

Gold-Catalyzed Hydrofluorination of Terminal Alkynes Using Potassium Hydrogen Fluoride (KHF₂)

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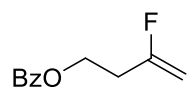
General information

All reactions were carried out in argon, unless otherwise noted. Solvents and all other reagents were purchased and used as received without further purification unless otherwise stated. All substrates (**1a-m**) were either purchased or synthesized according to known procedures.^[1] Unless otherwise noted deionized water was used. Reactions were monitored by TLC on pre-coated plates (Silicycle silica gel 60 Å F254 230-240 mesh) and products were visualized under 254 nm UV light followed by staining with KMnO₄ when appropriate. Purifications by flash column chromatography were carried out on silica gel (Silicycle silica gel 60 Å F254). ¹H and ¹⁹F Nuclear Magnetic Resonance (NMR) spectra were recorded on an Agilent DD2 500 spectrometer at 298 K. Chemical shifts for ¹H spectra are reported on the δ scale in parts per million and were referenced to residual solvent references or an internal TMS reference. For ¹⁹F spectra, calibration was performed using a unified scale.^[2] Peaks are assigned as: s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (heptuplet), m (multiplet) and br. s (broad signal). NMR yields were determined by ¹⁹F NMR analysis, using 2-fluoro-4-nitrotoluene as the internal standard.

Gold-catalyzed hydrofluorination reaction (General procedure)

In a 13 mL PTFE conical tube with screw cap (SPI Supplies Brand), potassium hydrogenfluoride (2 equiv.) and [Au(IPr)(OH)] (1 mol%) were added on a solution of alkyne (1 equiv.) in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP, 0.1 M) Then, MsOH (20 mol%) was added. The reaction was stirred at 60 °C for 18 hours and was then quenched with saturated aq. NaHCO₃. The reaction mixture was extracted with Et₂O (3x). Combined organic layers were washed with brine (1x), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The desired monofluoroalkene was isolated after purification by flash column chromatography.

Gold-catalyzed hydrofluorination reaction (Scope)

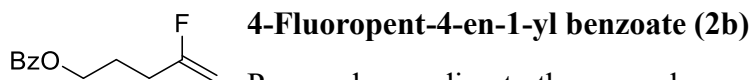


3-Fluorobut-3-en-yl benzoate (2a)

Prepared according to the general procedure on a 0.394 mmol scale of **1a**. The desired product (64.5 mg, 0.332 mmol, 84%) was isolated as a colorless oil after purification by flash column chromatography (4% AcOEt/hexanes). Spectroscopic data are in accordance with the literature.^[1]

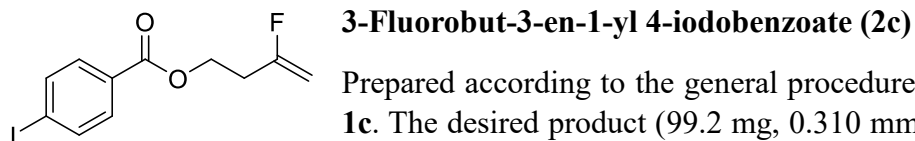
¹H NMR (500 MHz, CDCl₃) δ (ppm) = 8.08-8.00 (m, 2H), 7.61-7.52 (m, 1H), 7.47-7.40 (m, 2H), 4.66 (dd, *J* = 17.3, 3.0 Hz, 1H), 4.48 (t, *J* = 6.5 Hz, 2H), 4.39 (ddt, *J* = 49.6, 3.0, 0.8 Hz, 1H), 2.68

(dtd, $J = 16.2, 6.5, 0.8$ Hz, 2H); ^{19}F NMR (470 MHz, CDCl_3) δ (ppm) = -96,4 (dtd, $J = 49.8, 16.6, 16.6$ Hz, 1F).



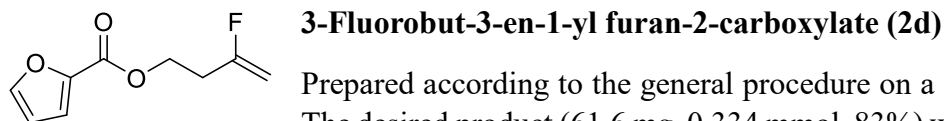
Prepared according to the general procedure on a 0.405 mmol scale of **1b**. The desired product (66.1 mg, 0.317 mmol, 78%) was isolated as a colorless oil after purification by two flash column chromatography (25% DCM/hexanes and 3% AcOEt/hexanes). Spectroscopic data are in accordance with the literature.^[1]

^1H NMR (500 MHz, CDCl_3) δ (ppm) = 8.10-8.01 (m, 2H), 7.60-7.53 (m, 1H), 7.48-7.41 (m, 2H), 4.57 (dd, $J = 17.4, 2.8$ Hz, 1H), 4.38 (t, $J = 6.4$ Hz, 2H), 4.29 (dtd, $J = 50.0, 2.9, 0.8$ Hz, 1H), 2.38 (dtd, $J = 16.0, 7.5, 0.8$ Hz, 2H), 2.01 (m, 2H); ^{19}F NMR (470 MHz, CDCl_3) δ (ppm) = -95,5 (dtd, $J = 49.8, 16.6, 16.6$ Hz, 1F).



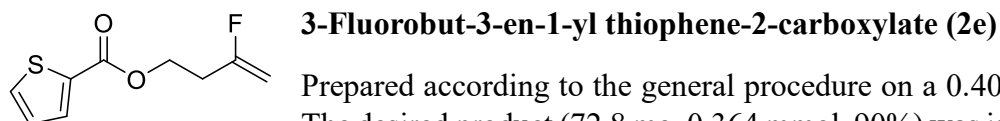
Prepared according to the general procedure on a 0.401 mmol scale of **1c**. The desired product (99.2 mg, 0.310 mmol, 77%) was isolated as a colorless oil after purification by flash column chromatography (15% DCM/hexanes). Spectroscopic data are in accordance with the literature.^[1]

^1H NMR (500 MHz, CDCl_3) δ (ppm) = 7.82-7.78 (m, 2H), 7.76-7.71 (m, 2H), 4.65 (dd, $J = 17.2, 3.0$ Hz, 1H), 4.47 (t, $J = 6.4$ Hz, 2H), 4.37 (dtd, $J = 49.6, 3.0, 0.8$ Hz, 1H), 2.67 (dtd, $J = 16.3, 6.5, 0.7$ Hz, 2H); ^{19}F NMR (470 MHz, CDCl_3) δ (ppm) = -96,5 (dtd, $J = 49.6, 16.6, 16.4$ Hz, 1F).



Prepared according to the general procedure on a 0.404 mmol scale of **1d**. The desired product (61.6 mg, 0.334 mmol, 83%) was isolated as a colorless oil after purification by two flash column chromatography (10% EtOAc/hexanes and 6% EtOAc/hexanes). Spectroscopic data are in accordance with the literature.^[1]

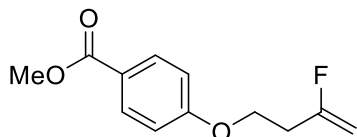
^1H NMR (500 MHz, CDCl_3) δ (ppm) = 7.59 (dd, $J = 1.7, 0.9$ Hz, 1H), 7.19 (dd, $J = 3.5, 0.9$ Hz, 1H), 6.51 (dd, $J = 3.5, 1.7$ Hz, 1H), 4.65 (dd, $J = 17.3, 3.0$ Hz, 1H), 4.46 (t, $J = 6.6$ Hz, 2H), 4.37 (dtd, $J = 49.6, 3.0, 0.8$ Hz, 1H), 2.66 (dtd, $J = 16.2, 6.6, 0.8$ Hz, 2H); ^{19}F NMR (470 MHz, CDCl_3) δ (ppm) = -96,4 (dtd, $J = 49.7, 16.6, 16.6$ Hz, 1F).



Prepared according to the general procedure on a 0.404 mmol scale of **1e**. The desired product (72.8 mg, 0.364 mmol, 90%) was isolated as a colorless

oil after purification by flash column chromatography (5% AcOEt/hexanes). Spectroscopic data are in accordance with the literature.^[1]

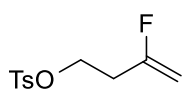
¹H NMR (500 MHz, CDCl₃) δ (ppm) = 7.81 (dd, J = 3.7, 1.3 Hz, 1H), 7.56 (dd, J = 4.9, 1.3 Hz, 1H), 7.10 (dd, J = 5.0, 3.8 Hz, 1H), 4.65 (dd, J = 17.3, 3.0 Hz, 1H), 4.45 (t, J = 6.5 Hz, 2H), 4.38 (ddt, J = 49.7, 3.0, 0.7 Hz, 1H), 2.65 (dtd, J = 16.3, 6.5, 0.8 Hz, 2H); **¹⁹F NMR (470 MHz, CDCl₃)** δ (ppm) = -96,4 (ddt, J = 49.7, 16.6, 16.4 Hz, 1F).



Methyl 4-((3-fluorobut-3-en-1-yl)oxy)benzoate (**2f**)

Prepared according to the general procedure on a 0.406 mmol scale of **1f**. The desired product (74.1 mg, 0.330 mmol, 81%) was isolated as a colorless oil after purification by flash column chromatography (8% AcOEt/hexanes). Spectroscopic data are in accordance with the literature.^[1]

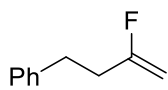
¹H NMR (500 MHz, CDCl₃) δ (ppm) = 8.01-7.97 (m, 2H), 6.94-6.90 (m, 2H), 4.67 (dd, J = 17.4, 3.0 Hz, 1H), 4.39 (ddt, J = 49.9, 3.0, 0.8 Hz, 1H), 4.18 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 2.71 (dtd, J = 16.3, 6.6, 0.8 Hz, 2H); **¹⁹F NMR (470 MHz, CDCl₃)** δ (ppm) = -96,6 (ddt, J = 49.8, 16.6, 16.6 Hz, 1F).



3-Fluorobut-3-en-1-yl 4-methylbenzenesulfonate (**2g**)

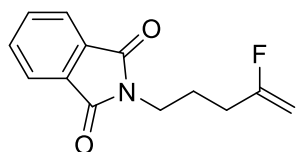
Prepared according to the general procedure on a 0.405 mmol scale of **1g**. The desired product (96.3 mg, 0.394 mmol, 97%) was isolated as a colorless oil after purification by flash column chromatography (10% AcOEt/hexanes). Spectroscopic data are in accordance with the literature.^[1]

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 7.82-7.78 (m, 2H), 7.39-7.34 (m, 2H), 4.62 (dd, J = 17.2, 3.1 Hz, 1H), 4.32 (dd, J = 49.4, 3.0 Hz, 1H), 4.17 (t, J = 6.5 Hz, 2H), 2.56 (dtd, J = 16.2, 6.5, 0.9 Hz, 2H), 2.47 (s, 3H); **¹⁹F NMR (470 MHz, CDCl₃)** δ (ppm) = -97.8 (ddt, J = 49.7, 16.6, 16.5 Hz, 1F).



(3-Fluorobut-3-en-1-yl)benzene (**2h**)

Prepared according to the general procedure on a 0.395 mmol scale of **1h**. After the quench, 2-fluoro-4-nitrotoluene (41.7 mg, 0.269 mmol) was added and the ¹⁹F NMR yield was determined (19%). The product (**2h**) is a known compound.^[1]

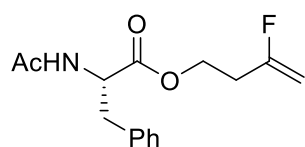


2-(4-Fluoro-4-en-1-yl)isoindoline-1,3-dione (**2i**)

Prepared according to the general procedure on a 0.400 mmol scale of **1i**. The desired product (72.5 mg, 0.311 mmol, 78%) was isolated as a

colorless oil after purification by two flash column chromatography (50% DCM/hexanes and 15% AcOEt/hexanes). Spectroscopic data are in accordance with the literature.^[1]

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 7.89-7.79 (m, 2H), 7.79-7.67 (m, 2H), 4.54 (dd, J = 17.6, 2.9 Hz, 1H), 4.30 (ddt, J = 50.2, 2.9, 1.0 Hz, 1H), 3.75 (t, J = 7.1 Hz, 2H), 2.27 (m, 2H), 1.92 (m, 2H); **¹⁹F NMR (470 MHz, CDCl₃)** δ (ppm) = -95.1 (ddt, J = 49.0, 16.0, 15.9 Hz, 1F).



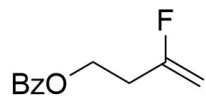
3-Fluorobut-3-en-1-yl acetyl L-phenylalaninate (2j)

Prepared according to the general procedure on a 0.400 mmol scale of **2j**. The desired product (67.2 mg, 0.241 mmol, 60%) was isolated as a colorless oil after purification by two flash column chromatography (50% AcOEt/hexanes and 30% acetone/hexanes). Spectroscopic data are in accordance with the literature.^[1]

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 7.32 – 7.23 (m, 3H), 7.13 – 7.09 (m, 2H), 5.93 (d, J = 5.5 Hz, 1H), 4.88 (dt, J = 7.8, 6.0 Hz, 1H), 4.62 (dd, J = 17.3, 3.0 Hz, 1H), 4.36 – 4.21 (m, 3H), 3.17 – 3.05 (m, 2H), 2.50 (dt, J = 15.9, 6.5 Hz, 2H), 1.98 (s, 3H); **¹⁹F NMR (470 MHz, CDCl₃)** δ (ppm) = -96.9 (dq, J = 49.7, 16.6 Hz, 1F)

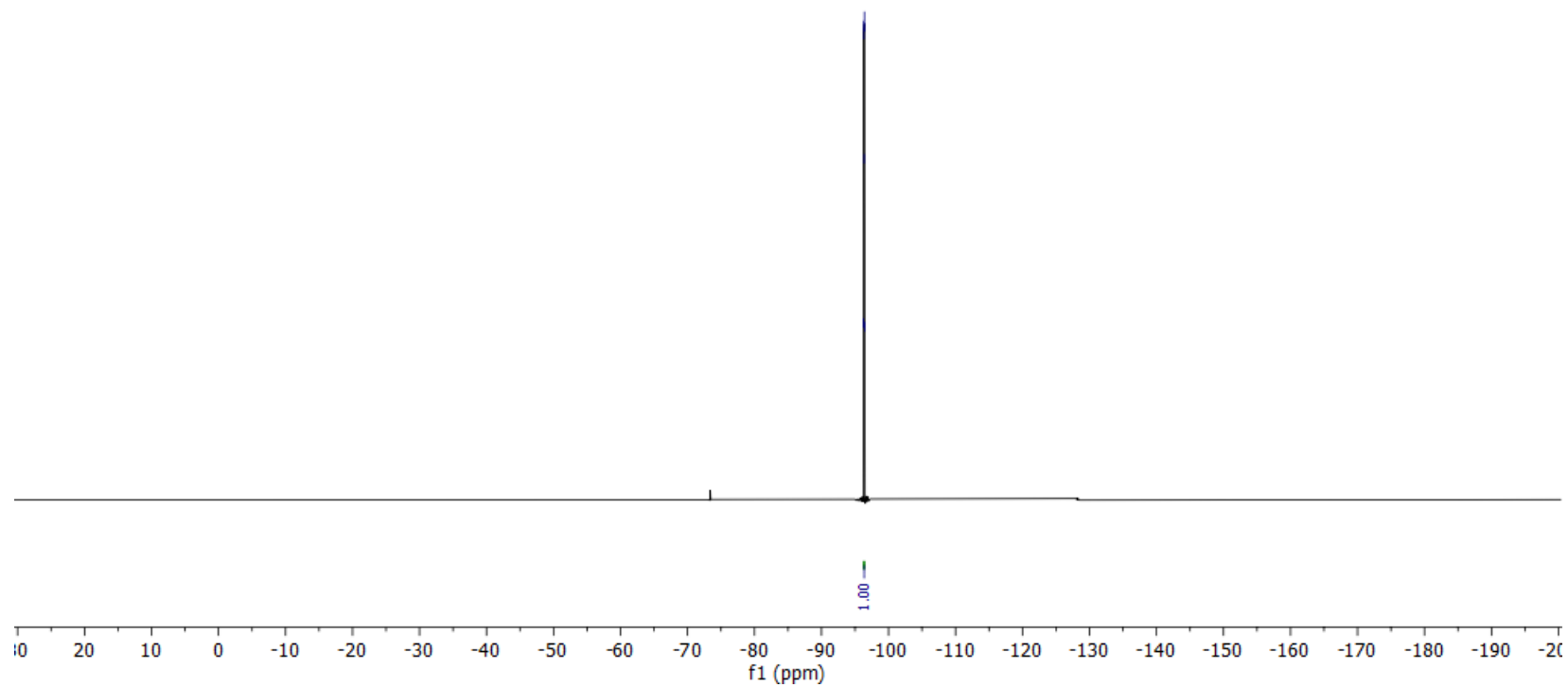
References

- [1] R. Gauthier, N. V. Tzouras, Z. Zhang, S. Bédard, M. Saab, L. Falivene, K. Van Hecke, L. Cavallo, S. P. Nolan, J.-F. Paquin, *Chem. Eur. J.* **2022**, *28*, e202103886.
- [2] R. K. Harris, E. D. Becker, S. M. Cabral De Menezes, R. Goodfellow, P. Granger, *Pure Appl. Chem.* **2001**, *73*, 1795.

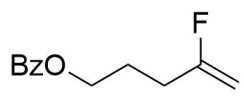


2a ^{19}F NMR (CDCl_3 , 470 MHz)

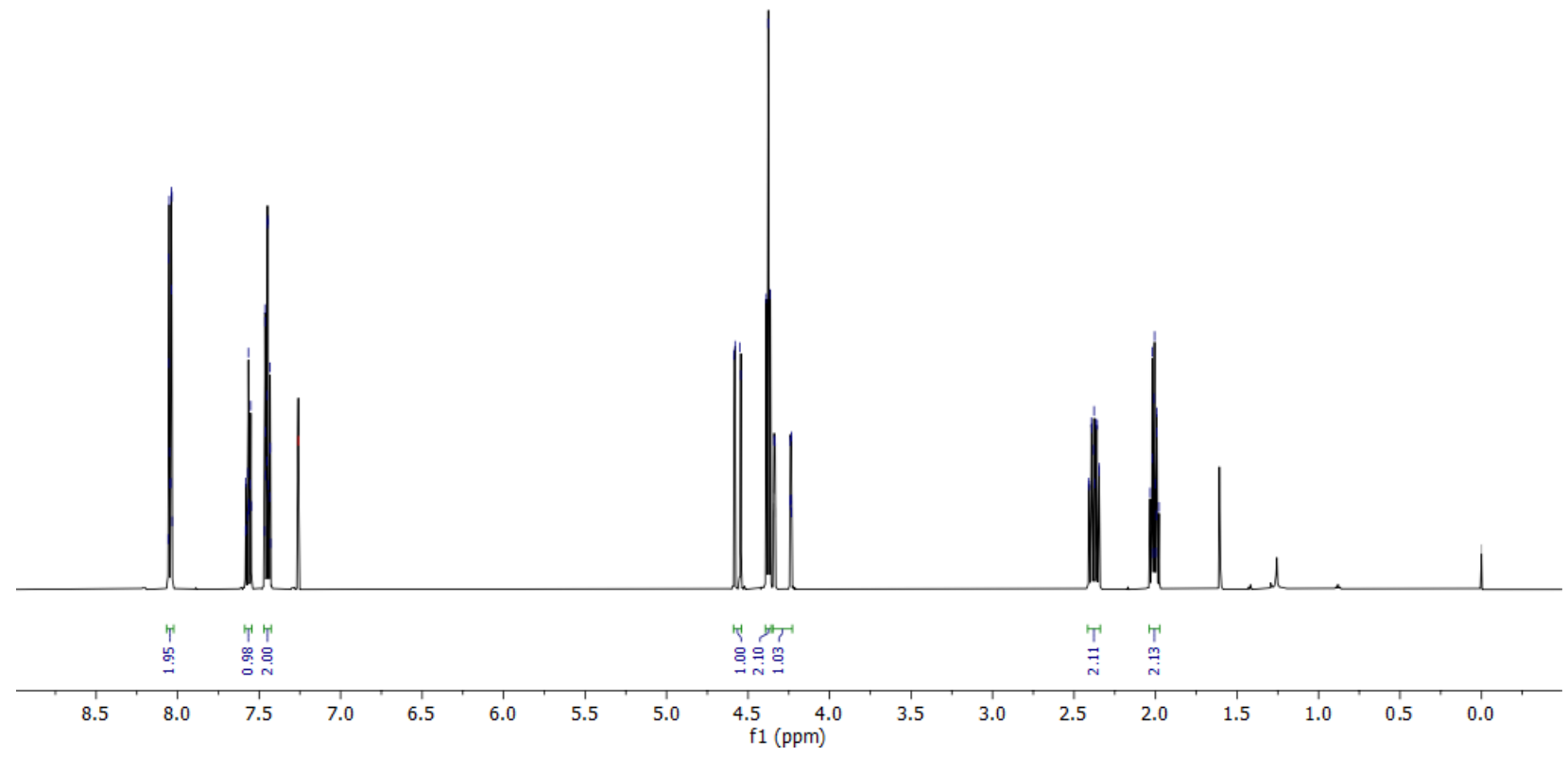
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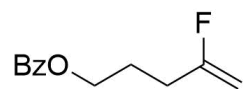


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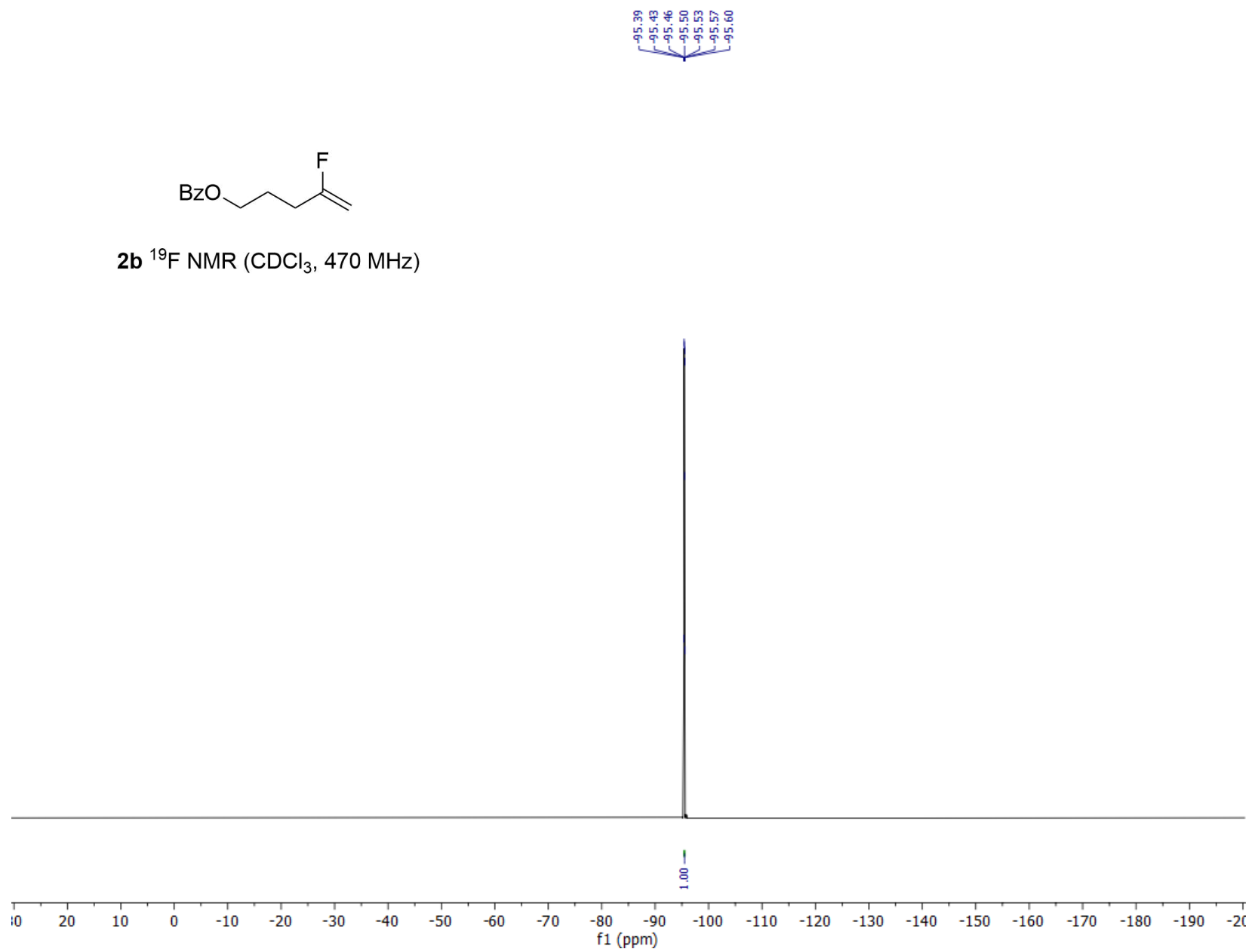


2b ¹H NMR (CDCl₃, 500 MHz)

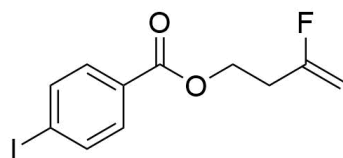




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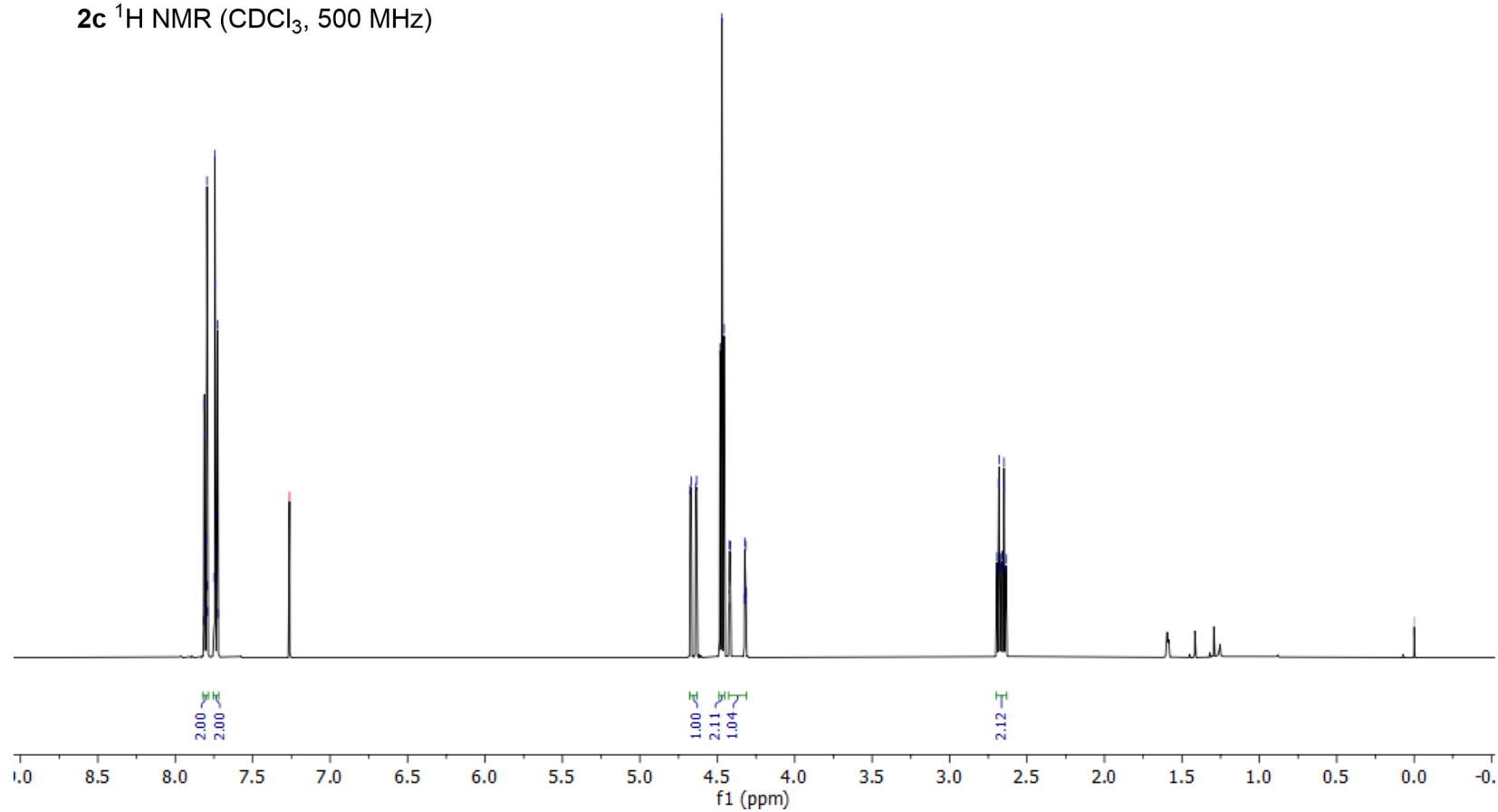
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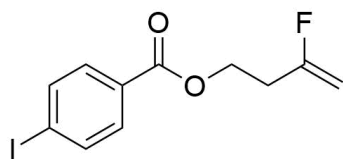


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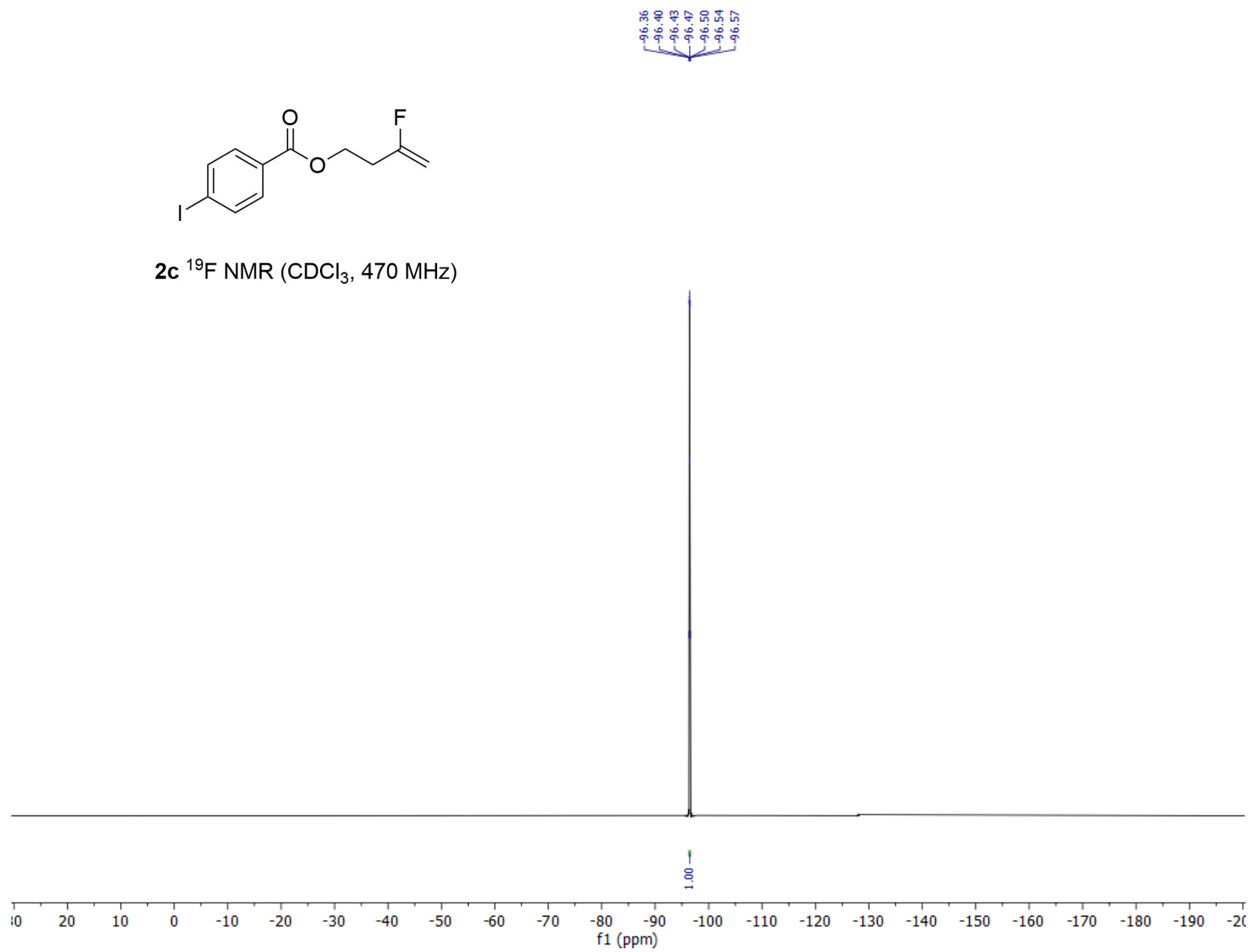
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2c ^{19}F NMR (CDCl_3 , 470 MHz)

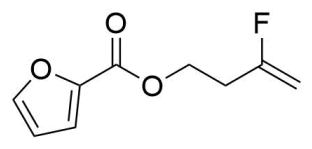


S11

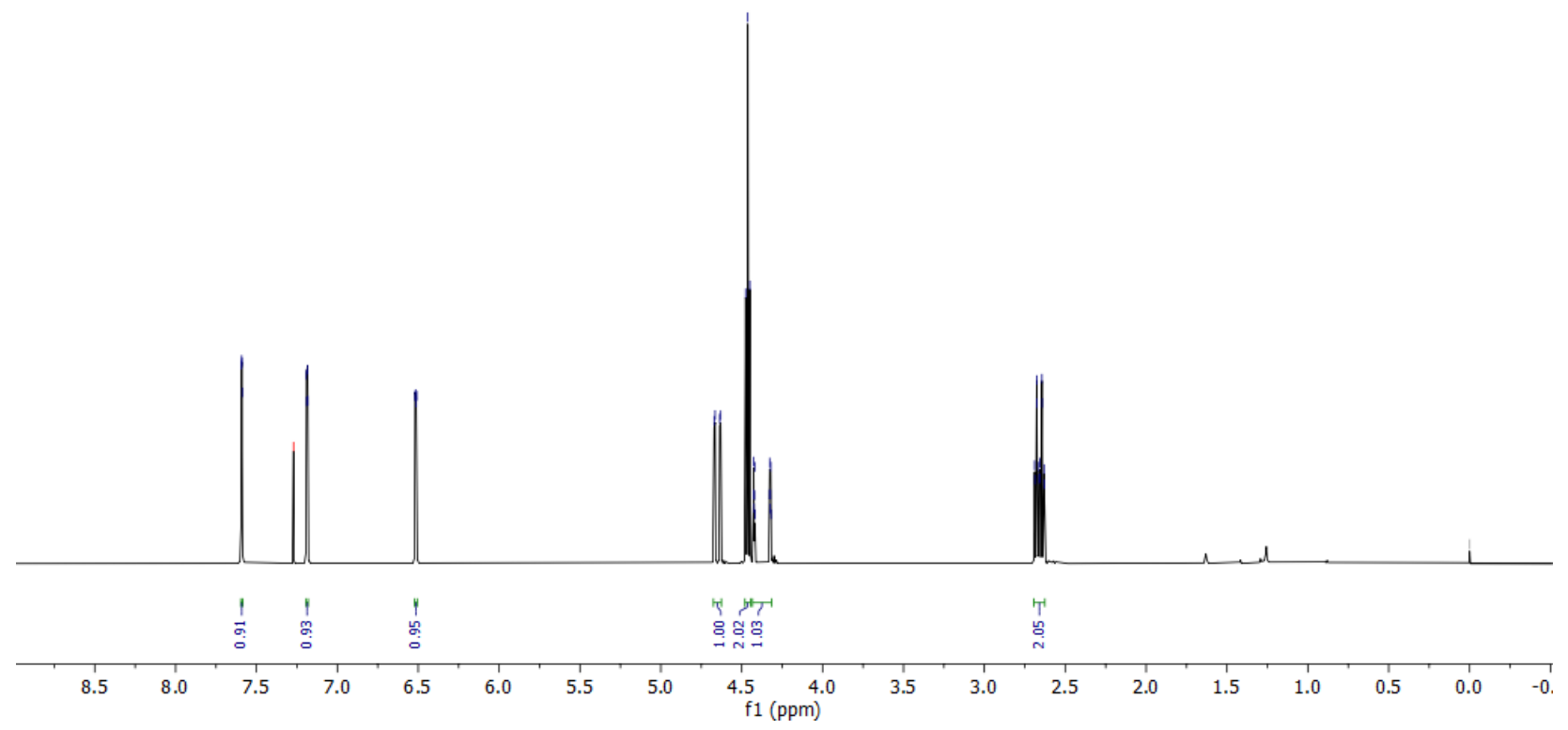
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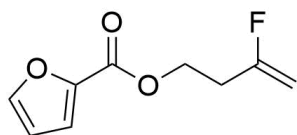
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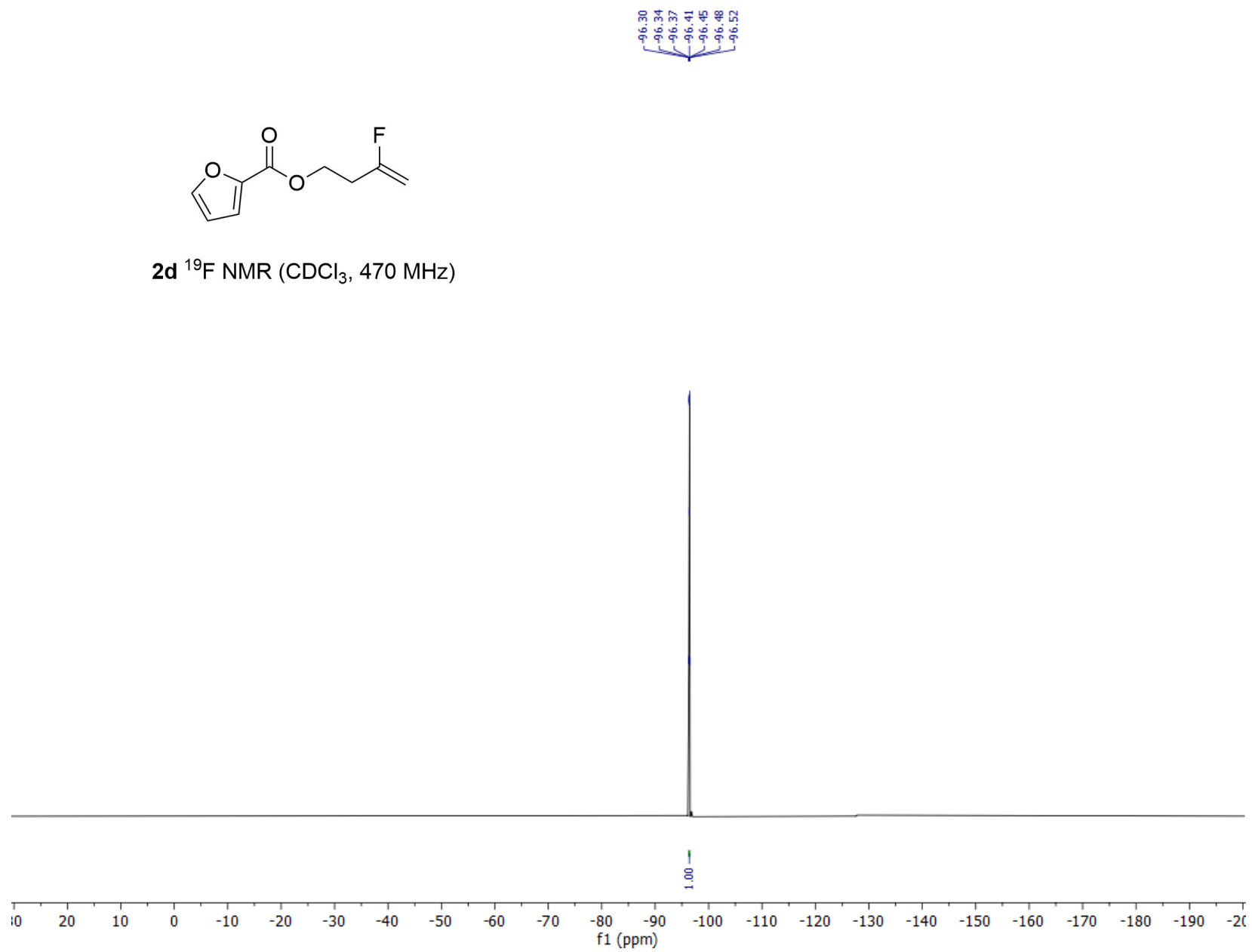


2d ¹H NMR (CDCl₃, 500 MHz)





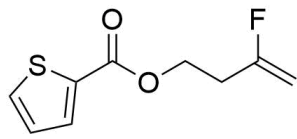
2d ^{19}F NMR (CDCl_3 , 470 MHz)



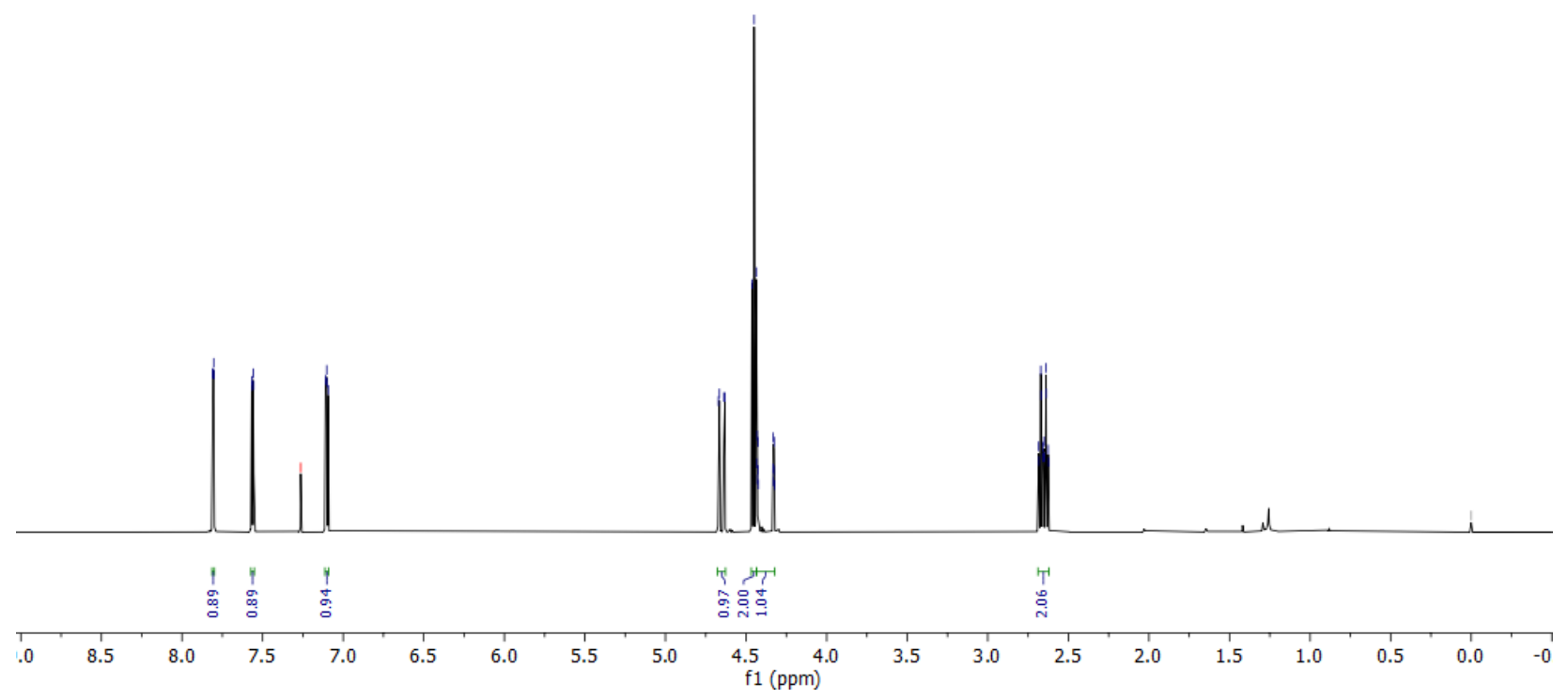
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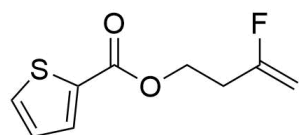
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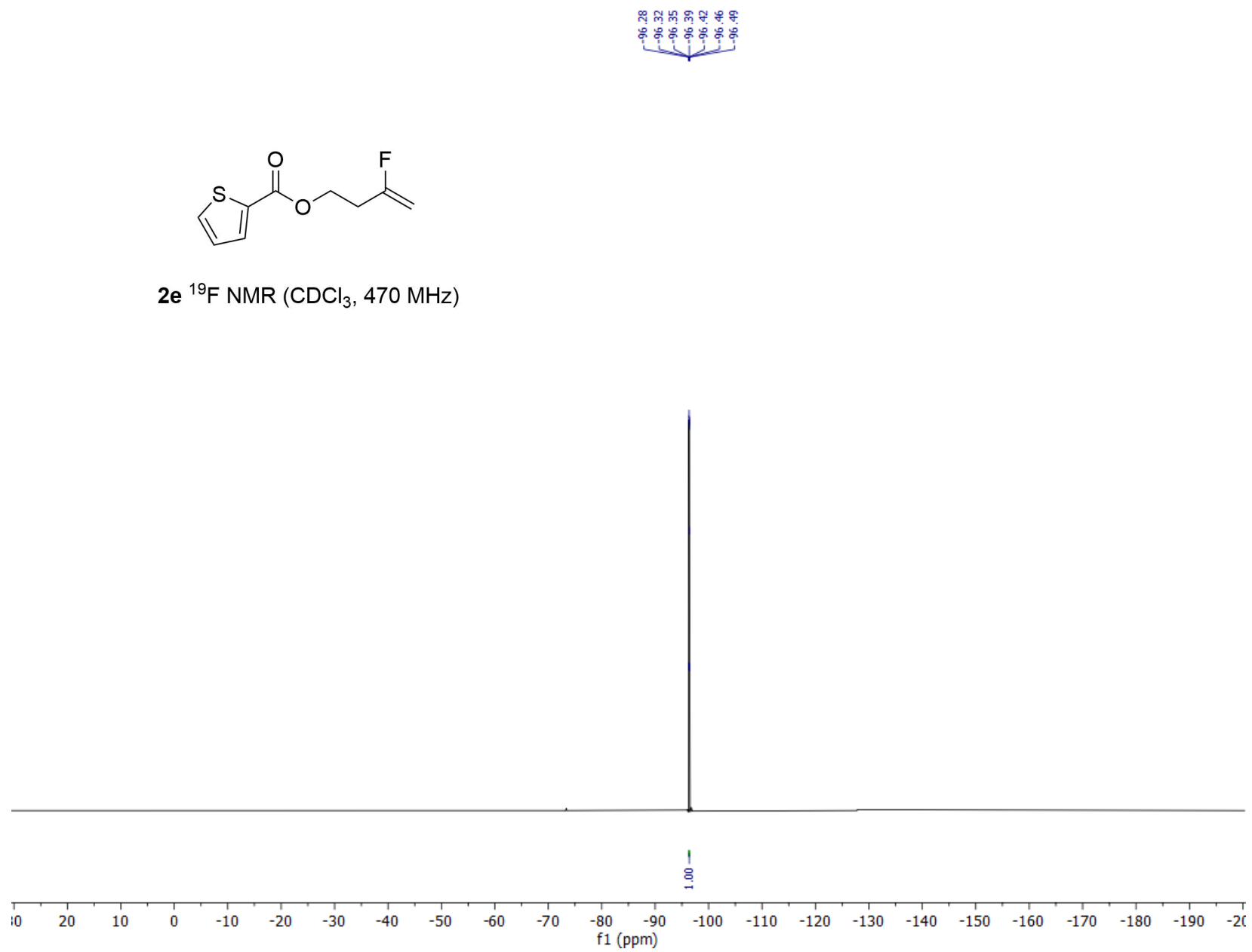


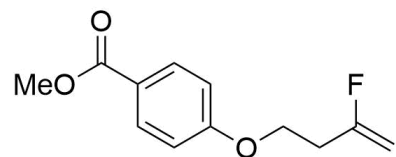
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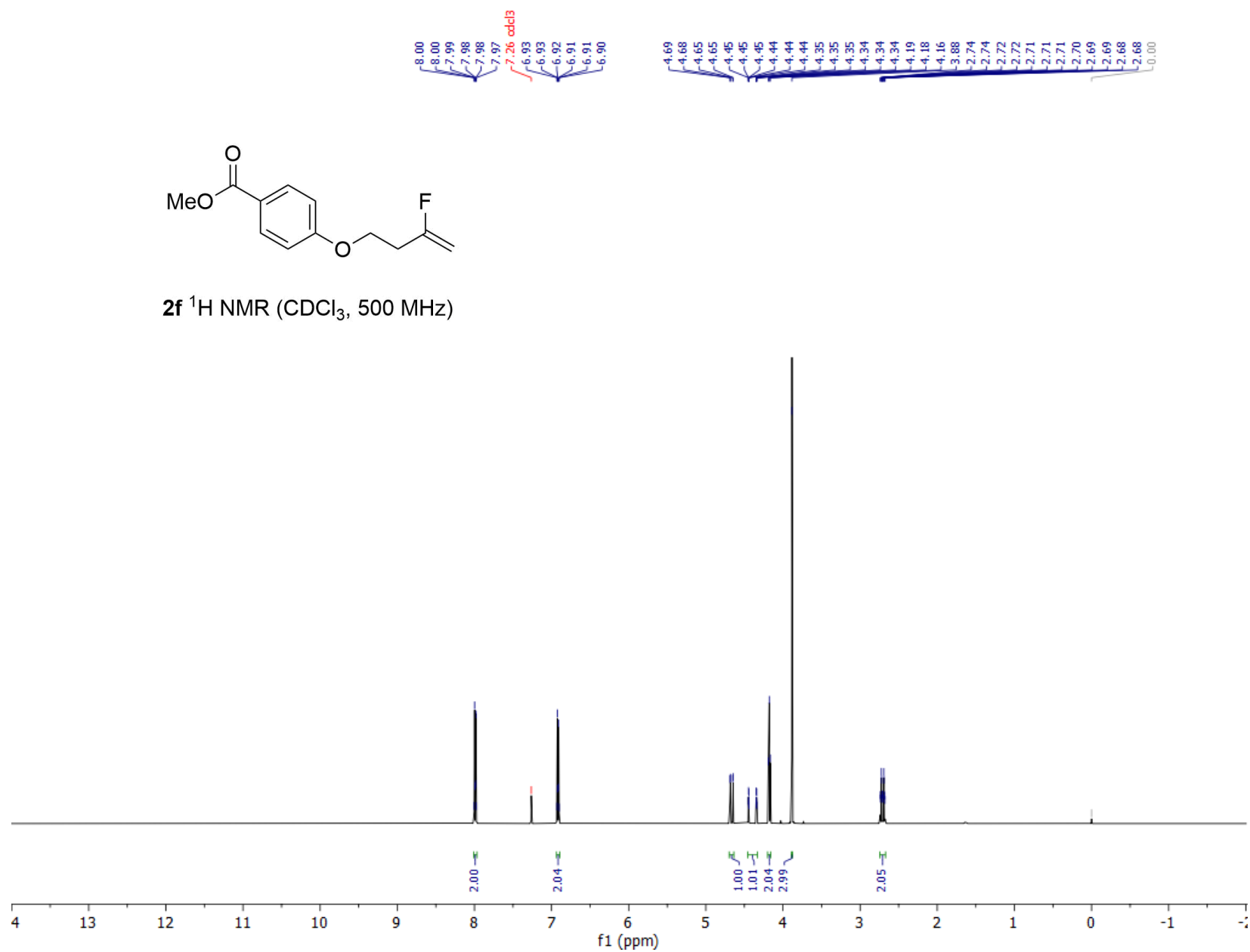


2e ^{19}F NMR (CDCl_3 , 470 MHz)

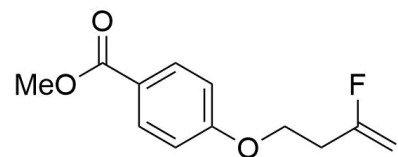




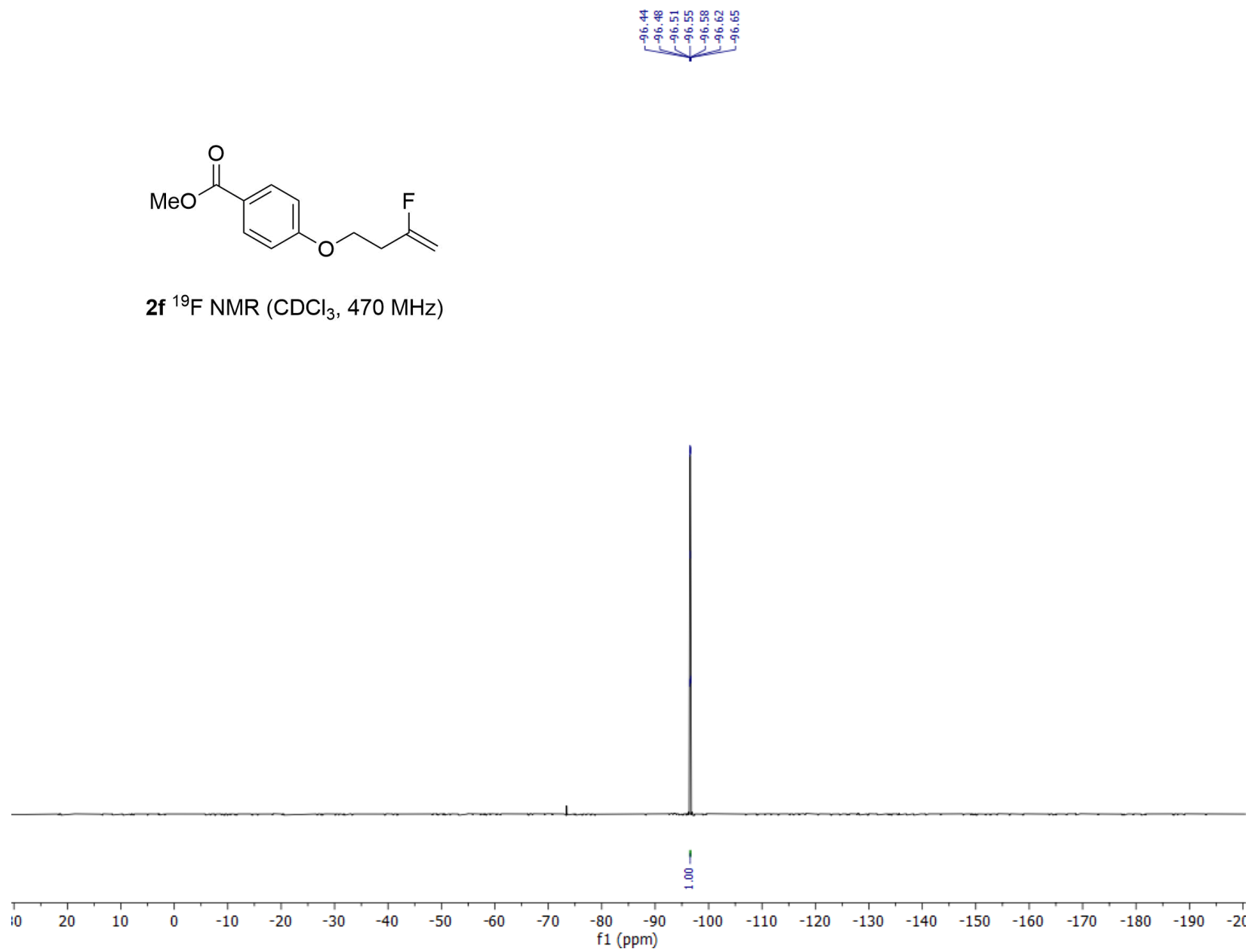
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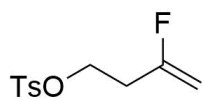


S16

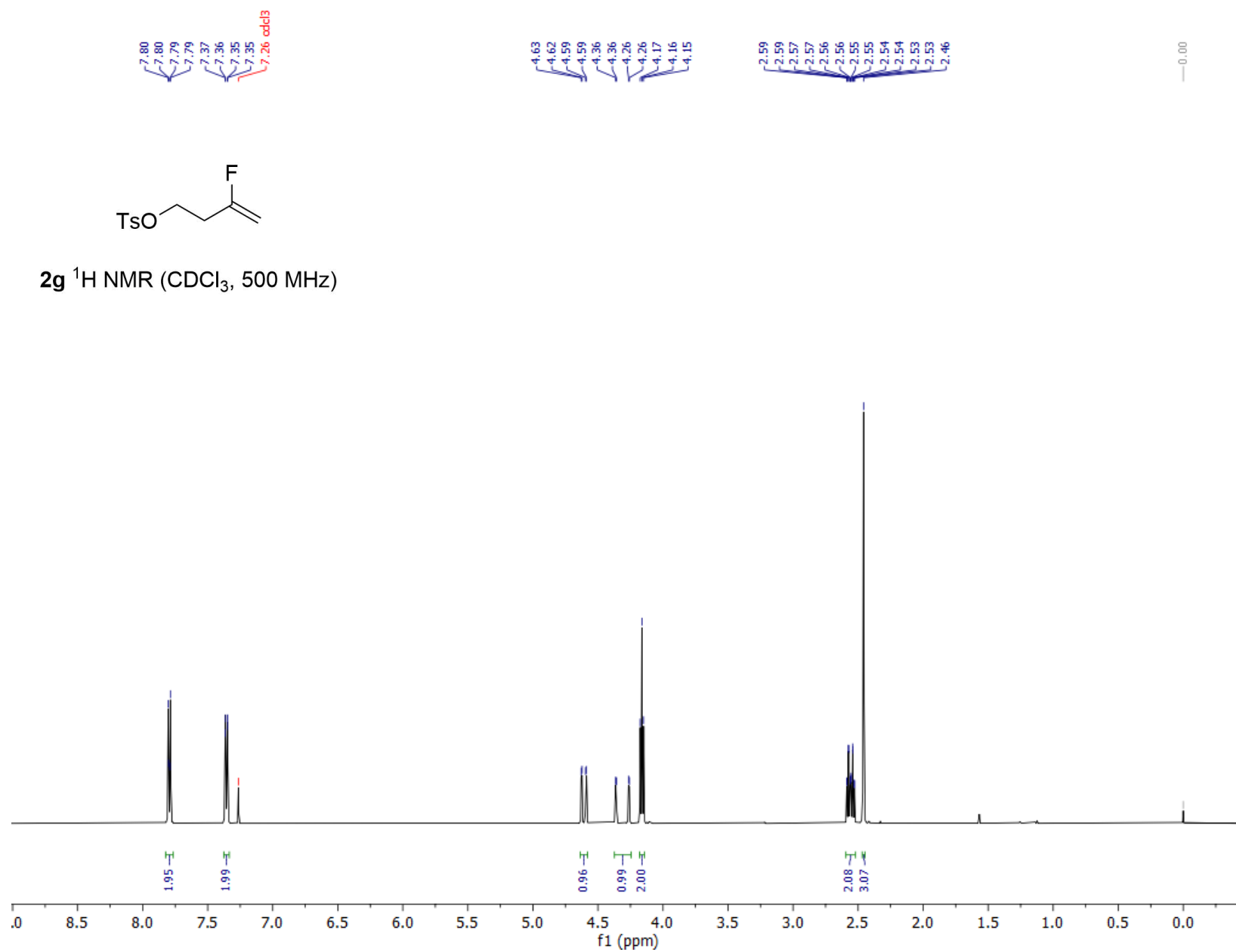


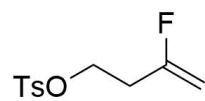
2f ^{19}F NMR (CDCl_3 , 470 MHz)



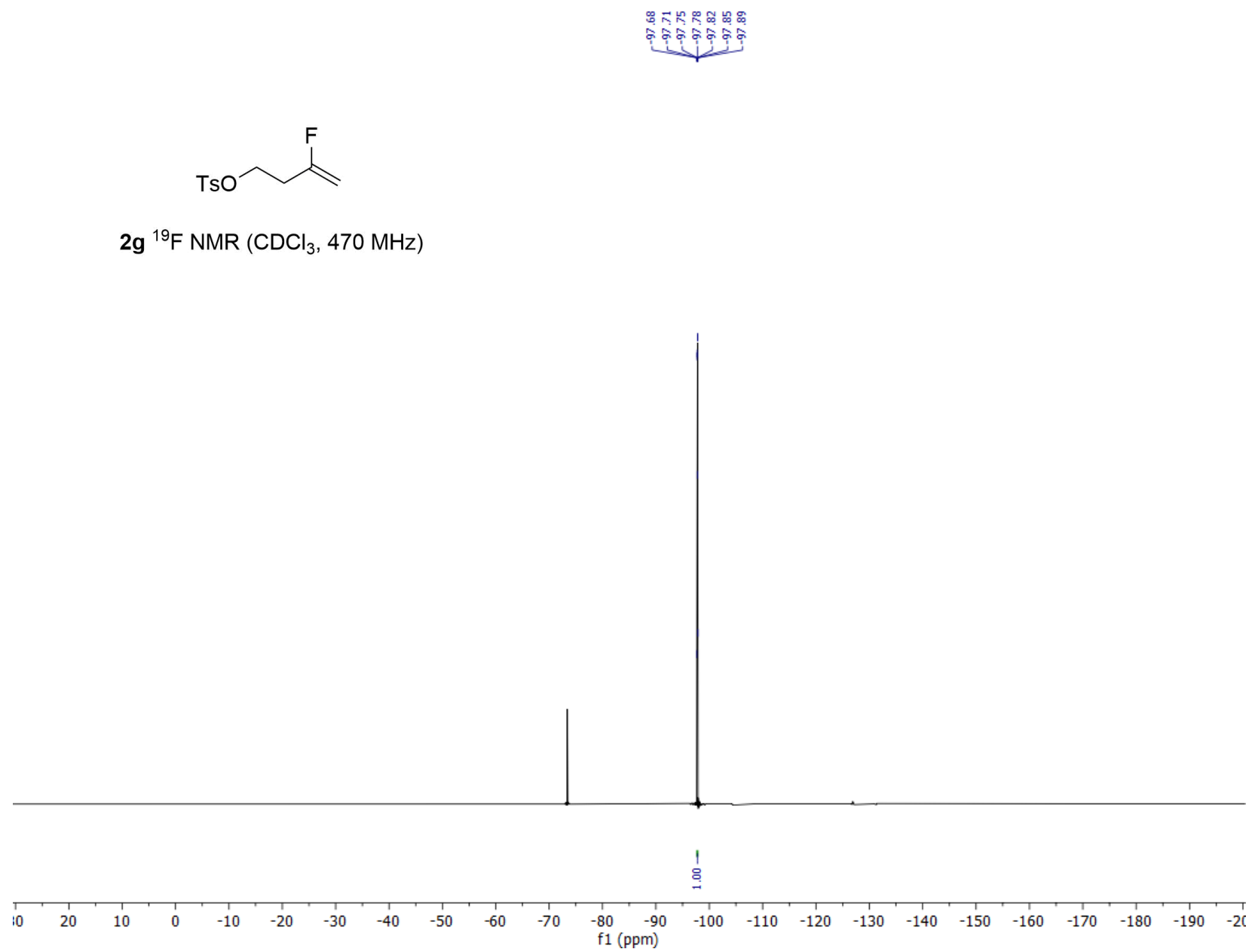


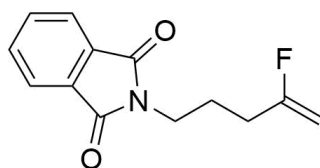
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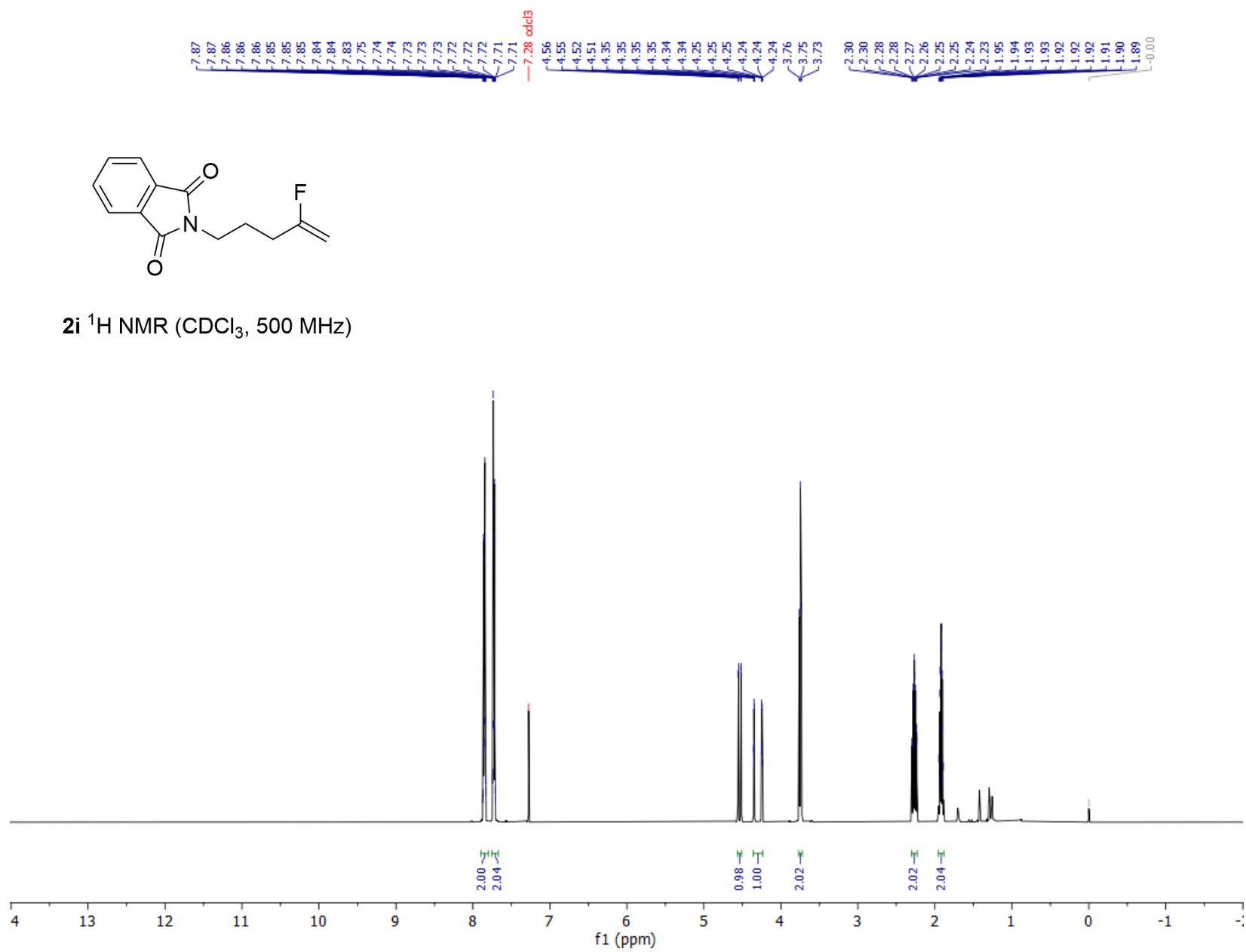


2g ^{19}F NMR (CDCl_3 , 470 MHz)

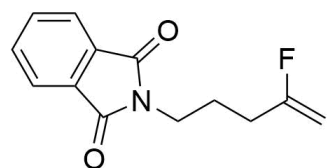




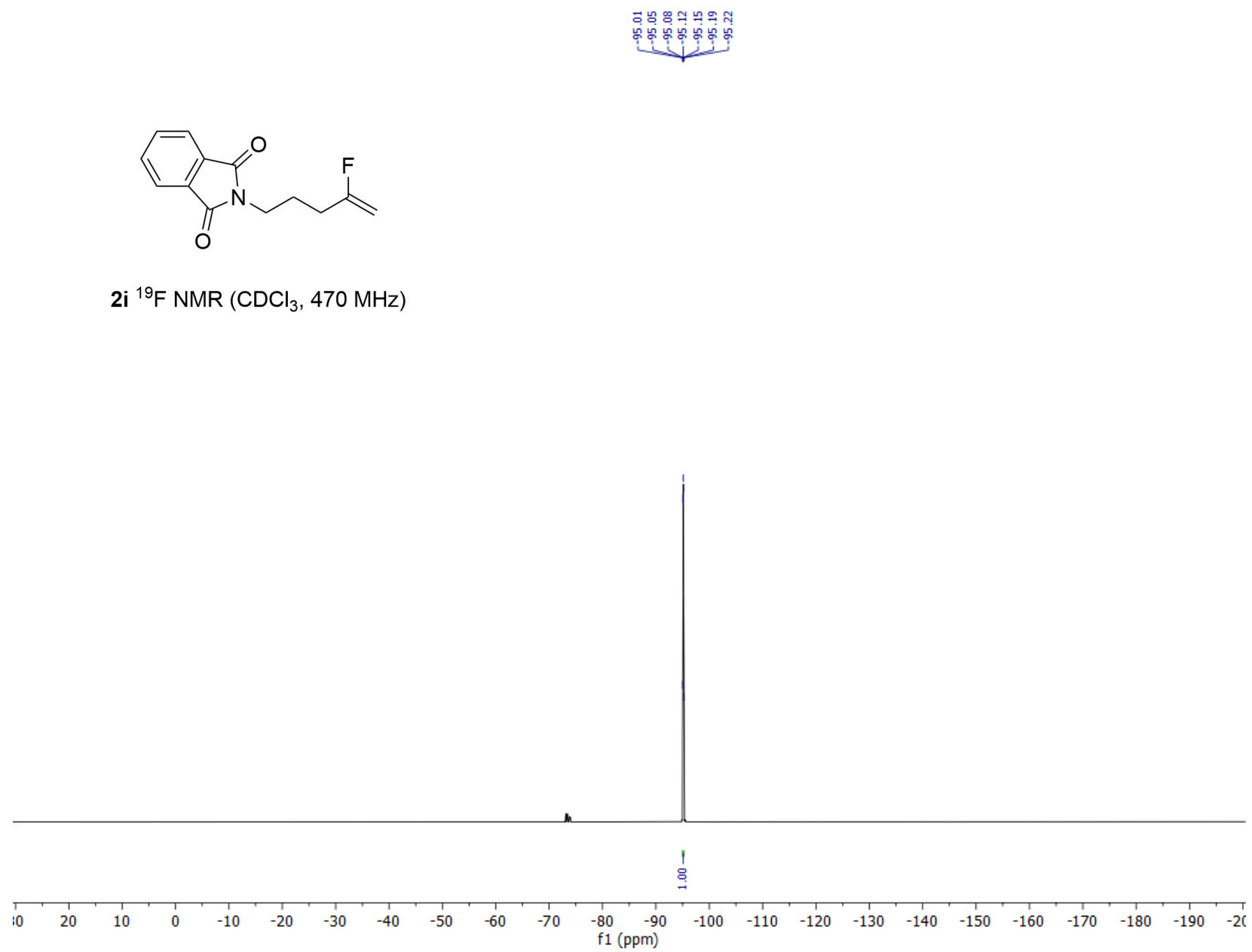
2i ^1H NMR (CDCl_3 , 500 MHz)



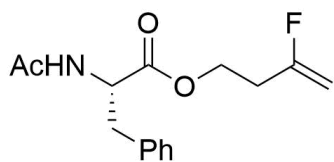
S20



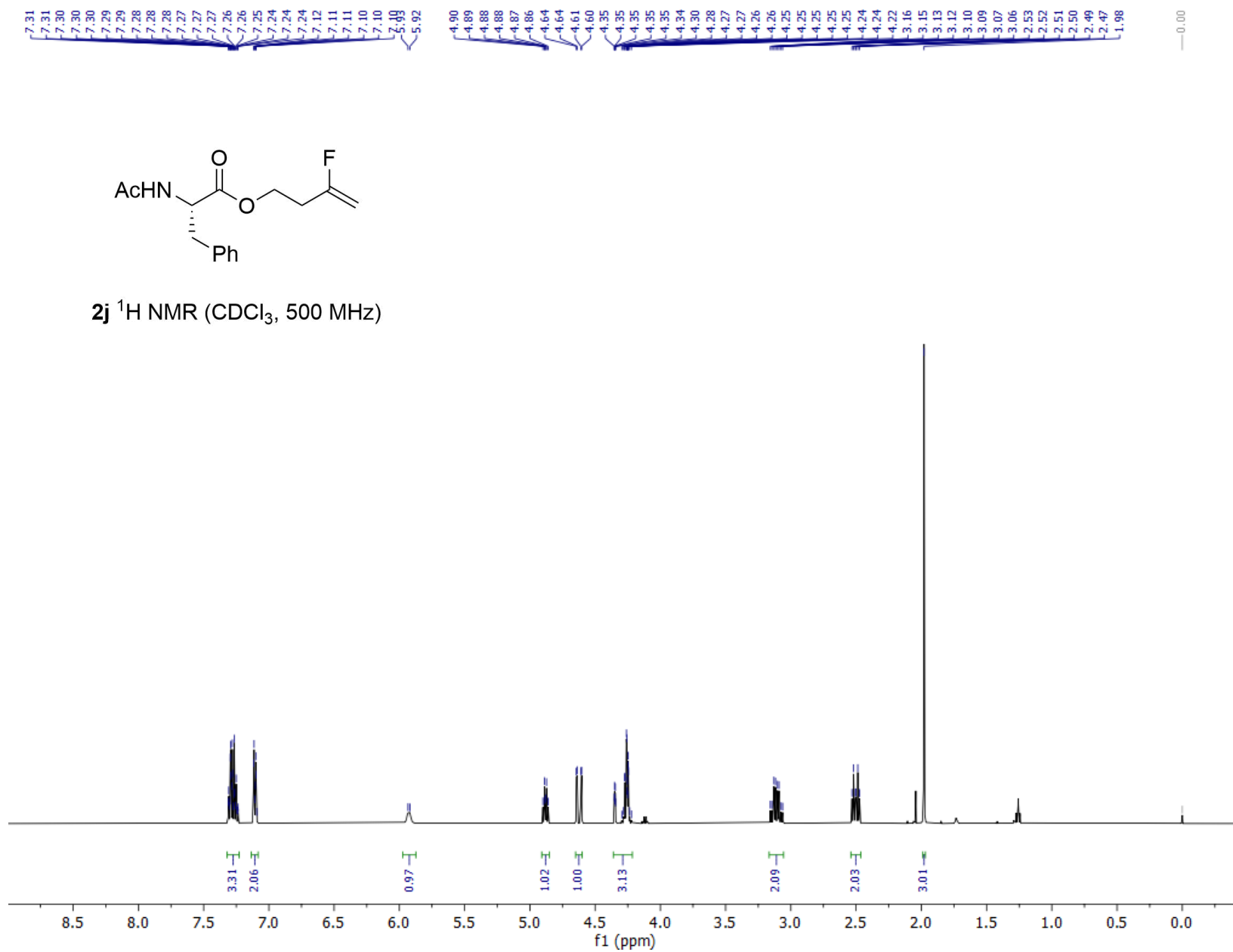
2i ^{19}F NMR (CDCl_3 , 470 MHz)



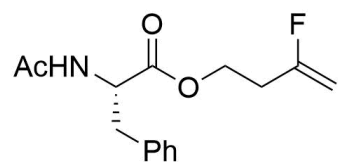
S21



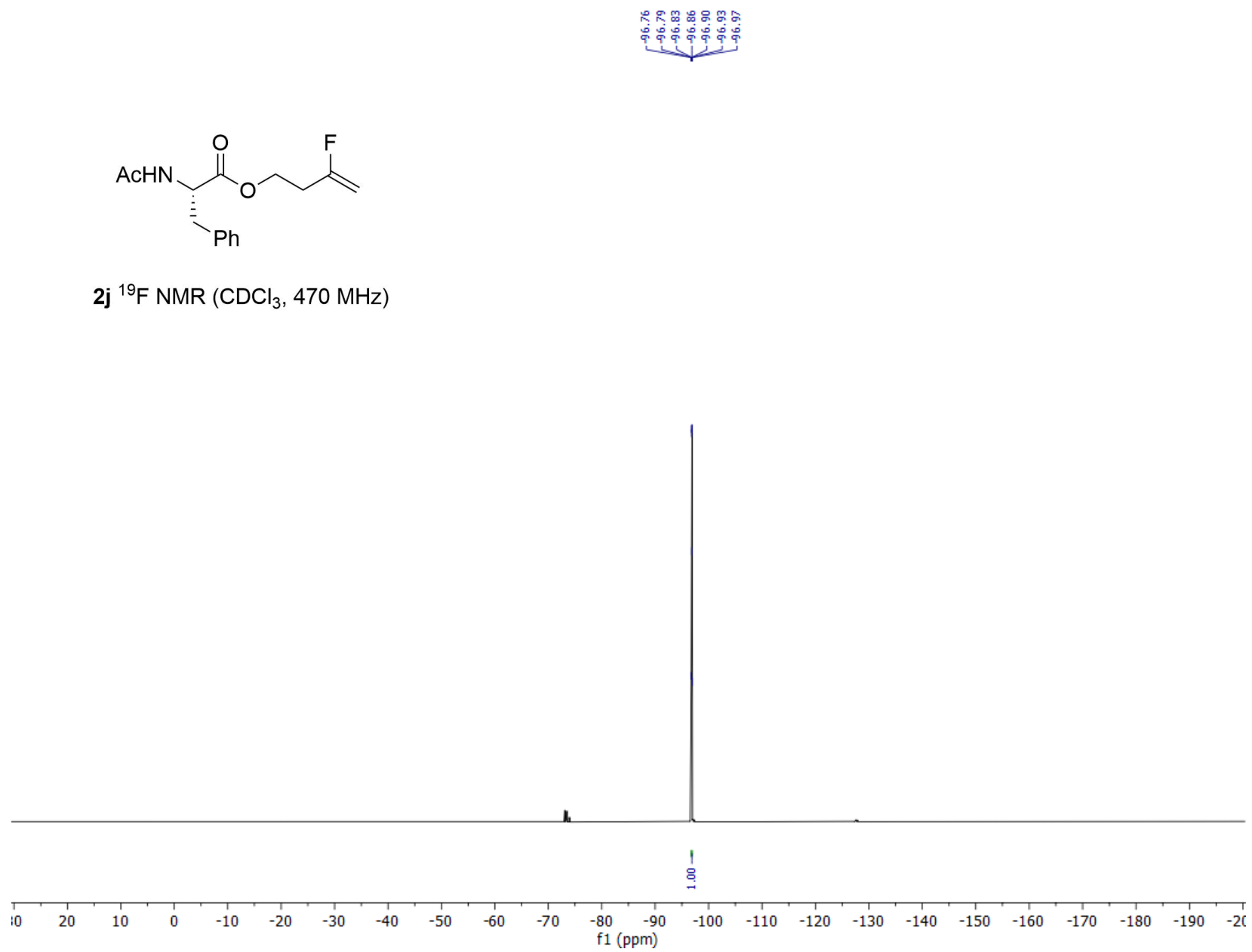
2j ^1H NMR (CDCl_3 , 500 MHz)



S22



2j ^{19}F NMR (CDCl_3 , 470 MHz)



S23