

Supporting Information

Synthesis of ^{18}F -Difluoromethylarenes Using Aryl Boronic Acids, Ethyl bromofluoroacetate and [^{18}F]Fluoride

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S1: General Information

All chemicals purchased from commercial sources were used without further purification prior to use. All NMR spectra were recorded at a temperature of 298.15 K on Bruker AV400, or AV500 spectrometers. Appropriate deuterated solvents were used as an internal reference depending on the compound measured. All corresponding compound peaks were referenced to the residual solvent peak and reported in parts per million (ppm) using the Bruker internal referencing procedure (edlock). ^{19}F NMR spectral peaks were referenced to CFCl_3 . All coupling constants are denoted as J and reported in Hz. The following abbreviations were used to define peak multiplicities s = singlet, d = doublet, t = triplet, q = quartet, pent = pentet, sept = septet, br = broad, m = multiplet. All NMR spectra were processed using Mestrenova 11.0 software. Mass spectra were recorded on Micromass GCT (CI) or Autospec-oaTof instruments. IR spectra were recorded as thin films on Bruker Tensor 27 FT-IR spectrometer. IR absorption are reported in wavenumbers (cm^{-1}). All reactions which required anhydrous conditions were carried out in flame-dried glassware under an inert atmosphere of nitrogen or argon. When dry solvents were used these were purified *a priori* on an alumina column using standard procedures. All reactions were monitored by TLC using Merck Kieselgel 60 F254 plates. High resolution mass spectra (HRMS, m/z) were recorded on a Bruker MicroTOF spectrometer using negative or positive electrospray ionization (ESI). Melting point measurements were recorded using a Griffin melting point apparatus.

S2: Optimisation of the Cu-catalysed cross coupling reaction

General Screening Procedure:

To a 4 mL vial containing a magnetic stir bar was added ligand (if solid), boronic acid, copper source and base. The vial was then evacuated and refilled with N₂ three times. Solvent (0.5 mL) and ligand (if liquid) were then added before heating the reaction mixture to 100 °C and stirring for 18 hours. The resulting solution was cooled to 0 °C before 0.1 mmol of PhCF₃ was added as an internal standard, the corresponding sample was then diluted with CDCl₃. Yields were calculated by quantitative ¹⁹F NMR and referenced to PhCF₃. **Note:** All screening reactions were run on a 0.1 mmol scale, isolations were performed on 0.3 mmol scale and in some cases scaled up to illustrate scalability.

Table 1. Optimisation of Cu-catalysed cross-coupling of (hetero)aryl boronic acids with ethyl 2-bromo-2-fluoroacetate towards 2-fluoro-2-(hetero)arylacetic acids.

Reaction scheme: Phenylboronic acid (**6a**) reacts with BrCFHCO₂Et in the presence of Cu/L (20 mol %), Cs₂CO₃ in toluene at 100 °C for 18 h to form intermediate **7a** (R = Et) or **8a** (R = H). Intermediate **7a** is then converted to **8a** using K₂CO₃ (10 equiv.) in MeOH/H₂O at r.t. for 5 h.

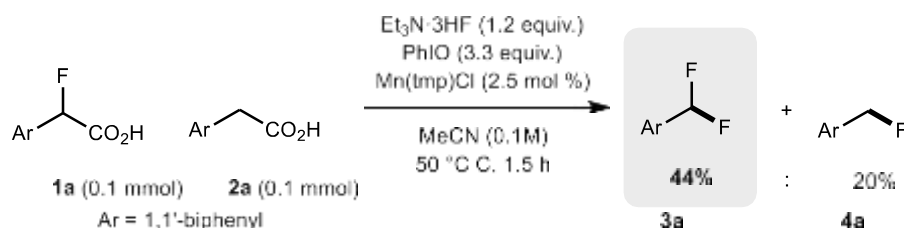
Chemical structures of ligands: **L1** (1,10-phenanthroline), **L2** (2,2'-bipyridine), and **L3** (tris(4-tert-butylphenyl)amine derivative).

Entry	Solvent	Cu-Source	Ligand	Product	Yield ^a
1 ^b	Dioxane (0.2 M)	CuI	L1	7a	7%
2 ^b	Dioxane (0.2 M)	CuI	L2	7a	58%
3	Toluene (0.2 M)	CuI	L3	7a	63%
4 ^c	Toluene (0.4 M)	CuI	L3	7a	82% ^d
5 ^c	Toluene (0.4 M)	CuI	L3	8a	75% ^{d,e}
6 ^c	Toluene (0.4 M)	CuI	-	7a	0%
7 ^c	Toluene (0.4 M)	-	-	7a	0%
8 ^c	Toluene (0.4 M)	CuCl ₂	L2	7a	0%
9 ^c	DMF or DMSO (0.2 M)	CuI	L3	7a	0%

Screening reactions performed on 0.1 mmol scale. ^aYield determined by ¹⁹F-NMR using PhCF₃ as internal standard. ^bReactions with 2 equiv. of **6a** and 1 equiv. of 2-bromo-2-fluoroacetate. ^cReactions with 1 equiv. of **6a** and 2 equiv. of 2-bromo-2-fluoroacetate ^dYield of isolated product. ^eOne-pot procedure.

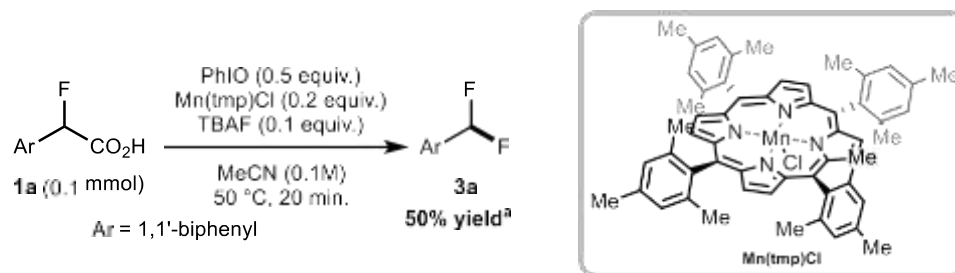
S3: Preliminary Fluorodecarboxylation Experiments

A. Competition studies evaluating the effect of fluorine substitution on fluorodecarboxylation.



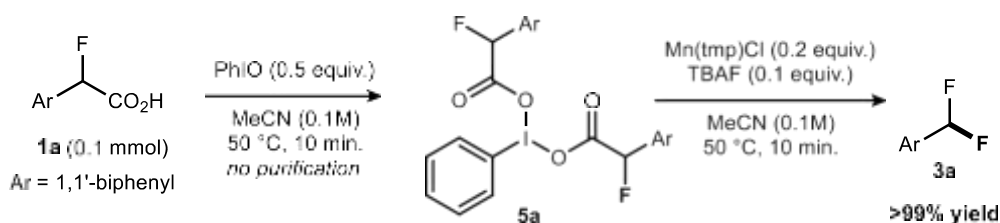
An oven-dried, 5 mL Schlenk flask equipped with a stir bar was placed under an atmosphere of N_2 . $\text{Mn}(\text{tmp})\text{Cl}$ Catalyst (2.2 mg, 0.0025 mmol, 2.5 mol%), 2-([1,1'-biphenyl]-4-yl)-2-fluoroacetic acid (23.0 mg, 0.1 mmol), 2-([1,1'-biphenyl]-4-yl)acetic acid (21.2 mg, 0.1 mmol, 1 equiv.), $\text{Et}_3\text{N}\cdot 3\text{HF}$ (200 μL , 0.12 mmol, 1.2 equiv.) were then added, followed by 1.0 mL of MeCN. The reaction mixture was then heated to 50°C . Under a stream of N_2 , iodosylbenzene (73 mg, 0.33 mmol, 3.3 equiv.) was added slowly to the reaction mixture in solid form over a period of 1.5 hours. After the addition of iodosylbenzene, the solution was cooled to r.t, 0.1 mmol of PhCF_3 was added as internal standard and conversion was measured by ^{19}F NMR.

B. Reaction with sub-stoichiometric fluoride.



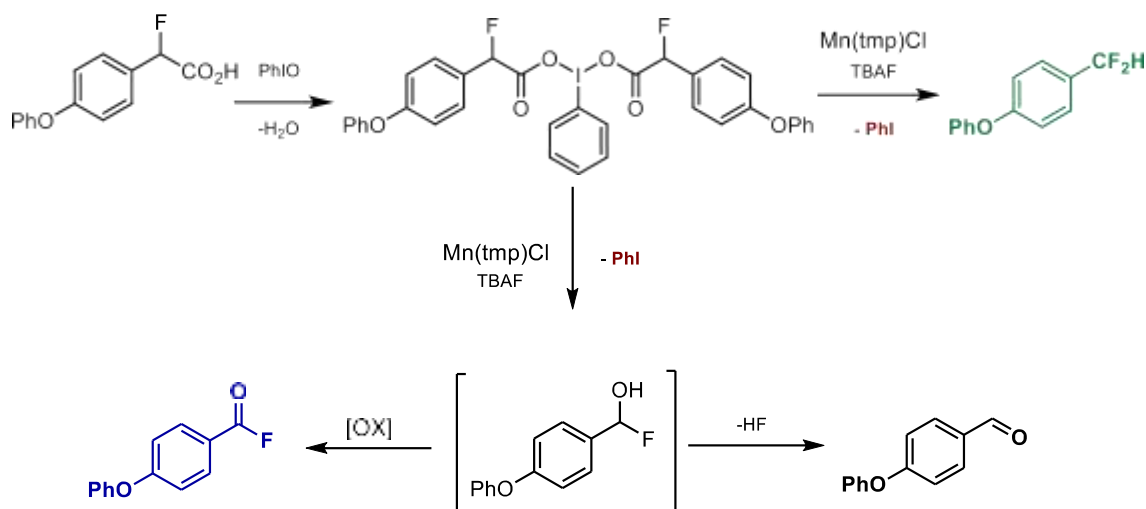
An oven-dried, 5 mL Schlenk flask equipped with a stir bar was placed under an atmosphere of N₂. Mn(tmp)Cl Catalyst (2.0 mg, 0.0020 mmol, 2 mol%), 2-([1,1'-biphenyl]-4-yl)-2-fluoroacetic acid, (23.0 mg, 0.1 mmol) TBAF (1M in THF) (10 μ L, 0.01 mmol, 0.1 equiv.) were then added, followed by 1.0 mL of MeCN. The reaction mixture was then heated to 50 °C. Under a stream of N₂, iodosylbenzene (11.1 mg, 0.05 mmol, 0.5 equiv.) was added slowly to the reaction mixture in solid form over a period of 20 minutes. After the addition of iodosylbenzene, the solution was cooled to r.t, diluted with H₂O (5 mL) and extracted with EtOAc (3 x 5 mL). The organic extracts was dried over MgSO₄ and concentrated under vacuum, prior to silica gel column chromatography.

C. Reaction of iodine(III) complex 5a with sub-stoichiometric fluoride.



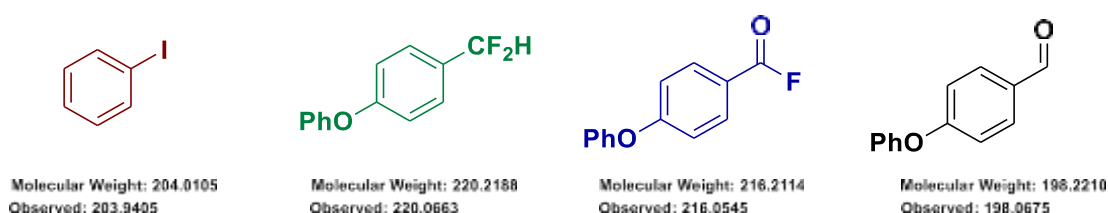
2-([1,1'-biphenyl]-4-yl)-2-fluoroacetic acid (0.2 mmol, 10 equiv.), PhIO (0.1 mmol, 5 equiv.) were added to a 4 mL vial containing a stir magnetic stir bar. *d*₃-CH₃CN (2 mL) was then added to the reaction mixture and the mixture was stirred for 10 minutes at 50 °C. The solvent removed under vacuum. The residue was redissolved in *d*₃-CH₃CN (2 mL). Mn(tmp)Cl (0.04 mmol, 2 equiv.) and TBAF (0.02 mmol, 1 equiv.) were then added to the reaction mixture, which was subsequently stirred for a further 10 minutes before cooling to 0 °C. 0.1 mmol of PhCF₃ was then added as internal standard. The yield was determined by quantitative ¹⁹F NMR (99 %, based on TBAF).

S4: GC-Impurity Analysis of Manganese-Mediated Decarboxylative Fluorination



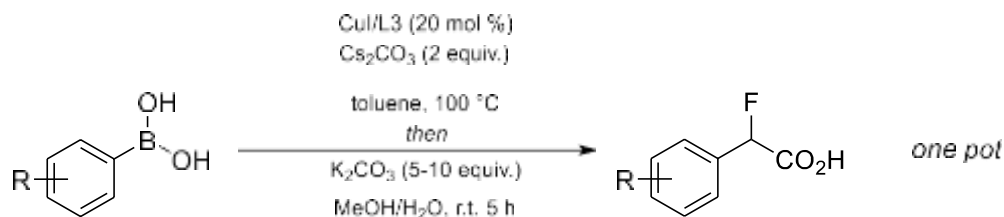
Scheme SI-1: GC-MS impurity analysis of manganese-mediated decarboxylative fluorination. For competitive hydroxylation in Manganese catalysed C-H fluorination see reference.¹

TBAF (1 mmol, 1 equiv., 1.0 M in THF) and anhydrous CH₃CN (2 mL) were added to a vial containing a magnetic stir bar. 2-fluoro-2-(4-phenoxyphenyl)acetic acid (1 mmol, 10 equiv.) and PhIO (5 mmol, 5 equiv.) were added to the solution (Note: PhIO dissolves as it reacts with 2-fluoro-2-(4-phenoxyphenyl)acetic acid). The mixture was stirred for 2 minutes at 50 °C before Mn(tmp)Cl (2 mmol, 2 equiv.) was added to the solution. The mixture was stirred for another 18 minutes at 50 °C before it was cooled to r.t and analysed by GC-MS (LRMS) to obtain an impurity profile, the products obtained are outlined (**Scheme SI-1**).



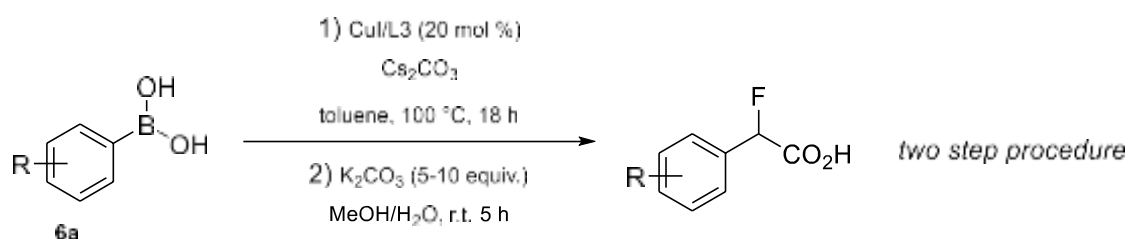
S5: Synthetic Procedures and Characterisation of Compounds

General Procedure (GP) 1: Synthesis of α -aryl- α -fluoroacetic acids.



To a flame-dried pear-shaped round bottomed flask were added CuI (20 mol%), 4,4',4''-Tri-*tert*-butyl-2,2':6',2''-terpyridine (20 mol%), boronic acid (1 equiv.) and Cs₂CO₃ (2 equiv.), followed by argon degassed toluene (1.5 mL). The reaction mixture is stirred for 18 hours at 100 °C. The reaction mixture is cooled to r.t, solvent removed under reduced pressure. The resulting suspension was then dissolved in a 2:1 MeOH and aqueous K₂CO₃ (10 equiv.) mixture before it was left to stir at r.t until all the ester had been consumed (determined by TLC). MeOH was then removed under reduced pressure. The aqueous suspension was then washed with Et₂O (3 x 10 mL), acidified using HCl (5 M) to pH = 2. The aqueous layer was then extracted with Et₂O (3 x 10 mL) and washed with Brine (2 x 10 mL). The organic extracts were then dried over MgSO₄ and concentrated under vacuum and washed with pentane, resulting in an off-white solid. The resulting crude 2-fluoro-2-phenylacetic acids were then subjected to column chromatography (gradient of hexane/ethyl acetate with acetic acid (1%) to ethyl acetate/MeOH with acetic acid (1%)). *Note: Alternatively, the α -(hetero)aryl- α -fluoroacetates can be purified via column chromatography and then hydrolysed without subsequent column chromatography of the carboxylic acid (GP 2).*

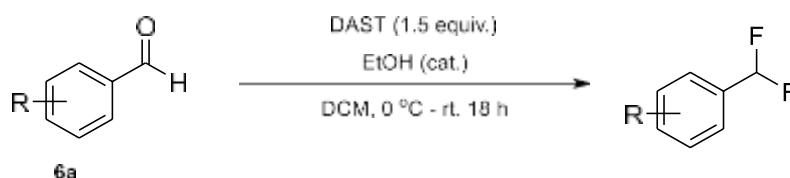
General Procedure (GP) 2: Synthesis of α -(hetero)aryl- α -fluoroacetate and subsequent hydrolysis



To a flame-dried pear-shaped round bottomed flask were added CuI (20 mol%), 4,4',4''-Tri-*tert*-butyl-2,2':6',2''-terpyridine (20 mol%), boronic acid (1 equiv.) and Cs₂CO₃ (2 equiv.).

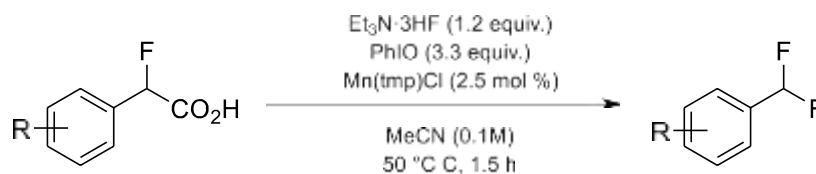
followed by argon degassed toluene (1.5 mL). The reaction mixture is stirred for 18 hours at 100 °C. The mixture is cooled to r.t, solvent removed under reduced pressure. The residue is then diluted with EtOAc and filtered through a plug of celite. EtOAc is then removed under reduced pressure. The resulting oil is purified by silica gel chromatography (EtOAc/Hexane), resulting in a clear colourless oil. This oil was then dissolved in a 2:1 MeOH and aqueous K₂CO₃ (5 equiv.) mixture before it was left to stir at r.t until all the ester had been consumed (determined by TLC). The resulting mixture was then acidified using HCl (5 M) to pH = 2. The aqueous layer was then extracted with Et₂O (3 x 10 mL) and washed with Brine (2 x 10 mL). The organic extracts were dried using MgSO₄ and were then concentrated under vacuum and washed with pentane.

General Procedure (GP) 3: Synthesis of (difluoromethyl)arenes reference compounds



A flame-dried two-necked round-bottomed flask was charged with a stir-magnetic stir bar and a starting material (if solid). To this flask was added anhydrous DCM and a drop of EtOH. The resulting mixture was cooled to 0 °C and DAST (1.5 equiv.) was added dropwise. The resulting mixture was stirred at 0 °C for a further 10 minutes before it was allowed to warm to r.t. The resulting reaction mixture was stirred until TLC showed all starting material had been consumed. The reaction mixture was then quenched with NaHCO₃ until gas evolution stopped and then purified by column chromatography (eluent: *n*-pentane/DCM). *Note: electron rich title compounds such as 1-(difluoromethyl)-2-methoxybenzene and 1-(difluoromethyl)-4-phenoxybenzene are unstable when neat in standard glassware. When removing solvent these compounds should be transferred into a falcon tube and stored in a freezer. In case of decomposition, the compound will turn deep purple, but can be recovered if it is passed through a plug of silica.*

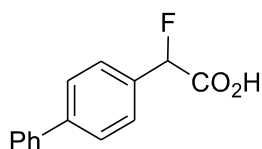
General Procedure (GP) 4: Synthesis of (difluoromethyl)arenes reference compounds



An oven-dried, 5 mL Schlenk flask equipped with a stir bar was placed under an atmosphere of N_2 . Mn(tmp)Cl Catalyst (2.5 mol%) substrate (0.1 mmol) and DCE were then added, followed by $\text{Et}_3\text{N} \cdot 3\text{HF}$ (1.2 equiv.). The reaction mixture was then heated to 50°C . Under a stream of N_2 , iodosylbenzene (3.3 equiv.) was added slowly to the reaction mixture in solid form over a period of 1.5 hours. After the addition of iodosylbenzene, the reaction was stirred until completion.

Synthesis of α -aryl- α -fluoroacetic acids

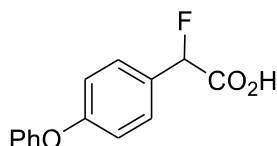
2-([1,1'-Biphenyl]-4-yl)-2-fluoroacetic acid²



The title compound was prepared following GP1 using [1,1'-biphenyl]-4-ylboronic acid (59.4 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μL , 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (51.8 mg, 75% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 75%). $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 7.74 (d, J = 7.8 Hz, 2H), 7.70 – 7.66 (m, 2H), 7.56 – 7.52 (m, 2H), 7.48 (dd, J = 8.4, 6.9 Hz, 2H), 7.42 – 7.37 (m, 1H), 6.04 (d, J = 47.5 Hz, 1H). $^{13}\text{C NMR}$ (101 MHz, $\text{DMSO}-d_6$) δ 170.2 (d, J = 27.4 Hz), 141.7 (d, J = 2.3 Hz), 140.0, 134.6 (d, J = 19.6 Hz), 129.5, 128.3, 128.0 (d, J = 6.0 Hz), 127.5, 127.3, 89.8 (d, J = 183.2 Hz); $^{19}\text{F NMR}$ (376 MHz, $\text{DMSO}-d_6$) δ -175.73 (d, J = 47.5 Hz). The physical data were identical in all respects to those previously reported.²

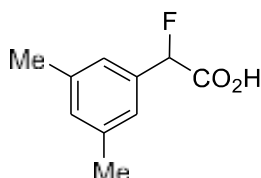
2-Fluoro-2-(4-phenoxyphenyl)acetic acid



The title compound was prepared following General Procedure GP1 using (4-phenoxyphenyl)boronic acid (64.2 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (51.0 mg, 69% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 69%). **Mp:** 86 – 88 °C; **^1H NMR** (400 MHz, CDCl_3) δ : 7.45 (d, J = 9.4 Hz, 1H), 7.42 – 7.34 (m, 2H), 7.23 – 7.12 (m, 1H), 7.10 – 6.99 (m, 5H), 5.82 (d, J = 47.4 Hz, 1H); **^{13}C NMR** (101 MHz, CDCl_3) δ : 173.45 (d, J = 28.6 Hz), 159.25 (d, J = 2.4 Hz), 156.33, 130.08, 128.72 (d, J = 5.6 Hz), 127.74, 124.22, 119.76, 118.69, 88.59 (d, J = 186.4 Hz); **^{19}F NMR** (376 MHz, CDCl_3) δ : -177.21 (d, J = 47.7 Hz); Found, 245.06156; **IR** (film, cm^{-1}) ν 3038, 2917, 1768, 1589, 1243; **HRMS** (ESI) m/z calculated for $\text{C}_{14}\text{H}_{10}\text{FO}_3$ [$\text{M} - \text{H}$] $^-$ 245.06195, found, 245.06156.

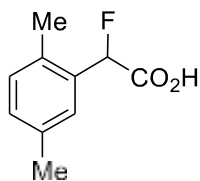
2-(3,5-Dimethylphenyl)-2-fluoroacetic acid



The title compound was prepared following General Procedure GP1 using (3,5-dimethylphenyl)boronic acid (45.0 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (34.4 mg, 63% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 63%). **Mp:** 68 – 70 °C; **^1H NMR** (400 MHz, CDCl_3) δ : 7.04 – 6.96 (m, 3H), 5.67 (d, 1H, J = 48.9 Hz), 2.26 (s, 6H). **^{13}C NMR** (101 MHz, CDCl_3) δ : 173.37 (d, J = 27.8 Hz), 138.70, 133.21 (d, J = 20.3 Hz), 131.65 (d, J = 2.4 Hz), 124.50 (d, J = 5.9 Hz), 88.99 (d, J = 186.0 Hz), 21.23. **^{19}F NMR** (376 MHz, CDCl_3) δ : -179.17 (d, J = 47.4 Hz). **IR** (film, cm^{-1}) ν . 2919, 2166, 1725, 1066. **HRMS** (ESI) m/z calculated for $\text{C}_{10}\text{H}_{10}\text{FO}_2$ [$\text{M} - \text{H}$] $^-$ 181.06703, found, 181.06673.

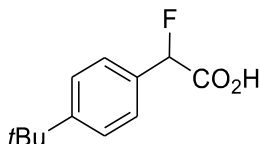
2-(2,5-Dimethylphenyl)-2-fluoroacetic acid



The title compound was prepared following General Procedure GP1 (3-iodophenyl)boronic acid (74.4 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol%). The title compound (42.0 mg, 52% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 52%). **Mp:** 85 – 88 °C; **^1H NMR** (400 MHz, CDCl_3) δ : 7.22 (d, 1H, J = 10.9 Hz), 7.10 (s, 2H), 5.98 (d, 1H, J = 47.2 Hz), 2.38 (s, 3H), 2.31 (s, 3H); **^{13}C NMR** (101 MHz, CDCl_3) δ : 174.49 (d, J = 28.7 Hz), 136.13, 133.41 (d, J = 3.9 Hz), 131.68 (d, J = 19.1 Hz), 130.93, 130.72 (d, J = 2.5 Hz), 127.76 (d, J = 6.7 Hz), 86.64 (d, J = 185.6 Hz), 20.88, 18.68; **^{19}F NMR** (376 MHz, CDCl_3) δ : -180.02 (d, J = 47.2 Hz); **IR** (film, cm^{-1}) ν : 3024, 2929, 2845, 1708, 1243; **HRMS** (ESI) m/z calculated for $\text{C}_{10}\text{H}_{10}\text{FO}_2$ [$\text{M} - \text{H}$] $^-$ 181.06703, found, 181.06680.

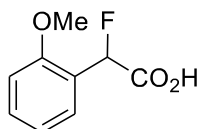
2-(4-(*tert*-Butyl)phenyl)-2-fluoroacetic acid³



The title compound was prepared following General Procedure GP1 using (4-(*tert*-butyl)phenyl)boronic acid (53.4 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (44.2 mg, 70% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 70%). **^1H NMR** (400 MHz, CDCl_3) δ : 7.41 – 7.29 (m, 4H), 5.73 (d, J = 47.9 Hz, 1H), 1.25 (s, 9H); **^{13}C NMR** (101 MHz, CDCl_3) δ : 173.9 (d, J = 27.8 Hz), 153.3 (d, J = 2.0 Hz), 130.4 (d, J = 20.5 Hz), 126.6 (d, J = 5.7 Hz), 125.9, 88.7 (d, J = 185.4 Hz), 34.8, 31.2; **^{19}F NMR** (376 MHz, CDCl_3) δ : -179.1 (d, J = 48.2 Hz). The physical data were identical in all respects to those previously reported.³

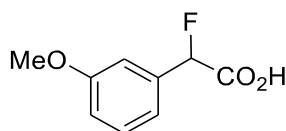
2-Fluoro-2-(2-methoxyphenyl)acetic acid³



The title compound was prepared following General Procedure GP1 using (2-methoxyphenyl)boronic acid (45.6 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol%). The title compound (38.1 mg, 30% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 30%). ¹H NMR (400 MHz, CDCl₃) δ : 7.36 (t, *J* = 7.8 Hz, 1H), 7.05 (m, 1H), 7.02 (m, 1H), 6.99-6.94 (m, 1H), 5.84 (d, *J* = 46.9 Hz, 1H), 3.88 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 173.66 (d, *J* = 28.8 Hz), 157.64 (d, *J* = 3.0 Hz), 132.17 (d, *J* = 2.8 Hz), 129.80 (d, *J* = 5.3 Hz), 122.62 (d, *J* = 19.2 Hz), 121.47 (d, *J* = 1.6 Hz), 111.81 (d, *J* = 1.0 Hz), 85.31 (d, *J* = 183.7 Hz), 56.27; ¹⁹F NMR (376 MHz, CDCl₃) δ : -178.49 (d, *J* = 46.4 Hz). The physical data were identical in all respects to those previously reported.³

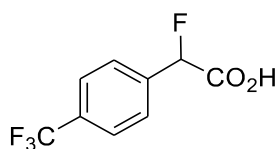
1-(1-Fluoro-2-hydroperoxy-2l2-ethyl)-3-methoxybenzene²



The title compound was prepared following General Procedure GP1 using (3-methoxyphenyl)boronic acid (45.6 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (32.6 mg, 56% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 56%). ¹H NMR (400 MHz, CDCl₃) δ : 7.52 (bs, 1H), 7.30 – 7.21 (m, 1H), 7.02 – 6.91 (m, 2H), 6.88 (ddt, *J* = 8.3, 2.3, 1.0 Hz, 1H), 5.72 (d, *J* = 47.9 Hz, 1H), 3.75 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 173.6 (d, *J* = 27.5 Hz), 159.9, 134.8 (d, *J* = 20.4 Hz), 130.00, 118.9 (d, *J* = 6.2 Hz), 115.7 (d, *J* = 1.4 Hz), 111.8 (d, *J* = 6.3 Hz), 88.6 (d, *J* = 186.8 Hz), 55.3; ¹⁹F NMR (376 MHz, CDCl₃) δ -181.19 (d, *J* = 48.2 Hz). The physical data were identical in all respects to those previously reported.²

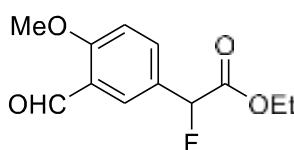
1-(1-Fluoro-2-hydroperoxy-2l2-ethyl)-4-(trifluoromethyl)benzene



The title compound was prepared following General Procedure GP1 using (4-(trifluoromethyl)phenyl)boronic acid (57.0 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (40.0 mg, 60% yield) was isolated as a yellow solid.

Physical appearance: Yellow solid (yield: 60%). **Mp:** 80 – 83 °C; **^1H NMR** (400 MHz, CDCl_3) δ : 7.66 – 7.51 (m, 4H), 5.83 (d, J = 47.1 Hz, 1H); **^{13}C NMR** (101 MHz, CDCl_3) δ : 173.2 (d, J = 27.3 Hz), 133.5 – 131.1 (m), 127.7, 126.7 (d, J = 6.7 Hz), 125.9 (q, J = 3.8 Hz), 88.0 (d, J = 178.2 Hz); **^{19}F NMR** (376 MHz, CDCl_3) δ : -62.9 (s), -185.2 (d, J = 47.2 Hz); **IR** (neat, cm^{-1}) ν 2853, 1739, 1418, 1321, 1119, 1066. **HRMS** (ESI) m/z calculated for $\text{C}_9\text{H}_5\text{F}_4\text{O}_2$ $[\text{M} - \text{H}]^-$, 221.02312. found, 221.02290.

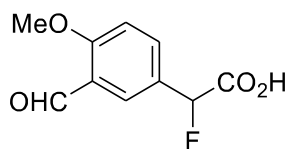
Ethyl 2-fluoro-2-(3-formyl-4-methoxyphenyl)acetate



The title compound was prepared following General Procedure GP2 (3-formyl-4-methoxyphenyl)boronic acid (111.1 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol%).

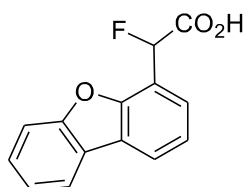
Physical appearance: Colourless Oil. **^1H NMR** (400 MHz, CDCl_3) δ 10.45 (s, 1H), 7.91 (t, J = 2.0 Hz, 1H), 7.67 (ddd, J = 8.7, 2.5, 1.0 Hz, 1H), 7.05 (d, J = 8.6 Hz, 1H), 5.74 (d, J = 47.5 Hz, 1H), 4.33 – 4.16 (m, 2H), 3.96 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl_3) δ 188.99, 168.25 (d, J = 27.9 Hz), 162.51 (d, J = 2.0 Hz), 134.05 (d, J = 5.4 Hz), 127.48 (d, J = 5.7 Hz), 126.84 (d, J = 21.5 Hz), 124.73, 112.29, 88.53 (d, J = 185.8 Hz), 61.97, 55.93, 14.04. **^{19}F NMR** (376 MHz, CDCl_3) δ -177.89 (d, J = 47.6 Hz). **IR** (neat, cm^{-1}) ν 2921, 2159, 1978, 1758, 1644. **HRMS** (ESI) m/z calculated for $\text{C}_{12}\text{H}_{14}\text{FO}_4$ $[\text{M} + \text{H}]^+$, 241.0876, found, 241.0875.

2-Fluoro-2-(3-formyl-4-methoxyphenyl)acetic acid



Physical appearance: yellow solid (yield: 53% based on two steps). **Mp:** Decomposes between 120 – 150 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.61 (s, 1H), 7.39 – 7.30 (m, 1H), 7.12 – 6.92 (m, 3H), 5.80 (d, *J* = 47.5 Hz, 1H), 3.83 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 173.58 (d, *J* = 27.9 Hz), 159.89, 134.77 (d, *J* = 20.5 Hz), 130.00, 118.91 (d, *J* = 6.3 Hz), 115.71 (d, *J* = 2.0 Hz), 111.84 (d, *J* = 6.6 Hz), 88.67 (d, *J* = 187.2 Hz), 55.37; **¹⁹F NMR** (376 MHz, CDCl₃) δ -181.18 (d, *J* = 47.5 Hz); **IR** (film, cm⁻¹) ν. 2918, 2850, 1756, 1643, 1604, 1256, 1223; **HRMS** (ESI) *m/z* calculated for C₁₀H₈FO₄ [*M* – H]⁻, 211.04121, Found, 211.04101.

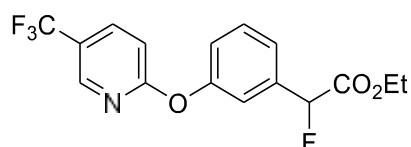
2-(Dibenzo[b,d]furan-4-yl)-2-fluoroacetic acid



The title compound was prepared following General Procedure GP1 using dibenzo[b,d]furan-4-ylboronic acid (63.6 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μL, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (38.1 mg, 52% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 52%). **Mp:** 96 – 98 °C; **¹H NMR** (400 MHz, DMSO-*d*₆) δ: 13.70 (bs, 1H), 8.36 – 8.21 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.69 – 7.43 (m, 4H), 6.51 (d, *J* = 48.2 Hz, 1H); **¹³C NMR** (101 MHz, DMSO-*d*₆) δ: 169.6 (d, *J* = Hz), 155.9, 153.4 (d, *J* = 2.9 Hz), 128.6, 127.4 (d, *J* = 5.0 Hz Hz), 124.8, 123.9 (d, *J* = 0.9 Hz), 123.7, 123.2 (d, *J* = 2.8 Hz) 121.9, 119.6 (d, *J* = 20.1 Hz), 112.3, 85.1 (d, *J* = 179.4 Hz); **¹⁹F NMR** (376 MHz, DMSO-*d*₆) δ: -176.0 (d, *J* = 48.5 Hz); **IR** (film, cm⁻¹) ν 3041, 1734, 1591, 1450, 743; **HRMS** (ESI) *m/z* calculated for C₁₄H₈FO₃ [*M* – H]⁻, 243.04630. Found, 243.04589.

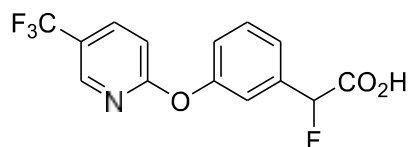
Ethyl 2-fluoro-2-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)acetate



The title compound was prepared following General Procedure GP2 using (3-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)boronic acid (84.9 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%).

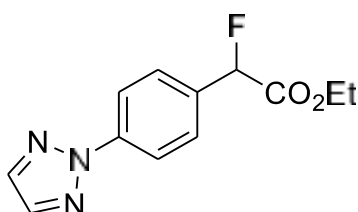
Physical appearance: Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.44 (dq, *J* = 2.8, 0.9 Hz, 1H), 7.96 – 7.91 (m, 1H), 7.48 (td, *J* = 7.9, 0.9 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.32 – 7.29 (m, 1H), 7.21 (ddt, *J* = 8.1, 2.2, 1.0 Hz, 1H), 7.05 (dt, *J* = 8.6, 0.7 Hz, 1H), 5.81 (d, *J* = 47.6 Hz, 1H), 4.34 – 4.18 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 168.09 (d, *J* = 27.0 Hz), 165.39 (d, *J* = 1.0 Hz), 153.39, 145.41 (q, *J* = 4.4 Hz), 136.83 (q, *J* = 3.2 Hz), 136.15 (d, *J* = 20.9 Hz), 124.97, 123.36 (d, *J* = 6.6 Hz), 122.55 (d, *J* = 1.9 Hz), 122.27, 121.86 (q, *J* = 34.3 Hz), 119.56 (d, *J* = 6.8 Hz), 111.57, 88.72 (d, *J* = 187.0 Hz), 62.03, 14.03; ¹⁹F NMR (376 MHz, CDCl₃) δ -61.71, -182.11 (d, *J* = 47.6 Hz); IR (film, cm⁻¹) ν 3005, 1751, 1280, 1126, 1064; HRMS (ESI) *m/z* calculated for C₁₆H₁₄F₄NO₃ [M + H]⁺ 344.09043, Found, 344.09054.

2-Fluoro-2-(3-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)acetic acid



Physical appearance: White Solid (Yield = 70% based on two steps). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.39 (s, 1H), 7.95 (d, *J* = 10.8 Hz, 1H), 7.67 – 7.52 (m, 4H), 6.88 (d, *J* = 8.6 Hz, 1H), 5.89 (d, *J* = 47.9 Hz, 1H), 3.95 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.27 (d, *J* = 27.5 Hz), 164.26, 152.25, 145.91 – 142.06 (m), 136.23 (q, *J* = 3.1 Hz), 134.61 (d, *J* = 20.8 Hz), 129.28, 123.81, 122.60 (d, *J* = 6.4 Hz), 121.77 (d, *J* = 1.7 Hz), 121.34 – 120.82 (m), 118.59 (d, *J* = 6.7 Hz), 110.83, 87.17 (d, *J* = 188.1 Hz), 28.68. ¹⁹F NMR (376 MHz, CDCl₃) δ -61.68 (s) -182.15 (d, *J* = 47.7 Hz); IR (film, cm⁻¹) ν 3735, 2361, 2341, 1748, 1329. HRMS (ESI) *m/z* calculated for C₁₄H₈F₄NO₃ [M – H]⁻, 316.05913. Found, 316.05911.

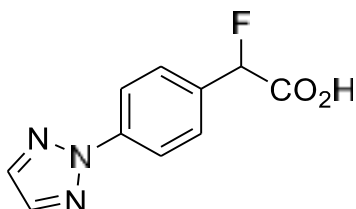
Ethyl 2-(4-(2H-1,2,3-triazol-2-yl)phenyl)-2-fluoroacetate



The title compound was prepared following General Procedure GP2 using (4-(2H-1,2,3-triazol-2-yl)phenyl)boronic acid (56.7 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol %) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol %).

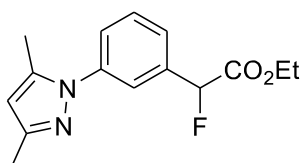
Physical appearance: Colourless oil. **¹H NMR** (400 MHz, Methanol-*d*₄) δ 8.17 – 8.10 (m, 2H), 7.93 (s, 2H), 7.65 – 7.59 (m, 2H), 5.98 (d, *J* = 47.2 Hz, 1H), 4.40 – 4.10 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H). **¹³C NMR** (101 MHz, Methanol-*d*₄) δ 170.00 (d, *J* = 28.0 Hz), 137.32, 135.39 (d, *J* = 20.6 Hz), 129.14 (d, *J* = 6.2 Hz), 120.04, 89.90 (d, *J* = 183.6 Hz), 62.99, 14.31. **¹⁹F NMR** (376 MHz, Methanol-*d*₄) δ -180.95 (d, *J* = 47.2 Hz). **IR** (neat, cm⁻¹) ν 1935, 1556, 1138, 1096; **HRMS** (ESI) *m/z* calculated for C₁₂H₁₃FN₃O₂ [M + H]⁺ for 250.09863, Found, 250.09874.

2-(4-(2H-1,2,3-Triazol-2-yl)phenyl)-2-fluoroacetic acid



Physical appearance: White solid (yield: 40%, based on two steps). **Mp:** 140 – 142 °C; **¹H NMR** (500 MHz, Acetonitrile-*d*₃) δ 8.30 (d, *J* = 8.0 Hz, 2H), 8.09 (s, 2H), 7.82 – 7.75 (m, 2H), 6.12 (d, *J* = 47.2 Hz, 1H); **¹³C NMR** (101 MHz, Methanol-*d*₄) δ 170.41 (d, *J* = 27.4 Hz), 140.35, 135.86, 134.42 (d, *J* = 20.7 Hz), 127.67 (d, *J* = 5.8 Hz), 118.57, 88.45 (d, *J* = 182.8 Hz); **¹⁹F NMR** (470 MHz, Acetonitrile-*d*₃) δ -178.45 (d, *J* = 47.2 Hz); **IR** (neat, cm⁻¹) ν 2849, 1736, 1118, 1066; **HRMS** (ESI) *m/z* calculated for C₁₀H₇FN₃O₂ [M – H]⁻, 220.05278, Found, 220.05232.

Ethyl 2-(3-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)-2-fluoroacetate

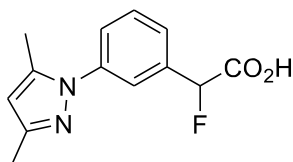


The title compound was prepared following General Procedure GP2 using (3-(3,5-dimethyl-1H-pyrazol-1-yl)phenyl)boronic acid (64.8 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L,

0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol %) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16mg, 20 mol %).

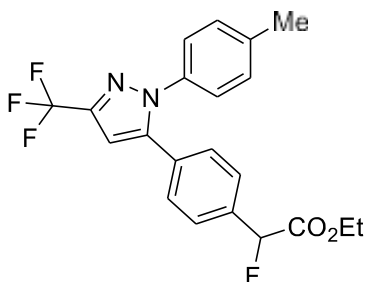
Physical appearance: Colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.56 (dt, *J* = 2.5, 1.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.48 – 7.43 (m, 1H), 6.02 (s, 1H), 5.83 (d, *J* = 47.5 Hz, 1H), 4.33 – 4.17 (m, 2H), 2.34 – 2.28 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 168.53 (d, *J* = 27.2 Hz), 149.78, 140.71, 139.86, 135.71 (d, *J* = 20.7 Hz), 129.92, 125.97 (d, *J* = 1.9 Hz), 125.38 (d, *J* = 6.4 Hz), 123.06 (d, *J* = 6.7 Hz), 107.80, 89.21 (d, *J* = 186.9 Hz), 62.45, 14.45, 13.90, 12.86. ¹⁹F NMR (470 MHz, CDCl₃) δ -181.63 (d, *J* = 47.6 Hz). IR (film, cm⁻¹) ν 1935, 1710, 1201; HRMS (ESI) *m/z* calculated for C₁₅H₁₇FN₂O₂ [M + H]⁺ for 277.13468, Found, 277.13473.

2-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)phenyl)-2-fluoroacetic acid



Physical appearance: White solid (yield: 60%, based on two steps). **Mp:** 122 – 125 °C; ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.61 – 7.53 (m, 3H), 7.51 (d, *J* = 2.6 Hz, 1H), 6.09 (1, 1H), 5.97 (d, *J* = 47.6 Hz, 1H), 2.28 (s, 3H), 2.25 (s, 3H); ¹³C NMR (101 MHz, Methanol-*d*₄) δ 170.18 (d, *J* = 26.8 Hz), 149.30, 140.51, 139.63, 136.58 (d, *J* = 20.7 Hz), 129.38, 126.70 – 125.12 (m), 122.97, 106.80, 88.39 (d, *J* = 183.4 Hz), 11.76, 10.76; ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -181.91 (d, *J* = 47.7 Hz); IR (film, cm⁻¹) ν 2917, 2849, 1745, 1148; HRMS (ESI) *m/z* calculated for C₁₃H₁₄FN₂O₂ [M + H]⁺, 249.10338, Found, 249.10327.

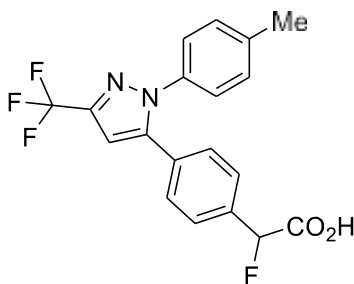
Ethyl 2-fluoro-2-(4-(5-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)acetate



The title compound was prepared following General Procedure GP2 (4-(1-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)phenyl)boronic acid (104 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol%).

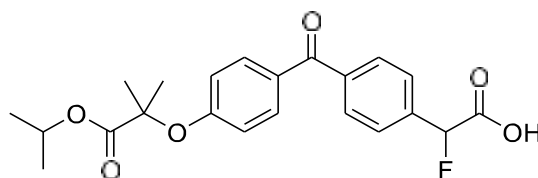
Physical appearance: Colourless Oil. ¹H NMR (500 MHz, CDCl₃) δ 7.52 – 7.47 (m, 2H), 7.42 – 7.37 (m, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.14 – 7.12 (m, 2H), 6.75 (s, 1H), 5.82 (d, *J* = 47.6 Hz, 1H), 4.27 (qq, *J* = 10.8, 7.1 Hz, 2H), 2.39 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 167.99 (d, *J* = 27.2 Hz), 144.92, 144.26 – 142.70 (m), 140.22 (d, *J* = 2.4 Hz), 139.37, 134.30 (d, *J* = 20.9 Hz), 129.53, 128.68, 127.28 (d, *J* = 6.4 Hz), 125.60, 124.69 – 117.40 (m), 105.69 (d, *J* = 2.4 Hz), 88.64 (d, *J* = 186.8 Hz), 62.09, 29.72, 21.32, 14.03; ¹⁹F NMR (470 MHz, CDCl₃) δ -62.33, -181.94 (d, *J* = 48.7 Hz); IR (film, cm⁻¹) ν 2985, 1759, 1235, 1131; HRMS (ESI) *m/z* calculated for C₂₁H₁₉F₄N₂O₂ [M + H]⁺, 407.13772, Found, 407.13719

2-Fluoro-2-(4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)acetic acid



Physical appearance: White solid (yield: 41%, based on two steps). **Mp:** 148 – 152 °C. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.46 – 7.40 (m, 2H), 7.31 – 7.24 (m, 2H), 7.09 – 7.02 (m, 4H), 6.77 (s, 1H), 5.82 (d, *J* = 47.6 Hz, 1H), 2.23 (s, 3H); ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -63.77, -181.72 (d, *J* = 47.9 Hz); ¹³C NMR (101 MHz, Methanol-*d*₄) δ 170.12 (d, *J* = 27.1 Hz), 145.49, -142.98 (q, *J* = 38.5 Hz), 139.96 (d, *J* = 2.3 Hz), 139.38, 135.72 (d, *J* = 20.6 Hz), 129.09, 128.59, 127.23 (d, *J* = 6.2 Hz), 125.92, 125.58, 121.31 (q, *J* = 290.3 Hz), 105.0, 88.30 (d, *J* = 183.4 Hz), 19.86; IR (film, cm⁻¹) ν 2918, 2360, 1748, 1510, 1475, 1456; HRMS (ESI) *m/z* calculated for C₁₉H₁₄F₄N₂O₂ [M + H]⁺, 379.10642, Found, 379.10639.

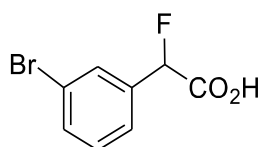
2-Fluoro-2-(4-(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)acetic acid



The title compound was prepared following General Procedure GP2 using 4-(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenylboronic acid (111.1 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol%). The title compound (60.4 mg, 72% yield) was isolated as a brown solid.

Physical appearance: brown solid (yield: 72%). **Mp:** 140 – 142 $^{\circ}\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ : 7.69 (dd, J = 8.4, 4.2 Hz, 4H), 7.52 (d, J = 7.9 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.82 (d, J = 47.5 Hz, 1H), 5.00 (m, 1H), 1.59 (s, 6H), 1.13 (d, J = 6.2 Hz, 6H); **^{13}C NMR** (101 MHz, CDCl_3) δ : 195.41, 173.17, 171.80 (d, J = 28.9 Hz), 160.05, 139.18, 137.31 (d, J = 20.4 Hz), 132.32, 130.09, 129.87, 126.27 (d, J = 6.6 Hz), 117.24, 88.35 (d, J = 188.8 Hz), 79.48, 69.49, 25.36, 21.51; **^{19}F NMR** (376 MHz, CDCl_3) δ : -183.28 (d, J = 47.8 Hz); **IR** (film, cm^{-1}) ν : 2985, 2361, 1718, 1558, 1503, 1252, 1146, 680; **HRMS** (ESI) m/z calculated for $[\text{M} + \text{H}]^+$, 403.15514, Found, 403.15535.

2-(3-Bromophenyl)-2-fluoroacetic acid

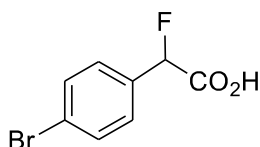


The title compound was prepared following General Procedure GP1 using (3-bromophenyl)boronic acid (60.2 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol%). The title compound (35.0 mg, 58% yield) was isolated as a brown solid.

Physical appearance: Brown Solid (yield: 58%). **Mp:** 81 – 83 $^{\circ}\text{C}$; **^1H NMR** (400 MHz, CDCl_3) δ : 10.10 (bs, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.47 (dd, J = 8.0, 2.0 Hz, 1H), 7.34 (dd, J = 7.8, 1.5 Hz, 1H), 7.21 (t, J = 7.9 Hz, 1H), 5.71 (d, J = Hz, H); **^{13}C NMR** (100 MHz, CDCl_3) δ : 173.7 (d, J = 27.3 Hz), 135.4 (d, J = 21.2 Hz), 133.0 (d, J = 2.1 Hz), 130.5, 129.5 (d, J = 7.1 Hz), 125.1 (d, J = 6.0 Hz), 122.9, 87.3 (d, J = 178.3 Hz); **^{19}F NMR** (376 MHz, CDCl_3) δ -

183.16 (d, $J = 47.1$ Hz); **IR** (film, cm^{-1}) ν 3035, 1759, 1689, 156, 818; **HRMS** (ESI) m/z calculated for $\text{C}_8\text{H}_5\text{BrFO}_2$ $[\text{M} - \text{H}]^-$, 230.94624. Found, 230.94586.

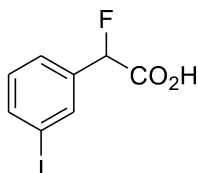
2-(4-Bromophenyl)-2-fluoroacetic acid³



The title compound was prepared following General Procedure GP1 using (4-bromophenyl)boronic acid (60.3 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μL , 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (36.3 mg, 52% yield) was isolated as a brown solid.

Physical appearance: Brown solid (yield: 52%). **^1H NMR** (400 MHz, CDCl_3) δ : 10.44 (bs, 1H), 7.58 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.2$ Hz, 2H), 5.80 (d, $J = 47.2$ Hz, 1H); **^{13}C NMR** (100 MHz, CDCl_3) δ : 173.8 (d, $J = 27.4$ Hz), 132.4 (d, $J = 21.1$ Hz), 132.1, 128.2 (d, $J = 6.1$ Hz), 124.3 (d, $J = 2.9$ Hz), 88.2 (d, $J = 175.4$ Hz); **^{19}F NMR** (376 MHz, CDCl_3) δ -182.3 (d, $J = 47.2$ Hz). The physical data were identical in all respects to those previously reported.³

2-Fluoro-2-(3-iodophenyl)acetic acid

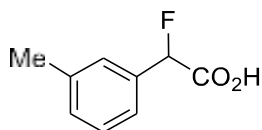


The title compound was prepared following General Procedure GP1 (3-iodophenyl)boronic acid (74.4 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μL , 0.6 mmol), Cs_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (16.6 mg, 20 mol%). The title compound (42.0 mg, 50% yield) was isolated as a white solid.

Physical appearance: White Solid (yield: 50%). **Mp:** 102 – 104 $^\circ\text{C}$; **^1H NMR** (400 MHz, Methanol- d_4) δ 7.83 (s, 1H), 7.77 (d, $J = 8.7$ Hz, 1H), 7.48 (d, $J = 6.8$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 5.83 (d, $J = 47.6$ Hz, 1H). **^{13}C NMR** (101 MHz, Methanol- d_4) δ 171.6 (d, $J = 27.4$ Hz), 139.7, 138.8 (d, $J = 20.6$ Hz), 136.7 (d, $J = 6.4$ Hz), 127.1 (d, $J = 6.1$ Hz), 89.5 (d, $J = 183.2$ Hz); **^{19}F NMR** (376 MHz, Methanol- d_4) δ -181.77 (d, $J = 47.8$ Hz); **IR** (film, cm^{-1}) ν

3021, 2613, 1689, 1766, 1703; **HRMS** (ESI) m/z calculated for $C_8H_5FIO_2 [M - H]^-$ for 278.93237, Found, 278.93228.

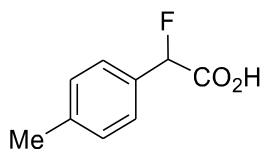
2-Fluoro-2-(*m*-tolyl)acetic acid⁴



The title compound was prepared following General Procedure GP1 using *m*-tolylboronic acid (40.8 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), CS_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (36.3 mg, 74% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 74%). **1H NMR** (400 MHz, $CDCl_3$) δ : 10.16 (bs, 1H), 7.26 – 7.12 (m, 4H), 5.70 (d, J = 48.8 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ : 174.4 (d, J = 28.1 Hz), 138.8, 133.3 (d, J = 20.1 Hz), 130.8 (d, J = 2.4 Hz), 128.8, 127.3 (d, J = 6.1 Hz), 123.9 (d, J = 6.3 Hz), 88.9 (d, J = 186.2 Hz), 21.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -180.3 (d, J = 48.9 Hz). The physical data were identical in all respects to those previously reported.⁴

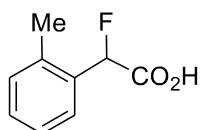
2-Fluoro-4-(*p*-tolyl)acetic acid⁴



The title compound was prepared following General Procedure GP1 using *p*-tolylboronic acid (40.8 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), CS_2CO_3 (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (36.3 mg, 72% yield) was isolated as a white solid.³

Physical appearance: White solid (yield: 72%). **1H NMR** (400 MHz, $CDCl_3$) δ : 7.11 (d, 2H), 7.30 (d, 2H), 5.45 (d, J = 47.6 Hz, 1H), 2.15 (s, 3H); **^{19}F NMR** (376 MHz, $CDCl_3$) δ : 178.4 (d, J = 47.4 Hz); The physical data were identical in all respects to those previously⁴

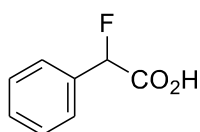
2-Fluoro-2-(*o*-tolyl)acetic acid⁵



The title compound was prepared following General Procedure GP1 using *o*-tolylboronic acid (40.8 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (15.1 mg, 30% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 30%). ¹H NMR (400 MHz, CDCl₃) δ : 7.18-7.28 (m, 4H), 5.48 (d, *J* = 48.2 Hz, 1H), 2.28 (t, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ : 178.8 (d, *J* = 48.4 Hz). The physical data were identical in all respects to those previously reported.⁵

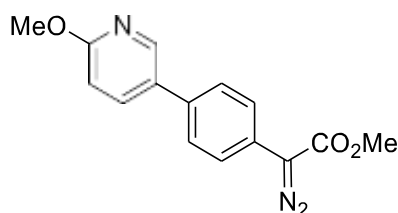
2-Fluoro-2-phenylacetic acid²



The title compound was prepared following General Procedure GP1 using phenylboronic acid (36.6 mg, 0.3 mmol), ethyl bromofluoroacetate (67.2 μ L, 0.6 mmol), Cs₂CO₃ (196 mg, 0.6 mmol), CuI (11.4 mg, 20 mol%) and 4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine (24.1 mg, 20 mol%). The title compound (27.3 mg, 59% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 59%). ¹H NMR (400 MHz, CDCl₃) δ : 8.67 (bs, 1H), 7.46 – 7.31 (m, 5H), 5.75 (d, *J* = Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ : 173.8 (d, *J* = 27.8 Hz), 133.4 (d, *J* = 20.6 Hz), 130.0 (d, *J* = 2.2 Hz), 128.9, 126.7 (d, *J* = 5.9 Hz), 88.8 (d, *J* = 186.8 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -180.8 (d, *J* = 47.5 Hz). The physical data were identical in all respects to those previously reported.²

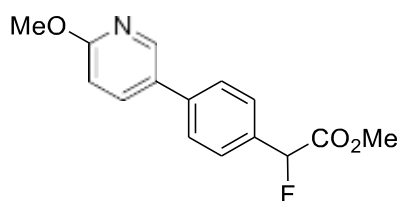
Ethyl 2-diazo-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate



To a mixture of methyl 2-(4-(6-methoxypyridin-3-yl)phenyl)acetate (10 mmol, 1 equiv.) and *p*-ABSA (12 mmol, 1.2 equiv.) in anhydrous MeCN (30 mL), DBU (14 mmol, 1.4 equiv.) was added at 0°C. The reaction mixture was stirred at r.t overnight. Upon the complete consumption of the starting materials, the reaction mixture was diluted with distilled water (20 mL), followed by extraction with Et₂O (3 × 10 mL). After washing with 10% NH₄Cl solution (3×10 mL) and brine (3×10 mL), the combined organic extracts were dried over MgSO₄, concentrated and chromatographed EtOAc:Hexane (10:90) to yield the diazoester.

Physical appearance: Orange solid. **Mp:** 135 – 137 °C; **¹H NMR** (400 MHz, CDCl₃) δ: 8.39 (dd, *J* = 2.7, 0.8 Hz, 1H), 7.79 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.56 (bs, 4H), 6.82 (dd, *J* = 8.6, 0.7 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ: 165.5, 163.7, 144.8, 137.2, 135.4, 129.3, 127.1, 124.5, 124.5, 110.9, 53.6, 52.1. **IR** (film, cm⁻¹) ν 3012, 2951, 2094, 1686, 1160, 815. **HRMS** (ESI) *m/z* calculated for C₁₅H₁₄N₃O₃ [M + H]⁺, 284.10297 Found, 284.10294.

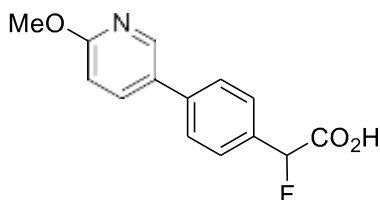
Methyl 2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate



In a 20 mL falcon tube was charged with methyl 2-diazo-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate (0.3 mmol) in 2mL of DCM and cooled to 0°C. HF pyridine (70 %) (0.36 mmol) was then added slowly. The reaction temperature was raised to r.t after gas evolution. The reaction was monitored by TLC until completion. The reaction was then quenched with NaHCO₃ and the organic layer was extracted with DCM (3 x 5 mL). The organic layer was dried over MgSO₄, concentrated and chromatographed EtOAc:Hexane (10:90).

Physical appearance: White solid. **Mp:** 64 – 65 °C; **¹H NMR** (400 MHz, CDCl₃) δ: 8.32 (dd, *J* = 2.6, 0.8 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.54 – 7.43 (m, 4H), 6.76 (dd, *J* = 8.6, 0.7 Hz, 2H), 5.76 (d, *J* = 48.2 Hz, 1H), 3.92 (s, 3H), 3.74 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ: 168.9 (d, *J* = 27.2 Hz), 163.9, 145.1, 139.4 (d, *J* = 3.2 Hz), 137.4, 133.1 (d, *J* = 20.0 Hz), 129.2, 127.3 (d, *J* = 6.2 Hz), 127.1, 111.0, 89.1 (d, *J* = 184.3 Hz), 53.6, 52.8; **¹⁹F NMR** (376 MHz, CDCl₃) δ -179.9 (d, *J* = 48.2 Hz); **IR** (film, cm⁻¹) ν 3014, 2949, 1498, 1195, 822; **HRMS** (ESI) *m/z* calculated for C₁₅H₁₅FNO₃ [M + H]⁺, 276.10305. Found, 276.10293.

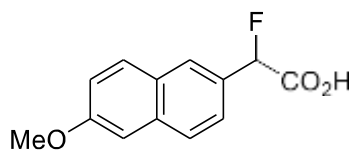
2-Fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetic acid



In a 50 mL round bottom flask, methyl 2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate (5 mmol, 1.0 equiv.) was added to a mixture of MeOH (15 mL, 0.3 M) and 1 M K₂CO₃ aq. (15 mL) and stirred at r.t until TLC showed consumption of starting material. The reaction was then poured into 1 M HCl aq. to acidify to pH 5, and the aqueous phase was extracted with Et₂O (3 × 10 mL), washed with brine (10 mL), dried over MgSO₄. The resulting gum was then washed with pentane, until a white free-flowing white solid formed.

Physical appearance: White solid (yield: 45% (over 3 steps)). **Mp:** 150 – 153 °C; **¹H NMR** (400 MHz, Methanol-*d*₄) δ : 8.44 – 8.38 (m, 1H), 7.97 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 1H), 5.91 (d, *J* = 48.7 Hz, 1H), 3.97 (s, 3H); **¹³C NMR** (100 MHz, Methanol-*d*₄) δ : 170.8 (d, *J* = 27.9 Hz), 163.9, 144.5, 138.7 (d, *J* = 2.1 Hz), 134.3 (d, *J* = 20.1 Hz), 127.2 (d, *J* = 6.1 Hz), 126.5, 110.4, 88.8 (d, *J* = 180.2 Hz), 52.8; **¹⁹F NMR** (376 MHz, Methanol-*d*₄) -179.6 (d, *J* = 47.9 Hz); **IR** (film, cm⁻¹) ν 2360, 1736, 1607, 1041, 825; **HRMS** (ESI) *m/z* calculated for C₁₄H₁₃FNO₃ [M + H]⁺ 262.08740 Found, 262.08731.

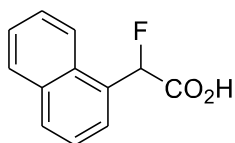
2-Fluoro-2-(6-methoxynaphthalen-2-yl)acetic acid



An oven-dried Schlenk tube containing a magnetic stir bar was charged with Pd(OAc)₂ (5.6 mg, 0.025 mmol, 5 mol%), PPh₃ (26.2 mg, 0.10 mmol, 20 mol%), boronic acid (1.0 mmol, 2.0 equiv.), and K₃PO₄·3 H₂O (400 mg, 1.5 mmol, 3.0 equiv.). The Schlenk tube was sealed with a rubber septum and then evacuated and backfilled with N₂ three times. Toluene (5.0 mL) was added through the septum via syringe and the resulting mixture was stirred at r.t for 5 min. Ethyl *α*-bromo-*α*-fluoroacetate (92.5 mg, 0.50 mmol, 1.0 equiv.) was then added dropwise via syringe. The Schlenk tube was sealed and the mixture was heated at 100 °C with vigorous stirring for 3 h. The mixture was then allowed to cool to r.t and quenched with H₂O (10 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (20 mL), dried with MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel (Pentane–EtOAc, 50:1) to give the title the ester product. The ester was then dissolved in a 2:1 MeOH and aqueous K₂CO₃ (5-10 equiv.) mixture before it was left to stir at r.t until all the ester had been consumed (determined by TLC). The resulting mixture was then acidified using HCl (5 M) to pH = 2. The aqueous layer was then extracted with Et₂O (3 x 20 mL) and washed with Brine (2 x 20 mL). The organic extracts were dried using MgSO₄ and were then concentrated under vacuum and washed with pentane, resulting in the title compound as a white solid.

Physical appearance: White solid (yield: 50% over two steps). **Mp:** 150 – 152 °C; **¹H NMR** (400 MHz, Methanol-*d*₄) δ : 7.78 (t, *J* = 2.0 Hz, 1H), 7.70 (t, *J* = 9.4 Hz, 2H), 7.40 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.16 (d, *J* = 2.5 Hz, 1H), 7.07 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.86 (d, 1H, *J* = 47.8 Hz), 3.82 (s, 3H); **¹³C NMR** (100 MHz, Methanol-*d*₄) δ : 158.58, 135.19 (d, *J* = 1.8 Hz) 130.03 (d, *J* = 20.4 Hz), 129.29, 128.44, 127.12, 126.40 (d, *J* = 6.8 Hz) 123.95 (d, *J* = 5.1 Hz), 119.09, 105.32, 89.35 (d, *J* = 181.3 Hz) 54.39. **¹⁹F NMR** (376 MHz, Methanol-*d*₄) δ : -177.22 (d, *J* = 48.0 Hz); **IR** (film, cm⁻¹) ν : 3157, 1764, 1703, 1606. 1267, 1234, 1051, 1029, 815; **HRMS** (ESI) *m/z* calculated for C₁₃H₁₀FO₃ [M – H]⁻ for 233.06195, Found, 233.06185.

2-Fluoro-2-(naphthalen-1-yl)acetic acid³

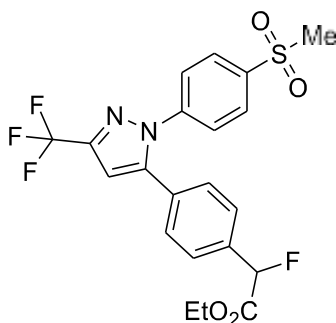


Step 1: A flame dried flask containing a solution of arylacetic acid (559 mg, 3.0 mmol, 1.0 equiv.) and TBSCl (1.04 g, 6.90 mmol, 2.3 equiv.) in THF (0.50 M) was cooled to 0 °C. LiHMDS (1.0 M in THF; 2.2 equiv.) was added slowly and the resulting mixture was stirred at 0 °C for 15 min and then warmed to r.t. It was then stirred at r.t over night before volatiles were removed in vacuo. The crude was taken up in hexane and solid LiCl was filtered off. The filtrate was washed with hexane and the combined organic fractions were concentrated to dryness in vacuo.

Step 2: The residue was dissolved in MeCN (0.50 M) and slowly added to a solution of Selectfluor (2.30 g, 6.50 mmol, 1.3 equiv.) in MeCN (30 mL) at r.t. After stirring for 15 min at r.t the reaction mixture was poured into aq. HCl (1.0 M, 10 mL/mmol acid). This solution was extracted with Et₂O (2x) and the combined Et₂O layers were then extracted with NaOH (1.0 M; 2x). The combined aqueous layers were washed with Et₂O (2x), acidified with HCl (6.0 M) until pH = 1 and extracted with Et₂O (3x). The combined organic fractions were dried over MgSO₄ and concentrated to dryness in vacuo to give the desired aryl(fluoro)acetic acid. The title compound (817 mg, 80%) as a white solid.

Physical appearance: White solid (yield: 80%). ¹H NMR (400 MHz, CDCl₃): δ = 9.55 (br s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.96 -7.89 (m, 2H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.61 -7.52 (m, 2H), 7.52 -7.47 (m, 1H), 6.42 (d, *J* = 46.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃): δ = 174.3 (d, *J* = 28.6 Hz), 133.9, 130.8 (d, *J* = 2.2 Hz), 130.5 (d, *J* = 1.5 Hz), 129.3 (d, *J* = 18.3 Hz), 128.9, 127.2, 126.9 (d, *J* = 8.1 Hz), 126.3, 125.0, 123.5 (d, *J* = 1.5 Hz), 88.0 (d, *J* = 186.3 Hz); ¹⁹F NMR (376 MHz, CDCl₃): δ = -178.7 (d, *J* = 46.3 Hz); The physical data were identical in all respects to those previously reported.³

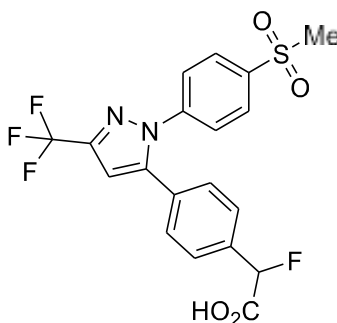
Ethyl 2-fluoro-2-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)phenyl)acetate



To a dry screw-cap tube equipped with a magnetic stirrer, 30 mg of 1-(4-(methylsulfonyl)phenyl)-1H-pyrazole (0.13 mmol, 1.1 equiv.), 1.5 mg of Pd(OAc)₂ (0.006 mmol, 5 mol%), 5 mg of L-proline (0.012 mmol, 10 mol%), 18 mg of K₂CO₃ (0.18 mmol, 1.5 equiv.), 17 mg of Ag₂CO₃ (0.06 mmol, 0.5 equiv.) and 4 mg of PivOH (0.04 mmol, 30 mol%) were added. After 3 cycles of vacuum/nitrogen, ethyl 2-fluoro-2-(4-iodophenyl)acetate (0.12 mmol, 1.0 eq.) and DMA (2 mL) were added. The tube was closed and stirred at 100 °C overnight. The reaction was cooled, diluted with a solution of saturated LiCl and extracted with Et₂O (3 x 10 mL), dried over MgSO₄. Solvent was removed under reduced pressure and the corresponding crude compound was purified using column chromatography (hexane/EtOAc = 7:3).

Physical appearance: Colourless oil (yield: 43%). **¹H NMR** (500 MHz, CDCl₃) δ 8.00 – 7.96 (m, 2H), 7.58 – 7.52 (m, 4H), 7.34 – 7.30 (m, 2H), 6.84 (s, 1H), 5.84 (d, *J* = 47.5 Hz, 1H), 4.36 – 4.25 (m, 2H), 3.10 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (126 MHz, CDCl₃) δ 167.91 (d, *J* = 26.8 Hz), 144.98 – 144.30 (m), 144.24, 143.15, 140.19, 135.84 (d, *J* = 20.6 Hz), 129.68, 129.16, 128.70, 127.15 (d, *J* = 6.5 Hz), 125.73, 120.86 (q, *J* = 269.3 Hz), 107.13, 88.65 (d, *J* = 187.3 Hz), 62.22, 44.49, 14.09; **¹⁹F NMR** (376 MHz, CDCl₃) δ -62.55 (s), -182.97 (d, *J* = 47.7 Hz). **IR** (film, cm⁻¹) ν 2985, 1756, 1151, 1096; **HRMS** (ESI) *m/z* calculated for: C₂₁H₁₈F₄N₂O₄Na [M + Na]⁺, 493.08156, found, 493.08145.

2-Fluoro-2-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)phenyl)acetic acid

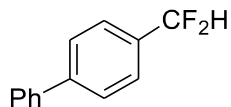


Ethyl 2-fluoro-2-(4-(1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)phenyl)acetate (42 mg, 0.1 mmol, 1 equiv.) was dissolved in a 2:1 MeOH and aqueous K_2CO_3 (5 equiv.) (5 mL) mixture before it was left to stir at r.t until all the ester had been consumed (determined by TLC). The resulting mixture was then acidified using HCl (5 M) to pH = 2. The aqueous layer was then extracted with Et_2O (3 x 5 mL) and washed with Brine (2 x 5 mL). The organic extracts were dried using $MgSO_4$ and were then concentrated under vacuum and washed with pentane, resulting in the titled compound in 76% yield.

Physical appearance: White solid (yield 76%). **Mp** = 158 °C. **1H NMR** (400 MHz, Methanol- d_4) δ 7.97 – 7.85 (m, 2H), 7.55 – 7.46 (m, 2H), 7.42 (dd, J = 8.2, 1.2 Hz, 2H), 7.32 – 7.20 (m, 2H), 5.79 (d, J = 47.7 Hz, 1H), 3.06 (s, 3H); **^{13}C NMR** (101 MHz, Methanol- d_4) δ 170.22 (d, J = 26.8 Hz), 144.89, 143.97 (t, J = 38.5 Hz), 143.08, 140.71, 136.65 (d, J = 20.5 Hz), 129.61 (d, J = 2.1 Hz), 129.11, 128.41, 126.96 (d, J = 6.1 Hz), 125.94, 122.52, 119.86, 106.43, 88.50 (d, J = 183.4 Hz), 42.77; **^{19}F NMR** (376 MHz, Methanol- d_4) δ -63.94, -181.97 (d, J = 48.4 Hz). **IR** (film, cm^{-1}) ν 2919, 2361, 1749, 1136, 1095. **HRMS** (ESI) m/z calculated for $C_{19}H_{14}F_4N_2O_4SNa$ $[M + Na]^+$, 465.05026, found, 465.05000.

Synthesis of (difluoromethyl)arenes.

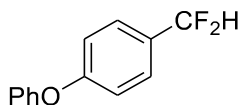
4-(Difluoromethyl)-1,1'-biphenyl³



The title compound was prepared following General Procedure GP3 using 4-(difluoromethyl)-1,1'-biphenyl (55 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (48 mg, 78% yield) was isolated as a white solid.

Physical appearance: White solid (yield: 78 %). **¹H NMR** (400 MHz, CDCl₃) δ : 7.68 (d, J = 8.0 Hz, 2H), 7.64 – 7.55 (m, 4H), 7.47 (dd, J = 8.4, 6.8 Hz, 2H), 7.44 – 7.34 (m, 1H), 6.70 (t, J = 56.2 Hz, 1H); **¹⁹F NMR** (376 MHz, CDCl₃) δ -110.35 (d, J = 55.9 Hz). The physical data were identical in all respects to those previously reported.³

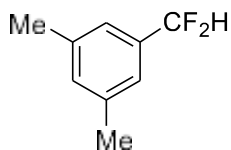
1-(Difluoromethyl)-4-phenoxybenzene⁶



The title compound was prepared following General Procedure GP3 using 4-phenoxybenzaldehyde (59 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (28 mg, 43% yield) was isolated as a colourless oil.

Physical appearance: Colourless Oil (yield: 43%). **¹H NMR** (400 MHz, CDCl₃) δ : 7.39 (d, J = 8.2 Hz, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.09 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 8.1 Hz, 4H), 6.55 (t, J = 58.3 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ : 159.6, 156.2, 130.0, 128.9 (t, J = 22.4 Hz) 127.3 (t, J = 6.1 Hz), 124.1, 119.6, 118.2, 114.6 (t, J = 235.8 Hz); **¹⁹F NMR** (376 MHz, CDCl₃) δ : -109.0 (d, J = 56.4 Hz). The physical data were identical in all respects to those previously reported.⁶

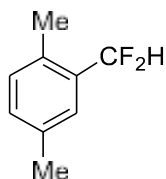
1-(Difluoromethyl)-3,5-dimethylbenzene⁷



The title compound was prepared following General Procedure GP3 using 3,5-dimethylbenzaldehyde (40 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (25 mg, 54%) was isolated as a yellow oil

Physical appearance: Yellow Oil (yield: 54%). ¹H NMR (400 MHz, CDCl₃) δ 7.12 (d, *J* = 5.4 Hz, 3H), 6.58 (t, *J* = 56.6 Hz, 1H), 2.37 (s, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ -110.17 (d, *J* = 56.6 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 138.44, 132.27 (t, *J* = 2.1 Hz), 123.20 (t, *J* = 6.0 Hz), 114.99 (t, *J* = 238.4 Hz), 21.23. The physical data were identical in all respects to those previously reported.⁷

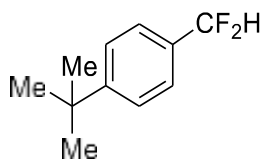
2-(Difluoromethyl)-1,4-dimethylbenzene⁶



The title compound was prepared following General Procedure GP3 using 3,5-dimethylbenzaldehyde (40 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (20 mg, 43%) was isolated as yellow oil.

Physical appearance: Yellow oil (yield: 43%). ¹H NMR (400 MHz, CDCl₃) δ 7.35 (s, 1H), 7.23 – 7.17 (m, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.76 (t, *J* = 55.6 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 135.61, 133.01 (t, *J* = 4.6 Hz), 131.99 (t, *J* = 20.6 Hz), 131.21 (d, *J* = 2.2 Hz), 130.97, 126.35 (t, *J* = 7.3 Hz), 114.53 (t, *J* = 237.7 Hz), 20.91, 17.99. ¹⁹F NMR (376 MHz, CDCl₃) δ -112.87 (d, *J* = 56.0 Hz); The physical data were identical in all respects to those previously reported.⁶

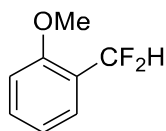
1-(*tert*-Butyl)-4-(difluoromethyl)benzene⁶



The title compound was prepared following General Procedure GP3 using 4-(*tert*-butyl)benzaldehyde (49 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (29 mg, 52%) was isolated as a colourless oil.

Physical appearance: Colourless oil (yield: 52%). ¹H NMR (400 MHz, CDCl₃) δ 7.58 – 7.41 (m, 4H), 6.66 (t, *J* = 56.6 Hz, 1H), 1.36 (s, 9H); ¹⁹F NMR (376 MHz, CDCl₃) δ -109.87 (d, *J* = 56.6 Hz). The physical data were identical in all respects to those previously reported.⁶

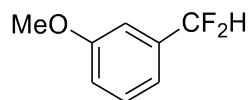
1-(Difluoromethyl)-2-methoxybenzene³



The title compound was prepared following General Procedure GP3 using 2-methoxybenzaldehyde (41 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (19 mg, 40%) was isolated as a yellow oil.

Physical appearance: Yellow oil (yield: 40%). ¹H NMR (400 MHz, CDCl₃): δ = 7.59 (d, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 55.8 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 157.2 (t, *J* = 6.0 Hz), 131.9 (t, *J* = 1.8 Hz), 126.1 (t, *J* = 6.0 Hz), 122.6 (t, *J* = 22.2 Hz), 120.5, 111.6 (t, *J* = 234.9 Hz), 110.8, 55.5; ¹⁹F NMR (376 MHz, CDCl₃): δ = -115.3 (d, *J* = 55.9 Hz). The physical data were identical in all respects to those previously reported.³

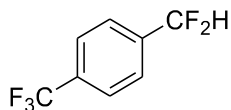
1-(Difluoromethyl)-3-methoxybenzene³



The title compound was prepared following General Procedure GP3 using 3-methoxybenzaldehyde (41 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (24 mg, 50%) was isolated as a colourless oil.

Physical appearance: Colourless Oil (yield = 50%) ¹H NMR (400 MHz, CDCl₃) δ: δ = 7.38 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.06 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.63 (t, *J* = 56.5 Hz, 1H), 3.85 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ = 159.8, 135.7 (t, *J* = 22.0 Hz), 129.8, 117.8 (t, *J* = 6.2 Hz), 116.6 (t, *J* = 1.8 Hz), 114.6 (t, *J* = 239.2 Hz), 110.7 (t, *J* = 5.9 Hz), 55.3; ¹⁹F NMR (376 MHz, CDCl₃): δ = -110.7 (d, *J* = 55.9 Hz). The physical data were identical in all respects to those previously reported.³

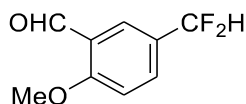
1-(Difluoromethyl)-4-(trifluoromethyl)benzene⁶



The title compound was prepared following General Procedure GP3 using 4-(trifluoromethyl)benzaldehyde (52 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (36 mg, 61%) was isolated as a colourless oil.

Physical appearance: Colourless oil (yield: 61%) ¹H NMR (400 MHz, CDCl₃) δ 7.65 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 6.62 (t, *J* = 56.0 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 137.79 (d, *J* = 1.4 Hz), 132.85 (d, *J* = 32.7 Hz), 126.08 (t, *J* = 6.1 Hz), 125.78 (q, *J* = 3.8 Hz), 122.61 (q, *J* = 271.5 Hz), 113.70 (t, *J* = 240.0 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -63.04 (s), -112.37 (d, *J* = 55.8 Hz); The physical data were identical in all respects to those previously reported.⁶

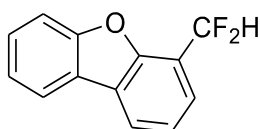
5-(Difluoromethyl)-2-methoxybenzaldehyde



To a mixture of 2-bromo-4-(difluoromethyl)-1-methoxybenzene (450 mg, 1.9 mmol) in THF (20 mL) at -78 °C was added *n*BuLi (1.03 mL, 2.47 mmol, 2.4 M in hexanes). The mixture was stirred at -78 °C for 30 min and then DMF (208 mg, 2.85 mmol) was added. The mixture was stirred at -78 °C for an additional 30 min and then quenched with saturated NH₄Cl (20 mL). The mixture was extracted with EtOAc (2x) and the combined organic layers were washed with brine (2x), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with petroleum ether/ethyl acetate to yield the title compound as a white solid (150 mg, 42% yield).

Physical appearance: White solid (yield: 42%). **¹H NMR** (400 MHz, CDCl₃) δ 10.40 (s, 1H), 7.89 (dt, *J* = 2.5, 1.2 Hz, 1H), 7.65 (ddt, *J* = 8.8, 2.3, 1.1 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.56 (t, *J* = 56.4 Hz, 1H), 3.91 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 188.87, 163.17, 132.82 (t, *J* = 5.4 Hz), 127.04, 126.39 (t, *J* = 6.3 Hz), 124.62, 116.47, 114.10, 112.14, 111.73, 56.00. **¹⁹F NMR** (376 MHz, CDCl₃) δ -109.59 (d, *J* = 56.7 Hz). **IR** (film, cm⁻¹) ν 1980, 1461, 1257, 1180.

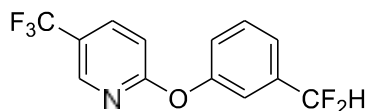
4-(Difluoromethyl)dibenzo[b,d]furan⁶



The title compound was prepared following General Procedure GP3 using dibenzo[b,d]furan-4-carbaldehyde (59 mg, 0.3 mmol), DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (29 mg, 45%) was isolated as a colourless oil.

Physical appearance: Colourless oil (yield: 45%). **¹H NMR** (400 MHz, CDCl₃) δ: 7.91 (d, 1H, *J* = 7.6 Hz), 7.83 (d, 1H), 7.55 (dd, 1H, *J* = 7.6 Hz, *J* = 1.1 Hz), 7.53 (d, 1H *J* = 7.6 Hz), 7.47 – 7.30 (td, 1H, *J* = 8.3 Hz, *J* = 1.1 Hz), 7.33 – 7.21 (m, 1H), 7.11 (t, 1H, *J* = Hz); **¹⁹F NMR** (376 MHz, CDCl₃) δ: -113.01 (d, *J* = 54.9 Hz); **¹³C NMR** (100 MHz, CDCl₃) δ: 156.33, 153.03 (t, *J* = 5.2 Hz), 127.83, 125.17, 123.72 (t, *J* = 6.2 Hz), 123.37, 123.25, 123.10 (t, *J* = 1.6 Hz), 122.74, 120.79, 118.47 (t, *J* = 23.3 Hz), 111.95, 111.91 (t, *J* = 236.6 Hz). The physical data were identical in all respects to those previously reported.⁶

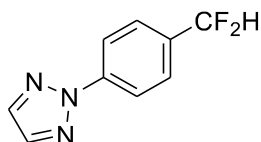
2-(3-(Difluoromethyl)phenoxy)-5-(trifluoromethyl)pyridine



To trifluoromethyl)pyridin-2-yl)oxy)benzaldehyde (0.3 g, 1.12 mmol) in CH₂Cl₂ (4 mL) was added Deoxo-Fluor (497 mg, 2.25 mmol) and heated at 40 °C for 16 hours. Starting material aldehyde remained and therefore the reaction mixture was charged with additional Deoxo-Fluor (497 mg, 2.25 mmol) and heated at 40 °C for 6 hours, followed by an additional addition of Deoxo-Fluor (497 mg, 2.25 mmol) and heating at 40 °C for 16 hours. Saturated NaHCO₃ was added and the mixture was extracted with CH₂Cl₂ (2x) and the combined organic fraction was concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with petroleum ether/ethyl acetate, followed by purification by preparative reverse-phase HPLC (Column: Gemini-C18, 100*21.2 mm 5 µm; Mobile phase: MeCN-H₂O (0.1% FA); Gradient: 55% to 65%; Flow rate: 25 ml/min) to yield the title compound as a yellow oil (108 mg, 33% yield).

Physical appearance: Yellow oil (yield: 33%). **¹H NMR** (400 MHz, CDCl₃) δ: 8.35 (dt, *J* = 2.6, 1.0 Hz, 1H), 7.85 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.32 (dp, *J* = 7.8, 1.2 Hz, 1H), 7.21 – 7.17 (m, 1H), 6.98 (dt, *J* = 8.7, 0.8 Hz, 1H), 6.59 (t, *J* = 56.4 Hz, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 165.32, 153.36, 145.40 (q, *J* = 4.4 Hz), 136.90 (q, *J* = 3.2 Hz), 136.20 (t, *J* = 22.7 Hz), 130.22, 123.88 (t, *J* = 1.8 Hz), 123.50 (q, *J* = 271.6 Hz), 122.56 (t, *J* = 6.2 Hz), 118.83 (t, *J* = 6.2 Hz), 116.36, 113.98, 111.61 (d, *J* = 3.1 Hz); **¹⁹F NMR** (376 MHz, CDCl₃) δ: -61.71, -111.43 (d, *J* = 56.4 Hz); **IR** (film, cm⁻¹) ν 2916, 1448, 1395, 1030. **HRMS** (ESI) *m/z* calculated for C₁₃H₉F₅NO [M + Na]⁺ 290.05988 Found, 290.05998.

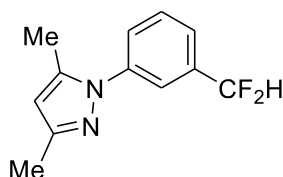
2-(4-(Difluoromethyl)phenyl)-2H-1,2,3-triazole



To a mixture of 4-(2H-1,2,3-triazol-2-yl)benzaldehyde (400 mg, 2.3 mmol) in CH₂Cl₂ (10 mL) was added EtOH (21.3 mg, 0.462 mmol) and Deoxo-Fluor (869 mg, 3.93 mmol) and heated at 40 °C for 18 hours. The reaction mixture was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with petroleum ether/ethyl acetate to yield the title compound as a white solid (131 mg, 29% yield).

Physical appearance: White solid (yield: 29%). ¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, *J* = 7.9, 2H), 7.78 (s, 2H), 7.57 (t, *J* = 8.7 Hz, 2H), 6.63 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 136.05, 133.37, 126.82 (t, *J* = 6.1 Hz), 119.04, 114.20 (t, *J* = 239.1 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ -110.77 (d, *J* = 56.3 Hz).

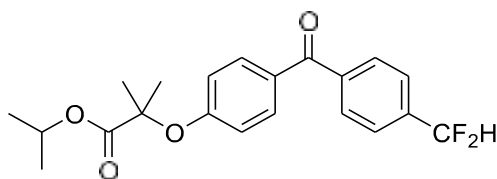
1-(3-(Difluoromethyl)phenyl)-3,5-dimethyl-1H-pyrazole



To a mixture of 3-(3,5-dimethyl-1H-pyrazol-1-yl)benzaldehyde (200 mg, 1 mmol) in CH₂Cl₂ (10 mL) was added EtOH (9.2 mg, 0.20 mmol) and Deoxo-Fluor (376 mg, 1.70 mmol) and heated at 40 °C for 18 hours. The reaction mixture was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with petroleum ether/ethyl acetate to yield the titled compound as a yellow oil (88 mg, 40% yield).

Physical appearance: Yellow oil (yield: 40%). ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.51 (m, 1H), 7.49 – 7.37 (m, 3H), 6.60 (t, *J* = 56.3 Hz, 1H), 5.94 (s, 1H), 2.24 (d, *J* = 0.8 Hz, 3H), 2.22 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -111.30 (d, *J* = 56.2 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 149.53, 140.35, 139.49, 135.48 (t, *J* = 22.7 Hz), 129.49, 126.46 (t, *J* = 1.9 Hz), 124.05 (t, *J* = 6.0 Hz), 121.79 (t, *J* = 6.3 Hz), 117.62 – 110.90 (m), 107.56, 13.49, 12.46; IR (film, cm⁻¹) ν 2982, 1452, 1275, 1059, 1024. HRMS (ESI) *m/z* calculated for C₁₂H₁₃F₂N₂ [M + H]⁺, 223.10413, Found 223.10418.

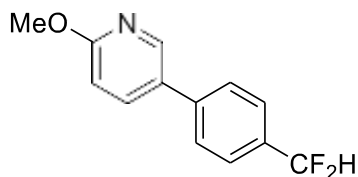
Isopropyl 2-(4-(4-(difluoromethyl)benzoyl)phenoxy)-2-methylpropanoate⁸



The title compound was prepared following General Procedure GP 4 using isopropyl 2-(4-(4-(difluoromethyl)benzoyl)phenoxy)-2-methylpropanoate (37.6 mg, 0.1 mmol, 1.0 equiv.), Mn(tmp)Cl (2.5 mol%), PhIO (0.33 mmol, 3.3 equiv.) Et₃N·3HF (0.12 mmol, 1.2 equiv.) and DCE (1 mL) and purified using column chromatography (DCM/*n*-pentane)

Physical appearance: White solid (yield: 22%). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.67 (t, *J* = 56.2 Hz, 1H), 5.56-4.36 (m, 1H), 1.62 (s, 6H), 1.18 (d, *J* = 6.1 Hz, 6 H); ¹⁹F NMR (376 MHz, CDCl₃) δ -111.64 (d, *J* = 56.1 Hz). The physical data were identical in all respects to those previously reported.⁸

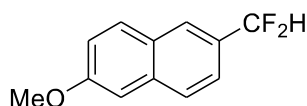
5-(4-(Difluoromethyl)phenyl)-2-methoxypyridine



The title compound was prepared following General Procedure GP 4 using 2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetic acid (26.1 mg, 0.1 mmol, 1.0 equiv.), Mn(tmp)Cl (2.5 mol%), PhIO (0.33 mmol, 3.3 equiv.) Et₃N·3HF (0.12 mmol, 1.2 equiv.) and DCE (1 mL) and purified using column chromatography (DCM/*n*-pentane)

Physical appearance: White Solid (yield: 21%). **Mp:** 59 – 62 °C; ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.47 – 8.27 (m, 1H), 7.96 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 1H), 6.80 (t, *J* = 52.6 Hz, 1H), 3.95 (s, 3H); ¹³C NMR (101 MHz, Methanol-*d*₄) δ 165.56, 146.12, 141.49, 139.13, 135.22 (t, *J* = 22.4 Hz), 130.64, 129.53 – 125.64 (m), 116.36 (t, *J* = 236.6 Hz), 111.94, 54.31; ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -111.83 (d, *J* = 56.3 Hz); **IR** (film, cm⁻¹) ν 3010, 1402, 1256, 1120. **HRMS** (ESI) *m/z* calculated for C₁₃H₁₂F₂NO [M + H]⁺, 236.08924, Found, 236.08813.

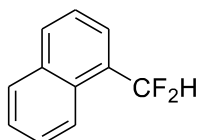
2-(Difluoromethyl)-6-methoxynaphthalene⁹



A dried Schlenk tube was charged with (0.2 mmol), PDFA (356 mg, 1.0 mmol), 1,3-Cyclopentadione (19.6 mg, 0.2 mmol), $\text{Ca}(\text{OH})_2$ (59.3 mg, 0.8 mmol), $\text{Pd}(\text{PPh}_3)_4$ (46.2 mg, 0.04 mmol), H_2O (9 mg, 0.5 mmol) and p-xylene (2 mL). The mixture was stirred at 90 °C for 3 h under N_2 atmosphere. After being cooled to room temperature, the mixture was subjected to flash column chromatography (petroleum ether / dichloromethane) to afford the pure product as a white solid.

Physical appearance: White solid (yield: 42%). ^1H NMR (200 MHz, CDCl_3) δ 7.95 – 7.76 (m, 3H), 7.57 (dd, J = 8.5, 1.8 Hz, 1H), 7.26 – 7.15 (m, 2H), 6.78 (t, J = 56.5 Hz, 1H), 3.95 (s, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -109.13 (d, J = 56.5 Hz). The physical data were identical in all respects to those previously reported.⁹

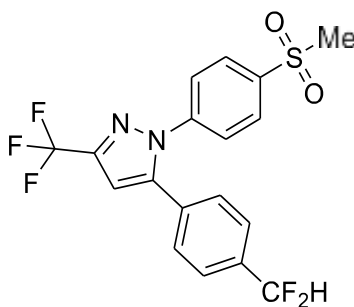
1-(Difluoromethyl)naphthalene⁶



The title compound was prepared following General Procedure GP3 using 1-naphthaldehyde (47 mg, 0.3 mmol). DAST (73 mg, 0.45 mmol) and ethanol (few drops), in DCM (0.5 M). The title compound (27 mg, 55%) was isolated as a white solid.

Physical appearance: White solid (yield: 55%). ^1H NMR (400 MHz, CDCl_3) δ 8.09 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.65 – 7.57 (m, 1H), 7.56 – 7.39 (m, 3H), 7.05 (s, 1H); ^{19}F NMR (376 MHz, CDCl_3) δ -110.88 (d, J = 55.4 Hz). The physical data were identical in all respects to those previously reported.⁶

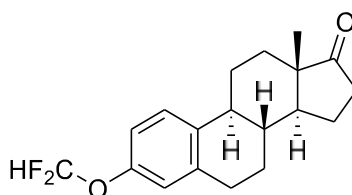
5-(4-(Difluoromethyl)phenyl)-1-(4-(methylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole⁸



Synthesised according to a reported procedure.⁸

Physical appearance: Colourless oil (yield: 20%). ¹H NMR (400 MHz, CDCl₃) δ 8.02 – 7.96 (m, 2H), 7.61 – 7.52 (m, 4H), 7.40 – 7.34 (m, 2H), 6.86 (s, 1H), 6.70 (t, 1H), 3.10 (s, 3H); ¹⁹F NMR (376 MHz, CDCl₃) δ -62.55, -111.83 (d, *J* = 56.3 Hz). The physical data were identical in all respects to those previously reported.⁸

(8R,9S,13S,14S)-3-(Difluoromethoxy)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one¹⁰



In a 10 mL round-bottomed flask was placed estrone (136 mg, 0.5 mmol, 1.0 equiv.), acetonitrile (1.0 mL) and 6M aqueous KOH (1.0 mL). The mixture was stirred rapidly at r.t and HCF₂OTf (0.21 mL, 1.5 mmol, 3.0 equiv.) was added at once at 0 °C. The mixture was stirred vigorously for 2 minutes, warmed to r.t and stirred for a further 20 minutes. The reaction was diluted with H₂O (10 mL) and extracted with ether (2 x 10 mL). The combined organic layers were dried over MgSO₄, concentrated, and purified by silica gel chromatography.

Physical appearance: White solid (yield: 43%). ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.5, 1H), 6.88 (s, 1H), 6.50 (t, *J* = 74.3 Hz, 1H), 2.94 (dd, *J* = 9.0, 4.3 Hz, 2H), 2.58 – 2.47 (m, 1H), 2.42 – 2.37 (m, 1H), 2.27 (t, *J* = 10.6 Hz, 1H), 2.1 (ddd, *J* = 23.7, 13.3, 5.8 Hz, 2H), 1.98 (d, *J* = 10.4 Hz, 1H), 1.70 – 1.41 (m, 7H), 0.94 (s, 3H). ¹⁹F NMR (376 MHz, CDCl₃) δ -80.36 (d, *J* = 74.6 Hz). The physical data were identical in all respects to those previously reported.¹⁰

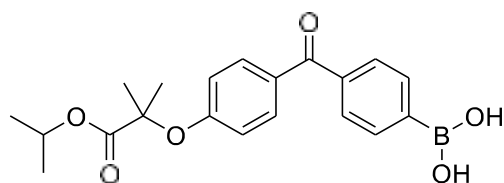
Preparation of Boronic Acid Precursors

Boronic acid precursors used in the synthesis towards 8a-8h, 8j and 8p-8v were purchased from commercial vendors.

Boronic acid precursors used in the synthesis towards 8i and 8k-8m were kindly donated by Pfizer inc.

Boronic acid precursors used in the synthesis of 8n and 8o were synthesized according to known literature procedures.

(4-(4-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)benzoyl)phenyl)boronic acid

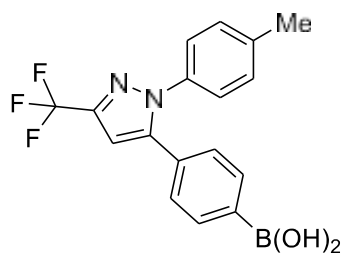


Prepared according to a known literature procedure¹¹

¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (s, 2H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.67 – 7.60 (m, 2H), 6.94 – 6.87 (m, 2H), 5.04 – 4.93 (m, 1H), 1.61 (s, 6H), 1.16 (d, *J* = 6.3 Hz, 6H). **HRMS** (ESI, *m/z*) calcd [*M* - H]⁻ for 369.15149, Found, 369.15117. The physical data were identical in all respects to those previously reported.¹¹ **Note: if ¹H NMR is taken in CDCl₃ peaks corresponding to the boroxine trimer may be observed!**

(4-(1-(*p*-tolyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)phenyl)boronic acid

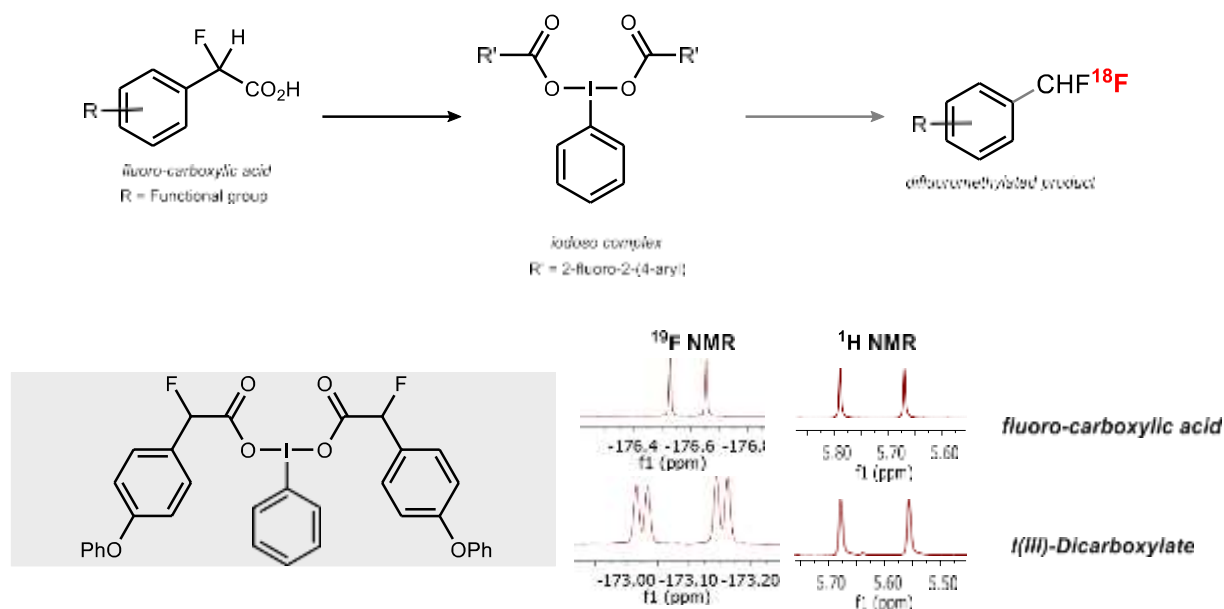
Prepared according to a known literature procedure¹²



¹H NMR (400 MHz, DMSO-*d*₆) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.07-7.15 (m, 5H), 2.21 (s, 3H); **LRMS**: (ESI⁺, *m/z*) 347.1 ([*M*+H]⁺, 100%). The physical data were identical in all respects to those previously reported.¹² **Note: if ¹H NMR is taken in CDCl₃ peaks corresponding to the boroxine trimer may be observed!**

In Situ Preparation of Iodine(III) dicarboxylates

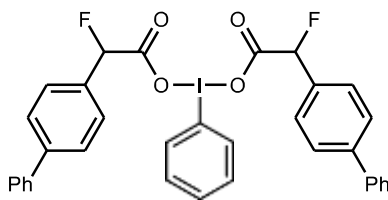
In each radiochemical reaction, α -aryl- α -fluoroacetic acid and iodosylbenzene were pre-stirred in acetonitrile, solvent was removed under vacuum *a priori* to ^{18}F being dispensed into the reaction vial. To prove that iodine(III) dicarboxylate intermediate is formed during the pre-stirring step, the model radiochemistry substrate 2-fluoro-2-(4-phenoxyphenyl)acetic acid Iodine(III) dicarboxylate was fully characterised. For other substrates where appropriate, the Iodine (III) dicarboxylate intermediate complex formation was confirmed by ^1H NMR and ^{19}F NMR to prove a similar reaction mechanism. Notable shifts of both the benzylic α proton and fluorine were observed in ^1H and ^{19}F NMR respectively. Iodine(III) dicarboxylates diastereoisomer have peaks which stem from the stereogenic centre of the benzylic $\text{Ar}-\text{CFHCO}_2\text{H}$ carbon which were made in a racemic fashion (**Scheme SI-8**).



Scheme SI-8 Synthesis of Iodine(III) dicarboxylates.

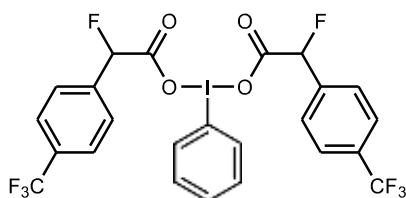
^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, J = 6.7 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.40 (dt, J = 24.6, 8.2 Hz, 8H), 7.29 (s, 2H), 7.16 (t, J = 7.4 Hz, 2H), 7.04 (d, J = 1.1 Hz, 4H), 6.94 (d, J = 8.4 Hz, 4H), 5.70 (d, J = 48.0 Hz, 2H); **^{13}C NMR** (101 MHz, CDCl_3) δ 172.69 (d, J = 27.1 Hz), 158.59, 156.58, 134.80, 132.43, 131.33, 130.02, 129.36 (d, J = 20.9 Hz), 128.41, 124.01, 122.96, 119.52, 118.60, 88.33 (d, J = 189.0 Hz); **^{19}F NMR** (376 MHz, CDCl_3) -173.83 (d, J = 48.1 Hz, 1F), -173.85 (d, J = 48.1 Hz, 1F); **HRMS** (ESI) m/z calculated for $[\text{M} + \text{Na}]^+$, 717.05561, Found, 717.05588. **IR** (film, cm^{-1}) ν : 3062, 1755, 1677, 1232, 1025.

Phenyl- λ 3-iodanediyl bis(2-([1,1'-biphenyl]-4-yl)-2-fluoroacetate)



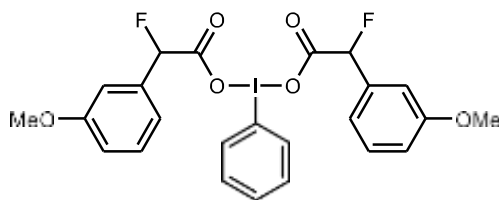
^1H NMR (400 MHz, CDCl_3) δ 7.97 – 7.89 (m, 2H), 7.56 (dd, J = 11.0, 7.9 Hz, 10H), 7.46 (t, J = 7.5 Hz, 5H), 7.42 – 7.36 (m, 6H), 5.77 (d, 49.0 Hz, 2H). **^{19}F NMR** (376 MHz, CDCl_3) δ -175.90 (d, J = 48.7 Hz, 2H).

Phenyl- λ 3-iodanediyl bis(2-fluoro-2-(4-(trifluoromethyl)phenyl)acetate)



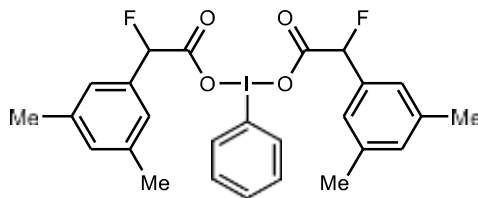
^1H NMR (400 MHz, Acetonitrile- d_3) δ 8.06 – 7.86 (m, 2H), 7.73 – 7.55 (m, 5H), 7.56 – 7.33 (m, 6H), 5.92 (d, J = 47.9 Hz, 2H). **^{19}F NMR** (376 MHz, Acetonitrile- d_3) δ -178.89 (d, J = 48.0 Hz).

Phenyl- λ 3-iodanediyl bis(2-fluoro-2-(3-methoxyphenyl)acetate)



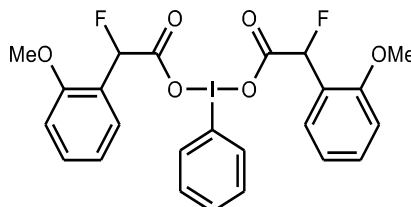
^1H NMR (400 MHz, CDCl_3) δ 7.84 – 7.73 (m, 2H), 7.51 – 7.38 (m, 1H), 7.37 – 7.27 (m, 2H), 7.23 – 7.12 (m, 2H), 6.93 – 6.65 (m, 6H), 5.61 (d, J = 48.4 Hz, 2H), 3.68 (s, 6H). **^{19}F NMR** (376 MHz, CDCl_3) δ -176.59 (d, J = 48.7 Hz).

Phenyl- Λ^3 -iodanediyl bis(2-(3,5-dimethylphenyl)-2-fluoroacetate)



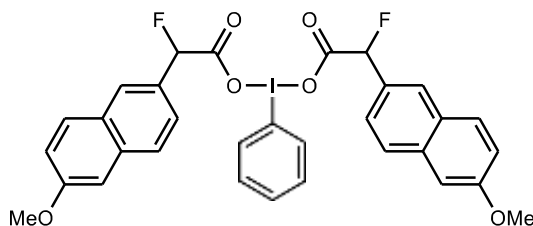
^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, J = 11.2 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.30 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 20.8 Hz, 6H), 5.56 (d, J = 48.7 Hz, 2H), 2.20 (s, 12H). **^{19}F NMR** (376 MHz, CDCl_3) δ -174.65 (d, J = 48.7 Hz, 1F) , -174.66 (d, J = 48.7 Hz, 1F).

Phenyl- Λ^3 -iodanediyl bis(2-fluoro-2-(2-methoxyphenyl)acetate)



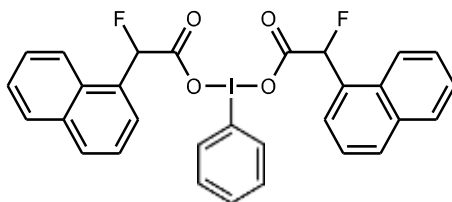
^1H NMR (400 MHz, CDCl_3) δ 7.96 (s, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.37 (dt, J = 21.5, 8.1 Hz, 4H), 7.24 – 7.13 (m, 2H), 7.00 – 6.84 (m, 4H), 6.06 (d, J = 48.0 Hz, 2H), 3.77 (s, 6H). **^{19}F NMR** (376 MHz, CDCl_3) δ -173.78 (d, J = 47.4 Hz).

Phenyl- Λ^3 -iodanediyl bis(2-fluoro-2-(6-methoxynaphthalen-2-yl)acetate)



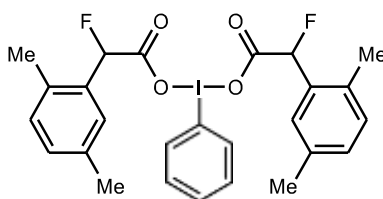
^1H NMR (400 MHz, CDCl_3) δ 7.70 (dq, J = 8.4, 1.9, 1.4 Hz, 2H), 7.60 (ddd, J = 16.7, 8.6, 2.3 Hz, 6H), 7.33 – 7.24 (m, 3H), 7.11 – 7.01 (m, 6H), 5.75 (d, J = 48.5 Hz, 2H), 3.84 (s, 6H). **^{19}F NMR** (376 MHz, CDCl_3) δ -173.76 (d, J = 48.7), -173.75 (d, J = 48.6 Hz).

Phenyl- λ^3 -iodanediyl bis(2-fluoro-2-(naphthalen-1-yl)acetate)



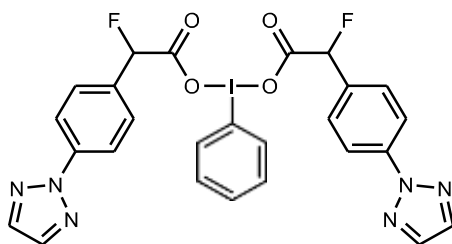
^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.0 Hz, 4H), 7.46 (ddt, J = 33.1, 24.3, 9.9 Hz, 11H), 7.15 – 7.05 (m, 2H), 6.27 (d, J = 47.6 Hz, 2H). **^{19}F NMR** (376 MHz, CDCl_3) δ -174.22 (d, J = 47.6 Hz).

Phenyl- λ^3 -iodanediyl bis(2-(2,5-dimethylphenyl)-2-fluoroacetate)



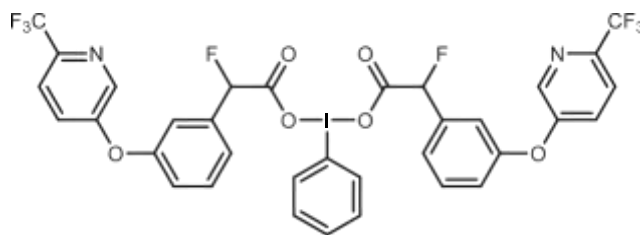
^1H NMR (400 MHz, Acetonitrile- d_3) δ 8.03 – 7.96 (m, 1H), 7.72 – 7.60 (m, 1H), 7.56 – 7.42 (m, 2H), 7.38 – 7.19 (m, 1H), 7.22 – 6.97 (m, 6H), 6.07 – 5.82 (d, J = 48.2 Hz, 2H), 2.26 (s, 6H), 2.22 (s, 6H), 2.26 (s, 6H). **^{19}F NMR** (376 MHz, Acetonitrile- d_3) δ -174.41 (d, J = 48.1 Hz).

Phenyl- λ^3 -iodanediyl bis(2-(4-(2H-1,2,3-triazol-2-yl)phenyl)-2-fluoroacetate)



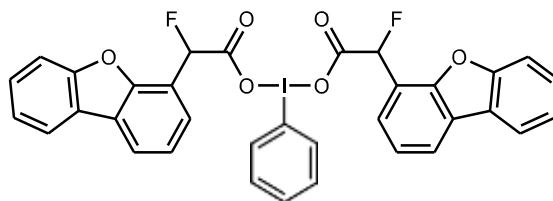
^1H NMR (400 MHz, CDCl_3) δ 8.03 (d, J = 8.7 Hz, 4H), 7.94 – 7.88 (m, 2H), 7.83 (s, 4H), 7.53 (d, J = 15.0 Hz, 1H), 7.46 – 7.34 (m, 6H), 5.77 (d, J = 48.3 Hz, 2H). **^{19}F NMR** (376 MHz, CDCl_3) δ -176.96 (d, J = 48.3 Hz, 1F), -176.98 (d, J = 48.3 Hz, 1F).

Phenyl- λ^3 -iodanediyl bis(2-fluoro-2-(3-((6-(trifluoromethyl)pyridin-3-yl)oxy)phenyl)acetate)



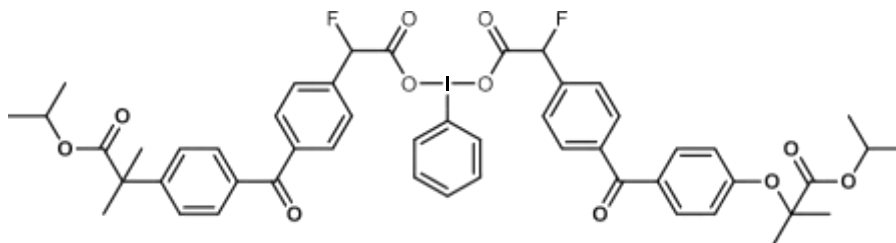
¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 2H), 7.91 – 7.65 (m, 4H), 7.65 – 7.22 (m, 6H), 7.17 – 7.05 (m, 5H), 6.94 (d, *J* = 8.6 Hz, 2H), 5.67 (d, *J* = 48.3 Hz, 2H). **¹⁹F NMR** (376 MHz, CDCl₃) δ -61.64 (s), -178.45 (d, *J* = 48.4 Hz), -178.45 (d, *J* = 48.4 Hz).

Phenyl-λ3-iodanediyl bis(2-(dibenzo[b,d]furan-4-yl)-2-fluoroacetate)



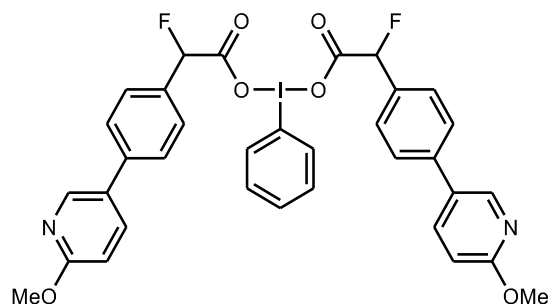
¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 7.6 Hz, 4H), 7.62 – 7.54 (m, 2H), 7.47 – 7.33 (m, 4H), 7.33 – 7.23 (m, 4H), 7.23 – 7.13 (m, 3H), 6.95 – 6.88 (m, 2H), 6.23 (d, *J* = 47.8 Hz, 2H). **¹⁹F NMR** (376 MHz, CDCl₃) δ -176.02 (d, *J* = 47.8 Hz), -176.04 (d, *J* = 47.8 Hz).

Diisopropyl 2,2'-(((4,4'-(((phenyl-λ3-iodanediyl)bis(oxy))bis(1-fluoro-2-oxoethane-2,1-diyl))bis(benzoyl))bis(4,1-phenylene))bis(oxy))bis(2-methylpropanoate)



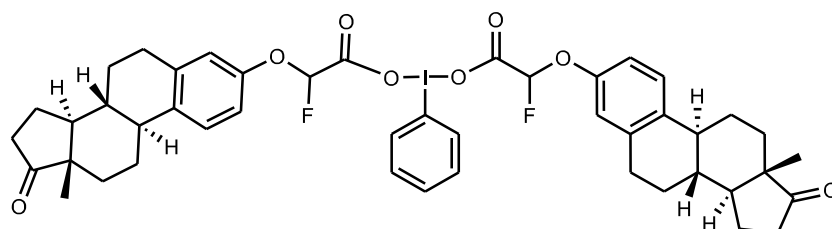
¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 7.9 Hz, 1H), 7.64 (dd, *J* = 23.7, 8.2 Hz, 8H), 7.51 (t, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 5H), 6.79 (d, *J* = 8.6 Hz, 4H), 5.73 (d, *J* = 48.3 Hz, 2H), 5.02 (p, *J* = 6.4 Hz, 2H), 1.60 (s, 12H), 1.14 (d, *J* = 6.1 Hz, 12H). **¹⁹F NMR** (376 MHz, CDCl₃) δ -179.56 (d, *J* = 48.3 Hz), -179.58 (d, *J* = 48.3 Hz).

Phenyl- Λ^3 -iodanediyl bis(2-fluoro-2-(4-(6-methoxypyridin-3-yl)phenyl)acetate)



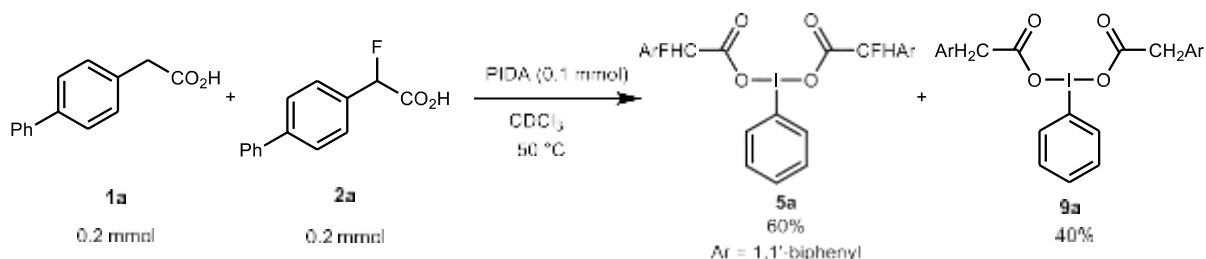
^1H NMR (400 MHz, CDCl_3) δ 8.39 (d, J = 2.3 Hz, 2H), 7.94 (d, J = 8.3 Hz, 2H), 7.78 (dd, J = 8.6, 2.5 Hz, 2H), 7.61 – 7.52 (m, 2H), 7.48 (d, J = 8.1 Hz, 4H), 7.39 (d, J = 8.0 Hz, 5H), 6.84 (d, J = 8.6 Hz, 2H), 5.76 (d, J = 48.4 Hz, 2H), 3.99 (s, 6H). ^{19}F NMR (376 MHz, CDCl_3) δ -176.27 (d, J = 48.4 Hz).

Phenyl- Λ^3 -iodanediyl bis(2-fluoro-2-(((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)acetate)



^1H NMR (400 MHz, CDCl_3) δ 8.13 – 8.03 (m, 2H), 7.63 – 7.54 (m, 1H), 7.47 (dd, J = 8.5, 7.2 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.81 – 6.62 (m, 4H), 5.80 (dd, J = 60.3, 1.1 Hz, 2H), 2.81 (dd, J = 8.9, 4.2 Hz, 4H), 2.44 (dd, J = 18.9, 8.6 Hz, 2H), 2.36 – 2.27 (m, 2H), 2.19 (d, J = 11.1 Hz, 2H), 2.13 – 1.84 (m, 8H), 1.63 – 1.29 (m, 12H), 0.84 (s, 6H). ^{19}F NMR (376 MHz, CDCl_3) δ -125.93 (d, J = 60.6 Hz), -125.94 (d, J = 60.6 Hz).

Iodine(III) Dicarboxylates Formation Competition Experiment



1a (0.2 mmol) and **2a** (0.2 mmol) were placed in 4 mL vial with PIDA (0.1 mmol). CDCl_3 (2 mL) was added and the reaction was stirred for 20 minutes at 50 °C prior to ^{19}F NMR analysis.

S6: Radiochemistry:

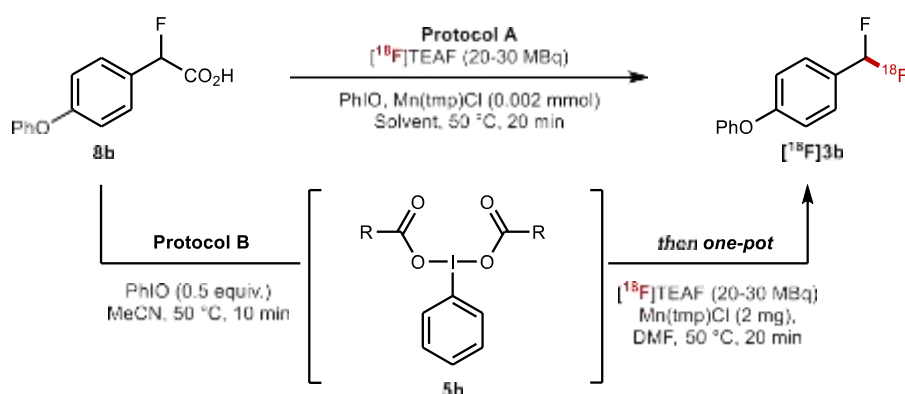
[¹⁸F]Fluoride was produced by Alliance Medical (UK) via the ¹⁸O(p,n)¹⁸F reaction and delivered as [¹⁸F]fluoride in ¹⁸O-enriched-water. Radiosynthesis and azeotropic drying was performed on a NanoTek microfluidic device (Advion).

Procedure for preparation of a solution of [¹⁸F]TEAF in MeCN:

A solution of tetraethylammonium bicarbonate (9 mg) in 1 mL of MeCN/H₂O, 4:1 was freshly prepared. [¹⁸F]Fluoride (3.0 - 4.0 GBq) was separated from ¹⁸O-enriched-water using a Chromafix PSHCO₃ ¹⁸F separation cartridge (45 mg) and subsequently released with 900 µL (in 6 x 150 µL portions) of the tetraethylammonium bicarbonate solution into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The solution was dried with five cycles of azeotropic drying with MeCN (5 x 200 µL) under a flow of N₂ at 105 °C. The dried [¹⁸F]TEAF residue was re-dissolved in anhydrous MeCN (500 - 1000 µL).

Optimisation

Table SI-2 Optimisation studies for the [¹⁸F]fluorodecarboxylation of **8b**

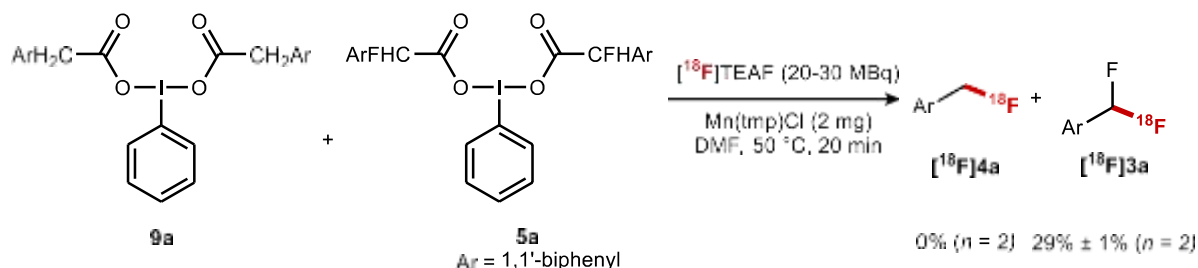


Entry	Starting Material (mmol)	Protocol	Solvent	PhIO (mmol)	RCC ^a (<i>n</i> = 2) ^b
1	8b (0.11)	A	MeCN ^[c]	0.33	3% ± 1%
2	8b (0.11)	A	MeCN	0.02	6% ± 1%
3	8b (0.11)	A	DMF	0.02	7% ± 2%
4	8b (0.055)	A	DMF ^d	0.02	22% ± 7%
5	5b (0.014)	B	DMF ^d	-	40% ± 10% ^e
6	5b (0.014)	B	DMF ^d	-	0% ± 0% ^f

7	8b (0.014)	A	MeCN	0.02	0%± 0% ^g
8	5b (0.014)	B	DMF ^d	-	0% ± 0% ^h

^aRadiochemical conversion. ^b*n* = number of reactions. ^c600 µL of MeCN used. ^dMeCN removed at 100 °C after dispensing [¹⁸F]TEAF. ^e(*n* = 10). ^fReaction Temperature = 100 °C. ^gcatalyst: Mn(tmp)OTs. ^hNo Mn Catalyst.

¹⁸F-fluorodecarboxylation competition experiment



Into a 3 mL vial was weighed **9a** (0.014 mmol), **5a** (0.014 mmol) and manganese catalyst (2 mgs). To this vial was dispensed [¹⁸F]TEAF (20 – 30 MBq) in a solution of anhydrous MeCN. The MeCN was removed at 100 °C under a flow of nitrogen. Upon cooling, DMF (300 µL) was added to the vial and the reaction was stirred at 50 °C for 20 minutes. The reaction was quenched with water (200 µL) and an aliquot was removed for analysis by radioTLC and radioHPLC for radiochemical conversion and product identity. Analysis was performed using a Waters Nova-Pak C18 column (4 µm, 3.9 x 150 mm) at a flow rate 1 mL/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using DCM/MeOH (9:1) as eluent. Analysis was performed using a plastic scintillator/PMT detector.

General Procedure for the Small Scale ¹⁸F-Fluorination of substrates [¹⁸F]3a – [¹⁸F]3o, [¹⁸F]3w – [¹⁸F]3z, [¹⁸F]11a:

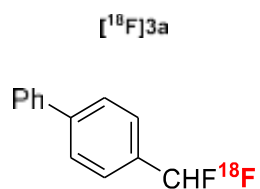
Into a 3 mL vial was weighed substrate (0.014 mmol) and manganese catalyst (2 mgs). To this vial was dispensed [¹⁸F]TEAF (20 – 30 MBq) in a solution of anhydrous MeCN. The MeCN was removed at 100 °C under a flow of nitrogen. Upon cooling, DMF (300 µL) was added to the vial and the reaction was stirred at 50 °C for 20 minutes. The reaction was quenched with water (200 µL) and an aliquot was removed for analysis by radioTLC and radioHPLC for radiochemical conversion and product identity. Analysis was performed using a Waters Nova-Pak C18 column (4 µm, 3.9 x 150 mm) at a flow rate 1 mL/min. Radio-TLC was performed on Merck Kiesegel 60 F254 plates, using DCM/MeOH (9:1) as eluent. Analysis was performed using a plastic scintillator/PMT detector.

HPLC gradient A for small scale ^{18}F -Fluorination of substrates $[^{18}\text{F}]\text{3a}$ – $[^{18}\text{F}]\text{3o}$, $[^{18}\text{F}]\text{3w}$ – $[^{18}\text{F}]\text{3z}$, $[^{18}\text{F}]\text{11a}$:

Water/MeCN, 1 mL/min, Waters Nova-Pak C18 Column, 4 μm , 3.9 x 150 mm 0 - 1 min (5% MeCN) isocratic 1 - 10 min (5% MeCN to 95% MeCN) linear increase 10 - 14 min (95% MeCN) isocratic 14 - 15 min (95% MeCN to 5% MeCN) linear decrease 15 - 17 min (5% MeCN) isocratic.

Radio-HPLC of substrates $[^{18}\text{F}]\text{3a}$ – $[^{18}\text{F}]\text{3o}$, $[^{18}\text{F}]\text{3w}$ – $[^{18}\text{F}]\text{3z}$, $[^{18}\text{F}]\text{11a}$

Crude Radio-HPLC traces of the crude mixture following the general procedure, with authentic UV references overlaid are shown below. The solid black line indicates the UV trace for cold reference material and the solid red line is the crude radio-HPLC trace. All samples were run using HPLC gradient A.



Reaction	Radio-TLC	Radiochemical Conversion
1	13%	10%
2	14%	11%
3	28%	28%
4	30%	30%
Radiochemical Conversion + Standard Deviation		20% $\pm$ 10%

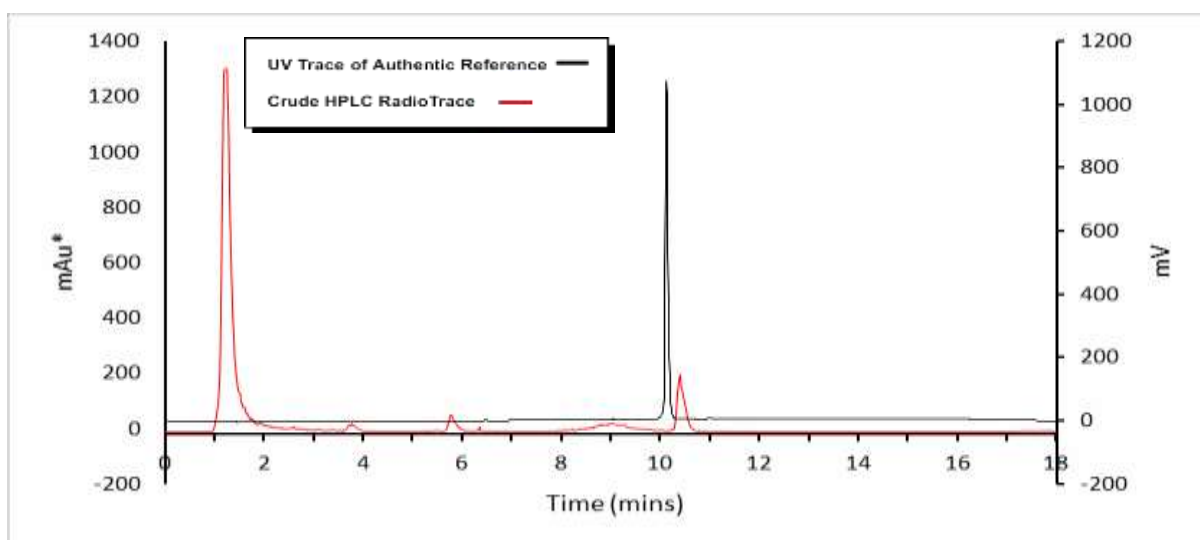
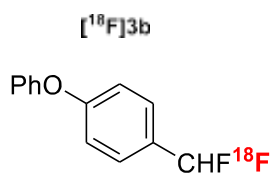


Figure SI-1 HPLC radio-trace of $[^{18}\text{F}]\mathbf{3a}$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ^{19}F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	50%	50%
2	37%	37%
3	45%	45%
4	37%	37%
5	46%	46%
6	53%	53%
7	34%	34%
8	22%	22%
9	30%	30%
10	43%	43%
Radiochemical Conversion + Standard Deviation		40% ± 9%

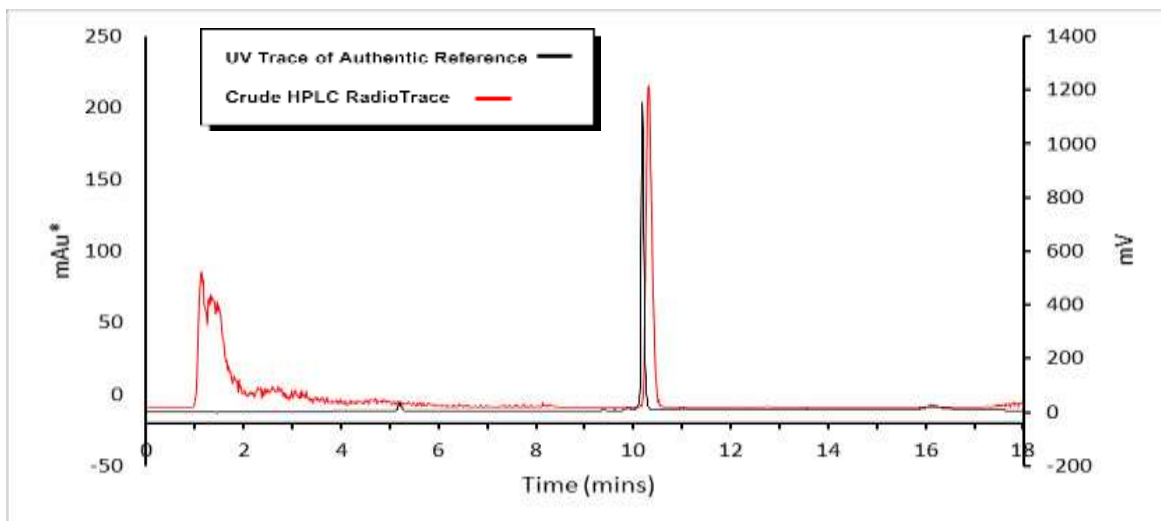
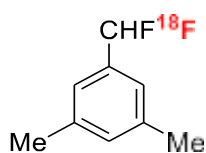


Figure SI-2 HPLC radio-trace of [¹⁸F]3b (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).

[¹⁸F]3c



Reaction	Radio-TLC	Radiochemical Conversion
1	20%	20%
2	20%	20%
3	21%	19%
4	27%	26%
Radiochemical Conversion + Standard Deviation		21% ± 3%

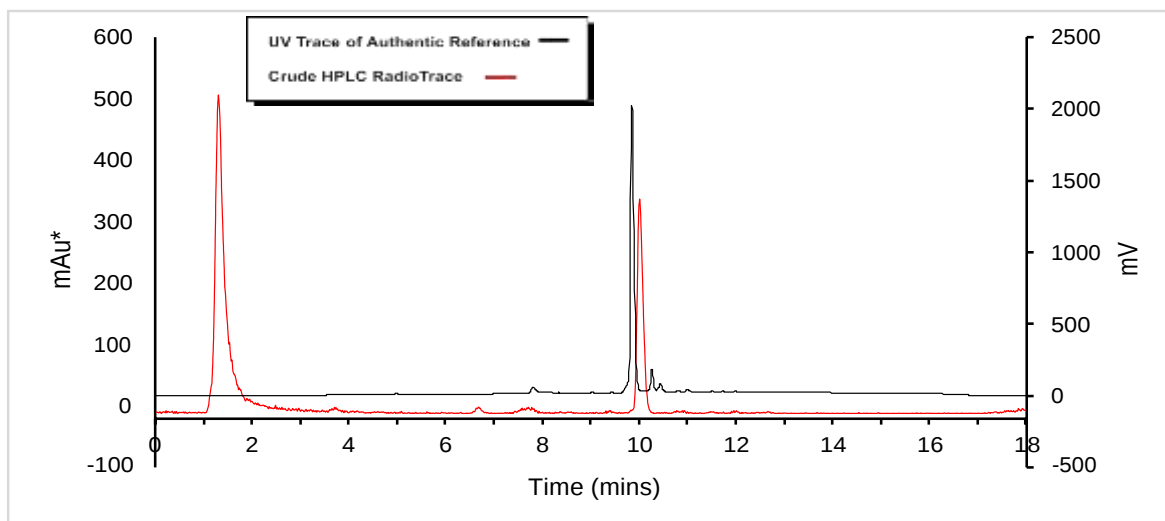
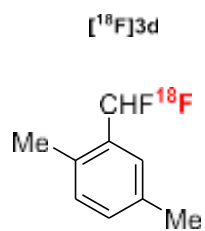


Figure SI-3 HPLC radio-trace of [¹⁸F]3c (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	36%	34%
2	33%	31%
3	42%	37%
4	36%	32%
Radiochemical Conversion + Standard Deviation		34% ± 3%

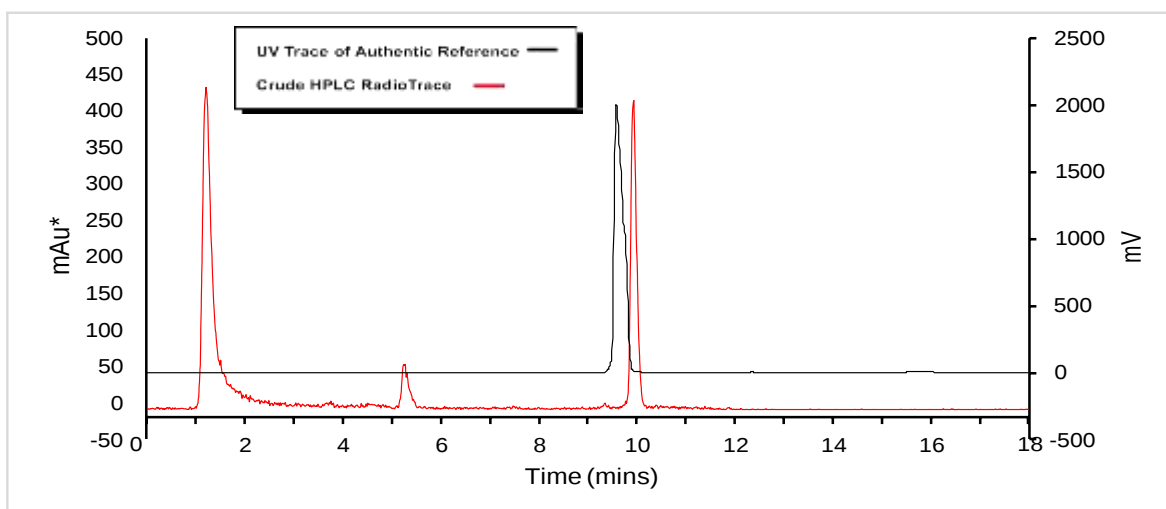
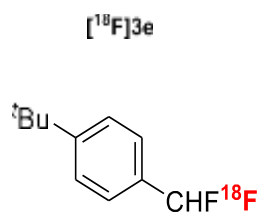


Figure SI-4 HPLC radio-trace of [¹⁸F]3d (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	33%	33%
2	29%	29%
3	13%	13%
4	36%	36%
Radiochemical Conversion + Standard Deviation		28% $\pm$ 10%

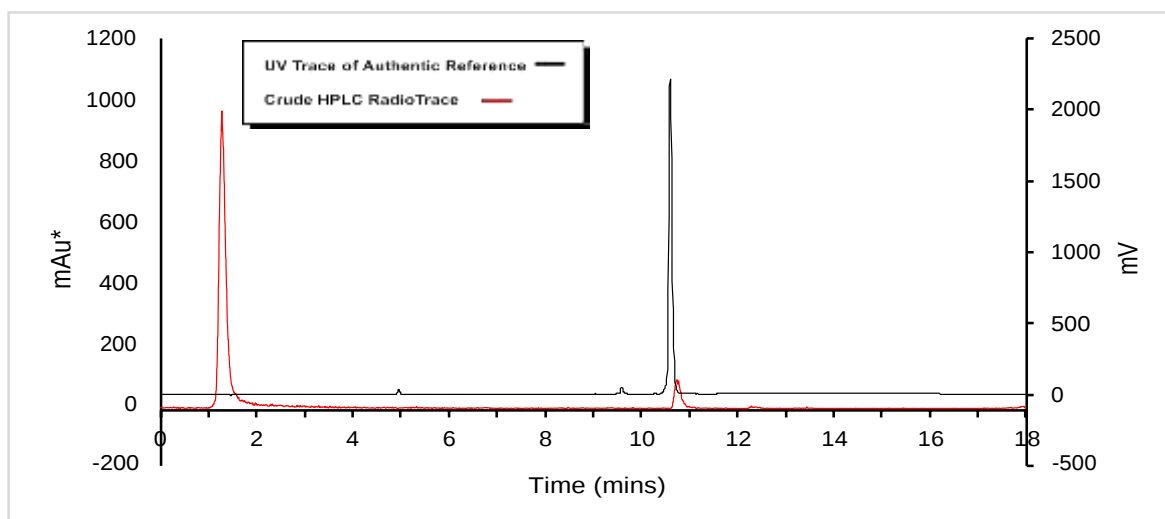
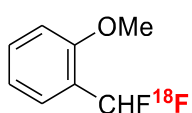


Figure SI-5 HPLC radio-trace of $[^{18}\text{F}]\mathbf{3e}$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ^{19}F reference compound (black).

[¹⁸F]3f



Reaction	Radio-TLC	Radiochemical Conversion
1	27%	23%
2	26%	21%
3	15%	12%
4	8%	7%
Radiochemical Conversion + Standard Deviation		16% ± 7%

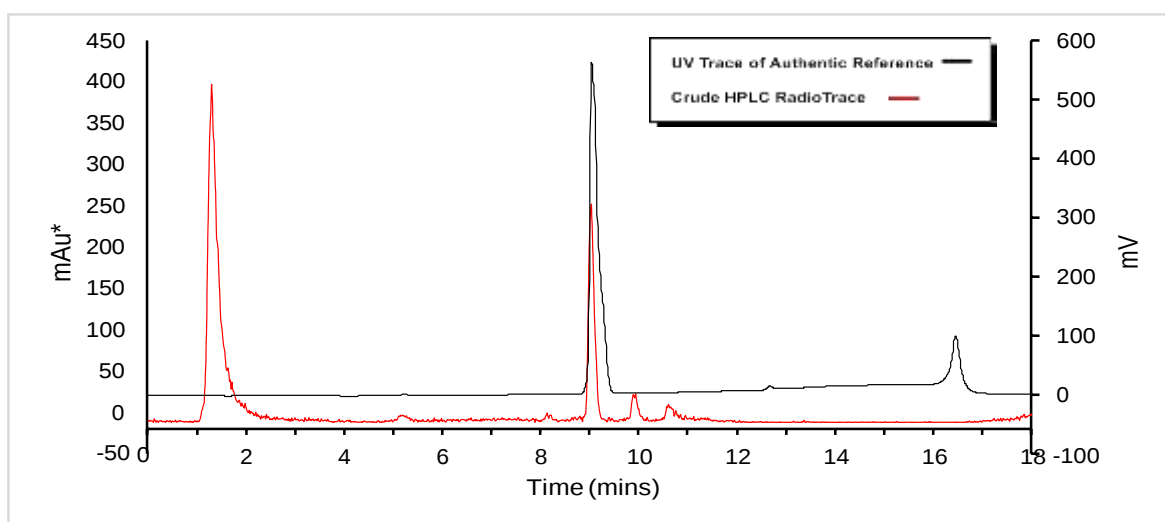
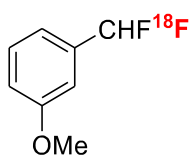


Figure SI-6 HPLC radio-trace of [¹⁸F]3f (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).

[¹⁸F]3g



Reaction	Radio-TLC	Radiochemical Conversion
1	23%	21
2	22%	21
3	26%	26%
4	14%	14%
Radiochemical Conversion + Standard Deviation		21% ± 5%

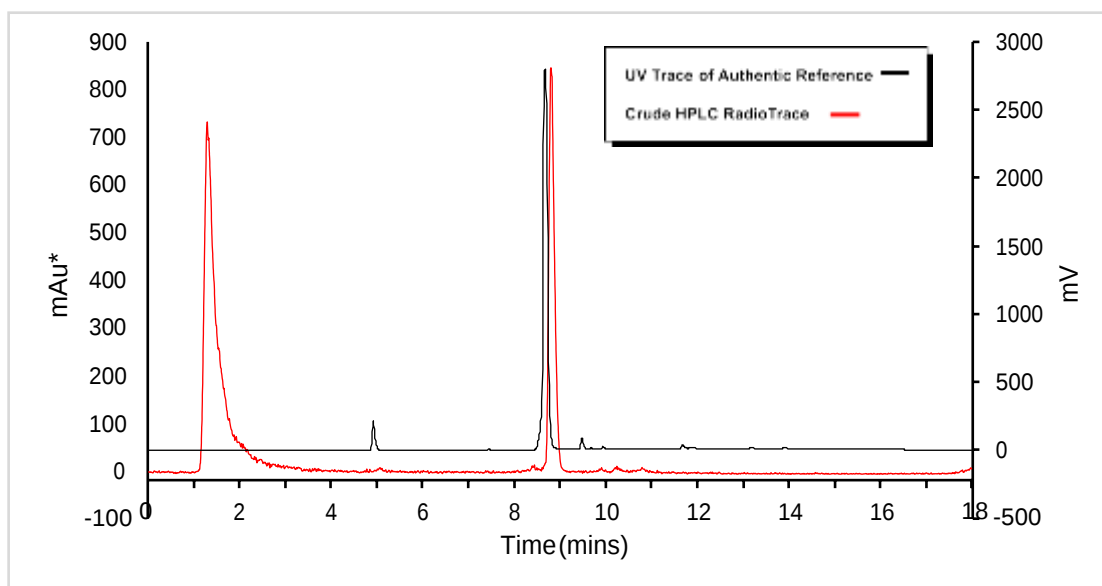
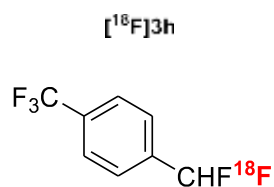


Figure SI-7 HPLC radio-trace of [¹⁸F]3g (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	16%	5%
2	9%	3%
Radiochemical Conversion + Standard Deviation		4% ± 1%

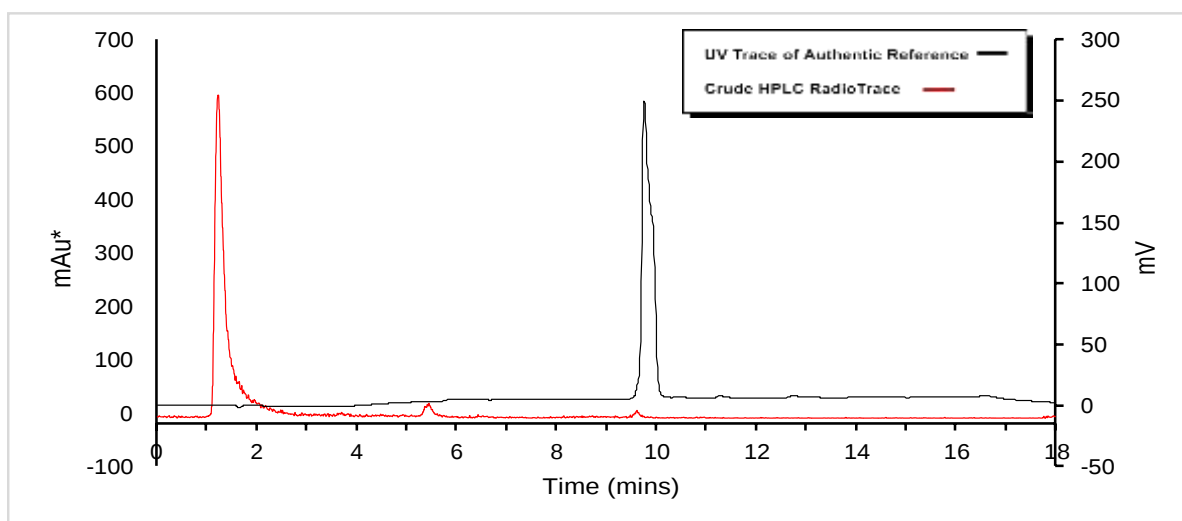
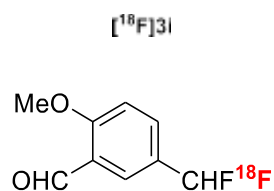


Figure SI-8 HPLC radio-trace of $[^{18}\text{F}]\mathbf{3h}$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ^{19}F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	10%	10%
2	8%	8%
3	8%	8%
4	10%	10%
Radiochemical Conversion + Standard Deviation		9% $\pm$ 1%

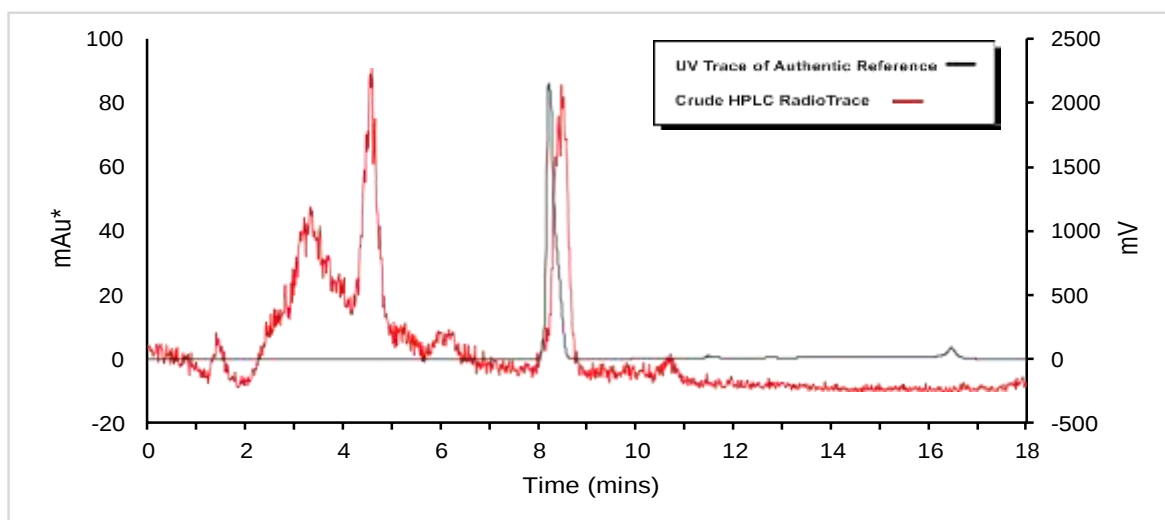
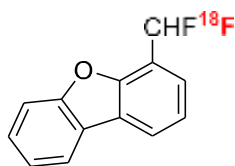


Figure SI-9 HPLC radio-trace of $[^{18}\text{F}]\mathbf{3i}$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ^{19}F reference compound (black).

[¹⁸F]3j



Reaction	Radio-TLC	Radiochemical Conversion
1	27%	27%
2	39%	39%
3	31%	26%
4	43%	35%
Radiochemical Conversion + Standard Deviation		32% ± 6%

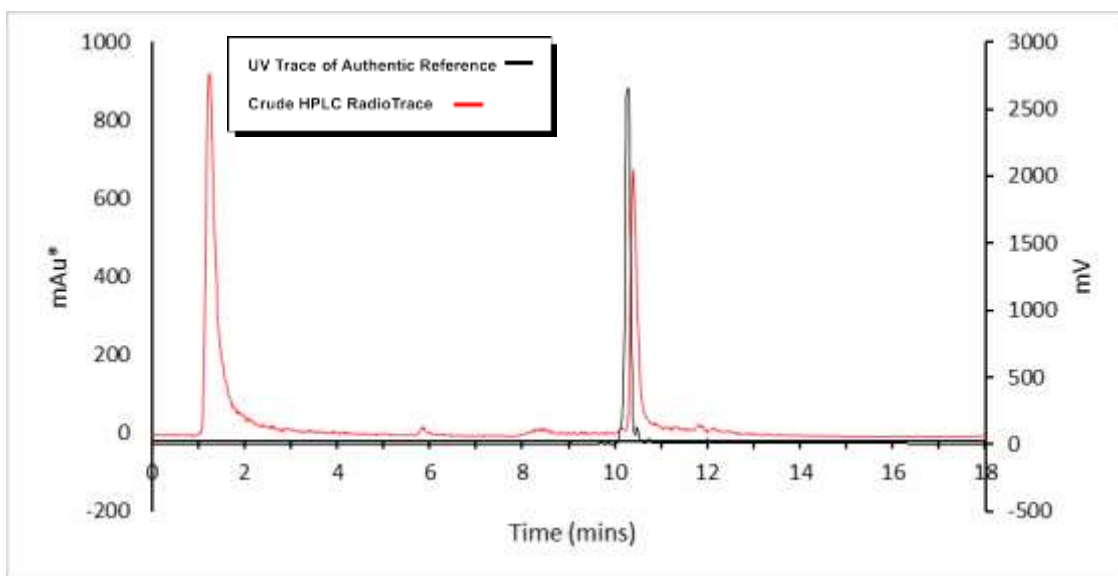
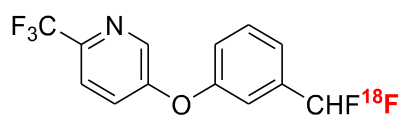


Figure SI-10 HPLC radio-trace of [¹⁸F]3j (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).

[¹⁸F]3k



Reaction	Radio-TLC	Radiochemical Conversion
1	23%	21%
2	16%	15%
3	16%	15%
4	14%	13%
Radiochemical Conversion + Standard Deviation		16% ± 4%

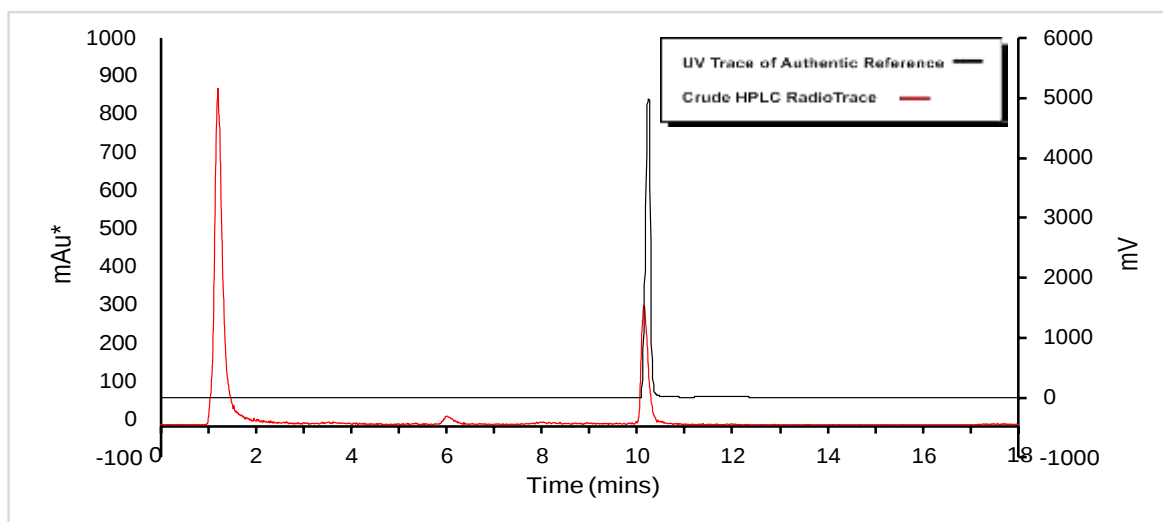
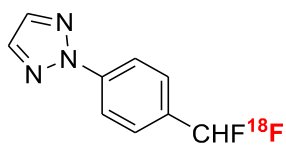


Figure SI-11 HPLC radio-trace of [¹⁸F]3k (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).

[¹⁸F]3I



Reaction	Radio-TLC	Radiochemical Conversion
1	18%	11%
2	24%	17%
3	9%	9%
4	8%	8%
Radiochemical Conversion + Standard Deviation		12% ± 4%

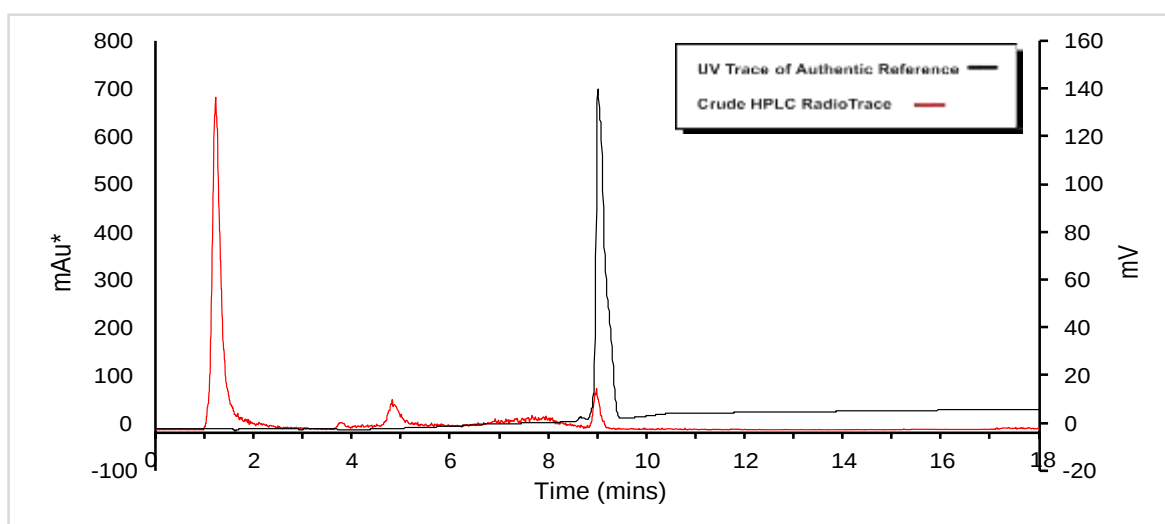
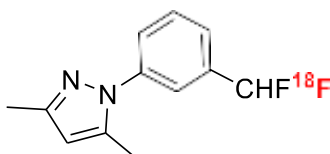


Figure SI-12 HPLC radio-trace of [¹⁸F]3I (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).

[¹⁸F]3m



Reaction	Radio-TLC	Radiochemical Conversion
1	20%	16%
2	7%	7%
3	12%	12%
4	19%	19%
Radiochemical Conversion + Standard Deviation		14% ± 5%

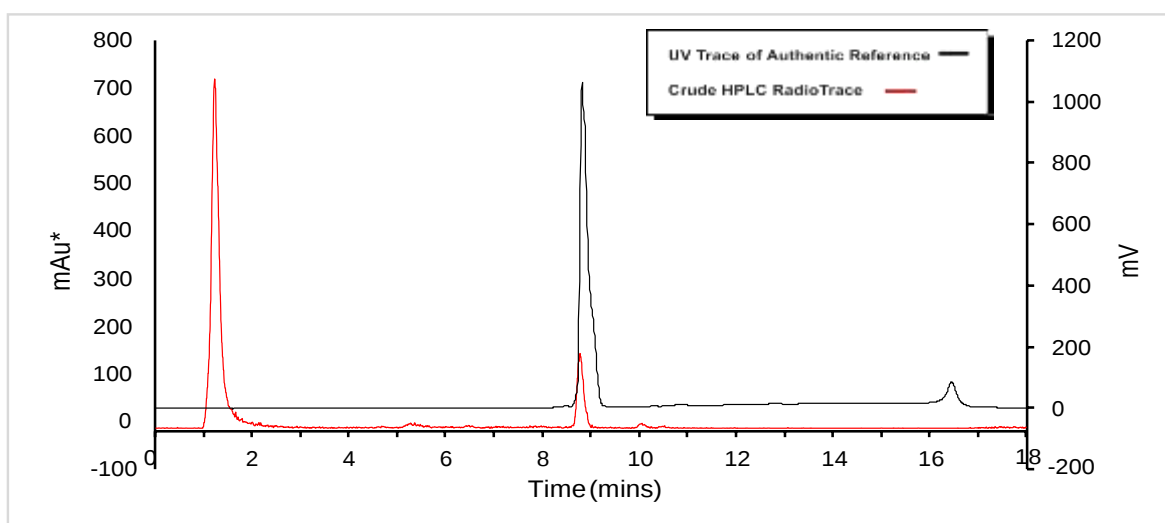
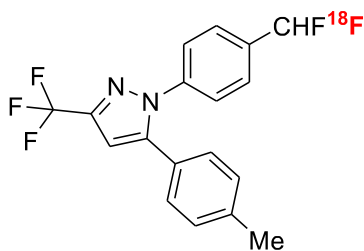


Figure SI-13 HPLC radio-trace of [¹⁸F]3m (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).

[¹⁸F]3n



Reaction	Radio-TLC	Radiochemical Conversion
1	30%	30%
2	19%	19%
3	23%	23%
4	12%	12%
Radiochemical Conversion + Standard Deviation		21% ± 6%

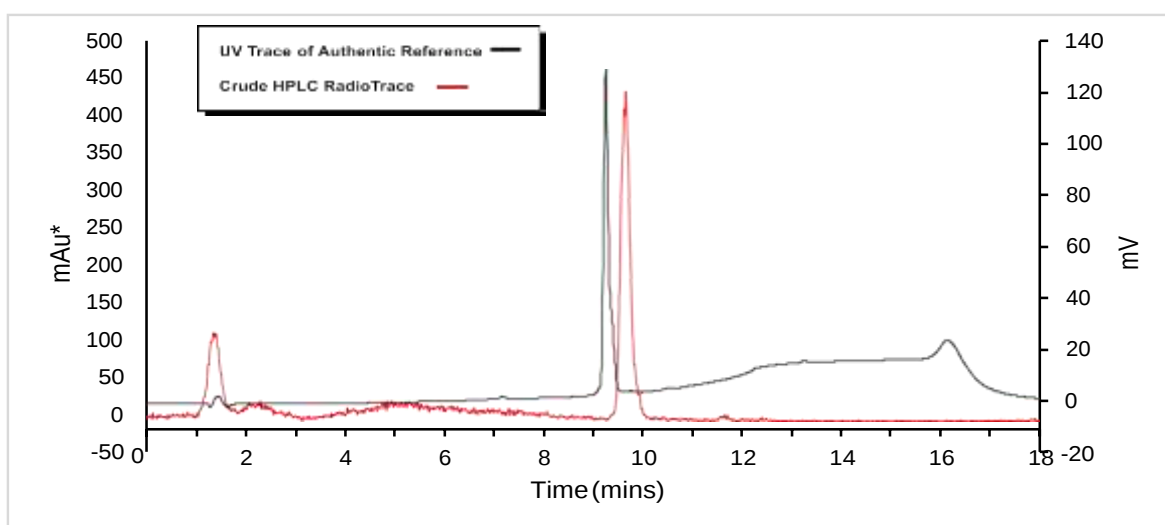
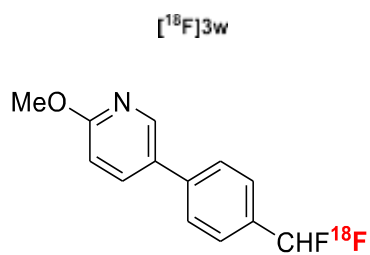


Figure SI-14. HPLC radio-trace of [¹⁸F]3n (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	30%	30%
2	27%	27%
3	7%	7%
4	31%	31%
Radiochemical Conversion + Standard Deviation		24% ± 11%

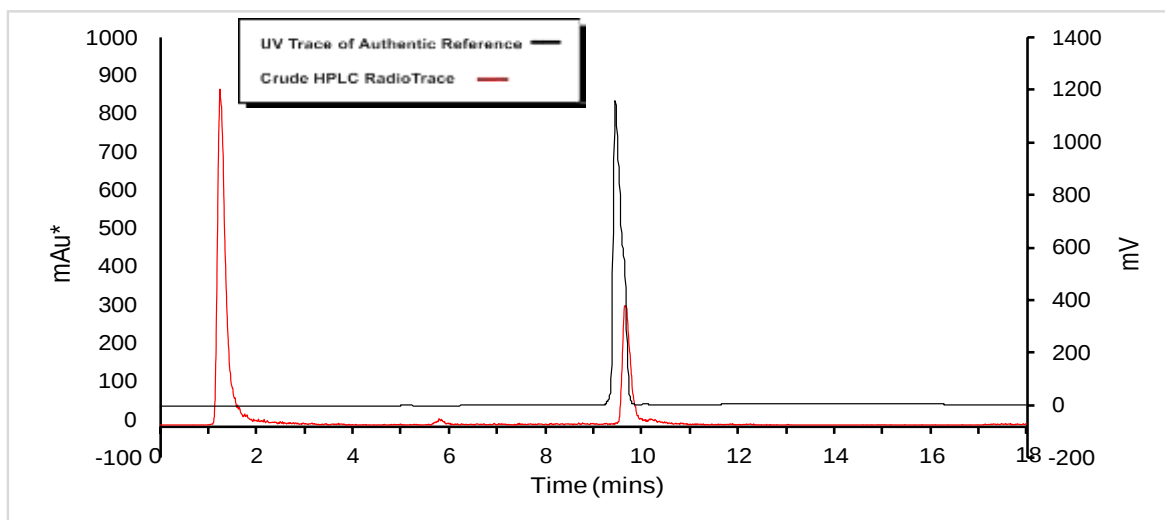
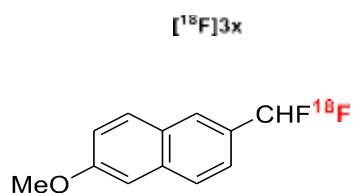


Figure SI-16 HPLC radio-trace of [¹⁸F]3w (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ¹⁹F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	40%	40%
2	27%	27%
3	22%	22%
4	34%	34%
Radiochemical Conversion + Standard Deviation		30% $\pm$ 8%

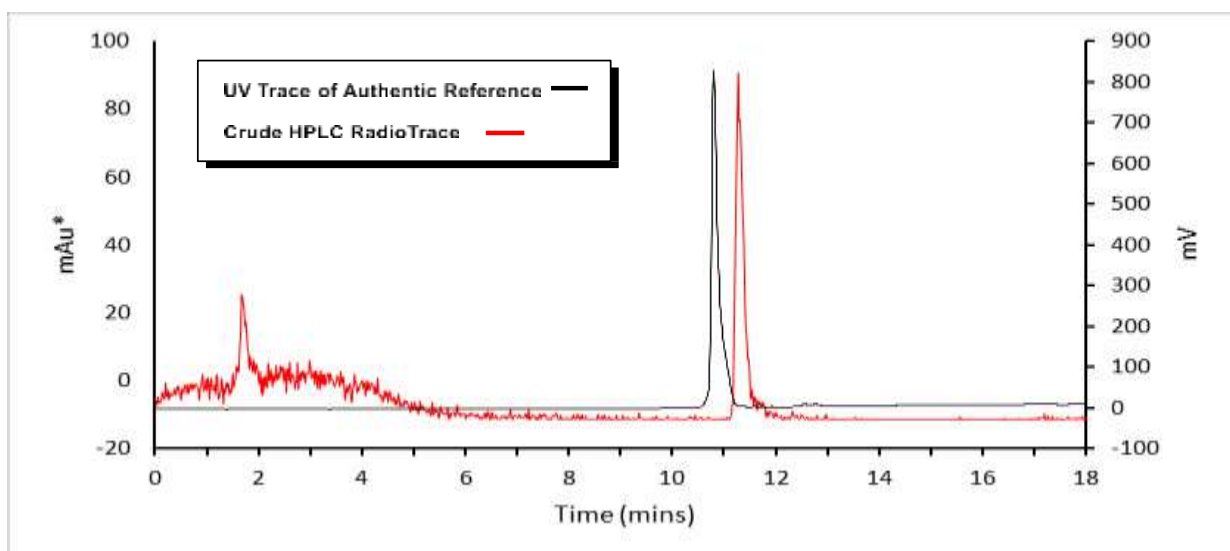
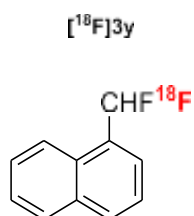


Figure SI-17 HPLC radio-trace of $[^{18}\text{F}]\mathbf{3x}$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ^{19}F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	49%	47%
2	42%	39%
3	23%	22%
4	36%	34%
Radiochemical Conversion + Standard Deviation		36% $\pm$ 10%

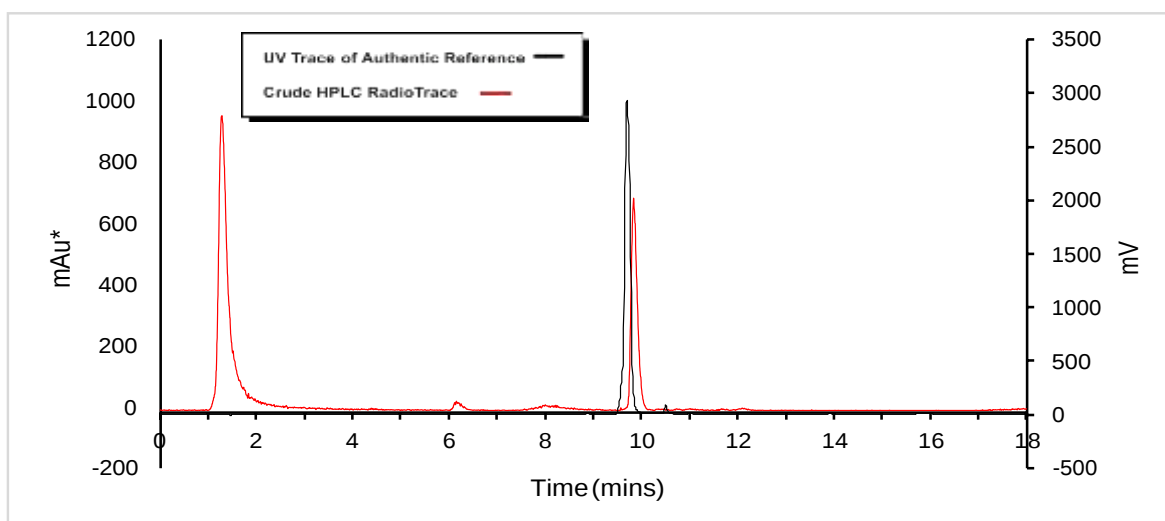
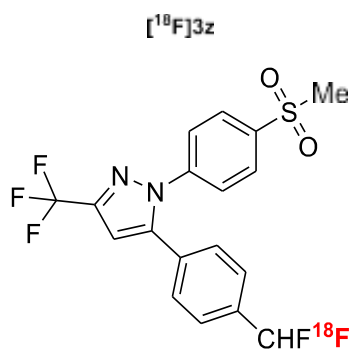


Figure SI-18 HPLC radio-trace of $[^{18}\text{F}]\mathbf{3y}$ (red) overlaid with HPLC UV-trace ($\lambda = 220 \text{ nm}$) of ^{19}F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	18%	17%
2	13%	12%
3	16%	15%
Radiochemical Conversion + Standard Deviation		15% $\pm$ 2%

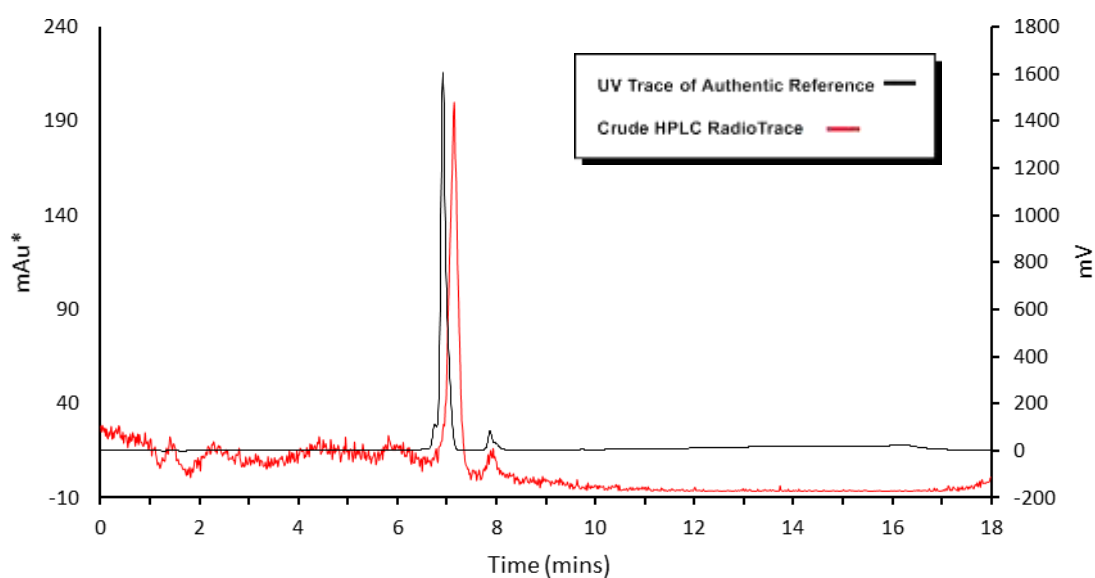
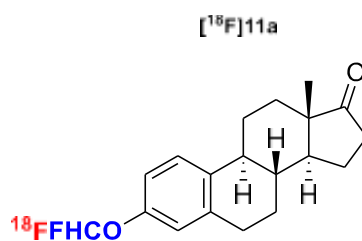


Figure SI-19 HPLC radio-trace of $[^{18}\text{F}]\mathbf{3z}$ (red) overlaid with HPLC UV-trace ($\lambda = 220$ nm) of ^{19}F reference compound (black).



Reaction	Radio-TLC	Radiochemical Conversion
1	18%	18%
2	31%	31%
3	16%	16%
Radiochemical Conversion + Standard Deviation		21% ± 6%

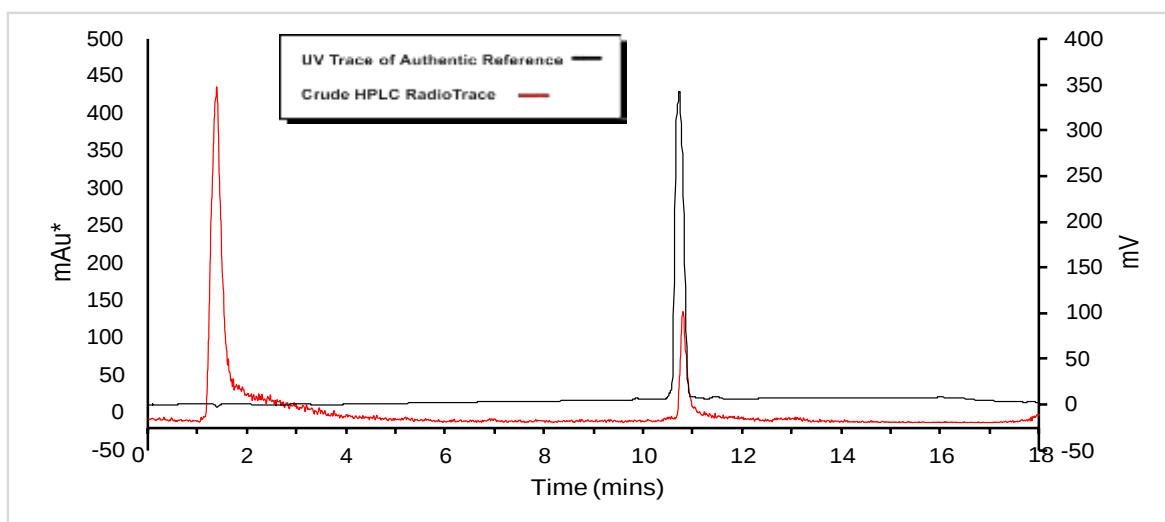


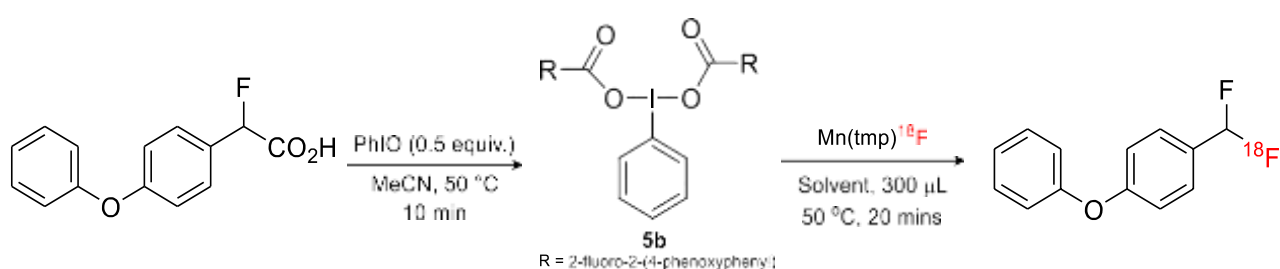
Figure SI-20 HPLC radio-trace of [¹⁸F]11a (red) overlaid with HPLC UV-trace (λ = 220 nm) of ¹⁹F reference compound (black).

Re-optimisation for Large ^{18}F dose applications:

Elution Procedure:

$[\text{}^{18}\text{F}]$ Fluoride was separated from ^{18}O -enriched-water using an anion exchange cartridge (Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 μm particle size, Waters) and released with A solution of $\text{Mn}(\text{tmp})\text{Cl}$ (8 mg) in 600 μL of anhydrous MeOH into a 5 mL V-vial containing a magnetic stir bar in the concentrator.

Optimisation under $\text{Mn}(\text{tmp})^{18}\text{F}$ Elution Conditions:



^a4 mg of

Entry	Substrate (mmol) (5b)	Solvent	RCC (n = 2)
1	0.014	DMF	0%
2	0.014	CH ₃ CN	4% $\pm$ 1%
3	0.014	DCM	0%
4	0.014	DCE	25% $\pm$ 6%
5	0.056	DCE	3% $\pm$ 1%
6 ^a	0.056	DCE	10% $\pm$ 1%
7	0.007	DCE	37% $\pm$ 0%

$\text{Mn}(\text{tmp})\text{Cl}$ spiked into reaction mixture.

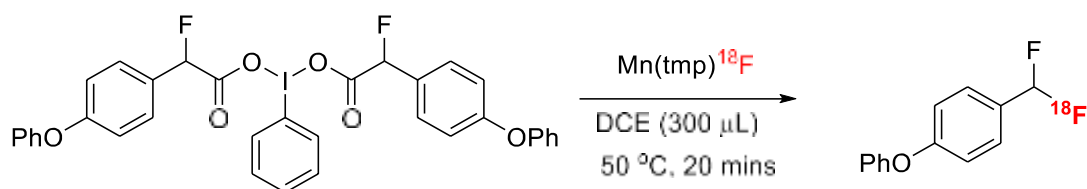
Re-optimisation for clinically relevant doses of ^{18}F :

Elution Procedure:

^{18}F Fluoride was separated from ^{18}O -enriched-water using an anion exchange cartridge (Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 μm particle size, Waters) and released with A solution of $\text{Mn}(\text{tmp})\text{Cl}$ (8 mg) in 600 μL of anhydrous MeOH into a 5 mL V-vial containing a magnetic stir bar in the concentrator.

Procedure for the ^{18}F -fluorination of 5b under Batch Scale Isolation:

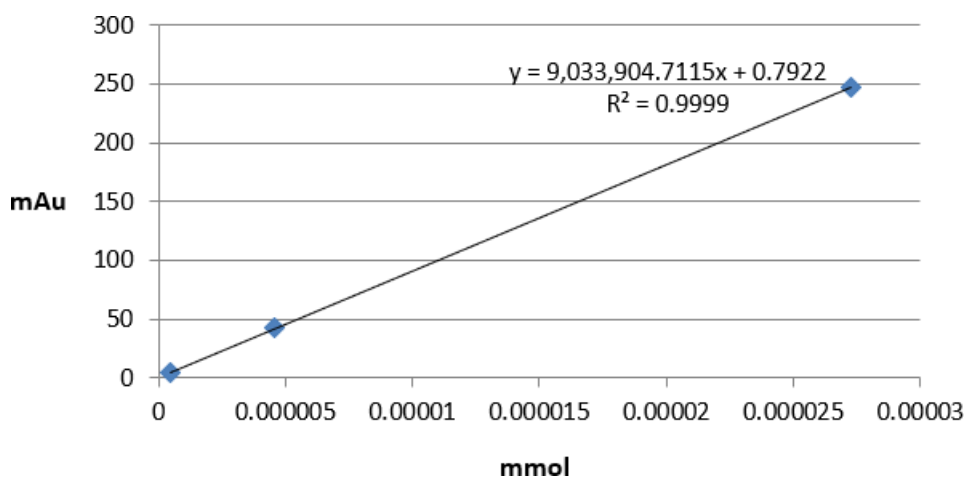
^{18}F Fluoride was separated from ^{18}O -enriched-water using an anion exchange cartridge (Sep-Pak Accell Plus QMA Carbonate Plus Light Cartridge, 46 mg Sorbent per Cartridge, 40 μm particle size, Waters) and released with A solution of $\text{Mn}(\text{tmp})\text{Cl}$ (8 mg) in 600 μL of anhydrous MeOH into a 5 mL V-vial containing a magnetic stir bar in the concentrator. The methanol was then removed at 80 $^{\circ}\text{C}$ under a flow of N_2 . Once dry, the $\text{Mn}(\text{tmp})^{18}\text{F}$ was dissolved in DCM (1 mL) and transferred to a 5 mL vial. Upon transfer, the DCM was removed at 80 $^{\circ}\text{C}$ under a flow of N_2 . Once dry, substrate (0.007 mmol) dissolved in DCE (300 μL) was added and the reaction stirred at 60 $^{\circ}\text{C}$ for 20 minutes. Upon completion, the DCE was removed at 70 $^{\circ}\text{C}$ under a flow of N_2 . The crude material was dissolved in DMF (300 μL). Upon cooling, the crude solution was diluted in H_2O (6 mL) and eluted over a C18 SepPak cartridge (preconditioned with 2 mL MeOH followed by 10 mL H_2O). The 5 mL vial was rinsed again with 10% MeCN in H_2O (2 mL) and passed over the C18 SepPak cartridge. The desired product was then eluted of the C18 SepPak cartridge with MeCN (2 mL) upon with RadioHPLC analysis was carried out to confirm the radiochemical purity of the product. Analysis was performed using a Waters Nova-Pak C18 column (4 μm , 3.9 x 150 mm) at a flow rate 1 mL/min. The overall synthesis time was 60 minutes.



Starting Activity (MBq)	Eluted (MBq)	Activity after drying MeOH (MBq)	Activity after transfer and DCM drying (MBq)	Activity after C18 (MBq)	RCY (decay corrected)
841	720	704	594	67	12%

Molar Activity Calculation:

The Molar Activity of $[^{18}\text{F}]$ 1-(difluoromethyl)-4-phenoxybenzene was assessed by radio-HPLC, using an analytical Analysis was performed using a Waters Nova-Pak C18 column (4 μm , 3.9 x 150 mm) at a flow rate 1 mL/min under HPLC gradient A.



Run	MA (GBq/ μmol)	Activity (MBq)	mmol	Area (mAu)
First injection	3.22	3.07	9.52412E-07	8.604
Second injection	2.77	2.76	9.95915 E-07	8.997

First Injection

$$y = 9,033,904.7115x + 0.7922 \text{ (y = mAu, x = mmol)}$$

Area measured from isolated sample: 8.604 mAu

Activity of isolated sample: 3.07 MBq = 3.07E-03 GBq

mmol of isolated sample = 8.604/9,033,904 = 9.52412E-07 mmol

9.52412E-07 mmol = 9.52412E-04 μ mol

MA = 0.00307/9.52412E-04 = 3.22 GBq μ mol⁻¹

Second Injection

$$y = 9,033,904.7115x + 0.7922 \text{ (y = mAu, x = mmol)}$$

Area measured from isolated sample: 8.997 mAu

Activity of isolated sample: 2.76 MBq = 2.76E-03 GBq

mmol of isolated sample = 8.997/9,033,904 = 9.95915E-07 mmol

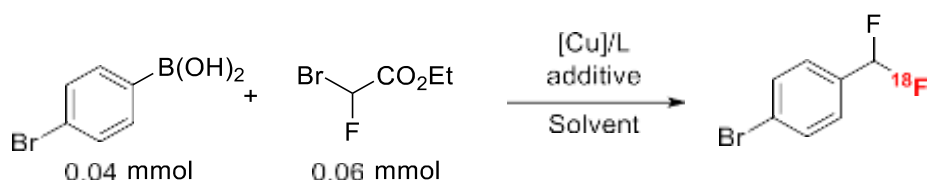
9.95915E-07 mmol = 9.95915E-04 μ mol

MA = 0.00276/9.95915E-04 = 2.77 GBq μ mol⁻¹

Average

$$\text{M.A} = 3.0 \text{ GBq}/\mu\text{mol}$$

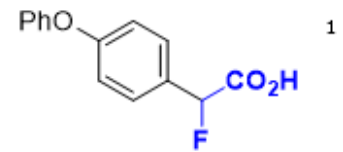
Attempt at one-pot procedure with the aryl boron reagent, ethyl 1-fluoro-2-bromoacetate and ¹⁸F-fluoride



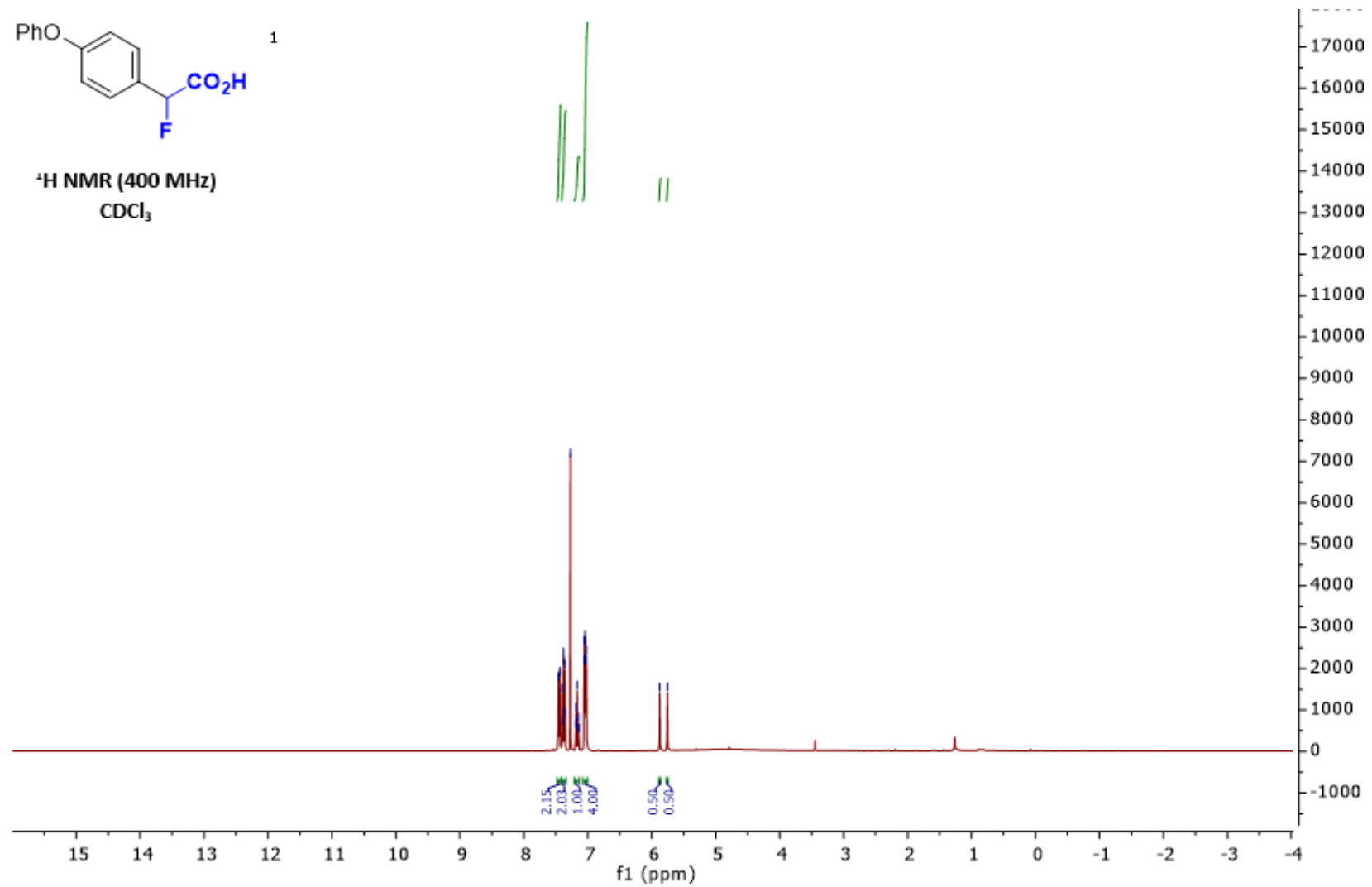
Entry	Copper source (0.06 mmol)	Additive (mmol)	Temperature (°C)	RCC (n = 2)
1	CuI	TMEDA (0.1)	r.t	0%
2	CuI	TMEDA (0.1)	r.t	0%
3	Cu(II)OTf ₂ (py) ₄	n/a	r.t	0%
4	Cu(II)OTf ₂ (py) ₄	n/a	r.t	0%
5	[(iPr)CuCl]	n/a	r.t	0%
6 ^a	[(iPr)CuCl]	n/a	r.t	0%
7	CuI	TMEDA (0.1)	90	0%
8	CuI	TMEDA (0.1)	90	0%

References

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- 12) Y. Chen, P. R. Murray, A. T. Davies and M. C. Willis, *J. Am. Chem. Soc.*, 2018, **140**, 8781.

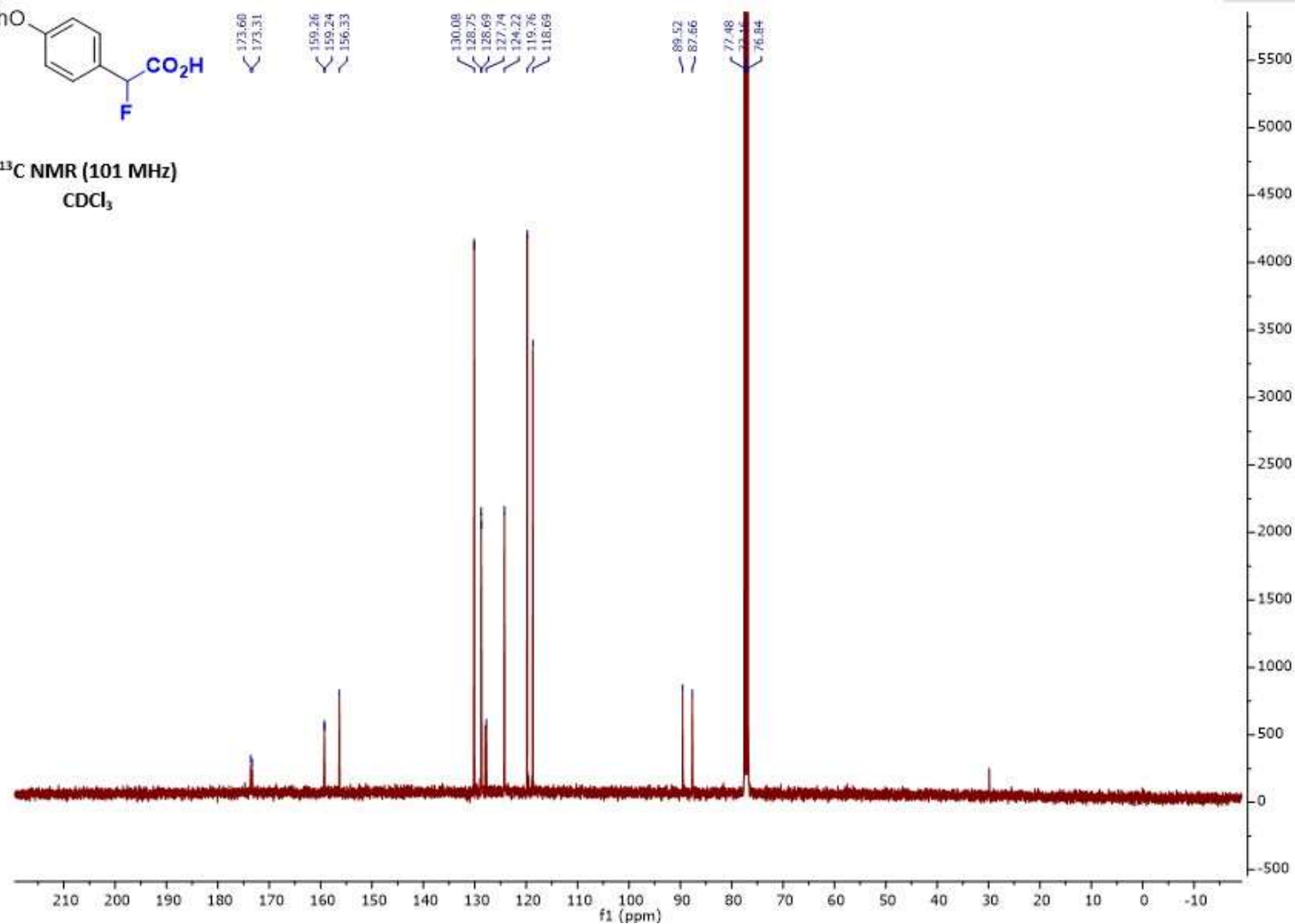


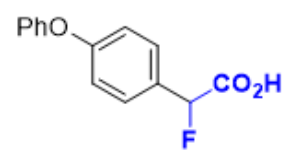
^1H NMR (400 MHz)
CDCl₃



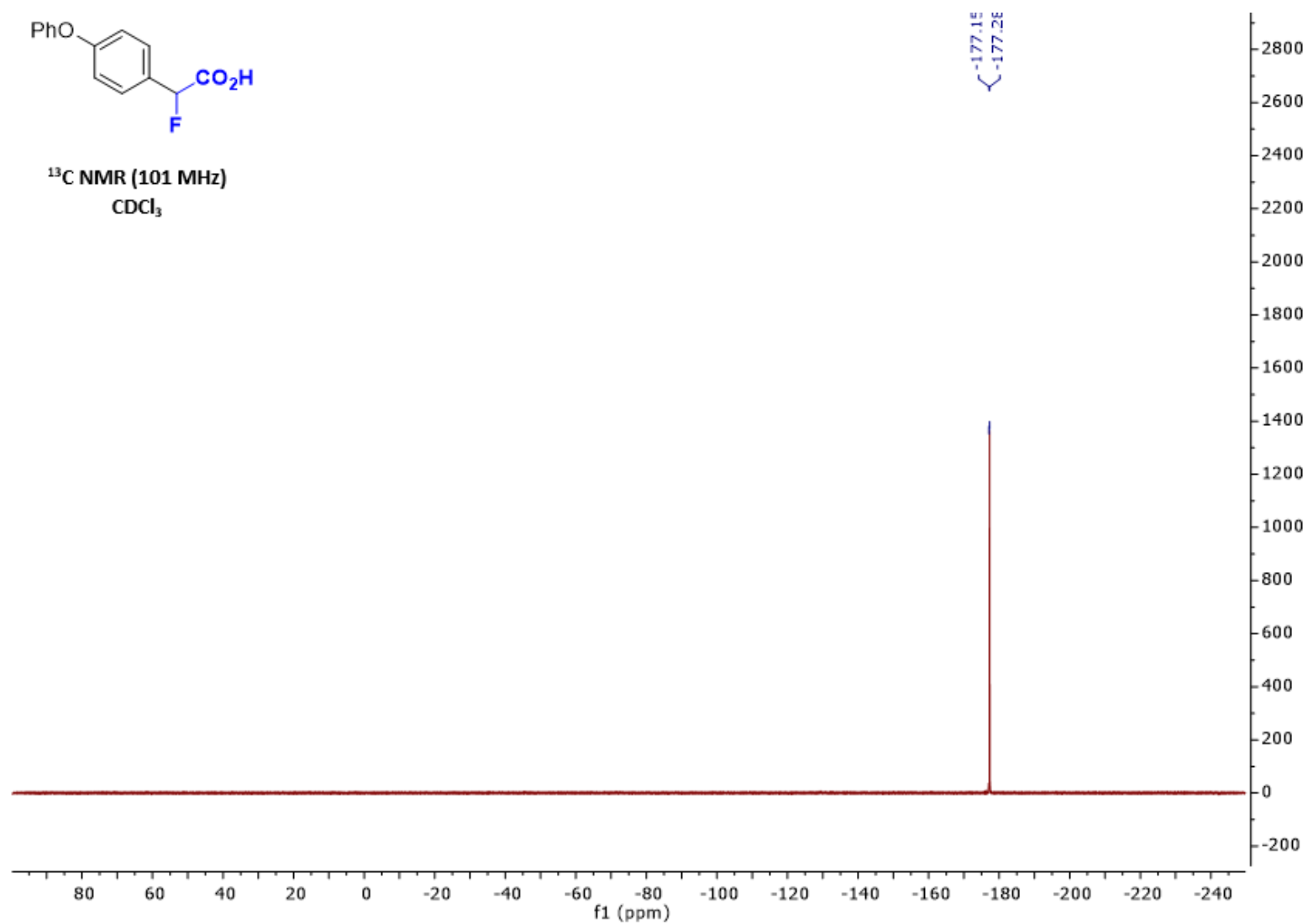


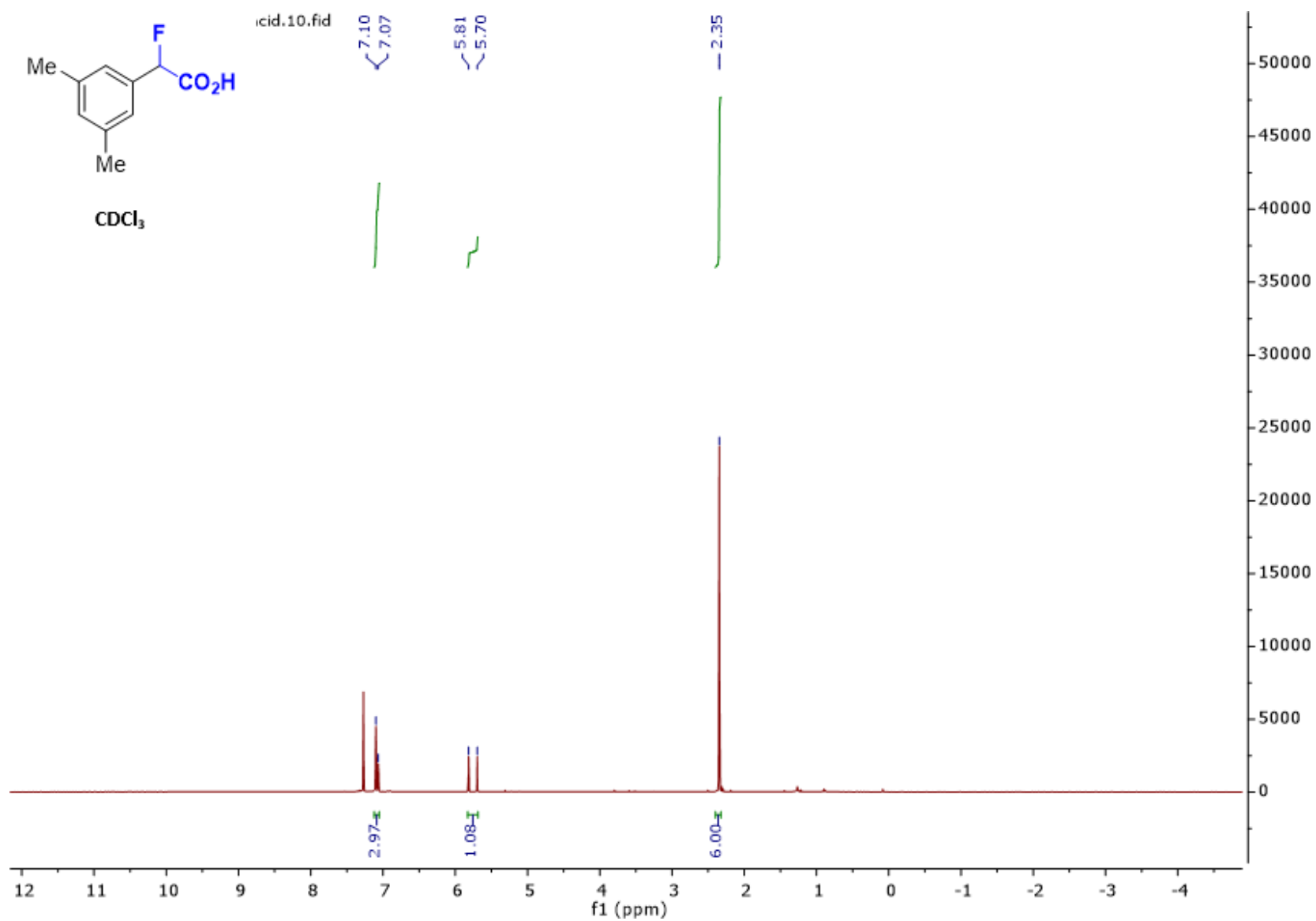
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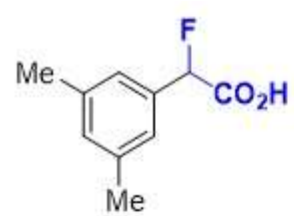




^{13}C NMR (101 MHz)
 CDCl_3

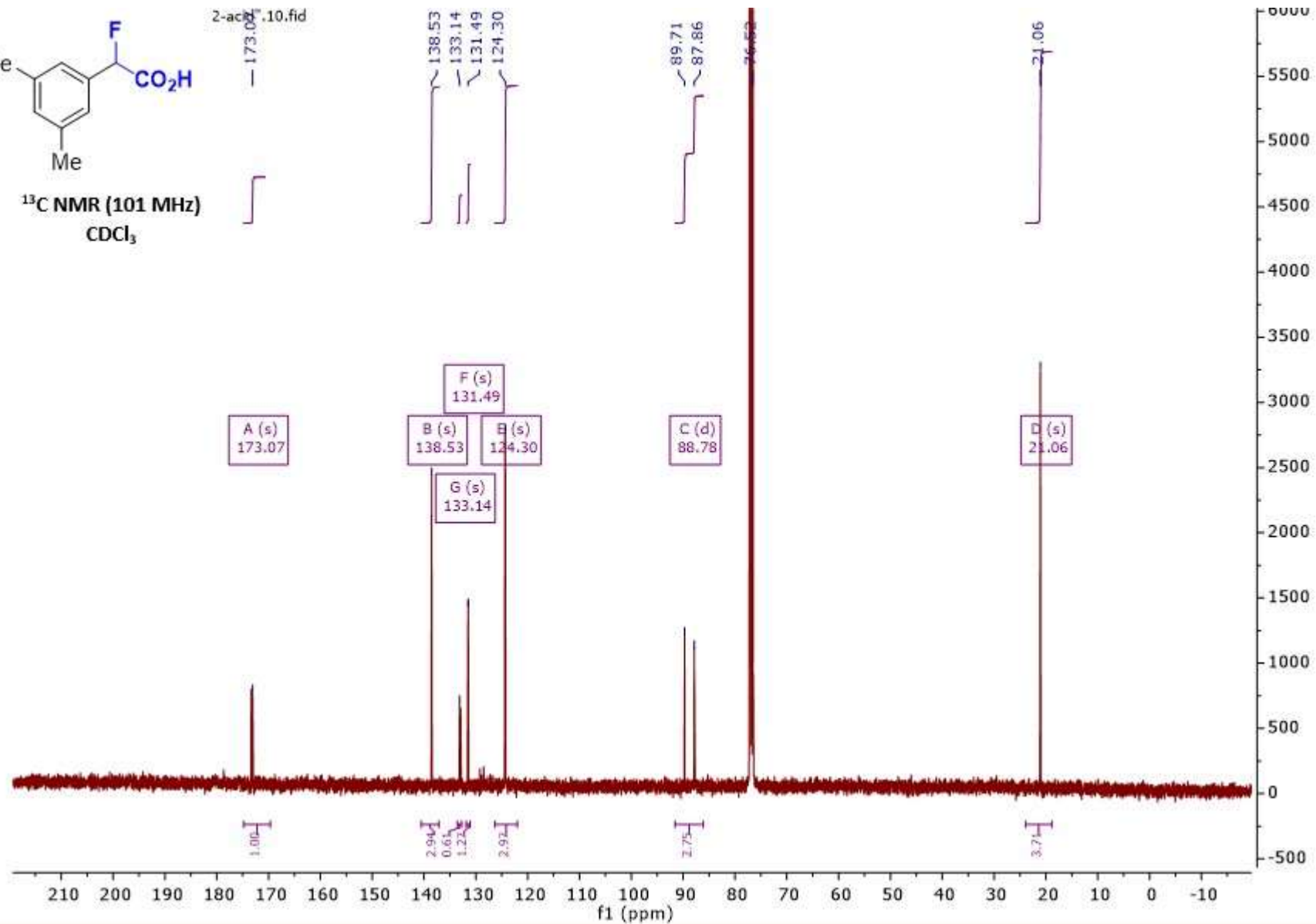






^{13}C NMR (101 MHz)
 CDCl_3

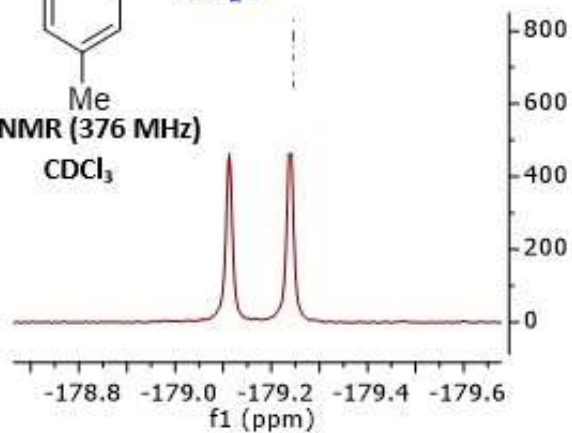
2-acid.10.fid



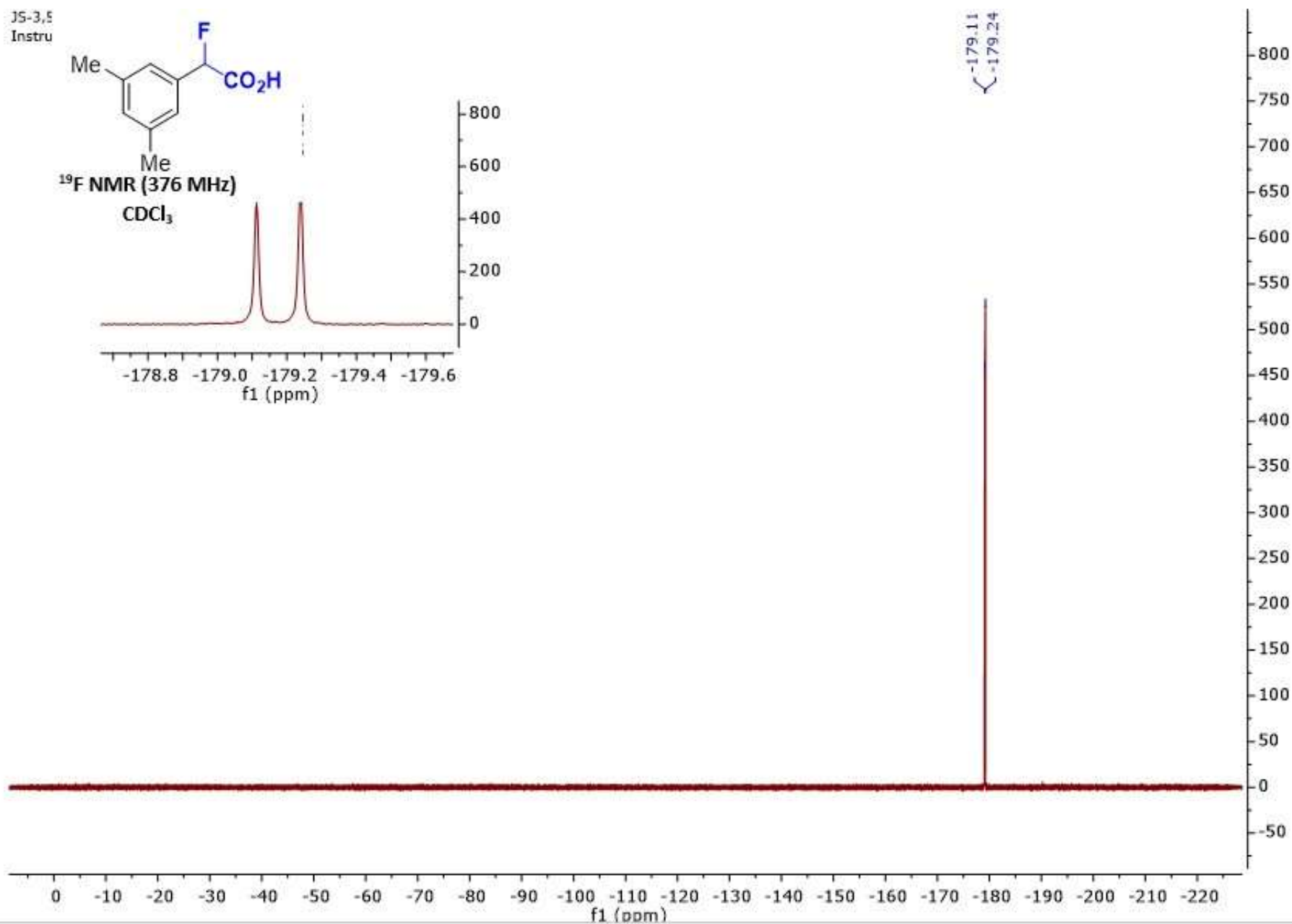
JS-3,5
Instru

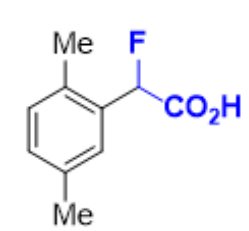


^{19}F NMR (376 MHz)
 CDCl_3



-179.11
-179.24

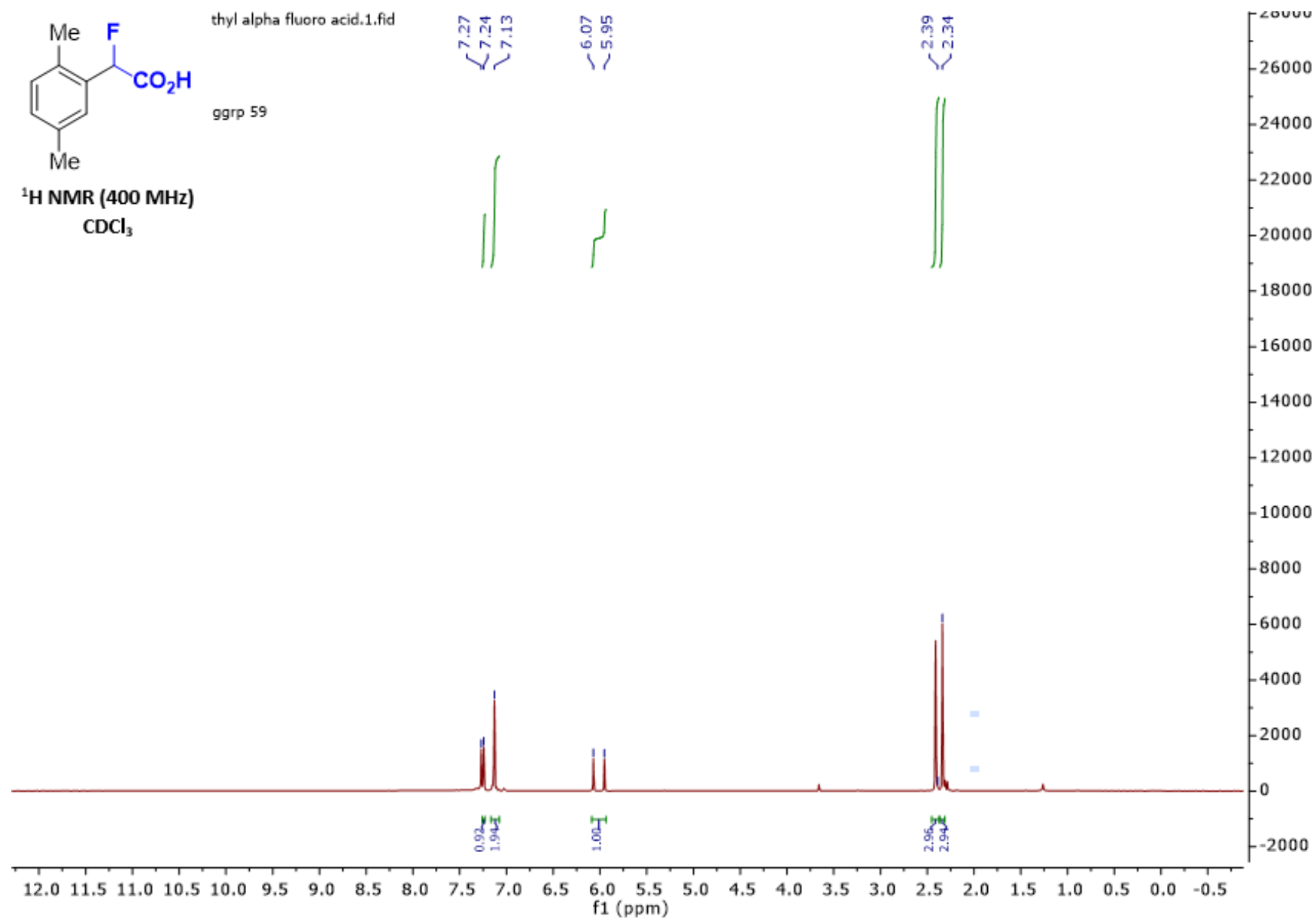


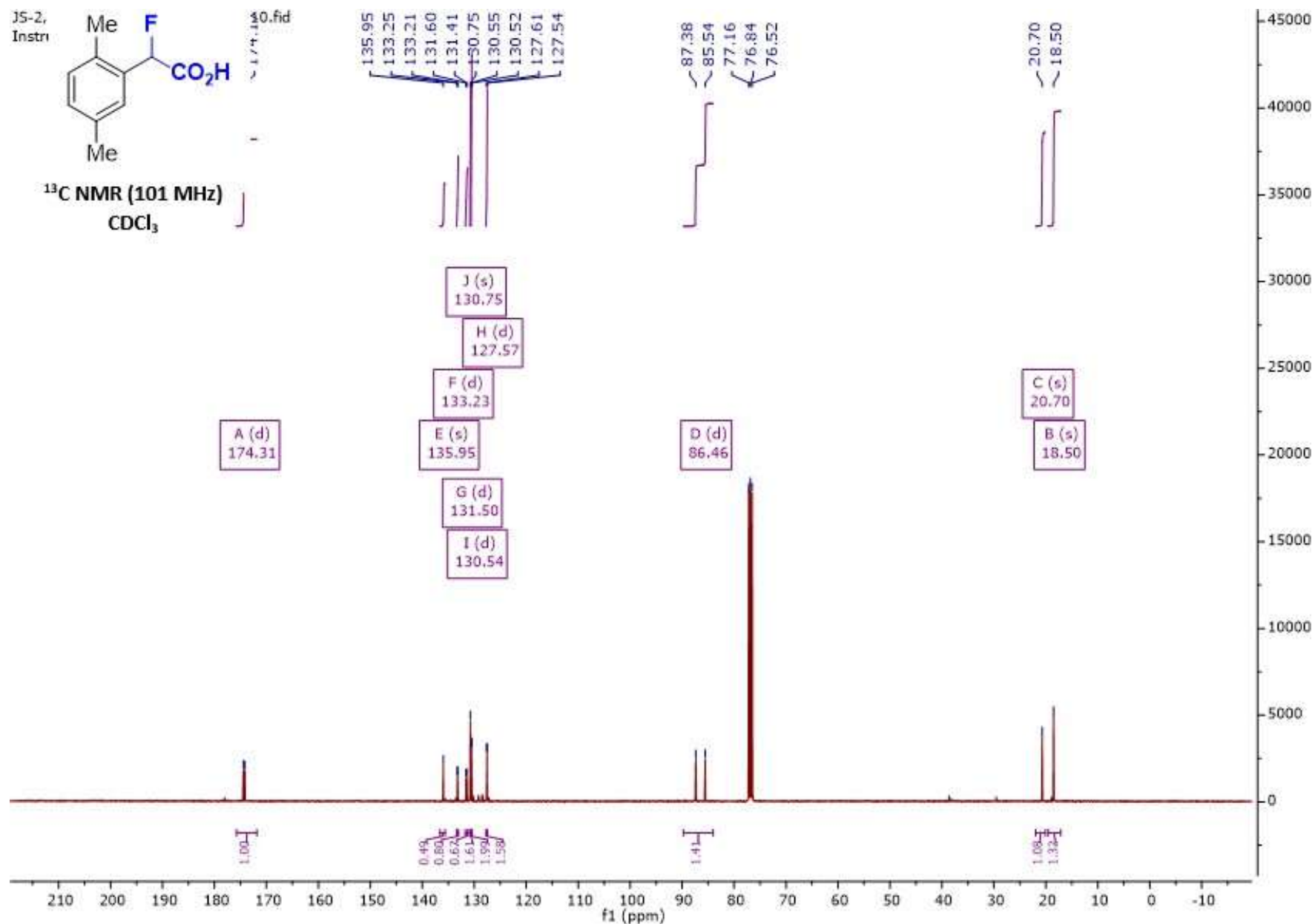
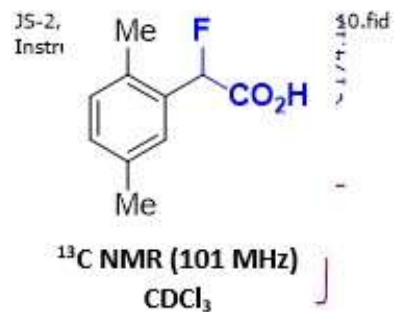


thyl alpha fluoro acid.1.fid

ggrp 59

¹H NMR (400 MHz)
CDCl₃





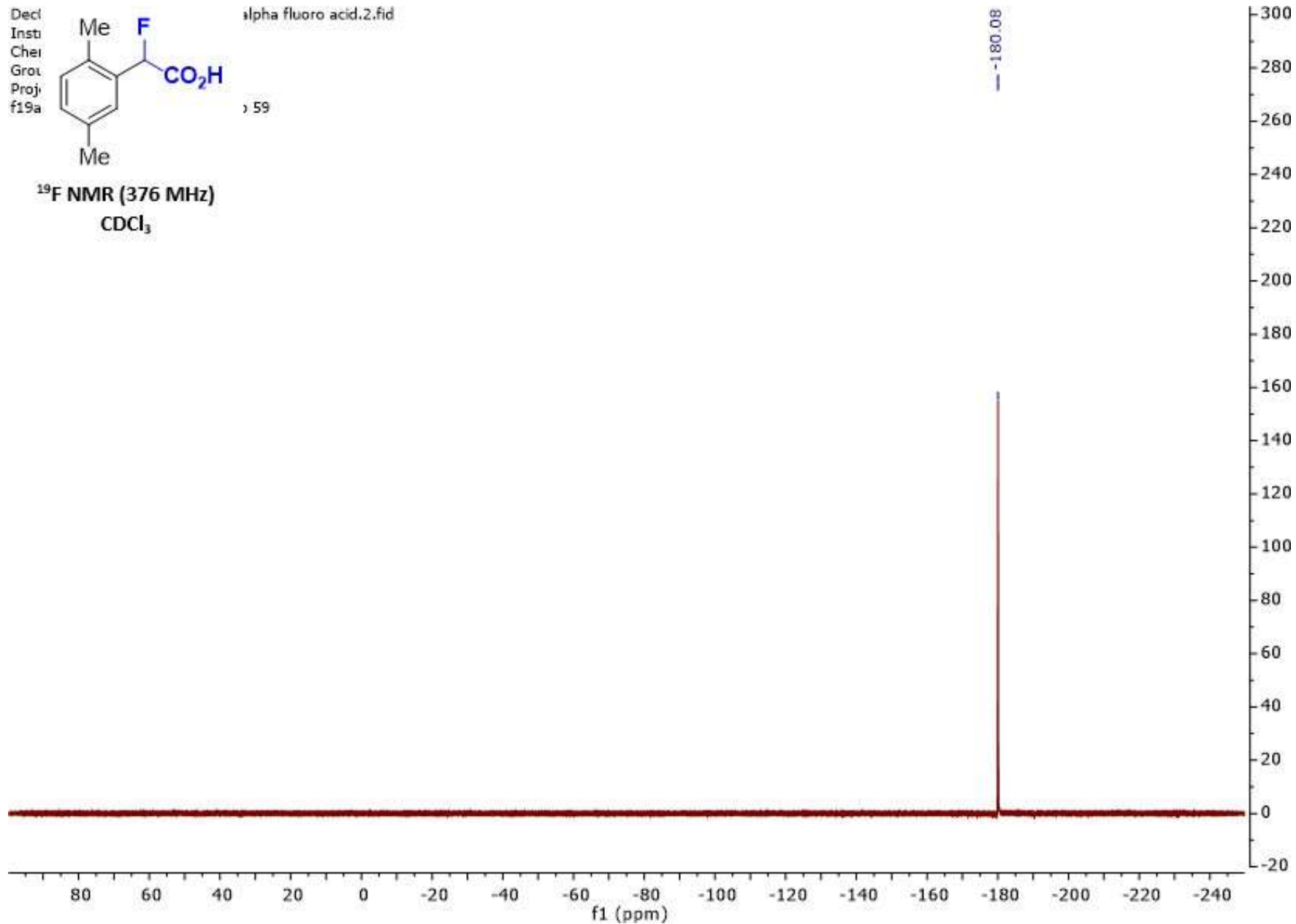
Dec
Inst
Chem
Grou
Proj
f19a

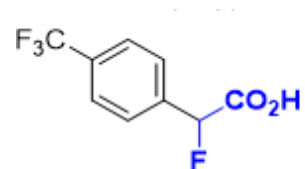


alpha fluoro acid.2.fid

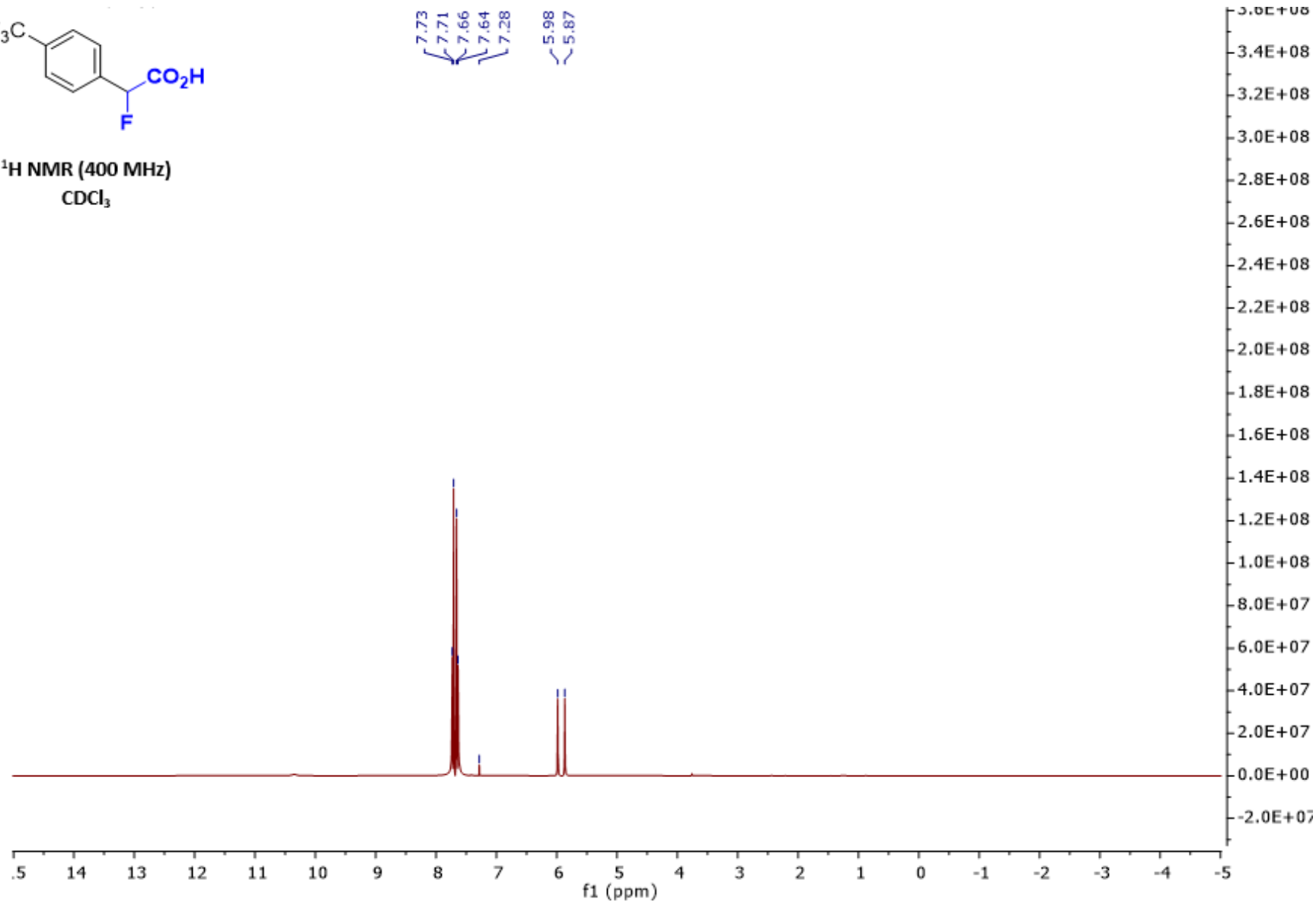
59

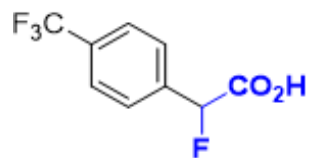
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CDCl₃



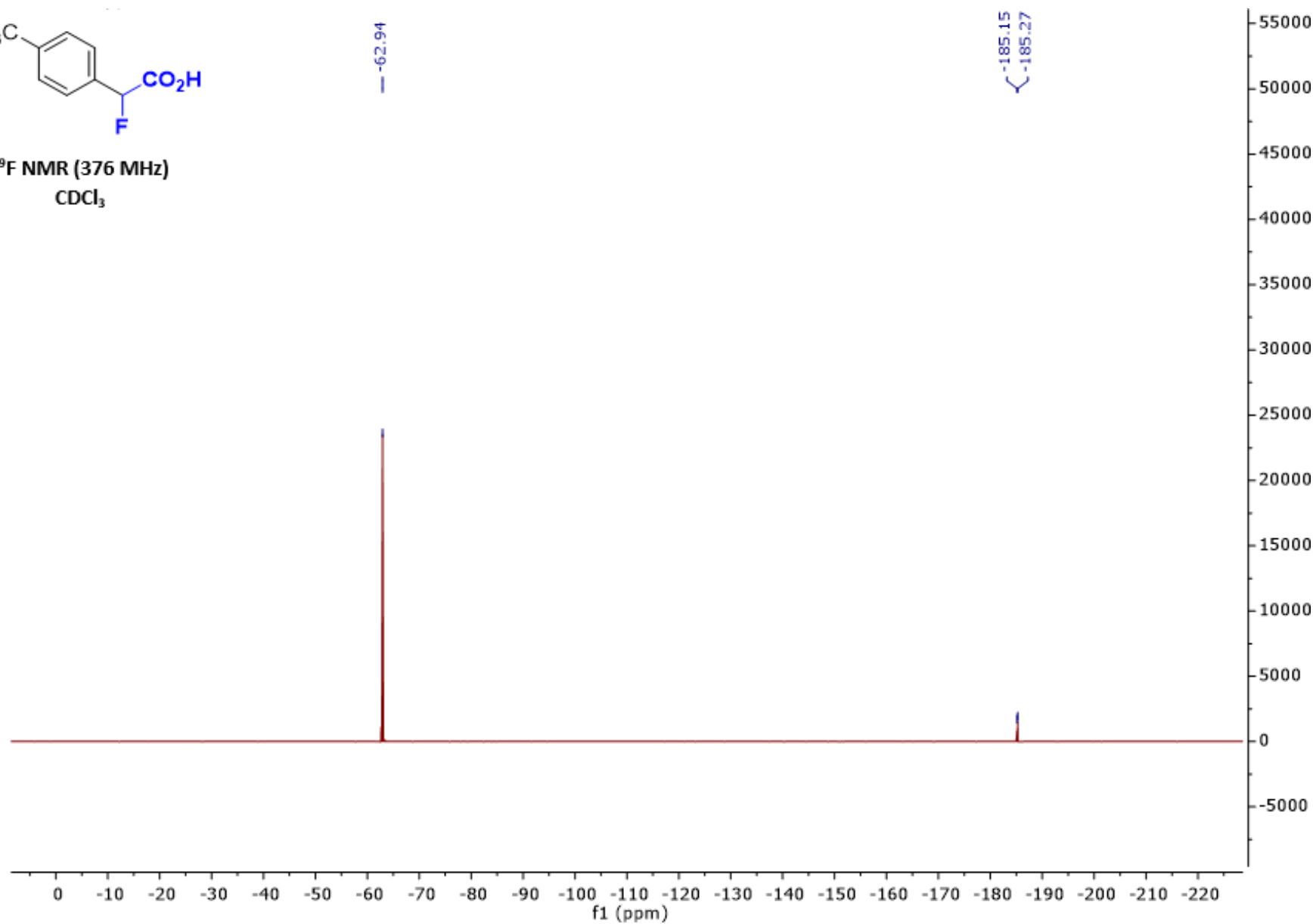


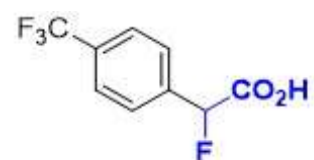
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 CDCl_3



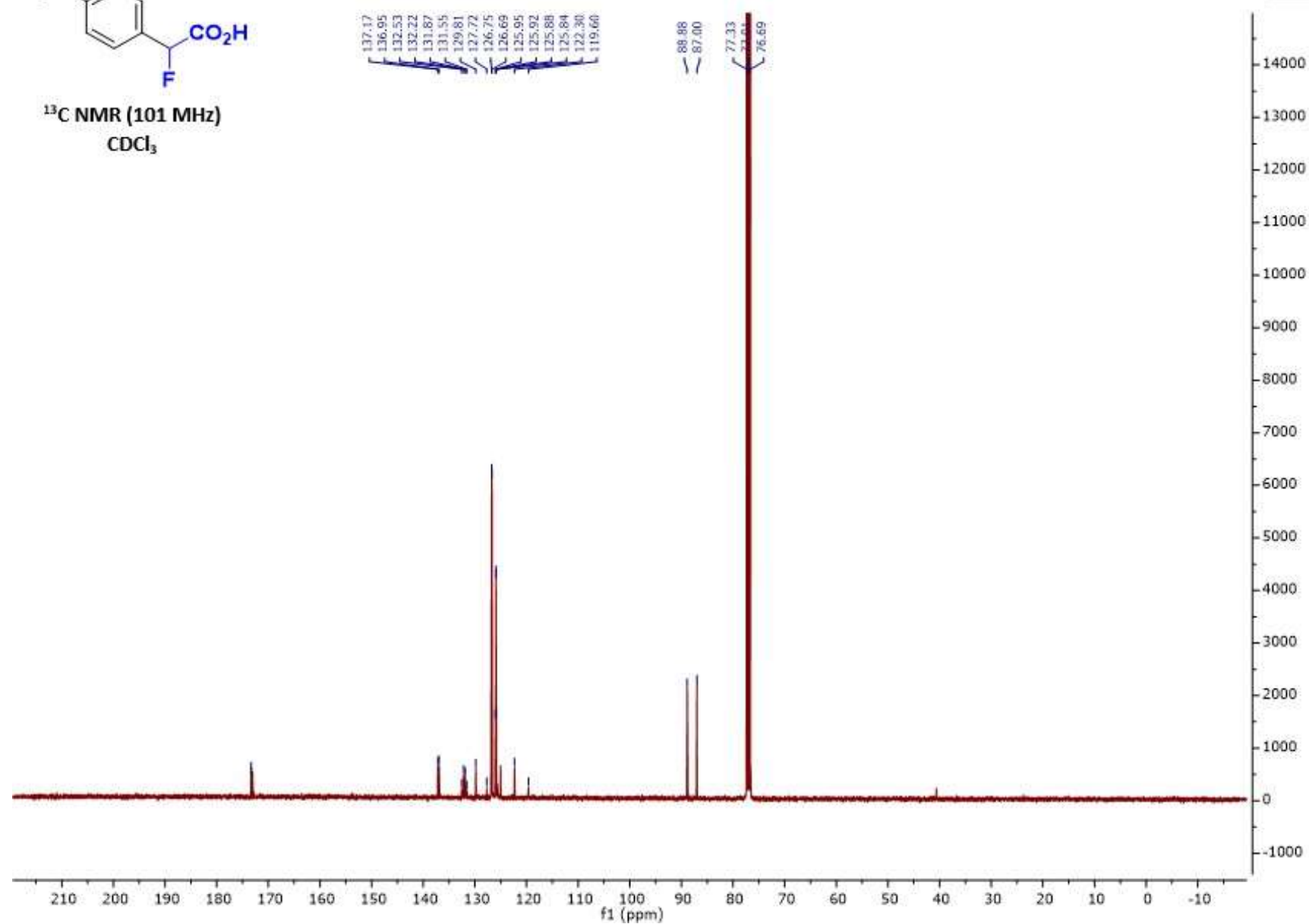


^{19}F NMR (376 MHz)
 CDCl_3



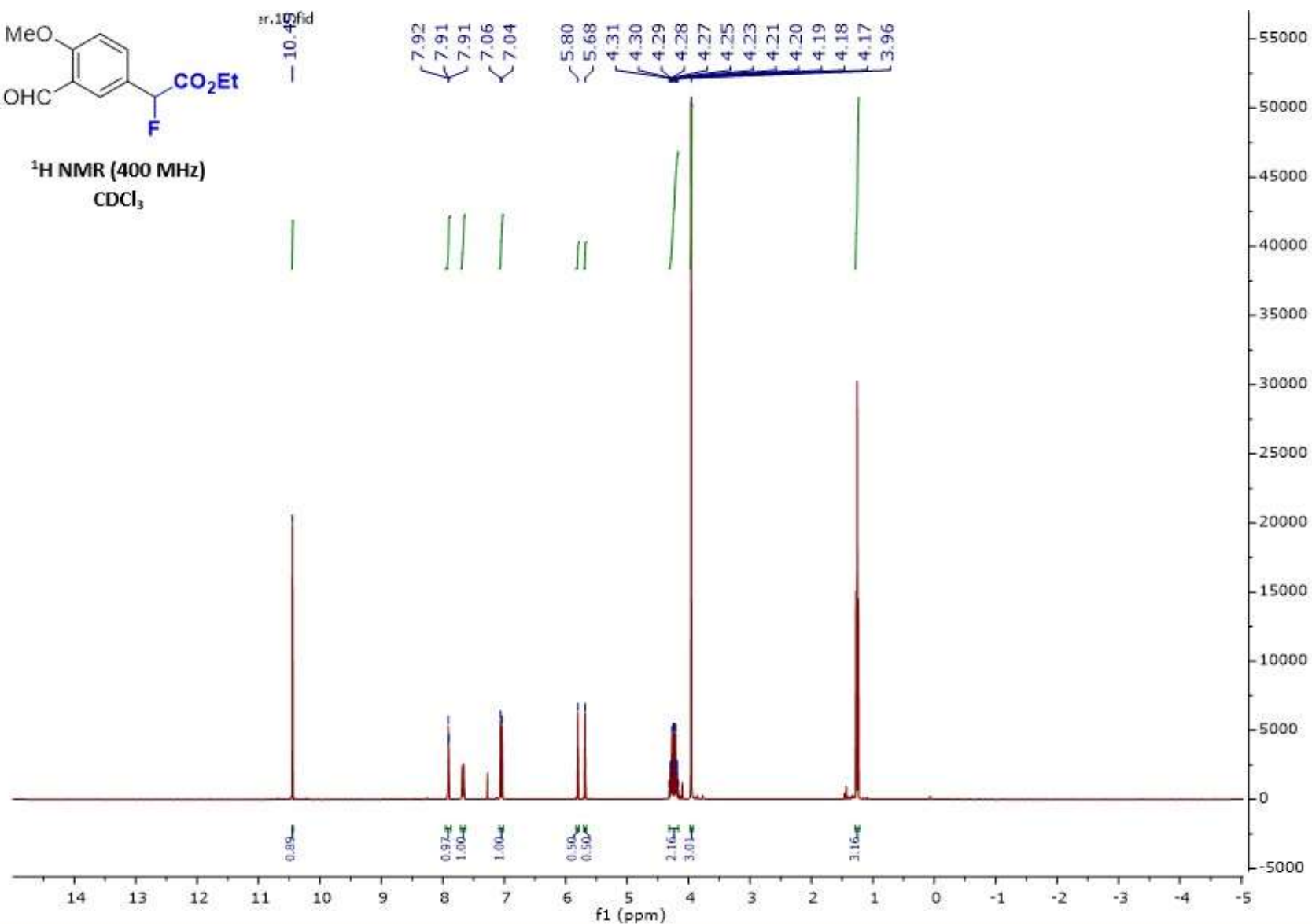


^{13}C NMR (101 MHz)
 CDCl_3





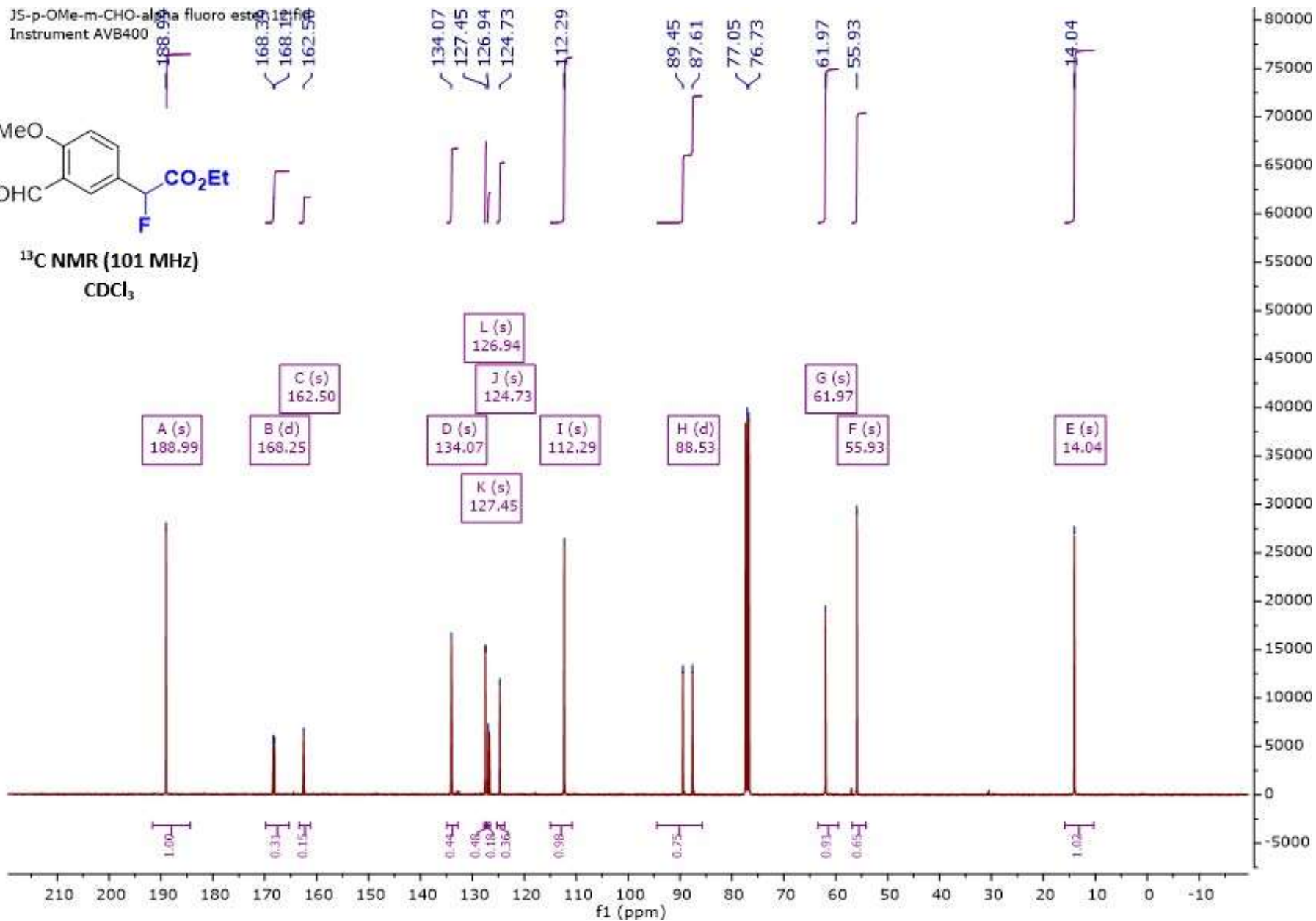
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CDCl₃

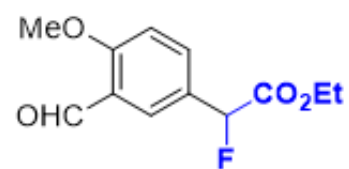


J5-p-OMe-m-CHO-alpha fluoro ester 12.f10
Instrument AVB400

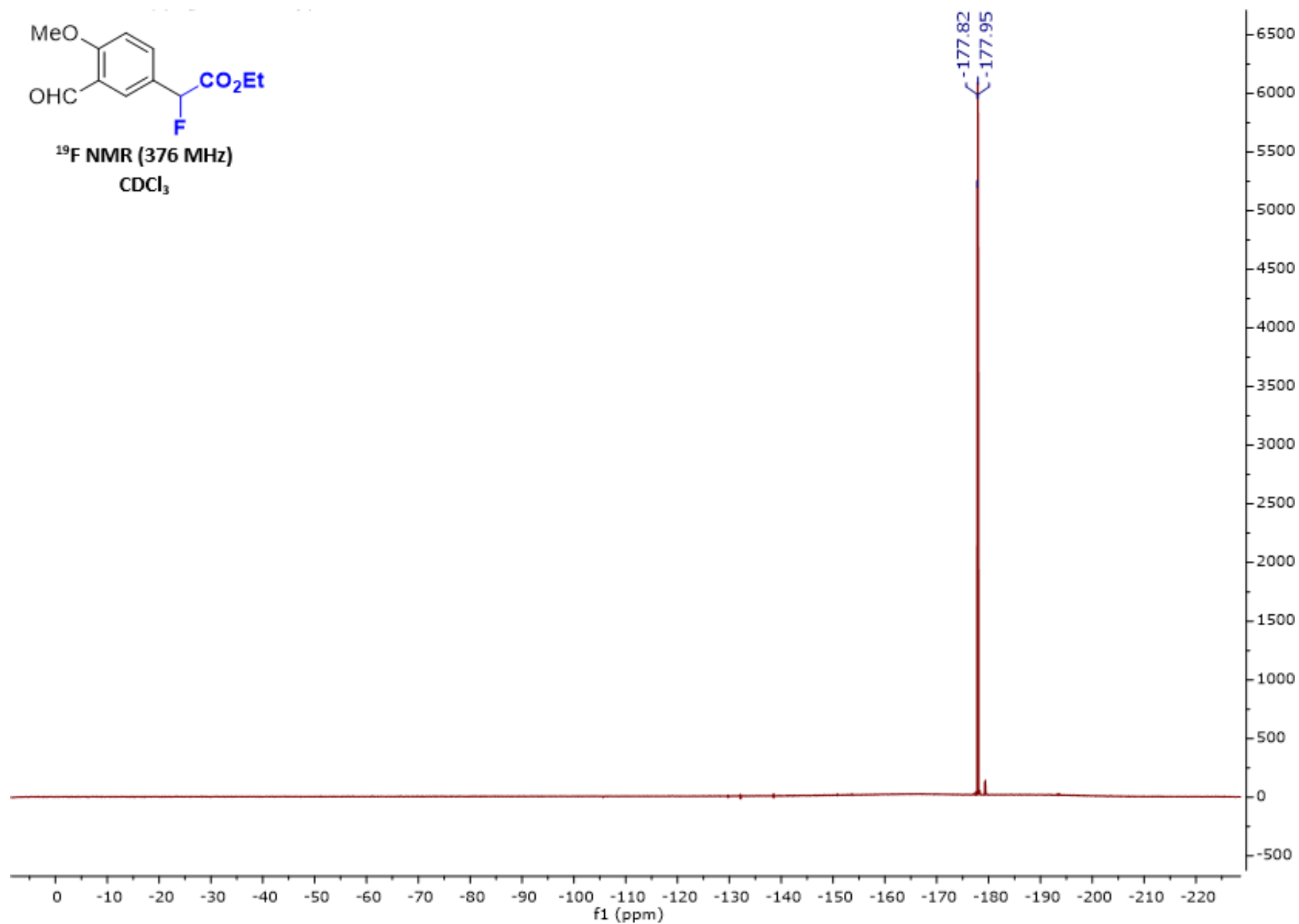


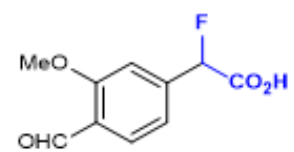
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 CDCl_3



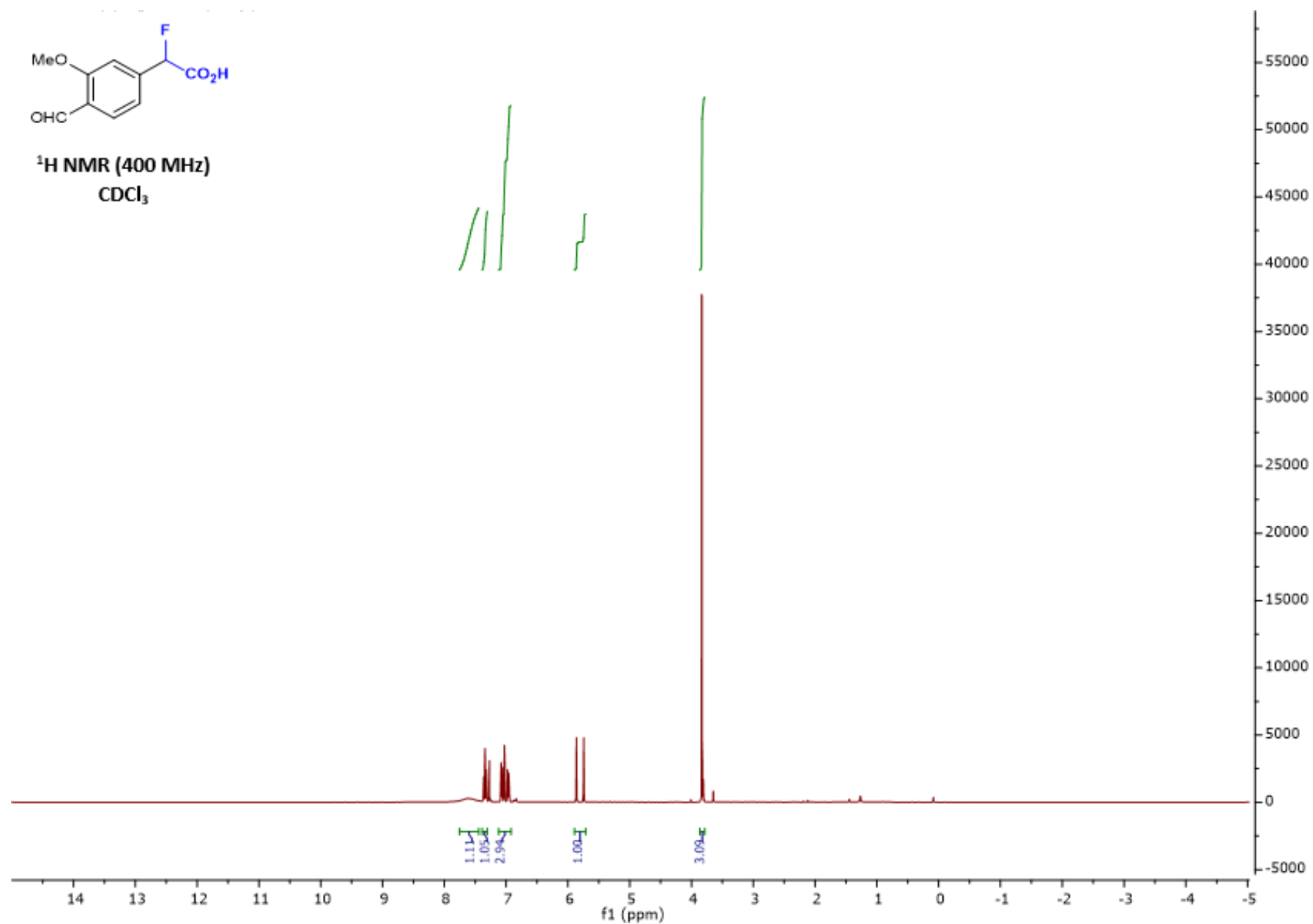


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CDCl₃



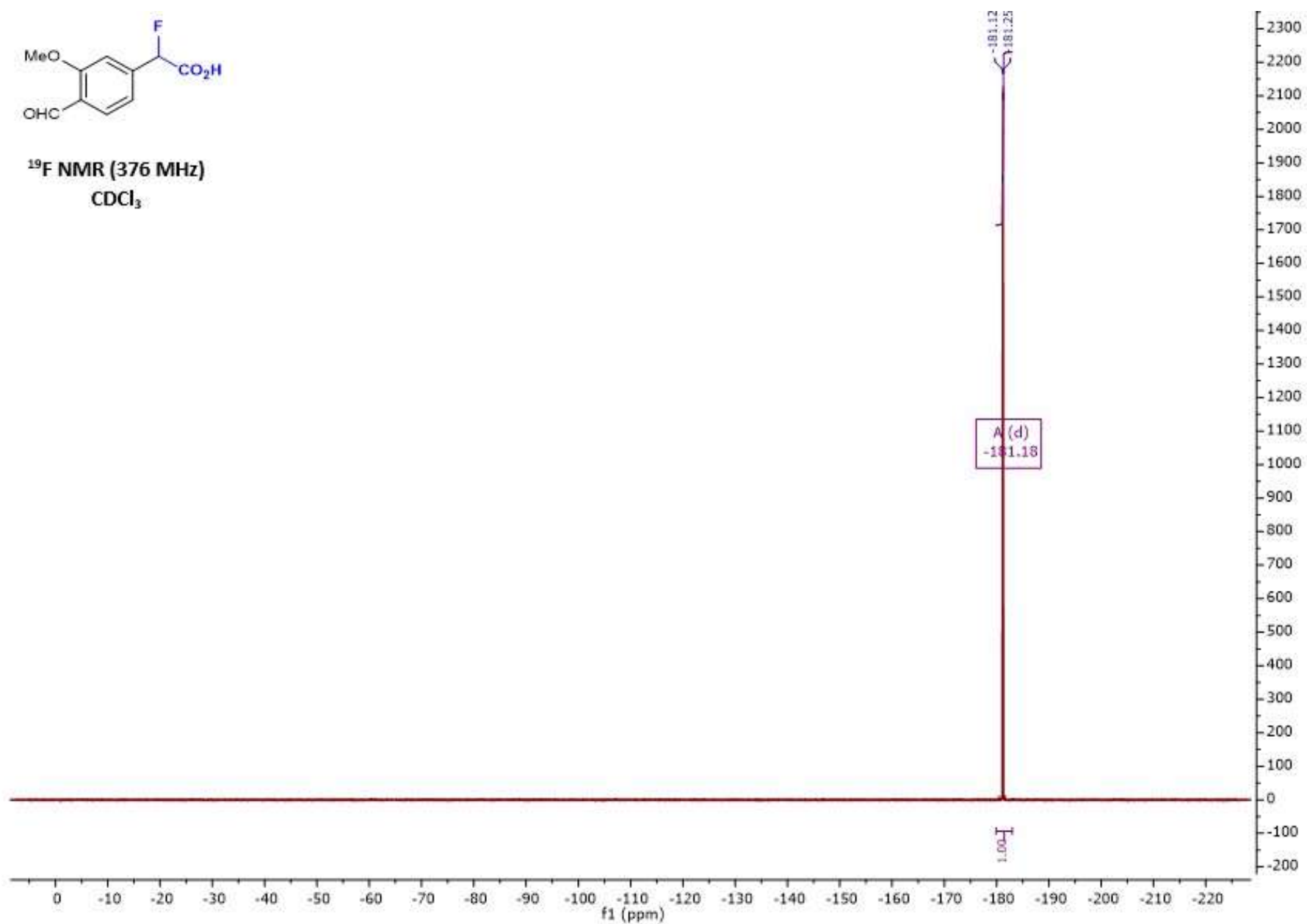


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 CDCl_3



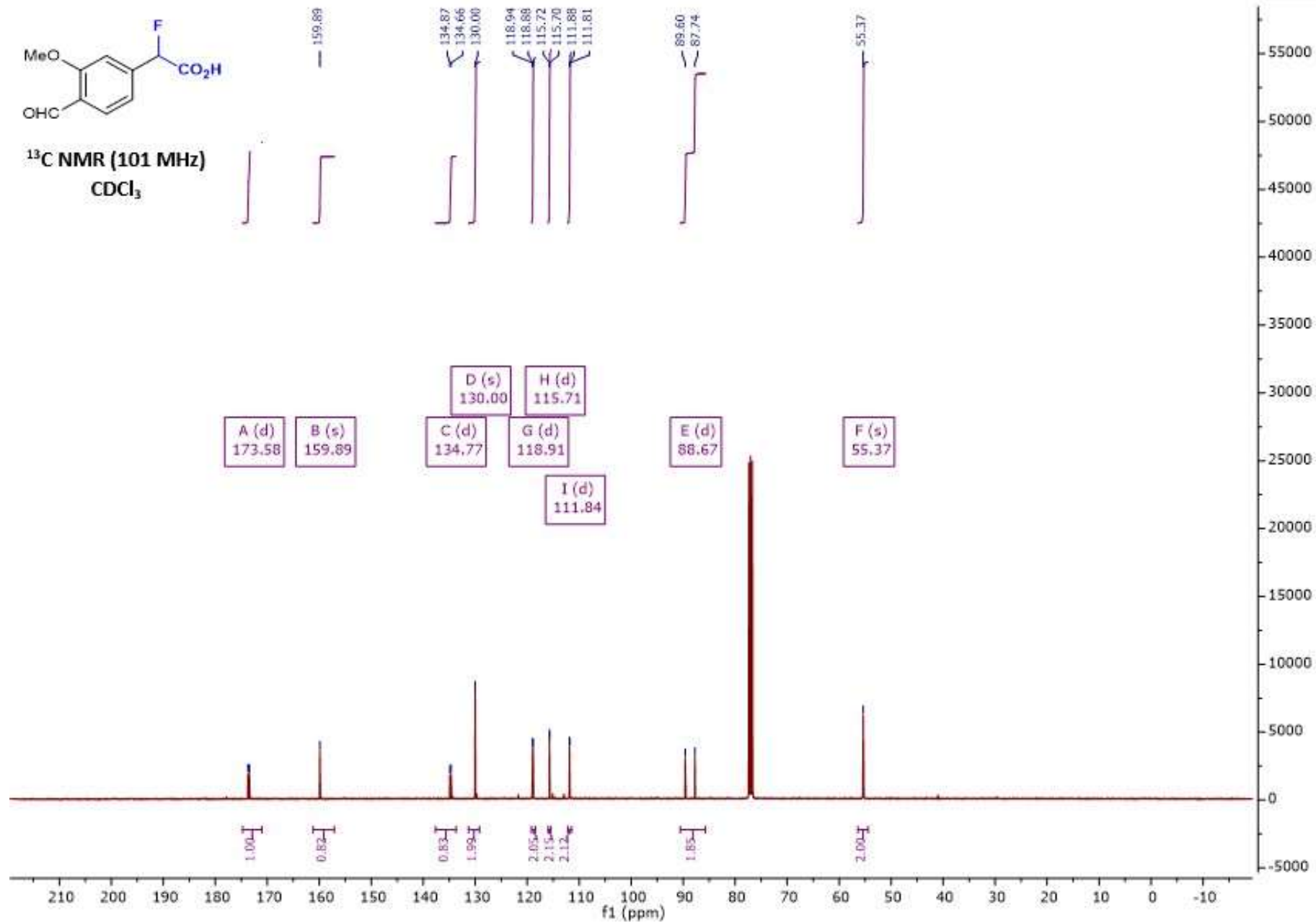


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 CDCl_3



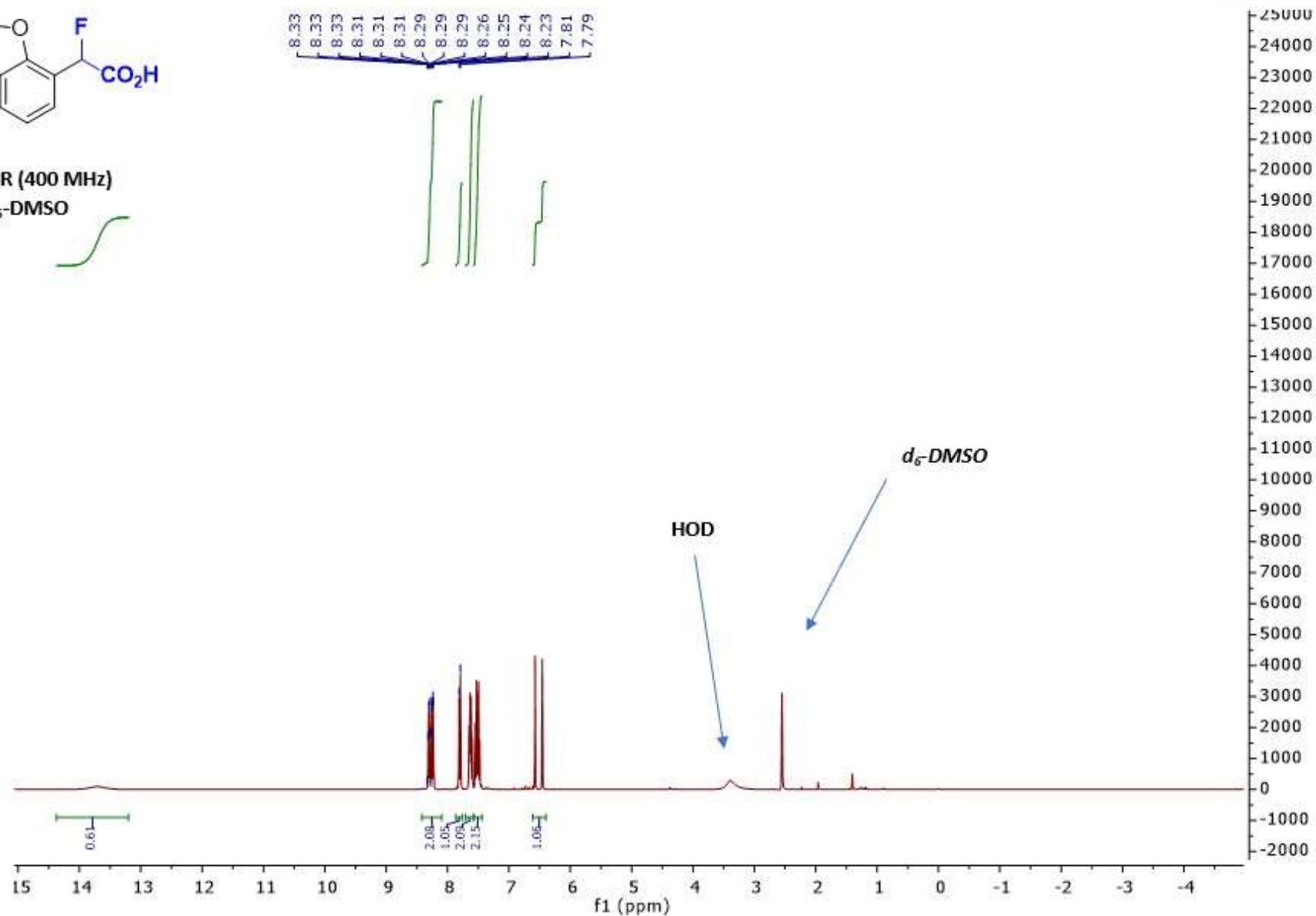


¹³C NMR (101 MHz)
CDCl₃



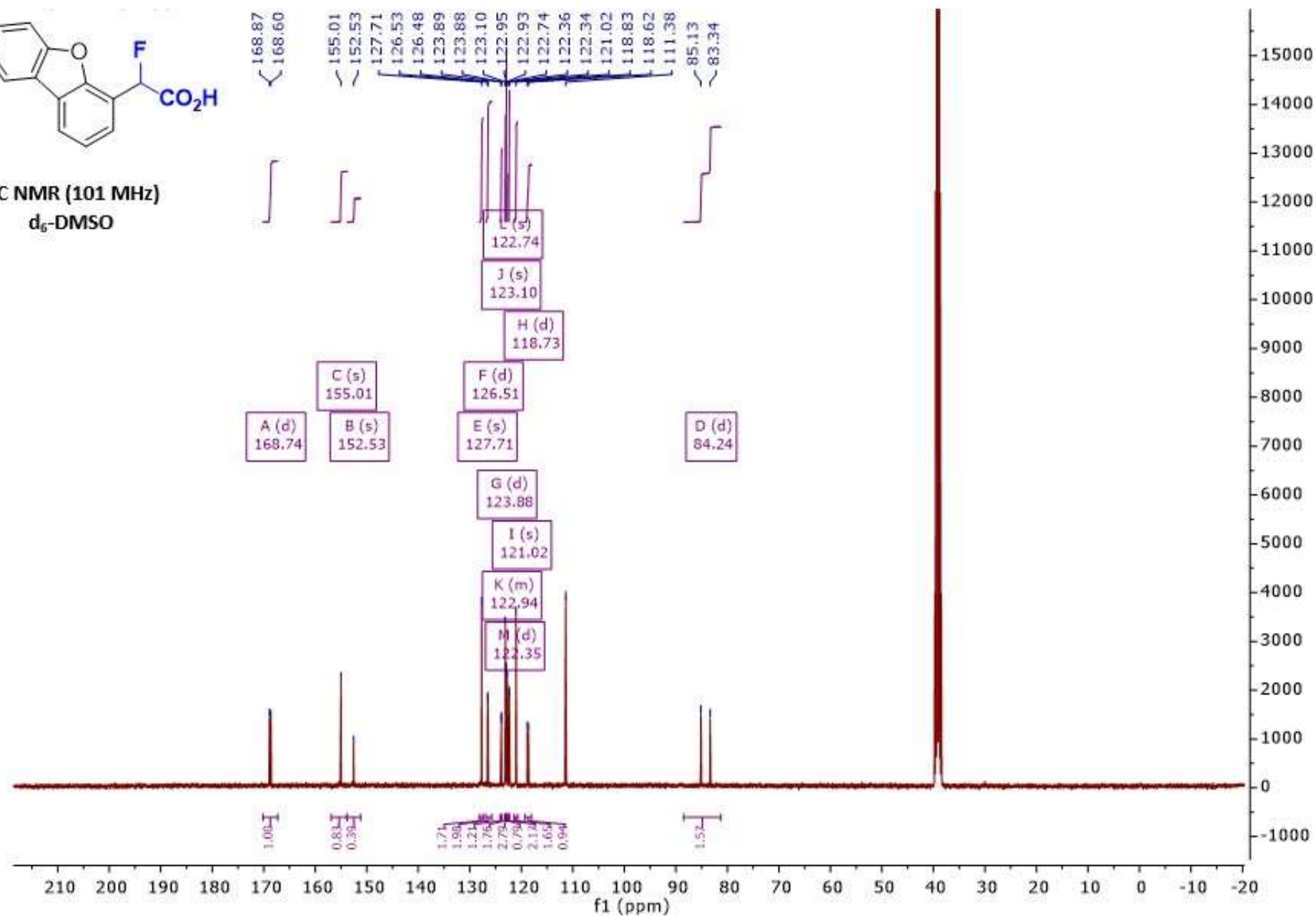


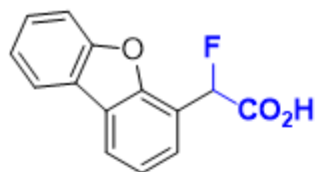
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 $\text{d}_6\text{-DMSO}$



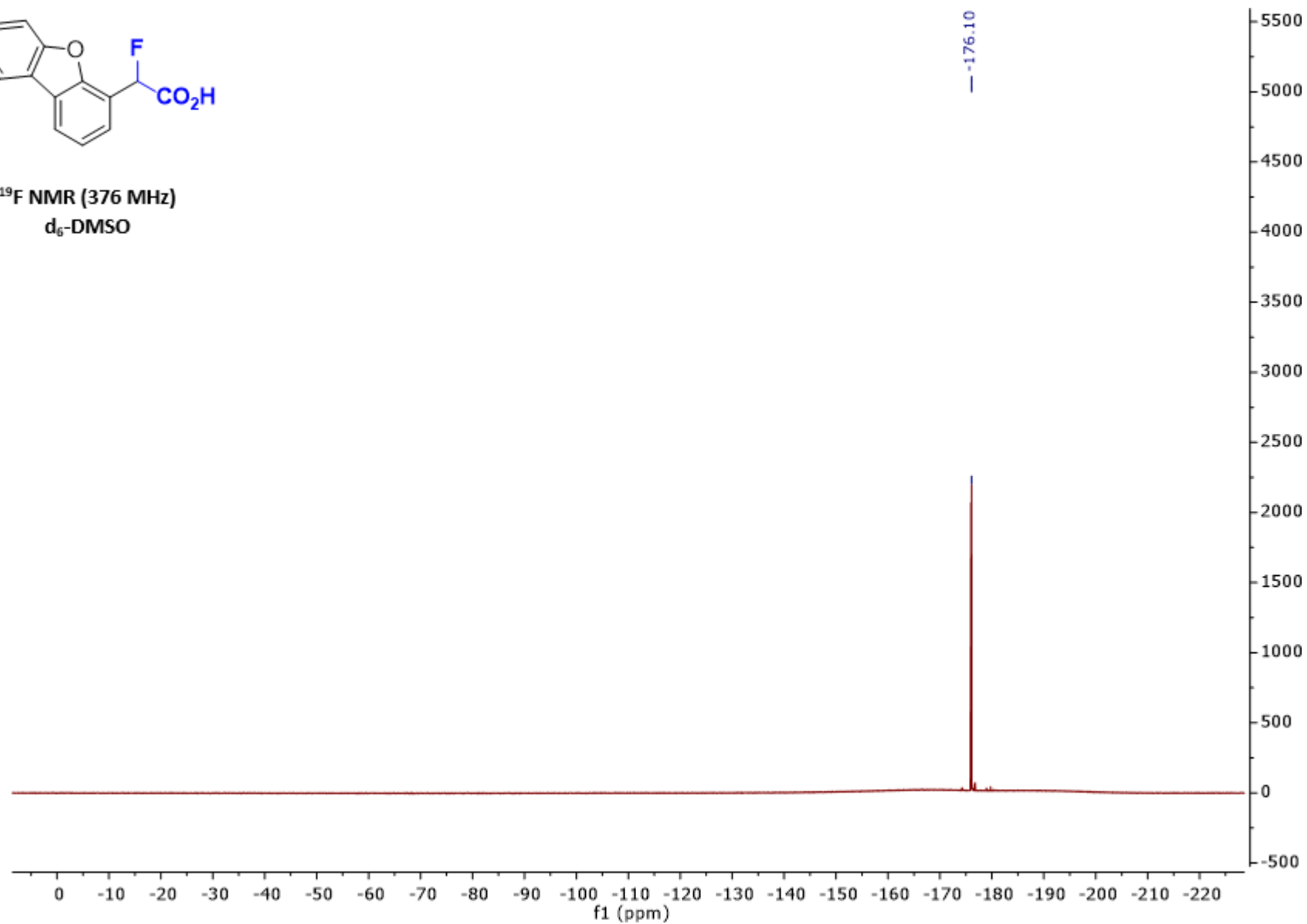


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d₆-DMSO

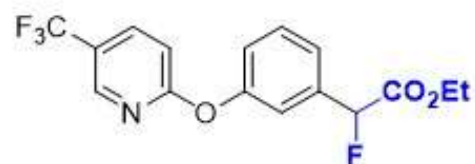




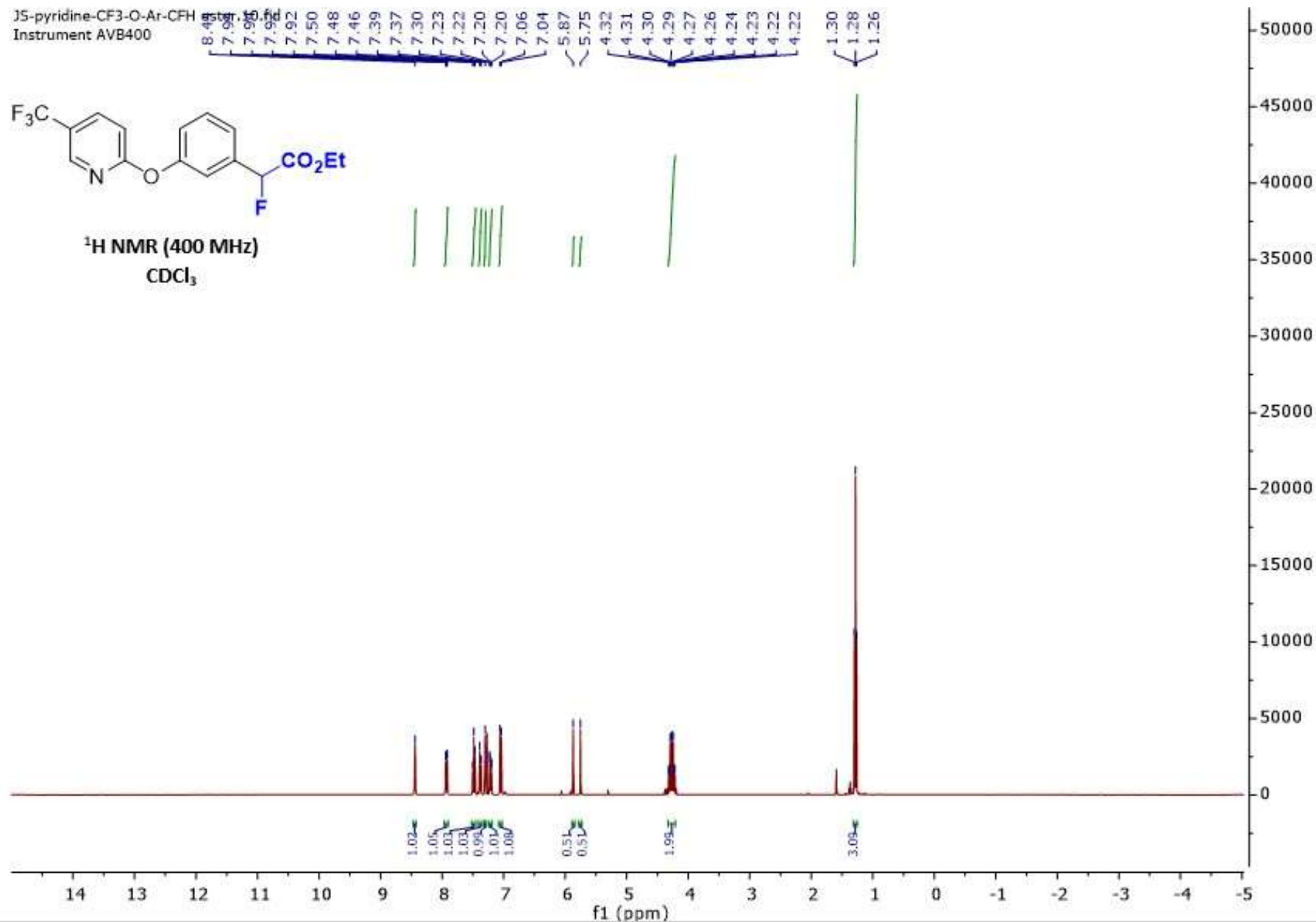
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 $\text{d}_6\text{-DMSO}$

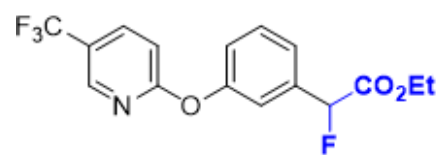


JS-pyridine-CF₃-O-Ar-CFH₂
Instrument AVB400

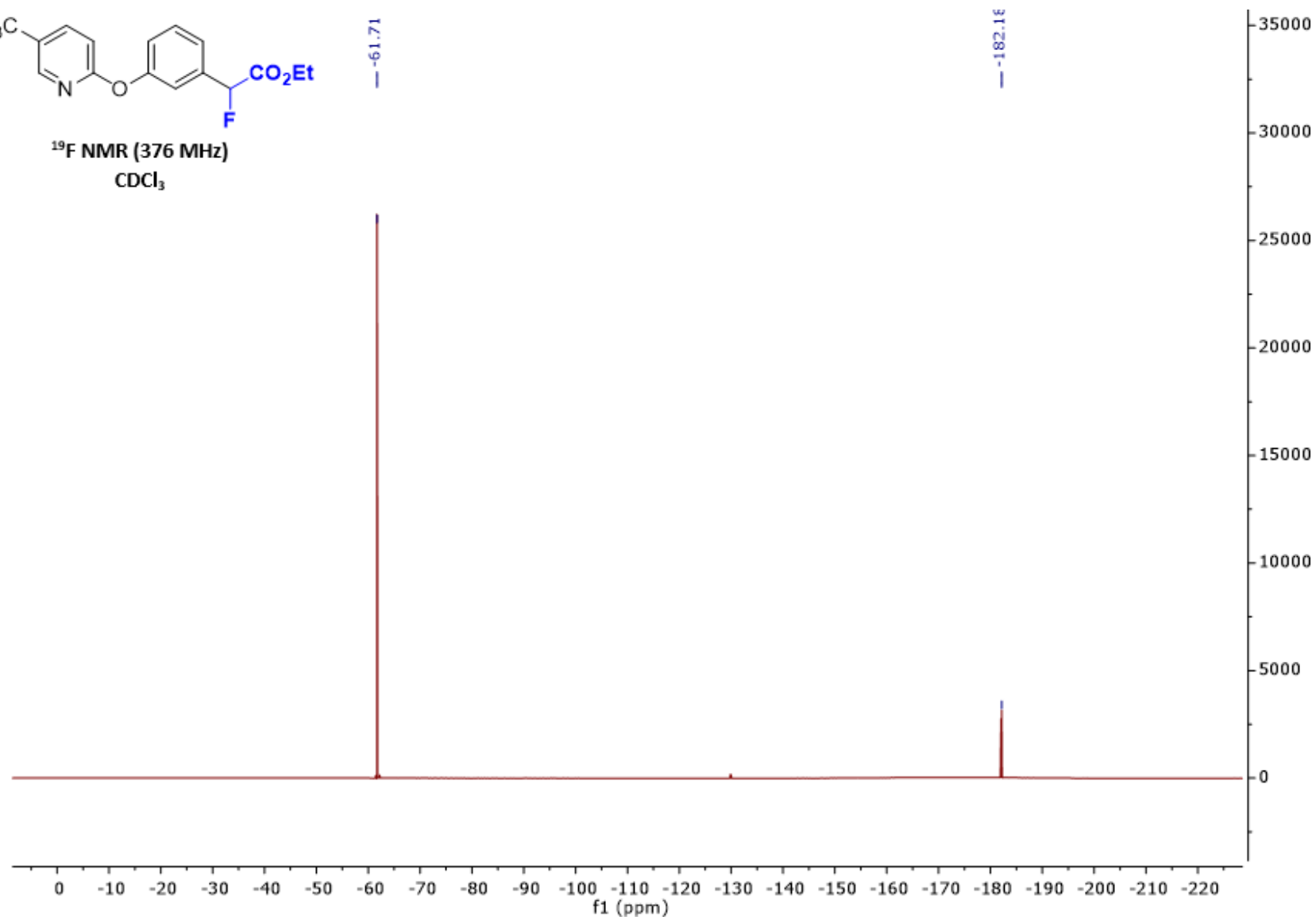


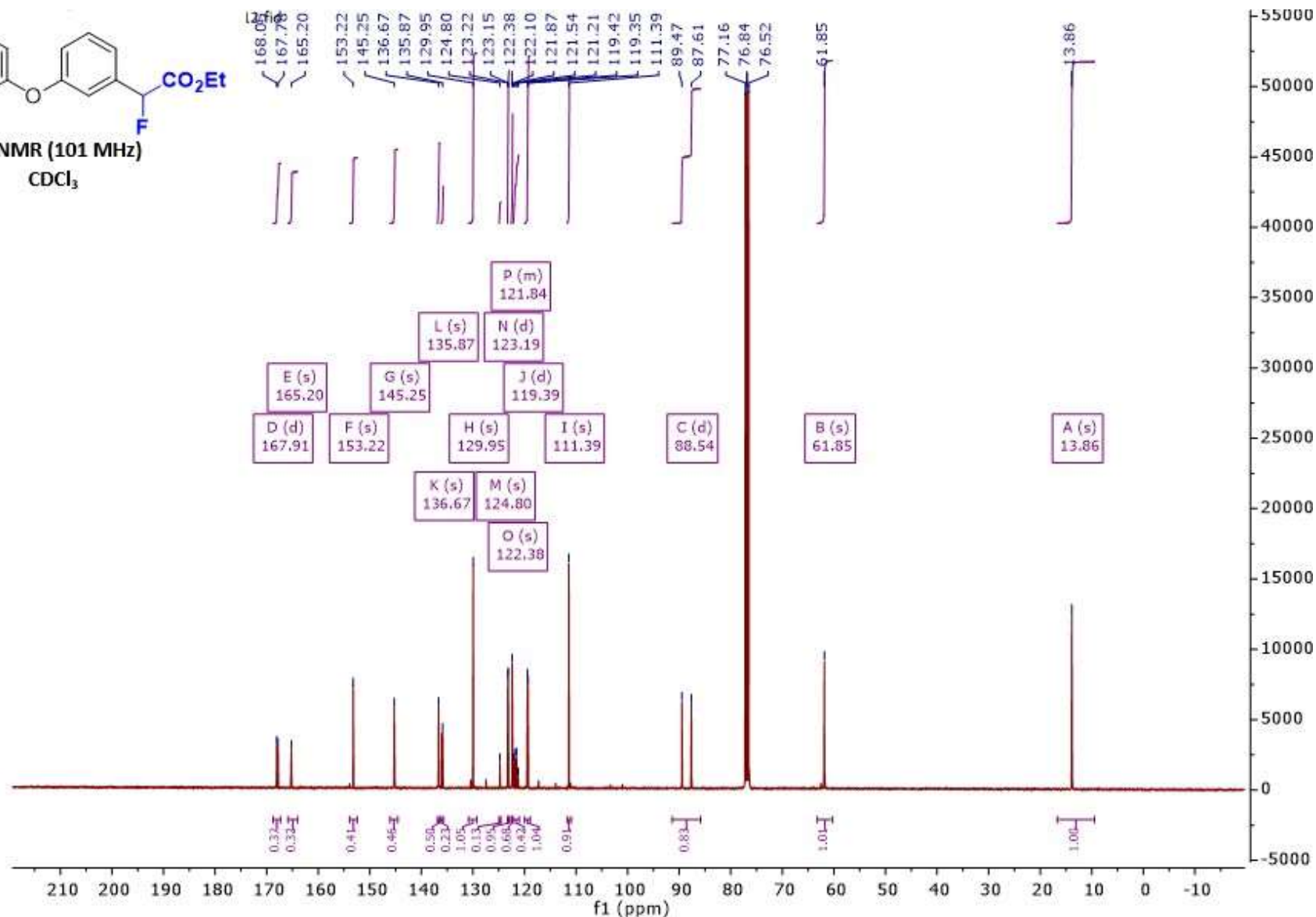
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CDCl₃

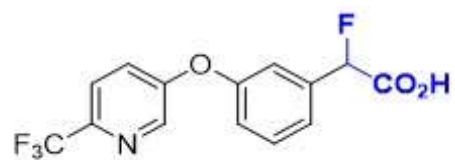




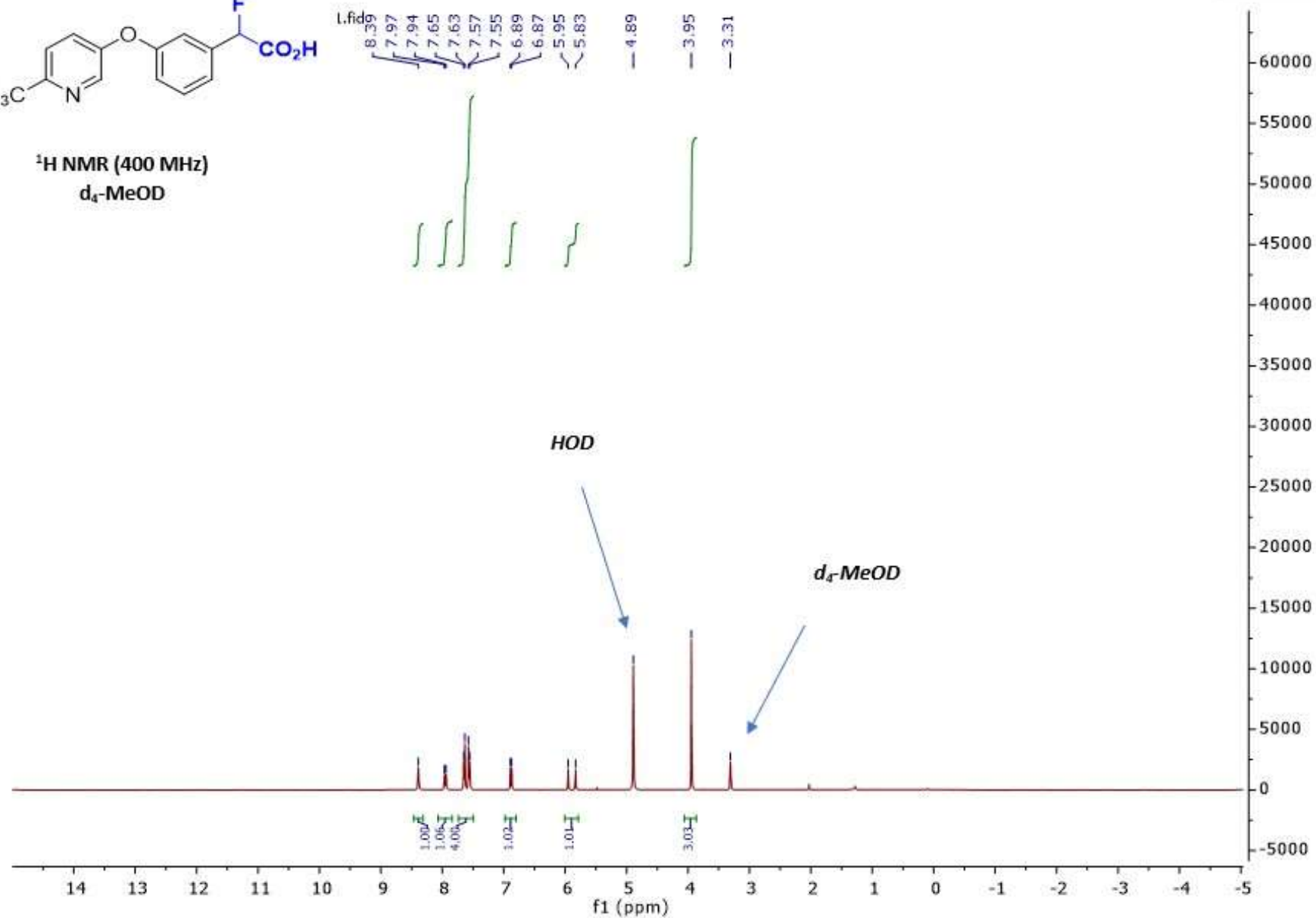
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 CDCl_3

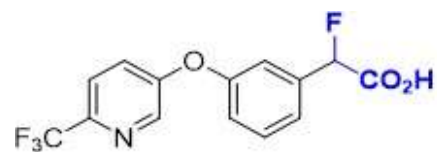




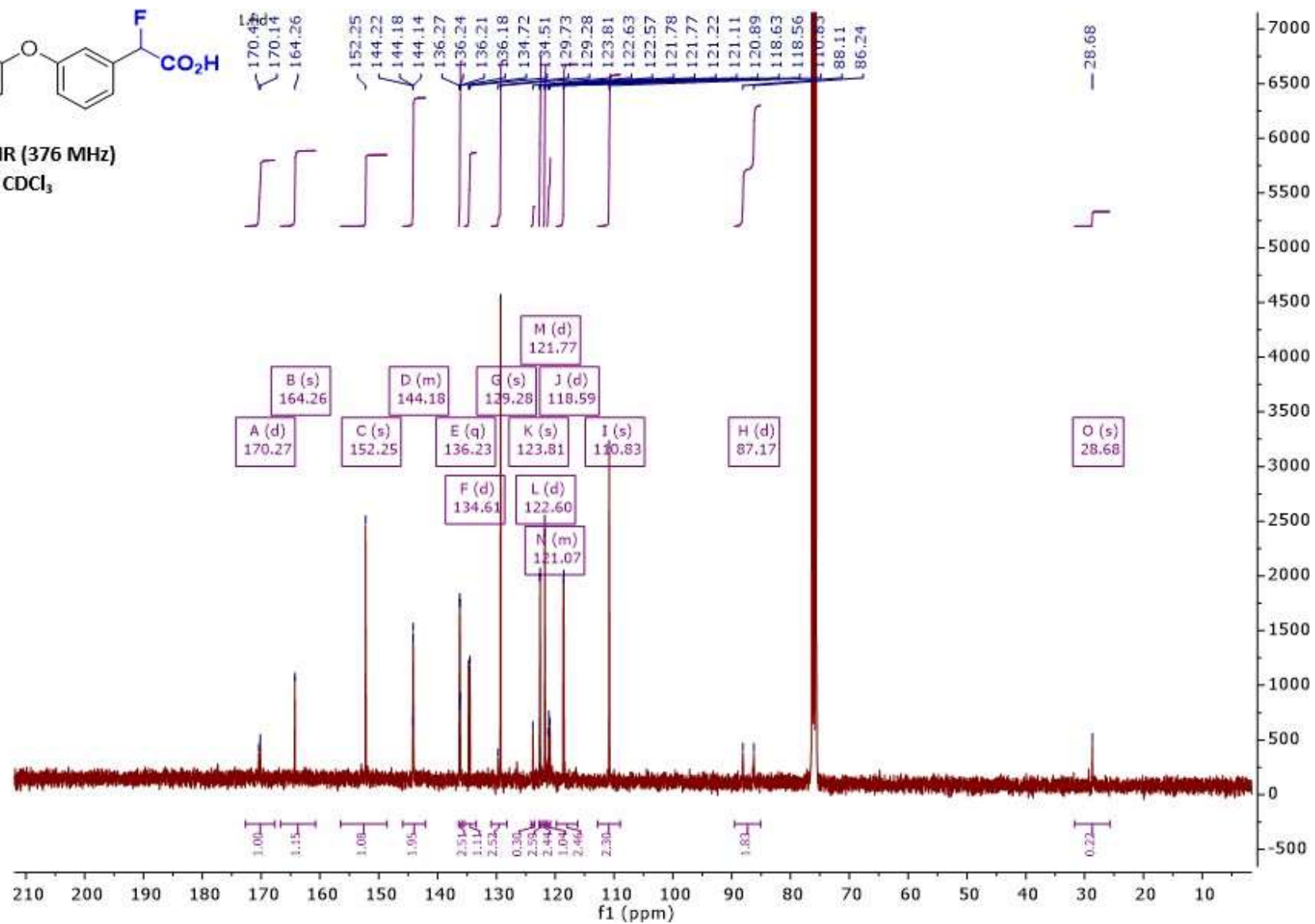


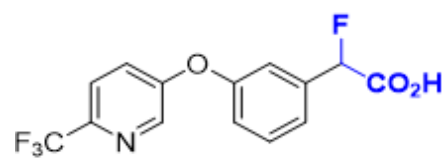
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 $\text{d}_4\text{-MeOD}$



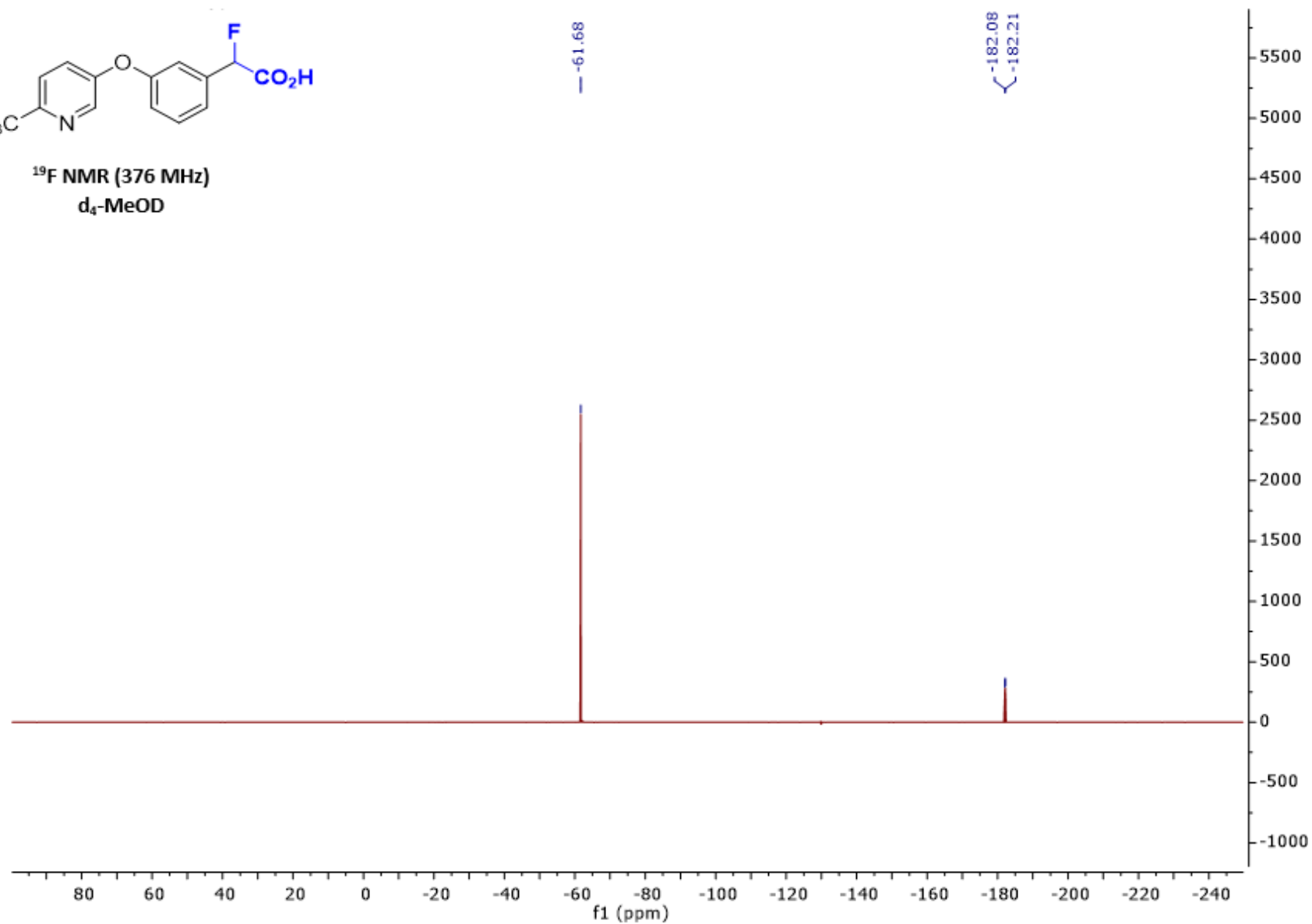


¹⁹F NMR (376 MHz)
CDCl₃



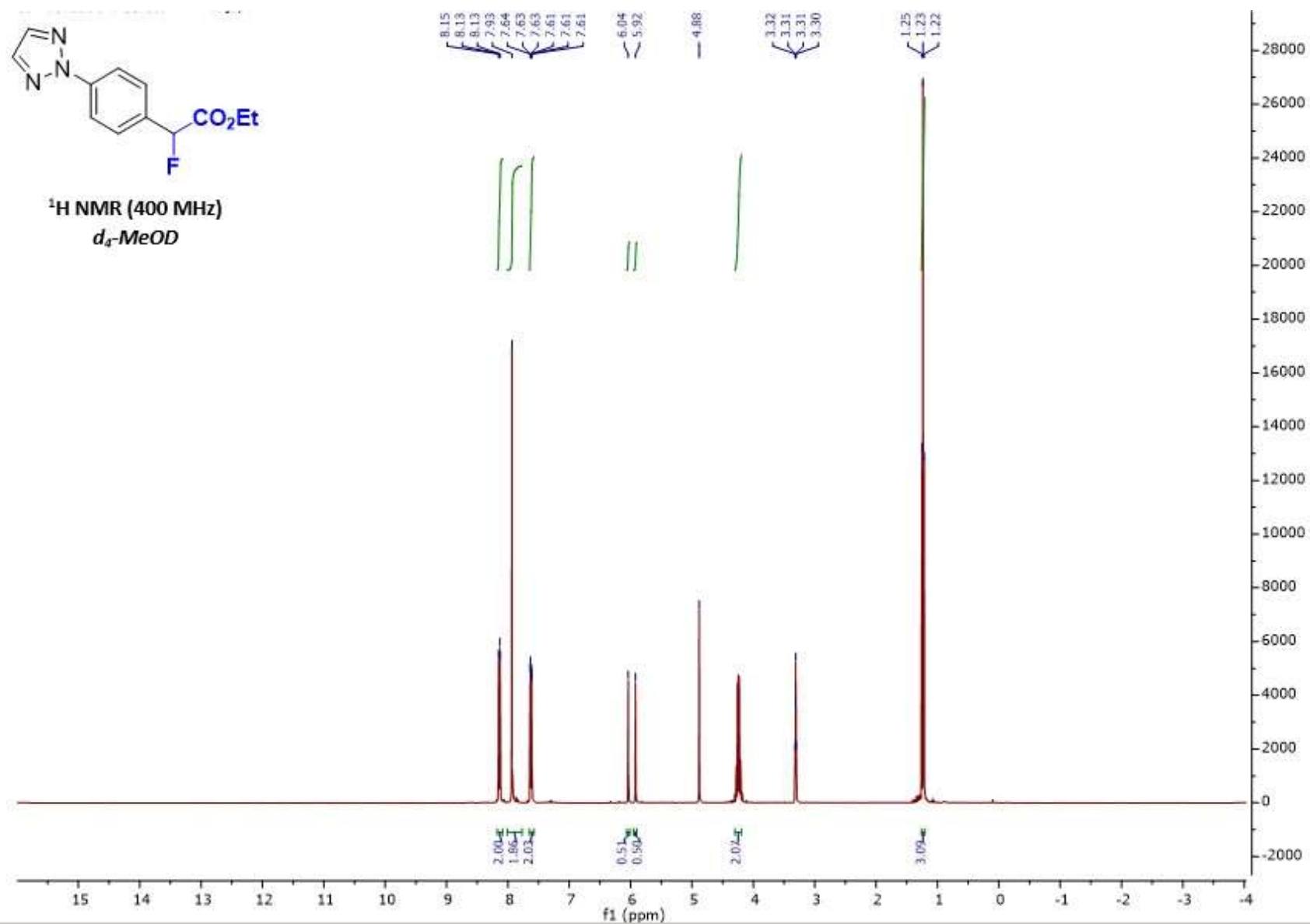


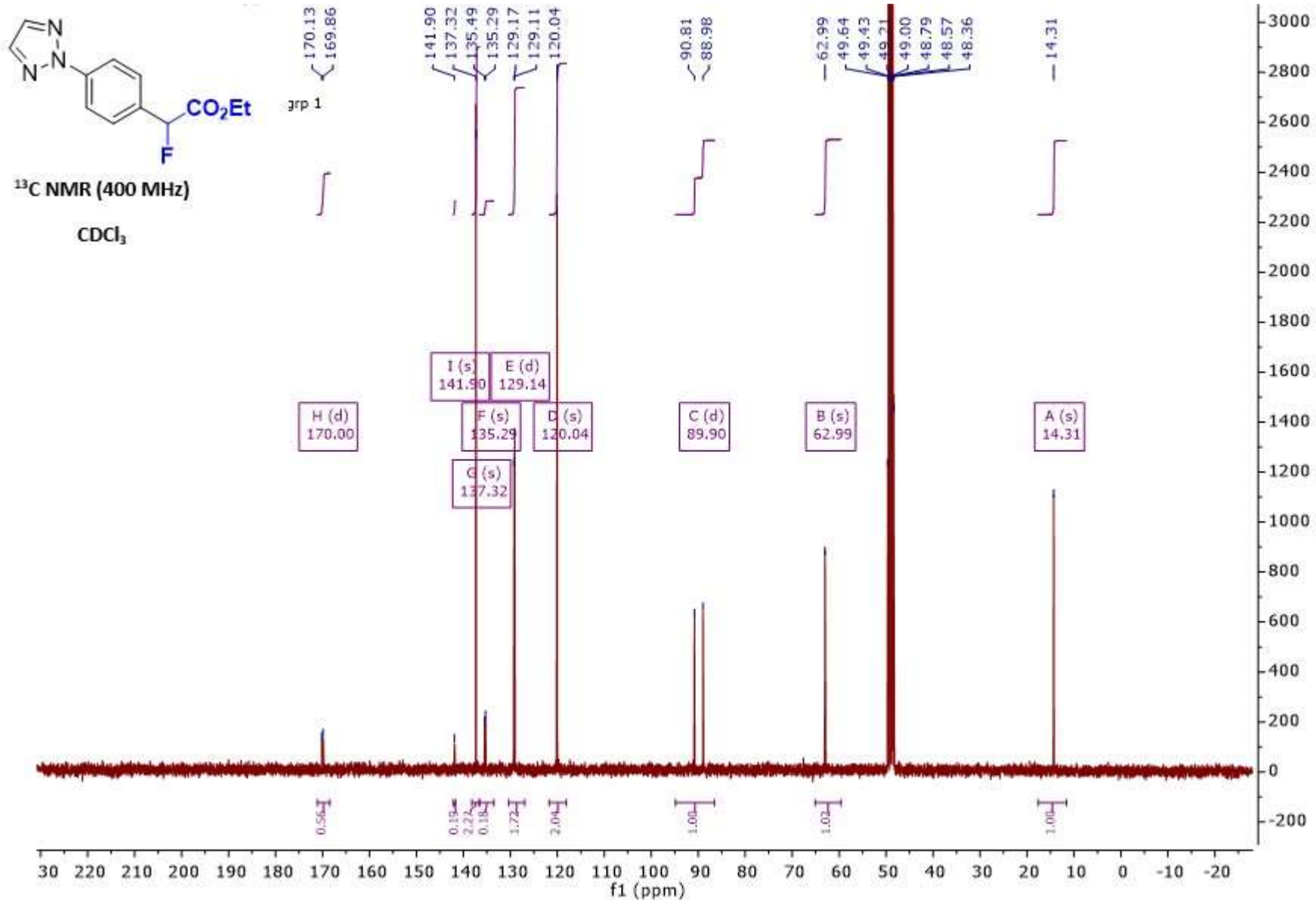
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d₄-MeOD

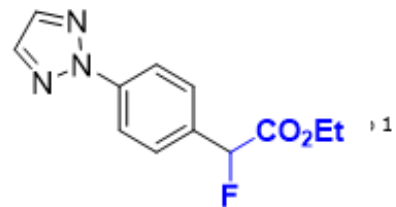




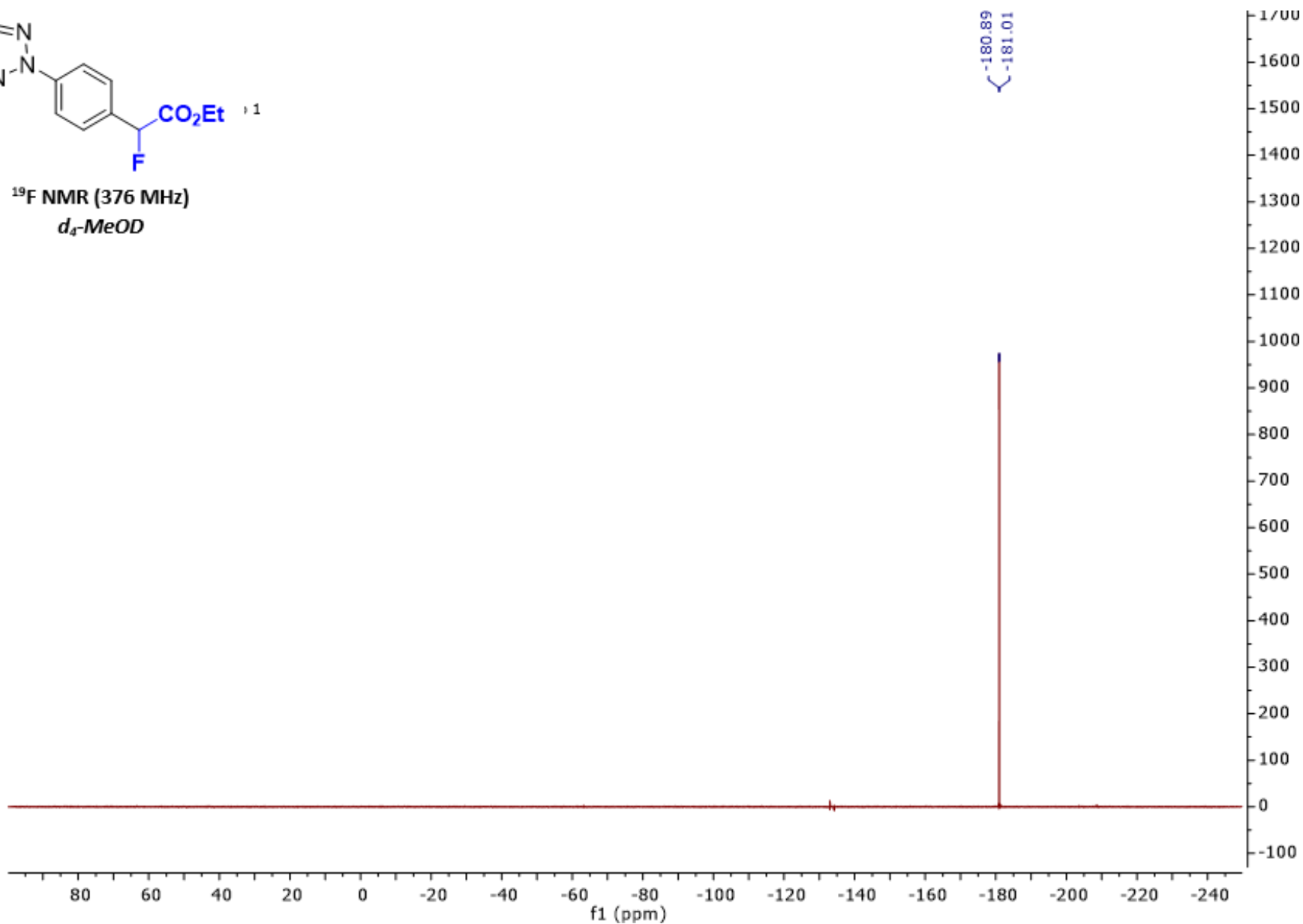
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*d*₅-MeOD







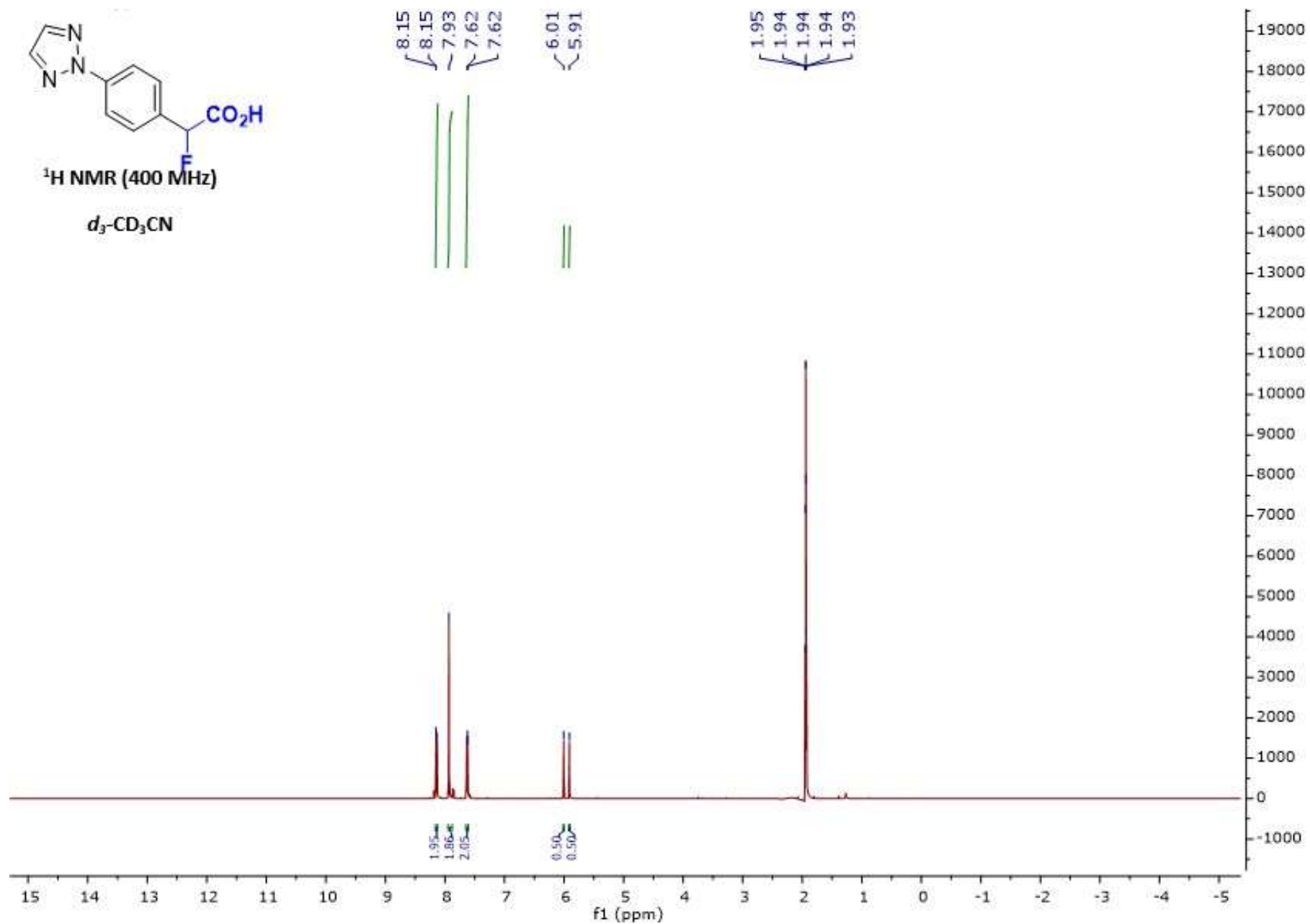
^{19}F NMR (376 MHz)
*d*₄-MeOD





^1H NMR (400 MHz)

$d_3\text{-CD}_3\text{CN}$

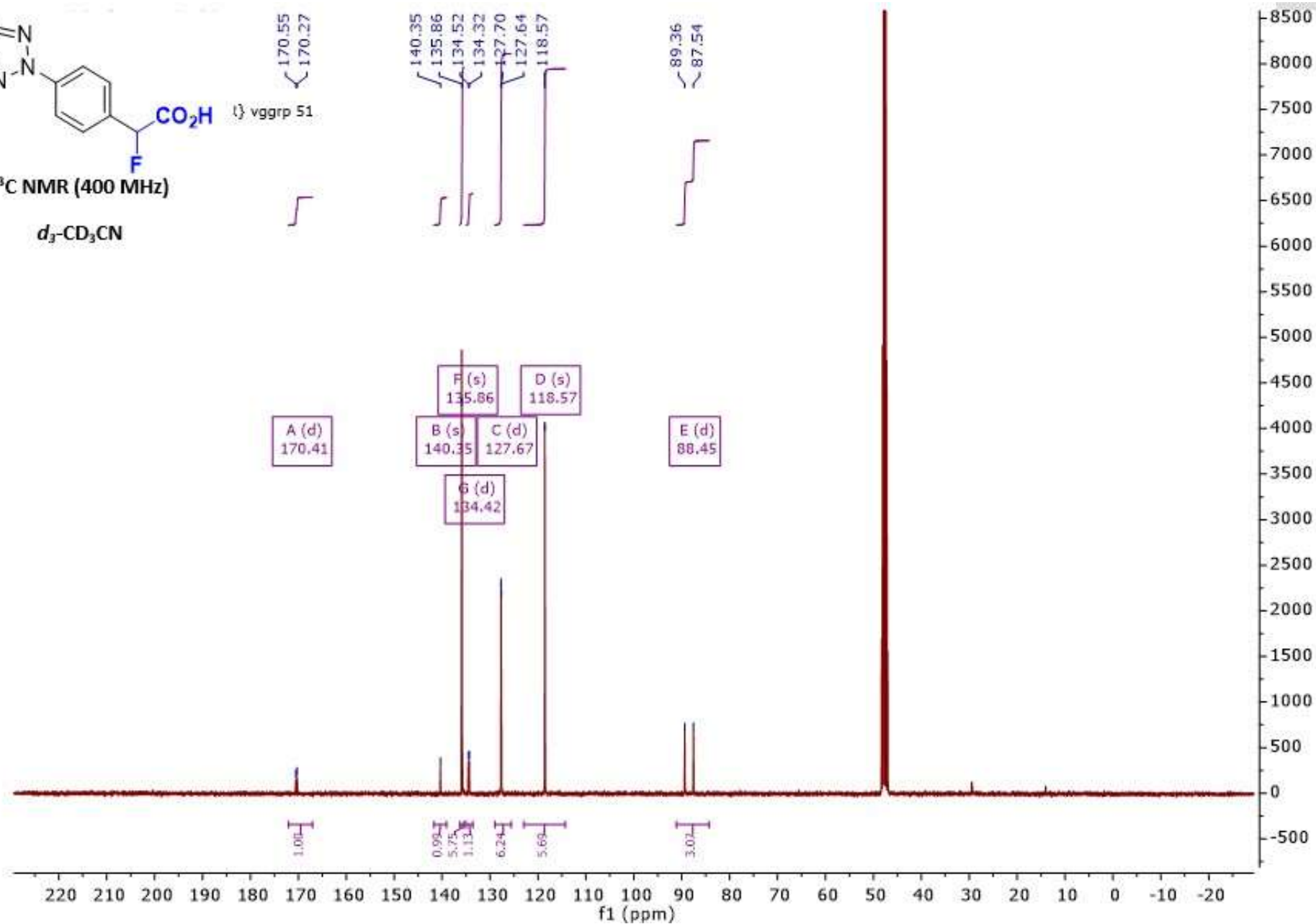


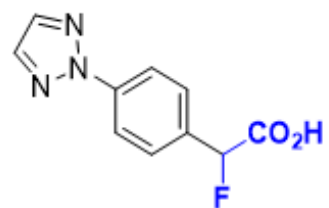


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$d_3\text{-CD}_3\text{CN}$

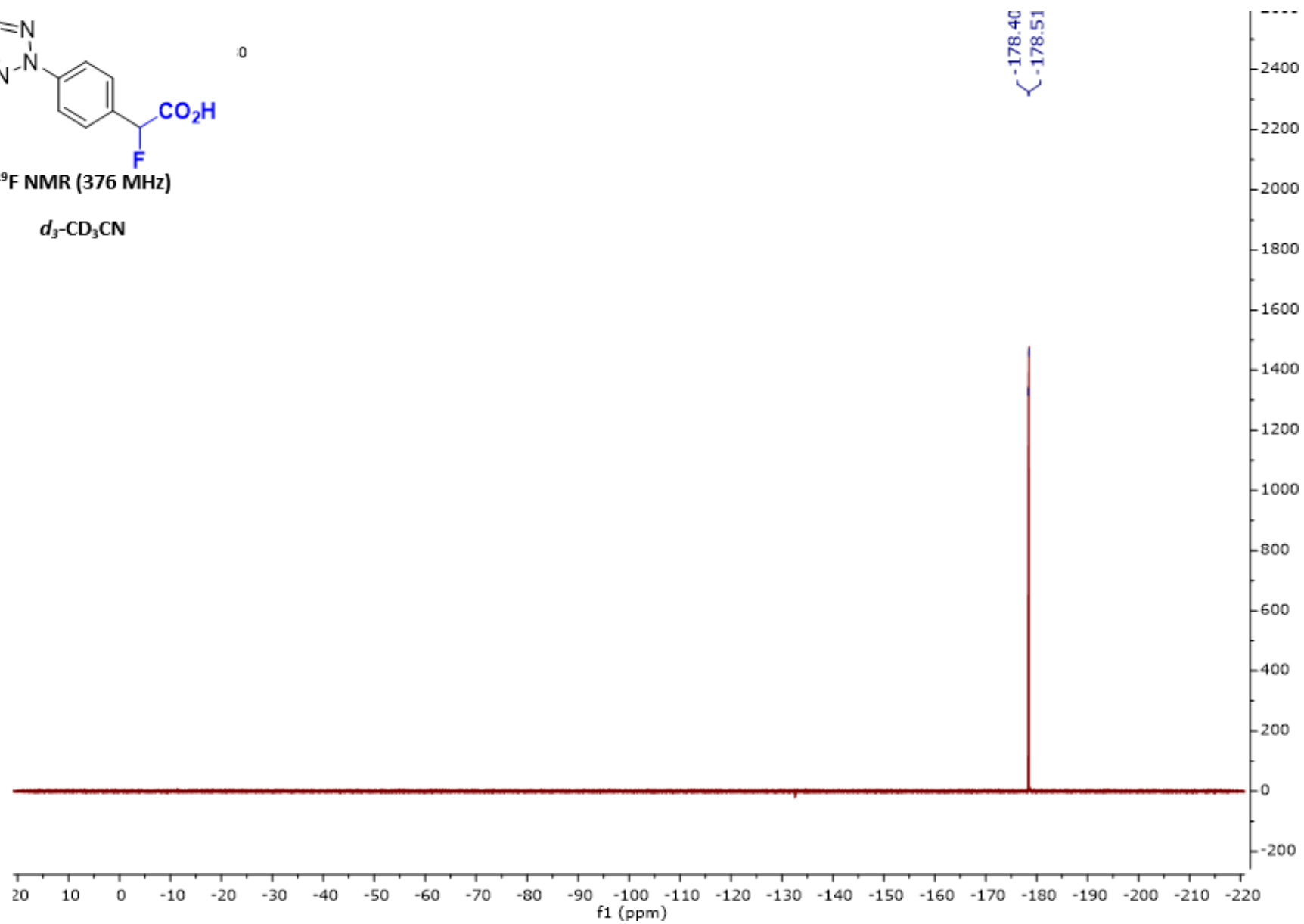
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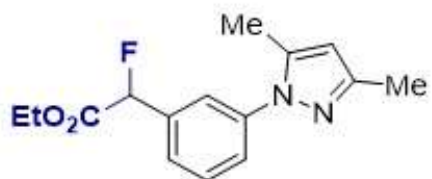


^{19}F NMR (376 MHz)

$d_3\text{-CD}_3\text{CN}$

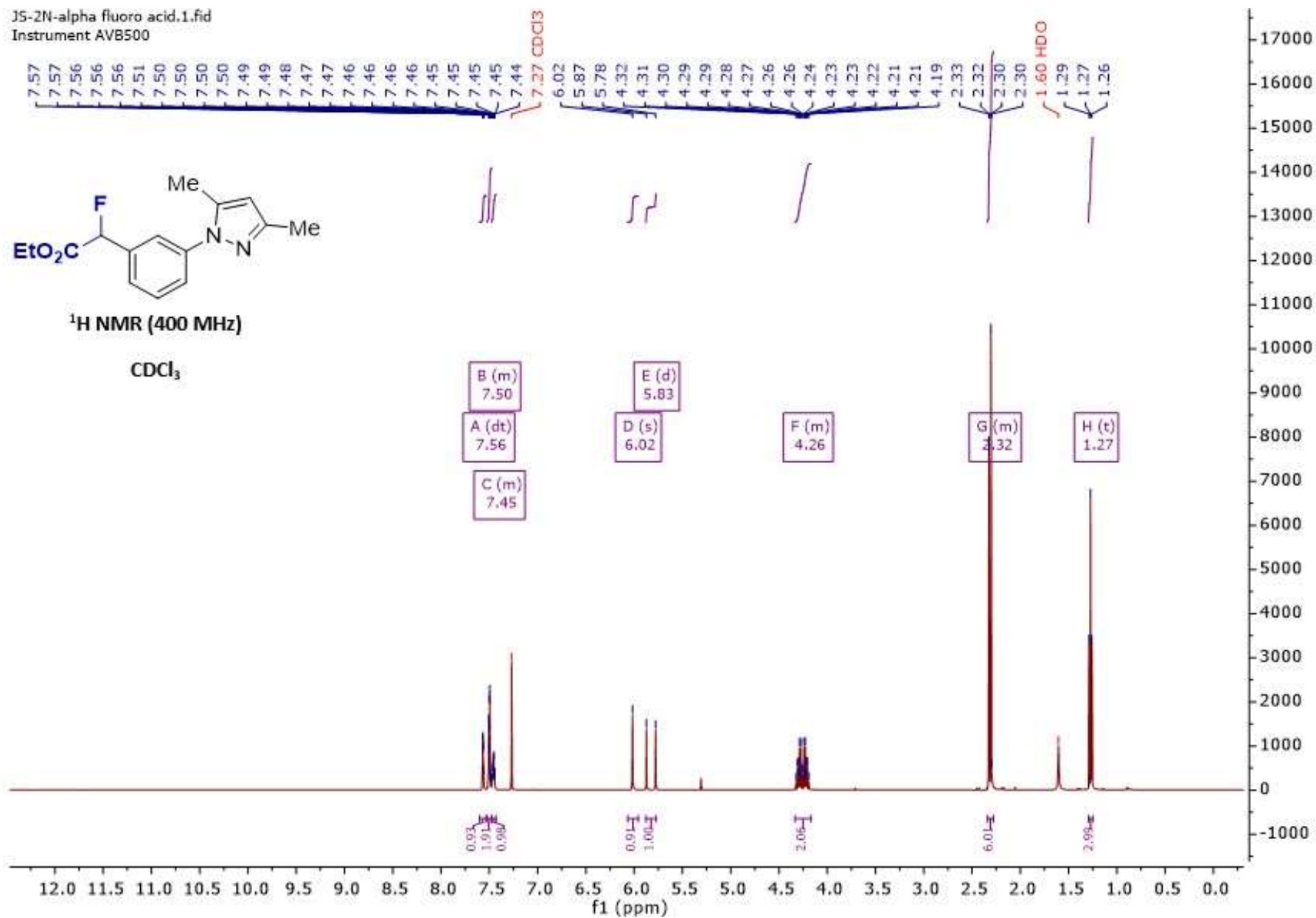


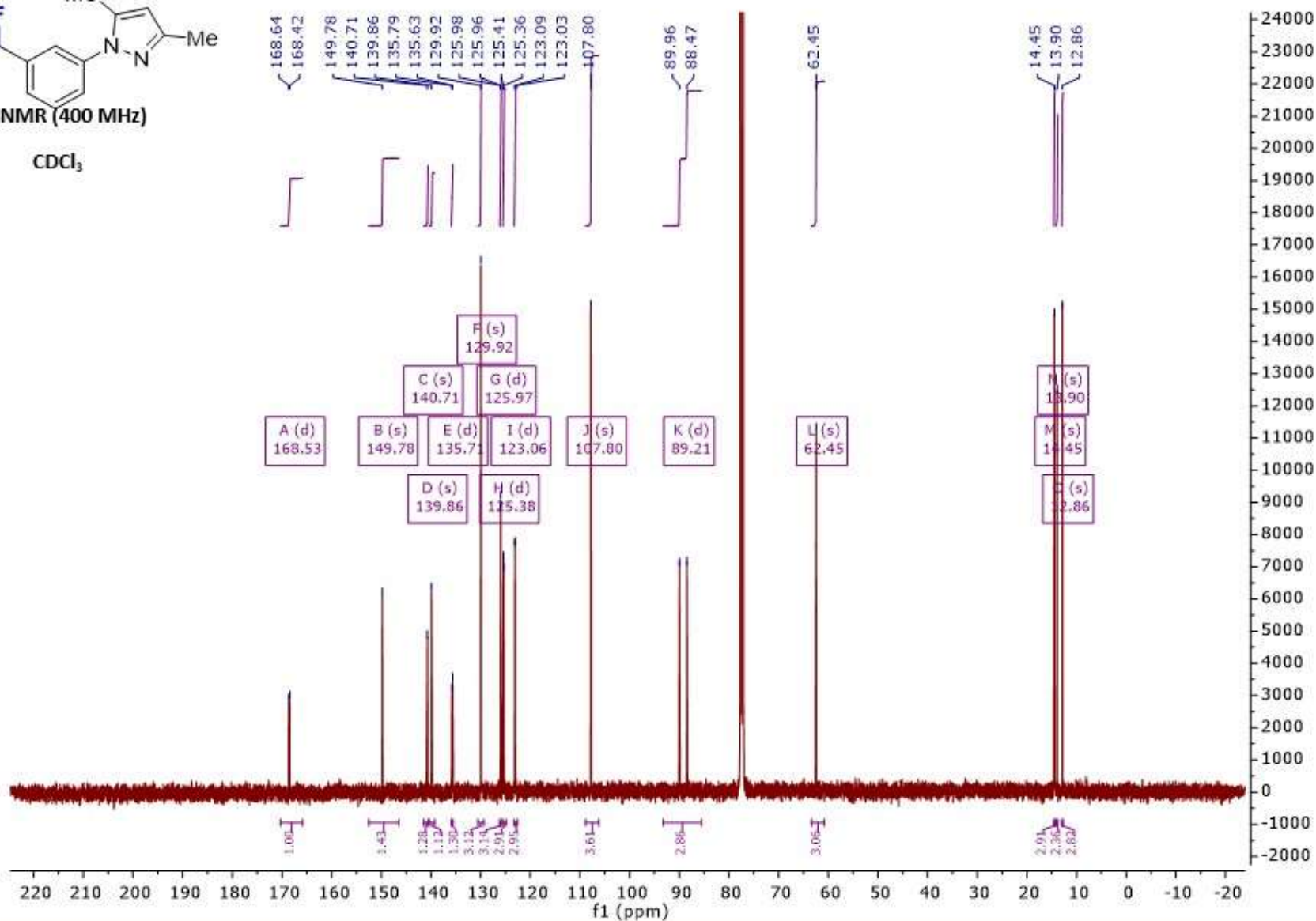
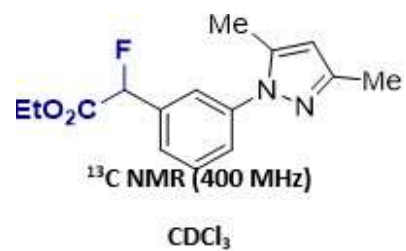
JS-2N-alpha fluoro acid.1.fid
Instrument AVB500

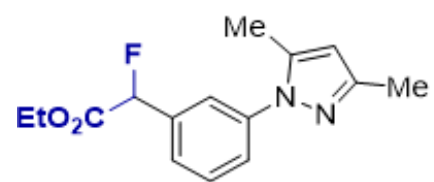


^1H NMR (400 MHz)

CDCl_3

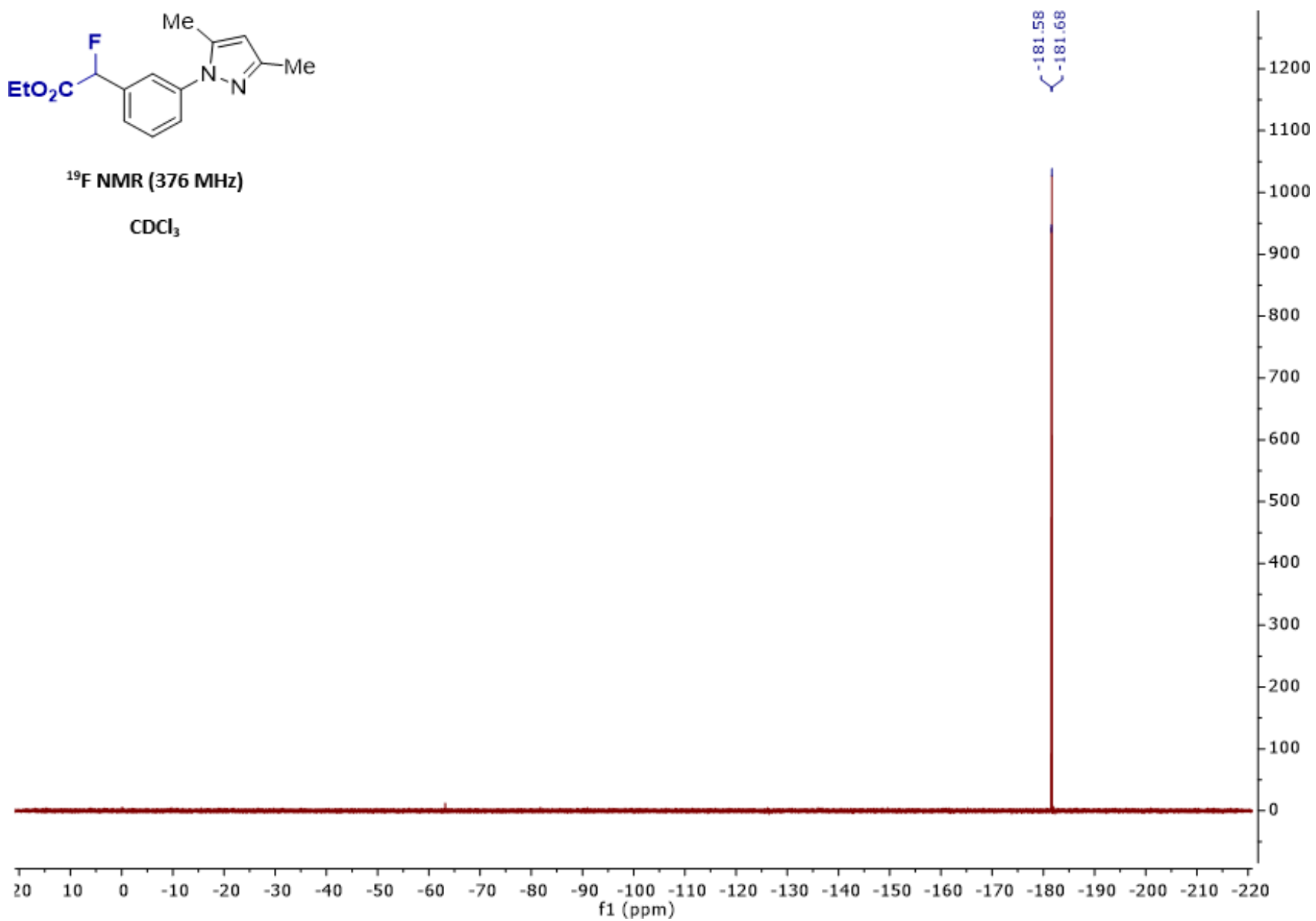






^{19}F NMR (376 MHz)

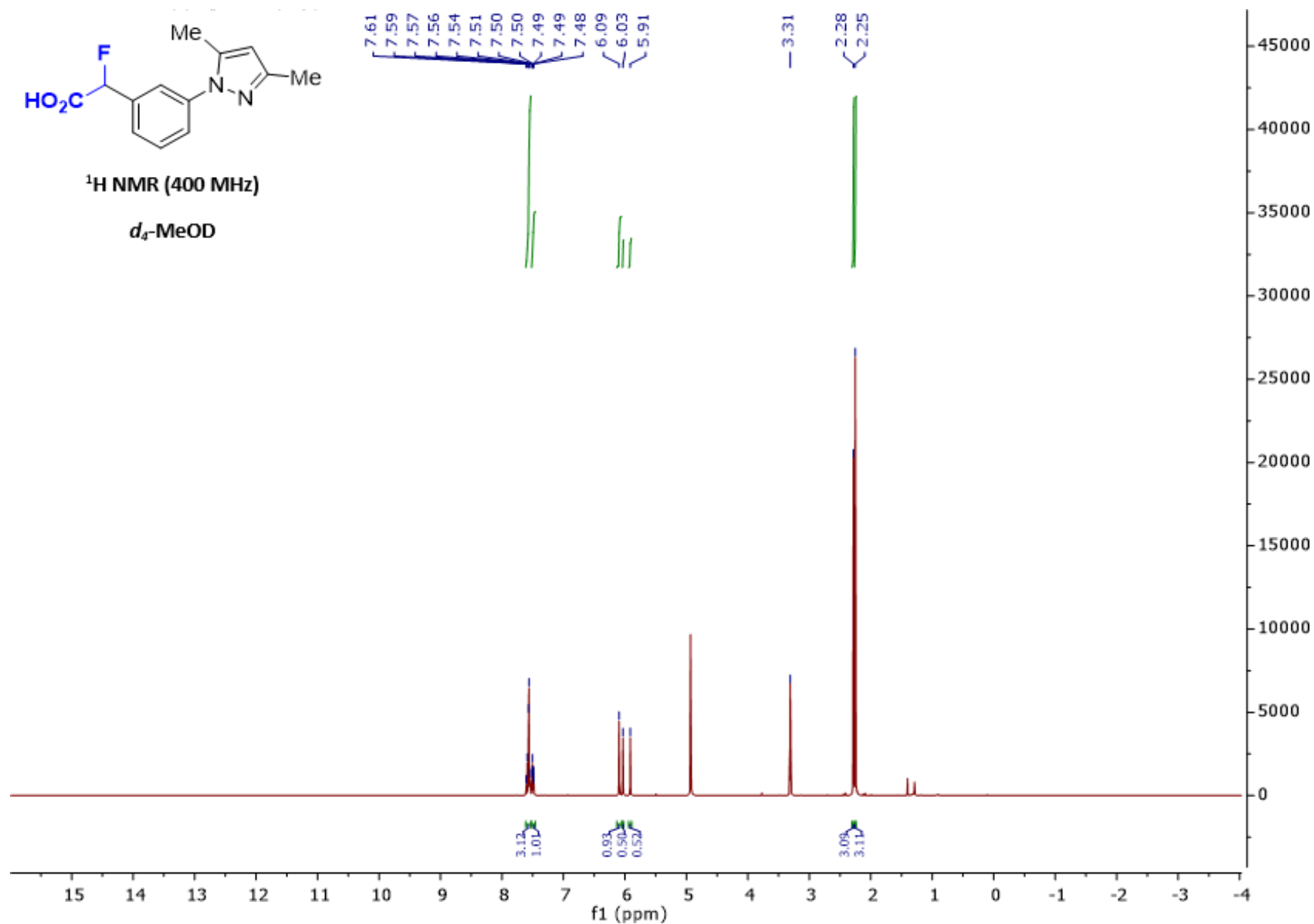
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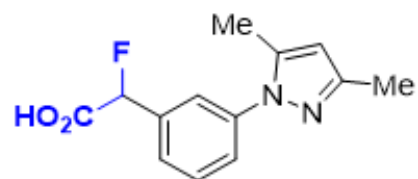




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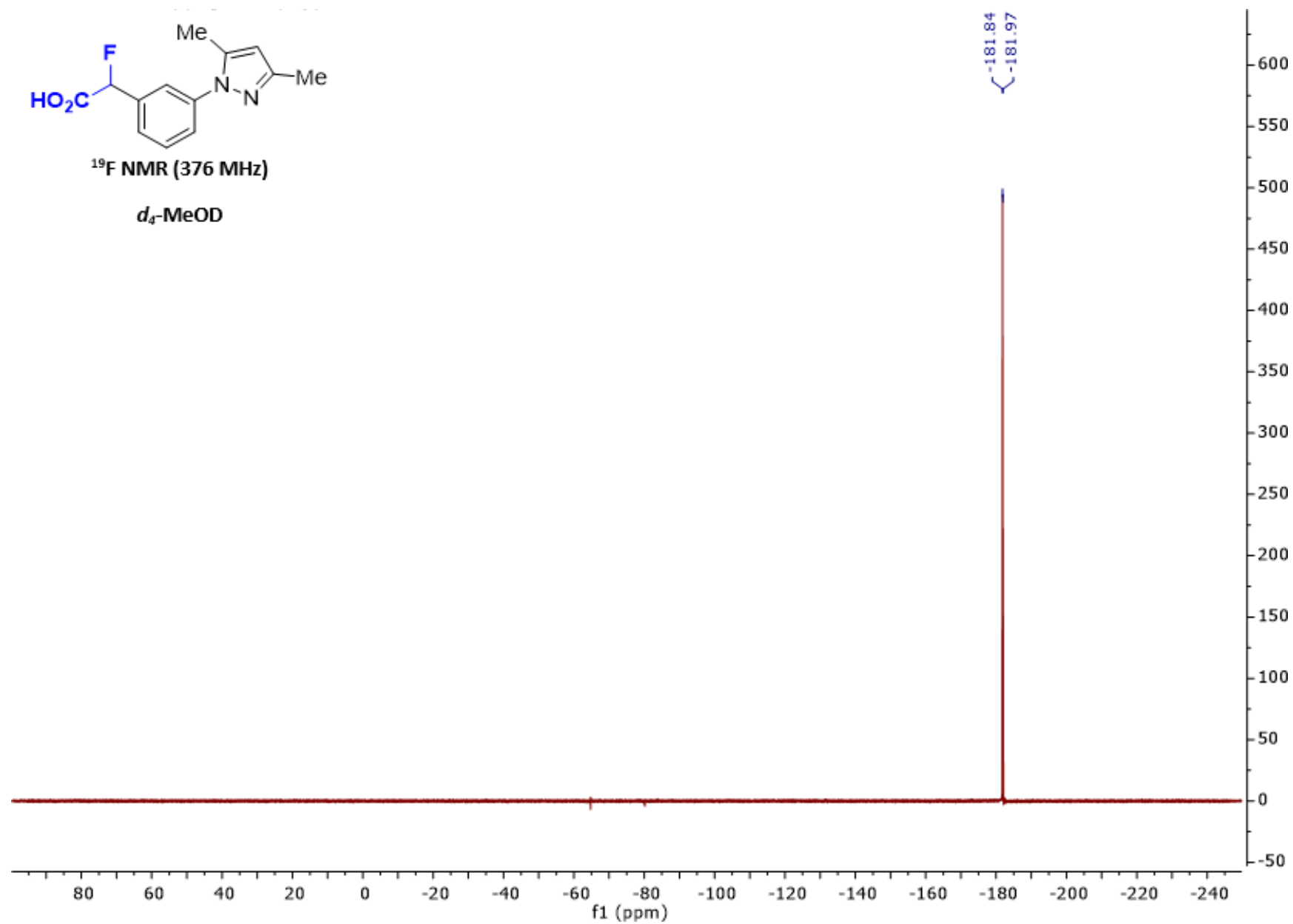
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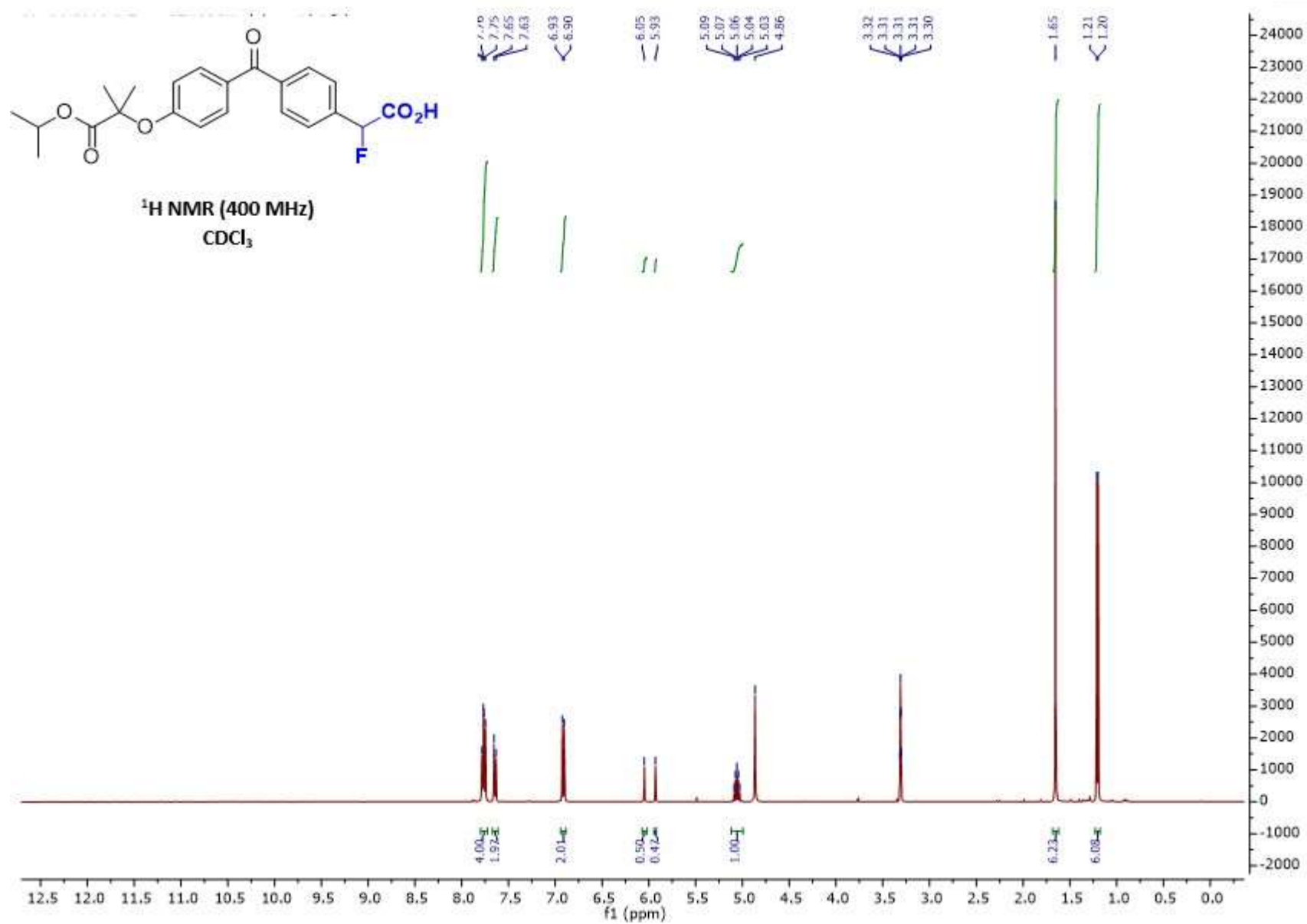




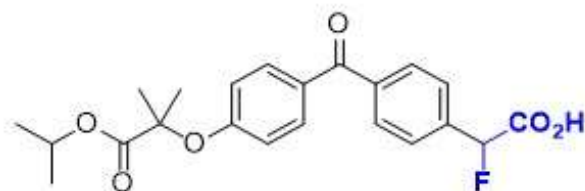
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d_4 -MeOD

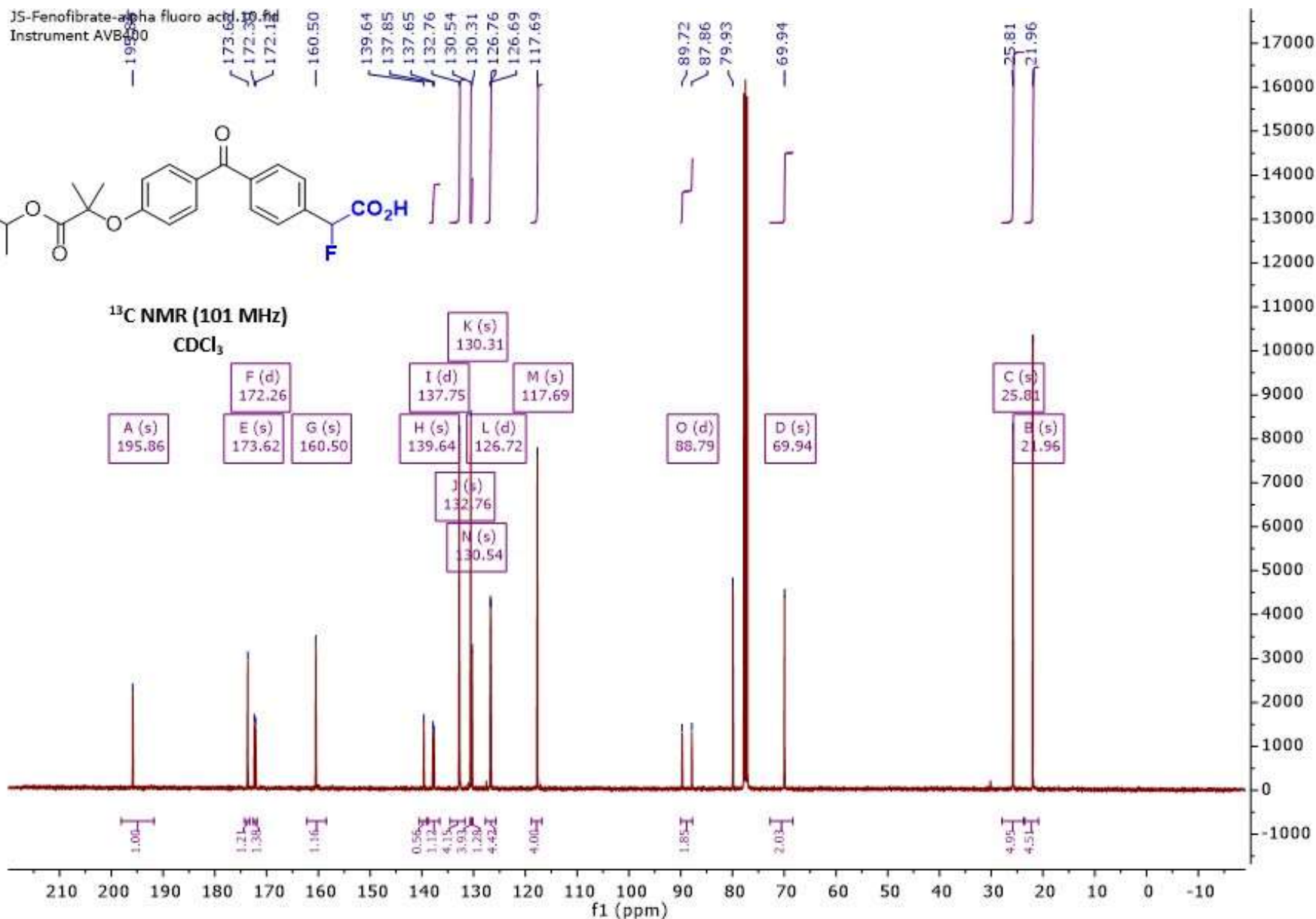


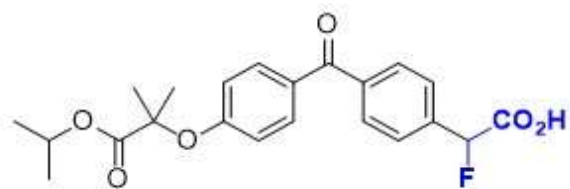


JS-Fenofibrate- α -fluoro acid, 10.96
Instrument AVB400

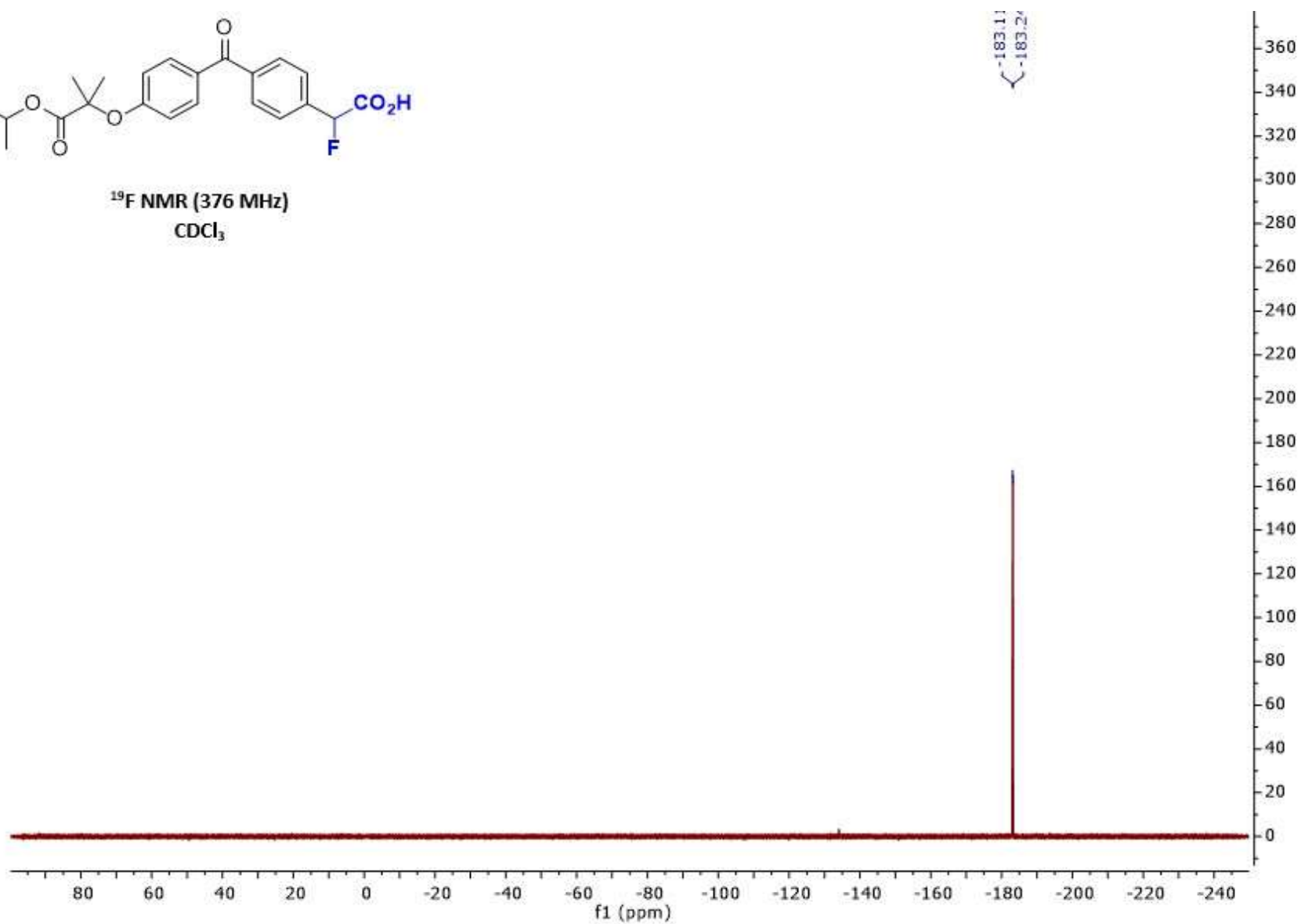


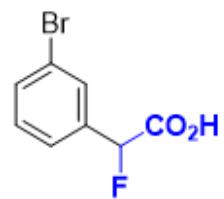
^{13}C NMR (101 MHz)
 CDCl_3



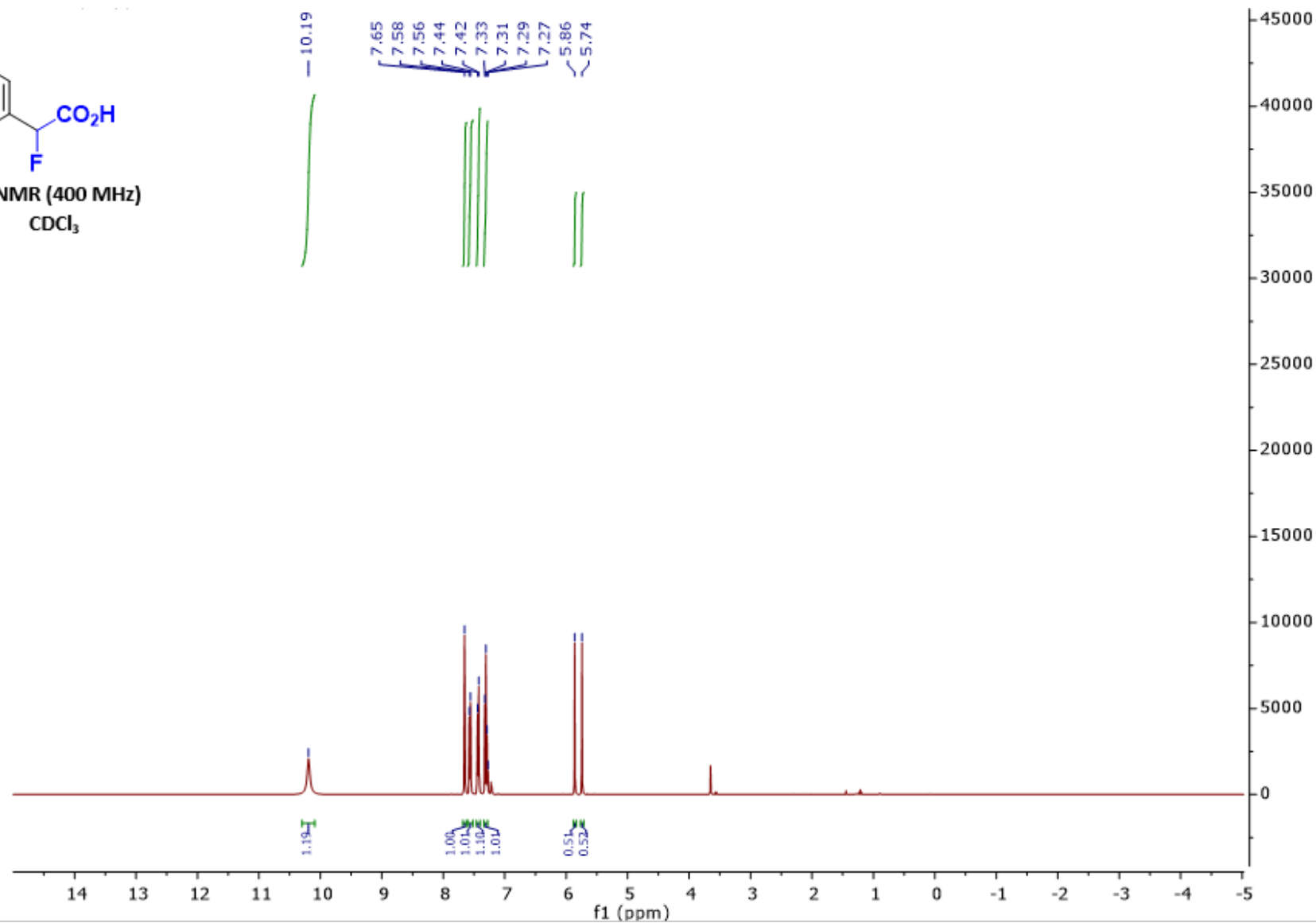


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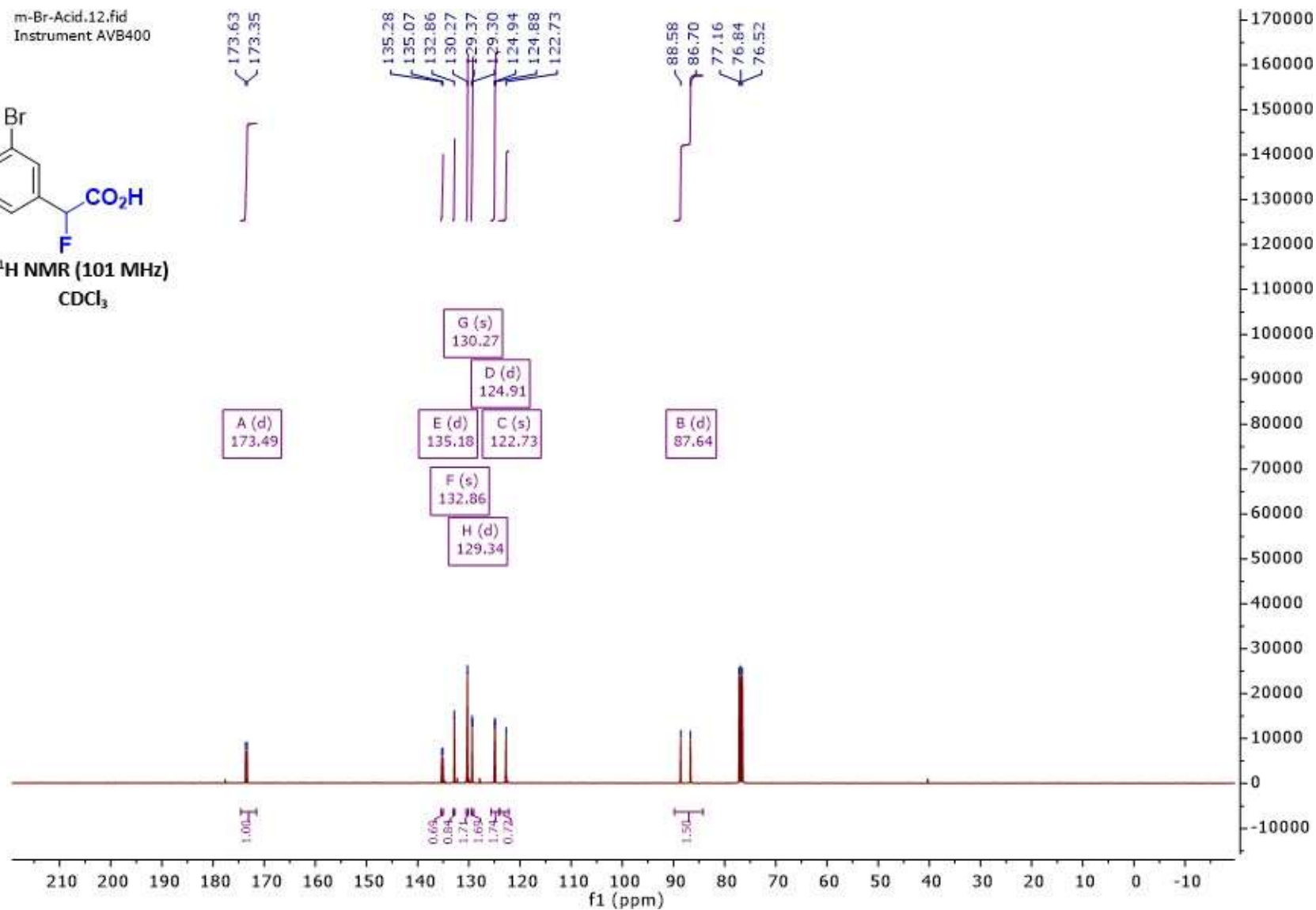


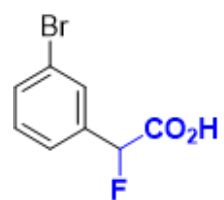


^1H NMR (400 MHz)
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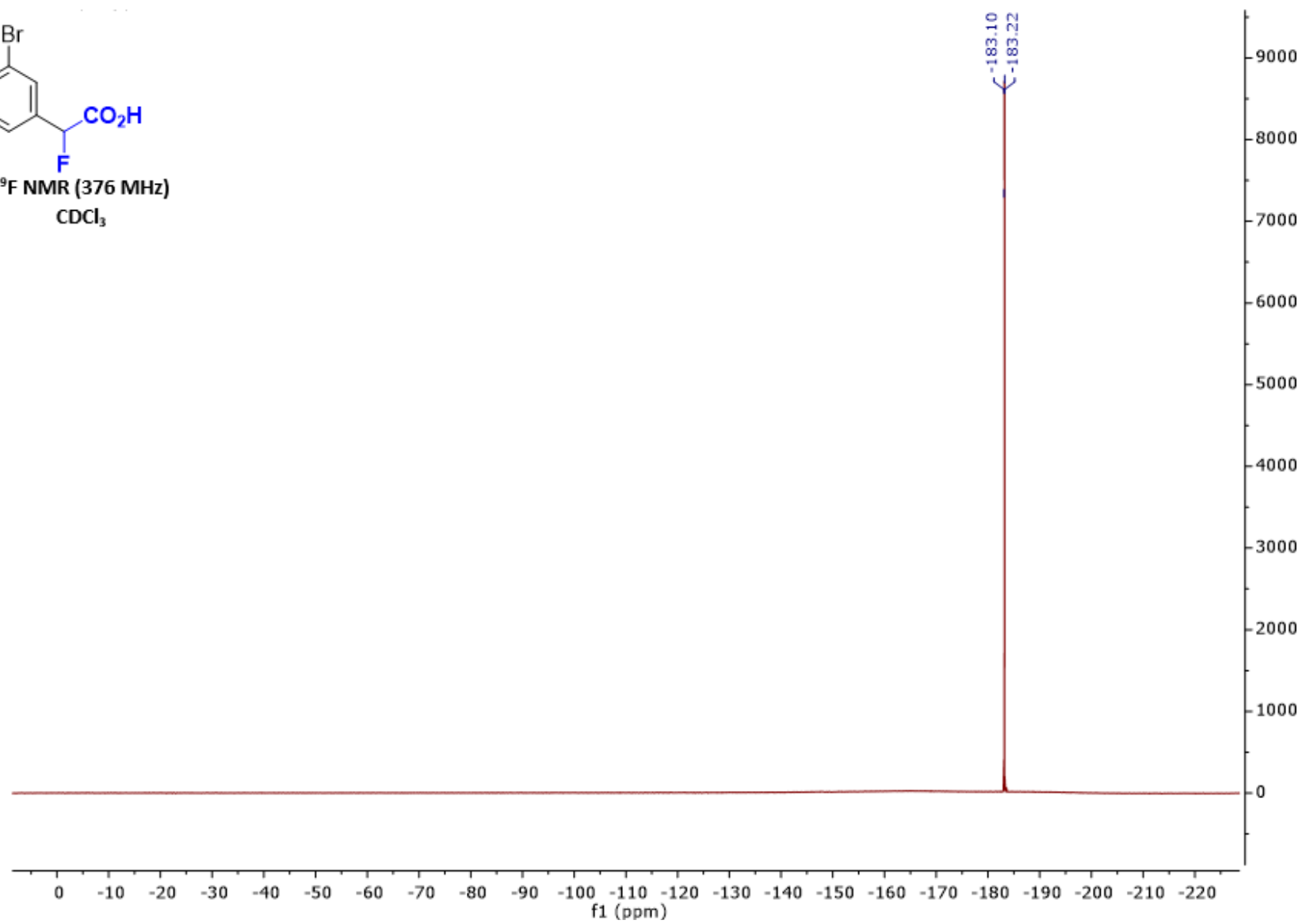


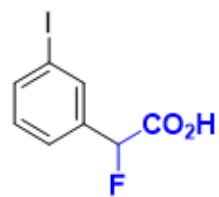
m-Br-Acid.12.fid
Instrument AVB400



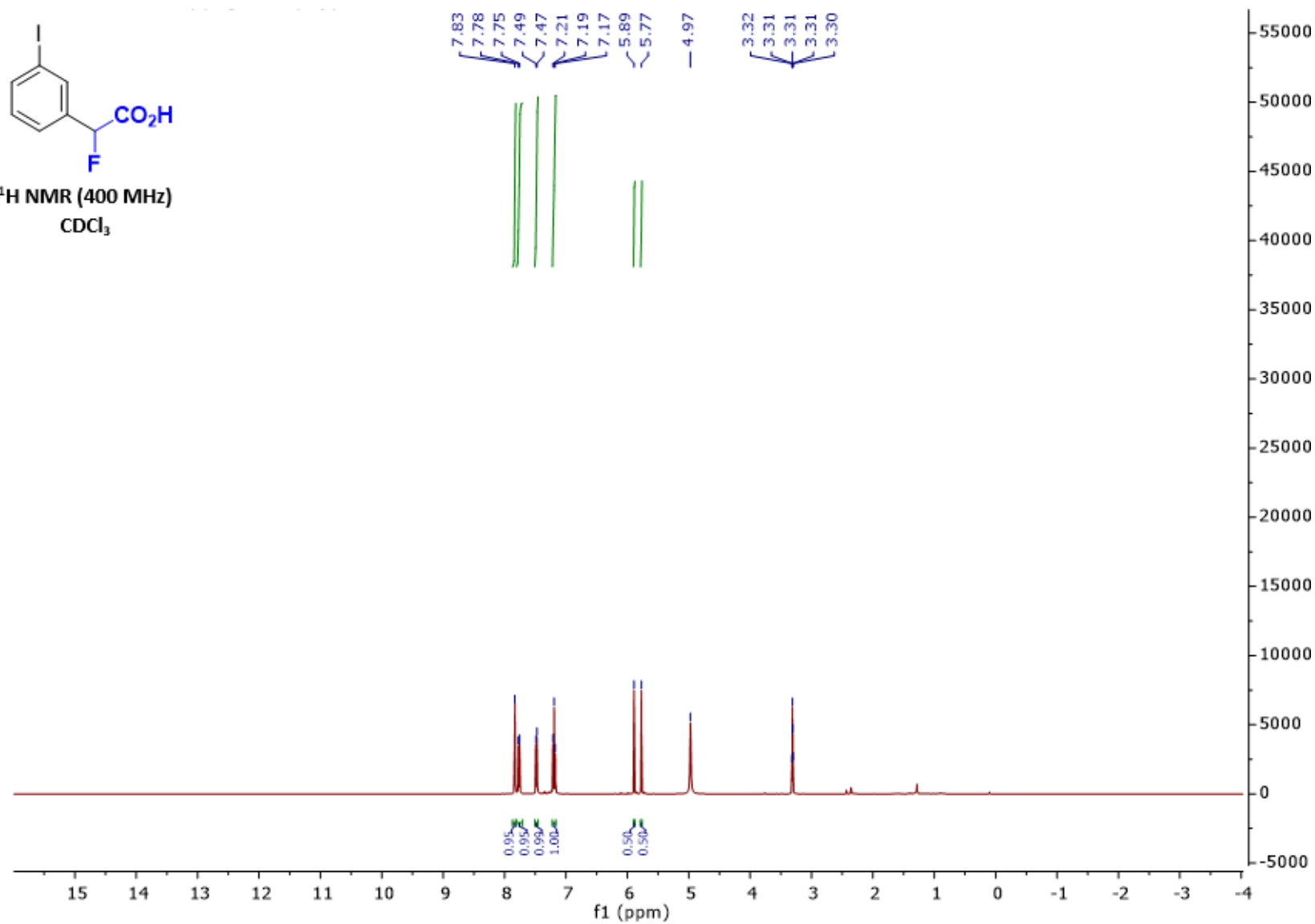


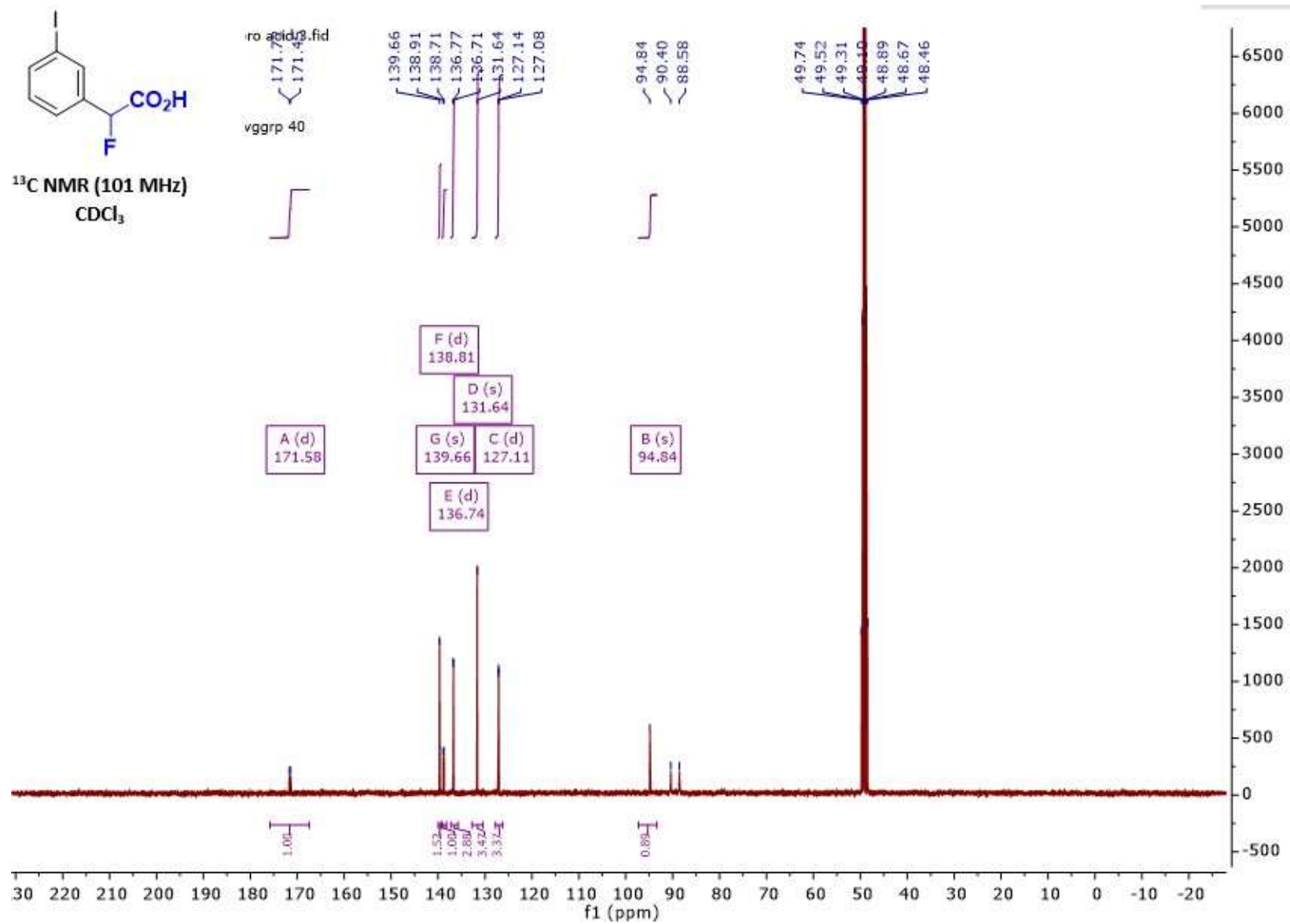
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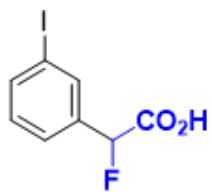




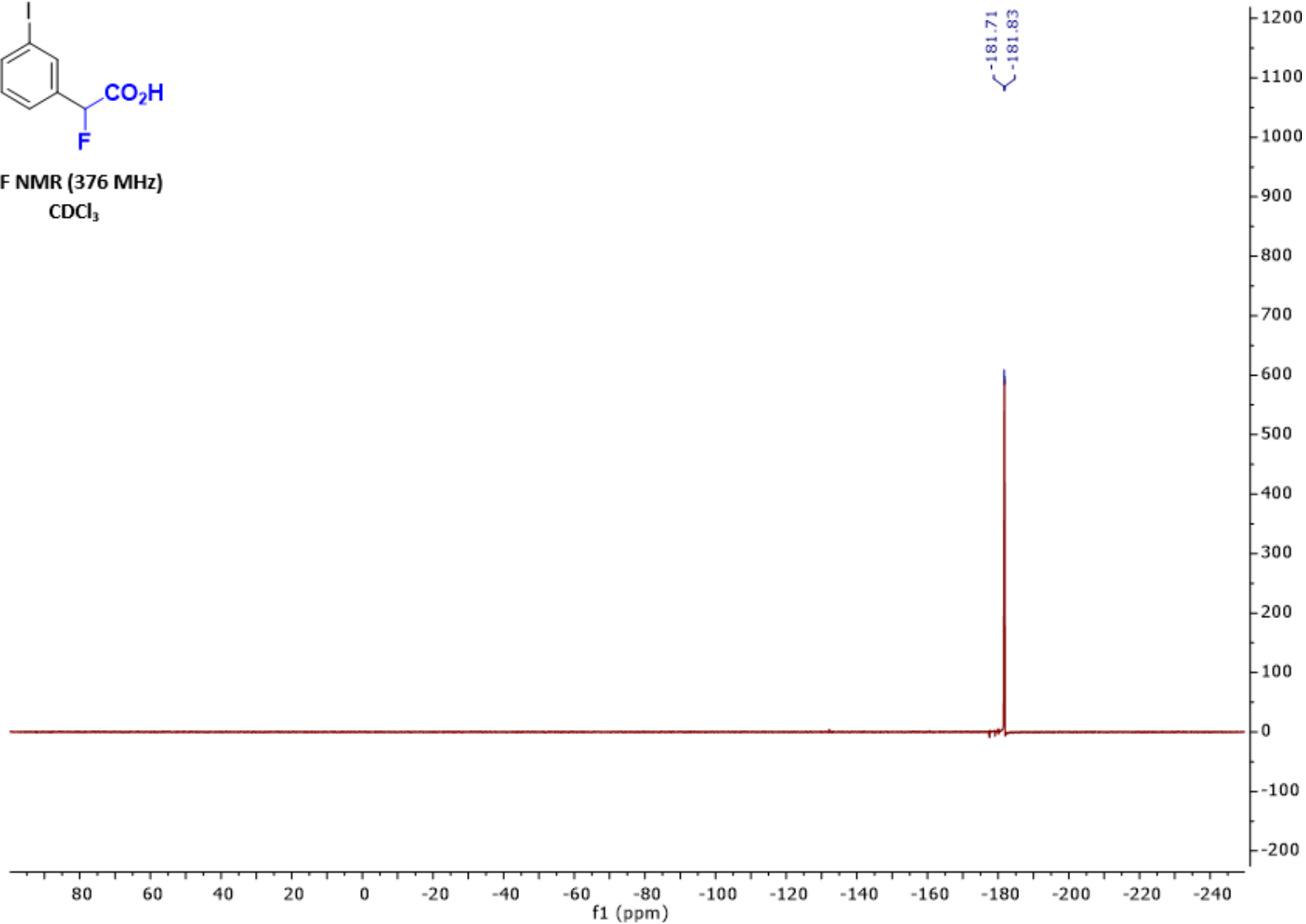
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 CDCl_3

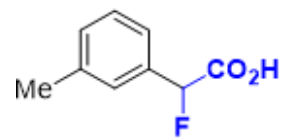




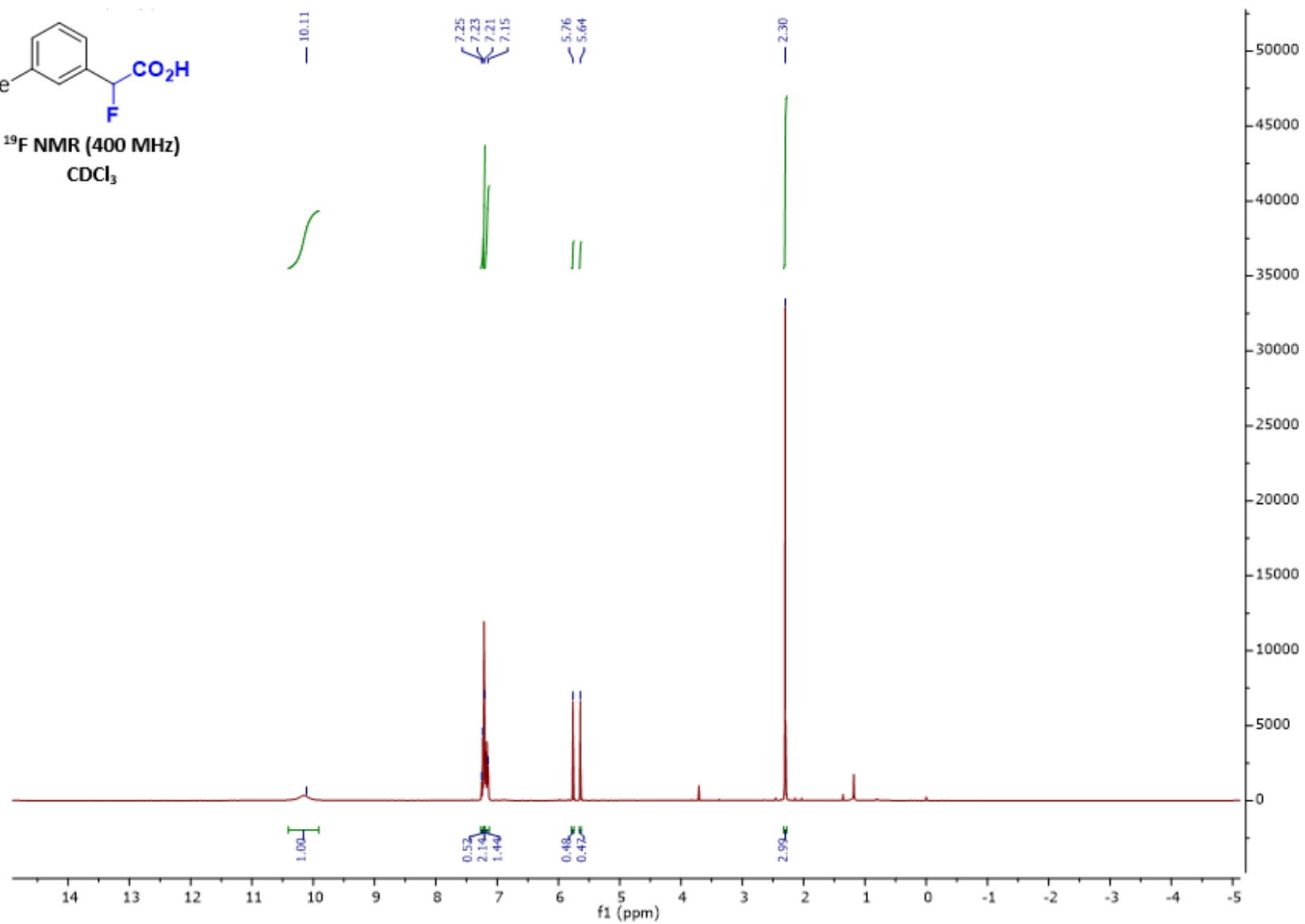


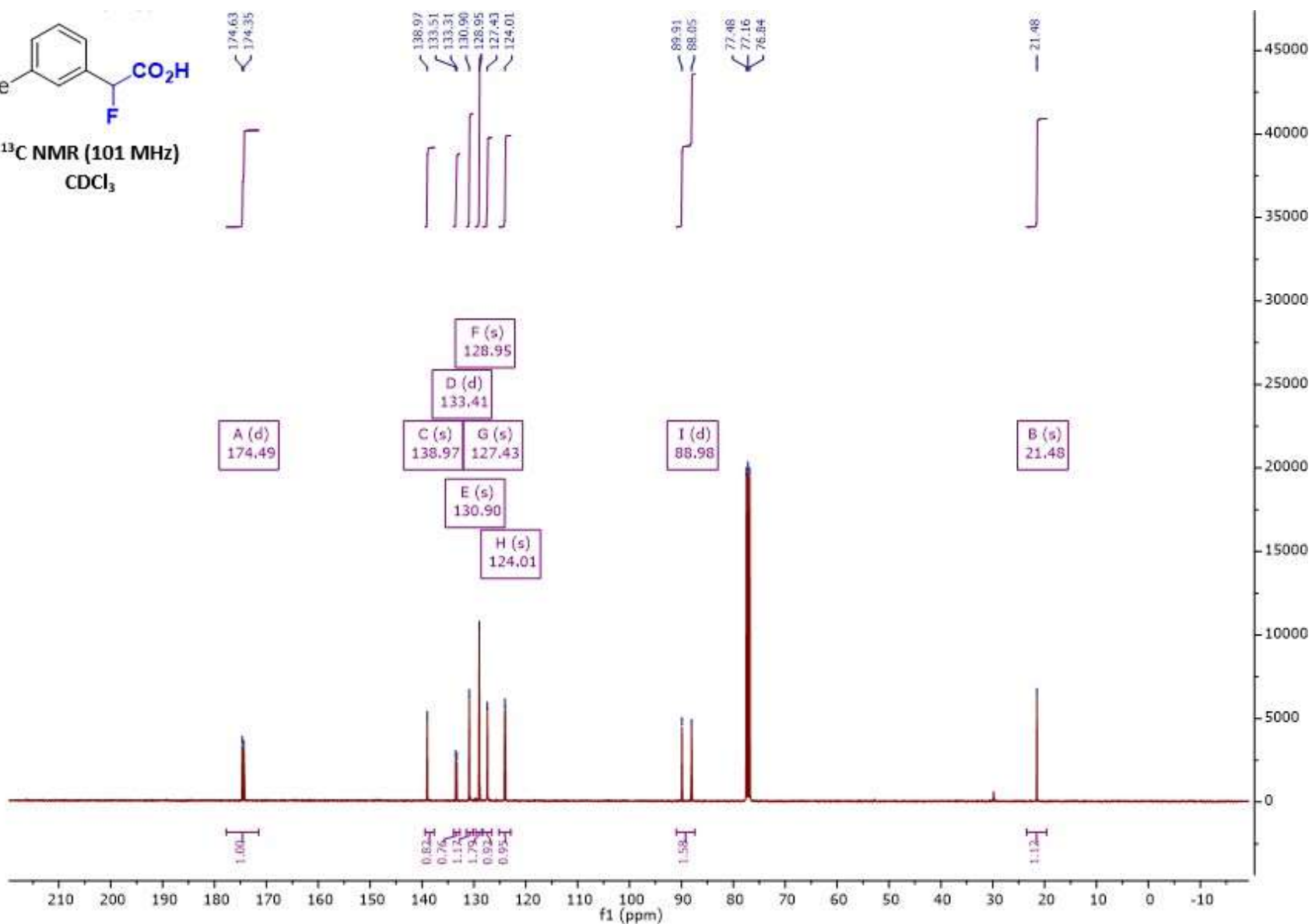
^{19}F NMR (376 MHz)
 CDCl_3

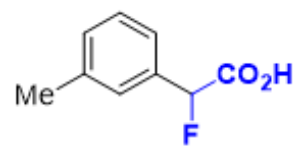




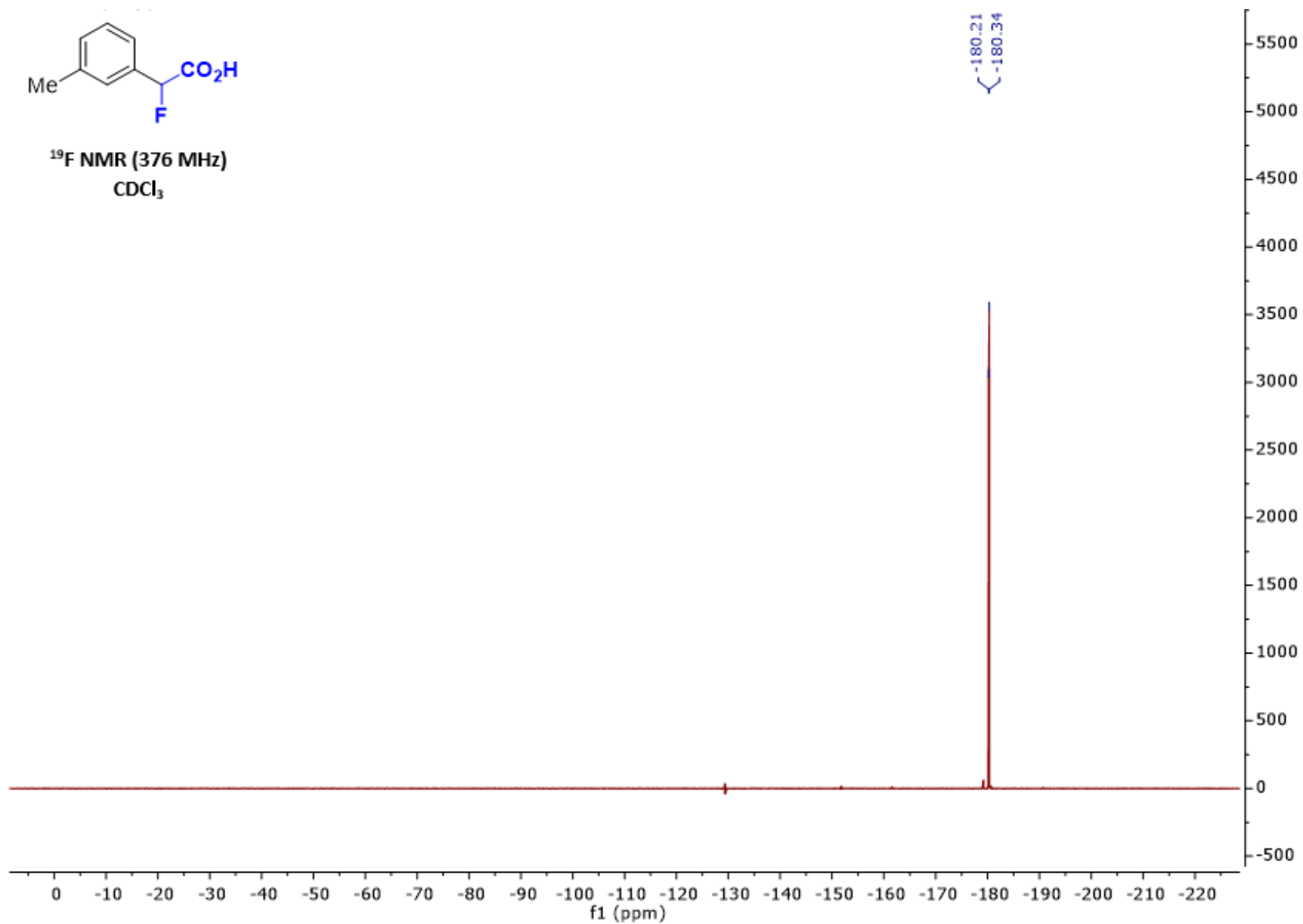
¹⁹F NMR (400 MHz)
CDCl₃

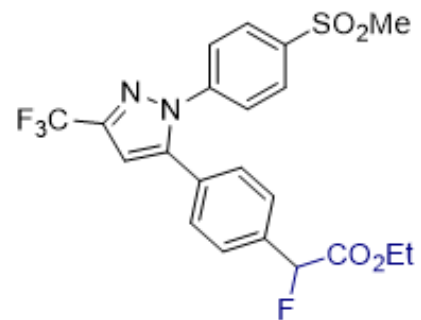




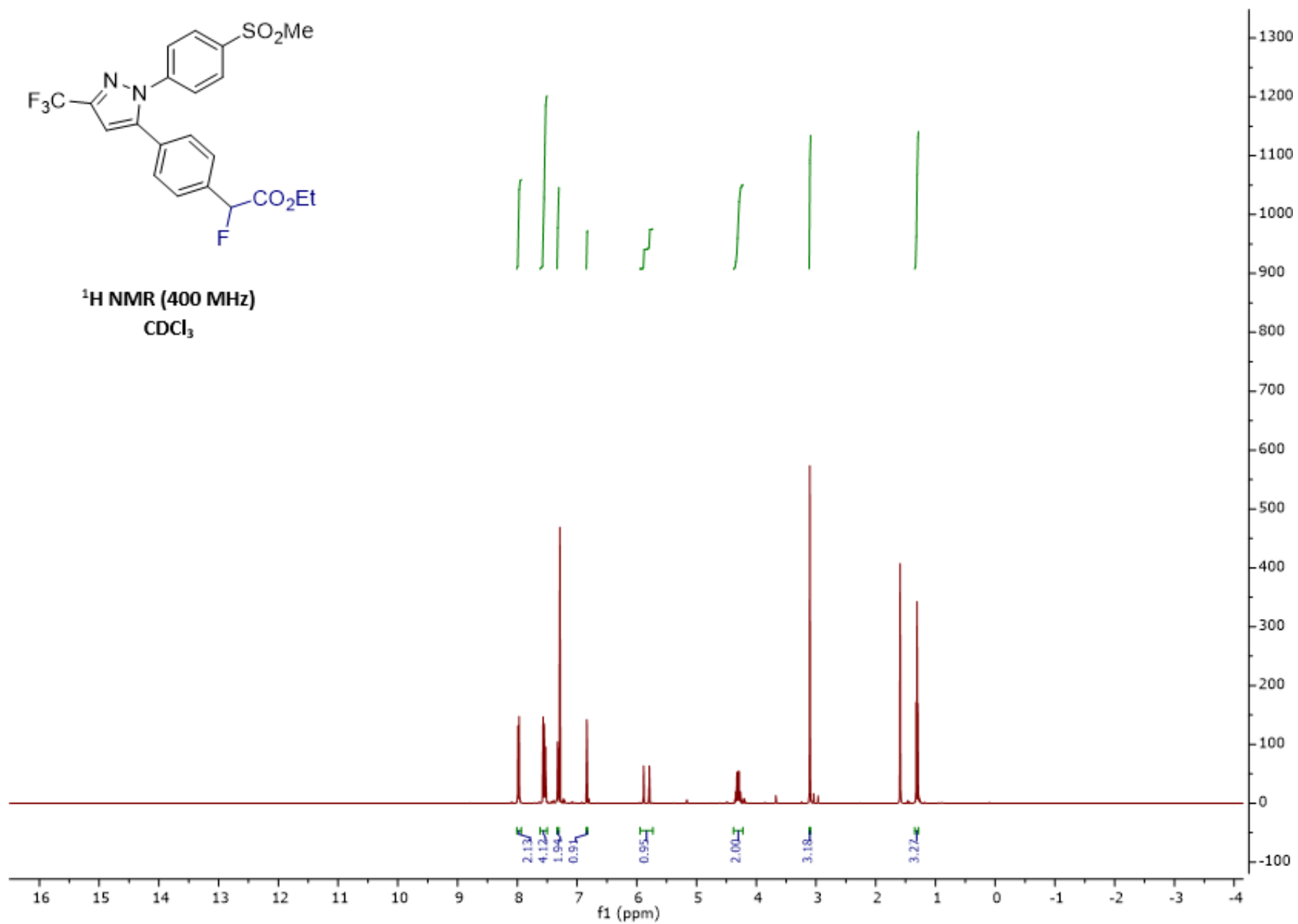


¹⁹F NMR (376 MHz)
CDCl₃



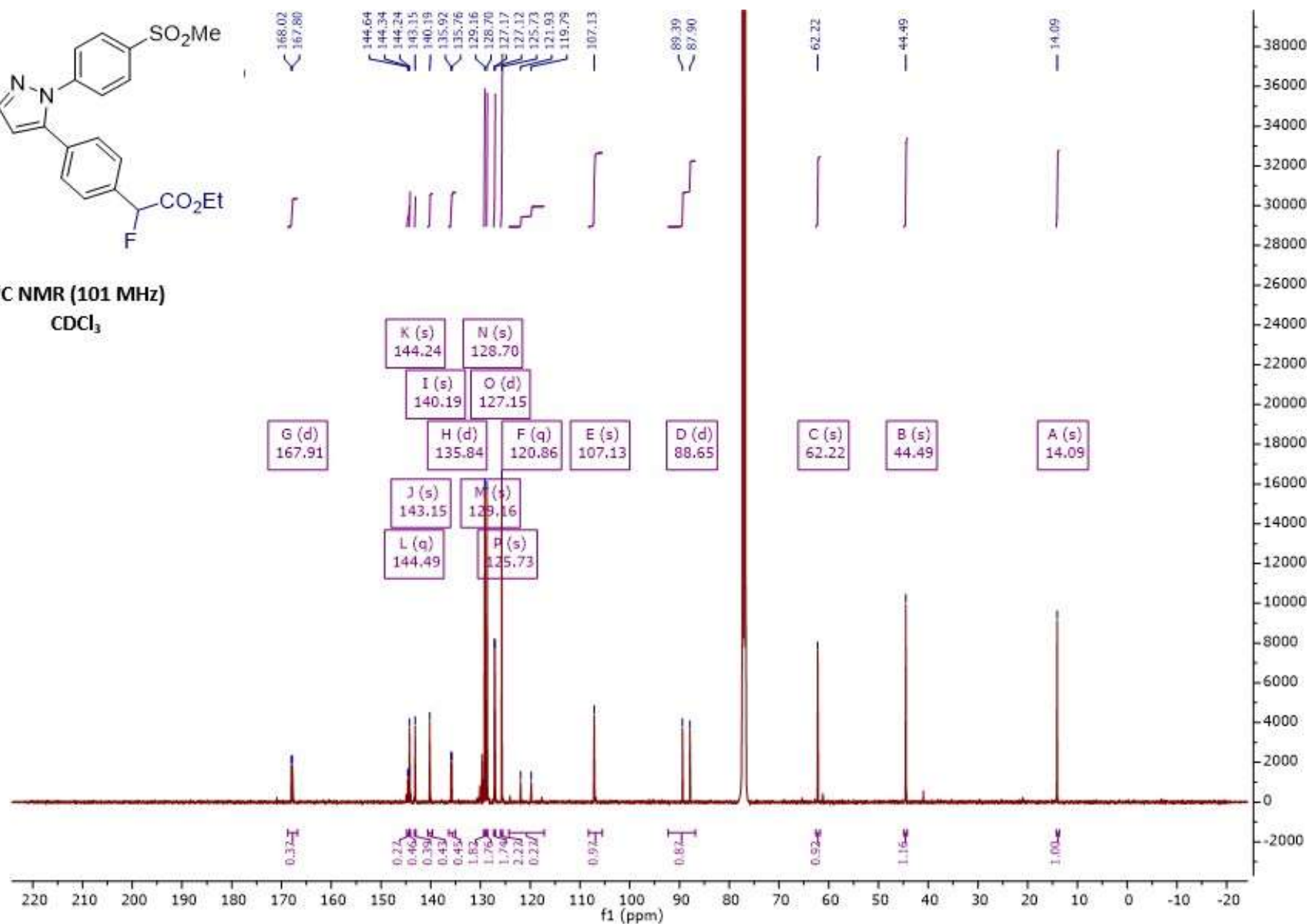


¹H NMR (400 MHz)
CDCl₃



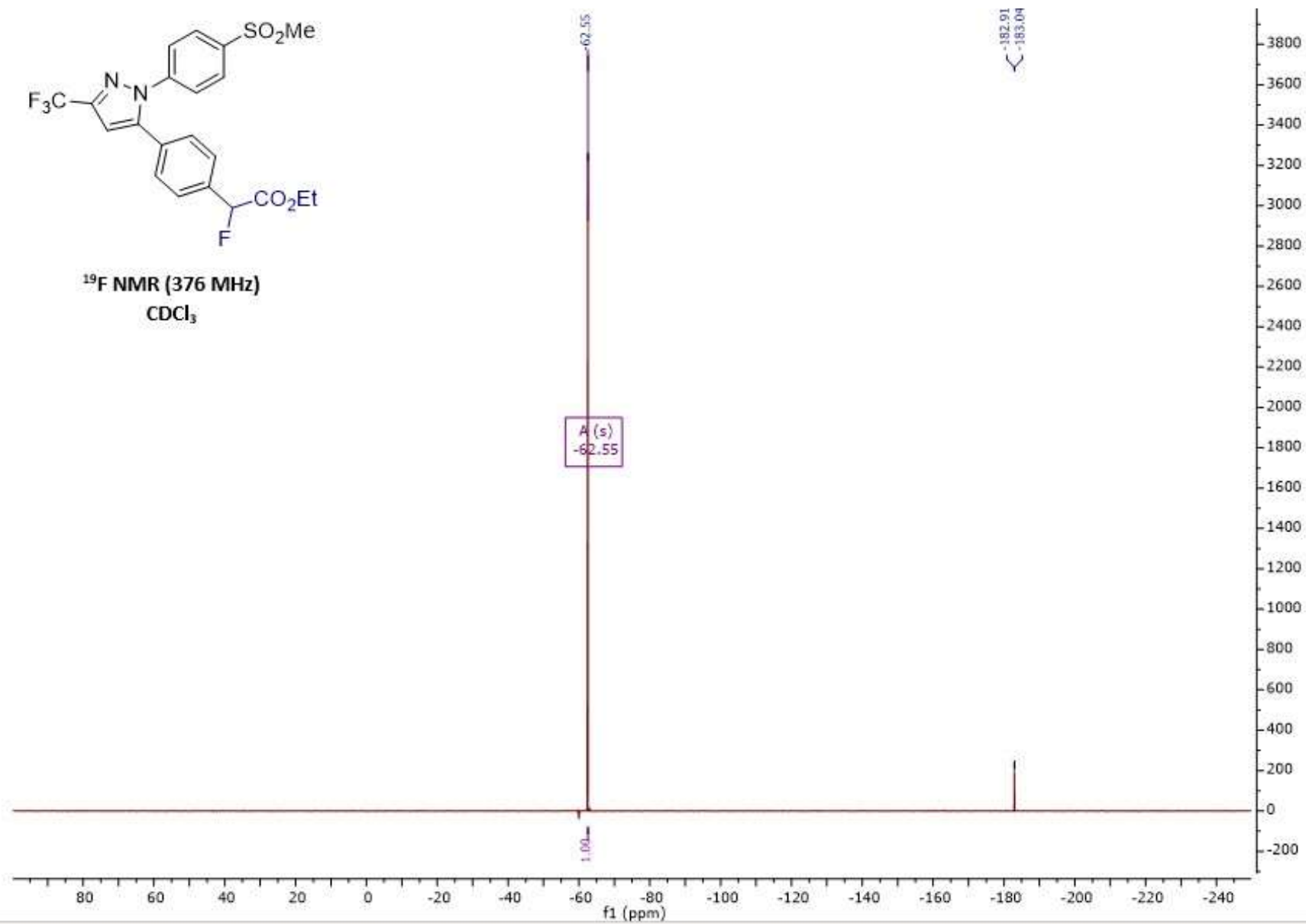


^{13}C NMR (101 MHz)
 CDCl_3



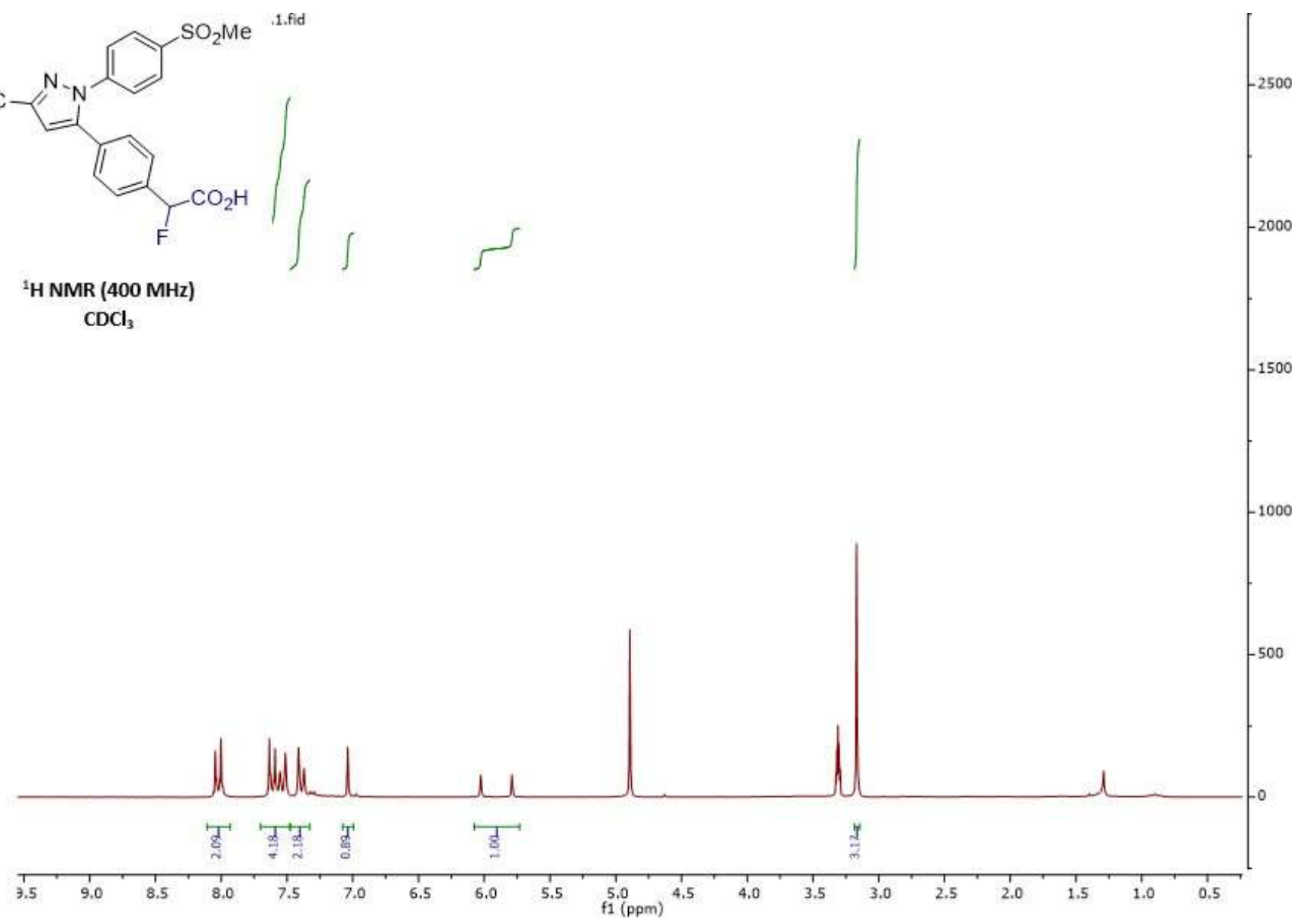


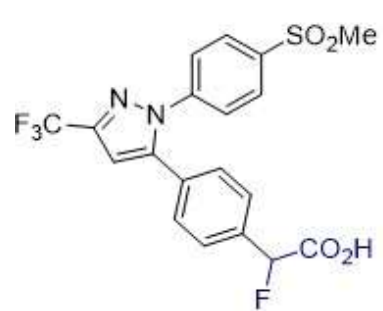
^{19}F NMR (376 MHz)
 CDCl_3



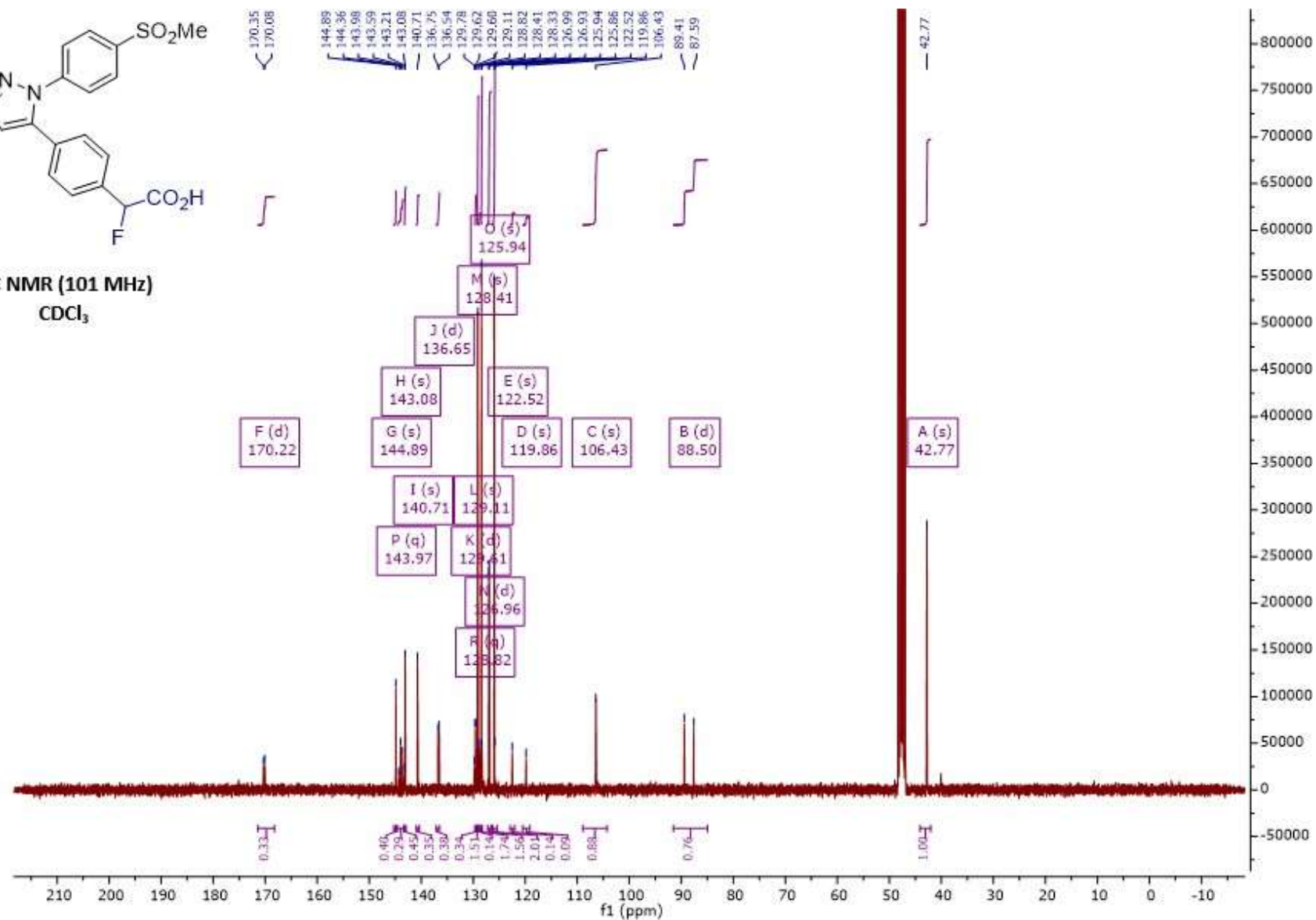


^1H NMR (400 MHz)
 CDCl_3



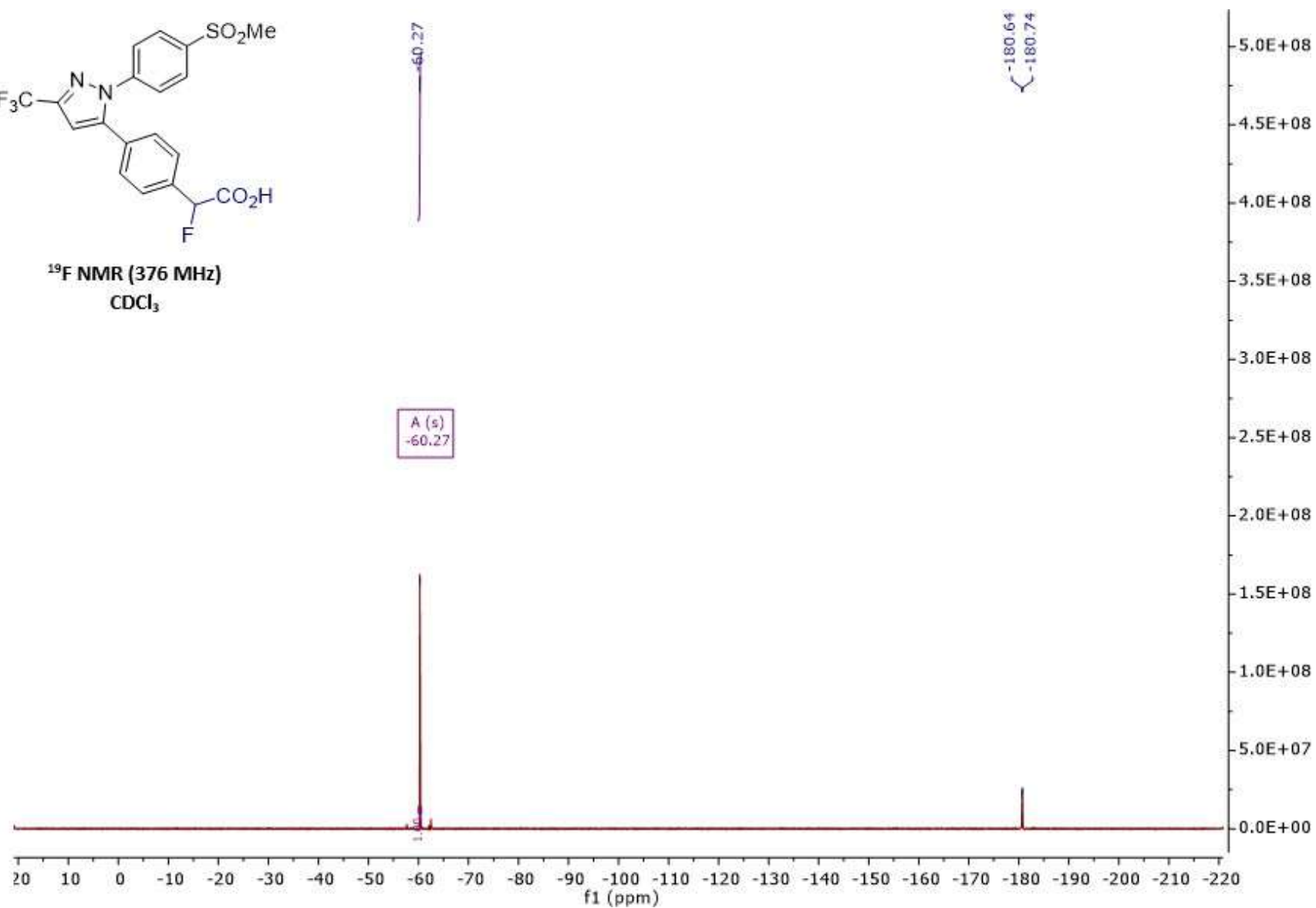


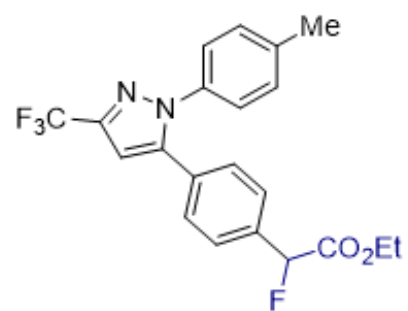
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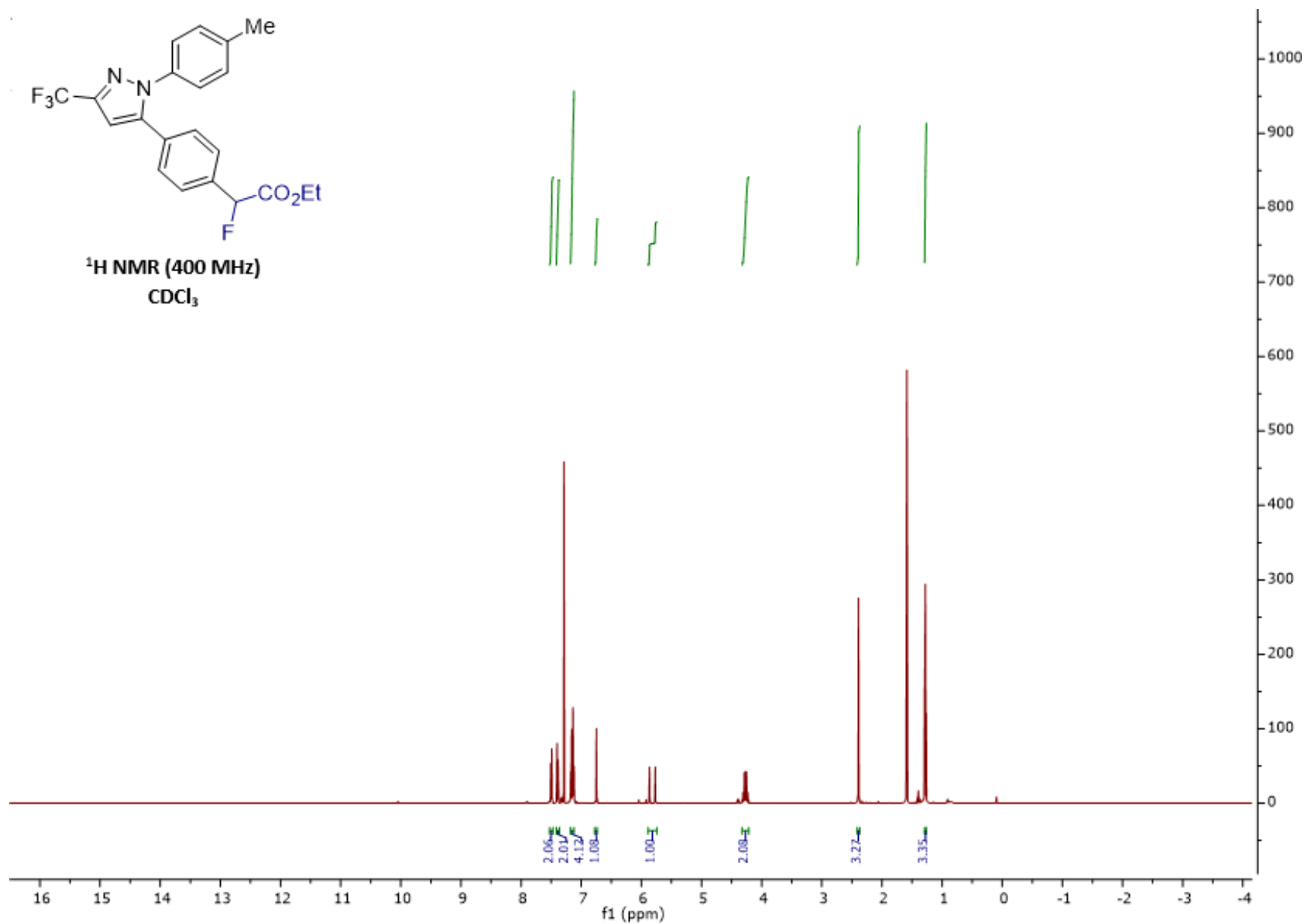


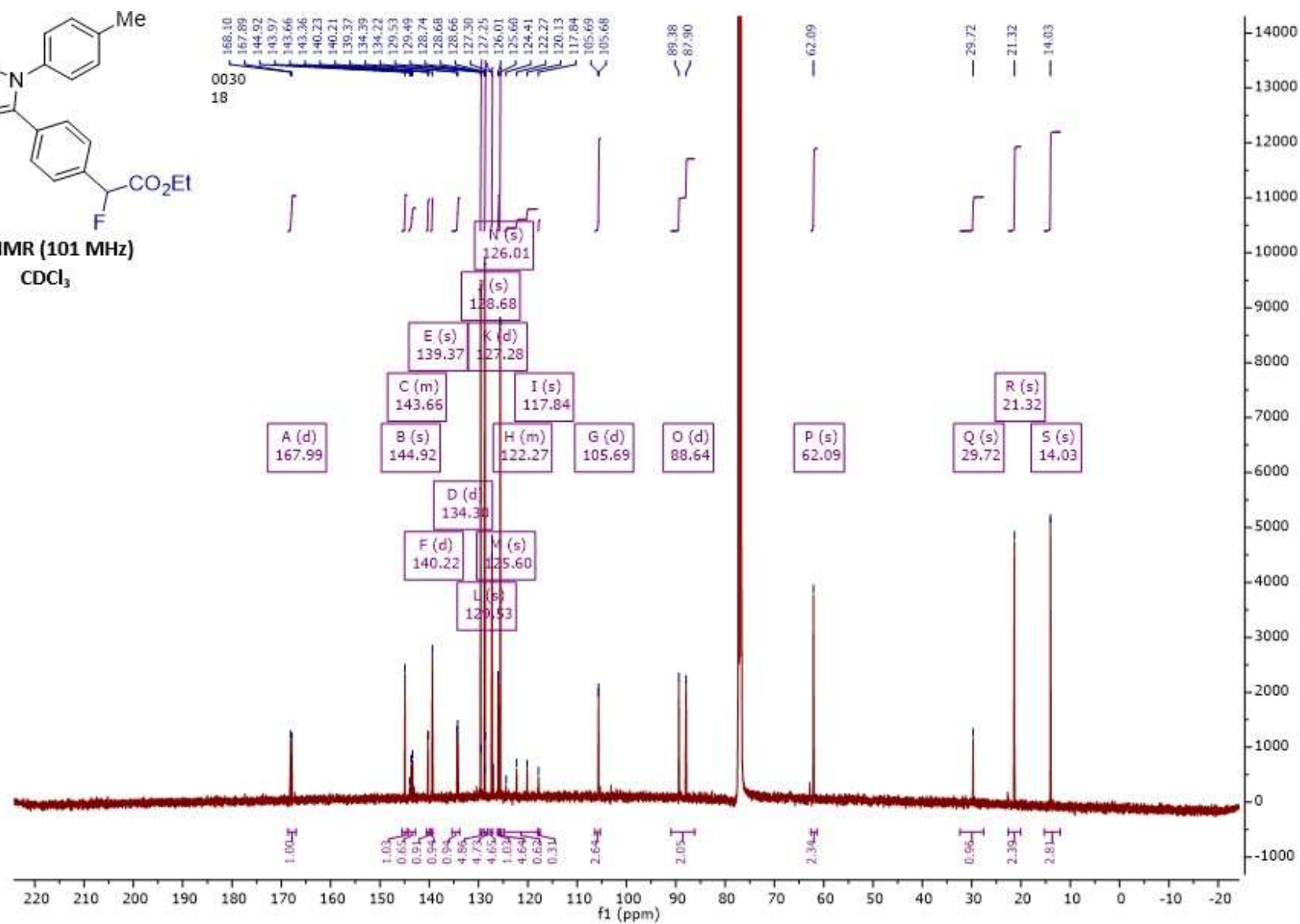
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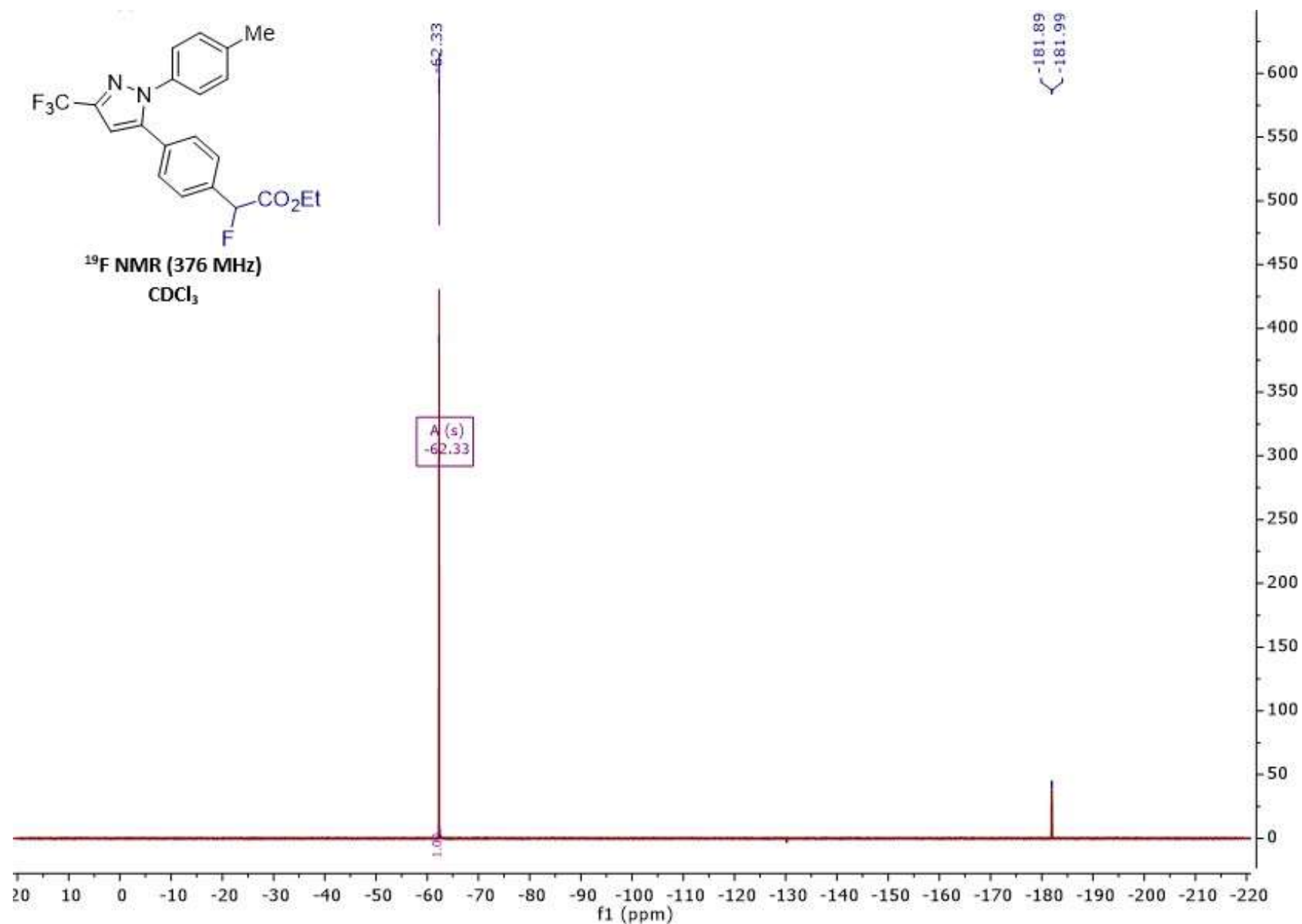
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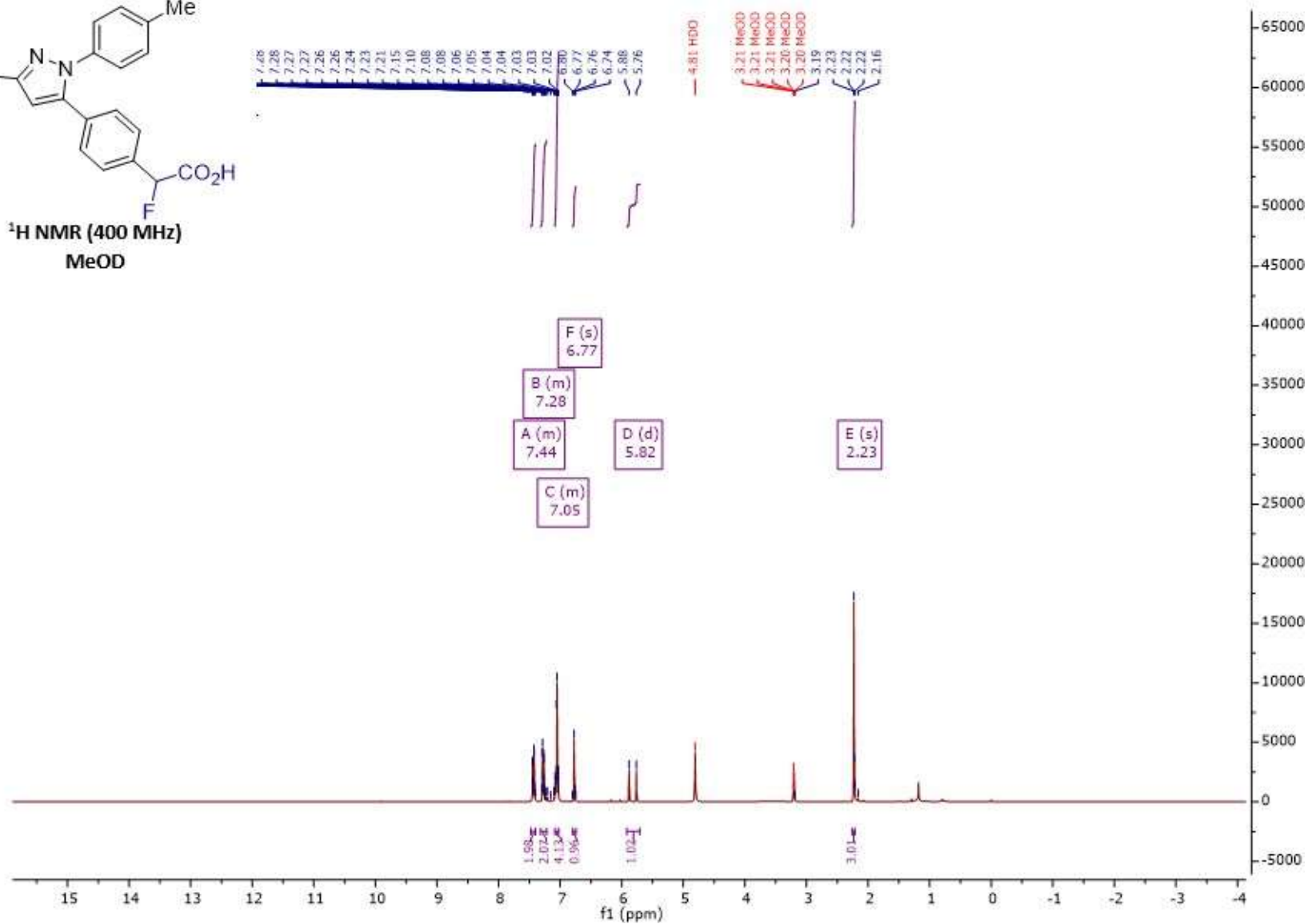


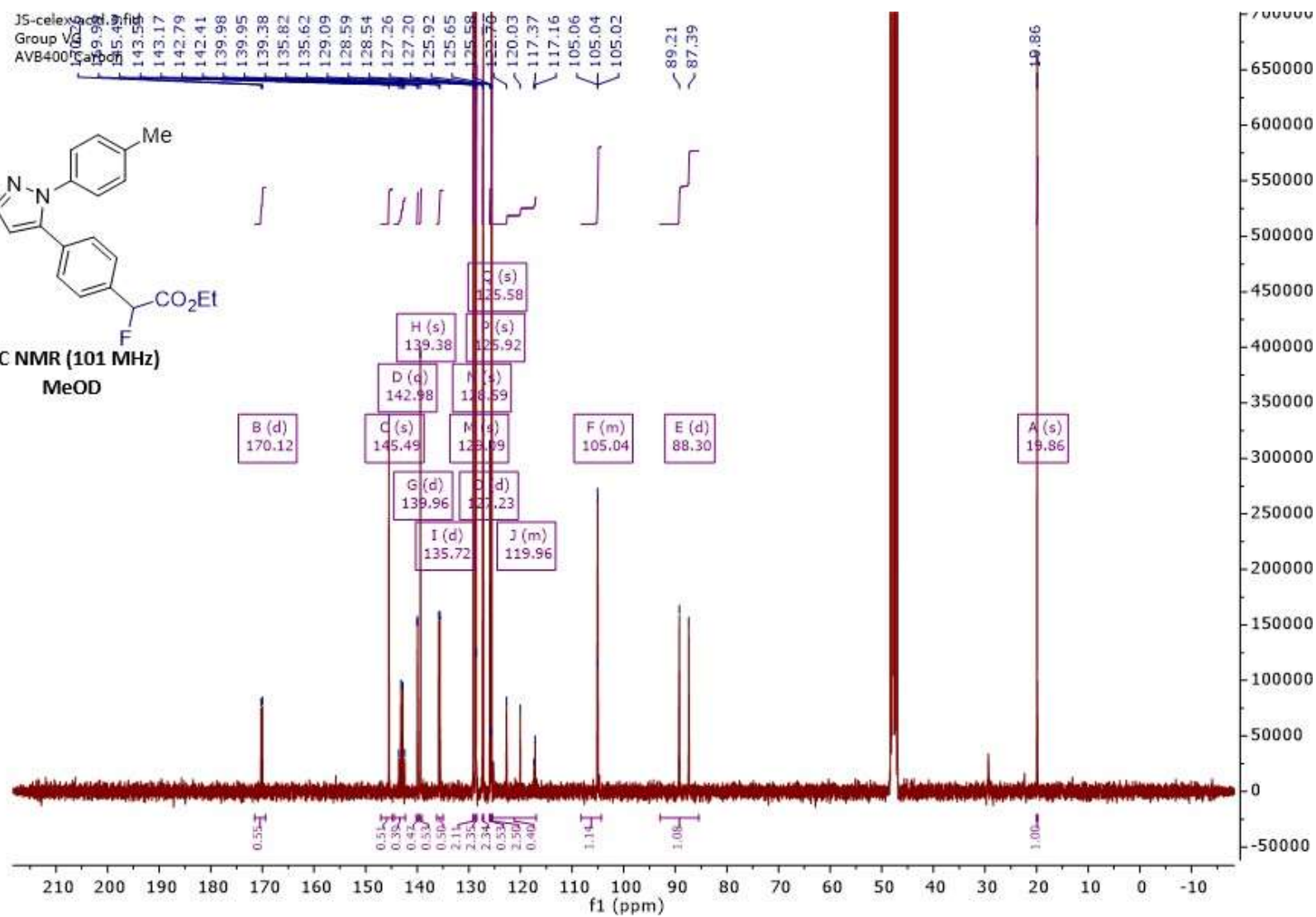


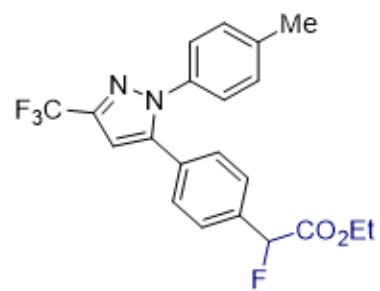


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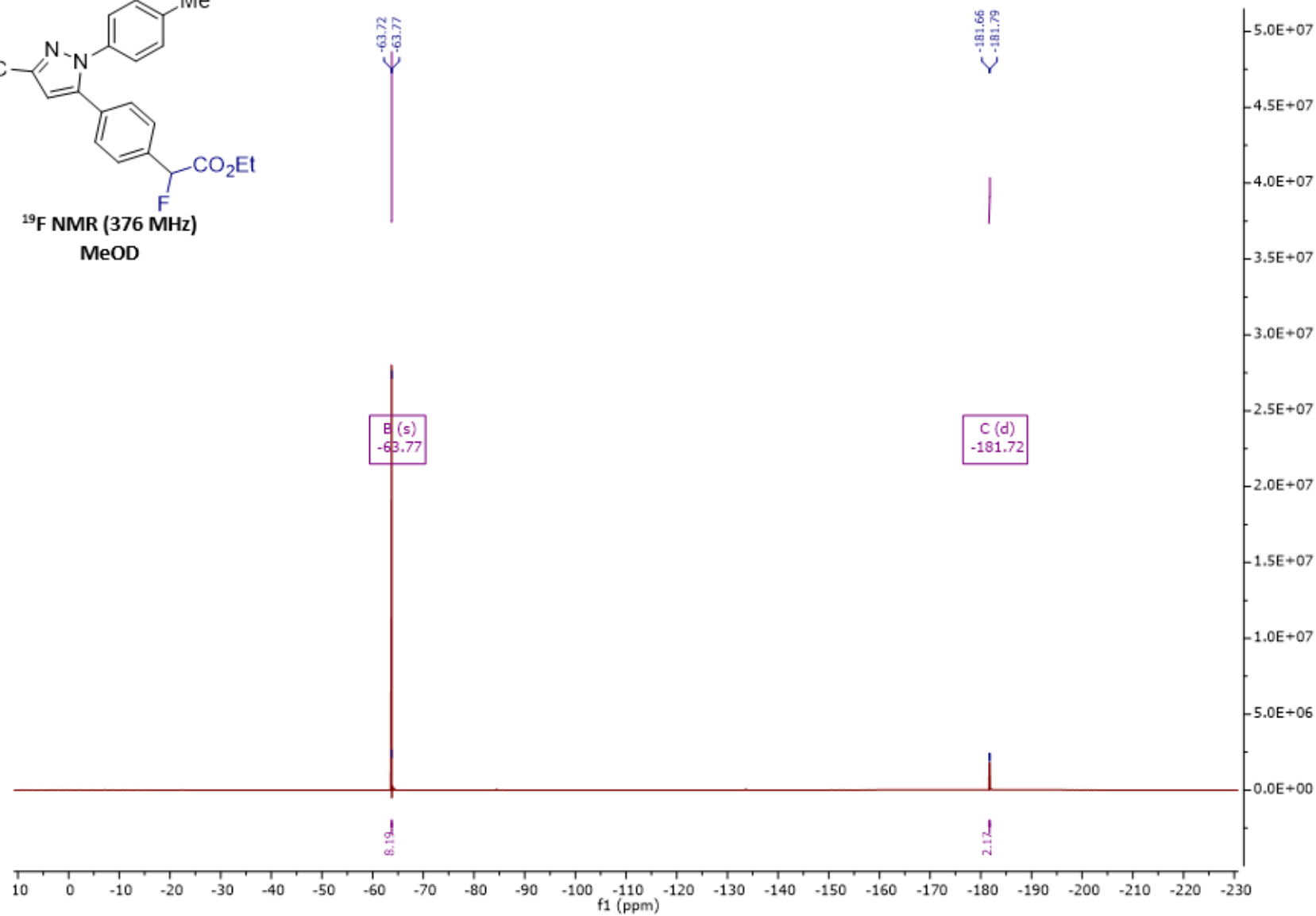


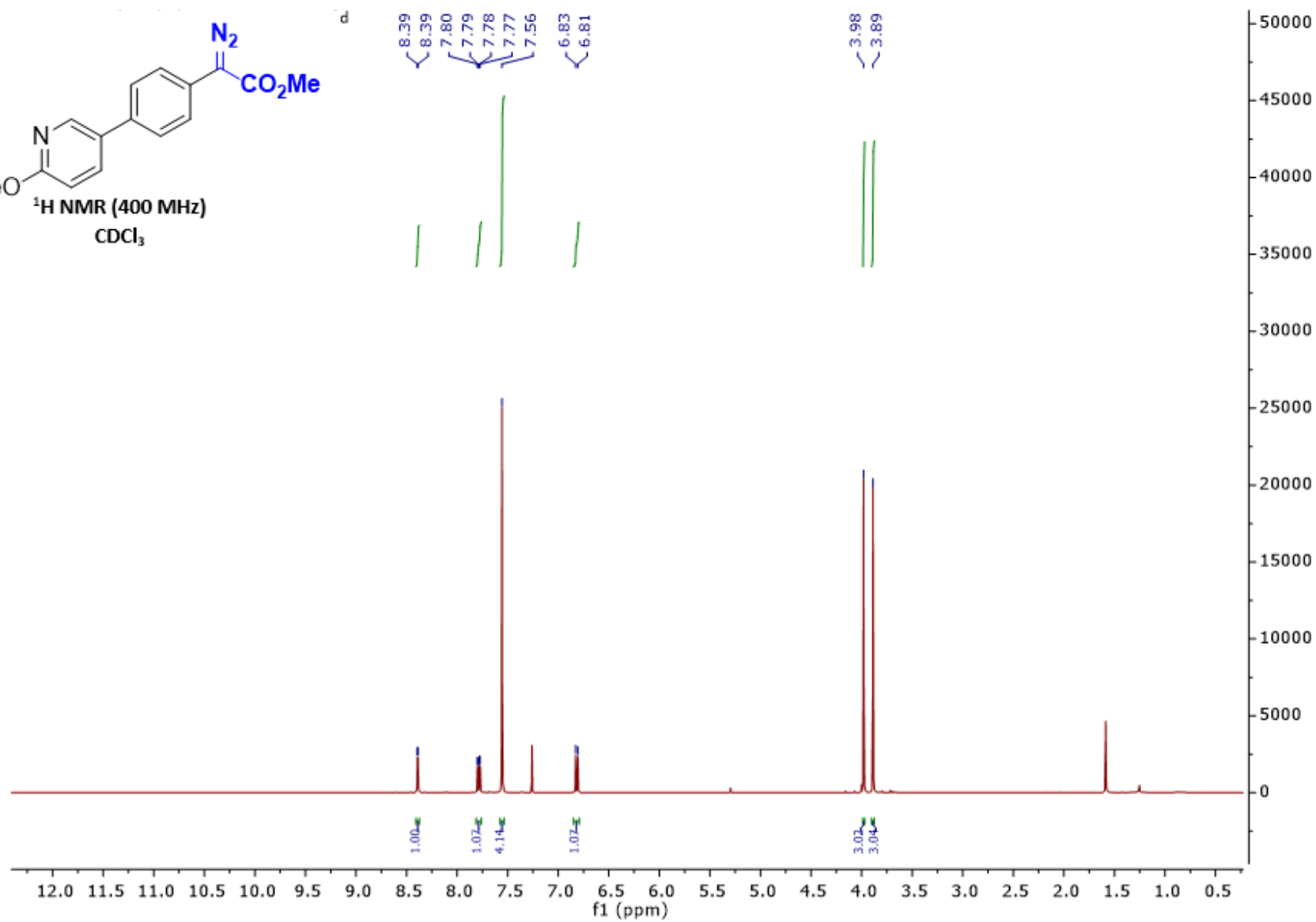
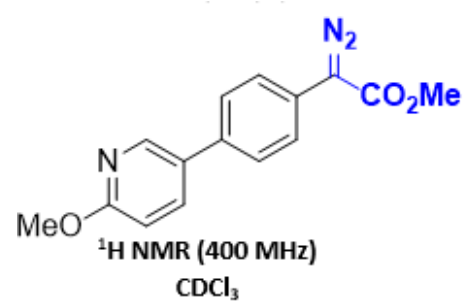


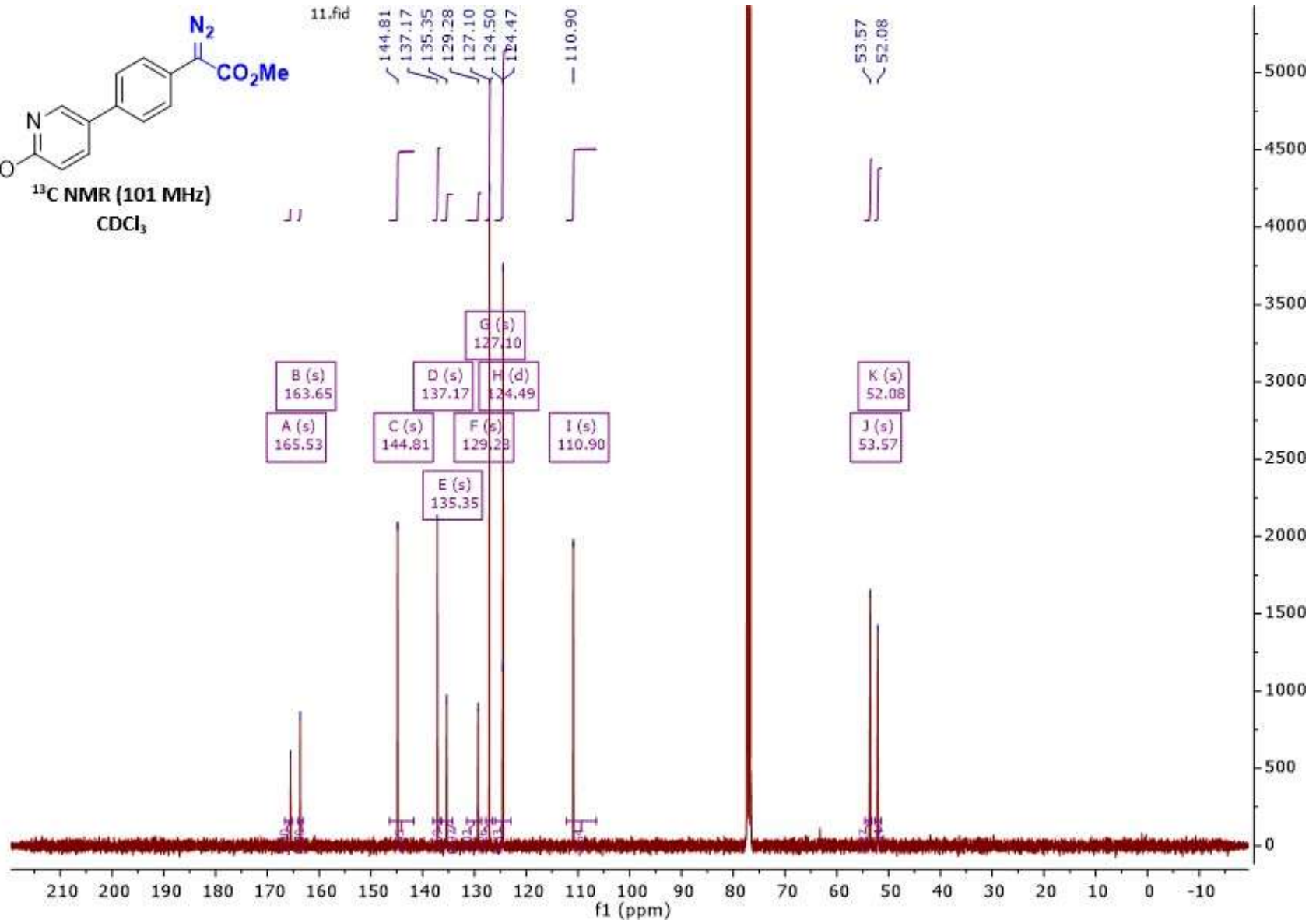
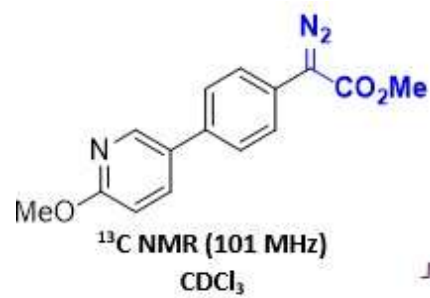


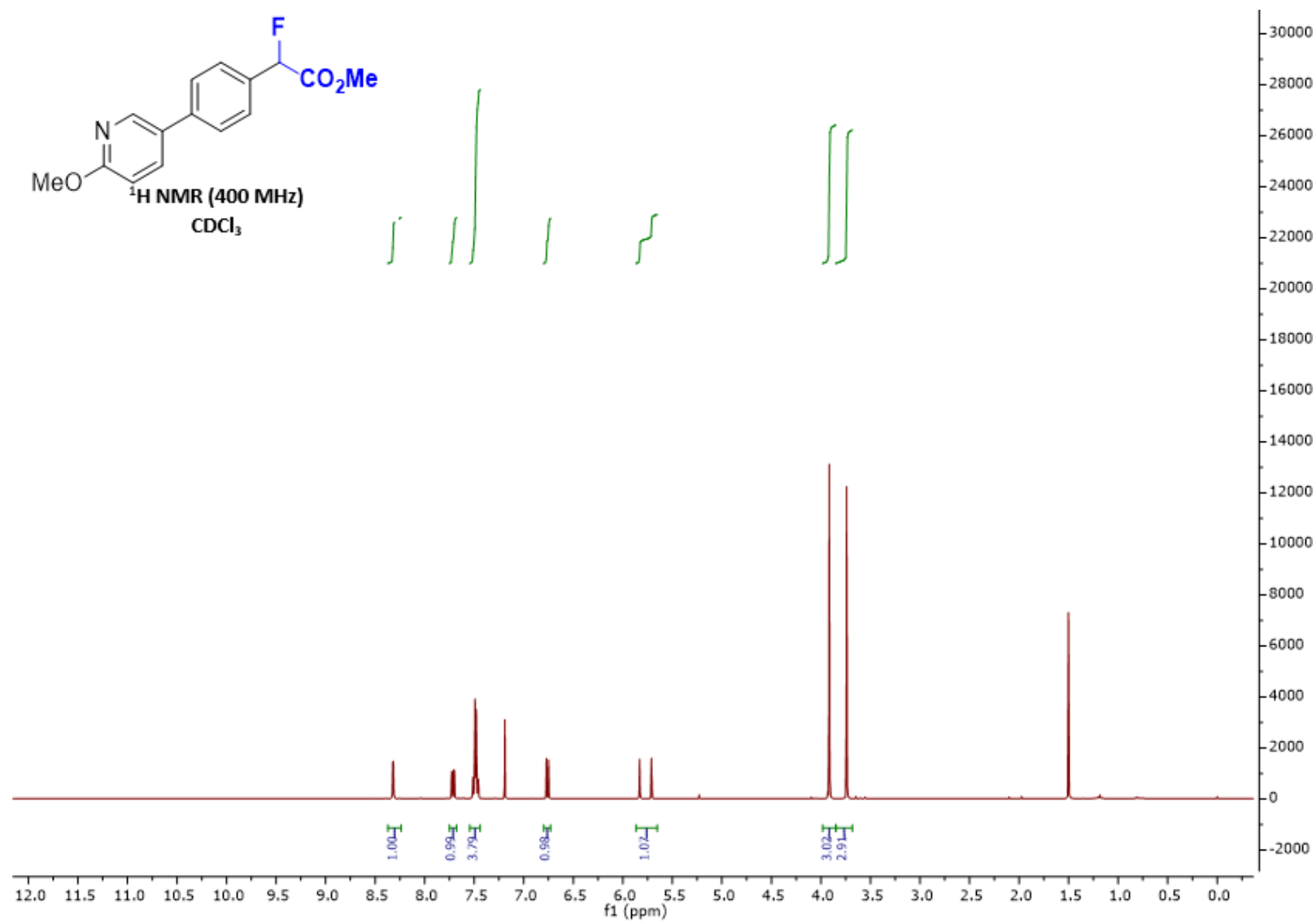
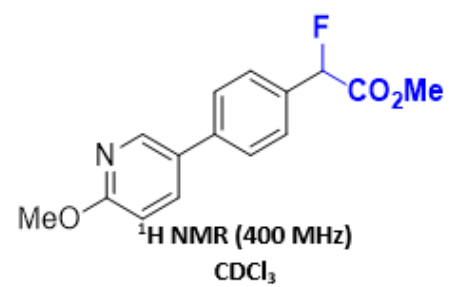


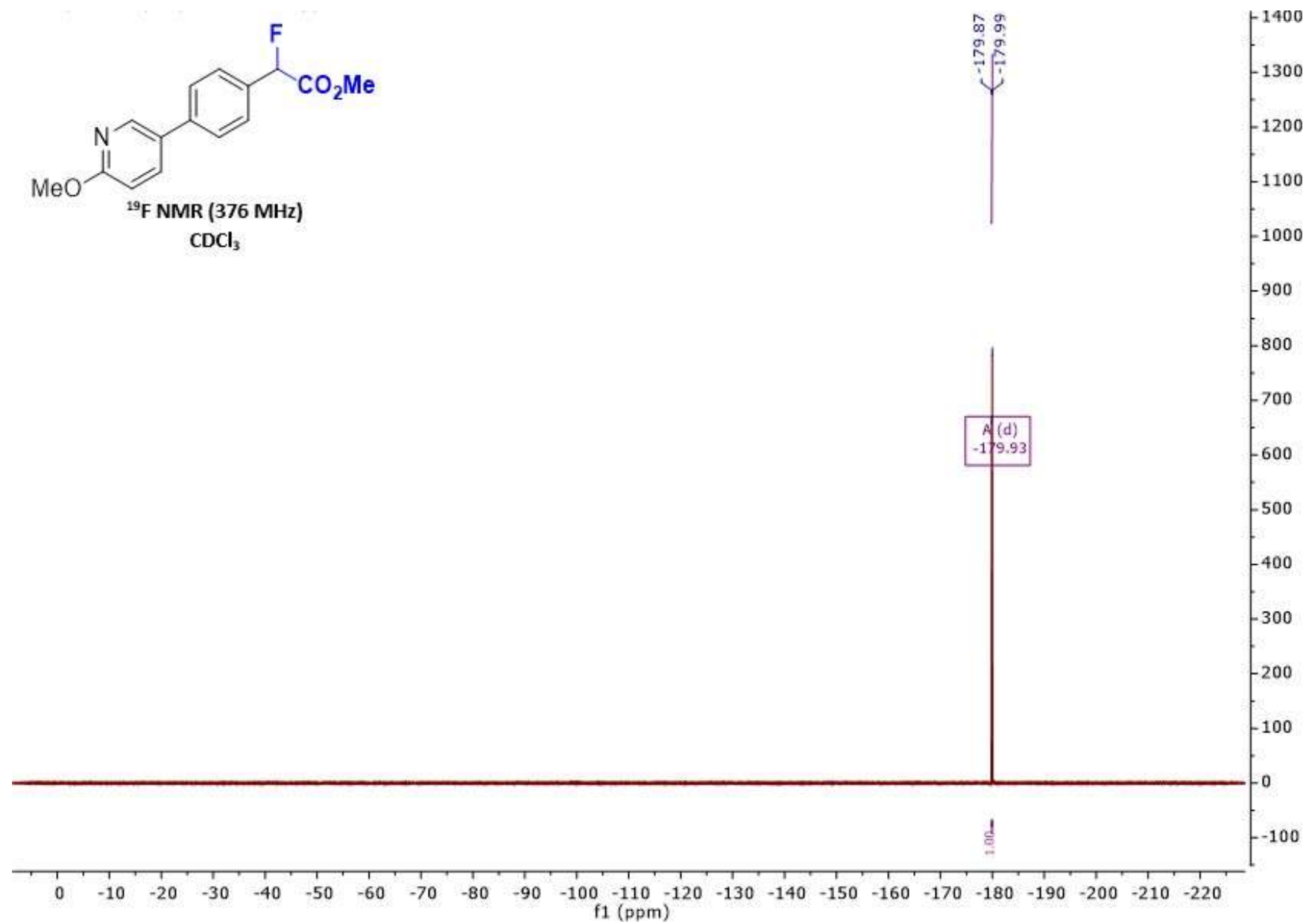
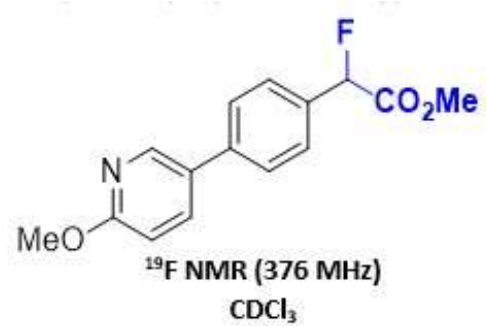
¹⁹F NMR (376 MHz)
MeOD

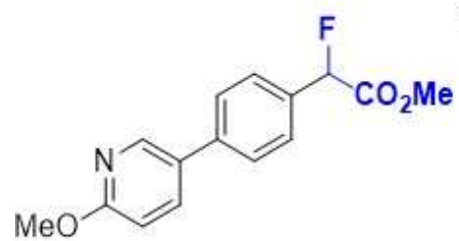




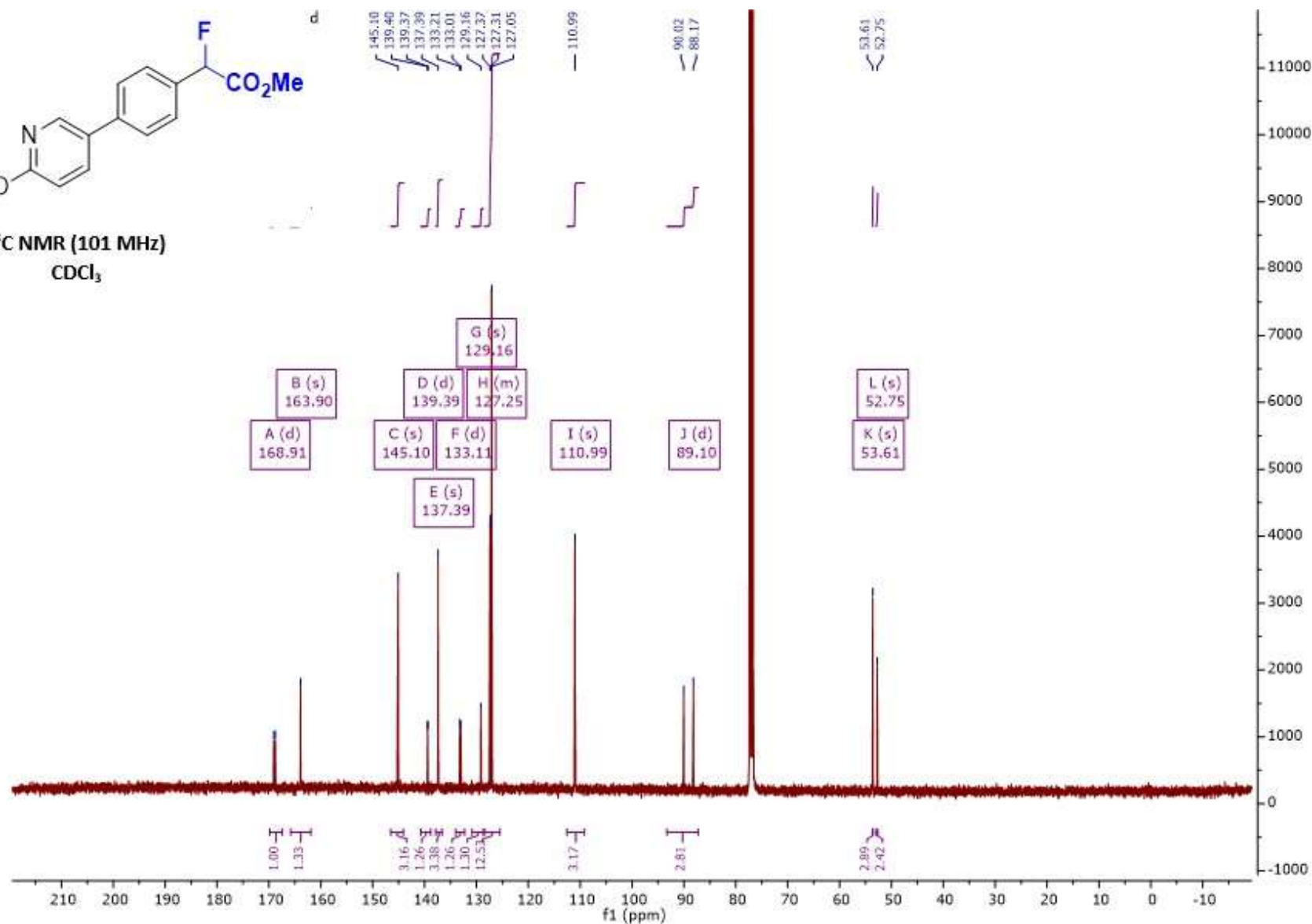






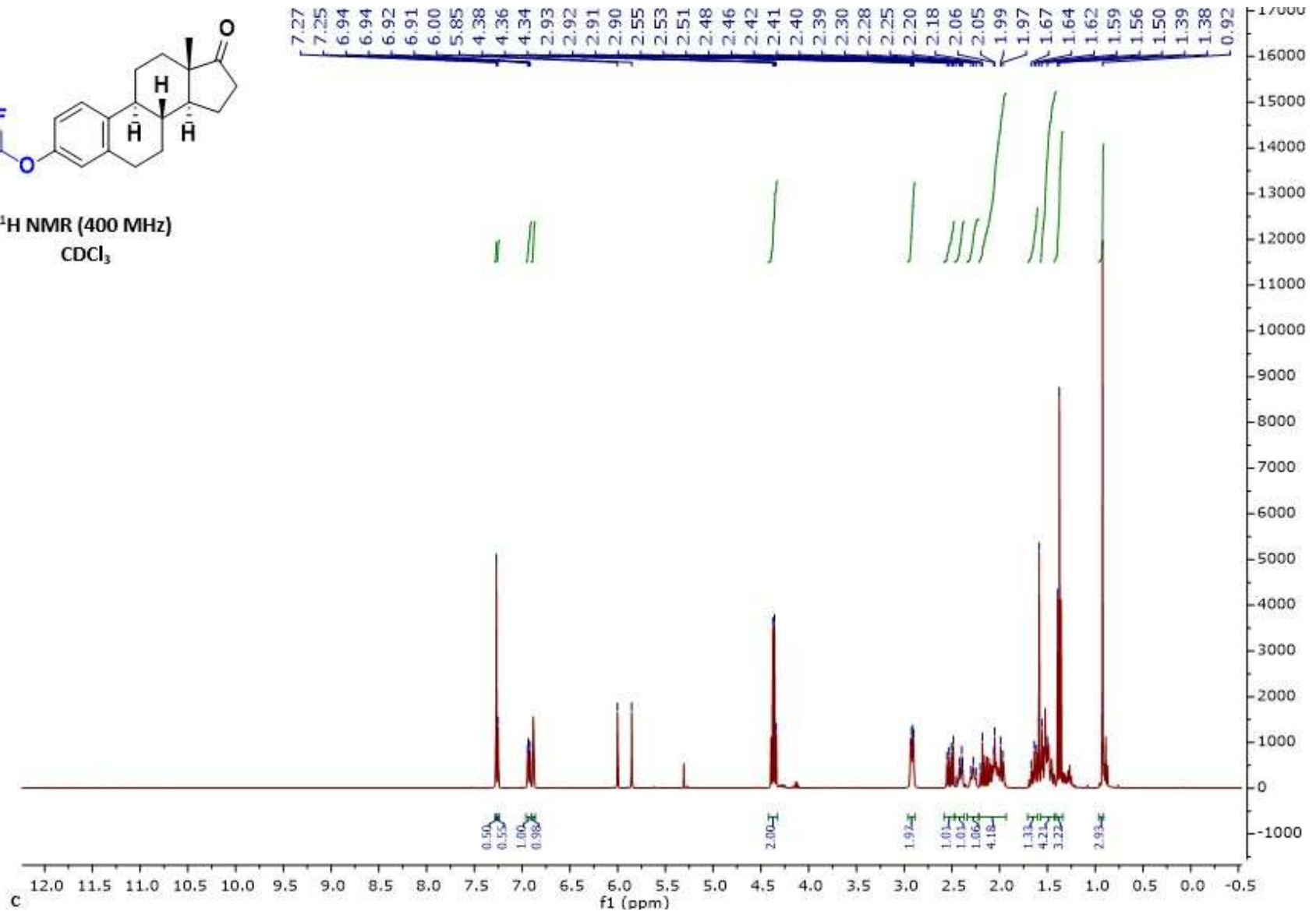


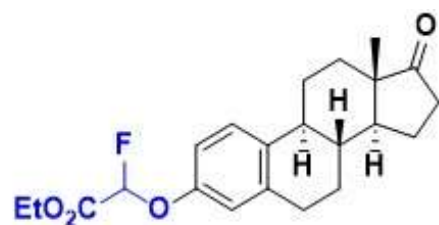
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 CDCl_3



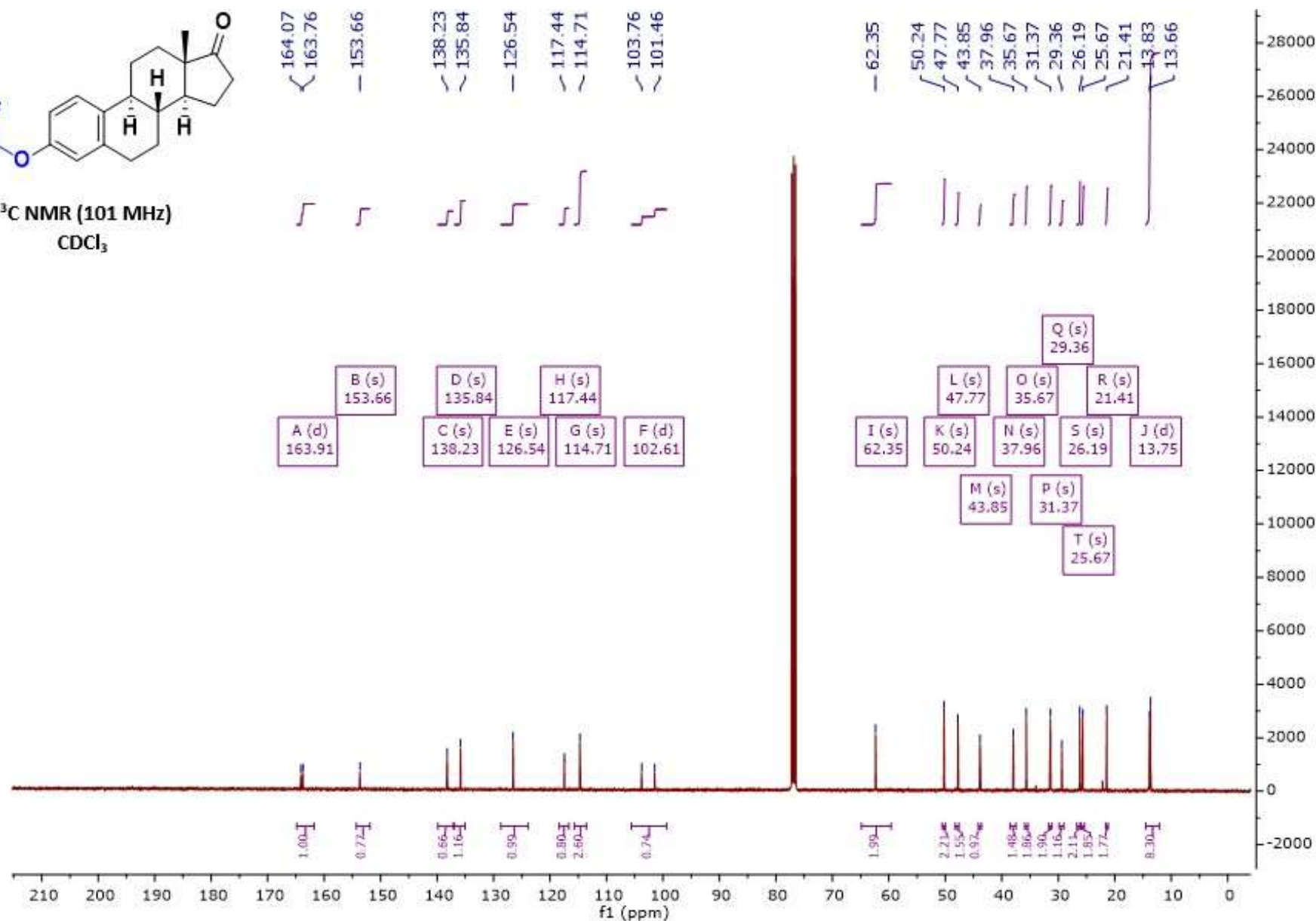


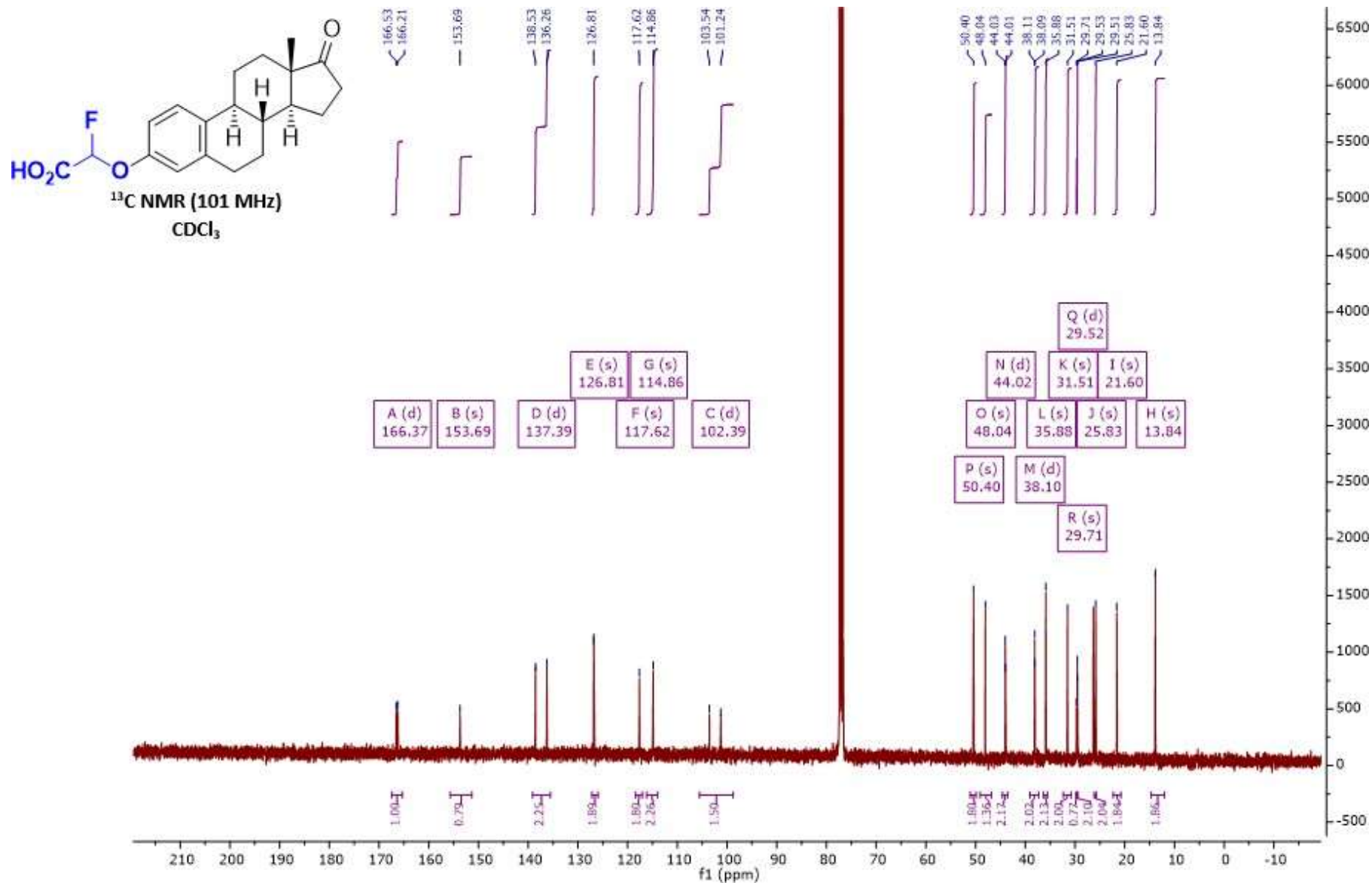
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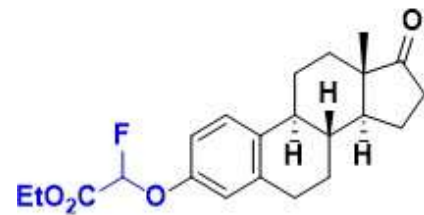




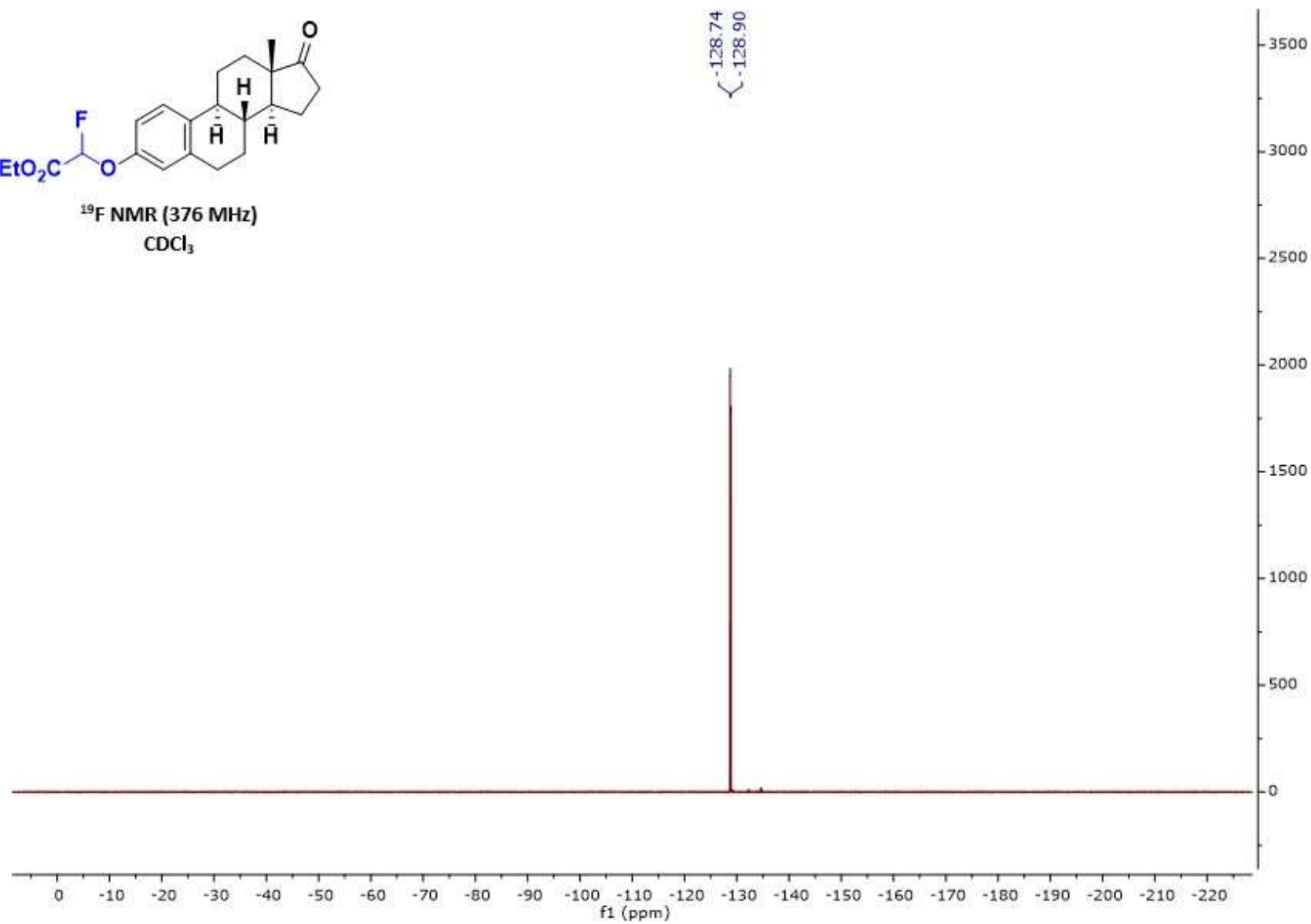
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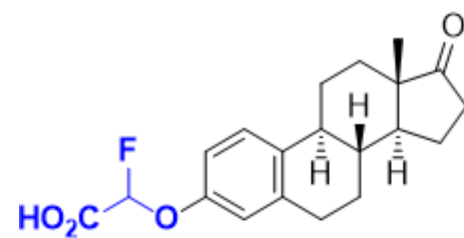




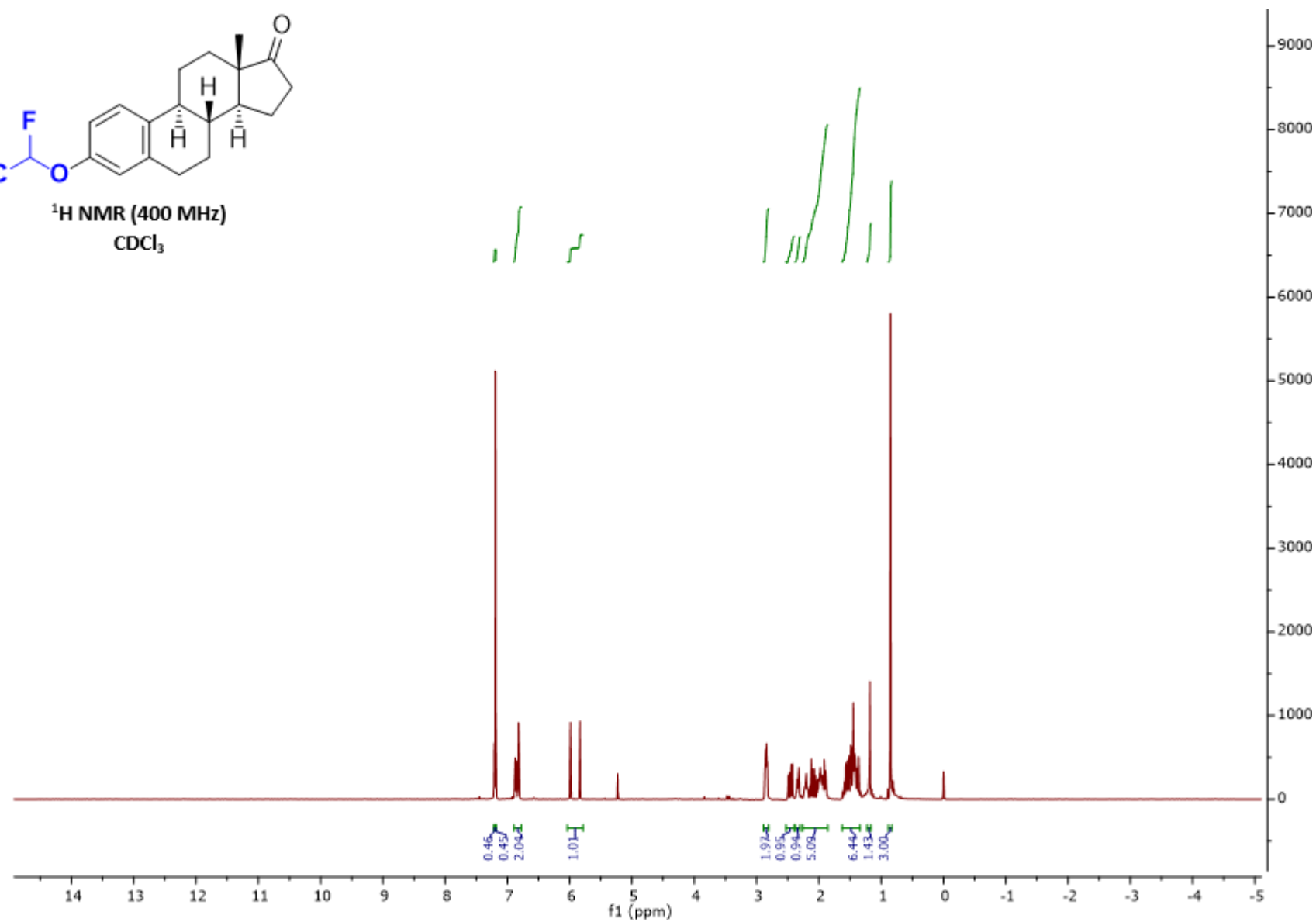


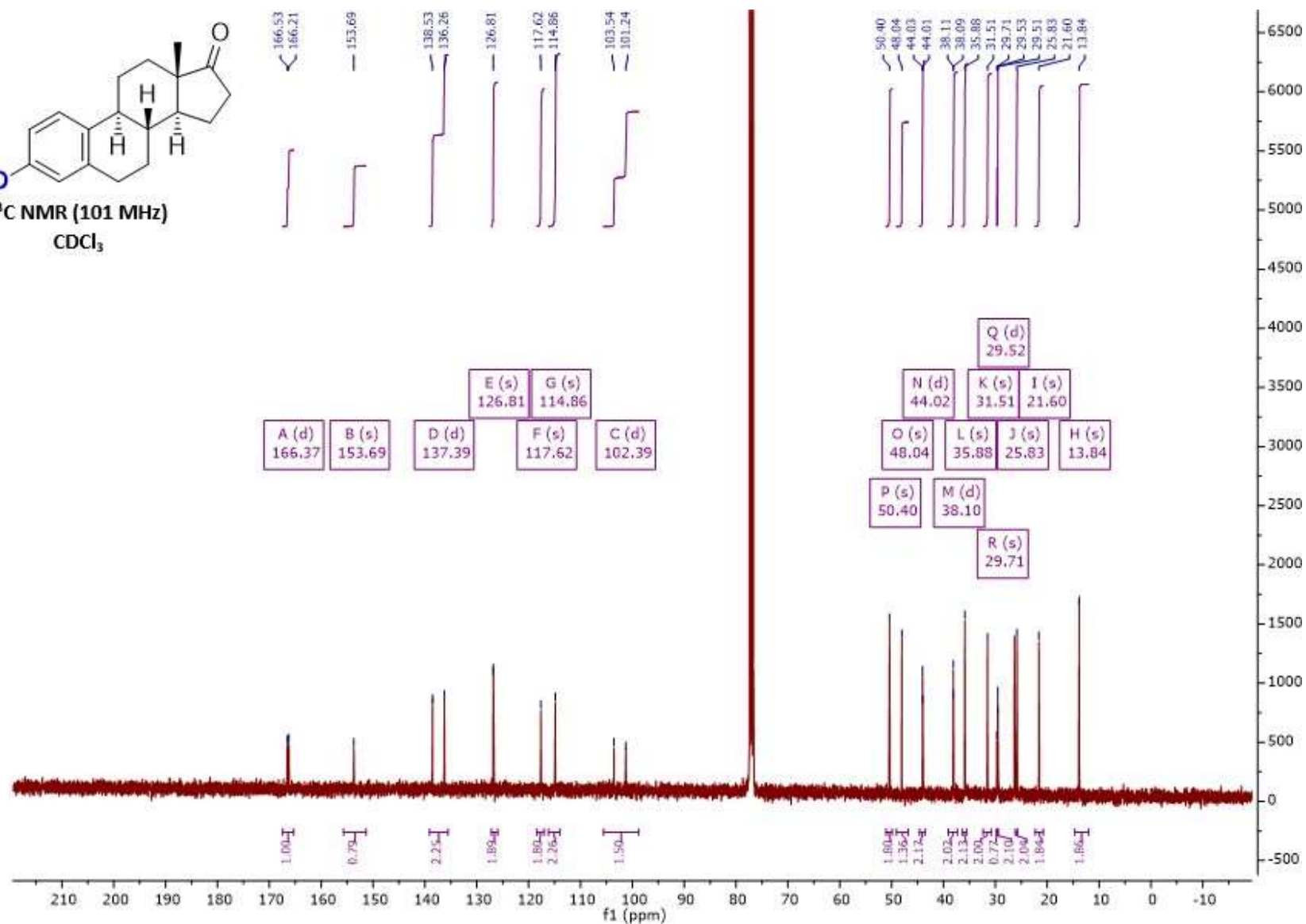
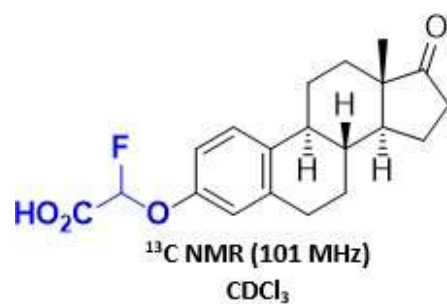
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 CDCl_3

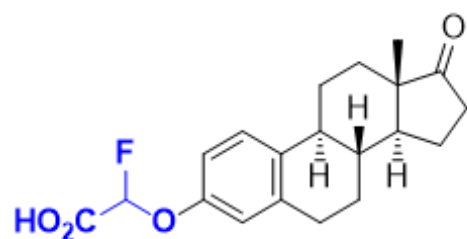




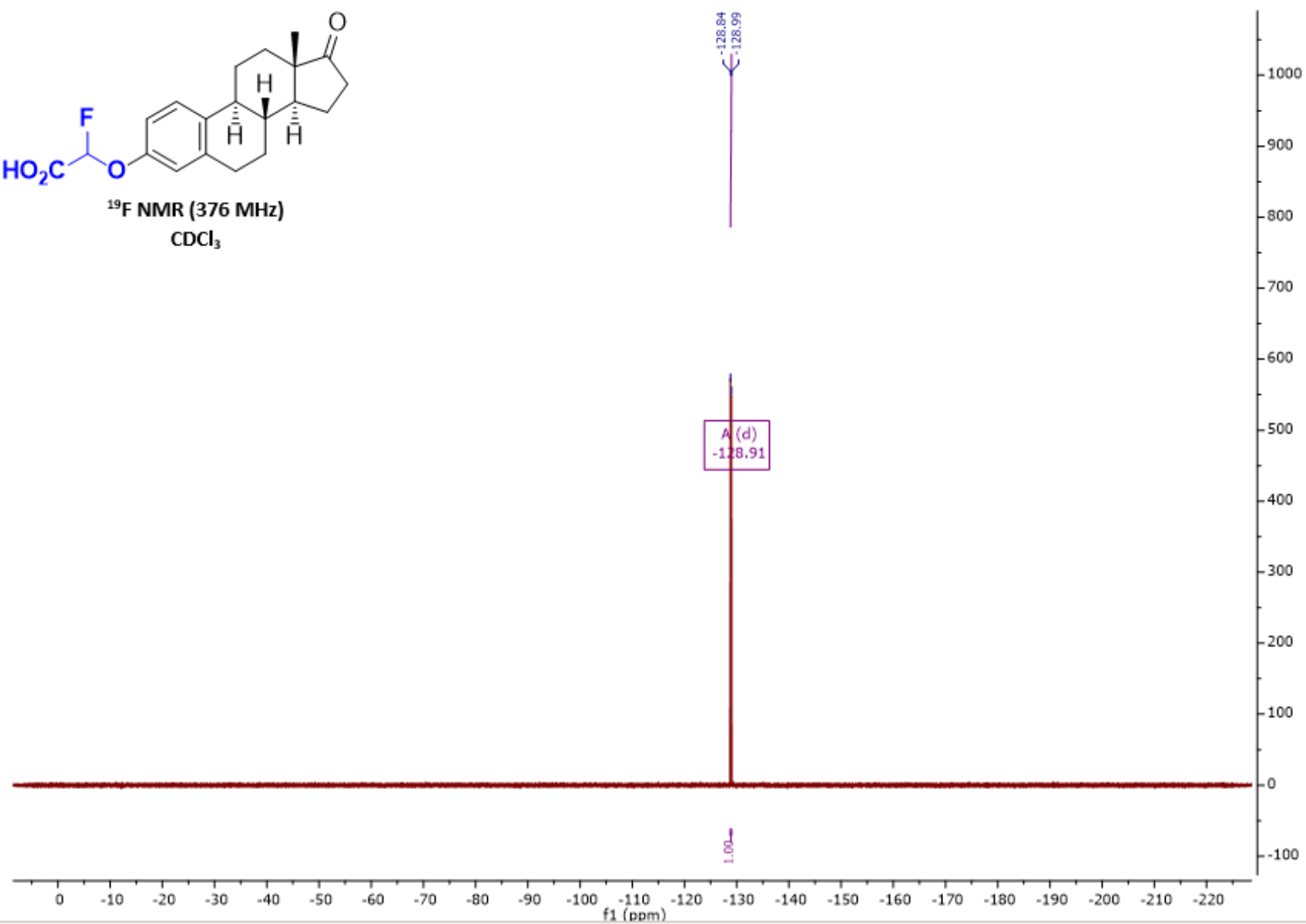
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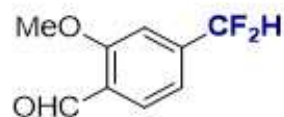




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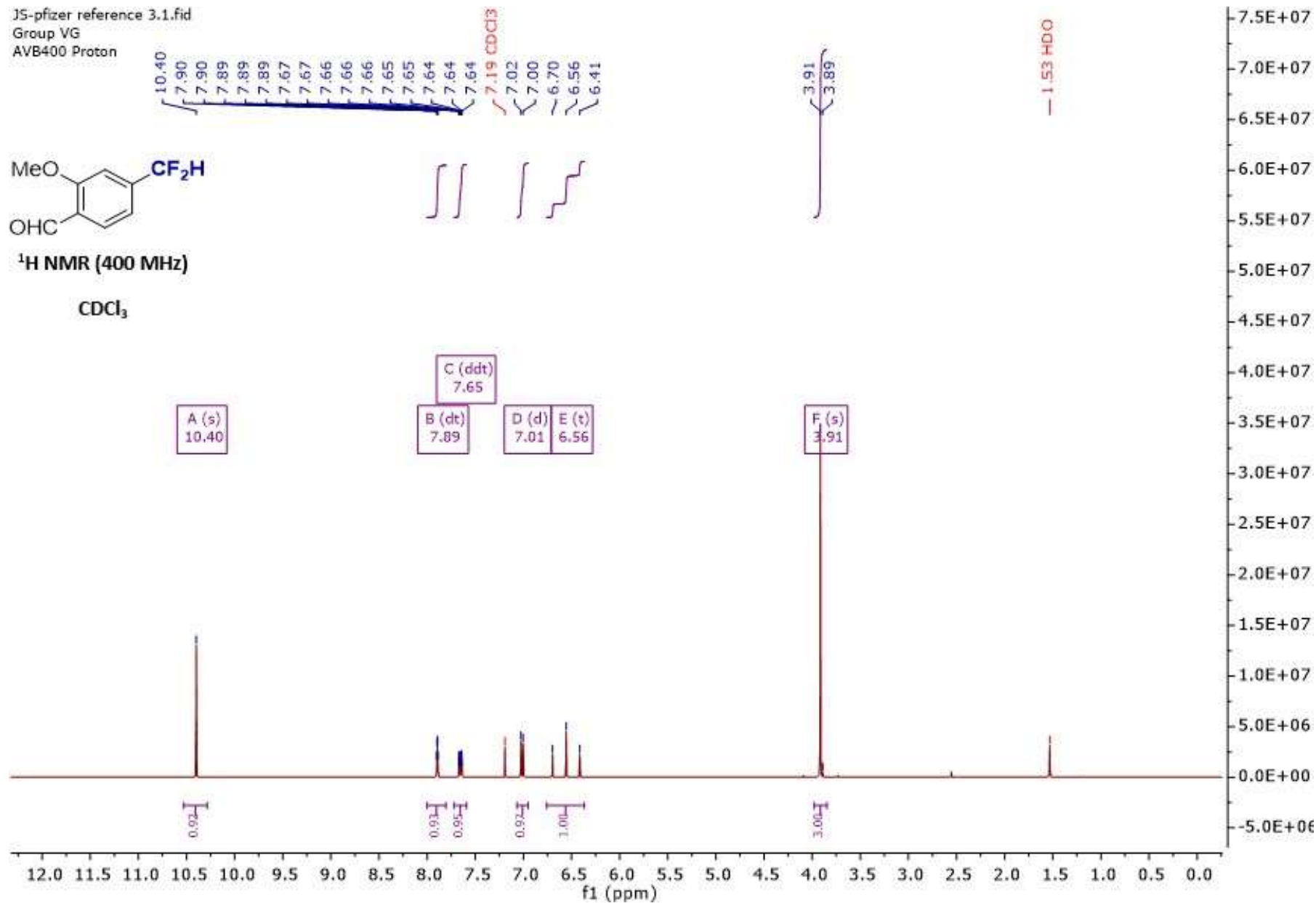


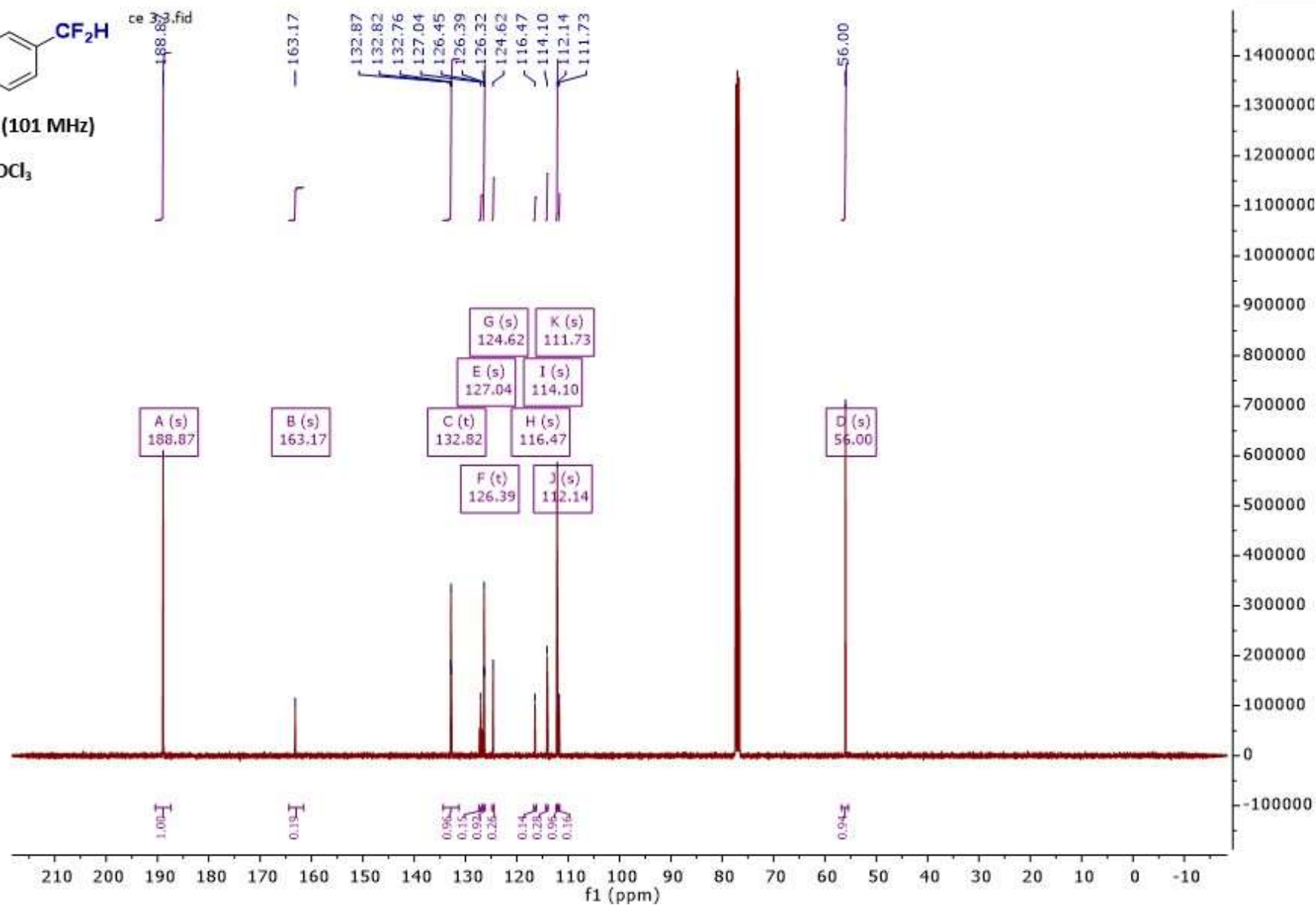
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Group VG
AVB400 Proton

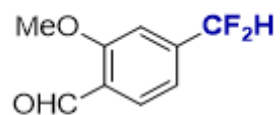


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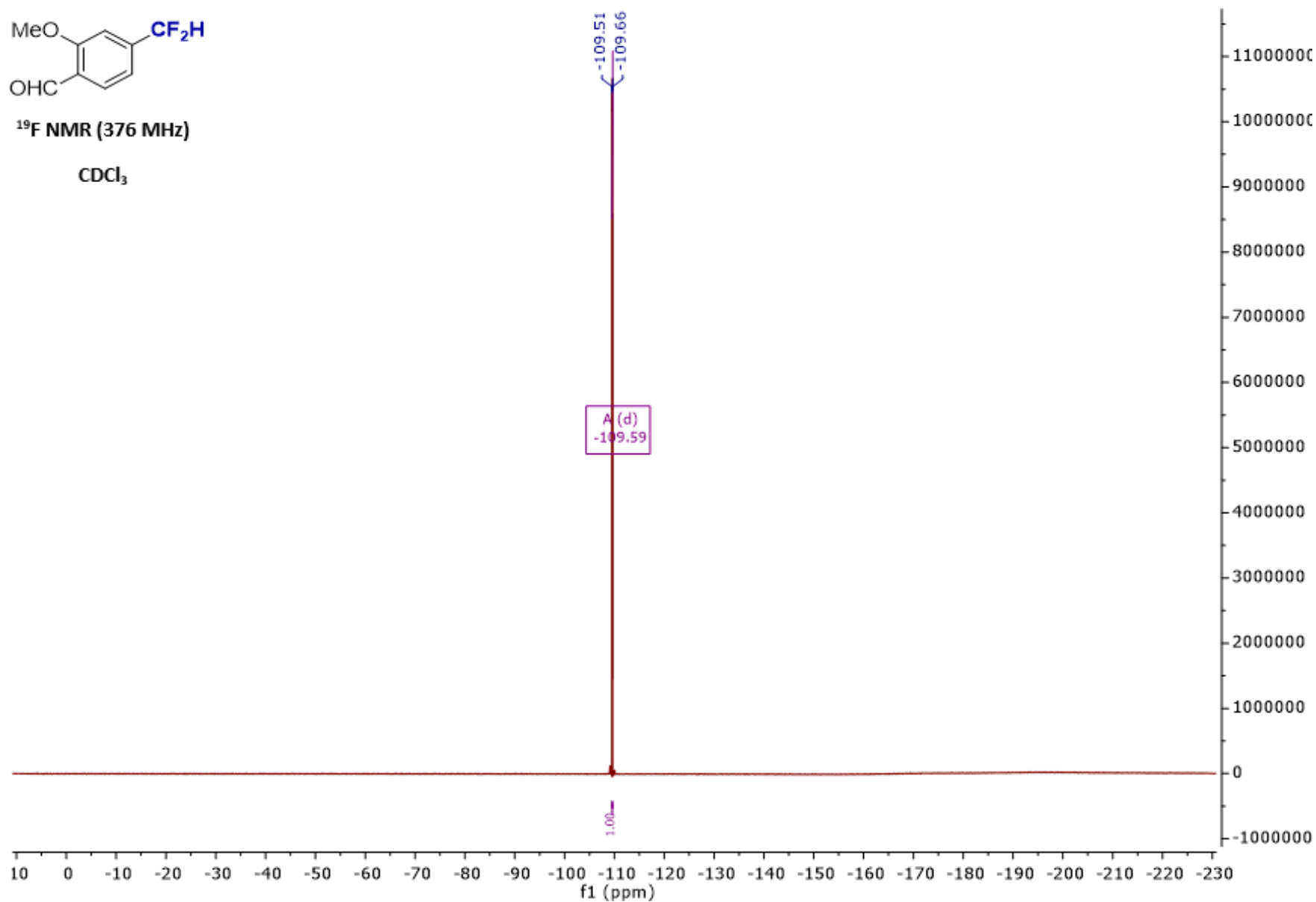




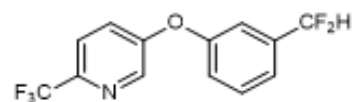


^{19}F NMR (376 MHz)

CDCl_3

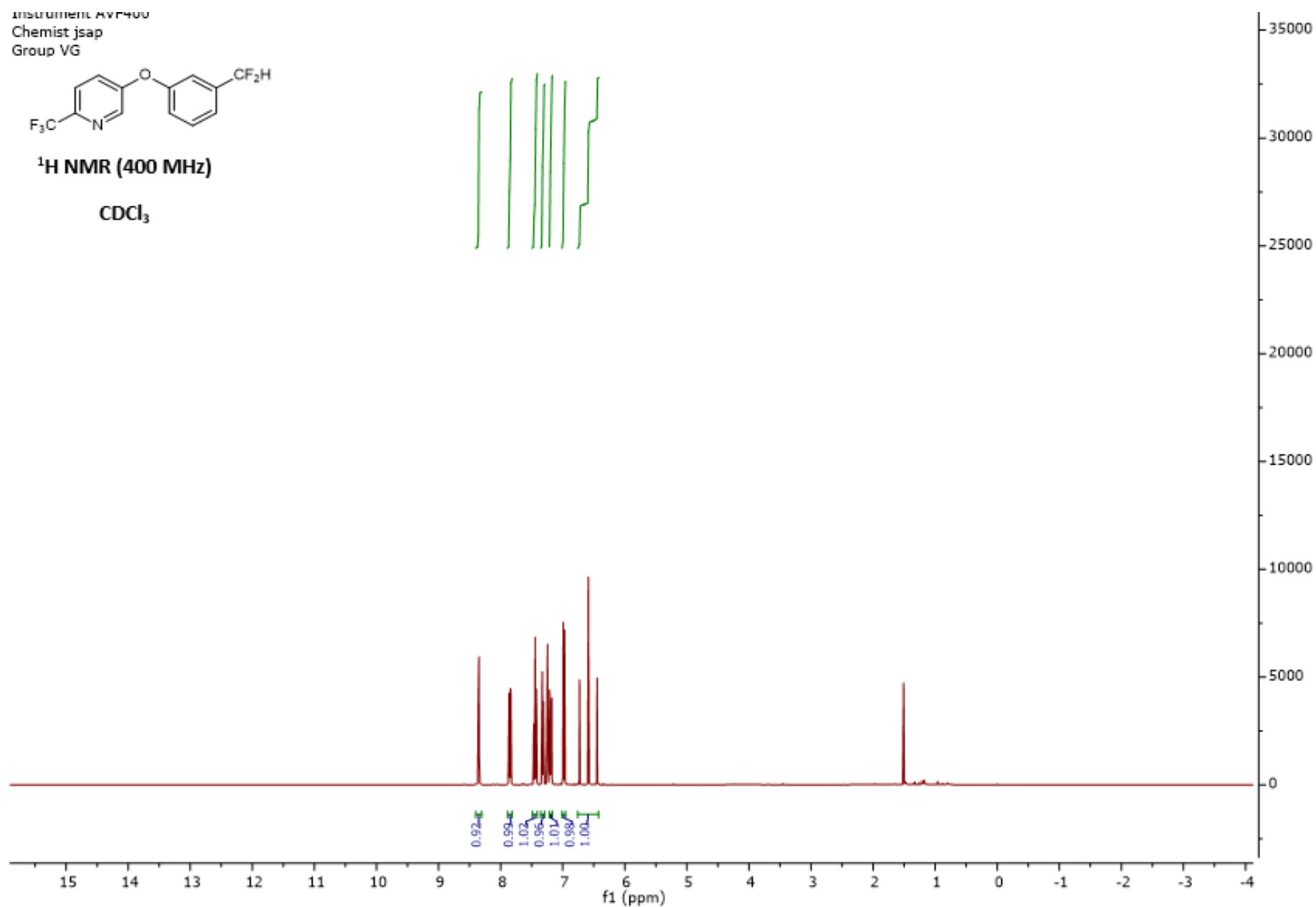


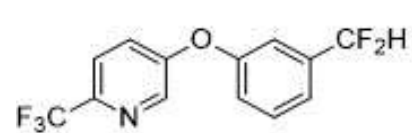
Instrument AVF400
Chemist jsap
Group VG



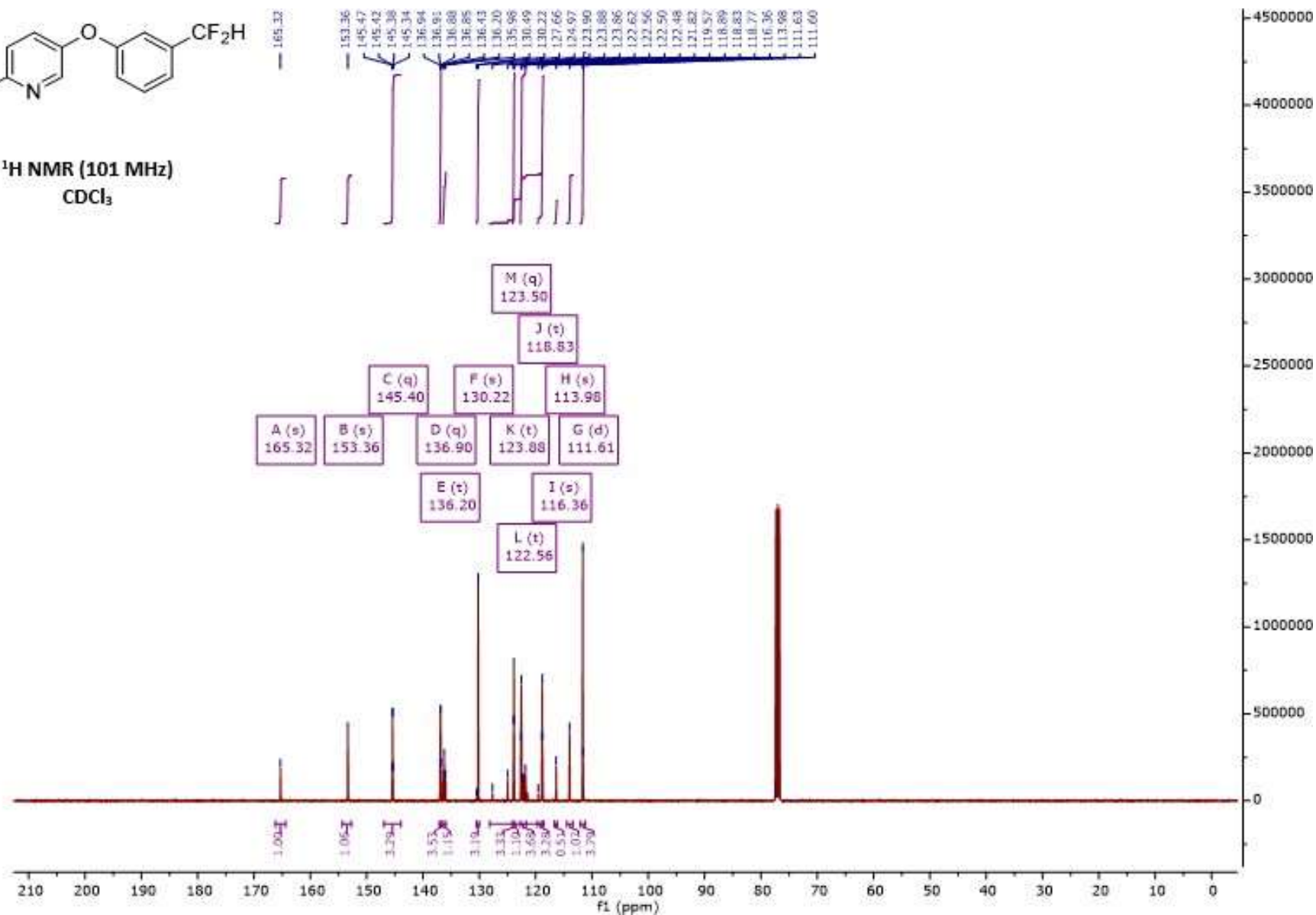
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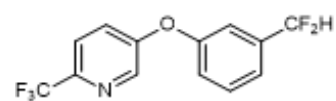
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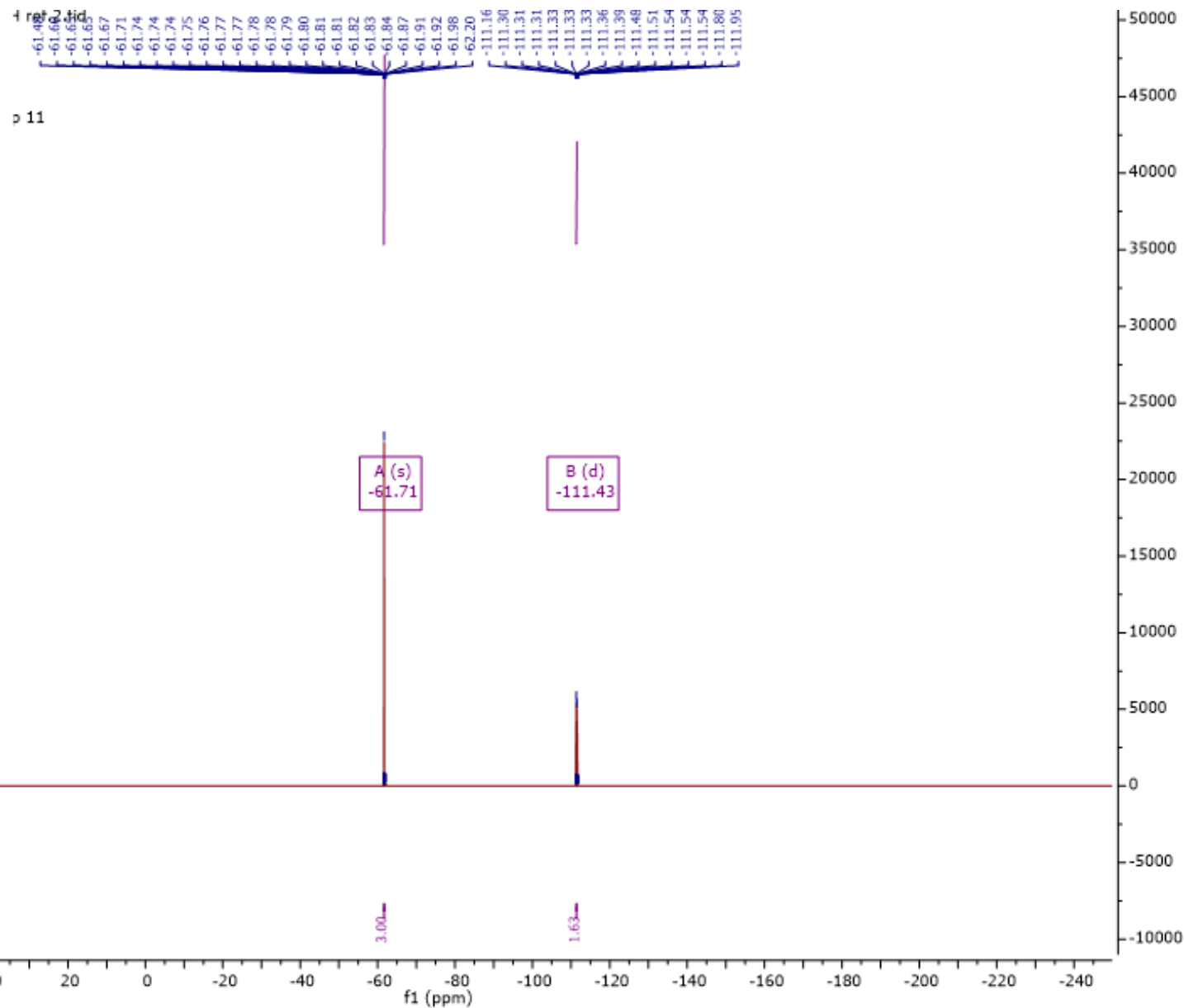
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CDCl₃

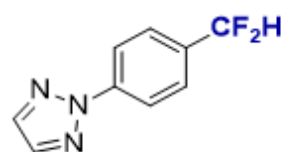




¹⁹F NMR (376 MHz)

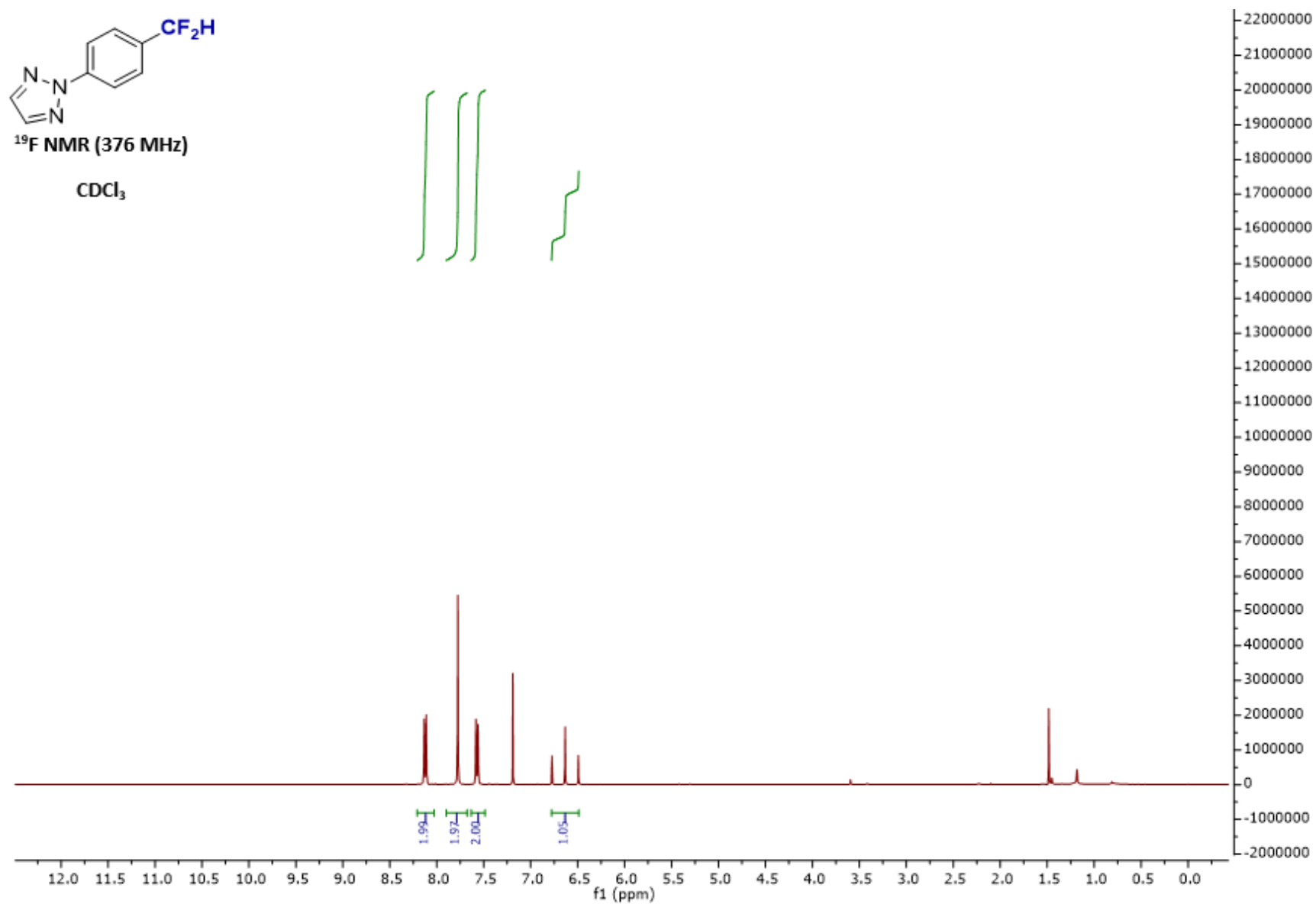
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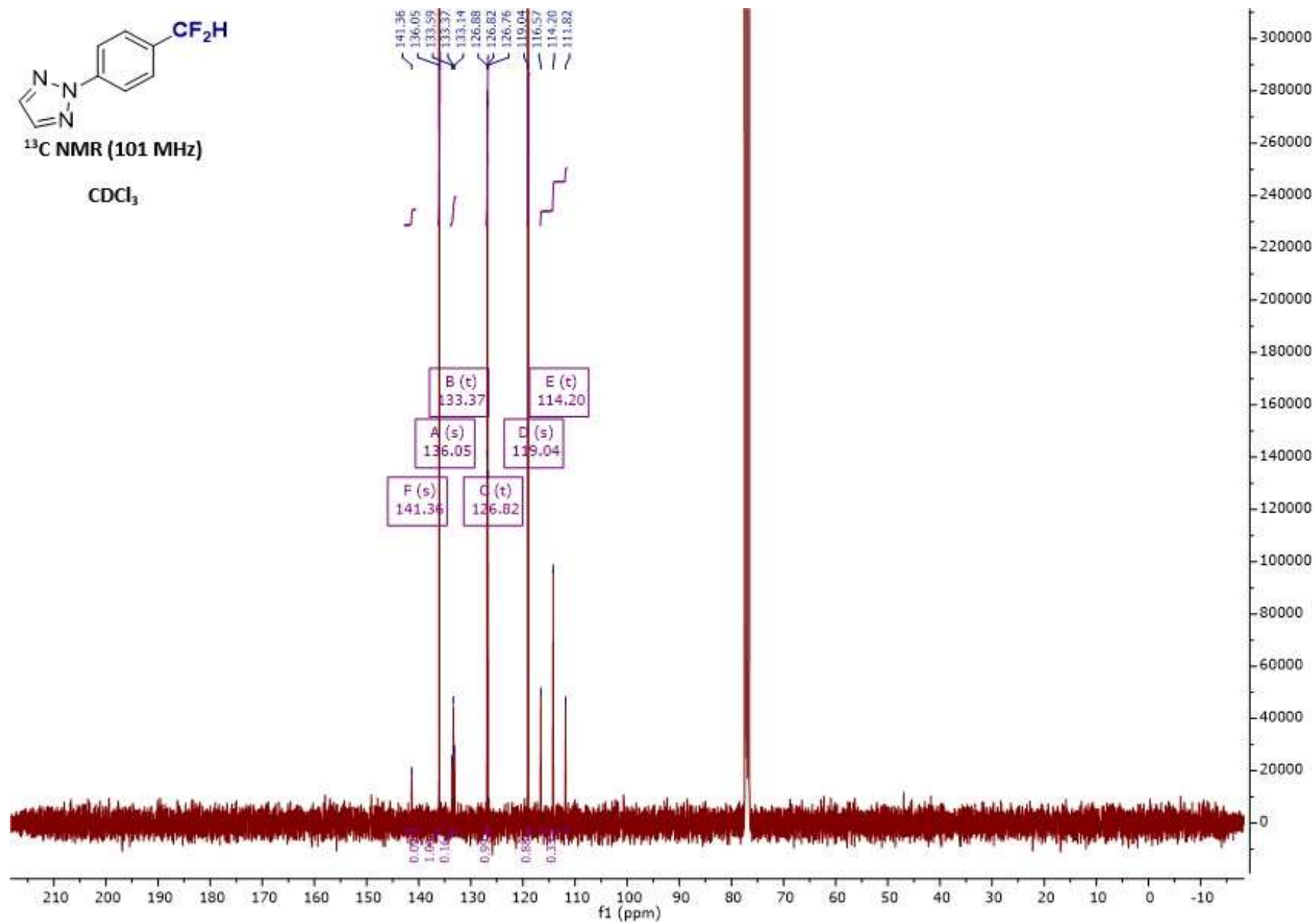
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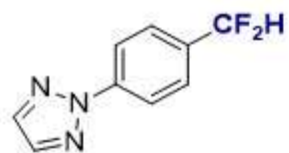
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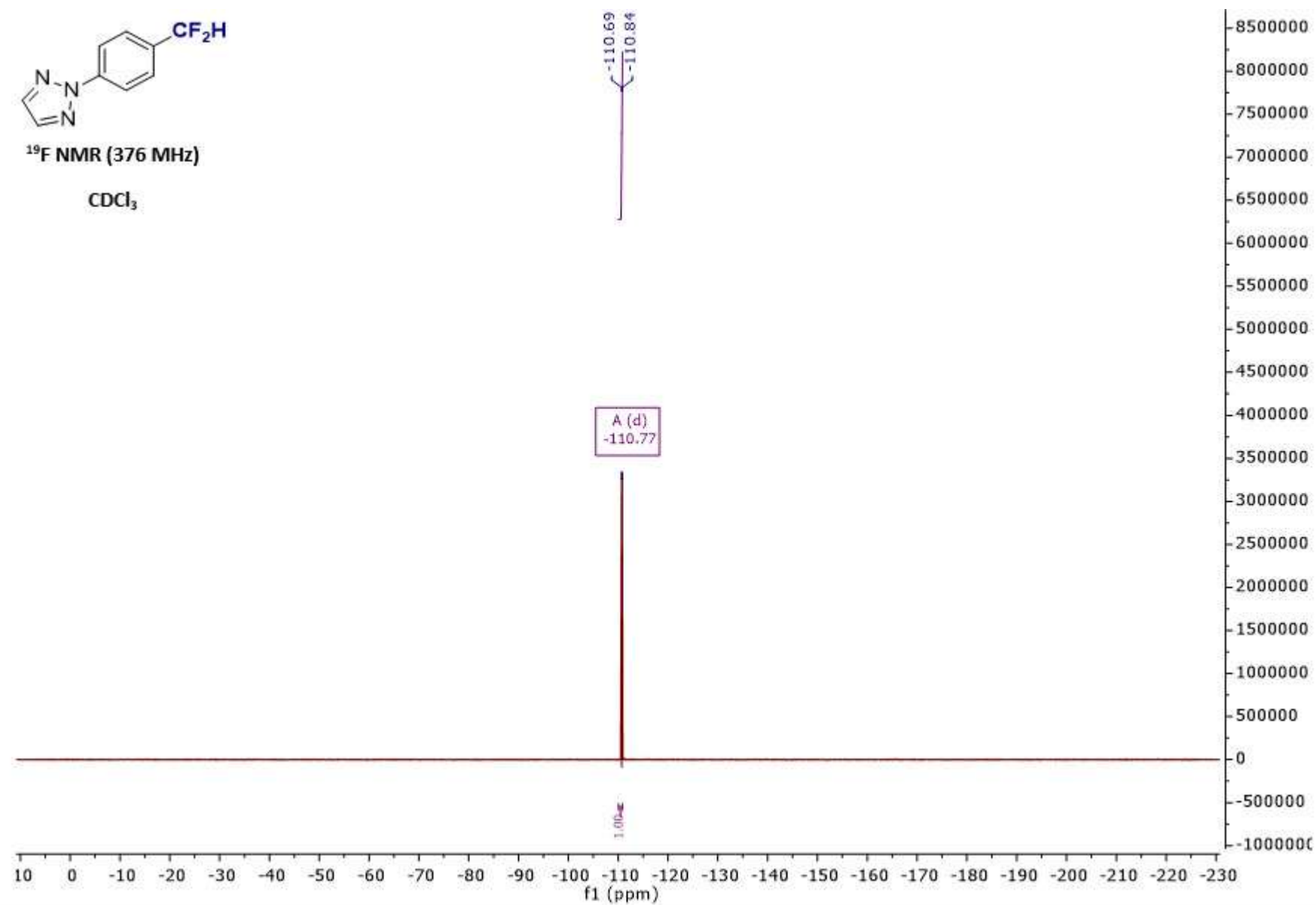
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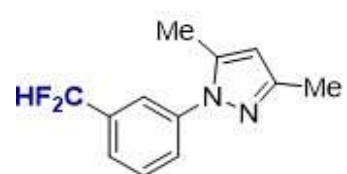




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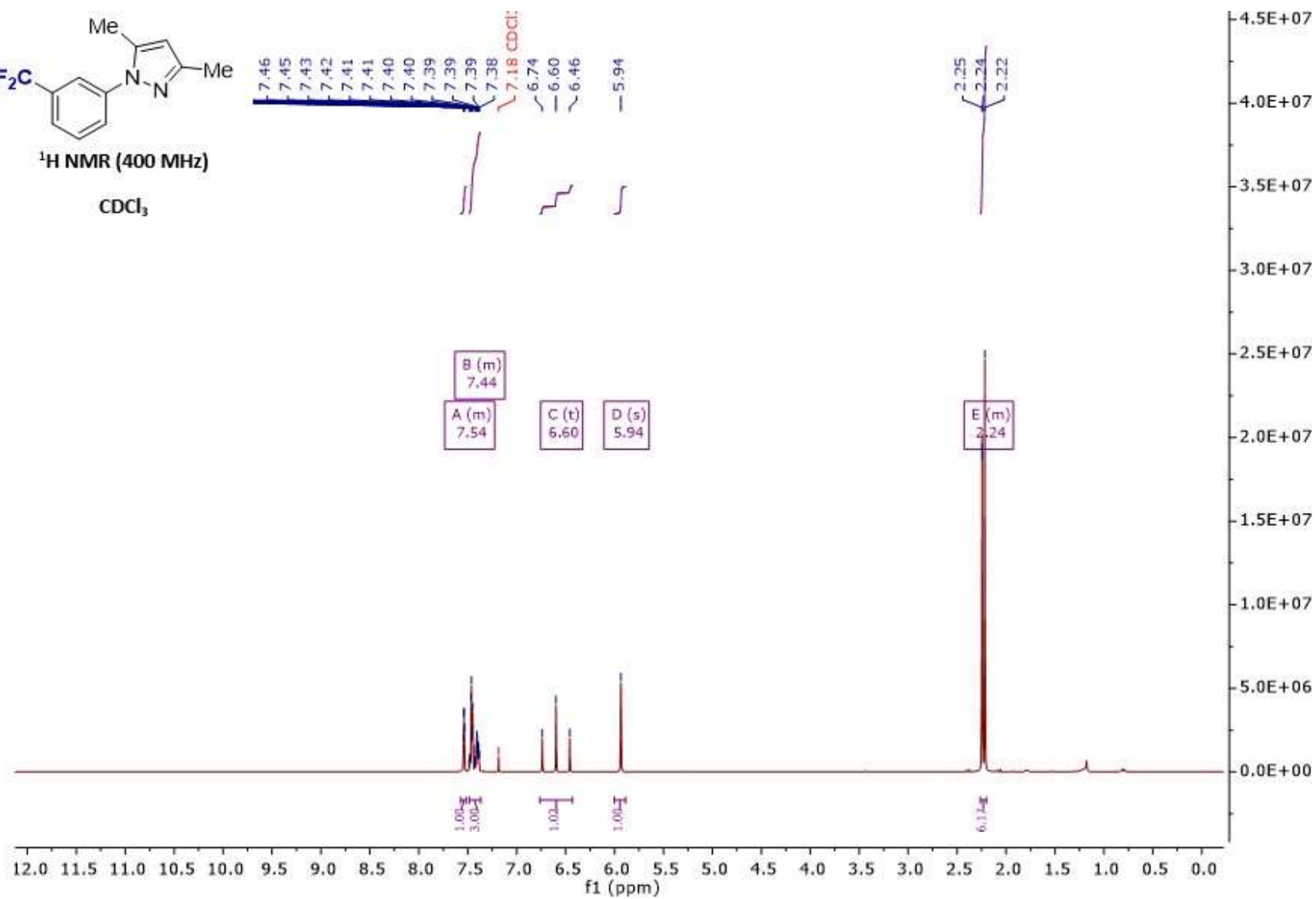
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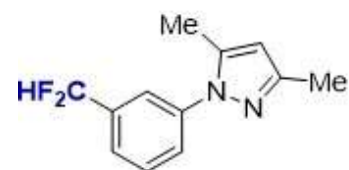




¹H NMR (400 MHz)

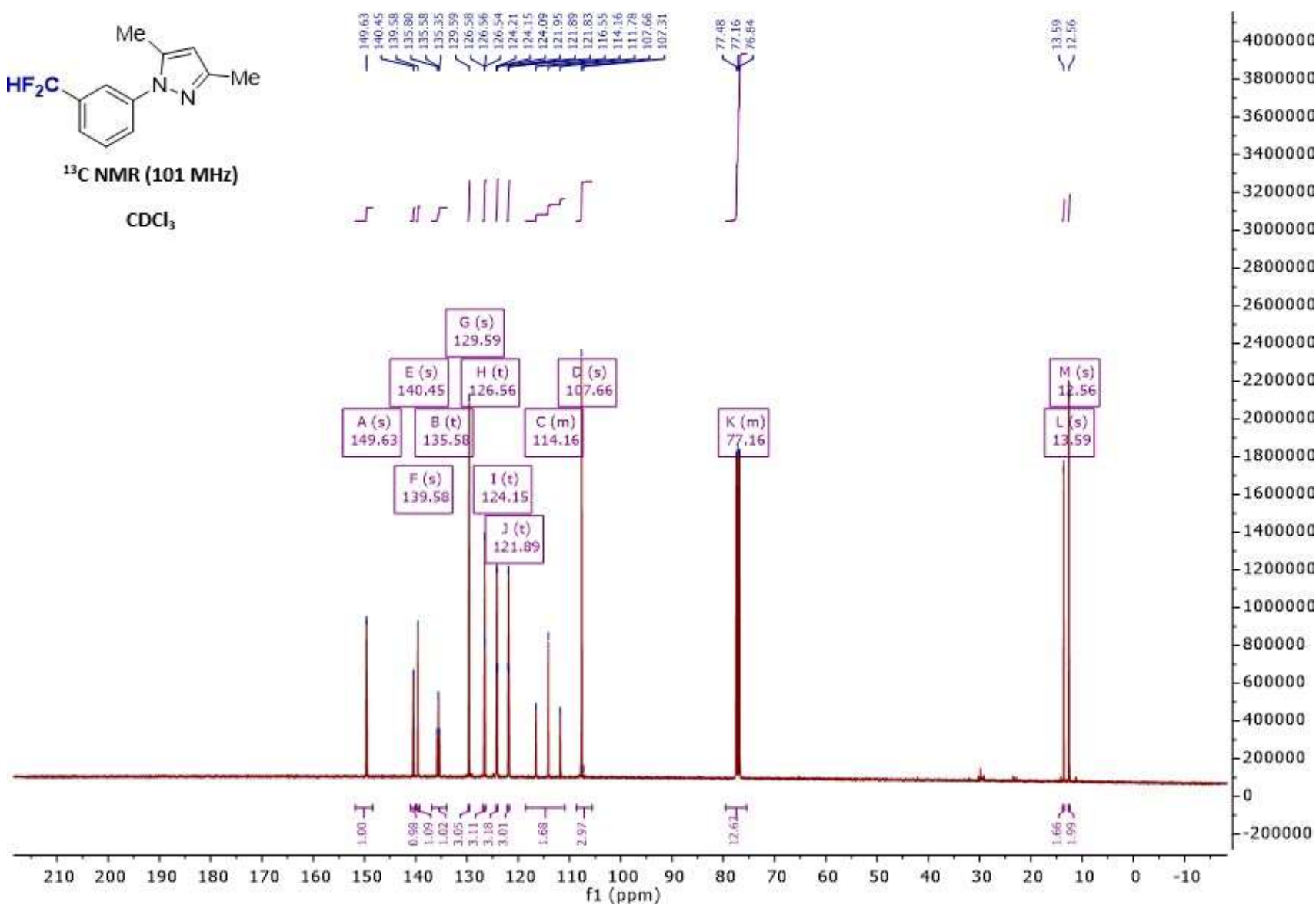
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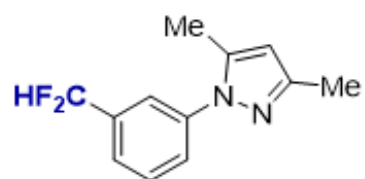




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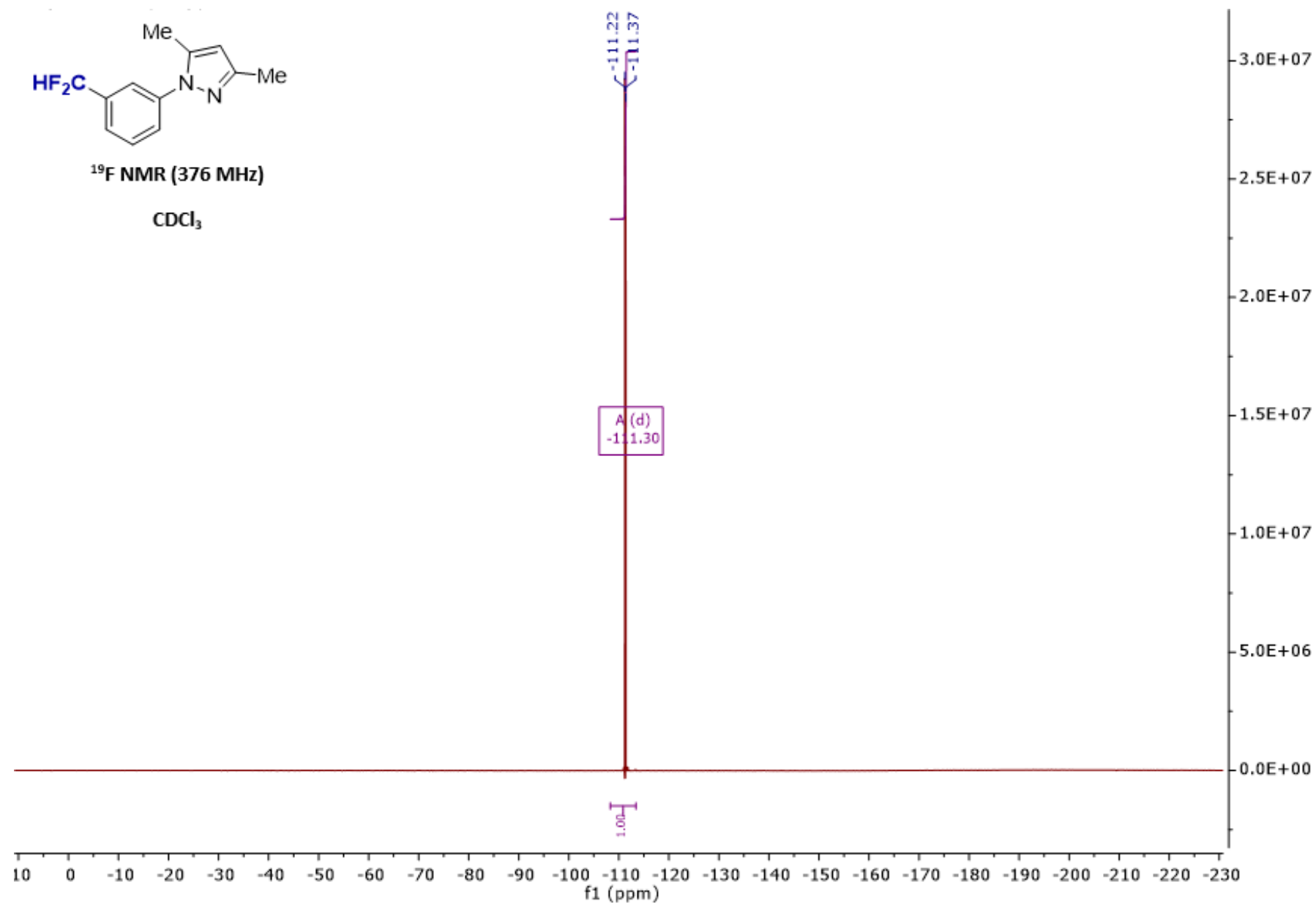
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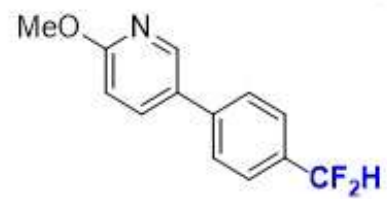




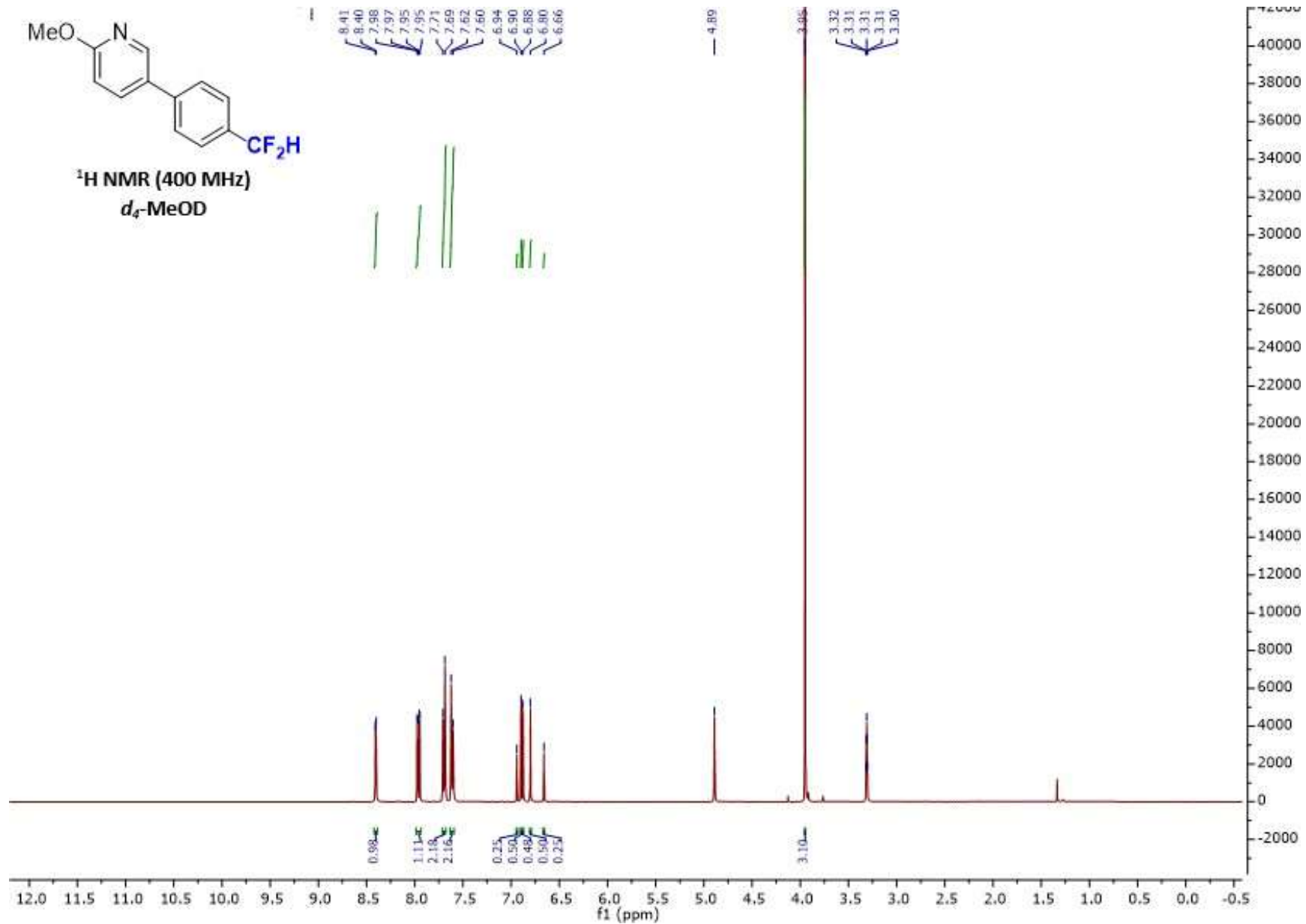
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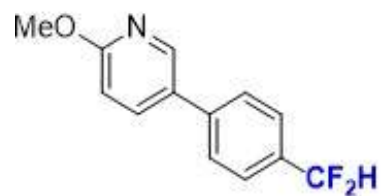
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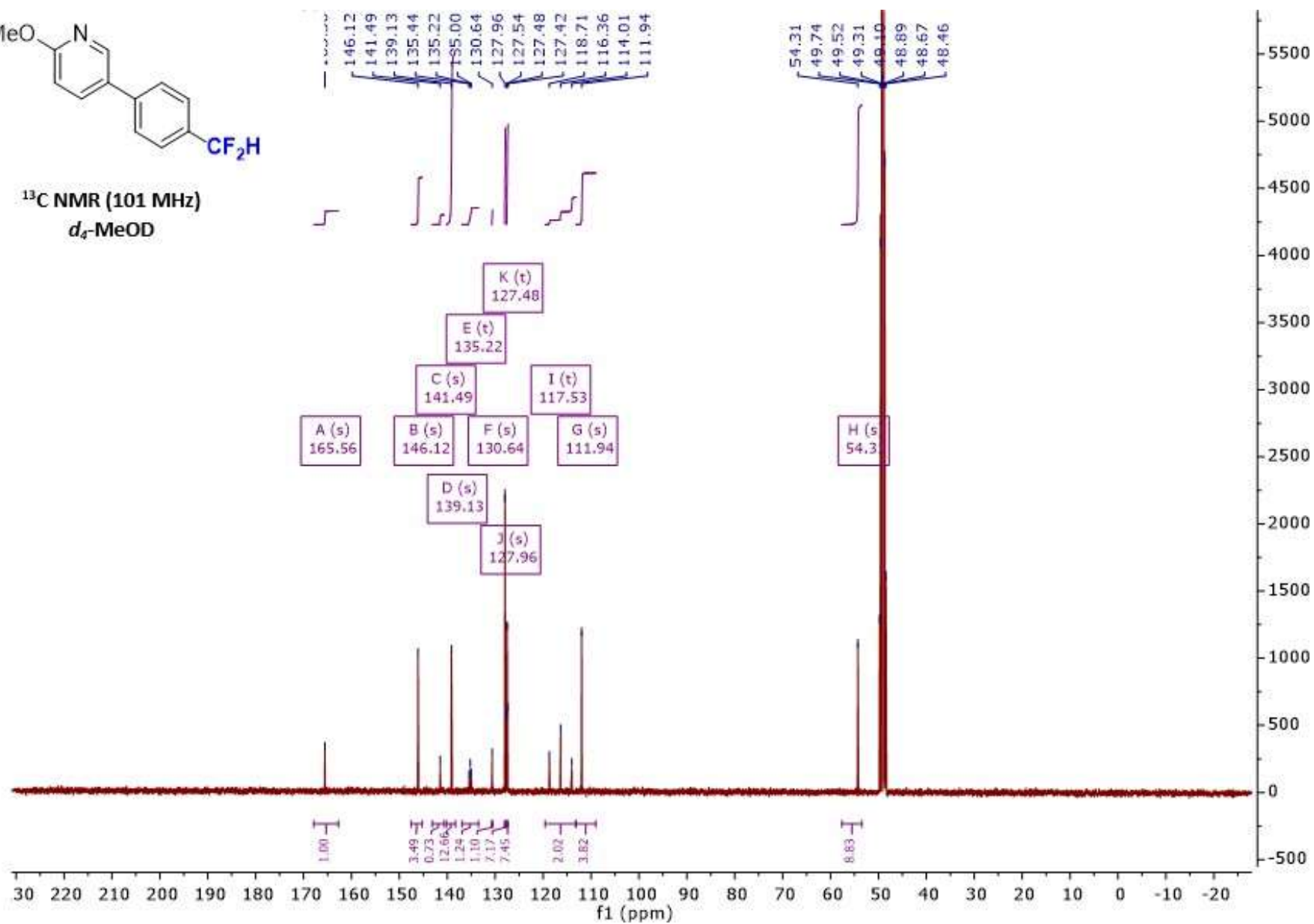


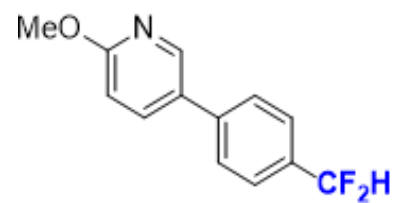
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d₄-MeOD



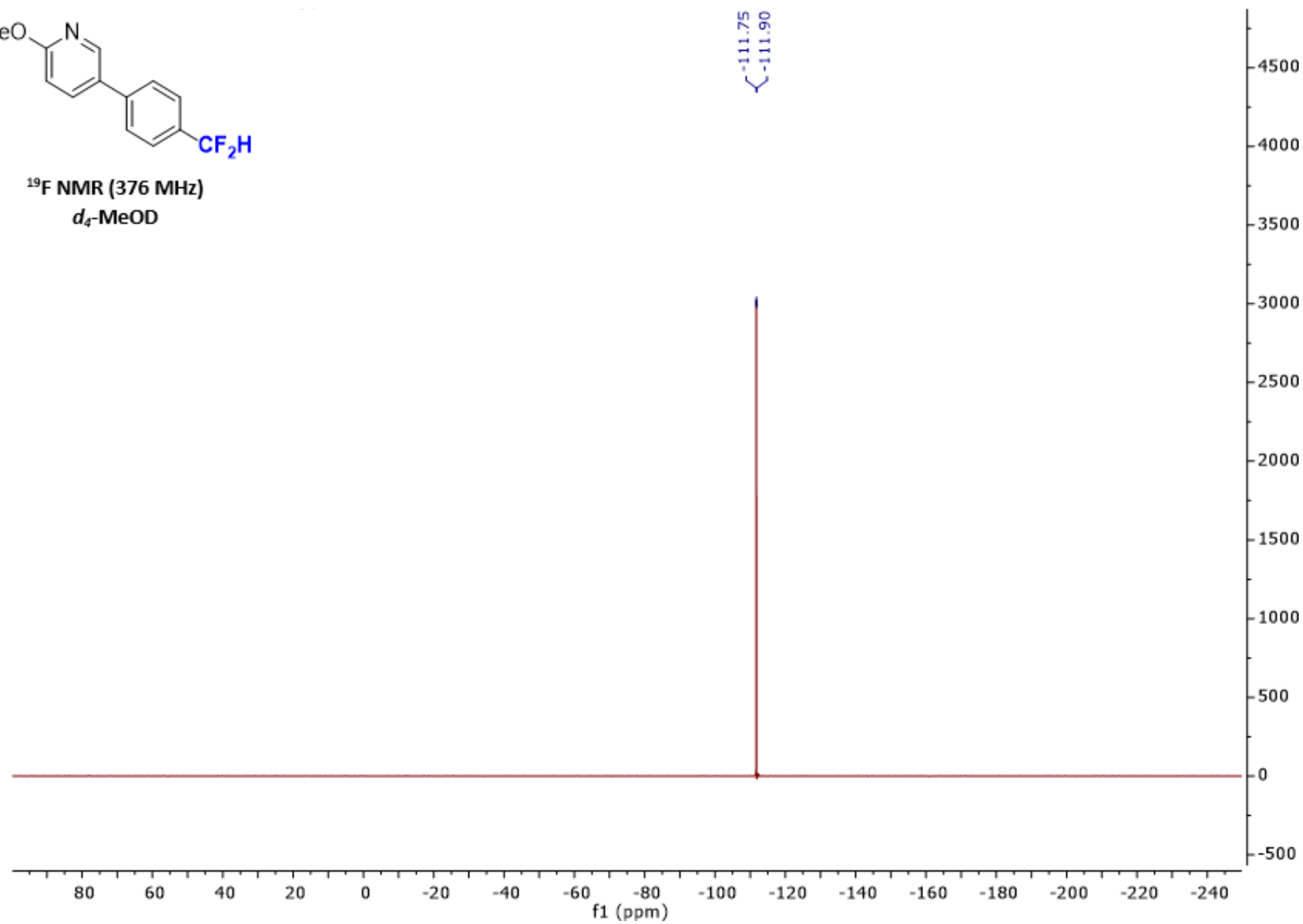


^{13}C NMR (101 MHz)
 d_4 -MeOD

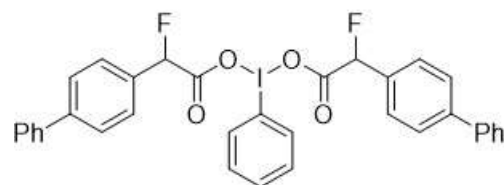




¹⁹F NMR (376 MHz)
*d*₄-MeOD

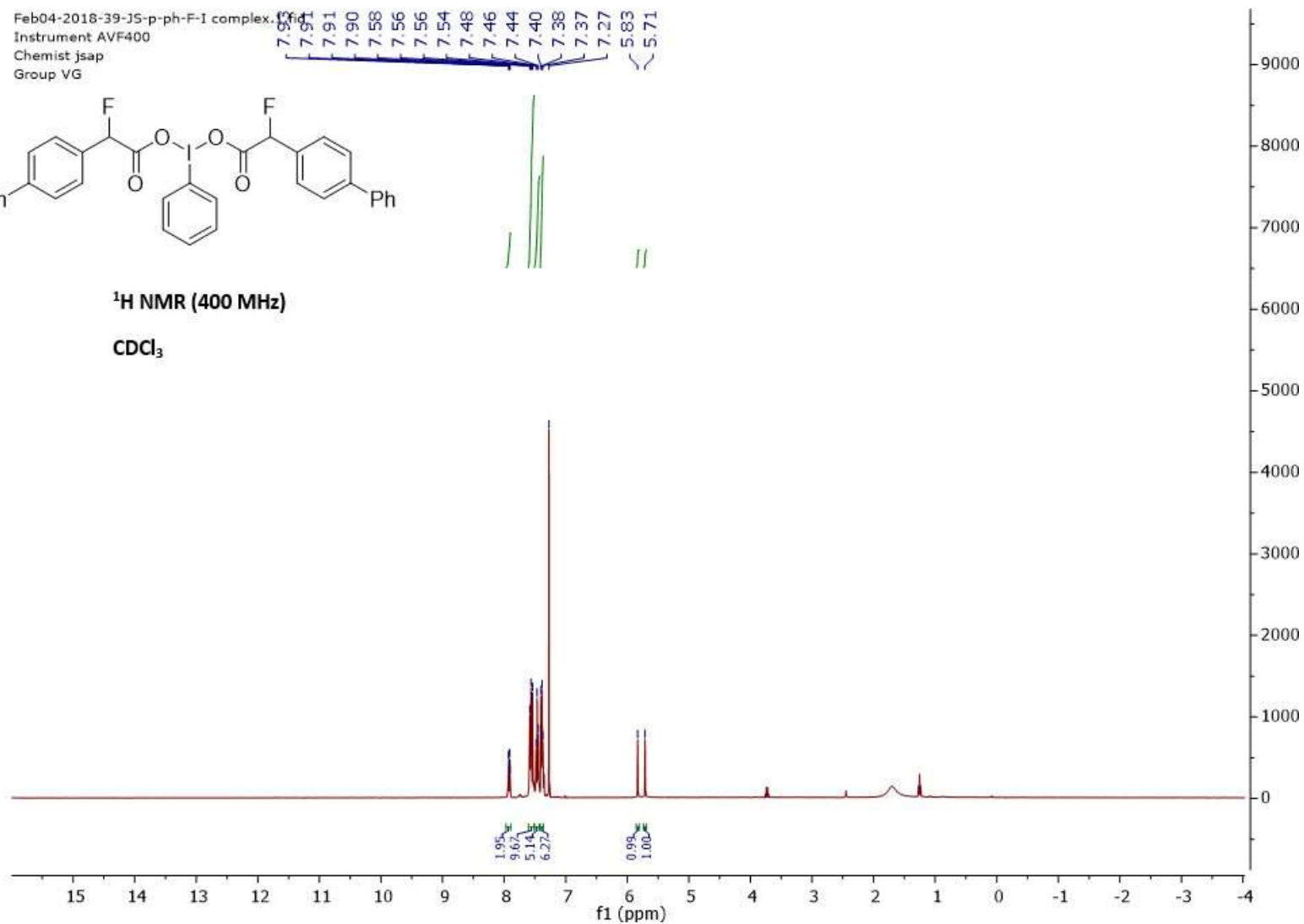


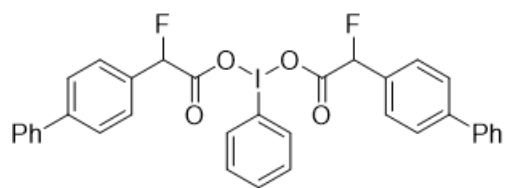
Feb04-2018-39-JS-p-ph-F-I complex.
 Instrument AVF400
 Chemist jsap
 Group VG



¹H NMR (400 MHz)

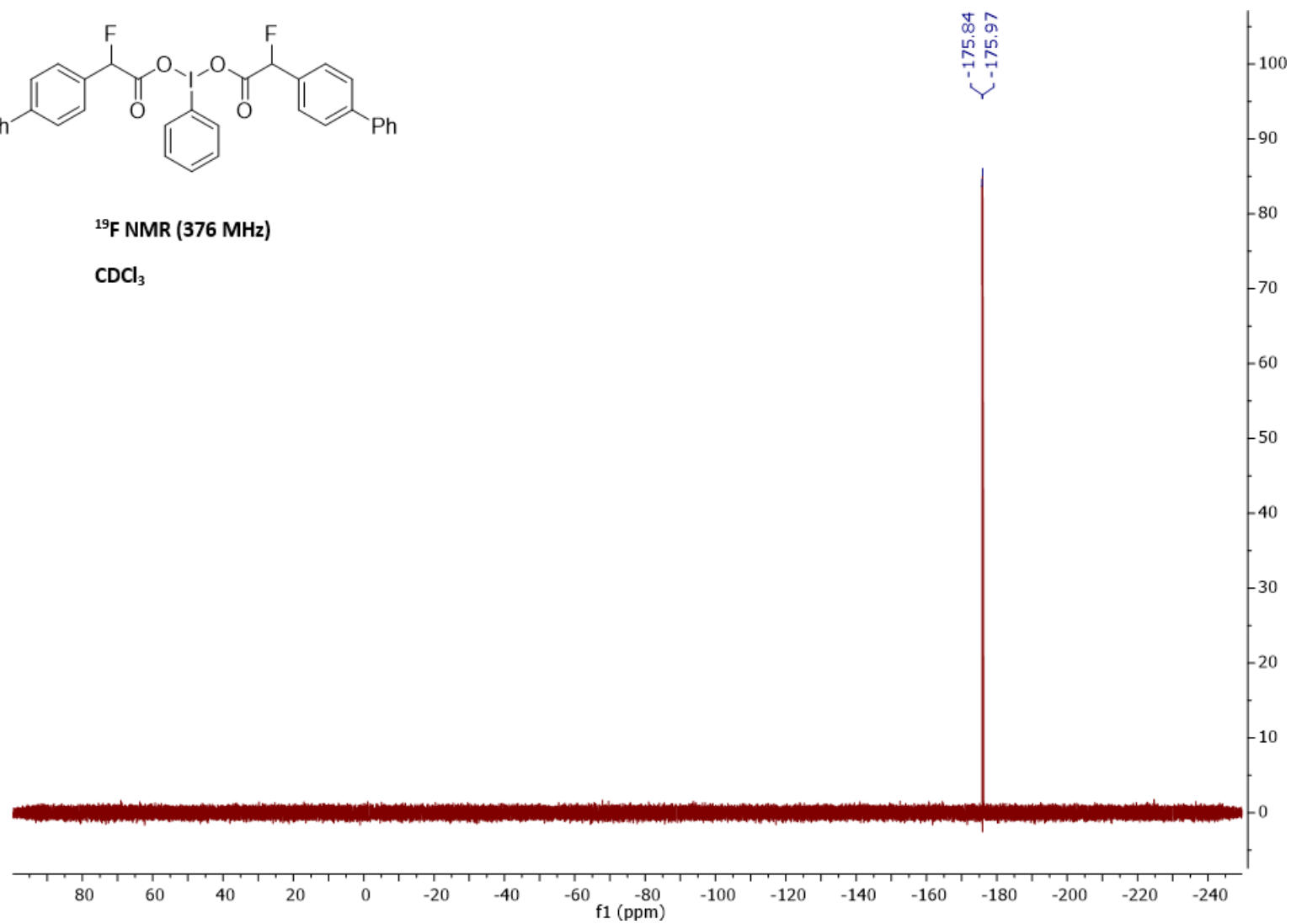
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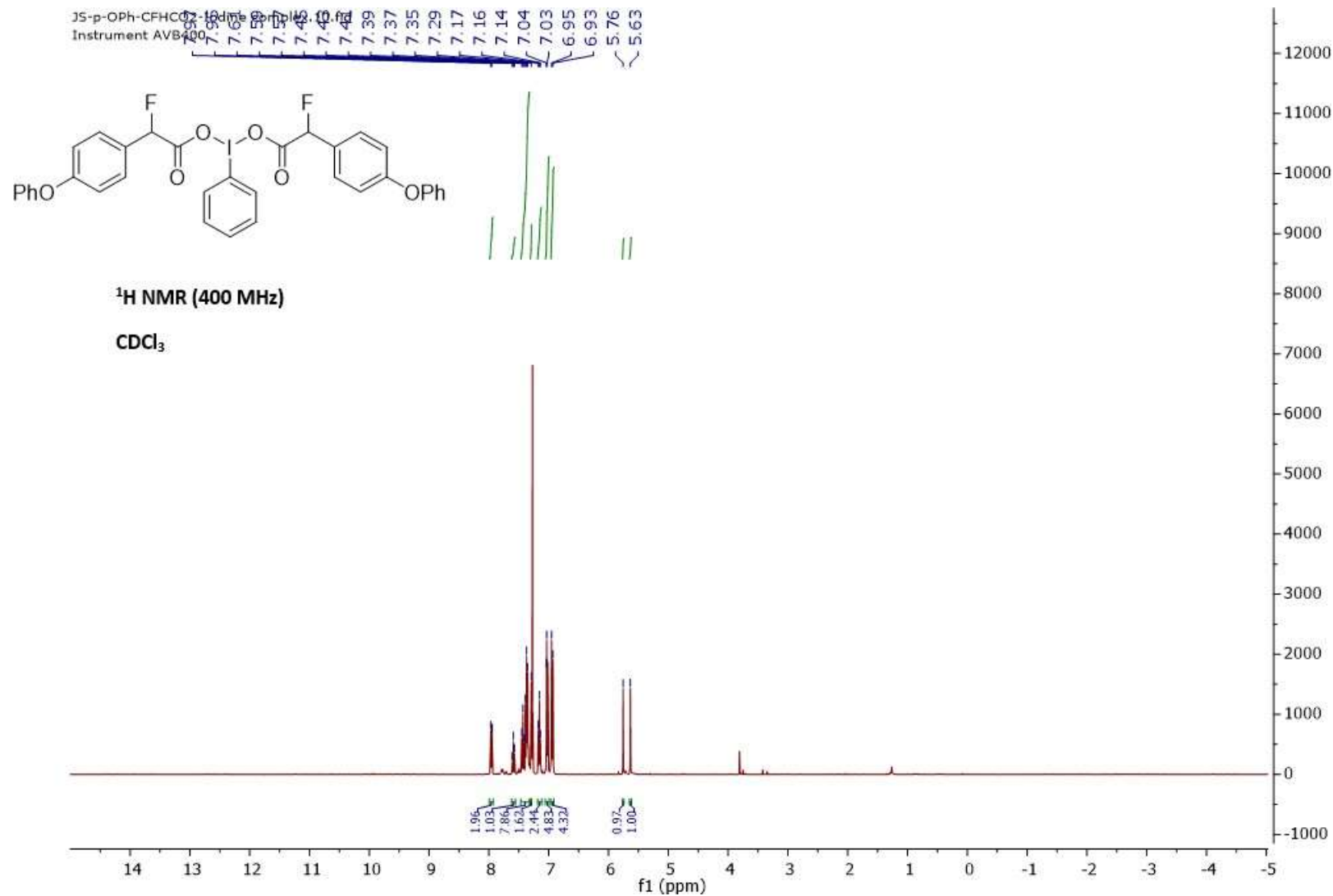




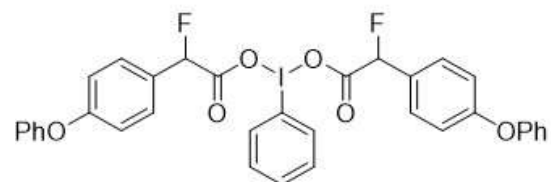
^{19}F NMR (376 MHz)

CDCl_3



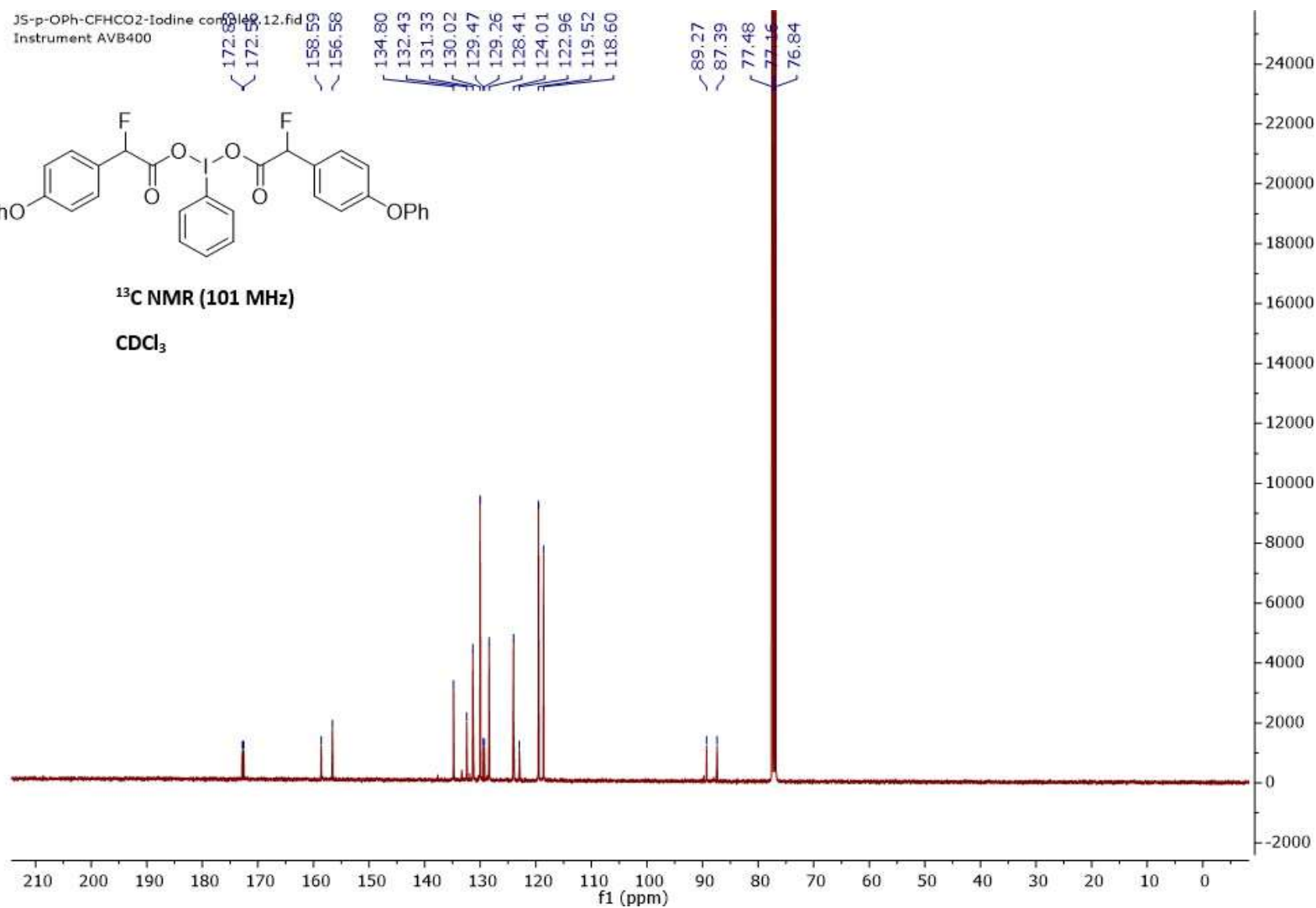


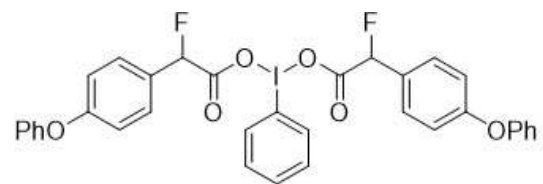
J5-p-OPh-CFHCO2-Iodine compound 12.fid
Instrument AVB400



¹³C NMR (101 MHz)

CDCl₃

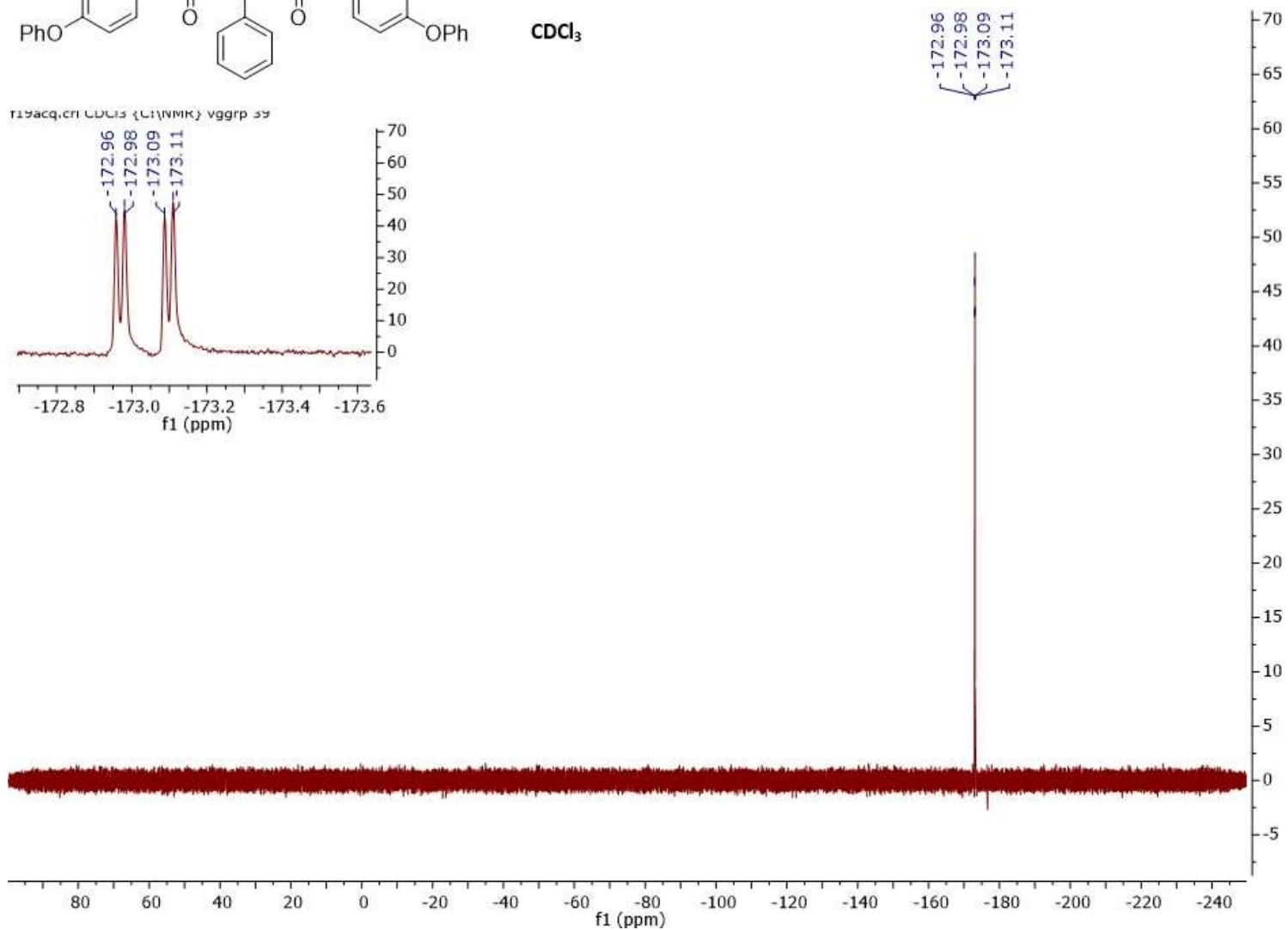
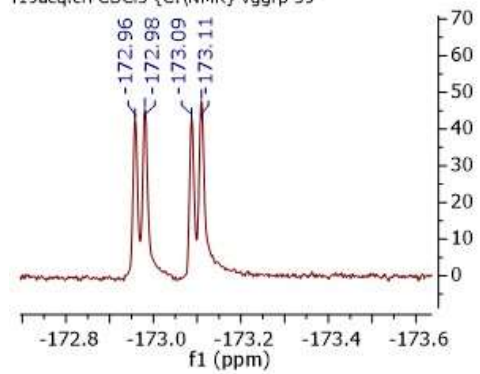


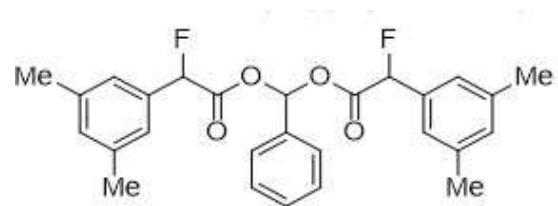


^{19}F NMR (376 MHz)

CDCl_3

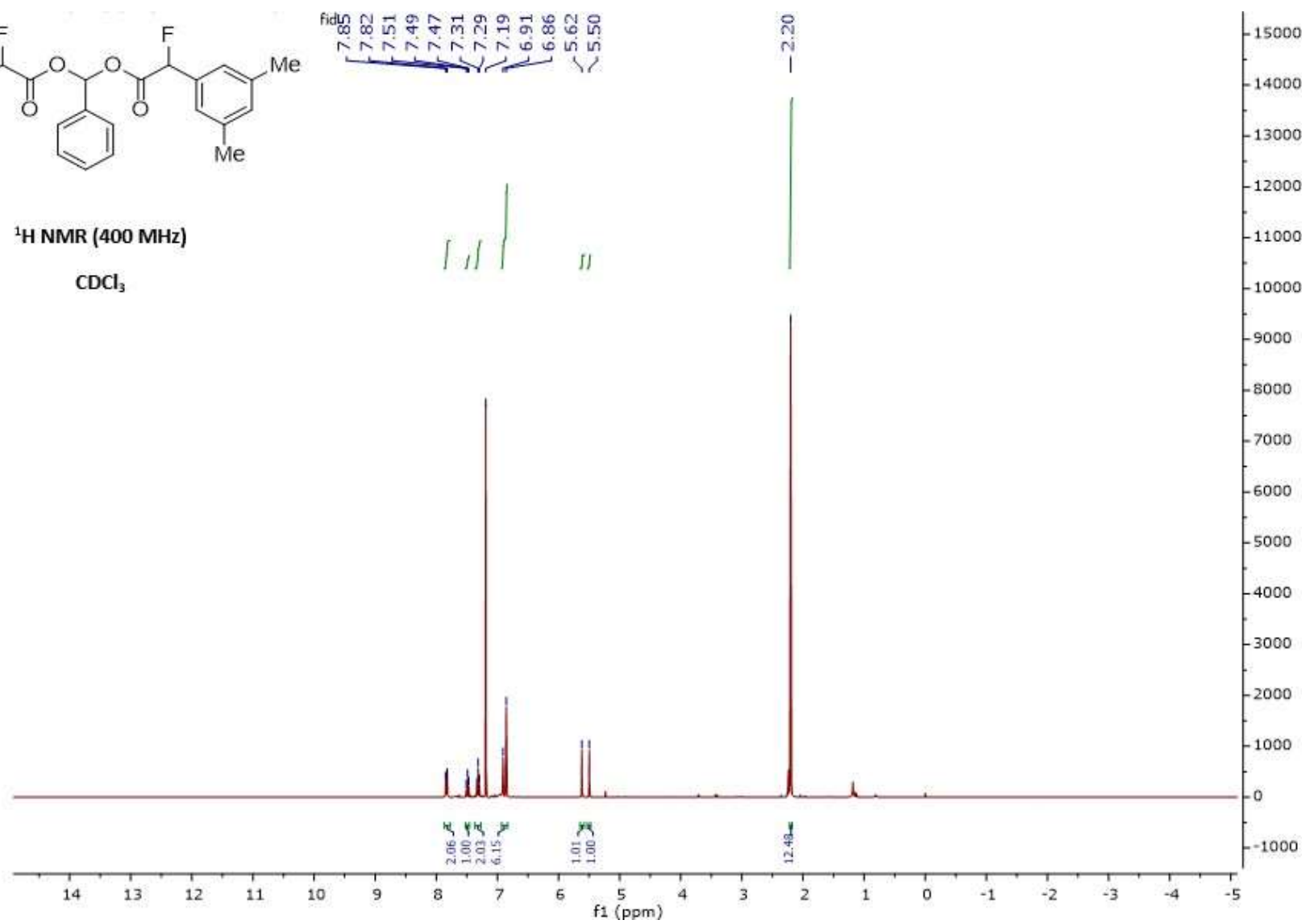
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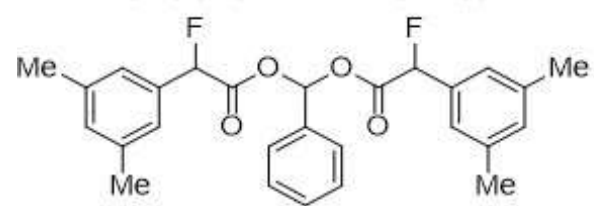




^1H NMR (400 MHz)

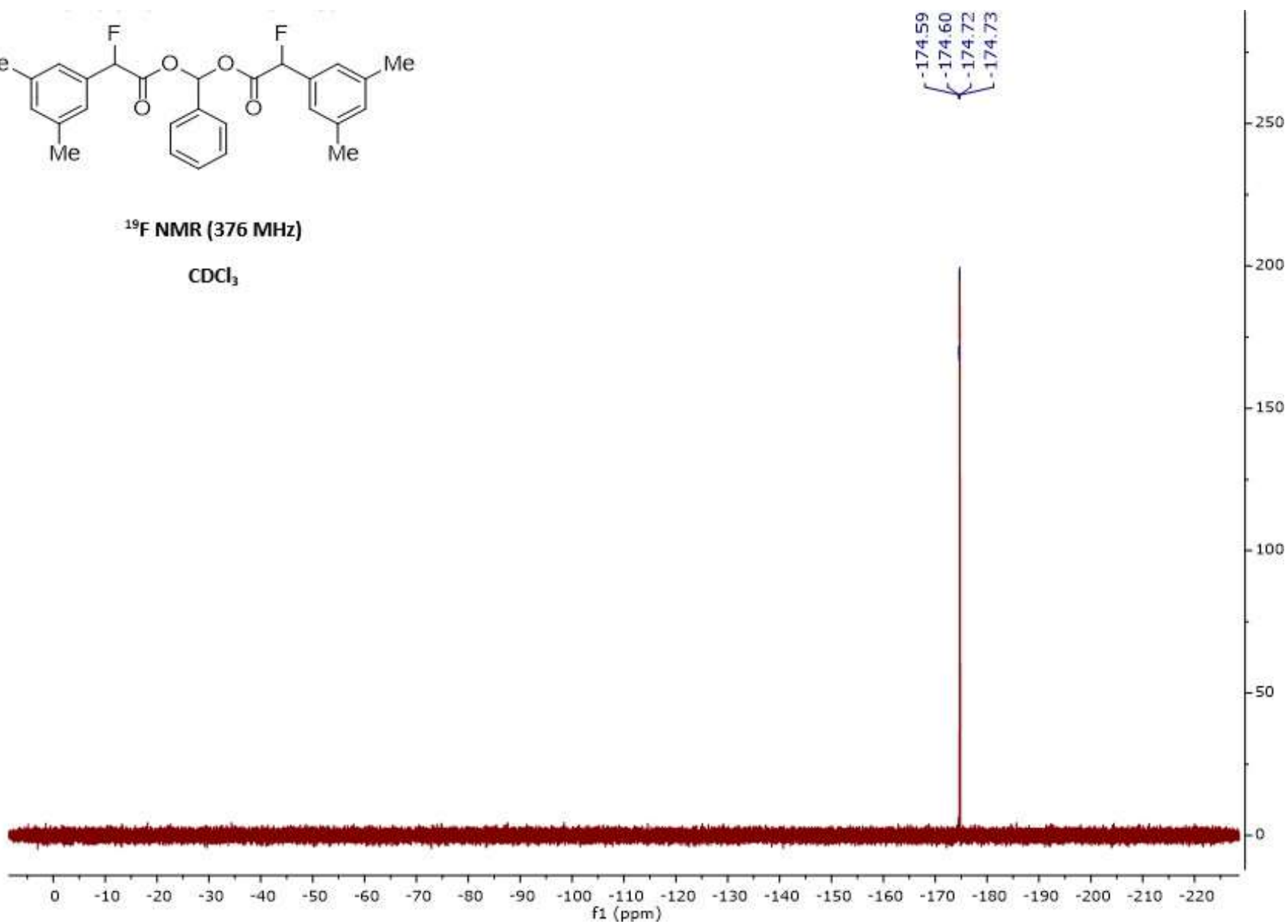
CDCl_3

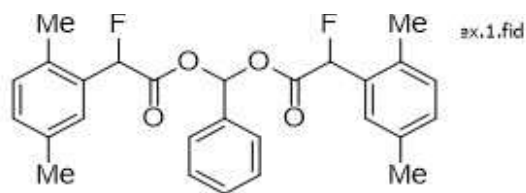




^{19}F NMR (376 MHz)

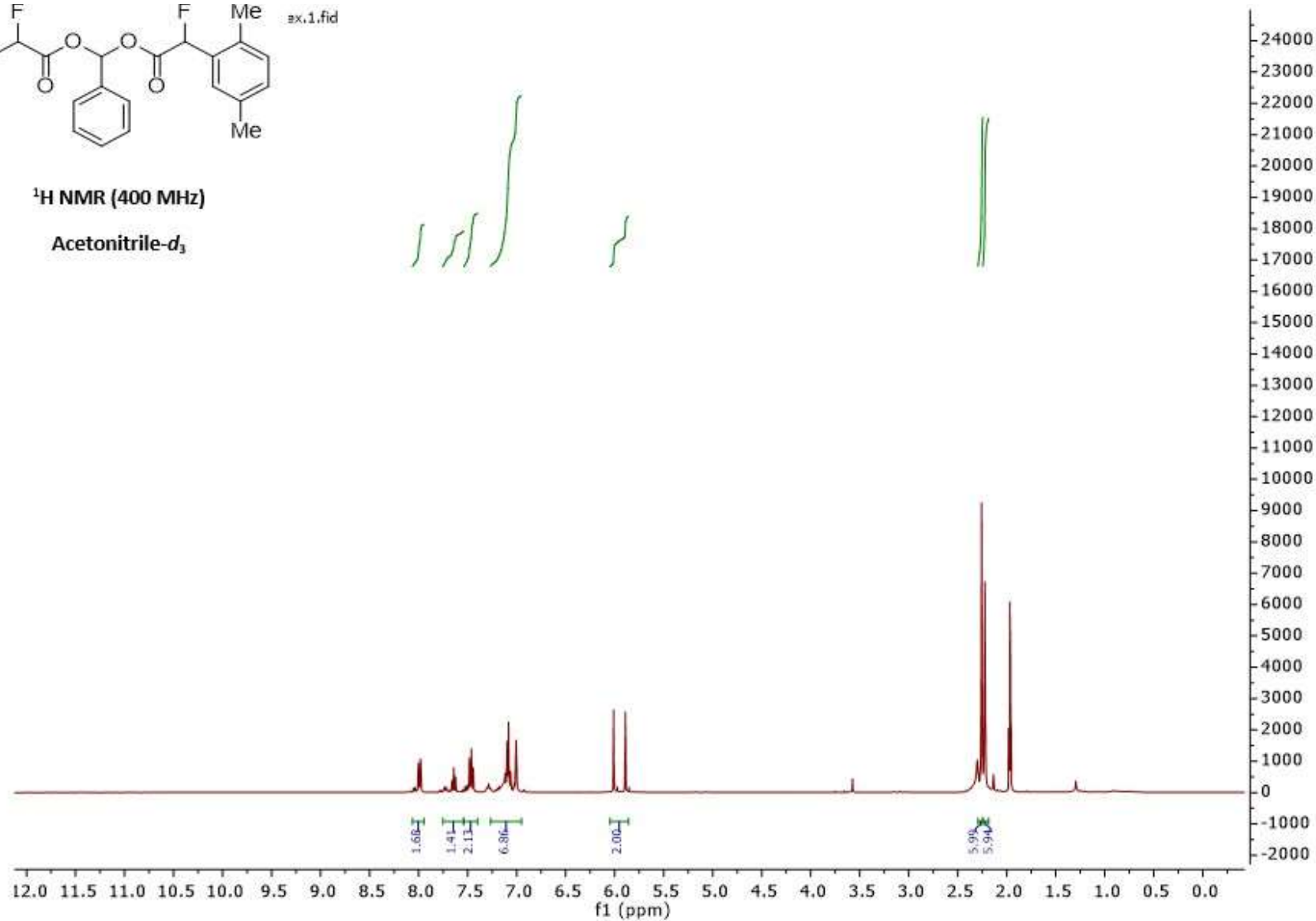
CDCl_3

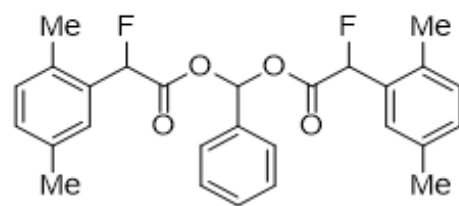




^1H NMR (400 MHz)

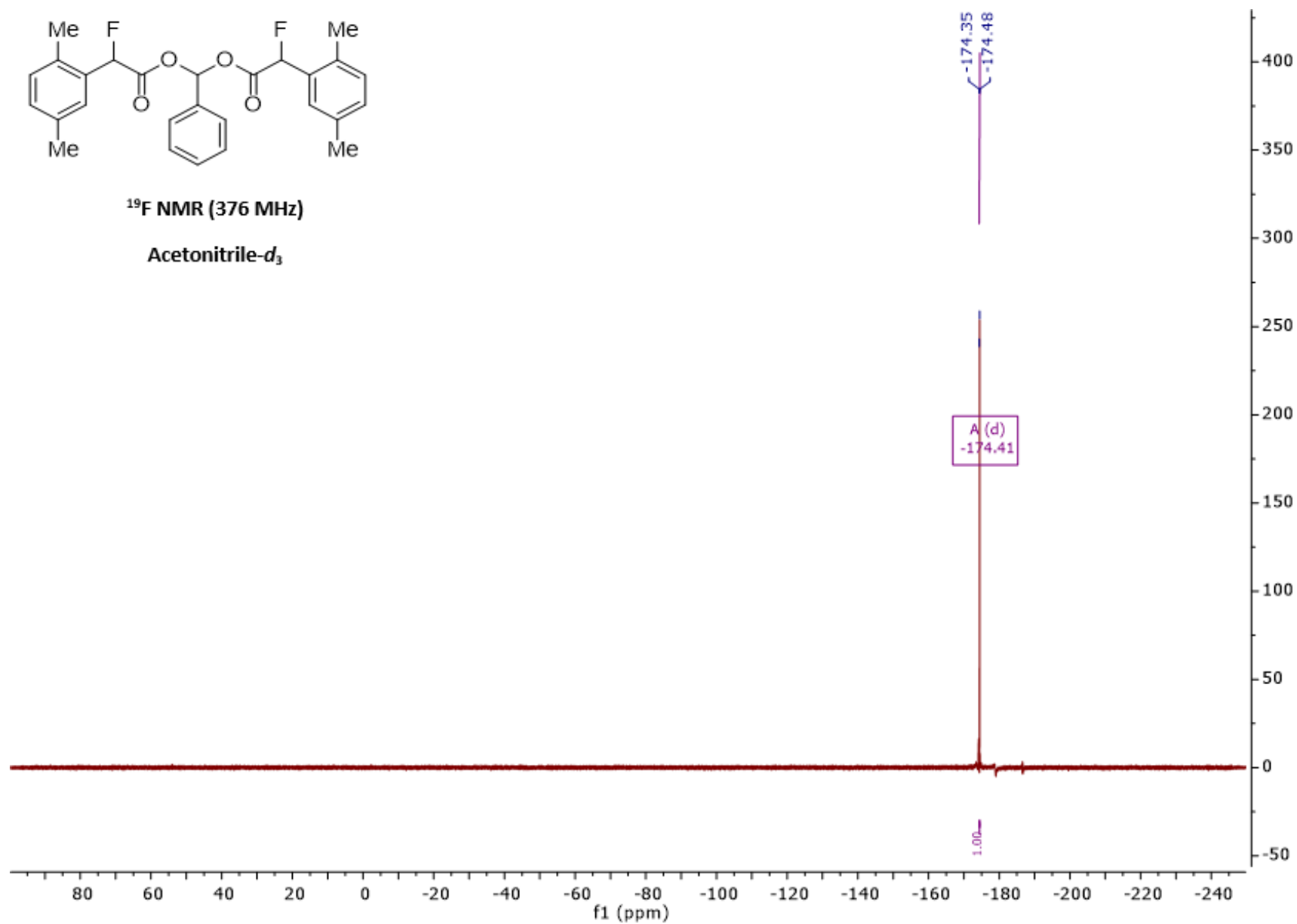
Acetonitrile- d_3

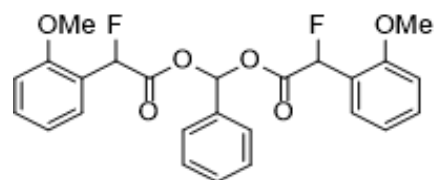




¹⁹F NMR (376 MHz)

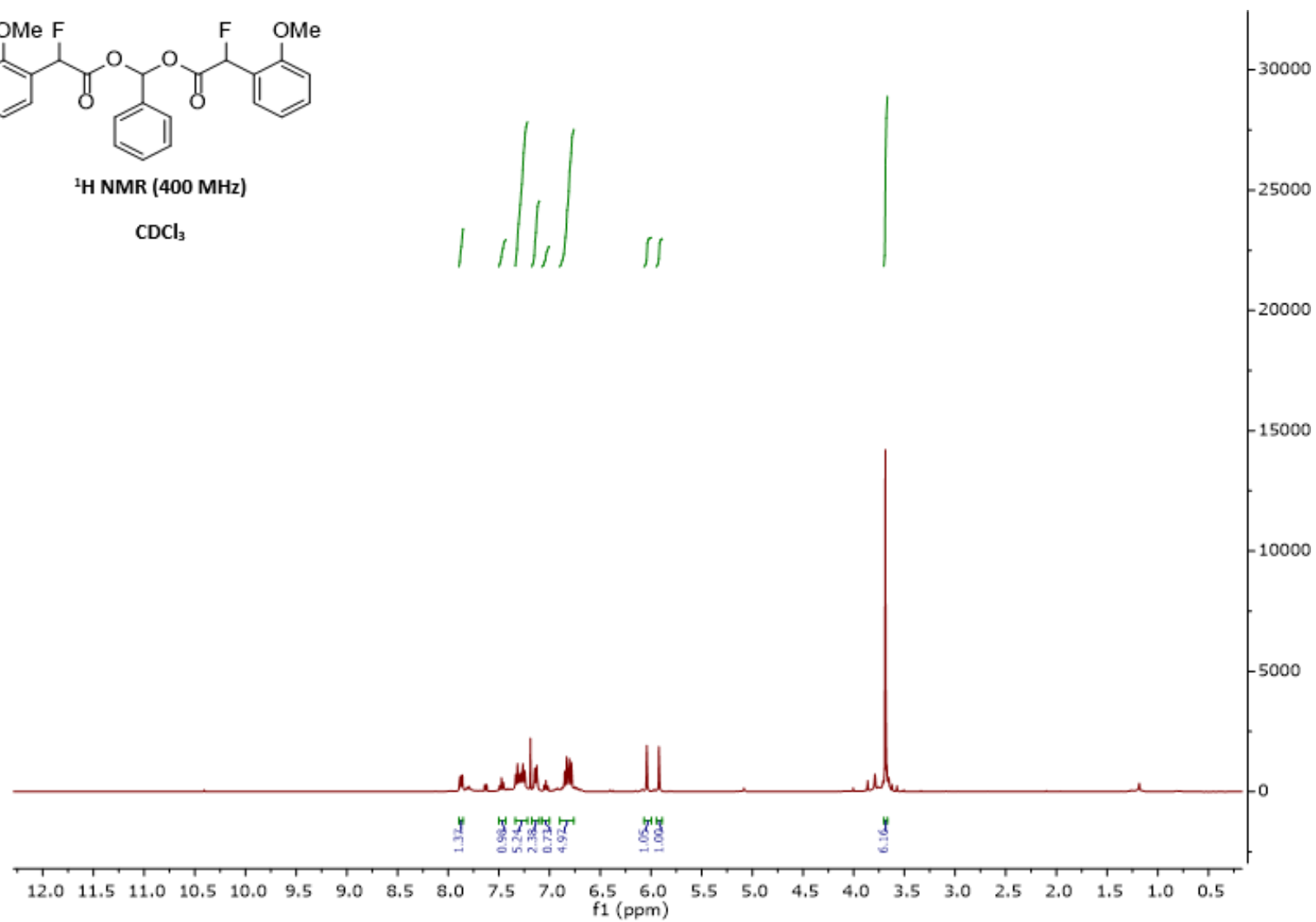
Acetonitrile-*d*₃

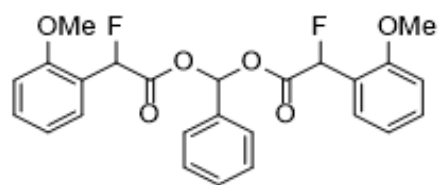




^1H NMR (400 MHz)

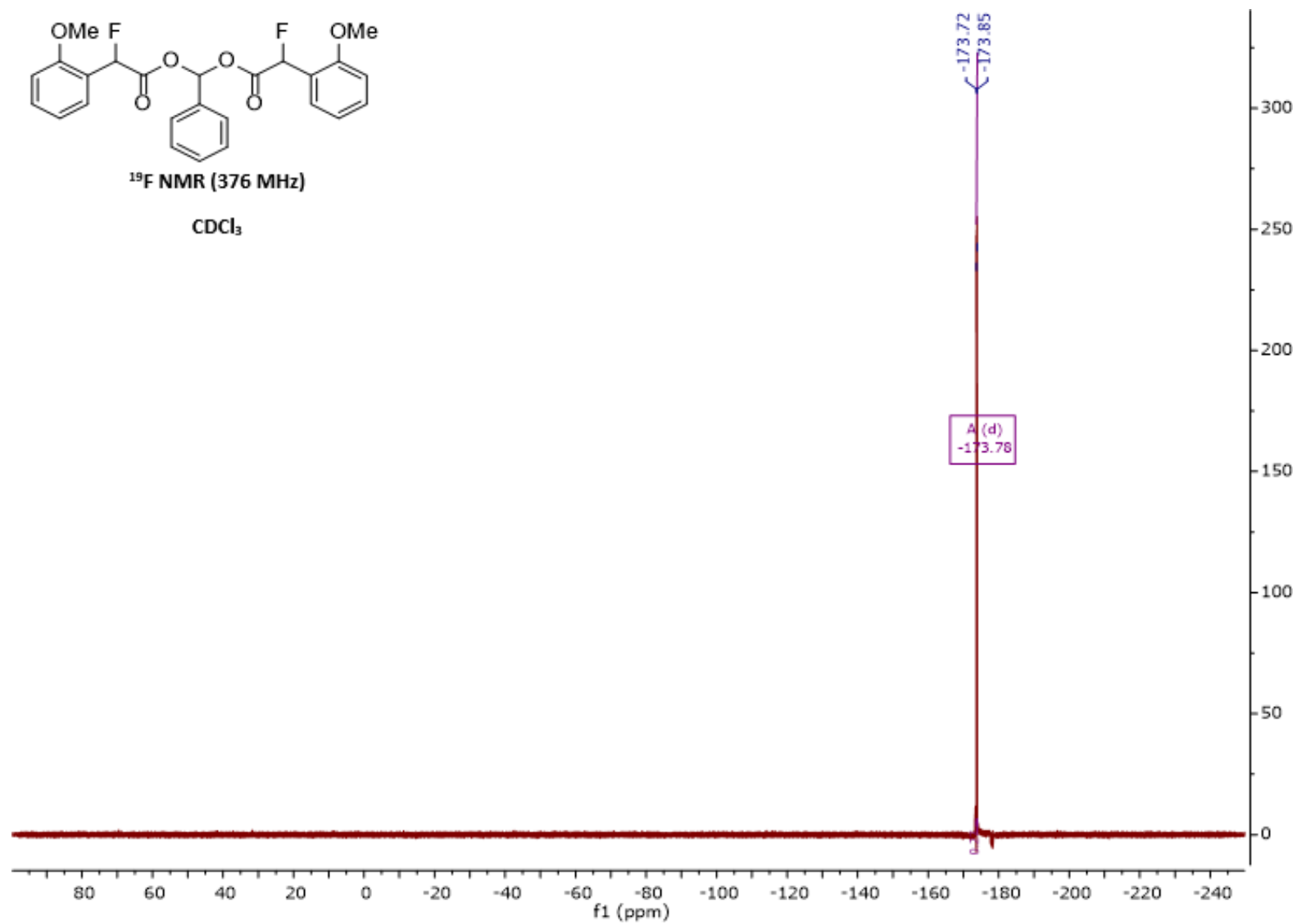
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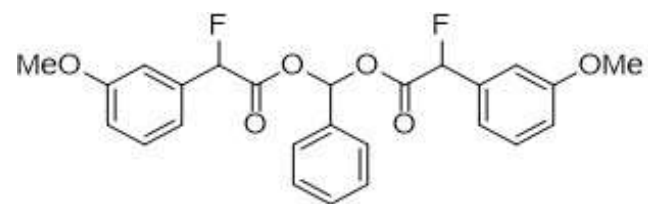




^{19}F NMR (376 MHz)

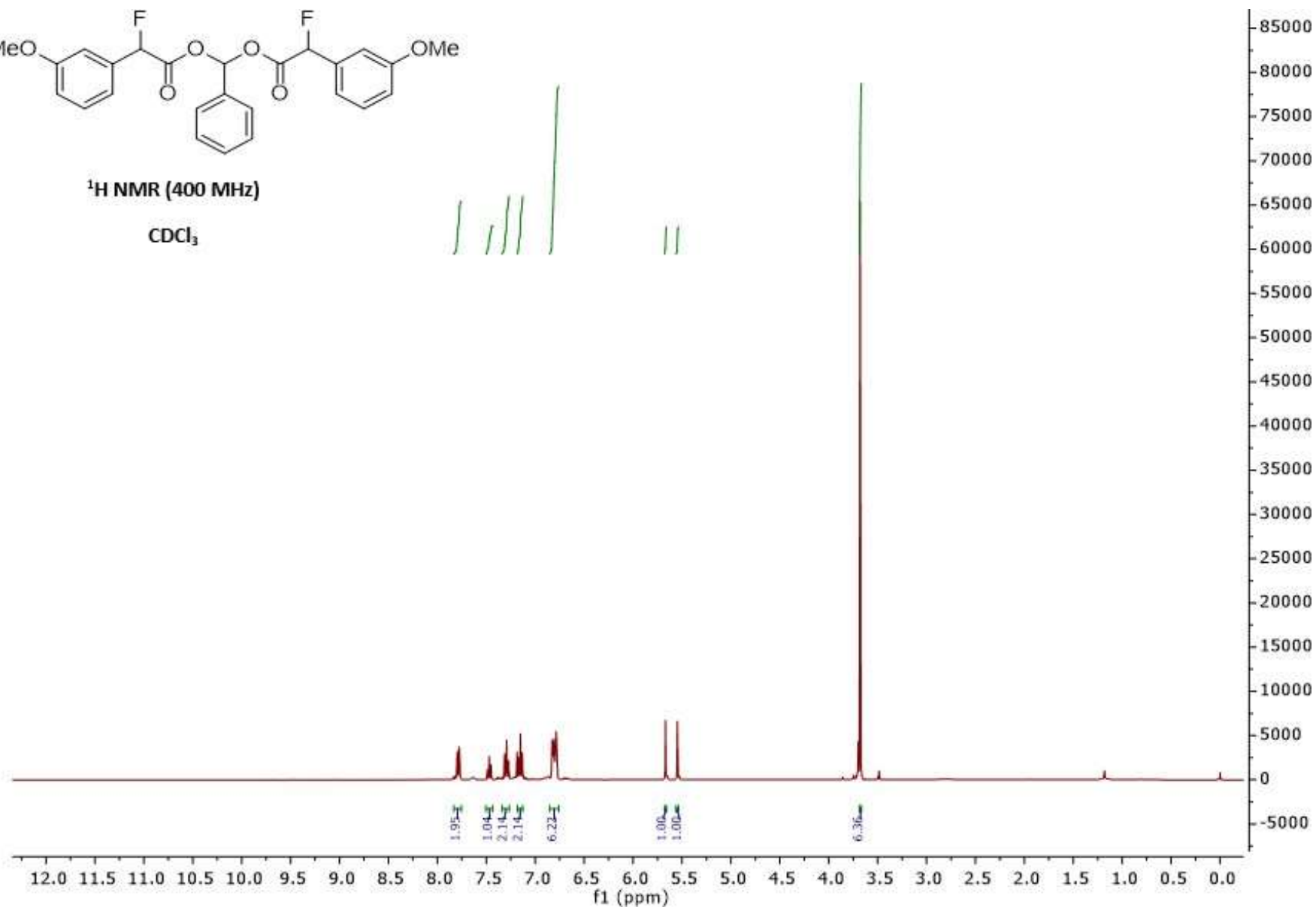
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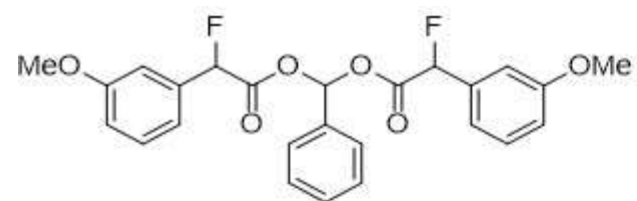




^1H NMR (400 MHz)

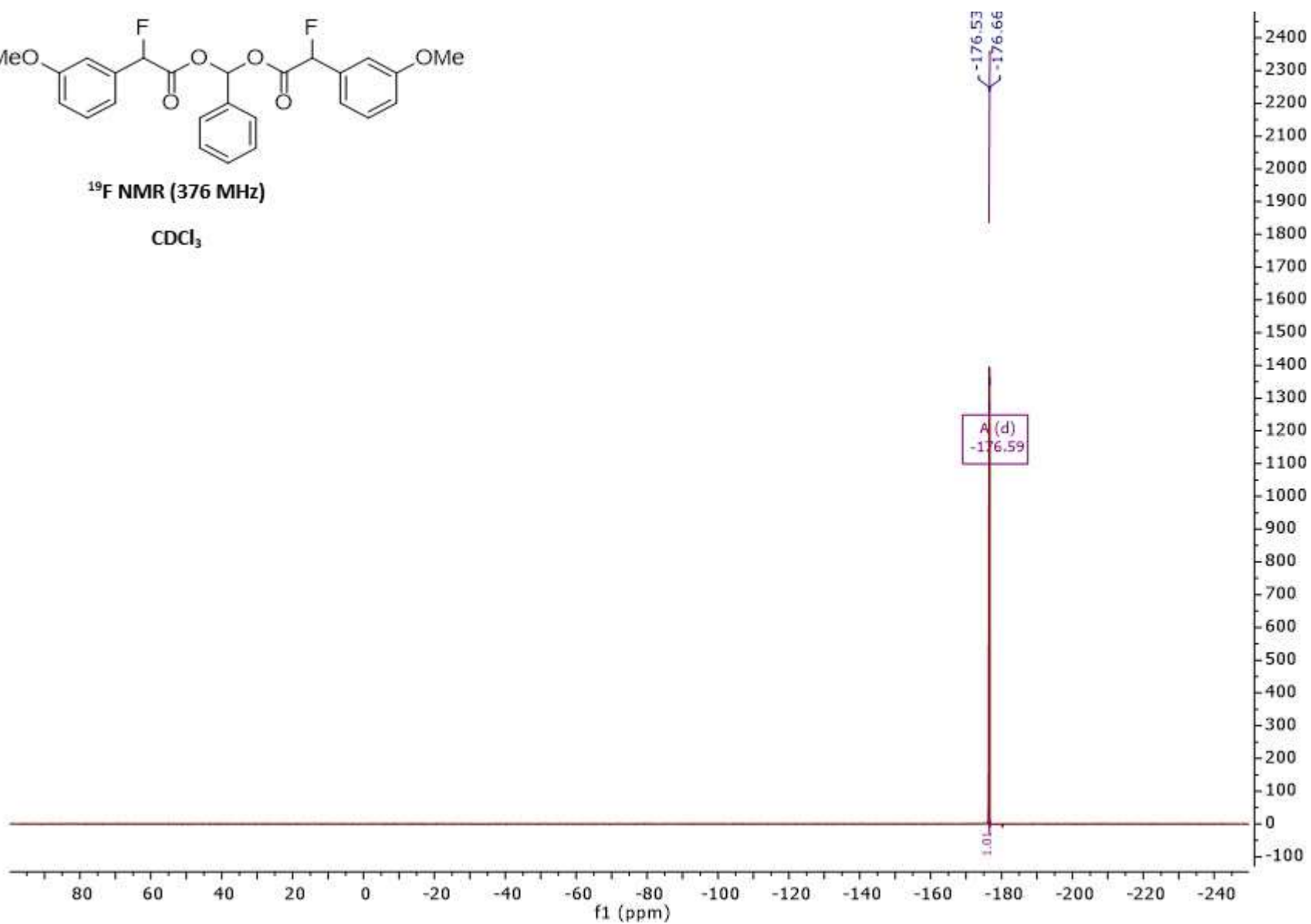
CDCl_3

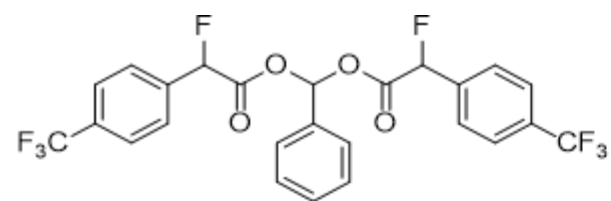




^{19}F NMR (376 MHz)

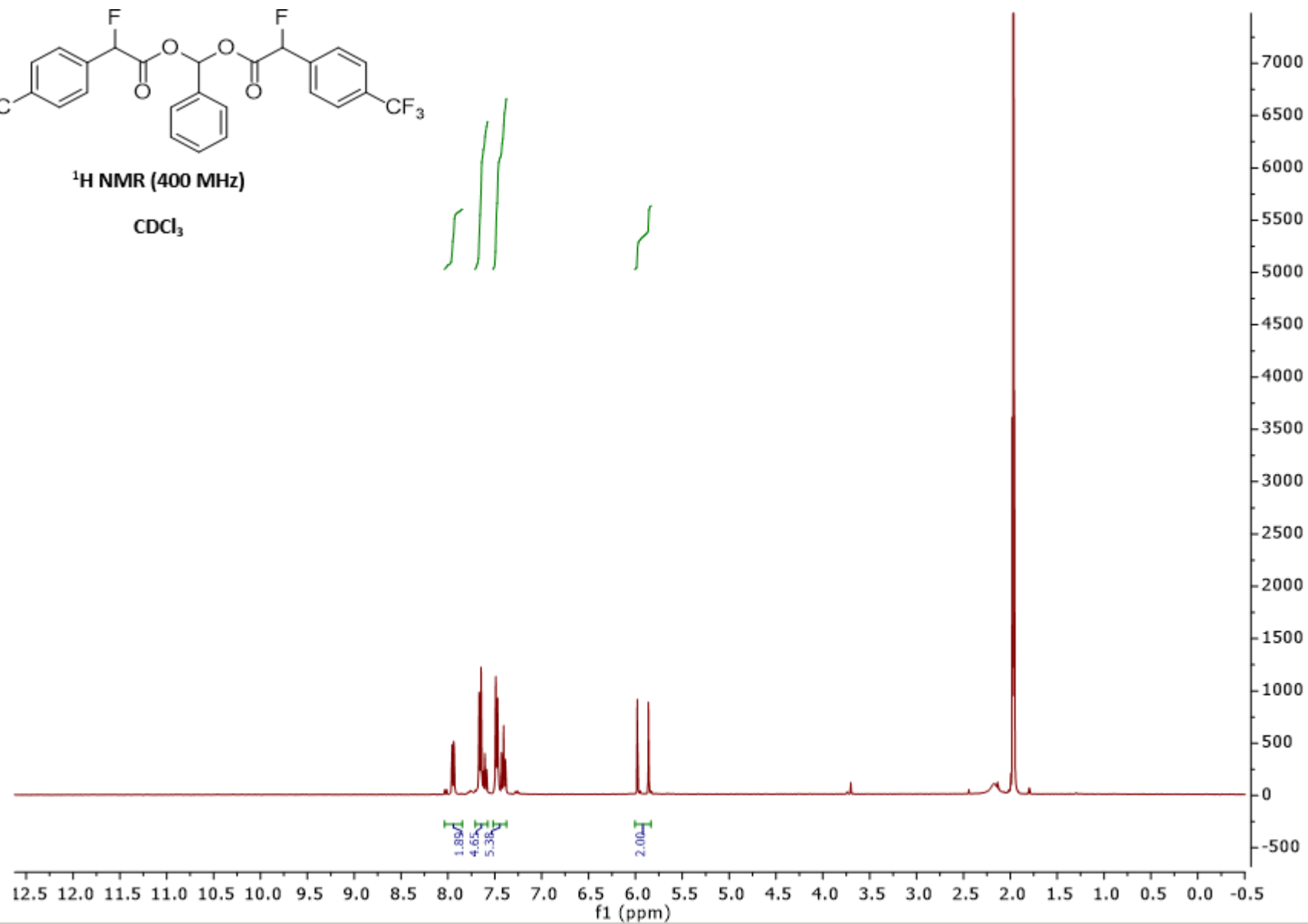
CDCl_3

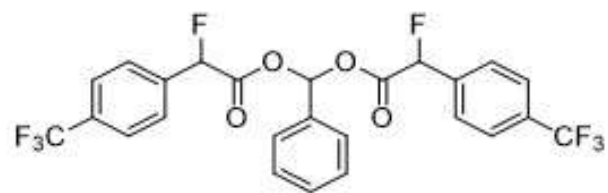




^1H NMR (400 MHz)

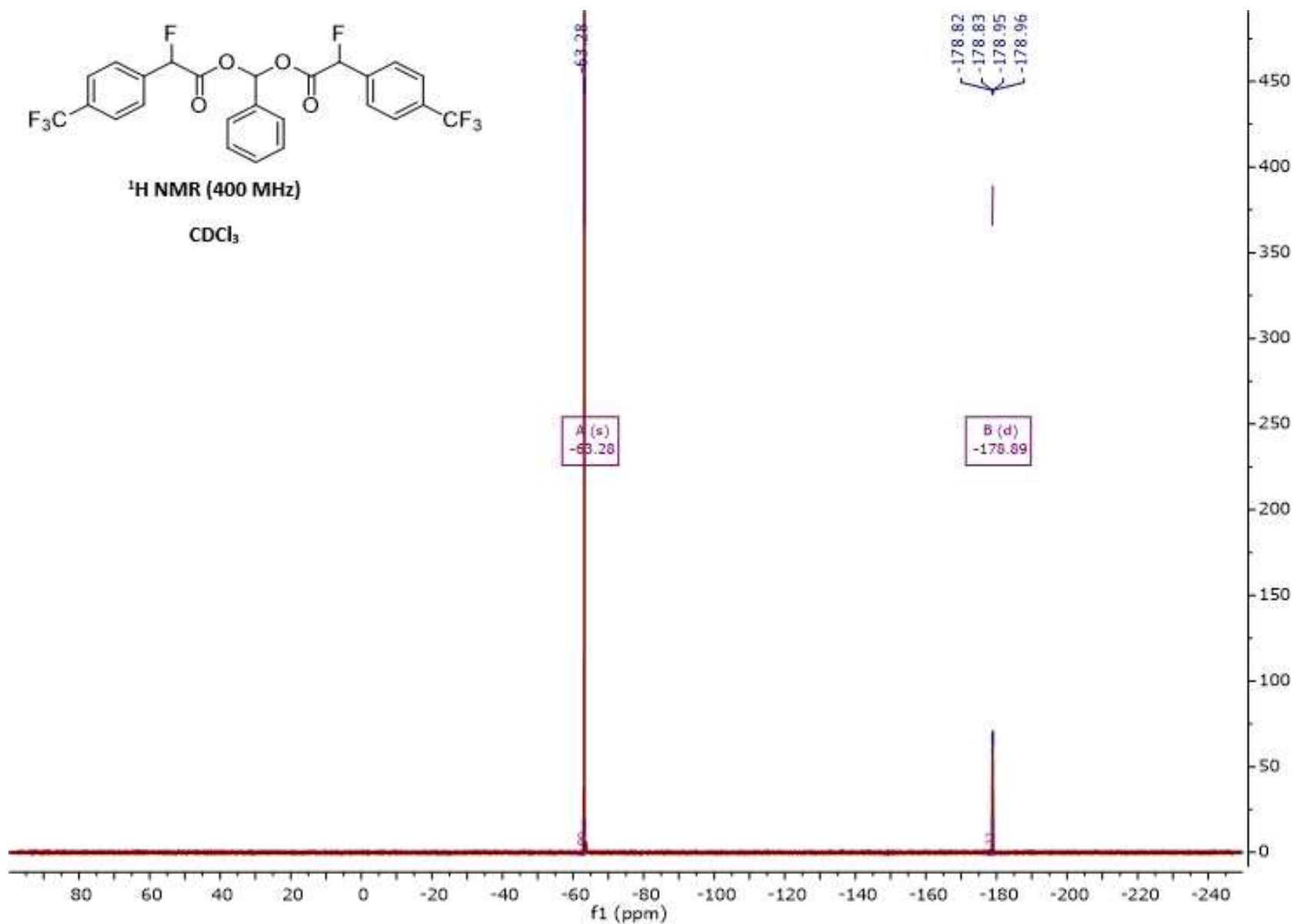
CDCl_3



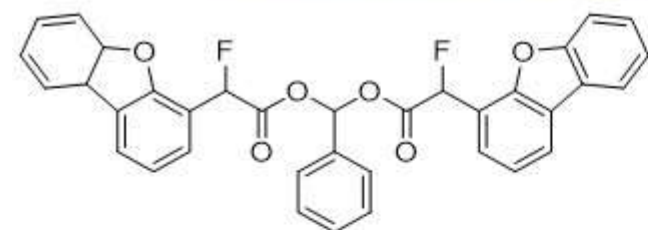


^1H NMR (400 MHz)

CDCl_3

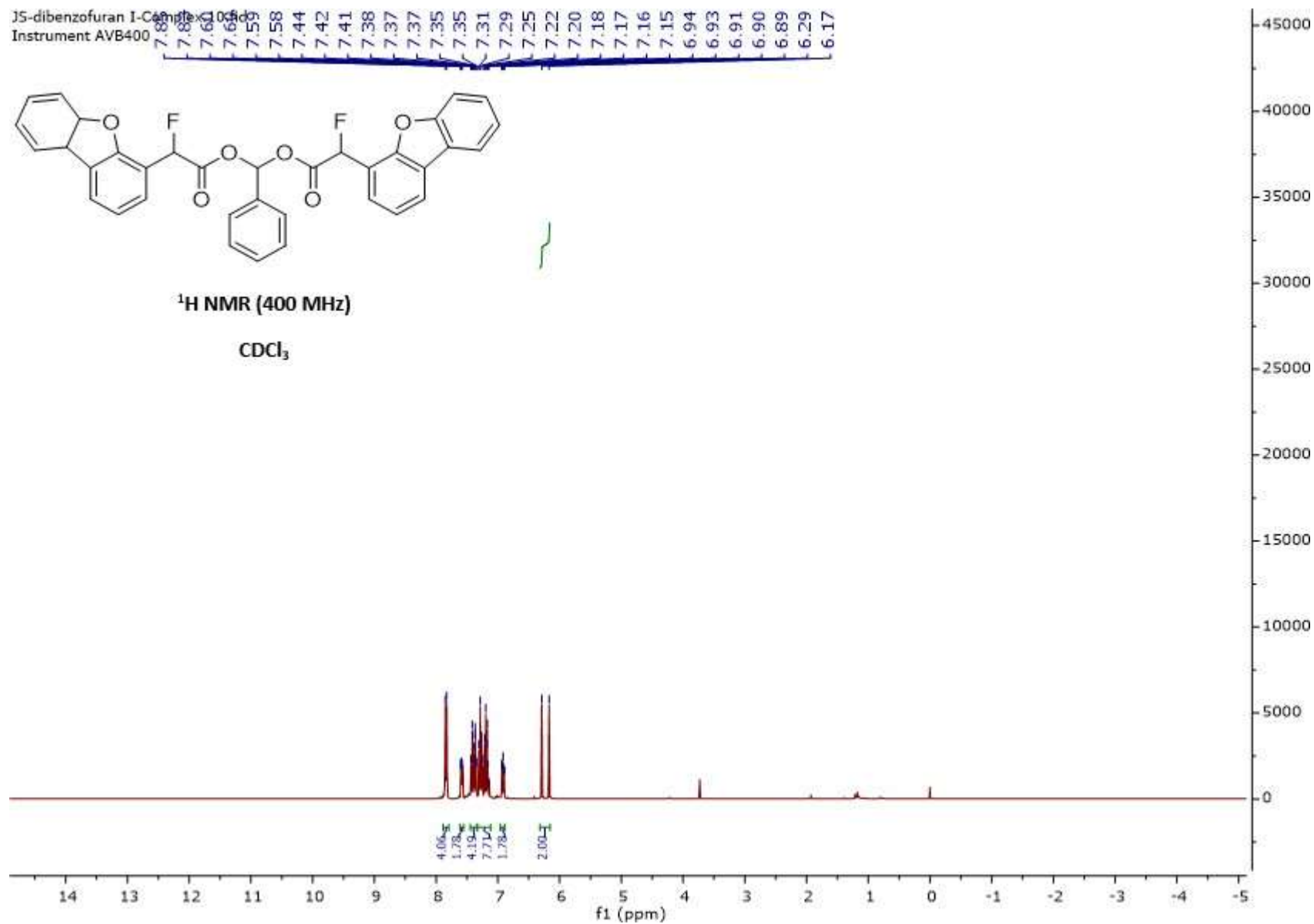


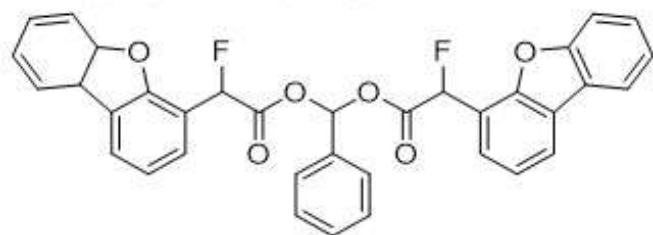
35-dibenzofuran 1-Compound
Instrument AVB400



^1H NMR (400 MHz)

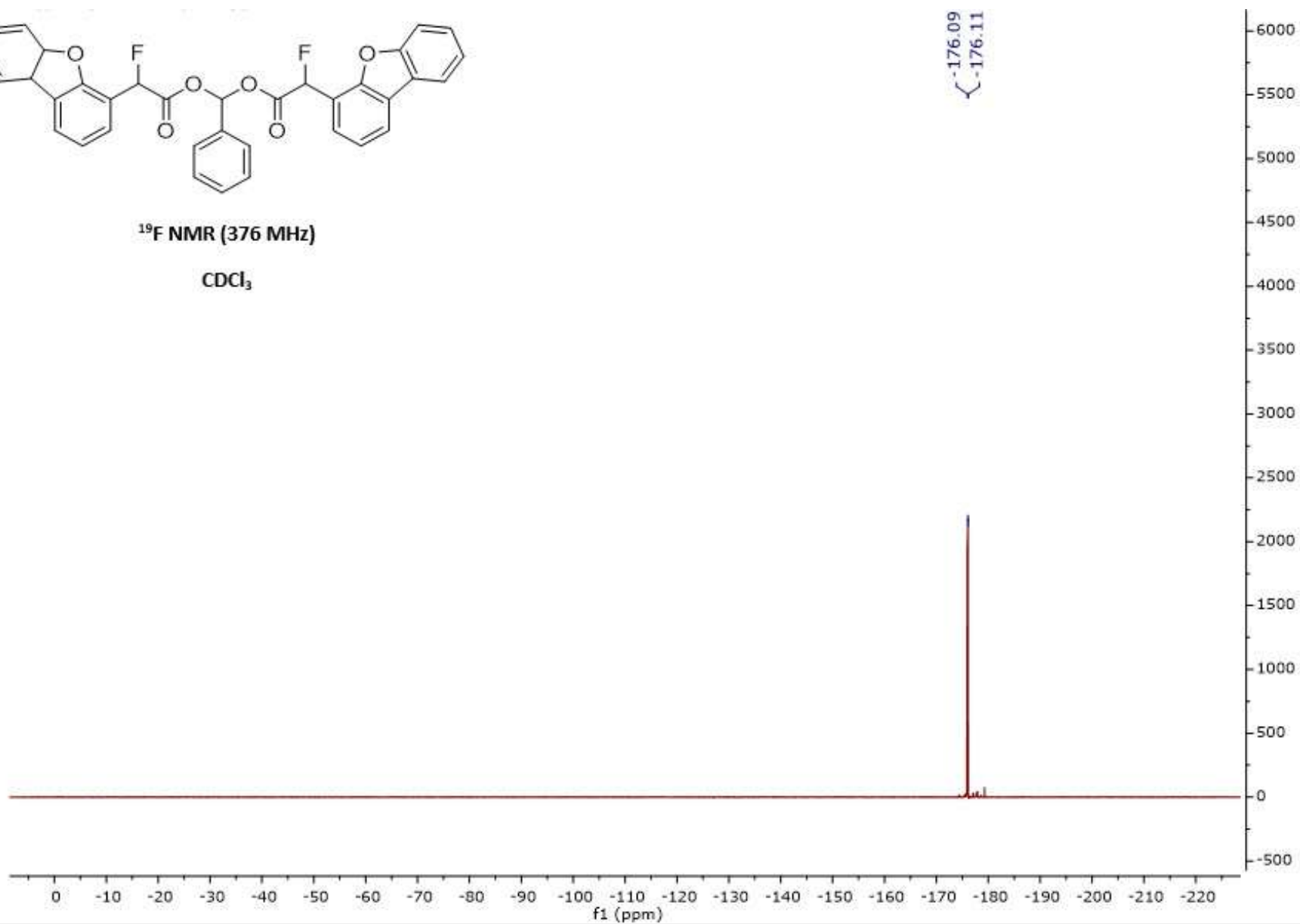
CDCl_3



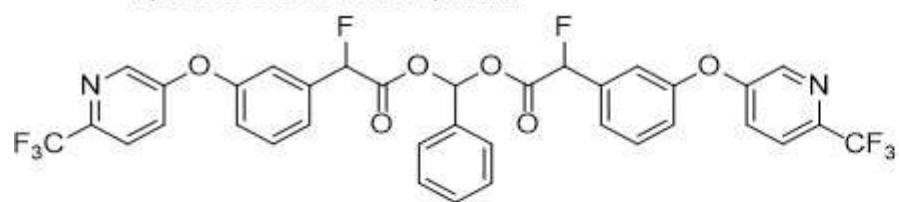


^{19}F NMR (376 MHz)

CDCl_3

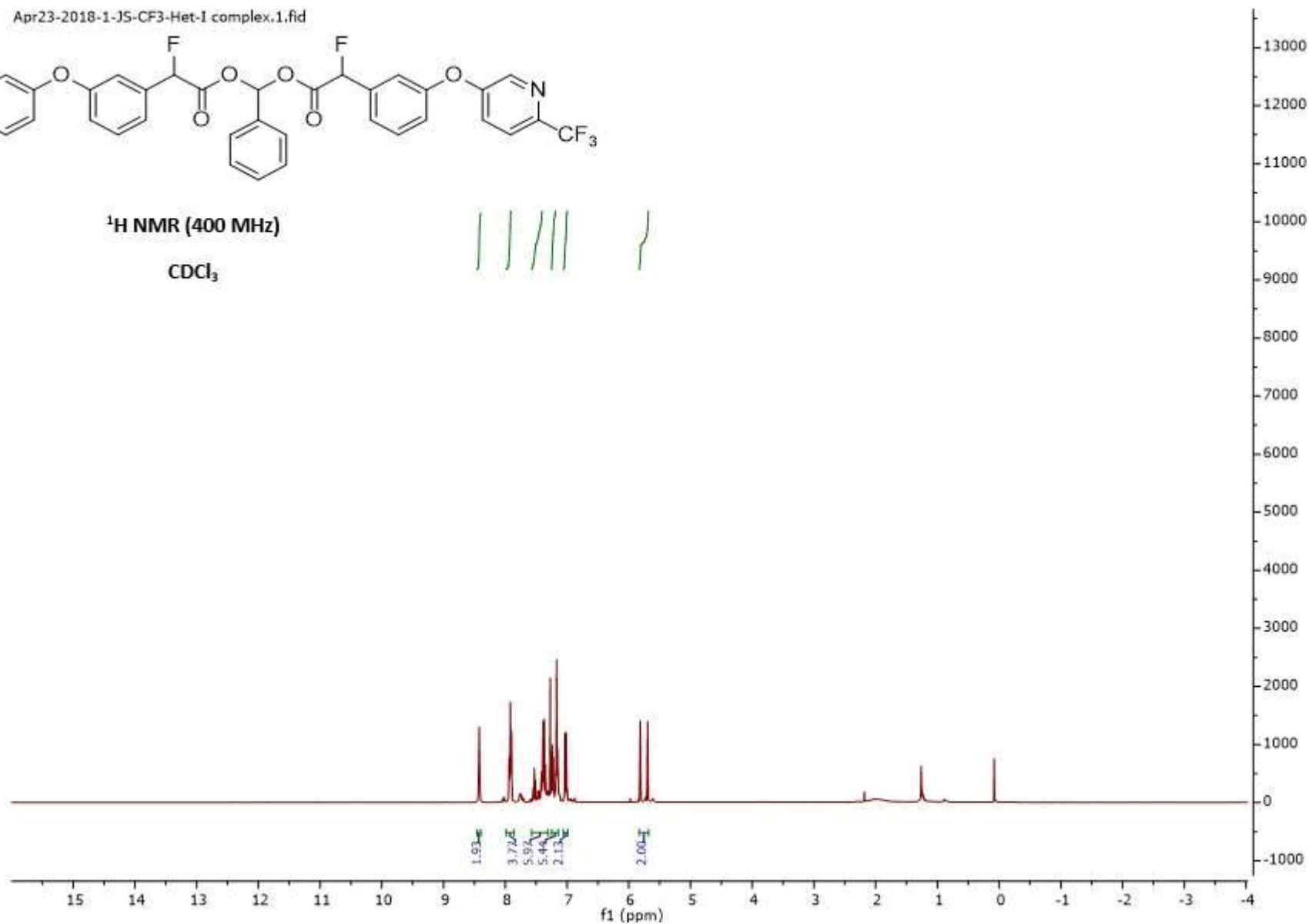


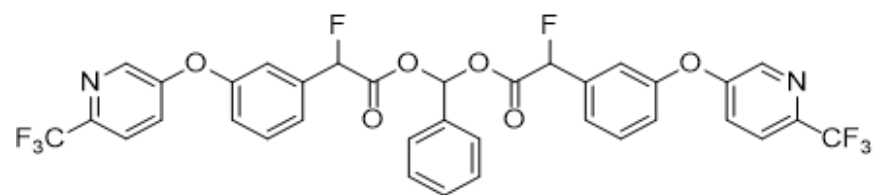
Apr23-2018-1-J5-CF3-Het-I complex.1.fid



^1H NMR (400 MHz)

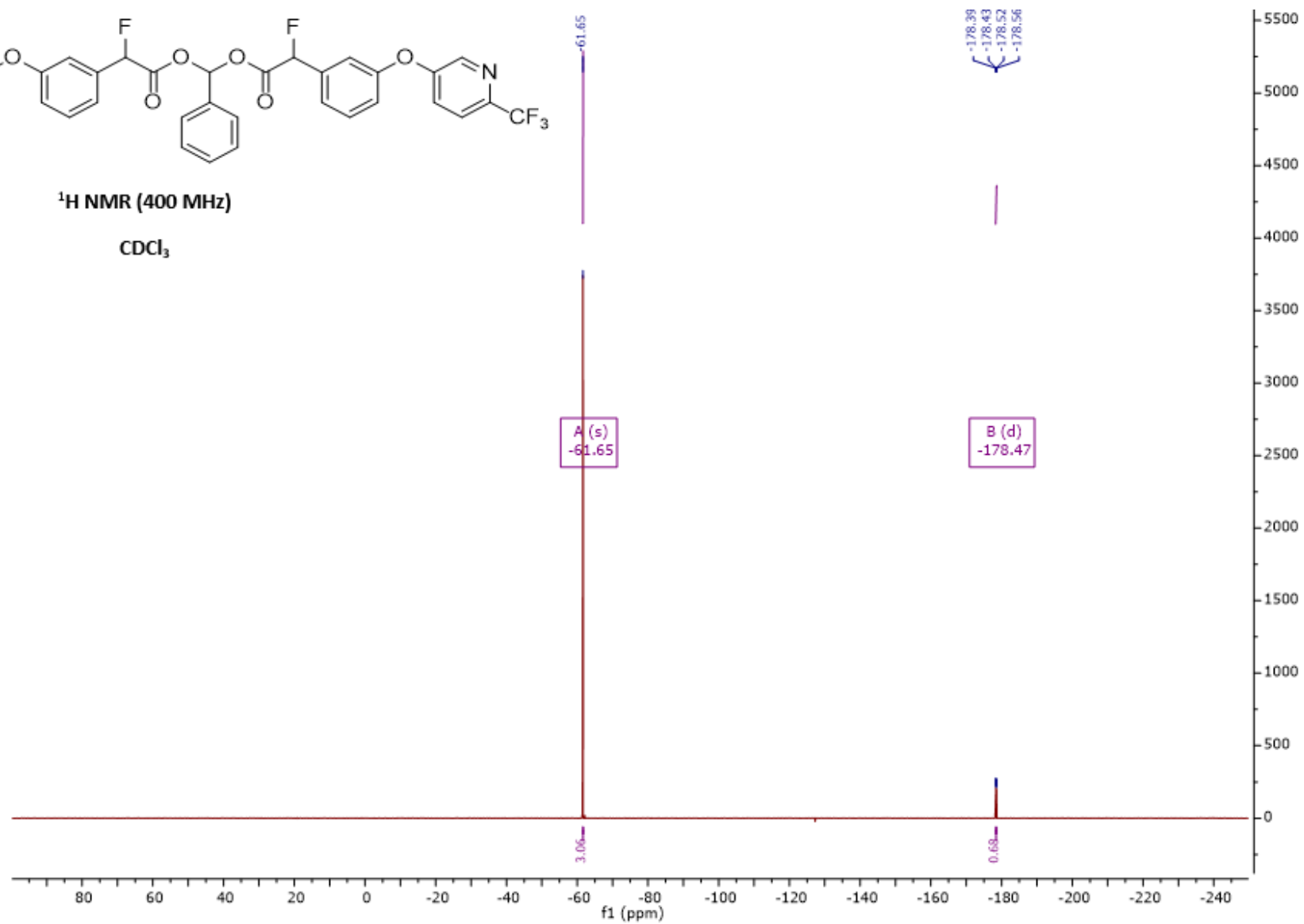
CDCl_3

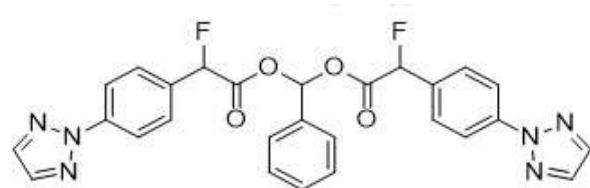




^1H NMR (400 MHz)

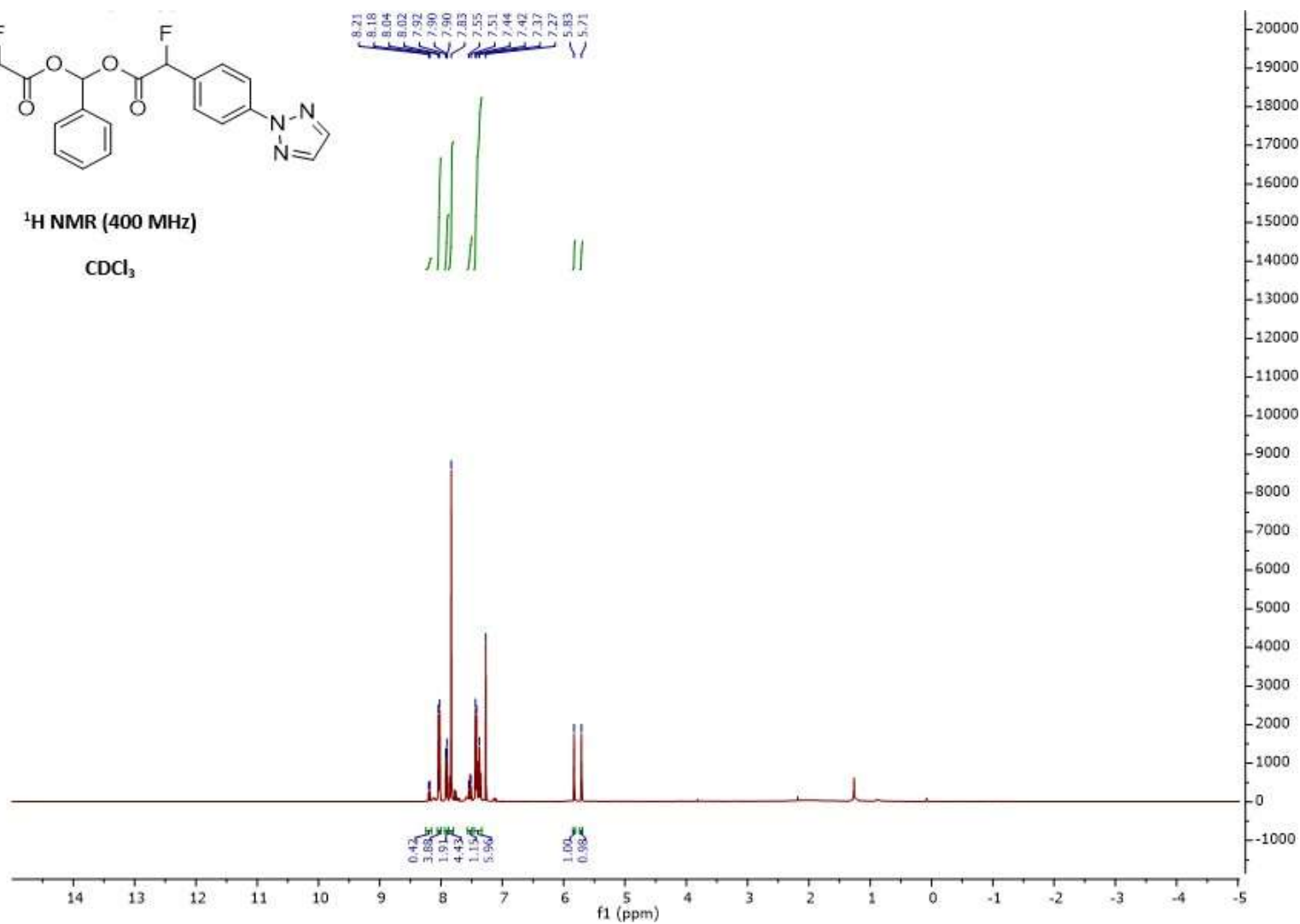
CDCl_3

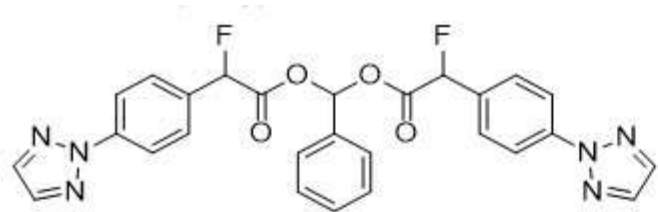




¹H NMR (400 MHz)

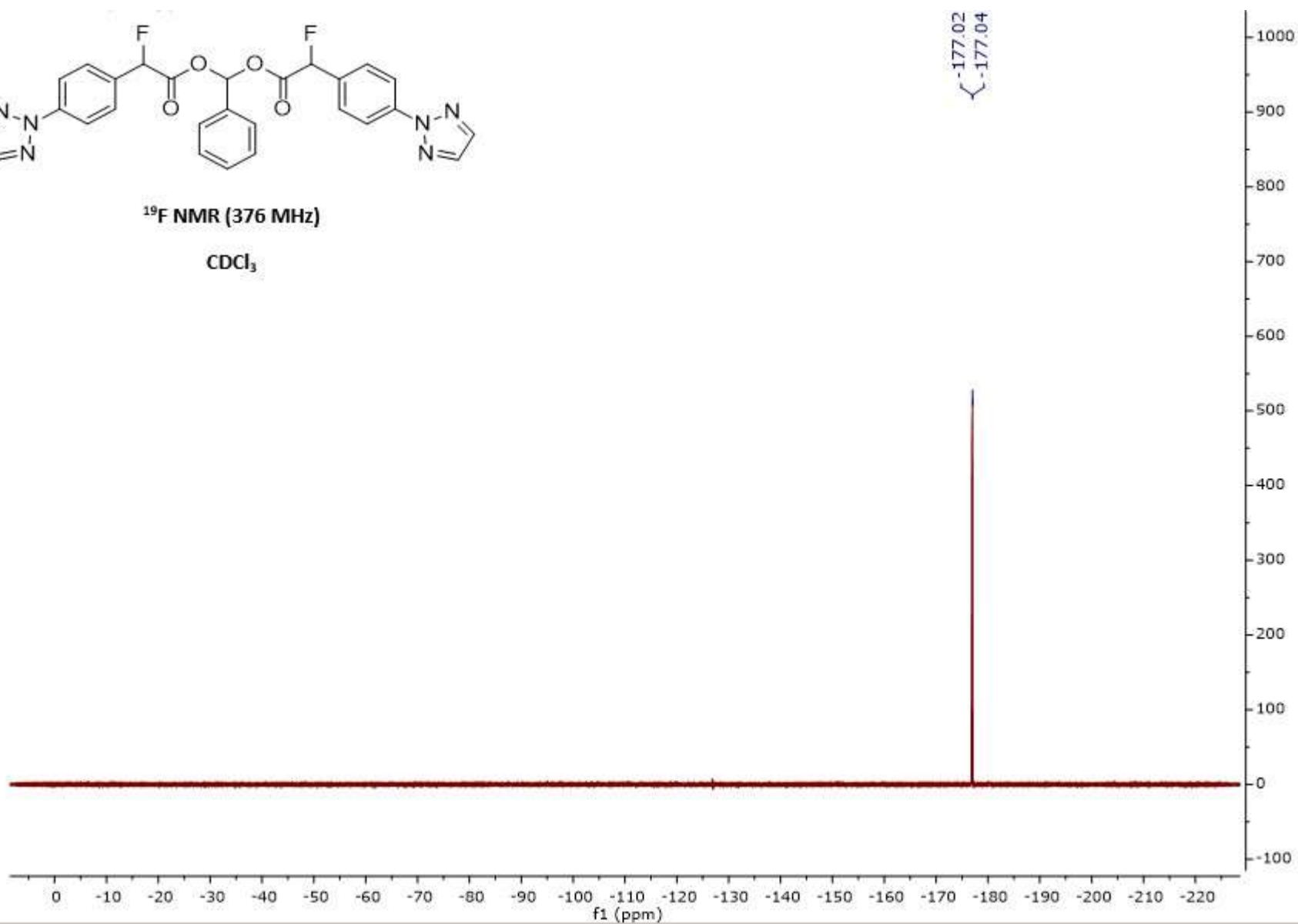
CDCl₃



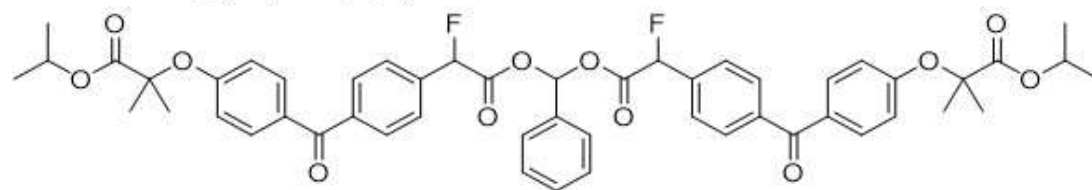


^{19}F NMR (376 MHz)

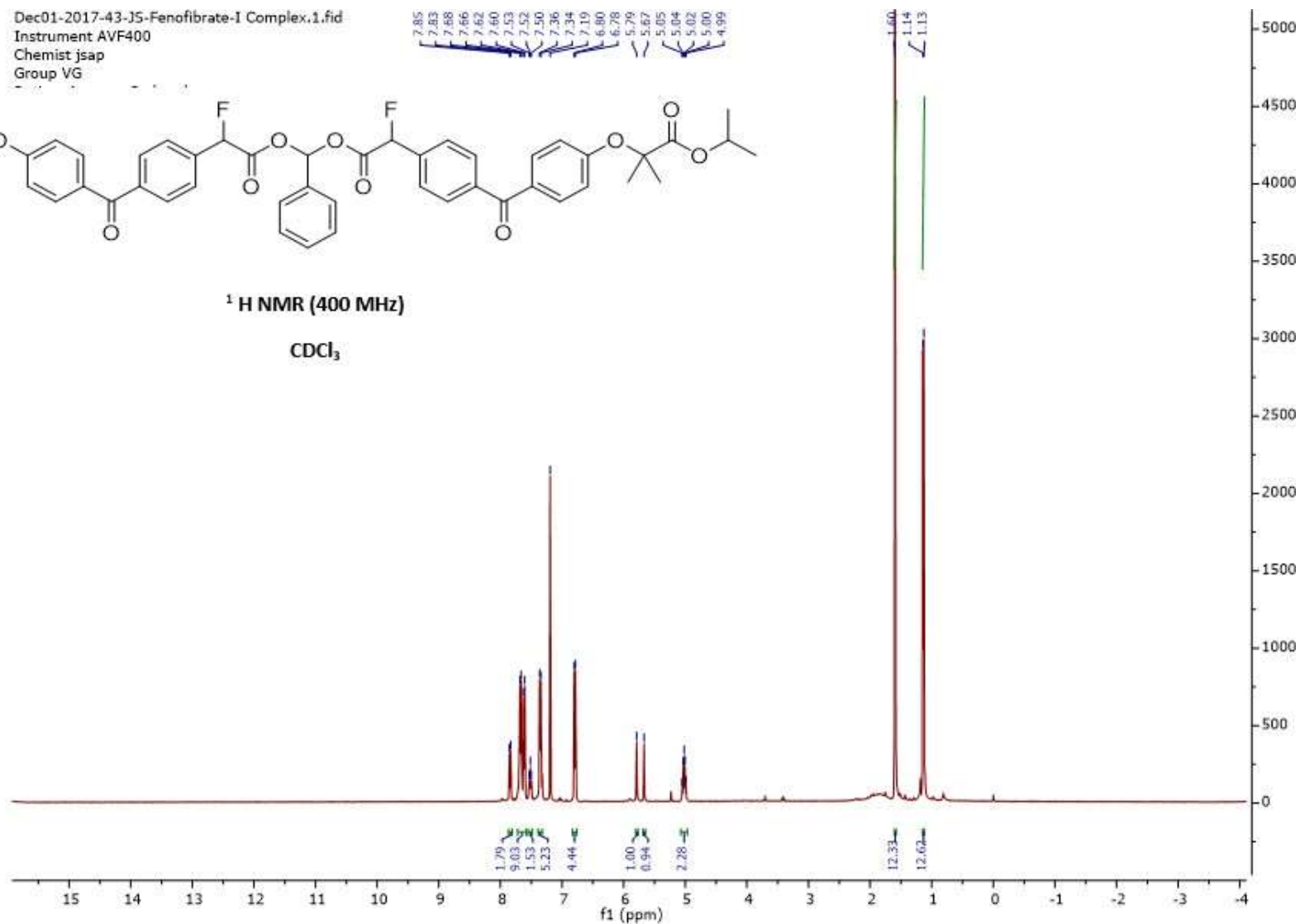
CDCl_3

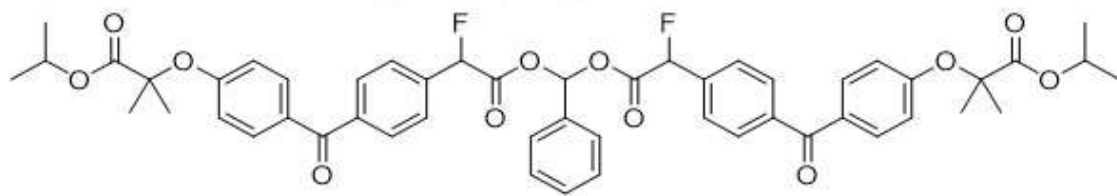


Dec01-2017-43-J5-Fenofibrate-I Complex.1.fid
 Instrument AVF400
 Chemist jsap
 Group VG



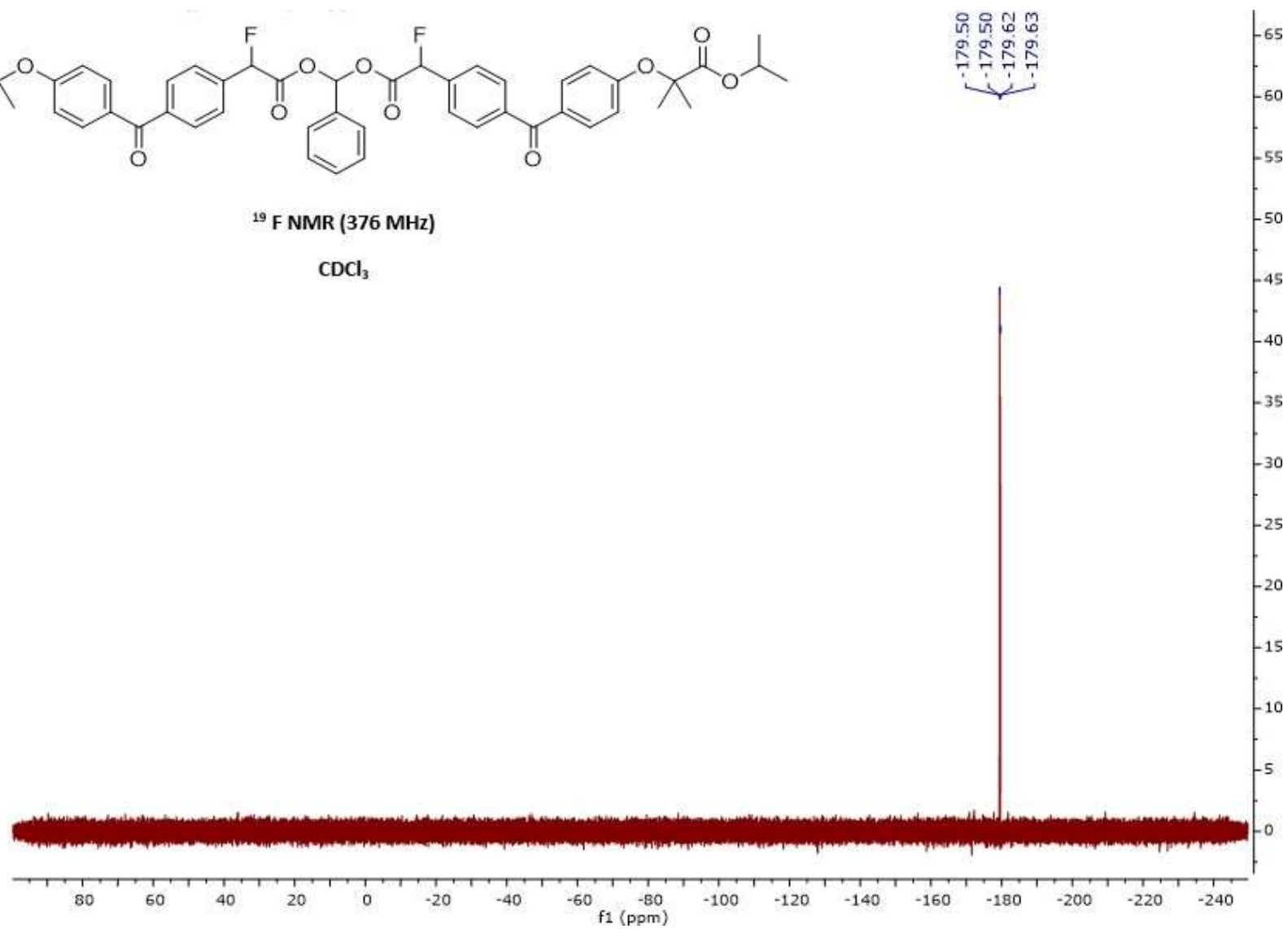
¹H NMR (400 MHz)
 CDCl₃

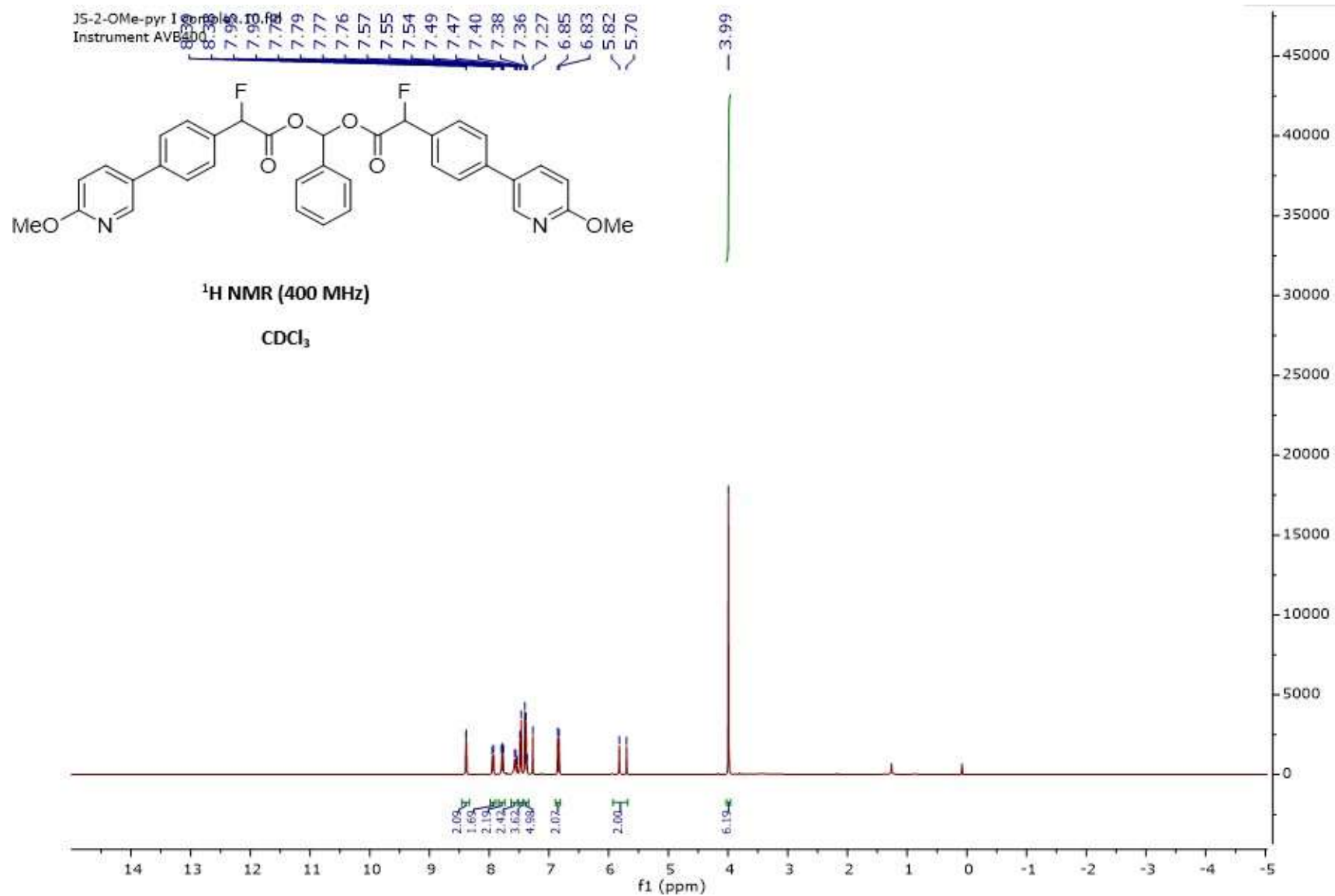


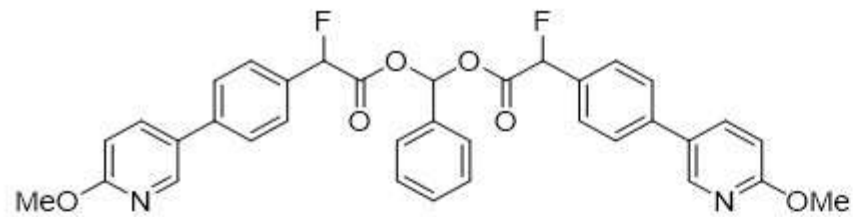


^{19}F NMR (376 MHz)

CDCl_3

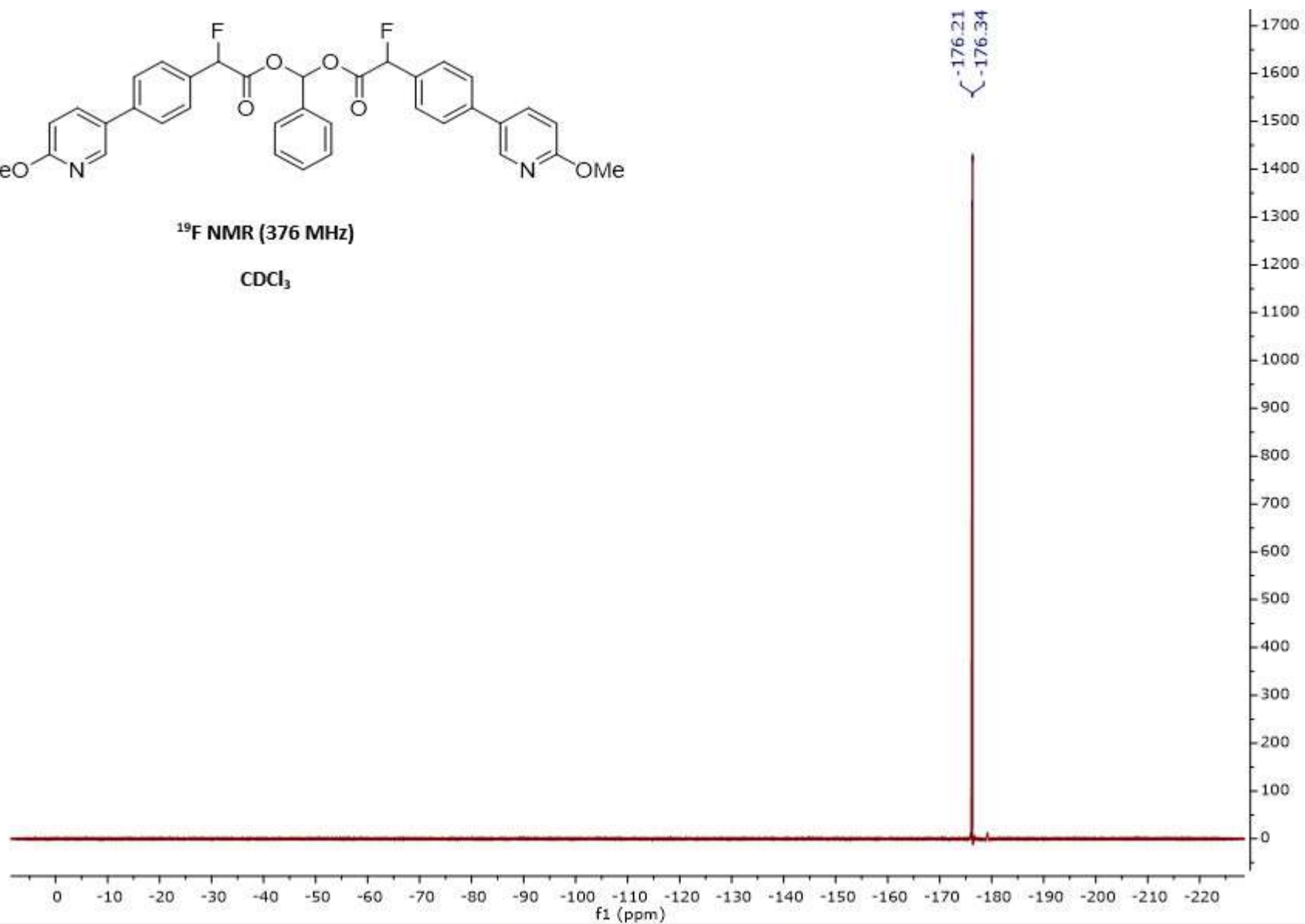


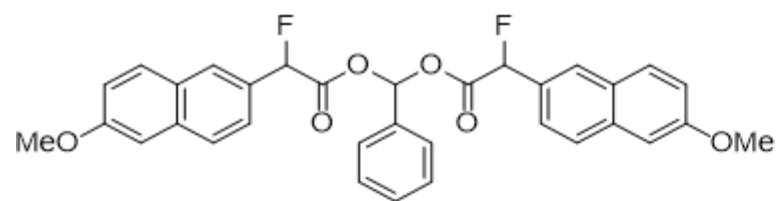




¹⁹F NMR (376 MHz)

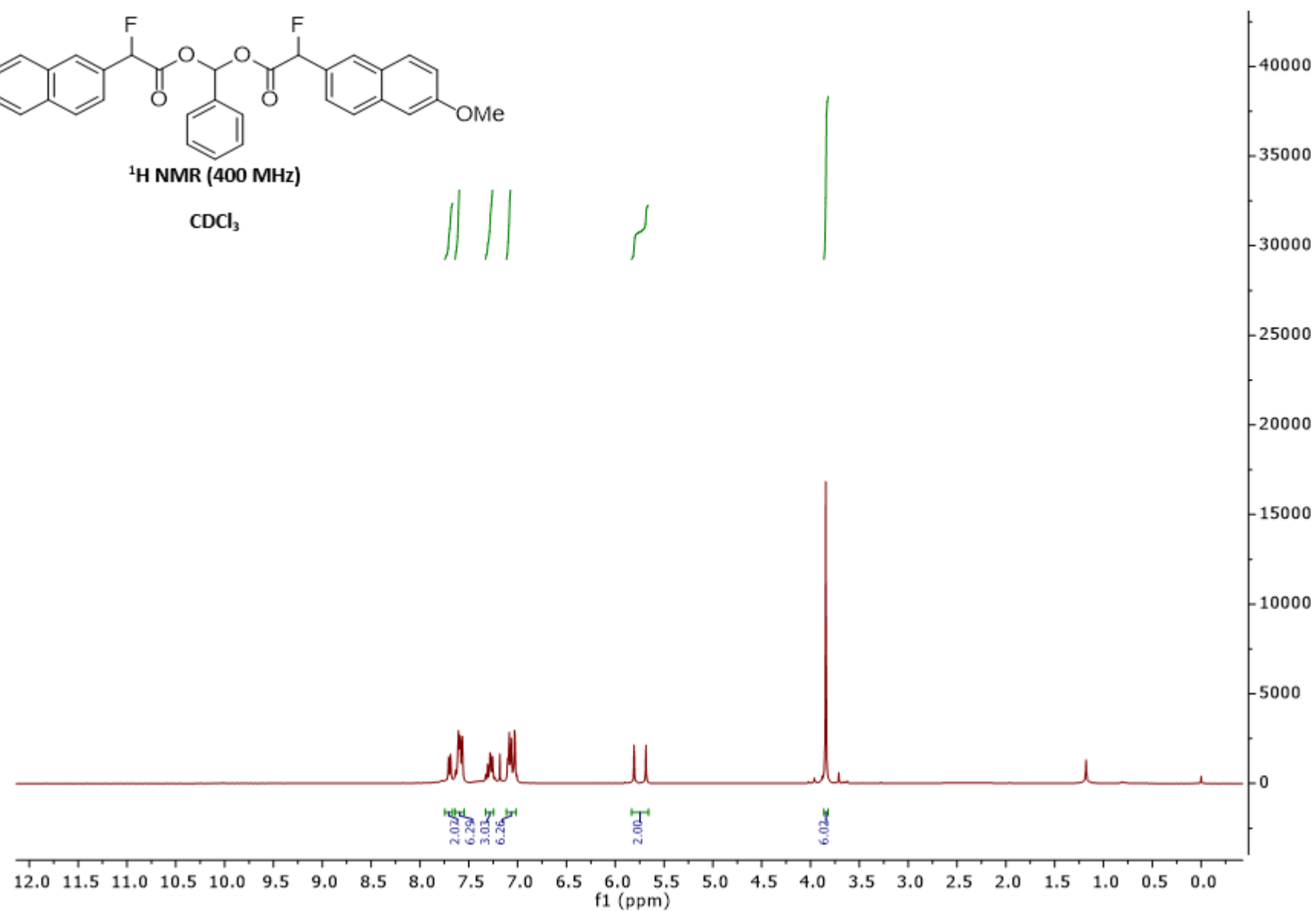
CDCl₃

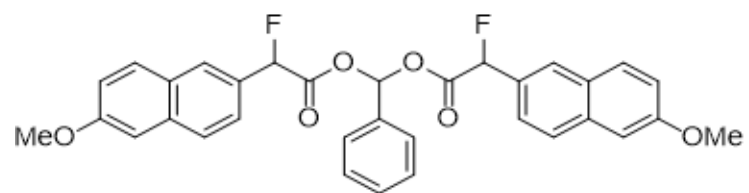




^1H NMR (400 MHz)

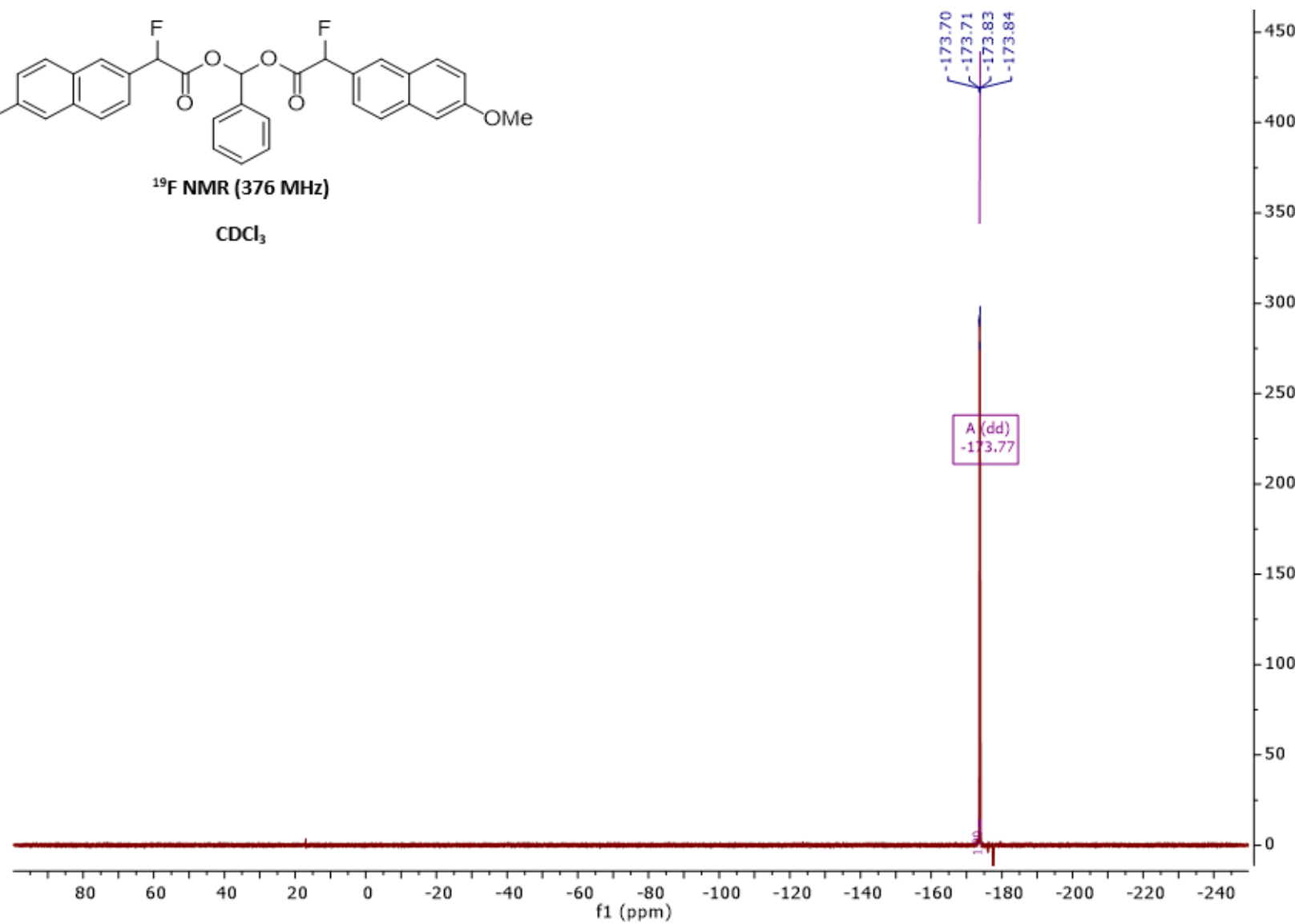
CDCl_3



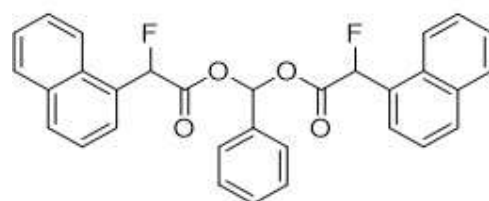


^{19}F NMR (376 MHz)

CDCl_3

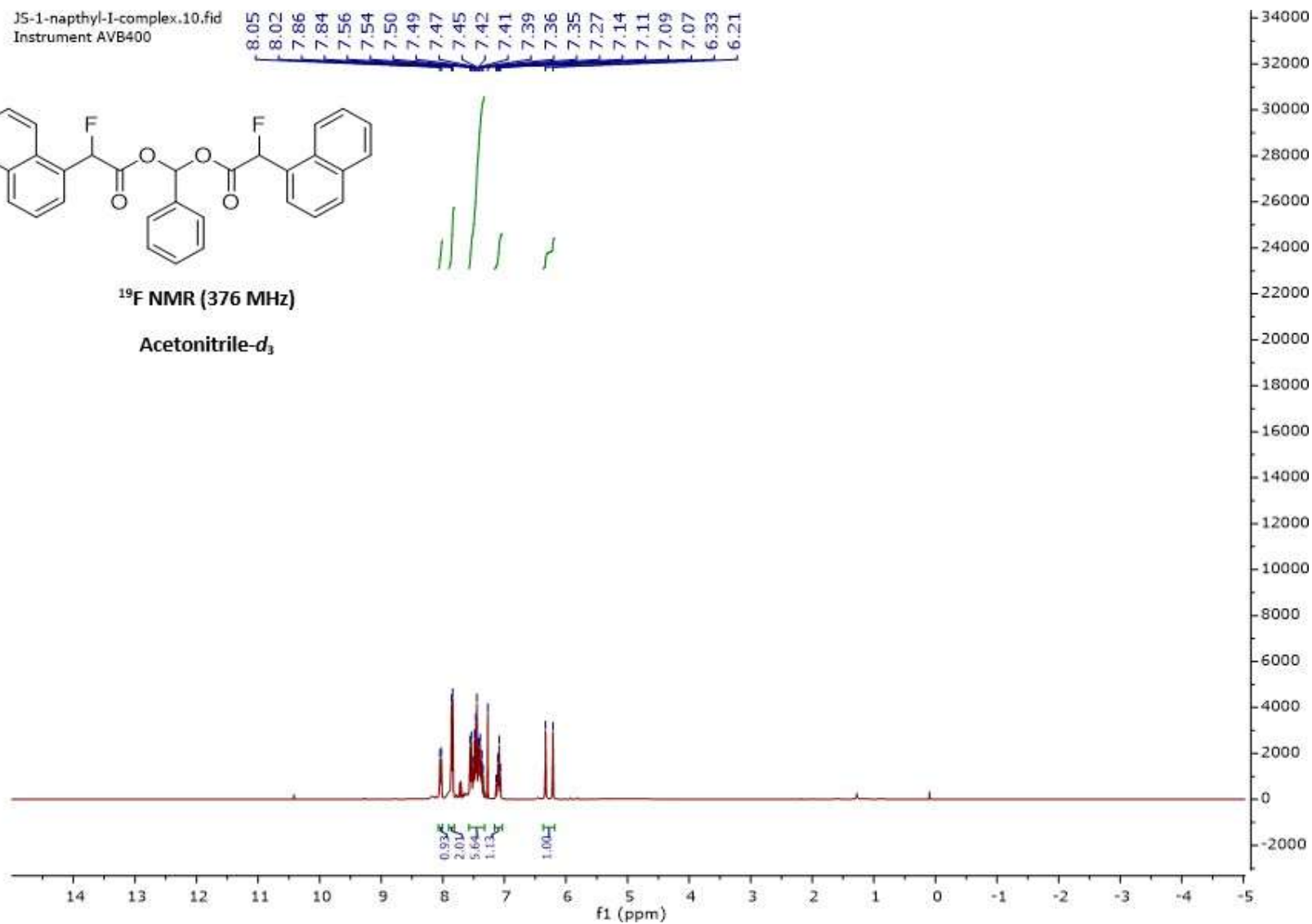


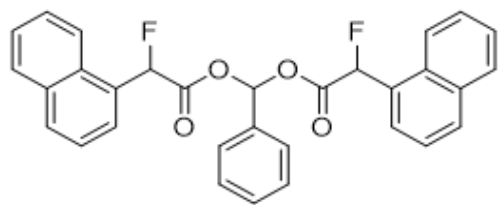
J5-1-naphthyl-I-complex.10.fid
Instrument AVB400



^{19}F NMR (376 MHz)

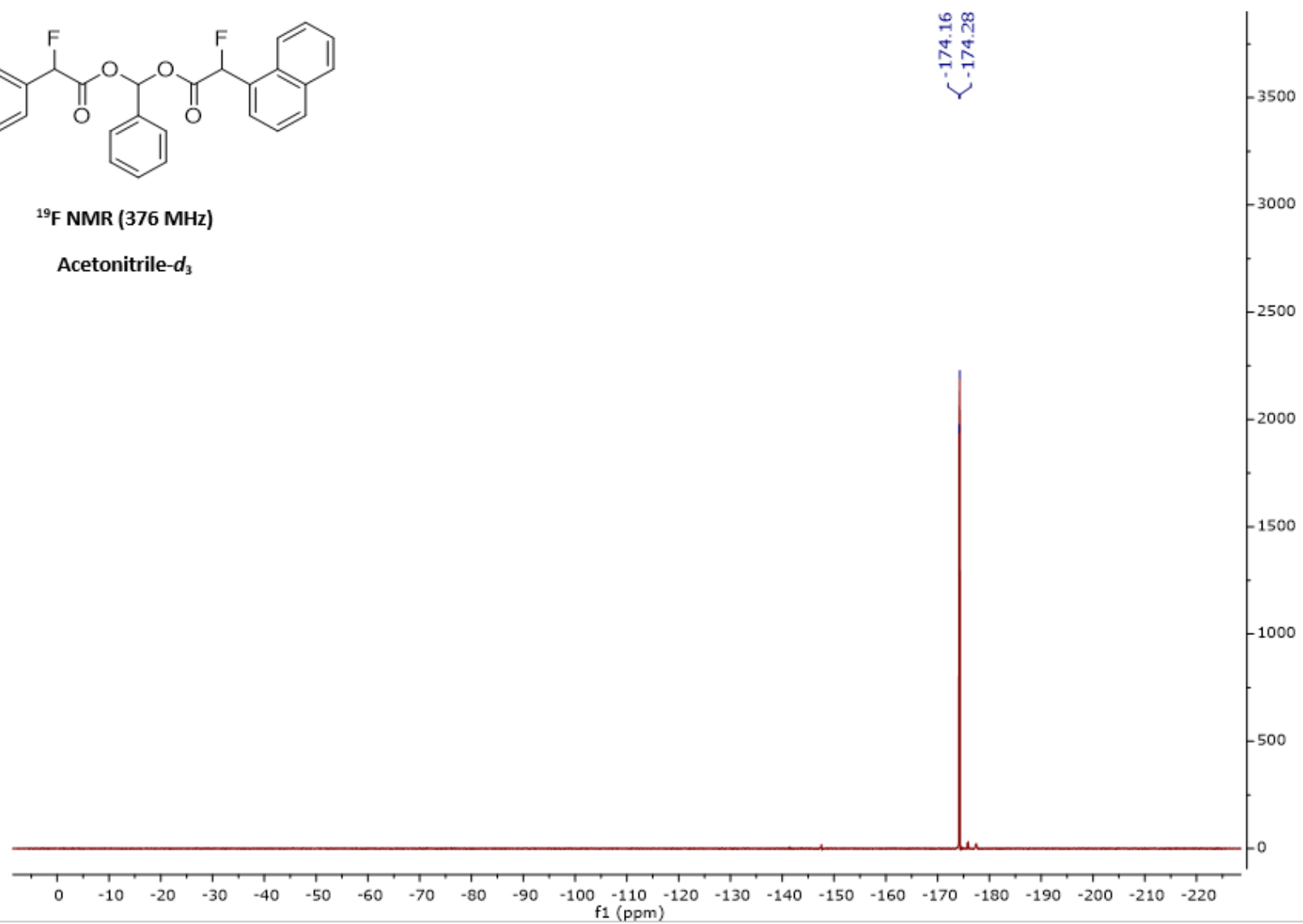
Acetonitrile- d_3

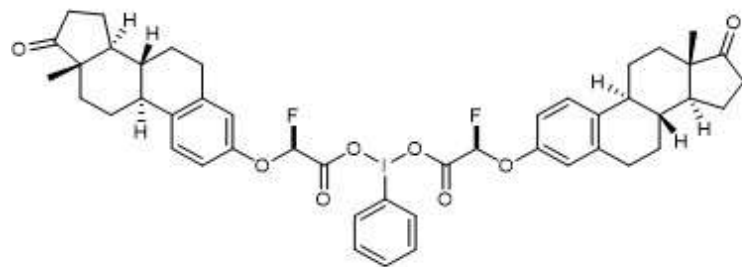




^{19}F NMR (376 MHz)

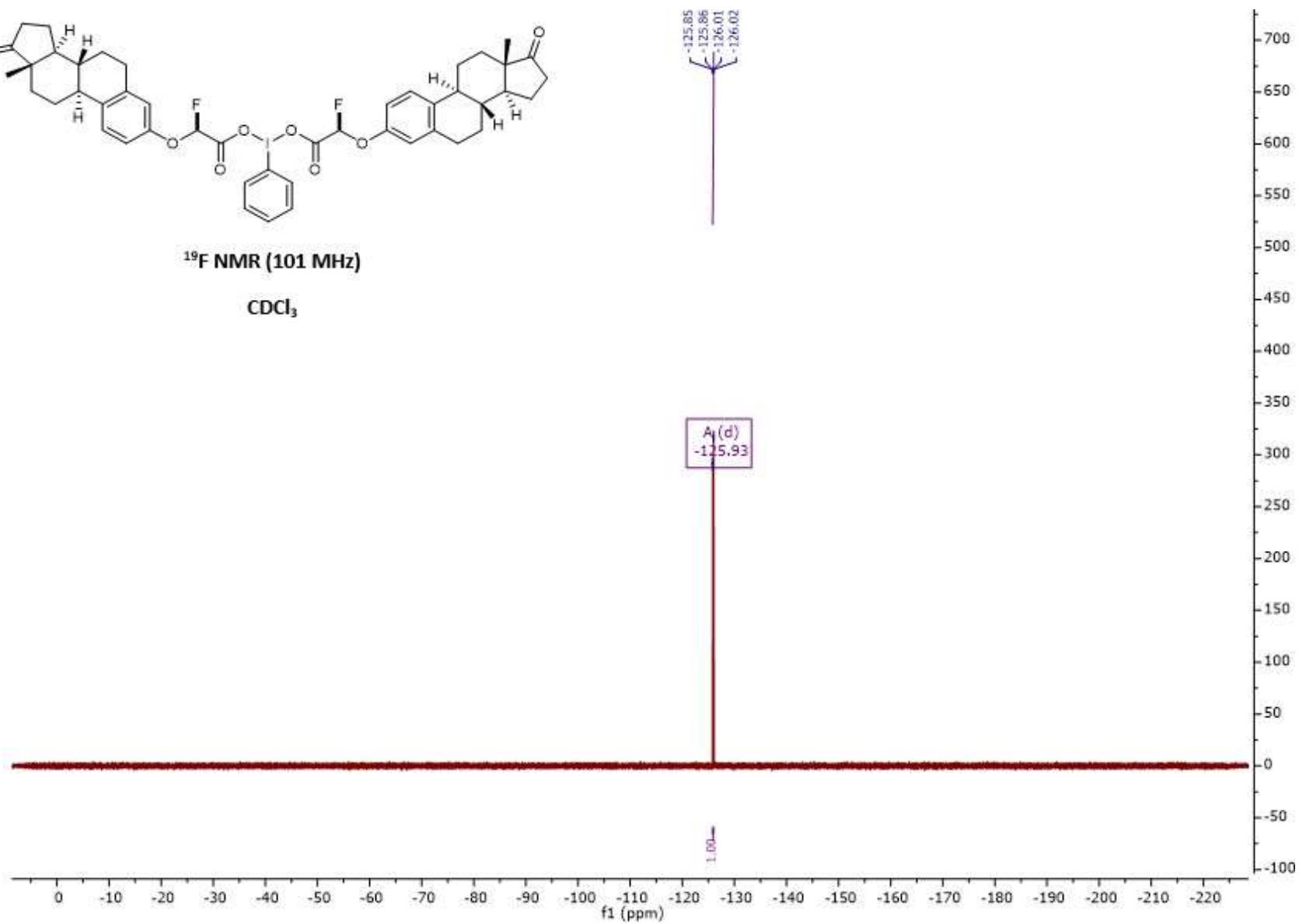
Acetonitrile- d_3

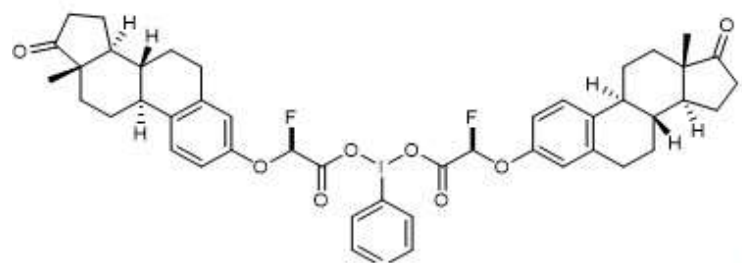




^{19}F NMR (101 MHz)

CDCl_3





^1H NMR (400 MHz)

CDCl_3

