

Gold Redox Catalysis for Cyclization/Arylation of Allylic Oximes: Synthesis of Isoxazoline Derivatives

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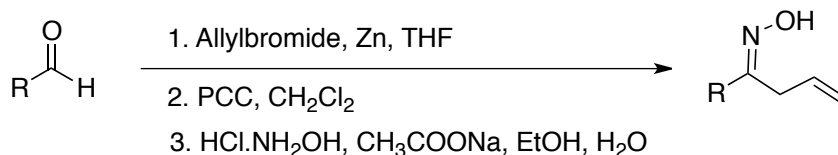
I. General Methods and Materials	S2
II. X-Ray Crystallographic Data	S7
III. Compounds Characterization	S9
IV. NMR Spectra Data	S20

I. General Methods and Materials

All commercial reagents and solvents were obtained from the commercial provider and used without further purification. Analytical thin layer chromatography was performed with pre-coated, glass-baked plates (250 μ) and visualized by fluorescence or charring with potassium permanganate stain. Flash column chromatography was performed on 230 - 430 mesh silica gel. ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on Agilent 400 MHz. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl_3 (δ 7.26 ppm) for ^1H , CDCl_3 (δ 77.0 ppm) for ^{13}C . Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br = broad), coupling constant J (Hz) and integration. HRMS were recorded on Agilent 6540 LC/QTOF spectrometer.

1.1 General Procedure for the synthesis of Allyl-oximes 1a- 1n

They were synthesized according to literature procedure^{1, 2}.



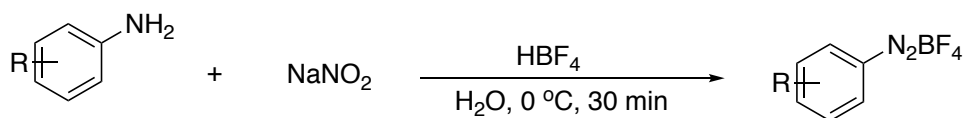
Zinc dust (229 mg, 3.50 mmol) was slowly added to a solution of allylbromide (423 mg, 3.50 mmol) in anhydrous THF (2 mL). The aldehyde (1.00 mmol) was dissolved in anhydrous THF (2 mL) and was added to the stirring solution. The resulting suspension was stirred (sonication was used for a much faster reaction) overnight at room temperature. The reaction was quenched with NH_4Cl (aq.) carefully at 0°C , filtered and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 , filtered and concentrated in vacuo.

The crude homoallylic alcohol product was dissolved in dichloromethane (5 mL) and the solution was stirred at 0°C . Pyridinium chlorochromate (1.75 mL, 3.50 mmol) was added slowly. The resulting suspension was stirred for 1 h at room temperature. The reaction was diluted with H_2O (5 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (1 x 10 mL), dried over MgSO_4 , filtered and concentrated in vacuo. The crude mixture was used in the next step without further purification.

A flask was charged with a solution of hydroxylamine hydrochloride (347 mg, 5.00 mmol) in ethanol (3 mL). Sodium acetate (595 mg, 7.00 mmol) was dissolved in water (3 mL) and the solution was added to the flask. The crude ketone was dissolved in ethanol (3 mL) and added to the solution. The resulting suspension was stirred until the reaction was shown to be complete by TLC (about 6 hrs). The reaction was concentrated in vacuo and extracted with ethyl acetate (3 x 15 mL). The organic layers were dried over MgSO_4 , filtered and concentrated in vacuo. The crude product was purified by column chromatography eluting with hexane: acetate (90:10).

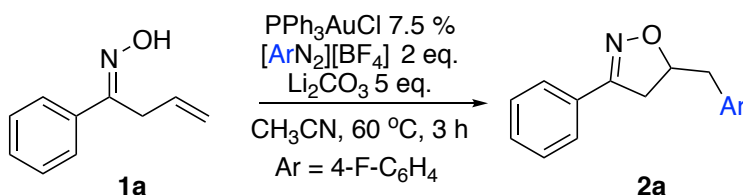
1.2 Procedures for the Synthesis of arenediazonium tetrafluoroborates

All diazonium salts were prepared according to literature procedure³.



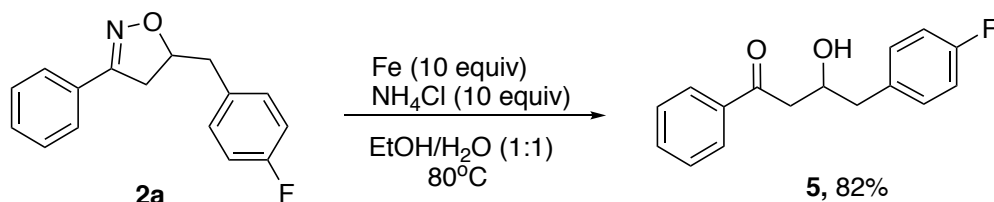
In a 25 mL round-bottom flask, the aniline (5.0 mmol) was dissolved in a mixture of H₂O (1 mL) and an aqueous solution of HBF₄ (50%, 1.9 mL). The mixture was cooled at 0 °C with an ice bath and an solution of NaNO₂ (0.68 g, in 1 mL H₂O) was added dropwise. The reaction was stirred at 0 °C for 30 min. The arenediazonium tetrafluoroborate was removed by filtration, washed successively with a small amount ice water, alcohol, and diethyl ether. The arenediazonium tetrafluoroborate was dried in vacuo (10-3 mbar) for 10 minutes and was then directly used without further purification.

1.3 General Procedure for Gold Catalyzed Cyclization/Arylation of Allylic Oximes



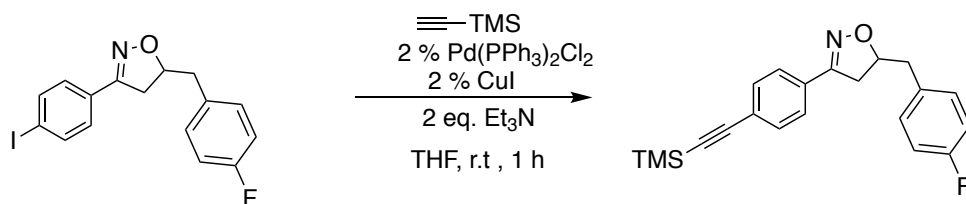
In a 5 ml vial, to a solution of oxime **1a** (0.33 mmol) in 0.83 ml acetonitrile (0.4 M), gold catalyst (12 mg, 7.5%), diazonium salt (0.66 mmol) and lithium carbonate (122 mg, 5 mmol) was added respectively. The resulting mixture was stirred at 60 °C for 3 hours. After that, the reaction mixture was directly loaded on column chromatography on silica gel for purification by hexane/ethyl acetate (20:1) as solvent to isolate the desired product.

1.4 Procedure for Isoxazoline Ring Opening



Fe powder (112 mg, 2 mmol, 10 equiv) was added to isoxazoline **2a** (51 mg, 0.2 mmol) and NH₄Cl (107 mg, 2 mmol, 10 equiv) in ethanol and water (1:1, 10 mL). The mixture was stirred at 80 °C. After the reaction was completed by TLC monitoring, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered. The filtrate was washed with brine and the organic layer was separated, dried over Na₂SO₄, and evaporated in vacuo. The residue was then purified by flash chromatography on silica gel to give product **5** in 82% yield.

1.5 Procedure for Palladium-catalyzed cross-coupling of Isoxazoline.

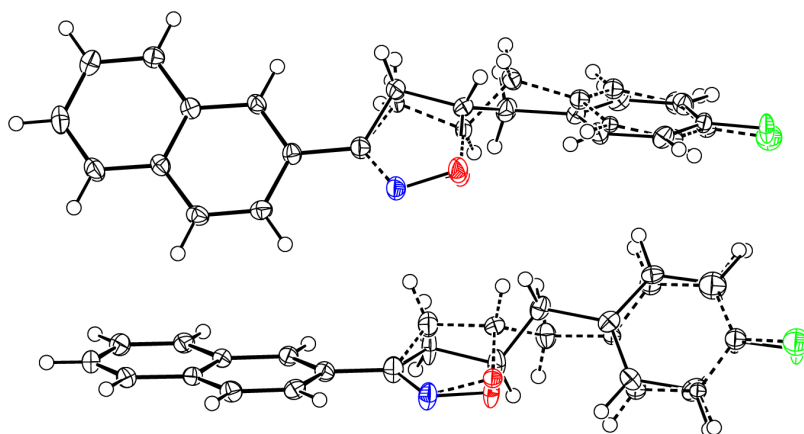


A vial was charged with Pd(PPh₃)₂Cl₂ (5.47 mg, 0.0078 mmol, 0.03 equiv) and copper iodide (2.95 mg, 0.0156 mmol, 0.06 equiv). To this were added THF (1.5 mL) and triethylamine (0.145 mL, 1.04 mmol, 4 equiv) via syringe. Isoxazoline **6** (100 mg, 0.26 mmol, 1 equiv) was then introduced, and the resulting solution was carefully sparged with nitrogen for 10 min. Ethynyltrimethylsilane (0.072 mL, 0.52 mmol, 2 equiv) was then added via syringe, and the resulting brown-black solution was stirred for 45 min. The mixture was partitioned between water and EtOAc and the organic layer collected and then dried over anhydrous MgSO₄, filtered, and concentrated. The product was purified by column chromatography on silica gel eluting with hexanes then 5% EtOAc in hexanes to afford compound **8**, 91% as white solid.

1. Kong, W.; Guo, Q.; Xu, Z.; Wang, G.; Jiang, X.; Wang, R. *Org. Lett.* **2015**, *17*, 3686-3689.
2. Triandafillidi, I.; Kokotos, C. G. *Org. Lett.* **2017**, *19*, 106
3. Wu, J.; Gu, Y.; Leng, X.; Shen, Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 7648

X-Ray Crystallographic Data

The X-ray diffraction data were measured on Bruker D8 Venture PHOTON 100 CMOS diffractometer equipped with a Cu K α INCOATEC ImuS micro-focus source ($\lambda = 1.54178$ Å). Indexing was performed using Apex3 [1]. Data integration and reduction were performed using Saint [2]. Absorption correction was performed by multi-scan method implemented in SADABS [3]. Space group was determined using XPREP implemented in APEX3 [1]. Structure was solved using SHELXT [4] and refined using SHELXL-2018 [5-7] (full-matrix least-squares on F²) within OLEX2 interface program [8]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in geometrically calculated positions and were included in the refinement process using riding model with isotropic thermal parameters. Crystal data and refinement conditions are shown in Table 1. The crystal is a racemic mixture that crystallized in non-centrosymmetric space group. Opposite enantiomers occupy positions across pseudo-inversion center and also share the same site. This leads to observed disorder. Occupancy of disordered parts was refined using free variables (FVAR) in Shelxl and disordered parts of molecules were refined using restraints. Although the average structure could be solved in P21/m centrosymmetric space group, the resulting R-factor is very high (40%) and high residual peaks are observed. Careful analysis of packing indicates the mirror plane is not present in the structure.



X-Ray Diffraction Analysis of Compound 2i(CCDC 1882657)

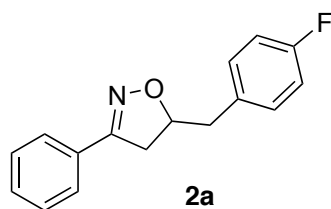
Table 1 Crystal data and structure refinement for AAJ_2055.

Identification code	AAJ_2055
Empirical formula	C ₂₀ H ₁₆ FNO
Formula weight	305.34
Temperature/K	100
Crystal system	monoclinic
Space group	P2 ₁
a/Å	5.84790(10)
b/Å	14.8989(4)
c/Å	17.0994(4)
α/°	90
β/°	95.9410(10)
γ/°	90
Volume/Å ³	1481.82(6)
Z	4
ρ _{calc} /cm ³	1.369
μ/mm ⁻¹	0.751
F(000)	640.0
Crystal size/mm ³	0.429 × 0.408 × 0.196
Radiation	CuKα (λ = 1.54178)
2θ range for data collection/°	5.196 to 144.722
Index ranges	-6 ≤ h ≤ 7, -18 ≤ k ≤ 18, -21 ≤ l ≤ 21
Reflections collected	21984
Independent reflections	5786 [R _{int} = 0.0334, R _{sigma} = 0.0316]
Data/restraints/parameters	5786/1090/542
Goodness-of-fit on F ²	1.026
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0348, wR ₂ = 0.0878
Final R indexes [all data]	R ₁ = 0.0361, wR ₂ = 0.0888
Largest diff. peak/hole / e Å ⁻³	0.17/-0.22

Flack parameter	0.20(7)
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- [1] Bruker (2017). *APEX3* (Version 2015.9). Bruker AXS Inc., Madison, Wisconsin, USA.
- [2] Bruker (2017) SAINT V8.35A. Data Reduction Software.
- [3] Sheldrick, G. M. (1996). *SADABS. Program for Empirical Absorption Correction*. University of Gottingen, Germany.
- [4] Sheldrick, G. M. (2015) "SHELXT - Integrated space-group and crystal structure determination" *Acta Cryst.* A71, 3-8
- [5] Sheldrick, G.M. (1990) *Acta Cryst.* A46, 467-473
- [6] Sheldrick, G. M. (2008) *Acta Cryst.* A64, 112-122.
- [7] G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", *Acta Cryst.*, C71, 3-8
- [8] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H., OLEX2: A complete structure solution, refinement and analysis program (2009). *J. Appl. Cryst.*, 42, 339-341.

II. Compounds Characterization



Chemical name: 5-(4-fluorobenzyl)-3-phenyl-4,5-dihydroisoxazole

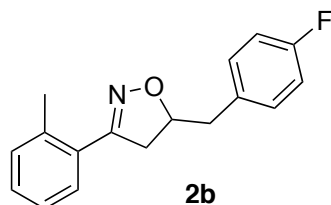
2a was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as light-yellow solid, 63 mg, 74% yield.

¹H NMR (400MHz, CDCl₃): δ 7.62 (dd, 2H), 7.38 (dd, 3H), 7.22 (t, 2H), 7.01 (t, 2H), 4.94 (m, 1H), 3.31(m, 1H), 3.05 (dd, 2H), 2.86 (dd, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 161.8 (d, *J* = 245.4 Hz), 156.4, 132.6 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 8.1 Hz), 130.0, 129.6, 128.7, 126.6, 115.4 (d, *J* = 21.2 Hz), 81.6, 40.2, 38.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.3

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₅FNO⁺ requires 256.1132, found 256.1131.



Chemical name: 5-(4-fluorobenzyl)-3-(o-tolyl)-4,5-dihydroisoxazole

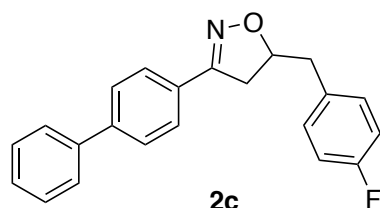
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as brown solid, 52 mg, 58% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.21 (m, 6H), 6.99 (t, *J* = 8.6 Hz, 2H), 4.94 – 4.89 (m, 1H), 3.38 (dd, *J* = 16.5, 10.2 Hz, 1H), 3.13 – 2.97 (m, 2H), 2.90 (dd, *J* = 14.1, 6.2 Hz, 1H), 2.51 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 244.4 Hz), 157.3, 137.9, 132.6, 131.5, 130.9 (d, *J* = 7.1 Hz), 129.3, 128.7, 125.7, 115.4 (d, *J* = 21.2 Hz), 80.5, 41.9, 40.0, 22.8.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.4

HRMS exact mass calcd for [M+H]⁺ C₁₇H₁₇FNO⁺ requires 270.1289, found 270.1286



Chemical name: 3-([1,1'-biphenyl]-4-yl)-5-(4-fluorobenzyl)-4,5-dihydroisoxazole

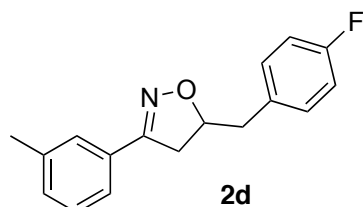
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as brown solid, 85 mg, 78 % yield.

¹H NMR (400 MHz, CDCl₃) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.63 – 7.53 (m, 4H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.23 (dd, *J* = 8.5, 4.7 Hz, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 5.02 – 4.94 (m, 1H), 3.42 – 3.34 (dd, *J* = 16.5, 10.3 Hz, 1H), 3.11 – 3.03 (m, 2H), 2.90 (dd, *J* = 14.0, 6.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 246.4 Hz), 156.2, 142.8, 140.1, 132.6, 130.9 (d, *J* = 8.1 Hz), 128.9, 128.4, 127.8, 127.6, 127.3, 127.0 (d, *J* = 3.0 Hz), 115.4 (d, *J* = 21.2 Hz), 81.7, 40.2, 39.4.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.2

HRMS exact mass calcd for [M+H]⁺ C₂₂H₁₉FNO⁺ requires *m/z* 332.1445, found *m/z* 332.1448



Chemical name: 5-(4-fluorobenzyl)-3-(m-tolyl)-4,5-dihydroisoxazole

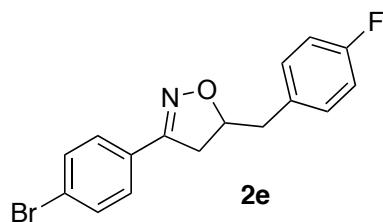
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as light-yellow solid, 54.7 mg, 61% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.14 (m, 4H), 6.99 (t, *J* = 8.5 Hz, 2H), 5.02 – 4.79 (m, 1H), 3.31 (dd, *J* = 16.5, 10.3 Hz, 1H), 3.04 (ddd, *J* = 24.3, 15.3, 7.0 Hz, 1H), 2.87 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.35 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 246.4 Hz), 156.5, 138.4, 132.6 (d, *J* = 3.0 Hz), 130.9, 130.8 (d, *J* = 7.1 Hz), 129.4, 128.5, 127.2, 123.8, 115.4 (d, *J* = 21.2 Hz), 81.6, 40.2, 39.4, 21.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.3

HRMS exact mass calcd for [M+H]⁺ C₁₇H₁₇FNO⁺ requires *m/z* 270.1289, found *m/z* 270.1289



Chemical name: 3-(4-bromophenyl)-5-(4-fluorobenzyl)-4,5-dihydroisoxazole

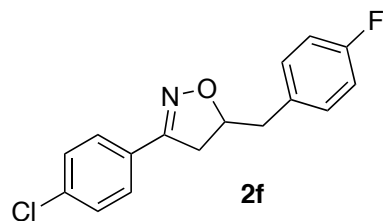
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as brown solid, 80 mg, 72% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 6.5, 3.0 Hz, 2H), 7.47 – 7.33 (m, 2H), 7.24 (dd, *J* = 9.1, 6.3 Hz, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 4.96 (dq, *J* = 10.2, 6.6 Hz, 1H), 3.34 (dd, *J* = 16.6, 10.3 Hz, 1H), 3.06 (ddd, *J* = 24.3, 15.3, 7.1 Hz, 1H), 2.90 (dd, *J* = 14.1, 6.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 245.4 Hz), 155.6, 132.4 (d, *J* = 3.0 Hz), 131.9, 130.8 (d, *J* = 8.1 Hz), 128.5, 128.0, 124.3, 115.4 (d, *J* = 21.2 Hz), 81.9, 40.1, 39.1.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.1

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₄BrFNO⁺ requires *m/z* 334.0237, found *m/z* 334.0234



Chemical name: 3-(4-chlorophenyl)-5-(4-fluorobenzyl)-4,5-dihydroisoxazole

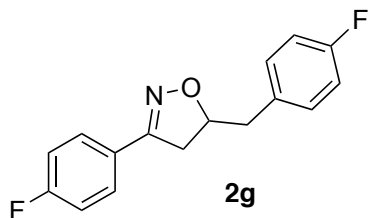
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 68.4 mg, 71% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.15 (m, 2H), 6.98 (t, *J* = 8.6 Hz, 2H), 5.13 – 4.80 (m, 1H), 3.29 (dd, *J* = 16.5, 10.3 Hz, 1H), 3.06 (dt, *J* = 18.1, 9.1 Hz, 1H), 2.97 (dd, *J* = 16.5, 7.9 Hz, 1H), 2.88 (dd, *J* = 14.1, 6.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 245.4 Hz), 155.5, 135.9, 132.4 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 8.1 Hz), 128.9, 128.1, 127.8, 115.4 (d, *J* = 21.2 Hz), 81.9, 40.1, 39.2.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.2

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₄ClFNO⁺ requires *m/z* 290.0742, found *m/z* 290.0744



Chemical name: 3-(4-fluorophenyl)-5-(4-fluorobenzyl)-4,5-dihydroisoxazole

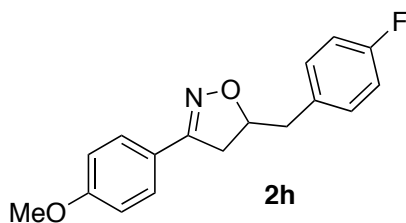
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 57.3mg, 63% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.61 – 7.57 (m, 2H), 7.22 (m, 2H), 7.21 – 7.03 (m, 4H), 4.94 (ddt, *J* = 10.3, 7.9, 6.4 Hz, 1H), 3.29 (dd, *J* = 16.5, 10.3 Hz, 1H), 3.14 – 2.92 (m, 2H), 2.87 (dd, *J* = 14.1, 6.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 163.7 (d, *J* = 252.5 Hz), 161.8 (d, *J* = 245.4 Hz), 155.4, 132.5, 130.8, 128.4, 125.8 (d, *J* = 2.0 Hz), 115.7 (d, *J* = 21.2 Hz), 115.5 (d, *J* = 21.2 Hz), 81.7, 40.1, 39.4.

¹⁹F NMR (376 MHz, CDCl₃) δ -110.0, -116.2.

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₄F₂NO⁺ requires *m/z* 274.1038, found *m/z* 274.1034.



Chemical name: 5-(4-fluorobenzyl)-3-(4-methoxyphenyl)-4,5-dihydroisoxazole

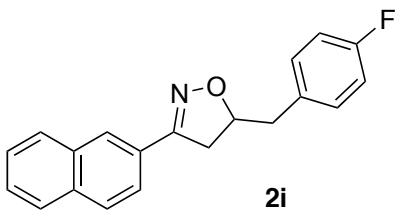
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 53 mg, 56% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.55 (d, 2H), 7.23 (t, 2H), 7.01 (m, 2H), 6.90 (m, 2H), 4.92 (t, *J* = 8.2 Hz, 1H), 3.81 (s, 3H), 3.31 (dd, *J* = 16.2, 10.9 Hz, 1H), 3.12 – 2.95 (m, 2H), 2.88 (dd, *J* = 14.5, 5.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 245.4 Hz), 161.0, 156.0, 132.7 (d, *J* = 3.0 Hz), 130.9, 128.1 (d, *J* = 10.0 Hz), 122.1, 115.4 (d, *J* = 21.2 Hz), 114.1, 81.4 (d, *J* = 15.0 Hz), 55.3, 40.2, 39.6.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.3

HRMS exact mass calcd for [M+H]⁺ C₁₇H₁₇FNO₂⁺ requires *m/z* 286.1238, found *m/z* 286.1236.



Chemical name: 5-(4-fluorobenzyl)-3-(naphthalen-2-yl)-4,5-dihydroisoxazole

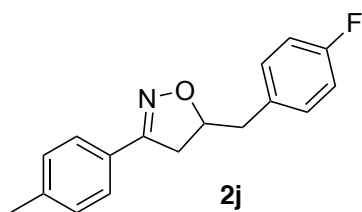
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 77 mg, 76% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.96 – 7.77 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.16 (m, 3H), 7.00 (t, *J* = 8.7 Hz, 3H), 4.45 (ddd, *J* = 10.5, 8.9, 3.3 Hz, 1H), 3.11 (qd, *J* = 17.6, 5.8 Hz, 2H), 2.98 – 2.85 (m, 1H), 2.83 (dd, *J* = 13.8, 6.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 246.4 Hz), 156.6, 134.0, 132.9, 132.6 (d, *J* = 2.0 Hz), 130.9 (d, *J* = 8.1 Hz), 128.5, 128.3, 127.9, 127.2, 127.1, 126.8, 126.7, 123.5, 115.4 (d, *J* = 21.2 Hz), 81.9, 40.2, 39.3.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.7

HRMS exact mass calcd for [M+H]⁺ C₂₀H₁₇FNO⁺ requires m/z 306.1289, found m/z 306.1295



Chemical name: 5-(4-fluorobenzyl)-5-methyl-3-phenyl-4,5-dihydroisoxazole

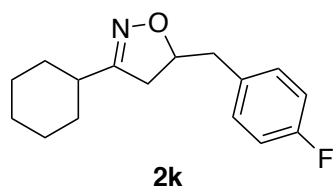
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as yellow solid, 60 mg, 67% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.52 (dd, *J* = 31.4, 12.0 Hz, 2H), 7.24 – 7.17 (m, 4H), 6.99 (m, 2H), 4.92 (m, 1H), 3.31 (dd, *J* = 16.6, 10.3 Hz, 1H), 3.13 – 2.93 (m, 2H), 2.87 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.36 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 246.4 Hz), 156.4, 140.3, 132.6, 130.8 (d, *J* = 3.0 Hz), 129.3, 126.5, 125.6, 115.4 (d, *J* = 21.2 Hz), 81.5, 40.2, 39.5, 21.5.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.4

HRMS exact mass calcd for [M+H]⁺ C₁₇H₁₇FNO⁺ requires m/z 270.1289, found m/z 270.1288.



It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 26.1 mg, 30% yield.

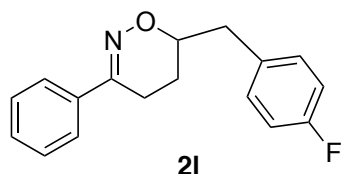
Chemical name: 3-cyclohexyl-5-(4-fluorobenzyl)-4,5-dihydroisoxazole

¹H NMR (400 MHz, CDCl₃) δ 7.17 (dd, *J* = 8.4, 5.4 Hz, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 4.73 (dd, *J* = 10.1, 6.7 Hz, 1H), 2.91 – 2.79 (dd, *J* = 15.0, 5.8 Hz, 3H), 2.78 (m, 1H), 2.34 (dd, *J* = 16.8, 7.2 Hz, 1H), 1.83 – 1.58 (m, 5H), 1.28 – 1.17 (m, 5H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 245.4 Hz), 162.6, 132.8 (d, *J* = 3.0 Hz), 130.7 (d, *J* = 7.1 Hz), 115.2 (d, *J* = 21.2 Hz), 79.9, 79.8, 40.0, 39.5, 37.2, 30.3, 25.8, 25.7.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.6

HRMS exact mass calcd for [M+H]⁺ C₁₆H₂₁FNO⁺ requires *m/z* 262.1602, found *m/z* 262.1598.



Chemical name: 6-(4-fluorobenzyl)-3-phenyl-5,6-dihydro-4H-1,2-oxazine

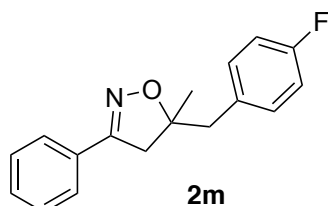
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 62 mg, 69% yield.

¹H NMR (400MHz, CDCl₃): δ 7.66 (dd, 2H), 7.36 (t, 3H), 7.22 (t, 2H), 6.98 (t, 2H), 3.94 (m, 1H), 3.05 (m, 1H), 2.84 (dd, 1H), 2.60 (m, 2H), 2.01(m, 1H) 1.75 m, 1H).

¹³C NMR (400 MHz, CDCl₃): δ 161.7 (d, *J* = 245.4 Hz), 156.6, 135.7, 132.8 (d, *J* = 3.0 Hz), 131.0 (d, *J* = 8.1 Hz), 129.5, 128.4, 125.3, 115.2 (d, *J* = 21.2 Hz), 75.7, 39.6, 23.8, 21.9

¹⁹F NMR (400 MHz, CDCl₃): δ -116.7

HRMS exact mass calcd for [M+H]⁺ C₁₇H₁₇FNO⁺ requires *m/z* 270.1289, found *m/z* 270.1288



Chemical name: 5-(4-fluorobenzyl)-5-methyl-3-phenyl-4,5-dihydroisoxazole

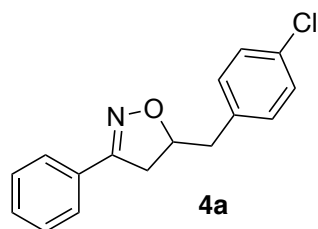
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as yellow solid, 55 mg, 61% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.60 – 7.48 (m, 2H), 7.40 – 7.30 (m, 3H), 7.26 – 7.16 (m, 3H), 7.02 – 6.81 (m, 2H), 3.14 (d, *J* = 16.5 Hz, 1H), 3.00 – 2.89 (m, 3H), 1.40 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 161.9 (d, *J* = 245.4 Hz), 156.4, 132.3 (d, *J* = 2.0 Hz), 131.8 (d, *J* = 8.1 Hz), 129.8, 128.6, 126.4, 115.0 (d, *J* = 21.2 Hz), 87.1, 44.8, 44.5, 36.6, 25.8.

¹⁹F NMR (376 MHz, CDCl₃) δ -116.40

HRMS exact mass calcd for [M+H]⁺ C₁₇H₁₇FNO⁺ requires *m/z* 270.1289, found *m/z* 270.1289.



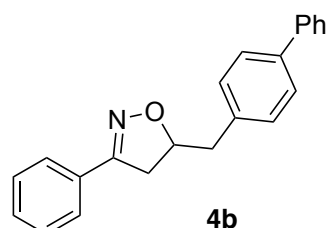
Chemical name: 5-(4-chlorobenzyl)-3-phenyl-4,5-dihydroisoxazole

It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 75.6 mg, 72% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.61 (m, 2H), 7.37 (dd, *J* = 5.2, 2.0 Hz, 3H), 7.31 – 7.17 (m, 5H), 4.93 (ddt, *J* = 10.3, 7.8, 6.5 Hz, 1H), 3.32 (dd, *J* = 16.6, 10.3 Hz, 1H), 3.17 – 2.94 (m, 2H), 2.85 (dd, *J* = 14.0, 6.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 156.5, 140.8, 139.7, 136.0, 130.0, 129.8, 128.7, 127.4, 126.7, 81.8, 40.7, 39.5

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₅ClNO⁺ requires m/z 272.0837, found m/z 272.0838.



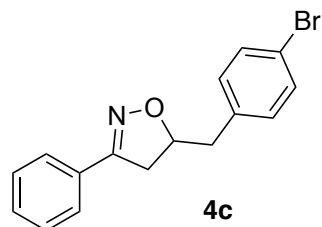
Chemical name: 5-([1,1'-biphenyl]-4-ylmethyl)-3-phenyl-4,5-dihydroisoxazole

It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 71 mg, 79% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.55 (dd, *J* = 9.9, 7.7 Hz, 4H), 7.48 – 7.27 (m, 8H), 5.02 (dq, *J* = 10.1, 7.0 Hz, 1H), 3.35 (dd, *J* = 16.5, 10.2 Hz, 1H), 3.24 – 3.17 (m, 1H), 3.08 (m, 1H), 2.93 (dd, *J* = 13.9, 7.1 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 156.4, 135.4, 132.7, 130.7, 130.1, 129.5, 128.7, 128.7, 126.6, 81.4, 40.3, 39.4

HRMS exact mass calcd for [M+H]⁺ C₂₂H₂₀NO⁺ requires m/z 314.1539, found m/z 314.1539.



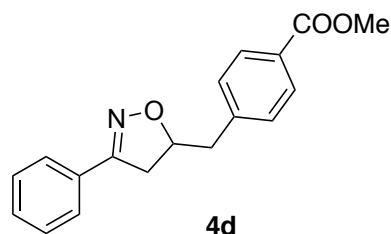
Chemical name: 5-(4-bromobenzyl)-3-phenyl-4,5-dihydroisoxazole

It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as brown solid, 75.6 mg, 72% yield.

¹H NMR (400 MHz, CDCl₃) 7.63 (m, 2H), 7.45-7.39 (dd, *J* = 19.4, 6.5 Hz, 5H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.96 (dq, *J* = 14.1, 6.9 Hz, 1H), 3.35 (dd, *J* = 16.5, 10.3 Hz, 1H), 3.22 – 2.94 (m, 2H), 2.87 (dd, *J* = 14.0, 6.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 156.4, 135.9, 131.7, 131.1, 130.1, 129.5, 128.7, 126.6, 120.7, 81.4, 40.4, 39.4.

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₅BrNO⁺ requires m/z 316.0332 found m/z 316.0332.



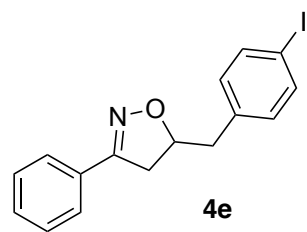
Chemical name: methyl 4-((3-phenyl-4,5-dihydroisoxazol-5-yl) methyl) benzoate

It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 67.9 mg, 69% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.60 (dd, *J* = 6.8, 2.9 Hz, 2H), 7.43 – 7.31 (m, 5H), 5.01 (dq, *J* = 10.3, 6.9 Hz, 1H), 3.88 (s, 1H), 3.34 (dd, *J* = 16.6, 10.3 Hz, 1H), 3.17 – 3.13 (m, 1H), 3.04 - 2.92 (dd, *J* = 14.0, 6.4 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 166.9, 156.5, 142.3, 130.1, 129.9, 129.4, 129.3, 128.9, 128.7, 126.6, 81.2, 52.1, 41.0, 39.5.

HRMS exact mass calcd for [M+H]⁺ C₁₈H₁₈NO₃⁺ requires m/z 296.1281, found m/z 296.1284



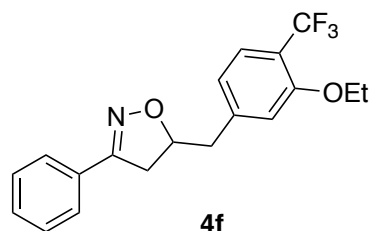
Chemical name: 5-(4-iodobenzyl)-3-phenyl-4,5-dihydroisoxazole

It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as brown solid, 65 mg, 53% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.62 (d, *J* = 7.8 Hz, 4H), 7.38 (s, 3H), 7.01 (d, *J* = 7.7 Hz, 2H), 5.03 – 4.84 (m, 1H), 3.33 (dd, *J* = 16.5, 10.3 Hz, 1H), 3.14 – 2.92 (m, 2H), 2.84 (dd, *J* = 14.0, 6.4 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 156.4, 137.6, 136.6, 131.4, 130.1, 129.5, 128.7, 126.6, 92.2, 81.4, 40.5, 39.4.

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₅INO⁺ requires m/z 364.0193, found m/z 364.0196



Name: Ethyl 4-((3-phenyl-4,5-dihydroisoxazol-5-yl) methyl)-2-(trifluoromethyl)benzoate.

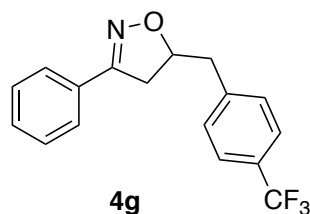
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 82.6 mg, 71% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.50 – 7.33 (m, 5H), 6.92 (d, *J* = 8.5 Hz, 1H), 4.94 (dt, *J* = 8.4, 6.1 Hz, 1H), 4.10 (q, 2H), 3.36 (dd, *J* = 16.5, 10.2 Hz, 1H), 3.16 – 2.97 (m, 2H), 2.86 (dd, *J* = 14.2, 6.1 Hz, 1H), 1.41 (t, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 156.5, 155.8, 134.1, 130.1, 129.5, 128.7, 128.5, 127.8 (q, *J* = 5.0 Hz), 126.6, 123.6 (q, *J* = 272.7 Hz), 119.0 (q, *J* = 30.3 Hz), 113.3, 81.6, 64.6, 40.0, 39.4, 14.6.

¹⁹F NMR (376 MHz, CDCl₃) δ -62.4.

HRMS exact mass calcd for [M+H]⁺ C₁₉H₁₉F₃NO₂⁺ requires *m/z* 350.1362, found *m/z* 350.1363



Chemical name: 3-phenyl-5-(4-(trifluoromethyl) benzyl)-4,5-dihydroisoxazole

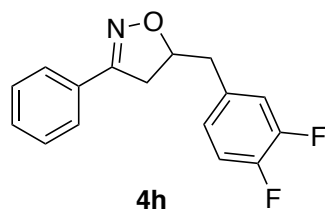
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as yellow solid, 71mg, 70% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.64 – 7.57 (m, 4H), 7.40 (dd, *J* = 4.5, 2.8 Hz, 5H), 4.99 (dq, *J* = 10.0, 6.9 Hz, 1H), 3.38 (dd, *J* = 16.5, 10.3 Hz, 1H), 3.17 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.07 – 2.84 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 156.5, 141.1, 130.1, 129.7, 129.4 (q, *J* = 32.3 Hz), 128.7, 126.6, 125.5 (q, *J* = 3.0 Hz), 121.5 (q, *J* = 272.7 Hz), 81.2, 40.8, 39.6.

¹⁹F NMR (376 MHz, CDCl₃) δ -62.5

HRMS exact mass calcd for [M+H]⁺ C₁₇H₁₅F₃NO⁺ requires *m/z* 306.1100 found *m/z* 306.1113



Chemical name: 5-(3,4-difluorobenzyl)-3-phenyl-4,5-dihydroisoxazole

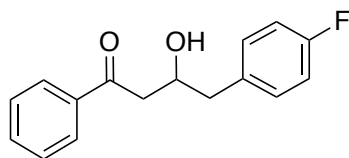
It was prepared following the General Procedure 1.3 and purified by flash chromatography (Hexane: EA = 20:1) as brown solid, 56 mg, 62% yield.

¹H NMR (400 MHz, CDCl₃) 7.64 (dd, *J* = 6.2, 2.7 Hz, 2H), 7.40 (m, 3H), 7.18 – 7.03 (m, 2H), 7.03 – 6.91 (m, 1H), 4.95 (dq, *J* = 10.2, 6.9 Hz, 1H), 3.38 (dd, *J* = 16.6, 10.3 Hz, 1H), 3.10 – 2.97 (m, 2H), 2.89 (dd, *J* = 14.2, 5.9 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 156.4, 151.0 (dd, *J* = 304.6, 48.9 Hz), 148.5 (dd, *J* = 300.8, 48.9 Hz), 133.9 (dd, *J* = 18.8, 18.8 Hz), 130.1, 129.4, 128.9, 126.6, 125.3 (dd, *J* = 18.8, 18.8 Hz), 118.2 (d, *J* = 63.9 Hz), 117.2 (d, *J* = 63.9 Hz), 81.2, 40.1, 39.4

¹⁹F NMR (376 MHz, CDCl₃) δ -137.7, -140.8 (m, *J*_{F-F} = 18.8 Hz)

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₄F₂NO⁺ requires *m/z* 274.1038, found 274.1045



5a

Chemical name: 4-(4-fluorophenyl)-3-hydroxy-1-phenylbutan-1-one

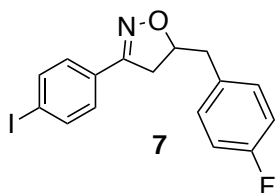
It was prepared following the General Procedure 1.4 and purified by flash chromatography (Hexane: EA = 20:1) as white solid, 42 mg, 82% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.9 (d, *J* = 7.7 Hz, 2H), 7.59 (dt, *J* = 48.2, 7.5 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.44 – 7.26 (m, 2H), 7.22 – 6.98 (t, *J* = 8.5 Hz, 2H), 4.45 (t, *J* = 7.7 Hz, 1H), 3.18 – 3.03 (m, 2H), 2.95 – 2.80 (m, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 200.4, 161.7 (d, *J* = 245.4 Hz), 136.6, 133.7 (d, *J* = 3.0 Hz), 133.6, 130.8 (d, *J* = 8.1 Hz), 128.7, 128.0, 115.3 (d, *J* = 21.2 Hz), 68.8, 44.0, 42.0

¹⁹F NMR (376 MHz, CDCl₃) δ -116.7

HRMS exact mass calcd for [M+H]⁺ C₁₆H₁₆FO₂⁺ requires *m/z* 259.1129, found 259.1128



7

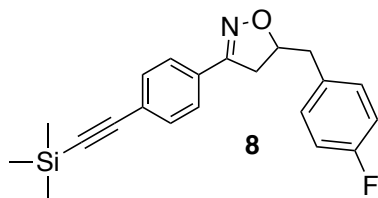
It was prepared following the General Procedure 1.4 and purified by flash chromatography (Hexane: EA = 20:1) as off-white solid, 42 mg, 71% yield.

¹H NMR (400 MHz, CDCl₃) δ 7.72 (m, 2H), 7.35 (m, 2H), 7.22 (dt, *J* = 16.9, 9.4 Hz, 2H), 7.0 (m, 2H), 4.99 – 4.93 (m, 1H), 3.33 – 3.16 (m, 1H), 3.08 (dt, *J* = 15.1, 7.5 Hz, 1H), 2.99 – 2.82 (ddd, *J* = 20.5, 15.3, 7.1 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 161.8 (d, *J* = 246.4 Hz), 155.7, 137.8, 132.4 (d, *J* = 2.0 Hz), 130.8 (d, *J* = 8.1 Hz), 129.0, 128.1, 115.4 (d, *J* = 21.2 Hz), 96.2, 82.0, 40.1, 39.0

^{19}F NMR (376 MHz, CDCl_3) δ -116.3

HRMS exact mass calcd for $\text{M}+\text{H}^+$ $\text{C}_{16}\text{H}_{14}\text{FINO}^+$ requires m/z 382.0099, found m/z 382.0106



It was prepared following the General Procedure 1.4 and purified by flash chromatography (Hexane: EA = 20:1) as off-white solid, 91% yield

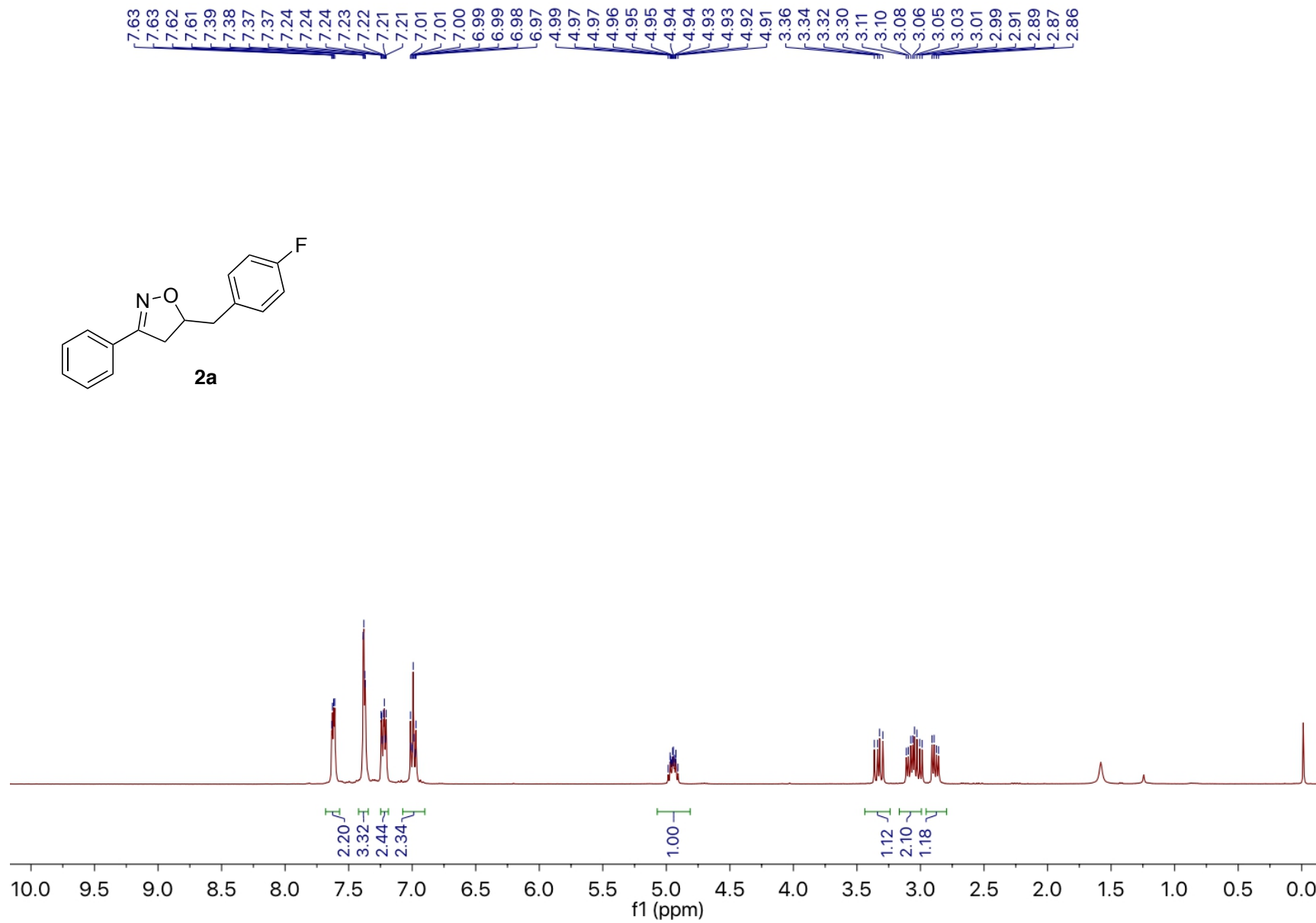
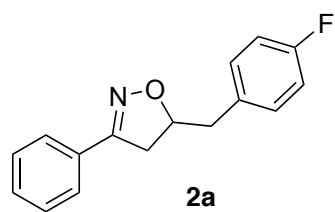
^1H NMR (400 MHz, CDCl_3) δ 7.55 (dd, 2H), 7.46 (m, 2H), 7.24 (m, 2H), 7.00 (m, 2H), 4.96 (m, 1H), 3.34 – 3.28 (m, 1H), 3.08 (dd, 1H), 2.98 (dd, 1H), 2.88 (dd, 1H), 0.25 (s, 9H).

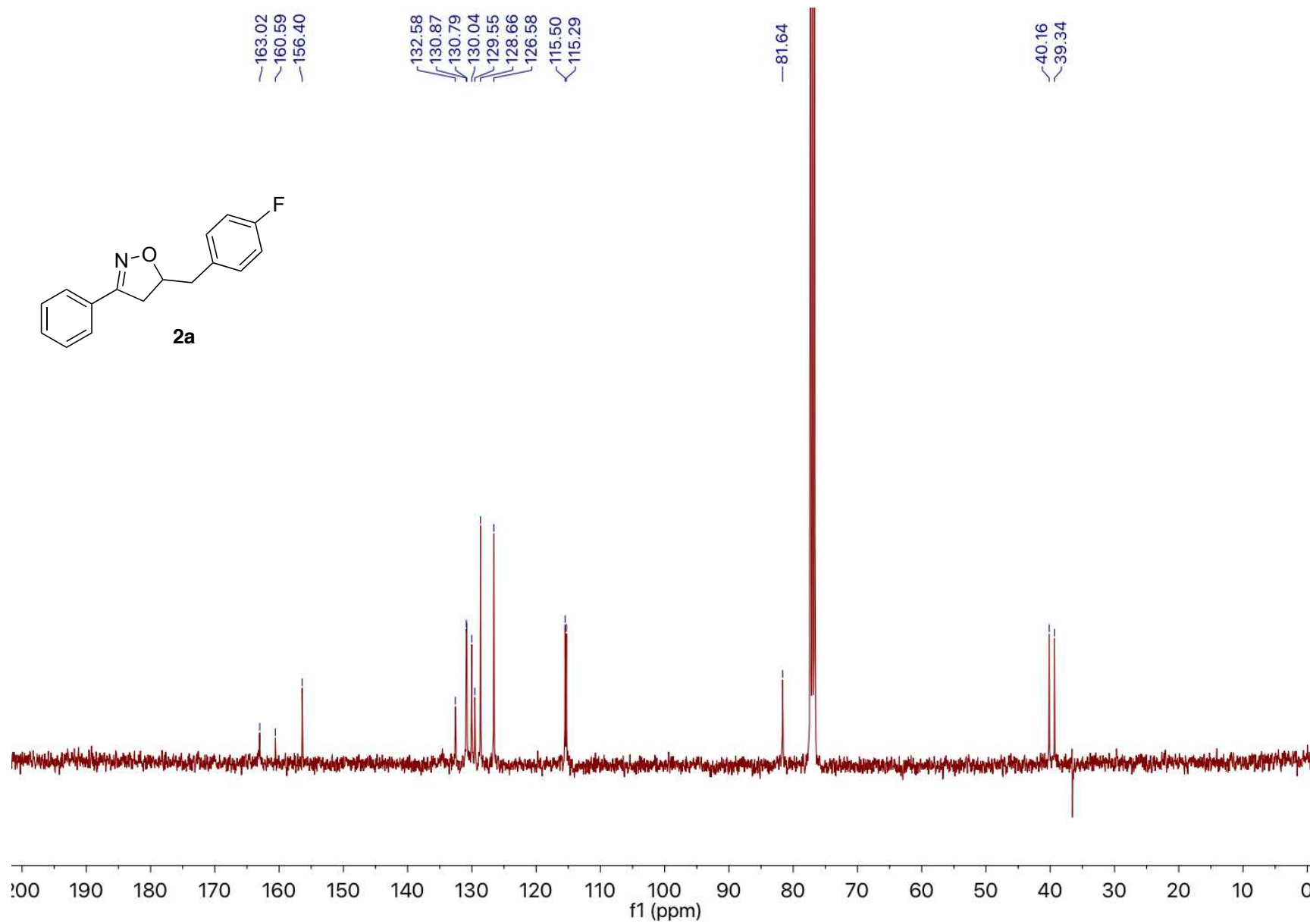
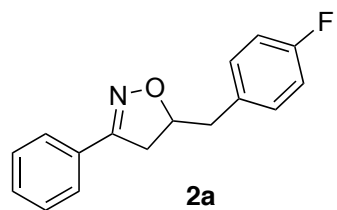
^{13}C NMR (101 MHz, CDCl_3) δ 161.9 (d, $J = 246.4$ Hz), 155.9, 132.4, 132.2, 130.8 (d, $J = 7.1$ Hz), 129.4, 126.3, 124.7, 115.4 (d, $J = 21.2$ Hz), 104.4, 96.4, 81.9 (d, $J = 10.0$ Hz), 40.2, 39.1, -0.1

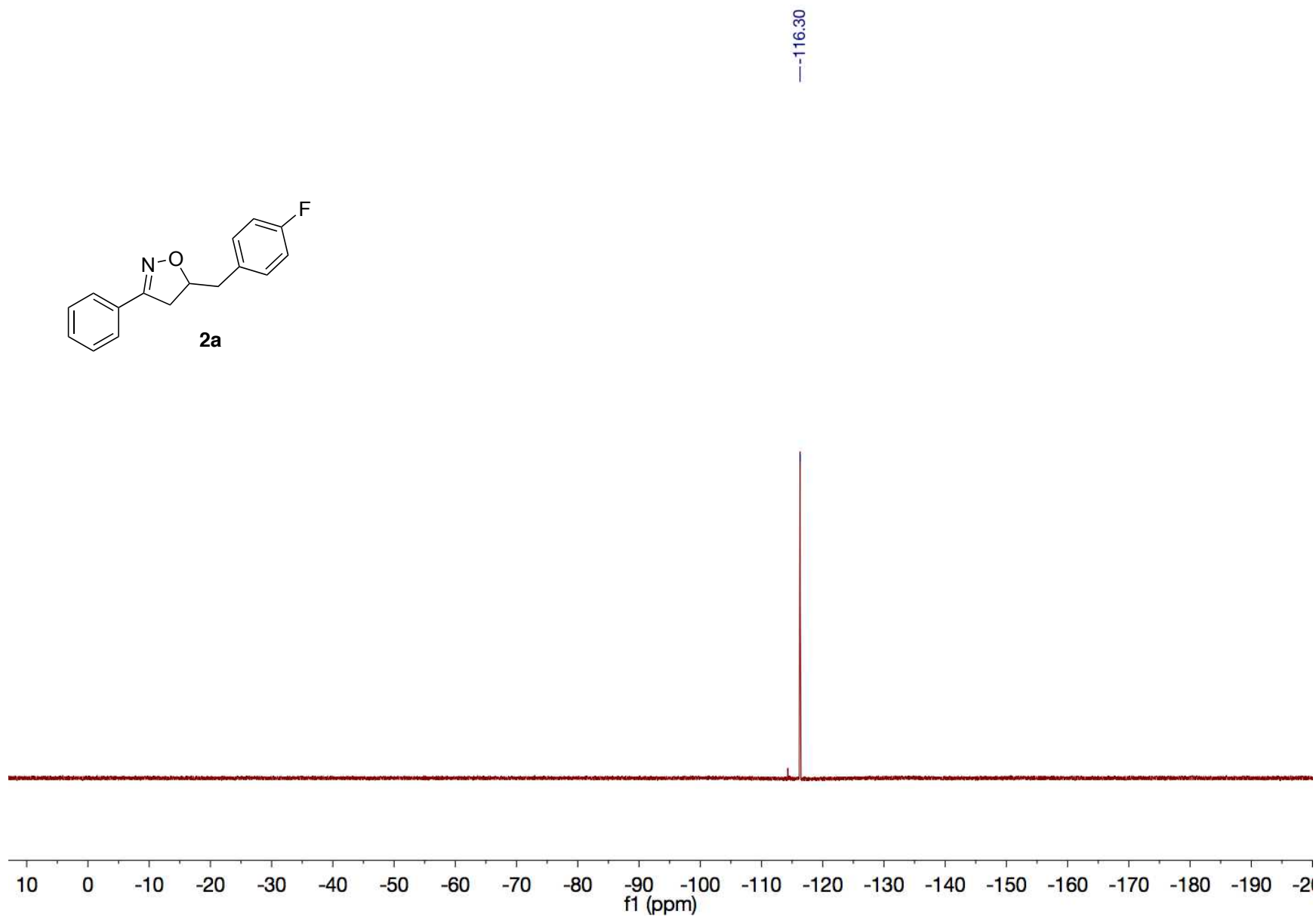
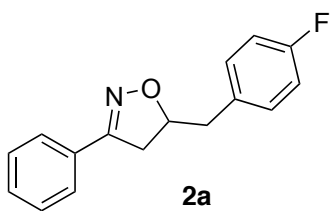
^{19}F NMR (376 MHz, CDCl_3) δ -116.2

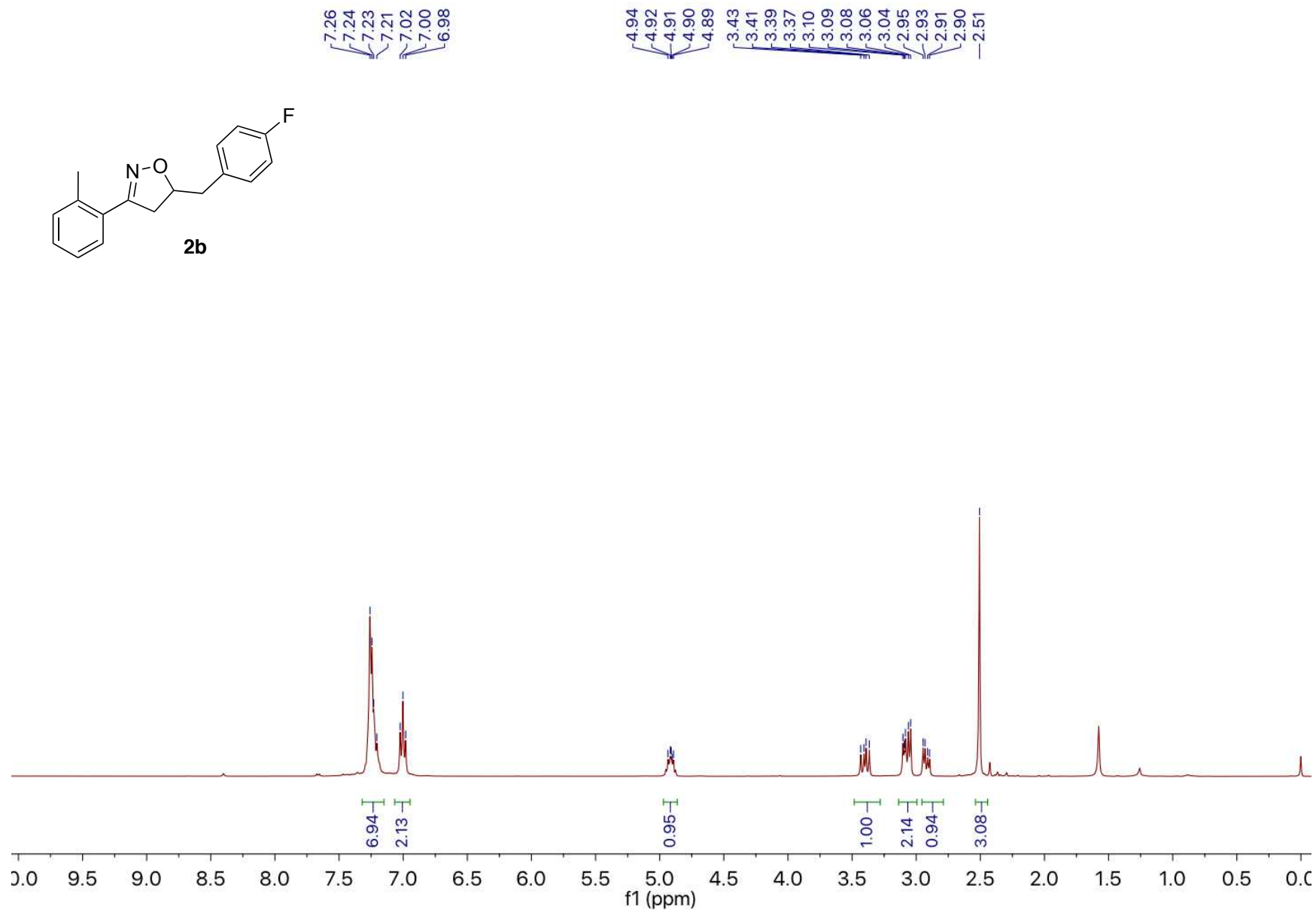
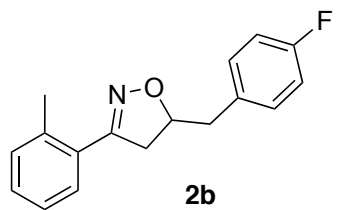
HRMS exact mass calcd for $\text{C}_{21}\text{H}_{23}\text{FNOSi}^+$ requires m/z 352.1527, found m/z 352.1538

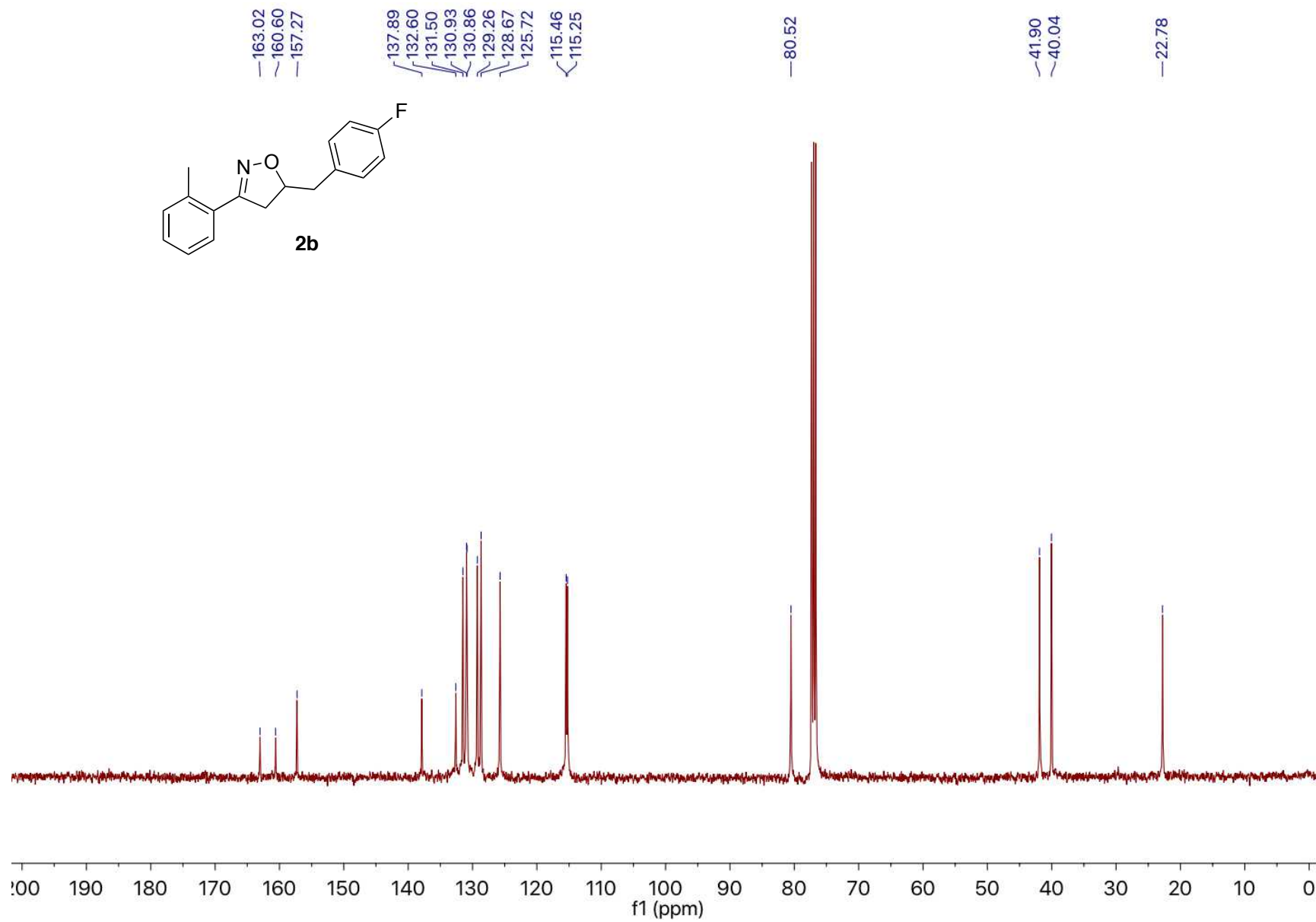
III. NMR Spectra Data

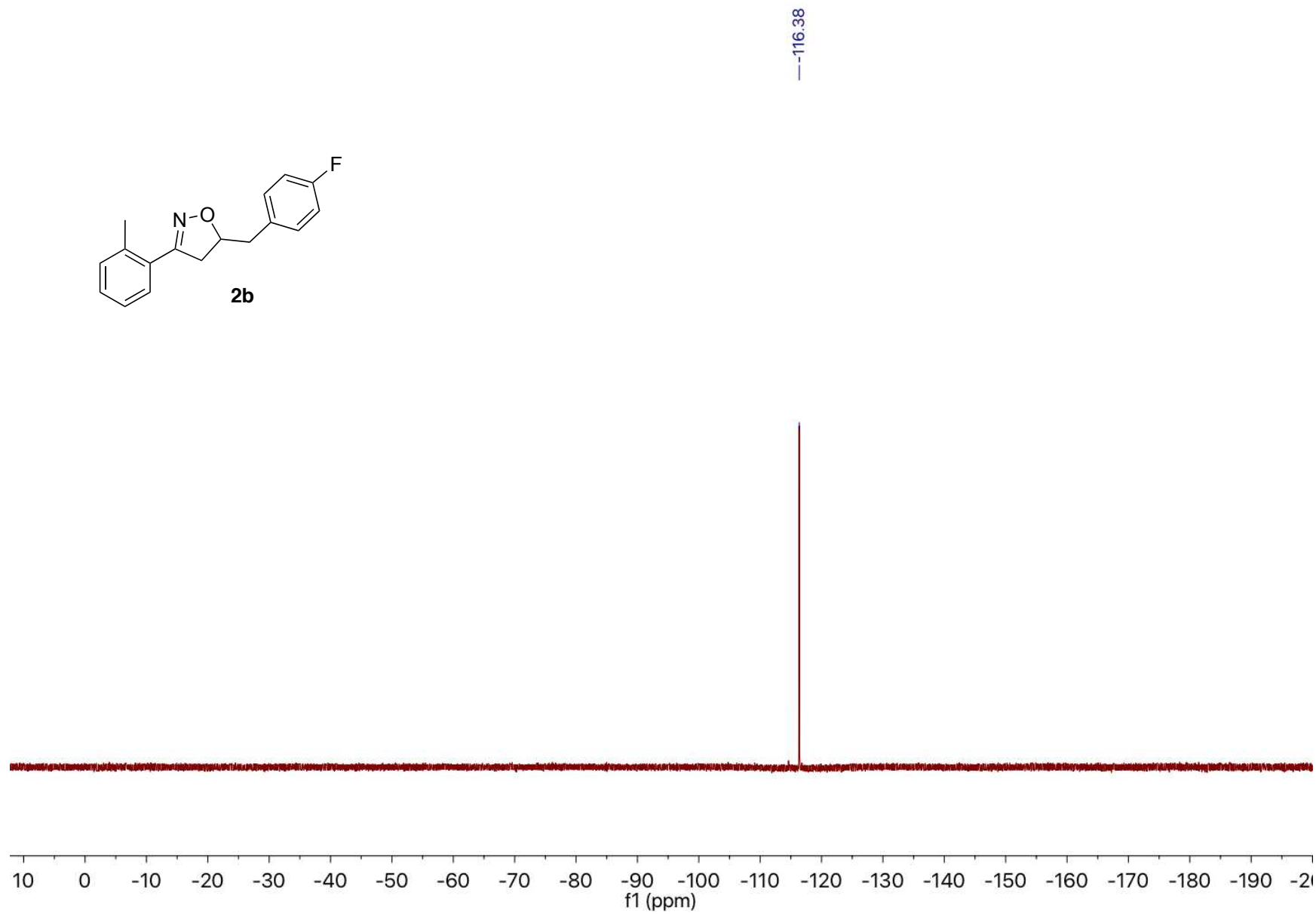
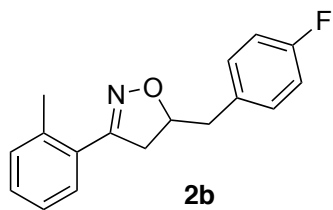


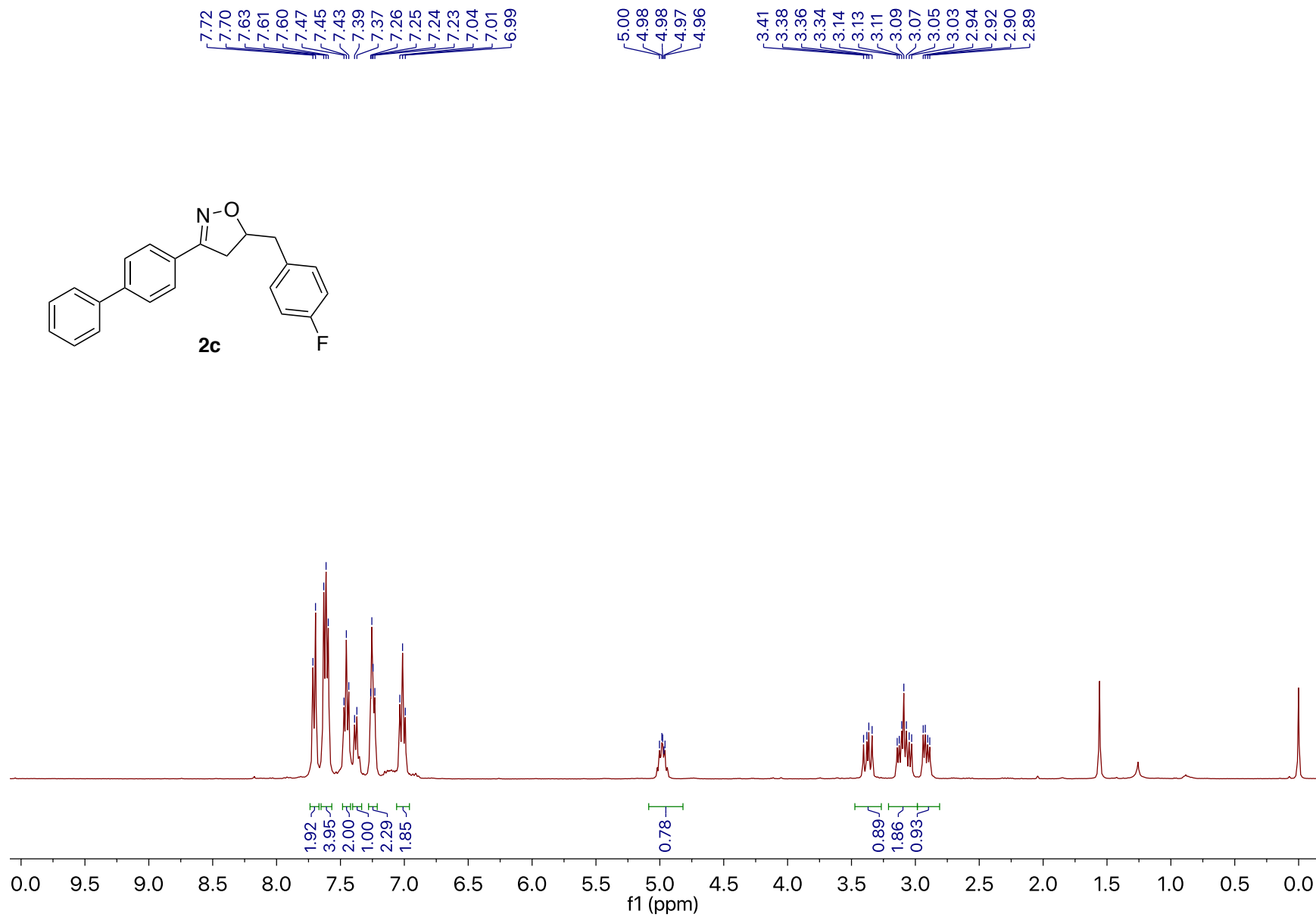
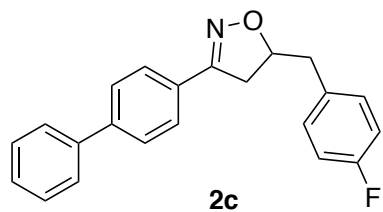


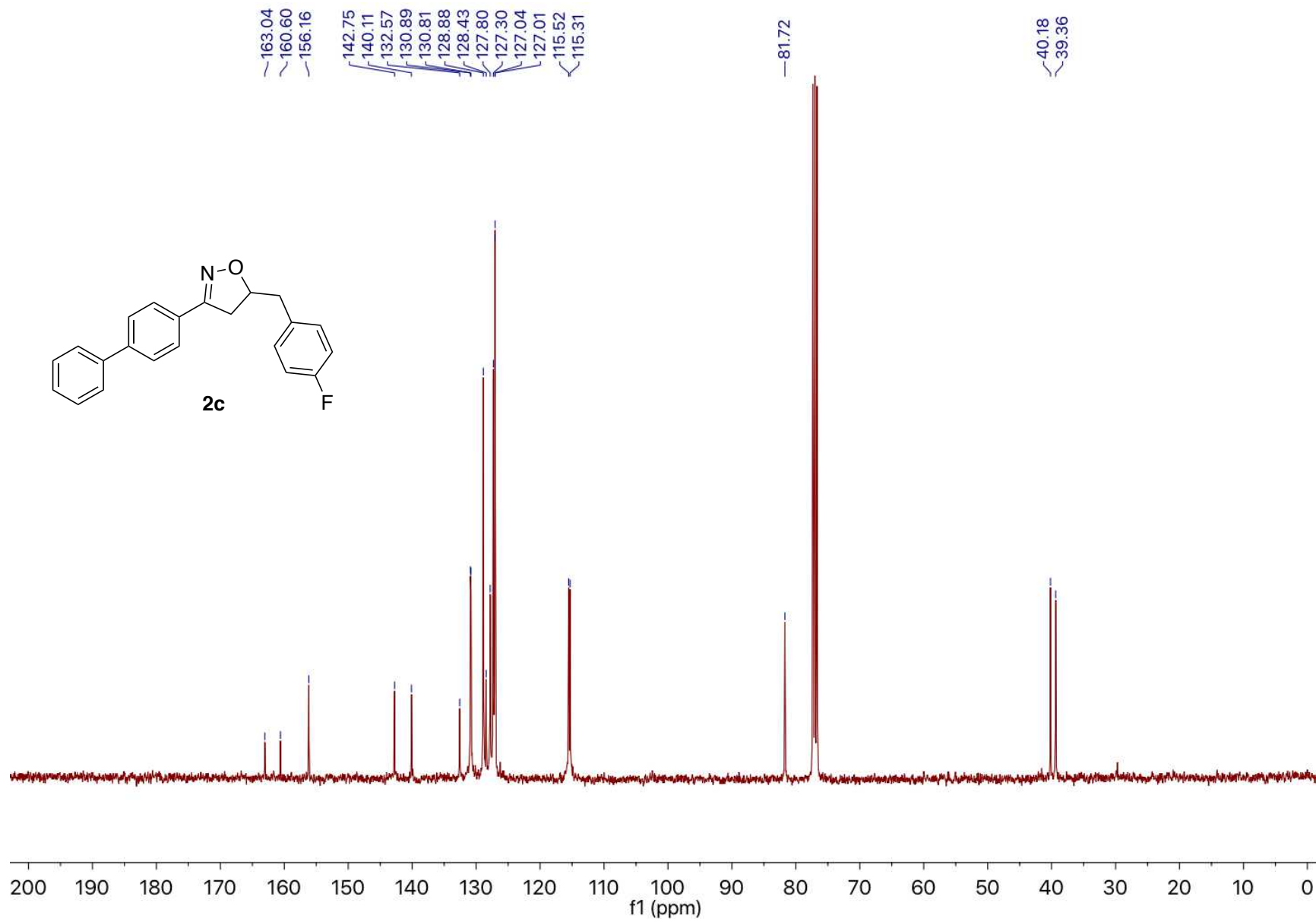


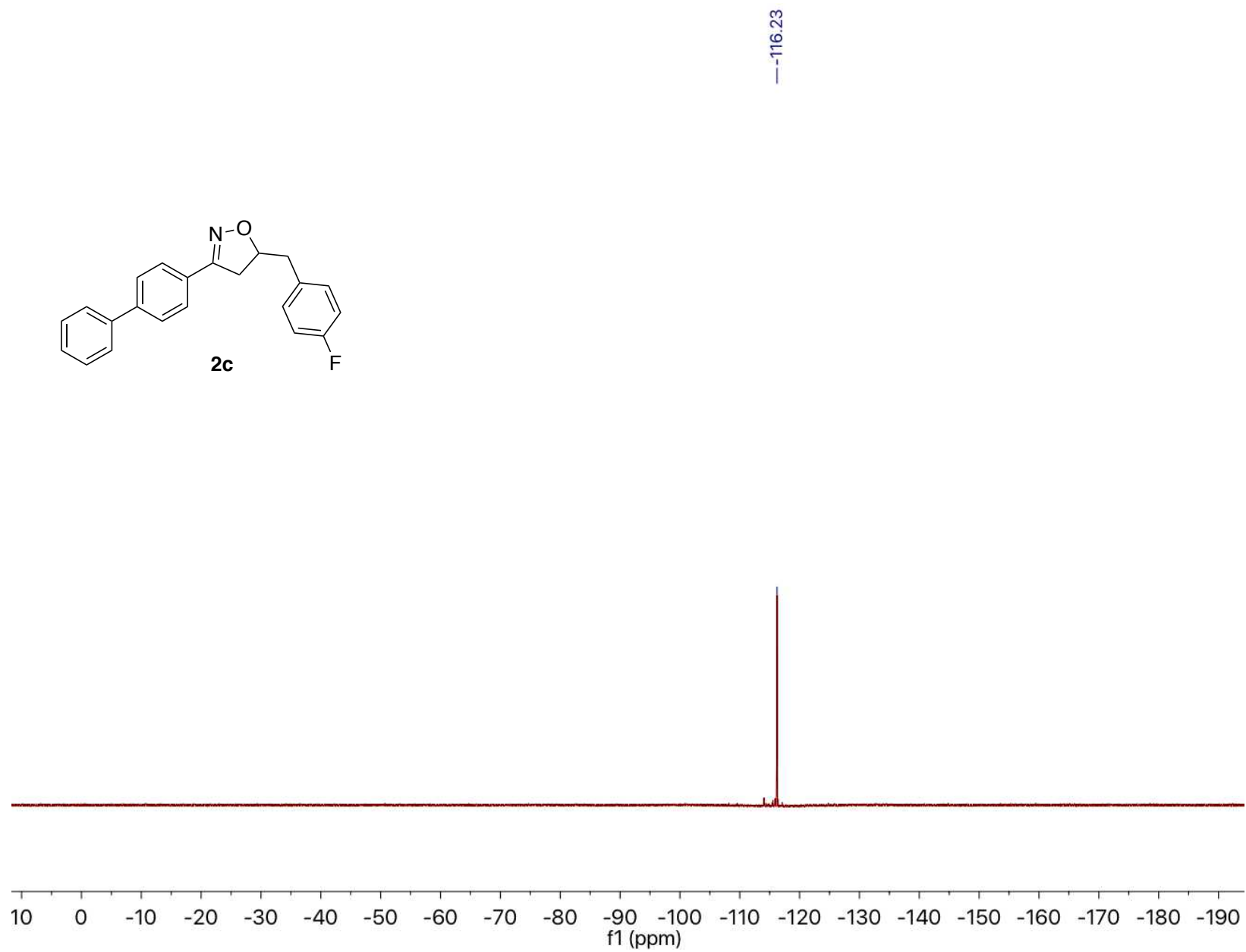
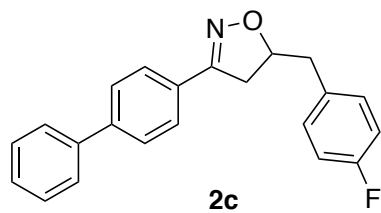


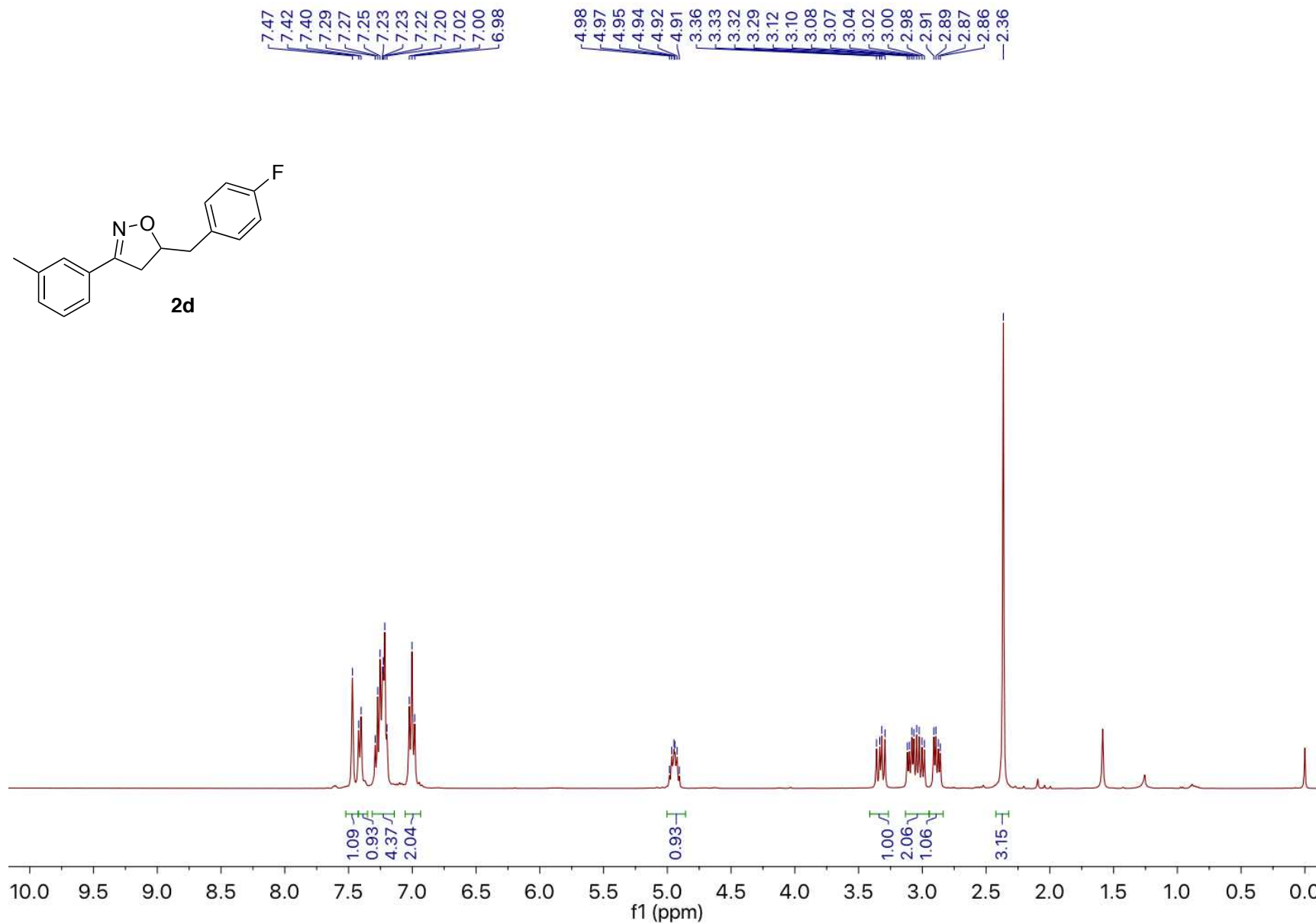


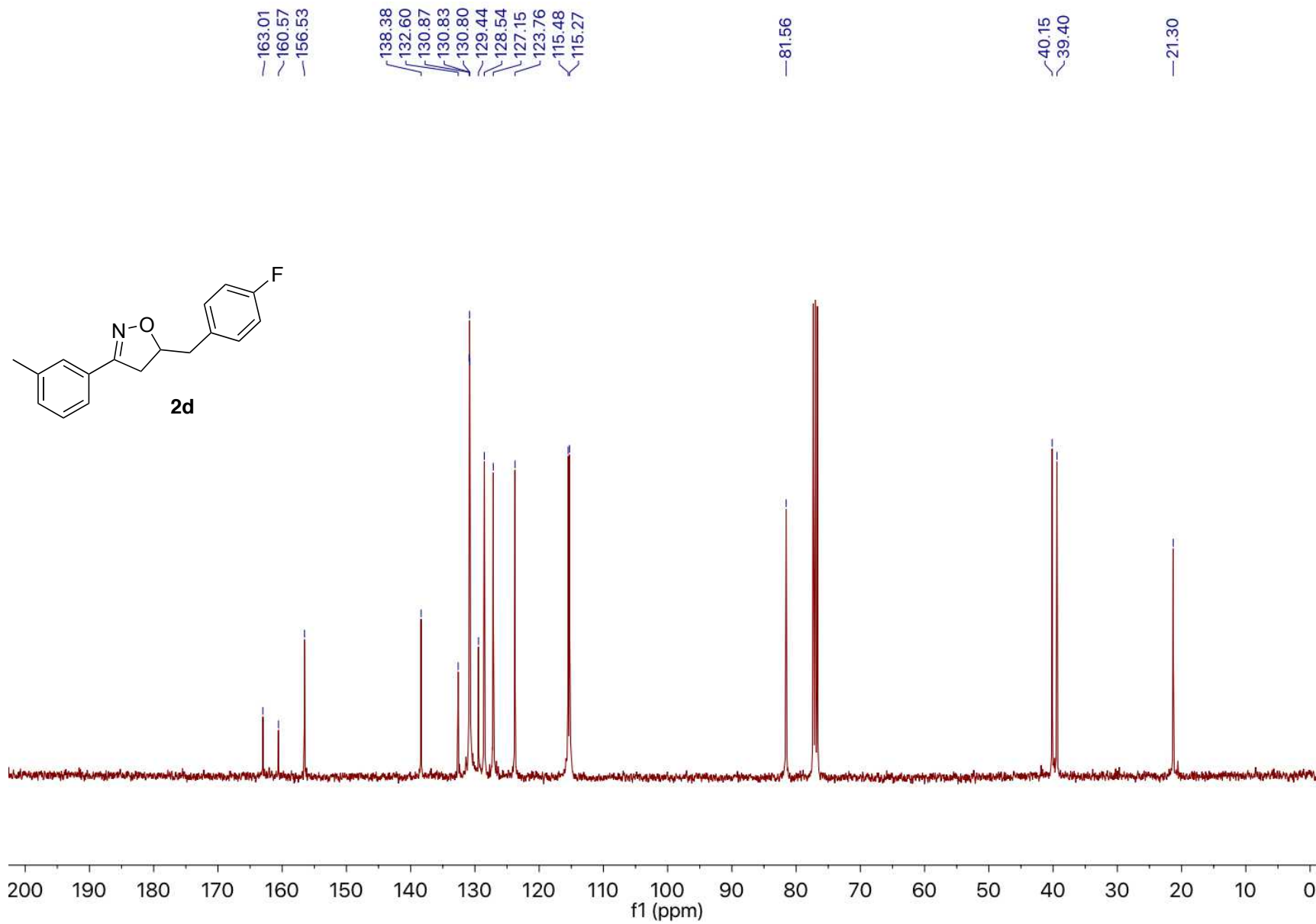


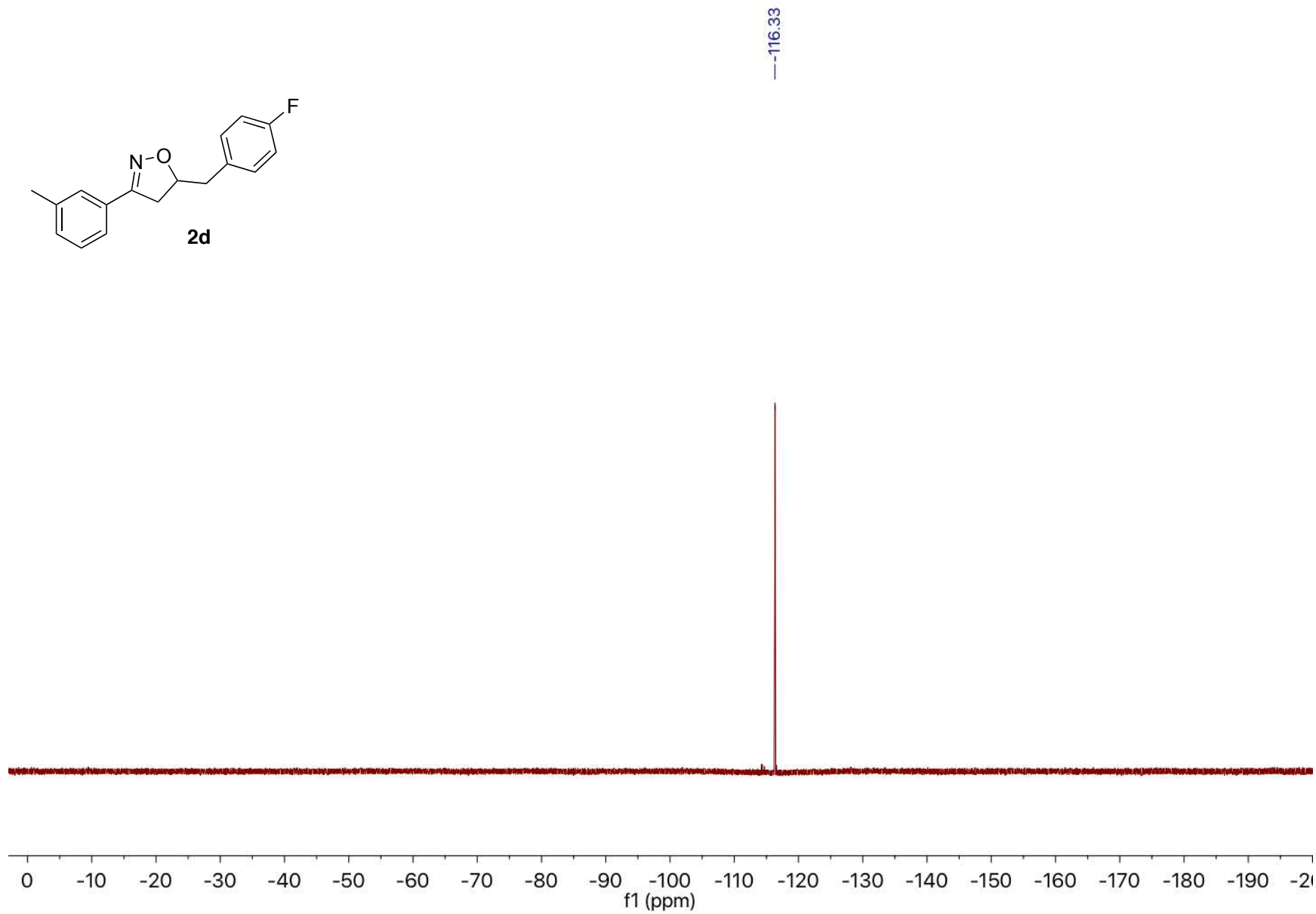
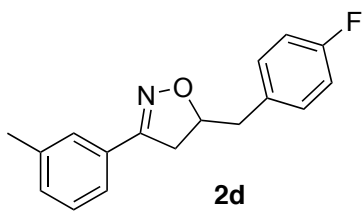


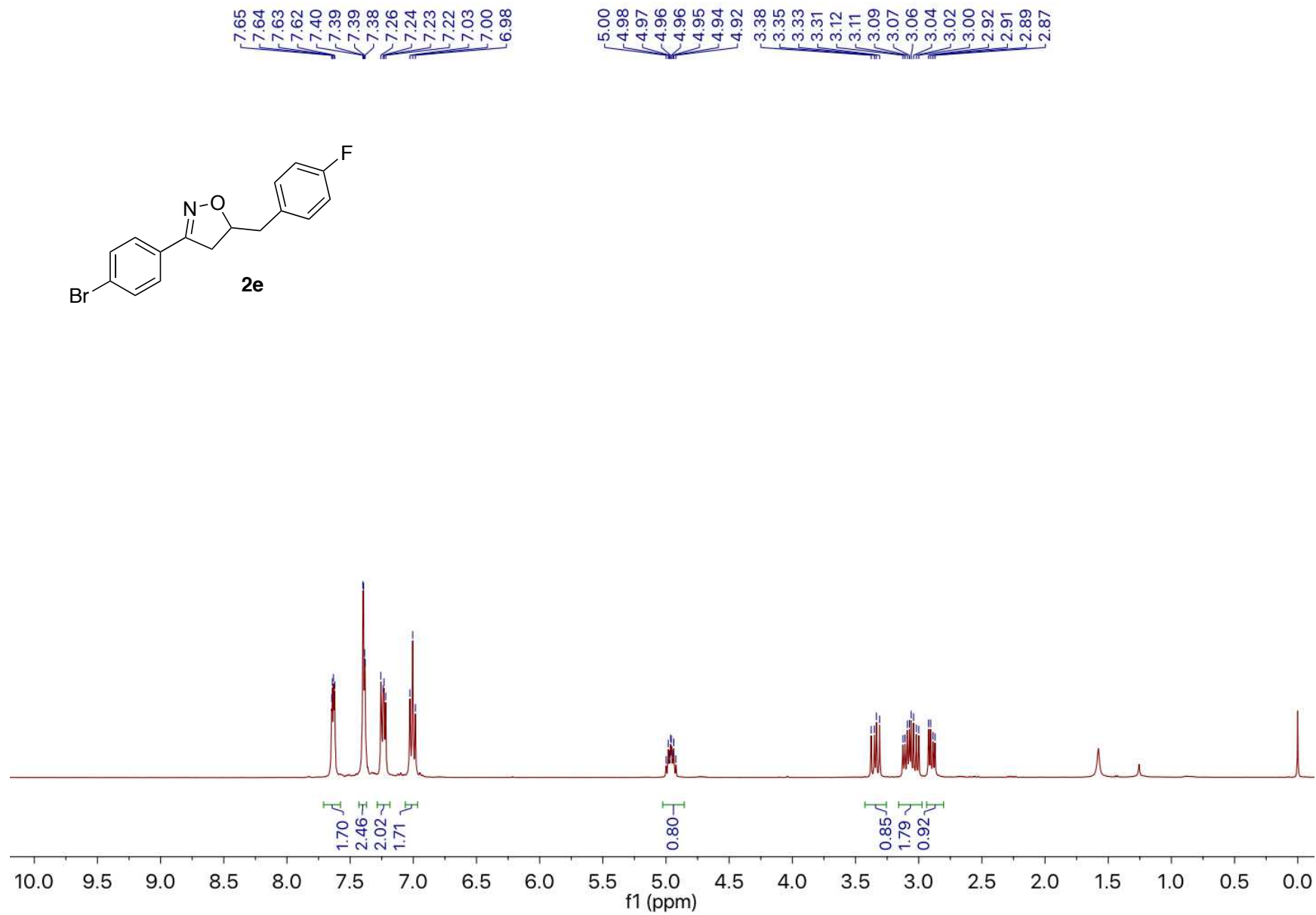
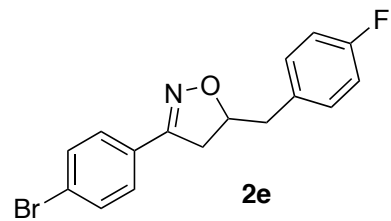


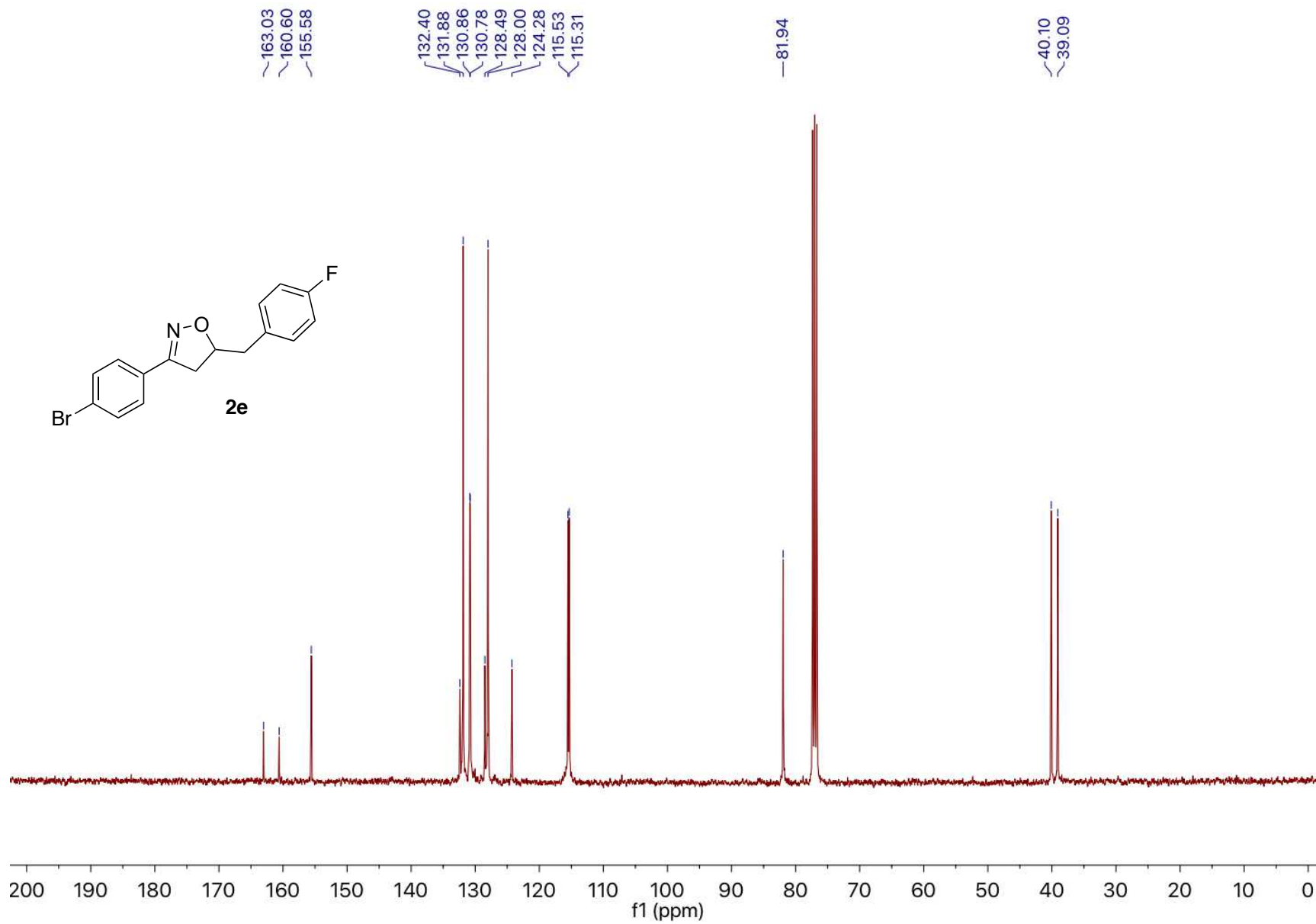
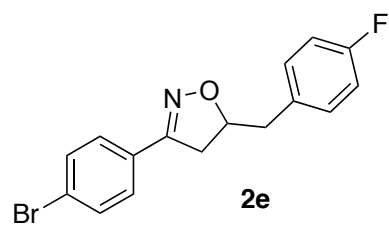


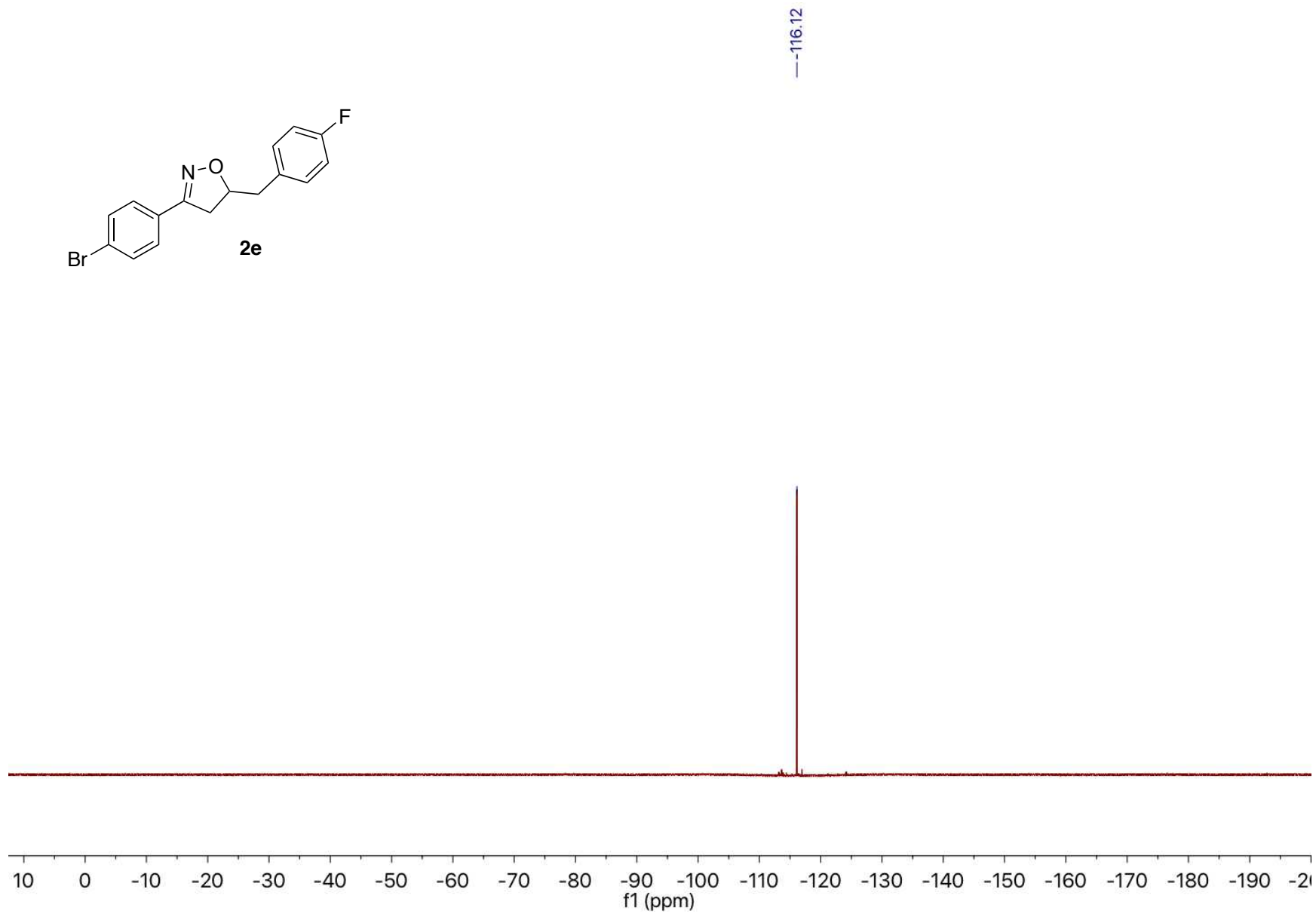
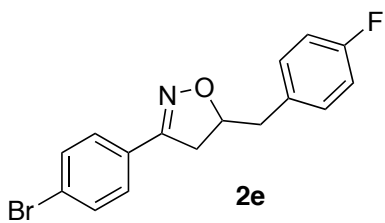


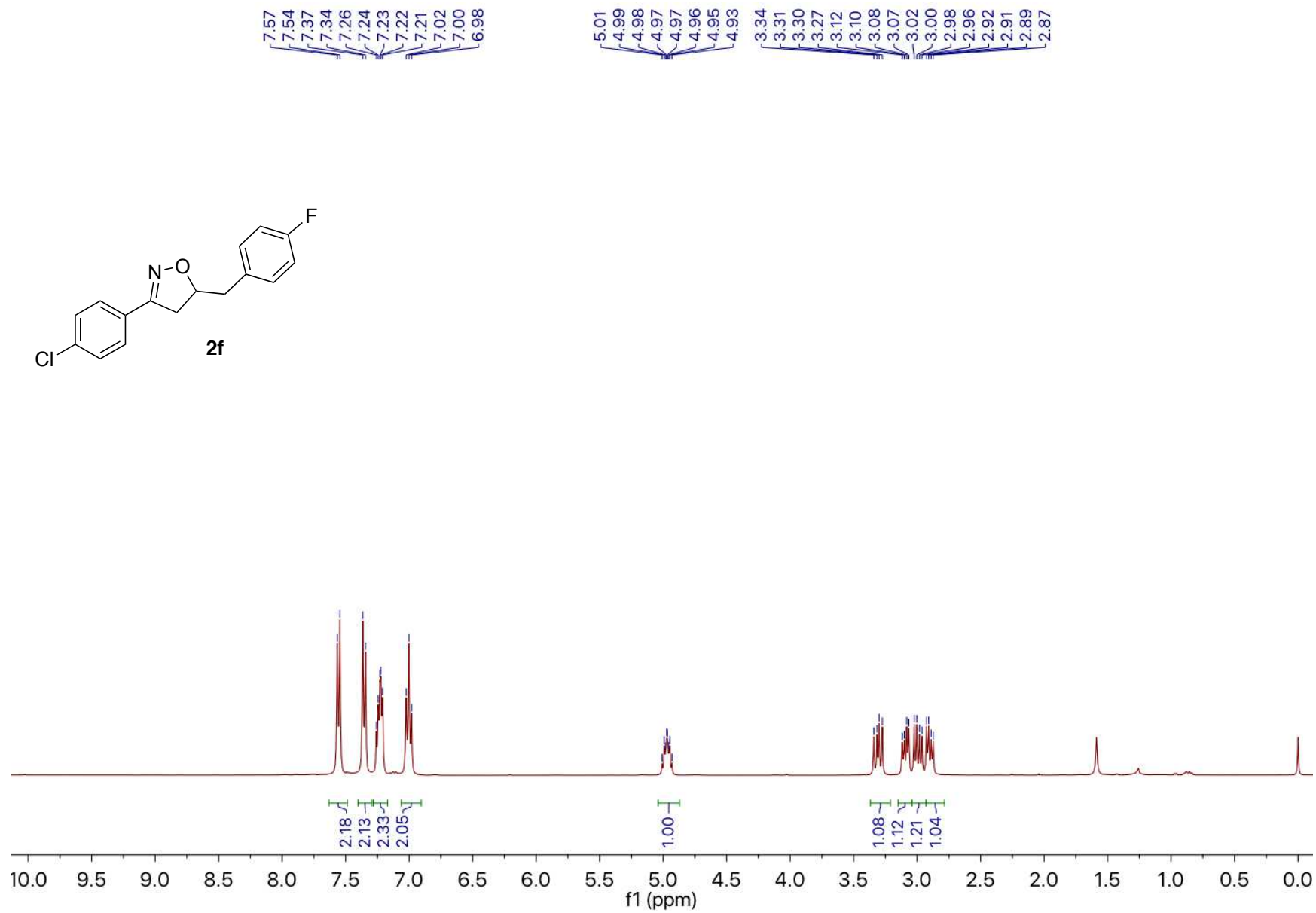
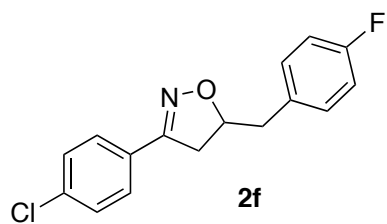


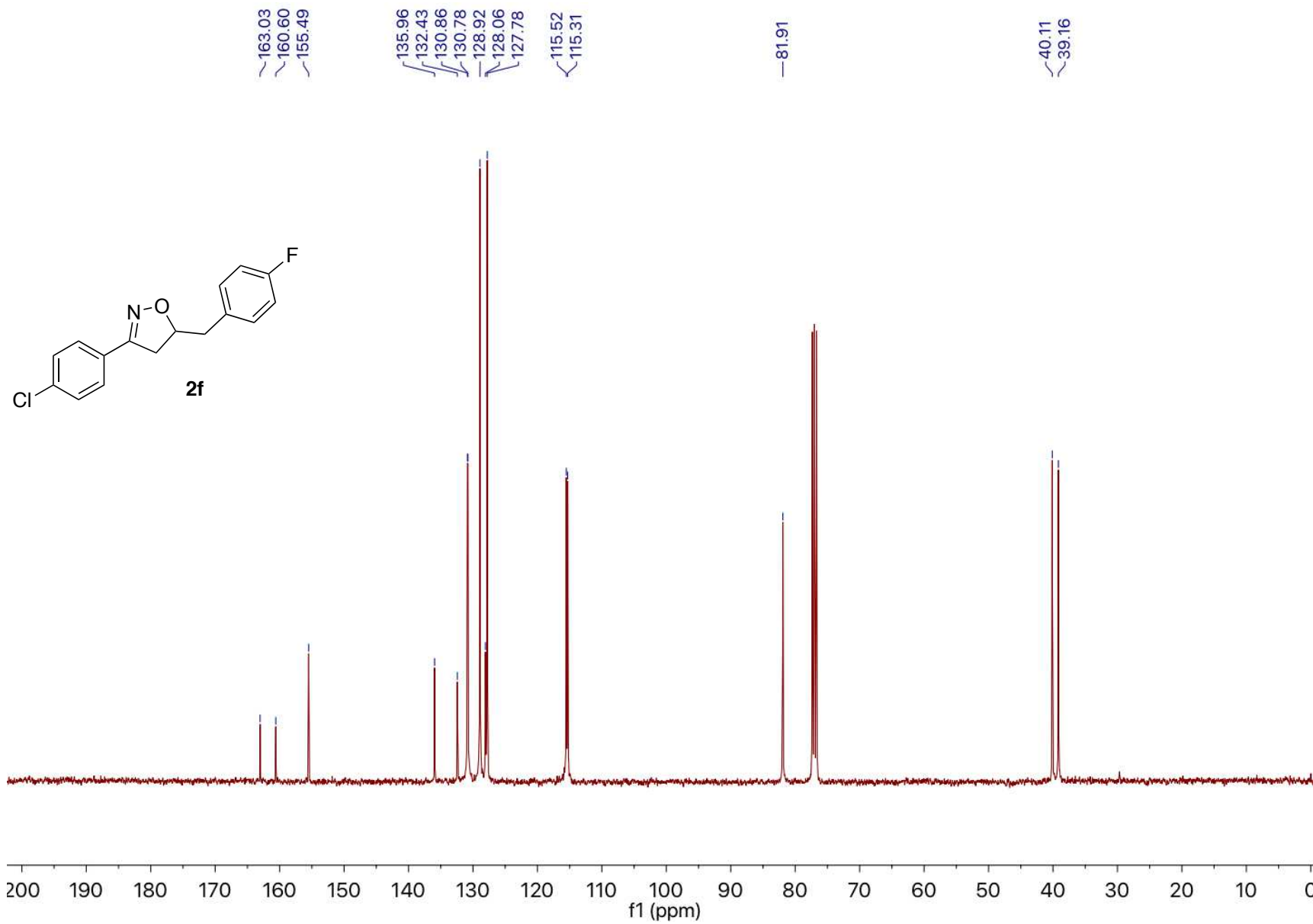


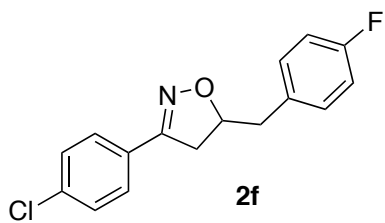




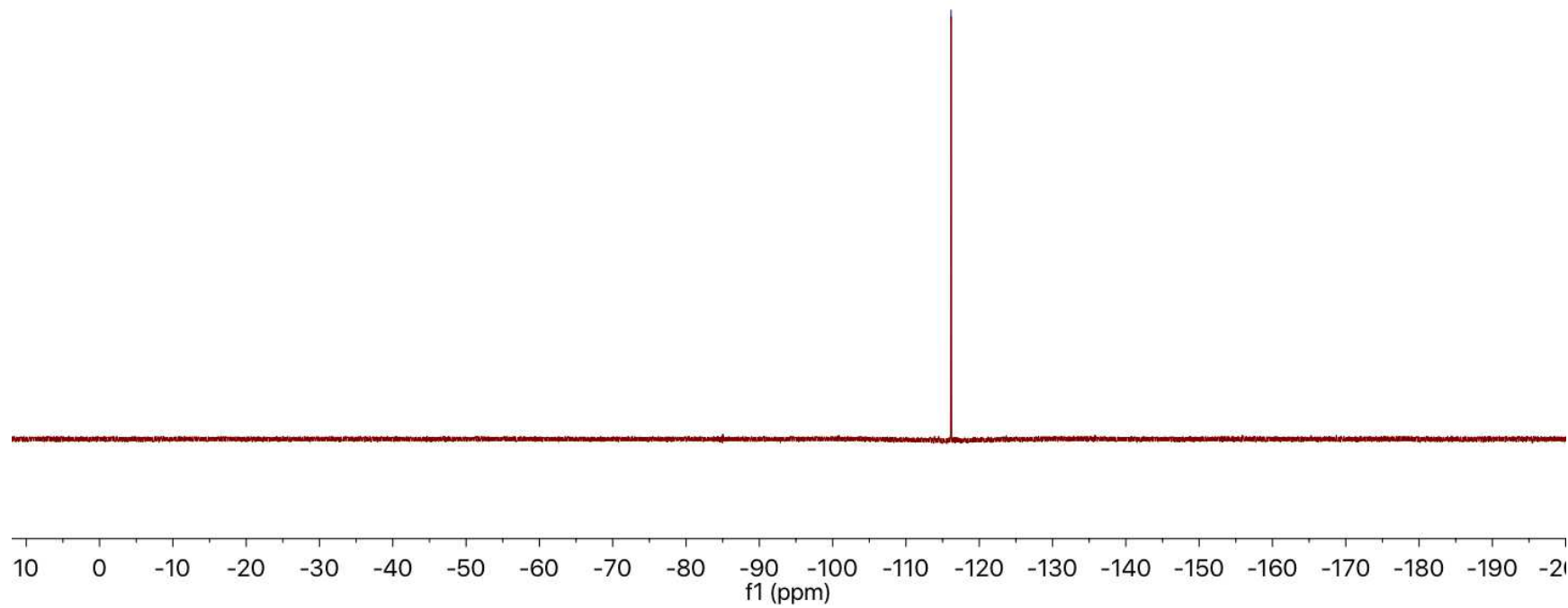


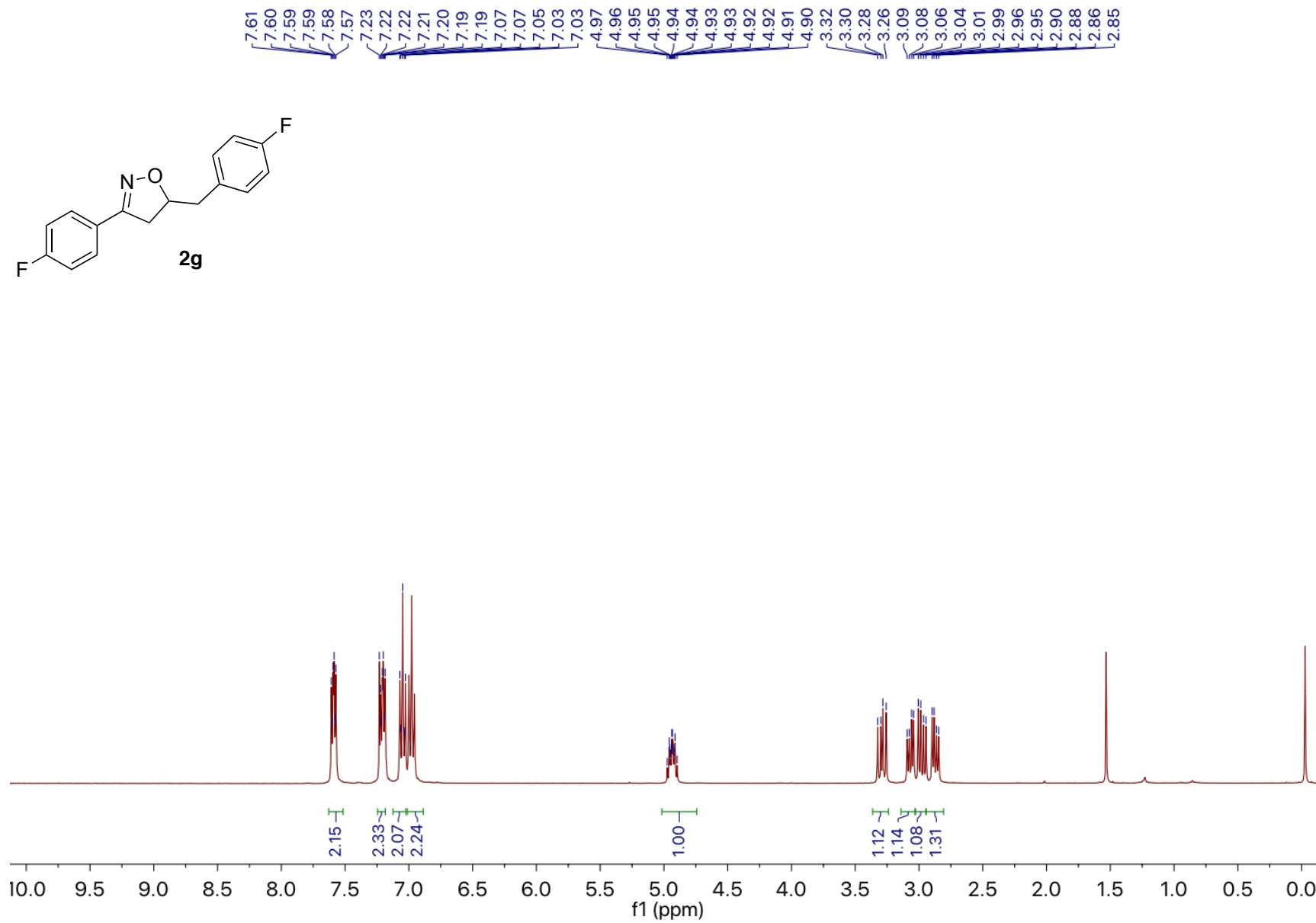
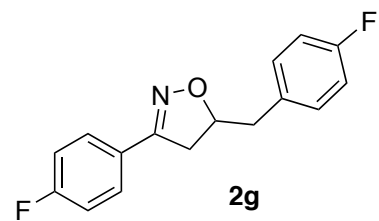


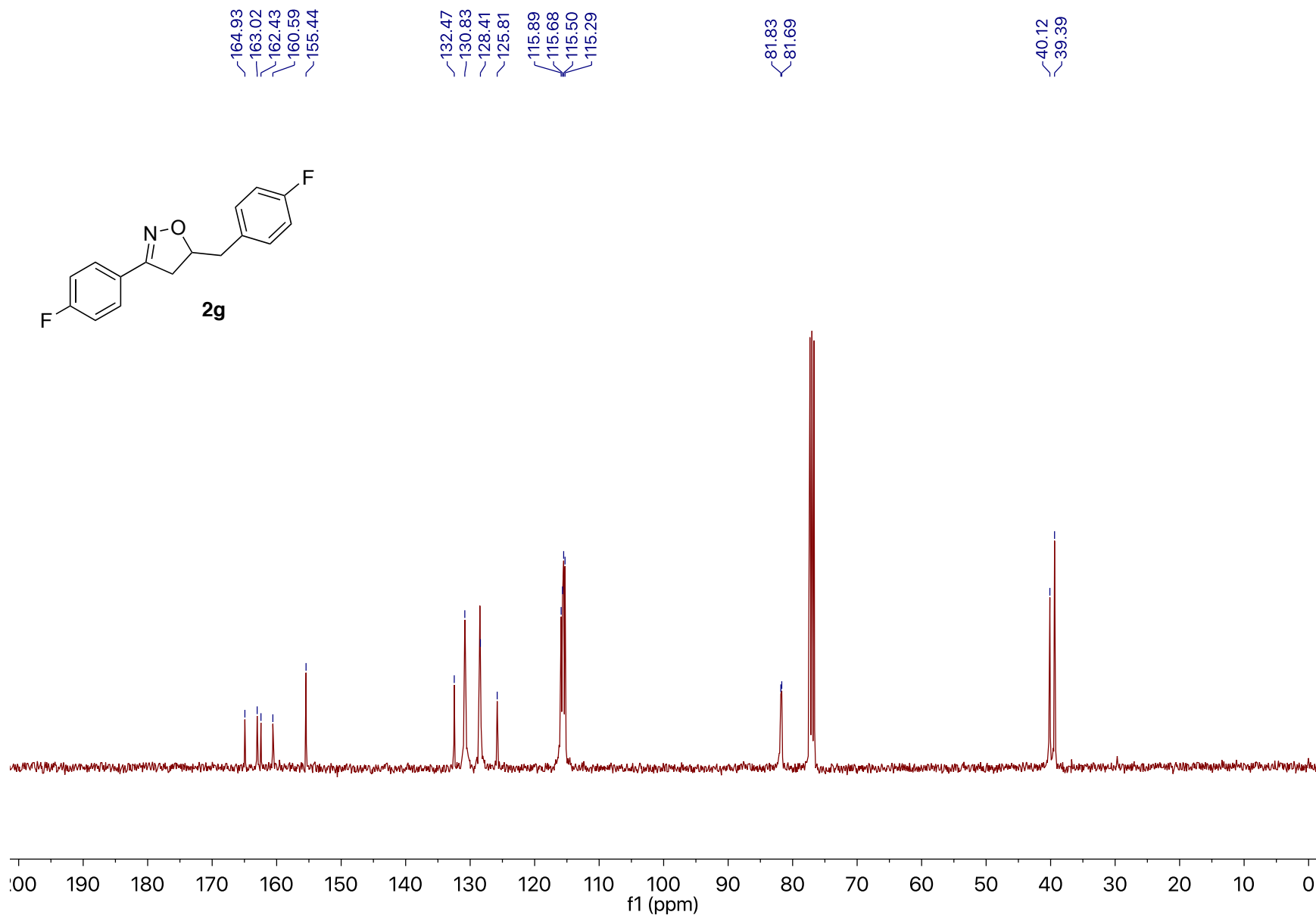
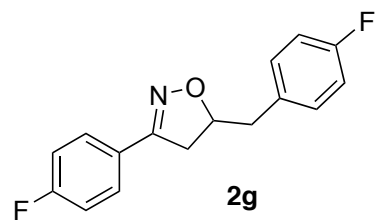


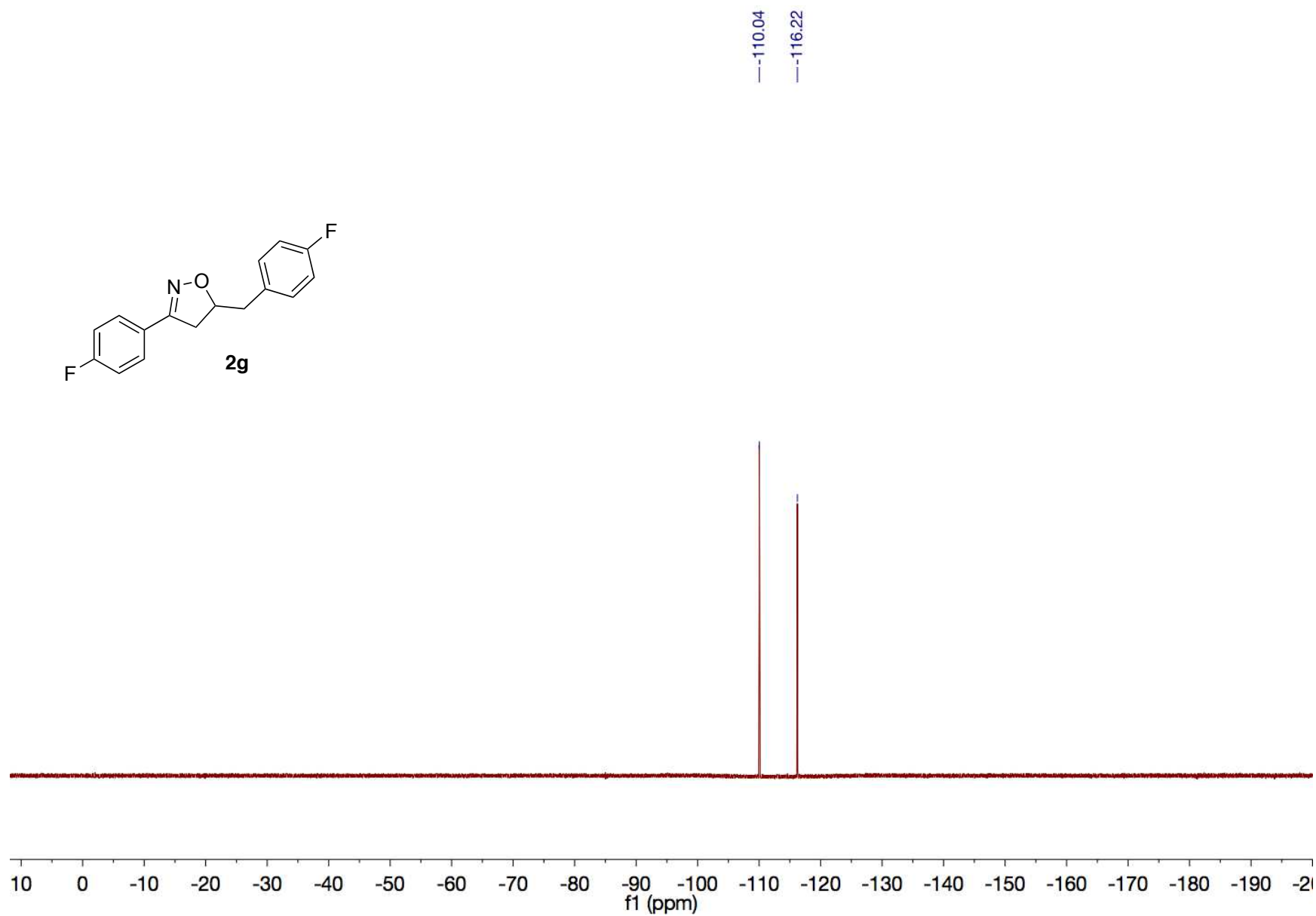
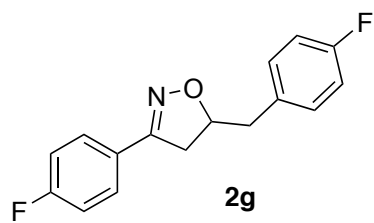


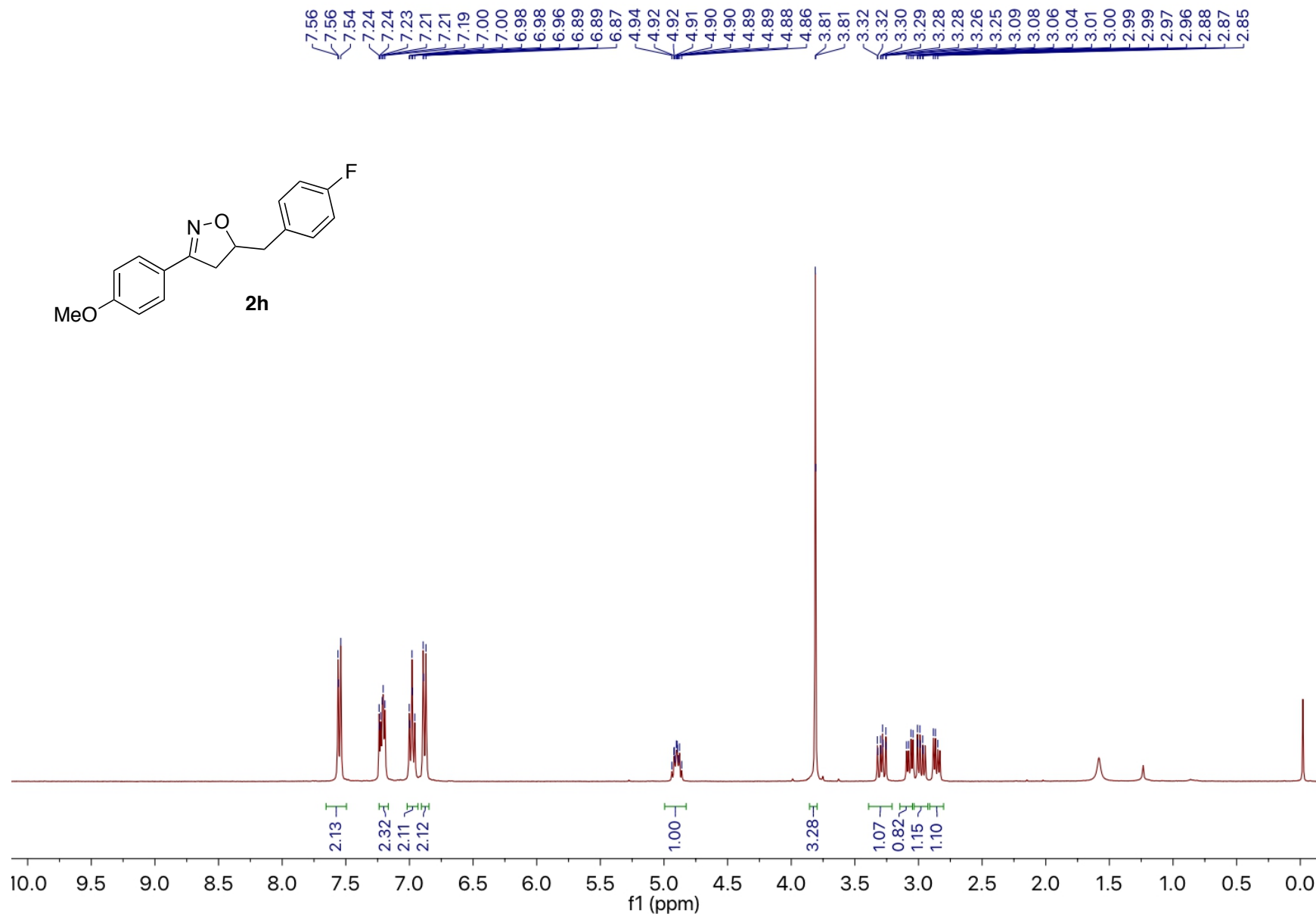
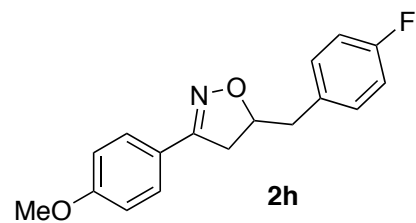
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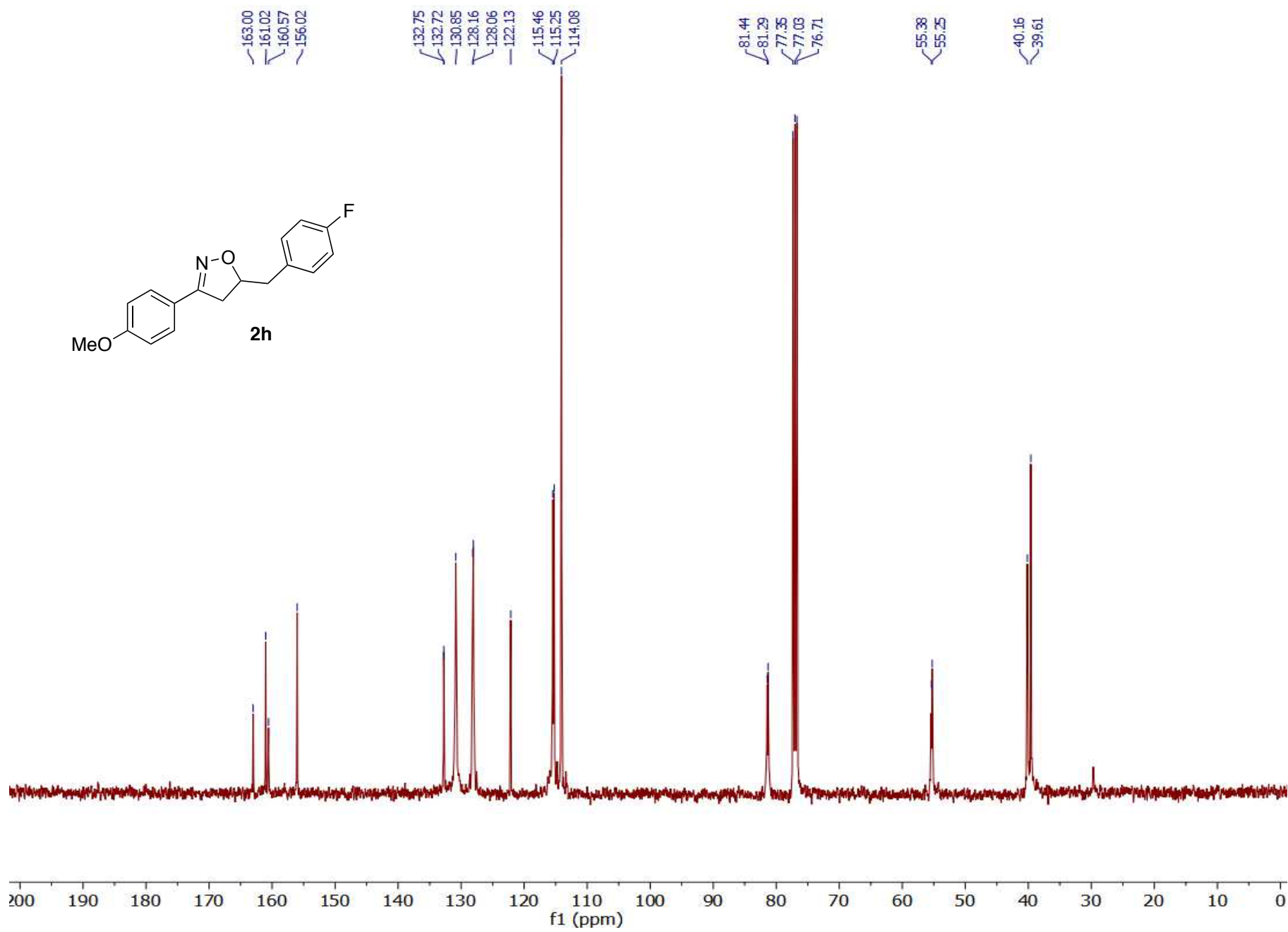
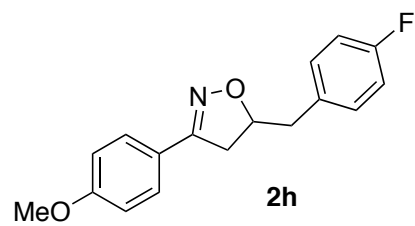


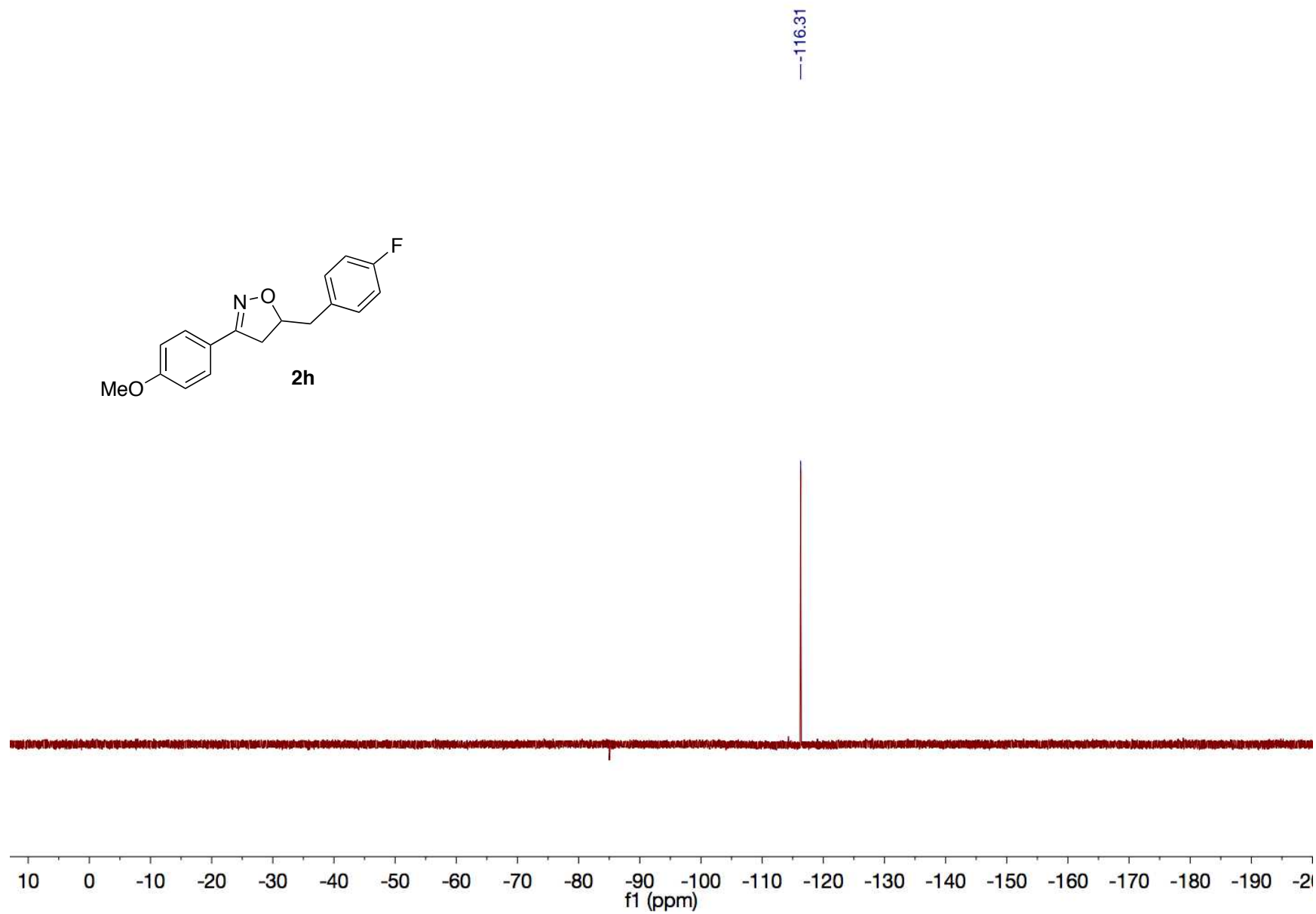
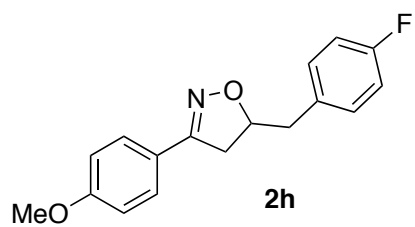


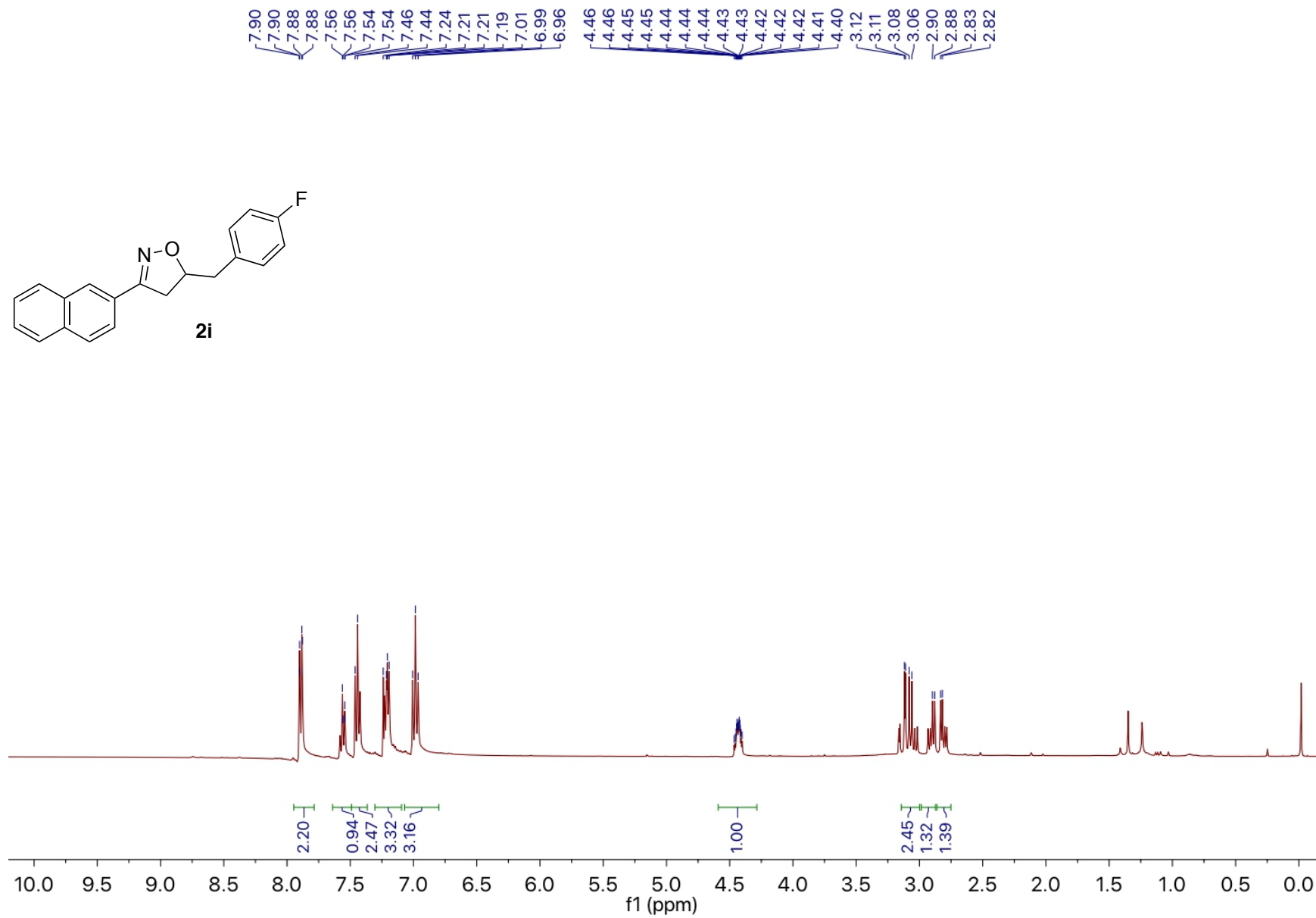
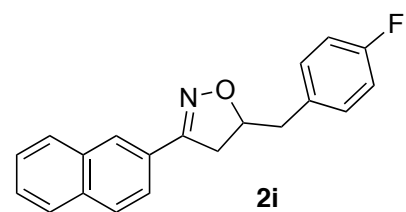


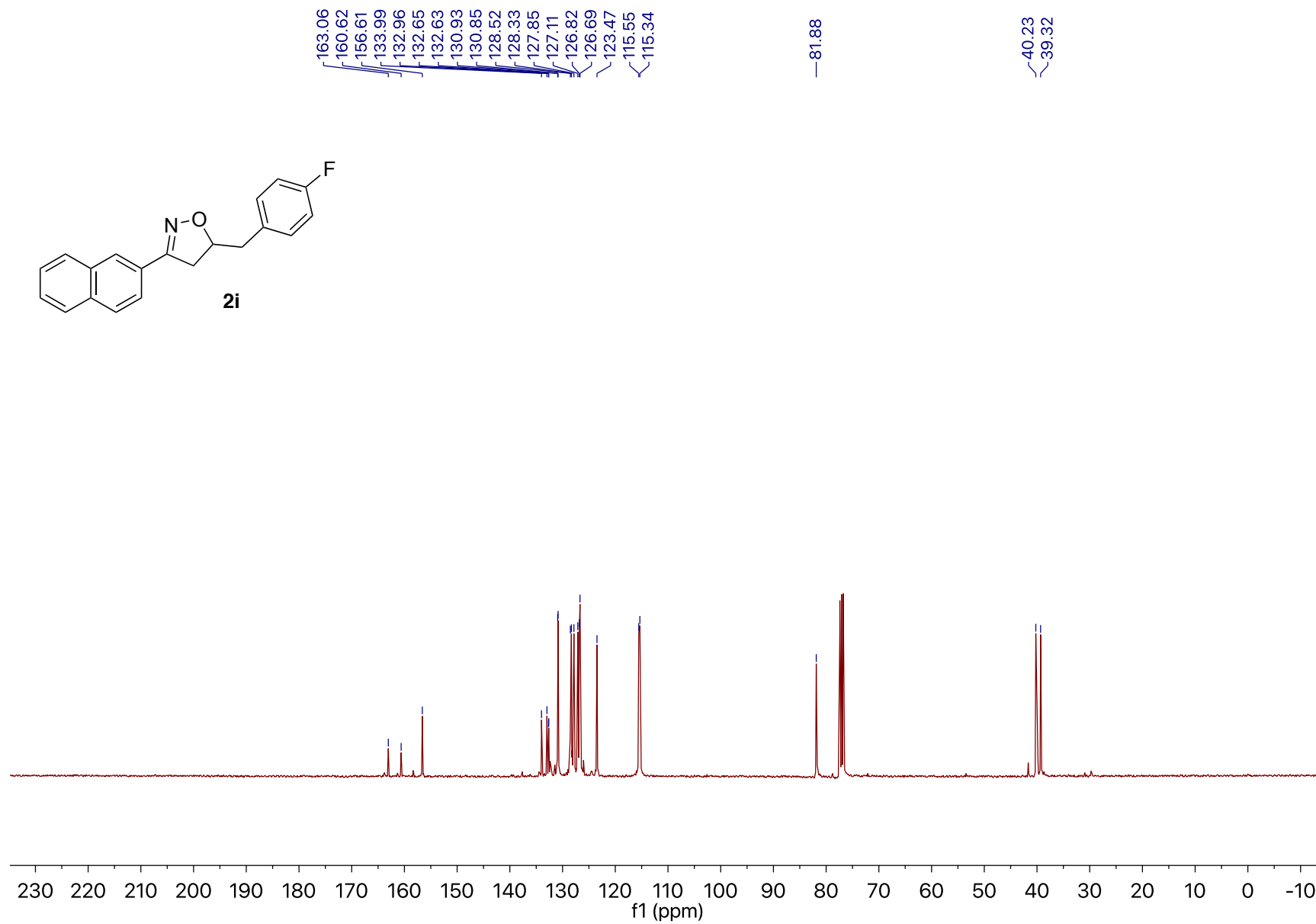
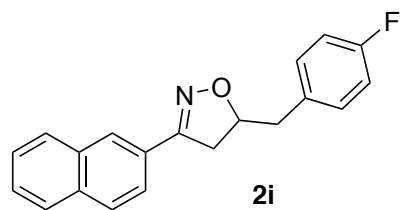


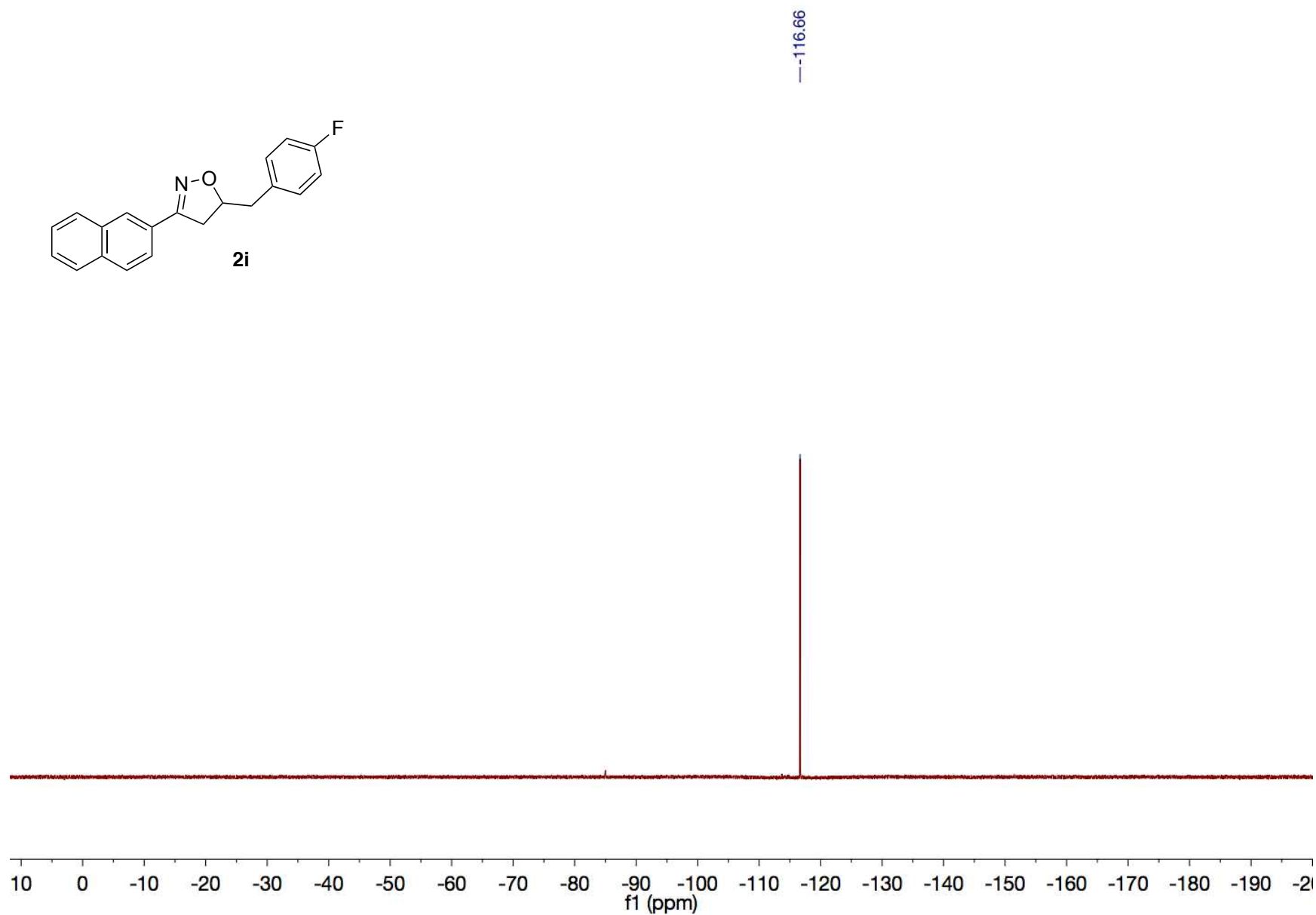
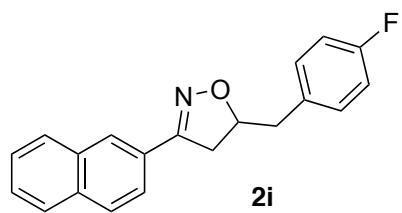


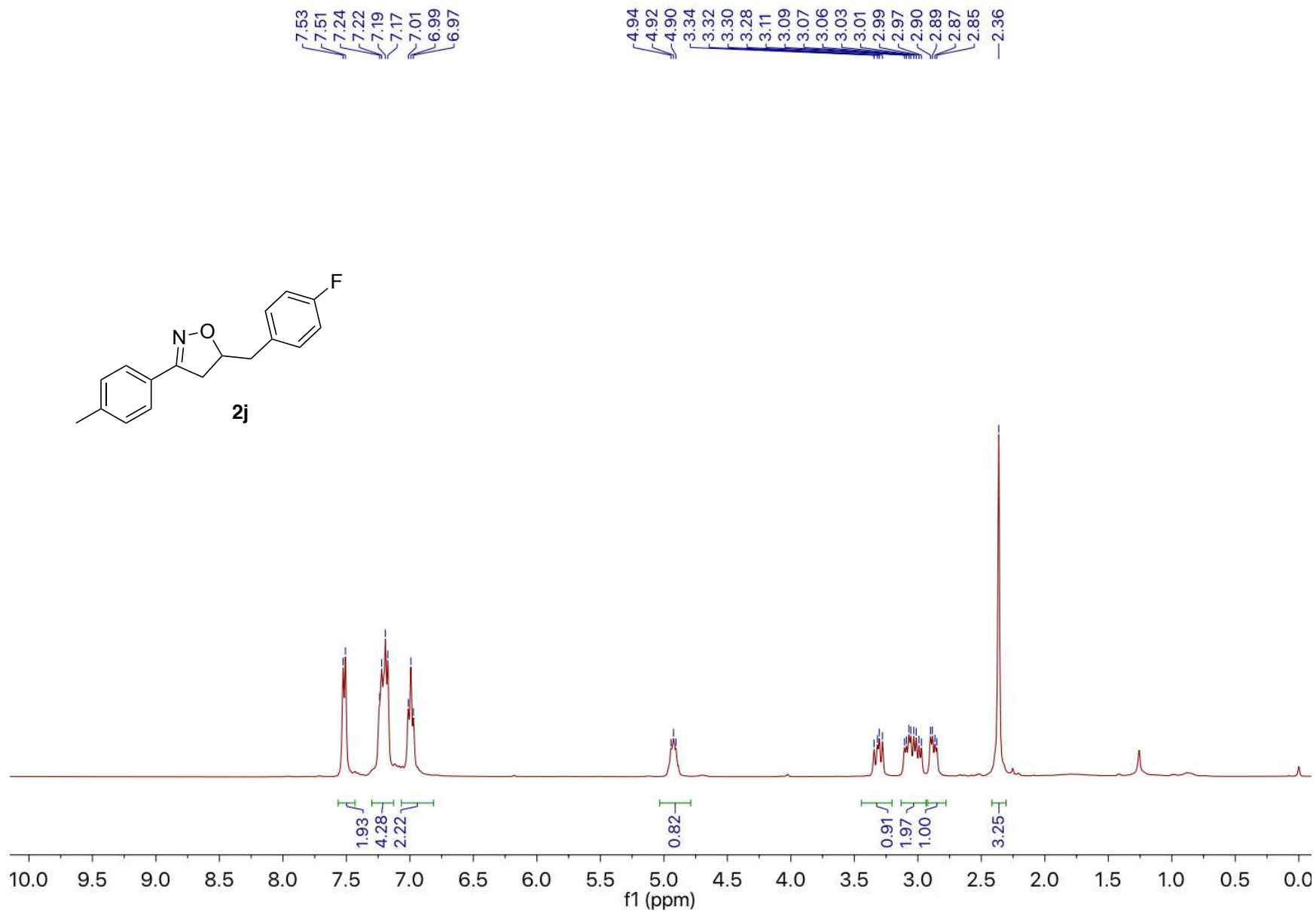
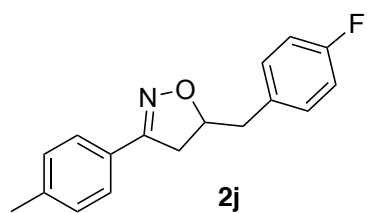


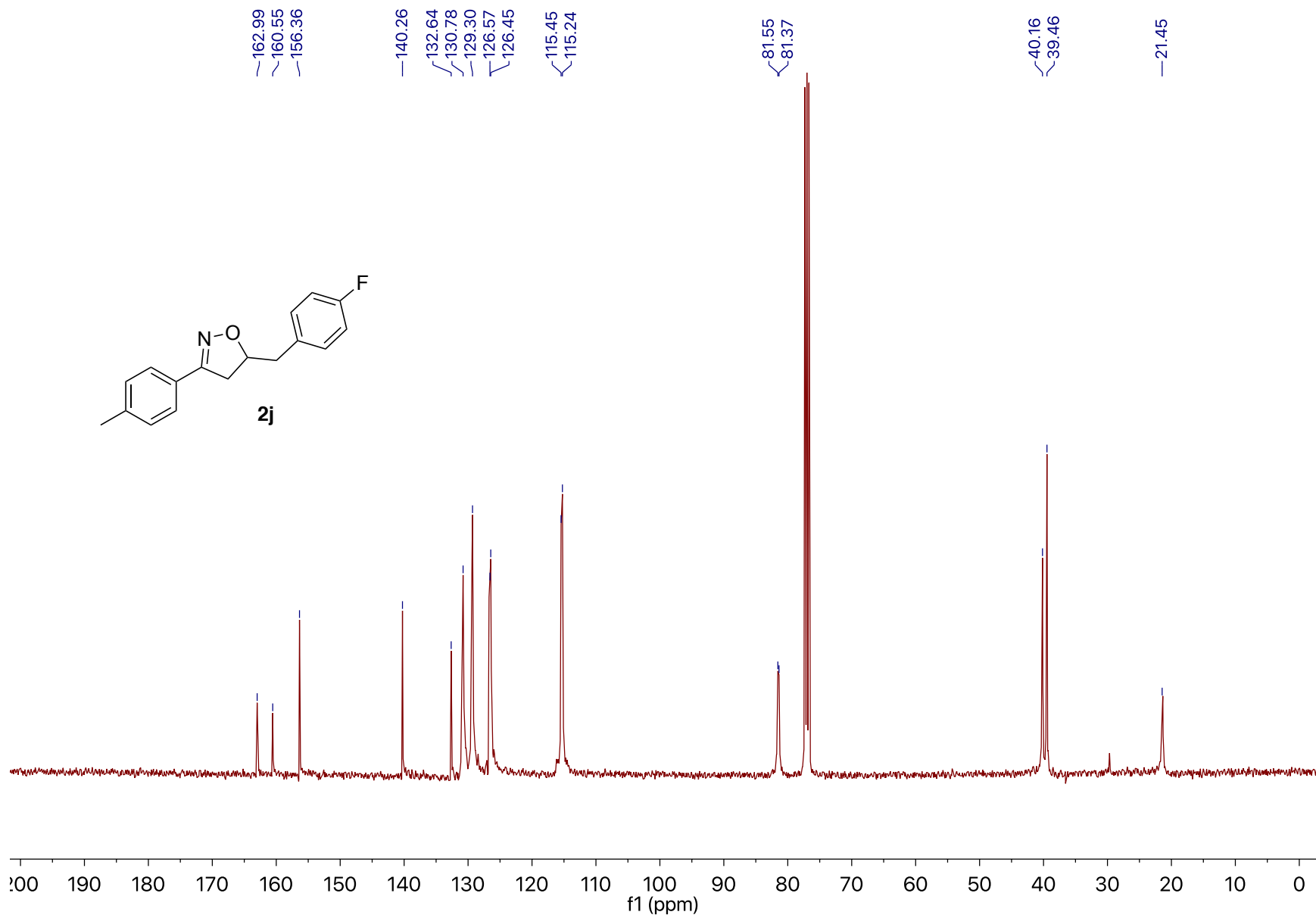
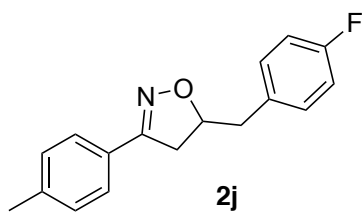


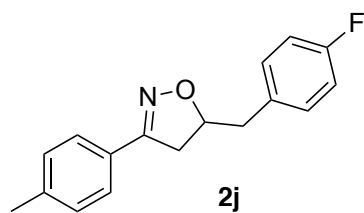




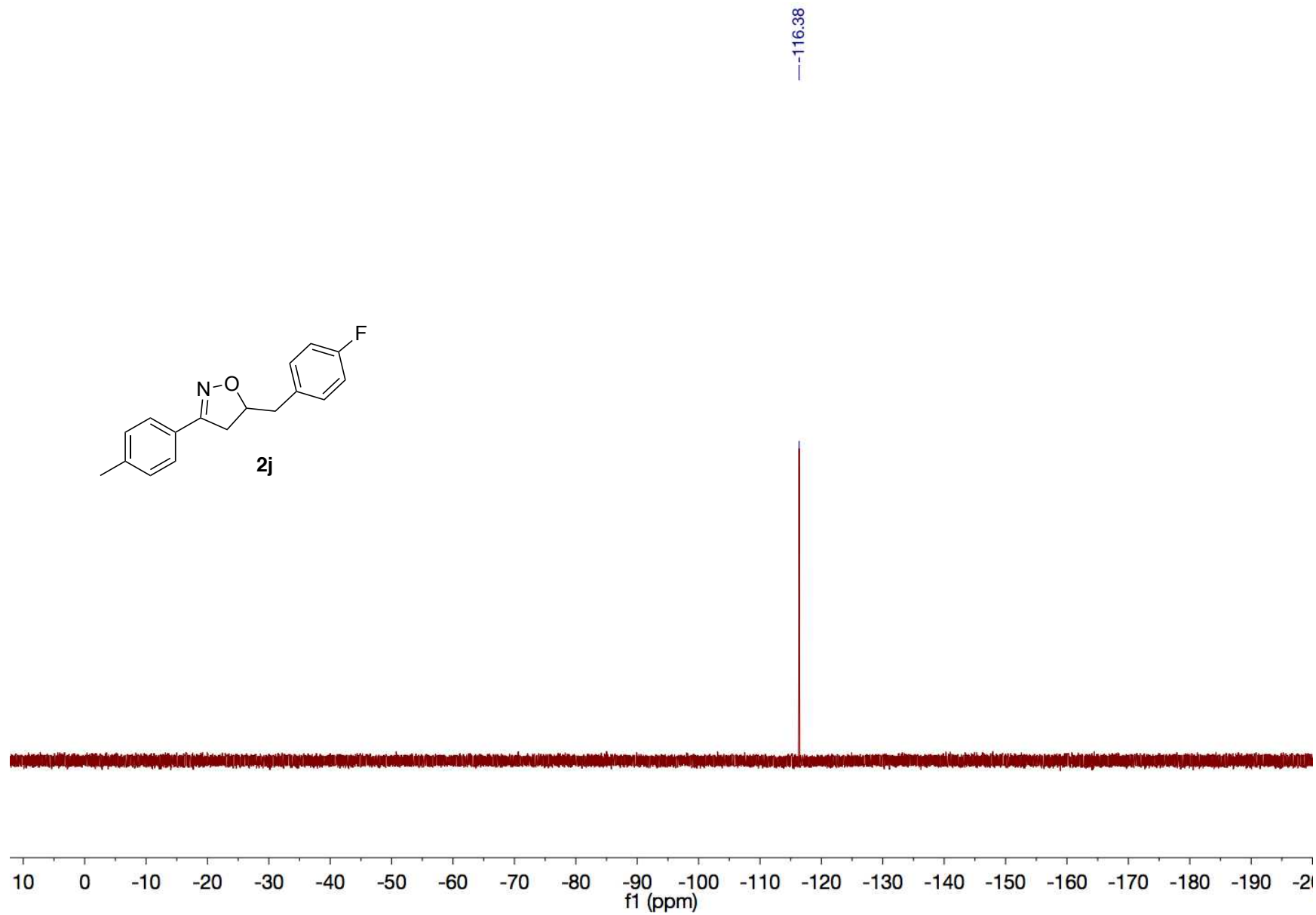


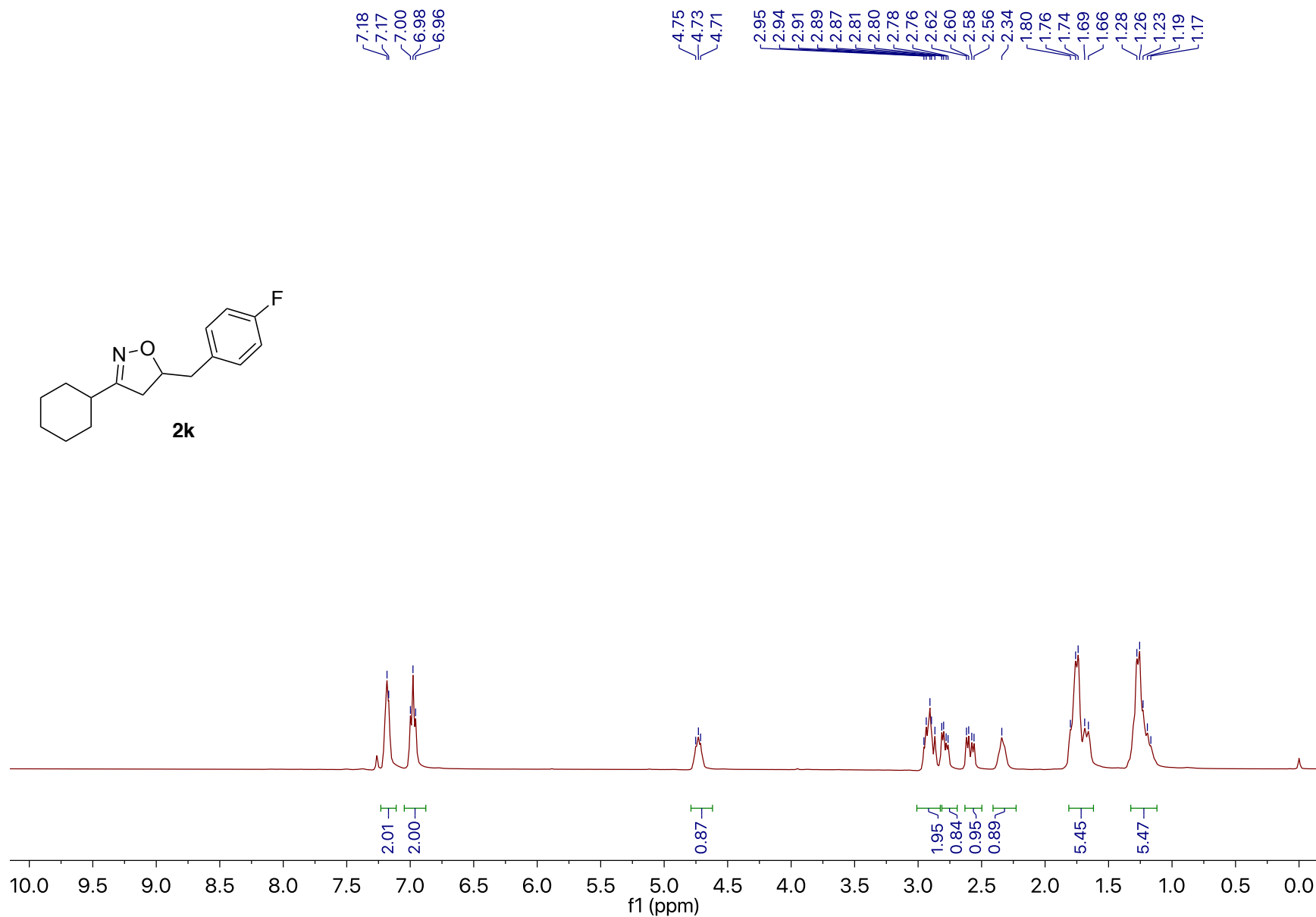
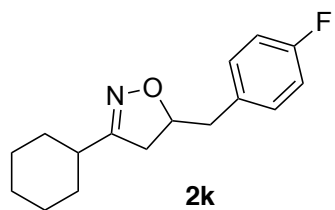


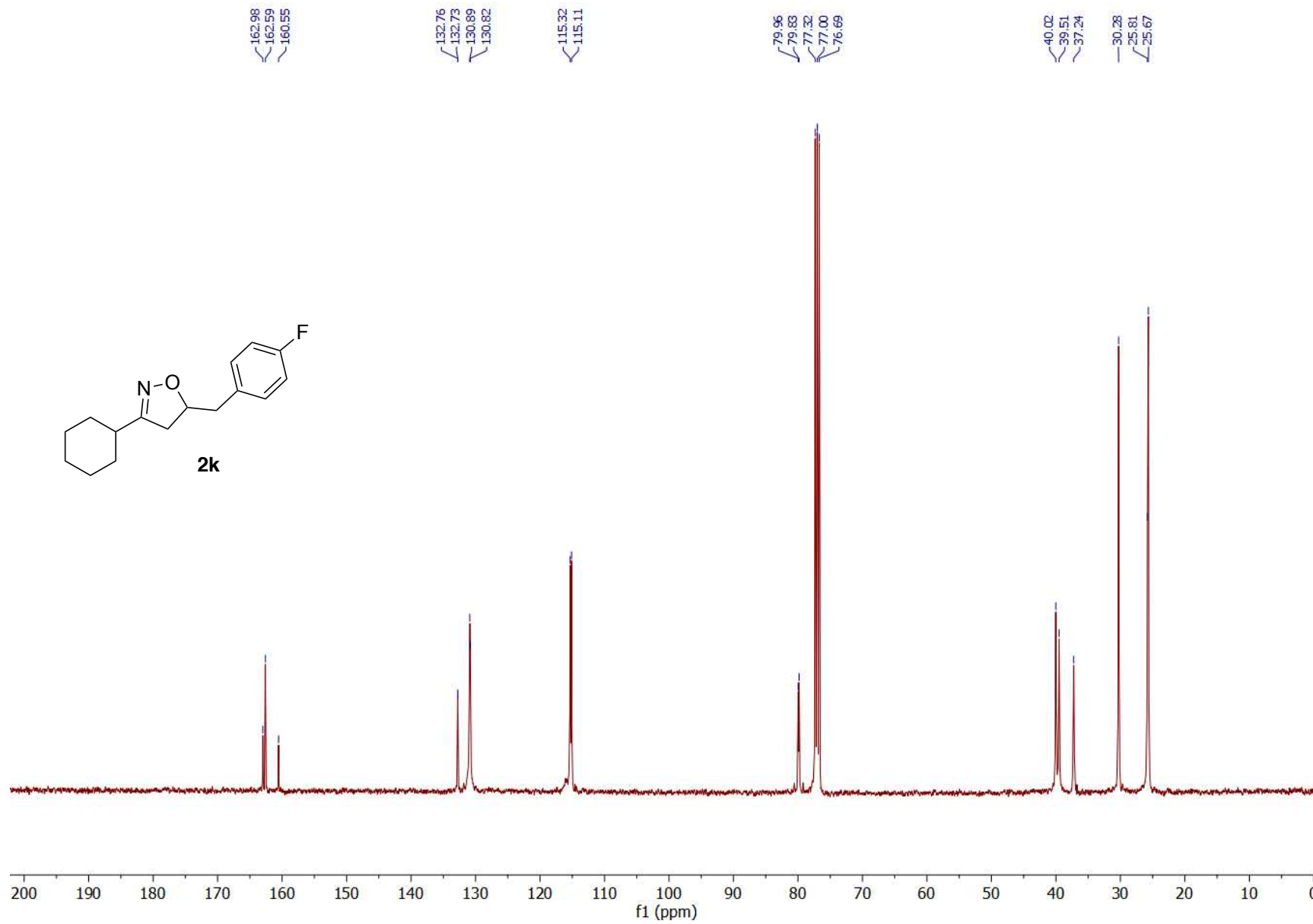
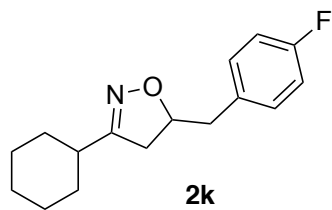


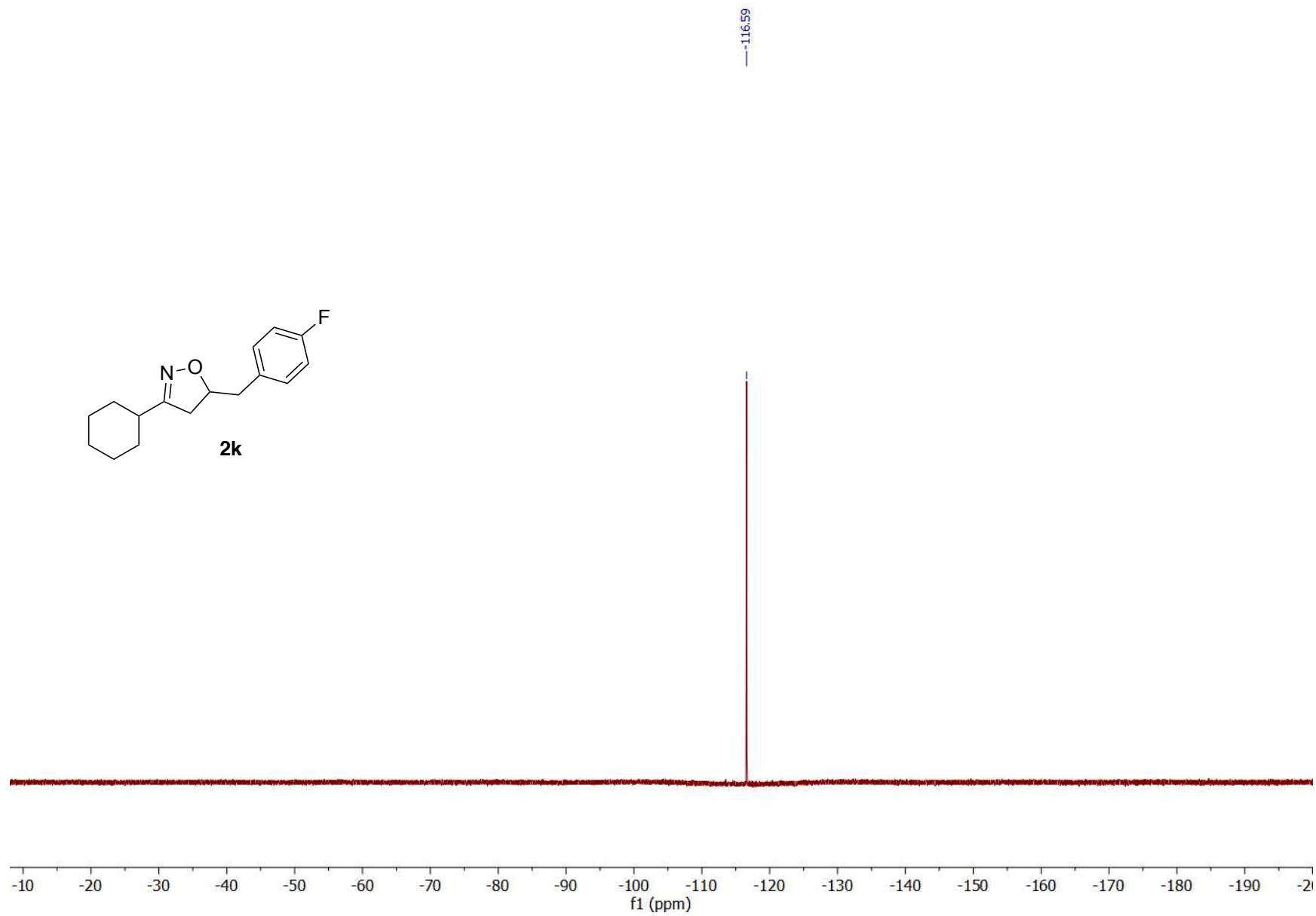
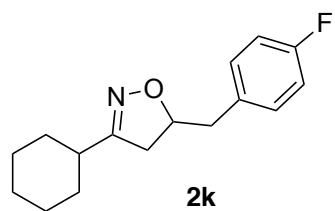


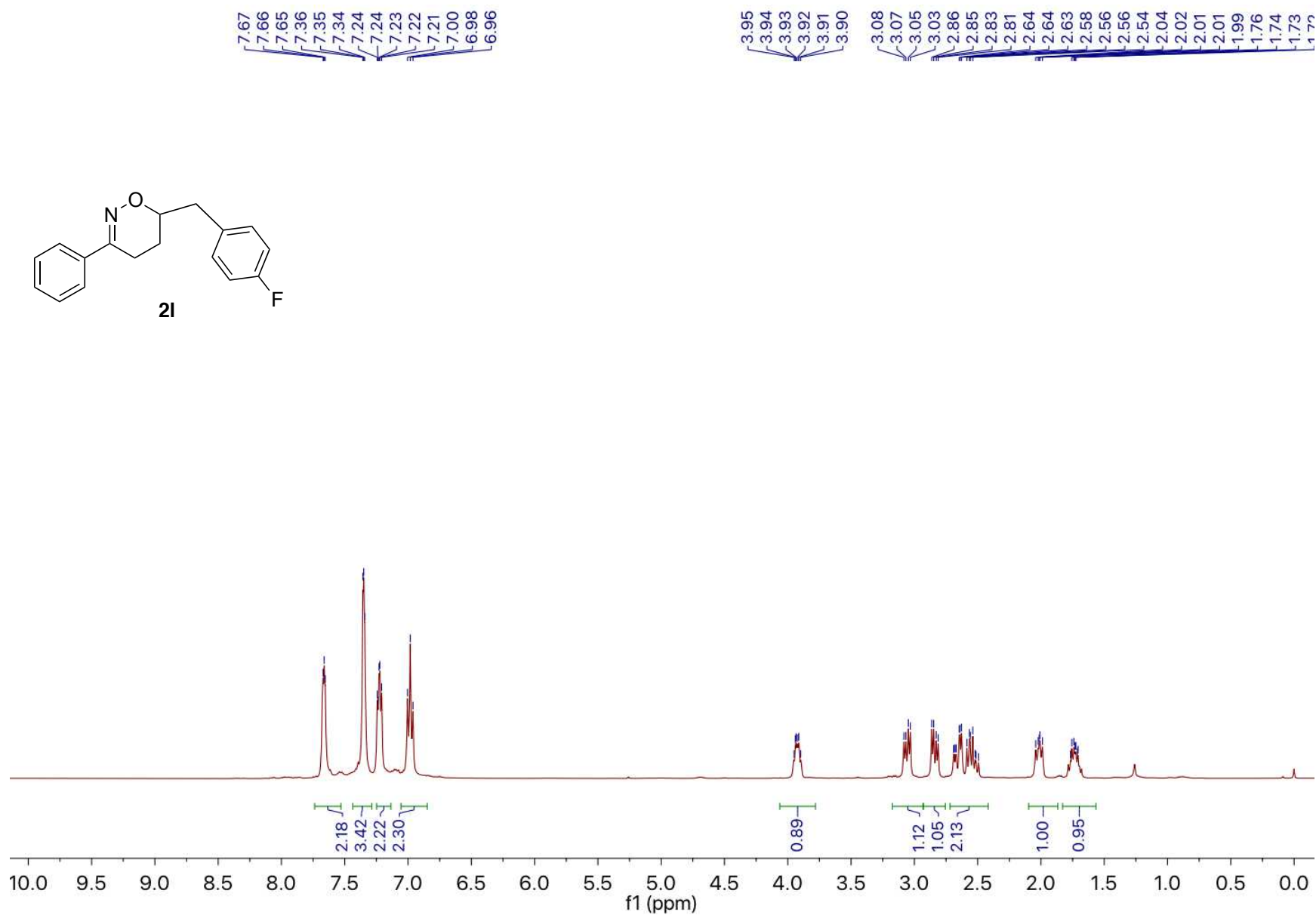
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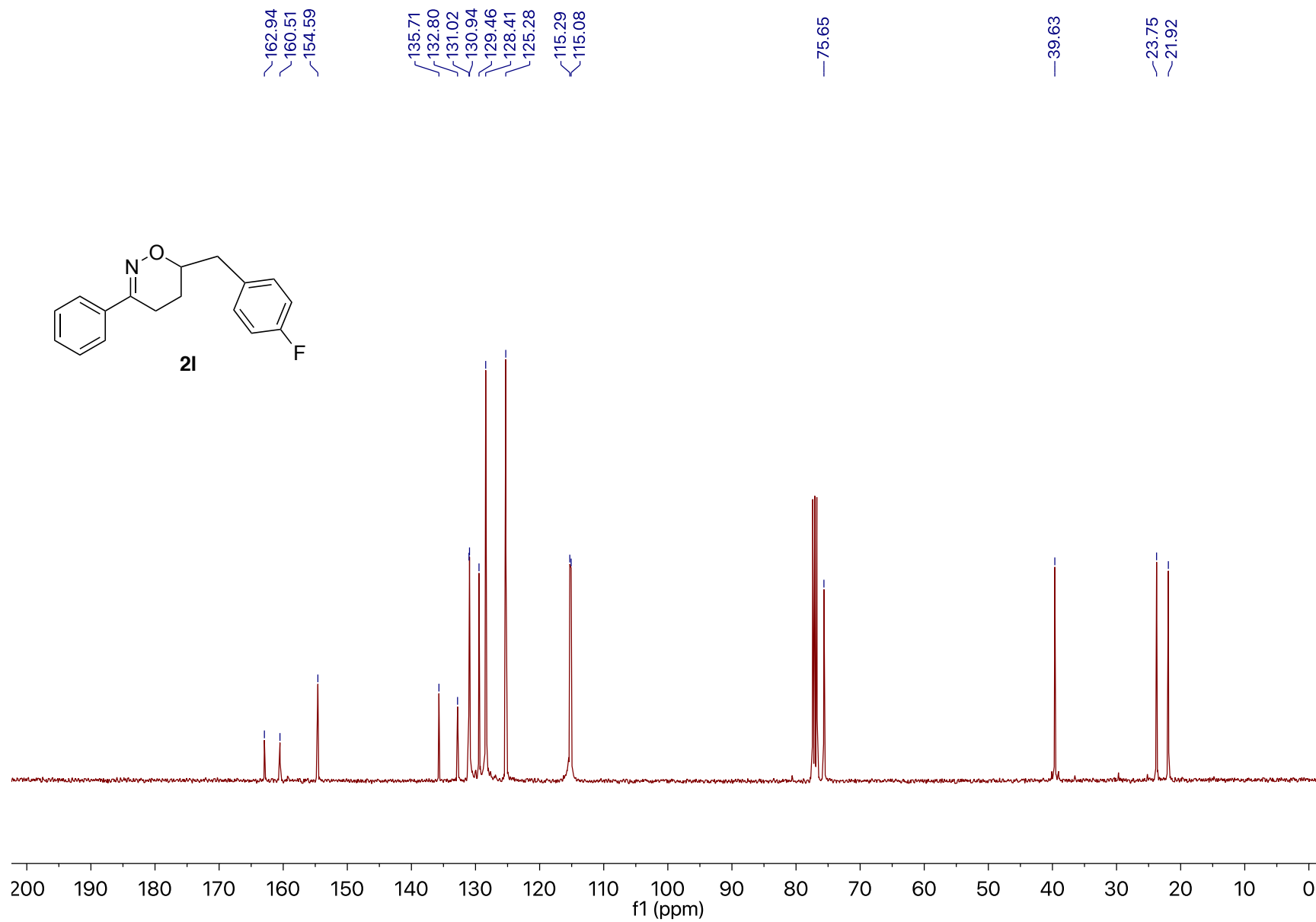
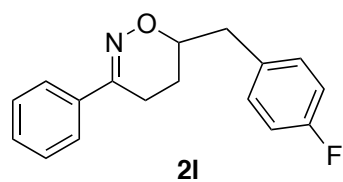


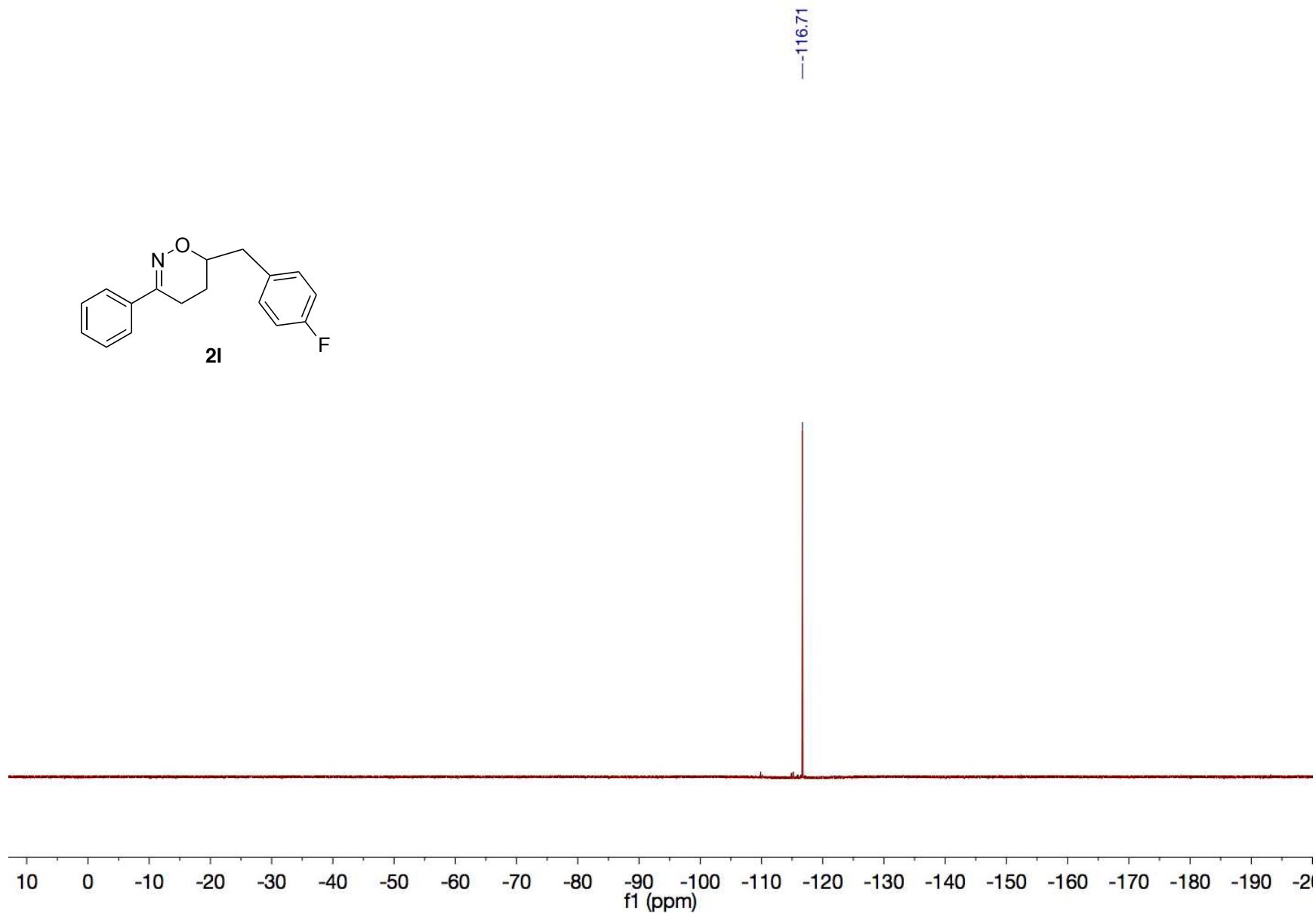
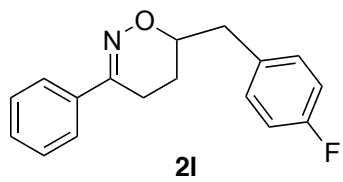


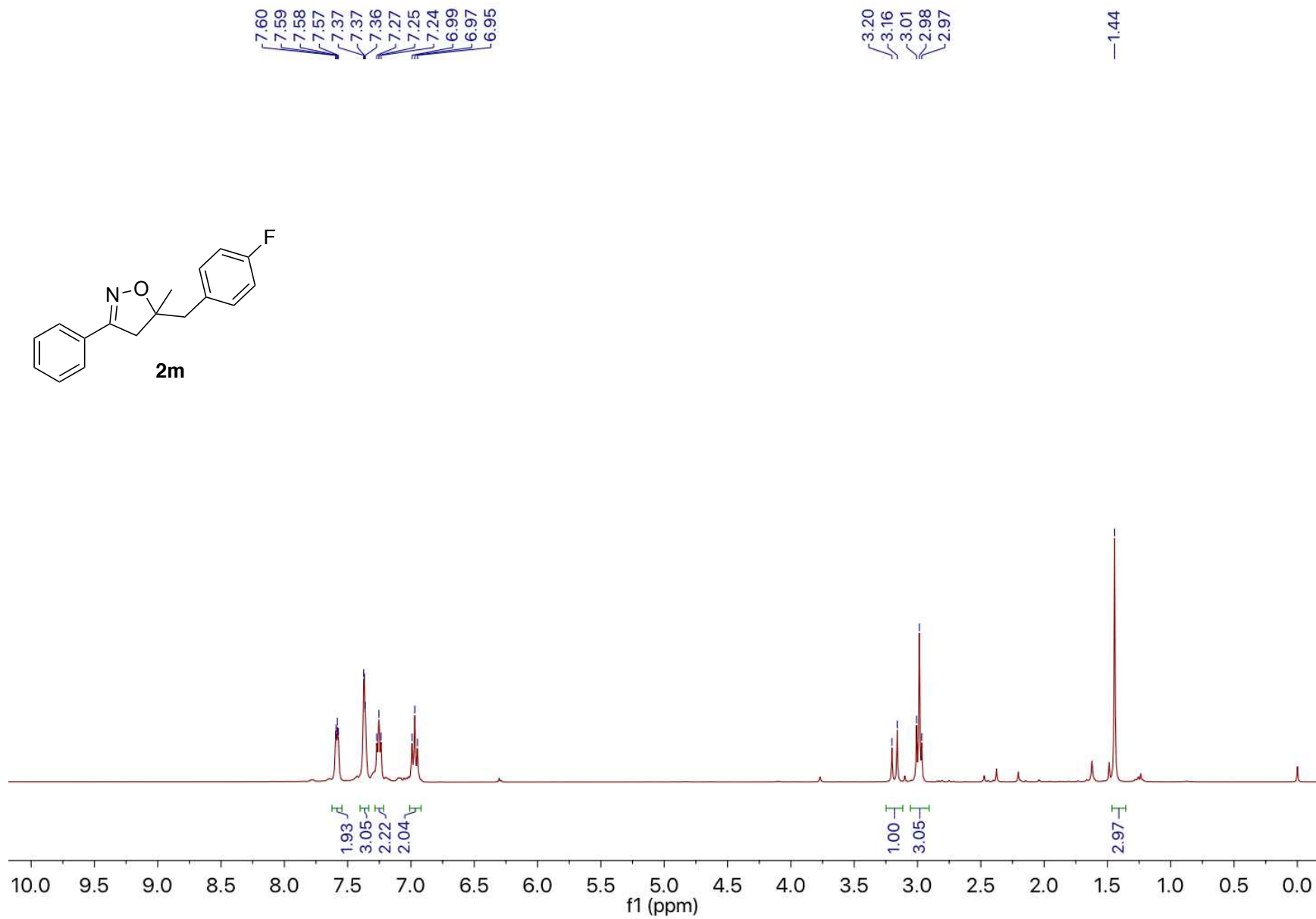
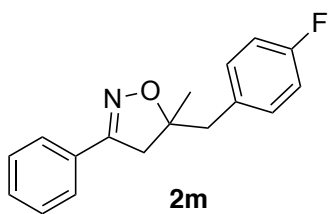


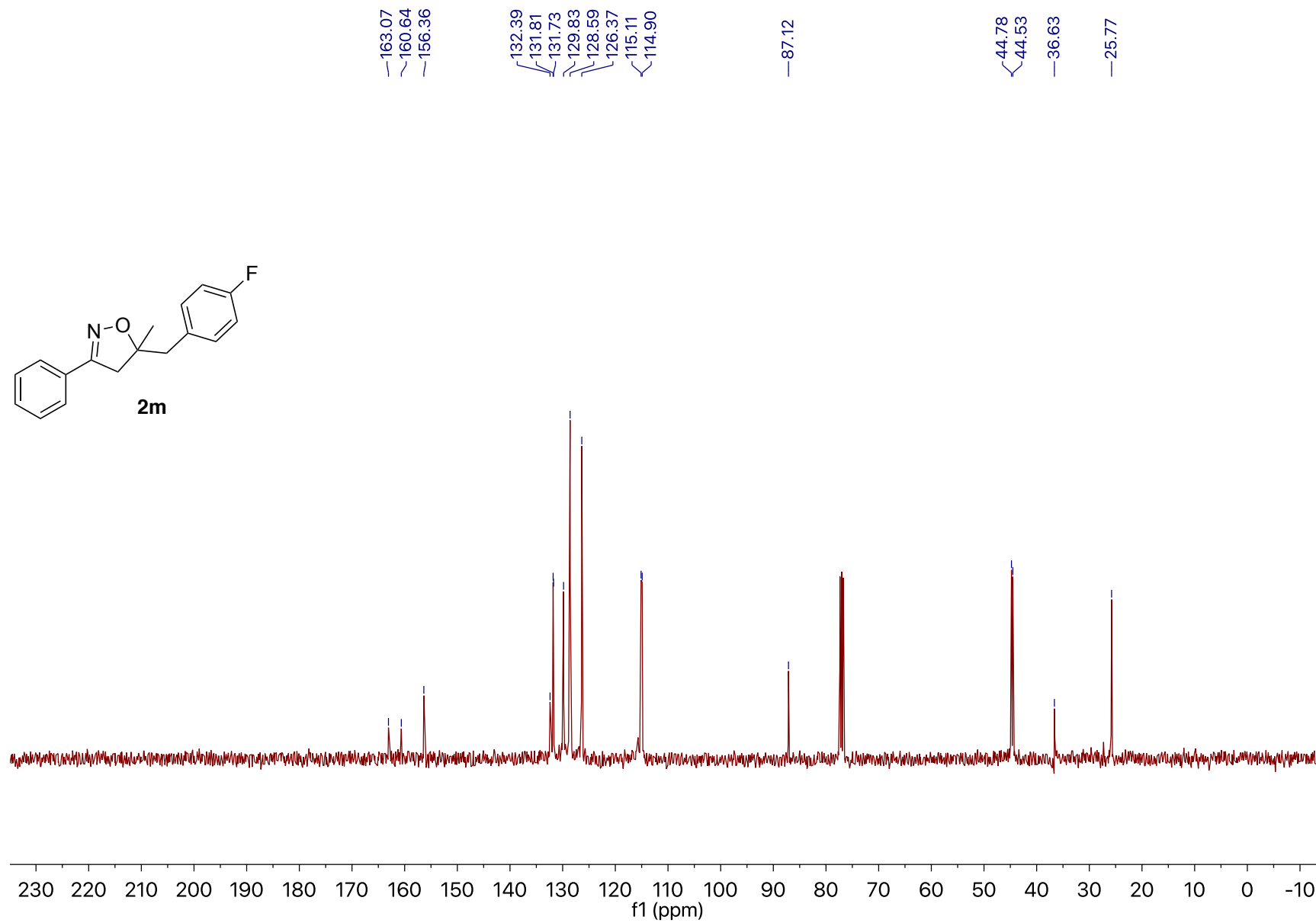
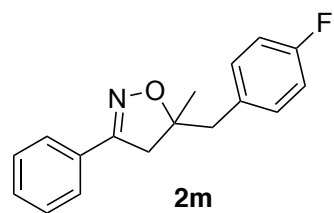


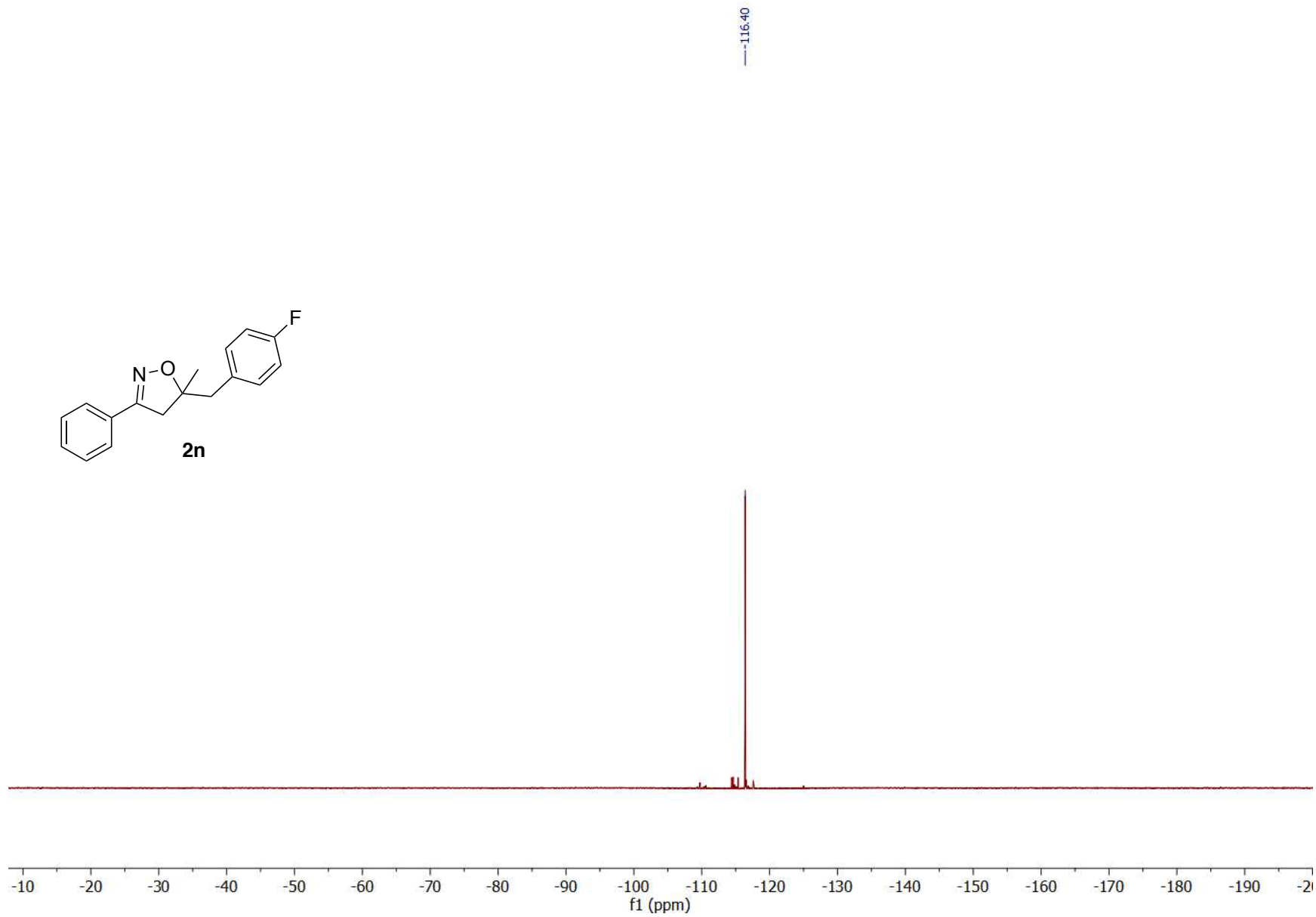
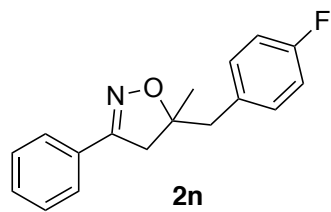


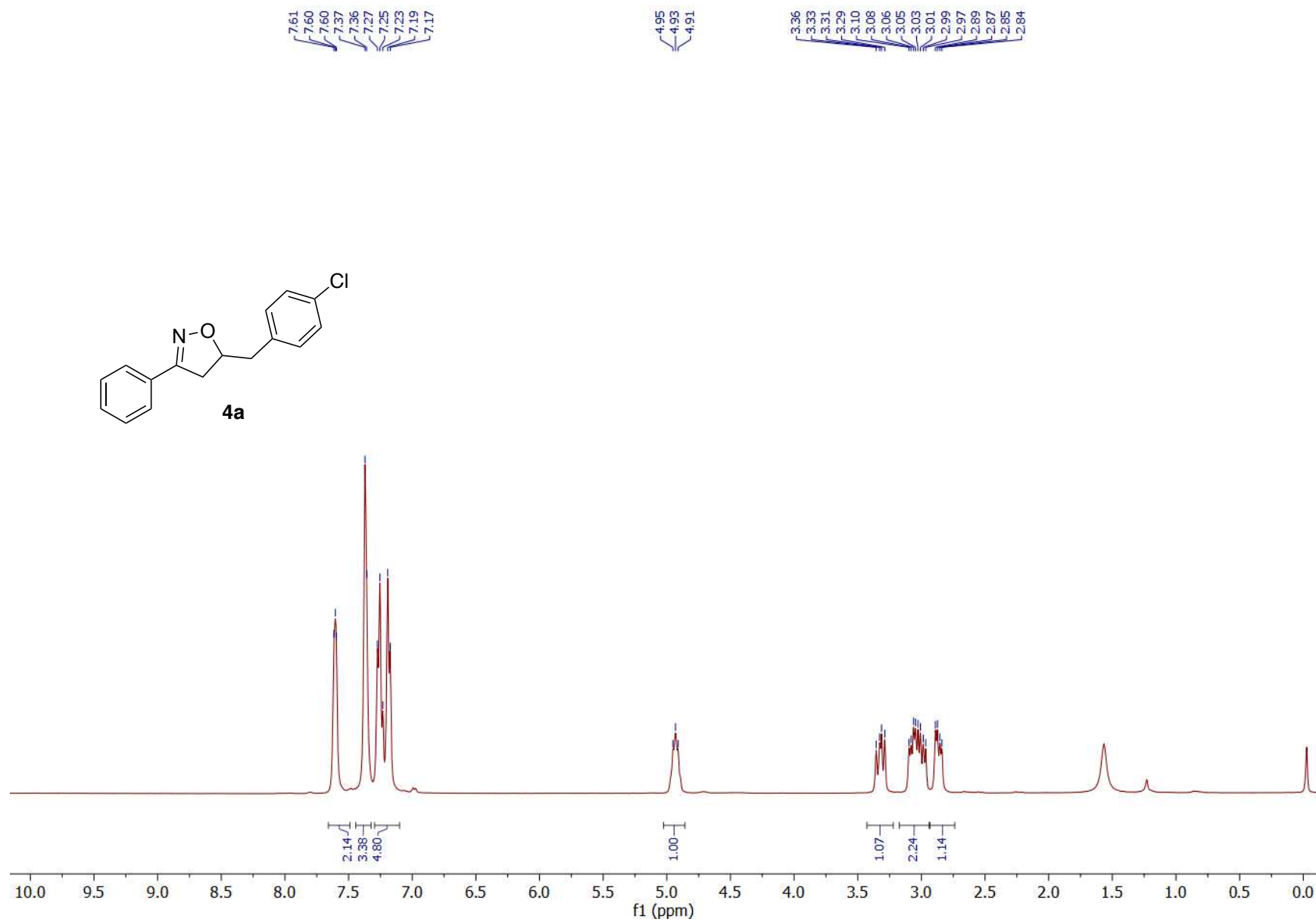


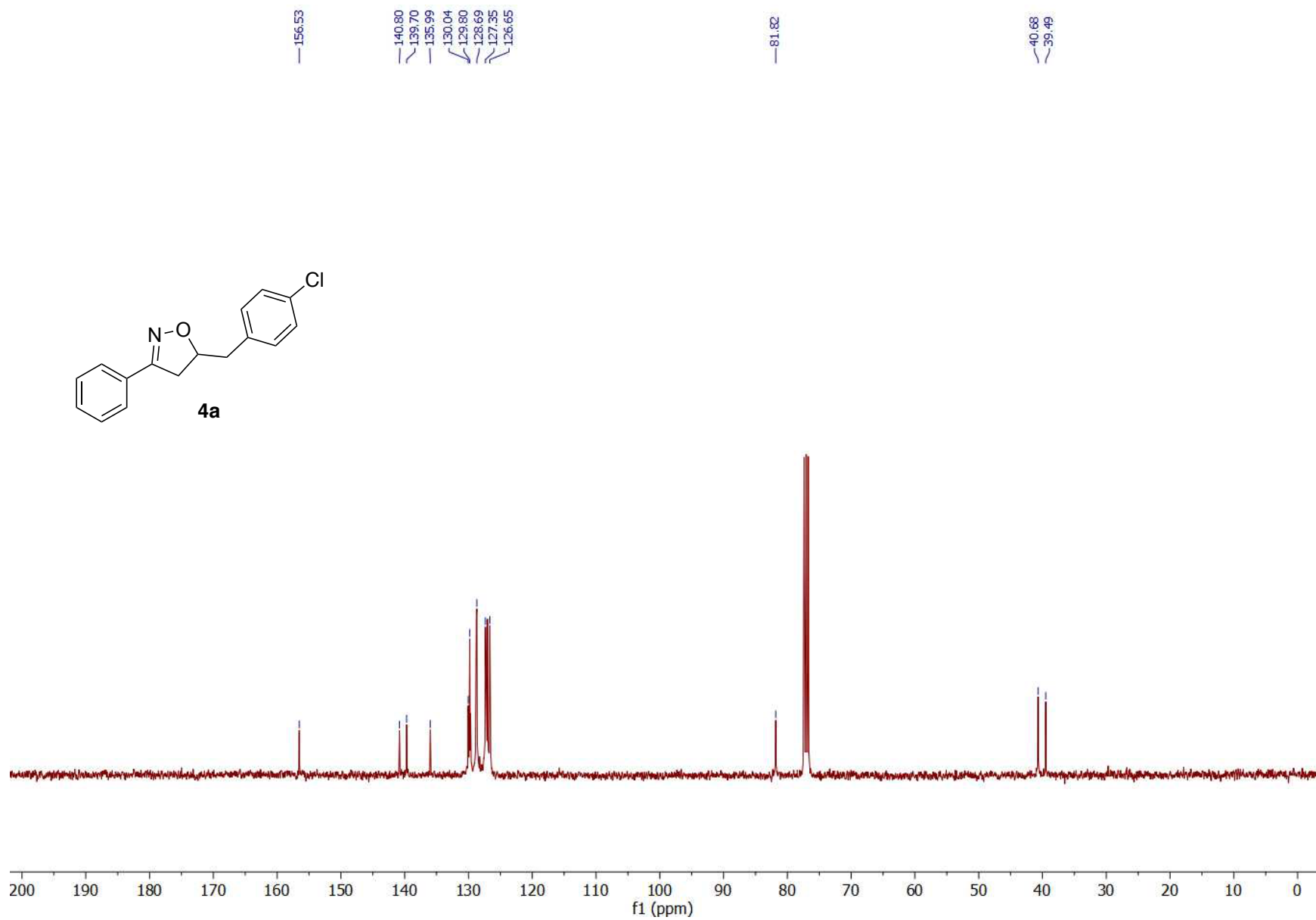
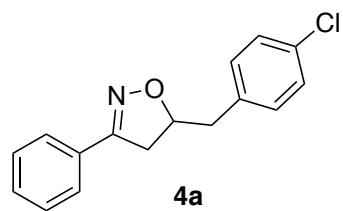


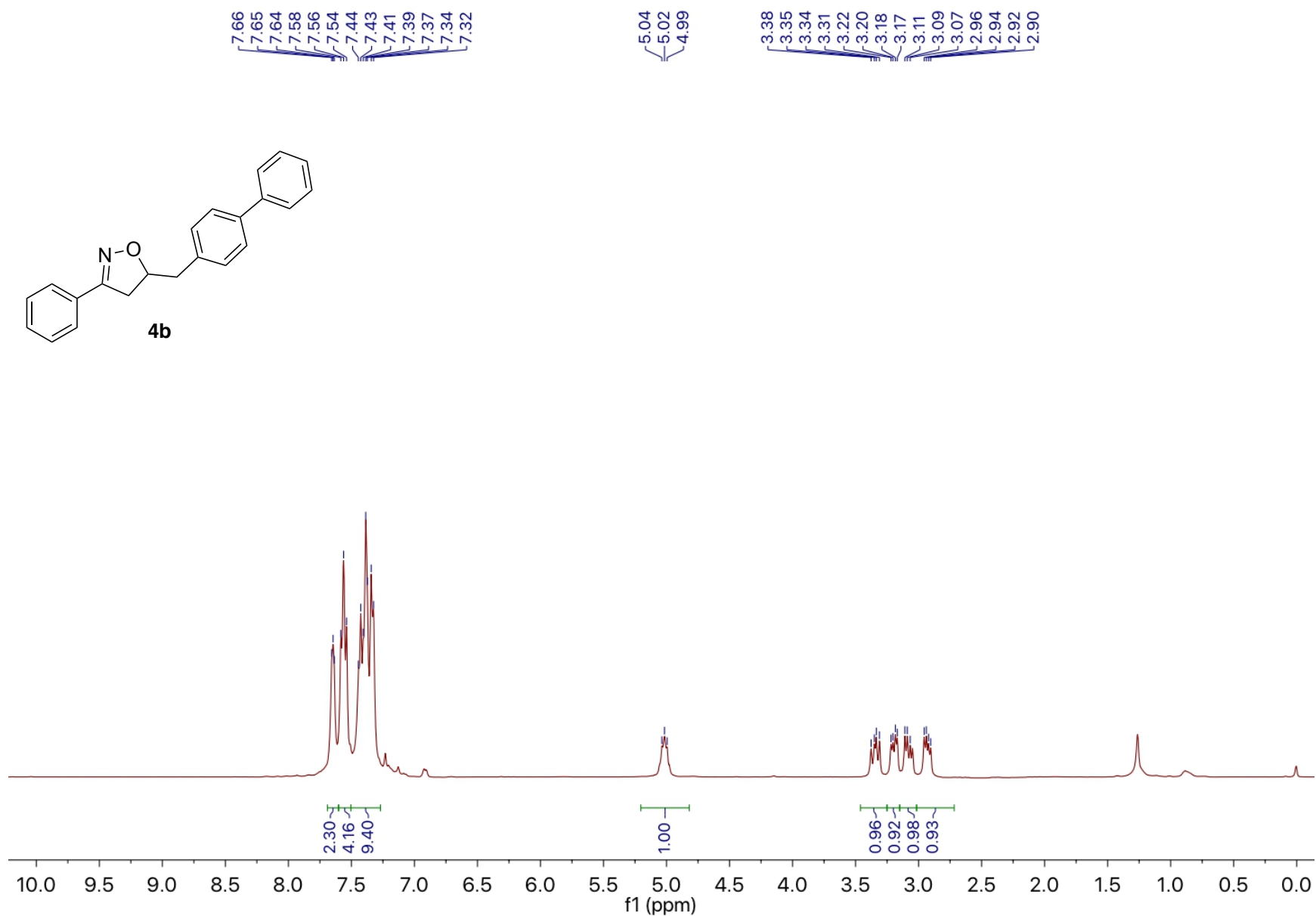
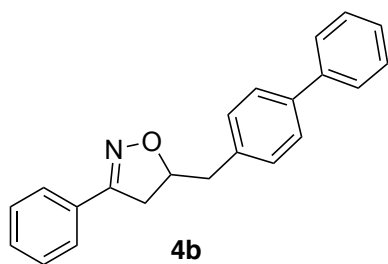


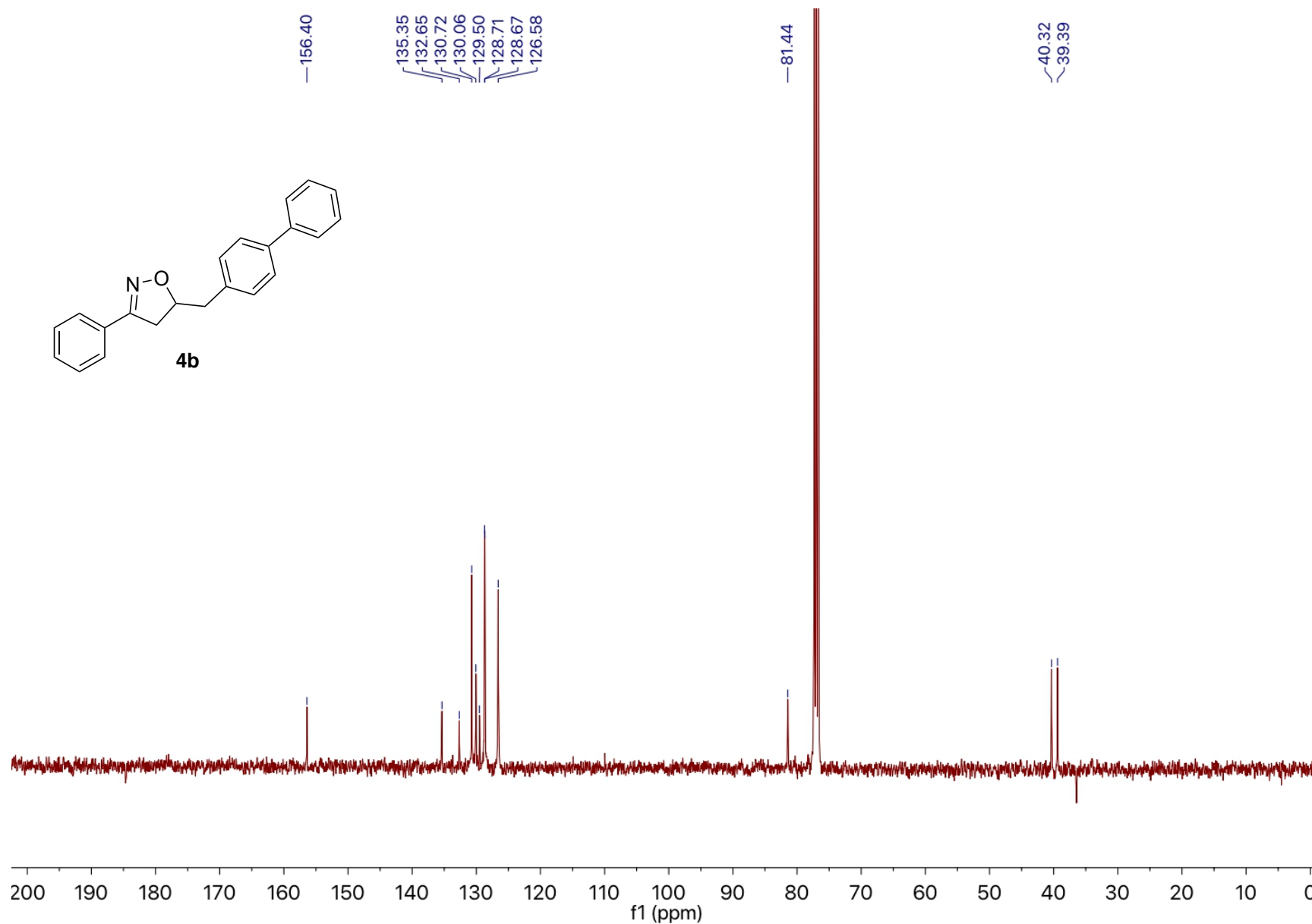
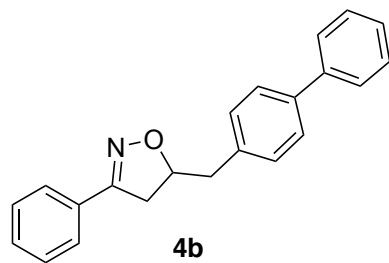


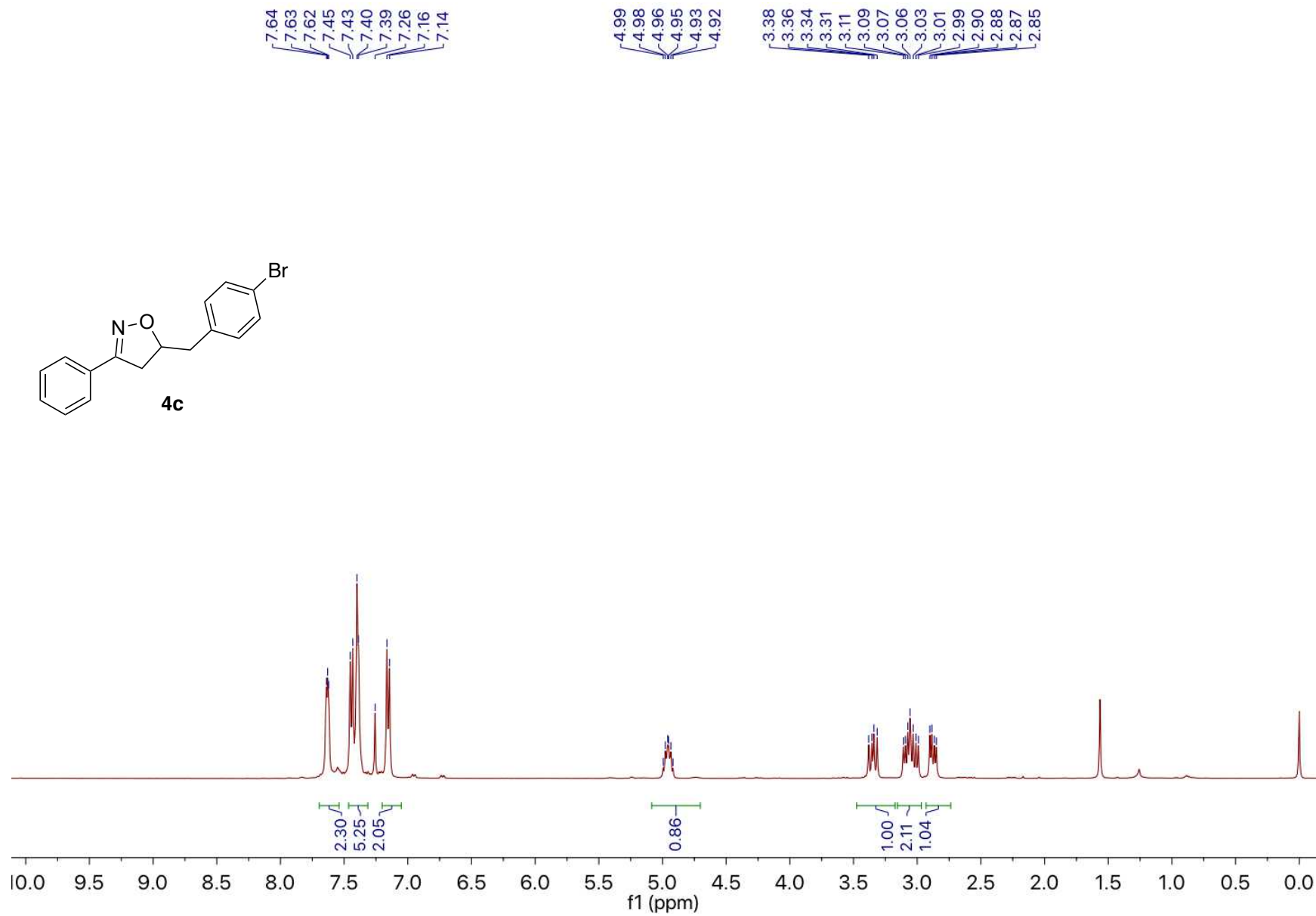
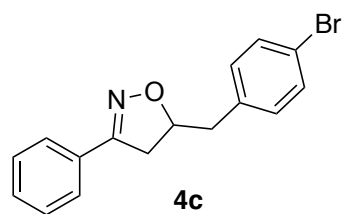


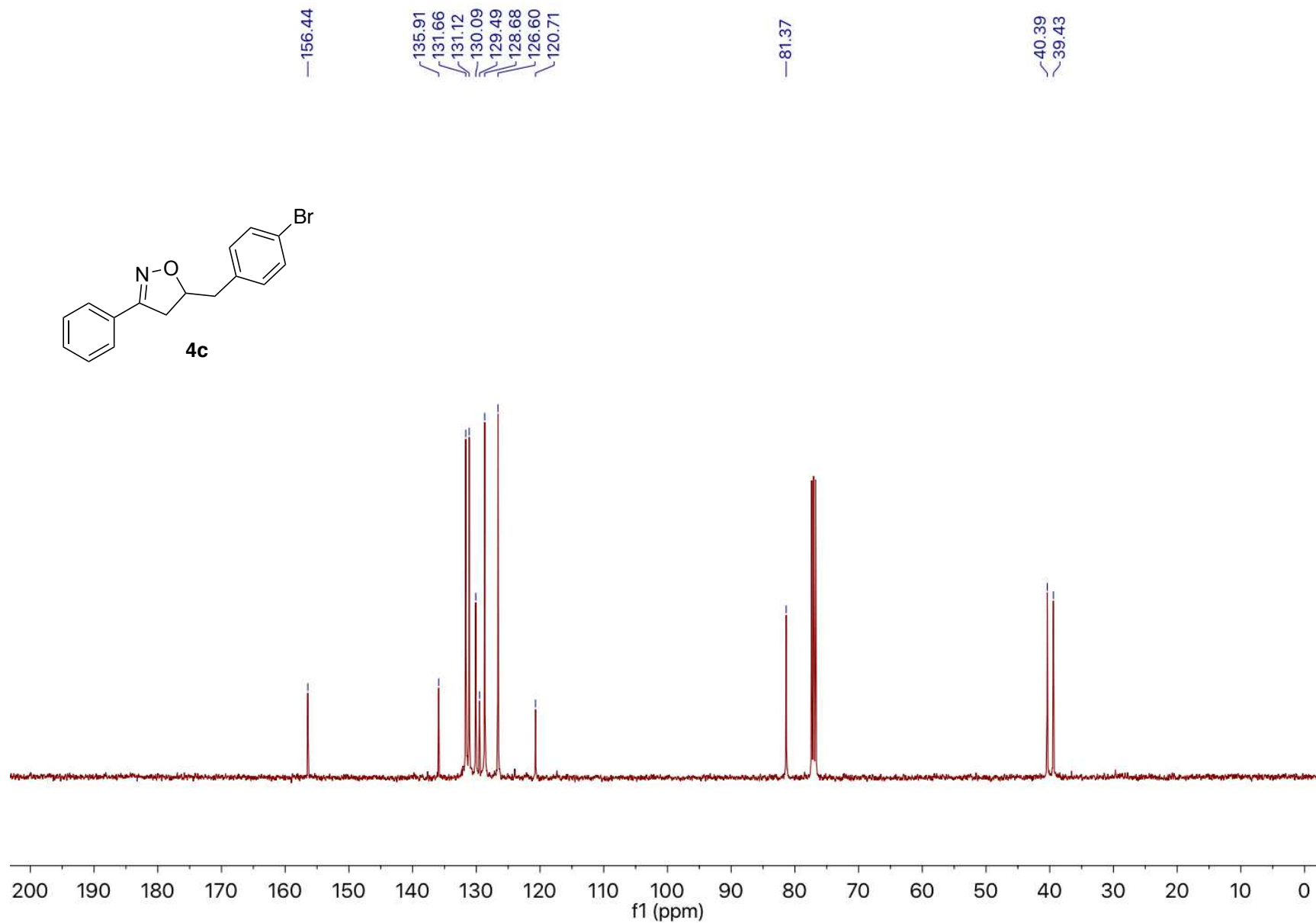
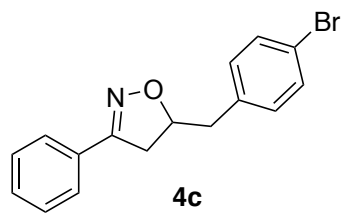


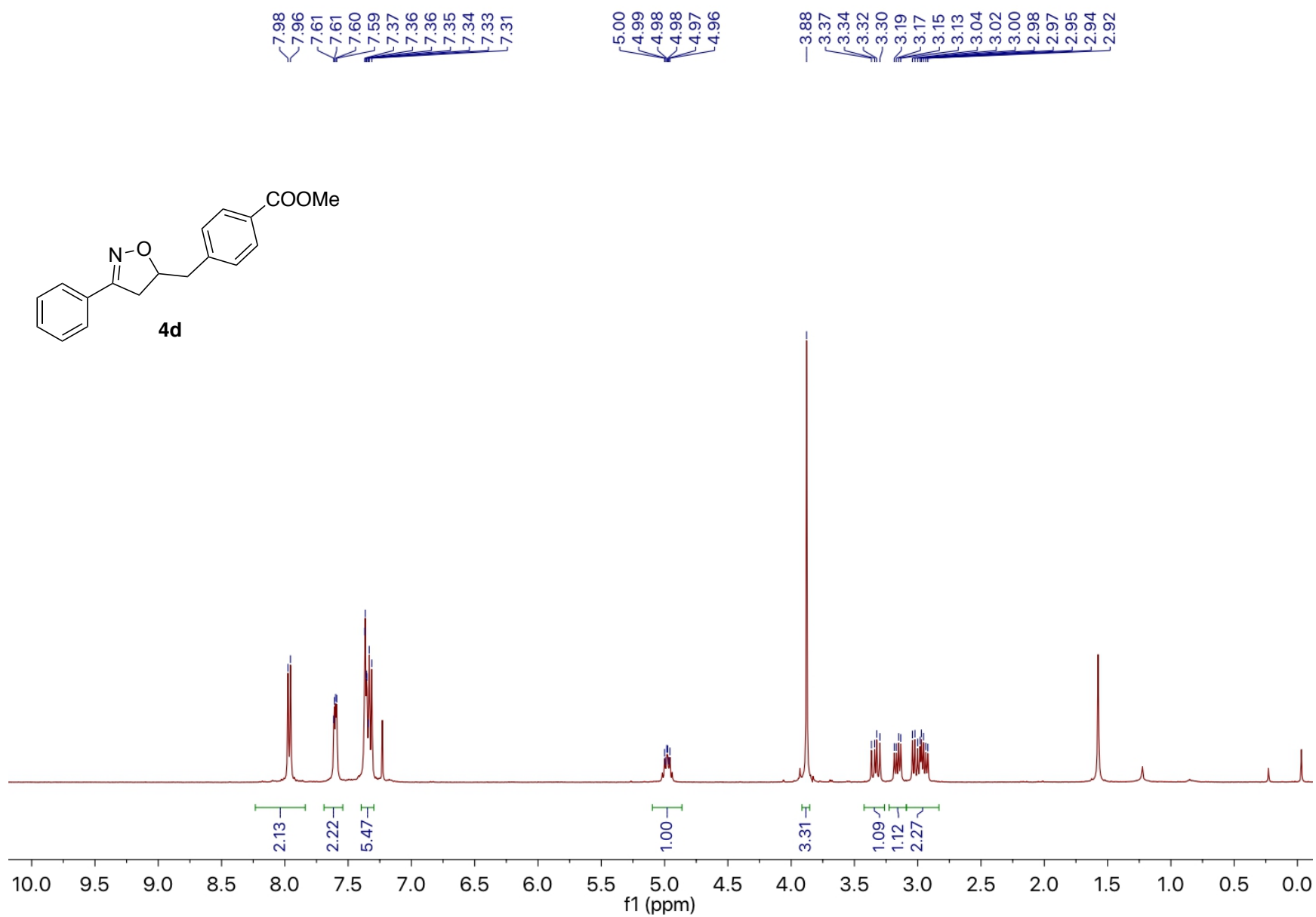


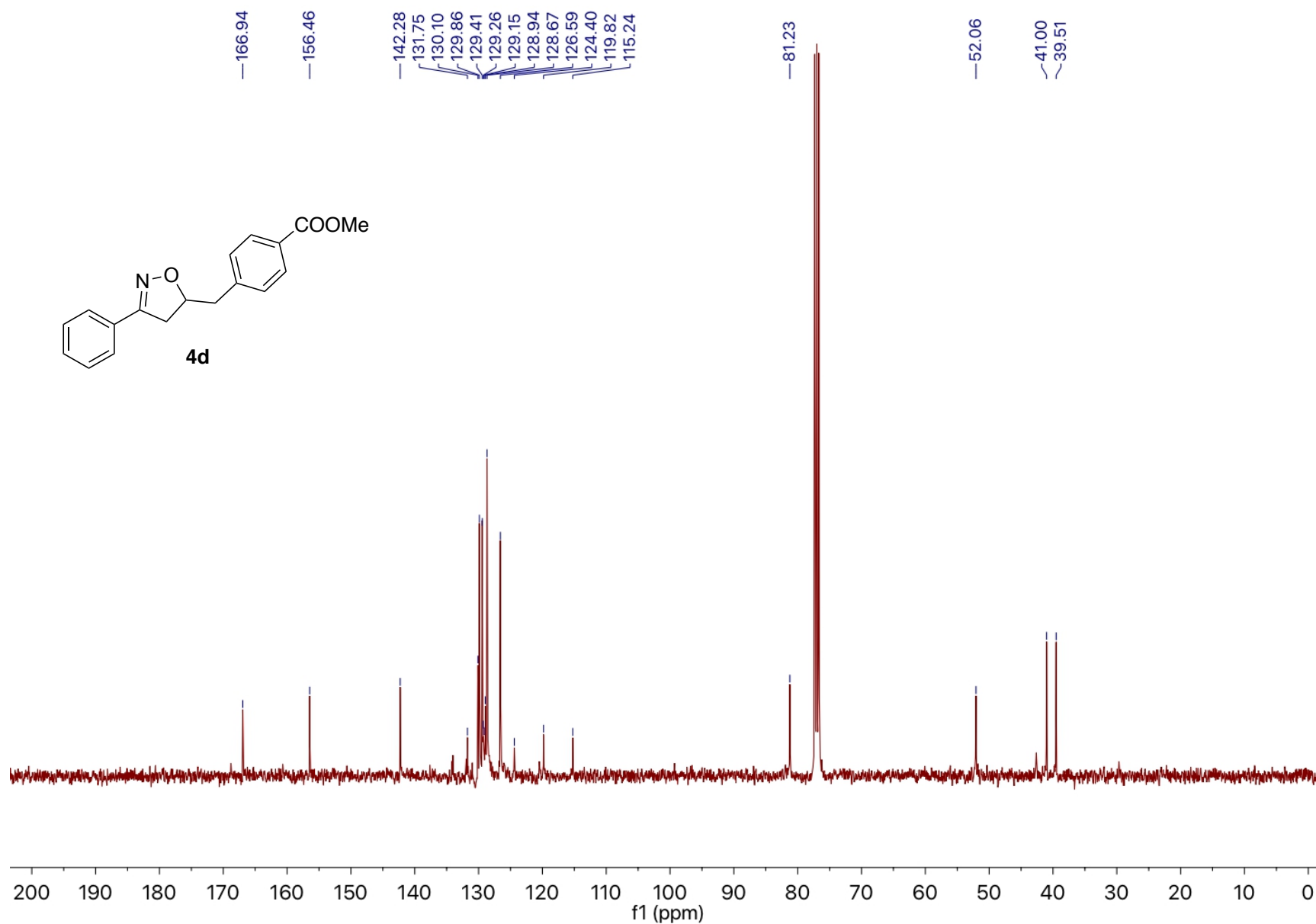
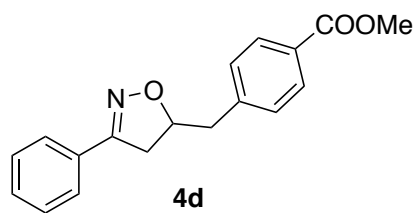


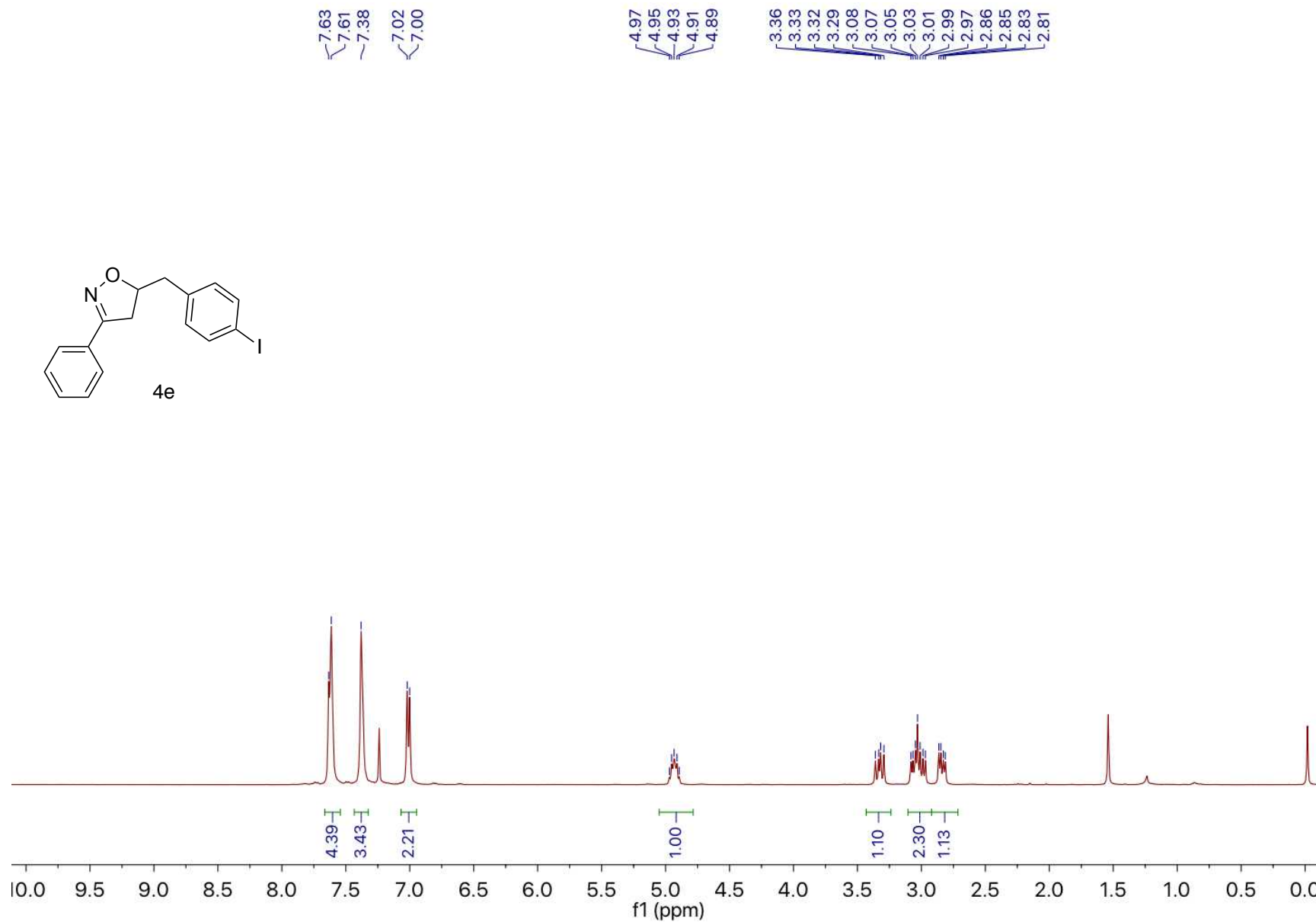
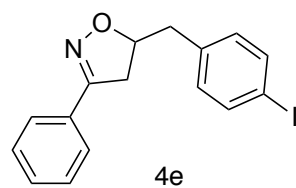


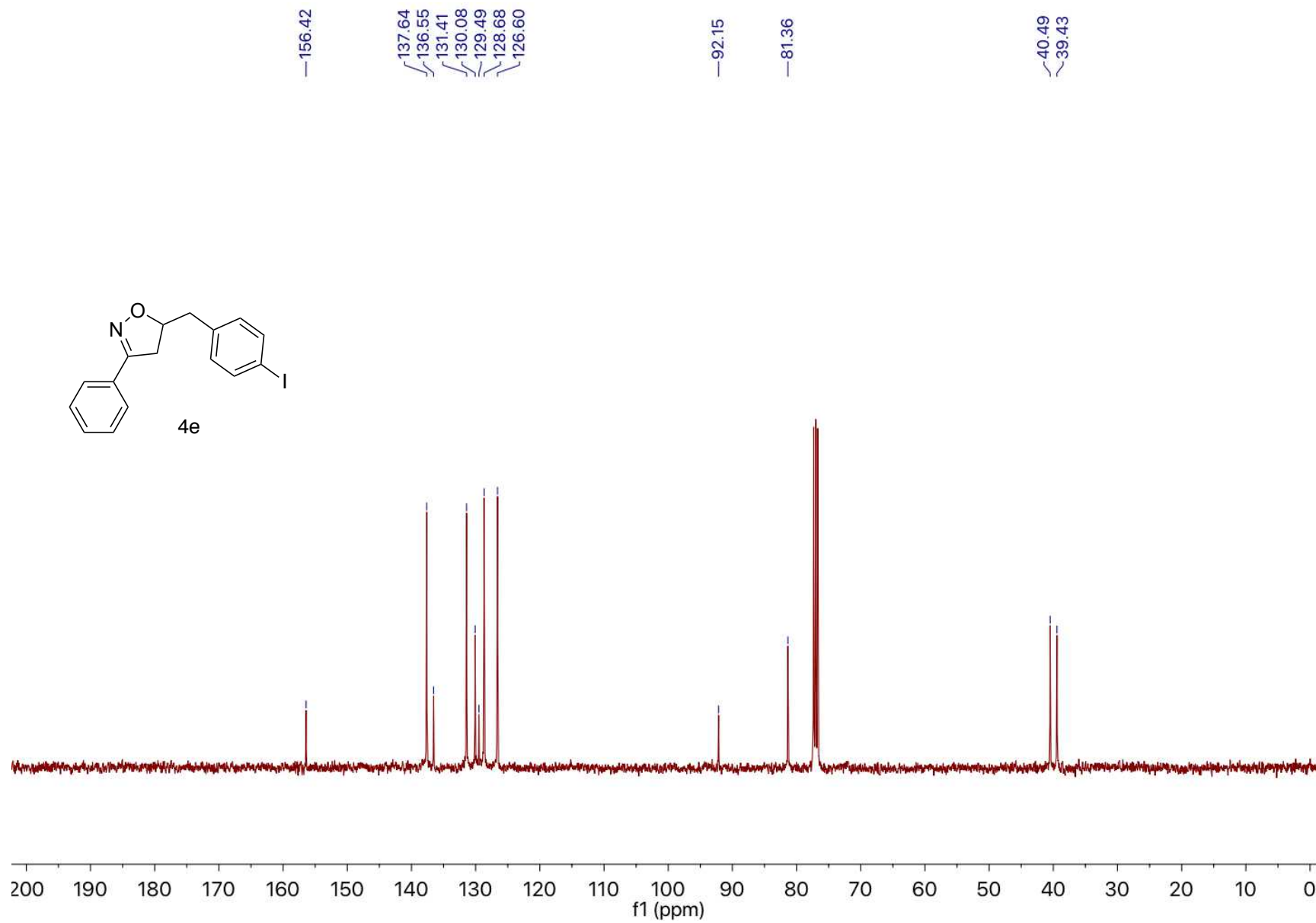
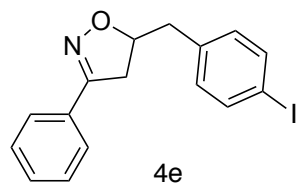


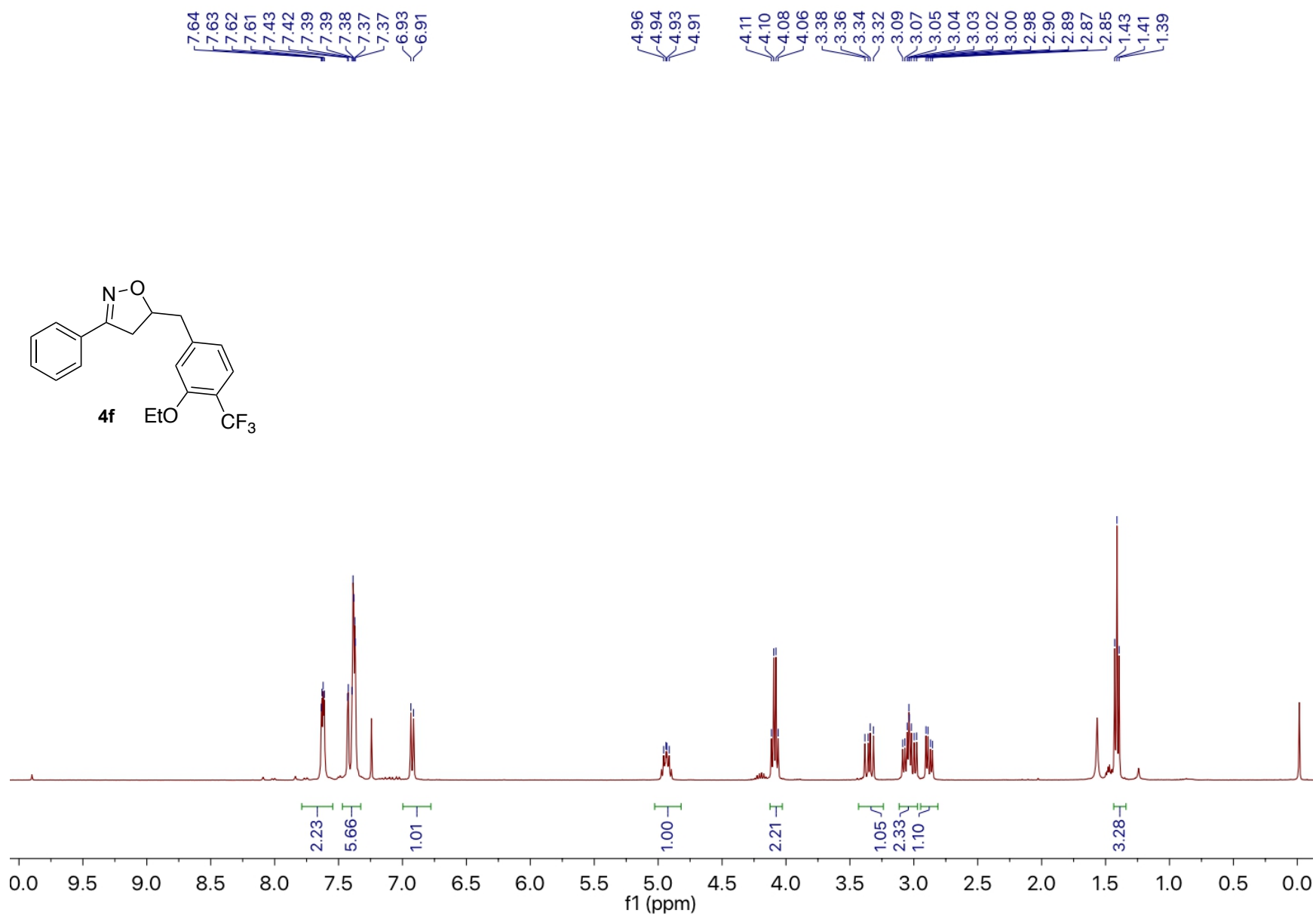


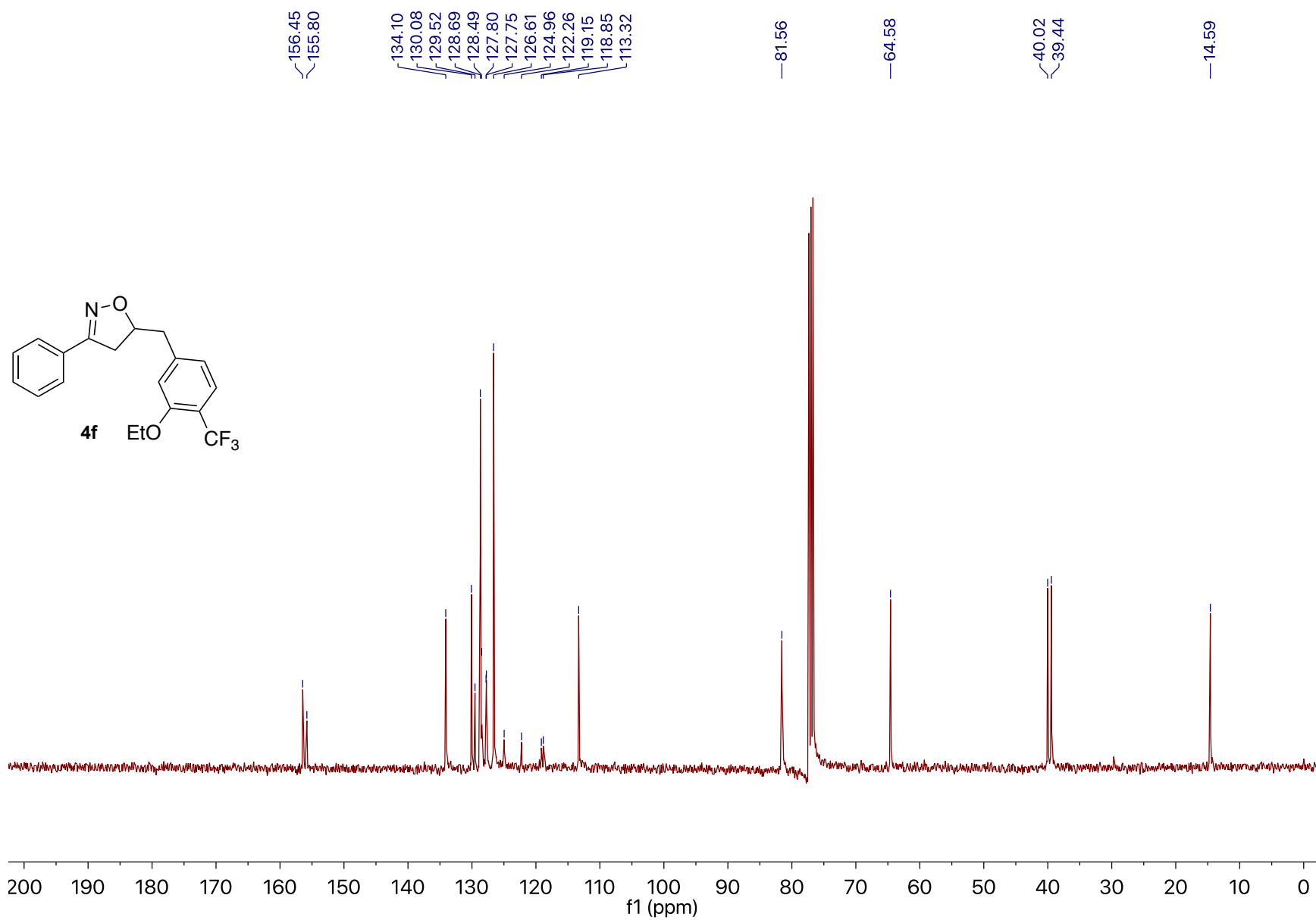


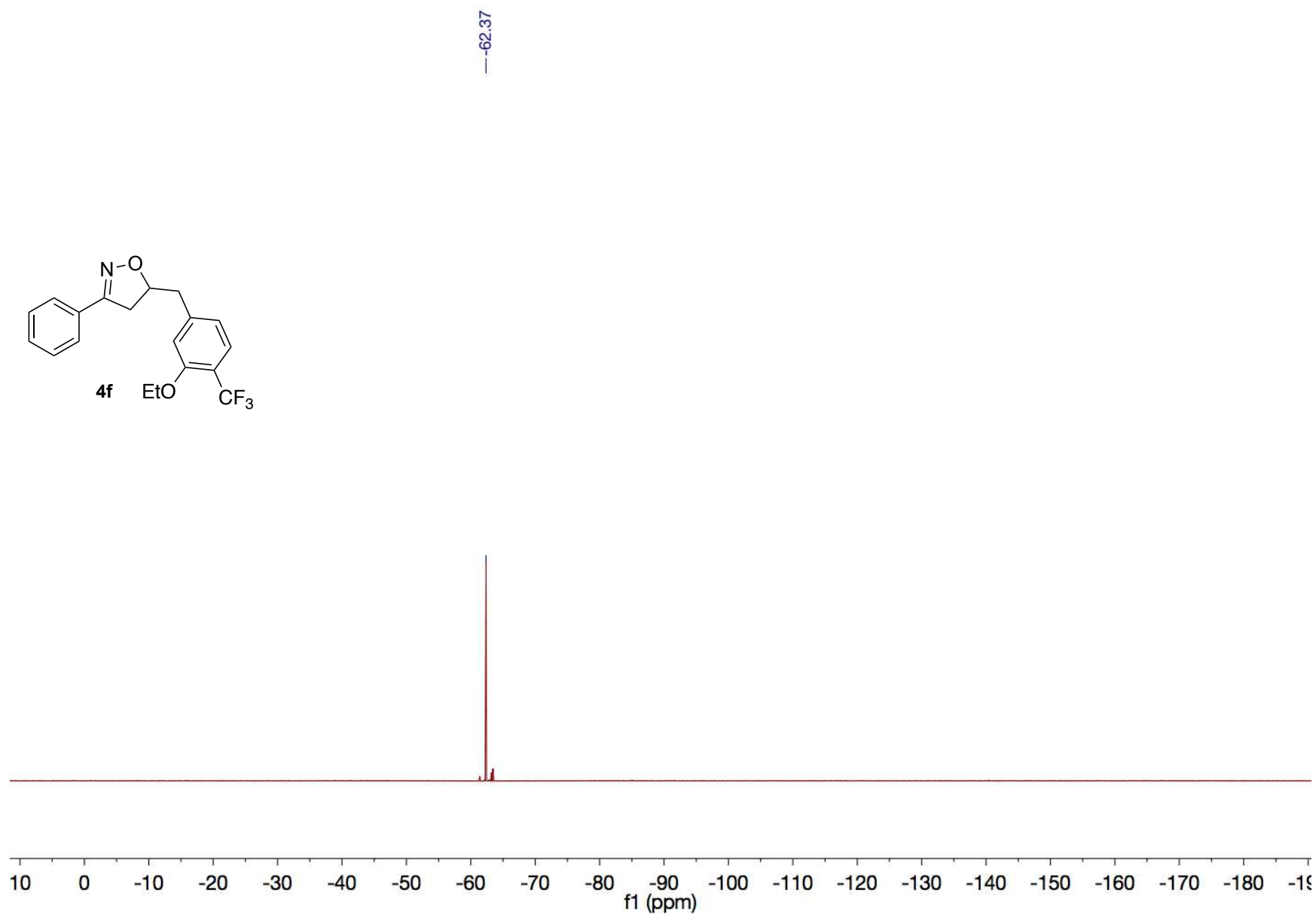


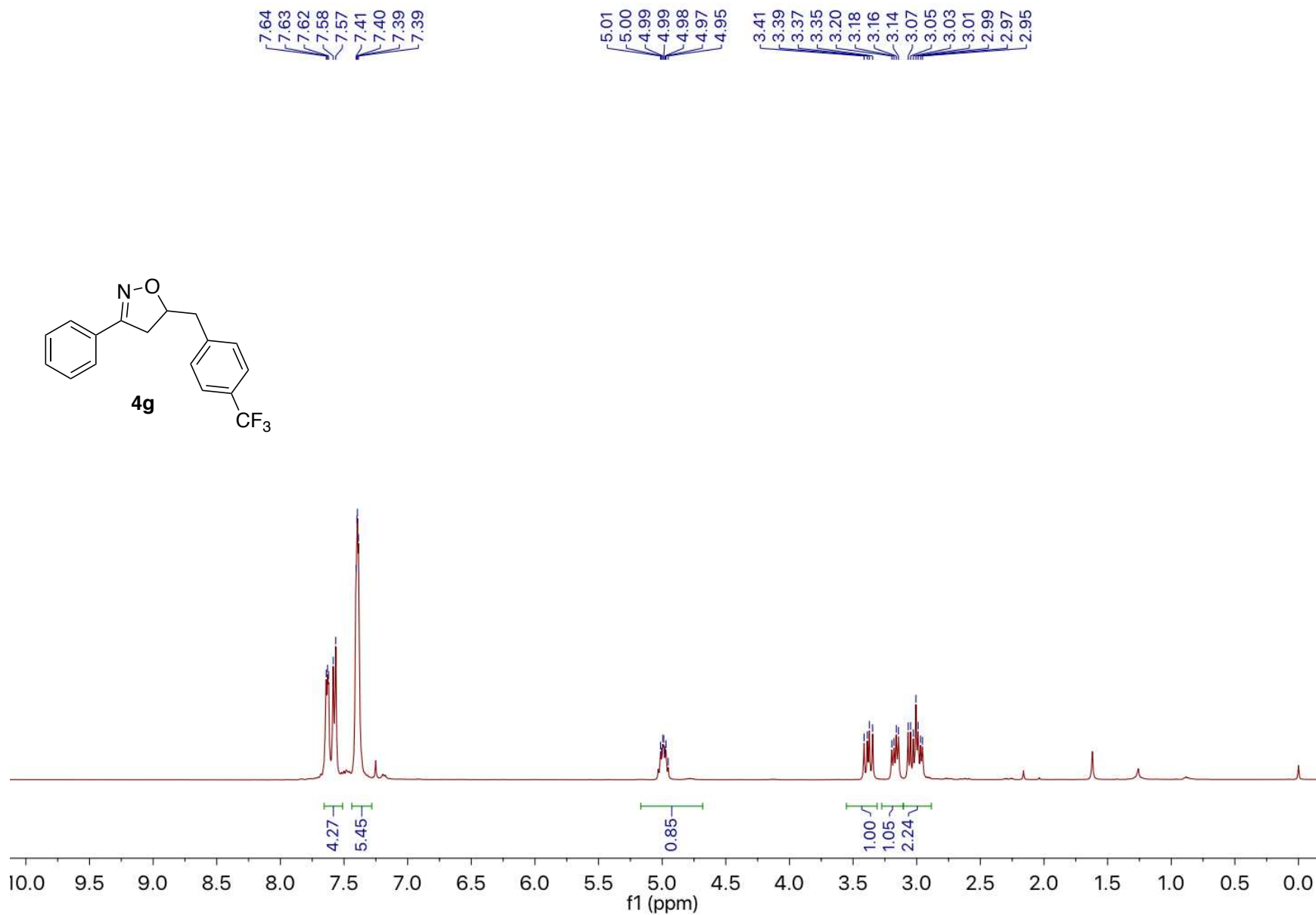
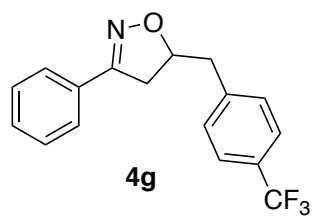


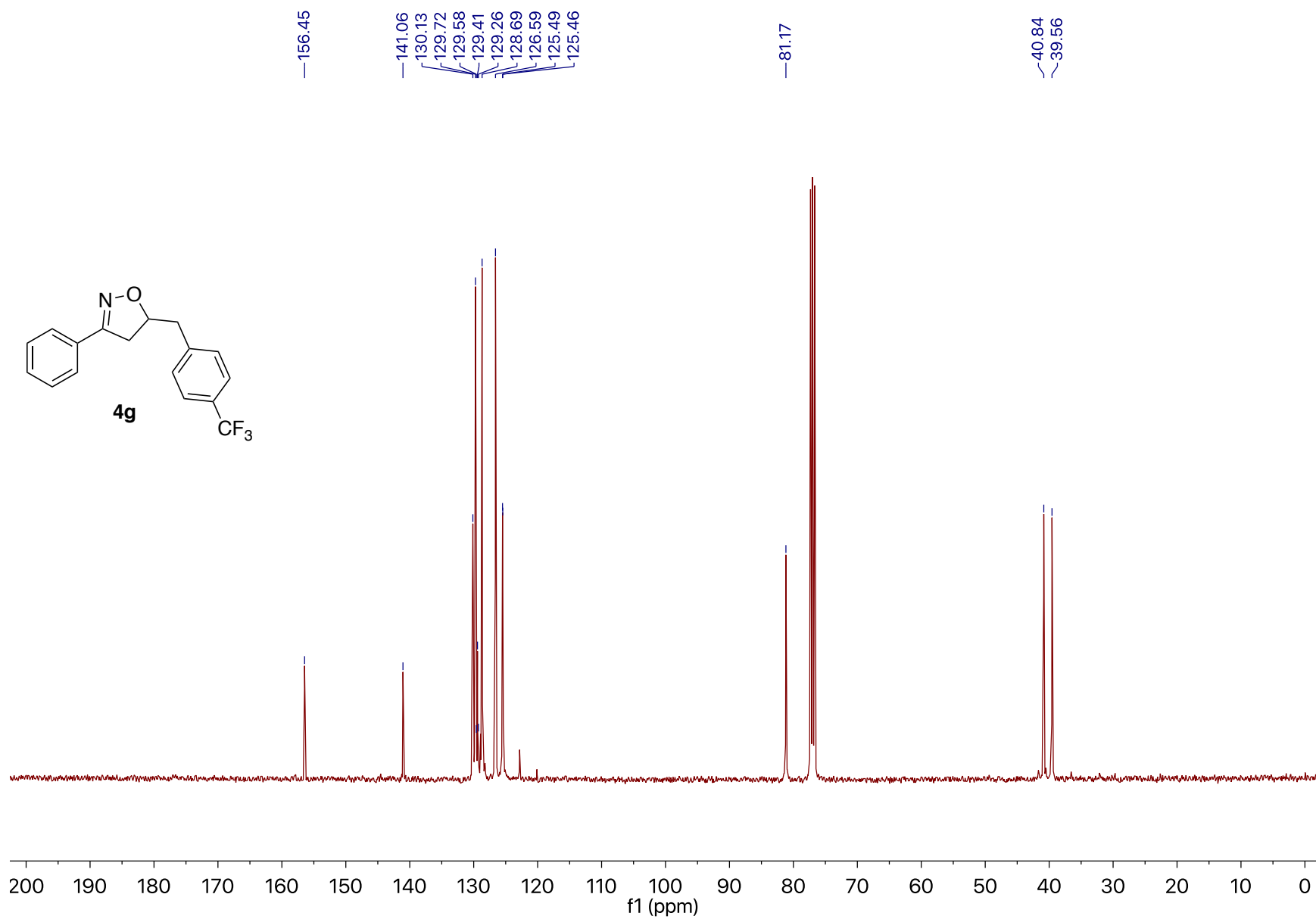


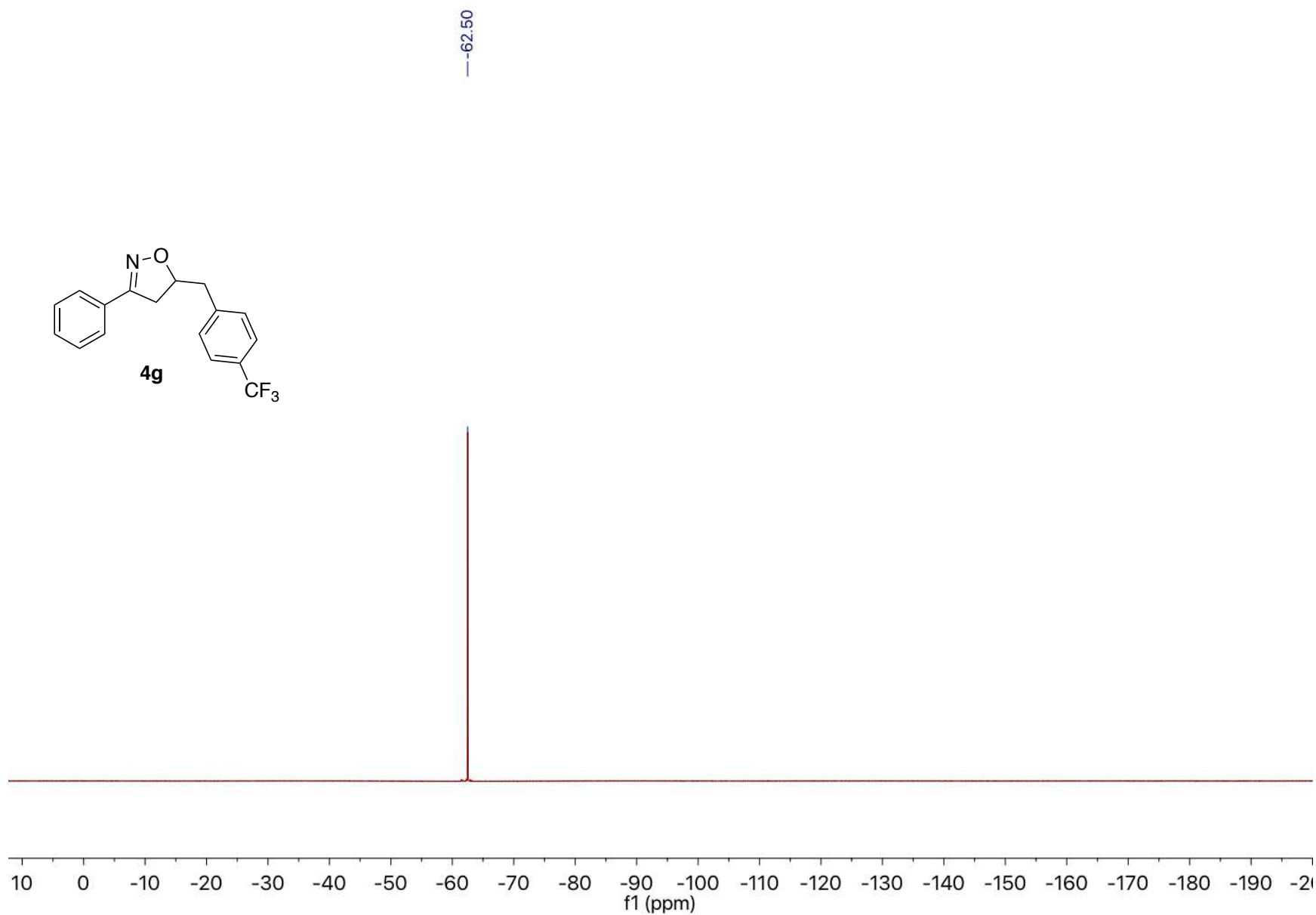
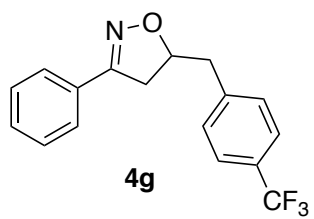


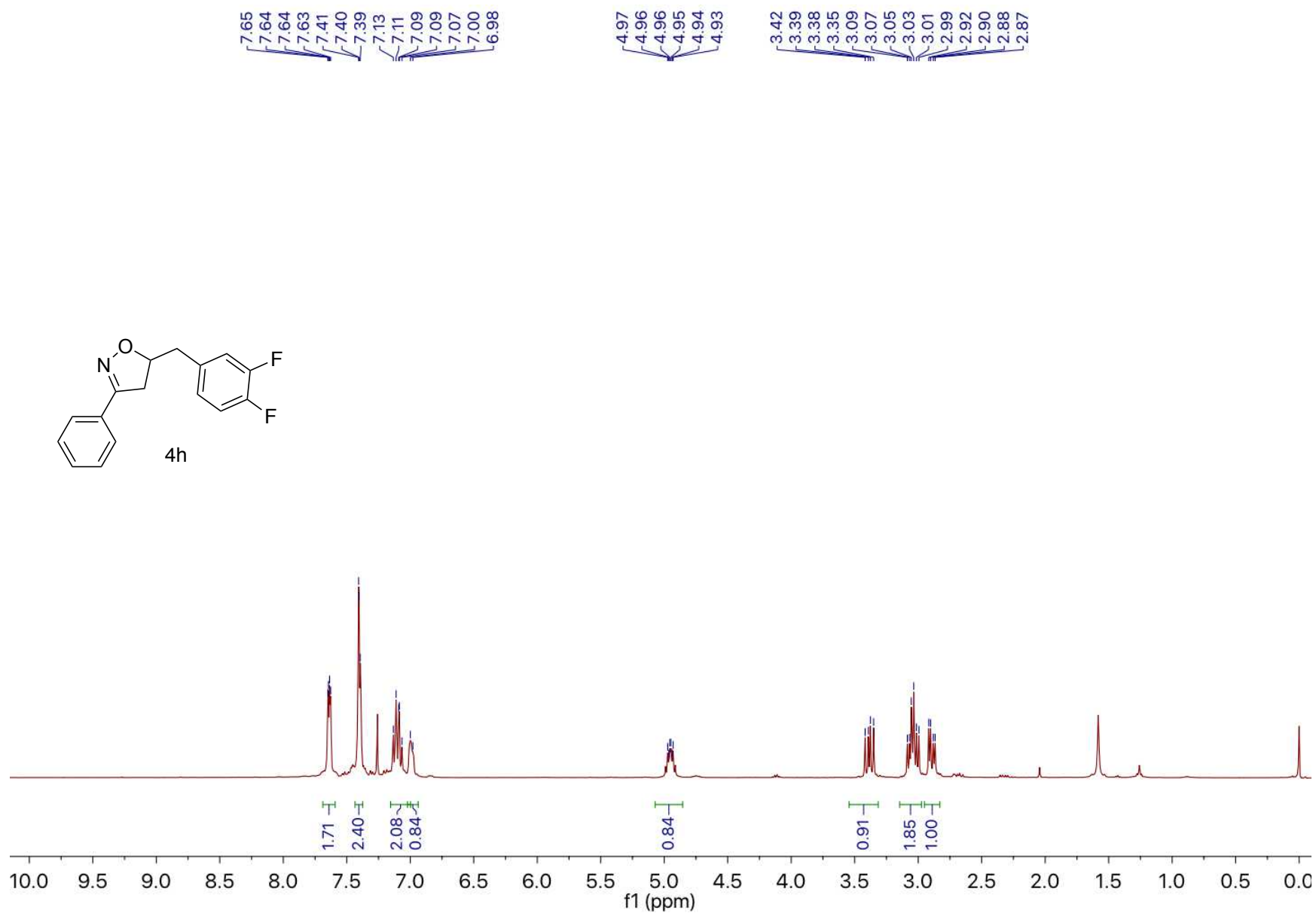
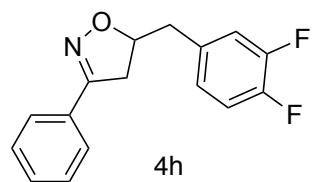


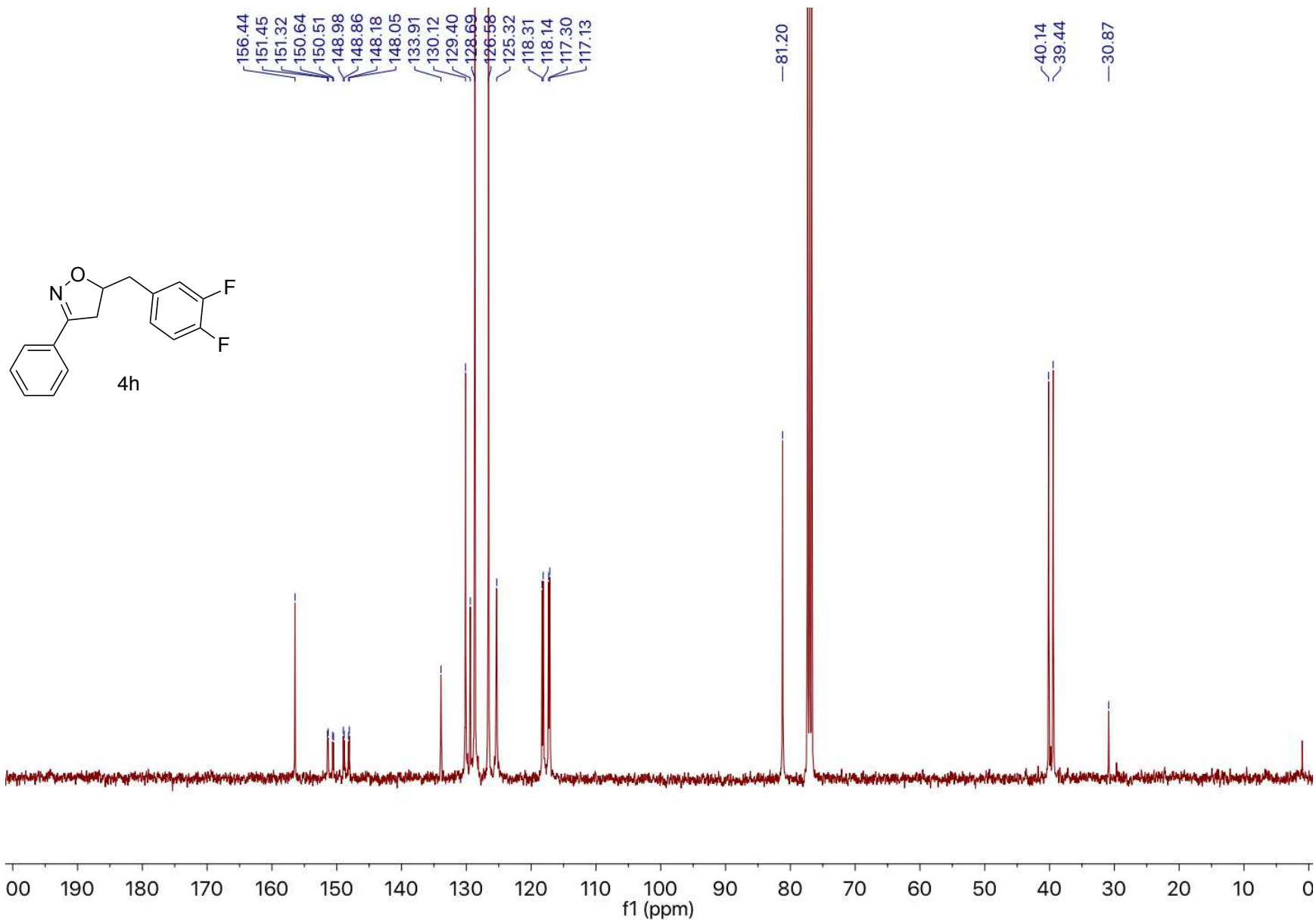


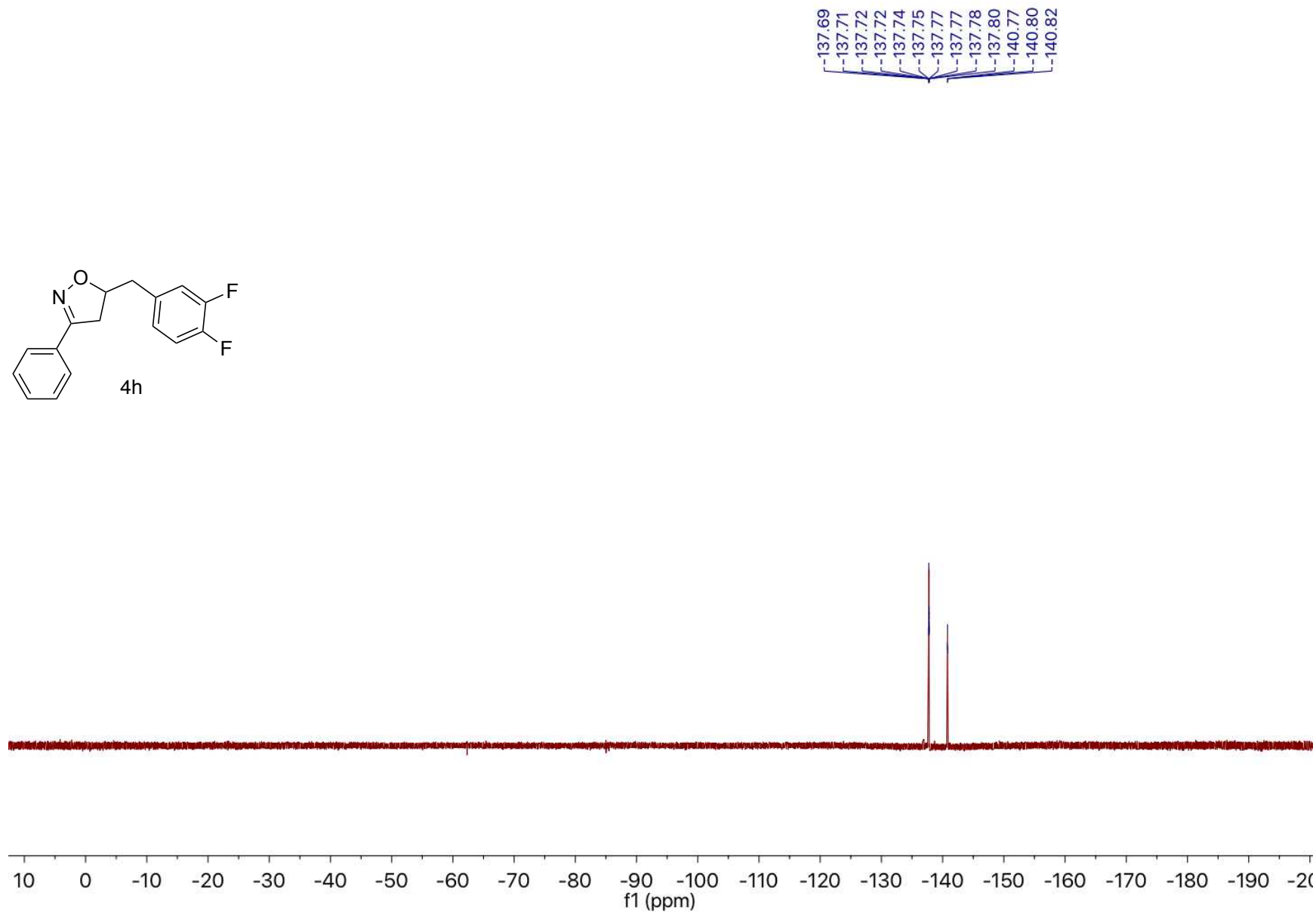
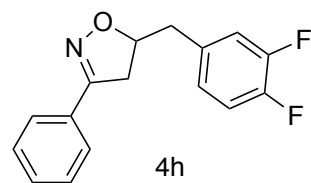


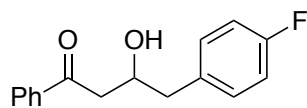




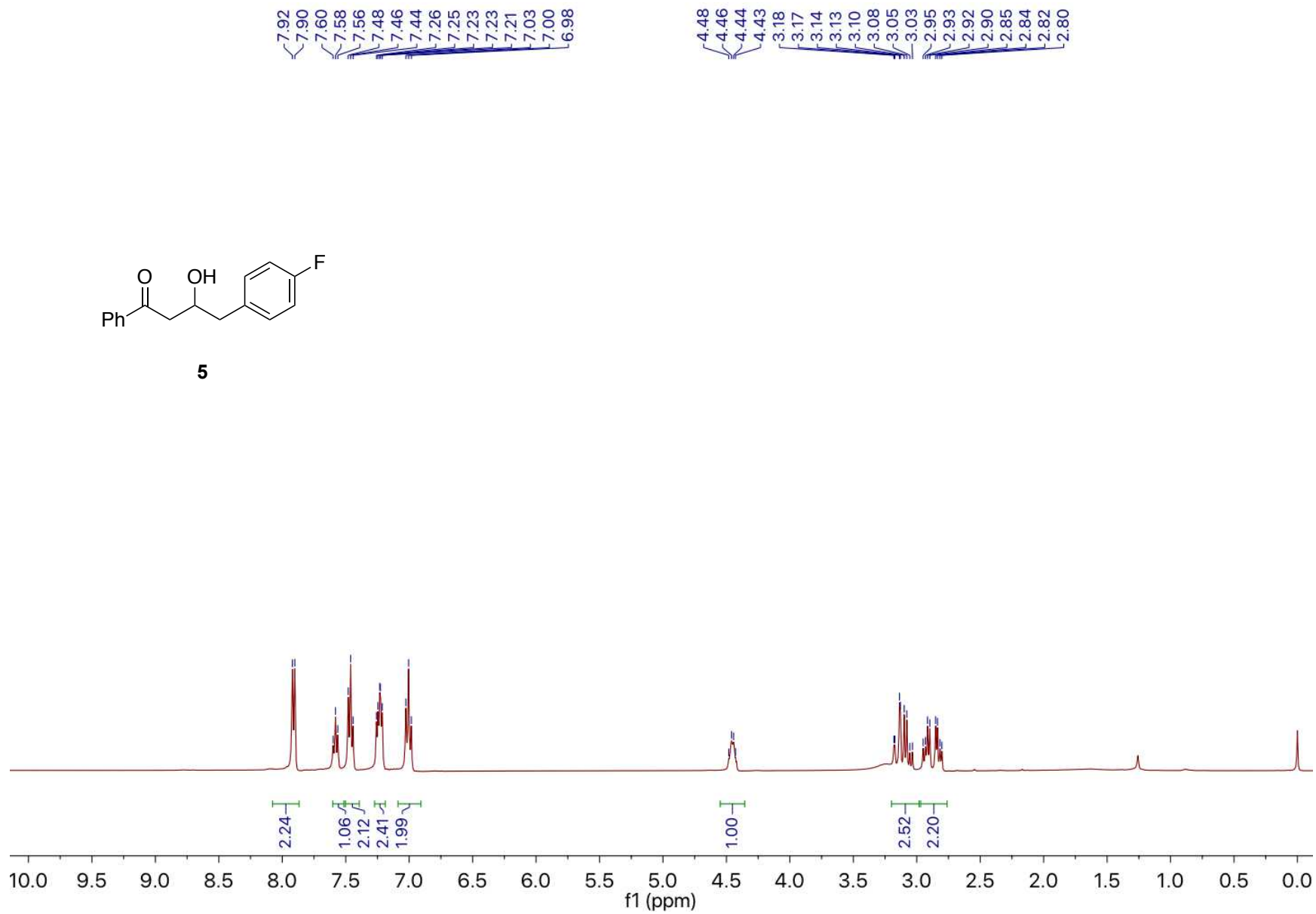


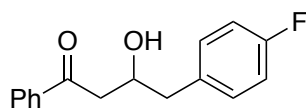




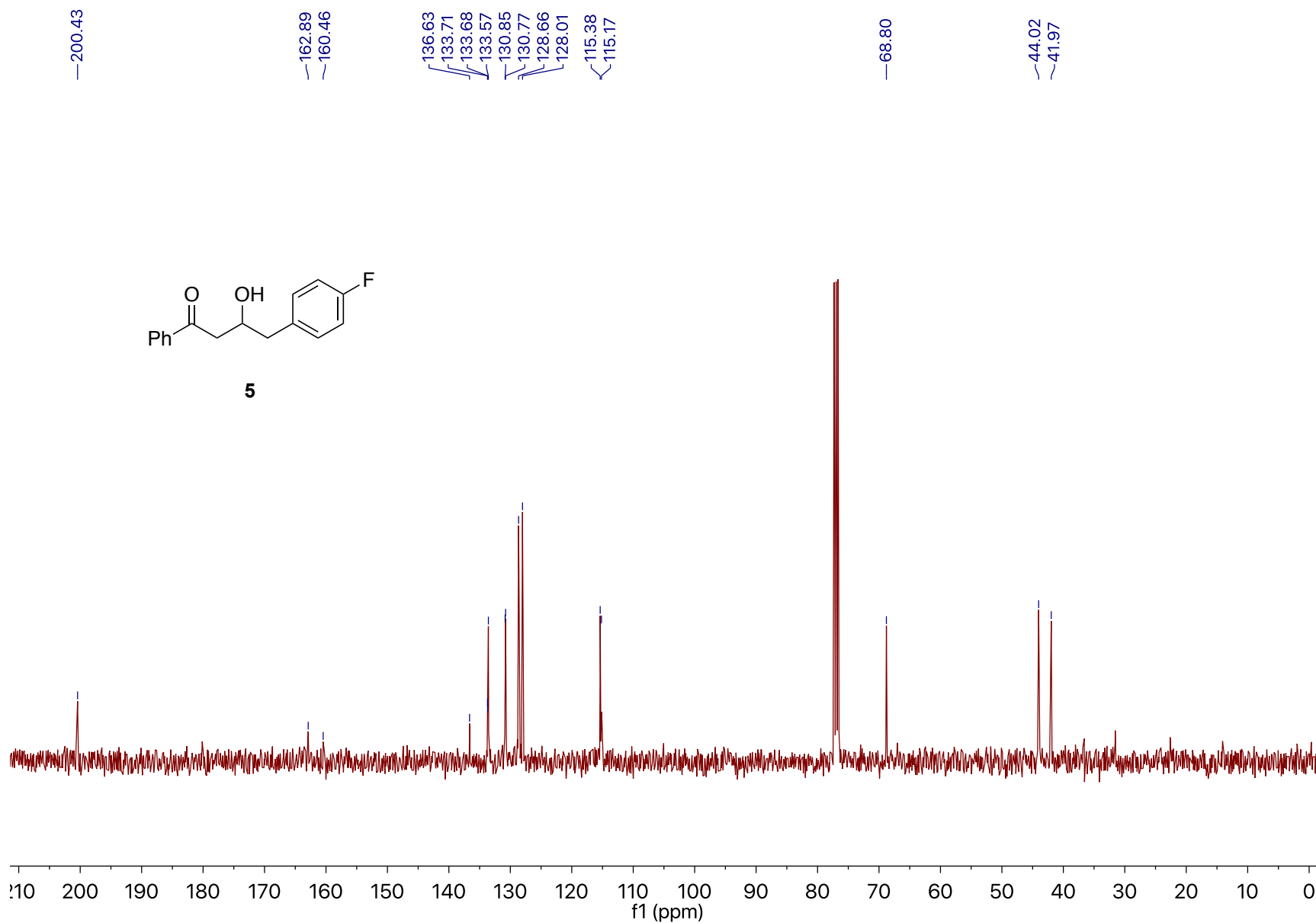


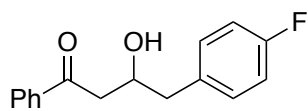
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