Toward Serotonin Fluorescent False Neurotransmitters: Development of Fluorescent Dual Serotonin and Vesicular Monoamine Transporter Substrates for Visualizing Serotonin Neurons

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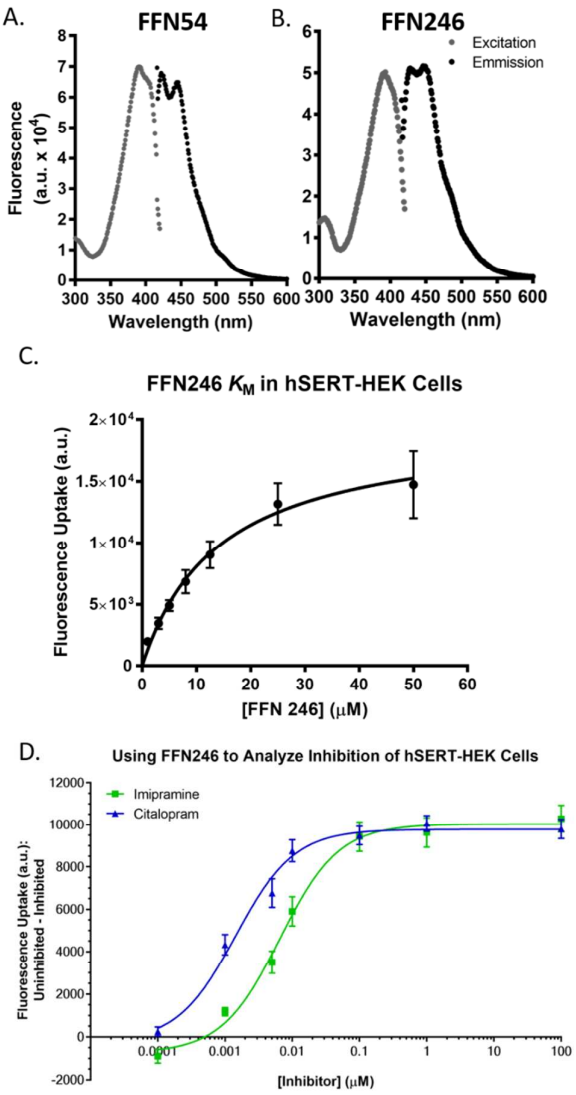
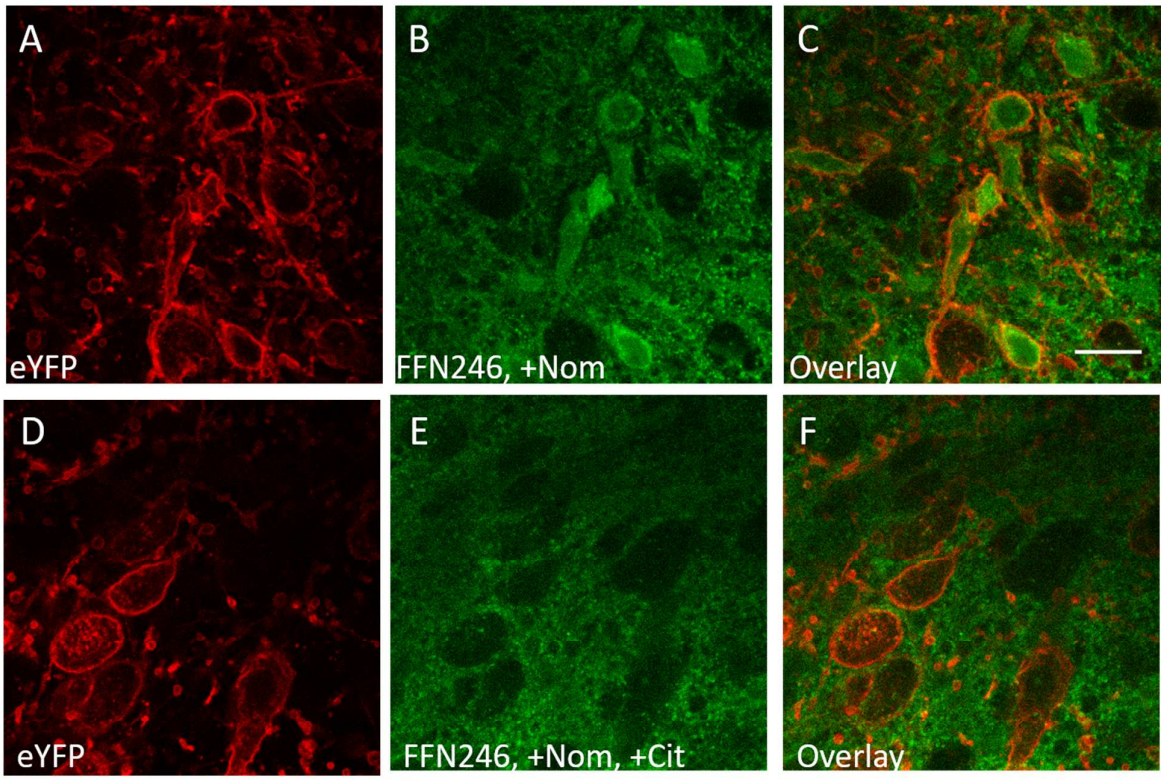
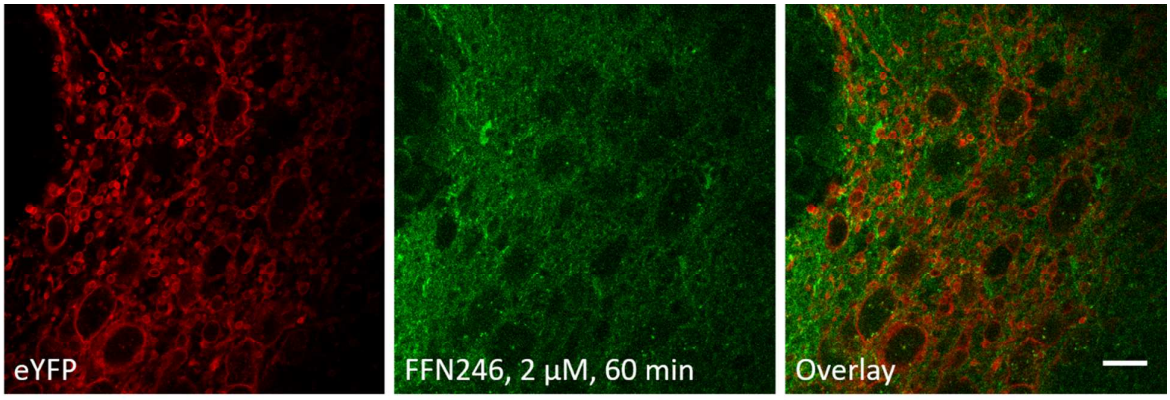
SUPPLEMENTAL FIGURES



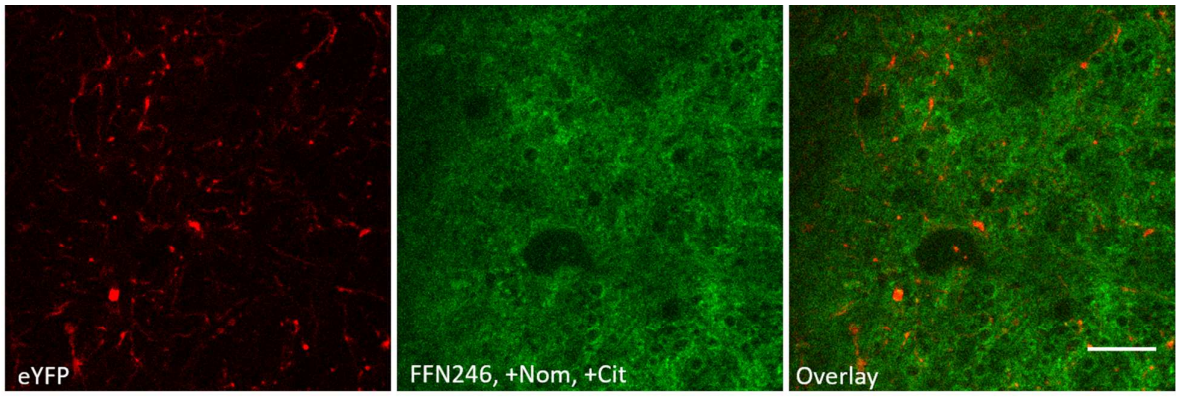
Supplemental Figure S1. A) Fluorescence excitation and emission spectra of FFN54 and FFN246. B) K_M determination of FFN246 in hSERT-HEK cells using 2 μM imipramine (K_M = 14.3 ± 1.9 μM). C) Demonstration of using FFN246 to measure K_i's of imipramine (K_i = 4.8 ± 1.1 nM) and citalopram (K_i = 1.6 ± 0.4 nM) at hSERT.



Supplemental Figure S2. Uptake of FFN246 in 5-HT neurons in the dorsal raphe of acute murine brain slices in the presence of nomifensine (2 µM) or nomifensine and citalopram (200 nM). A-C) 76.3% of 5-HT neurons accumulate FFN246 (29/38 cells, 2-3 slices per animal, 2 different animals) when just using nomifensine. D-F) Uptake decreases to 0% when using both nomifensine and citalopram (0/19 cells, 2-3 slices per animal, 2 different animals). Scale bar, 20 µm.



Supplemental Figure S3. Uptake of a lower concentration of FFN246 (2 µM) in 5-HT neurons in the dorsal raphe nucleus of acute murine brain slices during a 60 min perfusion. Scale bar, 20 µm.



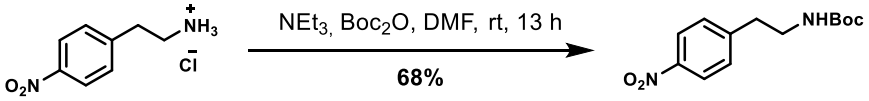
Supplemental Figure S4. Uptake of FFN246 in the 5-HT projections within the substantia nigra reticulata of acute murine brain slices in the presence of both nomifensine (2 μM) and citalopram (200 nM). Scale bar, 20 μm.

General Notes

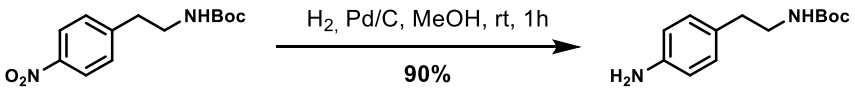
Unless otherwise noted, all chemicals were purchased from commercial companies and used without further purification. Nuclear Magnetic Resonance spectra were recorded on Bruker 400 and 500 MHz Fourier transform NMR spectrometers. Proton chemical shifts δ are expressed in parts per million (ppm) and are referenced to residual proton in the NMR solvent ($CDCl_3$, δ = 7.26 ppm; methanol-d_4, δ = 3.31 ppm; DMSO-d_6, δ = 2.50 ppm; acetone-d_6, δ = 2.05 ppm; D_2O, δ = 4.79 ppm). Data for ^{1}H NMR and ^{19}F NMR are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad peak), and coupling constant in Hz. Carbon chemical shifts are referenced to the carbon resonance of the NMR solvent ($CDCl_3$, δ = 77.2 ppm; methanol-d_4, δ = 49.0 ppm; DMSO-d_6, δ = 39.5 ppm; acetone-d_6, δ = 29.8 ppm). $^{13}C\{^1H\}$ NMR spectra were recorded without ^{19}F decoupling and therefore J_{C-F} splitting of ^{13}C signals was observed for fluorinated compounds unless otherwise noted. Low-resolution mass spectra were recorded on a JEOL LCmate instrument in $APCI^+$ ionization mode or on an Advion expression-L CMS quadrupole mass spectrometer equipped with APCI source.

Preparative HPLC was performed on Waters 600 Controller equipped with a Vydac C_{18} Protein & Peptide column (mobile phase – gradient of solvents A and B, where A = deionized water containing 0.1% (v/v) formic acid (FA); B = HPLC grade methanol containing 0.1% (v/v) formic acid (FA)), Waters 2487 Dual Wavelength Absorbance Detector (λ_{abs} = 254 nm) and Waters 2767 Sample Manager. Analytical HPLC was performed on the same instrument equipped with a Phenomenex reverse phase column (Prodigy 5 micron ODS3 100A 250 × 4.6 mm) using isocratic methanol:water (30:70) mobile phase.

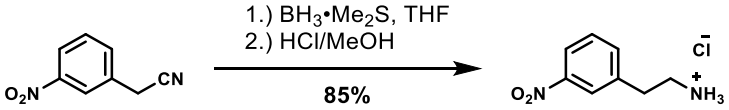
Synthesis



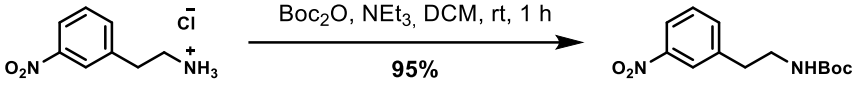
***tert*-Butyl (4-nitrophenethyl)carbamate**: A solution of Boc_2O (4.70 g, 21.5 mmol) in DMF (5 mL) was slowly added to a mixture of 2-(4-nitrophenyl)ethan-1-amine hydrochloride (4.15 g, 20.5 mmol) and NEt_3 (3.15 mL, 22.5 mmol) in DMF (75 mL) at ambient temperature and stirred for 13 h. The mixture was then poured to water and the precipitate was filtered and washed with water. The crude product was dissolved in EtOAc, washed with brine and dried over $MgSO_4$. After removing the solvent, the crude product was crystalized from chloroform/*n*-hexane (insoluble solid/oil was removed by filtration of the warm solution) to afford the desired product as a yellowish solid in 68% yield (3.7 g). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.02 (d, J = 7.9 Hz, 2H), 6.77 (d, J = 8.3 Hz, 2H), 3.19 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.42 (s, 9H).



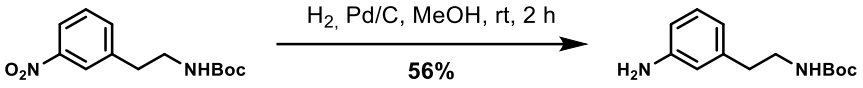
***tert*-Butyl (4-aminophenethyl)carbamate**: *tert*-Butyl (4-nitrophenethyl)carbamate (1.6 g, 6.0 mmol) was dissolved in MeOH (30 mL) and 10% (w/w) Pd/C was added (0.5 g) and the reaction mixture was stirred under H_2 atmosphere (Parr reactor, p = 50 psi) for 1 h at room temperature. The catalyst was removed by filtration and the crude product was crystalized from chloroform/*n*-hexane to afford the desired product as a white solid in 90% yield (1.28 g). Obtained product was used in the next step without further purification. ^{1}H NMR (400 MHz, methanol-d_4) δ 6.95 (d, J = 7.9 Hz, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.46 (br s, 1H), 3.17 (t, J = 6.9 Hz, 2H), 2.62 (t, J = 7.5 Hz, 2H), 1.42 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, methanol-d_4) δ 158.4, 146.7, 130.4, 130.3, 116.9, 79.9, 43.4, 36.4, 28.8.



2-(3-Nitrophenyl)ethan-1-amine hydrochloride: A solution of (3-nitro-phenyl)-acetonitrile (1.0 g, 6.2 mmol) in dry THF (10 ml) was heated to reflux and borane dimethylsulfide (7 mL, 2M in THF, 14 mmol) was added. The mixture was stirred for 2 h under reflux. After complete conversion the mixture was allowed to come to room temperature and a solution of HCl in methanol (19 mL, 1.25M) was added. The reaction mixture was then stirred overnight and volatiles were removed under reduced pressure. The residue was triturated with diethyl ether, filtered, washed with diethyl ether and dried under the vacuum to give the product as a white solid in 85% yield (1.05 g). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.21 (m, 1H), 8.18 (ddd, J = 8.1, 2.4, 1.1 Hz, 1H), 7.72 (m, 1H), 7.63 (t, J = 7.9 Hz, 1H), 3.26 (t, J = 7.7 Hz, 2H), 3.11 (t, J = 7.7 Hz, 2H).

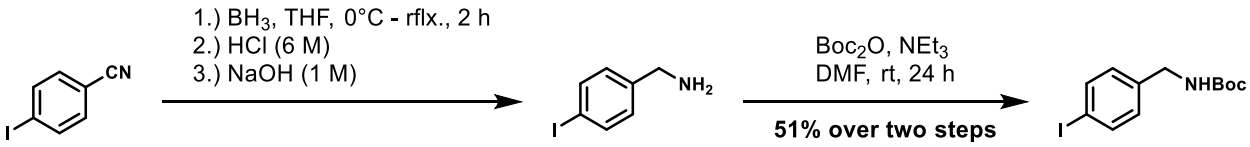


***tert*-Butyl (3-nitrophenethyl)carbamate**: 2-(3-Nitrophenyl)ethan-1-amine hydrochloride (1.0 g, 4.93 mmol) was dissolved in dry DCM (20 mL) and Boc_2O (1.2 g, 5.43 mmol) and NEt_3 (1.09 g, 1.5 mL, 10.9 mmol) were added and the resulting solution was stirred at room temperature for 1 hour. Volatiles were removed under reduced pressure. The crude material was dissolved in DCM and applied to flash column chromatography. The pure product was obtained as a colorless powder in 95% yield (1.25 g). ^{1}H NMR (400 MHz, methanol-d_4) δ 8.13 – 8.06 (m, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 2.90 (t, J = 7.0 Hz, 2H), 1.39 (s, 9H).[1]



***tert*-Butyl (3-aminophenethyl)carbamate**: *tert*-Butyl (3-nitrophenethyl)carbamate (1.3 g, 4.9 mmol) was dissolved in MeOH (30 mL) and 10% Pd/C (w/w) was added (0.26 g). The reaction mixture was stirred under H_2 atmosphere (Parr reactor, p = 50 psi) for 2 h at room temperature. The catalyst was removed by filtration and the crude product was crystalized from EtOAc/*n*-hexane to afford the desired product as a white solid in 56% yield (0.65 g). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.01 (t, J = 7.7 Hz, 1H), 6.61 – 6.52 (m, 3H), 3.22 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.43 (s, 9H). Spectral data are in accordance with literature data.[2]

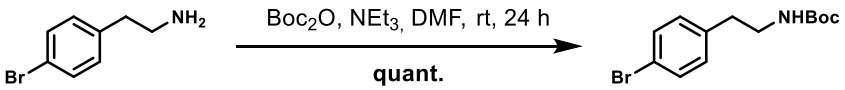
Halide coupling partners



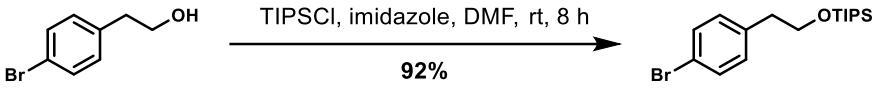
***tert*-Butyl (4-iodobenzyl)carbamate**: To a solution of the 4-iodobenzonitrile (942 mg, 4.11 mmol) in dry THF (12 mL) at 0 °C was added dropwise a solution of BH_3 (1 M in THF, 20 mL, 20 mmol) and after complete addition the reaction mixture was further stirred at reflux temperature for 2 hours. The reaction mixture was then cooled to 0 °C and HCl (aq, 6 M, 2 mL) was added at 0°C dropwise and afterwards the reaction mixture was basified with NaOH (aq, 1 M). The reaction mixture was extracted

[1] Second methylene signal overlapped by methanol-d_4 solvent signal
[2] US7470815 B1, **2008**

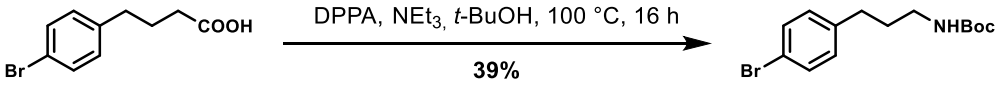
with DCM and the combined organic phases were washed with H_2O, and dried over Na_2SO_4, filtered and volatiles were removed under reduced pressure to yield the crude product. All obtained material was dissolved in dry DMF (4.1 mL) and Boc_2O (988 mg, 4.52 mmol) and NEt_3 (625 mg, 0.86 mL, 6.17 mmol) were added and the resulting solution was stirred at room temperature for 24 hours. Volatiles were removed in vacuo. The crude material was dissolved in DCM and purified by column chromatography (50 g silica gel, *n*-hexane/EtOAc = 5/1, (v/v)) to yield the pure product as a colorless powder in 51% yield (693 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 4.82 (br s, 1H), 4.25 (d, J = 6.1 Hz, 2H), 1.45 (s, 9H). Spectral data are in accordance with literature data.[3]



***tert*-Butyl (4-bromophenethyl)carbamate**: 2-(4-Bromophenyl)-ethyl-1-amine (2.6 g, 13.0 mmol) was dissolved in dry DMF (12.9 mL) and Boc_2O (3.1 g, 14.3 mmol) and NEt_3 (2.0 g, 2.75 mL, 19.5 mmol) were added and the reaction mixture was stirred at room temperature for 12 hours. Volatiles were removed in vacuo and obtained material was dissolved in DCM and purified by flash column chromatography (125 g silica gel, *n*-hexane/EtOAc = 5/1, (v/v)). The pure product was obtained as a colorless powder in a quantitative yield (3.8 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 4.51 (br s, 1H), 3.41 – 3.27 (m, 2H), 2.75 (t, J = 7.0 Hz, 2H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.9, 138.1, 131.8, 130.7, 120.4, 79.5, 41.7, 35.8, 28.5. Spectral data are in accordance with literature data.[4]



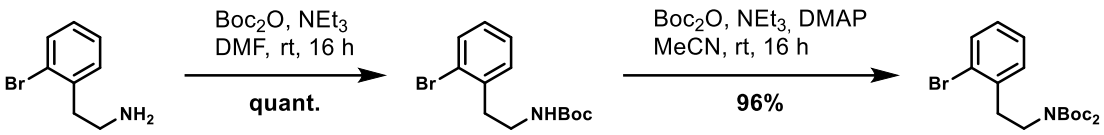
(4-Bromophenethoxy)triisopropylsilane: 2-(4-Bromophenyl)-ethan-1-ol (1.0 g, 5.0 mmol) and imidazole (0.51 g, 7.5 mmol) were dissolved in dry DMF (5.3 mL). TIPSCl (1.2 g, 6.0 mmol) was added and the solution was stirred at room temperature for 8 hours. H_2O (5 mL) was added and the reaction mixture was further stirred for 10 minutes. The reaction mixture was portioned between additional portion of H_2O and Et_2O. The aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and volatiles were removed in vacuo and the crude product was purified by flash column chromatography (150 g silica gel, 1% EtOAc in *n*-hexane → 2% → 3%). The product was obtained as a colorless liquid in 92% yield (1.64 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 3.85 (t, J = 6.9 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 1.11 – 0.99 (m, 21H). Spectral data are in accordance with literature data.[5]



***tert*-Butyl (3-(4-bromophenyl)propyl)carbamate**: 4-(4-Bromophenyl)butanoic acid (243 mg, 0.1 mmol), diphenylphosphoryl azide (DPPA; 303 mg, 1.1 mmol) and dry NEt_3 (126 mg, 0.17 mL, 1.25 mmol) were placed in a 4 mL vial and anhydrous *t*-BuOH (1.65 mL) was added. The vial was flushed with dry Ar and closed tightly with a screw cap. The reaction mixture was stirred at 100 °C in a thermoblock for 16 hours. The reaction mixture was then allowed to cool down to room temperature and was portioned between EtOAc and brine. The organic phase was dried over Na_2SO_4. Volatiles were removed in vacuo and obtained crude residuum was further purified by flash column chromatography

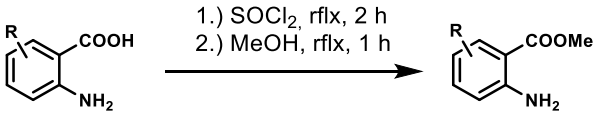
[3] *Angew. Chem. Int. Ed.*, **2013**, 8134
[4] *J. Phys. Chem. A.*, **2011**, 1222
[5] *Bioorg. & Med. Chem.*, **2011**, 7464

(crude material/silica gel = 1/100, (m/m), *n*-hexane/EtOAc = 7/1 → 6/1 → 5/1). The product was obtained as a colorless oil in 39% yield (121 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.3 Hz, 2H), 4.52 (br s, 1H), 3.19 – 3.08 (m, 2H), 2.59 (d, J = 7.7 Hz, 2H), 1.78 (tt, J = 7.6, 6.5 Hz, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.1, 140.7, 131.6, 130.3, 119.8, 79.4, 40.3, 32.7, 31.8, 28.6.



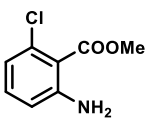
2-(2-Bromophenyl)ethyl imidodicarbonic acid, bis(1,1-dimethylethyl) ester: 2-(2-Bromophenyl)ethan-1-amine (1.0 g, 0.5 mmol) was dissolved in dry DMF (5 mL) and Boc_2O (1.2 g, 5.5 mmol) and NEt_3 (759 mg, 1.05 mL, 0.75 mmol) were added and the resulting solution was stirred at room temperature for 16 hours. Volatiles were then removed in vacuo. Obtained crude material was dissolved in DCM and purified by flash column chromatography (50 g silica gel, *n*-hexane/EtOAc = 10/1 → 5/1, (v/v)). The pure compound was obtained quantitatively as a colorless powder (1.5 g). This intermediate (1.1 g) was dissolved in MeCN (14.5 mL) and Boc_2O (2.4 g, 15.0 mmol), NEt_3 (548 mg, 0.75 mL, 7.5 mmol) and DMAP (88 mg, 0.1 mmol) were added and the resulting solution was stirred at room temperature for 16 hours. The reaction mixture was concentrated and diluted with NH_4Cl (aq, satd.) and EtOAc. The aqueous phase was further extracted with EtOAc (2 × 20 mL) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and volatiles were removed in vacuo. The crude material was purified by flash column chromatography (100 g silica gel, *n*-hexane/EtOAc 10:1 (v/v)). Pure product was obtained as a colorless oil in 96% yield (1.38 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.8, 1.1 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.07 (ddd, J = 7.9, 6.5, 2.6 Hz, 1H), 3.85 (t, J = 7.3 Hz, 2H), 3.04 (t, J = 7.1 Hz, 2H), 1.46 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.4, 138.6, 132.9, 131.5, 128.3, 127.7, 124.9, 82.4, 46.1, 35.8, 28.2.

2-Aminobenzoates



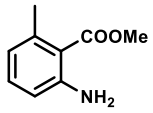
General procedure: esterification of 2-aminobenzoic acids

A suspension of the benzoic acid starting material in $SOCl_2$ (0.68 M) was refluxed for 2 hours under dry Ar. Volatiles were removed in vacuo. The residue was cooled with an ice bath and ice-cold MeOH (to final c = 0.45 M) was carefully added. The reaction mixture was further refluxed for 1 hour. Volatiles were removed in vacuo and the obtained residuum was portioned between $NaHCO_3$ (aq, satd.) and DCM. The aqueous phase was extracted with DCM two more times. The combined organic phase was dried over Na_2SO_4, filtered and volatiles were removed under reduced pressure. The crude material was purified by flash column chromatography (crude material/silica gel = 1/100 (m/m), *n*-hexane/EtOAc = 5:1, (v/v)).

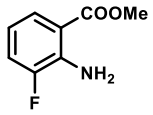


Methyl 2-amino-6-chlorobenzoate was prepared according to the general procedure from 2-amino-6-chlorobenzoic acid (3.35 mmol) and methanol in 80% yield (497 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (t, J = 8.1 Hz, 1H), 6.75 (dd, J = 7.9, 1.1 Hz, 1H), 6.58 (dd, J = 8.3, 1.0 Hz, 1H), 4.86 (br s, 2H), 3.93

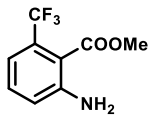
(s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 167.7, 149.0, 134.1, 132.2, 119.7, 115.0, 114.8, 52.2. Spectral data are in accordance with literature data.[6]



Methyl 2-amino-6-methylbenzoate was prepared according to the general procedure from 2-amino-6-chlorobenzoic acid (1.44 mmol) and methanol in 57% yield (136 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (dd, J = 8.1, 7.5 Hz, 1H), 6.54 – 6.53 (m, 1H), 6.53 – 6.51 (m, 1H), 5.10 (br s, 2H), 3.89 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.8, 149.2, 140.3, 132.1, 120.6, 114.6, 114.1, 51.5, 23.1. Spectral data are in accordance with literature data.[7]

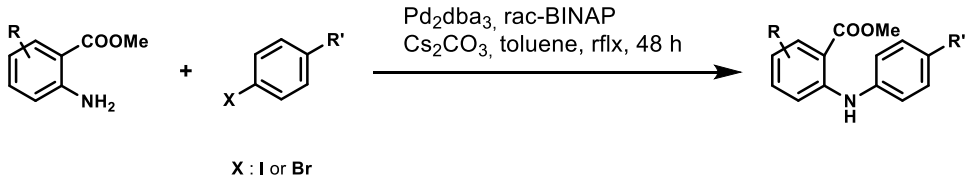


Methyl 2-amino-3-fluorobenzoate was prepared according to the general procedure from 2-amino-3-fluorobenzoic acid (6.32 mmol) and methanol in 68% yield (727 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 8.2 Hz, 1H), 7.10 (ddd, J = 11.3, 7.8, 1.5 Hz, 1H), 6.55 (td, J = 8.1, 5.1 Hz, 1H), 5.79 (br s, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 168.1, 152.6, 150.7, 139.9, 139.8, 126.4, 126.4, 118.6, 118.5, 114.8, 114.8, 112.8, 112.7, 51.8. Spectral data are in accordance with literature data.[8]



Methyl 2-amino-6-(trifluoromethyl)benzoate was prepared according to the general procedure 2-amino-6-trifluoromethyl-benzoic acid (2.44 mmol) and methanol in 91% yield (487 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.78 (br s, 2H), 3.91 (s, 3H). $^{13}C\{^1H,^{19}F\}$ NMR (101 MHz, $CDCl_3$) δ 168.1, 147.5, 131.5, 130.2, 123.9, 120.1, 116.2, 113.5, 52.6. Spectral data are in accordance with literature data.[9]

Acridone precursors

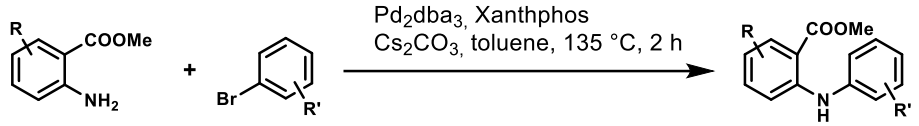


General procedure: Buchwald-Hartwig coupling, method A

Aniline (1.2 eq.) and arylhalogenide (1 eq.) starting materials, Pd_2dba_3 (2.5 mol%), *rac*-BINAP (7.5 mol%) and Cs_2CO_3 (2 eq.) were placed to a flame dried flask under dry Ar and diluted with dry and degassed toluene (*c*(aniline) = 0.1 M; degassed by 15 minutes bubbling of dry Ar and sonicated prior to use) and the reaction mixture was further degassed (5 minutes of bubbling with dry Ar under sonication). The flask was attached to a reflux condenser and the reaction mixture was refluxed under dry Ar for 48 hours. The reaction mixture was filtered through a short pad of silica gel and the silica

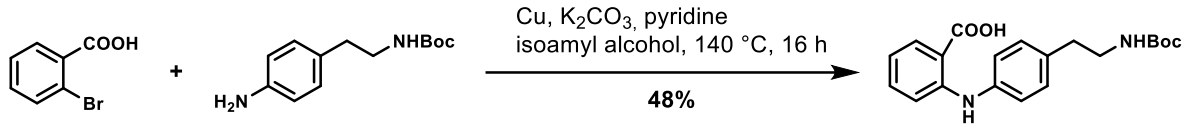
[6] *Bioorg. Med. Chem.*, **1999**, 1743
[7] *Tetrahedron*, **2009**, 563
[8] *J. Med. Chem.*, **2015**, 1630
[9] Eur. Pat. Appl. (1992), EP 516297 A1 19921202

was further eluted with EtOAc. Eluates were combined and volatiles were removed under reduced pressure and obtained residuum was purified by flash column chromatography (crude material/silica gel = 1/100 (m/m); DCM → 1% EtOAc in DCM → 2%).

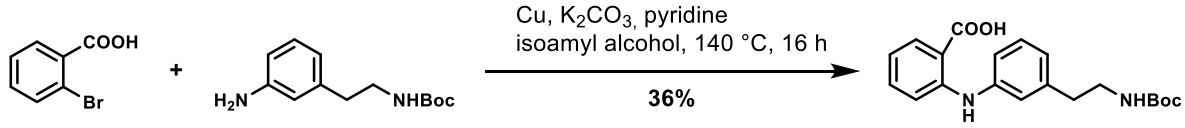


General procedure: Buchwald-Hartwig coupling, method B (optimized conditions)

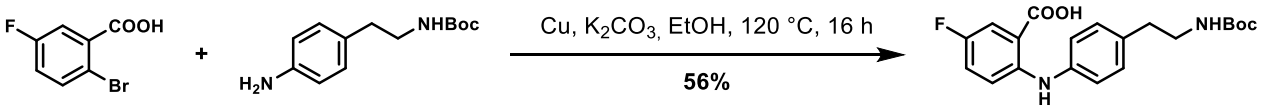
Aniline (0.24 mmol), arylbromide (0.2 mmol), Pd_2dba_3 (0.005 mmol), Xanthphos (0.015 mmol) and Cs_2CO_3 (0.4 mmol) were placed in a 4 mL vial and diluted with toluene (2 mL). The vial was briefly flushed with Ar and closed tightly with a screw cap. The reaction mixture was stirred at 135 °C in a thermoblock for 2 hours. For scale-up, multiple reactions were run in parallel. The reaction mixture was allowed to cool down to room temperature, filtered through a short pad of silica gel and then the pad was further eluted with EtOAc. Organic phases were combined, volatiles were removed in vacuo and the obtained crude product was further purified by flash column chromatography (crude material/silica gel = 1/100 (m/m), DCM → 1% EtOAc in DCM → 2%).



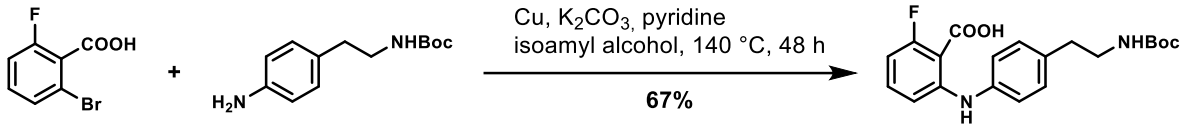
2-((4-(2-((*tert*-Butoxycarbonyl)amino)ethyl)phenyl)amino)benzoic acid: A suspension of *tert*-butyl (4-aminophenethyl)carbamate (600 mg, 2.54 mmol), 2-bromobenzoic acid (480 mg, 3.05 mmol), K_2CO_3 (430 mg, 3.1 mmol), Cu powder (25 mg) and pyridine (150 µL) in isoamyl alcohol (3 mL) in a 20 mL vial was stirred at 140 °C for 16 hours. The reaction mixture was then allowed to cool down to room temperature, diluted with EtOAc, washed with HCl (aq, 1M), brine, dried over $MgSO_4$, filtered and volatiles were removed under reduced pressure. The obtained crude brown oil was purified by flash column chromatography (EtOAc/*n*-hexane = 1/1, (v/v)) and further crystalized from EtOAc/*n*-hexane. The product was obtained as an orange solid in 78% yield after column chromatography and in 48% yield after crystallization (710 mg). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.01 (dd, J = 8.0, 1.7 Hz, 1H), 7.38 (ddd, J = 8.7, 7.1, 1.7 Hz, 1H), 7.27 – 7.17 (m, 5H), 6.76 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 3.31 (t, J = 7.4 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, acetone-d_6) δ 170.5, 156.6, 149.3, 139.7, 136.0, 135.1, 132.9, 130.7, 123.3, 117.8, 114.4, 112.5, 78.5, 42.7, 36.4, 28.7. LR-MS calcd. for $C_{20}H_{25}N_2O_4$ $[M+H]^+$ 357.18, found 356.97.



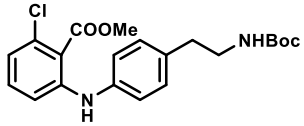
2-((3-(2-((*tert*-Butoxycarbonyl)amino)ethyl)phenyl)amino)benzoic acid was prepared from 2-bromobenzoic acid and *tert*-butyl (3-aminophenethyl)carbamate analogously to 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)benzoic acid in 36% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.97 (dd, J = 8.0, 1.7 Hz, 1H), 7.33 (ddd, J = 8.6, 7.0, 1.7 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.10 – 7.05 (m, 2H), 6.93 (d, J = 7.6 Hz, 1H), 6.73 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 3.27 (t, J = 7.3 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, methanol-d_4) δ 171.8, 158.5, 149.3, 142.3, 142.1, 135.1, 133.2, 130.4, 125.0, 123.5, 120.8, 118.1, 115.0, 113.5, 80.0, 42.9, 37.1, 28.8. LR-MS calcd. for $C_{20}H_{25}N_2O_4$ $[M+H]^+$ 357.2, found 356.7.



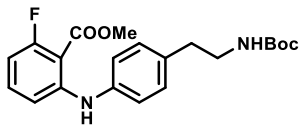
2-((4-(2-((*tert*-Butoxycarbonyl)amino)ethyl)phenyl)amino)-5-fluorobenzoic acid was prepared from 2-bromo-5-fluorobenzoic acid and *tert*-butyl (4-aminophenethyl)carbamate analogously to 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)benzoic acid upon stirring in ethanol at 120 °C in 56% yield. ^{1}H NMR (400 MHz, methanol-d_4) δ 7.63 (dd, J = 9.6, 3.1 Hz, 1H), 7.22 – 7.15 (m, 3H), 7.15 – 7.08 (m, 3H), 3.26 (t, J = 7.2 Hz, 5H), 2.74 (t, J = 7.2 Hz, 2H), 1.45 – 1.40 (m, 9H). ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 170.7, 158.5, 156.7, 154.4, 146.3, 140.6, 136.0, 130.9, 123.3, 122.6, 122.3, 118.2, 117.9, 116.6, 116.6, 113.9, 113.8, 80.0, 43.1, 36.6, 28.8. LR-MS calcd. for $C_{20}H_{24}FN_2O_4$ [M+H]$^+$ 375.2, found 374.6.



2-((4-(2-((*tert*-Butoxycarbonyl)amino)ethyl)phenyl)amino)-6-fluorobenzoic acid was prepared from 2-bromo-6-fluorobenzoic acid and *tert*-butyl (4-aminophenethyl)carbamate analogously to 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)benzoic acid upon stirring at 140 °C for 48 h. The crude product was purified by sequential column chromatography: 1st column (isocratic chloroform + 5% MeOH) and 2nd column (isocratic 1:1 EtOAc/*n*-hexane) and crystalized from EtOAc/*n*-hexane. The pure product was obtained as a red oil in 67% yield (500 mg). ^{1}H NMR (400 MHz, methanol-d_4) δ 7.25 – 7.18 (m, 3H), 7.13 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.6 Hz, 1H), 6.46 (ddd, J = 11.2, 8.1, 1.0 Hz, 1H), 3.26 (t, J = 7.3 Hz, 2H), 2.74 (t, J = 7.3 Hz, 2H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, methanol-d_4) δ 169.8, 169.8, 166.1, 163.5, 158.4, 150.4, 150.3, 140.3, 136.4, 134.7, 134.6, 130.9, 123.8, 110.7, 110.7, 105.8, 105.6, 80.0, 43.0, 36.7, 28.8. ^{19}F NMR (376 MHz, methanol-d_4) δ -106.79 (dd, J = 10.8, 5.9 Hz). LR-MS calcd. for $C_{20}H_{24}FN_2O_4$ [M+H]$^+$ 375.17, found 375.04.

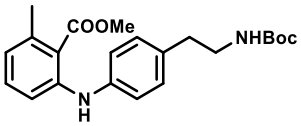


Methyl 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)-6-chlorobenzoate was prepared from methyl 2-amino-6-chlorobenzoate and *tert*-butyl (4-bromophenethyl)carbamate (0.54 mmol) according to the general procedure for Buchwald-Hartwig coupling A in 66% yield (144 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.15 – 7.09 (m, 4H), 7.07 (d, J = 8.4 Hz, 2H), 6.86 (dd, J = 6.9, 2.0 Hz, 1H), 4.55 (br s, 1H), 3.95 (s, 3H), 3.40 – 3.32 (m, 2H), 2.76 (t, J = 7.0 Hz, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.9, 156.0, 146.0, 139.6, 134.0, 133.9, 131.9, 129.9, 121.4, 121.1, 118.2, 114.1, 79.4, 52.5, 42.0, 35.7, 28.6. LR-MS calcd. for $C_{21}H_{26}ClN_2O_4$ [M+H]$^+$ 405.2, found 405.2.

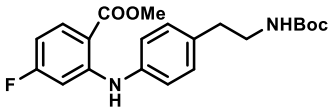


Methyl 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)-6-fluorobenzoate was prepared from methyl 2-amino-6-fluorobenzoate and *tert*-butyl (4-bromophenethyl)carbamate (2.7 mmol) according to the general procedure for Buchwald-Hartwig coupling B (optimized conditions) in 71% yield (745 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.21 – 7.13 (m, 5H), 6.93 (d, J = 8.5 Hz, 1H), 6.45 (dd, J = 11.2, 8.1 Hz, 1H), 4.57 (br s, 1H), 3.93 (s, 3H), 3.44 – 3.30 (m, 2H), 2.78 (t, J = 7.1 Hz, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.9, 167.8, 164.5, 162.4, 156.0, 149.1, 149.1, 139.0,

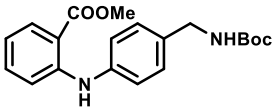
134.9, 133.9, 133.8, 129.9, 123.1, 109.9, 109.9, 105.2, 105.0, 103.2, 103.1, 79.4, 52.3, 42.0, 35.8, 28.6. LR-MS calcd. for $C_{21}H_{26}FN_2O_4$ $[M+H]^+$ 389.2, found 389.2.



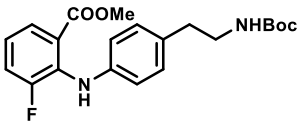
Methyl 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)-6-methylbenzoate was prepared from methyl 2-amino-6-methyl benzoate and *tert*-butyl (4-bromophenethyl)carbamate (0.69 mmol) according to the general procedure for Buchwald-Hartwig coupling A in 23% yield (61 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.16 – 7.06 (m, 6H), 6.67 (dd, J = 7.0, 0.8 Hz, 1H), 4.56 (br s, 1H), 3.91 (s, 3H), 3.40 – 3.32 (m, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.44 (s, 3H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.0, 156.0, 145.5, 140.4, 139.8, 133.1, 131.7, 129.8, 122.1, 121.1, 117.6, 113.7, 79.3, 51.8, 42.0, 35.7, 28.6, 22.7. LR-MS calcd. for $C_{22}H_{29}N_2O_4$ $[M+H]^+$ 385.2, found 385.2.



Methyl 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)-4-fluorobenzoate was prepared from methyl 2-amino-4-fluorobenzoate and *tert*-butyl (4-bromophenethyl)carbamate (0.94 mmol) according to the general procedure for Buchwald-Hartwig coupling A in 42% yield (153 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.96 (dd, J = 9.0, 6.7 Hz, 1H), 7.22 – 7.14 (m, 4H), 6.79 (dd, J = 12.1, 2.5 Hz, 1H), 6.39 (ddd, J = 9.0, 7.8, 2.5 Hz, 1H), 4.56 (br s, 1H), 3.89 (s, 3H), 3.43 – 3.35 (m, 2H), 2.80 (t, J = 7.0 Hz, 2H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 168.2, 165.7, 156.0, 150.9, 150.8, 138.4, 135.5, 134.4, 134.3, 130.0, 123.8, 108.0, 108.0, 104.8, 104.6, 100.0, 99.7, 79.4, 51.9, 41.9, 35.9, 28.6. LR-MS calcd. for $C_{21}H_{26}FN_2O_4$ $[M+H]^+$ 389.2, found 389.2.



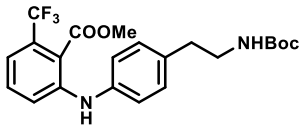
Methyl 2-((4-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)amino)benzoate was prepared from methyl 2-amino benzoate and *tert*-butyl (4-iodobenzyl)carbamate (1.00 mmol) according to the general procedure for Buchwald-Hartwig coupling A in 14% yield (50 mg) and 33% of starting *tert*-butyl (4-iodobenzyl)carbamate was recovered. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.96 (dd, J = 8.0, 1.7 Hz, 1H), 7.33 – 7.18 (m, 6H), 6.73 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 4.85 (br s, 1H), 4.29 (d, J = 5.9 Hz, 2H), 3.90 (s, 3H), 1.48 (s, 9H). ^{13}C{^{1}H} NMR[10] (126 MHz, $CDCl_3$) δ 169.0, 156.0, 148.0, 140.1, 134.2, 131.7, 128.7, 122.8, 117.3, 114.1, 112.0, 79.6, 51.9, 44.4, 28.6.



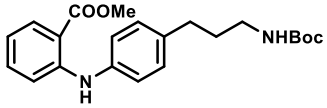
Methyl 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)-3-fluorobenzoate was prepared from methyl 2-amino-3-fluorobenzoate and *tert*-butyl (4-bromophenethyl)carbamate (0.3 mmol) according to the general procedure for Buchwald-Hartwig coupling B (optimized conditions) in 68% yield (79 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 12.1, 8.1 Hz, 1H), 7.08 (d, J = 7.9 Hz, 2H), 6.92 – 6.86 (m, 3H), 4.55 (br s, 1H), 3.89 (s, 3H), 3.42 – 3.29 (m, 2H), 2.74 (t, J = 7.1 Hz, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.3, 168.2, 156.0, 155.3, 153.3,

[10] One carbon signal was not distinguished, probably overlapping with another signal

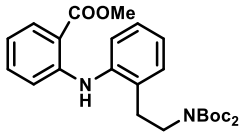
141.3, 141.2, 135.0, 134.9, 132.6, 129.1, 127.0, 127.0, 121.0, 120.8, 119.8, 119.7, 119.2, 119.1, 119.1, 119.0, 79.3, 52.4, 42.0, 35.6, 28.6. LR-MS calcd. for $C_{21}H_{26}FN_2O_4$ $[M+H]^+$ 389.2, found 389.2.



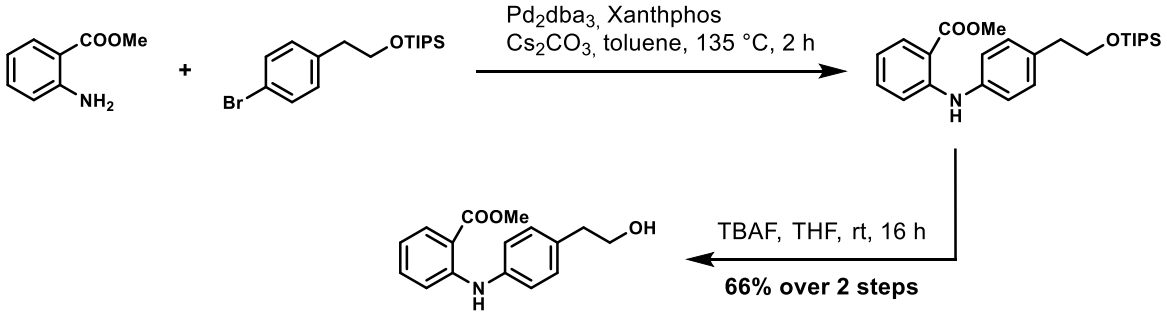
Methyl 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)-6-(trifluoromethyl)benzoate was prepared from methyl 2-amino-6-trifluoromethylbenzoate and *tert*-butyl (4-bromophenethyl)carbamate (1.0 mmol) according to the general procedure for Buchwald-Hartwig coupling B (optimized conditions) in 78% yield (342 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.4 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.18 – 7.13 (m, 3H), 7.07 (d, J = 8.4 Hz, 2H), 4.55 (br s, 1H), 3.93 (s, 3H), 3.42 – 3.30 (m, 2H), 2.77 (t, J = 7.0 Hz, 2H), 1.44 (s, 9H). ^{13}C{^{1}H,^{19}F} NMR (101 MHz, $CDCl_3$) δ 168.2, 156.0, 144.7, 139.4, 134.3, 131.3, 130.3, 130.0, 123.8, 121.4, 119.3, 117.6, 116.9, 52.9, 42.0, 35.8, 28.6. LR-MS calcd. for $C_{22}H_{26}F_3N_2O_4$ $[M+H]^+$ 439.2, found 439.3.



Methyl 2-((4-(3-((*tert*-butoxycarbonyl)amino)propyl)phenyl)amino)benzoate was prepared from methyl 2-aminobenzoate and *tert*-butyl [3-(4-bromophenyl)propyl]carbamate (0.4 mmol) according to the general procedure for Buchwald-Hartwig coupling B (optimized conditions). The compound was obtained in the mixture with impurities and the yield was calculated to ~60%. All obtained material was used in the next step without further purification.

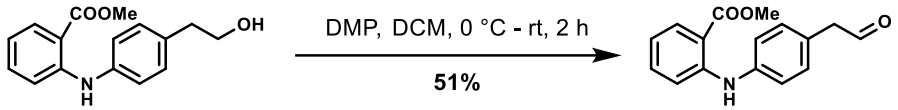


2-(2-(2-Methylcarboxyphenylamino)phenyl)ethyl imidodicarbonic acid, bis(1,1-dimethylethyl) ester was prepared from methyl 2-aminobenzoate and *tert*-butyl (2-bromophenethyl)carbamate (1.0 mmol) according to the general procedure for Buchwald-Hartwig coupling B (optimized conditions) in 62% yield (292 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.95 (dd, J = 8.0, 1.7 Hz, 1H), 7.30 (dd, J = 7.9, 1.3 Hz, 1H), 7.27 – 7.20 (m, 3H), 7.12 (td, J = 7.4, 1.4 Hz, 1H), 6.81 (dd, J = 8.5, 1.1 Hz, 1H), 6.67 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 3.90 (s, 3H), 3.85 (t, J = 7.2 Hz, 2H), 2.90 (t, J = 7.2 Hz, 2H), 1.40 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.1, 152.4, 149.5, 139.4, 134.7, 134.3, 131.6, 131.3, 127.6, 125.7, 125.4, 116.6, 114.0, 111.5, 82.2, 51.9, 46.5, 31.4, 28.1. LR-MS calcd. for $C_{26}H_{35}N_2O_6$ $[M+H]^+$ 471.2, found 471.3.

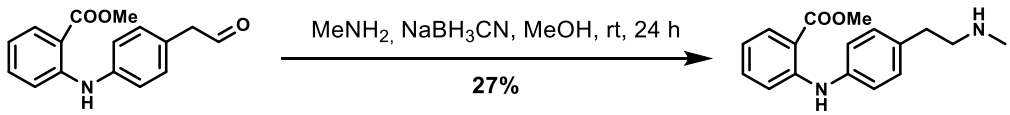


Methyl 2-((4-(2-hydroxyethyl)phenyl)amino)benzoate: Methyl 2-aminobenzoate (36.3 mg, 0.24 mmol), (4-bromophenethoxy)triisopropylsilane (71.5 mg, 0.20 mmol), Pd_2dba_3 (4.6 mg, 2.5 mol%), Xanthphos (8.7 mg, 7.5 mol%) and Cs_2CO_3 (130 mg, 0.40 mmol) were placed in a 4 mL vial and diluted

with toluene (2 mL) was added. The vial was flushed with dry Ar and closed tightly with a screw cap. The reaction mixture was stirred at 135 °C in a thermoblock (temperature was measured and maintained by a thermosensor which was placed in a vial in the thermoblock filled with oil) for 2 hours. For scale-up multiple reactions were run in parallel (in a total scale of 4.05 mmol). The reaction mixture was filtered through a short pad of silica gel and the pad was further eluted with EtOAc. Volatiles were removed in vacuo and the crude product was purified by flash column chromatography (crude material/silica gel, 1/100 (m/m), 2% EtOAc in *n*-hexane) resulting in an inseparable mixture of two compounds. The obtained material was dissolved in THF (32 mL) and TBAF (1 M in THF, 8.5 mL) was added and the solution was further stirred at room temperature for 16 hours. The reaction mixture was diluted with water and DCM. The aqueous phase was extracted further with DCM (2 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and volatiles were removed under reduced pressure. Obtained crude material was purified by flash column chromatography (crude material/silica gel, 1/100 (m/m), *n*-hexane/EtOAc = 5/1 → 5/2 → 5/3, (v/v)). The pure product was obtained as a colorless solid in 66% yield (730 mg) over two steps. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.96 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.30 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 1H), 7.23 – 7.18 (m, 5H), 6.72 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 3.90 (s, 3H), 3.87 (t, *J* = 6.6 Hz, 2H), 2.86 (t, *J* = 6.5 Hz, 2H), 1.49 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.1, 148.3, 139.3, 134.2, 133.9, 131.7, 130.1, 123.1, 117.1, 114.0, 111.8, 63.8, 51.9, 38.8. LR-MS calcd. for $C_{16}H_{18}NO_3$ $[M+H]^+$ 272.1, found 272.1.

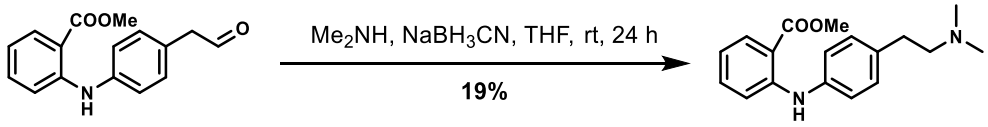


Methyl 2-((4-(2-oxoethyl)phenyl)amino)benzoate: To a solution of methyl 2-((4-(2-hydroxyethyl)phenyl)amino)benzoate (730 mg, 2.69 mmol) in dry DCM (13.5 mL) under dry Ar at 0 °C was added Dess-Martin periodinane (1.7 g, 4.04 mmol) and the reaction mixture was stirred 5 minutes at 0 °C and then 2 hours at room temperature. $Na_2S_2O_3$ (aq, satd.) was added and the reaction mixture was stirred for another 10 minutes. The reaction mixture was diluted with H_2O and DCM and the aqueous phase was further extracted with DCM (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and volatiles were removed under reduced pressure. Obtained crude product was purified by flash column chromatography (crude material/silica gel = 1/100 (m/m), *n*-hexane/EtOAc = 9/1 → 8/1, (v/v)). The pure product was obtained as a yellow oil in 51% yield (370 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, *J* = 2.4 Hz, 1H), 9.50 (s, 1H), 7.99 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.34 (ddd, *J* = 8.6, 7.0, 1.7 Hz, 1H), 7.30 – 7.25 (m, 3H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.77 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 3.93 (s, 3H), 3.70 (d, *J* = 2.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 199.5, 169.0, 147.7, 140.3, 134.2, 131.8, 130.7, 126.7, 122.8, 117.5, 114.2, 112.2, 51.9, 50.1. LR-MS calcd. for $C_{16}H_{16}NO_3$ $[M+H]^+$ 270.1, found 270.1.



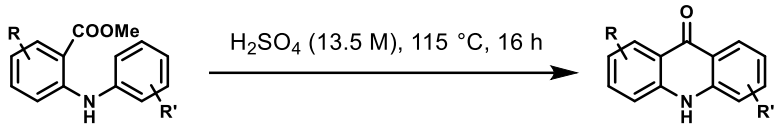
Methyl 2-((4-(2-(methylamino)ethyl)phenyl)amino)benzoate: Methylamine (2 M in MeOH, 1.05 mL, 2.1 mmol) and $NaBH_3CN$ (132 mg, 2.1 mmol) were sequentially added to a solution of methyl 2-((4-(2-oxoethyl)phenyl)amino)benzoate (189 mg, 0.70 mmol) in MeOH (2.46 mL) and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated in vacuo and the residue was portioned between H_2O and DCM and the aqueous phase was further extracted with DCM (2 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and volatiles were removed under reduced pressure. The obtained crude material was purified by flash column chromatography (crude material/silica gel, 1/100 (m/m), DCM/MeOH/NH_4OH = 90/10/1, (v/v)). The pure product was obtained as a yellowish oil in 27% yield (54 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s,

1H), 7.95 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.29 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 1H), 7.22 – 7.16 (m, 5H), 6.70 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 3.90 (s, 3H), 2.88 – 2.83 (m, 2H), 2.82 – 2.77 (m, 2H), 2.46 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ* 169.1, 148.4, 138.9, 135.6, 134.2, 131.7, 129.7, 123.1, 116.9, 114.0, 111.7, 53.4, 51.9, 36.5, 35.7. LR-MS calcd. for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ 285.2, found 285.0.



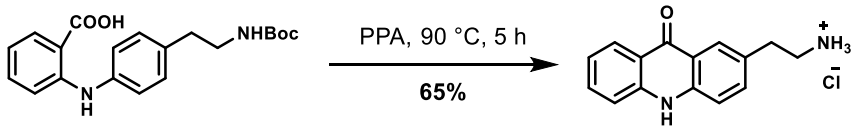
Methyl 2-((4-(2-(dimethylamino)ethyl)phenyl)amino)benzoate: Dimethylamine (2 M in THF, 0.92 mL, 1.85 mmol) and $NaBH_3CN$ (116 mg, 1.85 mmol) were sequentially added to a solution of the methyl 2-((4-(2-oxoethyl)phenyl)amino)benzoate (166 mg, 0.62 mmol) in THF (2.16 mL) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure and the obtained residue was portioned between H_2O and DCM. The aqueous phase was further extracted with DCM (2 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and volatiles were removed under reduced pressure. The obtained crude material was purified by flash column chromatography (crude material/silica gel, 1/100 (m/m), DCM/MeOH/NH_4OH = 95/5/0.5 (v/v)) to afford the product as yellowish oil in 19% yield (35 mg). ^1H NMR (500 MHz, $CDCl_3$) *δ* 9.40 (s, 1H), 7.95 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.28 (ddd, *J* = 8.7, 7.0, 1.7 Hz, 1H), 7.20 – 7.15 (m, 5H), 6.70 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 3.89 (s, 3H), 2.79 – 2.75 (m, 2H), 2.57 – 2.52 (m, 2H), 2.31 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ* 169.1, 148.5, 138.7, 136.0, 134.2, 131.7, 129.6, 123.2, 116.9, 114.0, 111.6, 61.7, 51.8, 45.6, 33.9. LR-MS calcd. for $C_{18}H_{23}N_2O_2$ $[M+H]^+$ 299.2, found 299.1.

Acridones



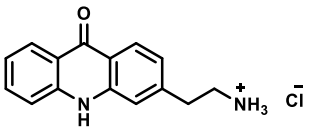
General procedure: preparation of acridone analogs

A solution of the starting substituted methyl 2-(phenylamino)benzoate in 13.5 M H_2SO_4 (0.1 M) was heated at 115 °C (oil bath) for 16 hours. The reaction mixture was cooled down to 0 °C and then was added dropwise to cold 10% NaOH (aq) until all the remaining H_2SO_4 was neutralized. Volatiles were carefully removed under reduced pressure to remove all residual water. The obtained solid was grounded, diluted with DCM/MeOH/NH_4OH (80/20/2 (v/v)) under sonication and the suspension was filtered through a short pad of silica gel. This step was repeated until no fluorescent product spot was visible (TLC). Obtained organic phases were combined and volatiles were removed under reduced pressure to afford the crude product. The obtained material was dissolved in DCM/MeOH/NH_4OH (80/20/2, (v/v)) and adsorbed onto celite. The celite with adsorbed material was transferred to the flash chromatography column and further chromatographed (silica gel/crude product, 100/1 (m/m), DCM/MeOH/NH_4OH, 90/10/1 → 80/20/2, (v/v)). Obtained free amine was transformed into the hydrochloride by dissolving the isolated compound in 1 N HCl (aq; heating and addition of MeOH when necessary) and evaporation of the volatiles (2 ×).



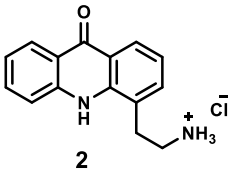
FFN54

2-(2-Aminoethyl)acridin-9(10*H*)-one hydrochloride (FFN54): A 20 mL vial was charged with 2-((4-(2-((*tert*-butoxycarbonyl)amino)ethyl)phenyl)amino)benzoic acid (50 mg, 0.14 mmol) and polyphosphoric acid (PPA, 1.3 g, 3.85 mmol). The mixture was heated to 90 °C for 5 hours, allowed to cool to room temperature and diluted with water/ice. The mixture was further basified with NaOH (aq, 15 wt%) and extracted with 3 x 10 mL DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to yield a bright yellow solid. The obtained solid was dissolved in methanol (2-3 mL), and purified by RP-HPLC using a linear gradient of water/methanol with 0.1% (v/v) FA/H_2O. The fractions containing the desired product were collected and concentrated on vacuum. The solid was re-dissolved in a small amount of water and treated with 5 mL HCl (2.0 M in MeOH), concentrated again, and lyophilized to give the hydrochloride as a white solid in 65% yield (25 mg). Column chromatography (RP-C18 silica, water/dioxane, 1:20, (v/v)) was used as an alternative purification method for scaled-up batches. ^{1}H NMR (400 MHz, D_2O) δ 7.56 (dd, J = 8.2, 1.4 Hz, 1H), 7.37 (ddt, J = 8.0, 6.8, 1.1 Hz, 1H), 7.28 (s, 1H), 7.01 (dd, J = 8.6, 2.0 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 3.13 (t, J = 7.8 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 177.5, 139.5, 138.4, 134.1, 133.7, 129.4, 124.8, 123.9, 121.7, 118.6, 118.3, 117.4, 116.8, 40.2, 32.2. LR-MS calcd. for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.11, found 239.09.



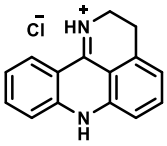
1

3-(2-Aminoethyl)acridin-9(10*H*)-one hydrochloride (1) was prepared from methyl 2-((3-(2-aminoethyl)phenyl)amino)benzoate analogously to **FFN54** in 43% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.23 – 8.17 (m, 2H), 8.02 (br s, 3H), 7.72 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H), 7.59 (dd, J = 8.6, 1.2 Hz, 1H), 7.41 (d, J = 1.5 Hz, 1H), 7.25 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.17 (dd, J = 8.3, 1.6 Hz, 1H), 3.16 – 3.10 (m, 2H), 3.06 – 3.02 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 176.5, 143.2, 141.1, 140.9, 133.4, 126.5, 126.0, 121.9, 121.0, 120.5, 119.4, 117.4, 116.9, 40.0, 39.5, 33.2.LR-MS calcd. for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1, found 238.8.



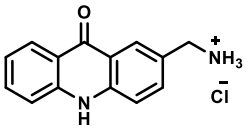
2

4-(2-Aminoethyl)-acridin-9(10*H*)-one hydrochloride (2) was prepared from methyl 2-((2-(2-aminoethyl)phenyl)amino)benzoate (0.56 mmol) according to the general procedure in 48% yield (74 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.25 – 8.13 (m, 5H), 7.73 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H), 7.65 (dd, J = 7.2, 1.6 Hz, 1H), 7.28 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H), 7.23 (dd, J = 8.1, 7.1 Hz, 1H), 3.44 (t, J = 7.9 Hz, 2H), 3.15 – 3.07 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 177.0, 141.3, 139.2, 134.8, 133.2, 125.6, 125.3, 124.6, 121.4, 121.2, 120.8, 120.2, 118.3, 38.7, 28.7. LR-MS calcd. for $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1, found 239.1.



3

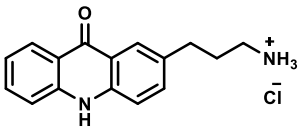
2,7-Dihydro-3*H*-pyrido[4,3,2-*kl*]acridine hydrochloride (3) was obtained as a side-product during the preparation of **1** in 26% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.75 (s, 1H), 11.02 (s, 1H), 8.64 (d, J = 8.6 Hz, 1H), 7.98 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.94 – 7.89 (m, 2H), 7.74 (d, J = 8.5 Hz, 1H), 7.56 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.31 (dd, J = 7.1, 1.1 Hz, 1H), 3.88 (td, J = 7.2, 2.3 Hz, 2H), 3.28 (t, J = 7.2 Hz, 2H).^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 154.5, 139.0, 138.9, 135.8, 135.2, 135.1, 124.3, 123.7, 121.0, 118.7, 115.8, 111.1, 109.3, 39.9, 25.5. LR-MS calcd. for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1, found 220.9.



4

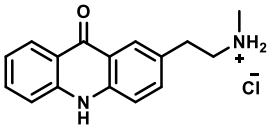
2-(Aminomethyl)-acridin-9(10*H*)-one hydrochloride (4) was prepared from methyl 2-((4-(aminomethyl)phenyl)amino)benzoate (0.14 mmol) according to the general procedure for the preparation of acridone analogs in 95% yield (35 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.43 – 8.29 (m, 4H), 8.24 (dd, J = 8.2, 1.5 Hz, 1H), 7.83 (dd, J = 8.6, 2.2 Hz, 1H), 7.75 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.27 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 4.14 (q, J = 5.8 Hz, 2H). ^{13}C{^{1}H} NMR

(126 MHz, DMSO-d_6) δ 176.6, 140.9, 140.8, 134.3, 133.6, 126.8, 126.5, 126.0, 121.3, 120.5, 120.1, 117.7, 117.5, 42.0. LR-MS calcd. for $C_{14}H_{13}N_2O$ $[M+H]^+$ 225.1, found 225.0.



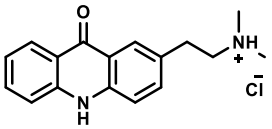
5

2-(3-Aminopropyl)-acridin-9(10*H*)-one hydrochloride (5) was prepared from methyl 2-((4-(3-aminopropyl)phenyl)amino)benzoate (0.23 mmol) according to the general procedure for the preparation of acridone analogs in 74% yield (49 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 8.10 – 7.94 (m, 4H), 7.71 (td, J = 7.6, 6.8, 1.5 Hz, 1H), 7.63 – 7.54 (m, 3H), 7.23 (t, J = 7.5 Hz, 1H), 2.84 – 2.75 (m, 4H), 1.92 (p, J = 7.6 Hz, 2H). ^{13}C{^{1}H} NMR[11] (126 MHz, DMSO-d_6) δ 176.6, 140.8, 139.4, 134.1, 133.5, 133.2, 125.9, 124.6, 120.8, 120.3, 117.6, 117.3, 38.3, 31.3, 28.8. LR-MS calcd. for $C_{16}H_{17}N_2O$ $[M+H]^+$ 253.1, found 253.1.



6

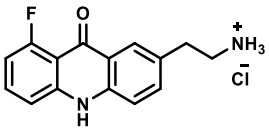
2-(2-(Methylamino)ethyl)acridin-9(10*H*)-one hydrochloride (6) was prepared from methyl 2-((4-(2-(methylamino)ethyl)phenyl)amino)benzoate (0.19 mmol) according to the general procedure for the preparation of acridone analogs in 60% yield (33 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.94 (br s, 2H), 8.15 (d, J = 8.0 Hz, 1H), 8.03 (s, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.57 (dd, J = 8.6, 2.1 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.17 (t, J = 7.5 Hz, 1H), 3.14 – 3.07 (m, 2H), 3.03 – 2.98 (m, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 176.6, 140.9, 139.9, 134.2, 133.3, 129.7, 126.0, 125.4, 120.9, 120.4, 120.4, 117.9, 117.4, 49.2, 32.4, 31.0. LR-MS calcd. for $C_{16}H_{17}N_2O$ $[M+H]^+$ 253.1, found 253.1.



7

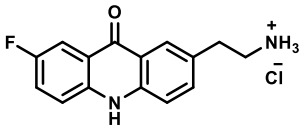
2-(2-(Dimethylamino)ethyl)acridin-9(10*H*)-one hydrochloride (7) was prepared from methyl 2-((4-(2-(dimethylamino)ethyl)phenyl)amino)benzoate (0.12 mmol) according to the general procedure for the preparation of acridone analogs in 69% yield (from 25 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (s, 1H), 10.62 (br s, 1H), 8.23 (dd, J = 8.2, 1.5 Hz, 1H), 8.14 (d, J = 2.0 Hz, 1H), 7.72 (ddd, J = 8.4, 6.9, 1.6 Hz, 1H), 7.65 (dd, J = 8.6, 2.1 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.24 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 3.36 – 3.30 (m, 2H), 3.17 – 3.12 (m, 2H), 2.82 (d, J = 5.0 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 176.5, 140.9, 139.9, 134.2, 133.4, 129.5, 126.0, 125.5, 121.0, 120.4, 120.4, 117.9, 117.4, 57.2, 42.1, 29.3. LR-MS calcd. for $C_{17}H_{19}N_2O$ $[M+H]^+$ 267.1, found 267.1.

[11] One quaternary carbon signal missing, probably overlapping with another signal



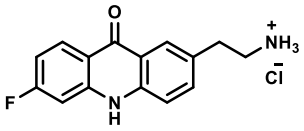
FFN246

7-(2-Aminoethyl)-1-flouroacridin-9(10*H*)-one hydrochloride (FFN246) was prepared from methyl 2-((4-(2-(dimethylamino)ethyl)phenyl)amino)-6-fluorobenzoate (1.89 mmol) analogously to **FFN54** in 8% yield (44 mg) or according to the general procedure for the preparation of acridone analogs in 21% yield (116 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.12 – 8.00 (m, 4H), 7.68 – 7.61 (m, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 6.90 (dd, J = 11.9, 7.9 Hz, 1H), 3.11 – 3.04 (m, 2H), 3.03 – 2.98 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 175.2, 162.5, 160.5, 143.0, 143.0, 139.2, 134.4, 133.8, 133.7, 130.4, 125.4, 121.5, 117.6, 113.3, 113.3, 110.4, 110.3, 106.7, 106.6, 39.9, 32.5. ^{19}F NMR (471 MHz, DMSO-d_6) δ -112.59 (dd, J = 12.2, 5.5 Hz). LR-MS calcd. for $C_{15}H_{14}FN_2O$ $[M+H]^+$ 257.1, found 257.1.



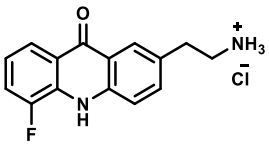
8

2-(2-Aminoethyl)-7-fluoroacridin-9(10*H*)-one hydrochloride (8) was prepared from methyl 2-((4-(2-(dimethylamino)ethyl)phenyl)amino)-5-fluorobenzoate analogously to **FFN54**. After basification of the reaction mixture the product precipitated and was isolated. Obtained precipitate was washed with H_2O and then with MeOH. Obtained pure free base was converted into the HCl salt. And the pure product was obtained in 84% yield. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.09 (s, 1H), 8.01 (br s, 3H), 7.86 (dd, J = 9.3, 2.7 Hz, 1H), 7.70 – 7.62 (m, 3H), 7.61 – 7.56 (m, 1H), 3.14 – 3.06 (m, 2H), 3.05 – 2.97 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO) δ 175.9, 157.8, 155.9, 139.8, 137.7, 134.5, 130.2, 125.4, 122.5, 122.3, 120.9, 120.8, 120.1, 120.1, 119.5, 118.0, 109.7, 109.5, 39.9, 32.6. ^{19}F NMR (471 MHz, DMSO-d_6) δ -120.78 (q, J = 7.3 Hz). LR-MS calcd. for $C_{15}H_{14}FN_2O$ $[M+H]^+$ 257.1, found 256.9.



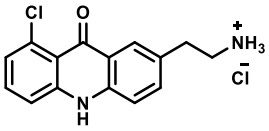
9

2-(2-Aminoethyl)-6-fluoroacridin-9(10*H*)-one hydrochloride (9) was prepared from methyl 2-((4-(2-(dimethylamino)ethyl)phenyl)amino)-4-fluorobenzoate (0.39 mmol) according to the general procedure for the preparation of acridone analogs in 57% yield (65 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.28 (dd, J = 9.0, 6.6 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 8.00 (br s, 3H), 7.66 (dd, J = 8.5, 2.1 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.31 (dd, J = 10.5, 2.5 Hz, 1H), 7.09 (td, J = 8.7, 2.4 Hz, 1H), 3.13 – 3.05 (m, 2H), 3.03 – 2.98 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 175.8, 166.0, 164.0, 142.5, 142.3, 140.0, 134.4, 130.4, 129.6, 129.5, 125.6, 120.5, 117.7, 117.6, 110.0, 109.8, 102.3, 102.1, 39.9, 32.5. ^{19}F NMR (471 MHz, DMSO-d_6) δ -105.35 (ddd, J = 10.3, 8.5, 6.9 Hz). LR-MS calcd. for $C_{15}H_{14}FN_2O$ $[M+H]^+$ 257.1, found 257.1.



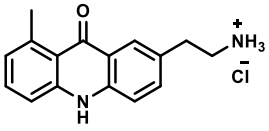
10

2-(2-Aminoethyl)-5-fluoroacridin-9(10*H*)-one hydrochloride (10) was prepared from methyl 2-((4-(2-(dimethylamino)ethyl)phenyl)amino)-3-fluorobenzoate (0.18 mmol) according to the general procedure for the preparation of acridone analogs in 87% yield (46 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.72 (s, 1H), 8.11 (d, J = 2.1 Hz, 1H), 8.05 (dd, J = 8.3, 1.2 Hz, 1H), 8.01 (br s, 3H), 7.82 (d, J = 8.6 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.23 (td, J = 8.0, 4.8 Hz, 1H), 3.14 – 3.06 (m, 2H), 3.05 – 2.98 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 175.9, 152.1, 150.2, 139.7, 134.6, 130.8, 130.3, 130.2, 125.5, 122.4, 122.4, 121.7, 121.7, 120.6, 120.3, 120.2, 118.5, 117.8, 117.6, 39.9, 32.5. ^{19}F NMR (471 MHz, DMSO-d_6) δ –130.84 (dd, J = 11.5, 4.8 Hz). LR-MS calcd. for $C_{15}H_{14}FN_2O$ $[M+H]^+$ 257.1, found 257.1.



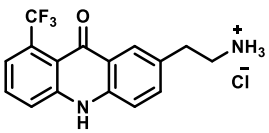
11

7-(2-Aminoethyl)-1-chloroacridin-9(10*H*)-one hydrochloride (11) was prepared from methyl 2-chloro-6-((4-(2-(dimethylamino)ethyl)phenyl)amino)benzoate (0.43 mmol) according to the general procedure for the preparation of acridone analogs in 23% yield (31 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.01 (s, 1H), 8.04 (d, J = 2.0 Hz, 1H), 7.94 (br s, 3H), 7.64 (dd, J = 8.5, 2.1 Hz, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.52 (dd, J = 8.5, 1.5 Hz, 2H), 7.21 (dd, J = 7.5, 1.1 Hz, 1H), 3.12 – 3.07 (m, 2H), 3.02 – 2.97 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 175.7, 143.3, 138.8, 134.4, 133.0, 132.9, 130.3, 125.8, 123.6, 121.6, 117.4, 116.9, 116.4, 39.9, 32.6. LR-MS calcd. for $C_{15}H_{14}ClN_2O$ $[M+H]^+$ 273.1, found 273.1.



12

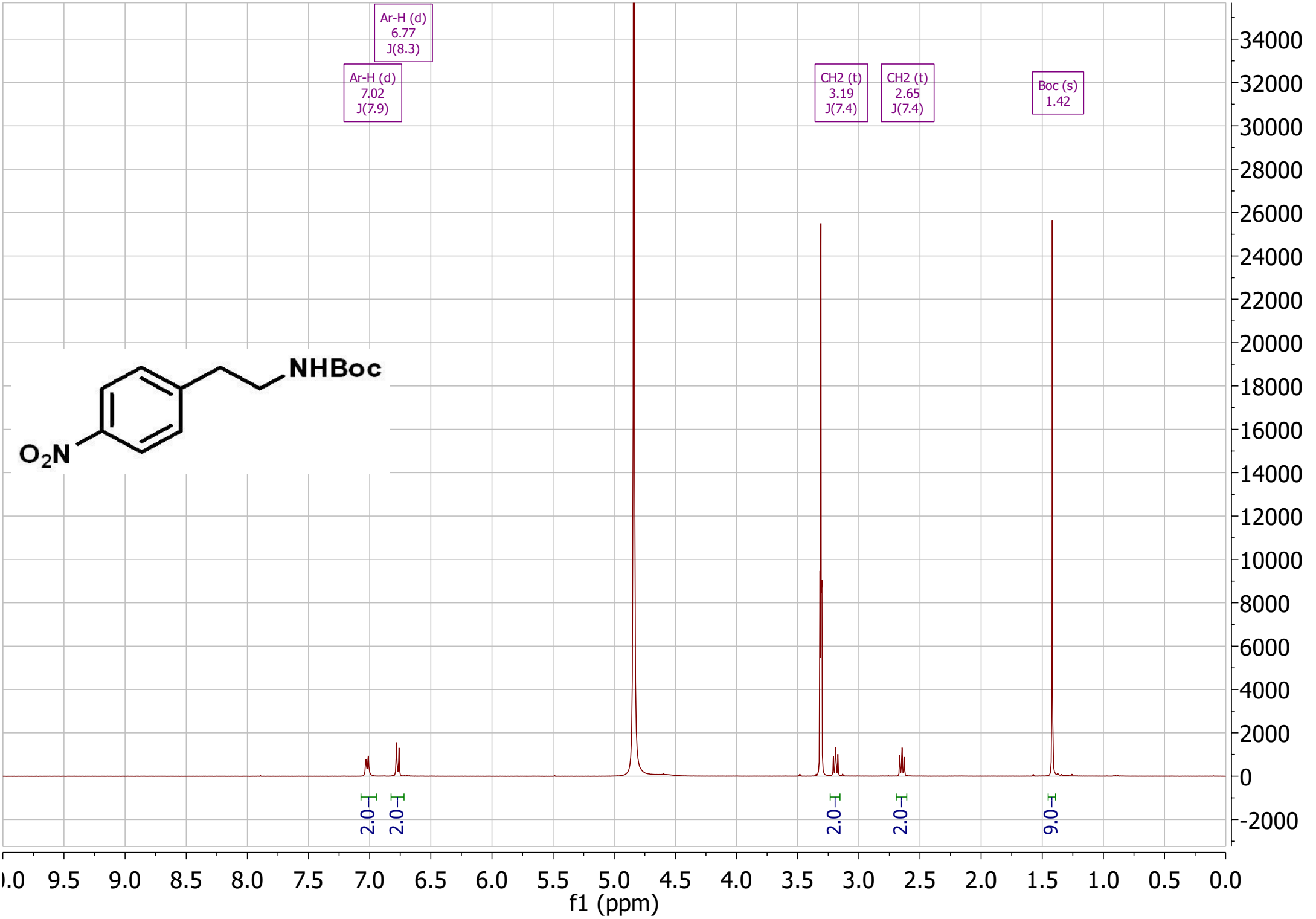
7-(2-Aminoethyl)-1-methylacridin-9(10*H*)-one hydrochloride (12) was prepared from methyl 2-((4-(2-(dimethylamino)ethyl)phenyl)amino)-6-methylbenzoate (0.16 mmol) according to the general procedure for the preparation of acridone analogs in 85% yield (39 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.04 (d, J = 2.1 Hz, 1H), 8.00 (br s, 3H), 7.59 (dd, J = 8.5, 2.1 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.39 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 7.1 Hz, 1H), 3.12 – 3.04 (m, 2H), 3.01 – 2.96 (m, 2H), 2.87 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 178.6, 142.5, 140.4, 139.1, 133.9, 132.4, 129.5, 125.7, 123.5, 121.7, 118.9, 117.2, 115.5, 39.9, 32.6, 23.7. LR-MS calcd. for $C_{16}H_{17}N_2O$ $[M+H]^+$ 253.1, found 253.1.

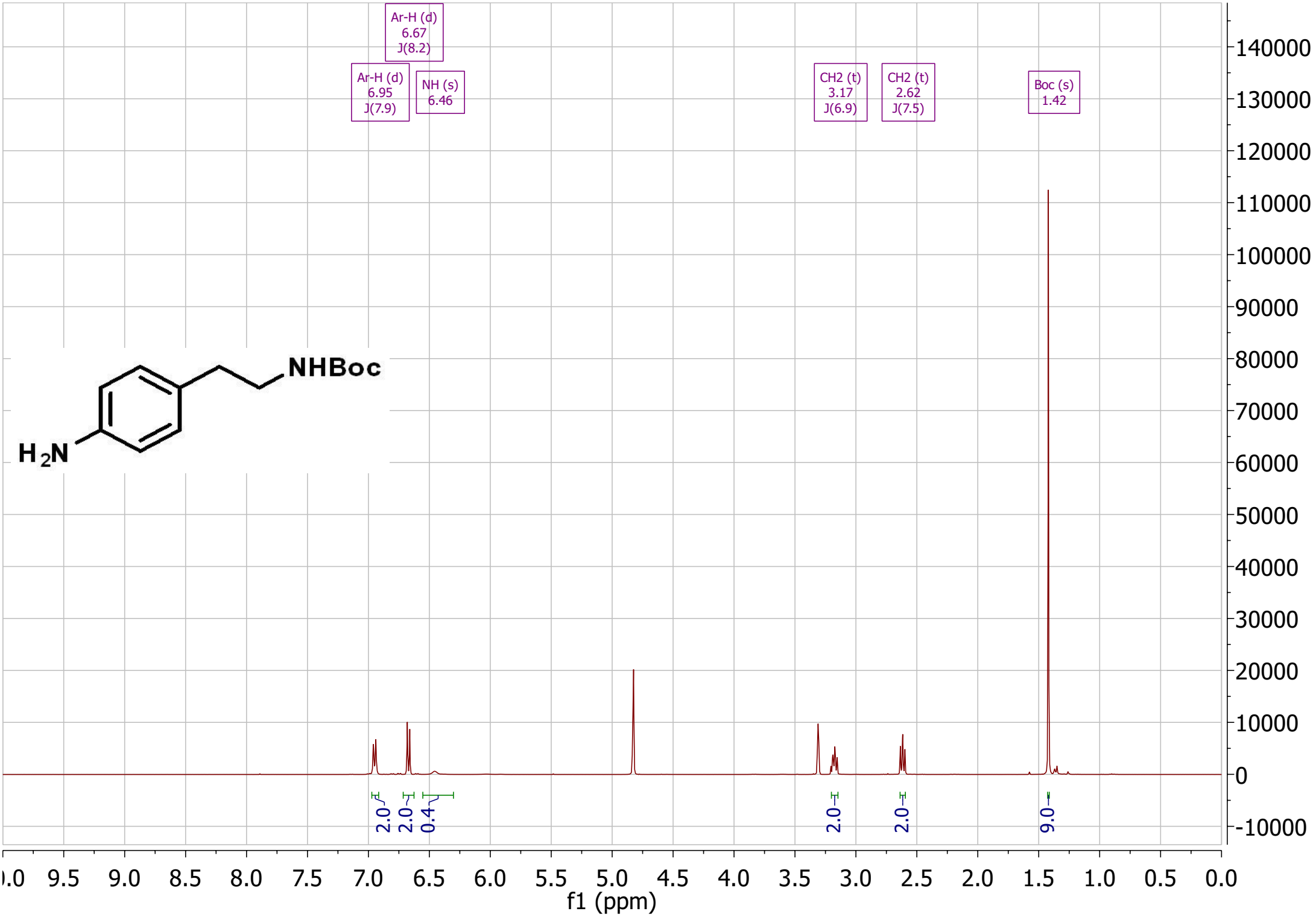


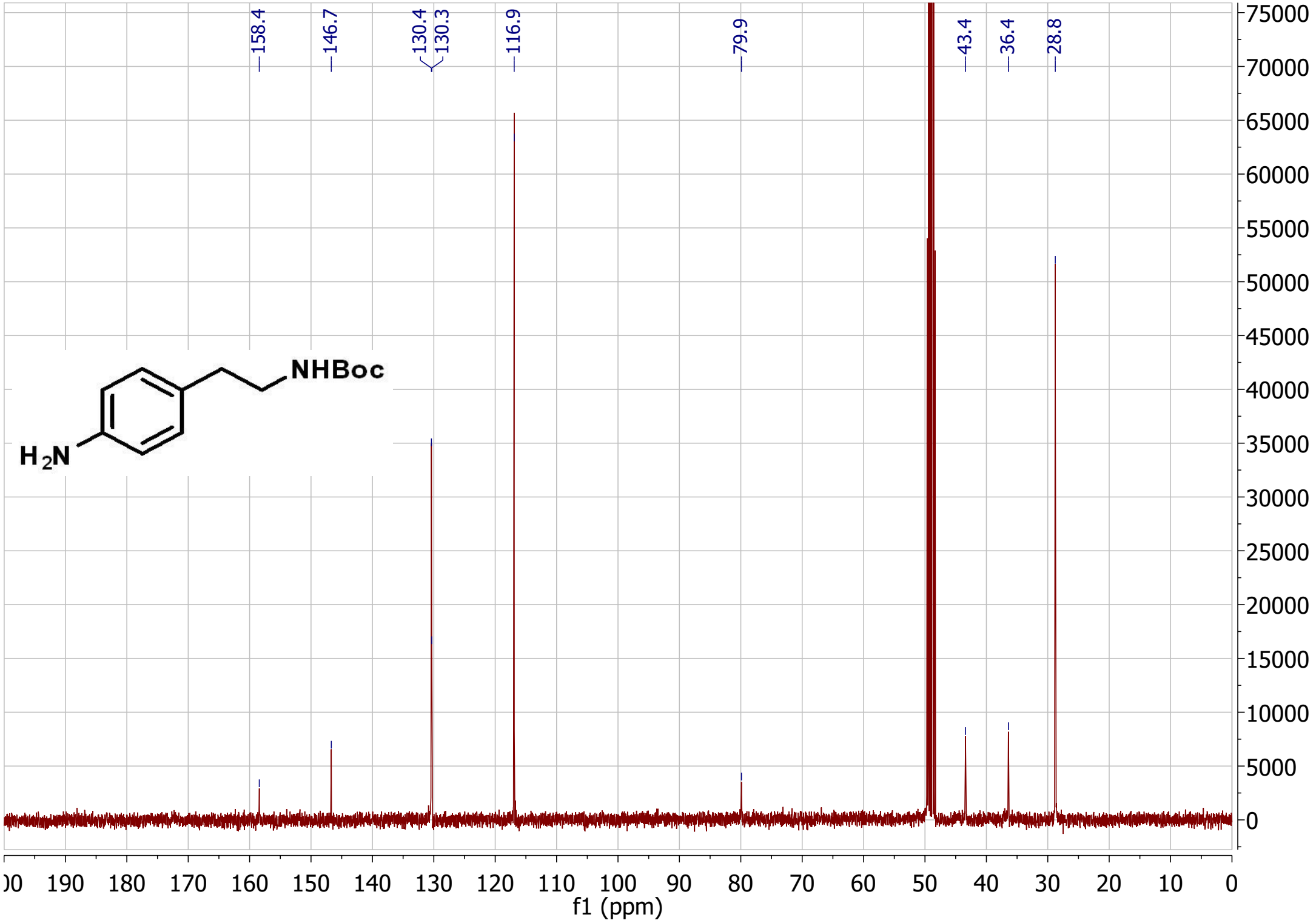
13

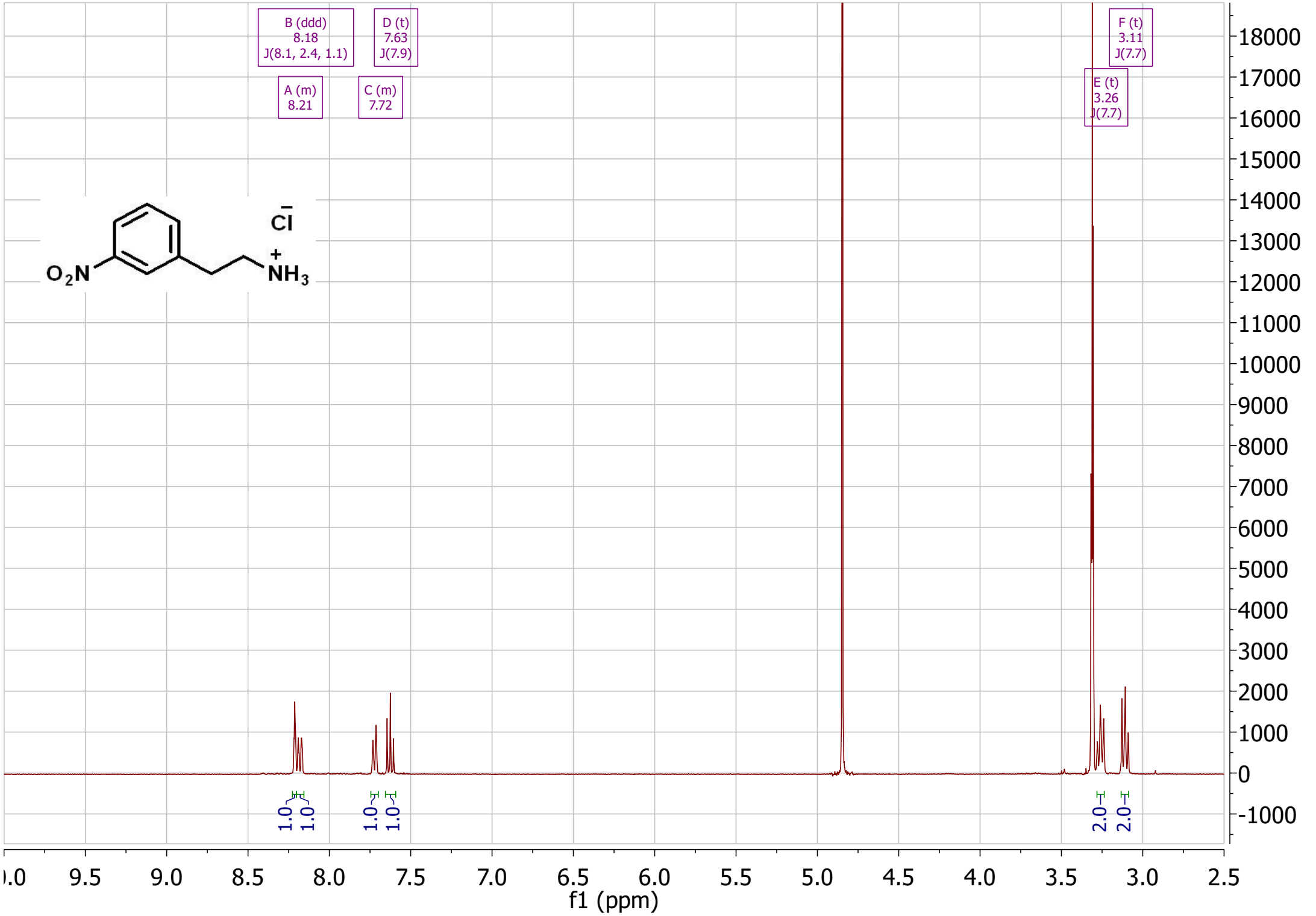
7-(2-Aminoethyl)-1-(trifluoromethyl)acridin-9(10*H*)-one hydrochloride (13) was prepared from methyl 2-((4-(2-(dimethylamino)ethyl)phenyl)amino)-6-(trifluoromethyl)benzoate (0.23 mmol) according to the general procedure for the preparation of acridone analogs in 31% yield (24 mg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.09 (d, J = 1.8 Hz, 1H), 7.99 (br s, 3H), 7.91 (d, J = 8.5 Hz,

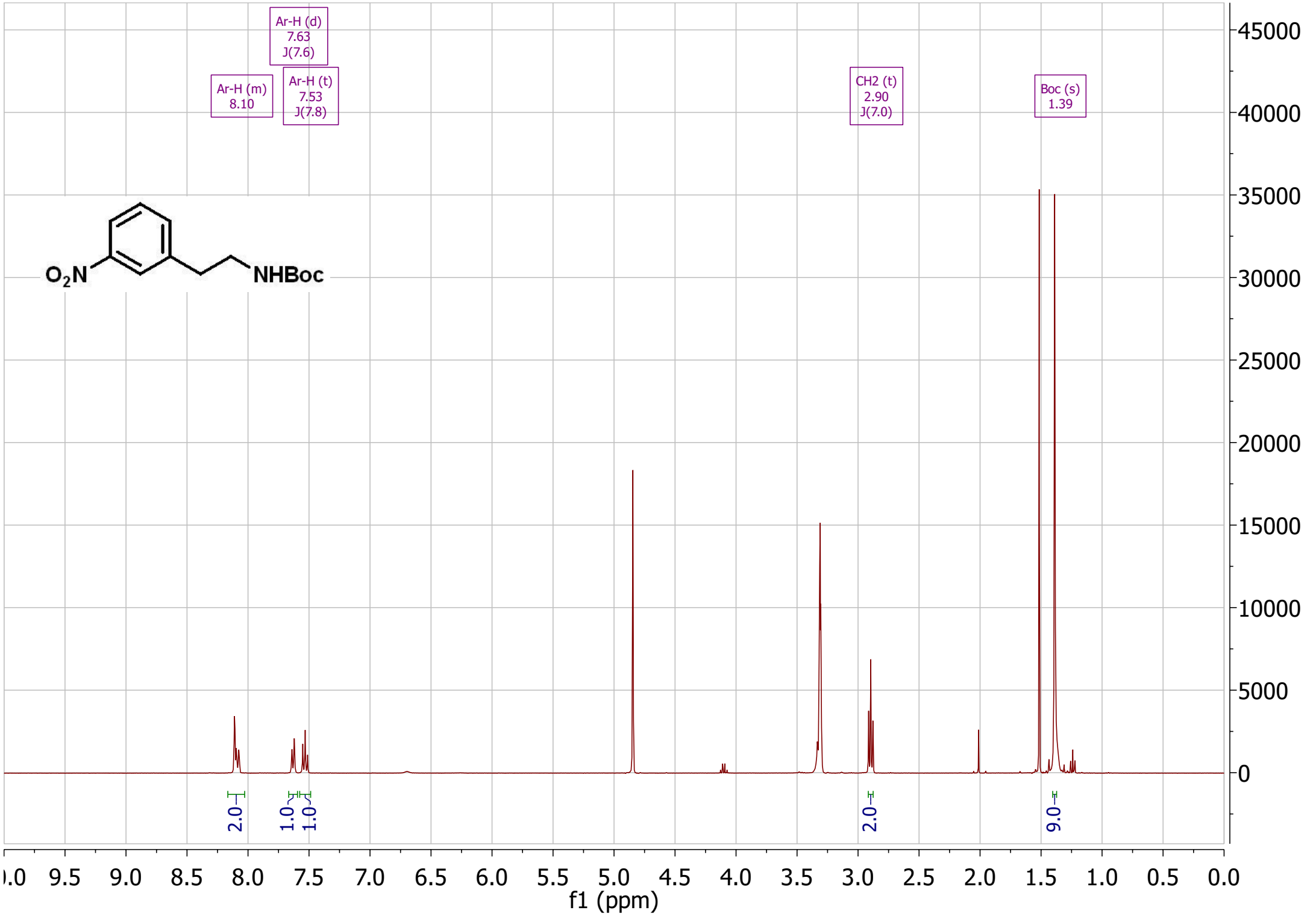
1H), 7.82 (t, *J* = 7.9 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 3.14 – 3.06 (m, 2H), 3.01 (t, *J* = 7.6 Hz, 2H). $^{13}C\{^{1}H,^{19}F\}$ NMR (101 MHz, DMSO-d_6) δ 174.6, 142.8, 138.7, 134.5, 132.1, 130.7, 127.3, 125.7, 123.2, 121.7, 120.7, 117.5, 116.3, 39.9, 32.6. ^{19}F NMR (471 MHz, DMSO-d_6) δ –56.65 (s, 3F). LR-MS calcd. for $C_{16}H_{14}F_3N_2O$ $[M+H]^+$ 307.1, found 307.1.

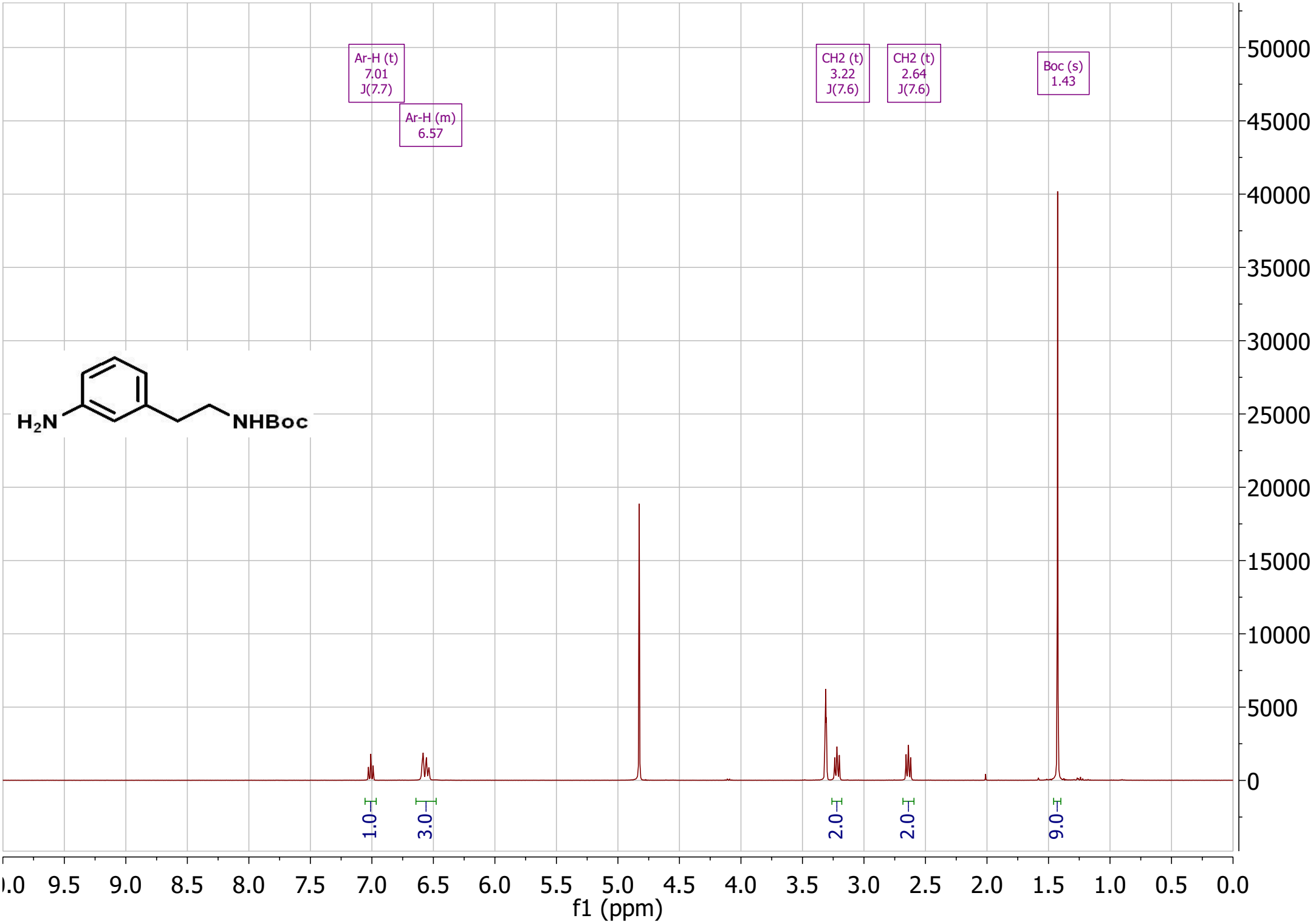

Ar-H (d)
6.77
J(8.3)
Ar-H (d)
7.02
J(7.9)
CH2 (t)
3.19
J(7.4)
CH2 (t)
2.65
J(7.4)
Boc (s)
1.42
NHBoc
O2N
2.0
2.0
2.0
2.0
9.0
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

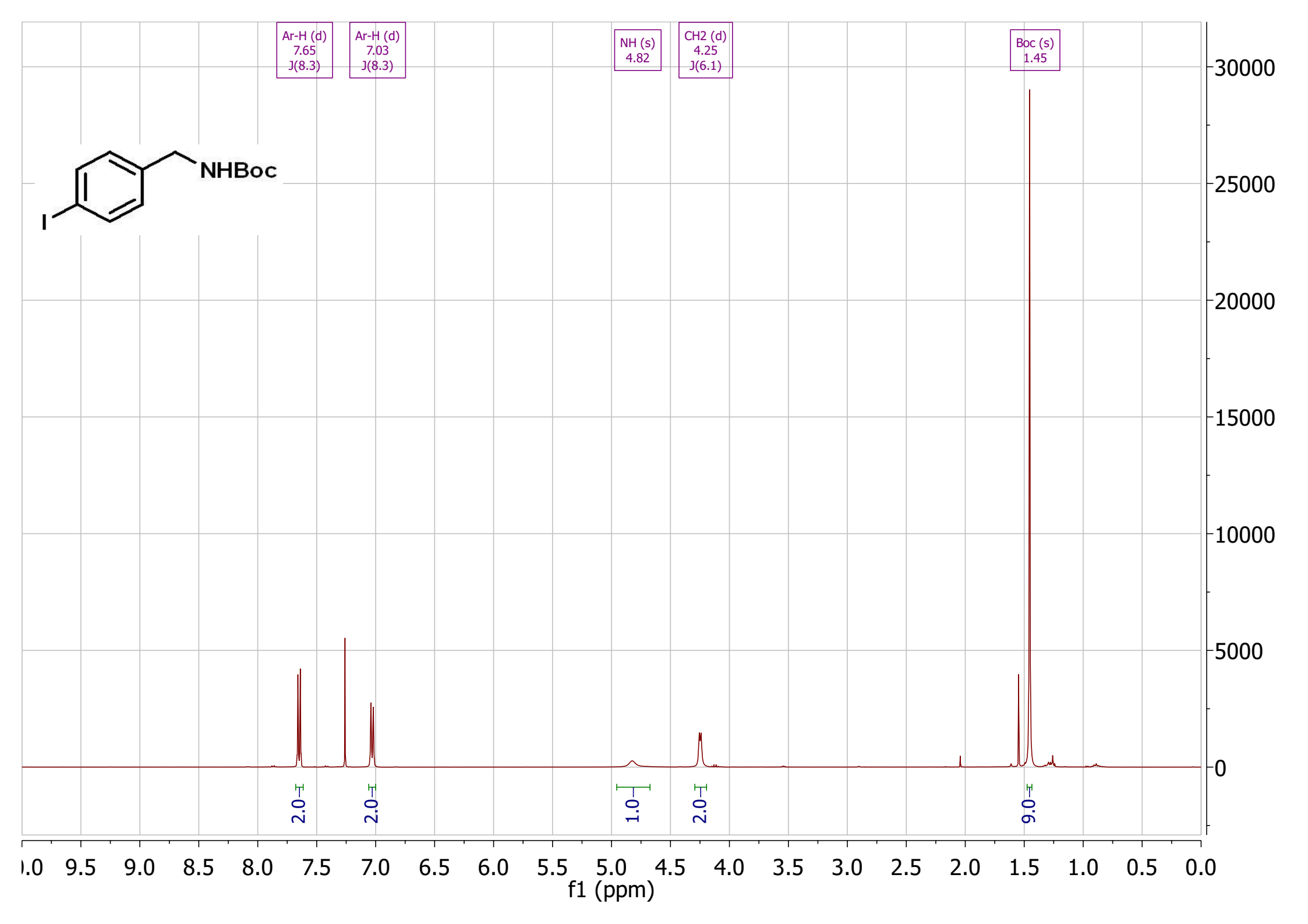

Ar-H (d)
6.67
J(8.2)
Ar-H (d)
6.95
J(7.9)
NH (s)
6.46
CH2 (t)
3.17
J(6.9)
CH2 (t)
2.62
J(7.5)
Boc (s)
1.42
NHBoc
H2N
2.0
2.0
0.4
2.0
2.0
9.0
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

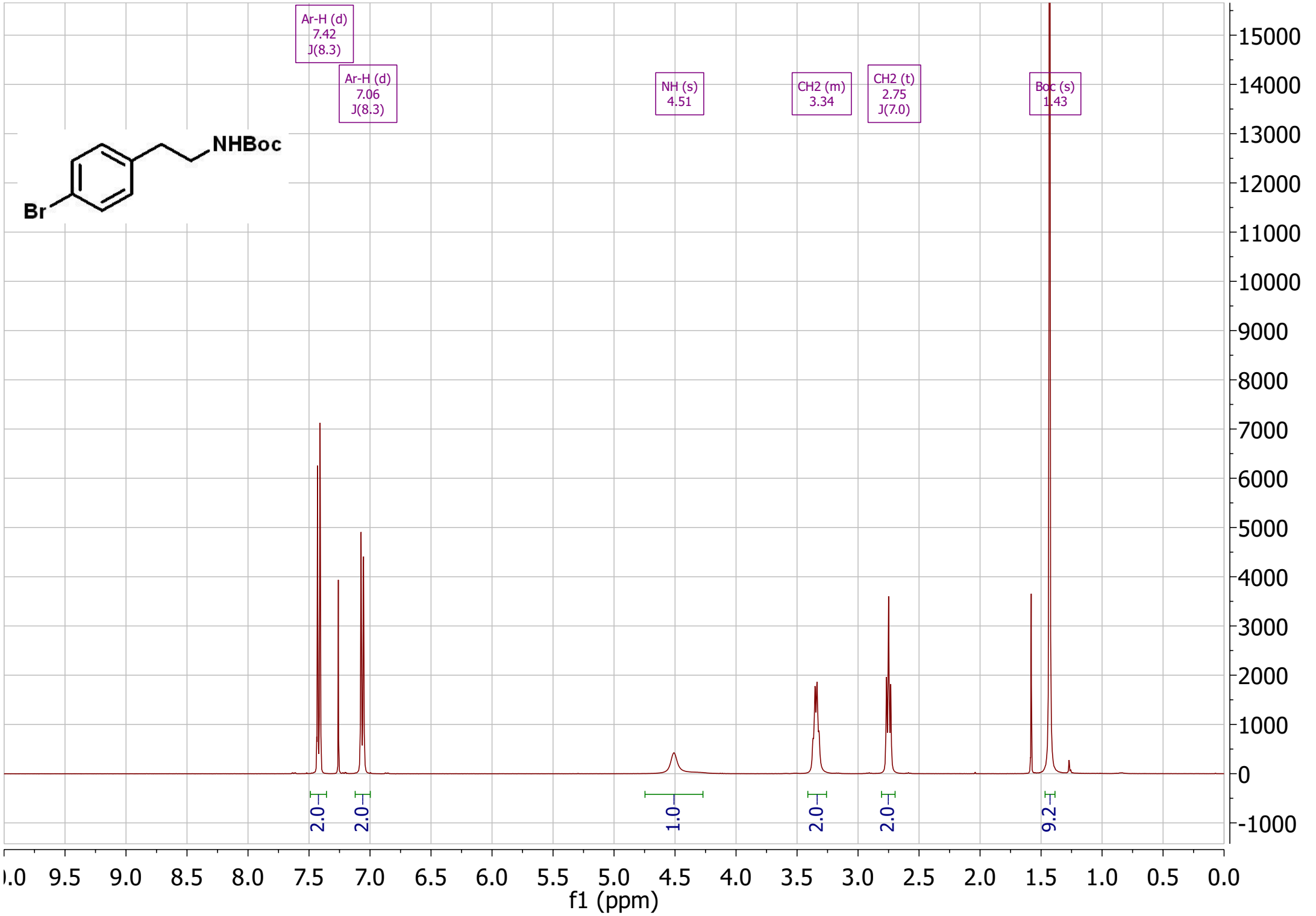

158.4
146.7
130.4
130.3
116.9
79.9
43.4
36.4
28.8
NHBoc
H2N
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

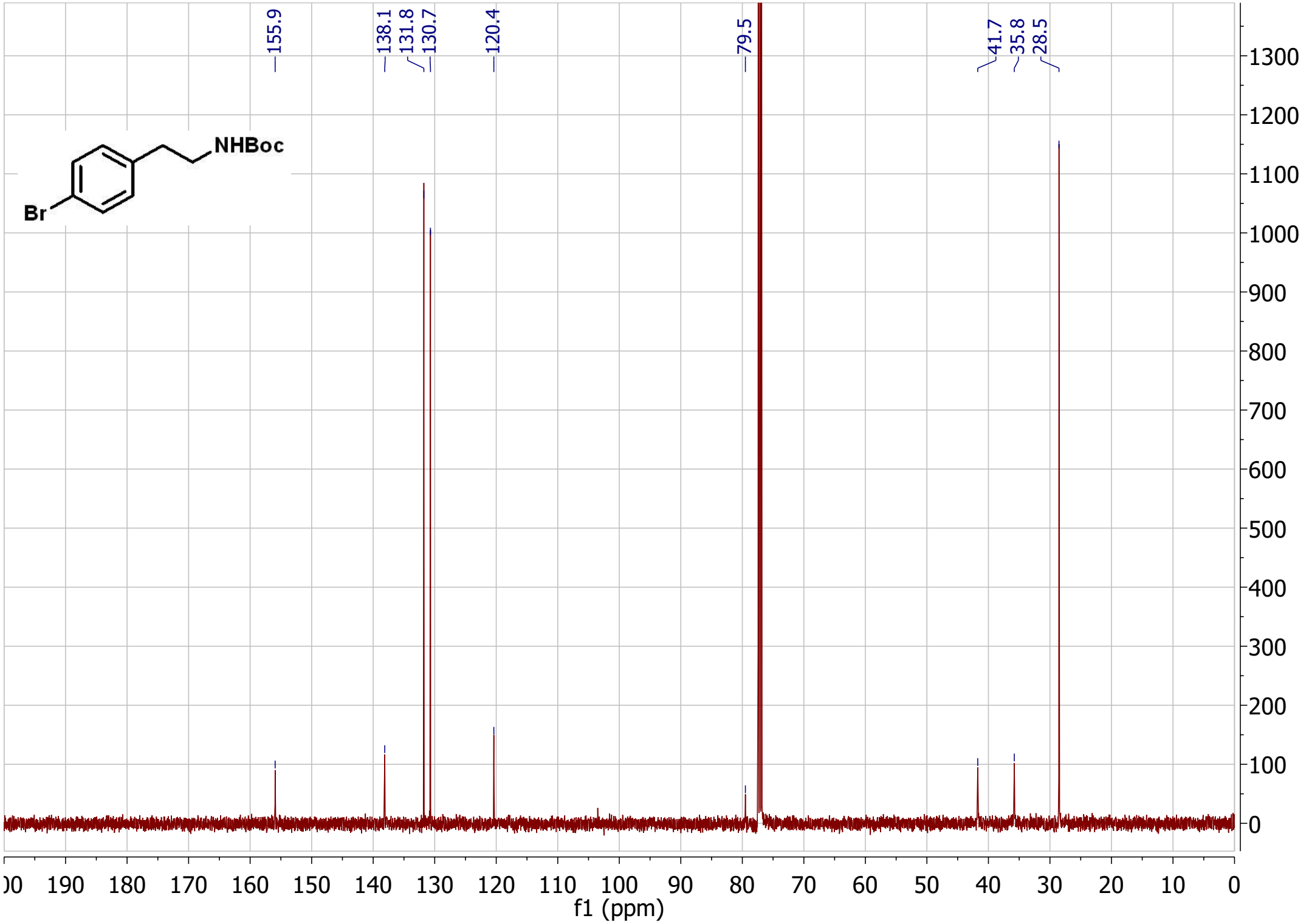

B (ddd)
8.18
J(8.1, 2.4, 1.1)
D (t)
7.63
J(7.9)
A (m)
8.21
C (m)
7.72
F (t)
3.11
J(7.7)
E (t)
3.26
J(7.7)
Cl
+
NH3
O2N
1.0
1.0
1.0
1.0
2.0
2.0
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)

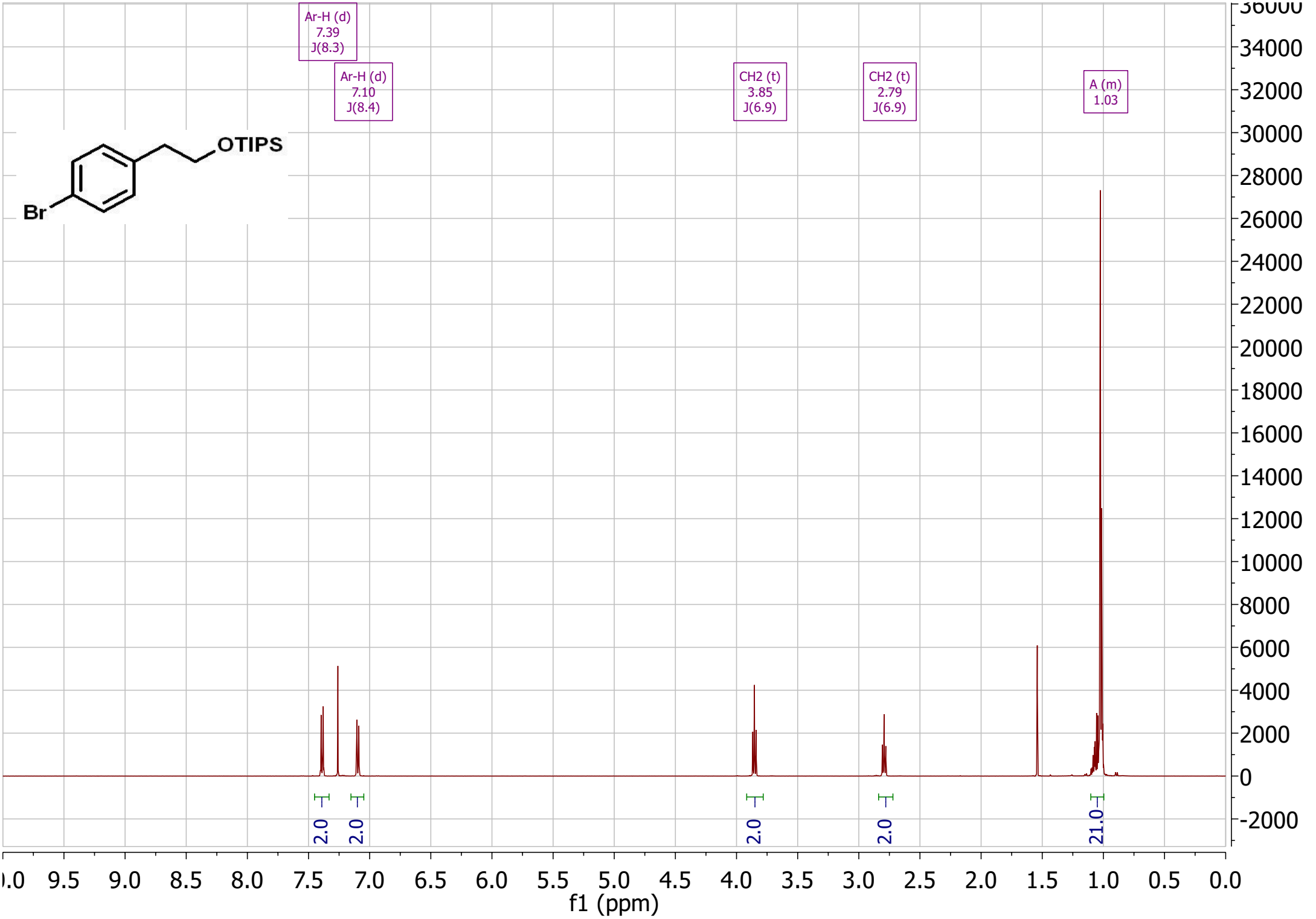

Ar-H (d)
7.63
J(7.6)
Ar-H (m)
8.10
Ar-H (t)
7.53
J(7.8)
CH2 (t)
2.90
J(7.0)
Boc (s)
1.39
O2N
NHBoc
2.0
1.0
1.0
2.0
9.0
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

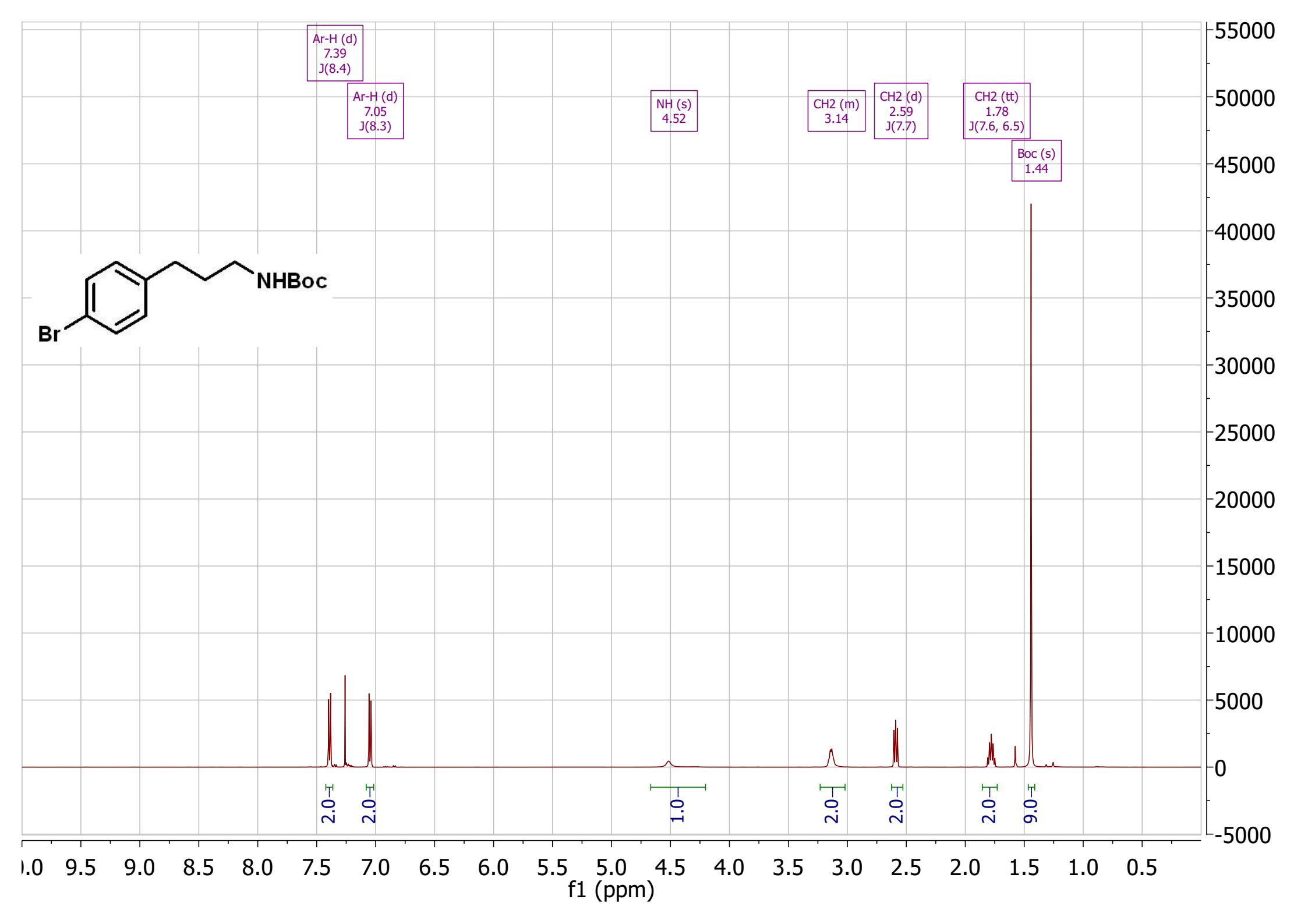

Ar-H (t)
7.01
J(7.7)
Ar-H (m)
6.57
CH2 (t)
3.22
J(7.6)
CH2 (t)
2.64
J(7.6)
Boc (s)
1.43
H2N
NHBoc
1.0
3.0
2.0
2.0
9.0
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

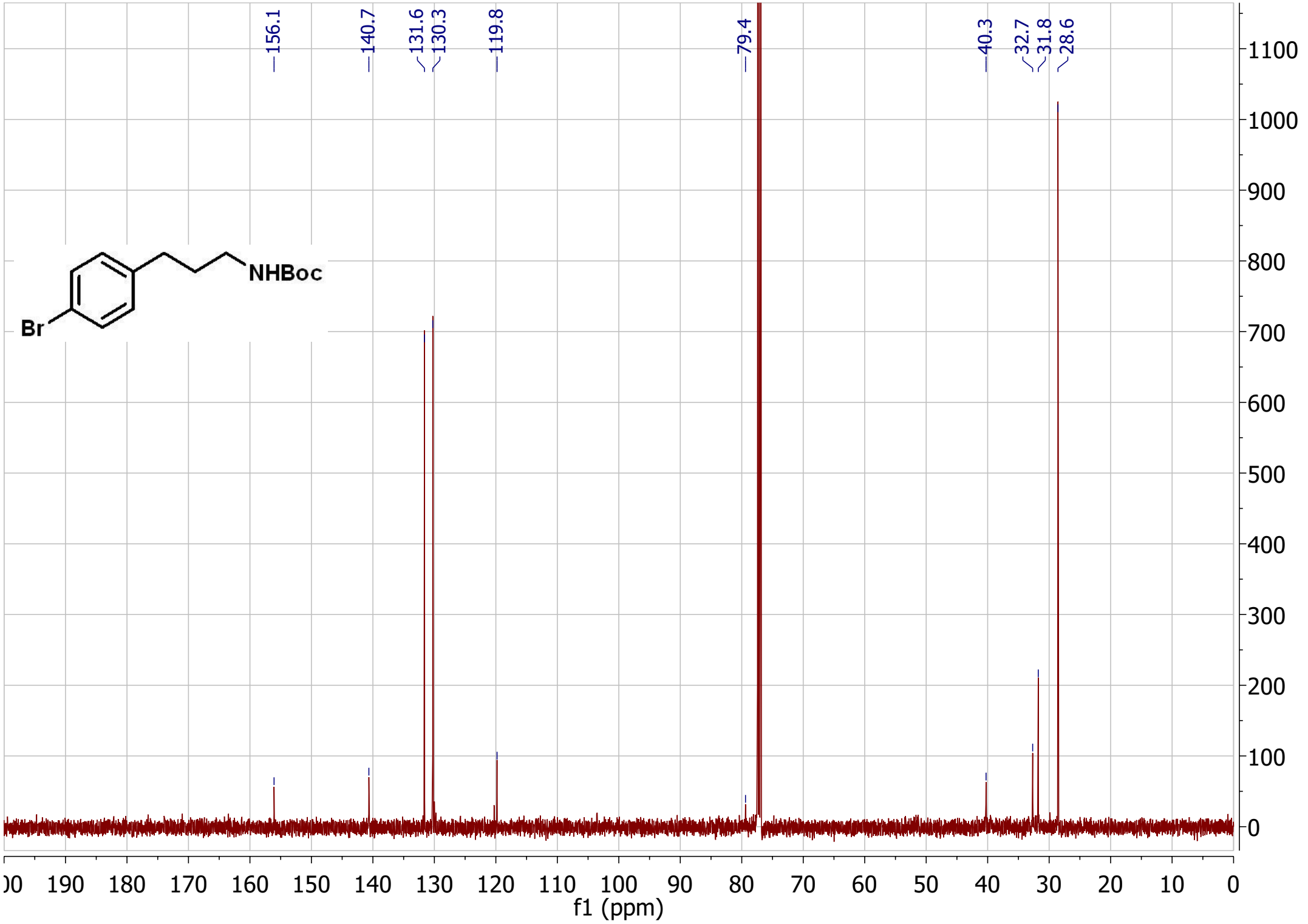

Ar-H (d)
7.65
J(8.3)
Ar-H (d)
7.03
J(8.3)
NH (s)
4.82
CH2 (d)
4.25
J(6.1)
Boc (s)
1.45
NHBoc
I
2.0
2.0
1.0
2.0
9.0
30000
25000
20000
15000
10000
5000
0
f1 (ppm)

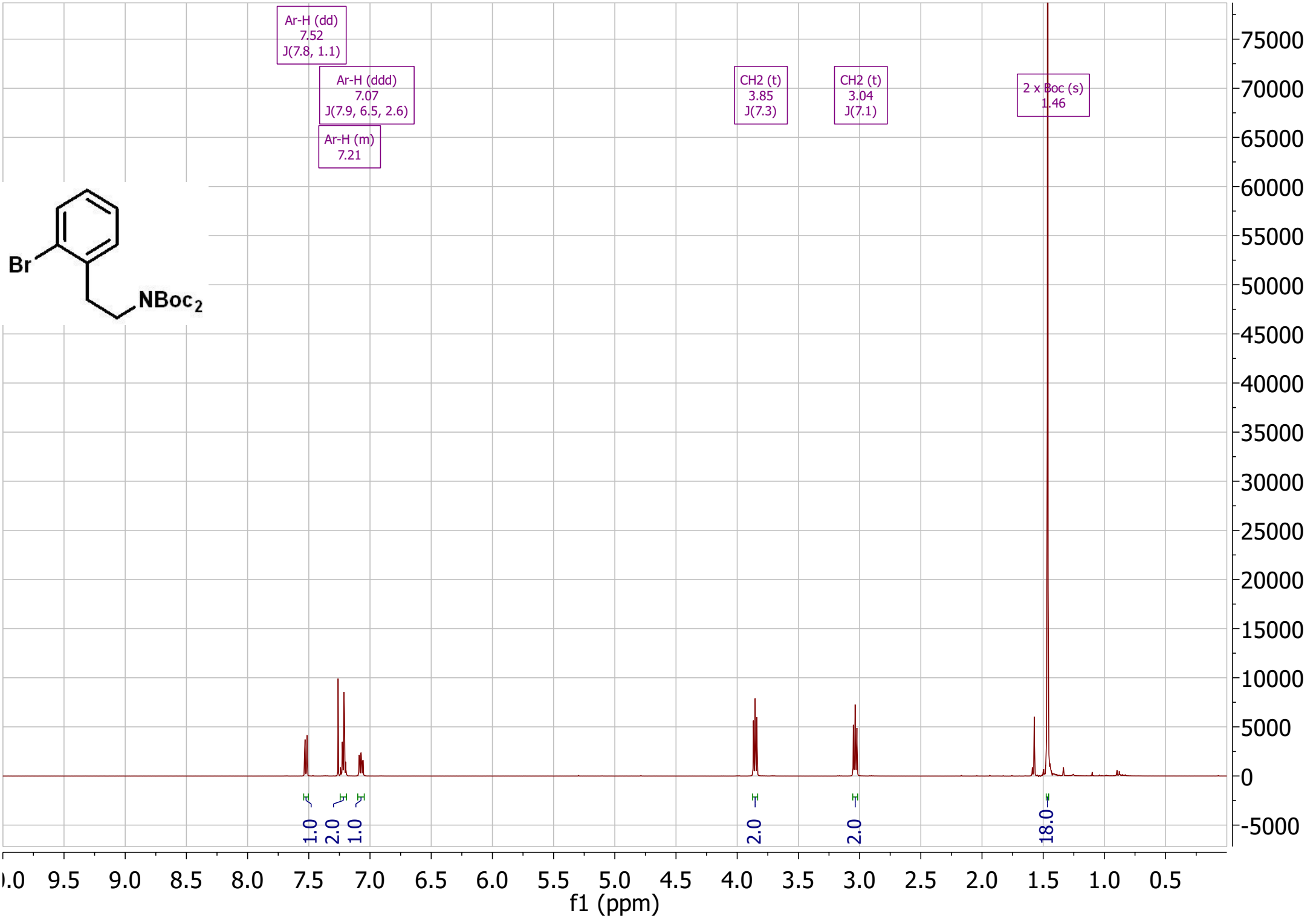

Ar-H (d)
7.42
J(8.3)
Ar-H (d)
7.06
J(8.3)
NH (s)
4.51
CH2 (m)
3.34
CH2 (t)
2.75
J(7.0)
Boc (s)
1.43
NHBoc
Br
2.0
2.0
1.0
2.0
2.0
9.2
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

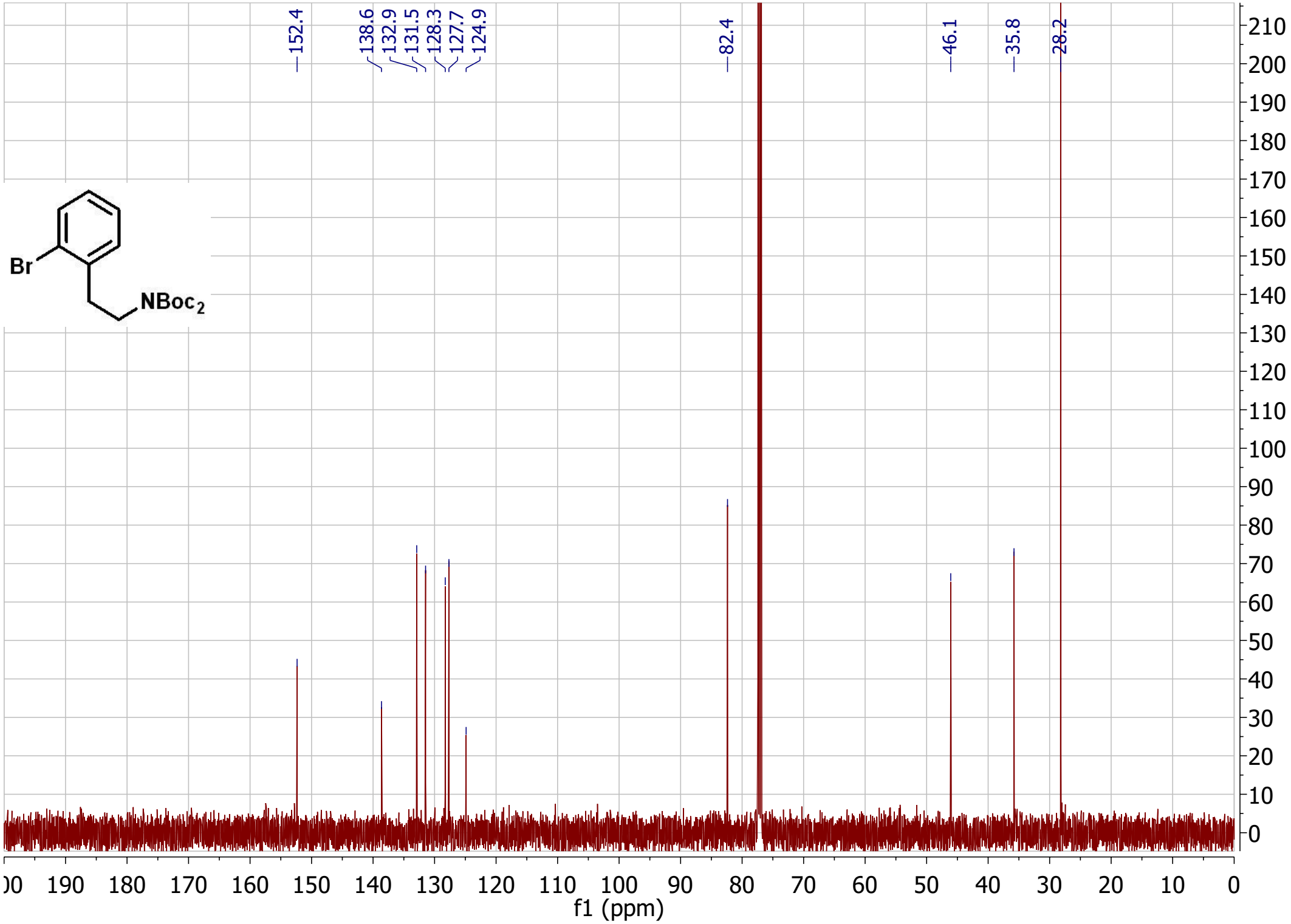

155.9
138.1
131.8
130.7
120.4
79.5
41.7
35.8
28.5
NHBoc
Br
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

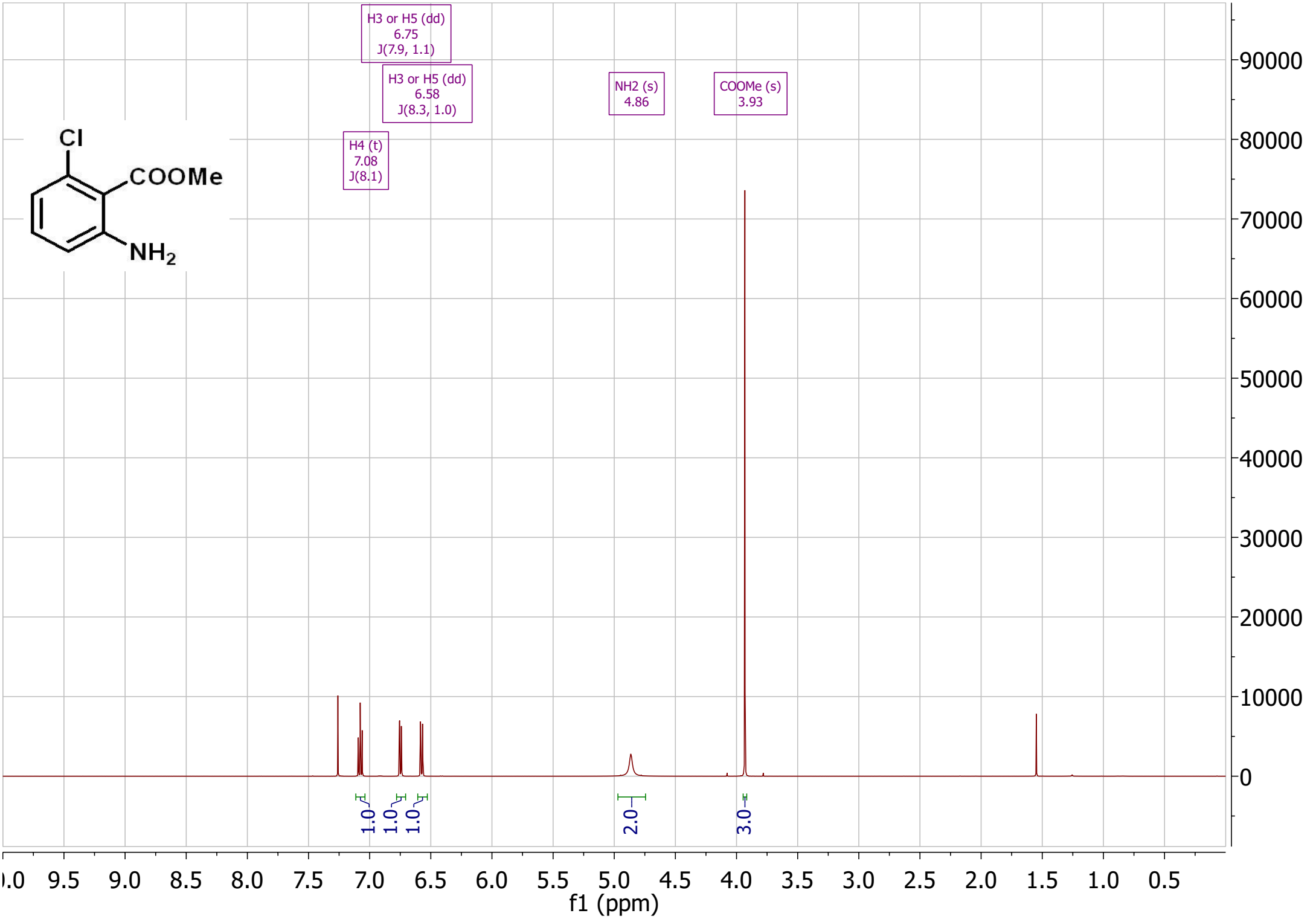

Ar-H (d)
7.39
J(8.3)
Ar-H (d)
7.10
J(8.4)
CH2 (t)
3.85
J(6.9)
CH2 (t)
2.79
J(6.9)
A (m)
1.03
OTIPS
Br
2.0
2.0
2.0
2.0
21.0
f1 (ppm)

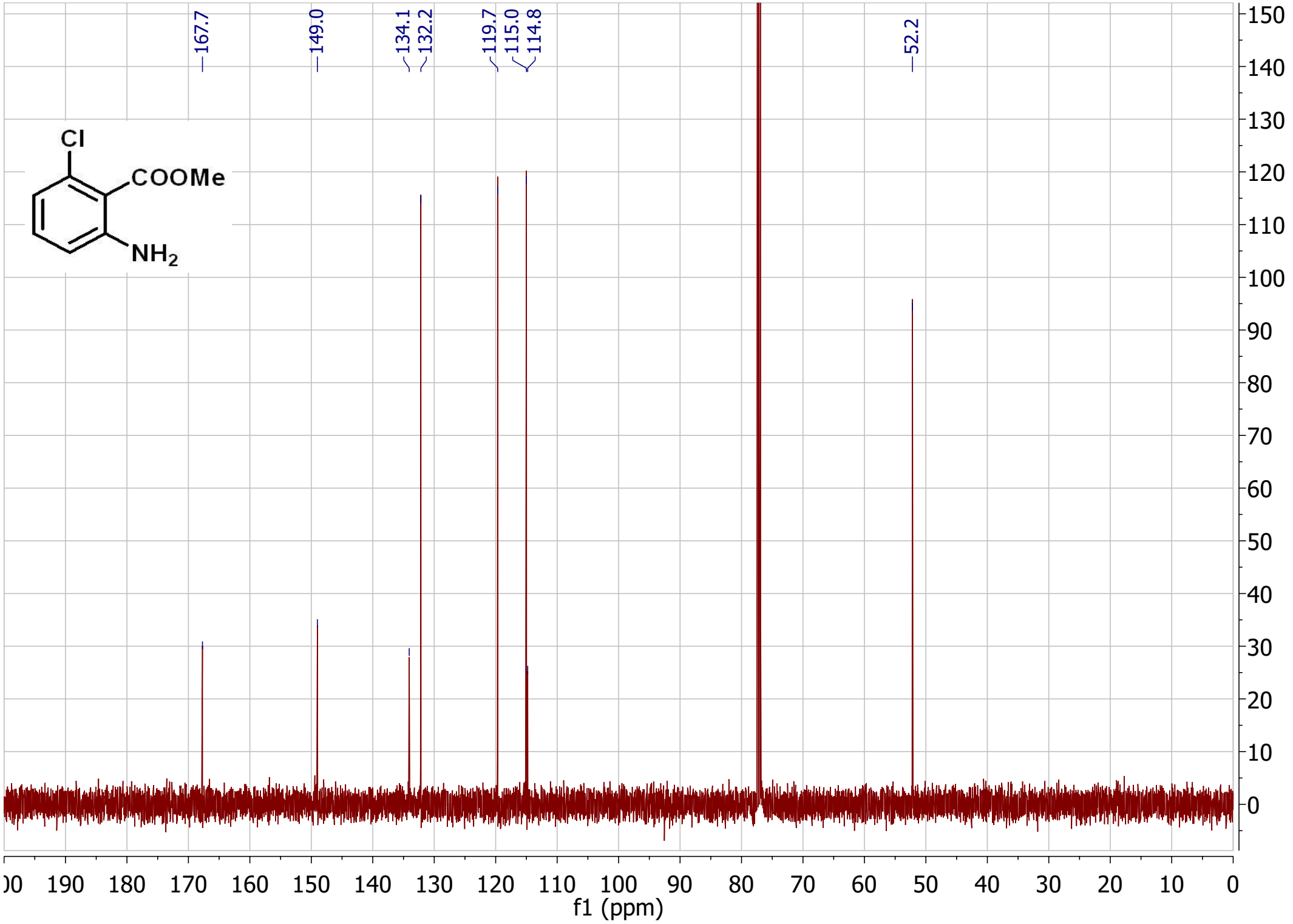

Ar-H (d)
7.39
J(8.4)
Ar-H (d)
7.05
J(8.3)
NH (s)
4.52
CH2 (m)
3.14
CH2 (d)
2.59
J(7.7)
CH2 (tt)
1.78
J(7.6, 6.5)
Boc (s)
1.44
NHBoc
Br
2.0
2.0
1.0
2.0
2.0
2.0
9.0
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

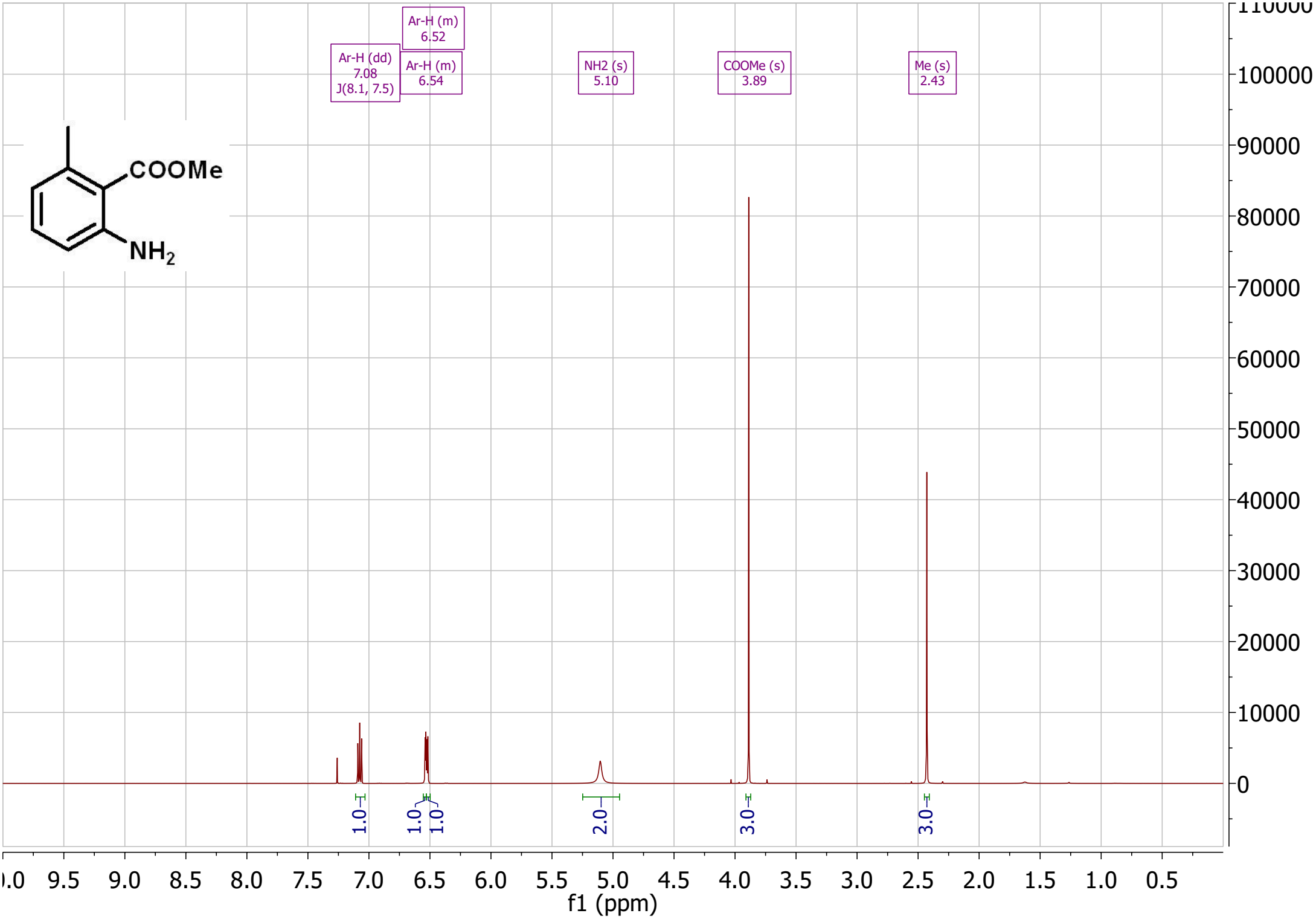

156.1
140.7
131.6
130.3
119.8
79.4
40.3
32.7
31.8
28.6
NHBoc
Br
1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

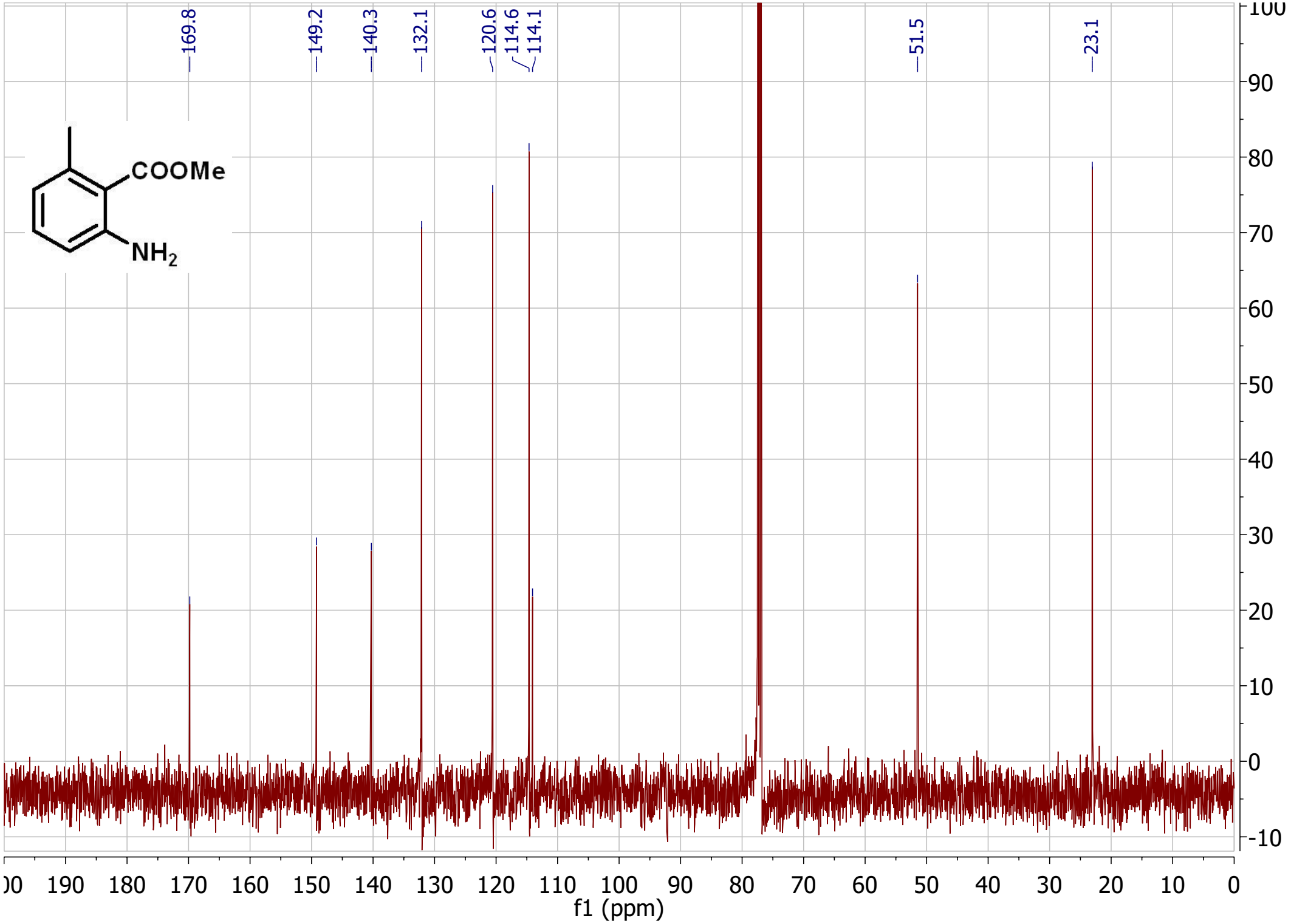

Ar-H (dd)
7.52
J(7.8, 1.1)
Ar-H (ddd)
7.07
J(7.9, 6.5, 2.6)
Ar-H (m)
7.21
CH2 (t)
3.85
J(7.3)
CH2 (t)
3.04
J(7.1)
2 x Boc (s)
1.46
Br
NBoc2
1.0
2.0
1.0
2.0
2.0
18.0
f1 (ppm)

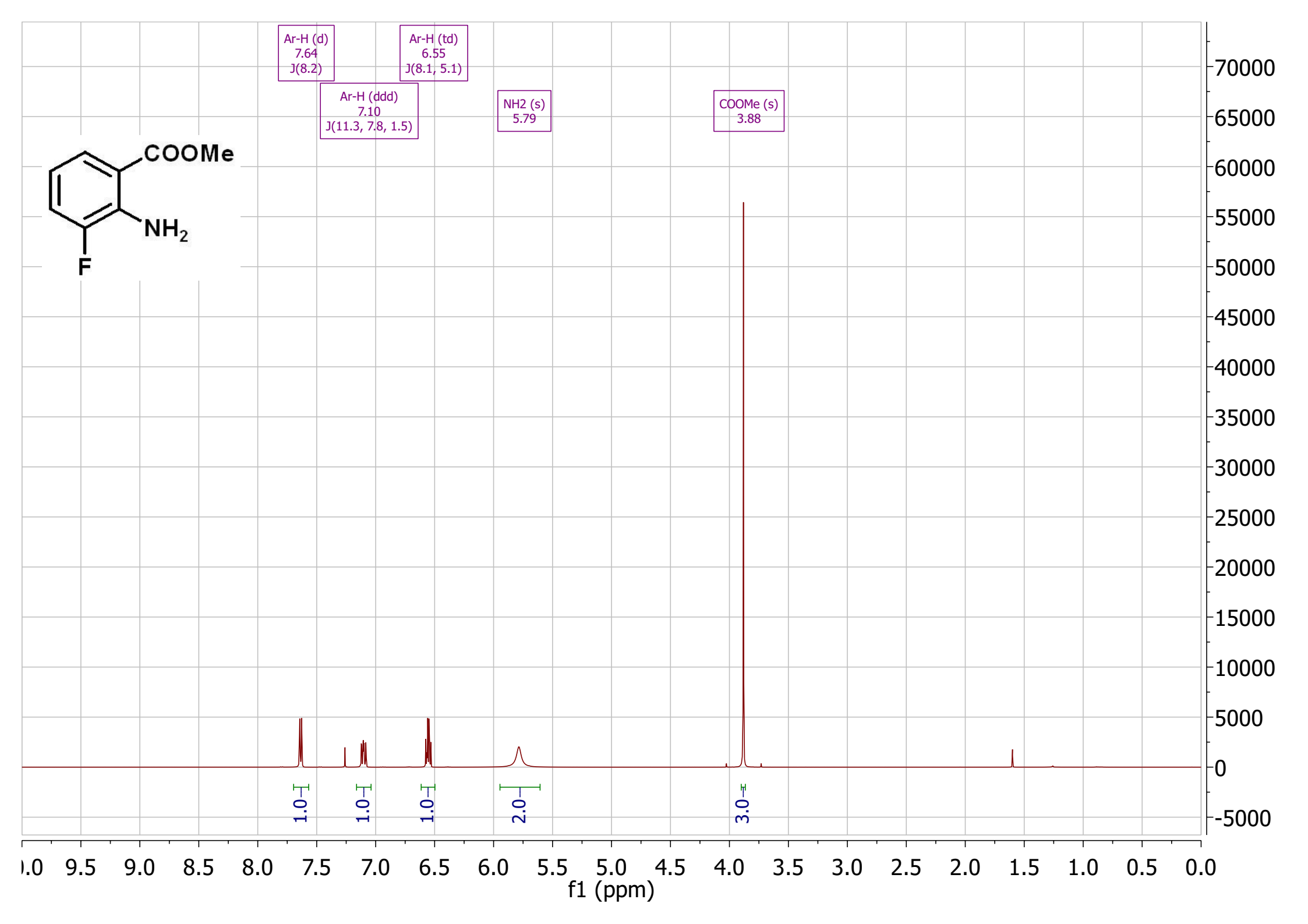

152.4
138.6
132.9
131.5
128.3
127.7
124.9
82.4
46.1
35.8
28.2
Br
NBoc2
f1 (ppm)

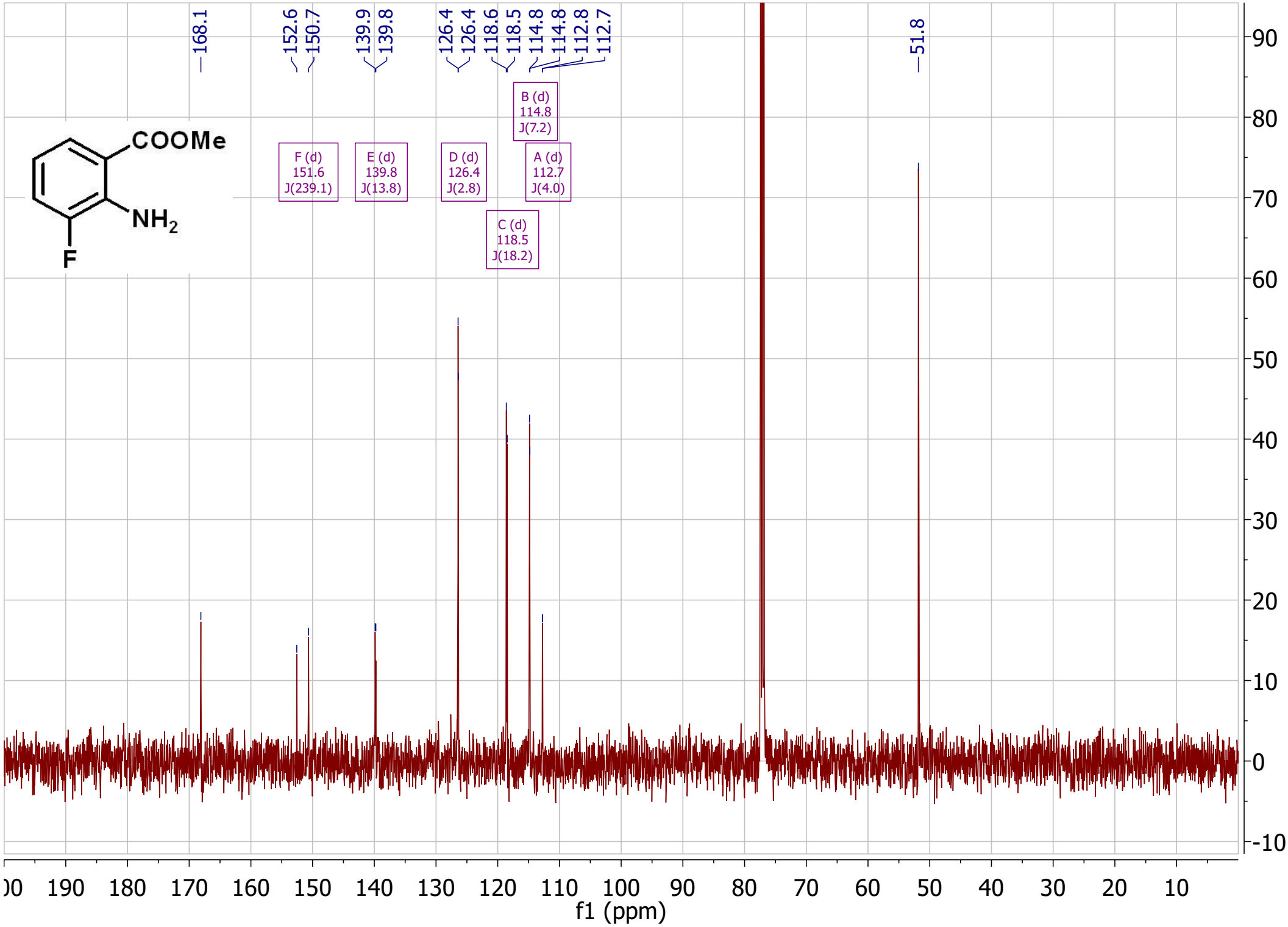

H3 or H5 (dd)
6.75
J(7.9, 1.1)
H3 or H5 (dd)
6.58
J(8.3, 1.0)
H4 (t)
7.08
J(8.1)
NH2 (s)
4.86
COOMe (s)
3.93
Cl
COOMe
NH2
1.0
1.0
1.0
2.0
3.0
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

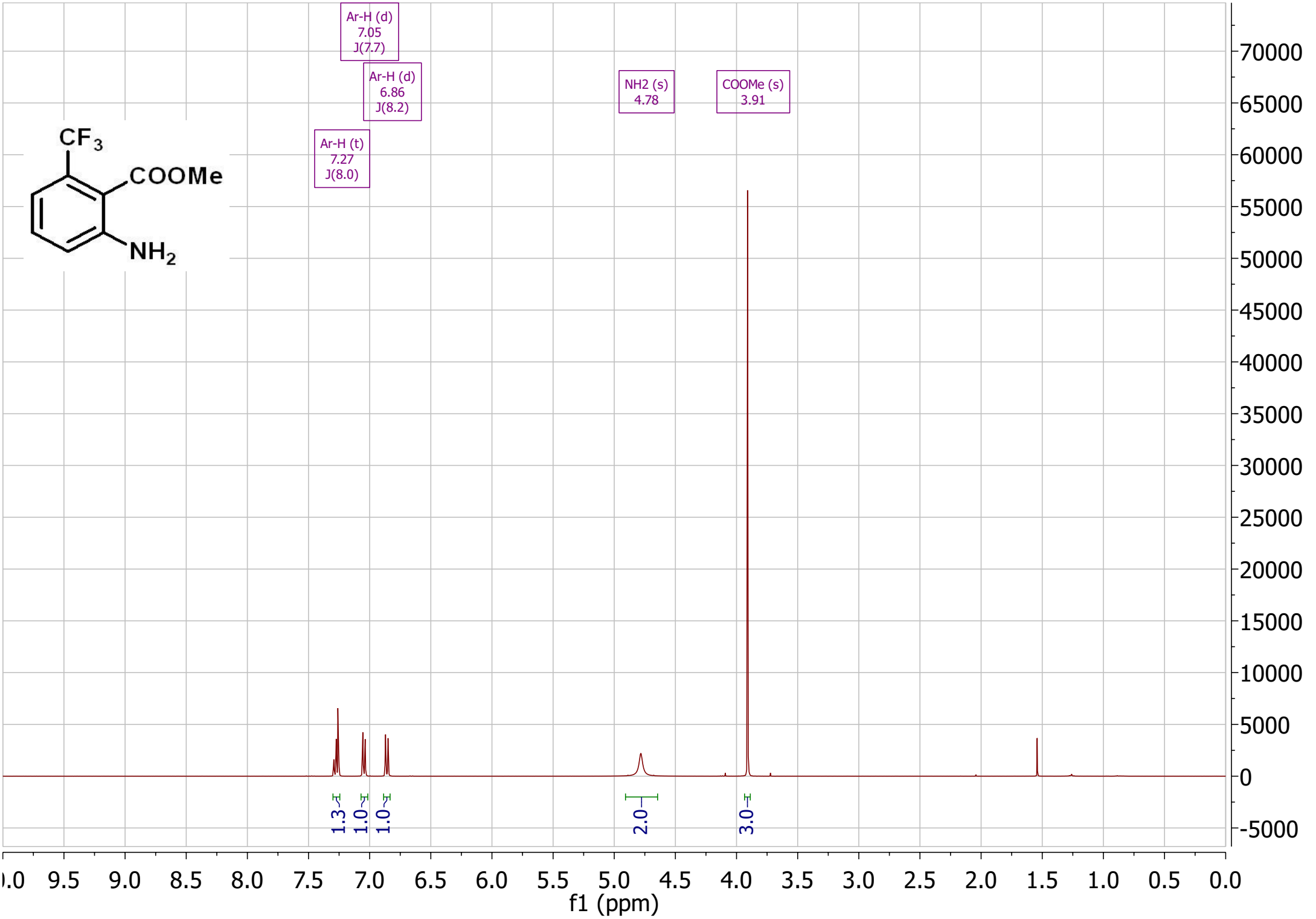

167.7
149.0
134.1
132.2
119.7
115.0
114.8
52.2
Cl
COOMe
NH2
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

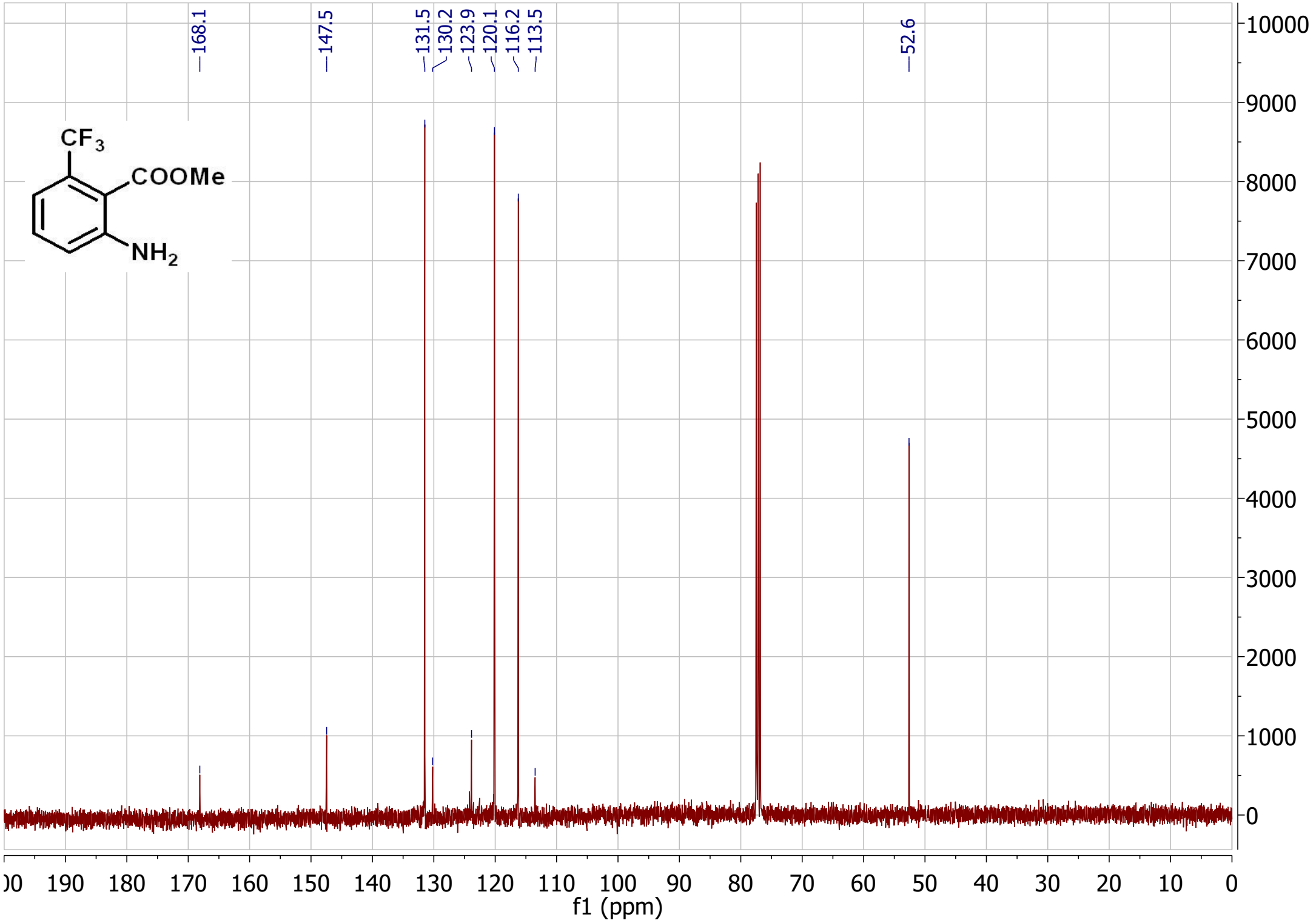

Ar-H (m)
6.52
Ar-H (dd)
7.08
J(8.1, 7.5)
Ar-H (m)
6.54
NH2 (s)
5.10
COOMe (s)
3.89
Me (s)
2.43
COOMe
NH2
1.0
1.0
1.0
2.0
3.0
3.0
f1 (ppm)

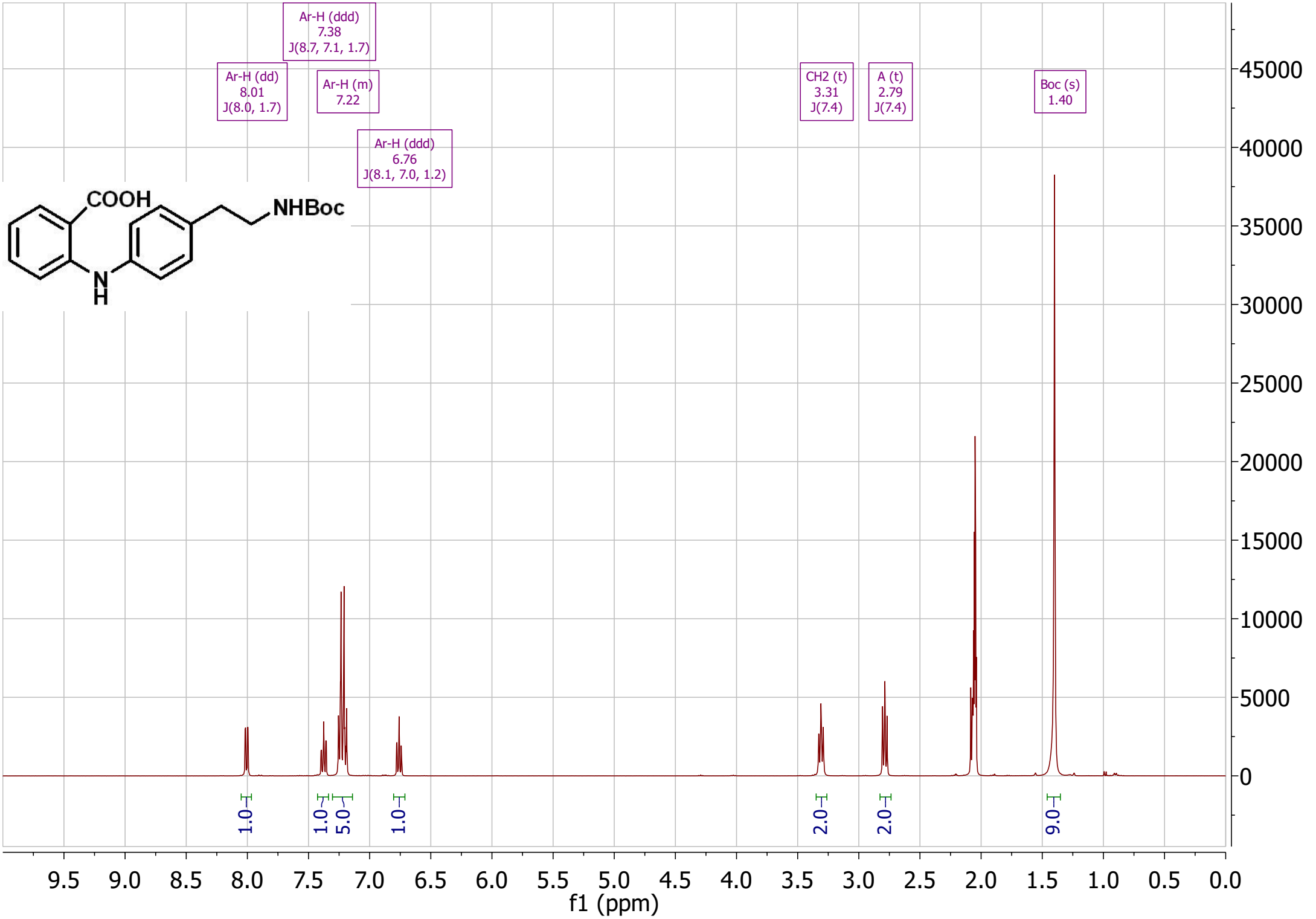

169.8
149.2
140.3
132.1
120.6
114.6
114.1
51.5
23.1
COOMe
NH2
f1 (ppm)

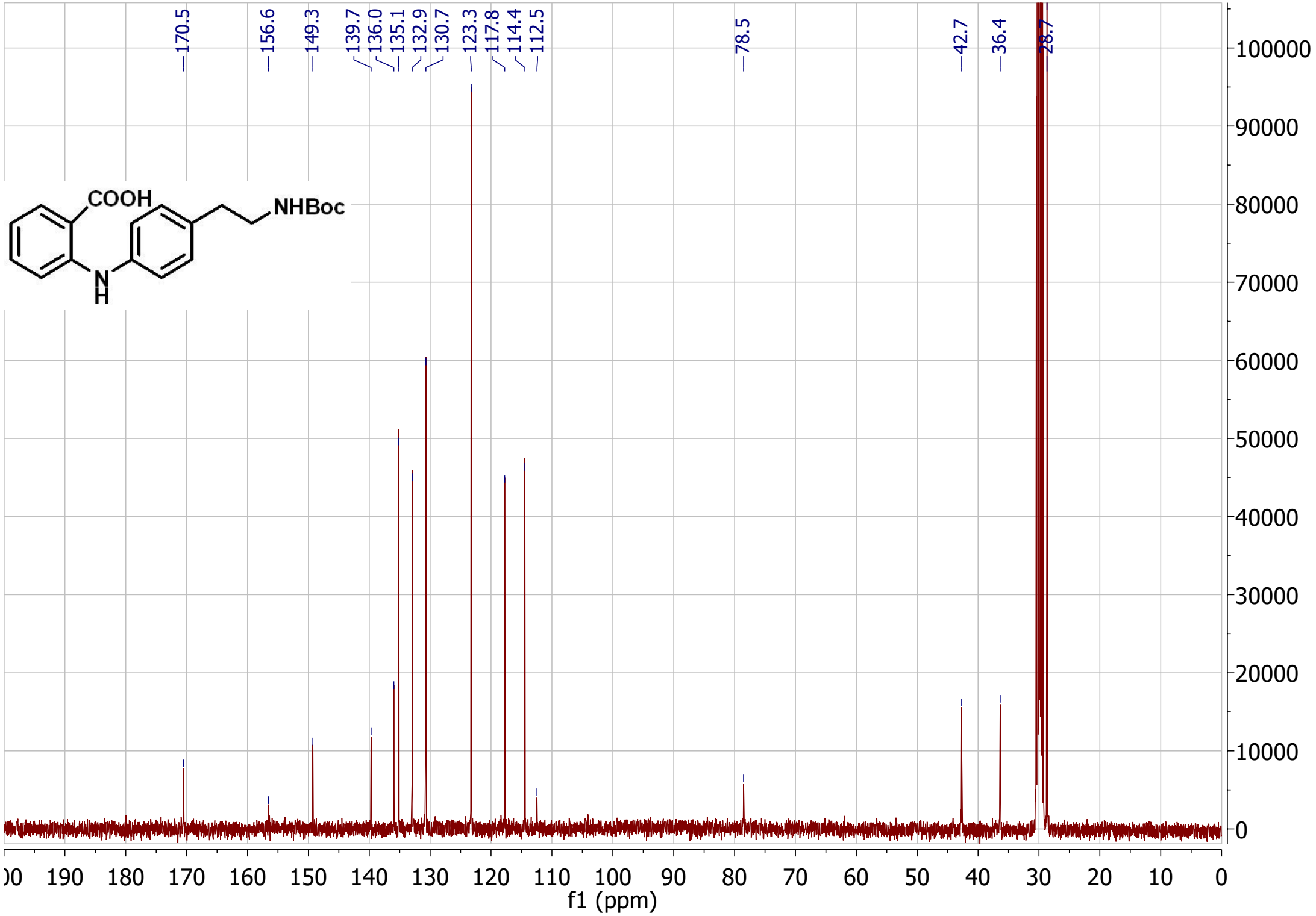

Ar-H (d)
7.64
J(8.2)
Ar-H (ddd)
7.10
J(11.3, 7.8, 1.5)
Ar-H (td)
6.55
J(8.1, 5.1)
NH2 (s)
5.79
COOMe (s)
3.88
COOMe
NH2
F
1.0
1.0
1.0
2.0
3.0
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

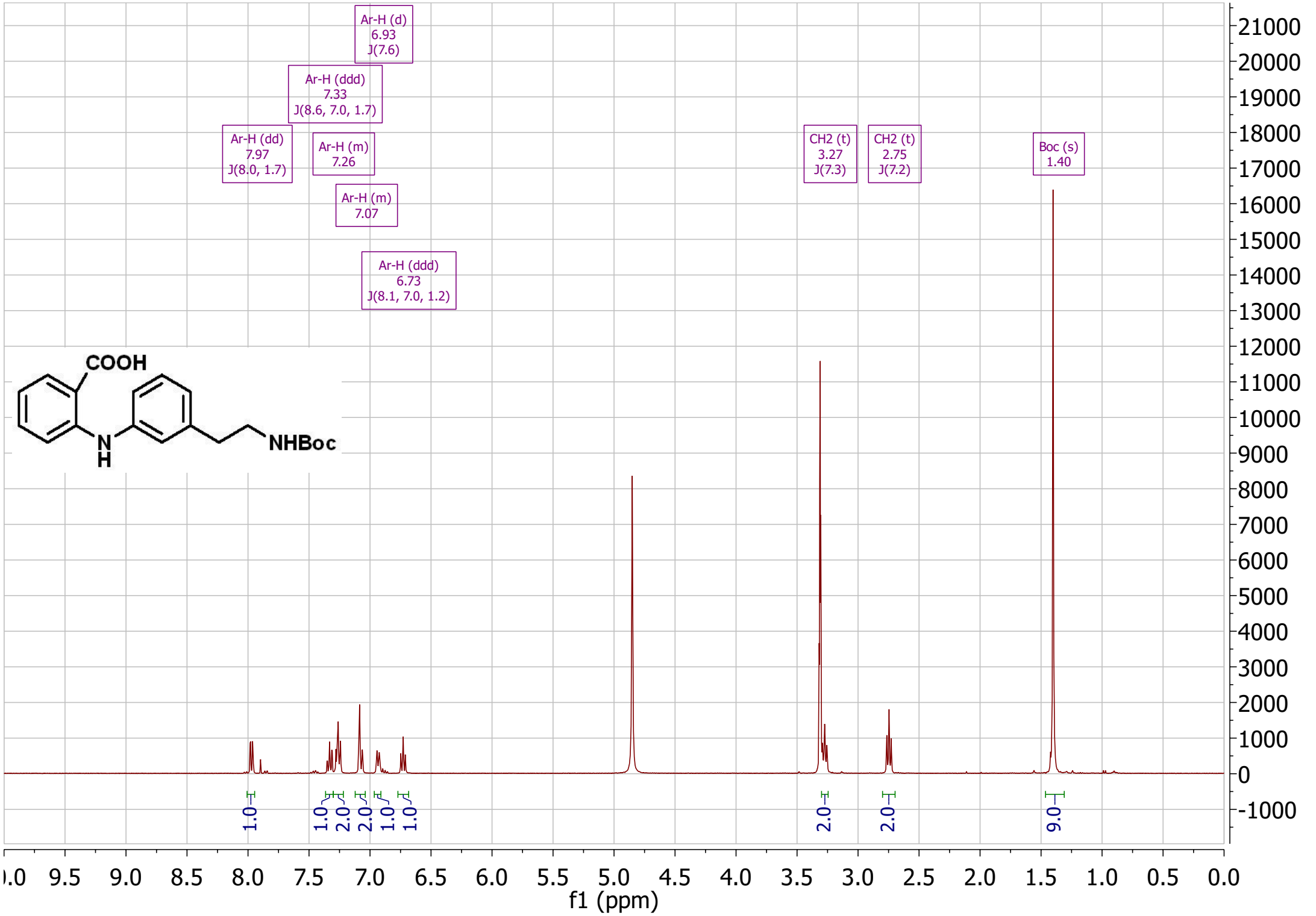

168.1
152.6
150.7
139.9
139.8
126.4
126.4
118.6
118.5
114.8
114.8
112.8
112.7
51.8
COOMe
NH2
F
F (d)
151.6
J(239.1)
E (d)
139.8
J(13.8)
D (d)
126.4
J(2.8)
C (d)
118.5
J(18.2)
B (d)
114.8
J(7.2)
A (d)
112.7
J(4.0)
90
80
70
60
50
40
30
20
10
0
-10
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

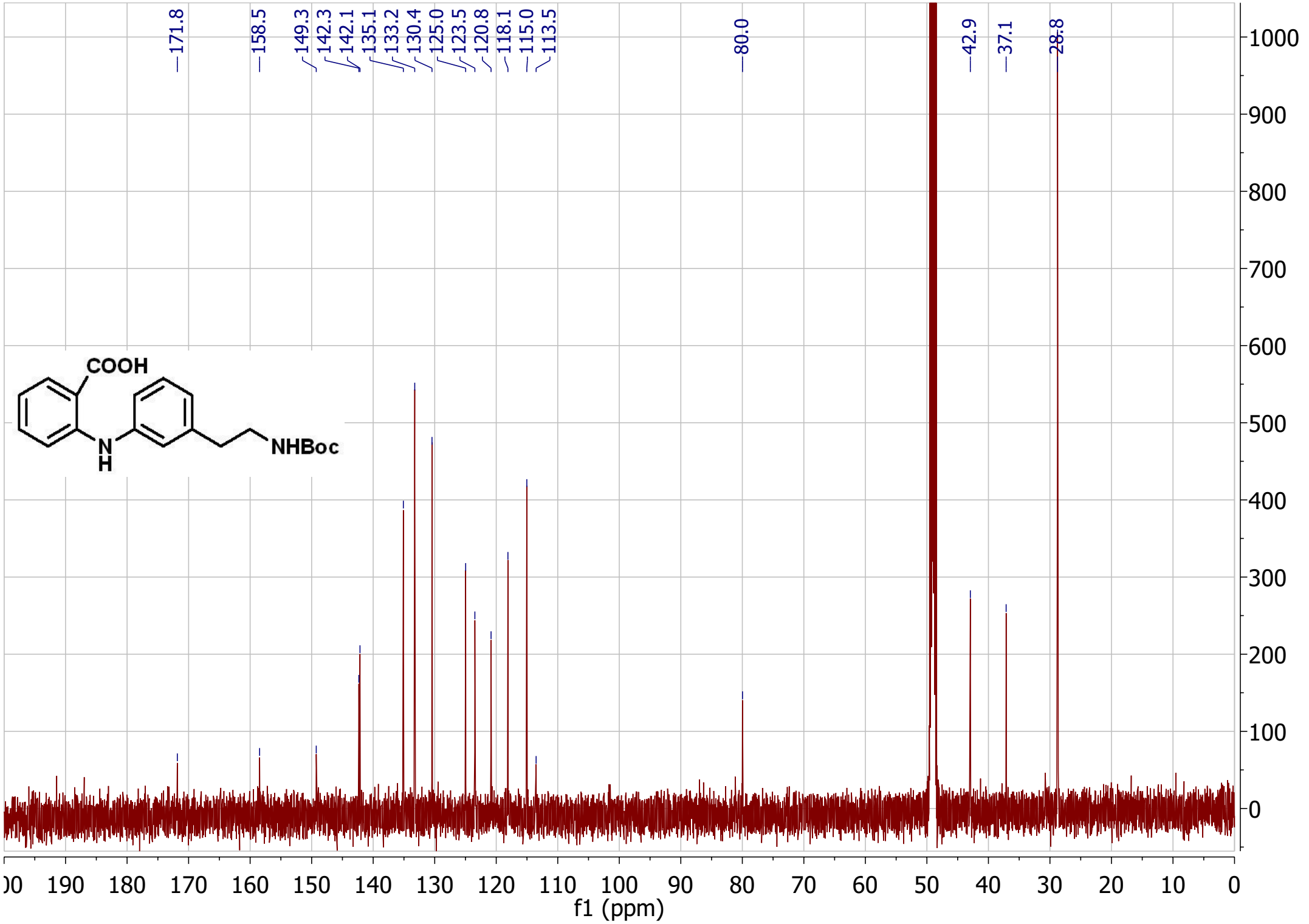

Ar-H (d)
7.05
J(7.7)
Ar-H (d)
6.86
J(8.2)
Ar-H (t)
7.27
J(8.0)
NH2 (s)
4.78
COOMe (s)
3.91
CF3
COOMe
NH2
1.3
1.0
1.0
2.0
3.0
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

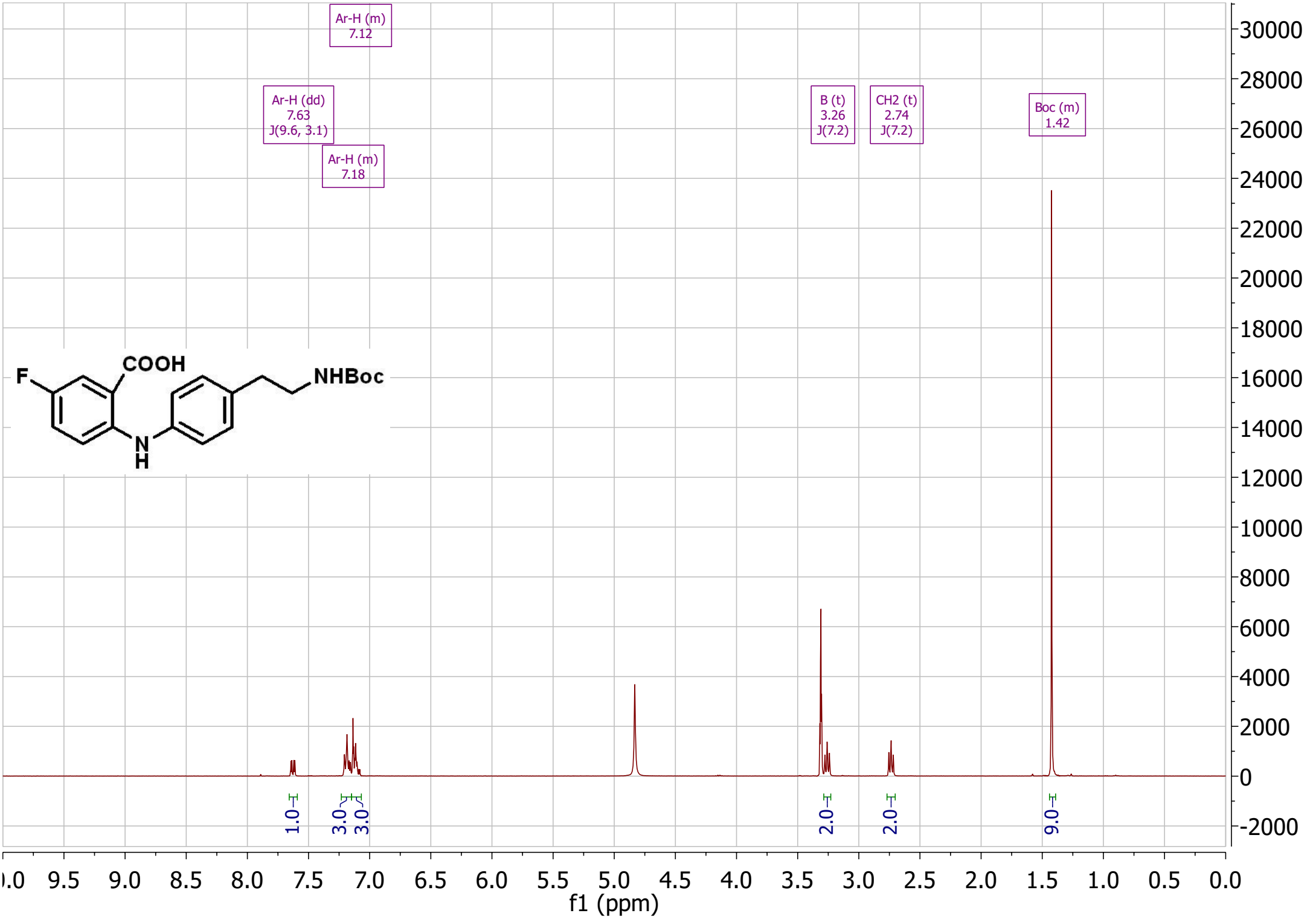

168.1
147.5
131.5
130.2
123.9
120.1
116.2
113.5
52.6
CF3
COOMe
NH2
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

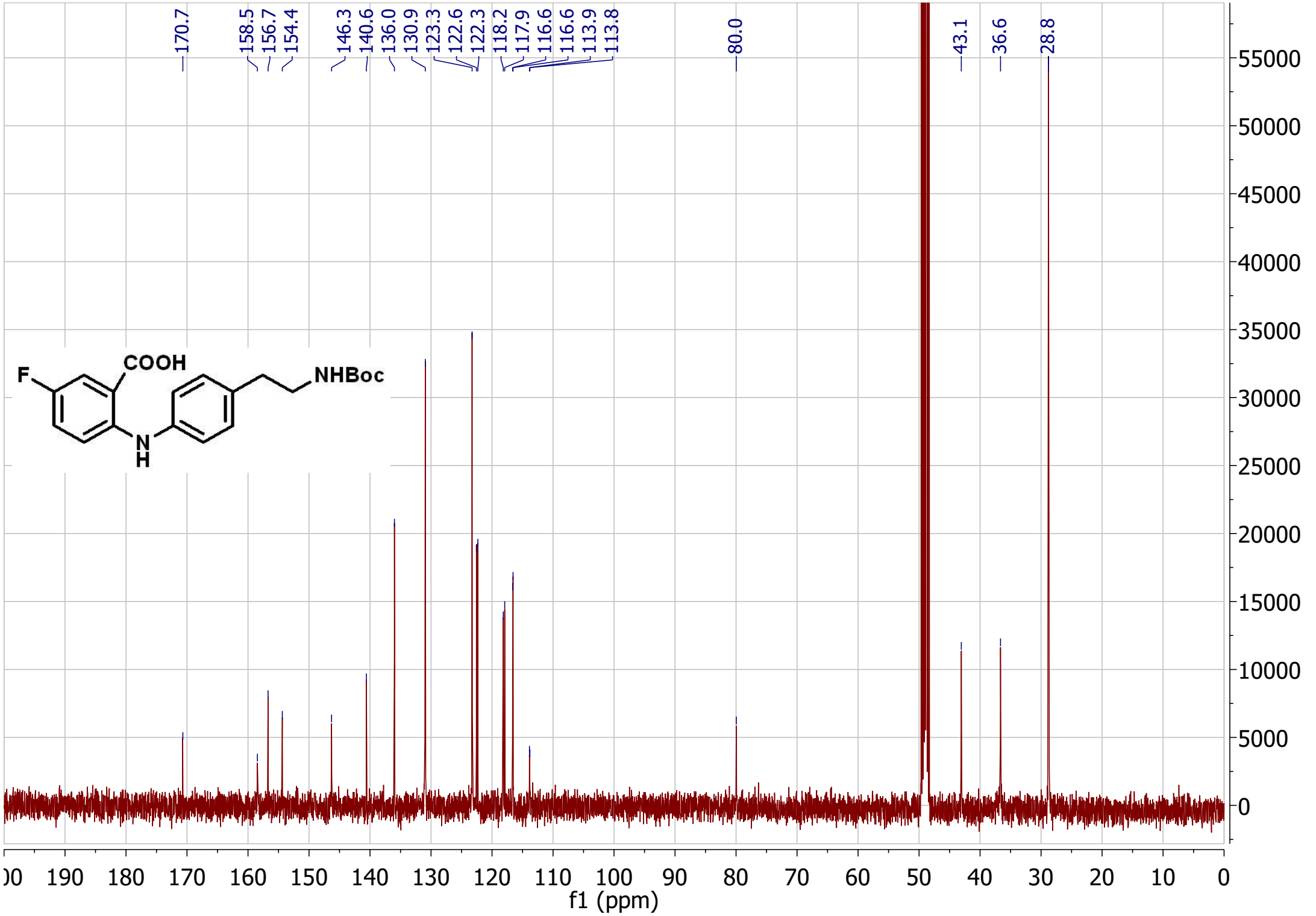

Ar-H (ddd)
7.38
J(8.7, 7.1, 1.7)
Ar-H (dd)
8.01
J(8.0, 1.7)
Ar-H (m)
7.22
Ar-H (ddd)
6.76
J(8.1, 7.0, 1.2)
CH2 (t)
3.31
J(7.4)
A (t)
2.79
J(7.4)
Boc (s)
1.40
COOH
NHBoc
N
H
1.0
1.0
5.0
1.0
2.0
2.0
9.0
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

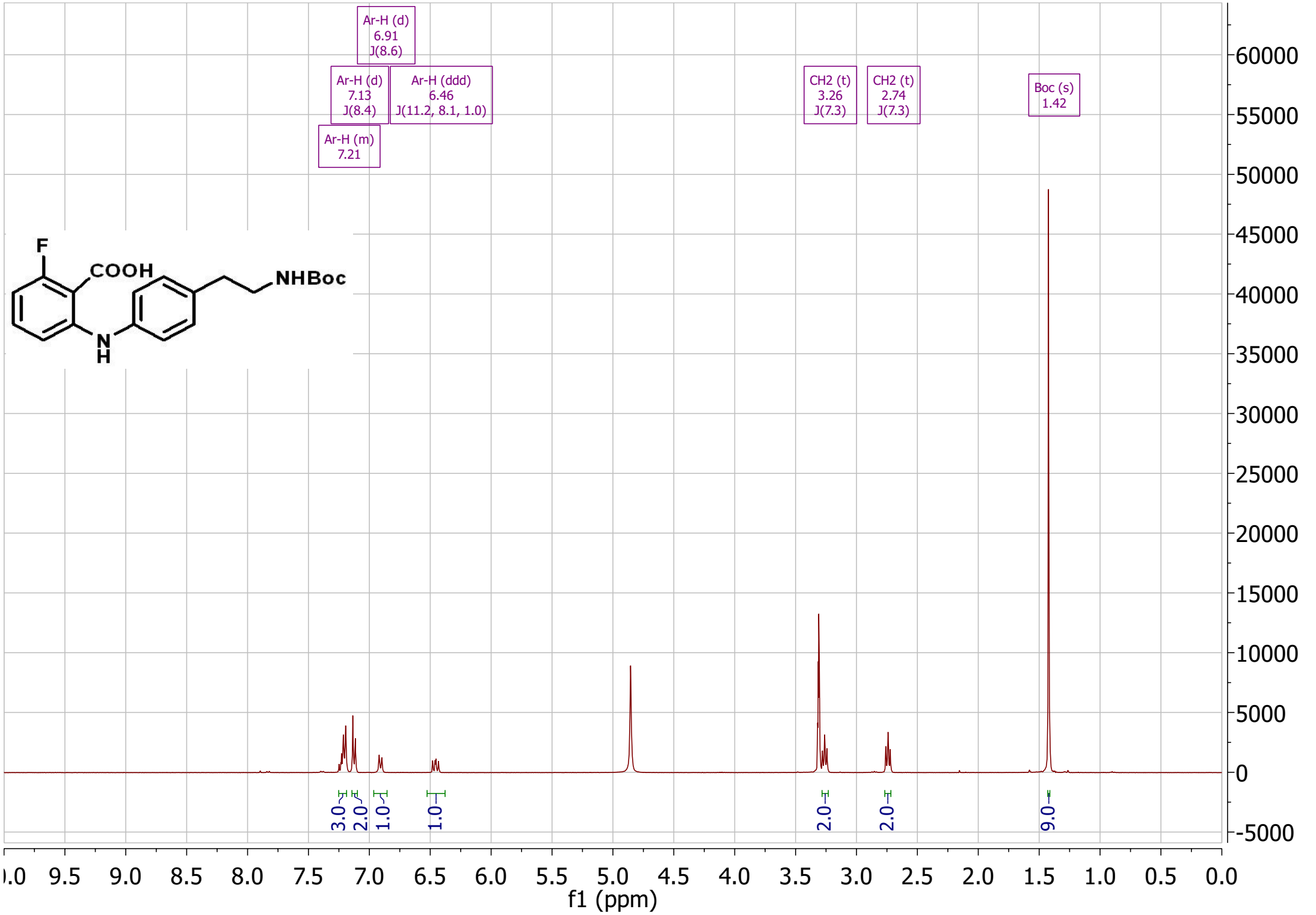

170.5
156.6
149.3
139.7
136.0
135.1
132.9
130.7
123.3
117.8
114.4
112.5
78.5
42.7
36.4
28.7
COOH
NHBoc
N
H
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

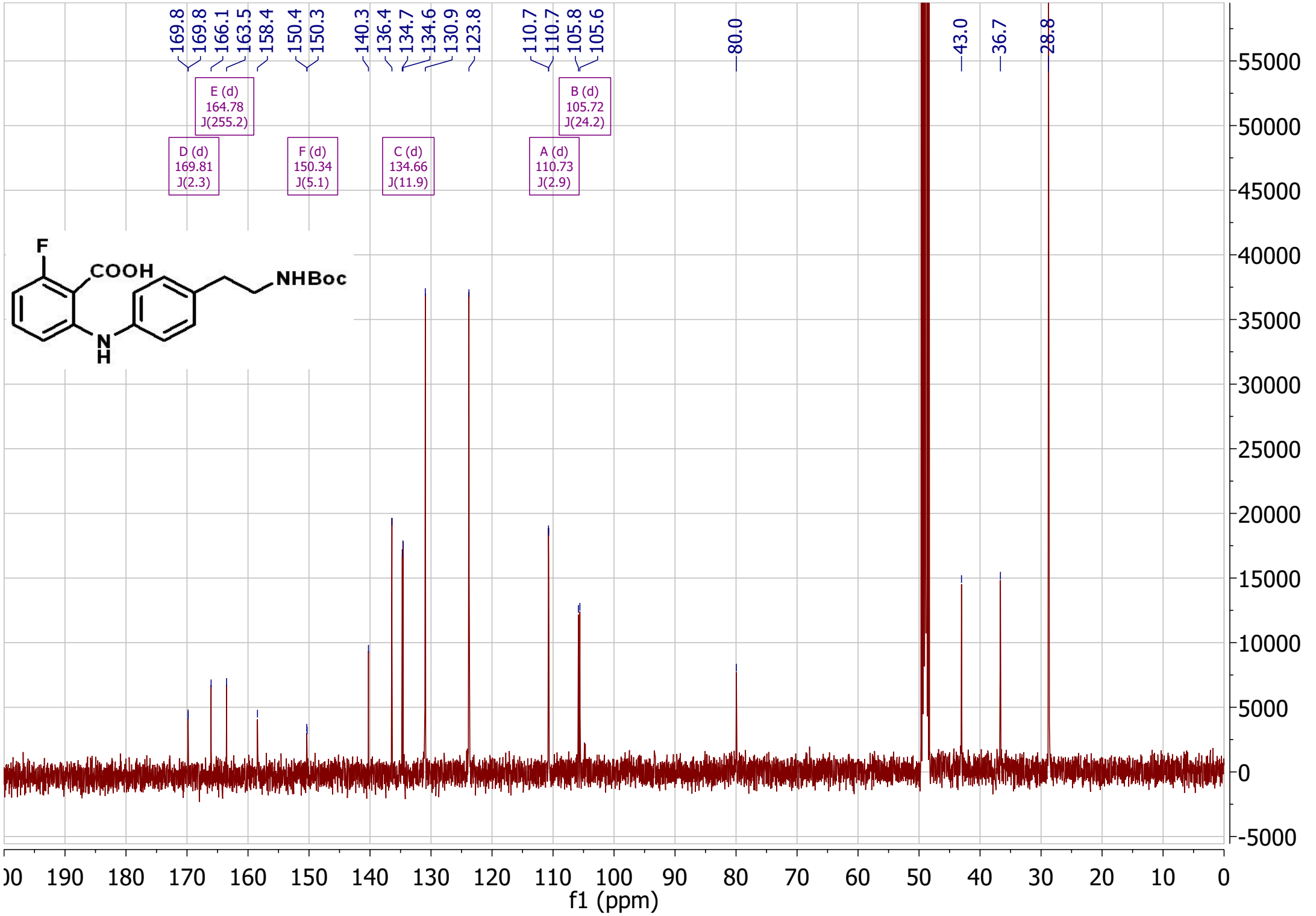

Ar-H (d)
6.93
J(7.6)
Ar-H (ddd)
7.33
J(8.6, 7.0, 1.7)
Ar-H (dd)
7.97
J(8.0, 1.7)
Ar-H (m)
7.26
Ar-H (m)
7.07
Ar-H (ddd)
6.73
J(8.1, 7.0, 1.2)
CH2 (t)
3.27
J(7.3)
CH2 (t)
2.75
J(7.2)
Boc (s)
1.40
COOH
N
H
NHBoc
1.0
1.0
2.0
2.0
1.0
1.0
2.0
2.0
9.0
f1 (ppm)

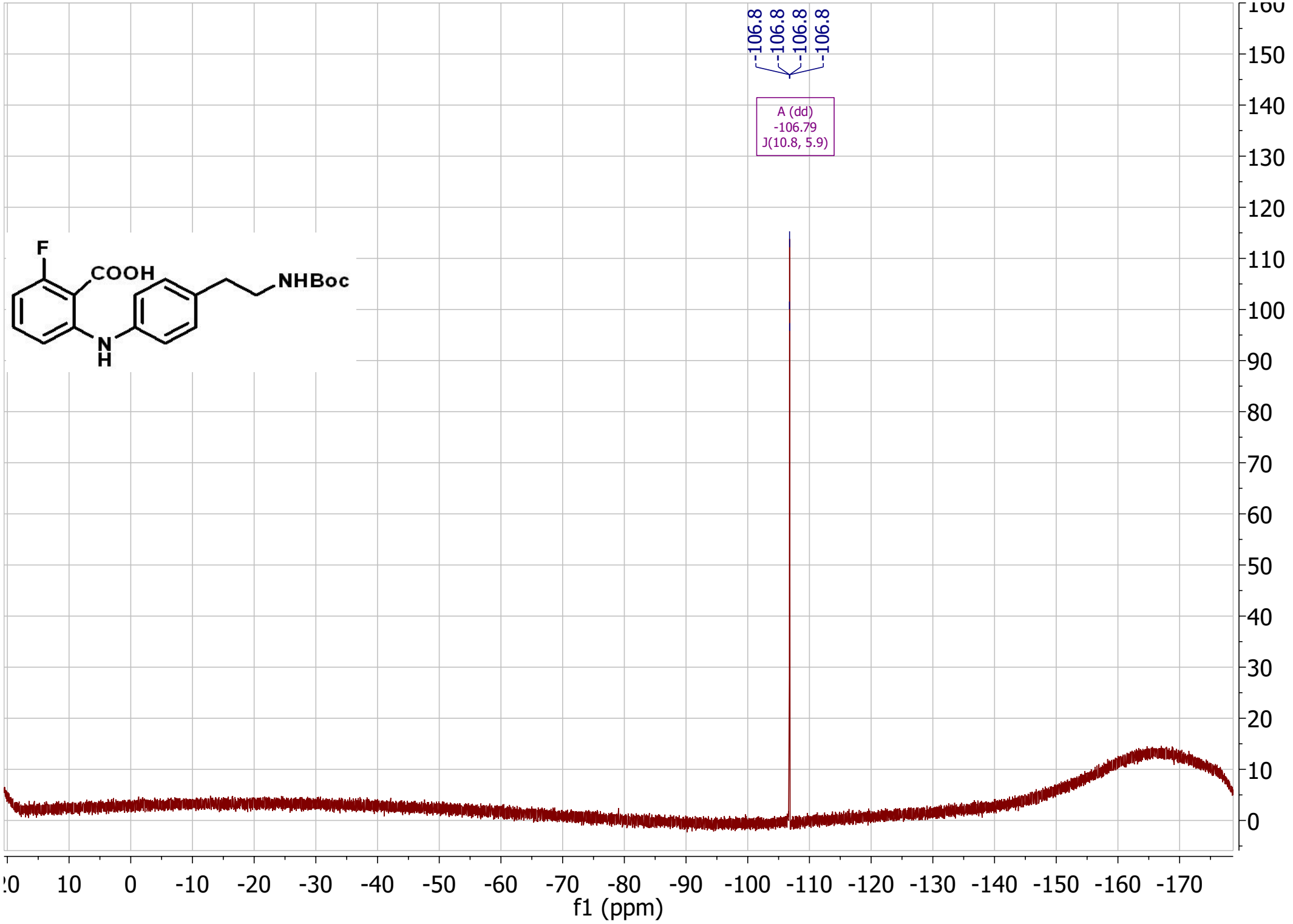

171.8
158.5
149.3
142.3
142.1
135.1
133.2
130.4
125.0
123.5
120.8
118.1
115.0
113.5
80.0
42.9
37.1
28.8
COOH
N
H
NHBoc
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

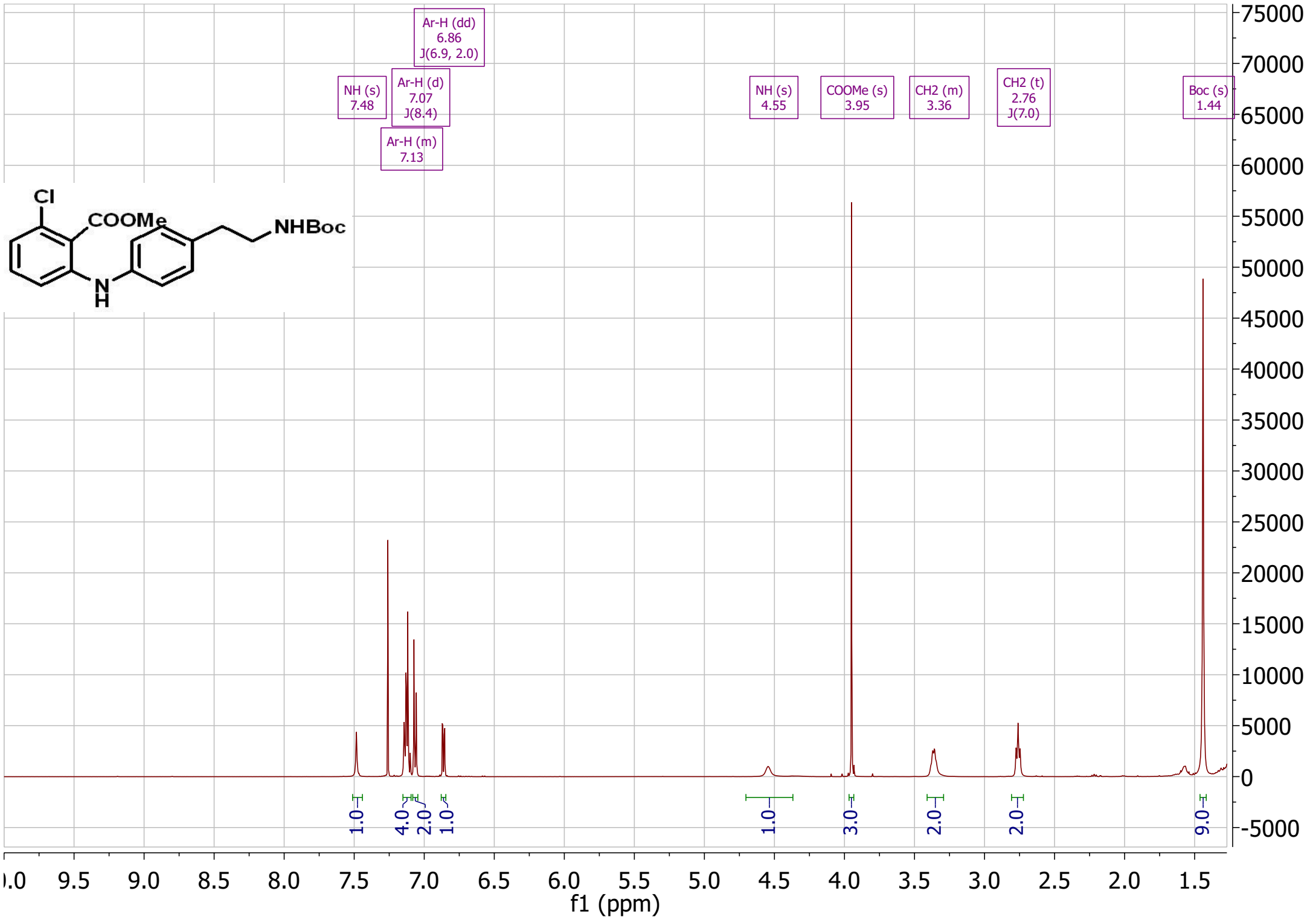

Ar-H (m)
7.12
Ar-H (dd)
7.63
J(9.6, 3.1)
Ar-H (m)
7.18
B (t)
3.26
J(7.2)
CH2 (t)
2.74
J(7.2)
Boc (m)
1.42
F
COOH
NHBoc
N
H
1.0
3.0
3.0
2.0
2.0
9.0
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

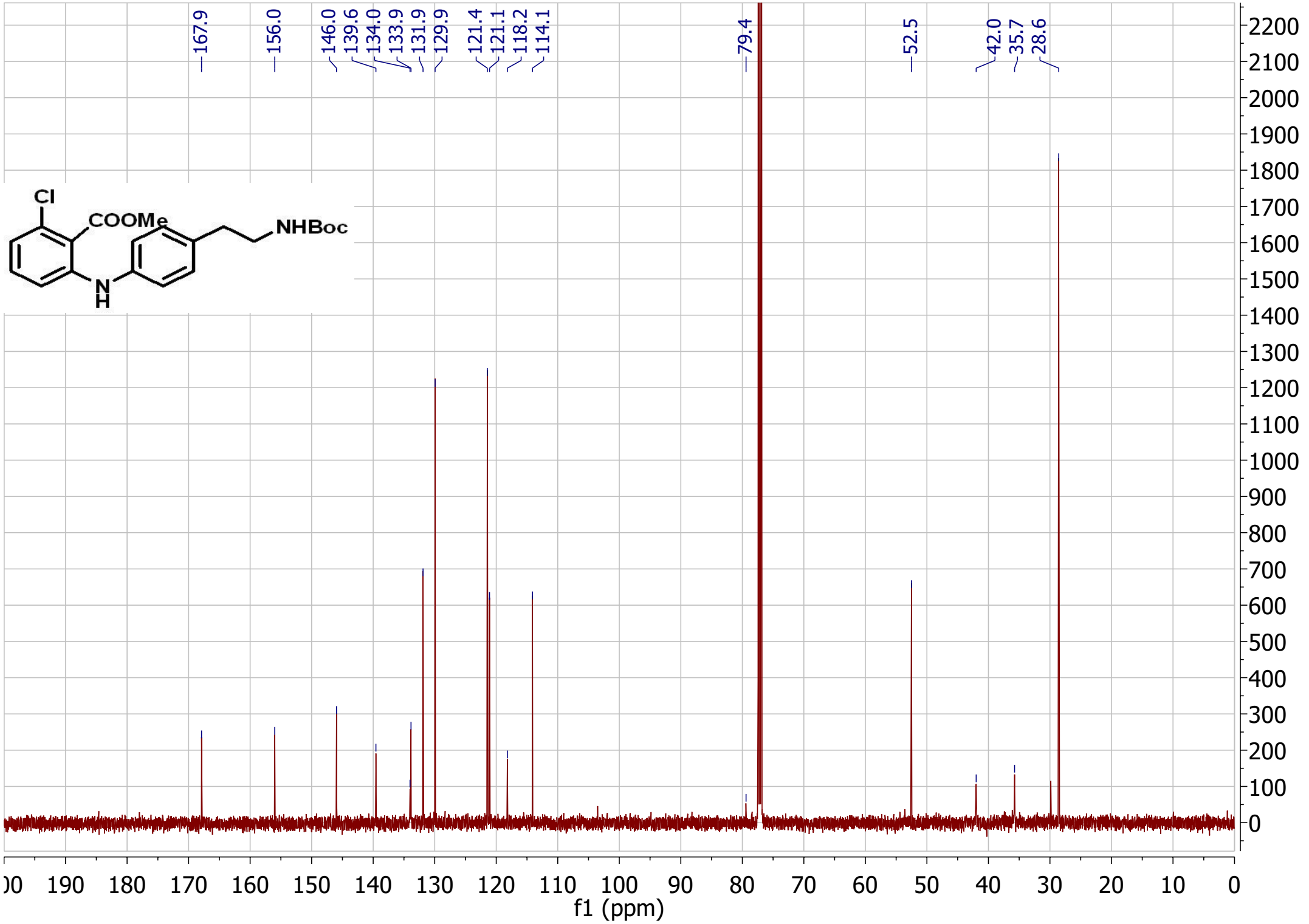

170.7
158.5
156.7
154.4
146.3
140.6
136.0
130.9
123.3
122.6
122.3
118.2
117.9
116.6
116.6
113.9
113.8
80.0
43.1
36.6
28.8
COOH
F
NHBoc
N
H
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

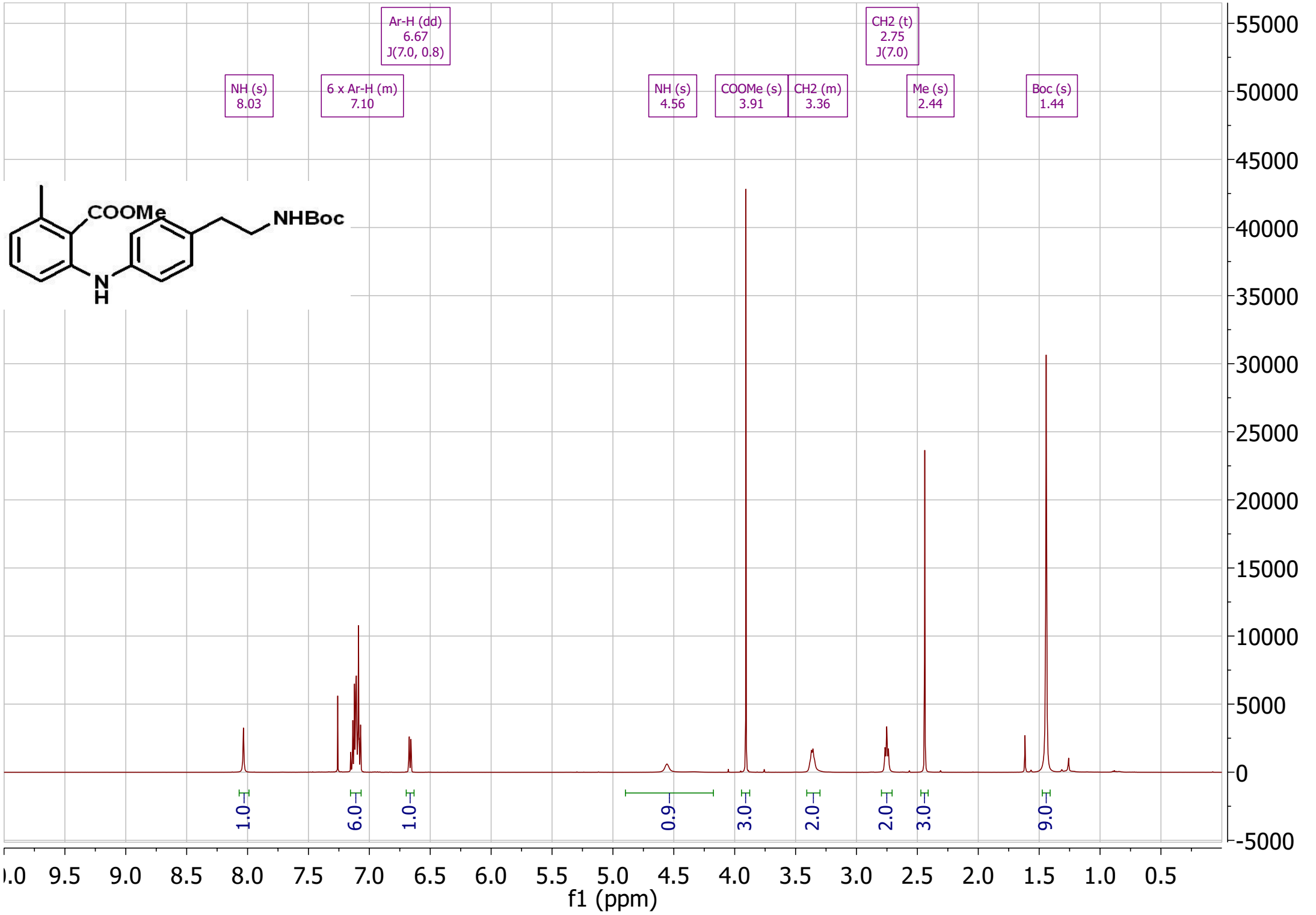

Ar-H (d)
6.91
J(8.6)
Ar-H (d)
7.13
J(8.4)
Ar-H (ddd)
6.46
J(11.2, 8.1, 1.0)
Ar-H (m)
7.21
CH2 (t)
3.26
J(7.3)
CH2 (t)
2.74
J(7.3)
Boc (s)
1.42
F
COOH
NHBoc
N
H
3.0
2.0
1.0
1.0
2.0
2.0
9.0
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

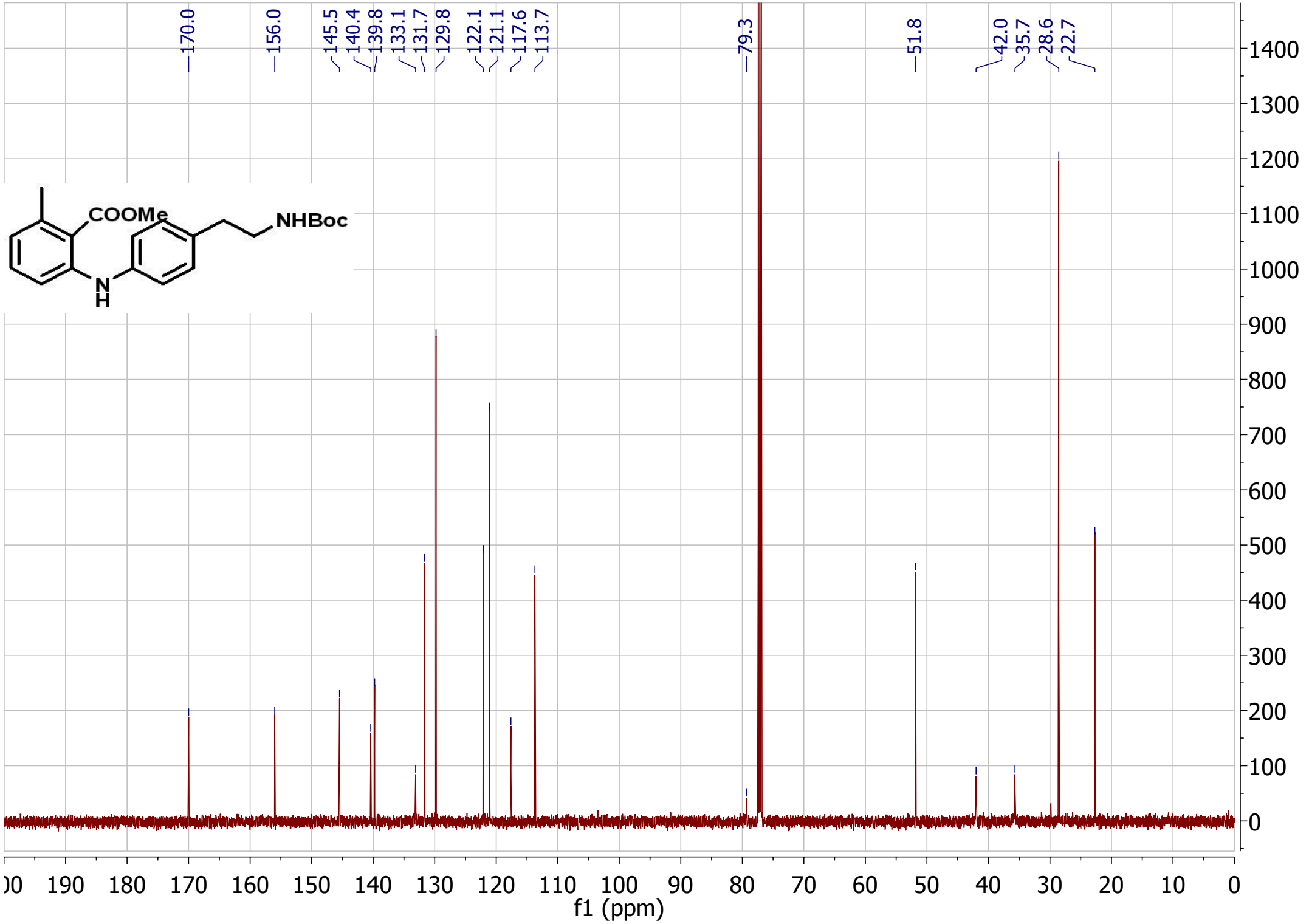

169.8
169.8
166.1
163.5
158.4
150.4
150.3
140.3
136.4
134.7
134.6
130.9
123.8
110.7
110.7
105.8
105.6
80.0
43.0
36.7
28.8
E (d)
164.78
J(255.2)
D (d)
169.81
J(2.3)
F (d)
150.34
J(5.1)
C (d)
134.66
J(11.9)
B (d)
105.72
J(24.2)
A (d)
110.73
J(2.9)
F
COOH
NHBoc
N
H
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

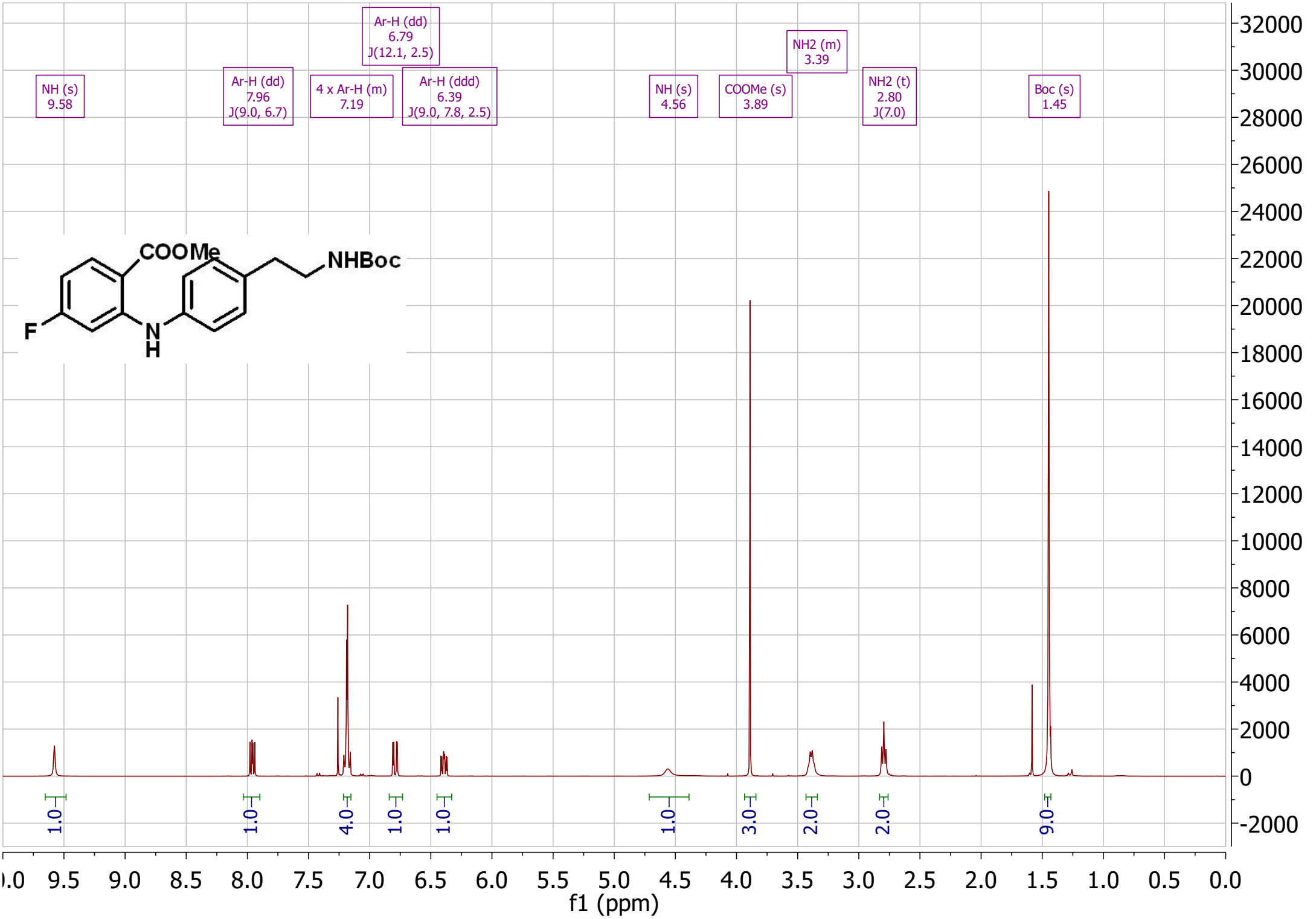

-106.8
-106.8
-106.8
-106.8
A (dd)
-106.79
J(10.8, 5.9)
F
COOH
NHBoc
N
H
f1 (ppm)

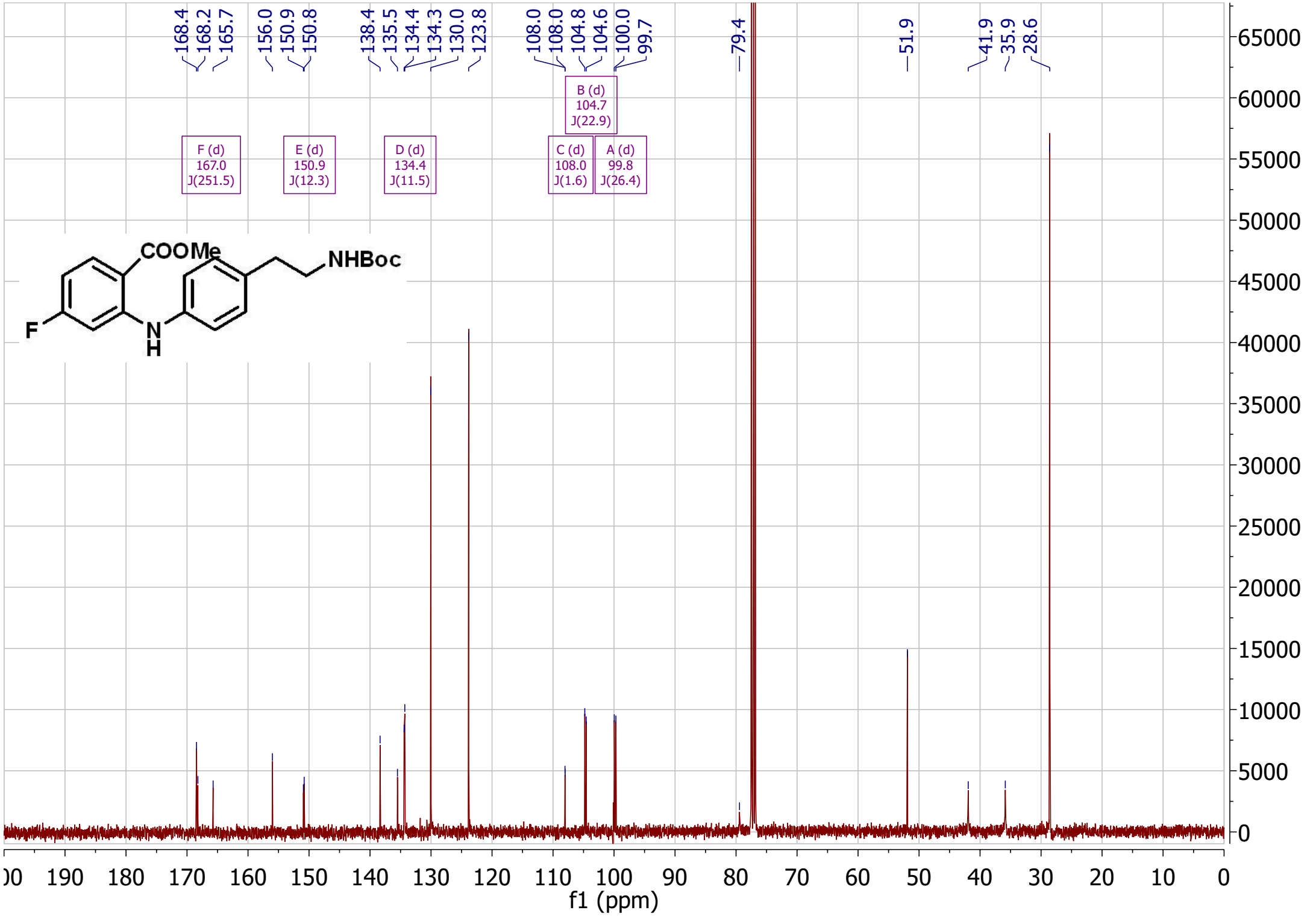

Ar-H (dd)
6.86
J(6.9, 2.0)
NH (s)
7.48
Ar-H (d)
7.07
J(8.4)
Ar-H (m)
7.13
NH (s)
4.55
COOMe (s)
3.95
CH2 (m)
3.36
CH2 (t)
2.76
J(7.0)
Boc (s)
1.44
Cl
COOMe
NHBoc
N
H
1.0
4.0
2.0
1.0
1.0
3.0
2.0
2.0
9.0
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
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
f1 (ppm)

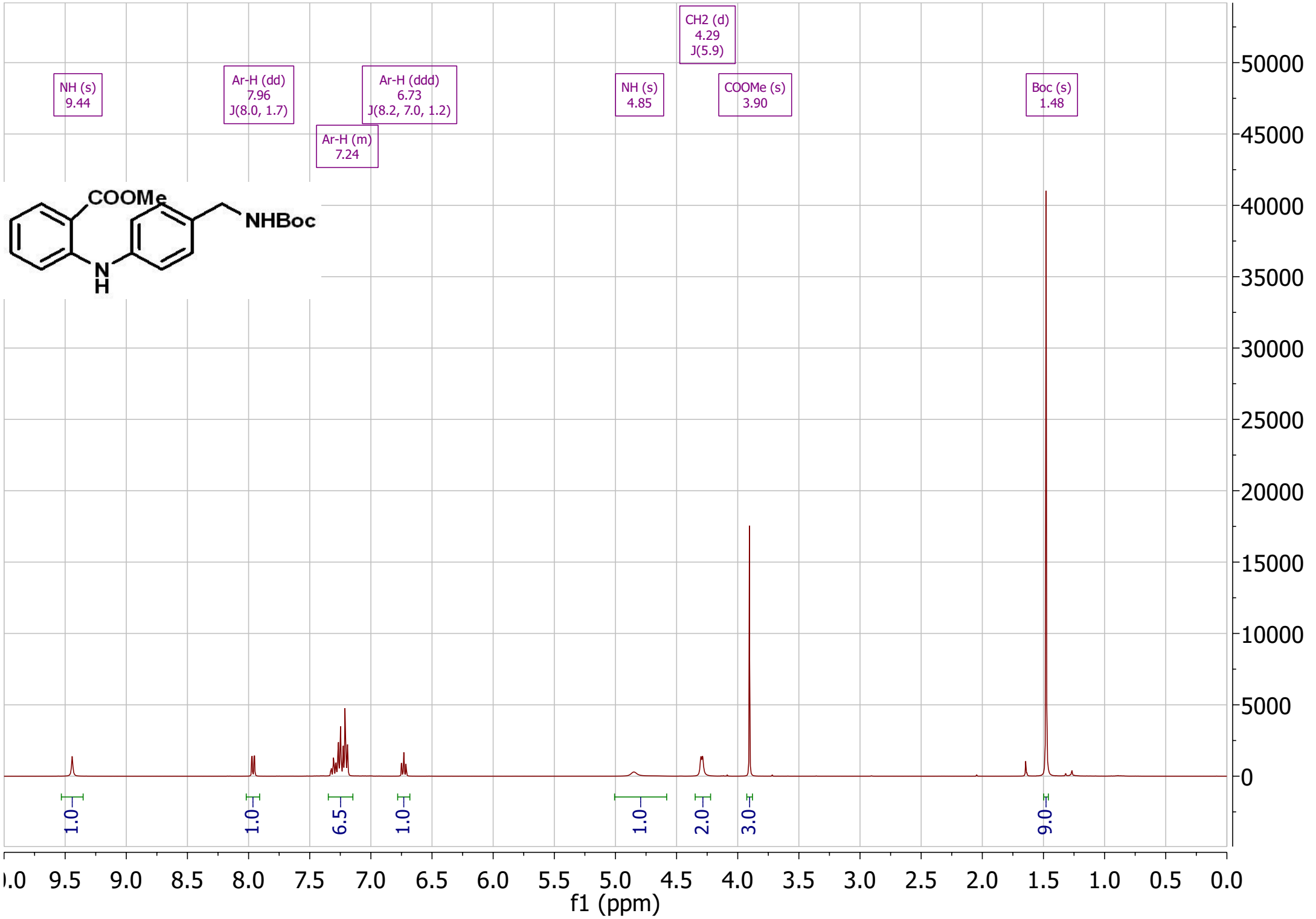

167.9
156.0
146.0
139.6
134.0
133.9
131.9
129.9
121.4
121.1
118.2
114.1
79.4
52.5
42.0
35.7
28.6
Cl
COOMe
NHBoc
N
H
f1 (ppm)

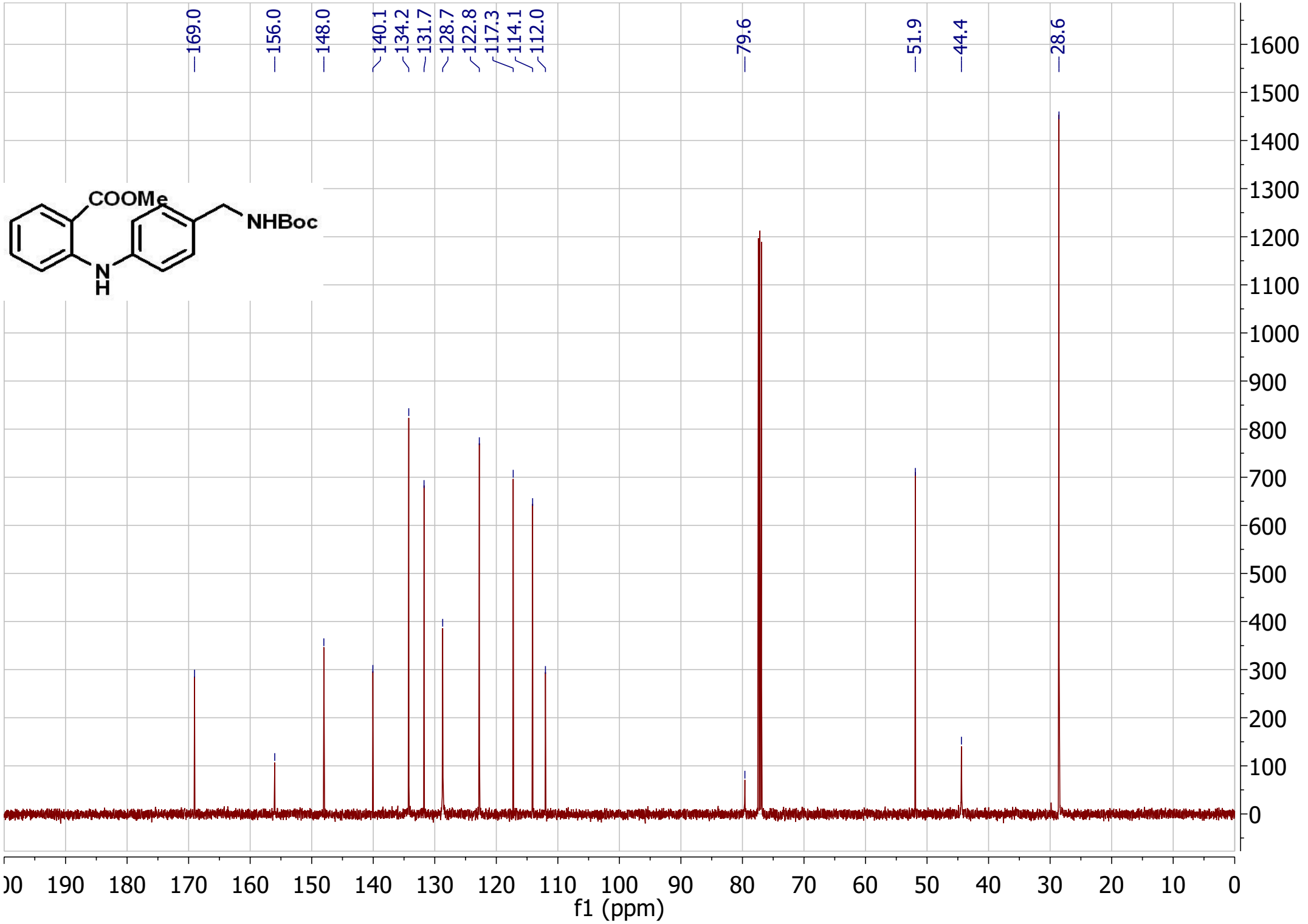

NH (s)
8.03
6 x Ar-H (m)
7.10
Ar-H (dd)
6.67
J(7.0, 0.8)
NH (s)
4.56
COOMe (s)
3.91
CH2 (m)
3.36
CH2 (t)
2.75
J(7.0)
Me (s)
2.44
Boc (s)
1.44
COOMe
NHBoc
N
H
1.0
6.0
1.0
0.9
3.0
2.0
2.0
3.0
9.0
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

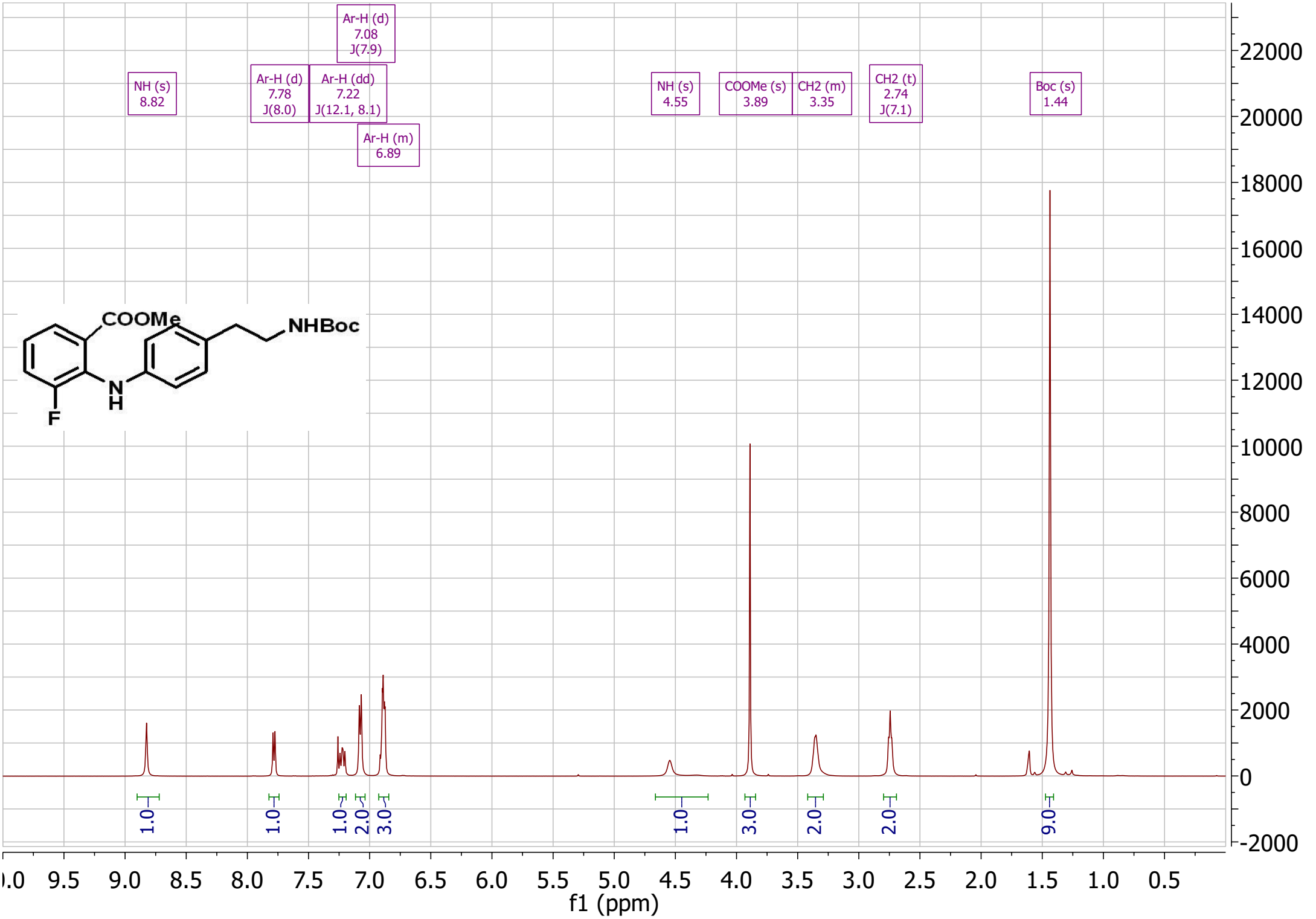

170.0
156.0
145.5
140.4
139.8
133.1
131.7
129.8
122.1
121.1
117.6
113.7
79.3
51.8
42.0
35.7
28.6
22.7
COOMe
NHBoc
N
H
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

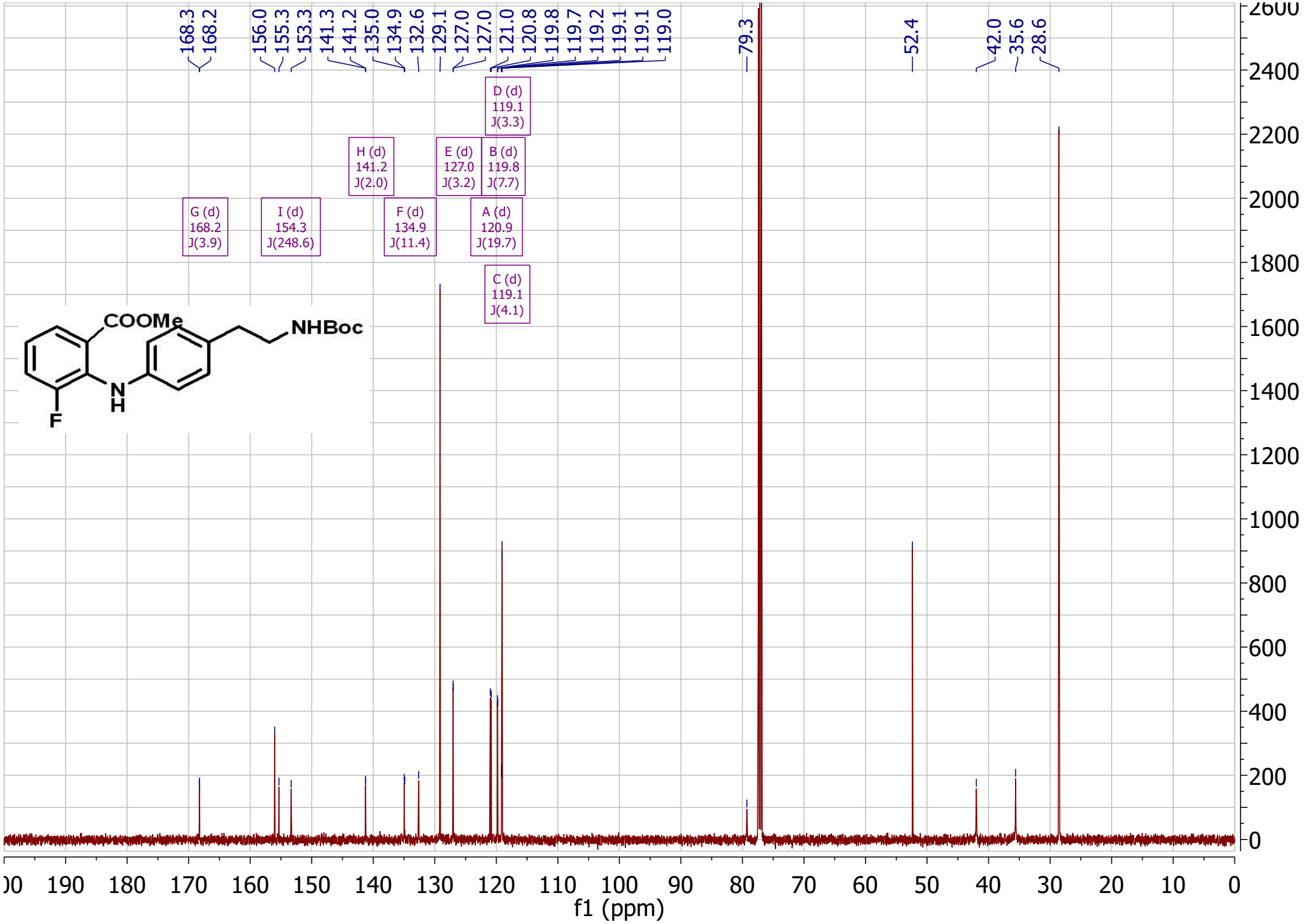

NH (s)
9.58
Ar-H (dd)
7.96
J(9.0, 6.7)
4 x Ar-H (m)
7.19
Ar-H (dd)
6.79
J(12.1, 2.5)
Ar-H (ddd)
6.39
J(9.0, 7.8, 2.5)
NH (s)
4.56
COOMe (s)
3.89
NH2 (m)
3.39
NH2 (t)
2.80
J(7.0)
Boc (s)
1.45
COOMe
NHBoc
F
N
H
1.0
1.0
4.0
1.0
1.0
1.0
3.0
2.0
2.0
9.0
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

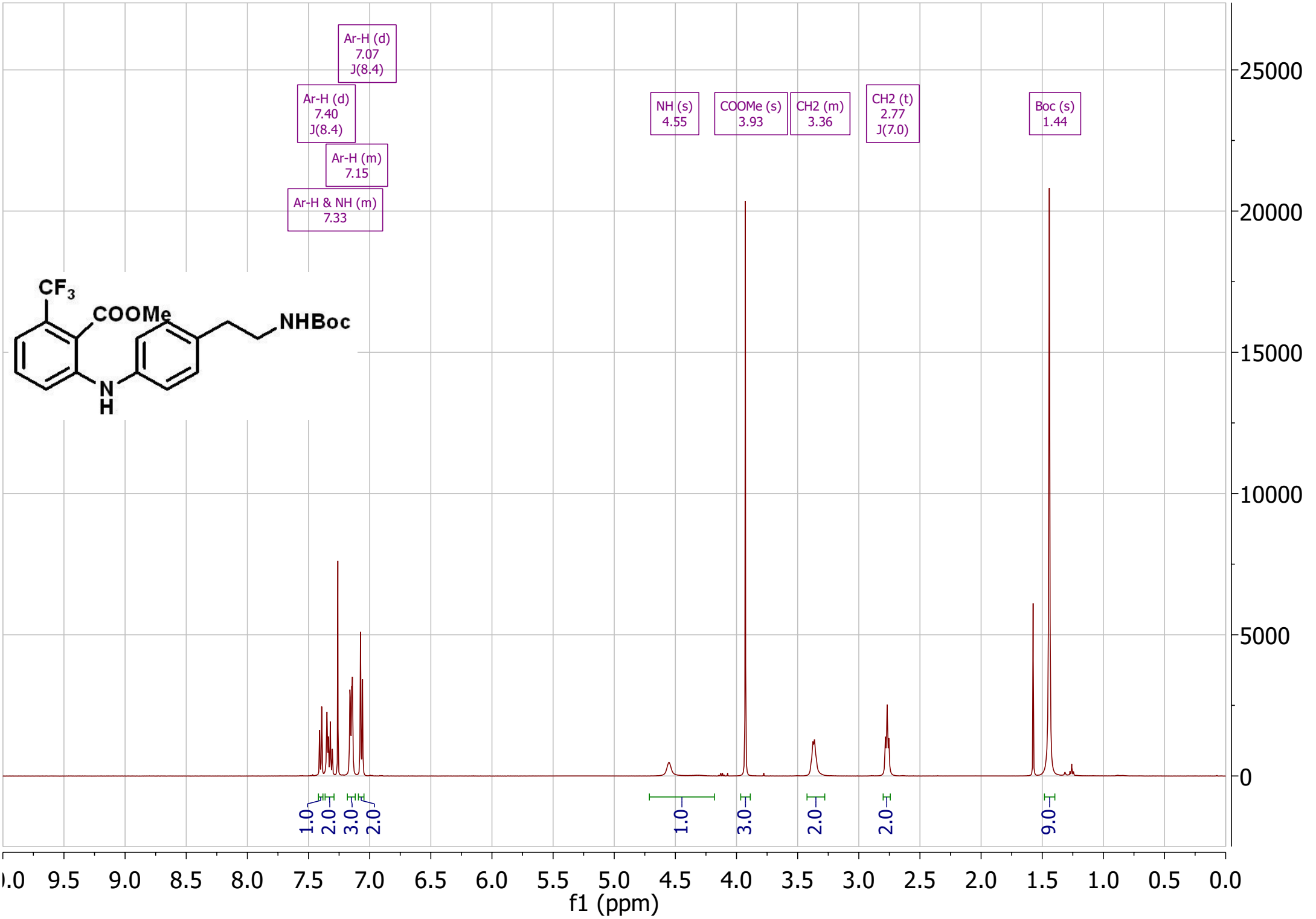

168.4
168.2
165.7
156.0
150.9
150.8
138.4
135.5
134.4
134.3
130.0
123.8
108.0
108.0
104.8
104.6
100.0
99.7
79.4
51.9
41.9
35.9
28.6
F (d)
167.0
J(251.5)
E (d)
150.9
J(12.3)
D (d)
134.4
J(11.5)
B (d)
104.7
J(22.9)
C (d)
108.0
J(1.6)
A (d)
99.8
J(26.4)
COOMe
NHBoc
F
N
H
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
f1 (ppm)

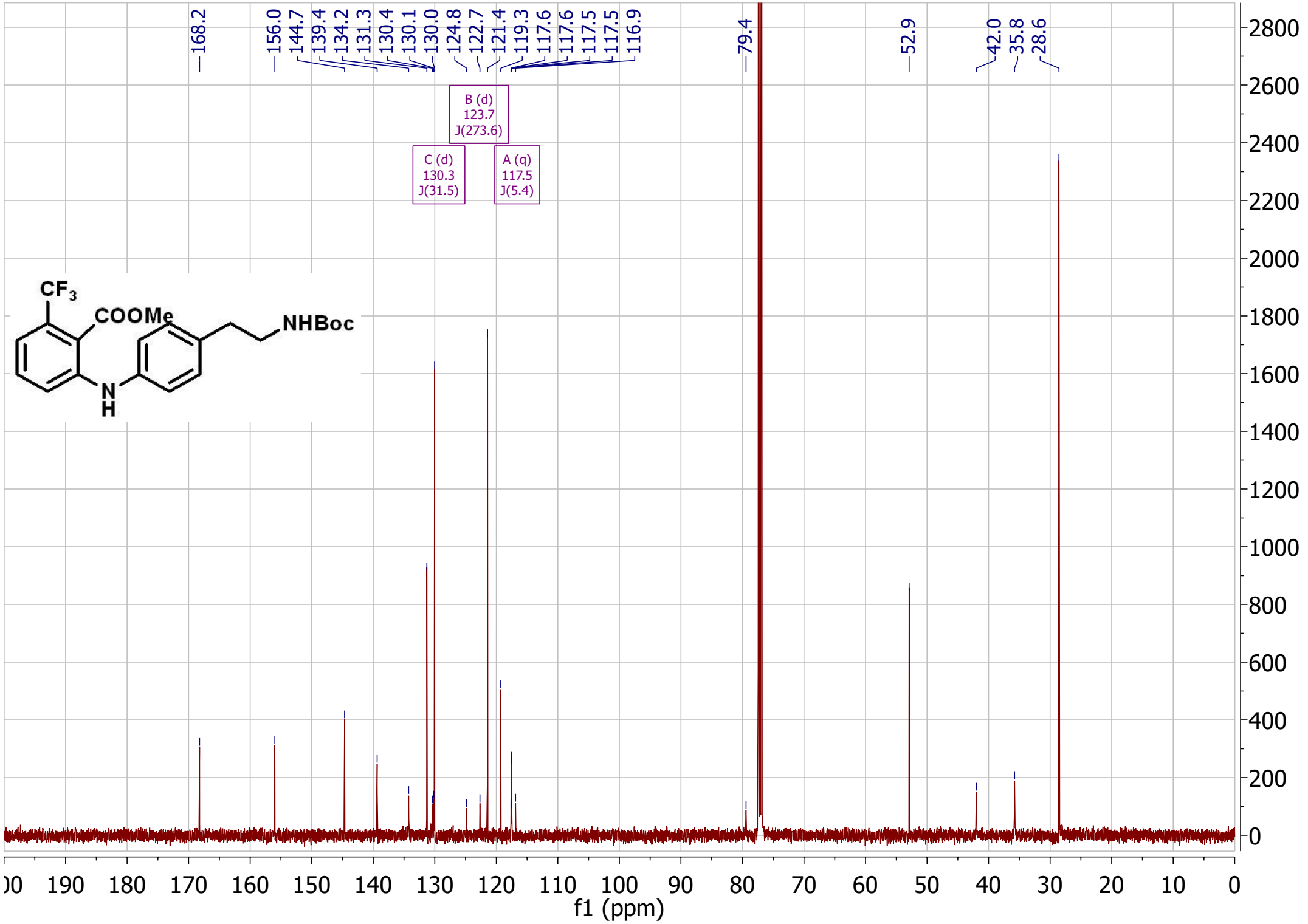

NH (s)
9.44
Ar-H (dd)
7.96
J(8.0, 1.7)
Ar-H (m)
7.24
Ar-H (ddd)
6.73
J(8.2, 7.0, 1.2)
NH (s)
4.85
CH2 (d)
4.29
J(5.9)
COOMe (s)
3.90
Boc (s)
1.48
COOMe
NHBoc
N
H
1.0
1.0
6.5
1.0
1.0
2.0
3.0
9.0
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

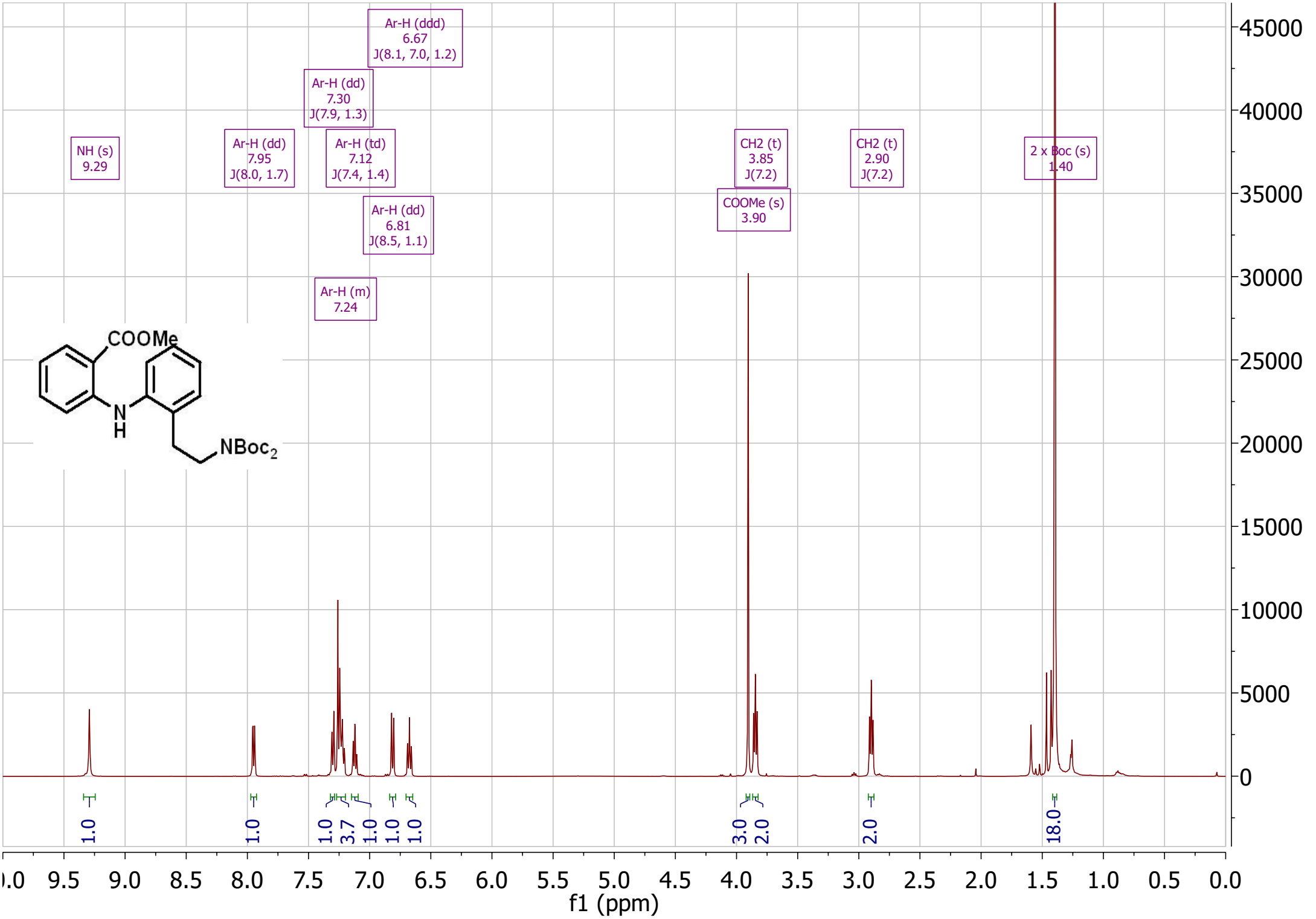

169.0
156.0
148.0
140.1
134.2
131.7
128.7
122.8
117.3
114.1
112.0
79.6
51.9
44.4
28.6
COOMe
NHBoc
N
H
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

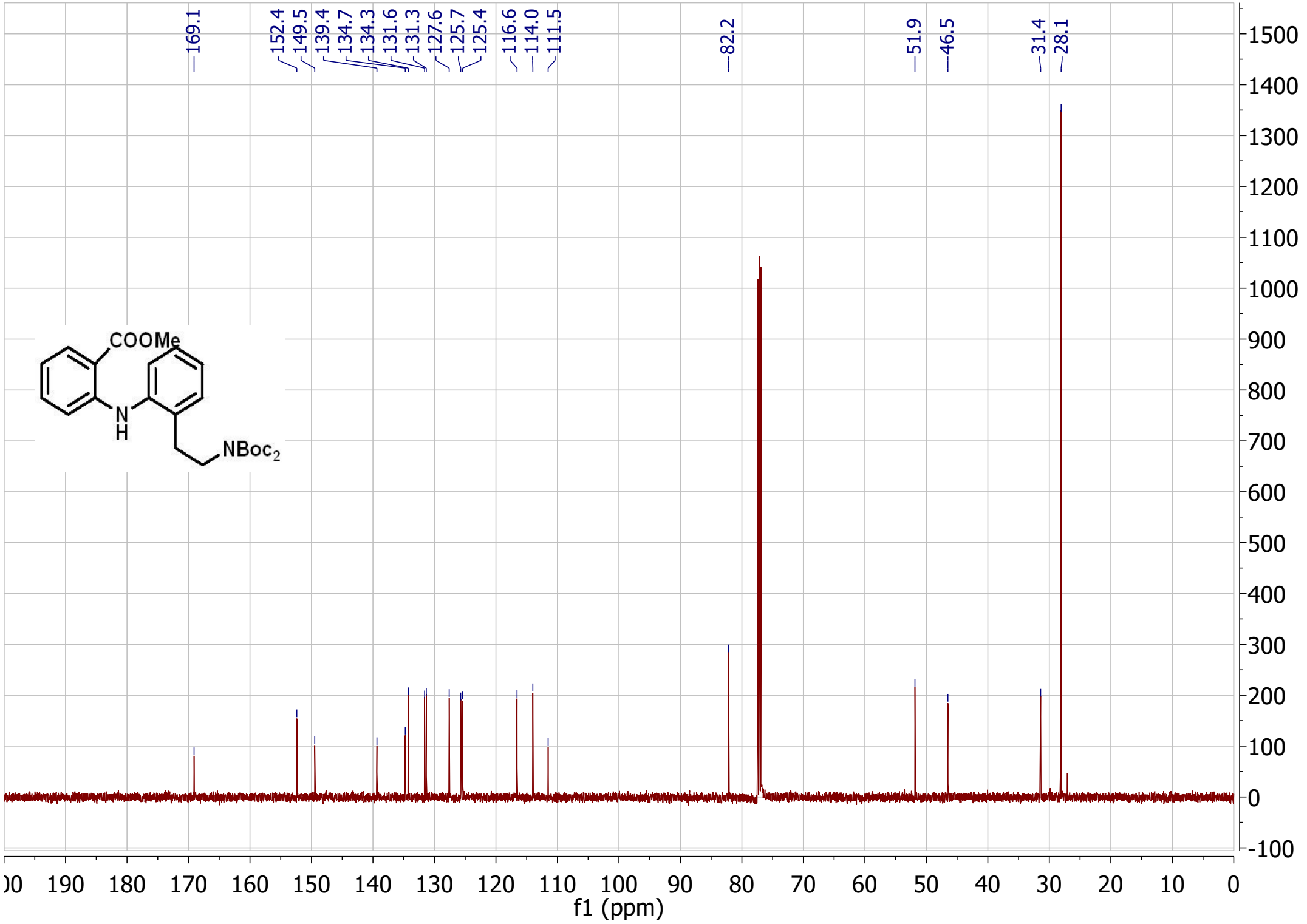

NH (s)
8.82
Ar-H (d)
7.78
J(8.0)
Ar-H (dd)
7.22
J(12.1, 8.1)
Ar-H (d)
7.08
J(7.9)
Ar-H (m)
6.89
NH (s)
4.55
COOMe (s)
3.89
CH2 (m)
3.35
CH2 (t)
2.74
J(7.1)
Boc (s)
1.44
COOMe
NHBoc
N
H
F
1.0
1.0
1.0
2.0
3.0
1.0
3.0
2.0
2.0
9.0
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

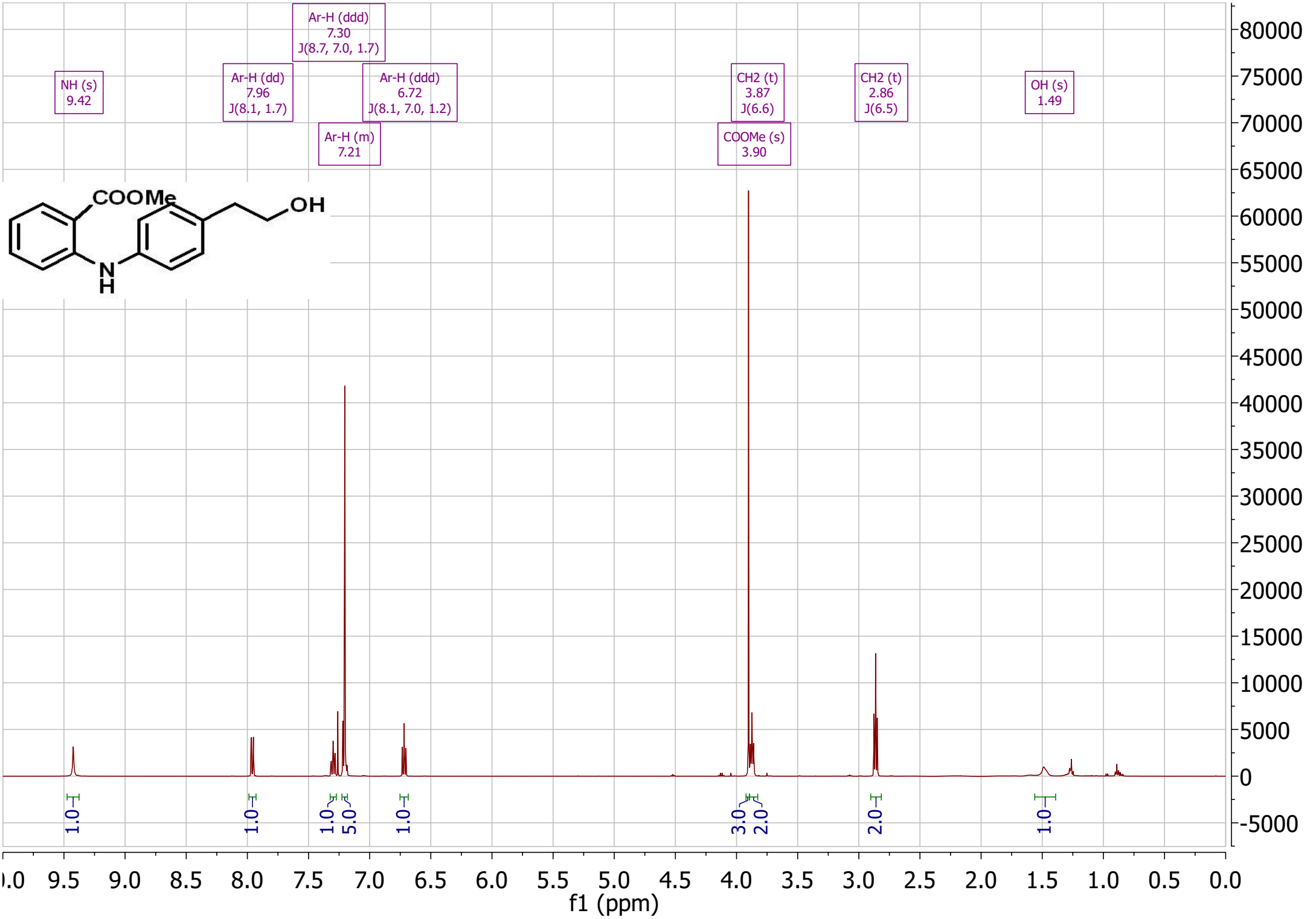

168.3
168.2
156.0
155.3
153.3
141.3
141.2
135.0
134.9
132.6
129.1
127.0
127.0
121.0
120.8
119.8
119.7
119.2
119.1
119.1
119.0
79.3
52.4
42.0
35.6
28.6
D (d)
119.1
J(3.3)
H (d)
141.2
J(2.0)
E (d)
127.0
J(3.2)
B (d)
119.8
J(7.7)
G (d)
168.2
J(3.9)
I (d)
154.3
J(248.6)
F (d)
134.9
J(11.4)
A (d)
120.9
J(19.7)
C (d)
119.1
J(4.1)
COOMe
NHBoc
N
H
F
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

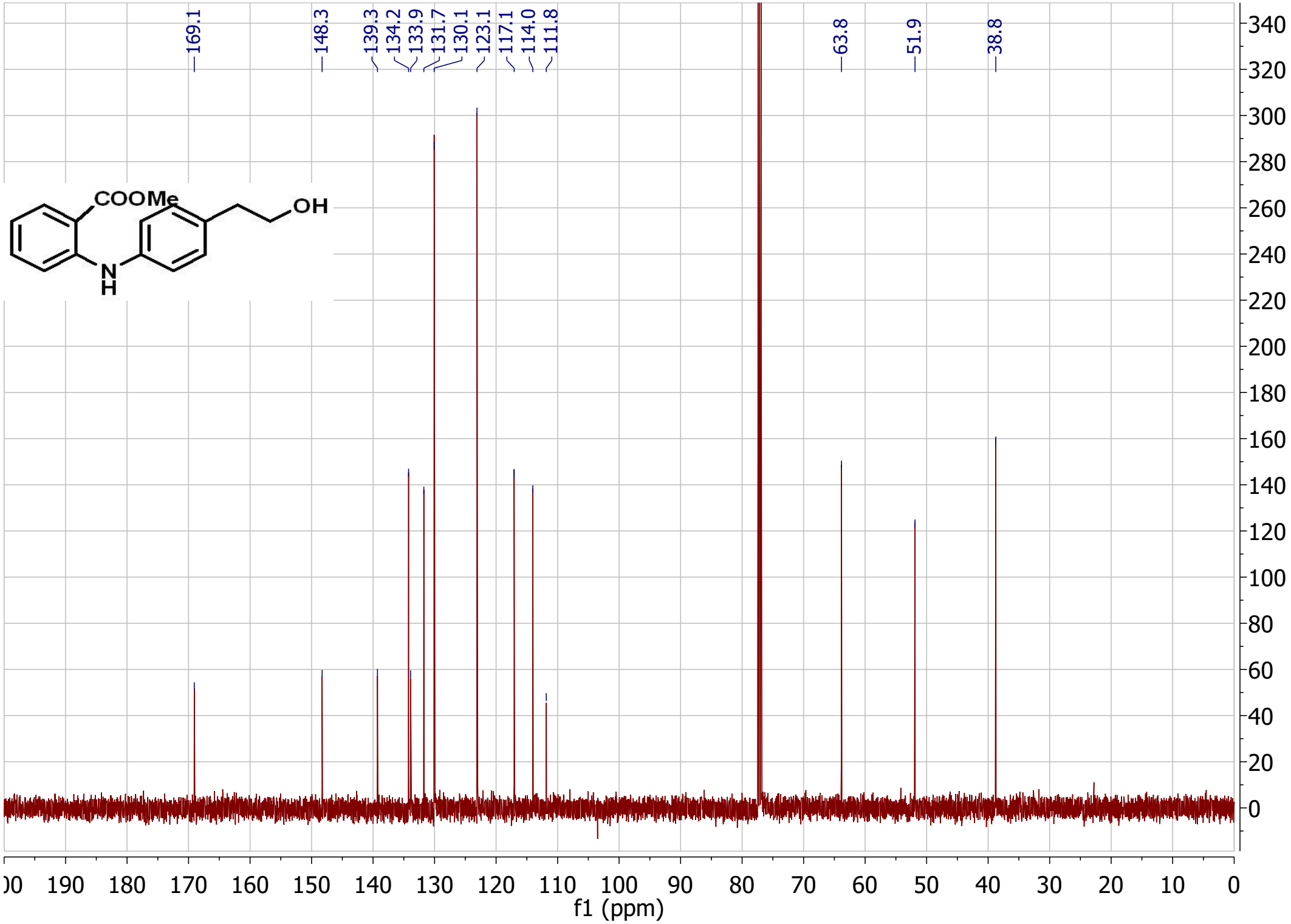

Ar-H (d)
7.07
J(8.4)
Ar-H (d)
7.40
J(8.4)
Ar-H (m)
7.15
Ar-H & NH (m)
7.33
NH (s)
4.55
COOMe (s)
3.93
CH2 (m)
3.36
CH2 (t)
2.77
J(7.0)
Boc (s)
1.44
CF3
COOMe
NHBoc
N
H
1.0
2.0
3.0
2.0
1.0
3.0
2.0
2.0
9.0
25000
20000
15000
10000
5000
0
f1 (ppm)

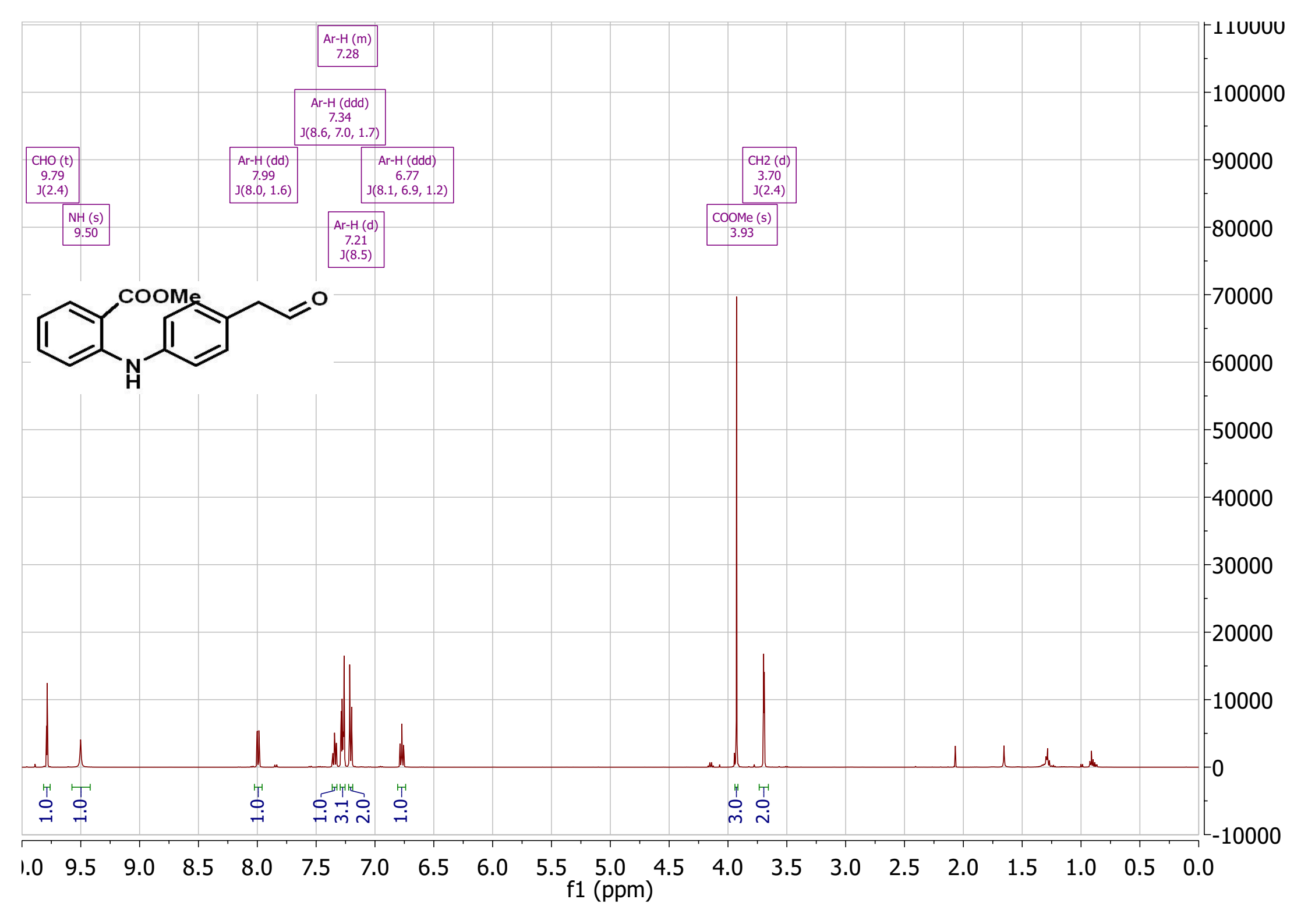

168.2
156.0
144.7
139.4
134.2
131.3
130.4
130.1
130.0
124.8
122.7
121.4
119.3
117.6
117.6
117.5
117.5
116.9
79.4
52.9
42.0
35.8
28.6
B (d)
123.7
J(273.6)
C (d)
130.3
J(31.5)
A (q)
117.5
J(5.4)
CF3
COOMe
NHBoc
N
H
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

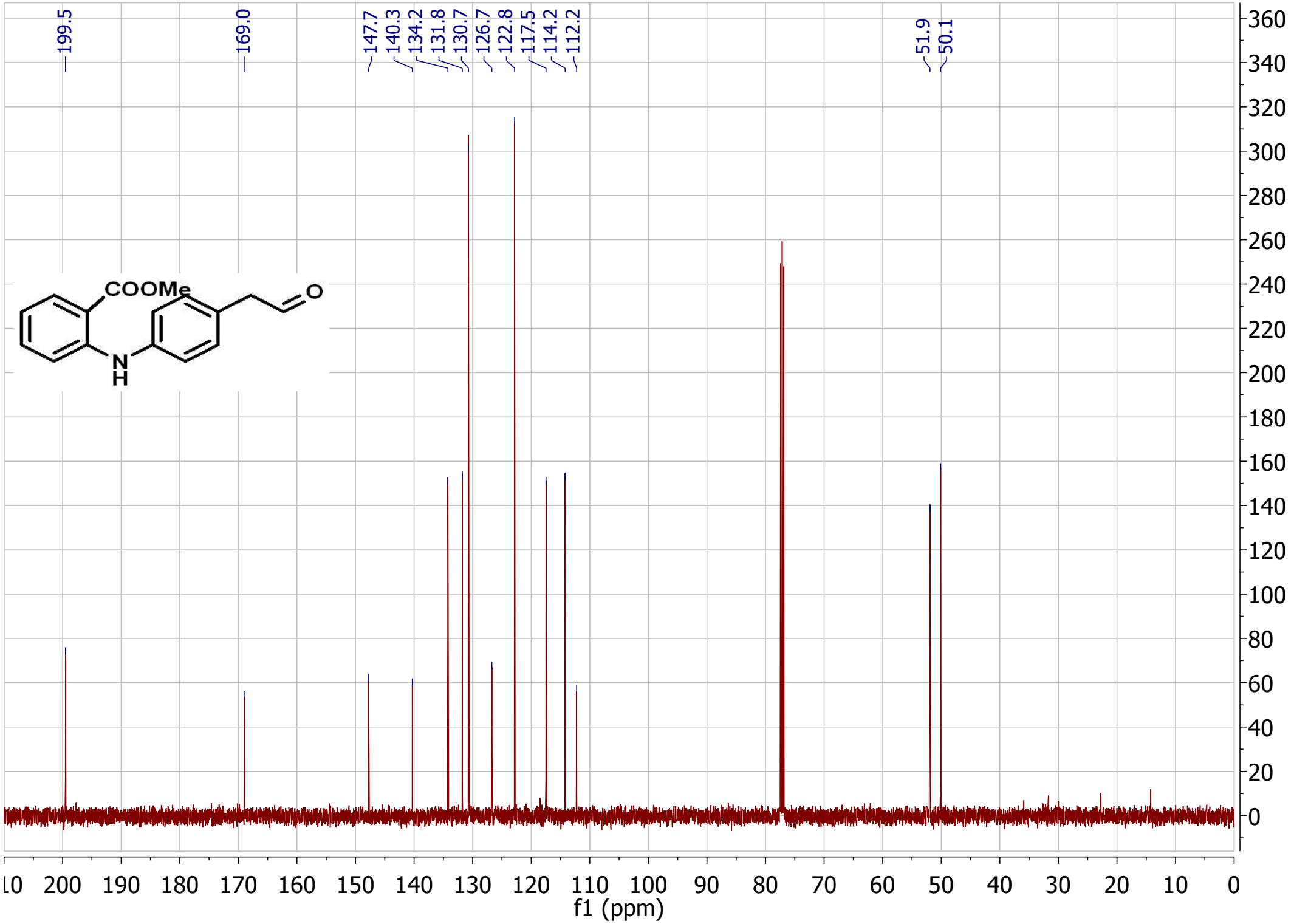

NH (s)
9.29
Ar-H (dd)
7.95
J(8.0, 1.7)
Ar-H (ddd)
6.67
J(8.1, 7.0, 1.2)
Ar-H (dd)
7.30
J(7.9, 1.3)
Ar-H (td)
7.12
J(7.4, 1.4)
Ar-H (dd)
6.81
J(8.5, 1.1)
Ar-H (m)
7.24
CH2 (t)
3.85
J(7.2)
COOMe (s)
3.90
CH2 (t)
2.90
J(7.2)
2 x Boc (s)
1.40
COOMe
N
H
NBoc2
1.0
1.0
1.0
3.7
1.0
1.0
1.0
3.0
2.0
2.0
18.0
45000
40000
35000
30000
25000
20000
15000
10000
5000
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
f1 (ppm)

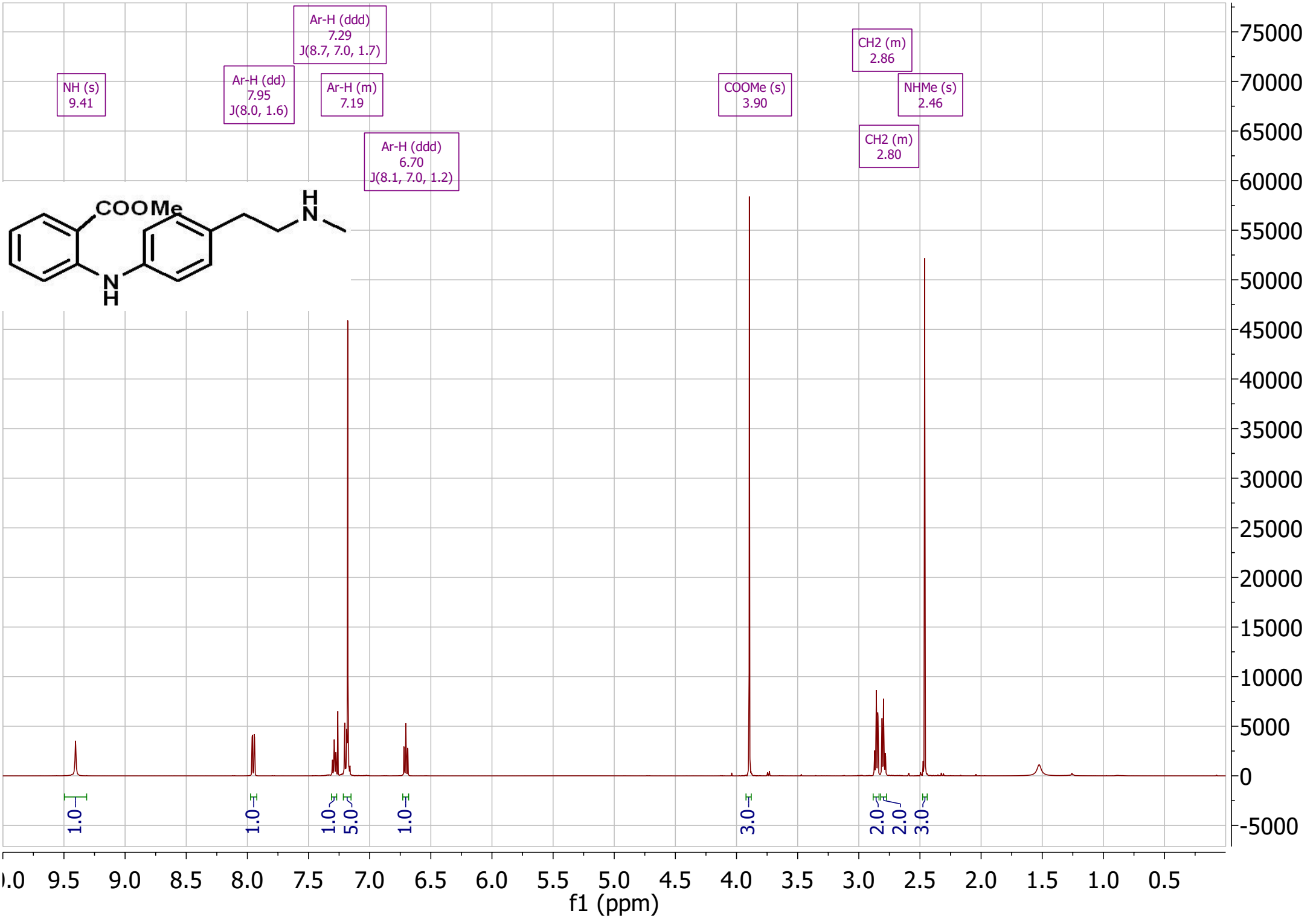

169.1
152.4
149.5
139.4
134.7
134.3
131.6
131.3
127.6
125.7
125.4
116.6
114.0
111.5
82.2
51.9
46.5
31.4
28.1
COOMe
N
H
NBoc2
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

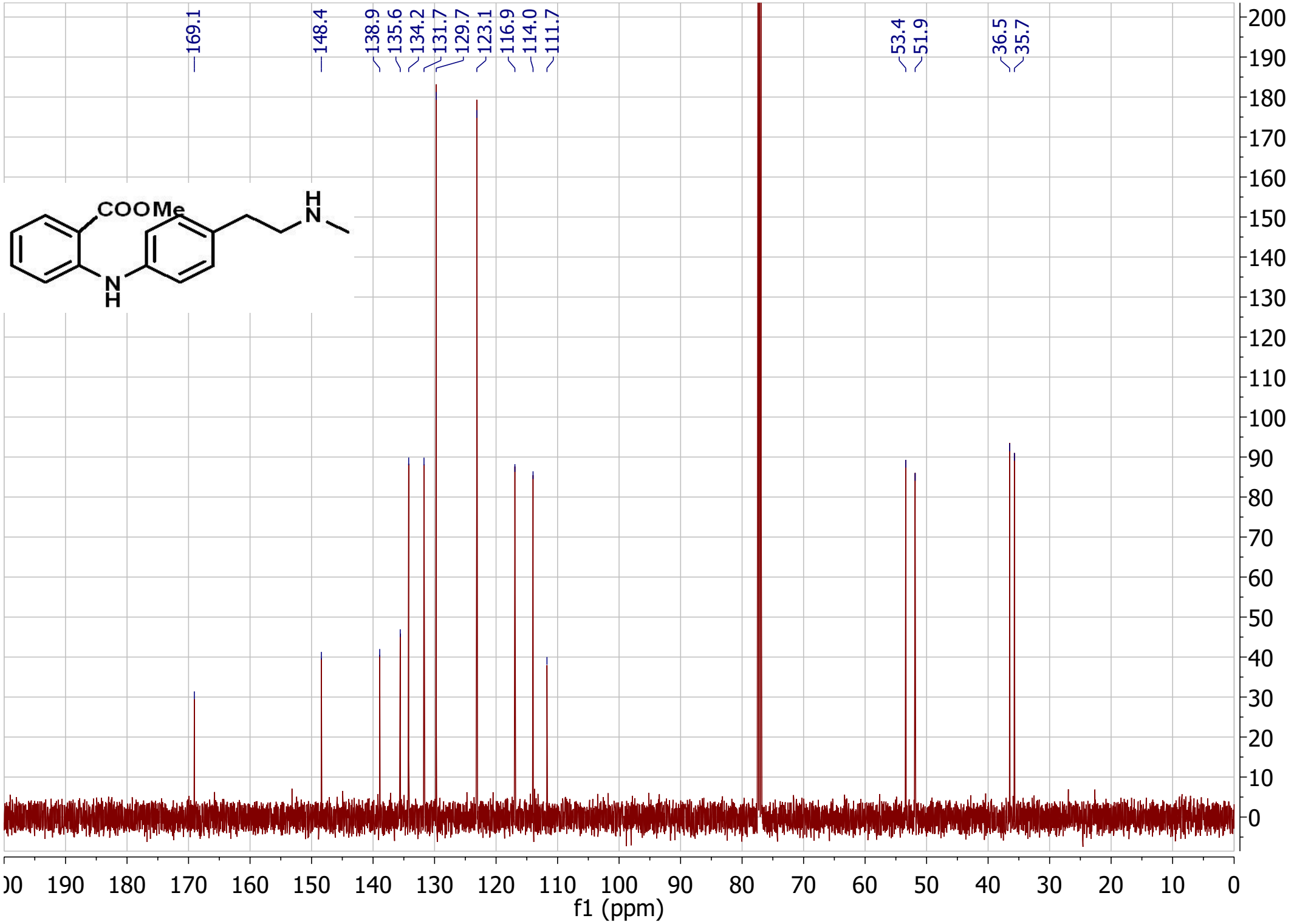

NH (s)
9.42
Ar-H (dd)
7.96
J(8.1, 1.7)
Ar-H (ddd)
7.30
J(8.7, 7.0, 1.7)
Ar-H (m)
7.21
Ar-H (ddd)
6.72
J(8.1, 7.0, 1.2)
CH2 (t)
3.87
J(6.6)
COOMe (s)
3.90
CH2 (t)
2.86
J(6.5)
OH (s)
1.49
COOMe
OH
N
H
1.0
1.0
1.0
5.0
1.0
3.0
2.0
2.0
1.0
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

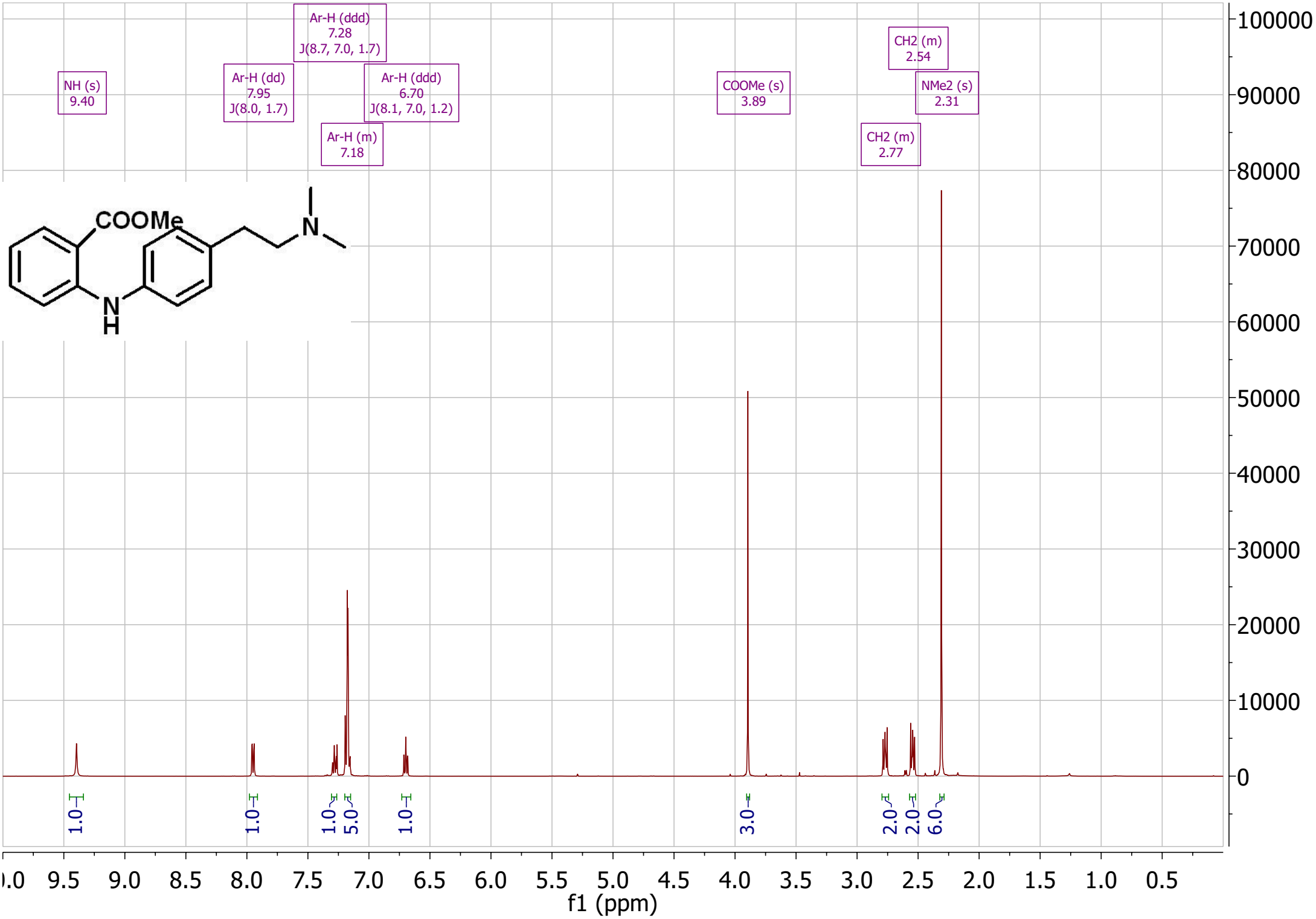

169.1
148.3
139.3
134.2
133.9
131.7
130.1
123.1
117.1
114.0
111.8
63.8
51.9
38.8
COOMe
OH
N
H
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

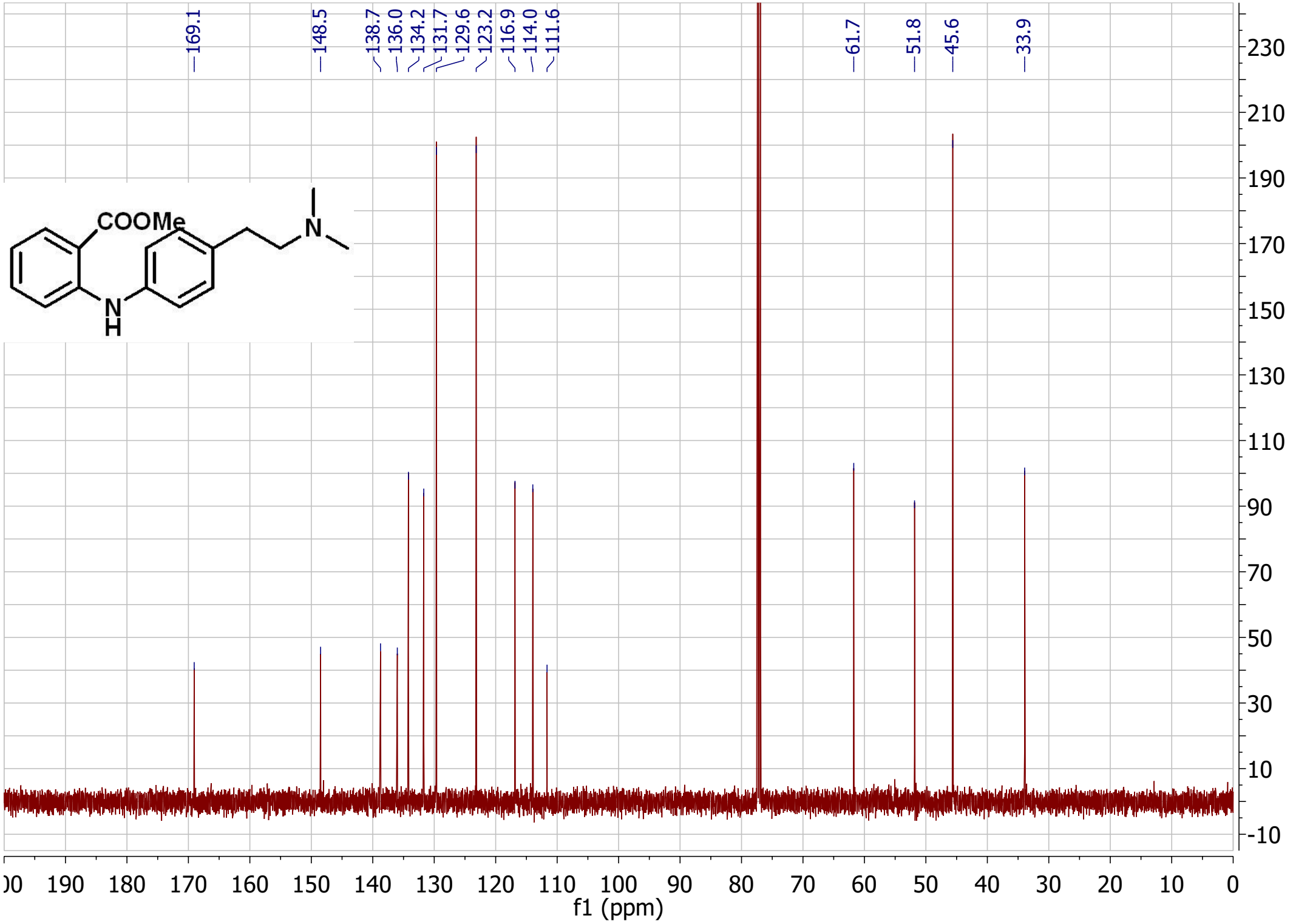

Ar-H (m)
7.28
Ar-H (ddd)
7.34
J(8.6, 7.0, 1.7)
CHO (t)
9.79
J(2.4)
Ar-H (dd)
7.99
J(8.0, 1.6)
Ar-H (ddd)
6.77
J(8.1, 6.9, 1.2)
CH2 (d)
3.70
J(2.4)
NH (s)
9.50
Ar-H (d)
7.21
J(8.5)
COOMe (s)
3.93
COOMe
O
N
H
1.0
1.0
1.0
1.0
3.1
2.0
1.0
3.0
2.0
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

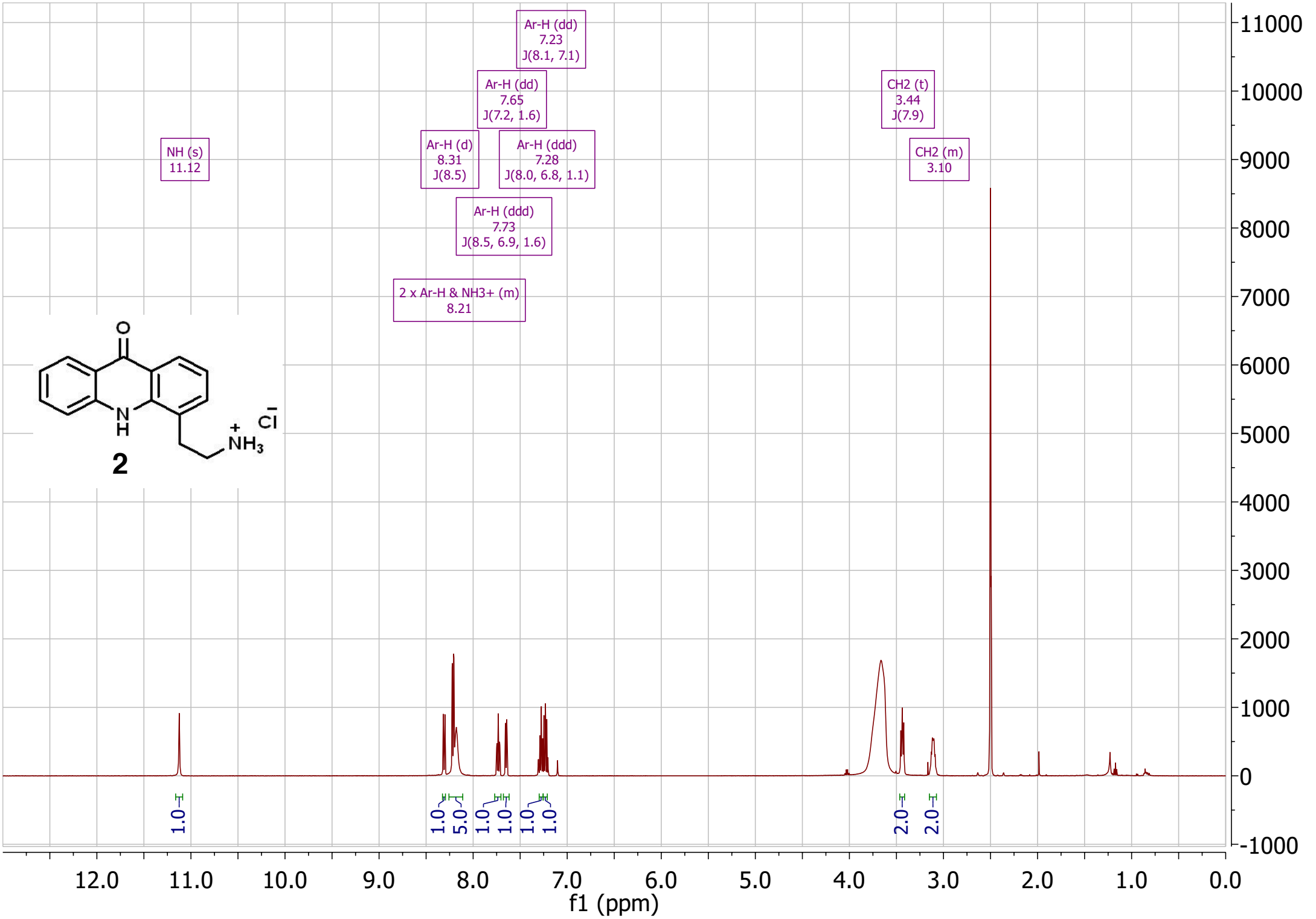

199.5
169.0
147.7
140.3
134.2
131.8
130.7
126.7
122.8
117.5
114.2
112.2
51.9
50.1
COOMe
O
N
H
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

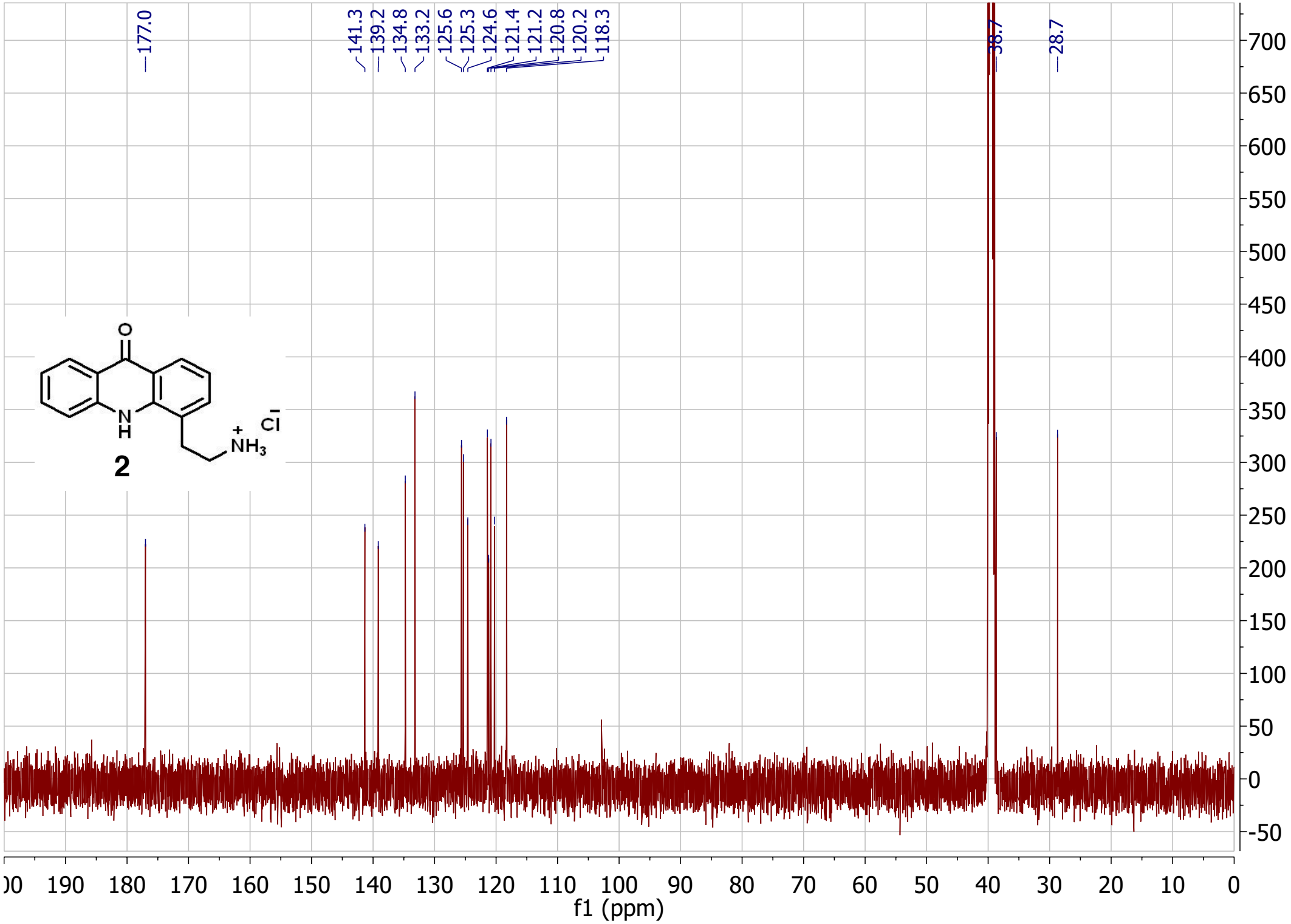

NH (s)
9.41
Ar-H (dd)
7.95
J(8.0, 1.6)
Ar-H (ddd)
7.29
J(8.7, 7.0, 1.7)
Ar-H (m)
7.19
Ar-H (ddd)
6.70
J(8.1, 7.0, 1.2)
COOMe (s)
3.90
CH2 (m)
2.86
NHMe (s)
2.46
CH2 (m)
2.80
COOMe
H
N
N
H
1.0
1.0
1.0
5.0
1.0
3.0
2.0
2.0
3.0
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

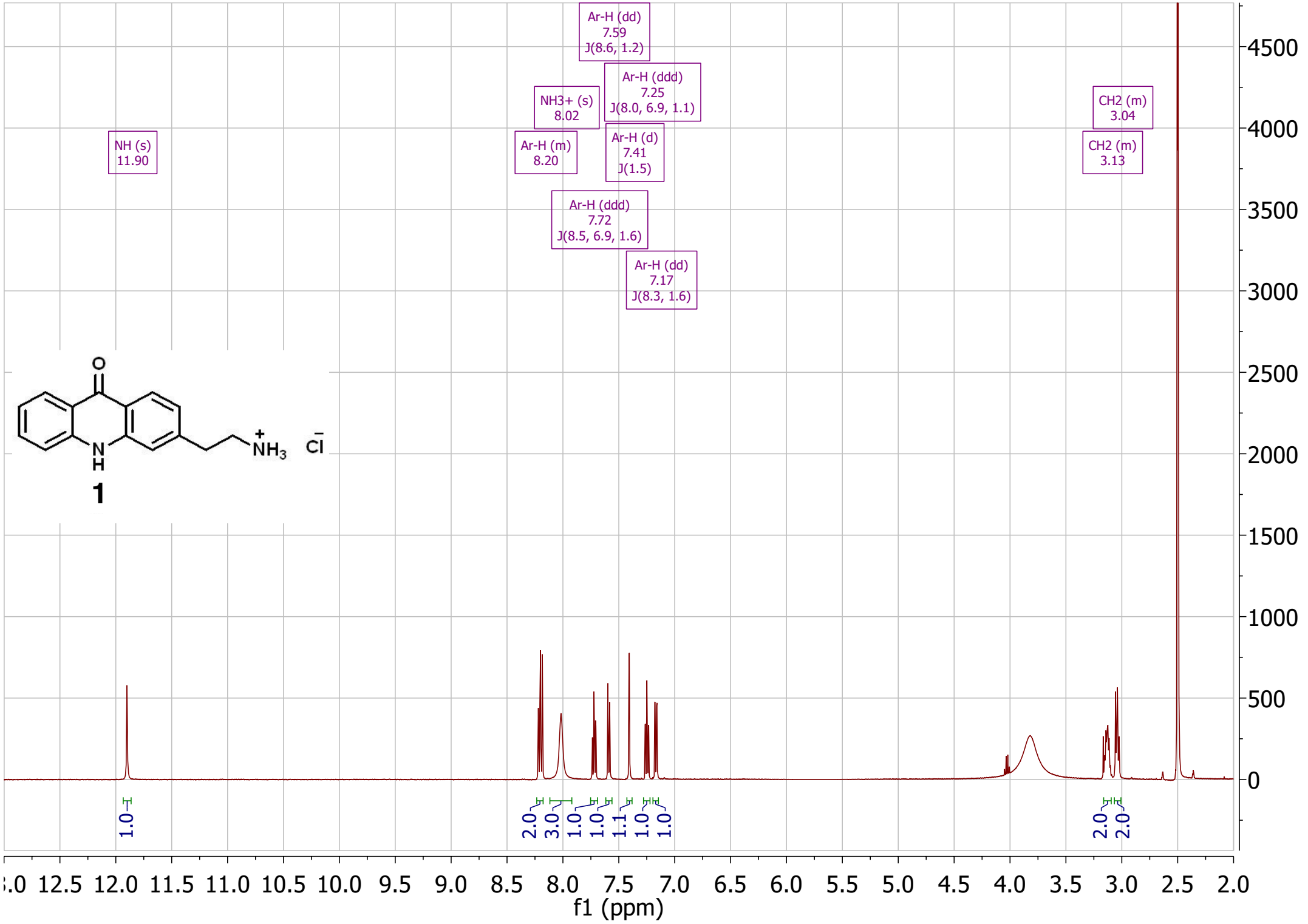

169.1
148.4
138.9
135.6
134.2
131.7
129.7
123.1
116.9
114.0
111.7
53.4
51.9
36.5
35.7
COOMe
H
N
N
H
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

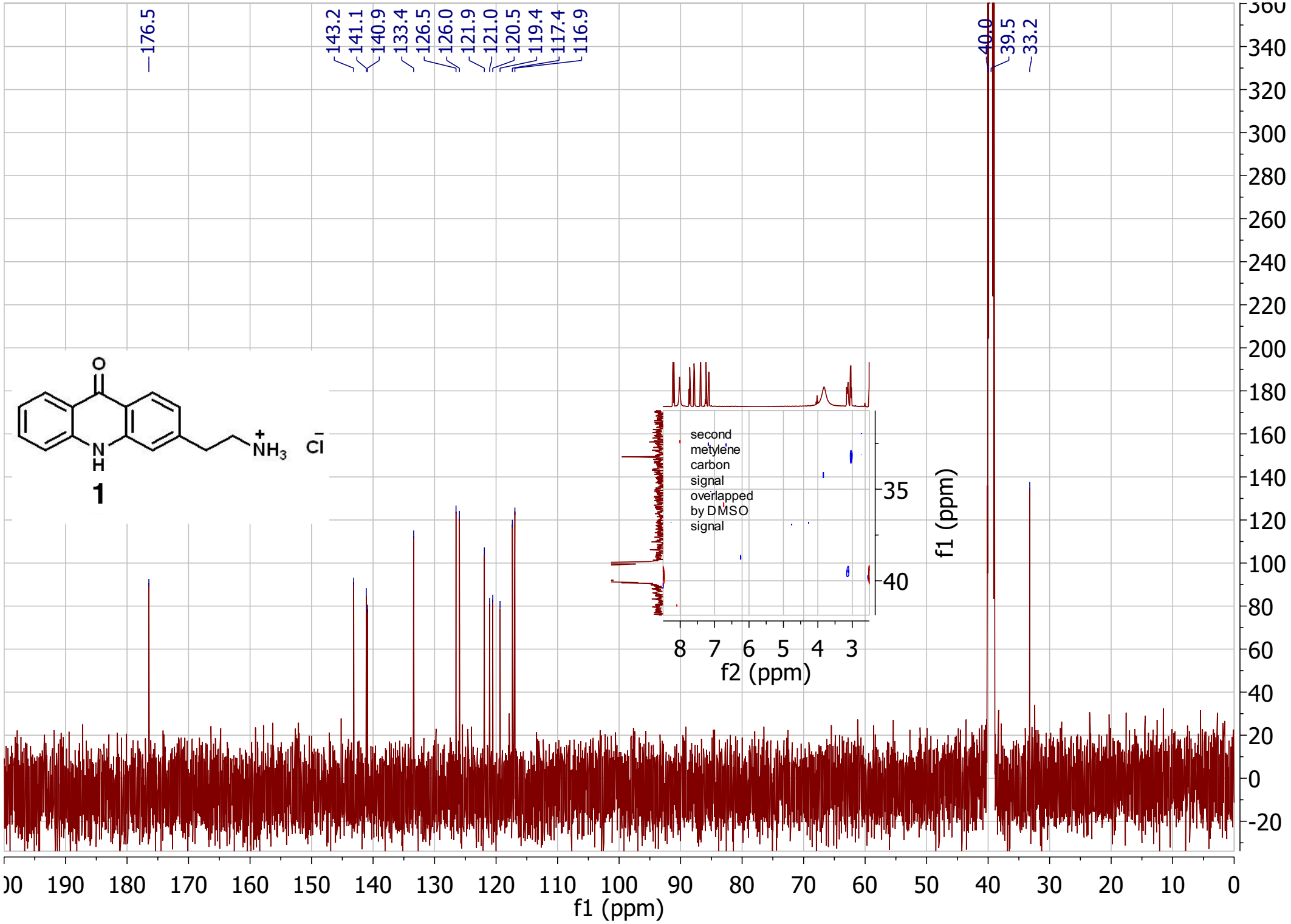

NH (s)
9.40
Ar-H (dd)
7.95
J(8.0, 1.7)
Ar-H (ddd)
7.28
J(8.7, 7.0, 1.7)
Ar-H (m)
7.18
Ar-H (ddd)
6.70
J(8.1, 7.0, 1.2)
COOMe (s)
3.89
CH2 (m)
2.77
CH2 (m)
2.54
NMe2 (s)
2.31
COOMe
N
N
H
1.0
1.0
1.0
5.0
1.0
3.0
2.0
2.0
6.0
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

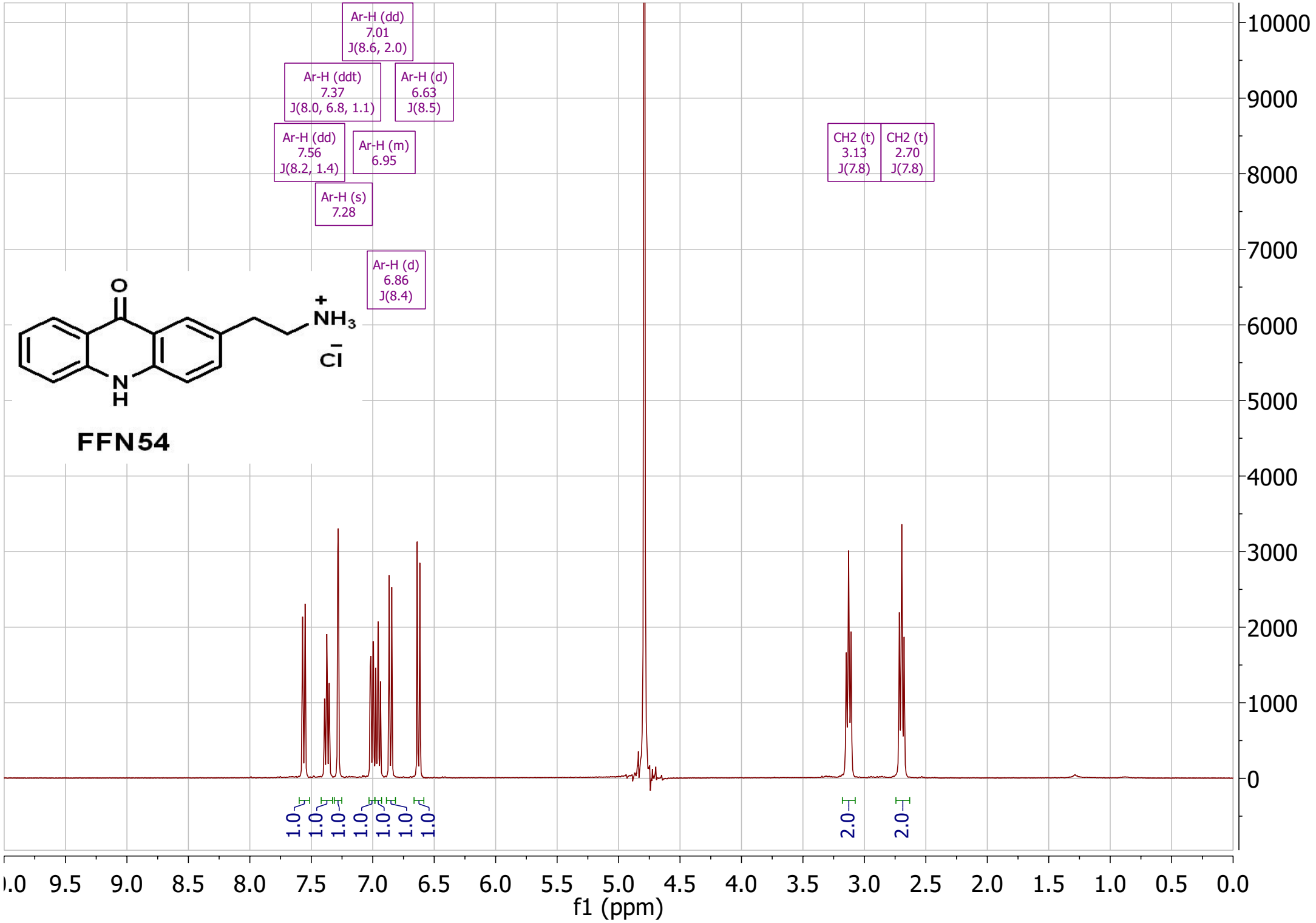

169.1
148.5
138.7
136.0
134.2
131.7
129.6
123.2
116.9
114.0
111.6
61.7
51.8
45.6
33.9
COOMe
N
N
H
230
210
190
170
150
130
110
90
70
50
30
10
-10
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

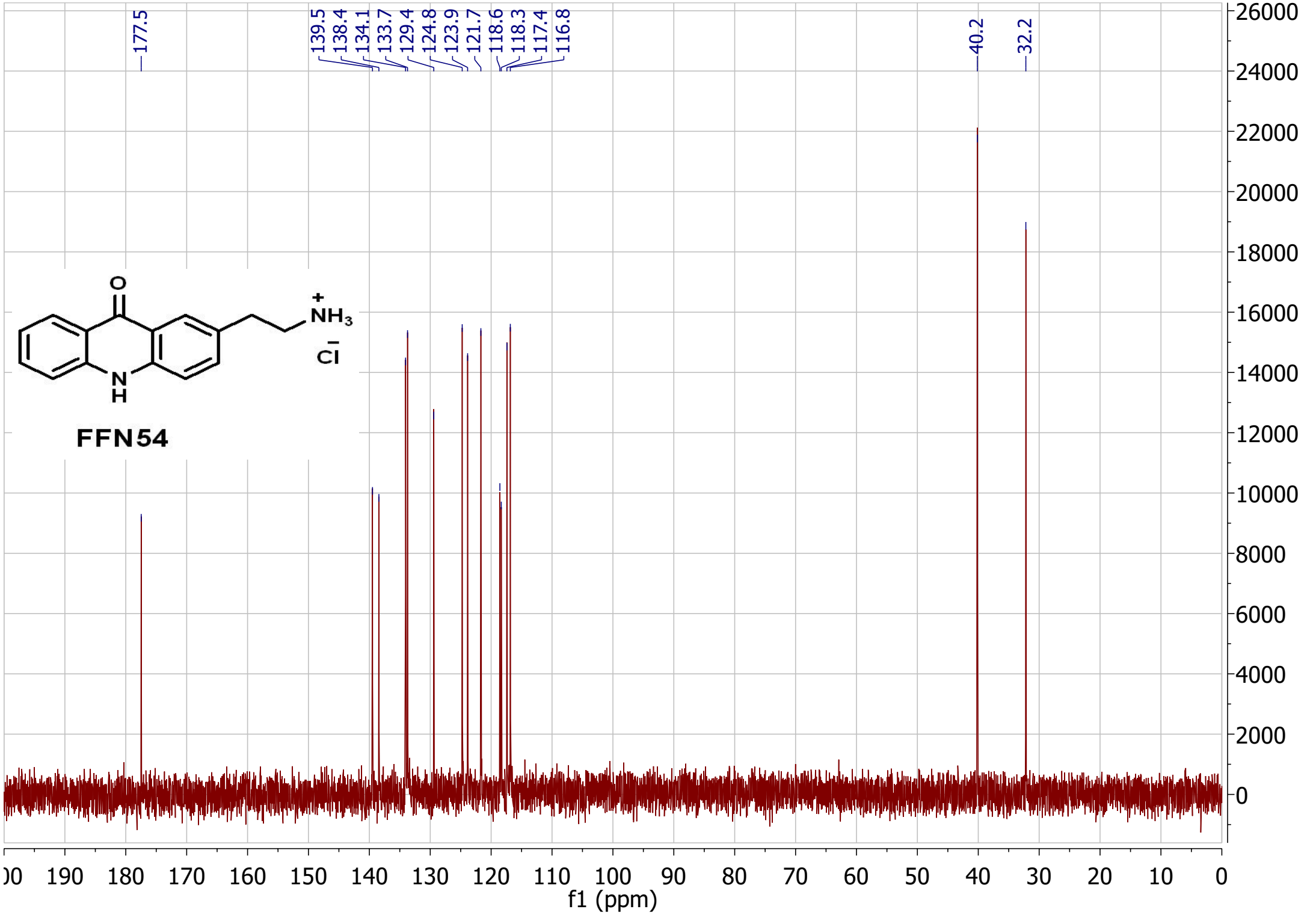

Ar-H (dd)
7.23
J(8.1, 7.1)
Ar-H (dd)
7.65
J(7.2, 1.6)
Ar-H (d)
8.31
J(8.5)
Ar-H (ddd)
7.28
J(8.0, 6.8, 1.1)
Ar-H (ddd)
7.73
J(8.5, 6.9, 1.6)
2 x Ar-H & NH3+ (m)
8.21
NH (s)
11.12
CH2 (t)
3.44
J(7.9)
CH2 (m)
3.10
O
N
H
+
NH3
Cl
2
1.0
1.0
5.0
1.0
1.0
1.0
1.0
2.0
2.0
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

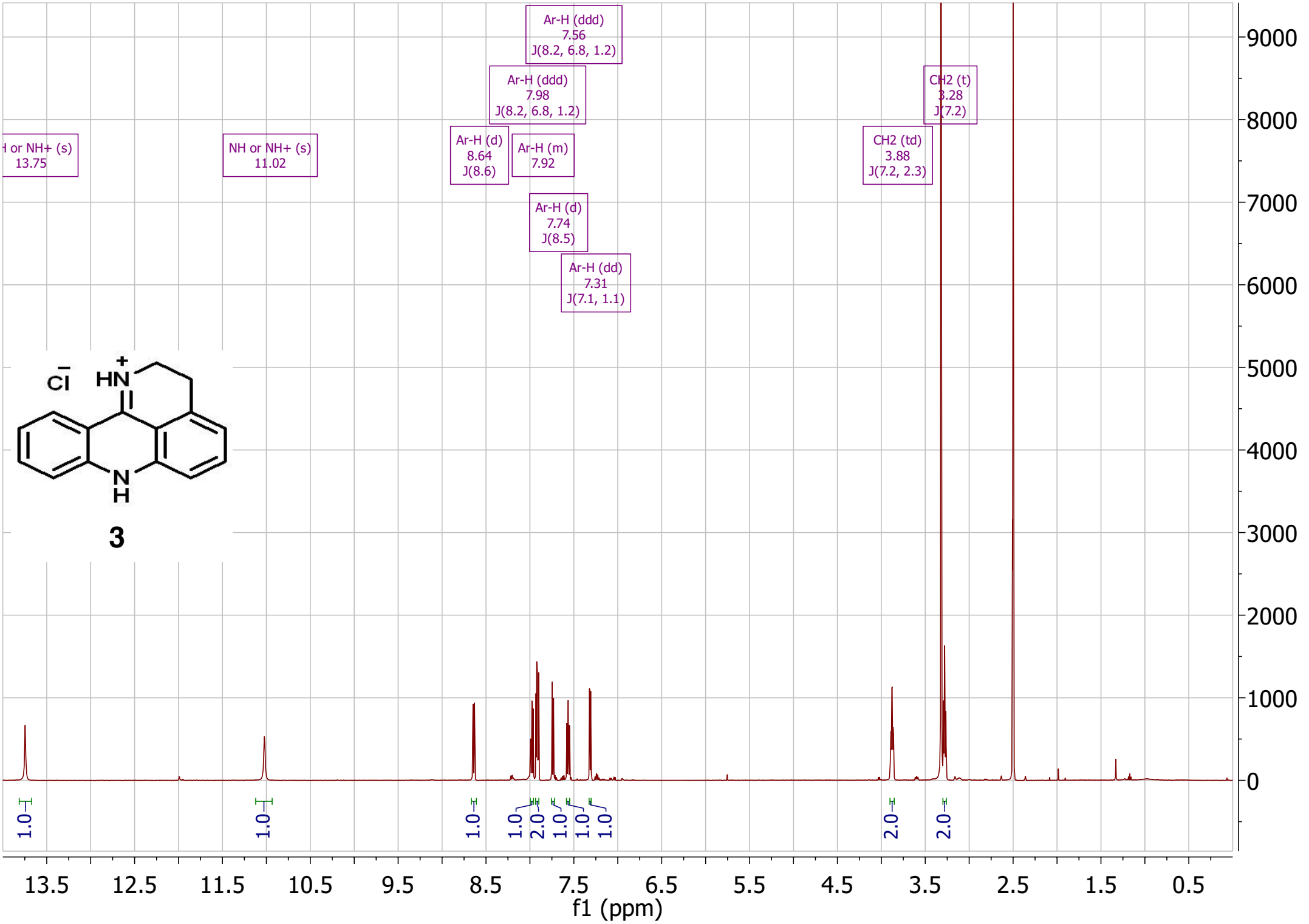

177.0
141.3
139.2
134.8
133.2
125.6
125.3
124.6
121.4
121.2
120.8
120.2
118.3
38.7
28.7
O
N
H
+
NH3
Cl
2
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

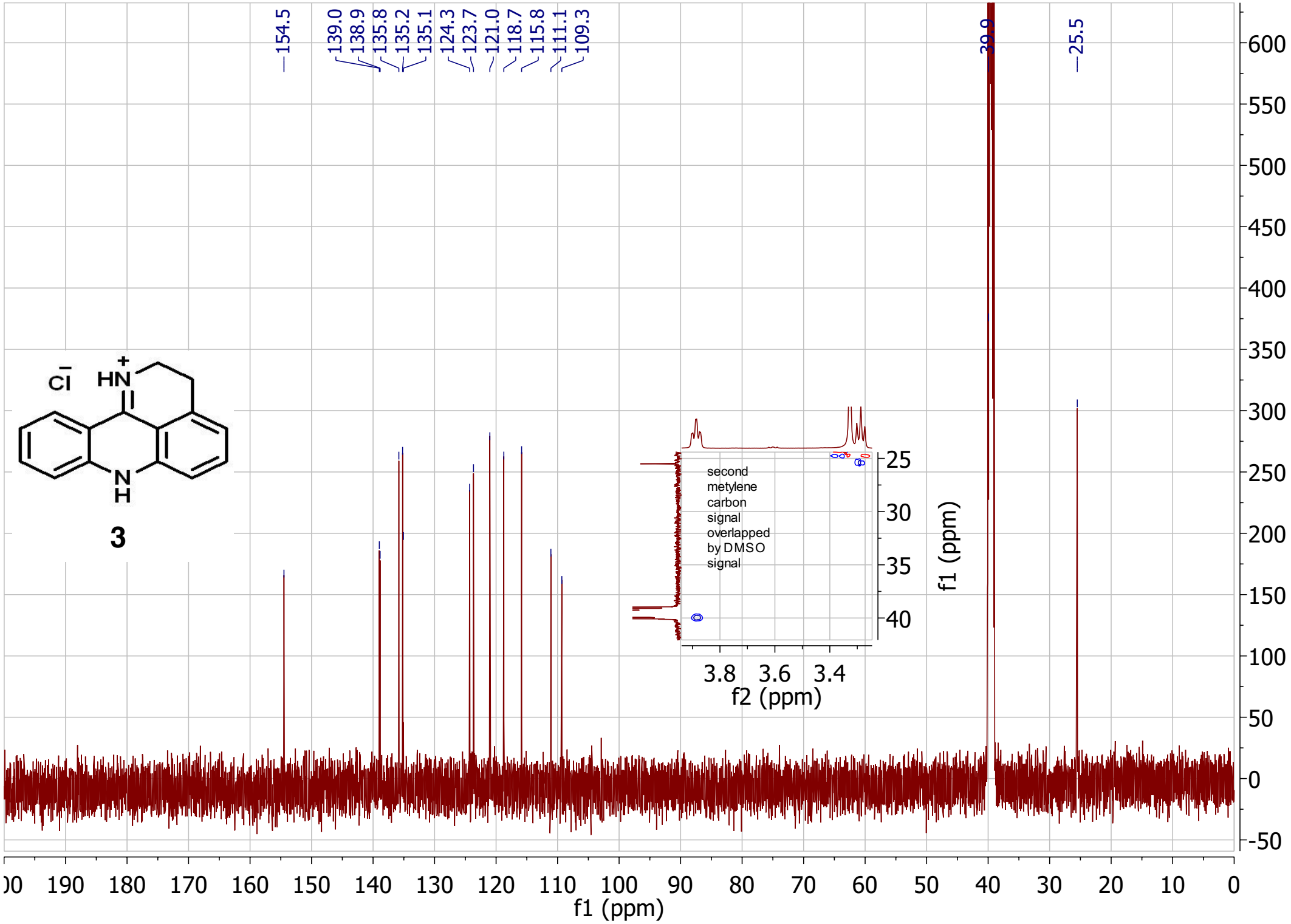

Ar-H (dd)
7.59
J(8.6, 1.2)
Ar-H (ddd)
7.25
J(8.0, 6.9, 1.1)
NH3+ (s)
8.02
Ar-H (m)
8.20
Ar-H (d)
7.41
J(1.5)
Ar-H (ddd)
7.72
J(8.5, 6.9, 1.6)
Ar-H (dd)
7.17
J(8.3, 1.6)
NH (s)
11.90
CH2 (m)
3.04
CH2 (m)
3.13
O
N
H
NH3
Cl
1
1.0
2.0
3.0
1.0
1.0
1.1
1.0
1.0
2.0
2.0
4500
4000
3500
3000
2500
2000
1500
1000
500
0
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
f1 (ppm)

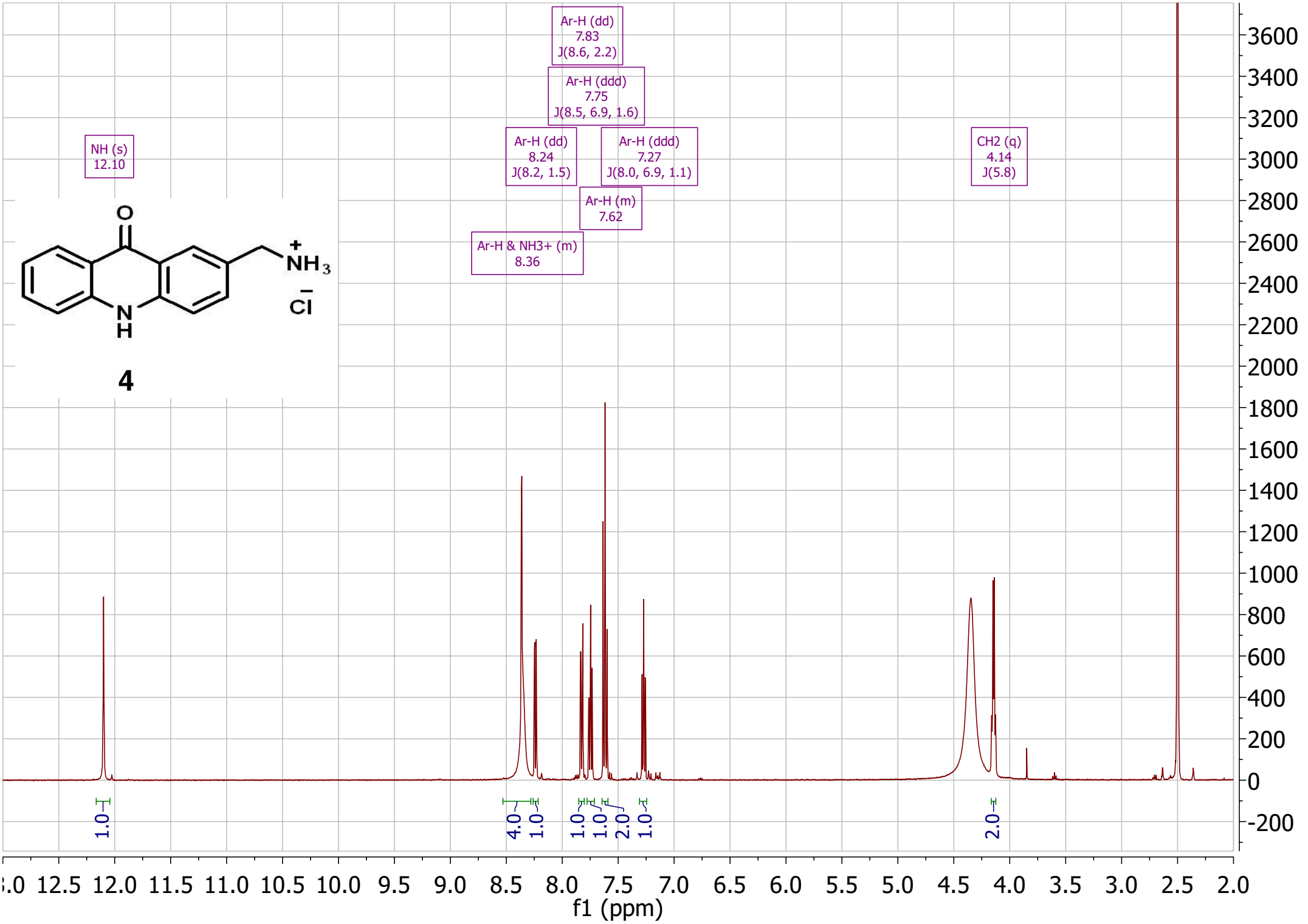

176.5
143.2
141.1
140.9
133.4
126.5
126.0
121.9
121.0
120.5
119.4
117.4
116.9
40.0
39.5
33.2
O
N
H
NH3
Cl
1
second
metylene
carbon
signal
overlapped
by DMSO
signal
35
40
8 7 6 5 4 3
f2 (ppm)
f1 (ppm)
f1 (ppm)

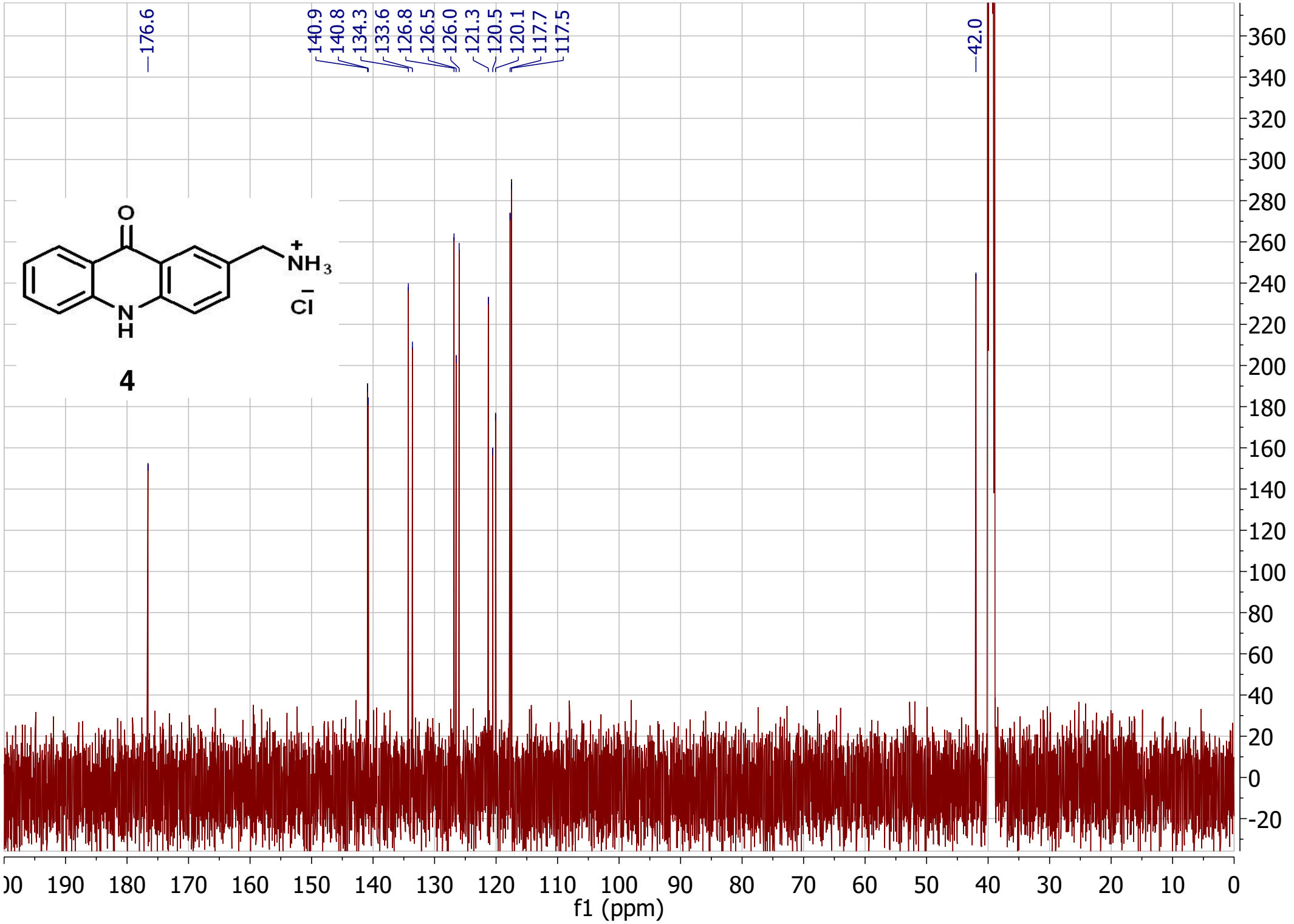

Ar-H (dd)
7.01
J(8.6, 2.0)
Ar-H (ddt)
7.37
J(8.0, 6.8, 1.1)
Ar-H (d)
6.63
J(8.5)
Ar-H (dd)
7.56
J(8.2, 1.4)
Ar-H (m)
6.95
Ar-H (s)
7.28
Ar-H (d)
6.86
J(8.4)
CH2 (t)
3.13
J(7.8)
CH2 (t)
2.70
J(7.8)
O
NH3
Cl
N
H
FFN54
1.0
1.0
1.0
1.0
1.0
1.0
1.0
2.0
2.0
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
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
f1 (ppm)

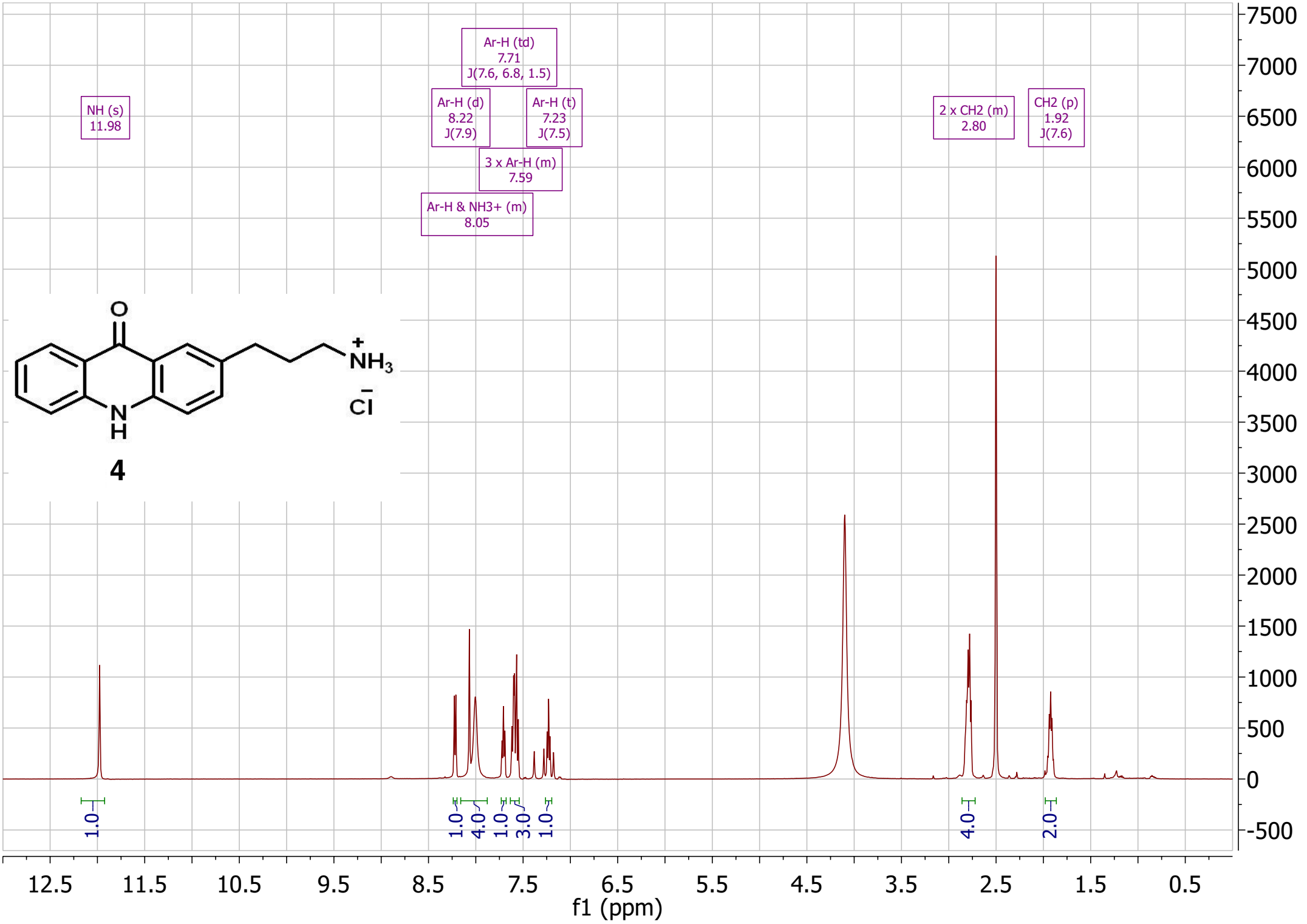

177.5
139.5
138.4
134.1
133.7
129.4
124.8
123.9
121.7
118.6
118.3
117.4
116.8
40.2
32.2
O
NH3
Cl
N
H
FFN54
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

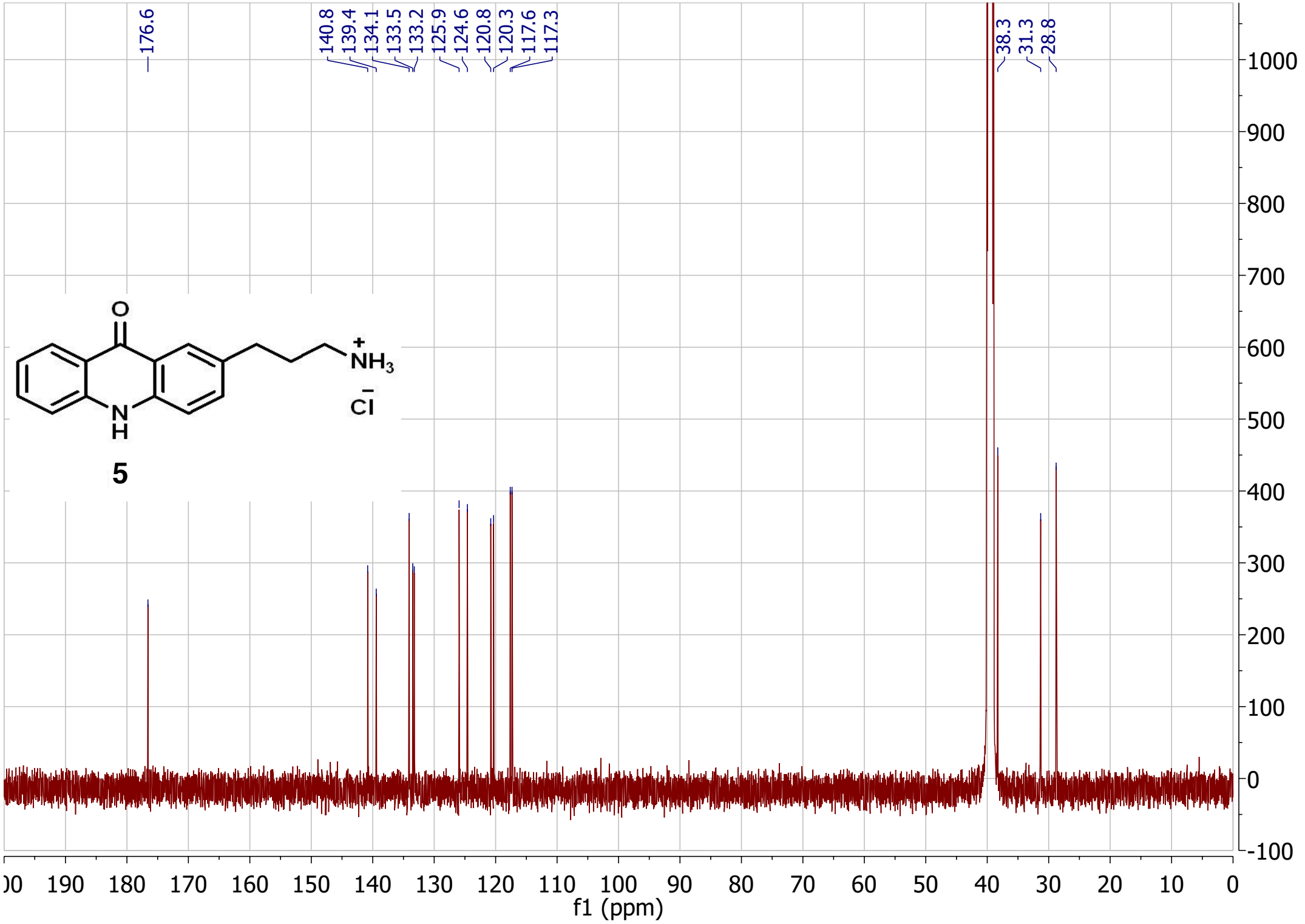

Ar-H (ddd)
7.56
J(8.2, 6.8, 1.2)
Ar-H (ddd)
7.98
J(8.2, 6.8, 1.2)
CH2 (t)
3.28
J(7.2)
H or NH+ (s)
13.75
NH or NH+ (s)
11.02
Ar-H (d)
8.64
J(8.6)
Ar-H (m)
7.92
CH2 (td)
3.88
J(7.2, 2.3)
Ar-H (d)
7.74
J(8.5)
Ar-H (dd)
7.31
J(7.1, 1.1)
Cl
HN
N
H
3
1.0
1.0
1.0
1.0
2.0
1.0
1.0
1.0
2.0
2.0
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
13.5
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

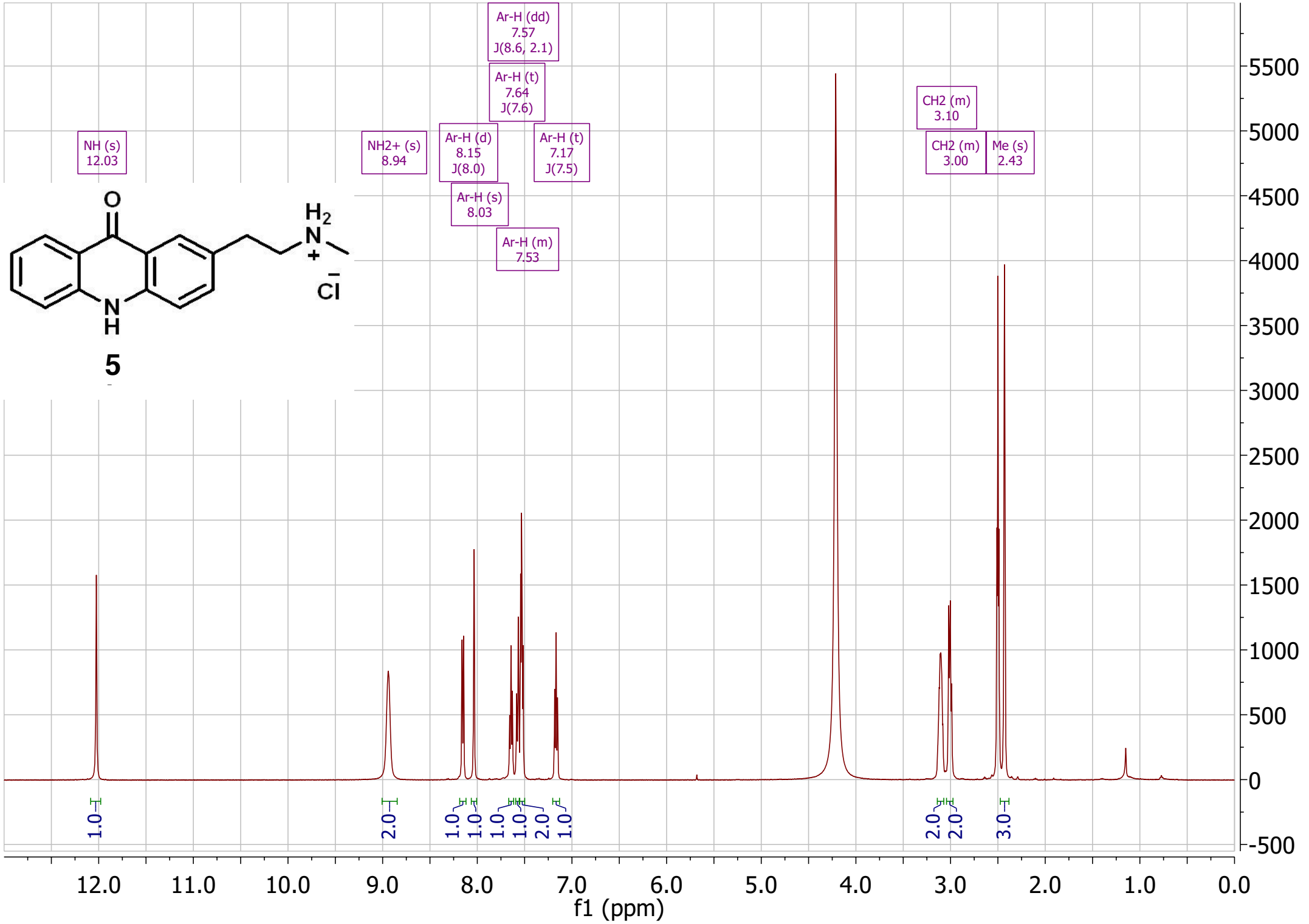

154.5
139.0
138.9
135.8
135.2
135.1
124.3
123.7
121.0
118.7
115.8
111.1
109.3
39.9
25.5
Cl⁻
HN⁺
N
H
3
second metylene carbon signal overlapped by DMSO signal
3.8 3.6 3.4
f2 (ppm)
f1 (ppm)
f1 (ppm)

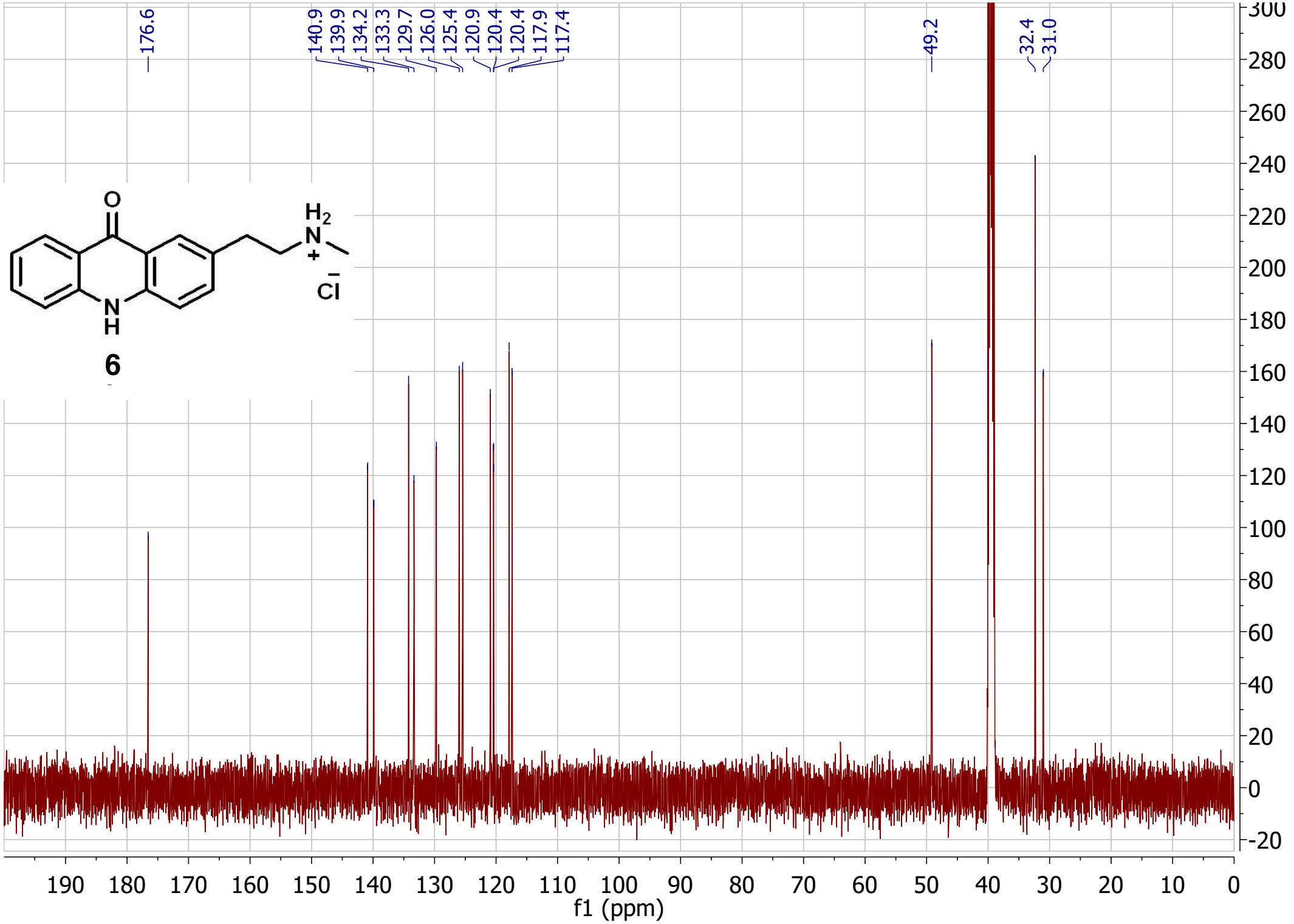

Ar-H (dd)
7.83
J(8.6, 2.2)
Ar-H (ddd)
7.75
J(8.5, 6.9, 1.6)
NH (s)
12.10
Ar-H (dd)
8.24
J(8.2, 1.5)
Ar-H (ddd)
7.27
J(8.0, 6.9, 1.1)
CH2 (q)
4.14
J(5.8)
Ar-H (m)
7.62
Ar-H & NH3+ (m)
8.36
O
NH3
Cl
N
H
4
1.0
4.0
1.0
1.0
1.0
2.0
1.0
2.0
f1 (ppm)

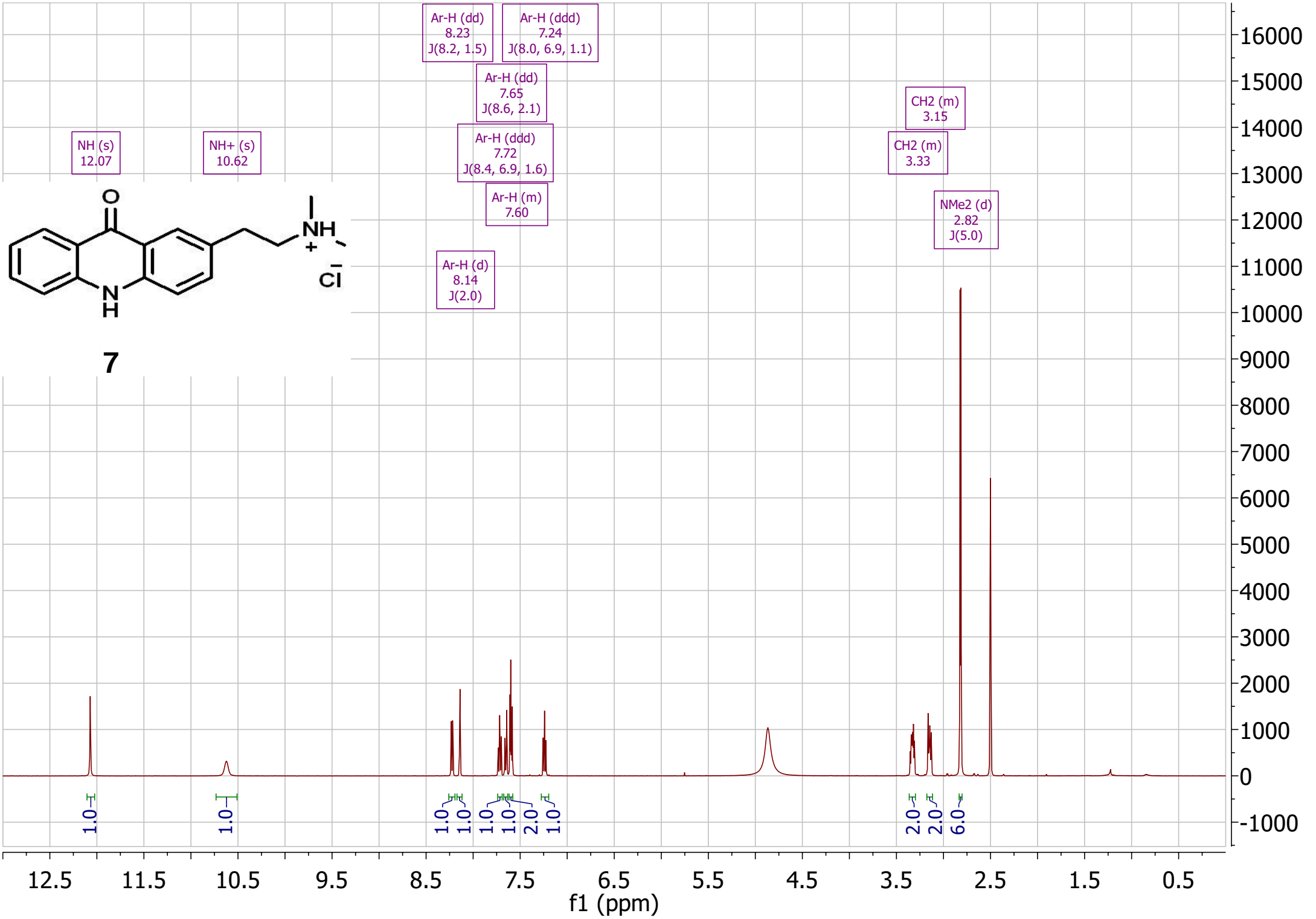

176.6
140.9
140.8
134.3
133.6
126.8
126.5
126.0
121.3
120.5
120.1
117.7
117.5
42.0
O
NH3
Cl
N
H
4
360
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

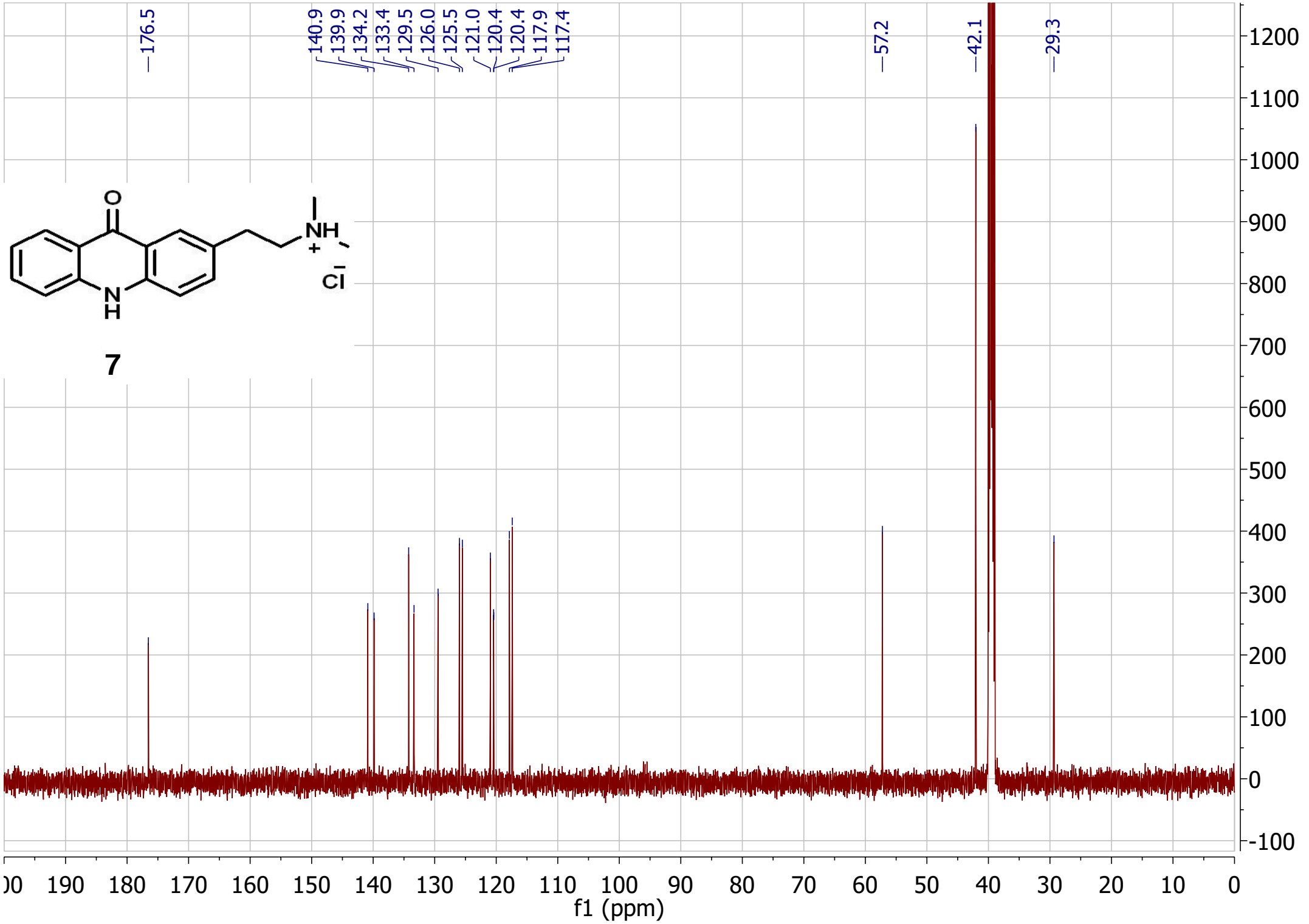

NH (s)
11.98
Ar-H (td)
7.71
J(7.6, 6.8, 1.5)
Ar-H (d)
8.22
J(7.9)
Ar-H (t)
7.23
J(7.5)
3 x Ar-H (m)
7.59
Ar-H & NH3+ (m)
8.05
2 x CH2 (m)
2.80
CH2 (p)
1.92
J(7.6)
O
NH3
Cl
N
H
4
1.0
1.0
4.0
1.0
3.0
1.0
4.0
2.0
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

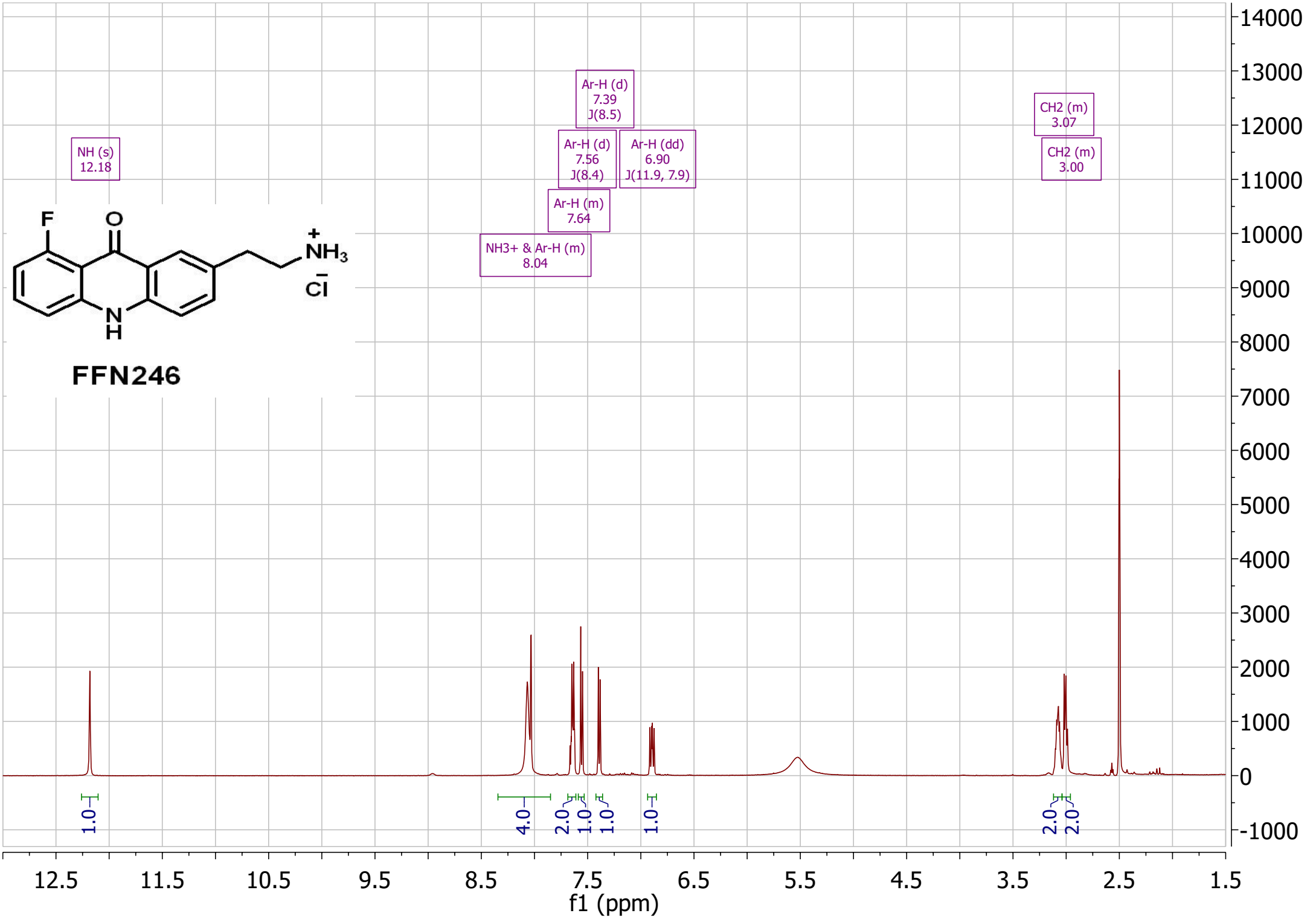

176.6
140.8
139.4
134.1
133.5
133.2
125.9
124.6
120.8
120.3
117.6
117.3
38.3
31.3
28.8
O
NH3
Cl
N
H
5
1000
900
800
700
600
500
400
300
200
100
0
-100
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

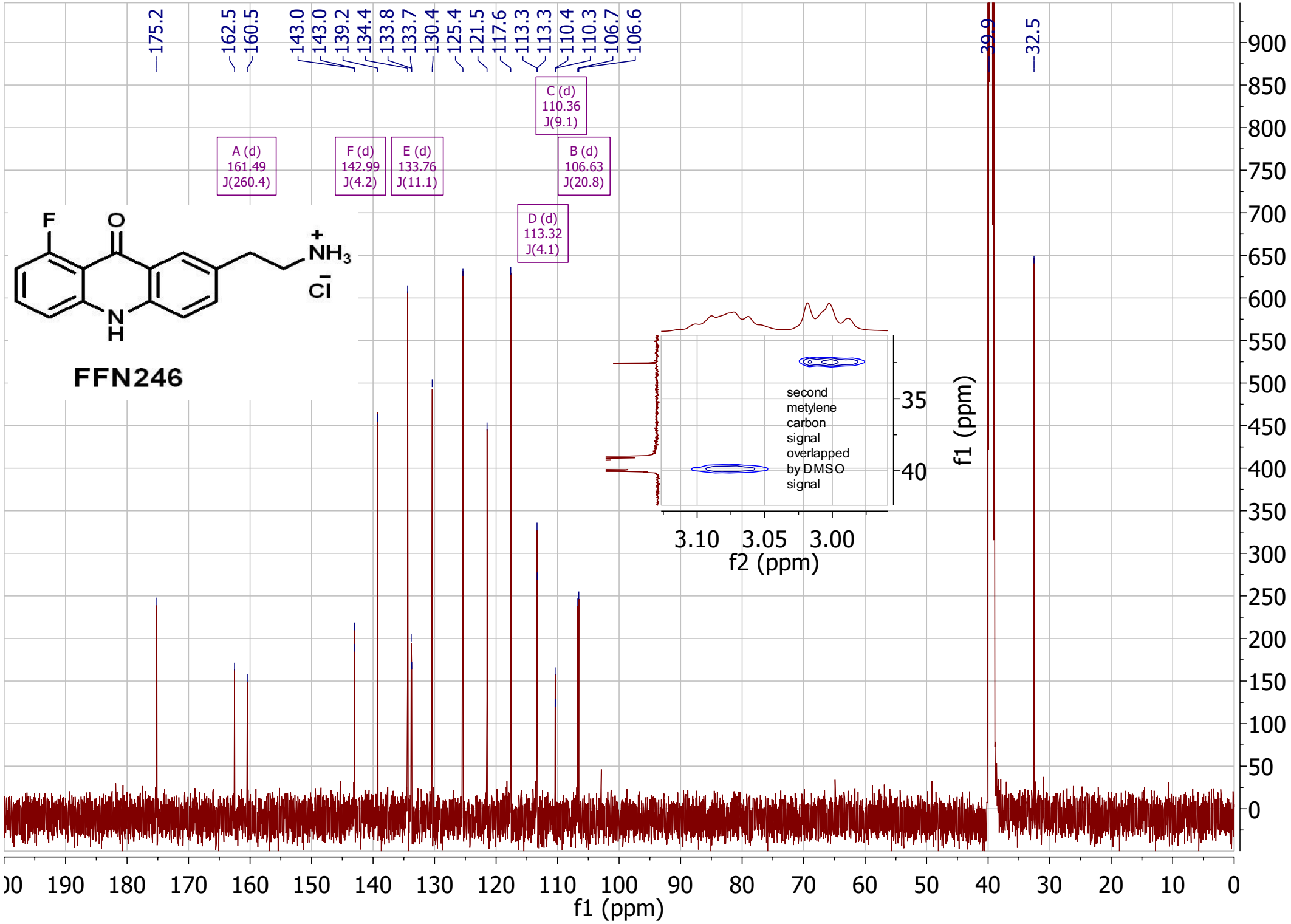

NH (s)
12.03
NH2+ (s)
8.94
Ar-H (d)
8.15
J(8.0)
Ar-H (dd)
7.57
J(8.6, 2.1)
Ar-H (t)
7.64
J(7.6)
Ar-H (t)
7.17
J(7.5)
Ar-H (s)
8.03
Ar-H (m)
7.53
CH2 (m)
3.10
CH2 (m)
3.00
Me (s)
2.43
O
H2
N
+
Cl
N
H
5
1.0
2.0
1.0
1.0
1.0
1.0
2.0
1.0
2.0
2.0
3.0
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

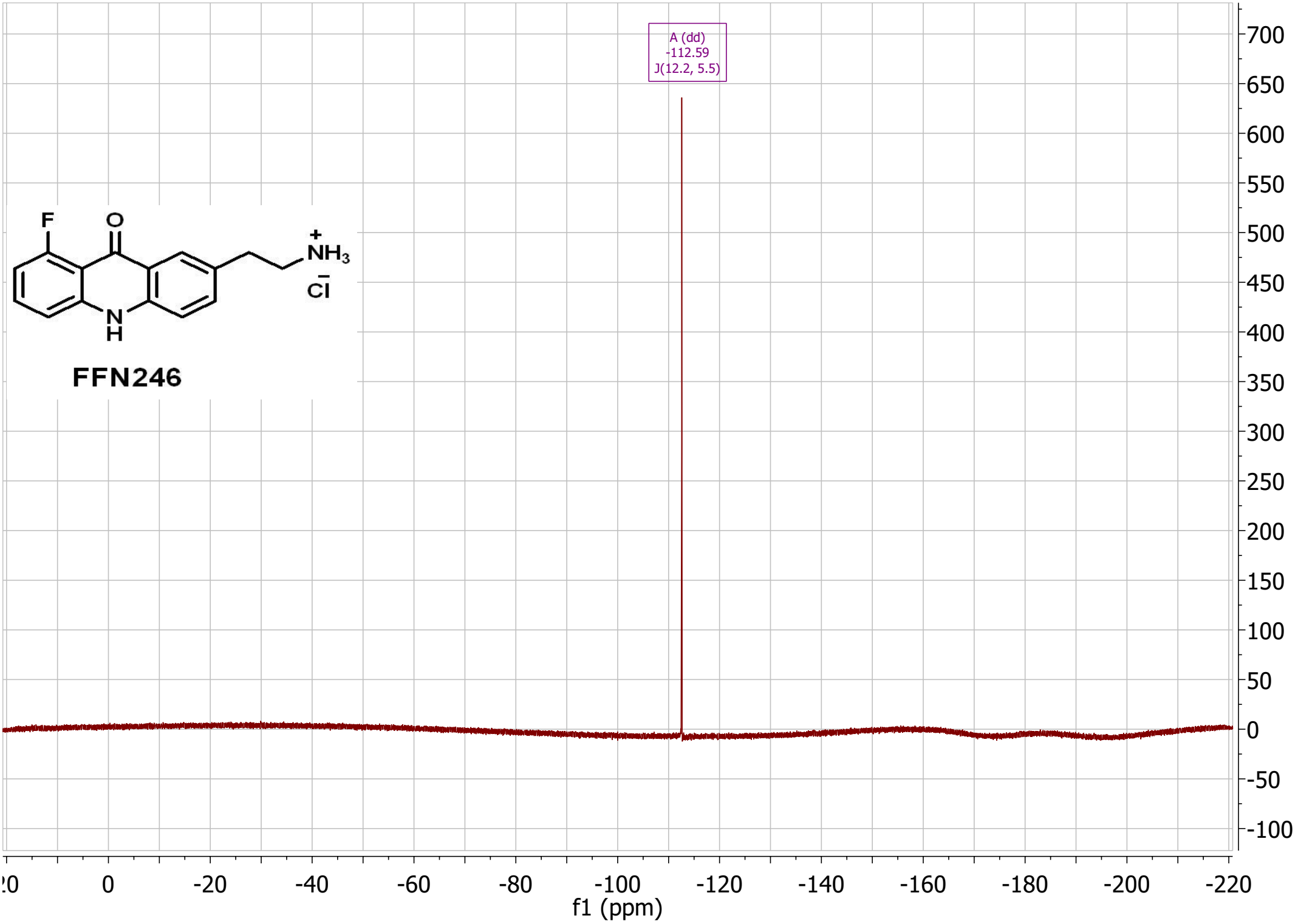

176.6
140.9
139.9
134.2
133.3
129.7
126.0
125.4
120.9
120.4
120.4
117.9
117.4
49.2
32.4
31.0
O
H2
N
+
Cl
N
H
6
f1 (ppm)

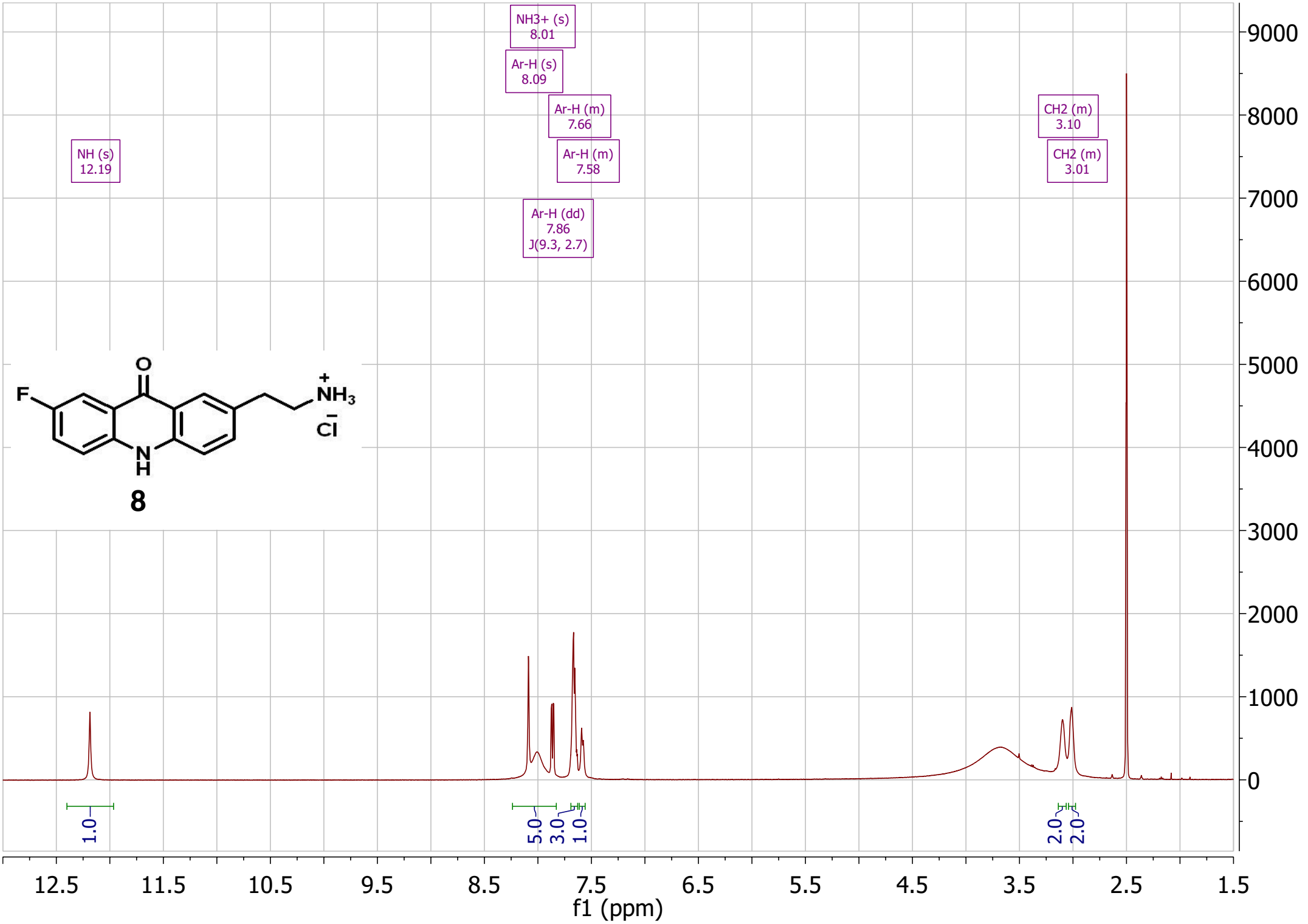

Ar-H (dd)
8.23
J(8.2, 1.5)
Ar-H (ddd)
7.24
J(8.0, 6.9, 1.1)
Ar-H (dd)
7.65
J(8.6, 2.1)
Ar-H (ddd)
7.72
J(8.4, 6.9, 1.6)
Ar-H (m)
7.60
Ar-H (d)
8.14
J(2.0)
NH (s)
12.07
NH+ (s)
10.62
CH2 (m)
3.15
CH2 (m)
3.33
NMe2 (d)
2.82
J(5.0)
O
NH
+
Cl⁻
N
H
7
1.0
1.0
1.0
1.0
1.0
1.0
2.0
1.0
2.0
2.0
6.0
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

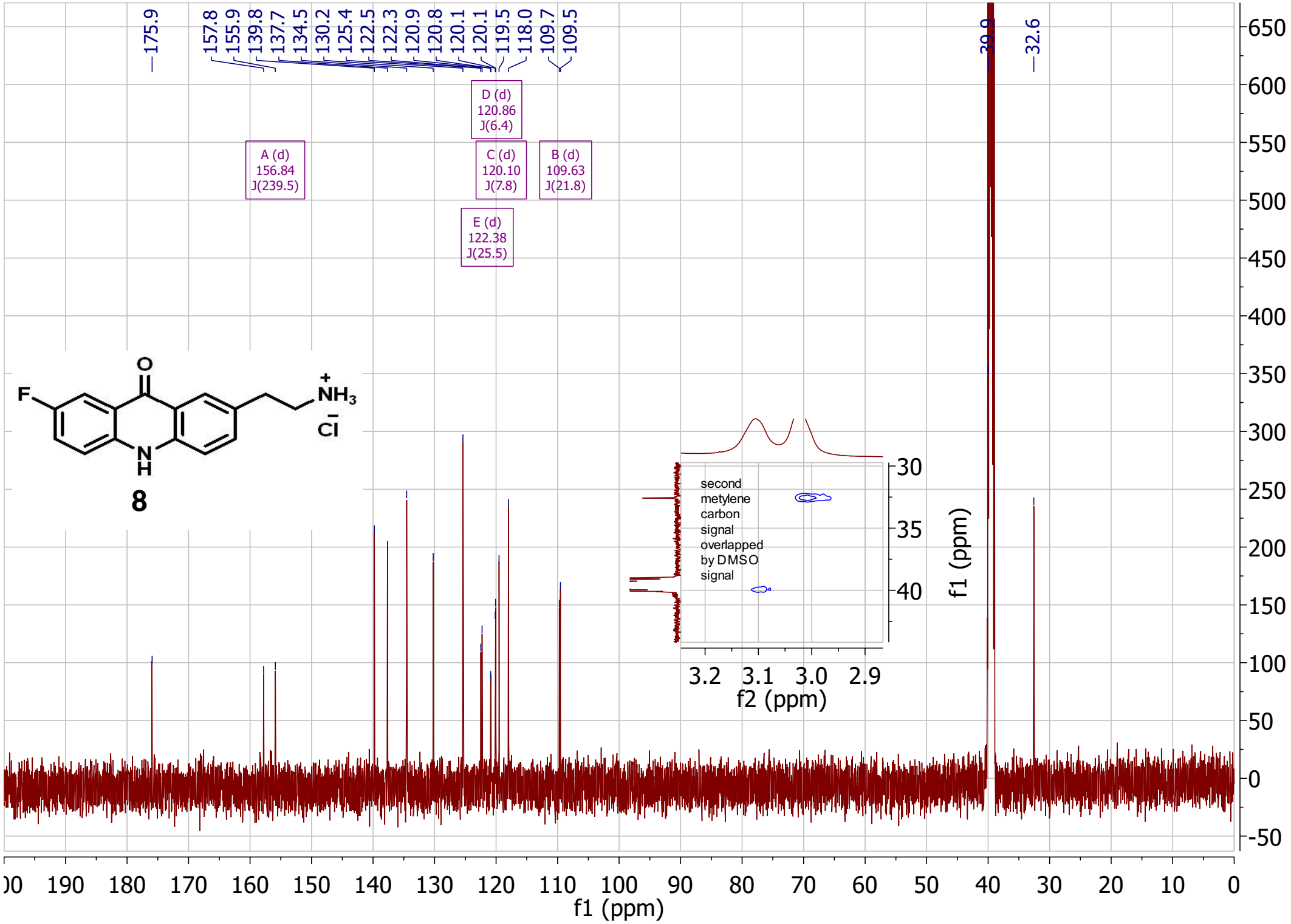

176.5
140.9
139.9
134.2
133.4
129.5
126.0
125.5
121.0
120.4
120.4
117.9
117.4
57.2
42.1
29.3
O
NH
Cl
N
H
7
f1 (ppm)

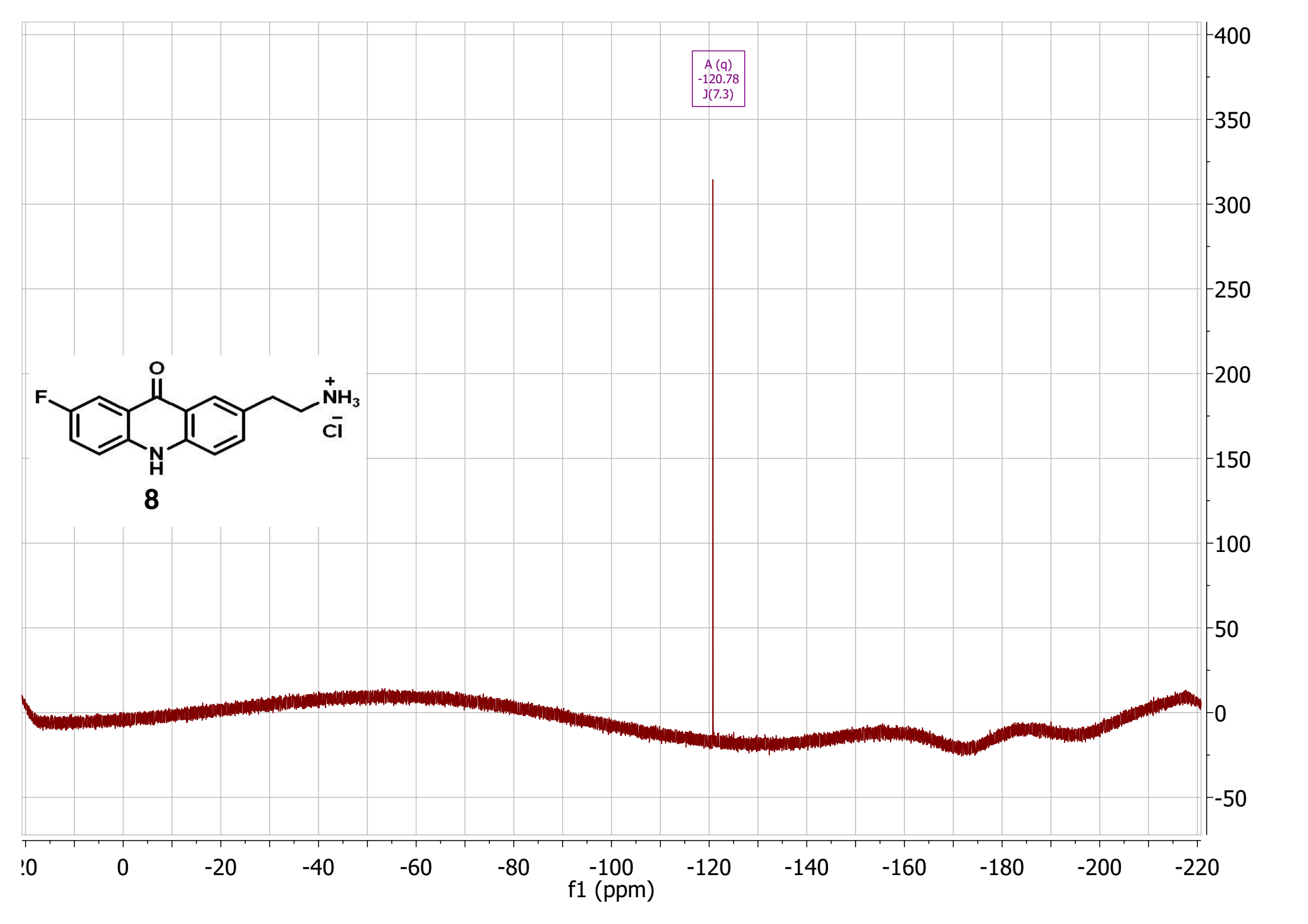

NH (s)
12.18
Ar-H (d)
7.39
J(8.5)
Ar-H (d)
7.56
J(8.4)
Ar-H (dd)
6.90
J(11.9, 7.9)
Ar-H (m)
7.64
NH3+ & Ar-H (m)
8.04
CH2 (m)
3.07
CH2 (m)
3.00
F
O
NH3
Cl
N
H
FFN246
1.0
4.0
2.0
1.0
1.0
1.0
2.0
2.0
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
f1 (ppm)

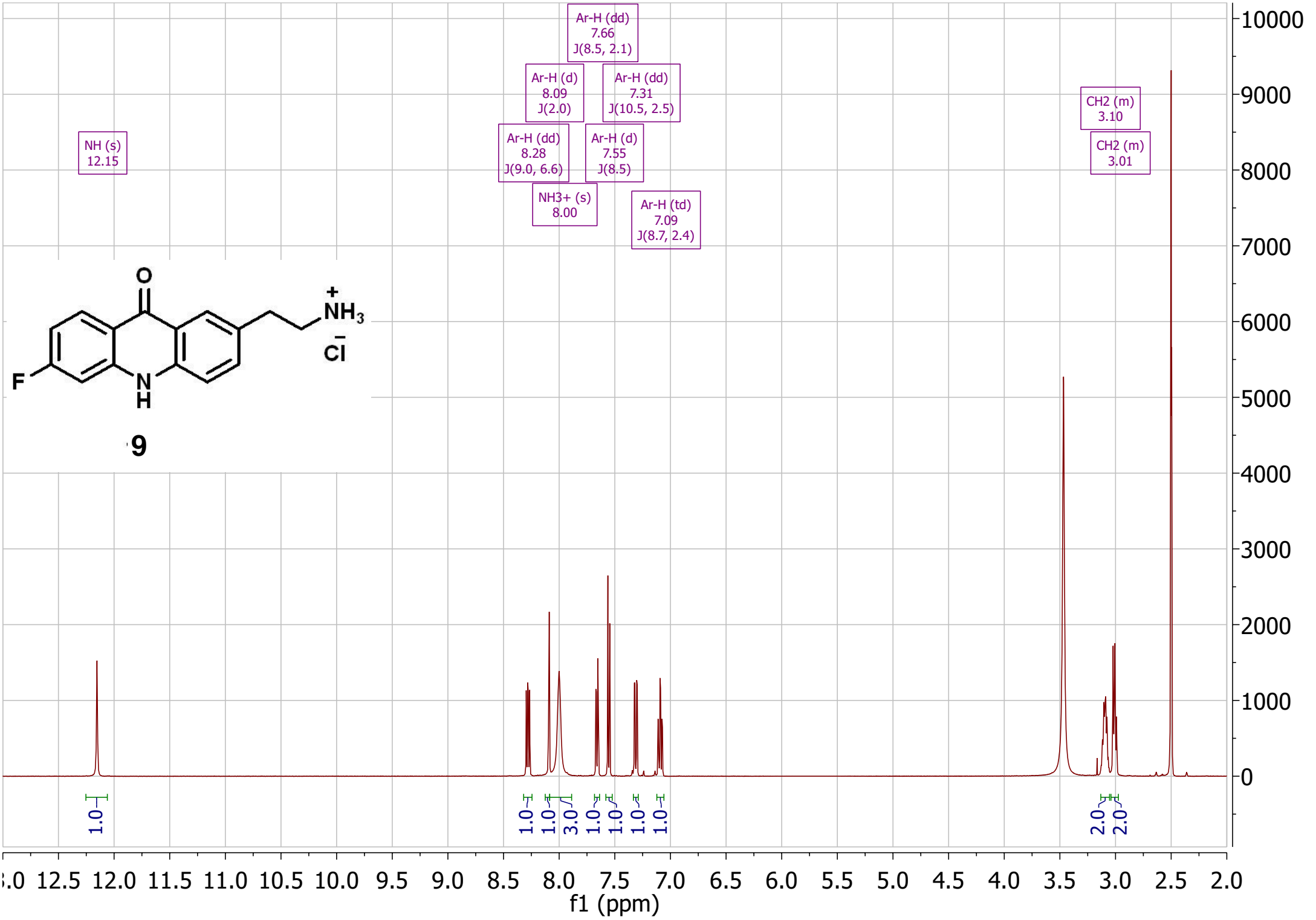

175.2
162.5
160.5
143.0
143.0
139.2
134.4
133.8
133.7
130.4
125.4
121.5
117.6
113.3
113.3
110.4
110.3
106.7
106.6
39.9
32.5
A (d)
161.49
J(260.4)
F (d)
142.99
J(4.2)
E (d)
133.76
J(11.1)
C (d)
110.36
J(9.1)
B (d)
106.63
J(20.8)
D (d)
113.32
J(4.1)
F
O
NH3
Cl
N
H
FFN246
second
metylene
carbon
signal
overlapped
by DMSO
signal
35
40
f1 (ppm)
3.10
3.05
3.00
f2 (ppm)
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

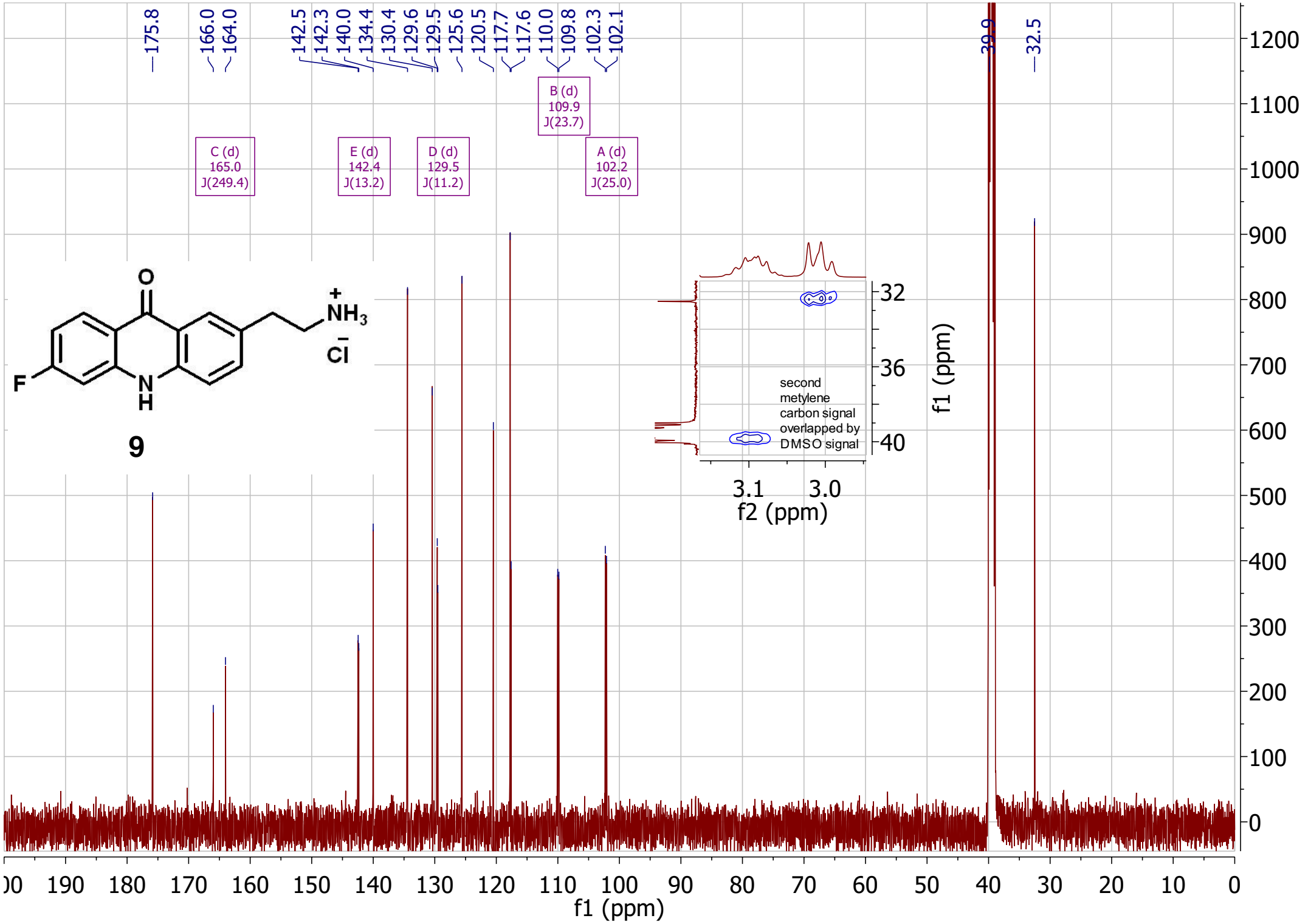

A (dd)
-112.59
J(12.2, 5.5)
F
O
NH3
Cl
N
H
FFN246
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)

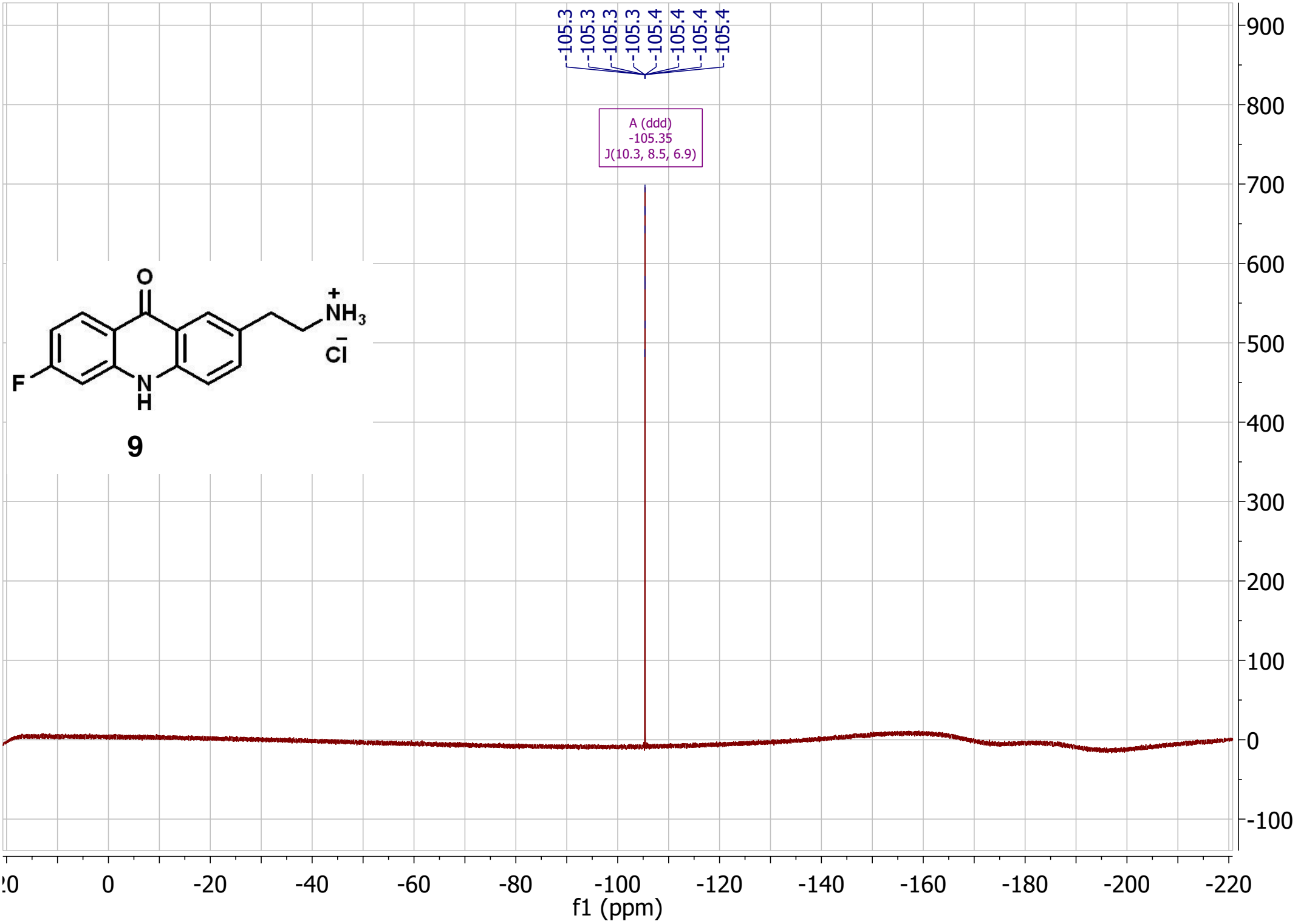

NH3+ (s)
8.01
Ar-H (s)
8.09
Ar-H (m)
7.66
Ar-H (m)
7.58
Ar-H (dd)
7.86
J(9.3, 2.7)
NH (s)
12.19
CH2 (m)
3.10
CH2 (m)
3.01
O
F
NH3
Cl
N
H
8
1.0
5.0
3.0
1.0
2.0
2.0
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
f1 (ppm)

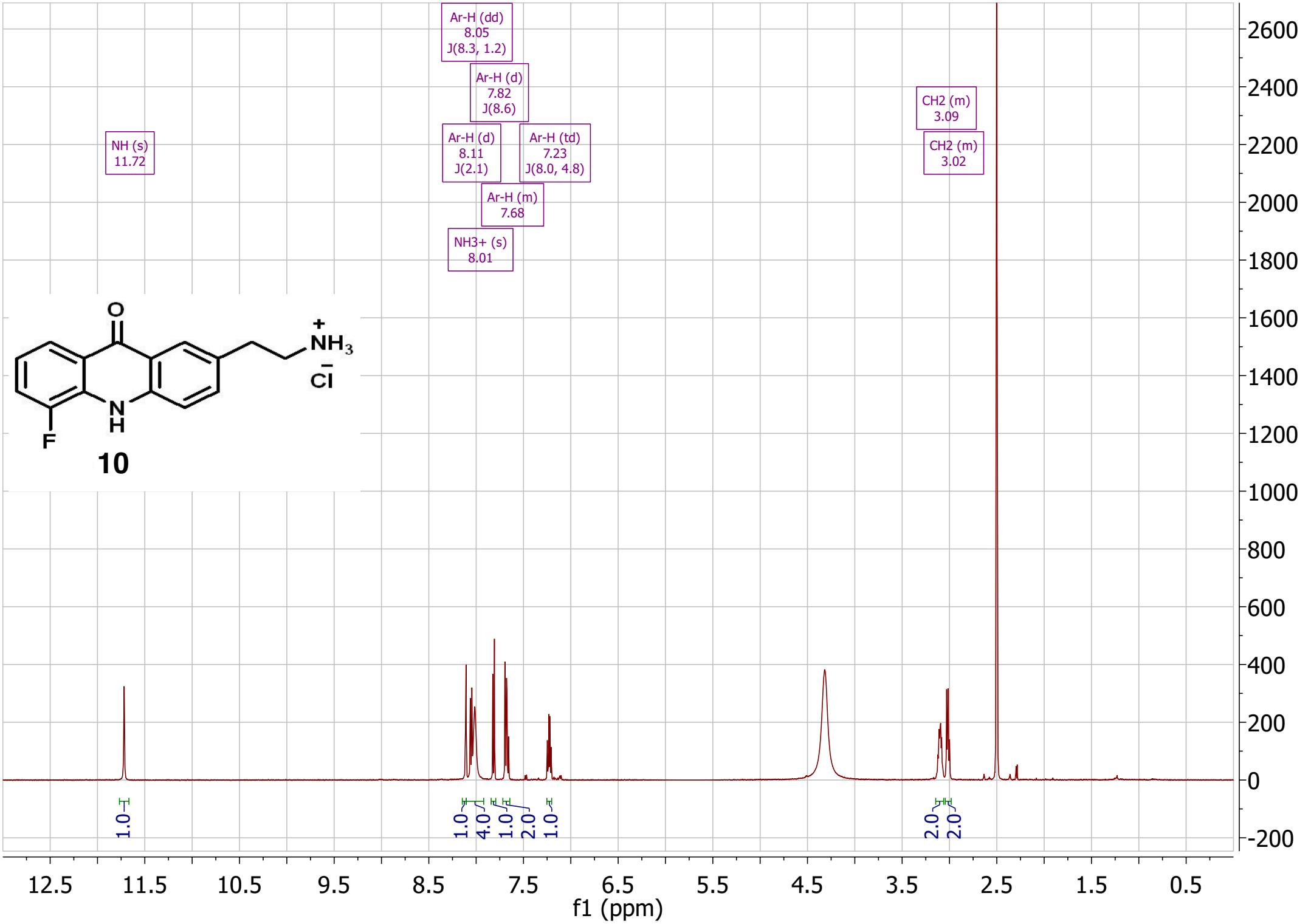

175.9
157.8
155.9
139.8
137.7
134.5
130.2
125.4
122.5
122.3
120.9
120.8
120.1
120.1
119.5
118.0
109.7
109.5
39.9
32.6
A (d)
156.84
J(239.5)
D (d)
120.86
J(6.4)
C (d)
120.10
J(7.8)
B (d)
109.63
J(21.8)
E (d)
122.38
J(25.5)
F
O
NH3
Cl
N
H
8
second
metylene
carbon
signal
overlapped
by DMSO
signal
3.2
3.1
3.0
2.9
f2 (ppm)
30
35
40
f1 (ppm)
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

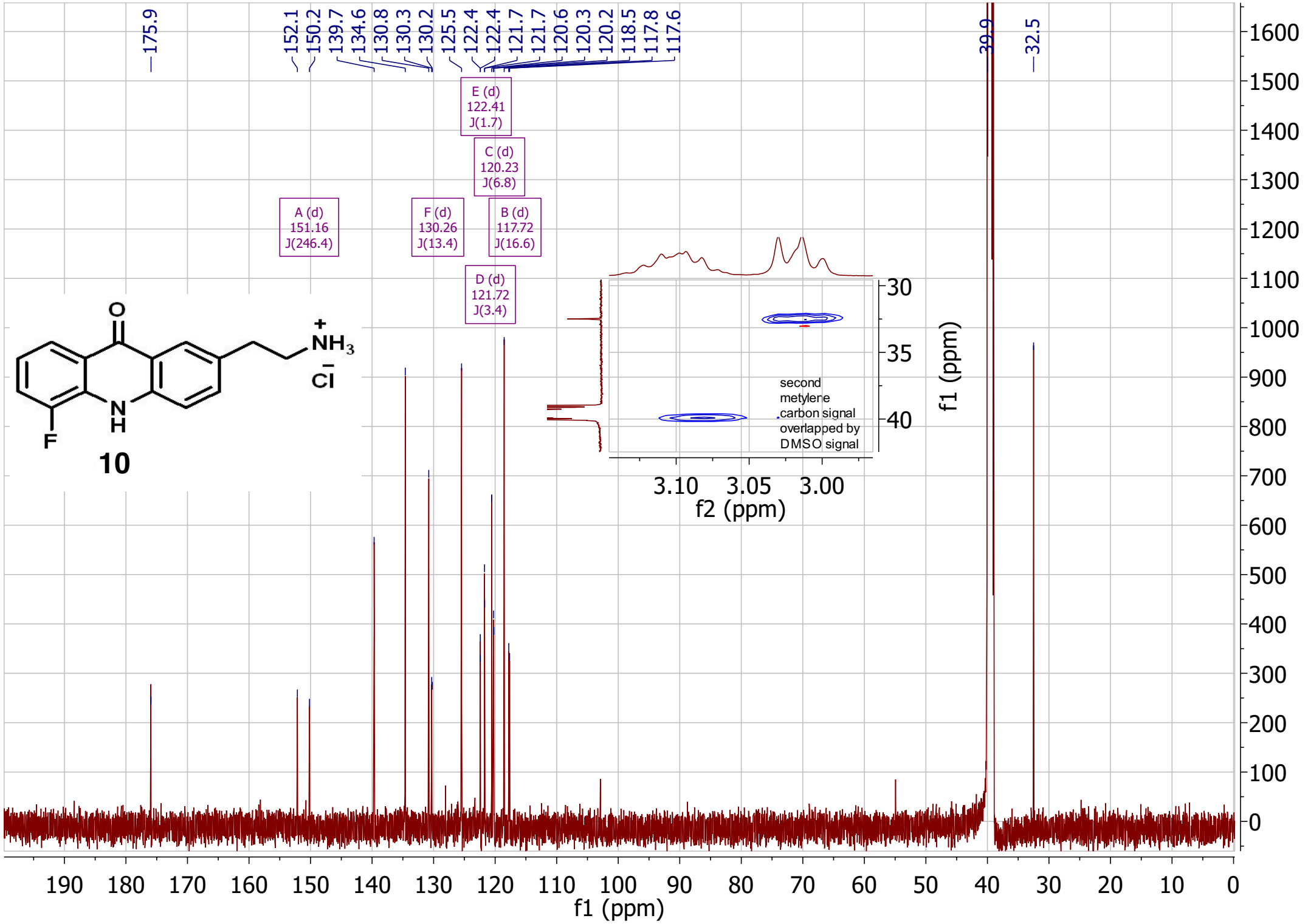

A (q)
-120.78
J(7.3)
O
F
NH3
Cl
N
H
8
400
350
300
250
200
150
100
50
0
-50
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)

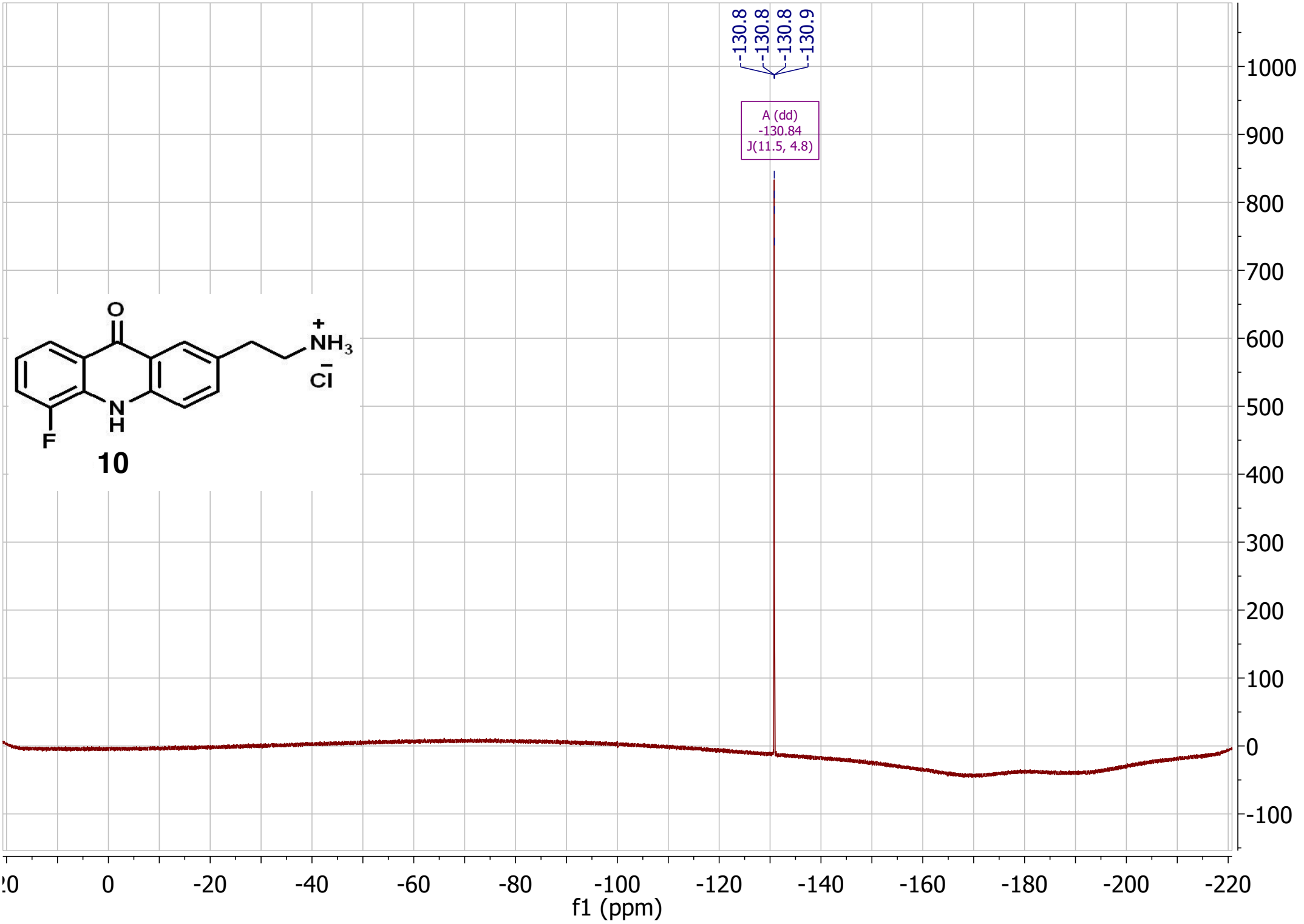

Ar-H (dd)
7.66
J(8.5, 2.1)
Ar-H (d)
8.09
J(2.0)
Ar-H (dd)
7.31
J(10.5, 2.5)
NH (s)
12.15
Ar-H (dd)
8.28
J(9.0, 6.6)
Ar-H (d)
7.55
J(8.5)
NH3+ (s)
8.00
Ar-H (td)
7.09
J(8.7, 2.4)
CH2 (m)
3.10
CH2 (m)
3.01
O
NH3
Cl
F
N
H
9
1.0
1.0
3.0
1.0
1.0
1.0
1.0
2.0
2.0
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
f1 (ppm)

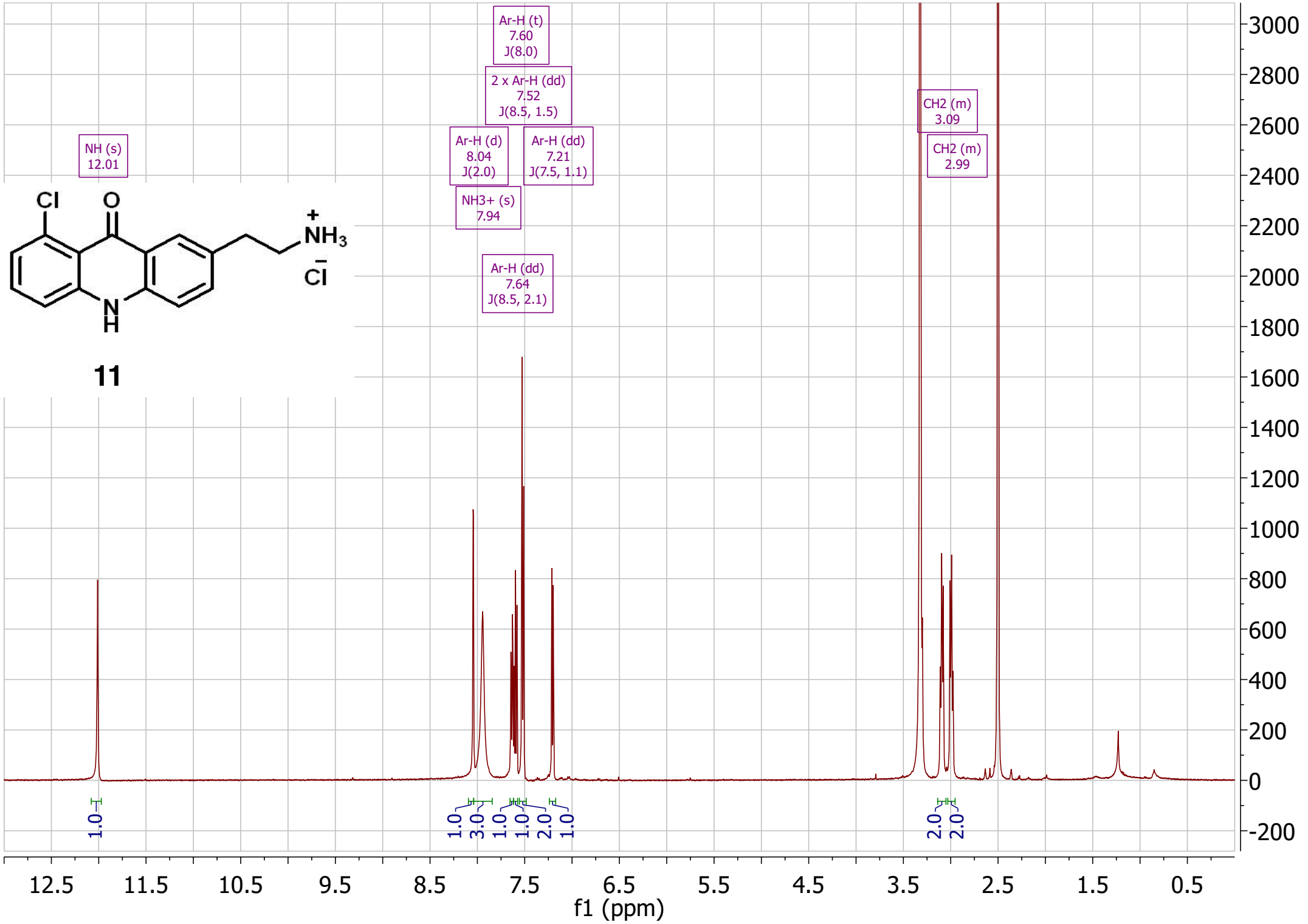

175.8
166.0
164.0
142.5
142.3
140.0
134.4
130.4
129.6
129.5
125.6
120.5
117.7
117.6
110.0
109.8
102.3
102.1
39.9
32.5
B (d)
109.9
J(23.7)
C (d)
165.0
J(249.4)
E (d)
142.4
J(13.2)
D (d)
129.5
J(11.2)
A (d)
102.2
J(25.0)
O
NH3
Cl
F
N
H
9
second
metylene
carbon signal
overlapped by
DMSO signal
3.1
3.0
f2 (ppm)
f1 (ppm)
f1 (ppm)

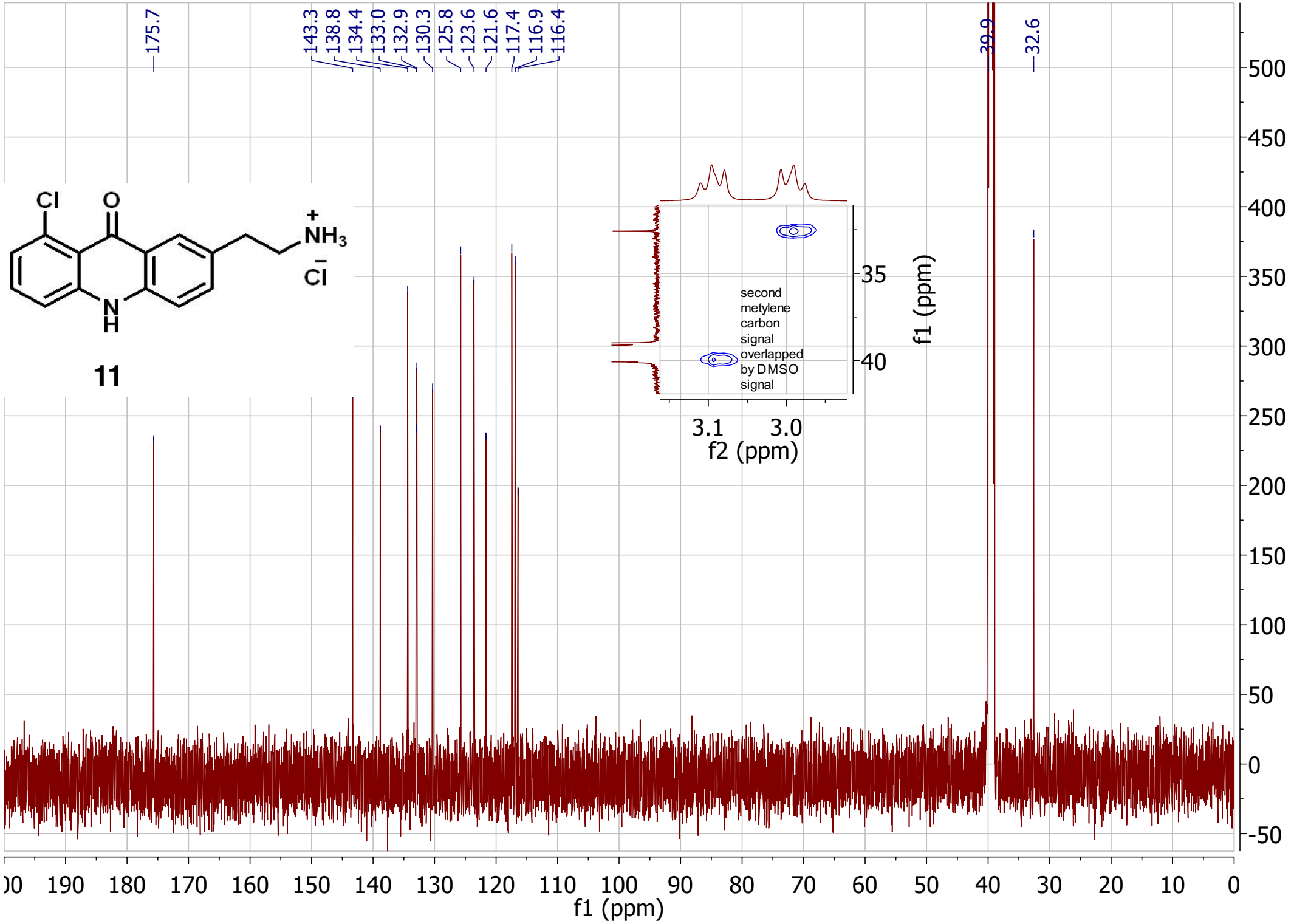

-105.3
-105.3
-105.3
-105.3
-105.4
-105.4
-105.4
-105.4
A (ddd)
-105.35
J(10.3, 8.5, 6.9)
O
NH3
Cl
F
N
H
9
900
800
700
600
500
400
300
200
100
0
-100
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)

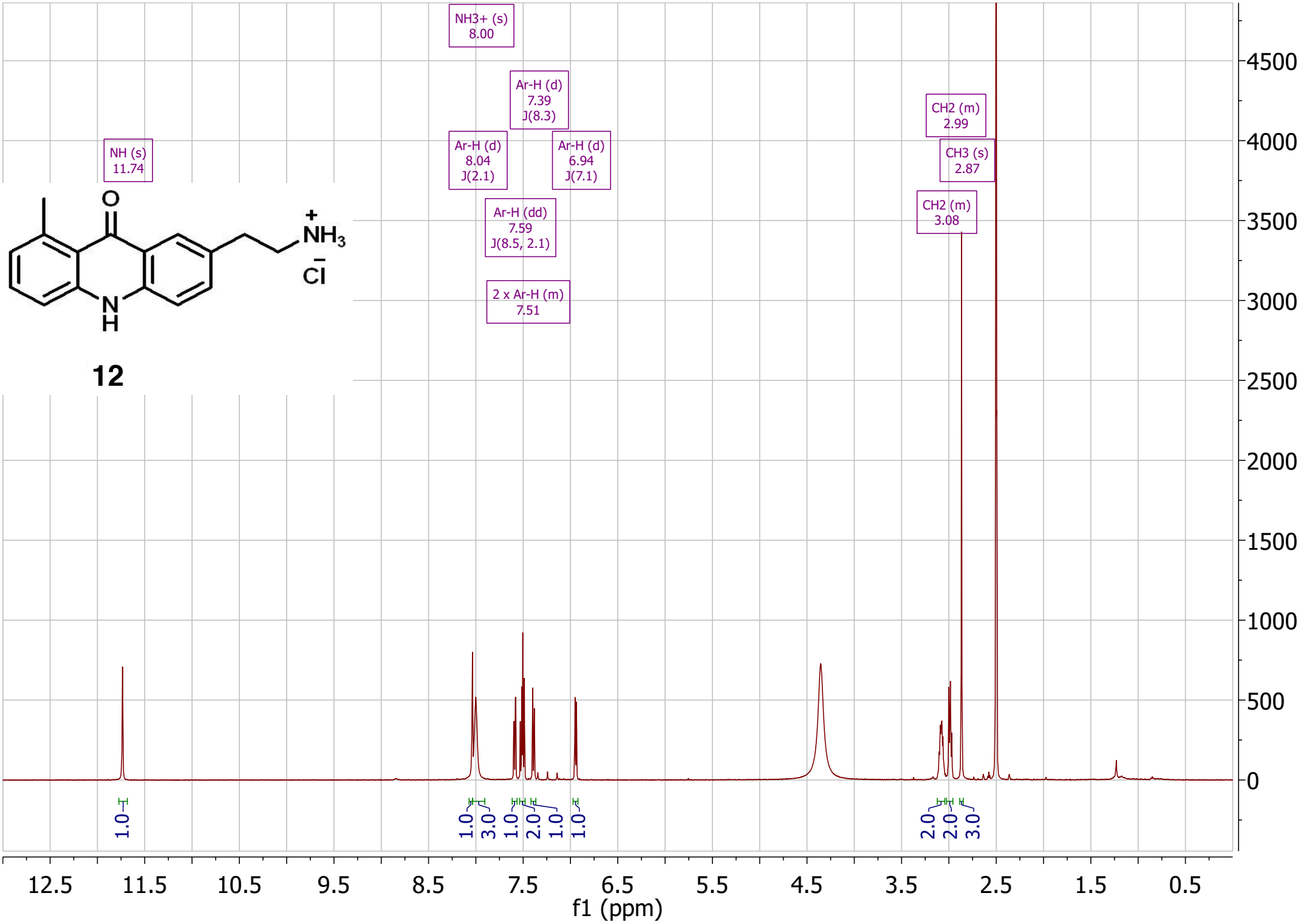

Ar-H (dd)
8.05
J(8.3, 1.2)
Ar-H (d)
7.82
J(8.6)
Ar-H (d)
8.11
J(2.1)
Ar-H (td)
7.23
J(8.0, 4.8)
Ar-H (m)
7.68
NH3+ (s)
8.01
NH (s)
11.72
CH2 (m)
3.09
CH2 (m)
3.02
O
NH3
Cl
N
H
F
10
1.0
1.0
4.0
1.0
2.0
1.0
2.0
2.0
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

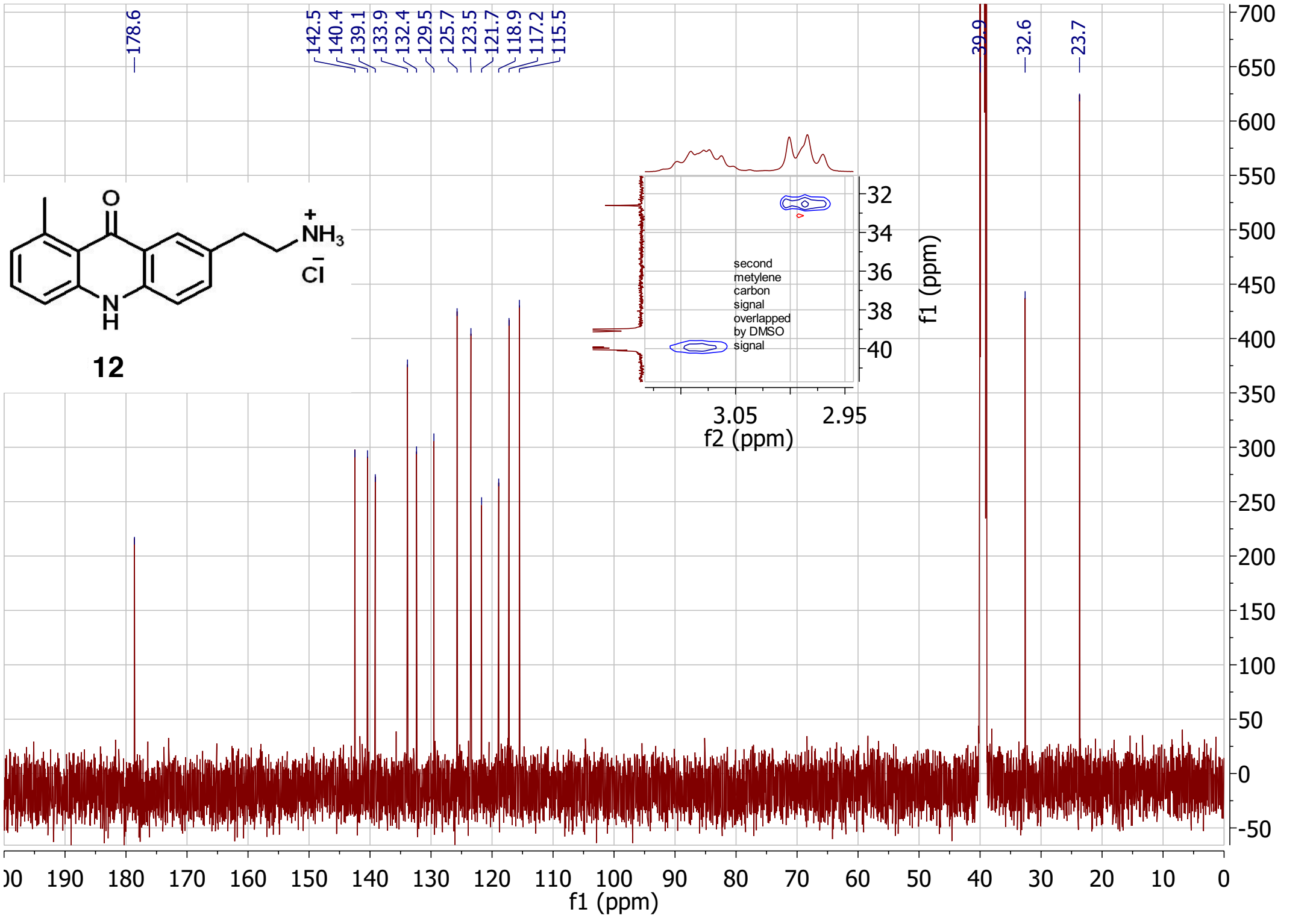

175.9
152.1
150.2
139.7
134.6
130.8
130.3
130.2
125.5
122.4
122.4
121.7
121.7
120.6
120.3
120.2
118.5
117.8
117.6
39.9
32.5
E (d)
122.41
J(1.7)
C (d)
120.23
J(6.8)
A (d)
151.16
J(246.4)
F (d)
130.26
J(13.4)
B (d)
117.72
J(16.6)
D (d)
121.72
J(3.4)
O
NH3
Cl
N
H
F
10
second
metylene
carbon signal
overlapped by
DMSO signal
3.10
3.05
3.00
f2 (ppm)
30
35
40
f1 (ppm)
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

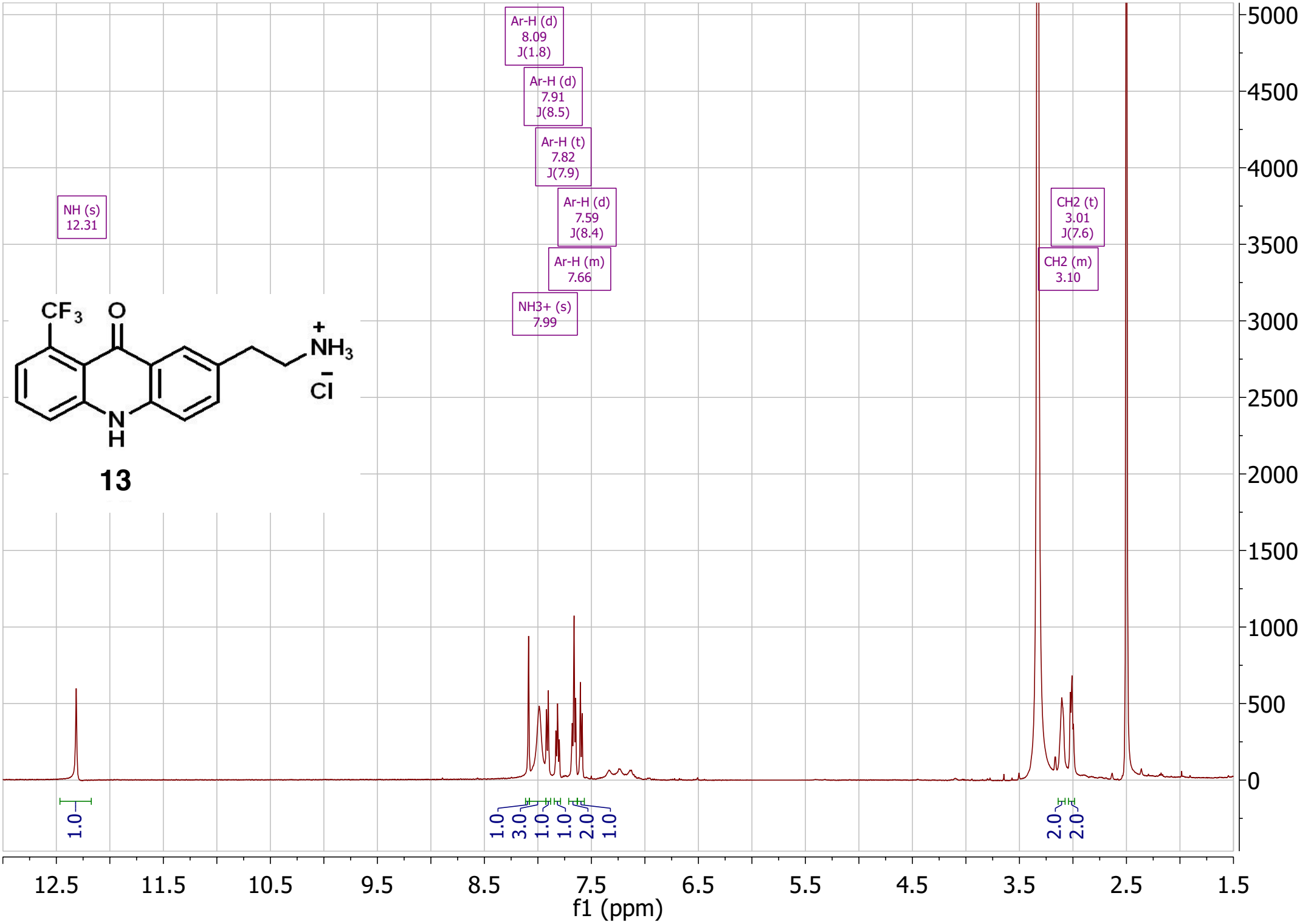

-130.8
-130.8
-130.8
-130.9
A (dd)
-130.84
J(11.5, 4.8)
O
NH3
Cl
N
H
F
10
1000
900
800
700
600
500
400
300
200
100
0
-100
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)

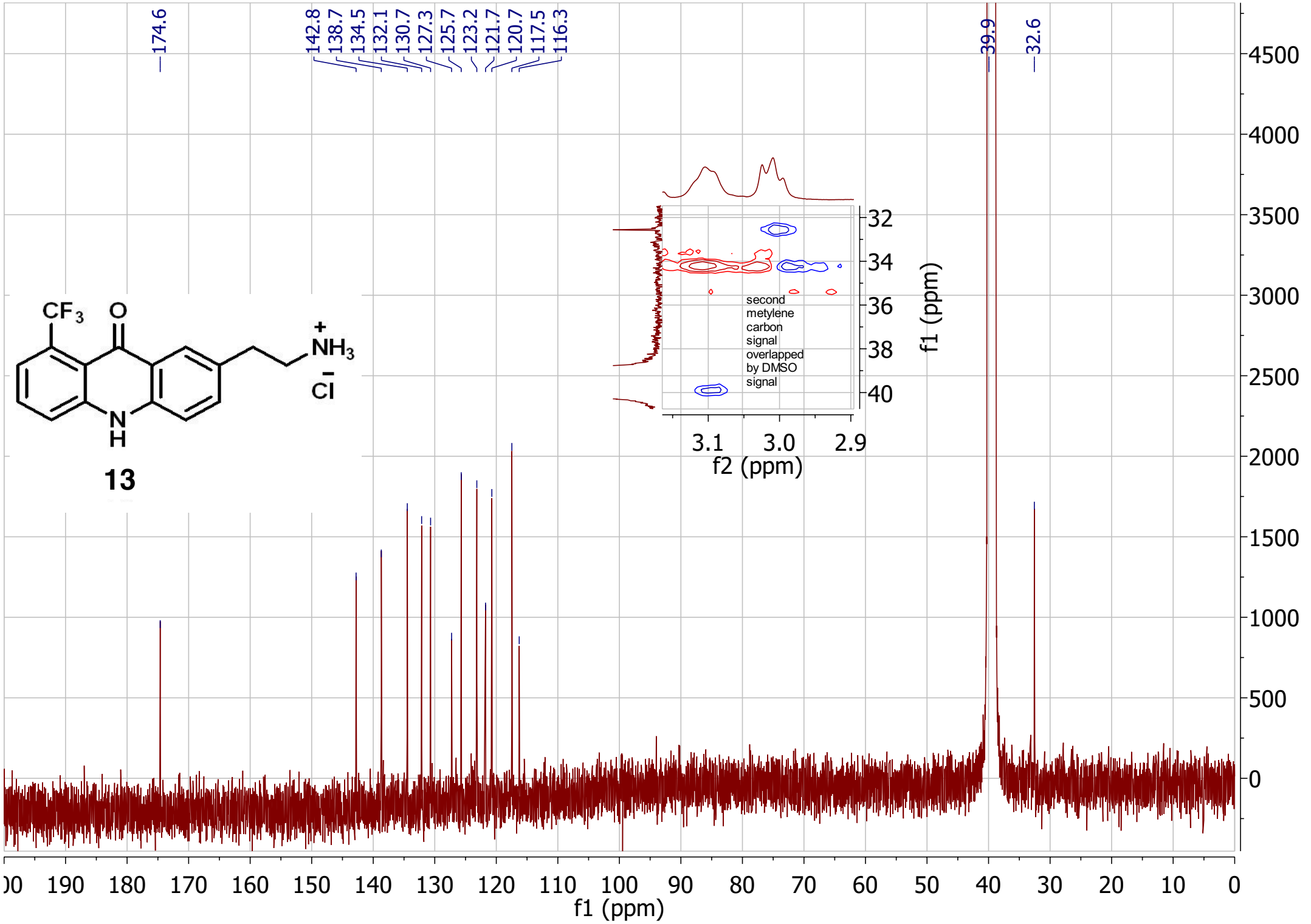

NH (s)
12.01
Ar-H (t)
7.60
J(8.0)
2 x Ar-H (dd)
7.52
J(8.5, 1.5)
Ar-H (d)
8.04
J(2.0)
Ar-H (dd)
7.21
J(7.5, 1.1)
NH3+ (s)
7.94
Ar-H (dd)
7.64
J(8.5, 2.1)
CH2 (m)
3.09
CH2 (m)
2.99
Cl
O
NH3
Cl
N
H
11
1.0
1.0
3.0
1.0
1.0
2.0
1.0
2.0
2.0
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)

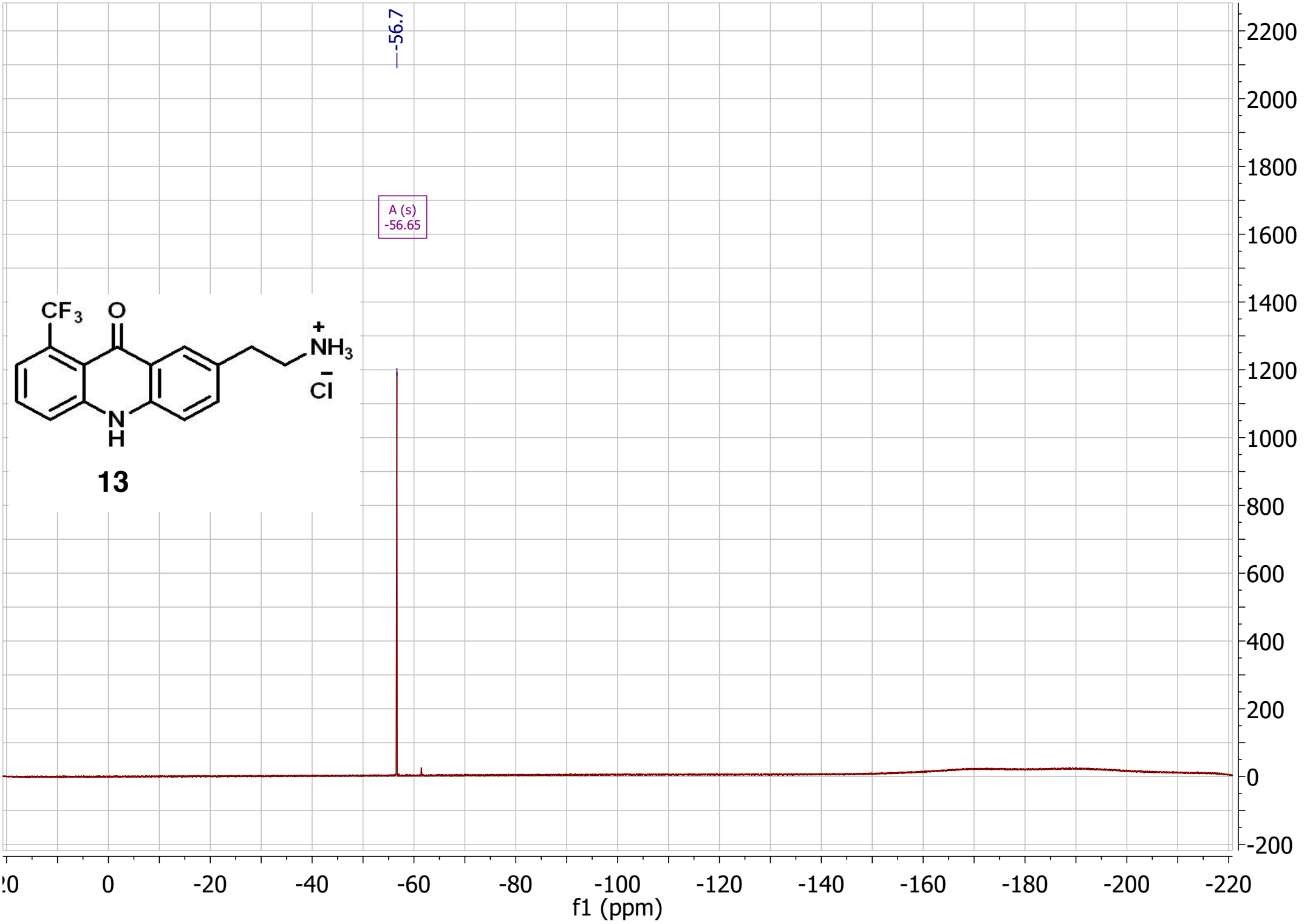

175.7
143.3
138.8
134.4
133.0
132.9
130.3
125.8
123.6
121.6
117.4
116.9
116.4
39.9
32.6
Cl
O
NH3
Cl
N
H
11
second metylene carbon signal overlapped by DMSO signal
3.1
3.0
f2 (ppm)
35
40
f1 (ppm)
500
450
400
350
300
250
200
150
100
50
0
-50
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NH3+ (s)
8.00
Ar-H (d)
7.39
J(8.3)
Ar-H (d)
8.04
J(2.1)
Ar-H (d)
6.94
J(7.1)
Ar-H (dd)
7.59
J(8.5, 2.1)
2 x Ar-H (m)
7.51
NH (s)
11.74
CH2 (m)
2.99
CH3 (s)
2.87
CH2 (m)
3.08
O
NH3
Cl
N
H
12
1.0
1.0
3.0
1.0
2.0
1.0
1.0
2.0
2.0
3.0
4500
4000
3500
3000
2500
2000
1500
1000
500
0
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
f1 (ppm)


178.6
142.5
140.4
139.1
133.9
132.4
129.5
125.7
123.5
121.7
118.9
117.2
115.5
39.9
32.6
23.7
O
NH3
Cl
N
H
12
second
metylene
carbon
signal
overlapped
by DMSO
signal
3.05
2.95
f2 (ppm)
f1 (ppm)
f1 (ppm)


Ar-H (d)
8.09
J(1.8)
Ar-H (d)
7.91
J(8.5)
Ar-H (t)
7.82
J(7.9)
Ar-H (d)
7.59
J(8.4)
Ar-H (m)
7.66
NH3+ (s)
7.99
NH (s)
12.31
CH2 (t)
3.01
J(7.6)
CH2 (m)
3.10
CF3
O
NH3
Cl
N
H
13
1.0
1.0
3.0
1.0
1.0
2.0
1.0
2.0
2.0
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
12.5
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
f1 (ppm)


174.6
142.8
138.7
134.5
132.1
130.7
127.3
125.7
123.2
121.7
120.7
117.5
116.3
39.9
32.6
CF3
O
NH3
Cl
N
H
13
second
metylene
carbon
signal
overlapped
by DMSO
signal
3.1
3.0
2.9
f2 (ppm)
32
34
36
38
40
f1 (ppm)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-56.7
A (s)
-56.65
CF3
O
NH3
Cl
N
H
13
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
f1 (ppm)