Electronic Supplementary Material (ESI) for Green Chemistry.

A Selective and Mild Electrochemical Defluorinative Carboxylation for Late-Stage C(sp^3)–F bond Functionalization

Supporting Information

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General Considerations

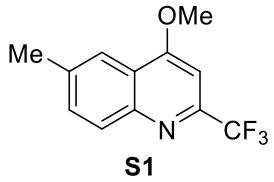
All reactions described were performed at ambient temperature and atmosphere unless otherwise specified. Column chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60). Concentration and removal of trace solvents was done via an IKA rotary evaporator using an IKA RC2 Green Basic circulating cooler and an IKA VacStar pump. Electrochemical reactions were carried on IKA's ElectraSyn 2.0 instrument. Any trace solvents remaining were accounted for in yield calculations.

Nuclear magnetic resonance (NMR) spectra were recorded using deuterochloroform ($CDCl_3$), deuteromethanol (MeOD), or deuteroacetone (acetone-d_6) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (**^{1}H NMR:** $CDCl_3$: δ 7.26; MeOD: δ 3.31; acetone-d_6: 2.04 ; **^{13}C NMR:** $CDCl_3$: δ 77.16; acetone-d_6: 29.84; MeOD: 49.00). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *sept*, septet; *m*, multiplet; *br* broad), coupling constants, number of protons. NMR spectra were recorded on either 400 or 500 MHz spectrometers. 2D NMR experiments such as COSY, HSQC, HMBC, and ROESY were used where necessary

High-resolution mass spectra were recorded using either electron impact (EI) or electrospray ionization (ESI) techniques by the mass spectrometry lab at the University of Alberta.

Preparation and Characterization of Starting Materials

*Preparation of Compound **S1***



S1

4-Hydroxy-6-methyl-2-(trifluoromethyl) quinolone (0.250 g, 1.10 mmol, 1 equiv.) was dissolved in dry DMF (2.20 mL) under nitrogen gas. Potassium carbonate (0.304 g, 2.20, 2 equiv.) and methyl iodide (0.103 mL, 1.65 mmol, 1.5 equiv.) were then added to the reaction mixture. The reaction was allowed to stir at room temperature for 16 h after which time it was then diluted with ethyl acetate. The organic phase was then washed twice with distilled water, separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was then purified using silica column chromatography (10% → 20% EtOAc in hexanes) to afford a white solid **S1** (197 mg, 82% yield).

Data for **S1**: IR (neat): υ = 3421, 1648, 1588, 1509, 1373, 750 cm^{-1}

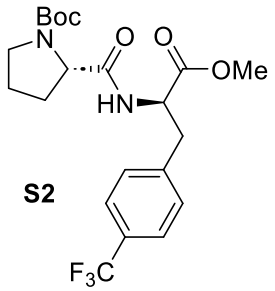
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, *J* = 1.4 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.70 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.29 (s, 1H), 4.21 (s, 3H), 2.56 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.4, 148.8 (q, *J* = 33.6 Hz), 147.5, 139.0, 134.0, 130.1, 122.8 (q, *J* = 274.1 Hz), 122.5, 121.5, 97.4, 57.1, 21.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -68.3.

HRMS (ESI): Expected mass ($M+H^+$): 242.0787; found: 242.0785.

*Preparation of Compound **S2***



N-Boc-L-proline (239 mg, 1.11 mmol, 1.1 equiv) was dissolved in dry dichloromethane (3.4 mL). Subsequently, HOBt (163.5 mg, 1.21 mmol, 1.2 equiv.), diisopropylethylamine (0.616 mL, 3.54 mmol, 3.5 equiv.), DMAP (12.3 mg, 0.10 mmol, 0.1 equiv) and EDC hydrogen chloride (232.8 mg, 1.21 mmol, 1.2 equiv.) were added and the reaction was allowed to stir for 10 minutes at 0°C. (4-trifluoromethyl)-D-phenylalanine methyl ester (0.250g, 1.01 mmol, 1 equiv.) was then added to the reaction mixture which was then allowed to slowly warm to room temperature over 16 h. Following completion of the reaction, the reaction mixture was diluted with dichloromethane and the organic layer was washed with water, separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified with silica flash column chromatography (25% → 50% ethyl acetate in hexanes) to afford **S2** as a sticky white solid (322 mg, 72% yield, *mixture of rotamers*).

Data for **S2**: IR (neat): υ = 3421, 1748, 1669, 1541, 1397, 1326, 1163, 1122 cm^{-1}

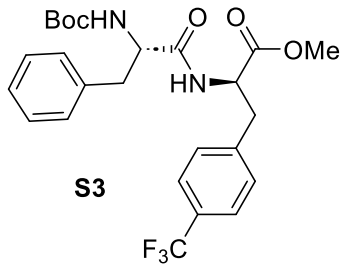
^{1}H NMR (600 MHz, acetone-d$_6$): 7.62 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 4.74-4.90 (m, 1H), 4.17 (br s, 1H), 3.20-3.35 (m, 3H), 3.12 (m, 1H), 2.77 (m, 1H) 1.62 -2.00 (m, 4H), 1.20-1.46 (m, 9H).

^{13}C NMR (125 MHz, acetone-d$_6$): δ 171.3, 171.2, 155.5, 140.0, 136.7, 129.7, 129.5 (q, *J* = 32.5 Hz), 129.4, 128.8, 127.1, 125.5 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.9 Hz), 80.4, 55.8, 53.0, 52.5, 38.2, 37.7, 28.3.

^{19}F NMR (376 MHz, acetone-d$_6$): δ -62.7.

HRMS (ESI): Expected mass ($M+Na^+$): 467.1764; found: 467.1762.

*Preparation of Compound **S3***



S3

N-Boc-L-phenylalanine (300 mg, 1.13 mmol, 1.1 equiv) was dissolved in dry dichloromethane (4.0 mL). Subsequently, HOBt (197 mg, 1.46 mmol, 1.3 equiv.), diisopropylethylamine (0.737 mL, 4.24 mmol, 3.85 equiv.), DMAP (14.8 mg, 0.121 mmol, 0.11 equiv) and EDC hydrogen chloride (0.279 mg, 1.46 mmol, 1.3 equiv.) were added and the reaction was allowed to stir for 10 minutes at 0°C. (4-trifluoromethyl)-D-phenylalanine methyl ester (0.254g, 1.10 mmol, 1 equiv.) was then added to the reaction mixture which was then allowed to slowly warm to room temperature over 16 h. Following completion of the reaction, the reaction mixture was diluted with dichloromethane and the organic layer was washed with water, separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified with silica flash column chromatography (20 → 40% ethyl acetate in hexanes) to afford **S3** as a white solid (322 mg, 72% yield).

Data for **S3**: IR (neat): υ = 3337, 1737, 1656, 1521, 1326, 1247, 1165, 1122, 735 cm^{-1}

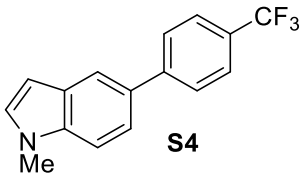
^{1}H NMR (600 MHz, $CDCl_3$): 7.48 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6, 1H), 7.18 (d, *J* =7.6 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.43 (br s, 1H), 4.86 (m, 2H), 4.37 (br s, 1H), 3.68 (s, 3H), 2.99-3.15 (m, 4H), 1.37 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 171.2, 155.5, 140.0, 136.7, 129.7, 129.5 (q, *J* = 32.5 Hz), 129.4, 128.8, 127.1, 125.5 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.9 Hz), 80.4, 55.8, 53.0, 52.5, 38.2, 37.7, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.9.

HRMS (ESI): Expected mass ($M+Na^+$): 517.1921; found: 517.1921.

*Preparation of Compound **S4***



S4

In a pressure tube equipped with a stir bar was added a mixture of dioxane (3 mL) and water (1 mL). This was followed by addition of 1-bromo-4-trifluoromethyl-benzene (0.223 g, 1 mmol, 1 eq.), 1-methylindole-5-boronic acid (0.262 g, 1.5 mmol, 1.5 eq.), Na_2CO_3 (0.317 g, 3 mmol, 3 equiv), and $Pd(PPh_3)_4$ (5 mol%). This mixture was then purged with argon for 15 minutes. The reaction mixture was heated to 90 ^oC for 10 h. The reaction completion was monitored using TLC. Once completed, the reaction mixture was cooled and diluted with distilled water and extracted with EtOAc. The organic layer was then separated, dried with sodium sulfate, filtered, and concentrated under reduced pressure. After flash chromatography using 5% EtOAc and hexane, 0.207 g of pure product **S4** was obtained in 93% yield as a white solid.

Data for **S4**: IR (neat): υ = 3414, 1641, 1240, 1090, 760 cm^{-1}

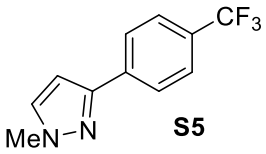
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, *J* = 1.2 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.48 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 3.1 Hz, 1H), 6.56 (dd, *J* = 3.1, 0.6 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 138.6, 134.5, 134.2, 132.0, 130.6, 130.4, 130.0, 129.0, 125.7 (q, *J* = 3.7 Hz), 125.0, 122.8, 106.7, 37.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.1.

HRMS (ESI): Expected mass ($M+H^+$): 276.0993; found: 276.0993.

*Preparation of Compound **S5***



S5

In a pressure tube equipped with a stir bar was added a mixture of dioxane (3 mL) and water (1 mL). This was followed by addition of 1-Bromo-4-trifluoromethyl-benzene (0.223 g, 1 mmol, 1 eq.), 1-methyl-1H-pyrazole-5-boronic acid (0.188 g, 1.5 mmol, 1.5 eq.), Na_2CO_3 (0.317 g, 3 mmol, 3 equiv), and $Pd(PPh_3)_4$ (5 mol%). This mixture was then purged with argon for 15 minutes. The reaction mixture was heated to 90 ^oC for 10 h. The reaction completion was monitored using TLC. Once completed, the reaction mixture was cooled and diluted with distilled water and extracted with EtOAc. The organic layer was then separated, dried with sodium sulfate, filtered, and concentrated under reduced pressure. After flash chromatography using 5% EtOAc and hexane, 0.209 g of pure product **S5** was obtained in 93% yield as a yellowish white crystalline solid.

Data for **S5**: IR (neat): υ = 3423, 1701, 1655, 1619 1561 1321, 1108 cm^{-1}

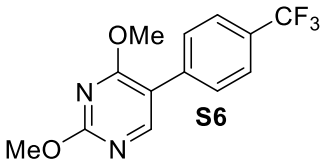
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.54 (m, 3H), 6.38 (d, *J* = 1.9 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 138.6, 130.5 (q, *J* = 32.5 Hz), 129.0, 125.7 (q, *J* = 3.7 Hz), 125.0, 122.8, 106.7, 37.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.6.

HRMS (ESI): Expected mass ($M+H^+$): 227.0788; found: 227.0788.

*Preparation of Compound **S6***



In a pressure tube equipped with a stir bar was added a mixture of dioxane (3 mL) and water (1 mL) This was followed by addition of 1-Bromo-4-trifluoromethyl-benzene (0.223 g, 1 mmol, 1 eq.), 2,4-Dimethoxy-5-pyrimidinylboronic acid (0.275 g, 1.5 mmol, 1.5 eq.), Na_2CO_3 (0.317 g, 3 mmol, 3 equiv), and $Pd(PPh_3)_4$ (5 mol%). This mixture was then purged with argon for 15 minutes. The reaction mixture was heated at 90 ^oC for 10 h. The reaction completion was monitored using TLC. Once completed, the reaction mixture was cooled and diluted with distilled water and extracted with EtOAc. The organic layer was then separated, dried with sodium sulfate, filtered, and concentrated under reduced pressure. After flash chromatography using 5% EtOAc and hexane, 0.242 g of pure product **S6** was obtained in 85% yield as a white solid.

Data for **S6**: IR (neat): υ = 3400, 1638, 1523, 1474, 1331, 1168 cm^{-1}

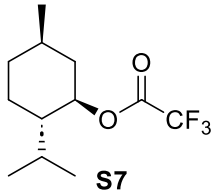
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 4.06 (s, 3H), 4.04 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 164.8, 136.8, 129.0, 125.4 (q, *J* = 3.7 Hz), 123.0, 120.3, 115.0, 55.1, 54.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.6.

HRMS (ESI): Expected mass ($M+H^+$): 285.0847; found: 285.0847.

*Preparation of Compound **S7***



S7

Menthol (1.00 g, 6.4 mmol, 1.1 equiv.) and triethylamine (0.980 mL, 7.0 mmol, 1.2 equiv.) were dissolved in dichloromethane (14.5 mL) at 0°C. Trifluoroacetic anhydride (0.81 mL, 5.8 mmol, 1 equiv.) was then added dropwise and the reaction mixture was allowed to slowly warm to room temperature over 16 h. Following completion of the reaction, the reaction mixture was diluted with dichloromethane and quench with water. The organic layer was then washed with 1M HCl, separated, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford S8 (1.40 g, 96%) as a light yellow liquid. The crude material (85% **S7** and 15% menthol) was then used without any additional purification.

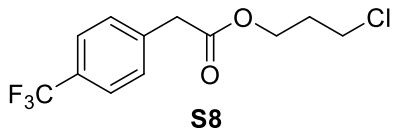
Data for **S7**: IR (neat): υ = 2960, 2874, 1779, 1458, 1373, 1221, 1169, 1147 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.87 (ddd, *J* = 10.9, 10.9, 4.4 Hz, 1H), 2.06 (m, 1H), 1.84 (m, 1H), 1.72 (m, 2H), 1.53 (m, 2H), 1.18 – 1.05 (m, 2H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.93 (m, 1H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.78 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2 (q, *J* = 41.7 Hz), 114.7 (q, *J* = 286.1 Hz), 79.4, 46.7, 40.0, 33.9, 31.4, 26.2, 23.4, 21.8, 20.5, 16.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -75.2.

*Preparation of Compound **S8***



S8

(4-Trifluoromethyl-phenyl)-acetic acid (0.204 g, 1 mmol, 1 eq.) was dissolved in dry CH_2Cl_2 (16 mL). DCC (0.310 g, 1.5 mmol, 1.5 eq.) was then added to the reaction mixture and stirred until a white precipitate was formed. Subsequently, catalytic amount of DMAP (5 mol%) was added followed by dropwise addition of 3-chloro-propan-1-ol (0.07 mL, 1 mmol, 1 eq.). The reaction was left to stir for 16 h. Following completion of the reaction, the reaction mixture was diluted with dichloromethane. The organic layer was then washed with water, separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. Crude product **S8** was purified using flash chromatography with 100% hexane as eluent to afford **S8** (0.12 g, 45% yield) as a colourless oil.

Data for **S8**:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.27 (t, *J* = 6.1 Hz, 2H), 3.69 (s, 2H), 3.56 (t, *J* = 6.3 Hz, 2H), 2.09 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 137.7, 129.8 (q, *J* = 14.7 Hz), 129.6, 125.5 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 271 Hz), 61.8, 48.9, 41.0, 31.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.6.

General Procedure for Electrochemical Defluorinative Carboxylation (eDFC) Reaction

Procedure A: A 5 mL ElectraSyn vial was charged with trifluoromethyl(hetero)arene or α,α,α-trifluorocarbonyl (0.25 mmol, 1.0 equiv.) and tetrabutylammonium tetrafluoroborate (0.25 mmol, 1.0 equiv.) in dry DMF (2.5 – 3.0 mL). The vial was then capped with an ElectraSyn vial cap equipped with a platinum cathode and a magnesium anode and the reaction mixture was stirred until it became homogenous. ~200 mg of grounded dry ice (CO_2(s)) was added and the reaction mixture was then electrolyzed under a constant current of 16 mA for 3 F/mol. ~200 mg portions of dry ice were added every 15 minutes over the course of the reaction (see Graphical Guide Section). *Note: For certain substrates with electron-donating groups we found a CO_2 balloon worked better and these are indicated in the procedures below*. Following electrolysis, the ElectraSyn vial cap was removed and the electrodes were rinsed with ethyl acetate (ca. 2 mL). The reaction mixture was then transferred to a separatory funnel, diluted with 10 mL of ethyl acetate, and washed with 1M or 3M HCl. The organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the crude product was purified by silica flash chromatography as indicated.

Procedure B: A 5 mL ElectraSyn vial was charged with trifluoromethylarene (0.25 mmol, 1.0 equiv.) and tetrabutylammonium tetrafluoroborate (0.50 mmol, 2.0 equiv.) in dry DMF (2.5 – 3.0 mL). The vial was then capped with an ElectraSyn vial cap equipped with a tin cathode and a magnesium anode and the reaction mixture was stirred until it became homogenous. The reaction mixture was then pre-electrolyzed under a constant voltage of 3V for 2 minutes (Note: no reference electrode was used for constant voltage – the IKA Electrasyn was simply set to this value). Subsequently, the voltage was changed to 0.8 V and the reaction mixture was electrolyzed for a further 2.5 F/mol. ~200 mg of grounded dry ice (CO_2(s)) was added and the reaction mixture was then electrolyzed under a constant current of 16 mA for 3 F/mol. ~200 mg portions of dry ice were added every 15 minutes over the course of the reaction (see Graphical Guide Section). Following electrolysis, the ElectraSyn vial cap was removed and the electrodes were rinsed with ethyl acetate (ca. 2 mL). The reaction mixture was then transferred to a separatory funnel, diluted with 10 mL of ethyl acetate, and washed with 1M or 3M HCl. The organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and the crude product was purified by silica flash chromatography as indicated.

Graphical Guide for Electrochemical Defluorinative Carboxylation

Figure S1. Remediation of black electrode fouling. **(Left)** The black electrode fouling occurs at the anode (magnesium). **(Centre)** Removal of the magnesium electrode from electrochemical apparatus allows for remediation of fouling of electrode. **(Right)** The black and raised electrode fouling can be removed via sanding with fine grain sandpaper purchased at Home Depot or with NaOH solution (not shown).

Figure S2. Remedied electrode. **(Left)** Magnesium anode has now completely removed the black, raised deposits on the electrode. **(Centre)** The magnesium electrode can now be reassembled back into the anode position of the conducting unit. **(Right)** The electrochemical vial now has all the reagents, solvent, stir bar, and clean electrodes assembled. This method yields a life of 20-25 experiments for the magnesium electrode.

Figure S3. Addition of dry ice methodology. **(Left)** A common mortar and pestle is all that is required to grind the large chunks of dry ice into small pellets to be added into the reaction vial. **(Centre)** Within seconds, the large chunks of dry ice are grinded into small pellets of dry ice. **(Right)** A small spatula full is all that is required to be added into the reaction vial at the start of the reaction and every 10-15 minutes intervals afterwards until completion.

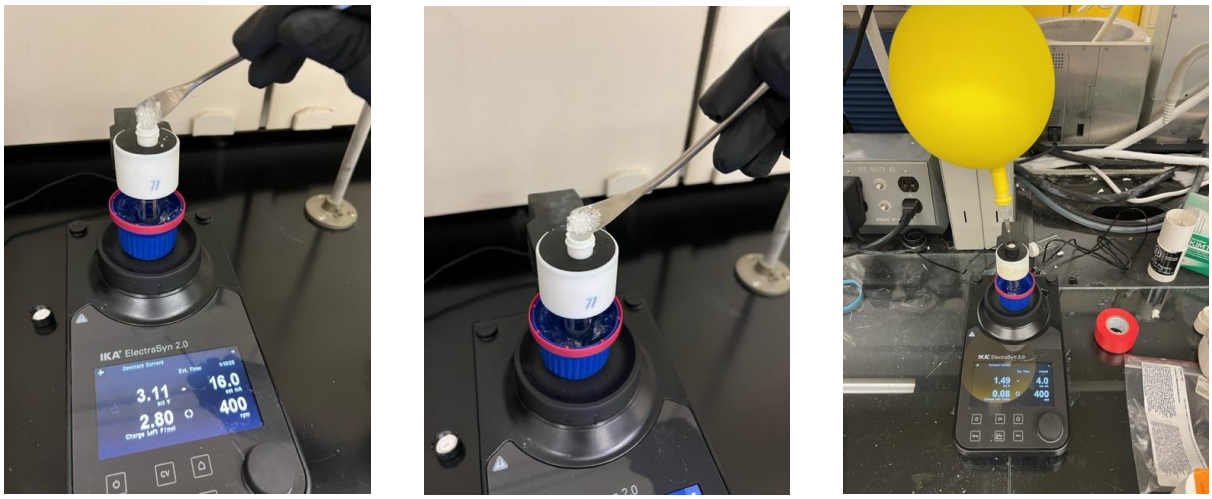


Figure S4. Methods of introducing CO_2 into the reaction system. **(Left)** Crushed dry ice (CO_2) is added directly to the reaction vial prior to starting the reaction and every 10-15 minutes intervals afterwards. **(Centre)** A close up of the aforementioned procedure. The top of the vial was uncapped and then recapped once addition of the crushed dry ice was accomplished. **(Right)** Carbon dioxide gas ($CO_{2(g)}$) was added via a balloon system. This involved filling a balloon with $CO_{2(g)}$ and with a syringe and hypodermic needle setup, puncture through the top of the vial to maintain constant flow of $CO_{2(g)}$ into the reaction vial. An escape needle for the pressure was required on occasion if the seal of the reaction had 100% integrity (not shown).

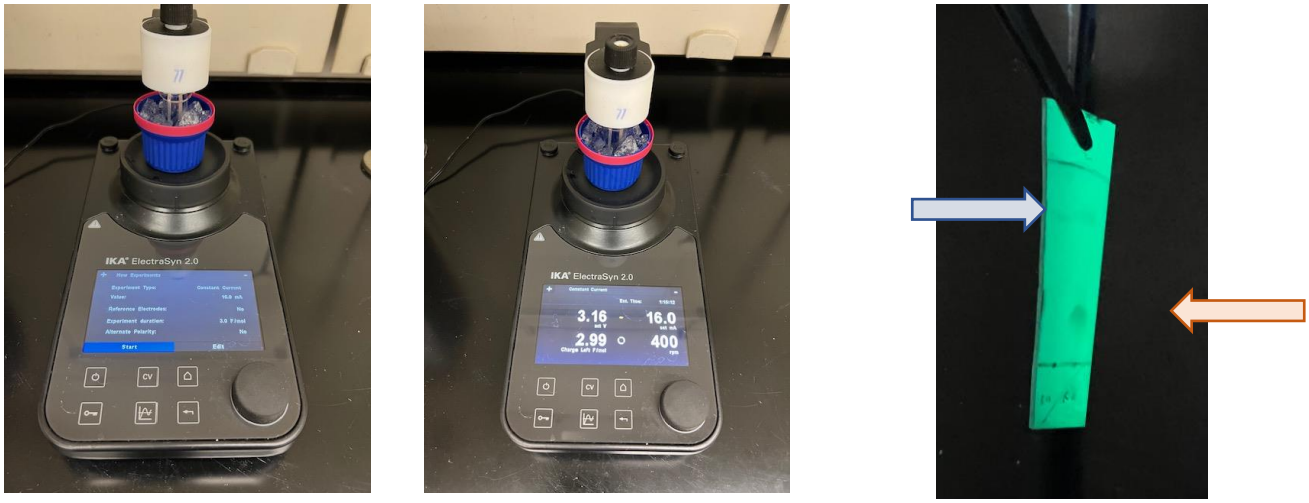


Figure S5. Electrochemical defluorinative carboxylation apparatus set up and TLC confirmation. **(Left)** The reaction vial is maintained at 0°C via sustaining an ice bath in large, standard beaker cap. The parameters are set to constant current 16mA with 3.0F/mol of 0.25 mmol of substrate. No reference electrode is used. **(Centre)** The electrochemical epxeriment running as normal with the voltage and duration displayed. **(Right)** Thin layer chromatography (TLC) was conducted with the reaction (red arrow) compared to the starting material (blue arrow). This was viewed under UV light of 254 nm.

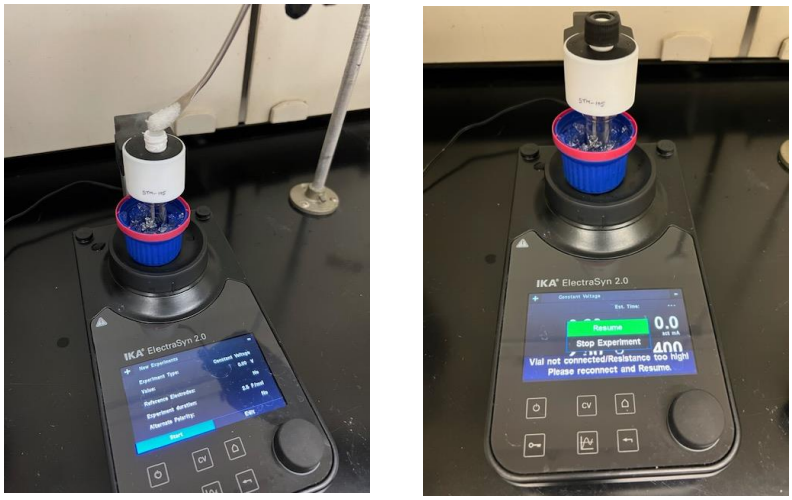


Figure S6. Constant voltage parameters. **(Left)** Constant voltage experiments were conducted at 0.8 volts with no reference electrode. To set no reference electrode, confirm with apparatus set up that no reference electrode is being employed. After the addition of crushed dry ice via spatula addition to the top of the reaction vial, the experiment was commenced. **(Centre)** The experiment is unable to proceed forward and displays error as depicted. Hence, as Figures 7 and 8 illustrate, the constant voltage setting of 2.0 volts is required to be run for a brief 30 seconds before ending and returning to the desired 0.8 volt setting.

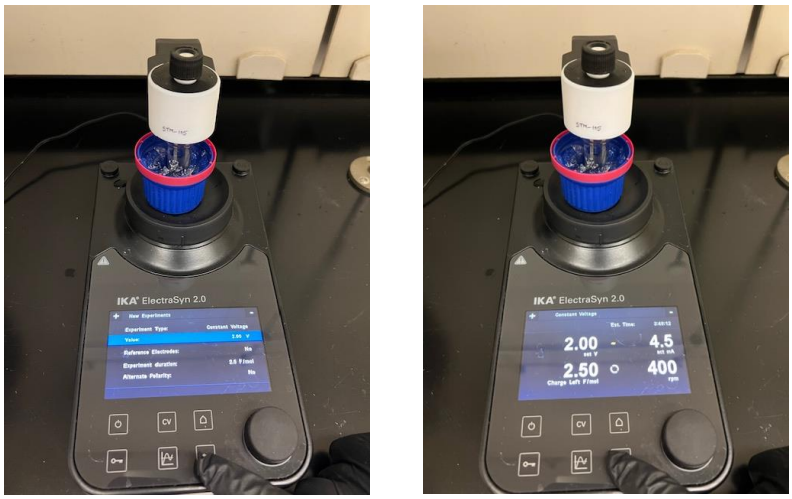


Figure S7. Modification in constant voltage parameters to remedy incapability. **(Left)** The experiment was stopped and the constant voltage was changed to 2.0 volts opposed to the desired 0.8 volts. **(Centre)** The experiment was run for 30 seconds at the 2.0 volts before returning to the constant 0.8 volts setting (see Figure 8).

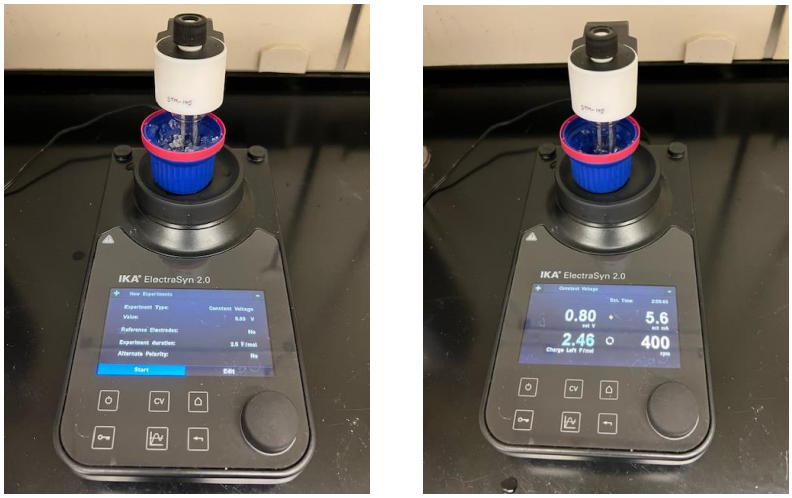


Figure S8. Returning to constant 0.8 volts settings. **(Left)** After running the experiment at constant 2.0 volts for 30 seconds, the experiment was returned to the original constant 0.8 volts setting. **(Centre)** The reaction now runs successfully at consant 0.8 volts. Please note, that for all of the constant voltage conditions, no reference electrode was employed. The IKA instruments allow for this condition by selecting no reference electrode.

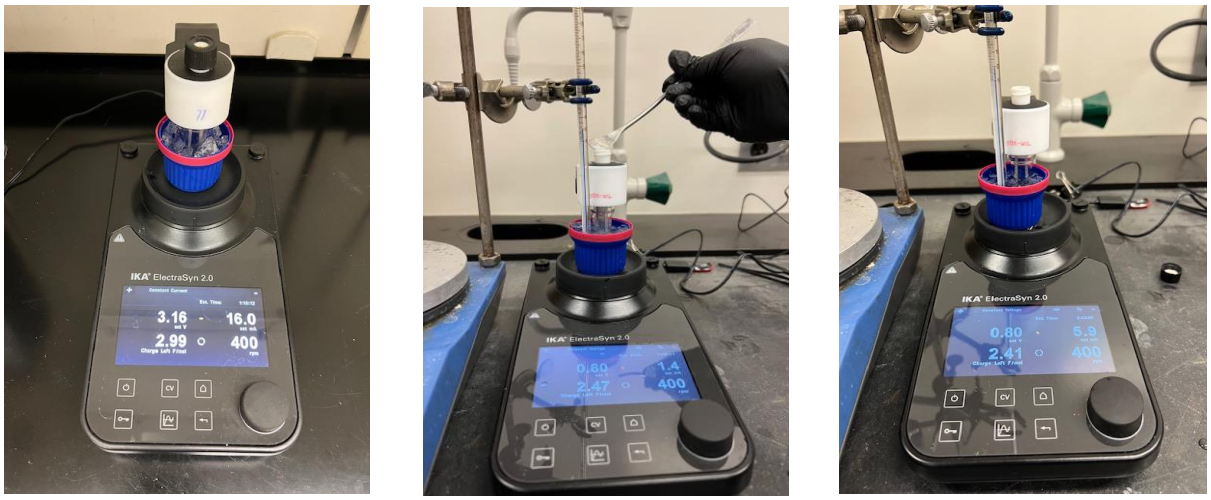


Figure S9. The determination of the effect of $CO_{2(s)}$ pressure in reaction vessel on product yield and selectivity. **(Left)** All reactions had crushed dry ice added and then the reaction vessel was capped (as shown in **Figure 4**). It is important to note that the reaction vessel is unable to withstand high pressures such that if capped tightly the cap will pop off a short time later. Hence, all reactions conducted with the addition of dry ice thus far had the cap placed loosely to disperse pressure accumulation. **(Centre)** In order to test the effects of $CO_{2(g)}$ pressure accumulating within the reaction vessel, we ran an experiment with no cap. Here we add the crushed dry ice to the uncapped reaction every 10-15 minutes as before. **(Right)** The reaction is then allowed to continue running uncapped until completion, with intervals of adding crushed dry ice every 10-15 minutes as before.

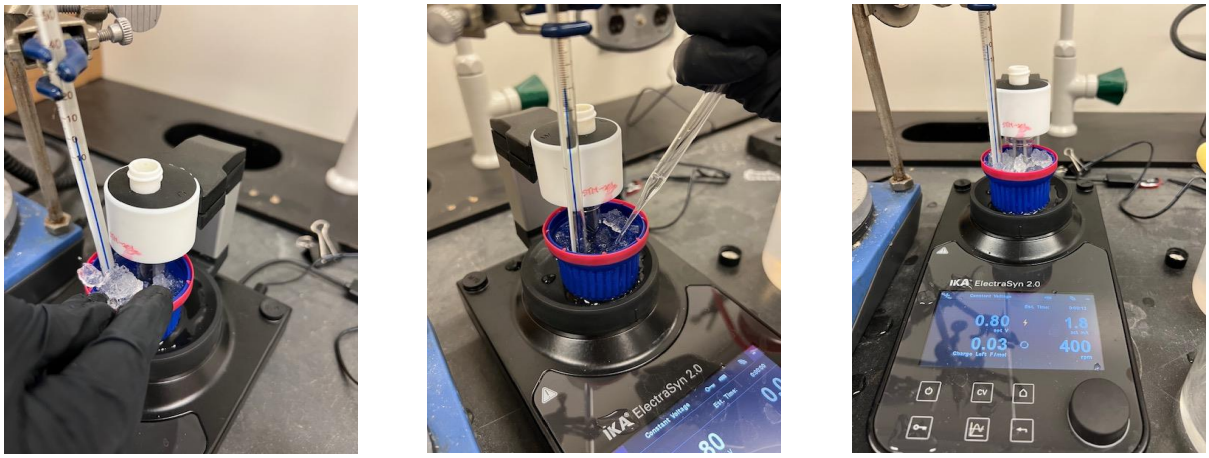


Figure S10. Maintenance of 0°C conditions using bottle cap ice bath. **(Left)** Every 10-20 minutes, more ice is added to the ice bath. Temperature was monitored via thermometer. **(Centre)** A glass pasteur pipette is used to remove excess melted ice to then allow further addition of ice. **(Right)** The reaction is allowed to run reliably at 0°C with minor fluctuations (0-2°C) through this minor maintenance every 10-15 minutes, which coincides with addition of $CO_{2(s)}$.

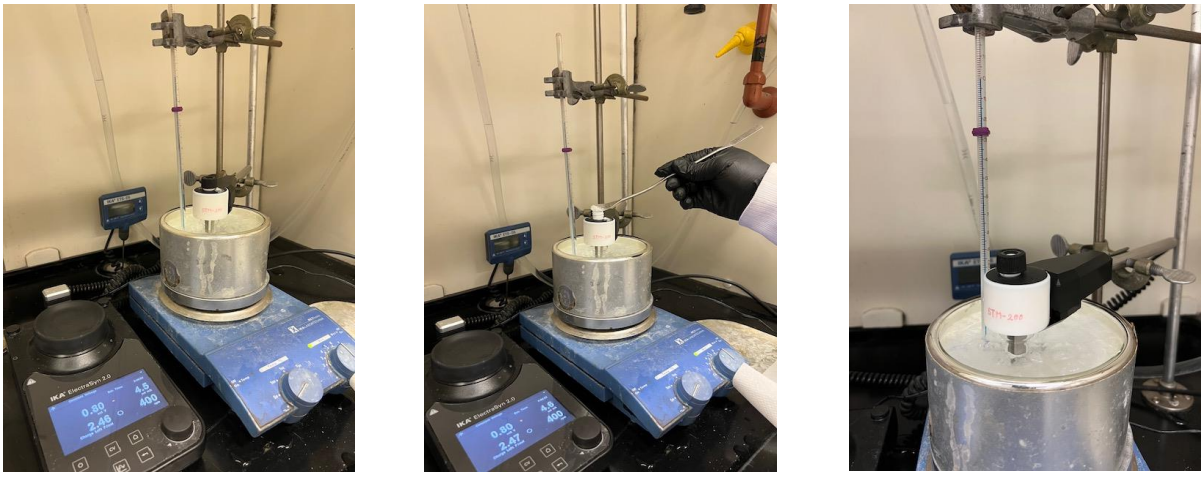
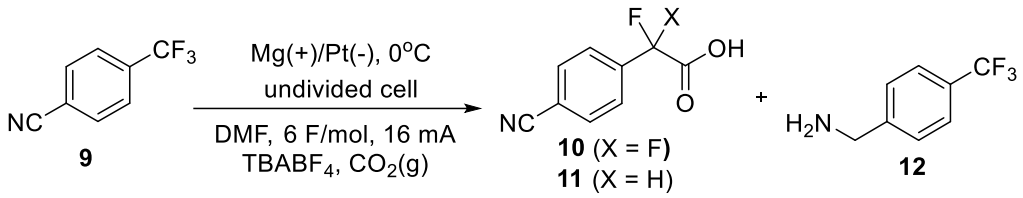


Figure S11. The setup and determination of the effects of using a dewar instead of a bottle cap for ice bath conditions. **(Left)** The IKA ElectraSyn 2.0 extension apparatus allows for set up of the electrochemical reaction in an adjacent ice bath on a stir plate (IKA RCT basic). The temperature was monitored with a thermometer. **(Centre)** The addition of crushed dry ice was done every 10-15 minutes as before. **(Right)** The reaction was capped loosely as before and then allowed to run with aforementioned intervals of dry ice addition. The ice bath was monitored throughout and needed only slight maintenance (every 45-60 minutes) and had only slight fluctuations in temperature (0-2ºC).

Please note, that for all of the constant voltage conditions, no reference electrode was employed. The IKA instruments allow for this condition by selecting no reference electrode.

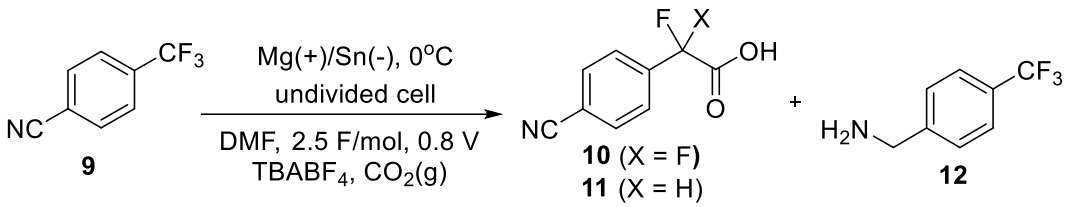
All electrochemical experiments were conducted using IKA instruments.

Optimization



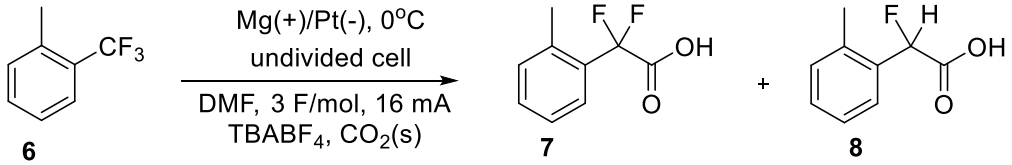
Optimization Table S1

Entry	Variation from above	Ratio of 10:11:12	NMR Yield (%)
1.	none	1:2.5:2	45
2.	10 mA (Constant Current)	1:1.5:2	30
3.	1V, 2F/mol (Constant Voltage)	6:4:1	40
4.	0.75V, 2F/mol (Constant Voltage)	4:4:1	46
5.	0.80V, 2.5F/mol (Constant Voltage)	12:5:1	51
6.	0.80V, 2.5F/mol (Constant Voltage), Sn cathode instead of Pt, Zn anode instead of Mg	-	None
7.	Al cathode instead of Pt	1.5:1:1.5	44
8.	Cu cathode instead of Pt	-	None
9.	Al anode instead of Mg	-	None
10.	Et_3SiH	1:1.5:2	20
11.	$Zn(OTf)_2$	-	Trace
12.	$TBAClO_4$ instead of $TBABF_4$	1:1.5:2	30
13.	TBAOAc instead of $TBABF_4$	-	None
14.	TBABr instead of $TBABF_4$	1.5:2:1	53



Optimization Table S2

Entry	Variation from above	Ratio of 10:11:12	NMR Yield (%)
1.	none	1:2.5:2	45
2.	RT	4:9:1	40
3.	RT, Dry Ice	3:10:1	49
4.	-10 °C, Dry Ice	3.5:1:1.5	45
5.	Dry Ice, DMA	3:6:1	4.5
6.	Dry Ice, DCM	-	None
7.	Dry Ice, MeCN	10:13:1	23
8.	Dry Ice, Acetone	2:4:1	19
9.	Dry Ice, DMSO	5:10:1	30
10.	Dry Ice, NMP	7:1:2	31
11.	Dry Ice, THF	-	None
12.	Dry Ice, Toluene	-	None
13.	Open Cap, Dry Ice	3.5:2:1	54
14.	Dry DMF	4:2:1	56
15.	1 vol% D_2O	4:9:1	52%(50% d-incorporation)



6 7 8

Optimization Table S3

Entry	Variation from above	Ratio of 7:8	NMR Yield (%)
1.	none	15:1	83
2.	Steel cathode instead of Pt	30:1	66
3.	Cu cathode instead of Pt	25:1	62
4.	Sn cathode instead of Pt	-	Trace
5.	Ni cathode instead of Pt	14:1	72
6.	Graphite cathode instead of Pt	7:1	42
7.	Co cathode instead of Pt	16:1	70
8.	-10 ˚C	34:1	74
9.	0.5 eq. $TBABF_4$ instead of 1.0 eq. $TBABF_4$	11:1	66
10.	17.5 mA instead of 16 mA	10:1	74
11.	20 mA instead of 16 mA	31:1	69
12.	4F/mol instead of 3F/mol	5:1	50
13.	2F/mol instead of 3F/mol	20:1	46
14.	MeCN instead of DMF	-	-
15.	Ni cathode instead of Pt, and ACN instead of DMF	1:1	40
16.	Steel cathode instead of Pt, and ACN instead of DMF	-	-
17.	Co cathode instead of Pt, and ACN instead of DMF	-	-
18.	Gr cathode instead of Pt, and ACN instead of DMF	-	-
19.	Napthalene as an additive	4:1	54
20.	$SmCl_3$ as an additive	5.5:1	60

Mechanistic Insights

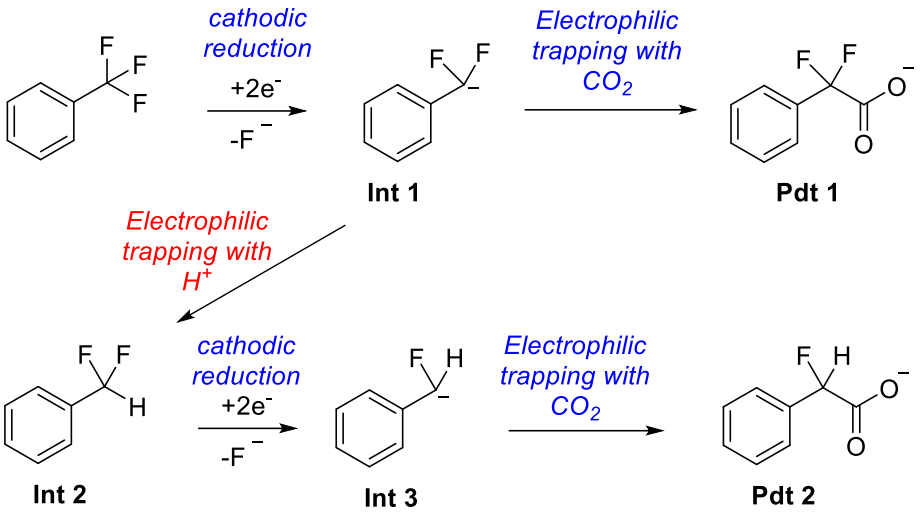


Figure S12. Proposed mechanism for formation of difluoro- and monofluoro- carboxylic acid products.

Formation of monofluoro-carboxylic acid product

The monofluoro-carboxylic acid product could form via either proton trapping of **Int 1** followed by a defluorinative carboxylation, or through protodefluorination of the difluoro-carboxylic acid product. To deduce which mechanism was operative, we re-exposed the difluorocarboxylic acid product to our reaction conditions and did not observed any formation of the monofluorocarboxylic acid product. Thus, suggesting that the monofluoro carboxylic acid product comes from protodefluorination of the trifluoromethylarene and subsequent defluorinative carboxylation. Additionally, given that we were able to convert **43** to **44** (see Figure 3 in manuscript), **Int 2** is a reasonable intermediate leading to the formation of the monofluoro carboxylic acid product (**Pdt 2**). Therefore, the product ratios are a result of competitive protodefluorination and defluorinative carboxylation of the trifluoromethylarene. Our mechanistic proposal agrees with previous accounts of electrochemical defluorinative electrophilic trapping (see refs 12 and 14 from manuscript). Finally, to confirm the presence of a benzylic anion rather than a radical intermediate we ran the eDFC of 4-trifluoromethyl benzonitrile in the presence of 1 vol% of D_2O. This led to 50% deuterium incorporation in the monofluoro carboxylic acid product supporting that the reaction does in fact proceed via benzylic anion intermediate.

Role of solid CO_2

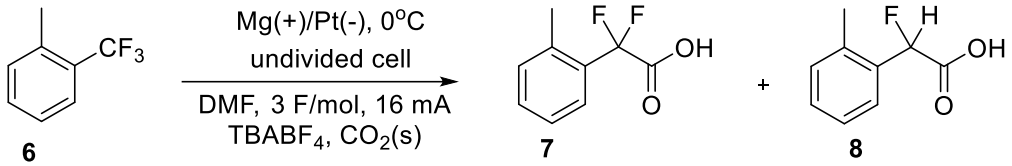


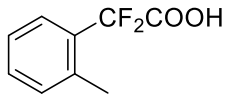
Table S4. Temperature dependence on product selectivity

Entry	Variation from above	Ratio of 7:8	NMR Yield (%)
1.	none	15:1	83
2.	RT	9:1	83
3.	-10 ˚C	60:1	61

We believe the solid CO_2 serves to both increase the amount of dissolved CO_2 as well as to cool the reaction mixture. We confirmed this first point through comparing results between running the reaction in a partially enclosed vessel vs an open vessel for the 4-trifluoromethyl benzonitrile. In an open system, the yield decreases from 65% to 54% and the difluoro:mono ratio decreases from 2.5:1 to 1.25:1 compared to a partially enclosed vessel that we had used for these reactions. Mechanistically, the mono-product forms via protodefluorination of the trifluoromethylarene followed by defluorinative carboxylation of this difluoromethyl intermediate (see above section for further details). Furthermore, no monofluoro carboxylic acid product can be formed via protodefluorination of the difluoro carboxylic acid. The product ratios is a result of competitive protodefluorination and defluorinative carboxylation of the trifluoromethyl arene. Given this, the above observations indicate CO_2 concentration as being responsible for improved yields and selectivity. We suspect that a cooling effect from the use of solid CO_2 may also play a role towards improving the difluoro:monofluoro selectivity. This is supported through our evaluation of this reaction at different temperatures (see Table S4). At RT (for 2-trifluoromethyl toluene), the ratio changes from 15:1 to 9:1. Conversely, further decreasing the temperature to -10˚C improves the ratio from 15:1 to 60:1: albeit with lower yield. These results suggest lower temperature serves to increase the CO_2 concentration in the reaction mixture. As such, a cooling effect from using solid CO_2 may be contributing factor towards improved selectivity.

Preparation and characterization of defluorinative carboxylation products

Preparation of 7



7

Following the General Procedure A, a solution of 2-methyl trifluorotoluene (**6**) (34.2 µL, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^1H NMR yield of the crude product was determined to be 83% (15:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **7** by flash chromatography (10 → 30 % EtOAc in hexanes and 2% acetic acid) afforded **7** (34.4 mg, 74%) as a colourless oil.

Data for **7**: IR (neat): υ = 3431, 1635, 1294, 1251, 1113 cm^{-1}

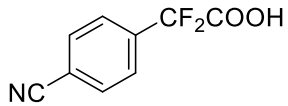
^{1}H NMR (500 MHz, acetone-d$_6$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.28 (m, 2H), 2.42 (s, 3H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 165.3 (t, *J* = 34.4 Hz), 137.2, 132.80, 132.3 (t, *J* = 23.2 Hz), 131.8, 126.9, 126.8 (t, *J* = 8.9 Hz), 115.4 (t, *J* = 249.9 Hz), 19.7 (t, *J* = 2.4 Hz).

^{19}F NMR (376 MHz, CDCl$_3$) δ -102.4.

HRMS (ESI): Expected mass ($M-H^+$): 185.0420; found: 185.0421.

Preparation of 10



10

Following the General Procedure B, a solution of 4-trifluoromethyl benzonitrile (42.8 mg, 0.250 mmol), and $TBABF_4$ (164.6 mg, 0.500 mmol) in DMF (3.0 mL) was electrolyzed for 2.5 F/mol at 0.8 V. The ^1H NMR yield of the crude product was determined to be 65% (2.5:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **10** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **10** (30.3 mg, 62%) as a yellowish oil.

Data for **10**: IR (neat): υ = 3427, 2238, 1650, 1401, 1263, 1106 cm^{-1}

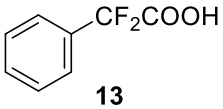
^{1}H NMR (500 MHz, acetone-d_6) δ 7.96 (d, *J* = 7.9 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H).

^{13}C NMR (176 MHz, acetone-d_6) δ 165.8 (t, *J* = 31.5 Hz), 139.1 (t, *J* = 26.0 Hz), 133.7, 127.5 (t, *J* = 6.1 Hz), 118.7, 115.8, 114.2 (t, *J* = 252.8 Hz).

^{19}F NMR (376 MHz, acetone-d_6) δ -105.0.

HRMS (ESI): Expected mass ($M-H^+$): 196.0216; found: 196.0216.

Preparation of 13



13

Following the General Procedure A, a solution of trifluorotoluene (30.8 µL, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA. The ^{1}H NMR yield of the crude product was determined to be 76% (24:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **13** by flash chromatography (10 → 30 % EtOAc in hexanes and 2% acetic acid) afforded **13** (27.1 mg, 63%) as a white solid.

Data for **13**: IR: 3397, 1652, 1264, 1131 cm^{-1}

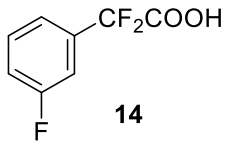
^{1}H NMR (500 MHz, acetone-d_6) δ 7.64 (d, *J* = 6.8 Hz, 2H), 7.60 – 7.51 (m, 3H).

^{13}C NMR (126 MHz, acetone-d_6) δ 165.3 (t, *J* = 36.5 Hz), 134.1 (t, *J* = 25.4 Hz), 132.0, 126.2 (t, *J* = 6.2 Hz), 129.7, 114.6 (t, *J* = 249.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.2.

HRMS (ESI): Expected mass ($M-H^+$): 171.0263; found: 171.0264.

Preparation of 14



14

Following the General Procedure A, a solution of 3-fluoro-trifluorotoluene (31.5 µL, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^{1}H NMR yield of the crude product was determined to be 78% (27:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **14** by flash chromatography (10 → 30 → 50 % EtOAc in hexanes and 2% acetic acid) afforded **14** (30.9 mg, 65%) as a colourless oil.

Data for **14**: IR (neat): υ = 3431, 1641, 1448, 1275, 1111 cm^{-1}

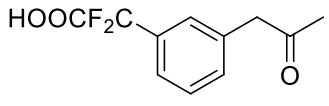
^{1}H NMR (500 MHz, acetone-d$_6$) δ 7.64 – 7.56 (m, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.40-7.31 (m, 2H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 165.2 (t, *J* = 33.7 Hz), 163.4 (d, *J* = 245.9 Hz), 136.8 (td, *J* = 26.3, 7.7 Hz), 132.01 (d, *J* = 8.1 Hz), 122.38, 118.86 (d, *J* = 21.2 Hz), 113.9 (t, *J* = 249.5 Hz), 113.46 (dt, *J* = 24.3, 6.4 Hz).

^{19}F NMR (376 MHz, acetone-d$_6$) δ -104.1, -113.2.

HRMS (ESI): Expected mass ($M-H^+$): 189.0169; found: 189.0168.

Preparation of 15



15

Following the General Procedure A, a solution of 3-(trifluoromethyl)phenylacetone (41.4 µL, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^{1}H NMR yield of the crude product was determined to be 62% (4:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **15** by flash chromatography (30 → 50 % EtOAc in hexanes and 2% acetic acid) afforded **15** (28.0 mg, 49%) as pale yellow oil.

Data for **15**: IR (neat): υ = 3426, 1712, 1640, 1277, 1117 cm^{-1}

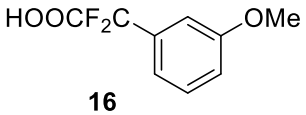
^{1}H NMR (500 MHz, acetone-d_6) δ 7.55 – 7.45 (m, 3H), 7.41 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 2H), 2.17 (s, 3H).

^{13}C NMR (126 MHz, acetone-d_6) δ 205.2, 165.3 (t, *J* = 35.5 Hz), 137.1, 134.1 (t, *J* = 25.4 Hz), 133.5, 129.7, 127.4 (t, *J* = 6.1 Hz), 124.5 (t, *J* = 6.1 Hz), 114.6 (t, *J* = 250.2 Hz), 50.12, 29.67.

^{19}F NMR (376 MHz, acetone-d_6) δ -104.2.

HRMS (ESI): Expected mass ($M-H^+$): 227.0525; found: 227.0524.

Preparation of 16



16

Following the General Procedure A, a solution of 1-methoxy-3-trifluoromethyl-benzene (44.0 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 6 F/mol with a 16 mA current. A CO_2 balloon (constant bubbling) was used instead of grounded dry ice. The ^{1}H NMR yield of the crude product was determined to be 93% (8:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **16** by flash chromatography (30 → 50% EtOAc in hexanes and 2% acetic acid) afforded **16** (43.0 mg, 84%) as a white solid.

Data for **16**: IR (neat): υ = 3418, 1637, 1280, 1218, 1115, 750 cm^{-1}

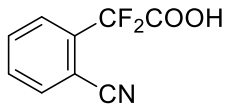
^{1}H NMR (400 MHz, acetone-d_6): δ 7.44 (t, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.13 (m, 2H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, acetone-d_6): δ 165.2 (t, *J* = 29.7 Hz), 160.8, 135.4 (t, *J* = 26.2 Hz), 130.9, 118.1 (t, *J* = 7.0 Hz), 117.39, 114.3 (t, *J* = 250.4 Hz), 111.7, 55.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -104.85.

HRMS (ESI): Expected mass ($M-H^+$): 201.0369; found: 201.0369.

Preparation of 17



17

Following the General Procedure B, a solution of 2-trifluoromethyl benzonitrile (42.8 mg, 0.250 mmol), and $TBABF_4$ (164.6 mg, 0.500 mmol) in DMF (3.0 mL) was electrolyzed for 2.5 F/mol at 0.8 V. The ^1H NMR yield of the crude product was determined to be 72% (7:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **17** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **17** (24.6 mg, 50%) as a yellow oil.

Data for **17**: IR (neat): υ = 3415, 2232, 1647, 1248, 1087 cm^{-1}

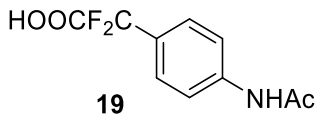
^{1}H NMR (500 MHz, acetone-d$_6$) δ 7.97 (d, *J* = 6.0 Hz, 1H), 7.90 (t, *J* = 11.0 Hz, 2H), 7.80 (t, *J* = 6.2 Hz, 1H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 164.10 (t, *J* = 32.4 Hz), 136.55 (t, *J* = 24.9 Hz), 135.8, 134.1, 132.6, 128.0 (t, *J* = 7.4 Hz), 116.9, 113.8 (t, *J* = 252.4 Hz), 111.0.

^{19}F NMR (376 MHz, acetone-d$_6$) δ -101.7.

HRMS (ESI): Expected mass ($M-H^+$): 196.0216; found: 196.0216.

Preparation of 19



19

Following the General Procedure A, a solution of *N*-(4-Trifluoromethyl-phenyl)-acetamide (50.75 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 6 F/mol with a 16 mA current. A CO_2 balloon (constant bubbling) was used instead of grounded dry ice. The ^1H NMR yield of the crude product was determined to be 85% where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **19** by flash chromatography (30 → 50% EtOAc in hexanes and 2% acetic acid) afforded **19** (36.5 mg, 72%) as a white solid.

Data for **19**: IR (neat): υ = 3422, 1701, 1655, 1636, 1545, 1509 cm^{-1}

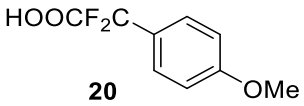
^{1}H NMR (400 MHz, DMSO-*d6*): 10.19 (1H, brs), 7.70 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 2.05 (s, 3H).

^{13}C NMR (125 MHz, acetone-*d6*): δ 169.2, 165.9 (t, *J* = 33.7 Hz), 142.7, 128.9 (t, *J* = 26.2 Hz), 126.9, 119.5, 114.8 (t, *J* = 249.0 Hz), 24.3.

^{19}F NMR (376 MHz, DMSO-*d6*): δ -101.47.

HRMS (ESI): Expected mass ($M+H^+$): 230.0621; found: 230.0621.

Preparation of 20



20

Following the General Procedure A, a solution of 1-Methoxy-4-trifluoromethyl-benzene (47.40mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 6 F/mol with a 16 mA current. A CO_2 balloon (constant bubbling) was used instead of grounded dry ice. The ^{1}H NMR yield of the crude product was determined to be 74% (6.6:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **20** by flash chromatography (30 → 50% EtOAc in hexanes and 2% acetic acid) afforded **20** (29.4 mg, 62%) as a white solid.

Data for **20**: IR (neat): υ = 3406, 1648, 1275, 740 cm^{-1}

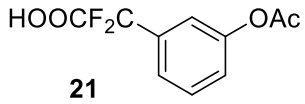
^{1}H NMR (500 MHz, acetone-*d6*): δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, acetone-*d6*): δ 165.5 (t, *J* = 35.0 Hz), 162.7, 127.8 (t, *J* = 5.0 Hz), 126.0 (t, *J* = 26.2 Hz), 115.0, 114.8 (t, *J* = 248 Hz), 55.9.

^{19}F NMR (468 MHz, acetone-*d6*): δ -102.83.

HRMS (ESI): Expected mass ($M-H^+$): 201.0369; found: 201.0369.

Preparation of 21



21

Following the General Procedure A, a solution of Acetic acid 3-trifluoromethyl-phenyl ester (51.0mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 6 F/mol with a 16 mA current. A CO_2 balloon (constant bubbling) was used instead of grounded dry ice. The ^1H NMR yield of the crude product was determined to be 82% (10:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **21** by flash chromatography (30 → 50% EtOAc in hexanes and 2% acetic acid) afforded **21** (30.5 mg, 60%) as a white solid.

Data for **21**: IR (neat): υ = 3449, 1736, 1656, 1628, 1220, 1115 cm^{-1}

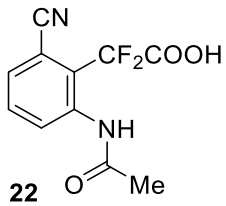
^{1}H NMR (500 MHz, acetone-d$_6$): δ 7.51 (s, 1H), 7.49 - 7.45 (m, 1H), 7.28 (m, 1H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, acetone-d$_6$): δ 169.5, 165.0 (t, *J* = 33.7 Hz), 152.1, 135.4 (t, *J* = 26.2 Hz), 130.9, 125.6, 123.4 (t, *J* = 5 Hz), 119.9, 114.0 (t, *J* = 250.9 Hz), 20.9.

^{19}F NMR (376 MHz, CDCl$_3$): δ -104.83.

HRMS (ESI): Expected mass ($M-H^+$): 229.0318; found: 229.0318.

Preparation of 22



22

Following the General Procedure B, a solution of 3-(*N*-acetyl)-2-trifluoromethyl benzonitrile (57.0 mg, 0.250 mmol), and $TBABF_4$ (164.6 mg, 0.500 mmol) in DMF (3.0 mL) was electrolyzed for 2.5 F/mol at 0.8 V. The ^1H NMR yield of the crude product was determined to be 67% (4.5:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard

(8.0 µL). Purification of the crude product **22** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **22** (35.6 mg, 56%) as an off-white solid.

Data for **22:** IR (neat): υ = 3434, 2232, 1643, 1538, 1419, 1262 cm^{-1}

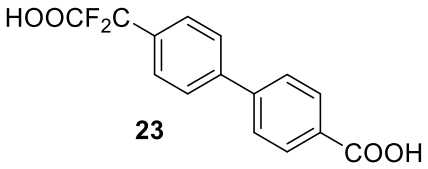
^{1}H NMR (500 MHz, acetone-d$_6$) δ 8.14 (d, *J* = 1.5 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 2.15 (s, 3H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 170.0, 164.0 (t, *J* = 33.1 Hz), 144.4, 137.5 (t, *J* = 24.9 Hz), 136.8, 121.4, 117.6, 117.1, 113.7 (t, *J* = 252.7 Hz), 104.2 (t, *J* = 3.3 Hz), 24.4.

^{19}F NMR (469 MHz, acetone-d$_6$) δ -101.9.

HRMS (ESI): Expected mass ($M-H^+$): 253.0430; found: 253.0429.

Preparation of 23



23

Following the General Procedure A, a solution of 4'-trifluoromethyl-biphenyl-4-carboxylic acid (66.5 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 5 F/mol with a 17 mA current. The ^{1}H NMR yield of the crude product was determined to be 37% (9:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **23** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **23** (18.3 mg, 25%) as a white solid.

Data for **23**: IR (neat): υ = 3427, 1641 cm^{-1}

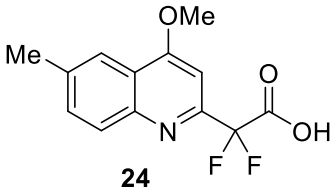
^{1}H NMR (400 MHz, acetone-d$_6$): δ 7.91 (dd, *J* = 6.4, 1.2 Hz, 1H), 7.68 – 7.61 (m, 3H), 7.54 – 7.50 (m, 3H), 7.42 (dd, *J* = 6.4, 1.2 Hz, 1H).

^{13}C NMR (125 MHz, acetone-d$_6$): δ 169.0, 165.4 (t, *J* = 35.0 Hz), 145.4, 142.2, 132.8 (t, *J* = 25.0 Hz), 132.2, 130.9, 129.8, 128.7, 125.9 (t, *J* = 6.3 Hz), 114.7 (t, *J* = 252.5 Hz).

^{19}F NMR (376 MHz, acetone-d$_6$): δ -103.75.

HRMS (ESI): Expected mass ($M-H^+$): 291.0469; found: 291.0469.

Preparation of 24



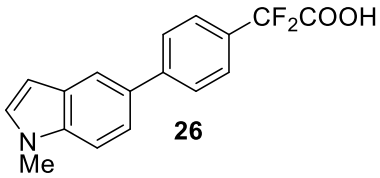
24

Following the General Procedure A, a solution of **S2** (60.5 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (2.5 mL) was electrolyzed for 3 F/mol with a 16 mA current. A CO_2 balloon (constant bubbling) was used instead of grounded dry ice. Purification of the crude product **24** by flash chromatography (30 → 50% EtOAc in hexanes and 2% acetic acid) afforded **24** (24.8 mg, 38%) as a colourless oil. ***24*** *readily undergoes protodecarboxylation upon isolation to give a mixture of products.*

Data for **24**: IR (neat): υ 3399, 2524, 1647, 1456, 1036 cm^{-1}

HRMS (ESI): Expected mass ($M-H^+$): 266.0634; found: 266.0632.

Preparation of 26



26

Following the General Procedure A, a solution of 1-methyl-5-(4-trifluoromethyl-phenyl)-1H-indole (75.3 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^1H NMR yield of the crude product was determined to be 58% (5:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **26** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **26** (46.4 mg, 62%) as a white solid.

Data for **26**: IR (neat): υ = 3430, 1644, 1248, 1107, 835, 800, 736 cm^{-1}

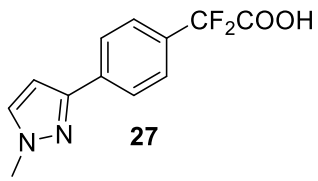
^{1}H NMR (400 MHz, acetone-d$_6$): δ 7.90 (dd, *J* = 1.5, 0.8 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.52 (m, 2H), 7.28 (d, *J* = 3.1 Hz, 1H), 6.50 (dd, *J* = 3.1, 0.6 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR (125 MHz, acetone-d$_6$): δ 165.6 (t, *J* = 33.5 Hz), 146.1, 137.7, 131.8, 131.0, 130.2, 128.1, 128.0, 126.6 (t, *J* = 6.2 Hz), 121.6, 120.1, 114.9 (t, *J* = 248.7 Hz), 110.8, 102.0, 33.0.

^{19}F NMR (376 MHz, acetone-d$_6$): δ -103.78.

HRMS (ESI): Expected mass ($M+H^+$): 302.0987; found: 302.0987.

Preparation of 27



27

Following the General Procedure A, a solution of 1-methyl-3-(4-trifluoromethyl-phenyl)-1H-pyrazole (63.0 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^{1}H NMR yield of the crude product was determined to be 64% (4.5:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **27** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **27** (36.6 mg, 58%) as a white solid.

Data for **27**: IR (neat): υ = 3432, 1643, 1268, 1091 cm^{-1}

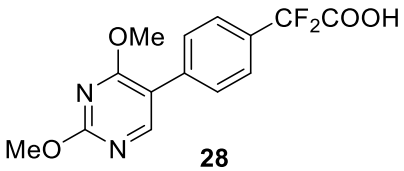
^{1}H NMR (400 MHz, acetone-d$_6$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 1.6 Hz, 1H), 6.42 (d, *J* = 1.5 Hz, 1H) 3.91(s, 3H).

^{13}C NMR (125 MHz, acetone-d$_6$): δ 165.2 (t, *J* = 33.7 Hz), 142.8, 138.9, 133.9 (t, *J* = 25.0 Hz), 129.8, 128.1, 126.7 (t, *J* = 6.2 Hz), 114.5 (t, *J* = 248.2 Hz), 107.1, 38.0.

^{19}F NMR (376 MHz, acetone-d$_6$): δ -104.3.

HRMS (ESI): Expected mass ($M-H^+$): 251.0639; found: 251.0639.

Preparation of 28



28

Following the General Procedure A, a solution of 2,4-dimethoxy-5-(4-trifluoromethyl-phenyl)-pyrimidine (71.0 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^{1}H NMR yield of the crude product was determined to be 64% (5.6:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **28** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **28** (40.0 mg, 56%) as a white solid.

Data for **28**: IR (neat): υ = 3400, 2361, 2108, 1641, 1472, 1400, 1263 cm^{-1}

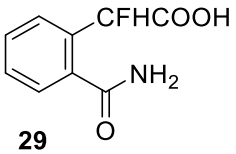
^{1}H NMR (400 MHz, acetone-d_6): δ 8.38 (s, 1H), 7.71 (m, 4H), 3.98 (s, 3H), 4.0 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6): δ 168.9, 165.6 (t, *J* = 43.7 Hz), 158.9, 137.2, 133.6 (t, *J* = 25 Hz, 130.0, 127.8, 126.3 (t, *J* = 6.2 Hz), 114.7, 112.7, 55.1, 54.4.

^{19}F NMR (376 MHz, acetone-d_6): δ -103.78.

HRMS (ESI): Expected mass ($M-H^+$): 309.0690; found: 309.0690.

Preparation of 29



29

Following the General Procedure A, a solution of 2-trifluroomethylbenzamide (47.3 mg, 0.250 mmol), and $TBABF_4$ (164.6 mg, 0.50 mmol, 2 equiv.) in DMF (3.0 mL) was electrolyzed for 5 F/mol with a 10 mA current. A CO_2 balloon (constant bubbling) was used instead of grounded dry ice. The ^{1}H NMR yield of the crude product was determined to be 42% where dibromomethane was used as an internal standard (8.0 µL). Following workup, **29** was crashed

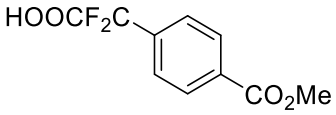
out from the crude reaction mixture using dichloromethane and hexanes to afford **29** as an off-white solid (12.3 mg, 25%).

^{1}H NMR (400 MHz, acetone-d$_6$): δ 7.82 (d, *J* = 7.7 Hz, 1H), 7.71-7.64 (m, 2H), 7.55 (dt, *J* = 7.4, 2.3 Hz, 1H), 6.36 (d, *J* = 46.8 Hz, 1H).

^{19}F NMR (376 MHz, acetone-d$_6$): δ -183.1.

HRMS (ESI): Expected mass (M-H$^+$): 196.0415; found: 196.0415.

Preparation of 30



30

Following the General Procedure A, a solution of 4-trifluoromethyl-benzoic acid methyl ester (54.0 mg, 0.250 mmol), $TBABF_4$ (82.3 mg, 0.250 mmol), and DMPU (0.5 mL) in DMF (3.0 mL) was electrolyzed at room temperature for 2.3 F/mol with a 4 mA current. The ^{1}H NMR yield of the crude product was determined to be 53% (24:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **30** by flash chromatography (30 → 50% EtOAc in hexanes and 2% acetic acid) afforded **30** (26.4 mg, 48%) as a white solid.

Data for **30**: IR (neat): υ = 3431, 1720, 1638, 1561, 1285, 1115 cm^{-1}

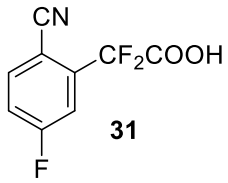
^{1}H NMR (500 MHz, acetone-d$_6$): δ 8.16 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, acetone-d$_6$): δ 165.5 (t, *J* = 35.0 Hz), 162.7, 127.8 (t, *J* = 5.0 Hz), 126.0 (t, *J* = 26.2 Hz), 115.0, 114.8 (t, *J* = 248 Hz), 55.9.

^{19}F NMR (376 MHz, acetone-d$_6$): δ -104.58.

HRMS (ESI): Expected mass (M-H$^+$): 229.0317; found: 229.0317.

Preparation of 31



31

Following the General Procedure B, a solution of (47.3 mg, 0.250 mmol), and $TBABF_4$ (164.6 mg, 0.500 mmol) in DMF (3.0 mL) was electrolyzed for 2.5 F/mol at 0.8 V The ^1H NMR yield of the crude product was determined to be 70% (2.5:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **31** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **31**(31.2 mg, 58%) as a light brown oil.

Data for **31**: IR (neat): υ = 3431, 2240, 1641, 1497, 1282, 1198 cm^{-1}

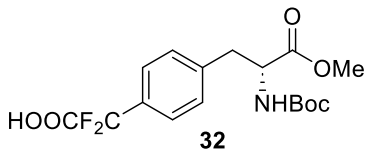
^{1}H NMR (500 MHz, acetone-d$_6$) δ 8.09 (dd, *J* = 8.5, 5.2 Hz, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.61 (td, *J* = 8.2, 2.0 Hz, 1H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 165.5 (d, *J* = 256.2 Hz), 163.4 (t, *J* = 33.0 Hz), 139.7 (td, *J* = 25.7, 8.7 Hz), 138.7 (d, *J* = 9.6 Hz), 119.9 (d, *J* = 22.5 Hz), 116.1(d, *J* = 11.0 Hz), 116.0 (m), 113.0 (t, *J* = 253.6 Hz), 107.5 (dd, *J* = 7.5, 3.7 Hz).

^{19}F NMR (376 MHz, acetone-d$_6$) δ -102.2, -103.3 (td, *J* = 8.5, 5.3 Hz).

HRMS (ESI): Expected mass ($M-H^+$): 214.0121; found: 214.0121.

Preparation of 32



32

Following the General Procedure A, a solution of Boc-4-(trifluoromethyl)-D-phenylalanine-OMe (87 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^1H NMR yield of the crude product was determined to be 76% where dibromomethane was used as an internal standard (8.0 µL).

Purification of the crude product **32** by flash chromatography (30 → 50 % EtOAc in hexanes and 2% acetic acid) afforded **32** (50.5 mg, 54%) as a colourless oil.

Data for **32**: IR (neat): υ = 3406, 1648, 1515, 1368, 1267, 1165, 1113 cm^{-1}

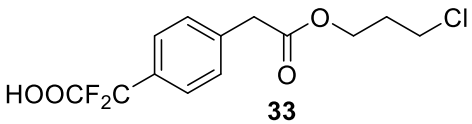
^{1}H NMR (500 MHz, acetone-d$_6$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 7.9 Hz, 2H), 6.24 (d, *J* = 7.5 Hz, 1H), 4.45 (s, 1H), 3.68 (s, 3H), 3.22 (dd, *J* = 13.8, 5.1 Hz, 1H), 3.05 (dd, *J* = 13.7, 9.4 Hz, 1H), 1.33 (s, 9H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 173.0, 172.4, 165.5 (t, *J* = 34.2 Hz), 156.3, 141.8, 130.6, 126.2 (t, *J* = 5.9 Hz), 114.7 (t, *J* = 249.8 Hz), 79.6, 55.7, 52.4, 38.0, 28.5.

^{19}F NMR (469 MHz, acetone-d$_6$) δ -103.9.

HRMS (ESI): Expected mass ($M-H^+$): 372.1264; found: 372.1264.

Preparation of 33



33

Following the General Procedure A, a solution of **S8** (70 mg, 0.250mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^{1}H NMR yield of the crude was determined to be 41% where dibromomethane was used as an internal standard (8 μL). Purification of the crude product **33** by flash chromatography (30 → 50→ 100 % EtOAc in hexane and 2% acetic acid) afforded **33** (28.3 mg, 37%) as a colourless oil.

Data for **33**:

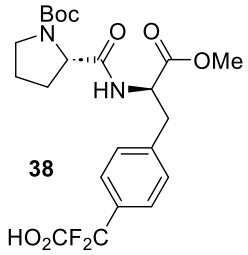
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 4.26 (t, *J* = 6.1 Hz, 2H), 3.69 (s, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 2.08 (m, 2H).

^{13}C NMR (125 MHz, CDCl$_3$): δ 171.1, 167.3 (t, *J* = 37.2 Hz), 137.1, 131.2 (t, *J* = 25.6 Hz), 129.7, 125.9 (t, *J* = 5.9 Hz), 113.0 (t, *J* = 252.5 Hz), 62.0, 40.9, 31.3, 20.3.

^{19}F NMR (376 MHz, CDCl$_3$): δ -104.8.

HRMS (ESI): Expected mass ($M-H^+$): 305.0395; found: 305.0395.

Preparation of 38



Following the General Procedure A, a solution of peptide **S3** (111 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^{1}H NMR yield of the crude product was determined to be 73% (15:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **38** by flash chromatography (30 → 50 % EtOAc in hexanes and 2% acetic acid) afforded **38** (77.6 mg, 66%, *mixture of rotamers*) as a yellow oil.

Data for **38**: IR (neat): υ = 3432, 1730, 1645, 1417, 1265, 1166 cm^{-1}

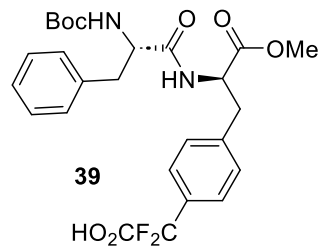
^{1}H NMR (500 MHz, acetone-d$_6$) δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 4.79 (1H), 4.17 (1H), 3.68 (s, 3H), 3.28 (3H), 3.09 (1H), 1.84 (4H), 1.51 – 1.23 (9H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 173.4, 172.4, 165.9 (t, *J* = 38.8 Hz), 154.7, 141.3, 133.0 (t, *J* = 26.2 Hz), 130.5, 126.3, 114.9 (t, *J* = 249.7 Hz), 79.6, 61.1, 53.5, 52.4, 47.4, 37.9, 31.9, 28.5, 24.0.

^{19}F NMR (376 MHz, acetone-d$_6$) δ -103.5.

HRMS (ESI): Expected mass (M-H$^+$): 469.1792; found: 469.1788.

Preparation of 39



Following the General Procedure A, a solution of peptide **S4** (123.5 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^{1}H NMR yield of the crude product was determined to be 55% (24:1 =

difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **39** by flash chromatography (30 → 50 % EtOAc in hexanes and 2% acetic acid) afforded **39** (59.8 mg, 46%) as a colourless oil.

Data for **39**: IR (neat): υ = 3431, 1760, 1649, 1520, 1454, 1264, 1167 cm^{-1}

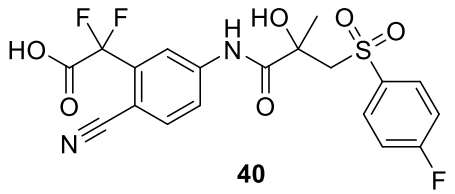
^{1}H NMR (500 MHz, acetone-d$_6$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.15 (m, 5H), 4.75 (bs, 1H), 4.38 (bs, 1H), 3.67 (s, 3H), 3.17 (dd, *J* = 13.9, 5.4 Hz, 1H), 3.08 (dd, *J* = 13.7, 7.8 Hz, 2H), 2.85 – 2.76 (m, 1H), 1.32 (s, 9H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 172.3, 172.2, 165.5 (t, *J* = 34.4 Hz), 156.2, 141.3, 138.7, 132.7 (t, *J* = 25.7 Hz), 130.7, 130.2, 129.0, 127.2, 126.3 (t, *J* = 6.0 Hz), 114.7 (t, *J* = 249.9 Hz), 79.5, 56.4, 54.1, 52.5, 38.7, 38.0, 28.5.

^{19}F NMR (469 MHz, acetone-d$_6$) δ -103.7.

HRMS (ESI): Expected mass ($M-H^+$): 519.1948; found: 519.1935.

Preparation of 40



40

Following the General Procedure B, a solution of Bicalutamide (107.5 mg, 0.250 mmol), and $TBABF_4$ (164.6 mg, 0.500 mmol) in DMF (3.0 mL) was electrolyzed for 2.5 F/mol at 0.8V. The ^{1}H NMR yield of the crude product was determined to be 64% (3.3:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **40** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **40** (62.7 mg, 55%) as a yellowish oil.

Data for **40**: IR: (neat): υ = 3407, 2233, 1650, 1499, 1404, 1145 cm^{-1}

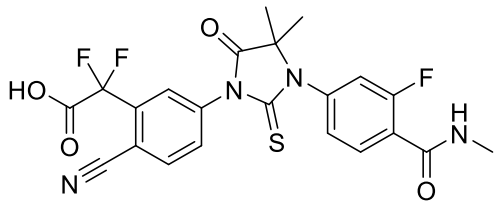
^{1}H NMR (500 MHz, acetone-d$_6$) δ 8.20 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.98 (dd, *J* = 7.9, 6.0 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.27 (t, *J* = 8.7 Hz, 2H), 4.07 (d, *J* = 14.8 Hz, 1H), 3.67 (d, *J* = 14.9 Hz, 1H), 1.54 (s, 3H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 173.8 (d, *J* = 9.5 Hz), 166.5 (d, *J* = 253.2 Hz), 165.1 (t, *J* = 33.8 Hz), 143.4 (d, *J* = 13.2 Hz), 138.6 – 137.9 (m), 136.4, 132.5 (d, *J* = 9.8 Hz), 122.1 (d, *J* = 10.2 Hz), 119.0 (dd, *J* = 17.4, 7.9 Hz), 117.4, 116.9 (d, *J* = 23.1 Hz), 114.1 (t, *J* = 253.0 Hz), 105.0, 74.7, 64.1, 30.6, 27.8.

^{19}F NMR (376 MHz, acetone-d$_6$) δ -101.2, -106.4.

HRMS (ESI): Expected mass (M-H$^+$): 455.0530; found: 455.0526.

Preparation of 41



41

Following the General Procedure B, a solution of Enzalutamide (116.1 mg, 0.250 mmol), and $TBABF_4$ (164.6 mg, 0.500 mmol) in DMF (3.0 mL) was electrolyzed for 2.5 F/mol at 0.8 V. The ^{1}H NMR yield of the crude product was determined to be 42% (4:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **41** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **41** (30.7 mg, 25% (52% brsm)) as a yellow oil.

Data for **41**: IR (neat): υ = 3432, 2112, 1642, 1436, 1313 cm^{-1}

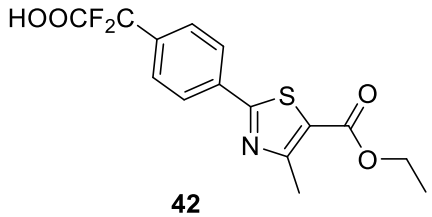
^{1}H NMR (500 MHz, acetone-d$_6$) δ 8.06 (d, *J* = 8.2 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 9.9 Hz, 2H), 2.94 (s, 3H), 1.63 (s, 6H).

^{13}C NMR (126 MHz, acetone-d$_6$) δ 181.7, 175.8, 172.1, 165.1 (t, *J* = 32.9 Hz), 163.8, 160.8 (d, *J* = 249.9 Hz), 140.4 (d, *J* = 10.6 Hz), 139.2 (t, *J* = 30.5 Hz), 138.5, 135.9, 132.3 (d, *J* = 59.1 Hz), 128.8 (t, *J* = 7.4 Hz), 127.3, 124.9 (d, *J* = 10.8 Hz), 119.2 (d, *J* = 25.3 Hz), 117.0 (t, *J* = 249.9 Hz), 116.9, 111.1, 67.5, 26.8, 23.7.

^{19}F NMR (376 MHz, acetone-d$_6$) δ -100.5, -113.3.

HRMS (ESI): Expected mass (M-H$^+$-CO_2): 445.0952; found: 445.0956.

Preparation of 42



42

Following the General Procedure A, a solution of 4-methyl-2-(4-trifluoromethyl-phenyl)-4,5-dihydro-thiazole-5-carboxylic acid ethyl ester (78.0 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^1H NMR yield of the crude product was determined to be 25% (32:1 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **42** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **42** (20.0 mg, 23%, 67% brsm) as a white solid. 48 mg of starting material was also recovered.

Data for **42**: IR (neat): υ = 3414, 1711, 1640, 1264, 1099 cm^{-1}

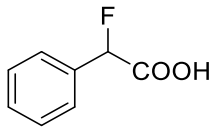
^{1}H NMR (500 MHz, acetone-d$_6$): δ 8.18 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.73 (3H, s), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d$_6$): δ 168.6, 165.1 (t, *J* = 33.7 Hz), 162.3, 161.6, 136.5 (t, J = 22.5 Hz), 136.0, 127.8, 127.2, 123.5, 114.3 (t, *J* = 247.5), 62.0, 17.6, 14.6.

^{19}F NMR (376 MHz, acetone-d$_6$): δ -104.29.

HRMS (ESI): Expected mass ($M-H^+$): 340.0459; found: 340.0459.

Preparation of 44



44

Following the General Procedure A, a solution of difluoromethyl-benzene (32.0 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^1H NMR yield of the crude product was determined to be 32%

where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **44** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **44** (16.2 mg, 42%) as a white solid.

Data for **44**: IR (neat): υ = 3449, 1655, 1543, 1459, 1237, 1045 cm^{-1}

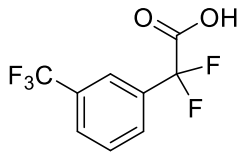
^{1}H NMR (400 MHz, acetone-d_6): δ 7.54 – 7.53 (m, 1H), 7.52 - 7.51 (m, 1H), 7.48 – 7.41 (m, 3H), 5.95 (d, *J* = 47.8 Hz, 1H).

^{13}C NMR (125 MHz, acetone-d_6): δ 169.9 (d, *J* = 27.5 Hz), 136.2 (d, *J* = 21.2 Hz), 130.3, 129.6, 127.8 (d, J = 6.2 Hz), 89.9.

^{19}F NMR (376 MHz, acetone-d_6): δ -178.30 (d, *J* = 47.8 Hz).

HRMS (ESI): Expected mass ($M-H^+$): 153.0356; found: 153.0356.

Preparation of 46



46

Following the General Procedure A, a solution of 1,3-bis(trifluoromethyl)-benzene (38.8 uL, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (2.5 mL) was electrolyzed for 3 F/mol with a 16 mA current. A CO_2 balloon (constant bubbling) was used instead of grounded dry ice. Purification of the crude product **46** by flash chromatography (30 → 50→ 75 % EtOAc in hexanes and 2% acetic acid) afforded **46** (32.3 mg, 54%) as a colourless oil.

Data for **46**: IR (neat): υ = 3394, 1648, 1339, 1259, 1123 cm^{-1}

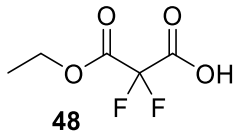
^{1}H NMR (400 MHz, acetone-d_6): δ 7.92-7.99 (m, 3H), 7.84 (m, 1H).

^{13}C NMR (125 MHz, acetone-d_6): δ 165.0 (t, *J* = 34.2 Hz), 135.5 (t, *J* = 26.0 Hz), 131.6 (q, *J* = 32.6 Hz), 131.2, 130.3 (t, *J* = 5.8 Hz), 128.9 (m), 124.8 (q, *J* = 271.1 Hz), 123.0 (m), 113.9 (t, *J* = 249.4).

^{19}F NMR (376 MHz, acetone-d_6): δ -63.6, -104.6.

HRMS (ESI): Expected mass (M-H^+): 239.0137; found: 239.0134.

Preparation of 48



48

Following the General Procedure A, a solution of ethyl trifluoromethyl acetate (30.0 uL, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (2.5 mL) was electrolyzed for 2.5 F/mol with a 16 mA current. A CO_2 balloon (constant bubbling) was used instead of grounded dry ice. Purification of the crude product **48** by flash chromatography (30 → 50→ 75 % EtOAc in hexanes and 2% acetic acid) afforded **48** (21.4 mg, 51%) as a colourless oil.

Data for **48**: IR (neat): υ = 3431, 1760, 1648, 1311, 1163 cm^{-1}

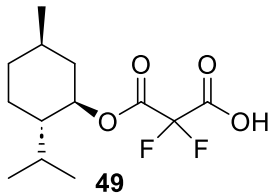
^{1}H NMR (500 MHz, acetone-d_6): δ 4.41 (q, *J* = 6.9 Hz), 1.33 (t, *J* = 6.9 Hz).

^{13}C NMR (125 MHz, acetone-d_6): δ 162.1 (t, *J* = 29.2 Hz), 161.7 (t, *J* = 30.6 Hz), 107.4 (t, *J* = 261.1 Hz), 64.6, 14.1.

^{19}F NMR (376 MHz, acetone-d_6): δ -112.6.

HRMS (ESI): Expected mass (M-H^+): 167.0161; found: 167.0158.

Preparation of 49



49

Following the General Procedure A, a solution of **S7** (34.6 mg, 0.210 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (2.5 mL) was electrolyzed for 2.5 F/mol with a 16 mA current. Purification of the crude product **49** by flash chromatography (15 → 30% EtOAc in hexanes and 2% acetic acid) afforded **49** (45.0 mg, 76%) as a colourless oil.

Data for **49**: IR (neat): υ = 3567, 2961, 1748, 1652, 1168 cm^{-1}

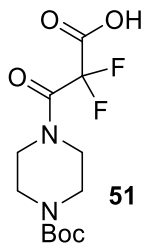
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.90 (td, *J* = 11.0, 4.5 Hz, 1H), 2.07 (d, *J* = 11.4 Hz, 1H), 1.86 (tt, *J* = 9.8, 3.4 Hz, 1H), 1.79 – 1.68 (m, 2H), 1.62 – 1.47 (m, 2H), 1.20 – 1.03 (m, 2H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.91 – 0.84 (m, 1H), 0.79 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.0 (t, *J* = 31.6 Hz), 160.2 (t, *J* = 30.5 Hz), 106.0 (t, *J* = 261.4 Hz), 79.2, 46.7, 40.0, 33.9, 31.4, 26.1, 23.4, 21.9, 20.6, 16.1.

^{19}F NMR (469 MHz, $CDCl_3$): δ -112.6.

HRMS (ESI): Expected mass ($M-H^+$): 277.1257; found: 277.1255.

Preparation of 51



51

Following the General Procedure A, a solution of tert-butyl 4-(2,2,2-trifluoroacetyl)piperazine-1-carboxylate (70.5 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (2.5 mL) was electrolyzed for 3.0 F/mol with a 16 mA current. Purification of the crude product **51** by flash chromatography (30 → 50% EtOAc in hexanes and 2% acetic acid) afforded **51** (44.7 mg, 58%) as a colourless oil.

Data for **51**: IR (neat): υ = 3430, 1652, 1435, 1260, 1163 cm^{-1}

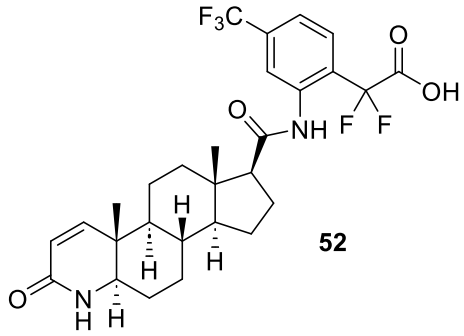
^{1}H NMR (498 MHz, acetone-d_6): δ 3.67 – 3.57 (m, 4H), 3.49 (s, 4H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.9 (t, *J* = 30.1 Hz), 159.7 (t, *J* = 27.1 Hz), 154.9 (s), 108.8 (t, *J* = 262.8 Hz), 81.5, 45.5, 43.2, 28.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -106.8.

HRMS (ESI): Expected mass ($M-H^+$): 307.1111; found: 307.1110.

Preparation of 52



52

Following the General Procedure A, a solution of Dutasteride (133.0 mg, 0.250 mmol), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (3.0 mL) was electrolyzed for 3 F/mol with a 16 mA current. The ^{1}H NMR yield of the crude product was determined to be 45% (1:1.5 = difluoro:monofluoro) where dibromomethane was used as an internal standard (8.0 µL). Purification of the crude product **52** by flash chromatography (30 → 50→ 100 % EtOAc in hexanes and 2% acetic acid) afforded **52** (51.2 mg, 37%) as a white crystalline solid.

Data for **52** (Difluoro):

^{1}H NMR (700 MHz, CD_3OD): δ 8.56 (s, 1H), 7.76 (t, *J* = 12.4 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 10.0 Hz, 1H), 5.74 (d, *J* = 9.9 Hz, 1H), 2.54 – 2.49 (m, 1H), 2.31 – 2.23 (m, 1H), 2.11 – 2.05 (m, 1H), 1.90 – 1.82 (m, 2H), 1.77 (m, 2H), 1.64 – 1.44 (m, 6H), 1.30 – 1.25 (m, 2H), 1.15 – 1.05 (m, 3H), 0.96 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (176 MHz, CD_3OD): δ 174.2, 169.7 (t, *J* = 29.5 Hz), 168.8, 153.7, 138.4, 133.3 (q, *J* = 32.3 Hz), 130.3 (t, *J* = 24.9 Hz), 128.0 (t, *J* = 9.1 Hz), 125,3 (q, *J* = 273 Hz), 123.1,123.0, 121.0 (q, *J* = 3.4 Hz) 120.7 (q, *J* = 3.4 Hz), 115.4 (confirmed with HMBC), 60.9, 59.2, 56.9, 48.7, 46.3, 40.4, 39.2, 36.7, 30.7, 26.4, 25.4, 24.6, 22.2, 14.2, 12.1.

^{19}F NMR (376 MHz, CD_3OD): δ -64.6, -103.4.

HRMS (ESI): Expected mass ($M\text{-}H^+$): 553.2131; found: 553.2131.

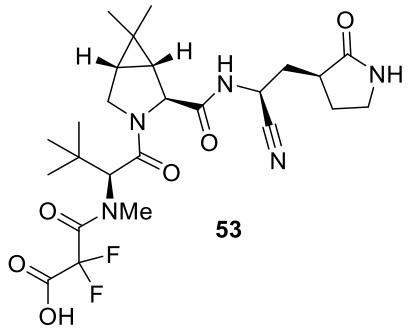
Data for **52M** (Monofluoro (mixture of diastereomers)):

^{1}H NMR (700 MHz, CD_3OD): δ 8.21, 8.11, 7.67, 7.53, 6.95, 6.19 – 6.11, 5.75, 2.51, 2.23, 2.13 – 2.02, 1.88 – 1.68, 1.65 – 1.34, 1.32 – 1.23, 1.15 – 1.06, 0.99 – 0.94, 0.83 – 0.77.

^{13}C NMR (176 MHz, CD_3OD): δ 174.3 (d, *J* = 45.2 Hz), 168.7, 153.5, 137.7, 129.3 (d, *J* = 103.5 Hz), 125.9, 124.3, 123.1, 122.7 (d, *J* = 59.3 Hz), 122.2, 122.1, 87.9 (dd, *J* = 185.2, 57.5 Hz), 60.9, 58.6, 57.0, 46.1, 46.0, 40.4, 39.2, 36.7, 30.7, 26.4, 25.4, 24.9, 24.5, 22.2, 14.1, 12.1.

^{19}F NMR (376 MHz, CD_3OD): δ -64.4, -185.6.

Preparation of 53



53

N-Methylation of Trifluoroacetamide in Nirmatrelvir

Nirmatrelvir (200 mg, 0.400 mmol, 1 equiv.) was dissolved in dry DMF (0.800 mL). Potassium carbonate (58 mg, 0.42 mmol, 1.05 equiv.) and methyl iodide (27.4 uL, 0.44 mmol, 1.1 equiv.) was then added and the reaction mixture was allowed to stir for 16 hours at room temperature. The reaction mixture was then diluted with ethyl acetate. The organic layer was then washed with distilled water, separated, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude reaction mixture was then purified by silica flash column chromatography (50% ethyl acetate in hexanes) to afford an inseparable mixture of starting material and *N*-methyl-Nirmatrelvir (150 mg, 53% by mass) as a white solid.

Defluorinative Carboxylation of N-methyl-Nirmatrelvir

Following the General Procedure A, a solution of *N*-methyl Nirmatrelvir/Nirmatrelvir (150.0 mg, 53% by mass *N*-methyl Nirmatrelvir (79.5 mg, 0.16 mmol)), and $TBABF_4$ (82.3 mg, 0.250 mmol) in DMF (2.5 mL) was electrolyzed for 3 F/mol with a 16 mA current. Purification of the crude product **53** by flash chromatography (15 → 40→ 70 % EtOAc in hexanes and 2% acetic acid) afforded **53** (36.0 mg, 41%) as an off-white solid.

Data for **53**: IR (neat): υ = 3440, 2089, 1647, 1436, 1275 cm^{-1}

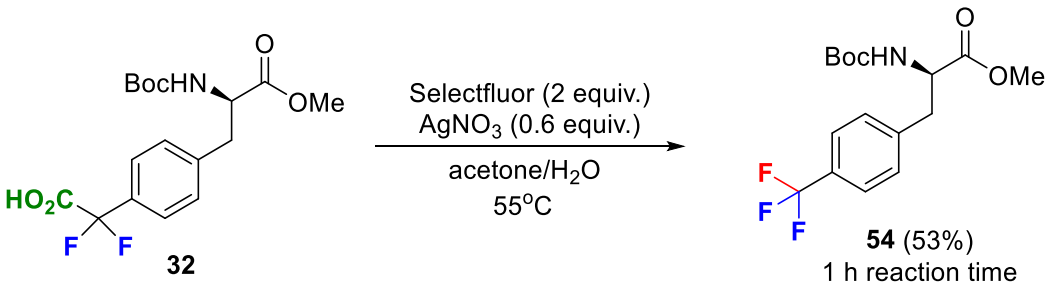
^{1}H NMR (500 MHz, CD_3OD): δ 5.14 (s, 1H), 5.04 (m, 1H), 4.21 (s, 1H), 3.97 (m, 1H), 3.55 (d, J = 10.6 Hz, 1H), 3.18 - 3.30 (m, 2H), 3.13 (s, 3H), 2.70 (m, 1H), 2.33 (m, 2H), 1.80 – 1.95 (m, 2H), 1.60 (m , 1H), 1.38 (d, *J* = 7.7 Hz, 1H), 1.07 (s, 3H), 1.06 (s, 9H), 0.90 (s, 3H).

^{13}C NMR (176 MHz, acetone-d_6): δ 179.4, 172.0, 168.0, 163.4 (t, *J* = 30.1 Hz), 163.2 (t, *J* = 26.3 Hz), 120.0, 110.3, 61.9, 61.4, 48.2, 40.9, 39.7, 38.6, 37.6, 35.4, 33.3, 31.7, 30.8, 30.3 28.9, 28.5, 28.0, 26.3, 19.9, 12.9.

^{19}F NMR (468 MHz, acetone-d_6): δ -108.3, -108.7.

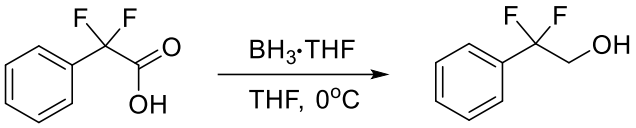
HRMS (ESI): Expected mass ($M-H^+$): 538.2483; found: 538.2483.

Fluoride-exchange protocol



Compound **32** was synthesized using General Procedure A for eDFC protocol. Subsequently, **32** (22.0 mg, 0.06 mmol, 1 equiv) was solubilized in a 1:1 mixture of H_2O:acetone (2 mL) under nitrogen. Selectfluor (42.5 mg, 0.12 mmol, 2 equiv) and silver nitrate (6.2 mg, 0.036 mmol, 0.6 equiv) were then added and the reaction mixture was then purged with nitrogen for 15 minutes. Then, the reaction mixture was heated to 55°C in a sealed vial. The reaction was stopped after 1 h at which point the reaction mixture was diluted with dichloromethane. The organic layer was then washed with H_2O, separated dried over sodium sulfate, filtered, and concentrated under reduced pressure. The yield of **54** was then determined to be 53% by analysis of the crude reaction mixture using ^{1}H NMR and dibromomethane as an internal standard.

Reduction of α,α-Difluorocarboxylic Acid



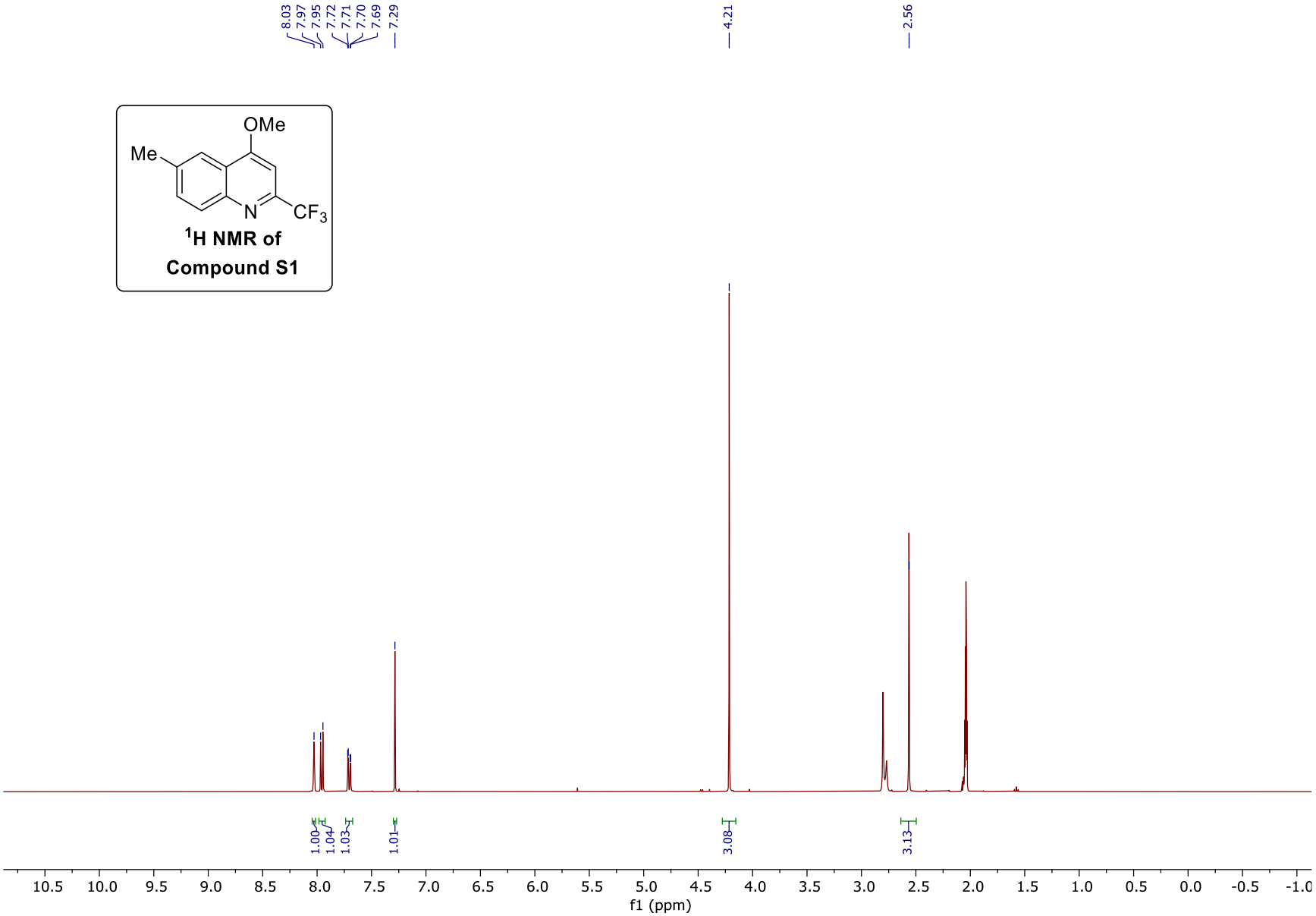
13 **56** (62%)

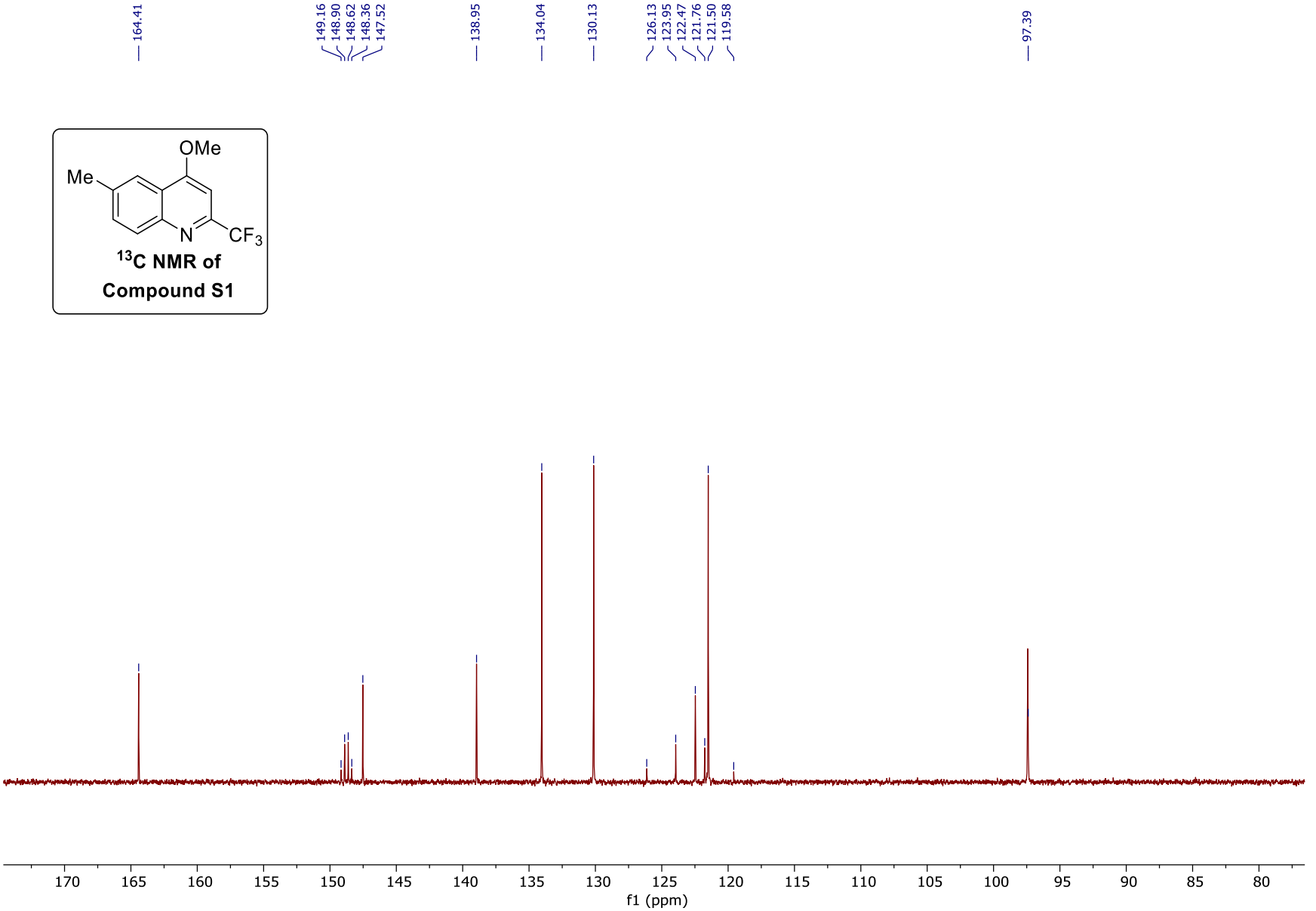
In a dry RB flask equipped with a stir bar, a solution of **13** (0.1 g, 0.41 mmol, 1 eq.) in dry THF (1 mL) was cooled to 0 °C and BH_3-THF (1 M, 1.2 mL, 0.62 mmol, 1.5 eq.) was added dropwise under argon atmosphere. The solution was slowly warmed to rt and left to stir for 16 h. Reaction completion was monitored using TLC. After completion the reaction was quenched using distilled water and extracted using CH_2Cl_2. The organic layer was then washed with H_2O, separated dried over sodium sulfate, filtered, and concentrated under reduced pressure. Compound **56** was purified using a flash chromatography (10 → 20% EtOAc in hexane) to afford pure **56** in 62% yield (0.058 g) as a white solid.

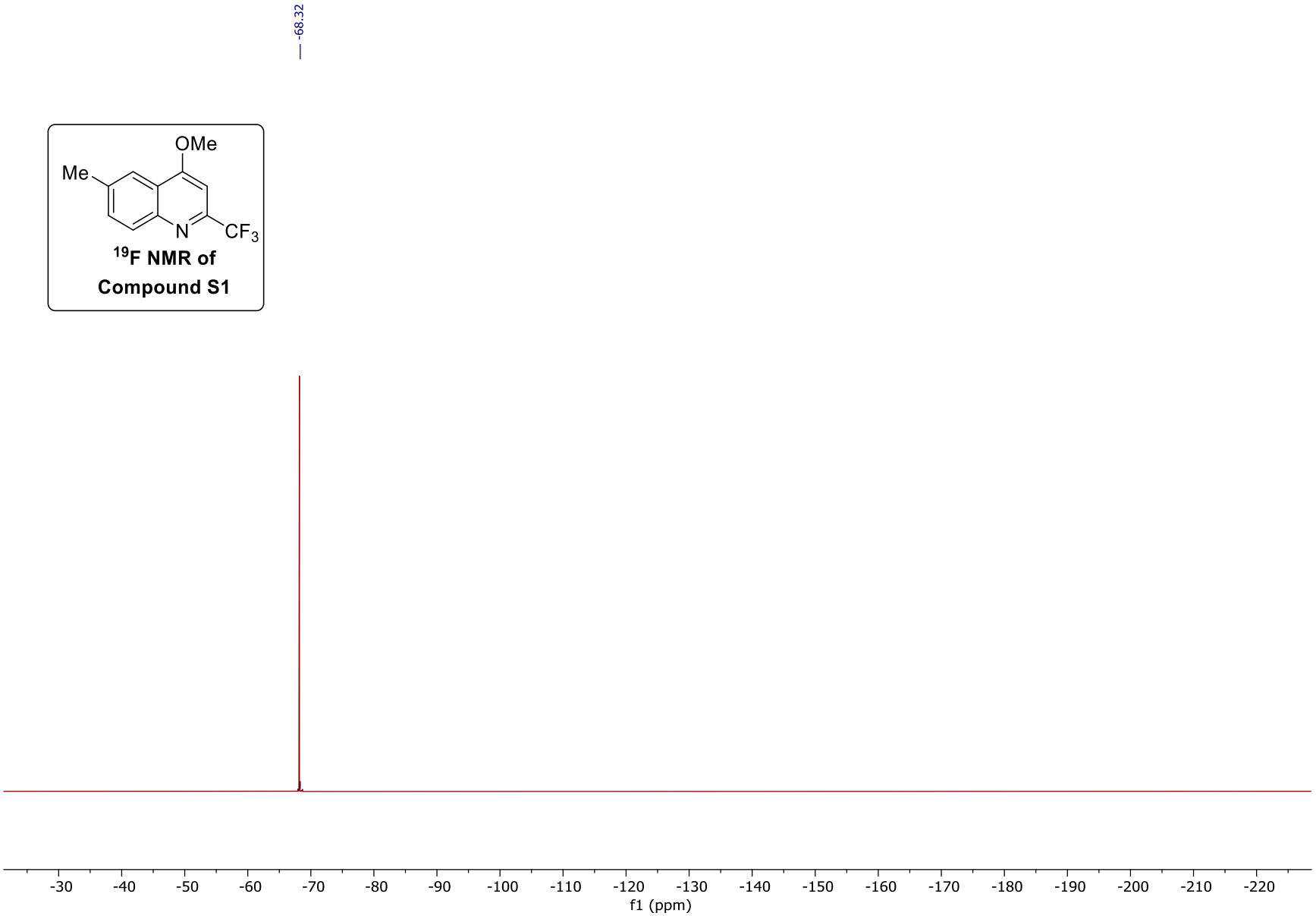
Spectroscopic data was consistent with a previous report.[1]

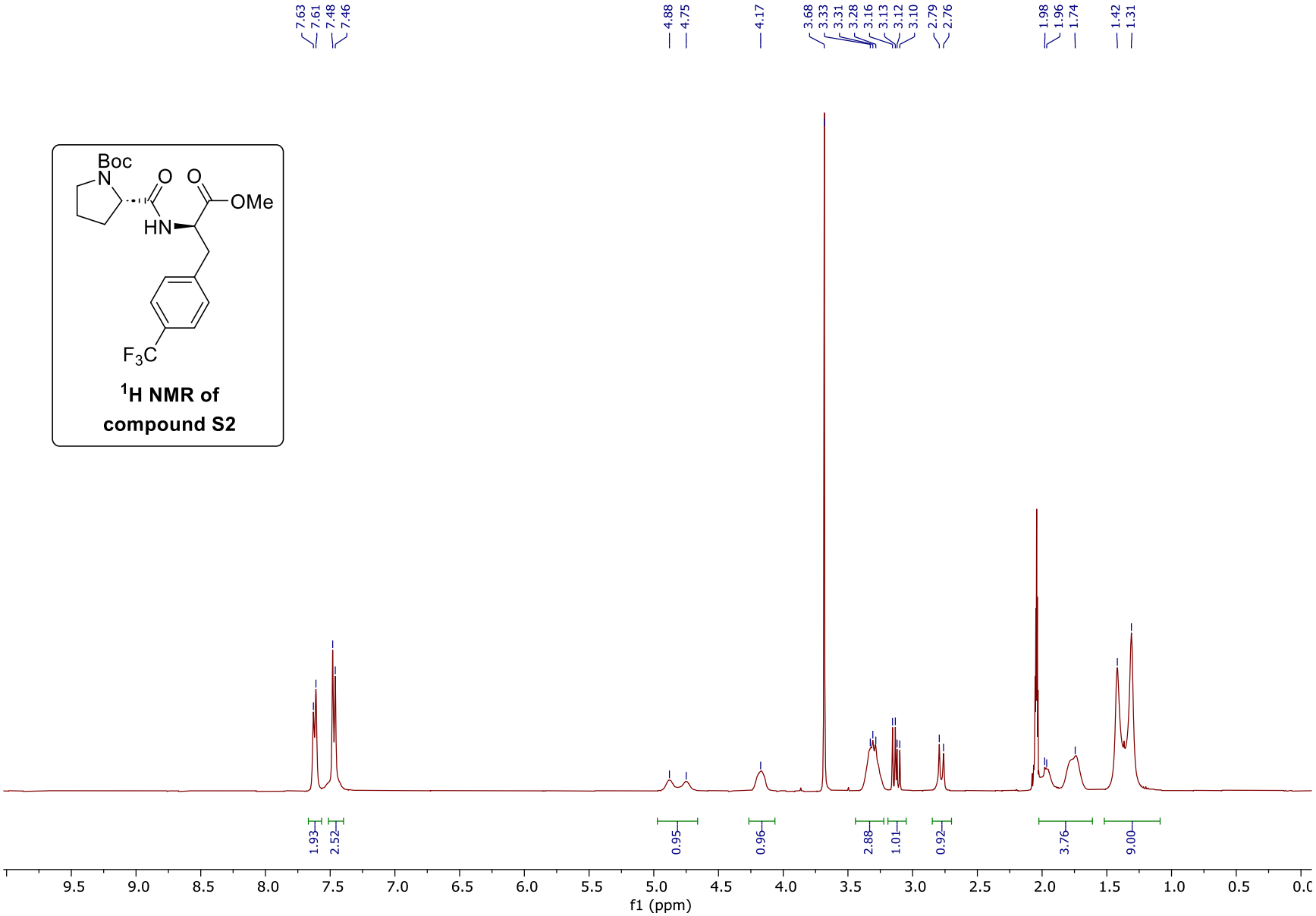
References

1. S. Ge, S. I. Arlow, M. G. Mormino, and J. F. Hartwig, *J. Am. Chem. Soc.* 2014, **136**, 14401–14404.

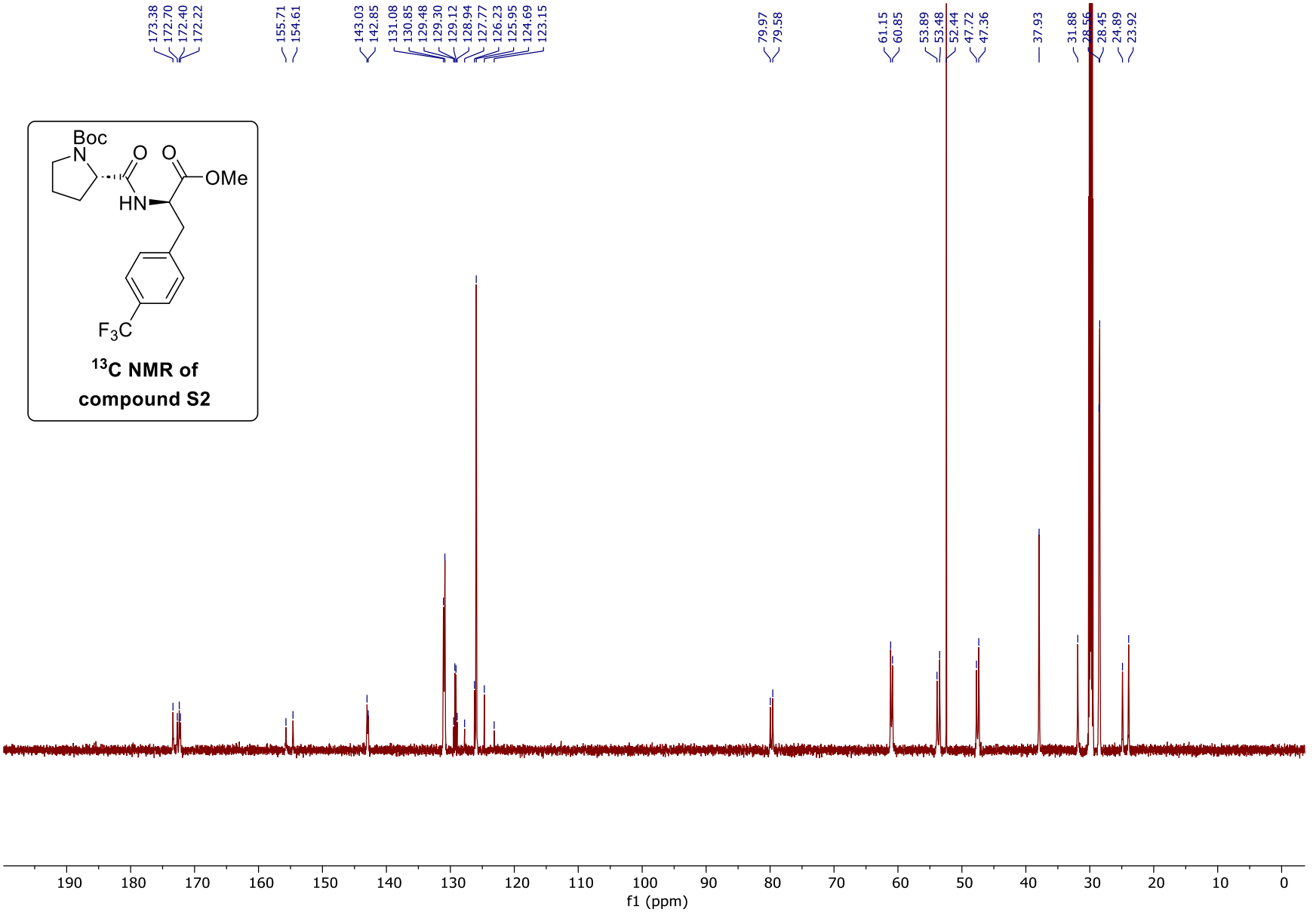

8.03
7.97
7.95
7.72
7.71
7.70
7.69
7.29
4.21
2.56
OMe
Me
N
CF3
1H NMR of
Compound S1
1.00
1.04
1.03
1.01
3.08
3.13
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

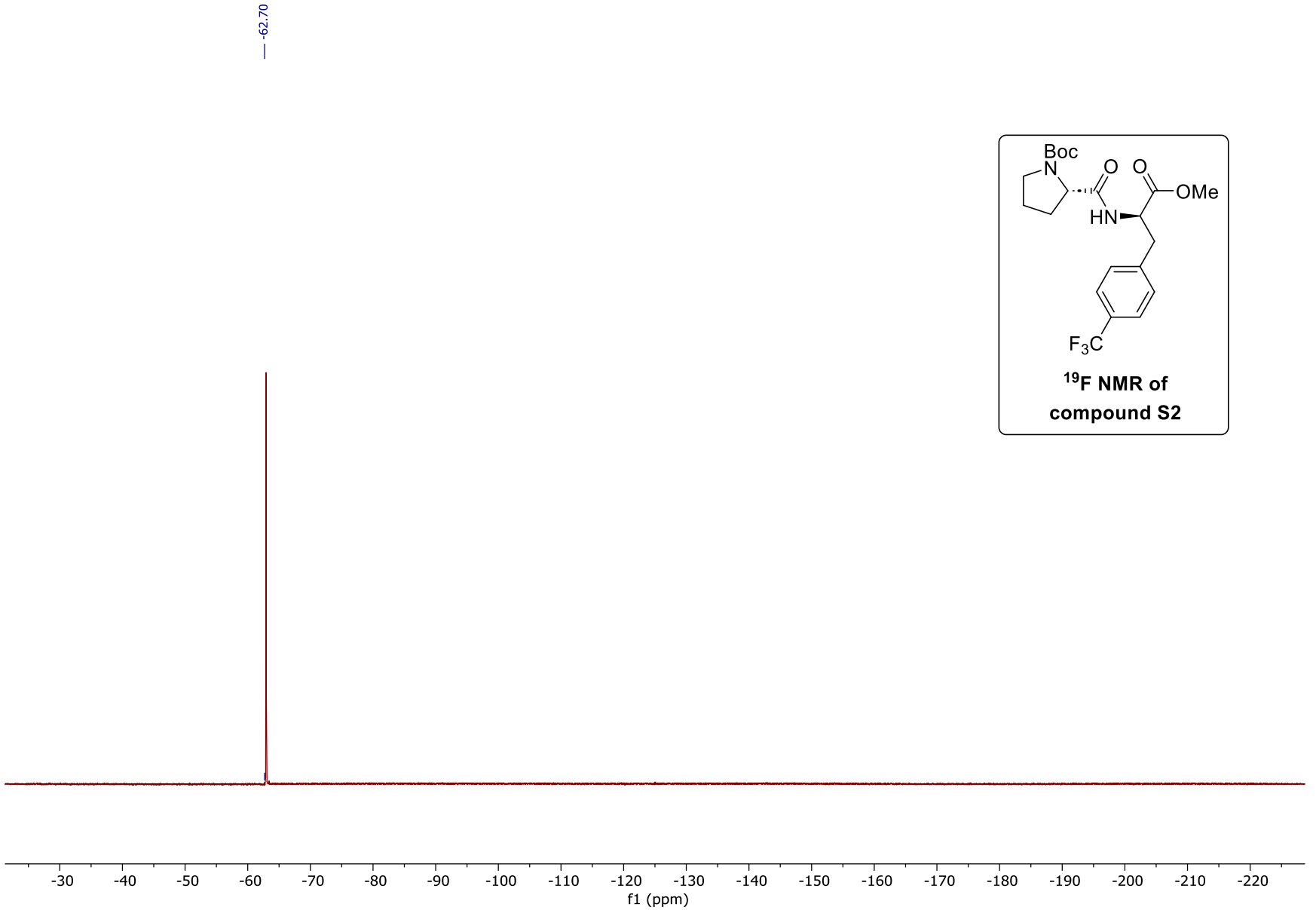

164.41
149.16
148.90
148.62
148.36
147.52
138.95
134.04
130.13
126.13
123.95
122.47
121.76
121.50
119.58
97.39
OMe
Me
N
CF3
13C NMR of
Compound S1
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
f1 (ppm)

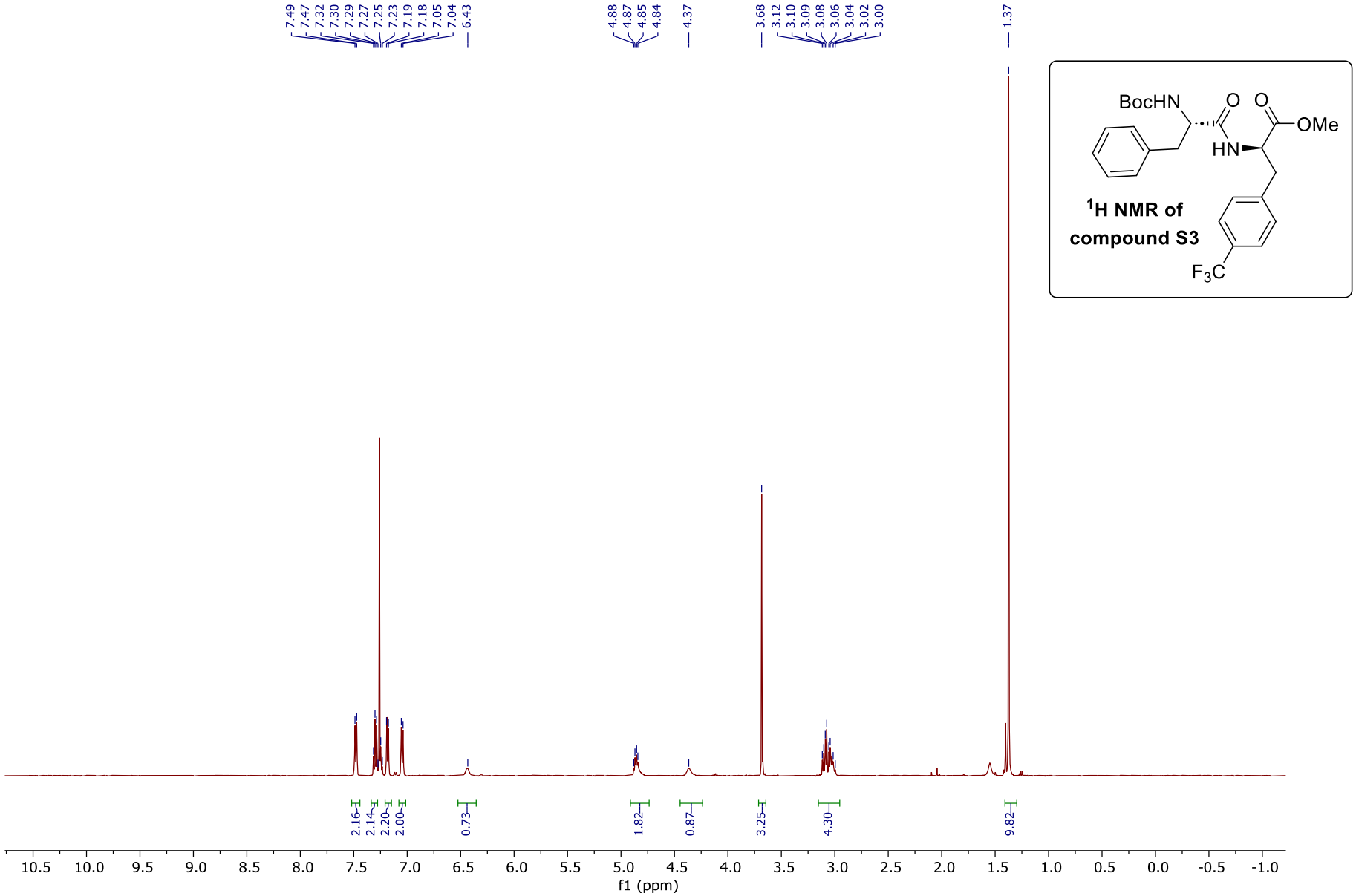

-68.32
OMe
Me
N
CF3
19F NMR of
Compound S1
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

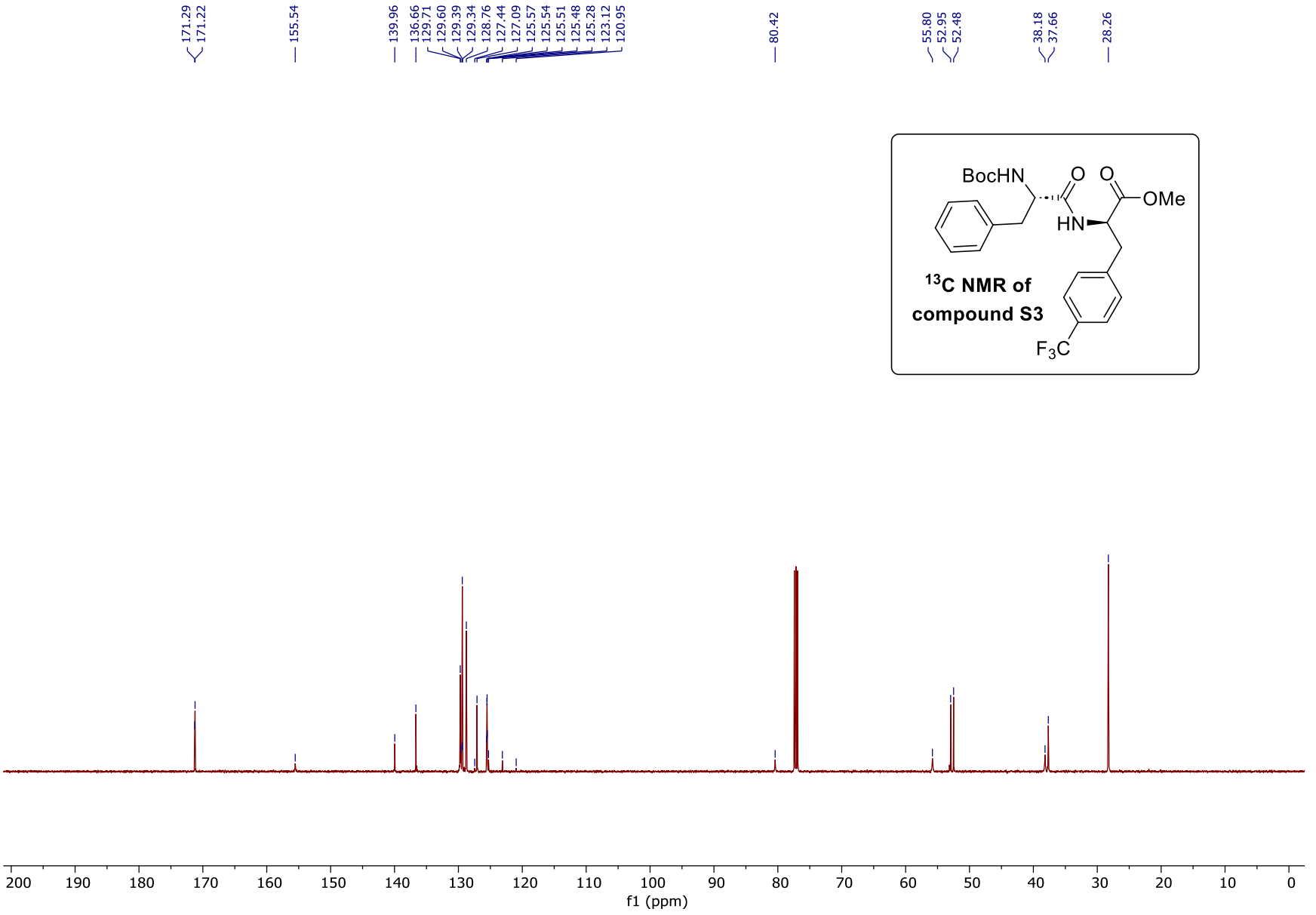


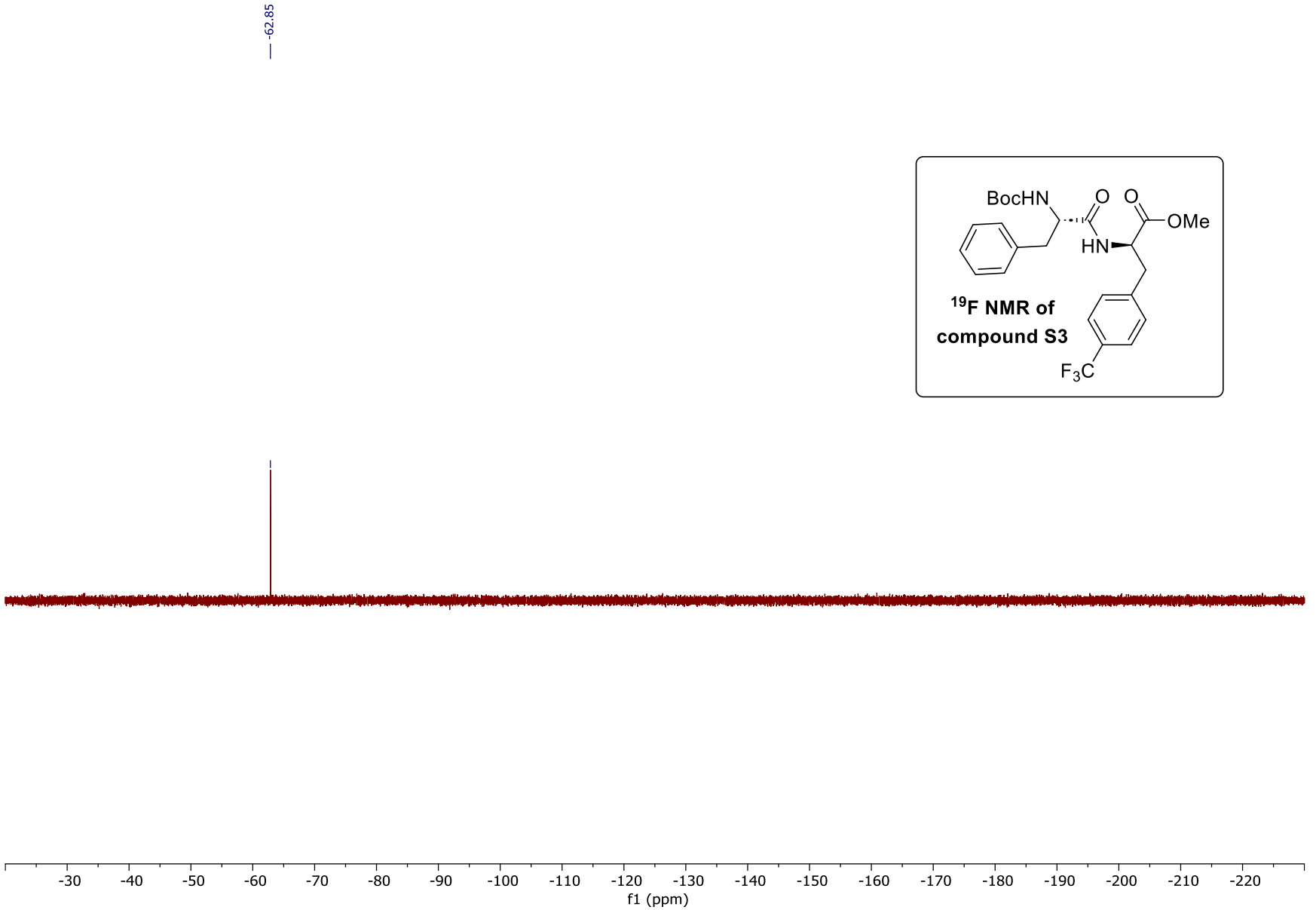
^{1}H NMR of compound S2

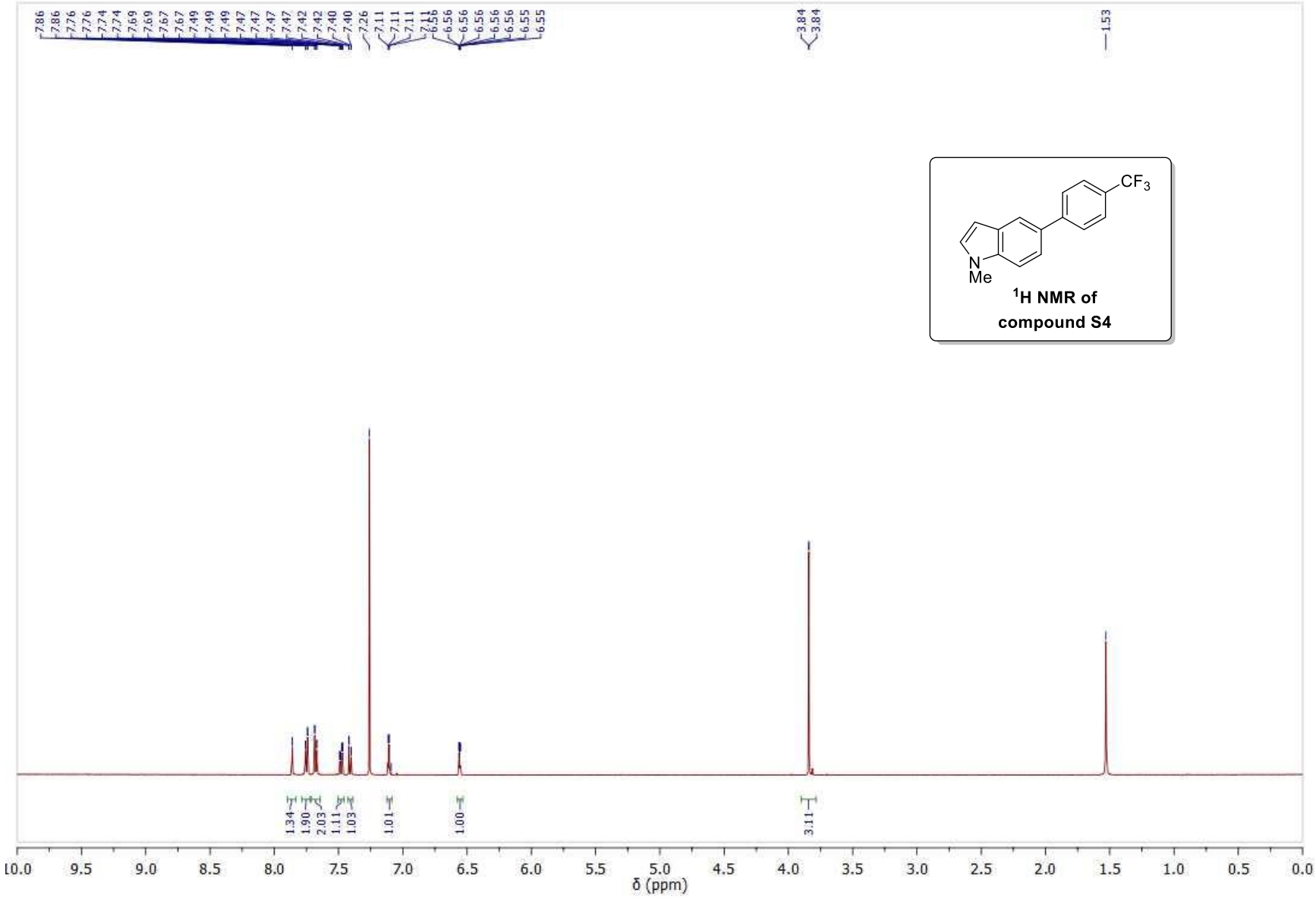

173.38
172.70
172.40
172.22
155.71
154.61
143.03
142.85
131.08
130.85
129.48
129.30
129.12
128.94
127.77
126.23
125.95
124.69
123.15
79.97
79.58
61.15
60.85
53.89
53.48
52.44
47.72
47.36
37.93
31.88
28.56
28.45
24.89
23.92
Boc
N
O
O
OMe
HN
F3C
13C NMR of compound S2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

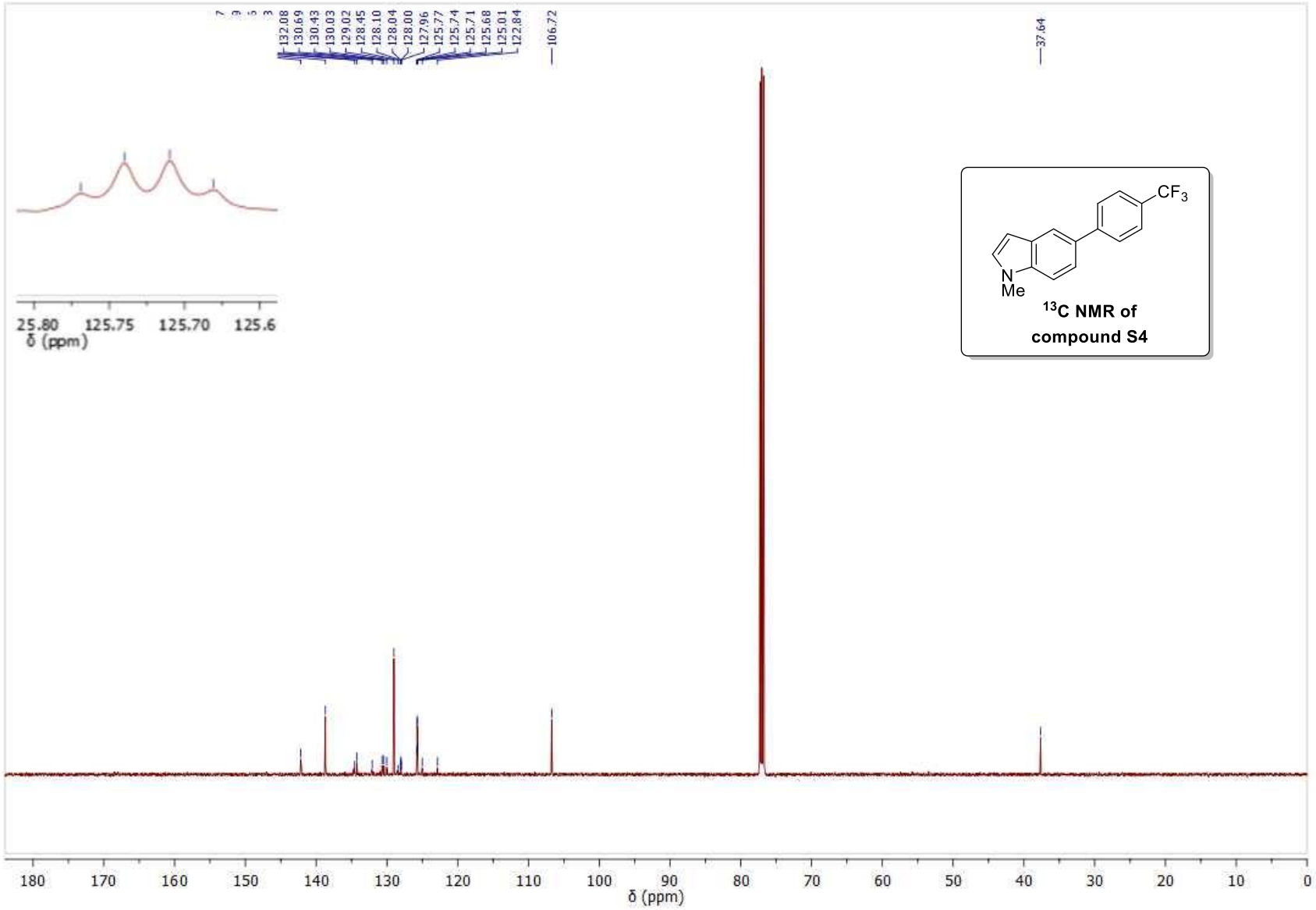

-62.70
Boc
N
O
O
OMe
HN
F3C
19F NMR of
compound S2
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)


7.49
7.47
7.32
7.30
7.29
7.27
7.25
7.23
7.19
7.18
7.05
7.04
6.43
4.88
4.87
4.85
4.84
4.37
3.68
3.12
3.10
3.09
3.08
3.06
3.04
3.02
3.00
1.37
BocHN
O
O
OMe
HN
F3C
1H NMR of
compound S3
2.16
2.14
2.20
2.00
0.73
1.82
0.87
3.25
4.30
9.82
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

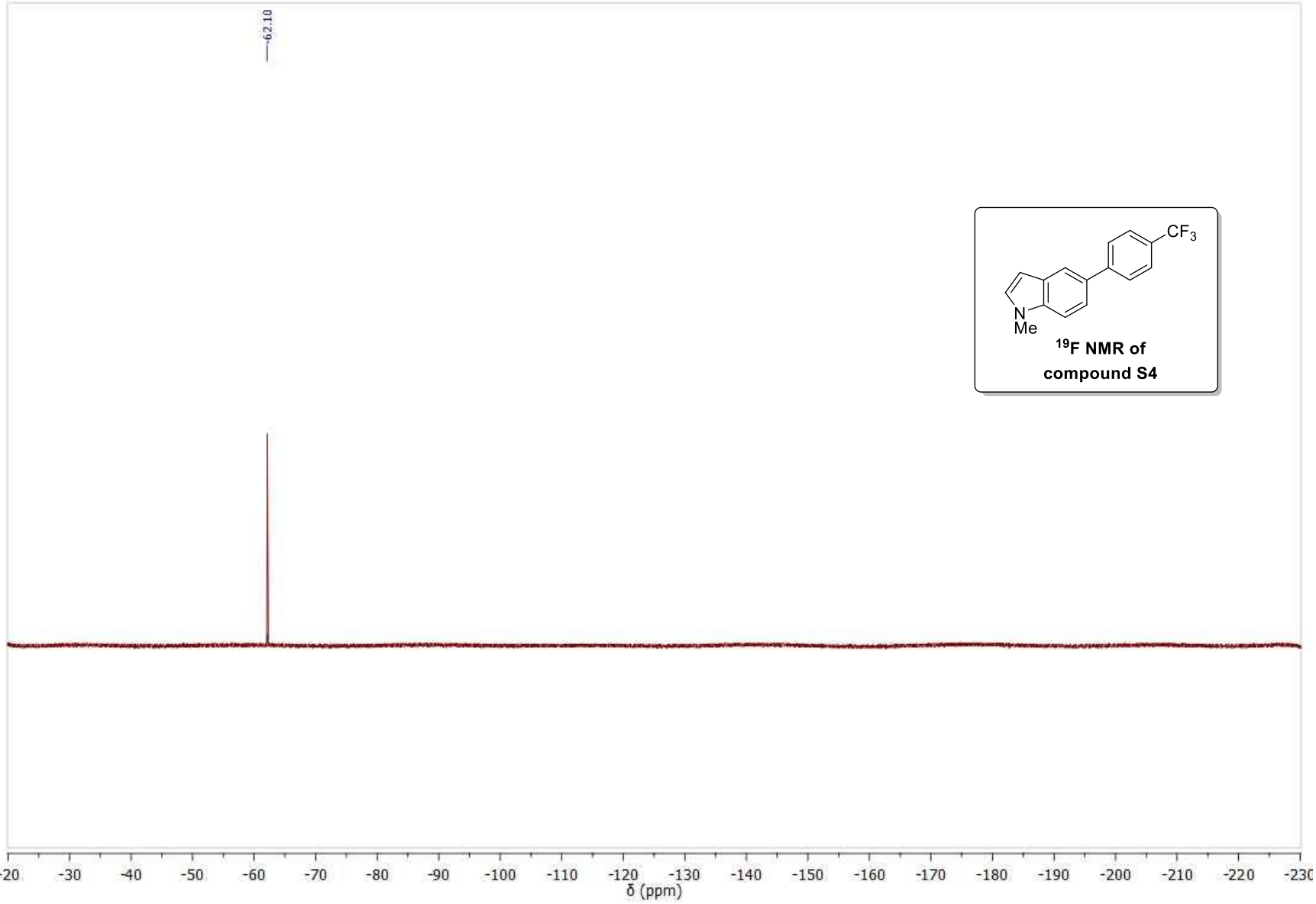

171.29
171.22
155.54
139.96
136.66
129.71
129.60
129.39
129.34
128.76
127.44
127.09
125.57
125.54
125.51
125.48
125.28
123.12
120.95
80.42
55.80
52.95
52.48
38.18
37.66
28.26
BocHN
O
O
OMe
HN
^{13}C NMR of
compound S3
F_3C
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

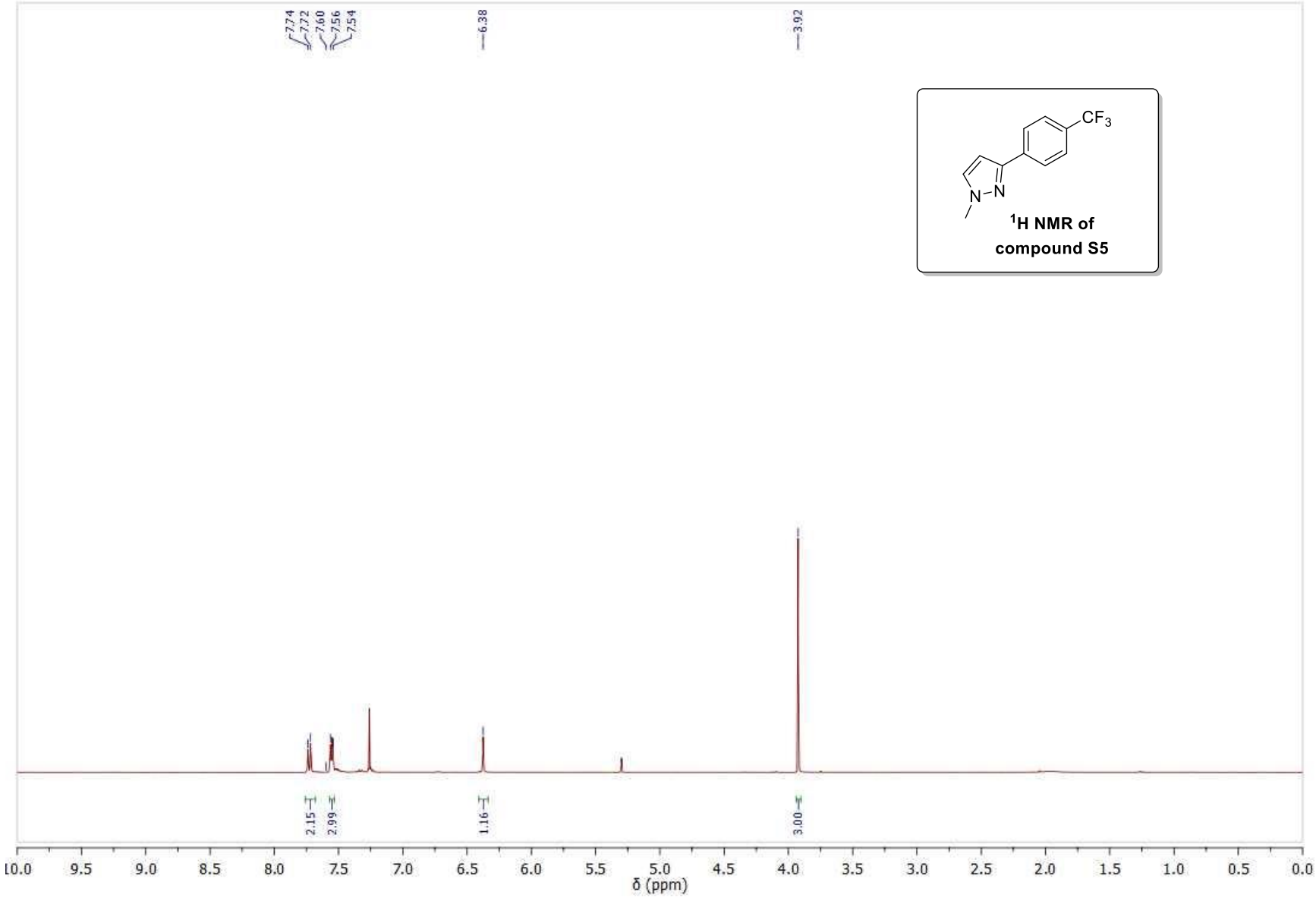

-62.85
BocHN
O
O
OMe
HN
^{19}F NMR of
compound S3
F_3C
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)


7.86
7.86
7.76
7.76
7.74
7.74
7.69
7.67
7.67
7.49
7.49
7.47
7.47
7.47
7.42
7.42
7.40
7.40
7.26
7.11
7.11
7.11
6.56
6.56
6.56
6.56
6.56
6.55
6.55
3.84
3.84
1.53
CF3
N
Me
1H NMR of
compound S4
1.34
1.90
2.03
1.11
1.03
1.01
1.00
3.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

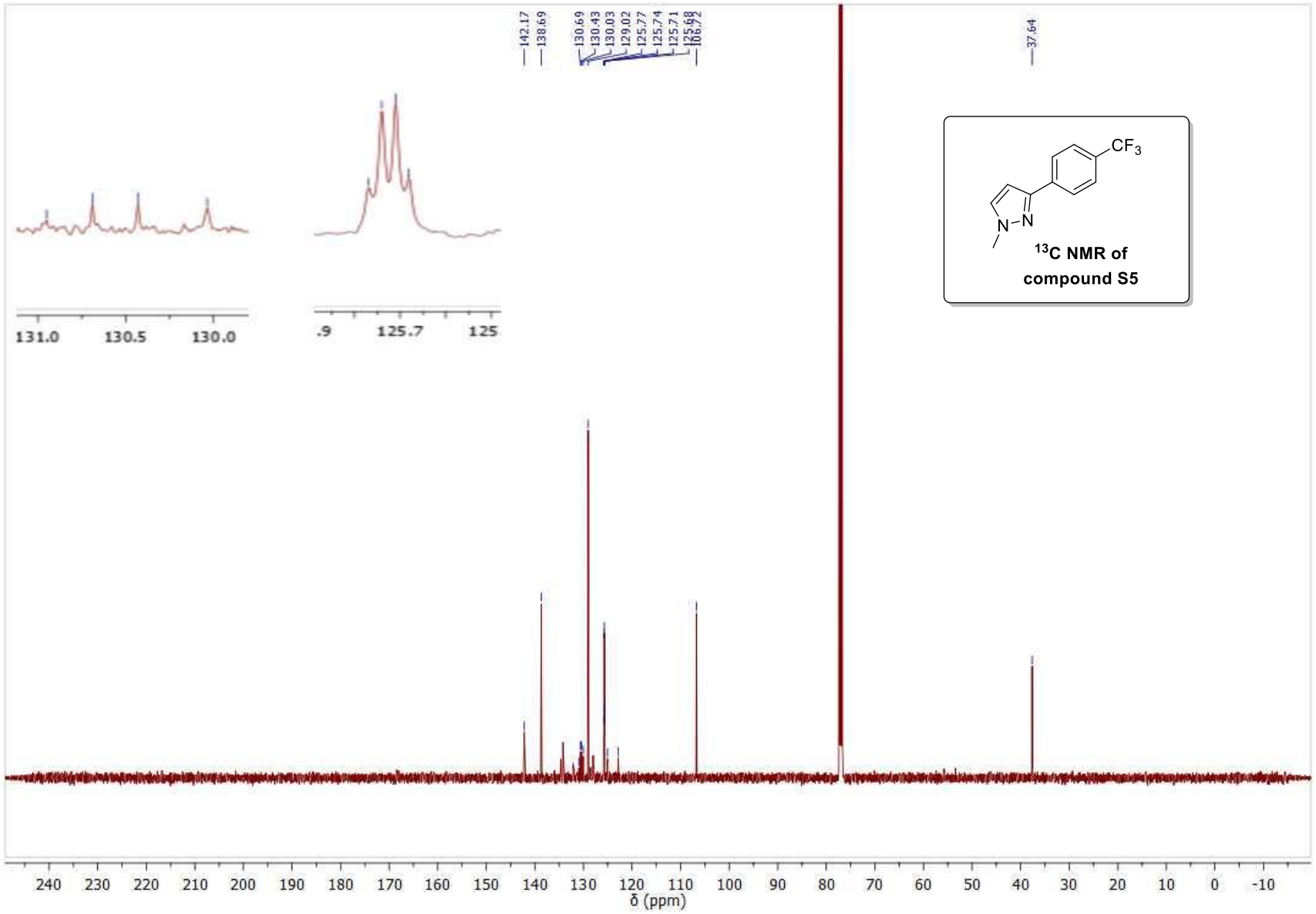


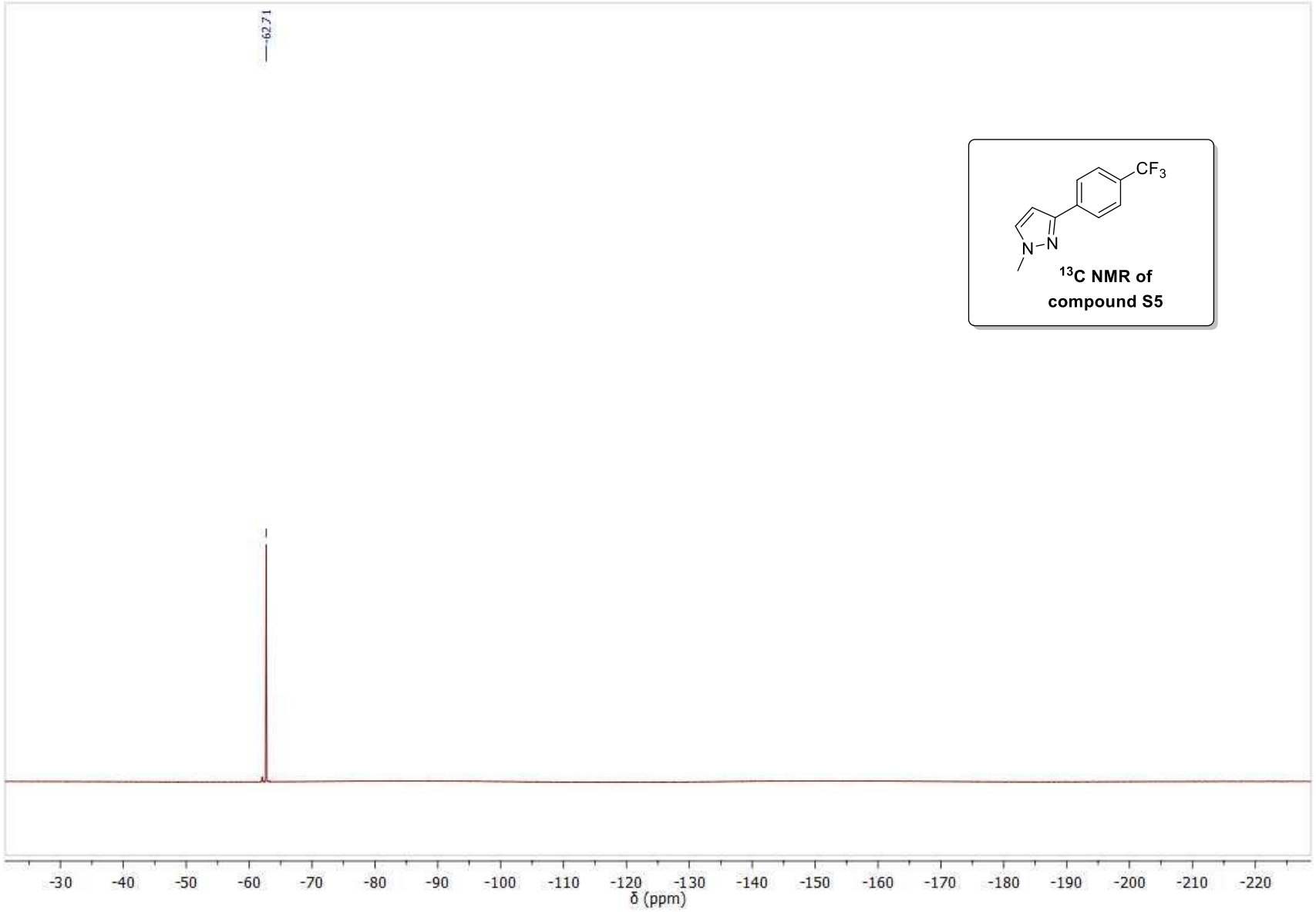
^{13}C NMR of compound S4


-62.10
CF3
N
Me
19F NMR of
compound S4
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

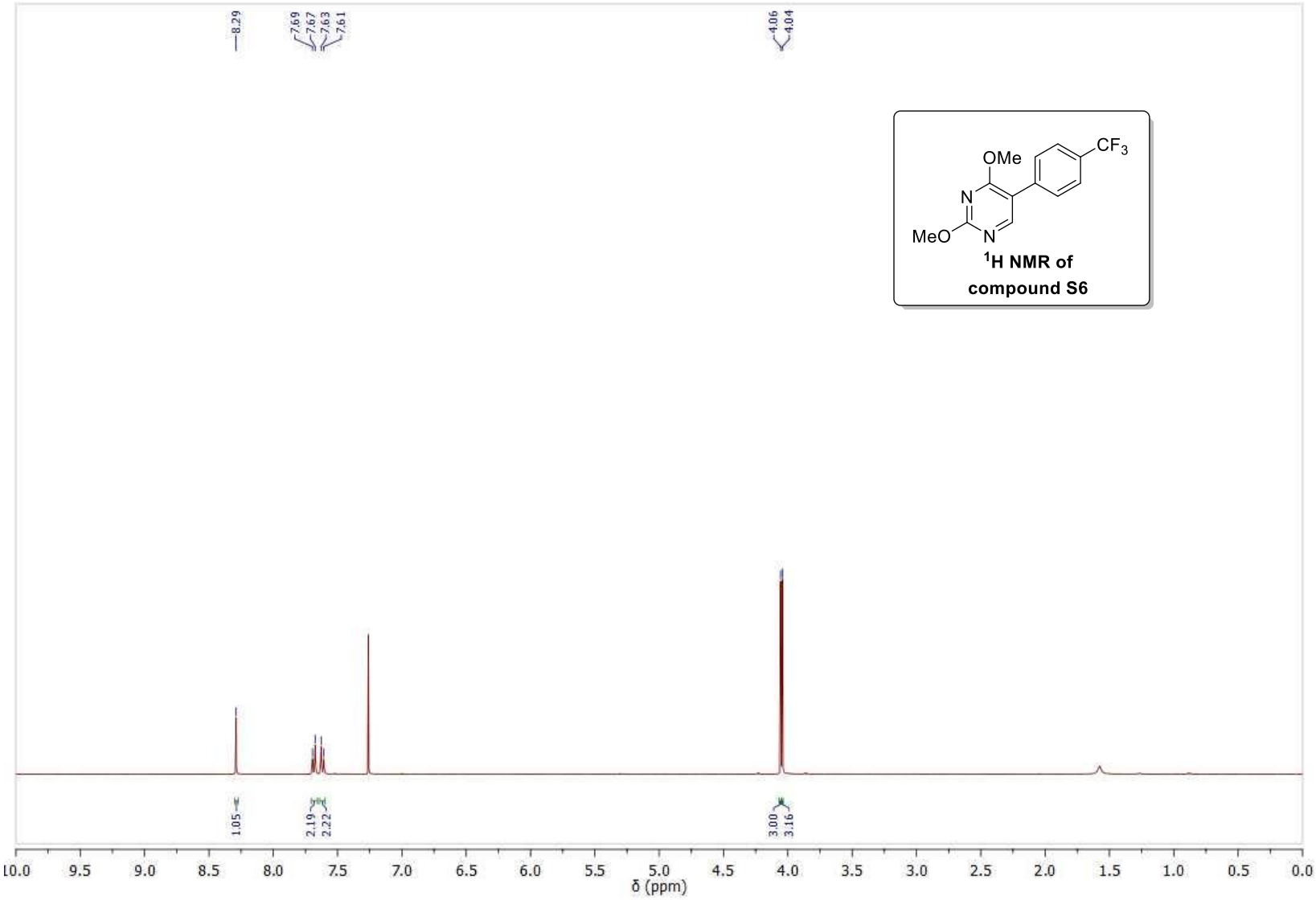


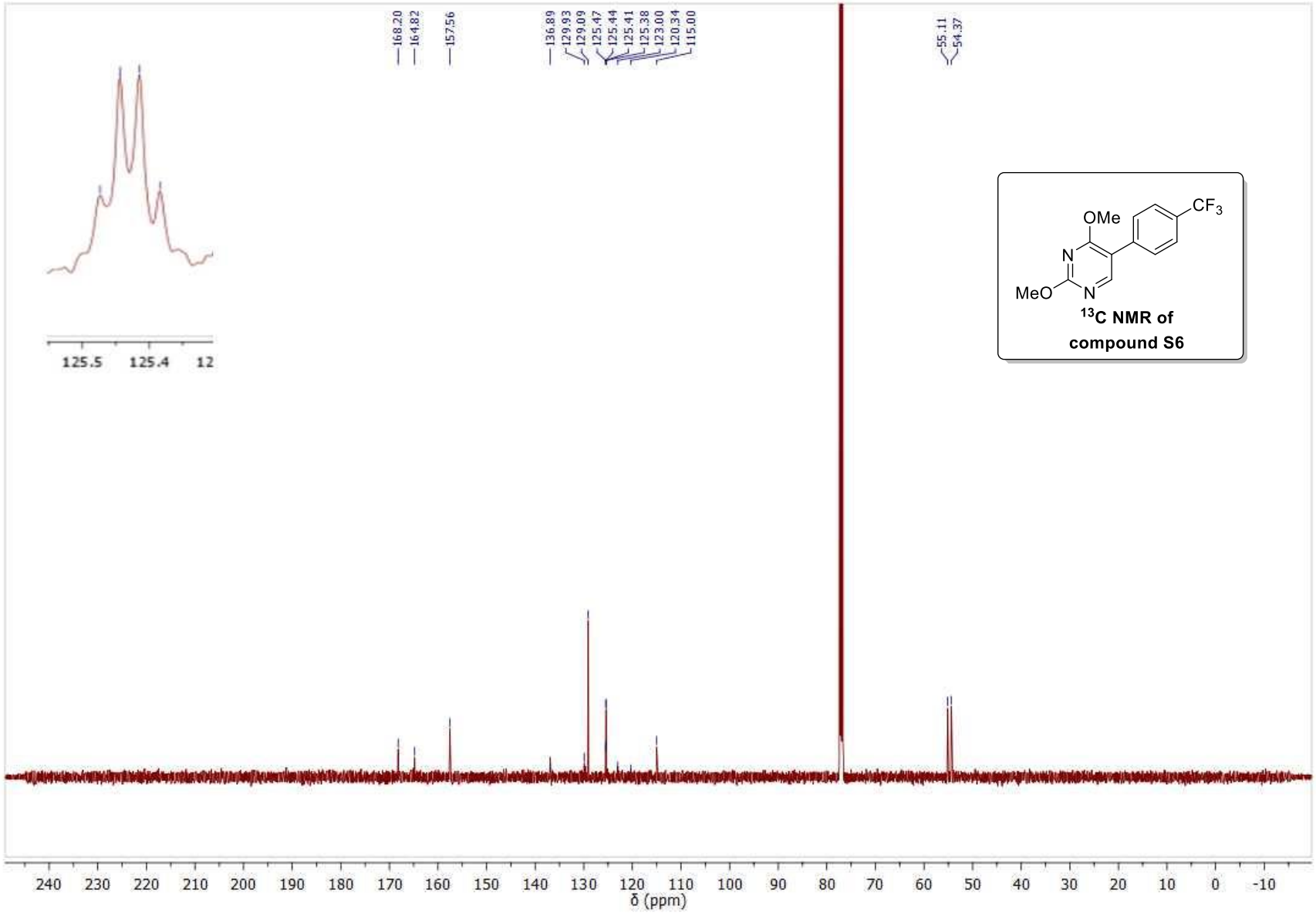
^{1}H NMR of compound S5

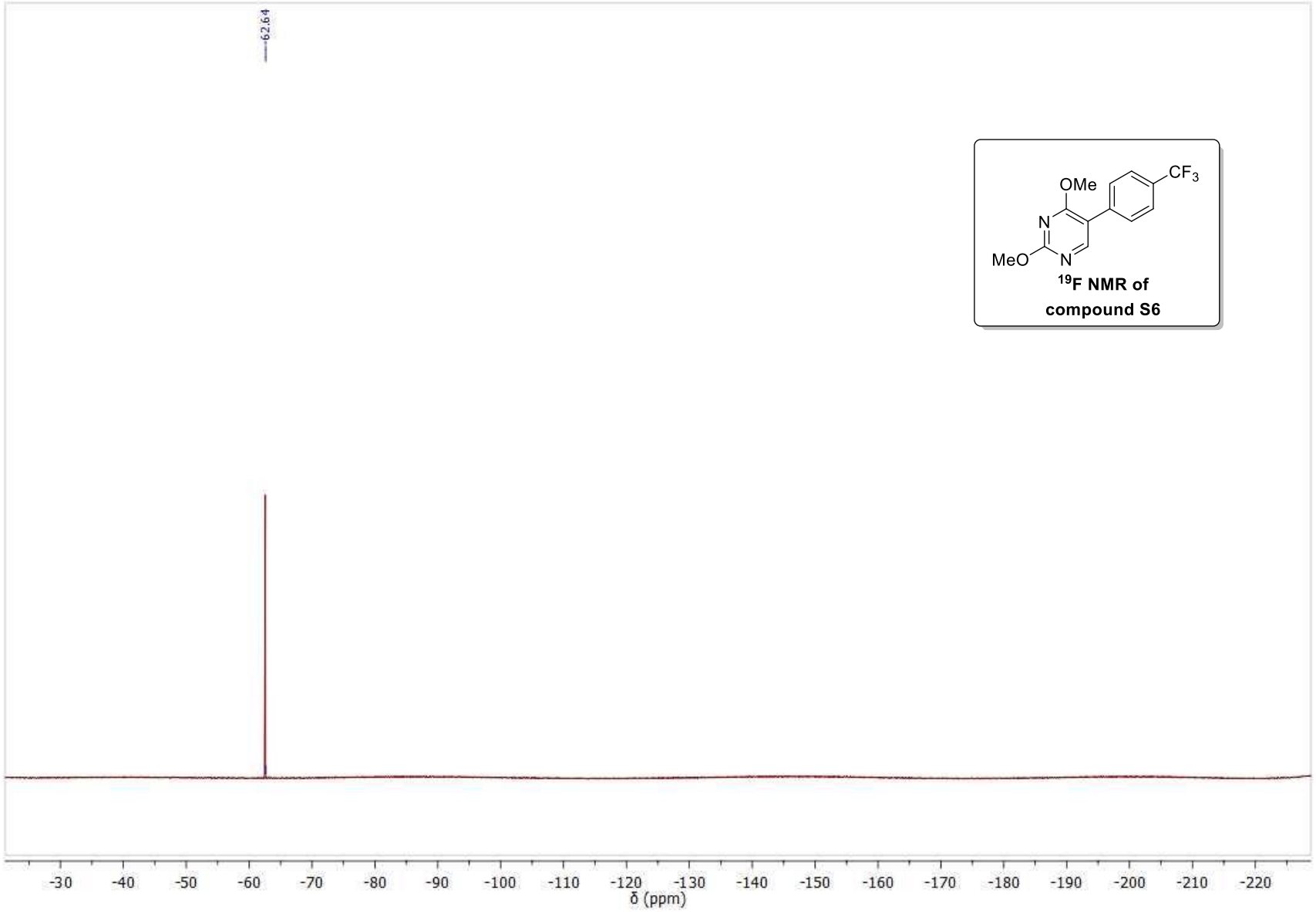

142.17
138.69
130.69
130.43
130.03
129.02
125.77
125.74
125.71
125.68
125.62
106.72
37.64
131.0
130.5
130.0
.9
125.7
125
CF3
N
N
13C NMR of compound S5
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)



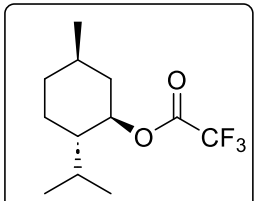
^{13}C NMR of compound S5


8.29
7.69
7.67
7.63
7.61
4.06
4.04
OMe
CF3
N
MeO
N
1H NMR of
compound S6
1.05
2.19
2.22
3.00
3.16
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

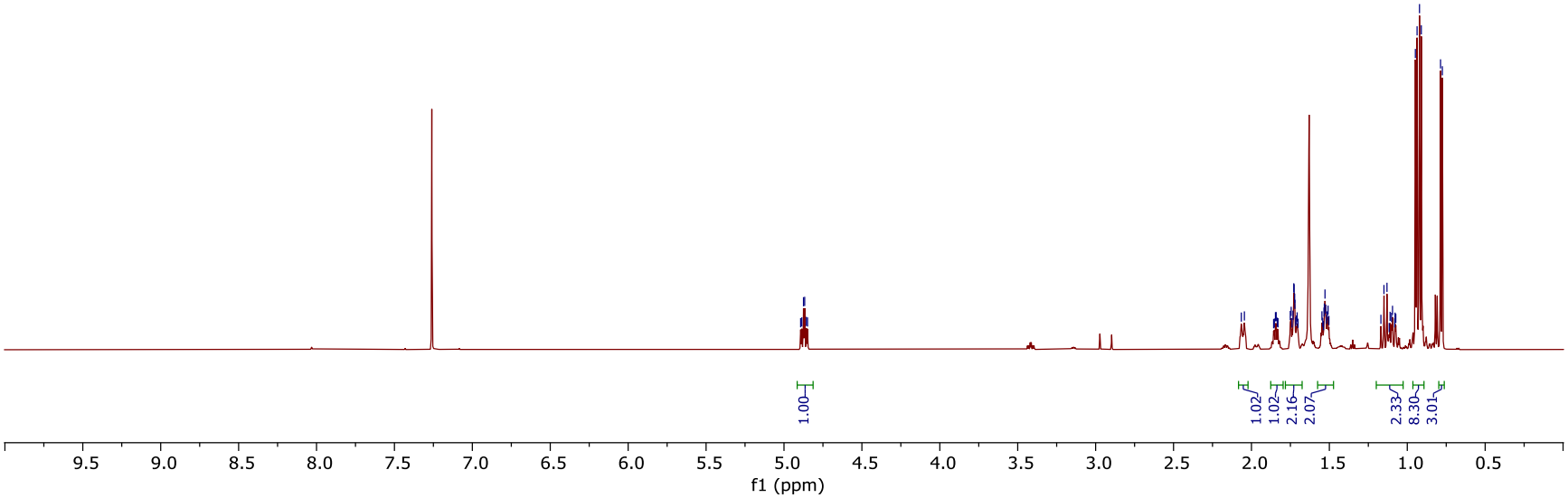

168.20
164.82
157.56
136.89
129.93
129.09
125.47
125.44
125.41
125.38
123.00
120.34
115.00
55.11
54.37
125.5
125.4
12
OMe
CF3
N
MeO
N
13C NMR of
compound S6
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)


-62.64
OMe
CF3
N
MeO
N
19F NMR of
compound S6
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

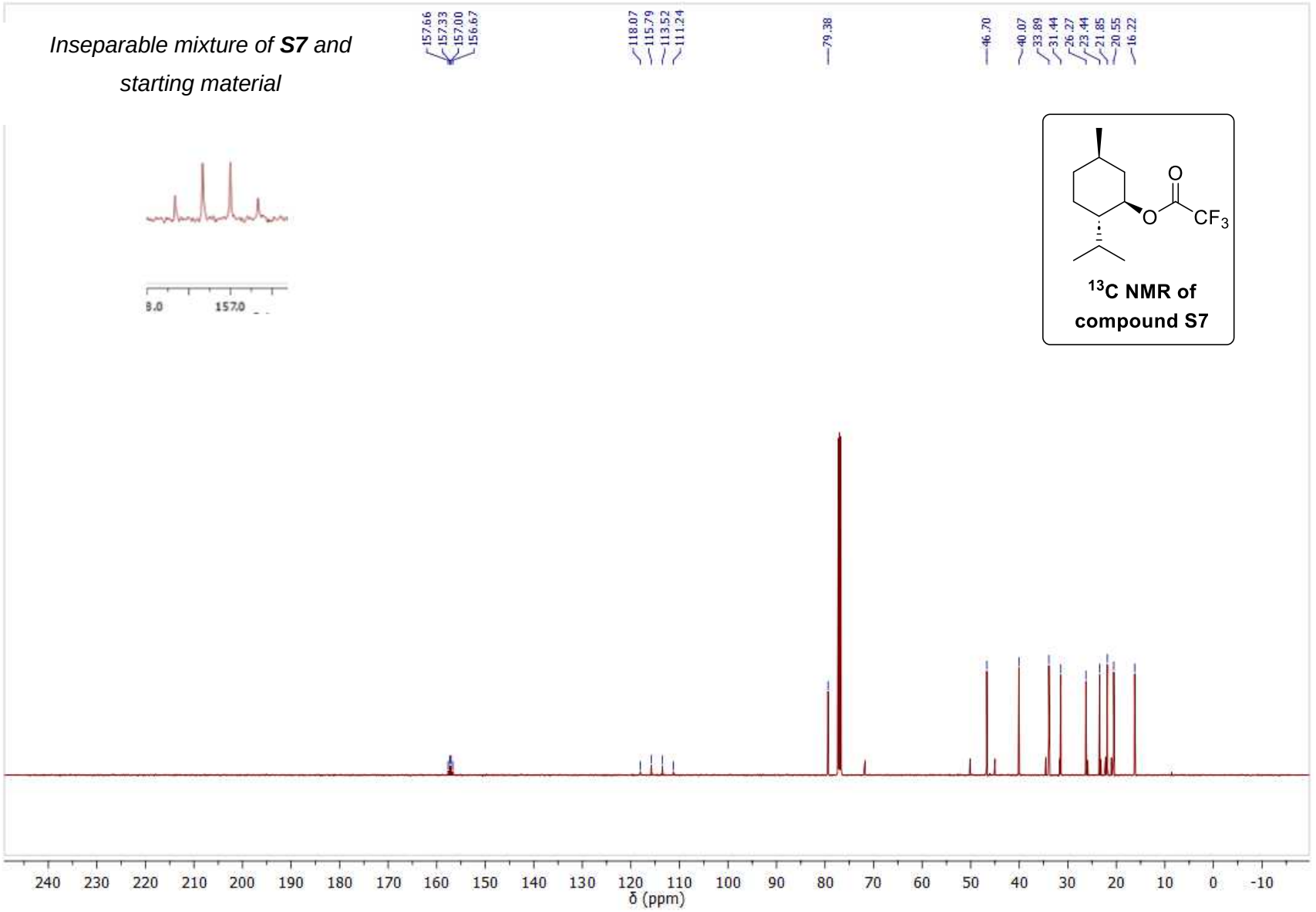
*Inseparable mixture of **S7** and starting material*



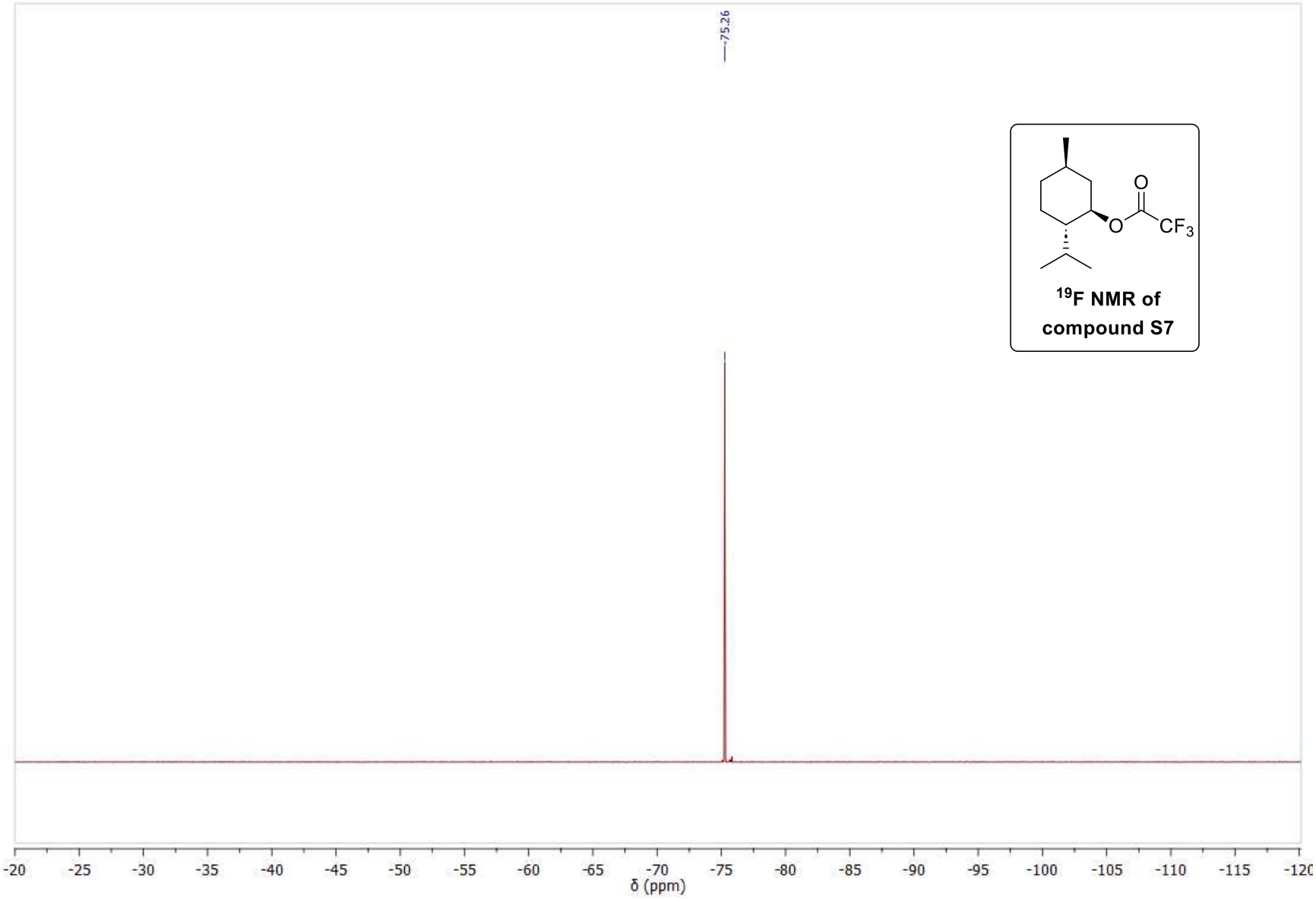
^{1}H NMR of compound S7

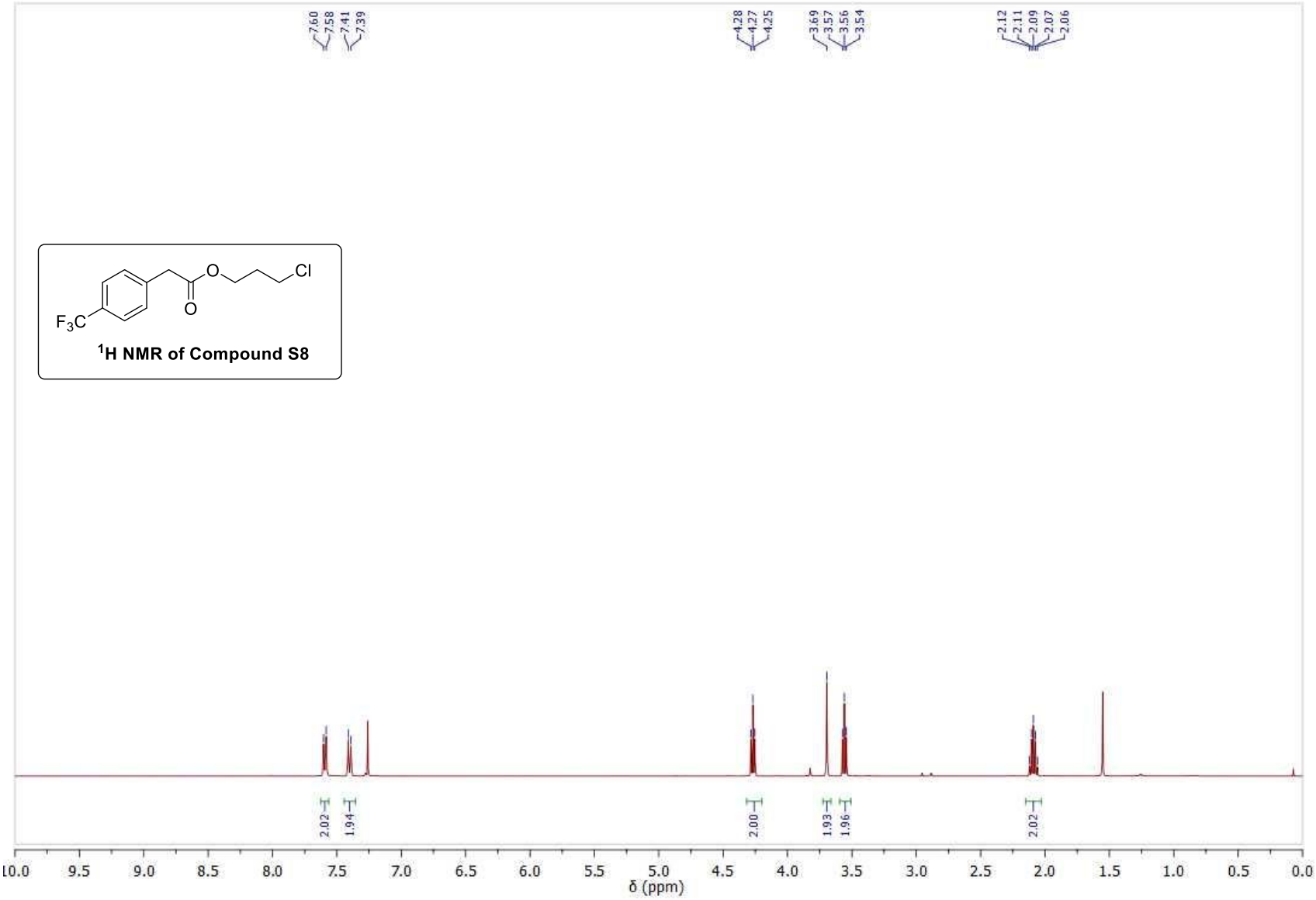


*Inseparable mixture of **S7** and starting material*

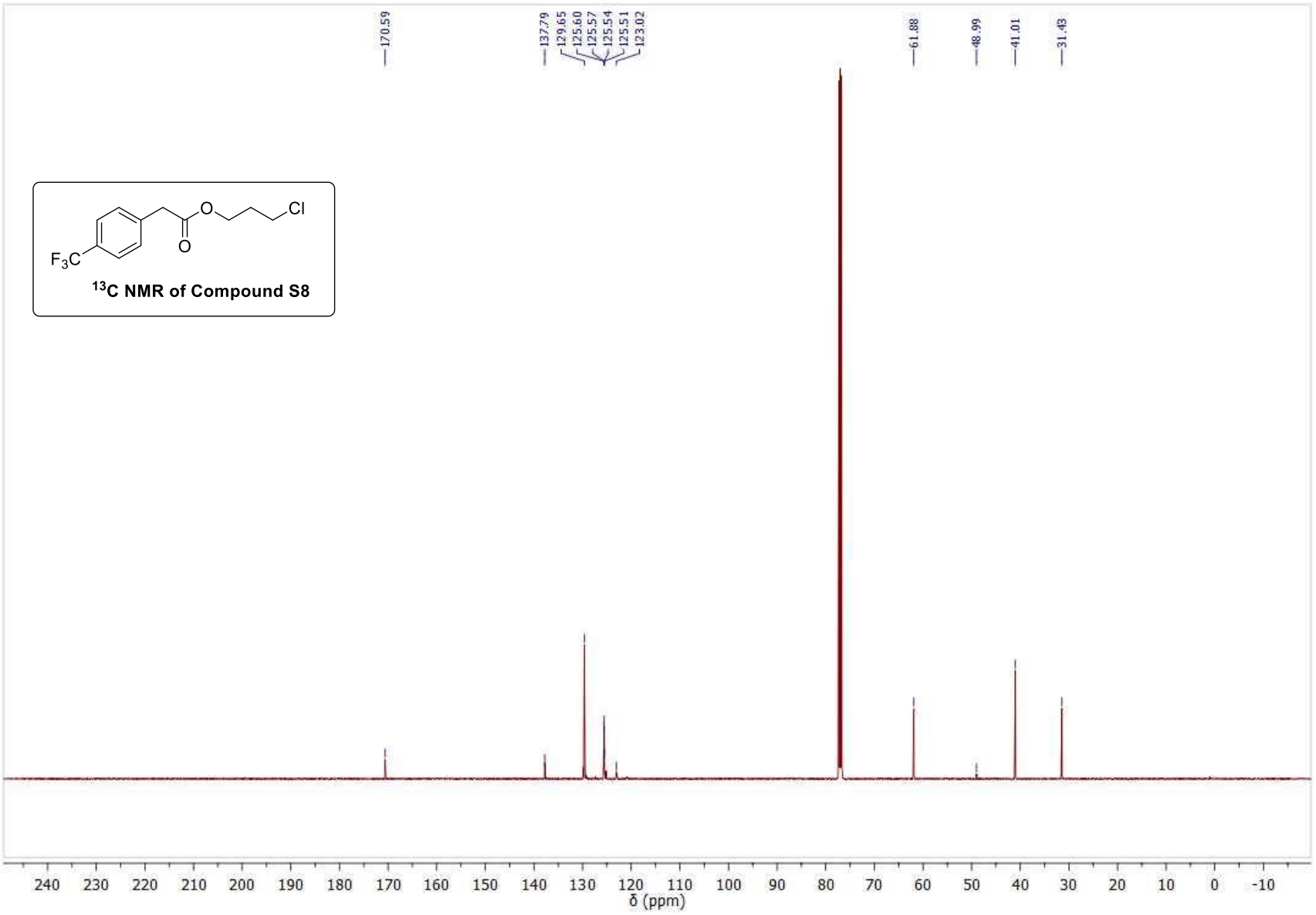


^{13}C NMR of compound S7

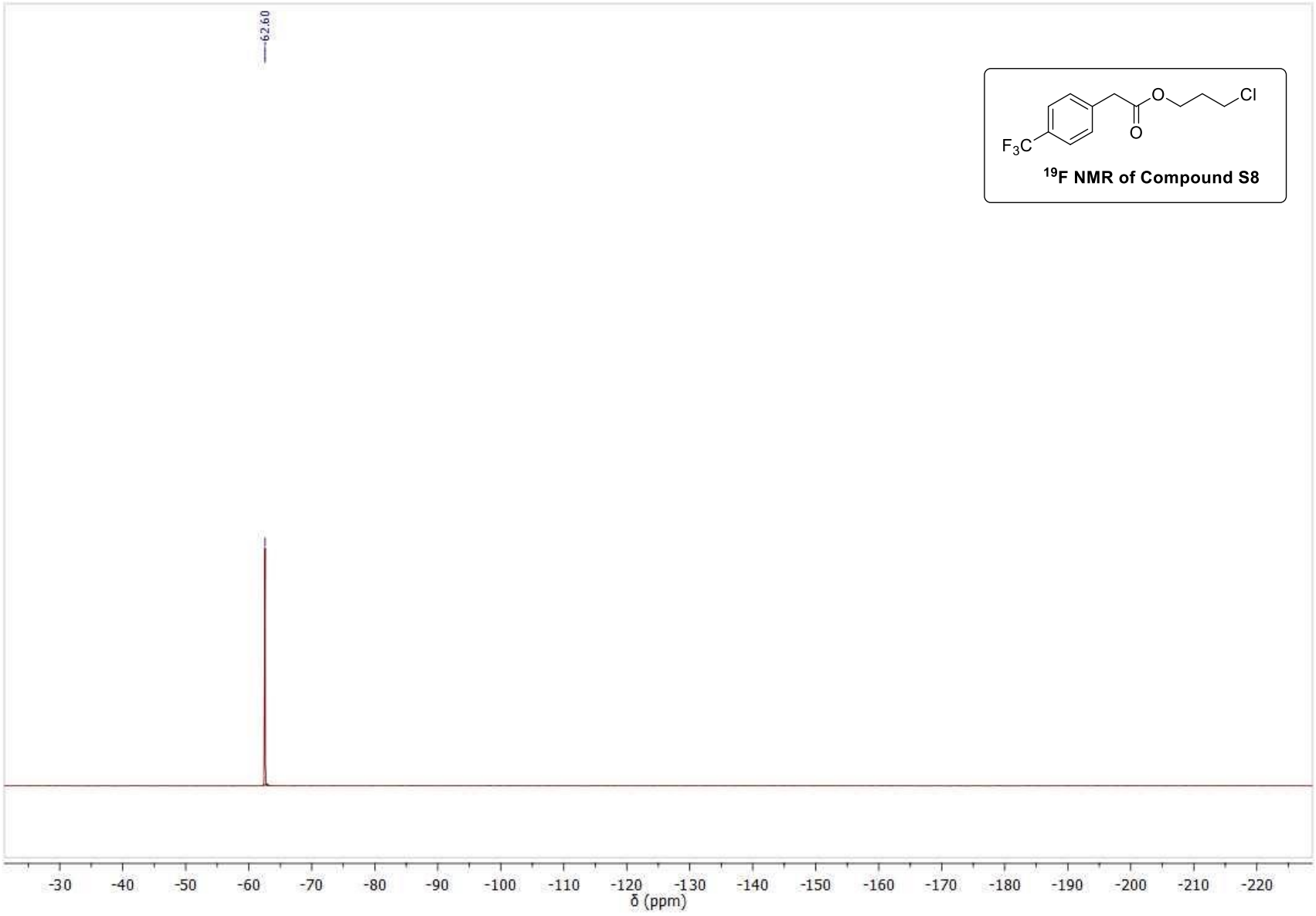

-75.26
O
O
CF3
19F NMR of
compound S7
-20
-25
-30
-35
-40
-45
-50
-55
-60
-65
-70
-75
-80
-85
-90
-95
-100
-105
-110
-115
-120
δ (ppm)



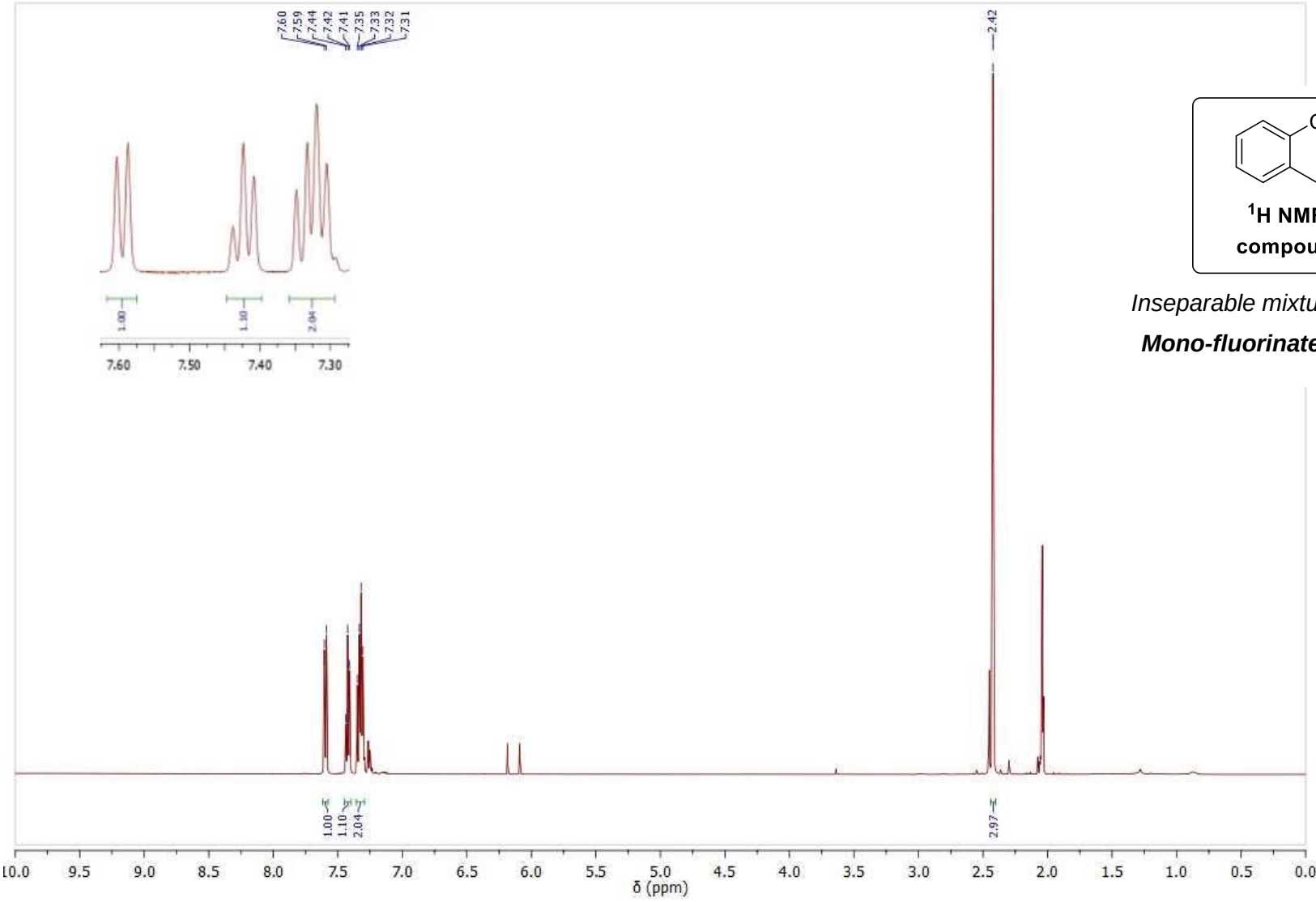
^{1}H NMR of Compound S8

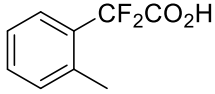


^{13}C NMR of Compound S8



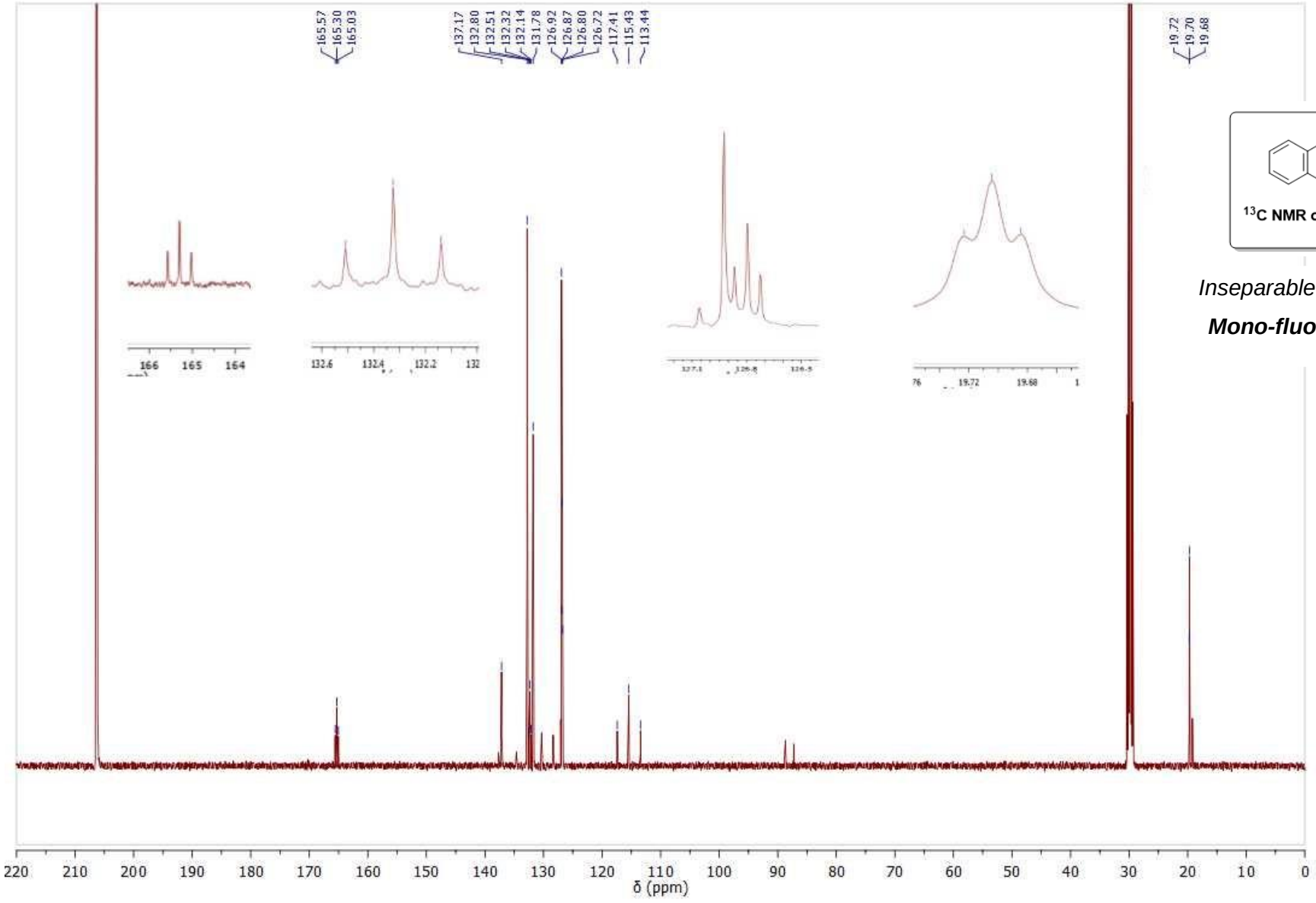
^{19}F NMR of Compound S8

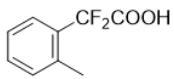




^{1}H NMR of compound 7

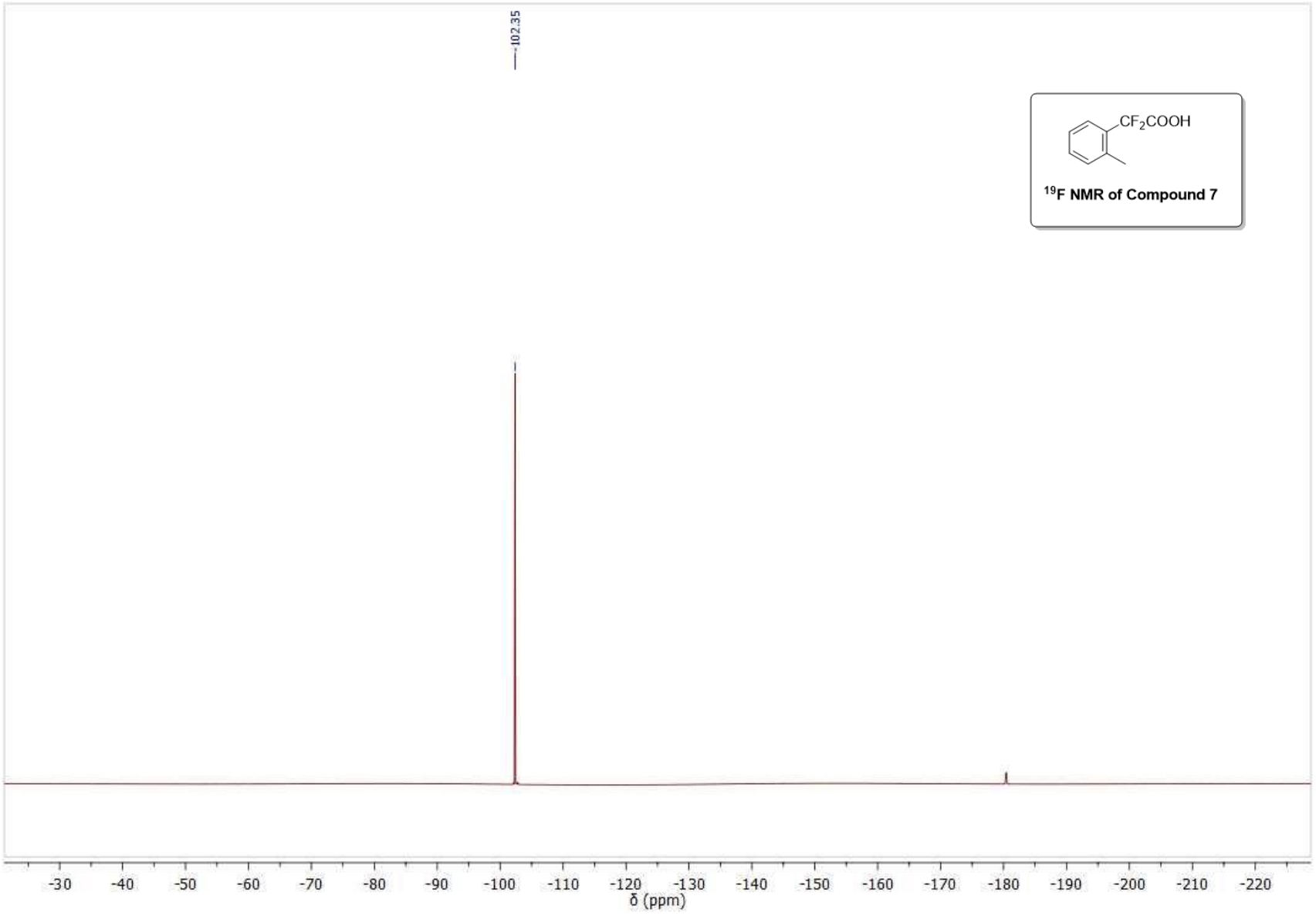
*Inseparable mixture of **Di- and Mono-fluorinated products***

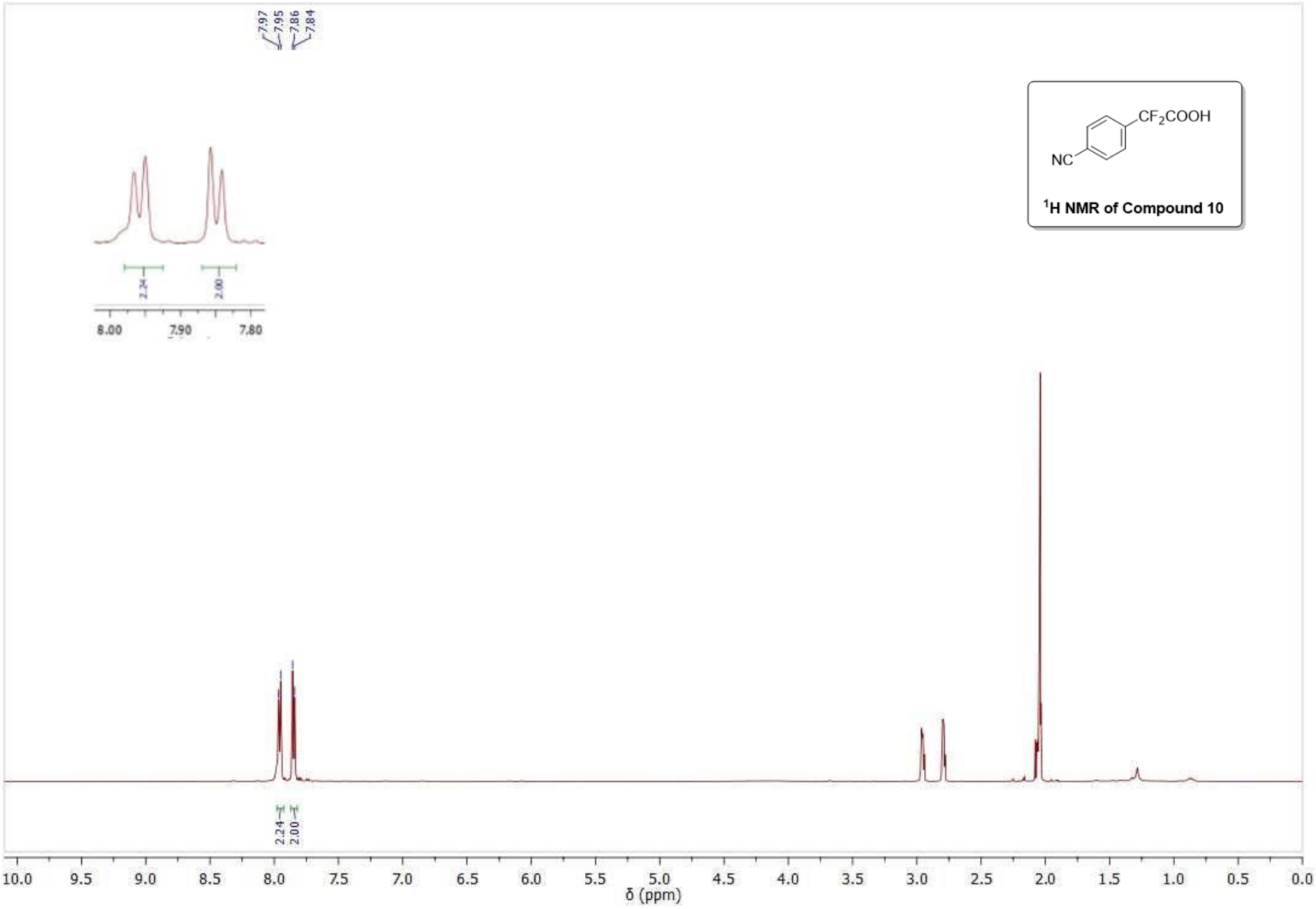


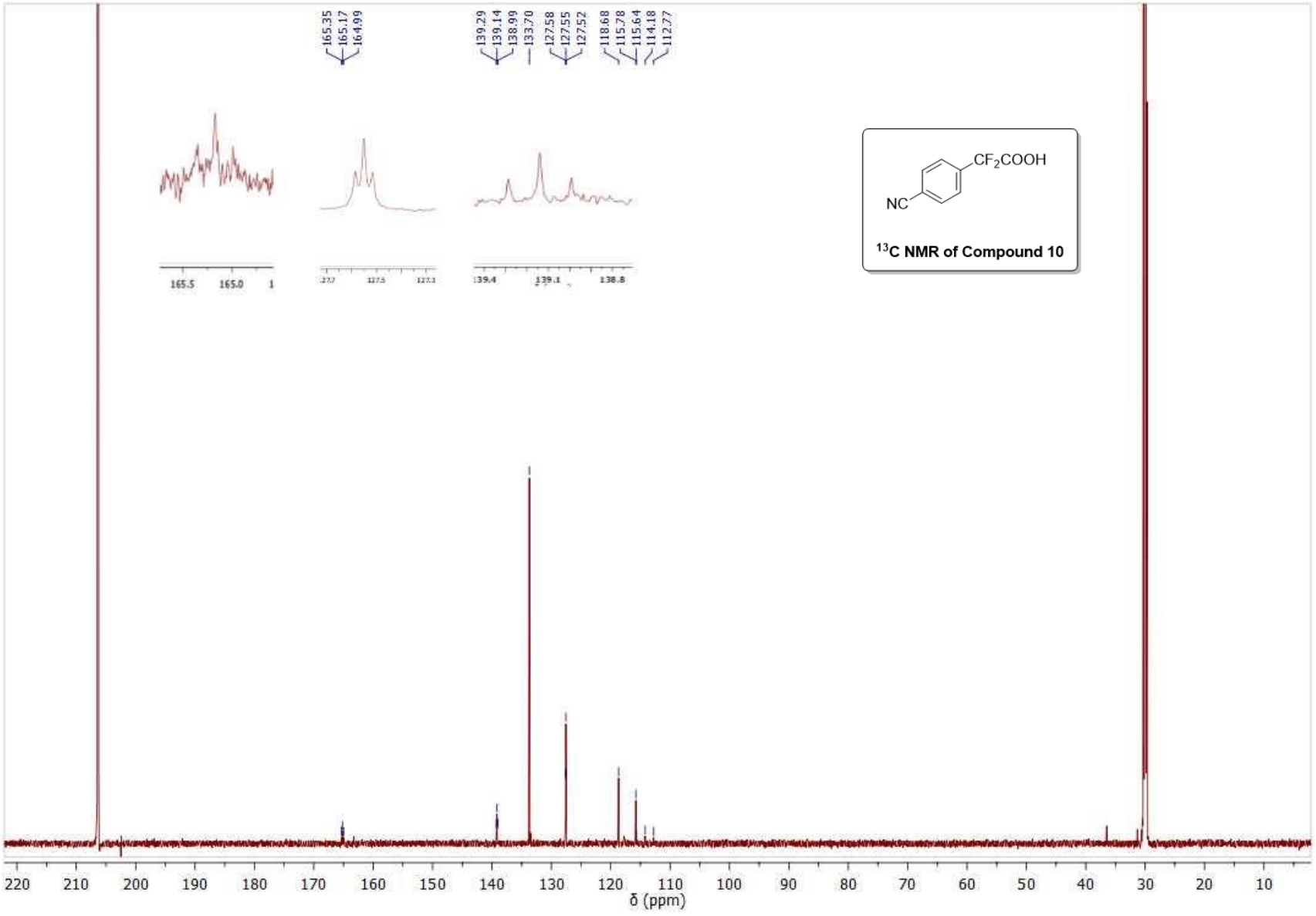


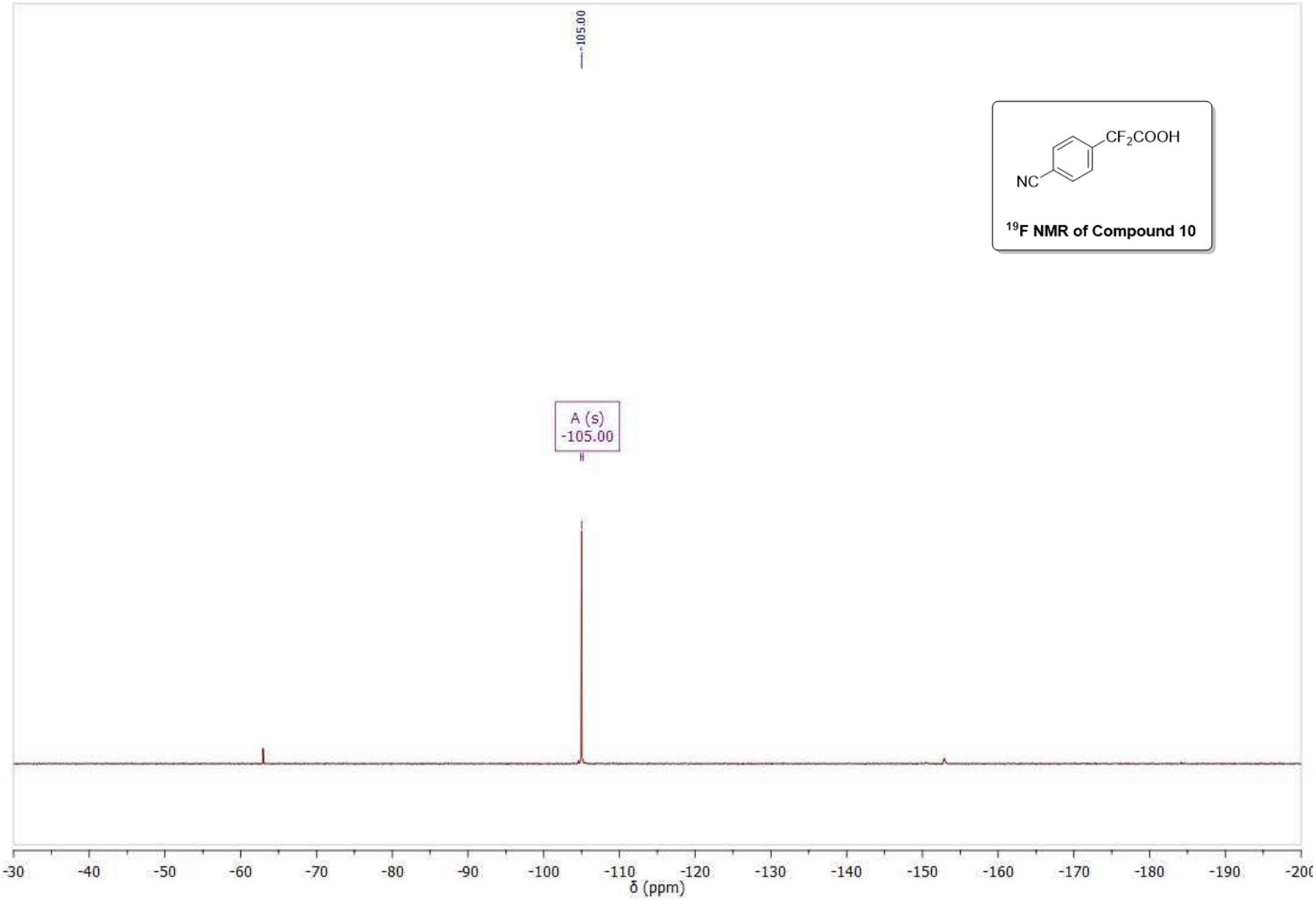
^{13}C NMR of Compound 7

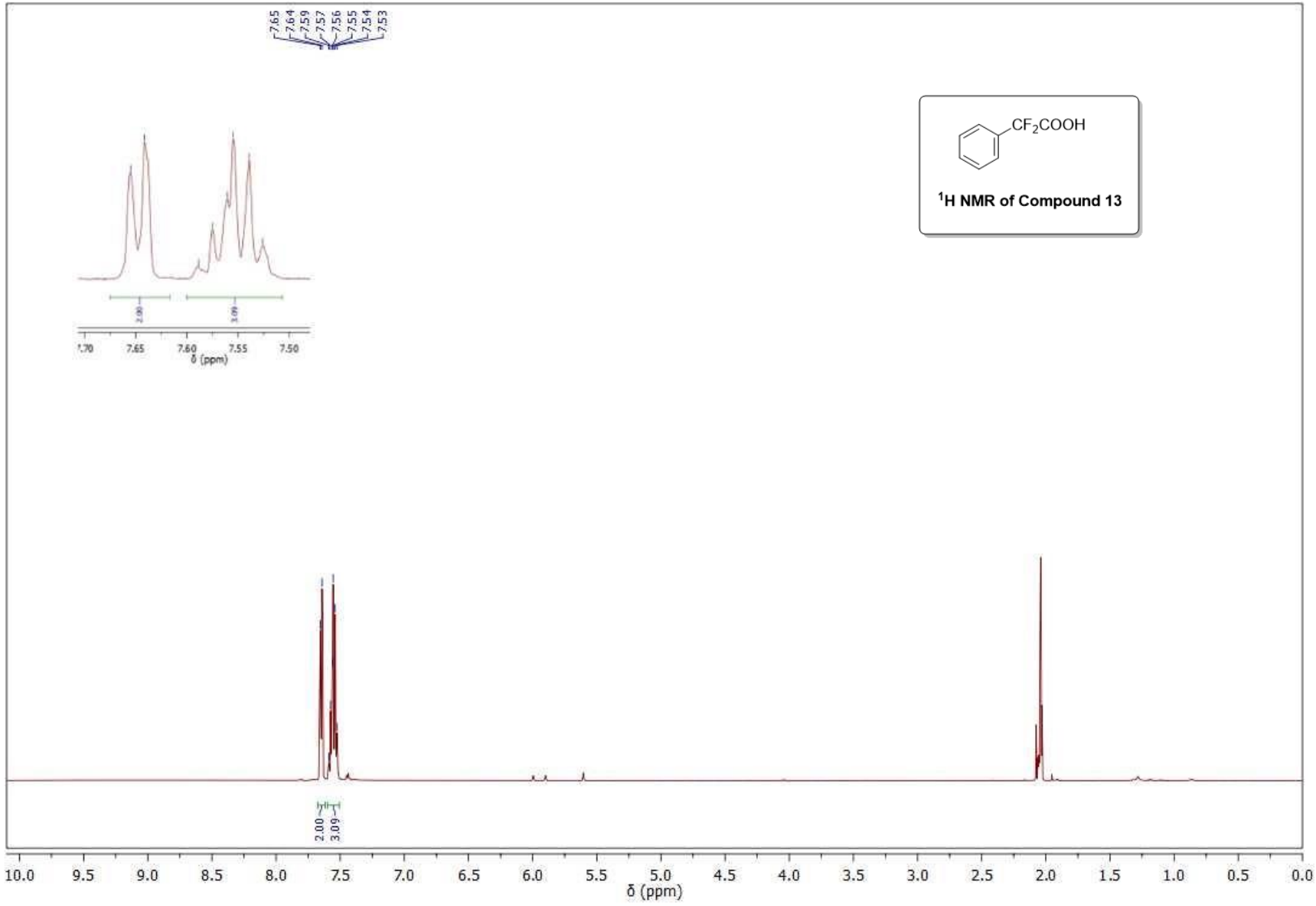
*Inseparable mixture of **Di- and Mono-fluorinated products***

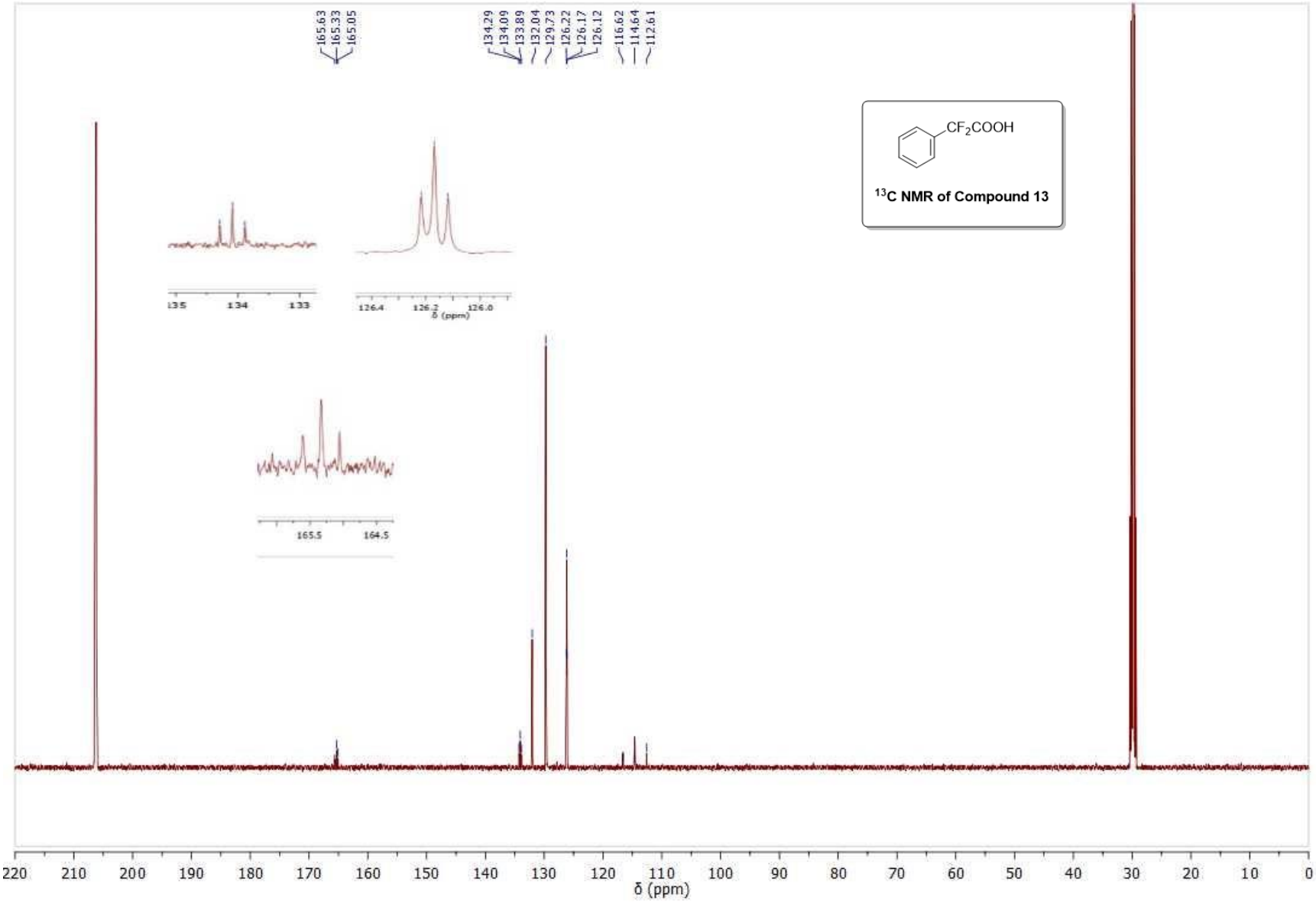

-102.35
CF2COOH
19F NMR of Compound 7
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

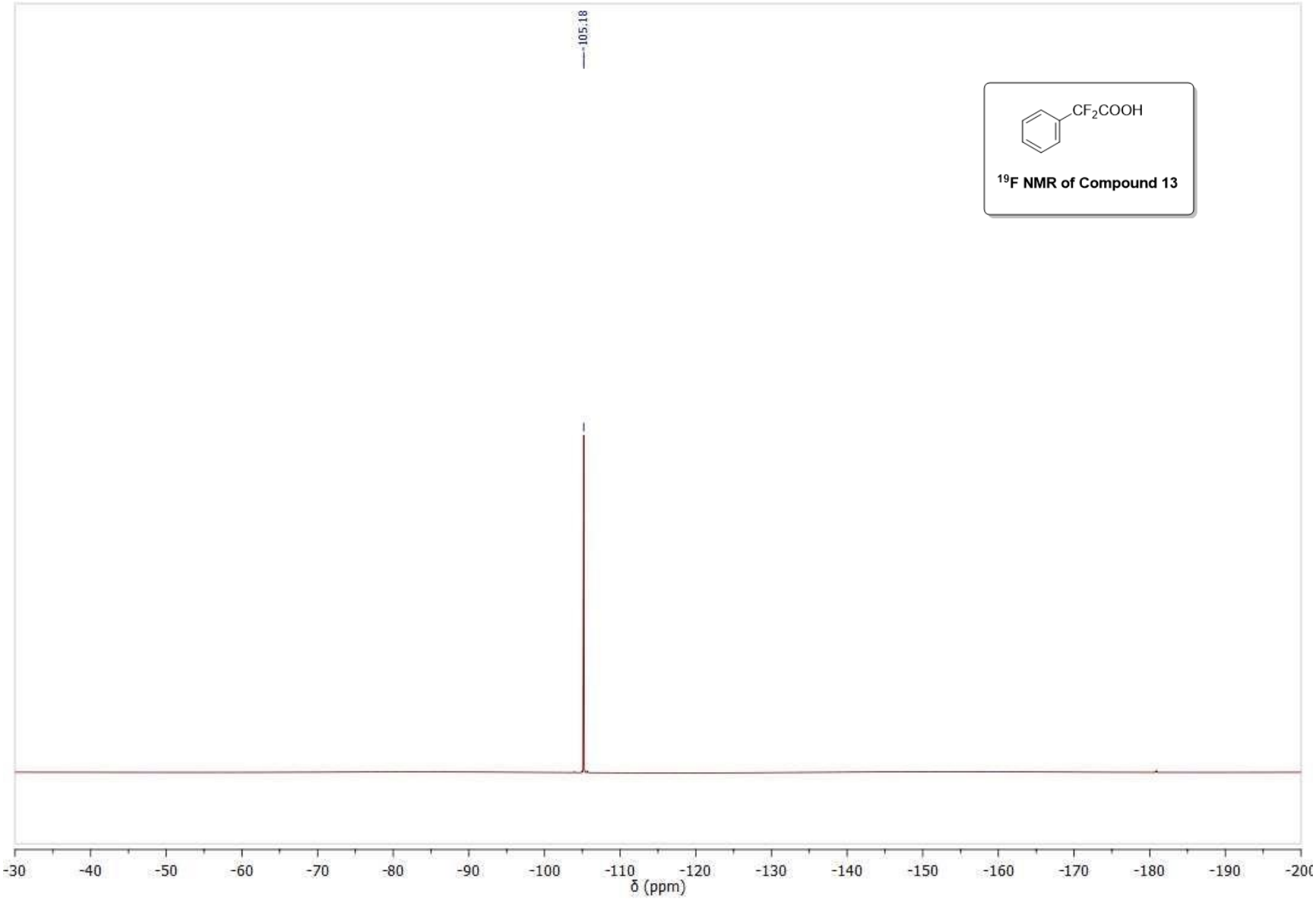

7.97
7.95
7.86
7.84
2.24
2.00
8.00
7.90
7.80
CF2COOH
NC
1H NMR of Compound 10
2.24
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

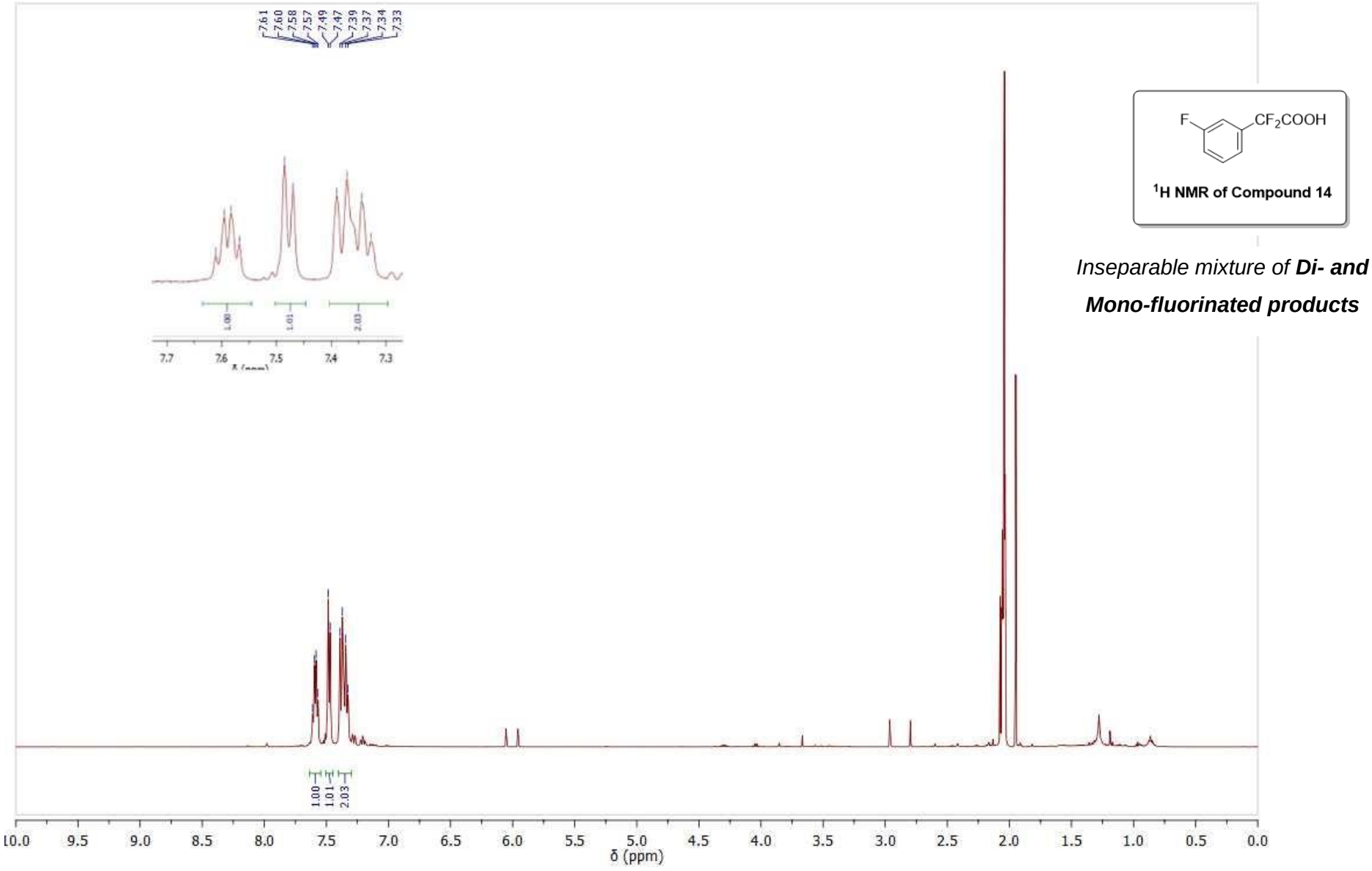

165.35
165.17
164.99
139.29
139.14
138.99
133.70
127.58
127.55
127.52
118.68
115.78
115.64
114.18
112.77
CF2COOH
NC
13C NMR of Compound 10
δ (ppm)


-105.00
A (s)
-105.00
CF2COOH
NC
19F NMR of Compound 10
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
δ (ppm)

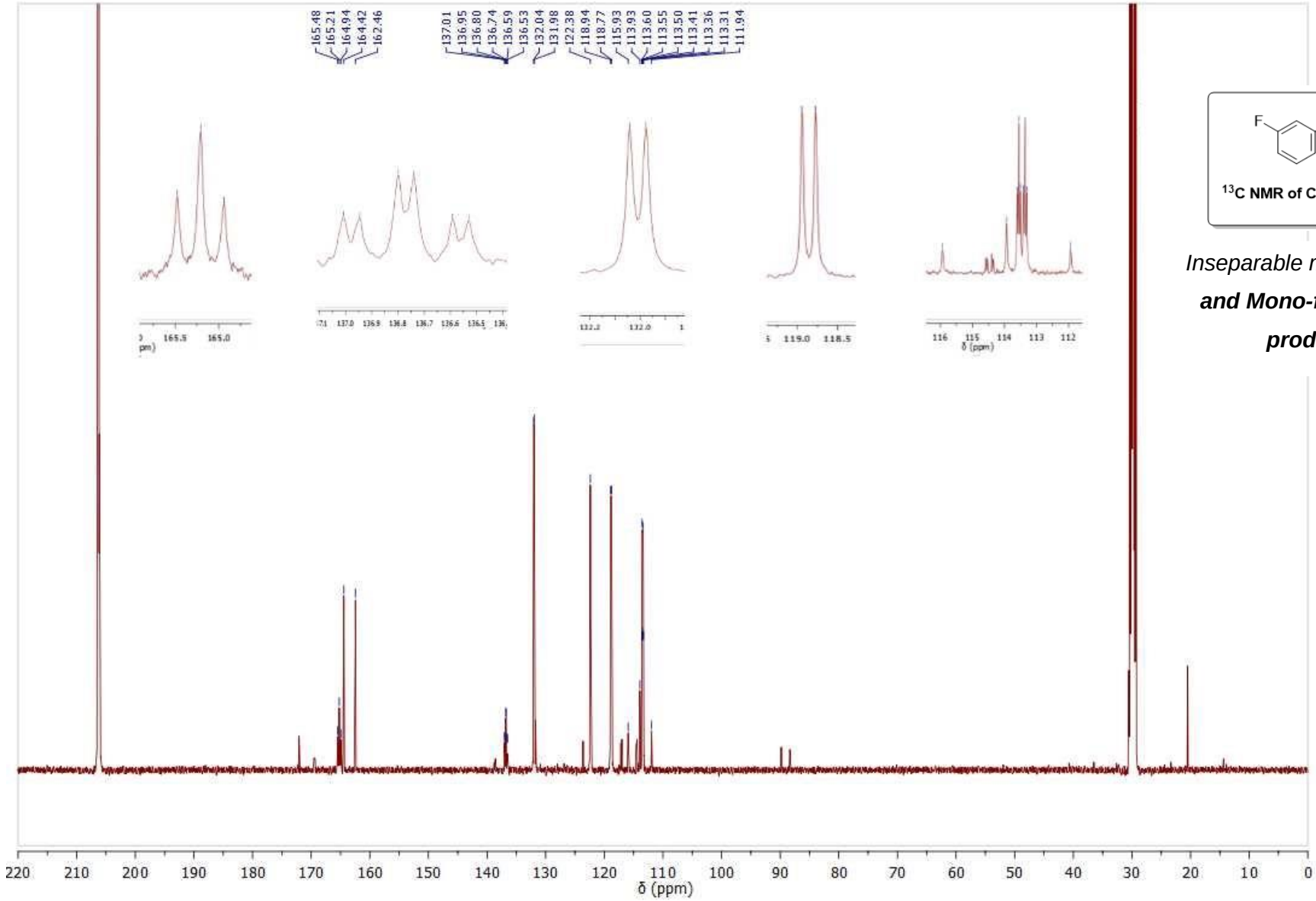

7.65
7.64
7.59
7.57
7.56
7.55
7.54
7.53
2.00
3.09
1.70
7.65
7.60
7.55
7.50
δ (ppm)
CF2COOH
1H NMR of Compound 13
2.00
3.09
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

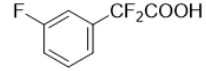

165.63
165.33
165.05
134.29
134.09
133.89
132.04
129.73
126.22
126.17
126.12
116.62
114.64
112.61
CF2COOH
13C NMR of Compound 13
δ (ppm)


-105.18
CF2COOH
19F NMR of Compound 13
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
δ (ppm)



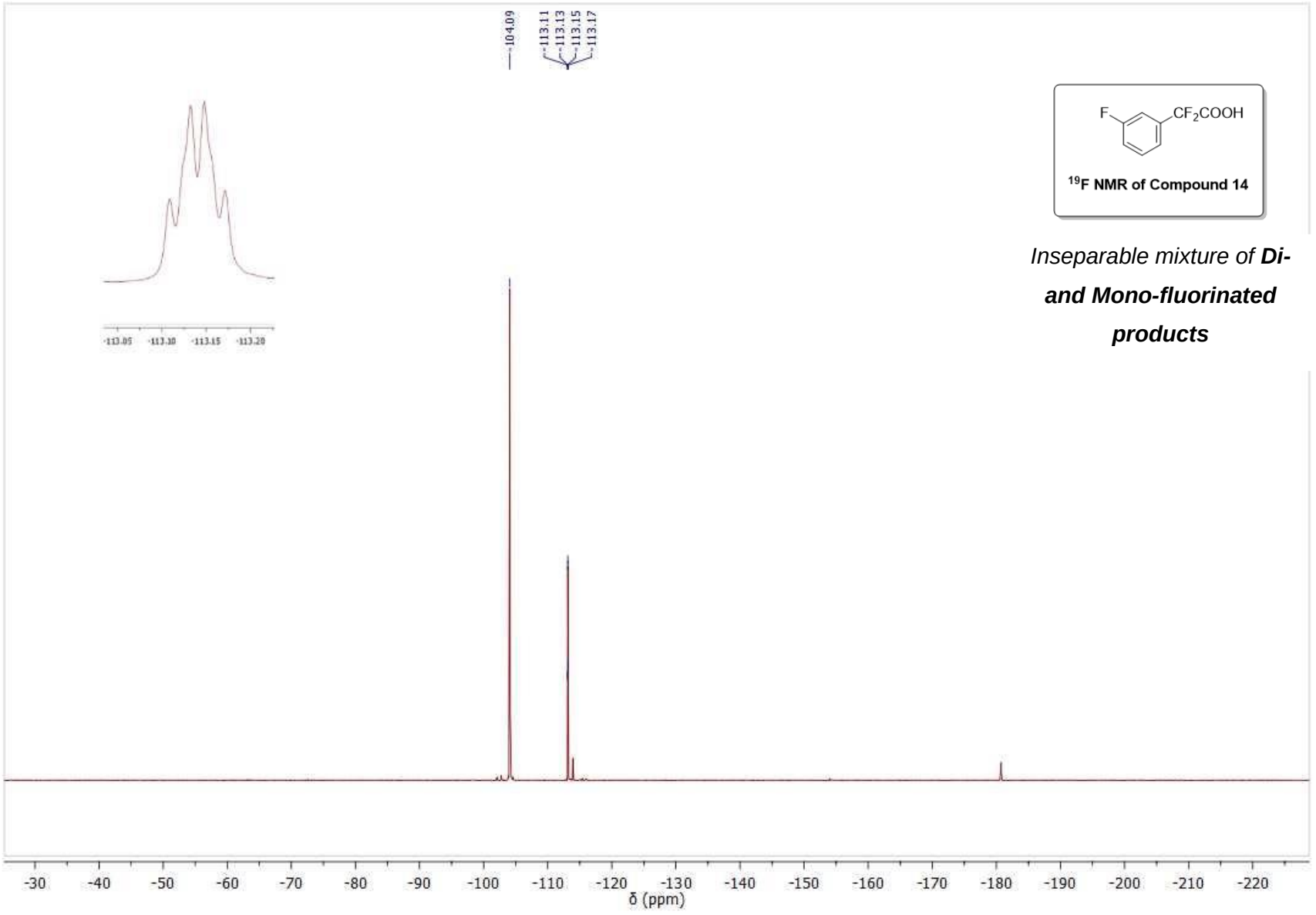
*Inseparable mixture of **Di- and Mono-fluorinated products***



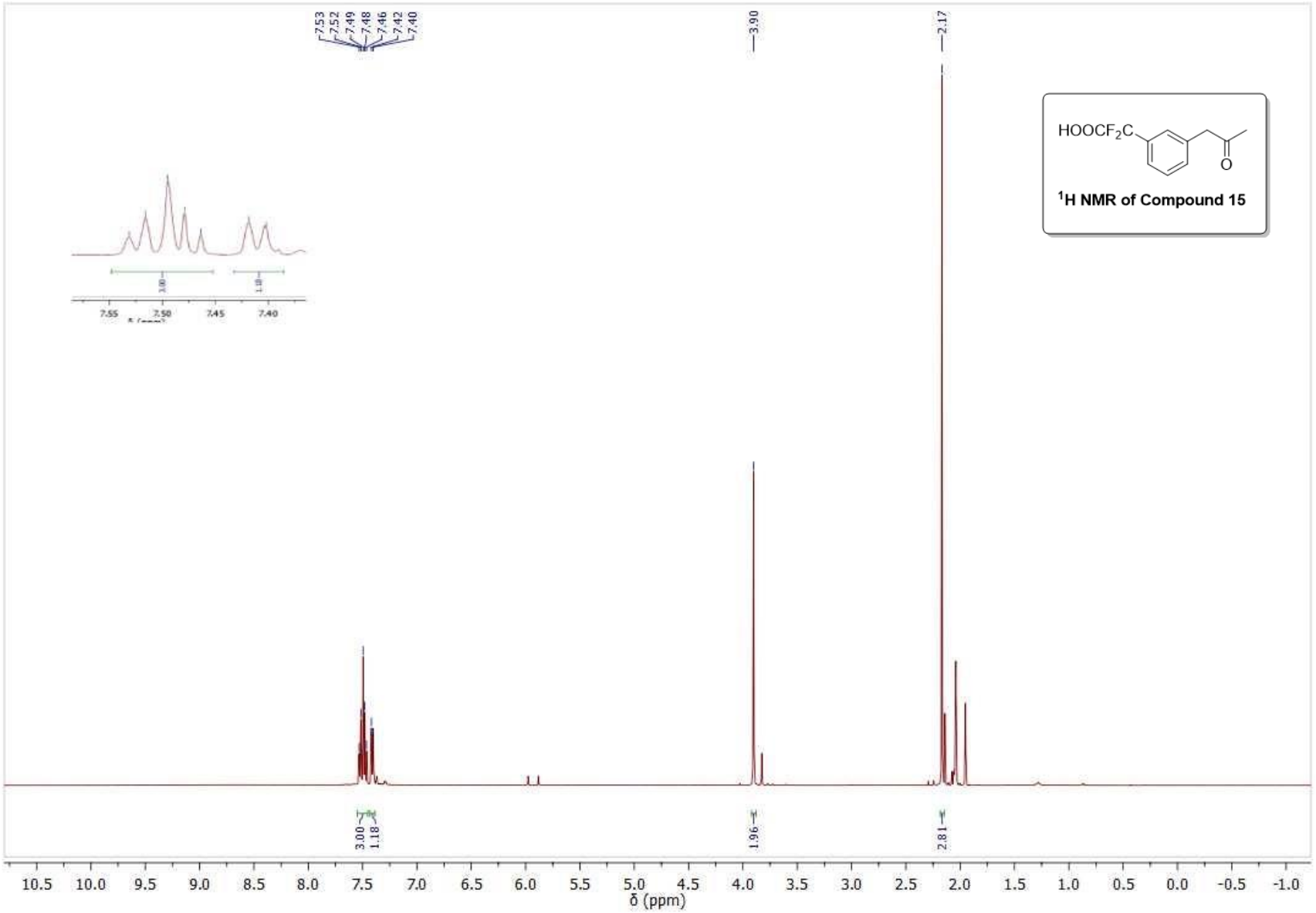


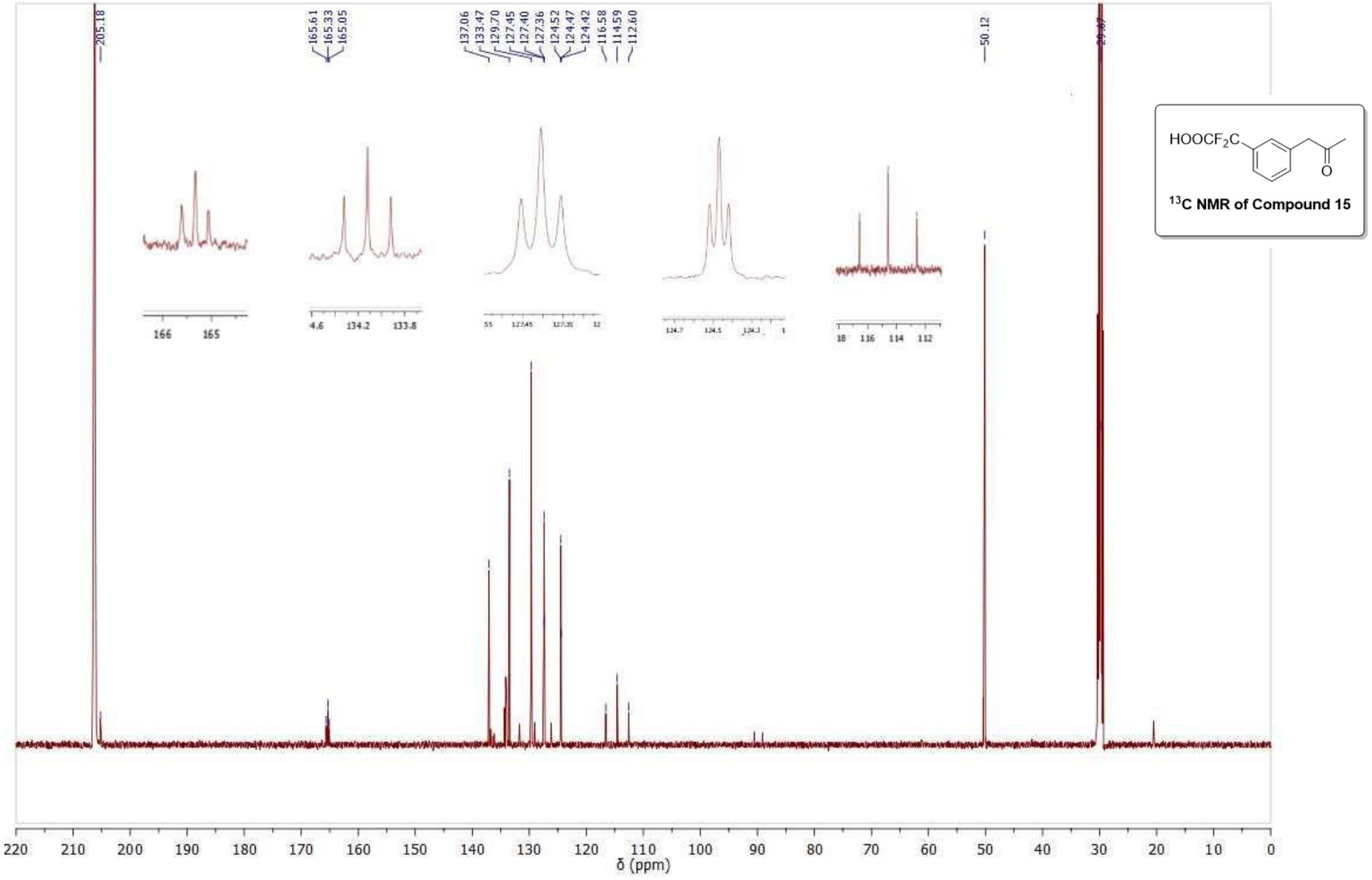
^{13}C NMR of Compound 14

*Inseparable mixture of **Di- and Mono-fluorinated products***

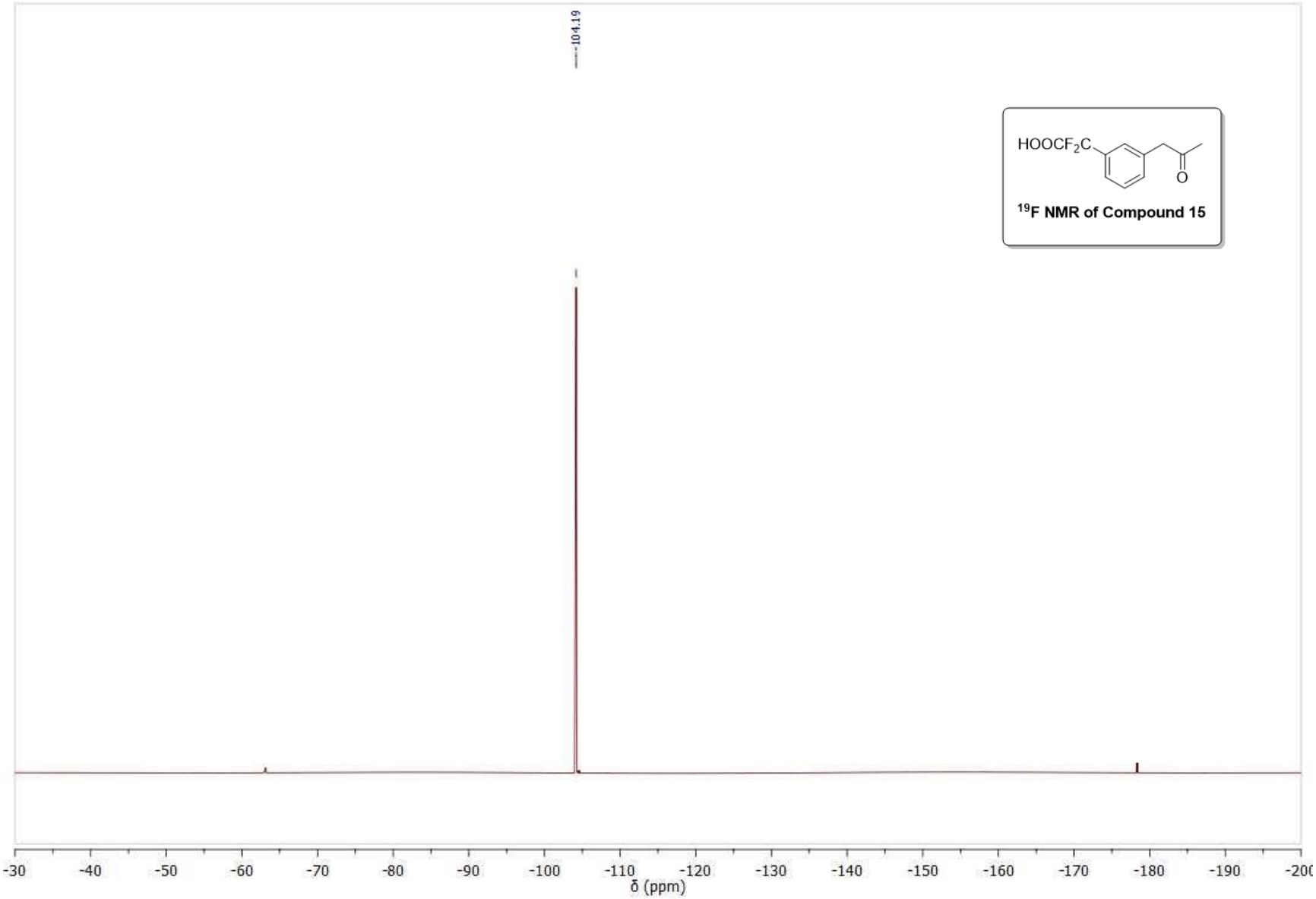


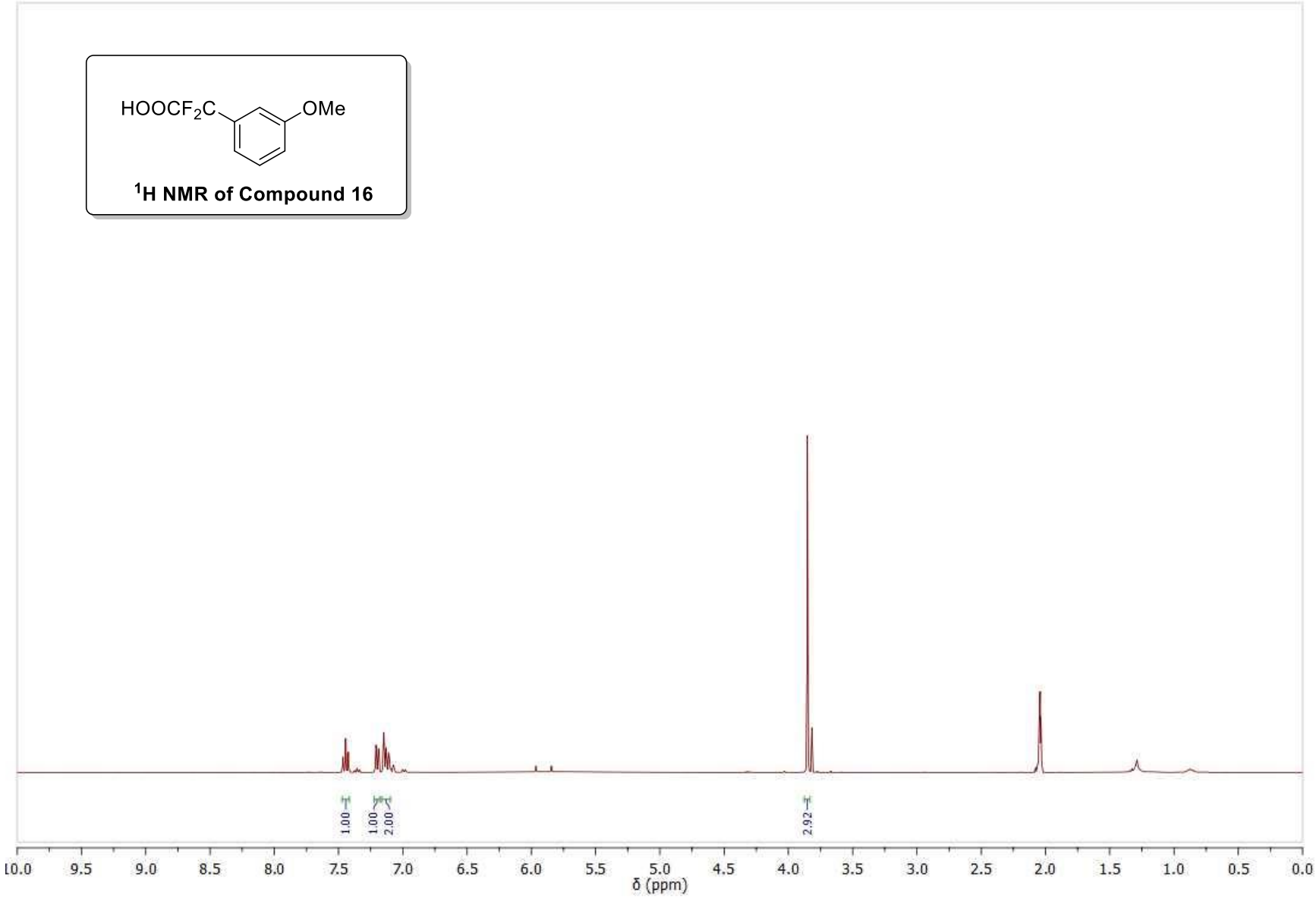
*Inseparable mixture of **Di- and Mono-fluorinated products***

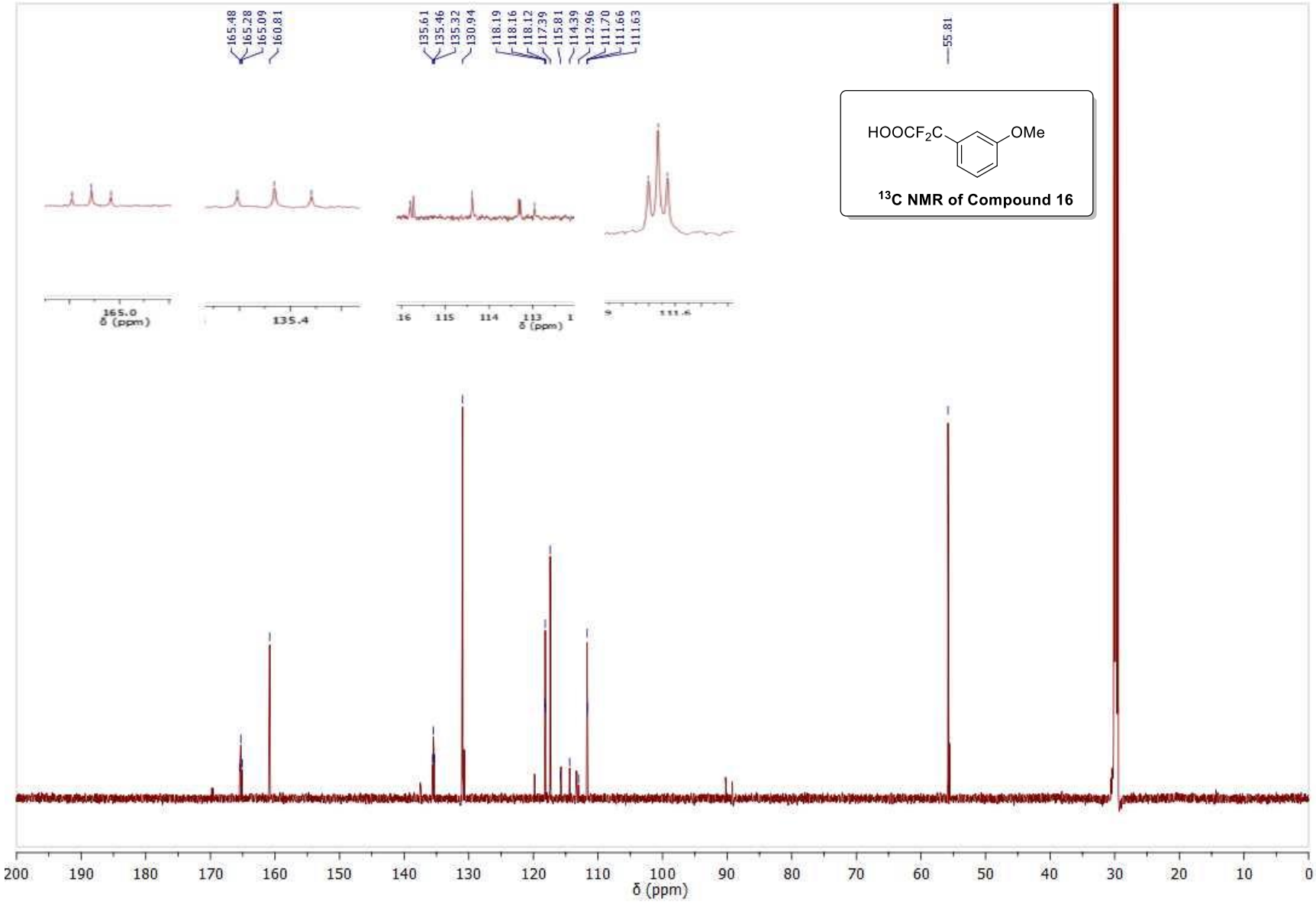

7.53
7.52
7.49
7.48
7.46
7.42
7.40
3.90
2.17
HOOCF2C
O
1H NMR of Compound 15
3.00
1.18
1.96
2.81
δ (ppm)

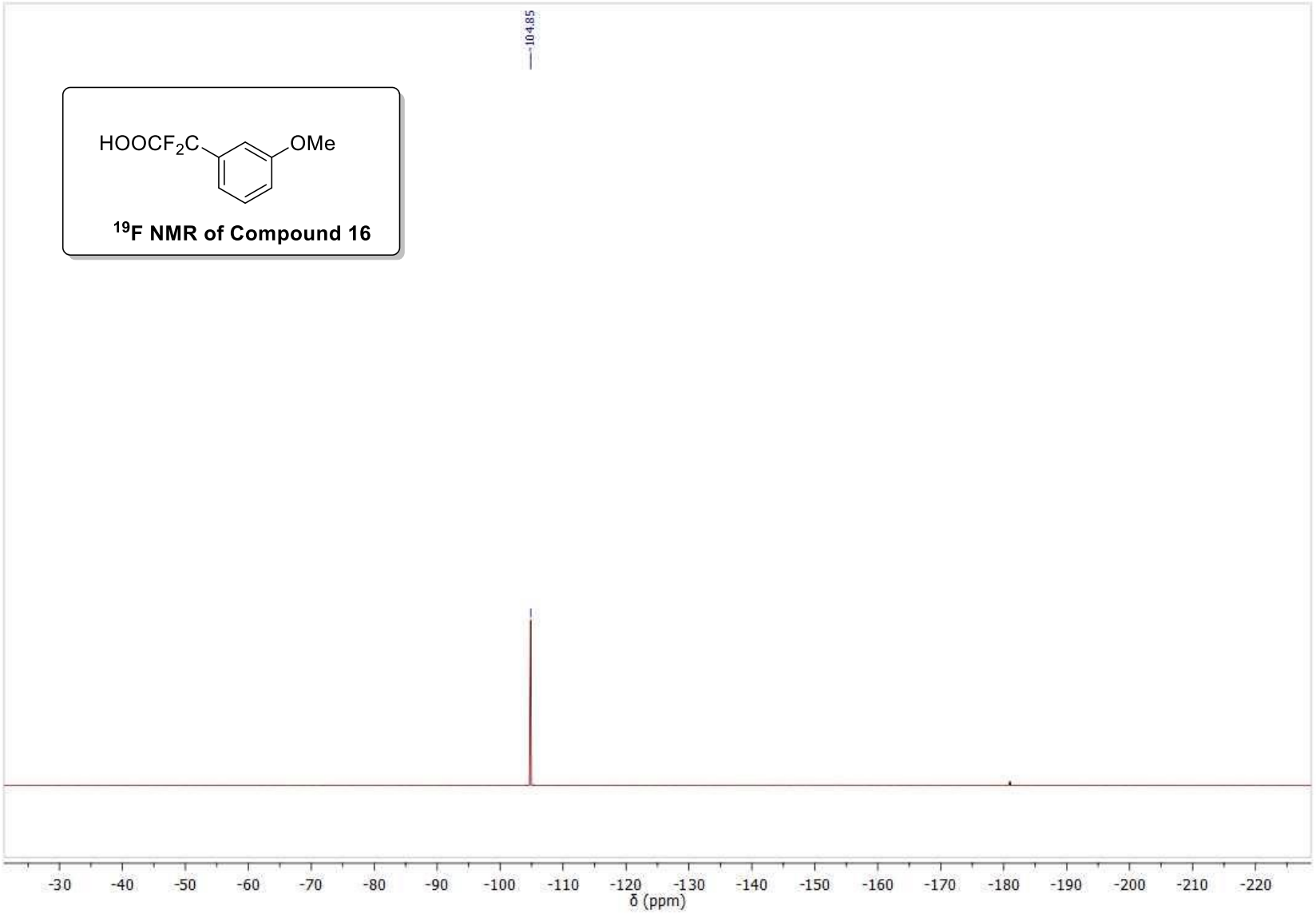


^{13}C NMR of Compound 15

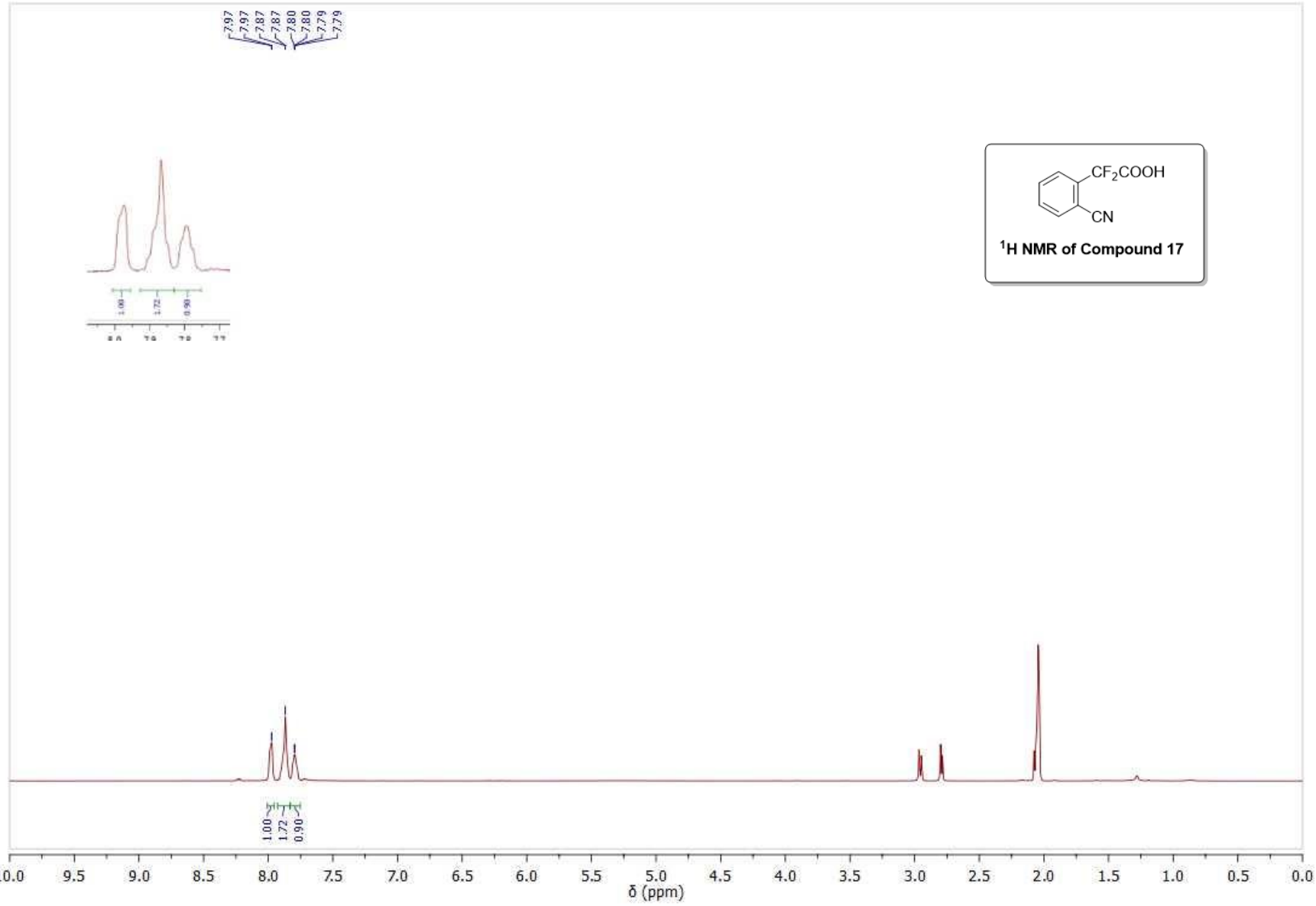

-104.19
HOOCF2C
O
19F NMR of Compound 15
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
δ (ppm)

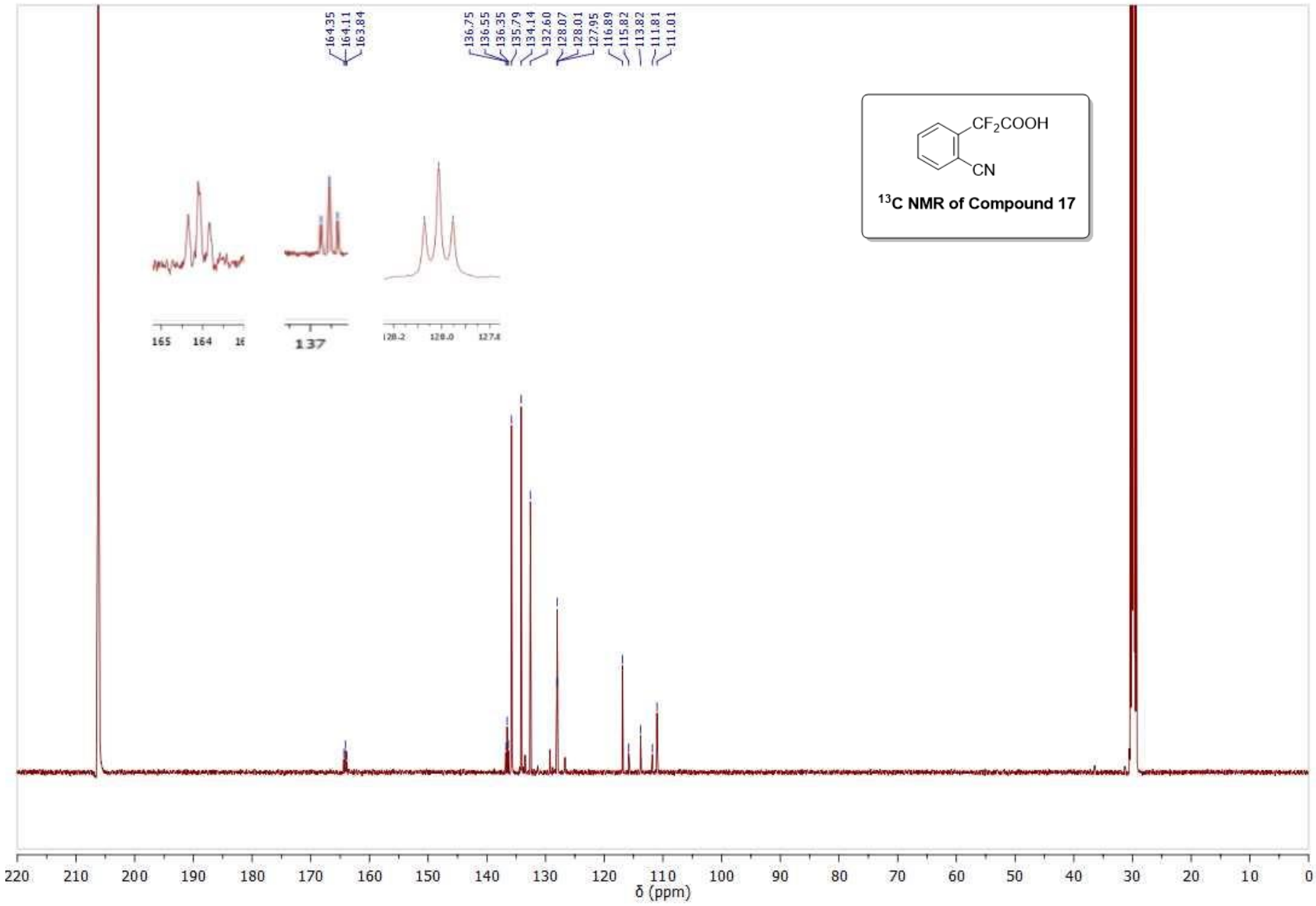

HOOCF2C
OMe
1H NMR of Compound 16
1.00
1.00
2.00
2.92
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

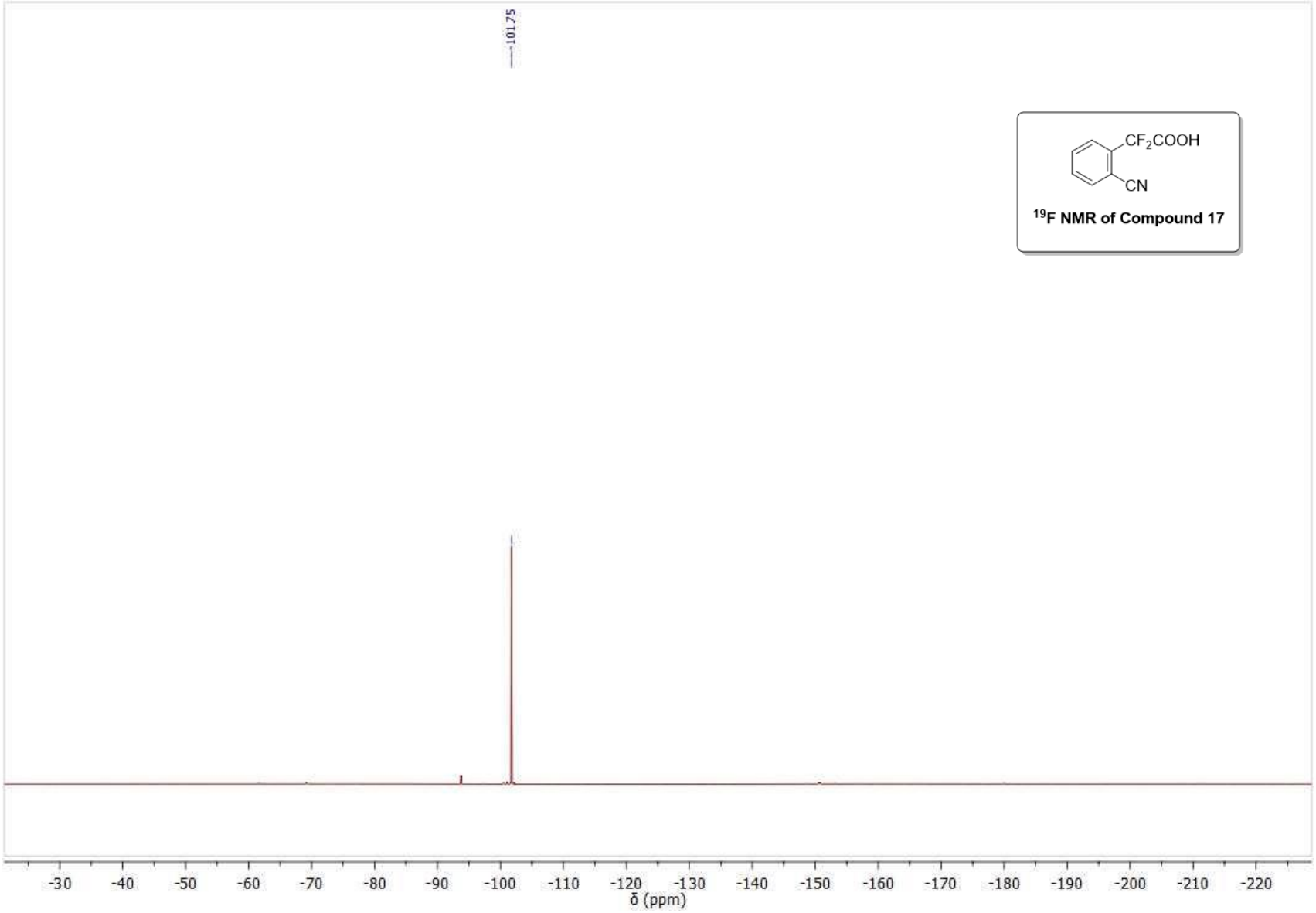

165.48
165.28
165.09
160.81
135.61
135.46
135.32
130.94
118.19
118.16
118.12
117.39
115.81
114.39
112.96
111.70
111.66
111.63
55.81
HOOCF2C
OMe
13C NMR of Compound 16
165.0
δ (ppm)
135.4
δ (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
δ (ppm)

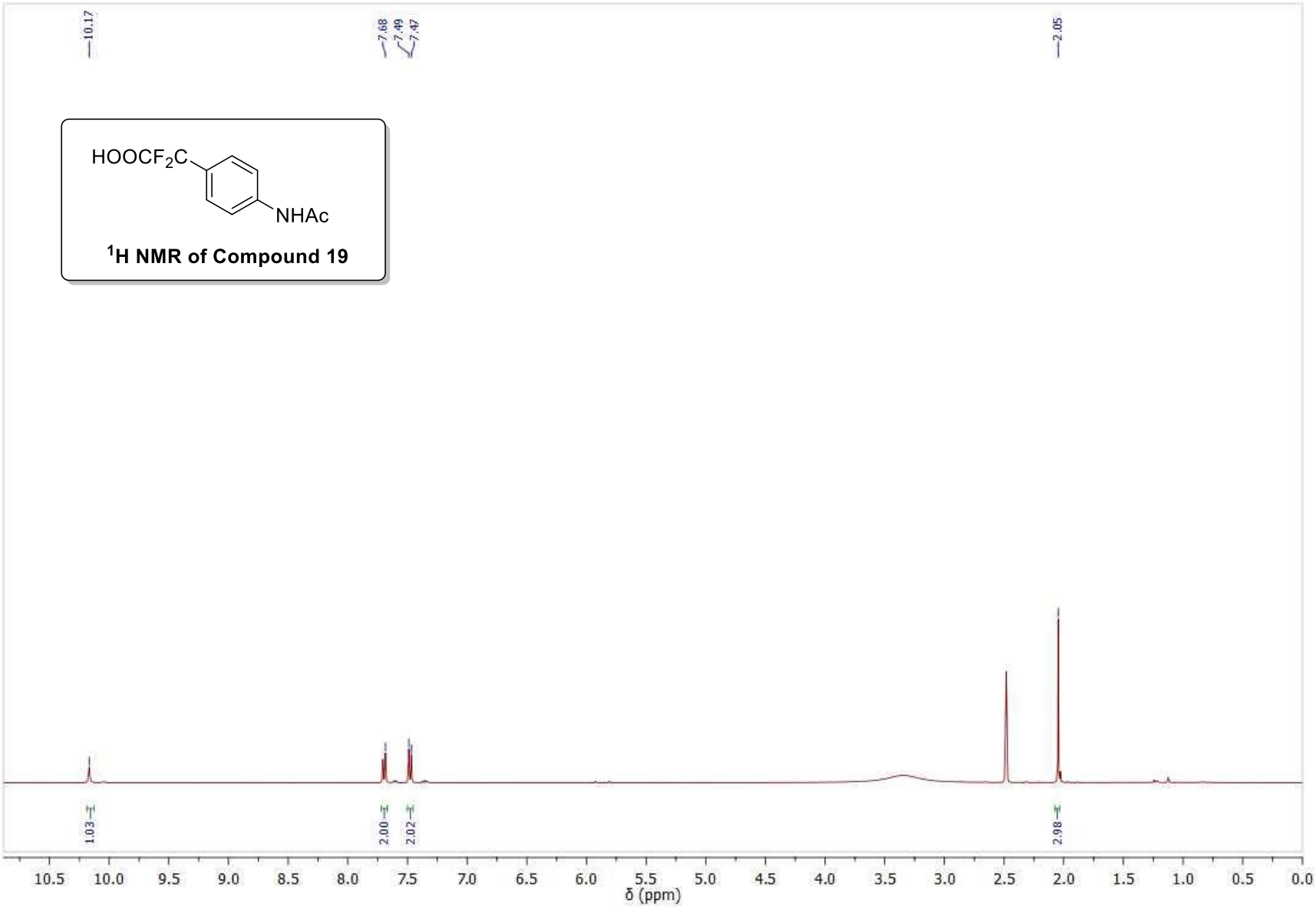


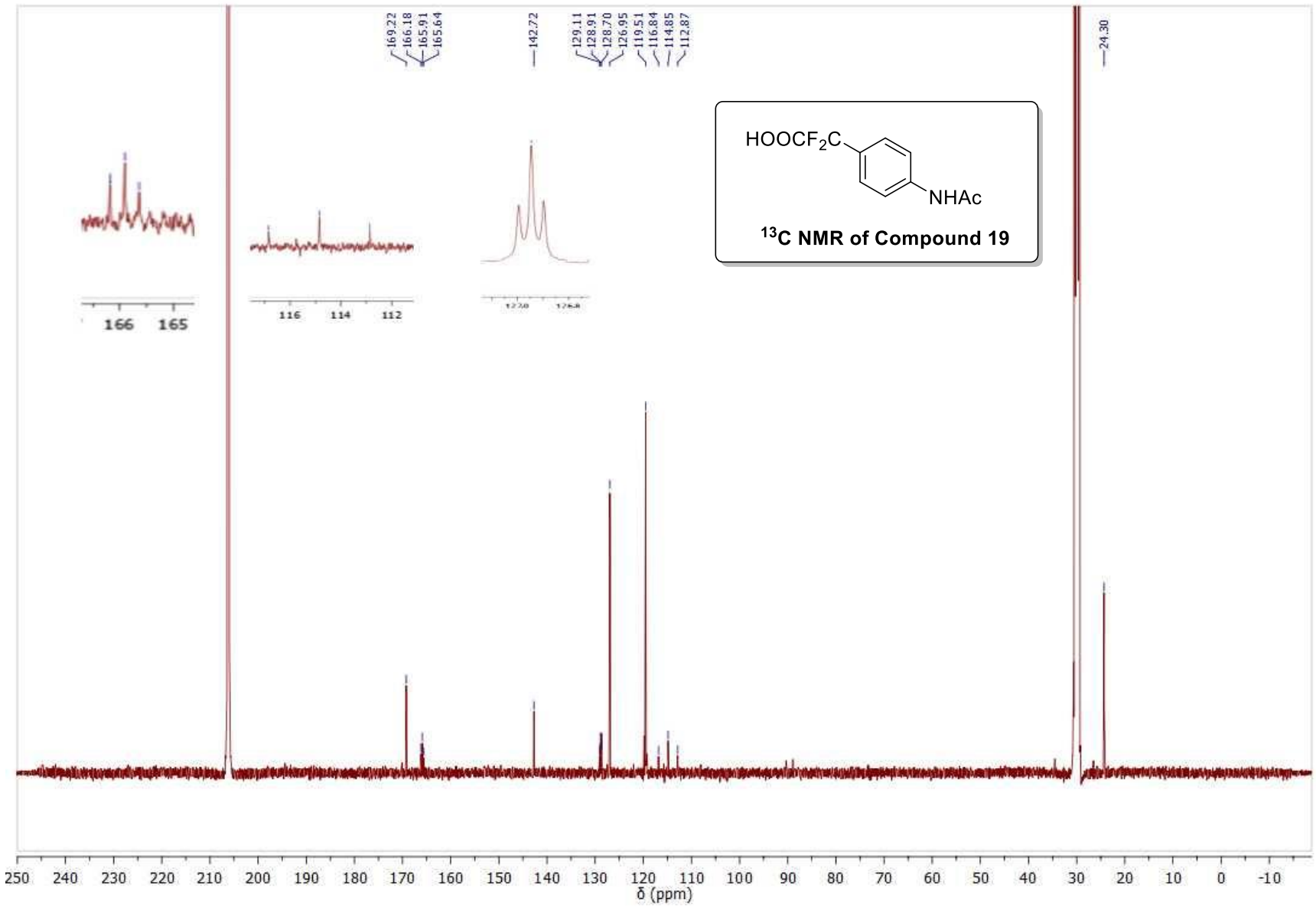
^{19}F NMR of Compound 16

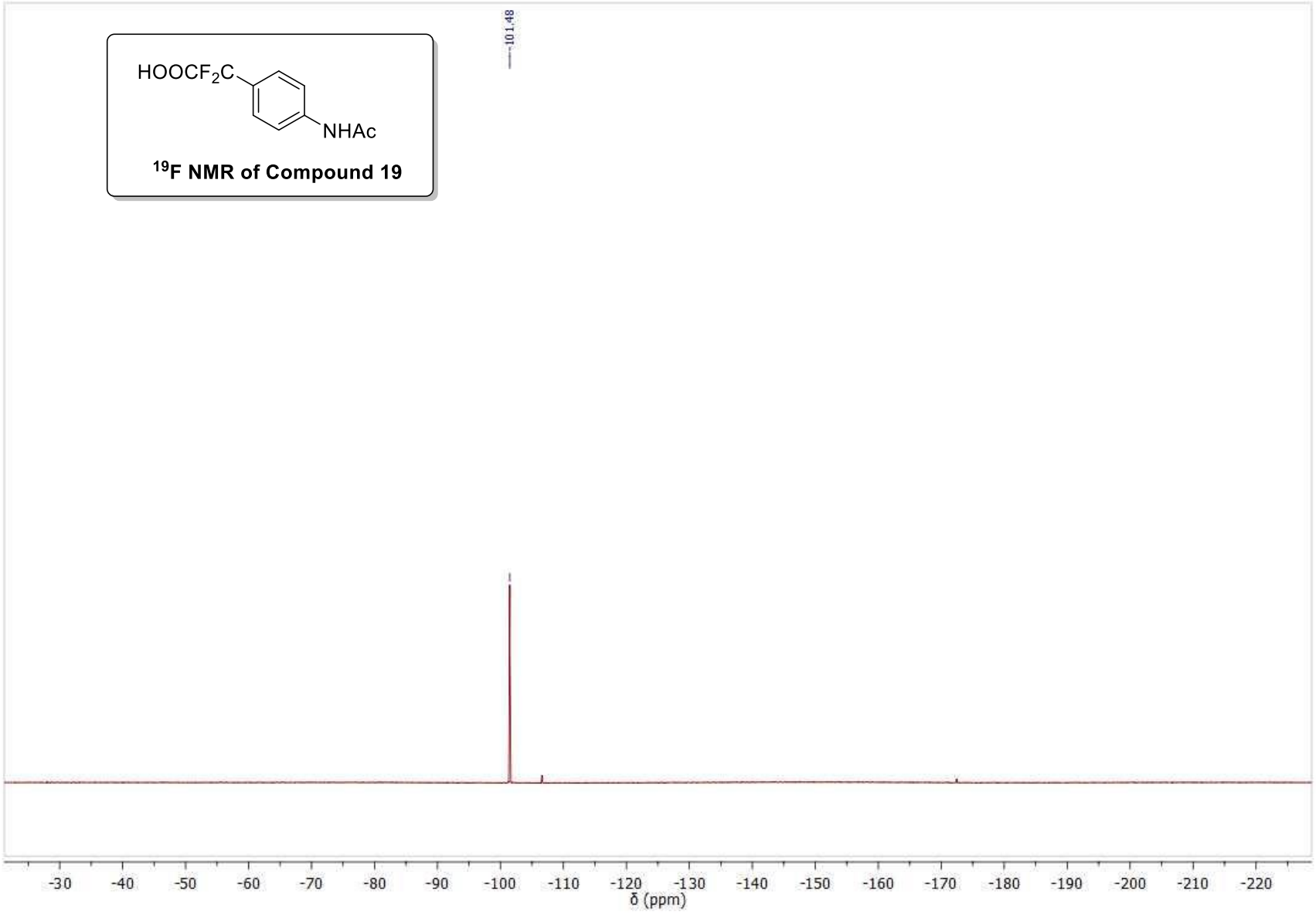

7.97
7.97
7.87
7.87
7.80
7.80
7.79
7.79
CF2COOH
CN
1H NMR of Compound 17
1.00
1.72
0.90
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

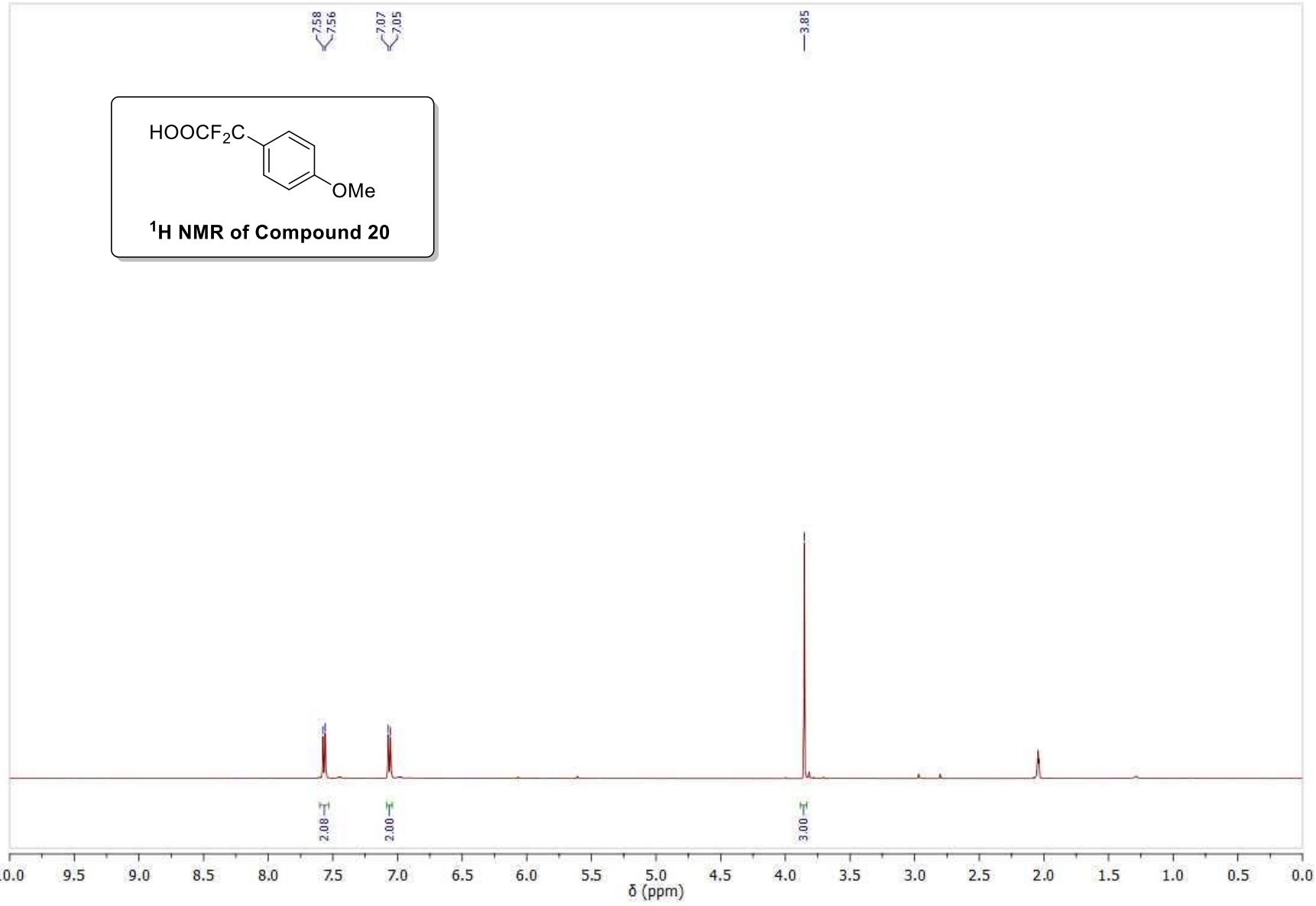

164.35
164.11
163.84
136.75
136.55
136.35
135.79
134.14
132.60
128.07
128.01
127.95
116.89
115.82
113.82
111.81
111.01
CF2COOH
CN
13C NMR of Compound 17
165
164
137
δ (ppm)

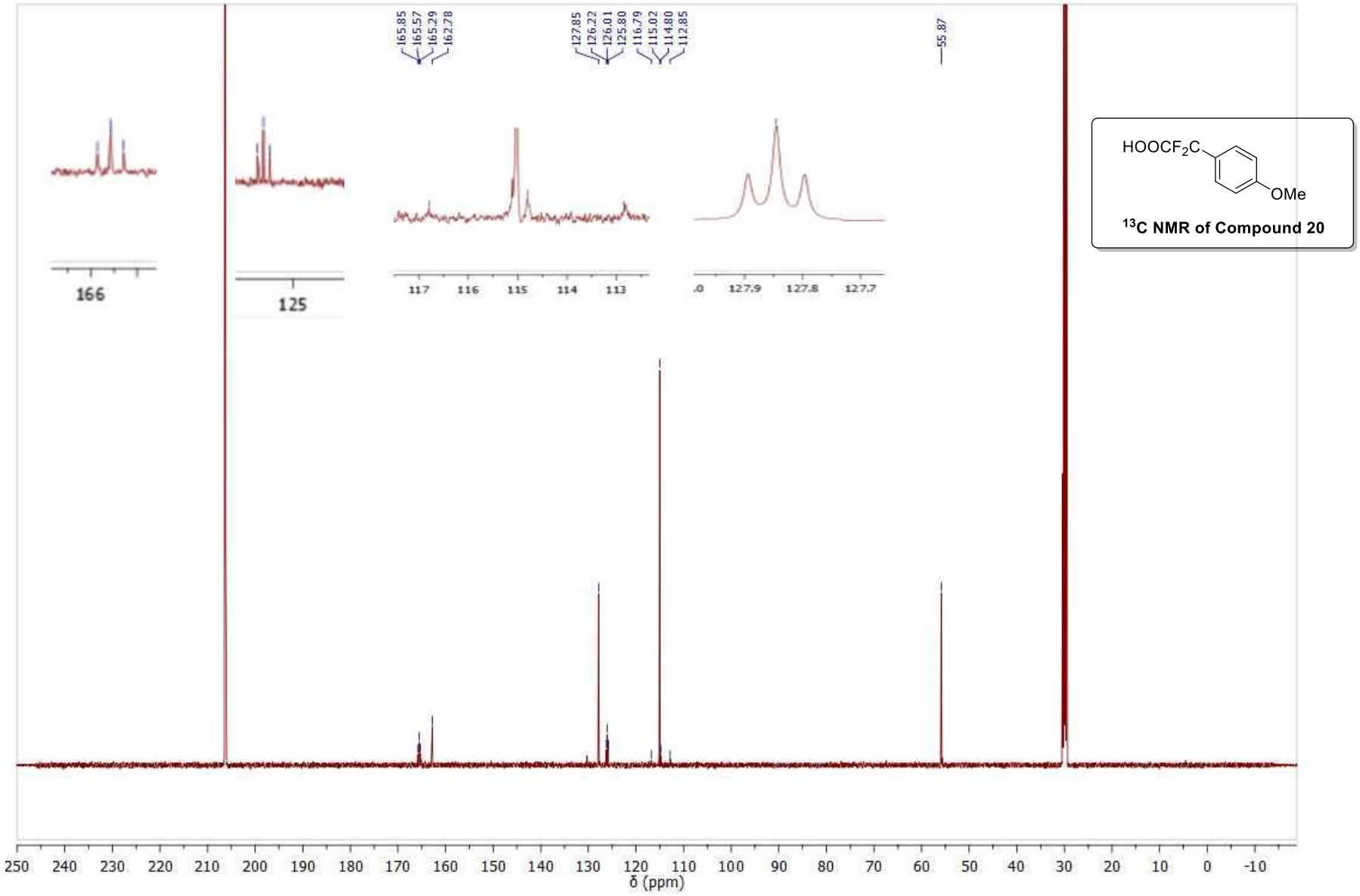

-101.75
CF2COOH
CN
19F NMR of Compound 17
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

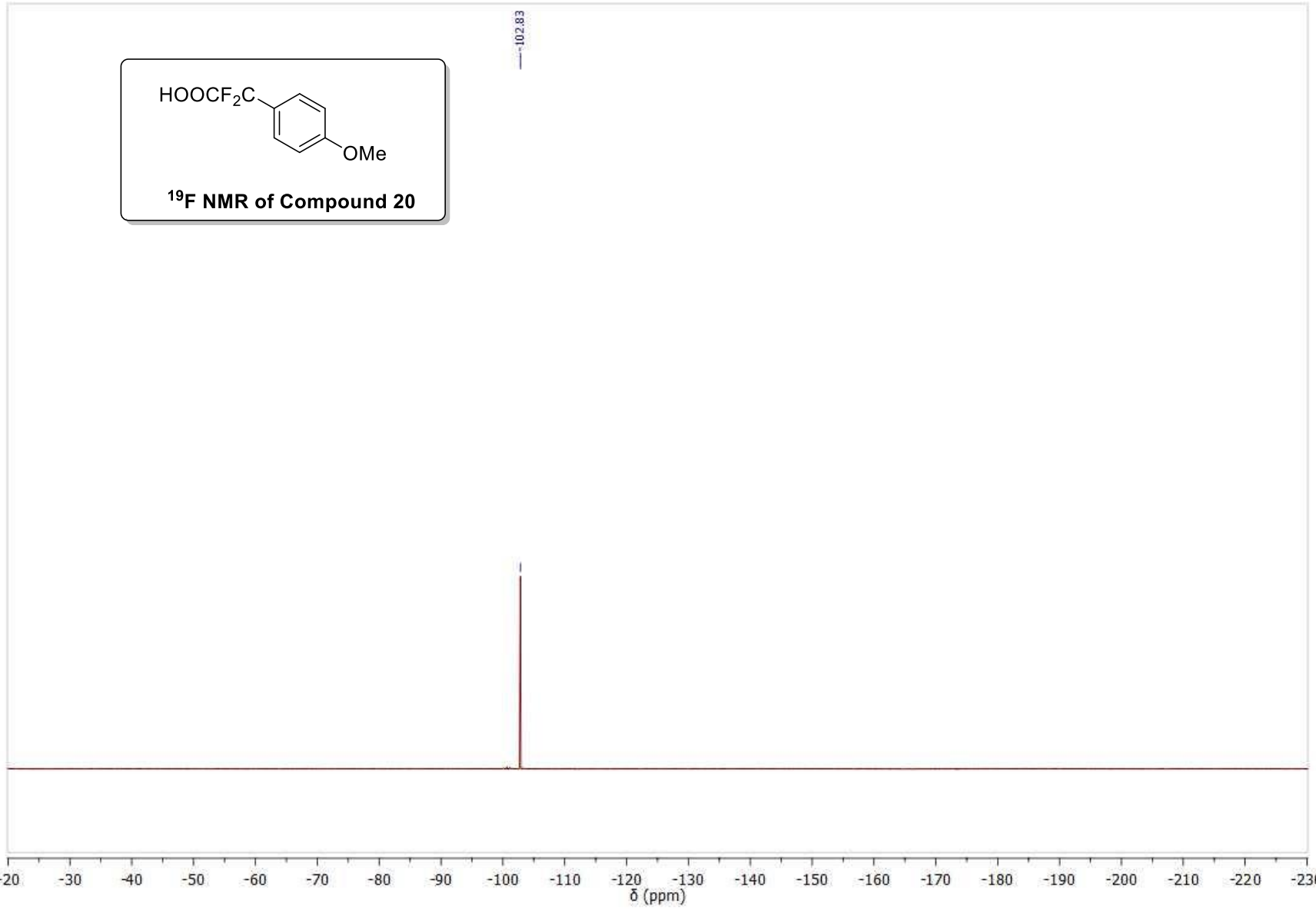

10.17
7.68
7.49
7.47
2.05
HOOCF2C
NHAc
1H NMR of Compound 19
1.03
2.00
2.02
2.98
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

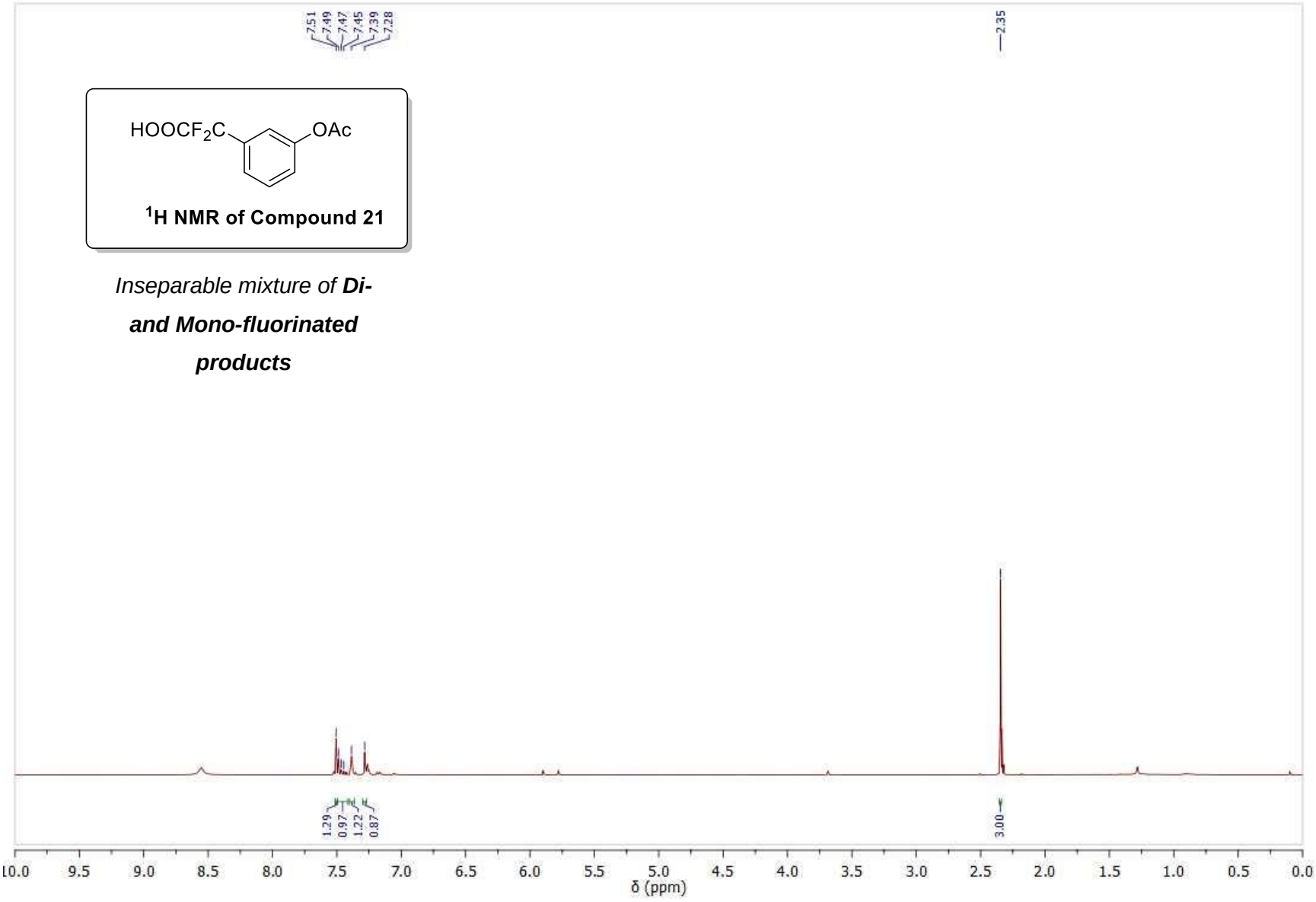

169.22
166.18
165.91
165.64
142.72
129.11
128.91
128.70
126.95
119.51
116.84
114.85
112.87
24.30
HOOCF2C
NHAc
13C NMR of Compound 19
166
165
116
114
112
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)


HOOCF2C
NHAc
19F NMR of Compound 19
-101.48
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

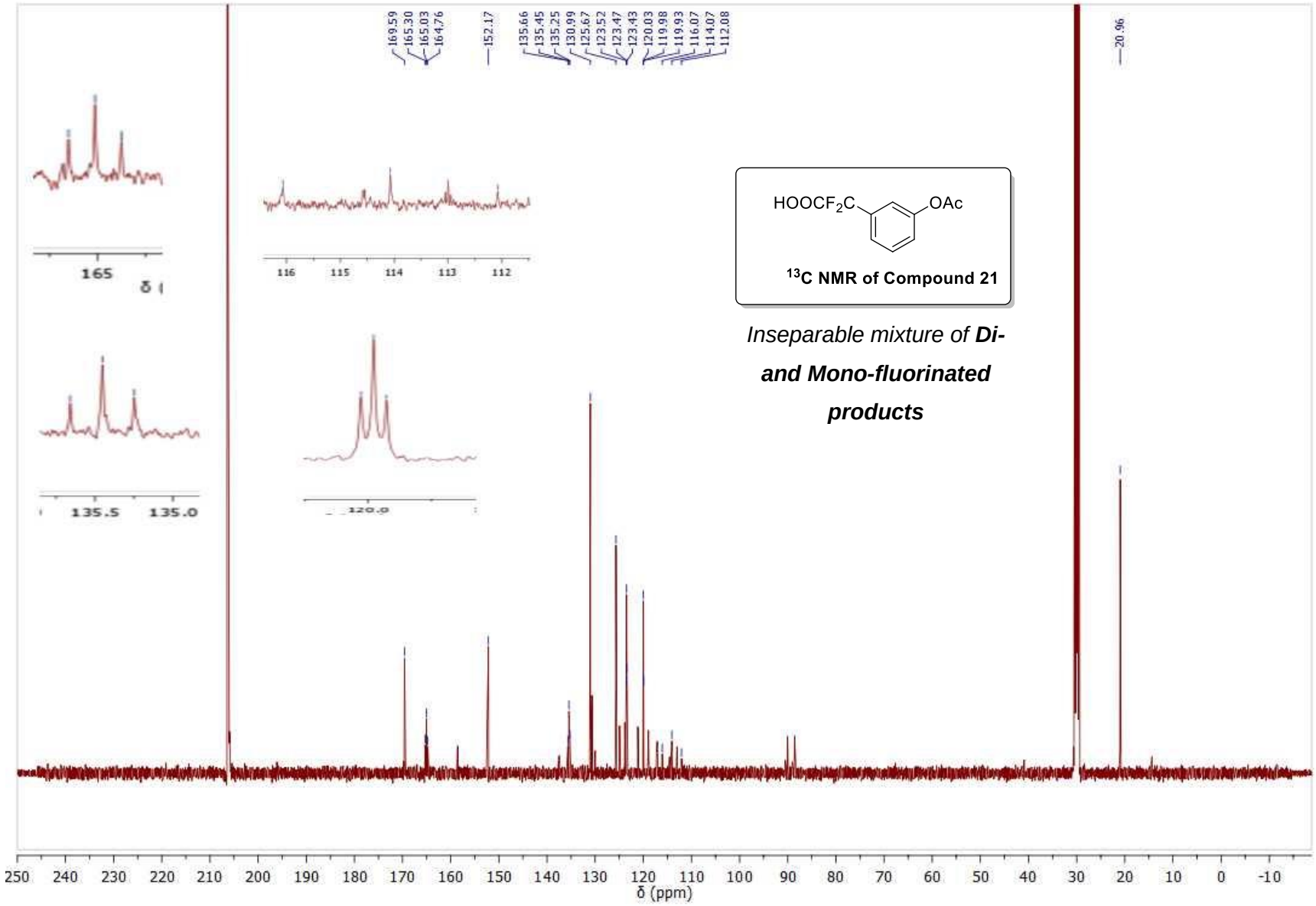

7.58
7.56
7.07
7.05
3.85
HOOCF2C
OMe
1H NMR of Compound 20
2.08
2.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

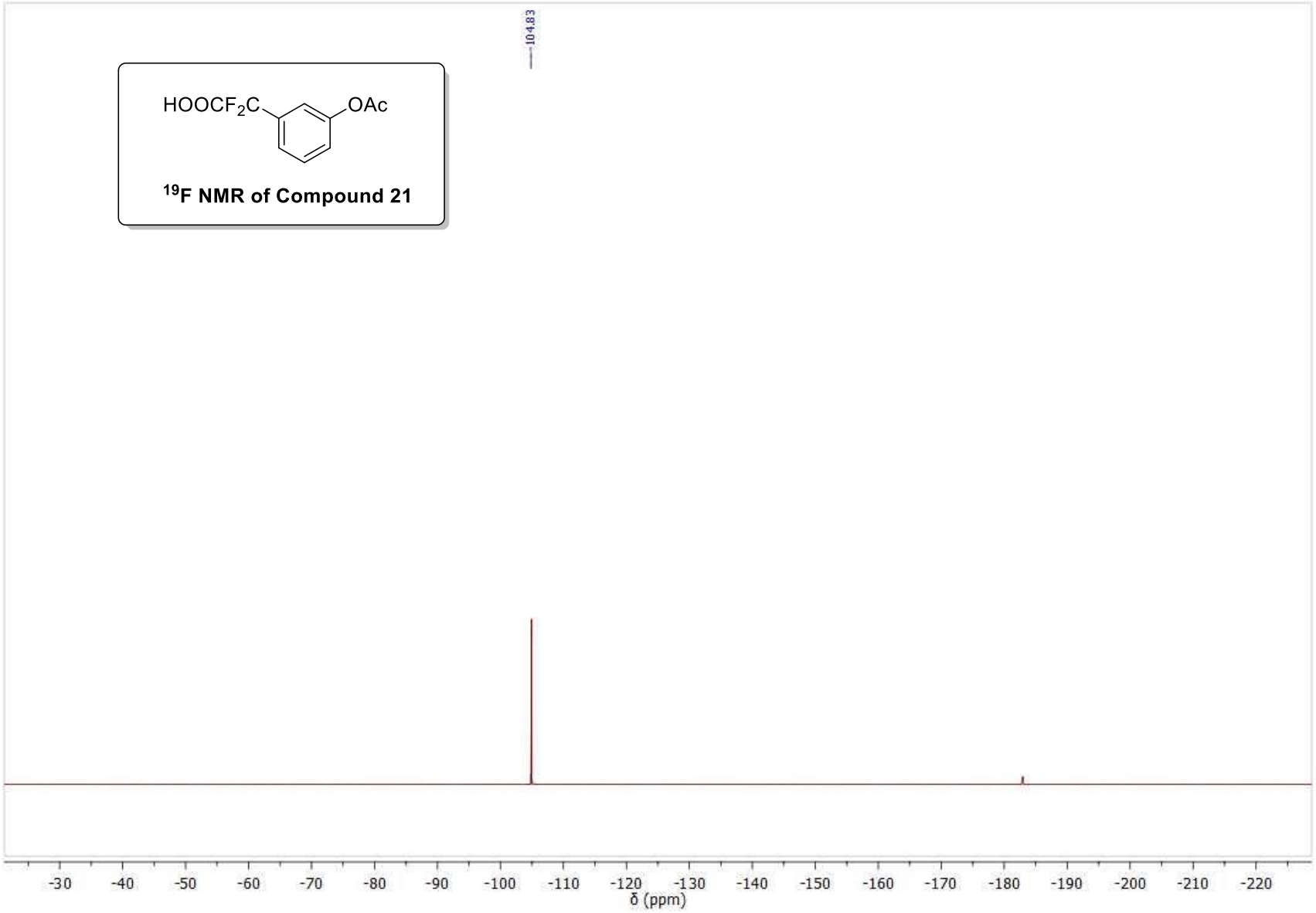

165.85
165.57
165.29
162.78
127.85
126.22
126.01
125.80
116.79
115.02
114.80
112.85
55.87
166
125
117
116
115
114
113
127.9
127.8
127.7
HOOCF2C
OMe
13C NMR of Compound 20
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

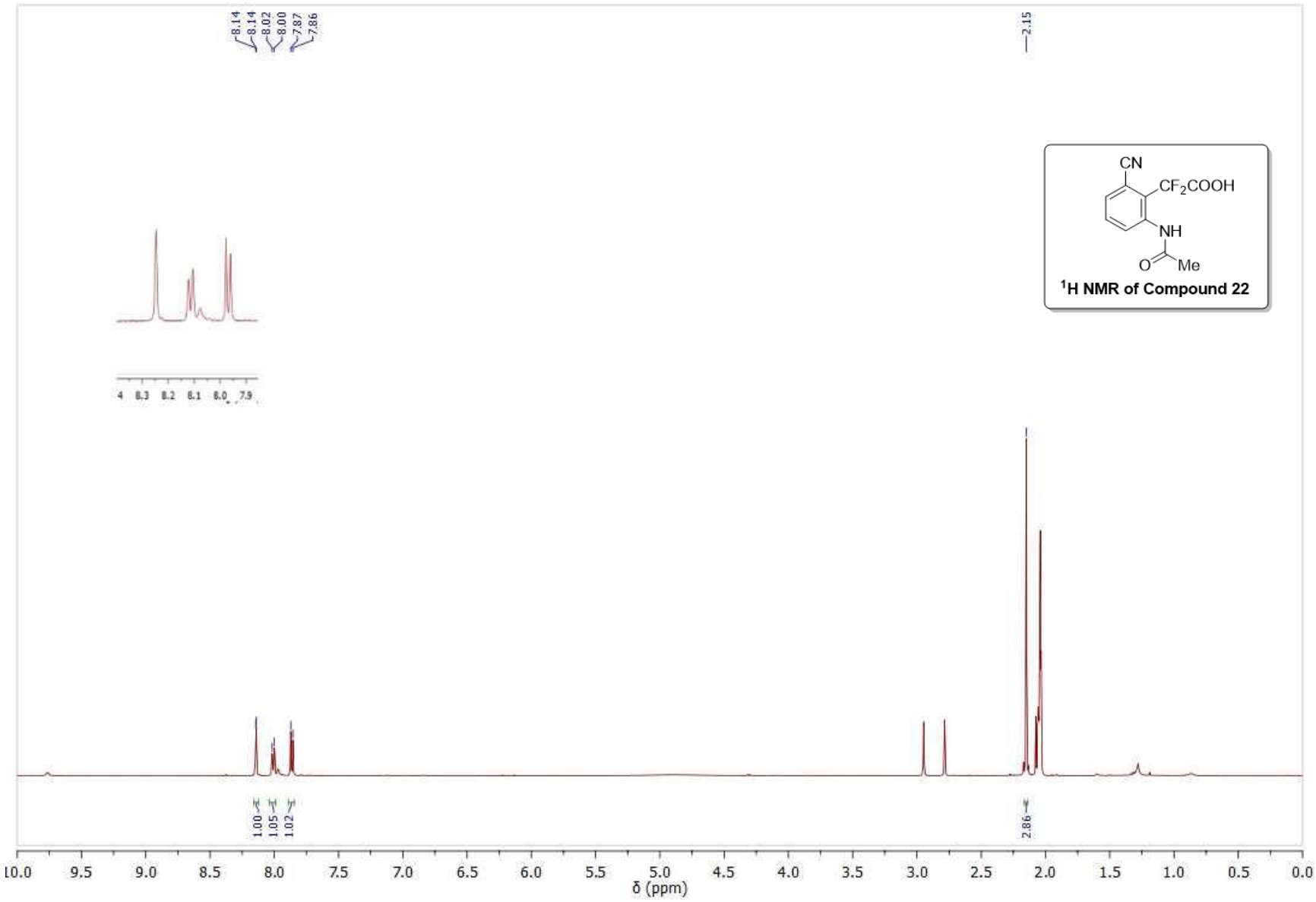

HOOCF2C
OMe
19F NMR of Compound 20
-102.83
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

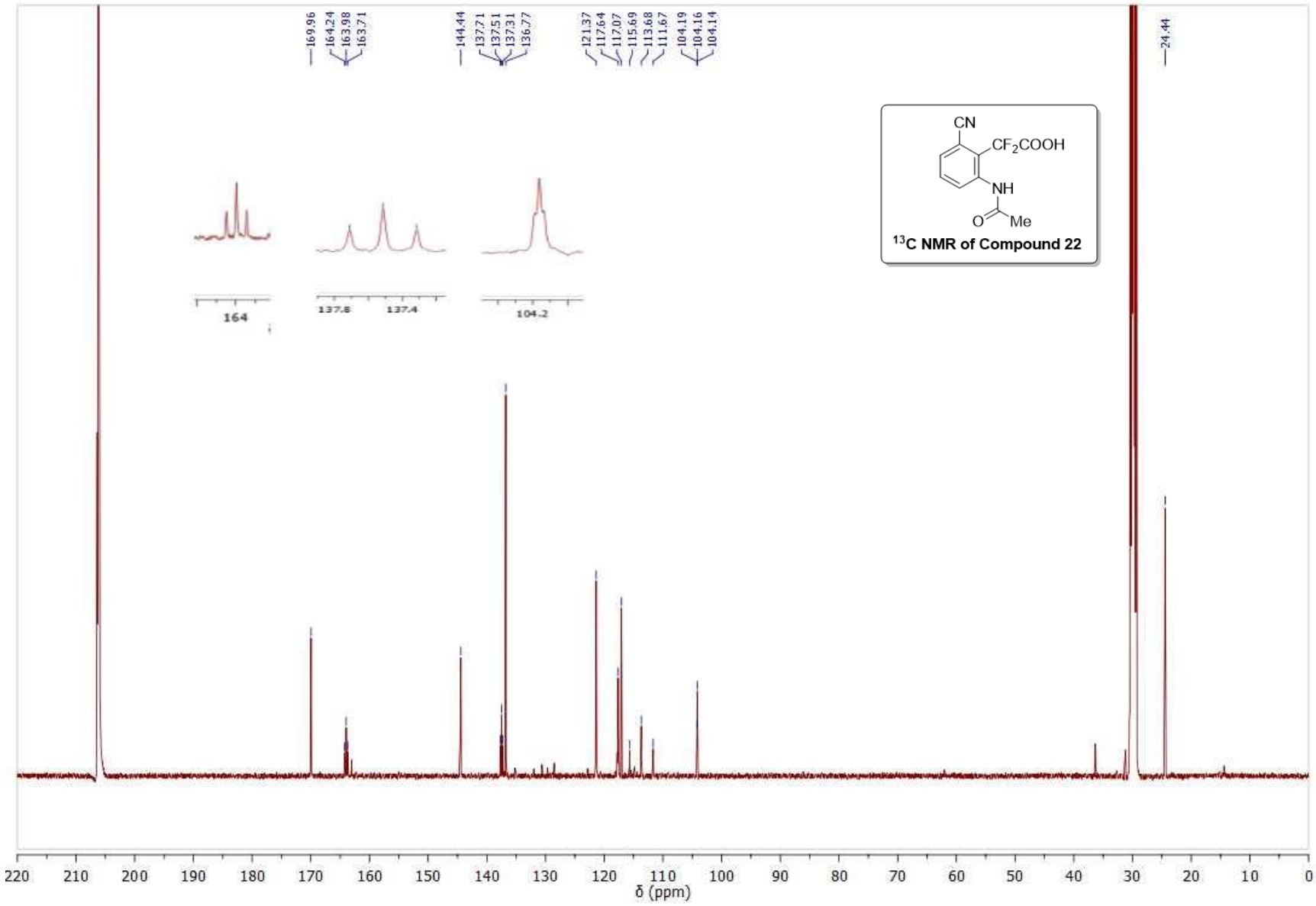


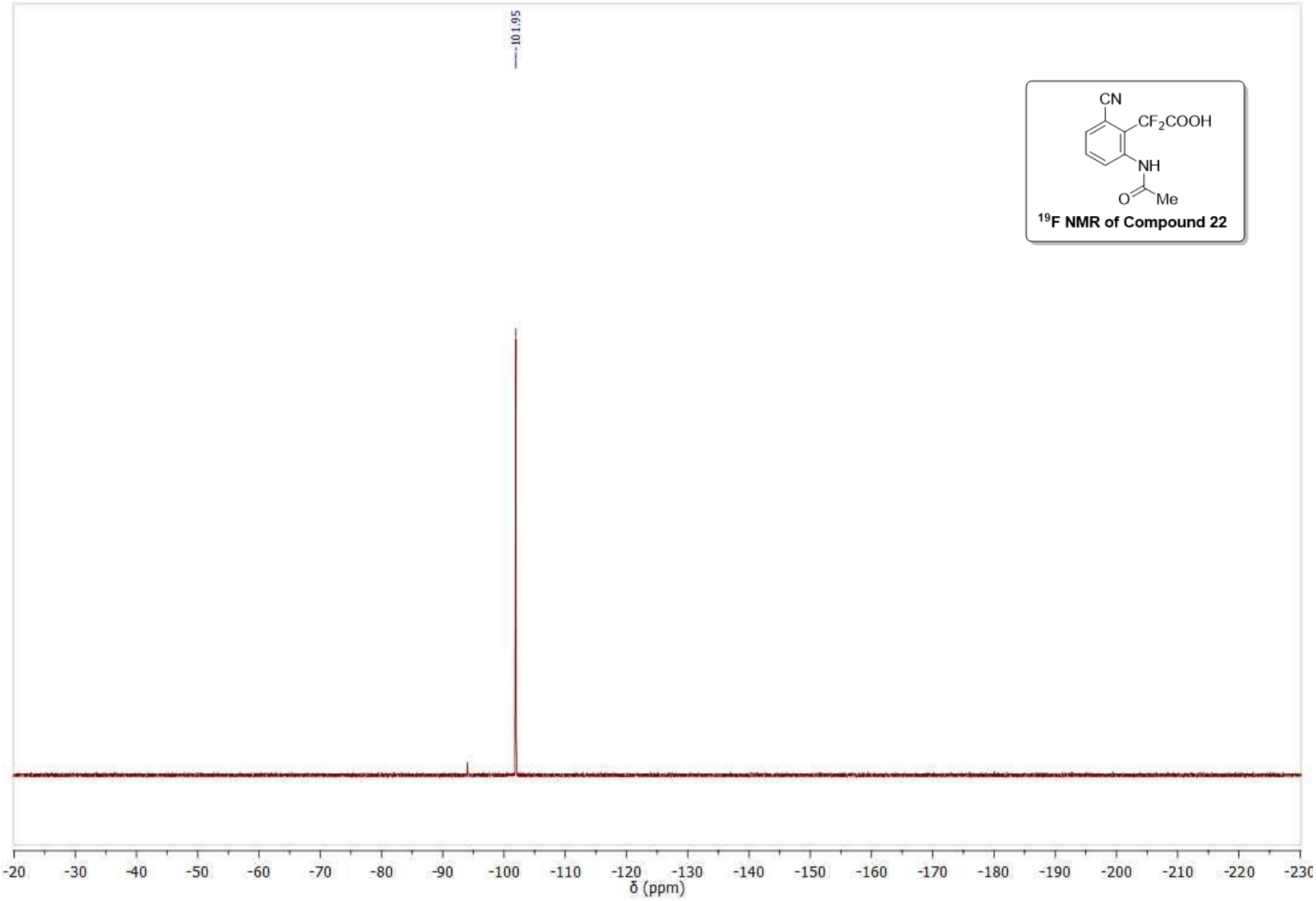
Inseparable mixture of ***Di- and Mono-fluorinated products***

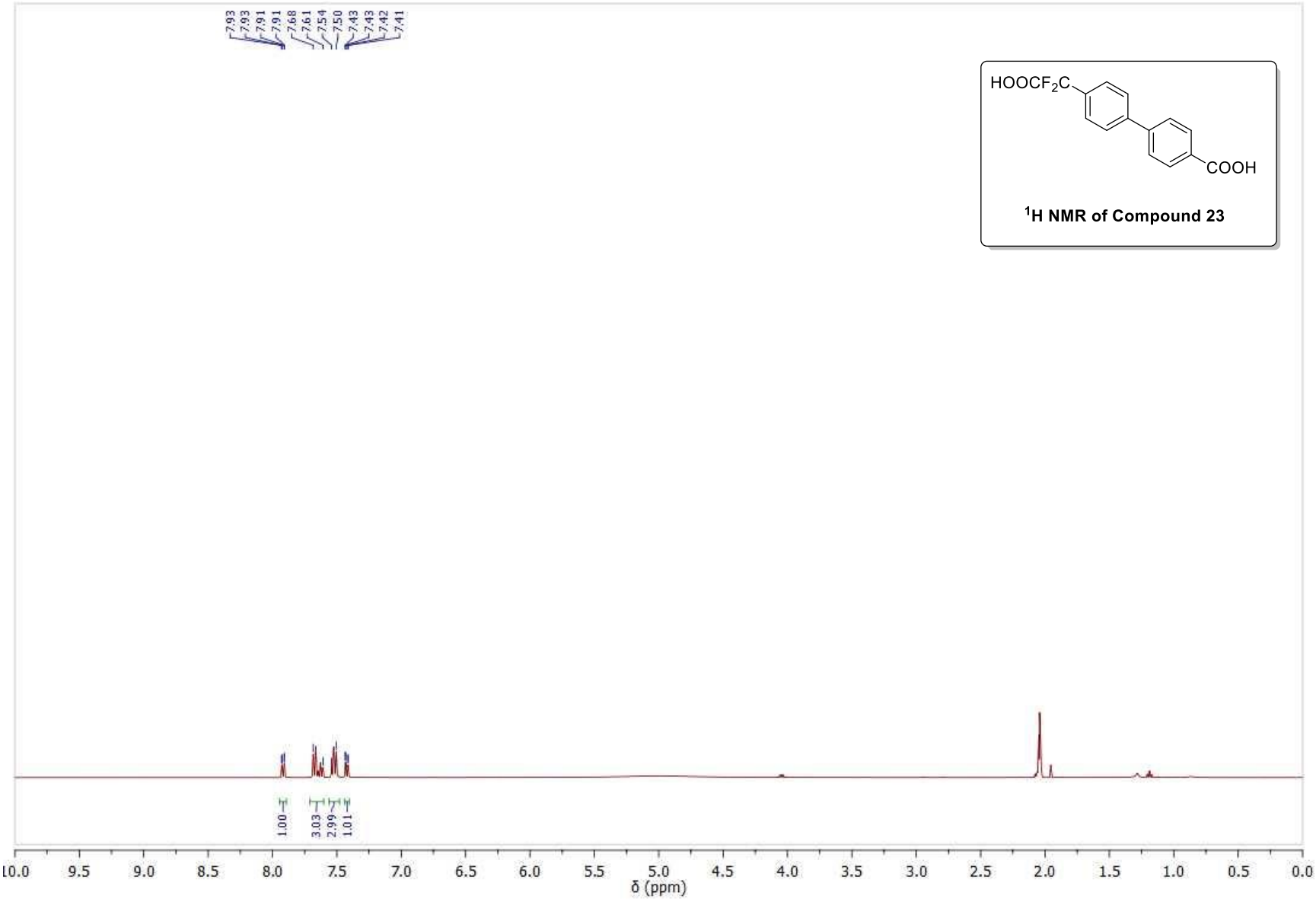

169.59
165.30
165.03
164.76
152.17
135.66
135.45
135.25
130.99
125.67
123.52
123.47
123.43
120.03
119.98
119.93
116.07
114.07
112.08
20.96
HOOCF2C
OAc
13C NMR of Compound 21
Inseparable mixture of Di- and Mono-fluorinated products
δ (ppm)

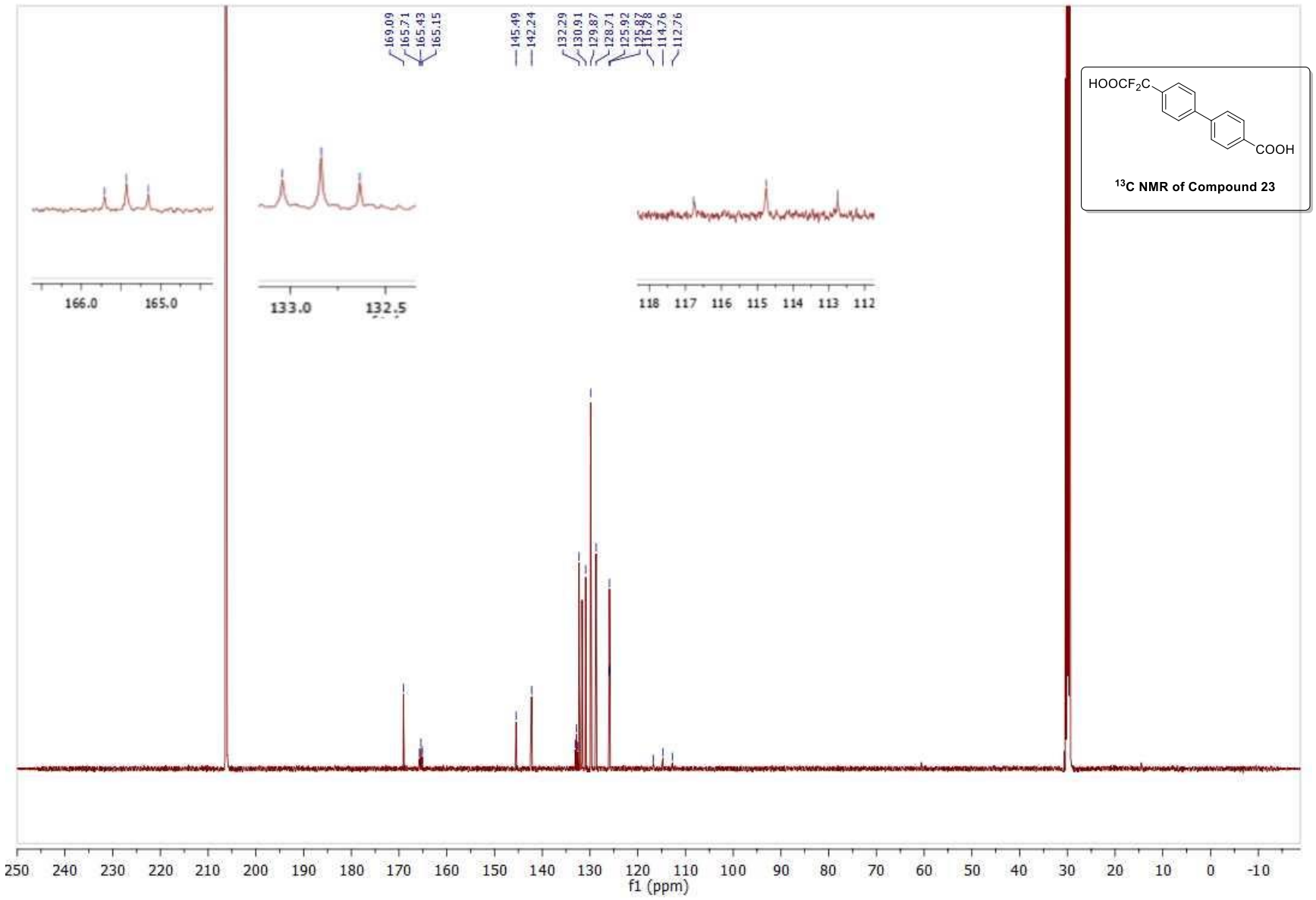

HOOCF2C
OAc
19F NMR of Compound 21
-104.83
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

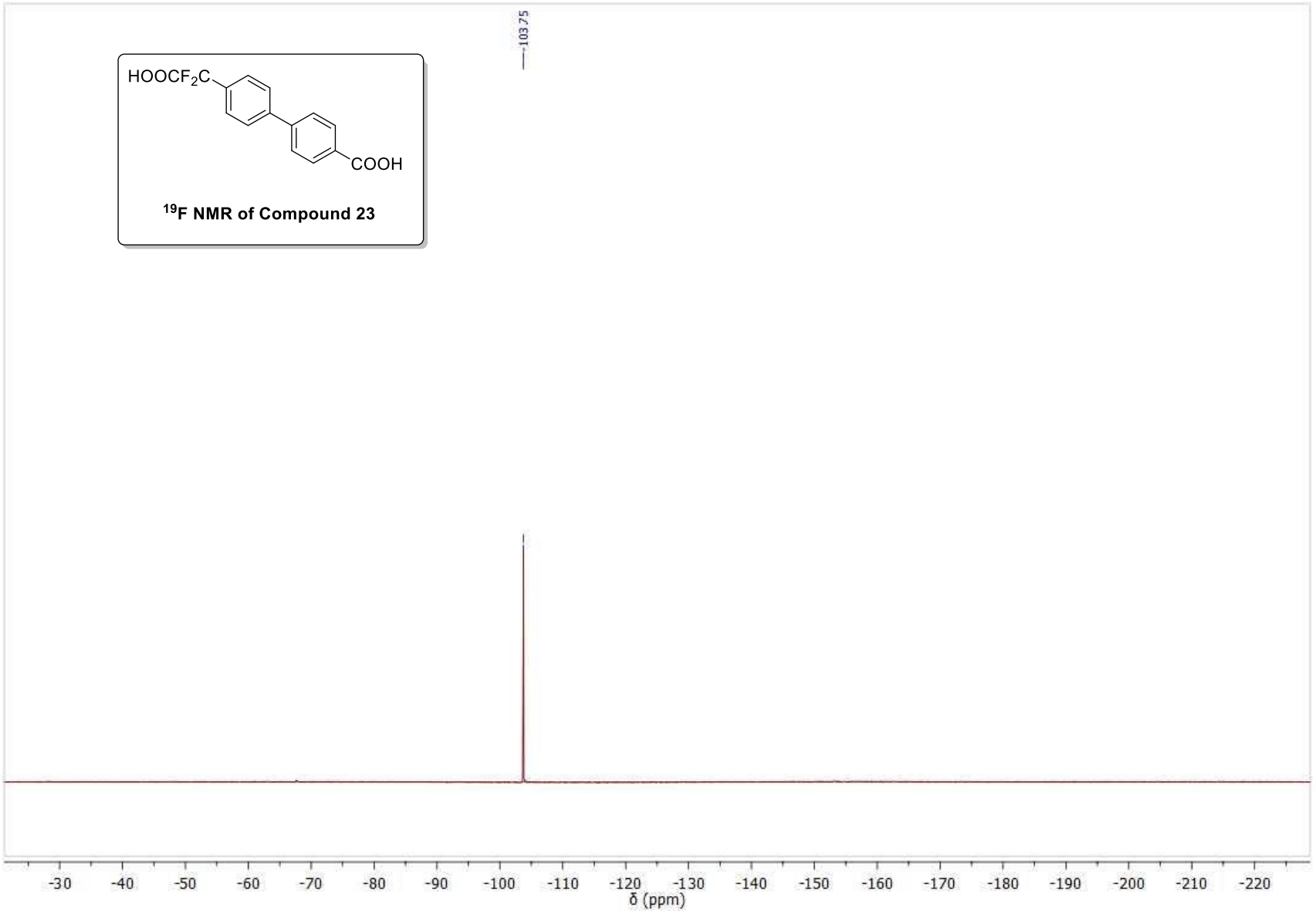

8.14
8.14
8.02
8.00
7.87
7.86
2.15
CN
CF2COOH
NH
O
Me
1H NMR of Compound 22
1.00
1.05
1.02
2.86
δ (ppm)


169.96
164.24
163.98
163.71
144.44
137.71
137.51
137.31
136.77
121.37
117.64
117.07
115.69
113.68
111.67
104.19
104.16
104.14
24.44
CN
CF2COOH
NH
O
Me
13C NMR of Compound 22
164
137.8
137.4
104.2
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
δ (ppm)

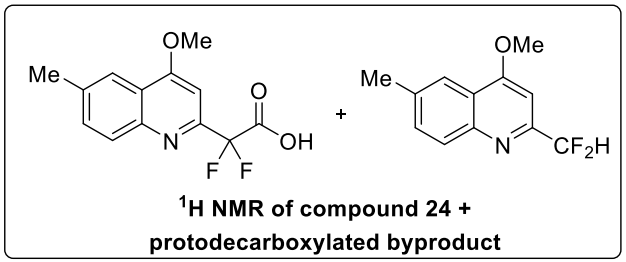

-101.95
CN
CF2COOH
NH
O
Me
19F NMR of Compound 22
-20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
δ (ppm)


7.93
7.93
7.91
7.91
7.68
7.61
7.54
7.50
7.43
7.43
7.42
7.41
HOOCF2C
COOH
1H NMR of Compound 23
1.00
3.03
2.99
1.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

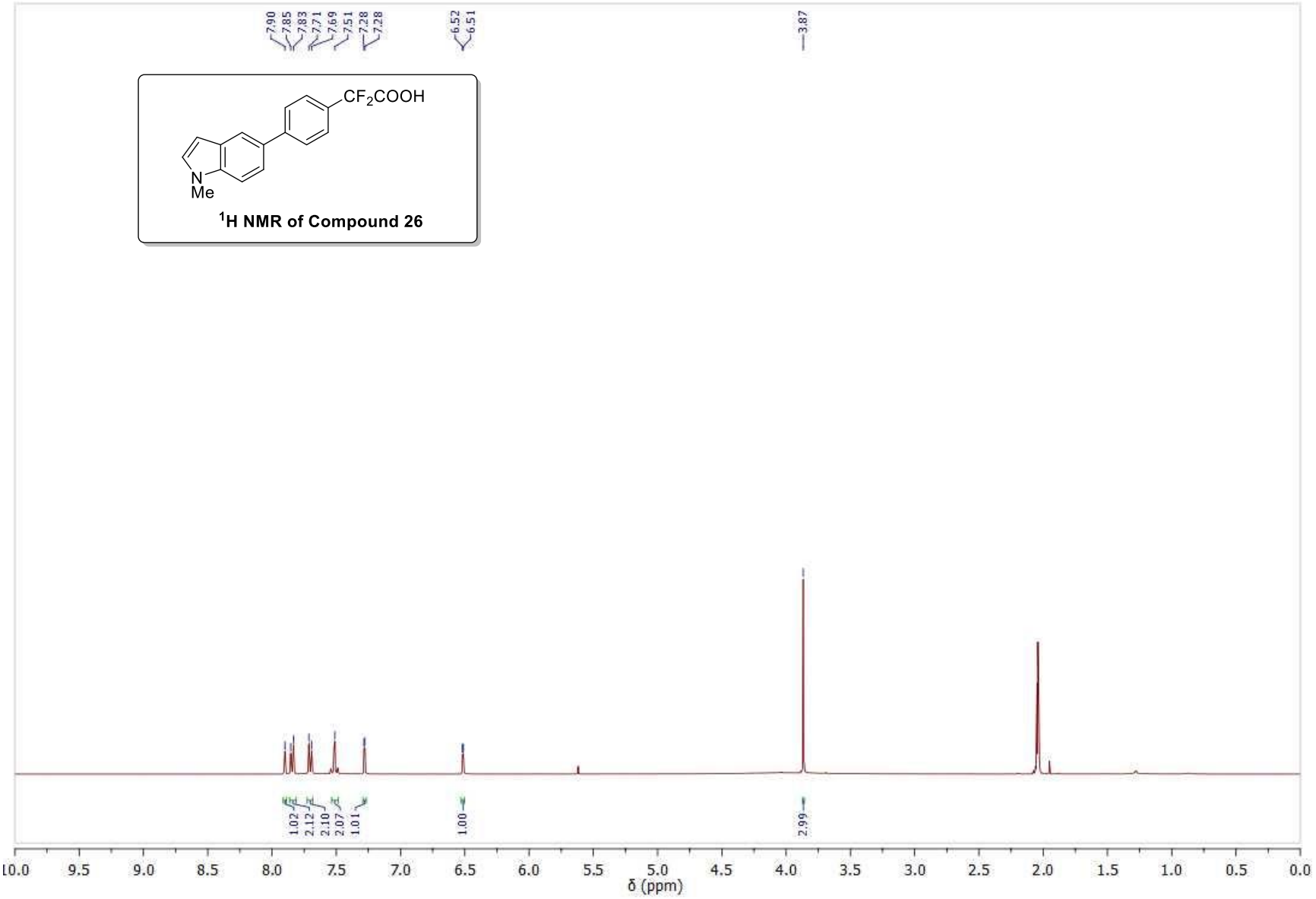

169.09
165.71
165.43
165.15
145.49
142.24
132.29
130.91
129.87
128.71
125.92
125.87
116.78
114.76
112.76
166.0
165.0
133.0
132.5
118
117
116
115
114
113
112
HOOCF2C
COOH
13C NMR of Compound 23
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

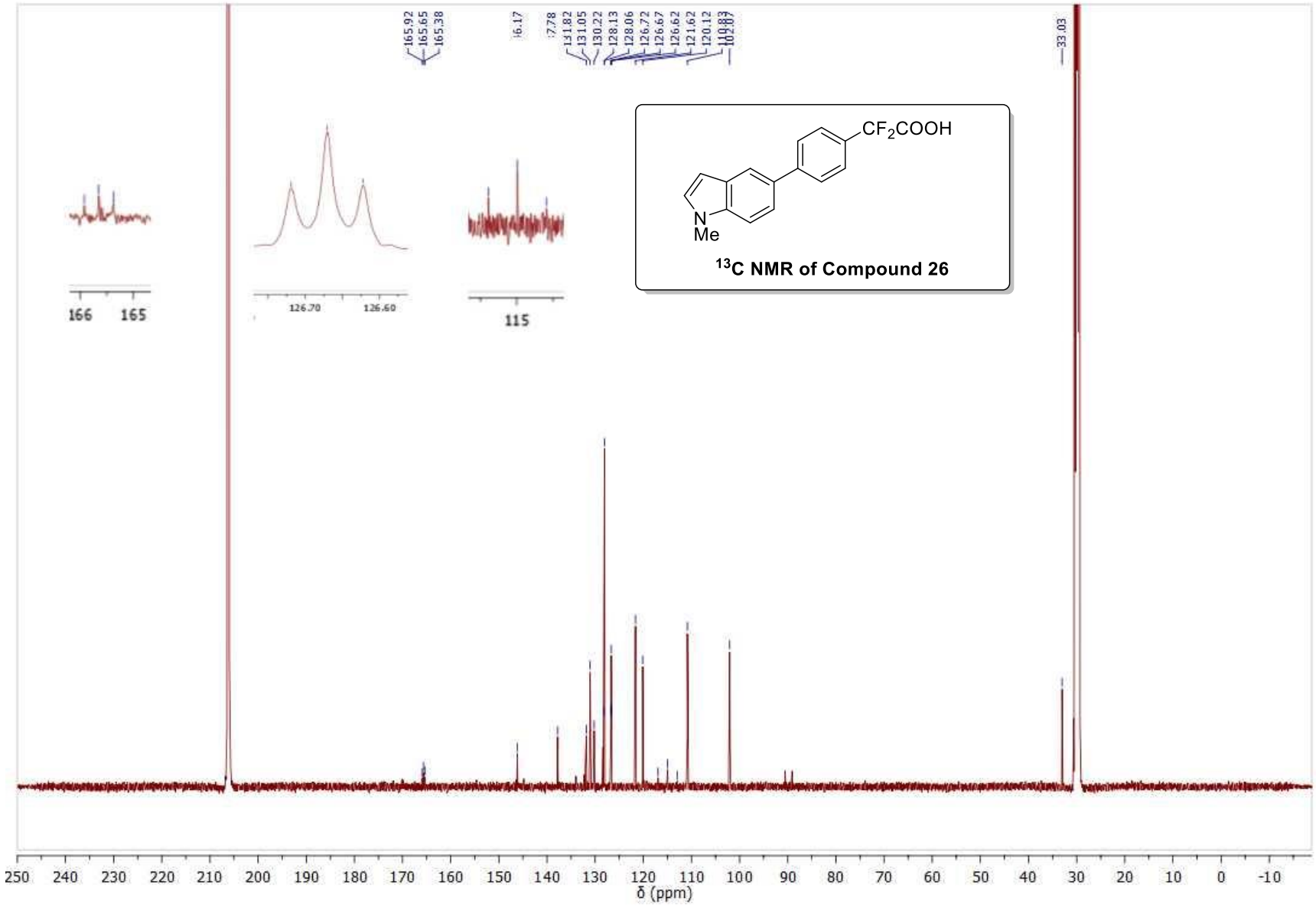


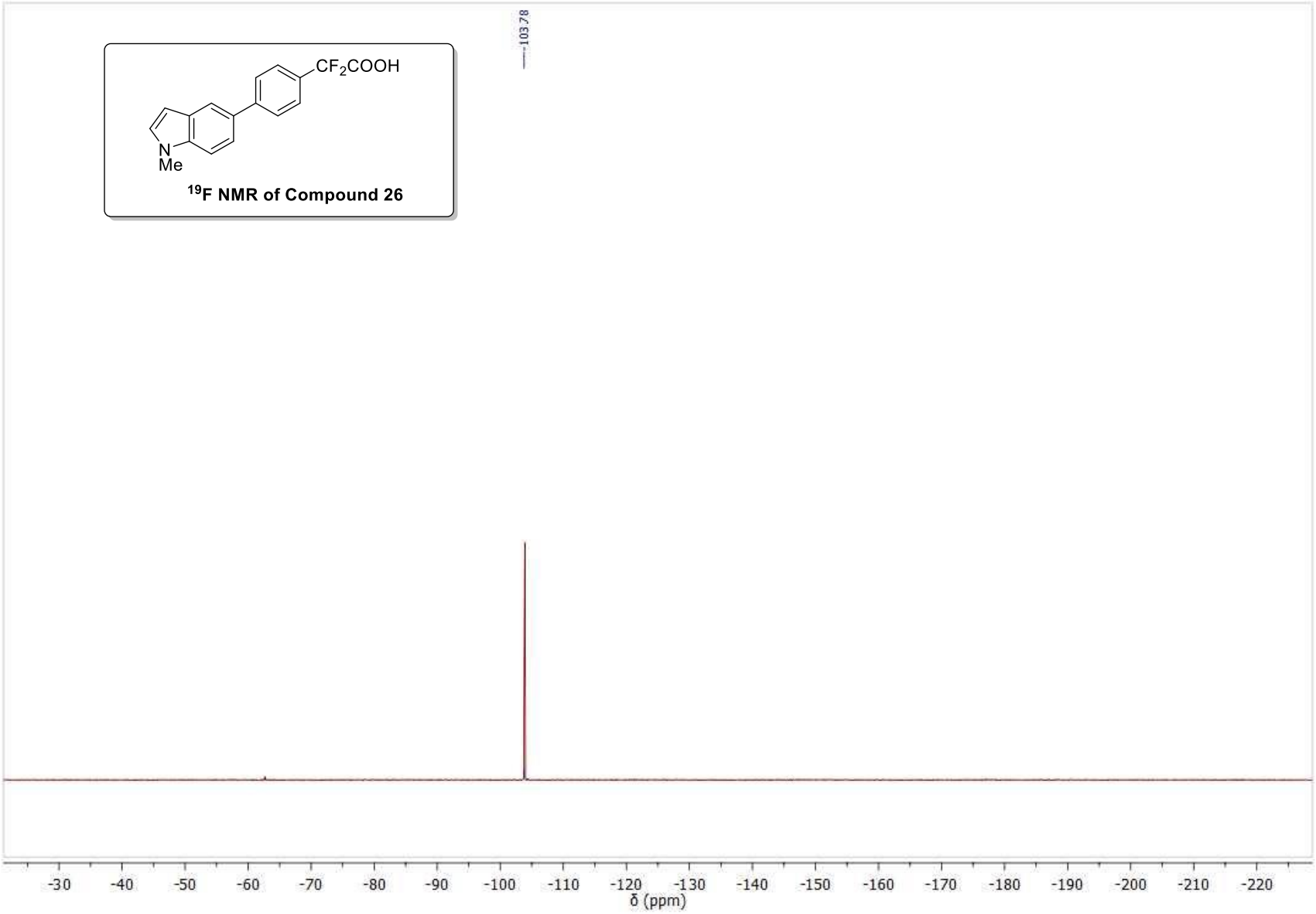
^{19}F NMR of Compound 23



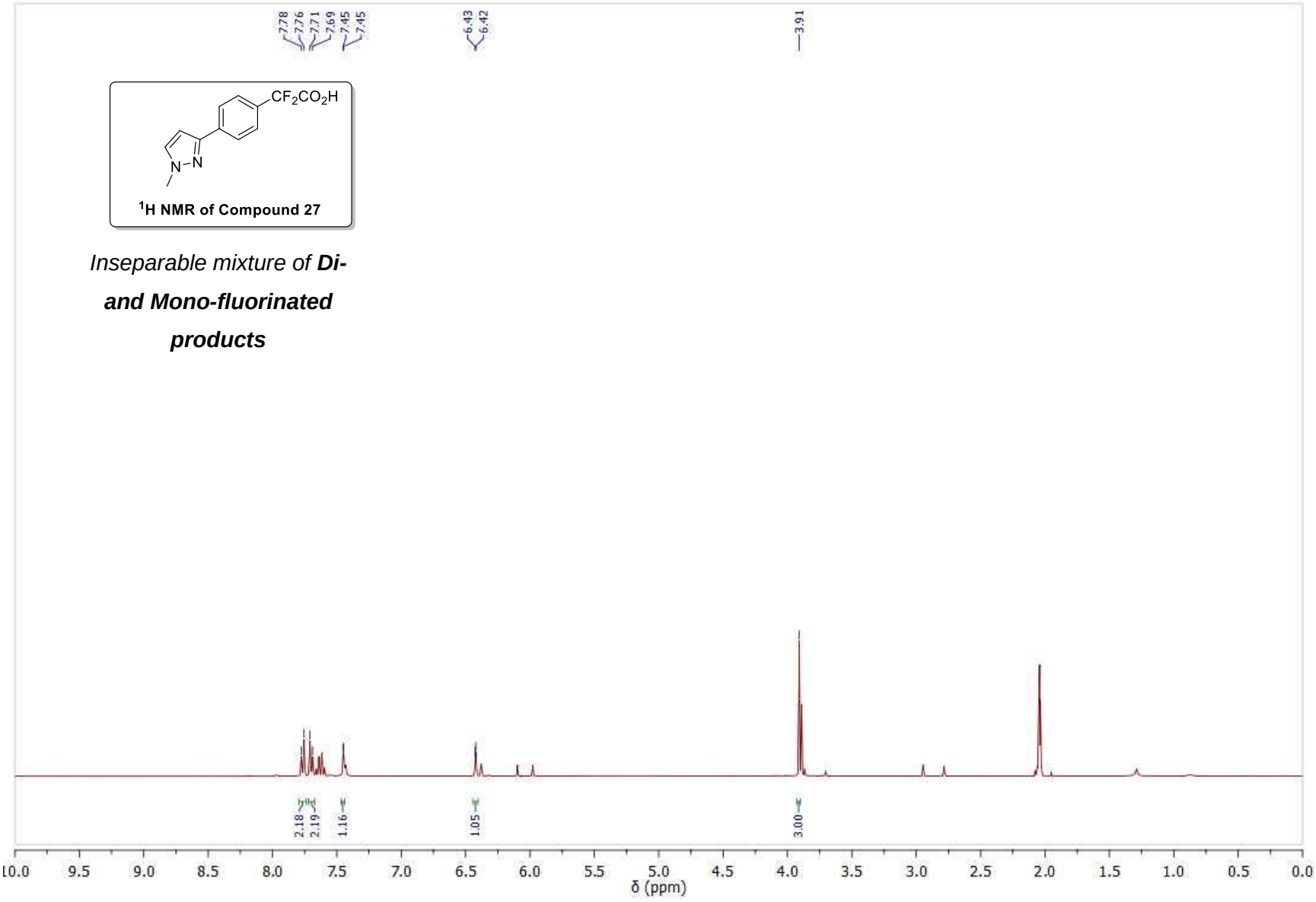
^{1}H NMR of compound 24 + protodecarboxylated byproduct


7.90
7.85
7.83
7.71
7.69
7.51
7.28
7.28
6.52
6.51
3.87
CF2COOH
N
Me
1H NMR of Compound 26
1.02
2.12
2.10
2.07
1.01
1.00
2.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)


165.92
165.65
165.38
141.82
131.05
130.22
128.13
128.06
126.72
126.67
126.62
121.62
120.12
33.03
CF2COOH
N
Me
13C NMR of Compound 26
166
165
126.70
126.60
115
δ (ppm)

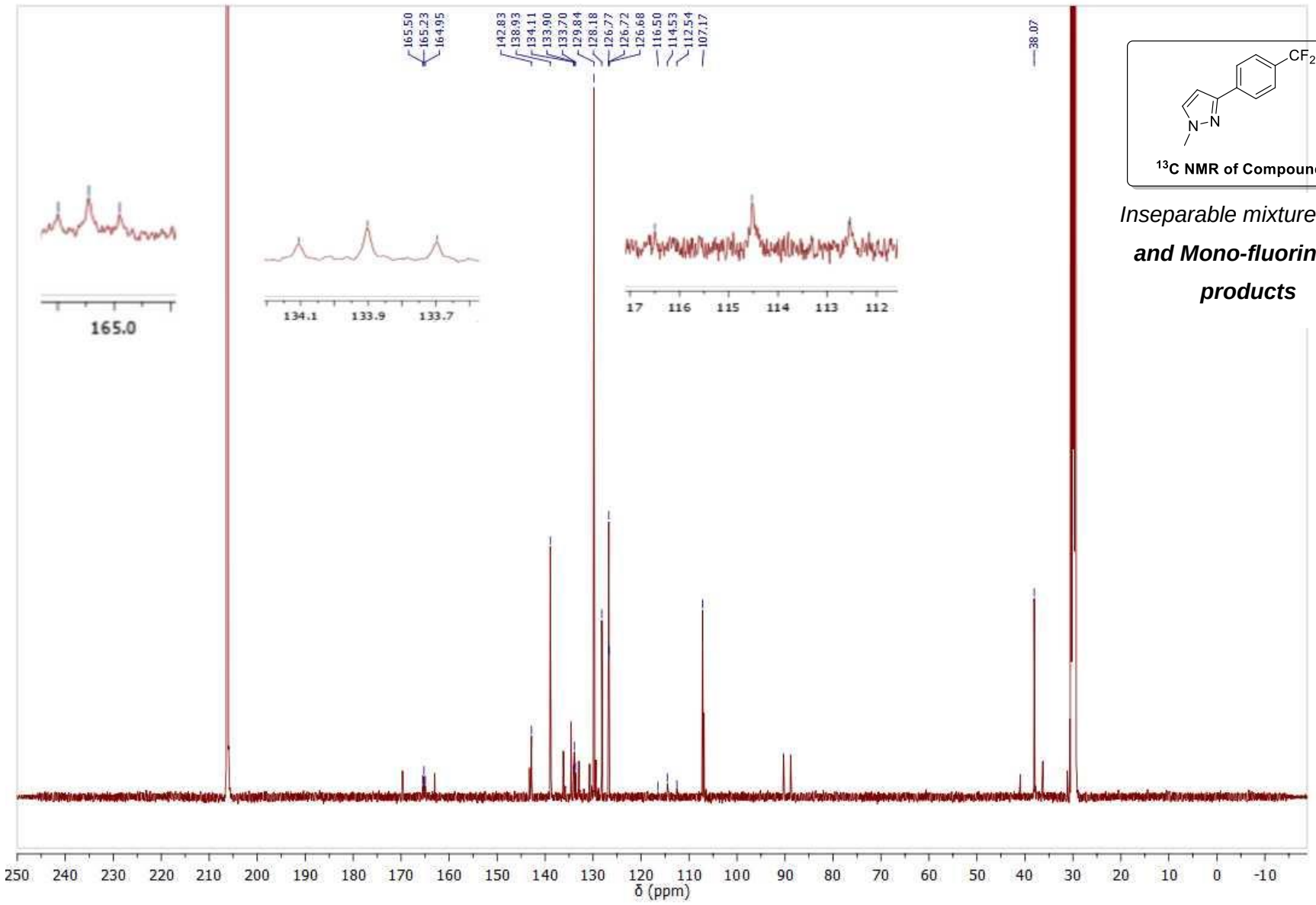


^{19}F NMR of Compound 26



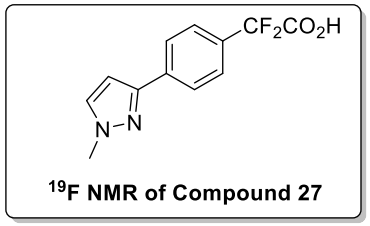
^{1}H NMR of Compound 27

Inseparable mixture of ***Di- and Mono-fluorinated products***



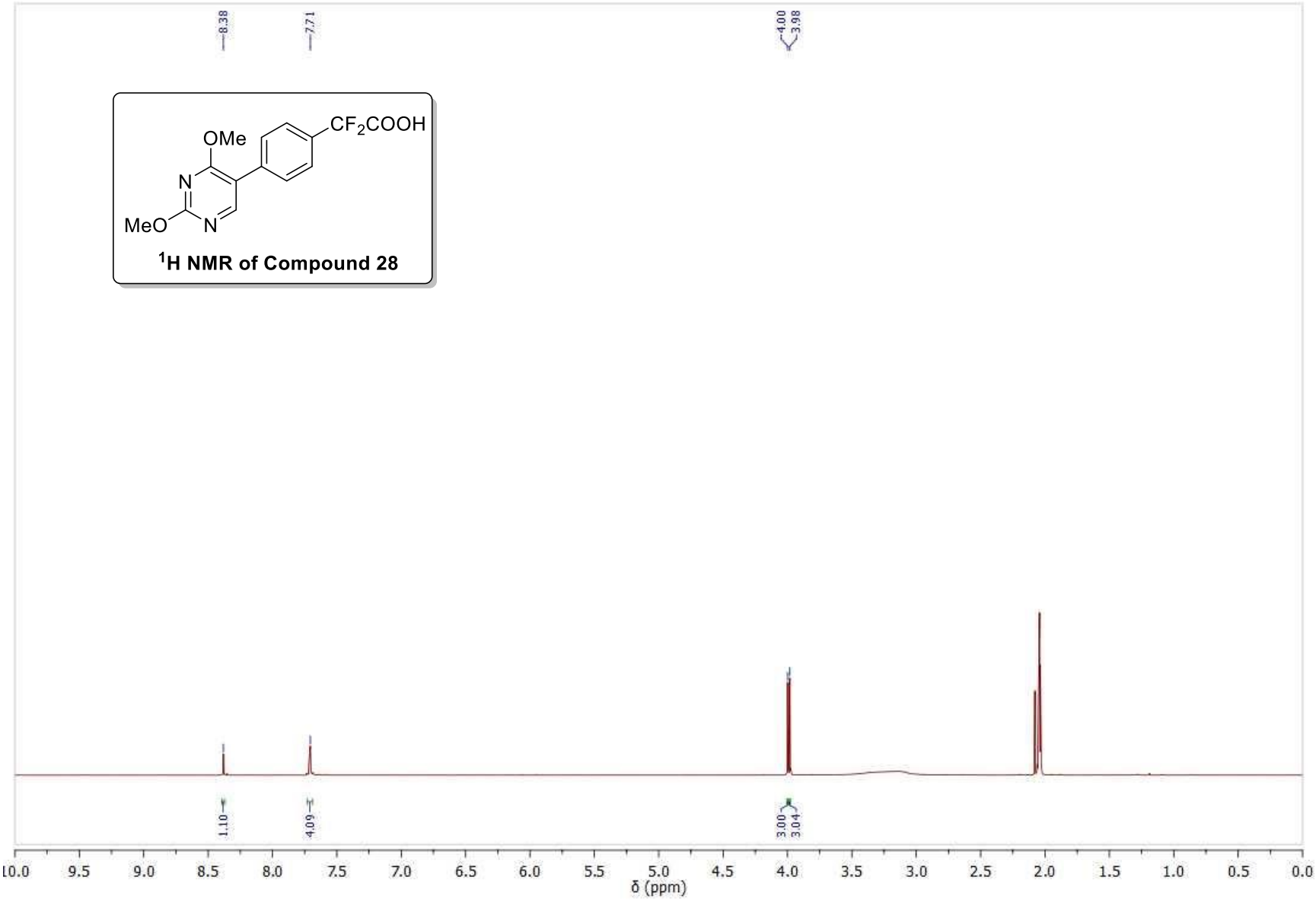
^{13}C NMR of Compound 27

*Inseparable mixture of **Di- and Mono-fluorinated products***

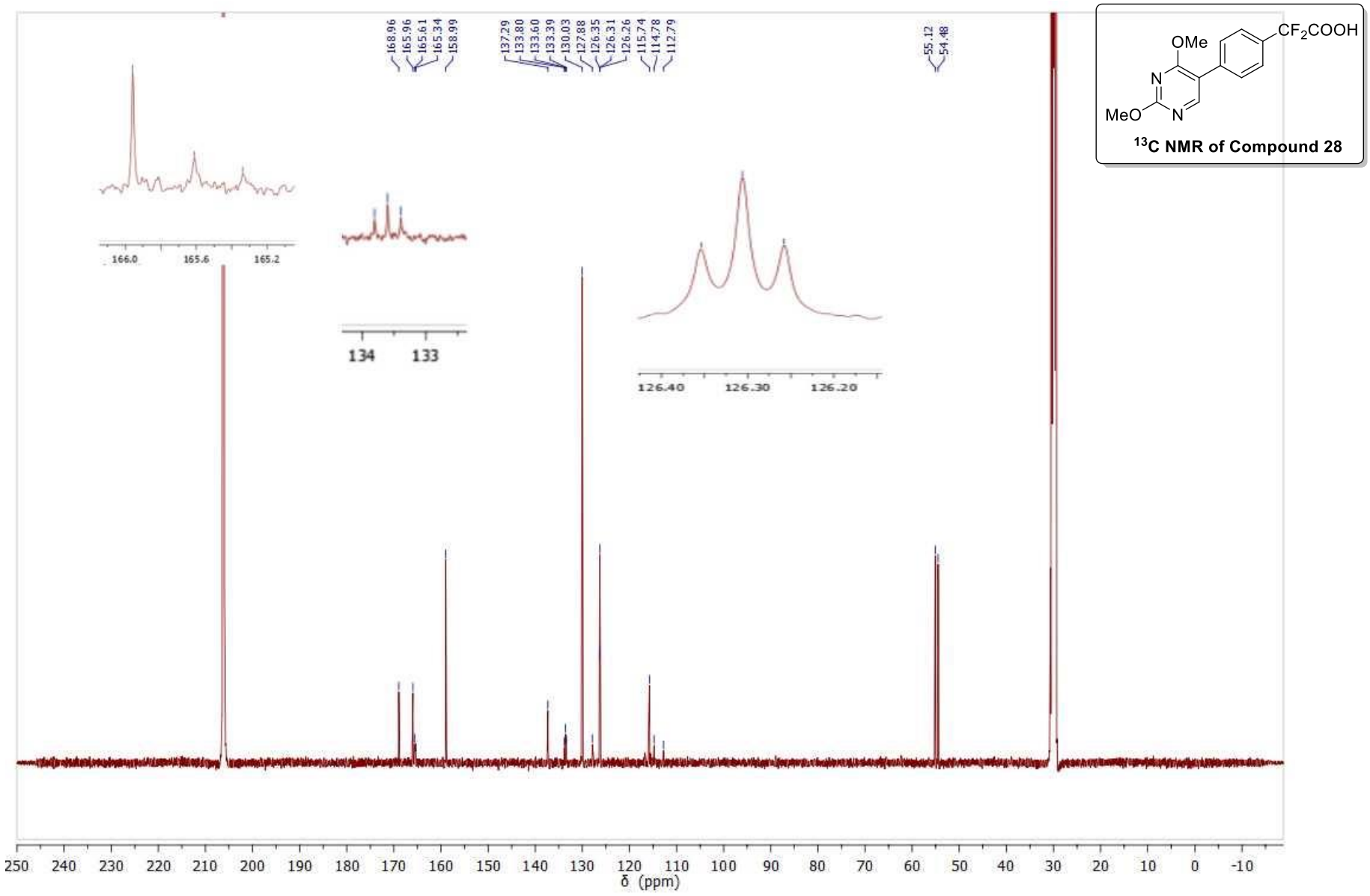


^{19}F NMR of Compound 27

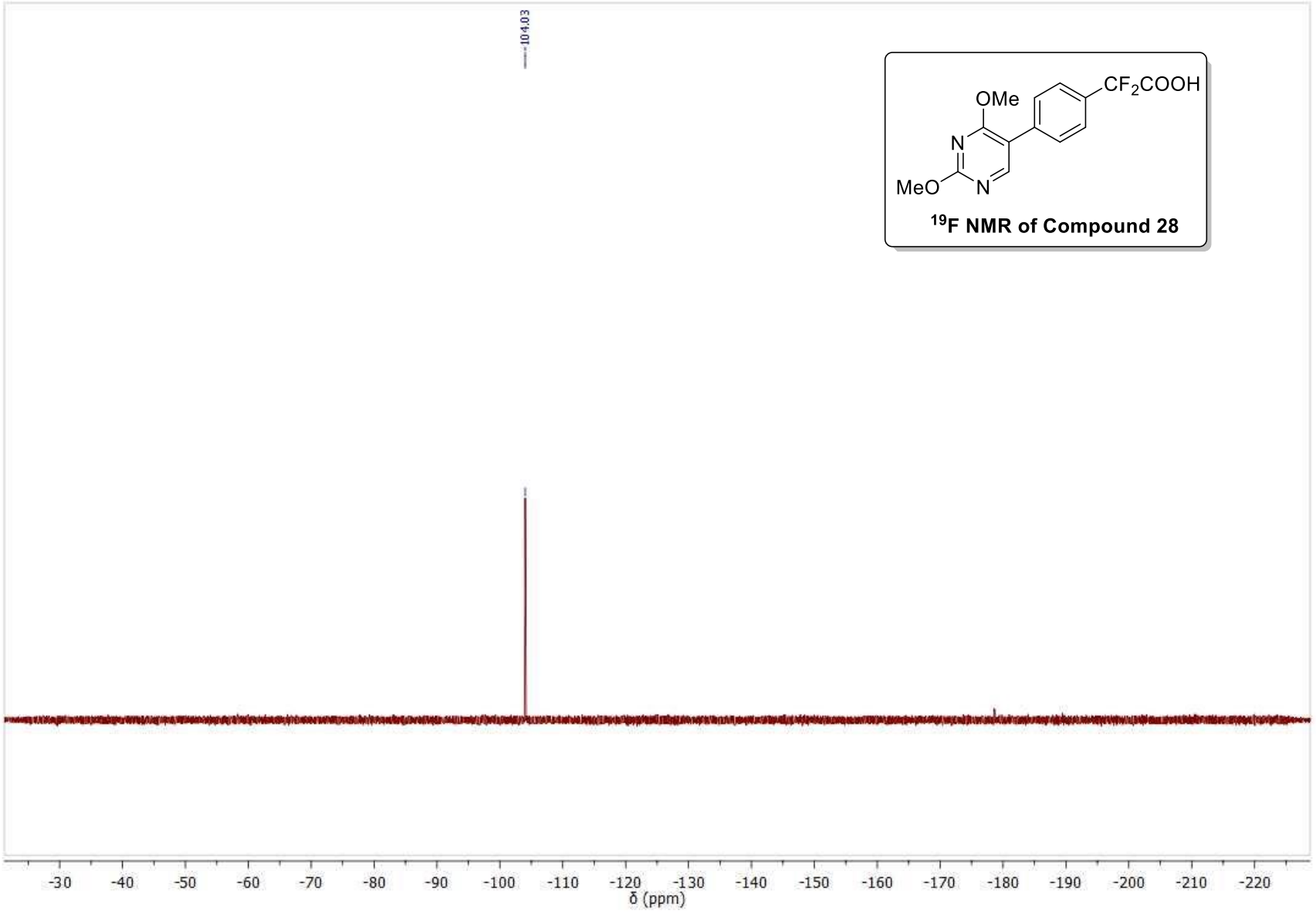
Inseparable mixture of ***Di- and Mono-fluorinated products***

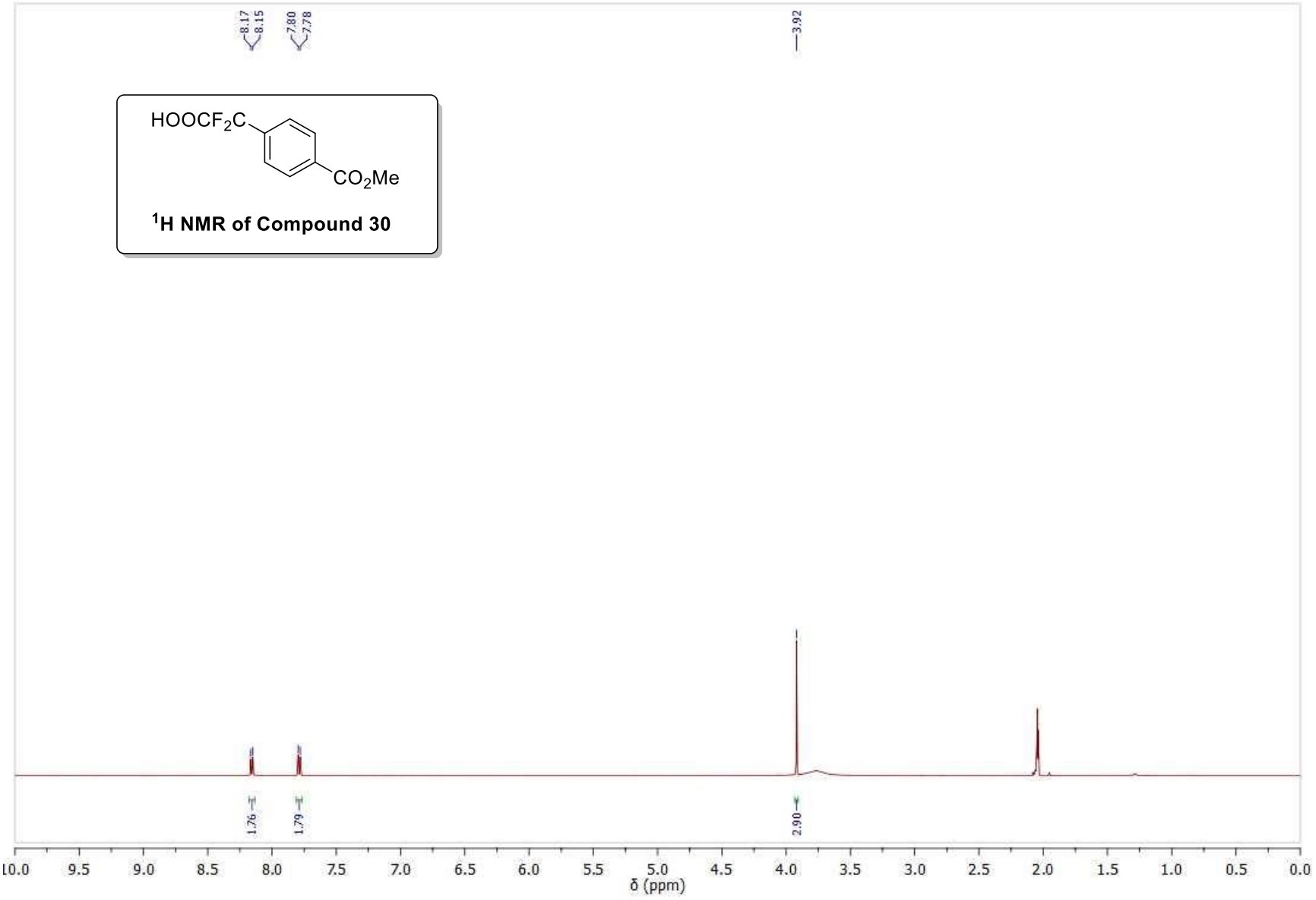


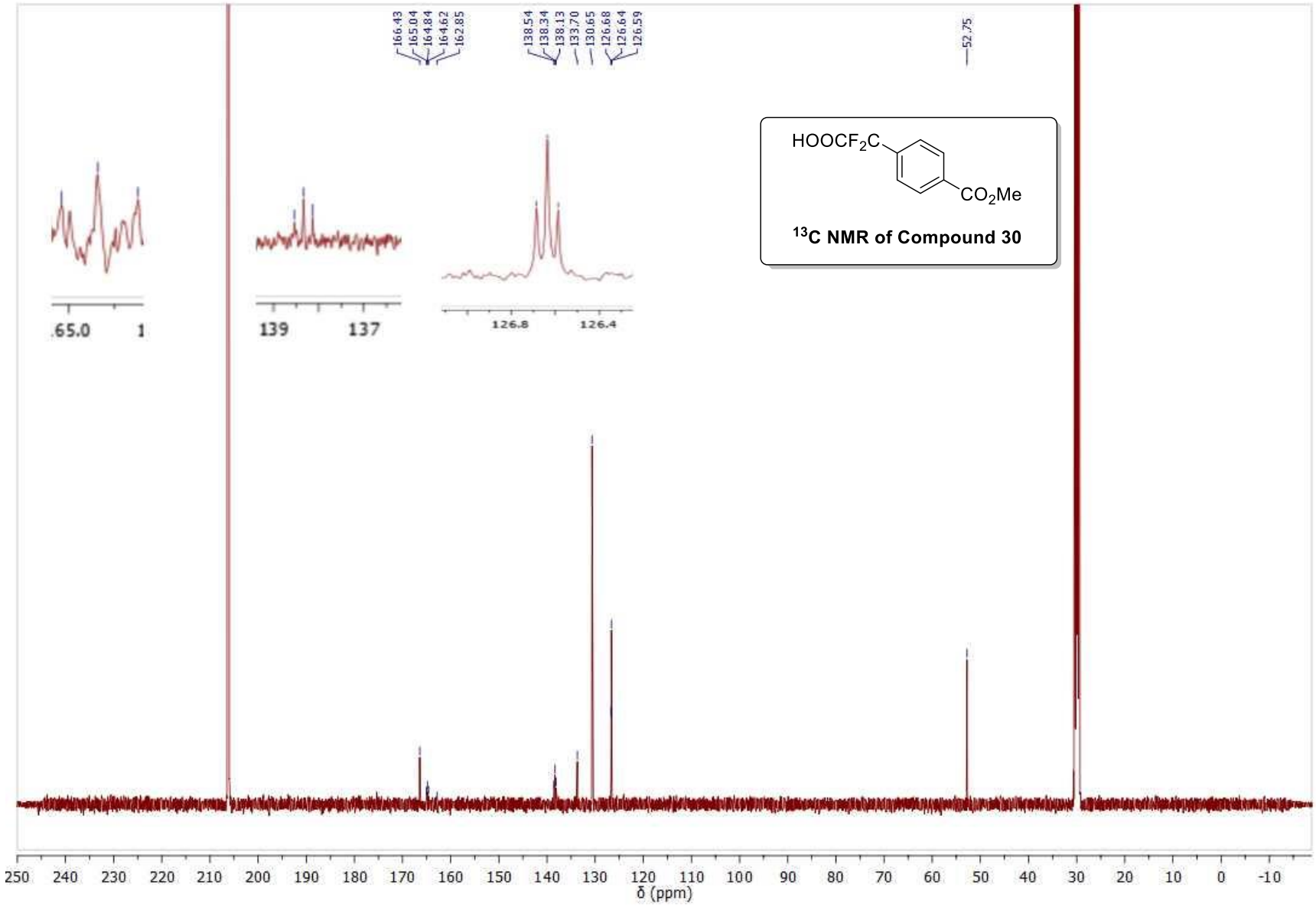
^{1}H NMR of Compound 28

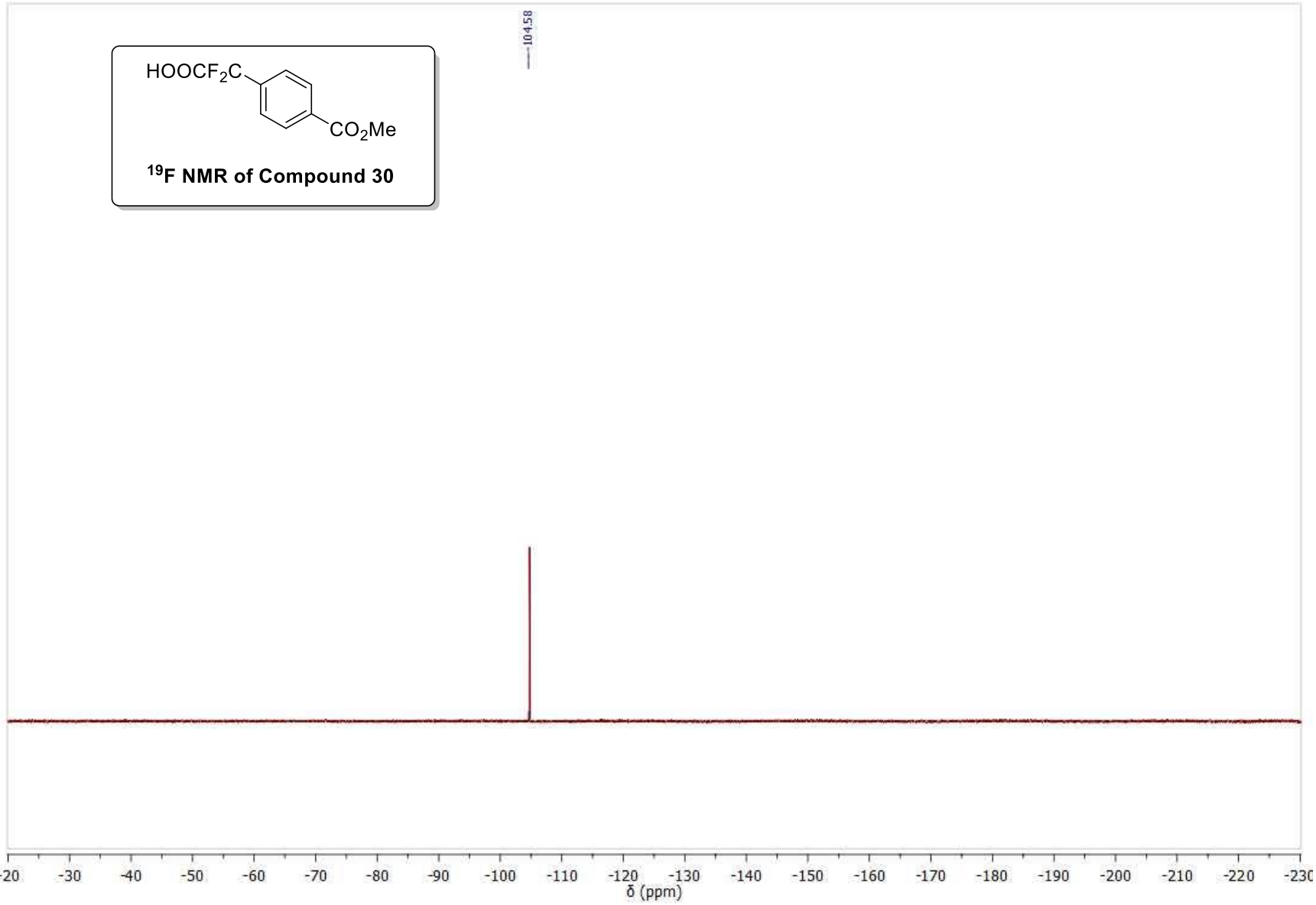


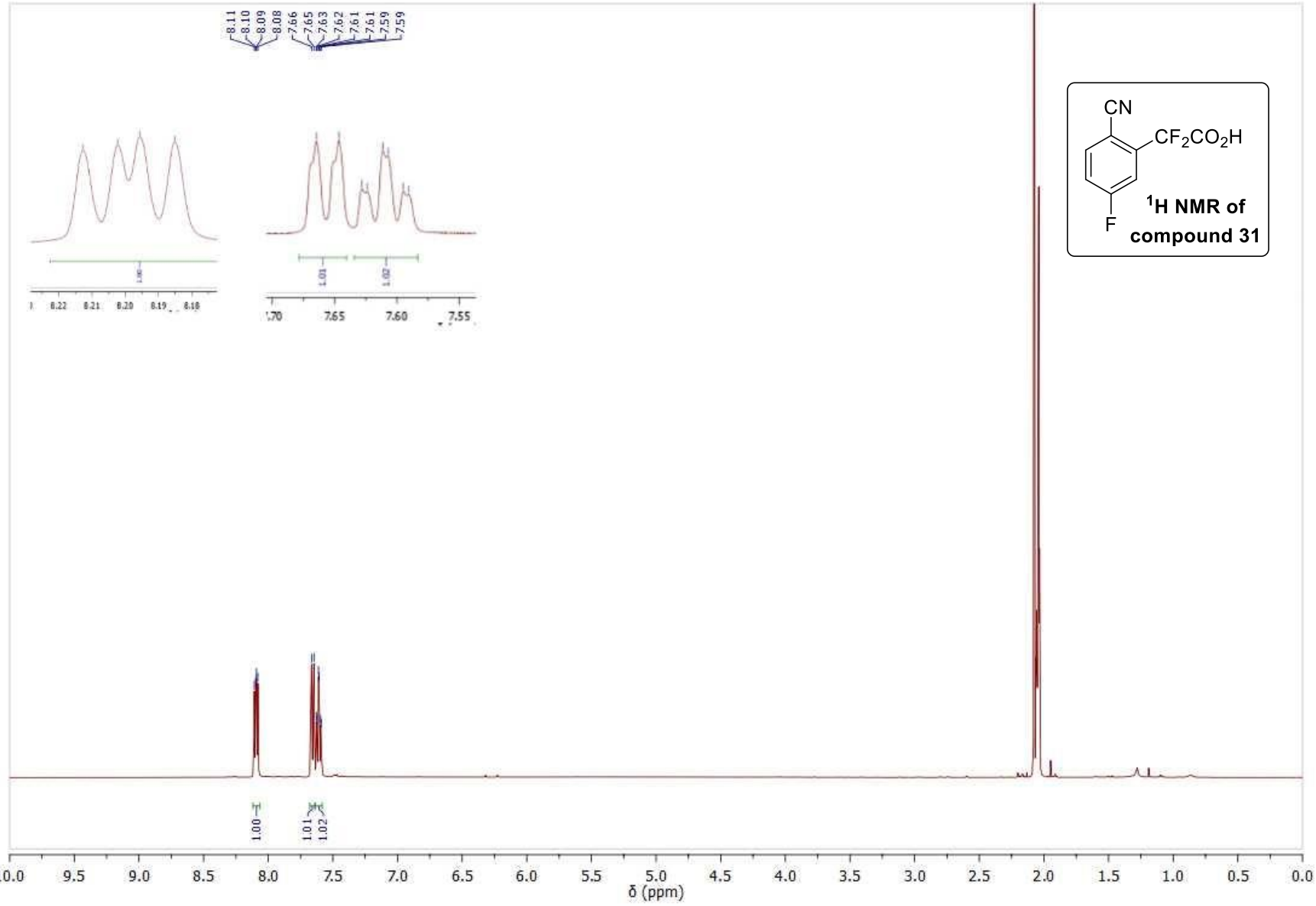
^{13}C NMR of Compound 28

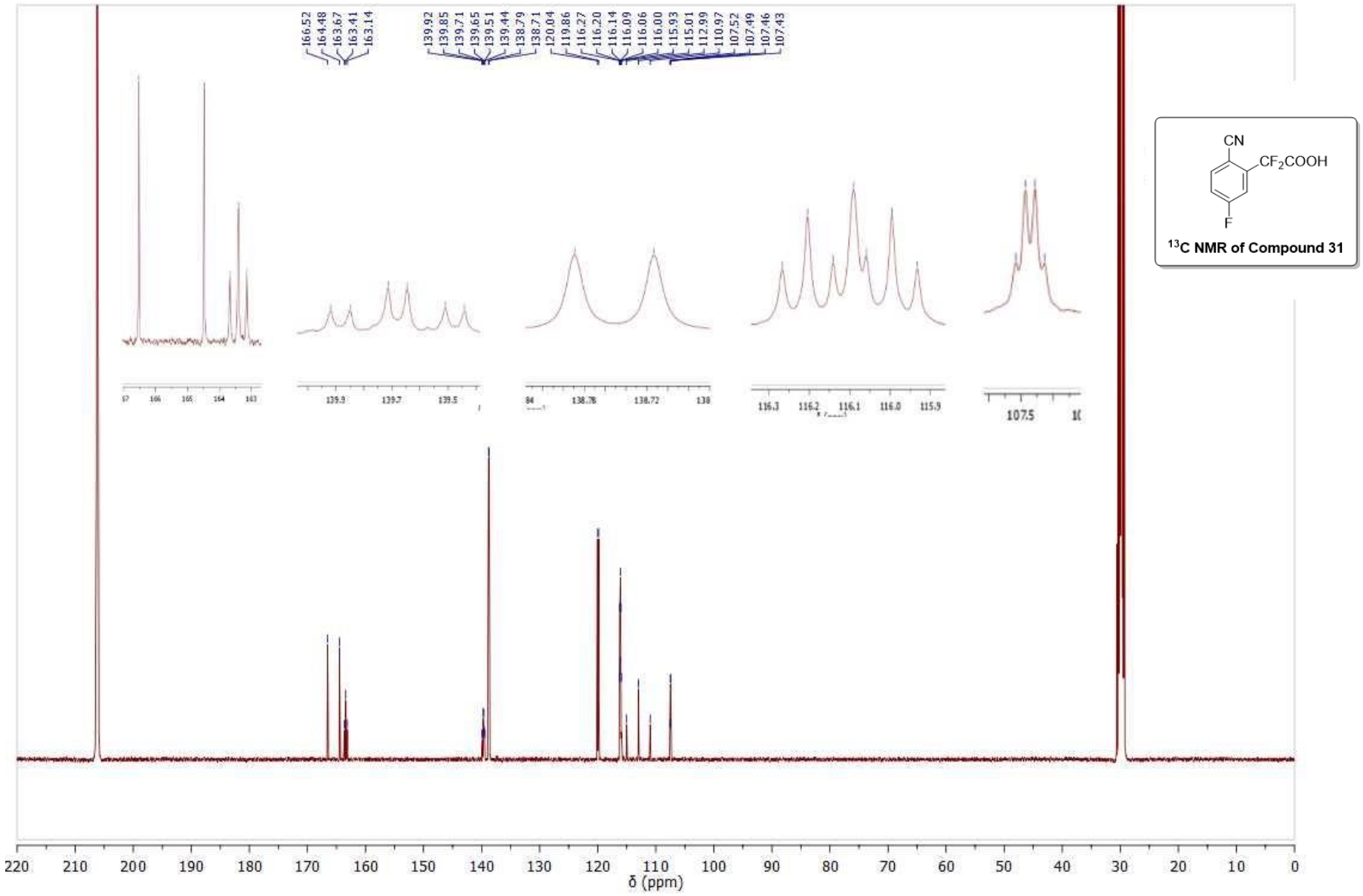

-104.03
OMe
N
MeO
N
CF2COOH
19F NMR of Compound 28
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)


8.17
8.15
7.80
7.78
3.92
HOOCF2C
CO2Me
1H NMR of Compound 30
1.76
1.79
2.90
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

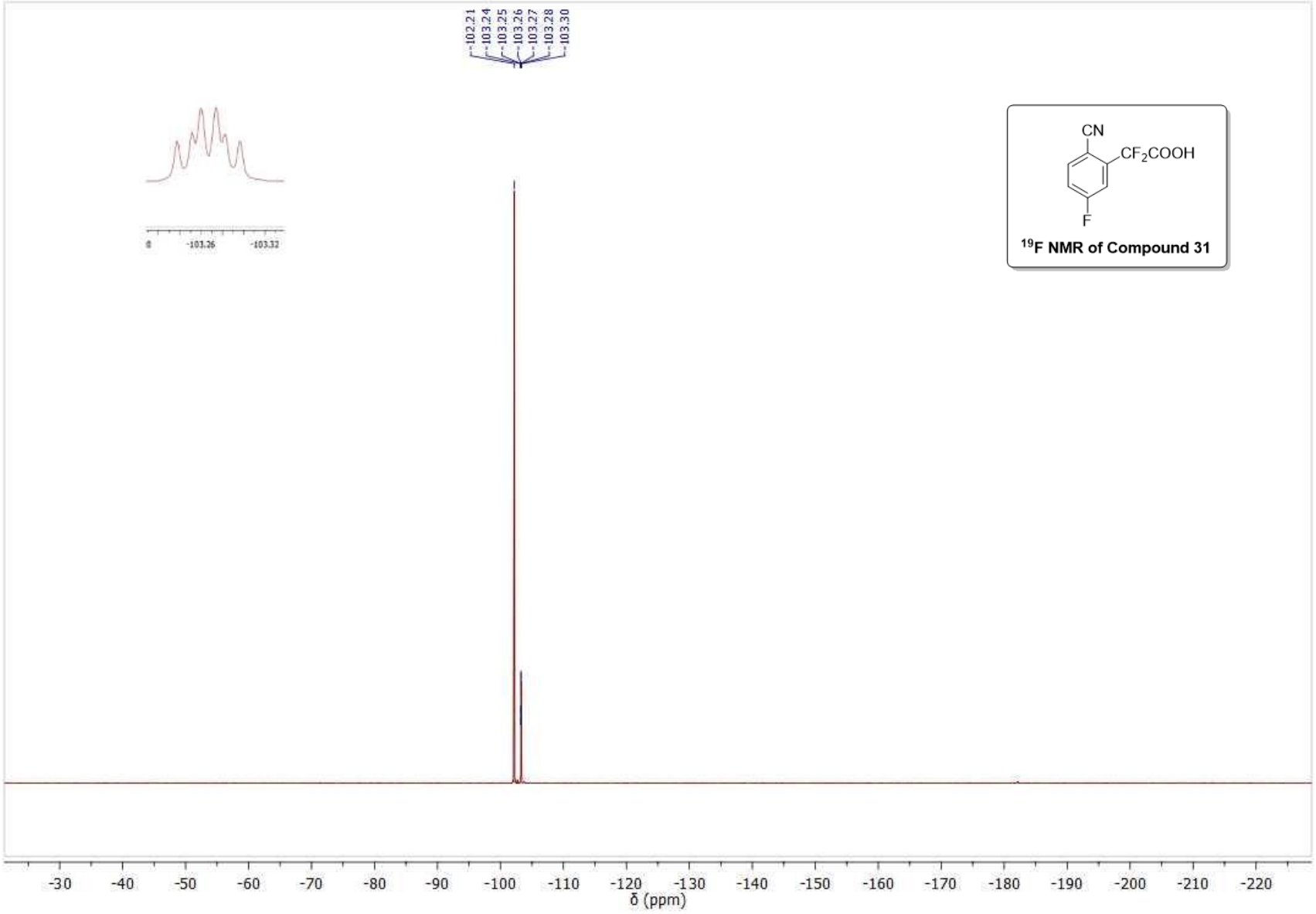

166.43
165.04
164.84
164.62
162.85
138.54
138.34
138.13
133.70
130.65
126.68
126.64
126.59
52.75
HOOCF2C
CO2Me
13C NMR of Compound 30
65.0
1
139
137
126.8
126.4
250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
δ (ppm)

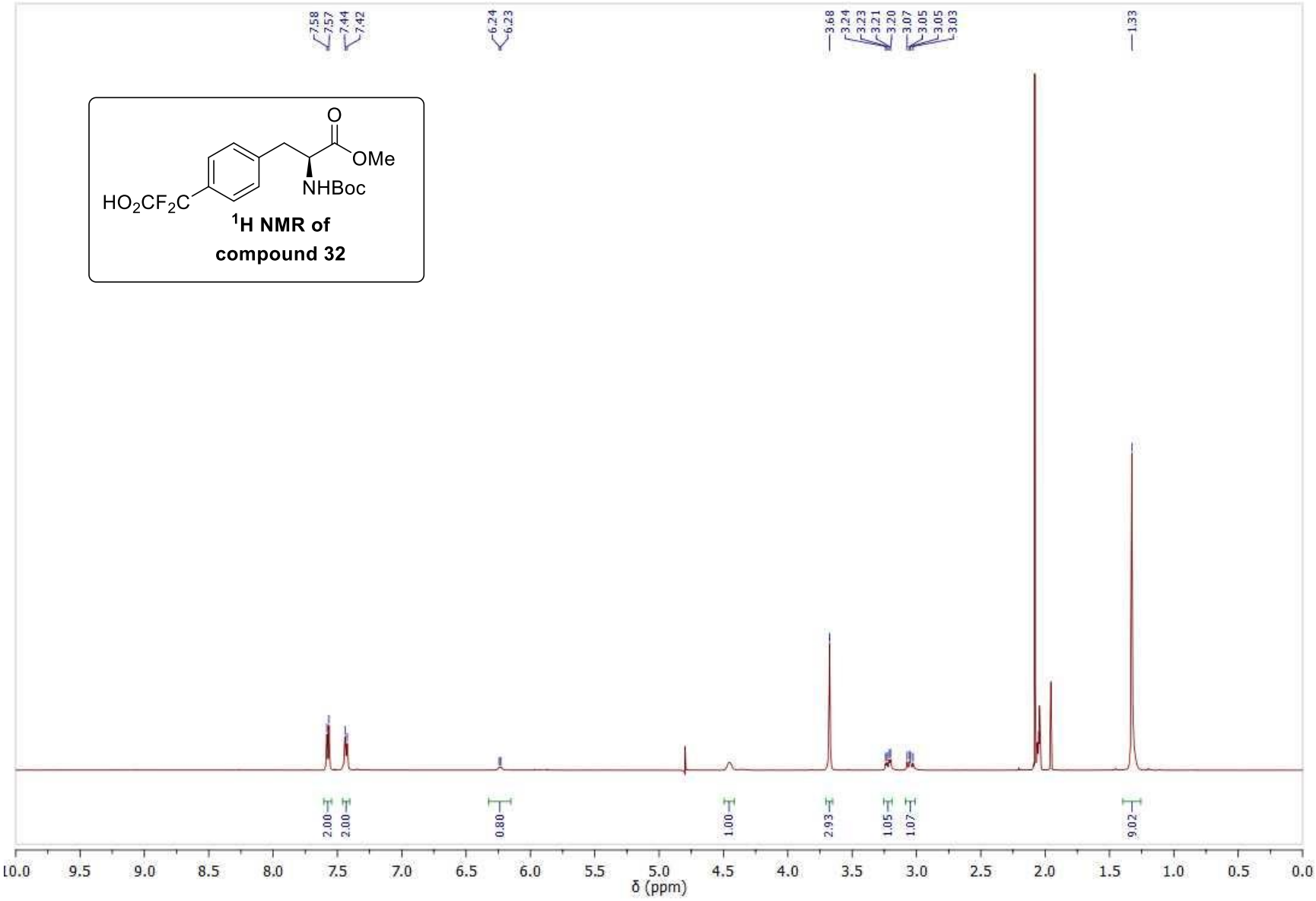

HOOCF2C
CO2Me
19F NMR of Compound 30
-104.58
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

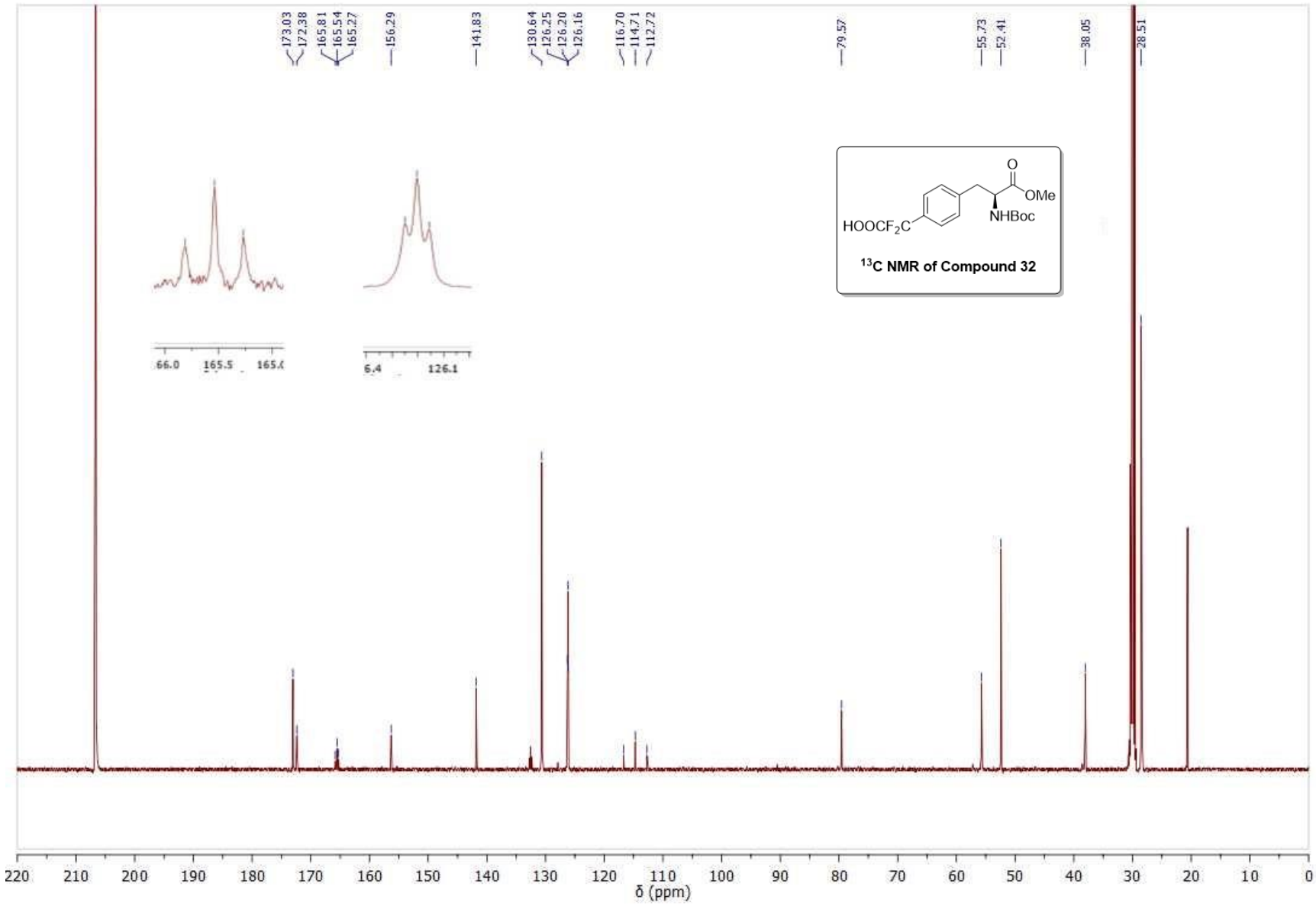

CN
CF2CO2H
F
1H NMR of compound 31
δ (ppm)



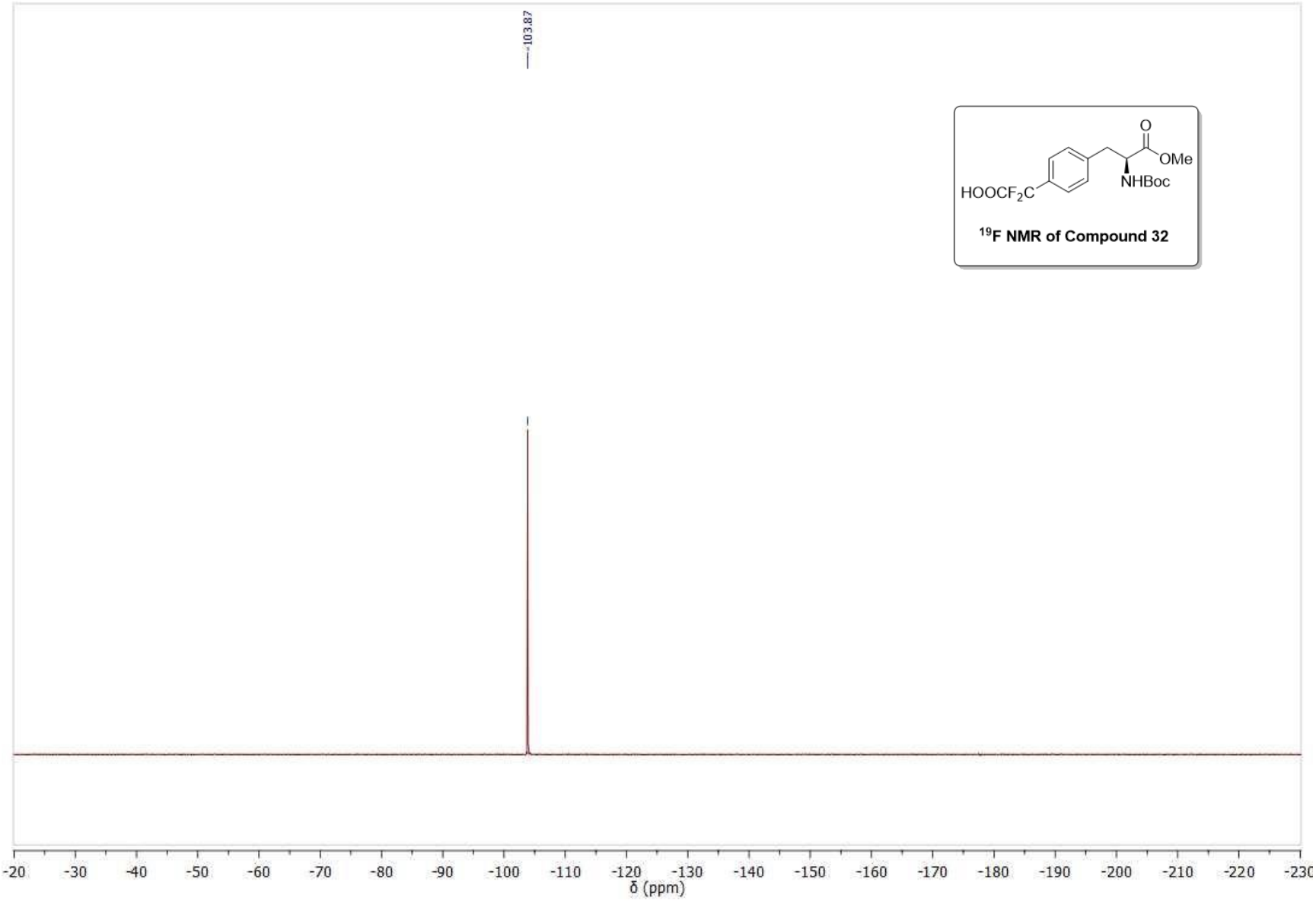
^{13}C NMR of Compound 31

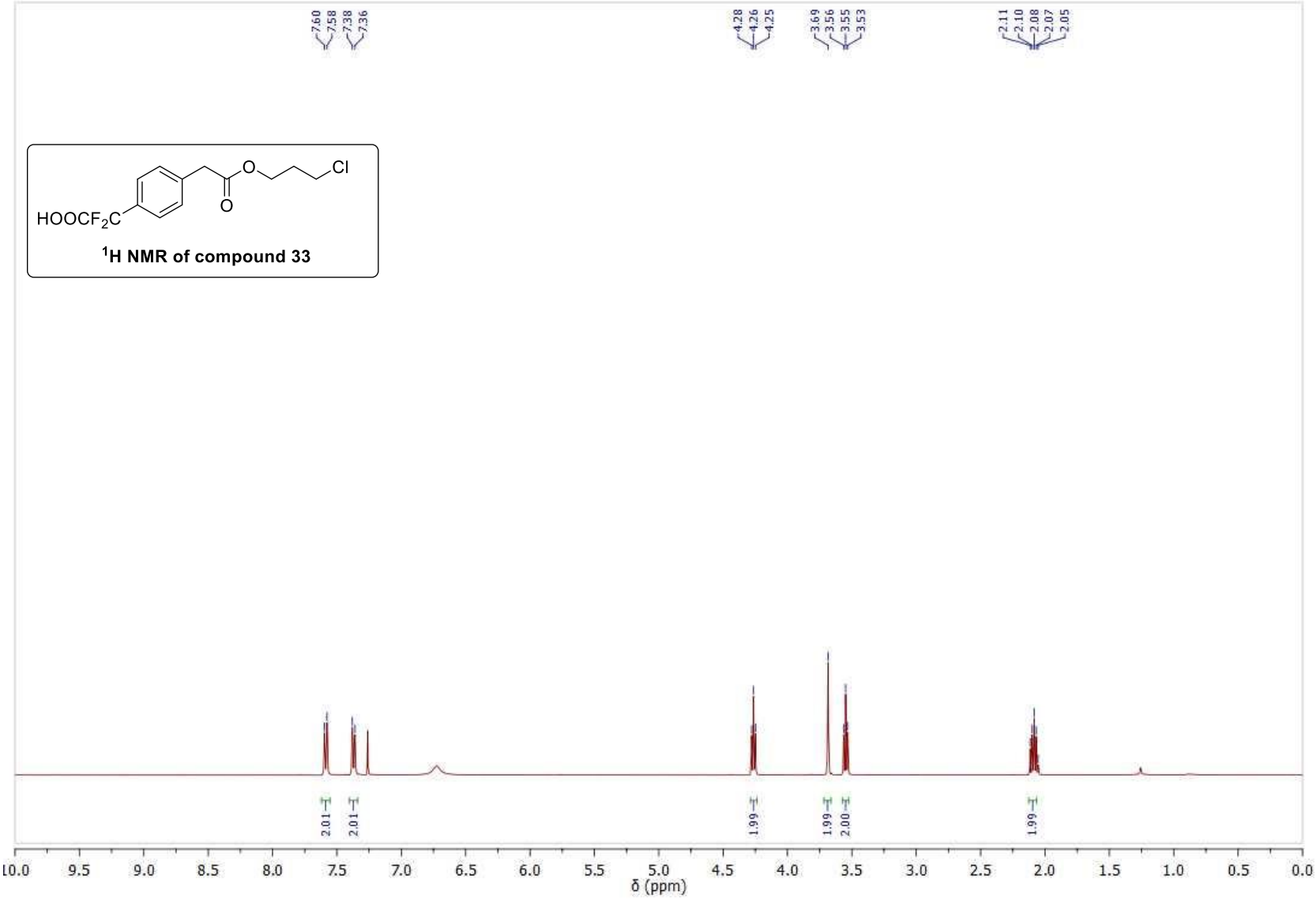

-102.21
-103.24
-103.25
-103.26
-103.27
-103.28
-103.30
-103.26
-103.32
CN
CF2COOH
F
19F NMR of Compound 31
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)


7.58
7.57
7.44
7.42
6.24
6.23
3.68
3.24
3.23
3.21
3.20
3.07
3.05
3.05
3.03
1.33
O
OMe
NHBoc
HO2CF2C
1H NMR of
compound 32
2.00
2.00
0.80
1.00
2.93
1.05
1.07
9.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

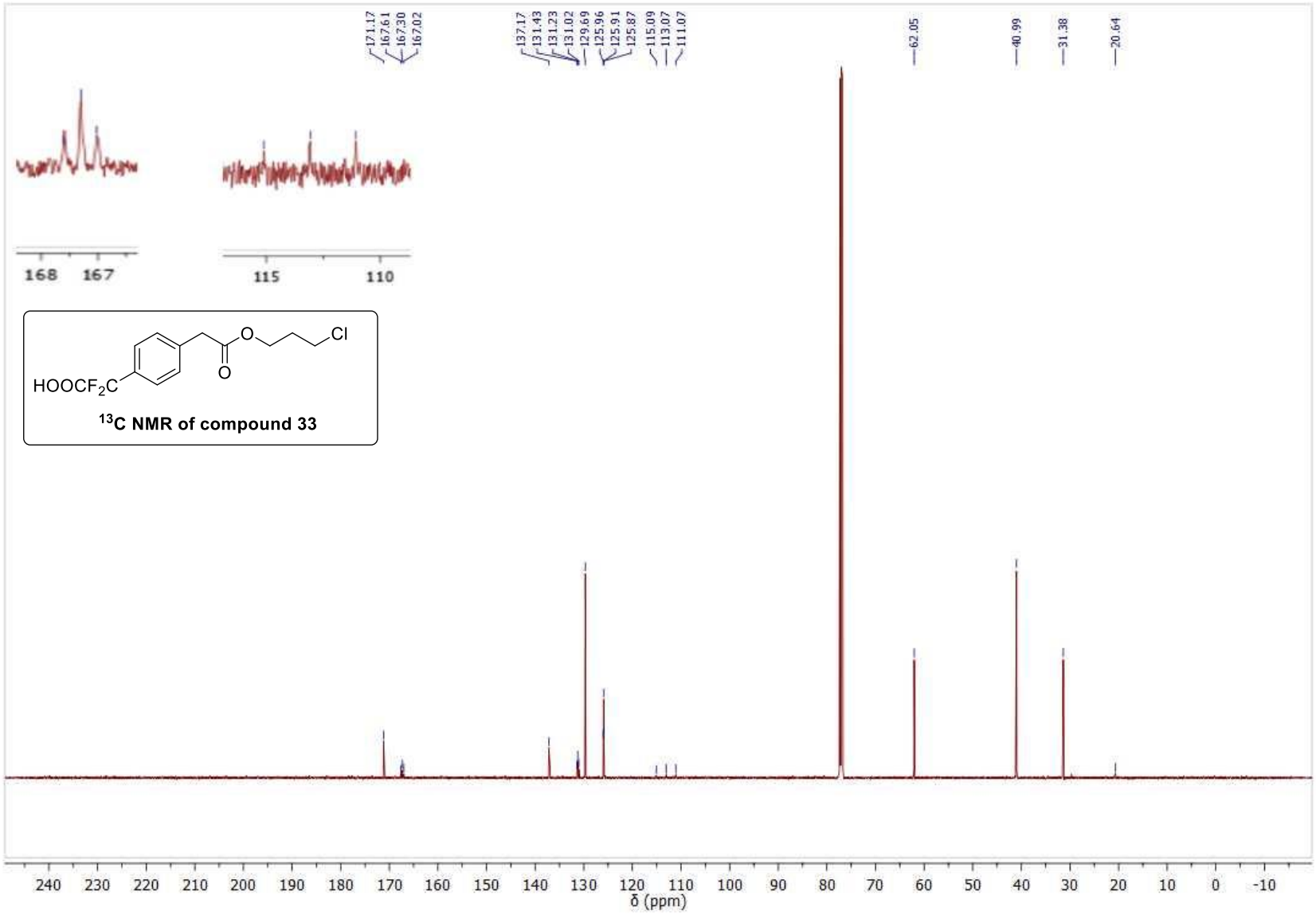


^{13}C NMR of Compound 32

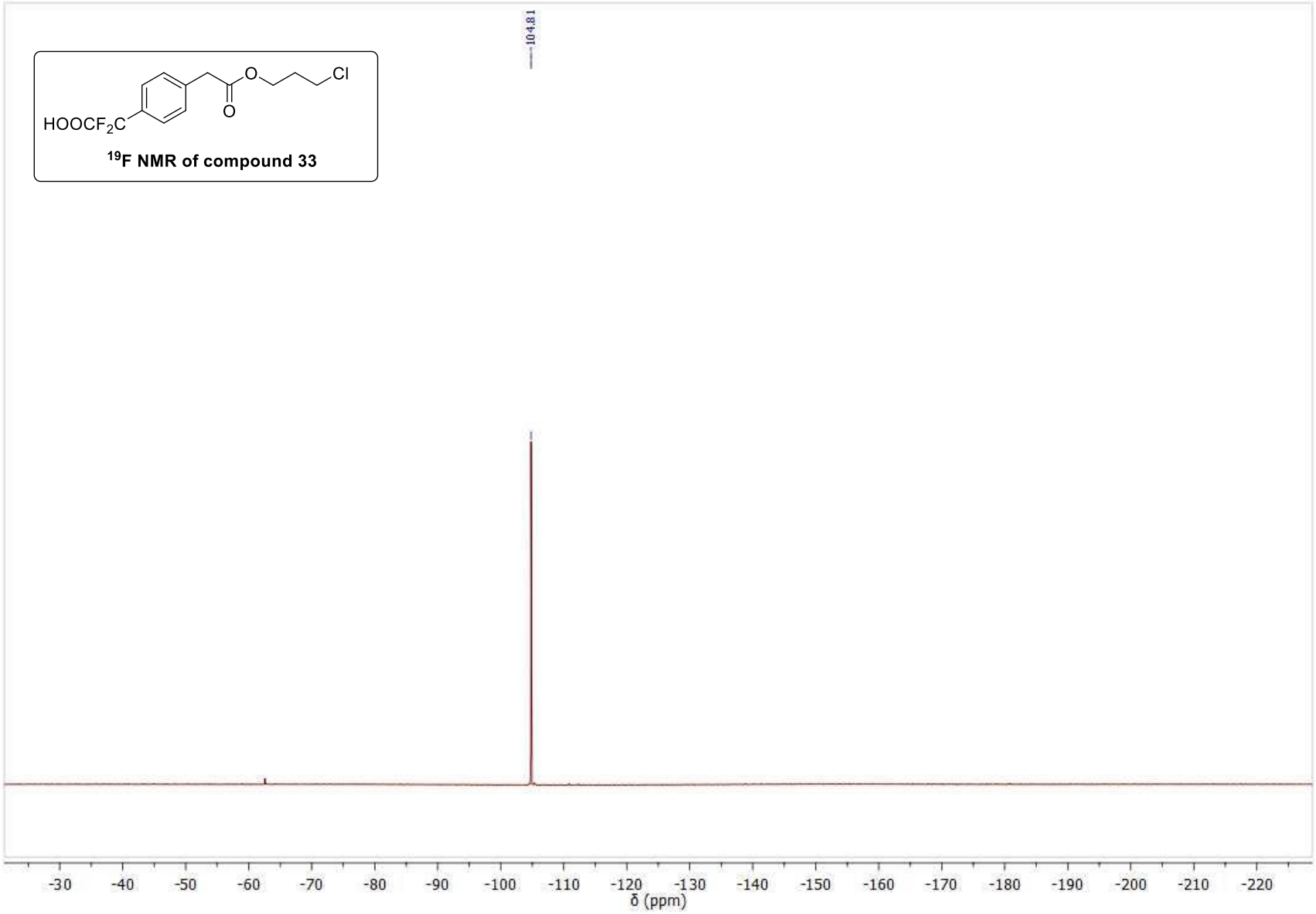

-103.87
HOOCF2C
O
OMe
NHBoc
19F NMR of Compound 32
-20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
δ (ppm)

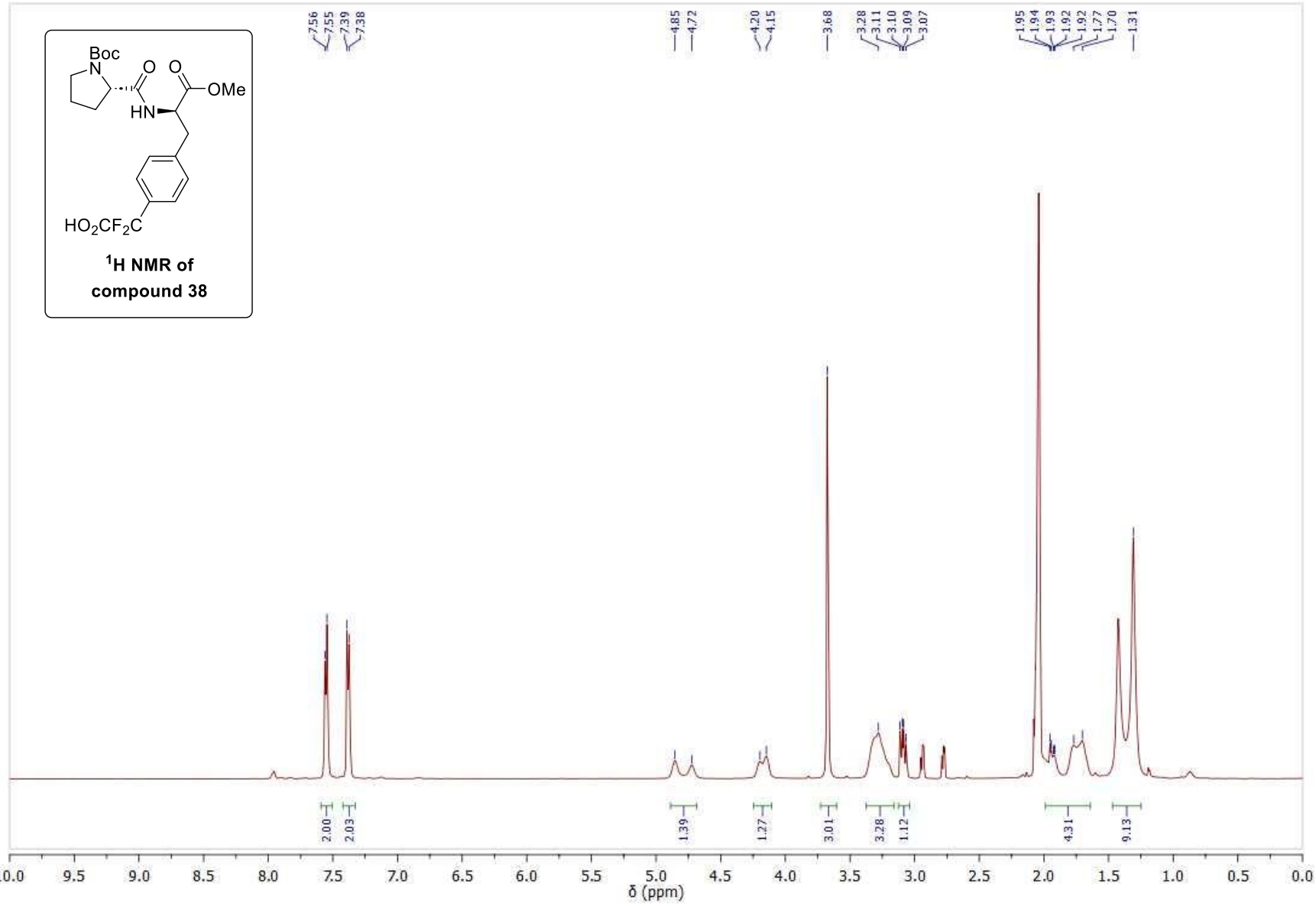


^{1}H NMR of compound 33

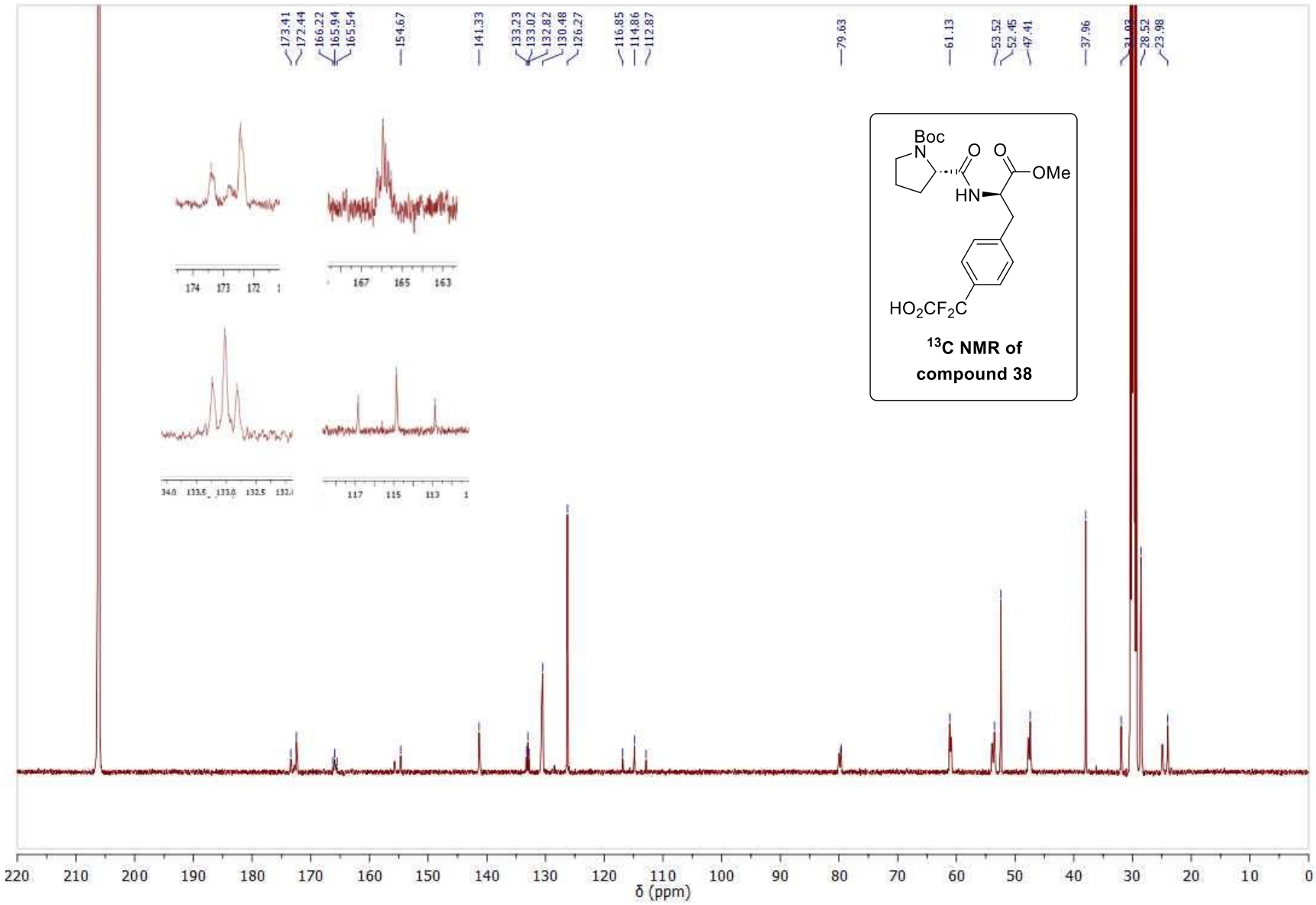


^{13}C NMR of compound 33

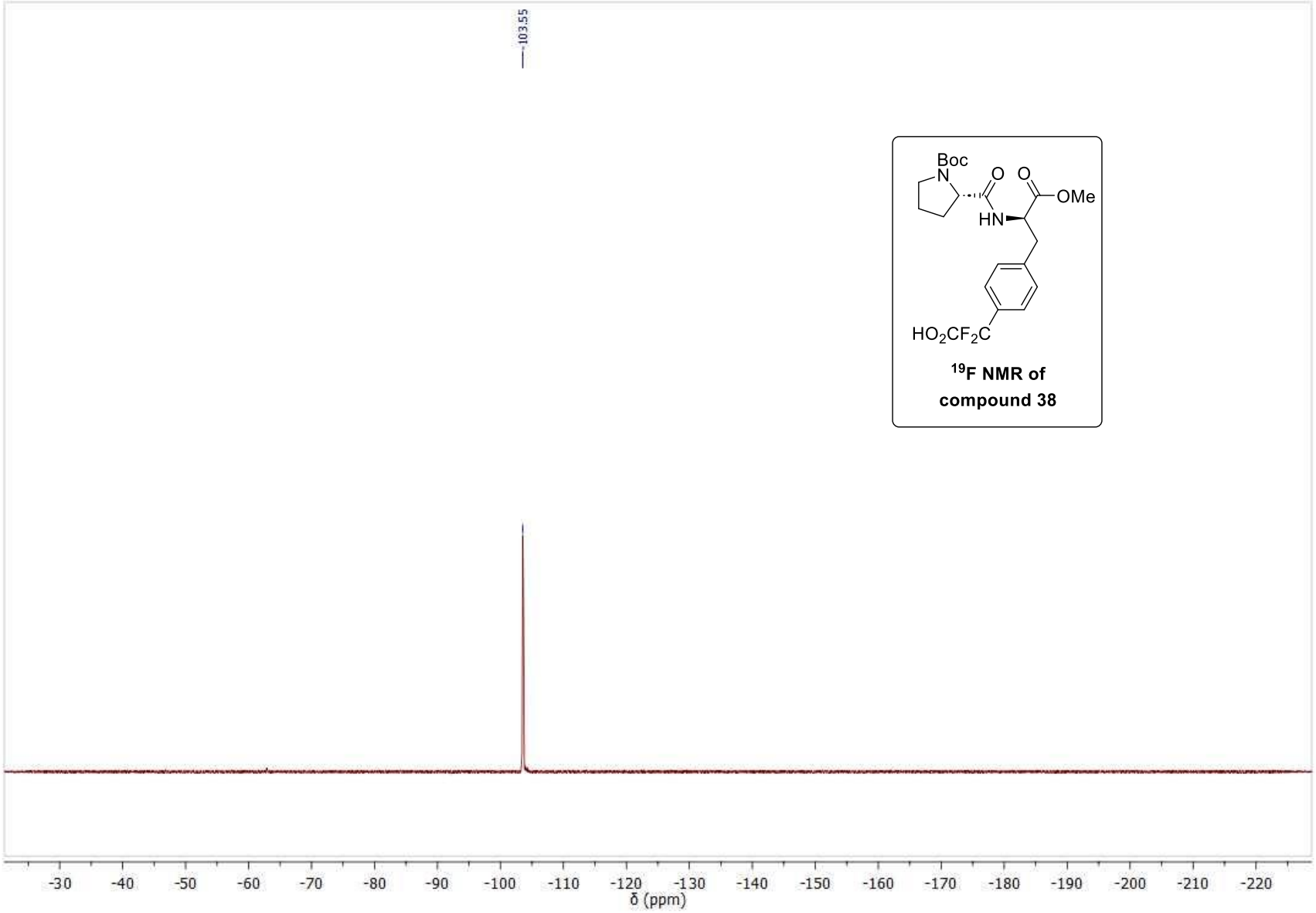

HOOCF2C
O
O
Cl
19F NMR of compound 33
-104.81
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)



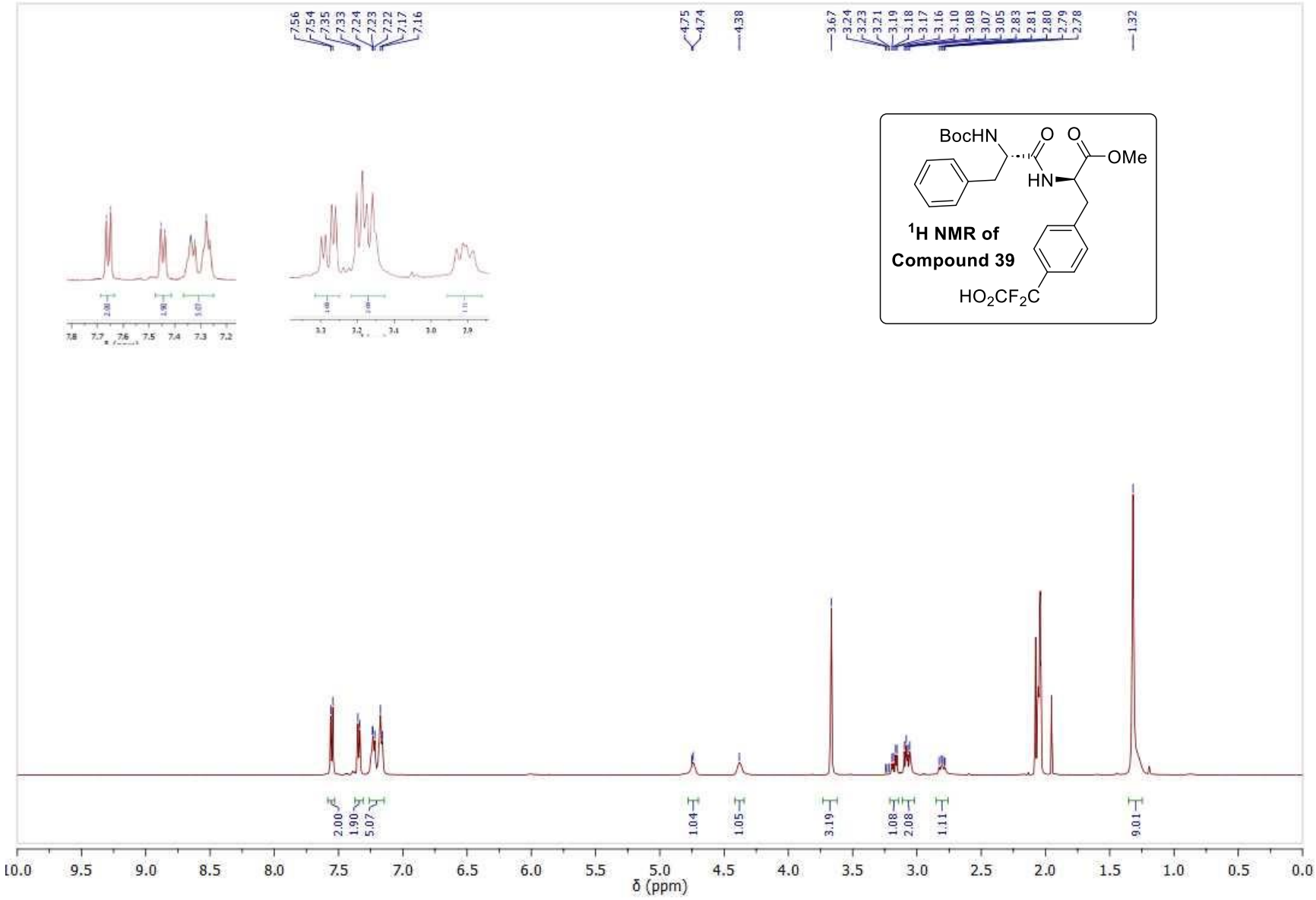
^{1}H NMR of compound 38

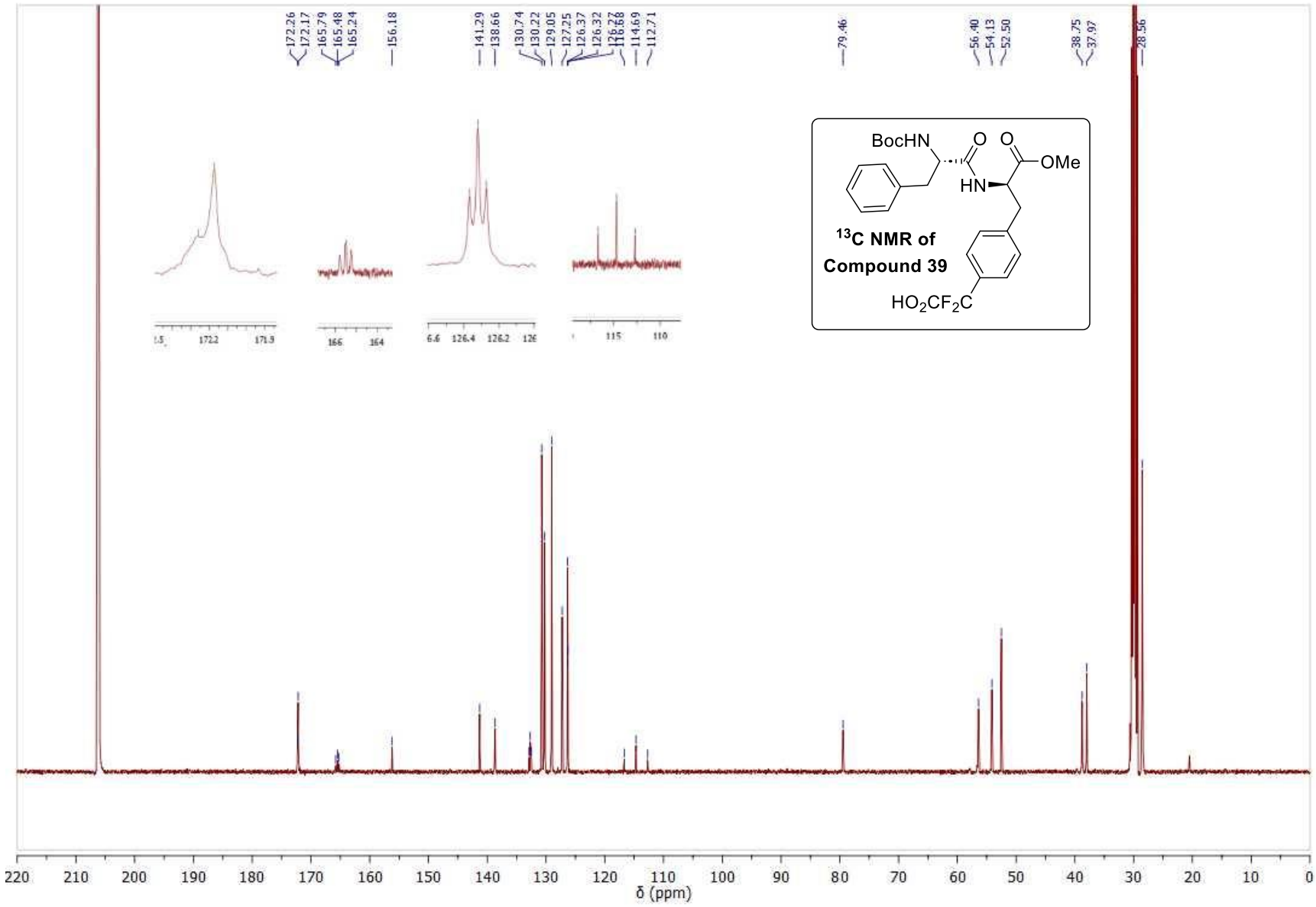


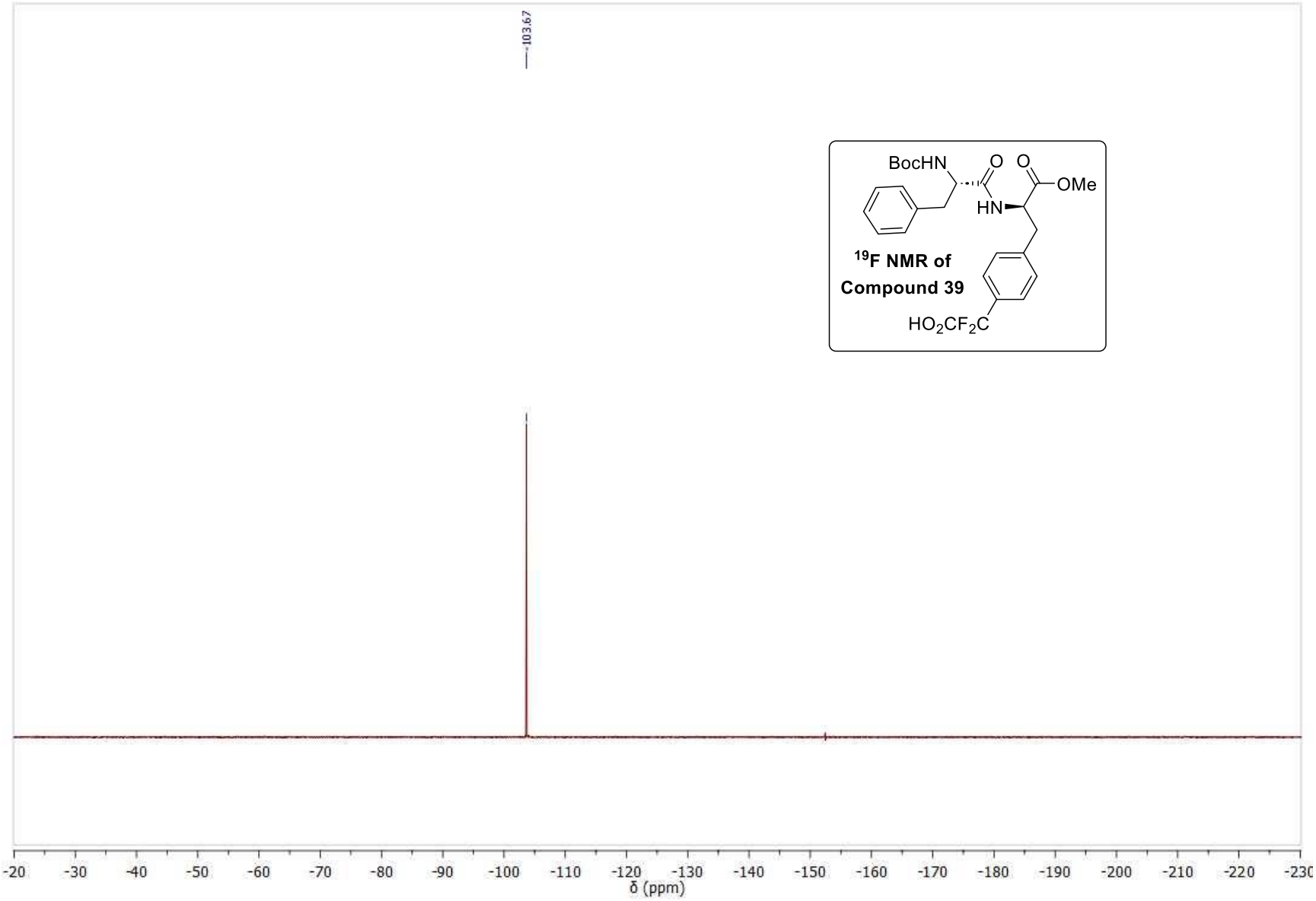
^{13}C NMR of compound 38

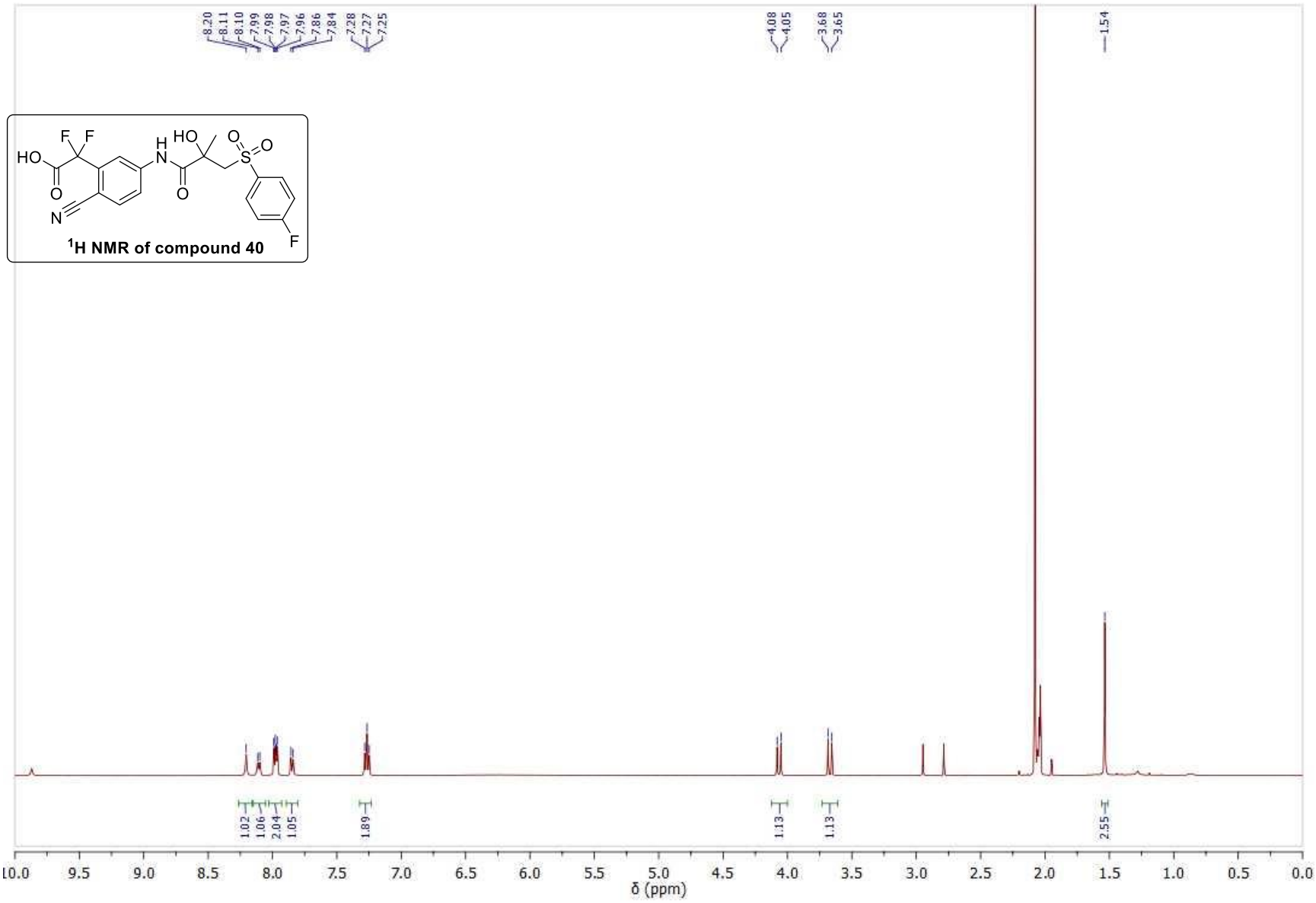


^{19}F NMR of compound 38

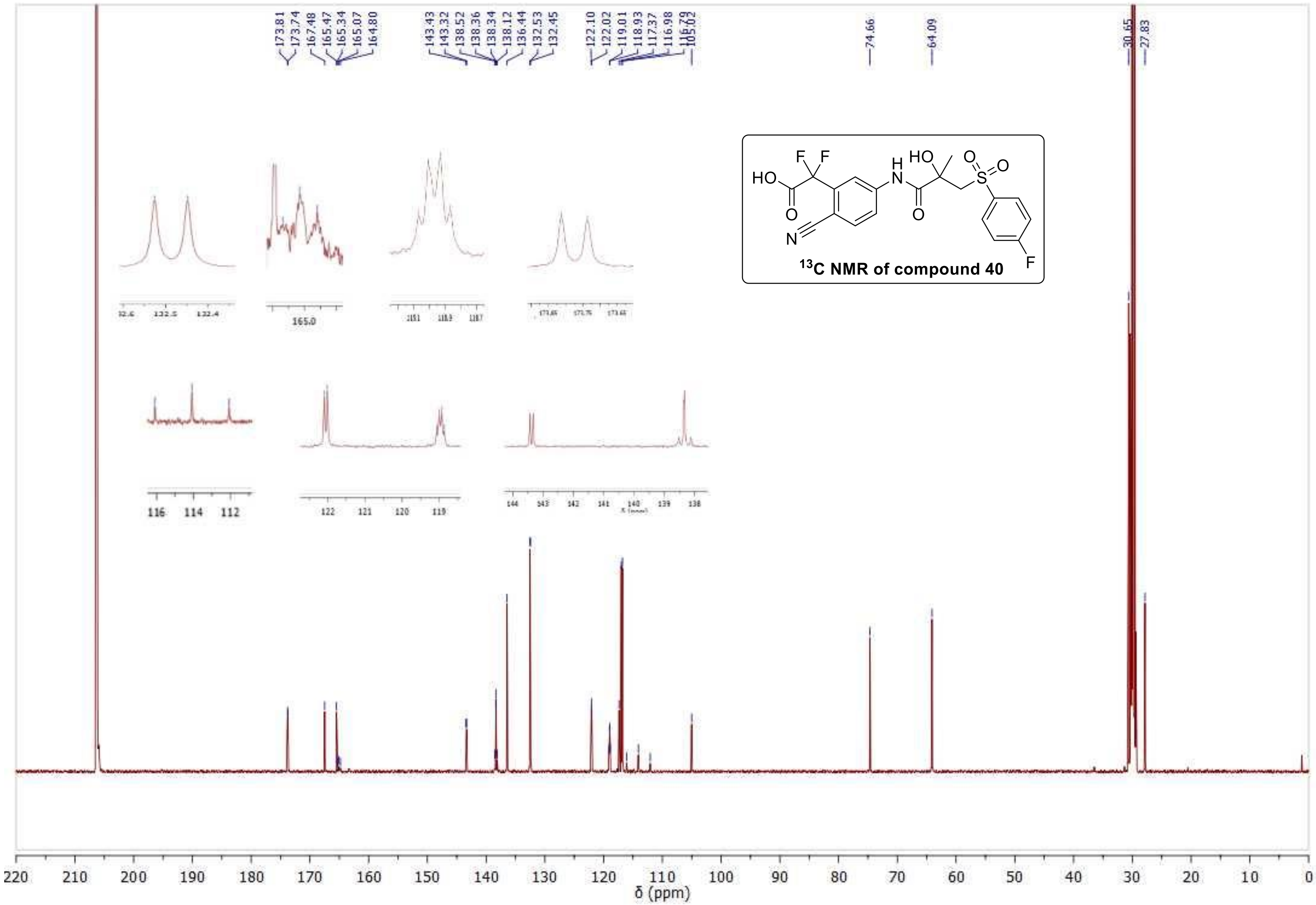

7.56
7.54
7.35
7.33
7.24
7.23
7.22
7.17
7.16
4.75
4.74
4.38
3.67
3.24
3.23
3.21
3.19
3.18
3.17
3.16
3.10
3.08
3.07
3.05
2.83
2.81
2.80
2.79
2.78
1.32
BocHN
O
O
OMe
HN
HO2CF2C
1H NMR of
Compound 39
2.00
1.90
5.07
1.04
1.05
3.19
1.08
2.08
1.11
9.01
δ (ppm)

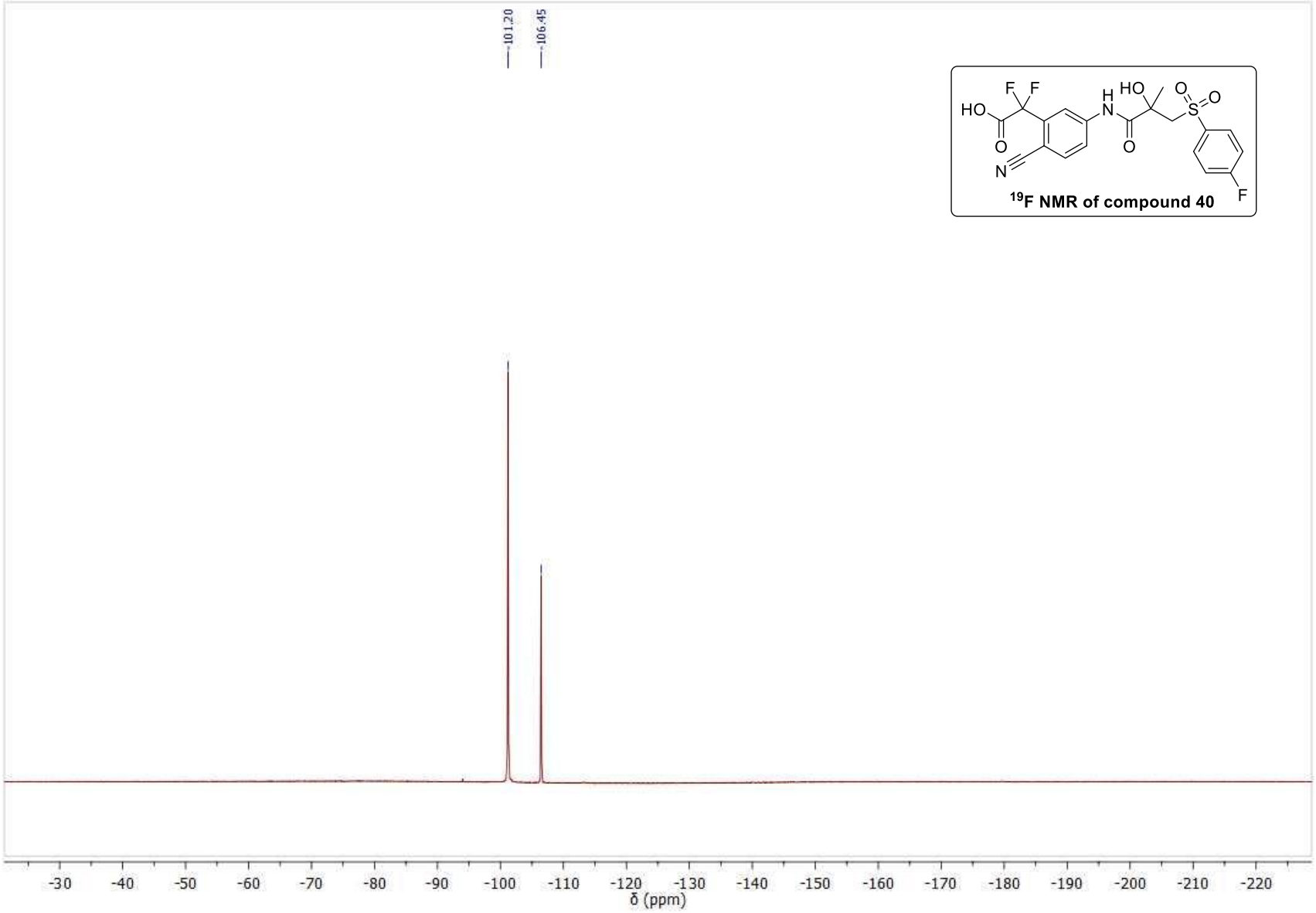

172.26
172.17
165.79
165.48
165.24
156.18
141.29
138.66
130.74
130.22
129.05
127.25
126.37
126.32
114.69
112.71
79.46
56.40
54.13
52.50
38.75
37.97
28.56
BocHN
O
O
OMe
HN
HO2CF2C
13C NMR of
Compound 39
δ (ppm)

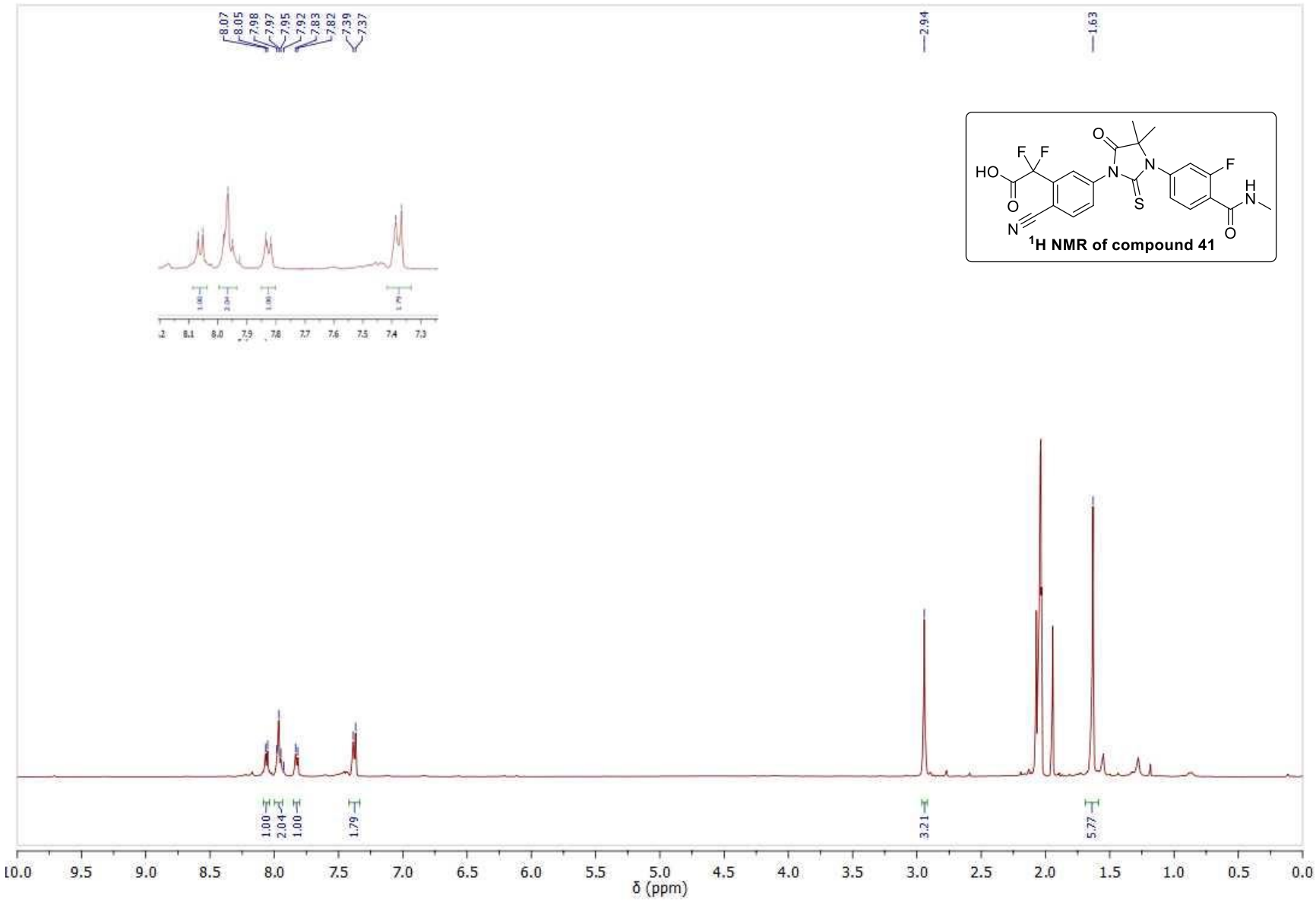

-103.67
BocHN
O
O
OMe
HN
^{19}F NMR of
Compound 39
HO_2CF_2C
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)

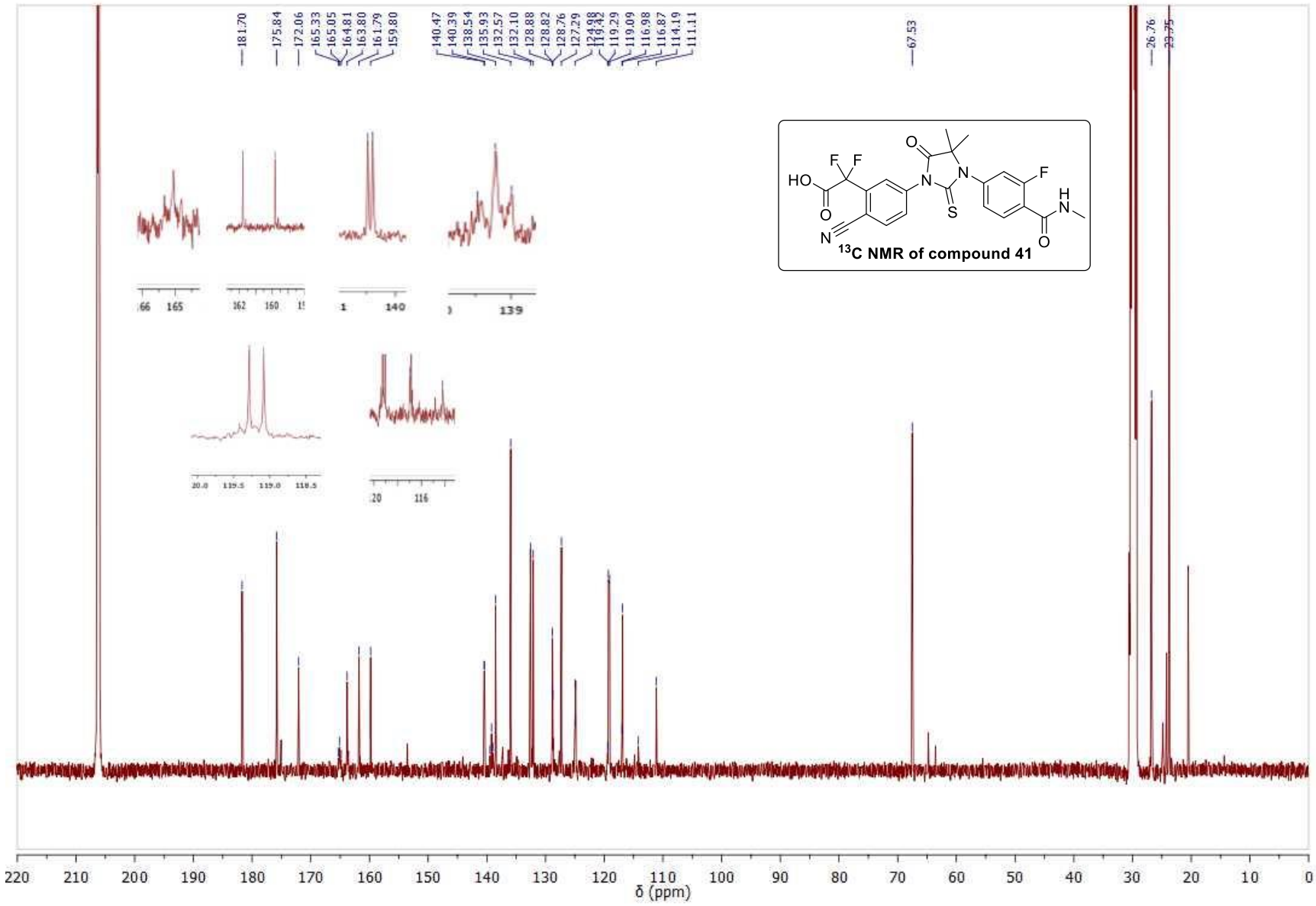


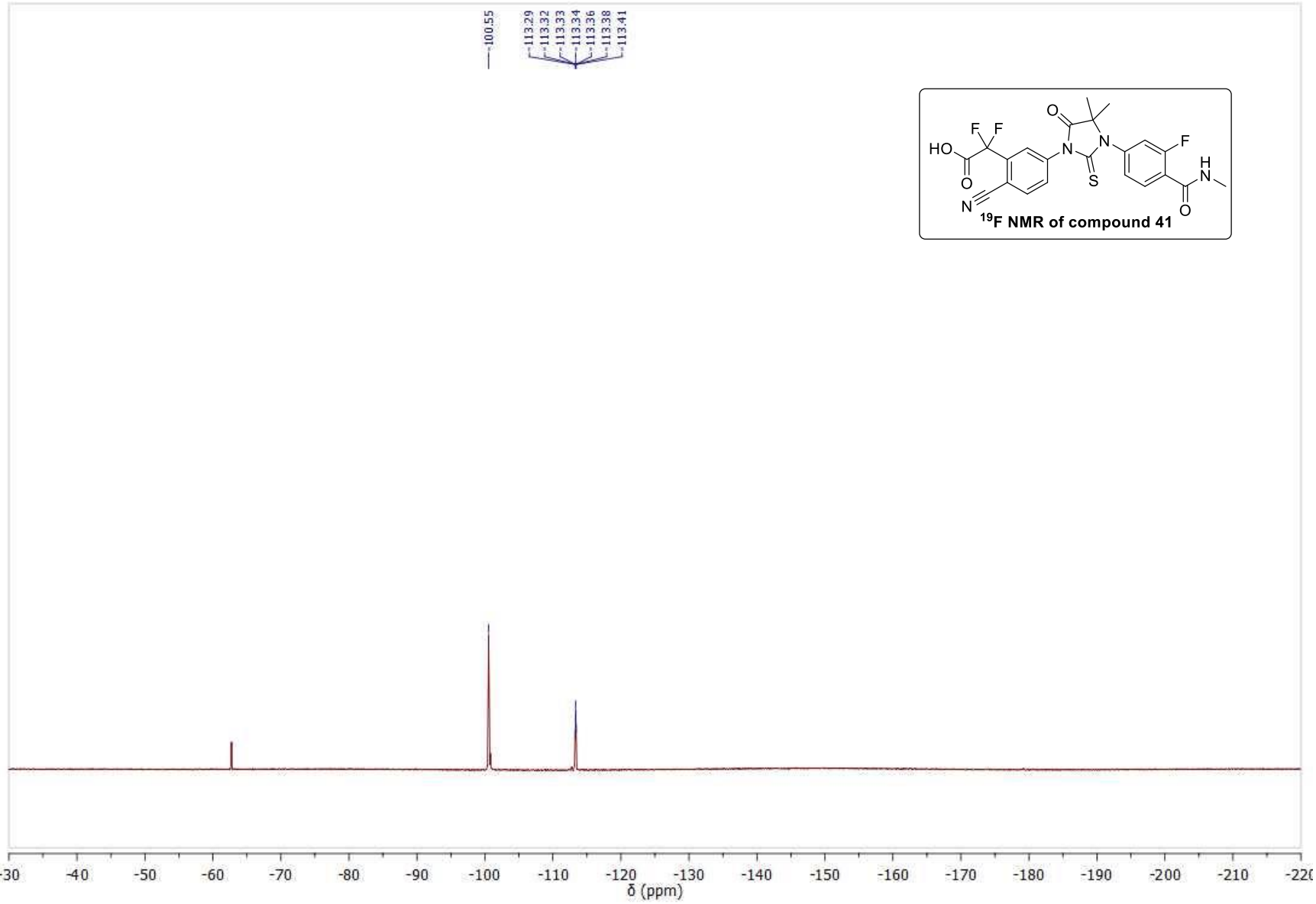
^{1}H NMR of compound 40


173.81
173.74
167.48
165.47
165.34
165.07
164.80
143.43
143.32
138.52
138.36
138.34
138.12
136.44
132.53
132.45
122.10
122.02
119.01
118.93
117.37
116.98
116.79
105.02
74.66
64.09
30.65
27.83
HO
F
F
H
N
HO
O
S
O
O
O
N
F
¹³C NMR of compound 40
δ (ppm)

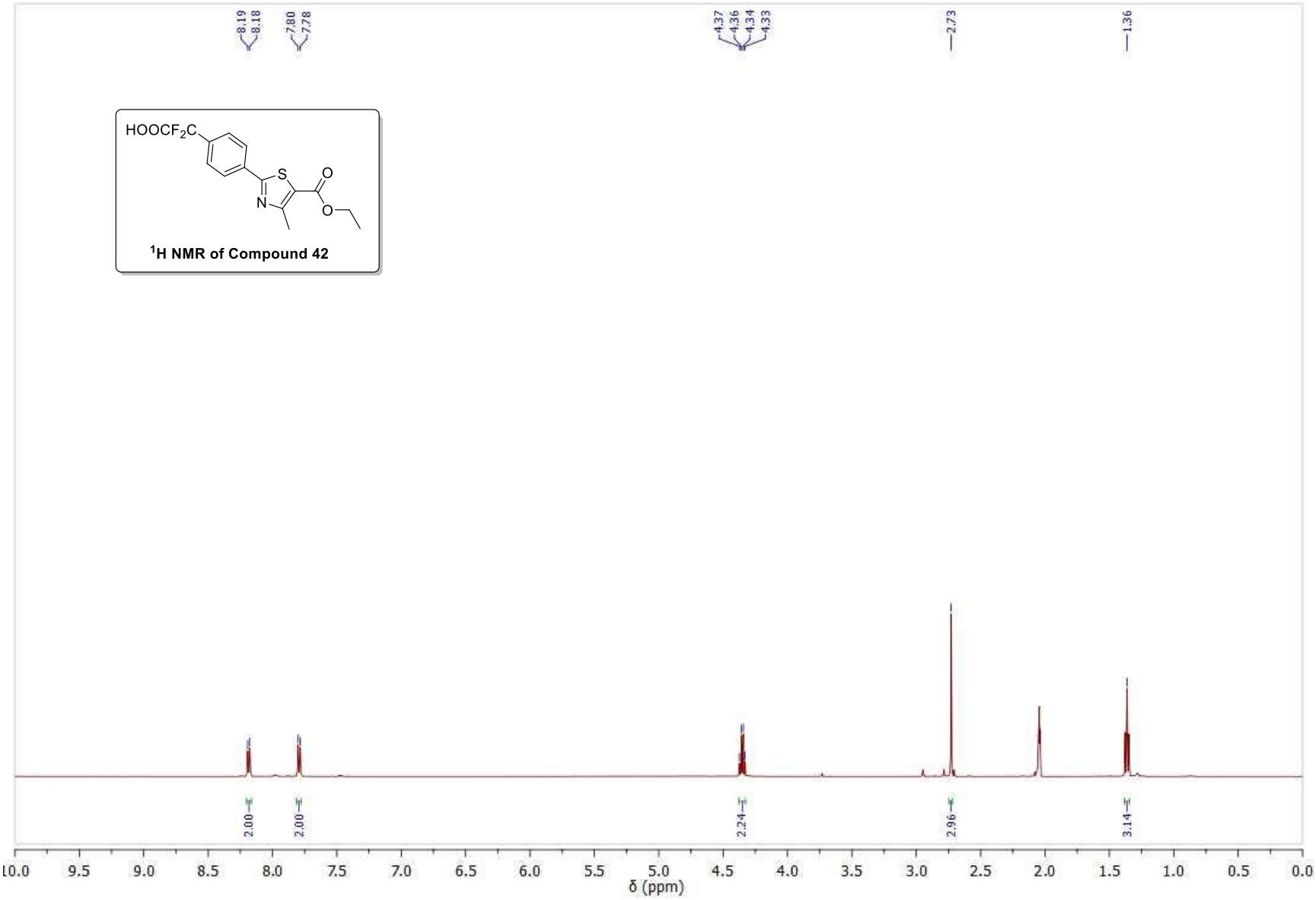

-101.20
-106.45
HO
F
F
O
N
H
N
HO
O
O
S
O
F
19F NMR of compound 40
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)


8.07
8.05
7.98
7.97
7.95
7.92
7.83
7.82
7.39
7.37
2.94
1.63
F F
HO
O
N
O
N
N
S
F
H
N
O
1H NMR of compound 41
1.00
2.04
1.00
1.79
3.21
5.77
δ (ppm)

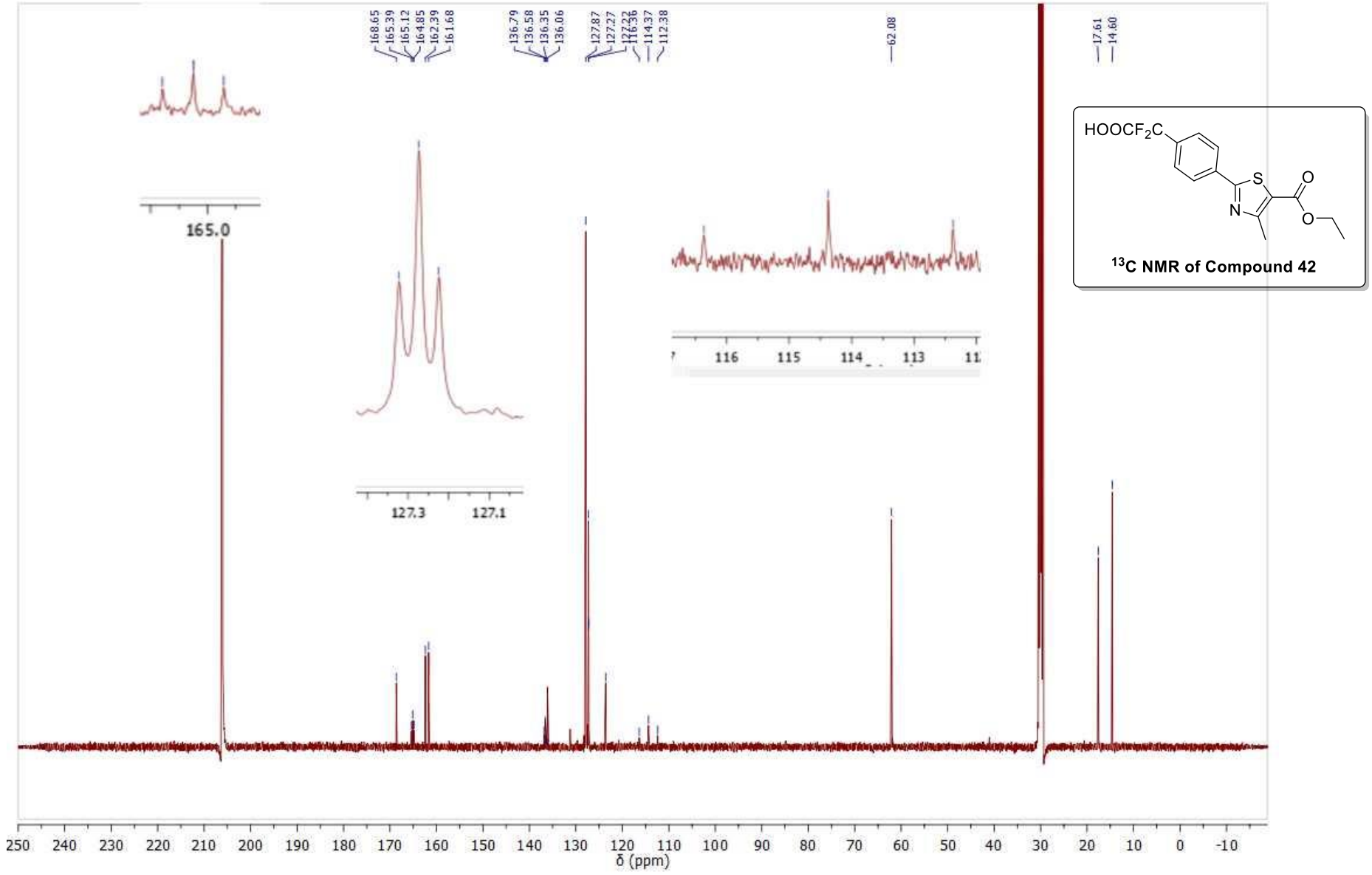

181.70
175.84
172.06
165.33
165.05
164.81
163.80
161.79
159.80
140.47
140.39
138.54
135.93
132.57
132.10
128.88
128.82
128.76
127.29
124.98
119.42
119.29
119.09
116.98
116.87
114.19
111.11
67.53
26.76
33.75
F
F
HO
O
O
N
N
S
F
H
N
O
N
13C NMR of compound 41
δ (ppm)



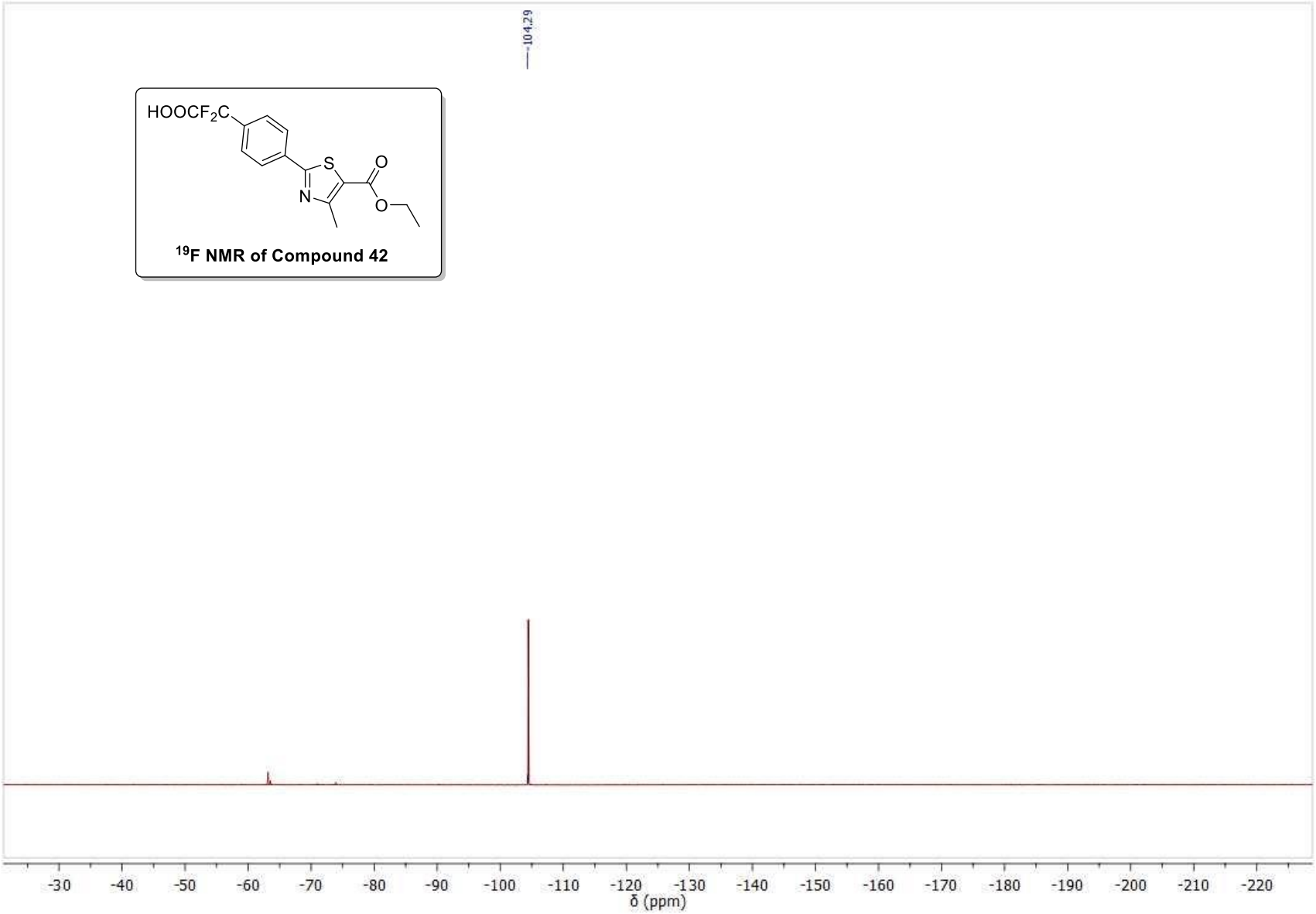
^{19}F NMR of compound 41



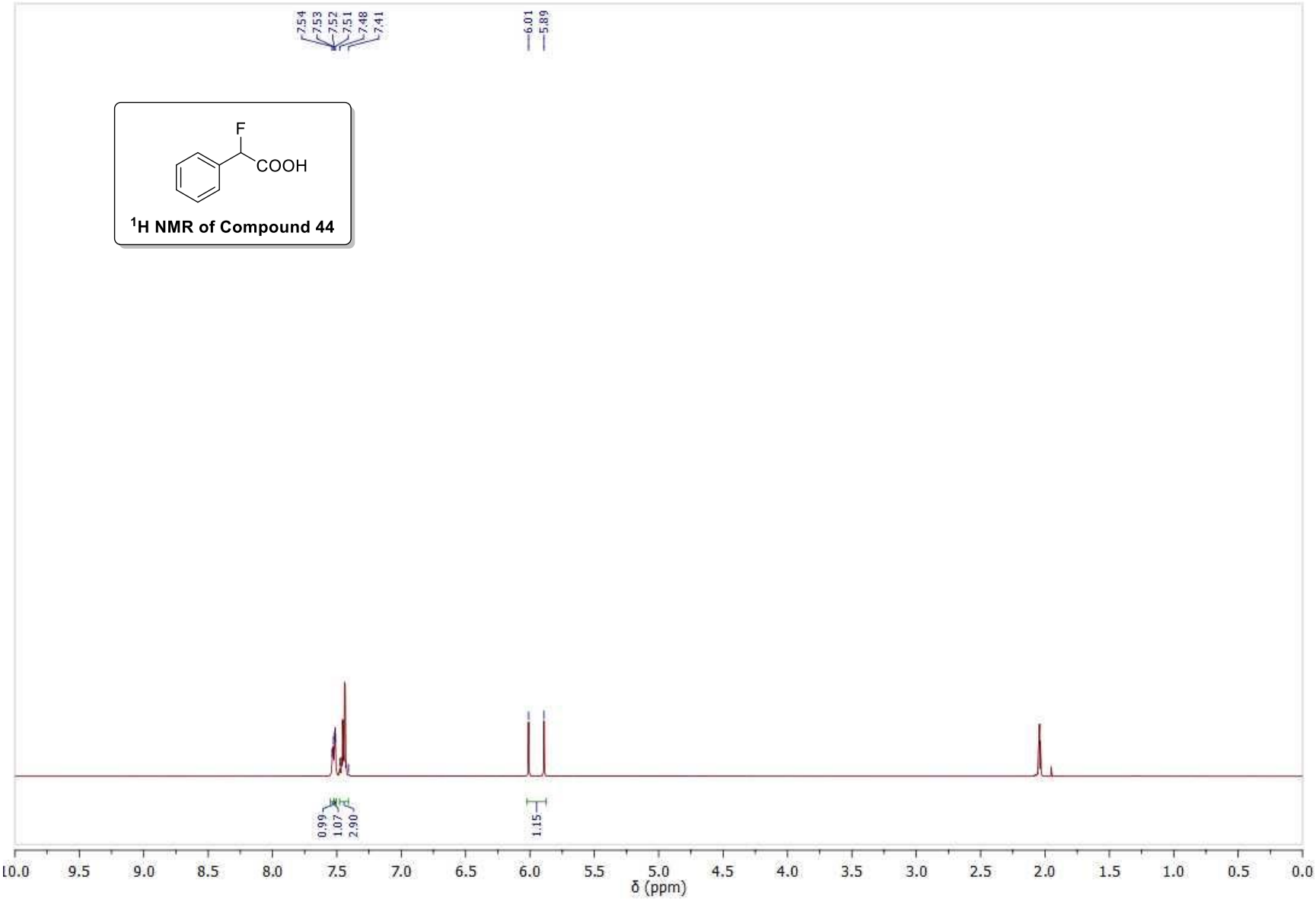
^{1}H NMR of Compound 42



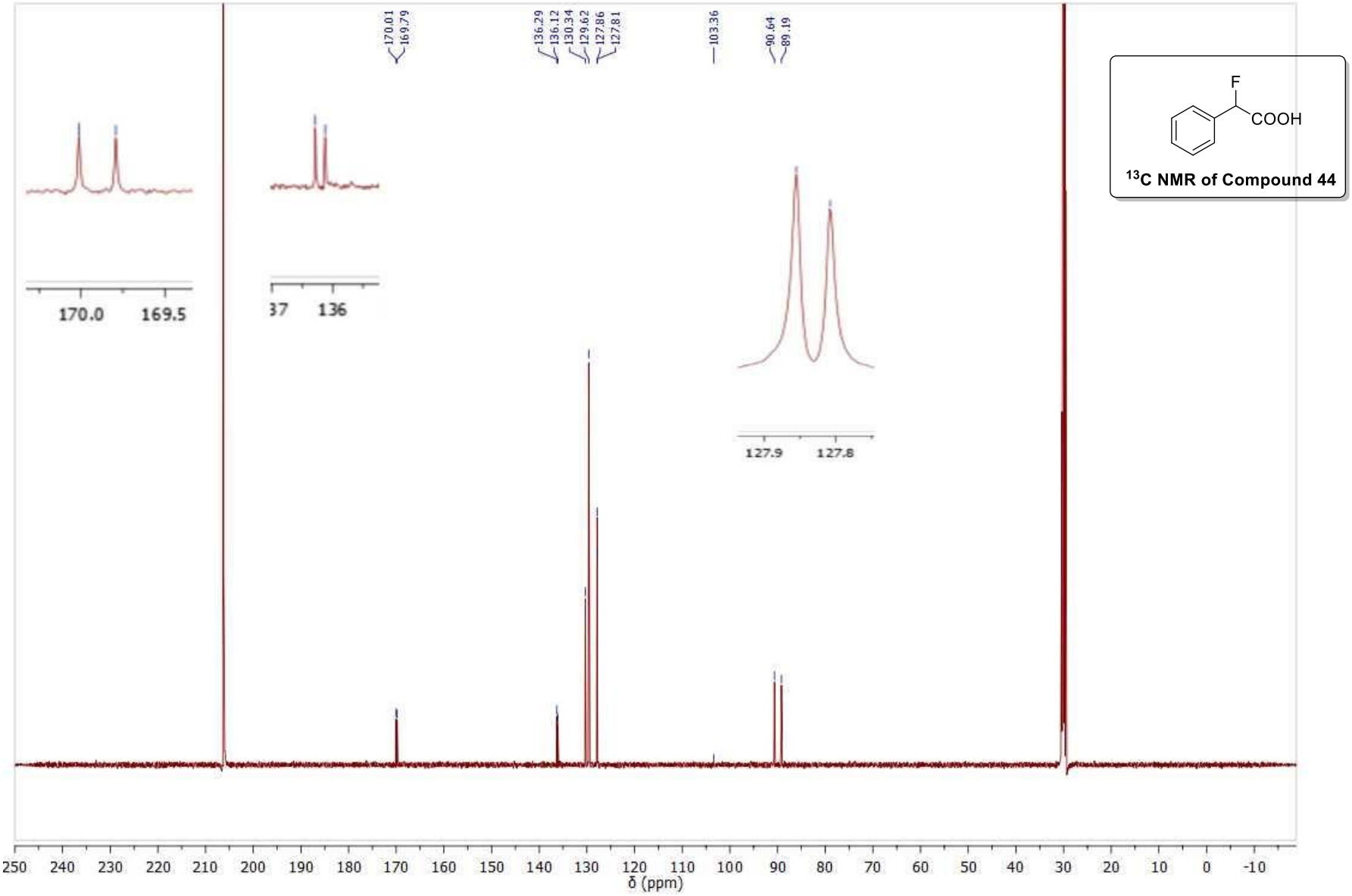
^{13}C NMR of Compound 42



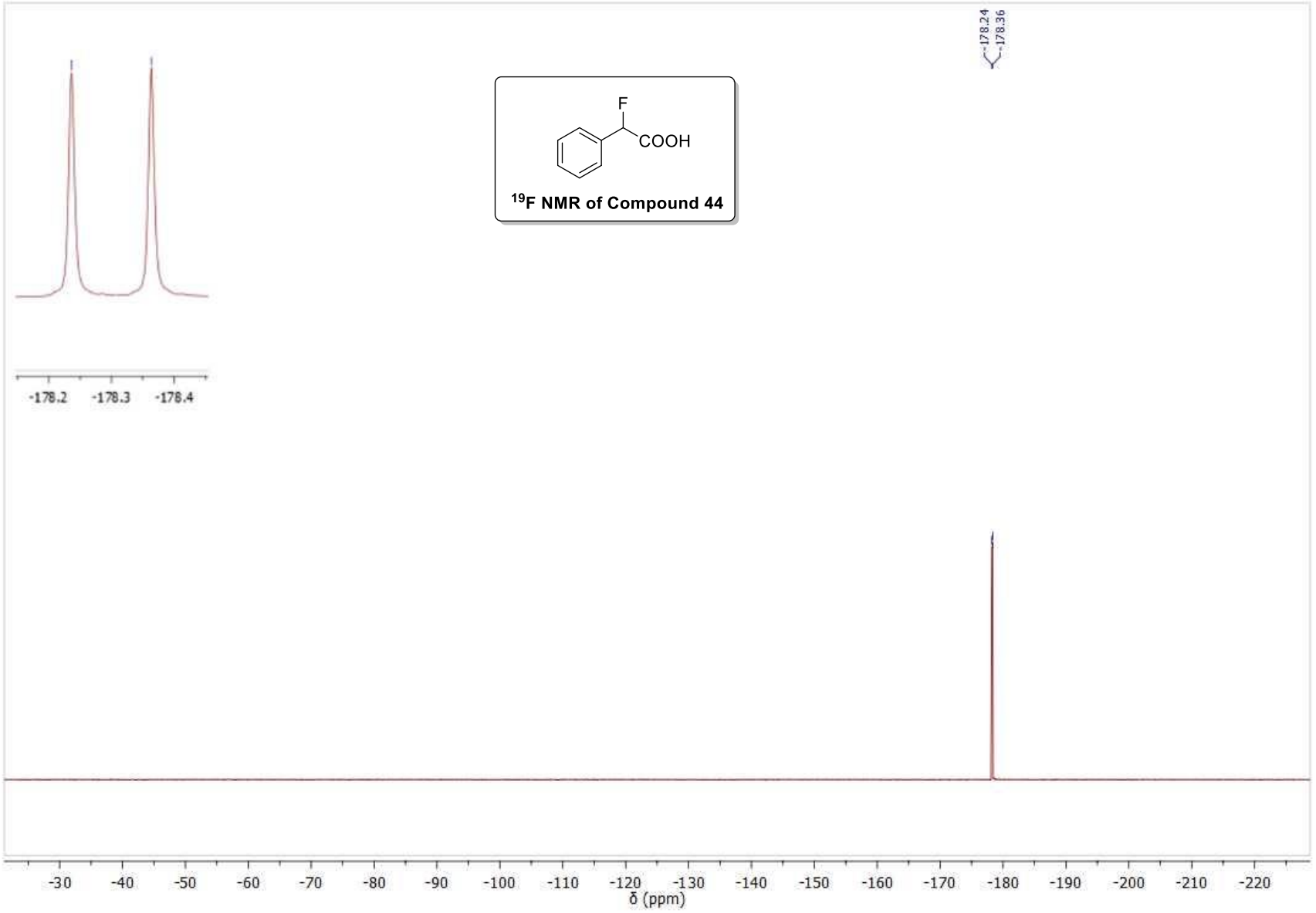
^{19}F NMR of Compound 42

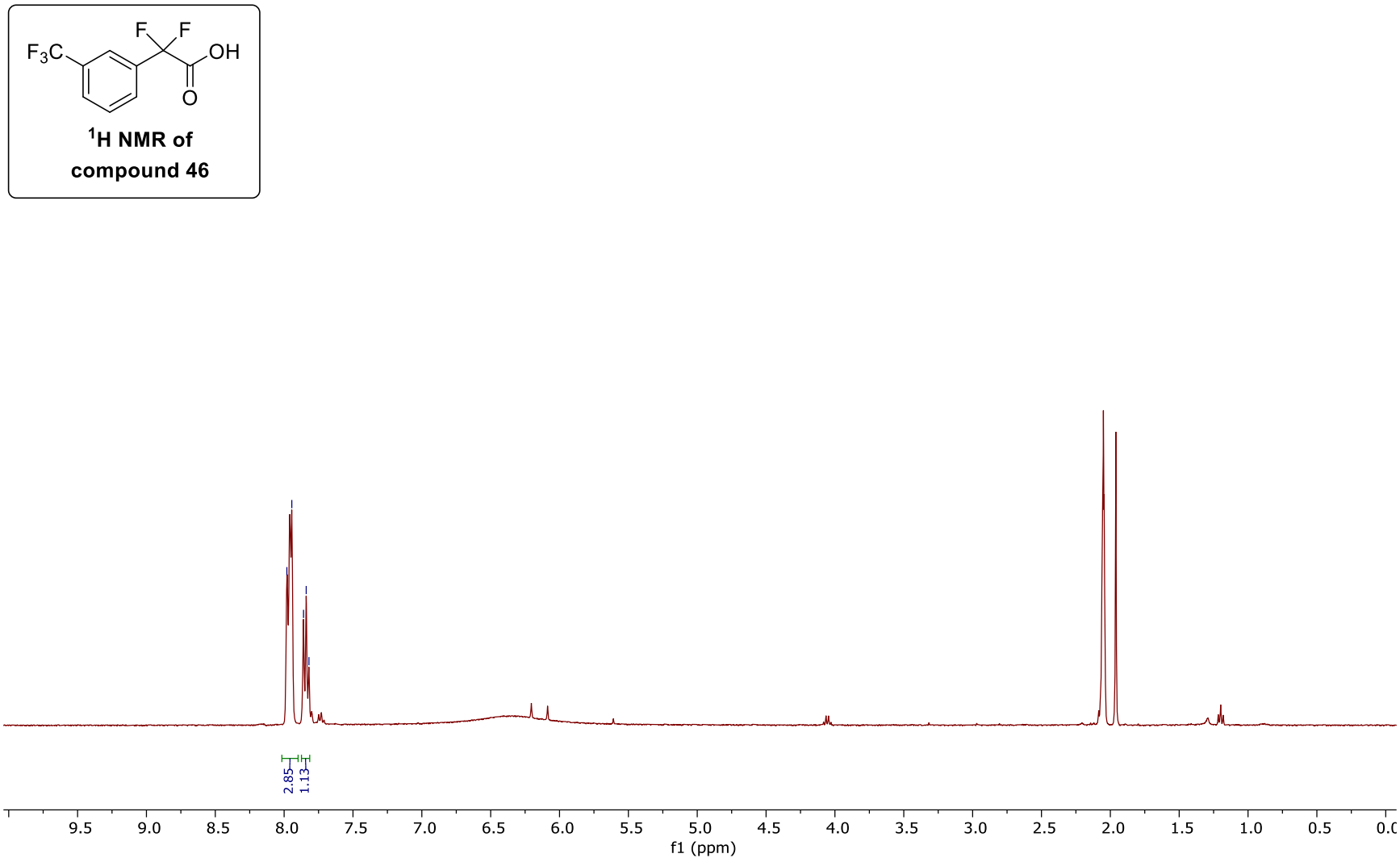


^{1}H NMR of Compound 44

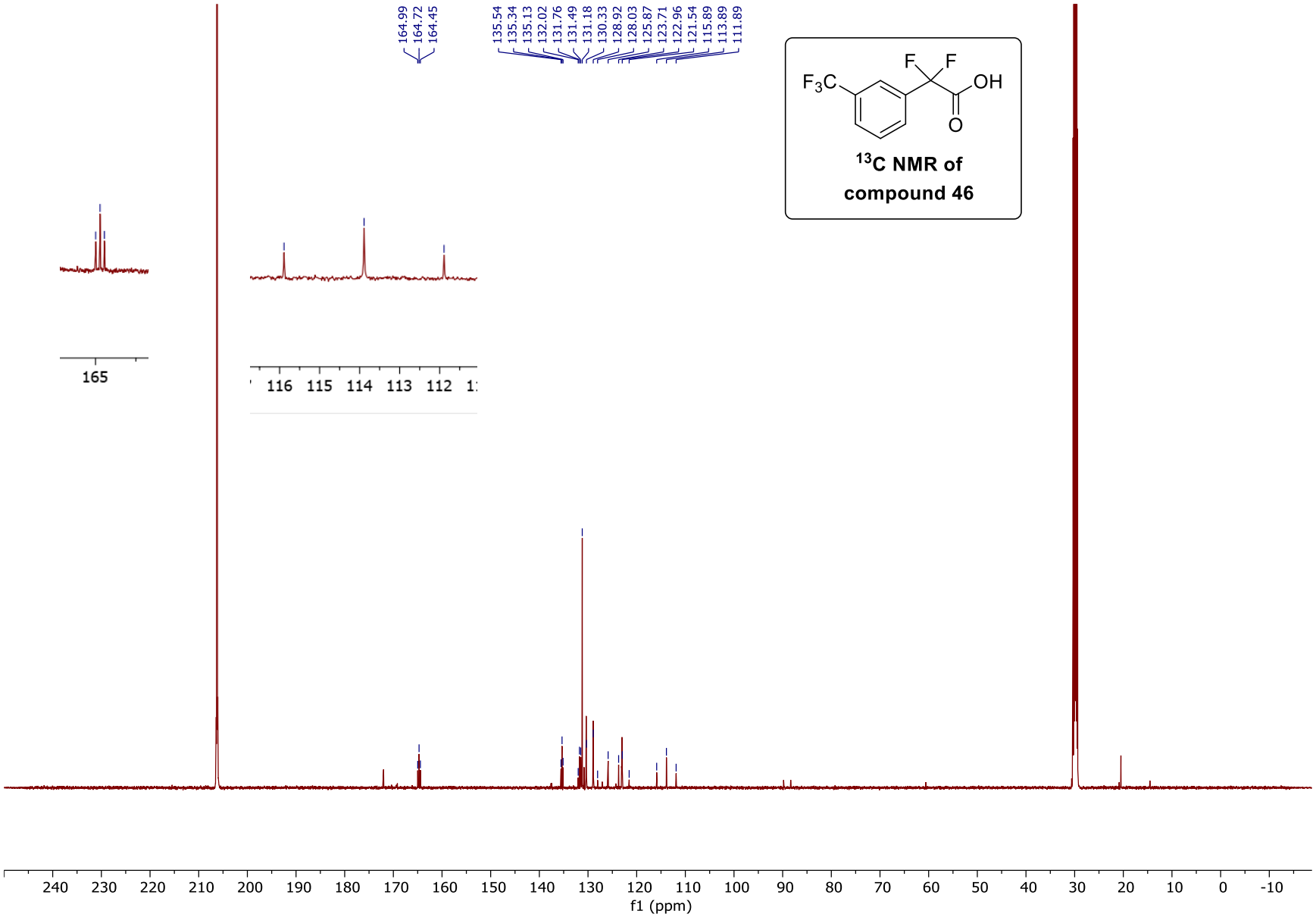


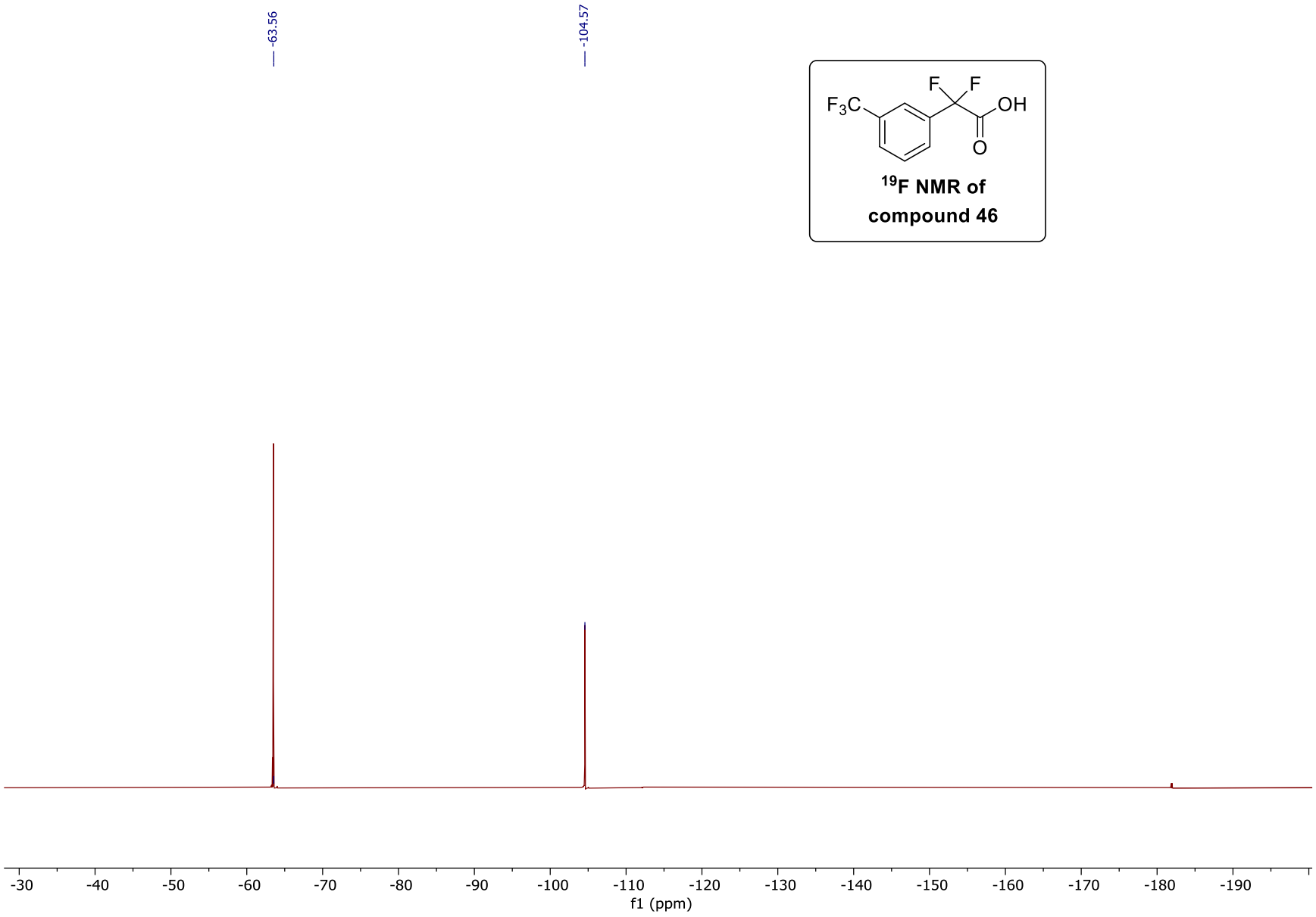
^{13}C NMR of Compound 44

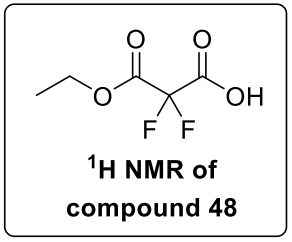

-178.24
-178.36
F
COOH
19F NMR of Compound 44
-178.2
-178.3
-178.4
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
δ (ppm)



^{1}H NMR of compound 46

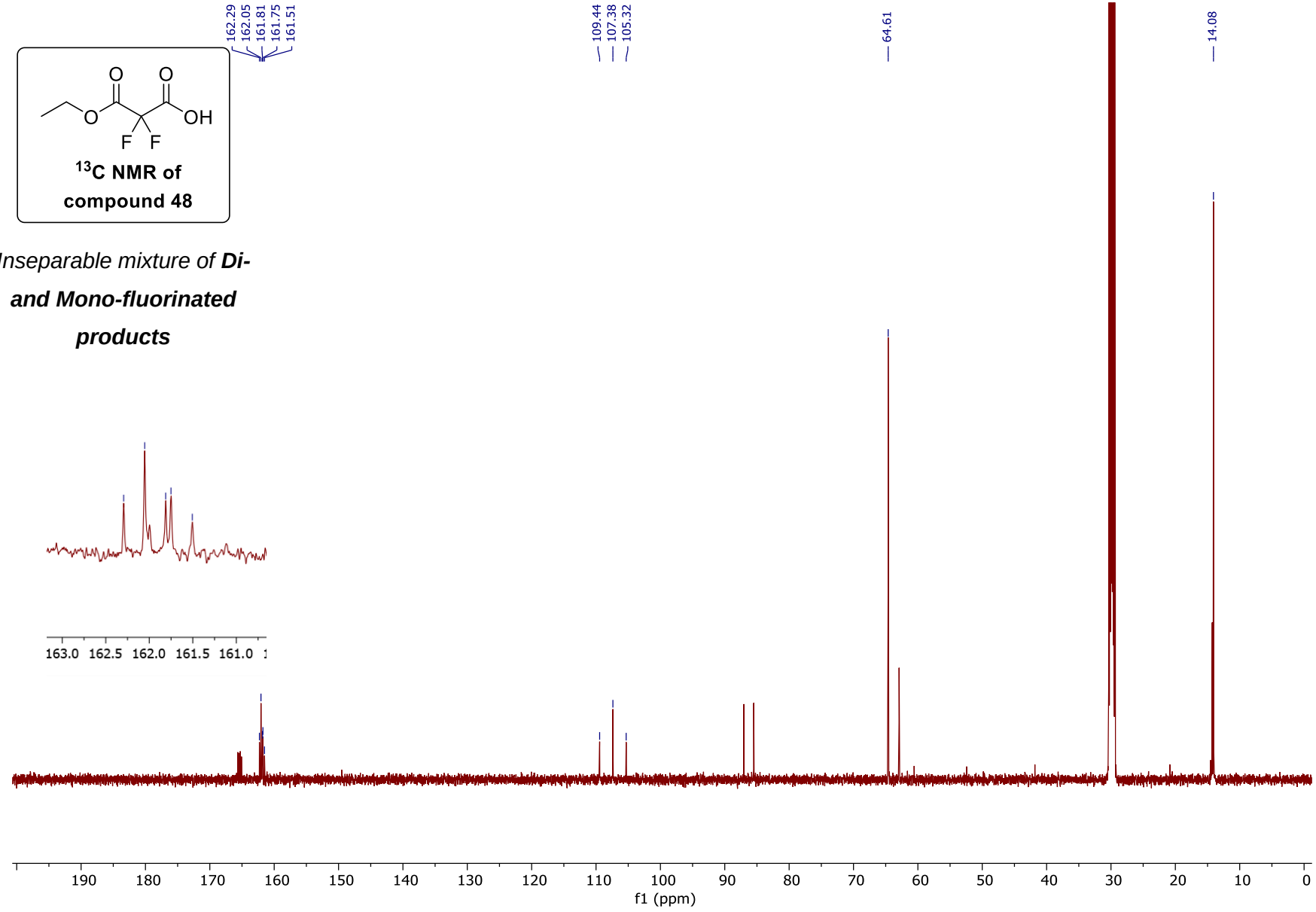

164.99
164.72
164.45
135.54
135.34
135.13
132.02
131.76
131.49
131.18
130.33
128.92
128.03
125.87
123.71
122.96
121.54
115.89
113.89
111.89
F
F
F3C
OH
O
13C NMR of compound 46
165
116 115 114 113 112
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

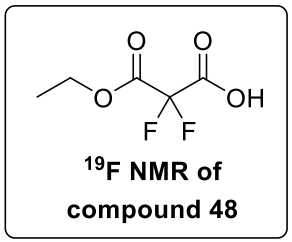

-63.56
-104.57
F
F
F3C
OH
O
19F NMR of
compound 46
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)



^{1}H NMR of compound 48

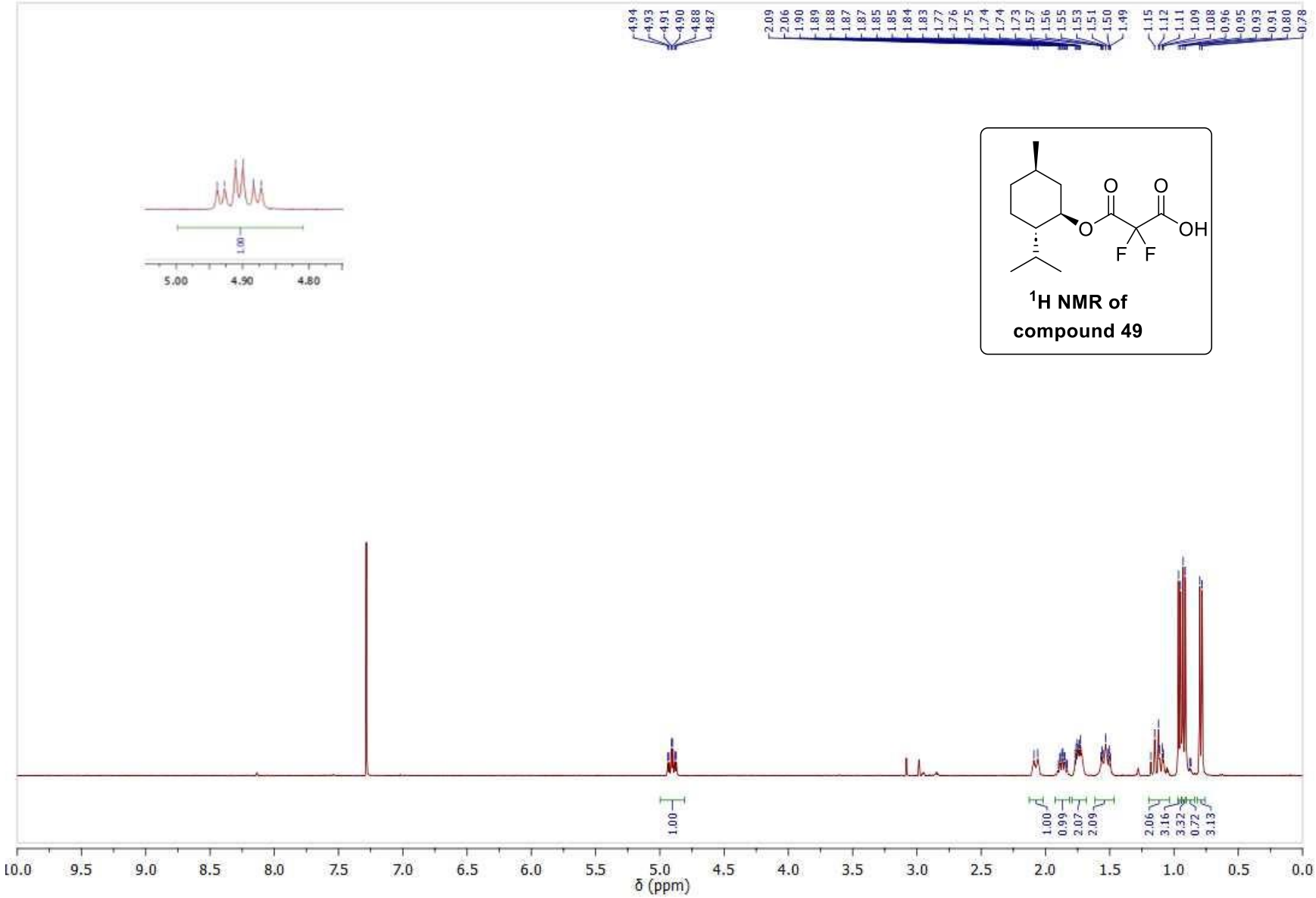
Inseparable mixture of ***Di- and Mono-fluorinated products***

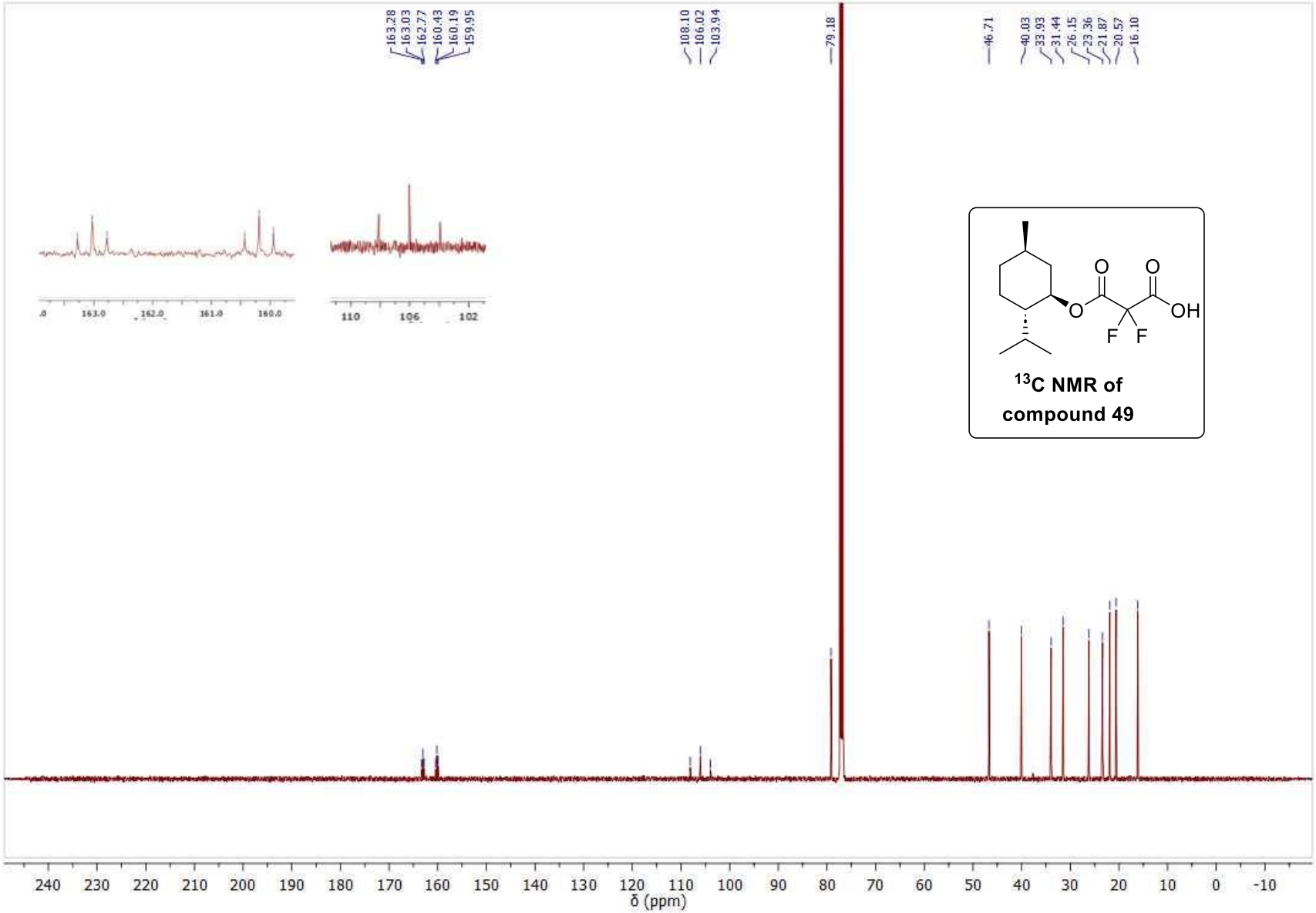

O
O
O
OH
F F
13C NMR of compound 48
Inseparable mixture of Di- and Mono-fluorinated products
162.29
162.05
161.81
161.75
161.51
109.44
107.38
105.32
64.61
14.08
163.0 162.5 162.0 161.5 161.0
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



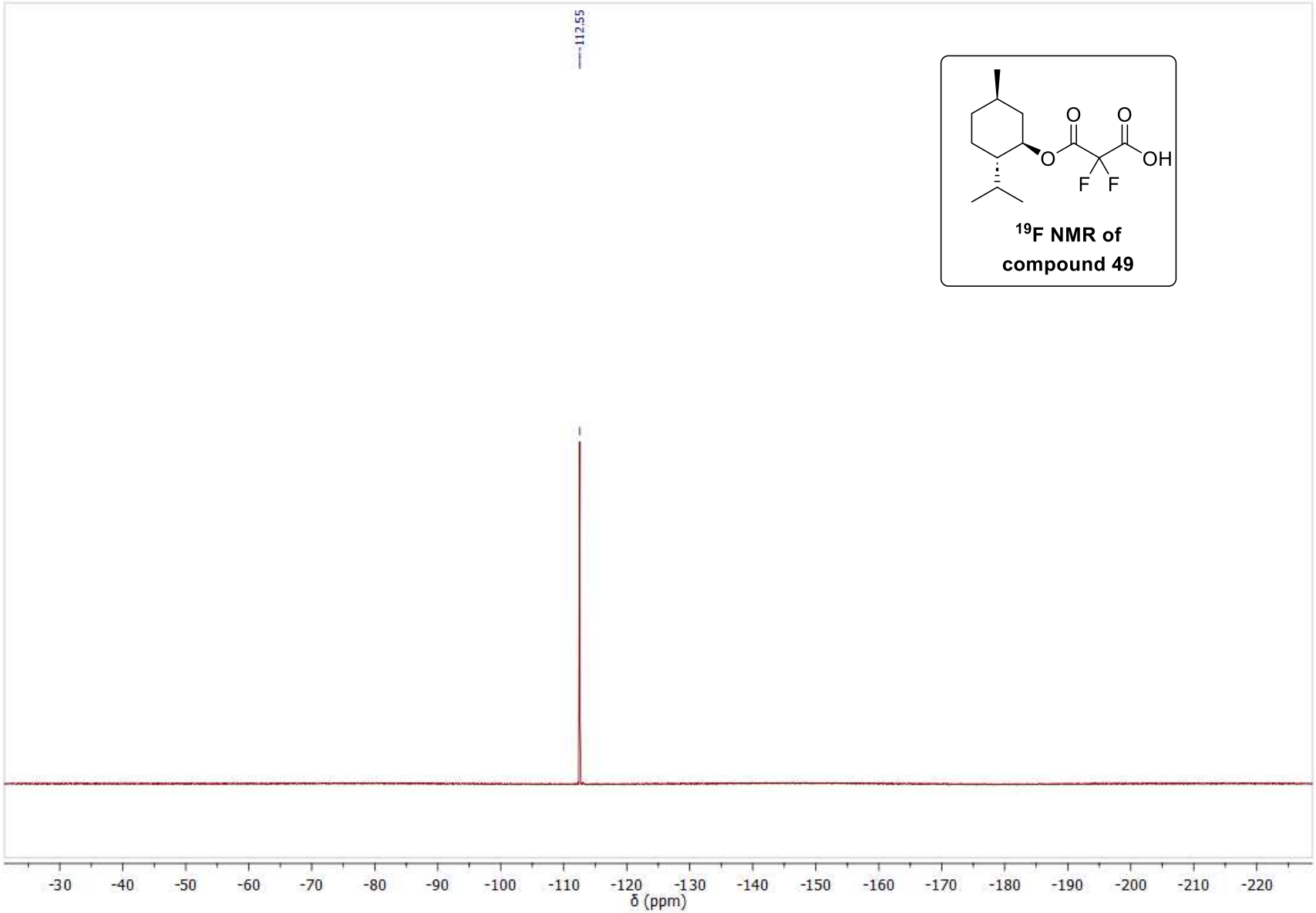
^{19}F NMR of compound 48

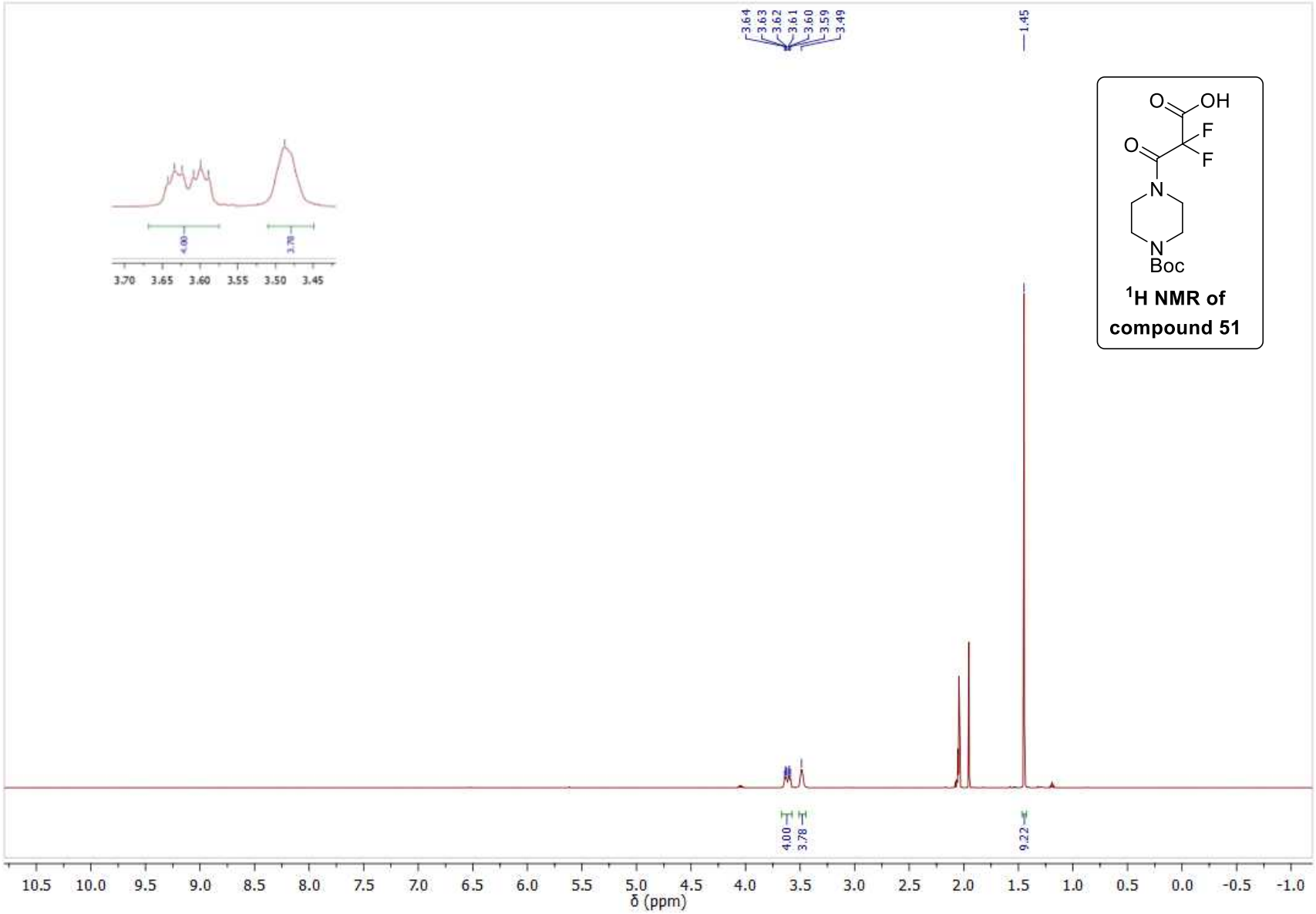
Inseparable mixture of ***Di- and Mono-fluorinated products***


4.94
4.93
4.91
4.90
4.88
4.87
2.09
2.06
1.90
1.89
1.88
1.87
1.87
1.85
1.85
1.84
1.83
1.77
1.76
1.75
1.74
1.74
1.73
1.57
1.56
1.55
1.53
1.51
1.50
1.49
1.15
1.12
1.11
1.09
1.08
0.96
0.95
0.93
0.91
0.80
0.78
1.00
5.00
4.90
4.80
O
O
O
OH
F
F
1H NMR of
compound 49
1.00
1.00
0.99
2.07
2.09
2.06
3.16
3.32
0.72
3.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
δ (ppm)

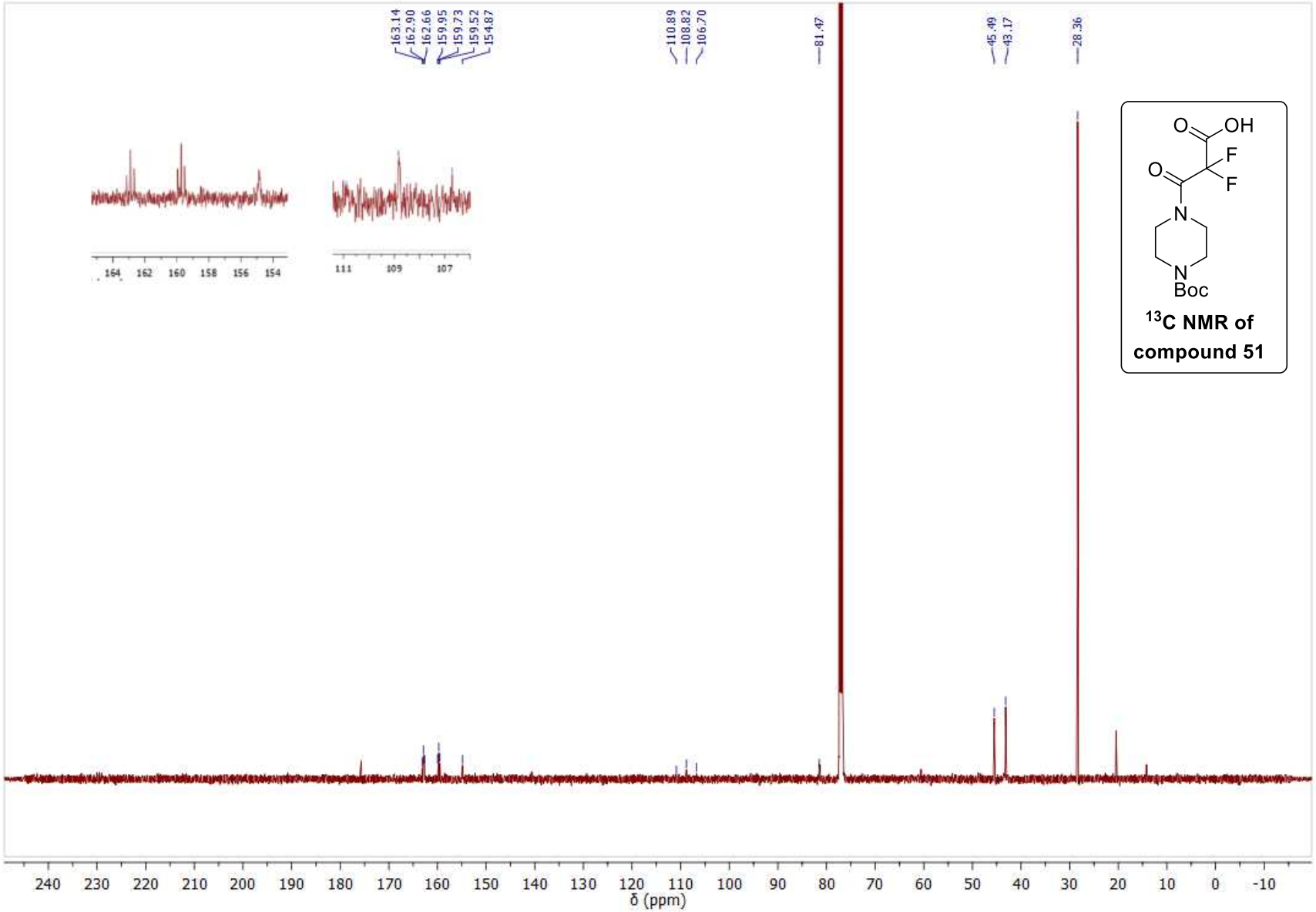


^{13}C NMR of compound 49

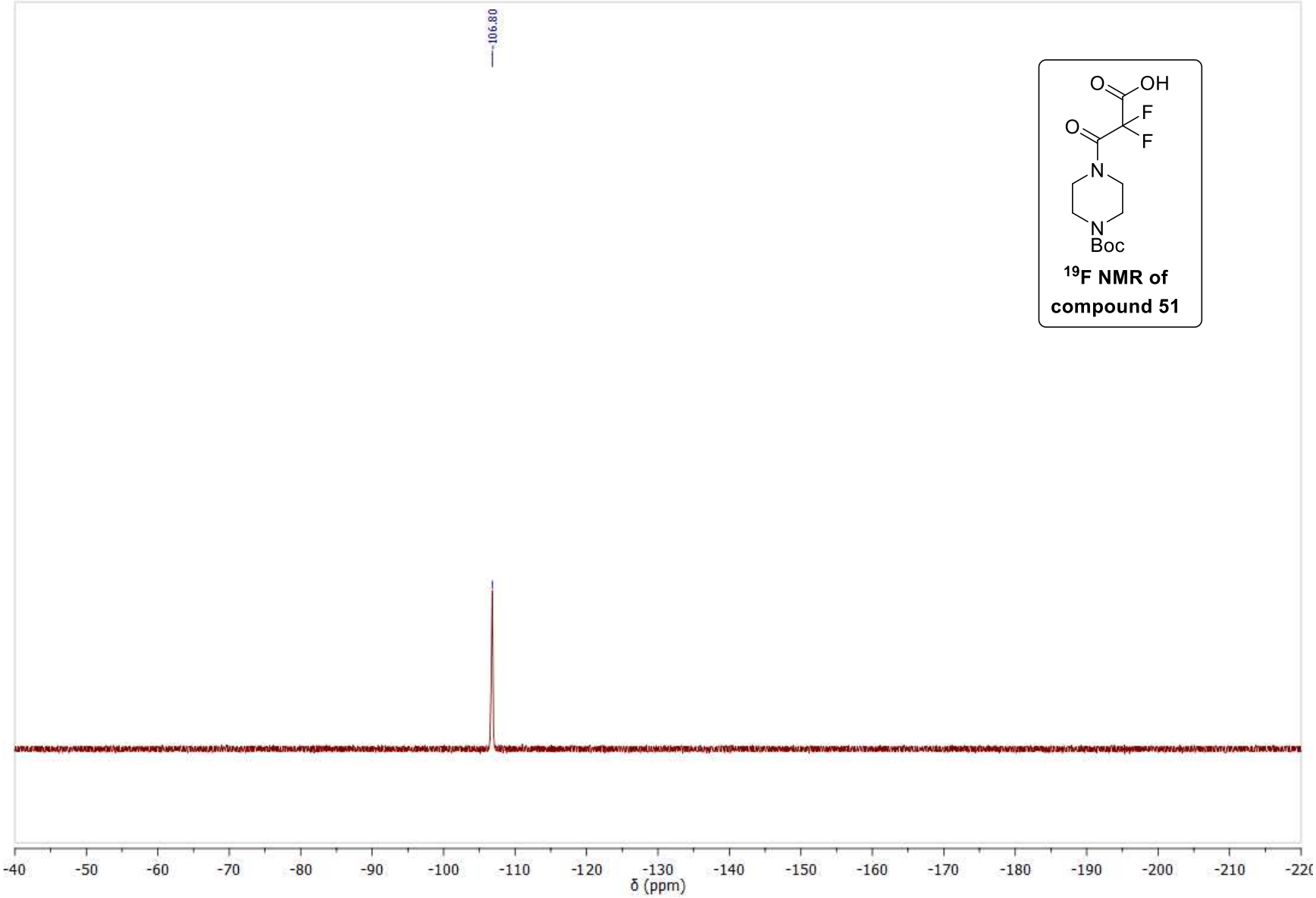

-112.55
O
O
O
OH
F F
19F NMR of compound 49
-30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
δ (ppm)



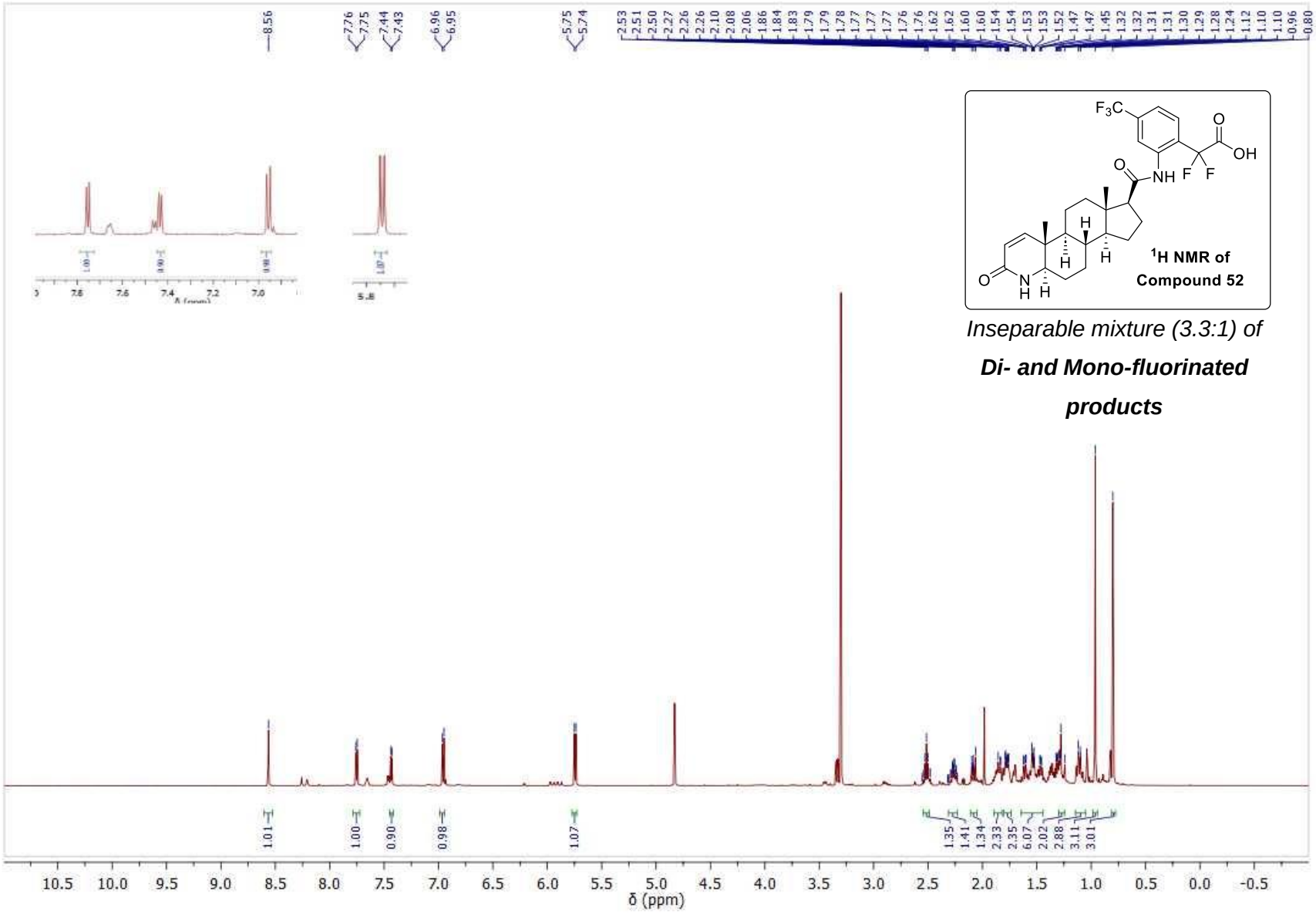
^{1}H NMR of compound 51

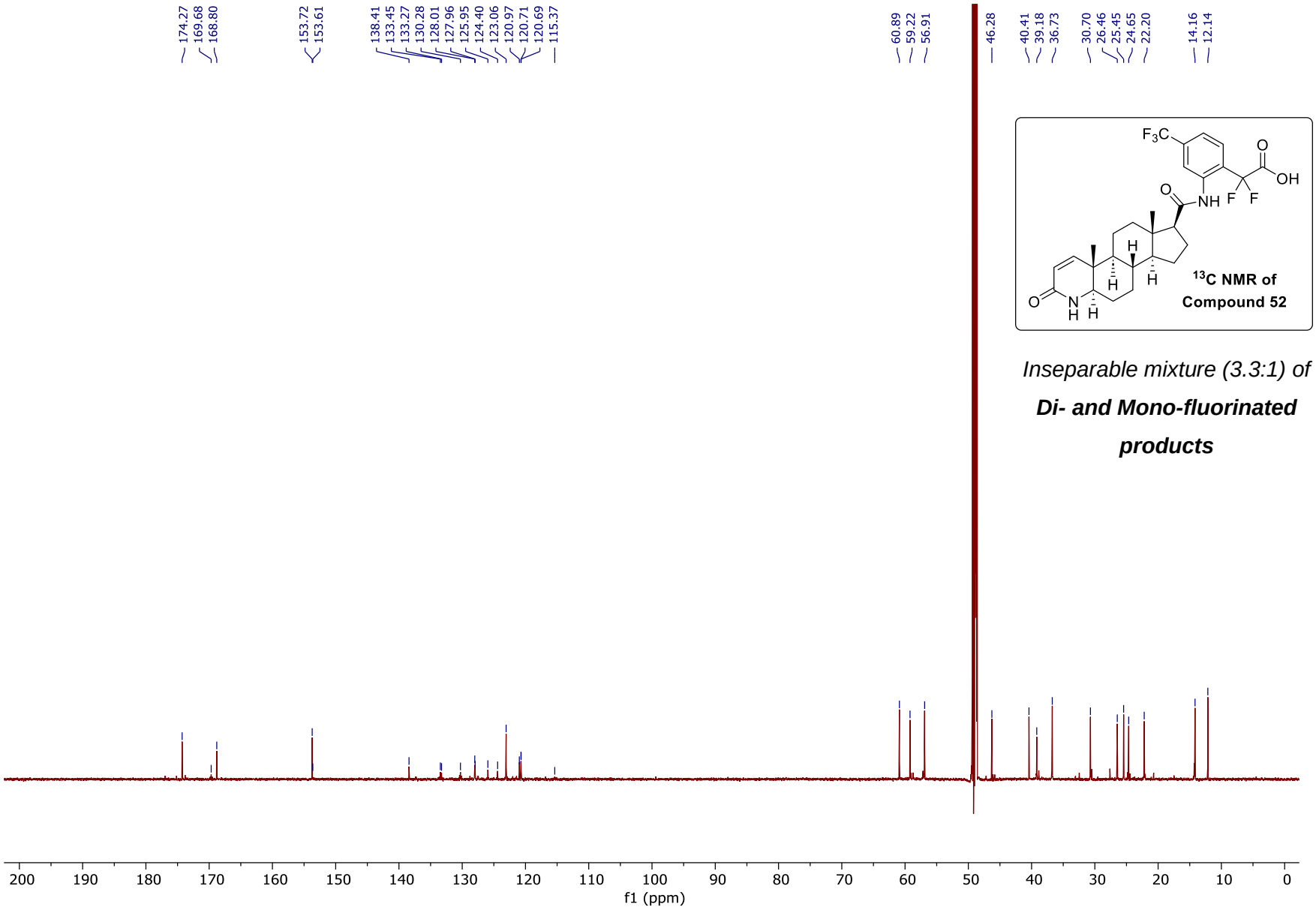


^{13}C NMR of compound 51



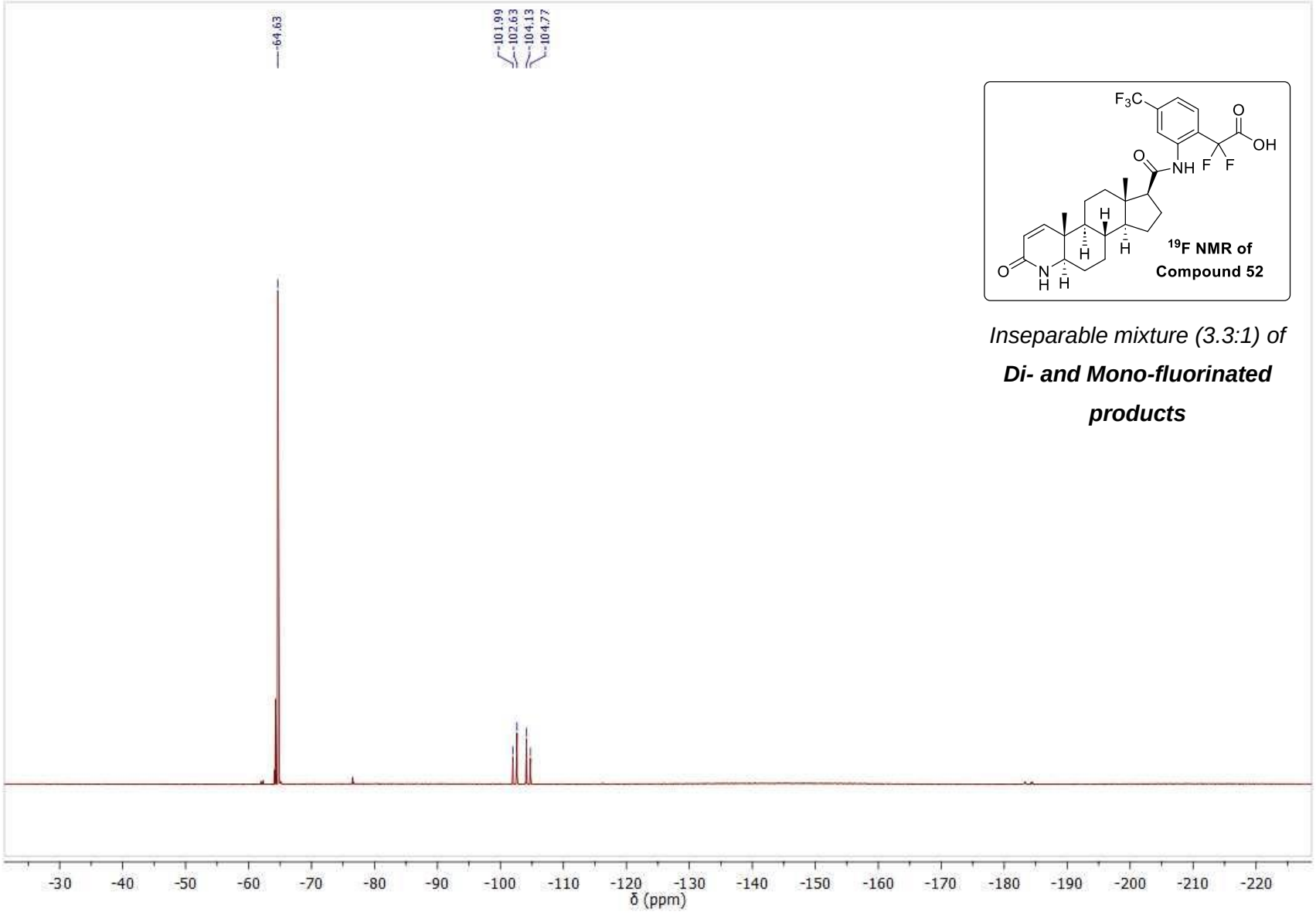
^{19}F NMR of compound 51


F3C
O
OH
O
NH F F
H
H
H
O
N
H H
1H NMR of
Compound 52
Inseparable mixture (3.3:1) of
Di- and Mono-fluorinated
products
δ (ppm)



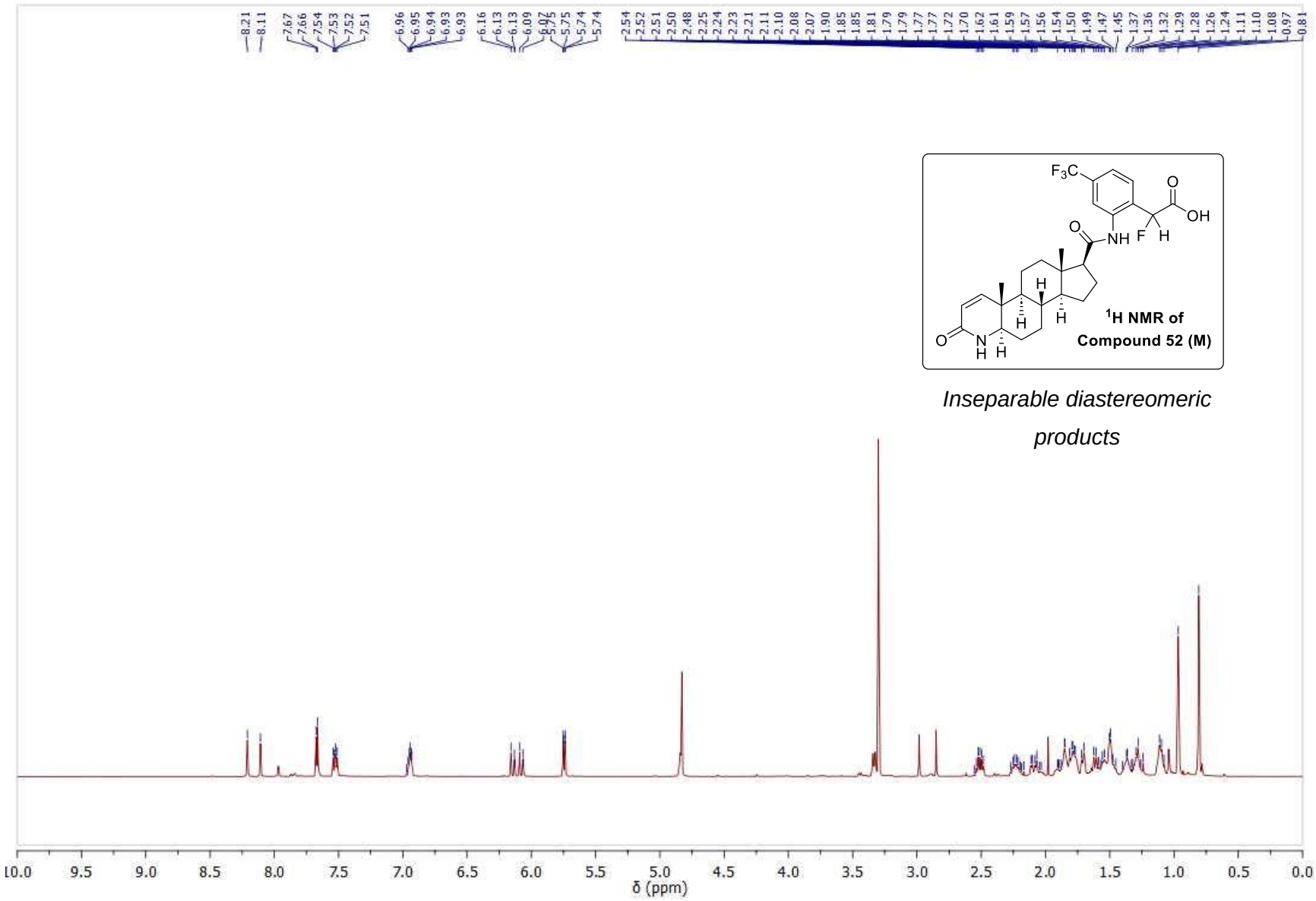
Inseparable mixture (3.3:1) of

Di- and Mono-fluorinated products

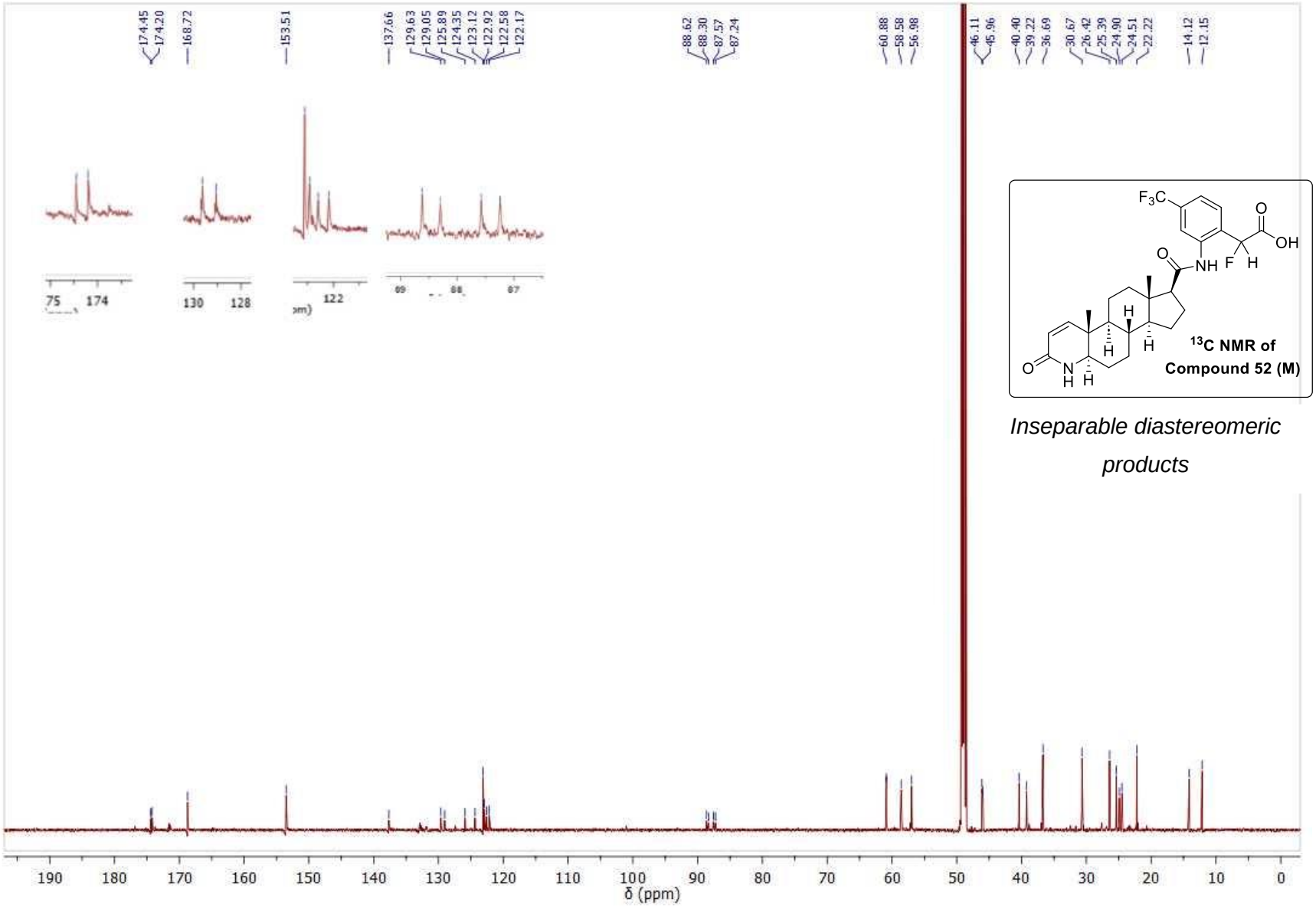


Inseparable mixture (3.3:1) of

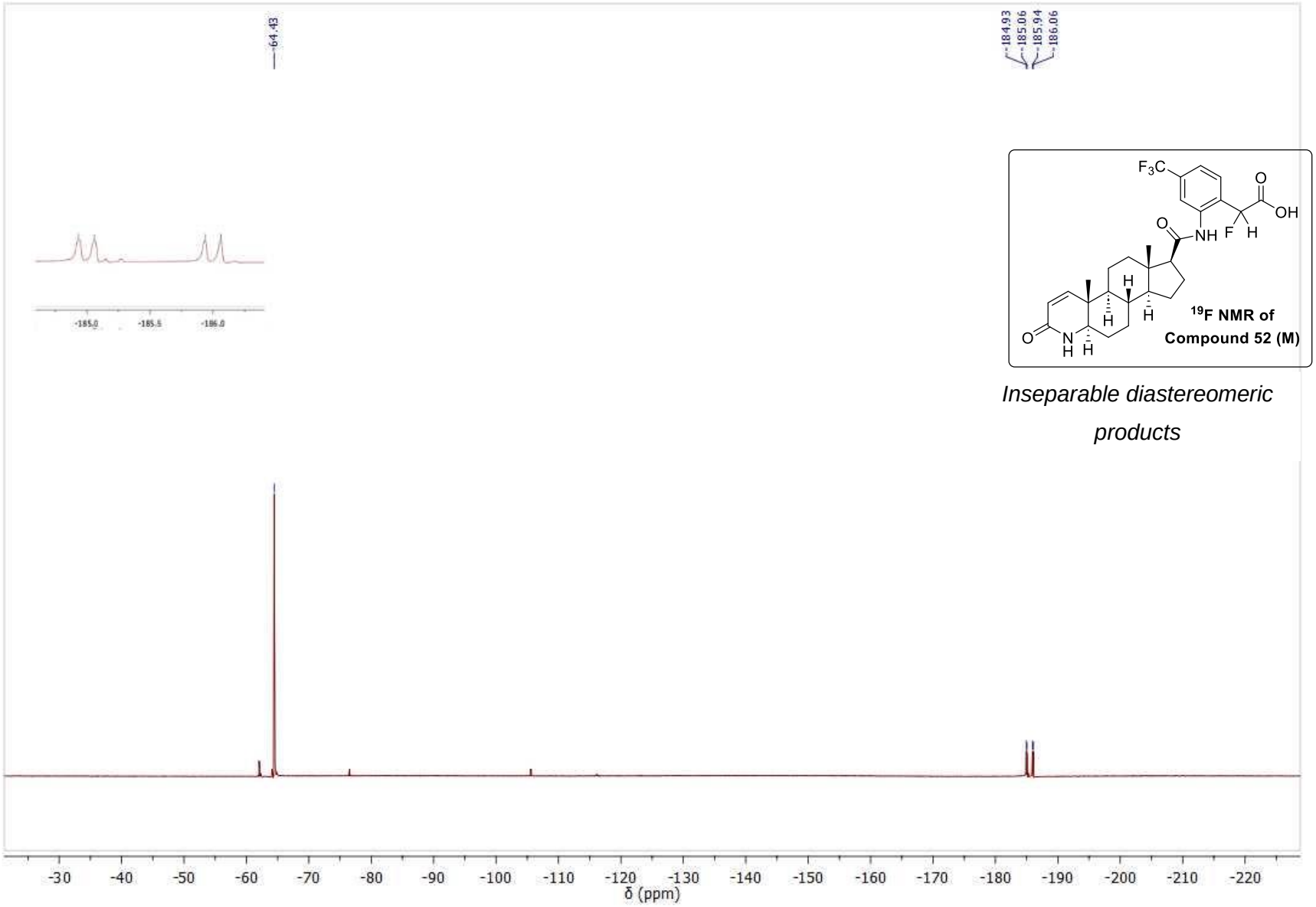
Di- and Mono-fluorinated products



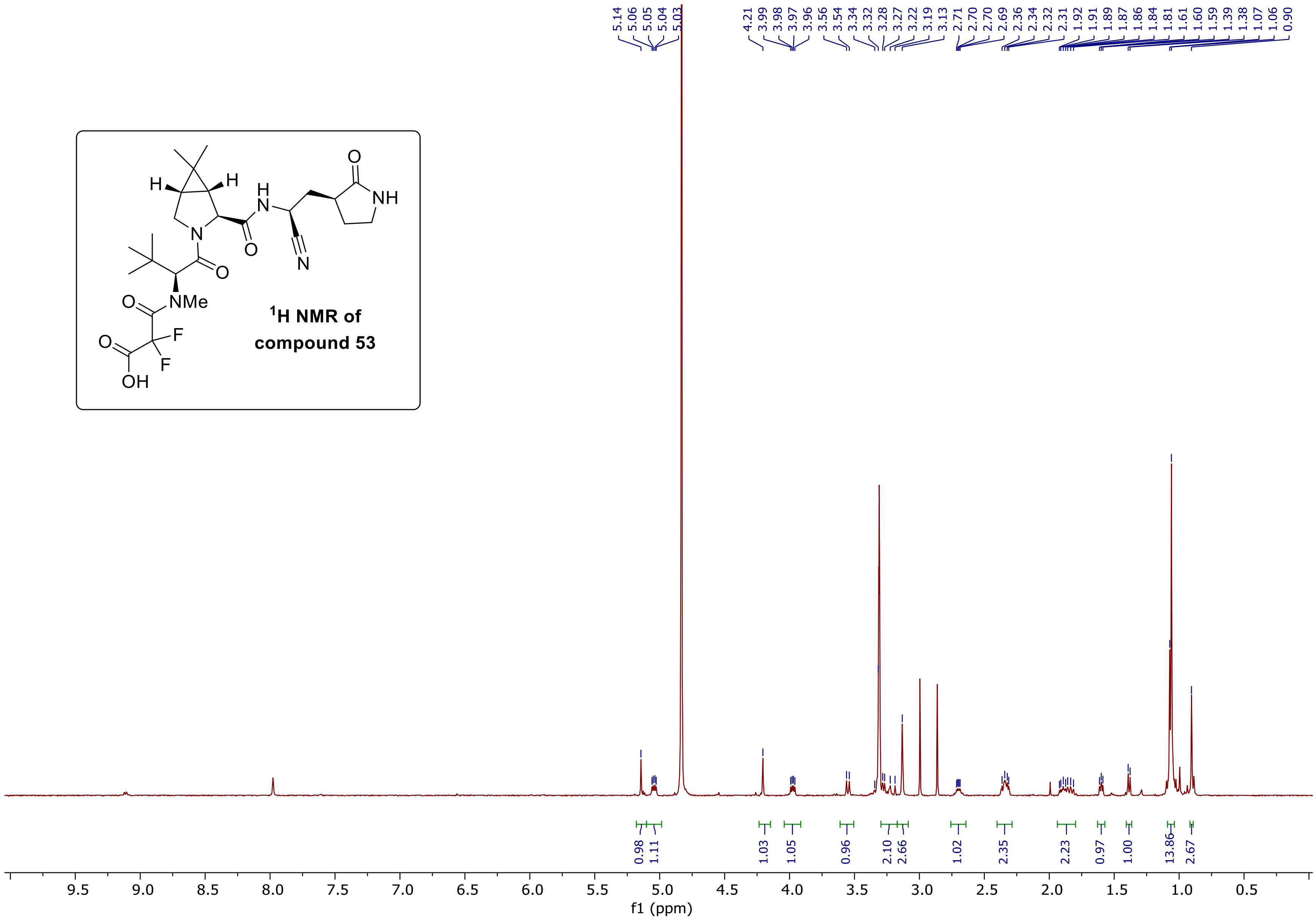
Inseparable diastereomeric products



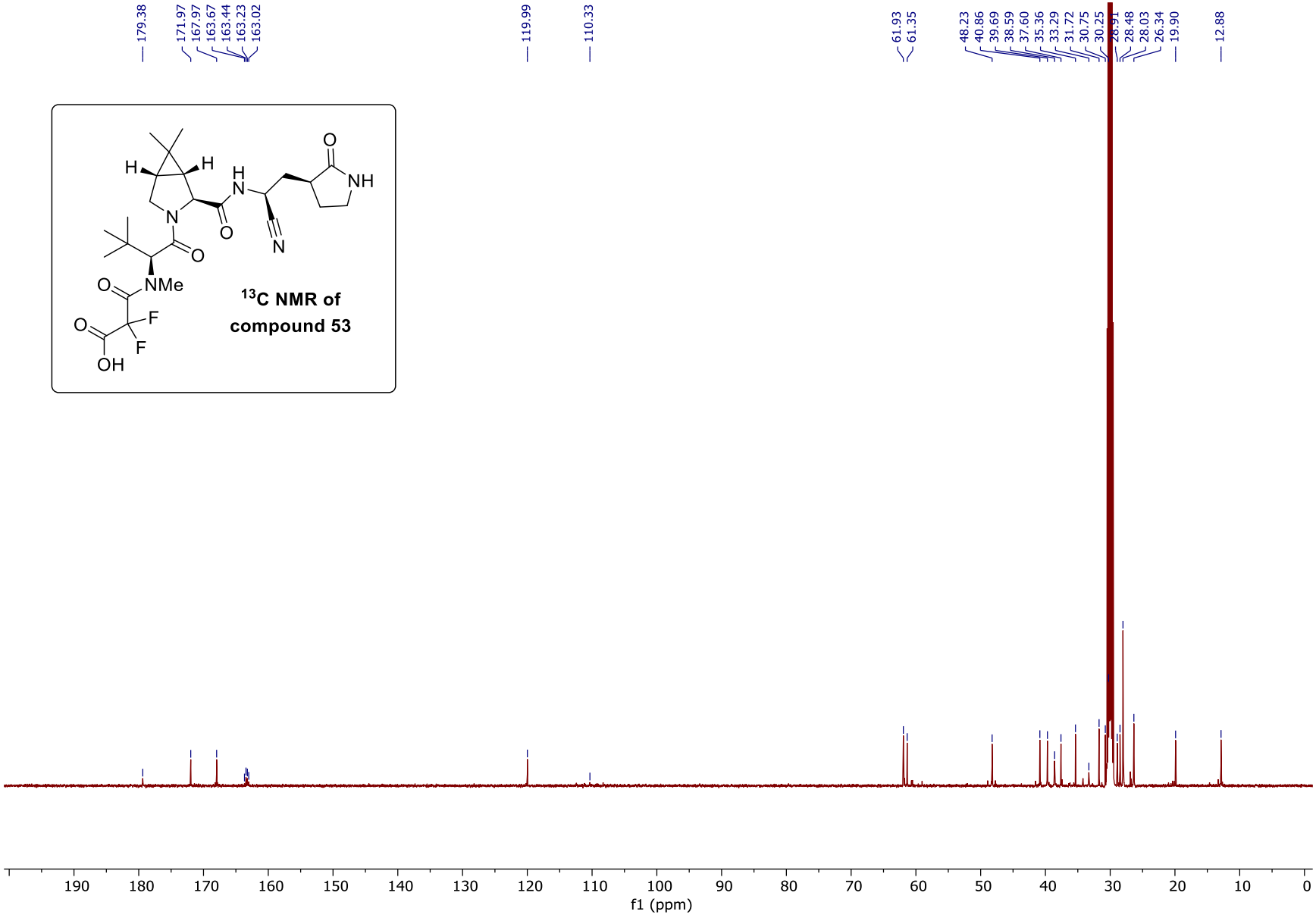
Inseparable diastereomeric products

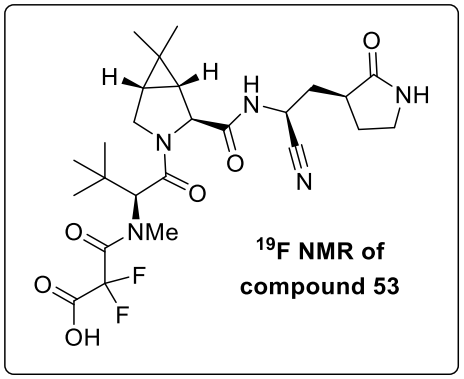


Inseparable diastereomeric products



5.14 5.06 5.05 5.04 5.03
4.21 3.99 3.98 3.97 3.96 3.56 3.54 3.34 3.32 3.28 3.27 3.22 3.19 3.13 2.71 2.70 2.70 2.69 2.36 2.34 2.32 2.31 1.92 1.91 1.89 1.87 1.86 1.84 1.81 1.61 1.60 1.59 1.39 1.38 1.07 1.06 0.90
H
H
O
H
N
NH
N
O
N
O
NMe
O
F
O
F
OH
¹H NMR of
compound 53
0.98 1.11 1.03 1.05 0.96 2.10 2.66 1.02 2.35 2.23 0.97 1.00 13.86 2.67
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)


179.38
171.97
167.97
163.67
163.44
163.23
163.02
119.99
110.33
61.93
61.35
48.23
40.86
39.69
38.59
37.60
35.36
33.29
31.72
30.75
30.25
28.91
28.48
28.03
26.34
19.90
12.88
^{13}C NMR of compound 53
f1 (ppm)



^{19}F NMR of compound 53

-108.34
-108.65

-25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160
f1 (ppm)