Electronic Supplementary Information (ESI)

Nucleophilic Fluorination Facilitated by a CsF-CaF_2 Packed Bed Reactor in Continuous Flow

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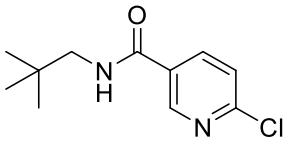
General considerations

All purchased chemicals were used as received without further purification. Solvents used in flow experiments were kept over 3 Å molecular sieves. CsF (98%) was purchased from Combi Blocks and synthetic CaF_2 was acquired from Solvay. Ethyl 3α-hydroxy-5β-cholan-24-oate was synthesized from lithocholic acid[1], propan-2-yl 2-chloro-5-nitrobenzoate was synthesized from 2-chloro-5-nitrobenzoic acid[2], and silyl ethers were synthesized from ethyl 3α-hydroxy-5β-cholan-24-oate[3], vanillin[4-5] and methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate[6], according to literature procedures. Flash column chromatography was carried out on silica gel 60 (230-400 mesh). The chemical shifts in ^{1}H NMR and ^{13}C NMR are reported in ppm relative to the solvent residual peak[7]. All ^{19}F NMR chemicals shifts are unlocked. ^{1}H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 101 MHz, and ^{19}F NMR spectra were recorded at 376 MHz on a 400 MHz spectrometer, all at room temperature on a Bruker 400 spectrometer. HRMS spectra were recorded on an LC TOF (ES) apparatus. Melting points (mp) were obtained on a capillary melting point apparatus and are uncorrected. The flow system consists of a HPLC pump (Knauer Azura P 4.1S), stainless stain tubing (1/16'' OD x 0.75 mm ID, Vici), an injection valve (2 position: load and inject, 6-port, 1/16'', Vici), a sample loop (2.0 mL, 453 cm length) made from stainless stain tubing (1/16'' OD x 0.75 mm ID, Vici), a spring loaded back pressure regulator (BPR) cartridge (500 psi, IDEX Health & Science), an empty stainless steel HPLC column (25 cm length, 0.46 cm ID) heated by a PID regulated oven, and all connections were made using HPLC fittings (IDEX Health & Science).

Synthesis of starting material



6-Chloro-N-neopentylnicotinamide. A 1.0 M solution of 6-chloronicotinoyl chloride (4.39 g, 24.5 mmol, 1.0 equiv.) in CH_2Cl_2 was added dropwise to a suspension of neopentylamine (5.8 mL, 49.6 mmol, 2.0 equiv.) and K_2CO_3 (3.24 g, 30.6 mmol, 1.2 equiv.) in 10 mL CH_2Cl_2 at 0°C. The reaction mixture was allowed to warm to room temperature and stirred continuously for 4 h. The crude reaction mixture was washed with sat. $NaHCO_3$ (3 x 30 mL), H_2O (3 x 30 mL) and brine (3 x 30 mL), dried above Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica-plug filtration eluting with CH_2Cl_2/Et_2O 1:1, affording title product (5.23 g, 93%) as a white solid. mp 102-103°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.2 Hz, 1H), 8.05 (dd, *J* = 8.3 Hz, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 6.30 (br. s, 1H), 3.26 (d, *J* = 6.3 Hz, 2H), 0.97 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 154.2, 147.9, 138.0, 129.7, 124.5, 51.3, 32.3, 27.4; HRMS *m/z* calculated for $C_{11}H_{16}ClN_2O$ $[M + H]^+$ 227.0946, found 227.0946.

Preparation of CsF supported on CaF_2[8]

The CaF_2-supported CsF (CsF on CaF_2) was prepared by slowly evaporating to dryness a suspension of a 0.3 M solution of CsF (15.03 g , 98.9 mmol) in methanol with added CaF_2 (13.23 g) for ca. 45 min at 55°C under reduced pressure using rotary evaporator. The resulting solid was grounded gently for ca. 1 min in a mortar and dried for 2 h at 100°C under vacuum affording a white solid [3.5 mmol CsF/(g CsF on CaF_2)].

CsF was also supported on CaF_2 with a loading of 2.2 mmol CsF/(g CsF on CaF_2) using the same procedure but with less CsF.

Preparation of KF supported on CaF_2[8]

The CaF_2-supported KF (KF on CaF_2) was prepared by slowly evaporating to dryness a suspension of a 0.75 M solution of KF (6.51 g , 112 mmol) in methanol with added CaF_2 (25.00 g) for ca. 45 min at 55°C under reduced pressure using rotary evaporator. The resulting solid was grounded gently for ca. 1 min in a mortar and dried for 2 h at 100°C under vacuum affording a white solid [3.5 mmol KF/(g KF on CaF_2)].

KF was also supported on CaF_2 with a loading of 4.0 mmol KF/(g KF on CaF_2) using the same procedure but with more KF.

Packed bed reactor

An empty HPLC column (25 cm length, 0.46 cm ID) was fitted with a small ball of cotton (20 mg) in 1 of the ends. Then the reactor was filled with the supported metal fluoride inside a fume hood. For CsF on CaF_2 with a loading of 3.5 mmol CsF/(g CsF on CaF_2), 21-22 mmol of CsF was packed into the column. For CsF on CaF_2 with a loading of 2.2 mmol CsF/(g CsF on CaF_2), 13-14 mmol of CsF was packed into the column. For KF on CaF_2 with a loading of 3.5 mmol CsF/(g KF on CaF_2), 18-19 mmol of KF was packed into the column. For KF on CaF_2 with a loading of 4.0 mmol CsF/(g KF on CaF_2), 22 mmol of KF was packed into the column. *Unless otherwise stated, the packed bed reactor was packed with CsF on CaF_2 with a loading of 3.5 mmol CsF/(g CsF on CaF_2).*

Determination of internal volume

The internal volume of the packed bed reactor was determined by weighing the freshly packed bed reactor, m_1. Then toluene or acetonitrile was pumped through the reactor to fill the reactor void with solvent and the packed bed reactor was weighed again, m_2. The reactor void volume, V_{void}, was determined by:

$$V_{void} = \frac{m_2 + m_1}{\rho_{solvent}}$$

General experimental Setup for Continuous Flow

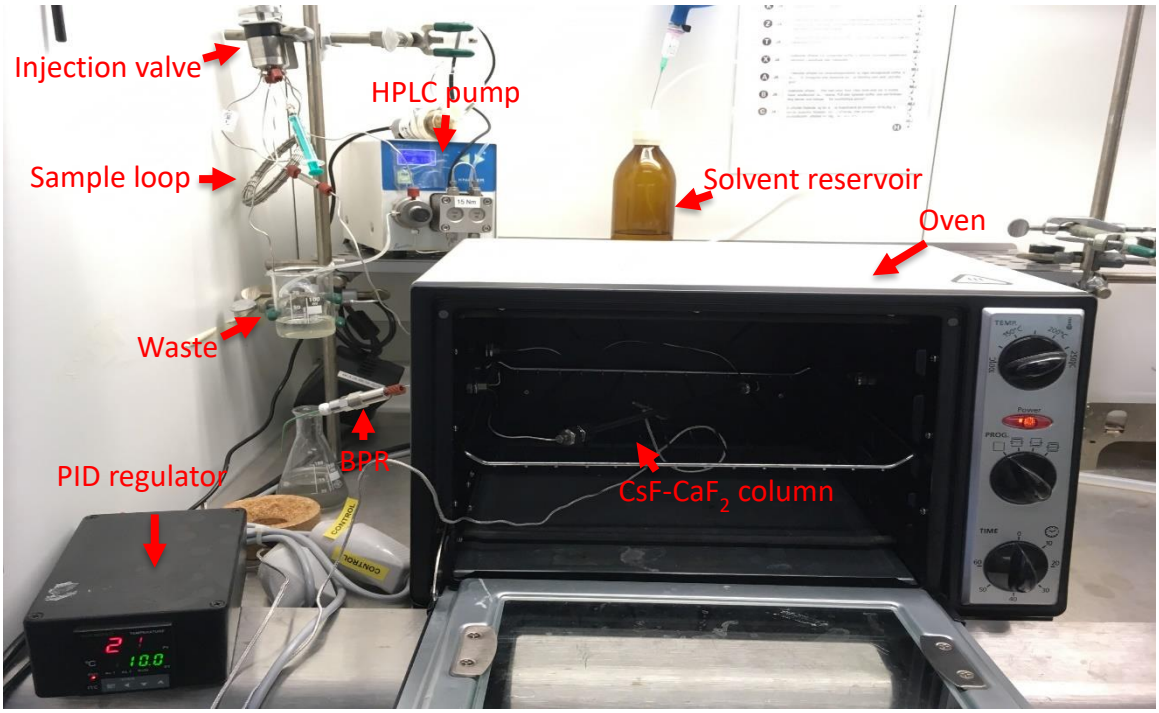


Figure S1: Picture of Continuous flow setup.

A HPLC pump (Knauer Azura P 4.1S) was used to pump solvent through the reactor. A sample loop (2 mL) was filled by syringe with a solution of substrate and additive in the chosen solvent. The sample loop was made of stainless steel tubing (1/16'' OD x 0.75 mm ID) and had a volume of 2 mL (453 cm length). An injection valve (2 position: load and inject, 6-port, 1/16'', Vici) was used to introduce the reagents from the sample loop. A backpressure regulator (BPR) was used to prevent solvent boiling. All units were connected using stainless steel tubing (1/16'' OD x 0.75 mm ID) and HPLC fittings (T-pieces, unions etc. all with 1/16'' ID). The packed bed was heated in an oven and was dried by passing dry acetonitrile or toluene through the system at 1.50 mL/min at 180°C for 30 min after which the column was ready for use.

In-line Drying of $CsF\text{-}CaF_2$ Reactor

A freshly packed $CsF\text{-}CaF_2$ reactor was heated to 230°C and flushed with acetonitrile with an initial water content of 9.2 ppm with a flow rate of 1.00 mL/min. The exiting flow was collected in fractions of 24 mL in septum-sealed round-bottomed flasks for a total of 240 mL. The water content of each fraction was determined by Karl-Fischer measurements and depicted in Figure S2.

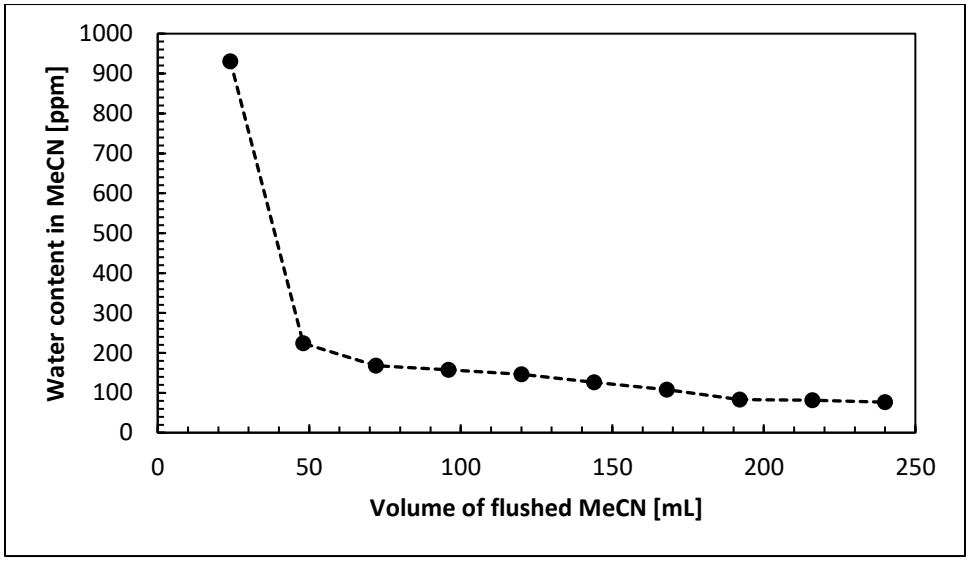


Figure S2: Water content of exiting solvent as a function of flushed acetonitrile (MeCN)

Influence of CsF Loading on CaF_2 in Nucleophilic Fluoride Substitution of 1-bromomethyl-4-*tert*butylbenzene in Continuous Flow

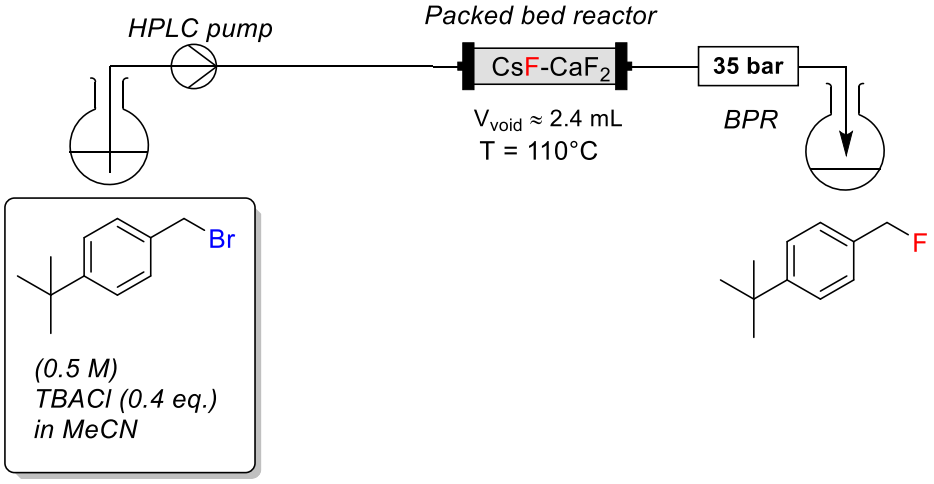


Figure S3: Schematic presentation of the scale-out experiment of the fluorination of 1-bromomethyl-4-*tert*butylbenzene.

1-bromomethyl-4-*tert*butylbenzene (5.68 g, 25 mmol, 1 equiv.) and tetrabutylammonium chloride (2.74 g, 9.9 mmol, 0.4 equiv.) was dissolved in acetonitrile (0.5 M). The reaction mixture was pumped through the packed bed reactor, containing 21 mmol CsF, with a flow rate of 0.097 mL/min corresponding to a residence time of 25 min at 110°C. The flow setup was run for 1.5 times the residence time, to reach steady state, before sample collection was initiated. A batch was collected every 20 minutes, concentrated under reduced pressure and conversion and purity was determined by ^{1}H-NMR analysis using dimethyl terephtalate as internal standard. Full conversion was observed in all fractions. ^{1}H NMR yields are depicted in the Figure S4. Fraction 1-10 were combined and purified by flash column chromatography eluting with

pentane/CH_2Cl_2 20:1 affording 1-fluoromethyl-4-*tert*butylbenzene (**2**) (1.07 g, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.36 (d, *J* = 48.1 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (d, *J* = 3.4 Hz), 133.4 (d, *J* = 17.1 Hz), 127.8 (d, *J* = 5.4 Hz), 125.7 (d, *J* = 1.6 Hz), 84.7 (d, *J* = 165.0 Hz), 34.8, 31.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -204.4 (t, *J* = 48.1 Hz, 1F); HRMS *m/z* calculated for $C_{11}H_{16}$ $[M - F]^+$ 147.1168, found 147.1166.

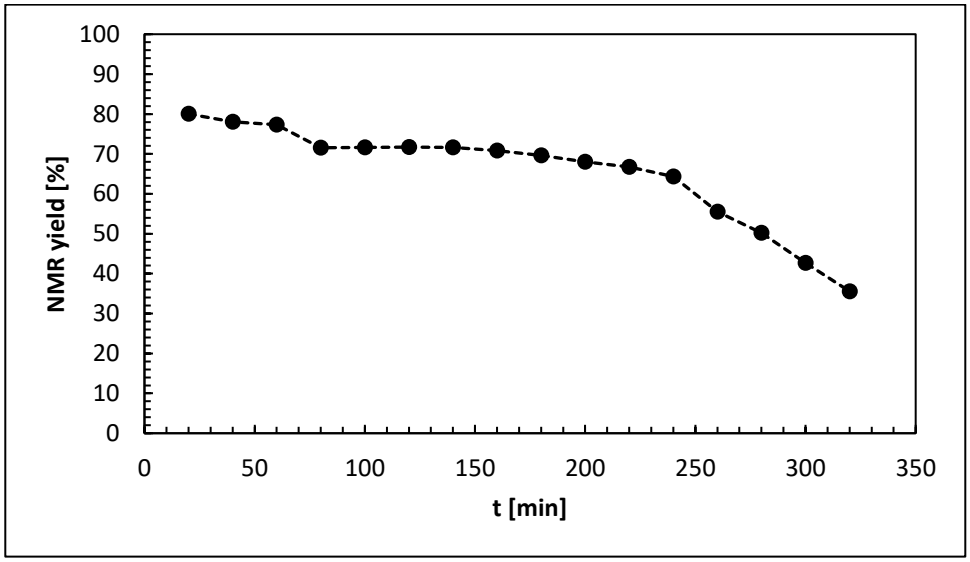


Figure S4: NMR yield of 1-fluoromethyl-4-*tert*butylbenzene as a function time using 3.5 mmol CsF/(g CsF-CaF_2).

1-bromomethyl-4-*tert*butylbenzene (5.68 g, 25 mmol, 1 equiv.) and tetrabutylammonium chloride (2.74 g, 9.9 mmol, 0.4 equiv.) was dissolved in acetonitrile (0.5 M). The reaction mixture was pumped through the packed bed reactor, containing 14 mmol CsF [2.2 mmol CsF/(g CsF on CaF_2)], with a flow rate of 0.089 mL/min corresponding to a residence time of 25 min at 110°C. The flow setup was run for 1.5 times the residence time, to reach steady state, before sample collection was initiated. A batch was collected every 20 minutes, concentrated under reduced pressure and yield was determined by ^{1}H-NMR analysis using dimethyl terephtalate as internal standard. ^{1}H NMR yields are depicted in the Figure S5.

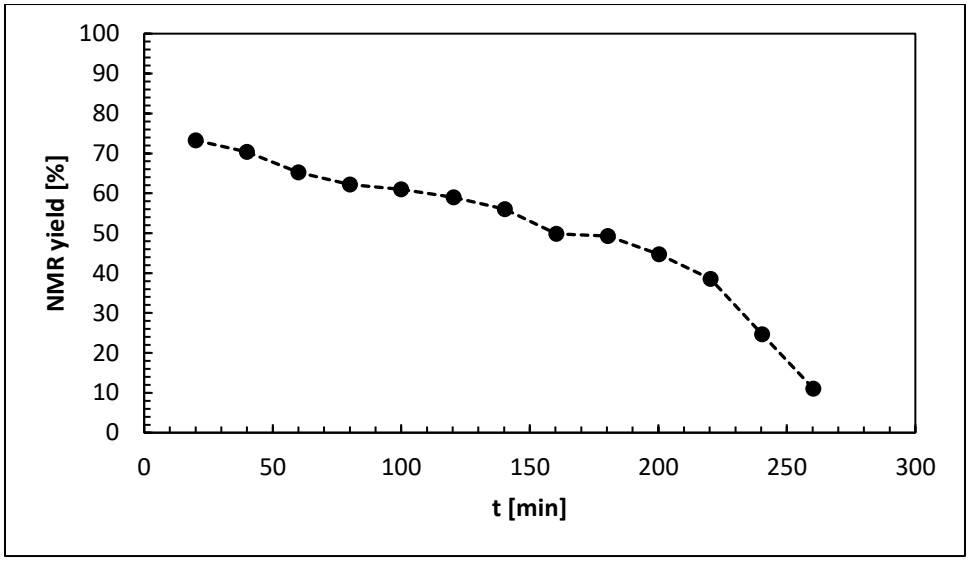


Figure S5: NMR yield of 1-fluoromethyl-4-*tert*butylbenzene as a function time using 2.2 mmol CsF/(g CsF-CaF_2).

1-bromomethyl-4-*tert*butylbenzene (5.68 g, 25 mmol, 1 equiv.) and tetrabutylammonium chloride (2.74 g, 9.9 mmol, 0.4 equiv.) was dissolved in acetonitrile (0.5 M). The reaction mixture was pumped through the packed bed reactor, containing 19 mmol KF [3.5 mmol KF/(g KF on CaF_2)], with a flow rate of 0.089 mL/min corresponding to a residence time of 25 min at 110°C. The flow setup was run for 1.5 times the residence time, to reach steady state, before sample collection was initiated. A batch was collected every 20 minutes, concentrated under reduced pressure and yield was determined by ^{1}H-NMR analysis using dimethyl terephtalate as internal standard. Full conversion was observed in all fractions. ^{1}H NMR yields are depicted in the Figure S6.

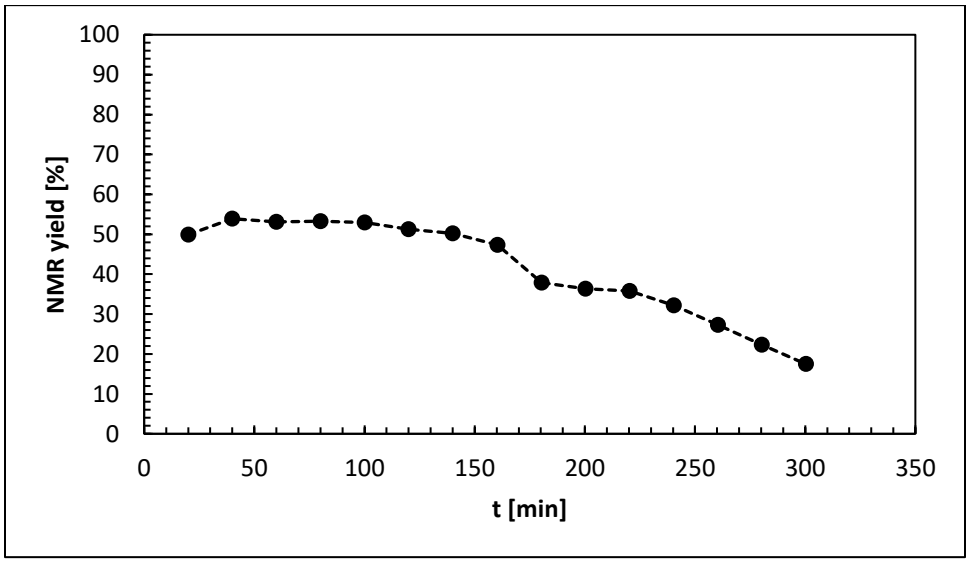


Figure S6: NMR yield of 1-fluoromethyl-4-*tert*butylbenzene as a function time using 3.5 mmol KF/(g KF-CaF_2).

Procedure for Nucleophilic Fluorination of Benzyl Bromides: Substrate Scope and Isolated Yields in Flow

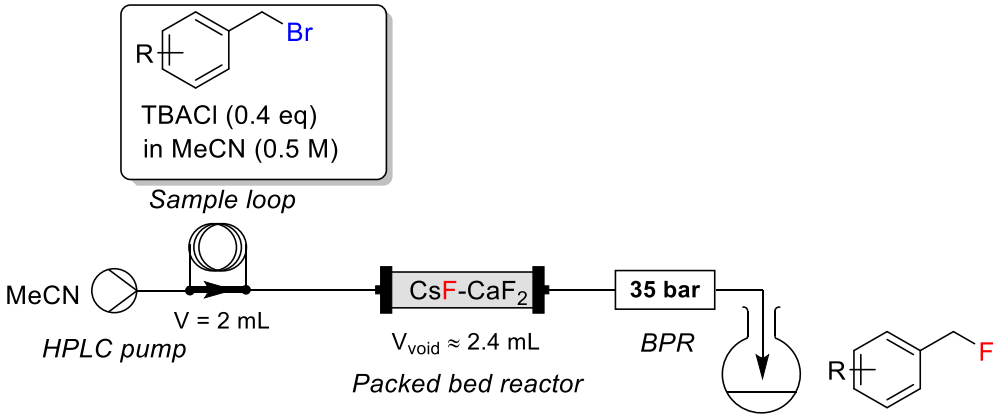
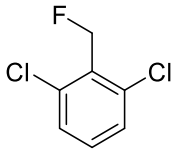


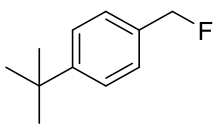
Figure S7: Schematic presentation of fluorination of benzyl bromides.

***General Method A**:* The benzyl bromide (1 equiv.) and tetrabutylammonium chloride (TBACl, 0.40 equiv.) were dissolved in acetonitrile (0.50 M). 2.0 mL of the stock solution was loaded into the sample loop and pumped through the packed bed reactor, containing 21 mmol CsF, with a flow rate of 0.098 mL/min corresponding to a residence time of 25 min at 110°C, Figure S7. Product was collected for 105 min, concentrated under reduced pressure and purified by flash column chromatography.



*1-Fluoromethyl-2,6-dichlorobenzene (**1**).* The crude product was obtained by using General Method A and purified using flash column chromatography eluting with pentane/CH_2Cl_2 10:1 affording the title product (129 mg, 70%) as a white solid. mp 63-64°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.32-7.20 (m, 1H), 5.69 (d, *J* = 47.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (d, *J* = 3.8 Hz), 131.4 (d, *J* = 4.0 Hz), 131.4 (d, *J* = 14.6 Hz), 128.7 (d, *J* = 2.9 Hz), 78.8 (d, *J* = 166.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -211.6 (t, *J* = 46.4 Hz, 1F); HRMS *m/z* calculated for $C_7H_6Cl_2F$ $[M+H]^+$ 178.9825, found 178.9810.

The title product (**1**) was also produced from 1-chloromethyl-2,6-dichlorobenzene otherwise following General Method A and purified using flash column chromatography eluting with pentane/CH_2Cl_2 20:1, affording an inseparable mixture of the title product (116 mg, 65%) and 1-chloromethyl-2,6-dichlorobenzene (26 mg, 13%) as a white solid. 1-Fluoromethyl-2,6-dichlorobenzene: ^{1}H NMR (400 MHz, $CDCl_3$) δ *inter alia* 5.72 (d, *J* = 47.4 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -211.6 (t, *J* = 47.4 Hz, 1F); 1-Chloromethyl-2,6-dichlorobenzene: ^{1}H NMR (400 MHz, $CDCl_3$) δ *inter alia* 4.91 (s, 2H); 1-Fluoromethyl-2,6-dichlorobenzene and 1-chloromethyl-2,6-dichlorobenzene: ^{13}C NMR (101 MHz, $CDCl_3$) δ *inter alia* 137.4 (d, *J* = 3.9 Hz), 136.3, 133.6, 131.4 (d, *J* = 4.0 Hz), 131.4 (d, *J* = 14.6 Hz), 130.4, 128.7, 128.7 (d, *J* = 3.1 Hz), 78.9 (d, *J* = 166.7 Hz), 40.8.

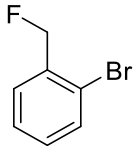


*1-Fluoromethyl-4-tertbutylbenzene (**2**)*.[9] The crude product was obtained by using General Method A and purified using flash column chromatography eluting with pentane/CH_2Cl_2 10:1 affording the title product (125 mg, 74%) as a colorless oil. ^{1}H

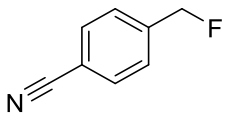
NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.34 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 2H), 5.36 (d, *J* = 48.1 Hz, 2H), 1.35 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1 (d, *J* = 3.4 Hz), 133.4 (d, *J* = 17.2 Hz), 127.8 (d, *J* = 5.5 Hz), 125.7 (d, *J* = 1.7 Hz), 84.7 (d, *J* = 165.0 Hz), 34.8, 31.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -204.4 (t, *J* = 48.2 Hz, 1F); HRMS *m/z* calculated for $C_{11}H_{15}$ $[M - F]^+$ 147.1168, found 147.1166.

The title product (**1**) was also produced from 1-chloromethyl-4-tertbutylbenzene otherwise following General Method A and purified using flash column chromatography eluting with pentane/CH_2Cl_2 20:1, affording the title product (118 mg, 72%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) 7.43 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 5.36 (d, *J* = 48.1 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (d, *J* = 3.4 Hz), 133.2 (d, *J* = 17.1 Hz), 127.6 (d, *J* = 5.5 Hz), 125.6 (d, *J* = 1.6 Hz), 84.6 (d, *J* = 165.0 Hz), 34.7, 31.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -204.4 (t, *J* = 48.1 Hz, 1F); HRMS *m/z* calculated for $C_{11}H_{15}$ $[M - F]^+$ 147.1168, found 147.1160.

The title product (**1**) was also produced using a KF-CaF_2 column containing 22 mmol KF [4.0 mmol KF/(g KF on CaF_2)] otherwise following General Method A and purified using flash column chromatography eluting with pentane/CH_2Cl_2 20:1, affording an inseparable mixture of the title product (100 mg, 60%), 1-bromomethyl-4-tertbutylbenzene (19 mg, 8%) and 1-chloromethyl-4-tertbutylbenzene (48 mg, 26%) as a colorless oil.
1-Fluoromethyl-4-tertbutylbenzene: ^1H NMR (400 MHz, $CDCl_3$) δ *inter alia* 5.36 (d, *J* = 48.1 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -204.4 (t, *J* = 48.1 Hz, 1F);
1-Bromomethyl-4-tertbutylbenzene: ^1H NMR (400 MHz, $CDCl_3$) δ *inter alia* 4.50 (s, 2H).
1-Chloromethyl-4-tertbutylbenzene: ^1H NMR (400 MHz, $CDCl_3$) δ *inter alia* 4.59 (s, 2H);
1-Fluoromethyl-4-tertbutylbenzene, 1-bromomethyl-4-tertbutylbenzene and 1-chloromethyl-4-tertbutylbenzene: ^{13}C NMR (101 MHz, $CDCl_3$) δ *inter alia* 152.10 (d, *J* = 3.4 Hz), 151.72, 151.67, 134.90, 134.65, 133.35 (d, *J* = 17.1 Hz), 128.91, 128.49, 127.77 (d, *J* = 5.5 Hz), 125.92, 125.85, 125.69 (d, *J* = 1.6 Hz), 84.71 (d, *J* = 165.0 Hz), 46.31, 34.82, 34.82, 34.78, 33.77, 31.44, 31.43, 31.41.



*1-Fluoromethyl-2-bromobenzene (**3**).*[10] The crude product was obtained by using method A and purified using flash column chromatography eluting with pentane/CH_2Cl_2 10:1 affording the title product (132 mg, 68%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 5.48 (d, *J* = 47.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (d, *J* = 18.0 Hz), 132.8, 130.0 (d, *J* = 2.3 Hz), 128.6 (d, *J* = 9.6 Hz), 127.7, 121.8 (d, *J* = 5.3 Hz), 83.8 (d, *J* = 169.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -216.4 (t, *J* = 47.2 Hz, 1F); HRMS *m/z* calculated for C_7H_6BrF $[M]^{\cdot+}$ 187.9637, found 187.9644.



*1-Fluoromethyl-4-Cyanobenzene (**4**).*[9] The crude product was obtained by using method A and purified using flash column chromatography eluting with pentane/EtOAc 20:1 affording the title product (96 mg, 68%) as a white solid. mp 29-30°C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 2H), 5.45 (d, *J* = 46.9 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (d, *J* = 18.0 Hz), 132.8, 130.0 (d, *J* = 2.3 Hz), 128.6 (d, *J* = 9.6 Hz), 127.7, 121.8 (d, *J* = 5.3 Hz), 83.8 (d, *J* = 169.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -216.4 (t, *J* = 47.2 Hz, 1F); HRMS *m/z* calculated for C_8H_7FN $[M + H]^+$ 136.0557, found 136.0554.

Procedure for Nucleophilic (hetero)aromatic Substitutions: Substrate Scope and Isolated Yields in Flow.

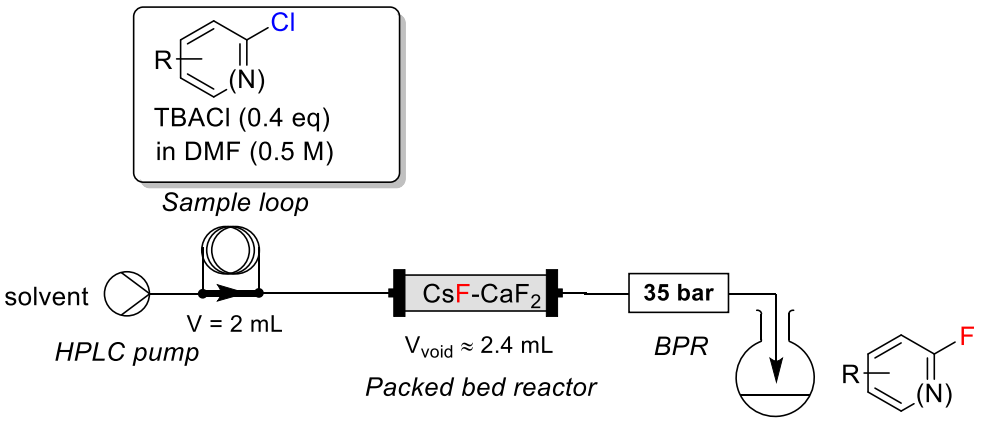
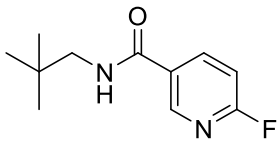
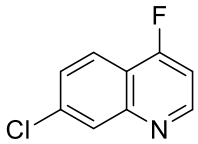


Figure S8: Schematic presentation of fluorination of chlorinated (hetero)aromates.

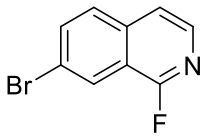
General Method B: The (hetero)aromatic chloride (1 equiv.) and tetrabutylammonium chloride (TBACl, 0.40 equiv.) were dissolved in DMF (0.50 M) unless otherwise stated. 2.0 mL of the stock solution was loaded into the sample loop and pumped through the packed bed reactor, containing 21 mmol CsF, with MeCN as background solvent unless otherwise stated, Figure S8. The residence time and temperature are stated individually below. The sample was collected for 4 times the residence time and extracted with Et_2O (4 x 20 mL). The combined ethereal phases was washed with water (4 x 20 mL), brine (2 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using flash column chromatography.



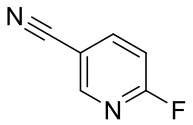
*6-Fluoro-N-neopentylnicotinamide (**6**).* The reaction was run in DMSO at 150°C with a residence time of 25 min and DMSO was used as background solvent, otherwise following General Method B. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 3:1 affording the title product (145 mg, 68%) as a white solid. mp 110-112°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 1.8 Hz, 1H), 8.23 (td, *J* = 8.2 Hz, *J* = 2.4 Hz, 1H), 7.00 (dd, *J* = 8.5 Hz, *J* = 2.8 Hz, 1H), 6.21 (br. s, 1H), 3.28 (d, *J* = 6.3 Hz, 2H), 0.98 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (d, *J* = 244.1Hz), 164.8, 126.5 (d, *J* = 15.9 Hz), 141.0 (d, *J* = 8.8 Hz), 129.2 (d, *J* = 4.5 Hz), 109.9 (d, *J* = 39.4 Hz), 51.3, 32.3, 27.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.6 (s, 1F); HRMS *m/z* calculated for $C_{11}H_{16}FN_2O$ $[M + H]^+$ 211.1241, found 211.1243.



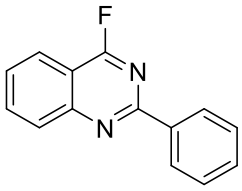
*7-Chloro-4-fluoroquinoline (**7**).*[11] The reaction was run at 130°C with a residence time of 30 min, otherwise following General Method B. The crude product was purified using flash column chromatography eluting with pentane/Et_2O 8:1 affording the title product (106 mg, 58%) as a white solid. mp 53-55°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (dd, *J* = 8.2 Hz, *J* = 5.0 Hz, 1H), 8.13 (s, 1H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.65-7.49 (m, 1H), 7.10 (dd, *J* = 9.5 Hz, *J* = 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (d, *J* = 269.5 Hz), 152.8 (d, *J* = 8.1 Hz), 151.0 (d, *J* = 4.2 Hz), 136.9, 128.4 (d, *J* = 3.5 Hz), 128.2, 122.1 (d, *J* = 4.9 Hz), 106.1 (d, *J* = 14.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.2-112.7 (m, 1F); HRMS *m/z* calculated for C_9H_6ClFN $[M + H]^+$ 182.0167, found 182.0182.



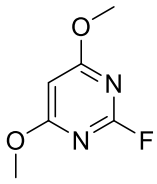
*7-Bromo-1-fluoroisoquinoline (**8**).*[12] The reaction was run at 120°C with a residence time of 30 min with a substrate concentration of 0.28 M, otherwise following General Method B. The crude product was purified using flash column chromatography eluting with pentane/CH_2Cl_2 1:1 affording the title product (83 mg, 64%) as a pale orange solid. mp 81-82°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 7.85 (dd, *J* = 8.8 Hz, *J* = 1.8 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (d, *J* = 246.9 Hz), 139.9 (d, *J* = 15.8 Hz), 138.2 (d, *J* = 5.3 Hz), 135.2, 128.2 (d, *J* = 3.9 Hz), 125.7, 121.9, 119.2 (d, *J* = 5.0 Hz), 118.8 (d, *J* = 32.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.6 (s, 1F); HRMS *m/z* calculated for C_9H_6BrFN $[M + H]^+$ 225.9662, found 225.9685.



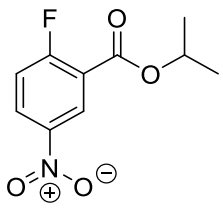
*6-Fluoronicotinonitrile (**9**).* The reaction was run at 50°C with a residence time of 40 min, otherwise following General Method B. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 20:1 affording the title product (73 mg, 59%) as a white solid. mp 52-53°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63-8.53 (m, 1H), 8.20-7.97 (m, 1H), 7.10 (dd, *J* = 8.5 Hz, *J* = 2.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (d, *J* = 249.2 Hz), 152.4 (d, *J* = 16.8 Hz), 144.5 (d, *J* = 9.3 Hz), 115.7, 111.0 (d, *J* = 38.0 Hz), 108.2 (d, *J* = 5.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4 (s, 1F); HRMS *m/z* calculated for $C_6H_4FN_2$ $[M + H]^+$ 123.0353, found 123.0353.



*4-Fluoro-2-phenylquinazoline (**10**).* The reaction was run at 60°C with a residence time of 40 min with a substrate concentration of 0.25 M, otherwise following General Method B. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 40:1 affording the title product (75 mg, 66%) as a white solid. mp 86-88°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66-8.48 (m, 2H), 8.12 (d, *J* = 8.6 Hz, 2H), 8.01-7.86 (m, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.59-7.51 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3 (d, *J* = 259.9 Hz), 160.6 (d, *J* = 14.5 Hz), 154.5 (d, *J* = 5.4 Hz), 136.8, 135.2, 131.3, 128.8 (2C), 128.4 (d, *J* = 5.0 Hz), 127.9, 122.8, 113.2 (d, *J* = 27.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.4 (s, 1F); HRMS *m/z* calculated for $C_{14}H_{10}FN_2$ $[M + H]^+$ 225.0823, found 225.0825.



*2-Fluoro-4,6-dimethoxypyrimidine (**11**).* The reaction was run at 90°C with a residence time of 25 min, otherwise following General Method B. No further purification was needed and the title product was isolated (104 mg, 65%) as a white solid. mp 85-87°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (d, *J* = 2.4 Hz, 1H), 3.94 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (d, *J* = 15.7 Hz), 161.9 (d, *J* = 216.0 Hz), 87.7 (d, *J* = 6.8 Hz), 54.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -44.4 (s, 1F); HRMS *m/z* calculated for $C_6H_8FN_2O_2$ $[M + H]^+$ 159.0564, found 159.0563.



*Isopropyl 2-fluoro-5-nitrobenzoate (**12**).* The reaction was run at 130°C with a residence time of 10 min with a substrate concentration of 0.25 M, otherwise following General Method B. The crude product was purified using flash column chromatography eluting with pentane/Et_2O 8:1 affording the title product (86 mg, 75%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 6.2 Hz, *J* = 2.9 Hz, 1H), 8.39 (ddd, *J* = 9.0 Hz, *J* = 3.9 Hz, *J* = 2.9 Hz, 1H), 7.31 (d, *J* = 9.2 Hz, 1H), 5.30 (hept, *J* = 6.3 Hz, 1H), 1.40 (d, *J* = 6.3Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2 (d, *J* = 270.9 Hz), 161.8 (d, *J* = 4.1 Hz), 144.0 (d, *J* = 3.0 Hz), 129.3 (d, *J* = 11.0 Hz), 128.2 (d, *J* = 3.0 Hz), 120.8 (d, *J* = 11.8 Hz), 118.5 (d, *J* = 25.0

Hz), 70.4, 22.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.7 (s, 1F); HRMS *m/z* calculated for $C_{10}H_{10}FNNaO_4$ $[M + Na]^+$ 250.0486, found 250.0487.

Procedure for Deprotection of Silyl Ethers: Substrate Scope and Isolated Yields in Flow.

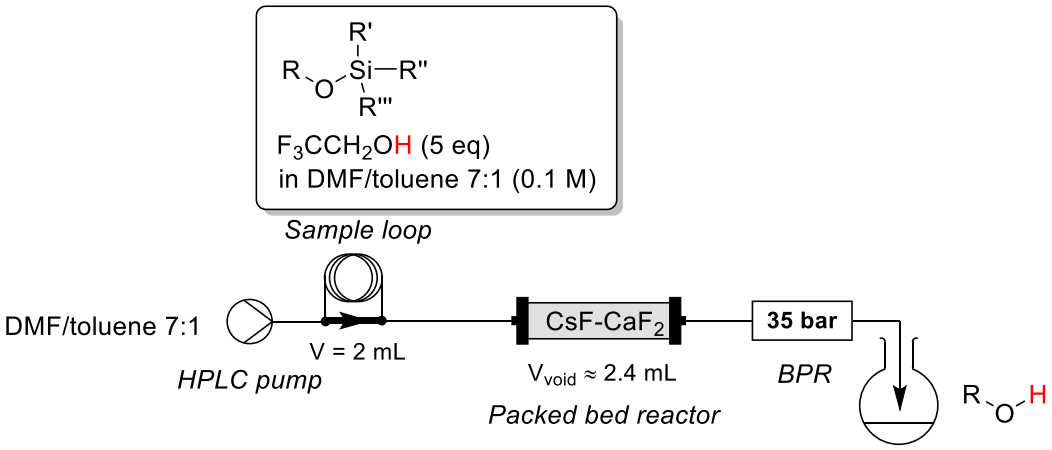
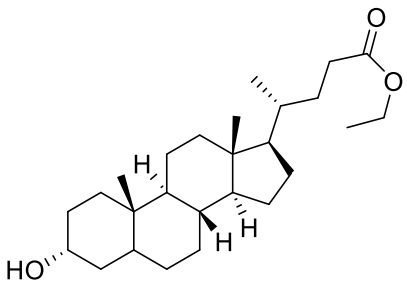
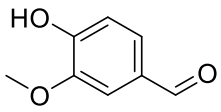


Figure S9: Schematic presentation of the deprotection of silyl ethers.

General Method C: Silyl ether (1 equiv.) and 2,2,2-trifluoroethanol (5.0 equiv.) was dissolved in DMF/toluene 7:1 (V/V) (0.10 M). 2.0 mL of the stock solution was loaded into the sample loop and pumped through the packed bed reactor, containing 22 mmol CsF, with a flow rate of 0.475 mL/min corresponding to a residence time of 5 min at 120°C with DMF/toluene 7:1 (V/V) as background solvent, Figure S9. The sample was collected for 20 min, diluted with water (10 mL), and extracted with Et_2O (4 x 10 mL). The combined ethereal phases was washed with water (4 x 10 mL), brine (2 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using flash column chromatography.



Ethyl 3α-hydroxy-5β-cholan-24-oate (***13***).[1] Ethyl 3α-((triisopropylsilyl)oxy)-5β-cholan-24-oate was deprotected following General Method C. The crude product was purified using flash column chromatography eluting with toluene/EtOAc 10:1 affording the title product (79 mg, 94%) as a colorless wax. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1 Hz, 2H), 3.62 (tt, *J* = 10.6, 4.7 Hz, 1H), 2.33 (ddd, *J* = 15.3, 10.1, 5.2 Hz, 1H), 2.20 (ddd, *J* = 15.6, 9.6, 6.6 Hz, 1H), 2.02 – 0.82 (m, 36H), 0.63 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 72.0, 60.3, 56.6, 56.1, 42.9, 42.2, 40.6, 40.3, 36.6, 36.0, 35.5 (2C), 34.7, 31.5, 31.1, 30.7, 28.3, 27.3, 26.6, 24.4, 23.5, 21.0, 18.4, 14.4, 12.2; HRMS *m/z* calculated for $C_{26}H_{44}NaO_3$ $[M + Na]^+$ 427.3183, found 427.3184.

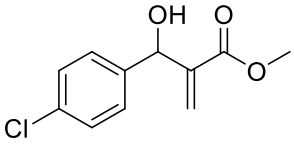


Vanillin (***14***).[13] 3-methoxy-4-((triethylsilyl)oxy)benzaldehyde was deprotected following General Method C. The crude product was purified using flash column chromatography eluting with toluene/EtOAc 10:1 affording the title product (29 mg, 93%) as a white solid. mp 81-82°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.51-7.39 (m, 2H), 7.04 (d, *J* =

8.5 Hz, 1H), 6.17 (s, 1H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0, 151.8,147.3, 130.1, 127.7, 114.5, 108.9, 56.3; HRMS *m/z* calculated for $C_8H_9O_3$ $[M + H]^+$ 153.0546, found 153.0545.

The title product (**14**) was also produced running with a silyl ether concentration on 0.5 M, affording the title product (146 mg, 93%) as an off-white solid.

3-Methoxy-4-((tert-butyldimethylsilyl)oxy)benzaldehyde was deprotected following General Method C. The crude product was purified using flash column chromatography eluting with toluene/EtOAc 10:1 affording the title product (28 mg, 90%) as a white solid.



*Methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate (**15**)*.[14] Methyl 2-(((tert-butyldimethylsilyl)oxy)(4-chlorophenyl)methyl)acrylate was deprotected at room temperature with a residence time of 20 min, otherwise following General Method C. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 8:1 affording the title product (39 mg, 86%) as a white solid. mp 39-40°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 6.34 (s, 1H), 5.82 (s, 1H), 5.52 (d, *J* = 5.1 Hz, 1H), 3.73 (s, 3H), 3.10 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 141.6, 139.8, 133.6, 128.6, 128.0, 126.4, 72.7, 52.1; HRMS *m/z* calculated for $C_{11}H_{10}ClNaO_3$ $[M + Na]^+$ 249.0289, found 249.0287.

Procedure for CsF-mediated Trifluoromethylation: Substrate Scope and Isolated Yields in Flow

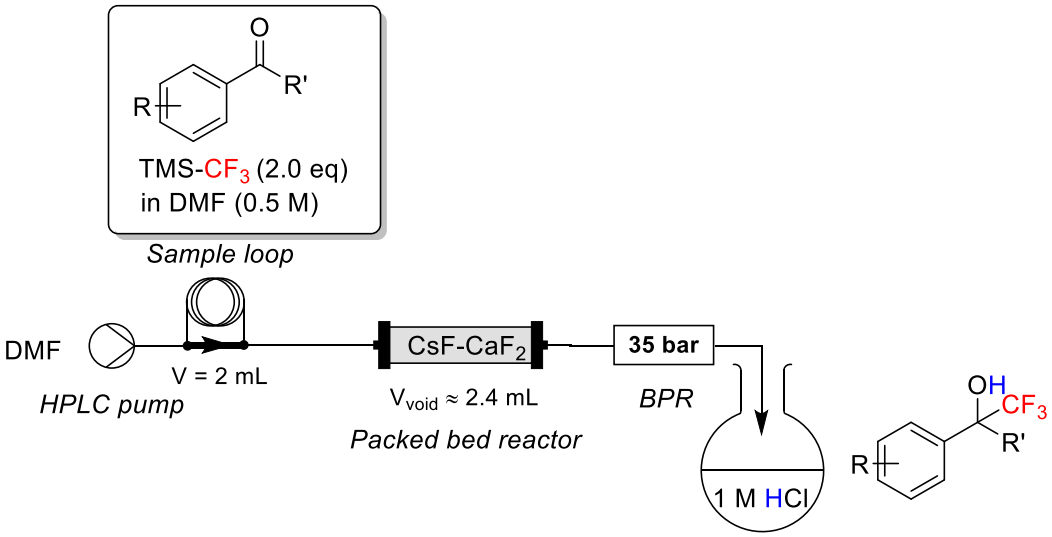
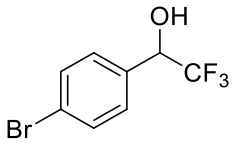


Figure S10: Schematic presentation of fluoride mediated trifluoromethylation.

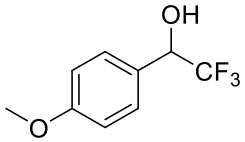
General Method D: Aldehyde/ketone (1 equiv.) and trimethyl(trifluoromethyl)silane (2 equiv.) was dissolved in DMF (0.50 M). 2.0 mL of the stock solution was loaded into the sample loop and pumped through the packed bed reactor, containing 21 mmol CsF, with a flow rate of 0.466 mL/min corresponding to a residence time of 5 min at room temperature, Figure S10. Product was collected in round-bottomed flask containing 20 mL 1 M HCl over 30 min and extracted with Et_2O (4 x 20 mL). The combined ethereal

phases was washed with water (4 x 20 mL), brine (2 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using flash column chromatography.

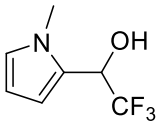
Derivatized MS Procedure[15]. Phosphorylation of 2,2,2-trifluoromethylcarbinols: Obtaining HRMS data proved difficult for 2 entries and these were therefore derivatized prior to HRMS analysis as their corresponding phosphorylated products. In a vial (4 mL) were added the 2,2,2-trifluoromethylcarbinol (10 mg), K_2CO_3 (35 mg, 0.25 mmol), diethyl chlorophosphate (43 mg, 0.25 mmol), and acetone (1 mL). The reaction mixture was stirred for 2 h at room temperature. The crude reaction mixture was filtered, and an aliquot was sampled for MS analysis detecting the corresponding diethyl (2,2,2-trifluoro-1-arylethyl)phosphate.



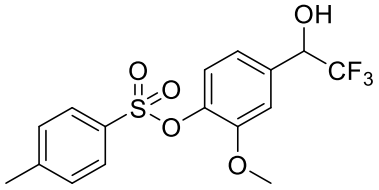
*1-(4-Bromophenyl)-2,2,2-trifluoroethan-1-ol (**16**).*[16] The crude product was obtained by using General Method D. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 10:1 affording the title product (213 mg, 83%) as a yellow solid. mp 49-51°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 5.00 (q, *J* = 6.4 Hz, 1H), 2.61 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 132.0, 129.2, 124.1 (q, *J* = 282.2 Hz), 123.9, 72.4 (q, *J* = 32.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.5 (d, *J* = 6.6 Hz, 3F); HRMS was determined using the derivatized MS procedure: HRMS *m/z* calculated for $C_{12}H_{16}BrF_3O_4P$ $[M + H]^+$ 390.9916, found 390.9917.



*1-(4-Methoxyphenyl)-2,2,2-trifluoroethan-1-ol (**17**).*[17] The crude product was obtained by using General Method D. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 10:1 affording the title product (161 mg, 77%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.97 (q, *J* = 6.7 Hz, 1H), 3.83 (s, 3H), 2.52 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 128.9, 126.2, 124.5 (q, *J* = 281.9 Hz), 114.2, 72.7 (q, *J* = 32.1 Hz), 55.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.6 (d, *J* = 6.7 Hz, 3F); HRMS was determined using the derivatized MS procedure: HRMS *m/z* calculated for $C_{13}H_{19}F_3O_5P$ $[M + H]^+$ 343.0917, found 343.0916.

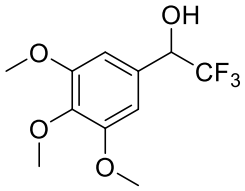


*1-(N-methyl-1H-pyrrole-2-yl)-2,2,2-trifluoroethan-1-ol (**18**).* The crude product was obtained by using General Method D. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 6:1 affording the title product (154 mg, 84%) as a brown solid. mp 45-47°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.97 (q, *J* = 6.7 Hz, 1H), 3.83 (s, 3H), 2.52 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 125.3, 124.9, 124.3 (q, *J* = 281.6 Hz), 109.4,, 107.7, 66.5 (q, *J* = 33.7 Hz), 34.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.0 (d, *J* = 6.8 Hz, 3F); HRMS *m/z* calculated for $C_7H_9F_3NO$ $[M + H]^+$ 180.0631, found 180.0628.

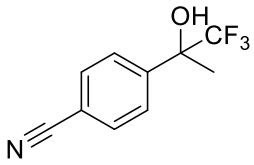


*1-(3-Trimethoxy-4-tosyl-phenyl)-2,2,2-trifluoroethan-1-ol (**19**).* The crude product was obtained by using General Method D. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 4:1 affording the title product (269 mg, 70%) as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.03-6.92 (m 2H), 4.99 (q, *J* = 6.6 Hz, 1H), 3.59 (s, 3H), 2.45

(s, 3H), 2.22 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 145.4, 139.2, 134.1, 133.2, 129.6, 128.7, 124.1 (q, *J* = 282.1Hz), 124.1, 120.0, 111.8, 72.3 (q, *J* = 32.2 Hz), 55.8, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.3 (d, *J* = 6.7 Hz, 3F); HRMS *m/z* calculated for $C_{16}H_{16}F_3O_5S$ $[M + H]^+$ 377.0665, found 377.0657.



*1-(3,4,5-Trimethoxyphenyl)-2,2,2-trifluoroethan-1-ol (**20**).*[18] The crude product was obtained by using General Method D. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 4:1 affording the title product (187 mg, 68%) as a white solid. mp 95-97°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 2H), 4.95 (q, *J* = 6.7 Hz, 1H), 3.86 (s, 6H), 3.85 (s, 3H), 2.81 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 138.8, 129.7, 124.3 (q, *J* = 282.1Hz), 104.7, 73.0 (q, *J* = 32.0 Hz), 61.0, 56.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.2 (d, *J* = 6.7 Hz, 3F); HRMS *m/z* calculated for $C_{11}H_{14}F_3O_4$ $[M + H]^+$ 267.0839, found 267.0833.



*4-(1,1,1-Trifluoro-2-hydroxypropan-2-yl)benzonitrile (**21**).*[19] The crude product was obtained by using General Method D. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 10:1 affording the title product (184 mg, 94%) as a yellow solid. mp 117-119°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 2.55 (s, 1H), 1.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 132.2, 127.2, 125.2 (q, *J* = 285.5 Hz), 118.5, 112.8, 74.8 (q, *J* = 29.6 Hz), 24.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.9 (s, 3F); HRMS *m/z* calculated for $C_{10}H_9F_3NO$ $[M + H]^+$ 216.0631, found 216.0626.

Trifluoromethylation of 4-acetylbenzonitrile in Continuous Flow - Scale-out experiment

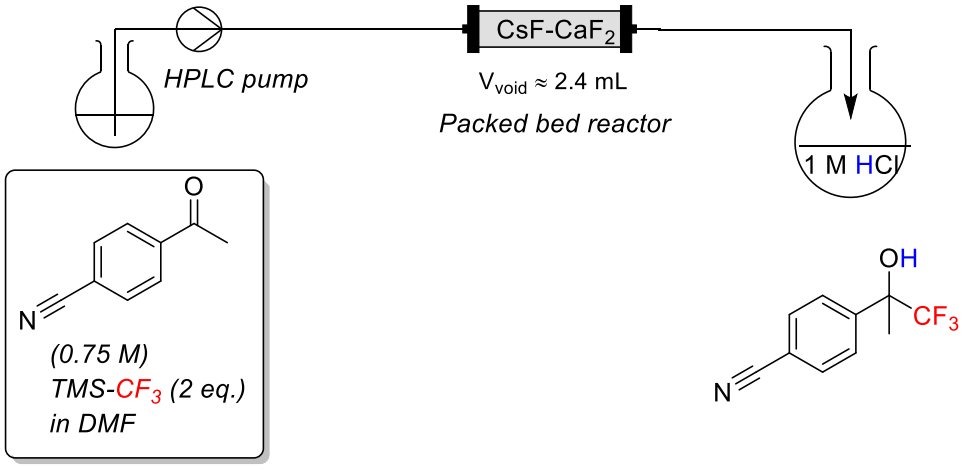


Figure S11: Schematic presentation of scale-out experiment of the trifluoromethylation of 4-acetylbenzonitrile.

4-Acetylbenzonitrile (10.88 g, 75 mmol, 1 equiv.) and trimethyl(trifluoromethyl)silane (21.34 g, 150 mmol, 2 equiv.) was dissolved in DMF (0.75 M). A packed bed reactor, containing 22 mmol CsF, was cooled using a water bath. The stock solution was pumped through the packed bed reactor with a residence time of 2.0 min at room temperature. The flow setup was run for 1.5 times the residence time, to reach steady state, before sample collection was initiated. A batch was collected every 15 minutes in round-bottomed

flasks containing 1 M HCl (20 mL). During the experiment the pressure drop over the packed bed reactor rose slowly and the reactor was shut down at 200 bar (42 minutes total collection time after reaching steady-state corresponding to a throughput of 36.4 mmol). TLC analysis was used to determine full conversion of the three batches, which was combined and extracted with Et_2O (4 x 60 mL). The combined ethereal phases was washed with water (4 x 60 mL), brine (2 x 60 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using flash column chromatography eluting with pentane/EtOAc 10:1 affording 4-(1,1,1-trifluoro-2-hydroxypropan-2-yl)benzonitrile (**21**) (7.37 g, 94%) as a yellow solid. mp 118-119°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 2.52 (s, 1H), 1.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.7, 132.2, 127.2, 125.2 (q, *J* = 285.5 Hz), 118.5, 112.8, 74.6 (q, *J* = 29.6 Hz), 24.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.9 (s, 3F); HRMS *m/z* calculated for $C_{10}H_9F_3NO$ $[M + H]^+$ 216.0631, found 216.0629.

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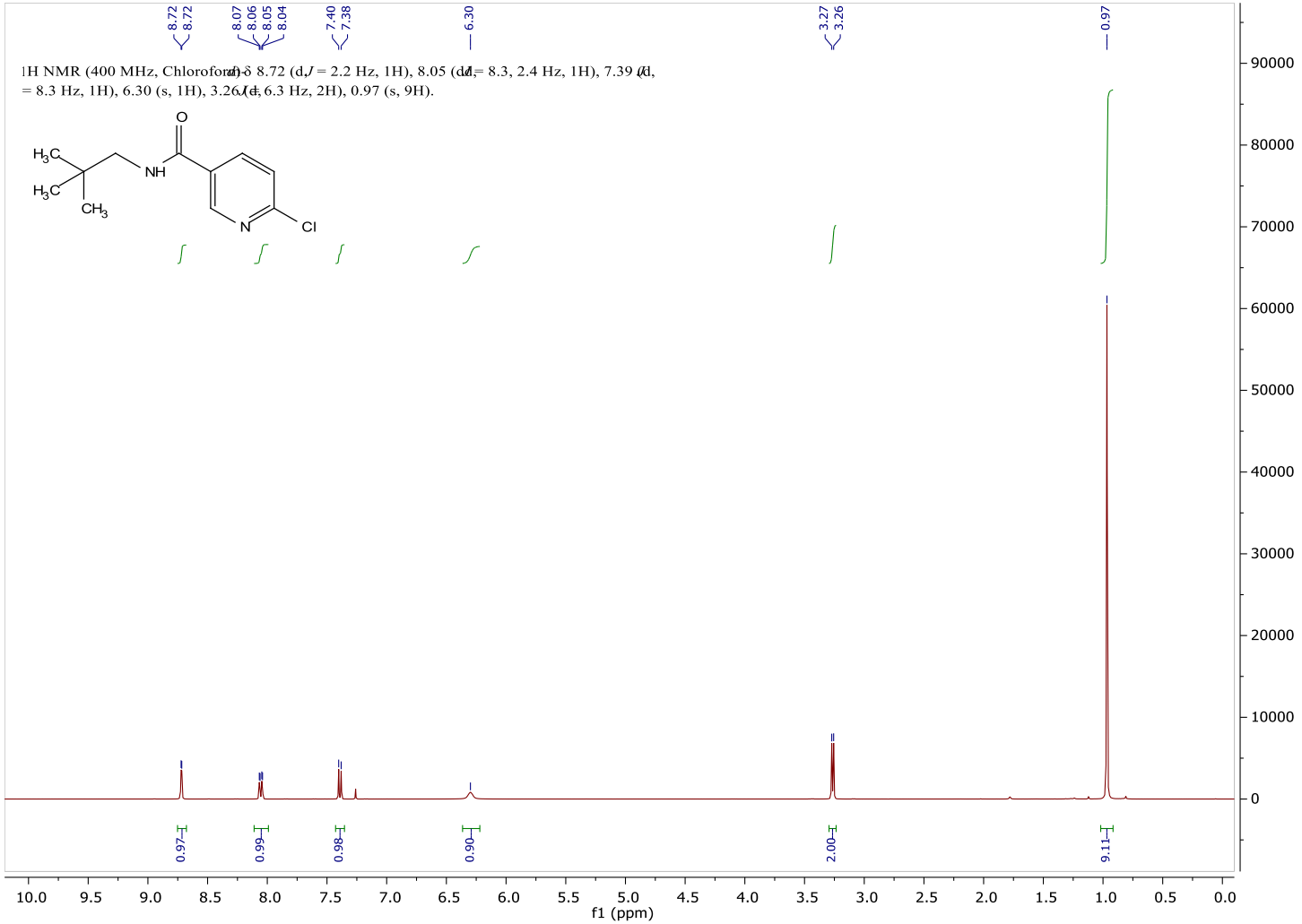
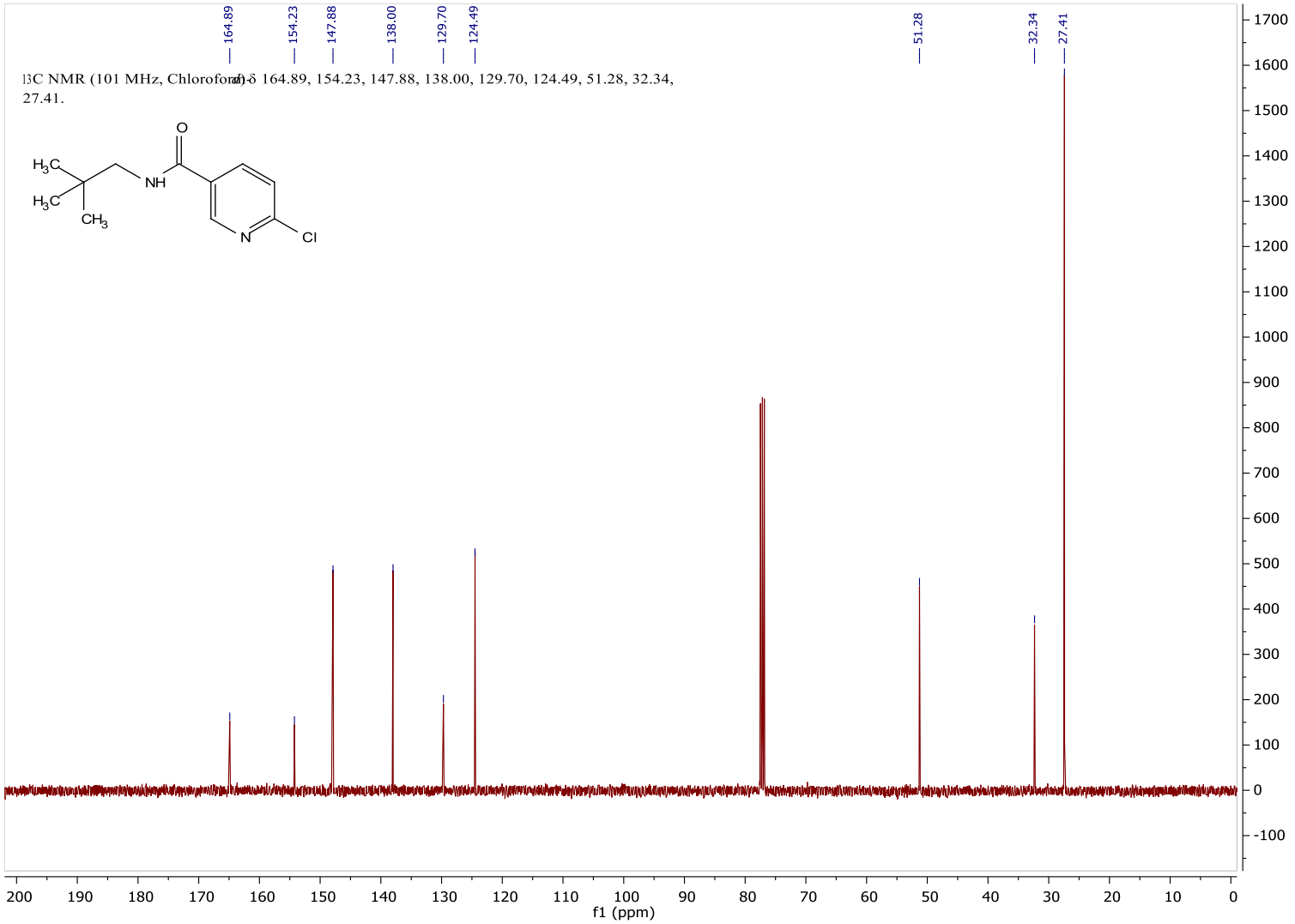
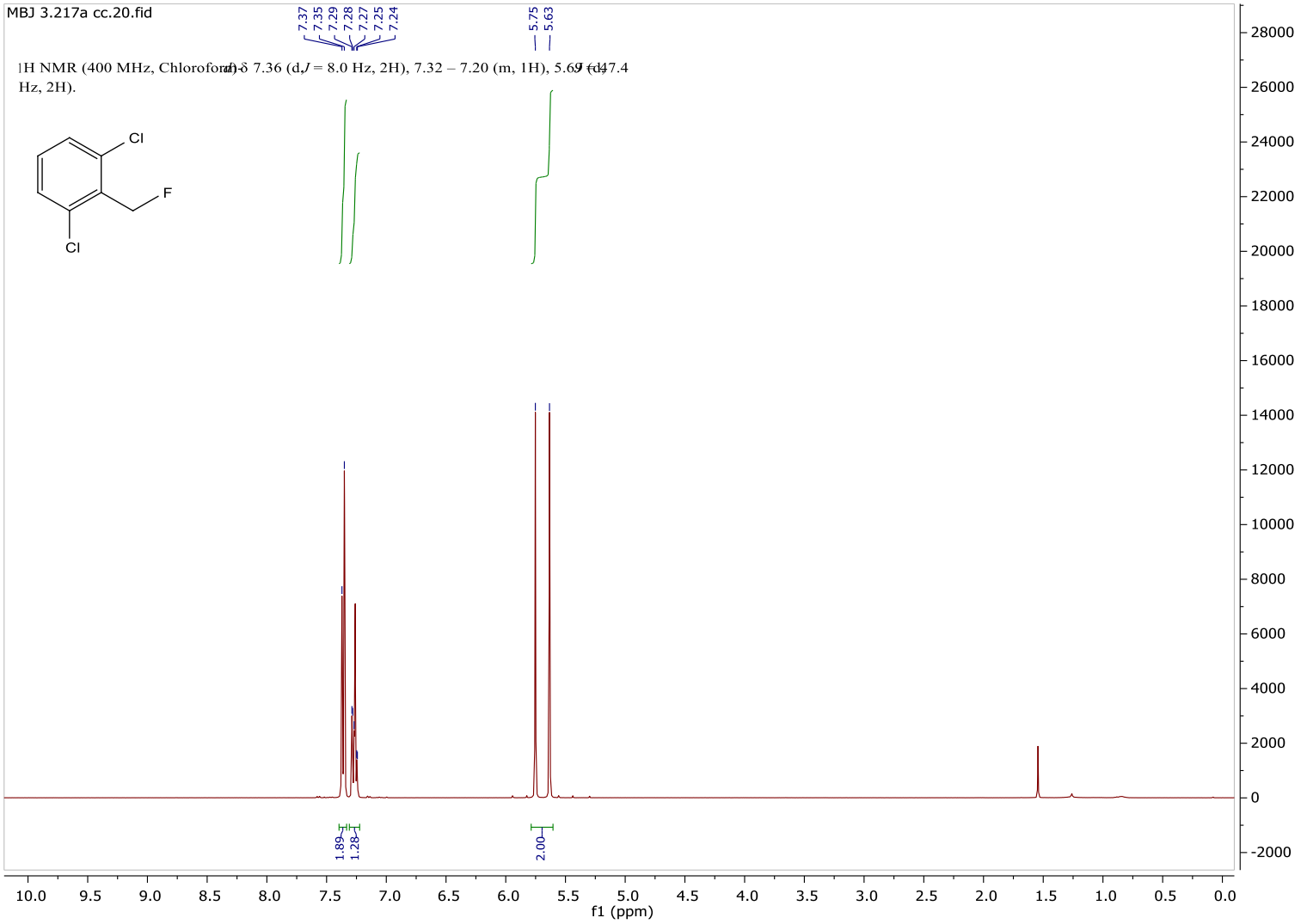
NMR Spectra

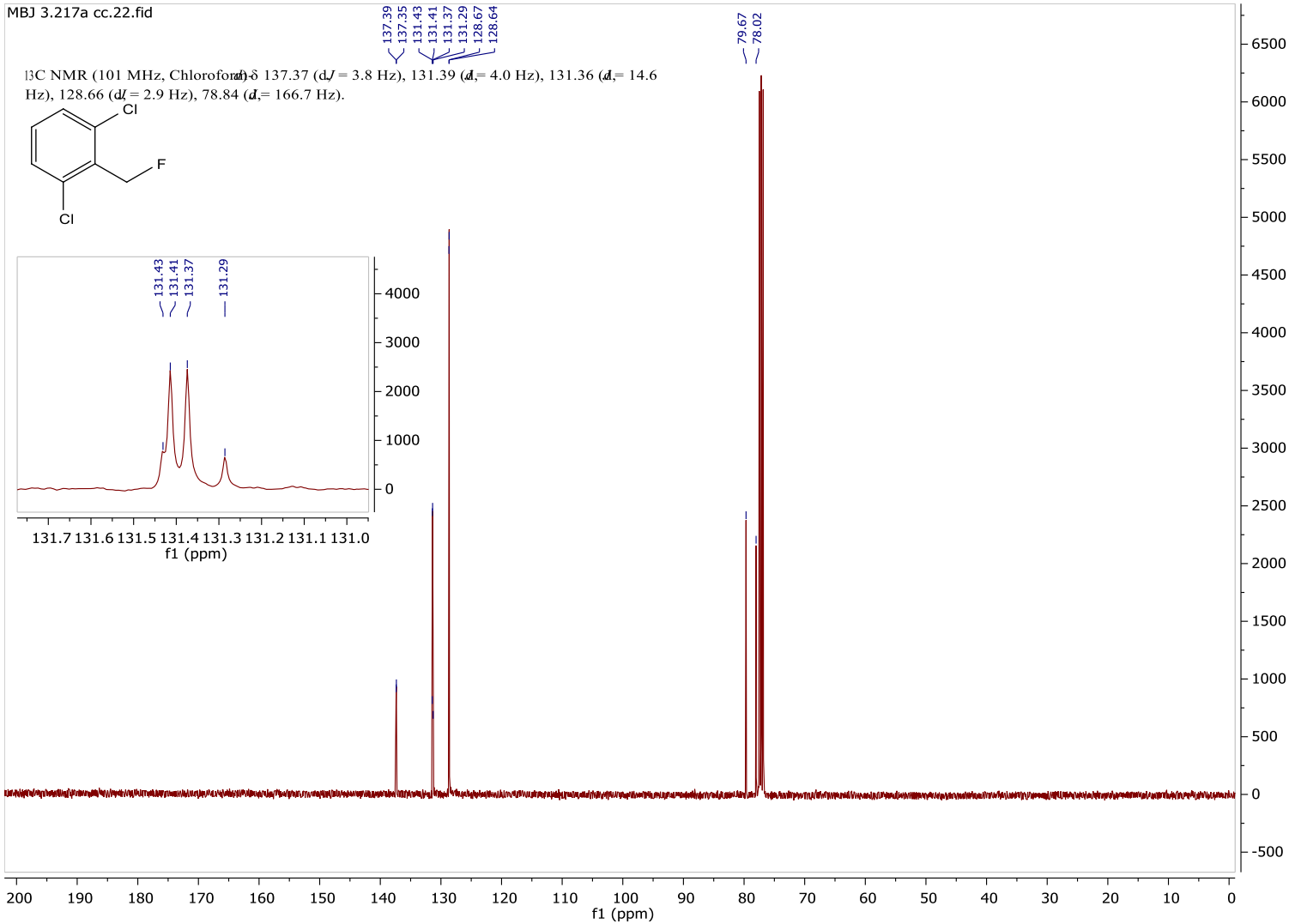
6-Chloro-N-neopentylnicotinamide

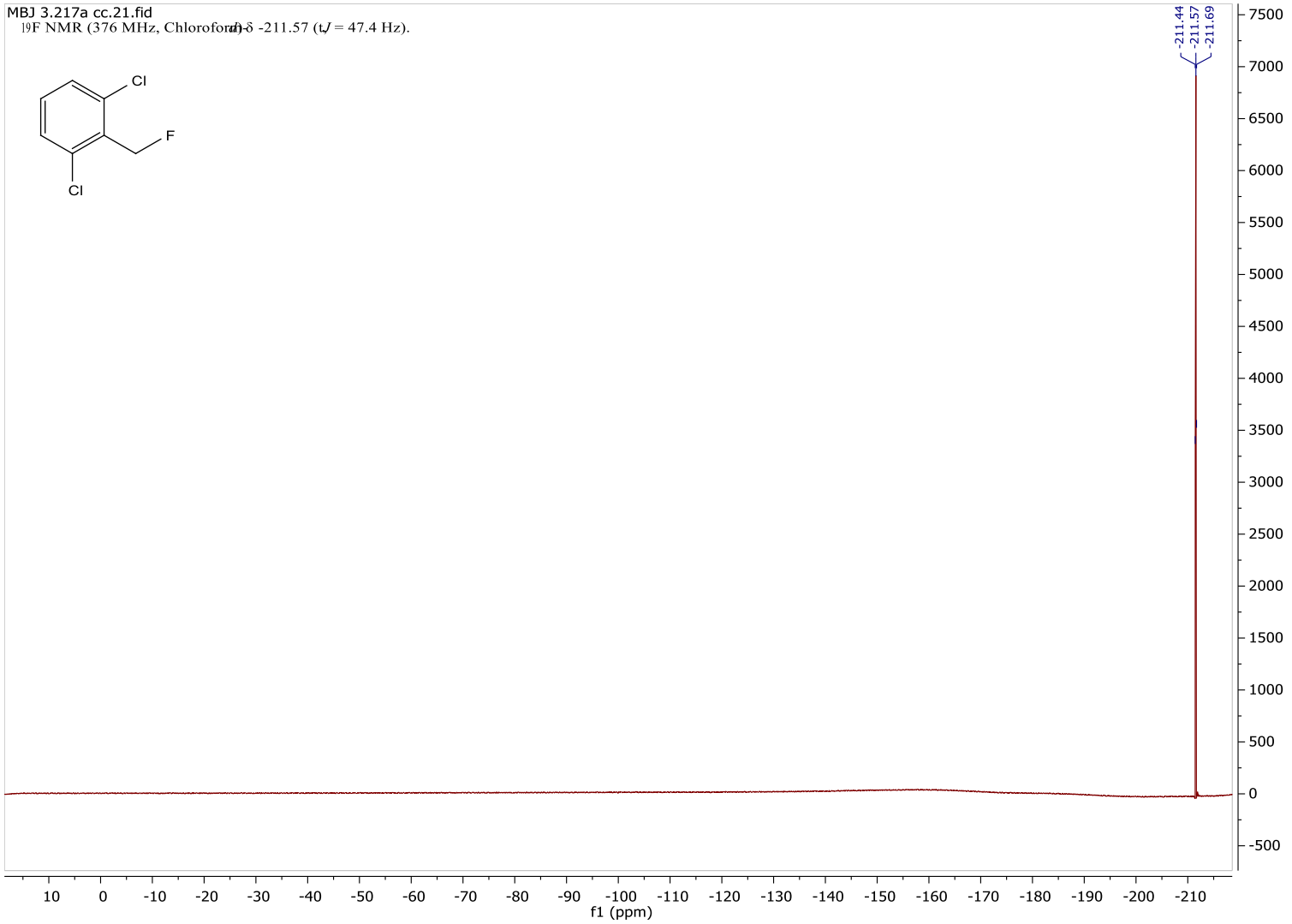



164.89
154.23
147.88
138.00
129.70
124.49
51.28
32.34
27.41
13C NMR (101 MHz, Chloroform-d) δ 164.89, 154.23, 147.88, 138.00, 129.70, 124.49, 51.28, 32.34, 27.41.
O
NH
H3C
H3C
CH3
N
Cl
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

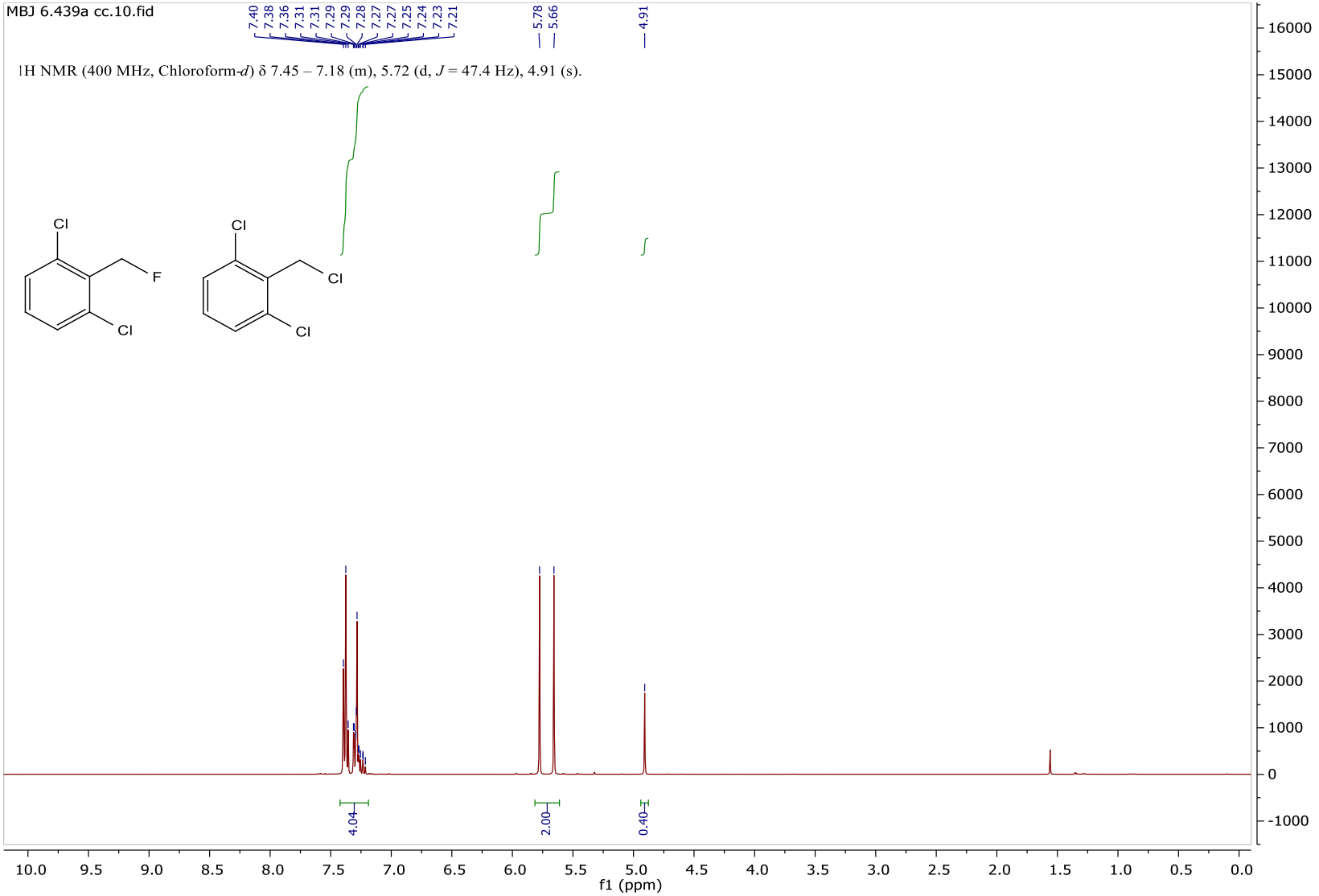
*1-Fluoromethyl-2,6-dichlorobenzene (**1**) from 1-bromomethyl-2,6-dichlorobenzene using CsF-CaF_2.*

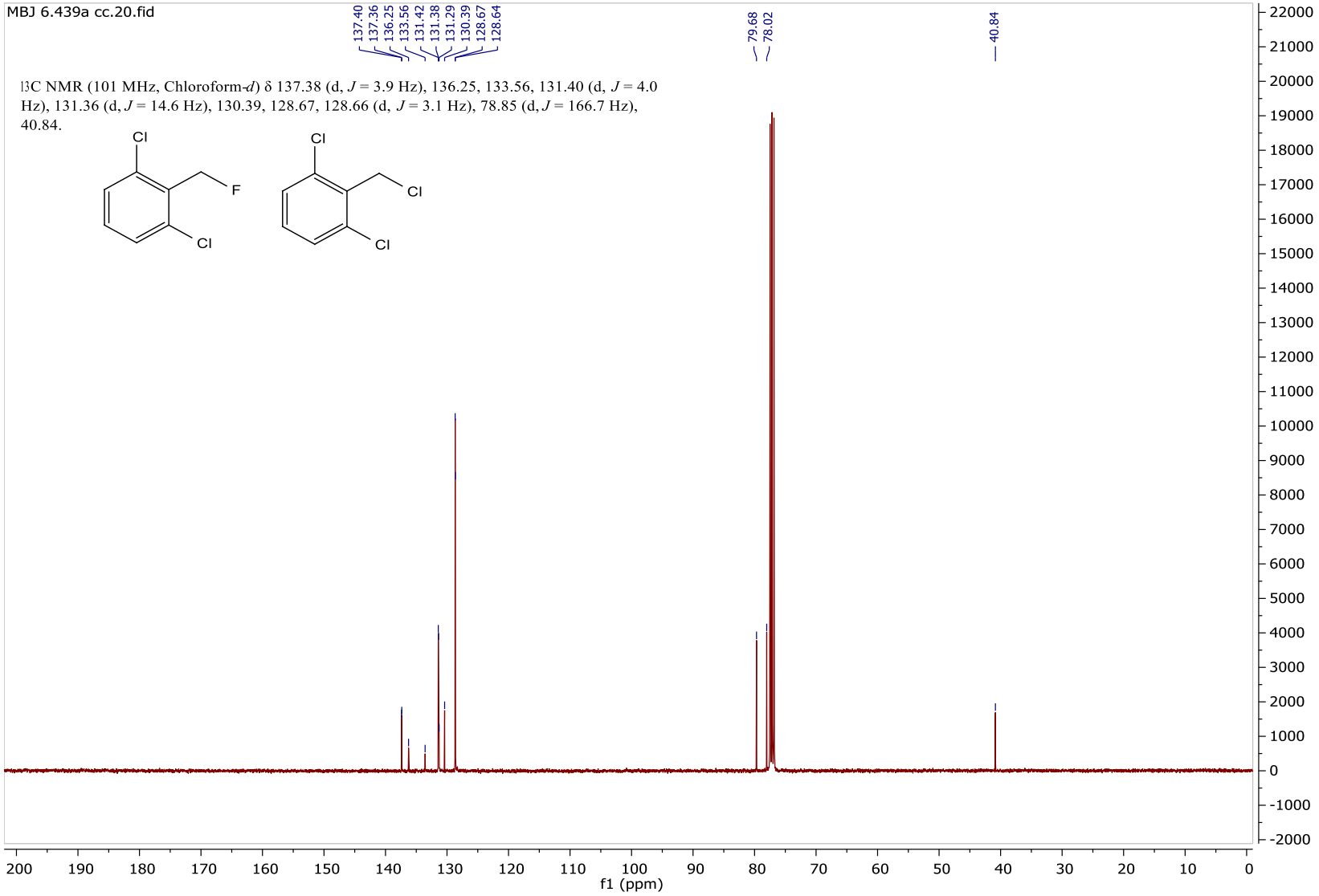



MBJ 3.217a cc.22.fid
137.39
137.35
131.43
131.41
131.37
131.29
128.67
128.64
79.67
78.02
13C NMR (101 MHz, Chloroform-d) δ 137.37 (d, J = 3.8 Hz), 131.39 (d, J = 4.0 Hz), 131.36 (d, J = 14.6 Hz), 128.66 (d, J = 2.9 Hz), 78.84 (d, J = 166.7 Hz).
Cl
F
Cl
131.43
131.41
131.37
131.29
131.7 131.6 131.5 131.4 131.3 131.2 131.1 131.0
f1 (ppm)
f1 (ppm)


MBJ 3.217a cc.21.fid
19F NMR (376 MHz, Chloroform-d) δ -211.57 (t, J = 47.4 Hz).
Cl
F
Cl
-211.44
-211.57
-211.69
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

*1-Fluoromethyl-2,6-dichlorobenzene (**1**) from 1-chloromethyl-2,6-dichlorobenzene using CsF-CaF_2.*

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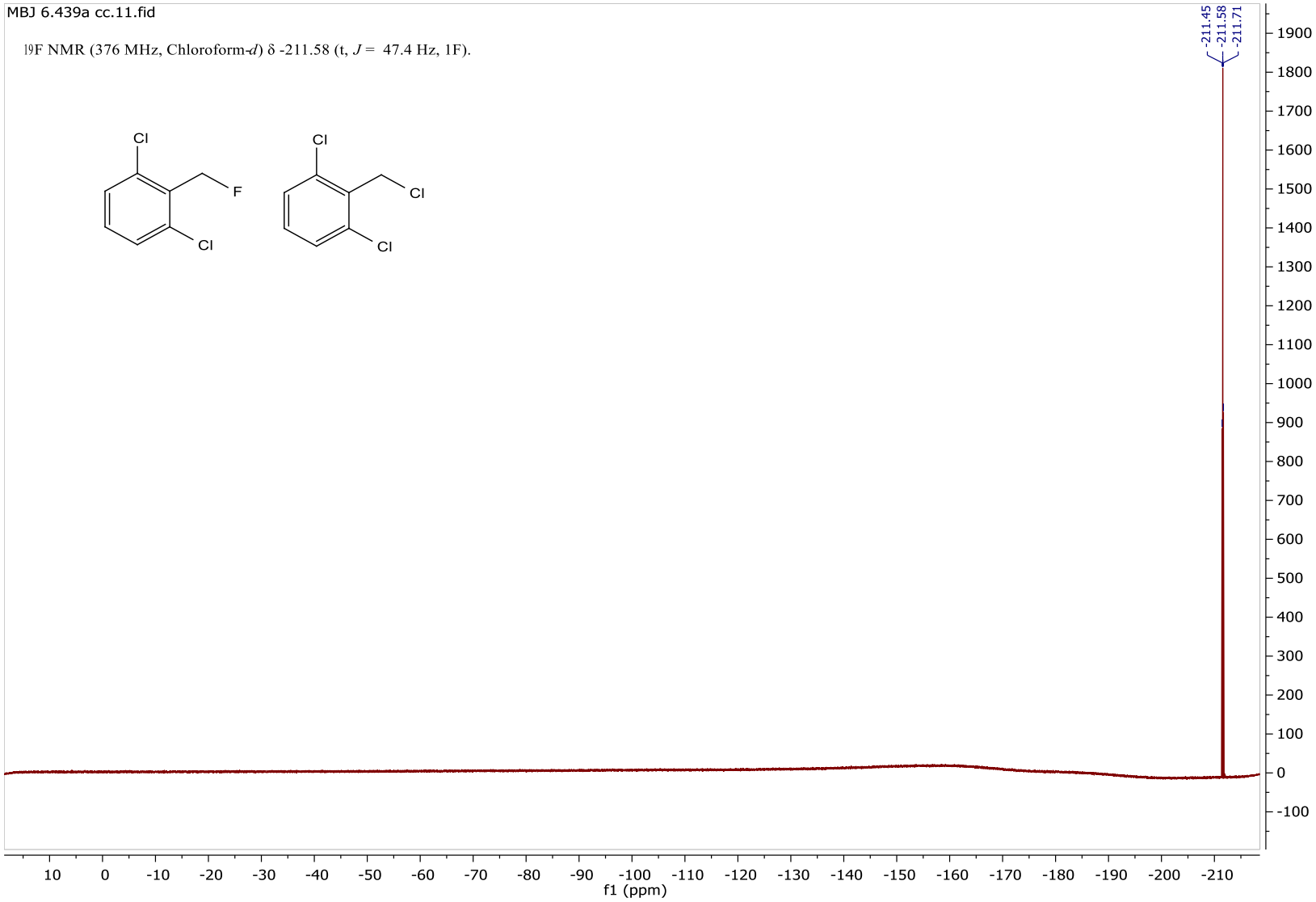
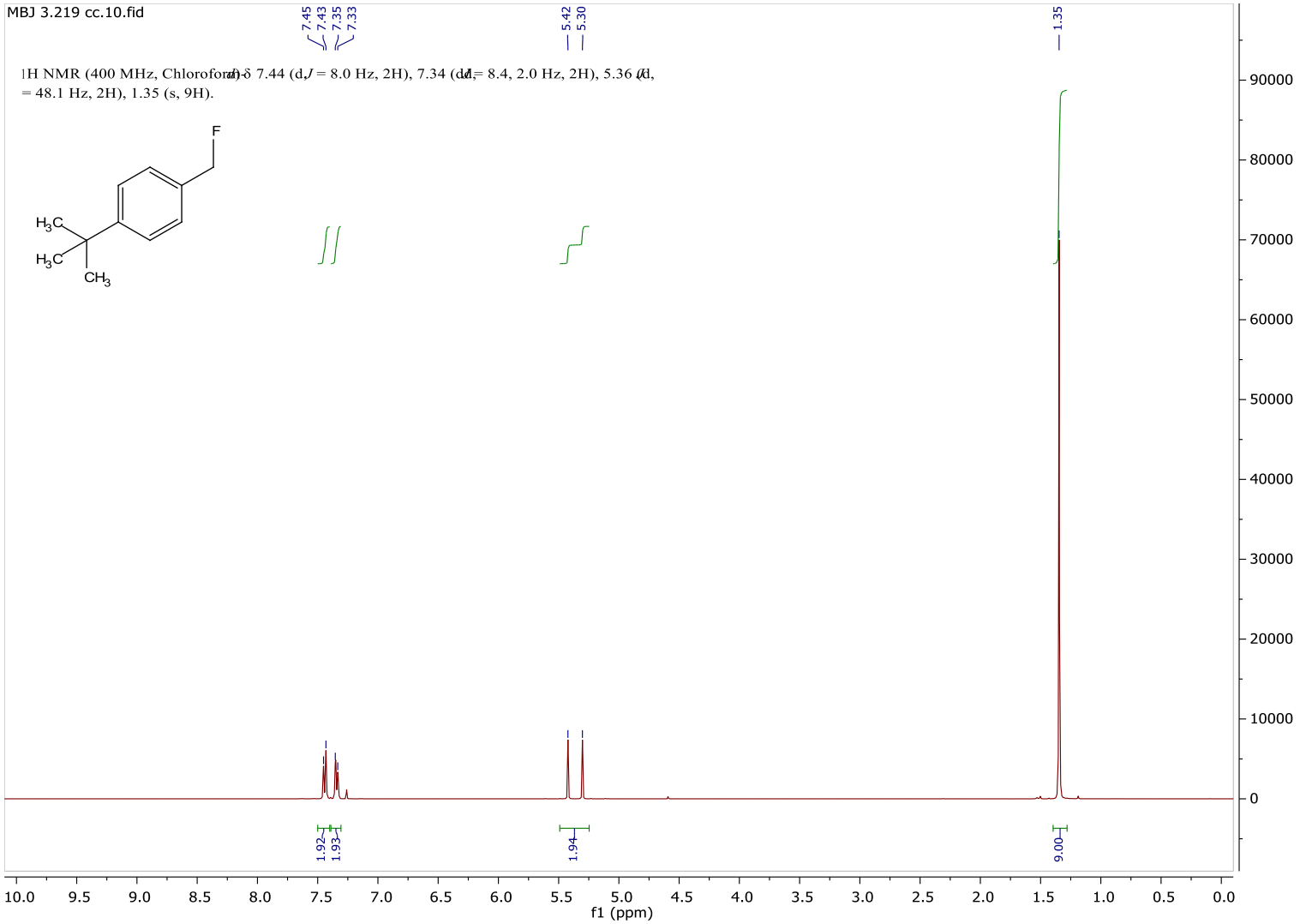
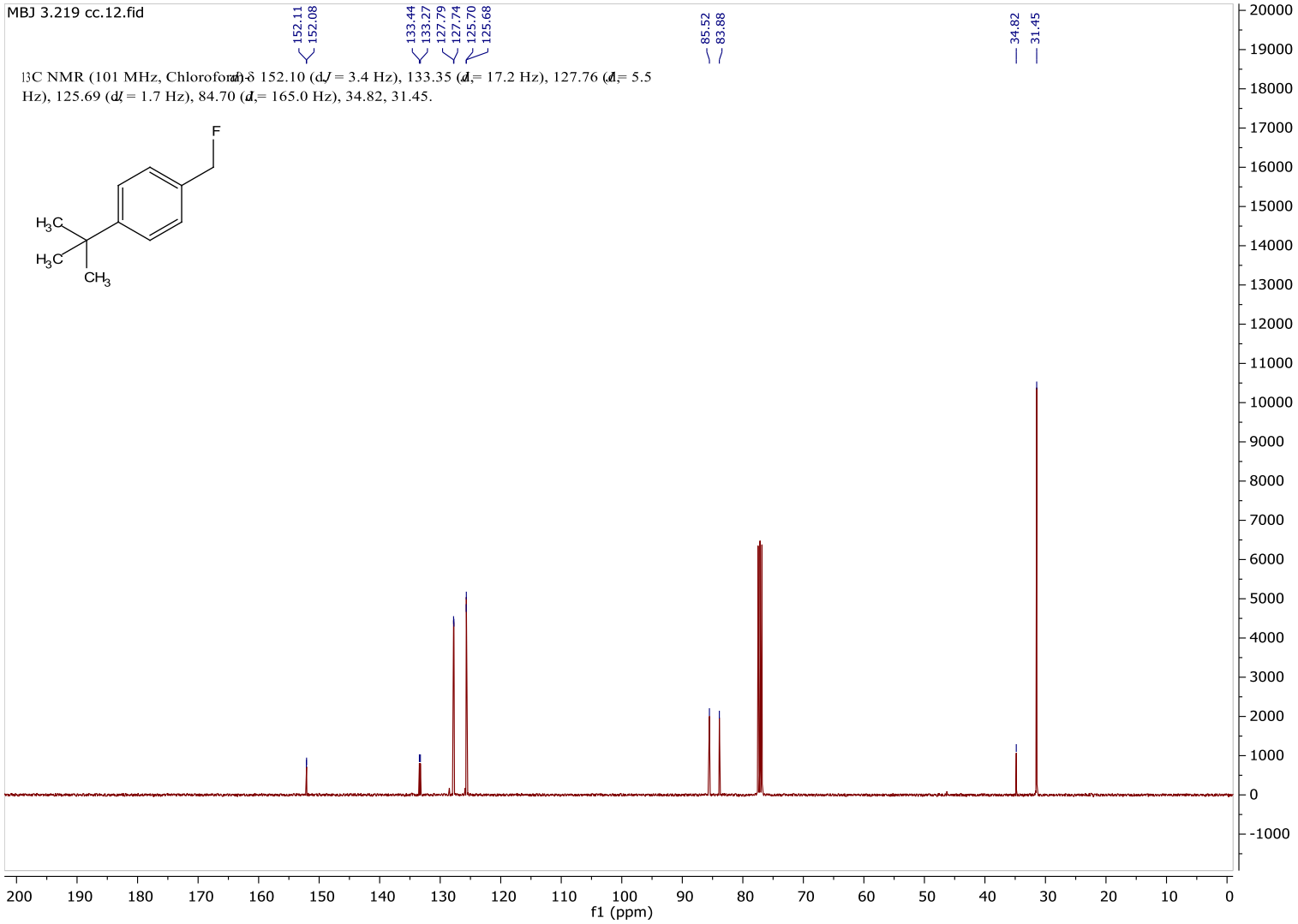
137.40
137.36
136.25
133.56
131.42
131.38
131.29
130.39
128.67
128.64
79.68
78.02
40.84
13C NMR (101 MHz, Chloroform-d) δ 137.38 (d, J = 3.9 Hz), 136.25, 133.56, 131.40 (d, J = 4.0 Hz), 131.36 (d, J = 14.6 Hz), 130.39, 128.67, 128.66 (d, J = 3.1 Hz), 78.85 (d, J = 166.7 Hz), 40.84.
Cl
F
Cl
Cl
Cl
Cl
f1 (ppm)


MBJ 6.439a cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -211.58 (t, J = 47.4 Hz, 1F).
Cl
F
Cl
Cl
Cl
Cl
-211.45
-211.58
-211.71
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

*1-Fluoromethyl-4-tertbutylbenzene (**2**) from 1-bromomethyl-4-tertbutylbenzene using CsF-CaF_2.*

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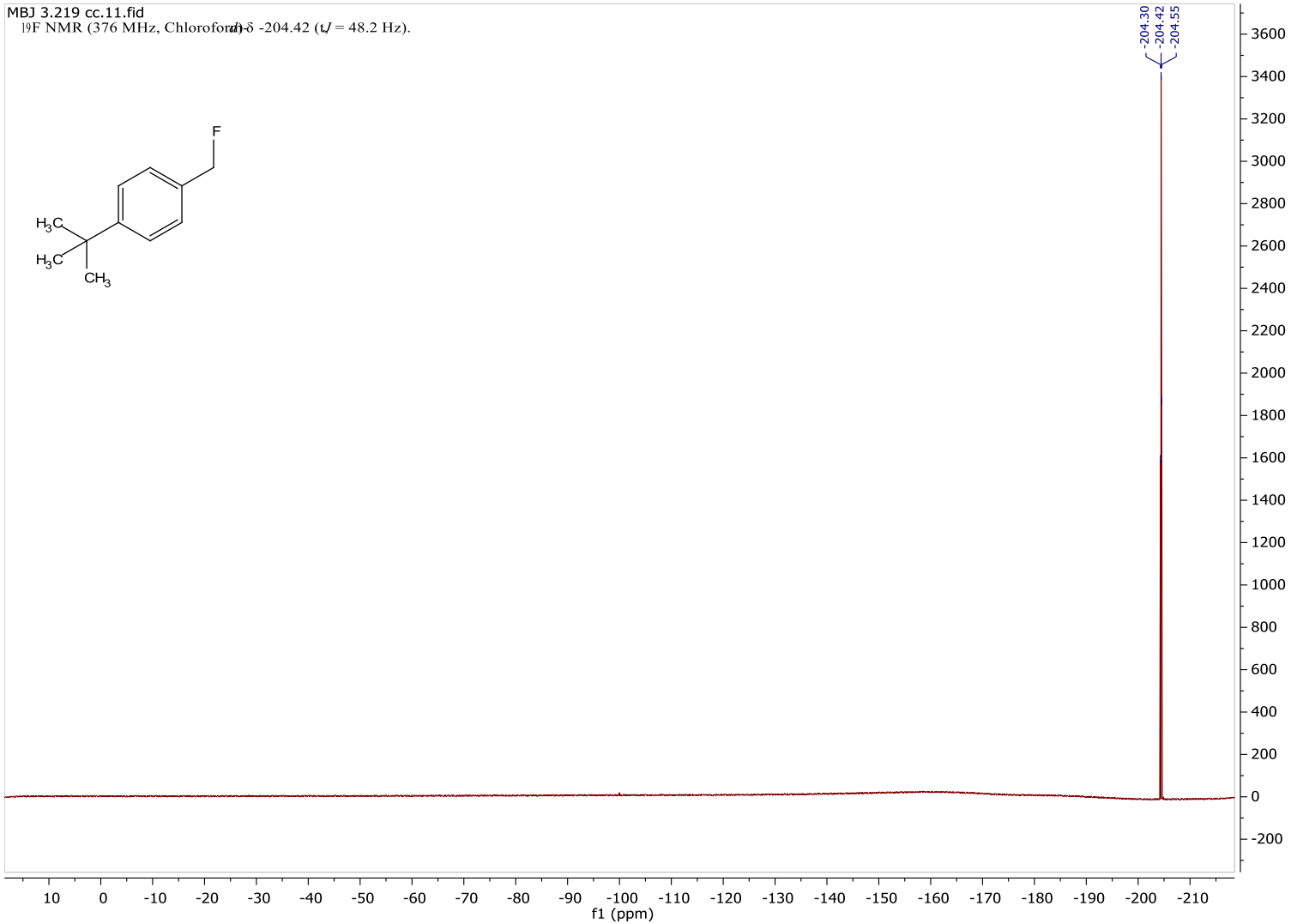
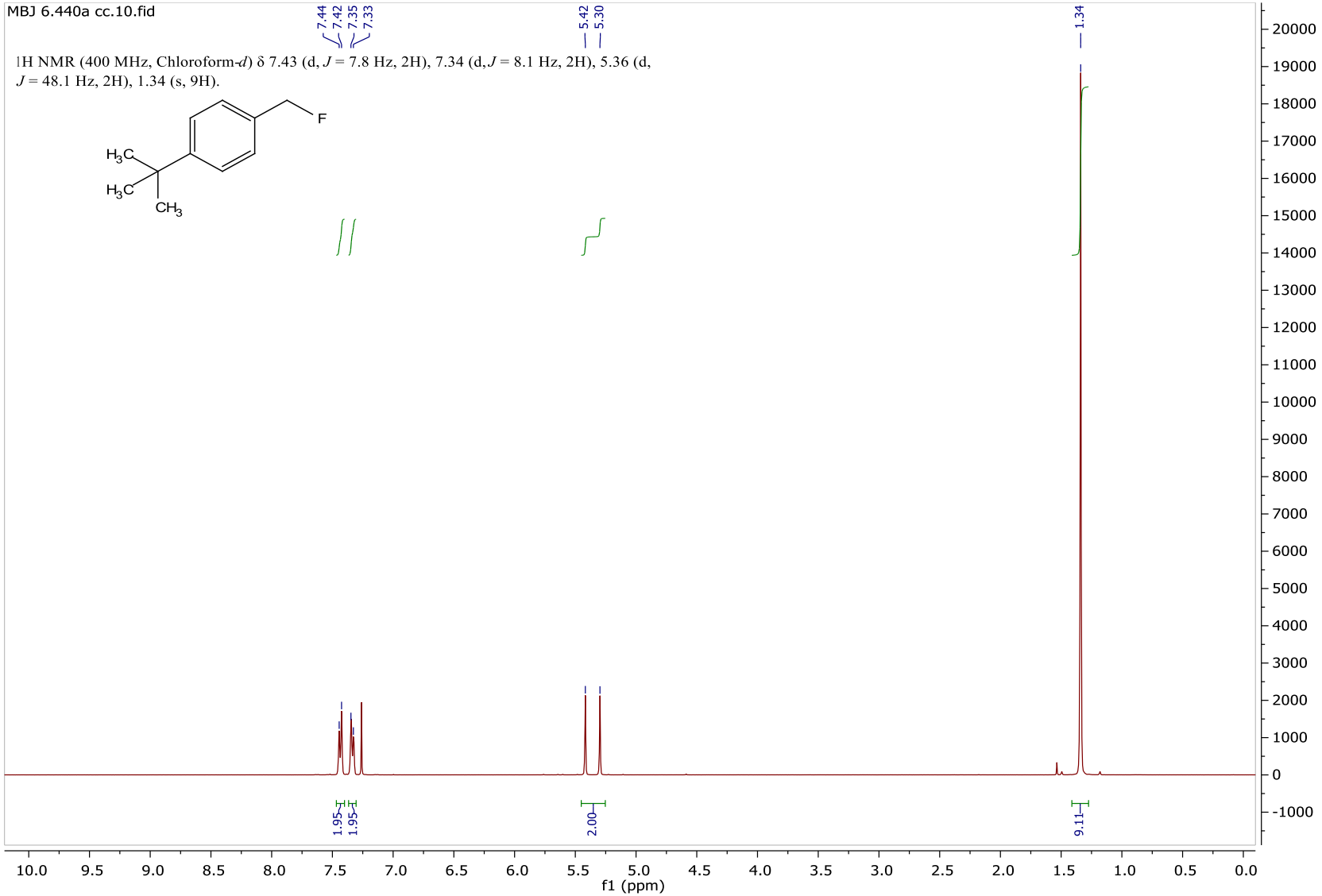
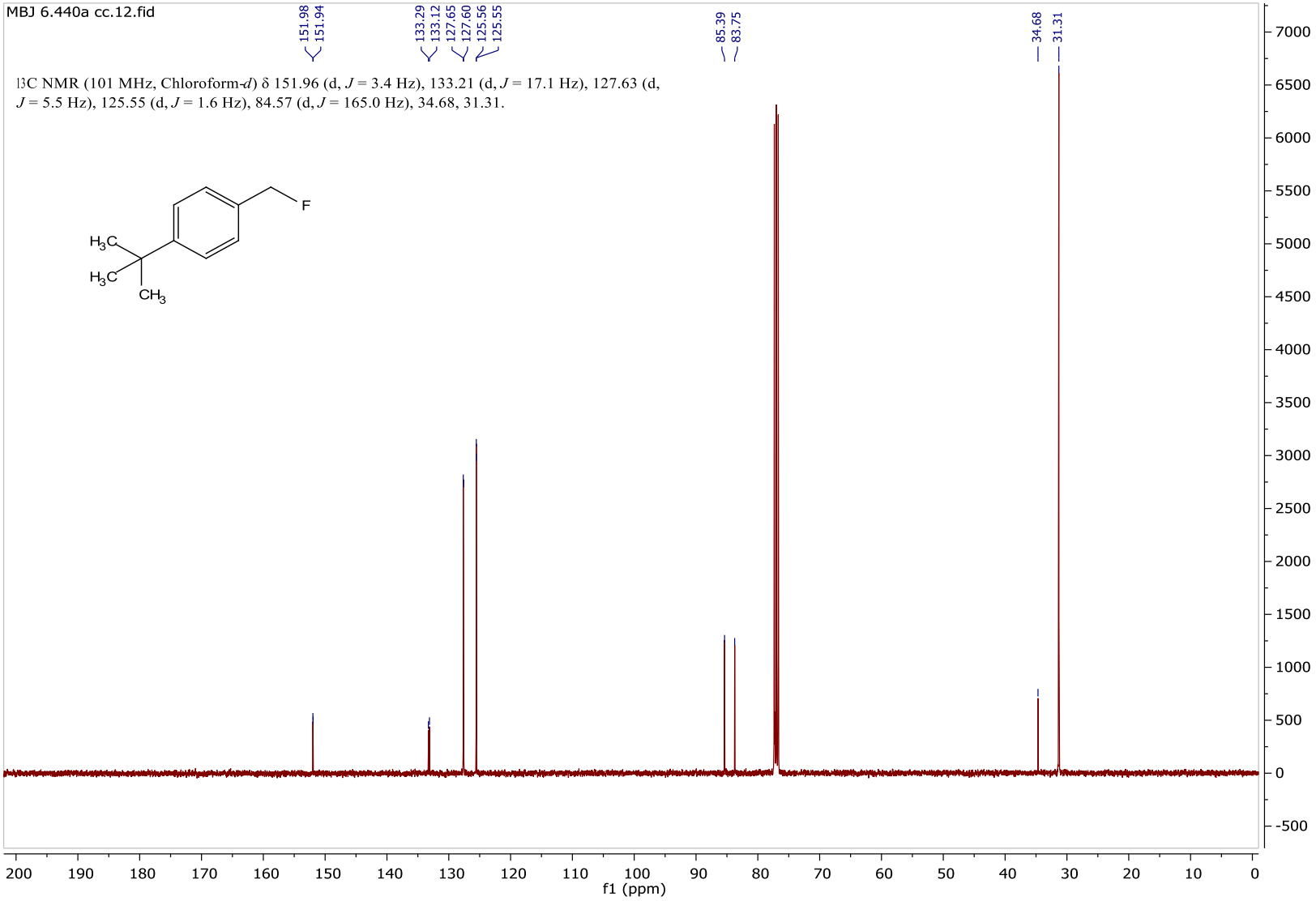
152.11
152.08
133.44
133.27
127.79
127.74
125.70
125.68
85.52
83.88
34.82
31.45
13C NMR (101 MHz, Chloroform-d) δ 152.10 (d, J = 3.4 Hz), 133.35 (d, J = 17.2 Hz), 127.76 (d, J = 5.5 Hz), 125.69 (d, J = 1.7 Hz), 84.70 (d, J = 165.0 Hz), 34.82, 31.45.
F
H3C
H3C
CH3
f1 (ppm)


MBJ 3.219 cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -204.42 (t, J = 48.2 Hz).
-204.30
-204.42
-204.55
F
H3C
H3C
CH3
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

*1-Fluoromethyl-4-tertbutylbenzene (**2**) from 1-chloromethyl-4-tertbutylbenzene using CsF-CaF_2.*

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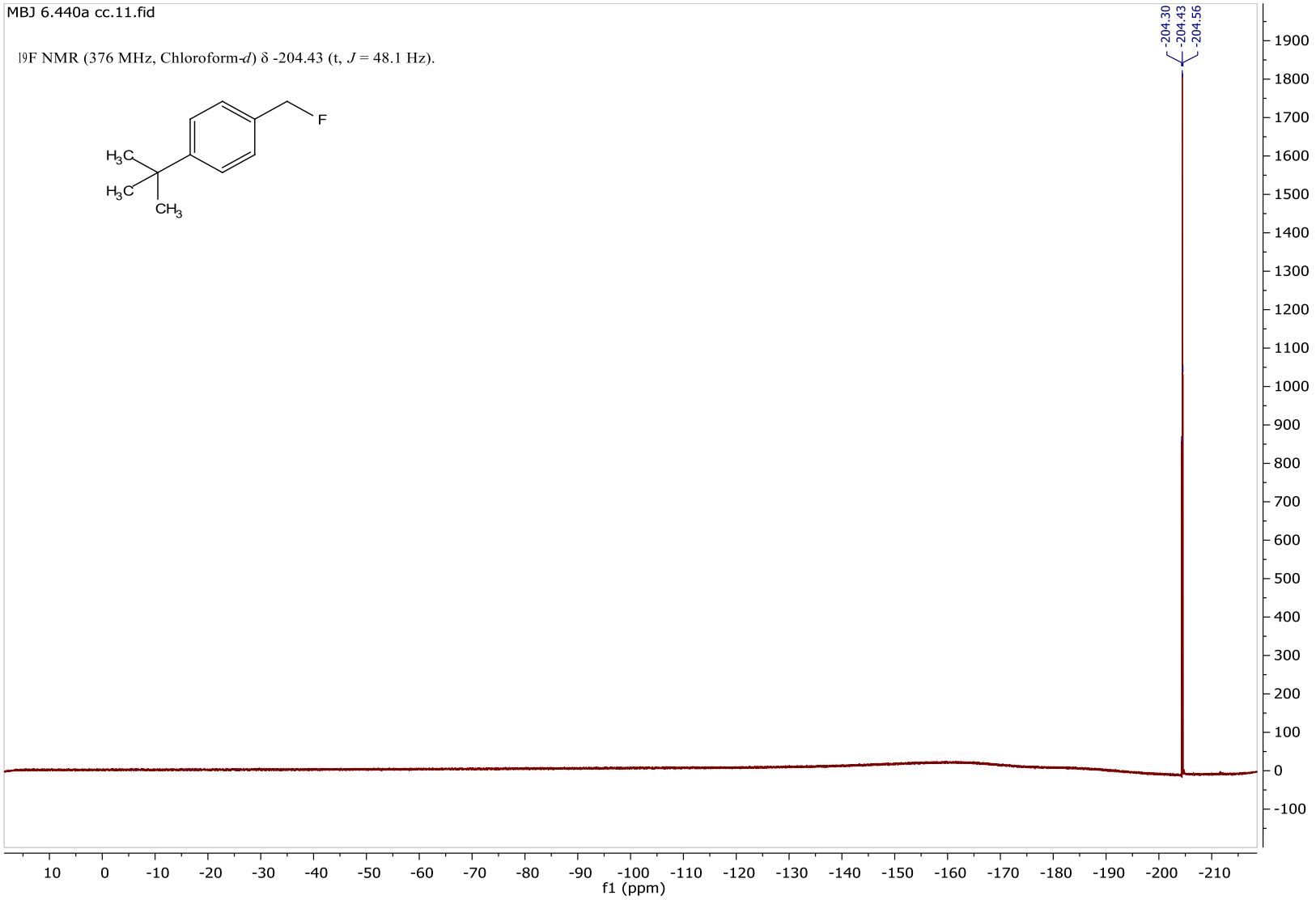
151.98
151.94
133.29
133.12
127.65
127.60
125.56
125.55
85.39
83.75
34.68
31.31
13C NMR (101 MHz, Chloroform-d) δ 151.96 (d, J = 3.4 Hz), 133.21 (d, J = 17.1 Hz), 127.63 (d, J = 5.5 Hz), 125.55 (d, J = 1.6 Hz), 84.57 (d, J = 165.0 Hz), 34.68, 31.31.
F
H3C
H3C
CH3
f1 (ppm)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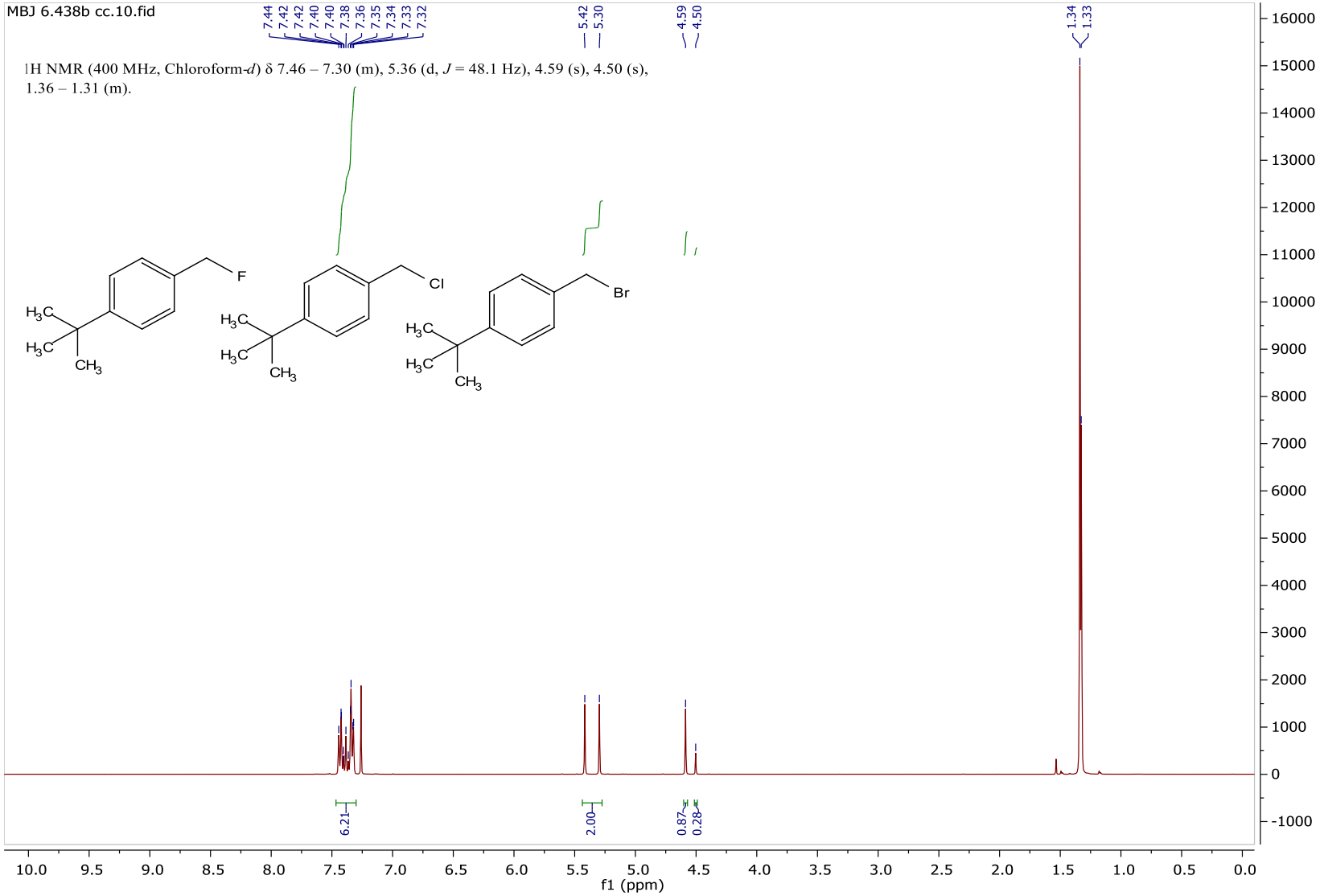
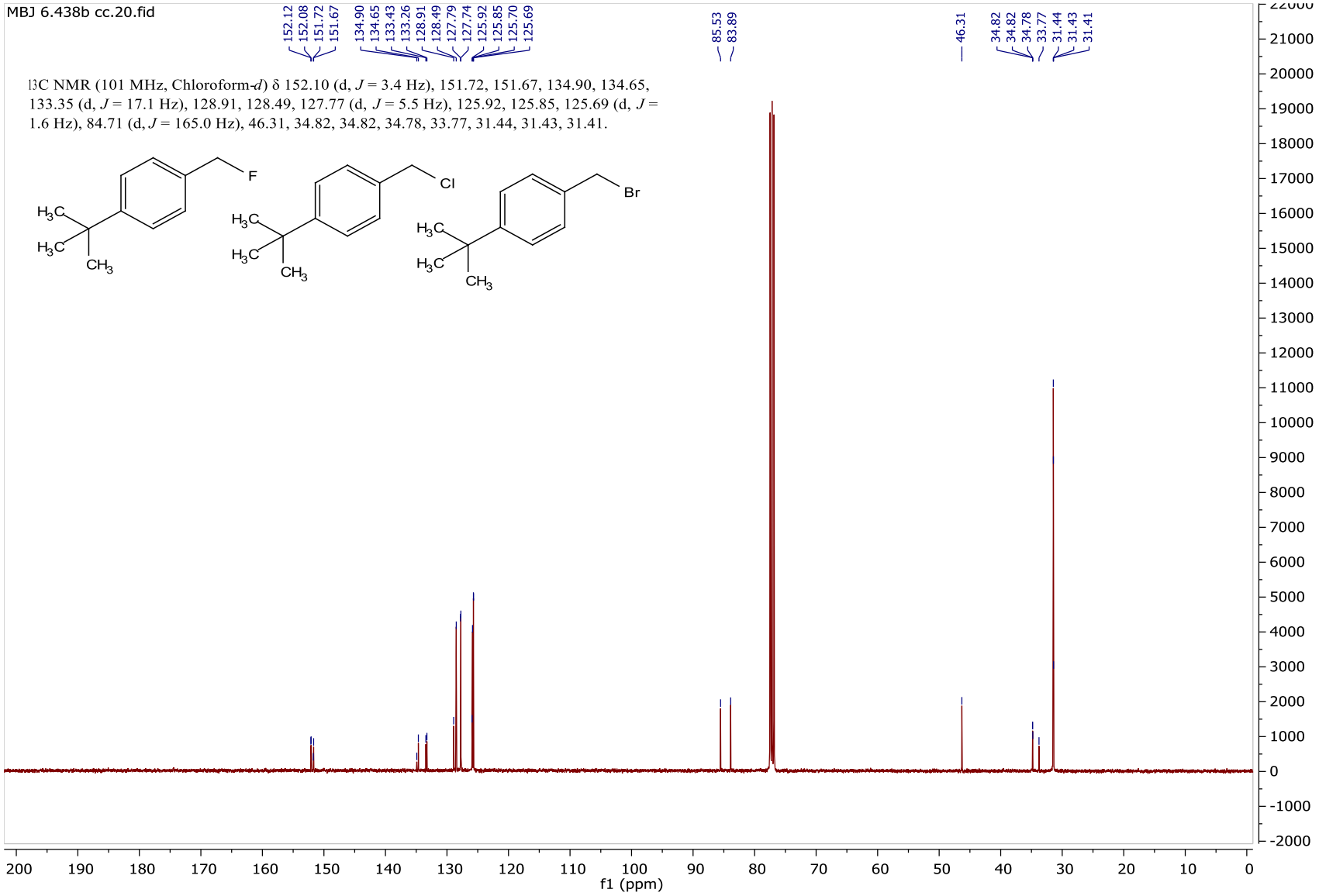
19F NMR (376 MHz, Chloroform-d) δ -204.43 (t, J = 48.1 Hz).
F
H3C
H3C
CH3
-204.30
-204.43
-204.56
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

*1-Fluoromethyl-4-tertbutylbenzene (**2**) from 1-bromomethyl-4-tertbutylbenzene using KF-CaF_2.*

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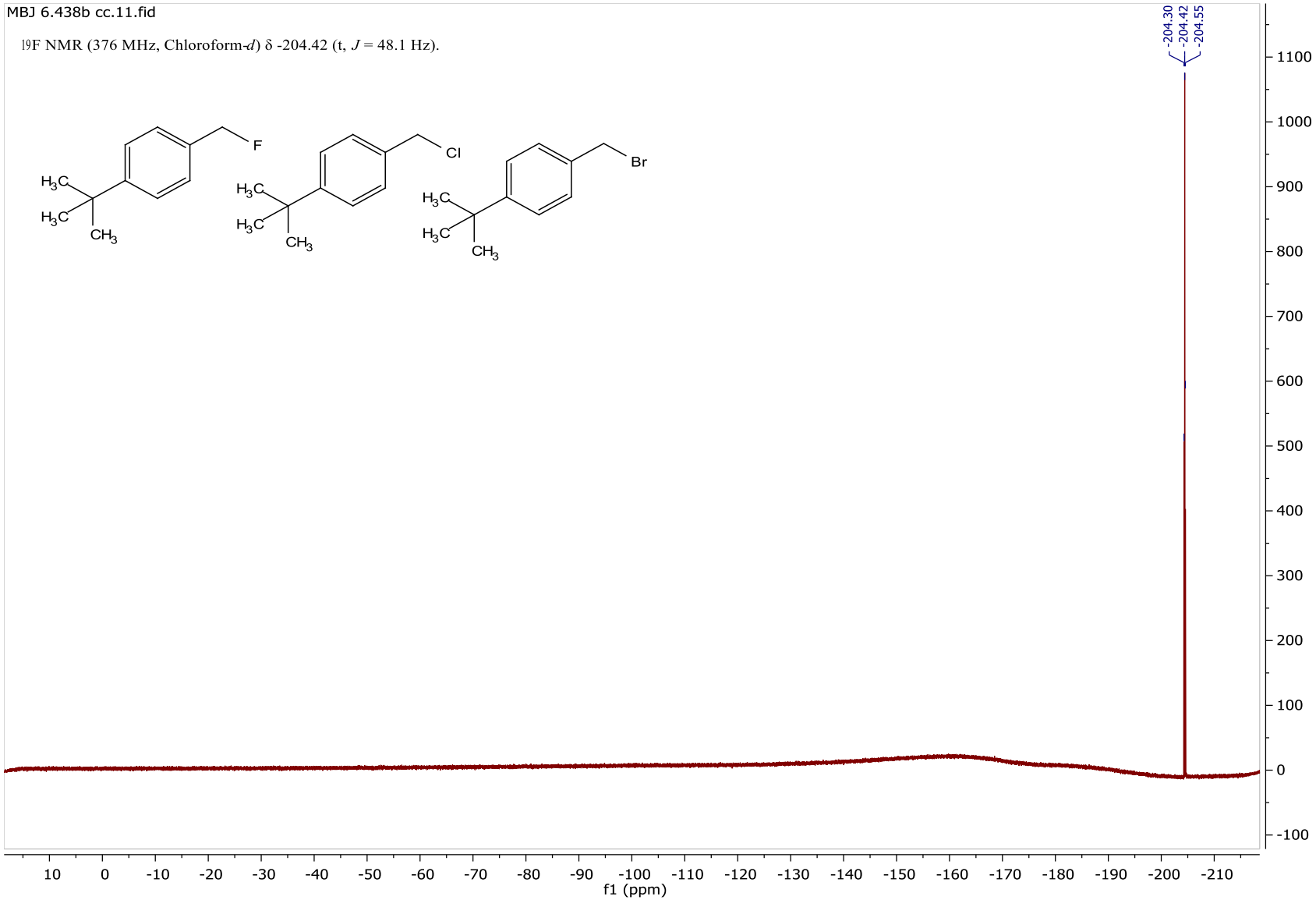
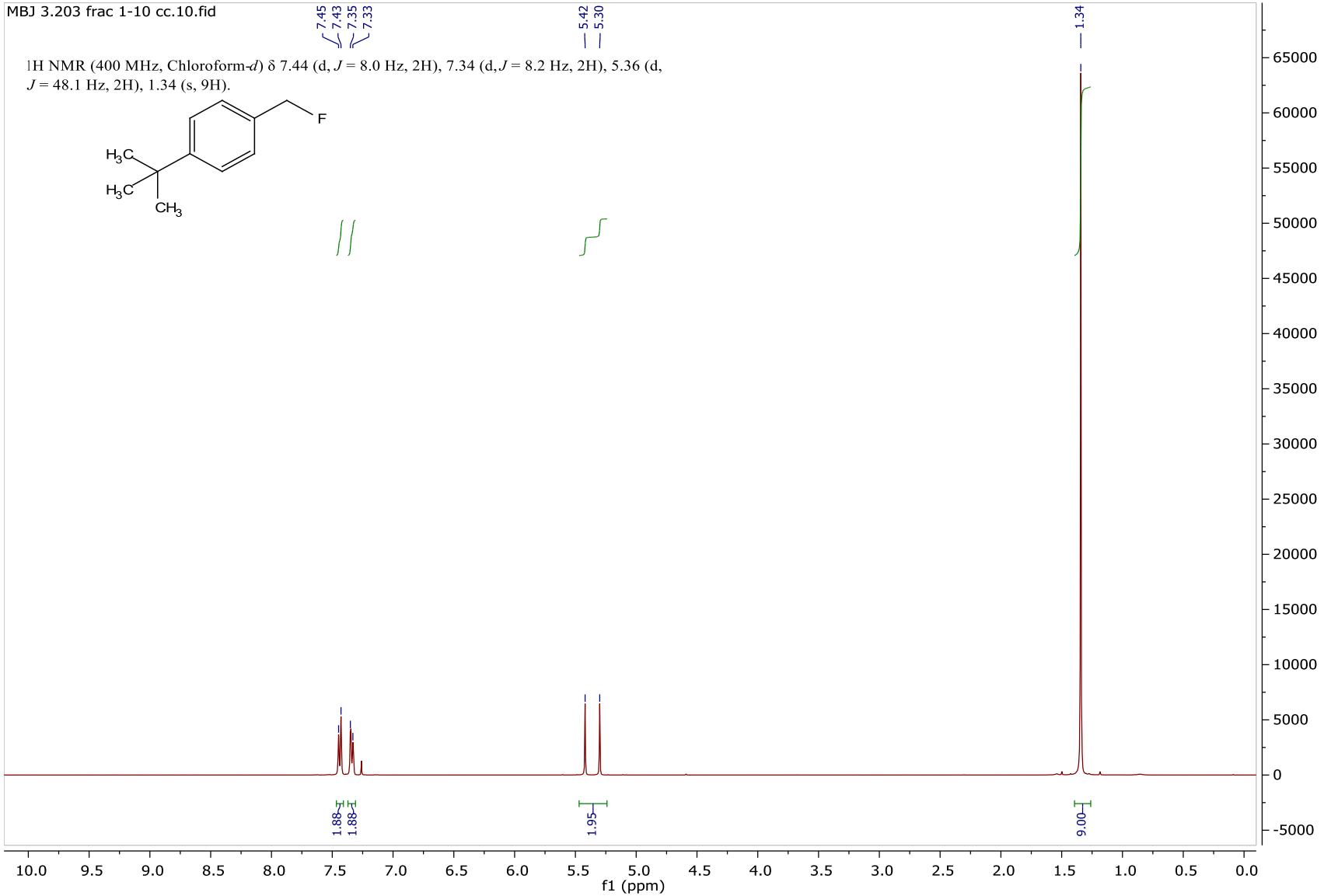
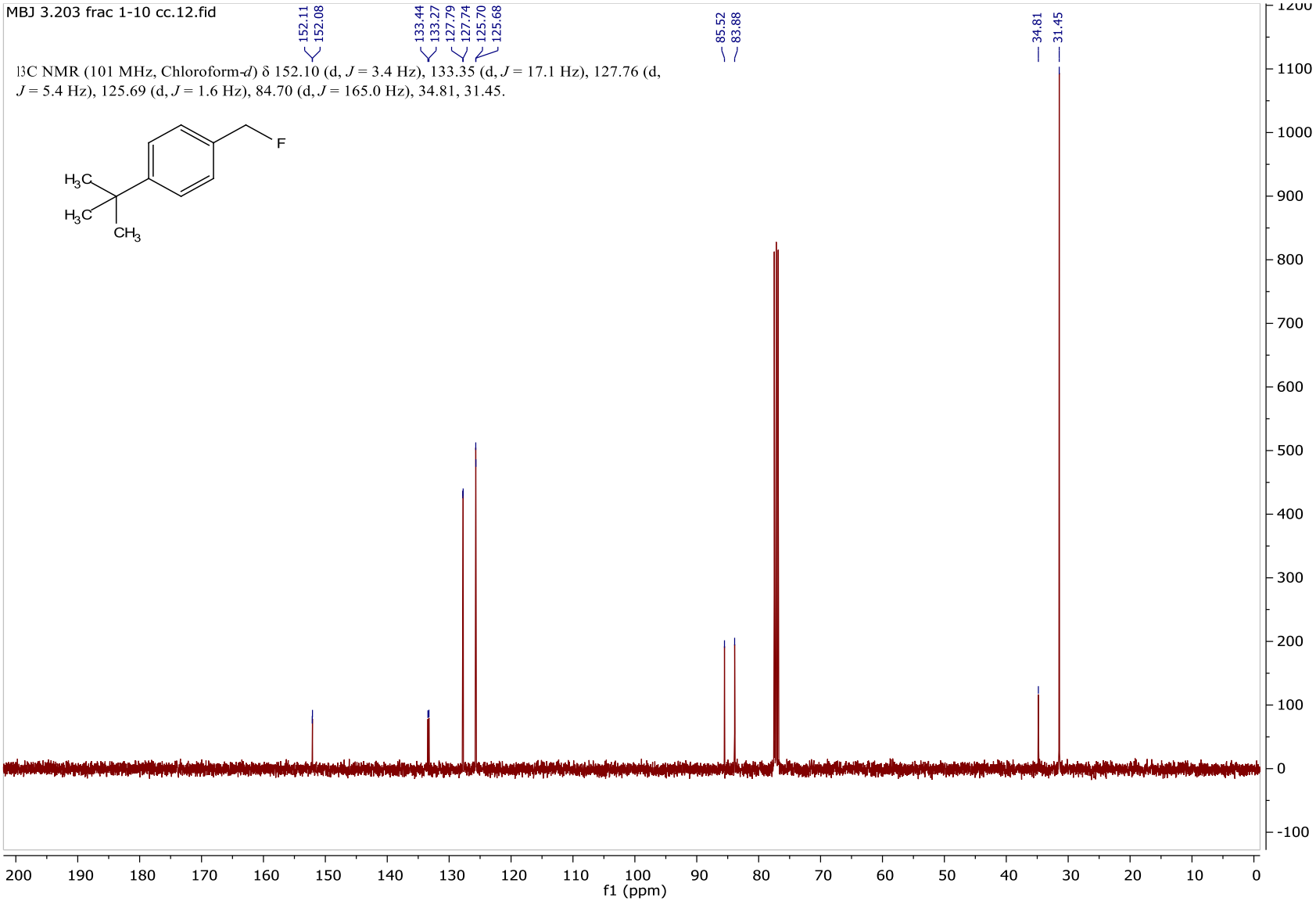
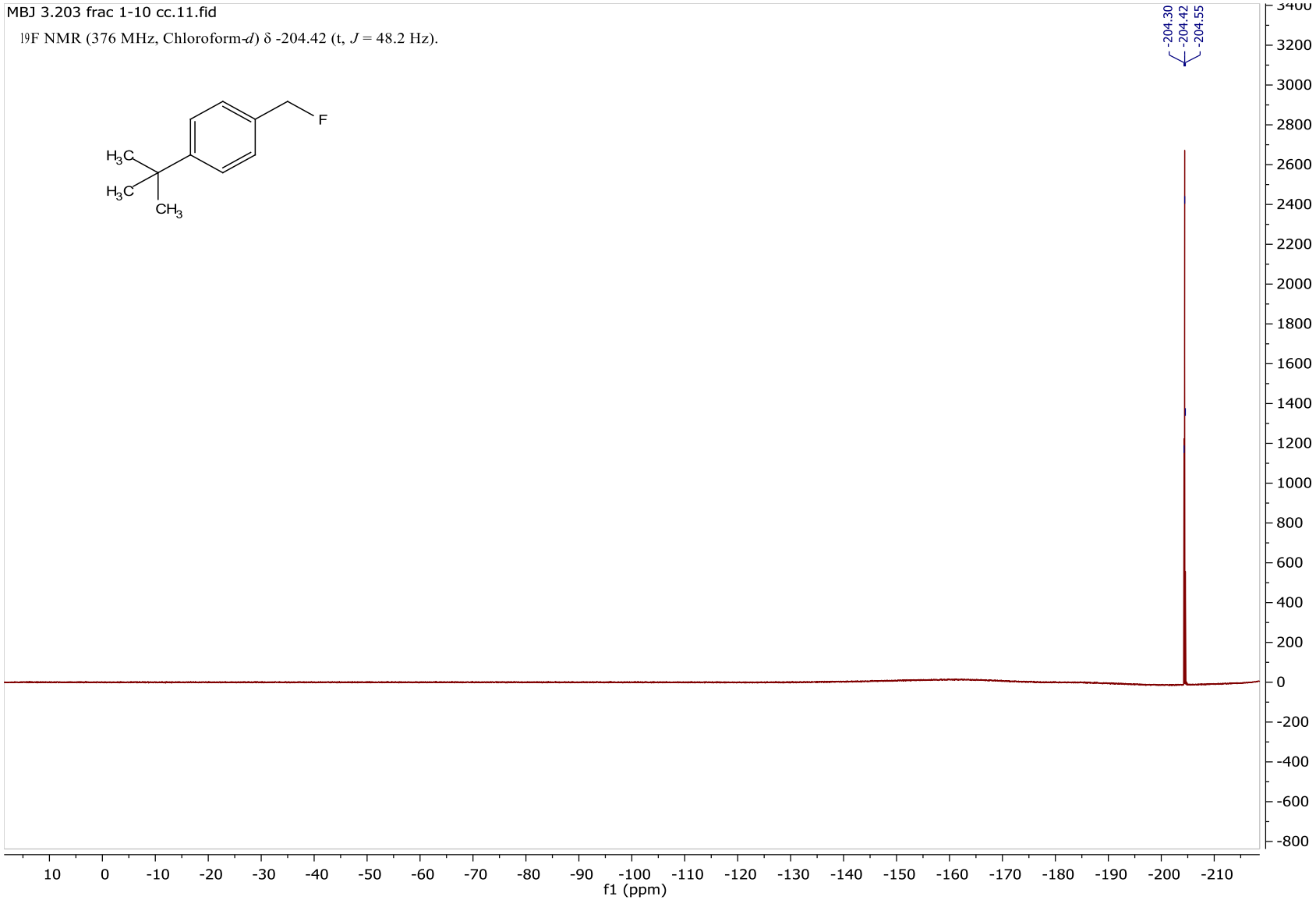
152.12
152.08
151.72
151.67
134.90
134.65
133.43
133.26
128.91
128.49
127.79
127.74
125.92
125.85
125.70
125.69
85.53
83.89
46.31
34.82
34.82
34.78
33.77
31.44
31.43
31.41
13C NMR (101 MHz, Chloroform-d) δ 152.10 (d, J = 3.4 Hz), 151.72, 151.67, 134.90, 134.65, 133.35 (d, J = 17.1 Hz), 128.91, 128.49, 127.77 (d, J = 5.5 Hz), 125.92, 125.85, 125.69 (d, J = 1.6 Hz), 84.71 (d, J = 165.0 Hz), 46.31, 34.82, 34.82, 34.78, 33.77, 31.44, 31.43, 31.41.
F
Cl
Br
H3C
CH3
f1 (ppm)


MBJ 6.438b cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -204.42 (t, J = 48.1 Hz).
F
Cl
Br
H3C
CH3
-204.30
-204.42
-204.55
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

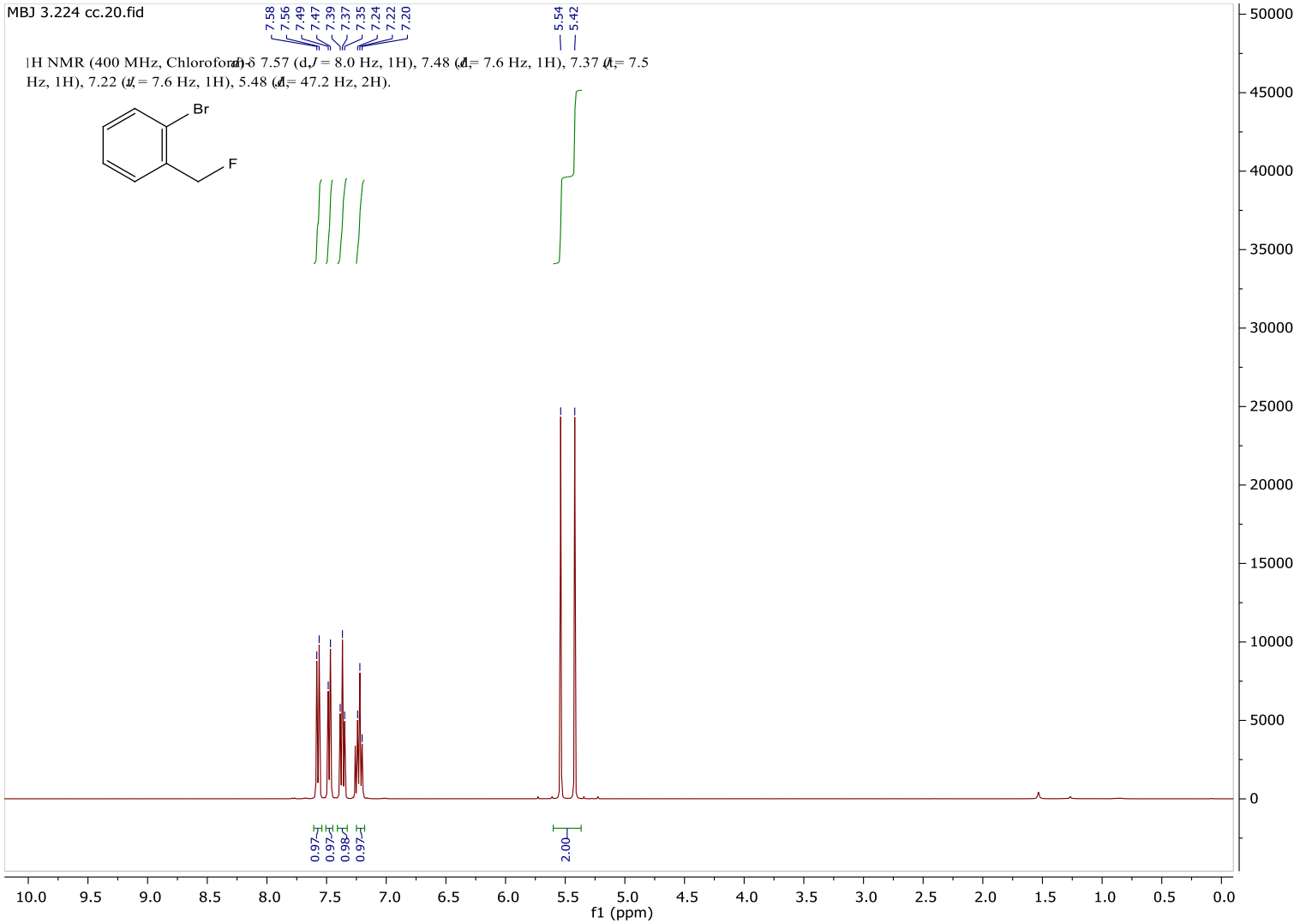
*1-Fluoromethyl-4-tertbutylbenzene (**2, Scale-out experiment**).*

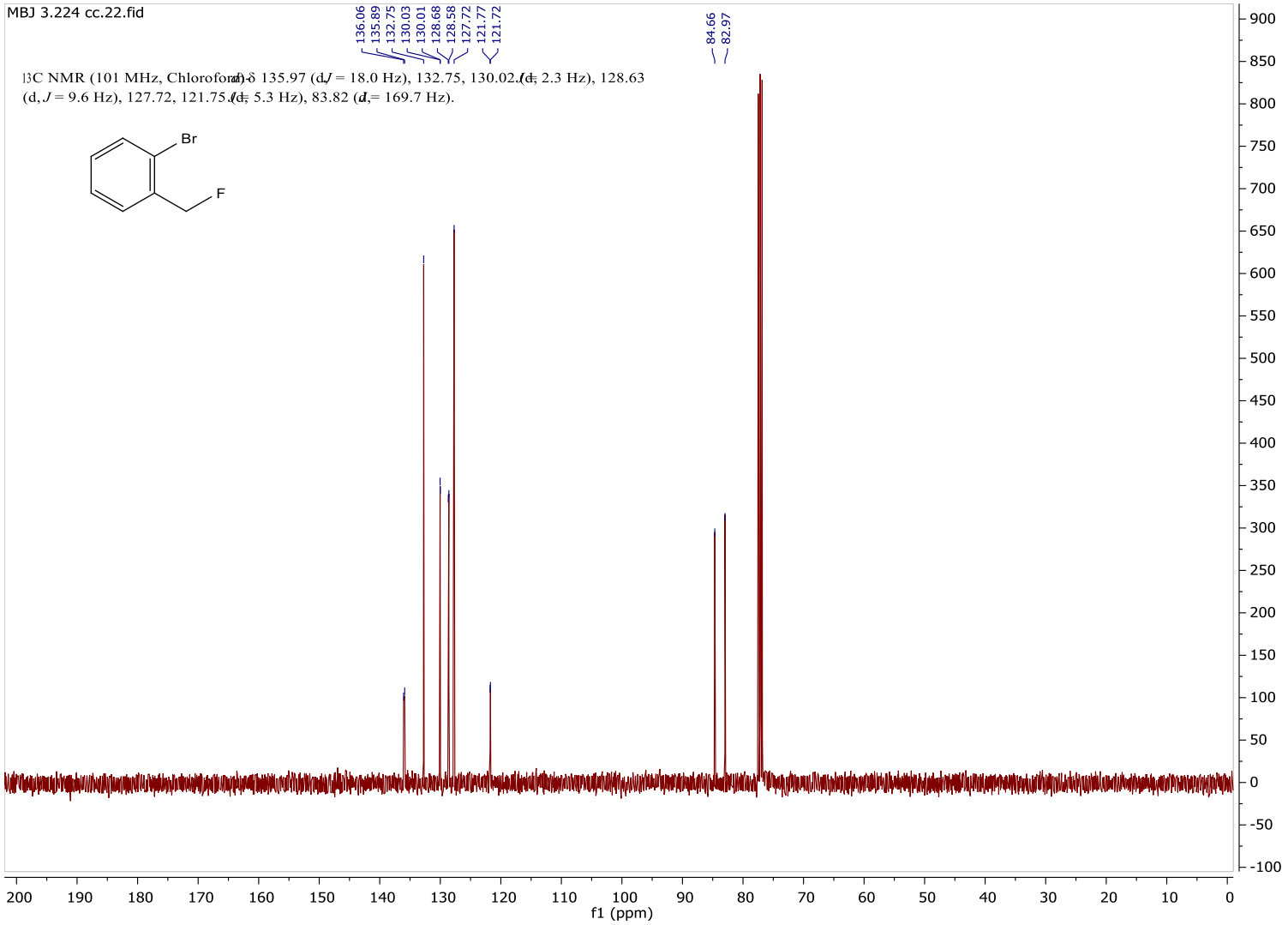


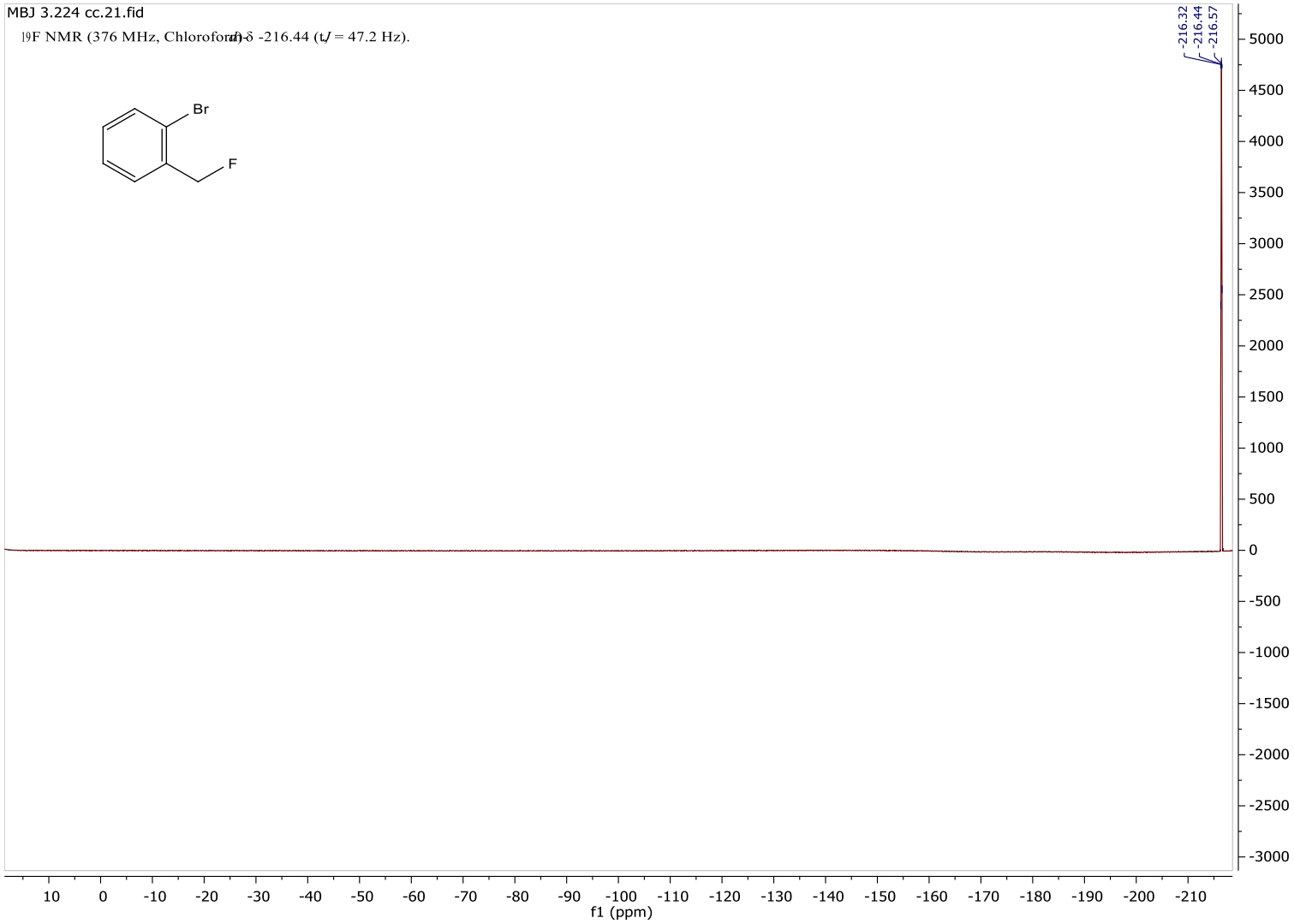

MBJ 3.203 frac 1-10 cc.12.fid
152.11
152.08
133.44
133.27
127.79
127.74
125.70
125.68
85.52
83.88
34.81
31.45
13C NMR (101 MHz, Chloroform-d) δ 152.10 (d, J = 3.4 Hz), 133.35 (d, J = 17.1 Hz), 127.76 (d, J = 5.4 Hz), 125.69 (d, J = 1.6 Hz), 84.70 (d, J = 165.0 Hz), 34.81, 31.45.
F
H3C
H3C
CH3
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


MBJ 3.203 frac 1-10 cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -204.42 (t, J = 48.2 Hz).
F
H3C
H3C
CH3
-204.30
-204.42
-204.55
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
-600
-800
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

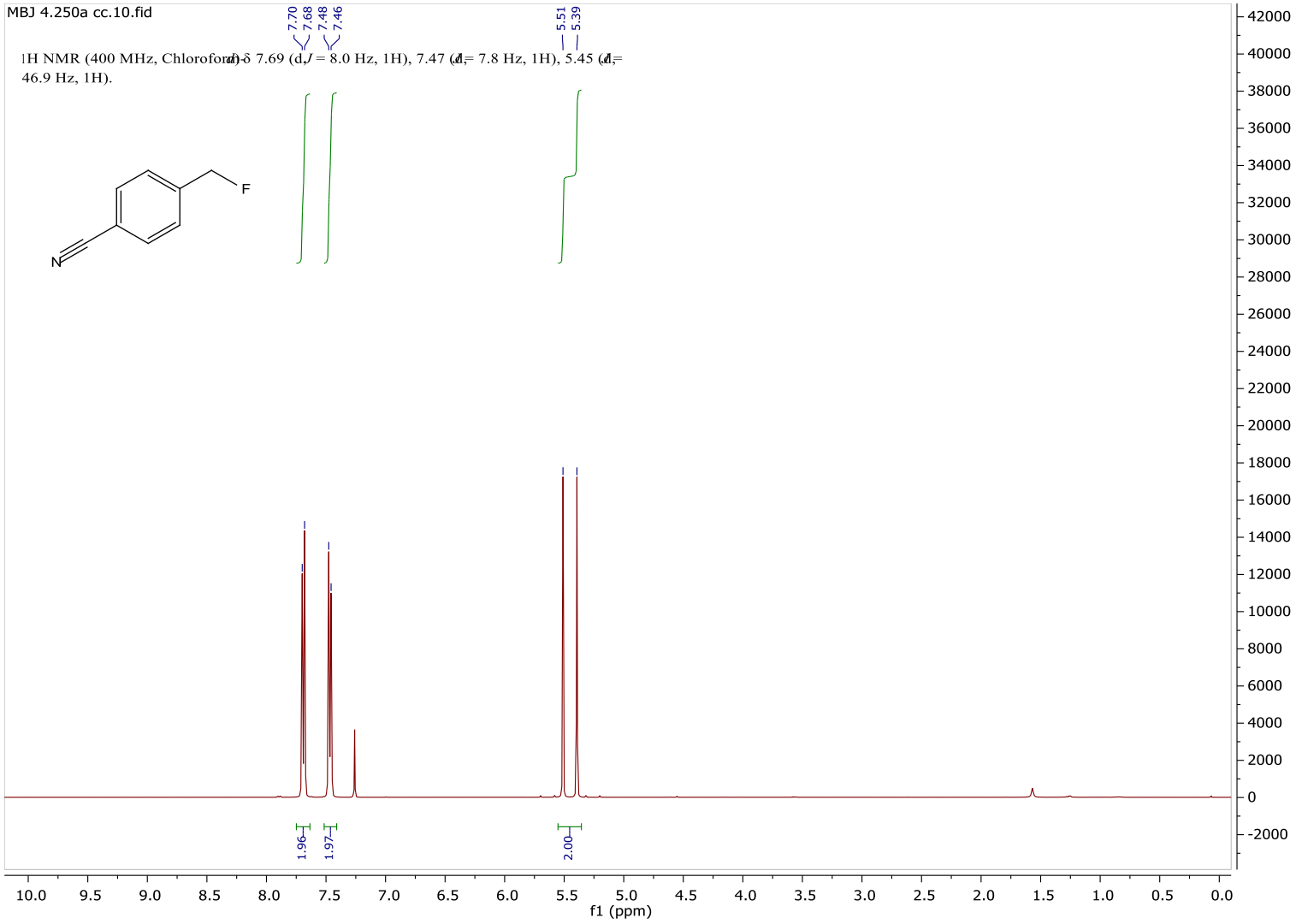
*1-Fluoromethyl-2-bromobenzene (**3**)*

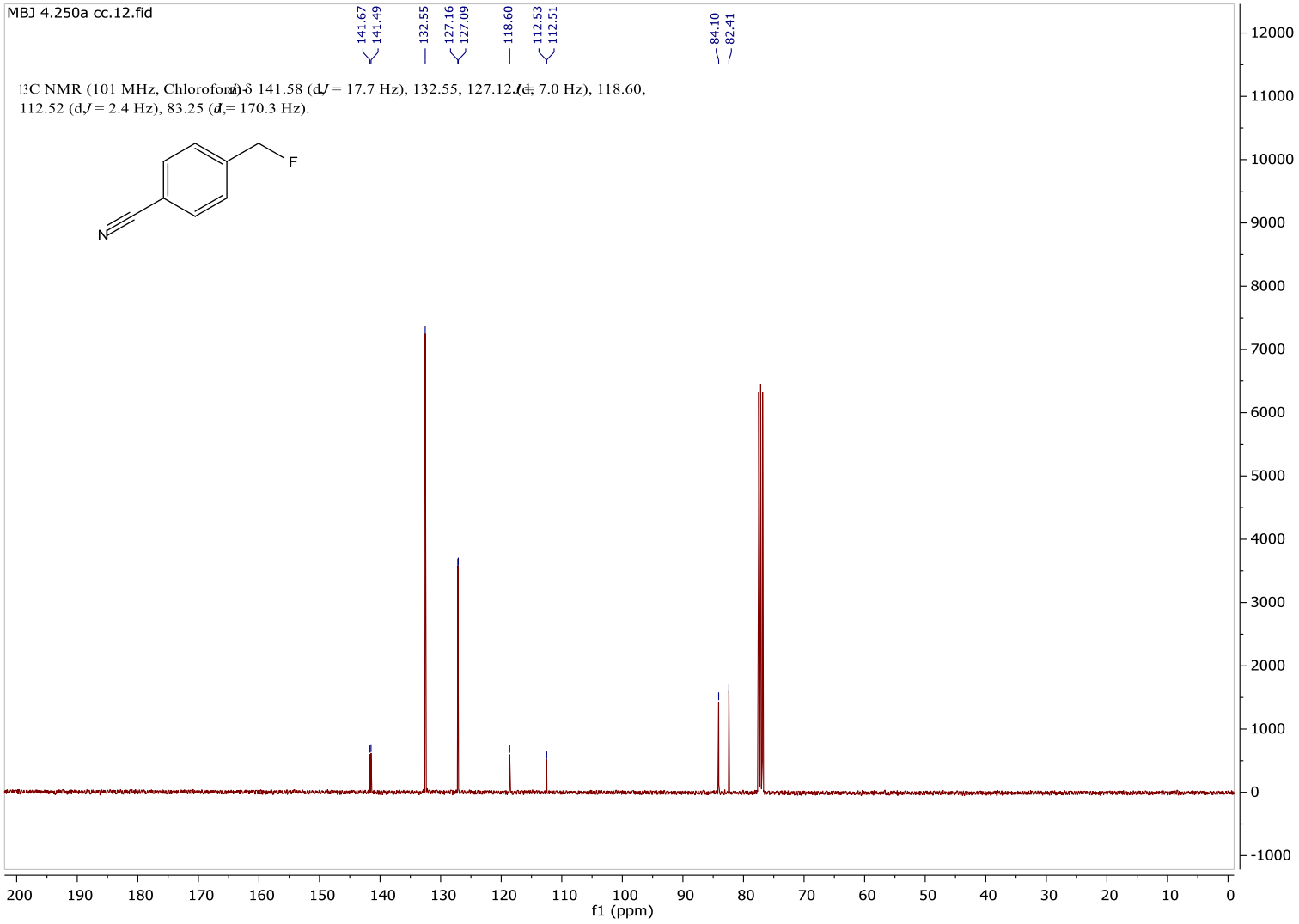


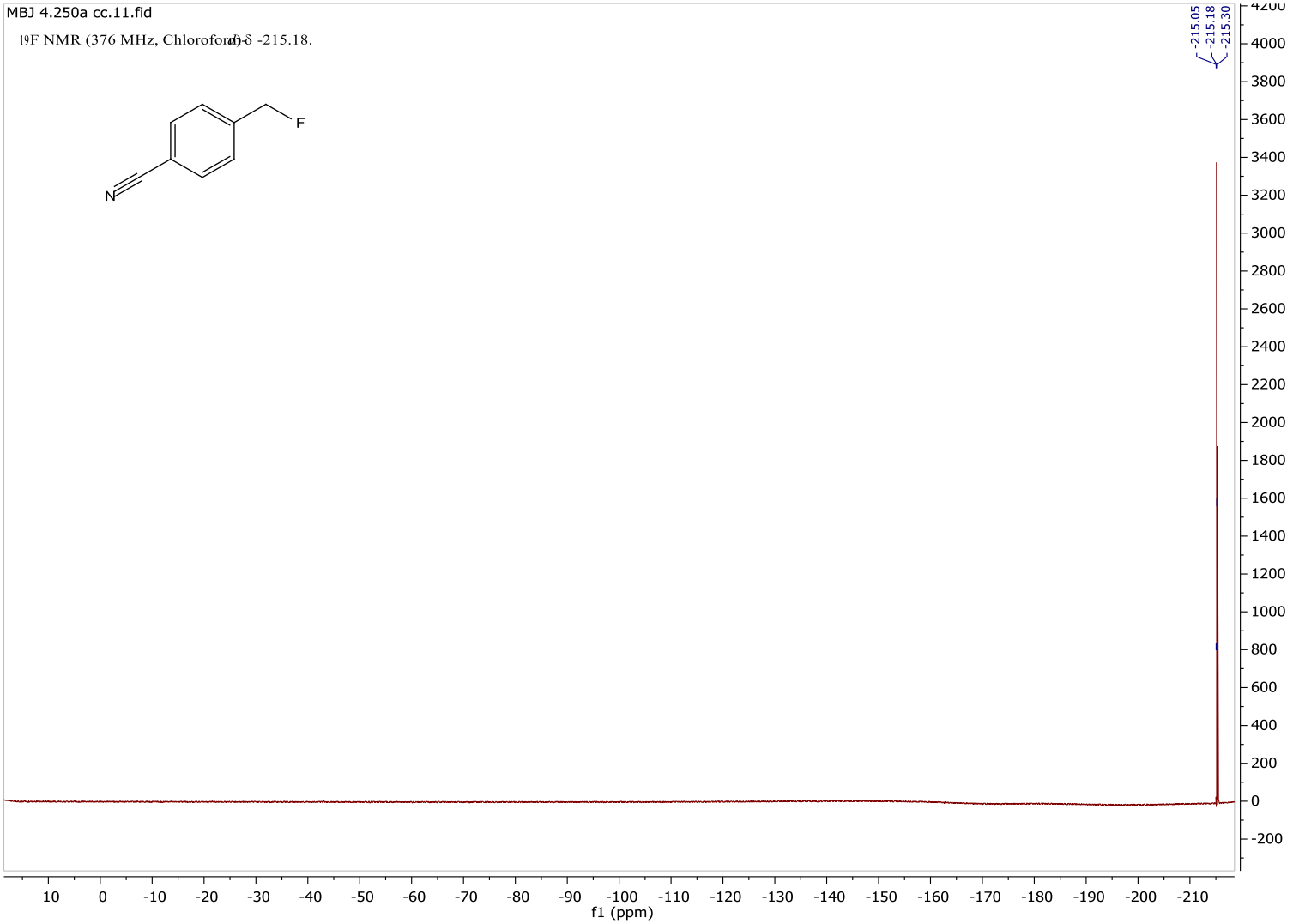

MBJ 3.224 cc.22.fid
136.06
135.89
132.75
130.03
130.01
128.68
128.58
127.72
121.77
121.72
84.66
82.97
13C NMR (101 MHz, Chloroform-d) δ 135.97 (d, J = 18.0 Hz), 132.75, 130.02 (d, J = 2.3 Hz), 128.63 (d, J = 9.6 Hz), 127.72, 121.75 (d, J = 5.3 Hz), 83.82 (d, J = 169.7 Hz).
Br
F
f1 (ppm)


MBJ 3.224 cc.21.fid
19F NMR (376 MHz, Chloroform-d) δ -216.44 (t, J = 47.2 Hz).
Br
F
-216.32
-216.44
-216.57
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
-1500
-2000
-2500
-3000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

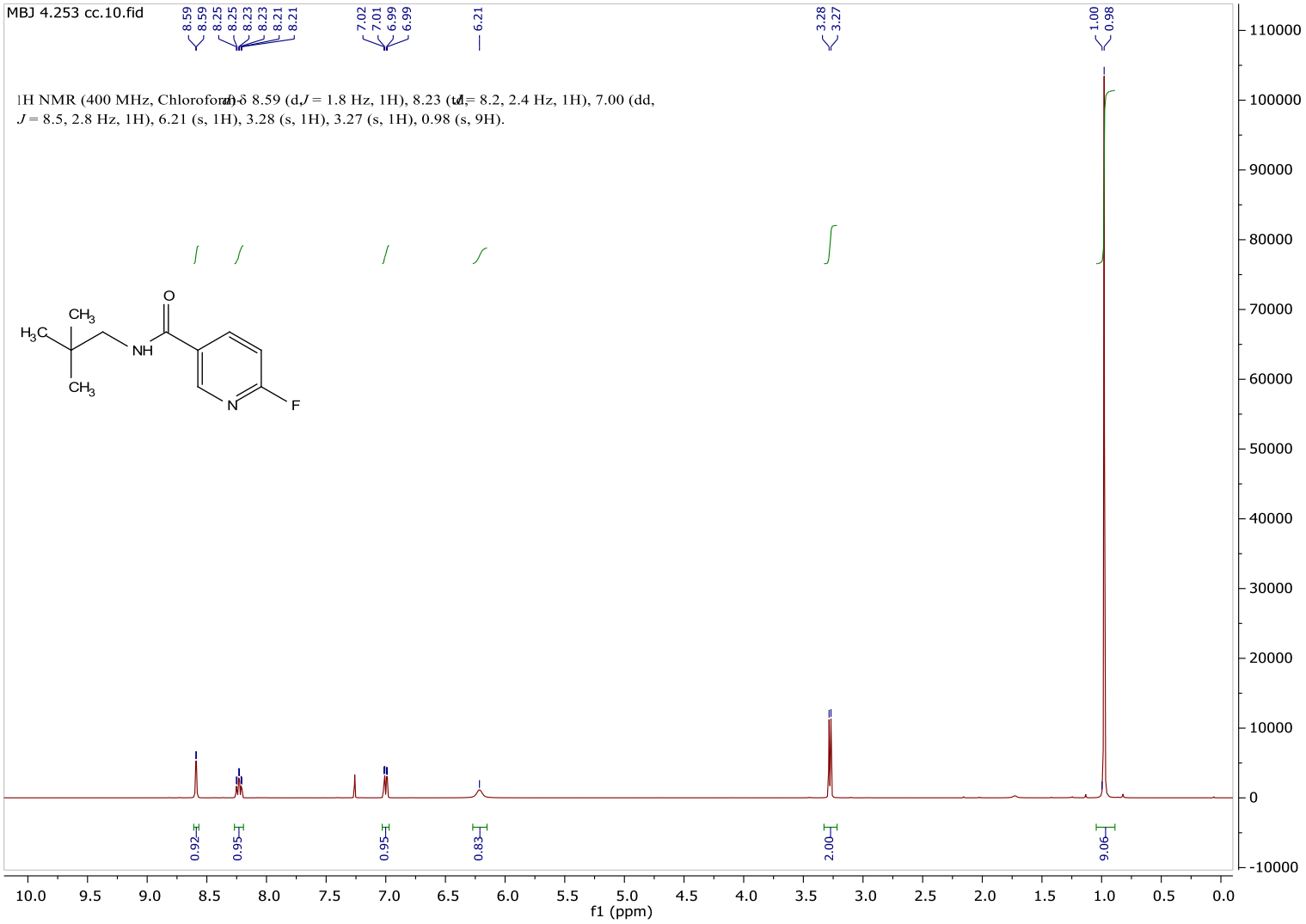
*1-Fluoromethyl-4-Cyanobenzene (**4**).*

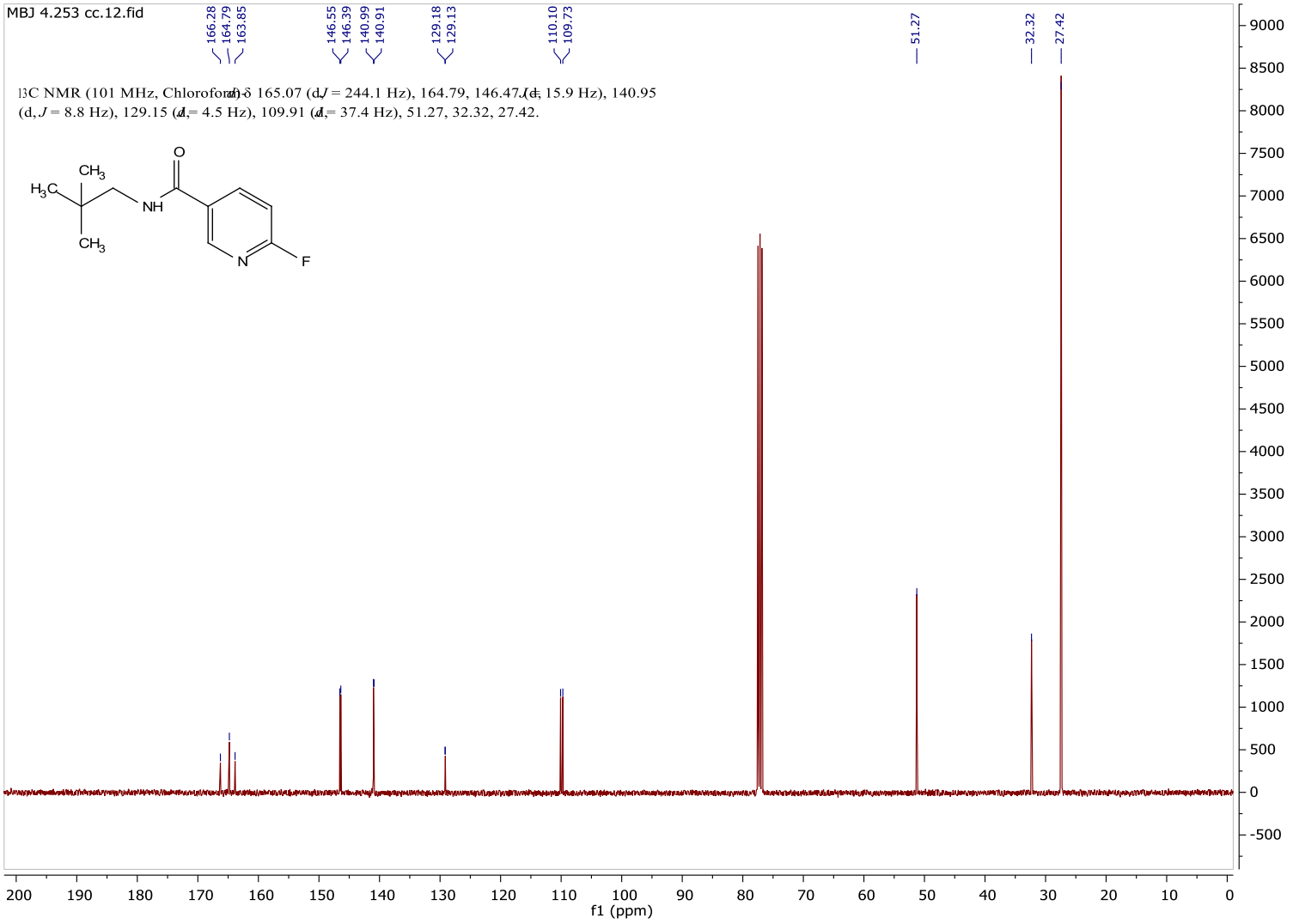


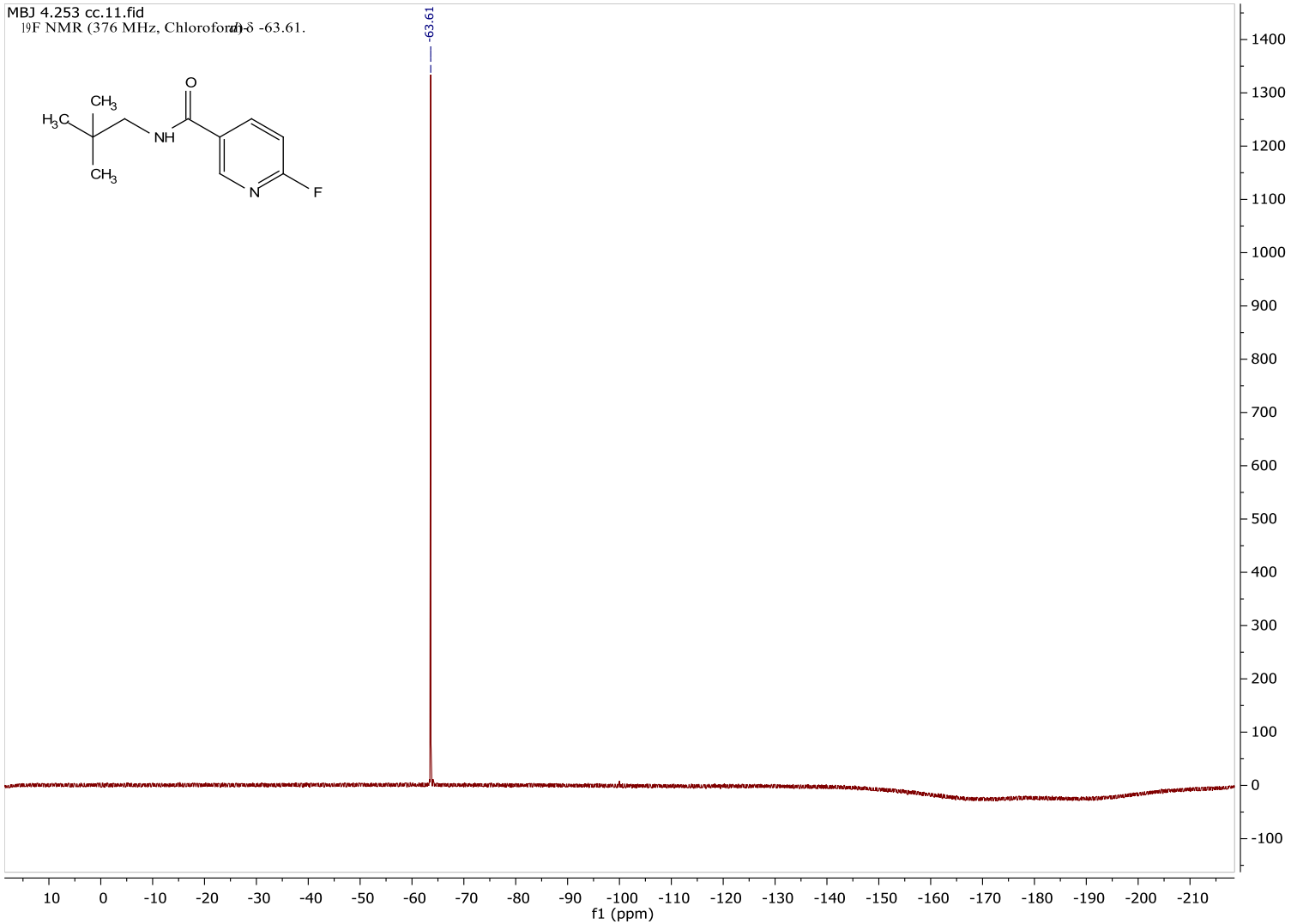

MBJ 4.250a cc.12.fid
141.67
141.49
132.55
127.16
127.09
118.60
112.53
112.51
84.10
82.41
13C NMR (101 MHz, Chloroform-d) δ 141.58 (d, J = 17.7 Hz), 132.55, 127.12 (d, J = 7.0 Hz), 118.60, 112.52 (d, J = 2.4 Hz), 83.25 (d, J = 170.3 Hz).
F
N
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MBJ 4.250a cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -215.18.
F
N
-215.05
-215.18
-215.30
f1 (ppm)

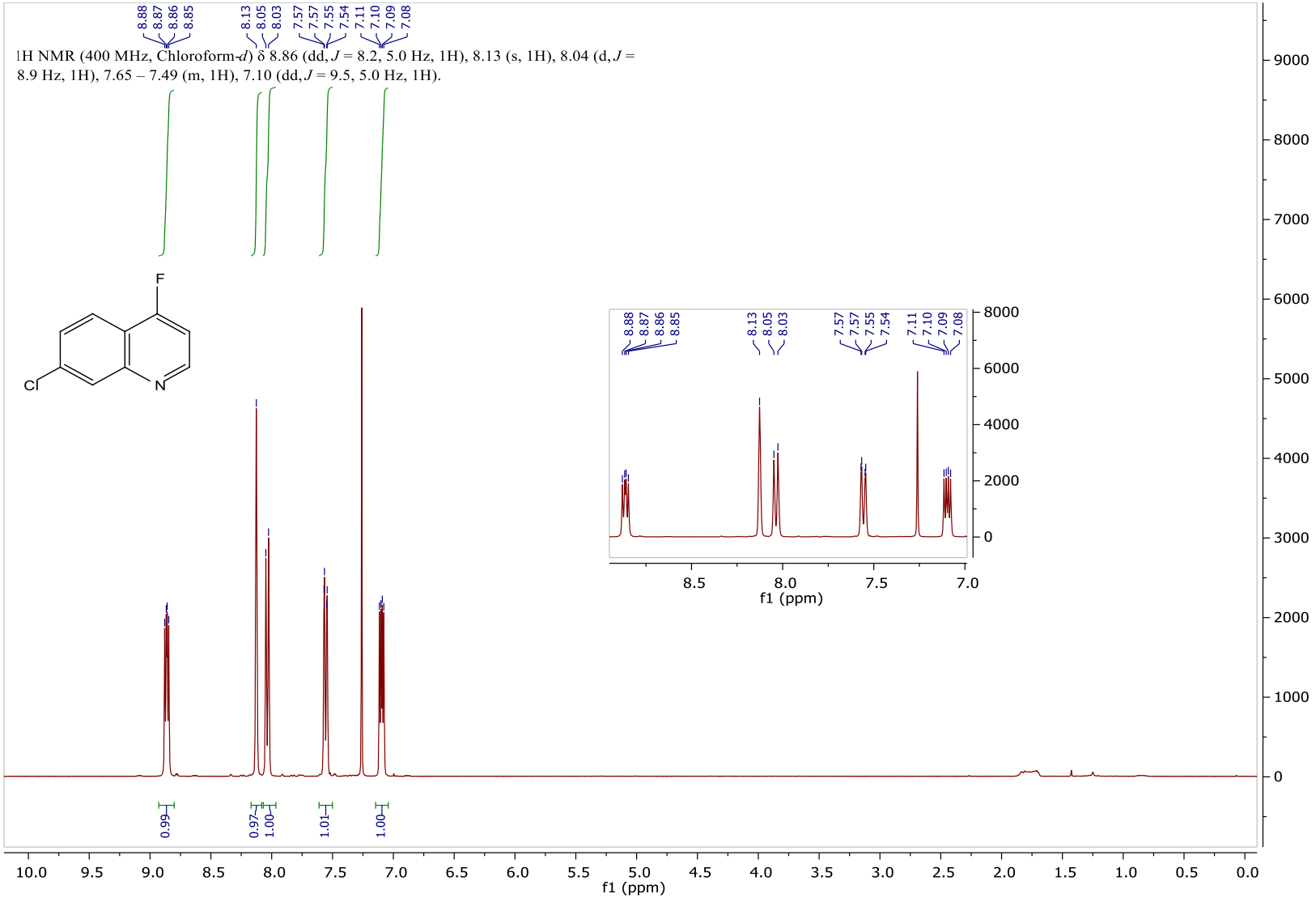
*6-Fluoro-N-neopentylnicotinamide (**6**).*

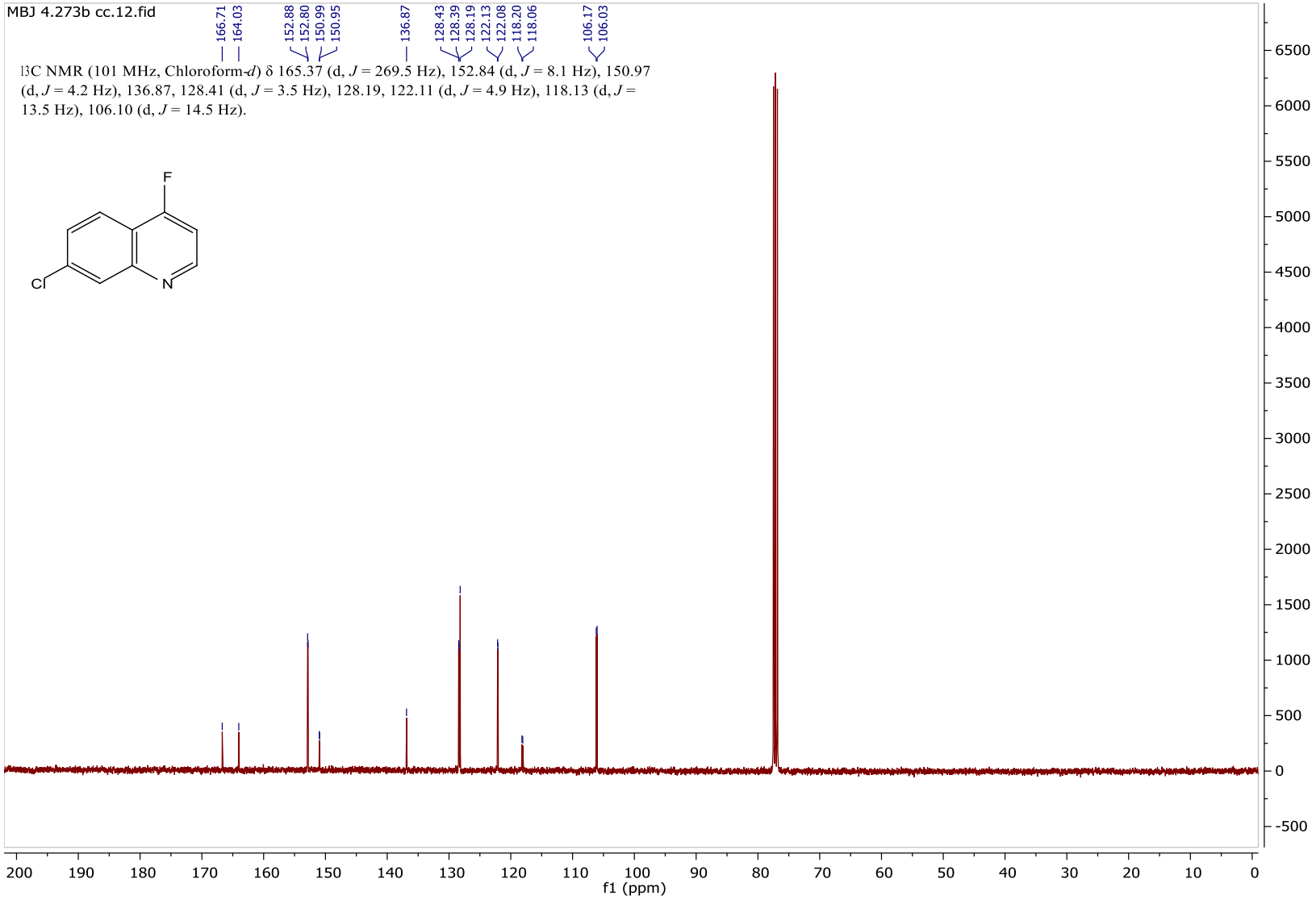


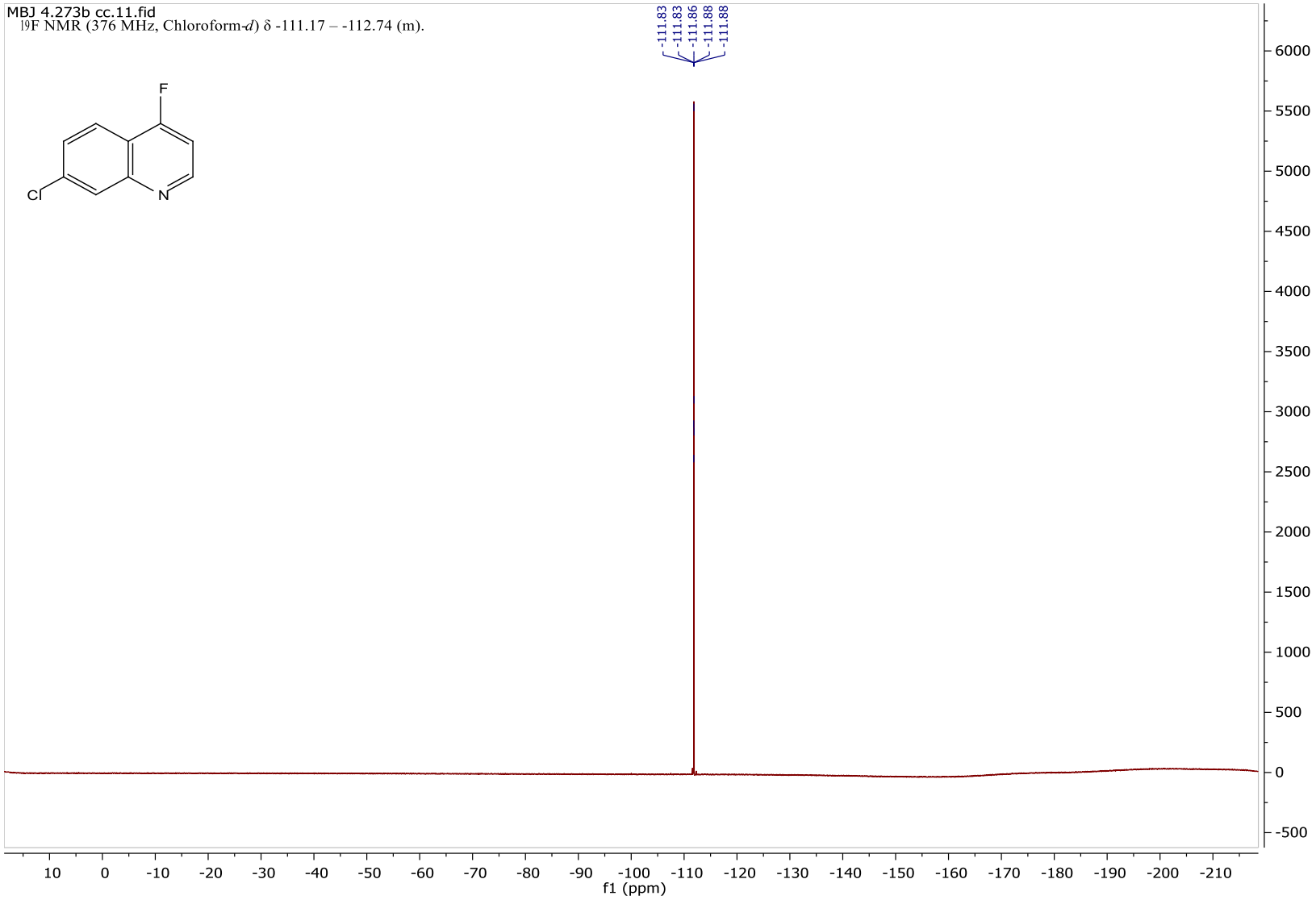

MBJ 4.253 cc.12.fid
166.28
164.79
163.85
146.55
146.39
140.99
140.91
129.18
129.13
110.10
109.73
51.27
32.32
27.42
13C NMR (101 MHz, Chloroform-d) δ 165.07 (d, J = 244.1 Hz), 164.79, 146.47 (d, J = 15.9 Hz), 140.95 (d, J = 8.8 Hz), 129.15 (d, J = 4.5 Hz), 109.91 (d, J = 37.4 Hz), 51.27, 32.32, 27.42.
O
CH3
H3C
NH
CH3
N
F
f1 (ppm)


MBJ 4.253 cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -63.61.
-63.61
O
CH3
H3C
NH
CH3
N
F
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

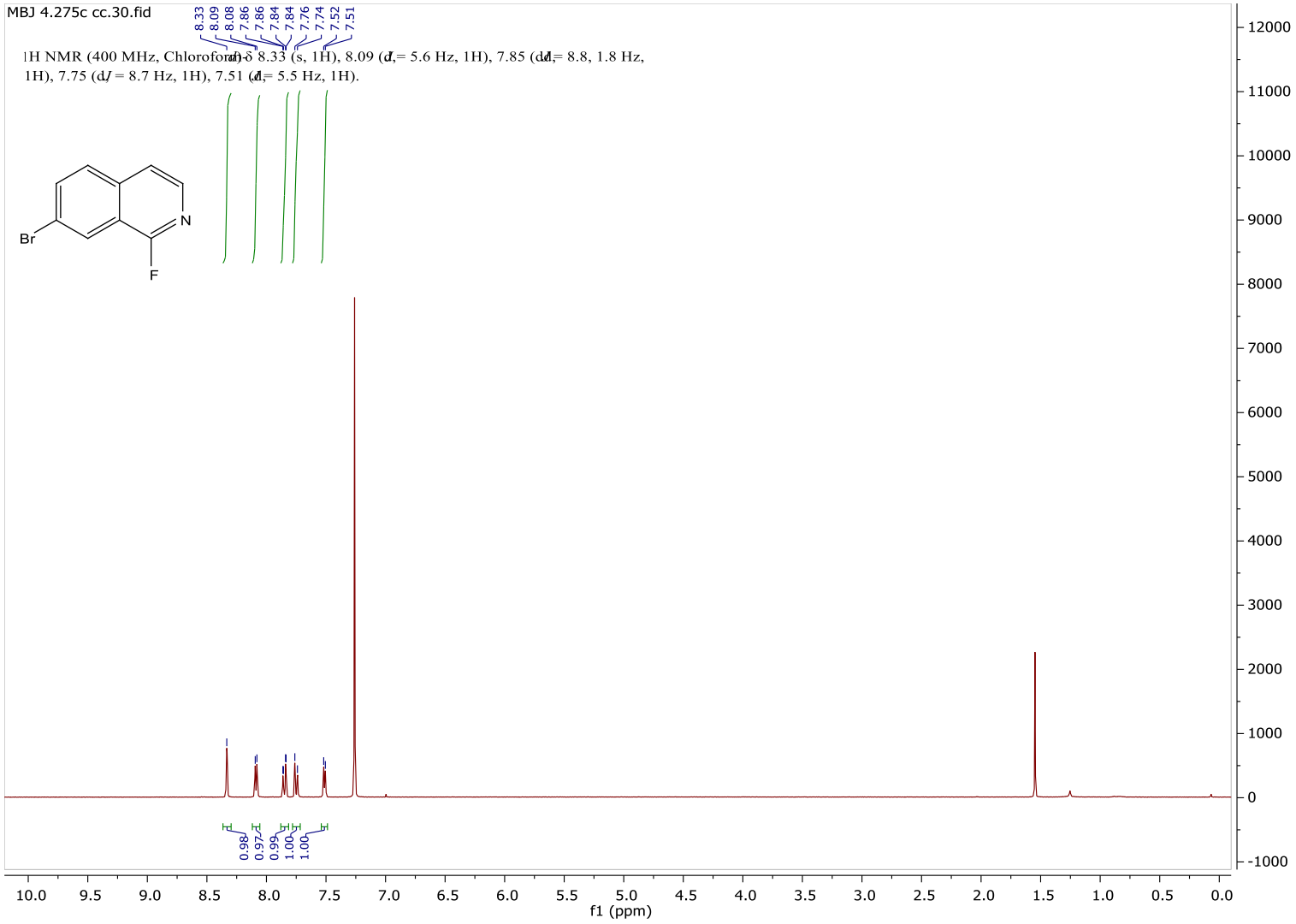
*7-Chloro-4-fluoroquinoline (**7**).*

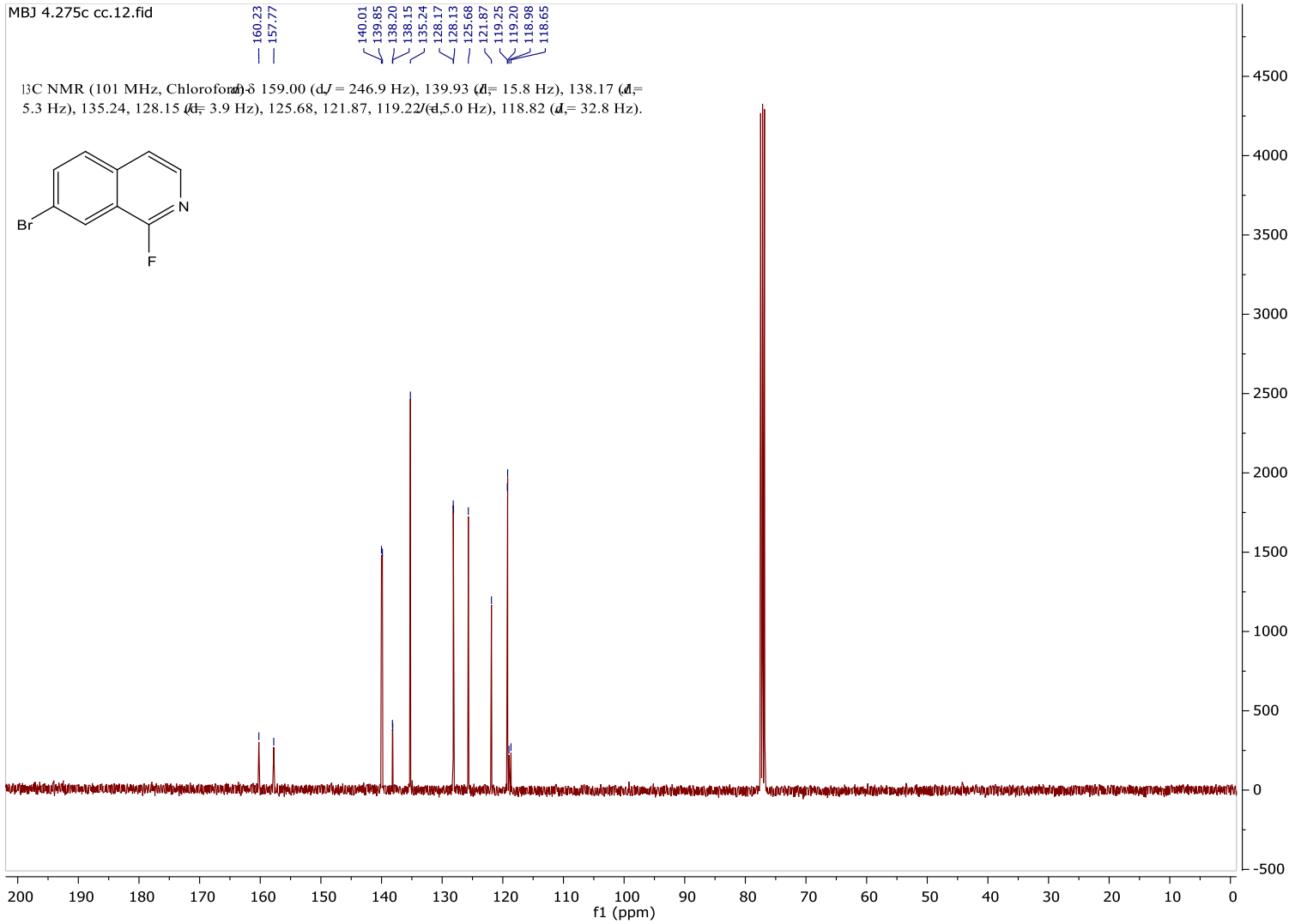


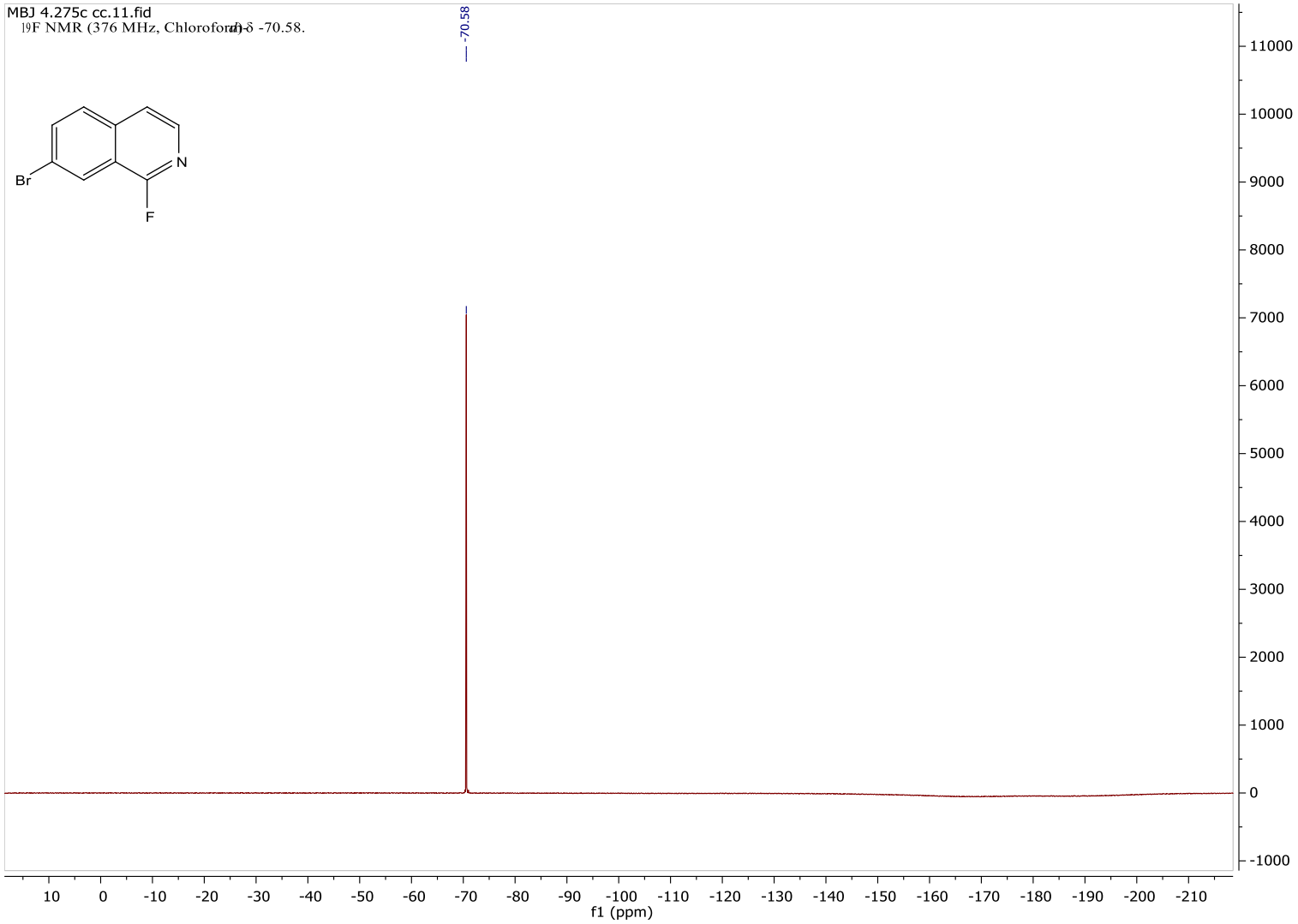

MBJ 4.273b cc.12.fid
166.71
164.03
152.88
152.80
150.99
150.95
136.87
128.43
128.39
128.19
122.13
122.08
118.20
118.06
106.17
106.03
13C NMR (101 MHz, Chloroform-d) δ 165.37 (d, J = 269.5 Hz), 152.84 (d, J = 8.1 Hz), 150.97 (d, J = 4.2 Hz), 136.87, 128.41 (d, J = 3.5 Hz), 128.19, 122.11 (d, J = 4.9 Hz), 118.13 (d, J = 13.5 Hz), 106.10 (d, J = 14.5 Hz).
F
Cl
N
f1 (ppm)


MBJ 4.273b cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -111.17 – -112.74 (m).
-111.83
-111.83
-111.86
-111.88
-111.88
F
Cl
N
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

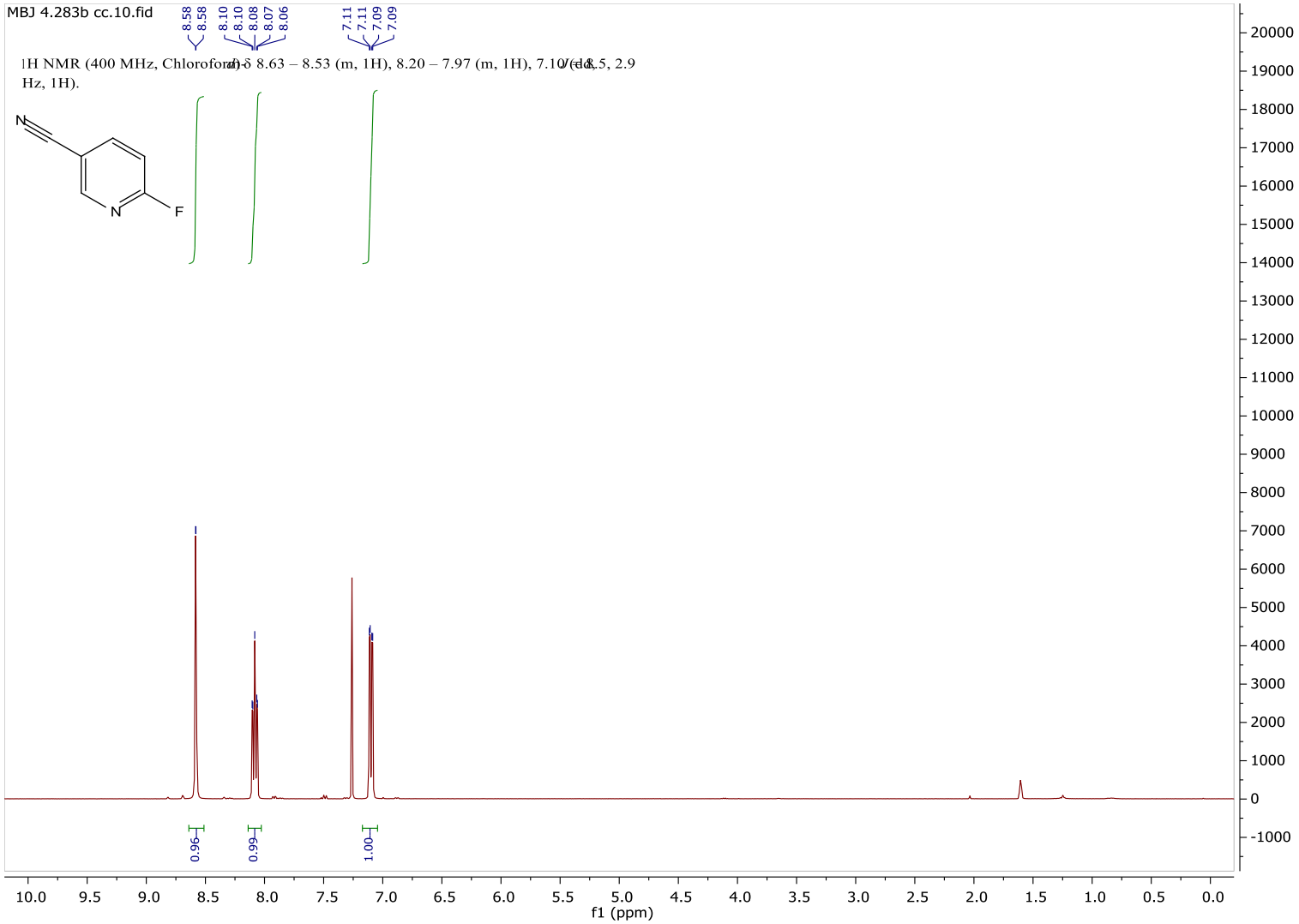
*7-Bromo-1-fluoroisoquinoline (**8**).*

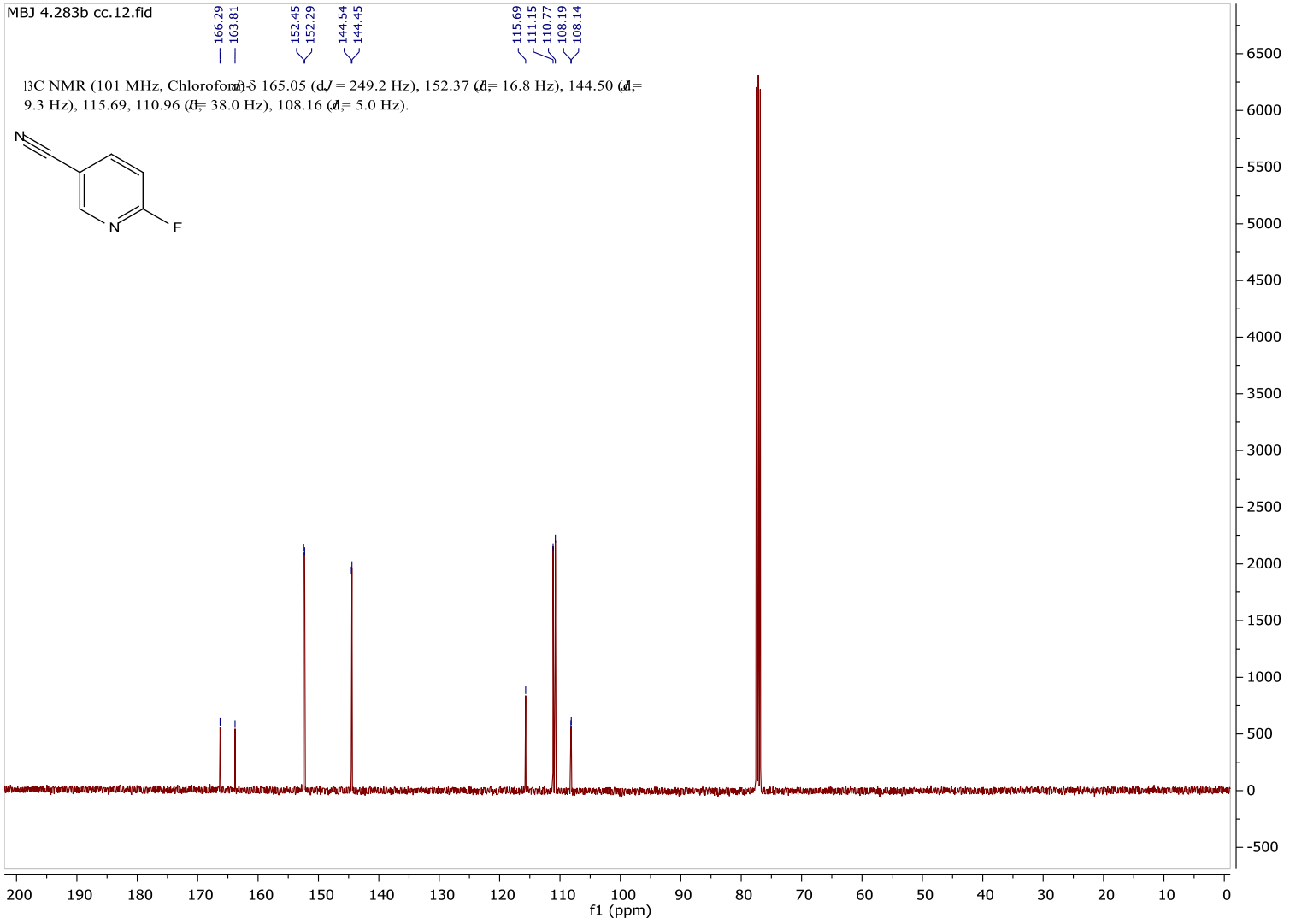


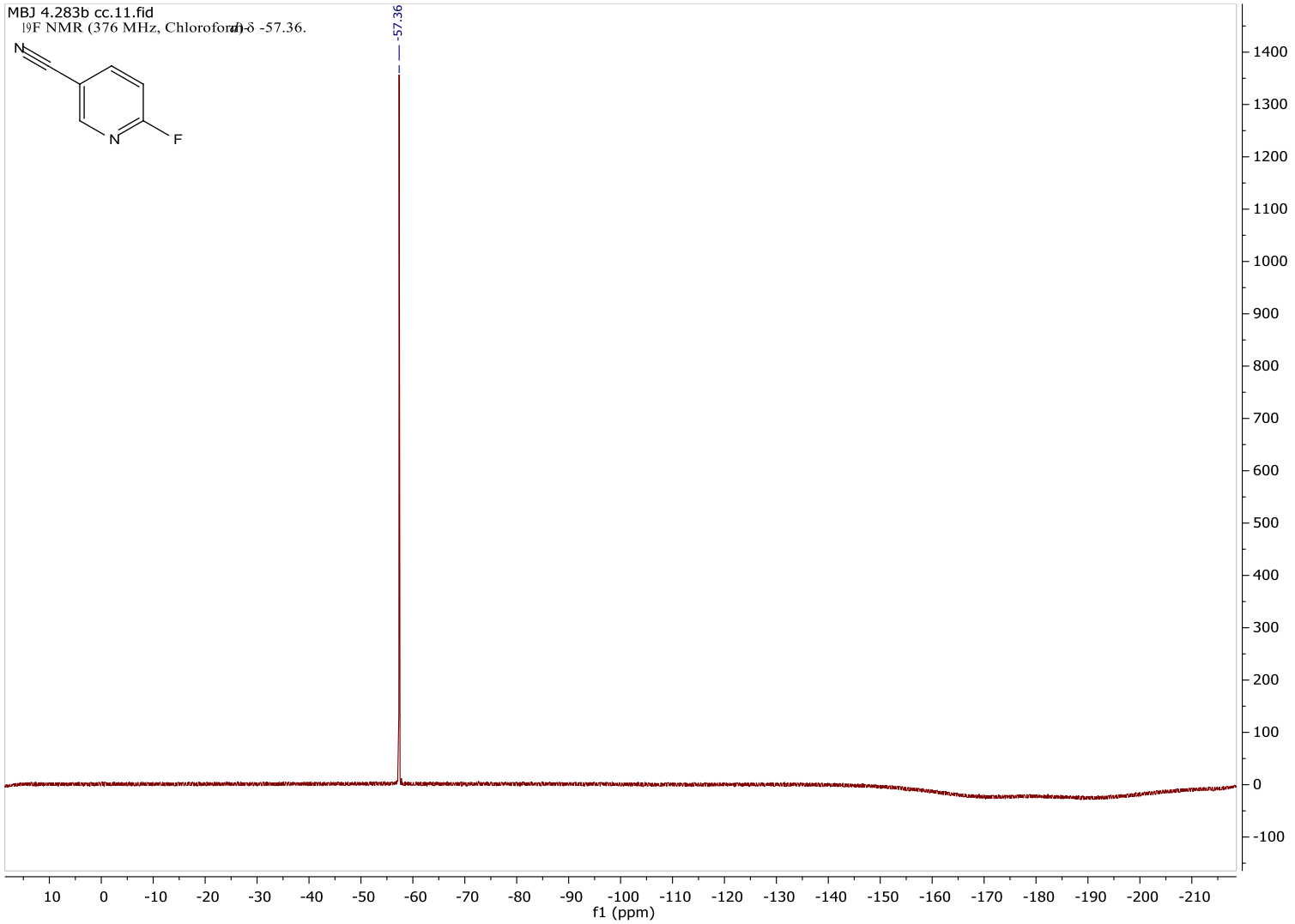

MBJ 4.275c cc.12.fid
160.23
157.77
140.01
139.85
138.20
138.15
135.24
128.17
128.13
125.68
121.87
119.25
119.20
118.98
118.65
13C NMR (101 MHz, Chloroform-d) δ 159.00 (d, J = 246.9 Hz), 139.93 (d, J = 15.8 Hz), 138.17 (d, J = 5.3 Hz), 135.24, 128.15 (d, J = 3.9 Hz), 125.68, 121.87, 119.22 (d, J = 5.0 Hz), 118.82 (d, J = 32.8 Hz).
Br
N
F
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MBJ 4.275c cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -70.58.
-70.58
Br
N
F
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

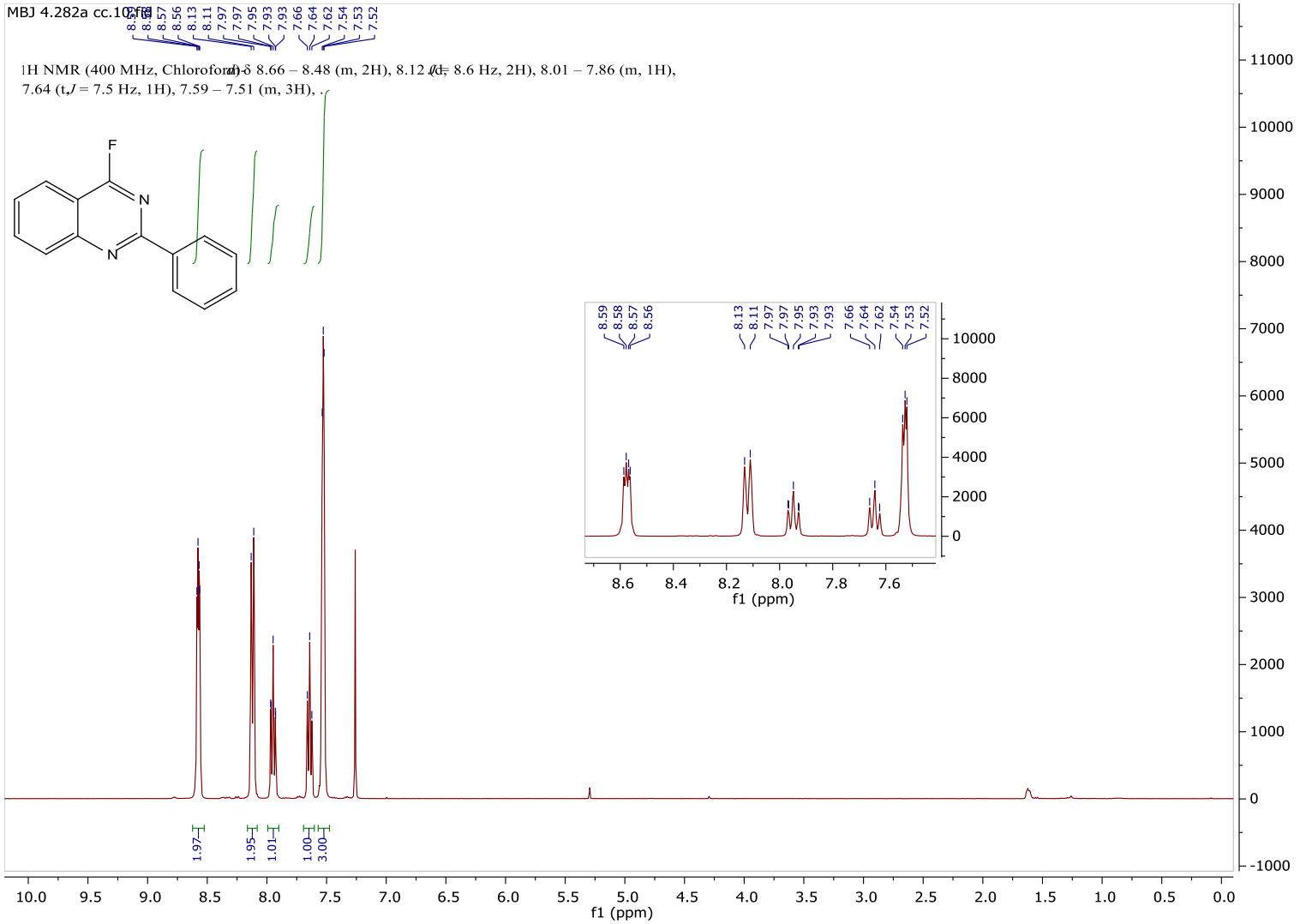
*6-Fluoronicotinonitrile (**9**).*

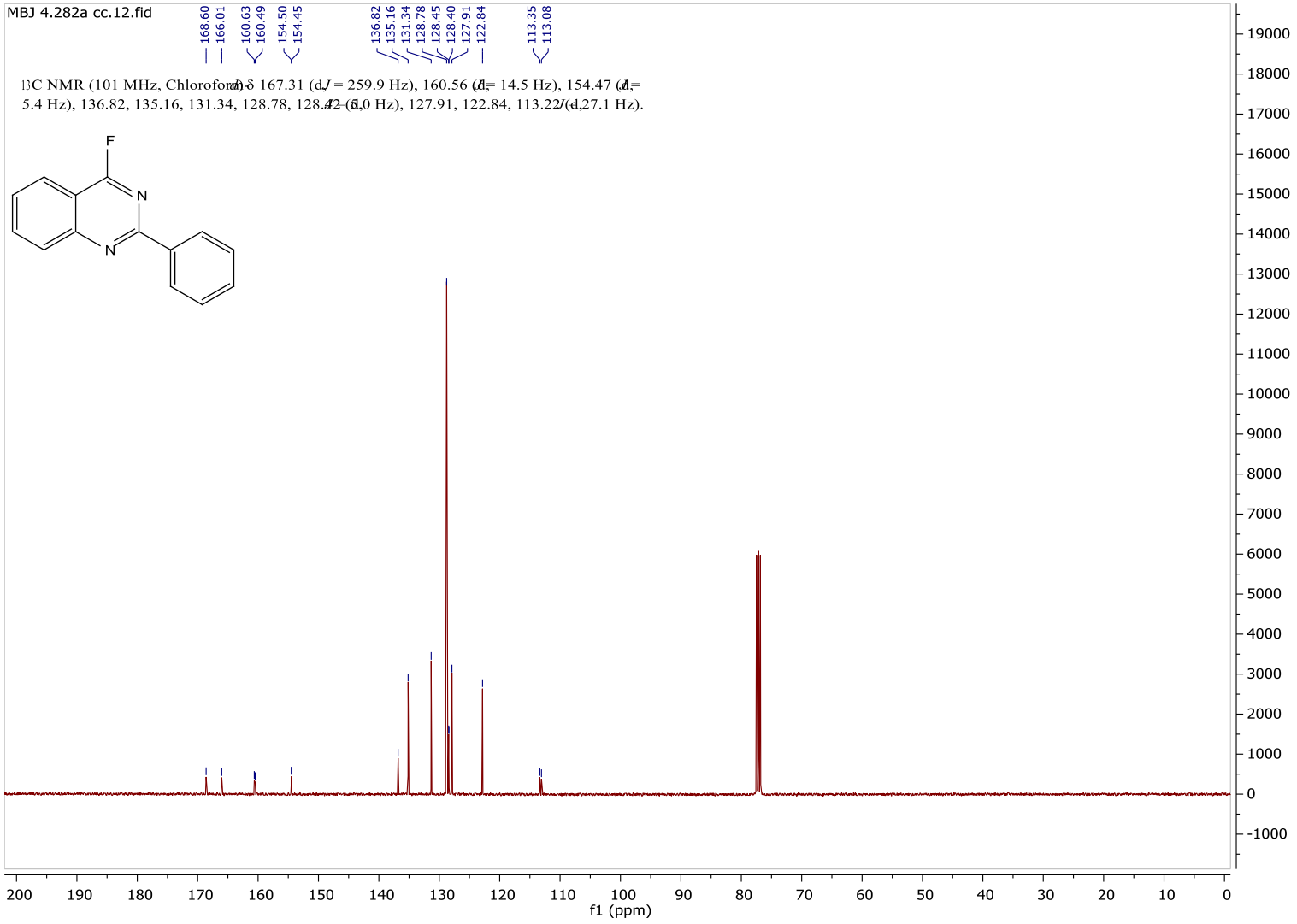


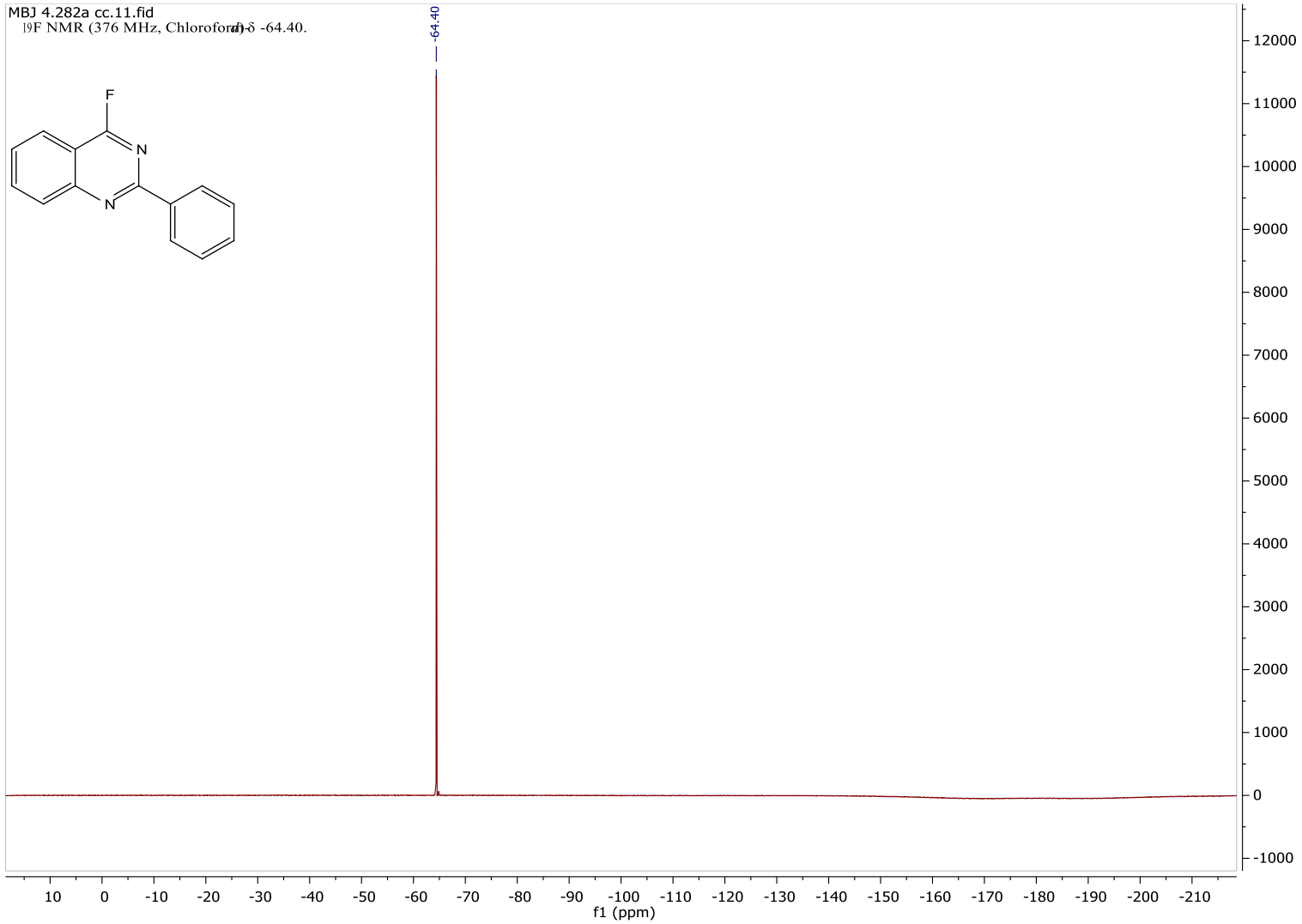

MBJ 4.283b cc.12.fid
166.29
163.81
152.45
152.29
144.54
144.45
115.69
111.15
110.77
108.19
108.14
13C NMR (101 MHz, Chloroform-d) δ 165.05 (d, J = 249.2 Hz), 152.37 (d, J = 16.8 Hz), 144.50 (d, J = 9.3 Hz), 115.69, 110.96 (d, J = 38.0 Hz), 108.16 (d, J = 5.0 Hz).
N
N
F
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MBJ 4.283b cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -57.36.
-57.36
N
N
F
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

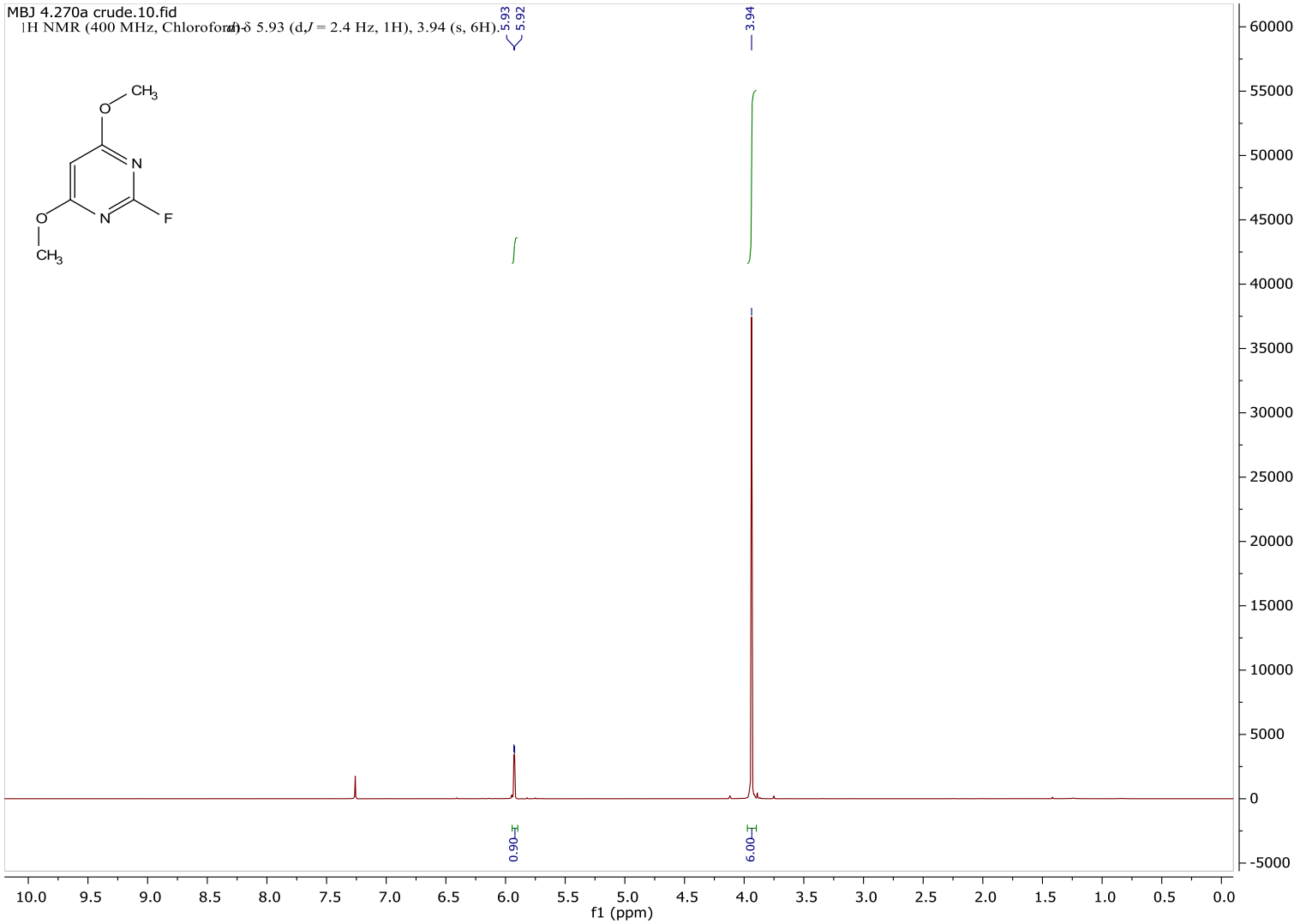
*4-Fluoro-2-phenylquinazoline (**10**).*

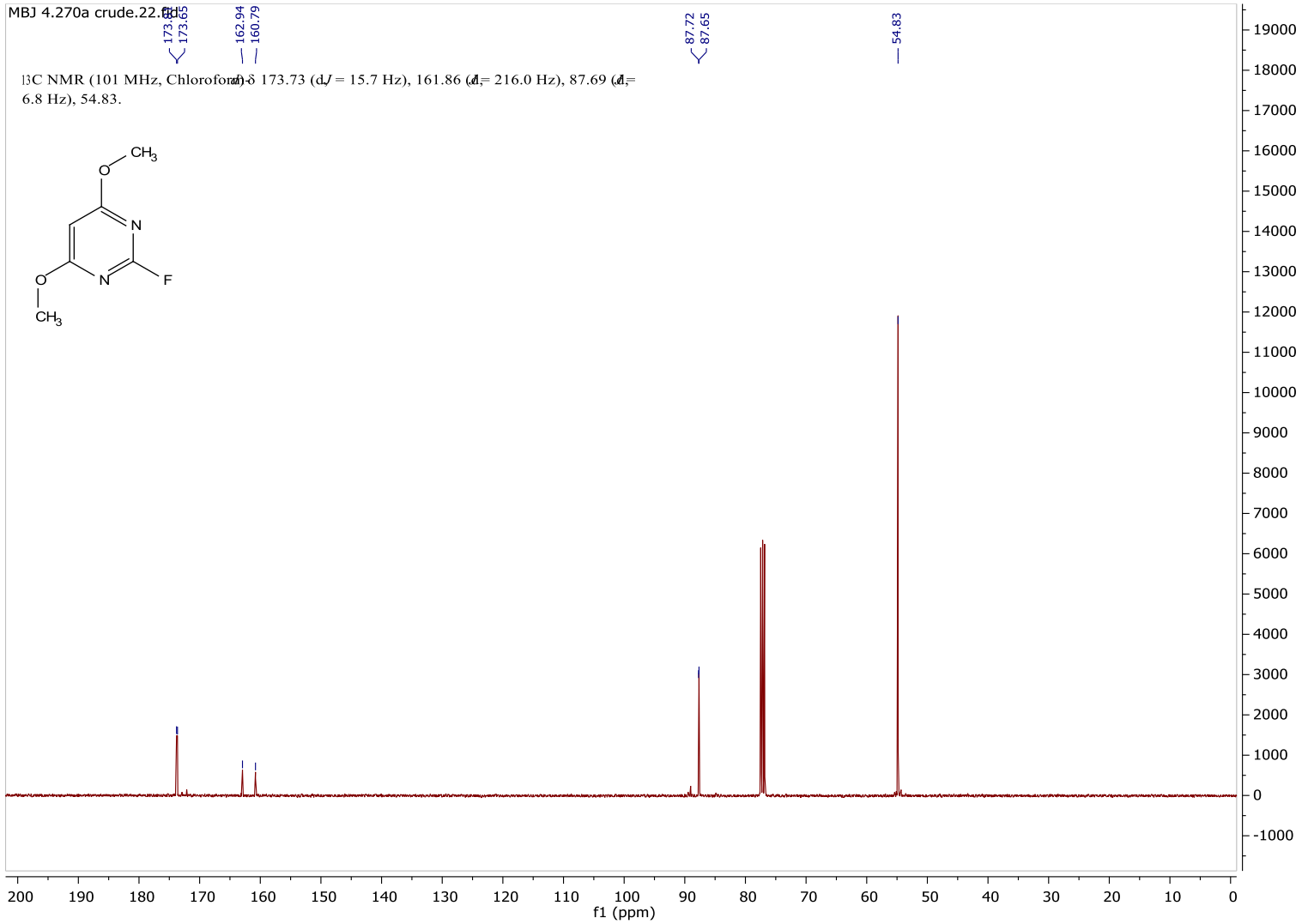


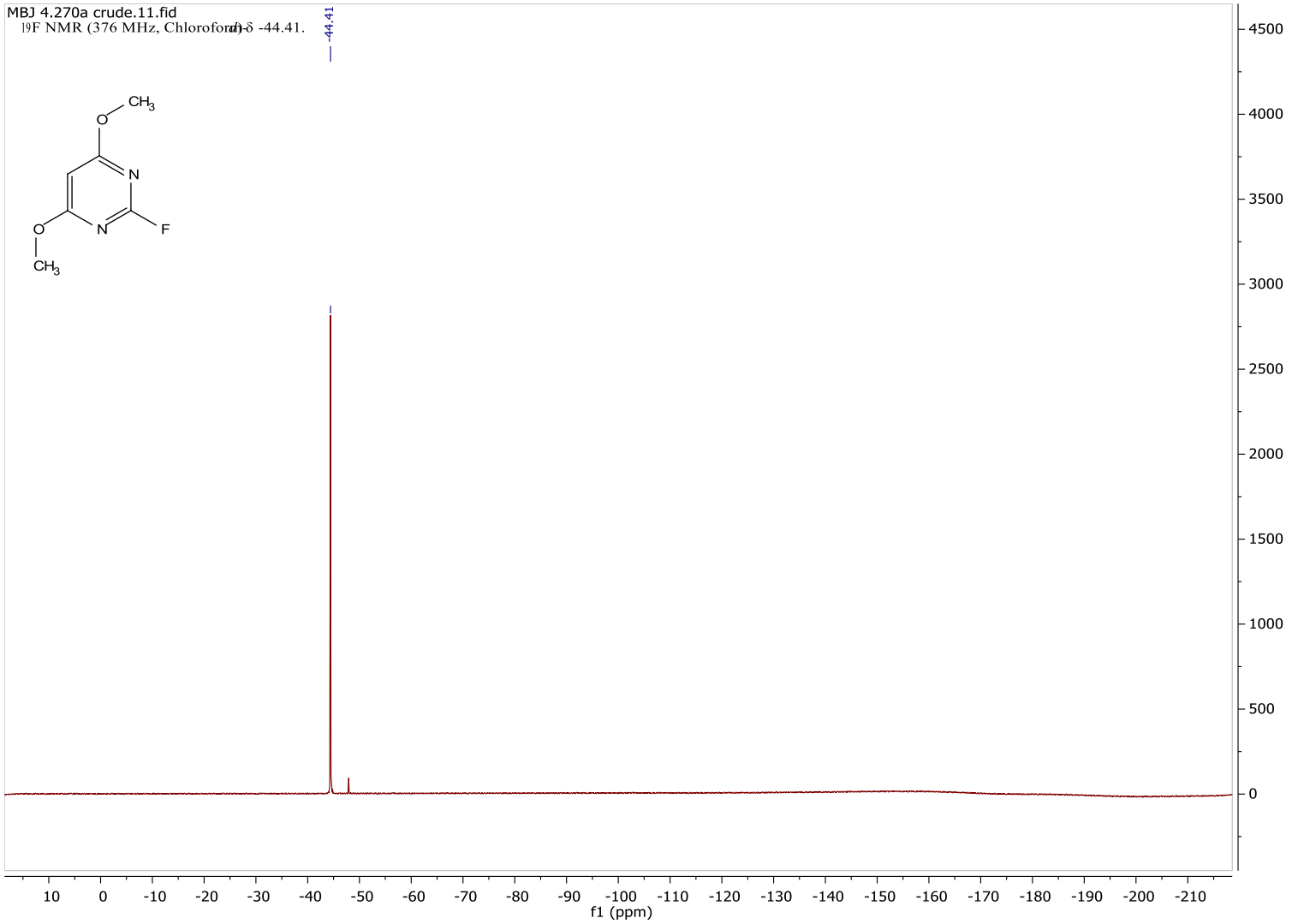

MBJ 4.282a cc.12.fid
168.60
166.01
160.63
160.49
154.50
154.45
136.82
135.16
131.34
128.78
128.45
128.40
127.91
122.84
113.35
113.08
13C NMR (101 MHz, Chloroform-d) δ 167.31 (d, J = 259.9 Hz), 160.56 (d, J = 14.5 Hz), 154.47 (d, J = 5.4 Hz), 136.82, 135.16, 131.34, 128.78, 128.45 (d, J = 3.0 Hz), 127.91, 122.84, 113.22 (d, J = 27.1 Hz).
F
N
N
f1 (ppm)


MBJ 4.282a cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -64.40.
-64.40
F
N
N
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

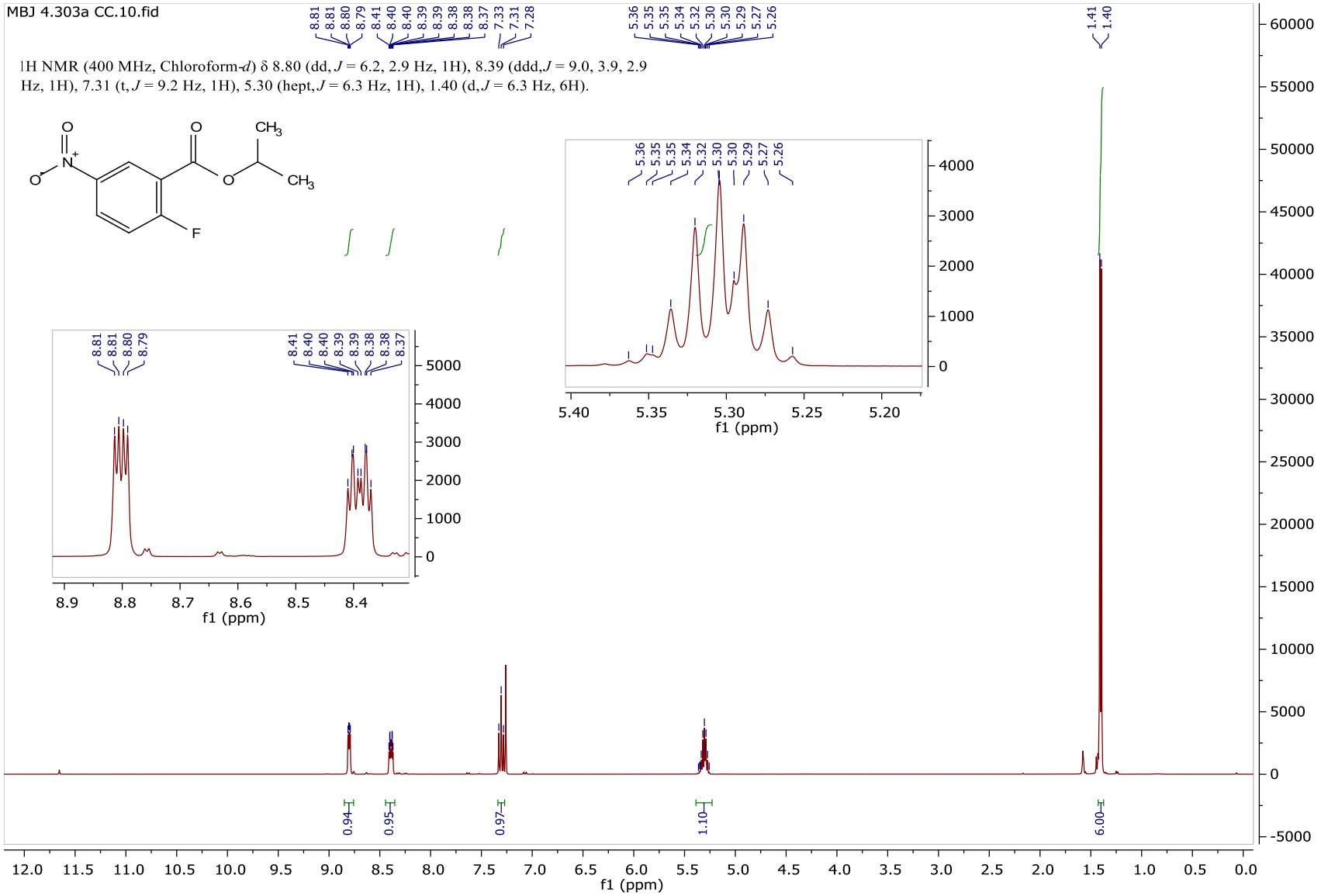
*2-Fluoro-4,6-dimethoxypyrimidine (**11**).*

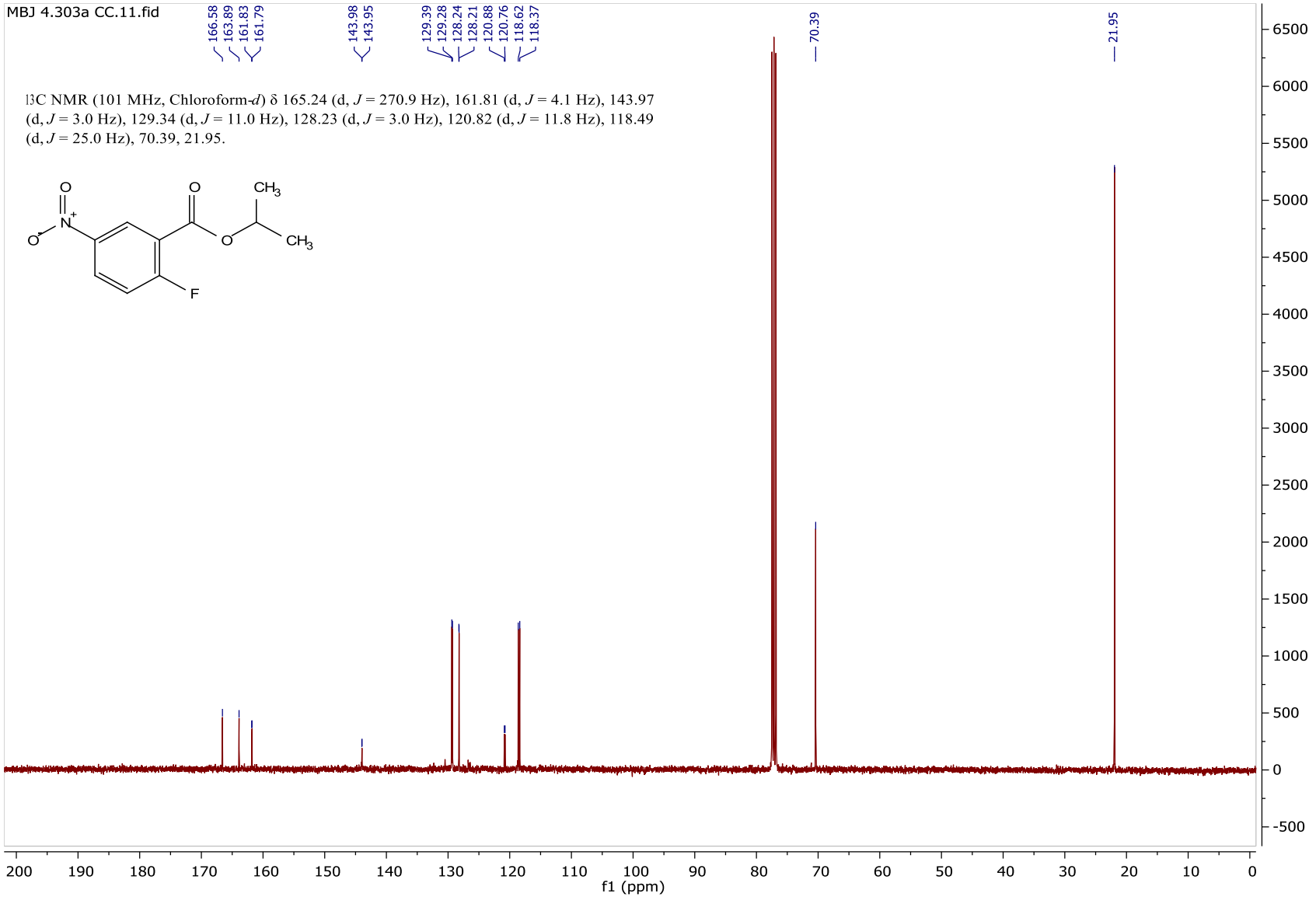


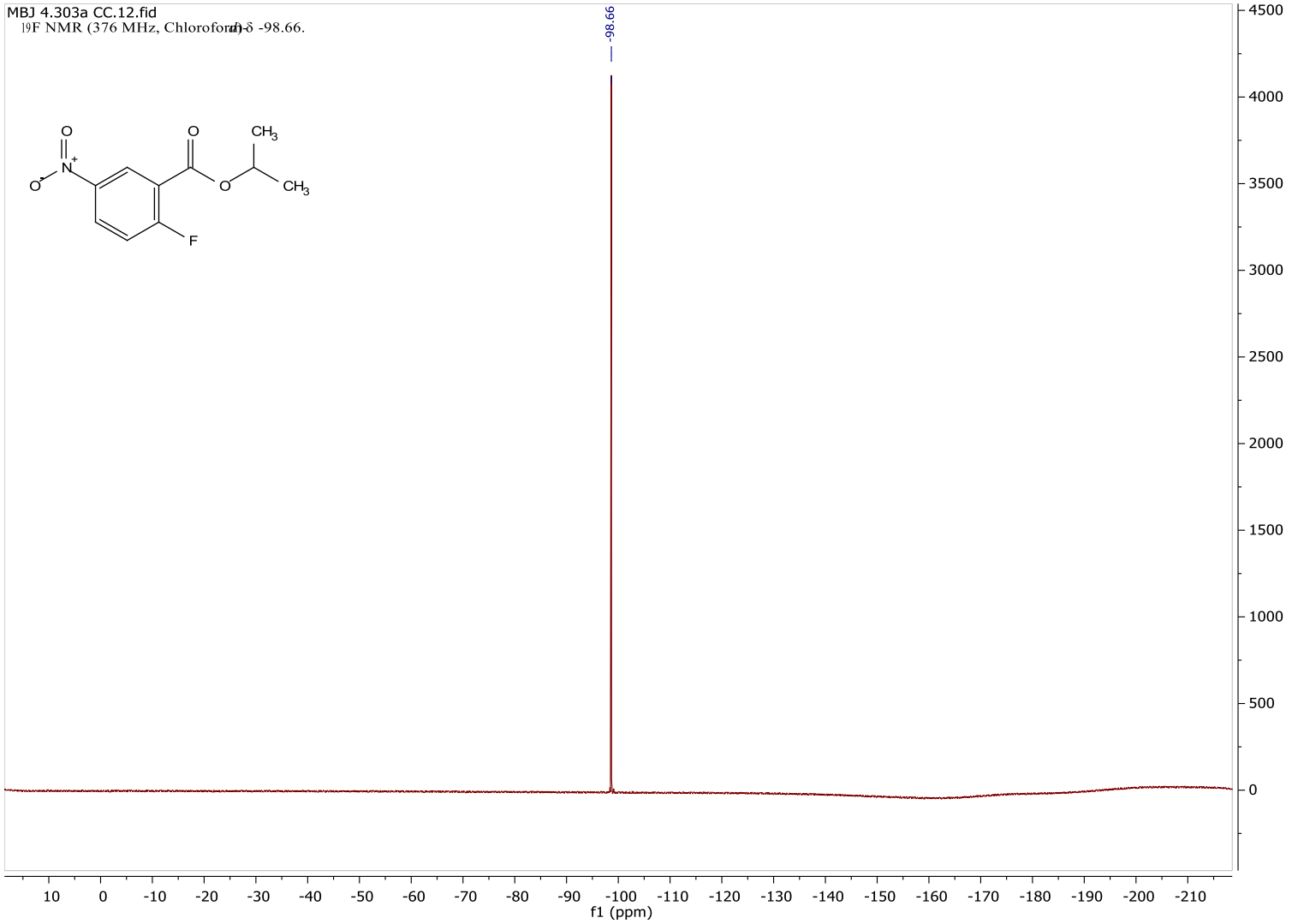

MBJ 4.270a crude.22.fid
173.73
173.65
162.94
160.79
87.72
87.65
54.83
13C NMR (101 MHz, Chloroform-d) δ 173.73 (d, J = 15.7 Hz), 161.86 (d, J = 216.0 Hz), 87.69 (d, J = 6.8 Hz), 54.83.
CH3
O
N
O
N
F
CH3
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MBJ 4.270a crude.11.fid
19F NMR (376 MHz, Chloroform-d) δ -44.41.
-44.41
O
CH3
N
O
N
F
CH3
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

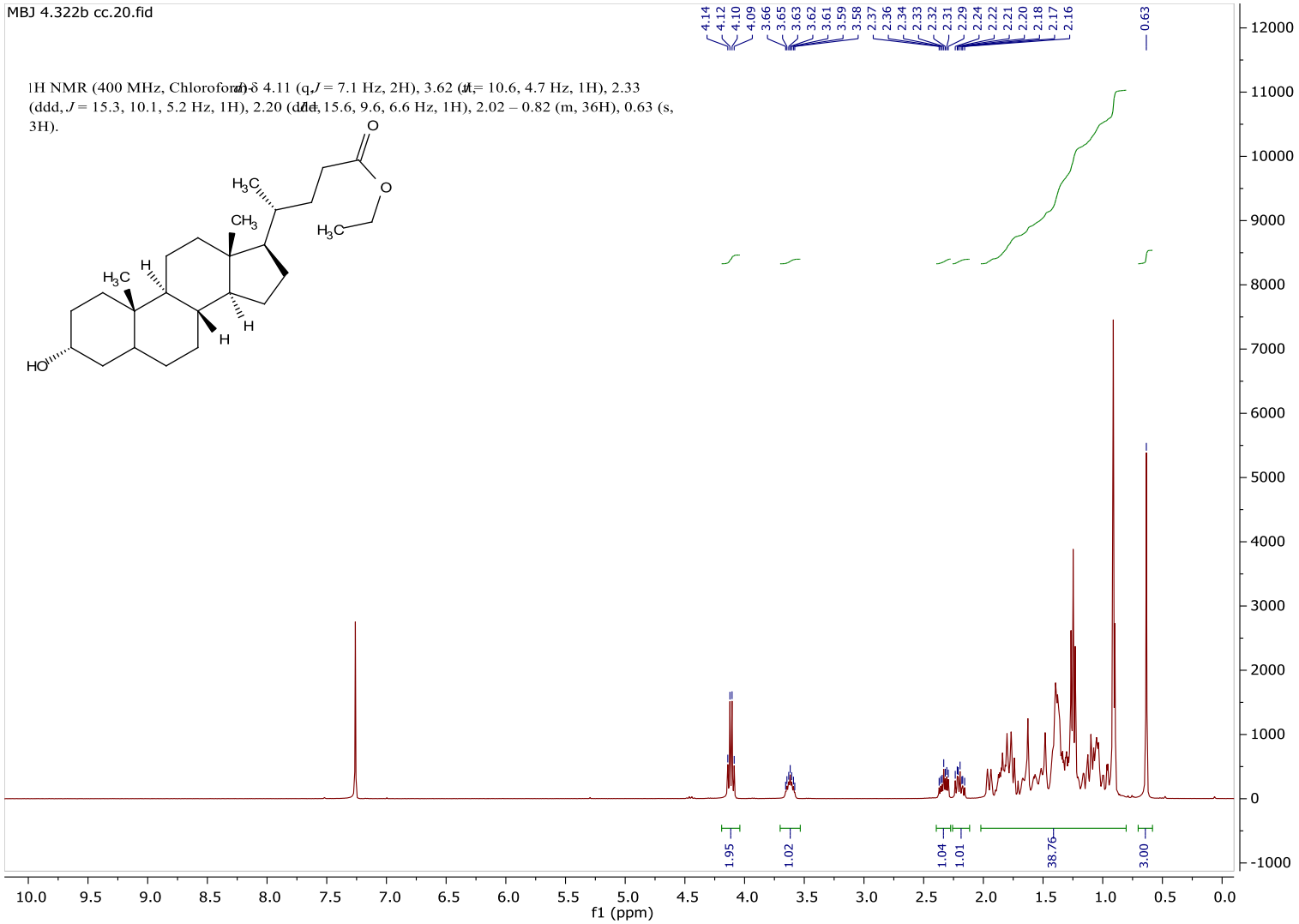
*Isopropyl 2-fluoro-5-nitrobenzoate (**12**).*

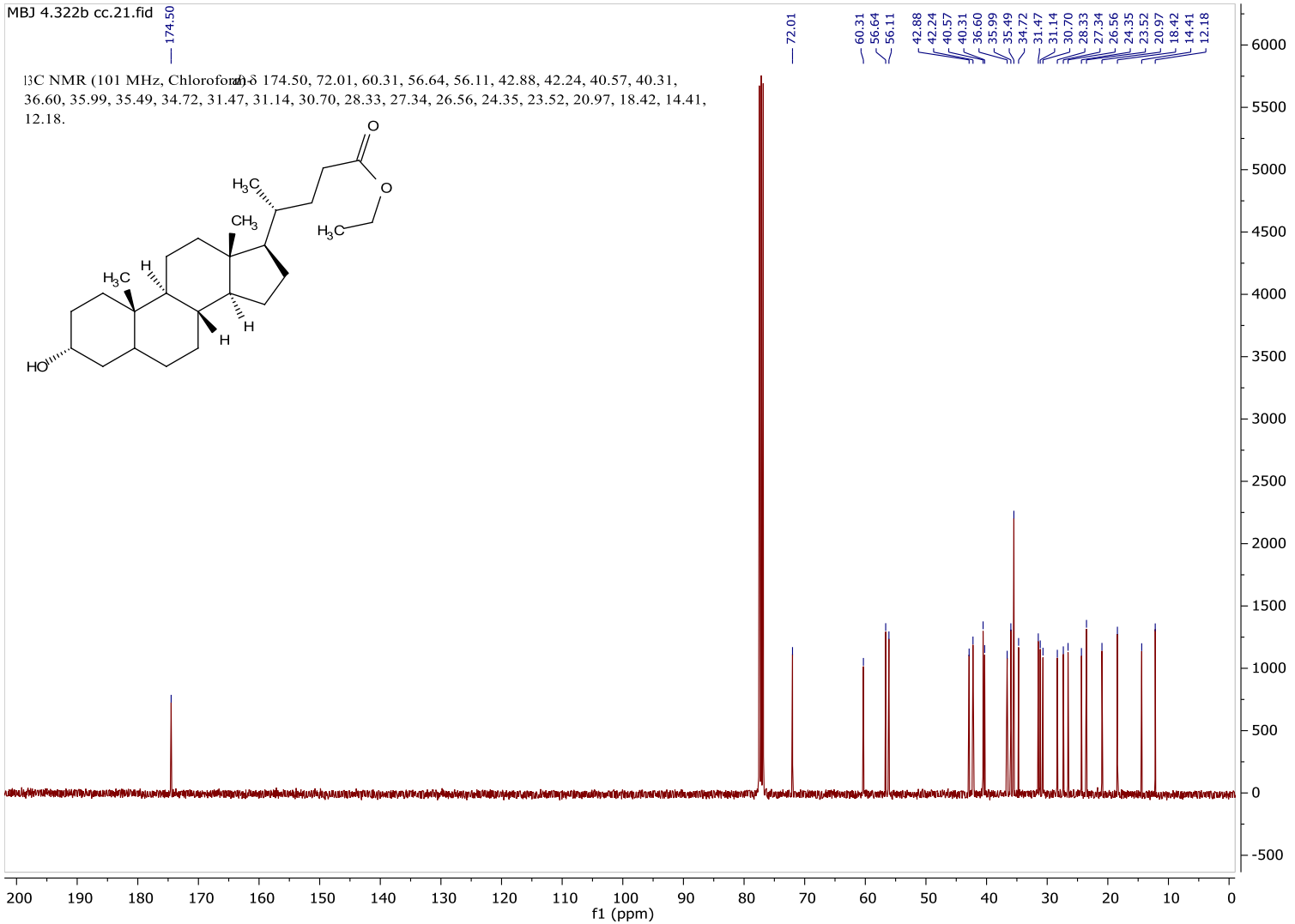



MBJ 4.303a CC.11.fid
166.58
163.89
161.83
161.79
143.98
143.95
129.39
129.28
128.24
128.21
120.88
120.76
118.62
118.37
70.39
21.95
13C NMR (101 MHz, Chloroform-d) δ 165.24 (d, J = 270.9 Hz), 161.81 (d, J = 4.1 Hz), 143.97 (d, J = 3.0 Hz), 129.34 (d, J = 11.0 Hz), 128.23 (d, J = 3.0 Hz), 120.82 (d, J = 11.8 Hz), 118.49 (d, J = 25.0 Hz), 70.39, 21.95.
O
O
CH3
N+
O-
O
CH3
F
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

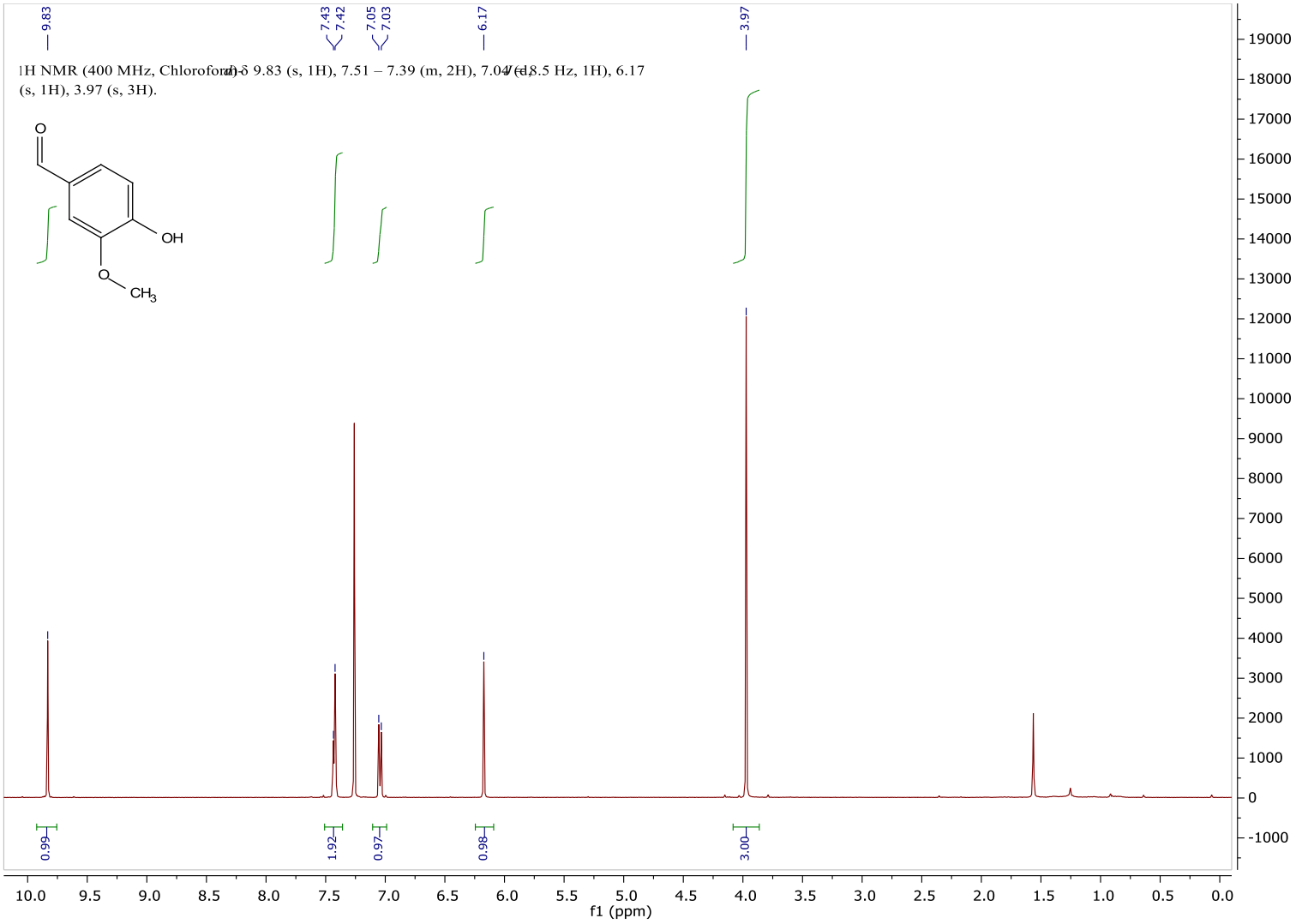

MBJ 4.303a CC.12.fid
19F NMR (376 MHz, Chloroform-d) δ -98.66.
-98.66
O
O
CH3
N+
O-
O
CH3
F
4500
4000
3500
3000
2500
2000
1500
1000
500
0
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

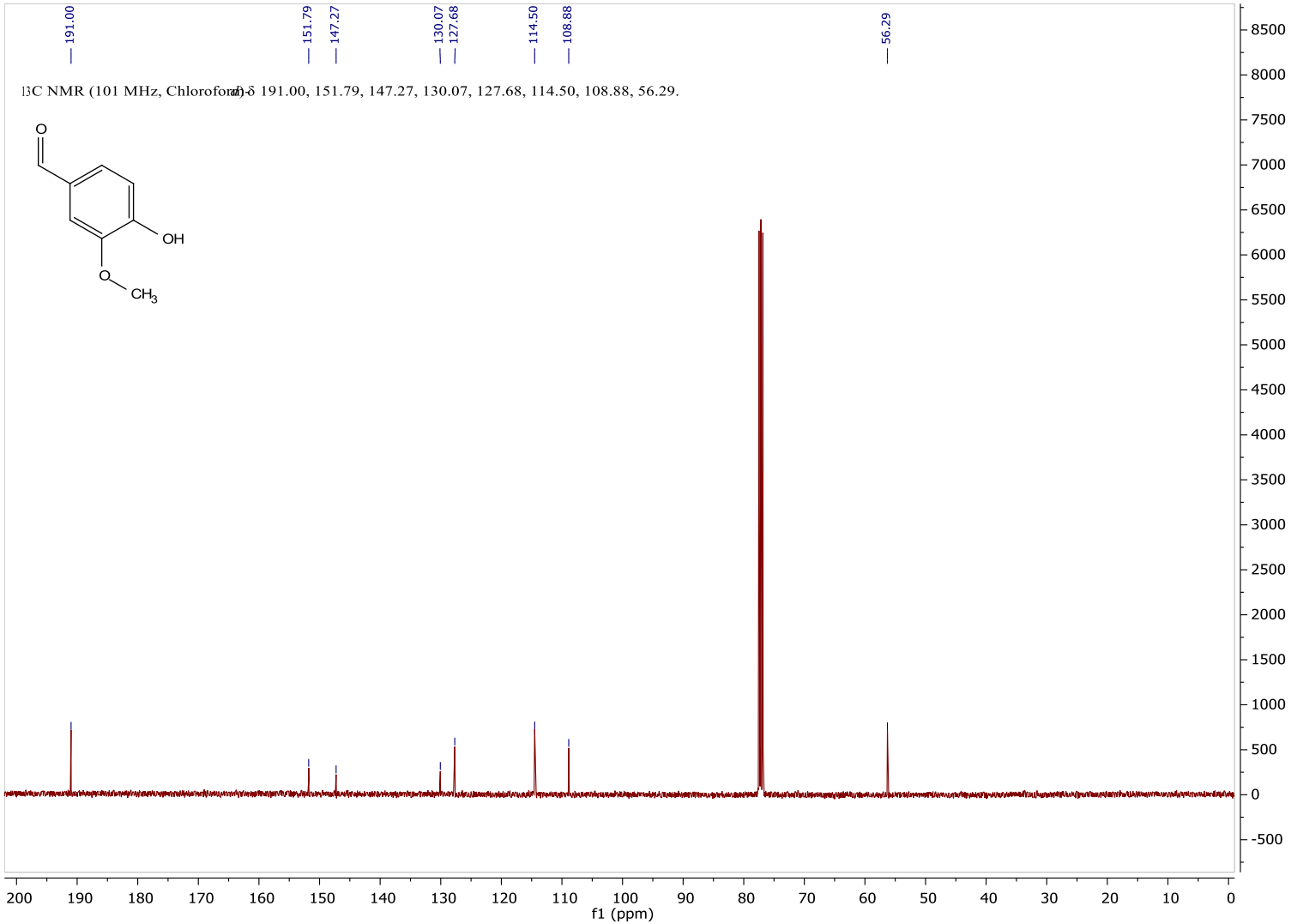
*Ethyl 3α-hydroxy-5β-cholan-24-oate (**13**)*



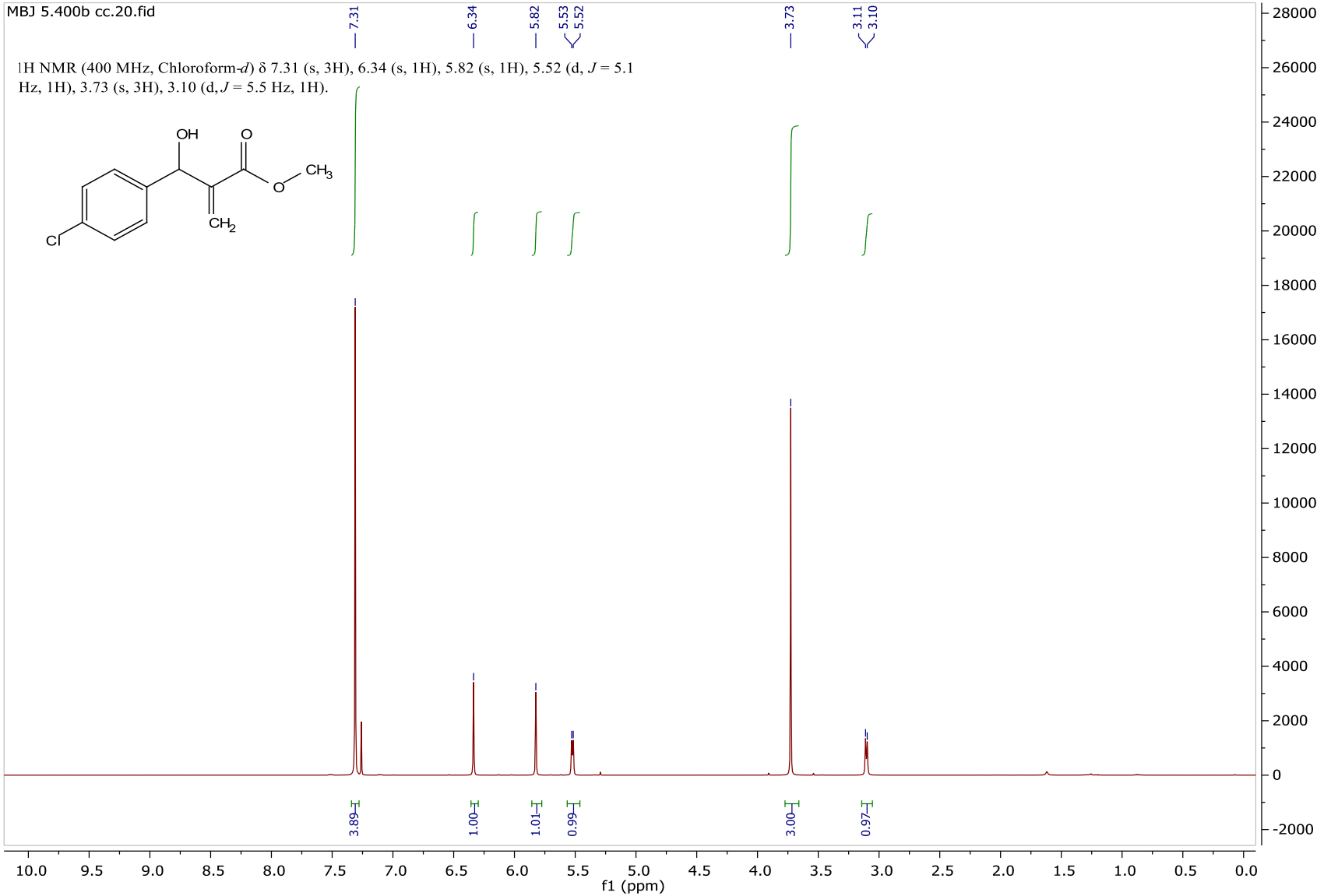

MBJ 4.322b cc.21.fid
174.50
72.01
60.31
56.64
56.11
42.88
42.24
40.57
40.31
36.60
35.99
35.49
34.72
31.47
31.14
30.70
28.33
27.34
26.56
24.35
23.52
20.97
18.42
14.41
12.18
13C NMR (101 MHz, Chloroform-d) δ 174.50, 72.01, 60.31, 56.64, 56.11, 42.88, 42.24, 40.57, 40.31, 36.60, 35.99, 35.49, 34.72, 31.47, 31.14, 30.70, 28.33, 27.34, 26.56, 24.35, 23.52, 20.97, 18.42, 14.41, 12.18.
O
O
H3C
CH3
H3C
H3C
H
H
H
HO
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

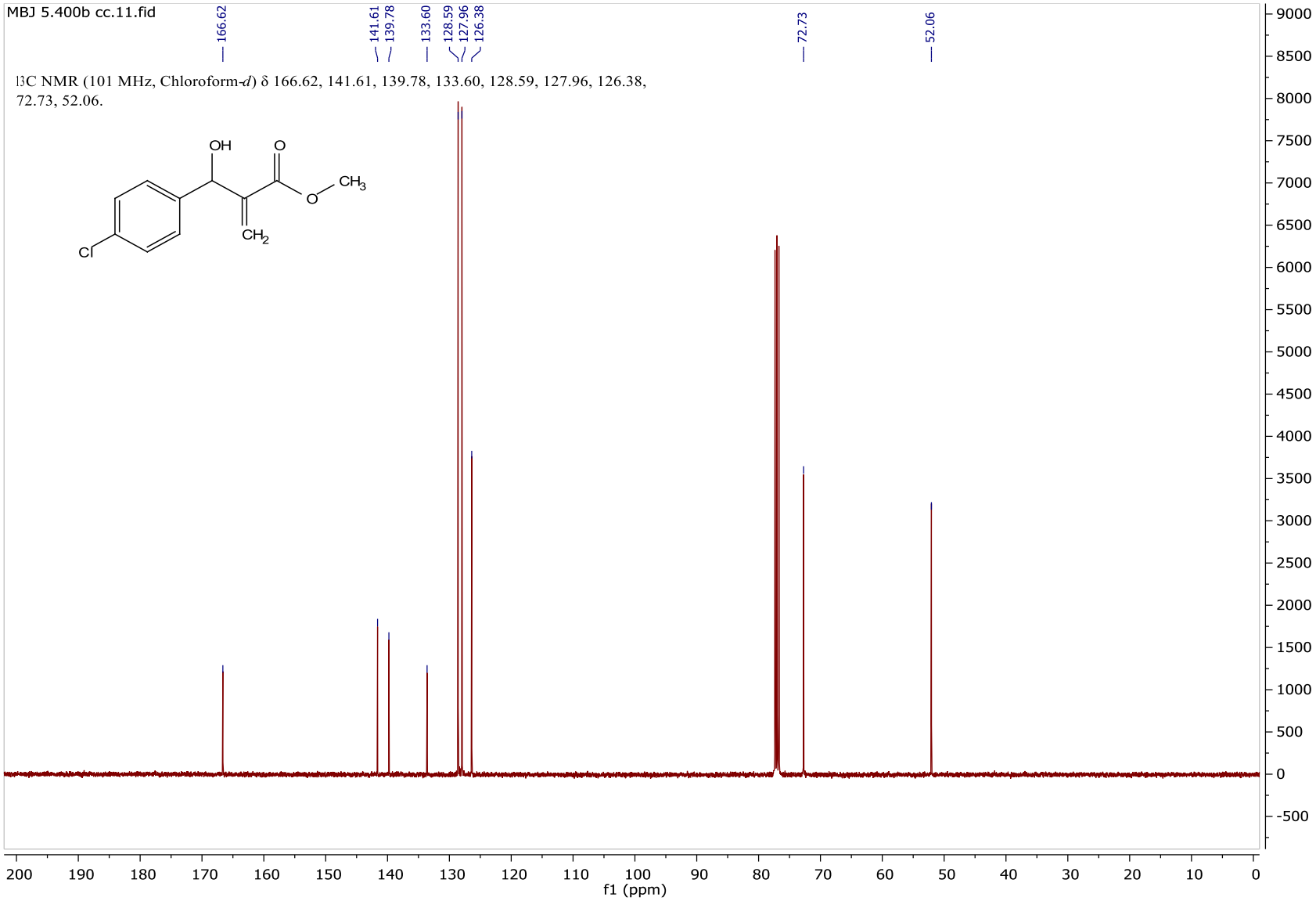
*Vanillin (**14**)*


9.83
7.43
7.42
7.05
7.03
6.17
3.97
1H NMR (400 MHz, Chloroform-d) δ 9.83 (s, 1H), 7.51 – 7.39 (m, 2H), 7.04 (d, J = 8.5 Hz, 1H), 6.17 (s, 1H), 3.97 (s, 3H).
O
OH
O
CH3
0.99
1.92
0.97
0.98
3.00
f1 (ppm)

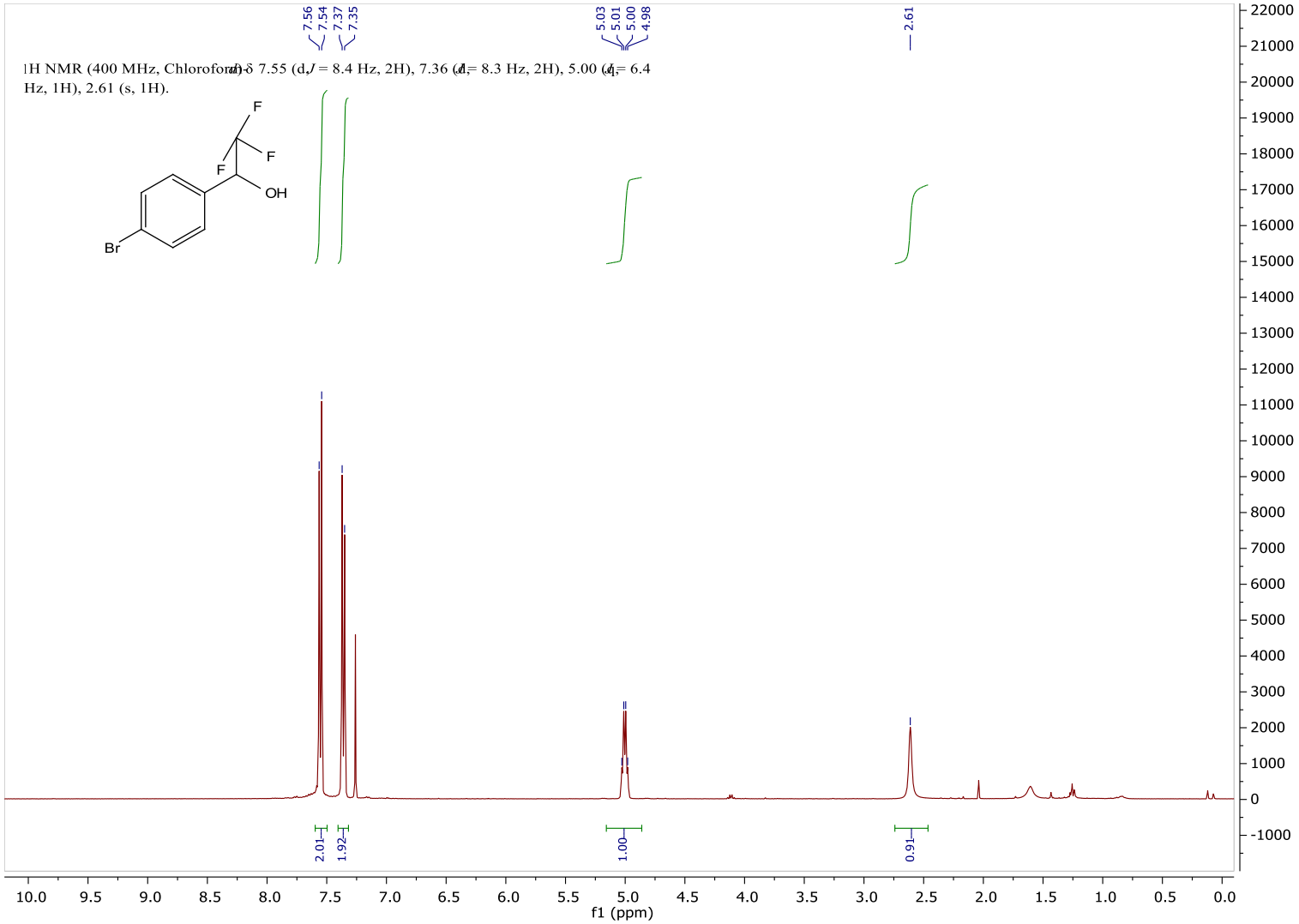

191.00
151.79
147.27
130.07
127.68
114.50
108.88
56.29
13C NMR (101 MHz, Chloroform-d) δ 191.00, 151.79, 147.27, 130.07, 127.68, 114.50, 108.88, 56.29.
O
OH
O
CH3
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

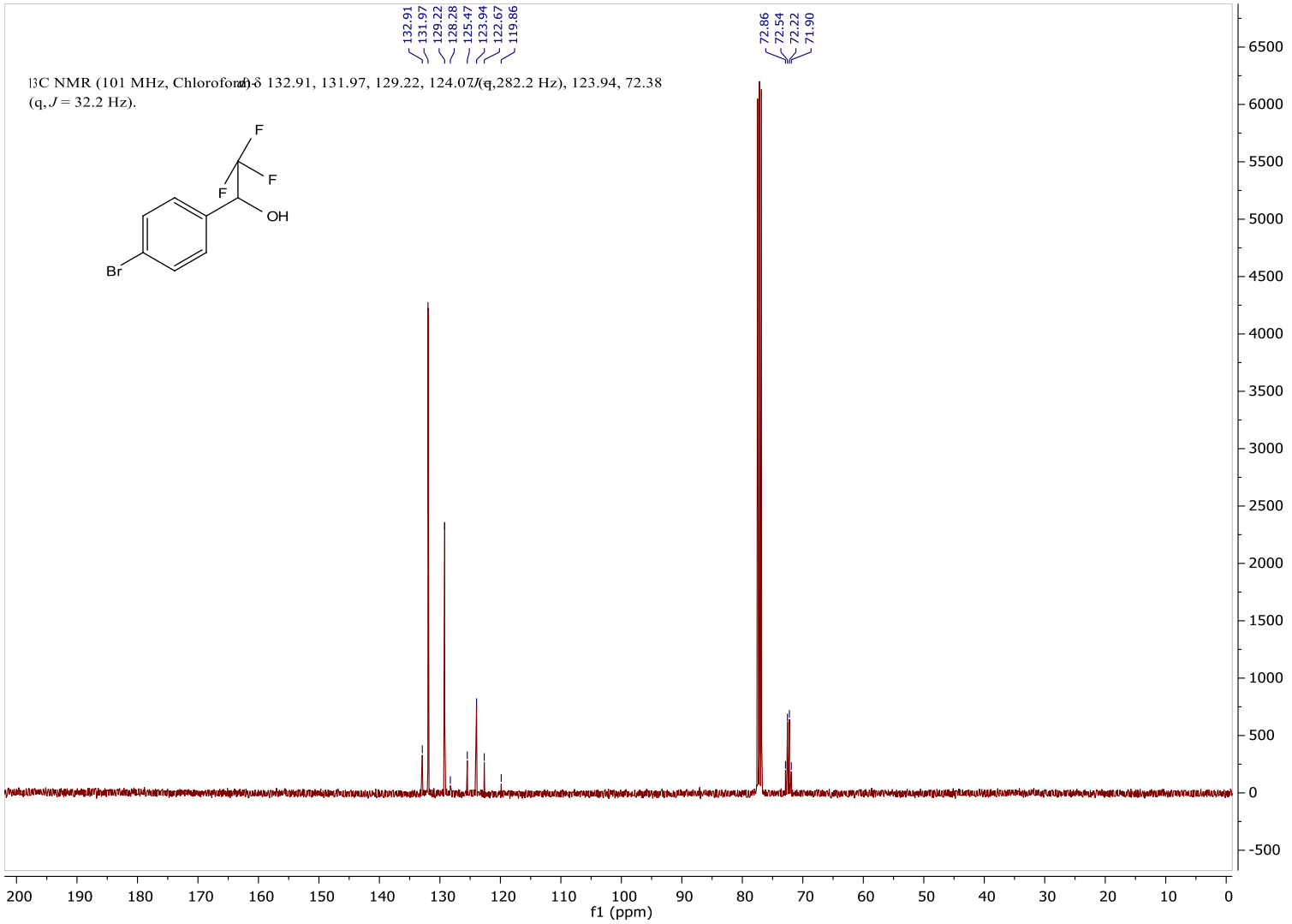
*Methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate (**15**)*



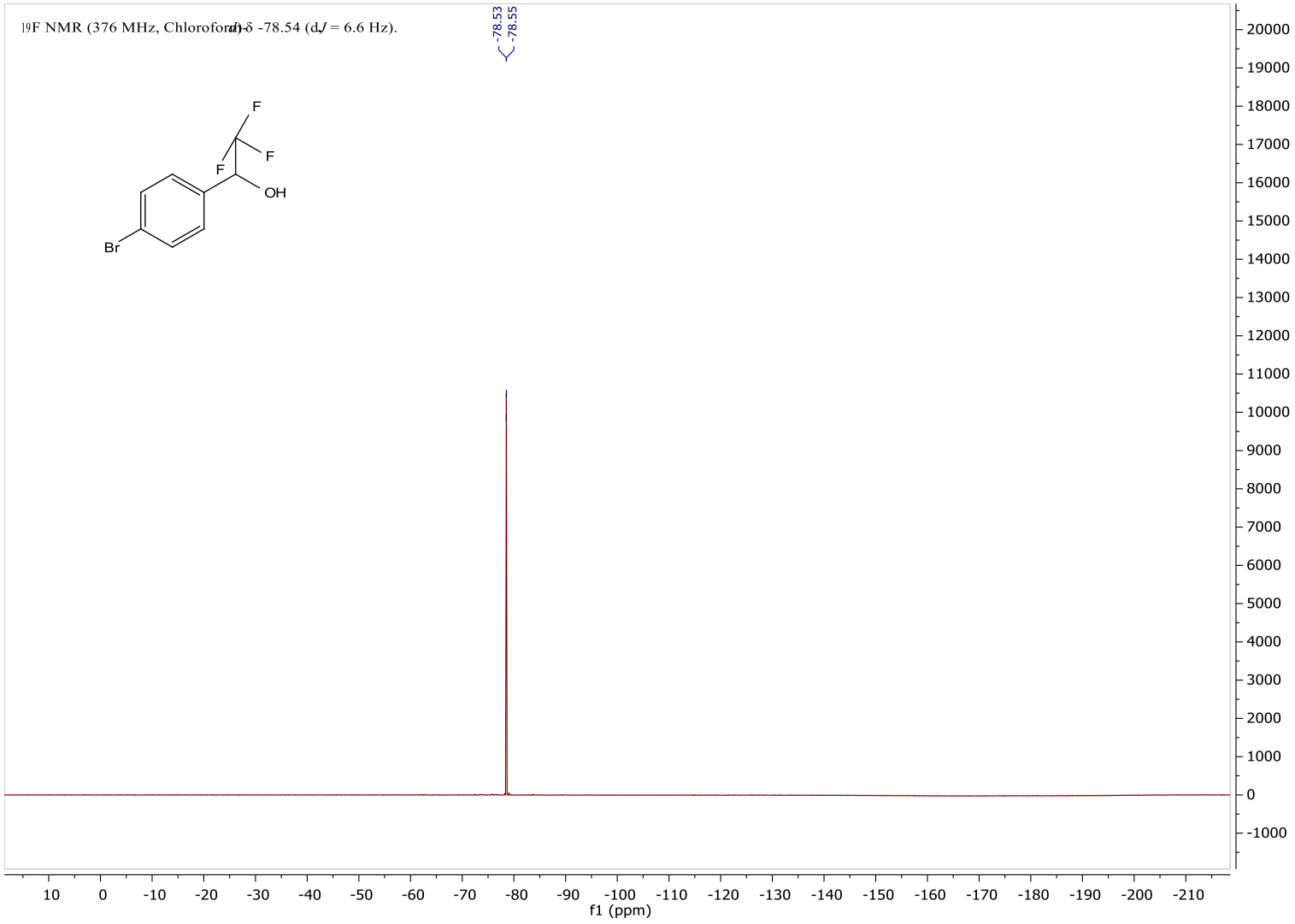

MBJ 5.400b cc.11.fid
166.62
141.61
139.78
133.60
128.59
127.96
126.38
72.73
52.06
13C NMR (101 MHz, Chloroform-d) δ 166.62, 141.61, 139.78, 133.60, 128.59, 127.96, 126.38, 72.73, 52.06.
OH
O
CH3
O
CH2
Cl
f1 (ppm)

*1-(4-Bromophenyl)-2,2,2-trifluoroethan-1-ol (**16**).*

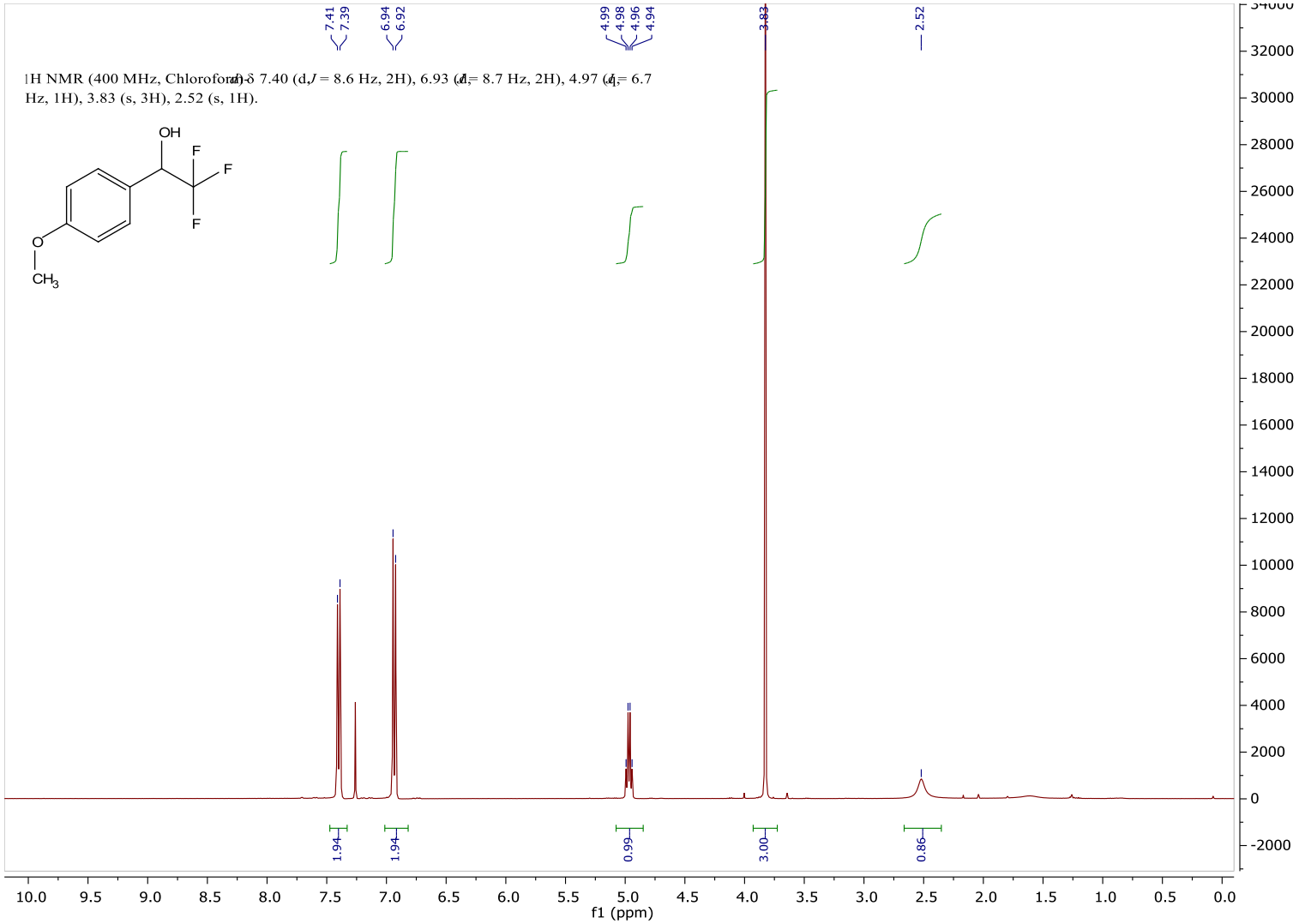


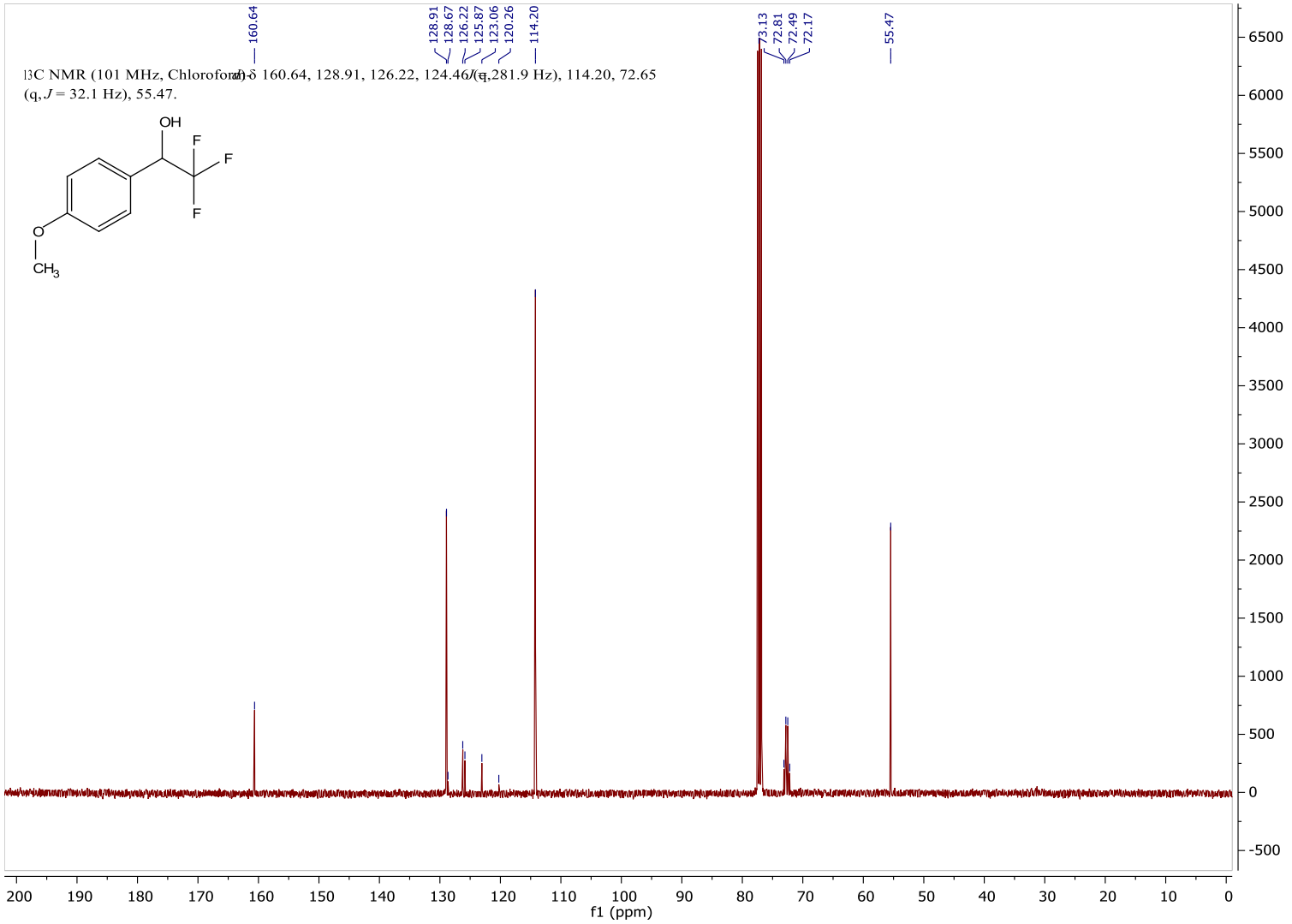

132.91
131.97
129.22
128.28
125.47
123.94
122.67
119.86
72.86
72.54
72.22
71.90
13C NMR (101 MHz, Chloroform-d) δ 132.91, 131.97, 129.22, 124.07 (q, J = 282.2 Hz), 123.94, 72.38 (q, J = 32.2 Hz).
F
F
F
OH
Br
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

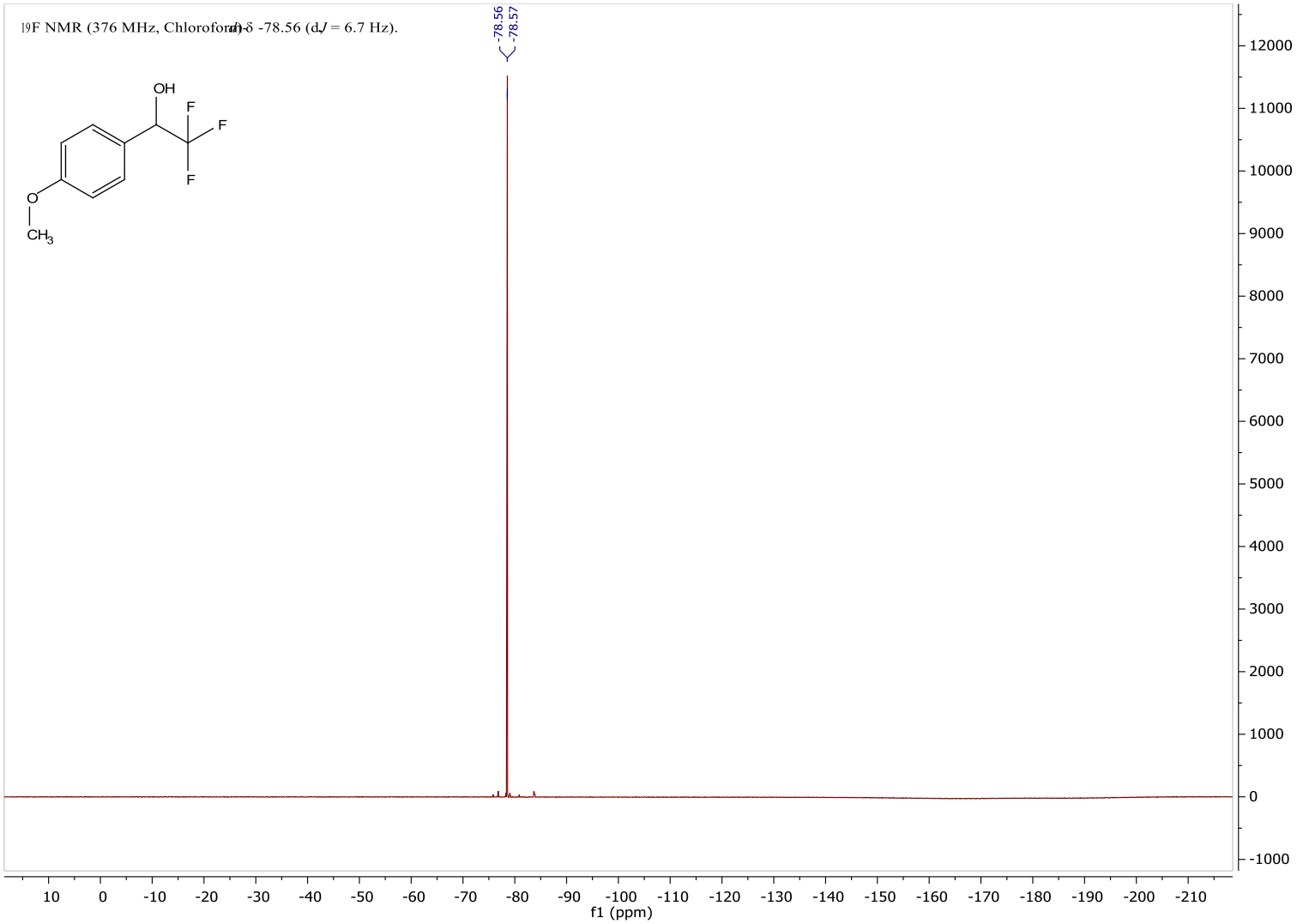
^{19}F NMR (376 MHz, Chloroform-*d*) δ -78.54 (d, *J* = 6.6 Hz).



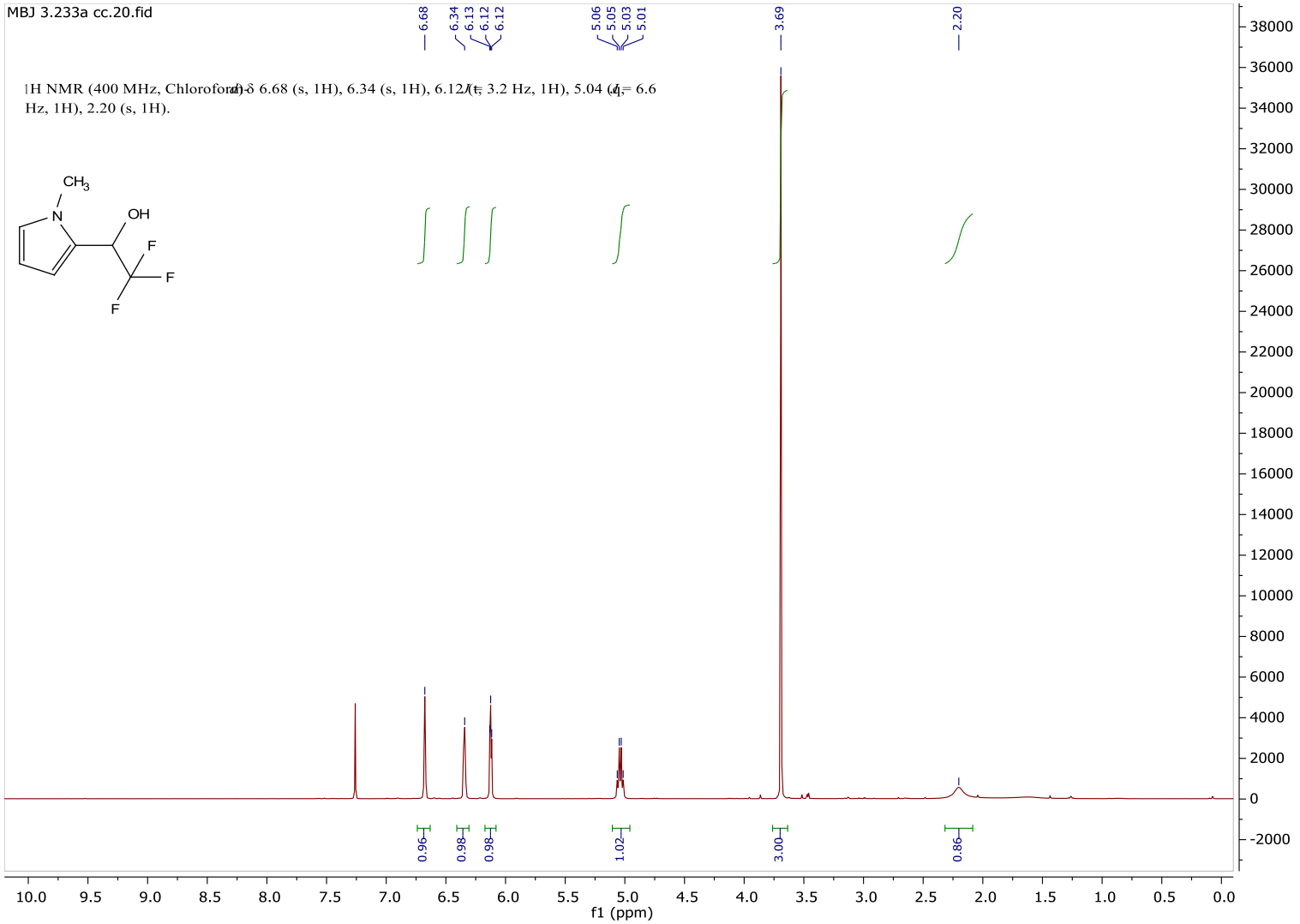
*1-(4-Methoxyphenyl)-2,2,2-trifluoroethan-1-ol (**17**).*

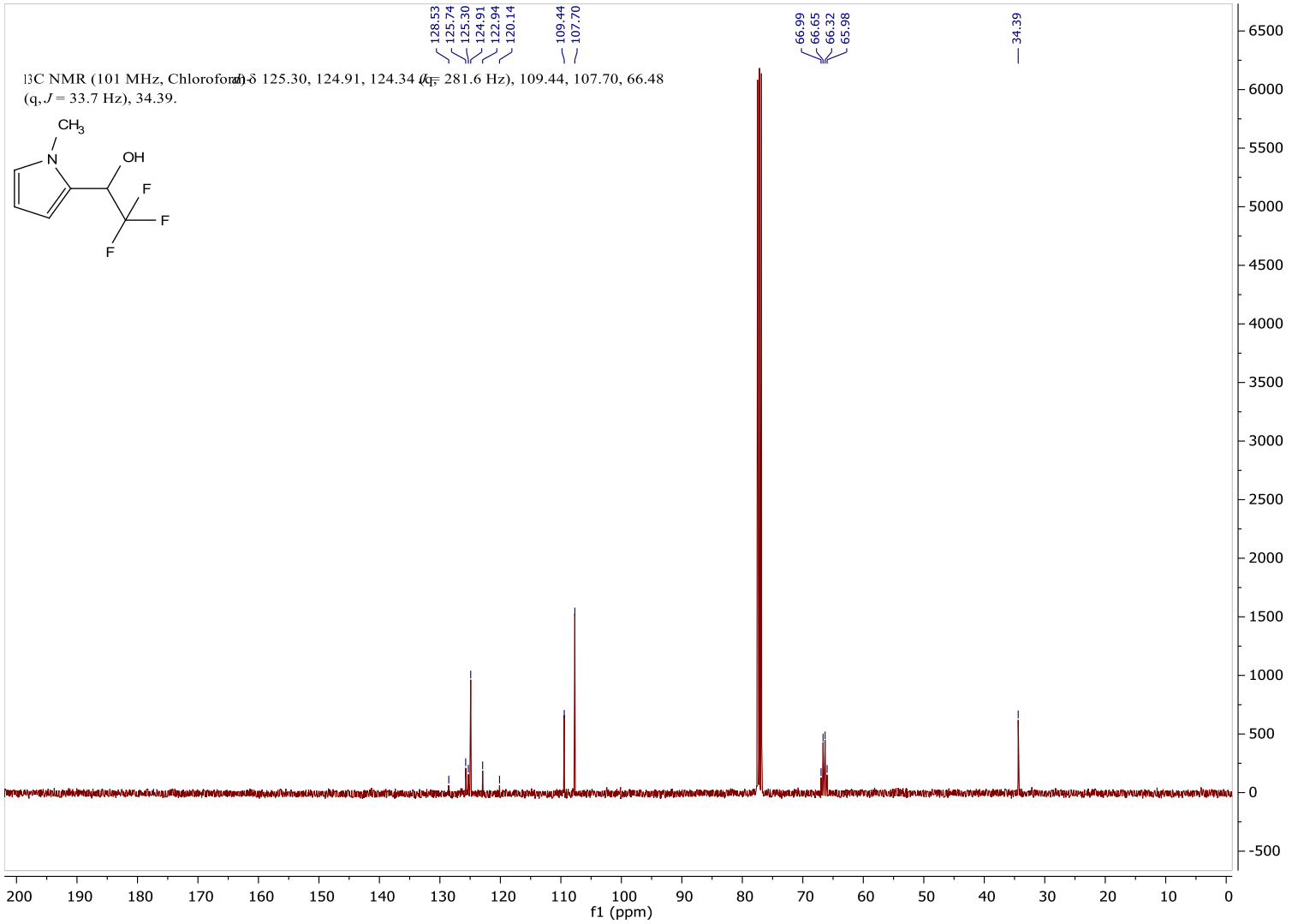


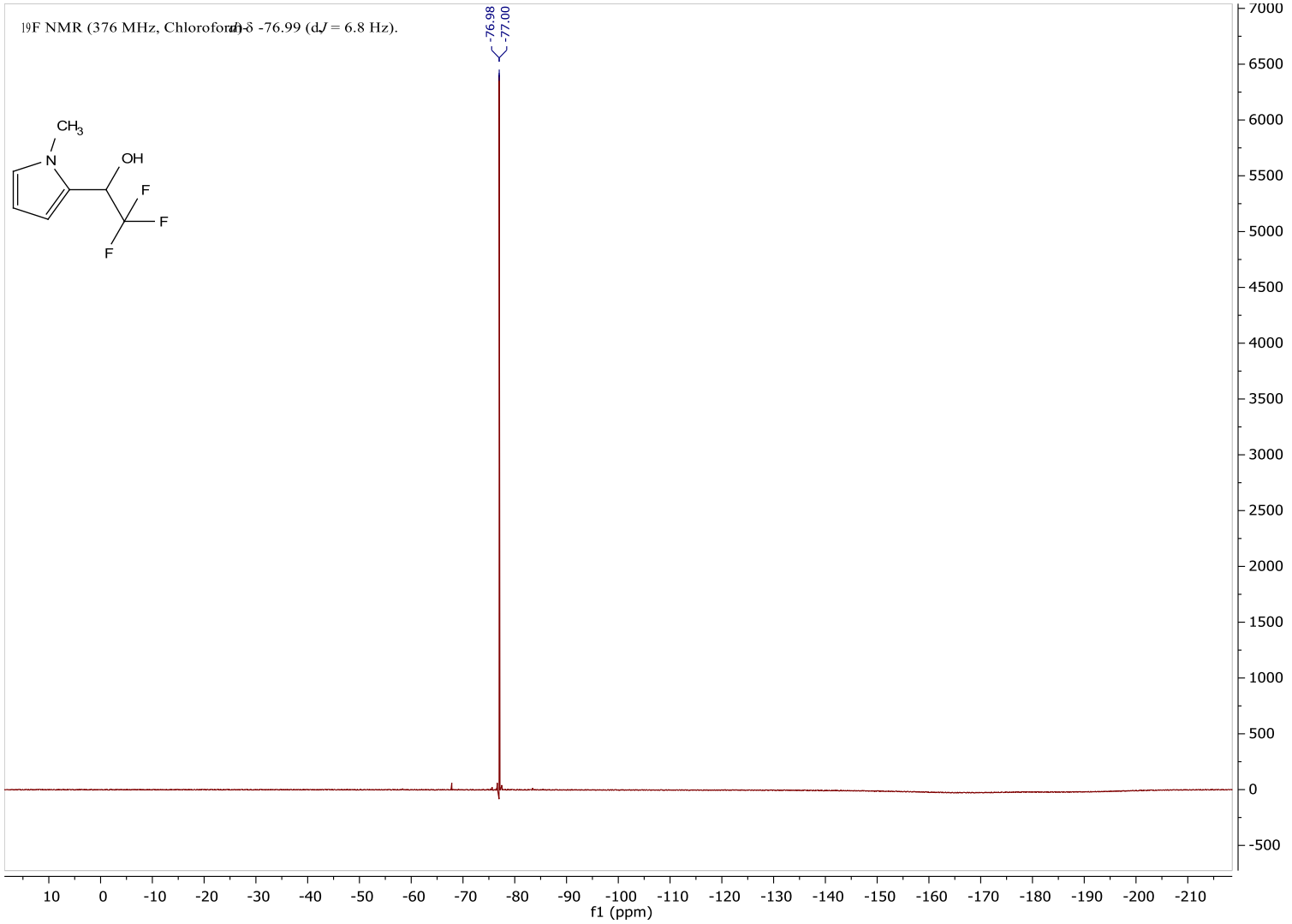

160.64
128.91
128.67
126.22
125.87
123.06
120.26
114.20
73.13
72.81
72.49
72.17
55.47
13C NMR (101 MHz, Chloroform-d) δ 160.64, 128.91, 126.22, 124.46 (q, 281.9 Hz), 114.20, 72.65 (q, J = 32.1 Hz), 55.47.
OH
F
F
F
O
CH3
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


19F NMR (376 MHz, Chloroform-d) δ -78.56 (d, J = 6.7 Hz).
-78.56
-78.57
OH
F
F
F
O
CH3
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

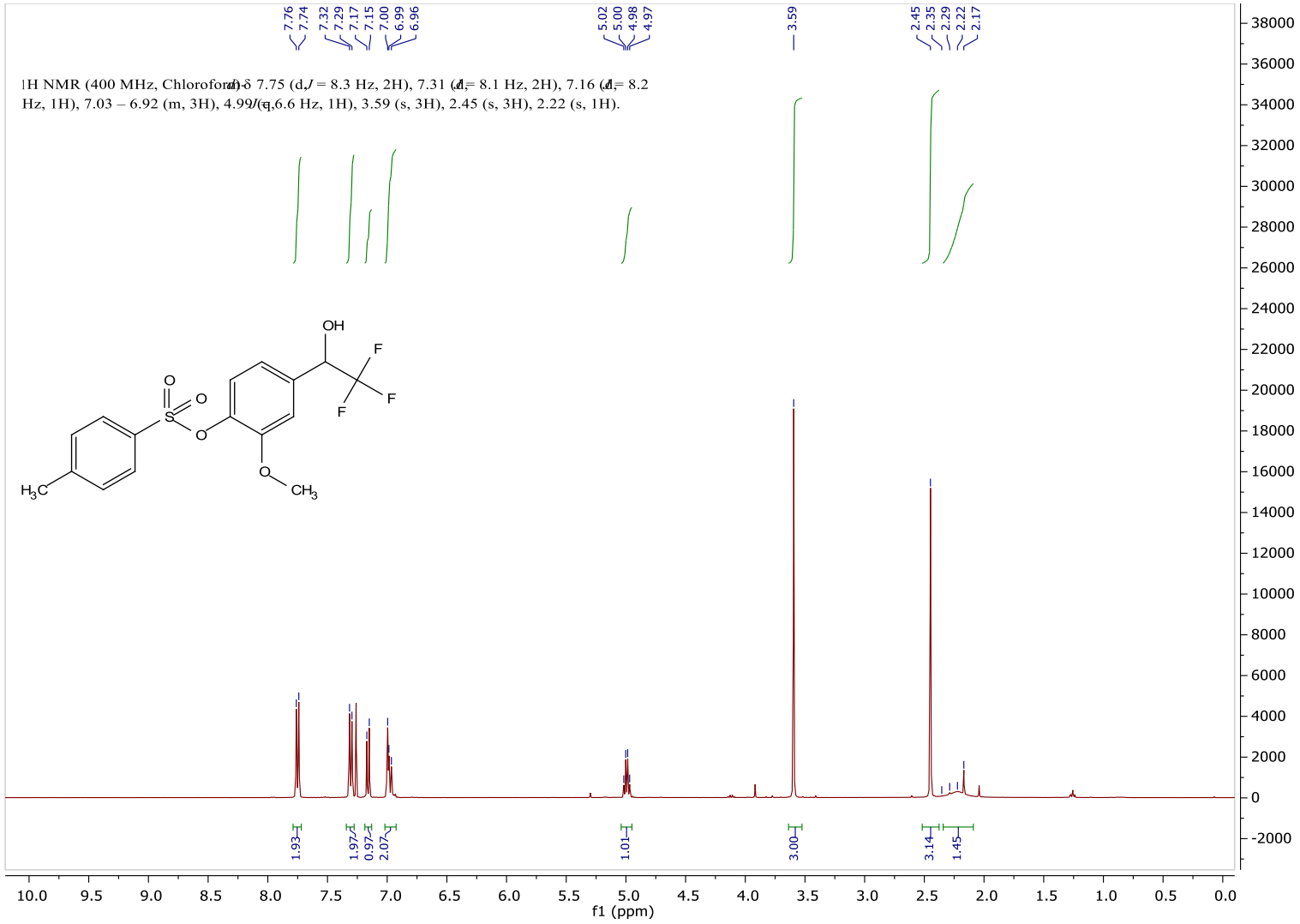
*1-(N-methyl-1H-pyrrole-2-yl)-2,2,2-trifluoroethan-1-ol (**18**).*

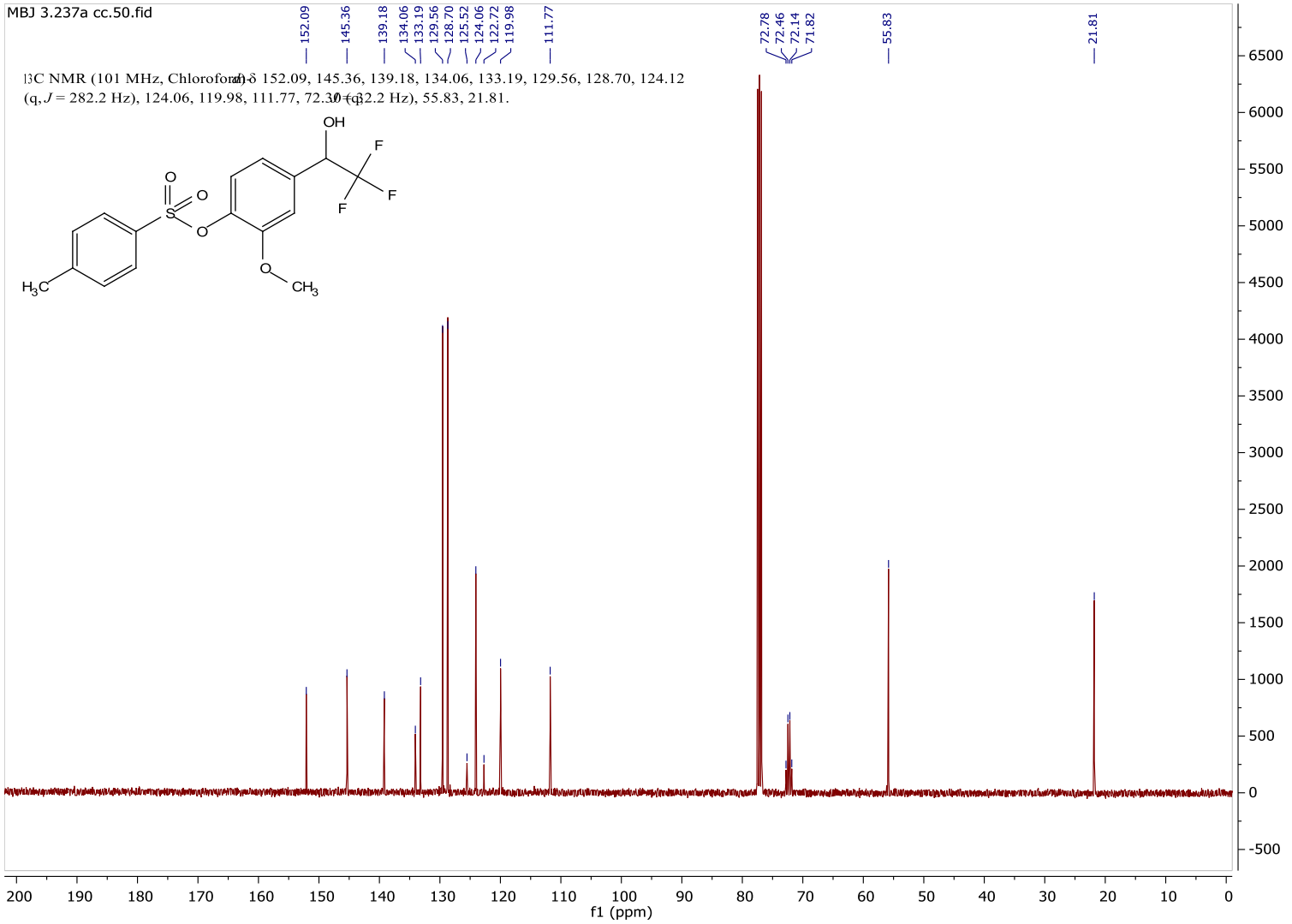


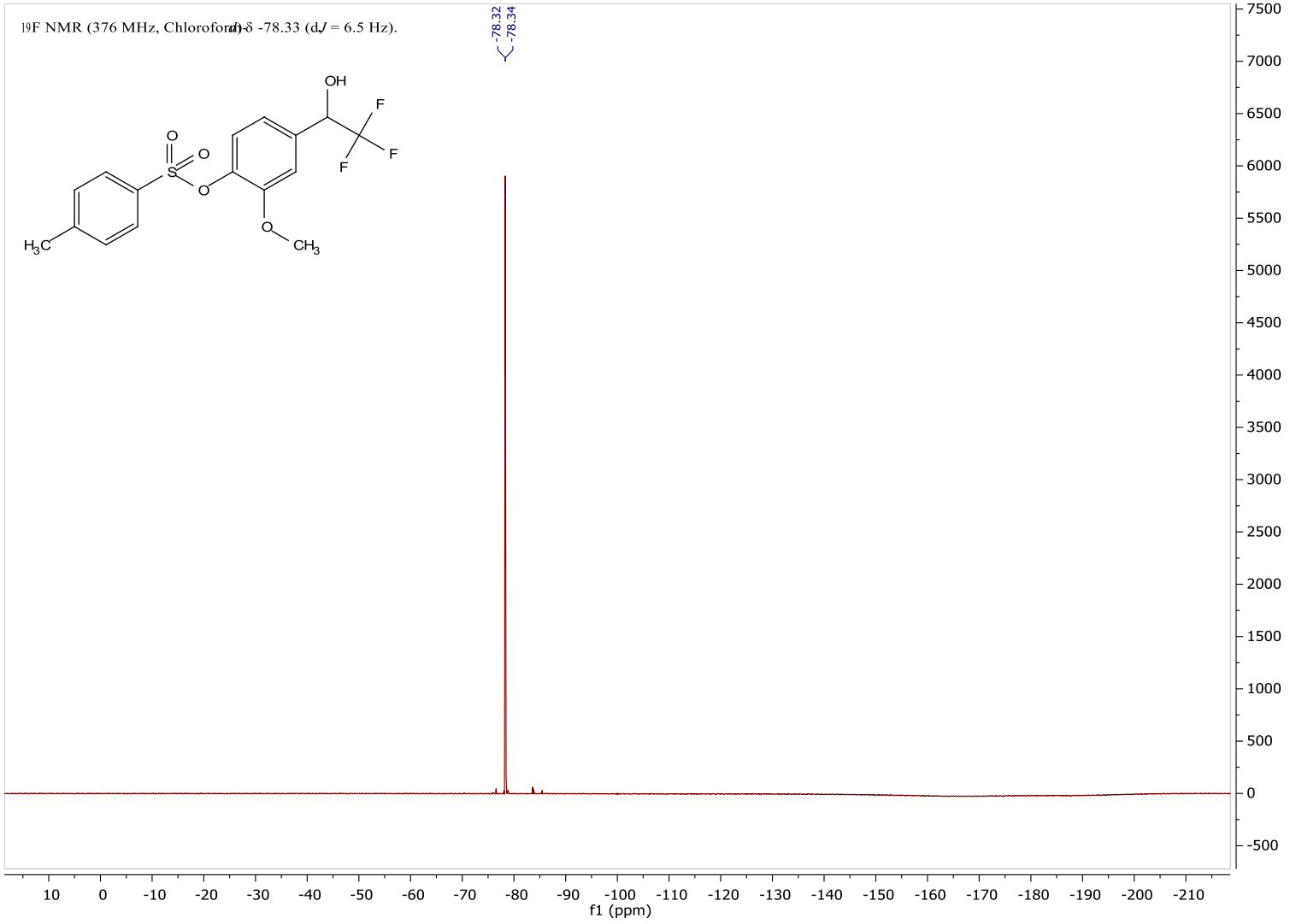

128.53
125.74
125.30
124.91
122.94
120.14
109.44
107.70
66.99
66.65
66.32
65.98
34.39
13C NMR (101 MHz, Chloroform-d) δ 125.30, 124.91, 124.34 (q, J = 281.6 Hz), 109.44, 107.70, 66.48 (q, J = 33.7 Hz), 34.39.
CH3
N
OH
F
F
F
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


19F NMR (376 MHz, Chloroform-d) δ -76.99 (dJ = 6.8 Hz).
-76.98
-77.00
CH3
N
OH
F
F
F
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

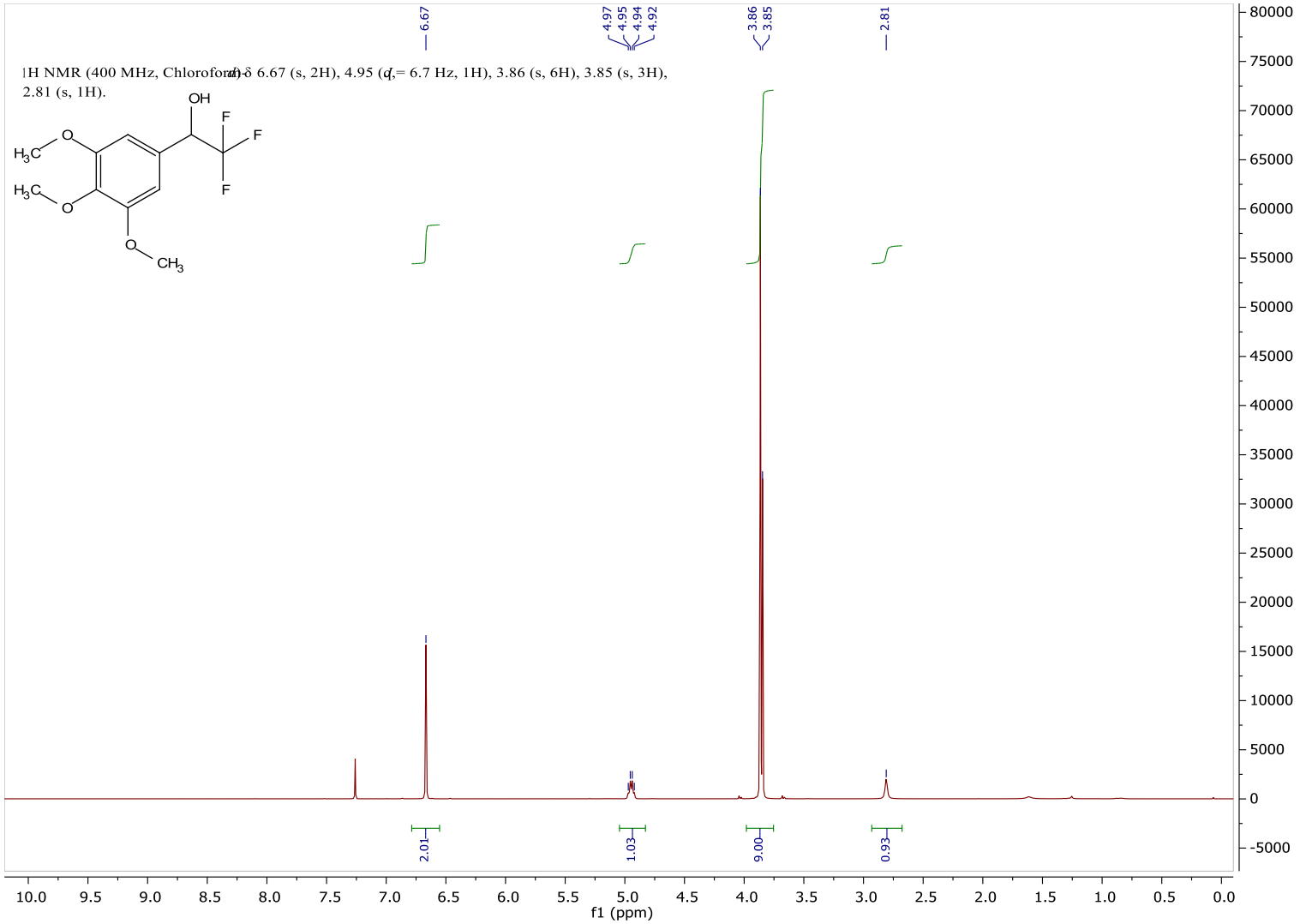
*1-(3-Trimethoxy-4-tosyl-phenyl)-2,2,2-trifluoroethan-1-ol (**19**).*

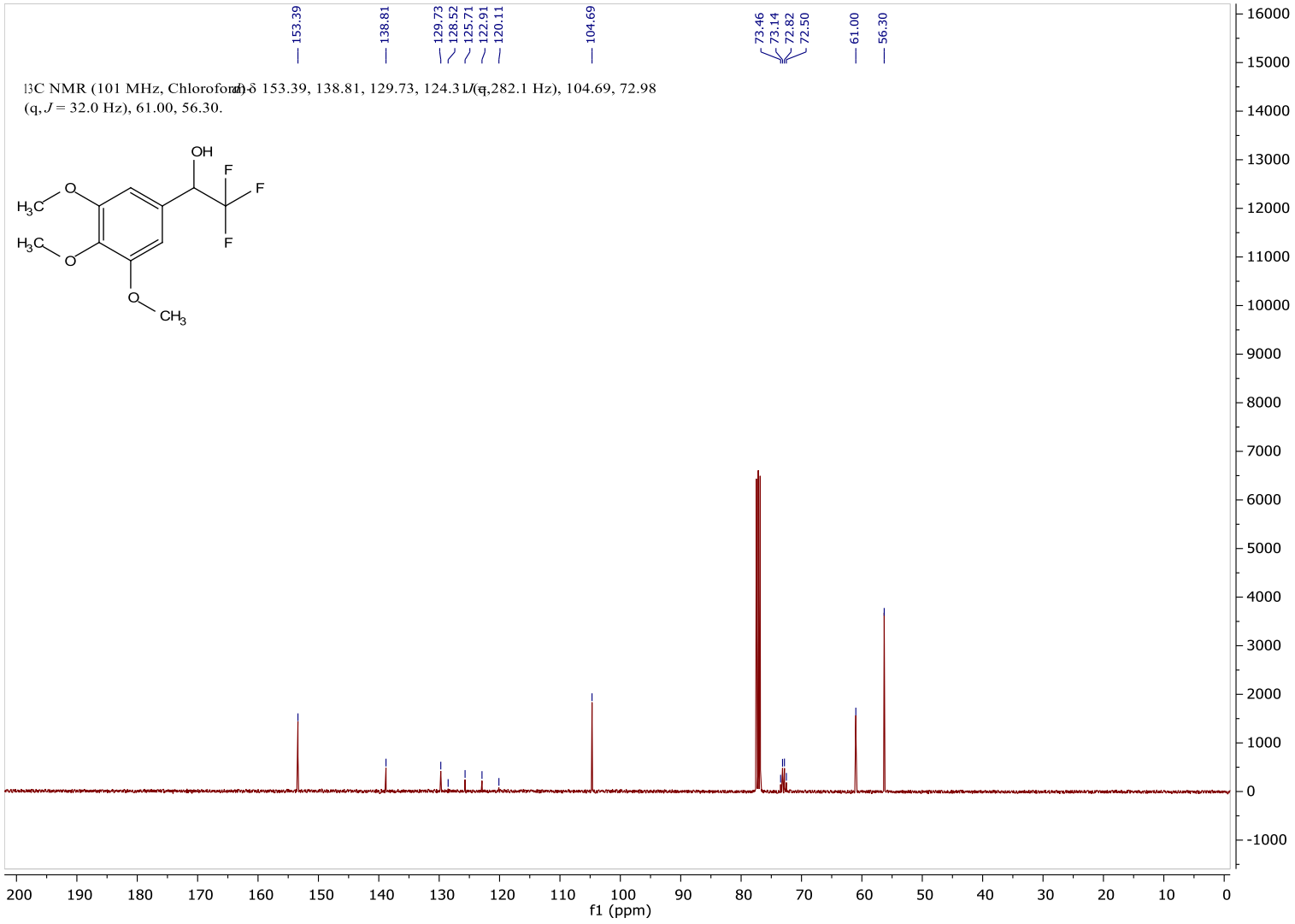



MBJ 3.237a cc.50.fid
152.09
145.36
139.18
134.06
133.19
129.56
128.70
125.52
124.06
122.72
119.98
111.77
72.78
72.46
72.14
71.82
55.83
21.81
13C NMR (101 MHz, Chloroform-d) δ 152.09, 145.36, 139.18, 134.06, 133.19, 129.56, 128.70, 124.12
(q, J = 282.2 Hz), 124.06, 119.98, 111.77, 72.30 (q, J = 32.2 Hz), 55.83, 21.81.
OH
F
F
F
O
O
S
O
O
H3C
CH3
f1 (ppm)

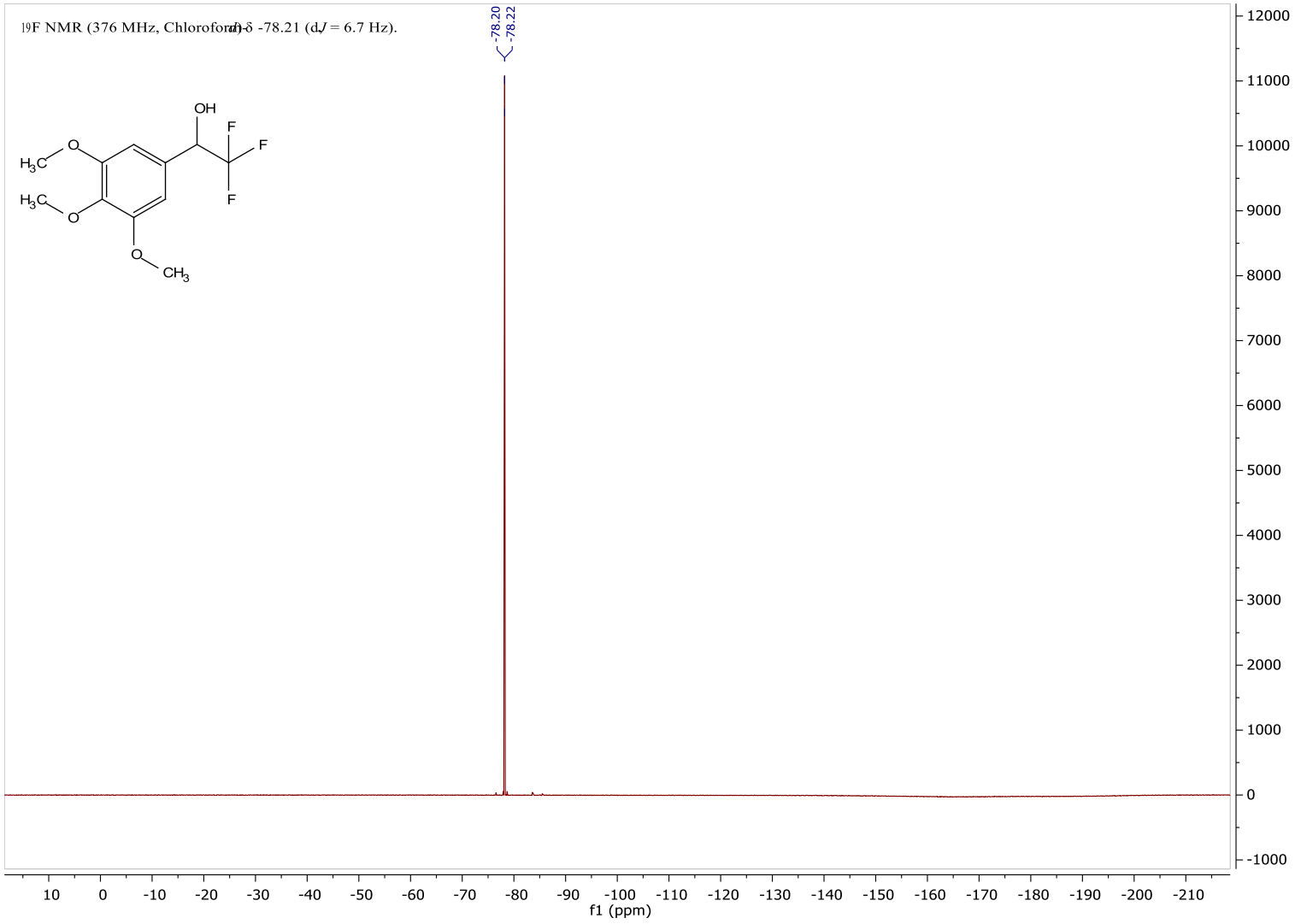

19F NMR (376 MHz, Chloroform-d) δ -78.33 (d, J = 6.5 Hz).
-78.32
-78.34
OH
F
F
F
O
O
S
O
O
H3C
CH3
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

*1-(3,4,5-Trimethoxyphenyl)-2,2,2-trifluoroethan-1-ol (**20**).*

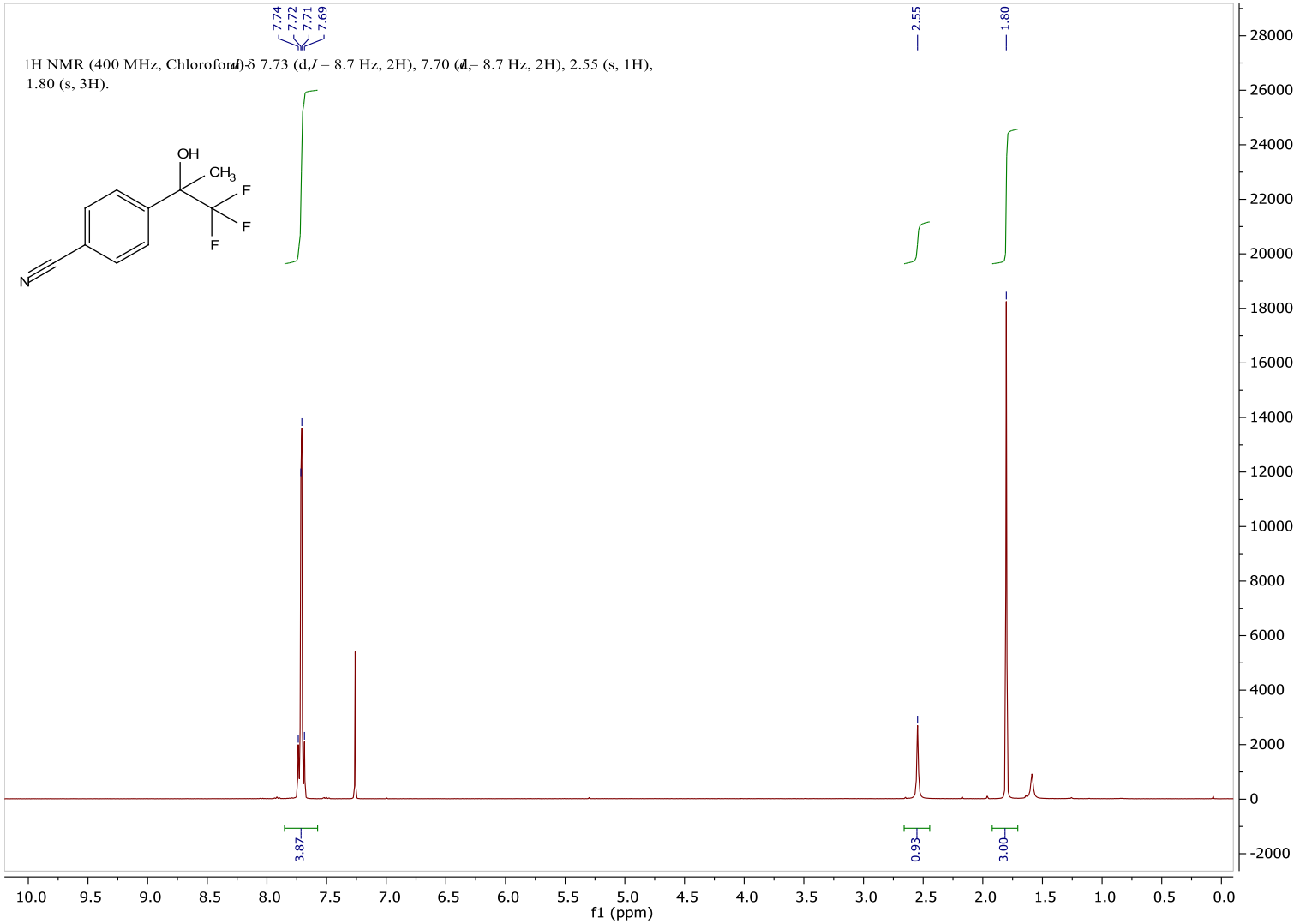


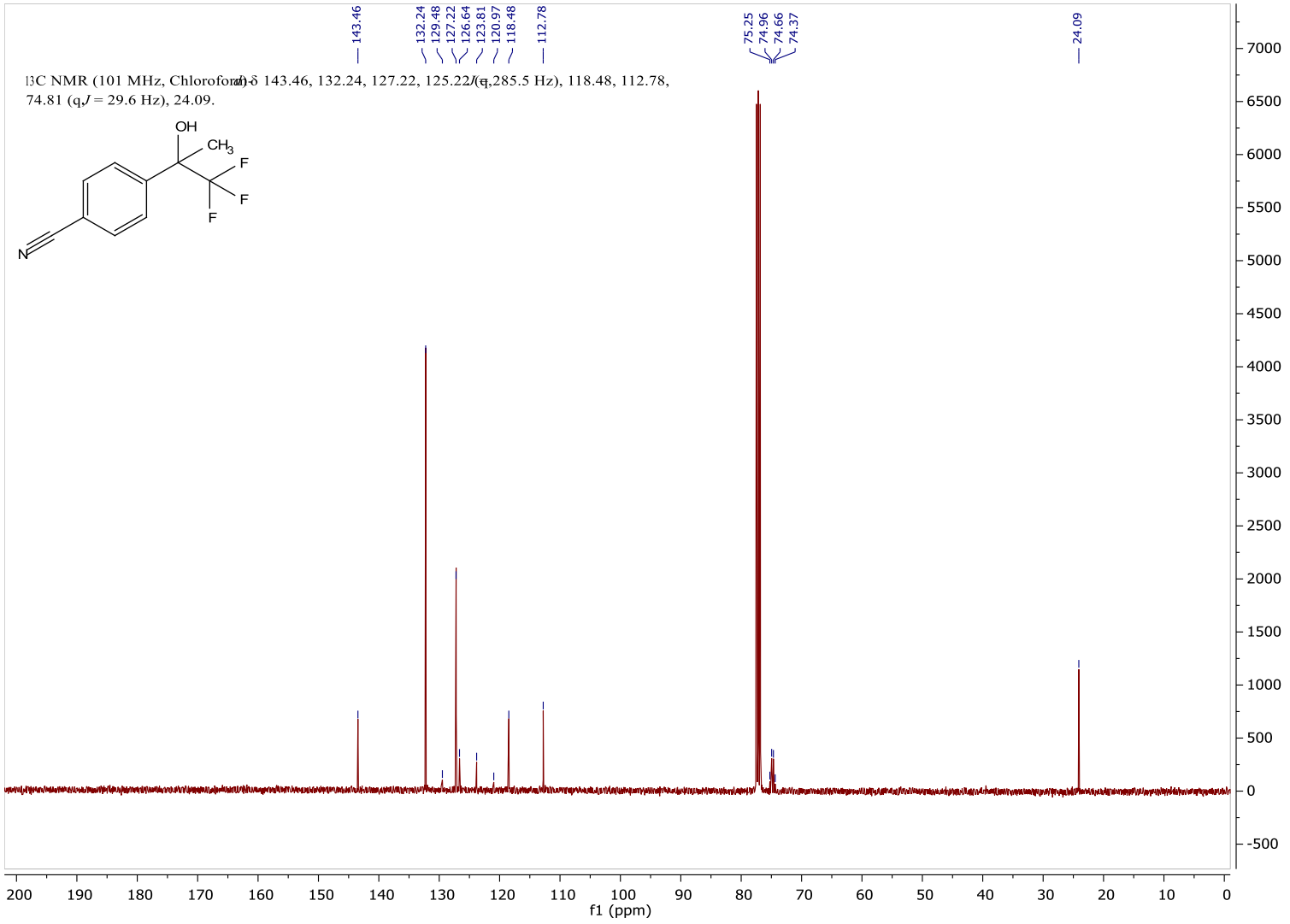


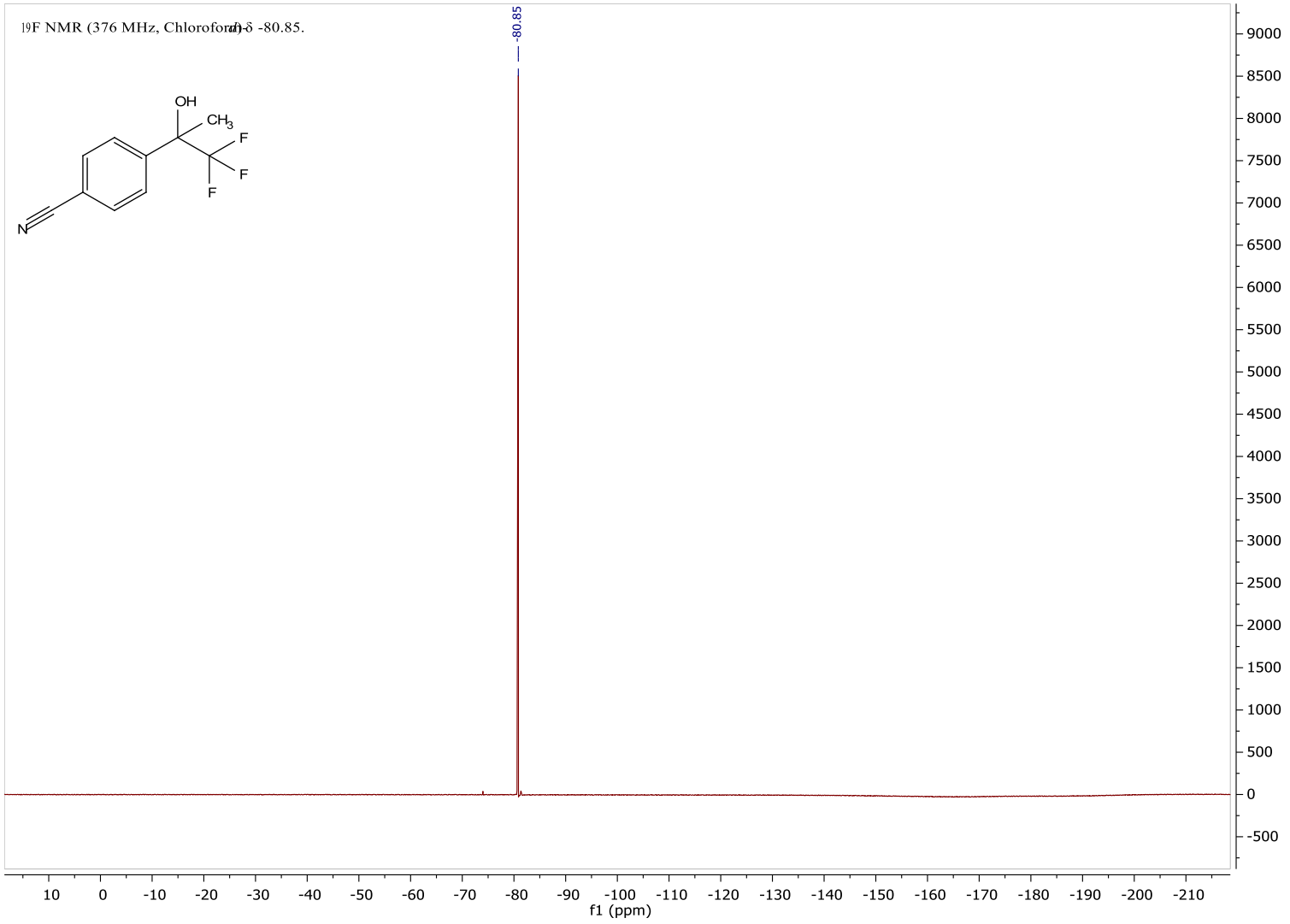
13C NMR (101 MHz, Chloroform-*d*) δ 153.39, 138.81, 129.73, 124.31 (q, *J* = 282.1 Hz), 104.69, 72.98 (q, *J* = 32.0 Hz), 61.00, 56.30.


19F NMR (376 MHz, Chloroform-d) δ -78.21 (d, J = 6.7 Hz).
-78.20
-78.22
OH
F
F
F
O
H3C
H3C
O
O
CH3
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

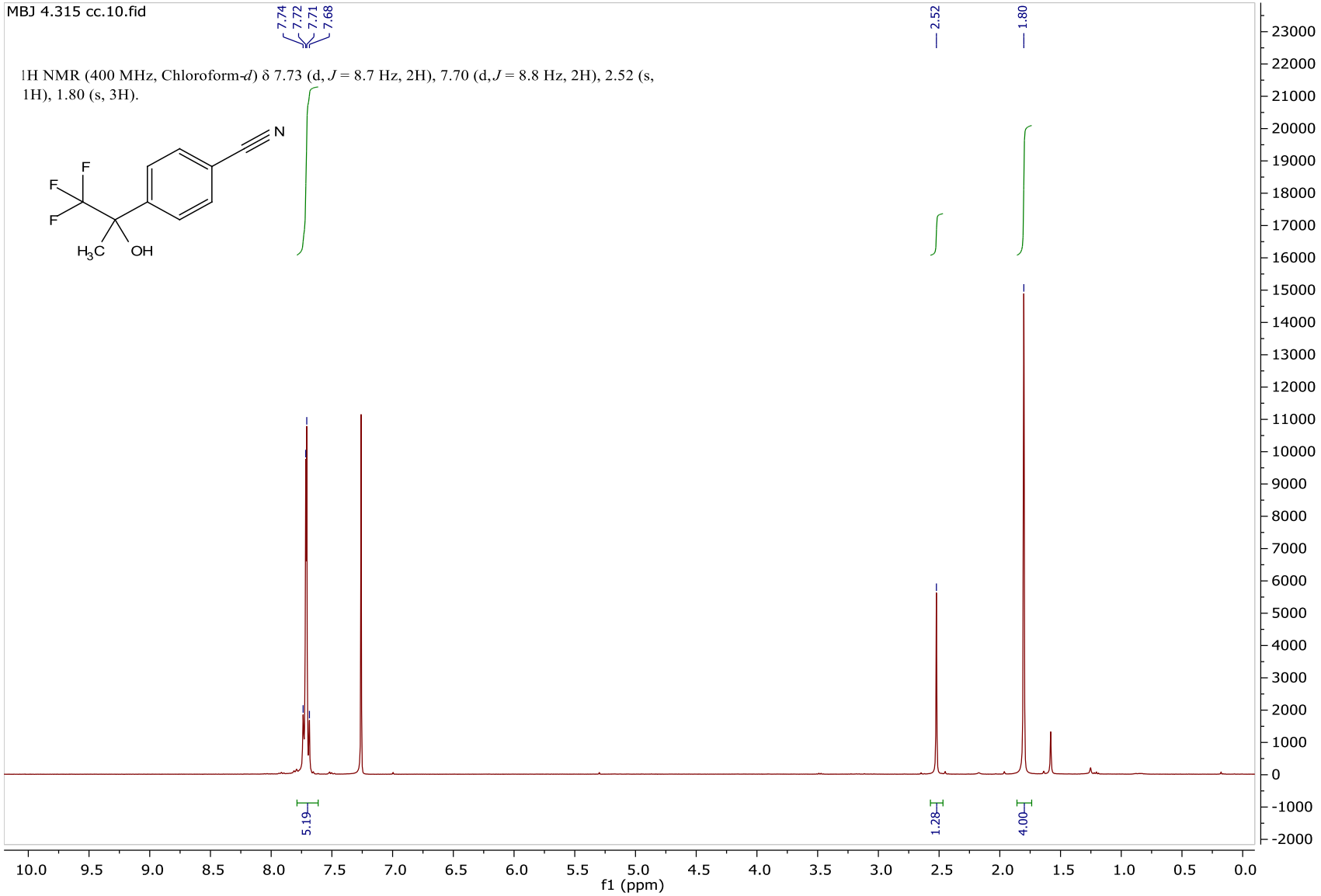
*4-(1,1,1-Trifluoro-2-hydroxypropan-2-yl)benzonitrile (**21**).*

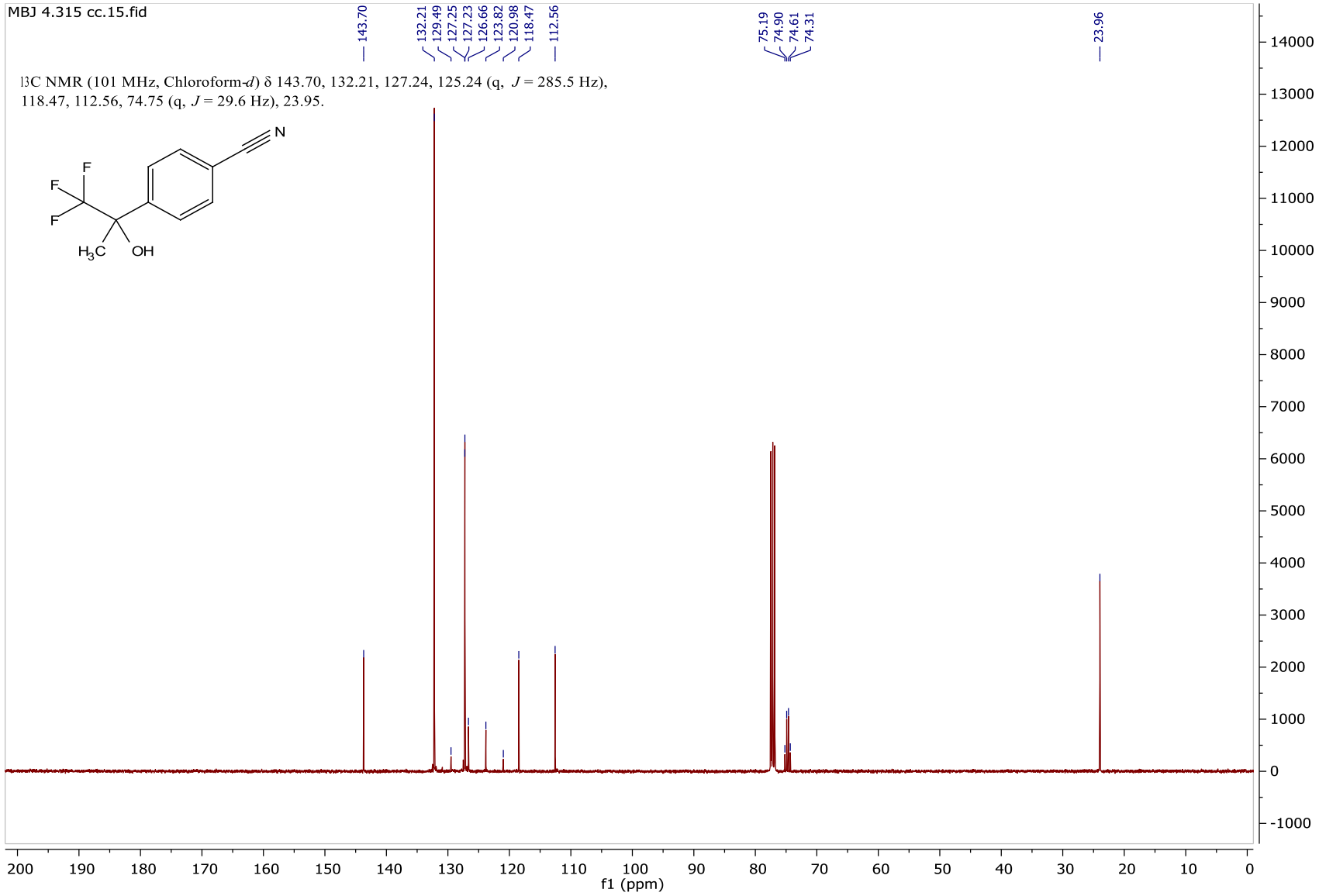


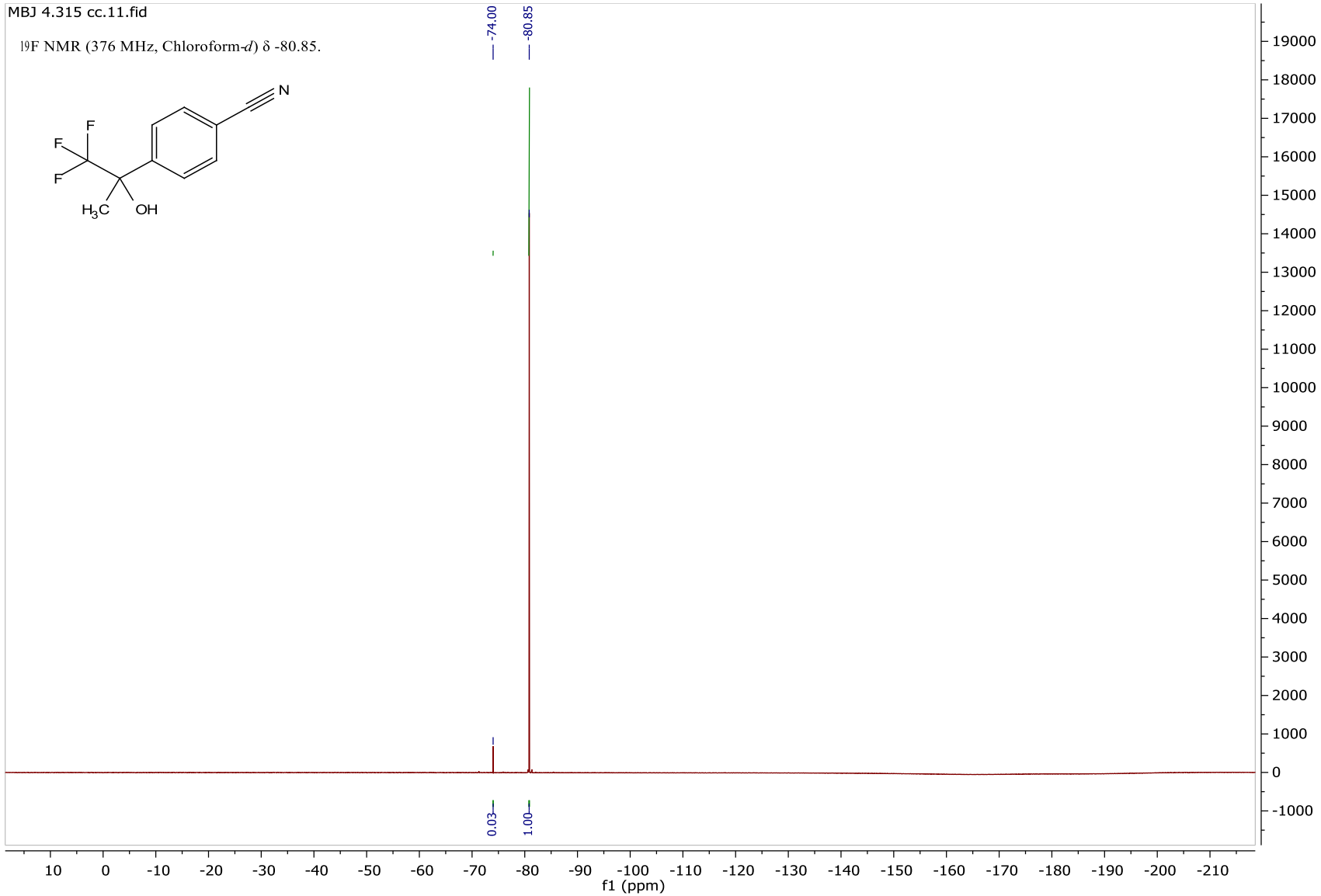

143.46
132.24
129.48
127.22
126.64
123.81
120.97
118.48
112.78
75.25
74.96
74.66
74.37
24.09
13C NMR (101 MHz, Chloroform-d) δ 143.46, 132.24, 127.22, 125.22 (q, J = 285.5 Hz), 118.48, 112.78, 74.81 (q, J = 29.6 Hz), 24.09.
OH
CH3
F
F
F
N
f1 (ppm)


19F NMR (376 MHz, Chloroform-d) δ -80.85.
-80.85
OH
CH3
F
F
F
N
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

*4-(1,1,1-Trifluoro-2-hydroxypropan-2-yl)benzonitrile (**21, Scale-out experiment**)*




MBJ 4.315 cc.15.fid
143.70
132.21
129.49
127.25
127.23
126.66
123.82
120.98
118.47
112.56
75.19
74.90
74.61
74.31
23.96
13C NMR (101 MHz, Chloroform-d) δ 143.70, 132.21, 127.24, 125.24 (q, J = 285.5 Hz), 118.47, 112.56, 74.75 (q, J = 29.6 Hz), 23.95.
N
F
F
F
H3C
OH
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MBJ 4.315 cc.11.fid
19F NMR (376 MHz, Chloroform-d) δ -80.85.
-74.00
-80.85
F
F
F
H3C
OH
N
0.03
1.00
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)