Supplementary Information for

A New Class of Ratiometric Small Molecule Intracellular pH Sensors for Raman Microscopy

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Table of Contents

1. Supplementary Figures and Tables

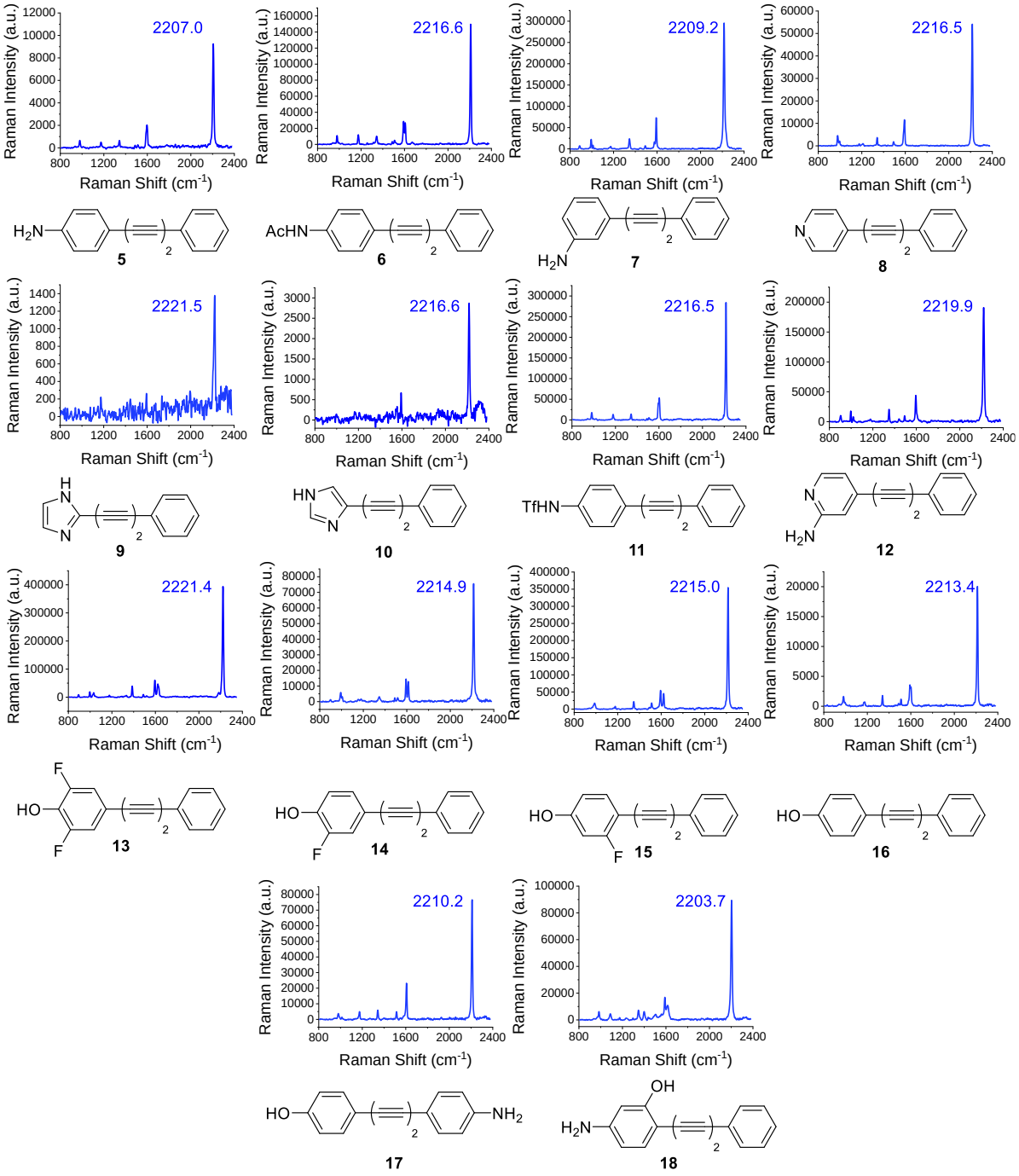


Figure S1: Raman spectra of compounds **5–18** as solids showing the alkyne stretching frequencies (532 nm, 1%, 0.2 mW, center 1600 cm^{-1}, 1 s, 10 accumulations).

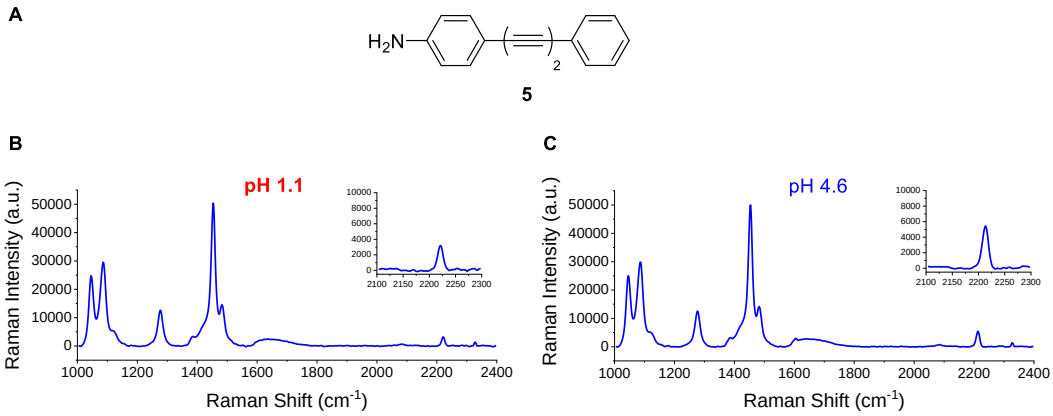


Figure S2: Example Raman spectra of **5** (100 µM in diyne analysis buffers, I = 0.2) (532 nm, 1 s, 20 accumulations). **A:** Structure of **5**; **B:** Spectrum at pH 1.1, showing an expansion of the alkyne region; **C:** Spectrum at pH 4.6, showing an expansion of the alkyne region.

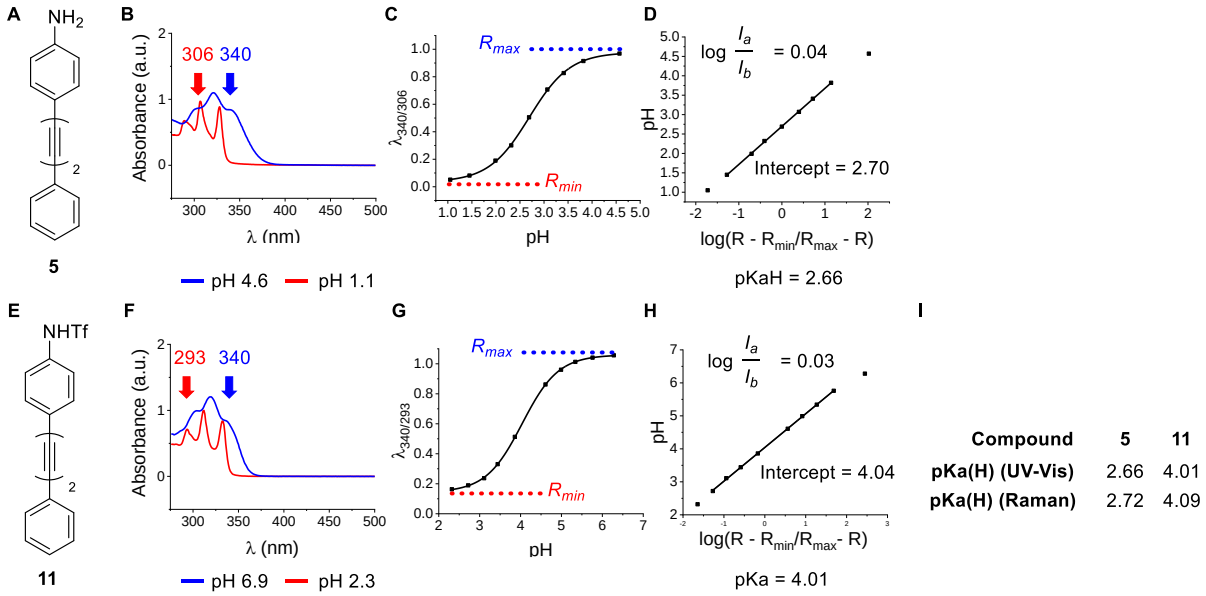


Figure S3: Determination of the apparent pKa(H) values of compounds **5** and **11** by UV-visible spectroscopy (25 µM in diyne analysis buffers). **A:** Structure of **5**; **B:** Sample UV-Vis spectra of **5** (25µM) at pH 1.1 (red), and 4.6 (blue); **C:** Plot of 340/306 nm absorbance ratio (*R*) as a function of pH for **5**. Data was fitted to a Boltzmann function in OriginPro2018 and values for R_{max} and R_{min} were derived from the asymptotes; **D**: Plot of $\log((R–R_{min})/(R_{max}–R))$ as a function of pH for **5**. pKaH was derived from the y intercept minus $\log(I_a/I_b)$; **E:** Structure of **11**; **F:** Sample UV-Vis spectra of **5** (25µM) at pH 2.3 (red), and 6.9 (blue); **G:** Plot of 340/293 nm absorbance ratio (*R*) as a function of pH for **11**. Data was fitted to a Boltzmann function in OriginPro2018 and values for R_{max} and R_{min} were derived from the asymptotes; **H:** Plot of $\log((R–R_{min})/(R_{max}–R))$ as a function of pH for **11**. pKa was derived from the y intercept minus $\log(I_a/I_b)$; **I:** Comparison of apparent pKa(H) values of **5** and **6** determined by Raman and UV-Visible spectroscopy.

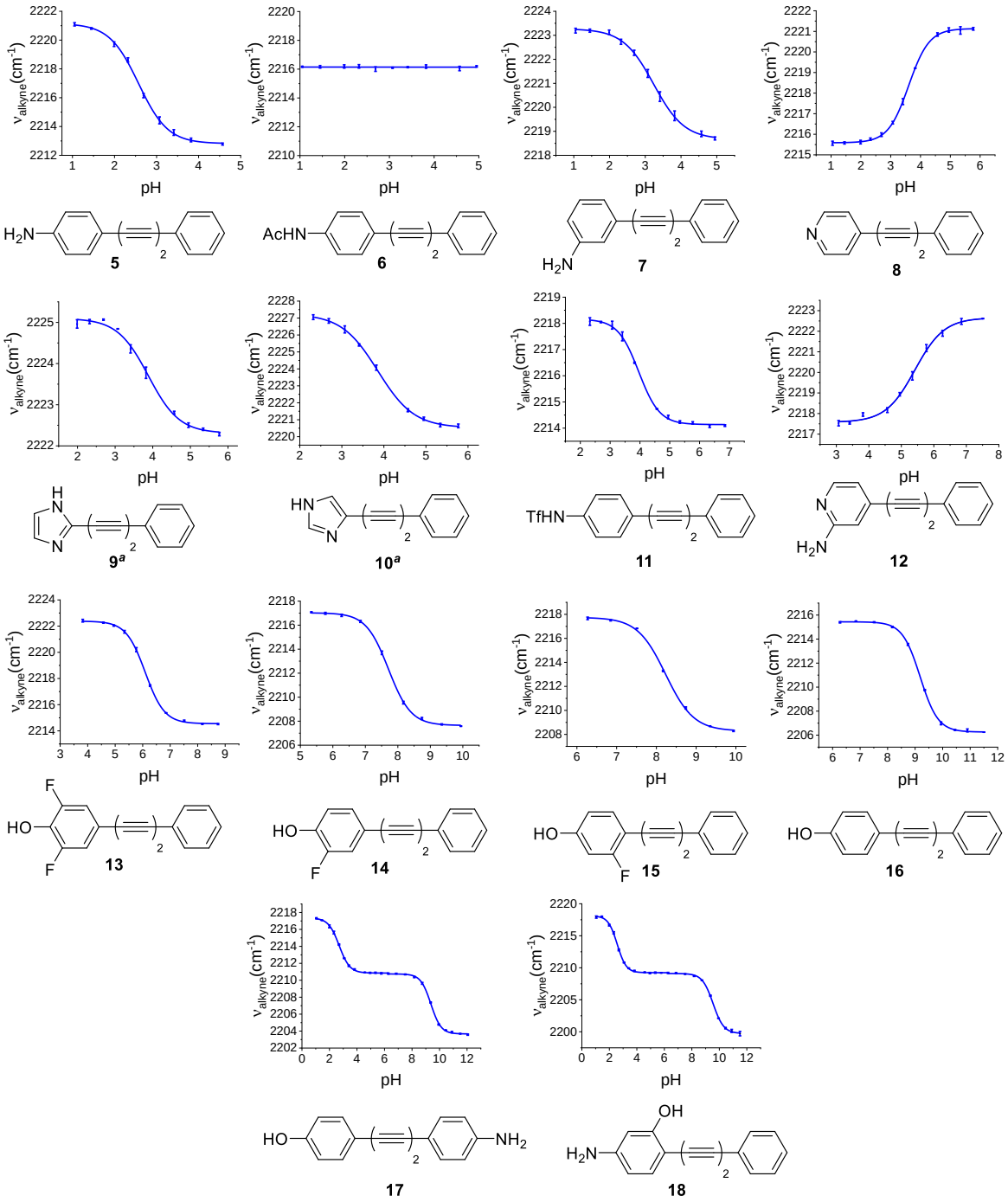


Figure S4: Plots of apparent ν_{alkyne} as a function of pH for compounds **5–18** in solution (100 µM, diyne analysis buffers, I = 0.2, 20 °C). Mean ν_{alkyne} values (n = 3, ± standard deviation, 532 nm, 1 s, 20 accumulations) were plotted as a function of pH. Curves were fitted to a Boltzmann function in OriginPro 2018 and ν_{max}, ν_{min} and $\Delta\nu_{alkyne}$ values were derived from the asymptotes. Notes: [a]Experiments were carried out at a compound concentration of 200 µM.

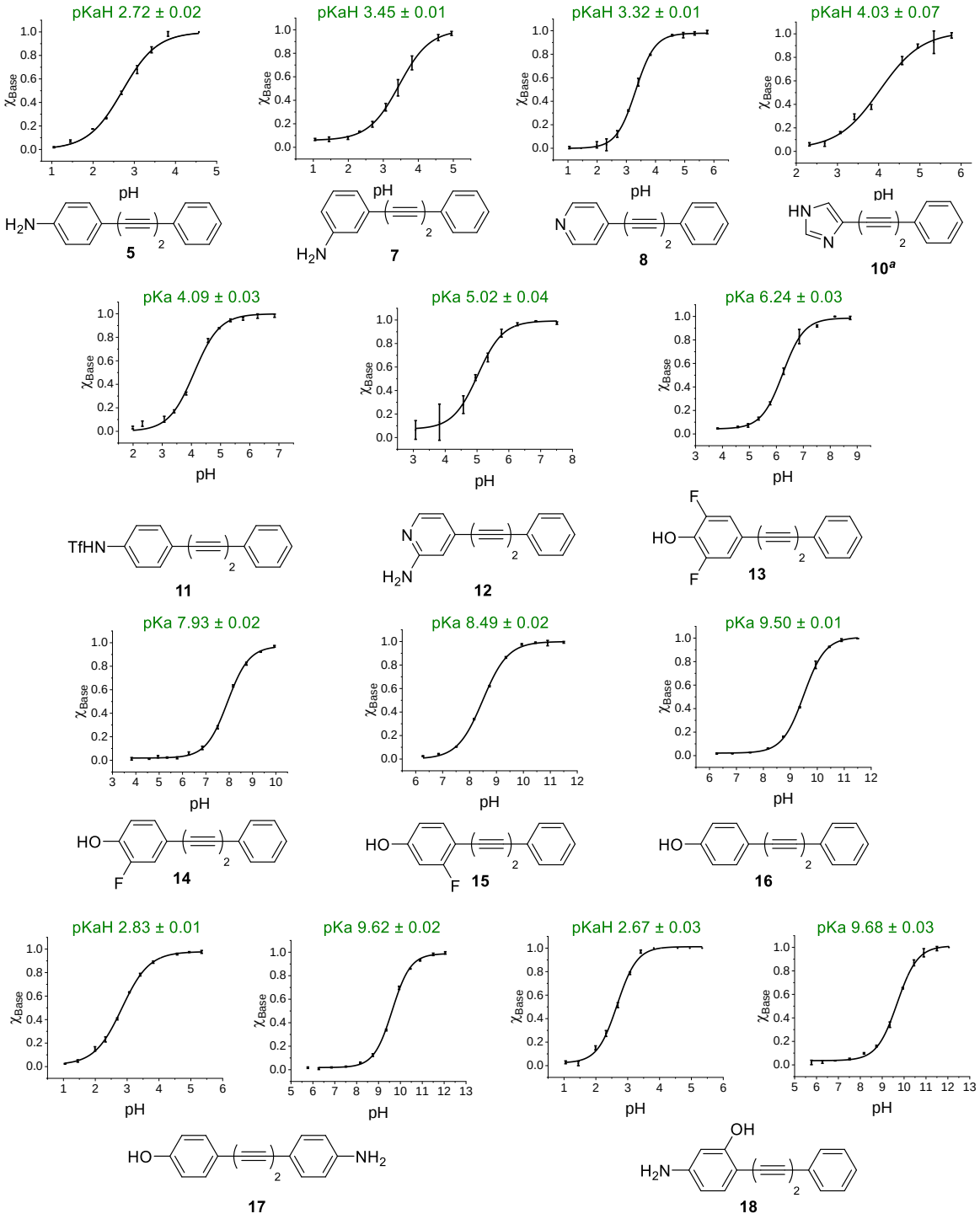


Figure S5: Plots of mole fraction conjugate base (χ_{Base}) as a function of pH for compounds **5–18** in solution (100 µM, diyne analysis buffers I = 0.2, 20 °C). χ_{Base} values were calculated using Equation 1 *via* the method described in the experimental section. Mean χ_{Base} values (n = 3, ± standard deviation) were plotted as a function of pH. Curves were fitted to a Boltzmann function and pKa(H) values were extracted from the resulting inflection points. Notes: [a]Experiments were carried out at a compound concentration of 200 µM.

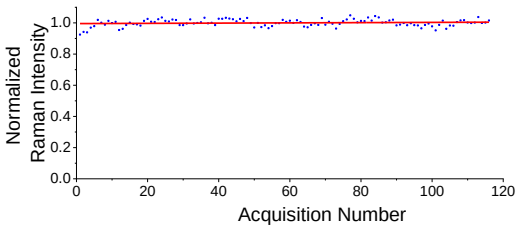


Figure S6: Photostability test of compound **13**. 120 continuous spectra (532 nm, 100 % laser power (ca. 20 mW) 0.5 s, 20x/NA 0.40 NPlanEPI objective, center 1800 cm^{-1}) were acquired from solution of **13** (5 mM in DMSO). Alkyne peak areas were integrated for each spectrum using OriginPro 2018 and an average value was calculated. Alkyne peak integration values were divided by the average value, and the resulting normalized alkyne intensities were plotted as a function of acquisition number. A linear line of best fit was applied in OriginPro 2018.

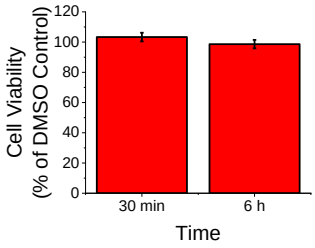


Figure S7: Single concentration cell toxicity test of compound **13**. PC3 cells were treated with either DMSO (2.5 µL mL^{-1}, control) or phenol **13** (25 µM) (n = 3 plates per condition). Treatments were carried out for 30 min and 6 h. Viable cell-count in each plate was established by Trypan blue exclusion. Data presented are average values as a percentage of DMSO control (n = 3, ± standard deviation). Treatment of PC3 cells with **13** caused no significant change in cell viability compared to the DMSO control.

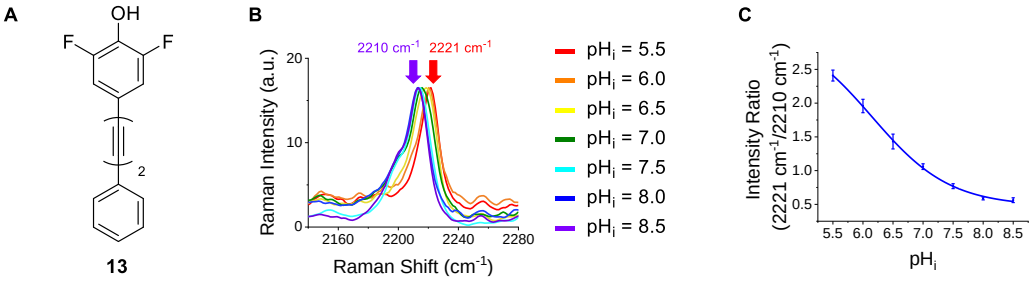


Figure S8: Calibration of **13** in PC3 cells (25 µM, 30 min) using the method of Thomas.[1] **A:** Structure of compound **13**; **B:** Overlay of average spectra derived from maps of PC3 cells (5 µm step size in x and y) fixed to the indicated pH_i values. Spectra have been normalized to the maximum intensity between 2140–2280 cm^{-1} using OriginPro 2018; **C:** Plot of mean 2221/2210 cm^{-1} (n = 5, ± standard deviation) as a function of pH_i,. Data points were fitted to a Boltzmann function using OriginPro 2018.

Raman band	**2851 cm^{-1}**	**2880 cm^{-1}**	**2933 cm^{-1}**	**2210 cm^{-1}**	**2221 cm^{-1}**
	CH_2 stretches (Endogenous lipid)	CH_2 and CH stretches (Endogenous lipid and protein)	CH_3 stretches (Endogenous Protein)	C≡C stretch (Deprotonated **13**)	C≡C stretch (Neutral **13**)
Ratio	$\frac{2851\ cm^{-1}}{2851\ cm^{-1}+2933\ cm^{-1}}$	$\frac{2880\ cm^{-1}}{2880\ cm^{-1}+2933\ cm^{-1}}$	$\frac{2210\ cm^{-1}}{2210\ cm^{-1}+2933\ cm^{-1}}$	$\frac{2221\ cm^{-1}}{2221\ cm^{-1}+2933\ cm^{-1}}$	$\frac{2210\ cm^{-1}}{2221\ cm^{-1}}$
	Endogenous lipid to protein ratio	Endogenous lipid to protein ratio	Alkyne signal (normalized to endogenous protein)	Alkyne signal (normalized to endogenous protein)	Deprotonated to neutral **13** ratio

Table S1: Assignments for Raman bands and ratios relevant for the ratiometric imaging of PC3 cells treated with **13**.[2–4]

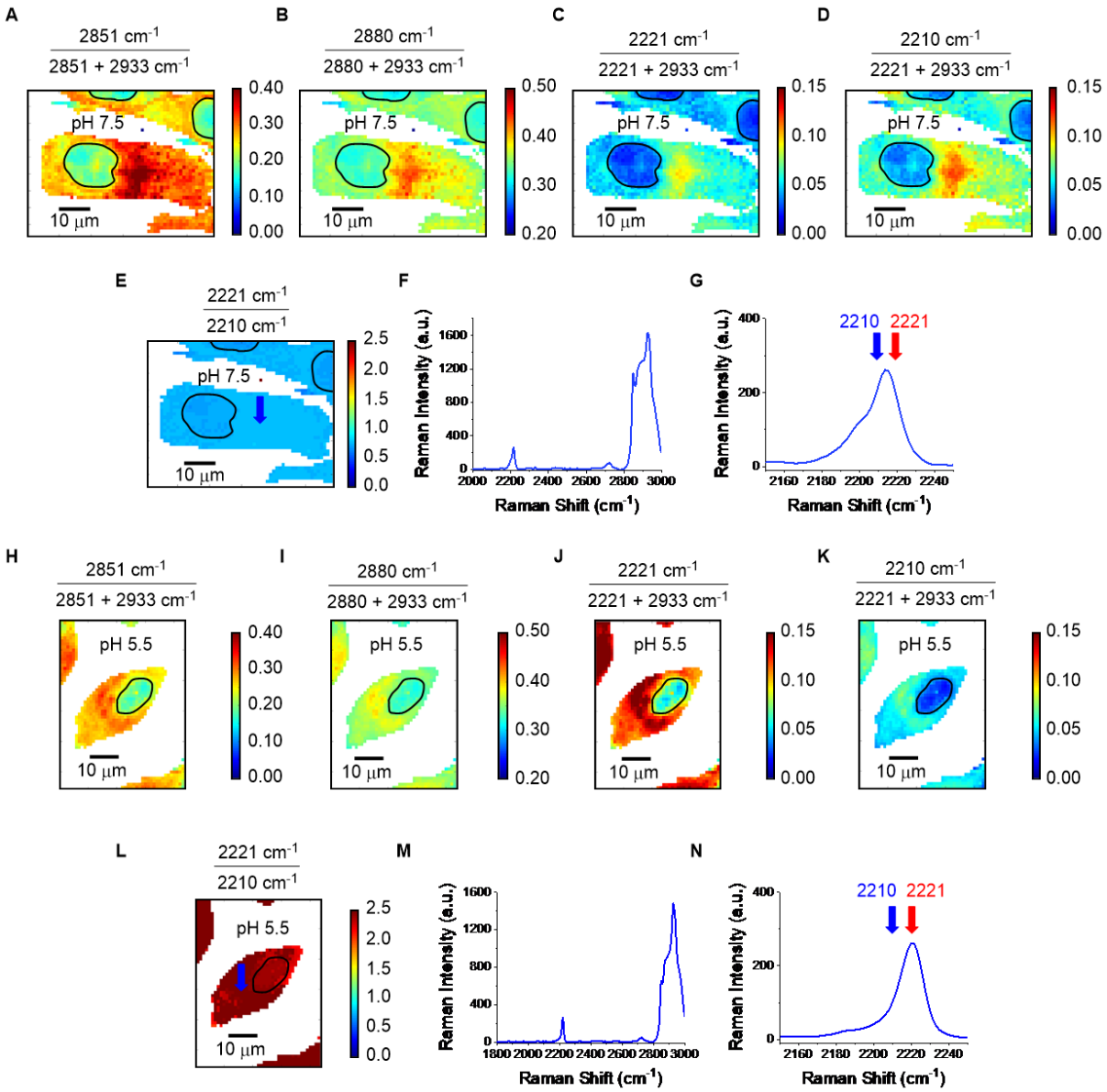


Figure S9: Raman mapping data (1 μm step size in x and y) from PC3 cells treated with **13** (25 μM, 30 min) and fixed to the pH_i values of 7.5 and 5.5 using the method of Thomas.[1] **A:** Assignments for Raman bands relevant to ratiometric imaging **A–E:** False colour images representing the indicated signal intensity ratios, derived from PC3 cells at pH_i 7.5; **F:** Sample spectrum from the cells in **A–E**, at the point indicated by the blue arrow; **G:** Expansion of the spectrum in **F**; **H–L** are false colour images representing the indicated signal intensity ratios, derived from PC3 cells at pH_i 5.5; **M:** Sample spectrum from the cells in **H–L**, at the point indicated by the blue arrow; **N:** Expansion of the spectrum in **M**. Lipid to protein ratio images (**A**, **B**, **H** and **I**) were used to identify the cell nuclei,[3] which are highlighted throughout using black bands. Alkyne intensity images (**C**, **D**, **J** and **K**) indicated that alkyne intensity was very low inside the cell nuclei, and these regions were considered below the intensity threshold cut-off for ratiometric analysis.

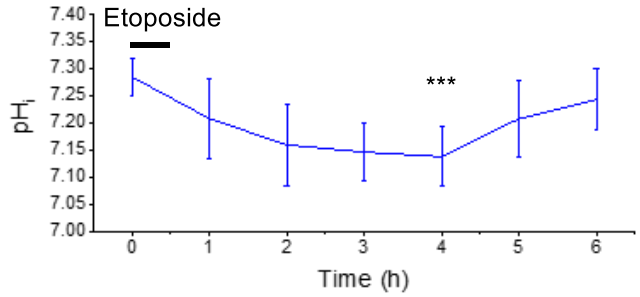


Figure S10: Repeat measurement of pH_i changes over time in PC3 cells treated with etoposide. 6 cell plates were treated with etoposide (80 μg mL^{-1}, 30 min) and incubated for varying additional times of 0.5, 1.5, 2.5, 3.5, 4.5 or 5.5 h, prior to analysis. Cells were treated with **13** (25 μM, 30 min) immediately before analysis. **A:** Plot of average PC3 cell pH_i as a function of time (n = 6 cells, ± standard deviation) (***p < 0.01, Student's t test). The 0 h time point represents no etoposide treatment. Values derive from the average 2221/2210 cm^{-1} ratio (n = 6 cells, 5 μm step size in x and y, ± standard deviation).

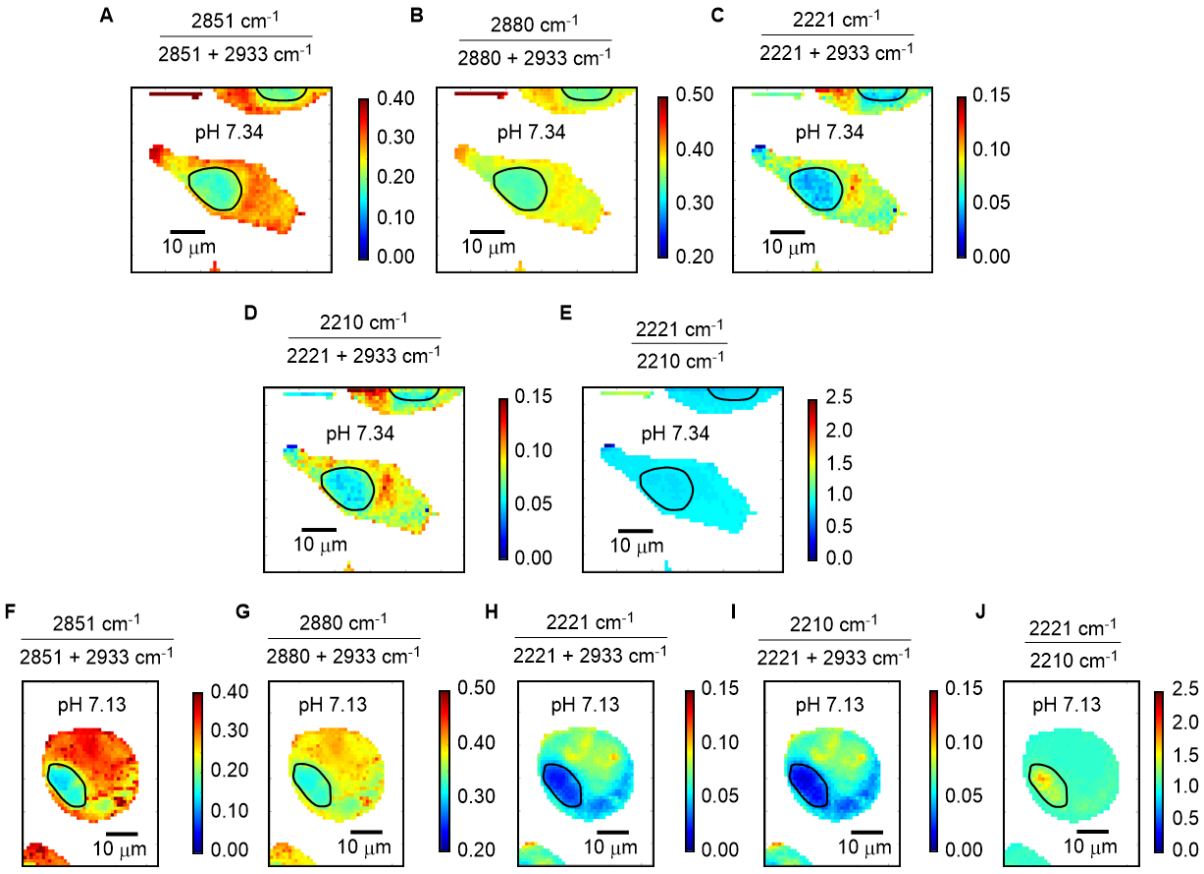


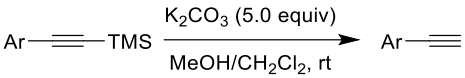
Figure S11: Raman mapping data (1 μm step size in x and y) from PC3 cells treated with **13** (25 μM, 30 min) before and after treatment with etoposide. **A–E:** False colour images representing the indicated signal intensity ratios, derived from PC3 cells with no etoposide treatment; **F–J:** False colour images representing the indicated signal intensity ratios, derived from PC3 cells after treatment with etoposide (80 μg mL^{-1}, 30 min) and a further 3.5 h incubation. Lipid to protein ratio images (**A**, **B**, **F** and **G**) were used to identify the cell nuclei,[3] which are highlighted throughout using black bands. Alkyne intensity images (**C**, **D**, **H** and **I**) indicated that alkyne intensity was very low inside the cell nuclei, and these regions were considered below the intensity threshold cut-off for ratiometric analysis.

2. Synthesis of pH Sensitive Diynes

2.1. General Information

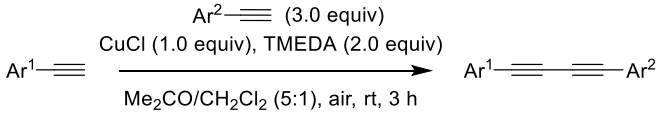
All reagents were obtained from commercial sources, including Sigma-Aldrich, Alfa Aesar and Fluorochem and used without purification unless otherwise stated. The anhydrous solvents tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), hexane and toluene were obtained from a PureSolv MD 5 Solvent Purification System by Innovative Technology Inc., and handled under inert atmosphere without further purification. Other solvents were acquired from commercial sources and used without further purification unless otherwise stated. Flash chromatography was carried out using Fischer Scientific chromatography grade silica 60 Å particle size 35–70 micron. Analytical thin layer chromatography was carried out using aluminium-backed plates coated with Machery-Nagel pre-coated TLC sheets, coated in 0.20 mm silica gel 60 with UV_{254} fluorescent indicator. Sheets were visualized under UV light (at 254 nm) or stained using *p*-anisaldehyde. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer operating at 400 MHz (^1H) and 101 MHz (^{13}C), or Bruker Avance 500 spectrometer, operating at 500 MHz (^1H) and 125 MHz (^{13}C). Chemical shifts were reported in parts per million (ppm) in the scale relative to $CDCl_3$, 7.26 ppm for ^1H NMR and 77.16 for ^{13}C NMR; $(CD_3)_2SO$ (dimethylsulfoxide), 2.50 ppm for ^1H NMR and 39.52 for ^{13}C NMR; $(CD_3)_2CO$, 2.05 for ^1H NMR and 29.84 for ^{13}C NMR. Multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublets of doublets; td, triplet of doublets; app.t, apparent triplet; app.td, apparent triplet of doublets; app.p, apparent pentet; hept, heptet; dhept, doublet of heptets; m, multiplet; br, broad. Coupling constants are measured in Hertz (Hz). Low-resolution mass spectra (LRMS) were recorded on an Agilent 6130 single quadrupole with APCI/ESI dual source, on a ThermoQuest Finnigan LCQ DUO electrospray, or on an Agilent 7890A GC system equipped with a 30 m DB5MS column connected to a 5975C inert XL CI MSD with Triple-Axis Detector and were determined using atmospheric pressure chemical ionization (APCI) unless otherwise stated. ESI refers to electrospray ionization, CI refers to chemical ionization (methane) and EI refers to electron ionization. High-resolution mass spectra were obtained courtesy of the EPSRC Mass Spectrometry Service at University of Wales, Swansea, U.K. or the Mass Spectrometry Laboratory, University Of Manchester, Manchester, U.K., using the ionization methods specified. Melting points were obtained on a Stuart SMP11 device. Infrared spectra were recorded in the range 4000–600 cm^{-1} on a Shimadzu IRAffinity-1 equipped with an ATR accessory. *In vacuo* refers to evaporation under reduced pressure using a rotary evaporator connected to a diaphragm pump, followed by the removal of trace volatiles using a high vacuum (oil) pump.

2.2. General Procedure 1[5]



In a round bottomed flask, silyl protected alkyne (1 equiv) was dissolved in methanol/dichloromethane ($MeOH/CH_2Cl_2$, 1:1, 0.1 M). Potassium carbonate (K_2CO_3, 5 equiv per protected alkyne) was then added and the reaction was stirred at rt, for 1–3 h. The reaction mixture was partitioned with brine/water (1:1, *ca*. 50 mL) and extracted with EtOAc (*ca*. 3–15 mL). The combined organics were washed with brine (*ca*. 10 mL), dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude deprotected alkyne product.

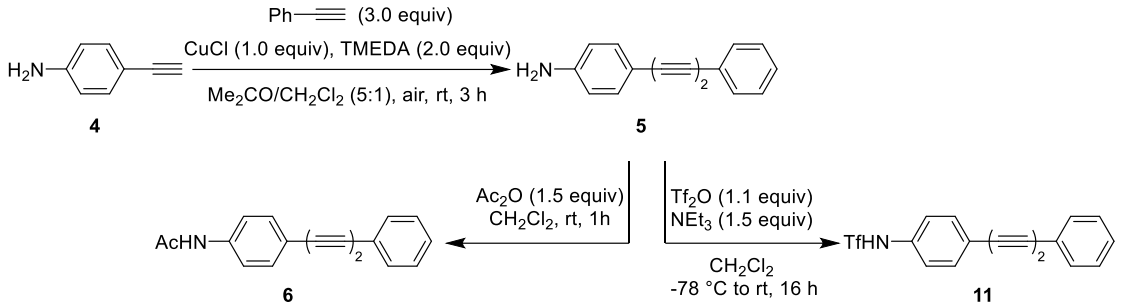
2.3. General Procedure 2[5]



To a stirred suspension of CuCl (1 equiv) in acetone (Me_2CO) (0.1 M) in a round bottomed flask was added tetramethylethylenediamine (TMEDA, 2 equiv), and the resulting blue solution was purged by bubbling with air for 15 min. A mixture of 2 alkyne coupling partners (1 equiv, 3 equiv), dissolved in CH_2Cl_2 (0.5 M), was added to the copper solution, and the reaction was stirred at room temperature for 3 h. The reaction mixture was partitioned with saturated NH_4Cl solution (*ca*. 30 mL) and extracted with EtOAc (*ca*. 3 × 15 mL). The combined organics were washed with brine (*ca*. 10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The resulting residue was purified by flash chromatography using an appropriate eluent to afford the desired product.

2.4. Experimental Procedures

*Synthesis of **5**, **6** and **11***



According to General Procedure 2: 4-Ethynylaniline **4** (117 mg, 1.00 mmol), phenylacetylene (330 µL, 3.00 mmol), CuCl (99 mg, 1.00 mmol) and TMEDA (300 µL, 2.00 mmol) in Me_2CO (10 mL) and CH_2Cl_2 (2 mL) were stirred at rt for 3 h. Purification by flash chromatography (20% EtOAc/petroleum ether 40–60) afforded the desired product **5**[6] as a yellow solid (147 mg, 0.68 mmol, 68%).

M.P: 120–122 °C; **FTIR (ATR, cm^{-1}):** 3474, 3381, 3208, 3034, 2207, 2141, 1618, 1597, 1512, 1487, 1294; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.51 (d, *J* = 6.4 Hz, 2H), 7.38–7.29 (m, 5H), 6.60 (d, *J* = 8.4 Hz, 2H), 3.89 (s, 2H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 147.7, 134.2, 132.5, 129.0, 128.5, 122.4, 114.8, 110.9, 82.9, 80.9, 74.6, 72.2; **LRMS (ES + APCI):** *m/z* calc. 217.1, found 218.1 $[M+H]^+$.

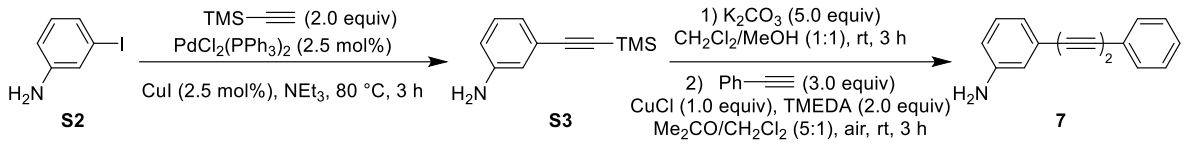
To a solution of aniline **5** (50 mg, 0.24 mmol) in anhydrous CH_2Cl_2 at rt was added Ac_2O (36 mg, 0.35 mmol) and the reaction was stirred for 1 h at rt. The reaction mixture was treated with saturated $NaHCO_3$ solution (20 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organics were dried over Na_2SO_4 and evaporated *in vacuo* to afford the desired product **6** as a pale-yellow solid (59 mg, 0.23 mmol, 95%).

M.P: 112–114 °C; **FTIR (ATR, cm^{-1}):** 3302.1, 3257.8, 3176.7, 3099.6, 3043.7, 2922.2, 2850.8, 2212.5, 2142.9, 1670.4, 1591.3, 1525.7, 1487.1, 1404.2, 1369.5, 1315.5, 1257.6; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.55–7.46 (m, 6H), 7.38–7.30 (m, 3H), 2.19 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.3, 138.9, 133.6, 132.6, 129.3, 128.6, 122.0, 119.5, 117.4, 81.7, 81.5, 74.1, 73.8, 24.9; **LRMS (ES + APCI):** *m/z* calc. 259.1, found 260.0 $[M+H]^+$; **HRMS (ESI):** $[M-H]^-$ calc. for $C_{18}H_{12}ON$ 258.0924; found 258.0924.

A stirred solution of aniline **5** (50 mg, 0.24 mmol) and triethylamine (NEt_3, 50 µL, 0.36 mmol) in anhydrous CH_2Cl_2 (1 mL) under Ar was cooled to -78 °C. Triflic anhydride (Tf_2O, 36 µL, 0.26 mmol) was added dropwise and the reaction was allowed to warm to room temperature gradually overnight. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1 M HCl (10 mL). The aqueous was extracted with further portions of CH_2Cl_2 (2 × 10 mL) and the combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (13% EtOAc/hexane + 1% acetic acid (AcOH)) afforded the desired product **11** as a beige solid (66 mg, 0.19 mmol, 79%).

M.P: 114–116 °C; **FTIR (ATR, cm^{-1}):** 3286.7, 3041.7, 2914.4, 2833.4, 2126.2, 2148.7, 1602.9, 1508.3, 1489.1, 1460.1, 1410.0, 1373.3, 1201.7, 1176.6, 1124.5; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.57–7.51 (m, 4H), 7.41–7.32 (m, 3H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.75 (s, 1H); **^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled):** δ -75.31; **^{13}C NMR (126 MHz, $CDCl_3$):** δ 134.4 (s), 134.0 (s), 132.7 (s), 129.6 (s), 128.7 (s), 122.9 (s), 121.7 (s), 121.3 (s), 119.8 (q, *J* = 322.6 Hz), 82.5 (s), 80.1 (s), 75.4 (s), 73.7 (s); **LRMS (ES + APCI):** *m/z* calc. 349.0, found 348.0 $[M-H]^-$; **HRMS (ESI):** $[M-H]^-$ calc. for $C_{17}H_9F_3NO_2S$ 348.0308; found 348.0312.

*Synthesis of **7***



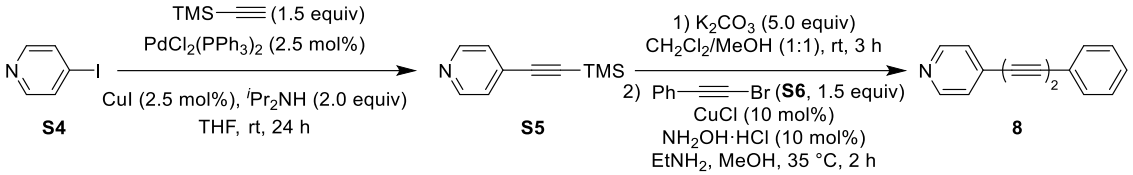
A flame dried 20 mL microwave vial was charged with 3-iodoaniline **S2** (438 mg, 2.00 mmol), bis(triphenylphosphine)palladium(II) dichloride ($PdCl_2(PPh_3)_2$, 35 mg, 0.05 mmol) and CuI (9 mg, 0.05 mmol). The vial was purged with Ar and sealed before the addition of NEt_3 (degassed by sonication under light vacuum, 8 mL), and (trimethylsilyl)acetylene (550 µL, 4.00 mmol). The reaction was heated with stirring to 80 °C for 3 h. After cooling to ambient temperature, the reaction mixture was diluted with Et_2O (50 mL) and filtered through Celite®. The filtrate was washed with water (50 mL) and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (15% 3:1 EtOAc:EtOH/petroleum ether 40–60) afforded the desired product **S3**[7] as a brown oil (362 mg, 1.91 mmol, 96%).

FTIR (ATR, cm^{-1}): 3464, 3375, 2957, 2154, 1620, 1597, 1578, 1487, 1248; **^{1}H NMR (500 MHz, $CDCl_3$)**: δ 7.07 (app.t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.79 (s, 1H), 6.63 (d, *J* = 7.8, 1H), 3.64 (s, 2H), 0.24 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 146.3, 129.3, 123.9, 122.6, 118.3, 115.7, 105.5, 93.6, 0.1; **LRMS (ES + APCI):** *m/z* calc. 189.1, found 190.1 $[M+H]^+$.

According to General Procedure 1: Silyl protected alkyne **S3** (189 mg, 1.00 mmol) and K_2CO_3 (691 mg, 5.00 mmol) were stirred in MeOH/CH_2Cl_2 (1:1, 0.1 M) for 3 h at rt. The crude deprotected alkyne was carried into the next step without further purification. According to General Procedure 2: Crude alkyne, phenylacetylene (330 µL, 3.00 mmol), CuCl (99 mg, 1.00 mmol) and TMEDA (300 µL, 2.00 mmol) in Me_2CO (10 mL) and CH_2Cl_2 (2 mL) were stirred at rt for 3 h. Purification by flash chromatography (50% CH_2Cl_2/petroleum ether 40–60) afforded the desired product **7**[8] as a pale yellow solid (141 mg, 0.65 mmol, 65%).

M.P: 88–90 °C [lit[9]: 92–94 °C]; **FTIR (ATR, cm^{-1}):** 3468.0, 3381.2, 3049.5, 2141.0, 1614.4, 1593.2, 1577.8, 1438.3, 1346.3, 1300.0, 1273.0; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.53 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.40–7.30 (m, 3H), 7.12 (app.t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.84–6.83 (m, 1H), 6.69 (dd, *J* = 7.8, 1.6 Hz, 1H), 3.70 (s, 2H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 146.5, 132.6, 129.5, 129.3, 128.6, 123.1, 122.6, 122.0, 118.5, 116.4, 82.1, 81.4, 74.2, 73.4; **LRMS (ES + APCI):** *m/z* calc. 217.3, found 218.0 $[M+H]^+$.

*Synthesis of **8***



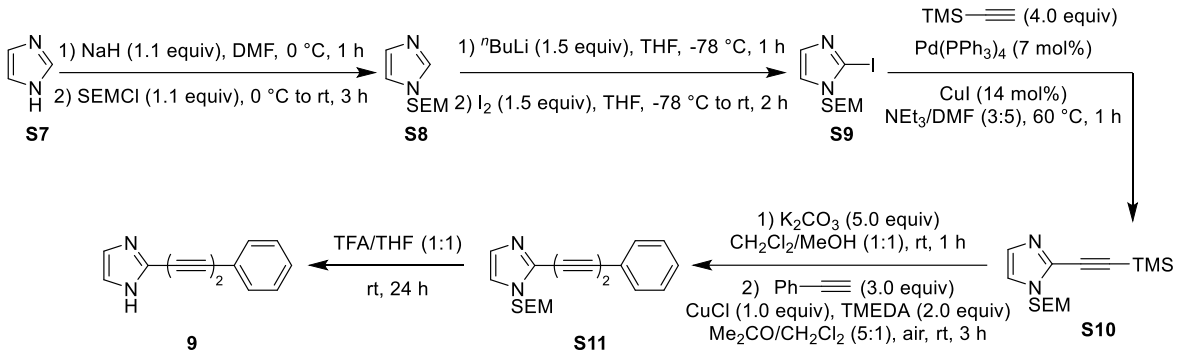
A flame dried 20 mL microwave vial was charged with 4-iodopyridine **S4** (1.02 g, 5.00 mmol), $PdCl_2(PPh_3)_2$ (87 mg, 0.13 mmol) and CuI (23 mg, 0.13 mmol). The vial was sealed and purged with Ar, prior to the addition of anhydrous THF (5 mL), ^{i}Pr_2NH (1.40 mL, 10.00 mmol) and (trimethylsilyl)acetylene (1.05 mL, 7.50 mmol). The reaction was stirred at rt for 24 h, diluted with Et_2O (50 mL) and filtered through Celite®. The filtrate was washed with saturated NH_4Cl (adjusted to pH 7 with NH_4OH, 50 mL) and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (10% EtOAc/petroleum ether 40–60 + 1% NEt_3) afforded the desired product **S5**[10] as a pale-yellow oil (782 mg, 4.46 mmol, 89%).

FTIR (ATR, cm^{-1}): 3038, 2959, 2899, 2164, 1591, 1487, 1404, 1250; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.56 (d, *J* = 6.0 Hz, 2H), 7.30 (d, *J* = 6.0 Hz, 2H), 0.26 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 149.9, 131.4, 126.0, 102.1, 100.1, -0.2; **LRMS (ES + APCI):** *m/z* calc. 175.1, found 176.1 $[M+H]^+$.

According to General Procedure 1: Silyl protected alkyne **S5** (175 mg, 1.00 mmol) and K_2CO_3 (691 mg, 5.00 mmol) in MeOH/CH_2Cl_2 (1:1, 5 mL) were stirred at rt for 1 h. The reaction mixture was poured onto saturated $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude alkyne product was carried to the next step without further purification. A round bottomed flask was charged with NH_2OH·HCl (7 mg, 0.10 mmol) and CuCl (10 mg, 0.10 mmol). The flask was purged with N_2 and the reactants were dissolved in MeOH (5 mL). $EtNH_2$ (70% *wt.* in water, 1.2 mL) was added dropwise and the reaction was stirred at rt for 5 min. A solution of the crude alkyne in MeOH/CH_2Cl_2 (2:1, 3 mL) was added dropwise and stirred for 10 min. The reaction was warmed to 35 °C and a solution of (bromoethynyl)benzene **S6** (synthesized according to literature procedure,[11] 271 mg, 1.50 mmol) in MeOH/CH_2Cl_2 (1:2, 3 mL) was added dropwise. The reaction was stirred at 35 °C for 2 h before cooling to rt and pouring onto saturated NH_4Cl solution (50 mL, adjusted to pH 7 with NH_4OH). The aqueous was extracted with EtOAc (3 × 25 mL) and the combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (10–15% EtOAc/petroleum ether 40–60 + 1% NEt_3) afforded the desired product **8**[12] as a white solid (65 mg, 0.32 mmol, 32%).

M.P: 114–115 °C [lit[12]: 122–124 °C]; **FTIR (ATR, cm^{-1}):** 3040, 2924, 2216, 1585, 1535, 1483, 1443, 1410; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.61 (d, *J* = 5.2 Hz, 2H), 7.57–7.52 (m, 2H), 7.44–7.33 (m, 5H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 150.0, 132.8, 130.3, 129.9, 128.7, 126.2, 121.3, 83.9, 78.4, 73.3 (1 signal missing); **LRMS (ES + APCI):** *m/z* calc. 192.1, found 193.1 $[M+H]^+$.

*Synthesis of **9***



A flame dried round bottomed flask was charged with NaH (60% dispersion in mineral oil, 840 mg, 21.0 mmol) and purged with Ar. The contents were suspended in anhydrous DMF (20 mL) and cooled to 0 °C with stirring. A solution of imidazole **S7** (1.36 g, 20.0 mmol) in anhydrous DMF (20 mL) was added dropwise and the reaction was stirred at 0 °C for 1 h. After this time 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl, 3.90 mL, 22.0 mmol) was added dropwise. The reaction was warmed to rt and stirred for 2 h, then quenched with water (200 mL). The aqueous was extracted with Et_2O (3 × 75 mL) and the combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by distillation (120–125 °C, 3.5 mbar) afforded the desired product **S8**[13] as a colourless oil (3.33 g, 16.8 mmol, 84%).

FTIR (ATR, cm^{-1}): 2955, 2895, 1503, 1381, 1250; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.59 (s, 1H), 7.10 (s, 1H), 7.04 (s, 1H), 5.27 (s, 2H), 3.47 (t, *J* = 8.1 Hz, 2H), 0.89 (t, *J* = 8.1 Hz, 2H), -0.02 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 137.5, 130.2, 119.0, 76.0, 66.5, 17.8, -1.3; **LRMS: (ES + APCI):** *m/z* calc. 198.1, found 199.1 $[M+H]^+$.

A flame dried flask was charged with imidazole **S8** (2.50 g, 12.6 mmol) and purged with Ar. The substrate was dissolved in anhydrous THF (60 mL) and cooled to -78 °C with stirring. ^{n}BuLi (2.5 M in THF, 7.6 mL, 19.0 mmol) was added dropwise over 30 min resulting in a yellow solution. The reaction was stirred for 1 h at -78 °C. After this time a solution of I_2 (4.80 g, 18.9 mmol) in anhydrous THF (40 mL) was added dropwise until a purple colour persisted for > 5 min. The reaction was warmed to rt and stirred for 2 h before quenching with saturated NH_4Cl solution (10 mL) and concentrating *in vacuo*. The residue was partitioned with EtOAc (100 mL) and saturated $Na_2S_2O_3$ solution (200 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organics were washed with water (100 mL) and brine (50 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (50% Et_2O/petroleum ether 40–60) afforded the desired product **S9**[14] as a pale-yellow oil (3.72 g, 11.5 mmol, 91%).

FTIR (ATR, cm^{-1}): 2951, 2928, 2901, 1460, 1423, 1375, 1248; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.15 (s, 1H), 7.13 (s, 1H), 5.23 (s, 2H), 3.53 (t, *J* = 8.5 Hz, 2H), 0.92 (t, *J* = 8.5 Hz, 2H), -0.01 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 133.2, 123.4, 90.1, 77.8, 66.7, 17.9, -1.3; **LRMS (EI):** *m/z* calc. 324.0, found 324.1 $[M]^+$.

A flame dried 20 mL microwave vial was charged with imidazole **S9** (811 mg, 2.50 mmol), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$, 218 mg, 0.35 mmol) and CuI (67 mg, 0.70 mmol), then sealed and purged with Ar. The contents were dissolved in anhydrous DMF (10 mL) prior to the addition of NEt_3 (5.9 mL, 42 mmol) and trimethylsilylacetylene (1.40 mL, 10.00 mmol). The reaction was heated to 60 °C for 1 h, cooled to rt and poured onto water (100 mL). The aqueous was extracted with Et_2O (3 × 30 mL) and the combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (0–20% EtOAc/petroleum ether 40–60) afforded the desired product **S10**[15] as a yellow oil (545 mg, 1.85 mmol, 37%).[16]

FTIR (ATR, cm^{-1}): 2955, 2897, 2162, 1506, 1465, 1373, 1248; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.08 (s, 1H), 7.05 (s, 1H), 5.38 (s, 2H), 3.52 (t, *J* = 8.0 Hz, 2H), 0.90 (t, *J* = 8.0 Hz, 2H), 0.26 (s, 9H), -0.01 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 132.4, 130.3, 120.2, 99.7, 93.3, 75.3, 66.7, 17.8, -0.2, -1.3; **LRMS (EI):** *m/z* calc. 294.2, found 294.4 $[M]^+$.

According to General Procedure 1: Silyl protected alkyne **S10** (147 mg, 0.50 mmol) and K_2CO_3 (691 mg, 5.00 mmol) in $MeOH/CH_2Cl_2$ (1:1, 5 mL) were stirred at rt for 1 h. The reaction mixture was poured onto water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo* to afford the crude deprotected alkyne, which was directly into the next step without further purification. According to General Procedure 2: Crude alkyne, phenylacetylene (165 µL, 1.50 mmol), CuCl (50 mg, 0.50 mmol) and TMEDA (150 µL, 1.00 mmol) in Me_2CO (5 mL) and CH_2Cl_2 (1 mL) were stirred at rt for 3 h. Purification by flash chromatography (20% EtOAc/petroleum ether 40–60) afforded the desired product **S11** as a yellow solid (76 mg, 0.24 mmol, 47%).

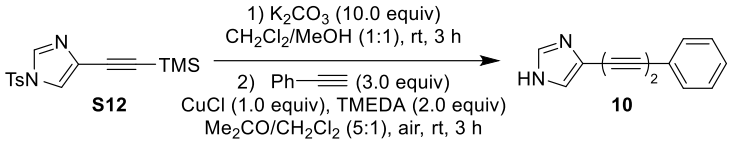
M.P: 40–41 °C; **FTIR (ATR, cm^{-1}):** 3103, 2951, 2870, 2149, 1487, 1441, 1381, 1248; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.57–7.51 (m, 2H), 7.44–7.32 (m, 3H), 7.14 (d, *J* = 1.0 Hz, 1H), 7.11 (d, *J* = 1.0 Hz, 1H), 5.41 (s, 2H), 3.58 (t, *J* = 8.0 Hz, 2H), 0.94 (t,

J = 8.0 Hz, 2H), 0.01 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 132.8, 131.5, 131.1, 129.9, 128.7, 121.2, 121.1, 83.6, 78.0, 75.4, 73.3, 70.1, 66.9, 17.8, -1.3; **LRMS (ES + APCI):** *m/z* calc. 322.2, found 323.1 $[M+H]^+$; **HRMS (ESI):** $[M+Na]^+$ calc. for $C_{19}H_{22}ON_2NaSi$ 345.1394; found 345.1380.

To a stirred solution of **S11** (50 mg, 0.16 mmol) in THF (1.5 mL) at rt was added trifluoroacetic acid (TFA, 1.5 mL) dropwise. The reaction was stirred at rt for 24 h before evaporating *in vacuo*. The residue was taken up in EtOAc (50 mL) and washed with saturated $NaHCO_3$ solution (30 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (0–50% EtOAc/petroleum ether 40–60) afforded the desired product **9** as a yellow solid (26 mg, 0.14 mmol, 87%).

M.P: decomposition > 160 °C; **FTIR (ATR, cm^{-1}):** 2916, 2849, 2159, 2222, 2152, 1564, 1489, 1443, 1421, 1312; **^{1}H NMR (500 MHz, $(CD_3)_2CO$):** δ 7.63–7.58 (m, 2H), 7.52–7.42 (m, 3H), 7.20 (s, 2H); **^{13}C NMR (126 MHz, $(CD_3)_2CO$)**: δ 133.4, 130.9, 129.7, 129.4, 121.8, 83.0, 74.0, 73.7, 73.5 (1 signal missing); **LRMS (ES + APCI):** *m/z* calc. 192.1, found 193.1 $[M+H]^+$; **HRMS (ESI):** $[M+Na]^+$ calc. for $C_{13}H_8N_2Na$ 215.0580; found 215.0569.

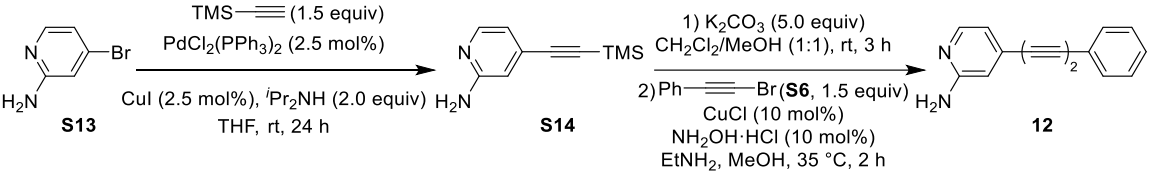
*Synthesis of **10***



According to General Procedure 1: Silyl protected alkyne **S12** (synthesized according to literature procedure,[16] 159 mg, 0.50 mmol) and K_2CO_3 (691 mg, 5.00 mmol) in MeOH/CH_2Cl_2 (1:1, 5 mL) were stirred at rt for 1 h. The reaction mixture was poured onto saturated $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude alkyne product was carried directly into the next step without further purification. According to General Procedure 2: Crude alkyne, phenylacetylene (165 µL, 1.50 mmol), CuCl (50 mg, 0.50 mmol) and TMEDA (150 µL, 1.00 mmol) in Me_2CO (5 mL) and CH_2Cl_2 (1 mL) were stirred at rt for 3 h. Purification by flash chromatography (2% 3M NH_3 in MeOH/CH_2Cl_2) afforded the desired product **10** as a yellow solid (37 mg, 0.19 mmol, 39%).

M.P: 150–152 °C; **FTIR (ATR, cm^{-1}):** 3126, 3076, 2830, 2220, 2151, 1557, 1510, 1441, 1342; **^{1}H NMR (500 MHz, $(CD_3)_2CO$)**: δ 11.67 (s, 1H), 7.72 (s, 1H), 7.61–7.55 (m, 3H), 7.48–7.38 (m, 3H); **^{13}C NMR (126 MHz, $(CD_3)_2CO$):** δ 137.4, 133.2, 130.3, 129.6, 129.6, 122.5, 81.8, 74.6 (3 signals missing); **LRMS (ES + APCI):** *m/z* calc. 192.1, found 193.0 $[M+H]^+$; **HRMS (ESI):** $[M-H]^-$ calc. for $C_{13}H_7N_2$ 191.0615; found 191.0616.

*Synthesis of **12***



A flame dried 20 mL microwave vial was charged with 2-amino-4-bromopyridine **S13** (865 mg, 5.00 mmol), $PdCl_2(PPh_3)_2$ (87 mg, 0.13 mmol) and CuI (23 mg, 0.13 mmol). The vial was sealed and purged with Ar, prior to the addition of anhydrous THF (5 mL), $^iPr_2NH$ (1.40 mL, 10.00 mmol) and (trimethylsilyl)acetylene (1.05 mL, 7.50 mmol). The reaction was stirred at rt for 24 h, diluted with Et_2O (50 mL) and filtered through Celite®. The filtrate was washed with saturated NH_4Cl (50 mL, adjusted to pH 9 with NH_4OH) and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (20–30% EtOAc/petroleum ether 40–60 + 1% NEt_3) afforded the desired product **S14**[17] as an off-white solid (935 mg, 4.91 mmol, 98%).

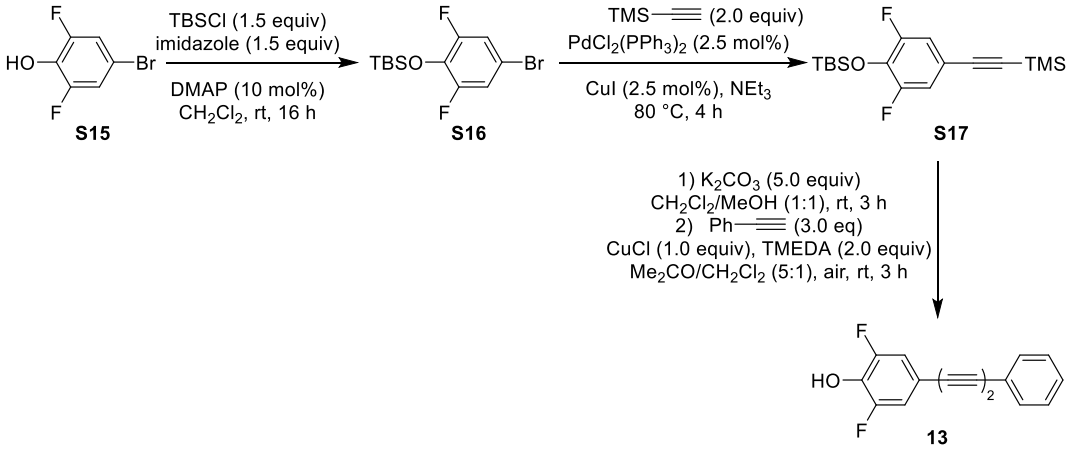
M.P: 106–108 °C; **FTIR (ATR, cm^{-1}):** 3460, 3283, 3144, 2158, 1628, 1595, 1535, 1485, 1435, 1252; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.02–7.98 (m, 1H), 6.68–6.64 (m, 1H), 6.56–6.53 (m, 1H), 4.46 (s, 2H), 0.24 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 158.4, 148.3, 132.6, 116.5, 110.9, 102.8, 98.3, -0.1; **LRMS (ES + APCI):** *m/z* calc. 190.1, found 191.1 $[M+H]^+$; **HRMS (ESI):** $[M+H]^+$ calc. for $C_{10}H_{15}N_2Si$ 191.0999; found 191.0991.

According to General Procedure 1: Silyl protected alkyne **S14** (190 mg, 1.00 mmol) and K_2CO_3 (691 mg, 5.00 mmol) in MeOH/CH_2Cl_2 (1:1, 5 mL) were stirred at rt for 1 h. The reaction mixture was poured onto saturated $NaHCO_3$ solution (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude alkyne product was carried directly into the next step without further purification. A round bottomed flask was charged with $NH_2OH{\cdot}HCl$ (7 mg, 0.10 mmol) and CuCl (10 mg, 0.10 mmol). The flask was purged with N_2 and the reactants were dissolved in MeOH (5 mL). $EtNH_2$ (70% *wt*. in water, 1.2 mL) was added dropwise and the reaction

was stirred at rt for 5 min. A solution of the crude alkyne in MeOH/CH_2Cl_2 (2:1, 3 mL) was added dropwise and stirred for 10 min. The reaction was warmed to 35 °C and a solution of (bromoethynyl)benzene **S6** (synthesized according to literature procedure,[3] 271 mg, 1.50 mmol) in MeOH/CH_2Cl_2 (1:2, 3 mL) was added dropwise. The reaction was stirred at 35 °C for 2 h before cooling to rt and pouring onto saturated NH_4Cl solution (50 mL, adjusted to pH 9 with NH_4OH). The aqueous was extracted with EtOAc (3 × 25 mL) and the combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by chromatography (10–50% EtOAc/petroleum ether 40–60 + 1% NEt_3) afforded the desired product **12** as a yellow solid (61 mg, 0.27 mmol, 27%).

M.P: decomposition > 180 °C; **FTIR (ATR, cm^{-1}):** 3281, 3183, 2922, 2853, 2218, 1653, 1587, 1539, 1421; **^{1}H NMR (500 MHz, $(CD_3)_2SO$):** δ 7.98 (s, 1H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 6.60 (d, *J* = 4.2 Hz, 1H), 6.57 (br.s, 1H), 6.18 (s, 2H); **^{13}C NMR (126 MHz, $(CD_3)_2SO$):** δ 159.8, 148.5, 132.5, 130.3, 129.0, 128.8, 120.0, 113.6, 110.2, 82.7, 80.0, 75.0, 73.0; **LRMS (ES + APCI):** *m/z* calc. 218.1, found 219.1 $[M+H]^+$; **HRMS (ESI):** $[M+H]^+$ calc. for $C_{15}H_{11}N_2$ 219.0917; found 219.0909.

*Synthesis of **13***



To a stirred solution of 4-bromo-2,6-difluorophenol **S15** (1.05 g, 5.00 mmol), imidazole (511 mg, 7.50 mmol) and 4-dimethylaminopyridine (DMAP, 61 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (12.5 mL) at rt was added *tert*-butyldimethylsilyl chloride (TBSCl, 1.13 g, 7.50 mmol). The reaction was stirred at rt for 16 h before partitioning with saturated NH_4Cl solution (50 mL) and extracting with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with water (20 mL), brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (petroleum ether 40–60) afforded the desired product **S16**[18] as a colourless oil (1.49 g, 4.60 mmol, 92%).

FTIR (ATR, cm^{-1}): 2951, 2930, 2859, 1593, 1580, 1503, 1425, 1312; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.08–7.01 (m, 2H), 1.01 (s, 9H), 0.19 (s, 6H); **^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled):** δ -126.8 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 155.3 (dd, $^{1,3}J_{CF}$ = 249.5, 6.2 Hz), 115.8 (dd, $^{2,4}J_{CF}$ = 18.8, 7.5 Hz), 111.4 (t, $^3J_{CF}$ = 11.3 Hz), 25.6 (s), 18.6 (s), -4.8 (s) (1 signal missing); **LRMS (EI):** *m/z* calc. 322.0, 324.0 found 332.2, 324.2 $[M]^+$.

A flame dried 20 mL microwave vial was charged with aryl bromide **S16** (970 mg, 3.00 mmol), $PdCl_2(PPh_3)_2$ (53 mg, 0.08 mmol) and CuI (14 mg, 0.08 mmol). The vial was purged with Ar and sealed before the addition of NEt_3 (degassed by sonication under light vacuum, 15 cycles, 12 mL) and (trimethylsilyl)acetylene (820 µL, 6.00 mmol). The reaction was heated with stirring to 80 °C for 4 h. After cooling to ambient temperature, the reaction mixture was diluted with Et_2O (50 mL) and filtered through Celite®. The filtrate was washed with saturated NH_4Cl (50 mL) and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (hexane) afforded the desired product **S17** as a colourless oil (970 mg, 2.85 mmol, 95%).

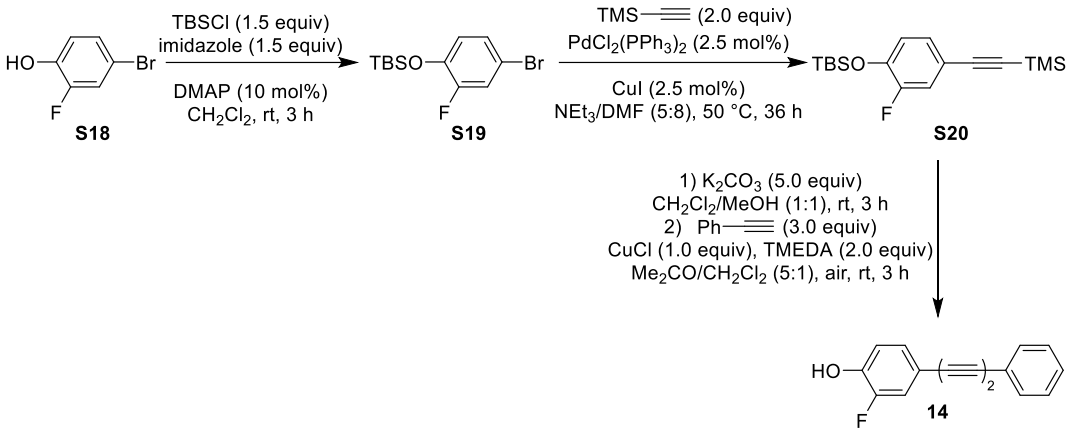
FTIR (ATR, cm^{-1}): 2960, 2860, 2162, 1560, 1516, 1354, 1250; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.02–6.94 (m, 2H), 1.00 (s, 9H), 0.23 (s, 9H), 0.19 (s, 6H); **^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled):** δ -128.7 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 154.8 (dd, $^{1,3}J_{CF}$ = 246.2, 6.4 Hz), 134.0 (t, $^2J_{CF}$ = 15.4 Hz), 116.0–115.5 (m), 103.0 (t, $^4J_{CF}$ = 3.1 Hz), 94.9 (s), 25.6 (s), 18.7 (s), 0.1 (s), -4.8 (s); **LRMS (EI):** *m/z* calc. 340.2 found 340.3 $[M]^+$; **HRMS (ESI):** $[M+H]^+$ calc. for $C_{17}H_{27}OF_2Si_2$ 341.1563; found 341.1556.

According to General Procedure 1: Silyl protected alkyne **S17** (341 mg, 1.00 mmol) and K_2CO_3 (1.38 g, 10.00 mmol, additional equivalents due to concomitant TBS-ether deprotection) in MeOH/CH_2Cl_2 (1:1, 10 mL) were stirred at rt for 3 h. The reaction mixture was poured onto water (30 mL), neutralized with 1 M HCl, and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude deprotected alkyne was carried into the next step without further purification. According to General Procedure 2: Crude deprotected alkyne, phenylacetylene (330 µL, 3.00 mmol), CuCl (99 mg, 1.00 mmol) and TMEDA (300 µL, 2.00 mmol) in Me_2CO (10 mL) and CH_2Cl_2

(2 mL) were stirred at rt for 3 h. Purification by flash chromatography (10% EtOAc/petroleum ether 40–60) afforded the desired product **13** as an off-white solid (137 mg, 0.54 mmol, 54%).

M.P: 110–112 °C; **FTIR (ATR, cm^{-1}):** 3536, 3082, 2924, 2145, 1593, 1518, 1487, 1435, 1387, 1333, 1290, 1227; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.55–7.50 (m, 2H), 7.41–7.31 (m, 3H), 7.13–7.05 (m, 2H), 5.23 (s, 1H); **^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled):** δ -134.6 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 151.3 (dd, $^{1,3}J_{CF}$ = 244.3, 6.3 Hz), 134.8 (t, $^{2}J_{CF}$ = 16.0 Hz), 132.7 (s), 129.6 (s), 128.6 (s), 121.6 (s), 116.3 (dd, $^{2,4}J_{CF}$ = 16.5, 6.8 Hz), 113.5 (t, $^{3}J_{CF}$ = 10.7 Hz), 82.3 (s), 79.2 (t, $^{4}J_{CF}$ = 3.6 Hz), 74.3 (s), 73.6 (s); **LRMS (ES + APCI):** *m/z* calc. 254.1 found 253.1[M-H]$^-$; **HRMS (ESI):** [M-H]$^-$ calc. for $C_{16}H_7OF_2$ 253.0470; found 253.0472.

*Synthesis of **14***



To a stirred solution of 4-bromo-2-fluorophenol **S18** (955 mg, 5.00 mmol), imidazole (511 mg, 7.50 mmol) and DMAP (61 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (15 mL) at rt was added TBSCl (1.13 g, 7.50 mmol). The reaction was stirred at rt for 3 h before partitioning with saturated NH_4Cl (50 mL) and extracting with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with water (20 mL), brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (0–5% EtOAc/petroleum ether 40–60) afforded the desired product **S19**[19] as a colourless oil (1.43 g, 4.70 mmol, 94%).

FTIR (ATR, cm^{-1}): 2955, 2930, 2859, 1601, 1578, 1493, 1290; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.21 (dd, *J* = 10.1, 2.1 Hz, 1H), 7.11 (app.d, *J* = 8.7 Hz, 1H), 6.79 (app.t, *J* = 8.7 Hz, 1H), 0.99 (s, 9H), 0.18 (s, 6H); **^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled):** δ -128.5 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 154.3 (d, $^{1}J_{CF}$ = 249.1 Hz), 143.0 (d, $^{2}J_{CF}$ = 12.2 Hz), 127.5 (d, J_{CF} = 3.7 Hz), 123.6 (s), 120.1 (d, $^{2}J_{CF}$ = 22.1 Hz), 112.9 (d, $^{3}J_{CF}$ = 8.1 Hz), 25.7 (s), 18.4 (s), -4.6 (s); **LRMS (EI):** *m/z* calc. 304.0, 306.0 found 304.2, 306.2 [M]$^+$.

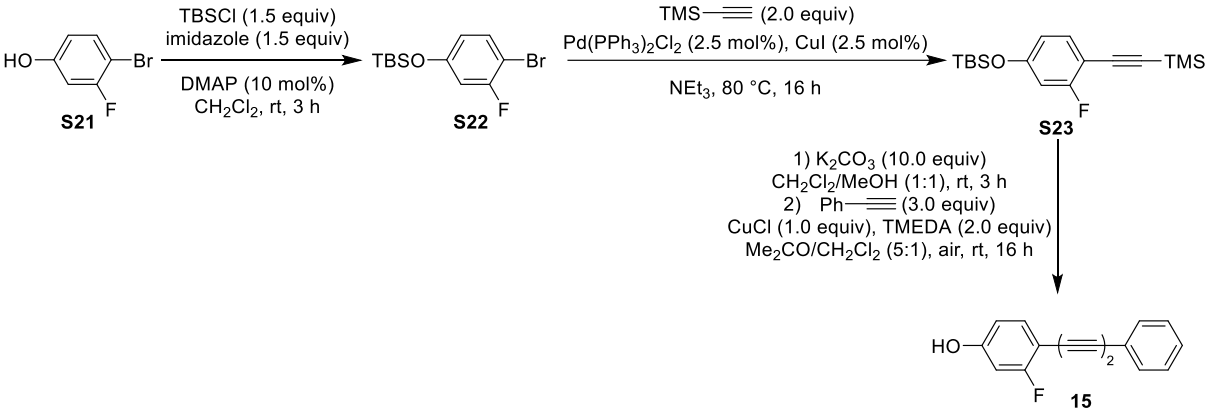
A flame dried 20 mL microwave vial was charged with aryl bromide **S19** (1.22 g, 4.00 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol) and CuI (20 mg, 0.10 mmol). The vial was sealed, purged with Ar, and the contents were dissolved in anhydrous DMF (16 mL). NEt_3 (9.50 mL, 68 mmol) was added, followed by (trimethylsilyl)acetylene (1.10 mL, 8.00 mmol) and the reaction was heated to 50 °C for 36 h. The reaction was cooled to rt, diluted with Et_2O (100 mL) and filtered through Celite®. The filtrate was washed with saturated NH_4Cl (50 mL), and the aqueous layer was extracted with further portions of Et_2O (2 × 50 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (hexane) afforded the desired product **S20** as a yellow oil (520 mg, 1.61 mmol, 32%), as well as unreacted starting material **S19** as a yellow oil (630 mg, 2.06 mmol, 51%).

FTIR (ATR, cm^{-1}): 2957, 2930, 2859, 2068, 1601, 1578, 1493, 1290; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.17 (dd, *J* = 11.2, 2.0 Hz, 1H), 7.11 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.81 (app.t, *J* = 8.5 Hz, 1H), 0.99 (s, 9H), 0.23 (s, 9H), 0.18 (s, 6H); **^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled):** δ -131.4 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 153.7 (d, $^{1}J_{CF}$ = 245.2 Hz), 144.4 (d, $^{2}J_{CF}$ = 12.6 Hz), 128.6 (d, J_{CF} = 3.4 Hz), 122.3 (s), 120.1 (d, $^{2}J_{CF}$ = 20.4 Hz), 116.8 (d, $^{3}J_{CF}$ = 8.3 Hz), 104.1 (d, $^{4}J_{CF}$ = 2.6 Hz), 93.7 (s), 25.7 (s), 18.5 (s), 0.1 (s), -4.6 (s); **LRMS (EI):** *m/z* calc. 322.2 found 322.3 [M]$^+$; **HRMS (ESI):** [M+H]$^+$ calc. for $C_{17}H_{28}OFSi_2$ 323.1657; found 323.1650.

According to General Procedure 1: Silyl protected alkyne **S20** (323 mg, 1.00 mmol) and K_2CO_3 (1.38 g, 10.00 mmol, additional equivalents due to concomitant TBS-ether deprotection) in MeOH/CH_2Cl_2 (1:1, 10 mL) were stirred at rt for 3 h. The reaction mixture was poured onto water (30 mL), neutralized with 1 M HCl, and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude deprotected alkyne was carried in its entirety into the next step without further purification. According to General Procedure 2: Crude deprotected alkyne, phenylacetylene (330 µL, 3.00 mmol), CuCl (99 mg, 1.00 mmol) and TMEDA (300 µL, 2.00 mmol) in Me_2CO (10 mL) and CH_2Cl_2 (2 mL) were stirred at rt for 3 h. Purification by flash chromatography (10% 3:1 EtOAc:EtOH/petroleum ether 40–60) afforded the desired product **14** as an off-white solid (157 mg, 0.67 mmol, 67%).

M.P: decomposition > 220 °C; **FTIR (ATR, cm^{-1}):** 3561, 3397(br), 3059, 2212, 2147, 1613, 1589, 1512, 1487, 1425, 1279; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.54–7.49 (m, 2H), 7.39–7.30 (m, 3H), 7.27–7.20 (m, 2H), 6.95 (t, *J* = 8.8 Hz, 1H), 5.29 (s, 1H); **^{19}F NMR (471 MHz, $CDCl_3$):** δ -138.0 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 150.4 (d, $^1J_{CF}$ = 238.7 Hz), 145.1 (d, $^2J_{CF}$ = 14.5 Hz), 132.7 (s), 130.1 (d, J_{CF} = 3.0 Hz), 129.4 (s), 128.6 (s), 121.9 (s), 119.7 (d, $^2J_{CF}$ = 19.6 Hz), 117.6 (d, J_{CF} = 2.4 Hz), 114.5 (d, $^3J_{CF}$ = 8.2 Hz), 81.7 (s), 80.5 (d, $^4J_{CF}$ = 3.1 Hz), 73.9 (s), 73.4 (s); **LRMS (ES + APCI):** *m/z* calc. 236.1 found 335.0 [M-H]$^-$; **HRMS (ESI):** [M-H]$^-$ calc. for $C_{16}H_8OF$ 235.0565; found 235.0566.

*Synthesis of **15***



To a stirred solution of 4-bromo-3-fluorophenol **S21** (955 mg, 5.00 mmol), imidazole (510 mg, 7.50 mmol) and DMAP (61 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (13 mL) at rt was added TBSCl (1.13 g, 7.50 mmol). The reaction was stirred at rt for 3 h before partitioning with saturated NH_4Cl solution (50 mL) and extracting with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with water (20 mL), brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (hexane) afforded the desired product **S22** as a colourless oil (1.42 g, 4.66 mmol, 93%).

FTIR (ATR, cm^{-1}): 2955.0, 2929.9, 2858.5, 1599.0, 1579.7, 1471.7, 1417.7, 1302.0, 1255.7, 1163.1; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.35 (app.t, *J* = 8.5 Hz, 1H), 6.63 (dd, *J* = 10.1, 2.7 Hz, 1H), 6.54 (ddd, *J* = 8.5, 2.7, 1.1 Hz, 1H), 0.97 (s, 9H), 0.20 (s, 6H); **^{19}F NMR (471 MHz, $CDCl_3$, ^{1}H decoupled):** δ -105.62 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (d, $^1J_{CF}$ = 246.9 Hz), 156.5 (d, $^3J_{CF}$ = 10.1 Hz), 133.3 (s), 117.5 (d, J_{CF} = 3.5 Hz), 109.1 (d, $^2J_{CF}$ = 23.2 Hz), 100.4 (d, $^2J_{CF}$ = 21.2 Hz), 25.7 (s), 18.3 (s), -4.38 (s); **LRMS (EI):** *m/z* calc. 304.0, found 304.1 [M]$^+$. **HRMS (ESI):** [M+H]$^+$ calc. for $C_{12}H_{19}O^{79}BrFSi$ 305.0367; found 305.0363.

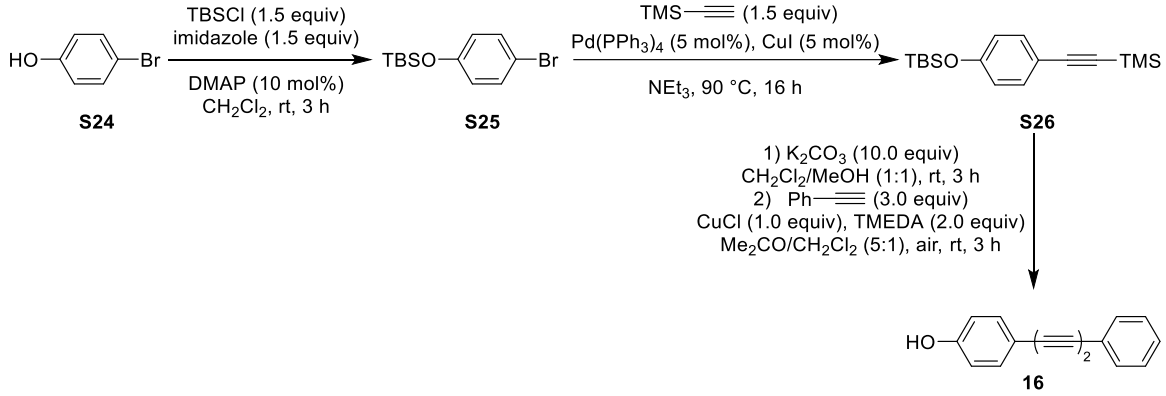
A flame dried 20 mL microwave vial was charged with aryl bromide **S22** (763 mg, 2.50 mmol), $PdCl_2(PPh_3)_2$ (44 mg, 0.06 mmol), CuI (12 mg, 0.06 mmol), then sealed and purged with Ar. The contents were dissolved in anhydrous NEt_3 (degassed by sonication under light vacuum, 10 mL) and (trimethylsilyl)acetylene (690 µL, 5.00 mmol) was added. The reaction was heated to 80 °C with stirring for 16 h. After cooling to rt, the reaction mixture was diluted with Et_2O (50 mL), filtered through Celite® and partitioned with saturated NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organics were washed with brine (20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (hexane) afforded the desired product **S23** as a pale-yellow oil (447 mg, 1.39 mmol, 55%).

FTIR (ATR, cm^{-1}): 2956.9, 2929.9, 2858.5, 2162.2, 1614.4, 1558.5, 1500.6, 1425.4, 1307.7, 1249.9, 1161.2; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.30 (t, *J* = 8.6 Hz, 1H), 6.58–6.52 (m, 2H), 0.97 (s, 9H), 0.25 (s, 9H), 0.20 (s, 6H); **^{19}F NMR (376 MHz, $CDCl_3$, ^{1}H decoupled):** δ -107.78 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** 163.9 (d, $^1J_{CF}$ = 252.3 Hz), 157.6 (d, $^3J_{CF}$ = 7.9 Hz), 134.4 (d, J_{CF} = 3.2 Hz), 116.2 (d, J_{CF} = 3.2 Hz), 107.9 (d, $^2J_{CF}$ = 22.4 Hz), 104.8 (d, $^2J_{CF}$ = 16.1 Hz), 98.5 (d, $^3J_{CF}$ = 3.2 Hz), 98.3 (s), 18.36 (s), 0.11 (s), -4.33 (s); **LRMS (EI):** *m/z* calc. 322.2, found 322.2 [M]$^+$.; **HRMS (ESI):** [M+H]$^+$ calc. for $C_{17}H_{28}OFSi_2$ 323.1657; found 323.1647.

According to General Procedure 1: Silyl protected alkyne **S23** (250 mg, 0.78 mmol) and K_2CO_3 (1.07 g, 7.78 mmol) in MeOH/CH_2Cl_2 (1:1, 8 mL) were stirred at rt for 3 h. The reaction mixture was poured onto water (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude deprotected alkyne was carried directly into the next step without further purification. According to General Procedure 2: Crude deprotected alkyne, phenylacetylene (237 µL, 2.33 mmol), CuCl (77 mg, 0.78 mmol) and TMEDA (180 µL, 1.55 mmol) in Me_2CO (8 mL) and CH_2Cl_2 (1 mL) were stirred at rt for 16 h. Purification by flash chromatography (20% EtOAc/petroleum ether 40–60) afforded the desired product **15** as a pale-yellow solid (36 mg, 0.15 mmol, 20%).

M.P: 140–142 °C; **FTIR (ATR, cm^{-1}):** 3269.3 (br), 3053.3, 2823.8, 2748.6, 2603.9, 2214.3, 2148.7, 1618.3, 1587.4, 1512.2, 1469.8, 1440.8, 1402.3, 1346.3, 1298.1, 1253.7, 1242.2, 1157.3; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.54–7.51 (m, 2H), 7.41–7.31 (m, 4H), 6.63–6.57 (m, 2H), 5.06 (s, 1H); **^{19}F NMR (376 MHz, $CDCl_3$):** δ -107.78 (s); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 164.9 (d, $^1J_{CF}$ = 253.5 Hz), 157.9 (d, $^3J_{CF}$ = 11.2 Hz), 135.3 (d, J_{CF} = 2.6 Hz), 132.6 (s), 129.4 (s), 128.6 (s), 121.9 (s), 111.9 (d, J_{CF} = 3.0 Hz), 103.8 (d, $^2J_{CF}$ = 24.0 Hz), 103.2 (d, $^2J_{CF}$ = 16.0 Hz), 82.2 (s), 77.6 (d, $^3J_{CF}$ = 3.1 Hz), 75.0 (s), 74.0 (s); **LRMS (ES + APCI):** *m/z* calc. 236.1 found 235.0 [M-H]$^-$; **HRMS (ESI):** [M-H]$^-$ calc. for $C_{16}H_8OF$ 235.0565; found 235.0565.

*Synthesis of **16***



To a stirred solution of 4-bromophenol **S24** (1.00 g, 5.78 mmol), imidazole (590 mg, 8.67 mmol) and 4-dimethylaminopyridine (DMAP, 87 mg, 0.58 mmol) in anhydrous CH_2Cl_2 (15 mL) at rt was added TBSCl (1.31 g, 8.67 mmol). The reaction was stirred at rt for 3 h before partitioning with saturated NH_4Cl solution (50 mL) and extracting with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with water (20 mL), brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (hexane) afforded the desired product **S25**[20] as a colourless oil (1.63 g, 5.68 mmol, 98%).

FTIR (ATR, cm^{-1}): 2955, 2930, 2856, 1585, 1252; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.34–7.29 (m, 2H), 6.74–6.69 (m, 2H), 0.97 (s, 9H), 0.18 (s, 6H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 155.0, 132.5, 122.1, 113.8, 25.8, 18.4, -4.3; **LRMS (EI):** *m/z* calc. 286.0, 288.0, found 286.2, 288.2 $[M]^+$.

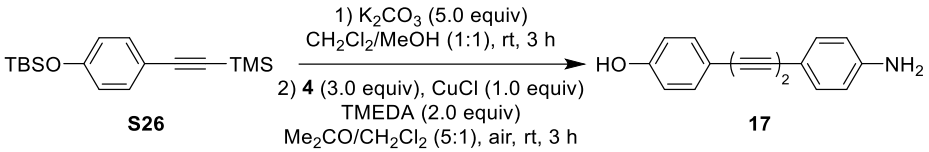
A flame dried 20 mL microwave vial was charged with aryl bromide **S25** (1.00 g, 3.48 mmol), $Pd(PPh_3)_4$ (216 mg, 0.17 mmol), CuI (33 mg, 0.17 mmol), then sealed and purged with Ar. The contents were dissolved in anhydrous NEt_3 (degassed by sonication under light vacuum, 15 mL) and (trimethylsilyl)acetylene (720 µL, 5.22 mmol) was added. The reaction was heated to 90 °C with stirring for 16 h. After cooling to rt, the reaction mixture was diluted with hexane (50 mL), filtered through Celite® and partitioned with saturated NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organics were washed with brine (20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (hexane) afforded the desired product **S26**[21] as a pale-yellow oil (889 mg, 2.92 mmol, 84%).

FTIR (ATR, cm^{-1}): 2957, 2859, 2156, 1601, 1504, 1250; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.35 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 0.97 (s, 9H), 0.23 (s, 9H), 0.19 (s, 6H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 156.3, 133.6, 120.2, 116.1, 105.4, 92.8, 25.8, 18.4, 0.2, -4.3; **LRMS (EI):** *m/z* calc. 304.2, found 304.3 $[M]^+$.

According to General Procedure 1: Silyl protected alkyne **S26** (152 mg, 0.50 mmol) and K_2CO_3 (691 mg, 5.00 mmol) in MeOH/CH_2Cl_2 (1:1, 5 mL) were stirred at rt for 3 h. The reaction mixture was poured onto water (30 mL), neutralized with 1 M HCl, and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude deprotected alkyne was carried directly into the next step without further purification. According to General Procedure 2: Crude deprotected alkyne, phenylacetylene (165 µL, 1.50 mmol), CuCl (50 mg, 0.50 mmol) and TMEDA (150 µL, 1.00 mmol) in Me_2CO (5 mL) and CH_2Cl_2 (1 mL) were stirred at rt for 3 h. Purification by flash chromatography (10% EtOAc/petroleum ether 40–60) afforded the desired product **16**[22] as an off-white solid (62 mg, 0.28 mmol, 57%).

M.P: 124–126 °C [lit[22]: 123–124 °C]; **FTIR (ATR, cm^{-1}):** 3229 (br), 3059, 2212, 2145, 1589, 1505, 1466, 1227; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.54–7.50 (m, 2H), 7.45–7.41 (m, 2H), 7.39–7.31 (m, 3H), 6.83–6.77 (m, 2H), 4.90 (s, 1H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 156.6, 134.5, 132.6, 129.2, 128.6, 122.1, 115.8, 114.3, 81.7, 81.2, 74.3, 72.9; **LRMS (ES + APCI):** *m/z* calc. 218.1, found 217.1 $[M-H]^-$.

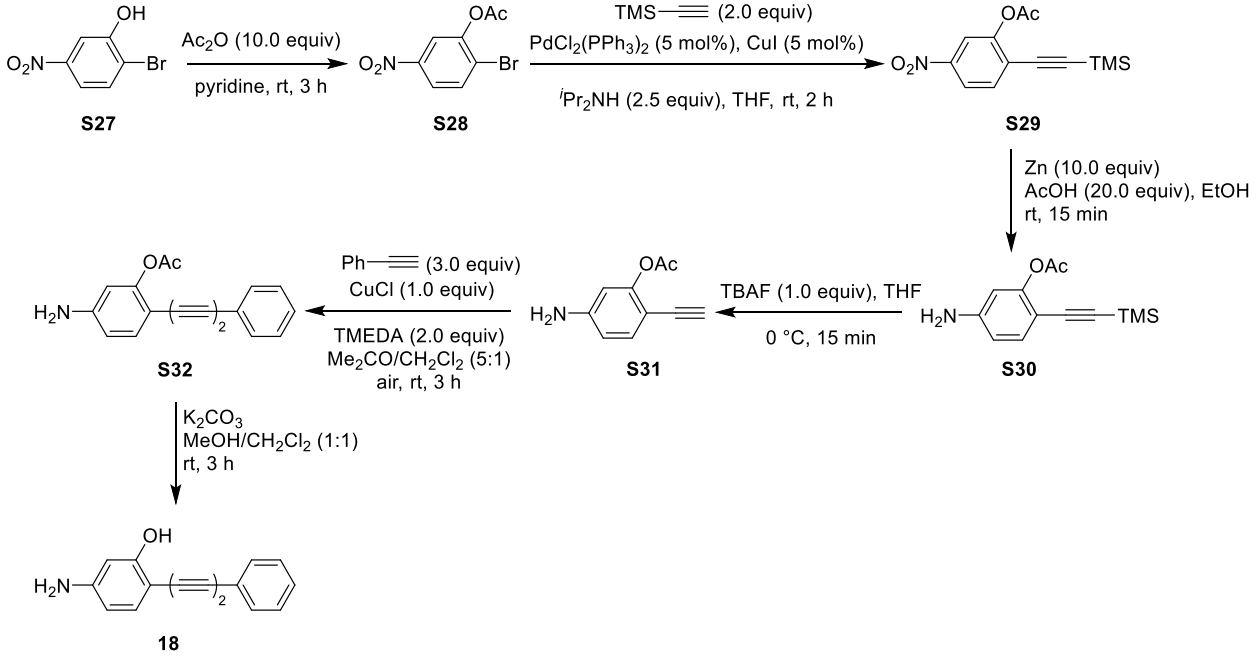
*Synthesis of **17***



According to General Procedure 1: Silyl protected alkyne **S26** (609 mg, 2.00 mmol) and K_2CO_3 (1.38 g, 10.00 mmol) in MeOH/CH_2Cl_2 (1:1, 20 mL) were stirred at rt for 3 h. The reaction mixture was poured onto water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude deprotected alkyne was carried directly into the next step without further purification. According to General Procedure 2: Crude deprotected alkyne, 4-ethynylaniline **S1** (117 mg, 1.00 mmol), CuCl (99 mg, 1.00 mmol) and TMEDA (300 µL, 2.00 mmol) in Me_2CO (10 mL) and CH_2Cl_2 (2 mL) were stirred at rt for 3 h. Purification by flash chromatography (0–25% 3:1 EtOAc:EtOH/petroleum ether 40–60) afforded the desired product **17** as an off-white solid (94 mg, 0.40 mmol, 40%).

M.P: decomposition > 168 °C; **FTIR (ATR, cm^{-1}):** 2270, 3275, 2994 – 2430 (multiple bands), 2137, 1601, 1580, 1501, 1449, 1387, 1236; **^{1}H NMR (500 MHz, DMSO-d_6):** δ 10.04 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.53 (d, *J* = 8.5 Hz, 2H), 5.74 (s, 2H); **^{13}C NMR (126 MHz, DMSO-d_6):** δ 158.7, 150.4, 133.9, 133.7, 115.9, 113.6, 111.1, 105.9, 83.4, 81.4, 72.8, 71.6; **LRMS (ES + APCI):** *m/z* calc. 233.1 found 234.0 $[M+H]^+$; **HRMS (ESI):** $[M-H]^-$ calc. for $C_{16}H_{10}ON$ 232.0768; found 232.0768.

*Synthesis of **18***



To a solution of 2-bromo-5-nitrophenol **S27** (1.31 g, 6.00 mmol) in anhydrous pyridine (6 mL) at rt was added Ac_2O (5.65 mL, 60.0 mmol) and the reaction was stirred at rt for 3 h. The reaction mixture was diluted with EtOAc (80 mL) and washed with water (30 mL), saturated $NaHCO_3$ (30 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography afforded the desired product **S28**[23] as a pale yellow solid (1.47 g, 5.65 mmol, 94%).

M.P: 78–80 °C [lit[23]: 86 °C]; **FTIR (ATR, cm^{-1}):** 3362, 3096, 1767, 1607, 1580, 1524, 1466, 1342; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.04 –7.98 (m, 2H), 7.80 (d, *J* = 8.6 Hz, 1H), 2.40 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 167.9, 148.9, 147.8, 134.1, 124.5, 122.0, 119.4, 20.8; **LRMS (ES + APCI):** *m/z* calc. 259.0, found 259.9 $[M+H]^+$.

A flame dried 20 mL microwave vial was charged with aryl bromide **S28** (780 mg, 3.00 mmol), $PdCl_2(PPh_3)_2$ (105 mg, 0.15 mmol) and CuI (29 mg, 0.15 mmol). The vial was sealed and purged with Ar, prior to the addition of anhydrous THF (12 mL), $^i Pr_2NH$ (1.13 mL, 8.00 mmol) and (trimethylsilyl)acetylene (840 µL, 6.00 mmol). The reaction was stirred at rt for 2 h, diluted with Et_2O (50 mL) and filtered through Celite®. The filtrate was washed with saturated NH_4Cl (50 mL) and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organics were washed with brine (10 mL), dried over

Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (2.5% EtOAc/petroleum ether 40–60) afforded the desired product **S29** as an off-white solid (755 mg, 2.72 mmol, 91%).

M.P: 76–78 °C; **FTIR (ATR, cm^{-1}):** 3102, 2961, 2162, 1723, 1593, 1514, 1479, 1344; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 8.07 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 2.36 (s, 3H), 0.27 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.1, 152.3, 147.7, 133.8, 124.4, 121.0, 118.2, 106.1, 97.9, 20.8, -0.2; **LRMS (ES + APCI):** *m/z* calc. 277.1, found 278.0 $[M+H]^+$; **HRMS (ESI):** $[M+H]^+$ calc. for $C_{13}H_{16}O_4NSi$ 278.0843; found 278.0842.

To a solution of nitro compound **S29** (300 mg, 1.08 mmol) in EtOH (22 mL) at rt was added AcOH (1.24 mL, 22.00 mmol) followed by zinc dust (706 mg, 10.80 mmol) portion wise. The reaction mixture was stirred for 15 min at rt, then diluted with Et_2O (50 mL) and filtered through Celite®. The filtrate was washed with water (20 mL), saturated $NaHCO_3$ (20 mL) and brine (10 mL), then dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) afforded the desired product **S30** as a yellow oil (265 mg, 1.01 mmol, 99%).

FTIR (ATR, cm^{-1}): 3466, 3372, 2956, 2149, 1749, 1738, 1620, 1504, 1447, 1368, 1325, 1211**; ^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.27 (d, *J* = 8.3 Hz, 1H), 6.45 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 3.87 (s, 2H), 2.30 (s, 3H), 0.22 (s, 9H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 168.8, 153.5, 148.2, 134.3, 112.4, 108.5, 106.7, 100.6, 96.9, 21.0, 0.2; **LRMS (ES + APCI):** *m/z* calc. 247.1, found 248.1 $[M+H]^+$; **HRMS (ESI):** $[M+H]^+$ calc. for $C_{13}H_{18}O_2NSi$ 248.1101; found 248.1100.

To a solution of silyl protected alkyne **S30** (275 mg, 1.11 mmol) in anhydrous THF (10 mL) at 0 °C was added tetrabutylammonium fluoride solution (TBAF, 1 M in THF, 1.11 mL, 1.11 mmol) dropwise. The reaction was stirred for 15 min before warming to rt and diluting with Et_2O (80 mL) and washing with saturated NH_4Cl (20 mL), water (20 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. Purification by flash chromatography (40% EtOAc/hexane) afforded the desired product **S31** as a yellow solid (188 mg, 1.01 mmol, 91%).

M.P: 168–170 °C; **FTIR (ATR, cm^{-1}):** 3472, 2260, 3267, 2926, 2100, 1755, 1740, 1618, 1607, 1506, 1373, 1335; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.30 (d, *J* = 8.3 Hz, 1H), 6.47 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.37 (d, *J* = 2.1 Hz, 1H), 3.89 (s, 2H), 3.11 (s, 1H), 2.31 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 169.0, 153.6, 148.5, 134.6, 112.5, 108.5, 105.4, 79.7, 79.4, 21.0; **LRMS (ES + APCI):** *m/z* calc. 175.1, found 176.1 $[M+H]^+$; **HRMS (ESI):** $[M+Na]^+$ calc. for $C_{10}H_9O_2NNa$ 198.0525; found 198.0518.

According to General Procedure 2: Alkyne **S31** (88 mg, 0.50 mmol), phenylacetylene (165 µL, 1.50 mmol), CuCl (50 mg, 0.50 mmol) and TMEDA (150 µL, 1.00 mmol) in Me_2CO (5 mL) and CH_2Cl_2 (1 mL) were stirred at rt for 3 h. Purification by flash chromatography (80% CH_2Cl_2/hexane) afforded the desired product **S32** as an orange solid (95 mg, 0.35 mmol, 69%).

M.P: 108–110 °C; **FTIR (ATR, cm^{-1}):** 3470, 3375, 3221, 2207, 2147, 1736, 1626, 1609, 1373; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.54–7.47 (d, 7.8 Hz, 2H), 7.39–7.29 (m, 4H), 6.47 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 3.98 (s, 2H), 2.36 (s, 3H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 169.1, 154.3, 148.9, 135.2, 132.6, 129.1, 128.5, 122.2, 112.6, 108.6, 105.0, 81.8, 77.7, 76.5, 74.4, 21.1; **LRMS (ES + APCI):** *m/z* calc. 275.1 found 276.0 $[M+H]^+$; **HRMS (ESI):** $[M+Na]^+$ calc. for $C_{18}H_{13}O_2NNa$ 298.0838; found 298.0824.

To a solution of ester **S32** (76 mg, 0.28 mmol) in MeOH/CH_2Cl_2 (1:1, 2.8 mL) at rt was added K_2CO_3 (191 mg, 1.38 mmol). The reaction was stirred at rt for 3 h, prior to diluting with CH_2Cl_2 (50 mL) and washing with water (20 mL) and saturated NH_4Cl (20 mL). The combined aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organics were washed with brine (10 mL), dried over Na_2SO_4 and evaporated *in vacuo* to afford the desired product **18** (55 mg, 0.24 mmol, 85%) as a yellow solid.

M.P: 122–124 °C; **FTIR (ATR, cm^{-1}):** 3404, 3329, 3030 (br), 2207, 2141, 1618, 1560, 1485, 1462, 1331, 1319; **^{1}H NMR (500 MHz, $CDCl_3$):** δ 7.54–7.49 (m, 2H), 7.39–7.30 (m, 3H), 7.20 (d, *J* = 8.3 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 6.20 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.67 (s, 1H), 3.92 (s, 2H); **^{13}C NMR (126 MHz, $CDCl_3$):** δ 159.9, 149.9, 134.1, 132.5, 129.3, 128.6, 122.0, 108.2, 100.7, 98.0, 83.1, 79.5, 77.1, 74.0; **LRMS (ES + APCI):** *m/z* calc. 233.1 found 234.0 $[M+H]^+$; **HRMS (ESI):** $[M+H]^+$ calc. for $C_{16}H_{12}ON$ 234.0913; found 234.0910.

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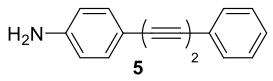
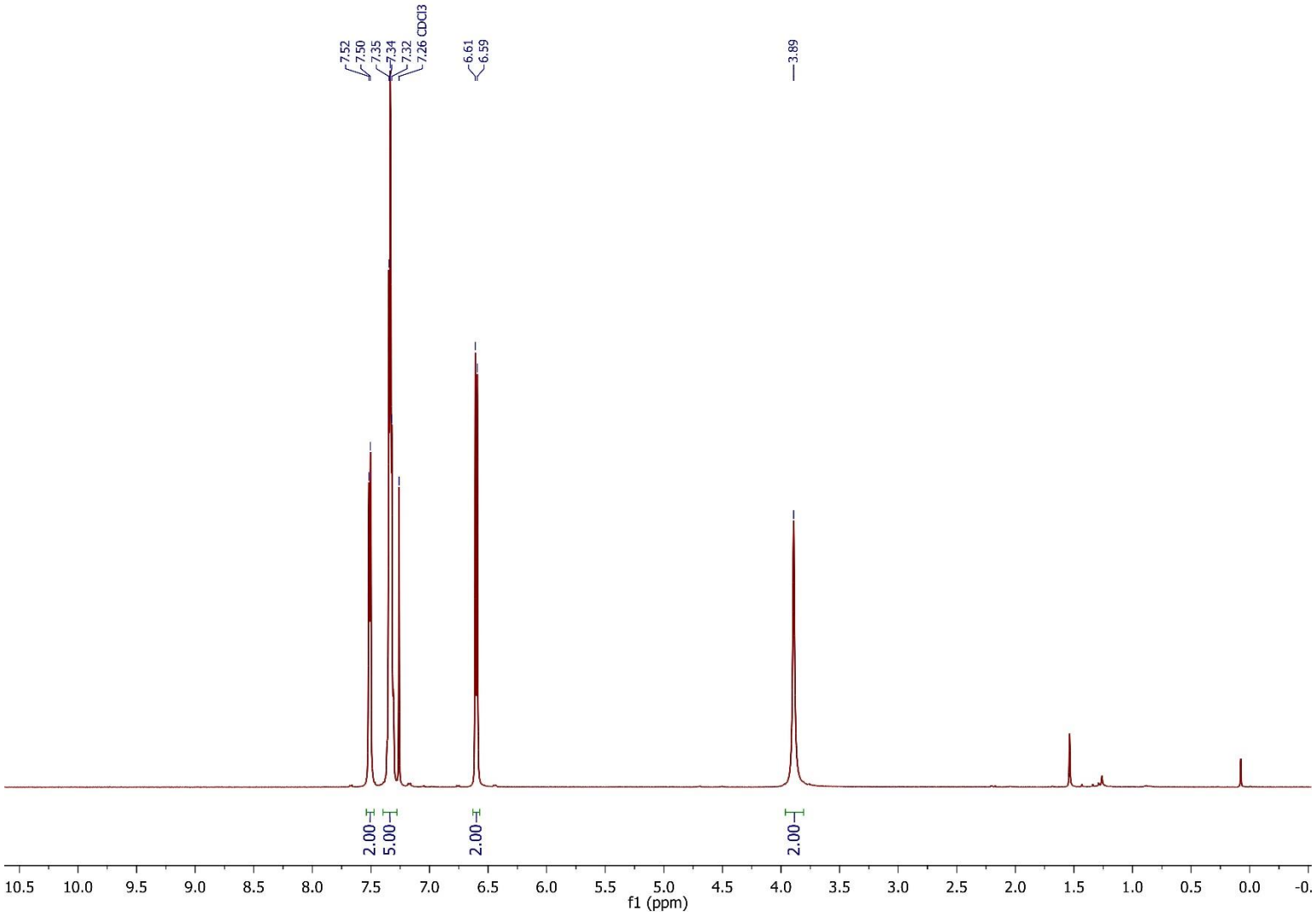
4. Copies of ^{1}H, ^{13}C and ^{19}F NMR Spectra of Synthetic Compounds



*^{1}H NMR Spectrum of **5** (500 MHz, $CDCl_3$)*



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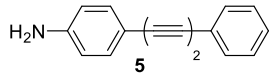

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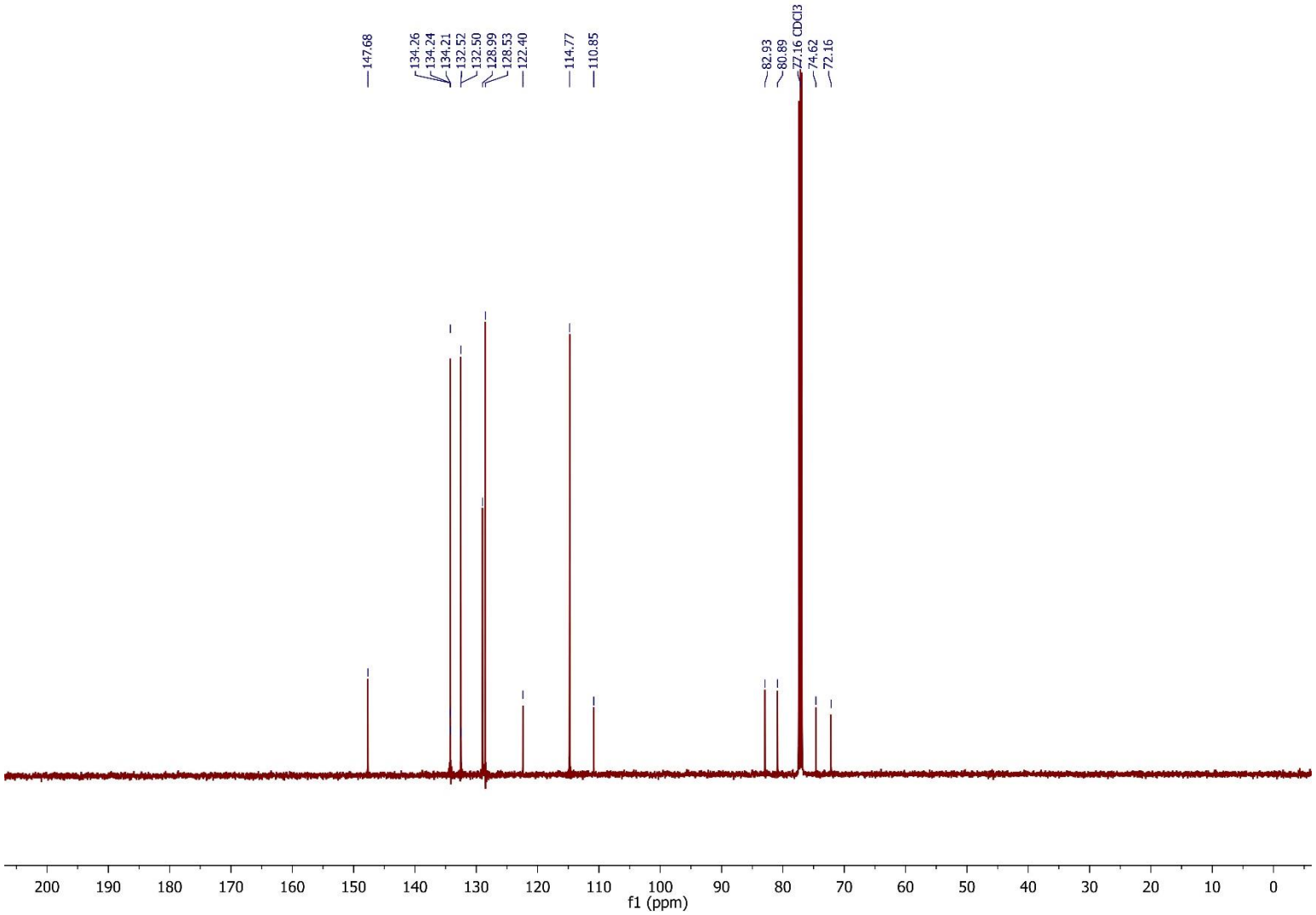

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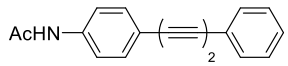

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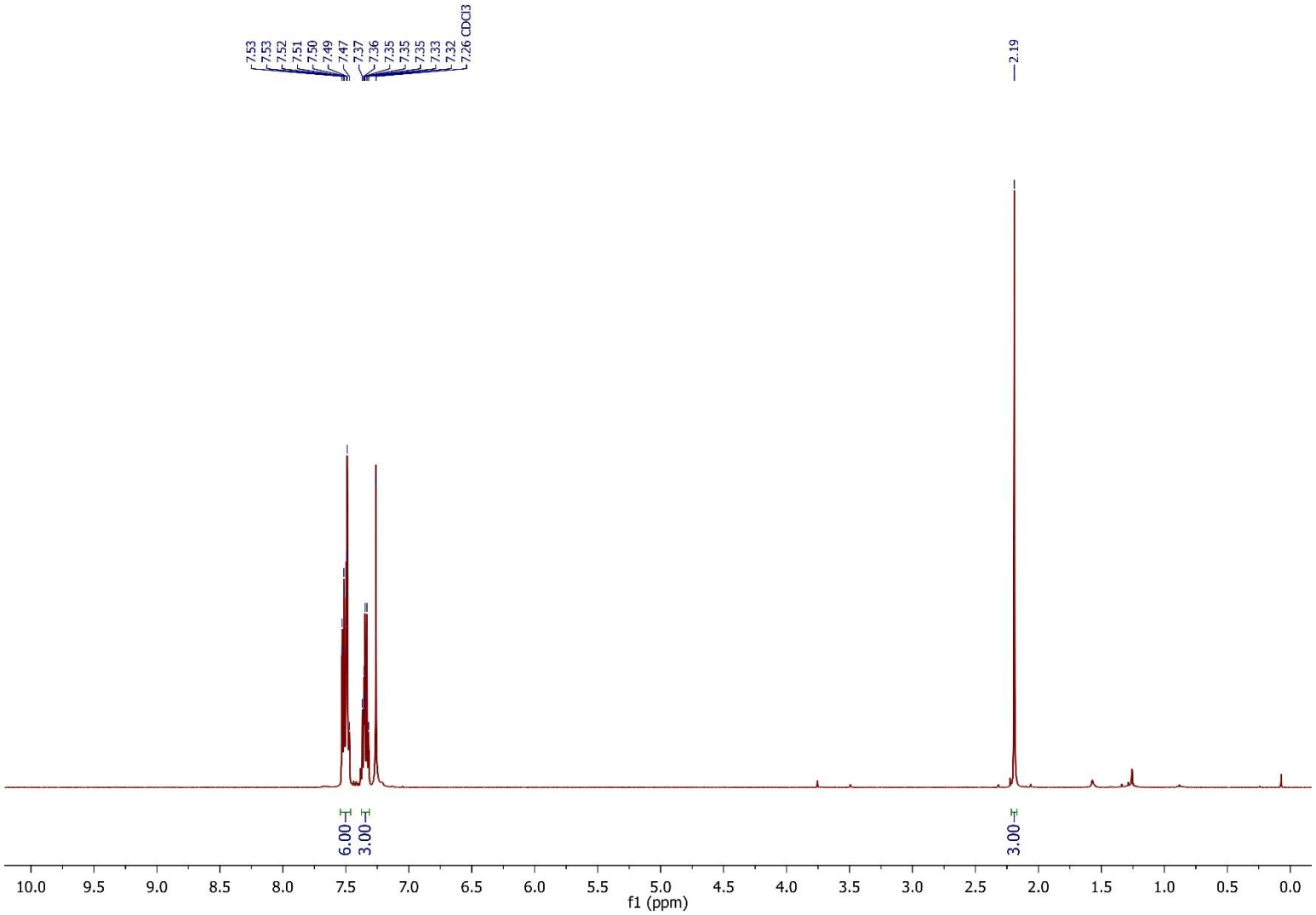

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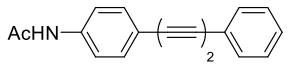

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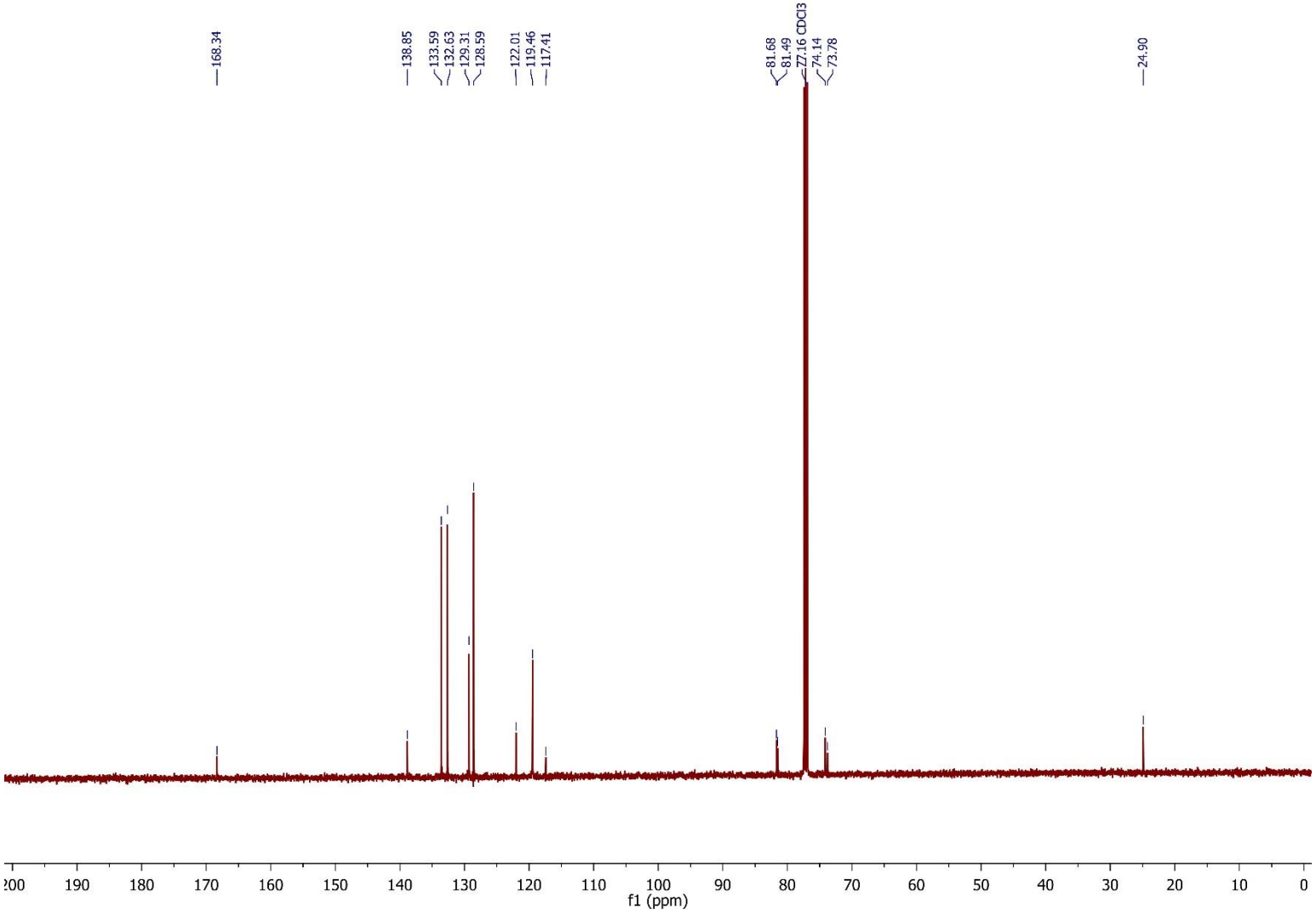

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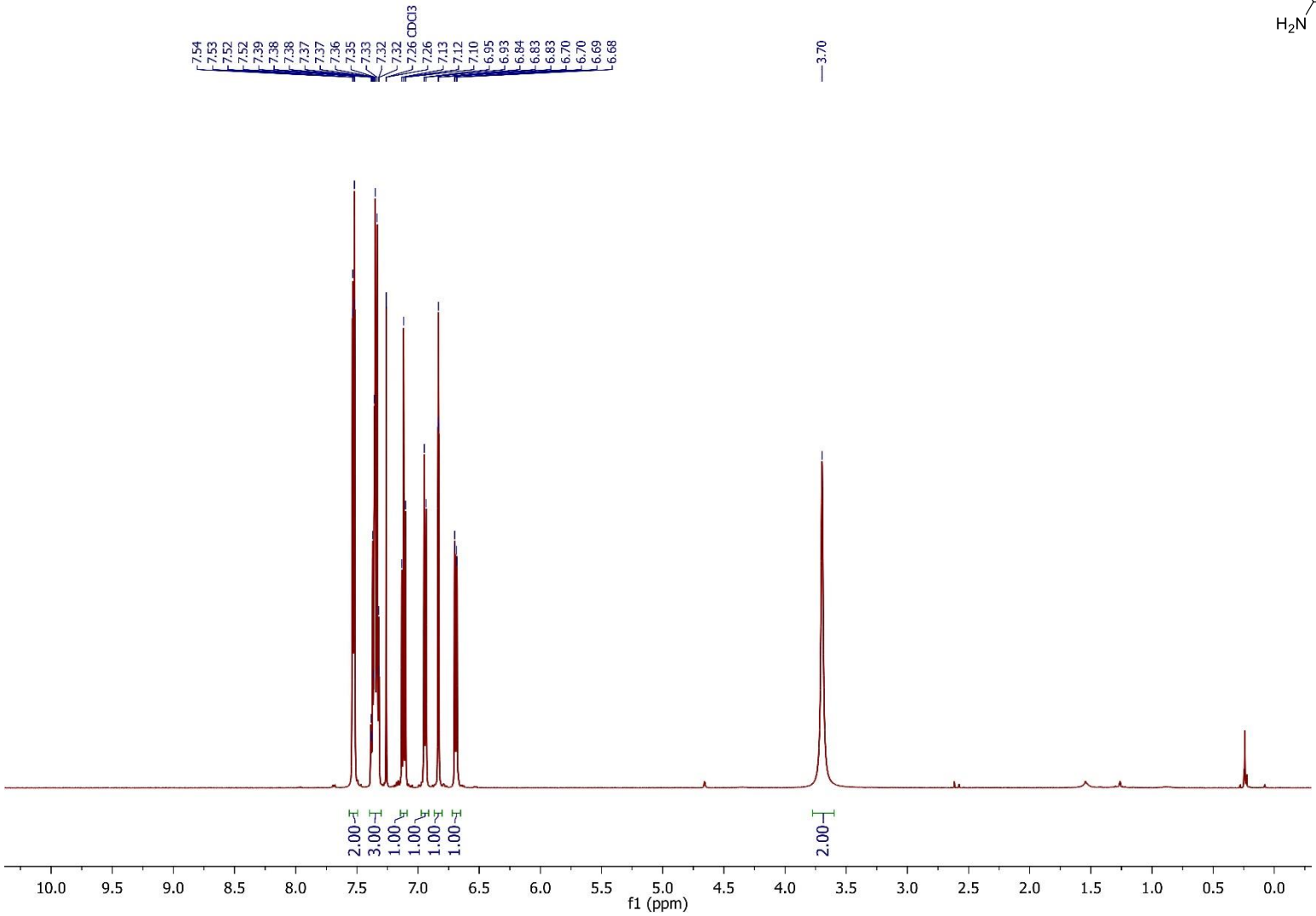

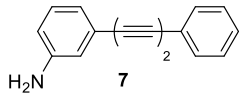

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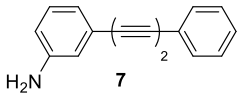

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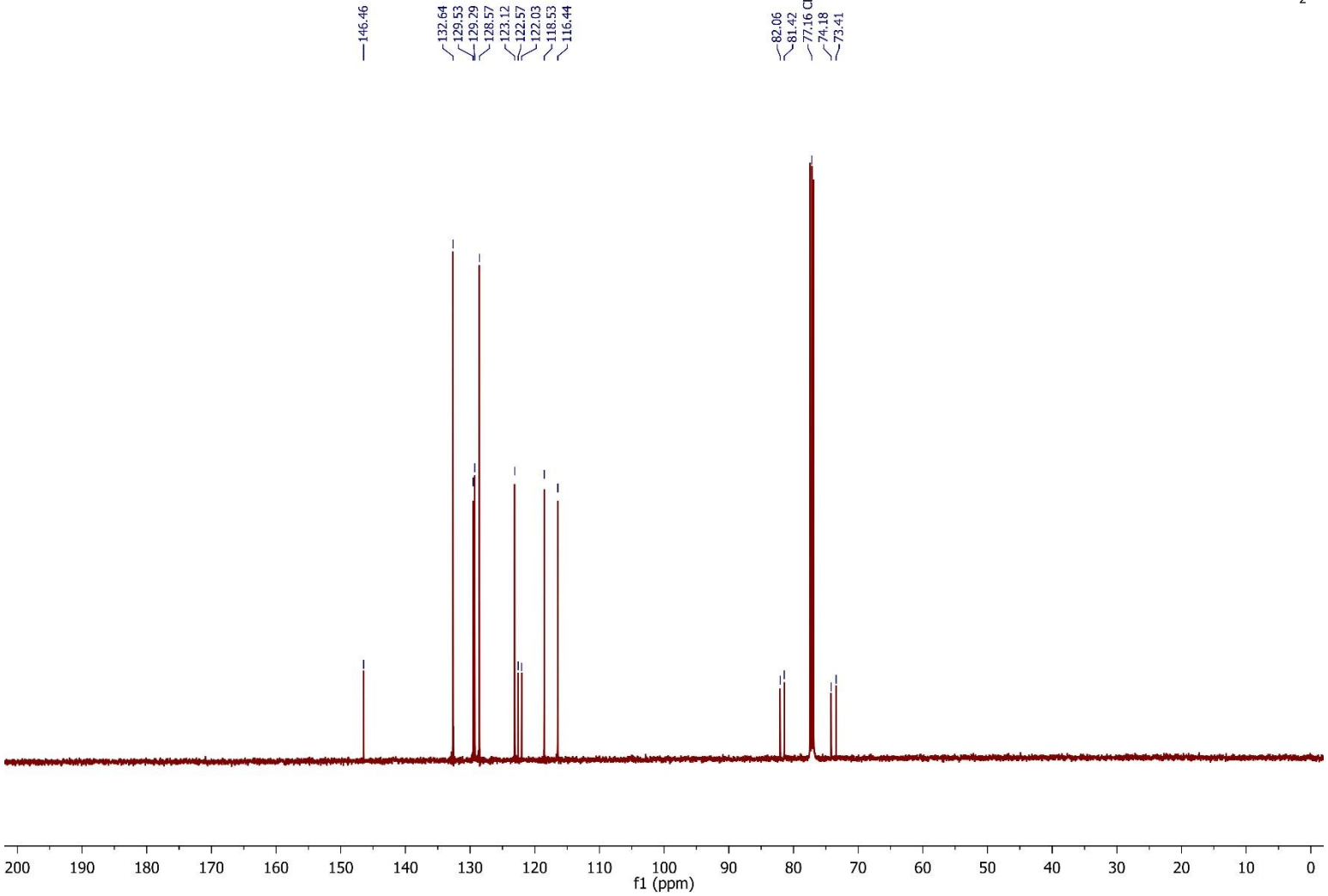

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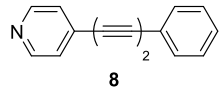

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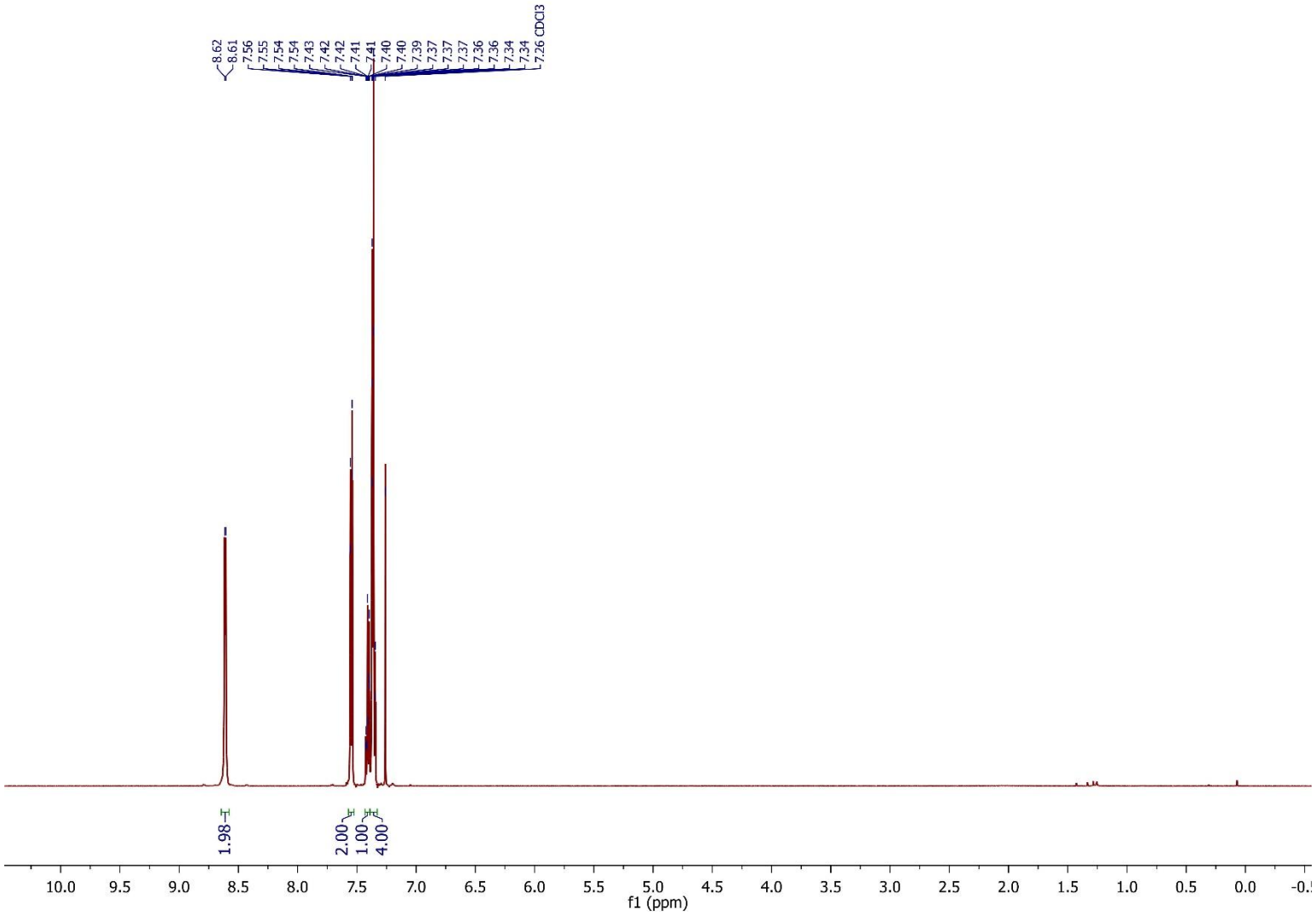

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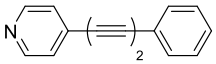

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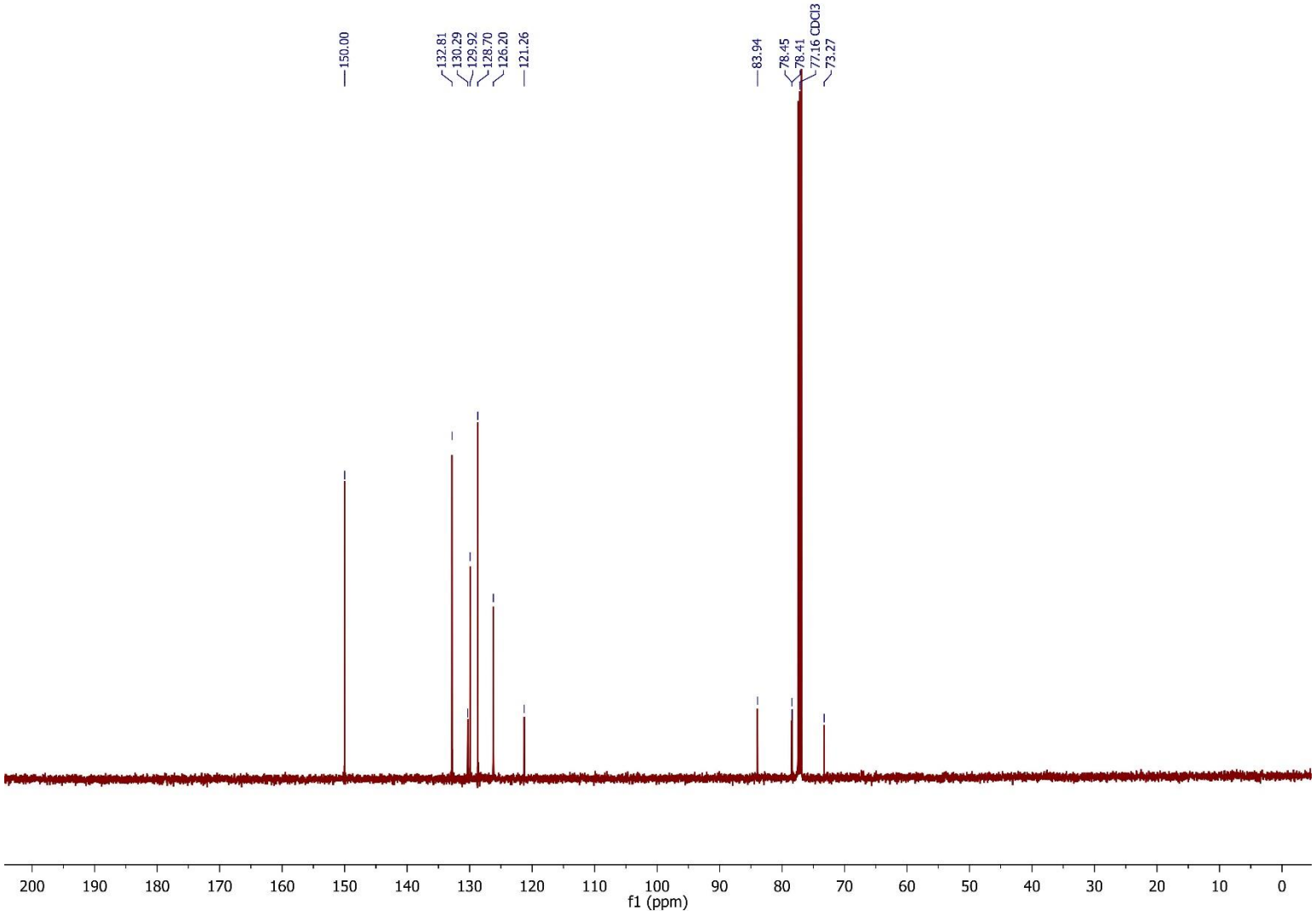
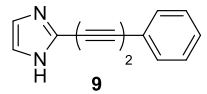
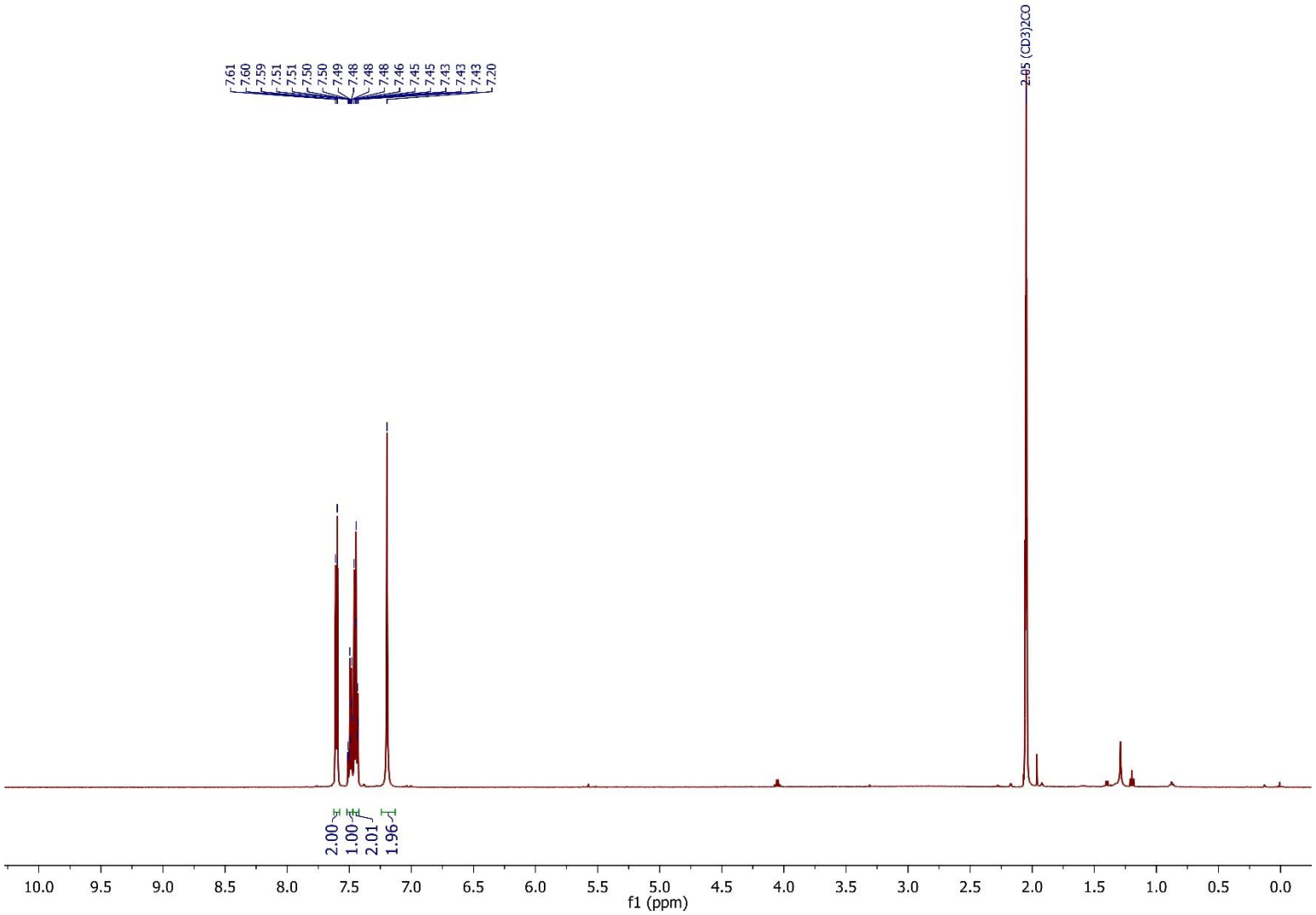


*^{1}H NMR of **9** (500 MHz, $(CD_3)_2CO$)*





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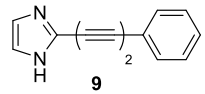

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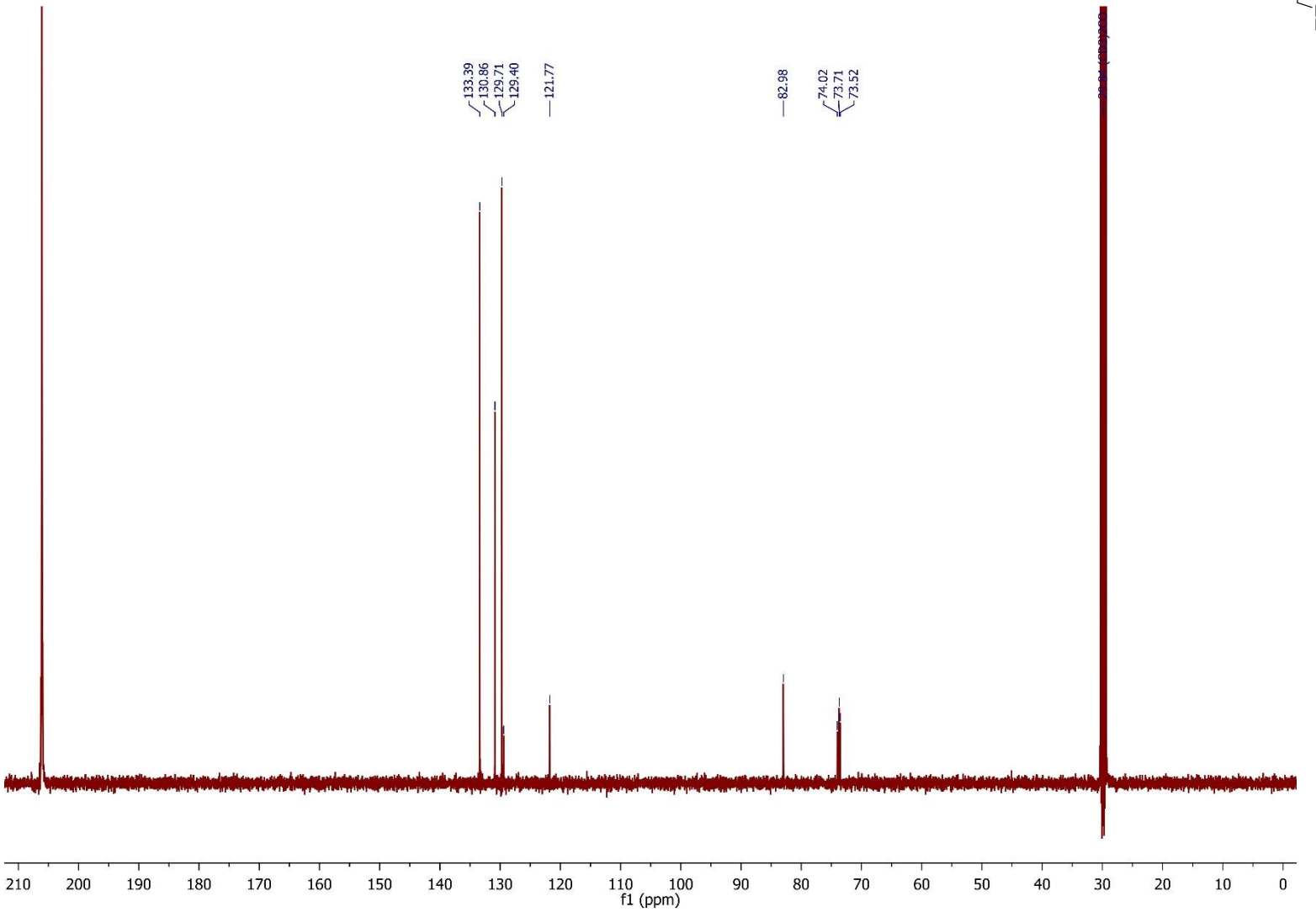

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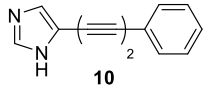

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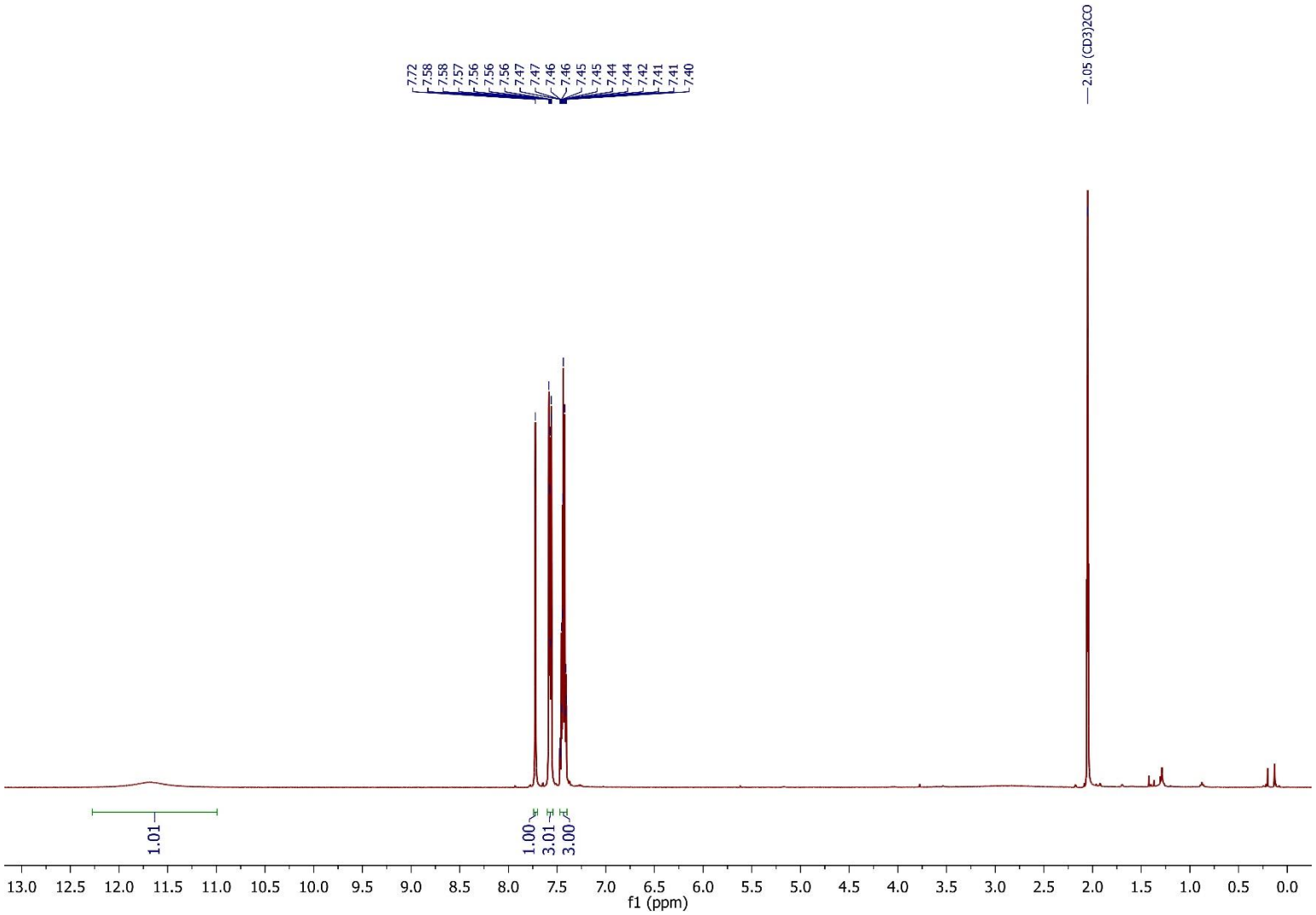

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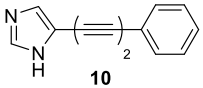

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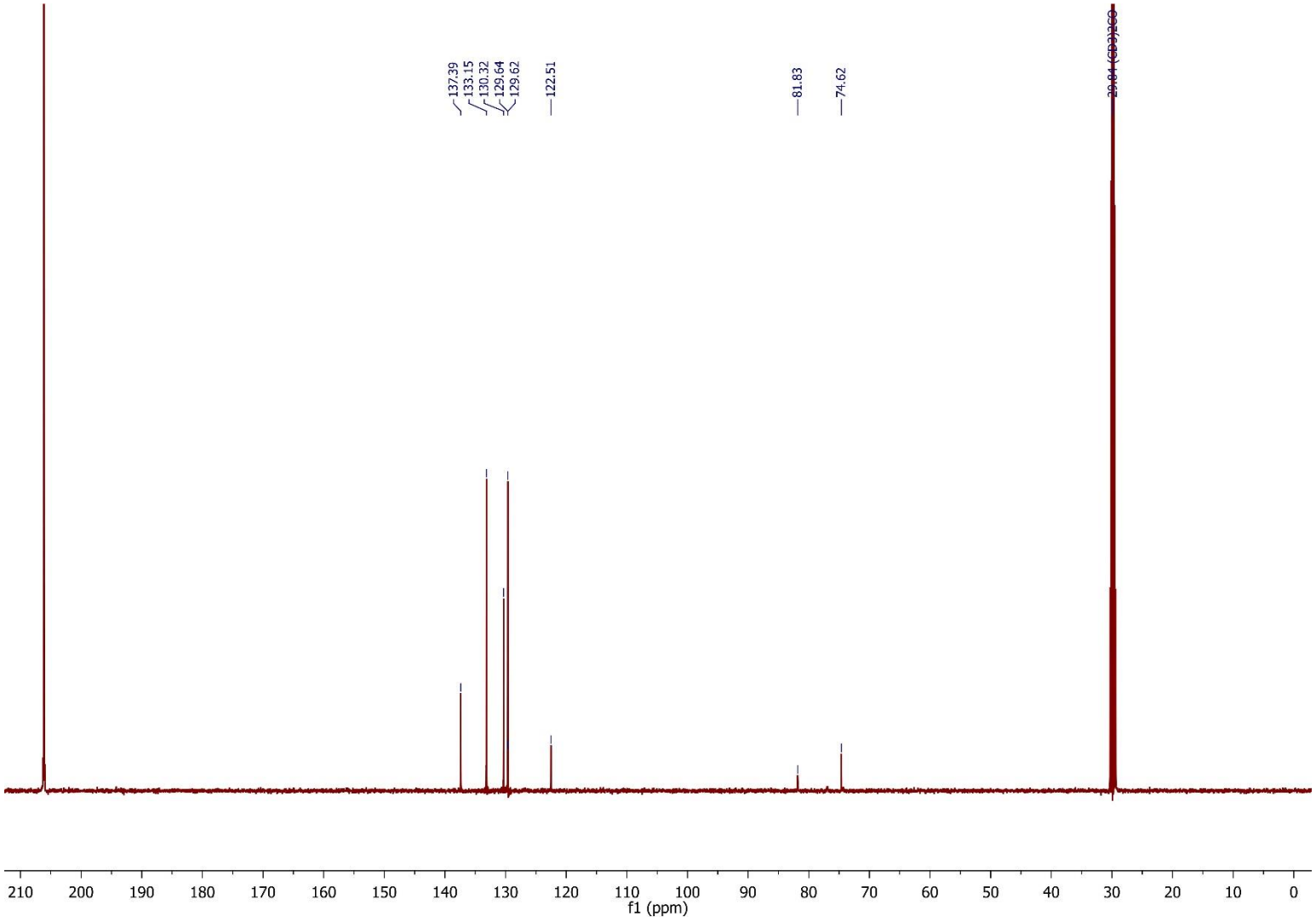
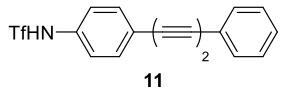
*^{13}C NMR of **10** (126 MHz, $(CD_3)_2CO$)*



*^{1}H NMR Spectrum of **11** (400 MHz, $CDCl_3$)*



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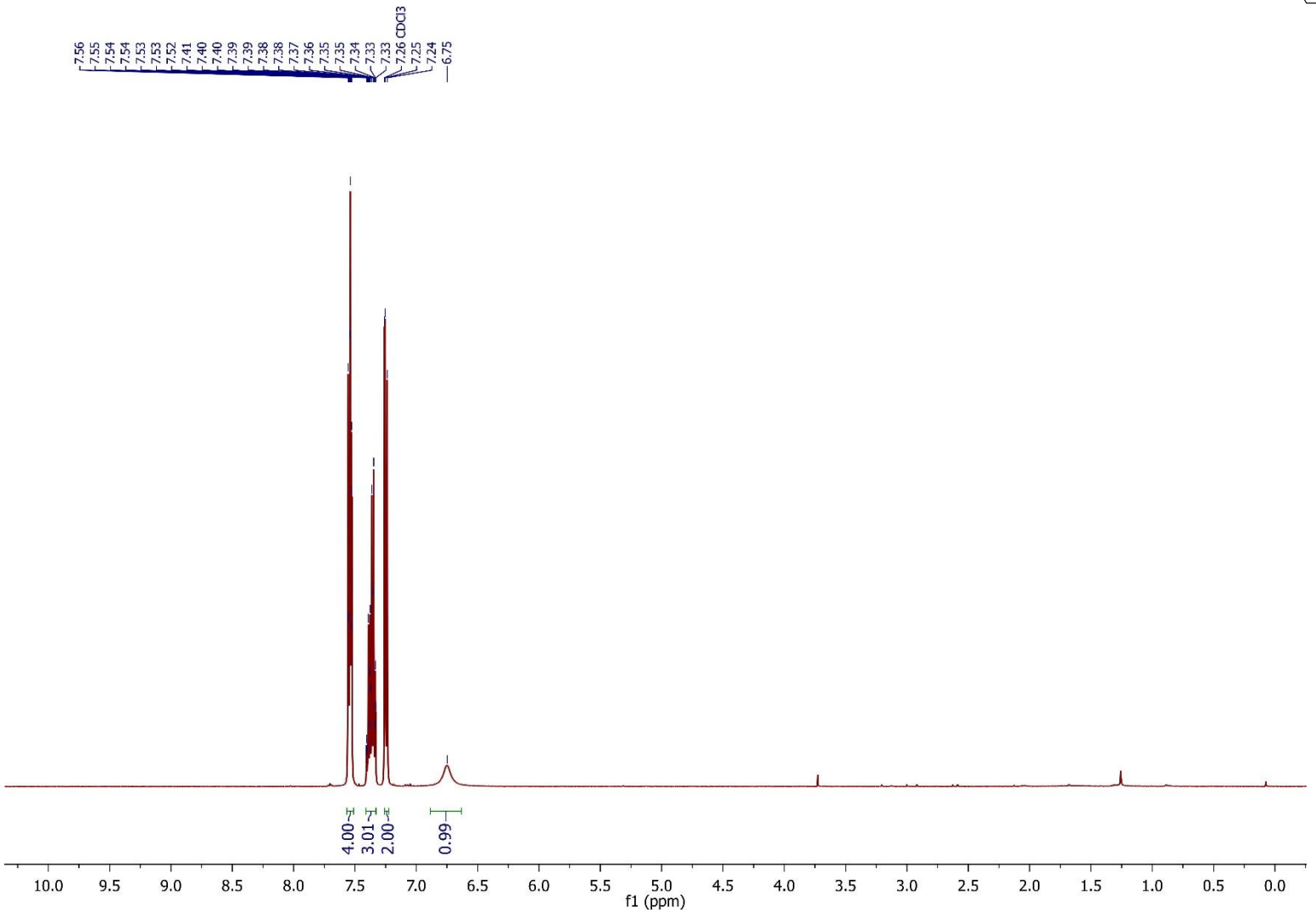
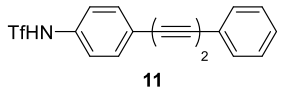


*^{19}F Spectrum of **11** (471 MHz, $CDCl_3$, ^{1}H decoupled)*



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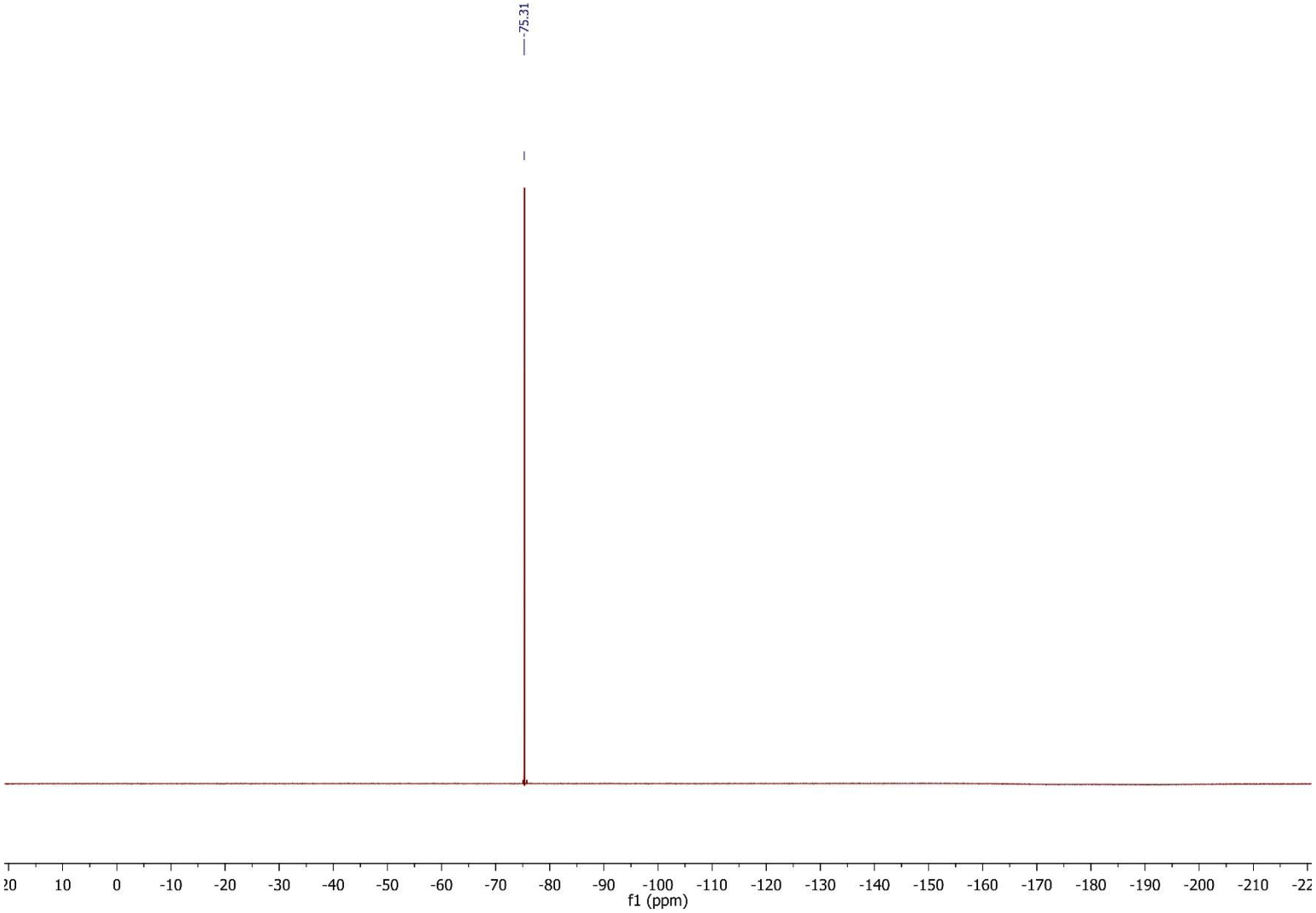
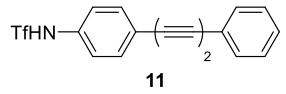


*^{13}C NMR Spectrum of **11** (126 MHz, $CDCl_3$)*



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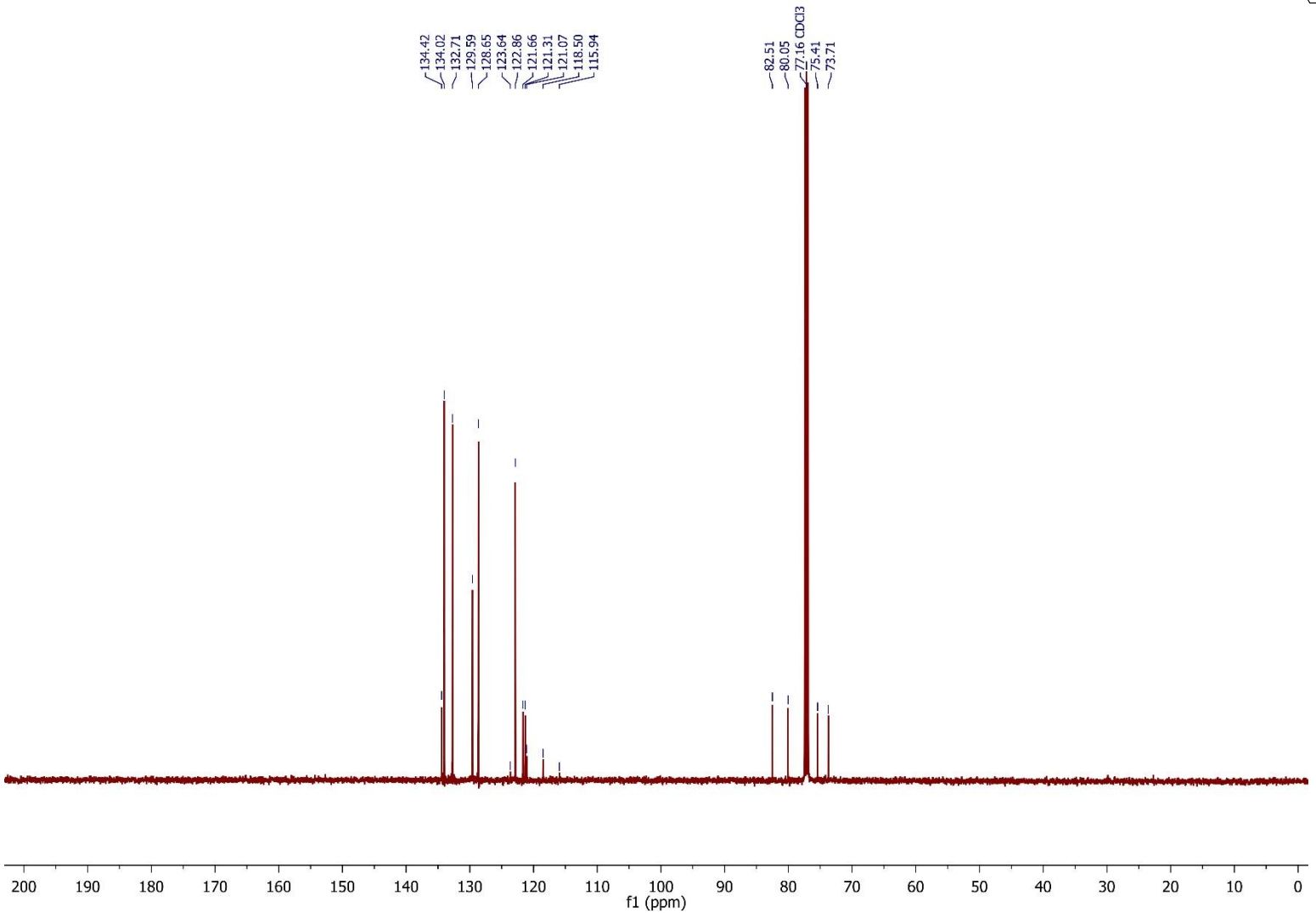
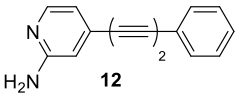


*^{1}H NMR of **12** (500 MHz, $(CD_3)_2SO$)*



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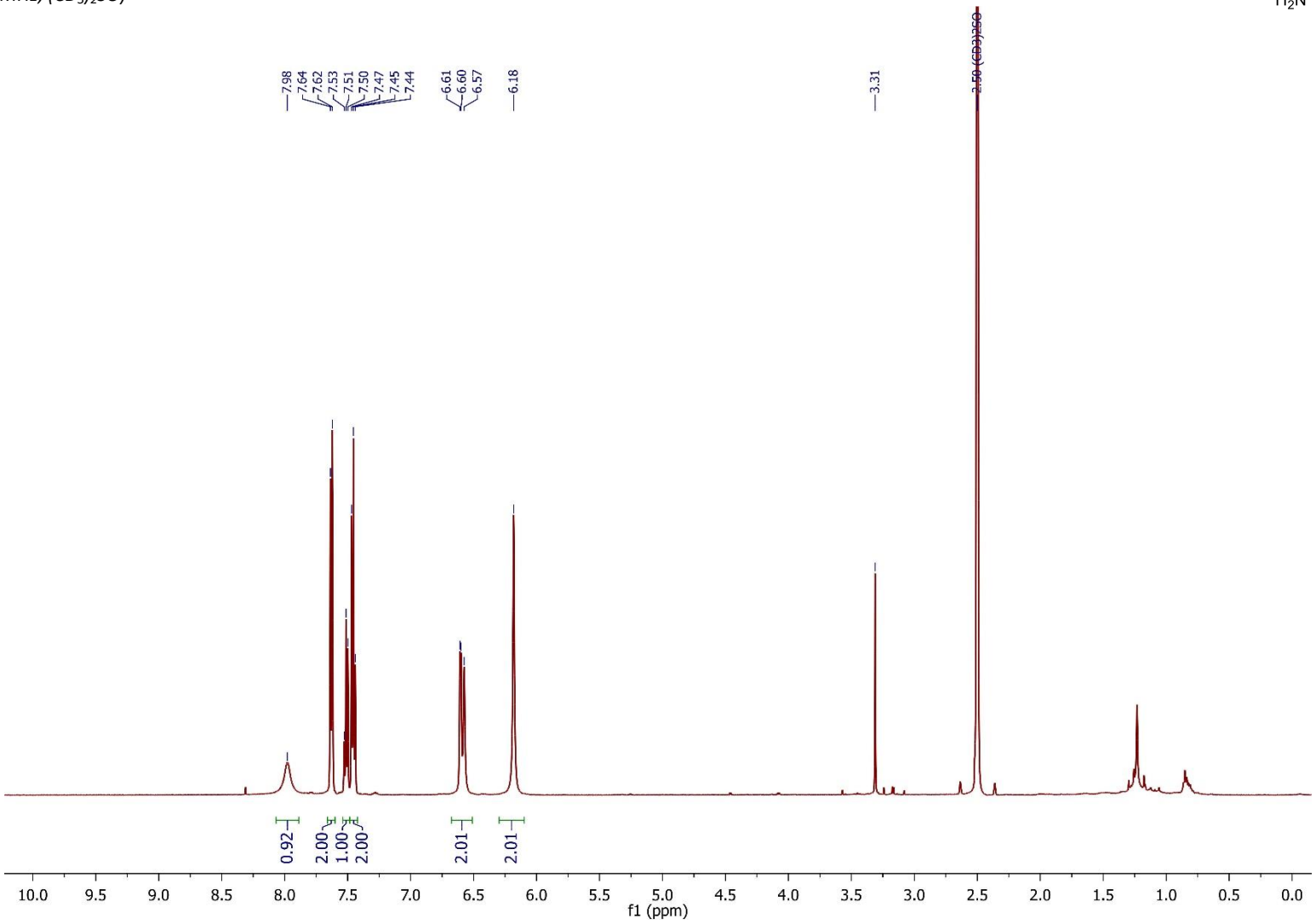
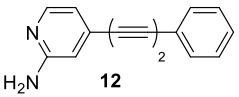


*^{13}C NMR of **12** (126 MHz, $(CD_3)_2SO$)*



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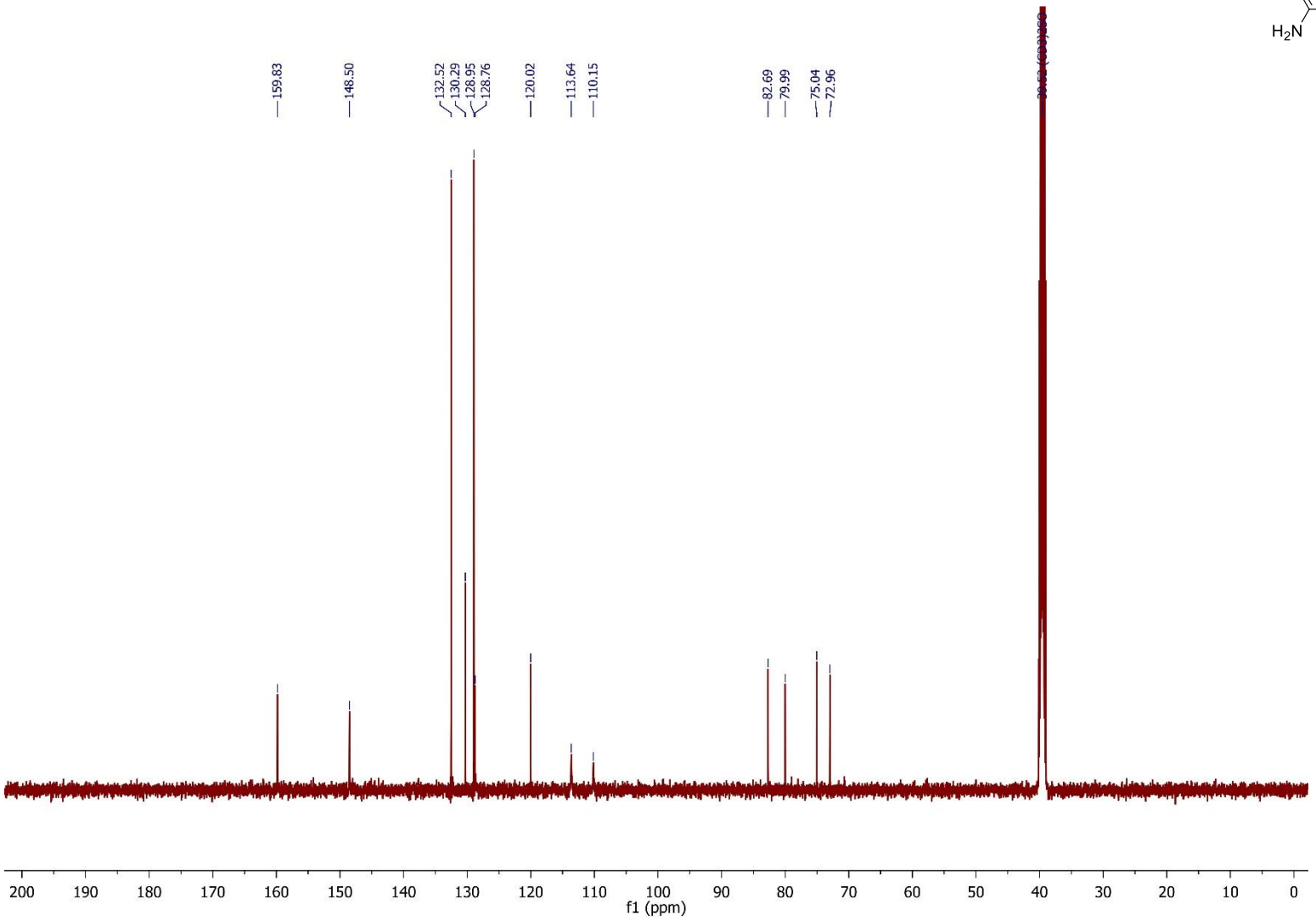
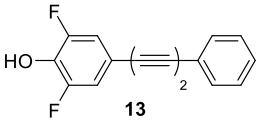


*^{1}H NMR of **13** (500 MHz, $CDCl_3$)*



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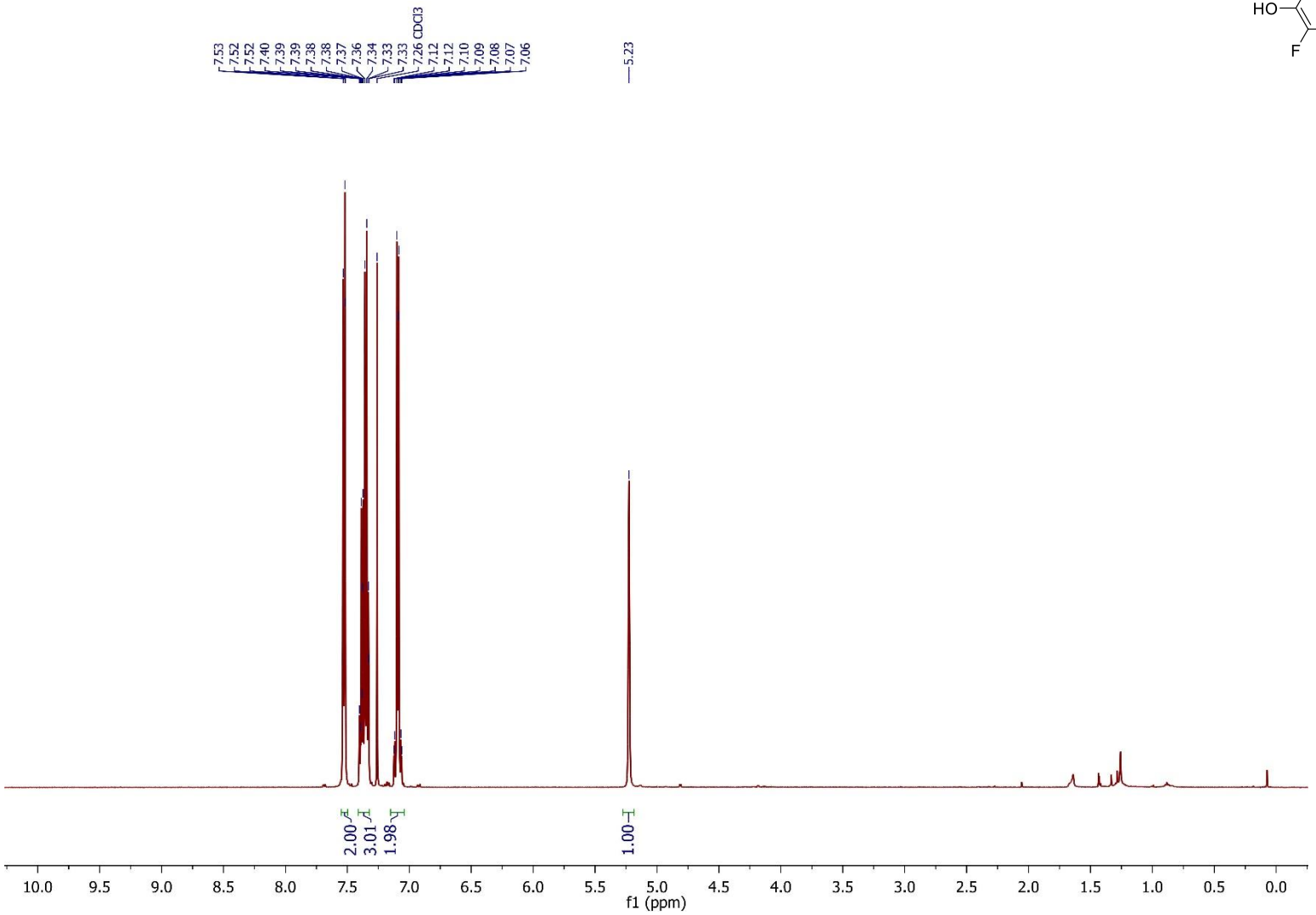
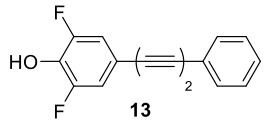


*^{19}F NMR of **13** (500 MHz, $CDCl_3$)*



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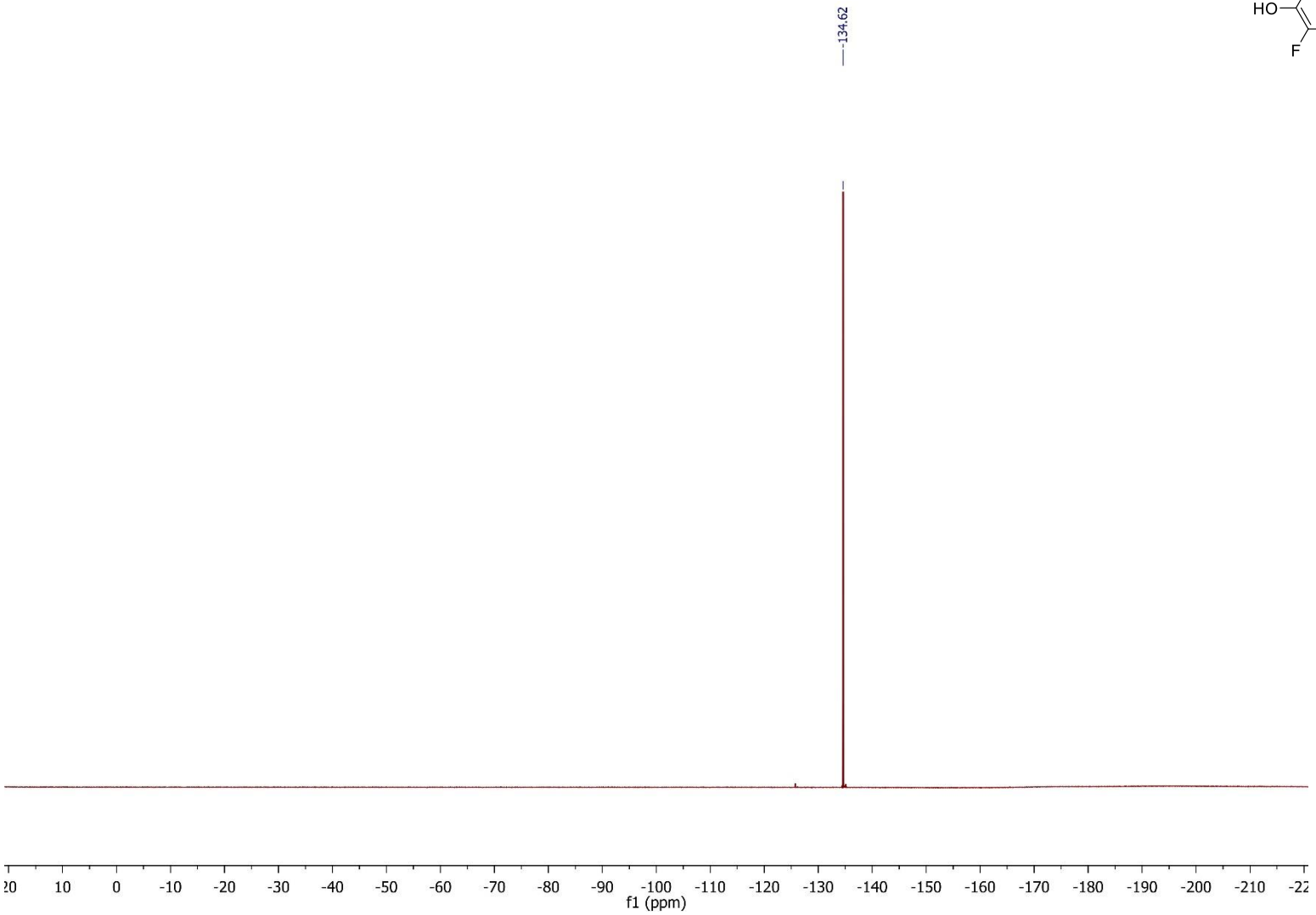
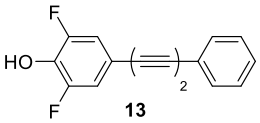
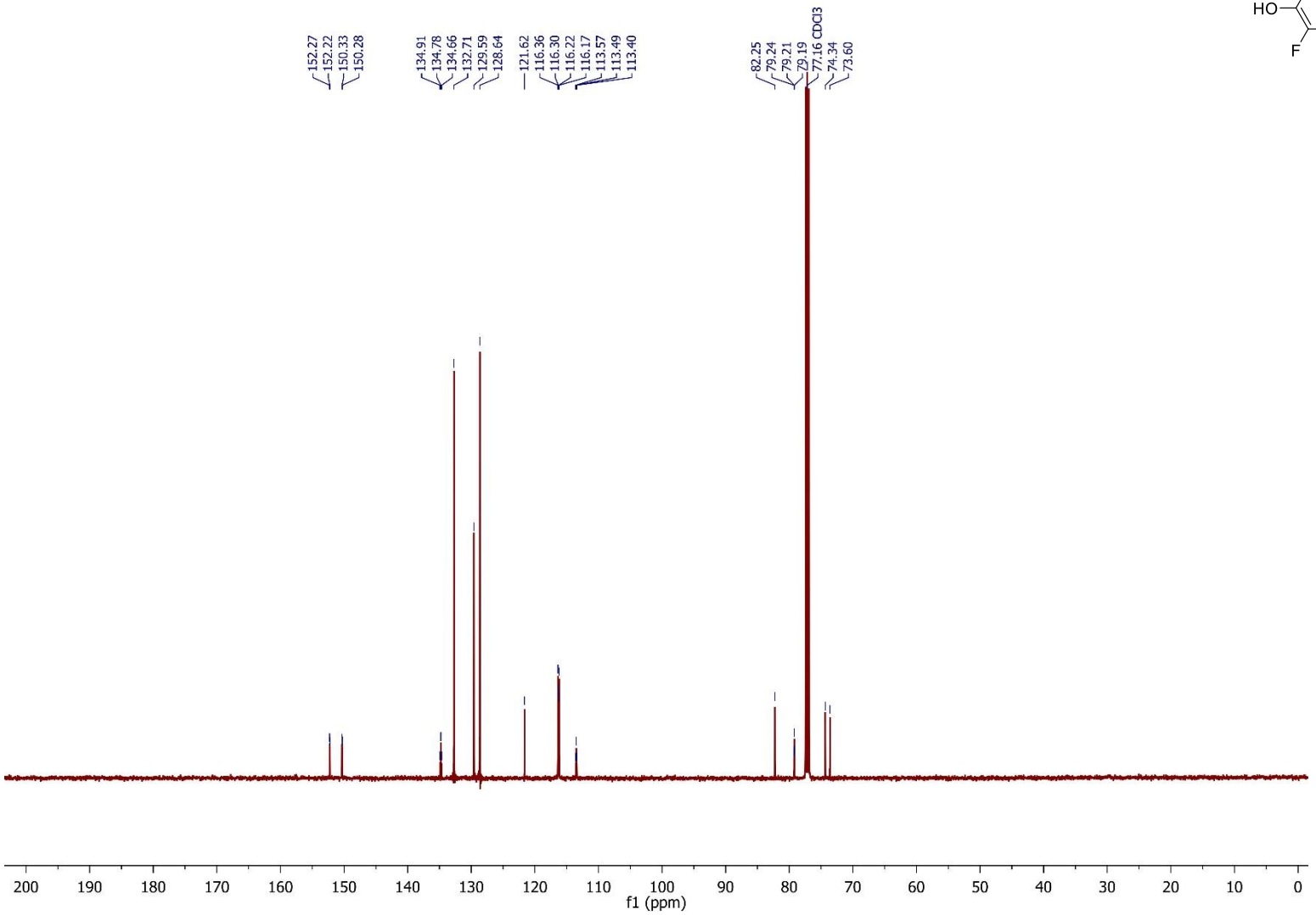
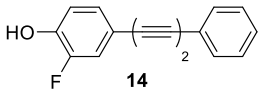


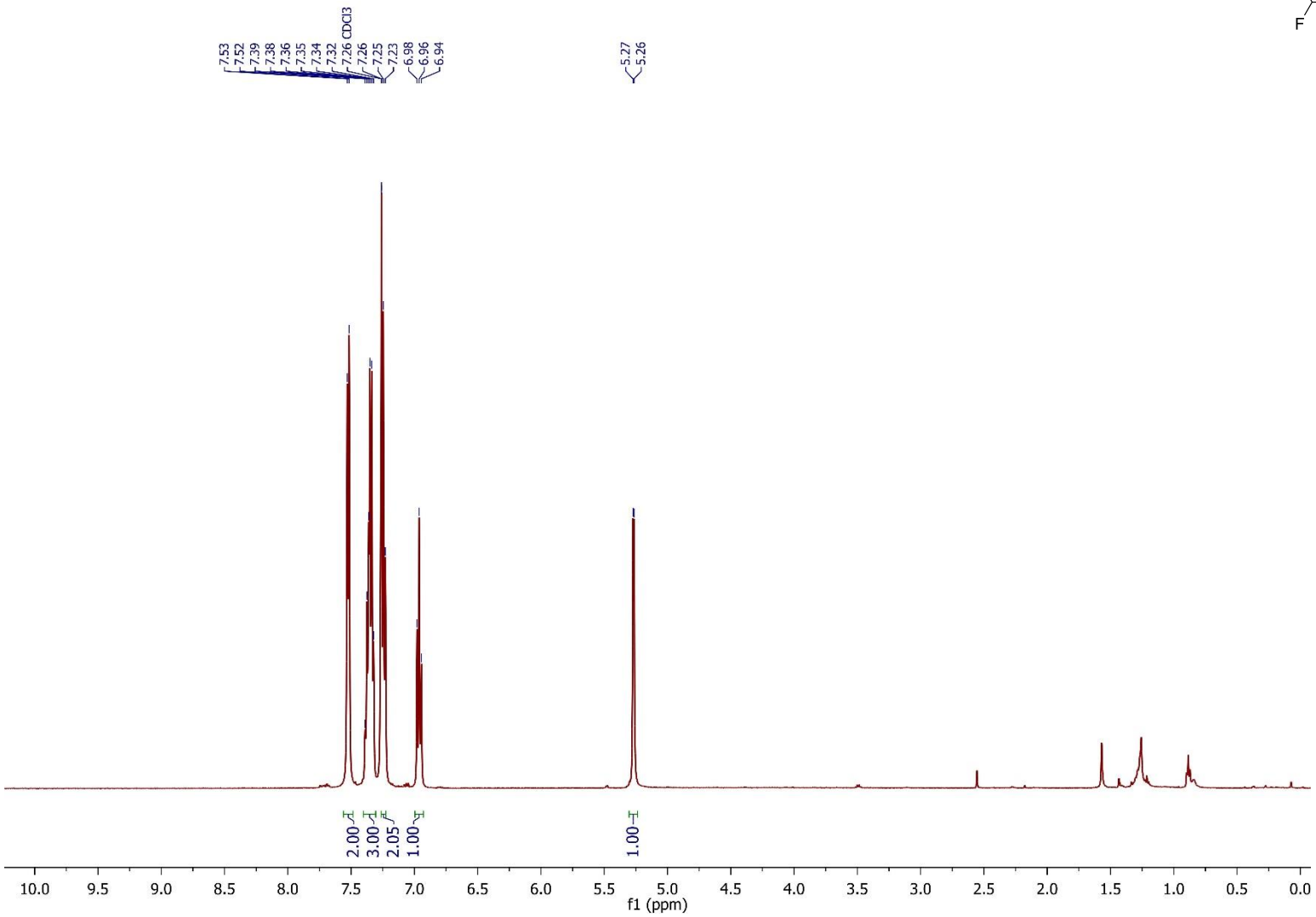
*^{13}C NMR of **13** (126 MHz, $CDCl_3$)*



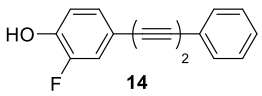


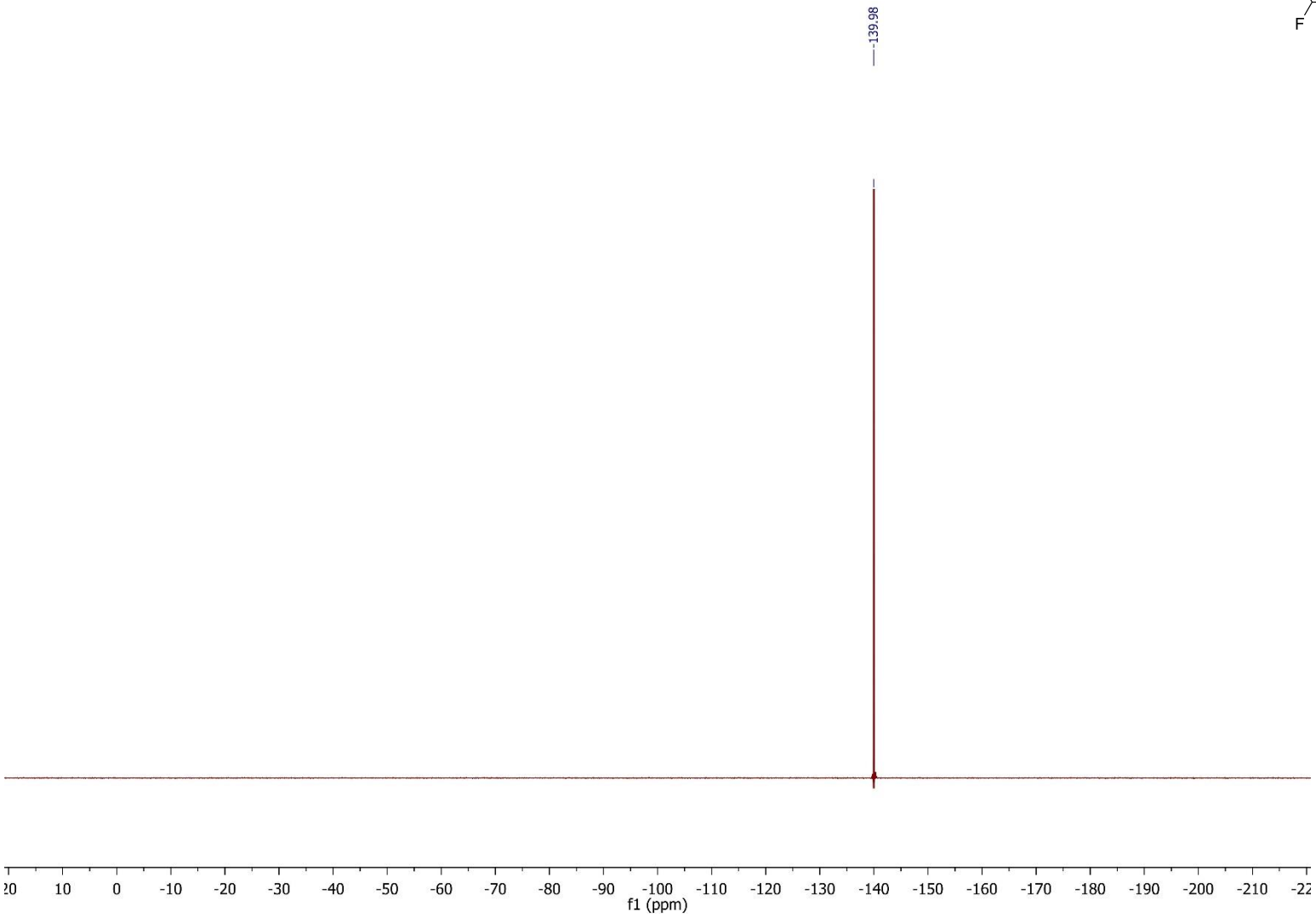
*^{1}H NMR of **14** (500 MHz, $CDCl_3$)*



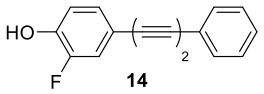


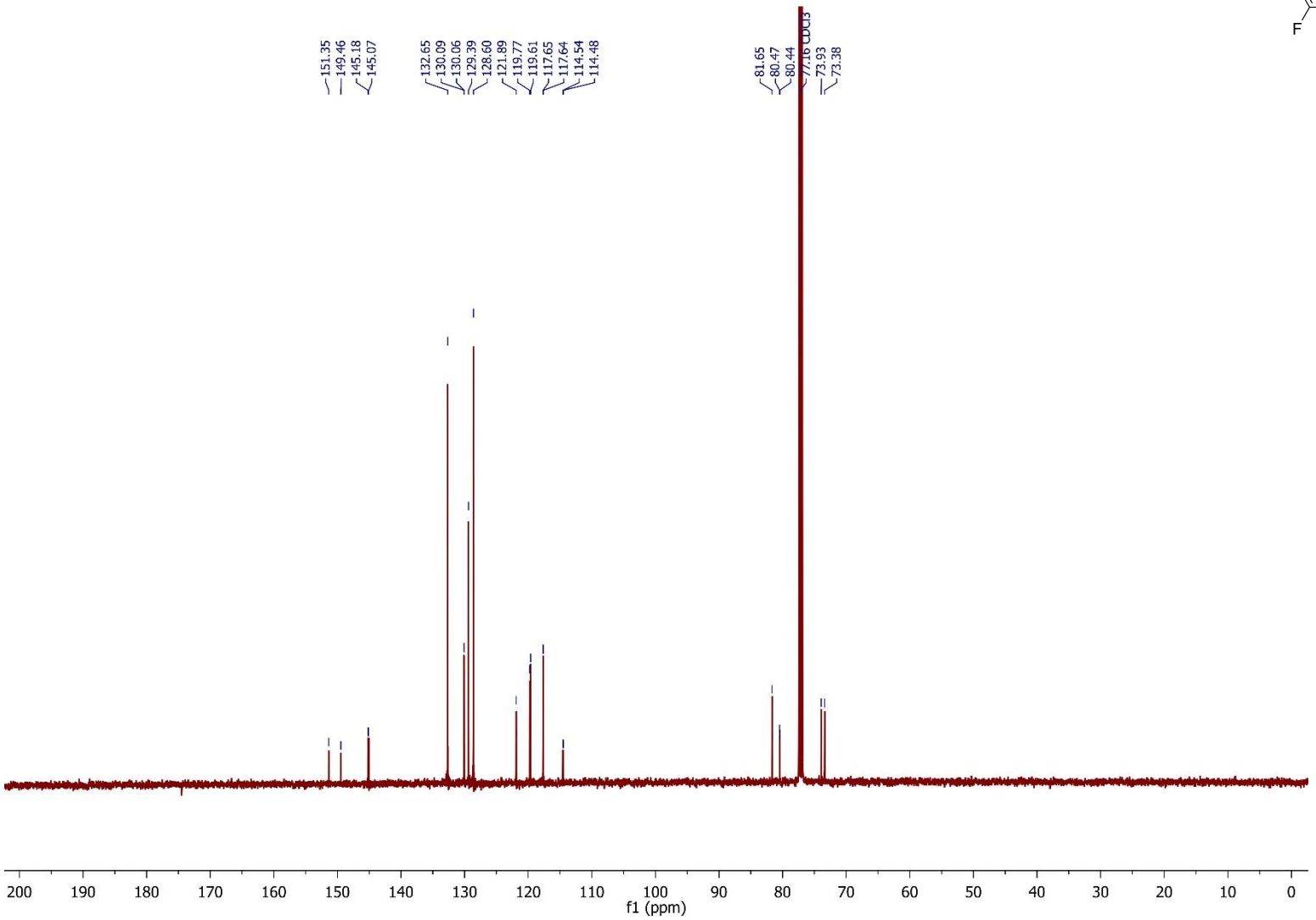
*^{19}F NMR of **14** (500 MHz, $CDCl_3$)*



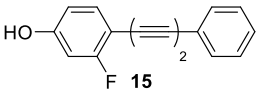


*^{13}C NMR of **14** (126 MHz, $CDCl_3$)*





*^{1}H NMR of **15** (500 MHz, $CDCl_3$)*



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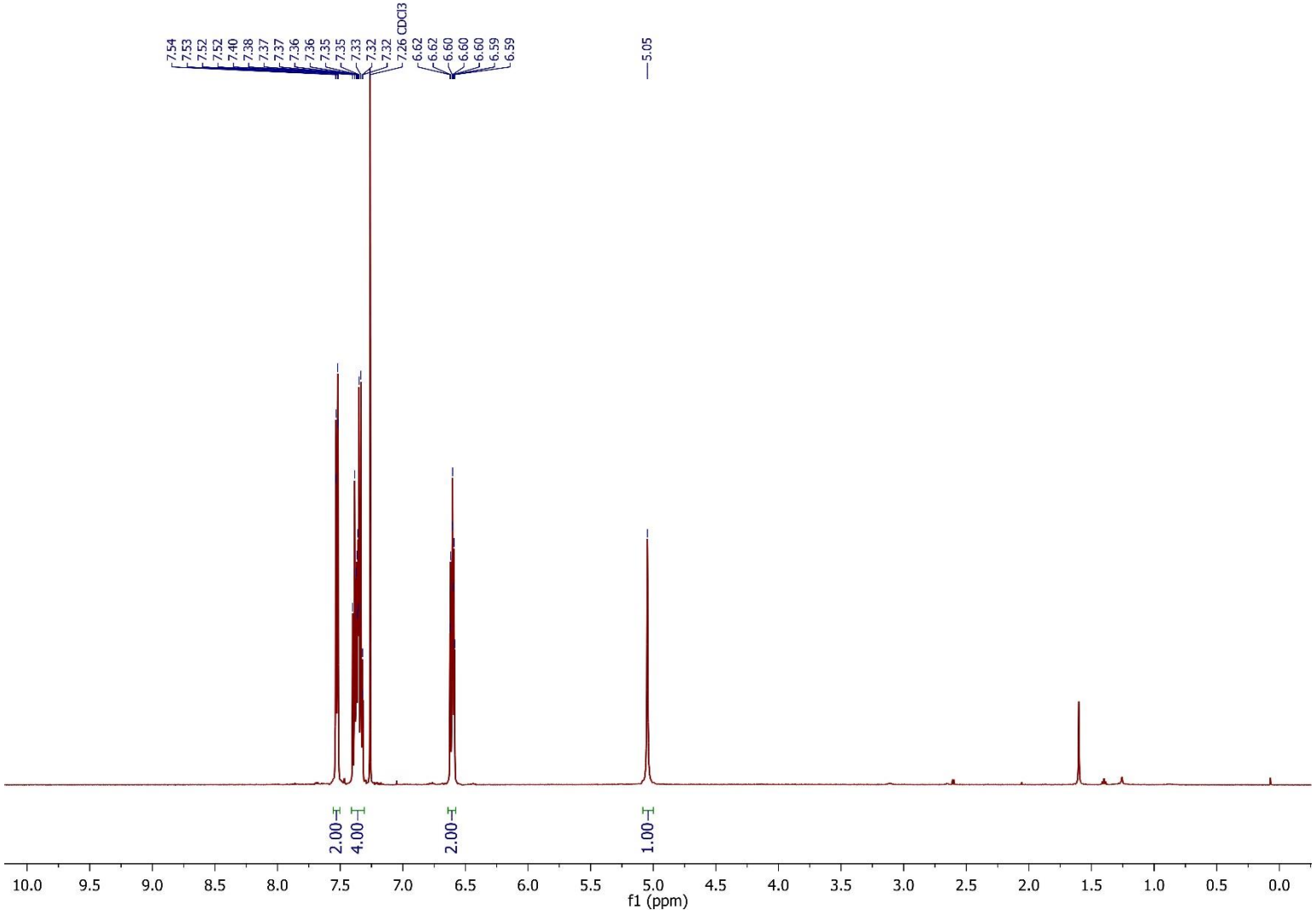
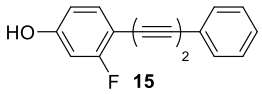
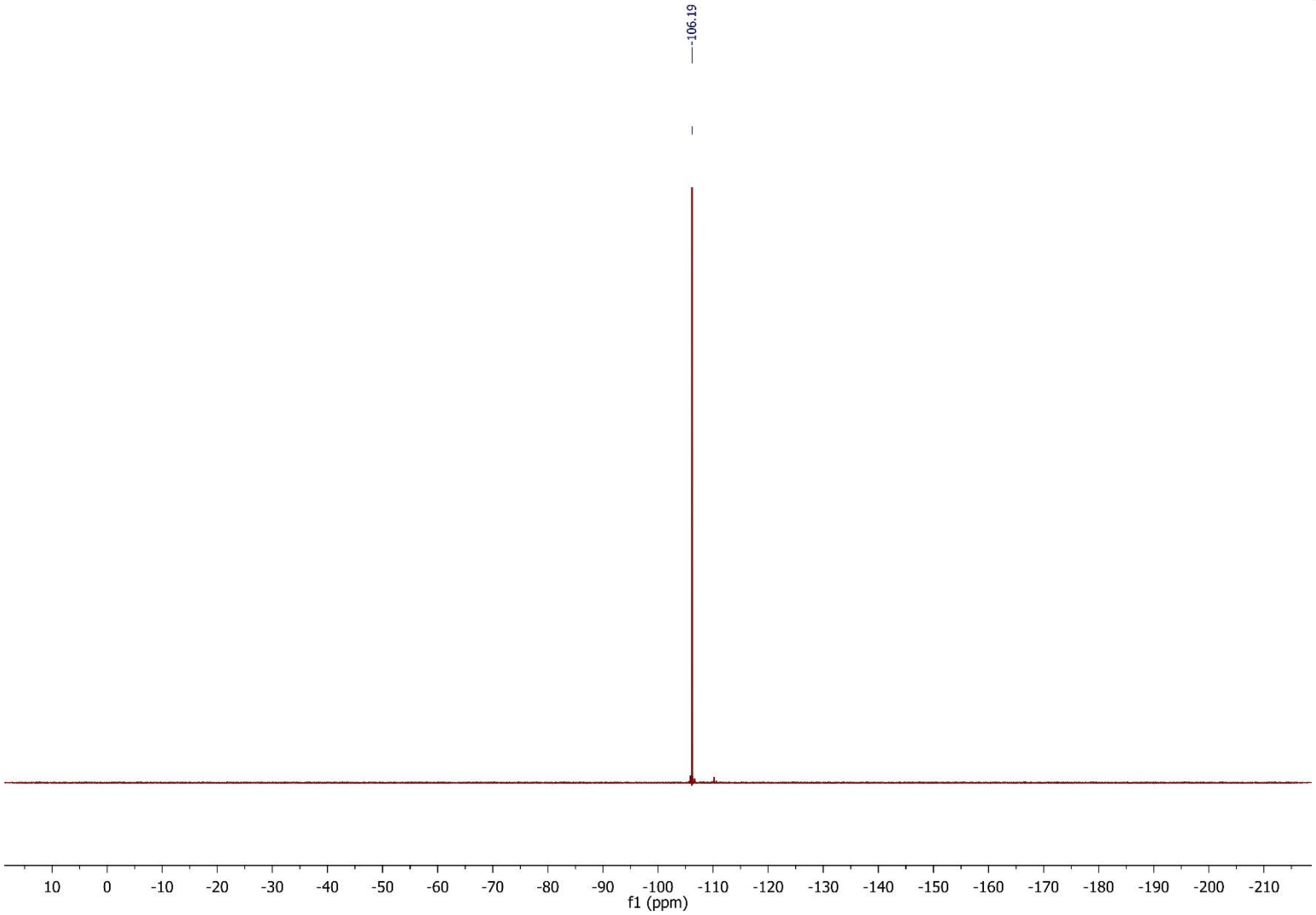
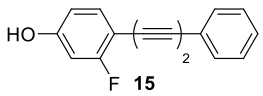


*^{19}F NMR of **15** (500 MHz, $CDCl_3$)*





*^{13}C NMR of **15** (126 MHz, $CDCl_3$)*



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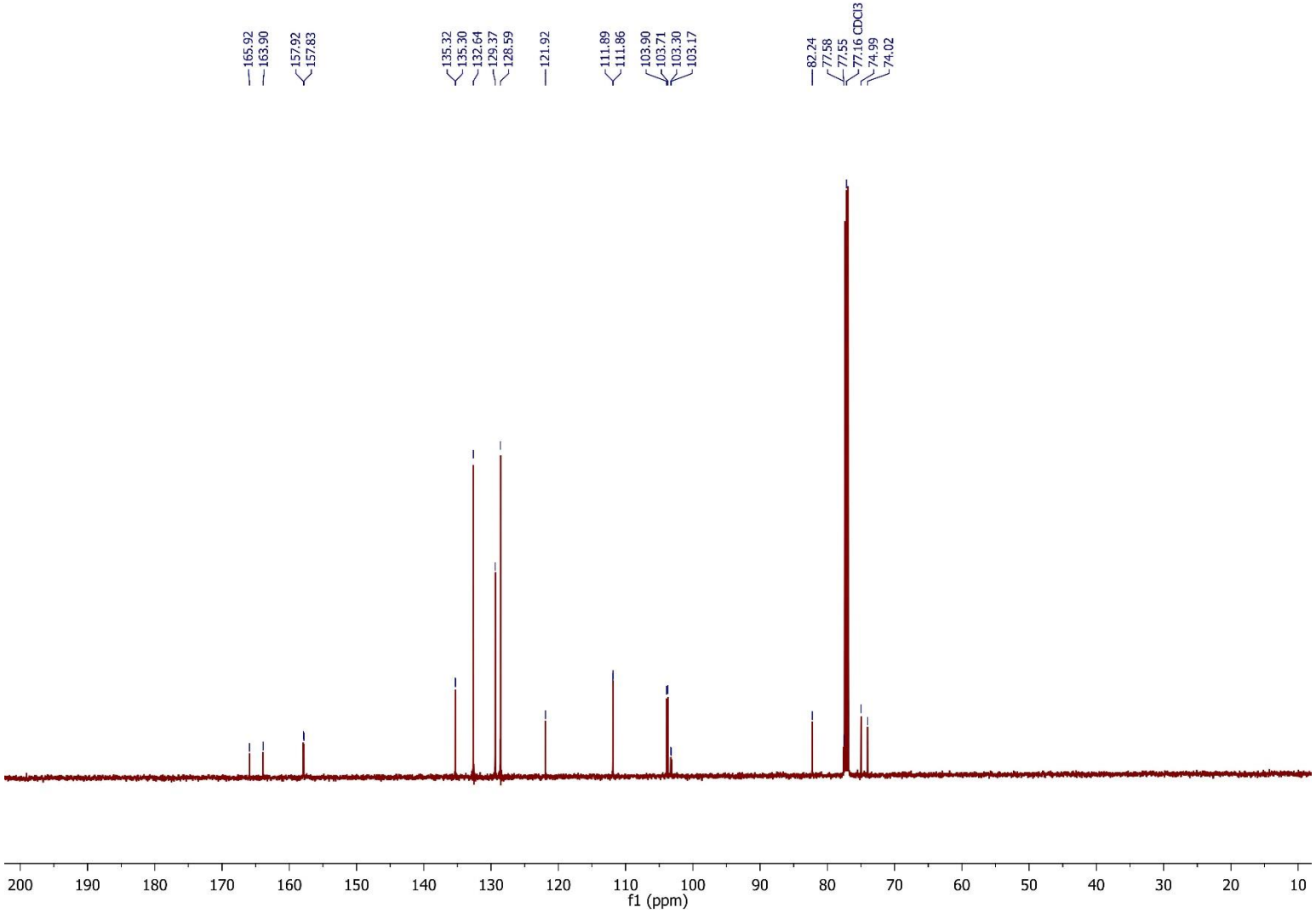
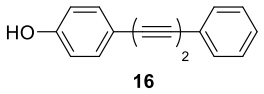


*^{1}H NMR of **16** (500 MHz, $CDCl_3$)*



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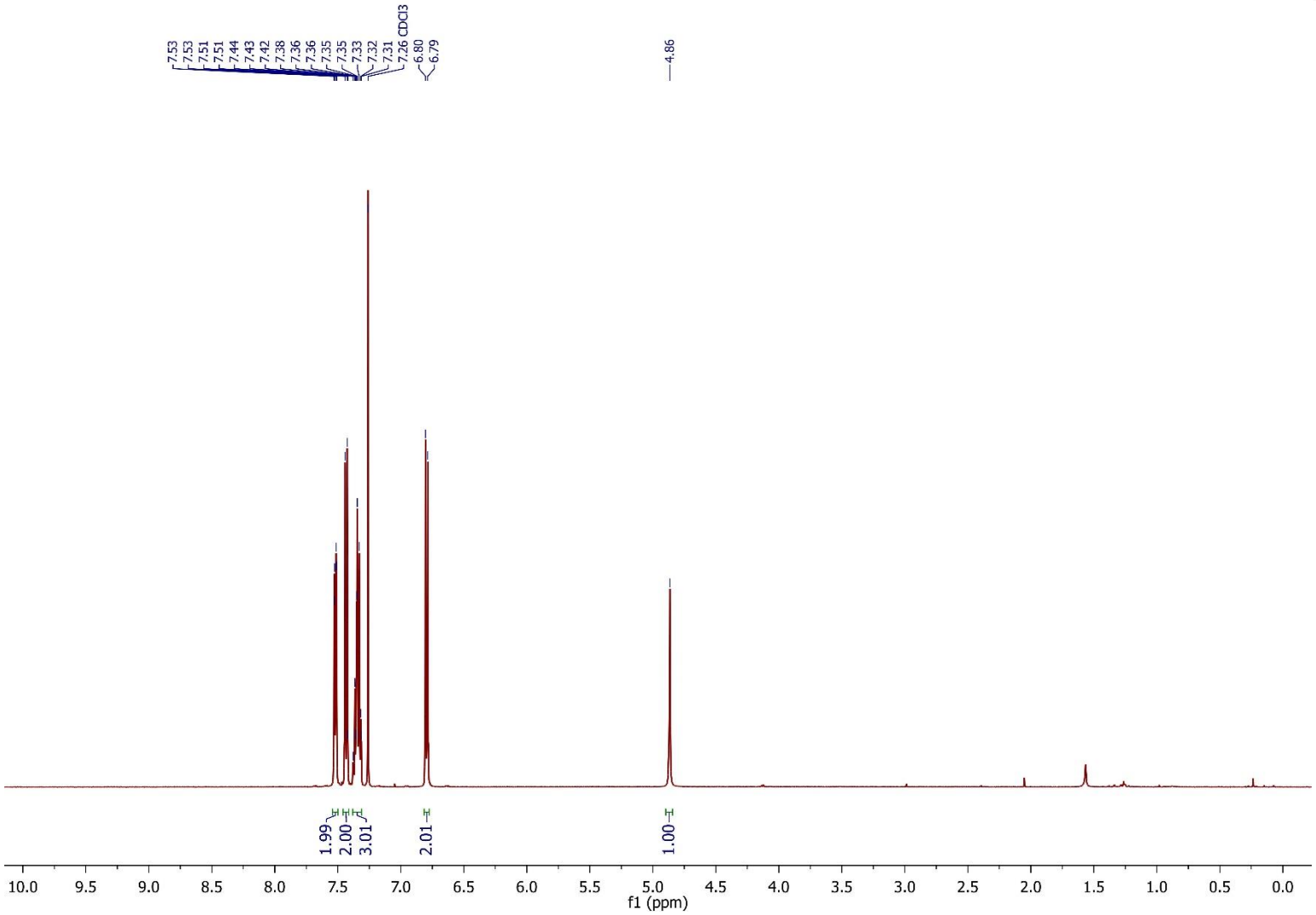
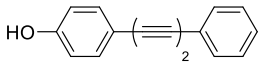


*^{13}C NMR of **16** (126 MHz, $CDCl_3$)*



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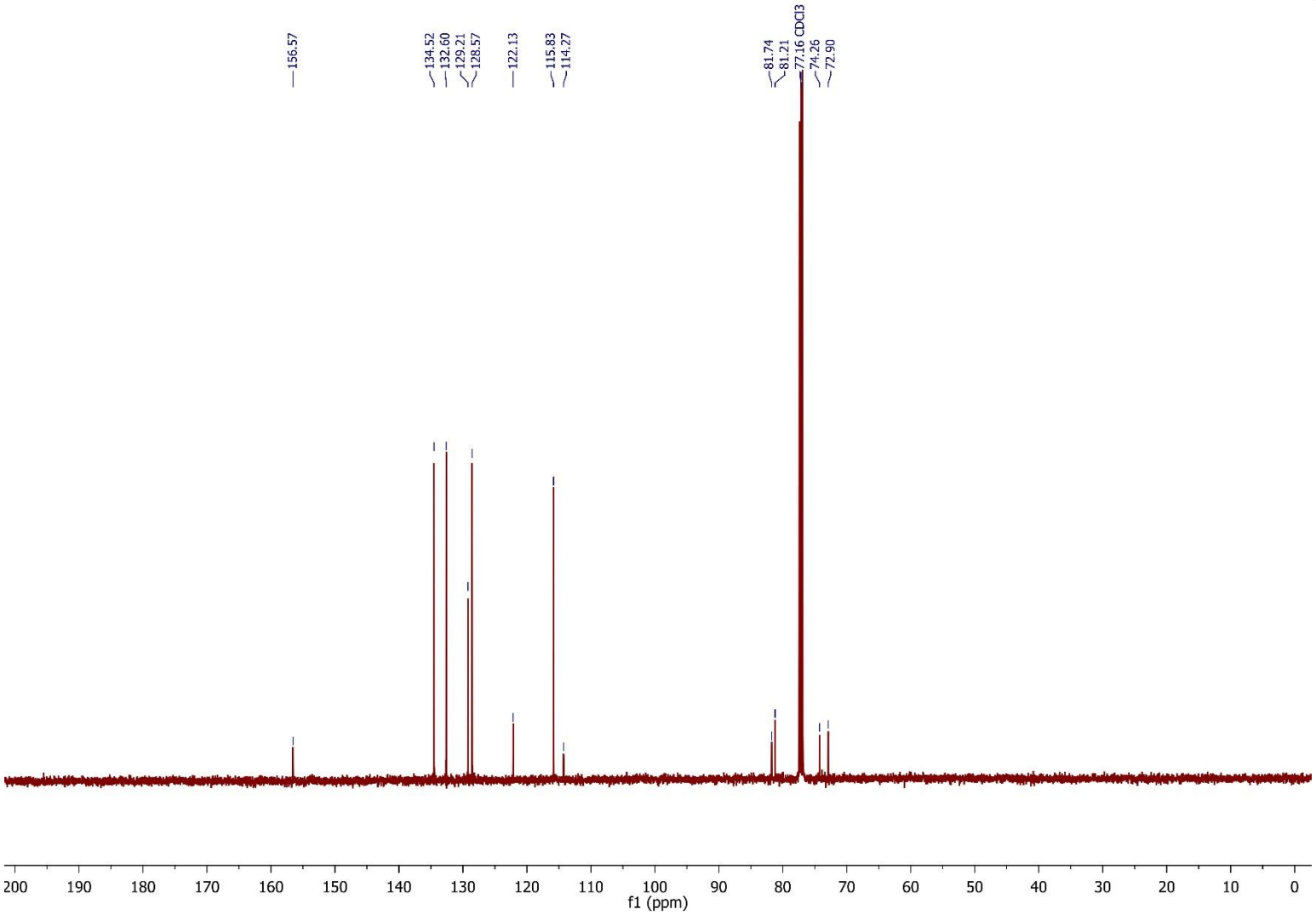
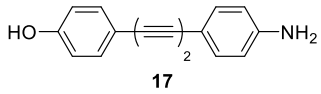


*^{1}H NMR of **17** (500 MHz, $CDCl_3$)*



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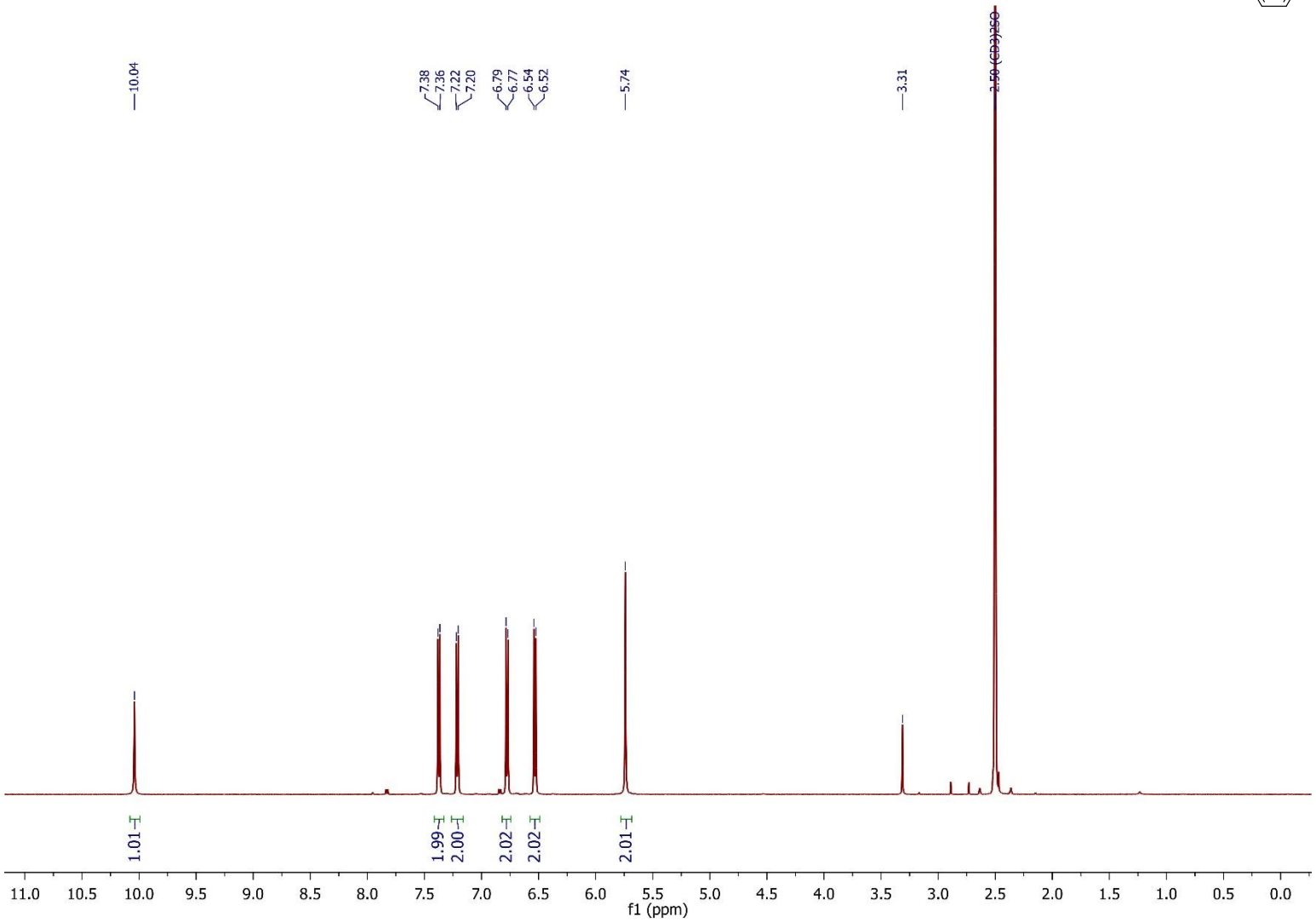
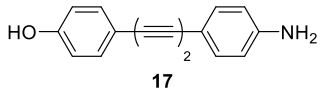


*^{13}C NMR of **17** (126 MHz, $CDCl_3$)*



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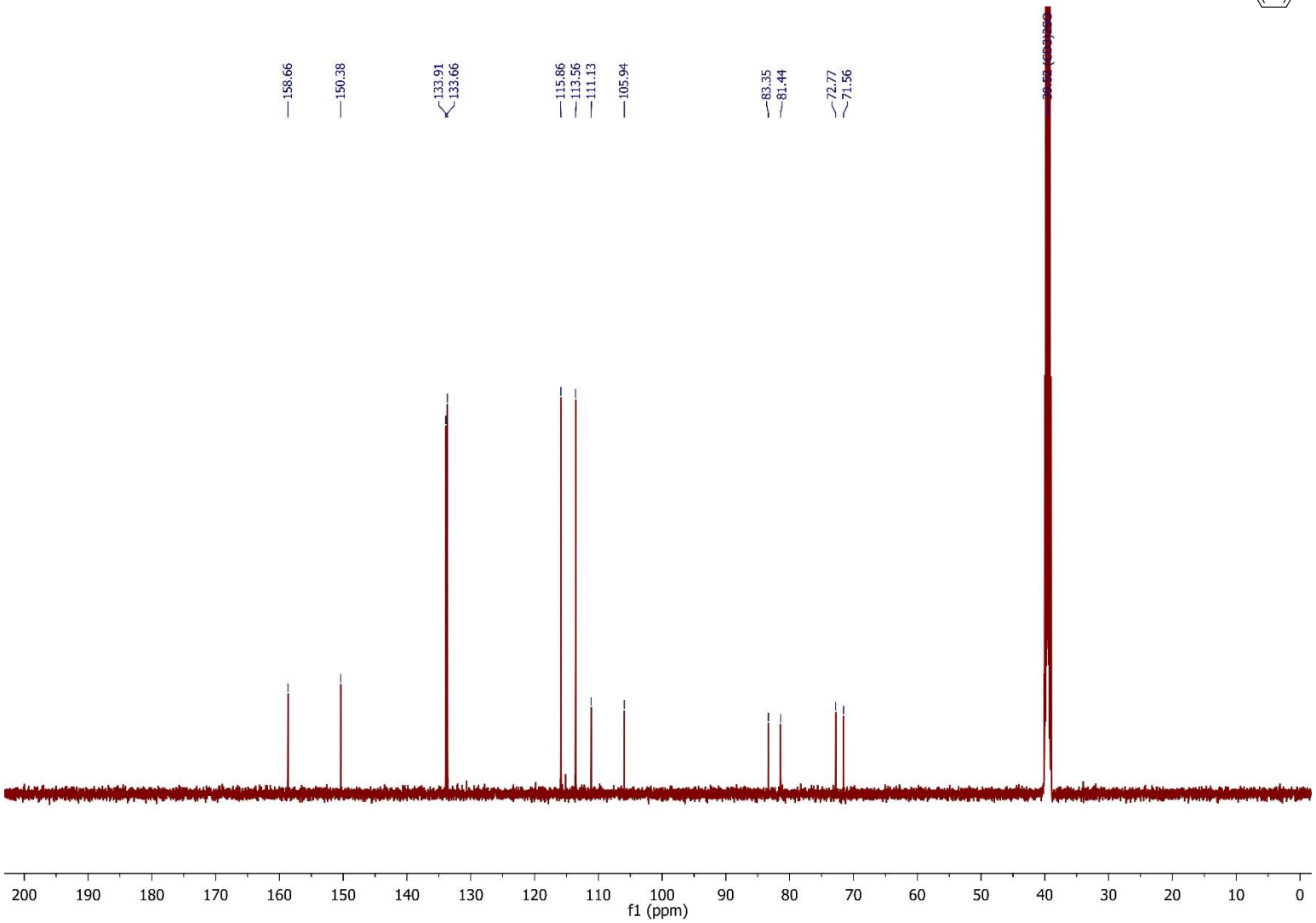
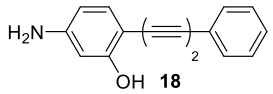
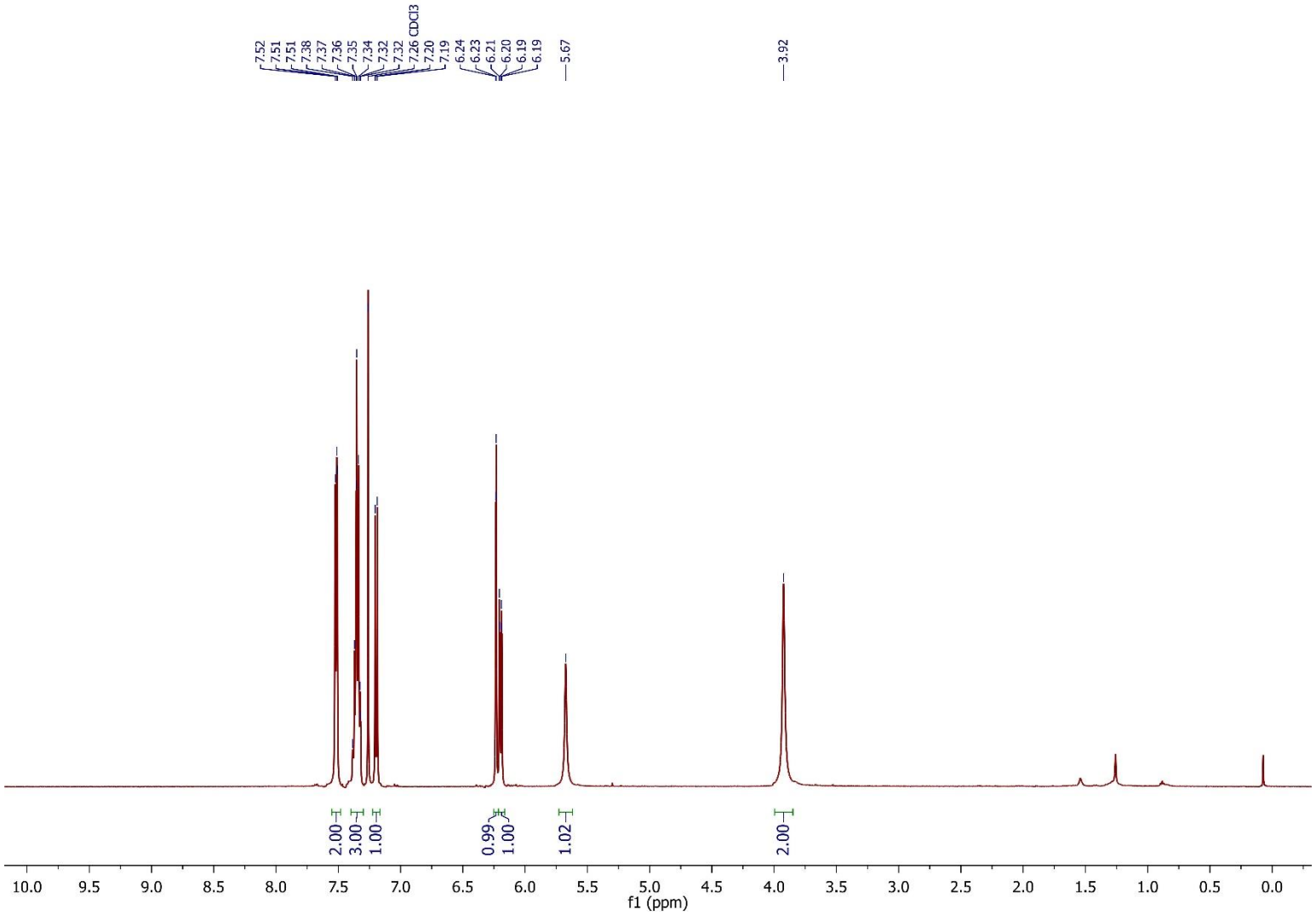
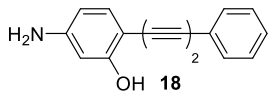


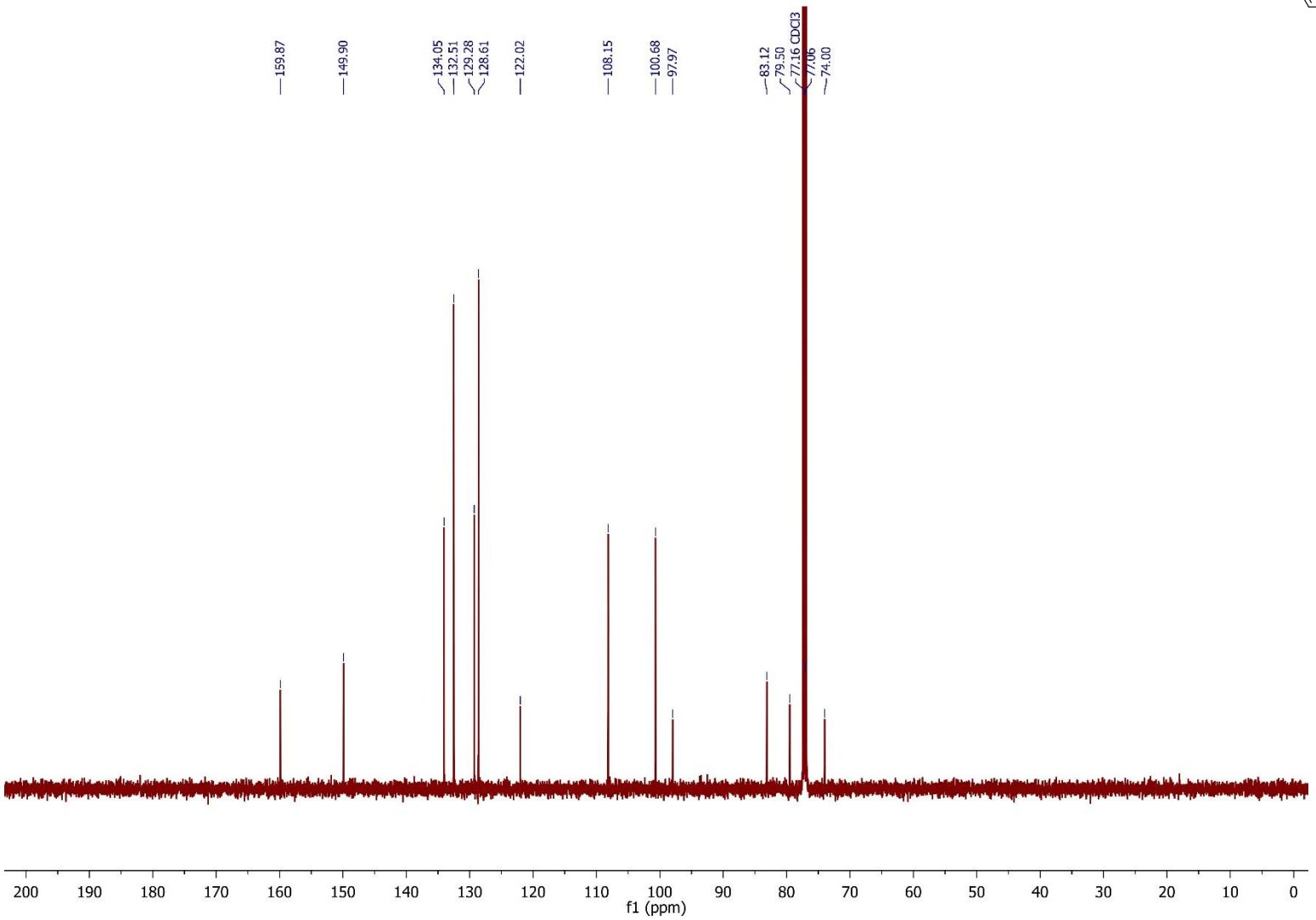
*^{1}H NMR of **18** (500 MHz, $CDCl_3$)*



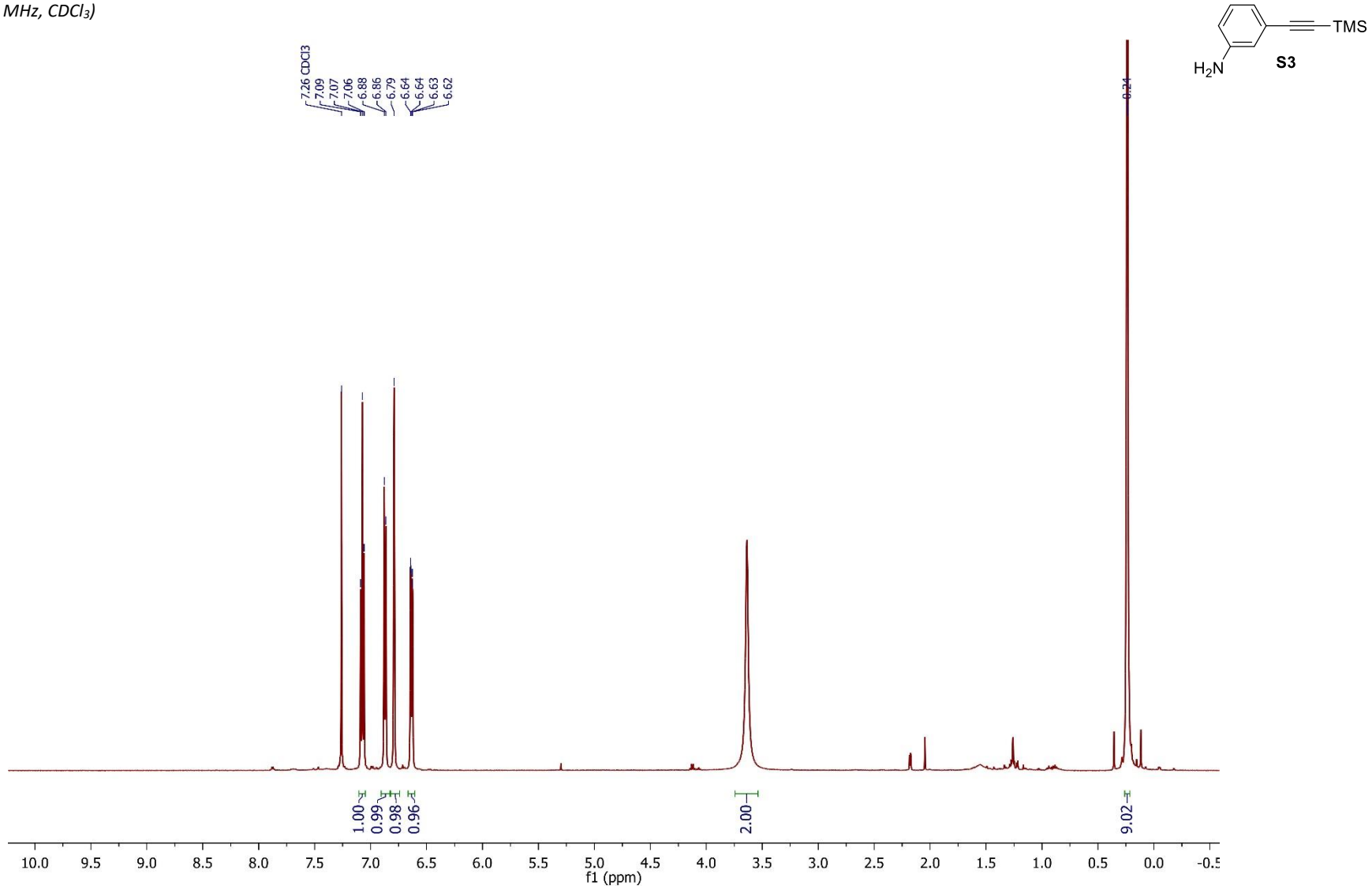


*^{13}C NMR of **18** (126 MHz, $CDCl_3$)*

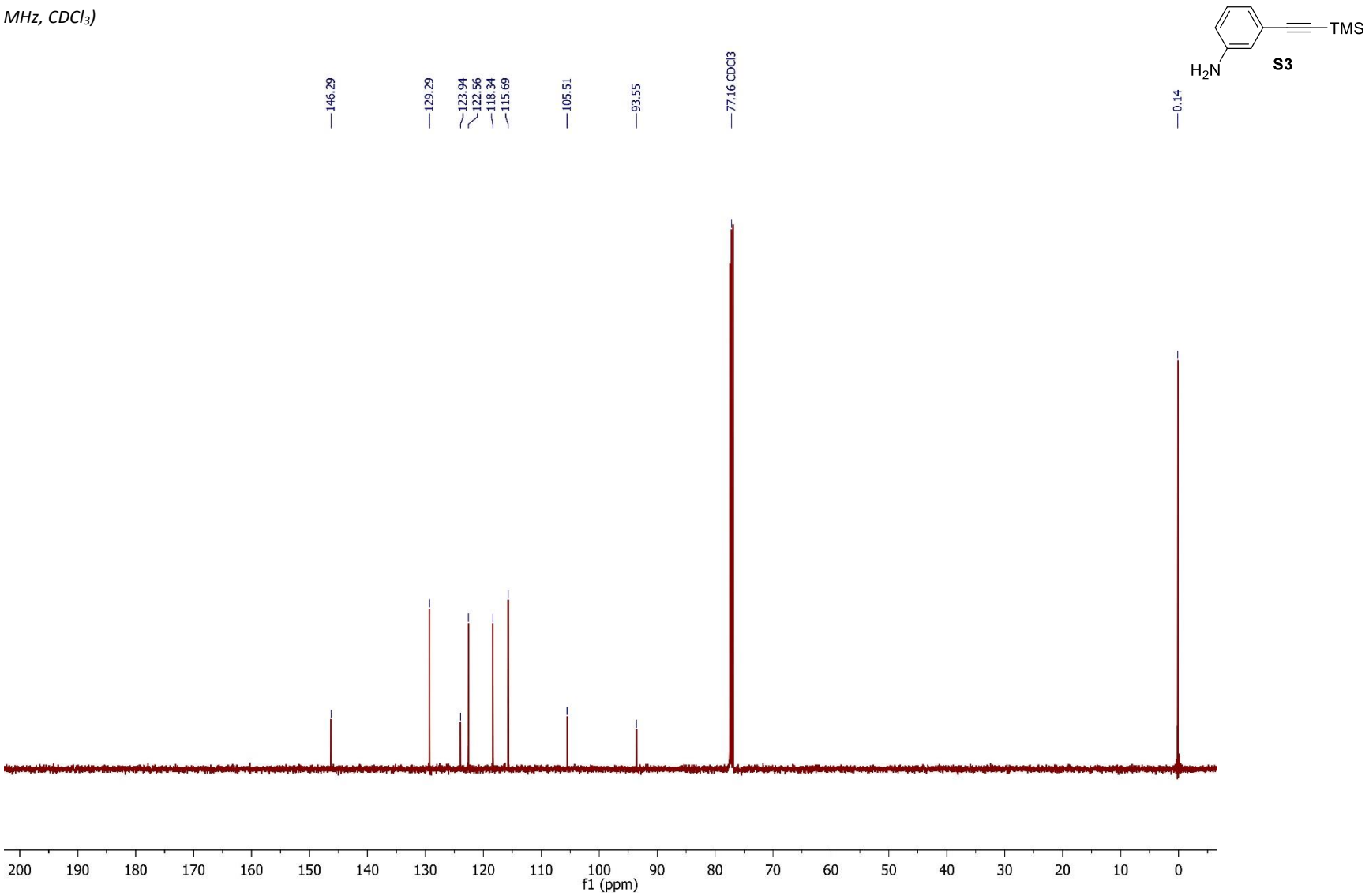




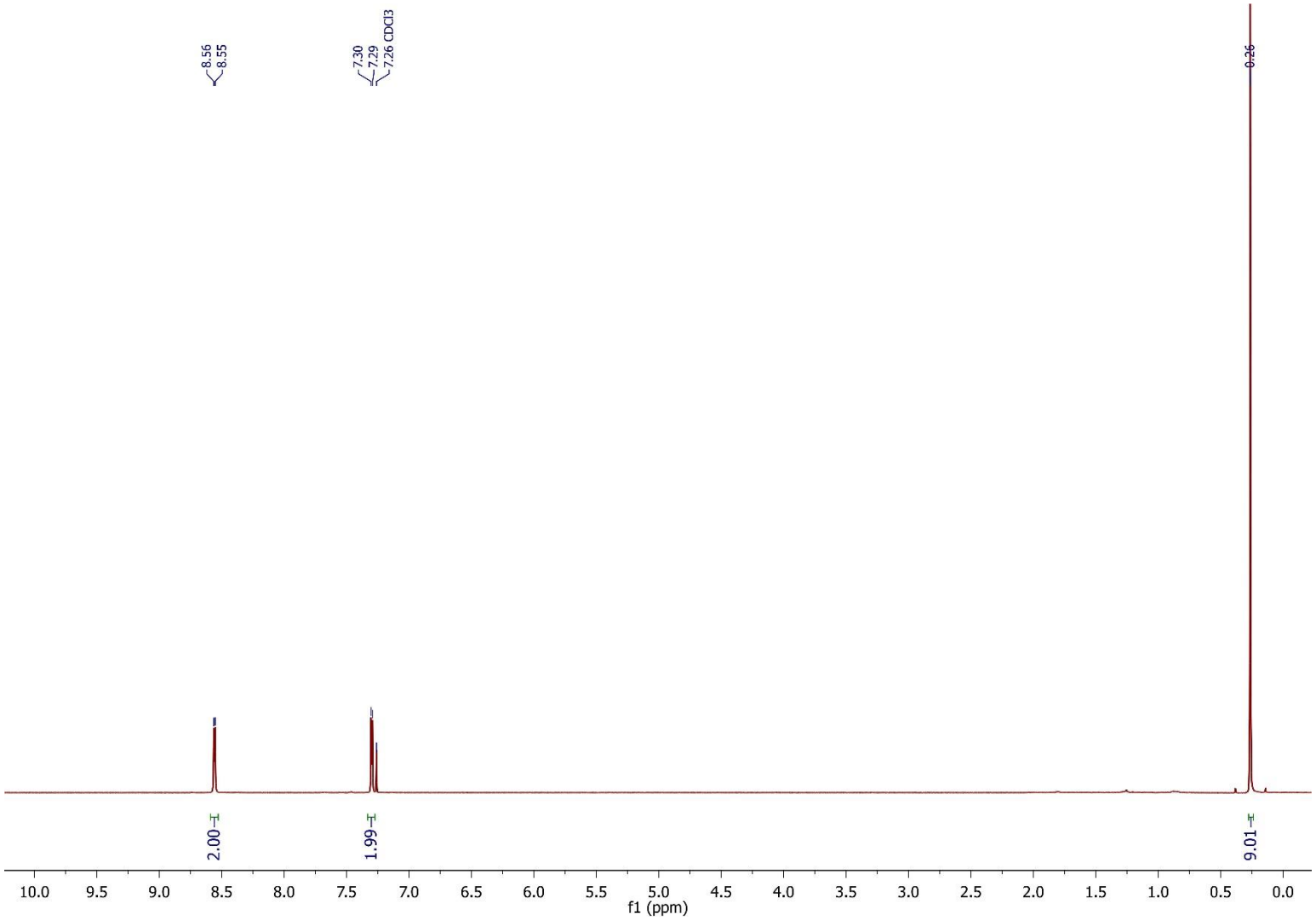
*^{1}H NMR of **S3** (500 MHz, $CDCl_3$)*

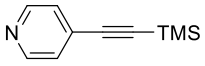


*^{13}C NMR of **S3** (126 MHz, $CDCl_3$)*



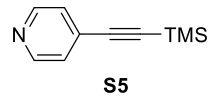
*^{1}H NMR of **S5** (500 MHz, $CDCl_3$)*



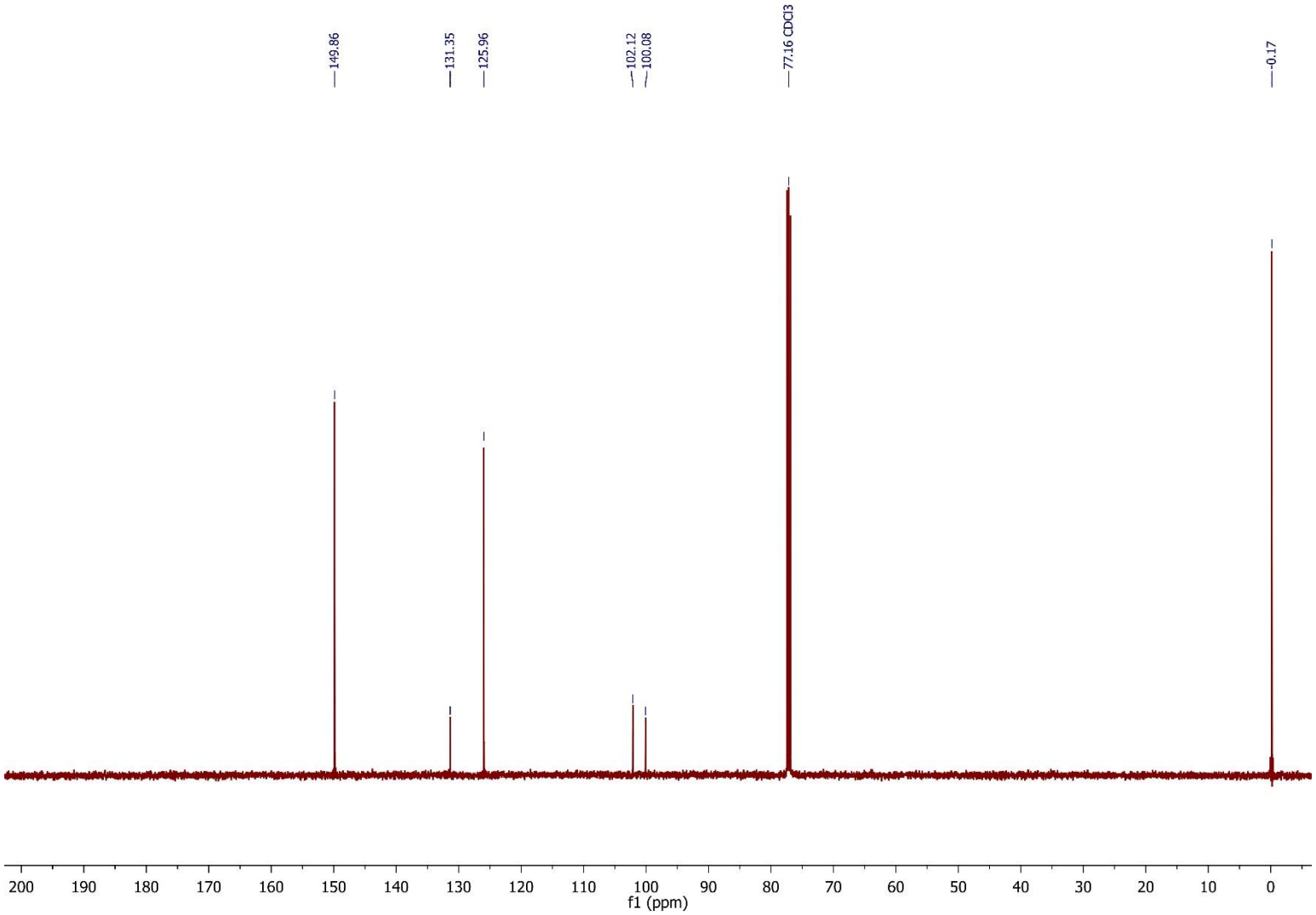


S5

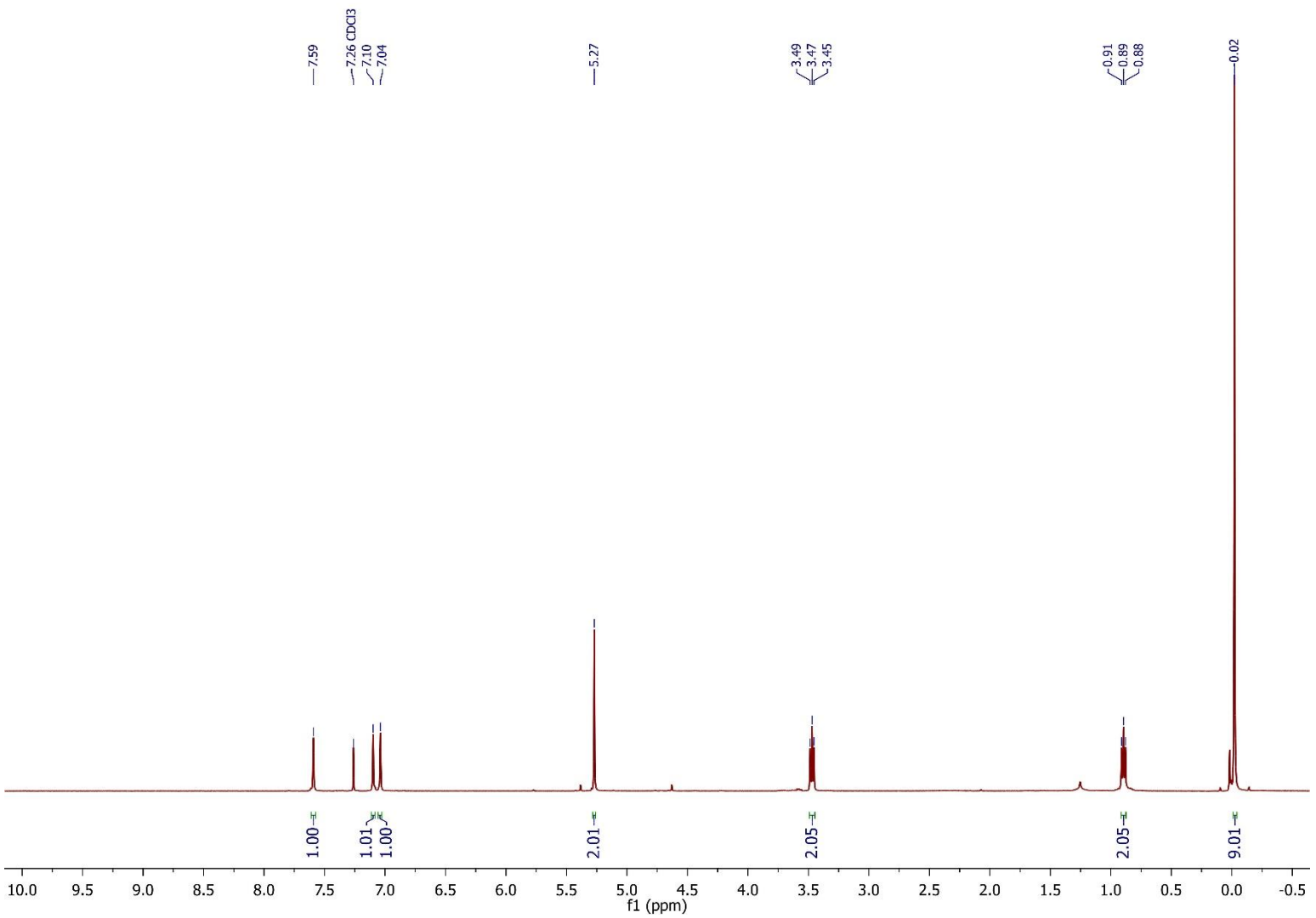
*^{13}C NMR of **S5** (126 MHz, $CDCl_3$)*



S5

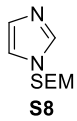


*^{1}H NMR of **S8** (500 MHz, $CDCl_3$)*

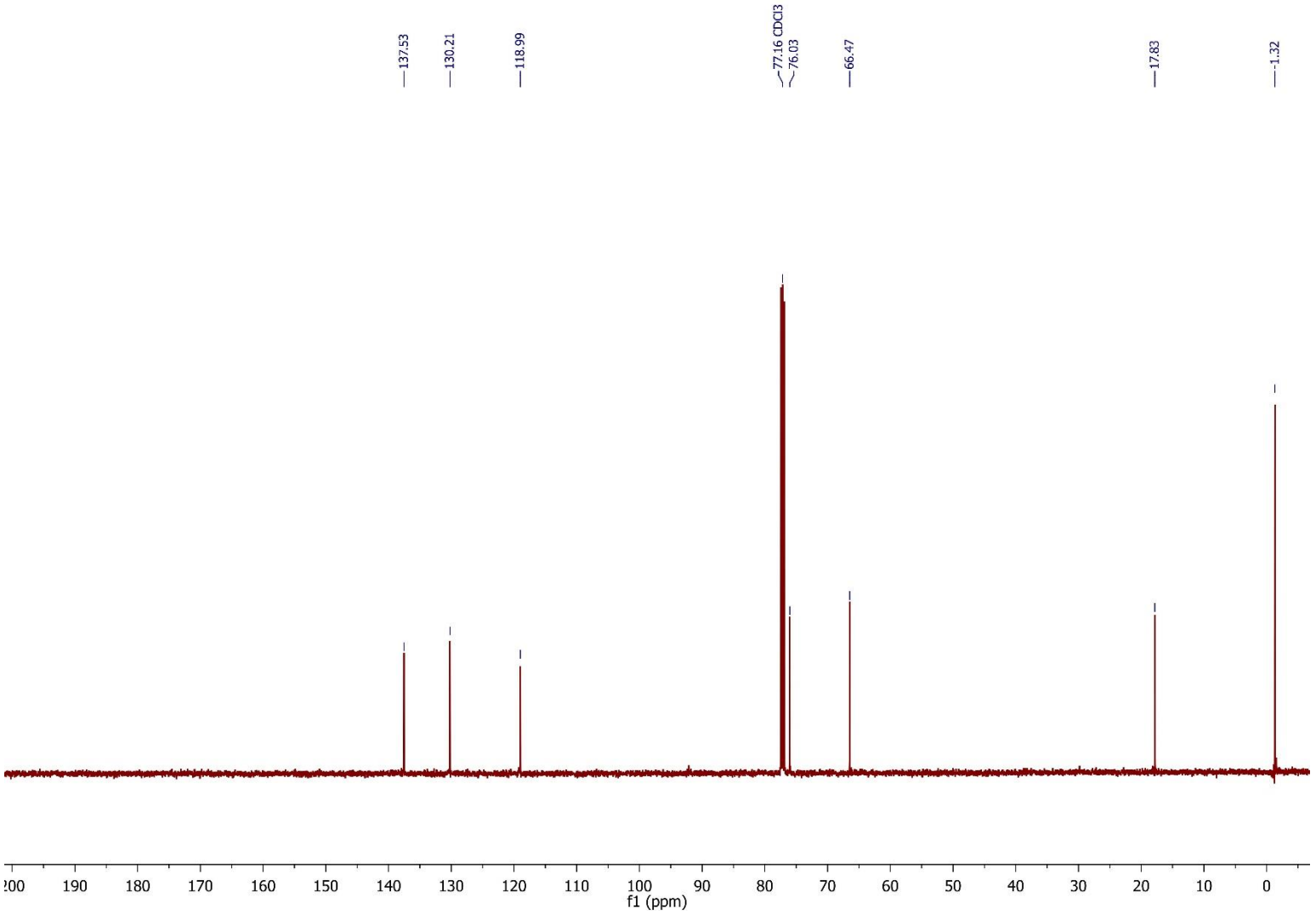


S8

*^{13}C NMR of **S8** (126 MHz, $CDCl_3$)*

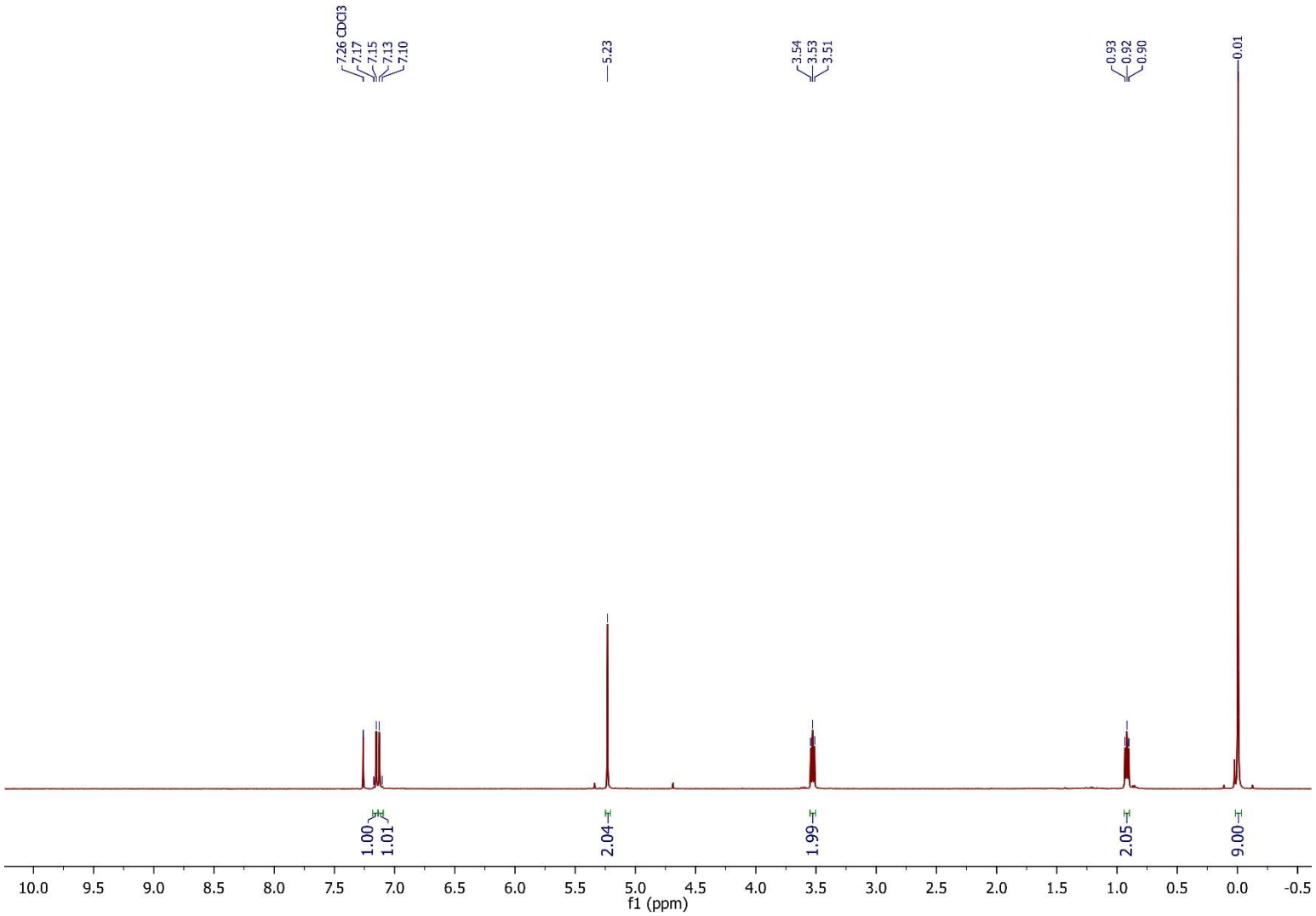


S8

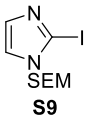


*^{1}H NMR of **S9** (500 MHz, $CDCl_3$)*

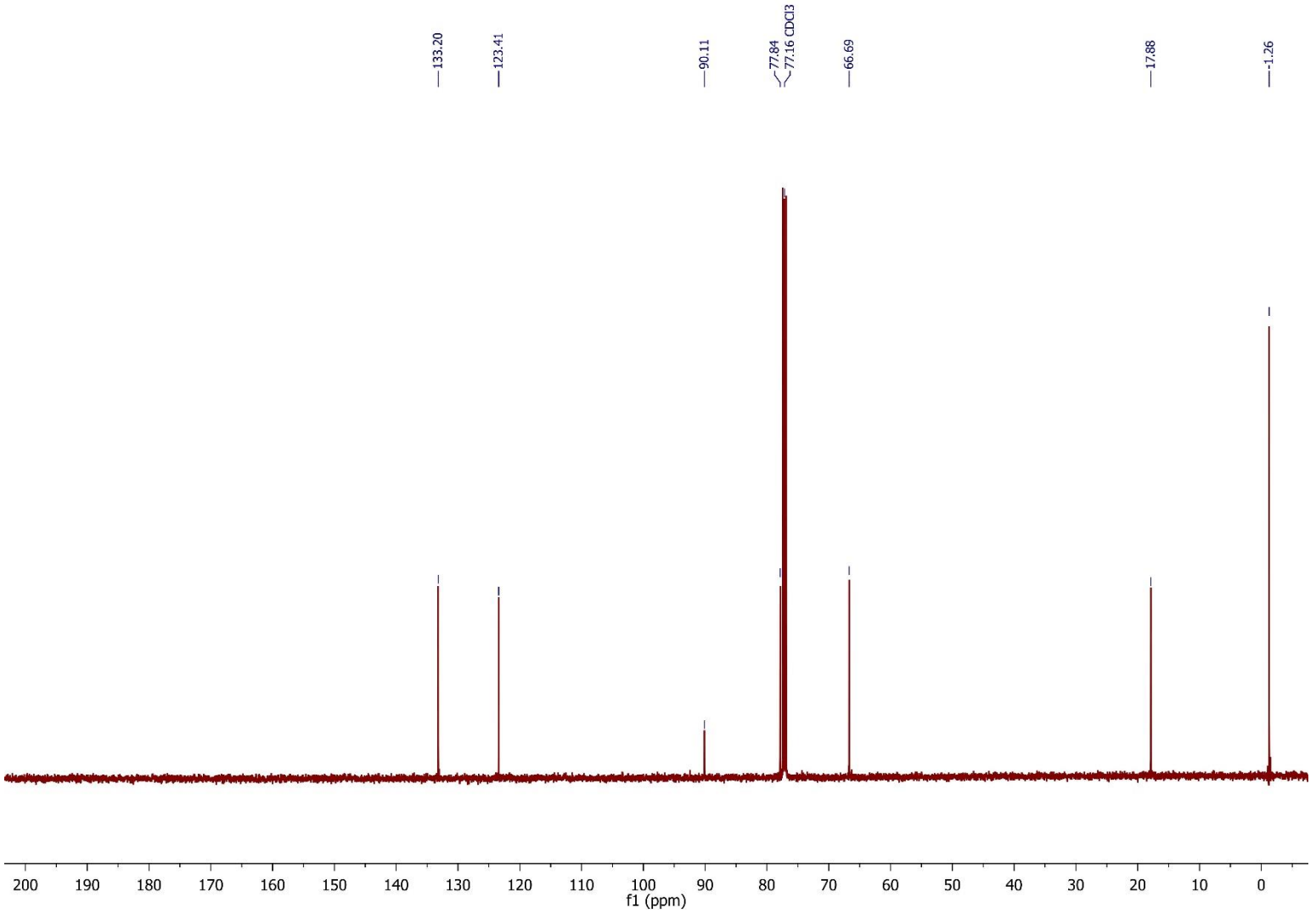
S9



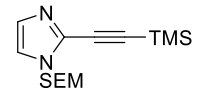
*^{13}C NMR of **S9** (126 MHz, $CDCl_3$)*



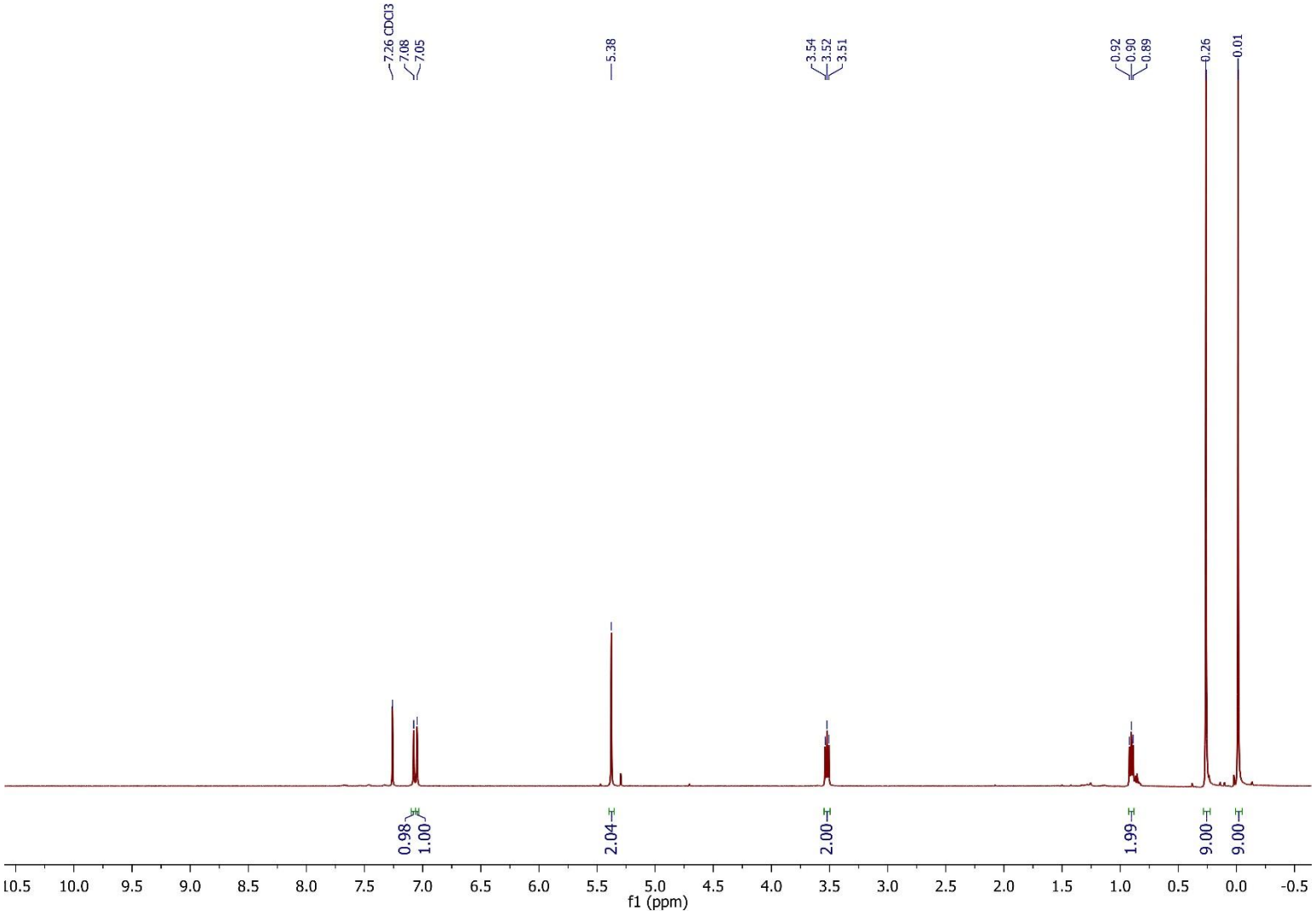
S9



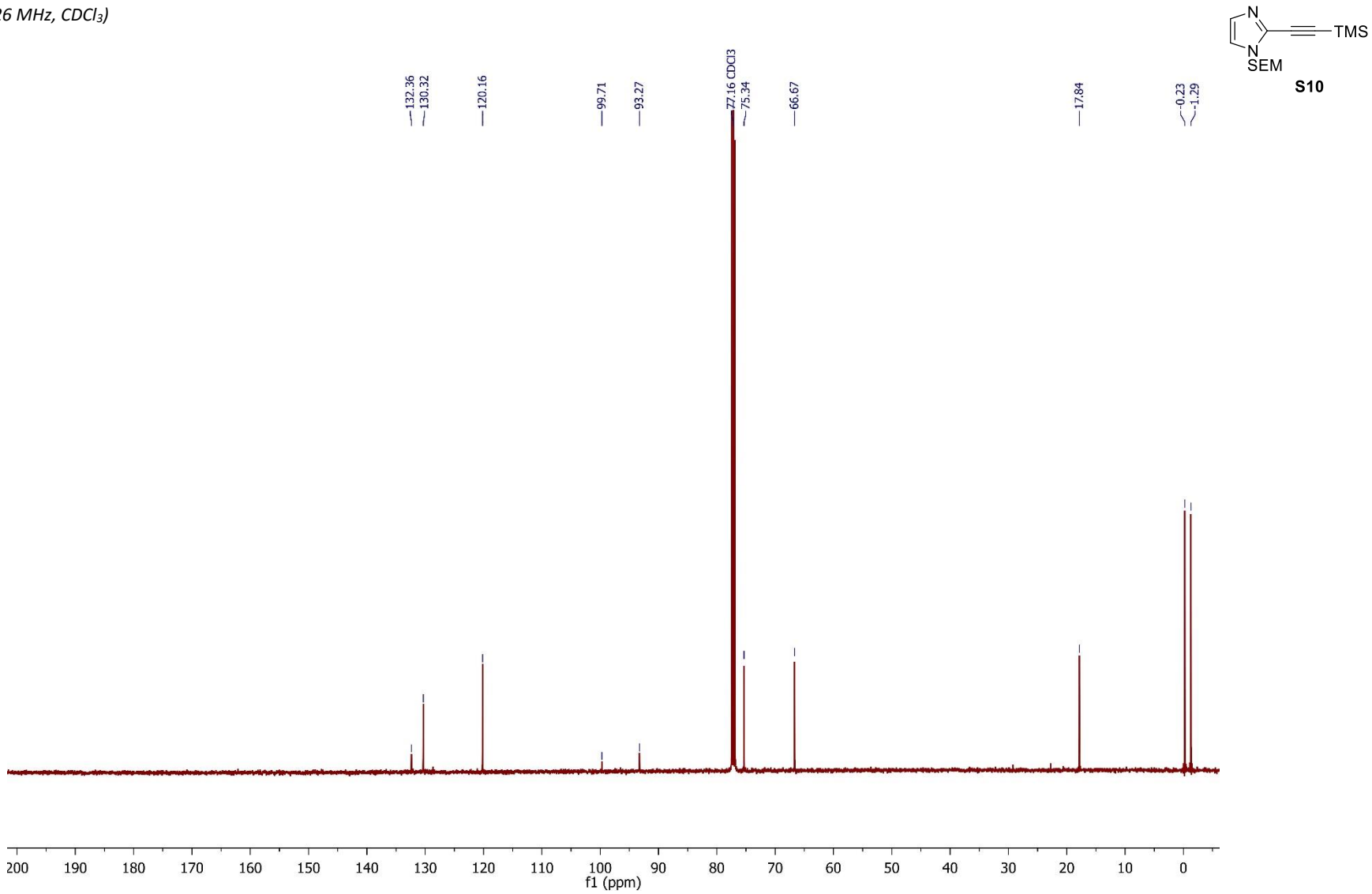
*^{1}H NMR of **S10** (500 MHz, $CDCl_3$)*



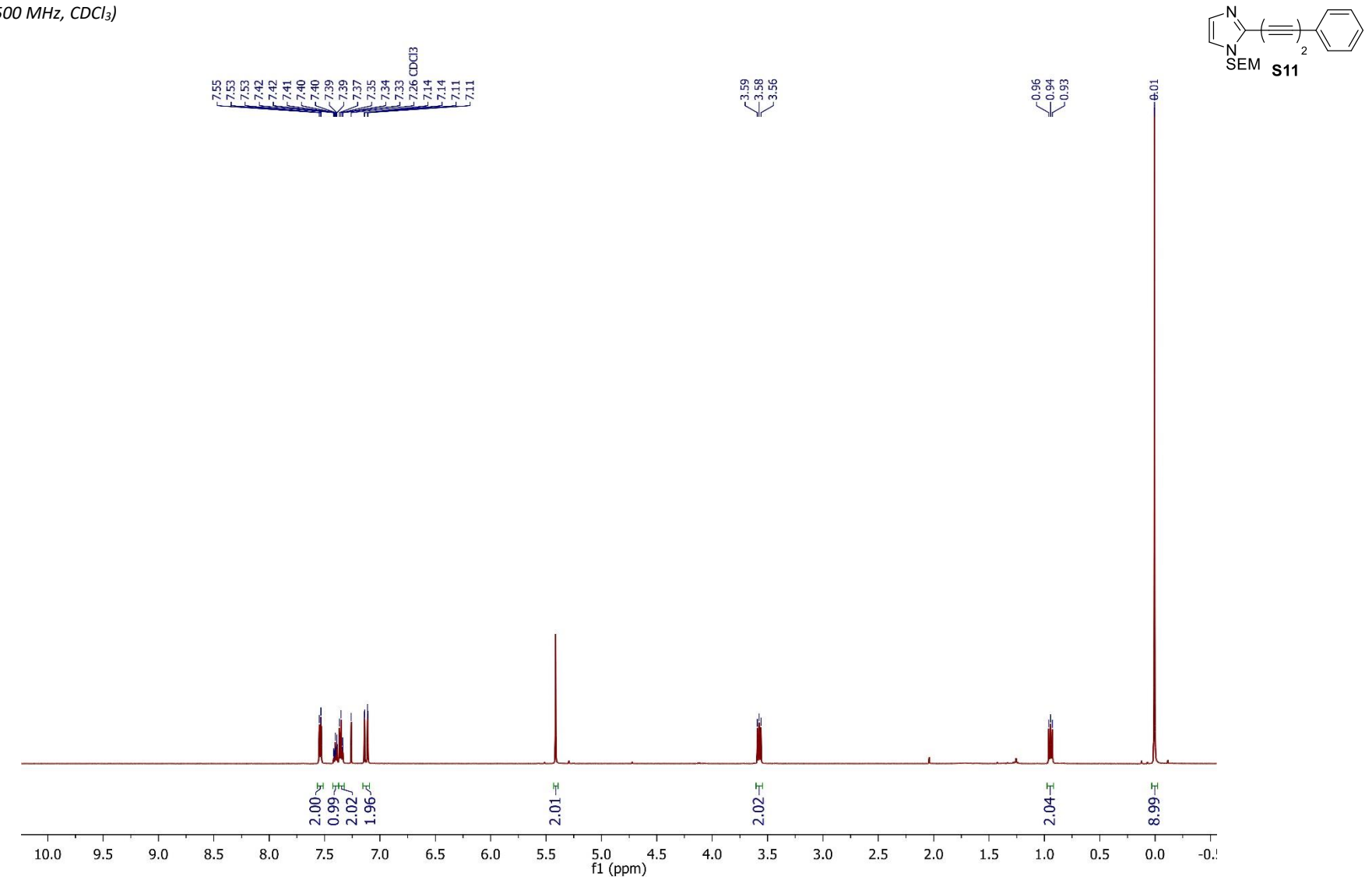
S10



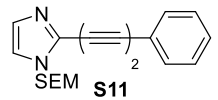
*^{13}C NMR of **S10** (126 MHz, $CDCl_3$)*



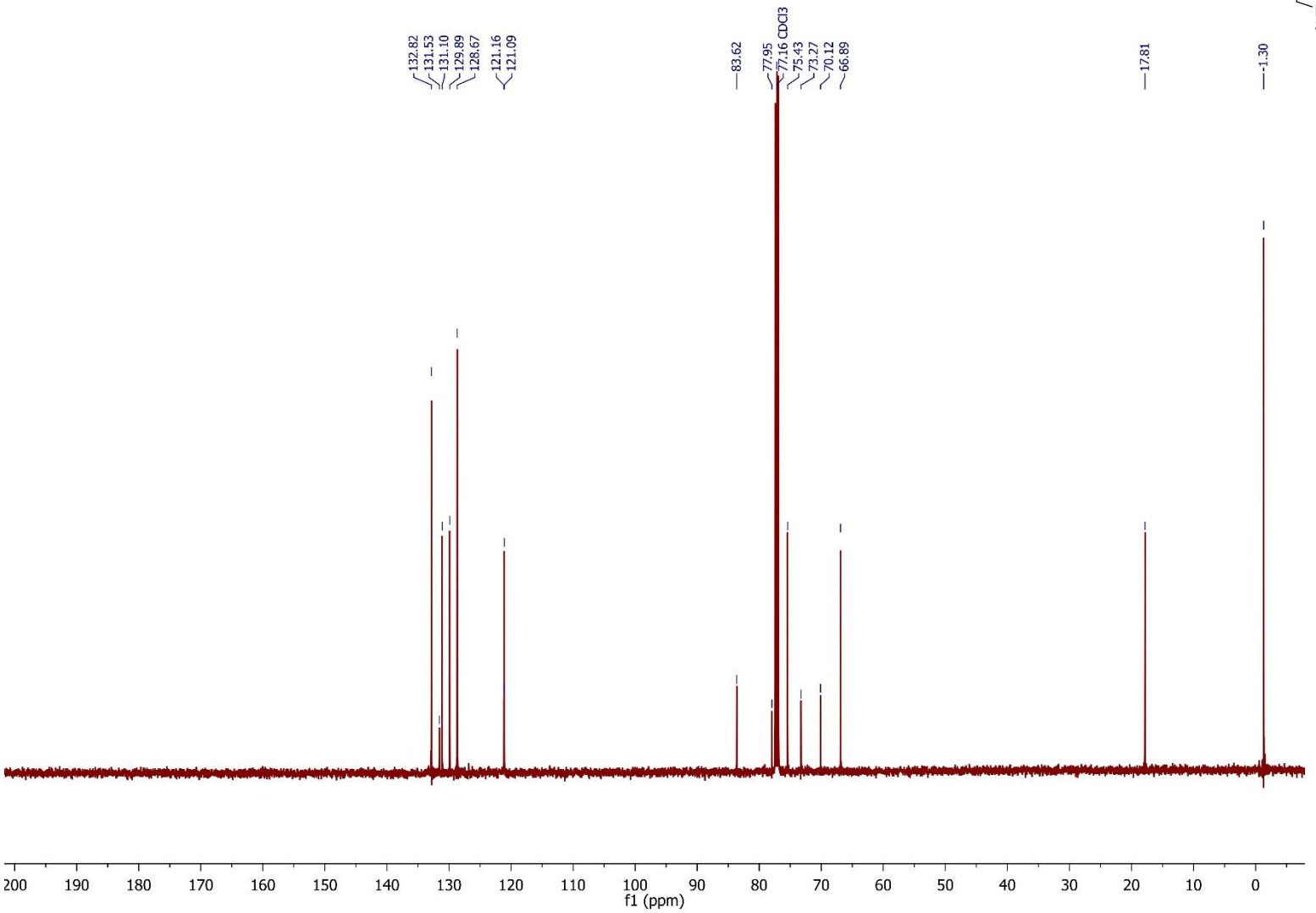
*^{1}H NMR of **S11** (500 MHz, $CDCl_3$)*



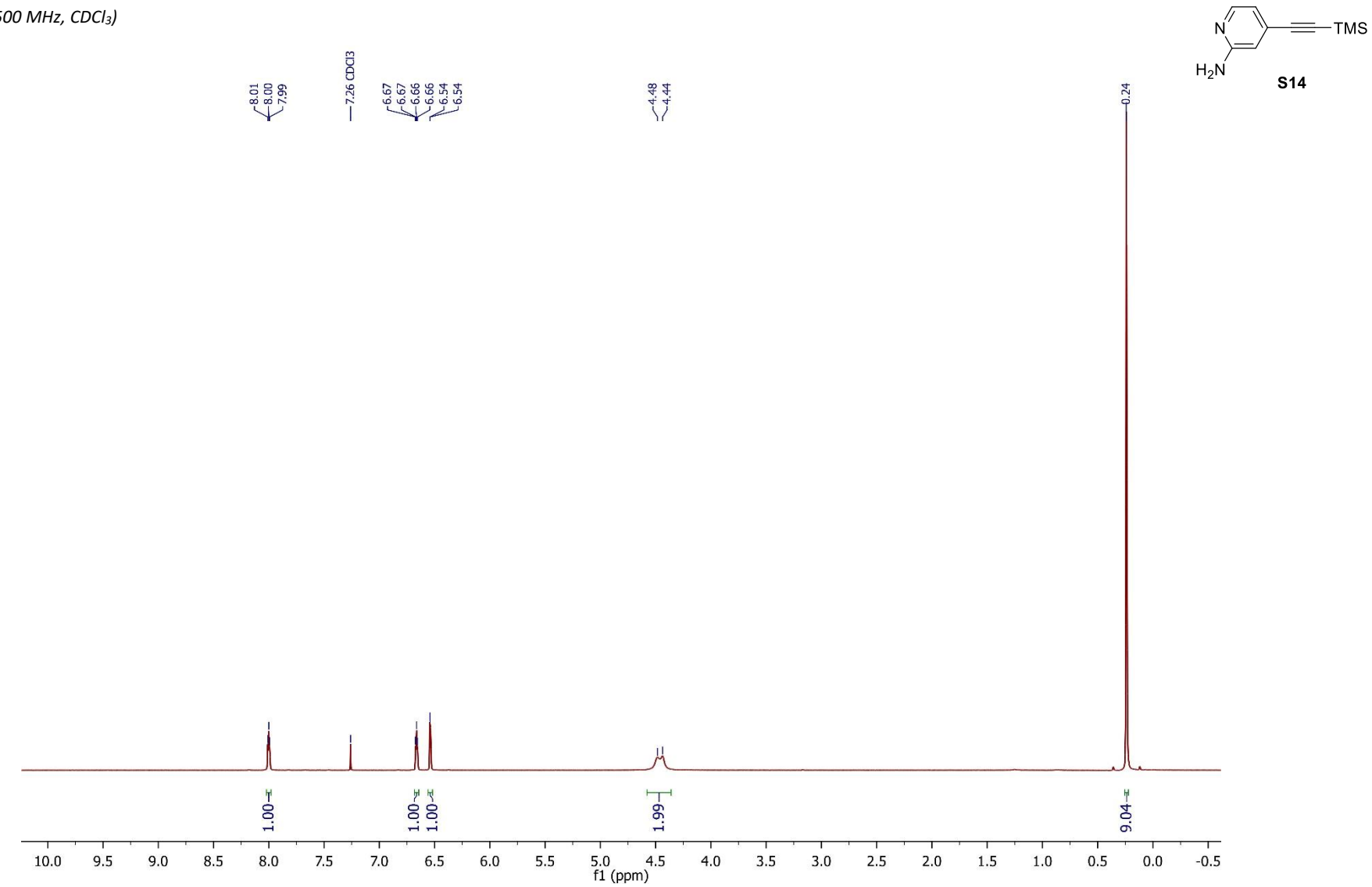
*^{13}C NMR of **S11** (126 MHz, $CDCl_3$)*



S11

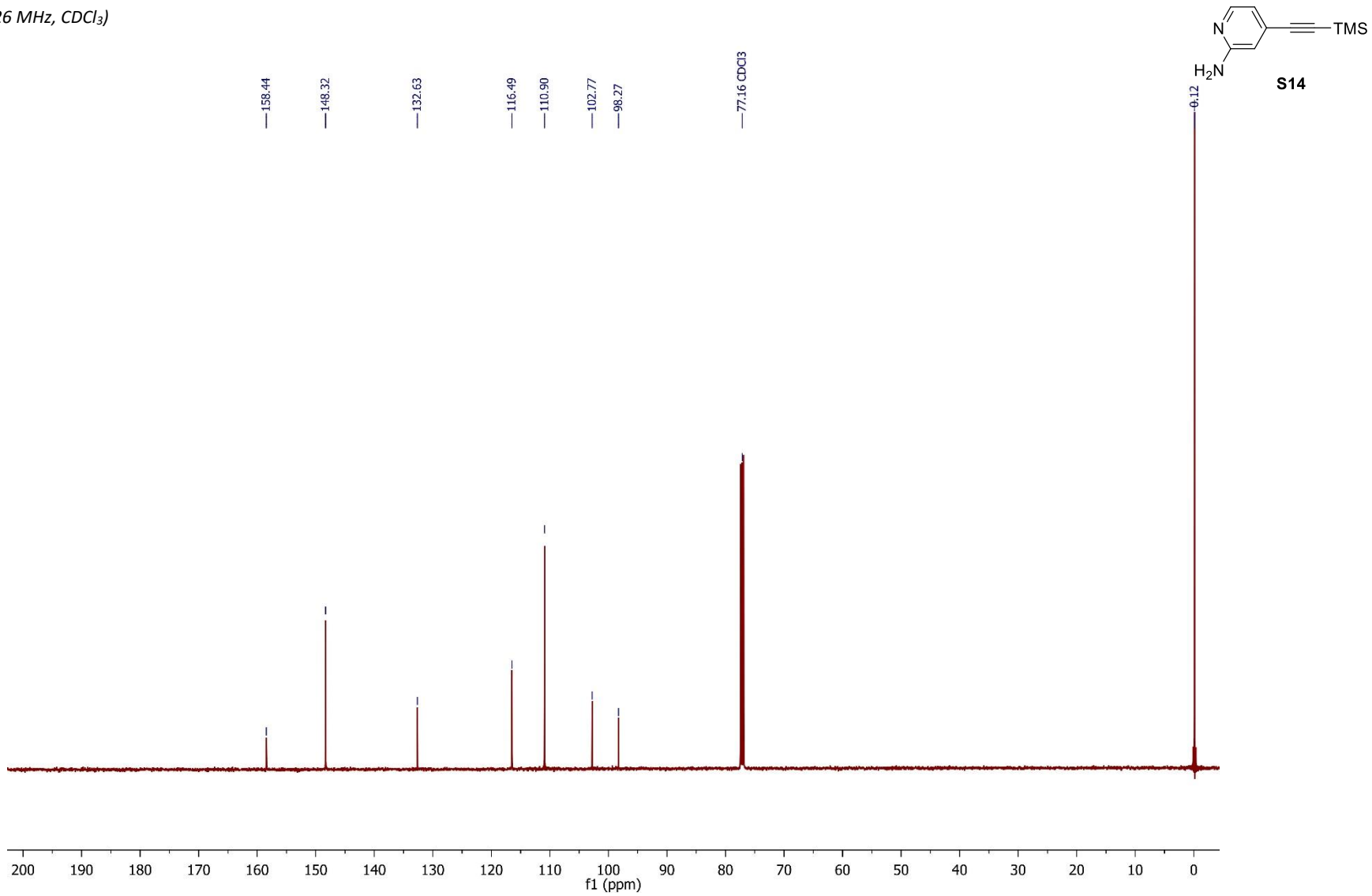


*^{1}H NMR of **S14** (500 MHz, $CDCl_3$)*



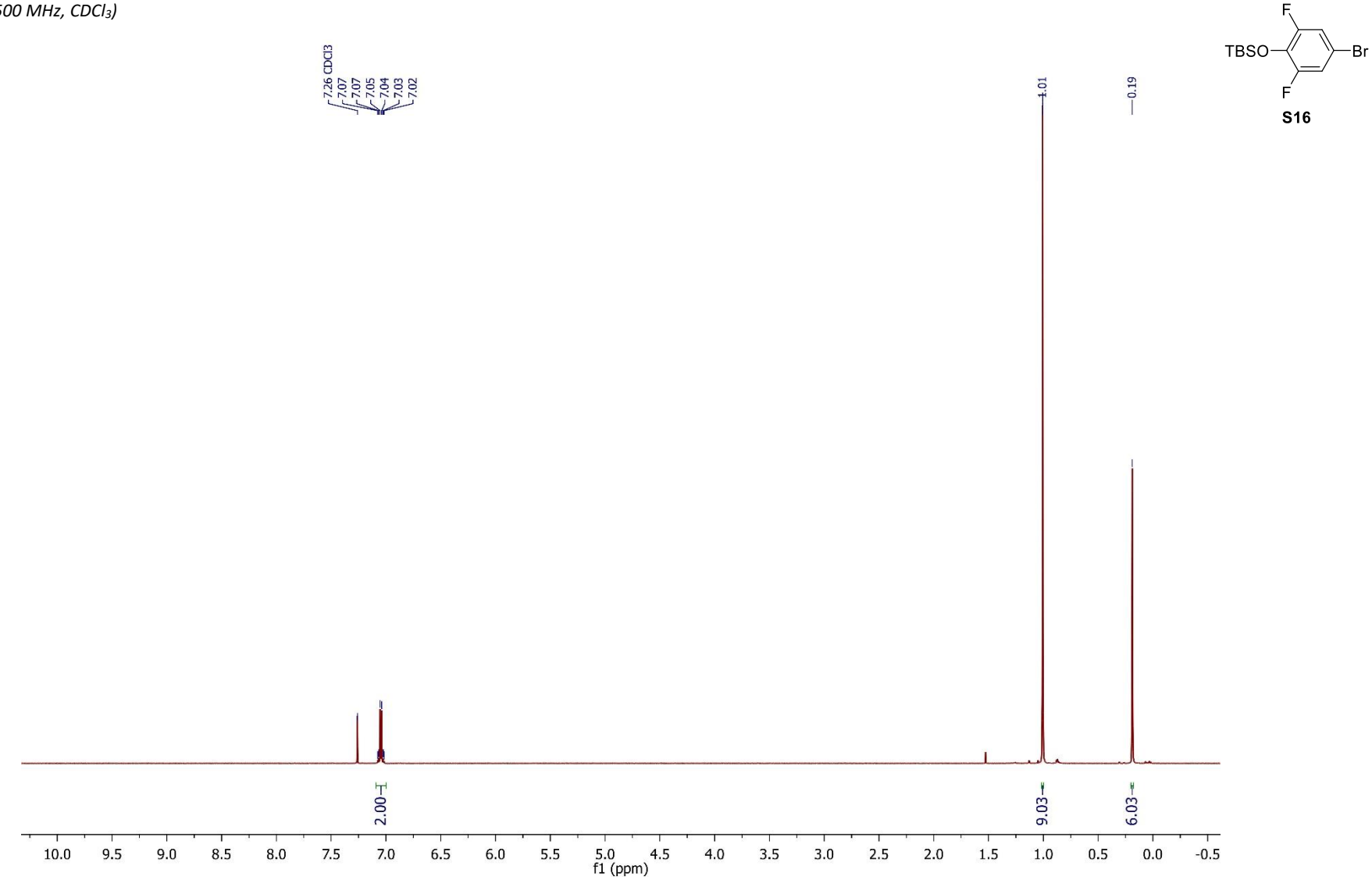
S14

*^{13}C NMR of **S14** (126 MHz, $CDCl_3$)*

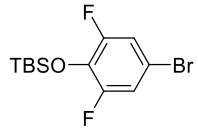


S14

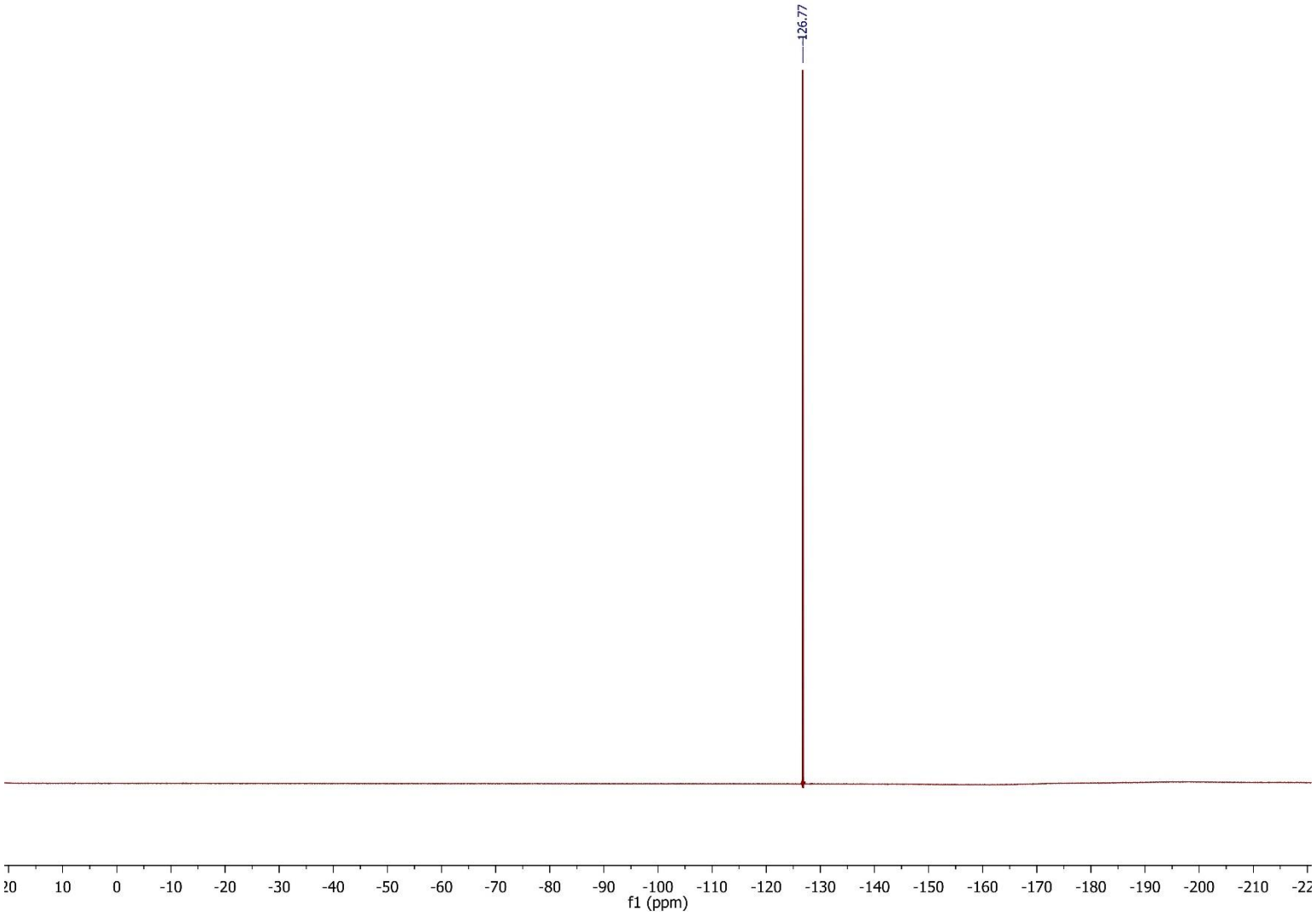
*^{1}H NMR of **S16** (500 MHz, $CDCl_3$)*



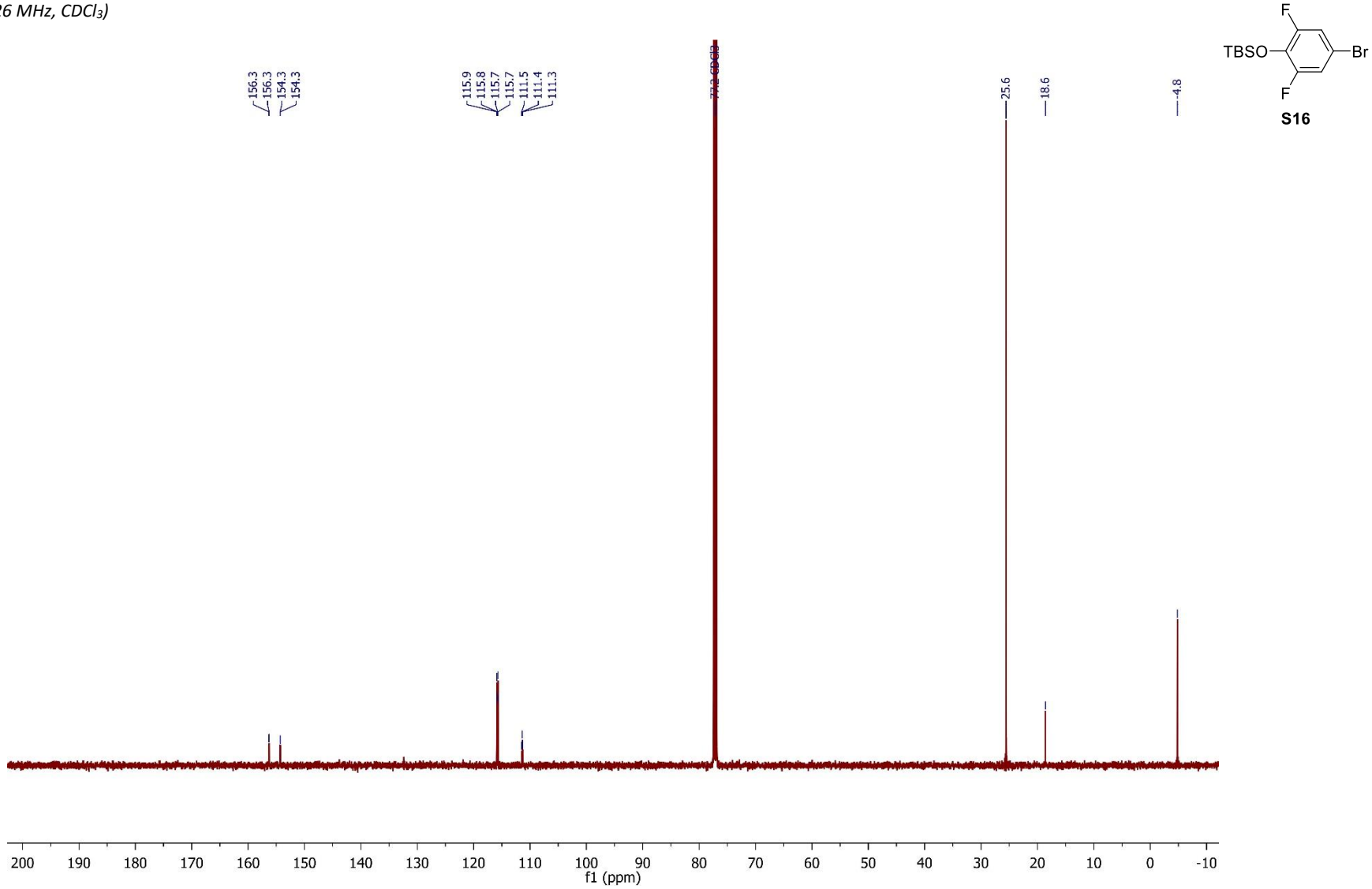
*^{19}F NMR of **S16** (500 MHz, $CDCl_3$)*



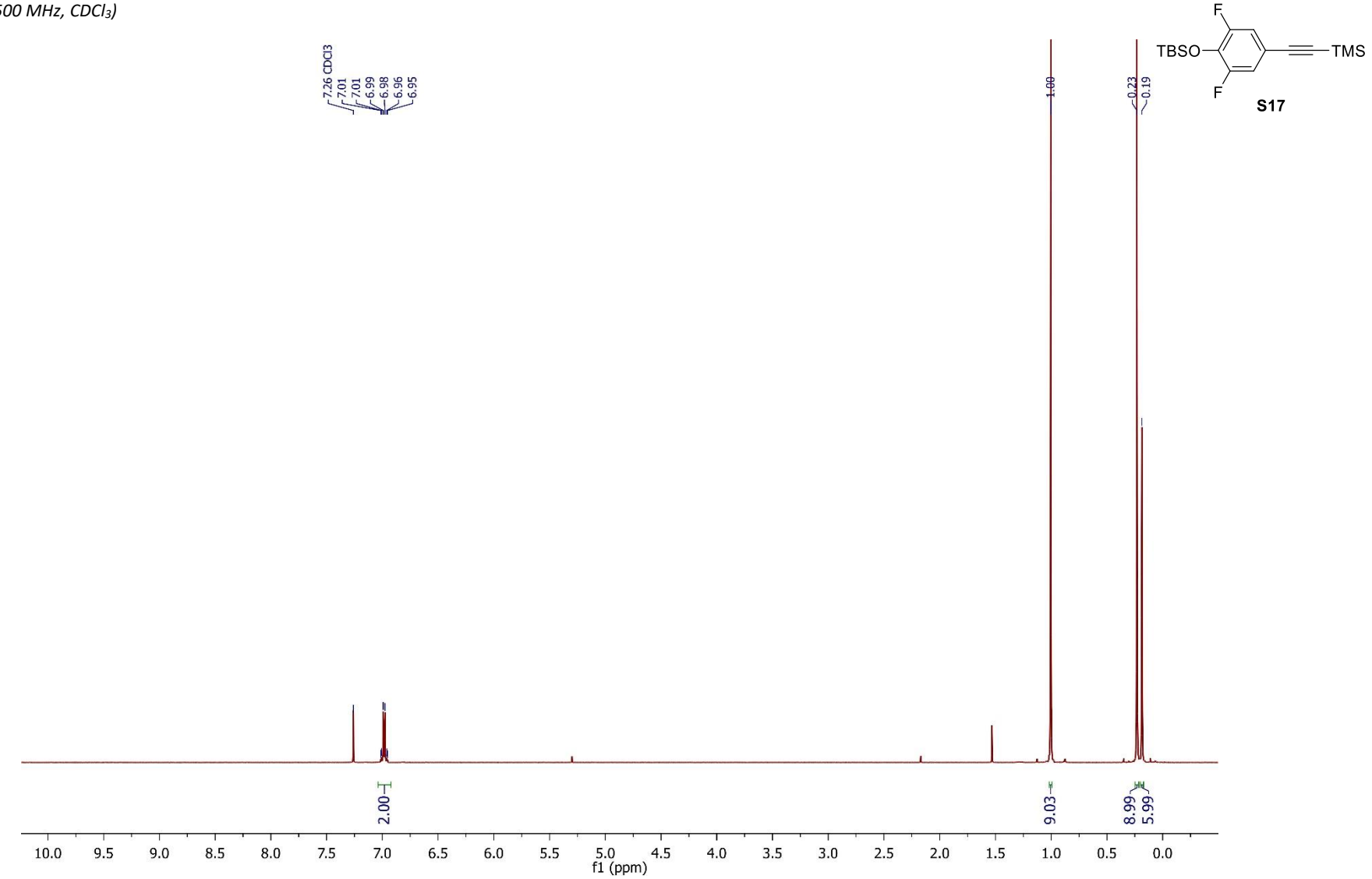
S16



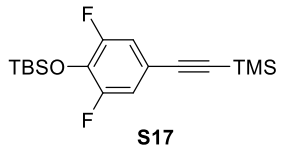
*^{13}C NMR of **S16** (126 MHz, $CDCl_3$)*



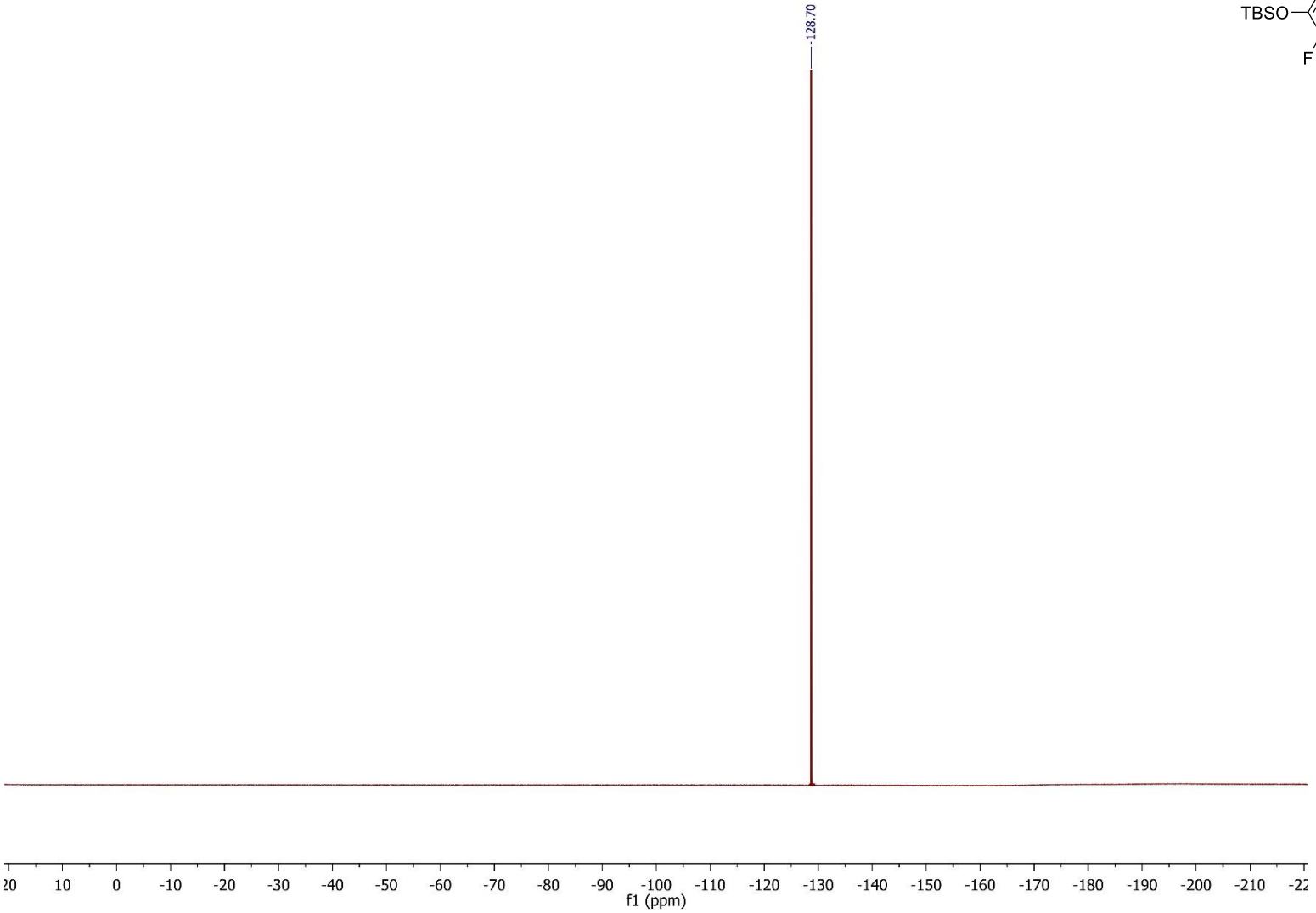
*^{1}H NMR of **S17** (500 MHz, $CDCl_3$)*



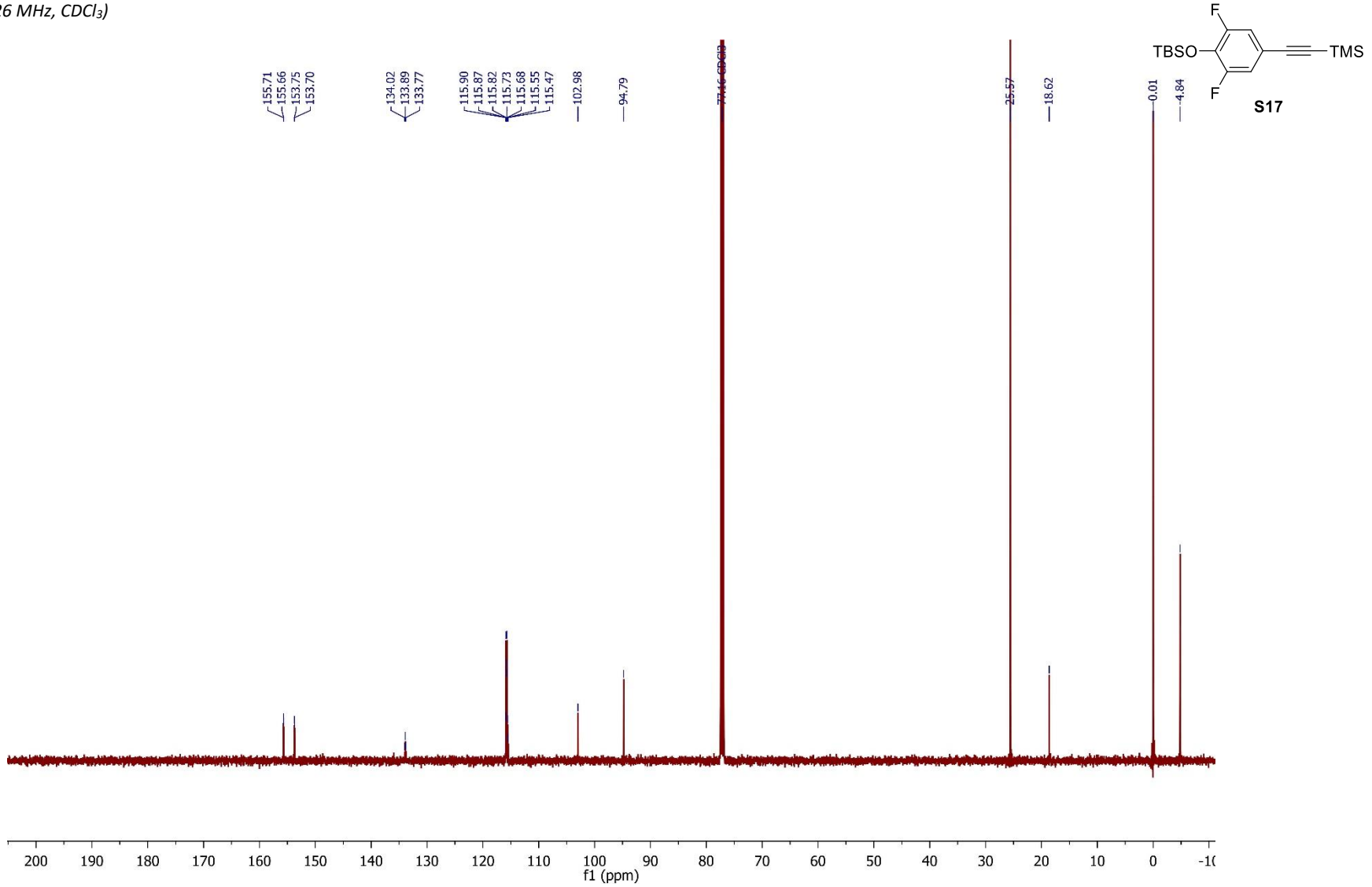
*^{19}F NMR of **S17** (500 MHz, $CDCl_3$)*



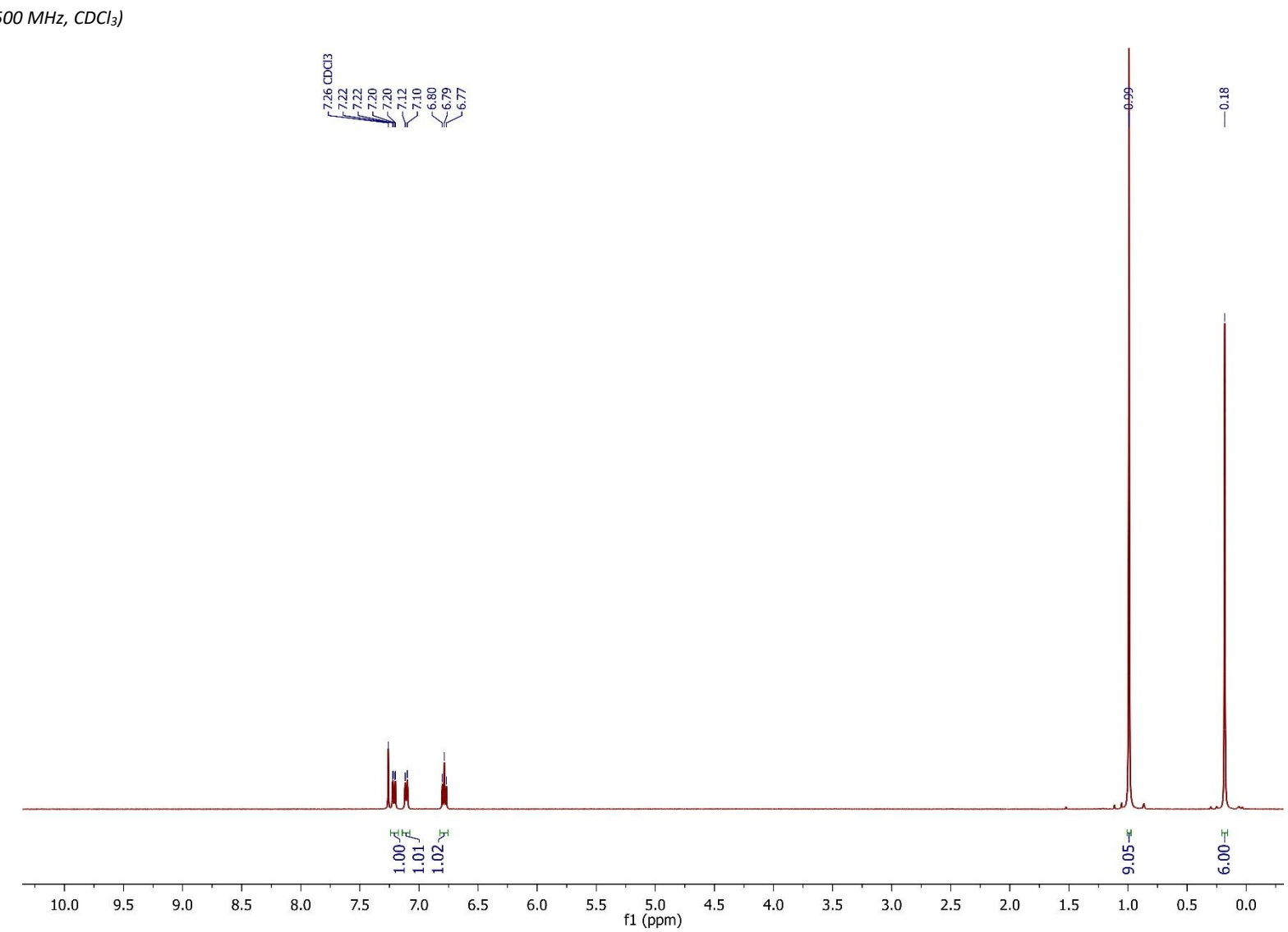
S17



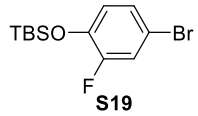
*^{13}C NMR of **S17** (126 MHz, $CDCl_3$)*

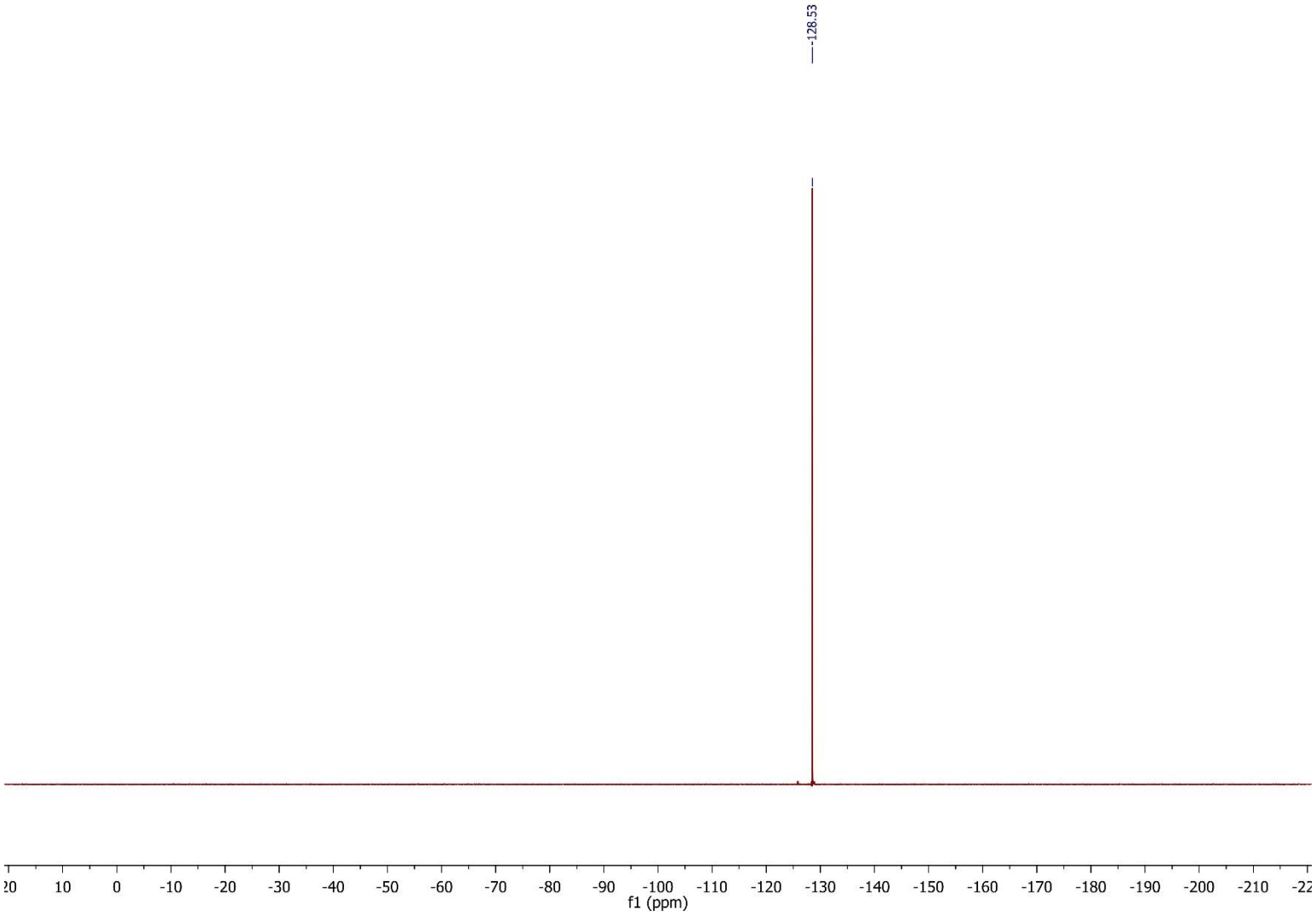


*^{1}H NMR of **S19** (500 MHz, $CDCl_3$)*

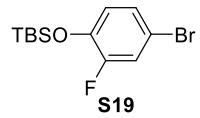


*^{19}F NMR of **S19** (500 MHz, $CDCl_3$)*

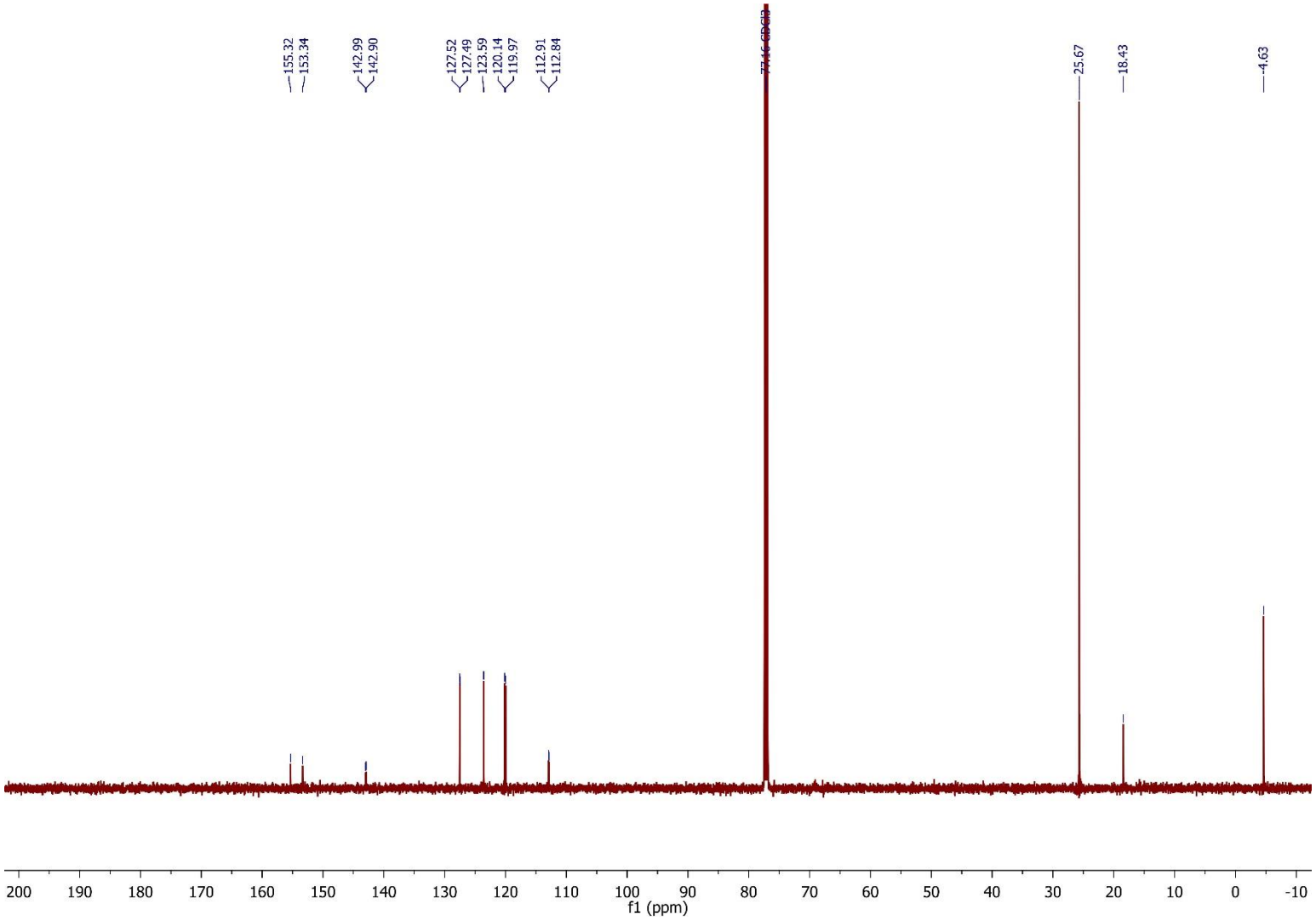




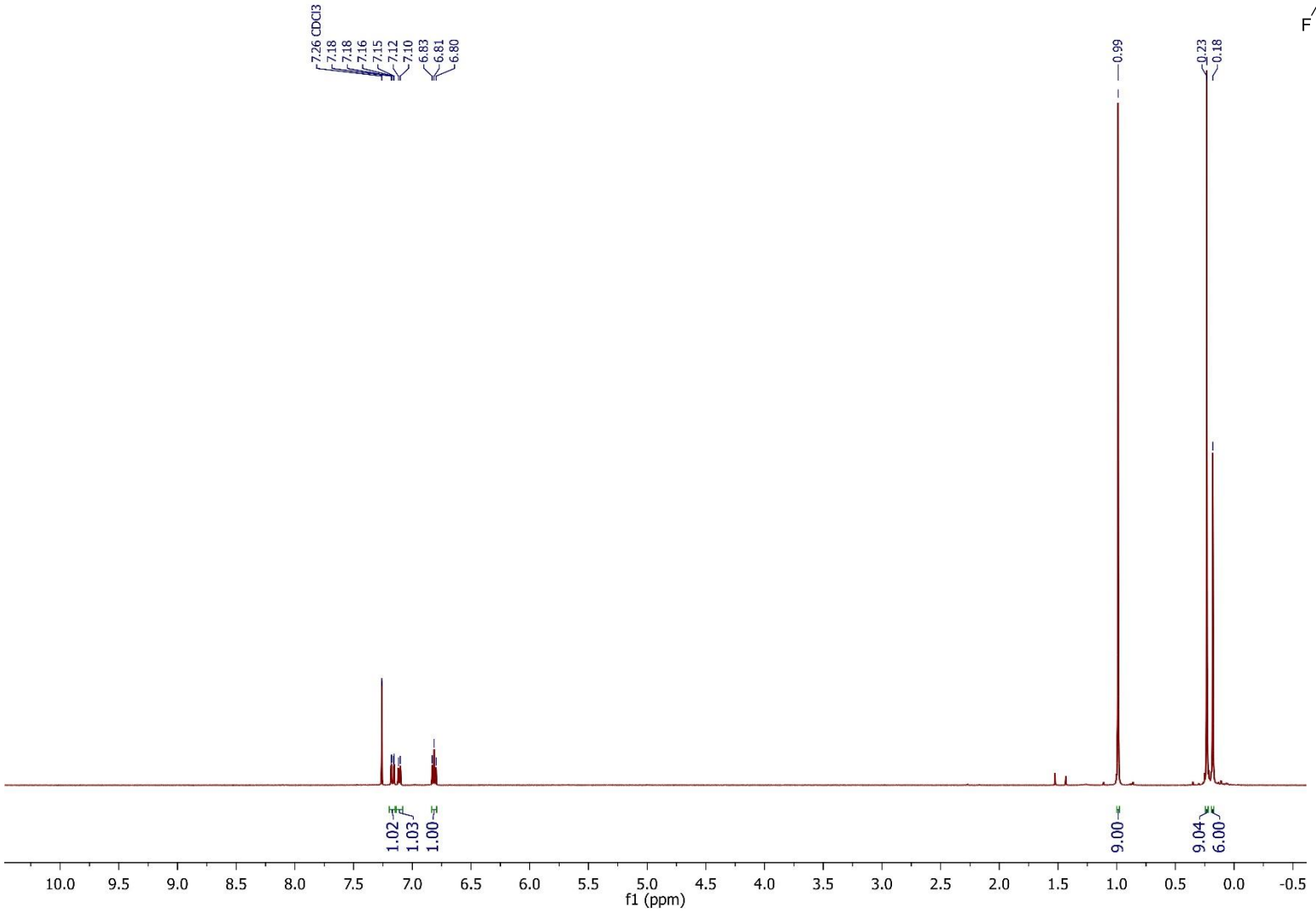
*^{13}C NMR of **S19** (126 MHz, $CDCl_3$)*



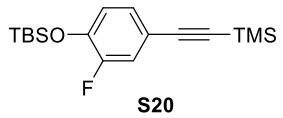
S19



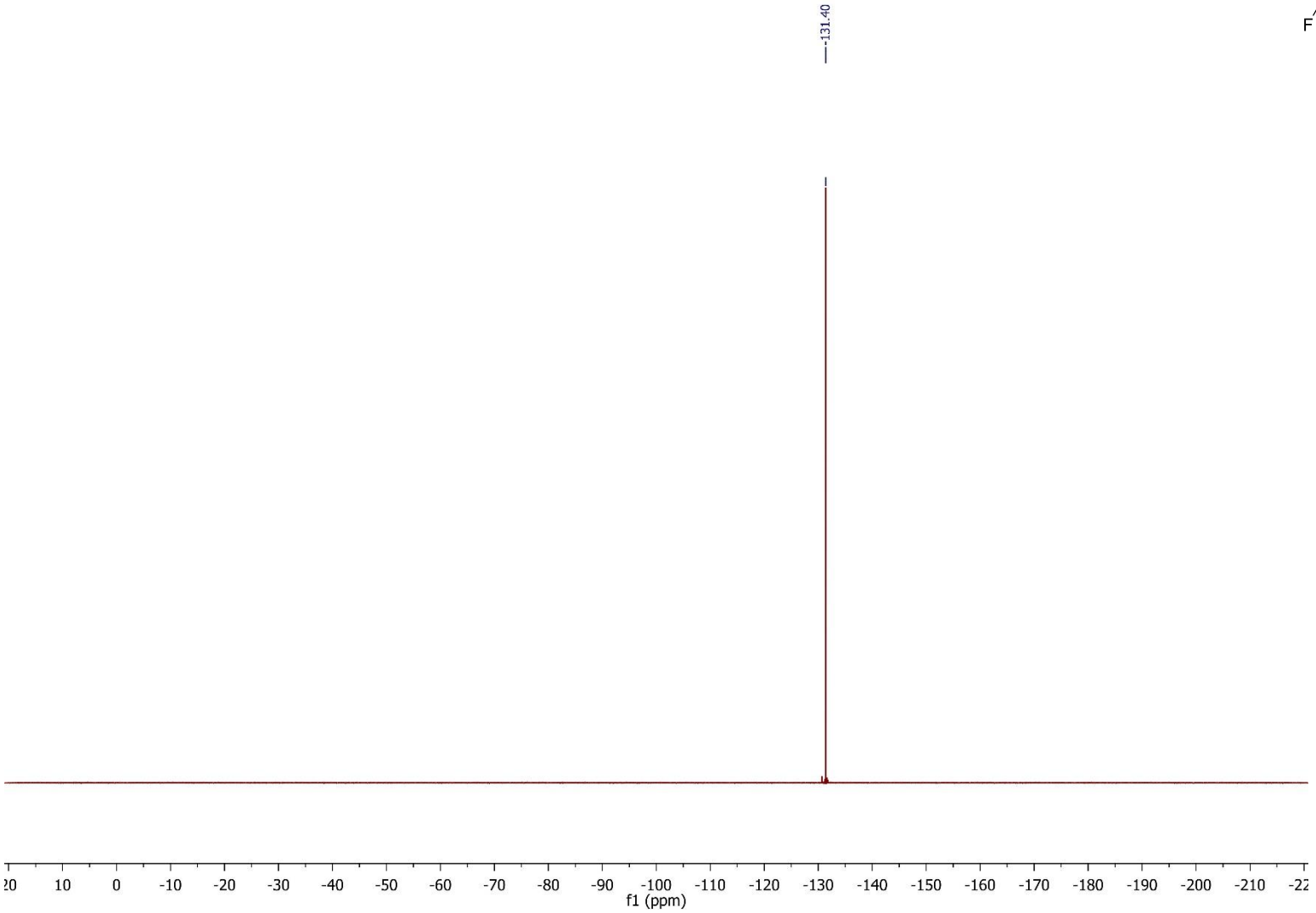
*^{1}H NMR of **S20** (500 MHz, $CDCl_3$)*



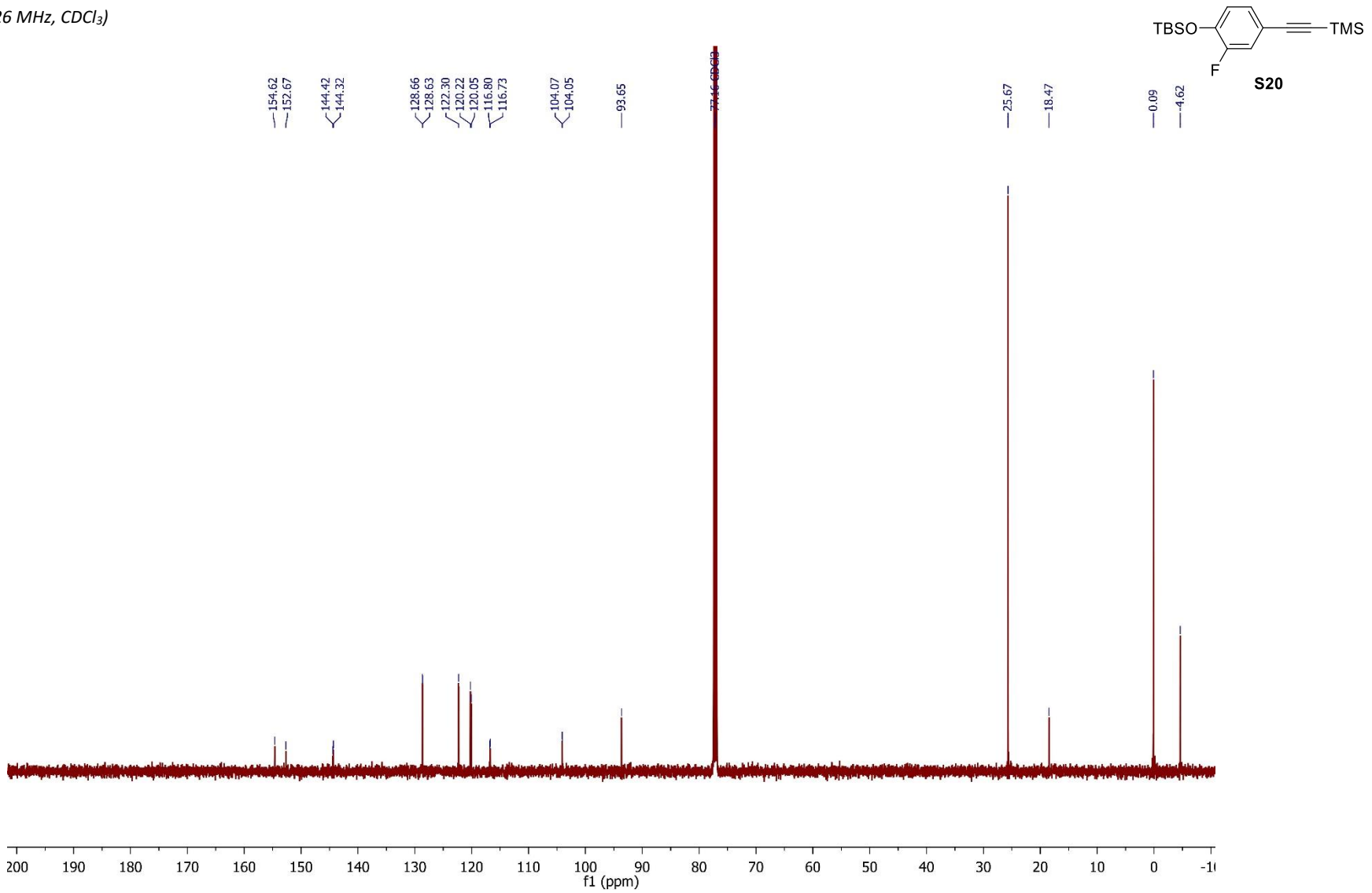
*^{19}F NMR of **S20** (500 MHz, $CDCl_3$)*



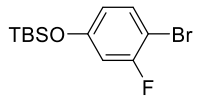
S20



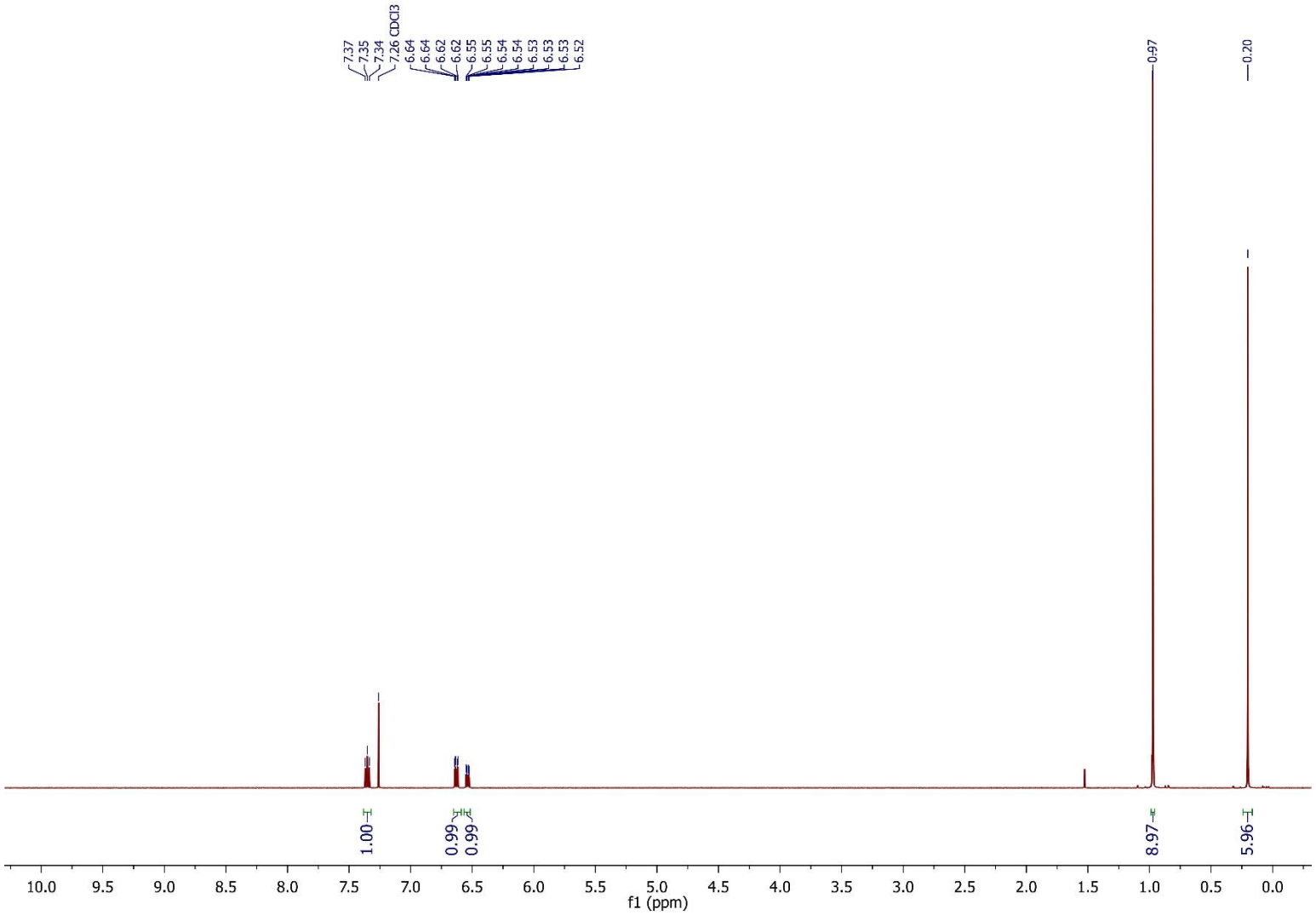
*^{13}C NMR of **S20** (126 MHz, $CDCl_3$)*



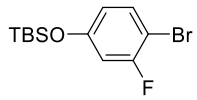
*^{1}H NMR of **S22** (500 MHz, $CDCl_3$)*



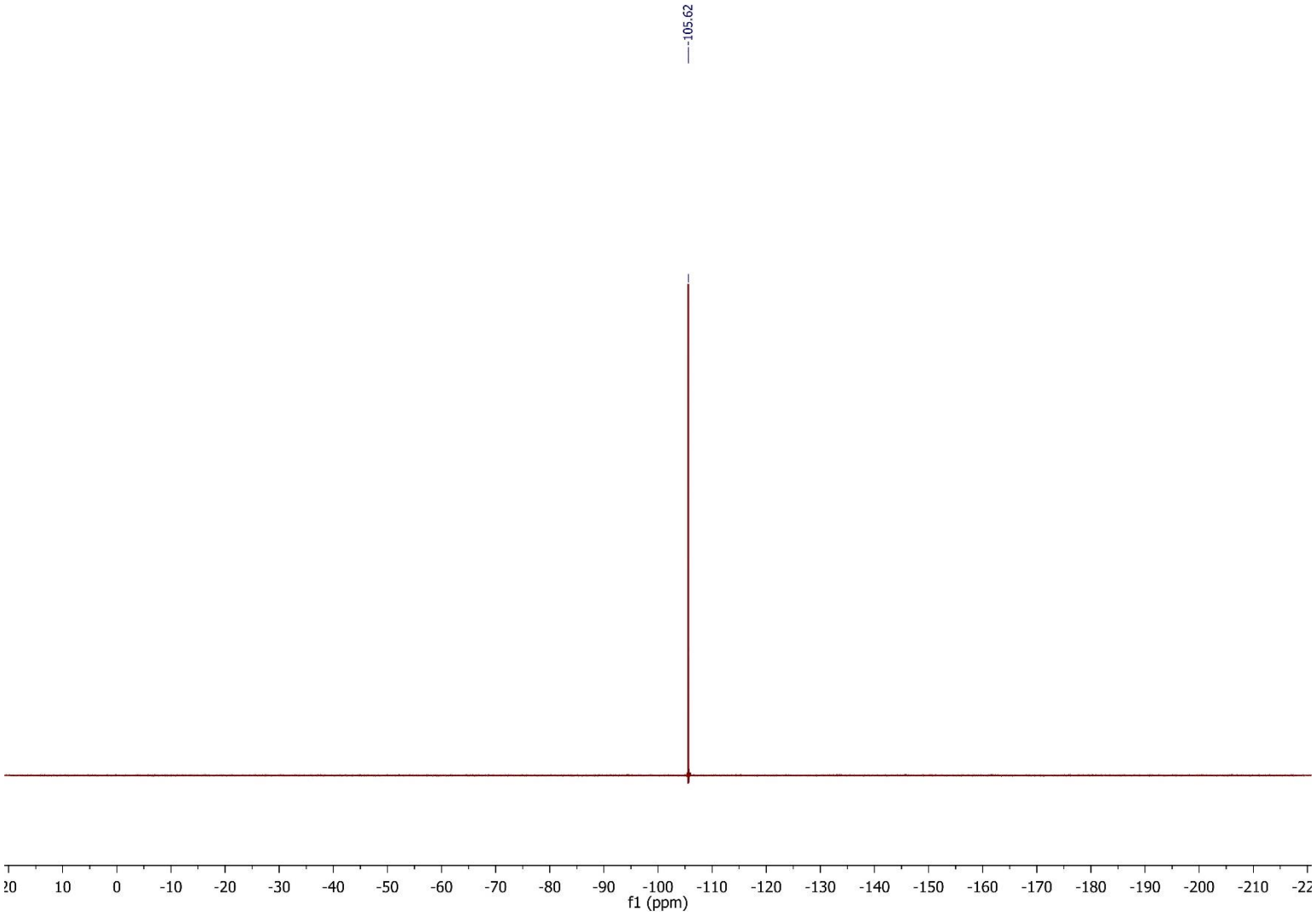
S22



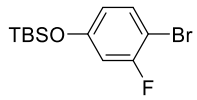
*^{19}F NMR of **S22** (500 MHz, $CDCl_3$)*



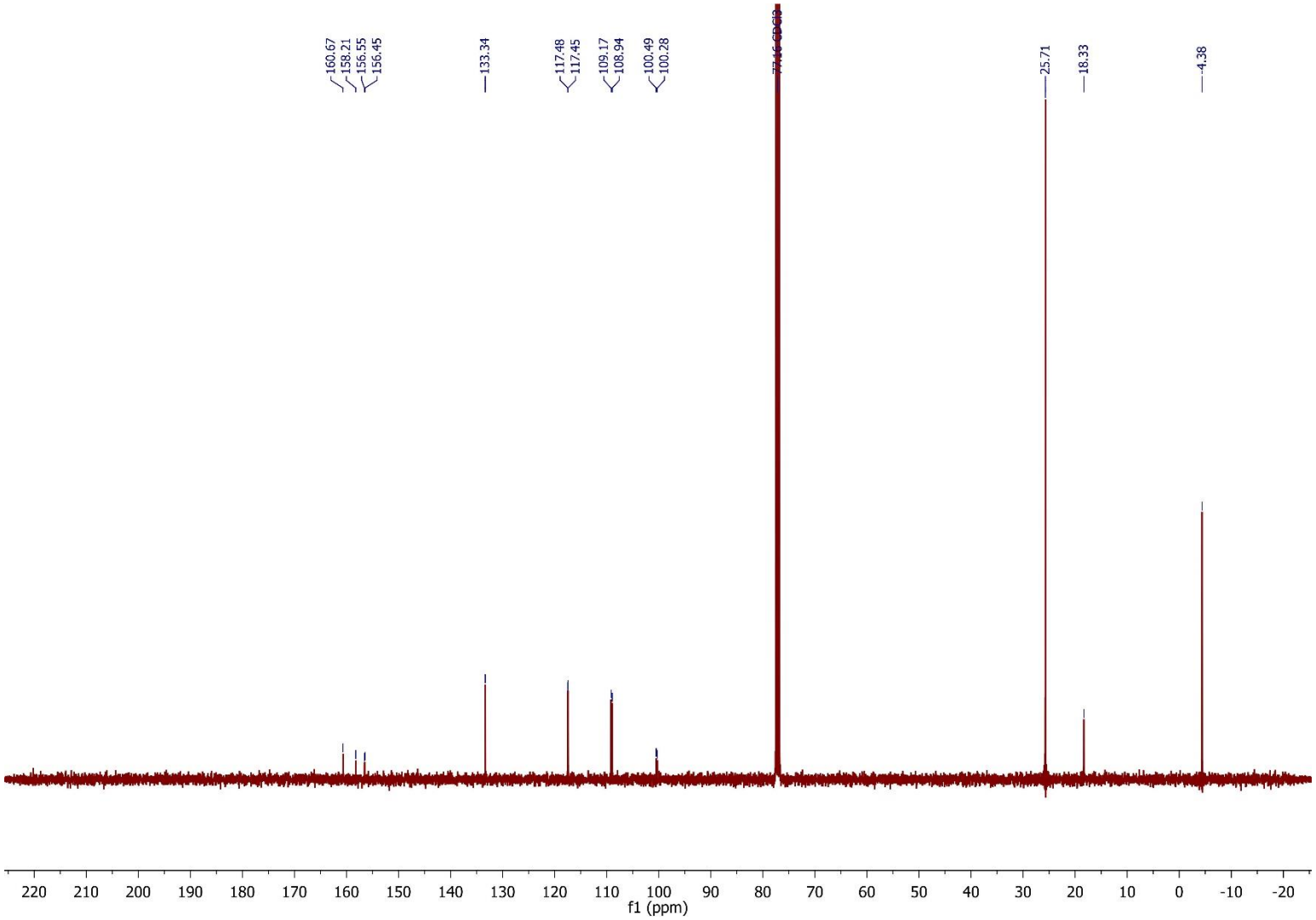
S22



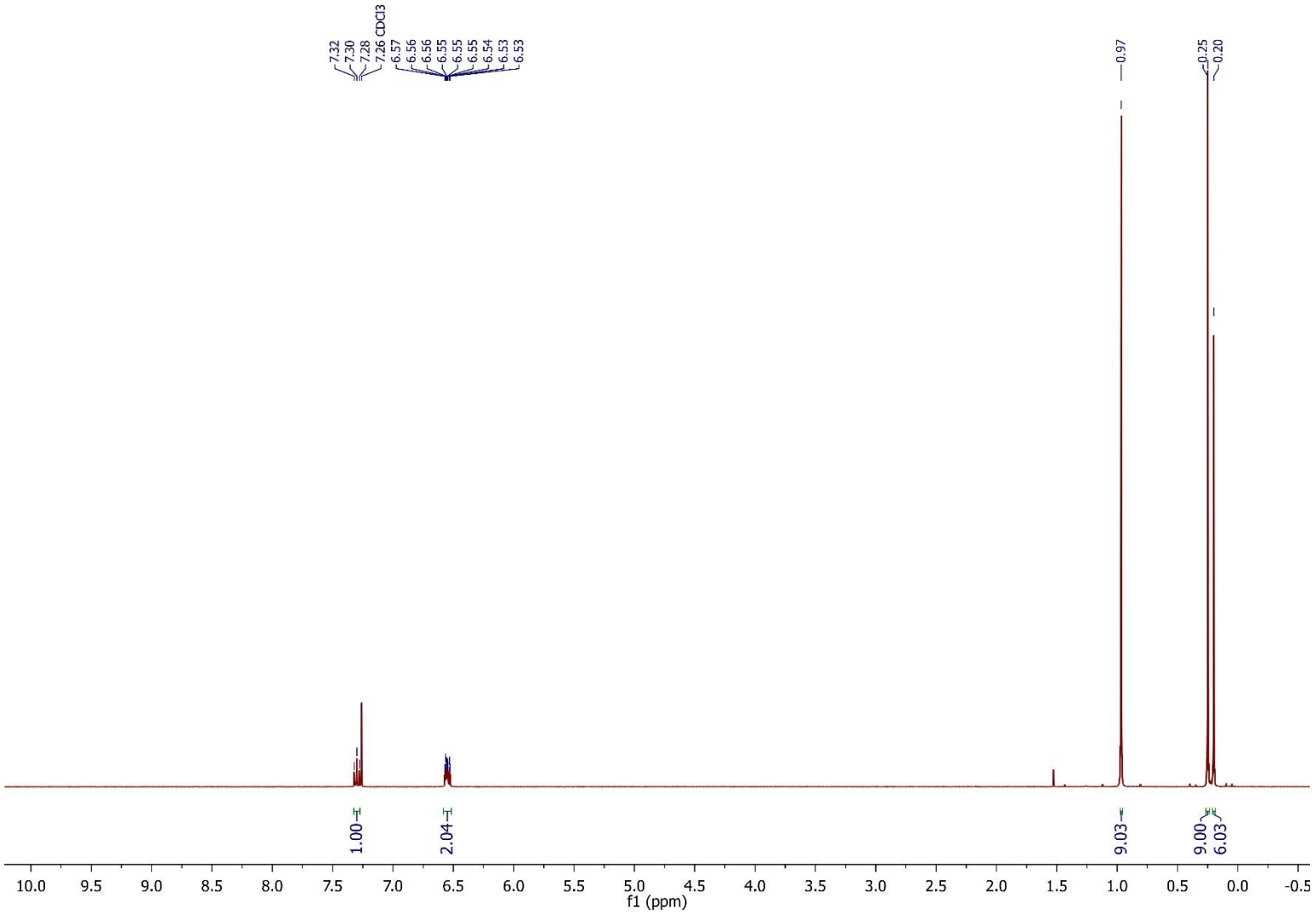
*^{13}C NMR of **S22** (126 MHz, $CDCl_3$)*



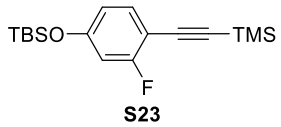
S22



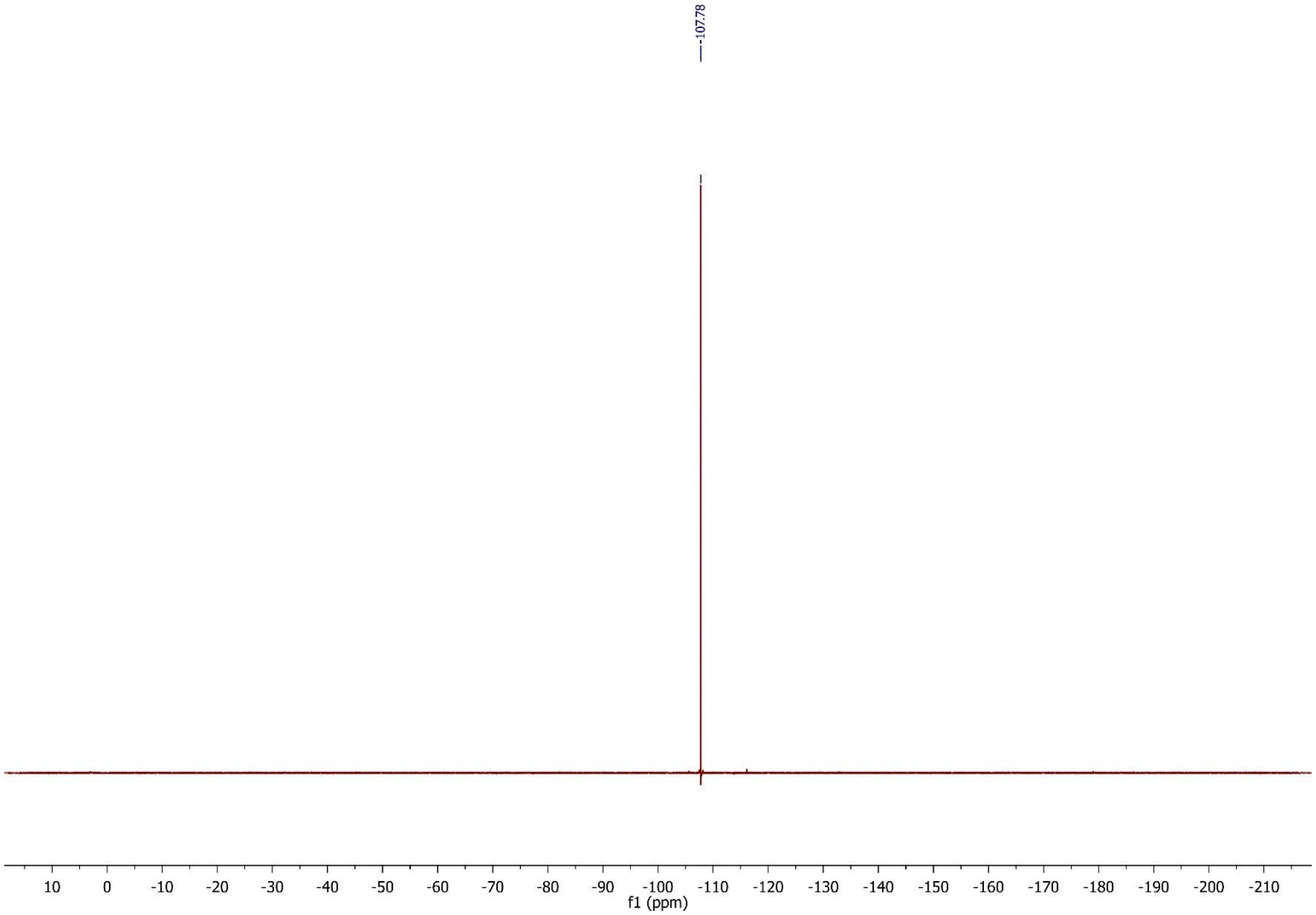
*^{1}H NMR of **S23** (500 MHz, $CDCl_3$)*



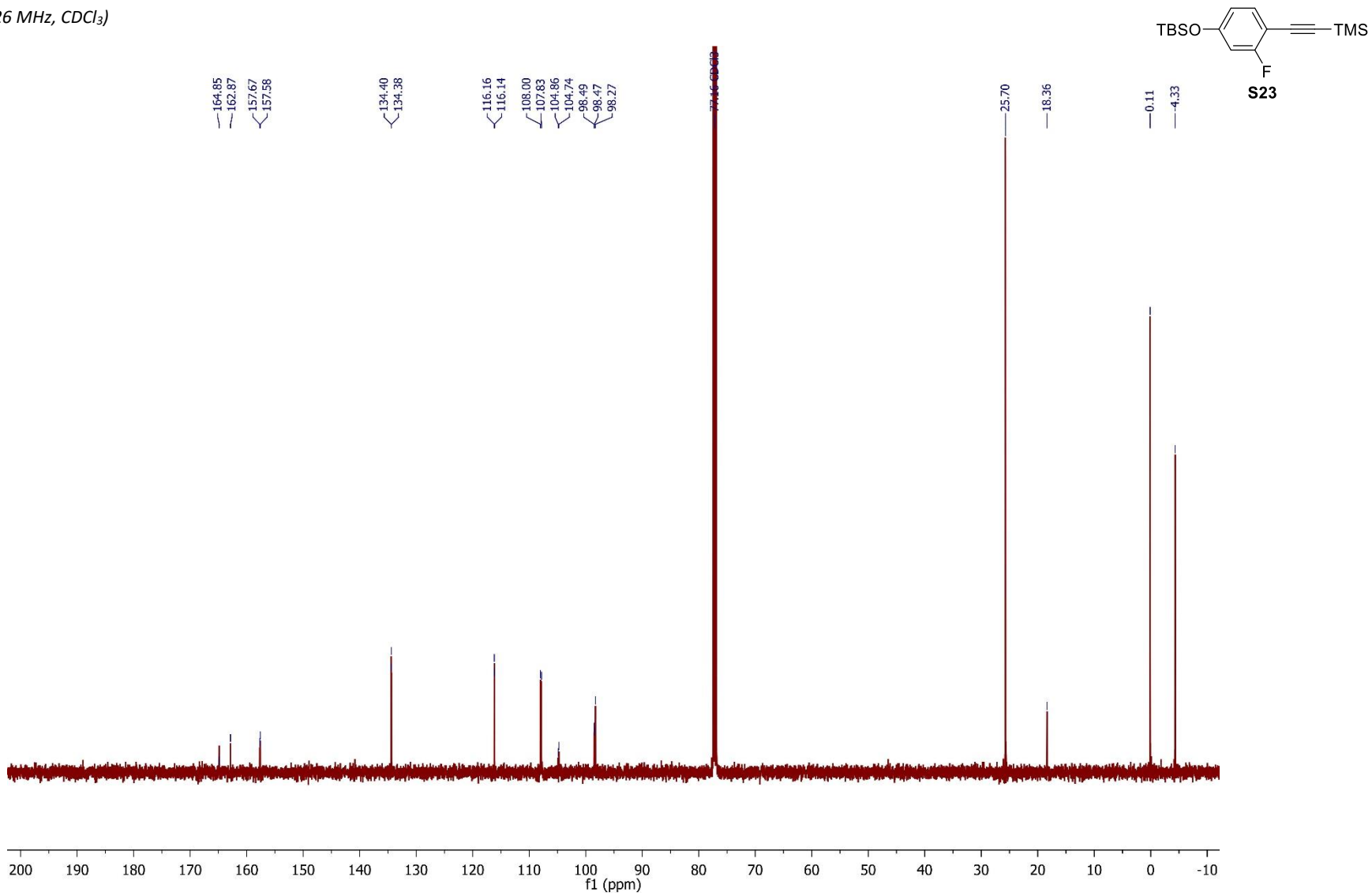
*^{19}F NMR of **S23** (500 MHz, $CDCl_3$)*



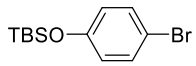
S23



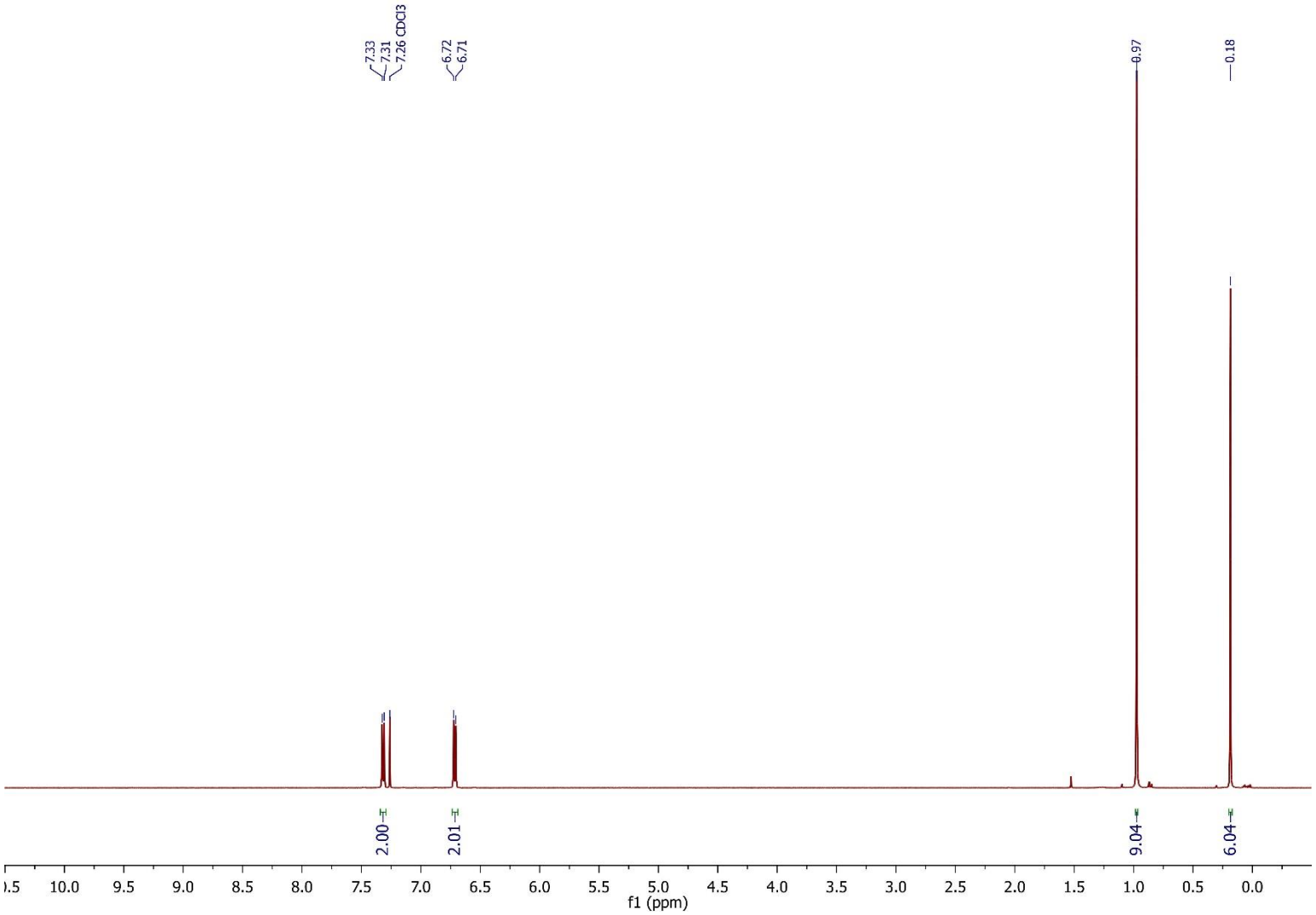
*^{13}C NMR of **S23** (126 MHz, $CDCl_3$)*



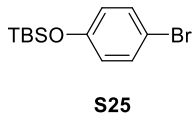
*^{1}H NMR of **S25** (500 MHz, $CDCl_3$)*



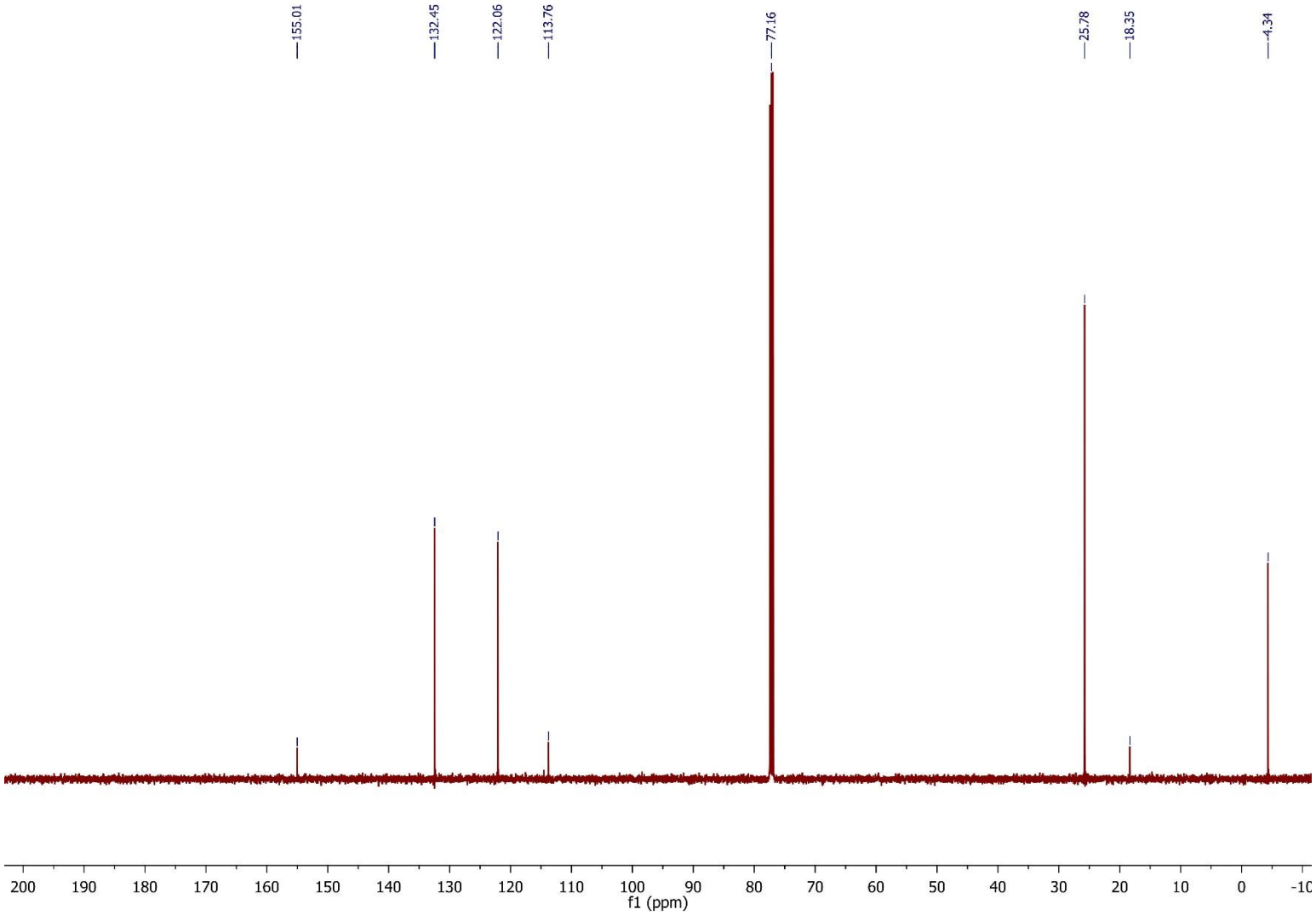
S25



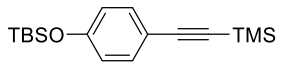
*^{13}C NMR of **S25** (126 MHz, $CDCl_3$)*



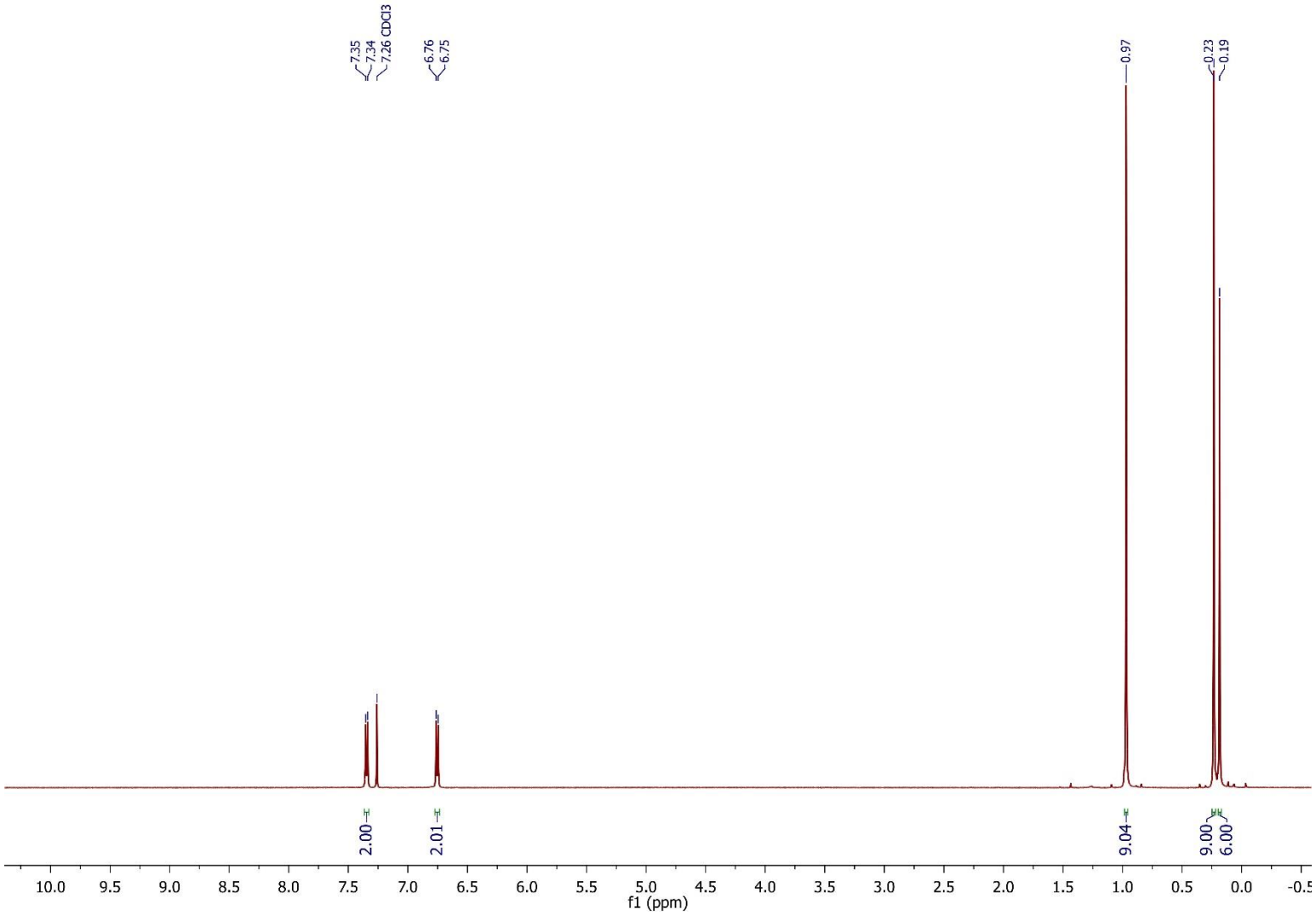
S25



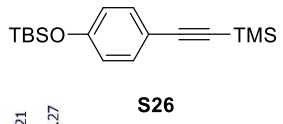
*^{1}H NMR of **S26** (500 MHz, $CDCl_3$)*



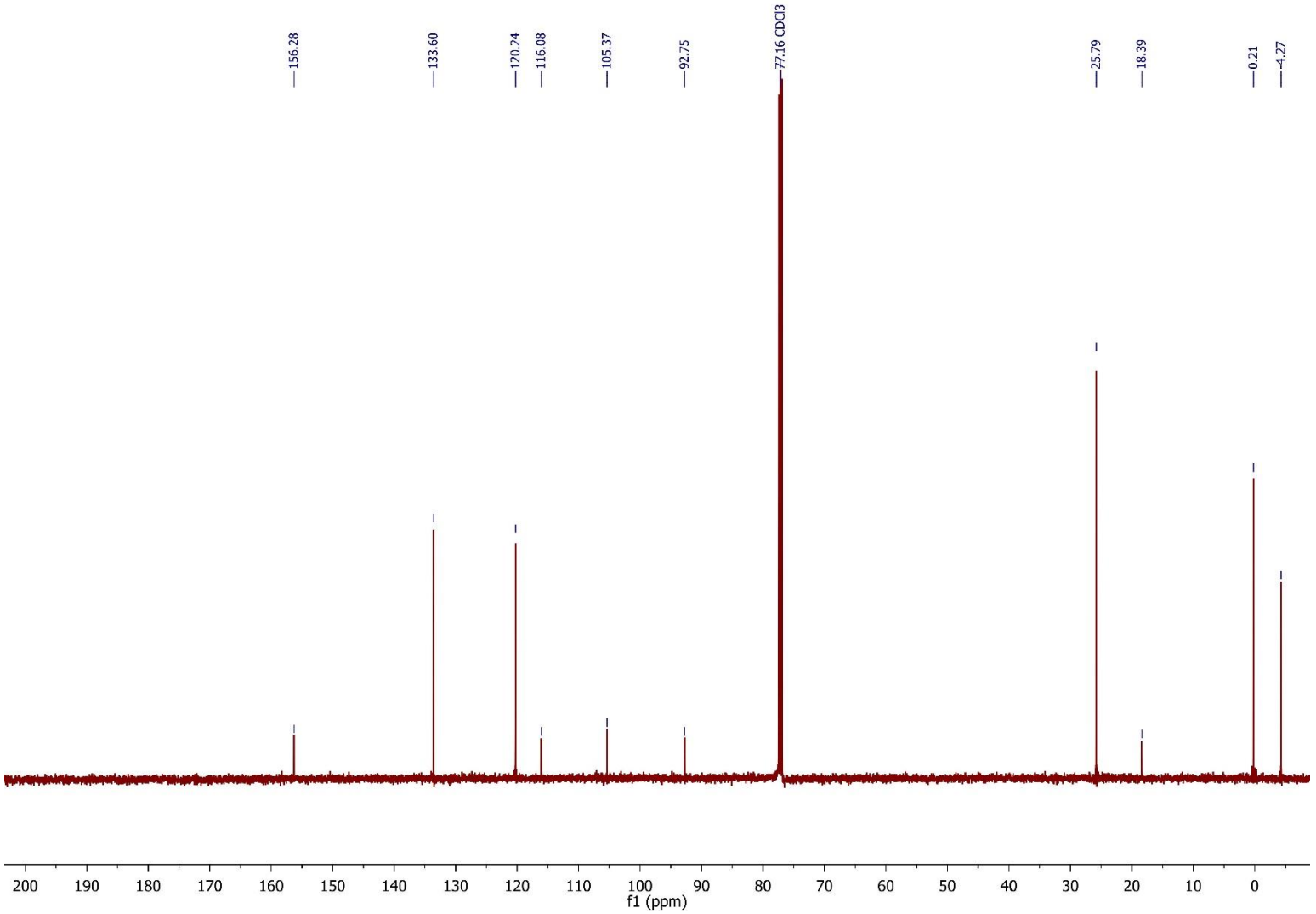
S26



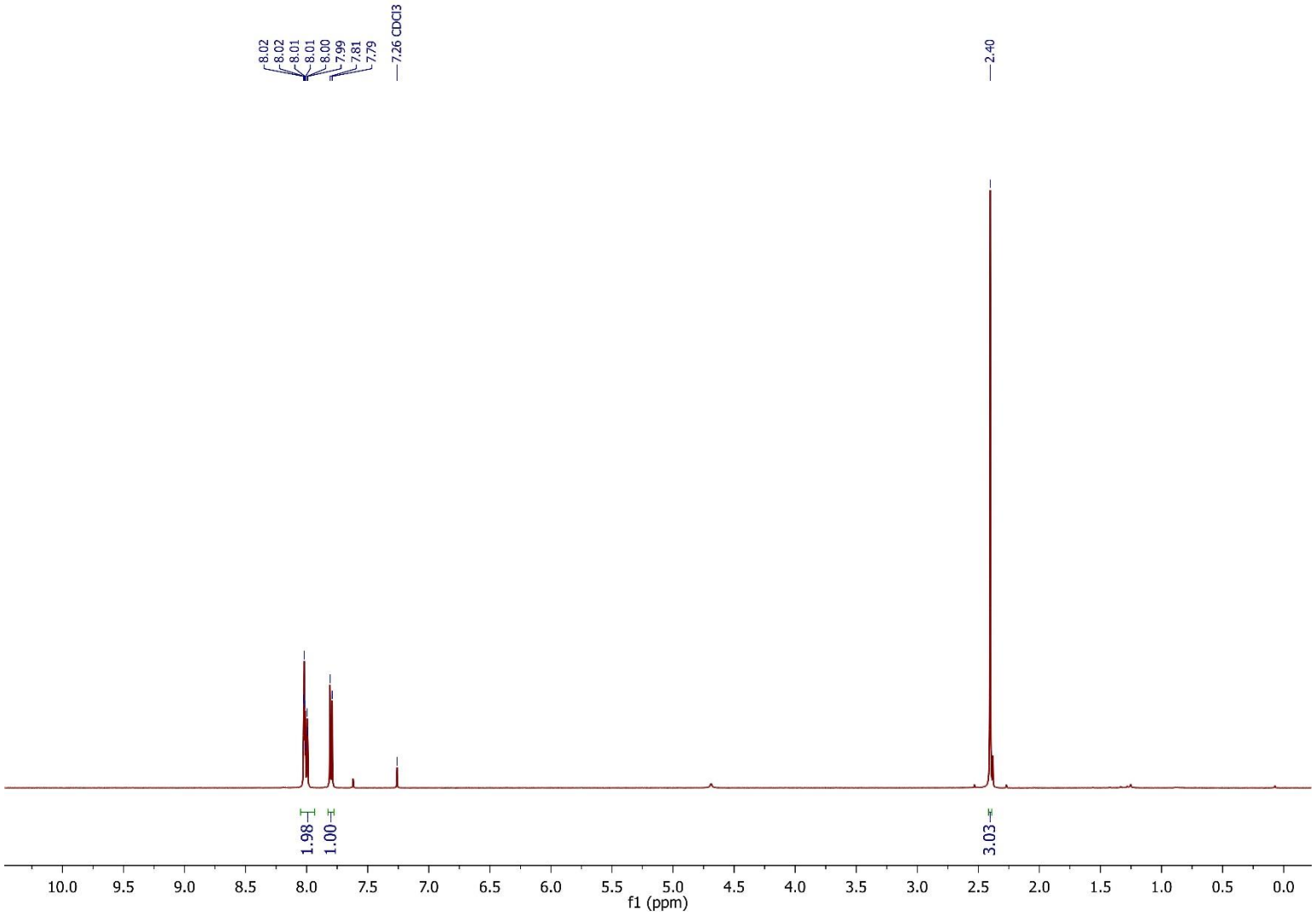
*^{13}C NMR of **S26** (126 MHz, $CDCl_3$)*

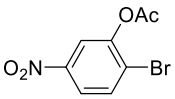


S26



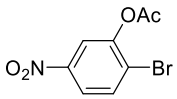
*^{1}H NMR of **S28** (500 MHz, $CDCl_3$)*



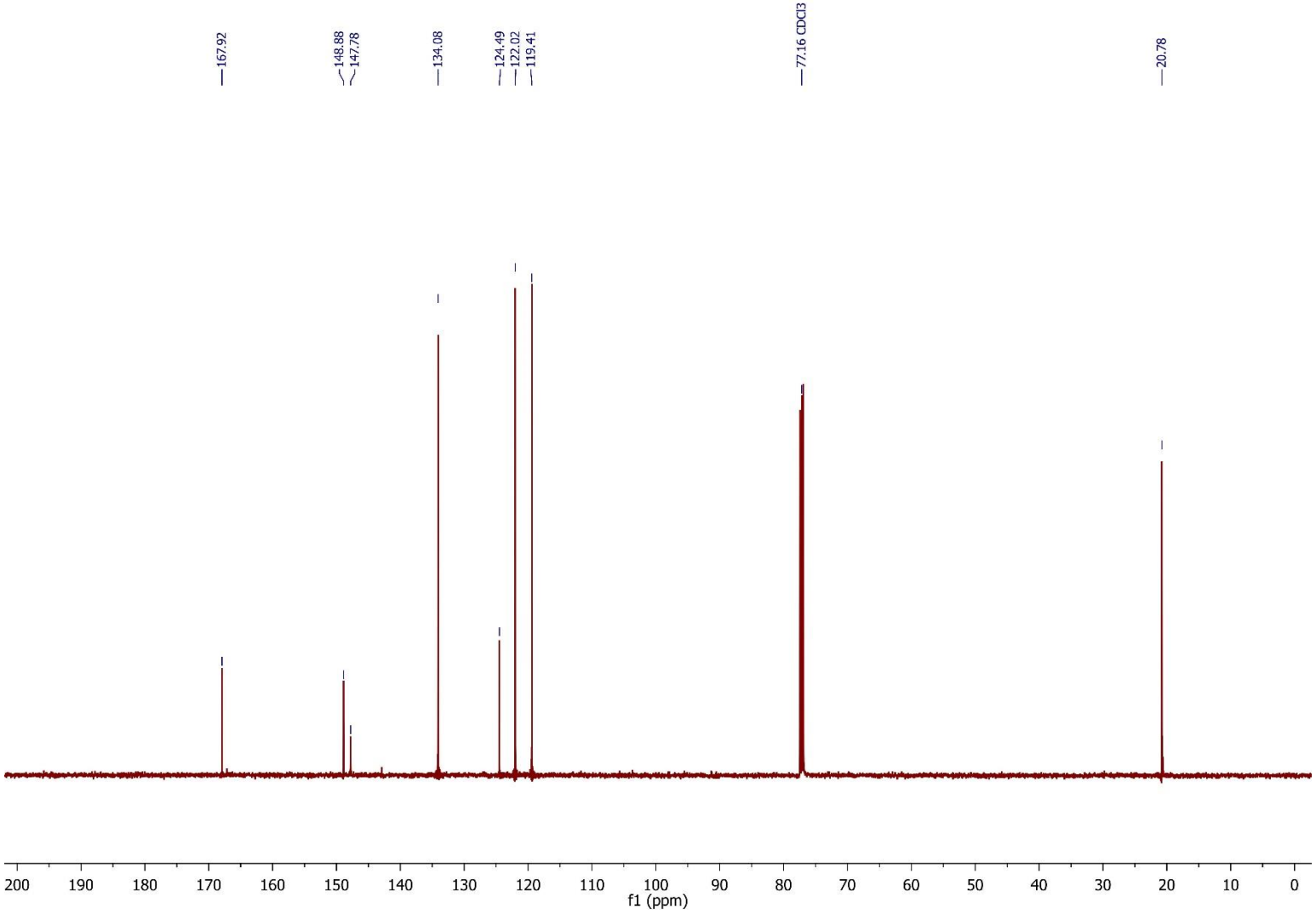


S28

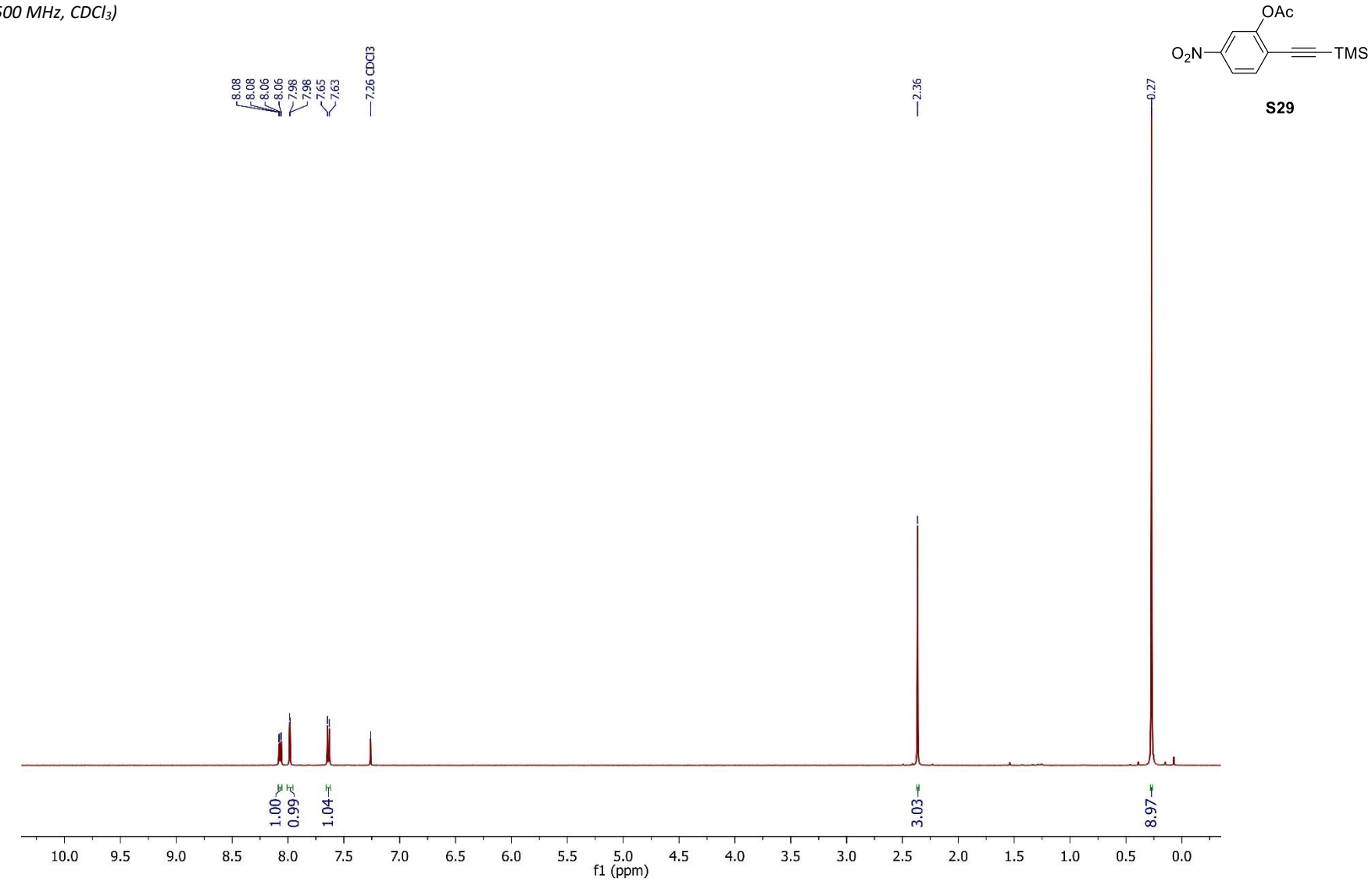
*^{13}C NMR of **S28** (126 MHz, $CDCl_3$)*



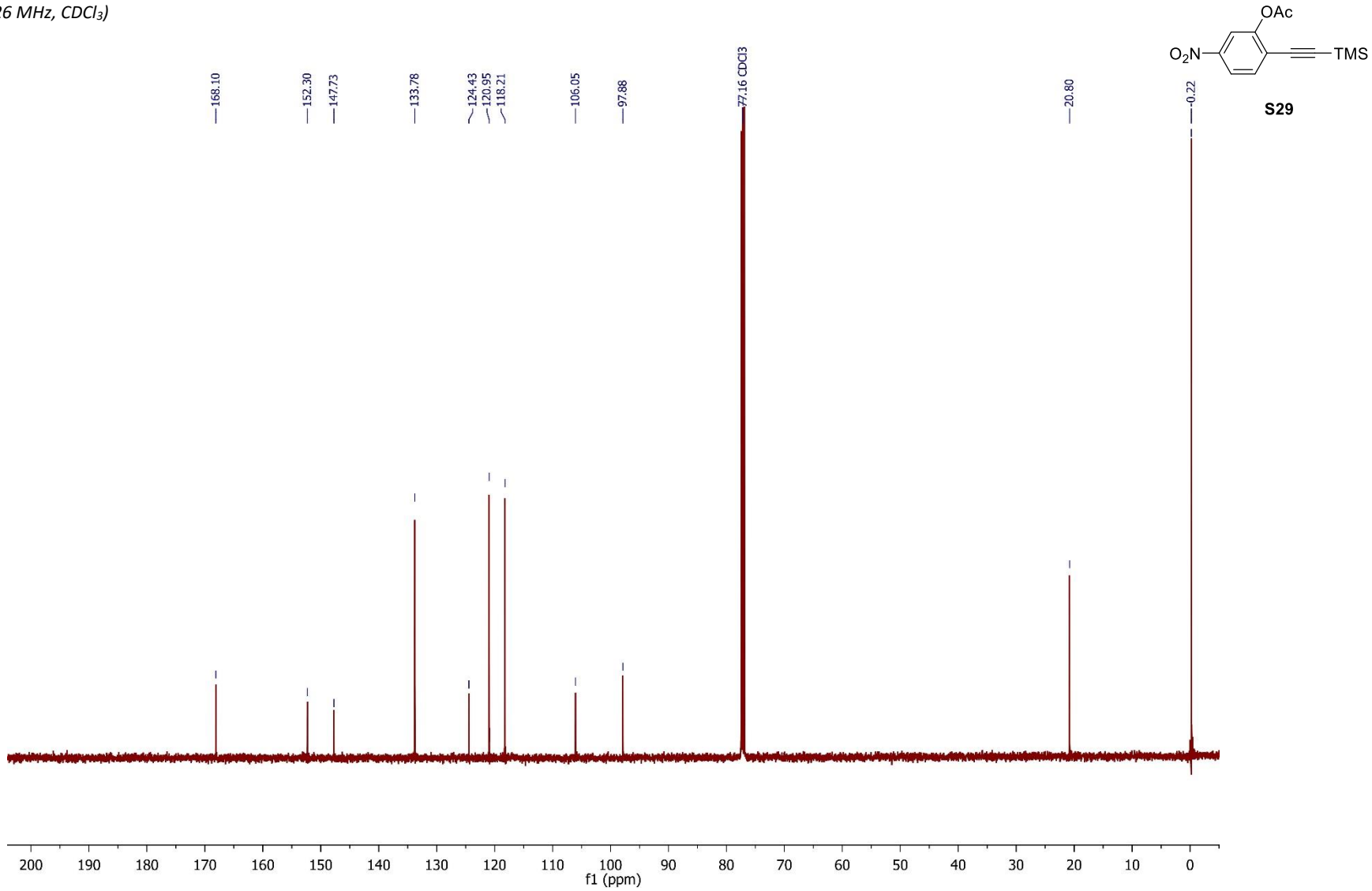
S28



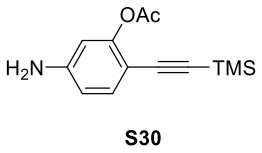
*^{1}H NMR of **S29** (500 MHz, $CDCl_3$)*



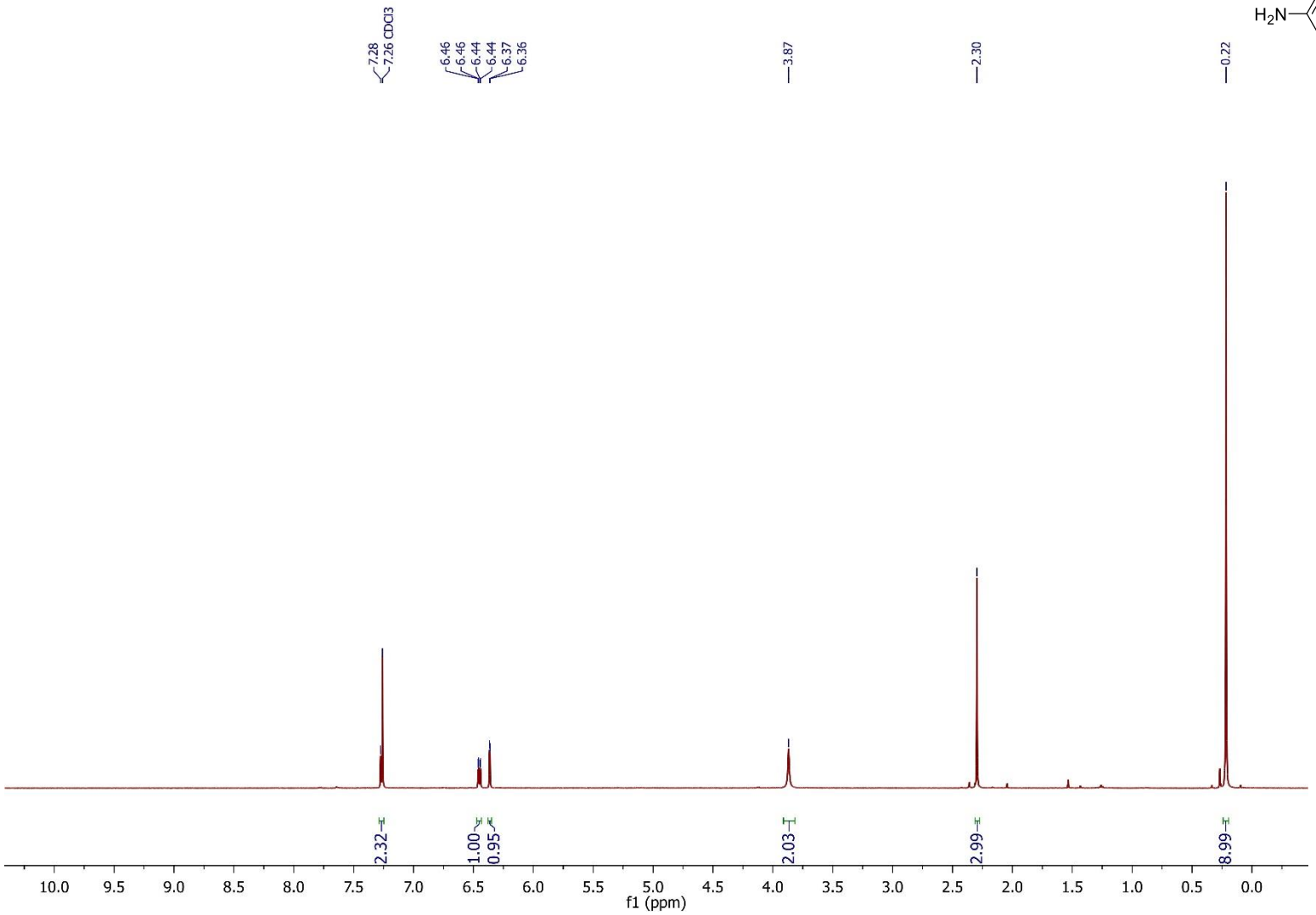
*^{13}C NMR of **S29** (126 MHz, $CDCl_3$)*



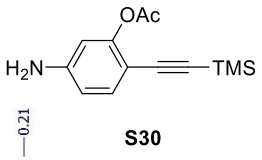
*^{1}H NMR of **S30** (500 MHz, $CDCl_3$)*



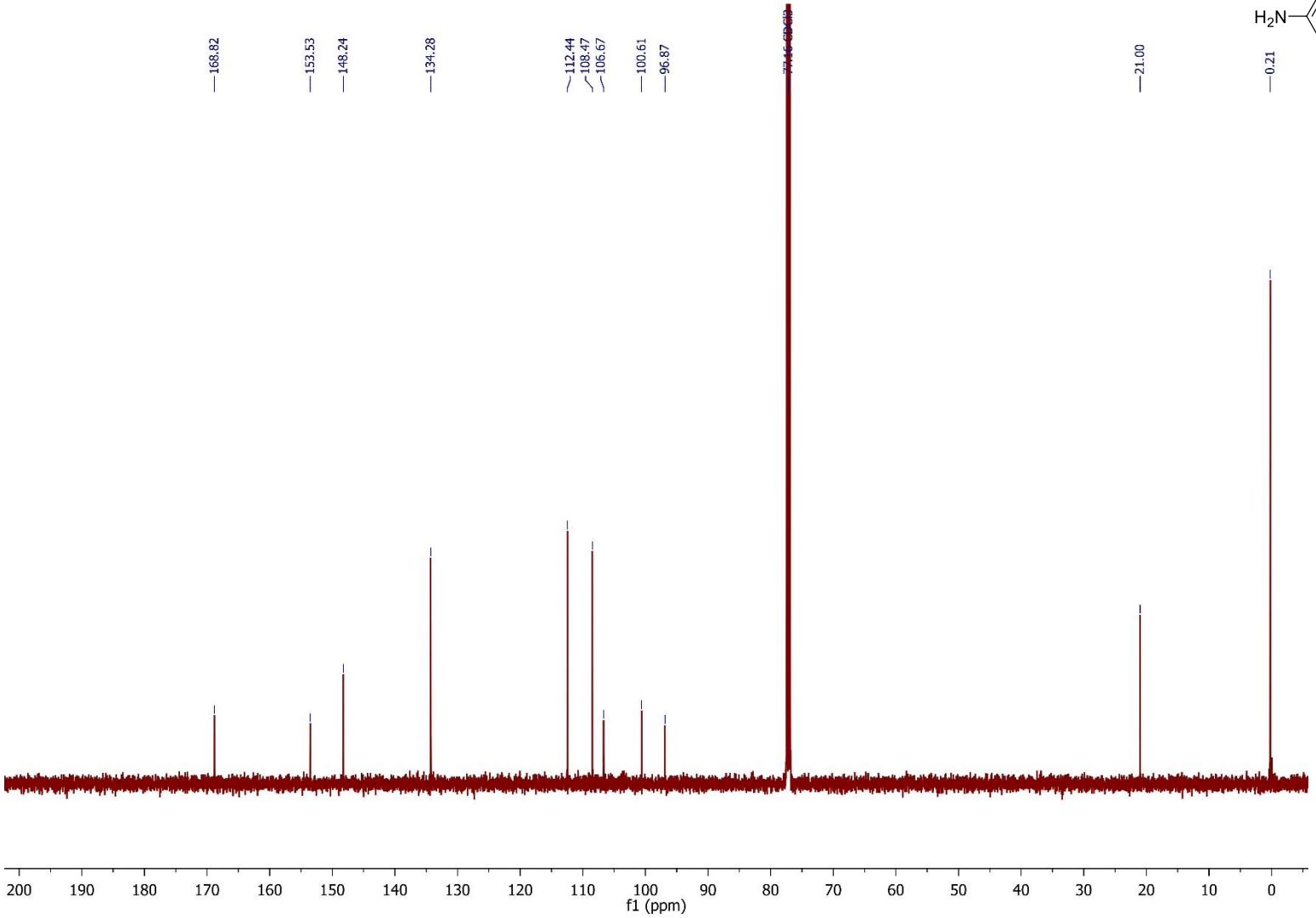
S30



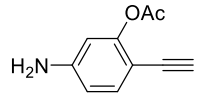
*^{13}C NMR of **S30** (126 MHz, $CDCl_3$)*



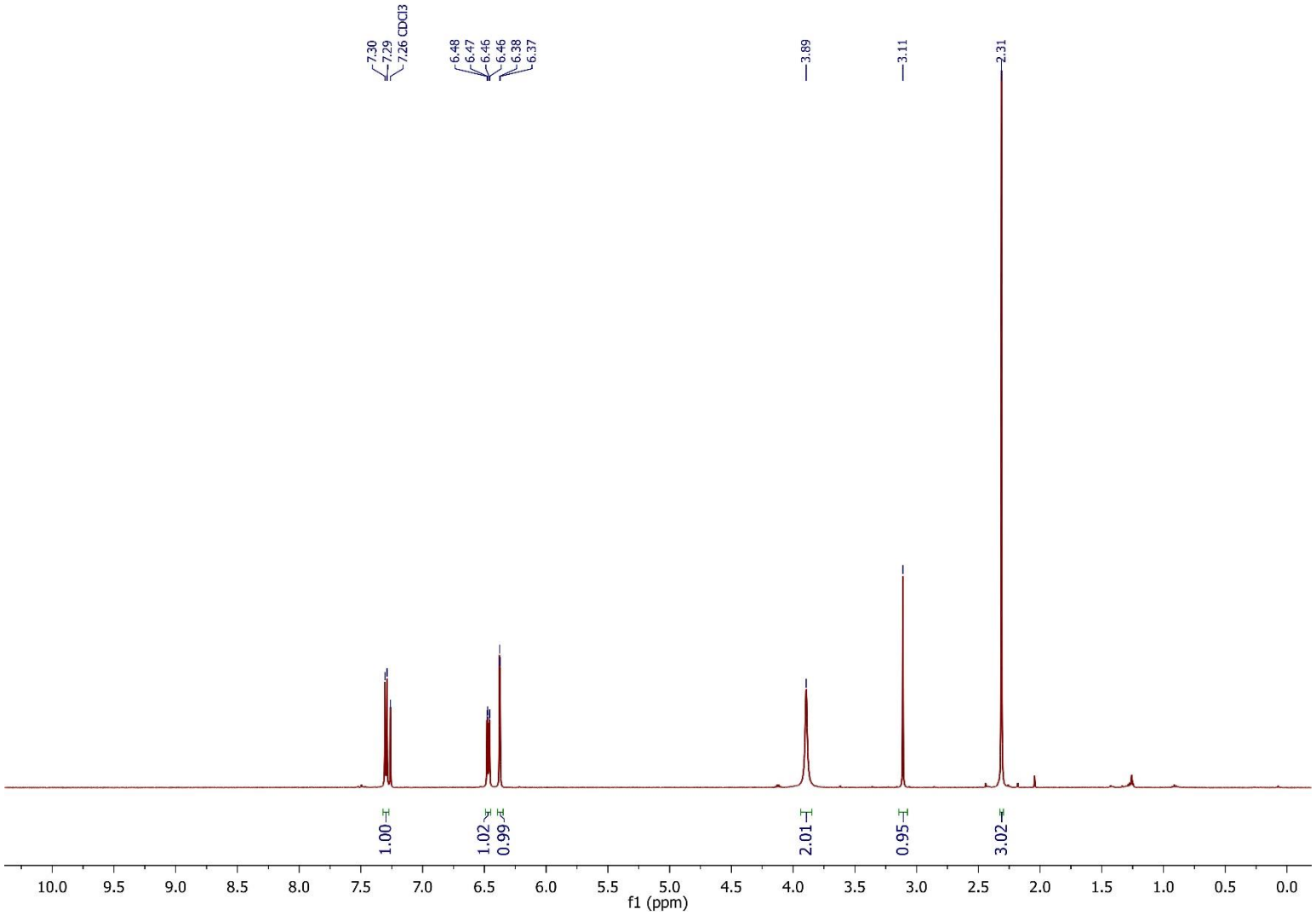
S30



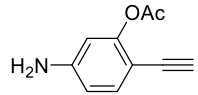
*^{1}H NMR of **S31** (500 MHz, $CDCl_3$)*



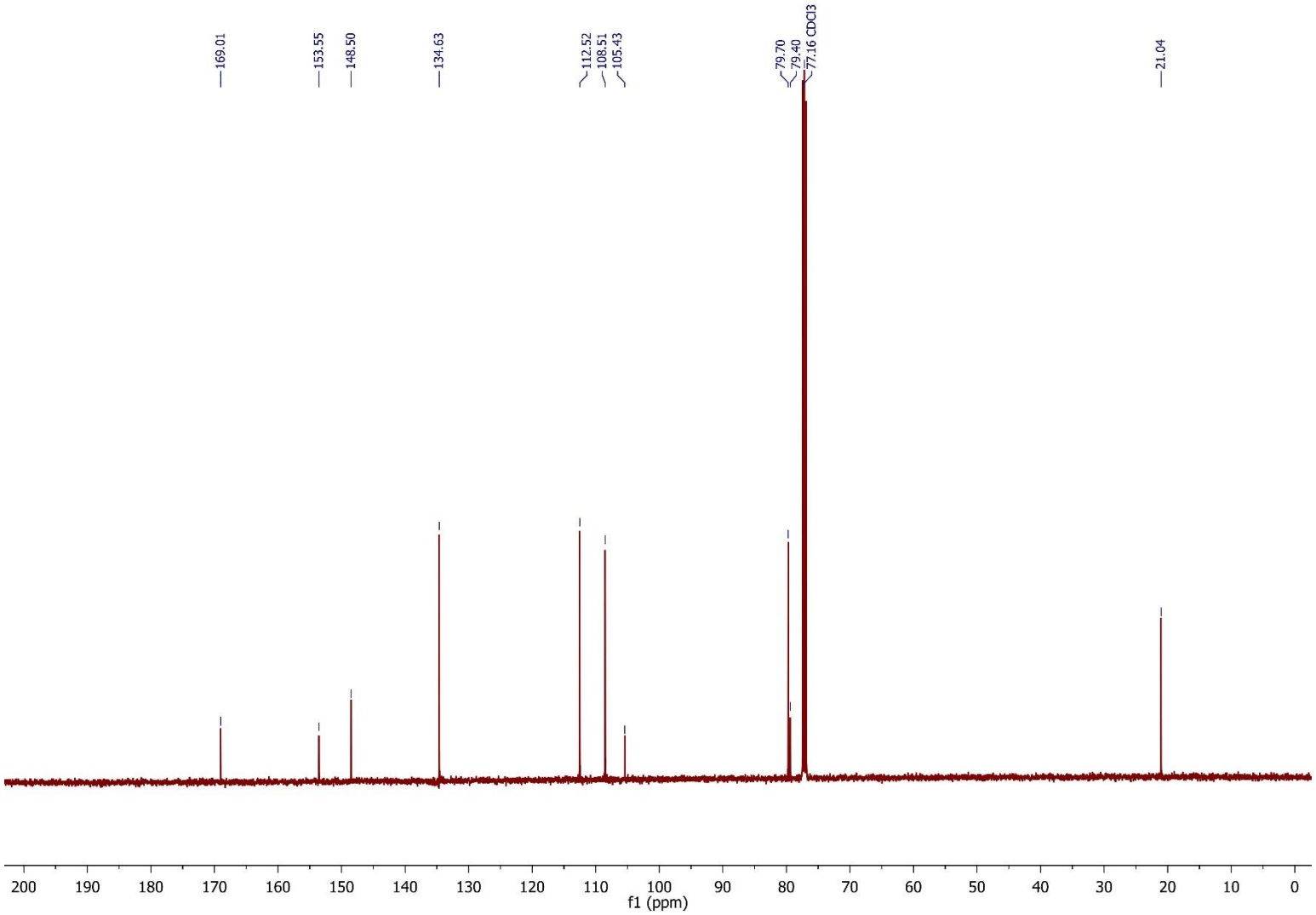
S31



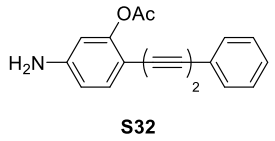
*^{13}C NMR of **S31** (126 MHz, $CDCl_3$)*

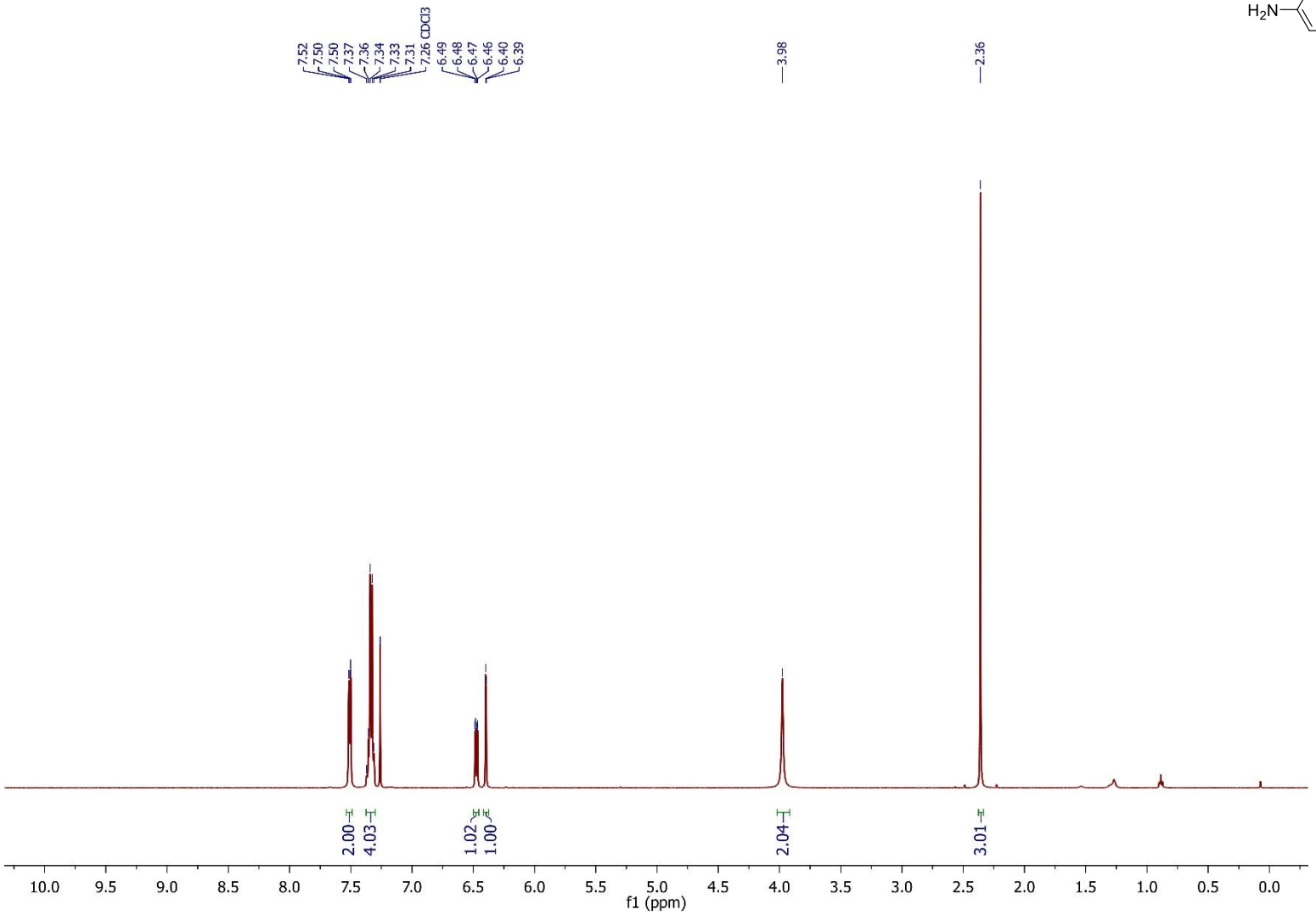


S31

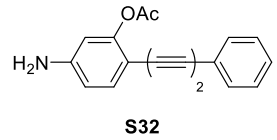


*^{1}H NMR of **S32** (500 MHz, $CDCl_3$)*





*^{13}C NMR of **S32** (126 MHz, $CDCl_3$)*



S32