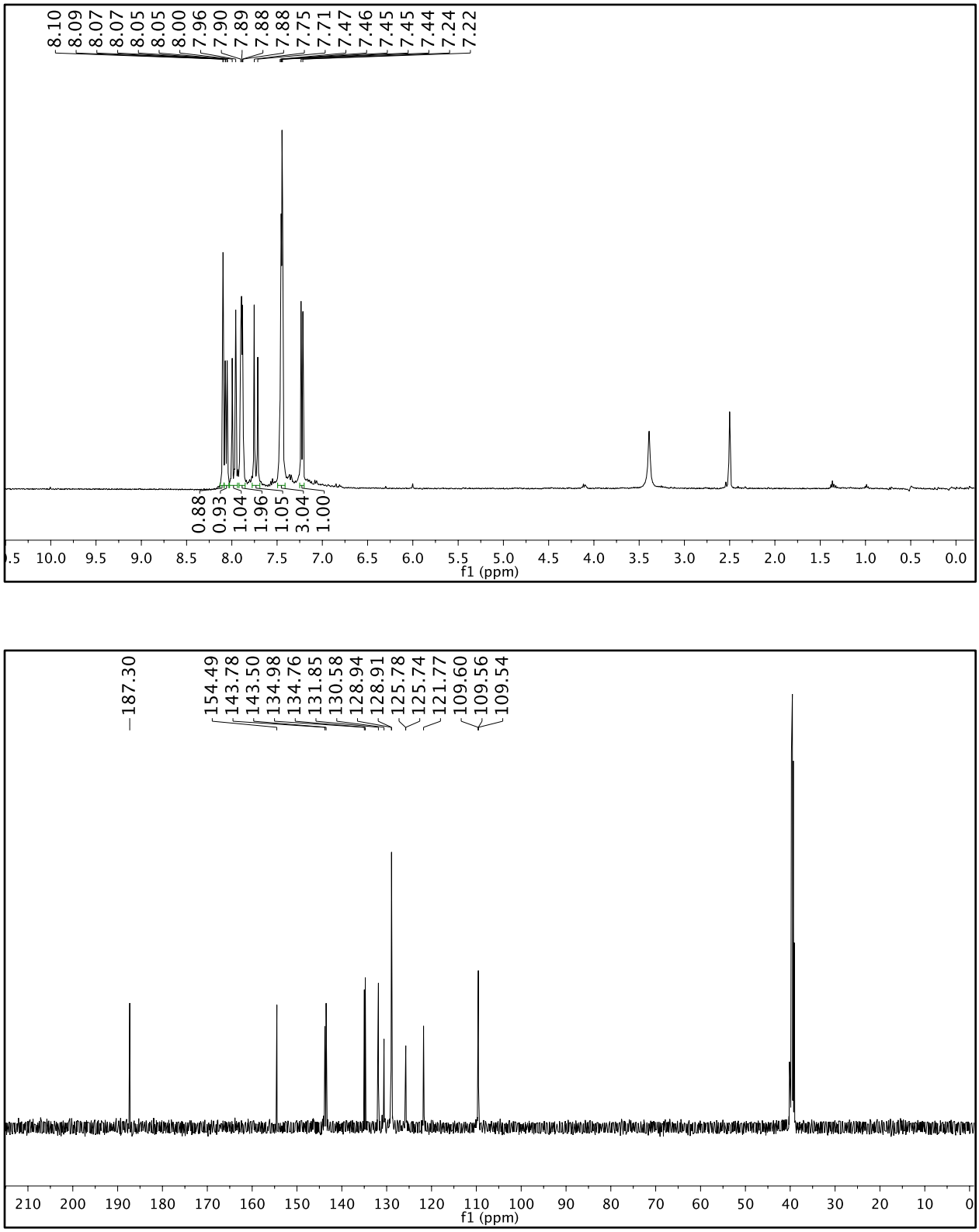


Fig. S17: ^{1}H NMR (400 MHz, DMSO-d_6) and ^{13}C NMR (100 MHz, DMSO-d_6) NMR spectra of **3**.

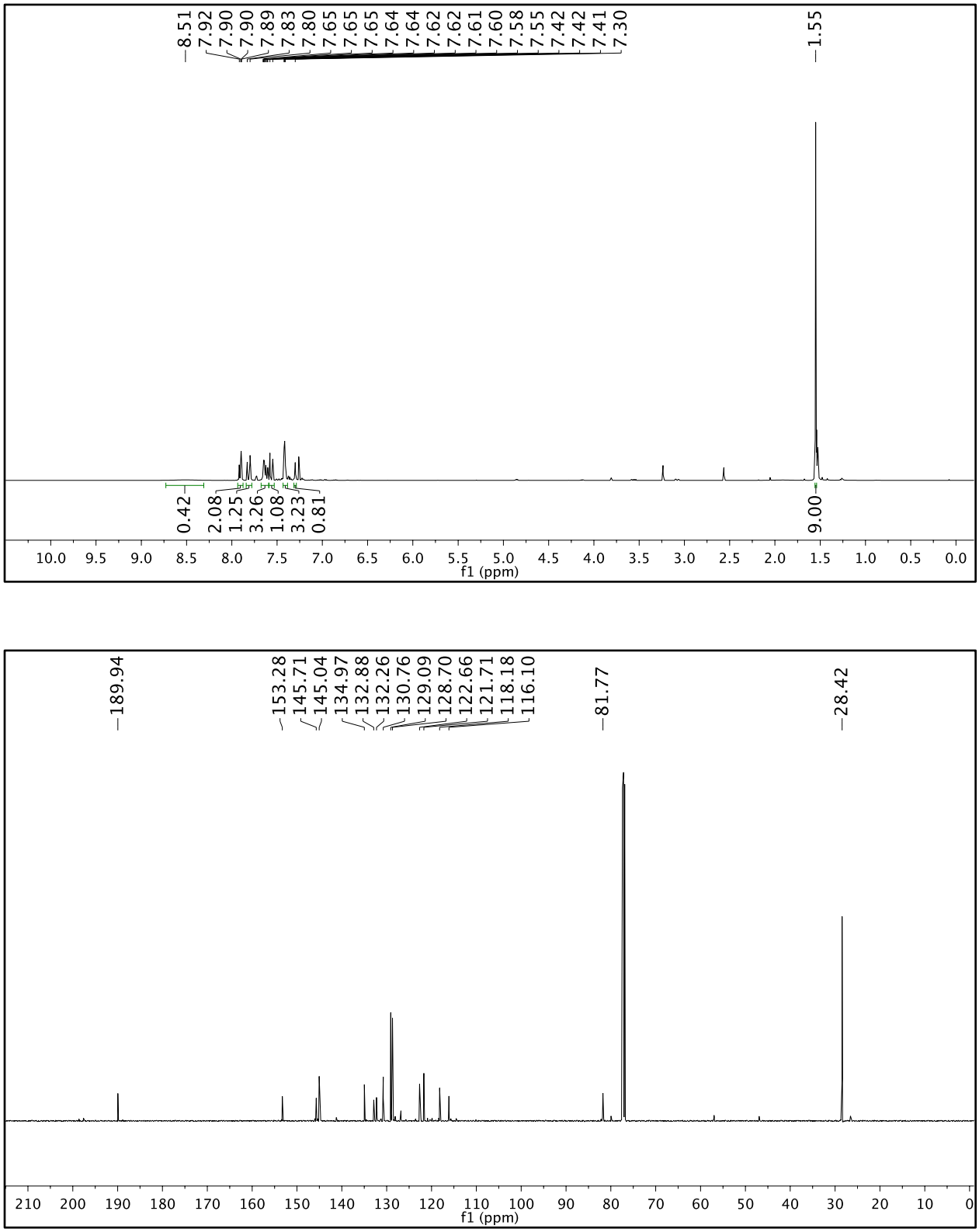


Fig. S18: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **4**.

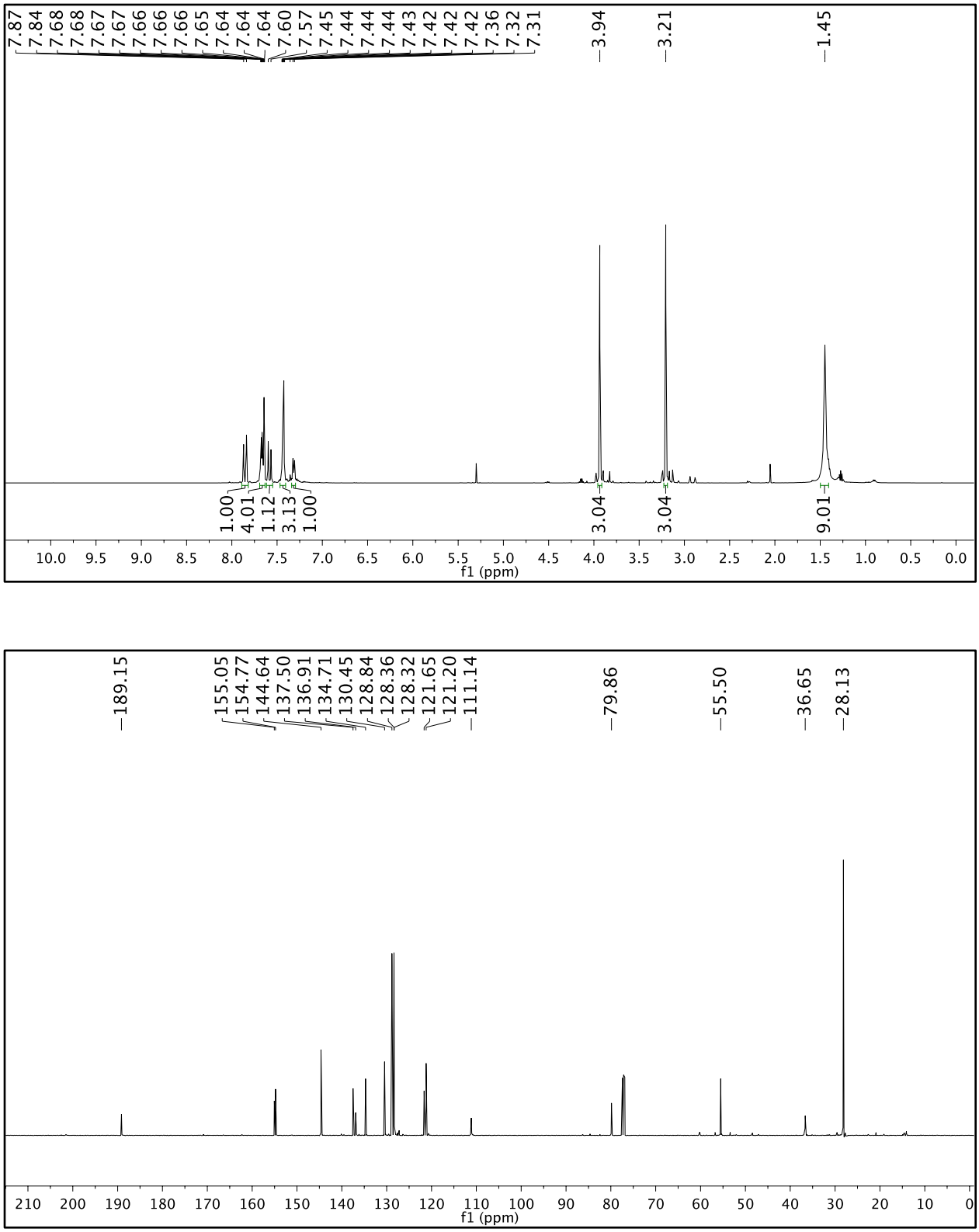


Fig. S19: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **5**.

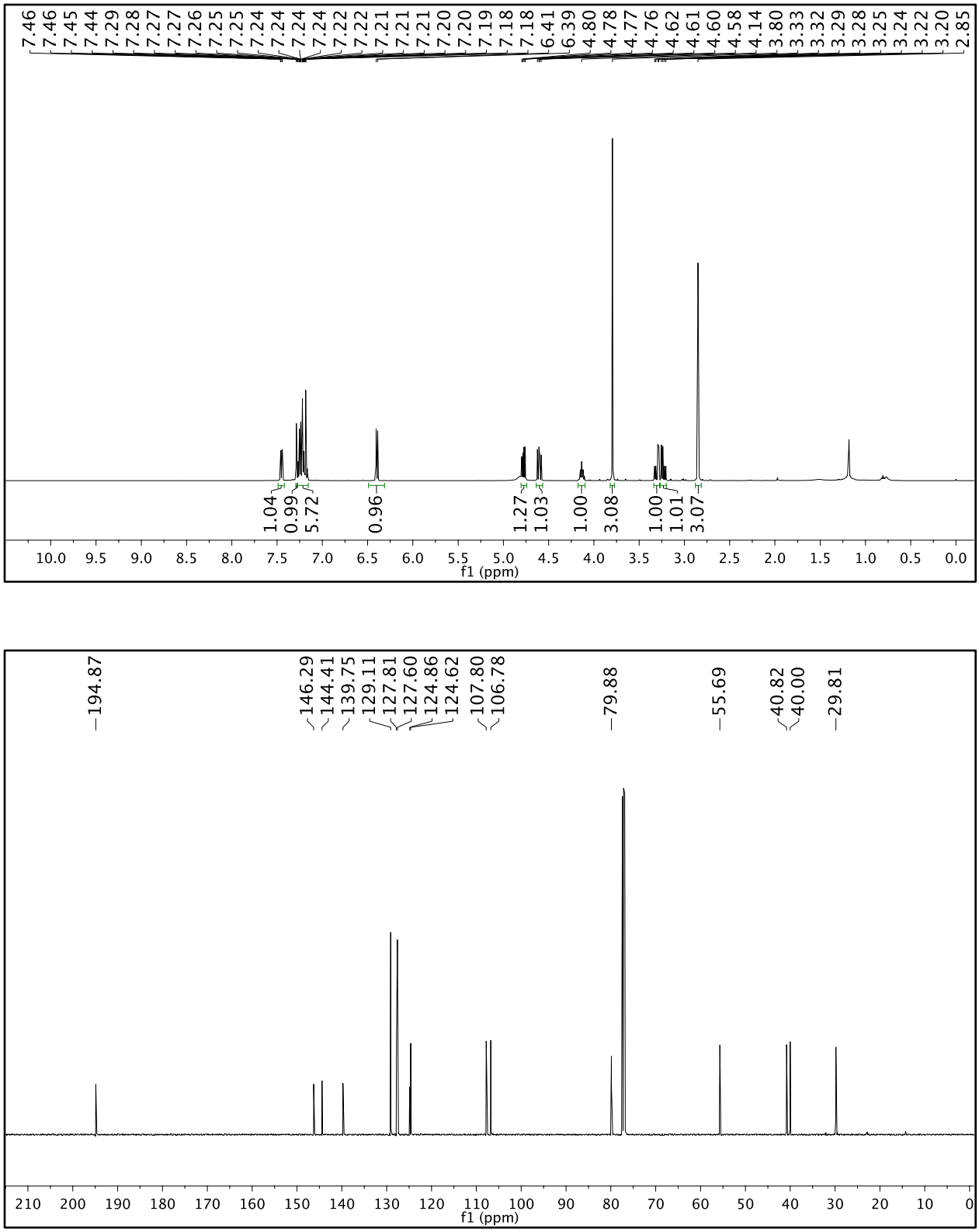


Fig. S20: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **6**.

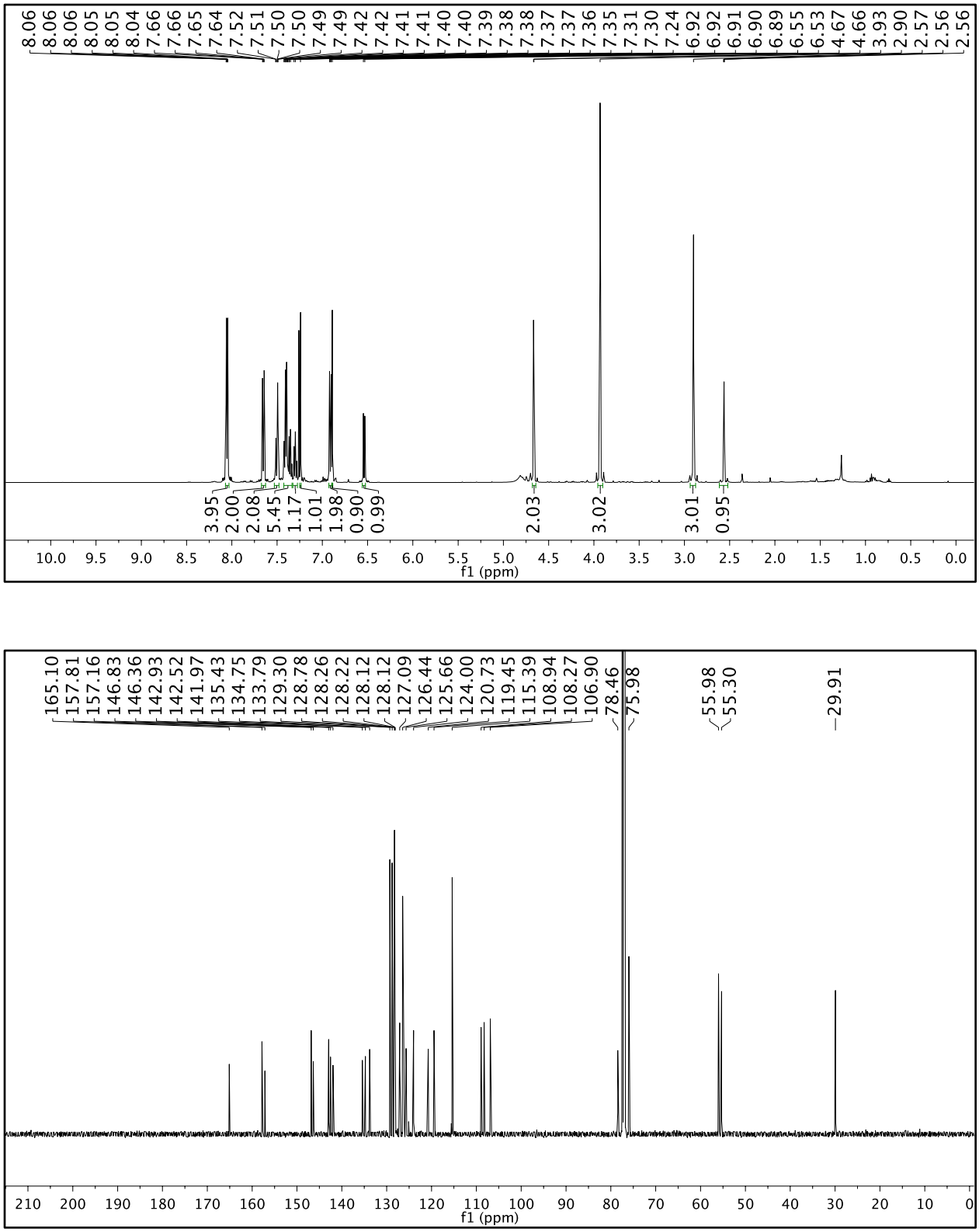
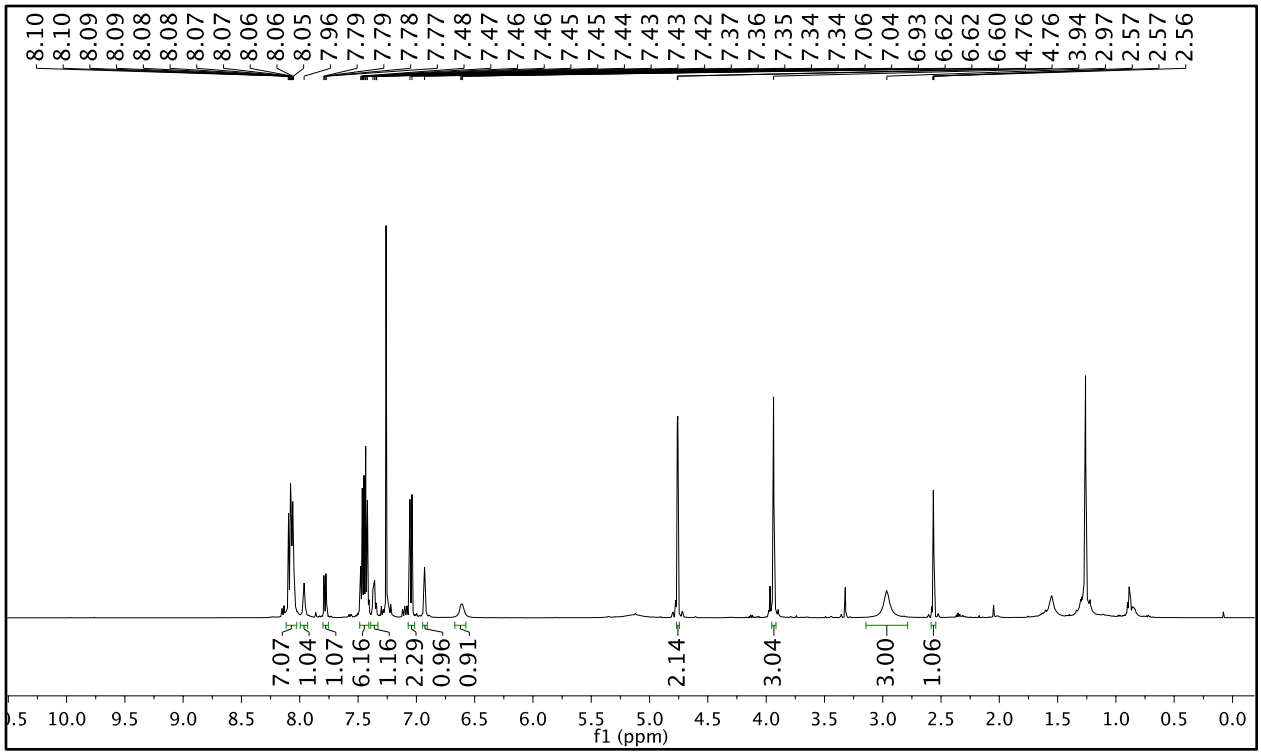


Fig. S21: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **7**.



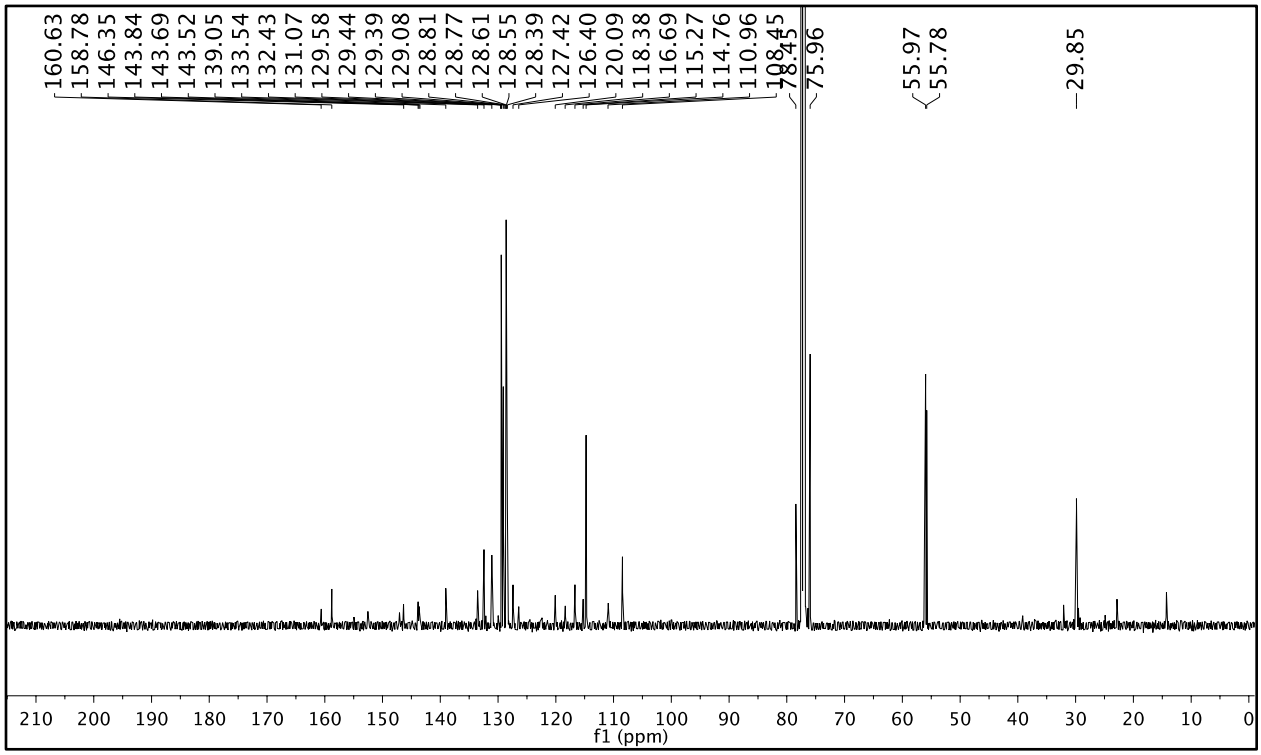


Fig. S22: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **8**.

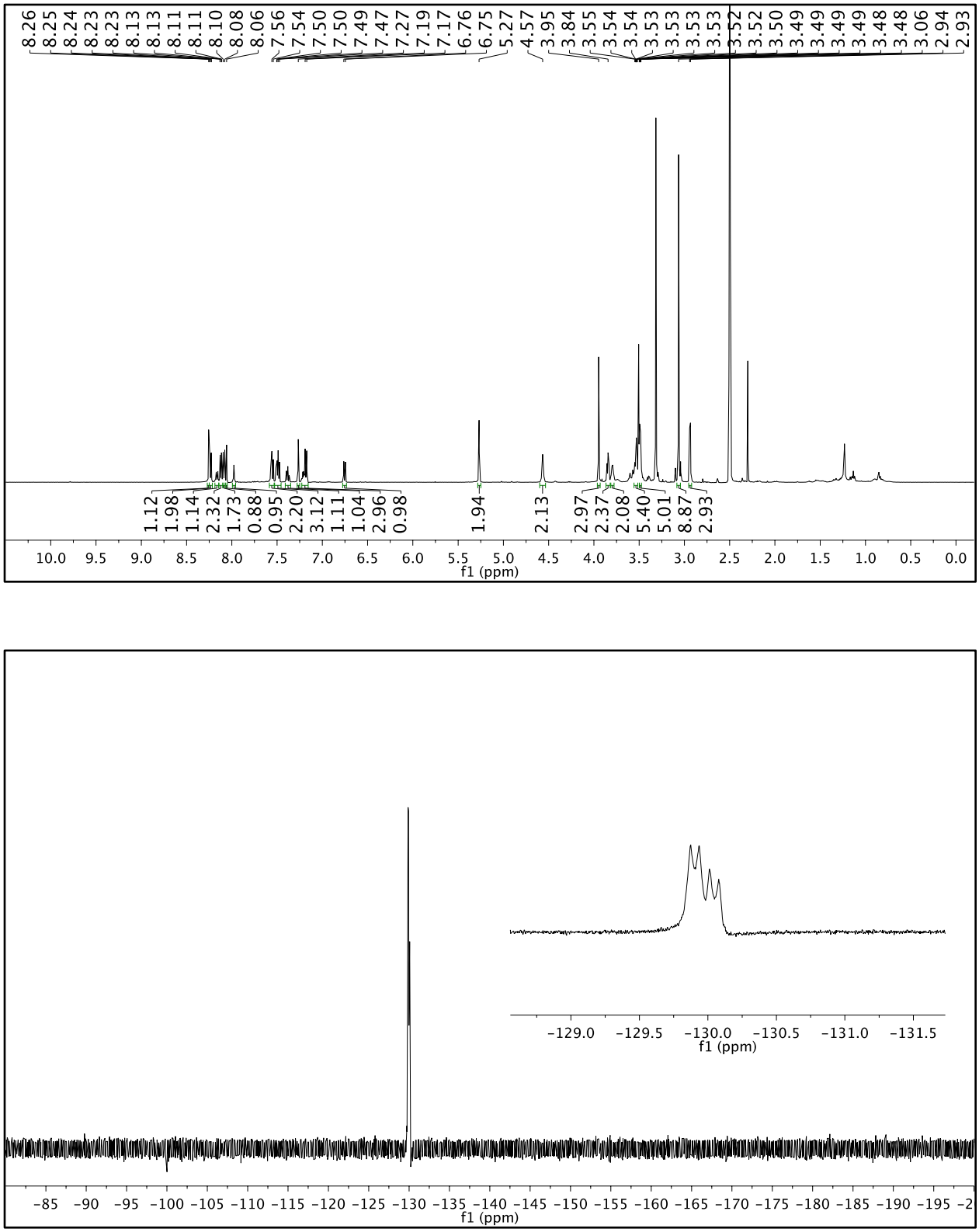


Fig. S23: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{19}F NMR (471 MHz, DMSO-d_6) NMR spectra of **APNO-5**.

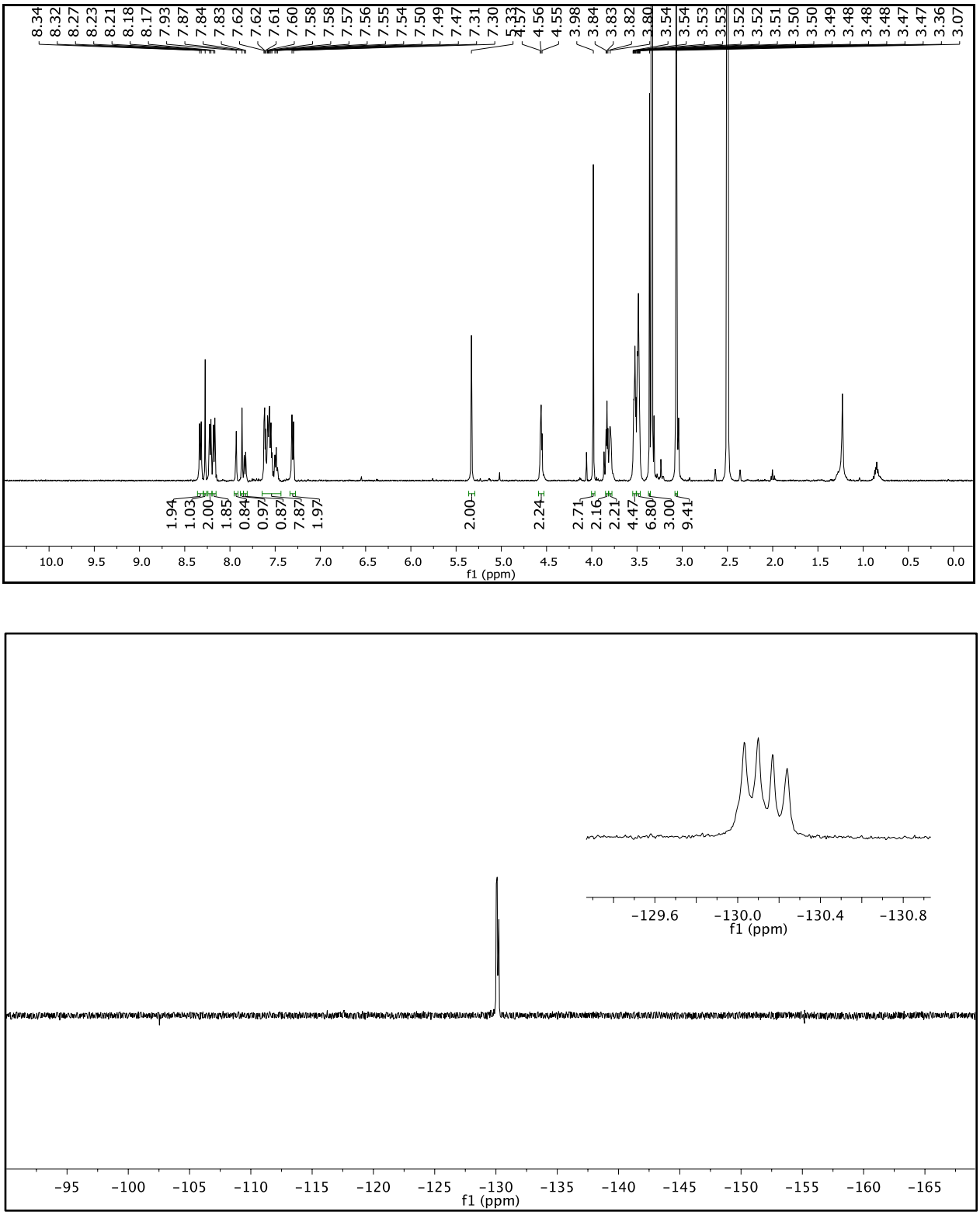


Fig. S24: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{19}F NMR (471 MHz, DMSO-d_6) NMR spectra of **tAPNO-5**.

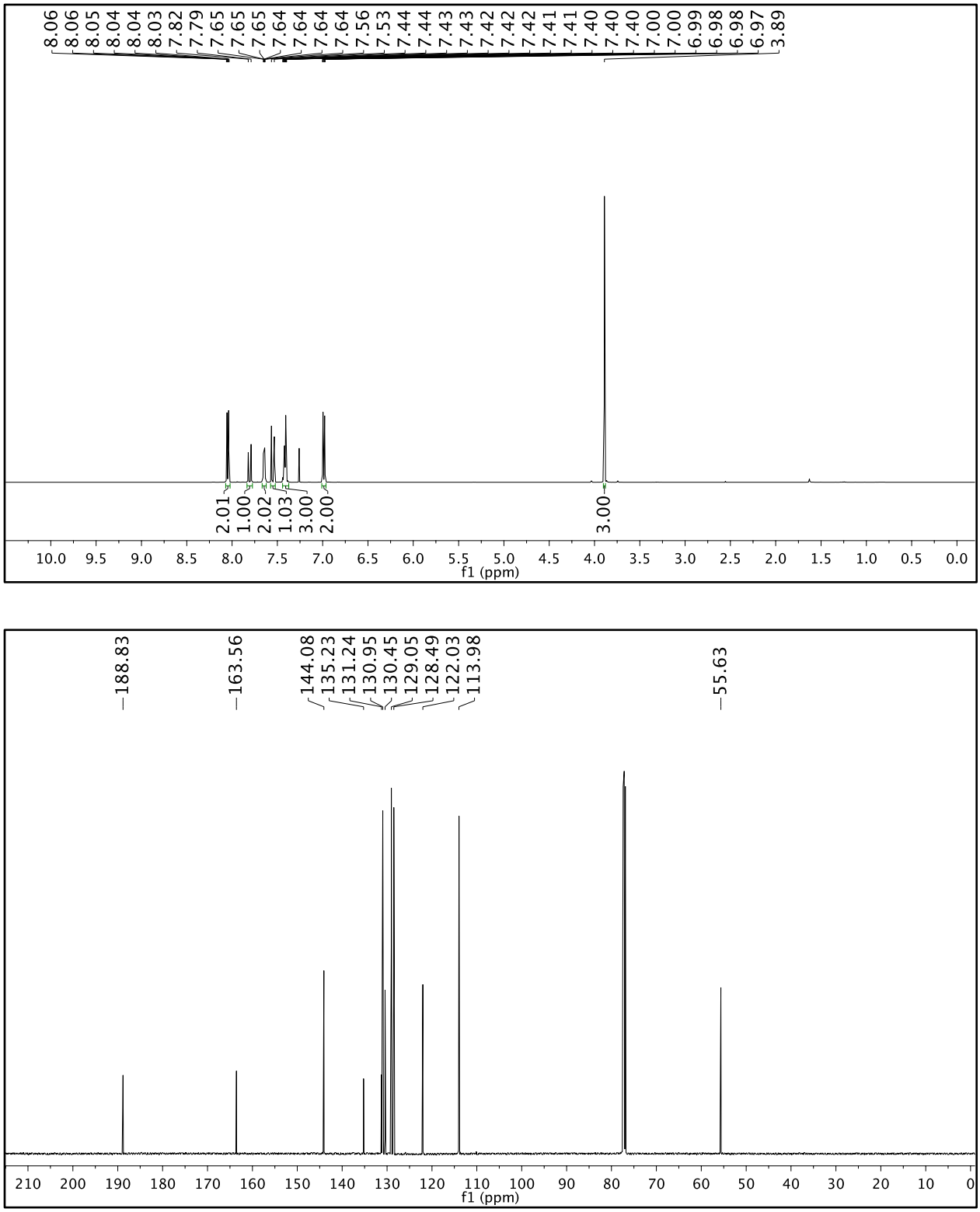
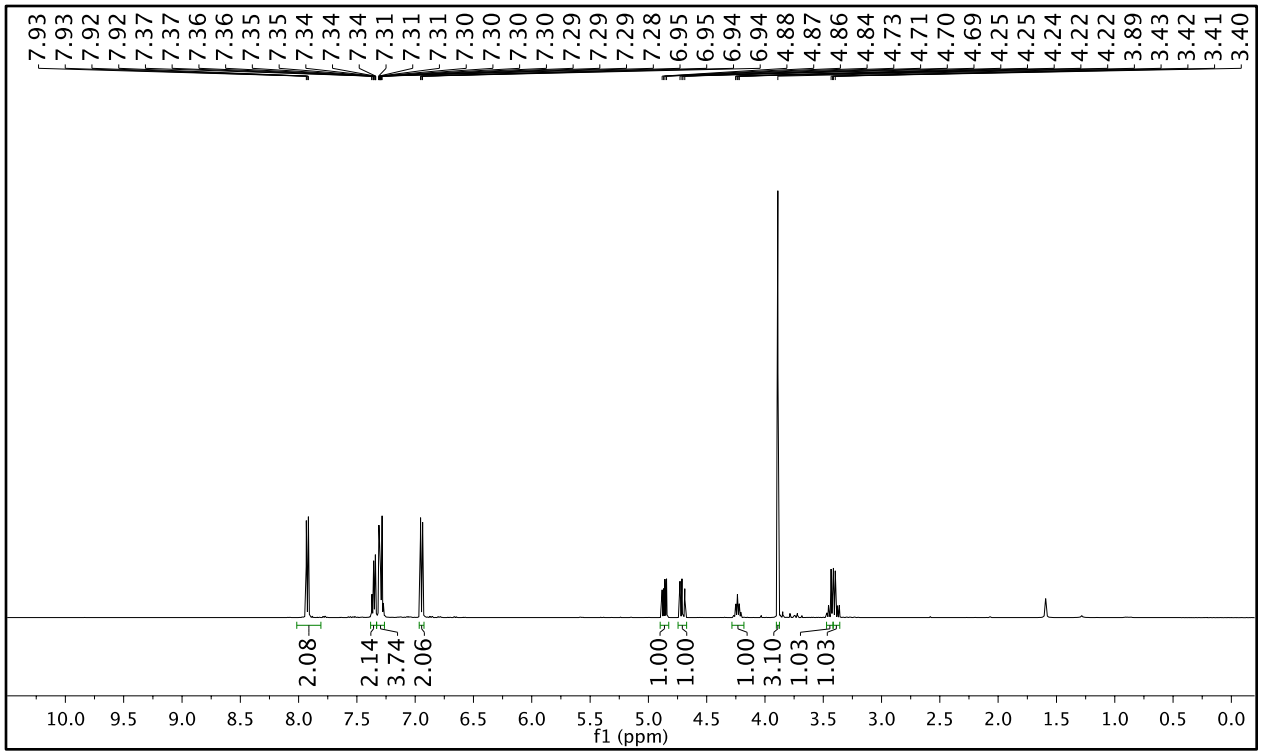


Fig. S25: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **9**.



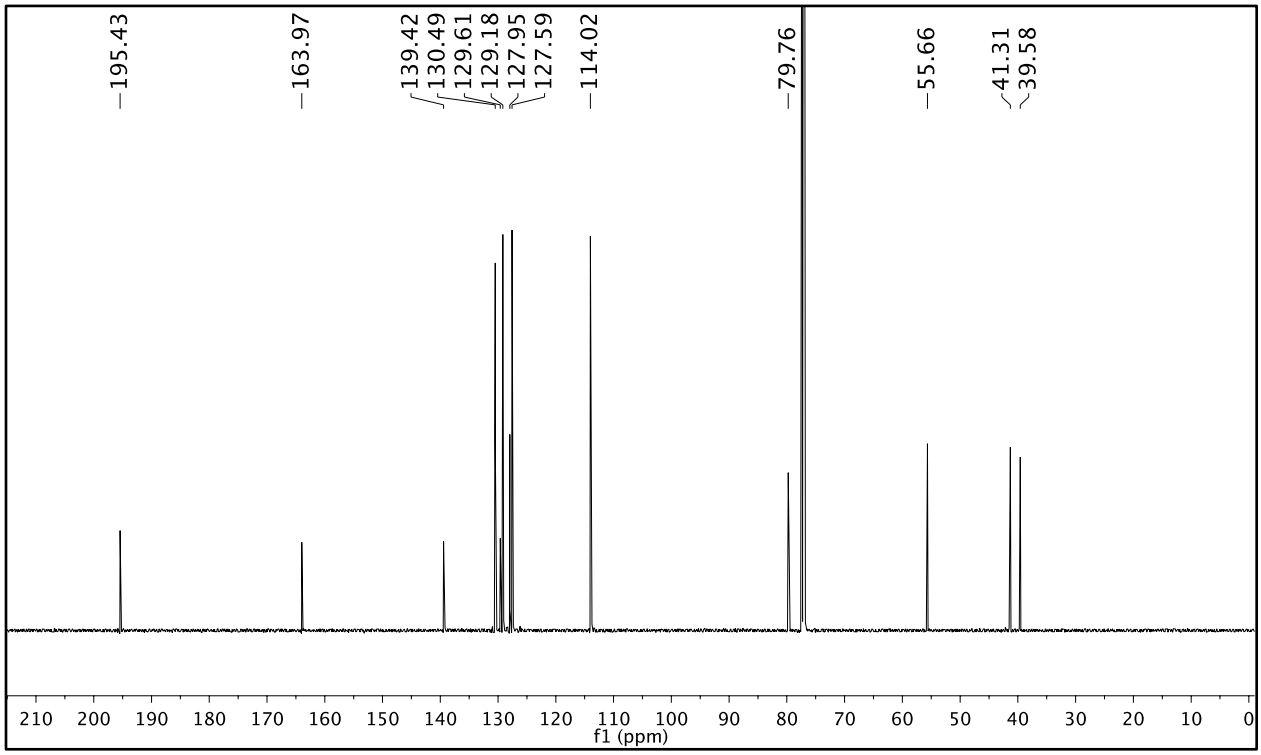


Fig. S26: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **10**.

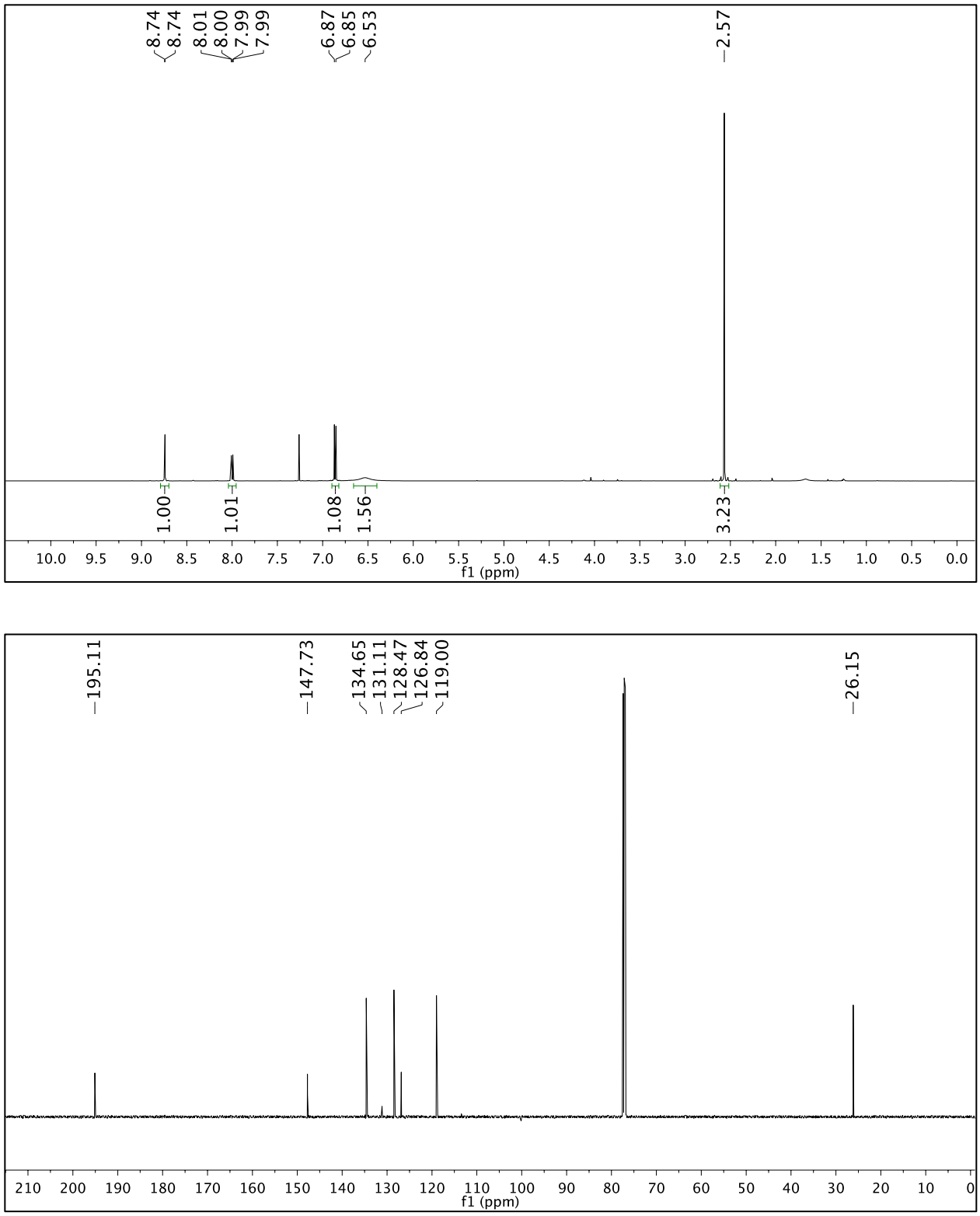


Fig. S27: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **11**.

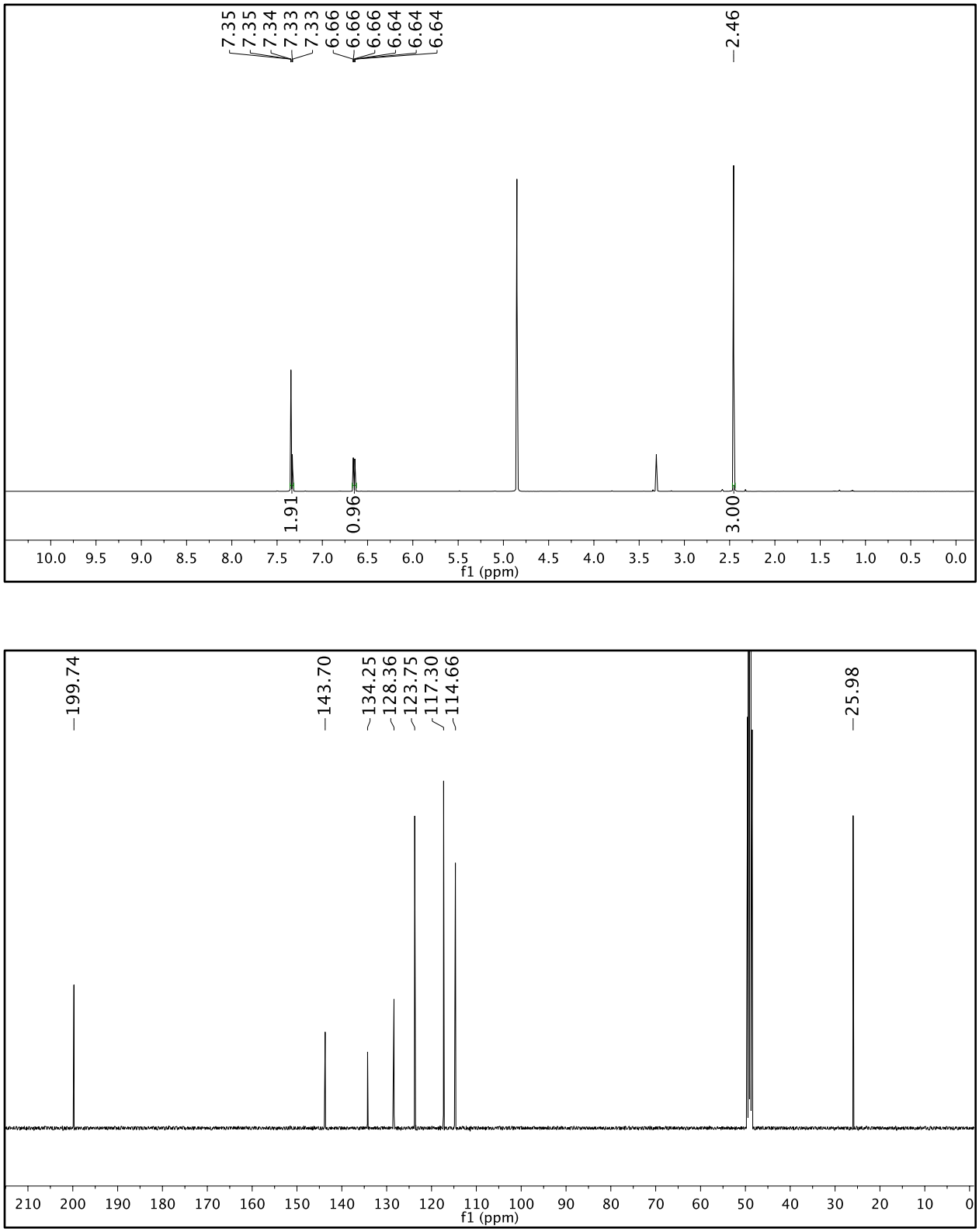


Fig. S28: ^{1}H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) NMR spectra of **12**.

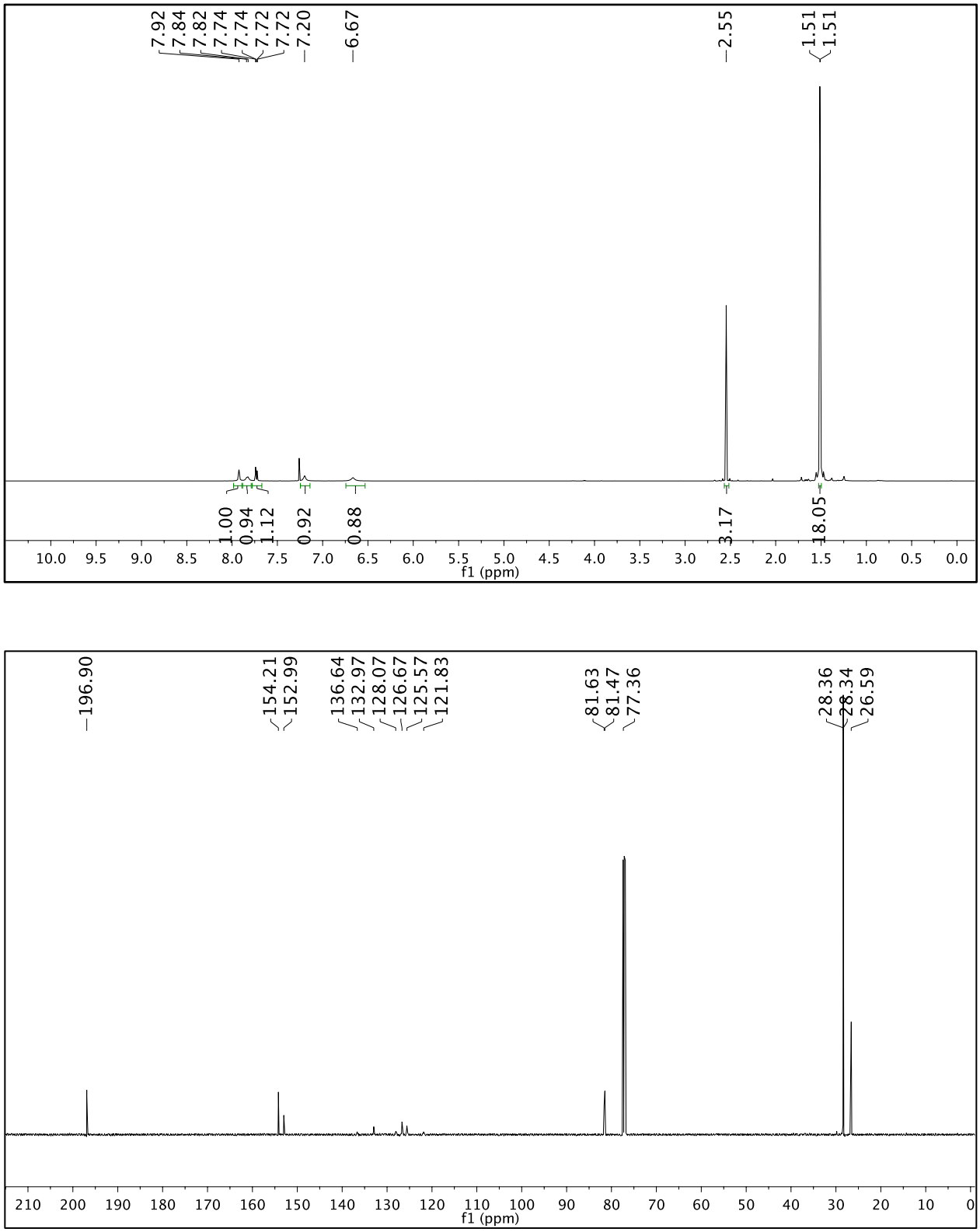
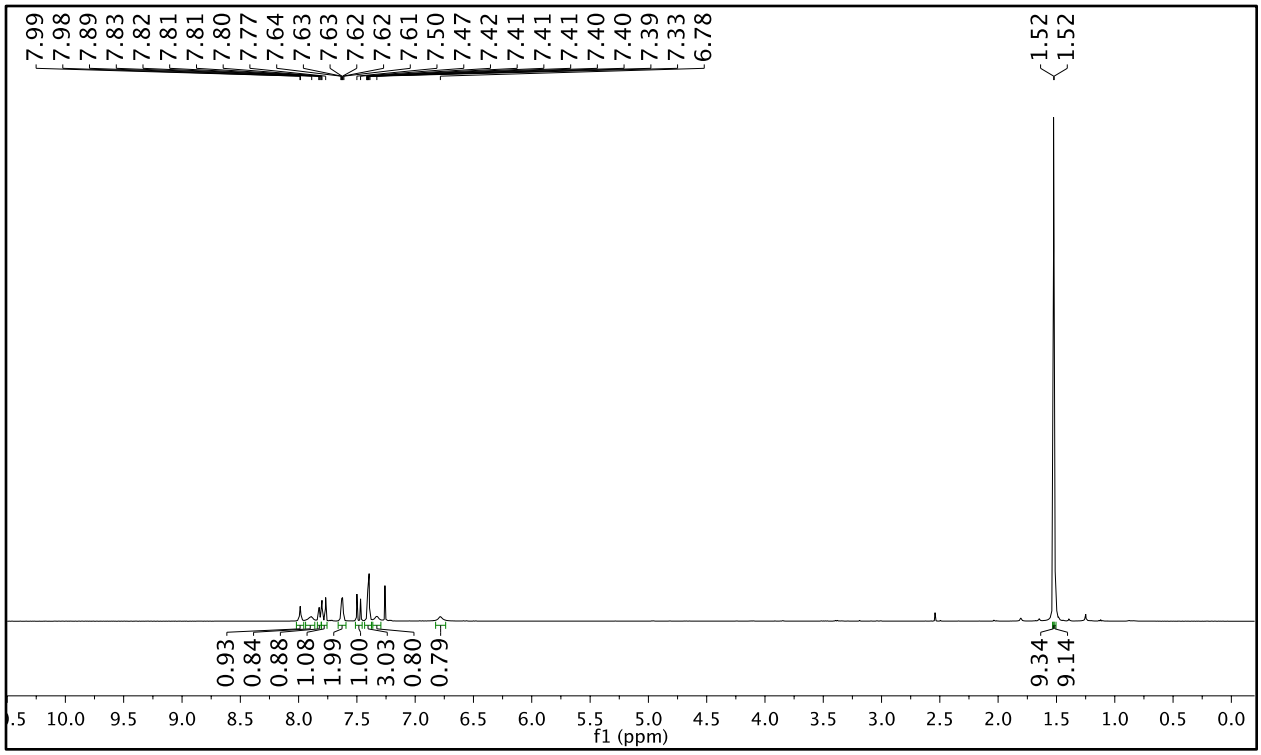


Fig. S29: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **13**.



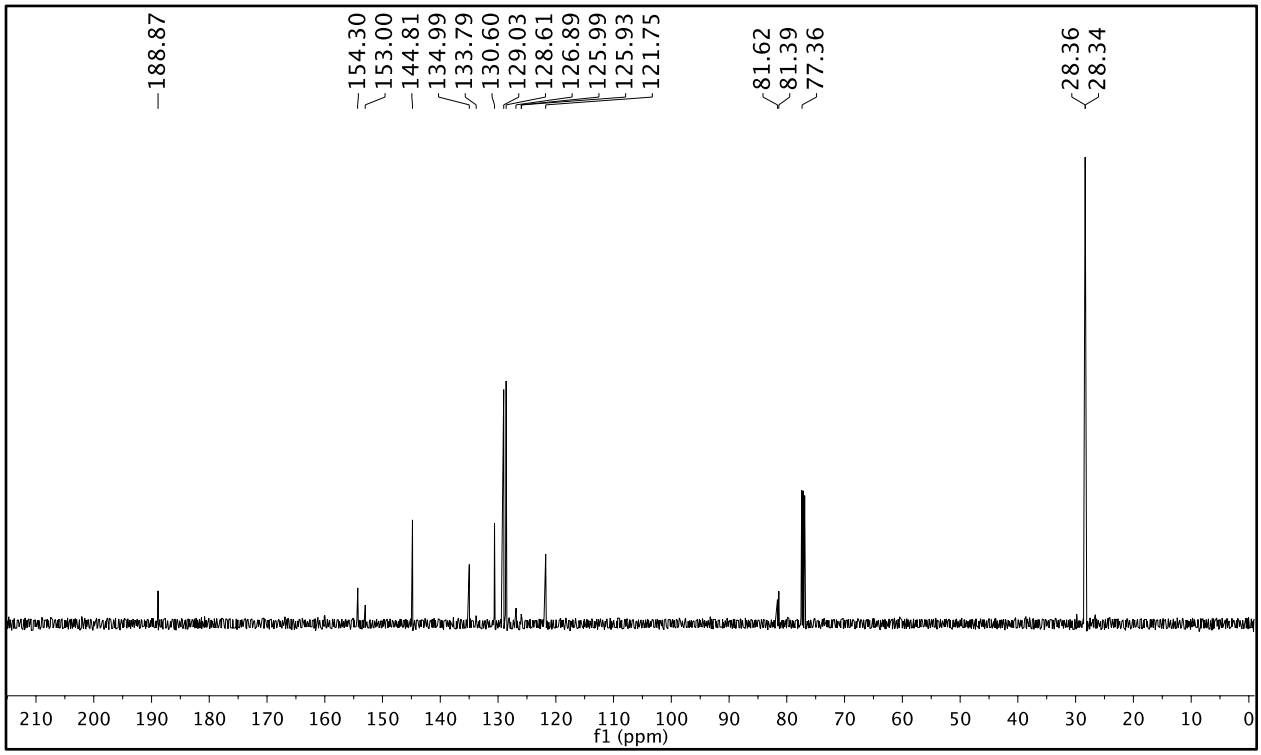
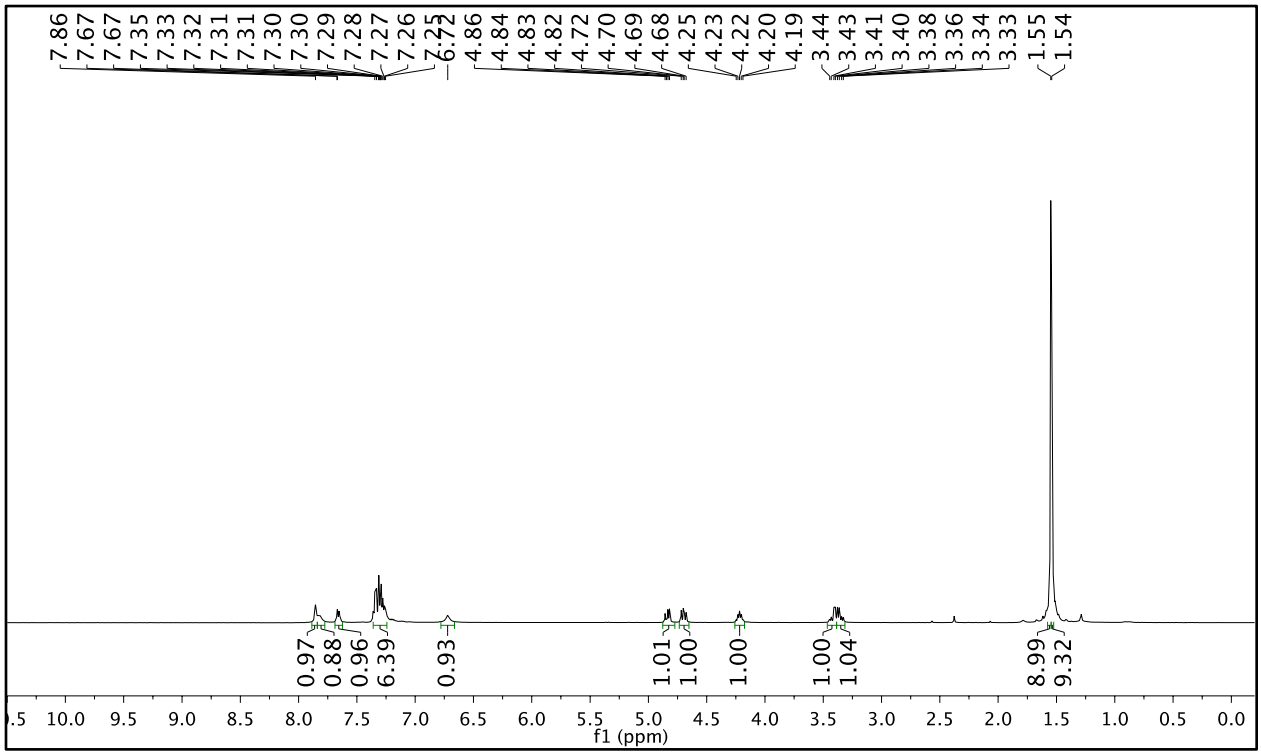


Fig. S30: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **14**.



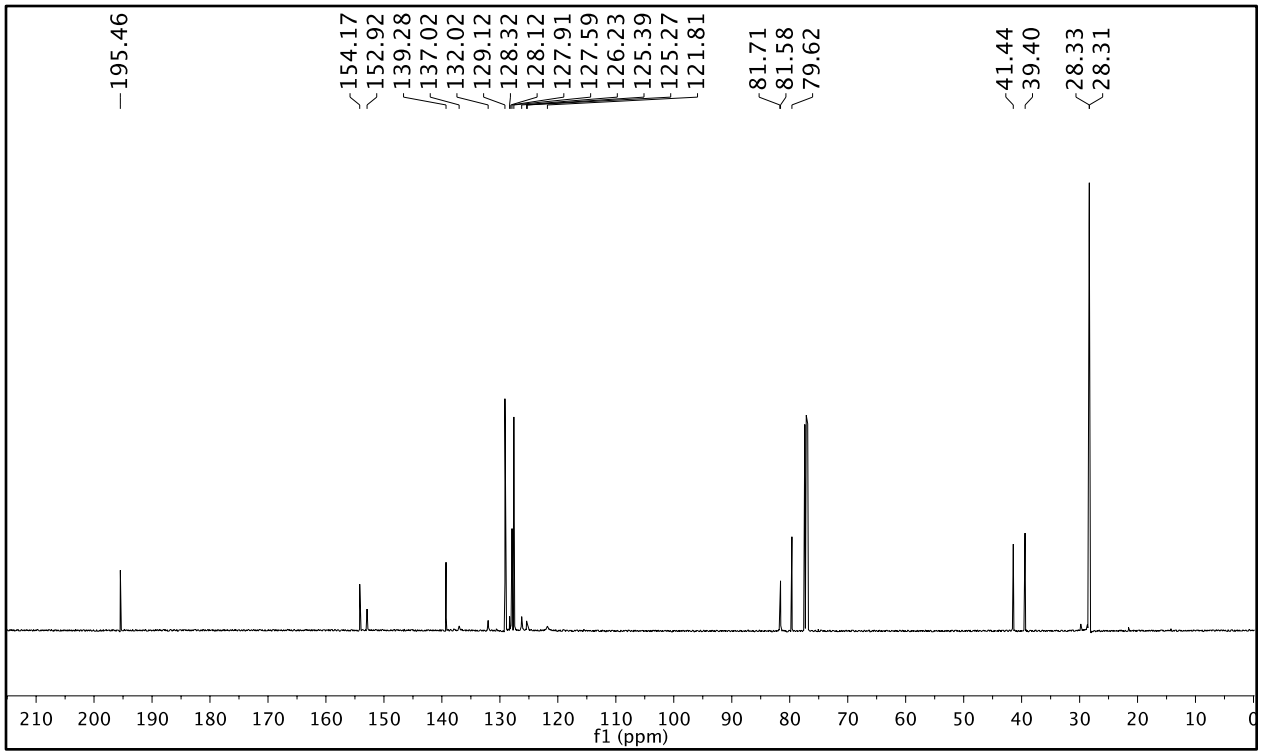


Fig. S31: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **15**.

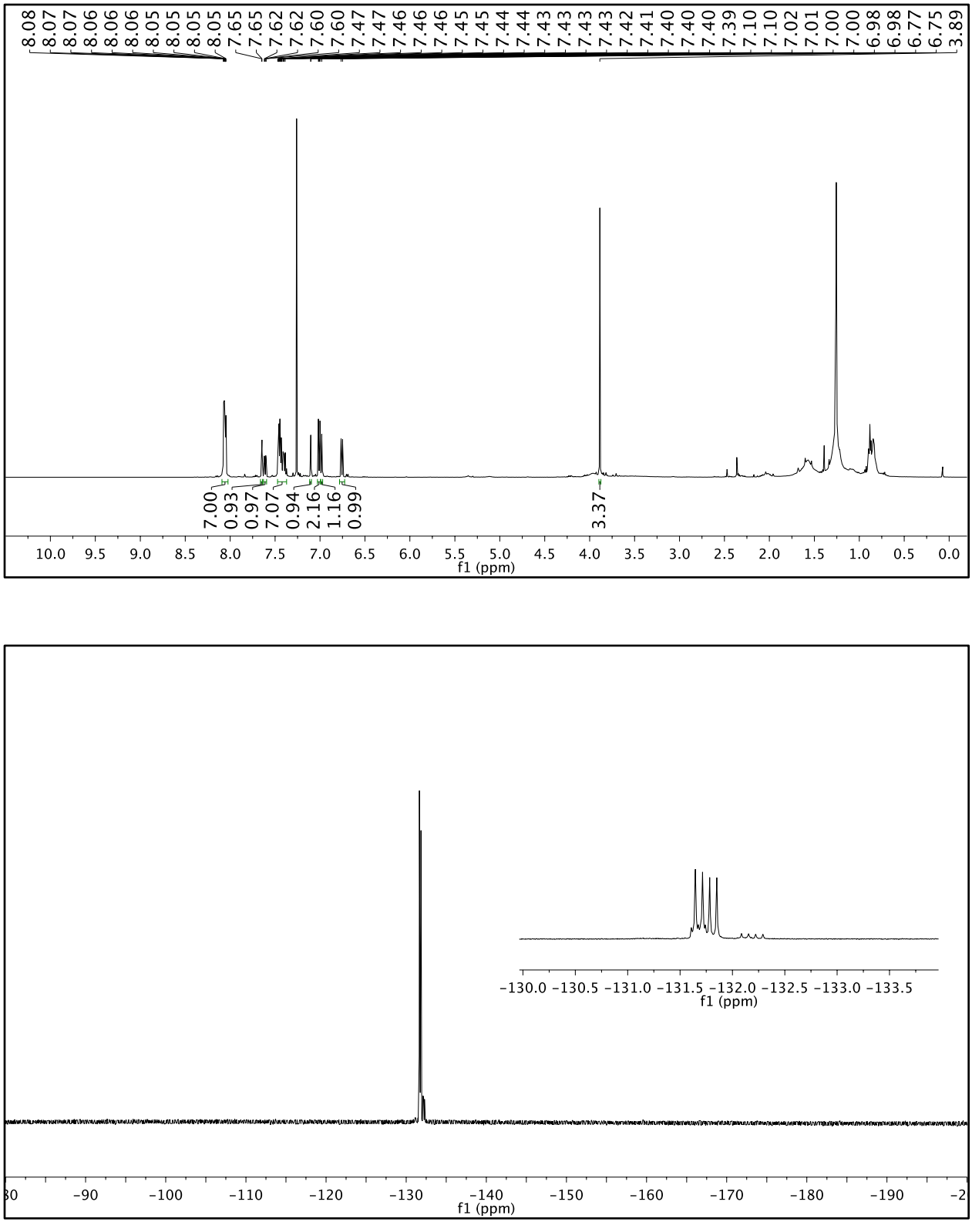


Fig. S32: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{19}F NMR (471 MHz, $CDCl_3$) NMR spectra of **APNO-1**.

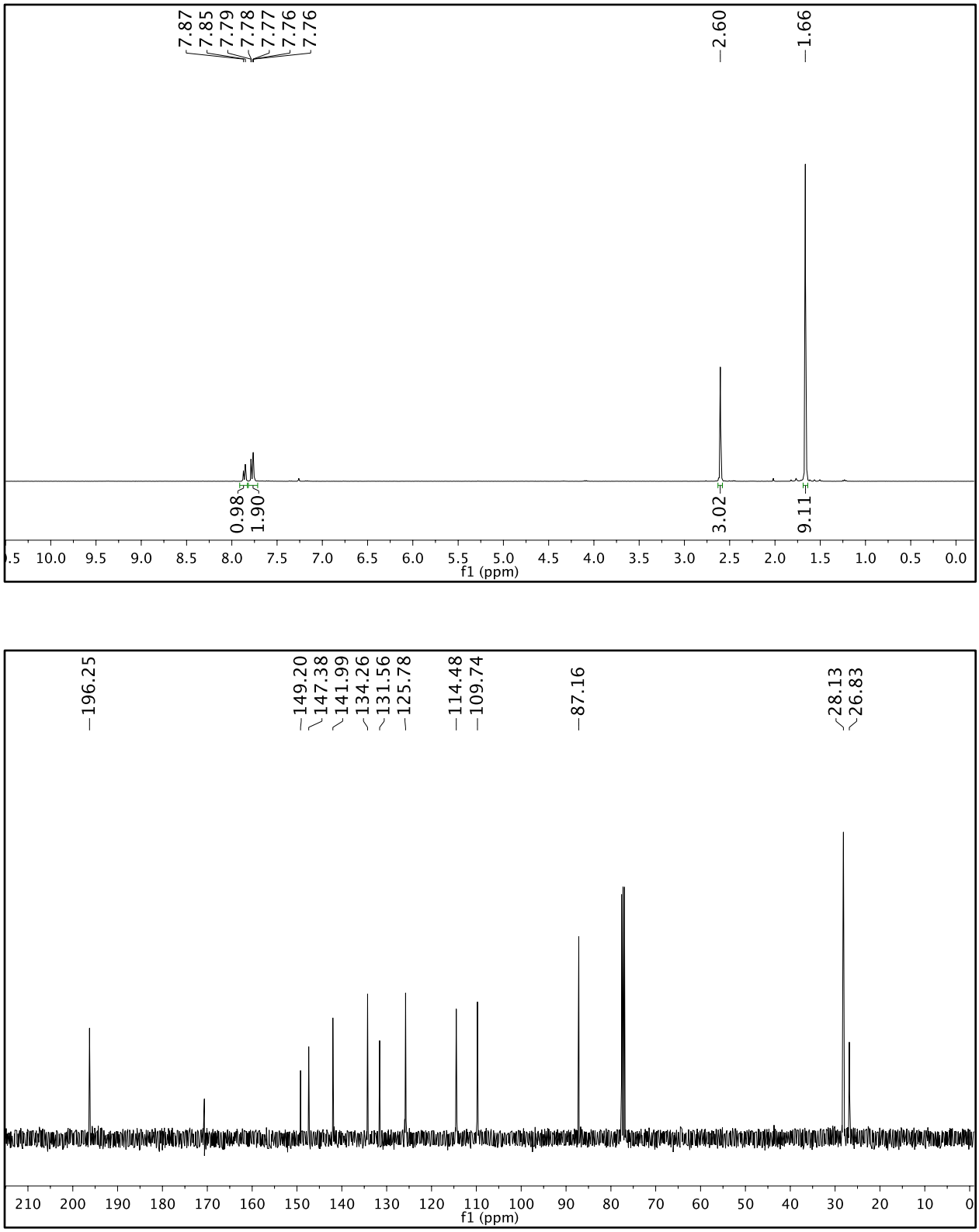


Fig. S33: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **17**.

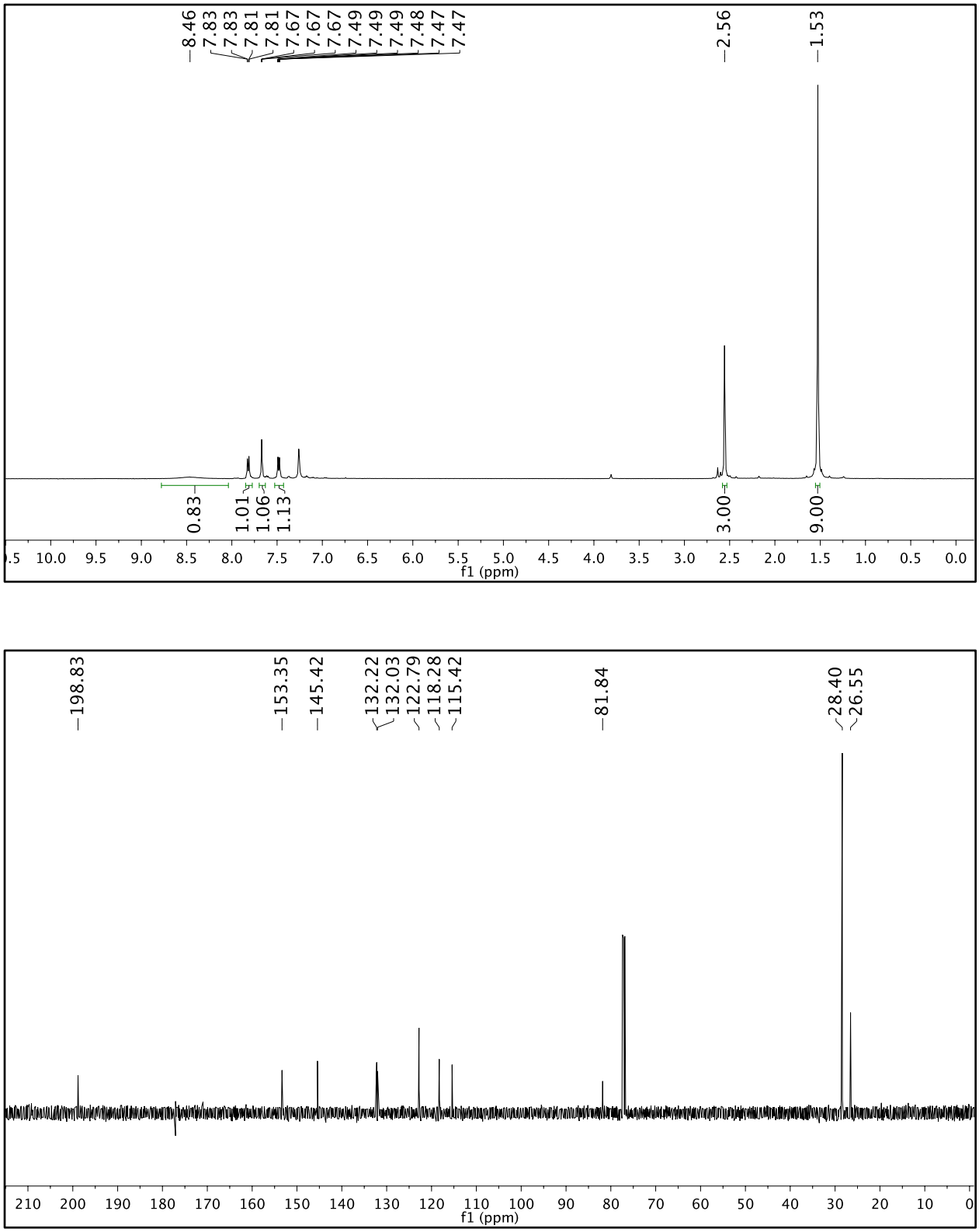
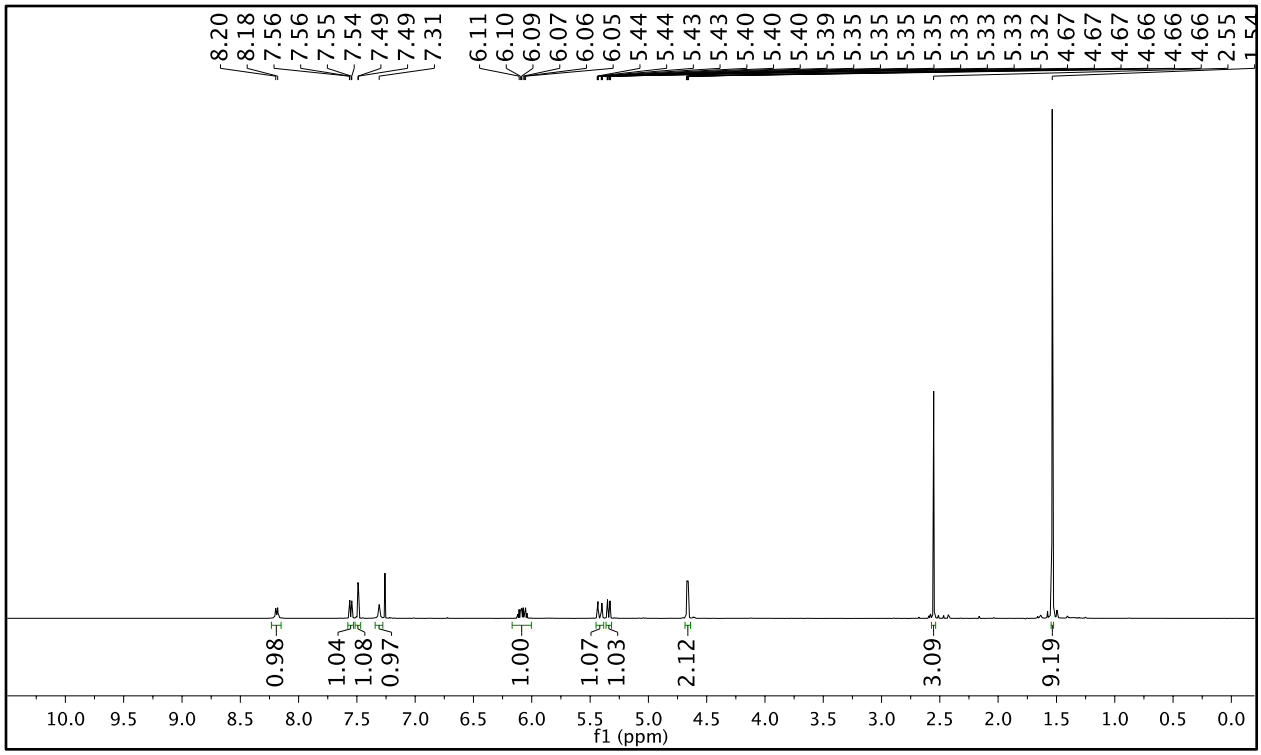


Fig. S34: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **18**.



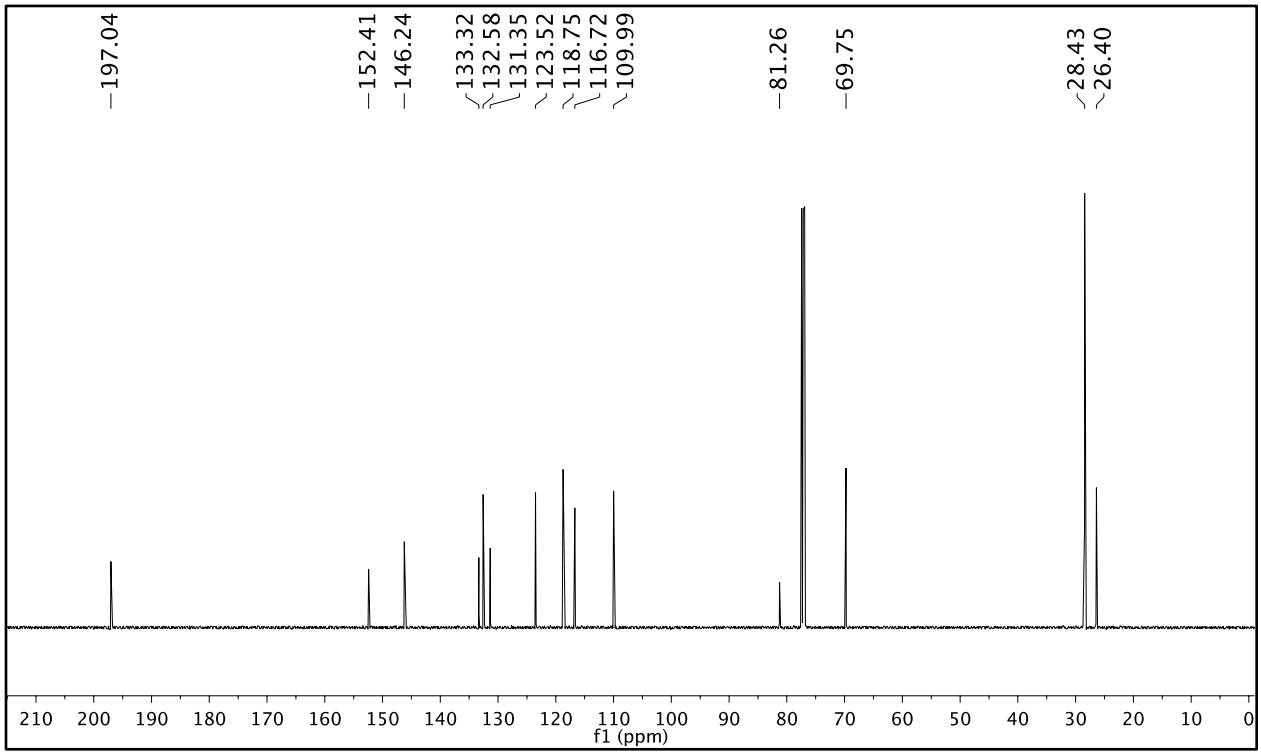
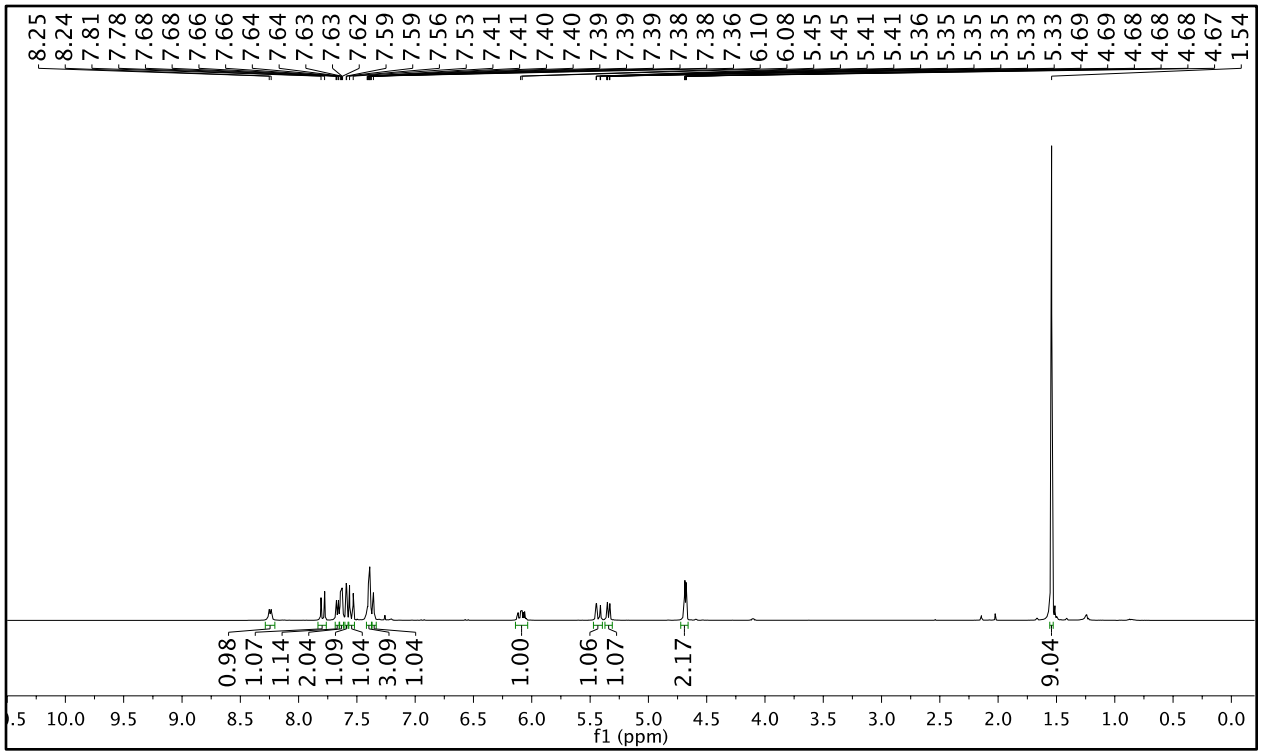


Fig. S35: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **19**.



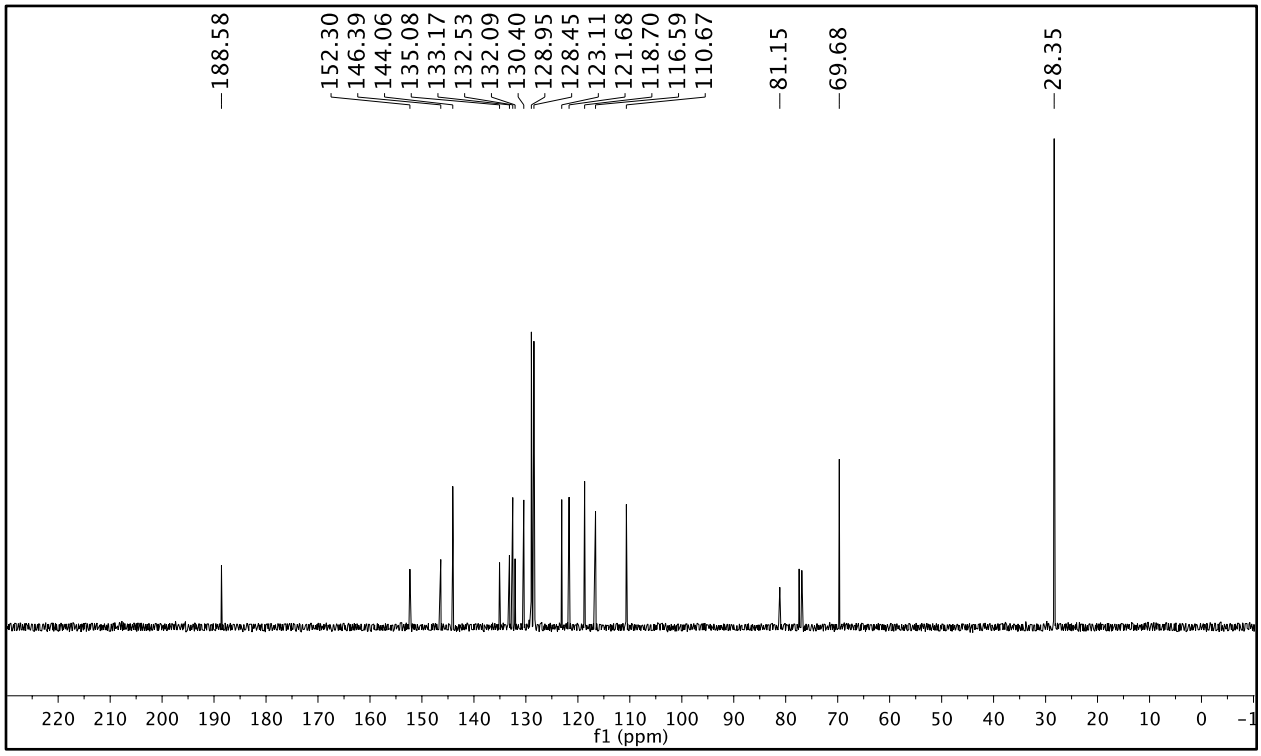


Fig. S36: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **20**.

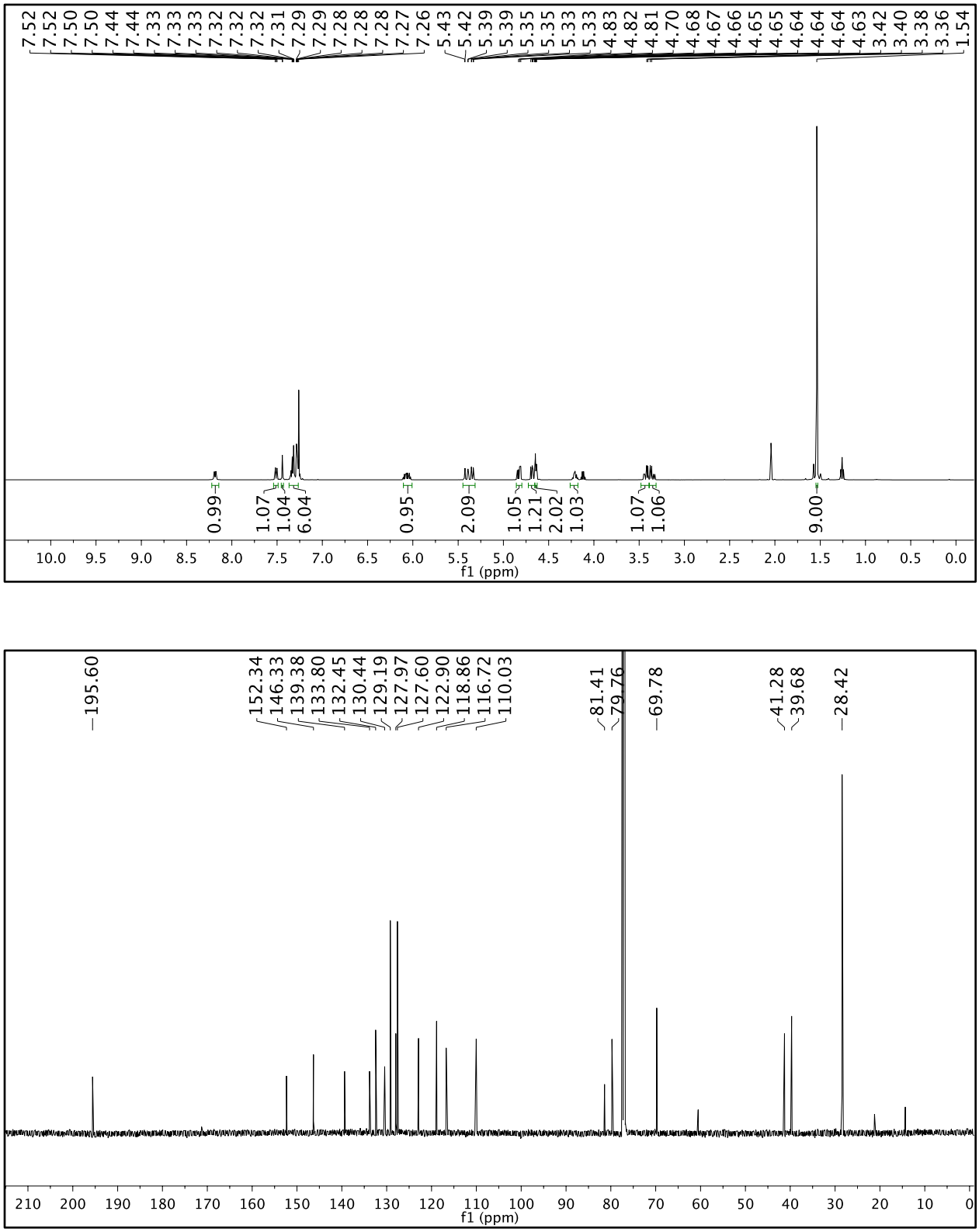


Fig. S37: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **21**.

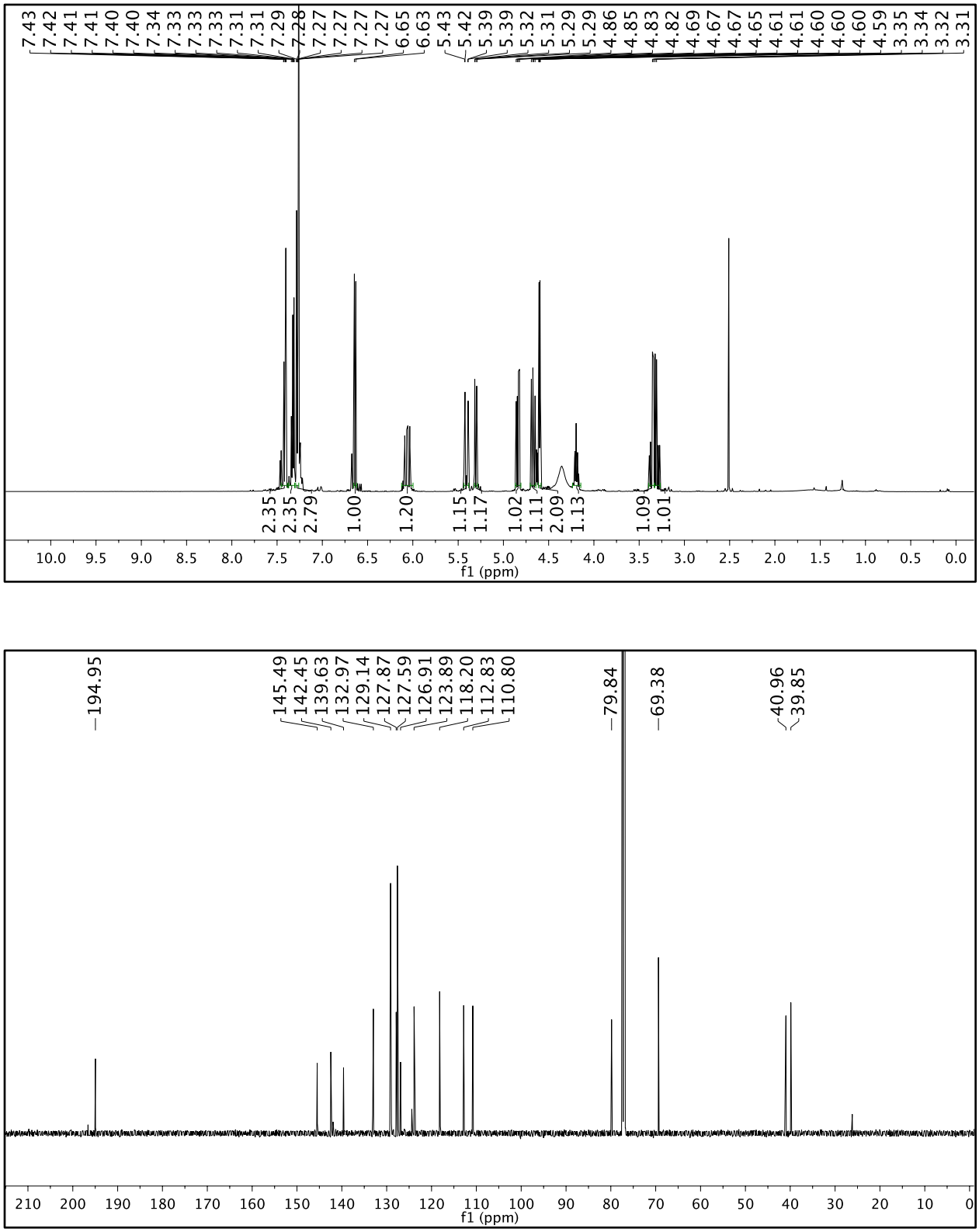


Fig. S38: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **22**.

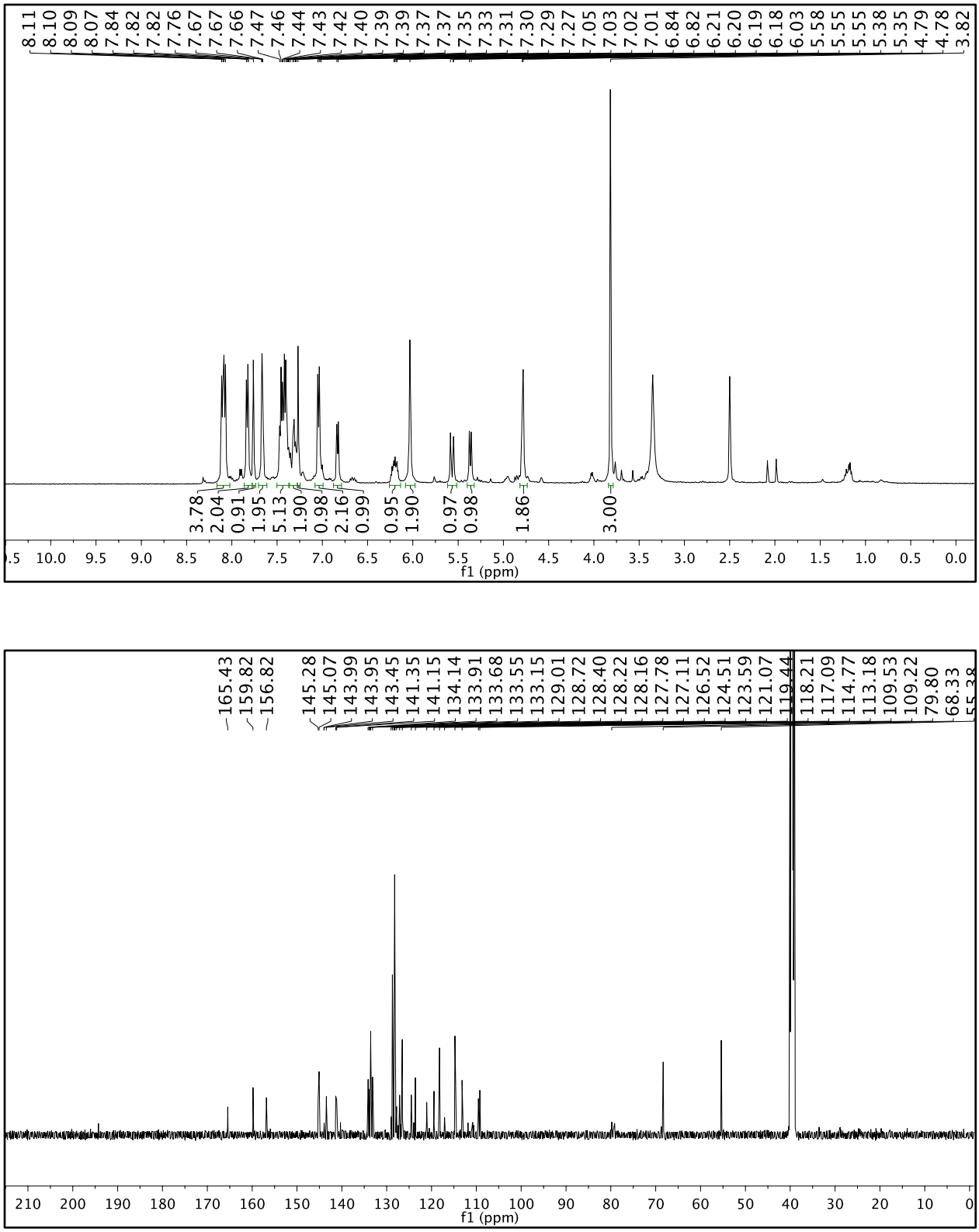


Fig. S39: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) NMR spectra of **23**.

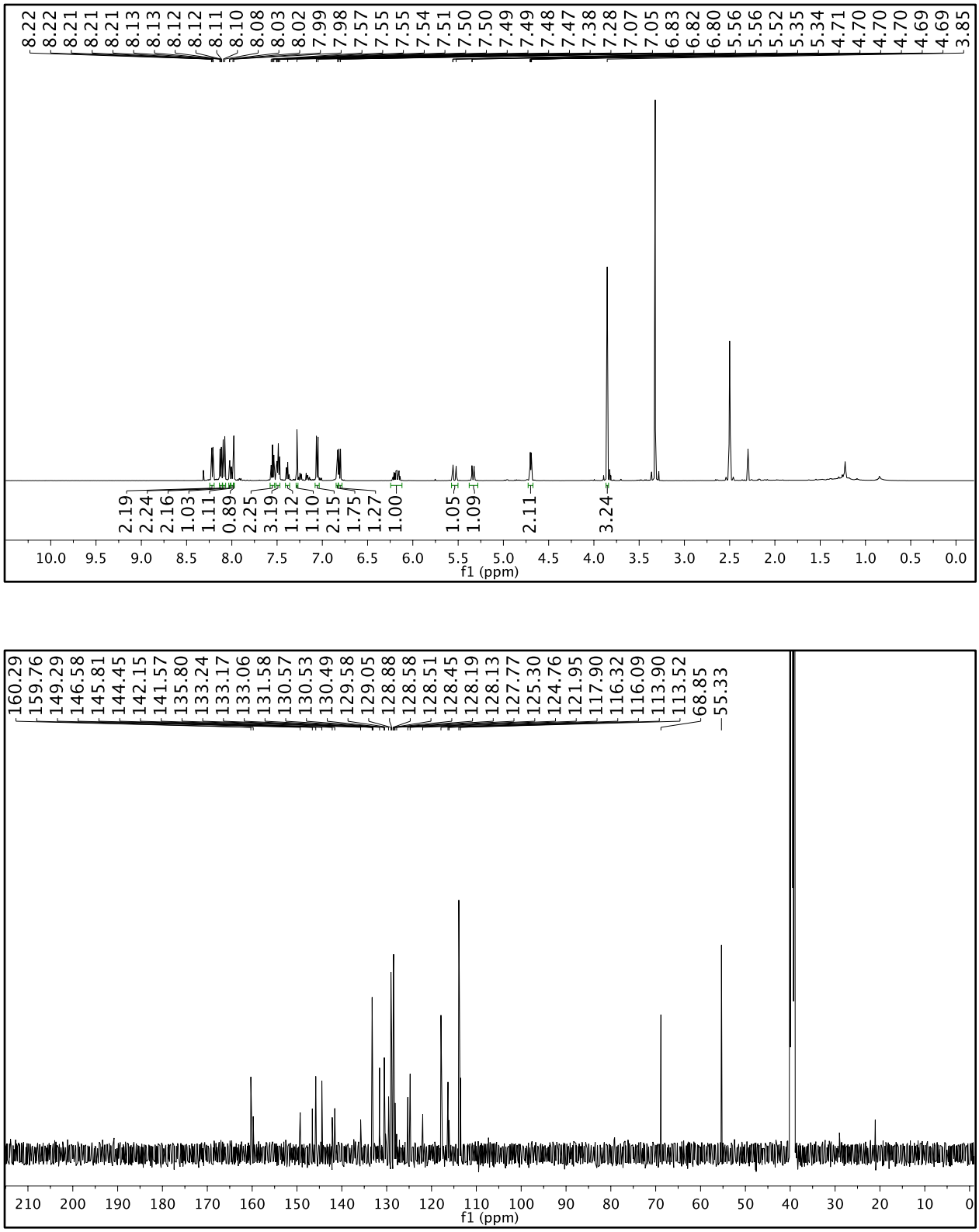


Fig. S40: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) NMR spectra of **24**.

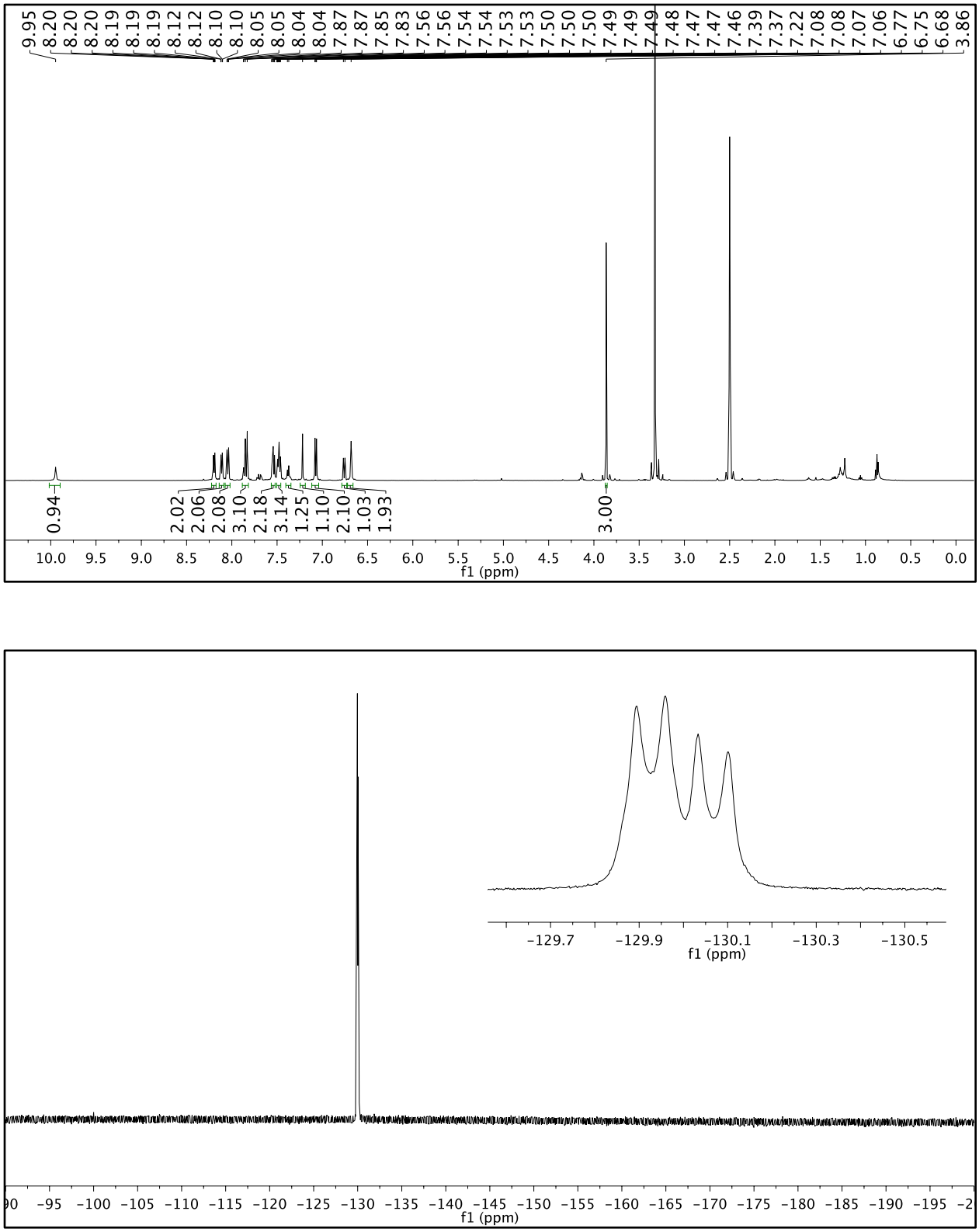


Fig. S41: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{19}F NMR (471 MHz, DMSO-d_6) NMR spectra of **APNO-2**.

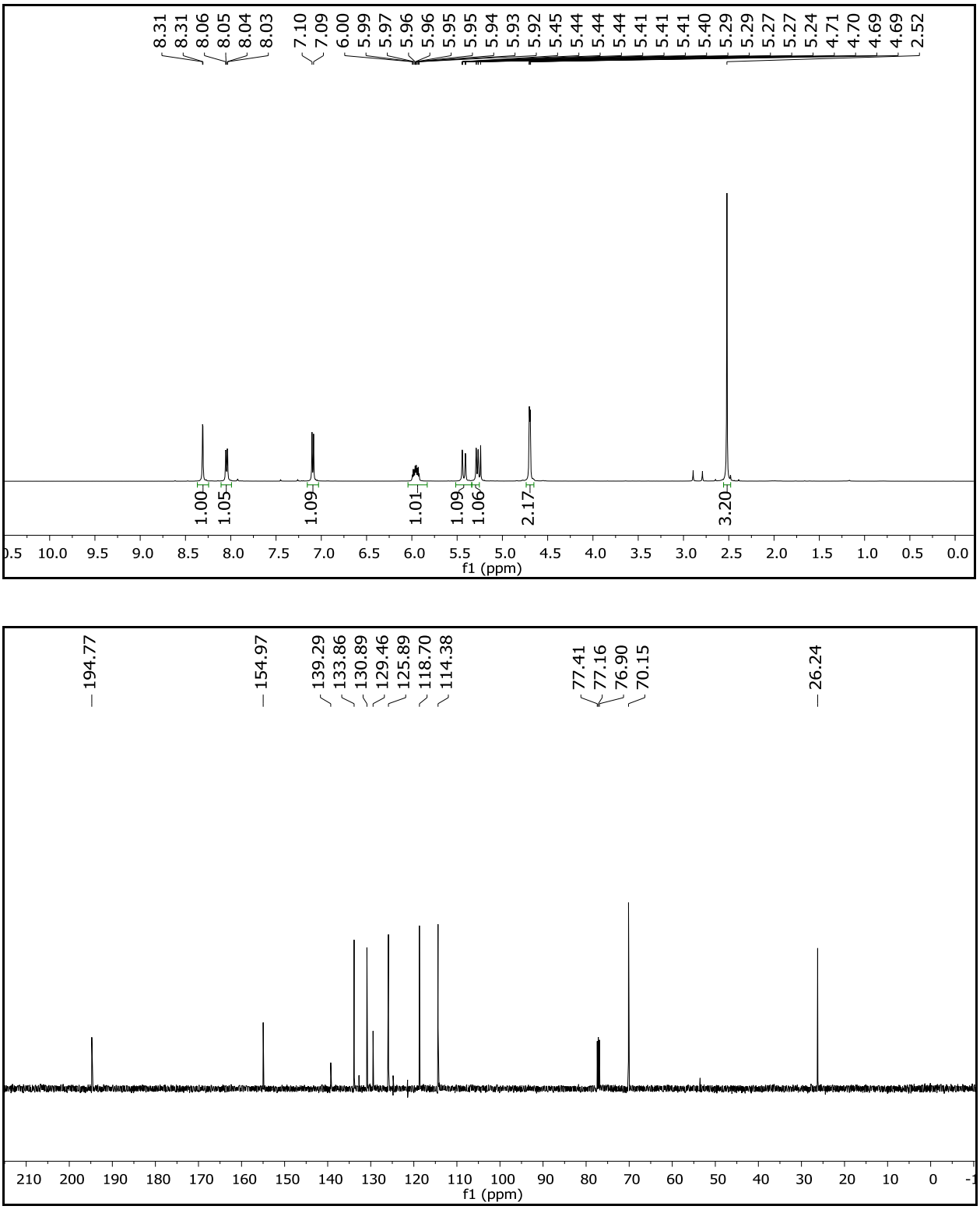


Fig. S42: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **25.**

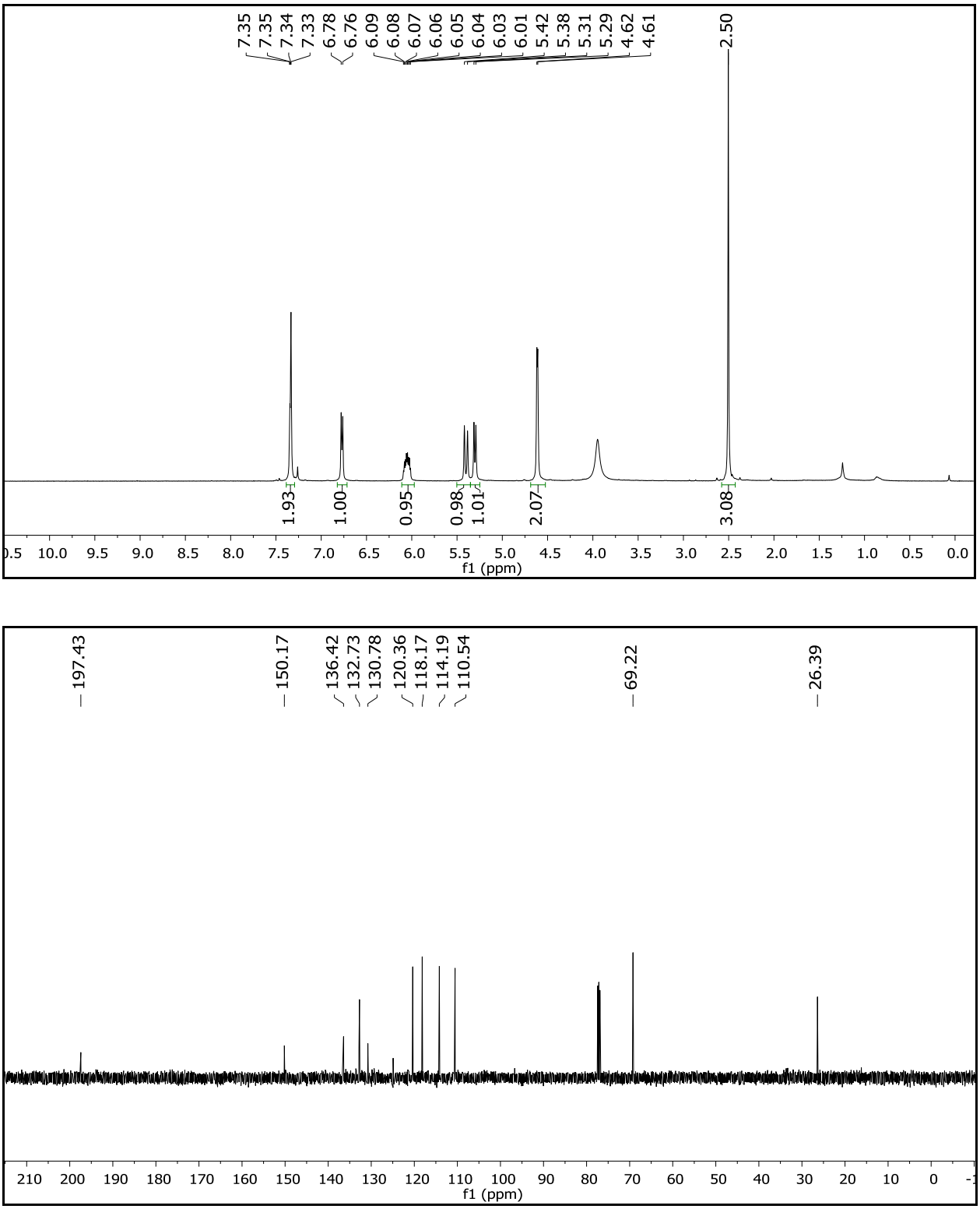


Fig. S43: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **26.**

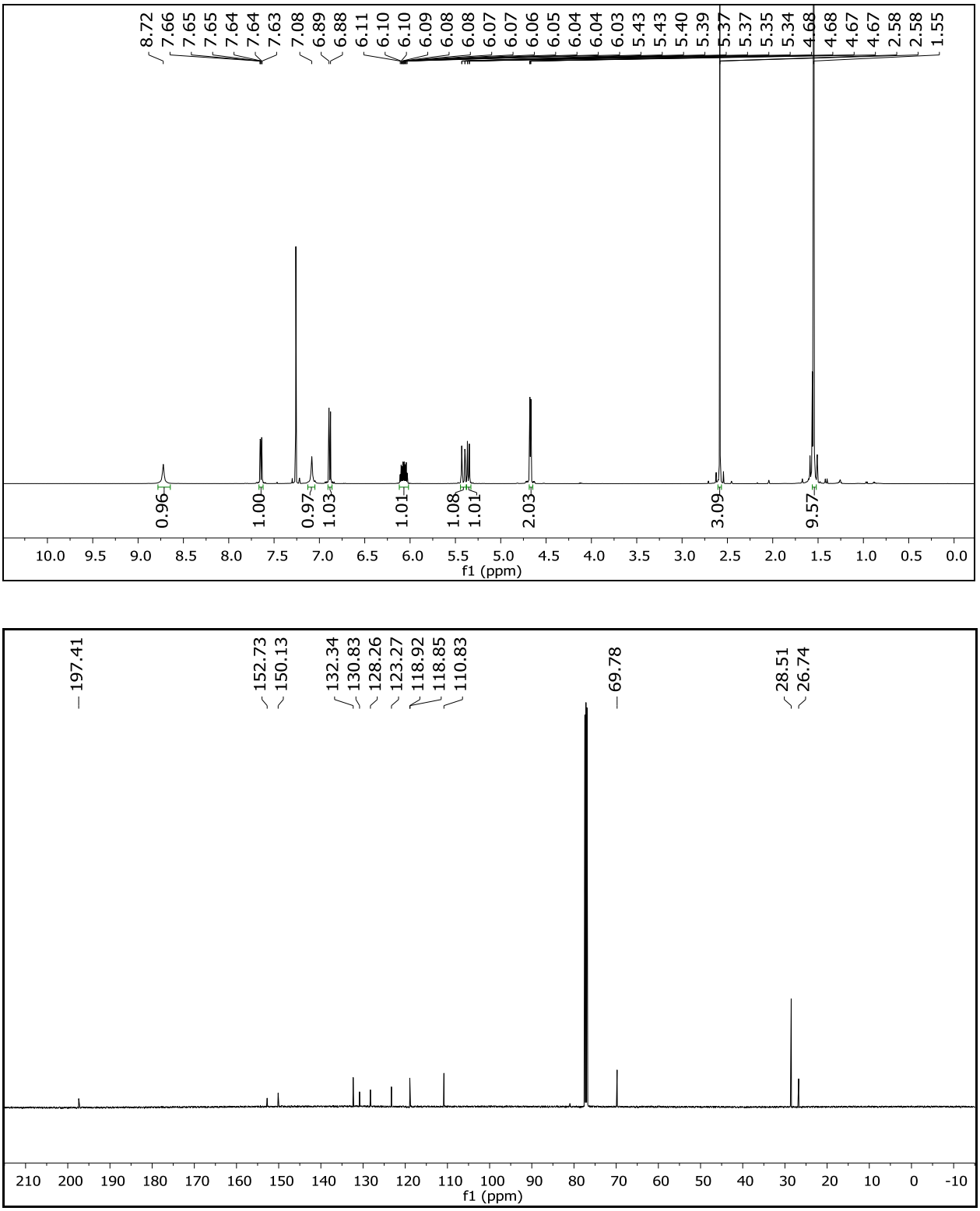


Fig. S44: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **27.**

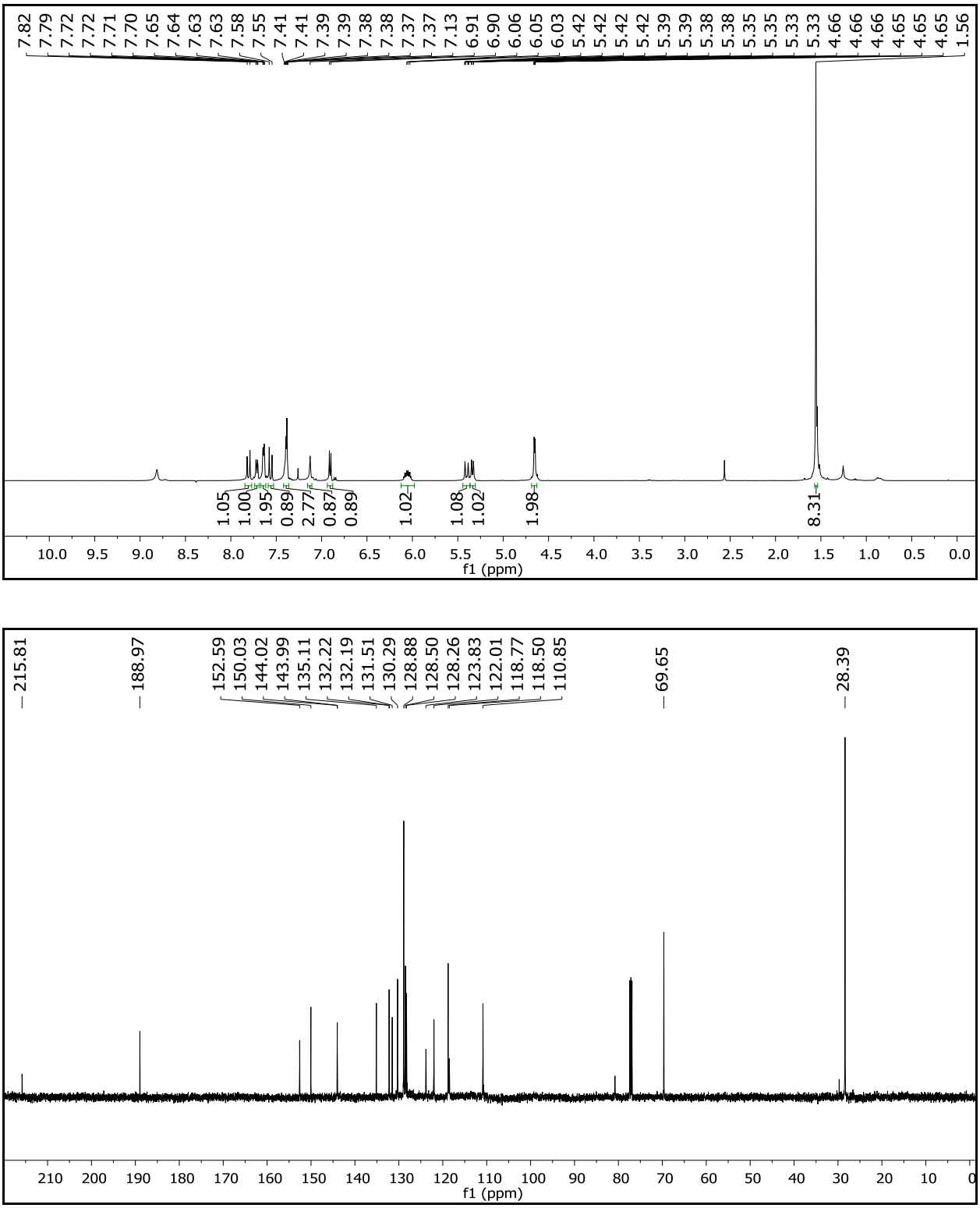


Fig. S45: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **28.**

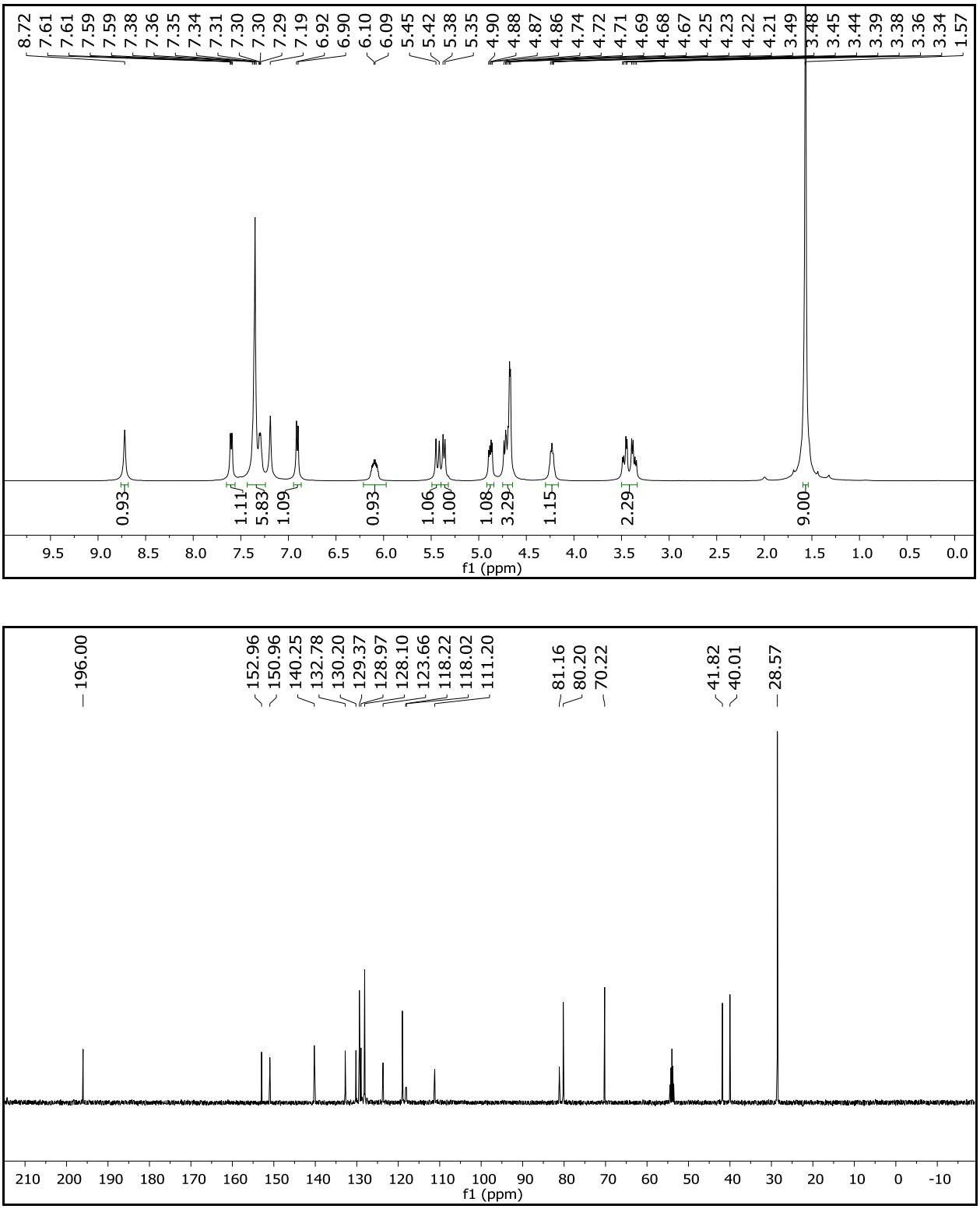


Fig. S46: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **29.**

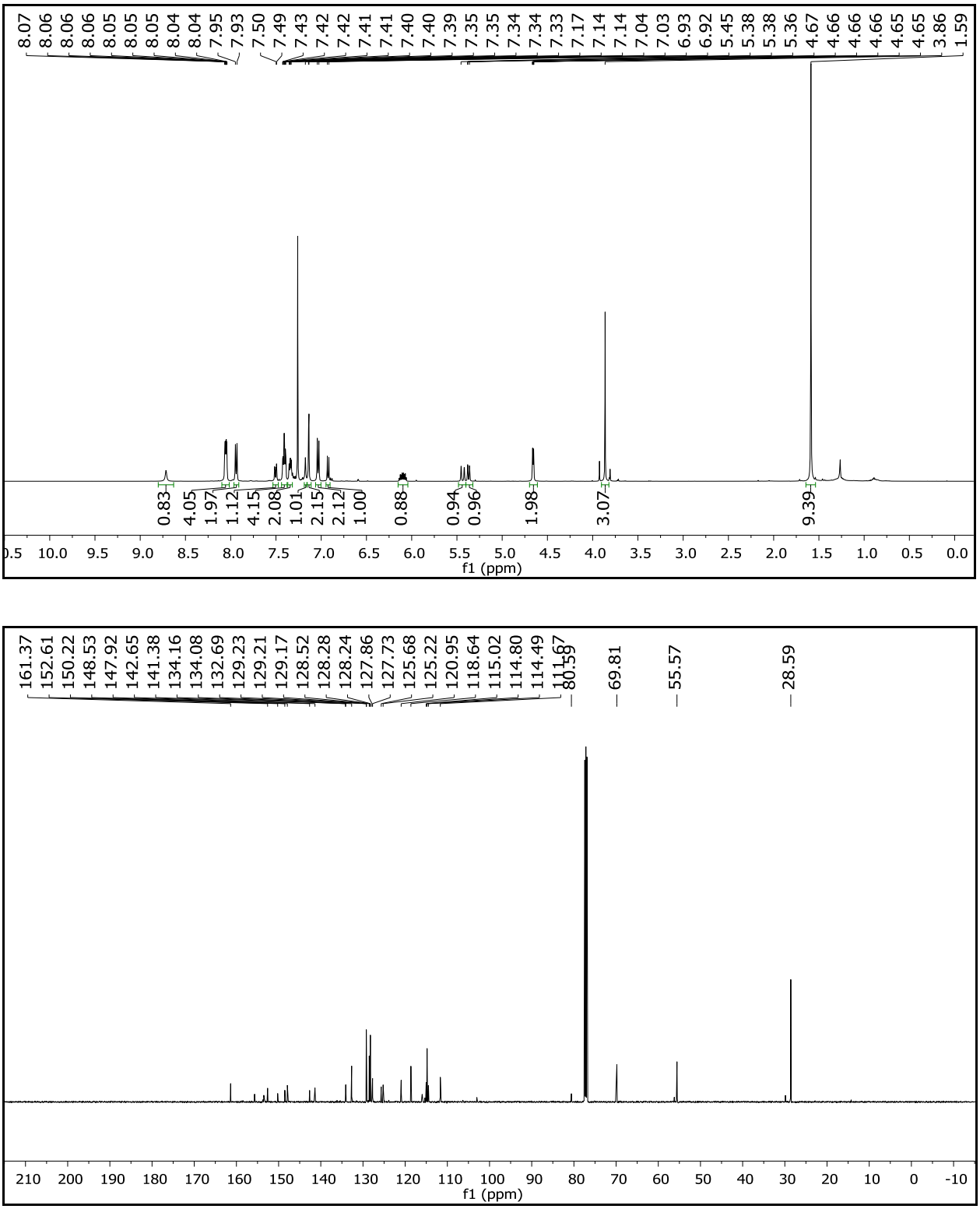


Fig. S47: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **30.**

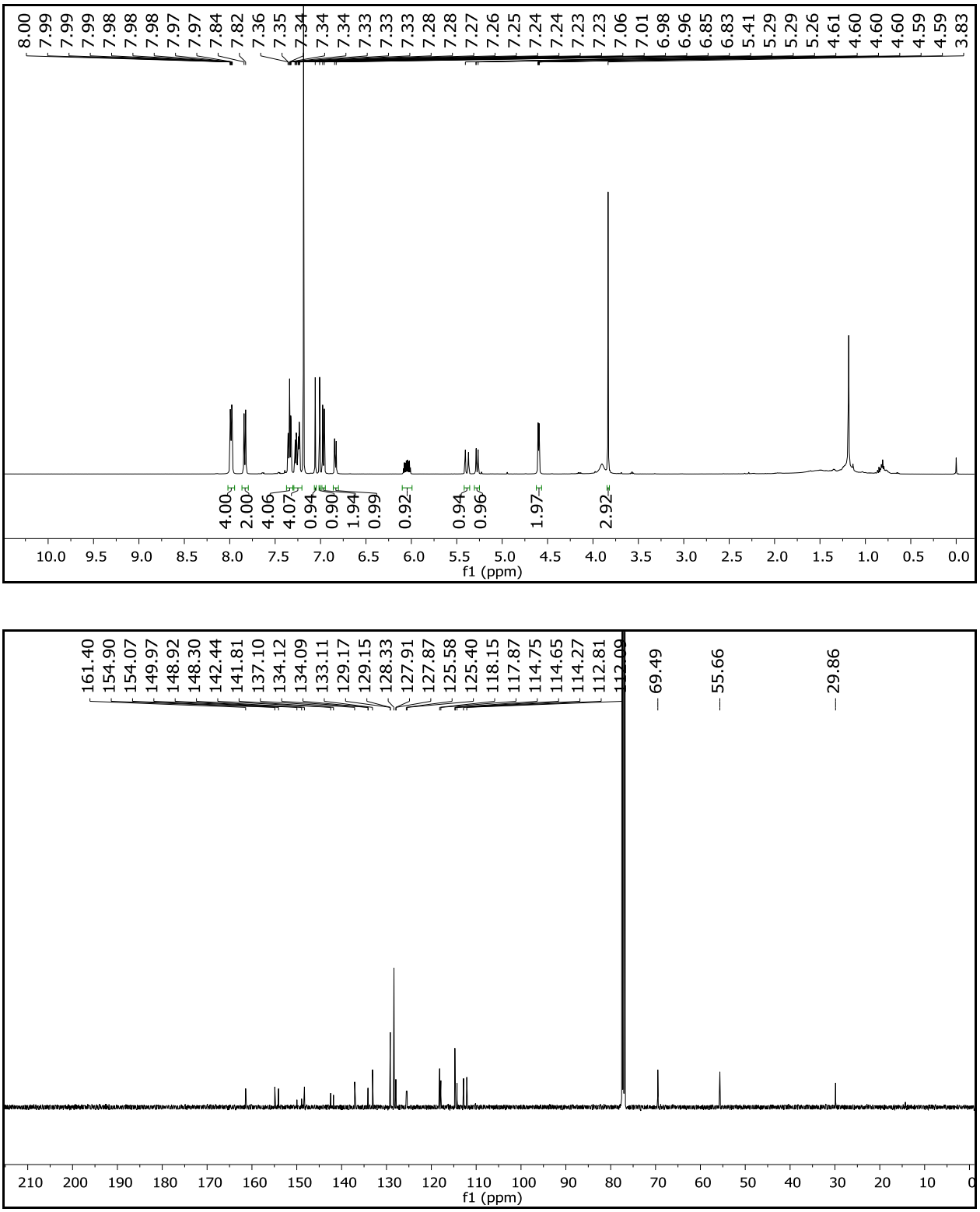


Fig. S48: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **31.**

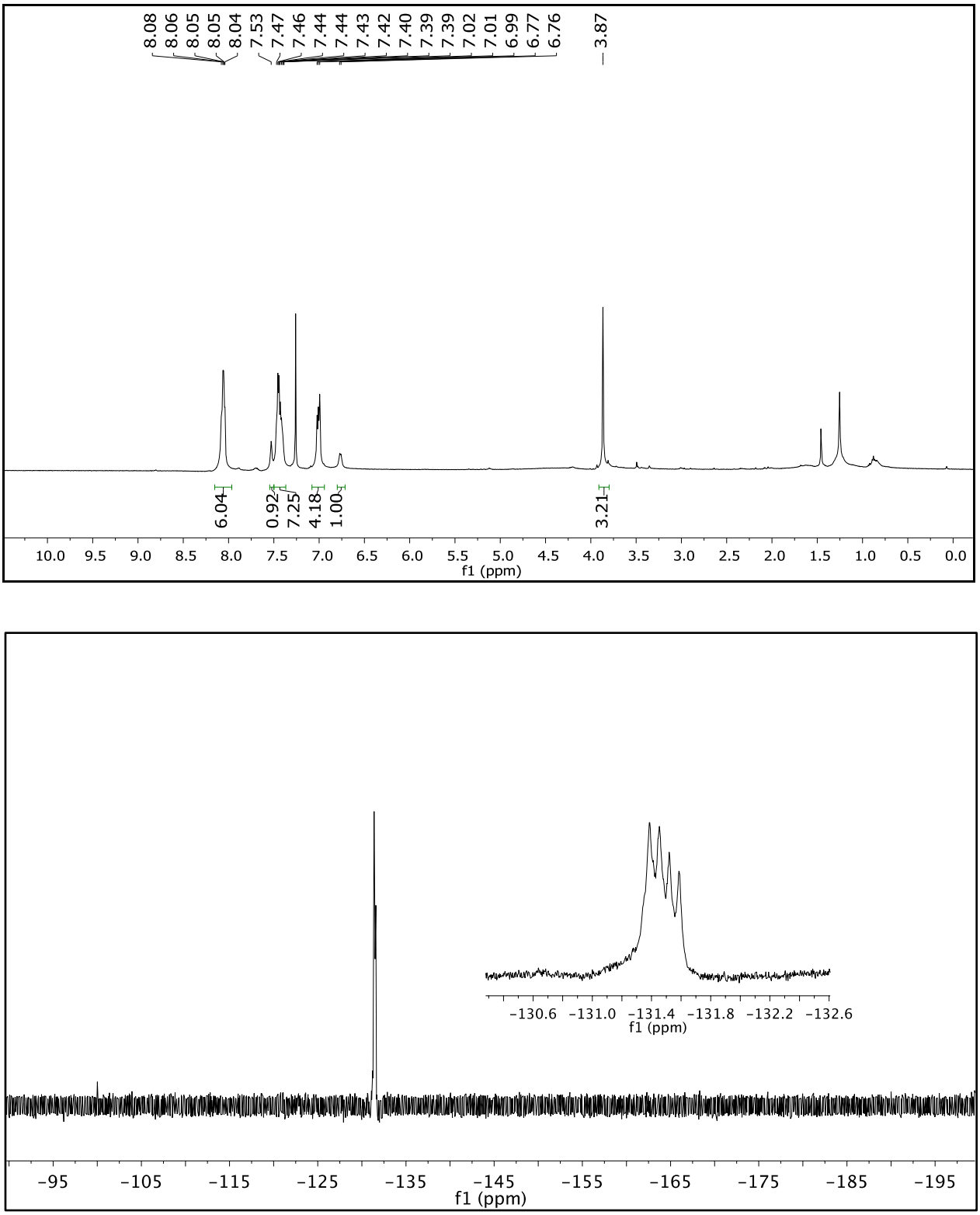


Fig. S49: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{19}F NMR (471 MHz, $CDCl_3$) NMR spectra of **APNO-3.**

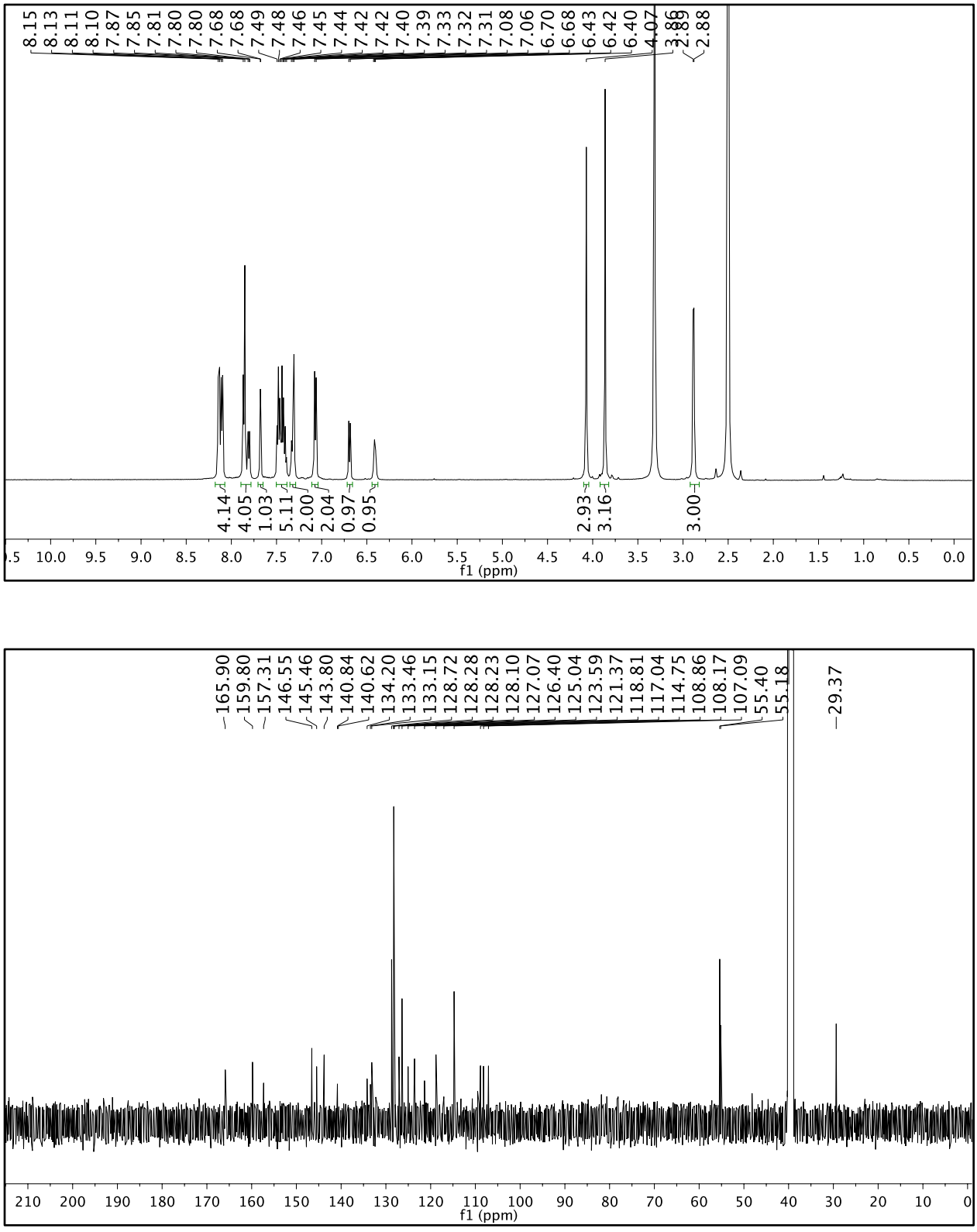


Fig. S50: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) NMR spectra of **32.**

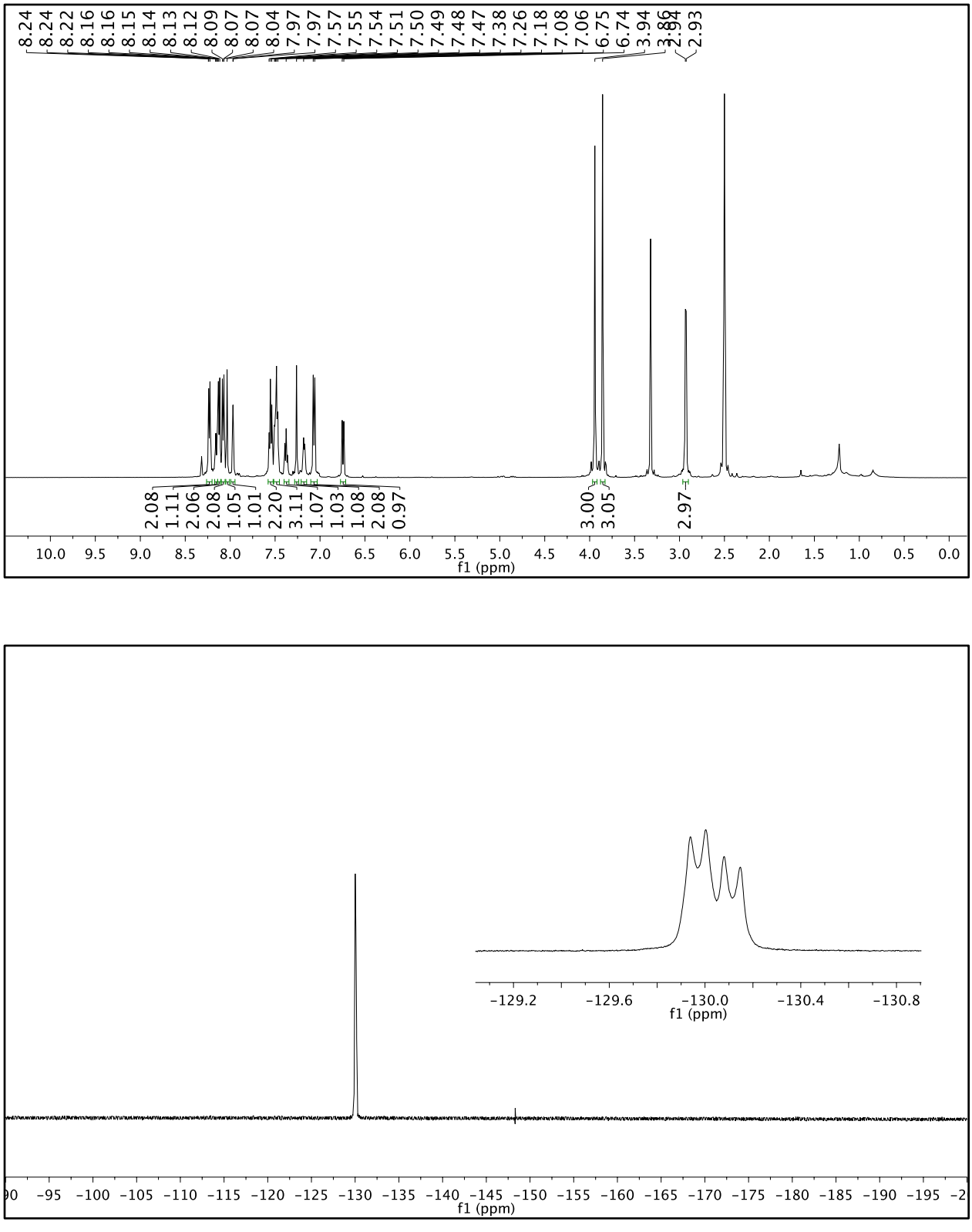


Fig. S51: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{19}F NMR (471 MHz, DMSO-d_6) NMR spectra of **APNO-4**.

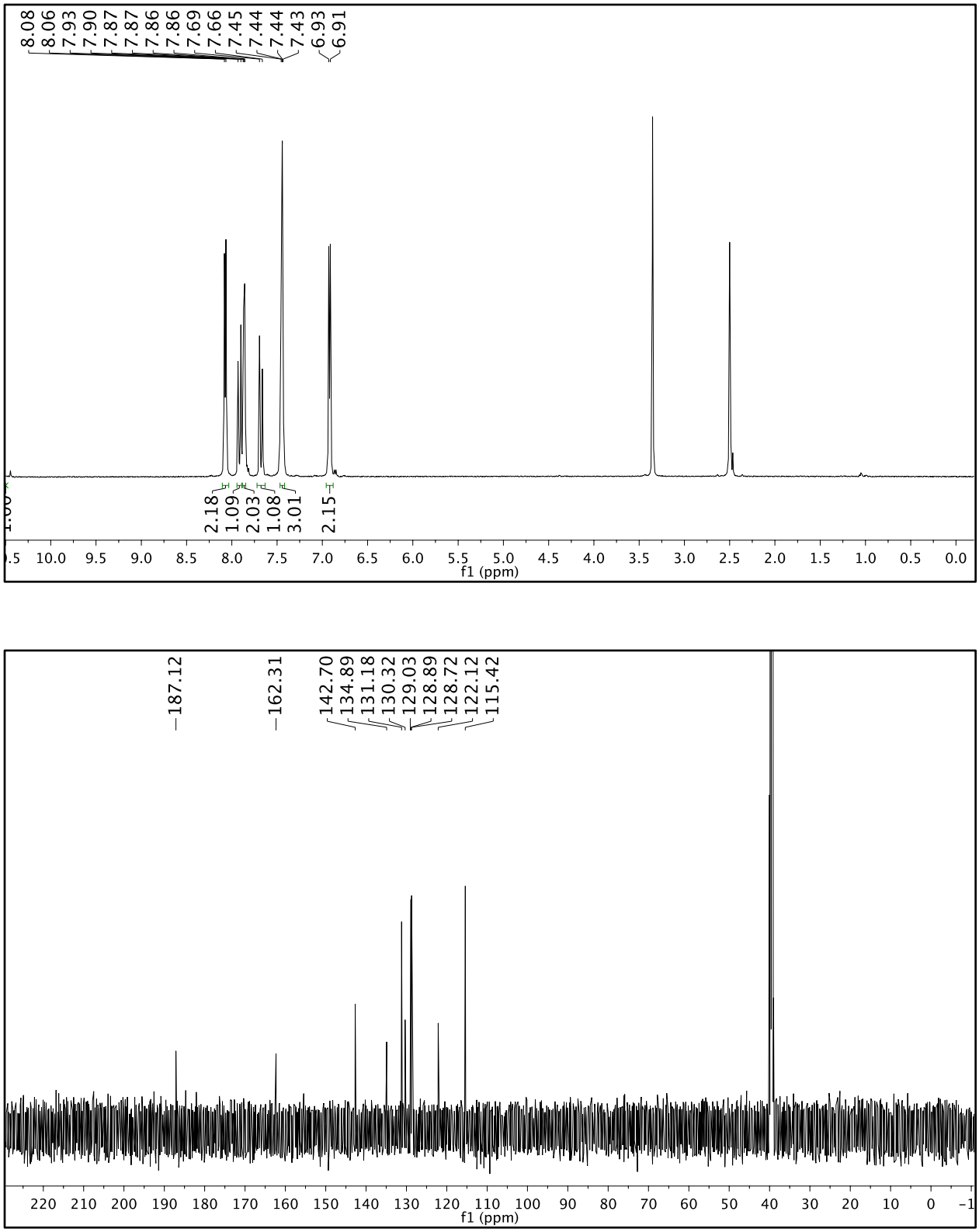


Fig. S52: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) NMR spectra of **33**.

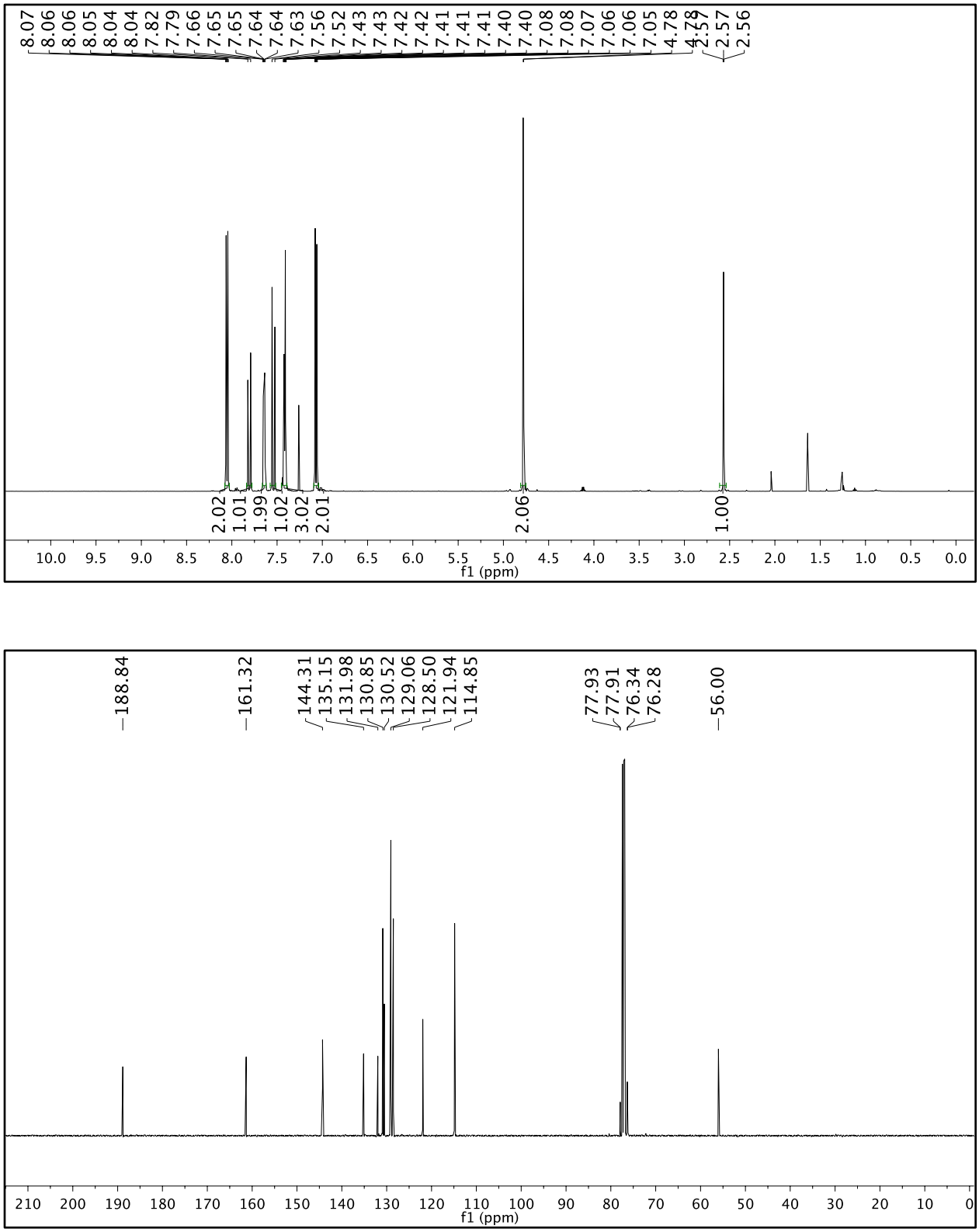


Fig. S53: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) NMR spectra of **34**.

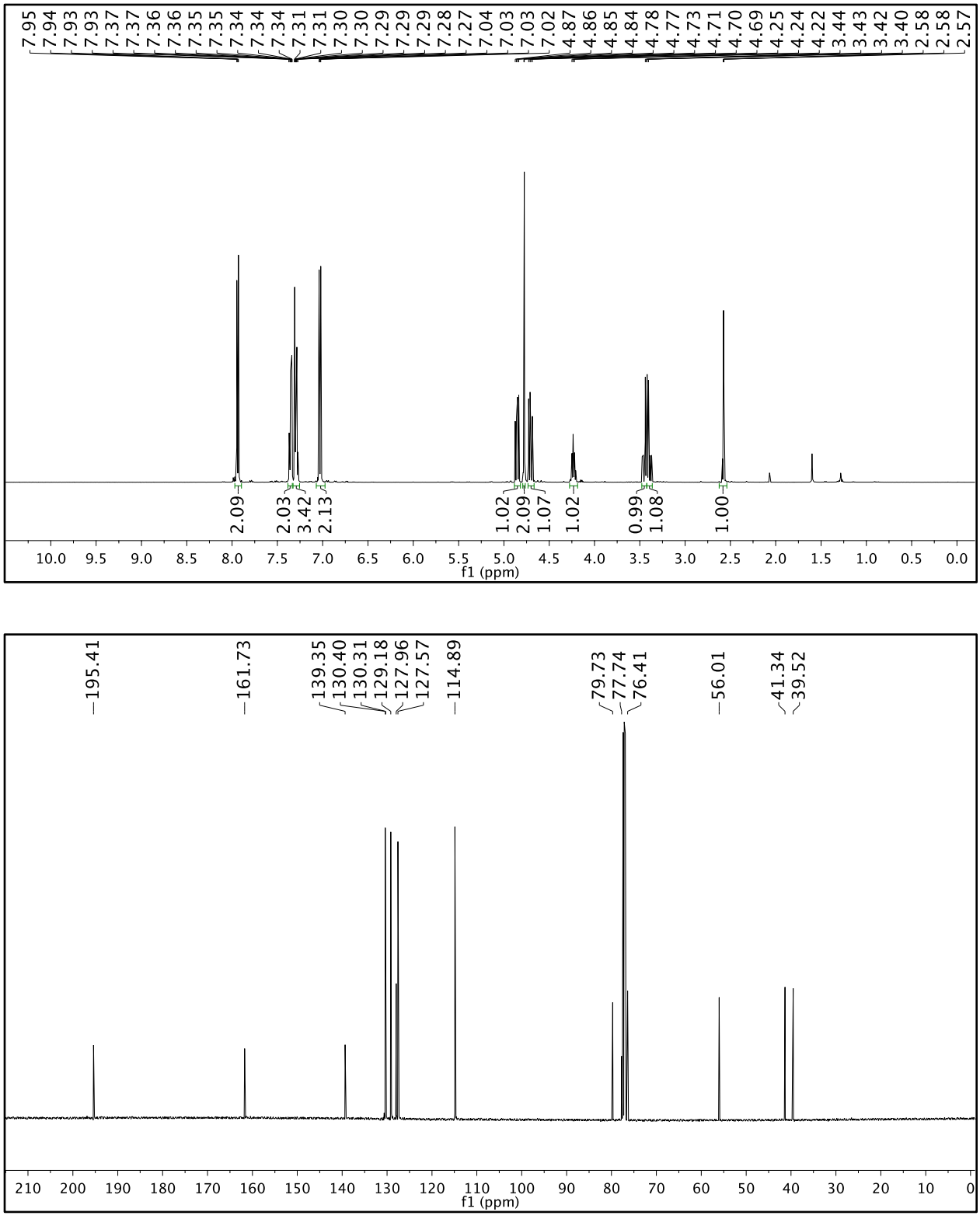


Fig. S54: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **35**.

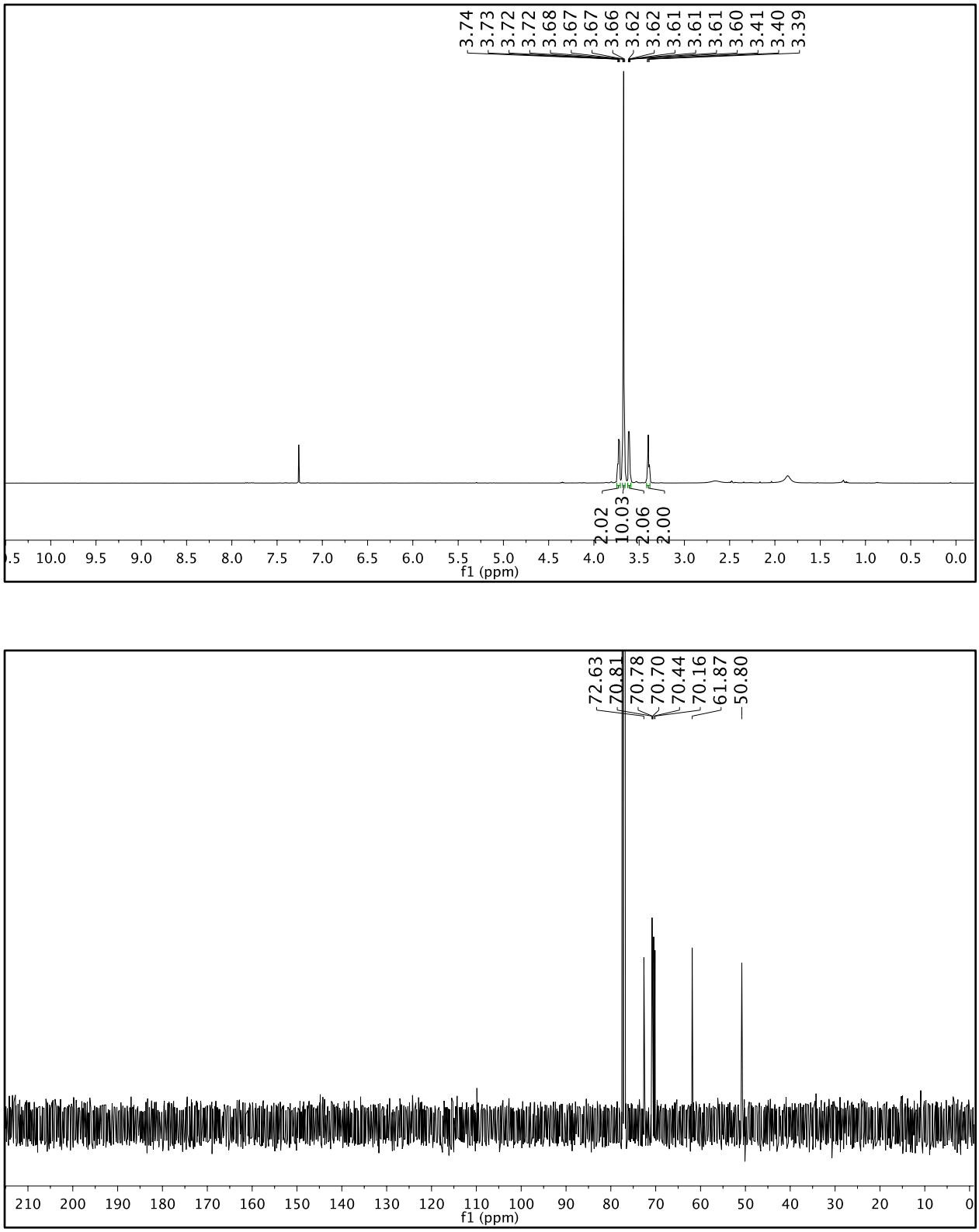
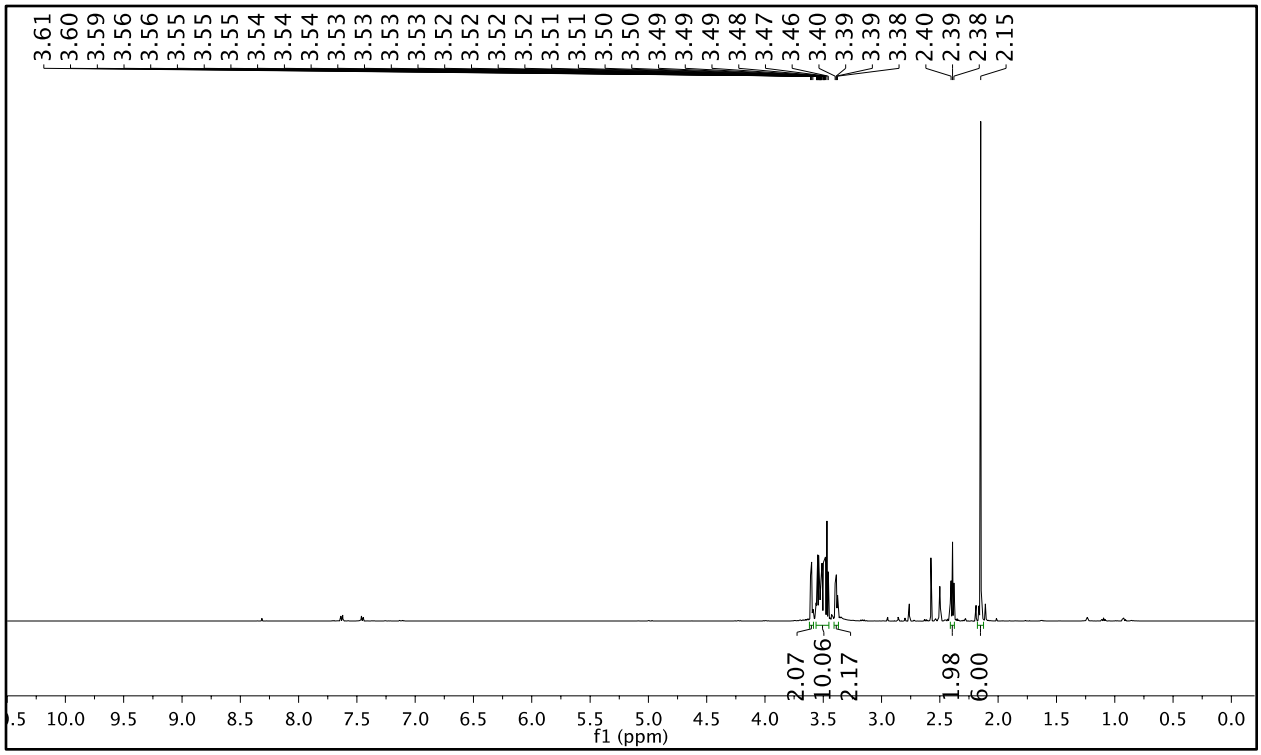


Fig. S55: ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) NMR spectra of **37**.



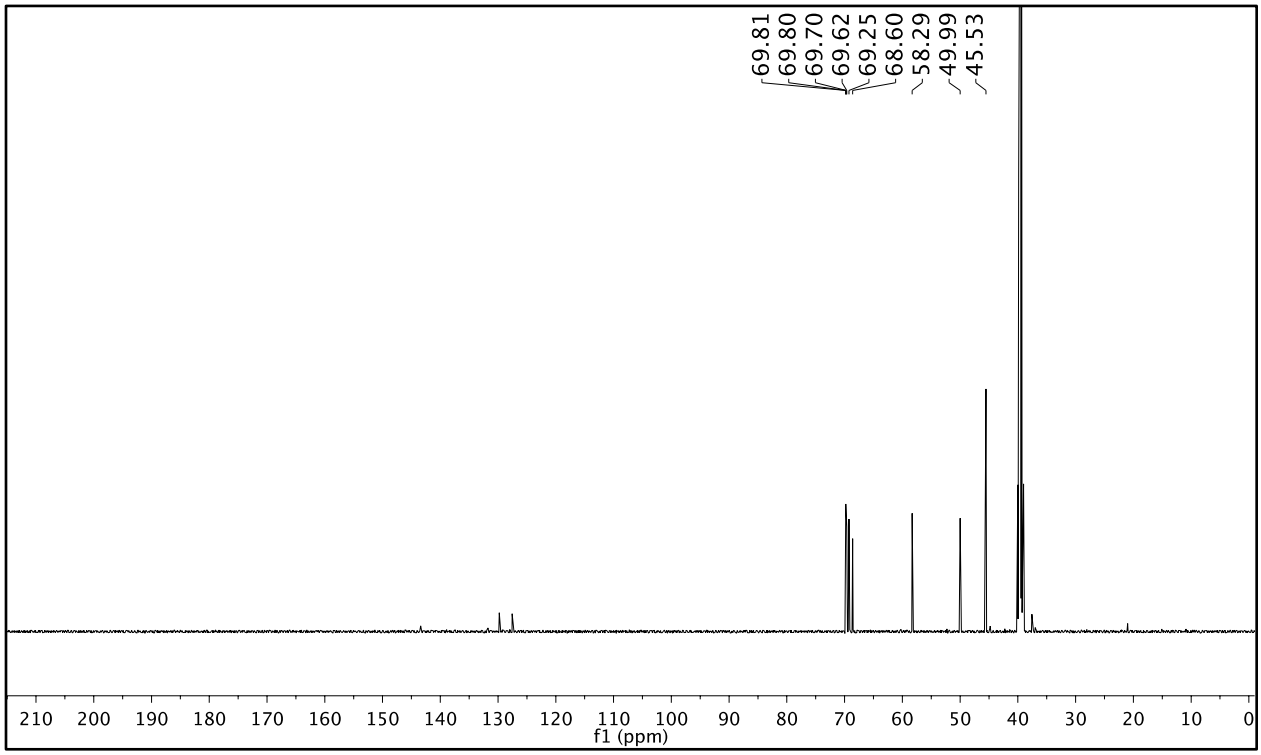
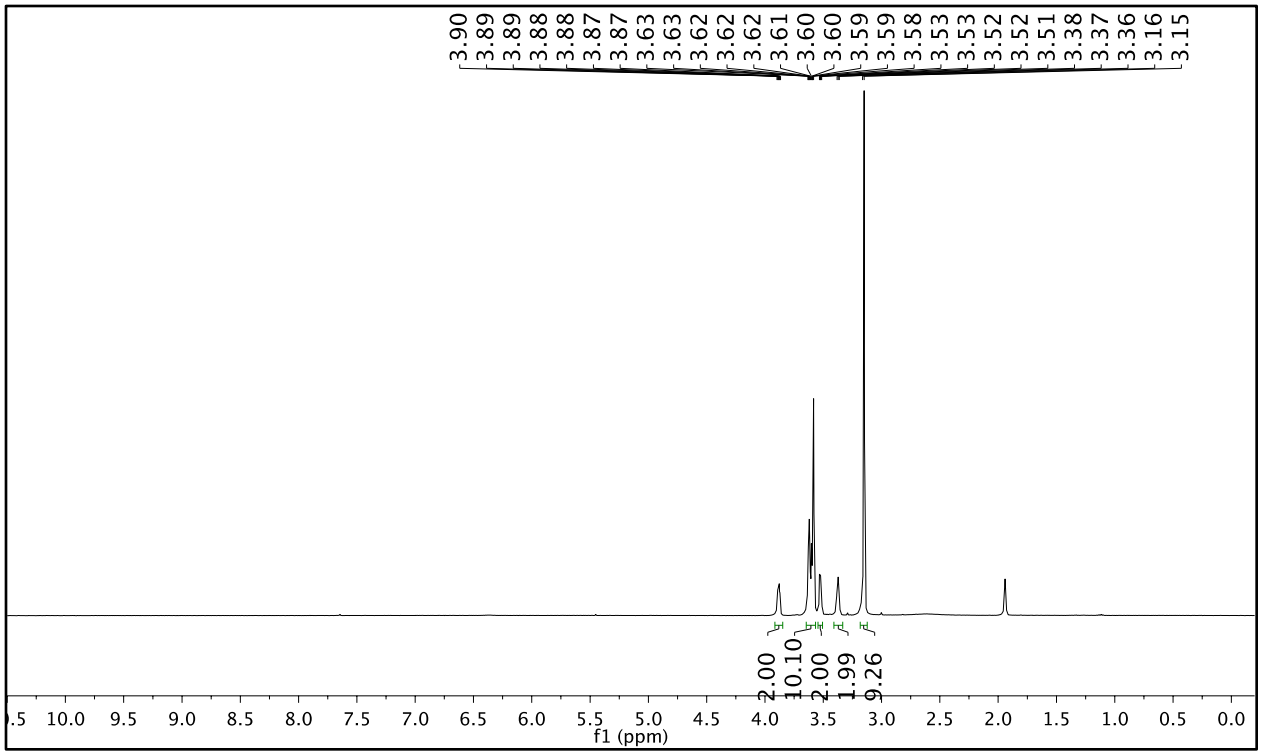


Fig. S56: ^{1}H NMR (500 MHz, DMSO-d_6) and ^{13}C NMR (125 MHz, DMSO-d_6) NMR spectra of **38**.



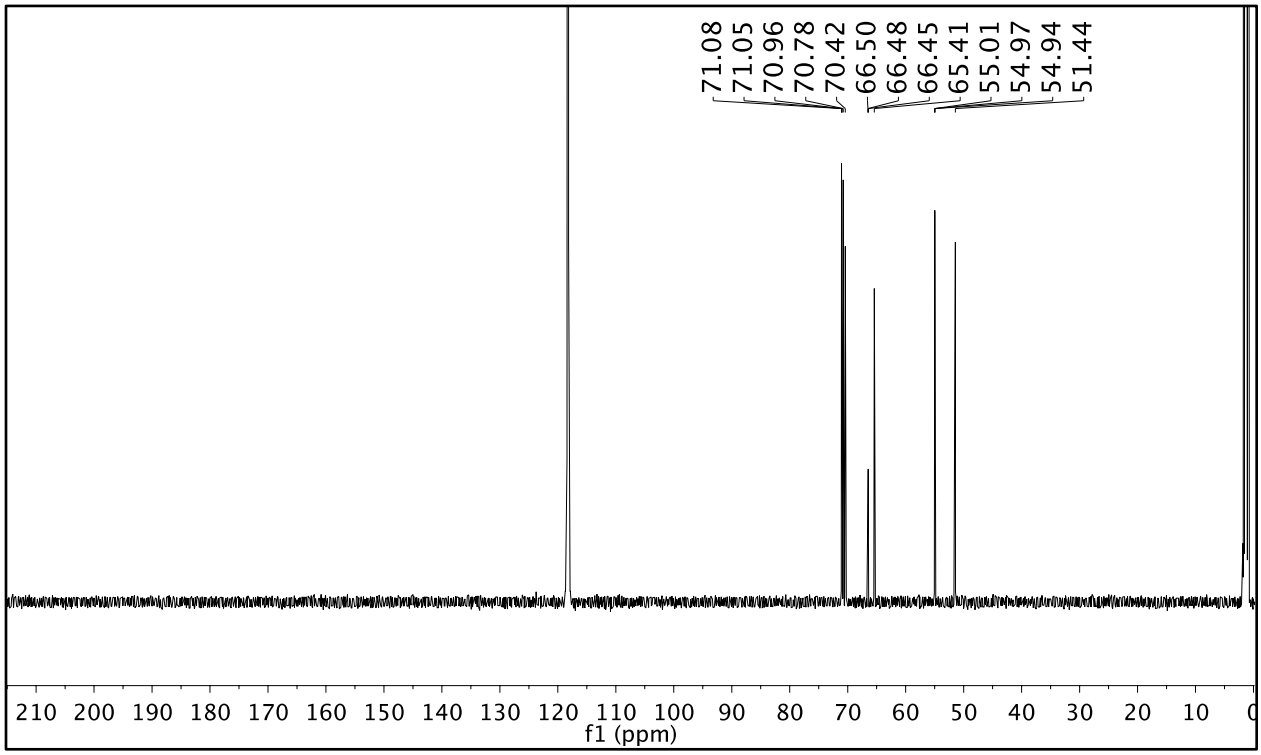


Fig. S57: ^{1}H NMR (500 MHz, CD_3CN) and ^{13}C NMR (125 MHz, CD_3CN) NMR spectra of **39**.

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