Silver Triflate/*p*-TSA Co-Catalysed Synthesis of 3-Substituted Isocoumarins from 2-Alkynylbenzoates

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General experimental details: All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere. All chemicals and solvents are commercially available and were used without further purification. The chromatographic column separations were performed by flash technique, using silica gel (pore size 60Å, particle size 230-400 mesh, Merck Grade 9385). For thin-layer chromatography (TLC), Silica on TLC Alu foils with fluorescent indicator (254 nm) was employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 366 nm). ^{1}H NMR analysis were performed with 300 MHz and 500 MHz spectrometers at room temperature. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shifts (δ) in ppm. The multiplicity of the proton spectra were described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), dt (double triplet), dd (double doublet), td (triple doublet), m (multiplet), br (broad), ps (pseudo). ^{13}C NMR analysis were performed with the same instruments at 75 MHz and 125 MHz; APT sequence was used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. All ^{13}C NMR spectra were recorded with complete proton decoupling. Low resolution MS spectra were recorded with an electrospray/ion trap instrument, using a syringe pump device to directly inject sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown in brackets. Infrared spectra were recorded using discs of NaCl for liquid samples and KBr tablets for solid samples. The absorbance is reported in wavenumbers (cm^{-1}) with values between 4000 and 400 cm^{-1}. High resolution MS spectra were recorded with a ICR-FTMS electrospray equipped instrument. The melting points are uncorrected.

General procedure for the synthesis of methyl 2-halo(hetero)arylcarboxylates: The proper 2-haloarylcarboxylic acid (12 mmol) was dissolved in 60 mL of methanol. To the stirred reaction mixture 7.7 mL (12 eq) of concentrated sulfuric acid were then added dropwise. The reaction mixture was stirred at reflux until no more starting product was detected by TLC analysis. The reaction mixture was then cooled to rt and concentrated under reduced pressure. The residue was diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ (30 × 3 mL). The organic phase was dried over Na2SO4, filtered and the solvent was removed at reduced pressure.

Methyl 2-iodobenzoate: Reaction time: 3.0 h; Colorless oil. Yield 99% (3.14 g). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.9 Hz, 1H, arom), 7.80 (d, J = 7.4 Hz, 1H, arom), 7.40 (t, J = 7.5 Hz, 1H, arom), 7.15 (t, J = 7.4 Hz, 1H, arom), 3.93 (s, 3H, CH_3).Spectral data are in good agreement with literature values.[1]

Methyl 3-bromotiophene-2-carboxylate: Reaction time: 5.5 h; White solid. Yield 99% (2.65 g); mp 46-48 °C (lit. 47-48 °C). **^{1}H NMR (300 MHz, $CDCl_3$):** δ = 7.47 (d, *J* = 5.2 Hz, 1H, arom), 7.10 (d, *J* = 5.2 Hz, 1H, arom), 3.90 (s, 3H, CH_3). Spectral data are in good agreement with literature values.[2]

General procedure for the synthesis of methyl 2-alkynyl(hetero)arylcarboxylates. Method A: Under a nitrogen atmosphere, to a stirred solution of the proper methyl 2-haloarylcarboxylate (0,5 mmol) in anhydrous TEA (2 mL) the appropriate alkyne (0,6 mmol, 1.2 equiv) and trans-dichlorobis-(triphenylphosphine)palladium(II) (2 mol%) were added. The reaction was stirred at rt for 10 min, and then CuI (1 mol%) was added. The reaction mixture was stirred at 50 °C until no more starting product was detected by TLC analysis. The reaction mixture was filtered on Celite and the solvent was removed at reduced pressure. The crude material was purified by flash column chromatography over silica gel. **Method B:** Under a nitrogen atmosphere, to a stirred solution of the proper methyl 2-haloarylcarboxylate (0,5 mmol) in anhydrous DMF (2 mL) the appropriate alkyne (0,6 mmol, 1.2 equiv), trans-dichlorobis-(triphenylphosphine)palladium(II) (2 mol%) and K_2CO_3 (2,5 mmol, 5 equiv) were added. The reaction was stirred at rt for 10 min, and then CuI (1 mol%) was added. The reaction mixture was stirred at 50 °C until no more starting product was detected by TLC analysis. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (15 mL × 3). The organic layer was dried on Na_2SO_4 and then evaporated under reduced pressure. The crude material was purified by flash column chromatography over silica gel.

Methyl 2-(p-tolylethynyl)benzoate **(1a):** Method A. Reaction time: 1.5 h. Eluent for chromatography: hexane/EtOAc 95:5. Colorless oil. Yield 95% (119 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 7.8, 1.4 Hz, 1H, arom), 7.64 (dd, *J* = 7.8, 1.3 Hz, 1H, arom), 7.49 (dd, *J* = 12.0, 4.7 Hz, 3H, arom), 7.37 (td, *J* = 7.6, 1.4 Hz, 1H, arom), 7.17 (d, *J* = 7.8 Hz, 2H, arom), 3.96 (s, 3H, -OCH_3), 2.38 (s, 3H, CH_3). Spectral data are in good agreement with literature values.[3]

Methyl 2-(phenylethynyl)benzoate **(1b):** Method A. Reaction time: 1 h. Eluent for chromatography: hexane/EtOAc 9:1. Yellow oil. Yield 89% (105 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.01 – 7.95 (m, 1H, arom), 7.65 (dd, *J* = 7.7, 0.9 Hz, 1H, arom), 7.61 – 7.55 (m, 2H, arom), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H, arom), 7.43 – 7.31 (m, 4H, arom), 3.97 (s, 3H, CH_3). Spectral data are in good agreement with literature values.[3]

Methyl 2-((4-methoxyphenyl)ethynyl)benzoate **(1c):** Method A. Reaction time: 3 h. Eluent for chromatography: hexane/EtOAc 9:1. Colorless oil. Yield 99% (133 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.8 Hz, 1H, arom), 7.62 (d, *J* = 7.7 Hz, 1H, arom), 7.49 (dd, *J* = 16.3, 8.1

Hz, 3H, arom), 7.35 (t, *J* = 7.6 Hz, 1H, arom), 6.89 (d, *J* = 8.5 Hz, 2H, arom), 3.96 (s, 3H, -$COOCH_3$), 3.83 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[4]

Methyl 2-((2-methoxyphenyl)ethynyl)benzoate **(1d):** Method A. Reaction time: 1 h. Eluent for chromatography: hexane/EtOAc 95:5. Yellow oil. Yield 99% (133 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 7.8, 1.3 Hz, 1H, arom), 7.68 (dd, *J* = 7.8, 1.2 Hz, 1H, arom), 7.55 (dd, *J* = 7.6, 1.7 Hz, 1H, arom), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H, arom), 7.41 – 7.27 (m, 2H, arom), 6.95 (dt, *J* = 16.3, 4.8 Hz, 2H, arom), 3.97 (s, 3H, -$COOCH_3$), 3.93 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[5]

Methyl 2-((2-hydroxyphenyl)ethynyl)benzoate **(1e):** Method A. Reaction time: 1 h. Eluent for chromatography: hexane/EtOAc 3:1. Orange solid. Yields 97% (122 mg); mp 65-66 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 7.9, 0.6 Hz, 1H, arom), 7.64 (d, *J* = 7.7 Hz, 1H, arom), 7.49 (td, *J* = 7.3, 0.9 Hz, 1H, arom), 7.44 – 7.34 (m, 1H, arom), 7.21 (t, *J* = 7.8 Hz, 1H, arom), 7.14 (d, *J* = 7.6 Hz, 1H, arom), 7.05 (s, 1H, arom), 6.84 (dd, *J* = 7.9, 2.5 Hz, 1H, arom), 5.25 (s, 1H, -OH), 3.96 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.8 (C=O), 155.4 (C-OH), 134.0 (CH, arom), 131.8 (C, arom), 131.7 (CH, arom), 130.5 (CH, arom), 129.6 (CH, arom), 127.9 (CH, arom), 124.43 (C, arom), 124.36 (CH, arom), 123.61 (C, arom), 118.3 (CH, arom), 116.0 (CH, arom), 94.0 (C sp), 88.11 (C sp), 52.26 (CH_3). **MS** ESI (+): m/z (%) = 275 $[M+Na]^+$ (100), 253 $[M+1]^+$ (30); $C_{16}H_{12}O_3$ [252.26]. **IR** (KBr): ν_{max} = 3401, 2212, 1712, 1591, 1302, 1131 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{16}H_{13}O_3$ 253.0859, found 253.0863.

Methyl 2-((4-chlorophenyl)ethynyl)benzoate **(1f):** Method A. Reaction time: 1 h. Eluent for chromatography: hexane/EtOAc 98:2. Yellow oil. Yield 99% (135 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.99 (dd, *J* = 7.8, 1.4 Hz, 1H, arom), 7.67 – 7.61 (m, 1H, arom), 7.55 – 7.46 (m, 3H, arom), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H, arom), 7.37 – 7.31 (m, 2H, arom), 3.96 (s, 3H, -CH_3). Spectral data are in good agreement with literature values.[4]

Methyl 2-((4-cyanophenyl)ethynyl)benzoate **(1g):** Method B. Reaction time: 5 h. Eluent for chromatography: hexane/EtOAc 8:2. Yellow solid. Yield 91% (119 mg); mp 81-82 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 7.8, 0.9 Hz, 1H, arom), 7.66 (d, *J* = 5.5 Hz, 5H, arom), 7.49 (dtd, *J* = 28.0, 7.5, 1.4 Hz, 2H, arom), 3.96 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.2 (C=O), 134.1 (CH, arom), 132.2 (CH, arom, 2C), 132.02 (CH, arom, 2C), 131.98 (C, arom), 131.85 (CH, arom), 130.6 (CH, arom), 128.7 (CH, arom), 128.3 (C, arom), 122.8 (C, arom), 118.5 (CN), 111.7 (C, arom), 92.5 (C sp), 92.3 (C sp), 52.3 (CH_3). **MS** ESI (+): m/z (%) = 262 $[M+1]^+$ (100); $C_{17}H_{11}NO_2$ [261.27]. **IR** (KBr): ν_{max} = 2223, 1706, 1604, 1296, 1125 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{17}H_{12}NO_2$ 262.0863, found 262.0855.

Methyl 2-((4-(trifluoromethyl)phenyl)ethynyl)benzoate **(1h):** Method A. Reaction time: 1 h. Eluent for chromatography: hexane/EtOAc 95:5. Yellow oil. Yield 87% (132 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.09 – 7.92 (m, 1H, arom), 7.66 (ddt, *J* = 15.9, 15.1, 4.6 Hz, 5H, arom), 7.52 (td, *J* = 7.6, 1.5 Hz, 1H, arom), 7.42 (td, *J* = 7.7, 1.4 Hz, 1H, arom), 3.96 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.4 (C=O), 134.1 (CH, arom), 131.94 (C, arom), 131.91 (CH, 2C, arom), 131.8 (CH, arom), 130.6 (CH, arom), 130.1 (q, $^2J_{(C,F)}$ = 32 Hz, 1C, C-CF_3), 128.5 (CH, arom), 127.1 (C, arom), 125.3 (q, $^3J_{(C,F)}$ = 4 Hz, 2C, CH-C-CF3), 123.0 (C, arom), 123.9 (q, $^1J_{(C,F)}$ = 272 Hz, 1C, CF_3), 92.7 (C sp), 90.5 (C sp), 52.3 (CH_3). **MS** ESI (+): m/z (%) = 305 $[M+1]^+$ (100), 327 $[M+Na]^+$ (20); $C_{17}H_{11}F_3O_2$ [304.26]. **IR** (NaCl): ν_{max} = 1726, 1610, 1321, 1257, 1163 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{17}H_{12}F_3O_2$ 305.0784, found 305.0802.

Methyl 2-((3-(trifluoromethyl)phenyl)ethynyl)benzoate **(1i):** Method A. Reaction time: 1.5 h. Eluent for chromatography: hexane/EtOAc 95:5. Colorless oil. Yield 77% (117 mg). **^{1}H NMR** (300 MHz, $CDCl_3$)**:** δ = 8.01 (dd, *J* = 7.8, 0.8 Hz, 1H, arom), 7.83 (s, 1H, arom), 7.75 (d, *J* = 7.7 Hz, 1H, arom), 7.66 (d, *J* = 7.7 Hz, 1H, arom), 7.59 (d, *J* = 7.9 Hz, 1H, arom), 7.50 (dt, *J* = 11.1, 7.1 Hz, 2H, arom), 7.42 (td, *J* = 7.7, 1.2 Hz, 1H, arom), 3.97 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.4 (C=O), 134.8 (CH, arom), 134.1 (CH, arom), 131.9 (C, arom), 131.8 (CH, arom), 131.0 (q, $^2J_{(C,F)}$ = 32 Hz, 1C, C-CF_3), 130.6 (CH, arom), 128.9 (CH, arom), 128.42 (q, $^3J_{(C,F)}$ = 4 Hz, 1C, CH-C-CF_3), 128.36 (CH, arom), 125.0 (q, $^3J_{(C,F)}$ = 4 Hz, 1C, CH-C-CF_3), 124.3 (C, arom), 123.7 (q, $^1J_{(C,F)}$ = 272 Hz, 1C, CF_3), 123.1 (C, arom), 92.5 (C sp), 89.7 (C sp), 52.2 (CH_3). **MS** ESI (+): m/z (%) = 305 $[M+1]^+$ (100), 367 $[M+Na]^+$ (80); $C_{17}H_{11}F_3O_2$ [304.26]. **IR** (NaCl): ν_{max} = 1730, 1657, 1340, 1255, 1128 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{17}H_{12}F_3O_2$ 305.0784, found 305.0795.

Methyl 2-((4-nitrophenyl)ethynyl)benzoate **(1j):** Method B. Reaction time: 2 h. Eluent for chromatography: hexane/EtOAc 9:1. Yellow solid. Yield 95% (120 mg); mp 119-120 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.26 – 8.21 (m, 2H, arom), 8.03 (dd, *J* = 7.8, 1.4 Hz, 1H, arom), 7.75 – 7.69 (m, 2H, arom), 7.68 (dd, *J* = 7.7, 1.3 Hz, 1H, arom), 7.55 (td, *J* = 7.6, 1.4 Hz, 1H, arom), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H, arom), 3.97 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.2 (C=O), 147.2 (C, arom), 134.2 (CH, arom), 132.43 (CH, arom), 132.4 (CH, arom), 132.0 (C, arom), 131.9 (CH, arom), 130.7 (CH, arom), 130.3 (C, arom), 128.9 (CH, arom), 123.64 (CH, arom), 123.61 (CH, arom), 122.7 (C, arom), 93.4 (C sp), 92.1 (C sp), 52.3 (CH_3). **MS** ESI (+): m/z (%) = 282 $[M+1]^+$ (100), 304 $[M+Na]^+$ (20); $C_{16}H_{11}NO_4$ [281.26]. **IR** (KBr): ν_{max} = 2217, 1710, 1590, 1513, 1346, 1301 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{16}H_{12}NO_4$ 282.0761, found 282.0775.

Methyl 2-((2-nitrophenyl)ethynyl)benzoate **(1k):** Method A. Reaction time: 3 h. Eluent for chromatography: hexane/EtOAc 8:2. Green solid. Yield 69% (97 mg); mp 90-91 °C. **^{1}H NMR** (300

MHz, $CDCl_3$): δ = 8.07 (ddd, *J* = 25.4, 8.0, 1.1 Hz, 2H, arom), 7.80 (ddd, *J* = 20.0, 7.7, 1.1 Hz, 2H, arom), 7.64 (td, *J* = 7.6, 1.2 Hz, 1H, arom), 7.50 (dddd, *J* = 15.2, 11.8, 7.6, 1.3 Hz, 3H, arom), 3.99 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.8 (C=O), 149.82 (C, arom), 135.4 (CH, arom), 135.1 (CH, arom), 133.3 (CH, arom), 132.4 (C, arom), 132.3 (CH, arom), 131.0 (CH, arom), 129.3 (CH, arom), 129.2 (CH, arom), 125.1 (CH, arom), 123.3 (C, arom), 119.3 (C, arom), 96.2 (C sp), 89.8 (C sp), 52.7 (CH_3). **MS** ESI (+): m/z (%) = 304 $[M+Na]^+$ (100), 282 $[M+1]^+$ (50); $C_{16}H_{11}NO_4$ [281.26]. **IR** (KBr): ν_{max} = 2217, 1720, 1607, 1517, 1341, 1301, 113 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{16}H_{12}NO_4$ 282.0761, found 282.0758.

Methyl 2-(3,3-diethoxyprop-1-yn-1-yl)benzoate **(1l):** Method A. Reaction time: 4 h. Eluent for chromatography: hexane/EtOAc 9:1. Green oil. Yield 96% (126 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 7.7, 1.1 Hz, 1H, arom), 7.59 (dd, *J* = 7.6, 1.1 Hz, 1H, arom), 7.42 (dtd, *J* = 22.4, 7.5, 1.5 Hz, 2H, arom), 5.53 (s, 1H, -CHO_2-), 3.91 (s, 3H, -OCH_3), 3.89 – 3.60 (m, 4H, -$\underline{CH_2}$-CH_3), 1.28 (t, *J* = 7.1 Hz, 6H, -CH_2-$\underline{CH_3}$). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.4 (C=O), 134.4 (CH, arom), 132.3 (C, arom), 131.6 (CH, arom), 130.3 (CH, arom), 128.4 (CH, arom), 122.3 (C, arom), 91.9 (CH sp^3), 89.4 (C sp), 83.7 (C sp), 61.0 (-$\underline{C}H_2$-CH_3, 2C), 52.1 (CH_3), 15.1 (-CH_2-$\underline{C}H_3$, 2C). **MS** ESI (+): m/z (%) = 203 $[M - C_2H_5O - CH_3]^+$ (100), 189 [aldehyde+1]$^+$ (96), 285 $[M+Na]^+$ (48), 217 $[M - C_2H_5O]^+$ (46), 249 $[M - CH_3]^+$ (3); $C_{15}H_{18}O_4$ [262.30]. **IR** (NaCl): ν_{max} = 2236, 1702, 1596 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{15}H_{19}O_4$ 263.1278, found 263.1269.

Methyl 2-(pent-1-yn-1-yl)benzoate **(1m):** Method A. Reaction time: 17.5 h. Eluent for chromatography: hexane/EtOAc 98:2. Colorless oil. Yield 81% (83 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.88 (dd, *J* = 1.2 Hz, 1H, arom), 7,50 (dd, *J* = 7.6, 1.2 Hz 1H, arom), 7.42 (td, *J* = 7.6, 1.2 Hz, 1H, arom), 7.29 (td, *J* = 7.6, 1.2 Hz, 1H, arom), 3.91 (s, 3H, -OCH_3), 2.45 (t, *J* = 7.2 Hz, 2H, -CH_2-), 1.66 (sex, *J* = 7.2 Hz, 2H, -CH_2-), 1.05 (t, *J* = 7.2 Hz, 3H, -CH_3). Spectral data are in good agreement with literature values.[6]

Methyl 2-(non-1-yn-1-yl)benzoate **(1n):** Method A. Reaction time: 24 h. Eluent for chromatography: hexane/EtOAc 98:2. Yellow oil. Yield 56% (72 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.92 – 7.85 (m, 1H, arom), 7.50 (d, *J* = 7.7 Hz, 1H, arom), 7.42 (td, *J* = 7.6, 1.1 Hz, 1H, arom), 7.30 (td, *J* = 7.6, 1.1 Hz, 1H, arom), 3.91 (s, 3H, -OCH_3), 2.47 (t, *J* = 7.1 Hz, 2H, -CH_2-), 1.72 – 1.56 (m, 3H, -CH_2-), 1.39 – 1.24 (m, 7H, -CH_2-), 0.89 (t, *J* = 6.7 Hz, 3H, -CH_2-$\underline{CH_3}$). **^{13}C NMR (75 MHz, $CDCl_3$):** δ = 167.0 (C=O), 134.2 (CH, arom), 132.0 (C, arom), 131.4 (CH, arom), 130.1 (CH, arom), 127.1 (CH, arom), 124.5 (C, arom), 96.1 (C sp), 79.2 (C sp), 52.0 (-COO$\underline{C}H_3$), 31.8, 28.92, 28.86, 28.72, 22.6, 19.8 (-CH_2-), 14.1 (-CH_2-$\underline{C}H_3$). **MS ESI (+):** m/z (%) = 259 $[M+1]^+$ (100), 281 $[M+Na]^+$ (85);

$C_{17}H_{22}O_2$ [258.36]. **IR (NaCl):** ν_{max} = 2928, 1718, 1597, 1293, 1083 cm^{-1} **HRMS** ESI $(M+1)^+$ calculated for $C_{17}H_{23}O_2$ 259.1693, found 259.1684.

Methyl 2-((trimethylsilyl)ethynyl)benzoate **(1o):** Method A. Reaction time: 21.5 h. Eluent for chromatography: hexane/EtOAc 95:5. Colorless oil. Yield 66% (77 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 7.8, 1.0 Hz, 1H, arom), 7.58 (dd, *J* = 7.6, 1.0 Hz, 1H, arom), 7.44 (td, *J* = 7.6, 1.5 Hz, 1H, arom), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H, arom), 3.92 (s, 3H, -OCH_3), 0.27 (s, 9H, -$Si(CH_3)_3$). Spectral data are in good agreement with literature values.[6]

Methyl 2-(thiophen-3-ylethynyl)benzoate **(1p):** Method A. Reaction time: 1.5 h. Eluent for chromatography: hexane/EtOAc 9:1. Yellow oil. Yield 96% (116 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.8 Hz, 1H, arom), 7.63 (d, *J* = 7.7 Hz, 1H, arom), 7.59 – 7.55 (m, 1H, arom), 7.49 (td, *J* = 7.6, 1.2 Hz, 1H, arom), 7.38 (td, *J* = 7.8, 1.1 Hz, 1H, arom), 7.31 (dd, *J* = 4.9, 3.0 Hz, 1H, arom), 7.24 (dd, *J* = 5.0, 0.8 Hz, 1H, arom), 3.96 (s, 3H, CH_3). Spectral data are in good agreement with literature values.[7]

Methyl 3-((4-chlorophenyl)ethynyl)thiophene-2-carboxylate **(1q):** Method A. Reaction time: 24 h. Eluent for chromatography: hexane/EtOAc 97:3. Orange solid. Yield 76% (105 mg); mp 75-76 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.55 – 7.48 (m, 2H, arom), 7.47 (d, *J* = 5.1 Hz, 1H, arom), 7.37 – 7.30 (m, 2H, arom), 7.20 (d, *J* = 5.1 Hz, 1H, arom), 3.93 (s, 3H, -CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 161.7 (C=O), 134.8 (C, arom), 133.6 (C, arom), 133.0 (CH, arom, 2C), 132.0 (CH, arom), 130.5 (CH, arom), 128.8 (CH, arom, 2C), 127.1 (C, arom), 121.5 (C, arom), 94.1 (C sp), 84.8 (C sp), 52.2 (CH_3). **MS** ESI (+) (+ AcOH): m/z (%) = 245 $[M(^{35}Cl)\text{-}CH_3O]^+$ (100), 247 $[M(^{37}Cl)\text{-}CH_3O]^+$ (51); $C_{14}H_9ClO_2S$ [276.74]. **IR** (KBr): ν_{max} = 3092, 2919, 2023, 1710, 1592, 1301, 1096, 774, 524 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{14}H_{10}ClO_2S$ 277.0085, found 277.0076.

Methyl 3-((4-methoxyphenyl)ethynyl)thiophene-2-carboxylate **(1r):** Method A. Reaction time: 8 h. Eluent for chromatography: hexane/EtOAc 9:1. Yellow solid. Yield 85% (116 mg); mp 95-97 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.61 – 7.49 (m, 2H, arom), 7.46 (d, *J* = 5.1 Hz, 1H, arom), 7.19 (d, *J* = 5.1 Hz, 1H, arom), 6.97 – 6.77 (m, 2H, arom), 3.93 (s, 3H, -$COOCH_3$), 3.83 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[8]

Methyl 2-((4-methoxyphenyl)ethynyl)nicotinate **(1s):** Method A. Reaction time: 2.5 h. Eluent for chromatography: hexane/EtOAc 7:3. Orange oil. Yield 99% (134 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7 8.73 (dd, *J* = 4.8, 1.8 Hz, 1H, arom), 8.27 (dd, *J* = 8.0, 1.8 Hz, 1H, arom), 7.67 – 7.52 (m, 2H, arom), 7.31 (dd, *J* = 8.0, 4.8 Hz, 1H, arom), 6.97 – 6.84 (m, 2H, arom), 4.00 (s, 3H, -$COOCH_3$), 3.84 (s, 3H, -OCH_3). Spectral data are in good agreement with literature values.[4]

Methyl 2-(pyridin-2-ylethynyl)benzoate **(1t):** Method A. Reaction time: 3 h. Eluent for chromatography: hexane/EtOAc 6:4. Yellow oil. Yield 74% (88 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 4.5 Hz, 1H, arom), 8.01 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.71 (ddd, *J* = 16.5, 7.7, 1.4 Hz, 2H. arom), 7.60 (d, *J* = 7.8 Hz, 1H, arom), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H, arom), 7.43 (td, *J* = 7.7, 1.3 Hz, 1H, arom), 7.29 – 7.21 (m, 1H, arom), 3.97 (s, 3H, CH_3). Spectral data are in good agreement with literature values.[6]

Methyl 5-nitro-2-((4-(trifluoromethyl)phenyl)ethynyl)benzoate (**1u**): Method B. Reaction time: 3 h. Eluent for chromatography: hexane/EtOAc 9:1. Orange solid. Yield 86% (175 mg); mp 114-116 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.88 (d, *J* = 2.4 Hz, 1H, arom), 8.38 (dd, *J* = 8.6, 2.4 Hz, 1H, arom), 7.84 (d, *J* = 8.6 Hz, 1H, arom), 7.71 (dd, *J* = 19.9, 8.3 Hz, 4H, arom), 4.04 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 164.3 (C=O), 146.8 (C, arom), 135.05 (CH, arom), 133.1 (C, arom), 132.3 (CH, arom, 2C), 131.1 (q, $^2J_{(C,F)}$ = 32 Hz, 1C, C-CF_3), 129.5 (C, arom), 126.2 (CH, arom), 126.0 (C, arom), 125.9 (CH, arom), 125.5 (q, $^3J_{(C,F)}$ = 4 Hz, 2C, CH-C-CF_3) 123.8 (q, $^1J_{(C,F)}$ = 272 Hz, 1C, CF_3), 98.2 (C sp), 88.8 (C sp), 52.9 (CH_3). **MS ESI (+):** m/z (%) = 350 $[M+1]^+$ (100), 372 $[M+Na]^+$ (15); $C_{17}H_{10}F_3NO_4$ [349.26]. **IR** (KBr): ν_{max} = 2955, 2220, 1735, 1606, 1522, 1341, 1324, 1255, 1063 cm^{-1} **HRMS** ESI $(M+1)^+$ calculated for $C_{17}H_{11}F_3NO_4$ 350.0635, found 350.0622.

Methyl 2-((4-chlorophenyl)ethynyl)-5-methoxybenzoate (**1v**): Method A. Reaction time: 24 h. Eluent for chromatography: hexane/EtOAc 95:5. Dark orange oil. Yield 61% (92 mg – 20% s.m. recovered). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.55 (1H, d, *J* = 8.6 Hz, arom), 7.50 – 7.44 (3H, m, arom), 7.31 (2H, d, *J* = 8.8, Hz, arom), 7.03 (1H, dd, *J* = 8.6, 2.8 Hz, arom), 3.95 (3H, s, CH_3), 3.86 (3 H, s, CH_3).**^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.4 (C=O), 159.2 (C arom), 135.3 (CH arom), 134.1(C arom), 133.2 (C arom), 132.7 (CH arom), 128.6 (CH arom), 122.2 (C arom), 118.3 (CH arom), 115.6 (C arom), 115.2 (CH arom), 91.4 (C sp), 89.2 (C sp), 55.5 (CH_3), 52.2 (CH_3). **MS ESI** (+): m/z (%) = 301 $[M+1]^+$ (100), 323 $[M+Na]^+$ (10); $C_{17}H_{13}ClO_3$ [300.74]. **HRMS** ESI $(M+1)^+$ calculated for $C_{17}H_{14}ClO_3$ 301.0626, found 301.0635.

Methyl 2-(3-hydroxy-3-methylbut-1-yn-1-yl)benzoate **(1w):** Method A. Reaction time: 24 h. Eluent for chromatography: hexane/EtOAc 6:4. Yellow oil. Yield 62% (68 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.97 – 7.88 (m, 1H, arom), 7.55 – 7.49 (m, 1H, arom), 7.45 (td, *J* = 7.5, 1.5 Hz, 1H, arom), 7.40 – 7.30 (m, 1H, arom), 3.92 (s, 3H, -$COOCH_3$), 2.06 (s, 1H, -OH), 1.64 (s, 6H, CH_3). Spectral data are in good agreement with literature values.[9]

General procedure for the synthesis of isocoumarins and thienopyranones: Under a nitrogen atmosphere, to a solution of the appropriate methyl 2-arylalkynylbenzoate (0.4 mmol) in dichloroethane (1.6 mL) AgOTf (1 mol%) and *p*-TSA·H_2O (0.12 mmol, 30 mol%) were added. The reaction was stirred at 60 °C until no more starting product was detected by TLC. The reaction mixture was then concentrated under reduced pressure, diluted with EtOAc (15 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL × 2) and brine (15 mL × 2). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed at reduced pressure. The crude material was purified by flash column chromatography over silica gel.

3-(p-Tolyl)-1H-isochromen-1-one **(2a):** Reaction time: 2.5 h. Eluent for chromatography: hexane/EtOAc 95:5. White solid. Yield 85% (80 mg); mp 113-115 °C (lit. 108-110 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 8.1, 0.7 Hz, 1H, arom), 7.78 (d, *J* = 8.3 Hz, 2H, arom), 7.71 (td, *J* = 7.4, 1.3 Hz, 1H, arom), 7.53 – 7.41 (m, 2H, arom), 7.27 (d, *J* = 7.9 Hz, 3H, arom), 6.91 (s, 1H, arom), 2.41 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 162.4 (C=O), 153.9 (C, arom), 140.3 (C, arom), 137.7 (C, arom), 134.8 (CH, arom), 129.6 (CH, arom), 129.5 (CH, arom, 2C), 129.2 (C, arom), 127.9 (CH, arom), 125.8 (CH, arom), 125.2 (CH, arom, 2C), 120.4 (C, arom), 101.1 (CH, arom), 21.4 (CH_3). **MS** ESI (+): m/z (%) = 259 $[M+Na]^+$ (100), 237 $[M+1]^+$ (35); $C_6H_{12}O_2$ [236.27]. **IR** (KBr): ν_{max} = 3032, 2918, 1730, 1603, 1307, 1182 cm^{-1}. Spectral data are in good agreement with literature values.[10]

***3**-Phenyl-1H-isochromen-1-one* **(2b):** Reaction time: 3 h. Eluent for chromatography: hexane/EtOAc 8:2. White solid. Yield 96% (85 mg); mp 81-83 °C (lit. 87-89 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.2 Hz, 1H, arom), 7.90 (dd, *J* = 7.9, 1.7 Hz, 2H, arom), 7.74 (t, *J* = 8.1 Hz, 1H, arom), 7.57 – 7.43 (m, 5H, arom), 6.97 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 162.7 (C=O), 154.1 (C, arom), 137.9 (C, arom), 135.3 (CH, arom), 132.4 (C, arom), 130.4 (CH, arom), 130.3 (CH, arom), 130.1 (CH, arom), 129.2 (CH, arom), 128.6 (CH, arom), 128.5 (CH, arom), 126.4 (CH, arom), 125.7 (CH, arom), 121.0 (C, arom), 102.2 (CH, arom). **MS** ESI (+): m/z (%) = 223 $[M+1]^+$ (100), 245 $[M+Na]^+$ (20); $C_{15}H_{10}O_2$ [222.24]. **IR** (KBr): ν_{max} = 3102, 1721, 1610, 1239, 1071 cm^{-1}. Spectral data are in good agreement with literature values.[10]

3-(4-Methoxyphenyl)-1H-isochromen-1-one **(2c):** Reaction time: 4 h. Eluent for chromatography: hexane/EtOAc 8:2. White solid. Yield 86% (87 mg); mp 110-114 °C (lit. 120-122). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 8.4 Hz, 1H, arom), 7.84 – 7.77 (m, 2H, arom), 7.68 (td, *J* = 7.4, 1.3 Hz, 1H, arom), 7.49 – 7.40 (m, 2H, arom), 6.96 (d, *J* = 9.0 Hz, 2H, arom), 6.81 (s, 1H, arom), 3.85 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 162.4 (C=O), 161.1 (C, arom), 153.7 (C, arom), 137.9 (C, arom), 134.8 (CH, arom), 129.8 (CH, arom), 129.6 (CH, arom), 128.0 (CH, arom), 127.6 (CH,

arom), 126.8 (CH, arom), 125.7 (CH, arom), 124.5 (C, arom), 120.1 (C, arom), 114.2 (CH, arom), 100.2 (CH, arom), 55.4 (-OCH_3). **MS** ESI (+): m/z (%) = 275 $[M+Na]^+$ (100), 253 $[M+1]^+$ (20); $C_{16}H_{12}O_3$ [252.26]. **IR** (KBr): ν_{max} = 3001, 2925, 1717, 1603, 1350, 1262, 1118, 1069 cm^{-1}. Spectral data are in good agreement with literature values.[6]

3-(2-Methoxyphenyl)-1H-isochromen-1-one **(2d):** Reaction time: 4.5 h. Eluent for chromatography: hexane/EtOAc 9:1. White solid. Yield 82% (83 mg); mp 113-115 °C (lit. 115-117 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.29 (dd, *J* = 7.8, 0.6 Hz, 1H, arom), 7.96 (dd, *J* = 7.9, 1.7 Hz, 1H, arom), 7.72 – 7.66 (m, 1H, arom), 7.51 – 7.43 (m, 2H, arom), 7.41 – 7.32 (m, 2H, arom), 7.06 (td, *J* = 7.6, 1.1 Hz, 1H, arom), 7.00 (d, *J* = 8.3 Hz, 1H, arom), 3.95 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 162.6 (C=O), 157.2 (C, arom), 150.4 (C, arom), 138.0 (C, arom), 134.6 (CH, arom), 130.7 (CH, arom), 129.3 (CH, arom), 128.8 (CH, arom), 127.9 (CH, arom), 126.3 (CH, arom), 120.8 (CH, arom), 120.7 (C, arom), 120.6 (C, arom), 111.3 (CH, arom), 107.0 (CH, arom), 55.6 (-OCH_3). **MS** ESI (+): m/z (%) = 253 $[M+1]^+$ (100), 275 $[M+Na]^+$ (50); $C_{16}H_{12}O_3$ [252.26]. **IR** (KBr): ν_{max} = 3011, 2925, 1719, 1596, 1253, 1179 cm^{-1}. Spectral data are in good agreement with literature values.[11]

3-(3-Hydroxyphenyl)-*1H*-isochromen-1-one (2e): Reaction time: 5.0 h. Eluent for chromatography: hexane/EtOAc 6:4. Red solid. Yield 89% (85 mg); mp 179-181 °C. **^{1}H NMR** (300 MHz, d_6-acetone): δ = 8.66 (s, 1H, -OH), 8.22 (dd, *J* = 7.9, 0.6 Hz, 1H, arom), 7.89 – 7.75 (m, 1H, arom), 7.68 (d, *J* = 7.7 Hz, 1H, arom), 7.63 – 7.53 (m, 1H, arom), 7.45 – 7.39 (m, 2H, arom), 7.35 (dd, *J* = 11.7, 4.5 Hz, 1H, arom), 7.28 (s, 1H, arom), 7.00 – 6.91 (m, 1H, arom). **^{13}C NMR** (75 MHz, d_6-acetone): δ = 161.3 (C=O), 157.9 (C, arom), 153.2 (C, arom), 137.7 (C, arom), 135.0 (CH, arom), 133.6 (C, arom), 130.0 (CH, arom), 129.0 (CH, arom), 128.2 (CH, arom), 126.4 (CH, arom), 120.5 (C, arom), 117.0 (CH, arom), 116.3 (CH, arom), 111.8 (CH, arom), 101.8 (CH, arom). **MS** ESI (+): m/z (%) = 261 $[M+Na]^+$ (100), 239 $[M+1]^+$ (35); $C_{15}H_{10}O_3$ [238.24]. **IR** (KBr): ν_{max} = 3301, 1717, 1602, 1332, 1256, 1184 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{15}H_{11}O_3$ 239.0703, found 239.0721.

3-(4-Chlorophenyl)-1H-isochromen-1-one **(2f):** Reaction time: 7.0 h. Eluent for chromatography: hexane/EtOAc 9:1. White solid. Yield 84% (86 mg); mp 143-145 °C (lit. 144-146 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.8 Hz, 1H, arom), 7.87 – 7.78 (m, 2H, arom), 7.73 (td, *J* = 7.6, 1.2 Hz, 1H, arom), 7.51 (t, *J* = 7.7 Hz, 2H, arom), 7.47 – 7.40 (m, 2H, arom), 6.93 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 162.0 (C=O), 152.5 (C, arom), 137.2 (C, arom), 136.0 (C, arom), 135.0 (CH, arom), 130.4 (C, arom), 129.7 (CH, arom), 129.1 (CH, arom, 2C), 128.4 (CH, arom), 126.5 (CH, arom, 2C), 126.0 (CH, arom), 120.6 (C, arom), 102.1 (CH, arom). **MS** ESI (+): m/z (%) = 257 $[M(^{35}Cl)+H]^+$ (100), 259 $[M(^{37}Cl)+H]^+$ (50), 279 $[M(^{35}Cl)+Na]^+$ (40), 281 $[M(^{37}Cl)+Na]^+$ (15);

$C_{15}H_9ClO_2$ [256.68]. **IR** (KBr): ν_{max} = 3100, 1726, 1603, 1486, 1071, 529 cm^{-1}. Spectral data are in good agreement with literature values.[10]

4-(1-Oxo-1H-isochromen-3-yl)benzonitrile **(2g):** Reaction time: 5.5 h. Eluent for chromatography: hexane/EtOAc 8:2. White solid. Yield 82% (81 mg); mp 208-210 °C. **^{1}H NMR** (300 MHz, d_6-DMSO): δ = 8.17 (d, *J* = 7.9 Hz, 1H, arom), 8.02 (dd, *J* = 28.6, 8.7 Hz, 4H, arom), 7.92 – 7.84 (m, 1H, arom), 7.72 (d, *J* = 4.6 Hz, 2H, arom), 7.67 – 7.59 (m, 1H, arom). **^{13}C NMR** (75 MHz, d_6-DMSO): δ = 161.3 (C=O), 150.9 (C, arom), 137.1 (C, arom), 136.3 (C, arom), 136.0 (CH, arom), 133.4 (CH, 2C, arom), 129.8 (CH, arom), 129.4 (CH, arom), 127.5 (CH, arom), 126.0 (CH, 2C, arom), 120.8 (C, arom), 118.9 (CN), 112.4 (C, arom), 105.3 (CH, arom). **MS** ESI (+): m/z (%) = 248 $[M+1]^+$ (100); $C_{16}H_9NO_2$ [247.25]. **IR** (KBr): ν_{max} = 3099, 2227, 1723, 1607 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{16}H_{10}NO_2$ 248.0706, found 248.0703.

3-[4-(Trifluoromethyl)phenyl]-1H-isochromen-1-one **(2h):** Reaction time: 5.0 h. Eluent for chromatography: hexane/EtOAc 95:5. White solid. Yield 84% (98 mg); mp 178-184 °C (lit. 151-154 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 7.7 Hz, 1H, arom), 8.02 (d, *J* = 8.3 Hz, 2H, arom), 7.84 – 7.70 (m, 3H, arom), 7.57 (t, *J* = 7.6 Hz, 2H, arom), 7.06 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 161.8 (C=O), 152.0 (C, arom), 136.9 (C, arom), 135.3 (C, arom), 135.1 (CH, arom), 131.6 (q, $^2J_{(C,F)}$ = 32 Hz, 1C, C-CF_3), 129.2 (CH, arom), 128.9 (CH, arom), 126.3 (CH, arom), 125.9 (q, $^3J_{(C,F)}$ = 4 Hz, 2C, CH-C-CF_3), 125.5 (CH, 2C, arom), 123.8 (q, $^1J_{(C,F)}$ = 272 Hz, 1C, CF_3), 120.9 (C, arom), 103.4 (CH, arom). **MS** ESI (+): m/z (%) = 291 $[M+1]^+$ (100); $C_{16}H_9F_3O_2$ [290.24]. **IR** (KBr): ν_{max} = 3094, 1722, 1640, 1328, 1111 cm^{-1}. Spectral data are in good agreement with literature values.[12]

3-[3-(Trifluoromethyl)phenyl]-1H-isochromen-1-one **(2i):** Reaction time: 4 h. Eluent for chromatography: hexane/EtOAc 8:2. White solid. Yield 91% (106 mg); mp 149-150 °C (lit. 100-102). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 7.7 Hz, 1H, arom), 8.12 (s, 1H, arom), 8.06 (d, *J* = 7.8 Hz, 1H, arom), 7.75 (t, *J* = 7.6 Hz, 1H, arom), 7.68 (d, *J* = 7.7 Hz, 1H, arom), 7.61 (d, *J* = 7.8 Hz, 1H, arom), 7.54 (dd, *J* = 7.6, 5.6 Hz, 2H, arom), 7.03 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 161.8 (C=O), 152.0 (C, arom), 136.9 (C, arom), 135.1 (CH, arom), 132.8 (C, arom), 131.4 (q, $^2J_{(C,F)}$ = 32 Hz, 1C, C-CF_3), 129.8 (CH, arom), 129.4 (CH, arom), 128.7 (CH, arom), 128.3 (CH, arom), 126.4 (q, $^3J_{(C,F)}$ = 4 Hz, 1C, CH-C-CF_3), 126.2 (CH, arom), 123.8 (q, $^1J_{(C,F)}$ = 272 Hz, 1C, CF_3), 122.0 (q, $^3J_{(C,F)}$ = 4 Hz, 1C, CH-C-CF_3), 120.8 (C, arom), 102.9 (CH, arom). **MS** ESI (+): m/z (%) = 291 $[M+1]^+$ (100), 313 $[M+Na]^+$ (55); $C_{16}H_9F_3O_2$ [290.24]. **IR** (KBr): ν_{max} = 3101, 1730, 1605, 1334, 1230, 1108 cm^{-1}. Spectral data are in good agreement with literature values.[10]

3-(4-Nitrophenyl)-1H-isochromen-1-one **(2j):** Reaction time: 6.0 h. Eluent for chromatography: hexane/EtOAc 8:2. Yellow solid. Yield 89% (95 mg); mp 219-221 °C (lit. 227-229 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.39 – 8.25 (m, 3H, arom), 8.04 (d, *J* = 8.8 Hz, 2H, arom), 7.68 (dt, *J* = 15.9, 7.6 Hz, 3H, arom), 7.12 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 161.4 (C=O), 151.0 (C, arom), 148.3 (C, arom), 137.7 (C, arom), 136.5 (C, arom), 135.21 (CH, arom), 129.9 (CH, arom), 129.4 (CH, arom), 126.6 (CH, arom), 125.9 (CH, 2C, arom), 124.2 (CH, 2C, arom), 121.0 (C, arom), 104.8 (CH, arom). **MS** ESI (+): m/z (%) = 268 $[M+1]^+$ (100); $C_{15}H_9NO_4$ [267.24]. **IR** (KBr): ν_{max} = 3016, 1721, 1602, 1517, 1349, 1106 cm^{-1}. Spectral data are in good agreement with literature values.[12]

3-(2-Nitrophenyl)-1H-isochromen-1-one **(2k):** Reaction time: 24 h. Eluent for chromatography: hexane/EtOAc 8:2. Yellow solid. Yield 41% (44 mg); mp 149-154 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 7.9 Hz, 1H, arom), 8.00 (d, *J* = 8.0 Hz, 1H, arom), 7.79 – 7.44 (m, 6H, arom), 6.70 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 161.4 (C=O), 151.3 (C, arom), 148.2 (C, arom), 136.7 (C, arom), 135.0 (CH, arom), 133.0 (CH, arom), 131.0 (CH, arom), 130.8 (CH, arom), 129.8 (CH, arom), 129.0 (CH, arom), 127.9 (C, arom), 126.1 (CH, arom), 124.8 (CH, arom), 120.7 (C, arom), 105.9 (CH, arom). **MS** ESI (+): m/z (%) = 290 $[M+Na]^+$ (100), 268 $[M+H]^+$ (95); $C_{15}H_9NO_4$ [267.24]. **IR** (KBr): ν_{max} = 3068, 1735, 1608, 1530, 1345, 1055 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{15}H_{10}NO_4$ 268.0604, found 268.0611.

1-Oxo-1H-isochromene-3-carbaldehyde **(2l):** Reaction time: 4 h. Eluent for chromatography: hexane/EtOAc 7:3. Yellow solid. Yield 44% (31 mg); mp 163-164 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 9.60 (s, 1H, -CHO), 8.37 (d, *J* = 7.9 Hz, 1H, arom), 7.83 (dd, *J* = 7.5, 1.2 Hz, 1H, arom), 7.71 (dd, *J* = 13.7, 7.3 Hz, 2H, arom), 7.30 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 183.3 (-CHO), 160.1 (C=O), 149.4 (C, arom), 135.3 (CH, arom), 134.4 (C, arom), 131.7 (CH, arom), 130.3 (CH, arom), 128.2 (CH, arom), 123.4 (C, arom), 115.3 (CH, arom). **MS** ESI (+): m/z (%) = 175 $[M+H]^+$ (100); $C_{10}H_6O_3$ [174.15]. **IR** (KBr): ν_{max} = 3096, 2852, 1727, 1693, 1599, 1291, 1110 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{10}H_7O_3$ 175.0390, found 175.0398.

3-Propyl-1H-isochromen-1-one **(2m):** Reaction time: 2 h. Eluent for chromatography: hexane/EtOAc 95:5. Colorless oil. Yield 65% (49 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.28 – 8.18 (m, 1H, arom), 7.65 (ddd, *J* = 7.8, 7.4, 1.4 Hz, 1H, arom), 7.47 – 7.39 (m, 1H, arom, arom), 7.34 (d, *J* = 7.8 Hz, 1H, arom), 6.24 (s, 1H), arom, 2.49 (t, *J* = 7.5 Hz, 2H, -$\underline{CH_2}$-CH_2-CH_3), 1.73 (sex, *J* = 7.8 Hz, 2H, -CH_2-$\underline{CH_2}$-CH_3), 0.98 (t, *J* = 7.4 Hz, 3H, -CH_2-CH_2-$\underline{CH_3}$). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 163.1 (C=O), 158.0 (C, arom), 137.6 (C, arom), 134.7 (CH, arom), 129.4 (CH, arom), 127.5 (CH, arom), 125.0 (CH, arom), 120.1 (C, arom), 103.0 (CH, arom), 35.4 (-$\underline{C}H_2$-CH_2-CH_3), 20.2 (-CH_2-$\underline{C}H_2$-CH_3), 13.5

(-CH_2-CH_2-$\underline{C}H_3$). **MS** ESI (+): m/z (%) = 189 $[M+1]^+$ (100); $C_{12}H_{12}O_2$ [188.22]. **IR** (NaCl): ν_{max} = 2963, 2874, 1728, 1607, 1292, 1097 cm^{-1}. Spectral data are in good agreement with literature values.[6]

3-Heptyl-1H-isochromen-1-one **(2n):** Reaction time: 1 h. Eluent for chromatography: hexane/EtOAc 97:3. Colorless oil. Yield 77% (75 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.25 (dd, *J* = 8.0, 0.5 Hz, 1H, arom), 7.67 (td, *J* = 7.8, 1.3 Hz, 1H, arom), 7.44 (t, *J* = 7.6 Hz, 1H, arom), 7.35 (d, *J* = 7.9 Hz, 1H, arom), 6.25 (s, 1H, arom), 2.52 (t, *J* = 7.6 Hz, 2H, -CH_2-), 1.50 – 1.10 (m, 10H, -CH_2-), 0.88 (t, *J* = 6.7 Hz, 3H, -CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 163.1 (C=O), 158.4 (C, arom), 137.6 (C, arom), 134.6 (CH, arom), 129.5 (CH, arom), 127.5 (CH, arom), 125.0 (CH, arom), 120.1 (C, arom), 102.8 (CH, arom), 33.5 (CH_2), 31.7 (CH_2), 29.7 (CH_2), 29.0 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 14.0 (CH_3). **MS** ESI (+): m/z (%) = 267 $[M+Na]^+$ (100), 245 $[M+1]^+$ (35); $C_{16}H_{20}O_2$ [244.33]. **IR** (NaCl): ν_{max} = 3069, 2928, 1732, 1607, 1327, 1107 cm^{-1}. Spectral data are in good agreement with literature values.[13]

3-(Thiophen-3-yl)-1H-isochromen-1-one **(2p):** Reaction time: 6 h. Eluent for chromatography: hexane/EtOAc 9:1. White solid. Yield 99% (90 mg); mp 111-112 °C (lit. 110-112 °C). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.4 Hz, 1H, arom), 7.89 (dd, *J* = 2.9, 1.3 Hz, 1H, arom), 7.72 (td, *J* = 7.7, 1.3 Hz, 1H, arom), 7.55 – 7.37 (m, 4H, arom), 6.79 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 162.1 (C=O), 150.4 (C, arom), 137.6 (C, arom), 134.9 (CH, arom), 134.3 (C, arom), 129.8 (CH, arom), 127.9 (CH, arom), 126.9 (CH, arom), 125.8 (CH, arom), 124.3 (CH, arom), 124.1 (CH, arom), 120.5 (C, arom), 101.4 (CH, arom). **MS** ESI (+): m/z (%) = 175 $[M+Na]^+$ (100), 229 $[M+H]^+$ (65); $C_{13}H_8O_2S$ [228.27]. **IR** (KBr): ν_{max} = 3122, 3101, 1723, 1604, 1333, 1072, 749 cm^{-1}. Spectral data are in good agreement with literature values.[10]

5-(4-Chlorophenyl)-7H-thieno[2,3-c]pyran-7-one **(2q):** Reaction time: 2 h. Eluent for chromatography: hexane/EtOAc 9:1. White solid. Yield 95% (99 mg); mp 180-182 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 5.1 Hz, 1H, arom), 7.78 (d, *J* = 8.6 Hz, 2H, arom), 7.41 (d, *J* = 8.6 Hz, 2H, arom), 7.23 (d, *J* = 5.1 Hz, 1H, arom), 7.09 (s, 1H, arom). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 157.9 (C=O), 155.2 (C, arom), 147.2 (C, arom), 136.9 (CH, arom), 136.1 (C, arom), 130.3 (C, arom), 129.2 (CH, arom, 2C), 126.6 (CH, arom, 2C), 124.7 (CH, arom), 123.1 (C, arom), 99.2 (CH, arom). **MS** ESI (+): m/z (%) = 285 $[M(^{35}Cl)+Na]^+$ (100), 287 $[M(^{37}Cl)+Na]^+$ (40); $C_{13}H_7ClO_2S$ [262.71]. **IR** (KBr): ν_{max} = 3123, 1714, 1606, 1414, 1089, 619 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{13}H_8ClO_2S$ 262.9928, found 262.9932.

5-(4-Methoxyphenyl)-7H-thieno[2,3-c]pyran-7-one **(2r):** Reaction time: 1 h. Eluent for chromatography: hexane/EtOAc 8:2. Pale green solid. Yield 93% (96 mg); mp 143-145 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.85 – 7.77 (m, 3H, arom), 7.20 (d, *J* = 5.1 Hz, 1H, arom), 6.99 (s, 1H, arom),

6.99 – 6.92 (m, 2H, arom), 3.86 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 161.2 (C=O), 158.4 (C, arom), 156.6 (C, arom), 147.8 (C, arom), 136.6 (CH, arom), 126.9 (CH, arom, 2C), 124.5 (CH, arom), 124.4 (C, arom), 122.1 (C, arom), 114.3 (CH, arom, 2C), 97.6 (CH, arom), 55.4 (CH_3). **MS** ESI (+): m/z (%) = 281 $[M+Na]^+$ (100); $C_{14}H_{10}O_3S$ [258.29]. **IR** (KBr): ν_{max} = 3085, 1713, 1608, 1336, 1263, 1114, 1020 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{14}H_{11}O_3S$ 259.0423, found 259.0436.

7-nitro-3-(4-(trifluoromethyl)phenyl)-1H-isochromen-1-one **(2u):** Reaction time: 24 h. Recrystallized from CH_3CN. Pale green solid. Yield 67% (90 mg); mp 223-225 °C. **^{1}H NMR** (300 MHz, d_6-DMSO): δ = 8.78 (d, *J* = 2.3 Hz, 1H, arom), 8.62 (dd, *J* = 8.7, 2.4 Hz, 1H, arom), 8.14 (d, *J* = 8.2 Hz, 2H, arom), 7.93 (t, *J* = 8.3 Hz, 3H, arom), 7.85 (s, 1H, arom). **^{13}C NMR** (75 MHz, d_6-DMSO): δ = 160.3 (C=O), 154.2 (C, arom), 147.2 (C, arom), 142.4 (C, arom), 135.2 (C, arom), 131.0 (q, $^2J_{(C,F)}$ = 32 Hz, 1C, C-CF_3), 129.8 (CH, arom), 129.2 (CH, arom), 126.6 (CH, arom, 2C), 126.5 (q, $^3J_{(C,F)}$ = 4 Hz, 2C, CH-C-CF_3), 124.7 (CH, arom), 124.3 (q, $^1J_{(C,F)}$ = 272 Hz, 1C, CF_3), 121.3 (C, arom), 103.8 (CH, arom). **MS** ESI (+): m/z (%) = 331 $[M-CO+Na]^+$ (100), 359 $[M+Na]^+$ (90), 381 $[M+2Na]^+$ (45); $C_{16}H_8F_3NO_4$ [335.23]. **IR** (KBr): ν_{max} = 3089, 1754, 1609, 1522, 1336, 1323, 1115, 1010 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{16}H_9F_3NO_4$ 336.0478, found 336.0463.

3-(4-chlorophenyl)-7-methoxy-1H-isochromen-1-one **(2v):** Reaction time: 24 h. Eluent for chromatography: hexane/EtOAc 85:15. White solid. Yield 70% (84 mg); mp 151-153 °C. **^{1}H NMR** (300 MHz, CD_2Cl_2): δ = 7.80 (2H, d, *J* = 8.7 Hz, arom), 7.70 (1H, d, *J* = 2.5 Hz, arom), 7.47 (3H, m, arom), 7.35 (1 H, dd, *J* = 8.6, 2.7), 6.95 (1 H, s, arom), 3.94 (3H, s, CH_3).**^{13}C NMR** (75 MHz, d_6-CD_2Cl_2): δ = 161.7 (C, arom), 159.8 (C, arom), 150.4 (C, arom), 135.2 (C, arom), 130.82 (C, arom), 130.80(C, arom), 129.0 (CH, arom), 127.7 (CH, arom), 126.1 (CH, arom), 124.3 (CH, arom), 121.8 (C, arom), 110.2(CH, arom), 101.9 (CH, arom), 55.8 (CH_3). **MS ESI (+):** m/z (%) = 287 $[M(^{35}Cl)+1]^+$ (96), 289 $[M(^{37}Cl)+1]^+$ (38), 309 $[M(^{35}Cl)+Na]^+$ (100), 311 $[M(^{37}Cl)+Na]^+$ (42) ; $C_{16}H_{11}ClO_3$ [286.71]. **HRMS** ESI $(M+1)^+$ calculated for $C_{16}H_{12}ClO_3$ 287.0469, found 287.0478.

Methyl 2-(3-methylbut-2-enoyl)benzoate **(3a):** Reaction time: 2 h. Eluent for chromatography: hexane/EtOAc 9:1. Yellow oil. Yield 30% (26 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 7.6, 1.2 Hz, 1H, arom), 7.51 (dddd, *J* = 23.6, 8.7, 7.4, 1.3 Hz, 3H, arom), 6.40 – 6.27 (m, 1H, CH sp^2), 3.86 (s, 3H, -$COOCH_3$), 2.20 (d, *J* = 1.1 Hz, 3H, -CH_3), 1.98 (d, *J* = 1.1 Hz, 3H, -CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 194.7 (C=O ketone), 167.7 (C=O ester), 156.4 (C, arom), 143.9 (C, arom), 131.8 (CH, arom), 129.7 (CH, arom), 129.6 (CH, arom), 129.4 (C sp^2), 127.0 (CH, arom), 123.9 (CH sp^2), 52.4 (-OCH_3), 27.9 (-CH_3), 21.0 (-CH_3). **MS** ESI (+): m/z (%) = 459 $[2M+Na]^+$ (100),

241 $[M+Na]^+$ (10); $C_{13}H_{14}O_3$ [218.25]. **IR** (NaCl): ν_{max} = 2917, 1727, 1668, 1613, 1288, 1196 cm^{-1}. **HRMS** ESI $(M+1)^+$ calculated for $C_{13}H_{15}O_3$ 219.1016, found 219.1029.

Procedure for the deuteration of *p*-TSA: 100 mg of *p*-TSA·H_2O (0.5 mmol) were dissolved in 500 µL of D_2O (28 mmol, 53 equiv). The reaction mixture was stirred at reflux for one hour, then the solvent was removed under reduced pressure. This sequence was repeated three times to give quantitatively a white solid. The percentage of deuteration (≈ 81% d) was determined by comparison of the ^{1}H-NMR spectra of the product obtained with a pure sample of *p*-TSA·H_2O using a mixture of CD_2Cl_2/d_6-DMSO (v/v 95:5) as solvent and a prolonged delay time (d1 = 10 s).

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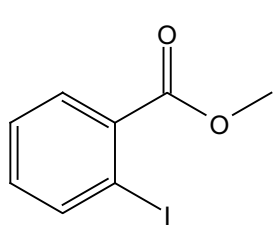
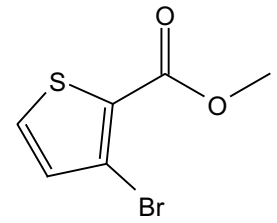


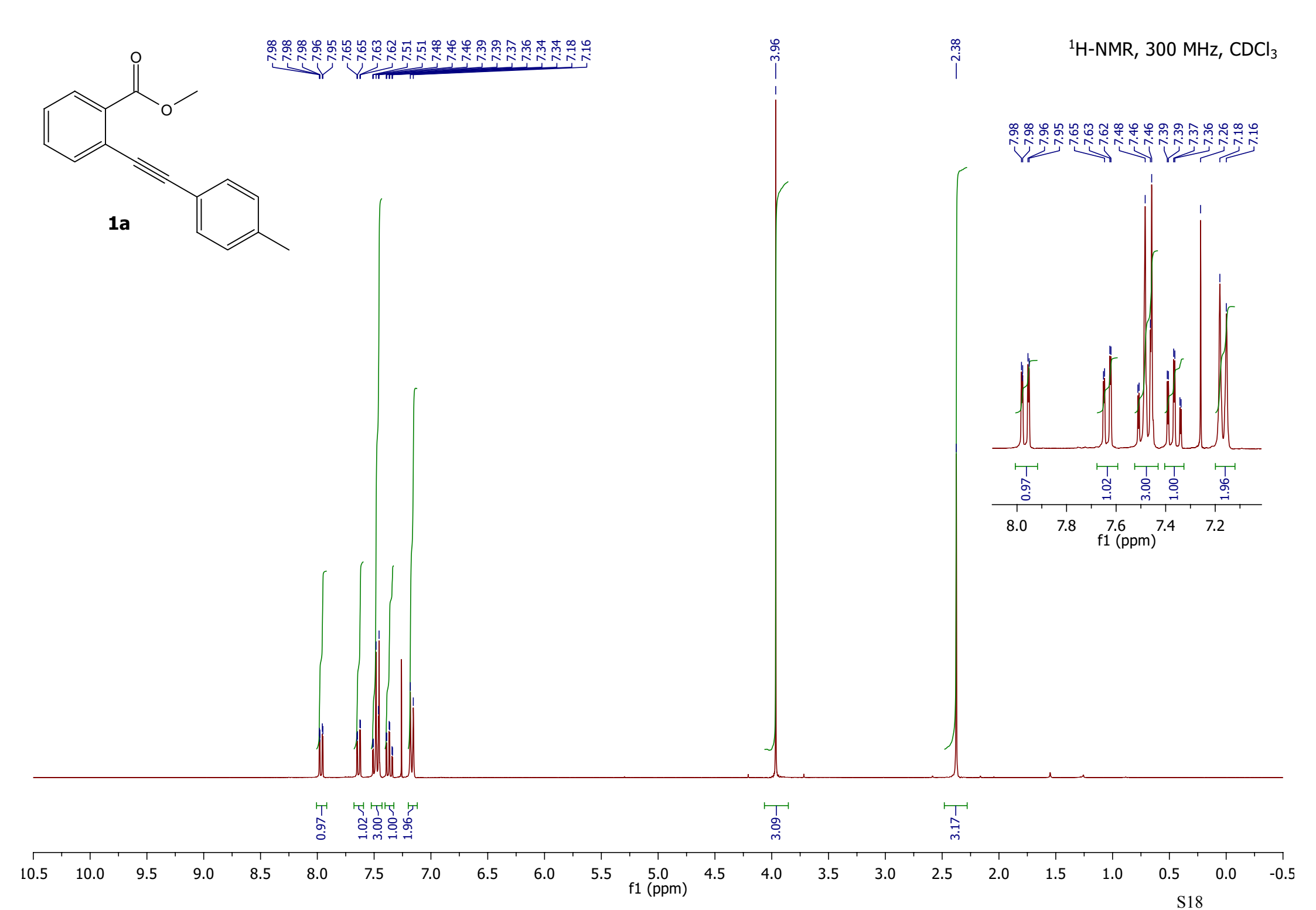
Methyl 2-iodobenzoate

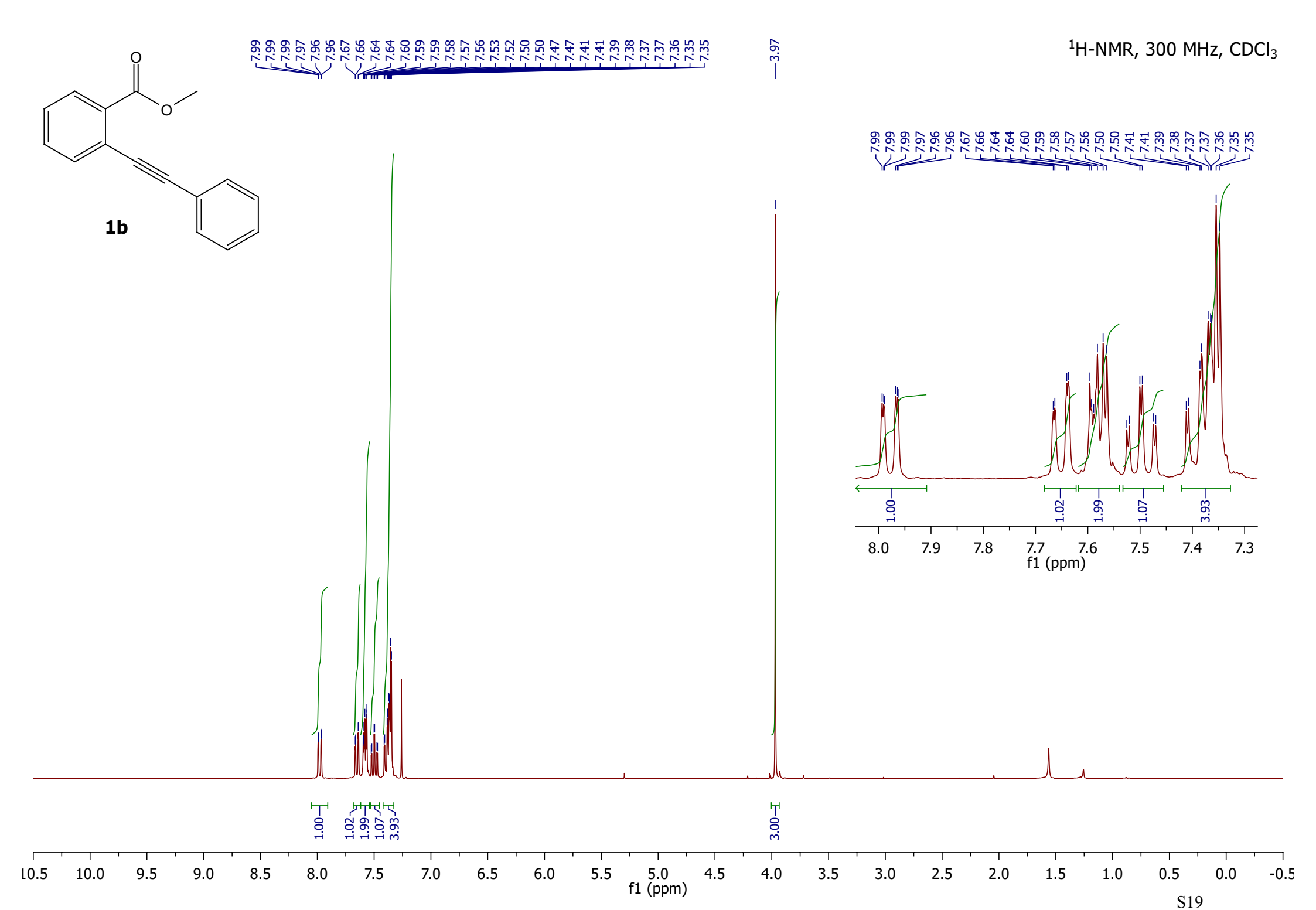
^{1}H-NMR, 300 MHz, $CDCl_3$



Methyl 3-bromotiophene-2-carboxylate

^{1}H-NMR, 300 MHz, $CDCl_3$


1a
^{1}H-NMR, 300 MHz, $CDCl_3$
7.98 7.98 7.98 7.96 7.95 7.65 7.65 7.63 7.62 7.51 7.51 7.48 7.46 7.46 7.39 7.39 7.37 7.36 7.34 7.34 7.18 7.16
3.96
2.38
0.97 1.02 3.00 1.00 1.96
3.09
3.17
f1 (ppm)


^{1}H-NMR, 300 MHz, $CDCl_3$
1b
7.99 7.99 7.99 7.97 7.96 7.96 7.67 7.66 7.64 7.64 7.60 7.59 7.59 7.58 7.57 7.56 7.53 7.52 7.50 7.50 7.47 7.47 7.41 7.41 7.39 7.38 7.37 7.37 7.36 7.35 7.35
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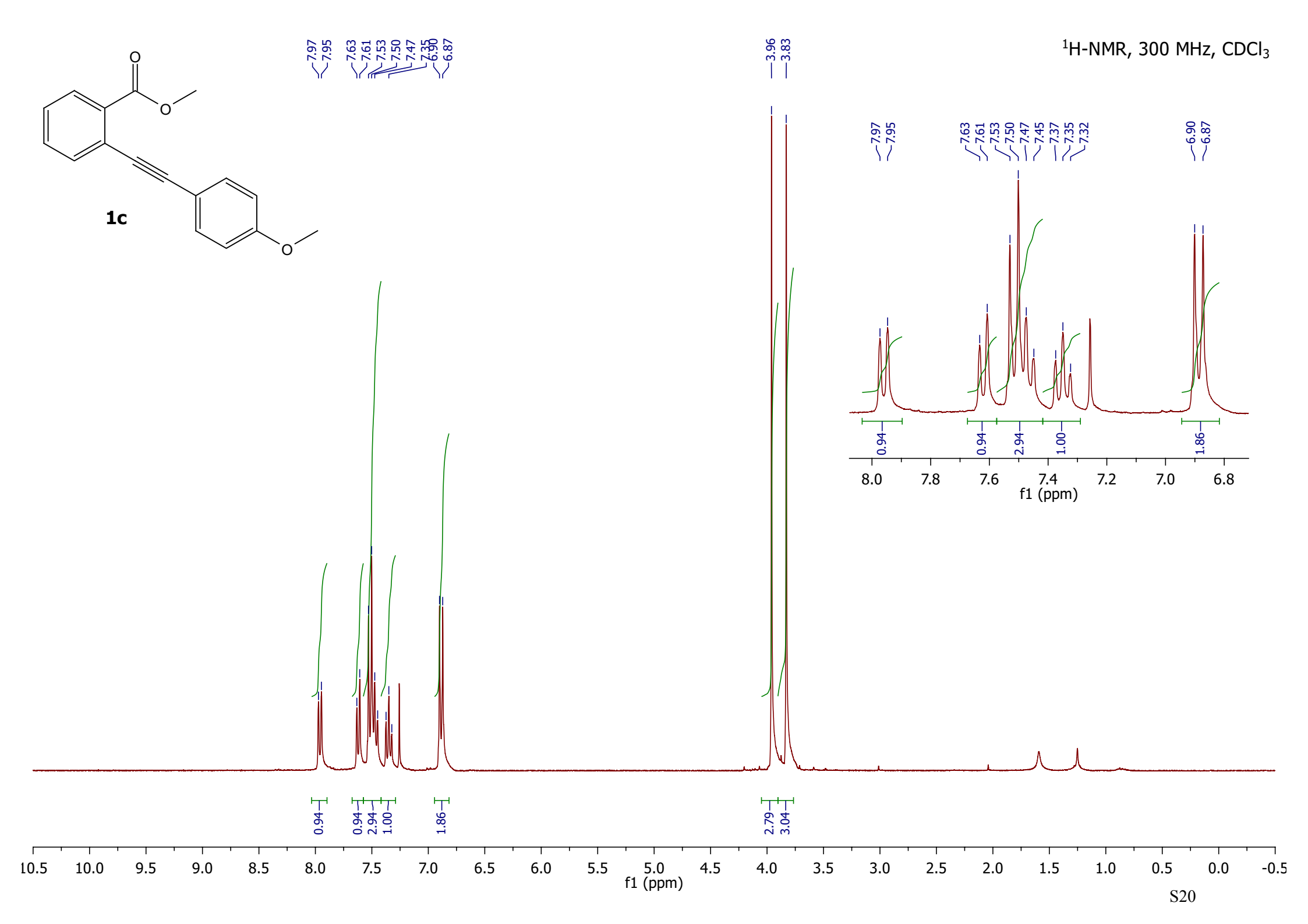
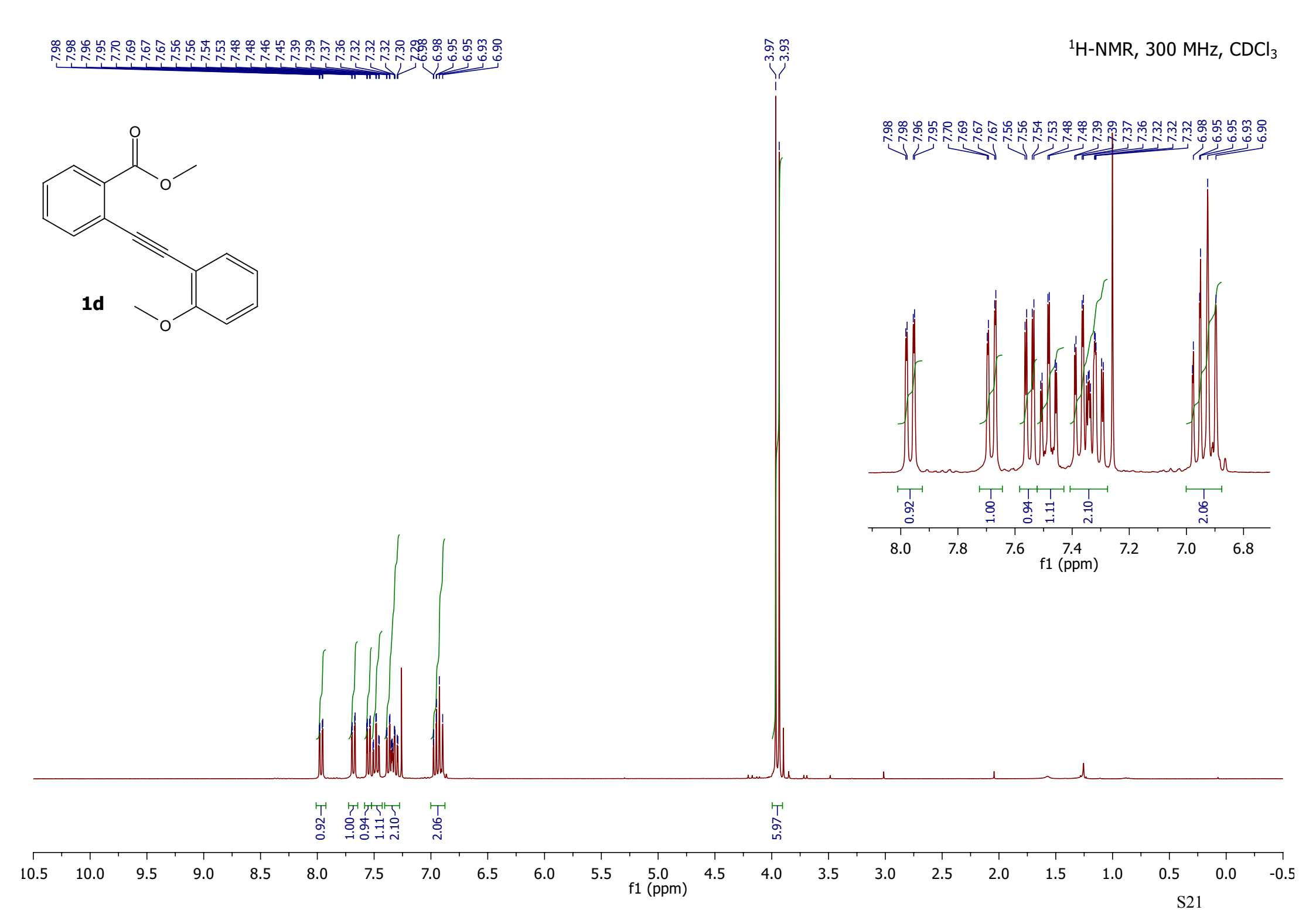
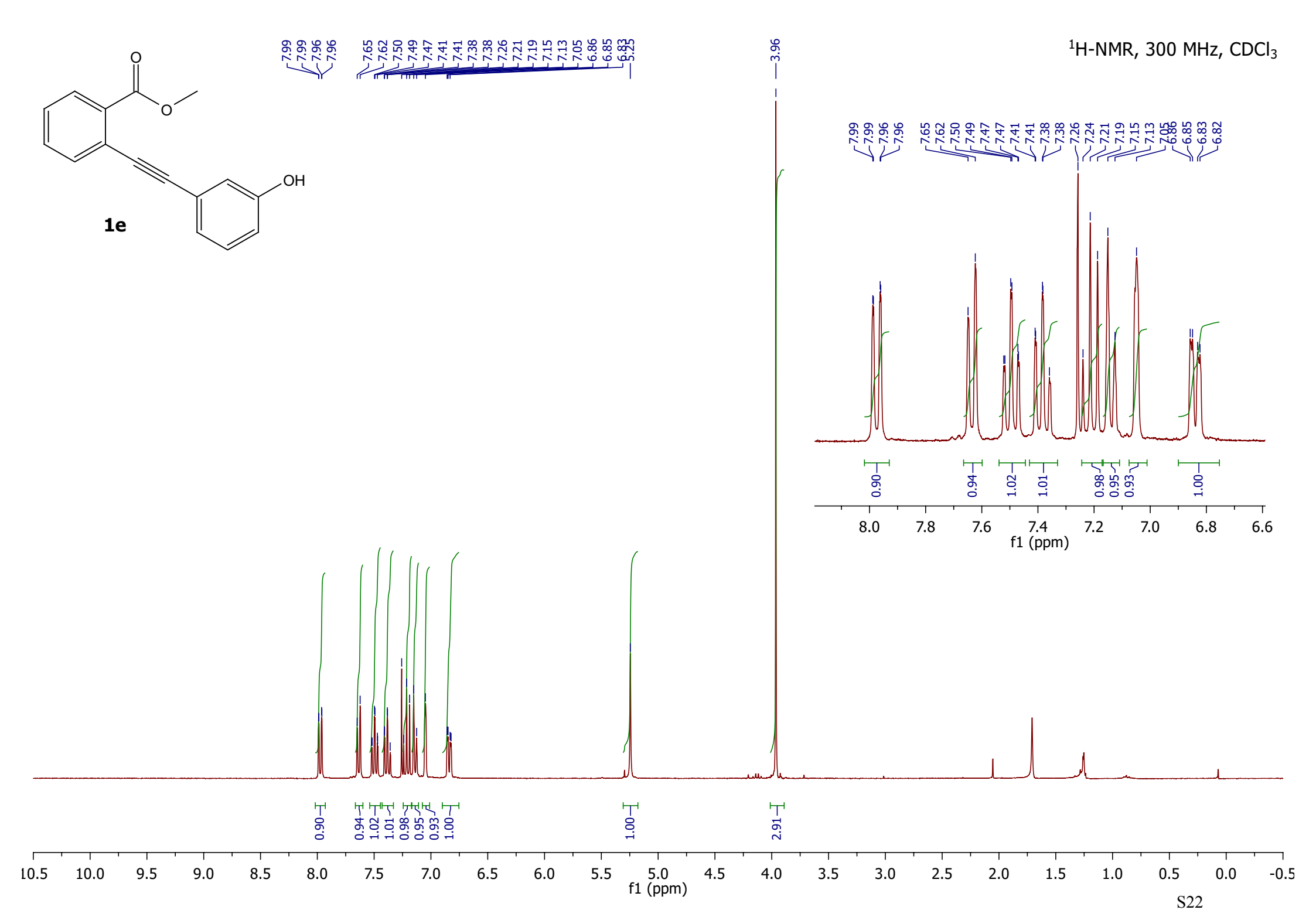
1.00 1.02 1.99 1.07 3.93
3.00
f1 (ppm)


1c
^{1}H-NMR, 300 MHz, $CDCl_3$
7.97
7.95
7.63
7.61
7.53
7.50
7.47
7.35
6.90
6.87
3.96
3.83
0.94
0.94
2.94
1.00
1.86
2.79
3.04
f1 (ppm)


^{1}H-NMR, 300 MHz, $CDCl_3$
1d
f1 (ppm)


1e
O
O
OH
^{1}H-NMR, 300 MHz, $CDCl_3$
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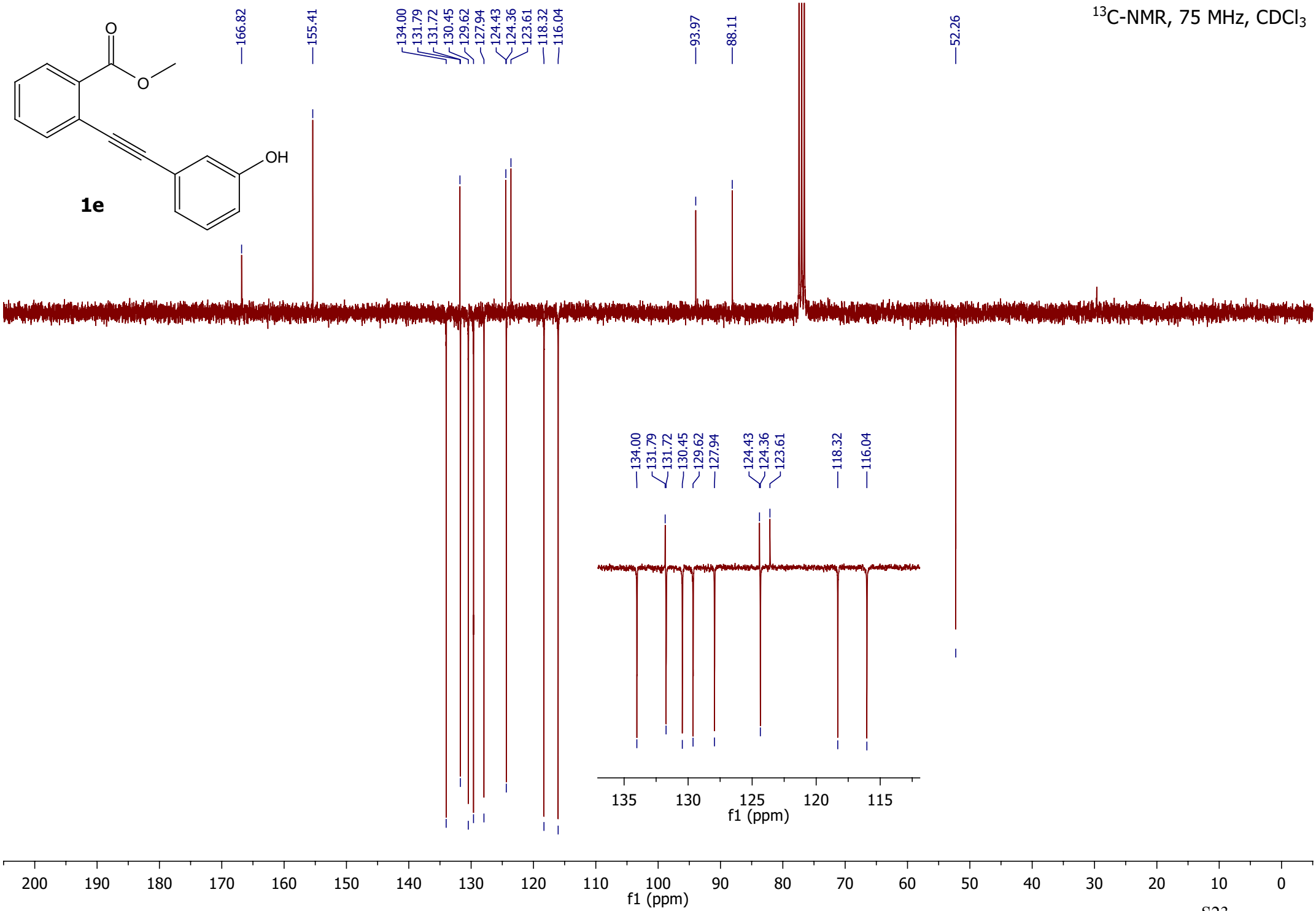
0.90 0.94 1.02 1.01 0.98 0.95 0.93 1.00 1.00 2.91
f1 (ppm)
7.99 7.99 7.96 7.96 7.65 7.62 7.50 7.49 7.47 7.47 7.41 7.41 7.38 7.38 7.26 7.24 7.21 7.19 7.15 7.13 7.05 6.86 6.85 6.83 6.82
0.90 0.94 1.02 1.01 0.98 0.95 0.93 1.00
f1 (ppm)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155.41
134.00
131.79
131.72
130.45
129.62
127.94
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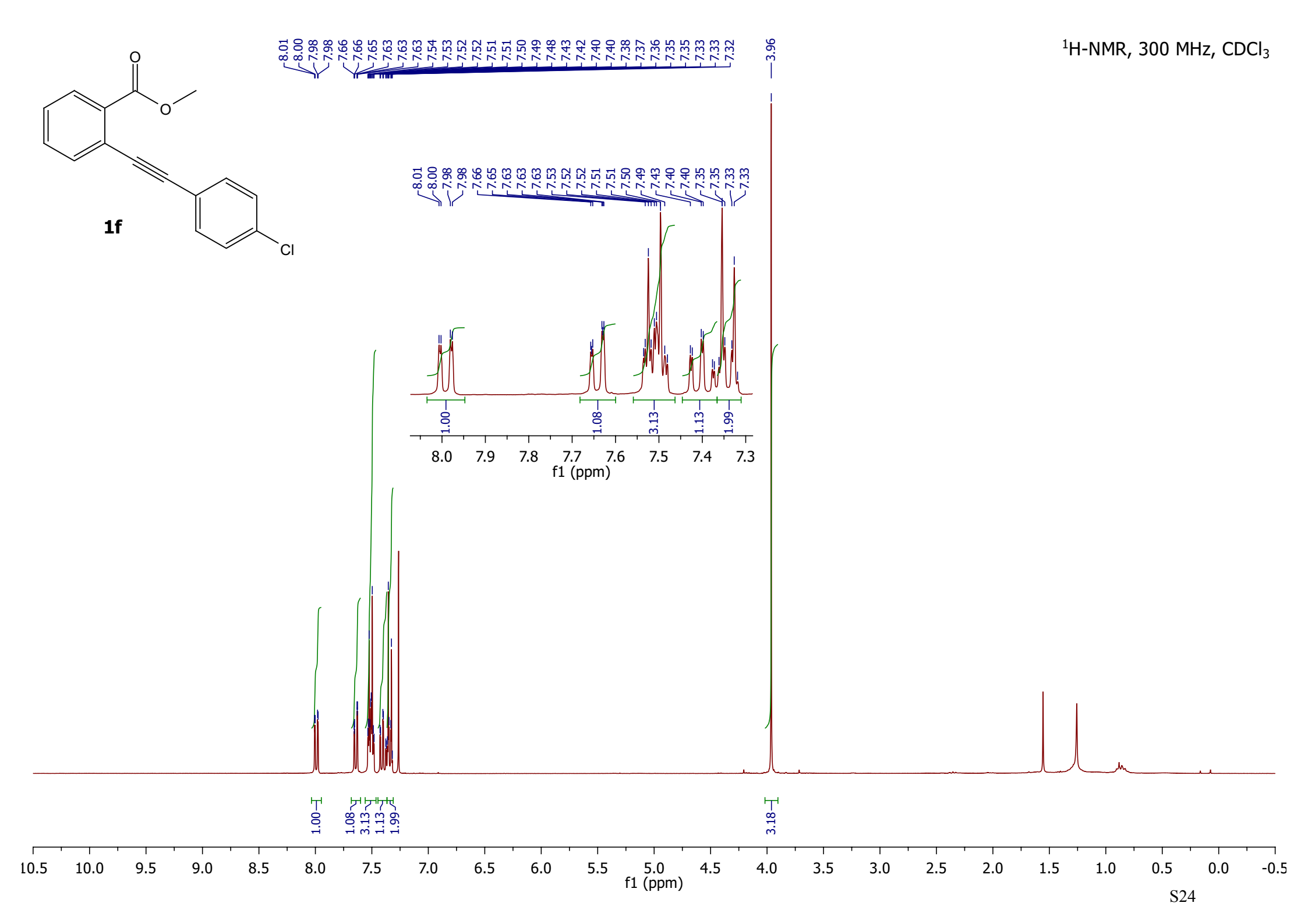
O
O
OH
1e
f1 (ppm)
f1 (ppm)


1f
Cl
O
O
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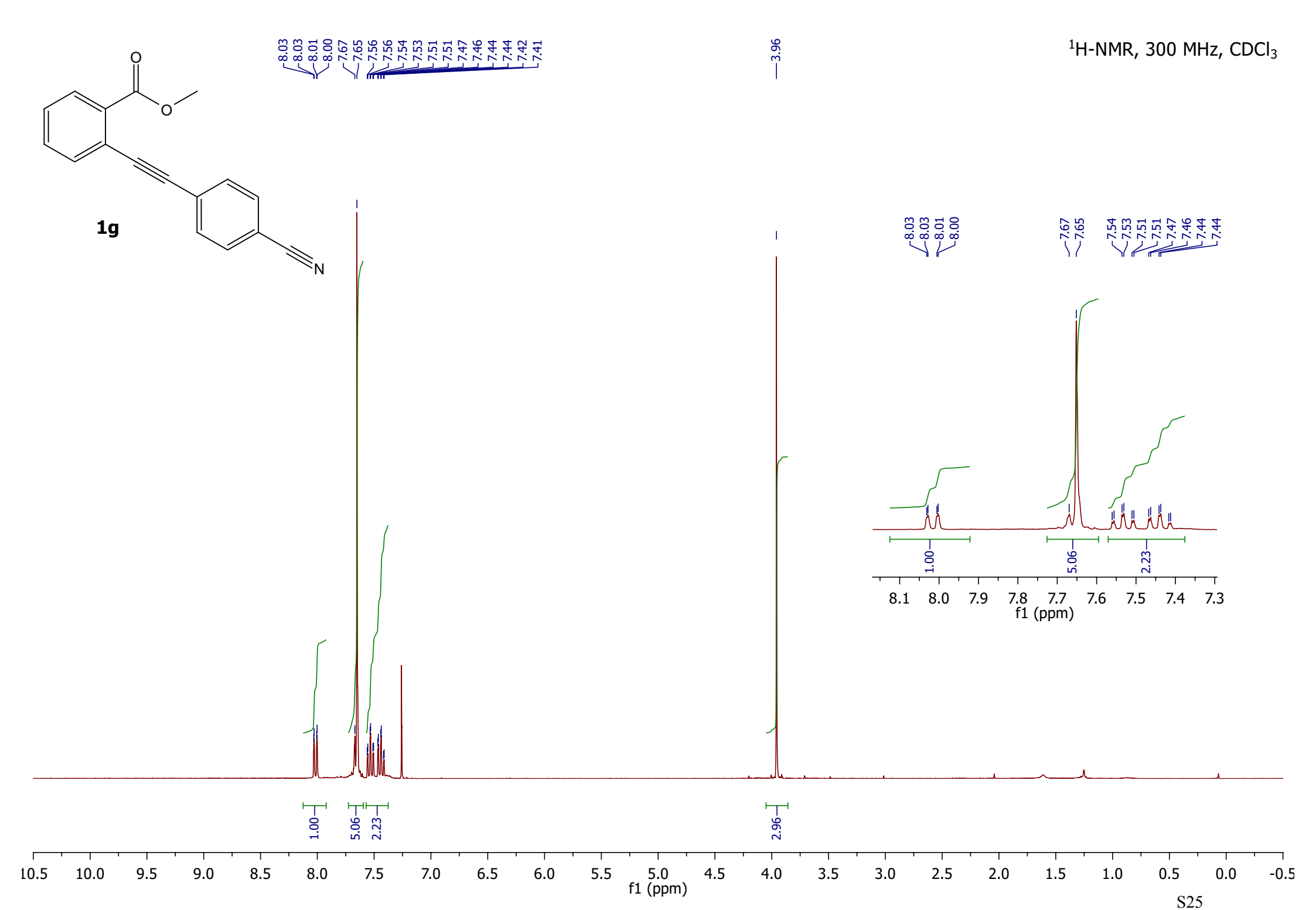
1.00 1.08 3.13 1.13 1.99
3.18
f1 (ppm)


^{1}H-NMR, 300 MHz, $CDCl_3$
1g
8.03
8.03
8.01
8.00
7.67
7.65
7.56
7.56
7.54
7.53
7.51
7.51
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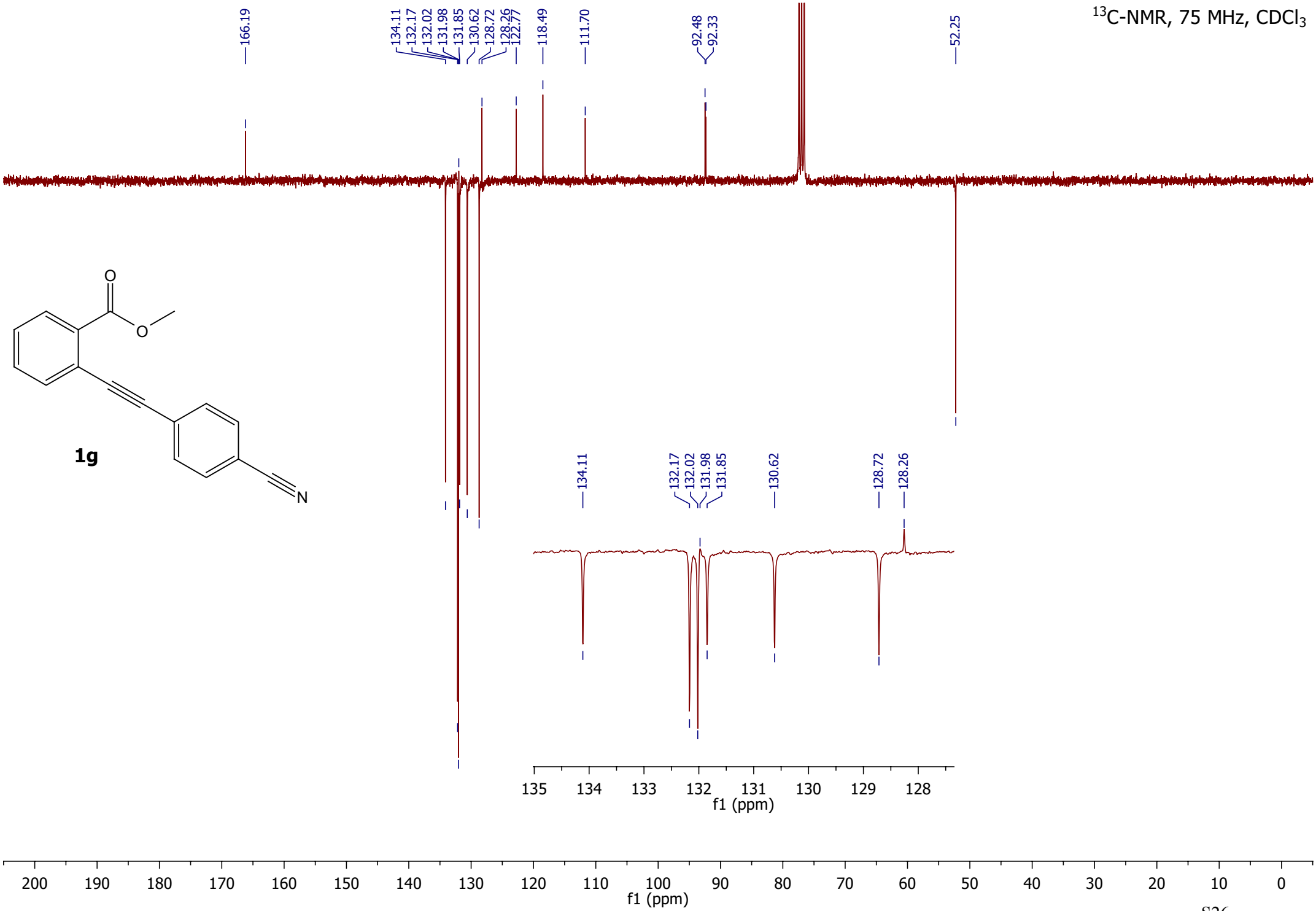
1.00
5.06
2.23
2.96
f1 (ppm)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134.11
132.17
132.02
131.98
131.85
130.62
128.72
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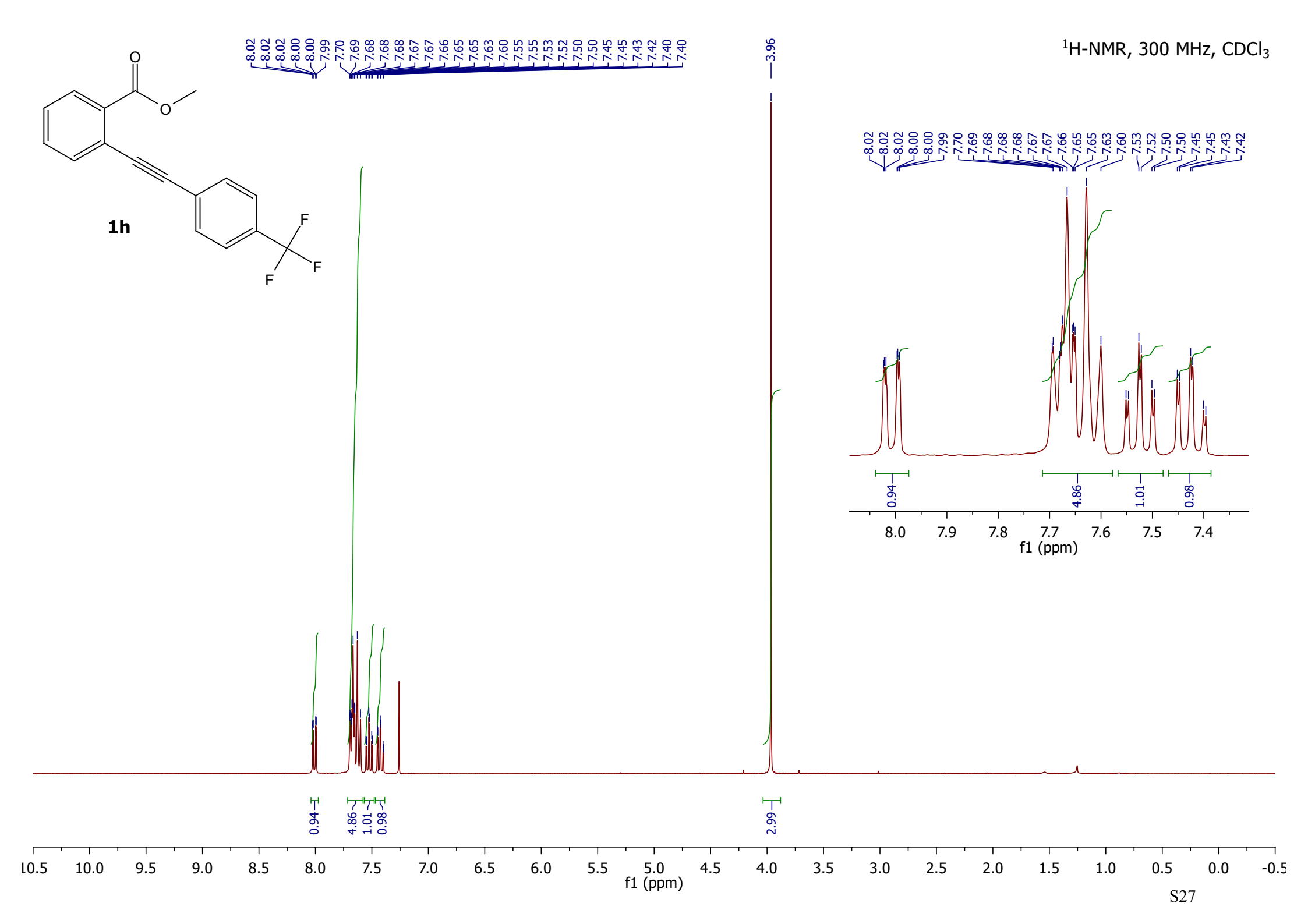
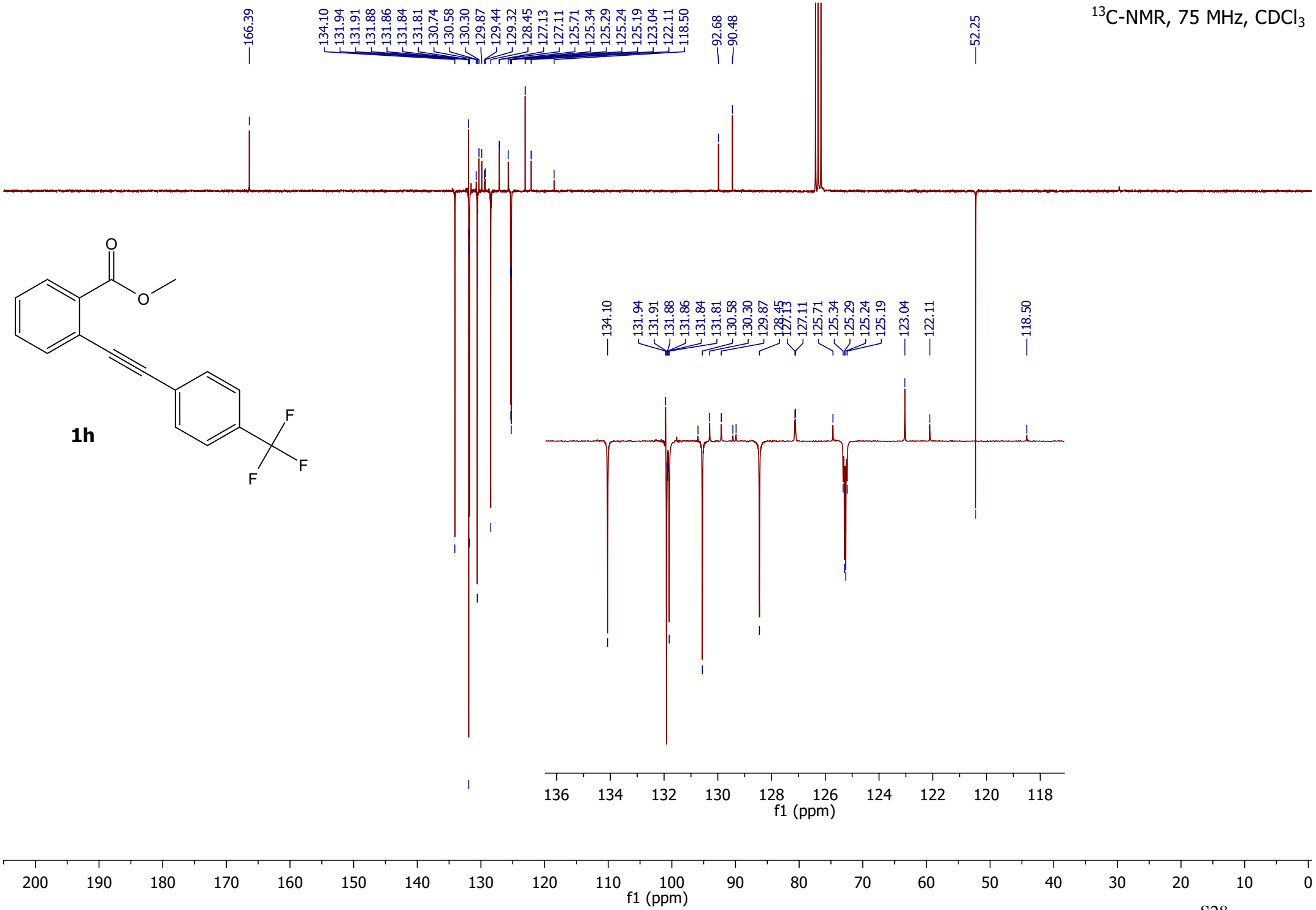
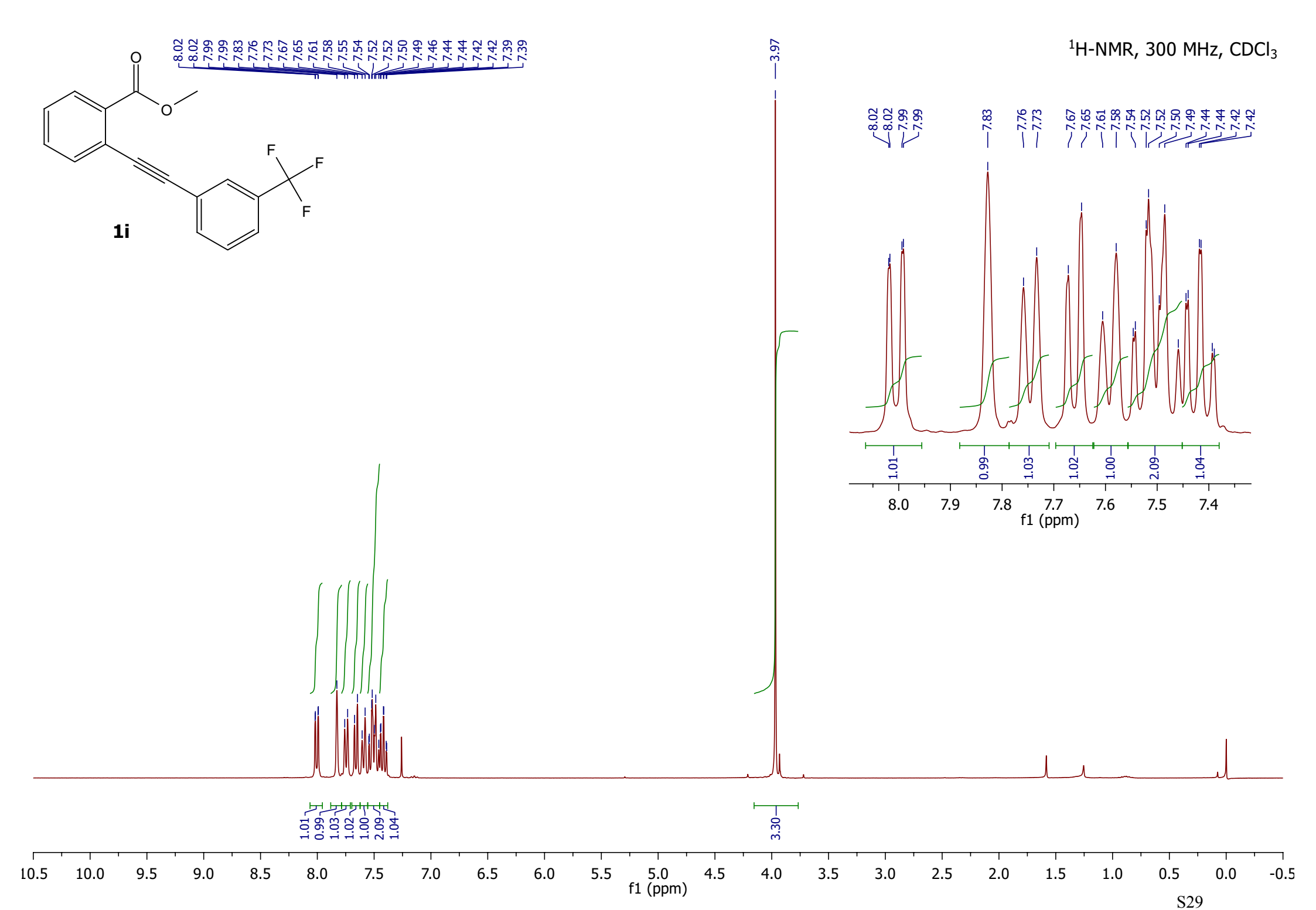
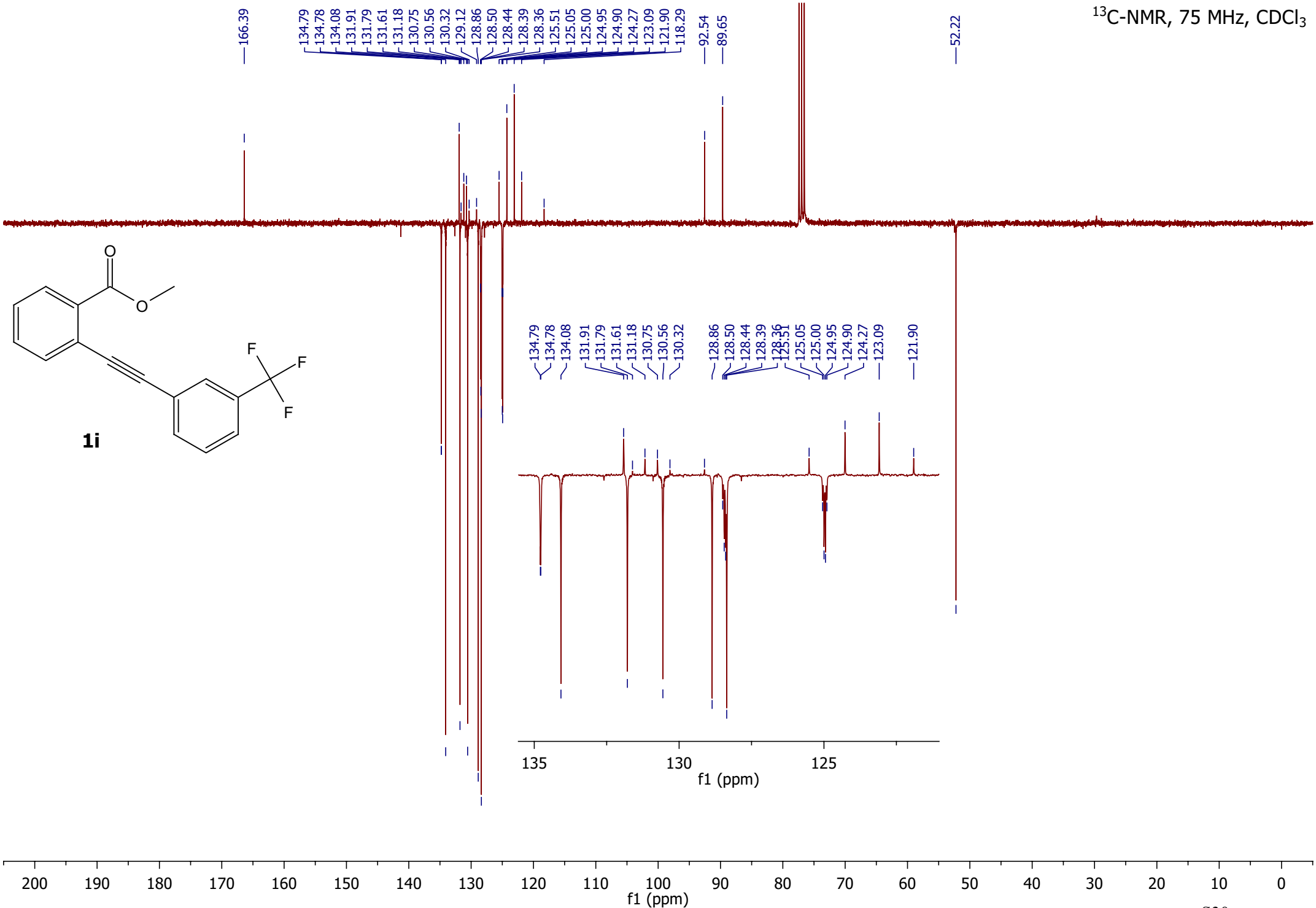
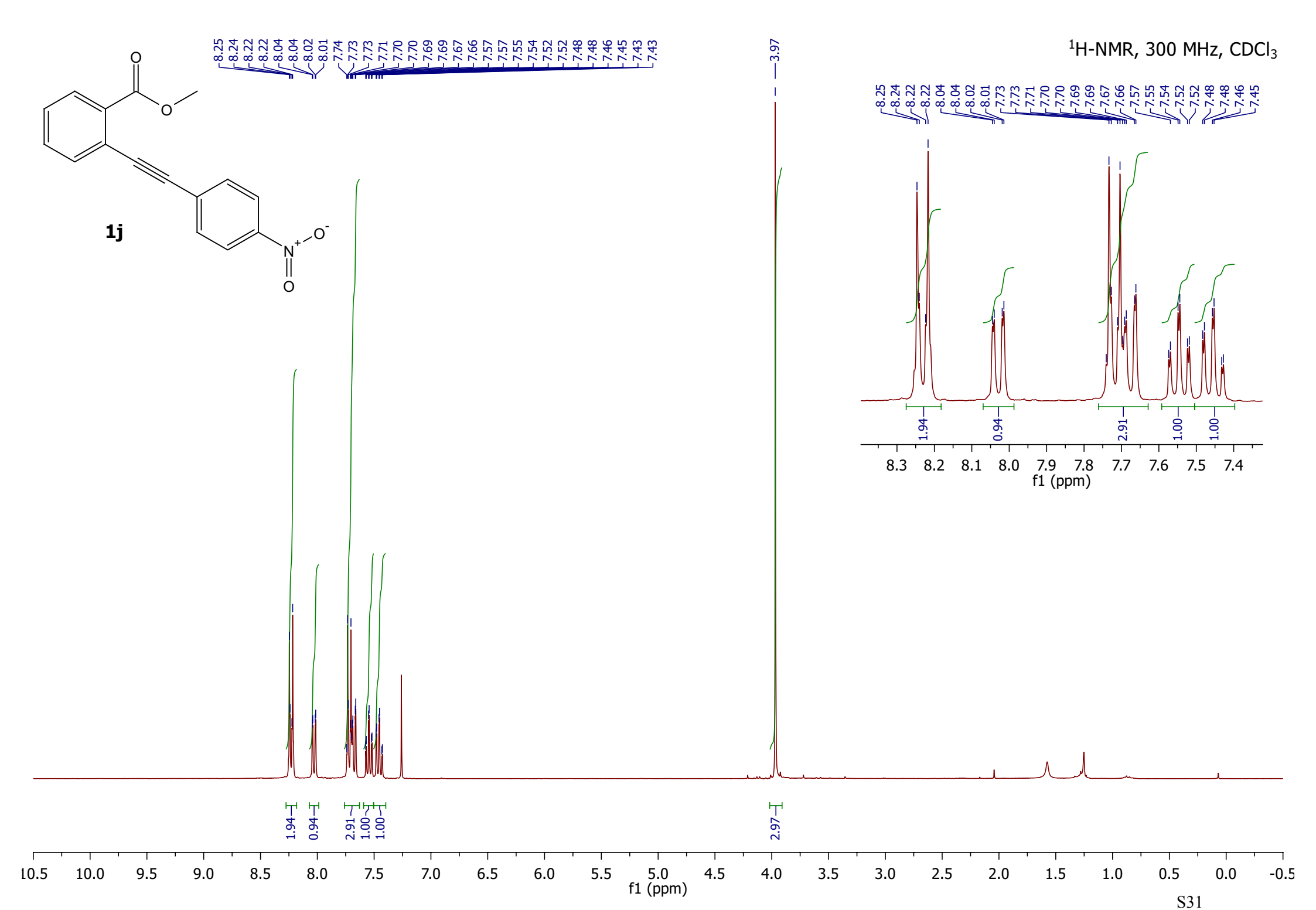
O
O
N
1g
f1 (ppm)
f1 (ppm)

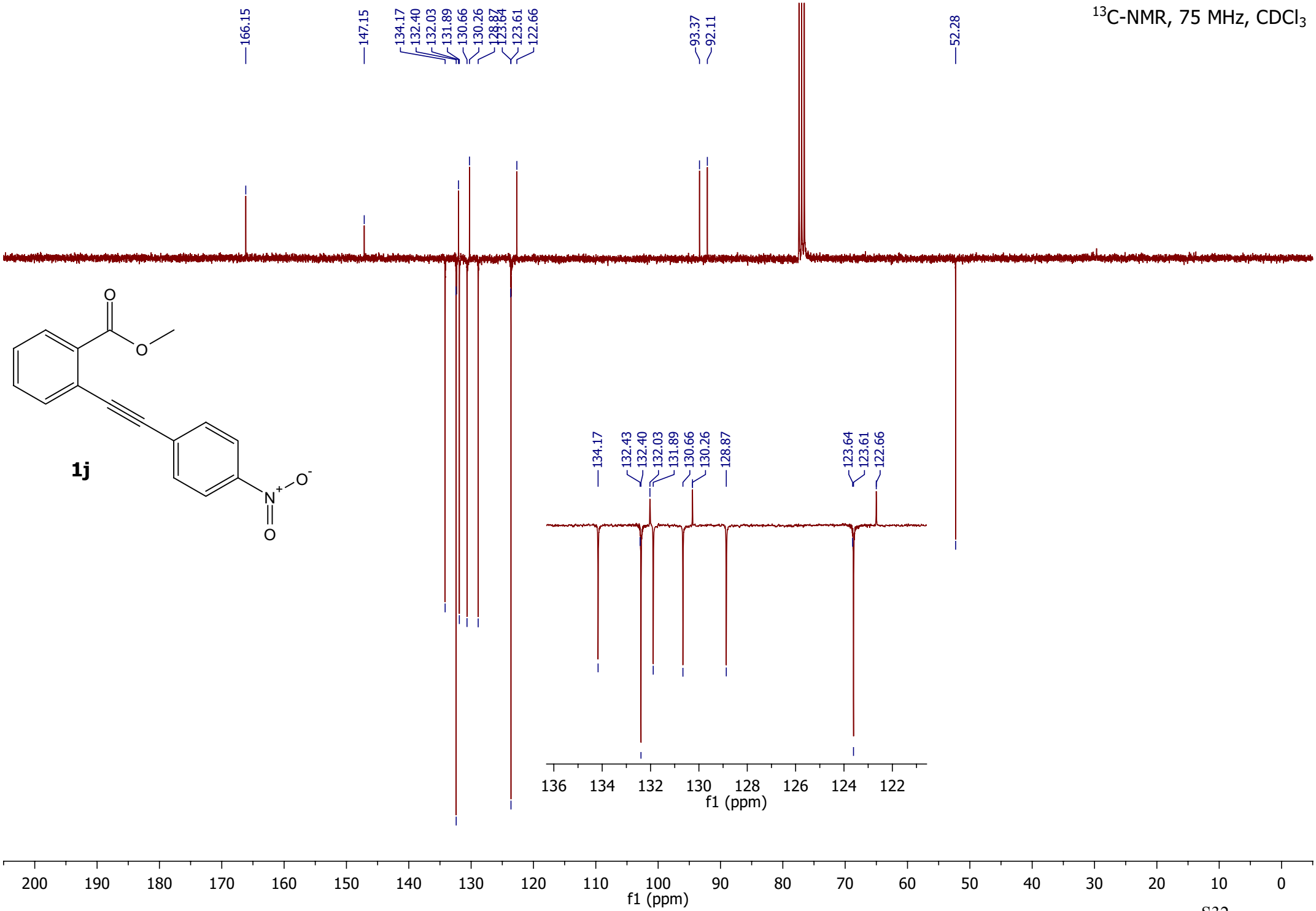

^{1}H-NMR, 300 MHz, $CDCl_3$
1h
f1 (ppm)

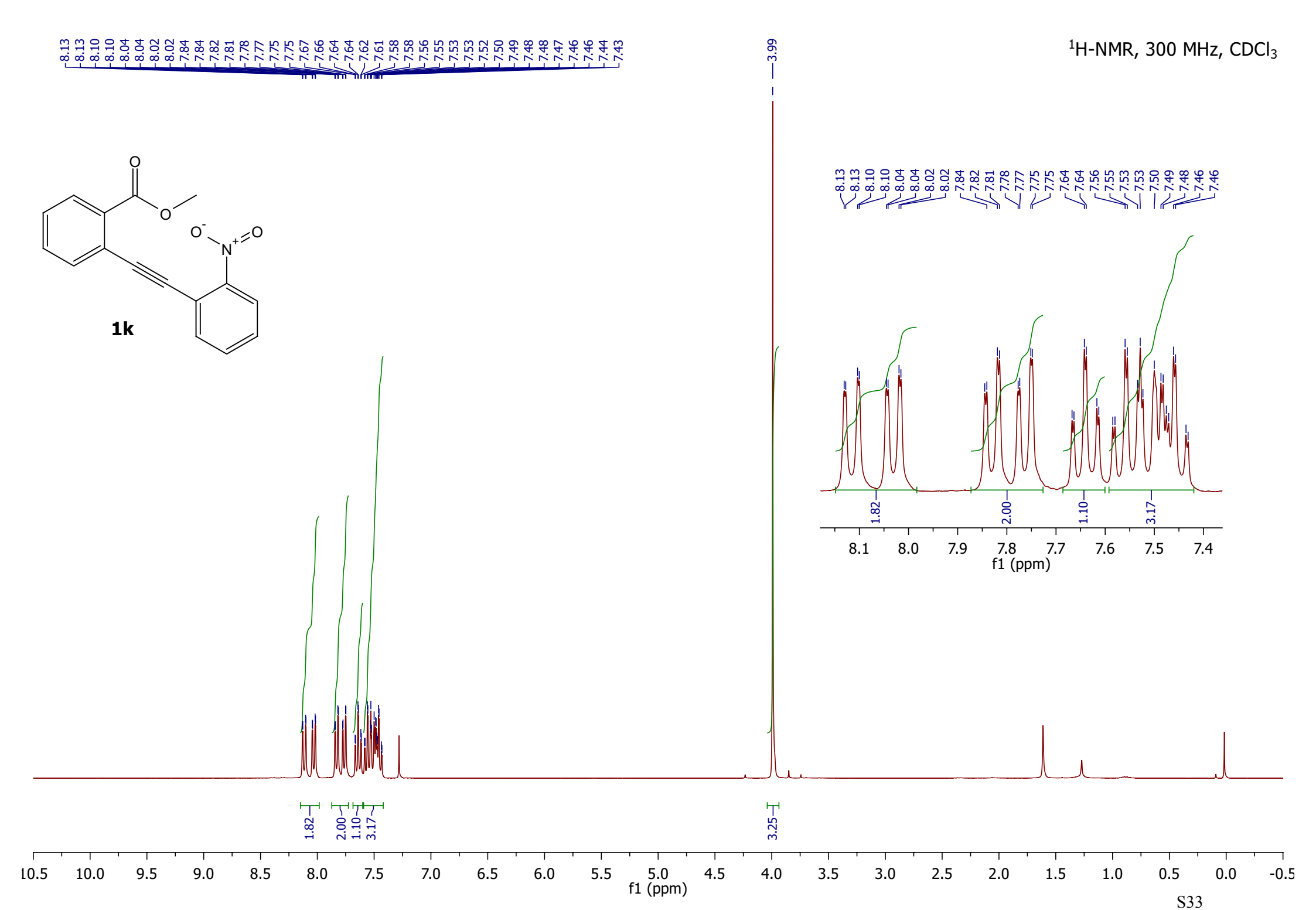

^{13}C-NMR, 75 MHz, $CDCl_3$
166.39
134.10
131.94
131.91
131.88
131.86
131.84
131.81
130.74
130.58
130.30
129.87
129.44
129.32
128.45
127.13
127.11
125.71
125.34
125.29
125.24
125.19
123.04
122.11
118.50
92.68
90.48
52.25
O
O
F
F
F
1h
f1 (ppm)
f1 (ppm)

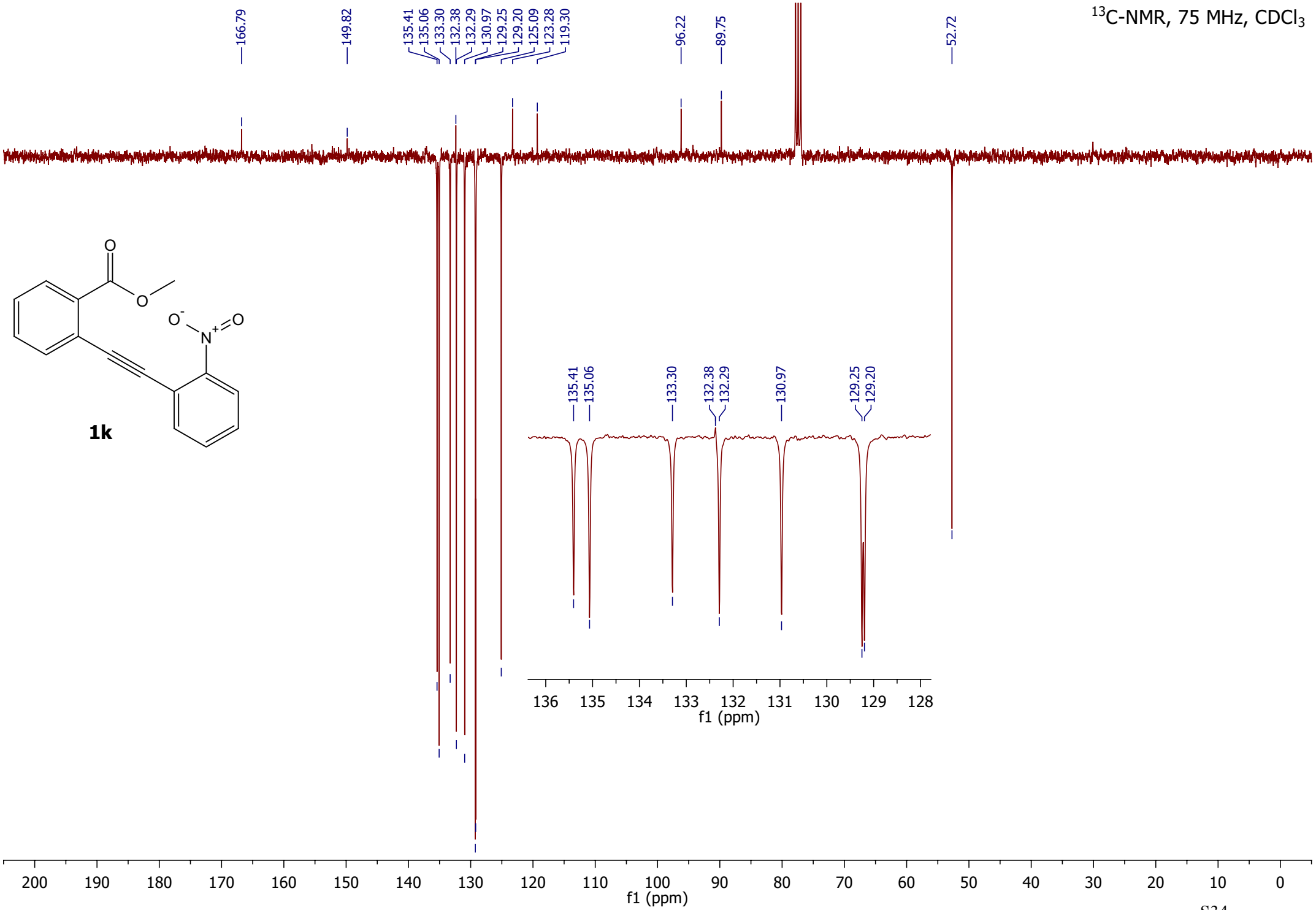

^{1}H-NMR, 300 MHz, $CDCl_3$
1i
f1 (ppm)

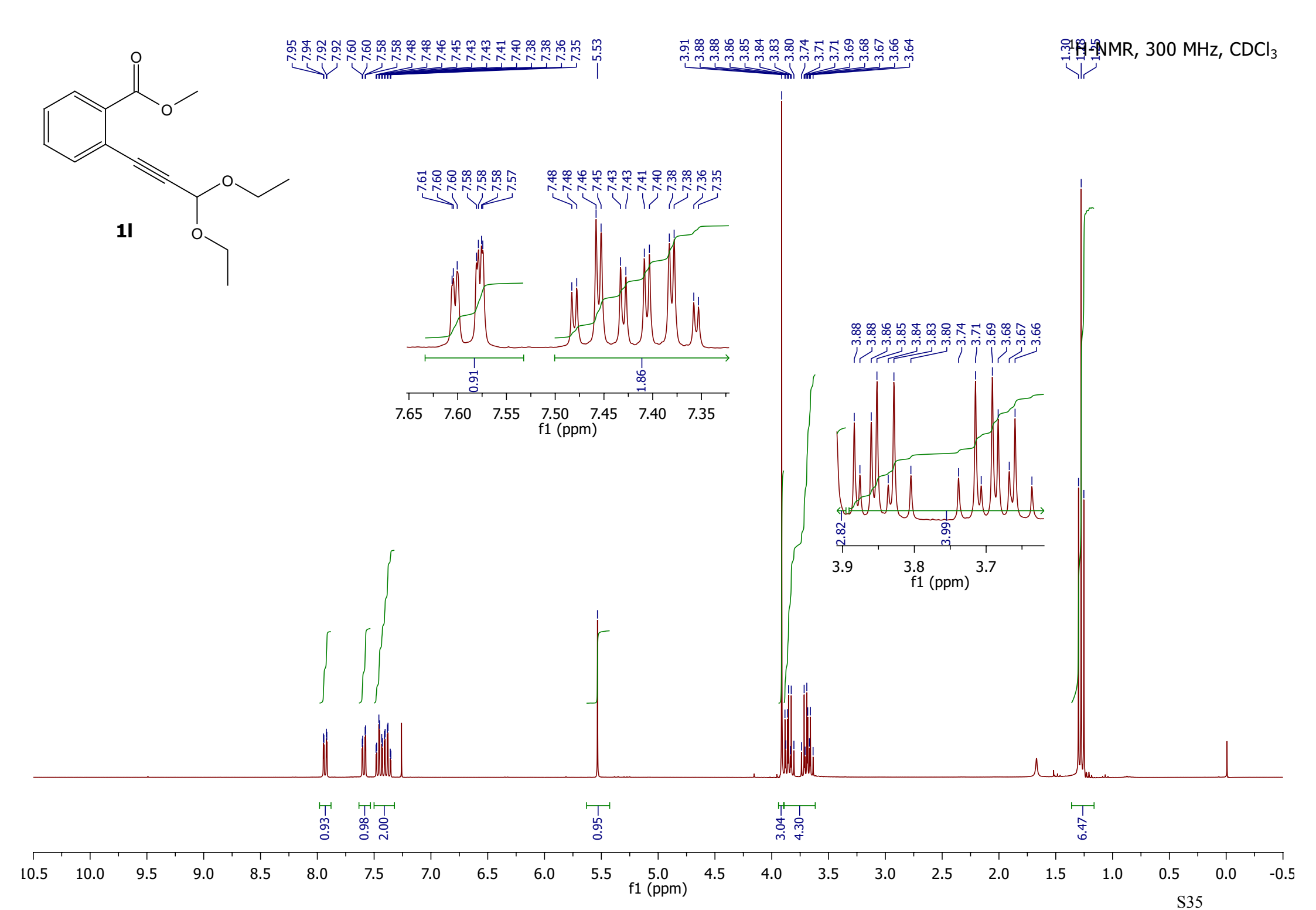

^{13}C-NMR, 75 MHz, $CDCl_3$
166.39
134.79
134.78
134.08
131.91
131.79
131.61
131.18
130.75
130.56
130.32
129.12
128.86
128.50
128.44
128.39
128.36
125.51
125.05
125.00
124.95
124.90
124.27
123.09
121.90
118.29
92.54
89.65
52.22
O
O
F
F
F
1i
f1 (ppm)
f1 (ppm)

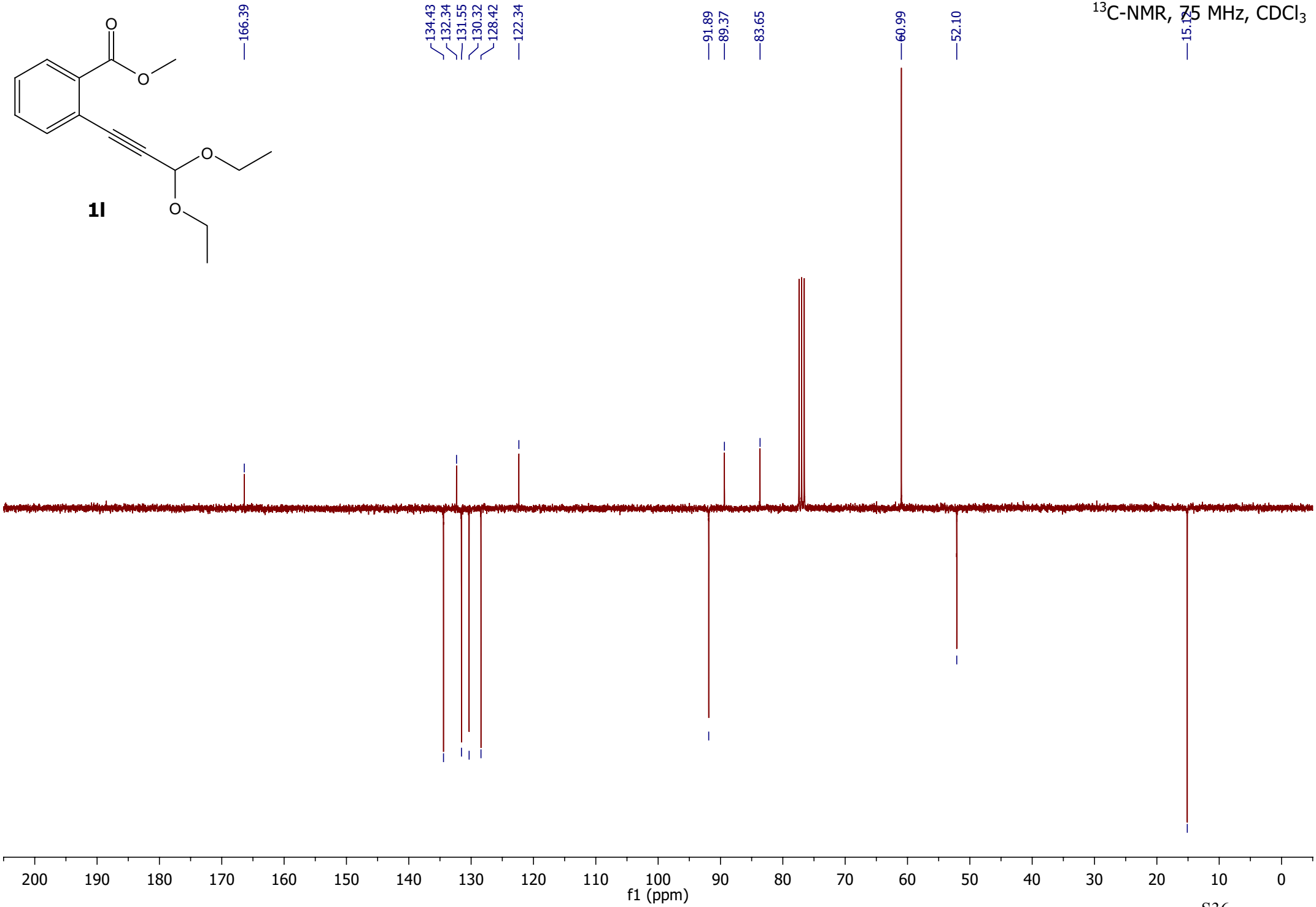

^{1}H-NMR, 300 MHz, $CDCl_3$
1j
f1 (ppm)

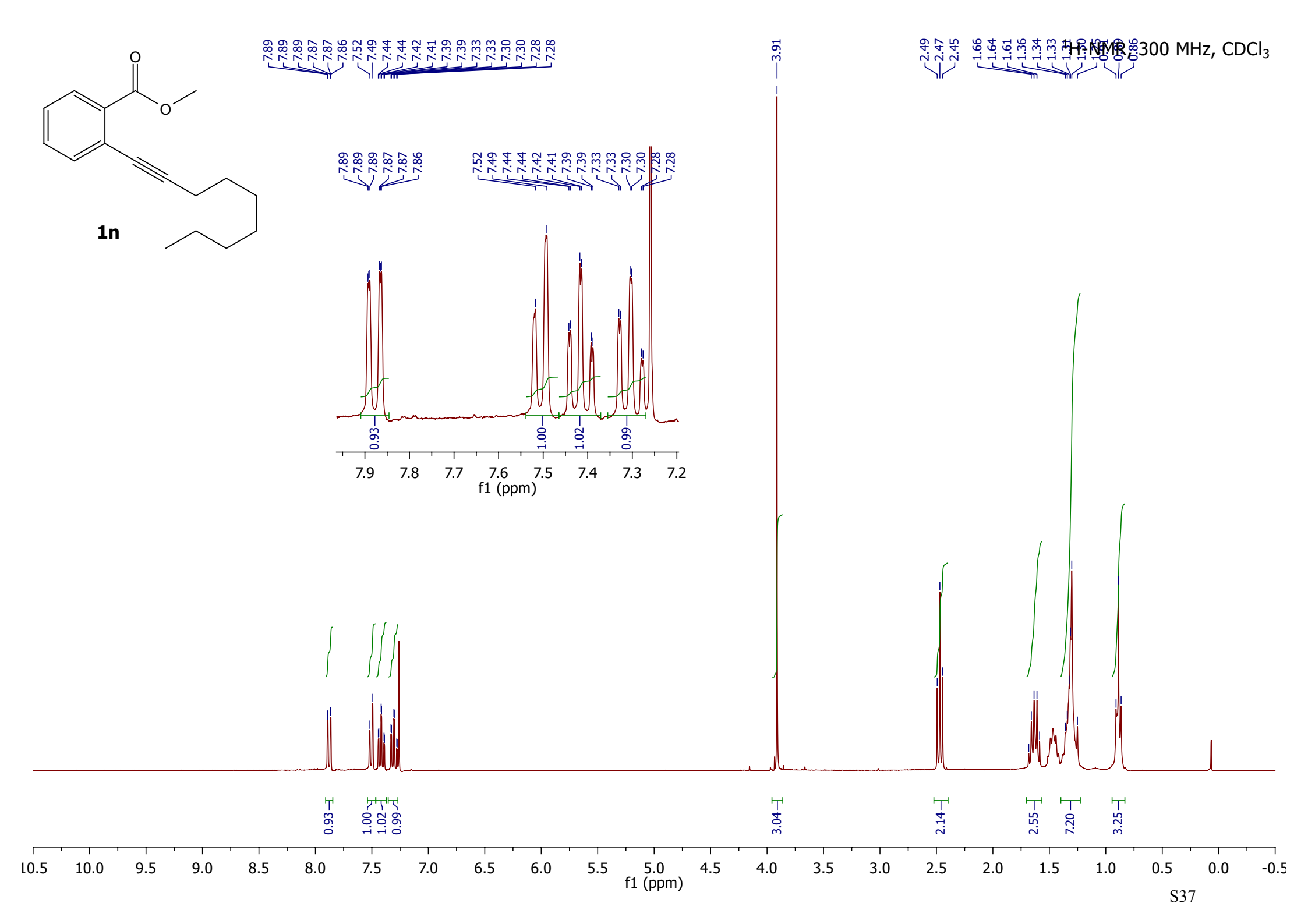

^{13}C-NMR, 75 MHz, $CDCl_3$
166.15
147.15
134.17
132.40
132.03
131.89
130.66
130.26
128.87
128.64
123.61
122.66
93.37
92.11
52.28
1j
O
O
N+
O-
O
134.17
132.43
132.40
132.03
131.89
130.66
130.26
128.87
123.64
123.61
122.66
136
134
132
130
128
126
124
122
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

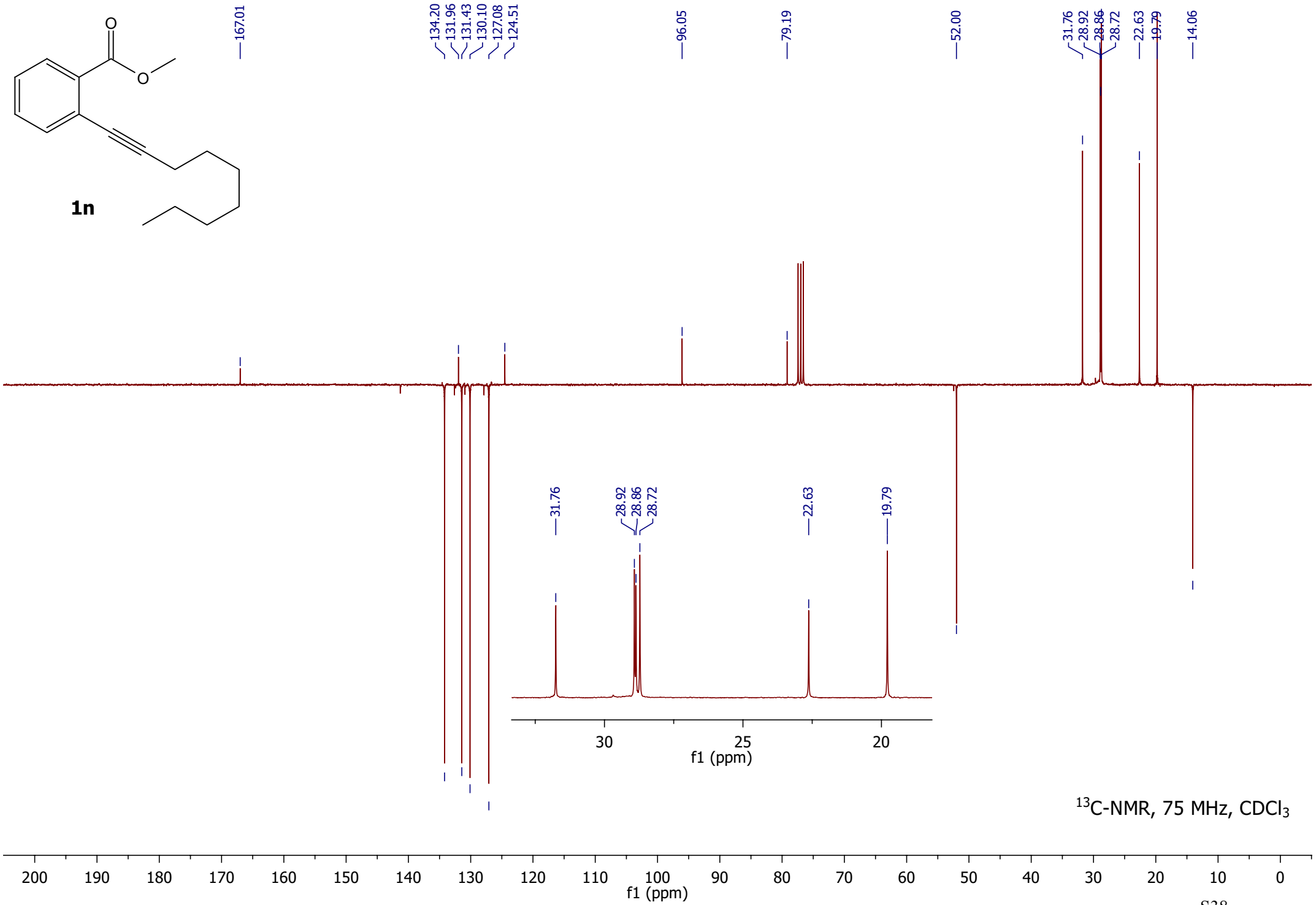

^{1}H-NMR, 300 MHz, $CDCl_3$
8.13 8.13 8.10 8.10 8.04 8.04 8.02 8.02 7.84 7.82 7.81 7.78 7.77 7.75 7.75 7.67 7.66 7.64 7.64 7.62 7.61 7.58 7.58 7.56 7.55 7.53 7.53 7.52 7.50 7.49 7.48 7.48 7.47 7.46 7.46 7.44 7.43
3.99
1k
1.82
2.00
1.10
3.17
3.25
f1 (ppm)

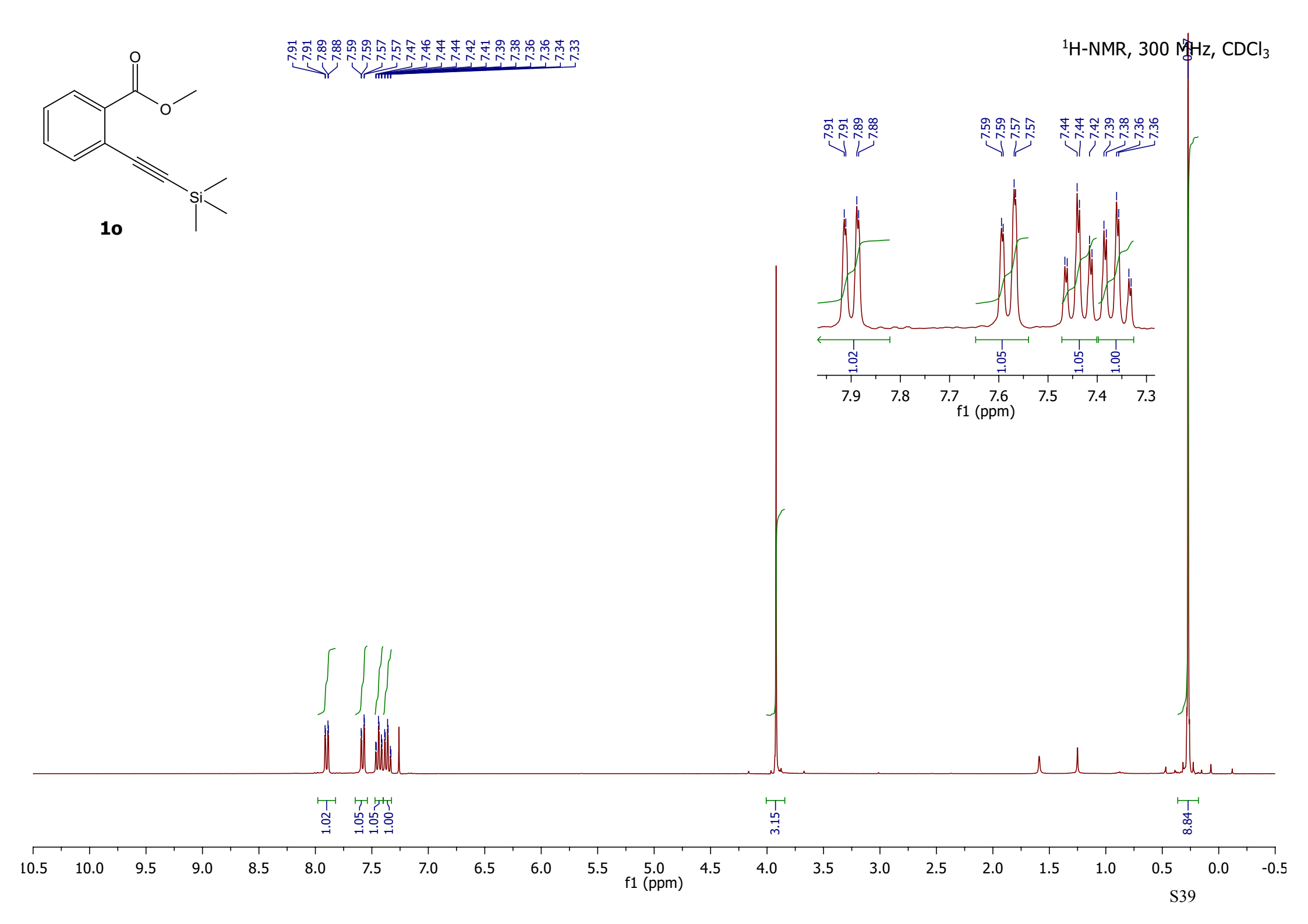

^{13}C-NMR, 75 MHz, $CDCl_3$
166.79
149.82
135.41
135.06
133.30
132.38
132.29
130.97
129.25
129.20
125.09
123.28
119.30
96.22
89.75
52.72
1k
135.41
135.06
133.30
132.38
132.29
130.97
129.25
129.20
136 135 134 133 132 131 130 129 128
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

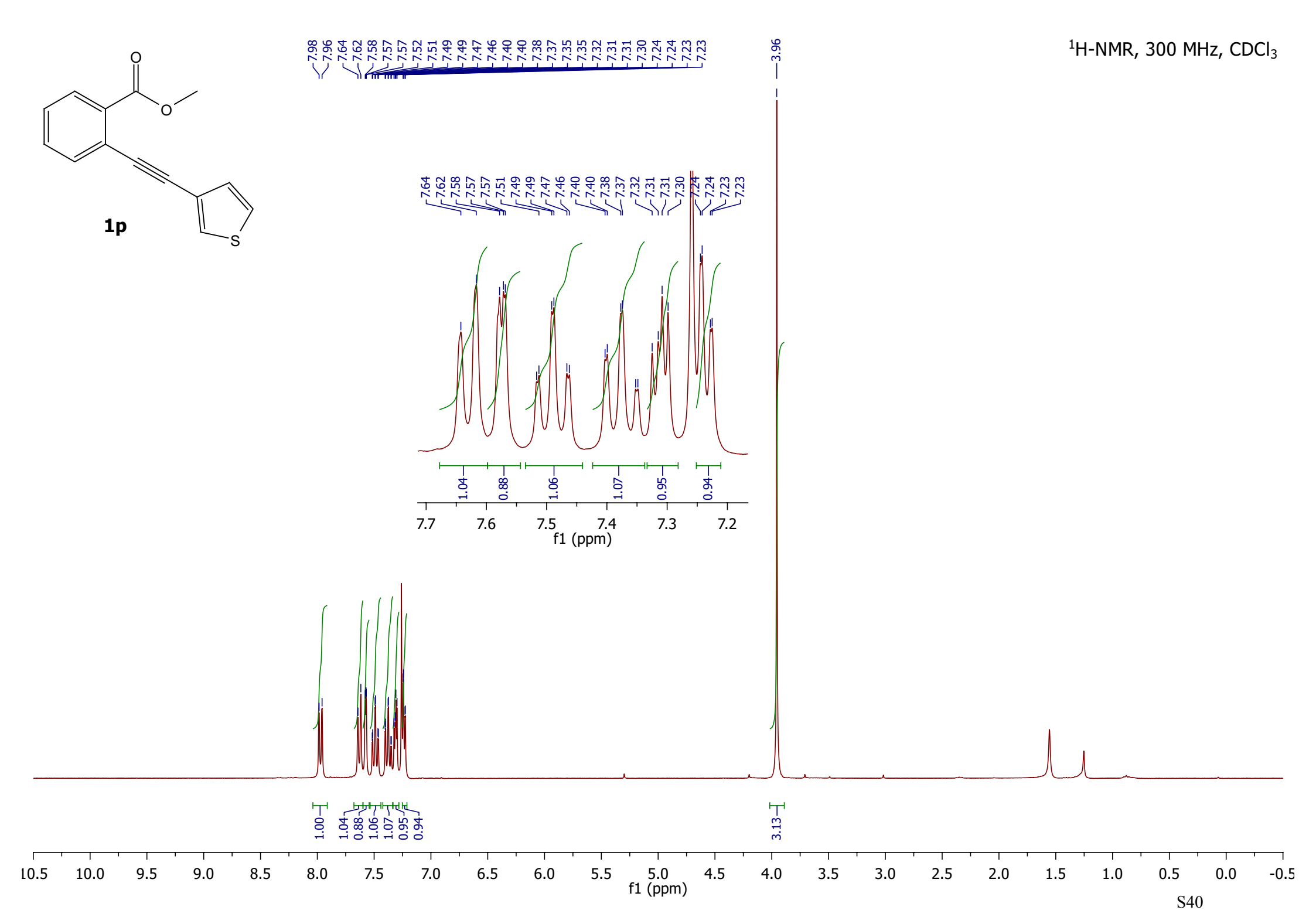

1H-NMR, 300 MHz, CDCl3
1l
f1 (ppm)

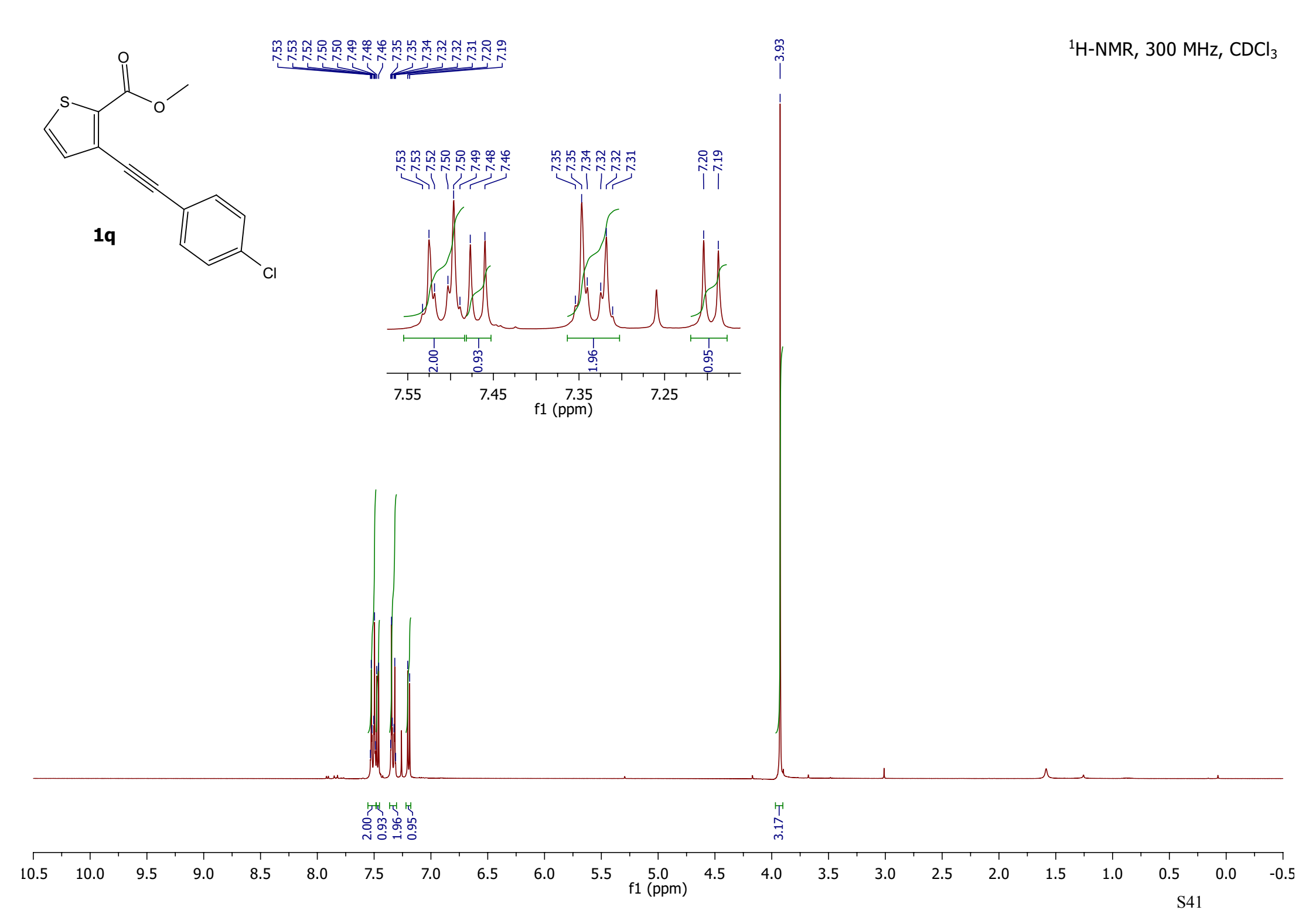

^{13}C-NMR, 75 MHz, $CDCl_3$
166.39
134.43
132.34
131.55
130.32
128.42
122.34
91.89
89.37
83.65
60.99
52.10
15.12
1l
O
O
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

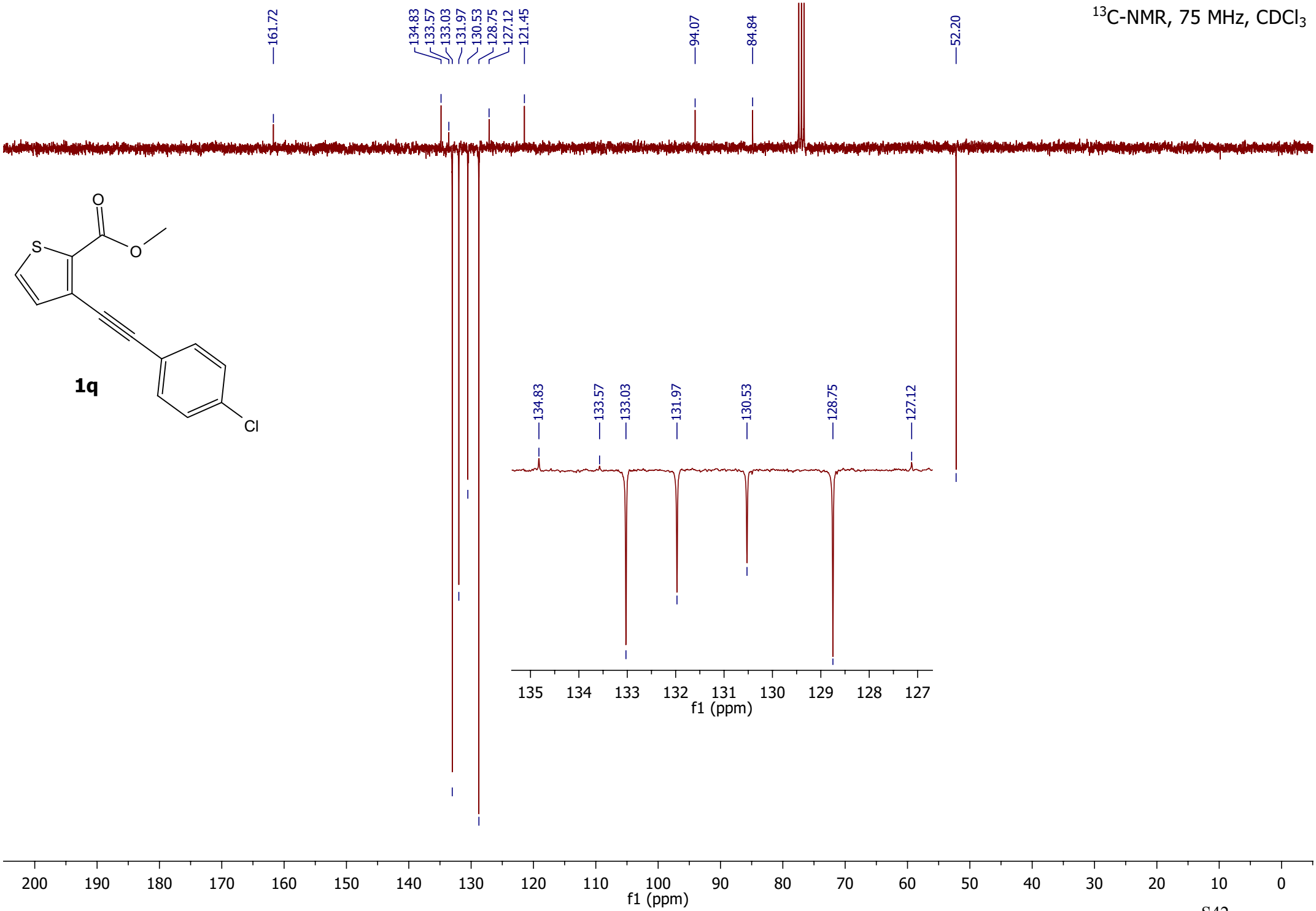

1n
¹H-NMR, 300 MHz, CDCl3
f1 (ppm)

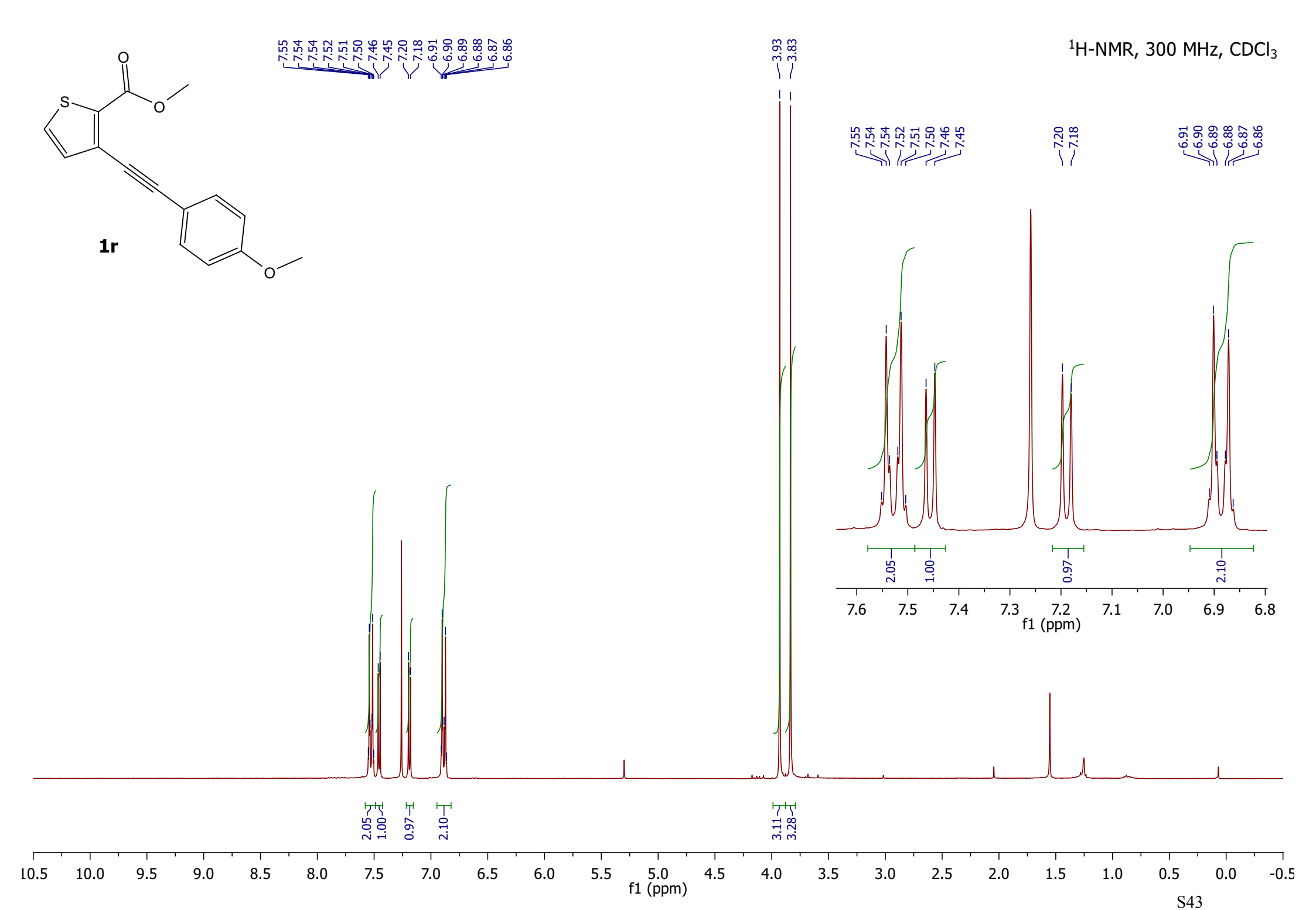

O
O
1n
167.01
134.20
131.96
131.43
130.10
127.08
124.51
96.05
79.19
52.00
31.76
28.92
28.86
28.72
22.63
19.79
14.06
31.76
28.92
28.86
28.72
22.63
19.79
30
25
20
f1 (ppm)
^{13}C-NMR, 75 MHz, CDCl$_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

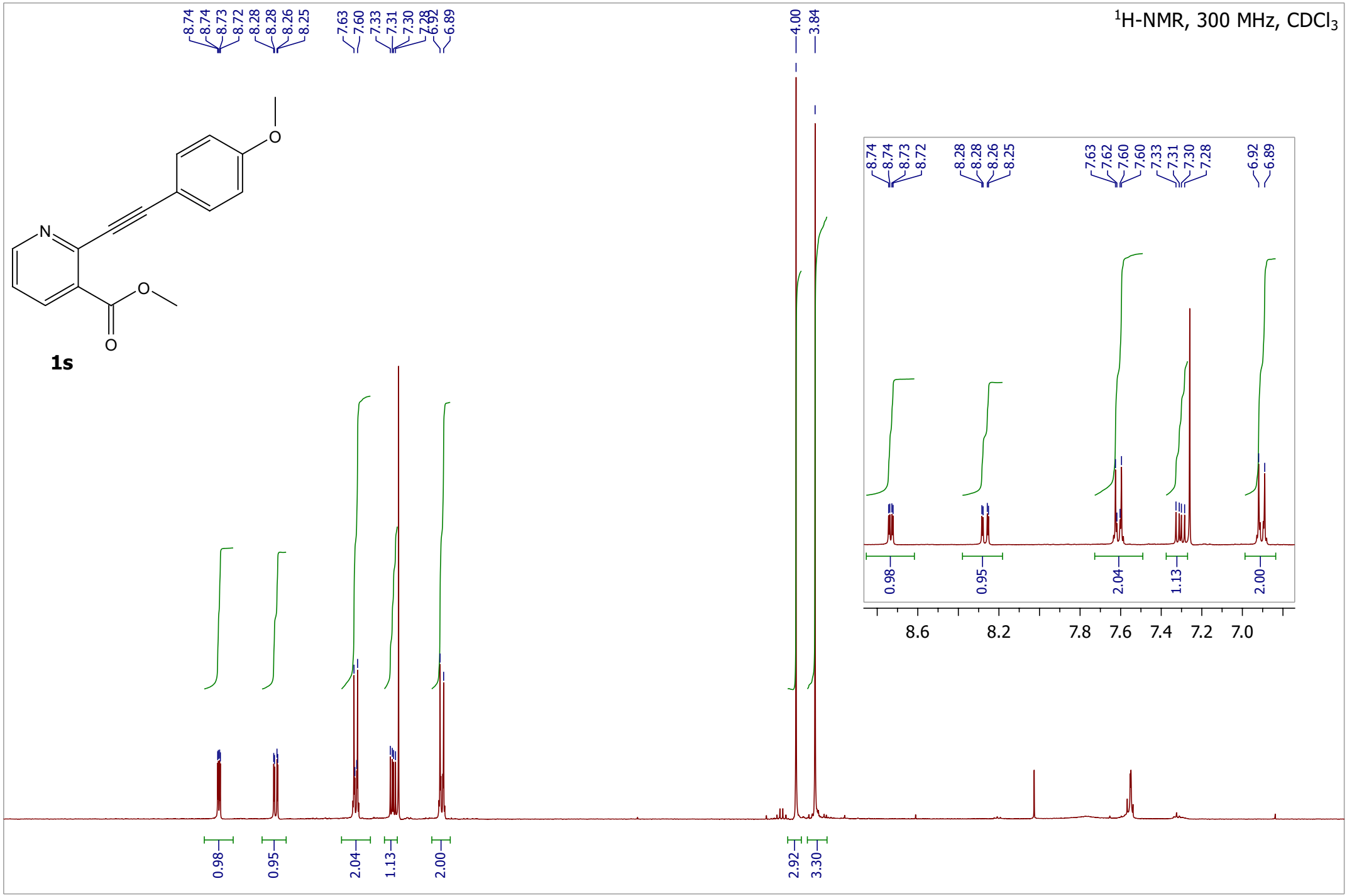

1o
^{1}H-NMR, 300 MHz, CDCl$_3$
f1 (ppm)

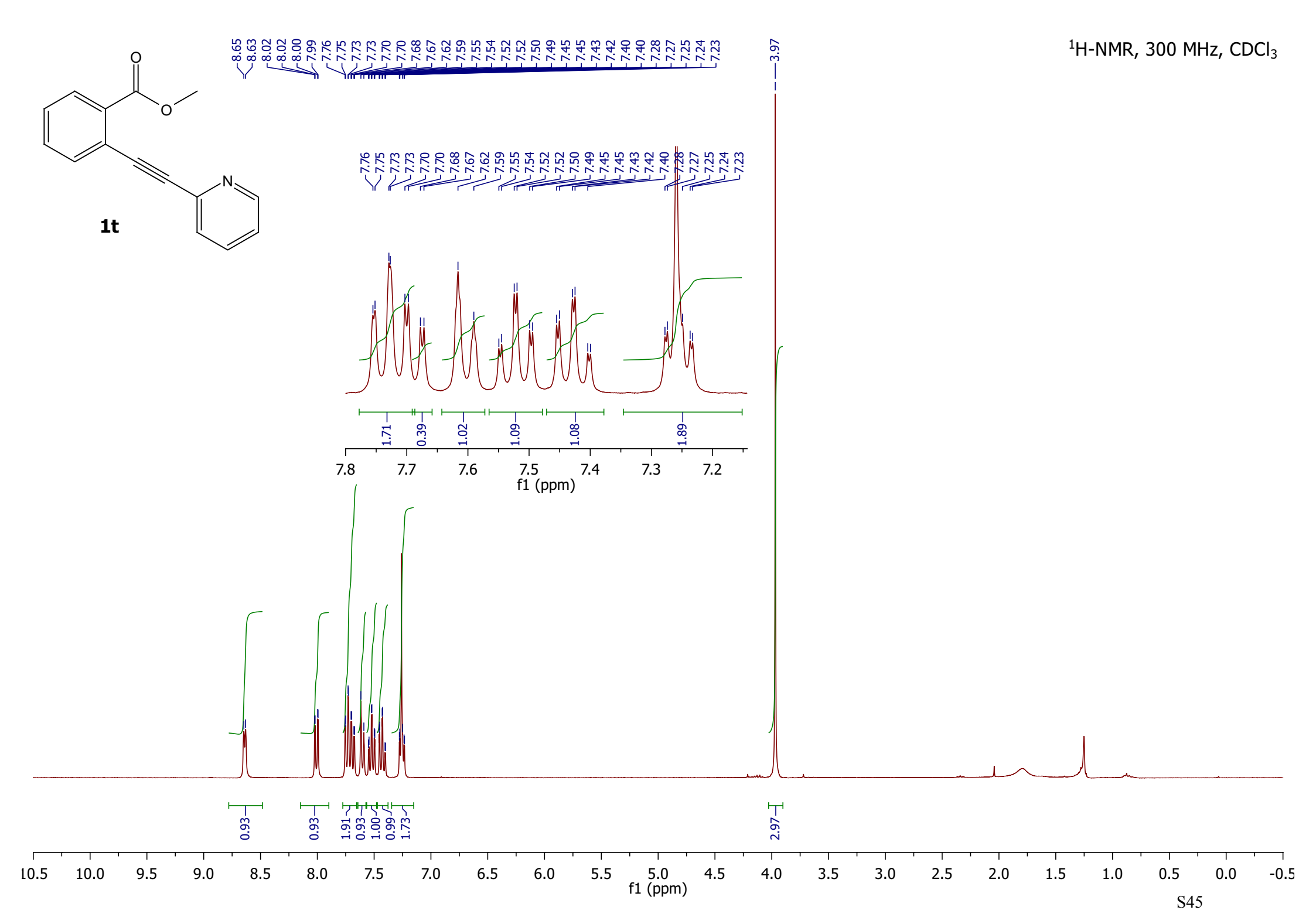

1p
O
O
S
^{1}H-NMR, 300 MHz, $CDCl_3$
7.98 7.96 7.64 7.62 7.58 7.57 7.57 7.52 7.51 7.49 7.49 7.47 7.46 7.40 7.40 7.38 7.37 7.35 7.35 7.32 7.31 7.31 7.30 7.24 7.24 7.23 7.23
3.96
1.04 0.88 1.06 1.07 0.95 0.94
7.7 7.6 7.5 7.4 7.3 7.2
f1 (ppm)
1.00 1.04 0.88 1.06 1.07 0.95 0.94
3.13
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

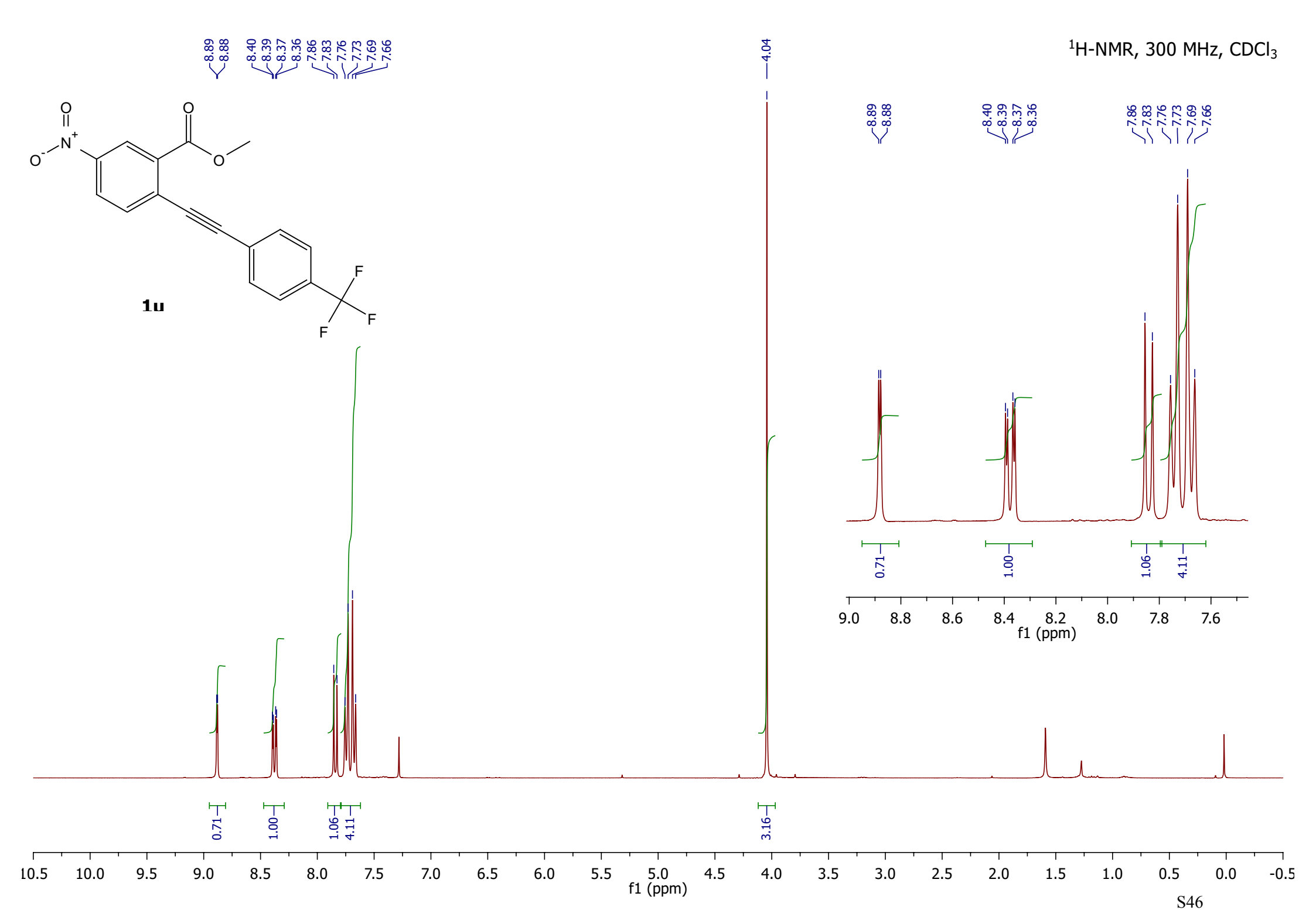

1q
Cl
O
S
O
^{1}H-NMR, 300 MHz, $CDCl_3$
7.53 7.53 7.52 7.50 7.50 7.49 7.48 7.46 7.35 7.35 7.34 7.32 7.32 7.31 7.20 7.19
3.93
2.00 0.93 1.96 0.95
7.55 7.45 7.35 7.25
f1 (ppm)
3.17
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

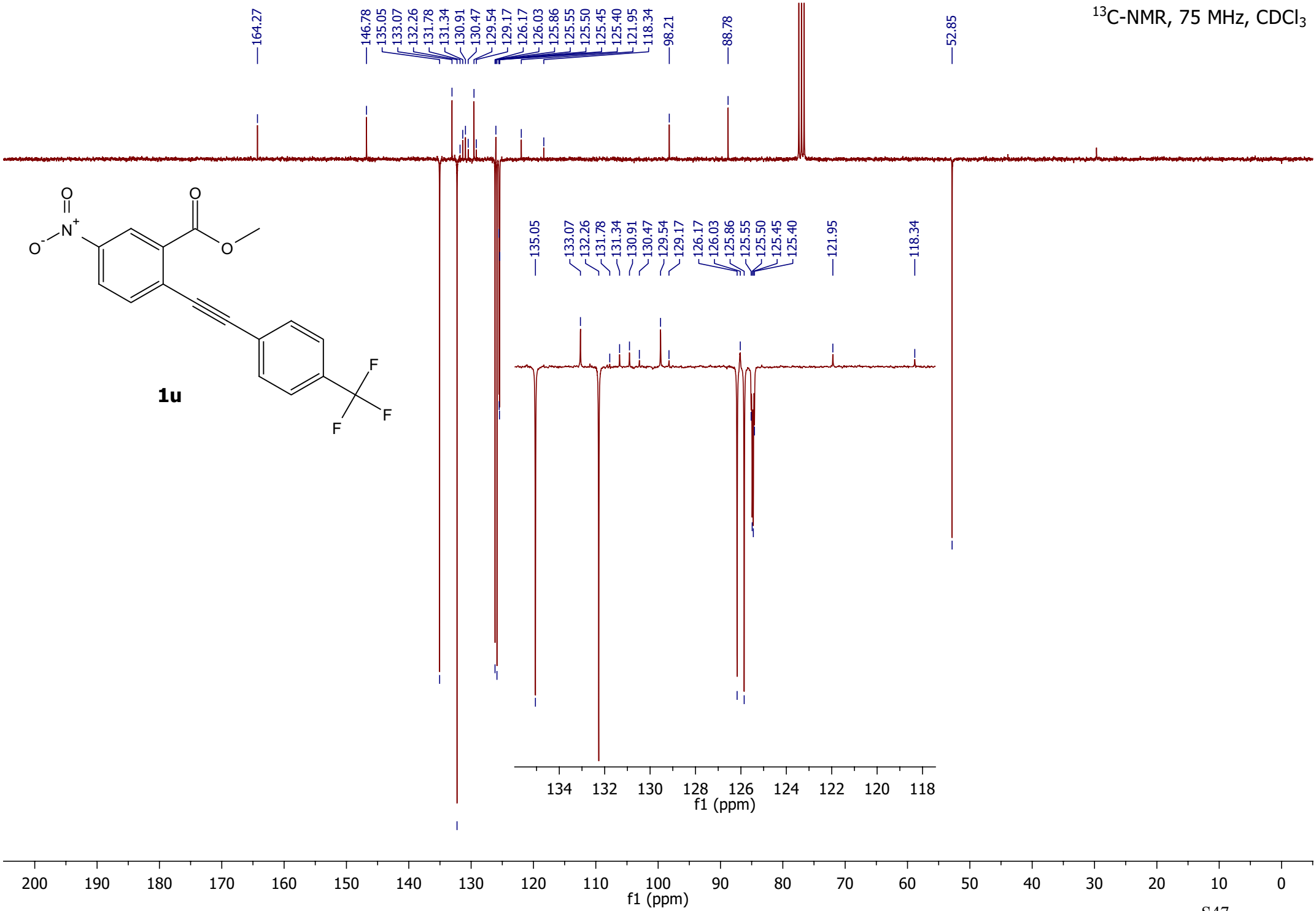

^{13}C-NMR, 75 MHz, $CDCl_3$
161.72
134.83
133.57
133.03
131.97
130.53
128.75
127.12
121.45
94.07
84.84
52.20
O
S
O
Cl
1q
134.83
133.57
133.03
131.97
130.53
128.75
127.12
135
134
133
132
131
130
129
128
127
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

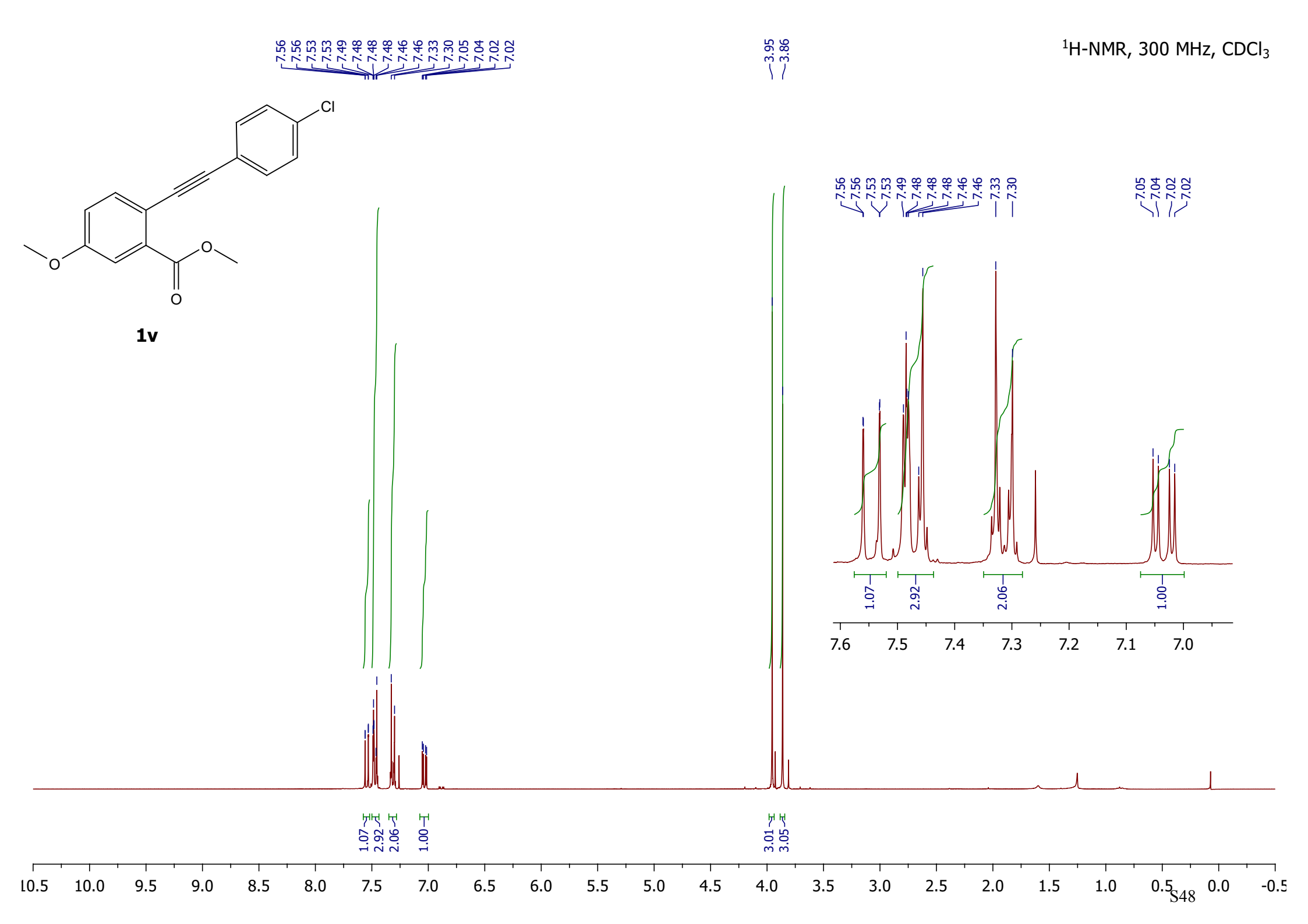

1r
^{1}H-NMR, 300 MHz, $CDCl_3$
7.55 7.54 7.54 7.52 7.51 7.50 7.46 7.45 7.20 7.18 6.91 6.90 6.89 6.88 6.87 6.86
3.93 3.83
2.05 1.00 0.97 2.10 3.11 3.28
f1 (ppm)

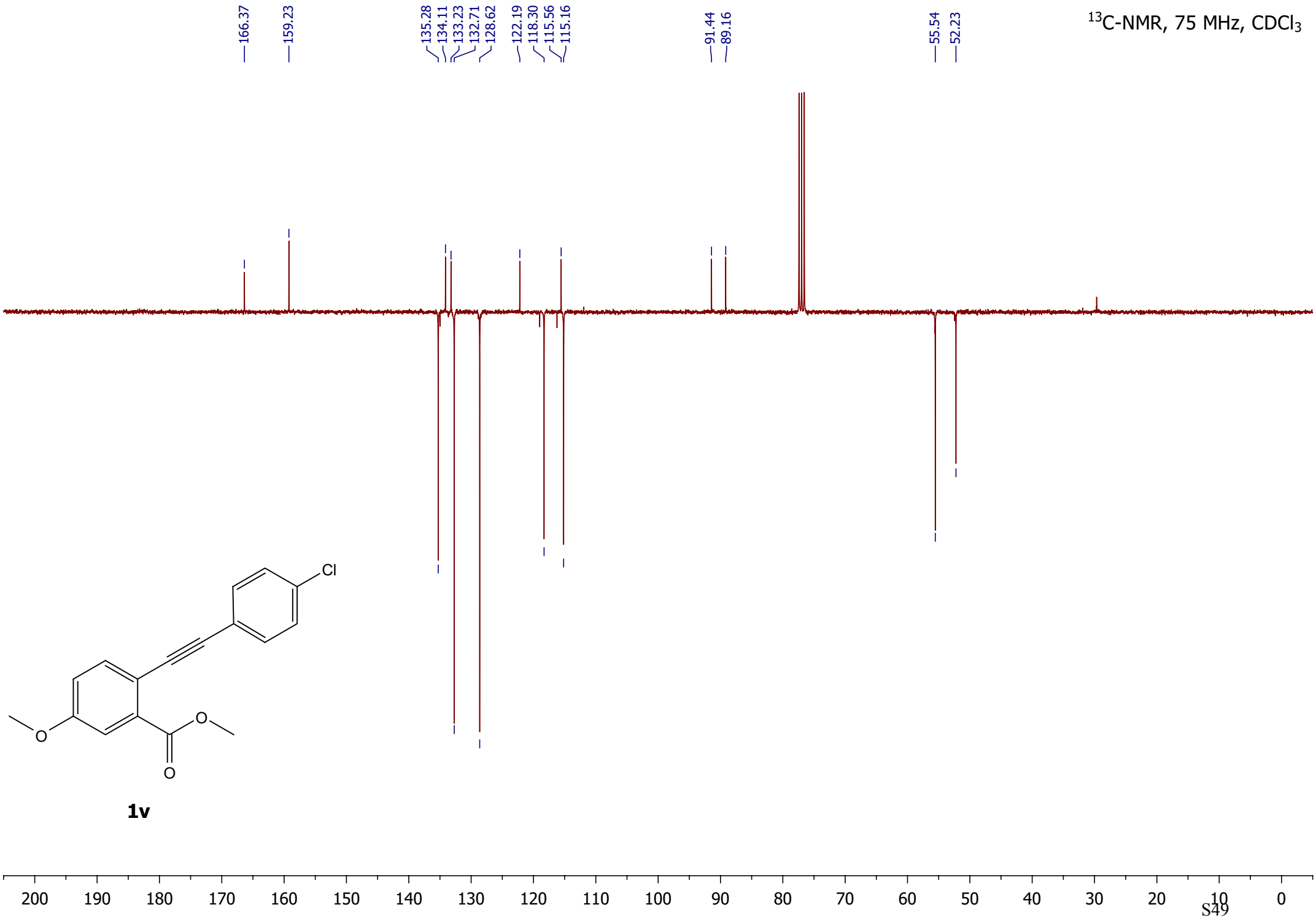

^{1}H-NMR, 300 MHz, $CDCl_3$
8.74
8.74
8.73
8.72
8.28
8.28
8.26
8.25
7.63
7.60
7.33
7.31
7.30
7.28
6.92
6.89
4.00
3.84
N
O
O
O
1s
0.98
0.95
2.04
1.13
2.00
2.92
3.30
8.74
8.74
8.73
8.72
8.28
8.28
8.26
8.25
7.63
7.62
7.60
7.60
7.33
7.31
7.30
7.28
6.92
6.89
0.98
0.95
2.04
1.13
2.00
8.6
8.2
7.8
7.6
7.4
7.2
7.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5


1t
^{1}H-NMR, 300 MHz, $CDCl_3$
f1 (ppm)

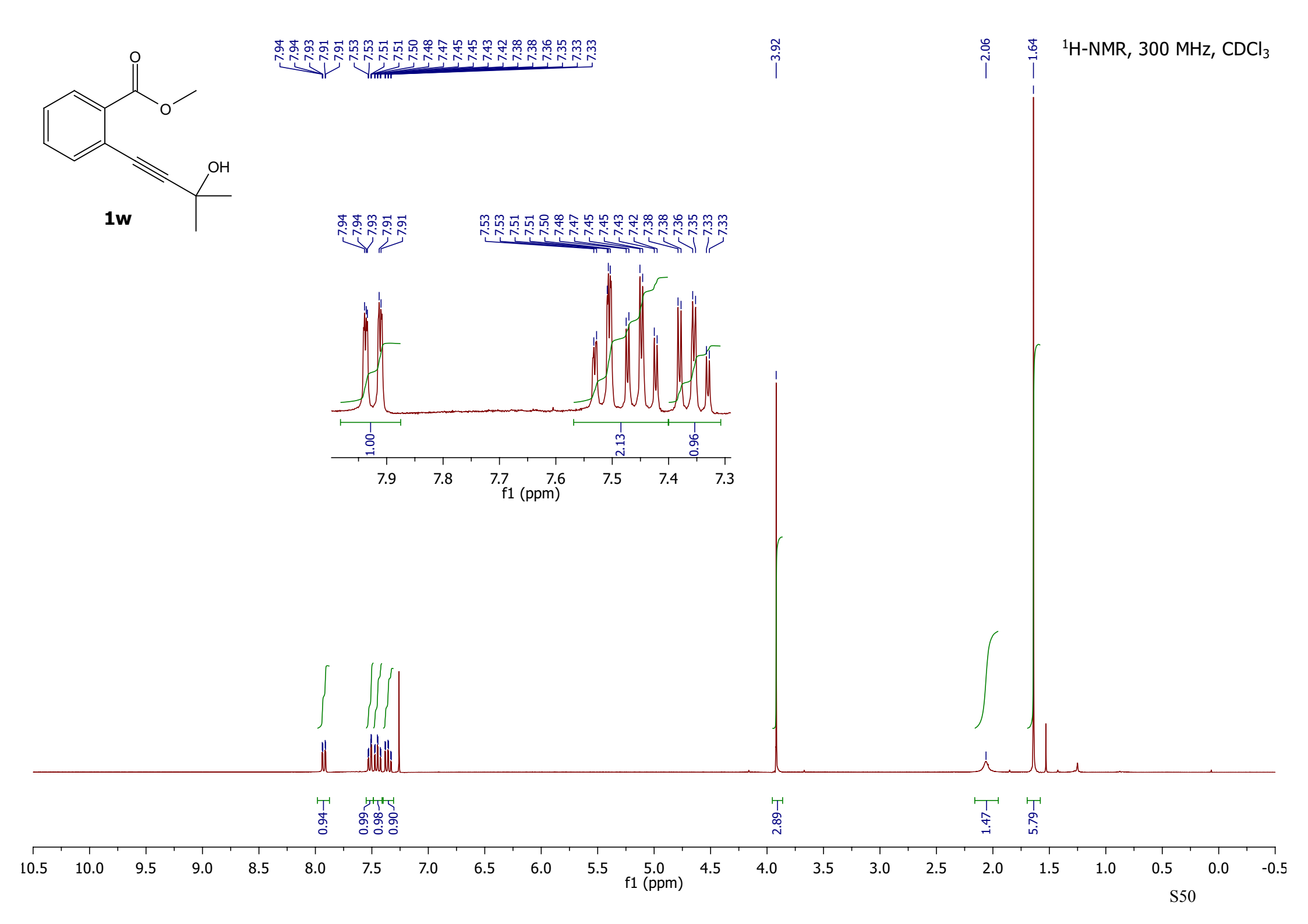

^{1}H-NMR, 300 MHz, $CDCl_3$
8.89
8.88
8.40
8.39
8.37
8.36
7.86
7.83
7.76
7.73
7.69
7.66
4.04
1u
F
F
F
O
O
O
N
O
0.71
1.00
1.06
4.11
3.16
f1 (ppm)

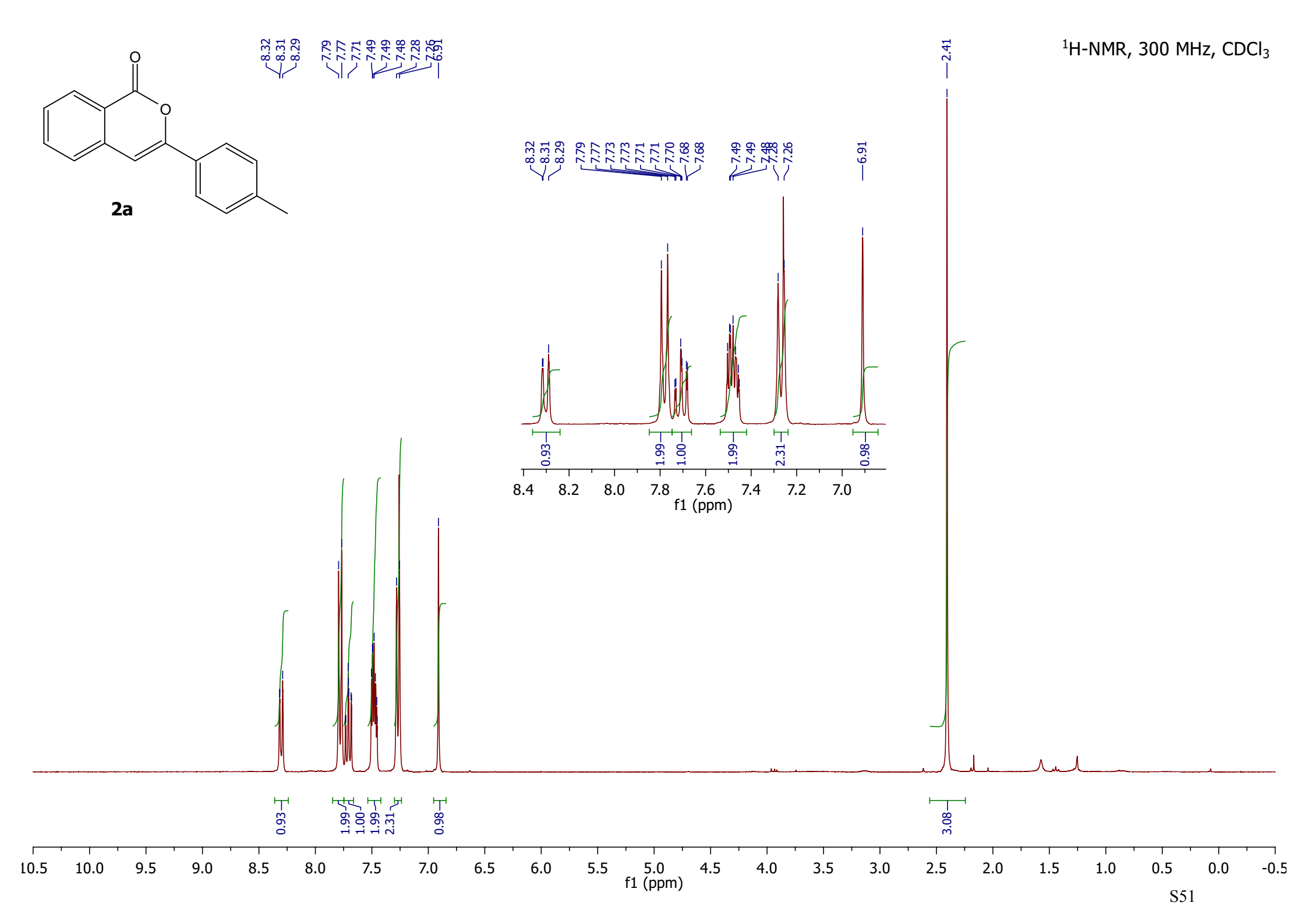

^{13}C-NMR, 75 MHz, $CDCl_3$
164.27
146.78
135.05
133.07
132.26
131.78
131.34
130.91
130.47
129.54
129.17
126.17
126.03
125.86
125.55
125.50
125.45
125.40
121.95
118.34
98.21
88.78
52.85
1u
f1 (ppm)
f1 (ppm)


^{1}H-NMR, 300 MHz, $CDCl_3$
7.56 7.56 7.53 7.53 7.49 7.48 7.48 7.48 7.46 7.46 7.33 7.30 7.05 7.04 7.02 7.02
3.95 3.86
Cl
O
O
O
1v
1.07 2.92 2.06 1.00
3.01 3.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
7.6 7.5 7.4 7.3 7.2 7.1 7.0

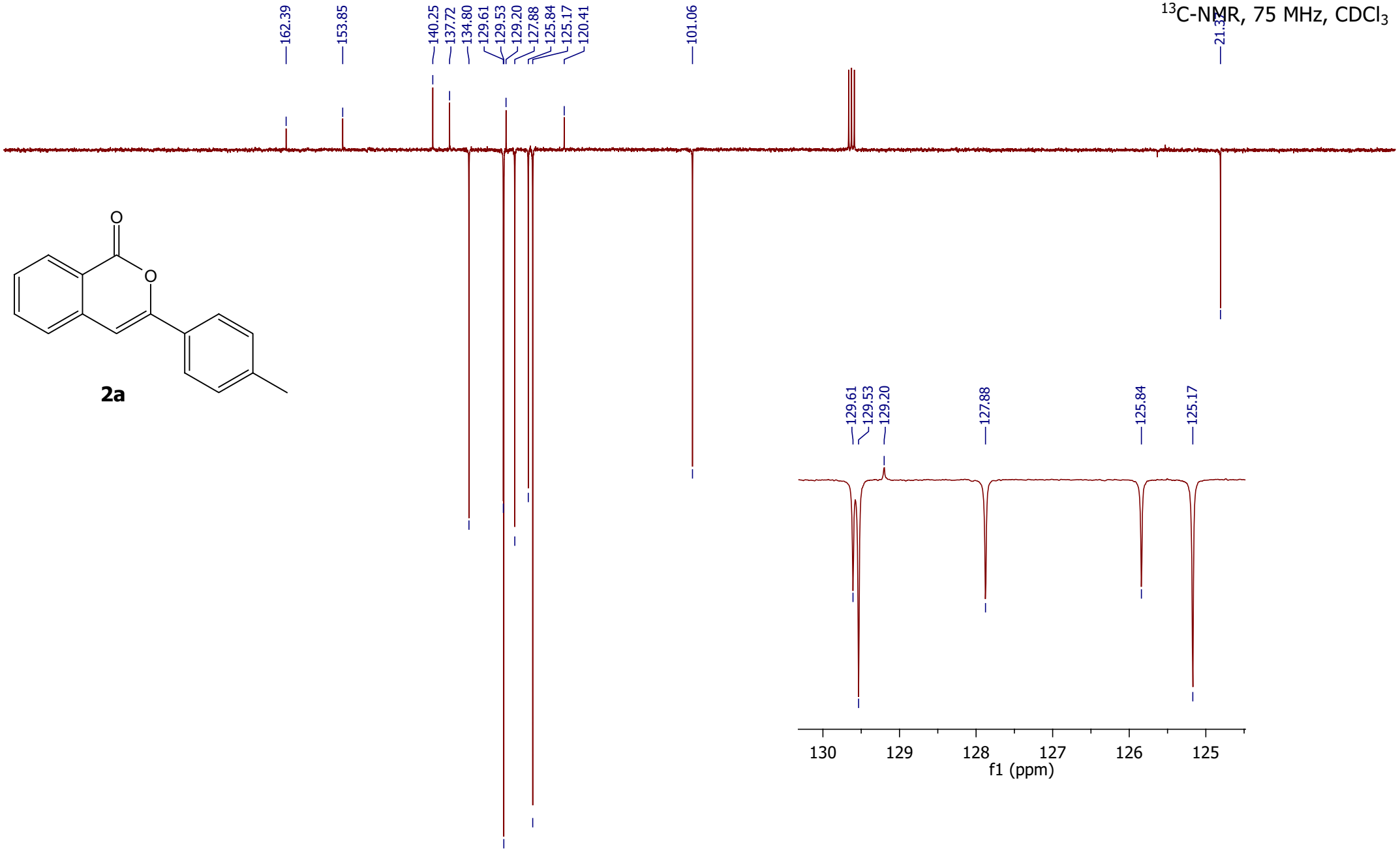

166.37
159.23
135.28
134.11
133.23
132.71
128.62
122.19
118.30
115.56
115.16
91.44
89.16
55.54
52.23
^{13}C-NMR, 75 MHz, $CDCl_3$
Cl
O
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

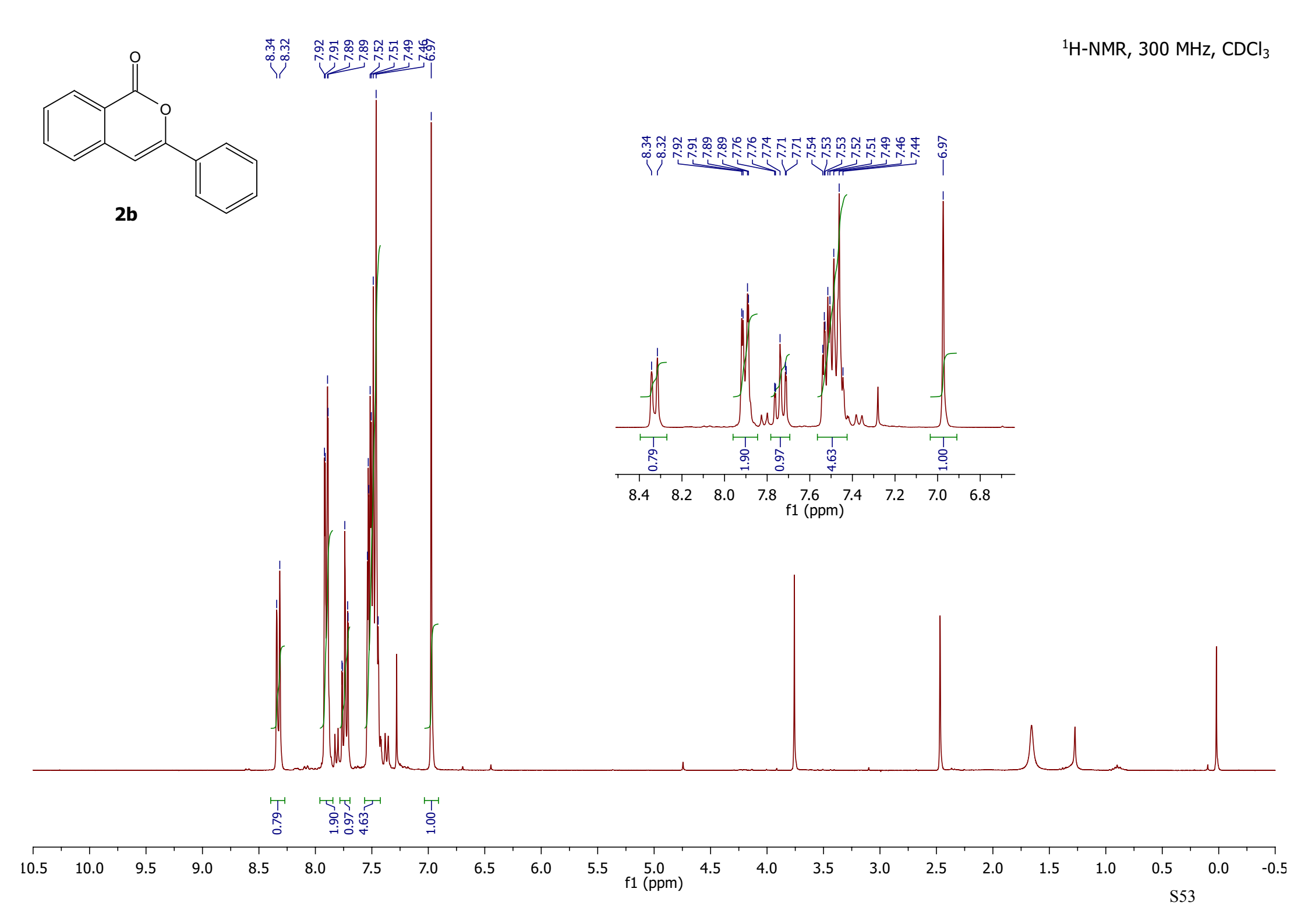
1v

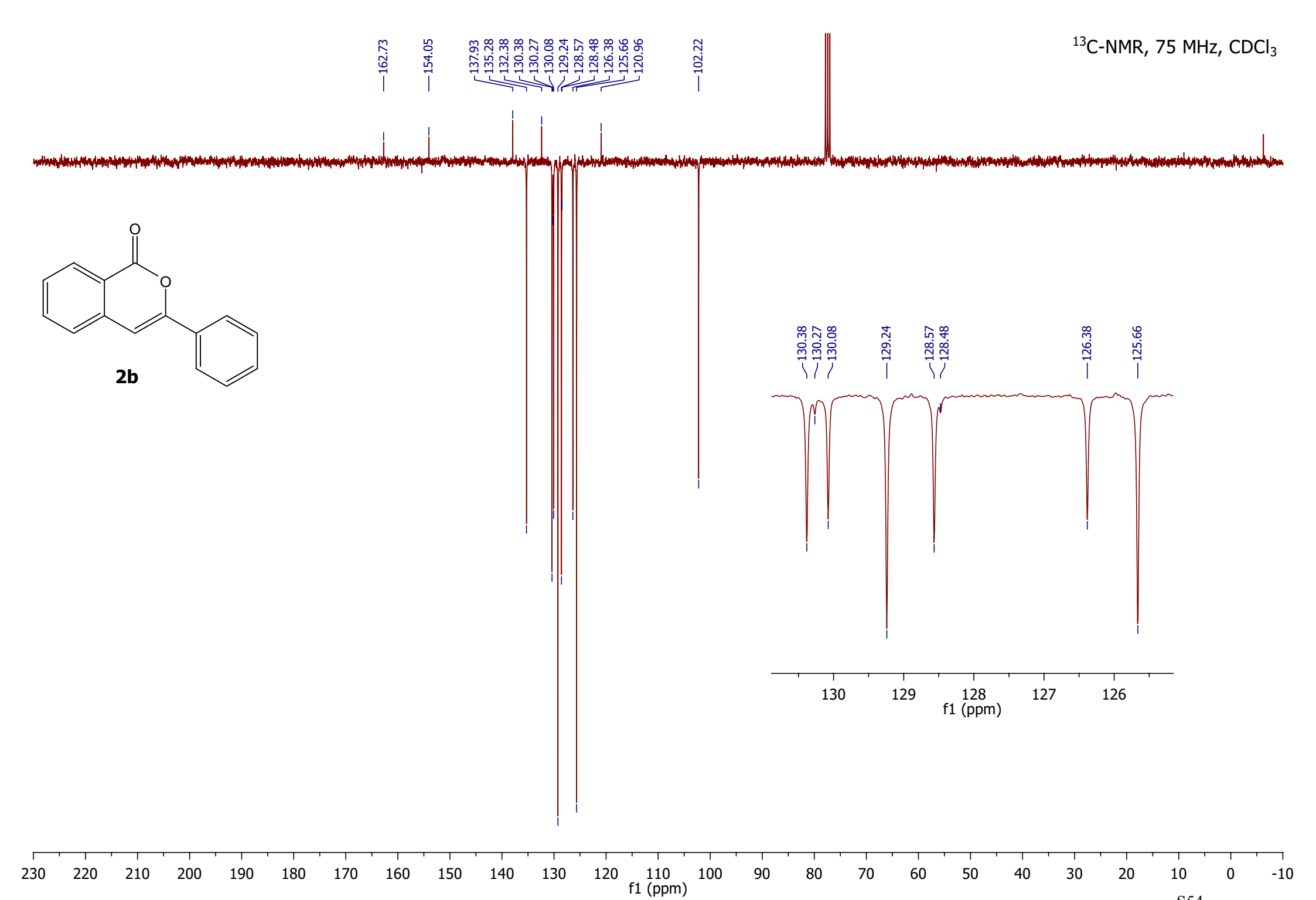

1w
O
O
OH
^{1}H-NMR, 300 MHz, $CDCl_3$
7.94 7.94 7.93 7.91 7.91 7.53 7.53 7.51 7.51 7.50 7.48 7.47 7.45 7.45 7.43 7.42 7.38 7.38 7.36 7.35 7.33 7.33
3.92
2.06
1.64
1.00
2.13
0.96
f1 (ppm)
0.94
0.99
0.98
0.90
2.89
1.47
5.79
f1 (ppm)

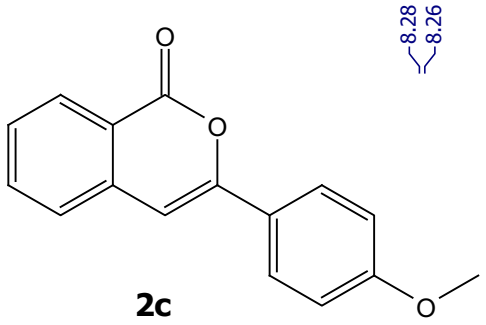

2a
^{1}H-NMR, 300 MHz, $CDCl_3$
8.32
8.31
8.29
7.79
7.77
7.71
7.49
7.49
7.48
7.28
7.26
6.91
2.41
0.93
1.99
1.00
1.99
2.31
0.98
3.08
f1 (ppm)

^{13}C-NMR, 75 MHz, $CDCl_3$



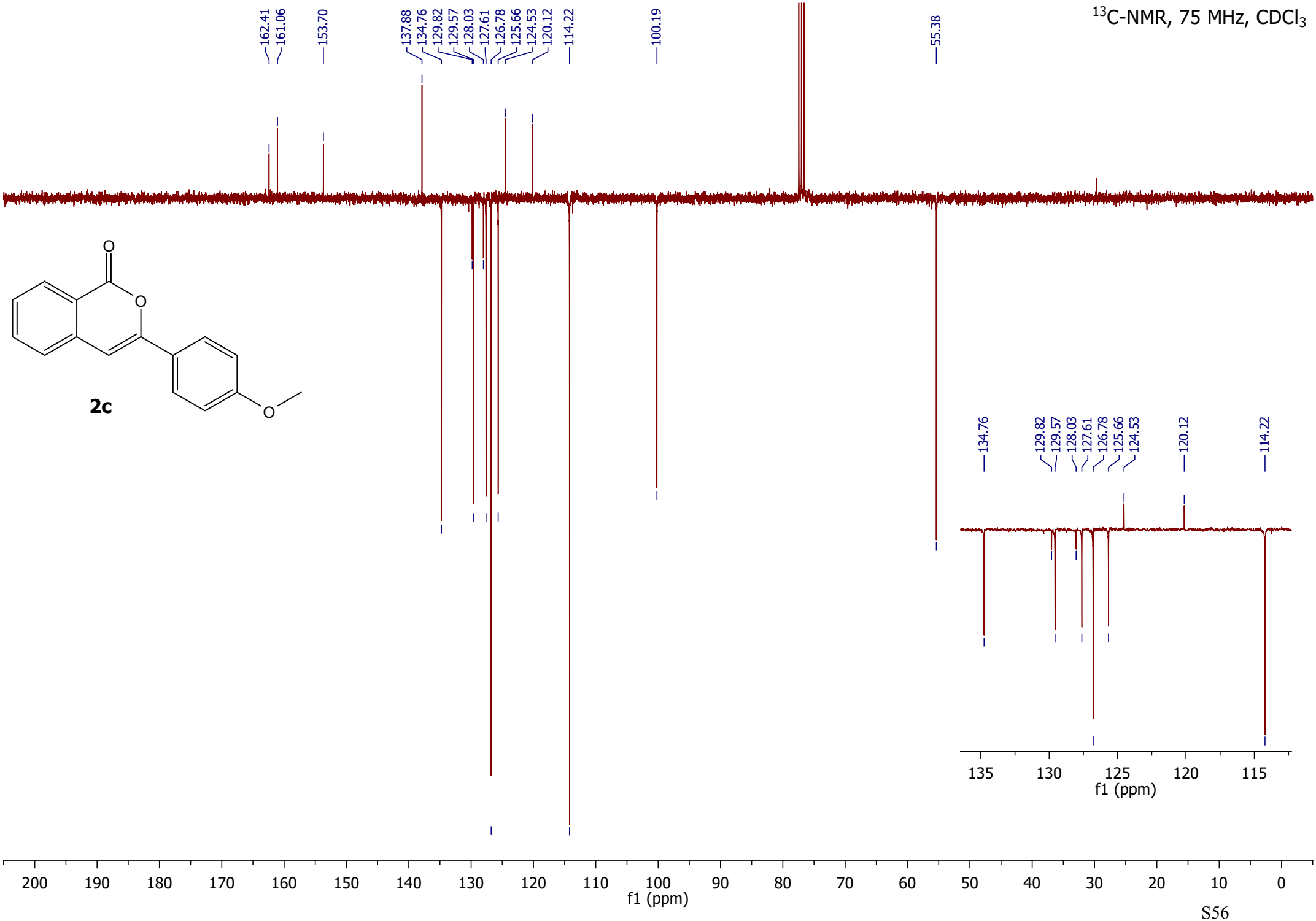

^{1}H-NMR, 300 MHz, $CDCl_3$
2b
8.34
8.32
7.92
7.91
7.89
7.89
7.52
7.51
7.49
7.46
6.97
0.79
1.90
0.97
4.63
1.00
f1 (ppm)

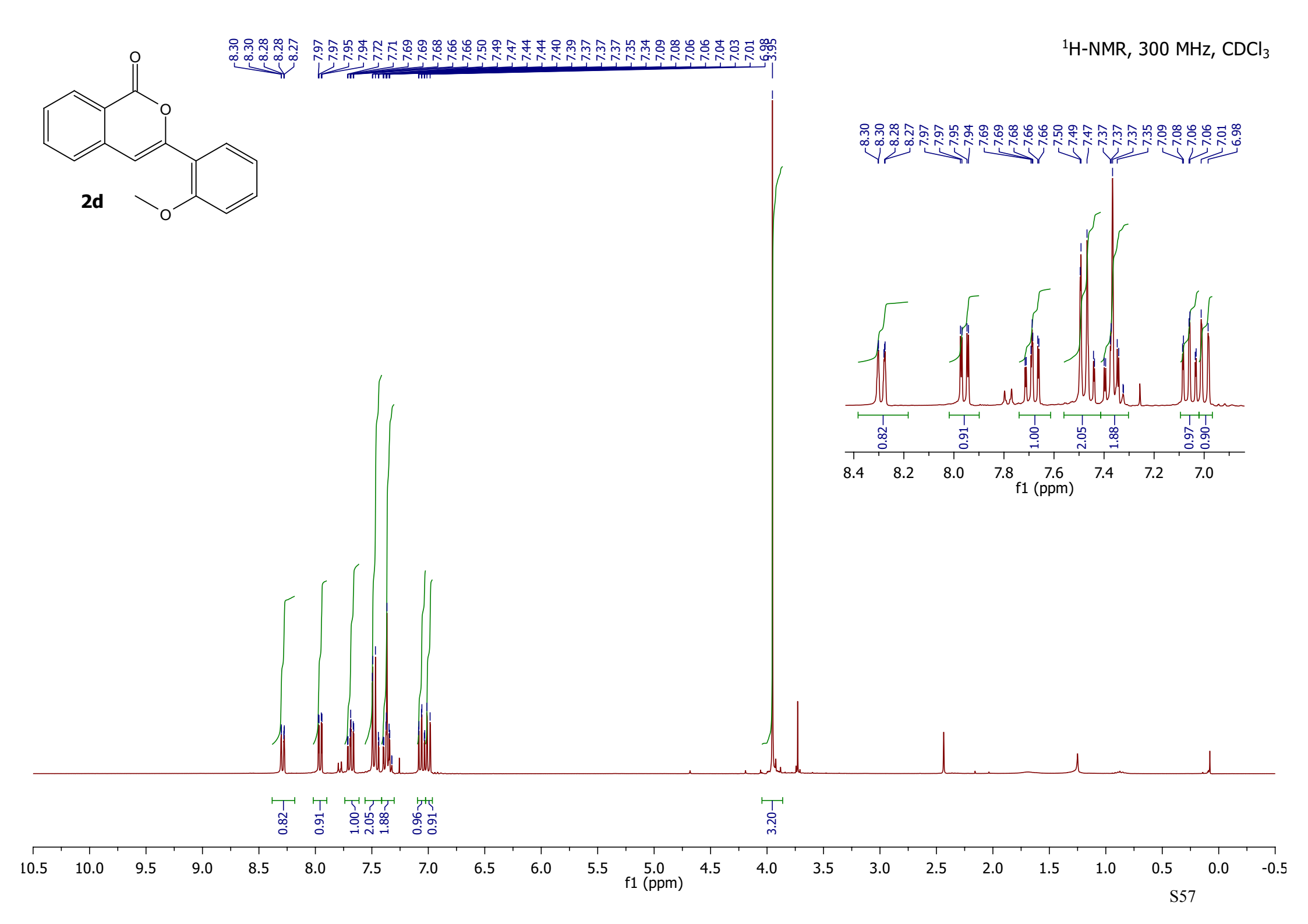

^{13}C-NMR, 75 MHz, $CDCl_3$
162.73
154.05
137.93
135.28
132.38
130.38
130.27
130.08
129.24
128.57
128.48
126.38
125.66
120.96
102.22
O
O
2b
130.38
130.27
130.08
129.24
128.57
128.48
126.38
125.66
130
129
128
127
126
f1 (ppm)
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

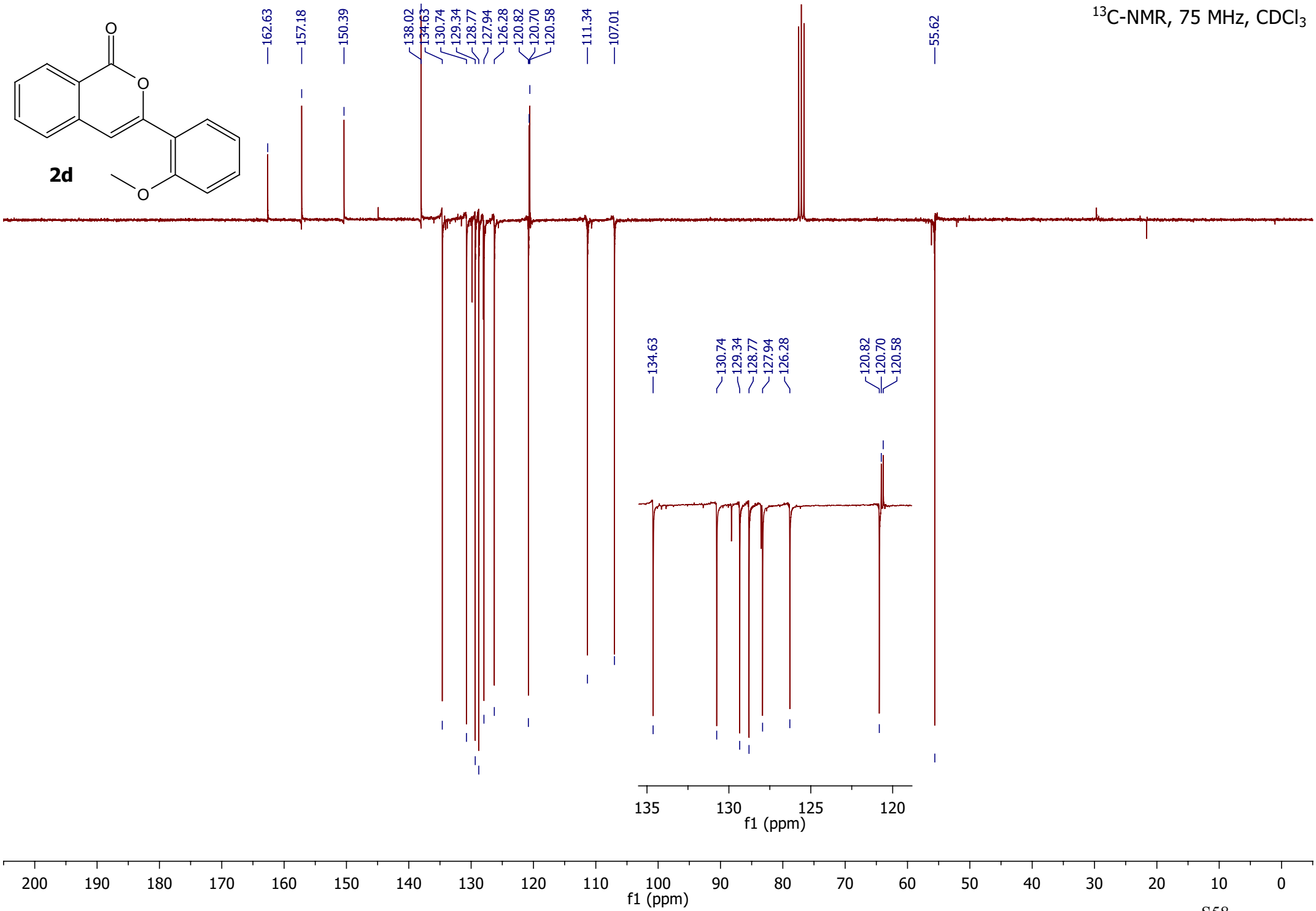


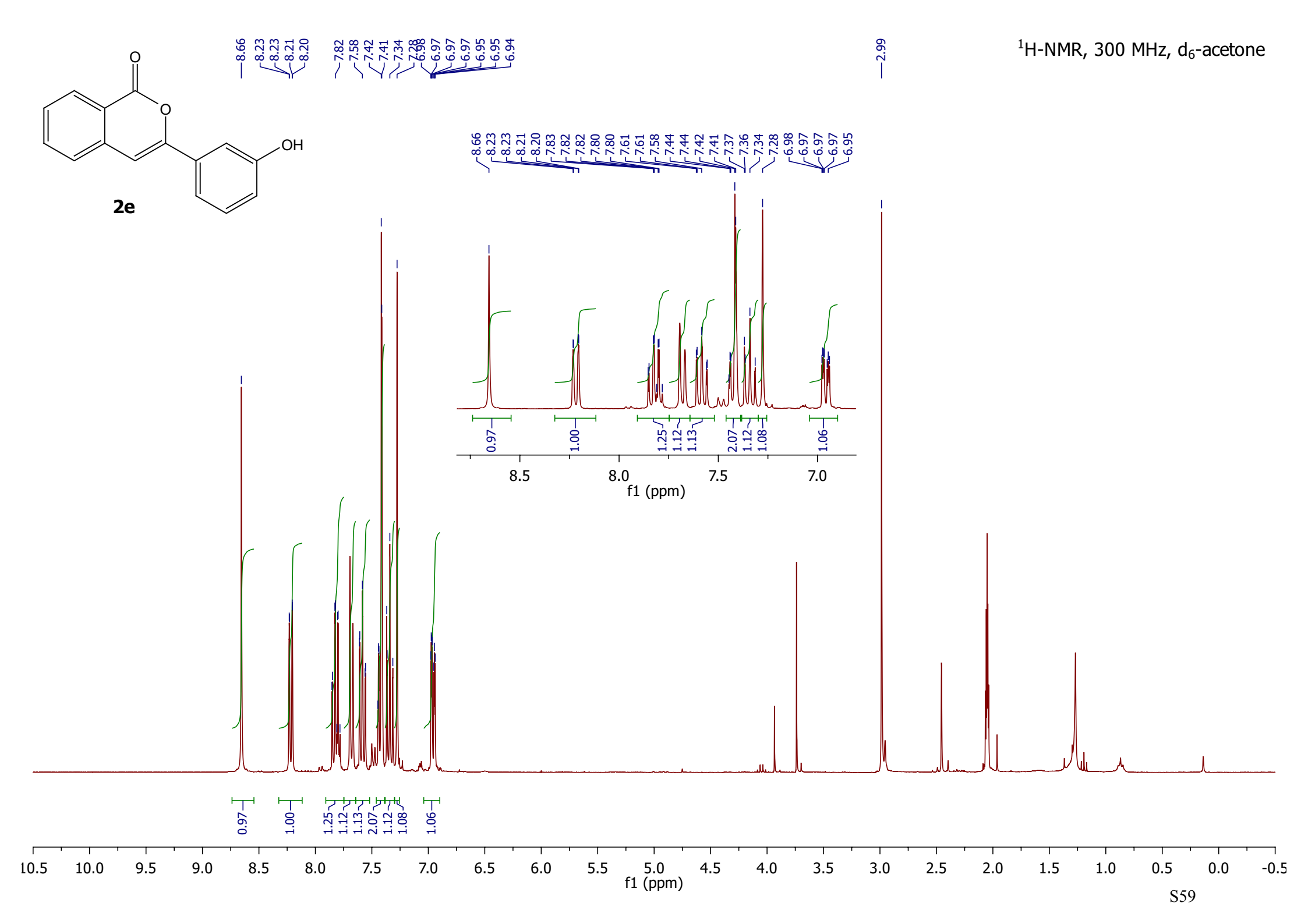
2c

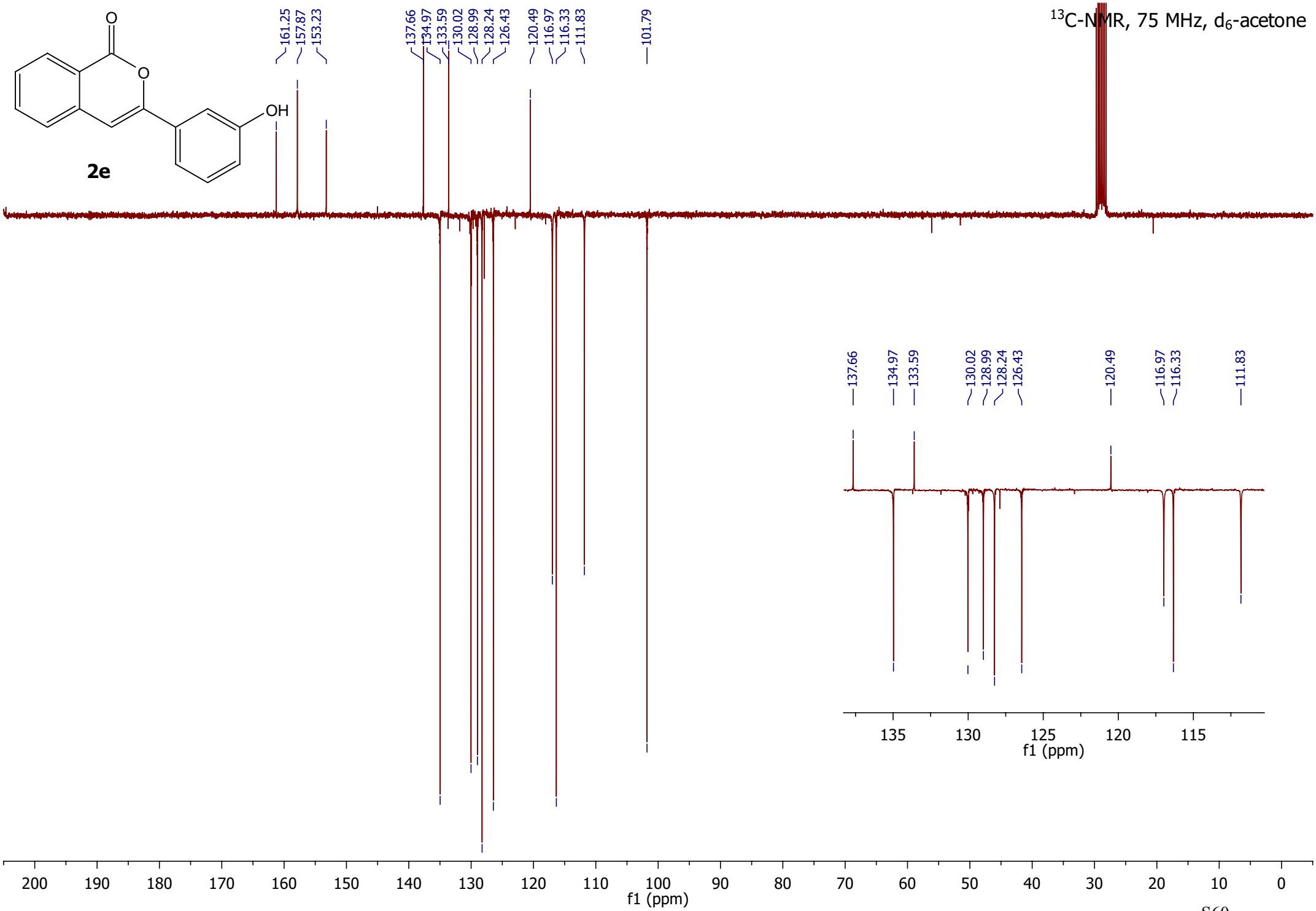
^{1}H-NMR, 300 MHz, $CDCl_3$

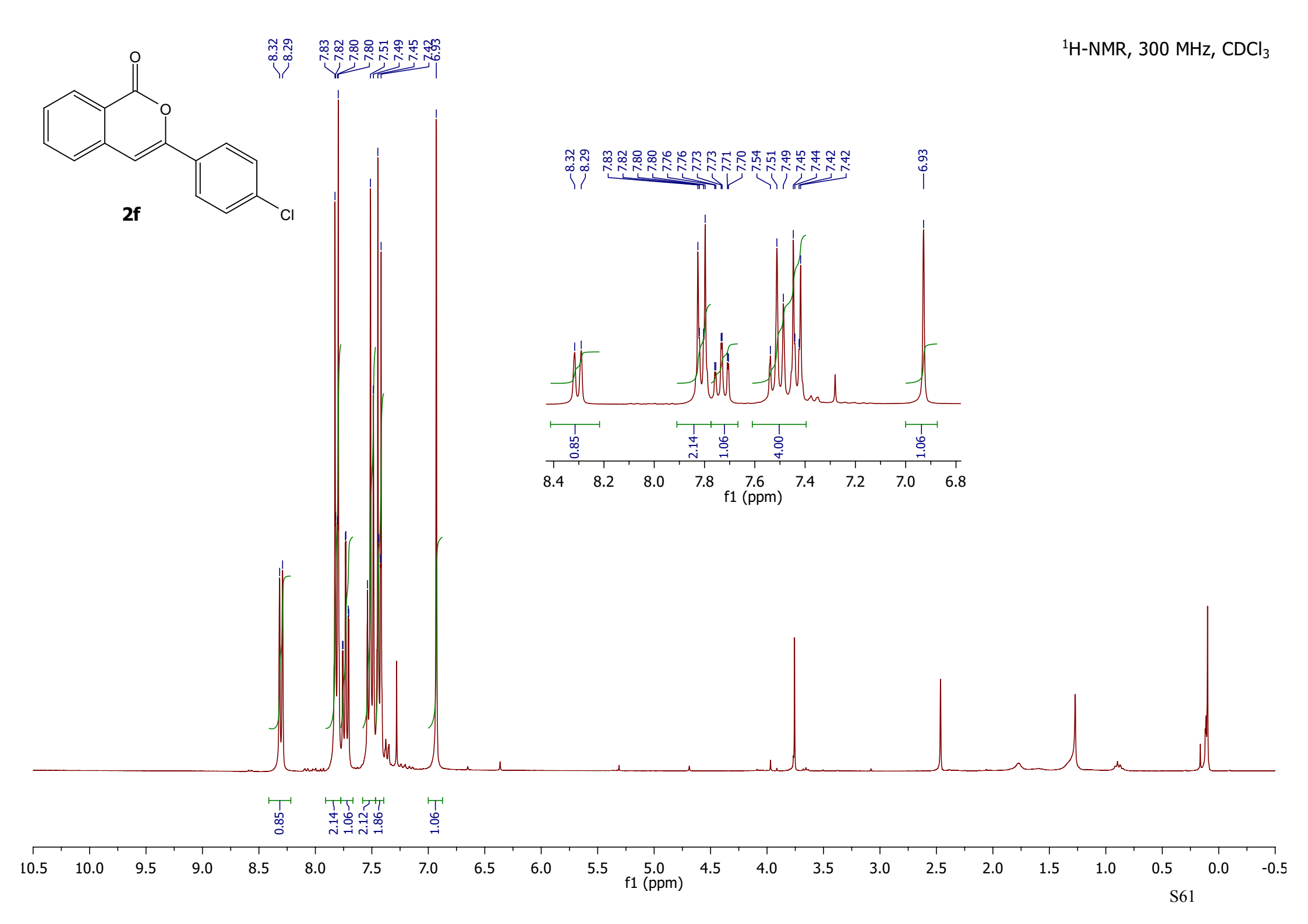

^{13}C-NMR, 75 MHz, $CDCl_3$
162.41
161.06
153.70
137.88
134.76
129.82
129.57
128.03
127.61
126.78
125.66
124.53
120.12
114.22
100.19
55.38
O
O
O
2c
134.76
129.82
129.57
128.03
127.61
126.78
125.66
124.53
120.12
114.22
135
130
125
120
115
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

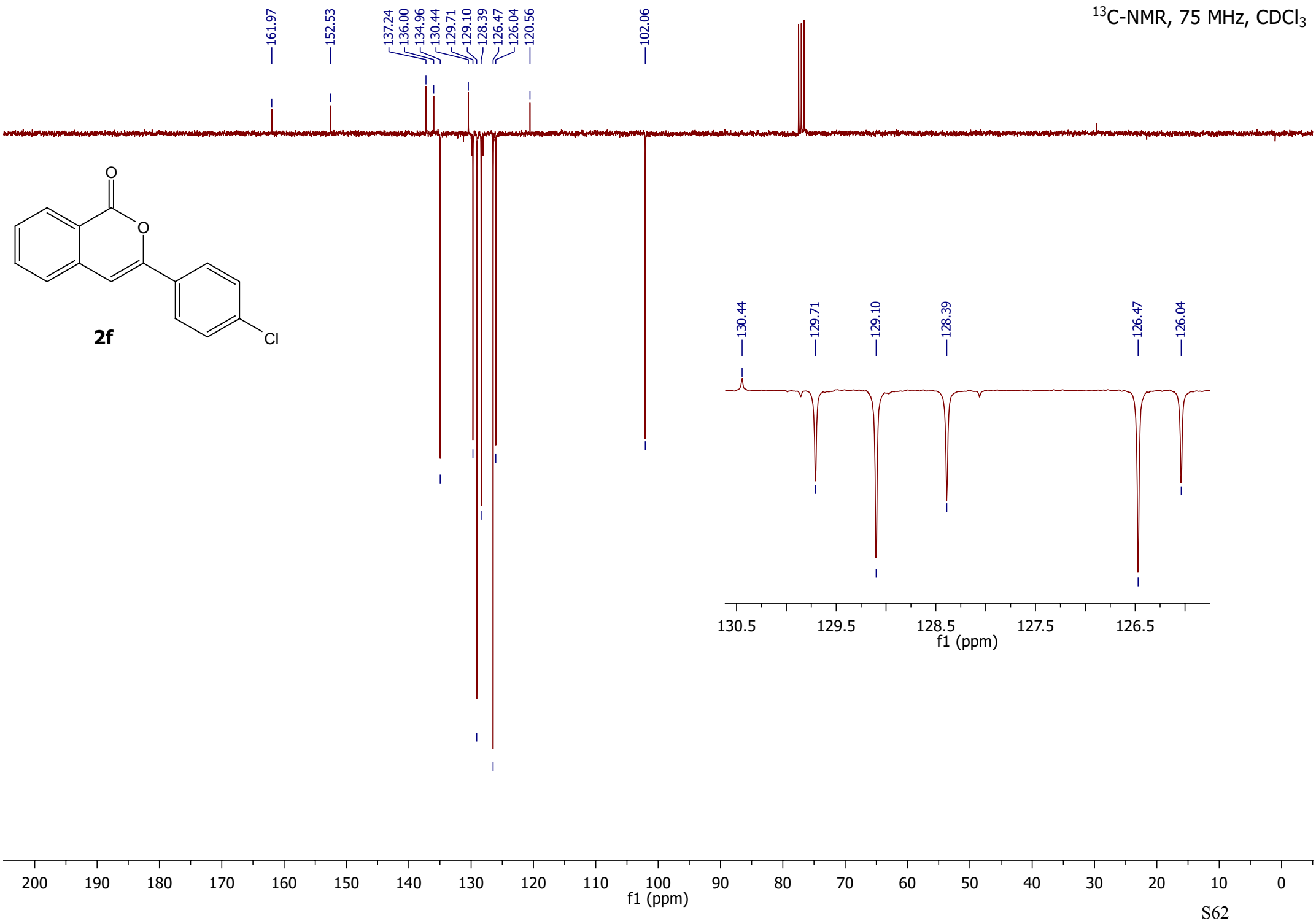

^{1}H-NMR, 300 MHz, $CDCl_3$
2d
f1 (ppm)

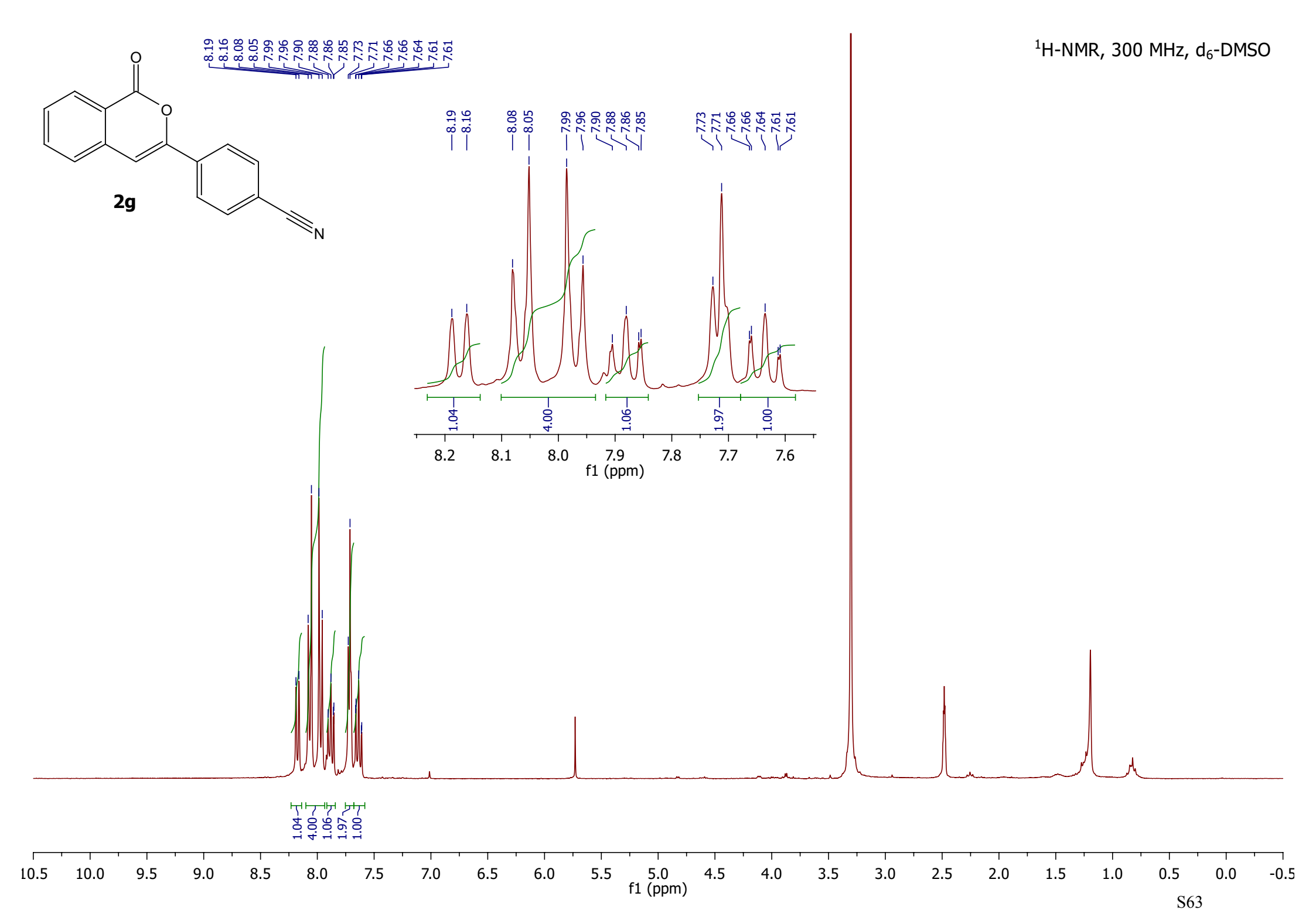

^{13}C-NMR, 75 MHz, $CDCl_3$
2d
162.63
157.18
150.39
138.02
134.63
130.74
129.34
128.77
127.94
126.28
120.82
120.70
120.58
111.34
107.01
55.62
f1 (ppm)

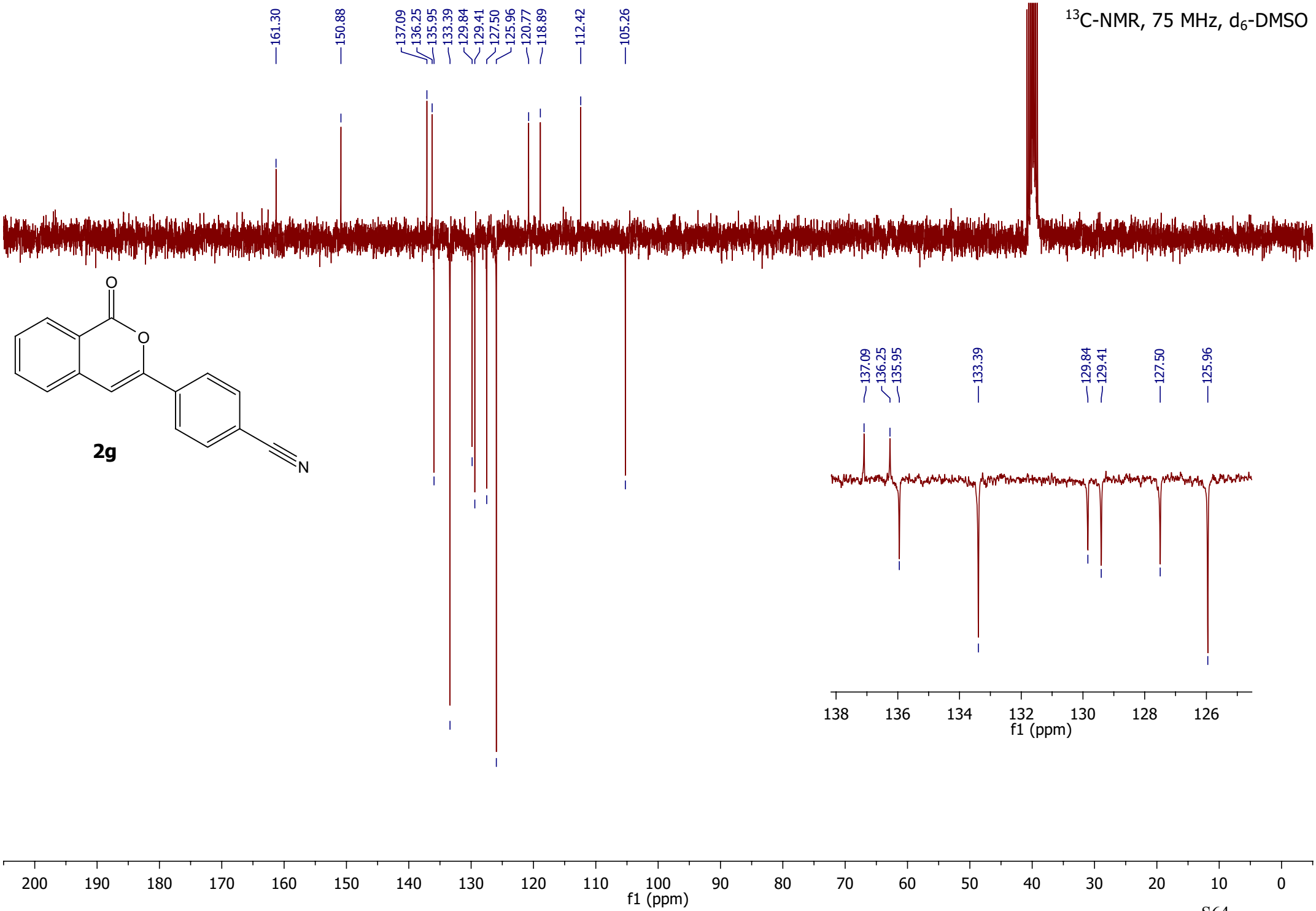

2e
OH
O
O
^{1}H-NMR, 300 MHz, d_6-acetone
8.66
8.23
8.23
8.21
8.20
7.82
7.58
7.42
7.41
7.34
7.28
6.98
6.97
6.97
6.97
6.95
6.95
6.94
2.99
0.97
1.00
1.25
1.12
1.13
2.07
1.12
1.08
1.06
f1 (ppm)

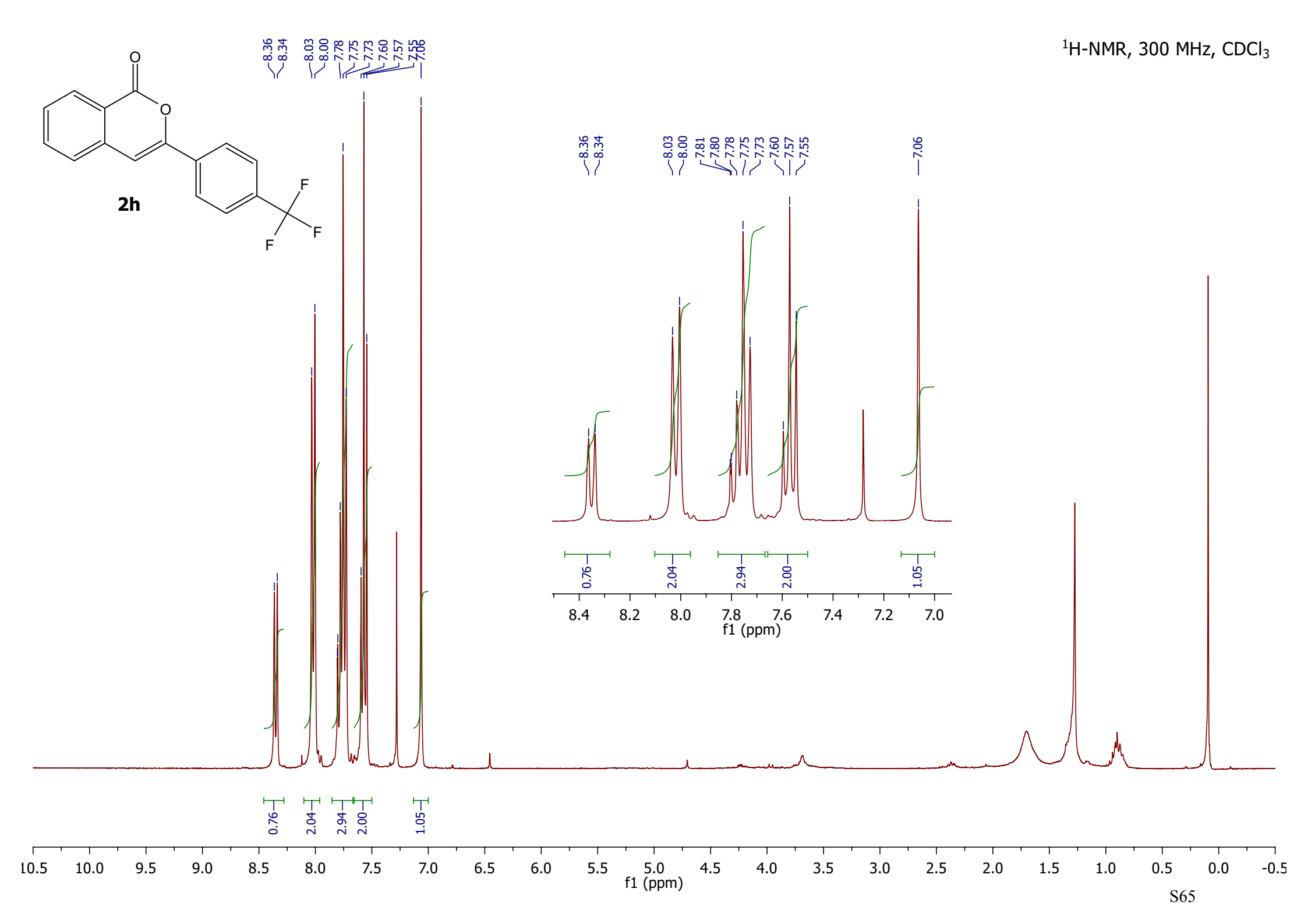

^{13}C-NMR, 75 MHz, d_6-acetone
2e
OH
O
O
161.25
157.87
153.23
137.66
134.97
133.59
130.02
128.99
128.24
126.43
120.49
116.97
116.33
111.83
101.79
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)
135
130
125
120
115
f1 (ppm)

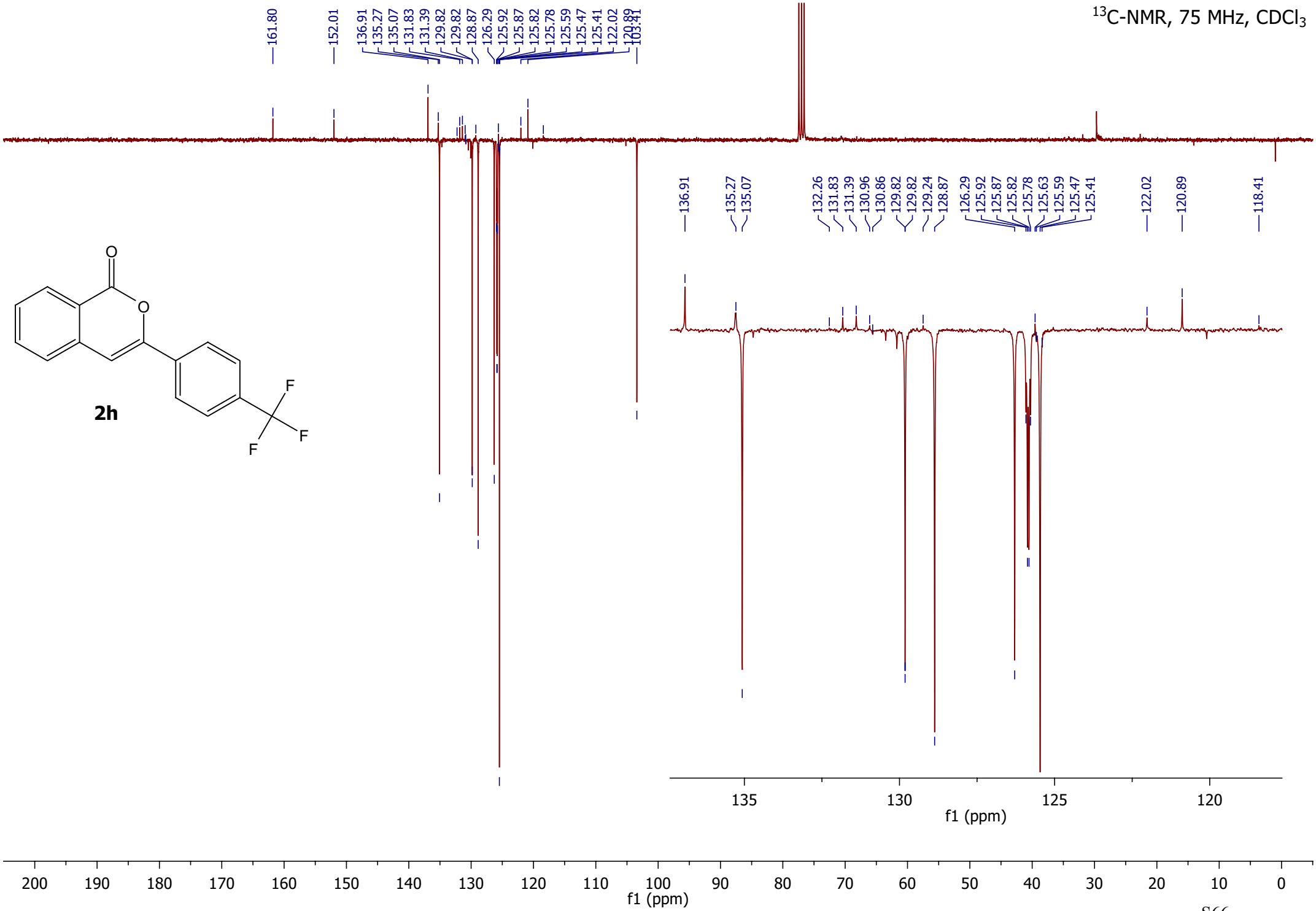

^{1}H-NMR, 300 MHz, $CDCl_3$
2f
Cl
8.32
8.29
7.83
7.82
7.80
7.80
7.51
7.49
7.45
7.42
6.93
0.85
2.14
1.06
2.12
1.86
1.06
f1 (ppm)
7.76
7.76
7.73
7.73
7.71
7.70
7.54
0.85
2.14
1.06
4.00
1.06

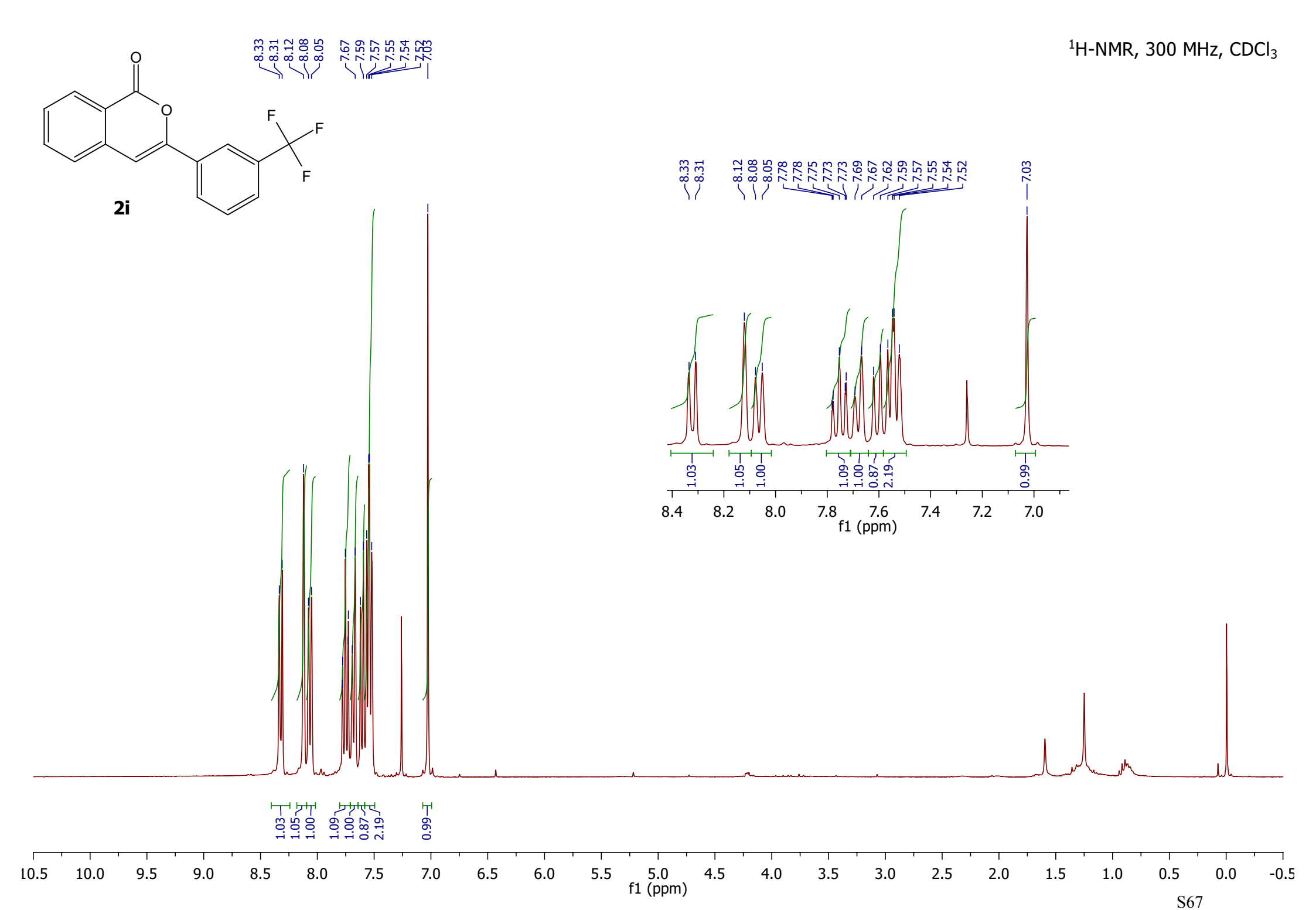

^{13}C-NMR, 75 MHz, $CDCl_3$
161.97
152.53
137.24
136.00
134.96
130.44
129.71
129.10
128.39
126.47
126.04
120.56
102.06
O
O
Cl
2f
130.44
129.71
129.10
128.39
126.47
126.04
130.5
129.5
128.5
127.5
126.5
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

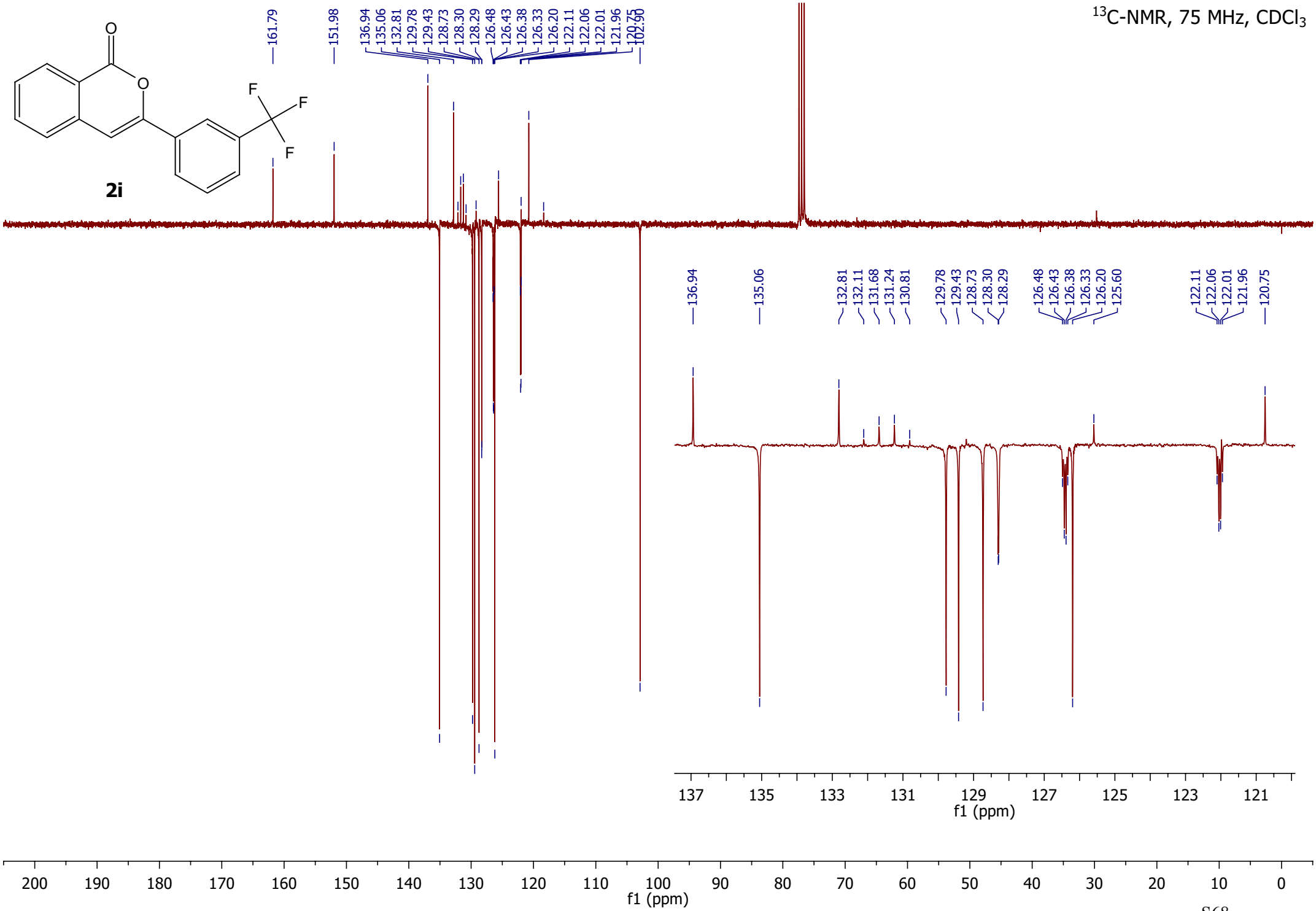

^{1}H-NMR, 300 MHz, d_6-DMSO
2g
8.19
8.16
8.08
8.05
7.99
7.96
7.90
7.88
7.86
7.85
7.73
7.71
7.66
7.66
7.64
7.61
7.61
1.04
4.00
1.06
1.97
1.00
f1 (ppm)

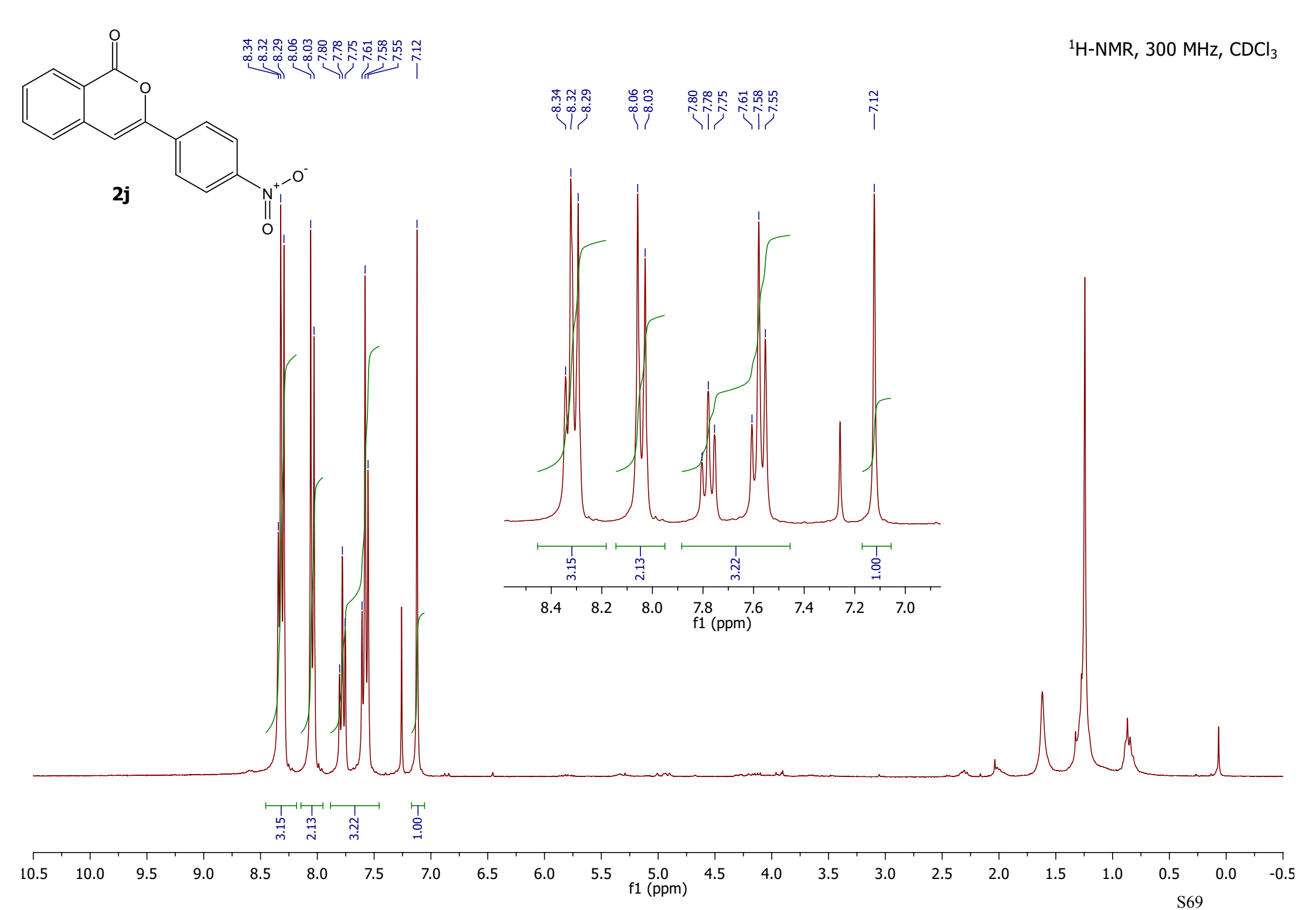

^{13}C-NMR, 75 MHz, d_6-DMSO
161.30
150.88
137.09
136.25
135.95
133.39
129.84
129.41
127.50
125.96
120.77
118.89
112.42
105.26
O
O
N
2g
f1 (ppm)
f1 (ppm)


^{1}H-NMR, 300 MHz, $CDCl_3$
2h
O
O
F
F
F
8.36
8.34
8.03
8.00
7.78
7.75
7.73
7.60
7.57
7.55
7.06
0.76
2.04
2.94
2.00
1.05
f1 (ppm)

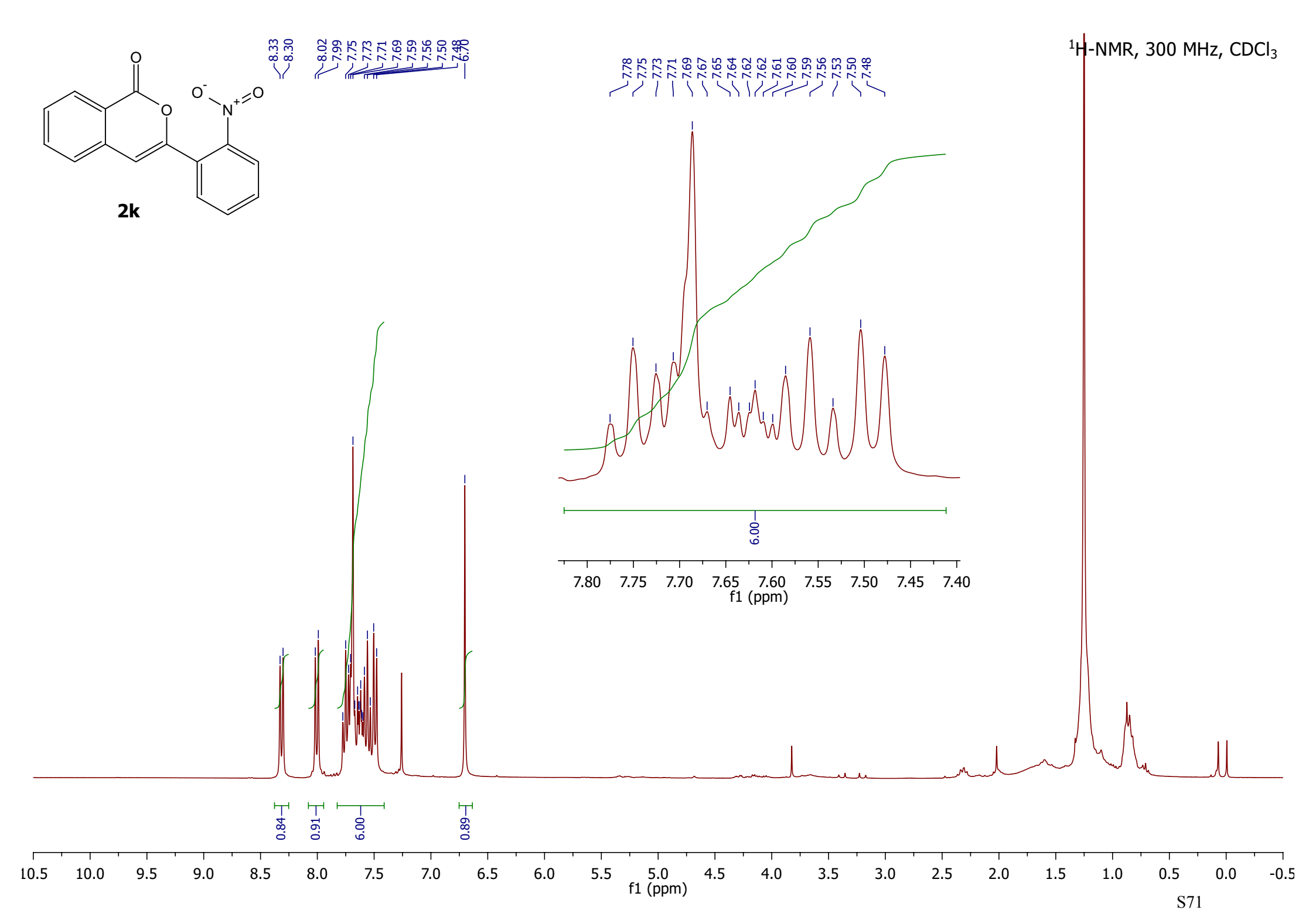

^{13}C-NMR, 75 MHz, $CDCl_3$
161.80
152.01
136.91
135.27
135.07
131.83
131.39
129.82
129.82
128.87
126.29
125.92
125.87
125.82
125.78
125.59
125.47
125.41
122.02
120.89
118.41
O
O
F
F
F
2h
f1 (ppm)
f1 (ppm)

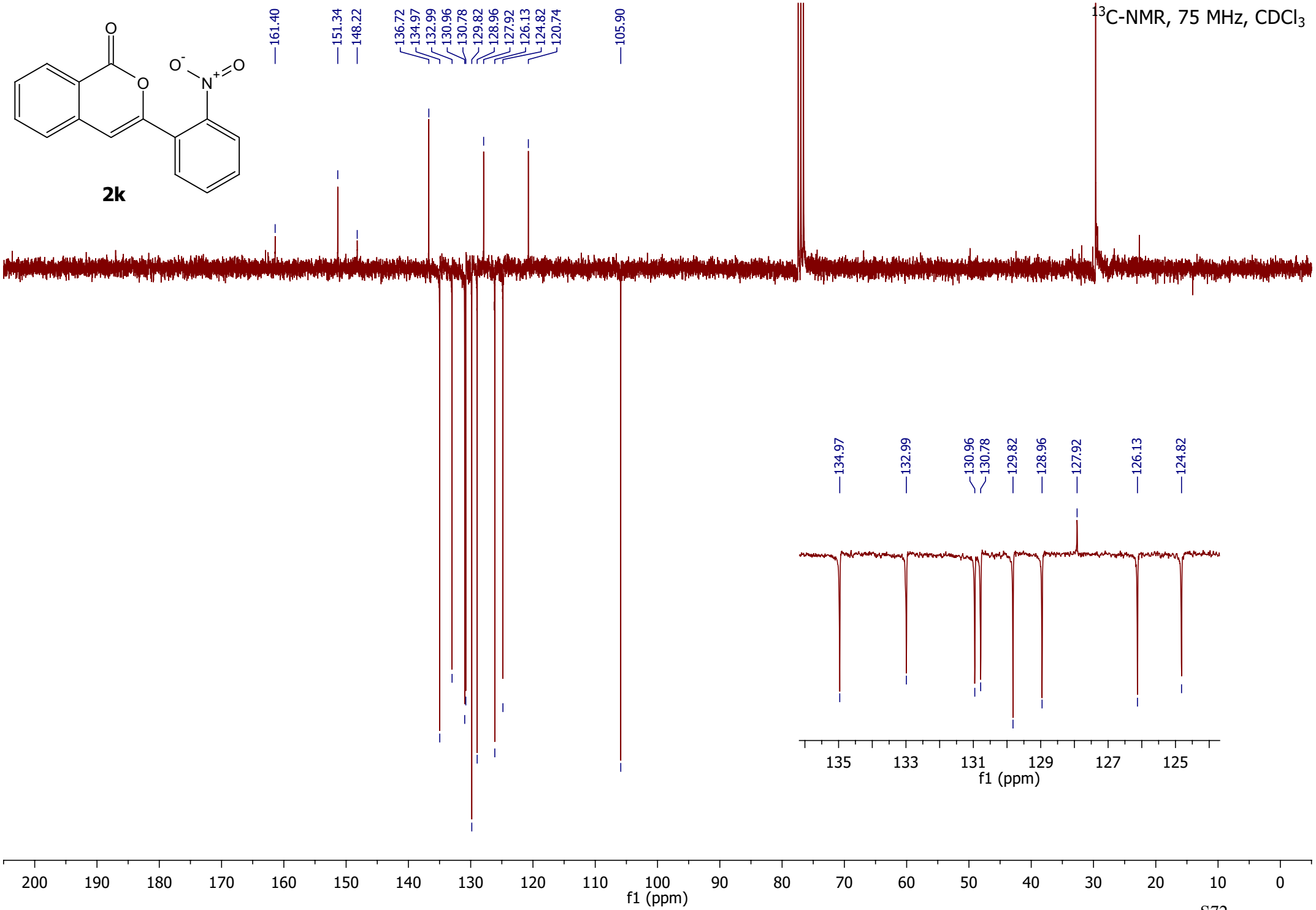

^{1}H-NMR, 300 MHz, $CDCl_3$
2i
f1 (ppm)

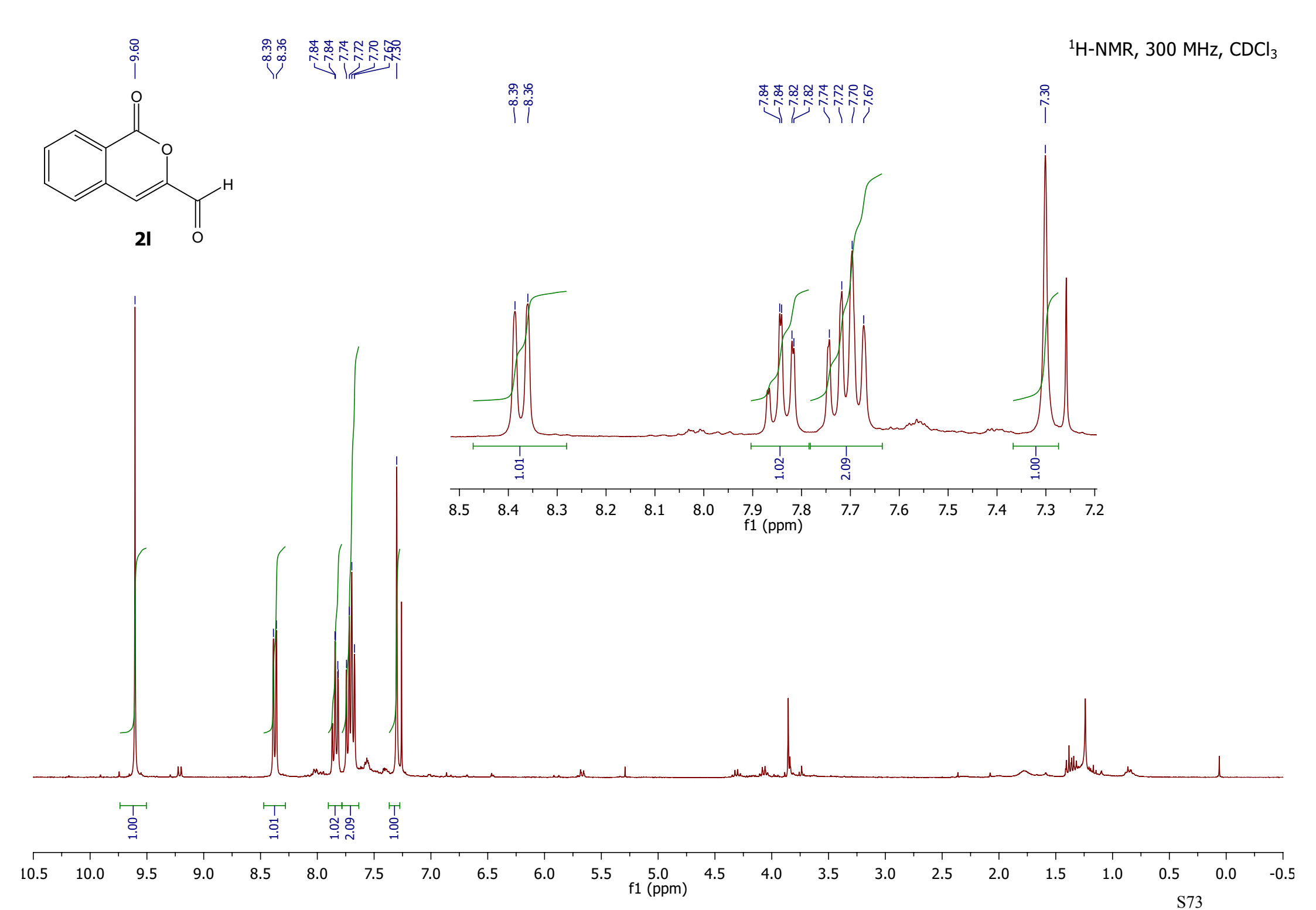

^{13}C-NMR, 75 MHz, $CDCl_3$
2i
O
O
F
F
F
161.79
151.98
136.94
135.06
132.81
129.78
129.43
128.73
128.30
128.29
126.48
126.43
126.38
126.33
126.20
122.11
122.06
122.01
121.96
120.75
102.90
136.94
135.06
132.81
132.11
131.68
131.24
130.81
129.78
129.43
128.73
128.30
128.29
126.48
126.43
126.38
126.33
126.20
125.60
122.11
122.06
122.01
121.96
120.75
137
135
133
131
129
127
125
123
121
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

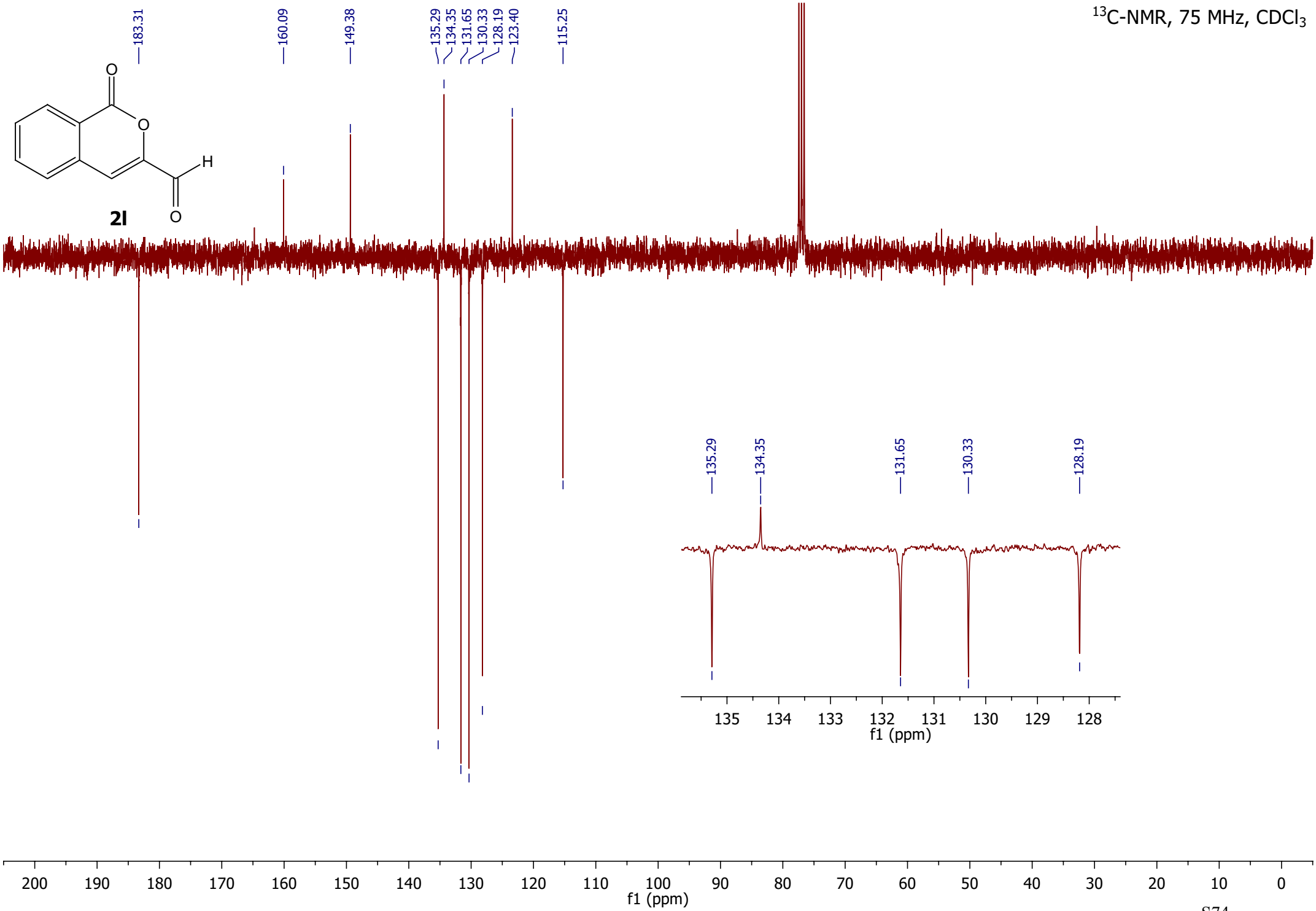

2j
^{1}H-NMR, 300 MHz, $CDCl_3$
8.34
8.32
8.29
8.06
8.03
7.80
7.78
7.75
7.61
7.58
7.55
7.12
3.15
2.13
3.22
1.00
f1 (ppm)

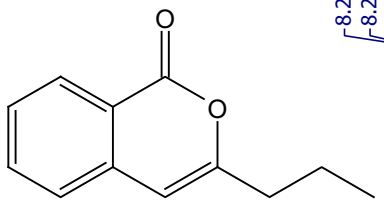

^{13}C-NMR, 75 MHz, $CDCl_3$
161.42
151.02
148.29
137.70
136.49
135.21
129.87
129.37
126.55
125.85
124.15
120.99
104.83
2j
f1 (ppm)


2k
^{1}H-NMR, 300 MHz, $CDCl_3$
8.33
8.30
8.02
7.99
7.75
7.73
7.71
7.69
7.59
7.56
7.50
7.48
6.70
7.78
7.75
7.73
7.71
7.69
7.67
7.65
7.64
7.62
7.62
7.61
7.60
7.59
7.56
7.53
7.50
7.48
6.00
7.80 7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40
f1 (ppm)
0.84
0.91
6.00
0.89
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


^{13}C-NMR, 75 MHz, $CDCl_3$
161.40
151.34
148.22
136.72
134.97
132.99
130.96
130.78
129.82
128.96
127.92
126.13
124.82
120.74
105.90
2k
134.97
132.99
130.96
130.78
129.82
128.96
127.92
126.13
124.82
135
133
131
129
127
125
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

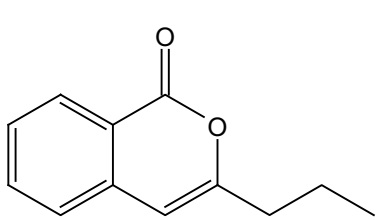

^{1}H-NMR, 300 MHz, $CDCl_3$
9.60
8.39
8.36
7.84
7.84
7.74
7.72
7.70
7.67
7.30
O
O
H
O
2l
1.00
1.01
1.02
2.09
1.00
f1 (ppm)
f1 (ppm)


^{13}C-NMR, 75 MHz, $CDCl_3$
183.31
160.09
149.38
135.29
134.35
131.65
130.33
128.19
123.40
115.25
O
O
H
O
2l
135.29
134.35
131.65
130.33
128.19
135
134
133
132
131
130
129
128
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



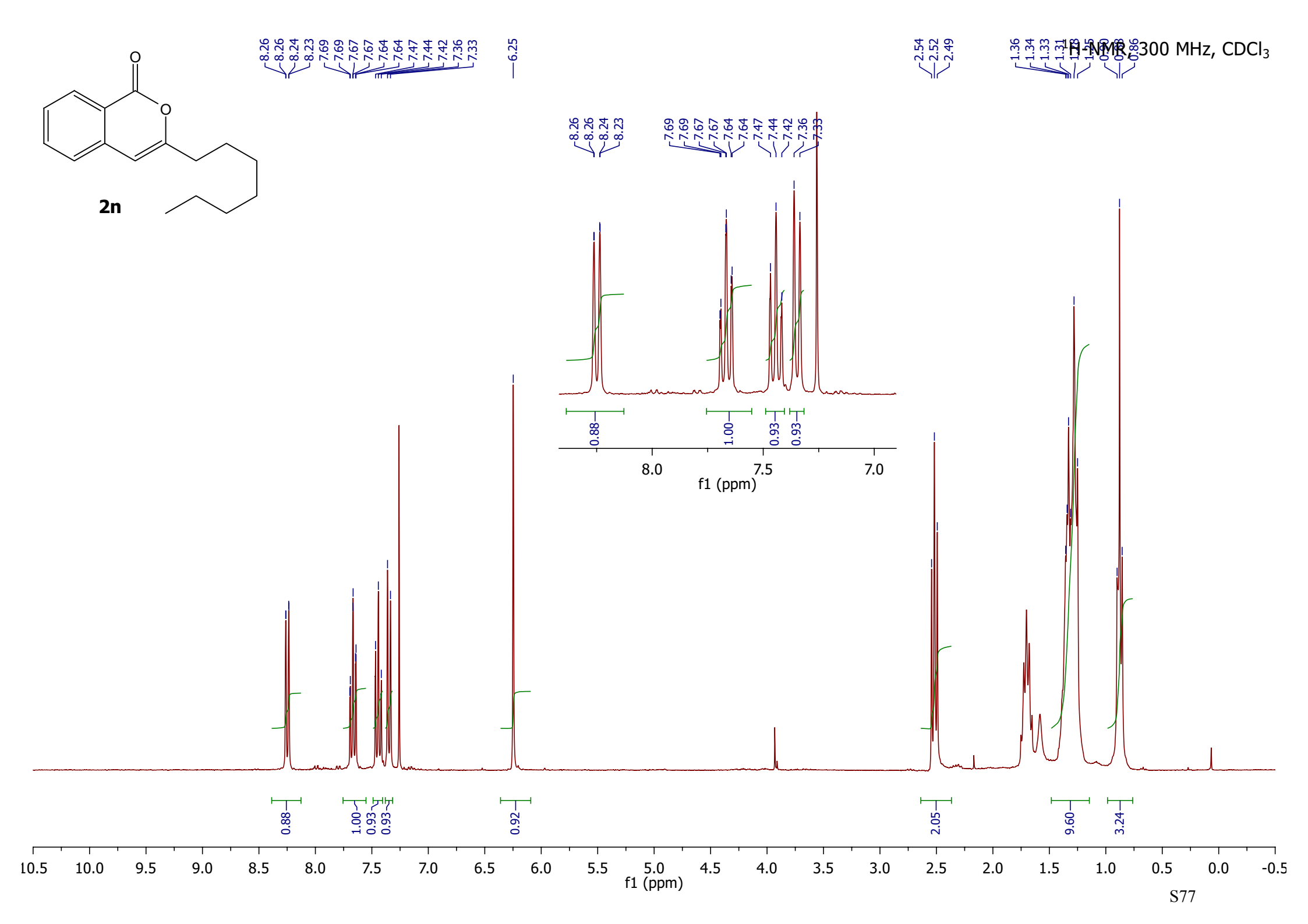
2m

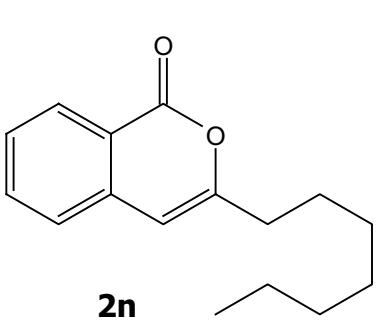
^{1}H-NMR, 300 MHz, $CDCl_3$



2m

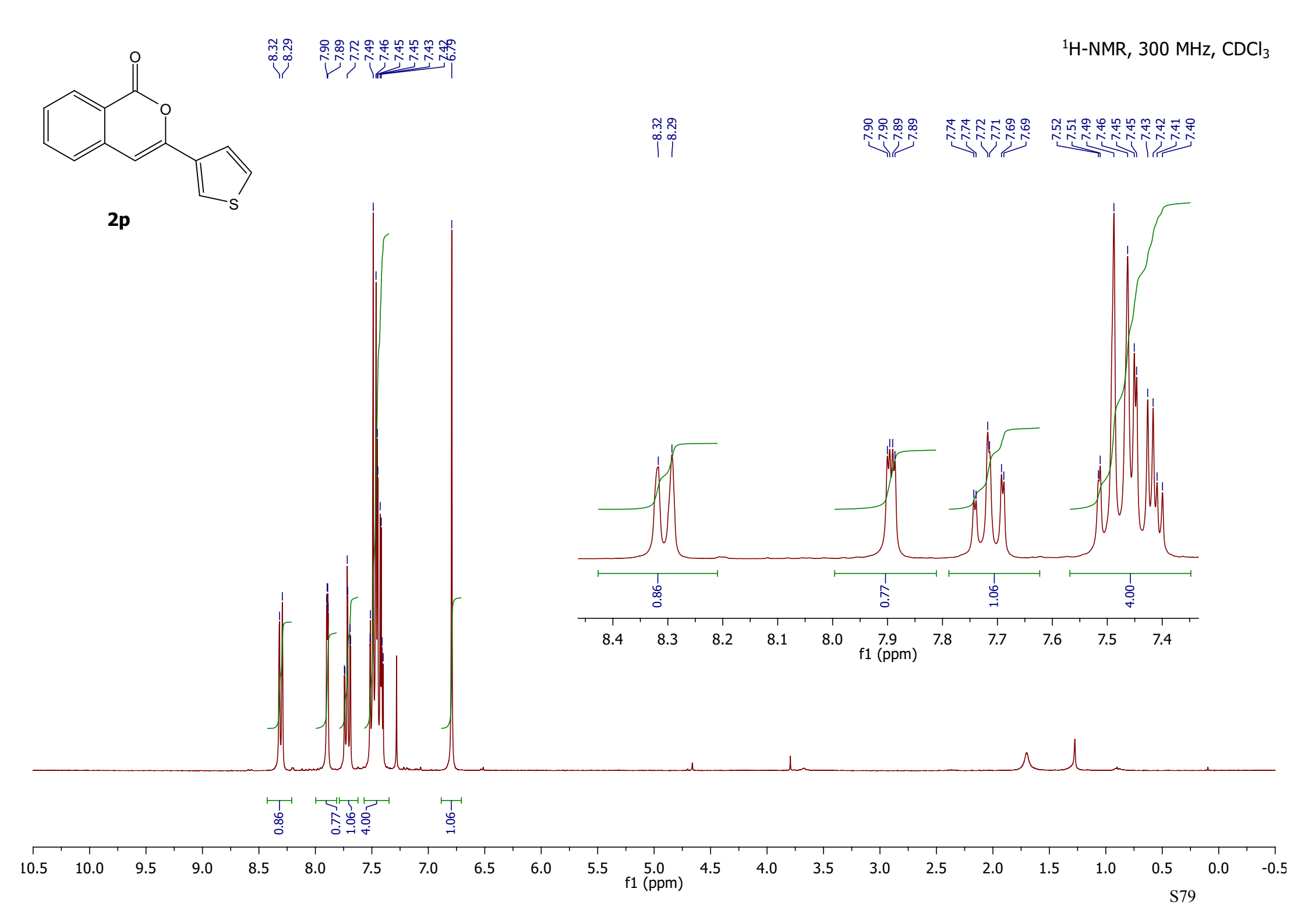
^{13}C-NMR, 75 MHz, $CDCl_3$

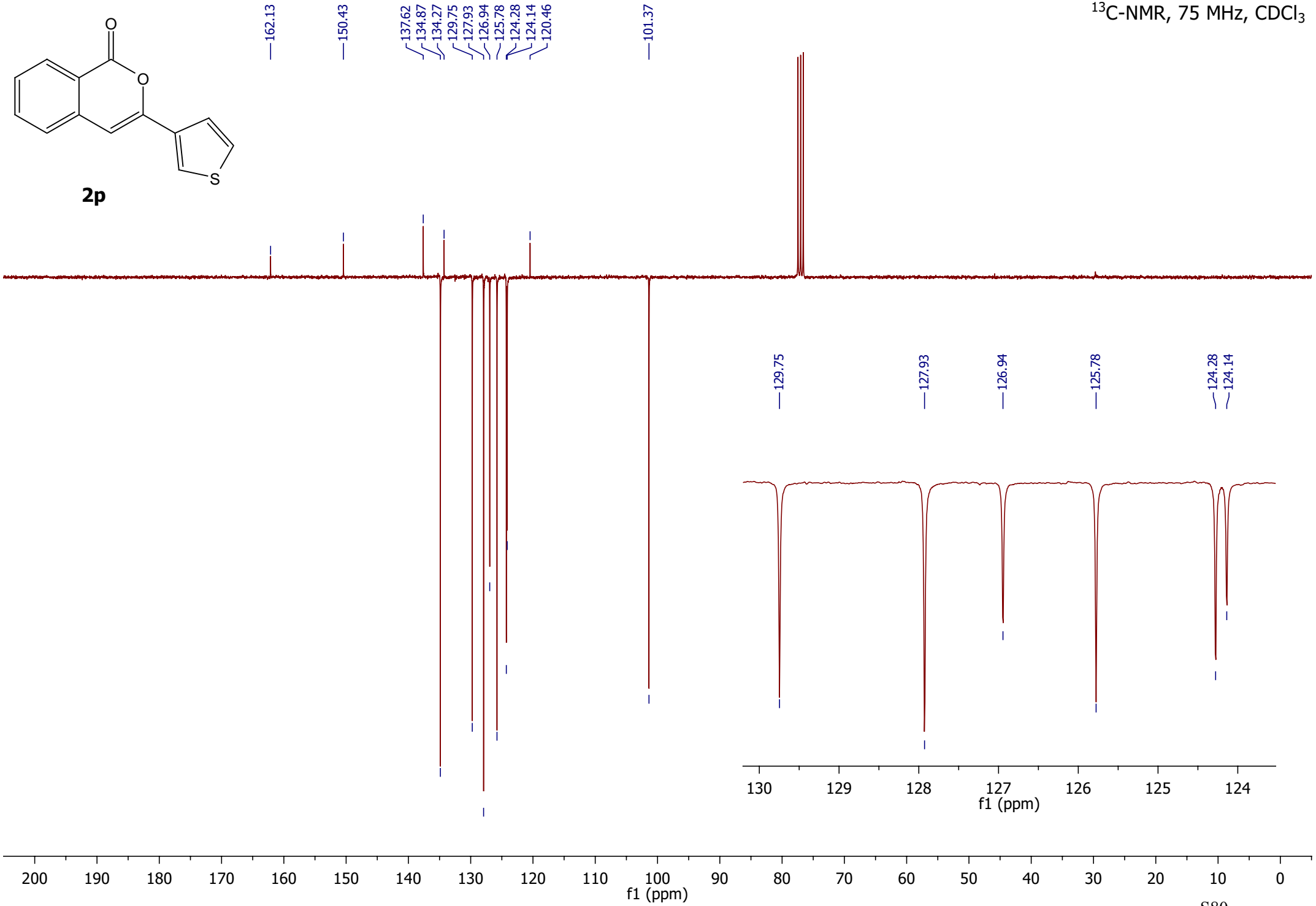

2n
1H-NMR, 300 MHz, CDCl3
f1 (ppm)

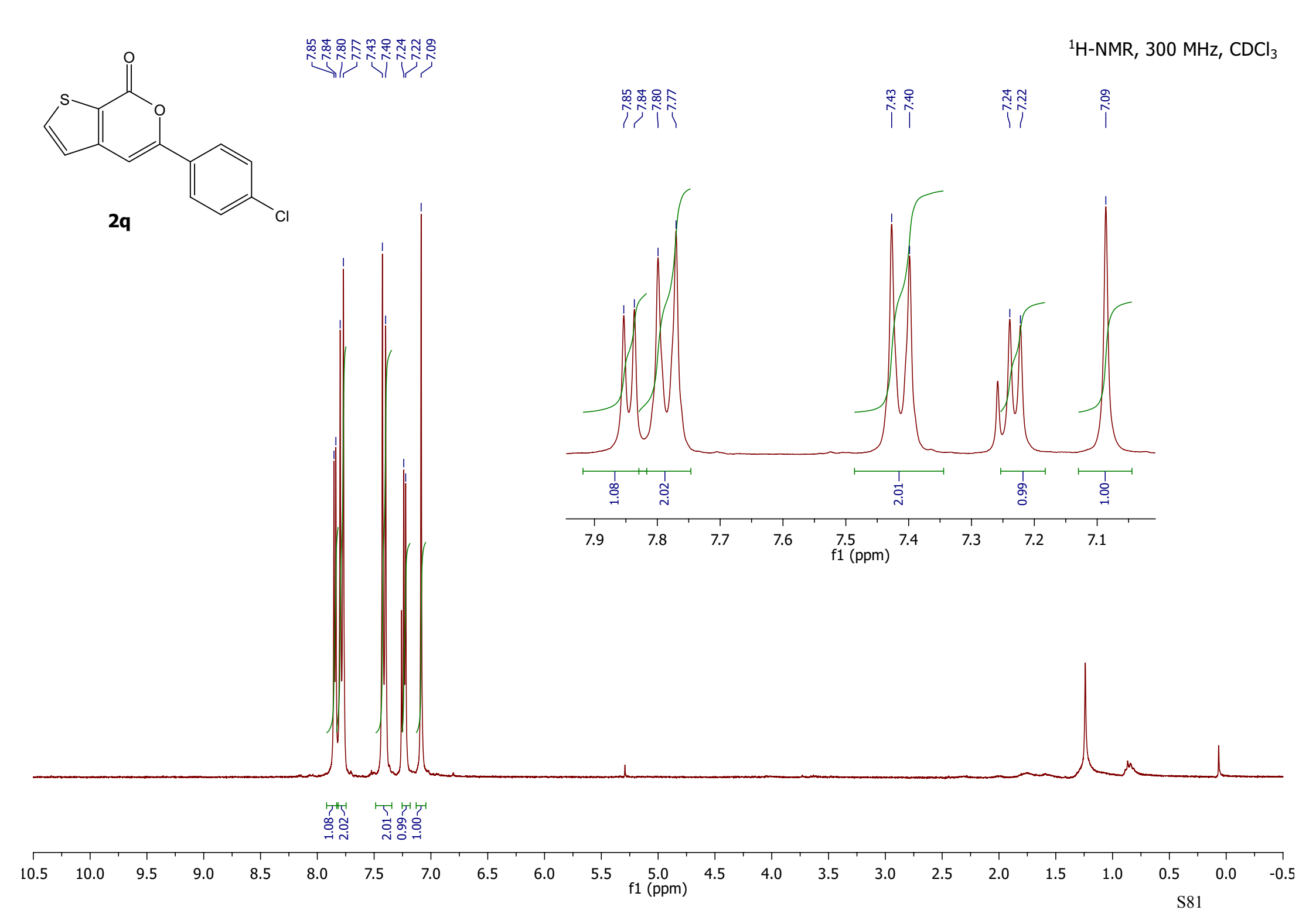


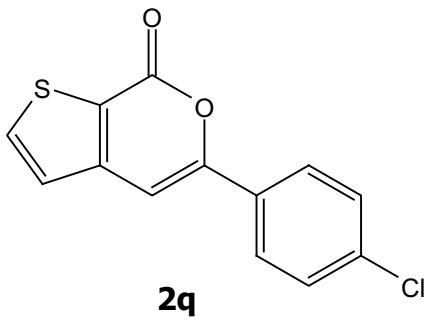
2n

163.08
158.35
137.63
134.64
129.49
127.48
124.96
120.12
102.80
33.52
31.67
29.67
28.96
26.84
22.58
14.02
^{13}C-NMR, 75 MHz, $CDCl_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H-NMR, 300 MHz, $CDCl_3$
2p
f1 (ppm)


^{13}C-NMR, 75 MHz, $CDCl_3$
O
O
S
2p
162.13
150.43
137.62
134.87
134.27
129.75
127.93
126.94
125.78
124.28
124.14
120.46
101.37
129.75
127.93
126.94
125.78
124.28
124.14
130
129
128
127
126
125
124
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H-NMR, 300 MHz, $CDCl_3$
2q
S
O
O
Cl
7.85
7.84
7.80
7.77
7.43
7.40
7.24
7.22
7.09
1.08
2.02
2.01
0.99
1.00
f1 (ppm)



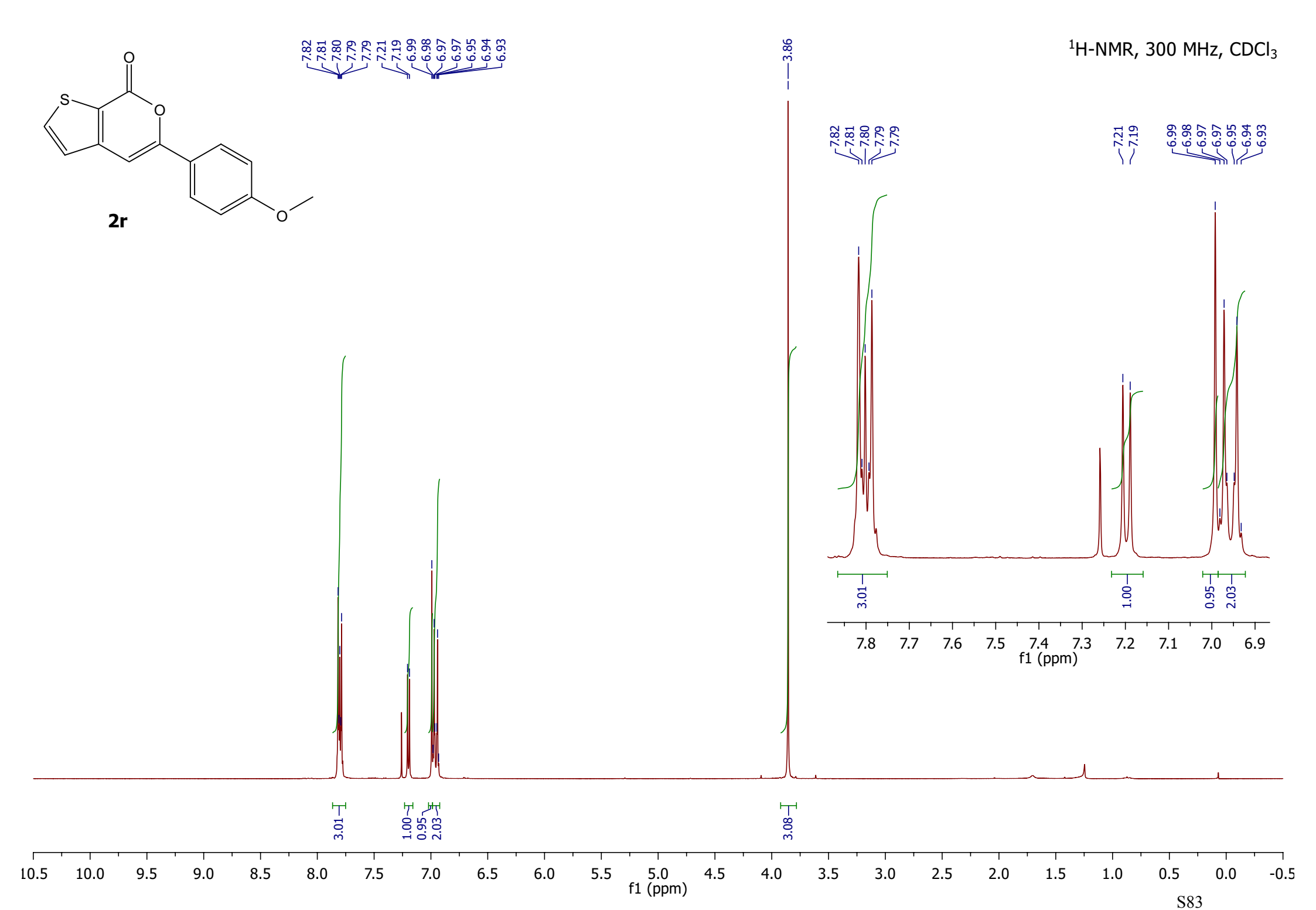
2q

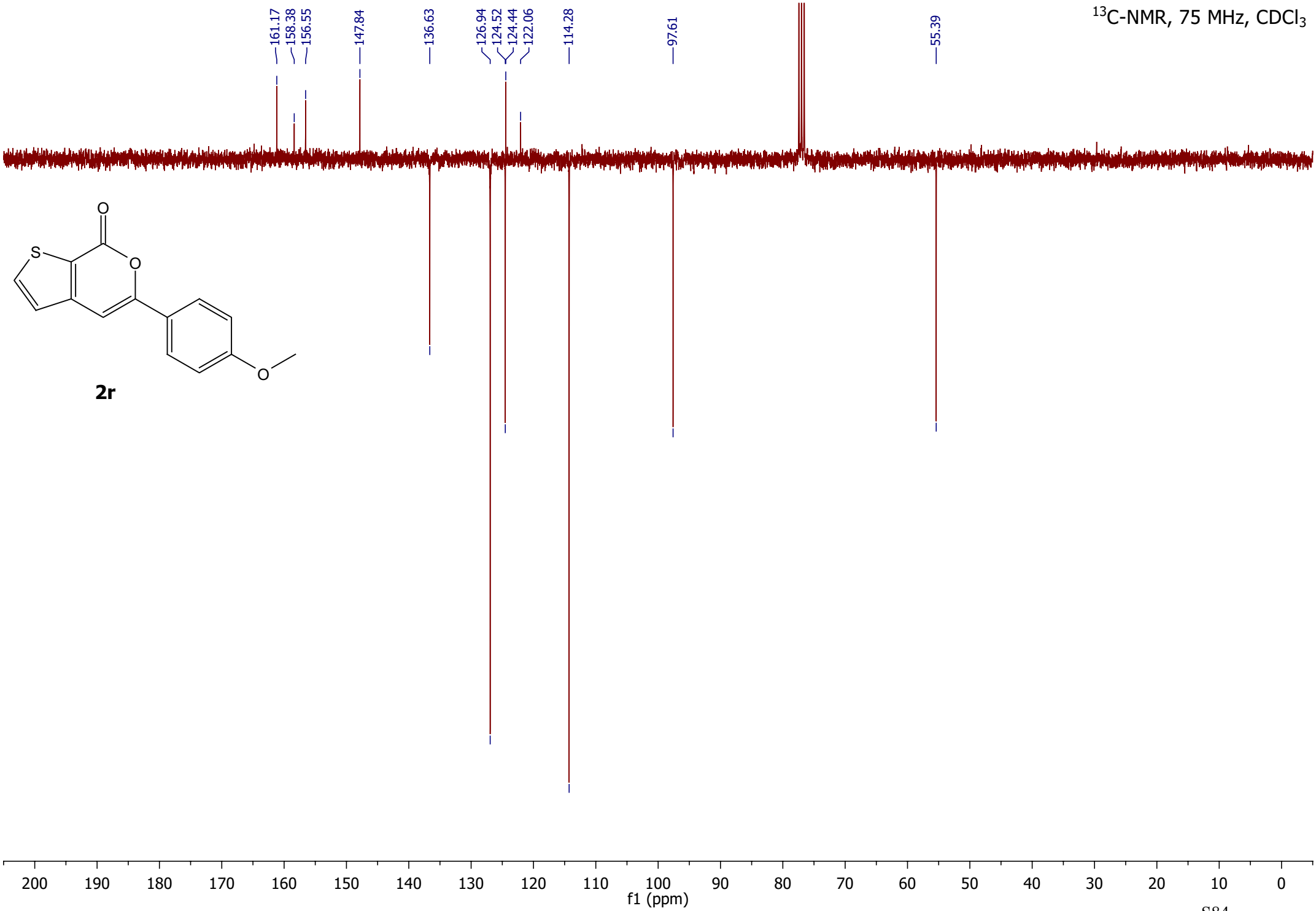
^{13}C-NMR, 75 MHz, $CDCl_3$

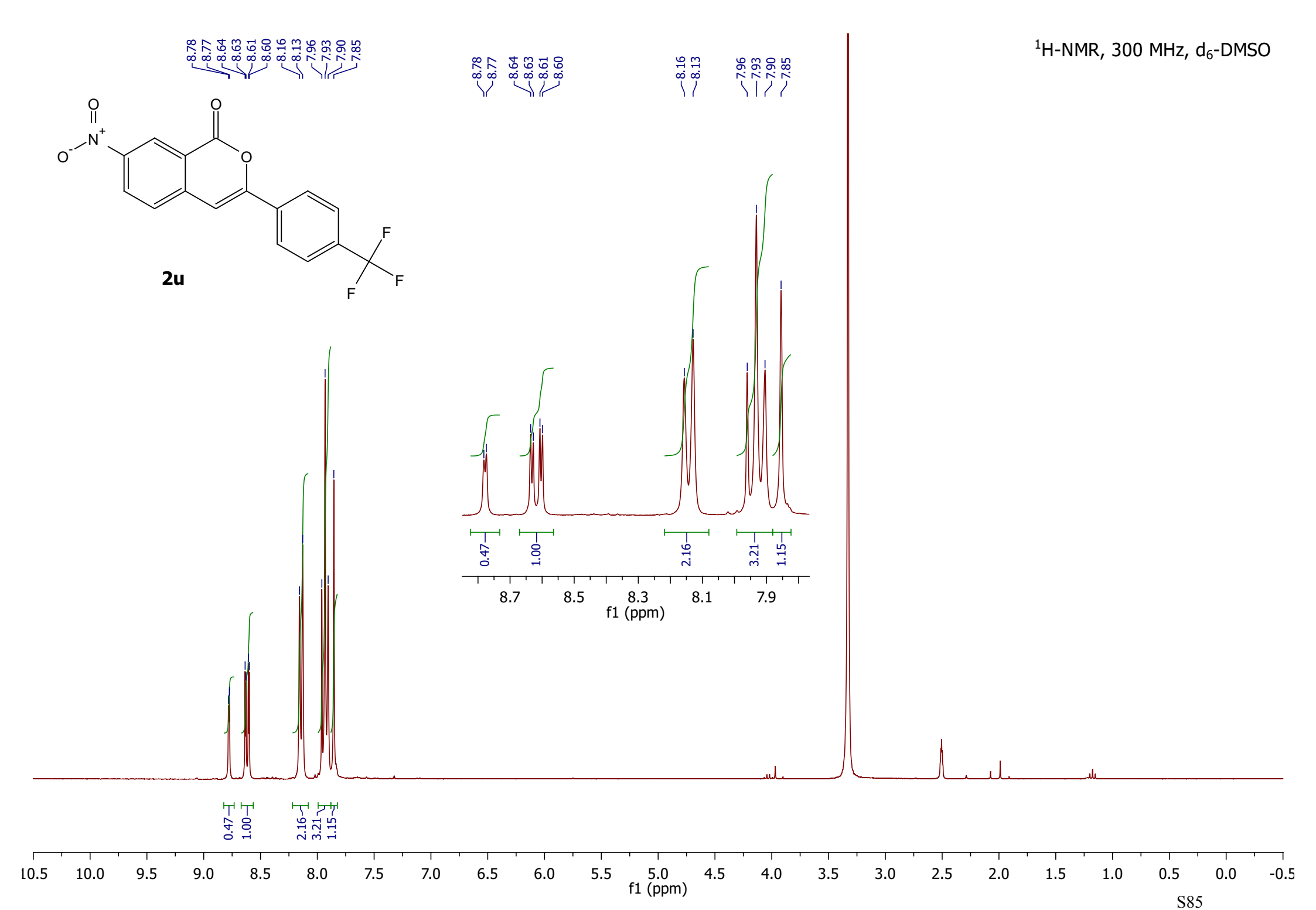
157.91
155.23
147.20
136.93
136.14
130.32
129.15
126.59
124.70
123.12
99.23

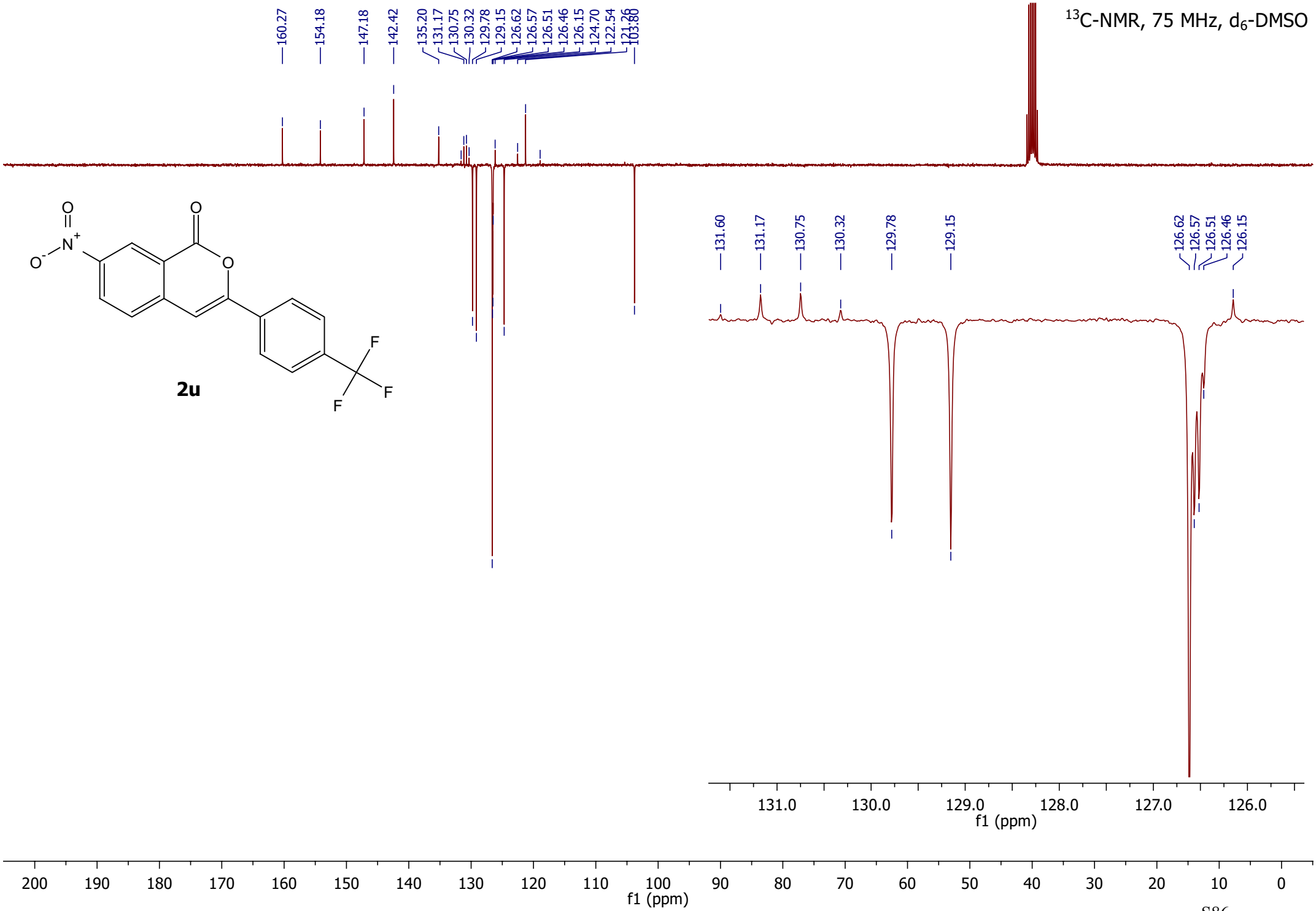
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

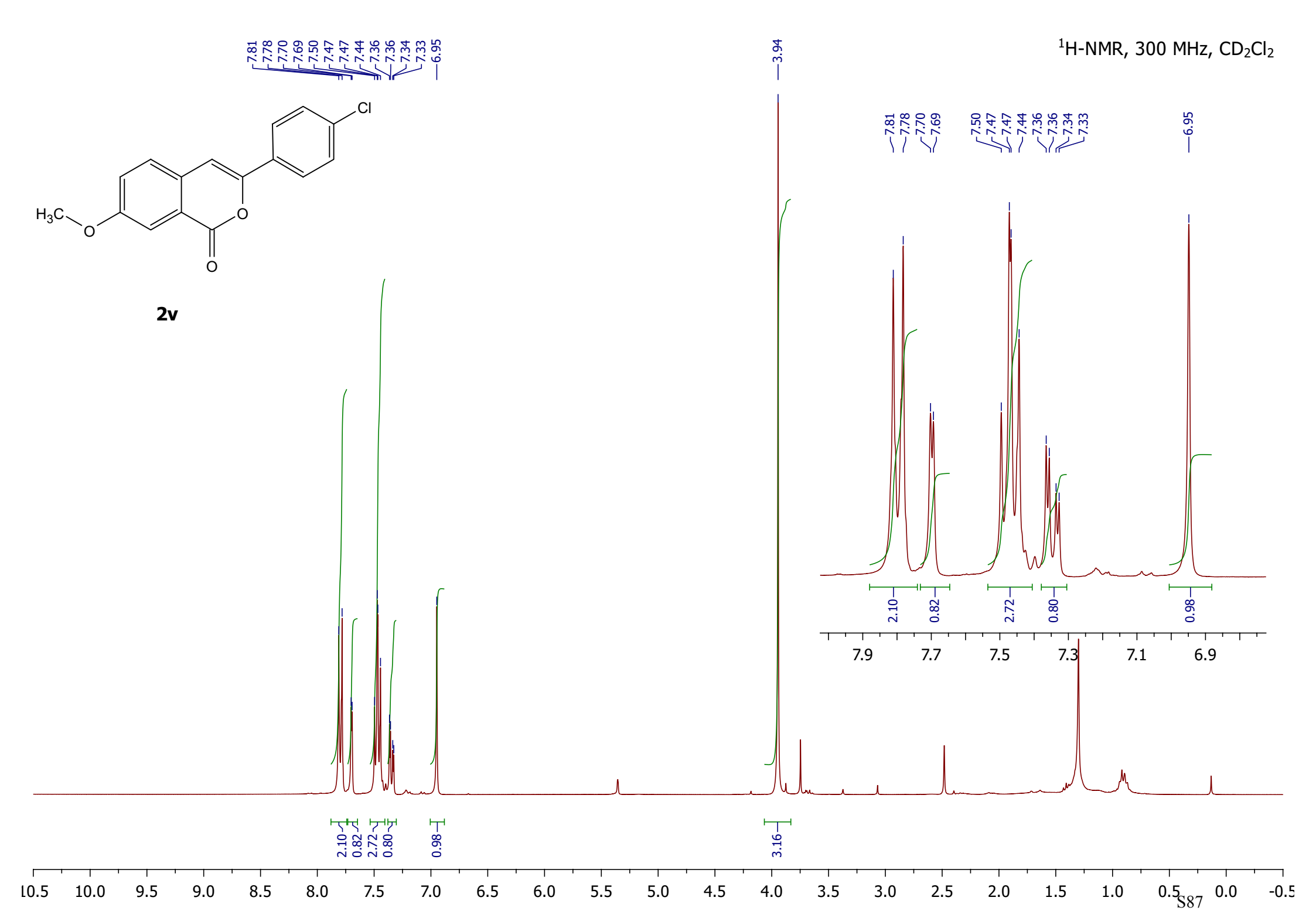
f1 (ppm)

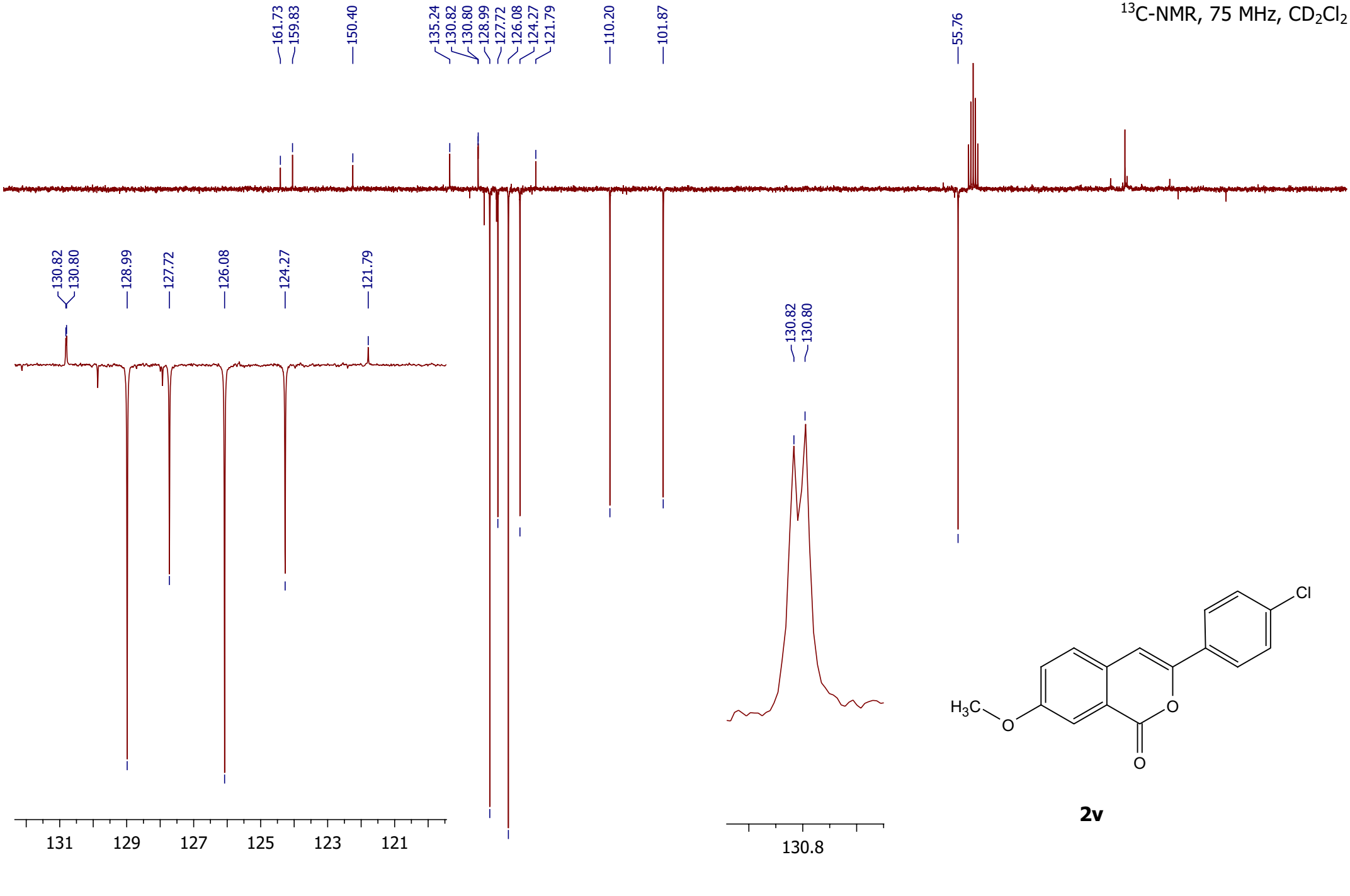

2r
^{1}H-NMR, 300 MHz, $CDCl_3$
7.82
7.81
7.80
7.79
7.79
7.21
7.19
6.99
6.98
6.97
6.97
6.95
6.94
6.93
3.86
3.01
1.00
0.95
2.03
3.08
f1 (ppm)

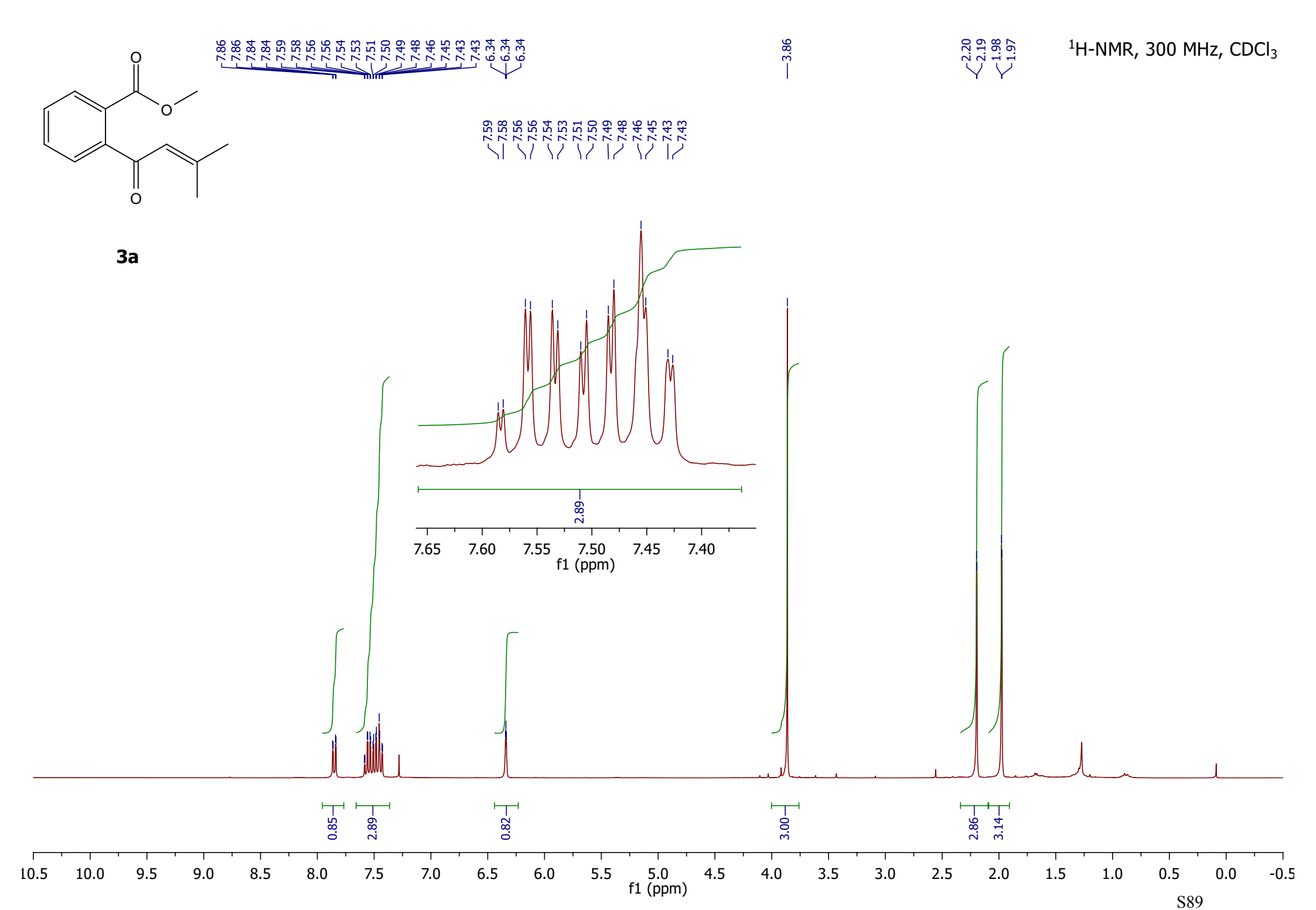

^{13}C-NMR, 75 MHz, $CDCl_3$
161.17
158.38
156.55
147.84
136.63
126.94
124.52
124.44
122.06
114.28
97.61
55.39
O
S
O
O
2r
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

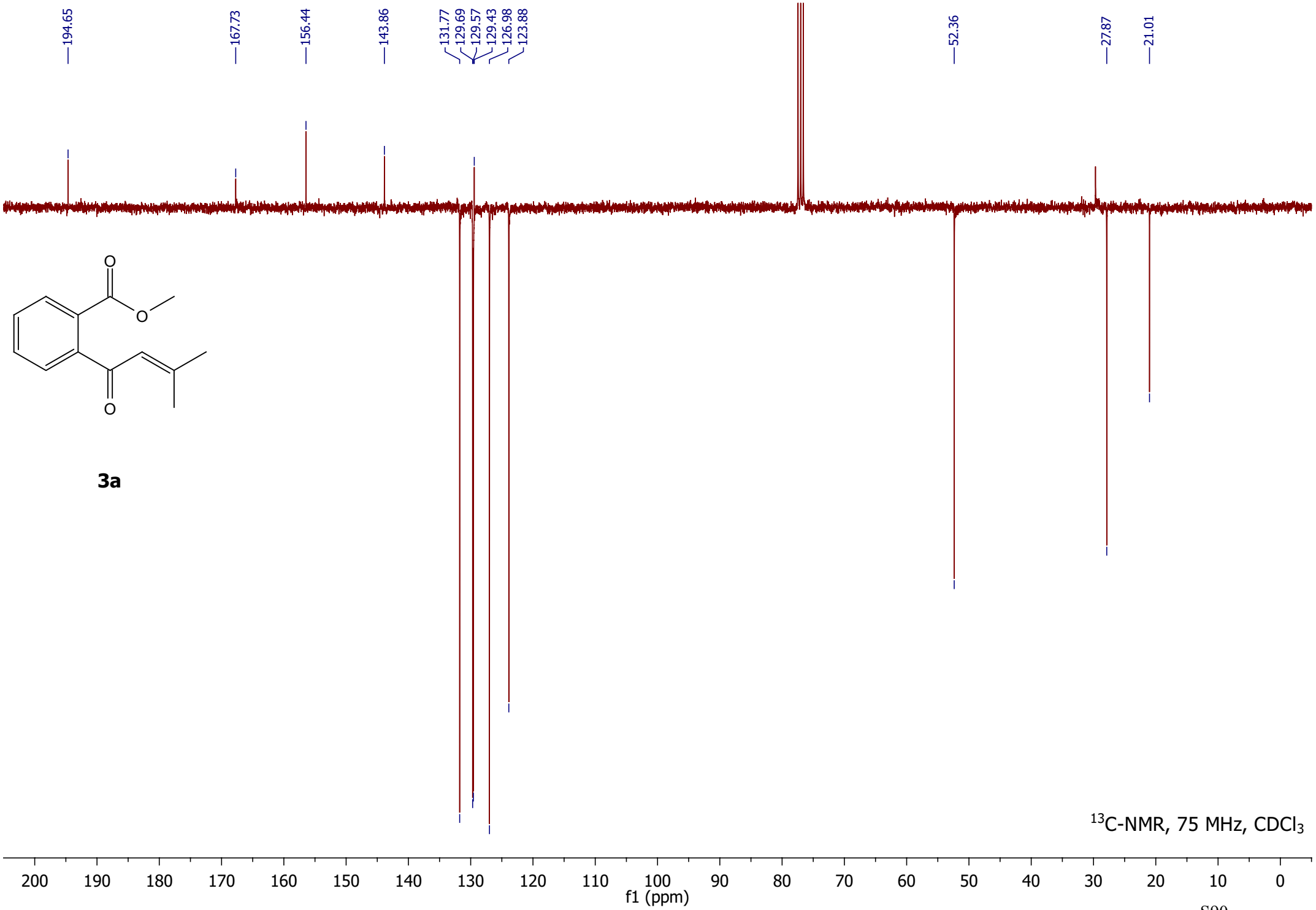

^{1}H-NMR, 300 MHz, d_6-DMSO
8.78
8.77
8.64
8.63
8.61
8.60
8.16
8.13
7.96
7.93
7.90
7.85
2u
0.47
1.00
2.16
3.21
1.15
f1 (ppm)

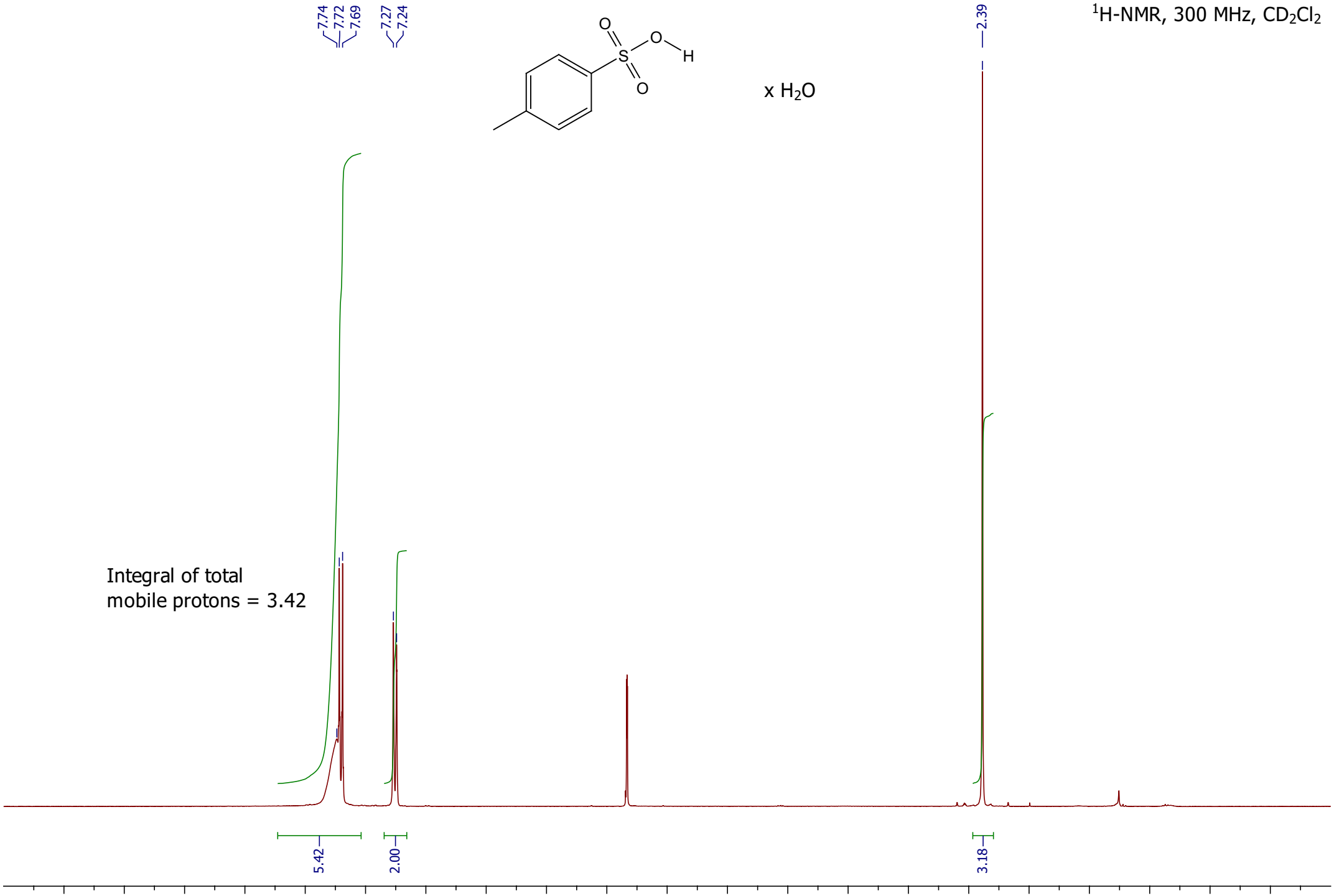

^{13}C-NMR, 75 MHz, d$_6$-DMSO
160.27
154.18
147.18
142.42
135.20
131.17
130.75
130.32
129.78
129.15
126.62
126.57
126.51
126.46
126.15
124.70
122.54
121.26
103.80
2u
131.60
131.17
130.75
130.32
129.78
129.15
126.62
126.57
126.51
126.46
126.15
131.0
130.0
129.0
128.0
127.0
126.0
f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

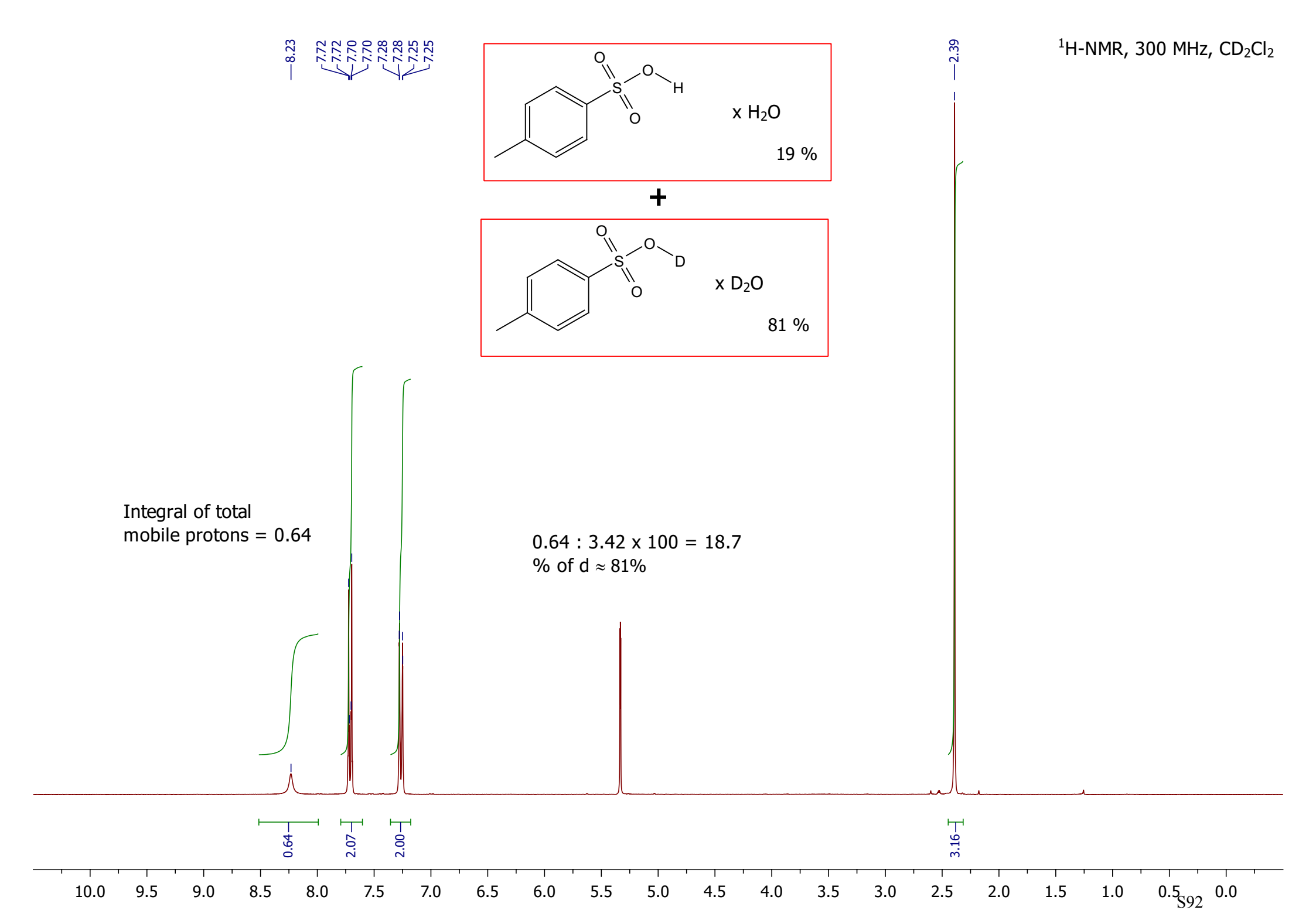

^{1}H-NMR, 300 MHz, CD_2Cl_2
7.81
7.78
7.70
7.69
7.50
7.47
7.47
7.44
7.36
7.36
7.34
7.33
6.95
3.94
Cl
H_3C
O
O
O
2v
2.10
0.82
2.72
0.80
0.98
3.16
7.9
7.7
7.5
7.3
7.1
6.9


^{13}C-NMR, 75 MHz, CD_2Cl_2
161.73
159.83
150.40
135.24
130.82
130.80
128.99
127.72
126.08
124.27
121.79
110.20
101.87
55.76
130.82
130.80
128.99
127.72
126.08
124.27
121.79
131
129
127
125
123
121
130.82
130.80
130.8
Cl
H_3C
O
O
O
2v
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


^{1}H-NMR, 300 MHz, $CDCl_3$
3a
7.86 7.86 7.84 7.84 7.59 7.58 7.56 7.56 7.54 7.53 7.51 7.50 7.49 7.48 7.46 7.45 7.43 7.43 6.34 6.34 6.34
3.86
2.20 2.19 1.98 1.97
7.59 7.58 7.56 7.56 7.54 7.53 7.51 7.50 7.49 7.48 7.46 7.45 7.43 7.43
2.89
7.65 7.60 7.55 7.50 7.45 7.40
f1 (ppm)
0.85 2.89 0.82 3.00 2.86 3.14
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


194.65
167.73
156.44
143.86
131.77
129.69
129.57
129.43
126.98
123.88
52.36
27.87
21.01
O
O
O
3a
^{13}C-NMR, 75 MHz, CDCl$_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.74
7.72
7.69
7.27
7.24
2.39
x H_2O
^{1}H-NMR, 300 MHz, CD_2Cl_2
Integral of total
mobile protons = 3.42
5.42
2.00
3.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


^{1}H-NMR, 300 MHz, CD_2Cl_2
8.23
7.72
7.72
7.70
7.70
7.28
7.28
7.25
7.25
2.39
x H_2O
19 %
+
x D_2O
81 %
Integral of total
mobile protons = 0.64
0.64 : 3.42 x 100 = 18.7
% of d ≈ 81%
0.64
2.07
2.00
3.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0