
Supplementary information

Synthesis of pyrroles from isoxazoles by an O-to-C skeletal edit

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Synthesis of Pyrroles from Isoxazoles by an O-to-C Skeletal Edit

Supporting Information

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1. General experimental

Reaction setup and solvents. Unless otherwise noted, all reactions were performed under inert N₂ atmosphere. Reagents were purchased from commercial suppliers and used without further purification. DCM, MeCN, Et₃N, and THF were dried by passing previously degassed solvents through a PPT Solvent Purification System. NMP (N-methyl pyrrolidone) was purchased from Oakwood Chemical or Sigma-Aldrich and used without further purification. Zinc powder (325 mesh, High Grade Material) was purchased from Oakwood Chemical and used without further purification. K₂CO₃ (325 mesh, anhydrous powder) was purchased from Oakwood Chemical and used without further purification. Reaction temperatures were reported as the temperatures of the oil bath surrounding the flask or vials.

Reagents. Reagents for synthesis were typically obtained from Ambeed, ChemScene, Combi-Blocks, Oakwood Chemical, or Sigma-Aldrich and used as received.

Chromatography. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254) and visualized by UV irradiation or staining. Flash column chromatography was performed under N₂ for all pyrrole isolations with Silica Gel, Technical Grade purchased from Sorbent Technologies (porosity 60 Å, 40-63 µm particle size).

Characterization by NMR and HRMS. Nuclear magnetic resonance spectra for characterization (¹H NMR, ¹³C NMR, and ¹⁹F NMR) were recorded with Bruker spectrometers operating at 400, 500, or 600 MHz (as indicated). Chemical shifts are reported in parts per million (ppm, δ), referenced to residual solvent [CDCl₃, δ = 7.26 ppm (¹H) and 77.16 ppm (¹³C); CD₃CN, δ = 1.94 ppm (¹H) and 1.32 ppm (¹³C); DMSO; δ = 2.50 ppm (¹H) and 39.52 ppm] Coupling constants were reported in Hertz (Hz). Data for ¹H-NMR spectra were reported as follows: chemical shift (ppm, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration). High resolution mass spectra were recorded on an Agilent 6224 TOF High Resolution Accurate MS with electrospray ionization (ESI).

X-Ray Crystallography. X-ray crystal structures were measured at 100(2) K on a Bruker D8 VENTURE diffractometer equipped with a microfocus Mo-target (λ = 0.71073 Å) and PHOTON 100 CMOS detector. Data were collected using φ and ω scans. The data reduction and integration were performed with the Bruker APEX4 software package (Bruker AXS, version 2017.3-0, 2018). Data were scaled and corrected for absorption effects using the multi-scan procedure as implemented in SADABS. The structures were solved by SHELXT and refined by a full-matrix least-squares procedure using SHELXL. Crystallographic data and details of the data collection and structure refinement are listed in Tables S11 and S12. X-ray crystal structures were rendered using OLEX2 software.

2. General Procedures and Characterization Data of Compounds 3, 4, and 6

Isoxazole to Pyrrole General Procedure (GP1):

To an 8 mL vial under N₂ atmosphere with a stir bar was added isoxazole (0.2 mmol, 1 equiv) and dissolved in anhydrous DCM (0.5 mL). A solution of propargyl triflate (prepared from 0.4 mmol of propargyl alcohol, 2 equiv) in DCM (typically concentrated to <2 mL total volume) was added dropwise to the isoxazole at room temperature. The reaction was stirred at room temperature for 16 hours. Upon full consumption of the starting material (monitored by ¹H NMR), the solvent was removed. The vial contents were evacuated to dryness for >1 hour before proceeding to the next step.

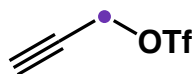
The same vial was placed under N₂ atmosphere. Zn⁰ powder (26.2 mg, 0.4 mmol, 2 equiv) and PTSA·H₂O (57.1 mg, 0.3 mmol, 1.5 equiv) were added. A 2 mL solution of 10:1 NMP/H₂O was prepared and subsequently added to the vial. The reaction was let stir at room temperature for 1 hour. Then, powdered K₂CO₃ (165.8 mg, 1.2 mmol, 6 equiv) was added. The vial was then brought to 90 °C and stirred for 16 hours. After reaction completion, the reaction was brought to room temperature, and the vial contents were transferred to a separatory funnel. LiCl (10%, aq.) was added and extracted 3 times with Et₂O. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation before purification by flash column chromatography.

Note: The pyrrole products were columned via flash column chromatography with N₂ to minimize oxidative decomposition.

Propargyl triflate synthesis (modified from literature procedure)¹

To a round-bottom flask under N₂ atmosphere with a stir bar was added anhydrous DCM (20 mL). Triflic anhydride (2.08 mL, 11 mmol) was added. The flask was cooled to 0 °C in an ice bath and stirred for 10 minutes. In a separate flask was prepared a solution of propargyl alcohol (577 µL, 10 mmol), pyridine (886 µL, 11 mmol), and anhydrous DCM (10 mL). The propargyl alcohol solution was added dropwise to the flask containing Tf₂O at 0 °C. The reaction was let stir for 1 h at 0 °C. Upon completion, H₂O (20 mL) was added to the flask while still cold. The flask contents were then transferred to a separatory funnel, and the layers were separated. The organic layer was dried over Na₂SO₄ and filtered. The DCM solution was concentrated slowly via rotary evaporation until the volume remaining was ~3-5 mL to avoid evaporation of the triflate reagent. The crude solution was carried forward without further purification.

Propargyl triflate



prop-2-yn-1-yl trifluoromethanesulfonate

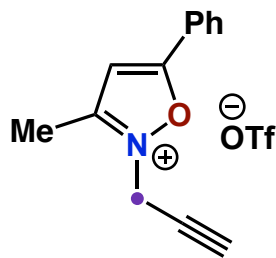
^1H NMR (600 MHz, CDCl_3) δ 5.07 (d, J = 2.4 Hz, 2H), 2.83 (t, J = 2.5 Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 118.4 (q, J = 319.5 Hz), 80.0, 73.6, 63.3.

^{19}F NMR (470 MHz, CDCl_3) δ -74.80 – -74.93 (m).

General alkylation procedure (GP2):

To a round-bottom flask under N_2 atmosphere with a stir bar was added 3-methyl-5-phenylisoxazole (795 mg, 5 mmol) and anhydrous DCM (5 mL). Propargyl triflate was added as a DCM solution (10 mmol scale preparation) dropwise at room temperature and let stir overnight. Upon reaction completion, Et_2O (10 mL) was added and let stir until a precipitate formed. After stirring for 10 minutes, the solid was collected via vacuum filtration and washed with Et_2O to give the desired isoxazolium triflate.



3-methyl-5-phenyl-2-(prop-2-yn-1-yl)isoxazol-2-ium trifluoromethanesulfonate (3a)

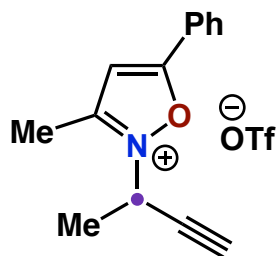
Synthesized according to the general alkylation procedure (GP2) using 3-methyl-5-phenylisoxazole (**1a**, 795 mg, 5 mmol). The title compound was isolated as a white solid in a 99% yield (1.72g, 5 mmol). Purity was determined to be 91% via ^1H NMR using TMB (trimethoxybenzene) as an internal standard. Recrystallization with Hexanes/ EtOH yielded single crystals suitable for X-Ray diffraction analysis.

^1H NMR (500 MHz, CDCl_3) δ 7.88 – 7.84 (m, 2H), 7.64 – 7.58 (m, 1H), 7.55 – 7.47 (m, 3H), 5.53 (d, J = 2.6 Hz, 2H), 2.78 (s, 3H), 2.73 (t, J = 2.6 Hz, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 171.9, 162.0, 134.5, 129.8, 127.7, 122.5, 120.70 (q, J = 320.1 Hz), 105.9, 78.3, 71.4, 42.3, 12.4.

¹⁹F NMR (470 MHz, CDCl₃) δ -78.45.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₃H₁₂NO⁺ 198.0913; found 198.0913.



2-(but-3-yn-2-yl)-3-methyl-5-phenylisoxazol-2-ium trifluoromethanesulfonate (3b)

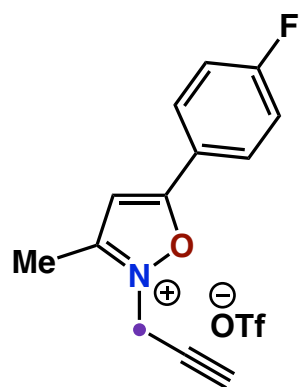
Synthesized according to the general alkylation procedure (GP2) using 3-methyl-5-phenylisoxazole (**1a**, 159 mg, 1 mmol) and but-3-yn-2-yl trifluoromethanesulfonate. The title compound was isolated as a light brown solid in a 56% yield (201 mg, 0.56 mmol) after purification by trituration with DCM and Et₂O.

¹H NMR (400 MHz, DMSO) δ 8.11 – 8.03 (m, 2H), 7.89 (s, 1H), 7.85 – 7.74 (m, 1H), 7.74 – 7.51 (m, 2H), 6.34 (qd, J = 6.8, 2.3 Hz, 1H), 4.05 (d, J = 2.3 Hz, 1H), 2.79 (s, 3H), 1.90 (d, J = 6.8 Hz, 3H).

¹³C NMR (101 MHz, DMSO) δ 170.2, 161.2, 134.2, 129.9, 127.4, 122.8, 106.1, 79.1, 77.2, 50.5, 20.1, 12.2. (OTf ¹³C not observed)

¹⁹F NMR (470 MHz, CDCl₃) δ -77.74.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₄H₁₄NO⁺ 212.1070; found 212.1075.



5-(4-fluorophenyl)-3-methyl-2-(prop-2-yn-1-yl)isoxazol-2-ium trifluoromethanesulfonate (3d)

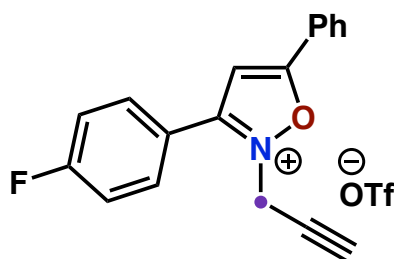
Synthesized according to the general alkylation procedure (GP2) using 5-(4-fluorophenyl)-3-methylisoxazole (**1b**, 354.3 mg, 2 mmol). The title compound was isolated as a light brown solid in a 90% yield (671.9 mg, 1.8 mmol) with no further purification necessary.

¹H NMR (400 MHz, CDCl₃) δ 7.98 – 7.88 (m, 2H), 7.50 (s, 1H), 7.28 – 7.17 (m, 2H), 5.53 (d, J = 2.6 Hz, 2H), 2.79 (s, 3H), 2.71 (t, J = 2.5 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 171.08, 166.32 (d, J = 258.7 Hz), 162.21, 130.54 (d, J = 9.6 Hz), 119.11 (d, J = 3.4 Hz), 117.52 (d, J = 22.7 Hz), 105.88, 78.17, 71.54, 42.42, 12.58. (OTf ¹³C not observed)

¹⁹F NMR (376 MHz, CDCl₃) δ -78.48, -101.10.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₃H₁₁FNO⁺ 216.0819; found 216.0821.



3-(4-fluorophenyl)-5-phenyl-2-(prop-2-yn-1-yl)isoxazol-2-ium trifluoromethanesulfonate (**3h**)

Synthesized according to the general alkylation procedure (GP2) using 3-(4-fluorophenyl)-5-phenylisoxazole (**1h**, 239.1 mg, 1 mmol) and 4 equiv of propargyl triflate. The title compound was isolated as a brown solid in a 86% yield (366.0 mg, 0.86 mmol) with no further purification necessary.

¹H NMR (400 MHz, DMSO) δ 8.41 (s, 1H), 8.14 – 8.07 (m, 2H), 8.05 (dd, J = 8.7, 5.2 Hz, 2H), 7.85 – 7.71 (m, 3H), 7.69 (t, J = 8.8 Hz, 2H), 5.89 (d, J = 2.6 Hz, 2H), 4.00 (t, J = 2.5 Hz, 1H).

¹³C NMR (126 MHz, DMSO) δ 170.7, 165.3 (d, J = 254.1 Hz), 159.7, 134.5, 132.8 (d, J = 9.9 Hz), 130.1, 127.4, 122.8, 120.7 (q, J = 322.3 Hz), 118.8 (d, J = 3.2 Hz), 117.4 (d, J = 22.7 Hz), 105.8, 80.3, 73.4, 43.7.

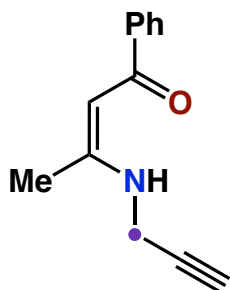
¹⁹F NMR (376 MHz, DMSO) δ -77.75, -103.89.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₈H₁₃FNO⁺ 278.0976; found 278.0975.

General reduction of isoxazolium triflate salt procedure (GP3)

To an 8 mL vial under N₂ with a stir bar was added 3-methyl-5-phenyl-2-(prop-2-yn-1-yl)isoxazol-2-ium trifluoromethanesulfonate **3a** (69.4 mg, 0.2 mmol, 1 equiv), Zn⁰ powder (26.2 mg, 0.4 mmol, 2 equiv), and PTSA·H₂O (57.1 mg, 0.3 mmol, 1.5 equiv). A 2 mL solution of 10:1 NMP/H₂O was prepared and subsequently added to the vial. The reaction was let stir at room temperature

for 1 hour. After reaction completion, vial contents were transferred to a separatory funnel. LiCl (10%, aq.) was added and extracted 3x with Et₂O. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation.



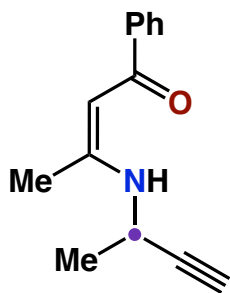
(Z)-1-phenyl-3-(prop-2-yn-1-ylamino)but-2-en-1-one (4a)

Synthesized from **3a** (69.4 mg, 0.2 mmol) according to the general reduction procedure (GP3). The title compound was isolated as an off-white solid 81% (32.4 mg, 0.16 mmol) after purification by flash column chromatography (10-20% EtOAc in hexanes).

¹H NMR (400 MHz, CDCl₃) δ 11.37 (s, 1H), 7.91 – 7.82 (m, 2H), 7.48 – 7.35 (m, 3H), 5.75 (s, 1H), 4.06 (dd, J = 6.1, 2.5 Hz, 2H), 2.31 (t, J = 2.5 Hz, 1H), 2.14 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 188.7, 164.3, 140.2, 130.8, 128.3, 127.1, 93.3, 79.1, 72.5, 32.6, 19.3.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₃H₁₄NO⁺ 200.1070; found 200.1073.



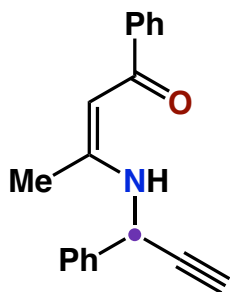
(Z)-3-(but-3-yn-2-ylamino)-1-phenylbut-2-en-1-one (4b)

Synthesized from **3b** (36.13 mg, 0.1 mmol) according to the general reduction procedure (GP3). The title compound was isolated in a 69% yield (14.7 mg, 0.069 mmol) as a yellow waxy solid after purification by flash column chromatography (15% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 11.37 (s, 1H), 7.90 – 7.81 (m, 2H), 7.47 – 7.35 (m, 3H), 5.73 (s, 1H), 4.39 (pd, J = 7.0, 2.2 Hz, 1H), 2.36 (d, J = 2.2 Hz, 1H), 2.19 (s, 3H), 1.61 (d, J = 6.9 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 188.6, 163.6, 140.2, 130.8, 128.3, 127.1, 93.1, 83.7, 71.5, 40.4, 22.5, 19.6.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₄H₁₆NO⁺ 214.1226; found 214.1225.



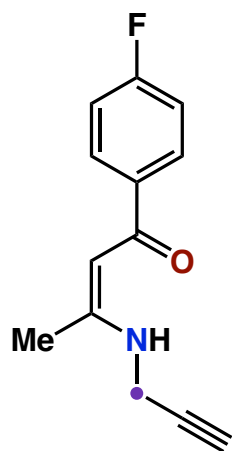
(Z)-1-phenyl-3-((1-phenylprop-2-yn-1-yl)amino)but-2-en-1-one (4c)

Synthesized from (Z)-3-amino-1-phenylbut-2-en-1-one (32.2 mg, 0.2 mmol) and 1-phenylprop-2-yn-1-amine hydrochloride (33.6 mg, 0.2 mmol) using previously published conditions.² The title compound was isolated as a yellow oil in a 78% yield (42.8 mg, 0.16 mmol) after purification by flash column chromatography (10% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 11.71 (d, J = 7.9 Hz, 1H), 8.06 – 7.58 (m, 2H), 7.55 (d, J = 7.3 Hz, 2H), 7.47 – 7.31 (m, 6H), 5.79 (s, 1H), 5.50 (dd, J = 7.9, 2.4 Hz, 1H), 2.59 (d, J = 2.4 Hz, 1H), 2.19 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 188.9, 163.1, 140.1, 138.0, 130.9, 129.2, 128.7, 128.3, 127.2, 127.0, 93.7, 81.7, 74.3, 49.0, 19.8.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₉H₁₈NO⁺ 276.1383; found 276.1373.



(Z)-1-(4-fluorophenyl)-3-(prop-2-yn-1-ylamino)but-2-en-1-one (4d)

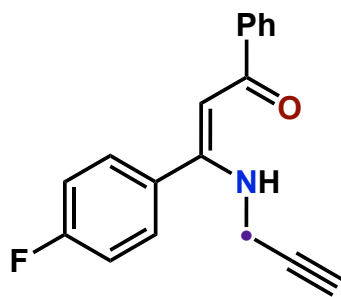
Synthesized from **3d** (51.1 mg, 0.14 mmol) according to the general reduction procedure (GP3). The title compound was isolated in a 49% yield (15.0 mg, 0.07 mmol) as an off-white solid after purification by flash column chromatography (20% EtOAc/hexanes).

¹H NMR (500 MHz, CDCl₃) δ 11.34 (s, 1H), 7.91 – 7.83 (m, 2H), 7.11 – 7.03 (m, 2H), 5.70 (s, 1H), 4.09 (dd, *J* = 6.1, 2.5 Hz, 2H), 2.32 (t, *J* = 2.5 Hz, 1H), 2.17 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 187.2, 164.5 (d, *J* = 250.6 Hz), 164.3, 136.3 (d, *J* = 2.9 Hz), 129.2 (d, *J* = 8.8 Hz), 115.1 (d, *J* = 21.6 Hz), 92.9, 78.9, 72.5, 32.5, 19.2.

¹⁹F NMR (470 MHz, CDCl₃) δ -109.87.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₃H₁₃FNO⁺ 218.0976; found 218.0985.



(Z)-3-(4-fluorophenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (4h)

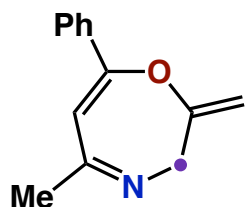
Synthesized from **3h** (42.7 mg, 0.1 mmol) according to the general reduction procedure (GP3). The title compound was isolated in a 27% yield (7.4 mg, 0.027 mmol) as a yellow oil after purification by flash column chromatography (5-10% EtOAc/hexanes).

¹H NMR (500 MHz, CD₃CN) δ 11.26 (s, 1H), 7.94 – 7.88 (m, 2H), 7.60 – 7.54 (m, 2H), 7.53 – 7.46 (m, 1H), 7.47 – 7.40 (m, 2H), 7.29 – 7.22 (m, 2H), 5.87 (s, 1H), 3.98 (dd, *J* = 6.3, 2.5 Hz, 2H), 2.58 (t, *J* = 2.5 Hz, 1H).

¹³C NMR (151 MHz, CD₃CN) δ 189.6, 166.1, 164.5 (d, *J* = 247.6 Hz), 140.8, 132.2, 132.1 (d, *J* = 3.4 Hz), 131.3 (d, *J* = 8.6 Hz), 129.3, 128.1, 116.6 (d, *J* = 22.0 Hz), 95.2, 81.1, 73.6, 34.7.

¹⁹F NMR (376 MHz, CDCl₃) δ -110.36.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₈H₁₅FNO⁺ 280.1132; found 280.1134.



5-methyl-2-methylene-7-phenyl-2,3-dihydro-1,4-oxazepine (6)

Synthesized from **2a** (398.4 mg, 2.0 mmol) using previously published conditions.³ The title compound was isolated as a yellow oil in a 53% yield (211 mg, 1.1 mmol) after purification by flash column chromatography (10% MeOH/EtOAc).

¹H NMR (600 MHz, CDCl₃) δ 7.71 – 7.65 (m, 2H), 7.45 – 7.36 (m, 3H), 5.88 (s, 1H), 4.70 (d, *J* = 1.4 Hz, 1H), 4.33 (d, *J* = 1.4 Hz, 1H), 4.31 (s, 2H), 2.17 (s, 3H).

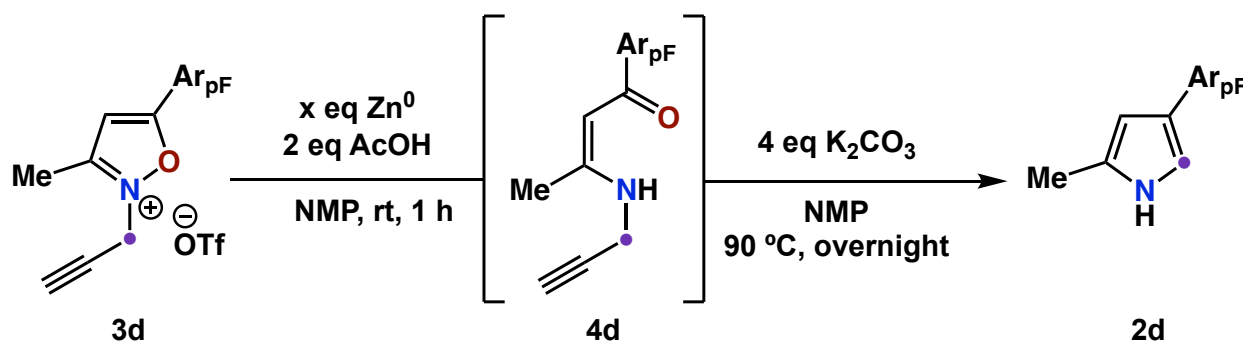
¹³C NMR (151 MHz, CDCl₃) δ 167.87, 157.58, 156.84, 135.07, 130.10, 128.60, 126.36, 101.35, 94.13, 55.19, 27.13.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₃H₁₄NO⁺ 200.1070; found 200.1065.

3. Optimization

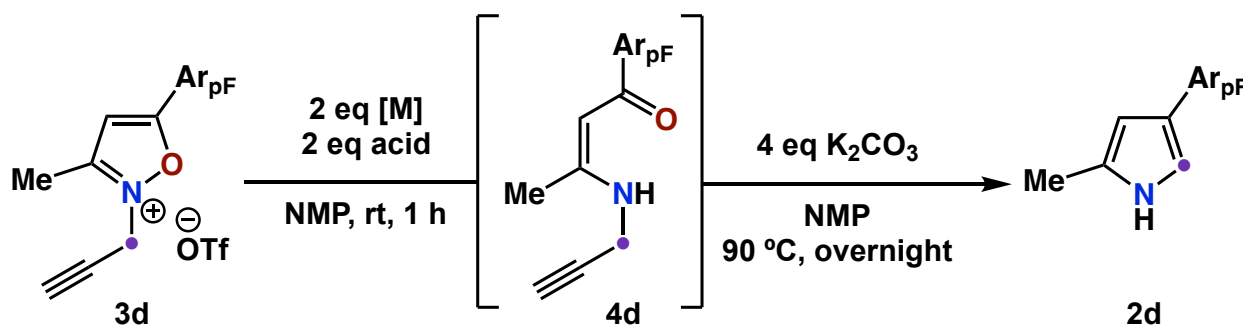
All optimization reactions were performed on a 0.1 mmol scale and analyzed with ^{19}F NMR. NMR samples for quantitative analysis were prepared by dissolving a known amount of 4,4'-difluorobenzophenone in the crude reaction after completion. Yields were calculated using quantitative ^{19}F NMR.

Table S1. Zinc equivalents screen.

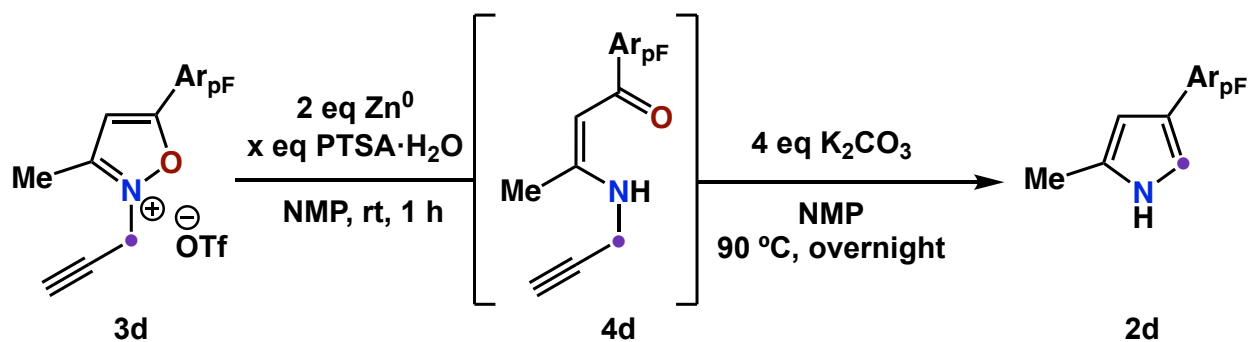


Entry	Zn^0 equiv	3d (%)	4d (%)	2d (%)
1	1.1	0	20	40
2	1.5	0	3	57
3	2	0	4	64
4	2.5	0	2	60

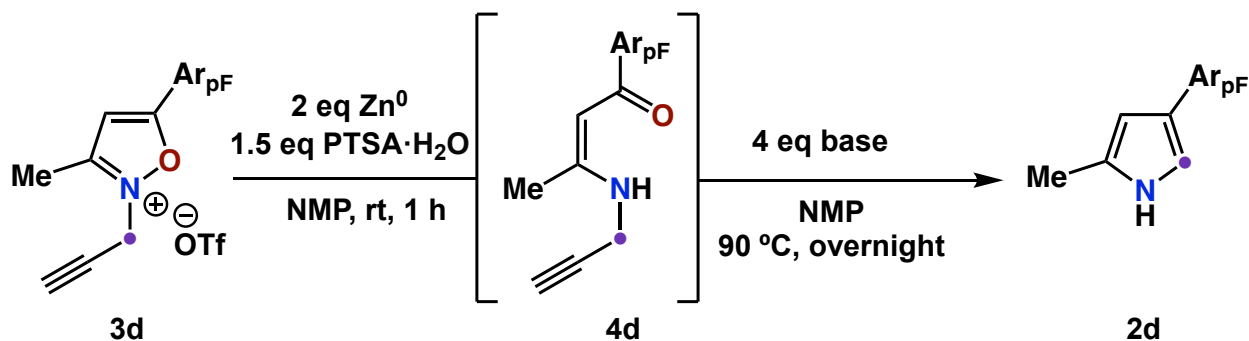
Table S2. Metal reductant and acid screen.



Entry	$[\text{M}]$	Acid	3d (%)	4d (%)	2d (%)
1	Zn^0	AcOH	0	17	41
2	Mg^0	AcOH	4	36	18
3	Mn^0	AcOH	2	19	35
4	Zn^0	TFA	0	3	47
5	Zn^0	Oxalic acid	15	41	6
6	Zn^0	KHCO_3	0	28	4
7	Zn^0	$\text{PTSA}\cdot\text{H}_2\text{O}$	0	2	70

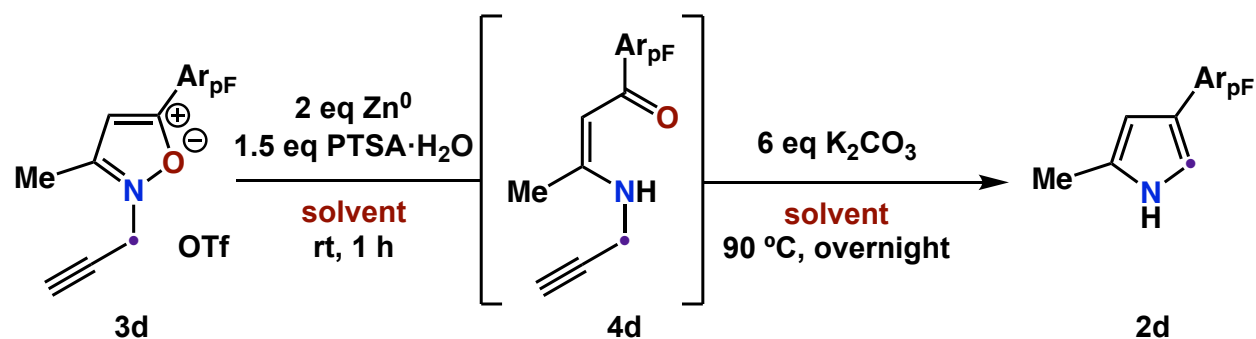
Table S3. Acid equivalents screen.

Entry	PTSA·H ₂ O equiv	3d (%)	4d (%)	2d (%)
1	1	0	18	50
2	1.5	0	3	78
3	2	0	1	77
4	2.5	0	12	67
5	3	0	42	32

Table S4. Base screen.

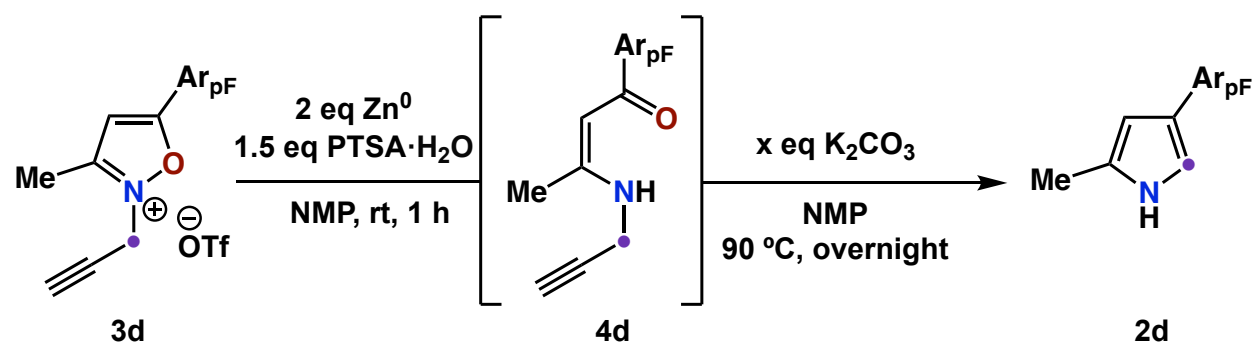
Entry	base	3d (%)	4d (%)	2d (%)
1	K ₂ CO ₃	0	0	76
2	K ₃ PO ₄	0	0	73
3	KOtBu	0	0	0
4	Na ₂ CO ₃	0	90	0
5	CS ₂ CO ₃	0	0	35
6	NaHCO ₃	0	82	0
7	KOH	0	0	6

Table S5. Solvent screen.



Entry	solvent	3d (%)	4d (%)	2d (%)
1	NMP	0	0	76
2	DMF	0	70	13
3	DMSO	0	15	68
4	1,4-dioxane	0	45	0
5	MeCN	10	29	0
6	DCE	20	23	0
7	DMA	0	61	3
8	DMA/ H_2O (10:1)	0	25	58

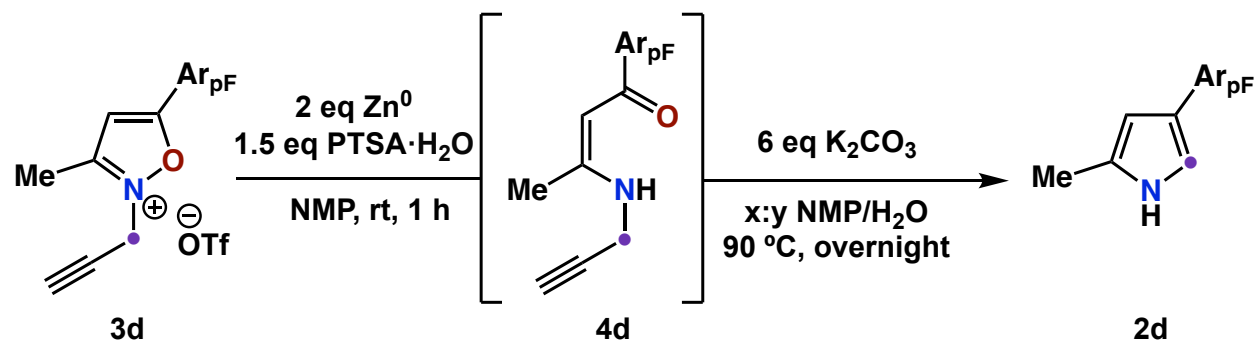
Table S6. Base equivalents screen.



Entry	K_2CO_3 equiv	3d (%)	4d (%)	2d (%)
1	2	0	77	5
2	3	0	12	73
3	4	0	2	75
4	5	0	2	77
5	6	0	2	88

Note: Over the course of this study, we found varying results based on the water content within the NMP solvent. We found that addition of water successfully promoted pyrrole formation and normalized differences between solvent bottles of different water contents.

Table S7. Water/NMP ratio screen.

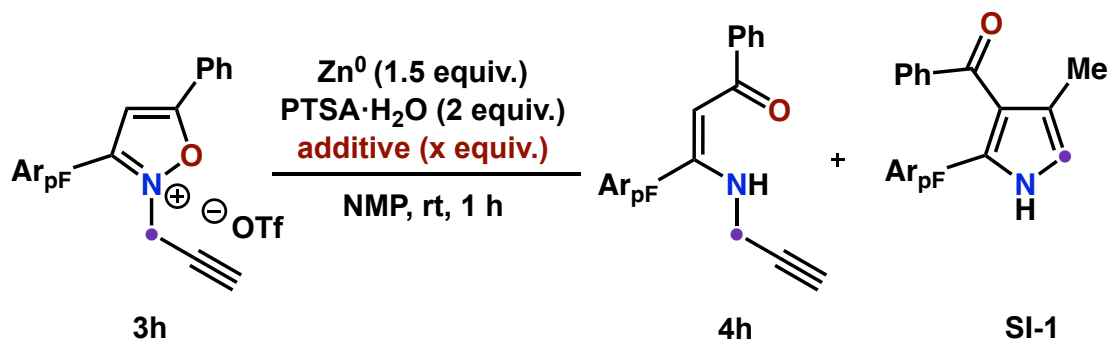


Entry	NMP/H ₂ O	3d (%)	4d (%)	2d (%)
1	10:0 (+ 4 Å MS)	0	69	4
2	10:0	0	5	68
3	10:0.01	0	11	54
4	10:0.5	0	6	73
5	10:1	0	0	78
6	10:2	0	0	66
7	10:3	0	0	63
8	10:5	0	0	51
9	10:7.5	0	0	28
10	10:10	0	0	11

3,5-diaryl isoxazoles

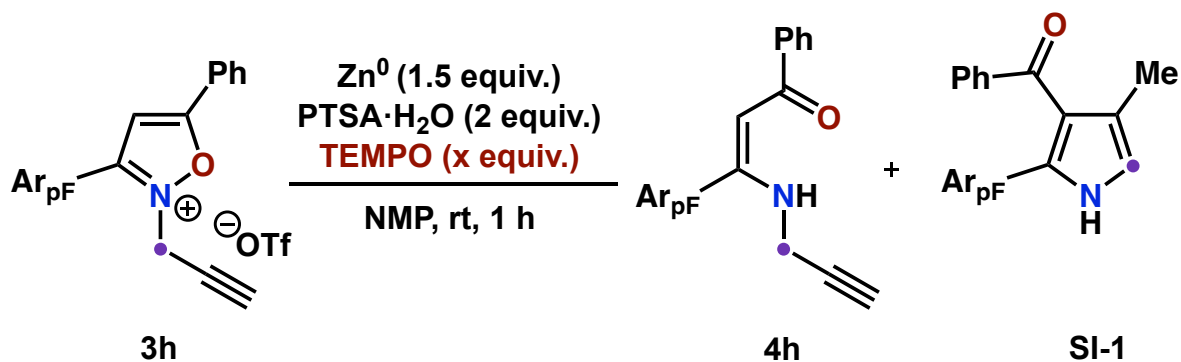
During our scope investigations, we discovered undesired pyrrole formation (**SI-1**) during the reduction step for 3,5-diaryl isoxazoles. Through additive screening, we were able to suppress this side product by addition of TEMPO during the reduction.

Table S8. Additive screen for reduction of 3,5-diaryl isoxazolium salt



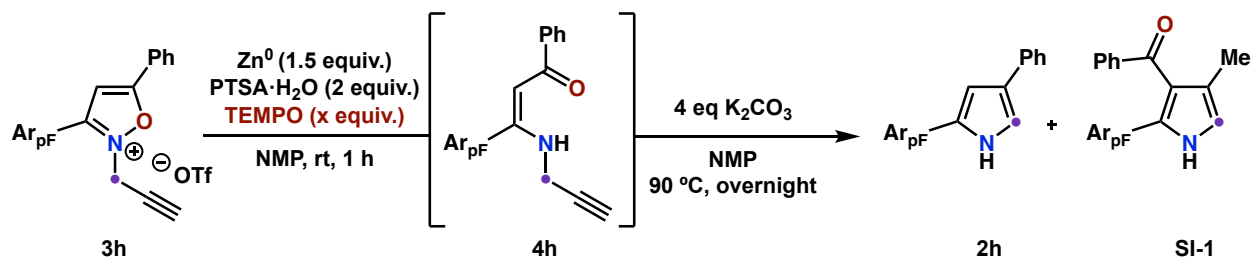
Entry	Additive (1 equiv.)	4h (%)	SI-1 (%)
1	None	19	22
2	TEMPO	53	10
3	BHT	23	22
4	ABNO	27	17
5	galvinoxyl	40	16
6	TEMPOL	51	11

Table S9. TEMPO equivalents screen for reduction of 3,5-diaryl isoxazolium salt



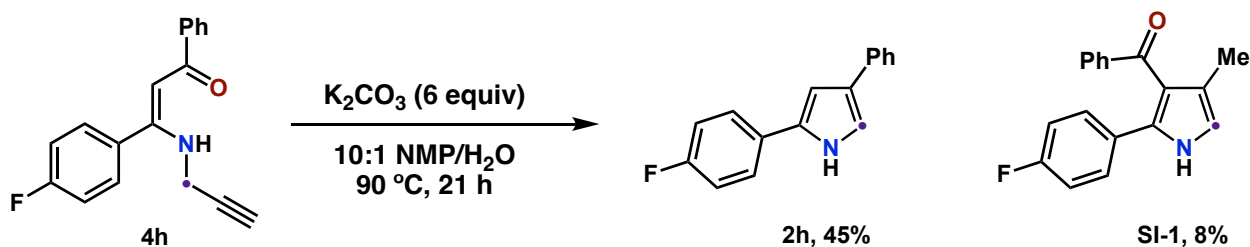
Entry	TEMPO equiv.	4h (%)	SI-1 (%)
1	1	51	12
2	2	51	3
3	4	60	0
4	10	66	0

Table S10. TEMPO equivalents screen for one-pot reduction and cyclization of 3,5-diaryl isoxazolium salt

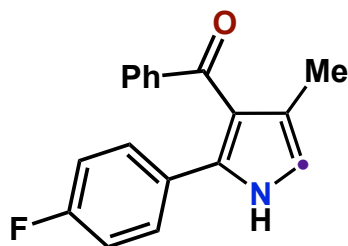


Entry	TEMPO equiv.	2h (%)	SI-1 (%)
1	1	35	20
2	2	28	6
3	4	27	0
4	10	15	0

It is relevant to note that the isolated 2° enaminone (**4h**) *does* cyclize productively (without the addition of TEMPO) under the cyclization conditions, providing >5:1 desired/undesired pyrrole (Scheme S1).



Scheme S1. Cyclization of **4h**. All qNMR yields using TMB (trimethoxybenzene) as an internal standard.



(2-(4-fluorophenyl)-4-methyl-1H-pyrrol-3-yl)(phenyl)methanone (SI-1)

Synthesized from **3h** (42.7 mg, 0.1 mmol) according to the general reduction procedure (GP3). The title compound was isolated in a 16% yield (4.4 mg, 0.016 mmol) as a yellow oil after purification by flash column chromatography (5-10% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.64 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.38 – 7.29 (m, 1H), 7.23 – 7.10 (m, 4H), 6.83 (t, *J* = 8.6 Hz, 2H), 6.70 – 6.63 (m, 1H), 2.17 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 194.5, 162.2 (d, *J* = 247.8 Hz), 139.6, 135.3, 132.0, 129.93 (d, *J* = 8.6 Hz), 129.87, 128.7 (d, *J* = 3.4 Hz), 128.0, 122.6, 120.8, 117.2, 115.5 (d, *J* = 21.7 Hz), 11.8.

¹⁹F NMR (376 MHz, CDCl₃) δ -114.01.

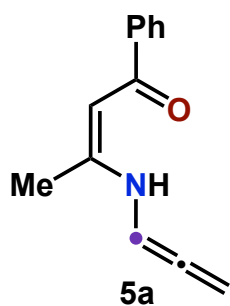
HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₈H₁₅FNO⁺ 280.1132; found 280.1129.

4. Kinetics

a) Allene **5a** synthesis + characterization

To an 8 mL vial under N₂ atmosphere with a stir bar was added (Z)-1-phenyl-3-(prop-2-yn-1-ylamino)but-2-en-1-one (19.9 mg, 0.1 mmol, 1 equiv). Anhydrous THF (0.5 mL) was added, and the vial was brought to 0 °C in an ice bath. After cooling for 5 minutes, KO^tBu (22.4 mg, 0.2 mmol, 2 equiv) was added in one portion and let stir at 0 °C for 5 minutes. The reaction was quenched by addition of 0.5 mL H₂O, followed by 0.5 mL NH₄Cl (aq). The vial contents were extracted 3x with Et₂O, and the combined organic layer was dried over Na₂SO₄ and filtered.

Note: The allene product is relatively unstable upon concentration, and therefore isolation attempts were unsuccessful. However, rotary evaporation to partially remove residual ethereal solvents reveals the allene as the major product. ¹H and ¹³C NMR were able to unambiguously characterize the diagnostic allenyl features.



(Z)-1-phenyl-3-(propa-1,2-dien-1-ylamino)but-2-en-1-one (**5a**)

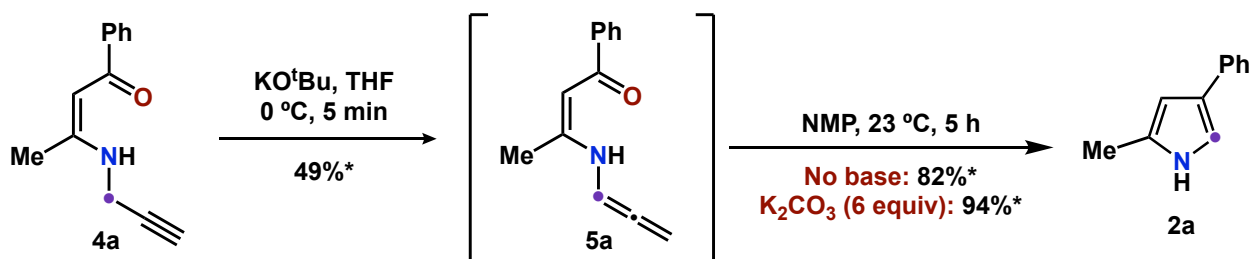
The title compound was characterized as a THF/Et₂O solution without further purification.

¹H NMR (500 MHz, CDCl₃) δ 12.32 (d, J = 10.2 Hz, 1H), 7.91 – 7.85 (m, 2H), 7.49 – 7.36 (m, 3H; *overlapping with unidentified aromatic impurity*), 6.60 (dt, J = 10.3, 6.3 Hz, 1H), 5.83 (s, 1H), 5.38 (d, J = 6.3 Hz, 2H), 2.13 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 203.8, 188.5, 159.1, 139.8, 130.8, 128.1, 126.9, 96.6, 94.5, 85.8, 19.3.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₃H₁₄NO⁺ 200.1070; found 200.1073.

It was found that solvent exchange by addition of a higher boiling point solvent (0.1M NMP or DMSO) *prior* to rotary evaporation (to avoid concentration of allene **5a** to dryness) was effective for initiating cyclization to pyrrole **2a** (Scheme S2).



Scheme S2. Yield of **5a** and subsequent reaction of the allene with the NMP cyclization conditions (with and without addition of base). Yield of pyrrole **2a** was calculated relative to the yield of **5a** calculated in the previous step. * indicates qNMR yield calculated with TMB (trimethoxybenzene) as an internal standard

b) Time-point kinetics

Due to the heterogeneous nature of our optimized reaction conditions (K_2CO_3 is largely insoluble in NMP), the rate constants could not be measured via *in situ* monitoring. We therefore opted to pursue time-point kinetics as a means of measuring the k_{obs} of allene consumption and subsequent pyrrole formation.

Procedure:

Allene **5a** was synthesized according to the procedure outlined above (0.1 mmol scale). TMB was added to the solution (as internal standard) after completion of the workup. Prior to rotary evaporation, 1 mL NMP was added to the ethereal solution to avoid concentration to complete dryness. Upon removal of most of the residual Et_2O /THF (as judged by measuring the volume after concentration to $\sim 1\text{ mL}$), the vial containing the allene was sparged with N_2 for 5 min and a stir bar was added. The reaction was let stir at room temperature under N_2 . [For monitoring reaction progress with base: K_2CO_3 (83 mg, 6 equiv) was also added at this point.]

Aliquots ($\sim 50\text{ }\mu\text{L}$) were taken out of the reaction every 30 minutes and diluted with CDCl_3 . Any insoluble particles were filtered during NMR sample preparation. The concentration of allene **5a** and pyrrole **2a** was measured with respect to the TMB aromatic NMR signal. At least 8 aliquots were taken to monitor the reaction until near completion (210 min). Time-point kinetic monitoring was conducted in triplicate.

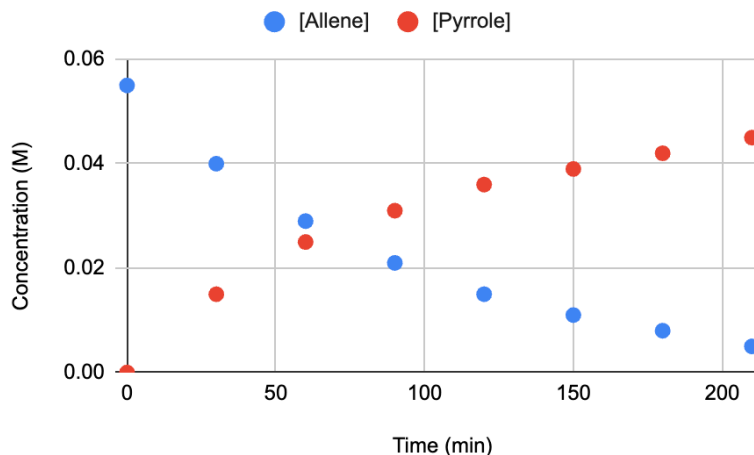


Figure S1. Representative time-point monitoring of allene **5a** and pyrrole **2a** over time. Conditions: **5a** (prepared on 0.1 mmol scale), NMP (1 mL), K_2CO_3 (6 equiv).

The rate constants for allene consumption were measured according to Eq. 1 by plotting $\ln[\text{allene}]$ vs. time. The magnitude of the slope of the trendline corresponds to the observed rate constant. The linear fit is in good agreement with first order kinetics in allene **5a**.

$$\ln[\mathbf{5a}] = \ln[\mathbf{5a}]_0 - k_{obs}t \quad (\text{Eq. 1})$$

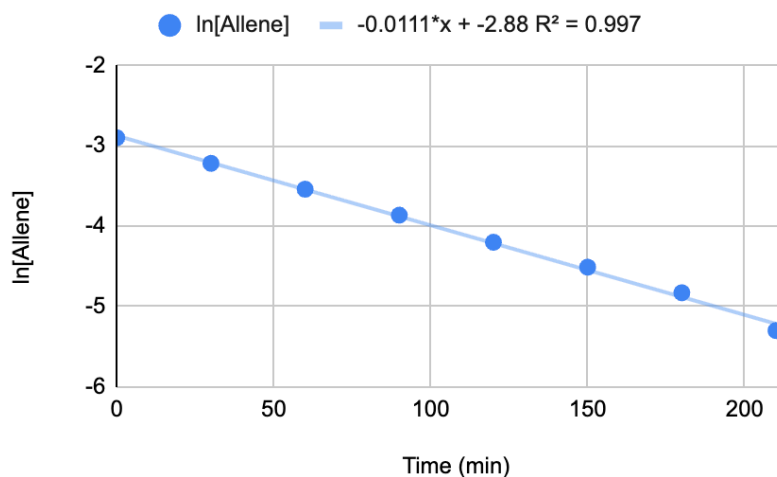


Figure S2. Representative $\ln[\mathbf{5a}]$ vs. time plot. $k_{obs} = 1.11 \times 10^{-2} \text{ min}^{-1} = 1.85 \times 10^{-4} \text{ s}^{-1}$.

A) No added base. Rate constants reported with units: s⁻¹

Run 1	Run 2	Run 3	Average	Std. Dev
1.61 x 10 ⁻⁴	1.45 x 10 ⁻⁴	1.53 x 10 ⁻⁴	1.53 x 10 ⁻⁴	7.58 x 10 ⁻⁶

B) With K₂CO₃ (6 equiv). Rate constants reported with units: s⁻¹

Run 1	Run 2	Run 3	Average	Std. Dev
1.85 x 10 ⁻⁴	1.73 x 10 ⁻⁴	1.61 x 10 ⁻⁴	1.73 x 10 ⁻⁴	1.19 x 10 ⁻⁵

To ensure that the allene consumption and pyrrole formation were indeed occurring at comparable rates, the rate constant for pyrrole **2a** formation was measured according to Eq. 2. The magnitude of the slope of the trendline corresponds to the observed rate constant. **[2a]_{final}** was estimated by inspection of the sum of **[2a]** + **[5a]** at each given timepoint.

$$\ln(1 - [\mathbf{2a}]_t / [\mathbf{2a}]_{\text{final}}) = -k_{\text{obs}}t \quad (\text{Eq. 2})$$

From this analysis, the measured rate constants are as follows, which are in good agreement with the kinetic data from measuring the allene **5a** consumption:

$$\text{Avg. } k_{\text{obs}} (\text{no added base}) = 1.46 \times 10^{-4} \text{ s}^{-1} \pm 7.86 \times 10^{-6} \text{ s}^{-1}$$

$$\text{Avg. } k_{\text{obs}} (\text{6 equiv. K}_2\text{CO}_3) = 1.59 \times 10^{-4} \text{ s}^{-1} \pm 1.30 \times 10^{-5} \text{ s}^{-1}$$

c) NMR kinetics

In order to conduct in-situ monitoring of our system, we opted to use a modified system with DMSO-*d*₆ and soluble bases, which also afforded the desired pyrrole **2a** from the isolated allene **5a**. NMR kinetics were conducted in triplicate.

Procedure:

Allene **5a** was synthesized according to the procedure outlined above (0.1 mmol scale). Mesitylene was added to the solution (as internal standard) after completion of the workup. Prior to rotary evaporation, DMSO-*d*₆ was added to the ethereal solution (1 mL for no base added runs; 0.8 mL for added base runs). Upon concentration until removal of most of the residual Et₂O/THF (as judged by measuring the volume after concentration to 1 or 0.8 mL), the DMSO-*d*₆ solution was directly added to an NMR tube under air.

For kinetic runs with added bases, a stock solution of 2 equiv. of base (Et_3N or Barton's base) in 0.2 mL $\text{DMSO}-d_6$ was separately prepared. This stock solution was directly added to the NMR tube directly before beginning NMR acquisition.

Note: Due to pyrrole formation occurring immediately after addition of DMSO to the vial containing **5a**, the NMR kinetics were set up immediately after completion of rotary evaporation (in order to maximize the monitoring time of the reaction).

Pseudo-2D ^1H NMR kinetics: The spectra were obtained while monitoring the allene consumption at room temperature in a 600 MHz Bruker spectrometer. The following parameters were used to acquire the spectra:

NS: 1

D20 (time between scans): 60 s

Number of FIDs collected: 120 (for 2 hours total of monitoring)

Relaxation delay: 10 s

Pulse angle: 35°

Spectral width: 16 ppm

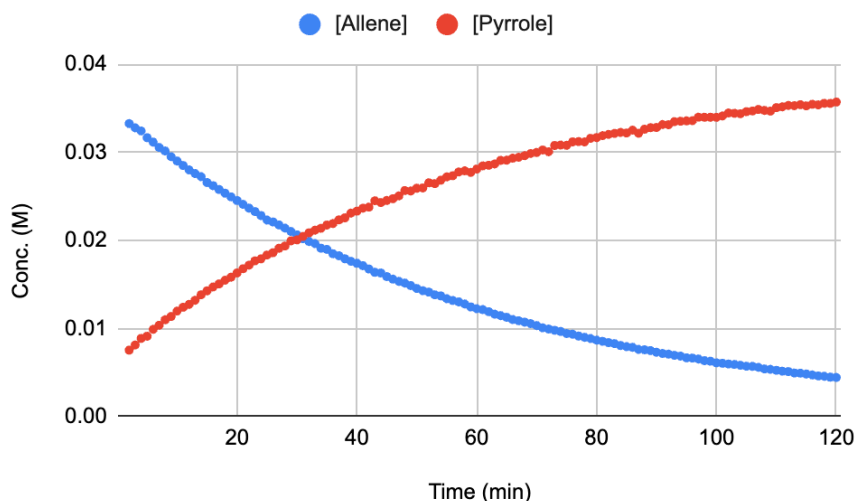


Figure S3. Representative NMR monitoring of allene **5a** and pyrrole **2a** over time. Conditions: **5a** (prepared on 0.1 mmol scale), $\text{DMSO}-d_6$ (1 mL), Et_3N (2 equiv).

The rate constants for allene consumption were measured according to Eq. 1 by plotting $\ln[\text{allene}]$ vs. time. The magnitude of the slope of the trendline corresponds to the observed rate constant. The linear fit is in good agreement with first order kinetics in allene **5a**.

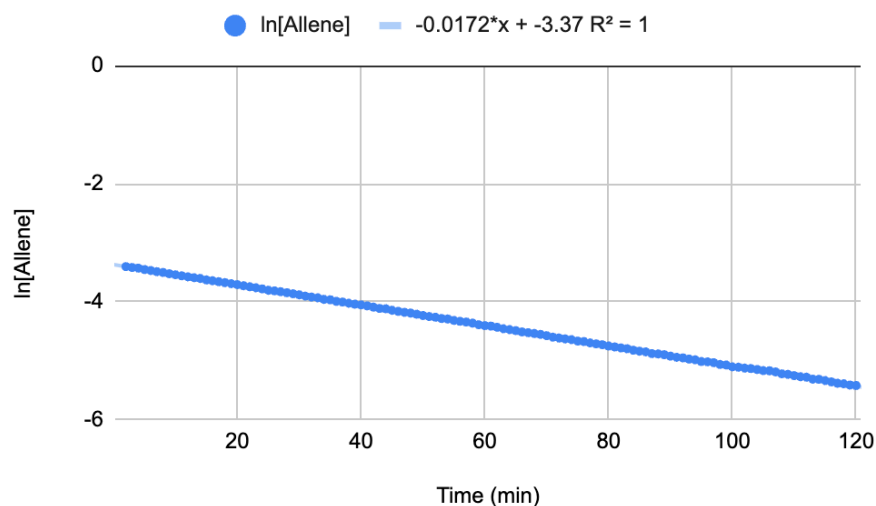


Figure S4. Representative $\ln[5a]$ vs. time plot. $k_{\text{obs}} = 1.72 \times 10^{-2} \text{ min}^{-1} = 2.87 \times 10^{-4} \text{ s}^{-1}$.

A) No added base. Rate constants reported with units: s^{-1}

Run 1	Run 2	Run 3	Average	Std. Dev
2.93×10^{-4}	2.92×10^{-4}	2.83×10^{-4}	2.89×10^{-4}	5.36×10^{-6}

B) With Et_3N (2 equiv). Rate constants reported with units: s^{-1}

Run 1	Run 2	Run 3	Average	Std. Dev
2.87×10^{-4}	3.05×10^{-4}	2.88×10^{-4}	2.93×10^{-4}	1.01×10^{-5}

C) With Barton's base (2 equiv). Rate constants reported with units: s^{-1}

Run 1	Run 2	Run 3	Run 4	Average	Std. Dev
5.95×10^{-4}	9.23×10^{-4}	6.77×10^{-4}	1.00×10^{-3}	8.00×10^{-4}	1.95×10^{-4}

To ensure that the allene consumption and pyrrole formation were indeed occurring at comparable rates, the rate constant for pyrrole **2a** formation was measured according to Eq. 2.

The magnitude of the slope of the trendline corresponds to the observed rate constant. $[2a]_{\text{final}}$ was estimated by inspection of the sum of $[2a] + [5a]$ over time.

From this analysis, the measured rate constants are as follows, which are in good agreement with the kinetic data from measuring the allene **5a** consumption:

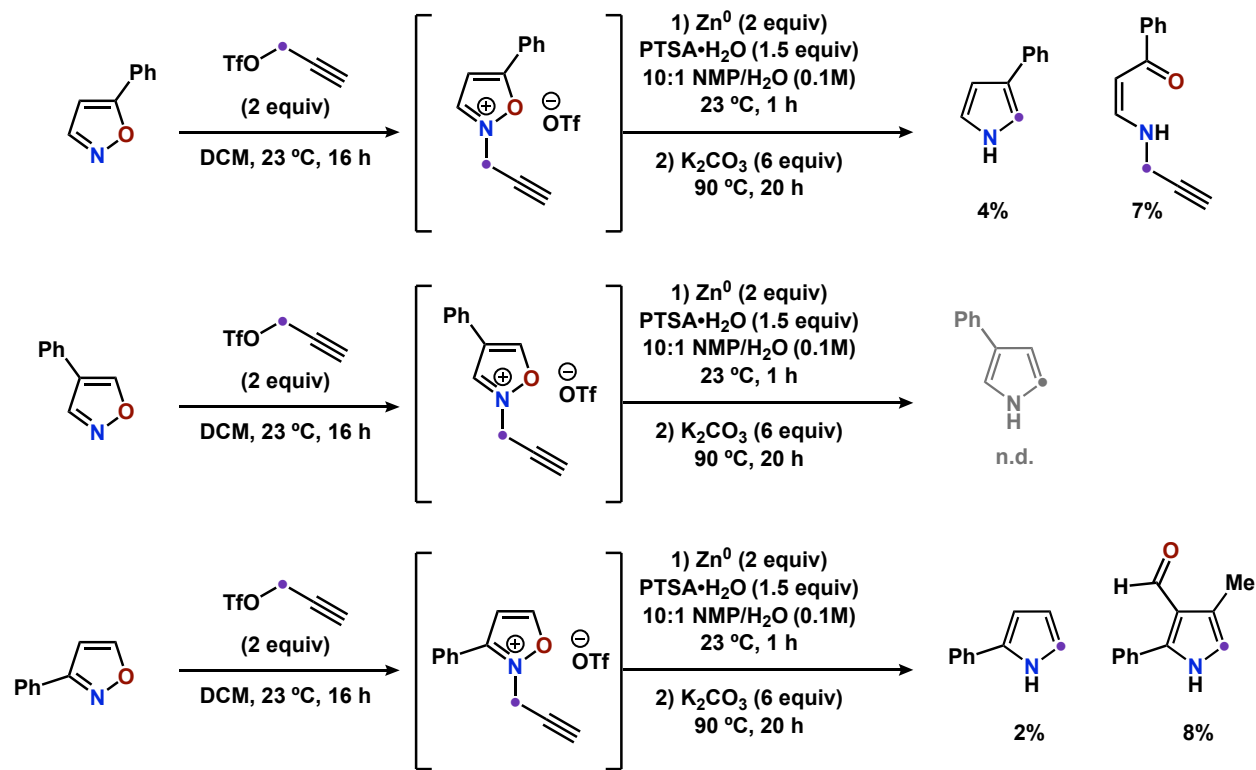
$$\text{Avg. } k_{\text{obs}} (\text{no added base}) = 3.01 \times 10^{-4} \text{ s}^{-1} \pm 2.06 \times 10^{-5} \text{ s}^{-1}$$

$$\text{Avg. } k_{\text{obs}} (\text{2 equiv. Et}_3\text{N}) = 2.94 \times 10^{-4} \text{ s}^{-1} \pm 9.18 \times 10^{-6} \text{ s}^{-1}$$

$$\text{Avg. } k_{\text{obs}} (\text{2 equiv. Barton's base}) = 8.09 \times 10^{-4} \text{ s}^{-1} \pm 2.05 \times 10^{-4} \text{ s}^{-1}$$

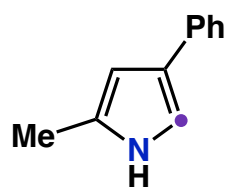
5. Scope limitation: Monosubstituted isoxazoles

3, 4, and 5-phenylisoxazoles were subjected to the general procedure (GP1). The yields reported (Scheme S3) are all qNMR yields using TMB as an internal standard. The low yields across the board are likely a result of destabilized reaction intermediates over the course of the cyclization.



Scheme S3. Representative examples of monosubstituted isoxazoles

6. Characterization of Pyrrole Products



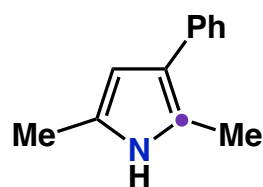
2-methyl-4-phenyl-1H-pyrrole (2a)

Synthesized according to the general procedure (GP1) using 3-methyl-5-phenylisoxazole (**1a**, 31.8 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a brown oil in a 61% yield (19.2 mg, 0.122 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

¹H NMR (500 MHz, CDCl₃) δ 7.92 (br, 1H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.94 (t, *J* = 2.1 Hz, 1H), 6.28 – 6.23 (m, 1H), 2.31 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 136.2, 128.9, 128.7, 125.4, 125.3, 125.2, 113.1, 104.5, 13.2.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₁H₁₂N⁺ 158.0964; found 158.0966.



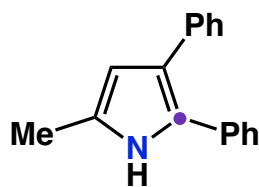
2,5-dimethyl-3-phenyl-1H-pyrrole (2b)

Synthesized from **4b** (42.6 mg, 0.2 mmol, 1 equiv) using modified cyclization conditions from GP1: powdered K₃PO₄ (254.7 mg, 1.2 mmol, 6 equiv) was added to a vial containing **4b** and a stir bar under N₂ atmosphere. A 2 mL solution of 10:1 NMP/H₂O was prepared and subsequently added to the vial. The vial was then brought to 90 °C to stir overnight (typically 16-20 hours). After reaction completion, the reaction was brought to room temperature, and the vial contents were transferred to a separatory funnel. LiCl (aq.) was added and extracted 3x with Et₂O. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation. The title compound was isolated as a white solid in a 16% yield (5.6 mg, 0.032 mmol) after purification by flash column chromatography (15% EtOAc in hexanes).

¹H NMR (500 MHz, CDCl₃) δ 7.62 (s, 1H), 7.40 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.35 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.18 (tt, *J* = 7.2, 1.4 Hz, 1H), 6.01 (dd, *J* = 3.0, 1.1 Hz, 1H), 2.38 (s, 3H), 2.28 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 137.4, 128.4, 127.6, 125.9, 125.0, 122.6, 121.2, 106.5, 13.0, 12.7.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₂H₁₄N⁺ 172.1121; found 172.1116.



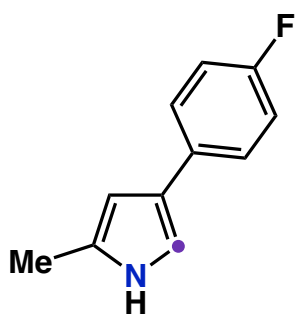
5-methyl-2,3-diphenyl-1H-pyrrole (2c)

Synthesized from **4c** (42.8 mg, 0.16 mmol, 1 equiv) using cyclization conditions from GP1: powdered K_2CO_3 (132.4 mg, 0.96 mmol, 6 equiv) was added to a vial containing **4c** and a stir bar under N_2 atmosphere. A 2 mL solution of 10:1 NMP/ H_2O was prepared and subsequently added to the vial. The vial was then brought to 90 °C to stir overnight (typically 16-20 hours). After reaction completion, the reaction was brought to room temperature, and the vial contents were transferred to a separatory funnel. LiCl (aq.) was added and extracted 3x with Et_2O . The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated via rotary evaporation. The title compound was isolated as a white solid in a 42% yield (15.3 mg, 0.032 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

^1H NMR (500 MHz, CDCl_3) δ 7.92 (s, 1H), 7.38 – 7.13 (m, 10H), 6.11 (dd, J = 2.8, 1.1 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 137.0, 133.7, 128.7, 128.5, 128.4, 128.3, 127.4, 127.0, 126.5, 125.7, 122.4, 109.2, 13.1.

HRMS (APCI/QTOF) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{16}\text{N}^+$ 234.1277; found 234.1283.



4-(4-fluorophenyl)-2-methyl-1H-pyrrole (2d)

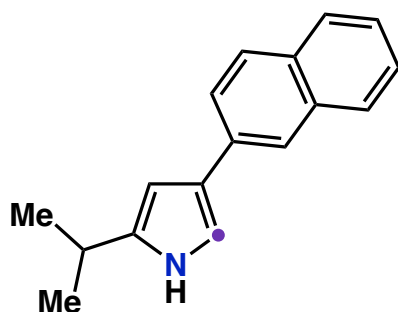
Synthesized according to the general procedure (GP1) using 5-(4-fluorophenyl)-3-methylisoxazole (**1d**, 35.4 mg, 0.2 mmol, 1 equiv). The title compound was isolated as an orange solid in a 63% yield (22.1 mg, 0.126 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

^1H NMR (600 MHz, CDCl_3) δ 7.89 (s, 1H), 7.43 (dd, J = 8.6, 5.6 Hz, 2H), 7.01 (t, J = 8.7 Hz, 2H), 6.87 (t, J = 2.1 Hz, 1H), 6.16 (s, 1H), 2.30 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 161.4 (d, J = 243.3 Hz), 132.4 (d, J = 3.0 Hz), 129.2, 126.6 (d, J = 7.7 Hz), 124.6, 115.5 (d, J = 21.3 Hz), 112.9, 104.7, 13.3.

¹⁹F NMR (565 MHz, CDCl₃) δ -118.31.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₁H₁₁FN⁺ 176.087; found 176.0868.



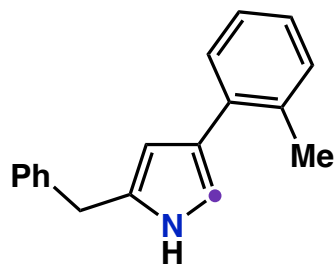
2-isopropyl-4-(naphthalen-2-yl)-1H-pyrrole (2e)

Synthesized according to the general procedure (GP1) using 3-isopropyl-5-(naphthalen-2-yl)isoxazole (**1e**, 47.5 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a white solid in a 44% yield (20.6 mg, 0.088 mmol) after purification by flash column chromatography (20% DCM in hexanes).

¹H NMR 500 MHz, CDCl₃) δ 8.00 (s, 1H), 7.94 (d, J = 1.8 Hz, 1H), 7.84 – 7.76 (m, 3H), 7.69 (dd, J = 8.4, 1.8 Hz, 1H), 7.45 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H), 7.39 (ddd, J = 8.0, 6.8, 1.3 Hz, 1H), 7.09 (t, J = 2.2 Hz, 1H), 6.40 (t, J = 2.4 Hz, 1H), 2.98 (hept, J = 6.9 Hz, 1H), 1.34 (d, J = 6.9 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 140.4, 134.2, 133.7, 132.0, 128.1, 127.76 (2 overlapping carbon signals), 126.1, 124.8, 124.8, 122.5, 113.4, 101.8, 27.3, 22.7.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₇H₁₈N⁺ 236.1434; found 236.1432.



2-benzyl-4-(o-tolyl)-1H-pyrrole (2f)

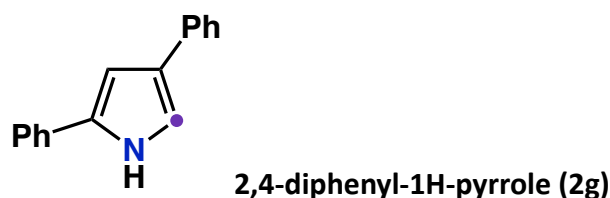
Synthesized according to the general procedure (GP1) using 3-benzyl-5-(o-tolyl)isoxazole (**1f**, 52.6 mg, 0.211 mmol, 1 equiv). The title compound was isolated as a pale brown oil in a 69% yield

(36.2 mg, 0.146 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

¹H NMR (500 MHz, CD₃CN) δ 9.05 (s, 1H), 7.34 – 7.27 (m, 5H), 7.24 – 7.18 (m, 2H), 7.14 (t, *J* = 7.0 Hz, 1H), 7.08 (td, *J* = 7.4, 1.5 Hz, 1H), 6.77 (t, *J* = 2.1 Hz, 1H), 6.11 (t, *J* = 2.3 Hz, 1H), 3.95 (s, 2H), 2.39 (s, 3H).

¹³C NMR (126 MHz, CD₃CN) δ 141.5, 137.1, 135.7, 132.3, 131.5, 129.6, 129.51, 129.45, 127.1, 126.8, 126.4, 124.6, 117.0, 107.9, 34.5, 21.8.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₈H₁₈N⁺ 248.1434; found 248.1433.

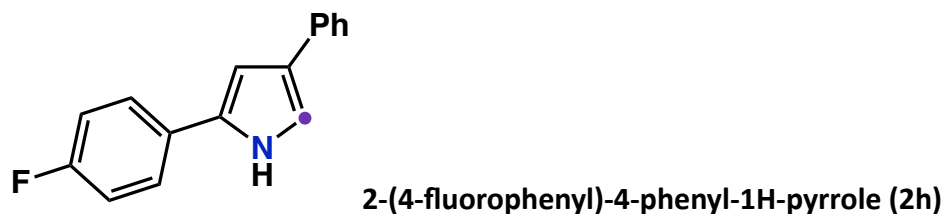


Synthesized according to the general procedure (GP1) modified by the addition of TEMPO (31.2 mg, 0.2 mmol, 1 equiv) during the reduction step, using 3,5-diphenylisoxazole (**1g**, 44.2 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a white solid in a 52% yield (43.9 mg, 0.104 mmol) after purification by flash column chromatography (20% EtOAc in hexanes).

¹H NMR (600 MHz, CDCl₃) δ 8.45 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.43 – 7.34 (m, 4H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 2.1 Hz, 1H), 6.84 (t, *J* = 2.1 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 135.6, 133.2, 132.6, 129.1, 128.8, 126.8, 126.6, 125.9, 125.3, 124.0, 115.7, 104.1.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₆H₁₄N⁺ 220.1121; found 220.1123.



Synthesized according to the general procedure (GP1) modified by the addition of TEMPO (31.2 mg, 0.2 mmol, 1 equiv) during the reduction step, using 3-(4-fluorophenyl)-5-phenylisoxazole (**1h**, 47.8 mg, 0.2 mmol, 1 equiv). The title compound was isolated as an off-white solid in a 31% yield

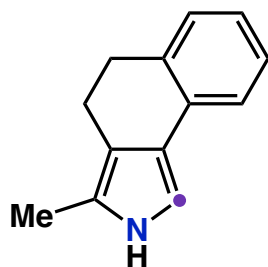
(14.7 mg, 0.062 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

¹H NMR (600 MHz, CDCl₃) δ 8.37 (s, 1H), 7.59 – 7.54 (m, 2H), 7.52 – 7.42 (m, 2H), 7.41 – 7.33 (m, 2H), 7.24 – 7.17 (m, 1H), 7.14 (dd, J = 2.7, 1.7 Hz, 1H), 7.12 – 7.04 (m, 2H), 6.76 (dd, J = 2.8, 1.7 Hz, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 161.8 (d, J = 246.0 Hz), 135.5, 132.4, 129.0 (d, J = 3.3 Hz), 128.8, 126.8, 126.0, 125.7 (d, J = 7.9 Hz), 125.3, 116.1 (d, J = 21.8 Hz), 115.6, 104.1.

¹⁹F NMR (376 MHz, CDCl₃) δ -115.75.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₆H₁₃FN⁺ 238.1027; found 238.1017.



3-methyl-4,5-dihydro-2H-benzo[e]isoindole (2i)

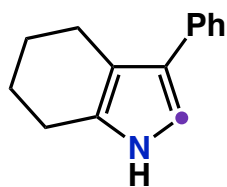
Synthesized according to the general procedure (GP1) using 3-methyl-4,5-dihydronaphtho[2,1-*d*]isoxazole (**1i**, 37 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a yellow oil in a 52% yield (19.1 mg, 0.104 mmol) after purification by flash column chromatography (5% EtOAc in hexanes).

Note: The title compound is air sensitive, especially upon concentration. Degassed CD₃CN (sparged with N₂) was used for characterization, and the NMR sample was prepared under N₂.

¹H NMR (500 MHz, CD₃CN) δ 8.74 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.91 (t, J = 2.1 Hz, 1H), 2.81 (t, J = 7.1 Hz, 2H), 2.58 (t, J = 7.2 Hz, 2H), 2.15 (s, 3H).

¹³C NMR (126 MHz, CD₃CN) δ 136.1, 134.1, 129.3, 127.4, 125.5, 123.1, 123.0, 121.5, 116.3, 111.0, 31.3, 20.5, 10.7.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₃H₁₄N⁺ 184.1121; found 184.1118.



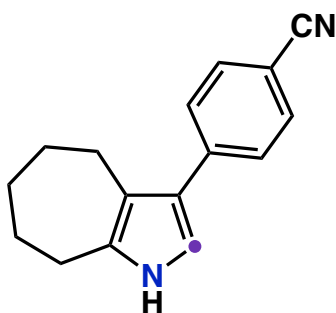
3-phenyl-4,5,6,7-tetrahydro-1H-indole (2j)

Synthesized according to the general procedure (GP1) using 3-phenyl-4,5,6,7-tetrahydrobenzo[*c*]isoxazole (**1j**, 39.8 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a pale-yellow oil in a 35% yield (13.8 mg, 0.070 mmol) after purification by flash column chromatography (30% DCM in hexanes) followed by a silica plug with CHCl₃.

¹H NMR (600 MHz, CDCl₃) δ 7.80 (s, 1H), 7.48 – 7.43 (m, 2H), 7.41 – 7.31 (m, 2H), 7.22 – 7.14 (m, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.63 (t, 2H), 1.91 – 1.83 (m, 2H), 1.82 – 1.74 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 136.7, 128.5, 128.3, 127.1, 125.3, 123.5, 115.4, 113.5, 24.1, 23.3, 23.15 (two overlapping carbon signals).

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₄H₁₆N⁺ 198.1277; found 198.1279.



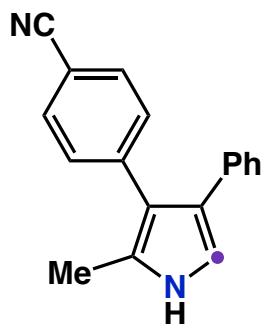
4-(1,4,5,6,7,8-hexahydrocyclohepta[b]pyrrol-3-yl)benzonitrile (2k)

Synthesized according to the general procedure (GP1) using 4-(5,6,7,8-tetrahydro-4*H*-cyclohepta[*c*]isoxazol-3-yl)benzonitrile (**1k**, 47.7 mg, 0.2 mmol, 1 equiv). The title compound was isolated as an orange solid in a 50% yield (23.9 mg, 0.101 mmol) after purification by flash column chromatography (20% EtOAc in hexanes).

¹H NMR (500 MHz, CD₃CN) δ 8.95 (s, 1H), 7.70 – 7.63 (m, 2H), 7.48 – 7.42 (m, 2H), 6.66 (d, *J* = 2.8 Hz, 1H), 2.72 – 2.67 (m, 2H), 2.66 – 2.60 (m, 2H), 1.87 – 1.79 (m, 2H), 1.70 – 1.59 (m, 4H).

¹³C NMR (126 MHz, CD₃CN) δ 143.3, 133.6, 133.2, 129.4, 124.2, 120.3, 119.7, 114.4, 108.8, 32.7, 29.8, 29.1, 28.4, 26.5.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₆H₁₇N₂⁺ 237.1386; found 237.1383.



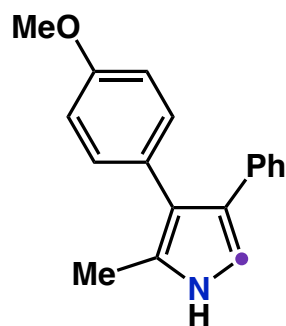
4-(2-methyl-4-phenyl-1H-pyrrol-3-yl)benzonitrile (2l)

Synthesized according to the general procedure (GP1) modified by the use of NMP (0.1M) instead of 10:1 NMP/H₂O (0.1M), using 4-(3-methyl-5-phenylisoxazol-4-yl)benzonitrile (**1l**, 52.1 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a pale-yellow solid in a 31% yield (16.0 mg, 0.062 mmol) after purification by flash column chromatography (10-20% EtOAc in hexanes).

¹H NMR (600 MHz, CDCl₃) δ 8.18 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.22 (m, 4H), 7.21 – 7.18 (m, 1H), 7.15 – 7.12 (m, 2H), 6.85 (d, *J* = 2.6 Hz, 1H), 2.34 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 141.5, 135.4, 132.0, 130.7, 128.5, 128.4, 126.9, 126.0, 124.7, 119.6, 118.5, 115.3, 108.9, 12.3.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₈H₁₅N₂⁺ 259.1230; found 259.1230.



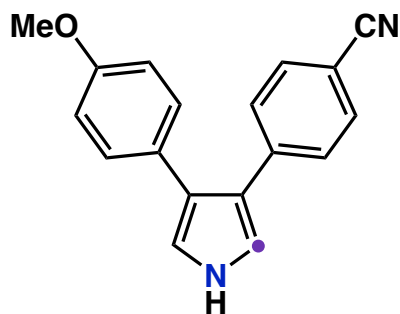
3-(4-methoxyphenyl)-2-methyl-4-phenyl-1H-pyrrole (2m)

Synthesized according to the general procedure (GP1) modified by the use of NMP (0.1M) instead of 10:1 NMP/H₂O (0.1M), using 4-(4-methoxyphenyl)-3-methyl-5-phenylisoxazole (**1m**, 49.7 mg, 0.187 mmol, 1 equiv). The title compound was isolated as a colorless oil in a 21% yield (10.5 mg, 0.040 mmol) after purification by flash column chromatography (5% EtOAc in hexanes; then fast silica plug with 1:1 hexanes/DCM). (**Note:** product showed signs of decomposition in air upon concentration, resulting in some mass loss during isolation)

¹H NMR (500 MHz, CD₃CN) δ 9.06 (s, 1H), 7.19 – 7.14 (m, 2H), 7.13 – 7.07 (m, 3H), 7.06 – 7.01 (m, 2H), 6.88 – 6.84 (m, 2H), 6.80 (d, *J* = 2.7 Hz, 1H), 3.78 (s, 3H), 2.16 (s, 3H).

¹³C NMR (126 MHz, CD₃CN) δ 158.8, 137.8, 132.2, 129.9, 129.0, 128.8, 126.7, 126.0, 124.5, 119.8, 115.4, 114.4, 55.8, 11.7.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₈H₁₈NO⁺ 264.1383; found 264.1385.



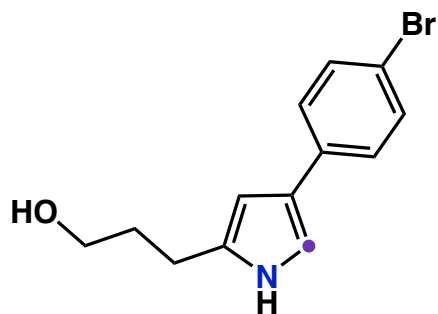
4-(4-(4-methoxyphenyl)-1H-pyrrol-3-yl)benzonitrile (2n)

Synthesized according to the general procedure (GP1) using 4-(4-(4-methoxyphenyl)isoxazol-5-yl)benzonitrile (**1n**, 50.5 mg, 0.183 mmol, 1 equiv). The title compound was isolated as a yellow solid in a 50% yield (24.9 mg, 0.091 mmol) after purification by flash column chromatography (15-25% EtOAc in hexanes).

¹H NMR (500 MHz, CD₃CN) δ 9.45 (s, 1H), 7.54 (dt, J = 8.9, 2.0 Hz, 2H), 7.34 (dt, J = 8.9, 2.2 Hz, 2H), 7.12 (dt, J = 8.9, 2.1 Hz, 2H), 7.03 (p, J = 2.5 Hz, 1H), 6.88 – 6.81 (m, 3H), 3.77 (s, 3H).

¹³C NMR (126 MHz, CD₃CN) δ 159.2, 142.5, 133.0, 130.7, 129.2, 129.1, 123.6, 121.9, 120.2, 119.7, 119.2, 114.7, 109.1, 55.9.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₈H₁₅N₂O⁺ 275.1179; found 275.1179.



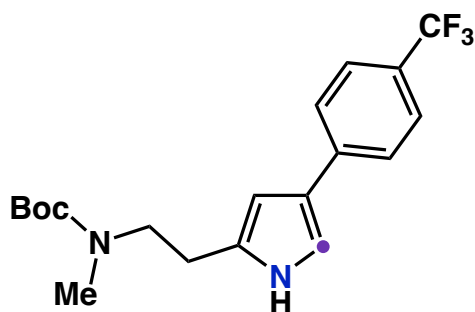
3-(4-(4-bromophenyl)-1H-pyrrol-2-yl)propan-1-ol (2o)

Synthesized according to the general procedure (GP1) modified by the addition of TfOH (1 equiv) during the alkylation step, using 3-(5-(4-bromophenyl)isoxazol-3-yl)propan-1-ol (**1o**, 56.4 mg, 0.2 mmol, 1 equiv). The title compound was isolated as an off-white solid in a 33% yield (18.5 mg, 0.066 mmol) after purification by flash column chromatography (10% acetone in DCM).

¹H NMR (500 MHz, CDCl₃) δ 8.32 (s, 1H), 7.45 – 7.39 (m, 2H), 7.39 – 7.31 (m, 2H), 6.95 (t, J = 2.2 Hz, 1H), 6.21 (t, J = 2.3 Hz, 1H), 3.75 (t, J = 6.0 Hz, 2H), 2.76 (t, J = 7.2 Hz, 2H), 2.18 (s, 1H), 1.96 – 1.85 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 135.2, 133.6, 131.8, 126.8, 124.1, 118.9, 113.6, 103.8, 62.5, 32.2, 24.5.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₃H₁₅BrNO⁺ 280.0332; found 280.0323.



tert-butyl methyl(2-(4-(4-(trifluoromethyl)phenyl)-1H-pyrrol-2-yl)ethyl)carbamate (2p)

Synthesized according to the general procedure (GP1) using *tert*-butyl methyl(2-(5-(4-(trifluoromethyl)phenyl)isoxazol-3-yl)ethyl)carbamate (**1p**, 74.1 mg, 0.2 mmol, 1 equiv). The title compound was isolated as an orange solid in a 26% yield (18.9 mg, 0.052 mmol) after purification by flash column chromatography (25% EtOAc in hexanes).

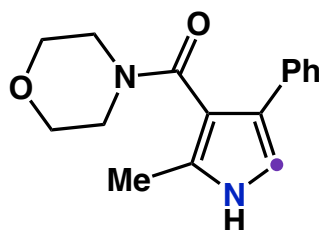
Note: NMR spectra were acquired at 60 °C to resolve rotamers.

¹H NMR (600 MHz, CD₃CN) δ 9.17 (br s, 1H), 7.65 (dq, J = 7.9, 0.9 Hz, 2H), 7.60 – 7.57 (m, 2H), 7.11 (dd, J = 2.8, 1.8 Hz, 1H), 6.30 – 6.28 (m, 1H), 3.47 (t, J = 7.1 Hz, 2H), 2.84 – 2.80 (m, 5H), 1.41 (s, 9H).

¹³C NMR (151 MHz, CD₃CN) δ 156.7, 141.9 (d, J = 1.6 Hz), 132.8, 127.3 (q, J = 32.0 Hz), 126.6 (q, J = 3.9 Hz), 126.1 (q, J = 270.5 Hz), 125.9, 124.2, 116.3, 105.3, 79.9, 49.7, 34.8, 28.9, 27.1.

¹⁹F NMR (376 MHz, CDCl₃) δ -62.17.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₉H₂₄F₃N₂O₂⁺ 369.1784; found 369.1784.



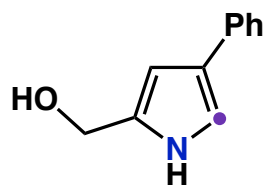
(2-methyl-4-phenyl-1H-pyrrol-3-yl)(morpholino)methanone (2q)

Synthesized according to the general procedure (GP1) using (3-methyl-5-phenylisoxazol-4-yl)(morpholino)methanone (**1q**, 54.5 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a white solid in a 66% yield (35.7 mg, 0.132 mmol) after purification by flash column chromatography (20% acetone in DCM).

¹H NMR (600 MHz, DMSO) δ 10.89 (s, 1H), 7.30 (d, J = 5.4 Hz, 4H), 7.16 (tt, J = 6.0, 3.1 Hz, 1H), 6.85 (d, J = 2.6 Hz, 1H), 3.30 (br, 8H), 2.17 (s, 3H). *Spectrum acquired at 60 °C.*

¹³C NMR (151 MHz, DMSO) δ 167.0, 135.6, 128.4, 128.1, 126.4, 125.4, 122.1, 114.1, 112.9, 65.7, 46.8, 41.7, 11.3. *Spectrum acquired at 23 °C.*

HRMS (APCI/QTOF) m/z : $[M+H]^+$ calculated for $C_{16}H_{19}N_2O_2^+$ 271.1441; found 271.1440.



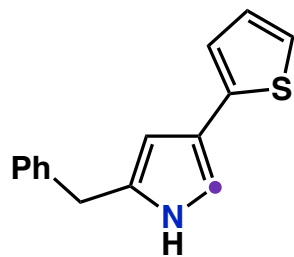
(4-phenyl-1H-pyrrol-2-yl)methanol (2r)

Synthesized according to general procedure (GP1) using 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-phenylisoxazole (**1r**, 53.9 mg, 0.187 mmol, 1 equiv). The title compound was isolated as an orange solid in a 42% yield (13.5 mg, 0.078 mmol) after purification by flash column chromatography (30-50% EtOAc in hexanes).

¹H NMR (500 MHz, CD_3CN) δ 9.23 (s, 1H), 7.51 (d, J = 6.8 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.16 – 7.11 (m, 1H), 7.07 (t, J = 2.2 Hz, 1H), 6.36 (t, J = 2.3 Hz, 1H), 4.50 (d, J = 3.5 Hz, 2H), 3.03 – 2.99 (m, 1H).

¹³C NMR (126 MHz, CD_3CN) δ 137.3, 134.5, 129.6, 126.1, 125.6, 125.0, 115.7, 105.1, 57.98.

HRMS (APCI/QTOF) m/z : $[M+H]^+$ calculated for $C_{11}H_{12}NO^+$ 174.0916; found 174.0913.



2-benzyl-4-(thiophen-2-yl)-1H-pyrrole (2s)

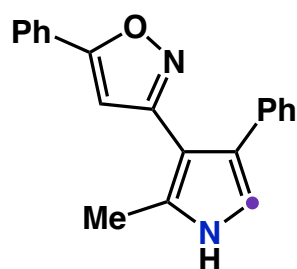
Synthesized according to the general procedure (GP1) using 3-benzyl-5-(thiophen-2-yl)isoxazole (**1s**, 48.3 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a yellow oil in a 65% yield

(31.1 mg, 0.130 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

¹H NMR (500 MHz, CDCl₃) δ 7.73 (s, 1H), 7.33 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.29 – 7.20 (m, 3H), 7.07 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.02 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.87 (t, *J* = 2.1 Hz, 1H), 6.23 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.97 (s, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 139.7, 139.1, 131.9, 128.9, 128.8, 127.5, 126.7, 121.7, 121.0, 119.2, 113.9, 105.6, 34.1.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₅H₁₄NS⁺ 240.0841; found 240.0835.



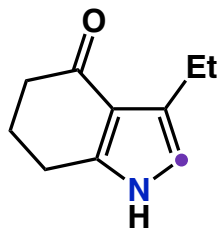
3-(2-methyl-4-phenyl-1*H*-pyrrol-3-yl)-5-phenylisoxazole (2t)

Synthesized according to the general procedure (GP1) using 3'-methyl-5,5'-diphenyl-3,4'-biisoxazole (**1t**, 40.4 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a white solid in a 28% yield (17.0 mg, 0.056 mmol) after purification by flash column chromatography (15% EtOAc in hexanes), followed by preparative TLC (10% DCM and 10% toluene in hexanes).

¹H NMR (600 MHz, CDCl₃) δ 8.17 (s, 1H), 7.70 – 7.65 (m, 2H), 7.44 – 7.36 (m, 3H), 7.36 – 7.34 (m, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.26 – 7.22 (m, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.11 (s, 1H), 2.53 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 168.5, 159.6, 135.5, 129.9, 129.3, 129.0, 128.8, 128.4, 128.0, 126.4, 125.9, 125.6, 115.2, 107.7, 100.8, 13.1.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₂₀H₁₇N₂O⁺ 301.1335; found 301.1339.



3-ethyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (2u)

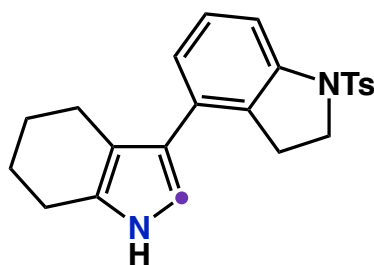
Synthesized according to the general procedure (GP1) using 3-ethyl-6,7-dihydrobenzo[*c*]isoxazol-4(5*H*)-one (**1u**, 33.0 mg, 0.2 mmol, 1 equiv). The title compound was isolated as an orange solid

in a 45% yield (14.7 mg, 0.090 mmol) after purification by flash column chromatography (5% acetone in DCM).

¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1H), 6.49 – 6.36 (m, 1H), 2.82 – 2.71 (m, 4H), 2.45 (dd, J = 7.1, 5.7 Hz, 2H), 2.12 (p, J = 6.4 Hz, 2H), 1.20 (t, J = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 195.3, 143.8, 126.6, 118.3, 114.7, 38.9, 24.1, 23.3, 19.80, 14.4.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₀H₁₄NO⁺ 164.1070; found 164.1067.



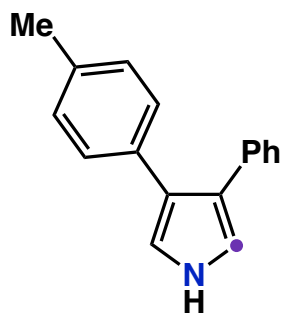
4-(4,5,6,7-tetrahydro-1H-indol-3-yl)-1-tosylindoline (2v)

Synthesized according to the general procedure (GP1) using 3-(1-tosylindolin-4-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole (**1v**, 78.9 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a colorless oil in a 40% yield (31.2 mg, 0.080 mmol) after purification by flash column chromatography (20% EtOAc in hexanes) followed by a silica plug with CHCl₃.

¹H NMR (500 MHz, CDCl₃) δ 7.79 (s, 1H), 7.69 (d, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 7.18 (t, J = 7.9 Hz, 1H), 7.03 (d, J = 1.4 Hz, 1H), 6.56 (s, 1H), 3.89 (t, 2H), 2.90 (t, J = 8.2 Hz, 2H), 2.60 (t, J = 6.4 Hz, 2H), 2.46 (t, J = 6.1 Hz, 2H), 2.37 (s, 3H), 1.87 – 1.79 (m, 2H), 1.76 – 1.67 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 144.0, 142.3, 134.3, 133.7, 129.7, 129.6, 127.8, 127.62, 127.58, 124.5, 120.9, 116.0, 114.7, 112.5, 50.2, 28.6, 24.0, 23.3, 23.2, 23.0, 21.7.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₂₃H₂₅N₂O₂S⁺ 393.1631; found 393.1638.



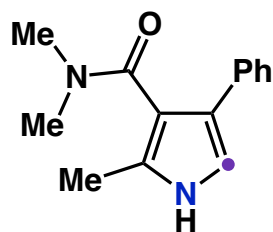
3-phenyl-4-(p-tolyl)-1H-pyrrole (2w)

Synthesized according to the general procedure (GP1) using 5-phenyl-4-(*p*-tolyl)isoxazole (**1w**, 47.0 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a yellow oil in a 49% yield (22.7 mg, 0.098 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

¹H NMR (500 MHz, CDCl₃) δ 8.26 (s, 1H), 7.32 – 7.23 (m, 4H), 7.21 – 7.15 (m, 3H), 7.07 (d, *J* = 7.7 Hz, 2H), 6.90 – 6.86 (m, 2H), 2.33 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 136.0, 135.4, 132.9, 129.0, 128.7, 128.6, 128.3, 125.8, 123.64 (2 overlapping carbon signals), 117.5, 117.4, 21.3.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₇H₁₆N⁺ 234.1277; found 234.1276.



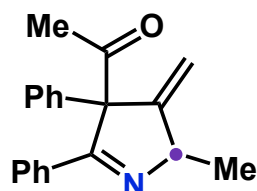
N,N,2-trimethyl-4-phenyl-1H-pyrrole-3-carboxamide (2x)

Synthesized according to the general procedure (GP1) using *N,N*,3-trimethyl-5-phenylisoxazole-4-carboxamide (**1x**, 46.0 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a brown oil in a 68% yield (31.0 mg, 0.136 mmol) after purification by flash column chromatography (20% to 50% acetone in DCM).

¹H NMR (400 MHz, CDCl₃) δ 9.77 (br, 1H), 7.31 – 7.20 (m, 4H), 7.19 – 7.08 (m, 1H), 6.61 (d, *J* = 2.5 Hz, 1H), 2.97 (s, 3H), 2.54 (s, 3H), 2.03 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.3, 136.2, 129.2, 128.6, 126.5, 125.7, 123.4, 114.2, 113.7, 38.4, 34.9, 11.6.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₄H₁₇N₂O⁺ 229.1355; found 229.1355.



1-(2-methyl-3-methylene-4,5-diphenyl-3,4-dihydro-2H-pyrrol-4-yl)ethan-1-one (7)

Synthesized according to a modified general procedure (GP1) (see modification below)* using 5-methyl-3,4-diphenylisoxazole (**1y**, 47.0 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a yellow oil in a 48% yield, 1.1:1 dr (28.0 mg, 0.097 mmol) after purification by flash column chromatography (2.5% to 10% EtOAc in hexanes). The diastereomers are separable by TLC, and NMR characterization is reported for each diastereomer.

*But-3-yn-2-ol was used as the propargyl alcohol to generate the corresponding α -methyl propargyl triflate (but-3-yn-2-yl trifluoromethanesulfonate). The alkylation required 4 equivalents of triflate reagent (added in two doses: initially and after 24 hours) and 48 total hours to reach completion.

Diastereomer A:

^1H NMR (500 MHz, CDCl_3) δ 7.73 – 7.66 (m, 2H), 7.39 – 7.31 (m, 3H), 7.28 (t, J = 7.6 Hz, 2H), 7.25 – 7.19 (m, 3H), 5.14 – 5.09 (m, 2H), 4.78 (dtd, J = 9.5, 6.8, 2.5 Hz, 1H), 2.06 (s, 3H), 1.60 (d, J = 7.0 Hz, 3H).

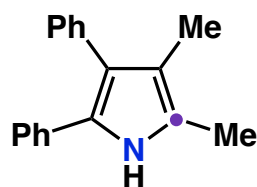
^{13}C NMR (101 MHz, CDCl_3) δ 203.6, 170.5, 158.2, 138.2, 133.2, 131.0, 128.8, 128.7, 128.3, 128.3, 127.3, 108.4, 78.1, 70.0, 28.0, 20.0.

Diastereomer B:

^1H NMR (500 MHz, CDCl_3) δ 7.73 – 7.67 (m, 2H), 7.38 – 7.33 (m, 3H), 7.31 – 7.19 (m, 5H), 5.21 (dd, J = 2.0, 1.0 Hz, 1H), 5.14 (dd, J = 2.4, 1.0 Hz, 1H), 5.03 (qt, J = 7.2, 2.2 Hz, 1H), 2.11 (s, 3H), 1.44 (d, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 203.0, 170.1, 157.7, 140.0, 133.0, 130.8, 129.1, 128.58, 128.58, 128.3, 127.2, 109.8, 78.0, 71.5, 27.5, 22.0.

HRMS (APCI/QTOF) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{20}\text{NO}^+$ 290.1539; found 290.1527



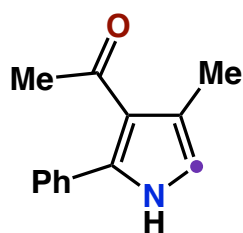
2,3-dimethyl-4,5-diphenyl-1H-pyrrole (2y)

To a vial under N₂ was added 1-(2-methyl-3-methylene-4,5-diphenyl-3,4-dihydro-2H-pyrrol-4-yl)ethan-1-one (**7**, 28.0 mg, 0.097 mmol, 1 equiv) and NMP (1 mL). K₂CO₃ (80 mg, 6 equiv) was subsequently added, and the reaction was brought to 90 °C to stir for 24 hours. After reaction completion, the vial was brought to room temperature, and the vial contents were transferred to a separatory funnel. LiCl (aq.) was added and extracted 3x with Et₂O. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation. The title compound was isolated as a pink oil in a 59% yield, (14.2 mg, 0.057 mmol) after purification by flash column chromatography (2.5% to 5% EtOAc in hexanes).

¹H NMR (600 MHz, CD₃CN) δ 9.03 (s, 1H), 7.35 – 7.29 (m, 2H), 7.27 – 7.22 (m, 1H), 7.21 – 7.12 (m, 6H), 7.12 – 7.06 (m, 1H), 2.24 (s, 3H), 1.88 (s, 3H).

¹³C NMR (151 MHz, CD₃CN) δ 138.4, 134.6, 131.3, 129.3, 129.2, 127.3, 126.8, 126.6, 126.4, 125.9, 123.3, 115.5, 11.0, 9.8.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₈H₁₈N⁺ 248.1434; found 248.1433



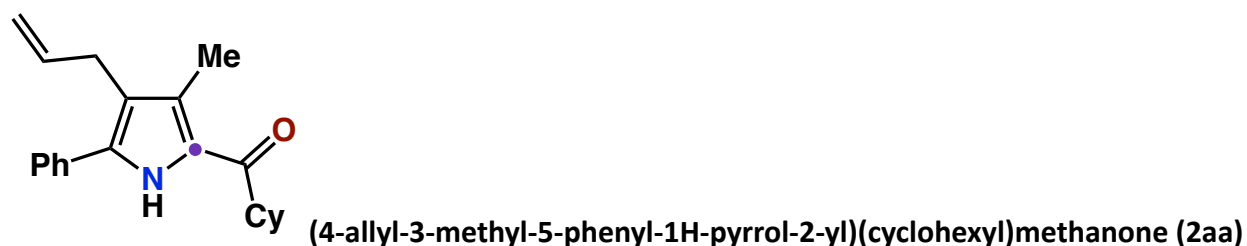
1-(4-methyl-2-phenyl-1H-pyrrol-3-yl)ethan-1-one (2z**)**

Synthesized according to the general procedure (GP1) using 5-methyl-3-phenylisoxazole (**1z**, 31.8 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a white solid in a 46% yield (18.3 mg, 0.092 mmol) after purification by flash column chromatography (20% EtOAc in hexanes) and preparative TLC (DCM).

¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.46 – 7.37 (m, 5H), 6.57 (s, 1H), 2.30 (s, 3H), 2.09 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 196.9, 137.4, 133.6, 129.5, 128.8, 128.7, 122.3, 122.2, 116.8, 30.8, 12.8.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₃H₁₄NO⁺ 200.1070; found 200.1079.

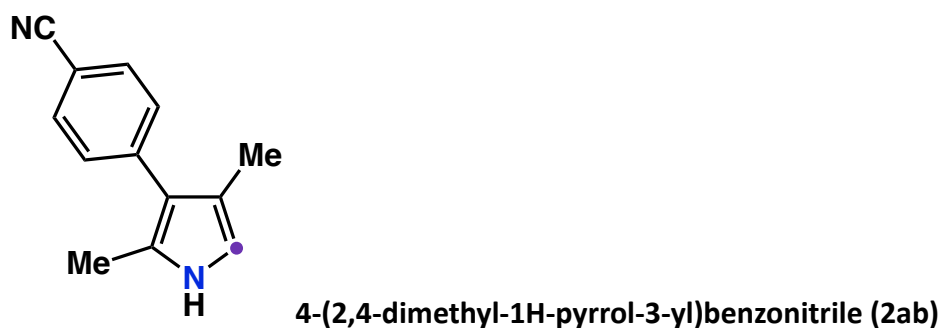


Synthesized according to the general procedure using 4-allyl-5-cyclohexyl-3-phenylisoxazole (**1aa**, 54.0 mg, 0.202 mmol 1 equiv). The title compound was isolated as a white solid in a 47% yield (29.6 mg, 0.094 mmol) after purification by flash column chromatography (5% EtOAc in hexanes; then 100% DCM).

¹H NMR (400 MHz, CDCl₃) δ 9.11 (s, 1H), 7.47 – 7.39 (m, 4H), 7.34 (t, J = 7.1 Hz, 1H), 6.02 (ddt, J = 15.7, 10.3, 5.2 Hz, 1H), 5.10 (d, J = 10.2 Hz, 1H), 4.99 (d, J = 17.1 Hz, 1H), 3.30 (d, J = 5.2 Hz, 2H), 3.00 (t, J = 11.7 Hz, 1H), 2.33 (s, 3H), 1.89 (d, J = 12.1 Hz, 4H), 1.75 (d, J = 12.1 Hz, 1H), 1.58 (d, J = 12.5 Hz, 2H), 1.42 – 1.26 (m, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 194.2, 137.1, 135.0, 132.1, 129.0, 128.6, 128.0, 127.5, 126.2, 120.1, 115.4, 46.9, 29.3, 28.8, 26.2, 26.1, 11.6.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₂₁H₂₆NO⁺ 300.2009; found 300.2008.

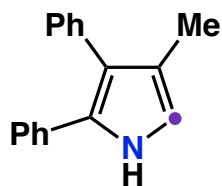


Synthesized according to the general procedure modified by the use of NMP (0.1M) instead of 10:1 NMP/H₂O (0.1M), using 4-(3-methyl-5-phenylisoxazol-4-yl)benzonitrile (**1l**, 52.5 mg, 0.202 mmol, 1 equiv). The title compound was isolated as a yellow solid in a 20% yield (7.9 mg, 0.040 mmol) after purification by flash column chromatography (10% to 20% EtOAc in hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.86 (s, 1H), 7.69 – 7.62 (m, 2H), 7.42 – 7.35 (m, 2H), 6.54 (dd, J = 2.4, 1.2 Hz, 1H), 2.28 (s, 3H), 2.09 (d, J = 1.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 142.0, 132.1, 130.0, 125.8, 120.1, 119.6, 117.7, 114.7, 108.7, 12.5, 11.4.

HRMS (APCI/QTOF) m/z : $[M+H]^+$ calculated for $C_{13}H_{13}N_2^+$ 197.1073; found 197.1077

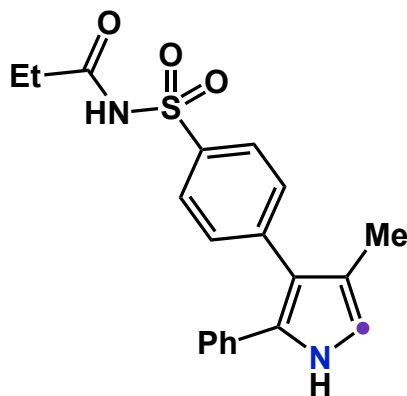


4-methyl-2,3-diphenyl-1H-pyrrole (2ac)

Synthesized according to the general procedure using 3,4,5-triphenylisoxazole (**1ac**, 59.5 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a white solid in a 36% yield (17 mg, 0.034 mmol) after purification by flash column chromatography (5% to 10% EtOAc in hexanes).

Characterization for 4-methyl-2,3-diphenyl-1H-pyrrole matches previously reported data:⁴

¹H NMR (500 MHz, $CDCl_3$) δ 8.11 (br, 1H), 7.35 (dd, J = 8.1, 6.8 Hz, 2H), 7.32 – 7.21 (m, 7H), 7.21 – 7.16 (m, 1H), 6.75 (dd, J = 2.6, 1.2 Hz, 1H), 2.13 (d, J = 1.0 Hz, 3H).



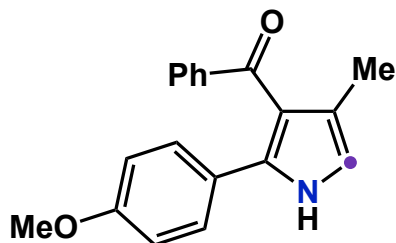
N-((4-(4-methyl-2-phenyl-1H-pyrrol-3-yl)phenyl)sulfonyl)propionamide (2ad)

Synthesized according to the general procedure using N-((4-(5-methyl-3-phenylisoxazol-4-yl)phenyl)sulfonyl)propionamide (**1ad**, 74.1 mg, 0.2 mmol, 1 equiv). The title compound was isolated as a white solid in a 49% yield (36.1 mg, 0.098 mmol) after purification by flash column chromatography (40% EtOAc in hexanes).

¹H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.21 (s, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.29 – 7.14 (m, 5H), 6.74 (s, 1H), 2.35 (q, J = 7.4 Hz, 2H), 2.12 (s, 3H), 1.11 (t, J = 7.4 Hz, 3H).

¹³C NMR (101 MHz, $CDCl_3$) δ 171.6, 143.1, 135.4, 132.8, 130.7, 130.2, 128.9, 128.3, 127.5, 127.1, 120.2, 119.5, 117.1, 29.7, 11.3, 8.4.

HRMS (APCI/QTOF) m/z : $[M+H]^+$ calculated for $C_{20}H_{21}N_2O_3S^+$ 369.1267; found 369.1258.



(2-(4-methoxyphenyl)-4-methyl-1H-pyrrol-3-yl)(phenyl)methanone (2ae)

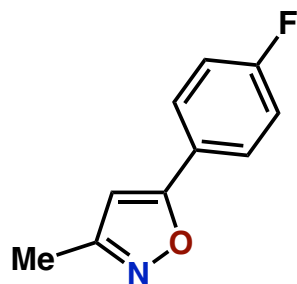
Synthesized according to the general procedure using (3-(4-methoxyphenyl)-5-methylisoxazol-4-yl)(phenyl)methanone (**1ae**, 60.9 mg, 0.208 mmol, 1 equiv). The title compound was isolated as a yellow solid in a 34% yield (20.4 mg, 0.070 mmol) after purification by flash column chromatography (5-10% EtOAc in hexanes, then 100% DCM)

¹H NMR (500 MHz, CDCl₃) δ 8.34 (s, 1H), 7.68 – 7.62 (m, 2H), 7.34 – 7.27 (m, 1H), 7.18 (t, J = 7.6 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 6.65 (d, J = 8.7 Hz, 2H), 6.61 (dd, J = 2.4, 1.2 Hz, 1H), 3.70 (s, 3H), 2.16 (d, J = 1.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 194.7, 159.1, 139.7, 136.5, 131.8, 129.9, 129.5, 127.9, 125.2, 122.3, 120.1, 116.8, 113.9, 55.4, 11.8.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₉H₁₈NO₂⁺ 292.1332; found 292.1337

7. Synthesis and Characterization of Starting Materials



5-(4-fluorophenyl)-3-methylisoxazole (1d)

Synthesized from 1-(4-fluorophenyl)butane-1,3-dione (3.60 g, 22 mmol, 1 equiv) according to previously published procedure.⁵ The title compound was isolated as a white crystalline solid in a 97% yield (3.45 g, 19.5 mmol) after recrystallization from H₂O.

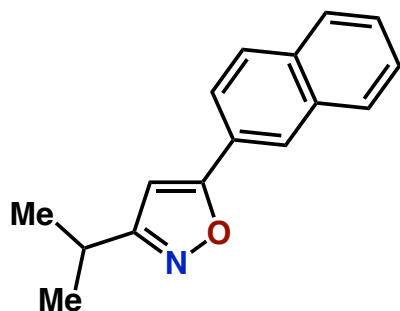
¹H NMR (400 MHz, CDCl₃) δ 7.79 – 7.69 (m, 2H), 7.14 (t, J = 8.7 Hz, 2H), 6.30 (s, 1H), 2.35 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 168.8, 163.7 (d, J = 250.8 Hz), 160.5, 127.9 (d, J = 8.6 Hz), 124.1 (d, J = 3.4 Hz), 116.2 (d, J = 22.1 Hz), 100.0 (d, J = 1.2 Hz), 11.6.

HRMS (APCI/QTOF) m/z : [M+H]⁺ calculated for C₁₀H₉FNO⁺ 178.0663; found 178.0657.

[3+2] Cycloaddition General Procedure 4 (GP4)⁶

To a solution of the corresponding aryl oxime (1 equiv) in H₂O (15 mL) was added aryl acetylene (1.5 mmol) at room temperature, followed by the slow addition of KCl (1 equiv) and then Oxone (2KHSO₅·KHSO₄·K₂SO₄) (1.5 equiv). The resulting mixture was stirred at room temperature overnight until complete. The mixture was poured into a separatory funnel, extracted with EtOAc, dried, and concentrated via rotary evaporation. The resulting product was purified using flash column chromatography as necessary.



3-isopropyl-5-(naphthalen-2-yl)isoxazole (1e)

Synthesized according to the general [3+2] procedure GP4 using (*E*)-isobutyraldehyde oxime (435.6 mg, 5 mmol) and 2-ethynylnaphthalene (1.522 g, 10 mmol). The title compound was

isolated as a white solid in a 9% yield (102.4 mg, 0.45 mmol) after purification by flash column chromatography (5% to 50% DCM/hexanes).

¹H NMR (500 MHz, CDCl₃) δ 8.31 – 8.27 (m, 1H), 7.91 (dd, J = 8.8, 4.9 Hz, 2H), 7.89 – 7.79 (m, 2H), 7.54 (dt, J = 6.2, 3.4 Hz, 2H), 6.52 (s, 1H), 3.15 (hept, J = 7.0 Hz, 1H), 1.37 (d, J = 7.0 Hz, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 170.2, 169.7, 134.0, 133.3, 128.9, 128.8, 128.0, 127.3, 127.0, 125.5, 125.2, 123.1, 98.1, 26.8, 22.0.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₆H₁₆NO⁺ 238.1226; found 238.1218.



Synthesized from phenylacetaldehyde (350 μl, 3 mmol) according to a previously published procedure.⁷ The title compound was isolated as a white solid in a 78% yield as a 1:1 E/Z mixture (316 mg, 2.3 mmol) after purification by flash column chromatography (10% to 20% EtOAc in hexanes).

Characterization for 2-phenylacetaldehyde oxime matches previously reported data:

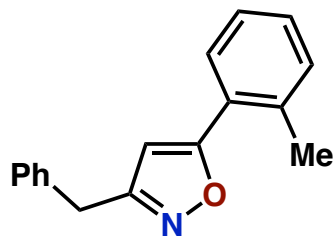
¹H NMR (500 MHz, CDCl₃) δ 7.54 (*E*; t, J = 6.3 Hz, 1H), 7.36 – 7.30 (m, 4H), 7.28 – 7.20 (m, 6H), 6.91 (*Z*; t, J = 5.4 Hz, 1H), 3.75 (*Z*; d, J = 5.3 Hz, 2H), 3.54 (*E*; d, J = 6.3 Hz, 2H).

[3+2] cycloaddition General Procedure 5 (GP5) (modified from literature procedure)⁸

To a round-bottom flask under N₂ atmosphere with a stir bar was added oxime (1 equiv) and dissolved in anhydrous DMF (1.2 M). N-chlorosuccinimide (NCS) (2 equiv) was added in one portion at room temperature. The reaction was let stir for 2 hours at room temperature. The flask contents were diluted with EtOAc and transferred to separatory funnel. H₂O was added, and the layers were separated. The aqueous layer was extracted x2 more with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation. The crude product was used without further purification.

To a round-bottom flask under N₂ atmosphere with a stir bar was added crude chlorinated oxime from the previous step and dissolved in anhydrous DMF (0.5 M). Alkyne (1.1 equiv) was added, followed by dropwise addition of Et₃N (5 equiv). The flask was brought to 50 °C to stir overnight. Upon reaction completion, the reaction was brought to room temperature, diluted with Et₂O, and transferred to a separatory funnel. The reaction contents were washed 3x with H₂O. The

combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation.



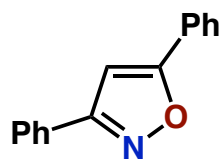
3-benzyl-5-(*o*-tolyl)isoxazole (1f)

Synthesized according to the general [3+2] procedure GP5 using 2-phenylacetaldehyde oxime (316 mg, 2.3 mmol). The title compound was isolated as a pale-yellow oil in a 10% yield over 2 steps (57.4 mg, 0.23 mmol) after purification by flash column chromatography (5-10% EtOAc in hexanes; then 2% DCM in toluene).

¹H NMR (500 MHz, CD₃CN) δ 7.66 (d, *J* = 7.7 Hz, 1H), 7.39 – 7.25 (m, 8H), 6.42 (d, *J* = 1.4 Hz, 1H), 4.06 (s, 2H), 2.43 (s, 3H).

¹³C NMR (126 MHz, CD₃CN) δ 170.5, 164.4, 138.8, 137.2, 132.3, 131.0, 129.8, 129.7, 129.2, 128.0, 127.7, 127.2, 103.9, 32.9, 21.5.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₇H₁₆NO⁺ 250.1226; found 250.1225.



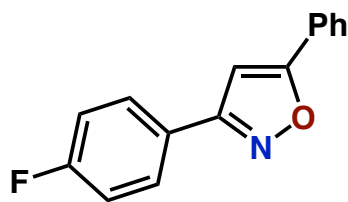
3,5-diphenylisoxazole (1g)

Synthesized from 1,3-diphenylpropane-1,3-dione (4.48 g, 20 mmol) according to previously published procedure.⁹ The title compound was isolated as a white crystalline solid in a 75% yield (3.33 g, 15 mmol).

¹H NMR (600 MHz, CDCl₃) δ 7.90 – 7.87 (m, 2H), 7.87 – 7.84 (m, 2H), 7.53 – 7.43 (m, 6H), 6.84 (s, 1H).

¹³C NMR (151 MHz, CDCl₃) δ 170.6, 163.1, 130.4, 130.2, 129.3, 129.2, 129.1, 127.6, 127.0, 126.0, 97.6.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₅H₁₂NO⁺ 222.0913; found 222.0910.



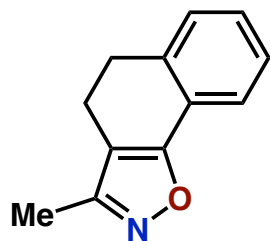
3-(4-fluorophenyl)-5-phenylisoxazole (1h)

Synthesized according to general [3+2] procedure GP4 using 4-fluorobenzaldoxime (4.17 g, 30 mmol) and isolated as a white crystalline solid in a 41% yield (2.94 g, 12.30 mmol) after trituration using diethyl ether.

Characterization for 3-(4-fluorophenyl)-5-phenylisoxazole matches previously reported data:¹⁰

¹H NMR (500 MHz, CDCl₃) δ 7.89 – 7.81 (m, 4H), 7.48 (dd, J = 10.2, 6.9 Hz, 3H), 7.17 (t, J = 8.5 Hz, 2H), 6.79 (s, 1H).

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₅H₁₁FNO⁺ 240.0819; found 240.0816.



3-methyl-4,5-dihydronaphtho[2,1-d]isoxazole (1i)

To a round-bottom flask under N₂ atmosphere with a stir bar was added 2-acetyl-3,4-dihydronaphthalen-1(2H)-one (565 mg, 3 mmol) and anhydrous EtOH (11.5 mL). The flask was cooled to 0 °C in an ice bath. Pyridine (1.15 mL) was added, then hydroxylamine hydrochloride (214 mg, 3.075 mmol). Reaction was let stir for 1 h at 0 °C, followed by 2 h at room temperature. The reaction mixture was diluted with EtOAc, washed with 1M HCl, and the layers were separated. The aqueous layer was extracted 2x with EtOAc, and the combined organic were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation. The title compound was isolated as an off-white solid in a 66% yield (273 mg, 0.132 mmol) after purification by flash column chromatography (5-10% EtOAc in hexanes).

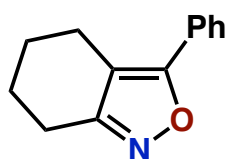
¹H NMR (500 MHz, CDCl₃) δ 7.70 – 7.64 (m, 1H), 7.34 – 7.26 (m, 3H), 3.06 (t, J = 7.9 Hz, 2H), 2.70 (t, J = 7.9 Hz, 2H), 2.32 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 165.1, 158.0, 136.5, 129.5, 128.4, 127.2, 125.6, 122.0, 112.5, 29.1, 18.0, 10.2.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₂H₁₂NO⁺ 186.0913; found 186.0917.

Annulated Isoxazole General Procedure 6 (GP6)¹¹

To a round-bottom flask under N₂ atmosphere with a stir bar was added a solution of oxime (1.5 equiv) in anhydrous THF. The flask was cooled to 0 °C and n-butyllithium (2.5 M in hexanes, 3 equiv) was added dropwise, then warmed to room temperature and stirred for 0.5 hours. A degassed solution of carboxylate (1 equiv) in THF (0.75 M) was added to the flask at room temperature and stirred for 1 hour. Then, concentrated H₂SO₄ (30 equiv) was added and stirred for 1 hour. The contents of the flask were quenched with sodium bicarbonate, then washed 3x with EtOAc. The combined organic layered were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation.



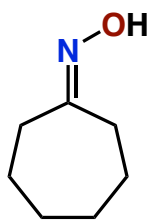
3-phenyl-4,5,6,7-tetrahydrobenzo[c]isoxazole (1j)

Synthesized from cyclohexanone oxime (849 mg, 7.5 mmol, 1.5 equiv) and ethyl benzoate (751 mg, 5 mmol, 1 equiv) using GP6. The title compound was isolated as a white solid in an 18% yield (183 mg, 0.92 mmol) after purification by column chromatography (15% EtOAc in hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.79 – 7.65 (m, 2H), 7.53 – 7.43 (m, 2H), 7.42 – 7.36 (m, 1H), 2.79 (q, J = 5.5 Hz, 4H), 1.90 – 1.76 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 162.6, 161.9, 129.3, 129.0, 128.9, 126.1, 110.7, 23.0, 22.2, 22.1, 21.3.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₃H₁₄NO⁺ 200.1070; found 200.1072.

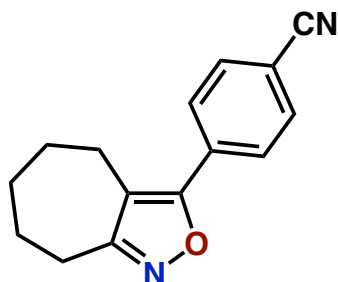


cycloheptanone oxime

Synthesized from cycloheptanone according to a previously published procedure.¹² The title compound was isolated as a colorless oil in a 99% yield (1.27 g, 9.9 mmol) without further purification.

Characterization of cycloheptanone oxime matches previously reported data¹³:

¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 2H), 2.62 – 2.54 (m, 2H), 2.41 – 2.34 (m, 2H), 1.57 (d, *J* = 2.7 Hz, 8H).



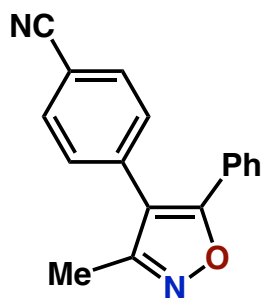
4-(5,6,7,8-tetrahydro-4H-cyclohepta[c]isoxazol-3-yl)benzonitrile (1k)

Synthesized from cycloheptanone oxime (381.5 mg, 3 mmol, 1.5 equiv) and 4-cyanobenzoic acid methyl ester (241.7 mg, 1.5 mmol, 1 equiv) using GP6. The title compound was isolated as a white solid in a 66% yield (234 mg, 0.99 mmol) after purification by column chromatography (20% EtOAc in hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.82 – 7.67 (m, 4H), 2.93 – 2.80 (m, 2H), 2.80 – 2.68 (m, 2H), 1.89 (dtd, *J* = 11.0, 5.1, 2.1 Hz, 2H), 1.82 – 1.65 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 166.9, 161.7, 132.9, 132.7, 127.9, 118.5, 118.2, 113.0, 32.0, 28.8, 27.4, 27.1, 24.3.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₅H₁₅N₂O⁺ 239.1179; found 239.1187.

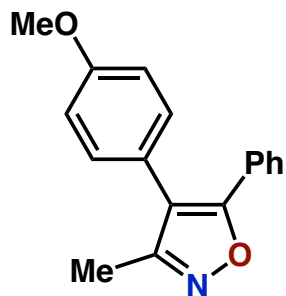


4-(3-methyl-5-phenylisoxazol-4-yl)benzonitrile (1l)

Synthesized from 3-methyl-5-phenylisoxazole (478 mg, 3 mmol) and 4-bromobenzonitrile (364 mg, 2 mmol) according to previously reported direct C4 arylation procedures.¹⁴ The title compound was isolated as a yellow-orange solid in a 67% yield (350 mg, 1.3 mmol) after purification by washing the crude product with hexanes/Et₂O.

Characterization for 4-(3-methyl-5-phenylisoxazol-4-yl)benzonitrile matches previously reported data:

¹H NMR (500 MHz, CDCl₃) δ 7.75 – 7.71 (m, 2H), 7.49 – 7.45 (m, 2H), 7.44 – 7.38 (m, 3H), 7.38 – 7.33 (m, 2H), 2.27 (s, 3H).

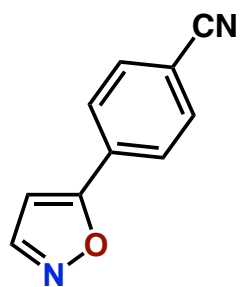


4-(4-methoxyphenyl)-3-methyl-5-phenylisoxazole (1m)

Synthesized from 3-methyl-5-phenylisoxazole (239 mg, 1.5 mmol) and 1-bromo-4-methoxybenzene (187 mg, 1 mmol) according to previously reported direct C4 arylation procedures.¹⁴ The title compound was isolated as a yellow solid in a 26% yield (68.4 mg, 0.26 mmol) after purification by flash column chromatography (30-50% DCM in hexanes).

Characterization for 4-(4-methoxyphenyl)-3-methyl-5-phenylisoxazole matches previously reported data:

¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, J = 7.0 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.21 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 8.1 Hz, 2H), 3.85 (s, 3H), 2.23 (s, 3H).



4-(isoxazol-5-yl)benzonitrile

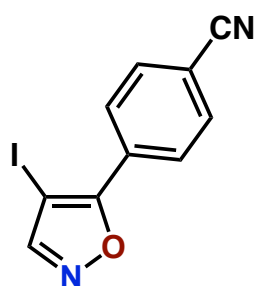
Synthesized from 4-acetylbenzonitrile (726 mg, 5 mmol) according to the previously reported procedure.¹⁵ The title compound was isolated as an orange solid in a 96% yield over 2 steps (814 mg, 4.8 mmol) with no further purification necessary.

Characterization for 4-(isoxazol-5-yl)benzonitrile matches previously reported data:¹⁶

¹H NMR (500 MHz, CDCl₃) δ 8.35 (d, J = 1.9 Hz, 1H), 7.91 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 1.9 Hz, 1H).

Isoxazole C4 iodination General Procedure 7 (GP7) (according to previously reported procedure)¹⁷

To a round-bottom flask under N₂ atmosphere with a stir bar was added isoxazole (1 equiv) and TFA (1M). N-iodosuccinimide (NIS) (1 equiv) was subsequently added. The reaction was let stir for 1 hour at room temperature until reaction completion as monitored by TLC. H₂O was added slowly (equal volume as TFA), followed by hexanes (equal volume as TFA). In batches, solid NaHSO₃ was added with vigorous stirring until bubbling ceased. The flask contents were transferred to a separatory funnel and washed with H₂O, followed by brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated via rotary evaporation.



4-(4-iodoisoxazol-5-yl)benzonitrile

Synthesized according to the general iodination procedure (GP7) using 4-(isoxazol-5-yl)benzonitrile (510 mg, 3 mmol, 1 equiv). (Note: EtOAc was added to assist with emulsions during extractions.) The title compound was isolated as a white solid in a 21% yield (189 mg, 0.63 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

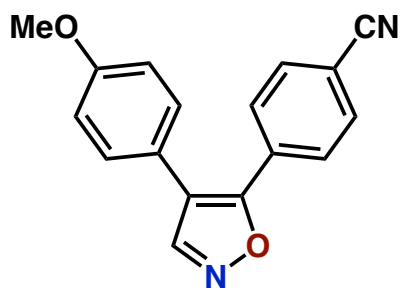
¹H NMR (500 MHz, CDCl₃) δ 8.35 (d, J = 1.0 Hz, 1H), 8.20 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ 165.1, 157.3, 132.7, 130.8, 127.9, 118.2, 114.3, 54.6.

HRMS (APCI/QTOF) m/z: [M-H]⁻ calculated for C₁₀H₄IN₂O⁻ 294.9374; found 294.9367.

Suzuki General Procedure 8 (GP8)¹⁸

To an oven dried vial with a stir bar were added isoxazole (1 equiv), aryl boronic acid (1 equiv), and NaHCO₃ (3 equiv). The vial was evacuated and filled with N₂, (3x). The vial contents were then dissolved in a 1:1 DME/H₂O solution (0.3M) followed by sparging with N₂ for 5 minutes. Pd(dppf)Cl₂ (0.03 equiv) was added. The vial was brought to 90 °C to stir overnight. Upon reaction completion as monitored by TLC, the vial contents were diluted with EtOAc and transferred to a separatory funnel. The organic was washed x2 with H₂O, then brine. The organic layer was dried over Na₂SO₄, filtered, and concentrated via rotary evaporation.



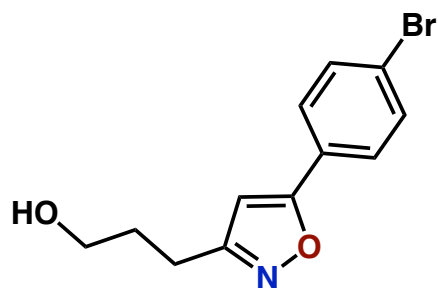
4-(4-(4-methoxyphenyl)isoxazol-5-yl)benzonitrile (1n)

Synthesized from using 4-(4-iodoisoxazol-5-yl)benzonitrile (0.41 mmol, 121 mg) according to the general Suzuki procedure (GP8). The title compound was isolated as a white solid in a 66% yield (74.2 mg, 0.27 mmol) after purification by flash column chromatography (10-20% EtOAc in hexanes).

¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 161.3, 160.1, 152.4, 132.7, 131.9, 130.0, 127.5, 121.4, 118.3, 118.2, 114.9, 113.4, 55.5.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₇H₁₃N₂O₂⁺ 277.0972; found 277.0972.



3-(5-(4-bromophenyl)isoxazol-3-yl)propan-1-ol (1o)

(Z)-1-(4-bromophenyl)-3,6-dihydroxyhex-2-en-1-one was prepared from γ-butyrolactone and 4-bromoacetophenone according to the previously published procedure and the crude product was taken forward without further purification.¹⁹ To a round-bottomed flask containing (Z)-1-(4-bromophenyl)-3,6-dihydroxyhex-2-en-1-one (2.5 mmol) in 5 mL ethanol was added hydroxylamine hydrochloride (347.4 mg, 5 mmol). The reaction was refluxed for 16 hours, until the starting material was consumed as indicated by TLC. The reaction was diluted with EtOAc, then washed with NaHCO₃ and extracted 3x with EtOAc. The title compound was isolated as a white solid in a 54% yield (381 mg, 1.35 mmol) following purification by flash column chromatography (5% to 10% acetone/DCM).

¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.55 (m, 4H), 6.40 (s, 1H), 3.75 (t, J = 6.2 Hz, 2H), 2.84 (t, J = 7.4 Hz, 2H), 2.17 (s, 1H), 1.99 (tt, J = 7.4, 6.2 Hz, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ 168.7, 164.3, 132.2, 127.2, 126.4, 124.4, 99.7, 61.8, 30.8, 22.7.

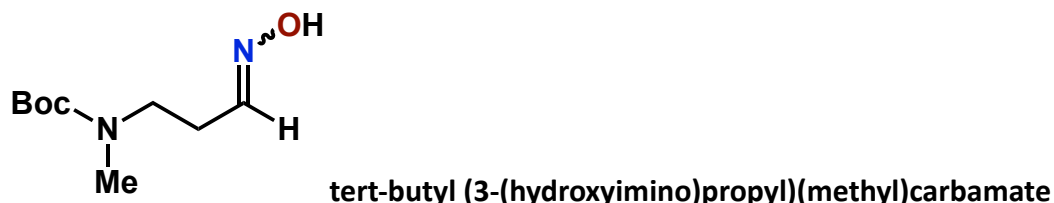
HRMS (APCI/QTOF) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{13}\text{BrNO}_2^+$ 282.0124; found 282.0119.



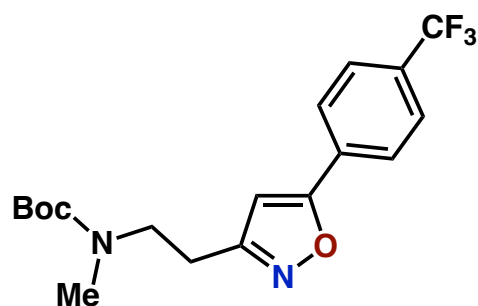
Synthesized from tert-butyl (3-hydroxypropyl)(methyl)carbamate according to the previously reported procedure.²⁰ The title compound was isolated as a colorless oil in a 78% yield (290 mg, 1.55 mmol) with no further purification necessary.

Characterization for tert-butyl methyl(3-oxopropyl)carbamate matches previously reported data:

^1H NMR (400 MHz, CDCl_3) δ 9.81 (t, J = 1.8 Hz, 1H), 3.55 (t, J = 6.6 Hz, 2H), 2.87 (s, 3H), 2.67 (td, J = 6.8, 1.7 Hz, 2H), 1.45 (s, 9H).



To a round-bottom flask under air atmosphere with a stir bar was added tert-butyl methyl(3-oxopropyl)carbamate (290 mg, 1.55 mmol, 1 equiv), hydroxylamine hydrochloride (162 mg, 2.33 mmol, 1.5 equiv), NaOAc (318mg, 3.88 mmol, 2.5 equiv), and dissolved in 2.5 mL of a 3:1 $\text{H}_2\text{O}/\text{EtOH}$ solution. The flask was brought to 70 $^\circ\text{C}$ for 3 hours. Upon reaction completion (monitored by NMR aliquots), the reaction contents were extracted 3x with Et_2O . The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated via rotary evaporation. The crude oxime was carried forward as a 1:1 E/Z mixture without further purification.



tert-butyl methyl(2-(5-(4-(trifluoromethyl)phenyl)isoxazol-3-yl)ethyl)carbamate (1p)

Synthesized according to the general [3+2] procedure GP5 using tert-butyl (3-(hydroxyimino)propyl)(methyl)carbamate (225 mg, 1.1 mmol, 1 equiv). The title compound was isolated as an off-white solid in a 47% yield over 2 steps (194.9 mg, 0.53 mmol) after purification by flash column chromatography (20% EtOAc in hexanes).

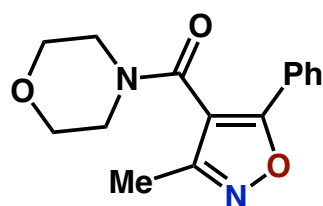
Note: NMRs acquired at 60 °C to resolve rotamers.

¹H NMR (600 MHz, CD₃CN) δ 7.96 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 6.74 (s, 1H), 3.58 (t, J = 7.0 Hz, 2H), 2.93 (t, J = 7.0 Hz, 2H), 2.85 (s, 3H), 1.37 (s, 9H).

¹³C NMR (151 MHz, CD₃CN) δ 169.0, 163.9, 156.5, 132.3 (q, J = 1.3 Hz), 132.3 (q, J = 32.5 Hz), 127.4, 127.3 (q, J = 3.9 Hz), 125.3 (q, J = 271.3 Hz), 103.0, 80.1, 48.3, 34.8, 28.8, 25.7.

¹⁹F NMR (376 MHz, CDCl₃) δ -62.94.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₈H₂₂F₃N₂O₃⁺ 371.1577; found 371.1563.



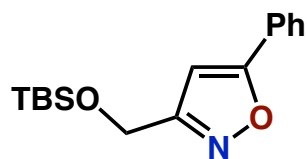
(3-methyl-5-phenylisoxazol-4-yl)(morpholino)methanone (1q)

To a round-bottomed flask containing 3-methyl-5-phenylisoxazole-4-carboxylic acid (203.2 mg, 1 mmol), was added 10 mL of dry DCM. Oxalyl chloride (0.25 mL, 380.8 mg, 3 mmol) was added to the flask, followed by 2 drop of DMF. The reaction was stirred at room temperature for 2 hours, then solvent was removed by rotary evaporation, and the crude product was carried forward without further purification. The crude mixture was dissolved in 10 mL of dry DCM and cooled to 0 °C. To the flask, morpholine (0.09 mL, 87.1 mg, 1 mmol) and Et₃N (0.28 mL, 202.4 mg, 2 mmol) were added and the reaction was allowed to warm to room temperature and stirred for 3 hours. The reaction was extracted with NaHCO₃ solution and the organic layer was dried over Na₂SO₄, filtered, and concentrated via rotary evaporation. The title compound was isolated as a clear, colorless oil in a quantitative yield (272 mg, 1 mmol) after purification by column chromatography (10% acetone/DCM).

¹H NMR (600 MHz, CDCl₃) δ 7.70 (dd, J = 6.7, 2.9 Hz, 2H), 7.51 – 7.44 (m, 3H), 3.80 (t, J = 4.8 Hz, 2H), 3.71 (t, J = 4.8 Hz, 2H), 3.31 (br, 2H), 3.20 (br, 2H), 2.34 (s, 3H).

¹³C NMR (151 MHz, CDCl₃) δ 165.9, 162.6, 159.2, 131.1, 129.3, 126.84, 126.82, 110.3, 66.7, 47.3, 42.4, 10.6.

HRMS (APCI/QTOF) m/z : $[M+H]^+$ calculated for $C_{15}H_{17}N_2O_3^+$ 273.1234; found 273.1237.



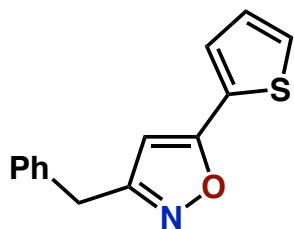
3-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-phenylisoxazole (1r)

Synthesized from (5-phenylisoxazol-3-yl)methanol (70 mg, 0.4 mmol) according to previously reported procedure.²¹ The title compound was isolated as a colorless oil in a 90% yield (104 mg, 0.36 mmol).

^1H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 2H), 7.49 – 7.39 (m, 3H), 6.57 (s, 1H), 4.81 (s, 2H), 0.94 (s, 9H), 0.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 164.8, 130.2, 129.0, 127.7, 125.9, 98.7, 57.7, 25.9, 18.4, -5.2.

HRMS (APCI/QTOF) m/z : $[M+H]^+$ calculated for $C_{16}H_{24}NO_2Si^+$ 290.1591; found 290.1590.



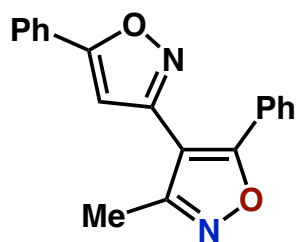
3-benzyl-5-(thiophen-2-yl)isoxazole (1s)

Synthesized according to the general [3+2] procedure GP4 using 2-ethynylthiophene (378 mg, 3.5 mmol, 1 equiv) and 2-phenylacetaldehyde oxime (945 mg, 7 mmol, 2 equiv). The title compound was isolated as an orange solid in a 36% yield (308.9 mg, 1.28 mmol) after purification by flash column chromatography (5% diethyl ether in hexanes).

^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 3.7, 1.1 Hz, 1H), 7.41 (dd, J = 5.0, 1.2 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.31 – 7.25 (m, 3H), 7.09 (dd, J = 5.0, 3.7 Hz, 1H), 6.14 (s, 1H), 4.04 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 163.8, 137.3, 129.6, 129.0, 128.9, 128.1, 128.0, 127.1, 127.0, 99.4, 32.6.

HRMS (APCI/QTOF) m/z : $[M+H]^+$ calculated for $C_{14}H_{12}NOS^+$ 242.0634; found 242.0635.



3'-methyl-5,5'-diphenyl-3,4'-biisoxazole (1t)

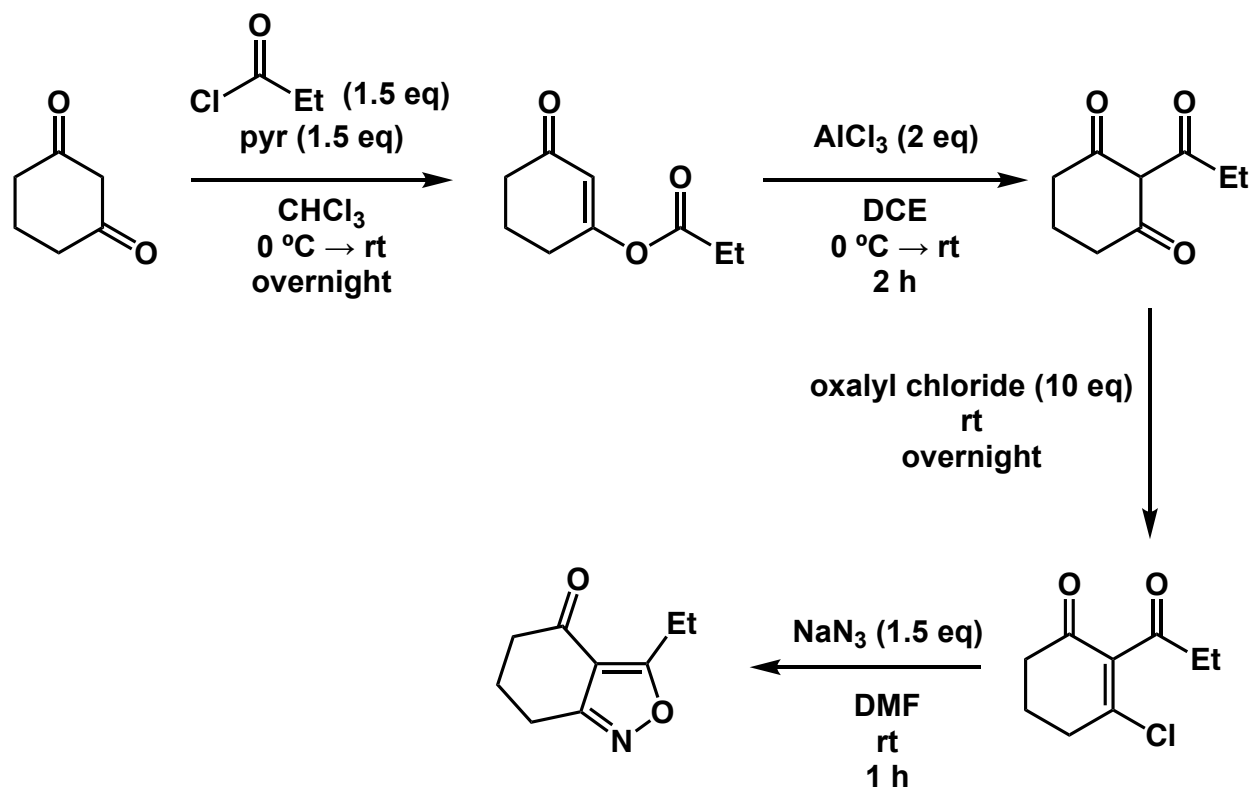
3-methyl-5-phenylisoxazole (1.59 g, 10 mmol, 1 equiv) was reacted with n-BuLi (2.5 M in hexanes) and DMF (0.77 mL, 10 mmol, 1 equiv) in THF according to previously published isoxazole C-4 functionalization procedure to furnish 3-methyl-5-phenylisoxazole-4-carbaldehyde.²² To the crude reaction was added EtOAc and NaHSO₃ solution, at which point the aqueous bisulfite adduct was extracted into the aqueous layer. Then the aqueous layer was treated with 1M NaOH and the solution was extracted with EtOAc and the organic layer was collected, filtered, and concentrated via rotary evaporation. The aldehyde was carried forward without further isolation. 1 mmol of the crude material was stirred with hydroxylamine hydrochloride (139.0 mg, 2 mmol, 2 equiv) and pyridine (0.24 mL, 3 mmol, 3 equiv) in ethanol (3 mL) overnight at room temperature, then diluted with EtOAc and extracted with H₂O. The combined organic layers were dried with Na₂SO₄ and solvent was removed with rotary evaporation. The resulting material was stirred with 5% NaOCl (1.3 equiv), Et₃N (0.14 mL, 1 mmol, 1 equiv), and phenyl acetylene (102.1 mg, 1 mmol, 1 equiv) in DCM at 0 °C overnight, followed by an additional 0.5 equiv of 5% NaOCl.²³ The reaction was diluted with DCM and extracted with H₂O, then the combined organic layers were dried with Na₂SO₄ and solvent was removed with rotary evaporation.

The title compound was isolated as a white solid in a 15% yield after purification by flash column chromatography (15% EtOAc in hexanes).

¹H NMR (500 MHz, CDCl₃) δ 7.81 – 7.71 (m, 4H), 7.53 – 7.41 (m, 6H), 6.45 (s, 1H), 2.50 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.4, 167.8, 160.0, 155.2, 130.8, 130.6, 129.1, 128.9, 127.9, 127.2, 127.0, 125.9, 105.4, 99.5, 11.5.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₉H₁₅N₂O₂⁺ 303.1128; found 303.1126.



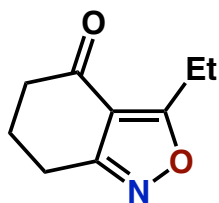
Scheme S4. Synthesis of 3-ethyl-6,7-dihydrobenzo[*c*]isoxazol-4(5*H*)-one (**1u**)

To a round-bottomed flask under N₂ atmosphere containing 1,3-cyclohexanedione (2.018 g, 18 mmol) was added 60 mL CHCl₃. The flask was cooled to 0 °C, then pyridine (2.17 mL, 27 mmol, 1.5 equiv) and propionyl chloride (2.36 mL, 27 mmol, 1.5 equiv). The reaction was warmed to room temperature and allowed to stir overnight. The reaction was diluted with EtOAc and washed with NaHCO₃ solution and dried with Na₂SO₄. After the solvent was removed with rotary evaporation, the crude mixture containing 3-oxocyclohex-1-en-1-yl propionate was used without further purification. Characterization of 3-oxocyclohex-1-en-1-yl propionate matches previously reported data²⁴:

¹H NMR (500 MHz, CDCl₃) δ 5.90 (d, *J* = 1.3 Hz, 1H), 2.56 – 2.44 (m, 4H), 2.40 (dd, *J* = 7.4, 6.0 Hz, 2H), 2.06 (p, *J* = 6.4 Hz, 2H), 1.20 (t, *J* = 7.5 Hz, 3H).

2-propionylcyclohexane-1,3-dione was prepared using a modified published procedure.²⁵ To the crude mixture in a round-bottomed flask was added 40 mL DCE. After cooling to 0 °C was added AlCl₃ (4.8 g, 36 mmol) portionwise. The reaction was warmed to room temperature and allowed to stir for 2 h. The crude mixture was poured into a mixture of ice and concentrated HCl and extracted with DCM. The combined organic layers were dried with Na₂SO₄ and solvent was removed with rotary evaporation. The resulting product was carried forward without further purification.

3-ethyl-6,7-dihydrobenzo[*c*]isoxazol-4(5*H*)-one was prepared using a modified published procedure.²⁶ To the crude mixture in a round-bottomed flask under N₂ atmosphere was added oxalyl chloride (15.4 mL, 180 mmol, 10 equiv). The reaction was allowed to stir overnight at room temperature then the reaction was concentrated with rotary evaporation, suspended in hexanes, then concentrated again. The crude mixture was dissolved in 20 mL DMF and NaN₃ (1.76 g, 27 mmol, 1.5 equiv) was added portionwise. The reaction was allowed to stir at room temperature for 1 hour. The reaction was diluted with EtOAc, washed with LiCl solution, extracted 3x with EtOAc, and dried with Na₂SO₄.



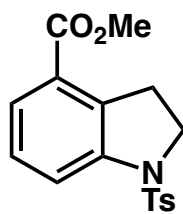
3-ethyl-6,7-dihydrobenzo[*c*]isoxazol-4(5*H*)-one (1u)

The title compound was isolated as a white solid in a 25% yield (744 mg, 4.5 mmol) after purification by flash column chromatography (15% EtOAc in hexanes).

¹H NMR (400 MHz, CDCl₃) δ 3.10 (q, *J* = 7.6 Hz, 2H), 2.93 – 2.86 (m, 2H), 2.54 – 2.46 (m, 2H), 2.12 (tt, *J* = 7.3, 5.7 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 193.8, 177.8, 163.9, 112.6, 39.4, 22.8, 21.56, 21.0, 11.2.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₉H₁₂NO₂⁺ 166.0863; found 166.0855.



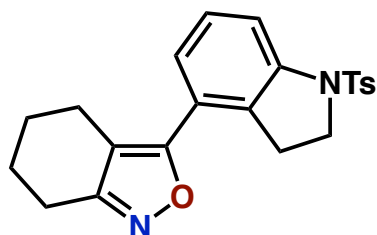
methyl 1-tosylindoline-4-carboxylate

To a round-bottomed flask under N₂ atmosphere was added methyl indoline-4-carboxylate (531.6 mg, 3 mmol), pyridine (711.9 mg, 0.72 mL, 9 mmol), and tosyl chloride (629.14 mg, 3.3 mmol). The reaction was stirred at room temperature for 16 hours, then extracted with aqueous NH₄Cl 3x and DCM 3x. The compound was isolated as a white solid in 90% yield (890.2 mg, 2.69 mmol) after purification by flash column chromatography (20% to 50% EtOAc in hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.84 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.72 – 7.57 (m, 3H), 7.31 – 7.19 (m, 3H), 3.94 (t, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 3.25 (t, *J* = 8.5 Hz, 2H), 2.36 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 166.6, 144.4, 143.3, 134.8, 134.0, 129.9, 128.0, 127.4, 127.1, 125.3, 118.9, 52.0, 50.1, 29.1, 21.7.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₇H₁₈NO₃S⁺ 332.0951; found 332.0946.



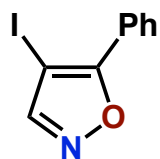
3-(1-tosylindolin-4-yl)-4,5,6,7-tetrahydrobenzo[c]isoxazole (1v)

Synthesized from cyclohexanone oxime (452.6 mg, 4 mmol, 1.5 equiv) and methyl 1-tosylindoline-4-carboxylate (662.8 mg, 2 mmol, 1 equiv) using GP6. The title compound was isolated as a white solid in a 28% yield (219.3 mg, 0.56 mmol) after purification by column chromatography (20% EtOAc in hexanes).

¹H NMR (600 MHz, CDCl₃) δ 7.71 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.28 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.8 Hz, 1H), 3.96 (t, J = 8.5 Hz, 2H), 3.24 (t, J = 8.5 Hz, 2H), 2.76 (t, J = 6.3 Hz, 2H), 2.68 (t, J = 6.2 Hz, 2H), 2.37 (s, 3H), 1.88 – 1.80 (m, 2H), 1.79 – 1.72 (m, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 162.5, 161.5, 144.4, 143.4, 134.1, 130.6, 129.9, 128.2, 127.4, 125.82, 122.0, 115.8, 112.1, 50.1, 28.7, 22.9, 22.1, 21.9, 21.7, 21.4.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₂₂H₂₃N₂O₃S⁺ 395.1424; found 395.1434.

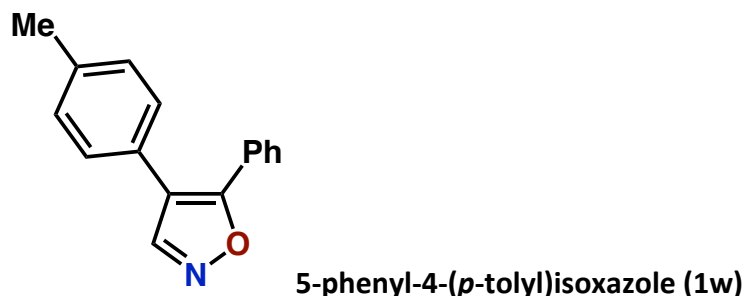


4-iodo-5-phenylisoxazole

Synthesized from 5-phenylisoxazole (117 mg, 0.8 mmol) according to general iodination procedure (GP7). The title compound was isolated as a colorless oil in a 92% yield (200 mg, 0.74 mmol) without further purification necessary.

Characterization for 4-iodo-5-phenylisoxazole matches previously reported data:²⁷

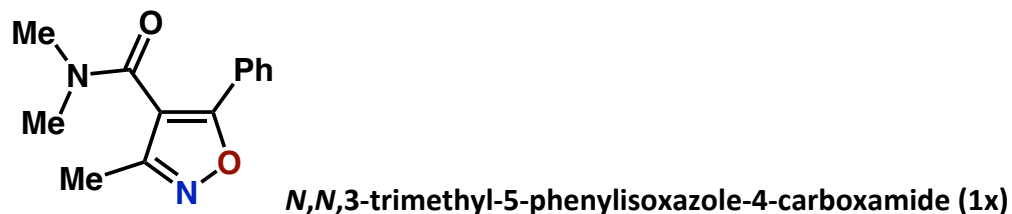
¹H NMR (500 MHz, CDCl₃) δ 8.29 (s, 1H), 8.08 – 8.02 (m, 2H), 7.53 – 7.49 (m, 3H).



Synthesized from 4-iodo-5-phenylisoxazole (200 mg, 0.74 mmol) according to general Suzuki procedure (GP8). The title compound was isolated as a white solid in a 68% yield (118 mg, 0.50 mmol) after purification by flash column chromatography (5-10% EtOAc in hexanes).

Characterization for 5-phenyl-4-(*p*-tolyl)isoxazole matches previously reported data.²⁸

¹H NMR (500 MHz, CDCl₃) δ 8.33 (s, 1H), 7.67 – 7.62 (m, 2H), 7.42 – 7.34 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 2.40 (s, 3H).

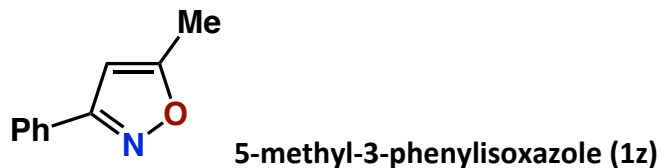


Synthesized from 3-methyl-5-phenylisoxazole (796.0 mg, 5 mmol) according to previously published procedure.²² The title compound was isolated as a yellow oil in a 58% yield (670 mg, 2.9 mmol) after purification by flash column chromatography (75% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.75 – 7.65 (m, 2H), 7.50 – 7.42 (m, 3H), 3.14 (s, 3H), 2.80 (s, 3H), 2.34 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 165.5, 163.9, 159.2, 130.8, 129.3, 127.2, 126.6, 111.2, 38.2, 35.1, 10.6.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₃H₁₅N₂O₂⁺ 231.1128; found 231.1128.

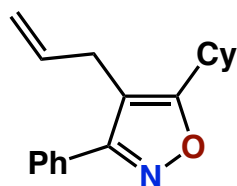


Synthesized from 4-phenylbut-3-yn-2-one (720.8 mg, 5 mmol) according to previously published procedure.²⁹ The title compound was isolated as an off-white solid in a 26% yield (203.7 mg, 1.3 mmol) after purification by flash column chromatography (5% EtOAc/hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.82 – 7.73 (m, 2H), 7.49 – 7.38 (m, 3H), 6.29 (d, J = 1.1 Hz, 1H), 2.48 (d, J = 0.9 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.0, 162.7, 129.9, 129.5, 129.0, 126.9, 99.8, 12.5.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₀H₁₀NO⁺ 160.0757; found 160.0764.

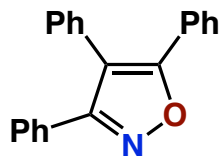


4-allyl-5-cyclohexyl-3-phenylisoxazole (1aa)

Synthesized from ethynylcyclohexane (785 μL, 6 mmol, 1 equiv) and benzoyl chloride (906 μL, 7.8 mmol, 1.3 equiv) according to previously published procedure.³⁰ The intermediate ynone and oxime were pushed forward without further purification. The title compound was isolated as a yellow oil in a 27% yield over 3 steps (428 mg, 1.6 mmol) after purification by flash column chromatography (1:1:1 hexanes/DCM/PhMe).

Characterization for 4-allyl-5-cyclohexyl-3-phenylisoxazole matches previously reported data:

¹H NMR (500 MHz, CDCl₃) δ 7.63 – 7.59 (m, 2H), 7.46 – 7.40 (m, 3H), 5.91 (ddt, J = 17.1, 10.4, 5.3 Hz, 1H), 5.08 (dq, J = 10.2, 1.8 Hz, 1H), 4.96 (dq, J = 17.1, 1.8 Hz, 1H), 3.22 (dt, J = 5.3, 1.9 Hz, 2H), 2.77 (tt, J = 12.2, 3.3 Hz, 1H), 1.93 – 1.83 (m, 4H), 1.78 – 1.65 (m, 3H), 1.43 – 1.29 (m, 3H).

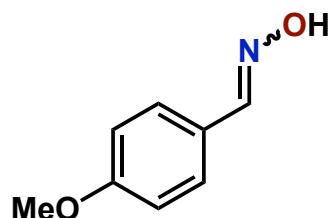


3,4,5-triphenylisoxazole (1ac)

Synthesized according to known procedure.³¹ The title compound was isolated as a white solid in a 22% yield (98.7 mg, 0.33 mmol) after purification by flash column chromatography (5% EtOAc in hexanes) and precipitation from cold Et₂O.

Characterization for 3,4,5-triphenylisoxazole matches previously reported data:

¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.29 (m, 9H), 7.29 – 7.22 (m, 2H).

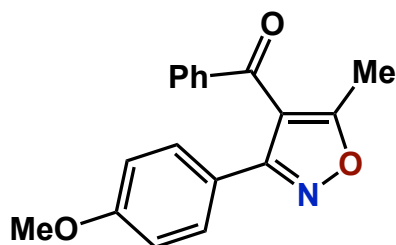


4-methoxybenzaldehyde oxime

Synthesized from 4-methoxy-benzaldehyde (613 μl, 5 mmol) according to a previously published procedure.³² The title compound was carried forward as a yellow oil without any further purification.

Characterization for 4-methoxybenzaldehyde oxime matches previously reported data:

¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H).



(3-(4-methoxyphenyl)-5-methylisoxazol-4-yl)(phenyl)methanone (1ae)

To a round-bottom flask under N₂ atmosphere with a stir bar was added 4-methoxy-benzaldehyde oxime (5 mmol, 1 equiv) and dissolved in anhydrous DMF (1.2 M). N-chlorosuccinimide (734 mg, 5.5 mmol) was added in one portion at room temperature. The reaction was let stir for 2 hours at room temperature. The flask contents were diluted with EtOAc and transferred to separatory funnel. H₂O was added, and the layers were separated. The aqueous layer was extracted x2 more with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation. The crude *N*-hydroxy-4-methoxybenzimidoyl chloride was used in the next step without further purification.

Synthesized from *N*-hydroxy-4-methoxybenzimidoyl chloride (5 mmol, 1 equiv) and 1-phenylbutan-1,3-dione (744 μL, 5 mmol, 1 equiv) according to a previously published procedure.³³ The title compound was isolated as an orange oil in a 20% yield over 3 steps (292 mg, 1 mmol) after purification by flash column chromatography (5-20% EtOAc/hexanes, followed by 1:1 PhMe/DCM).

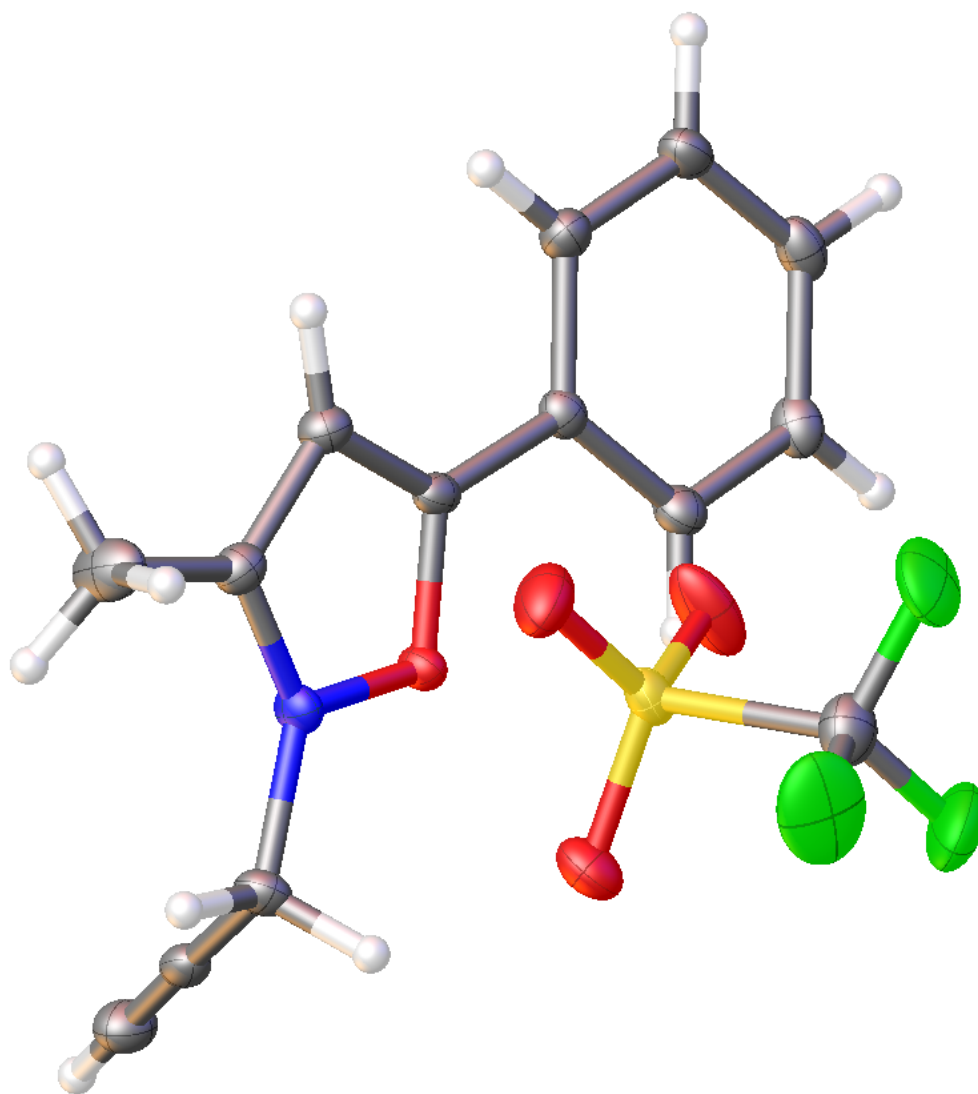
¹H NMR (500 MHz, CDCl₃) δ 7.74 – 7.68 (m, 2H), 7.49 (ddt, J = 8.7, 7.1, 1.3 Hz, 1H), 7.40 (dt, J = 4.7, 3.0 Hz, 2H), 7.37 – 7.30 (m, 2H), 6.78 (dt, J = 4.7, 3.0 Hz, 2H), 3.76 (s, 3H), 2.47 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 190.4, 172.7, 161.6, 160.9, 137.5, 133.6, 130.1, 129.7, 128.6, 120.6, 115.6, 114.1, 55.4, 12.9.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₈H₁₆NO₃⁺ 294.1125; found 294.1124.

8. X-Ray Crystallography

X-Ray-derived ORTEP of 3a



ORTEP drawing of **3a**

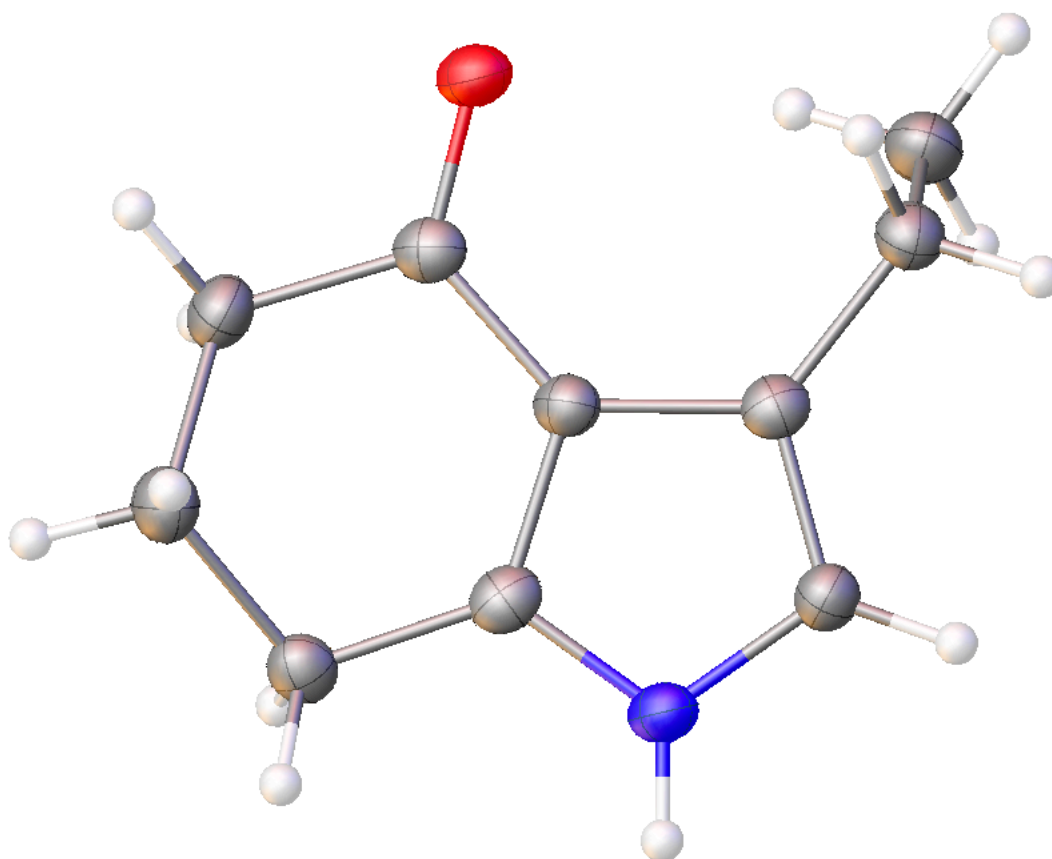
Crystallographic data is available free of charge from the Cambridge Crystallographic Data Centre (<https://summary.ccdc.cam.ac.uk/structure-summary-form> under deposition number **2534489**).

Table S11. Crystallographic and refinement data for **3a**.

Bond precision:	C-C = 0.0019 Å	Wavelength=0.71073	
Cell:	a= 9.8987(5)	b= 16.4348(9)	c= 18.8193(10)
	alpha=90	beta=11.3600	gamma=90
Temperature:	100 K		

	Calculated	Reported
Volume	3061.6(3)	3061.6(3)
Space group	P b c a	P b c a
Hall group	-P 2ac 2ab	-P 2ac 2ab
Moiety formula	C13 H12 N O, C F3 O3 S	C F3 O3 S, C13 H12 N O
Sum formula	C14 H12 F3 N O4 S	C14 H12 F3 N O4 S
Mr	347.31	347.31
Dx,g cm-3	1.507	1.507
Z	8	8
Mu (mm-1)	0.263	0.263
F000	1424.0	1424.0
F000'	1425.99	
h,k,lmax	13,21,25	13,21,25
Nref	3795	3795
Tmin,Tmax	0.962,0.974	0.715,0.746
Tmin'	0.962	
Correction method= # Reported T Limits: Tmin=0.715 Tmax=0.746 AbsCorr = NONE		
Data completeness= 1.000	Theta(max)= 28.278	
R(reflections)= 0.0325(2750)	wR2(reflections)= 0.0884(3795)	
S = 1.060	Npar= 211	

X-Ray-derived ORTEP of 2u



ORTEP drawing of 2u

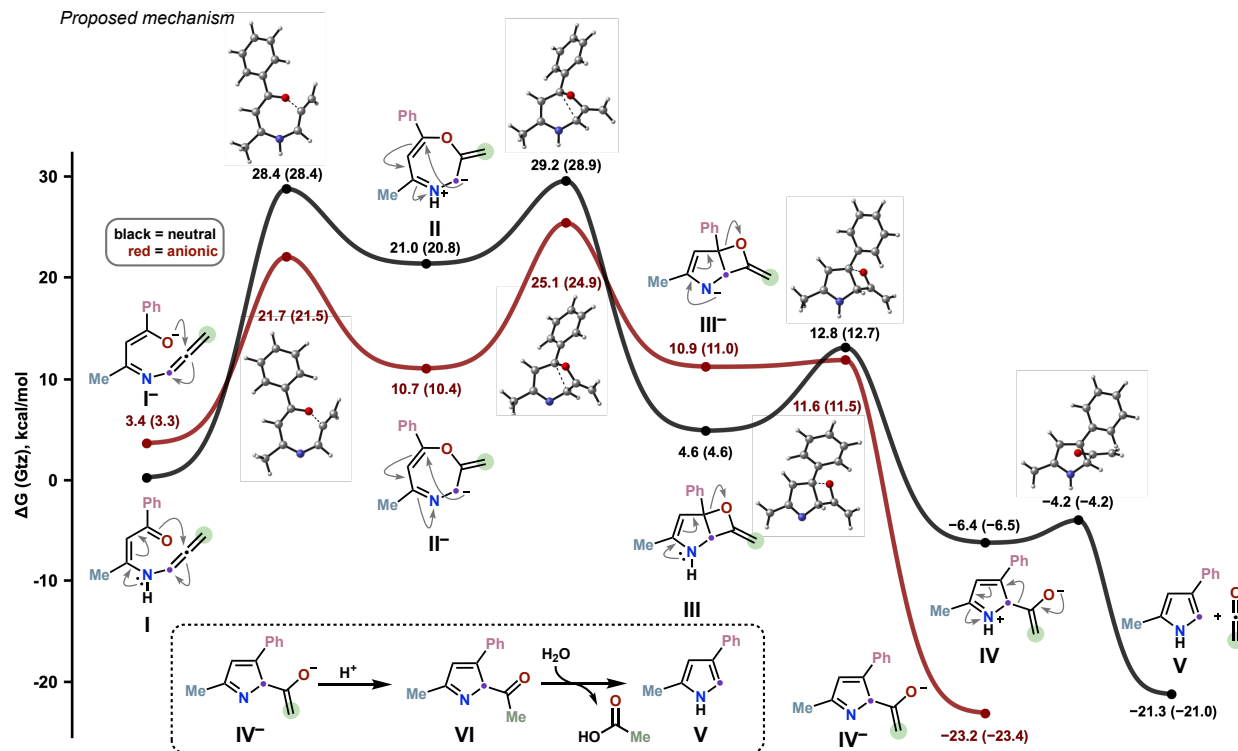
Crystallographic data is available free of charge from the Cambridge Crystallographic Data Centre (<https://summary.ccdc.cam.ac.uk/structure-summary-form> under deposition number **2534490**).

Table S12. Crystallographic and refinement data for **2u**.

Bond precision:	C-C = 0.0038 Å	Wavelength=0.71073	
Cell:	a=9.1846(6)	b=9.3305(6)	c=10.8928(6)
	alpha=87.742(3)	beta=70.355(3)	gamma=80.847(3)
Temperature:	100 K		

	Calculated	Reported
Volume	867.85(9)	867.85(9)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C ₁₀ H ₁₃ N O	C ₁₀ H ₁₃ N O
Sum formula	C ₁₀ H ₁₃ N O	C ₁₀ H ₁₃ N O
Mr	163.21	163.21
Dx,g cm ⁻³	1.249	1.249
Z	4	4
Mu (mm ⁻¹)	0.081	0.081
F000	352.0	352.0
F000'	352.14	
h,k,lmax	10,10,12	10,10,12
Nref	2964	2942
Tmin,Tmax	0.989,0.992	0.665,0.735
Tmin'	0.979	
Correction method= # Reported T Limits: Tmin=0.665 Tmax=0.735 AbsCorr = MULTI-SCAN		
Data completeness= 0.993	Theta(max)= 24.738	
R(reflections)= 0.0520(2048)	wR2(reflections)= 0.1192(2942)	
S = 1.086	Npar= 221	

Ground and transition state geometries were optimized with frequency calculations using density functional theory (DFT) in Gaussian16 (Revision A.03)³⁴ using the polarizable continuum solvation model (PCM) in N,N-dimethylformamide (DMF) at the B3LYP-D3BJ/6-31g(d) level of theory. Single point energy calculations for all structures were conducted using PCM(DMF) at the CAM-B3LYP-D3BJ/6-311+g(d,p) level. All the optimized geometries were verified by frequency calculations as ground states (zero imaginary frequencies) or transition states (one imaginary frequency). Transition states were verified by intrinsic reaction coordinate (IRC) calculations to connect to the corresponding ground states. Quasi-harmonic corrected free energies (Gtz) for each compound were computed using Grimme entropic corrections³⁵ and Head-Gordon enthalpic corrections³⁶ as implemented in Paton's GoodVibes python package.³⁷



S69

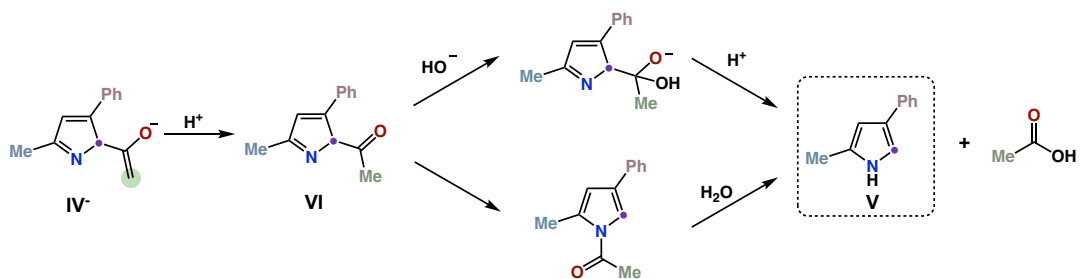
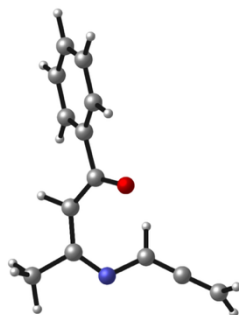


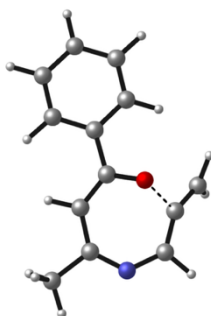
Figure S6. Possible mechanistic routes to **V** from **VI**, either via direct hydrolysis and rearomatization or acyl migration (1,5-sigmatropic rearrangement) and amide hydrolysis.

Γ



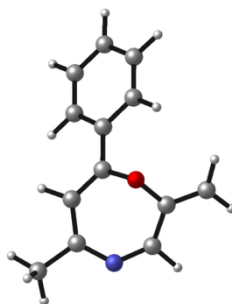
O	0.32189	-1.02465	-0.90314
C	-0.21967	-0.0389	-0.34049
C	-1.71057	-0.13484	-0.08776
C	-2.478	-0.95652	-0.9122
C	-3.84627	-1.08505	-0.71873
C	-4.47039	-0.40359	0.31982
C	-3.71415	0.40584	1.15868
C	-2.34681	0.5403	0.95393
C	0.40243	1.16819	0.01285
C	1.77596	1.52592	-0.17513
C	2.02695	2.96882	-0.54885
N	2.84244	0.78263	-0.05976
C	2.71342	-0.47511	0.52599
C	3.63498	-1.4057	0.46987
C	4.52969	-2.35149	0.41798
H	-1.98015	-1.49374	-1.70942
H	-4.42783	-1.72	-1.37715
H	-5.53741	-0.50699	0.47769
H	-4.18951	0.93037	1.97939
H	-1.76523	1.16399	1.6213
H	-0.25803	1.99736	0.2355
H	3.0869	3.20951	-0.47658
H	1.4624	3.63618	0.10739
H	1.68717	3.16486	-1.56982
H	1.81649	-0.67741	1.11058
H	5.34793	-2.4054	1.13196
H	4.49958	-3.1273	-0.34311

I⁻ TS



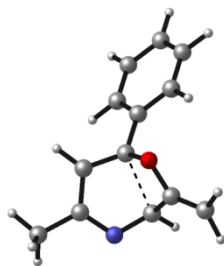
C	0.96153	2.79702	-0.69764
H	0.12521	3.27817	-0.20516
H	1.21333	3.13489	-1.69728
C	1.65642	1.82313	-0.1193
C	2.87977	1.22977	-0.06072
N	3.21732	-0.09092	0.00863
C	2.40259	-1.11566	-0.05042
C	3.06502	-2.4762	-0.14682
C	0.97287	-1.136	-0.0686
C	0.12978	-0.15904	0.40116
C	-1.34292	-0.22851	0.18277
C	-2.02114	-1.42602	-0.0747
C	-3.39348	-1.44119	-0.26953
C	-4.12616	-0.25962	-0.21596
C	-3.46768	0.93432	0.04549
C	-2.09422	0.94707	0.25087
O	0.57931	0.8984	1.02365
H	3.72823	1.90945	-0.0378
H	4.14065	-2.36505	-0.28001
H	2.66641	-3.04784	-0.99072
H	2.88727	-3.07501	0.75249
H	0.52733	-2.03894	-0.4691
H	-1.47692	-2.361	-0.11078
H	-3.89607	-2.38216	-0.46118
H	-5.19841	-0.27322	-0.37039
H	-4.0259	1.86227	0.09414
H	-1.58113	1.87326	0.46655

II



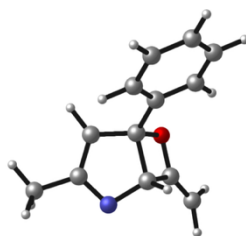
C	0.76794	3.0026	-0.35787
H	-0.09425	3.36585	0.18314
H	1.2352	3.64869	-1.08955
C	1.2657	1.77194	-0.11056
C	2.4706	1.21163	-0.65243
N	3.03749	0.04019	-0.4085
C	2.46986	-1.06727	0.07741
C	3.37352	-2.25956	0.27349
C	1.07508	-1.23595	0.22882
C	0.17719	-0.21625	0.35806
C	-1.25808	-0.28991	0.15207
C	-1.86947	-1.4142	-0.43638
C	-3.24057	-1.47744	-0.60462
C	-4.05524	-0.41415	-0.21812
C	-3.46697	0.711	0.34305
C	-2.09231	0.77472	0.53021
O	0.63594	1.00565	0.86596
H	3.07832	1.91548	-1.21792
H	4.21801	-2.22236	-0.41861
H	2.83169	-3.19666	0.11083
H	3.78692	-2.30906	1.28785
H	0.68932	-2.24909	0.14624
H	-1.25827	-2.23955	-0.77921
H	-3.68087	-2.35868	-1.0574
H	-5.12777	-0.46316	-0.36145
H	-4.0837	1.55002	0.64542
H	-1.64803	1.64903	0.98368

II-TS



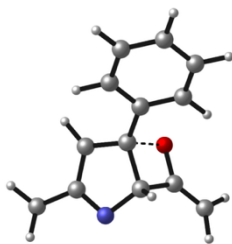
C	-1.70689	3.03797	0.11921
H	-1.38481	3.71889	-0.6588
H	-2.31331	3.42173	0.92767
C	-1.37247	1.74511	0.09411
C	-1.63133	0.6805	1.0899
N	-2.58195	-0.29149	0.88906
C	-2.32083	-1.16611	-0.08715
C	-3.36523	-2.18844	-0.42854
C	-1.03265	-1.20137	-0.61972
C	-0.23229	-0.08445	-0.27373
C	1.22446	-0.16509	-0.13288
C	1.81729	-1.34273	0.34658
C	3.19078	-1.44082	0.50272
C	4.01492	-0.36123	0.19903
C	3.44074	0.81534	-0.26668
C	2.06593	0.91384	-0.43329
O	-0.65394	1.16933	-0.89652
H	-1.59859	1.04133	2.12219
H	-3.93564	-2.46445	0.46103
H	-2.91066	-3.08466	-0.85689
H	-4.07339	-1.79743	-1.16472
H	-0.62564	-2.11837	-1.0333
H	1.18353	-2.18138	0.60864
H	3.62251	-2.36396	0.87277
H	5.08803	-0.43637	0.32719
H	4.06966	1.66494	-0.50822
H	1.62895	1.83033	-0.80625

III



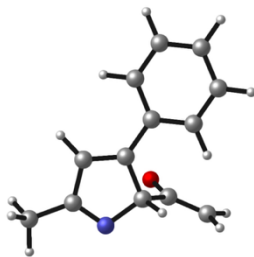
C	2.04372	2.91303	0.25279
C	1.38697	1.76625	0.10577
O	0.62682	1.38448	-0.96295
C	0.31054	0.02862	-0.31145
C	-1.17752	-0.09902	-0.16578
C	-2.03737	0.98866	-0.31796
C	-3.40605	0.84508	-0.1249
C	-3.94002	-0.38709	0.22919
C	-3.0916	-1.47666	0.38688
C	-1.72511	-1.33256	0.1902
C	1.09025	-1.09576	-0.82652
C	2.22423	-1.22506	-0.0285
C	3.28631	-2.26047	-0.25836
N	2.34538	-0.38557	1.00124
C	1.20165	0.50401	0.90851
H	2.02897	3.6725	-0.51948
H	2.61572	3.09558	1.15193
H	-1.6263	1.94891	-0.59782
H	-4.05806	1.7014	-0.25358
H	-5.00722	-0.49817	0.38003
H	-3.49589	-2.4438	0.66268
H	-1.06265	-2.18084	0.31108
H	0.77302	-1.78064	-1.5997
H	3.58901	-2.71636	0.68667
H	4.17542	-1.8017	-0.69951
H	2.9404	-3.04351	-0.93508
H	0.69947	0.65568	1.86838

III⁻ TS



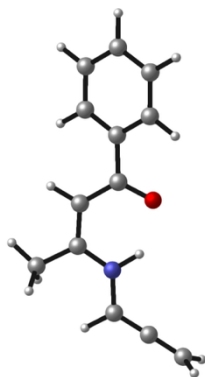
C	1.81632	2.99291	0.06933
C	1.28271	1.77547	-0.05882
O	0.62413	1.27121	-1.1252
C	0.31725	-0.1247	-0.23864
C	-1.17388	-0.1864	-0.12399
C	-1.95856	0.96787	-0.05964
C	-3.33329	0.88619	0.10927
C	-3.95653	-0.35231	0.21197
C	-3.18835	-1.5068	0.14851
C	-1.8107	-1.42218	-0.01188
C	1.09904	-1.25615	-0.61706
C	2.3195	-1.17864	0.08585
C	3.44455	-2.15221	-0.1027
N	2.44167	-0.19162	0.95146
C	1.20235	0.58028	0.84452
H	1.76197	3.71667	-0.73517
H	2.32913	3.26754	0.9811
H	-1.4855	1.93558	-0.15607
H	-3.92237	1.79476	0.1566
H	-5.03052	-0.41526	0.34065
H	-3.66065	-2.47909	0.22781
H	-1.21178	-2.32329	-0.04279
H	0.81563	-2.03244	-1.31236
H	4.06834	-2.19986	0.79051
H	4.076	-1.8403	-0.93935
H	3.06843	-3.15134	-0.33131
H	0.74406	0.75862	1.82138

IV⁻



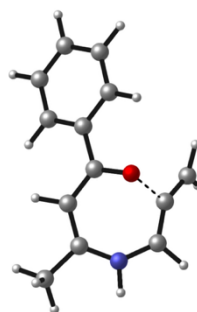
C	-0.78492	3.09811	-0.03315
C	-1.05545	1.85957	0.47743
O	-1.2117	1.53926	1.70266
C	-0.31818	-0.47817	-0.23851
C	1.14392	-0.43907	-0.1489
C	1.87855	0.52978	-0.83738
C	3.26446	0.55385	-0.76629
C	3.94241	-0.38633	-0.00167
C	3.22304	-1.35127	0.69488
C	1.83927	-1.37533	0.62357
C	-1.13161	-1.52896	-0.04048
C	-2.5035	-1.0607	-0.25254
C	-3.70548	-1.93782	-0.14179
N	-2.56105	0.18497	-0.56362
C	-1.19546	0.70423	-0.55586
H	-0.6732	3.9513	0.62805
H	-0.66474	3.25523	-1.09714
H	1.36168	1.26854	-1.43546
H	3.8163	1.31072	-1.31082
H	5.024	-0.36578	0.05565
H	3.74269	-2.08298	1.30189
H	1.28691	-2.11893	1.18493
H	-0.85466	-2.54577	0.20248
H	-4.61223	-1.3747	-0.35788
H	-3.77874	-2.35893	0.86413
H	-3.63195	-2.77791	-0.83716
H	-0.97741	1.10313	-1.55041

I

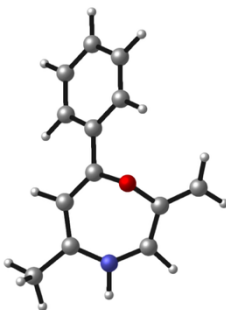


O	0.11022	-1.23515	0.09426
C	-0.49945	-0.14956	0.00508
C	0.16662	1.10517	-0.12905
C	1.53927	1.24457	-0.13842
N	2.34402	0.17467	-0.01509
C	3.74373	0.18655	0.00197
C	4.46957	-0.89378	0.11454
C	5.20538	-1.95786	0.22654
C	2.16205	2.59732	-0.28864
C	-1.99796	-0.17529	0.01961
C	-2.6437	-1.35866	-0.33783
C	-4.02773	-1.4353	-0.33827
C	-4.78545	-0.33156	0.03628
C	-4.15123	0.847	0.40769
C	-2.76558	0.92725	0.39435
H	-0.41815	2.00229	-0.25311
H	1.84419	-0.714	0.06846
H	4.22136	1.1534	-0.08255
H	5.53908	-2.51098	-0.64651
H	5.51269	-2.33527	1.19745
H	2.80134	2.63749	-1.17326
H	2.77862	2.84149	0.57918
H	1.38947	3.35569	-0.38617
H	-2.04322	-2.21407	-0.61867
H	-4.51765	-2.35669	-0.62901
H	-5.86714	-0.39103	0.04154
H	-4.73632	1.70643	0.71152
H	-2.28724	1.84865	0.6996

ITS

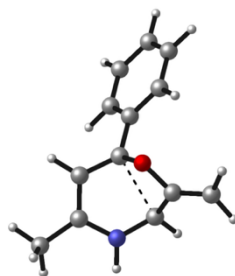


C	-0.65218	2.7205	0.88565
C	-1.44274	1.84434	0.28595
O	-0.56717	0.94016	-0.95671
C	-0.11959	-0.16444	-0.43929
C	1.34054	-0.26399	-0.20532
C	1.91999	-1.30734	0.52414
C	3.29121	-1.3566	0.71996
C	4.10968	-0.35971	0.20073
C	3.54472	0.68785	-0.51516
C	2.17313	0.7344	-0.71605
C	-0.9947	-1.1866	-0.10544
C	-2.38628	-1.08587	-0.0514
C	-3.21854	-2.338	-0.09171
N	-3.07785	0.05571	0.04663
C	-2.71254	1.36719	0.26029
H	0.20872	3.14197	0.38378
H	-0.84777	3.02333	1.90714
H	1.30021	-2.08045	0.95878
H	3.72255	-2.17076	1.28973
H	5.18072	-0.39791	0.35862
H	4.17477	1.47078	-0.91993
H	1.72709	1.54526	-1.27528
H	-0.59253	-2.16957	0.09552
H	-3.44653	-2.61401	-1.12474
H	-4.16049	-2.22236	0.44666
H	-2.67096	-3.16713	0.35478
H	-4.08152	-0.07	0.02052
H	-3.54817	2.0492	0.31762

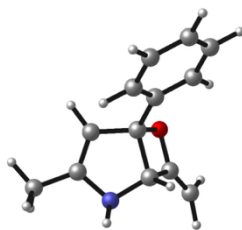


C	-0.66367	2.97138	0.43012
C	-1.22504	1.789	0.12717
O	-0.60372	0.98957	-0.84
C	-0.14597	-0.22392	-0.35319
C	1.299	-0.29991	-0.15461
C	1.8942	-1.38455	0.50718
C	3.26586	-1.44408	0.67577
C	4.07909	-0.41484	0.20796
C	3.50147	0.67224	-0.43175
C	2.12619	0.73099	-0.61388
C	-1.029	-1.24321	-0.19745
C	-2.42745	-1.09187	-0.09168
C	-3.35748	-2.24848	-0.29562
N	-2.97248	0.06621	0.30839
C	-2.46217	1.28111	0.60406
H	0.22253	3.30288	-0.09045
H	-1.09996	3.61222	1.18385
H	1.27729	-2.17788	0.90943
H	3.70525	-2.29088	1.18929
H	5.15199	-0.4605	0.34925
H	4.12367	1.48064	-0.79694
H	1.68241	1.57152	-1.12772
H	-0.64748	-2.25189	-0.09061
H	-3.62976	-2.37188	-1.34793
H	-4.28217	-2.12924	0.27442
H	-2.8807	-3.17589	0.02656
H	-3.9669	-0.00086	0.49705
H	-3.14927	1.94859	1.10061

II TS

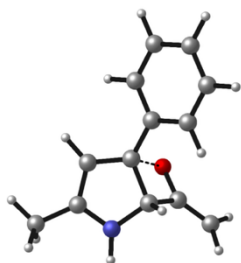


C	-1.08438	3.15532	0.17328
C	-1.15607	1.82865	0.09045
O	-0.63245	1.11051	-0.94343
C	-0.23306	-0.12078	-0.34145
C	1.21548	-0.24242	-0.15504
C	1.74914	-1.39564	0.43277
C	3.1154	-1.52659	0.61813
C	3.97643	-0.50245	0.23632
C	3.45592	0.65088	-0.336
C	2.08831	0.78168	-0.53368
C	-1.07486	-1.22305	-0.58309
C	-2.37138	-1.10795	-0.14774
C	-3.46885	-2.08428	-0.40735
N	-2.61598	-0.08083	0.7025
C	-1.66819	0.86565	1.0588
H	-0.5617	3.73251	-0.57758
H	-1.55255	3.67093	0.99969
H	1.08284	-2.18456	0.75985
H	3.51145	-2.42681	1.07277
H	5.04423	-0.60303	0.38793
H	4.11914	1.45326	-0.63674
H	1.68735	1.67466	-0.9932
H	-0.70169	-2.17976	-0.92663
H	-4.14212	-1.71617	-1.18488
H	-4.06352	-2.26197	0.49207
H	-3.05317	-3.03222	-0.74714
H	-3.44032	-0.15912	1.28474
H	-1.82163	1.23998	2.06667

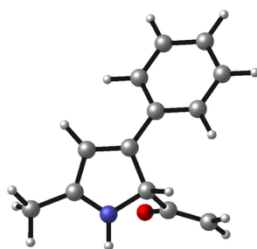


C	2.09727	2.92232	0.24659
C	1.40884	1.80326	0.10928
O	0.60499	1.43064	-0.94572
C	0.29	0.12244	-0.32227
C	-1.19156	-0.0546	-0.15991
C	-2.07265	1.01151	-0.31922
C	-3.43614	0.83107	-0.12291
C	-3.93296	-0.41362	0.24
C	-3.05777	-1.48075	0.40315
C	-1.69645	-1.30253	0.20229
C	1.05664	-1.01875	-0.89541
C	2.12887	-1.29078	-0.13674
C	3.13117	-2.37675	-0.3097
N	2.29089	-0.39731	0.93071
C	1.18165	0.53757	0.9006
H	2.09412	3.68275	-0.52375
H	2.68236	3.08472	1.14088
H	-1.68663	1.98067	-0.6047
H	-4.11206	1.66744	-0.25544
H	-4.99629	-0.55278	0.39326
H	-3.43648	-2.45595	0.68488
H	-1.01642	-2.13659	0.32687
H	0.76364	-1.56305	-1.78043
H	4.12093	-1.95473	-0.49737
H	2.86019	-3.02566	-1.14081
H	3.20072	-2.98278	0.5976
H	2.50763	-0.811	1.82722
H	0.70065	0.66069	1.86808

III TS

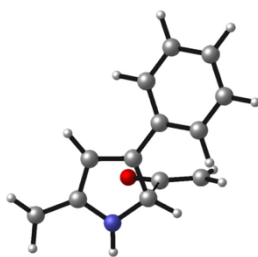


C	1.29028	3.091	-0.45912
C	1.03398	1.77935	-0.45736
O	0.54712	1.0087	-1.43151
C	0.31874	-0.26884	-0.03509
C	-1.14988	-0.29392	0.05516
C	-1.83859	0.6069	0.86645
C	-3.2239	0.569	0.94159
C	-3.93715	-0.36542	0.20339
C	-3.25803	-1.26591	-0.61006
C	-1.87512	-1.2324	-0.68138
C	1.12019	-1.41612	-0.21727
C	2.40062	-1.12803	0.21286
C	3.58077	-2.02936	0.20889
N	2.49606	0.13073	0.66318
C	1.18853	0.78798	0.65854
H	1.10796	3.69399	-1.34014
H	1.69999	3.56737	0.42136
H	-1.29707	1.34127	1.44868
H	-3.74592	1.27154	1.57949
H	-5.01834	-0.39404	0.26148
H	-3.80884	-1.99609	-1.19018
H	-1.35519	-1.93212	-1.3234
H	0.80832	-2.36529	-0.61958
H	3.28762	-3.04642	-0.04165
H	4.07267	-2.02615	1.18316
H	4.30572	-1.68216	-0.53089
H	3.2869	0.48885	1.17439
H	0.90408	1.0891	1.66743



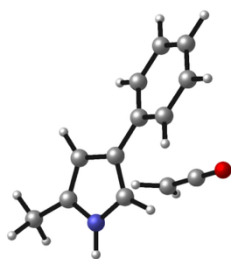
C	-0.66737	3.05431	0.10827
C	-1.07226	1.82422	0.52494
O	-1.42553	1.42105	1.66935
C	-0.27245	-0.46149	-0.26928
C	1.18255	-0.42301	-0.16361
C	1.92534	0.54889	-0.83914
C	3.30815	0.56889	-0.74332
C	3.96716	-0.37484	0.03347
C	3.2376	-1.34231	0.71551
C	1.85697	-1.3673	0.61741
C	-1.09448	-1.51212	-0.02016
C	-2.44189	-1.09386	-0.26049
C	-3.66975	-1.90192	-0.10202
N	-2.43479	0.14412	-0.67436
C	-1.10835	0.72303	-0.61837
H	-0.58324	3.866	0.8216
H	-0.40525	3.24538	-0.92271
H	1.42487	1.28786	-1.44982
H	3.87217	1.32361	-1.27701
H	5.04738	-0.35596	0.11012
H	3.74654	-2.07496	1.32934
H	1.29534	-2.11282	1.16582
H	-0.82405	-2.51159	0.28153
H	-3.59115	-2.80605	-0.70819
H	-4.55994	-1.3471	-0.39144
H	-3.7622	-2.21547	0.93953
H	-3.26622	0.6892	-0.85912
H	-0.8537	1.17978	-1.57319

IV TS



C	0.33446	2.81025	-0.40266
C	1.1496	1.76861	-0.62895
O	1.93532	1.31677	-1.42748
C	0.2514	-0.42181	0.33086
C	-1.20582	-0.40307	0.17807
C	-2.01516	0.23837	1.11813
C	-3.39368	0.25285	0.97
C	-3.98521	-0.37426	-0.11959
C	-3.18929	-1.01835	-1.0592
C	-1.81089	-1.03337	-0.91136
C	1.13728	-1.38095	-0.13773
C	2.42718	-1.01361	0.26862
C	3.72461	-1.67677	-0.02053
N	2.33079	0.09506	1.00793
C	1.03472	0.60908	0.93349
H	-0.28129	2.88135	0.47767
H	0.29308	3.59686	-1.14679
H	-1.56582	0.71759	1.97892
H	-4.00821	0.75174	1.70939
H	-5.06203	-0.36168	-0.23589
H	-3.6435	-1.50541	-1.91344
H	-1.19608	-1.52197	-1.65714
H	0.90355	-2.26502	-0.70931
H	4.42635	-1.54738	0.80392
H	4.17345	-1.2469	-0.91881
H	3.57601	-2.74155	-0.19437
H	3.12417	0.62115	1.34367
H	0.70713	1.28004	1.71152

V + ketene



C	1.32172	2.46618	-0.94691
C	0.28531	2.65438	-0.17888
O	-0.63789	2.84286	0.49766
C	0.43506	-0.66863	0.27736
C	-1.02077	-0.66304	0.0852
C	-1.89637	-0.66015	1.17522
C	-3.26995	-0.6231	0.98739
C	-3.80282	-0.60056	-0.29635
C	-2.94462	-0.61322	-1.38859
C	-1.56991	-0.64106	-1.1995
C	1.42569	-1.122	-0.65066
C	2.66244	-0.91383	-0.09258
C	4.02941	-1.20883	-0.60714
N	2.45648	-0.34897	1.13941
C	1.11771	-0.19404	1.37459
H	1.72828	3.30351	-1.49507
H	1.74451	1.47403	-1.02727
H	-1.49629	-0.69725	2.18155
H	-3.92844	-0.62042	1.84808
H	-4.87574	-0.57557	-0.44318
H	-3.34664	-0.59347	-2.39478
H	-0.91236	-0.62932	-2.06034
H	1.2492	-1.56775	-1.61746
H	3.96488	-1.62478	-1.612
H	4.54985	-1.93255	0.02536
H	4.64394	-0.30622	-0.65374
H	3.18681	-0.06659	1.77391
H	0.76225	0.26357	2.283

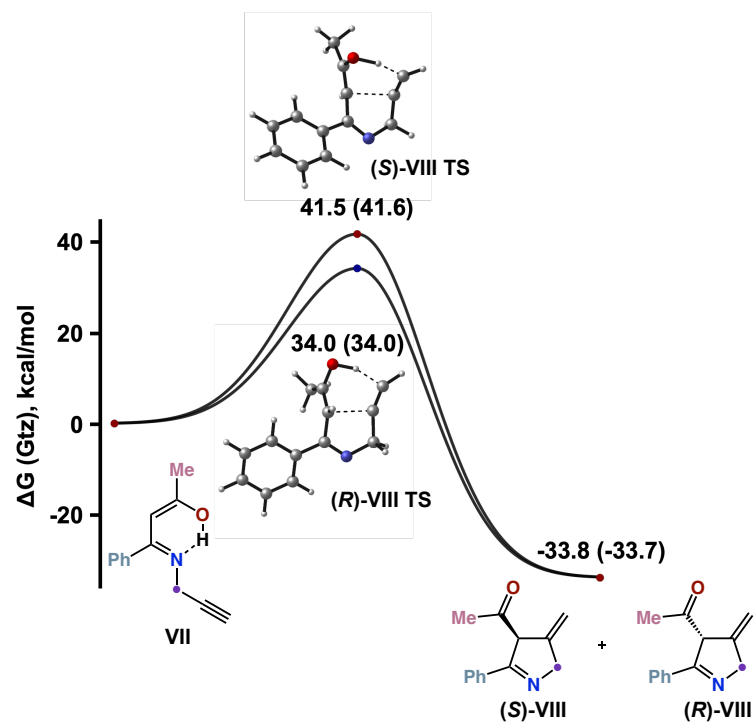
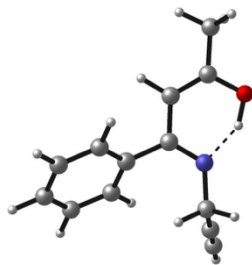
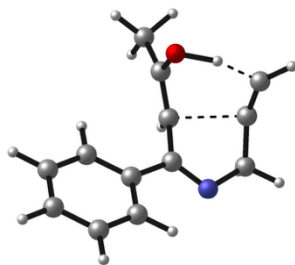


Figure S7. Proposed Conia-Ene intermediate formation. Energy diagram was created using EneRplot. (CAM-B3LYP-D3BJ/6-311+g(d,p)-PCM(DMF)//B3LYP-D3BJ/6-31g(d)-PCM(DMF)).



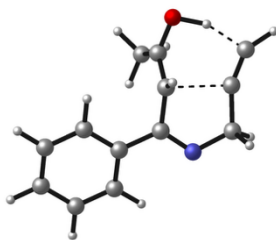
C	-0.371433	3.973445	0.691377
C	-0.200724	3.096196	-0.113973
C	0.005718	2.015715	-1.085475
N	0.908855	0.996997	-0.573338
C	0.487316	-0.153752	-0.147856
C	-0.948373	-0.552151	-0.047165
C	-1.374591	-1.74805	-0.629061
C	-2.701891	-2.145575	-0.527261
C	-3.612505	-1.361312	0.174035
C	-3.191688	-0.176201	0.768597
C	-1.867218	0.229568	0.656623
C	1.465215	-1.13795	0.263337
C	2.805972	-0.901938	0.20348
O	3.30785	0.247183	-0.231182
C	3.839903	-1.896477	0.617721
H	-0.520066	4.753822	1.404819
H	0.459929	2.43733	-1.988742
H	-0.966425	1.603376	-1.378285
H	-0.663043	-2.362191	-1.171792
H	-3.024506	-3.071034	-0.993183
H	-4.648013	-1.674846	0.259219
H	-3.895884	0.435664	1.323026
H	-1.542436	1.153237	1.124247
H	1.116207	-2.088062	0.64385
H	2.498541	0.827349	-0.465044
H	4.458082	-1.479768	1.419146
H	4.503723	-2.115134	-0.224684
H	3.384902	-2.825281	0.963973

(S)-VII TS



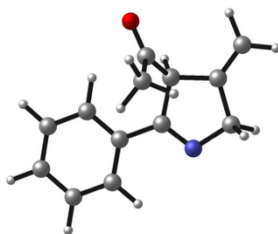
C	2.96079	-0.830892	1.278668
C	2.503134	-1.209491	0.184903
C	1.158217	0.315697	-0.727344
C	1.610031	1.379276	0.015972
C	2.36343	2.509386	-0.61551
O	1.622128	1.326404	1.312678
C	0.09953	-0.699226	-0.459972
C	-1.298454	-0.282494	-0.199424
C	-2.226212	-1.220871	0.260282
C	-3.537573	-0.850455	0.504234
C	-3.943624	0.463699	0.292236
C	-3.028659	1.40288	-0.161493
C	-1.711845	1.033094	-0.402249
N	0.387666	-1.938577	-0.581941
C	1.824976	-2.161258	-0.721312
H	2.3022	0.367357	1.500769
H	3.549856	-1.189212	2.104514
H	3.417132	2.4467	-0.327158
H	1.979043	3.45708	-0.23296
H	-1.900458	-2.238673	0.428525
H	-4.246519	-1.585276	0.865978
H	-3.337747	2.427421	-0.328451
H	-1.005254	1.771148	-0.757977
H	2.141075	-2.04557	-1.762103
H	2.06969	-3.177473	-0.405189
H	2.285227	2.505535	-1.701397
H	1.382276	0.37072	-1.791232
H	-4.969653	0.75298	0.484896

(R)-VII TS



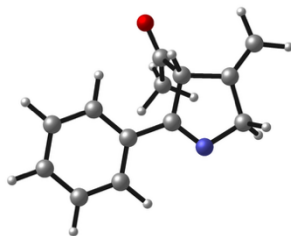
C	3.836633	0.365679	-0.243148
C	2.753817	0.968931	-0.179434
C	1.087168	-0.301438	-0.633003
C	1.560865	-1.331344	0.132749
C	1.084622	-1.664067	1.508428
O	2.661416	-1.916268	-0.276105
C	0.05863	0.677693	-0.199823
C	-1.376742	0.307813	-0.149075
C	-1.811321	-0.914659	-0.658178
C	-3.157048	-1.256486	-0.618877
C	-4.080005	-0.382129	-0.063826
C	-3.653248	0.839017	0.450669
C	-2.313091	1.182415	0.407182
N	0.428034	1.859416	0.099912
C	1.846461	2.137699	0.004783
H	3.369466	-1.059453	-0.389996
H	4.903537	0.472386	-0.186718
H	1.370218	-0.280383	-1.679209
H	0.945783	-2.743648	1.59245
H	0.148396	-1.16755	1.7567
H	1.848699	-1.374802	2.235513
H	-1.095508	-1.602548	-1.090182
H	-3.481961	-2.20807	-1.021332
H	-5.129264	-0.64923	-0.028724
H	-4.370505	1.522623	0.888506
H	-1.972857	2.128874	0.805592
H	2.155689	2.672454	0.906715
H	2.000296	2.82883	-0.830531

(S)-VIII



C	3.753355	-0.274201	-0.667812
C	2.506825	-0.656106	-0.428103
C	1.268792	0.212438	-0.571823
H	1.12865	0.559187	-1.60016
C	1.384061	1.456402	0.305535
C	1.303584	1.260622	1.796194
O	1.556724	2.546912	-0.200679
C	0.176332	-0.763593	-0.157166
C	-1.250683	-0.387228	-0.14704
C	-2.207689	-1.290486	0.328016
C	-3.550292	-0.947691	0.342177
C	-3.957771	0.303565	-0.117898
C	-3.014369	1.207323	-0.59106
C	-1.66652	0.86479	-0.606387
N	0.579464	-1.928382	0.173144
C	2.031163	-2.011346	0.060756
H	3.983826	0.730979	-1.00825
H	4.59014	-0.953482	-0.535151
H	1.595852	2.178184	2.306974
H	1.940366	0.432172	2.118332
H	0.273899	1.008273	2.072235
H	-1.876938	-2.259342	0.684084
H	-4.284125	-1.655579	0.713922
H	-5.009431	0.571421	-0.105438
H	-3.324843	2.182766	-0.950799
H	-0.942772	1.581577	-0.979065
H	2.296962	-2.819875	-0.629872
H	2.457645	-2.279838	1.034278

(R)-VIII



C	-3.753361	-0.274188	-0.667812
C	-2.506832	-0.656101	-0.428105
C	-1.268793	0.212436	-0.571824
H	-1.128649	0.559186	-1.600161
C	-1.384042	1.456412	0.305527
C	-1.303624	1.260635	1.79619
O	-1.556625	2.546931	-0.200694
C	-0.176339	-0.763599	-0.157165
C	1.250679	-0.387236	-0.147042
C	1.666518	0.864787	-0.606376
C	3.014368	1.207316	-0.591044
C	3.957768	0.303552	-0.117887
C	3.550287	-0.947708	0.342175
C	2.207682	-1.290501	0.328005
N	-0.579477	-1.928384	0.173155
C	-2.031177	-2.011343	0.060755
H	-3.983829	0.730992	-1.008254
H	-4.590149	-0.953465	-0.535148
H	-1.595733	2.178258	2.306951
H	-0.273991	1.008096	2.072254
H	-1.940567	0.43231	2.118328
H	0.942771	1.581579	-0.979046
H	3.324845	2.182762	-0.950774
H	5.009429	0.571407	-0.105423
H	4.284118	-1.655601	0.713914
H	1.876927	-2.259361	0.684061
H	-2.457669	-2.279838	1.034272
H	-2.29697	-2.81987	-0.629878

10. Predictive Model

Duplicates were determined by finding structures within 0.0001 Hartrees and containing buried volumes for all three atoms (C3, C4, and C5) within 0.5% of those of another structure. Both conditions must be met for a structure to be deemed duplicate. Boltzmann average calculated at 298.15 K. Buried volume calculated at 3.75 Å. Statistical analyses of parameters were performed using Claude. The xyz coordinates of the lowest energy conformers, the buried volumes of each relevant conformer, and the Boltzmann-averaged buried volumes and composite score Λ are reported below. This classification was calculated to have a cumulative AUROC (Area Under the Receiver Operating Characteristic) score of 0.968, indicating a very high probability of correctly predicting the result.³⁸

Table S13. Statistical analysis of steric and electronic parameters.

Parameter	Cum. AUROC	Spearman ρ	Kendall τ -c	Kendall τ -b	C-index	Test Correct (of 11)
V _{bur} C3	0.9359	0.7851	0.7347	0.6587	0.9219	6
V _{bur} C4	0.8187	0.5762	0.5510	0.4952	0.8164	8
V _{bur} C5	0.6603	0.2922	0.2857	0.2562	0.6641	5
C3 NBO	0.4584	-0.0720	-0.0544	-0.0488	0.4688	5
C4 NBO	0.5179	0.0367	0.0408	0.0366	0.5234	5
C5 NBO	0.7159	0.3864	0.3537	0.3172	0.7031	1
V _{bur} C3*C4/C5	0.9680	0.8434	0.7891	0.7075	0.9531	10
V _{bur} C3*C4	0.8991	0.7203	0.6803	0.6099	0.8906	7
V _{bur} C3/C5	0.8719	0.6678	0.5986	0.5367	0.8438	6

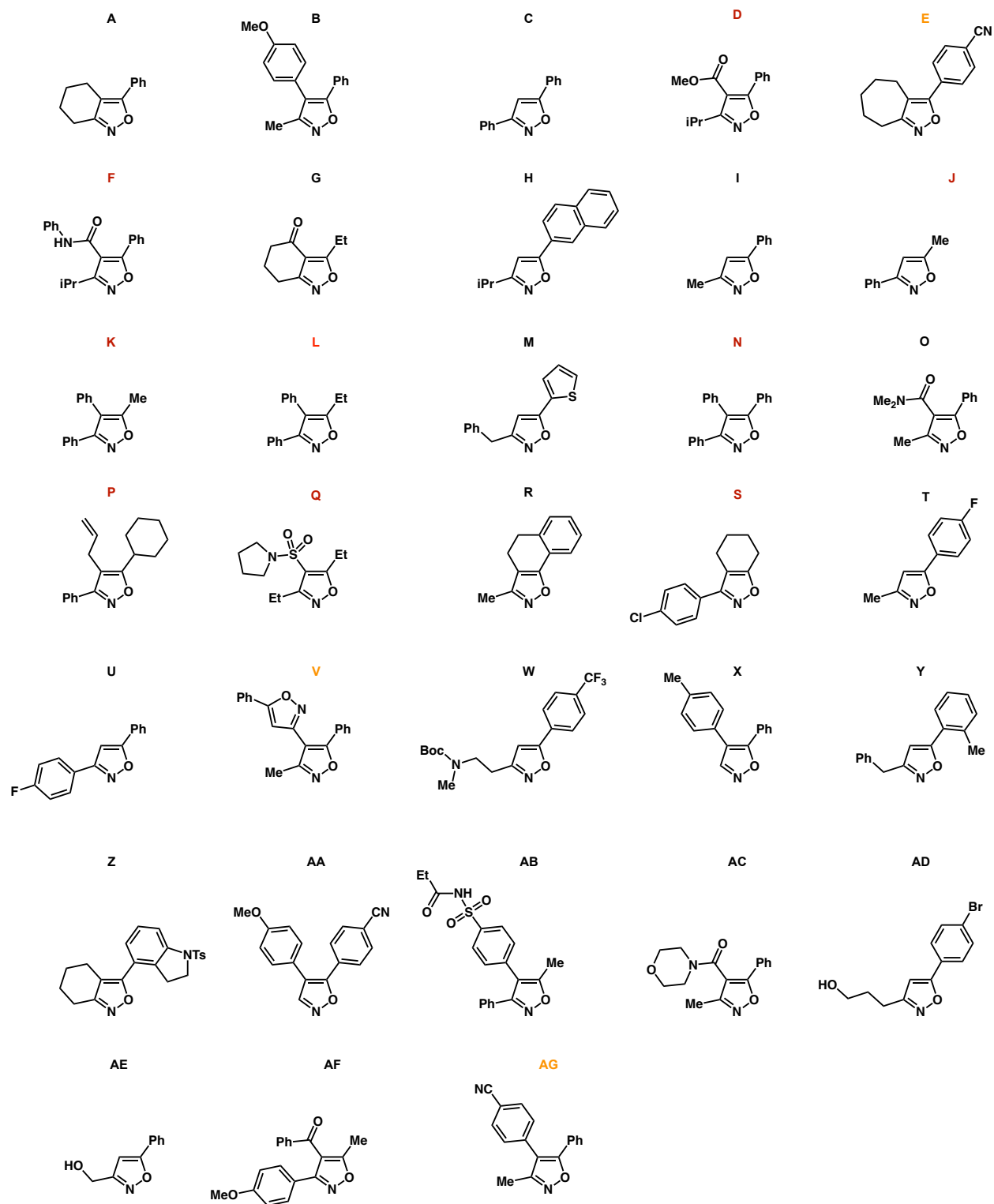


Figure S8. Substrates and associated labels used for predictive model. Black = desired product observed as major, orange = mixture of products observed, red = Conia-Ene product observed as major.

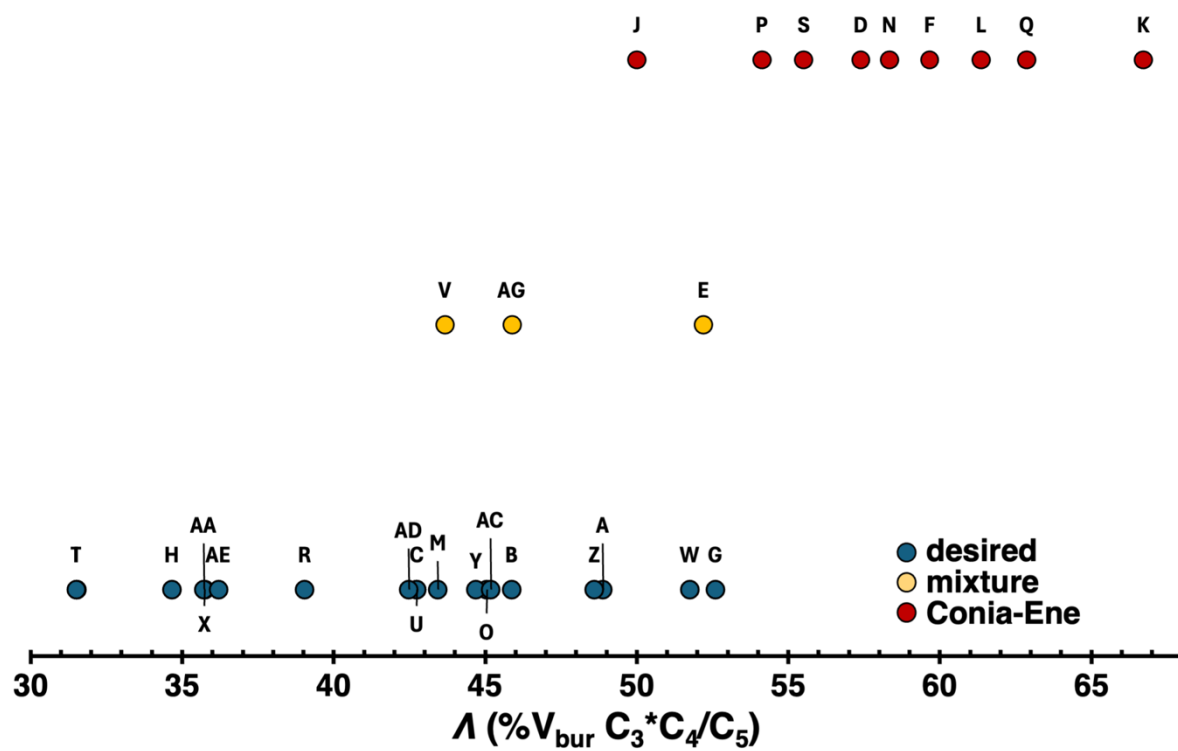
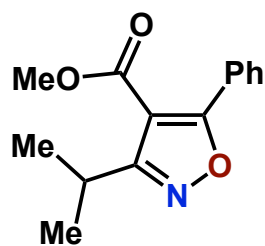


Figure S9. Labelled plot of predictive model for reaction outcome.

11. Synthesis of isoxazoles (exhibiting unsuccessful Conia-ene type reactivity)



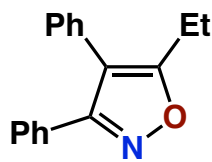
methyl 3-isopropyl-5-phenylisoxazole-4-carboxylate (1af)

Synthesized according to the general [3+2] procedure GP4 using (*E*)-isobutyraldehyde oxime (436 mg, 5 mmol) and phenylpropynoic acid methyl ester (2 g, 12.5 mmol). The title compound was isolated as a pale yellow oil in a 27% yield (332 mg, 1.35 mmol) after purification by flash column chromatography (25-50% DCM in hexanes).

¹H NMR (400 MHz, CDCl₃) δ 7.87 – 7.78 (m, 2H), 7.56 – 7.43 (m, 3H), 3.82 (s, 3H), 3.49 (hept, J = 6.9 Hz, 1H), 1.39 (d, J = 6.9 Hz, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 173.1, 169.0, 162.9, 131.2, 129.2, 128.4, 127.4, 107.3, 51.8, 27.0, 21.3.

HRMS (APCI/QTOF) m/z: [M+H]⁺ calculated for C₁₄H₁₆NO₃⁺ 246.1125; found 246.1124.

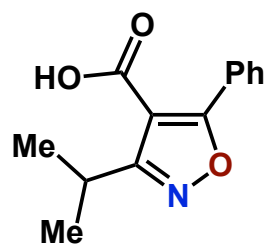


5-ethyl-3,4-diphenylisoxazole (1ag)

Synthesized according to a previously published procedure.³⁹ The title compound was isolated as a white solid in a 95% yield (708 mg, 2.84 mmol) after purification by flash column chromatography (10% EtOAc in hexanes).

Characterization for 5-ethyl-3,4-diphenylisoxazole matches previously reported data:

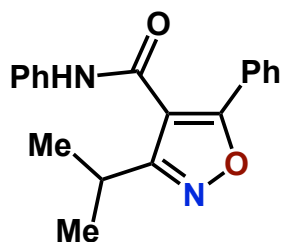
¹H NMR (500 MHz, CDCl₃) δ 7.46 – 7.41 (m, 2H), 7.40 – 7.34 (m, 4H), 7.33 – 7.28 (m, 2H), 7.20 – 7.16 (m, 2H), 2.81 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H).



3-isopropyl-5-phenylisoxazole-4-carboxylic acid

Synthesized from ethyl 3-isopropyl-5-phenylisoxazole-4-carboxylate **1af** (142 mg, 0.58 mmol) according to a previously published procedure.⁴⁰ The title compound was isolated as a white solid in a 90% yield (121 mg, 0.52 mmol) and carried forward without any further purification.

¹H NMR (500 MHz, CDCl₃) δ 7.88 – 7.81 (m, 2H), 7.58 – 7.45 (m, 3H), 3.56 (hept, J = 7.0 Hz, 1H), 1.41 (d, J = 6.9 Hz, 6H).



3-isopropyl-N,5-diphenylisoxazole-4-carboxamide (1ah)

To an oven dried vial under N₂ was added 3-isopropyl-5-phenylisoxazole-4-carboxylic acid (60 mg, 0.25 mmol) and dissolved in 0.25 mL SOCl₂. The vial was brought to 75 °C to stir for 3 hours. Upon reaction completion, the vial was brought to room temperature, and the excess SOCl₂ was removed via nitrogen blowdown. The crude product (3-isopropyl-5-phenylisoxazole-4-carbonyl chloride) was used in the next step without further purification.

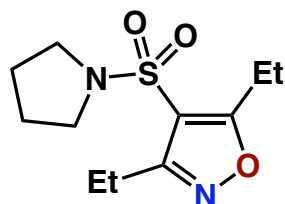
To a vial under N₂ was added crude 3-isopropyl-5-phenylisoxazole-4-carbonyl chloride (0.25 mmol) from the previous step, Et₃N (53 µL, 0.375 mmol), and anhydrous DCM (0.5 mL). The vial was brought to 0 °C in an ice bath, where aniline (23 µL, 0.25 mmol) was added dropwise. The vial was let stir overnight at room temperature. Upon reaction completion, the vial contents were diluted with DCM (1 mL), washed with H₂O (1 mL) and separated, and extracted 2x more with DCM. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation.

The title compound was isolated as an off-white solid in a 64% yield over 2 steps (49 mg, 0.16 mmol) after purification by washing the crude product with 2:1 hexanes/DCM.

¹H NMR (500 MHz, CDCl₃) δ 7.76 (dd, *J* = 7.2, 2.1 Hz, 2H), 7.51 (d, *J* = 7.3 Hz, 3H), 7.44 – 7.29 (m, 5H), 7.15 (t, *J* = 7.4 Hz, 1H), 3.44 (hept, *J* = 6.9 Hz, 1H), 1.41 (d, *J* = 7.0 Hz, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 168.7, 167.7, 160.4, 137.4, 131.4, 129.4, 129.3, 128.1, 126.7, 125.1, 120.0, 111.5, 26.7, 21.3.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₉H₁₉N₂O₂⁺ 307.1441; found 307.1441.



3,5-diethyl-4-(pyrrolidin-1-ylsulfonyl)isoxazole (1ai)

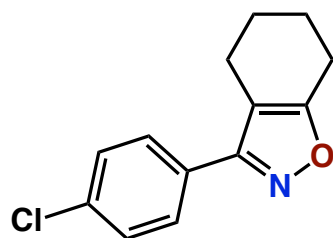
Synthesized according to a modified previously published procedure.³⁹ To a round-bottomed flask containing a stir bar and chlorosulfonic acid (0.93 mL, 14 mmol) cooled to 0 °C was added 3,5-diethylisoxazole (250.3 mg, 2 mmol) slowly dropwise (about 10 minutes). After addition was complete, the solution was heated to 130 °C for 3 hours, then heated to 150 °C for 30 minutes. The reaction was cooled to room temperature and poured into ice water, then extracted 3x with EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation. The crude 3,5-diethylisoxazole-4-sulfonyl chloride was used without further purification. To a round-bottom flask containing a stir bar was added pyrrolidine (0.18 mL, 2.2 mmol, 1.1 equiv), pyridine (0.32 mL, 4 mmol, 2 equiv), and dry DMF (6 mL). The crude 3,5-diethylisoxazole-4-sulfonyl chloride was added as a solution in DMF (1 mL). The reaction was stirred at room temperature overnight. The reaction was extracted 3x with EtOAc and aq. LiCl. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated via rotary evaporation.

The title compound was isolated as a white solid in a 17% yield (88.7 mg, 0.34 mmol) after purification by flash column chromatography (20% EtOAc in hexanes).

¹H NMR (500 MHz, CDCl₃) δ 3.31 – 3.20 (m, 4H), 3.06 (q, *J* = 7.6 Hz, 2H), 2.83 (q, *J* = 7.5 Hz, 2H), 1.95 – 1.84 (m, 4H), 1.32 (td, *J* = 7.6, 2.6 Hz, 6H).

¹³C NMR (126 MHz, CDCl₃) δ 177.7, 162.6, 113.6, 77.5, 77.2, 76.8, 47.4, 25.5, 20.6, 19.7, 11.9, 11.7.

HRMS (APCI/QTOF) *m/z*: [M+H]⁺ calculated for C₁₁H₁₉N₂O₃S⁺ 259.1111; found 259.1113.



3-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazole (1aj)

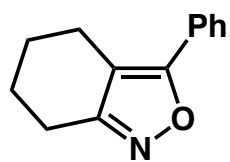
Synthesized according to previously published procedure.⁴¹ The title compound was isolated as a white solid in a 69% yield (403.1 mg, 1.72 mmol) after recrystallization from EtOH/H₂O.

Characterization for 3-(4-chlorophenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazole matches previously reported data:

¹H NMR (500 MHz, CDCl₃) δ 7.71 – 7.66 (m, 2H), 7.46 – 7.39 (m, 2H), 2.75 (tt, *J* = 6.3, 3.1 Hz, 2H), 2.62 (tt, *J* = 5.9, 1.6 Hz, 2H), 1.95 – 1.85 (m, 2H), 1.86 – 1.76 (m, 2H).

The following isoxazoles provided only Conia-Ene type products as the major product of the standard reaction conditions (GP1): **1af**, **1ag**, **1ah**, **1ai**, and **1aj**.

12. XYZ Coordinates of Lowest Energy Conformers and Boltzmann-averaged Steric Descriptors

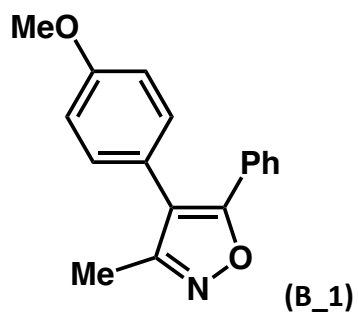


(A_1)

C	-1.031661	0.100709	0.004585
C	0.162727	-0.573317	-0.051345
C	1.562492	-0.162581	-0.034022
C	1.91916	1.175297	-0.277737
C	3.256989	1.563184	-0.248515
C	4.257323	0.625878	0.017587
C	3.911291	-0.707434	0.253079
C	2.576432	-1.101365	0.22897
O	-0.085047	-1.910129	-0.122938
N	-1.474037	-2.132634	-0.117705
C	-2.011496	-0.935183	-0.040533
C	-3.490655	-0.685342	0.022345
C	-3.784695	0.791843	-0.296259
C	-2.863037	1.726237	0.501988
C	-1.386492	1.556957	0.094678
H	1.155056	1.908542	-0.506633
H	3.517905	2.599646	-0.440615
H	5.299239	0.931042	0.038999
H	4.683658	-1.442389	0.459596
H	2.309352	-2.135195	0.418423
H	-3.846979	-0.918047	1.034776
H	-4.021198	-1.356877	-0.660701

H	-4.834037	1.009081	-0.071391
H	-3.642839	0.971408	-1.370436
H	-2.972555	1.508763	1.572983
H	-3.160563	2.769901	0.356011
H	-0.733705	2.07459	0.807271
H	-1.224965	2.039705	-0.879759

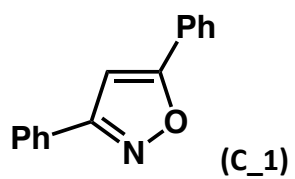
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
A_boltz		45.26	52.66	48.77	48.87
A_1	0.00	45.26	52.66	48.77	



C	0.459624	3.807277	0.066561
C	-0.612049	2.765662	0.008952
N	-1.879274	3.117086	0.002569
O	-2.605584	1.916318	-0.035217
C	-1.744062	0.866969	-0.044719
C	-2.340195	-0.466586	-0.102835
C	-3.641253	-0.679378	0.383528
C	-4.215796	-1.946852	0.321175
C	-3.502744	-3.01587	-0.226205
C	-2.211471	-2.808843	-0.718715
C	-1.632078	-1.544094	-0.661923
C	-0.452837	1.339418	-0.012676
C	0.813163	0.593759	0.078675
C	1.886782	0.88026	-0.772268
C	3.09744	0.19079	-0.679495
C	3.247813	-0.814532	0.282377
O	4.37915	-1.55134	0.461622
C	5.493426	-1.280781	-0.384833
C	2.180134	-1.113451	1.144084
C	0.986412	-0.415689	1.04415

H	0.985223	3.886709	-0.890945
H	1.2027	3.549243	0.827625
H	0.027463	4.782333	0.303575
H	-4.1926	0.149837	0.8137
H	-5.220315	-2.100359	0.704045
H	-3.951203	-4.003821	-0.271555
H	-1.655947	-3.633495	-1.155209
H	-0.635844	-1.385108	-1.057792
H	1.777357	1.645369	-1.534677
H	3.902841	0.440121	-1.359294
H	5.245956	-1.459829	-1.437845
H	6.279003	-1.970009	-0.073342
H	5.842956	-0.248603	-0.264237
H	2.313582	-1.890725	1.88975
H	0.171361	-0.649449	1.721986

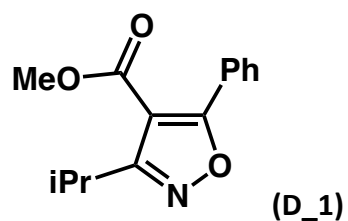
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
B_boltz		42.15	55.87	51.34	45.87
B_1	0	42.15	55.87	51.34	



C	-1.097379	-0.264225	-0.000076
C	-2.531874	0.000424	-0.000017
C	-3.45768	-1.055969	0.000212
C	-4.824656	-0.788526	0.000281
C	-5.284315	0.530356	0.000128
C	-4.367578	1.585341	-0.000105
C	-3.000377	1.325041	-0.000179
C	0.008376	0.539979	0.000073
C	1.11306	-0.362011	-0.000083
C	2.55009	-0.042612	-0.000006
C	3.509143	-1.069063	0.00008
C	4.867163	-0.763887	0.000143
C	5.289475	0.568764	0.000126
C	4.342656	1.594238	0.000043
C	2.981517	1.291697	-0.000023
N	0.700353	-1.619668	-0.000314
O	-0.696317	-1.561091	-0.000311
H	-3.102062	-2.080409	0.000344
H	-5.532166	-1.612199	0.000462
H	-6.350524	0.735848	0.000184
H	-4.718378	2.612867	-0.000235
H	-2.294149	2.149164	-0.000386

H	0.034275	1.617707	0.000316
H	3.180027	-2.102589	0.000101
H	5.598347	-1.566898	0.00021
H	6.349446	0.804996	0.000178
H	4.661702	2.632217	0.000028
H	2.255812	2.098404	-0.000098

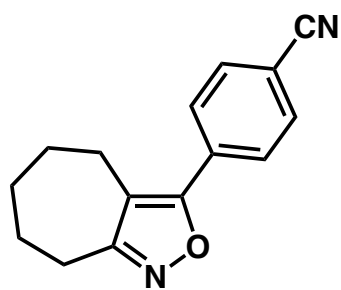
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
C_boltz		43.4	43.00	43.66	42.74
C_1	0.00	43.4	43.00	43.66	



O	-1.785177	2.231951	0.11795
C	-0.771844	1.566079	0.198901
O	0.426662	2.093616	0.462445
C	0.464969	3.517032	0.613715
C	-0.732868	0.107135	0.049677
C	0.334221	-0.753632	-0.015544
C	1.793625	-0.633378	-0.074811
C	2.57729	-1.573107	0.601426
C	3.962067	-1.501265	0.536085
C	4.573007	-0.500283	-0.212441
C	3.795321	0.428074	-0.898643
C	2.4107	0.364557	-0.832774
O	-0.131316	-2.009262	-0.036909
N	-1.523171	-2.006278	0.019855
C	-1.882089	-0.75329	0.060789
C	-3.336356	-0.371863	0.090937
C	-3.773763	0.103599	-1.301018
C	-4.219996	-1.513205	0.591535
H	1.511908	3.763089	0.779594
H	-0.140611	3.823753	1.468118
H	0.094202	4.005855	-0.288578
H	2.096877	-2.352017	1.18303

H	4.564291	-2.228126	1.070837
H	5.655563	-0.445268	-0.264289
H	4.268928	1.202819	-1.492356
H	1.806711	1.083099	-1.371784
H	-3.424467	0.478146	0.773398
H	-3.681037	-0.706818	-2.031309
H	-3.167696	0.948542	-1.633929
H	-4.82039	0.421272	-1.274722
H	-4.171172	-2.374183	-0.080951
H	-5.259981	-1.178524	0.641021
H	-3.917994	-1.846851	1.588058

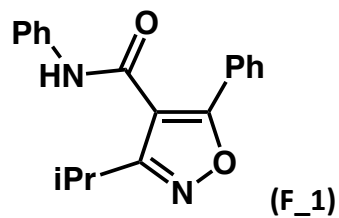
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
D_boltz		51.60	55.60	50.41	56.9
D_1	0	51.62	55.3	50.47	
D_2	0.23	51.72	55.09	50.14	
D_3	0.75	51.31	57.35	50.87	
D_4	1.3	51.43	56.93	50.48	



N	-6.407713	-0.791982	0.232392
C	-5.276736	-0.529381	0.152701
C	-3.8859	-0.207086	0.055619
C	-3.033387	-1.008634	-0.721052
C	-1.684455	-0.692175	-0.813985
C	-3.376691	0.915104	0.731587
C	-2.026467	1.22032	0.639018
C	-1.161833	0.41627	-0.125618
C	0.25832	0.747943	-0.206709
C	1.406437	0.010099	-0.340622
C	1.598222	-1.475815	-0.393034
C	2.596275	-2.012315	0.652016
C	4.073009	-1.671892	0.403013
C	4.478737	-0.204975	0.60459
C	3.91928	0.774497	-0.442388
C	2.443458	0.998158	-0.326205
N	1.963151	2.214842	-0.185163
O	0.572576	2.068731	-0.107216
H	-3.432613	-1.863081	-1.255899
H	-1.040718	-1.291229	-1.446658
H	-4.038894	1.533815	1.326877

H	-1.62986	2.08007	1.166655
H	1.936191	-1.774325	-1.39576
H	0.634762	-1.967853	-0.233782
H	2.496164	-3.104424	0.667738
H	2.297434	-1.65681	1.647235
H	4.346466	-1.98313	-0.615886
H	4.678792	-2.285071	1.082022
H	5.572642	-0.140553	0.565311
H	4.181458	0.128259	1.607814
H	4.141605	0.388885	-1.447075
H	4.418289	1.744869	-0.355059

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
E_boltz		47.53	54.77	49.86	52.21
E_1	0.00	47.55	54.68	49.82	
E_2	0.22	47.49	54.89	49.93	
E_3	2.03	47.63	54.98	49.68	
E_4	3.42	48.47	55.19	49.99	
E_5	3.52	47.59	54.70	49.58	
E_6	4.22	48.10	55.98	50.54	
E_7	4.41	48.44	56.02	51.01	
E_8	4.59	48.16	55.76	50.44	

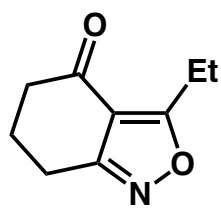


O	-1.858012	0.395344	2.569568
C	-1.079333	0.447735	1.615016
N	-0.02071	1.317175	1.613657
C	0.853407	1.656842	0.545663
C	2.229474	1.70741	0.786413
C	3.105326	2.023553	-0.250105
C	2.615178	2.279905	-1.532052
C	1.239009	2.242204	-1.765661
C	0.35507	1.948757	-0.728484
C	-1.255061	-0.429509	0.432154
C	-0.332989	-1.189715	-0.241619
C	1.095437	-1.428228	-0.055332
C	1.950569	-1.491948	-1.165128
C	3.318432	-1.672602	-0.978266
C	3.840056	-1.799393	0.311309
C	2.988964	-1.749594	1.417774
C	1.620827	-1.564739	1.238267
O	-0.946886	-1.820266	-1.266815
N	-2.315005	-1.475741	-1.277998
C	-2.489733	-0.665939	-0.258513
C	-3.829593	-0.046137	0.041176
C	-3.784331	1.465268	-0.257039

C	-4.97397	-0.72834	-0.715784
H	0.130352	1.773054	2.506887
H	2.606989	1.469601	1.775541
H	4.173583	2.050808	-0.057682
H	3.299954	2.512044	-2.342084
H	0.846998	2.456624	-2.755481
H	-0.714448	1.941427	-0.905068
H	1.541824	-1.37426	-2.162939
H	3.978847	-1.708153	-1.839245
H	4.907612	-1.938355	0.453543
H	3.390571	-1.856639	2.420756
H	0.956129	-1.53374	2.095275
H	-3.988791	-0.166514	1.118882
H	-3.010137	1.971122	0.328246
H	-4.746588	1.924422	-0.00763
H	-3.584927	1.642555	-1.319962
H	-5.928371	-0.276543	-0.427244
H	-5.01712	-1.799154	-0.494258
H	-4.853725	-0.612143	-1.797908

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
F_boltz		54.74	62.87	57.68	59.67
F_1	0.00	55.26	63.57	59.05	
F_2	0.14	55.27	65.60	59.51	
F_3	0.50	55.33	63.07	59.03	
F_4	0.90	52.00	56.75	51.48	
F_5	1.16	52.04	56.37	51.41	
F_6	1.17	51.81	58.85	51.98	

F_7	2.05	59.43	62.40	54.37	
F_8	2.27	58.92	63.33	54.82	
F_9	2.53	52.77	56.82	50.62	
F_10	3.07	52.68	55.97	50.59	
F_11	3.17	55.55	65.53	56.79	
F_12	3.21	52.81	55.68	50.31	
F_13	3.45	56.85	64.84	55.18	

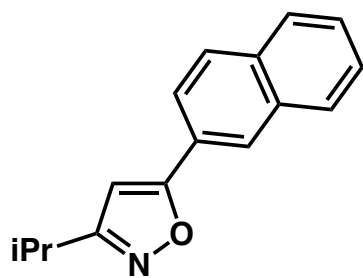


(G_1)

O	0.209583	2.332005	-0.359176
C	-0.518161	1.348018	-0.252434
C	-0.012139	-0.019865	-0.202117
C	1.264695	-0.526727	-0.279857
C	2.601181	0.114629	-0.411373
C	3.040389	0.79038	0.901051
O	1.207602	-1.860799	-0.170057
N	-0.150717	-2.280433	-0.009366
C	-0.844024	-1.170321	-0.038195
C	-2.33383	-1.071171	0.083111
C	-2.698655	0.323292	0.62775
C	-2.038024	1.453504	-0.184136
H	2.537238	0.869238	-1.201887
H	3.328192	-0.642324	-0.719957
H	3.099014	0.0632	1.716795
H	2.329323	1.5735	1.177171
H	4.026987	1.245526	0.771667
H	-2.725346	-1.867556	0.722501
H	-2.779336	-1.206281	-0.911743
H	-2.38152	0.395875	1.675267
H	-3.785238	0.449894	0.612356
H	-2.293985	2.439059	0.215341

H -2.406384 1.422829 -1.220892

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
G_boltz		44.79	53.90	45.91	52.59
G_1	0.00	44.85	54.35	45.93	
G_2	0.12	44.73	53.36	45.89	

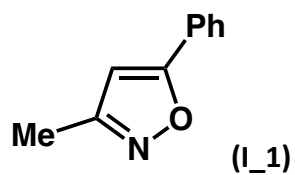


(H_1)

C	-5.15531	0.588671	1.269428
C	-4.729993	-0.168154	0.00009
C	-5.155356	0.586173	-1.27072
C	-3.246081	-0.41503	0.000295
N	-2.776173	-1.645361	0.001015
O	-1.374007	-1.516396	0.000971
C	-1.045272	-0.199966	0.00022
C	0.370546	0.14642	0.000096
C	1.346561	-0.836293	0.000014
C	2.72243	-0.501171	-0.000072
C	3.737218	-1.496274	-0.000166
C	5.067532	-1.14163	-0.000229
C	5.444302	0.224436	-0.000197
C	4.483655	1.212208	-0.000118
C	3.104603	0.879807	-0.000061
C	2.083469	1.869335	0.000012
C	0.757099	1.518827	0.000081
C	-2.193202	0.545088	-0.000245
H	-4.68791	1.579303	1.310576
H	-4.869329	0.039719	2.172562
H	-6.241684	0.727565	1.279717

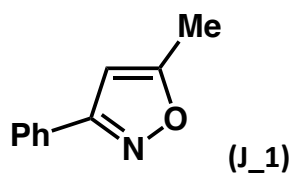
H	-5.214062	-1.151962	0.001056
H	-4.869349	0.035477	-2.172782
H	-4.687996	1.576736	-1.313789
H	-6.241737	0.724994	-1.281274
H	1.061374	-1.883334	0.00001
H	3.44338	-2.54253	-0.000186
H	5.835502	-1.909434	-0.000302
H	6.497369	0.489793	-0.000239
H	4.769469	2.260711	-0.000097
H	2.37008	2.917393	0.00003
H	-0.0064	2.289747	0.000175
H	-2.286658	1.619831	-0.000906

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
H_boltz		31.98	40.16	37.05	34.66
H_1	0.00	32.11	40.40	36.79	
H_2	0.29	32.11	39.77	36.93	
H_3	0.79	32.20	40.39	37.38	
H_4	0.79	31.27	40.39	37.38	
H_5	1.09	32.21	39.77	37.51	
H_6	1.09	31.27	39.77	37.51	



C	-4.173481	0.671598	-0.000013
C	-2.770855	0.151884	0.000009
N	-2.54171	-1.145861	0.000007
O	-1.142191	-1.282203	0.000002
C	-0.570244	-0.051794	0.000004
C	0.887519	0.015752	0.000001
C	1.661547	-1.156498	-0.000002
C	3.052289	-1.078026	-0.000005
C	3.687623	0.16579	-0.000004
C	2.92282	1.335649	0
C	1.532798	1.263954	0.000002
C	-1.556898	0.895855	0.000009
H	-4.354657	1.292976	-0.883475
H	-4.354665	1.293052	0.883391
H	-4.887443	-0.155511	0.000015
H	1.169498	-2.122838	-0.000003
H	3.640892	-1.990531	-0.000008
H	4.771915	0.224095	-0.000005
H	3.410219	2.305924	0.000001
H	0.945643	2.176795	0.000005
H	-1.450615	1.969704	0.000011

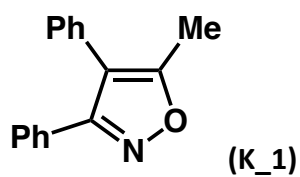
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
I_boltz		34.04	39.89	43.08	31.52
I_1	0.00	34.04	39.89	43.08	



C	-4.153846	0.687876	0.001637
C	-2.737208	0.235588	0.000511
C	-1.541458	0.885705	0.001696
C	-0.563136	-0.156686	-0.000395
C	0.903785	-0.030781	-0.000105
C	1.508245	1.234733	-0.001672
C	2.897525	1.355198	-0.00142
C	3.701007	0.213926	0.000376
C	3.1062	-1.051319	0.001923
C	1.719763	-1.174539	0.001716
N	-1.138437	-1.347189	-0.002754
O	-2.517744	-1.101633	-0.002145
H	-4.196168	1.778994	0.00368
H	-4.682113	0.314661	0.885836
H	-4.682516	0.317995	-0.883732
H	-1.384358	1.952827	0.003977
H	0.895111	2.130008	-0.003259
H	3.350617	2.342118	-0.002666
H	4.782916	0.308178	0.000588
H	3.724973	-1.943892	0.003371
H	1.257283	-2.155711	0.003042

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
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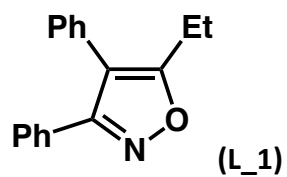
J_boltz		42.92	39.85	34.20	50.01
J_1	0.00	42.92	39.85	34.20	



C	-2.840436	2.574189	0.092363
C	-1.417314	2.151665	0.011926
C	-0.799092	0.929198	-0.005449
C	-1.434221	-0.396554	0.076079
C	-2.520073	-0.722854	-0.75097
C	-3.134588	-1.972199	-0.656892
C	-2.666486	-2.916787	0.257725
C	-1.581926	-2.603607	1.08176
C	-0.972724	-1.353892	0.994773
C	0.601322	1.256503	-0.054234
C	1.760829	0.347386	-0.104692
C	1.704335	-0.842834	-0.8457
C	2.81209	-1.686571	-0.903888
C	3.986303	-1.353097	-0.224675
C	4.0502	-0.16749	0.511187
C	2.944296	0.678552	0.572219
N	0.793284	2.561543	-0.071001
O	-0.487036	3.132529	-0.023839
H	-2.963087	3.372312	0.831211
H	-3.464207	1.724367	0.377767
H	-3.196458	2.952075	-0.873143
H	-2.870871	0.000375	-1.481052
H	-3.973331	-2.208859	-1.305143

H	-3.14131	-3.891037	0.327735
H	-1.213478	-3.332503	1.797838
H	-0.136125	-1.110784	1.642057
H	0.797035	-1.100875	-1.380567
H	2.758708	-2.603925	-1.482649
H	4.846892	-2.014176	-0.268144
H	4.959764	0.096097	1.042853
H	2.984674	1.596235	1.149762

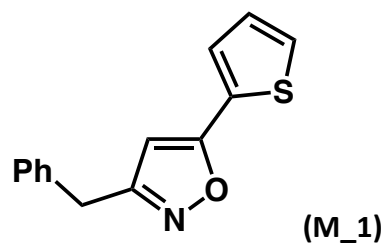
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
K_boltz		50.92	55.91	42.67	66.72
K_1	0.00	50.92	55.91	42.67	



C	3.89309	-2.029691	-0.84223
C	3.171222	-1.55518	0.431296
C	1.688374	-1.540916	0.283459
C	0.763126	-0.538318	0.155759
C	1.008053	0.913501	0.17421
C	0.252369	1.753492	1.008945
C	0.493119	3.125235	1.039254
C	1.497048	3.681405	0.241691
C	2.255282	2.855854	-0.589813
C	2.009294	1.482841	-0.627666
C	-0.490982	-1.239416	0.07233
C	-1.848514	-0.687572	-0.088682
C	-2.072771	0.429956	-0.90709
C	-3.362326	0.932538	-1.070804
C	-4.440497	0.327211	-0.420861
C	-4.224222	-0.787864	0.392223
C	-2.936004	-1.293115	0.558745
N	-0.320104	-2.546125	0.136109
O	1.061949	-2.740151	0.274701
H	4.975653	-2.034239	-0.682679
H	3.672723	-1.369429	-1.687567
H	3.580389	-3.042981	-1.112759
H	3.49392	-0.543323	0.694104

H	3.435325	-2.210427	1.269808
H	-0.521887	1.32357	1.636372
H	-0.099779	3.760678	1.690783
H	1.684709	4.750808	0.267519
H	3.033669	3.279838	-1.217557
H	2.583724	0.84835	-1.295808
H	-1.239053	0.897255	-1.419376
H	-3.525288	1.795996	-1.708961
H	-5.444002	0.723035	-0.546743
H	-5.058327	-1.261345	0.901684
H	-2.7606	-2.153474	1.196215

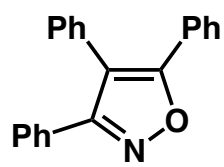
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
L_boltz		51.27	57.79	48.28	61.37
L_1	0.00	51.22	57.58	48.29	
L_2	0.27	51.25	57.31	48.26	
L_3	0.44	51.41	58.85	48.30	



C	1.367554	0.684015	-0.136526
C	2.661866	0.080927	0.063736
C	3.760403	0.625422	0.692723
C	4.880061	-0.252873	0.71297
C	4.625534	-1.45229	0.102394
S	3.006275	-1.535764	-0.513129
C	0.208192	0.265064	-0.731216
C	-0.684553	1.361791	-0.57522
C	-2.117284	1.451364	-1.017163
C	-2.974742	0.387427	-0.356622
C	-3.570108	-0.627517	-1.111281
C	-4.345466	-1.611933	-0.492985
C	-4.530373	-1.590809	0.889755
C	-3.935767	-0.580703	1.651824
C	-3.162209	0.399306	1.031952
N	-0.120924	2.364513	0.066064
O	1.193219	1.940935	0.348064
H	3.756377	1.620023	1.12204
H	5.834123	-0.003322	1.162458
H	5.289694	-2.296108	-0.025302
H	0.006926	-0.682735	-1.206841

H	-2.164346	1.340692	-2.1059
H	-2.488638	2.452854	-0.774986
H	-3.427754	-0.647221	-2.18878
H	-4.802845	-2.39364	-1.092918
H	-5.132724	-2.355202	1.372141
H	-4.074873	-0.557678	2.729019
H	-2.694262	1.180348	1.626129

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
M_boltz		43.19	44.14	43.89	43.44
M_1	0.00	43.27	44.83	43.94	
M_2	1.25	42.76	40.69	43.08	

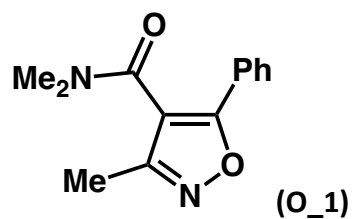


(N_1)

C	-0.03252	-0.315713	-0.012237
C	0.055882	1.156284	0.006778
C	-0.571518	1.921718	-0.987626
C	-0.48117	3.312901	-0.970832
C	0.242647	3.956722	0.035524
C	0.874008	3.201922	1.026687
C	0.78103	1.810817	1.013624
C	-1.15551	-1.108454	-0.010067
C	-2.591512	-0.840402	0.042321
C	-3.079943	0.34626	0.614957
C	-4.450465	0.58786	0.660998
C	-5.349571	-0.348331	0.143876
C	-4.870384	-1.534335	-0.417201
C	-3.500774	-1.782104	-0.468674
O	-0.781065	-2.412909	-0.043013
N	0.613944	-2.501943	-0.068518
C	1.052656	-1.257008	-0.042656
C	2.502238	-0.989917	-0.061873
C	3.02201	0.103049	-0.772044
C	4.396383	0.333894	-0.796333
C	5.265448	-0.520476	-0.114062
C	4.754277	-1.612686	0.591108
C	3.38087	-1.846888	0.618445

H	-1.128521	1.419273	-1.772563
H	-0.971598	3.893536	-1.746674
H	0.315144	5.040272	0.046519
H	1.437535	3.696198	1.812624
H	1.270163	1.223649	1.784716
H	-2.388101	1.068813	1.031112
H	-4.817364	1.506699	1.108421
H	-6.417637	-0.155874	0.180864
H	-5.563897	-2.266865	-0.81906
H	-3.128062	-2.70027	-0.909823
H	2.352366	0.763517	-1.311097
H	4.788518	1.180767	-1.351628
H	6.335551	-0.335837	-0.131256
H	5.42489	-2.279512	1.124979
H	2.977437	-2.688179	1.172314

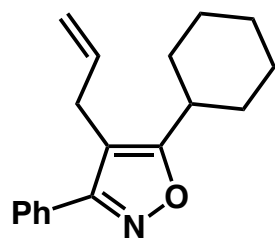
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
N_boltz		51.44	58.86	51.90	58.34
N_1	0.00	51.44	58.86	51.90	



O	-2.344524	1.23952	-1.263946
C	-1.565895	0.968372	-0.33998
N	-1.034756	1.916358	0.479772
C	-0.269513	1.65178	1.690319
C	-1.280729	3.32329	0.192957
C	-1.193257	-0.456314	-0.111673
C	0.03072	-1.078101	-0.068703
C	1.411154	-0.608393	-0.148777
C	2.443088	-1.349033	0.4511
C	3.757346	-0.89262	0.390657
C	4.056603	0.30316	-0.266683
C	3.035104	1.038849	-0.87283
C	1.719406	0.586195	-0.82047
O	-0.158211	-2.412701	0.064133
N	-1.537341	-2.690754	0.106514
C	-2.137952	-1.529036	-0.016823
C	-3.628719	-1.431847	-0.020902
H	0.781958	1.930896	1.557662
H	-0.327032	0.598241	1.95624
H	-0.687839	2.243019	2.512115
H	-1.774715	3.405995	-0.773072
H	-0.328233	3.864715	0.171734

H	-1.91752	3.767916	0.967182
H	2.206913	-2.27165	0.970166
H	4.548102	-1.468513	0.861612
H	5.0817	0.658513	-0.309693
H	3.263895	1.962509	-1.395429
H	0.934371	1.150122	-1.311553
H	-4.075726	-2.427283	0.025645
H	-3.966492	-0.918563	-0.925045
H	-3.97697	-0.847503	0.837783

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
O_boltz		42.43	57.20	53.88	45.04
O_1	0.00	42.43	57.20	53.88	



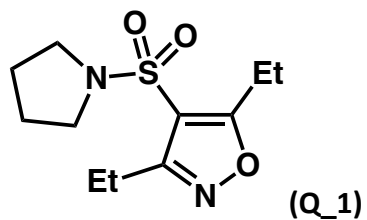
(P_1)

C	0.157981	2.888554	-0.779022
C	0.322285	2.730655	0.535292
C	0.386844	1.411592	1.27209
C	0.242136	0.190521	0.415108
C	-0.921281	-0.416338	0.032823
C	-2.358216	-0.090946	0.265358
C	-3.033839	0.415229	-1.030584
C	-4.505784	0.767356	-0.78593
C	-5.275971	-0.417603	-0.189094
C	-4.607624	-0.921782	1.096478
C	-3.136799	-1.284248	0.859223
O	-0.639912	-1.509085	-0.717242
N	0.750107	-1.640415	-0.847295
C	1.265126	-0.62619	-0.17431
C	2.728468	-0.476831	-0.084296
C	3.322957	0.794464	-0.082703
C	4.709734	0.921235	-0.002535
C	5.517249	-0.215061	0.073539
C	4.931796	-1.484021	0.065543
C	3.547117	-1.615344	-0.011074
H	0.122244	3.876373	-1.229282

H	0.053346	2.038448	-1.447755
H	0.424629	3.609446	1.171796
H	-0.393061	1.41004	2.045815
H	1.33556	1.362037	1.822708
H	-2.378268	0.730198	0.993954
H	-2.961477	-0.36975	-1.795084
H	-2.486511	1.285842	-1.409496
H	-4.96969	1.091906	-1.725168
H	-4.561063	1.620677	-0.094741
H	-5.306772	-1.234976	-0.923954
H	-6.315904	-0.132144	0.010656
H	-5.144657	-1.792956	1.490517
H	-4.666718	-0.139321	1.866698
H	-3.07308	-2.130162	0.162607
H	-2.662622	-1.604464	1.794493
H	2.702799	1.680133	-0.172665
H	5.158987	1.910052	-0.005763
H	6.596652	-0.113525	0.138193
H	5.554431	-2.37189	0.125755
H	3.086645	-2.597823	-0.005724

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
P_boltz		52.01	57.85	55.58	54.13
P_1	0.00	52.19	57.83	56.00	
P_2	0.89	52.53	60.22	55.41	
P_3	1.00	53.41	57.99	55.56	
P_4	1.10	50.38	55.49	53.97	
P_5	1.27	50.16	55.95	54.85	

P_6	1.35	51.88	55.77	53.37	
P_7	1.44	53.74	60.48	55.21	
P_8	1.69	52.55	58.58	59.87	
P_9	1.69	49.91	55.76	55.31	
P_10	1.90	52.19	58.51	53.31	
P_11	2.03	50.64	57.81	53.56	
P_12	2.28	51.60	58.32	53.38	
P_13	2.37	50.38	57.82	54.13	
P_14	2.38	52.46	59.75	56.06	
P_15	2.46	52.92	61.99	60.57	
P_16	2.48	49.56	56.11	55.17	
P_17	2.55	54.20	59.80	59.41	
P_18	2.55	50.53	57.56	53.74	
P_19	2.78	50.22	57.69	54.42	
P_20	2.79	50.70	56.23	57.89	
P_21	3.01	50.53	56.65	58.68	
P_22	3.08	52.28	56.62	57.34	
P_23	3.40	52.76	61.96	61.39	
P_24	3.44	51.55	57.00	58.10	
P_25	3.49	50.33	56.47	59.10	
P_26	3.61	50.45	58.00	59.47	
P_27	3.81	51.46	59.68	58.44	
P_28	3.95	54.81	62.22	58.82	
P_29	3.98	49.23	55.59	54.90	
P_30	4.11	53.01	61.70	58.48	
P_31	4.34	53.12	60.61	57.96	
P_32	4.73	52.57	62.52	58.44	
P_33	4.75	53.10	59.99	57.15	
P_34	6.10	52.18	57.82	56.13	
P_35	6.39	52.28	58.00	57.35	
P_36	6.96	52.61	60.21	55.50	
P_37	7.20	50.42	55.43	54.03	
P_38	7.36	50.19	55.93	54.94	
P_39	7.41	53.17	59.63	60.11	
P_40	7.47	50.52	55.66	55.43	
P_41	7.67	50.26	56.05	56.12	
P_42	7.74	50.00	55.77	55.36	
P_43	7.79	50.33	56.11	56.33	
P_44	8.12	49.99	55.84	56.62	

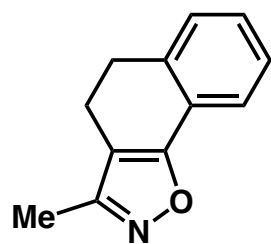


O	0.398593	1.200547	1.929605
S	0.387369	-0.067064	1.188985
C	-0.830049	0.071777	-0.078635
C	-1.515786	-0.963123	-0.669296
C	-1.645666	-2.424621	-0.405825
C	-2.760179	-2.711534	0.618193
O	-2.294052	-0.454172	-1.637241
N	-2.129576	0.947416	-1.704503
C	-1.257079	1.254841	-0.773132
C	-0.928406	2.695945	-0.514673
C	-1.792857	3.278171	0.616367
N	1.864734	-0.206117	0.459183
C	2.159972	-1.444764	-0.313739
C	3.193134	-0.987869	-1.363664
C	3.709187	0.363098	-0.840787
C	2.464412	0.975828	-0.200918
O	0.139141	-1.336986	1.884728
H	-0.696592	-2.806446	-0.026372
H	-1.861302	-2.925577	-1.354698
H	-2.520116	-2.245198	1.577422
H	-2.85491	-3.791067	0.768567
H	-3.722661	-2.324805	0.269527

H	-1.096732	3.252695	-1.441491
H	0.128156	2.793156	-0.255334
H	-2.855829	3.210778	0.363531
H	-1.541577	4.331771	0.774566
H	-1.618491	2.73666	1.549403
H	1.259579	-1.843382	-0.792528
H	2.54893	-2.201867	0.370374
H	2.698378	-0.846415	-2.329805
H	3.987767	-1.725497	-1.497816
H	4.119291	0.998017	-1.629974
H	4.480666	0.214778	-0.077992
H	1.798732	1.386247	-0.973374
H	2.673145	1.748478	0.539378

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
Q_boltz		50.95	63.28	51.28	62.87
Q_1	0.00	51.42	64.69	52.14	
Q_2	0.10	50.35	62.51	50.39	
Q_3	0.13	50.11	62.65	50.90	
Q_4	0.19	50.93	63.00	50.11	
Q_5	0.31	50.87	62.85	50.17	
Q_6	0.43	50.74	62.99	50.40	
Q_7	0.53	50.72	61.20	49.91	
Q_8	0.55	49.52	62.56	51.47	
Q_9	0.64	52.32	62.66	50.44	
Q_10	0.65	49.69	62.61	51.55	
Q_11	0.67	55.10	67.74	55.25	
Q_12	0.69	55.18	68.73	55.39	
Q_13	0.74	48.90	63.35	51.97	
Q_14	0.74	50.49	61.20	50.25	
Q_15	0.79	51.58	62.99	51.62	
Q_16	0.95	49.51	62.86	51.55	

Q_17	0.96	49.72	63.17	52.19	
Q_18	0.96	48.80	63.24	52.05	
Q_19	1.06	54.62	65.89	54.60	
Q_20	1.08	54.76	66.94	54.83	
Q_21	1.26	49.71	60.89	50.97	
Q_22	1.48	49.96	63.72	52.23	
Q_23	1.51	50.33	62.88	50.57	
Q_24	1.53	49.82	62.60	50.85	
Q_25	1.56	48.89	61.25	51.49	
Q_26	1.60	50.17	62.87	50.75	
Q_27	1.75	54.28	67.46	55.64	
Q_28	1.79	48.75	61.13	51.55	
Q_29	1.82	50.20	61.21	50.19	
Q_30	1.84	49.65	62.65	51.24	
Q_31	1.91	49.80	62.62	51.28	
Q_32	2.07	49.68	62.90	51.20	
Q_33	2.14	49.73	62.95	51.27	
Q_34	2.61	49.73	60.80	50.76	
Q_35	2.86	49.69	61.03	50.74	

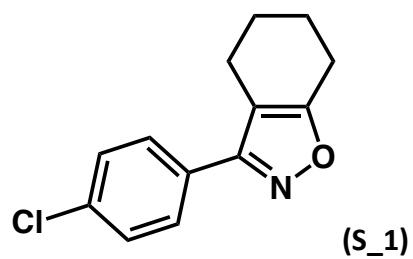


(R_1)

C	4.028654	0.389866	0.154571
C	2.670954	-0.224452	0.032752
N	2.540124	-1.527374	-0.142691
O	1.146448	-1.771666	-0.209553
C	0.506863	-0.590556	-0.074485
C	1.404185	0.426291	0.07697
C	0.947378	1.836617	0.298291
C	-0.435997	2.025767	-0.361467
C	-1.410303	0.885928	-0.111248
C	-2.785103	1.10176	-0.027955
C	-3.674606	0.031332	0.10871
C	-3.19555	-1.279197	0.162398
C	-1.824376	-1.519289	0.090603
C	-0.935575	-0.446575	-0.043641
H	4.144144	0.879664	1.127759
H	4.176707	1.153476	-0.616901
H	4.806231	-0.370573	0.050417
H	1.655394	2.560324	-0.118004
H	0.884641	2.042673	1.376577
H	-0.286143	2.103008	-1.448561
H	-0.881116	2.972269	-0.040216

H	-3.167108	2.118135	-0.07665
H	-4.741671	0.223114	0.172713
H	-3.886068	-2.110453	0.267602
H	-1.436605	-2.531641	0.147528

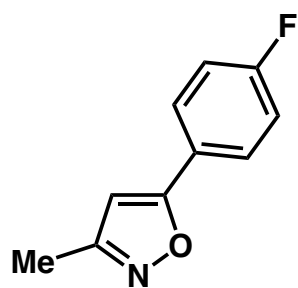
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
R_boltz		38.98	49.29	49.22	39.04
R_1	0.00	38.98	49.29	49.22	



Cl	5.193238	-0.55331	0.042402
C	3.476062	-0.165147	-0.003024
C	3.051697	1.09918	0.405606
C	1.693377	1.397219	0.37364
C	2.5709	-1.127132	-0.444006
C	1.21319	-0.8141	-0.47377
C	0.756631	0.44747	-0.065751
C	-0.676302	0.779419	-0.101684
N	-1.054425	2.044735	-0.199172
O	-2.458905	2.02644	-0.180398
C	-2.87415	0.745652	-0.074968
C	-1.806592	-0.098737	-0.02212
C	-1.960134	-1.583622	0.14349
C	-3.393238	-1.903781	0.615441
C	-4.452406	-1.133627	-0.190953
C	-4.318788	0.392884	-0.003724
H	3.770758	1.834119	0.749551
H	1.348813	2.372738	0.698446
H	2.918572	-2.102888	-0.763855
H	0.512562	-1.557141	-0.835967
H	-1.22817	-1.973019	0.860511

H	-1.764059	-2.096227	-0.808722
H	-3.488491	-1.640723	1.677262
H	-3.572168	-2.981074	0.534811
H	-5.458131	-1.447403	0.106003
H	-4.341345	-1.375016	-1.255915
H	-4.723905	0.697363	0.970972
H	-4.888743	0.936804	-0.765595

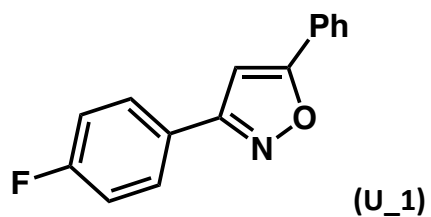
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
S_boltz		48.29	52.79	45.92	55.51
S_1	0.00	48.29	52.79	45.92	



(T_1)

F	-4.571507	-0.153984	0.000014
C	-3.222587	-0.099781	0.000002
C	-2.599457	1.142718	0.000206
C	-1.208748	1.192268	0.000211
C	-2.503124	-1.290265	-0.000161
C	-1.113925	-1.229236	-0.000171
C	-0.449962	0.009529	0.000011
C	1.0076	0.057549	-0.000004
C	1.98196	-0.902542	0.000186
C	3.204962	-0.17329	0.000037
C	4.600848	-0.71076	0.000184
N	2.992315	1.127153	-0.000258
O	1.593902	1.280804	-0.000303
H	-3.197728	2.047086	0.000354
H	-0.706154	2.152639	0.000384
H	-3.028089	-2.238996	-0.000311
H	-0.543085	-2.151751	-0.000342
H	1.862583	-1.975005	0.000449
H	4.773864	-1.334408	0.883662
H	5.325314	0.107132	0.00022
H	4.77403	-1.334473	-0.883217

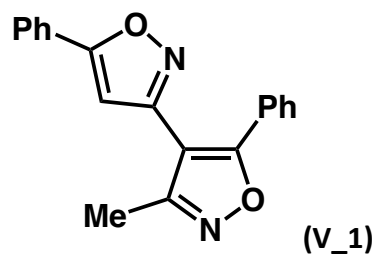
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
T_boltz		34.03	39.89	43.09	31.50
T_1	0.00	34.03	39.89	43.09	



F	6.1731	0.631079	-0.000055
C	4.846724	0.375398	-0.00003
C	4.417651	-0.94798	-0.000123
C	3.05114	-1.205407	-0.000099
C	2.120206	-0.152675	0.000018
C	2.590163	1.168863	0.000108
C	3.956396	1.441501	0.000084
C	0.676257	-0.433017	0.000048
N	0.23124	-1.679534	0.000116
O	-1.163401	-1.584356	0.000108
C	-1.530375	-0.277564	0.000032
C	-2.957427	0.024528	0.000002
C	-3.391319	1.360898	-0.000027
C	-4.75131	1.656562	-0.000051
C	-5.695094	0.625712	-0.000059
C	-5.269863	-0.704662	-0.000037
C	-3.910312	-1.007511	-0.000007
C	-0.404002	0.497706	0
H	5.145904	-1.751556	-0.000216
H	2.695789	-2.229745	-0.000177
H	1.890648	1.997706	0.000203
H	4.330576	2.459244	0.000153

H	-2.664156	2.166628	-0.000028
H	-5.075302	2.692845	-0.000069
H	-6.755611	0.858795	-0.00008
H	-5.998525	-1.509671	-0.000043
H	-3.58146	-2.040851	0.000009
H	-0.350242	1.574369	-0.000076

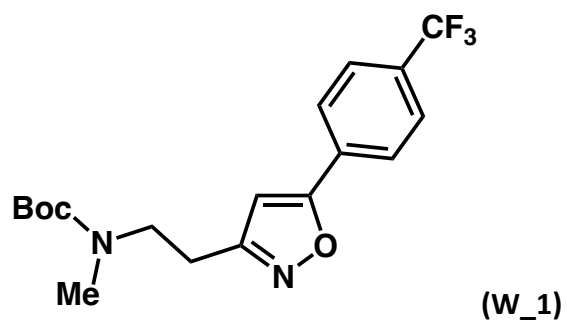
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
U_boltz		43.40	42.99	43.65	42.74
U_1	0.00	43.40	42.99	43.65	



C	-1.994652	-3.948134	-0.229852
C	-2.4669	-2.53129	-0.189718
N	-3.735705	-2.25091	-0.380131
O	-3.836794	-0.850887	-0.291395
C	-2.615299	-0.321258	-0.053471
C	-2.549699	1.132791	0.082873
C	-3.4097	1.946138	-0.673697
C	-3.35453	3.331695	-0.544498
C	-2.446295	3.919037	0.339784
C	-1.597341	3.114161	1.103502
C	-1.649905	1.727787	0.98222
C	-1.692028	-1.339446	0.015972
C	-0.2436	-1.254826	0.158641
N	0.434198	-2.262931	0.685892
O	1.778235	-1.879018	0.6296
C	1.8786	-0.646446	0.06881
C	3.211761	-0.07427	-0.078952
C	3.35929	1.242346	-0.54675
C	4.627936	1.795103	-0.694651
C	5.763295	1.044678	-0.376248
C	5.622401	-0.263747	0.091787

C	4.355797	-0.823802	0.240519
C	0.626281	-0.202522	-0.252411
H	-1.183173	-4.060177	-0.955671
H	-2.819027	-4.60998	-0.505122
H	-1.599114	-4.250085	0.744064
H	-4.108427	1.487323	-1.365104
H	-4.018062	3.953507	-1.137628
H	-2.403293	4.99965	0.436807
H	-0.899753	3.565485	1.802278
H	-1.005365	1.104799	1.592268
H	2.481091	1.832712	-0.7881
H	4.730948	2.813632	-1.056283
H	6.752033	1.478394	-0.491514
H	6.501055	-0.851047	0.340719
H	4.247274	-1.840747	0.601141
H	0.350363	0.724692	-0.726982

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
V_boltz		40.91	53.79	50.39	43.67
V_1	0.00	40.76	53.82	50.57	
V_2	1.13	41.45	53.80	49.85	
V_3	1.31	41.53	53.49	49.50	

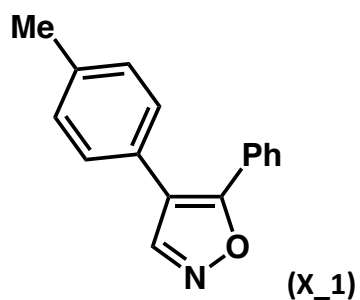


F	-6.175435	-0.190053	1.032858
C	-5.476727	0.255984	-0.035585
C	-4.065169	-0.254858	-0.038151
C	-3.40612	-0.479689	1.174103
C	-2.080927	-0.896015	1.174605
C	-3.395619	-0.448827	-1.248564
C	-2.069206	-0.865579	-1.249182
C	-1.397355	-1.091538	-0.037058
C	0.002157	-1.500082	-0.025746
C	0.902108	-1.741435	0.973387
C	2.11902	-2.035008	0.296572
C	3.466733	-2.287076	0.894136
C	4.197923	-0.968722	1.236455
N	4.486772	-0.149065	0.066901
C	5.517726	-0.622691	-0.848231
C	3.669356	0.859253	-0.368662
O	2.66912	1.099624	0.507271
C	1.713063	2.196631	0.289355
C	2.451092	3.535081	0.336761
C	0.952721	1.997882	-1.023348

C	0.768252	2.056067	1.482841
O	3.855289	1.470301	-1.416995
N	1.968628	-1.98635	-1.011619
O	0.621858	-1.648358	-1.224735
F	-6.154028	-0.1152	-1.14504
F	-5.519763	1.610873	0.011295
H	-3.928591	-0.333916	2.112868
H	-1.575803	-1.070658	2.118362
H	-3.909934	-0.278671	-2.187689
H	-1.549476	-1.015771	-2.188177
H	0.744083	-1.7017	2.039944
H	4.071388	-2.874082	0.196414
H	3.36045	-2.872547	1.813189
H	5.149745	-1.215232	1.719031
H	3.606683	-0.380973	1.936696
H	5.132318	-1.381421	-1.541341
H	6.333451	-1.059631	-0.266077
H	5.896811	0.217415	-1.428919
H	3.151364	3.622529	-0.495219
H	3.001542	3.631365	1.278719
H	1.727557	4.354977	0.277383
H	1.606972	2.141279	-1.883024
H	0.130504	2.719397	-1.075773
H	0.527698	0.992109	-1.068958
H	1.322364	2.134747	2.423635

H	0.256955	1.090023	1.458235
H	0.014862	2.849281	1.455253

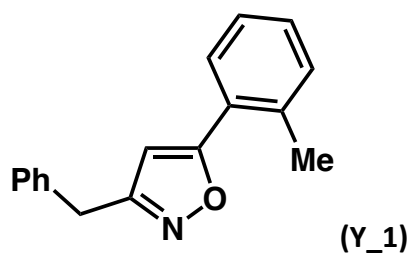
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
W_boltz		50.68	54.31	53.19	51.75
W_1	0.00	51.22	52.33	53.73	
W_2	0.34	51.26	56.08	53.79	
W_3	0.71	49.28	56.02	52.40	
W_4	0.95	51.42	52.19	53.20	
W_5	2.32	48.42	54.08	46.99	
W_6	2.69	48.77	46.99	46.64	
W_7	2.76	49.52	55.41	49.17	
W_8	2.86	48.94	46.63	46.15	
W_9	3.01	48.51	47.03	46.84	
W_10	3.26	41.92	45.27	43.74	
W_11	3.54	41.60	42.79	43.67	
W_12	3.78	41.21	43.29	43.69	
W_13	4.02	41.16	42.84	43.68	



C	-4.914127	-1.676707	0.165387
C	-3.654012	-0.847817	0.135905
C	-3.560946	0.302884	-0.655741
C	-2.385763	1.050973	-0.705945
C	-2.530824	-1.219152	0.889615
C	-1.35698	-0.47388	0.849862
C	-1.262126	0.671265	0.042145
C	-0.038527	1.486217	0.008458
C	1.288778	1.113593	-0.000802
C	1.99569	-0.164398	-0.070777
C	3.277594	-0.292397	0.489915
C	3.959074	-1.504875	0.4122
C	3.373248	-2.600868	-0.22525
C	2.102114	-2.476797	-0.792397
C	1.416369	-1.267326	-0.720468
O	2.065317	2.228291	0.036334
N	1.253711	3.370193	0.065685
C	0.025522	2.911574	0.041686
H	-4.828228	-2.54789	-0.4971
H	-5.781209	-1.096944	-0.165524
H	-5.118185	-2.056642	1.172118

H	-4.418472	0.616759	-1.245387
H	-2.33574	1.932672	-1.338682
H	-2.581724	-2.099632	1.525332
H	-0.507583	-0.772883	1.455791
H	3.729778	0.557606	0.989661
H	4.947294	-1.594504	0.853153
H	3.90513	-3.54584	-0.282584
H	1.646196	-3.322029	-1.2991
H	0.436406	-1.170818	-1.173478
H	-0.802683	3.608754	0.072585

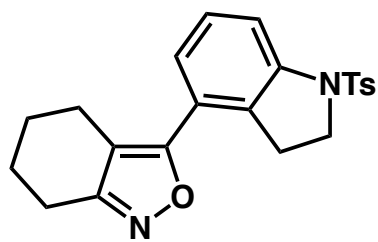
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
X_boltz		35.58	50.76	50.53	35.74
X_1	0.00	35.58	50.76	50.53	



C	-1.645505	2.261746	-0.440155
C	-2.754913	1.280987	-0.155979
C	-4.061505	1.761163	-0.007572
C	-5.133322	0.913222	0.265806
C	-4.911904	-0.45763	0.404215
C	-3.623898	-0.960756	0.263859
C	-2.53737	-0.111258	-0.018473
C	-1.21039	-0.714022	-0.148952
C	-0.023187	-0.353692	-0.729616
C	0.845167	-1.457165	-0.498105
C	2.284942	-1.591375	-0.903734
C	3.13915	-0.487406	-0.308144
C	3.768658	0.455723	-1.12565
C	4.539587	1.479081	-0.567914
C	4.685815	1.569569	0.816636
C	4.057102	0.631834	1.641285
C	3.288128	-0.387177	1.081588
N	0.245959	-2.413775	0.177739
O	-1.060137	-1.95171	0.40193
H	-0.779506	2.097301	0.2096
H	-1.996074	3.286322	-0.290702

H	-1.293152	2.183883	-1.476132
H	-4.235262	2.829298	-0.104858
H	-6.13365	1.322172	0.37321
H	-5.735992	-1.131405	0.617852
H	-3.445119	-2.025151	0.366022
H	0.218312	0.546951	-1.267081
H	2.354736	-1.562801	-1.996635
H	2.642326	-2.575133	-0.580743
H	3.656152	0.388724	-2.204801
H	5.023449	2.204036	-1.216387
H	5.284409	2.364486	1.252082
H	4.165871	0.695831	2.720321
H	2.793547	-1.111482	1.724083

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
Y_boltz		44.22	48.21	47.70	44.69
Y_1	0.00	44.32	48.90	47.77	
Y_1	0.07	44.29	48.87	47.73	
Y_2	0.73	43.90	45.82	47.76	
Y_3	1.36	43.79	44.62	46.86	
Y_4	1.98	43.39	41.78	46.85	



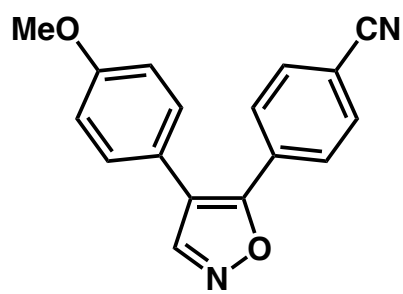
(Z_1)

C	0.55619	4.039565	1.448285
C	-0.496791	3.050678	1.019239
C	-0.815948	1.950474	1.829308
C	-1.787852	1.031254	1.446
C	-2.454806	1.219456	0.231703
S	-3.559347	-0.046882	-0.354761
N	-2.552934	-1.261235	-1.029203
C	-1.742979	-0.825261	-2.213814
C	-0.306327	-0.615611	-1.690164
C	-0.294419	-1.468067	-0.442862
C	-1.605099	-1.832111	-0.109145
C	-1.901167	-2.661594	0.965232
C	-0.831386	-3.135096	1.732942
C	0.480126	-2.781992	1.424997
C	0.769598	-1.931476	0.338131
C	2.156796	-1.547442	0.073933
C	2.780633	-0.364467	-0.221152
C	2.285369	1.037931	-0.415553
C	3.430482	2.038398	-0.175467
C	4.692294	1.629879	-0.951554
C	5.269564	0.298386	-0.434698

C	4.168343	-0.703497	-0.231287
N	4.374864	-1.975897	0.025808
O	3.094708	-2.524172	0.223673
O	-4.225144	-0.667927	0.796126
O	-4.348826	0.48735	-1.471005
C	-2.164515	2.310039	-0.591321
C	-1.188822	3.218138	-0.189121
H	1.009534	4.536793	0.58592
H	1.348731	3.551265	2.023334
H	0.119472	4.817889	2.086837
H	-0.289192	1.806641	2.768232
H	-2.022999	0.180938	2.074915
H	-2.18642	0.056596	-2.674298
H	-1.782605	-1.645483	-2.935048
H	-0.123387	0.43628	-1.453785
H	0.44426	-0.926435	-2.421859
H	-2.926151	-2.9243	1.195185
H	-1.026017	-3.788264	2.57756
H	1.298448	-3.154453	2.031624
H	1.438296	1.243711	0.245947
H	1.918496	1.170089	-1.442054
H	3.660193	2.085768	0.897604
H	3.105852	3.03944	-0.478177
H	5.45847	2.408138	-0.874353
H	4.441637	1.532649	-2.016381

H	5.770446	0.465162	0.527975
H	6.028308	-0.097763	-1.11794
H	-2.694211	2.440707	-1.528053
H	-0.956725	4.067152	-0.825372

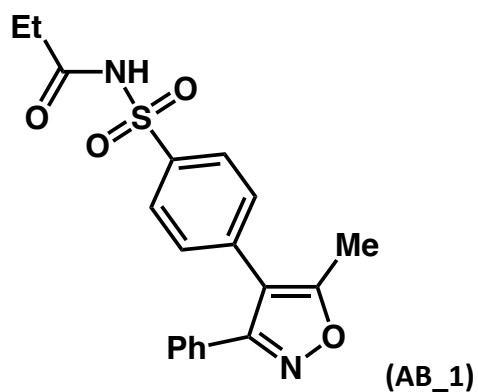
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
Z_boltz		46.28	56.58	53.88	48.60
Z_1	0.00	45.83	56.83	52.70	
Z_2	0.79	45.80	56.71	52.72	
Z_3	0.90	45.49	53.11	52.77	
Z_4	0.94	48.05	58.84	57.62	
Z_5	0.96	48.62	59.36	58.04	
Z_6	1.41	45.74	53.19	55.61	
Z_7	2.11	45.63	53.05	55.03	
Z_8	2.29	45.54	53.19	51.84	
Z_9	2.62	45.50	53.16	51.79	
Z_10	2.90	45.87	55.08	53.13	
Z_11	3.13	45.89	55.55	51.94	
Z_12	3.18	47.92	56.95	58.73	
Z_13	3.71	47.43	55.98	57.99	
Z_14	3.91	45.94	55.19	52.05	
Z_15	4.48	45.54	53.17	51.81	
Z_16	4.87	45.48	53.13	51.75	
Z_17	5.14	45.54	53.19	51.83	
Z_18	5.30	45.87	55.53	51.90	
Z_19	5.50	45.47	53.11	51.68	
Z_20	5.65	45.85	55.53	51.87	
Z_21	5.96	45.89	55.54	51.93	
Z_22	6.11	45.79	55.16	51.77	
Z_23	6.51	45.77	55.13	51.74	
Z_24	6.79	45.82	55.18	51.80	
Z_25	6.94	45.93	55.13	52.02	
Z_26	7.10	45.87	55.04	51.93	



C	-5.618678	-2.110297	-0.356729
O	-4.42231	-2.161238	0.417456
C	-3.517002	-1.157901	0.260687
C	-2.356646	-1.252684	1.046229
C	-1.373287	-0.27974	0.960023
C	-3.675543	-0.071768	-0.60853
C	-2.675053	0.89753	-0.689069
C	-1.509236	0.811582	0.081695
C	-0.482611	1.859421	-0.001654
C	0.892817	1.771495	-0.013839
C	1.848986	0.668237	-0.043922
C	1.490486	-0.575786	-0.592524
C	2.405851	-1.617286	-0.630806
C	3.702906	-1.426734	-0.123797
C	4.647523	-2.500935	-0.158815
N	5.414984	-3.375383	-0.187321
C	4.073902	-0.183119	0.413876
C	3.152091	0.853907	0.450592
O	1.423339	3.023564	-0.028509
N	0.394316	3.969355	-0.038892
C	-0.713796	3.268422	-0.026961

H	-6.201967	-1.210826	-0.127601
H	-6.190756	-2.996186	-0.079422
H	-5.398119	-2.137634	-1.430232
H	-2.253436	-2.093084	1.725034
H	-0.490163	-0.357931	1.586137
H	-4.56017	0.026909	-1.225424
H	-2.802417	1.728265	-1.377157
H	0.496645	-0.721862	-0.997129
H	2.127229	-2.574304	-1.057477
H	5.075929	-0.038734	0.802079
H	3.435457	1.81237	0.869725
H	-1.667844	3.780535	-0.015335

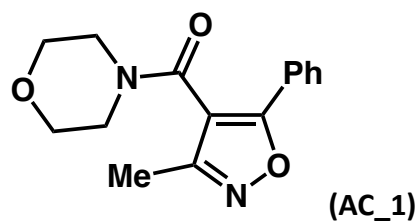
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
AA_boltz		35.55	50.75	50.52	35.71
AA_1	0.00	35.55	50.75	50.52	



O	3.184376	0.299345	-1.956616
C	3.454116	1.119921	-1.094902
C	3.310185	2.615115	-1.284326
C	1.837203	3.011846	-1.069095
N	3.840958	0.735125	0.18684
S	3.589264	-0.838267	0.801706
C	1.848051	-1.09235	0.554548
C	0.954183	-0.467277	1.429014
C	-0.408115	-0.585236	1.191376
C	1.407201	-1.833643	-0.539433
C	0.037474	-1.943697	-0.765468
C	-0.88373	-1.316297	0.087306
C	-2.327142	-1.414376	-0.16484
C	-3.059252	-2.542422	-0.429356
C	-2.707004	-3.979194	-0.574207
O	-4.364646	-2.21578	-0.538088
N	-4.521631	-0.832687	-0.354334
C	-3.310667	-0.36507	-0.126044
C	-3.108562	1.077815	0.099499

C	-2.001928	1.739592	-0.454959
C	-1.829425	3.10742	-0.251841
C	-2.755319	3.827534	0.506718
C	-3.860216	3.174919	1.058163
C	-4.037482	1.807209	0.856284
O	4.341839	-1.798716	-0.002806
O	3.867801	-0.685314	2.233737
H	3.618654	2.848329	-2.306952
H	3.960536	3.165592	-0.597432
H	1.50316	2.767746	-0.055188
H	1.193866	2.481558	-1.778014
H	1.711	4.087475	-1.222189
H	3.944184	1.433874	0.917035
H	1.320081	0.095511	2.280404
H	-1.113767	-0.109908	1.863253
H	2.122826	-2.29362	-1.208738
H	-0.31878	-2.492939	-1.630331
H	-2.741207	-4.288171	-1.625325
H	-3.411377	-4.603862	-0.016604
H	-1.697503	-4.157225	-0.197584
H	-1.28537	1.186324	-1.052543
H	-0.974821	3.61237	-0.691019
H	-2.616103	4.892571	0.666961
H	-4.582103	3.729734	1.650014
H	-4.889191	1.292688	1.288967

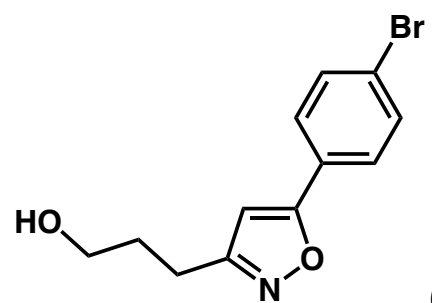
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
AB_boltz		51.02	42.62	55.98	67.01
AB_1	0.00	51.02	55.95	42.62	
AB_2	0.19	51.04	55.97	42.57	
AB_3	0.30	51.07	56.02	42.60	
AB_4	0.37	50.97	55.94	42.67	
AB_5	0.50	50.95	55.93	42.68	
AB_6	0.59	51.04	56.24	42.65	
AB_7	0.66	51.13	56.04	42.50	
AB_8	0.73	50.96	55.93	42.69	
AB_9	0.80	50.95	55.93	42.70	
AB_10	0.89	51.14	56.05	42.50	
AB_11	0.97	50.97	55.94	42.67	
AB_12	1.06	50.97	55.93	42.67	
AB_13	1.14	50.96	55.93	42.68	
AB_14	1.28	50.95	55.94	42.69	
AB_15	1.36	50.96	55.92	42.67	
AB_16	1.57	51.11	56.00	42.43	
AB_17	1.74	51.12	56.00	42.37	
AB_18	1.89	51.29	56.10	42.25	
AB_19	1.96	50.99	55.95	42.64	
AB_20	2.20	50.96	55.93	42.68	
AB_21	3.73	50.97	55.94	42.68	
AB_22	4.23	50.96	55.92	42.68	
AB_23	210.97	51.00	55.98	42.64	
AB_24	211.04	51.08	55.98	42.47	
AB_25	211.98	50.96	55.94	42.69	
AB_26	212.06	51.00	55.95	42.62	
AB_27	212.48	50.96	55.93	42.69	



O	1.598867	1.749546	1.631283
C	1.114166	1.213607	0.627667
N	0.072422	1.751543	-0.064996
C	-0.571516	2.970306	0.424807
C	-2.086622	2.804525	0.333125
O	-2.493284	2.485367	-0.994889
C	-1.904491	1.260006	-1.42406
C	-0.379864	1.346997	-1.398014
C	1.66201	-0.088379	0.154713
C	1.039391	-1.301045	0.013037
C	-0.34184	-1.732053	0.210951
C	-1.115084	-1.148352	1.227675
C	-2.445694	-1.523903	1.394597
C	-3.014421	-2.483202	0.5526
C	-2.244768	-3.074924	-0.45221
C	-0.912494	-2.705537	-0.623687
O	1.94739	-2.223352	-0.381536
N	3.211656	-1.611633	-0.498335
C	3.03182	-0.353494	-0.162602
C	4.166767	0.617814	-0.163711
H	-0.252608	3.824313	-0.187832
H	-0.25268	3.139296	1.453158

H	-2.587442	3.739087	0.598581
H	-2.413889	2.014649	1.026778
H	-2.251478	1.08579	-2.445785
H	-2.24407	0.433363	-0.784763
H	-0.049046	2.103389	-2.122834
H	0.064433	0.392656	-1.673355
H	-0.668785	-0.415861	1.891528
H	-3.036955	-1.070623	2.184155
H	-4.053044	-2.771925	0.682007
H	-2.683867	-3.821897	-1.106255
H	-0.314395	-3.154177	-1.409935
H	5.108506	0.106679	-0.374811
H	4.231198	1.117344	0.807053
H	4.007622	1.391856	-0.92255

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
AC_boltz		42.46	54.35	57.82	45.17
AC_1	0.00	42.49	57.89	54.66	
AC_2	0.36	42.42	57.68	53.80	
AC_3	4.56	42.41	57.57	54.23	
AC_4	4.72	42.41	58.05	55.01	
AC_5	5.59	42.50	57.83	54.17	
AC_6	6.44	44.05	58.75	52.75	
AC_7	6.89	42.59	57.52	53.23	
AC_8	7.28	45.45	58.39	52.23	
AC_9	160.97	42.37	57.57	54.00	



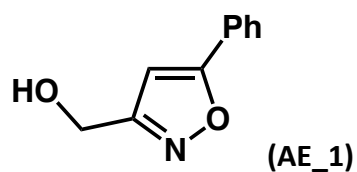
(AD_1)

O	5.545313	-1.794211	0.09503
C	6.154216	-0.557959	0.409323
C	5.700703	0.616412	-0.466406
C	4.472814	1.400369	0.013383
C	3.146285	0.703738	-0.025039
N	3.03935	-0.599802	-0.07512
O	1.68818	-0.889957	-0.06793
C	0.991734	0.262908	-0.015638
C	-0.46478	0.160728	-0.007968
C	-1.091015	-1.083366	-0.115188
C	-2.474885	-1.176901	-0.109098
C	-3.230974	-0.018327	0.004624
Br	-5.124601	-0.140406	0.012848
C	-2.6294	1.228973	0.113139
C	-1.245898	1.313422	0.107013
C	1.860687	1.308258	0.013544
H	4.580223	-1.639798	0.088716
H	7.227899	-0.710506	0.264039
H	6.010088	-0.297833	1.471062
H	5.545099	0.246835	-1.486082

H	6.523234	1.337824	-0.516301
H	4.376228	2.312052	-0.584694
H	4.641124	1.740011	1.043391
H	-0.493393	-1.982725	-0.204983
H	-2.960133	-2.141813	-0.192758
H	-3.233981	2.123344	0.202616
H	-0.774571	2.285978	0.195363
H	1.63892	2.363258	0.048877

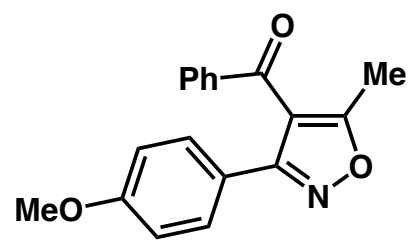
Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
AD_boltz		43.50	43.95	42.91	42.47
AD_1	0	43.63	40.75	43.24	
AD_2	0.04	45.56	43.55	44.47	
AD_3	0.84	44.07	44.53	44.43	
AD_4	1.03	40.52	42.84	43.61	
AD_5	1.11	43.13	44.49	44.39	
AD_6	1.15	40.56	42.82	43.6	
AD_7	1.18	43.08	44.45	44.37	
AD_8	1.21	44.56	47.84	45.16	
AD_9	1.29	40.18	42.87	43.61	
AD_10	1.36	44.01	41.28	43.48	
AD_11	1.39	40.19	42.88	43.62	
AD_12	1.52	40.52	42.78	43.59	
AD_13	1.63	40.37	40.44	43.1	
AD_14	1.7	45.33	46.97	45.72	
AD_15	1.77	43.43	41.52	43.39	
AD_16	1.82	42.95	45.21	44.54	
AD_17	1.84	43.43	41.58	43.41	
AD_18	1.89	40.03	40.44	43.1	
AD_19	1.89	42.91	45.04	44.49	
AD_20	1.93	44.87	46.09	45.34	
AD_21	2.03	40.04	40.45	43.1	
AD_22	2.11	42.55	41.2	43.35	
AD_23	2.12	43.99	46.13	44.49	

AD_24	2.14	40.37	40.44	43.1	
AD_25	2.23	43.97	41.83	43.39	
AD_26	2.24	45.33	46.84	46.14	
AD_27	2.25	44.59	45.52	44.63	
AD_28	2.27	42.58	41.22	43.36	
AD_29	2.53	43	47.15	44.47	
AD_30	2.6	43.7	47.44	44.76	
AD_31	3.57	43.44	47.95	44.56	



O	4.135026	-1.259389	0.530104
C	3.818601	-0.148708	-0.301357
C	2.37088	0.241536	-0.192509
N	2.026698	1.504346	-0.049986
O	0.624901	1.502512	0.012681
C	0.169493	0.226122	-0.082136
C	-1.273641	0.01892	-0.028549
C	-2.151052	1.104176	0.131354
C	-3.526604	0.890891	0.181386
C	-4.043178	-0.402245	0.073103
C	-3.174888	-1.485809	-0.086352
C	-1.799418	-1.279512	-0.137416
C	1.238991	-0.617869	-0.211974
H	4.002274	-0.980285	1.45054
H	4.034623	-0.474438	-1.323735
H	4.446618	0.725869	-0.08742
H	-1.751162	2.108589	0.215736
H	-4.196183	1.736638	0.305462
H	-5.115924	-0.565626	0.112474
H	-3.57016	-2.493472	-0.171494
H	-1.130932	-2.12536	-0.262418
H	1.239438	-1.692323	-0.304821

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
AE_boltz		37.67	43.42	41.72	36.20
AE_1	0.00	37.76	42.13	43.48	
AE_2	0.60	37.39	41.86	43.51	
AE_3	0.63	37.71	40.37	43.15	

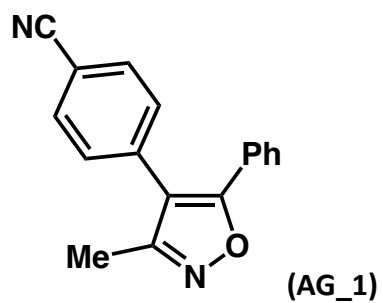


(AF_1)

C	4.789369	-0.569551	-0.151718
C	3.382678	-1.025382	-0.055628
C	2.176885	-0.398959	-0.212823
C	2.010033	1.032612	-0.538511
C	0.870467	1.787722	0.051497
C	0.319004	1.446282	1.287379
C	-0.740016	2.180854	1.803288
C	-1.259664	3.251926	1.082369
C	-0.705438	3.603441	-0.146054
C	0.364601	2.880899	-0.653754
O	2.814713	1.593257	-1.271816
C	1.215603	-1.438166	0.034527
C	-0.253567	-1.380656	-0.024055
C	-0.902673	-0.683409	-1.039449
C	-2.288321	-0.597334	-1.081277
C	-3.044986	-1.222793	-0.089826
O	-4.397325	-1.1915	-0.026261
C	-5.097115	-0.462338	-1.021402
C	-2.403116	-1.939855	0.9249
C	-1.023918	-2.017524	0.954422
N	1.81123	-2.568292	0.318416

O	3.178412	-2.301186	0.281091
H	4.819794	0.51182	-0.275362
H	5.274941	-1.02897	-1.018139
H	5.346873	-0.86085	0.742001
H	0.721107	0.610547	1.848849
H	-1.163325	1.914683	2.766058
H	-2.096951	3.816572	1.479964
H	-1.109184	4.440555	-0.705979
H	0.811242	3.141626	-1.606957
H	-0.323998	-0.194864	-1.816221
H	-2.761462	-0.045112	-1.882679
H	-4.815253	0.595807	-1.009861
H	-6.154352	-0.558517	-0.776845
H	-4.915409	-0.876071	-2.018873
H	-3.008953	-2.419403	1.685731
H	-0.529042	-2.560961	1.751985

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
AF_boltz		53.20	56.80	42.60	70.93
AF_1	0.00	53.35	56.80	42.45	
AF_2	1.80	50.65	56.80	45.10	
AF_3	2.58	50.45	56.45	45.24	



C	-0.590727	3.820126	0.075655
C	0.471607	2.768028	0.03252
N	1.740003	3.108475	0.084158
O	2.460354	1.903253	0.043335
C	1.597907	0.861118	-0.016111
C	2.187079	-0.474842	-0.083542
C	1.519881	-1.518622	-0.746334
C	2.091375	-2.786732	-0.806372
C	3.334202	-3.027543	-0.214801
C	4.007691	-1.99061	0.435067
C	3.440566	-0.720223	0.501617
C	0.308612	1.342476	-0.022993
C	-0.958173	0.598231	0.010808
C	-1.133891	-0.469188	0.909467
C	-2.331355	-1.168147	0.959545
C	-3.388541	-0.800443	0.108917
C	-4.627557	-1.514172	0.158186
N	-5.635311	-2.095152	0.198055
C	-3.229339	0.267727	-0.788102
C	-2.022508	0.955275	-0.833008
H	-1.372128	3.548772	0.792115

H	-1.067131	3.941492	-0.902887
H	-0.156948	4.779569	0.366554
H	0.564416	-1.331731	-1.222997
H	1.569312	-3.586135	-1.323295
H	3.777043	-4.017782	-0.263491
H	4.974638	-2.171841	0.894471
H	3.958859	0.084507	1.011915
H	-0.323179	-0.745107	1.574716
H	-2.45896	-1.988978	1.656633
H	-4.044248	0.547367	-1.446584
H	-1.898326	1.765833	-1.542441

Structure	E_rel (kcal/mol)	V _{bur} C3	V _{bur} C4	V _{bur} C5	C3*C4/C5
AF_boltz		42.19	55.91	51.41	45.88
AG_1	0	42.19	55.91	51.41	

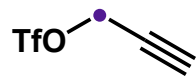
13. References

- (1) Kovarik, Z.; Kalisiak, J.; Hrvat, N. M.; Katalinić, M.; Zorbaz, T.; Žunec, S.; Green, C.; Radić, Z.; Fokin, V. V.; Sharpless, K. B.; Taylor, P. Reversal of Tabun Toxicity Enabled by a Triazole-Annulated Oxime Library—Reactivators of Acetylcholinesterase. *Chem. – Eur. J.* **2019**, *25* (16), 4100–4114. <https://doi.org/10.1002/chem.201805051>.
- (2) Alberola, A.; Andrés, J. M.; González, A.; Pedrosa, R.; Vicente, M. Differential Reactivity of β -Amino Enones and 3-Dimethylaminoacrylaldehyde towards α -Amino Derivatives. *J. Chem. Soc. Perkin 1* **1990**, No. 10, 2681–2685. <https://doi.org/10.1039/P19900002681>.
- (3) Kelgokmen, Y.; Cayan, Y.; Zora, M. Zinc Chloride Mediated Synthesis of 1,4-Oxazepines from N-Propargylic β -Enaminones. *Eur. J. Org. Chem.* **2017**, *2017* (47), 7167–7178. <https://doi.org/10.1002/ejoc.201701433>.
- (4) Wang, H.-Y.; Mueller, D. S.; Sachwani, R. M.; Londino, H. N.; Anderson, L. L. Carbon–Carbon Bond Formation and Pyrrole Synthesis via the [3,3] Sigmatropic Rearrangement of O-Vinyl Oxime Ethers. *Org. Lett.* **2010**, *12* (10), 2290–2293. <https://doi.org/10.1021/ol100659q>.
- (5) Joshi, K. C.; Pathak, V. N.; Grover, V. Studies in Potential Organo-Fluorine Antibacterial Agents. Part 2: Synthesis and Antibacterial Activity of Some New Fluorine-Containing 3,5-Disubstituted Isoxazoles. *Pharm.* **1979**, *34* (2), 68–69.
- (6) Han, L.; Zhang, B.; Zhu, M.; Yan, J. An Environmentally Benign Synthesis of Isoxazolines and Isoxazoles Mediated by Potassium Chloride in Water. *Tetrahedron Lett.* **2014**, *55* (14), 2308–2311. <https://doi.org/10.1016/j.tetlet.2014.02.118>.
- (7) Ferreira-Silva, B.; Lavandera, I.; Kern, A.; Faber, K.; Kroutil, W. Chemo-Promiscuity of Alcohol Dehydrogenases: Reduction of Phenylacetaldoxime to the Alcohol. *Tetrahedron* **2010**, *66* (19), 3410–3414. <https://doi.org/10.1016/j.tet.2010.03.050>.
- (8) Kamath, P.; Jadhav, V.; Lal, M. Heterocycle–Heterocycle Strategy for 4,5-Disubstituted Pyrrolidine 2,3-Diones: Reductive Rearrangement Approach from Isoxazole Esters. *Synlett* **2021**, *32*, 1146–1150. <https://doi.org/10.1055/a-1492-8216>.
- (9) Griesbeck, A. G.; Franke, M.; Neudörfl, J.; Kotaka, H. Photocycloaddition of Aromatic and Aliphatic Aldehydes to Isoxazoles: Cycloaddition Reactivity and Stability Studies. *Beilstein J. Org. Chem.* **2011**, *7* (1), 127–134. <https://doi.org/10.3762/bjoc.7.18>.
- (10) Paternoga, J.; Opatz, T. A Copper-Catalyzed Synthesis of Pyrroles through Photochemically Generated Acylazirines. *Eur. J. Org. Chem.* **2019**, *2019* (42), 7067–7078. <https://doi.org/10.1002/ejoc.201901176>.
- (11) He, Y.; Lin, N.-H. Studies On Isoxazole Formation from Alkyl Carboxylic Esters. *Synthesis* **2002**, *1994*, 989–992. <https://doi.org/10.1055/s-1994-25620>.
- (12) Ramalingan, C.; Park, Y.-T. Mercury-Catalyzed Rearrangement of Ketoximes into Amides and Lactams in Acetonitrile. *J. Org. Chem.* **2007**, *72* (12), 4536–4538. <https://doi.org/10.1021/jo070297k>.
- (13) Suzuki, K.; Watanabe, T.; Murahashi, S.-I. Oxidation of Primary Amines to Oximes with Molecular Oxygen Using 1,1-Diphenyl-2-Picrylhydrazyl and WO₃/Al₂O₃ as Catalysts. *J. Org. Chem.* **2013**, *78* (6), 2301–2310. <https://doi.org/10.1021/jo302262a>.
- (14) Fall, Y.; Reynaud, C.; Doucet, H.; Santelli, M. Ligand-Free-Palladium-Catalyzed Direct 4-Arylation of Isoxazoles Using Aryl Bromides. *EurJOC* **2009**, *2009* (24), 4041–4050. <https://doi.org/10.1002/ejoc.200900309>.

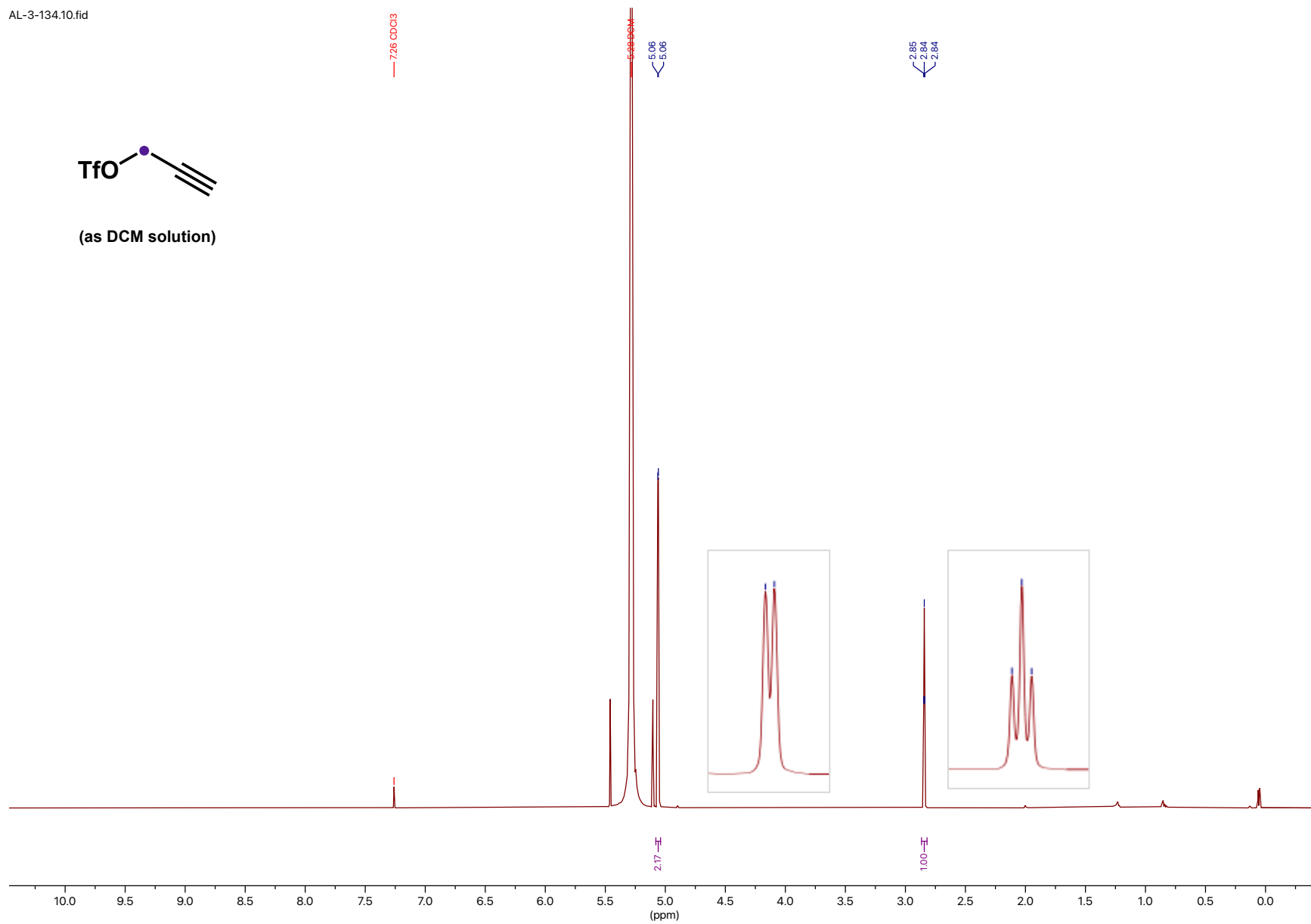
- (15) Debbarma, S.; Bera, S. S.; Maji, M. S. Harnessing Stereospecific Z-Enamides through Silver-Free Cp*Rh(III) Catalysis by Using Isoxazoles as Masked Electrophiles. *Org. Lett.* **2019**, *21* (3), 835–839. <https://doi.org/10.1021/acs.orglett.8b04130>.
- (16) Reuman, M.; Beish, S.; Davis, J.; Batchelor, M. J.; Hutchings, M. C.; Moffat, D. F. C.; Connolly, P. J.; Russell, R. K. Scalable Synthesis of the VEGF-R2 Kinase Inhibitor JNJ-17029259 Using Ultrasound-Mediated Addition of MeLi–CeCl₃ to a Nitrile. *J. Org. Chem.* **2008**, *73* (3), 1121–1123. <https://doi.org/10.1021/jo7021372>.
- (17) Liu, Y.; Ho, L. T. A.; Huang, G.-Z.; Chen, Y.-C.; Ungur, L.; Liu, J.-L.; Tong, M.-L. Magnetization Dynamics on Isotope-Isomorphic Holmium Single-Molecule Magnets. *Angew. Chem. Int. Ed.* **2021**, *60* (52), 27282–27287. <https://doi.org/10.1002/anie.202112764>.
- (18) Gilligan, P. J.; Clarke, T.; He, L.; Lelas, S.; Li, Y.-W.; Heman, K.; Fitzgerald, L.; Miller, K.; Zhang, G.; Marshall, A.; Krause, C.; McElroy, J. F.; Ward, K.; Zeller, K.; Wong, H.; Bai, S.; Saye, J.; Grossman, S.; Zaczek, R.; Arneric, S. P.; Hartig, P.; Robertson, D.; Trainor, G. Synthesis and Structure–Activity Relationships of 8-(Pyrid-3-Yl)Pyrazolo[1,5-a]-1,3,5-Triazines: Potent, Orally Bioavailable Corticotropin Releasing Factor Receptor-1 (CRF1) Antagonists. *J. Med. Chem.* **2009**, *52* (9), 3084–3092. <https://doi.org/10.1021/jm900025h>.
- (19) Hwang, S. H.; Wagner, K. M.; Morisseau, C.; Liu, J.-Y.; Dong, H.; Wecksler, A. T.; Hammock, B. D. Synthesis and Structure–Activity Relationship Studies of Urea-Containing Pyrazoles as Dual Inhibitors of Cyclooxygenase-2 and Soluble Epoxide Hydrolase. *J. Med. Chem.* **2011**, *54* (8), 3037–3050. <https://doi.org/10.1021/jm2001376>.
- (20) Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. Design, Synthesis, and Biological Evaluation of Cytotoxic 11-Aminoalkenylindenoisoquinoline and 11-Diaminoalkenylindenoisoquinoline Topoisomerase I Inhibitors. *Bioorg. Med. Chem.* **2004**, *12* (19), 5147–5160. <https://doi.org/10.1016/j.bmc.2004.07.027>.
- (21) Manning, J. R.; Davies, H. M. L. One-Pot Synthesis of Highly Functionalized Pyridines via a Rhodium Carbenoid Induced Ring Expansion of Isoxazoles. *J. Am. Chem. Soc.* **2008**, *130* (27), 8602–8603. <https://doi.org/10.1021/ja803139k>.
- (22) Alberola, A.; Calvo, L.; Rodríguez Rodríguez, M. T.; Sañudo, M. C. Comparative Reactivity of 3-Methyl-5-Phenylisoxazole and 3-Methyl-5-Phenylisothiazole against Electrophilic Compounds. *J. Heterocycl. Chem.* **1995**, *32* (2), 537–541. <https://doi.org/10.1002/jhet.5570320228>.
- (23) Kanemasa, S.; Norisue, Y.; Suga, H.; Tsuge, O. Generation of Sulfur-Functionalized Nitrile Oxide, (Phenylthio)Acetonitrile Oxide, and Synthetic Applications. *Bull. Chem. Soc. Jpn.* **1988**, *61* (11), 3973–3982. <https://doi.org/10.1246/bcsj.61.3973>.
- (24) Isobe, T.; Ishikawa, T. 2-Chloro-1,3-Dimethylimidazolinium Chloride. 1. A Powerful Dehydrating Equivalent to DCC. *J. Org. Chem.* **1999**, *64* (19), 6984–6988. <https://doi.org/10.1021/jo990210y>.
- (25) Lee, J. C.; Hong, K. H.; Becker, A.; Tash, J. S.; Schönbrunn, E.; Georg, G. I. Tetrahydroindazole Inhibitors of CDK2/Cyclin Complexes. *Eur. J. Med. Chem.* **2021**, *214*, 113232. <https://doi.org/10.1016/j.ejmech.2021.113232>.
- (26) Meyers, K.; Cogan, D. A.; Burke, J.; Arenas, R.; Balestra, M.; Brown, N. F.; Chen, Z.; Cerny, M. A.; Clifford, H. E.; Colombo, F.; Fader, L.; Frederick, K. S.; Guo, X.; Goldberg, D.; Hornberger, K. R.; Kugler, S.; Lord, J.; Marshall, D. R.; Moss, N.; Parmentier, J.-H.; Richman, J. R.; Schmenk, J.; Weldon, S. M.; Yu, M.; Zhang, M. Dihydrobenzisoxazole-4-One Compounds

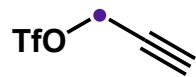
- Are Novel Selective Inhibitors of Aldosterone Synthase (CYP11B2) with *in Vivo* Activity. *Bioorg. Med. Chem. Lett.* **2018**, *28* (5), 979–984. <https://doi.org/10.1016/j.bmcl.2017.12.015>.
- (27) Waldo, J. P.; Larock, R. C. Synthesis of Isoxazoles via Electrophilic Cyclization. *Org. Lett.* **2005**, *7* (23), 5203–5205. <https://doi.org/10.1021/ol052027z>.
- (28) Komatsuda, M.; Ohki, H.; Kondo, H. Jr.; Suto, A.; Yamaguchi, J. Ring-Opening Fluorination of Isoxazoles. *Org. Lett.* **2022**, *24* (17), 3270–3274. <https://doi.org/10.1021/acs.orglett.2c01149>.
- (29) Kumar, G. R.; Kumar, Y. K.; Reddy, M. S. A Direct Access to Isoxazoles from Ynones Using Trimethylsilyl Azide as Amino Surrogate under Metal/Catalyst Free Conditions. *Chem. Commun.* **2016**, *52* (39), 6589–6592. <https://doi.org/10.1039/C6CC02047J>.
- (30) Li, C.; Li, J.; Zhou, F.; Li, C.; Wu, W. Palladium-Catalyzed Cascade Annulation/Allylation of Alkynyl Oxime Ethers with Allyl Halides: Rapid Access to Fully Substituted Isoxazoles. *J. Org. Chem.* **2019**, *84* (18), 11958–11970. <https://doi.org/10.1021/acs.joc.9b01593>.
- (31) Sun, Y.; Abdukader, A.; Zhang, H.; Yang, W.; Liu, C. Copper-Catalyzed Aerobic Oxidative C–O Bond Formation for the Synthesis of 3,5-Disubstituted Isoxazoles from Enone Oximes. *RSC Adv.* **2017**, *7* (88), 55786–55789. <https://doi.org/10.1039/C7RA11436B>.
- (32) Nakano, Y.; Kato, Y.; Imai, K.; Ochiai, E.; Namekawa, J.; Ishizuka, S.; Takenouchi, K.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. Practical Synthesis and Evaluation of the Biological Activities of 1 α ,25-Dihydroxyvitamin D3 Antagonists, 1 α ,25-Dihydroxyvitamin D3-26,23-Lactams. Designed on the Basis of the Helix 12-Folding Inhibition Hypothesis. *J. Med. Chem.* **2006**, *49* (8), 2398–2406. <https://doi.org/10.1021/jm050738x>.
- (33) Hossain, M. I.; Khan, M. I. H.; Kim, S. J.; Le, H. V. Synthesis of 3,4,5-Trisubstituted Isoxazoles in Water via a [3 + 2]-Cycloaddition of Nitrile Oxides and 1,3-Diketones, β -Ketoesters, or β -Ketoamides. *Beilstein J. Org. Chem.* **2022**, *18*, 446–458. <https://doi.org/10.3762/bjoc.18.47>.
- (34) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; et al. Gaussian 16, Revision A.03, 2016.
- (35) Grimme, S. Supramolecular Binding Thermodynamics by Dispersion-Corrected Density Functional Theory. *Chem. – Eur. J.* **2012**, *18* (32), 9955–9964. <https://doi.org/10.1002/chem.201200497>.
- (36) Li, Y.-P.; Gomes, J.; Mallikarjun Sharada, S.; Bell, A. T.; Head-Gordon, M. Improved Force-Field Parameters for QM/MM Simulations of the Energies of Adsorption for Molecules in Zeolites and a Free Rotor Correction to the Rigid Rotor Harmonic Oscillator Model for Adsorption Enthalpies. *J. Phys. Chem. C* **2015**, *119* (4), 1840–1850. <https://doi.org/10.1021/jp509921r>.
- (37) Luchini, G.; Alegre-Requena, J. V.; Funes-Ardoiz, I.; Paton, R. S. GoodVibes: Automated Thermochemistry for Heterogeneous Computational Chemistry Data. F1000Research April 24, 2020. <https://doi.org/10.12688/f1000research.22758.1>.
- (38) Hanley, J. A.; McNeil, B. J. The Meaning and Use of the Area under a Receiver Operating Characteristic (ROC) Curve. *Radiology* **1982**, *143* (1), 29–36. <https://doi.org/10.1148/radiology.143.1.7063747>.
- (39) Filimonov, S. I.; Korsakov, M. K.; Dorogov, M. V.; Kravchenko, D. V.; Tkachenko, S. E.; Ivachtchenko, A. V. Convenient Synthesis of Novel 5-Substituted 3-Methylisoxazole-4-

- Sulfonamides. *J. Heterocycl. Chem.* **2006**, *43* (3), 663–671.
<https://doi.org/10.1002/jhet.5570430320>.
- (40) Zhu, S.; Shi, S.; Gerritz, S. W. An Efficient One-Pot Synthesis of 3-Aryl-5-Methylisoxazoles from Aryl Aldehydes. *Tetrahedron Lett.* **2011**, *52* (31), 4001–4004.
<https://doi.org/10.1016/j.tetlet.2011.05.104>.
- (41) Fos, E.; Borràs, L.; Gasull, M.; Mauleón, D.; Carganico, G. Synthesis of Isomeric Series of Aryltetrahydrobenz-Isloxazoles and Arylcyclopentisoxazoles. *J. Heterocycl. Chem.* **1992**, *29* (1), 203–208. <https://doi.org/10.1002/jhet.5570290137>.

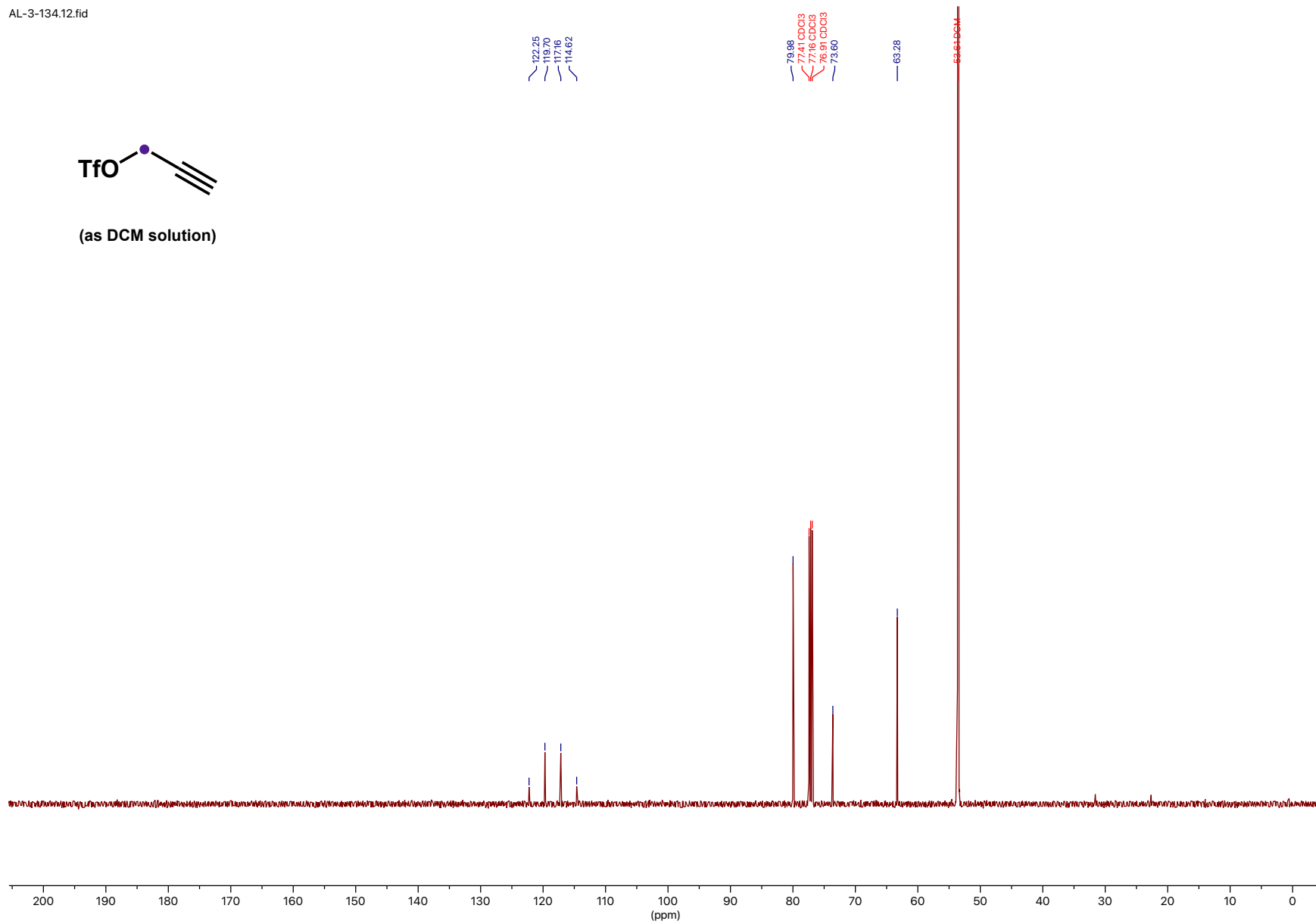


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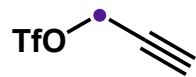




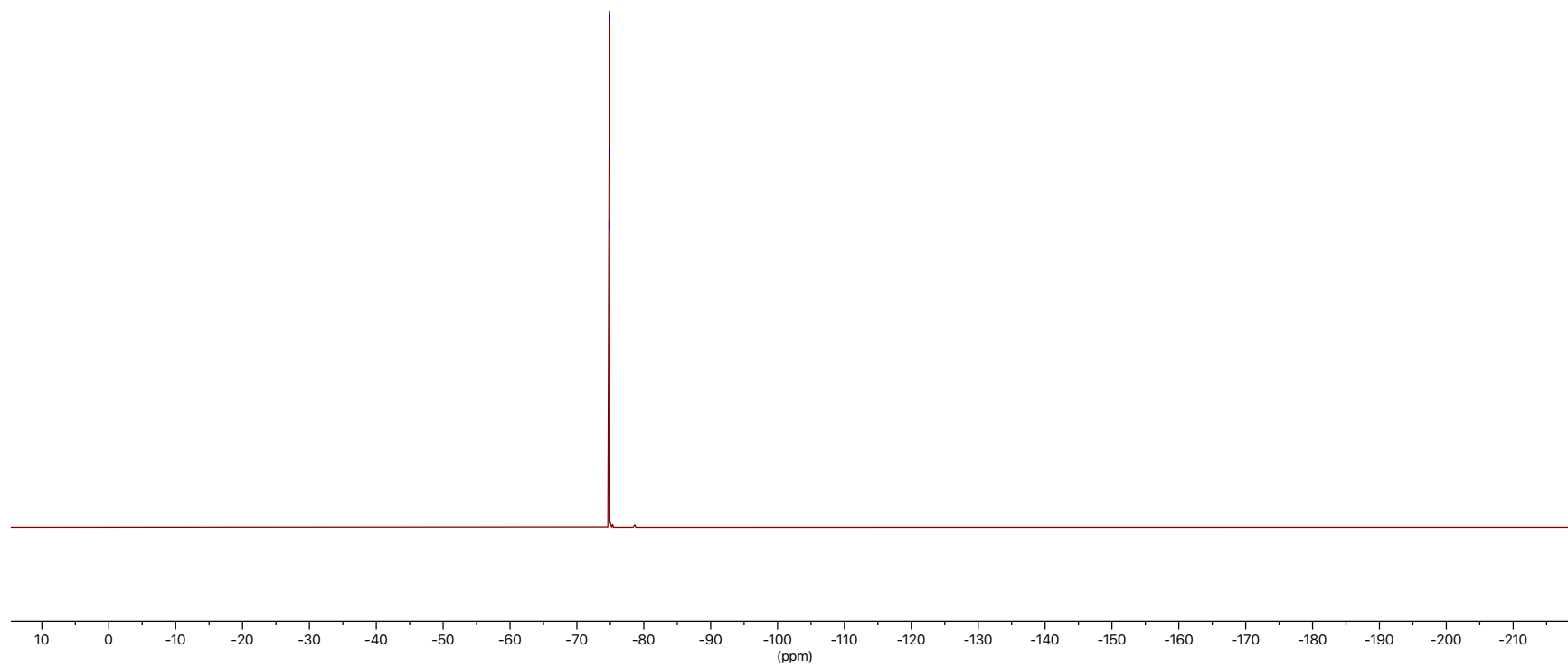
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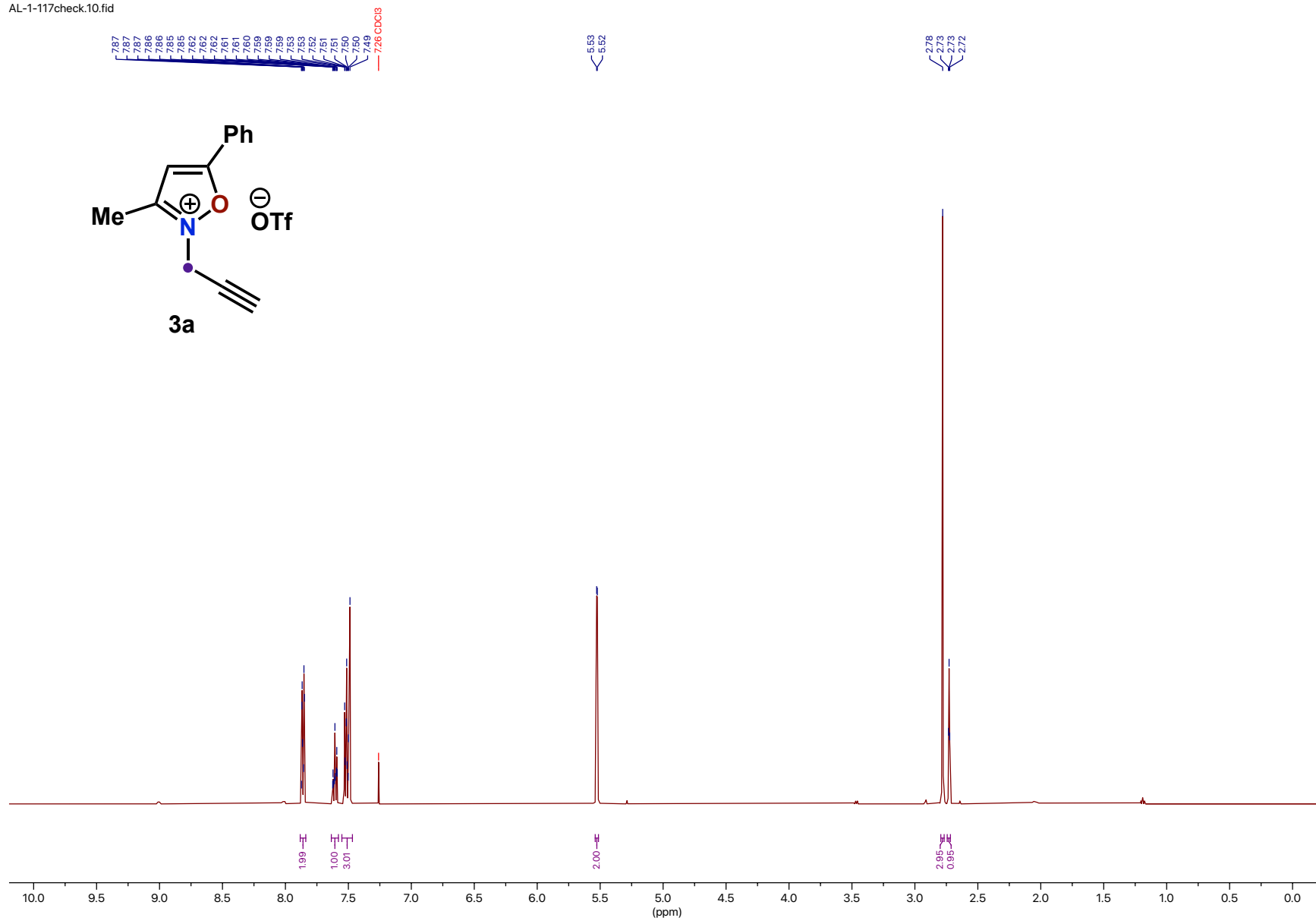
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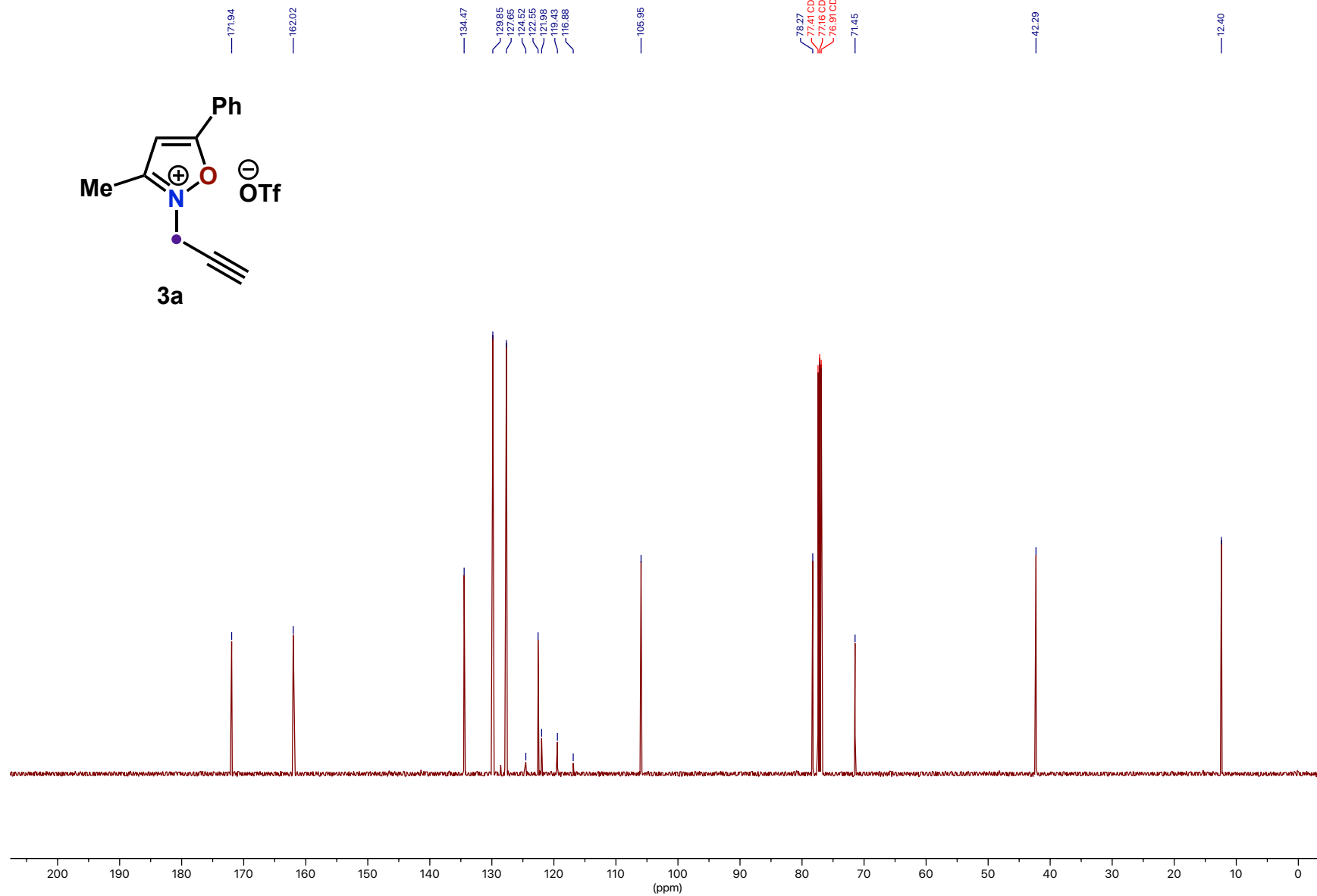
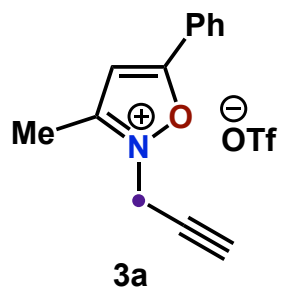


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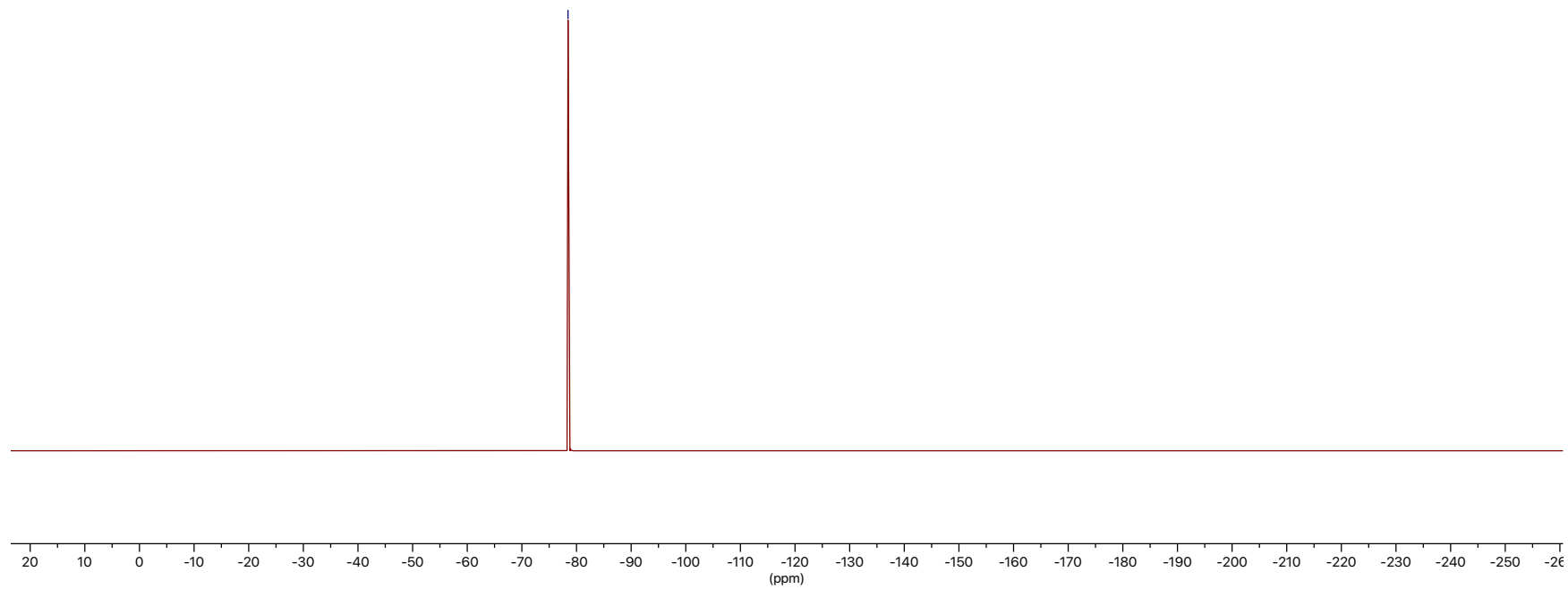
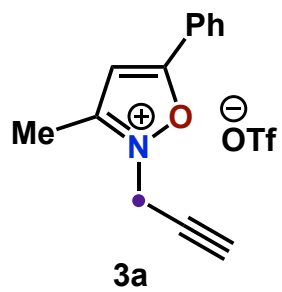


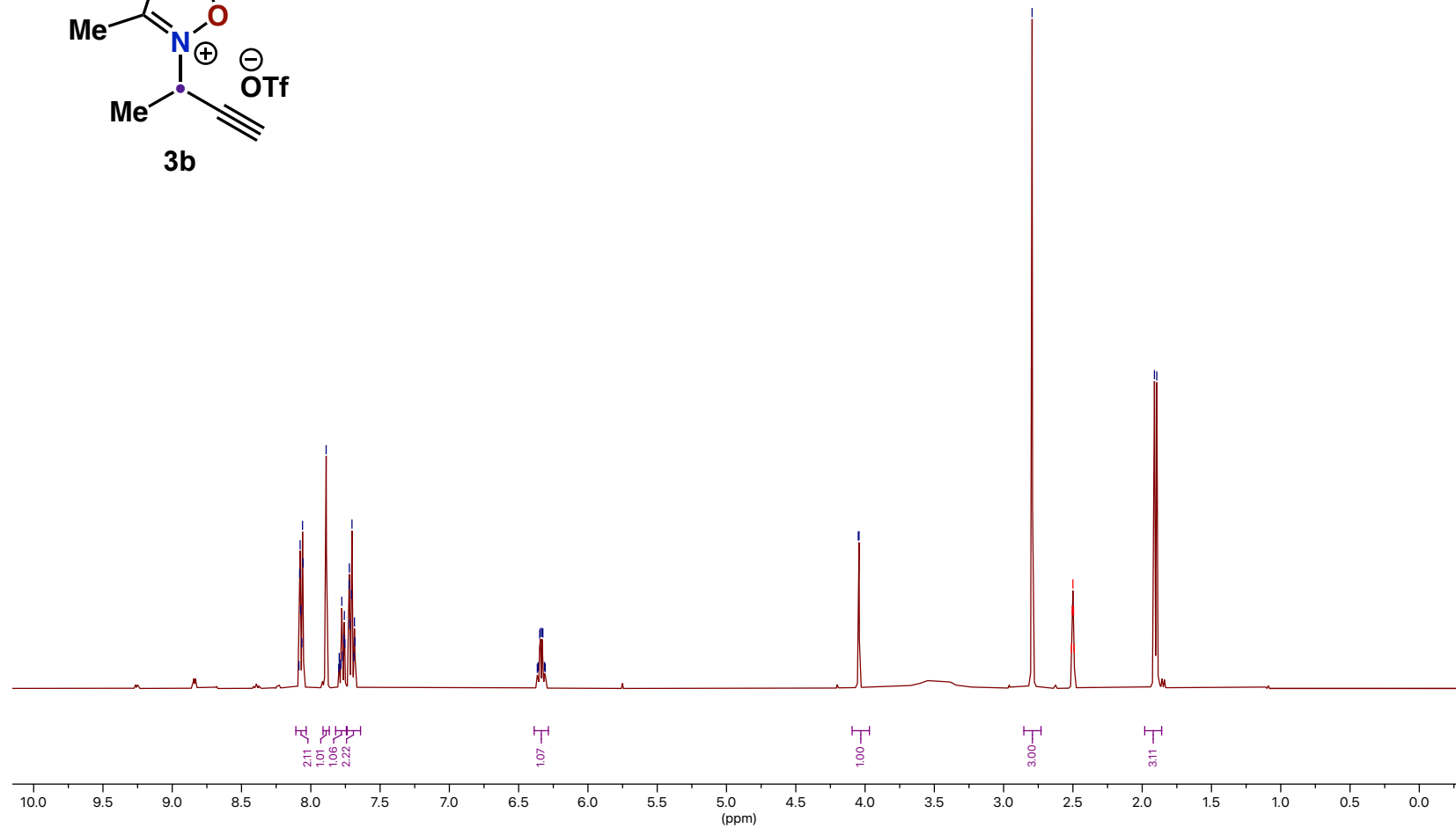
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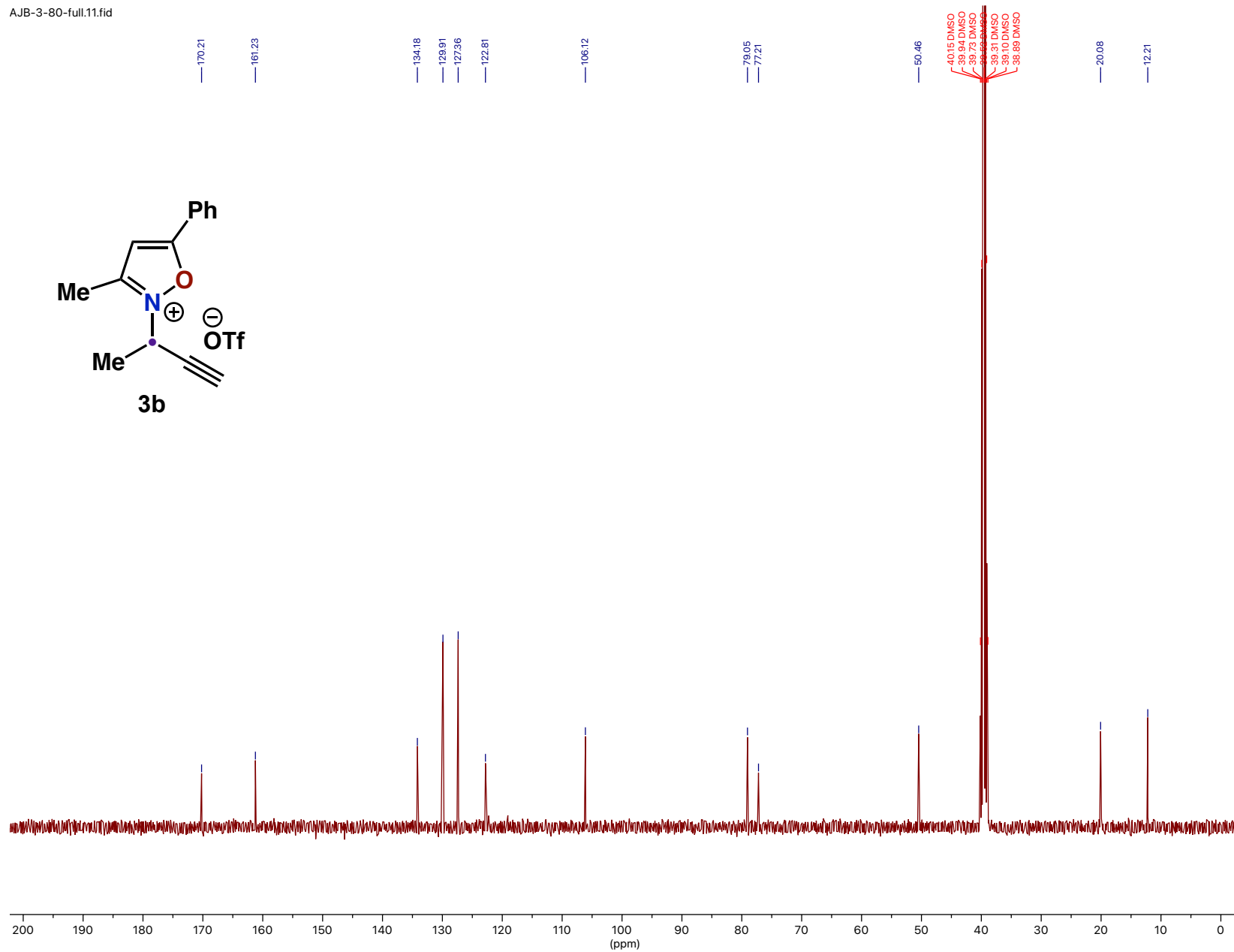




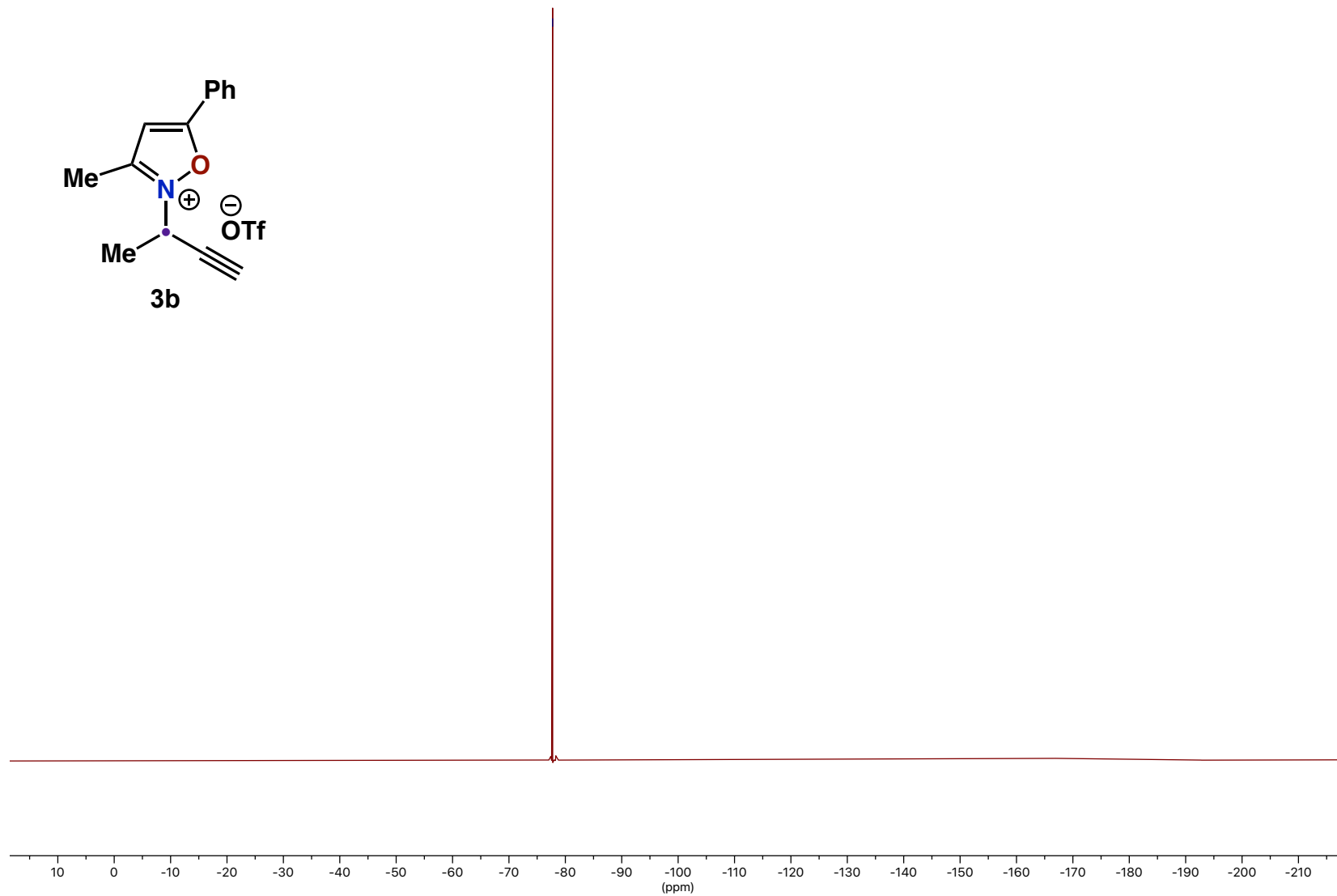
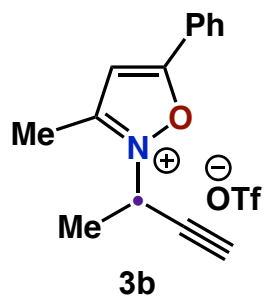
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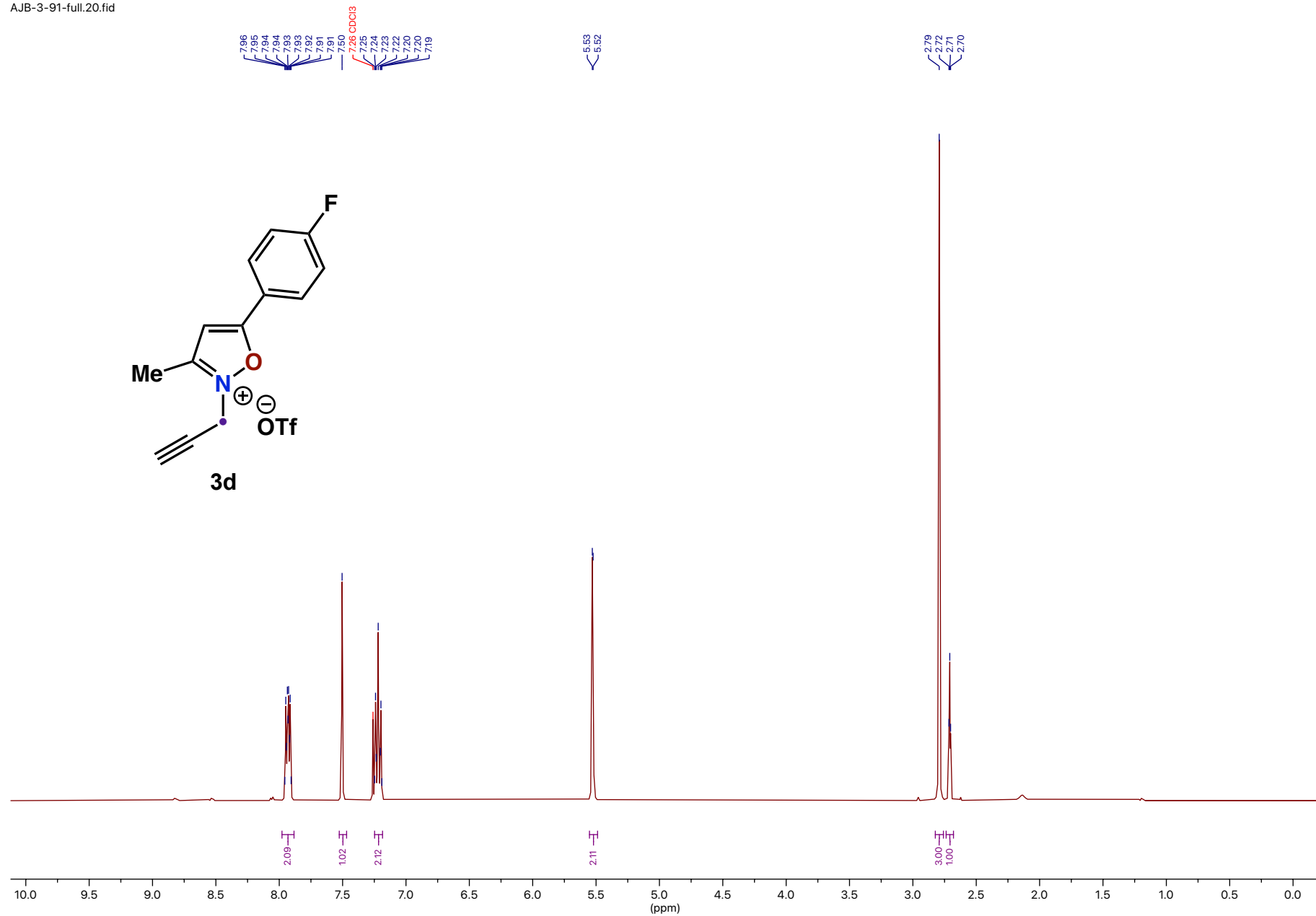
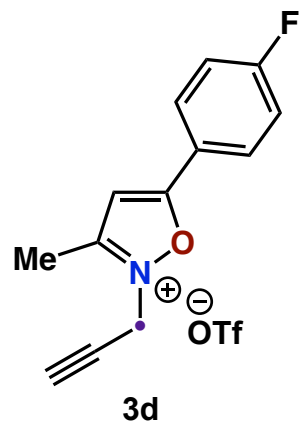


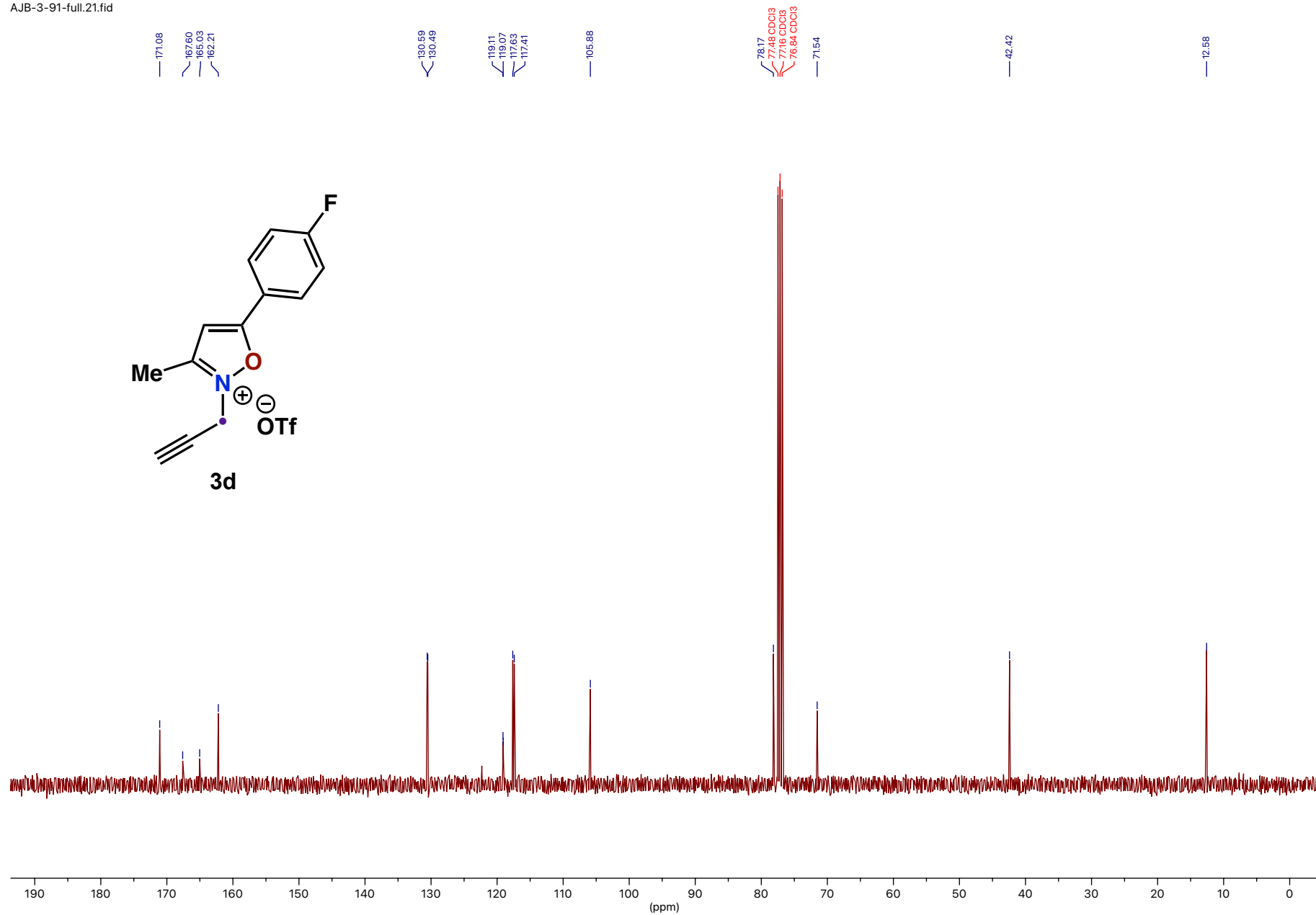
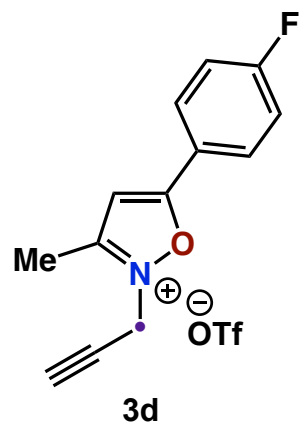


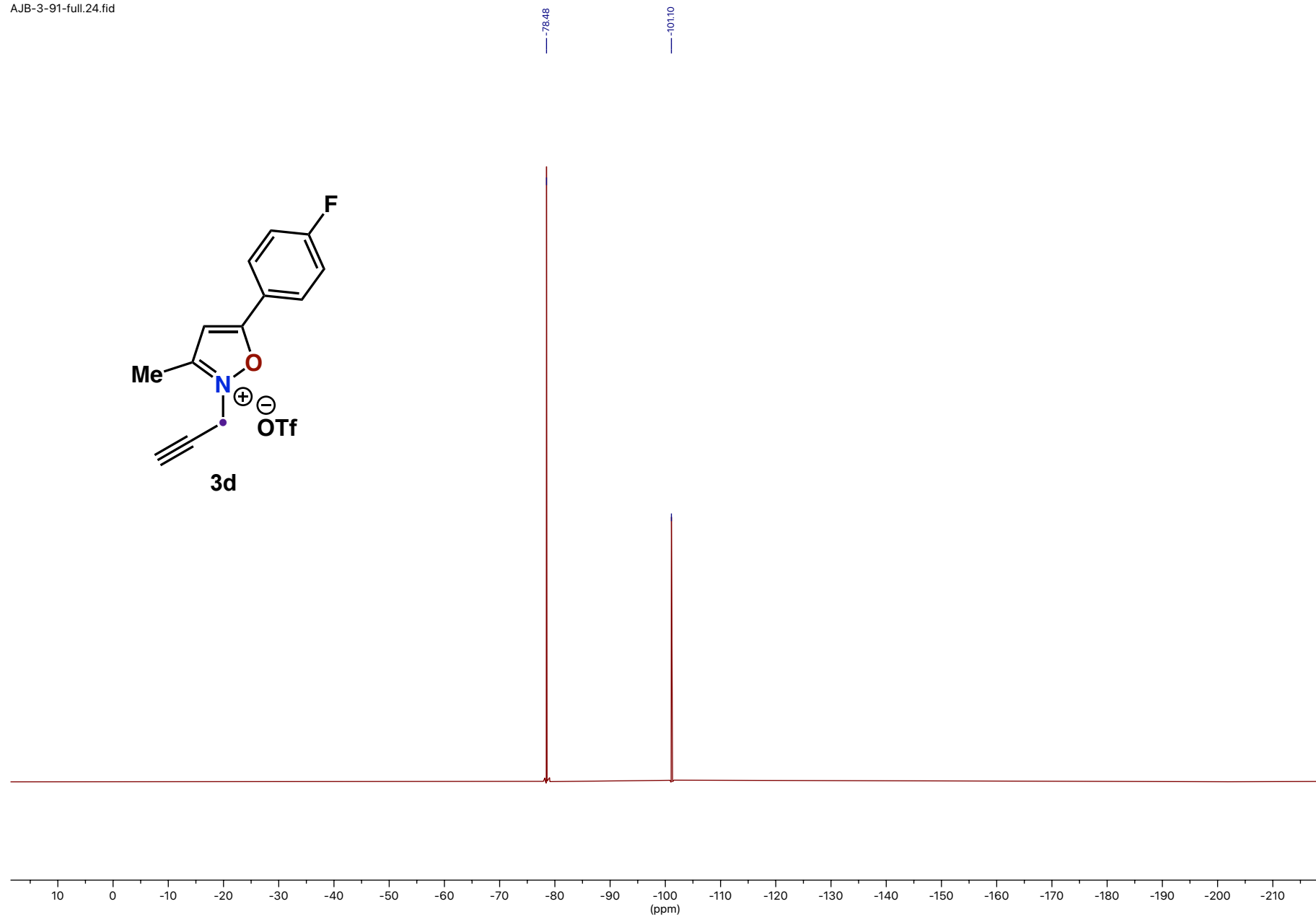
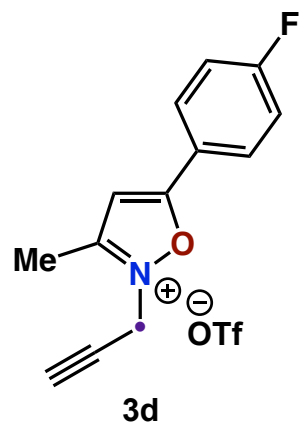


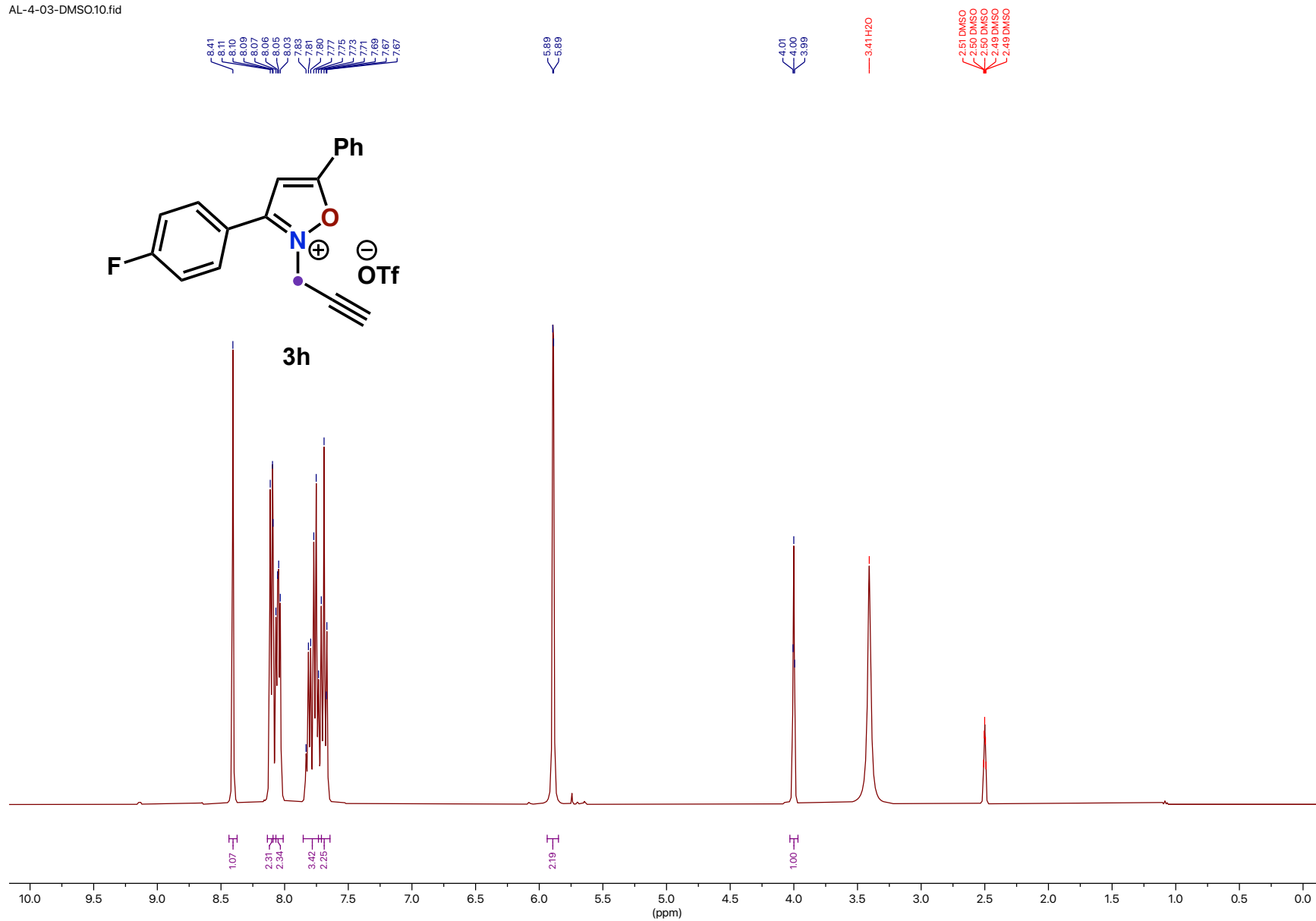
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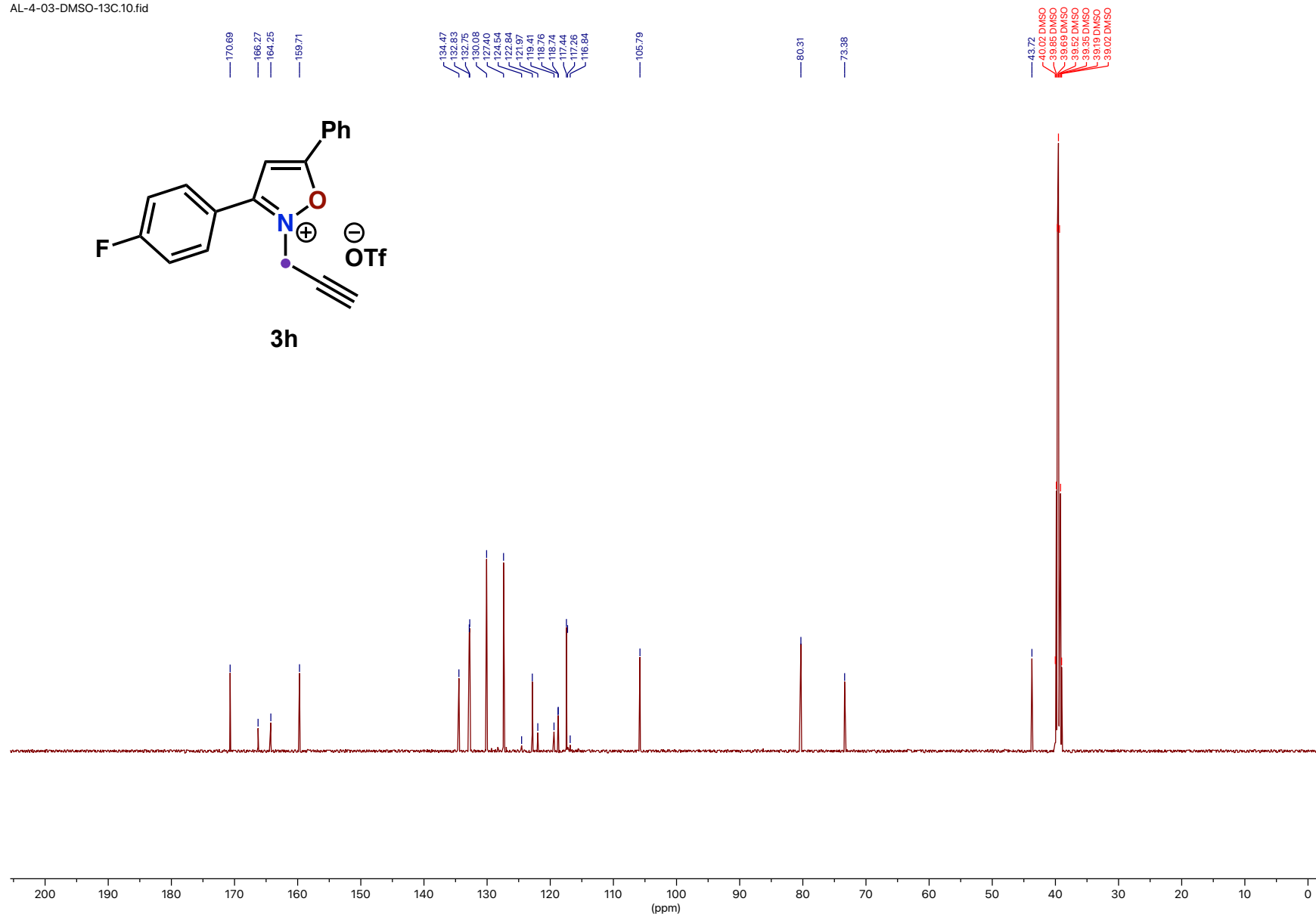


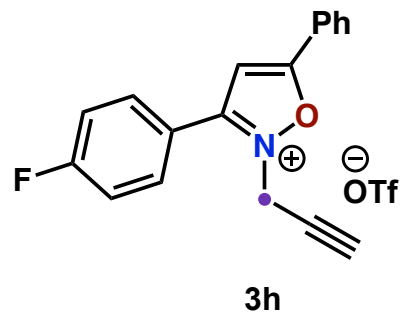






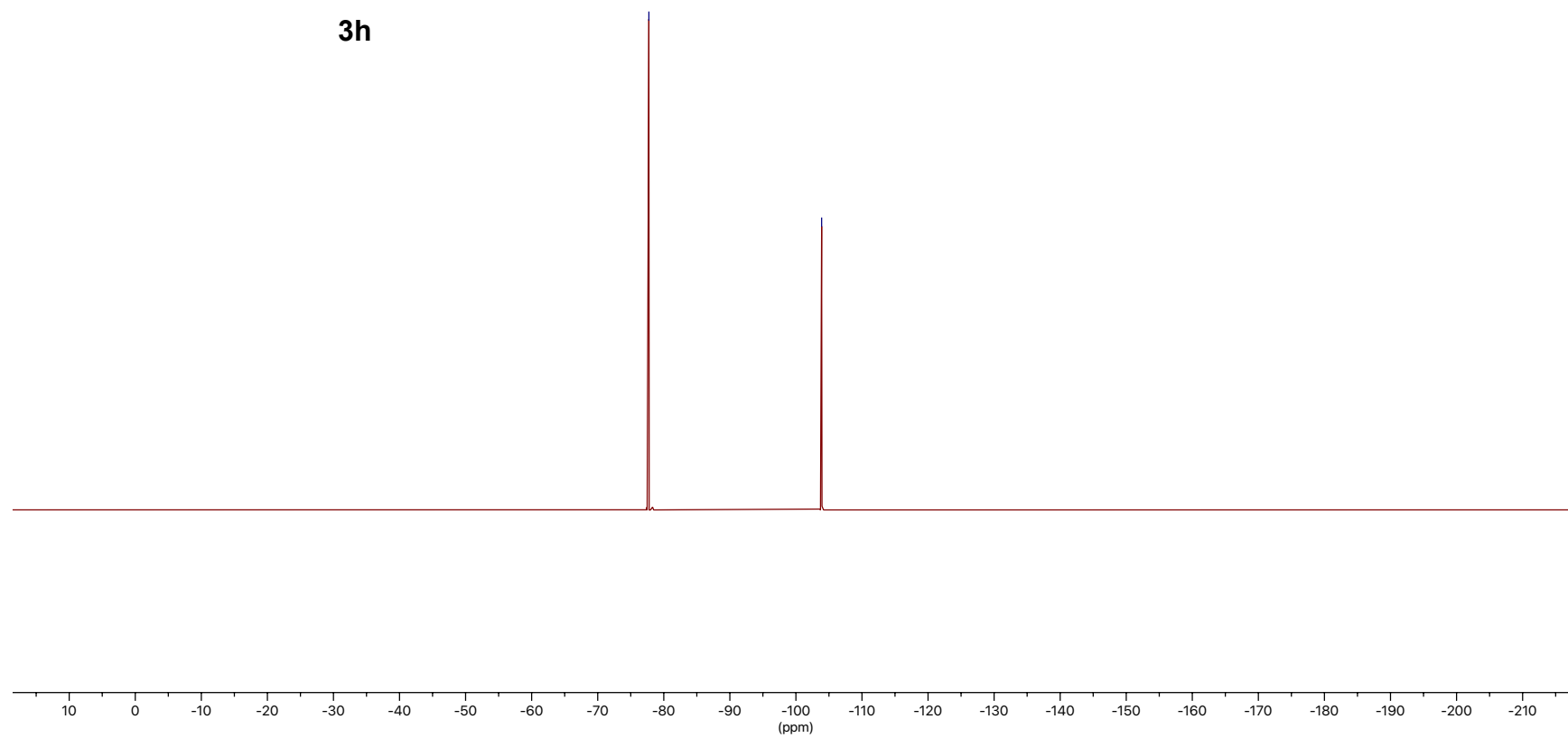


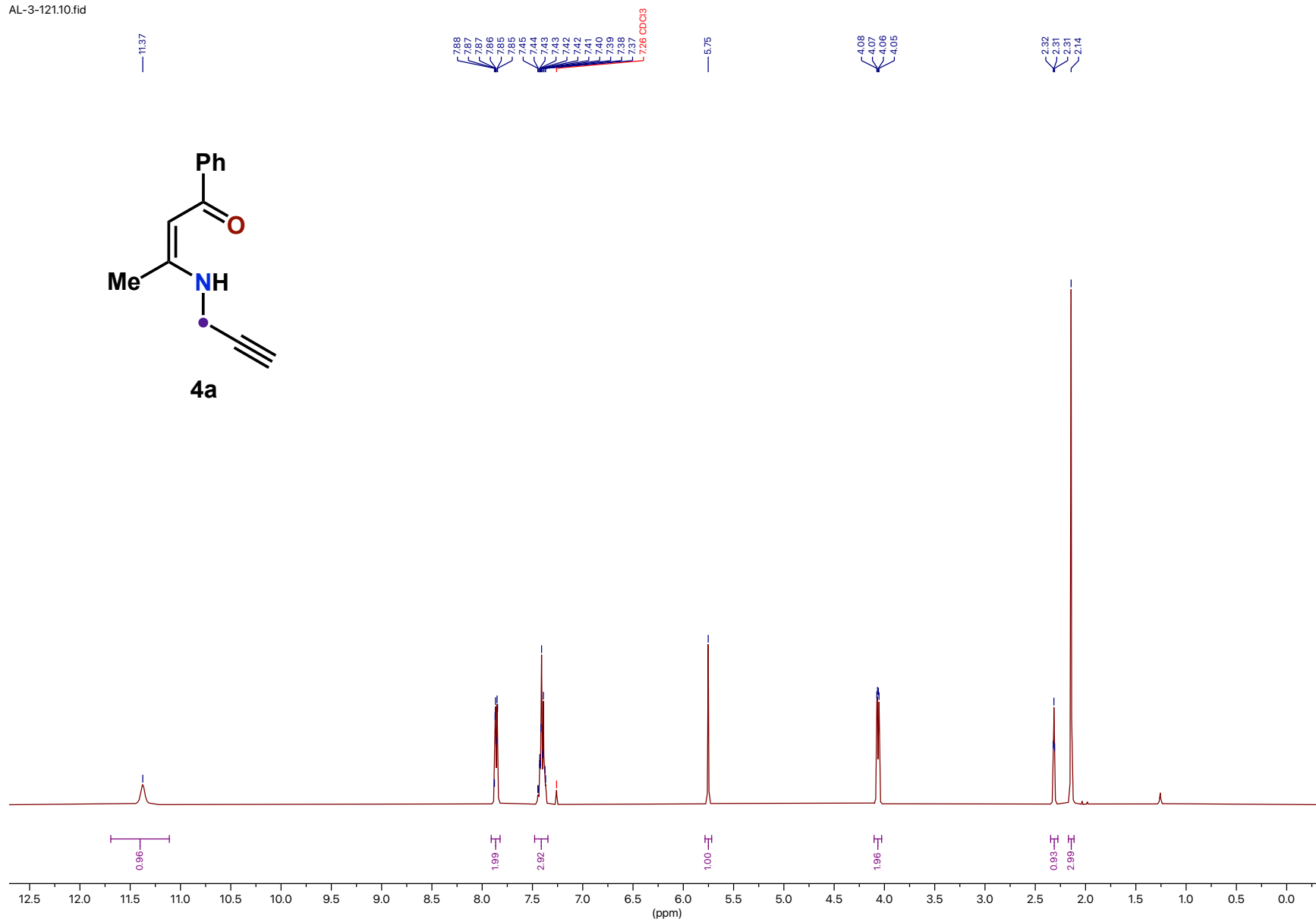




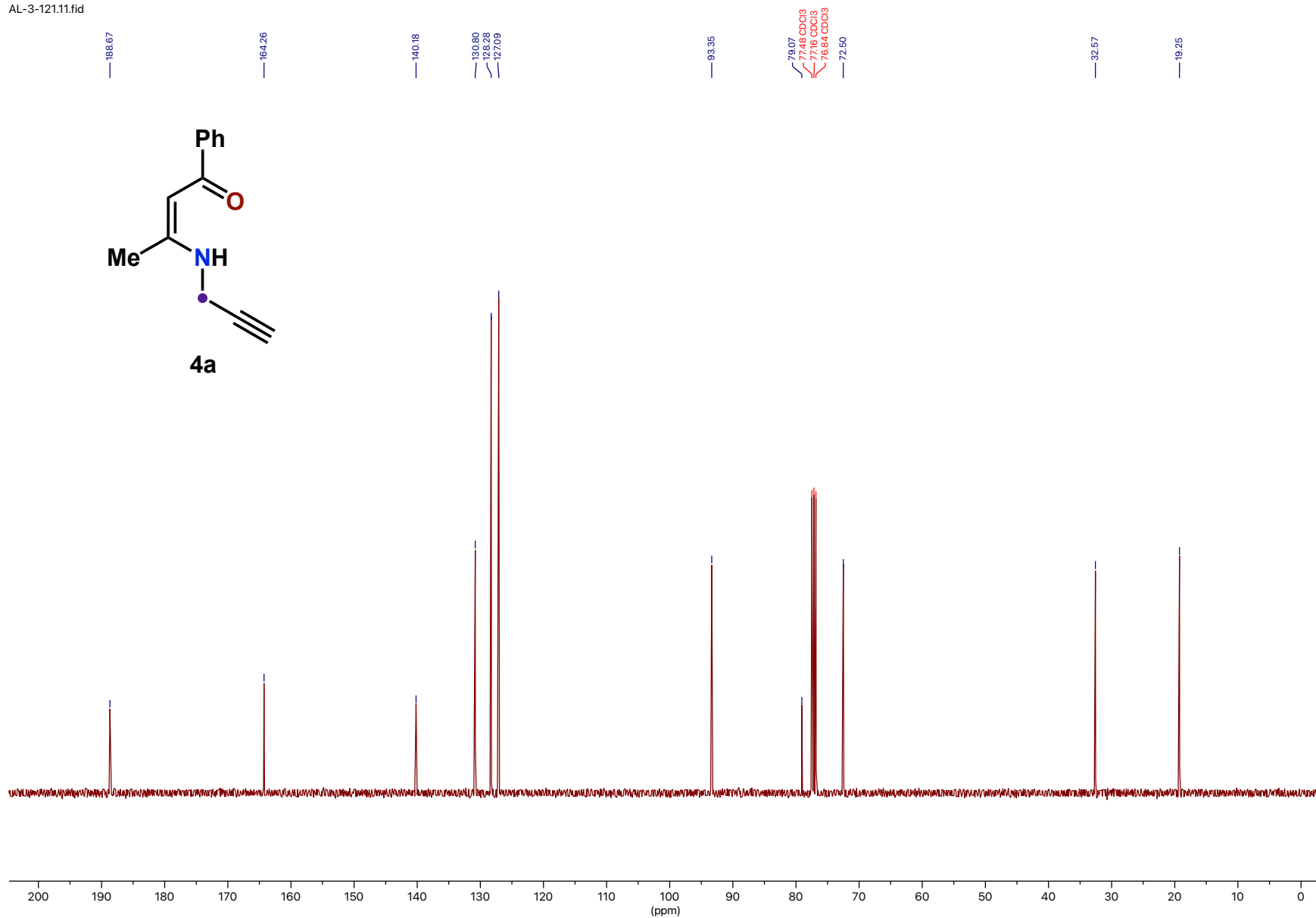
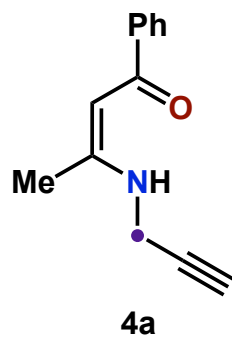
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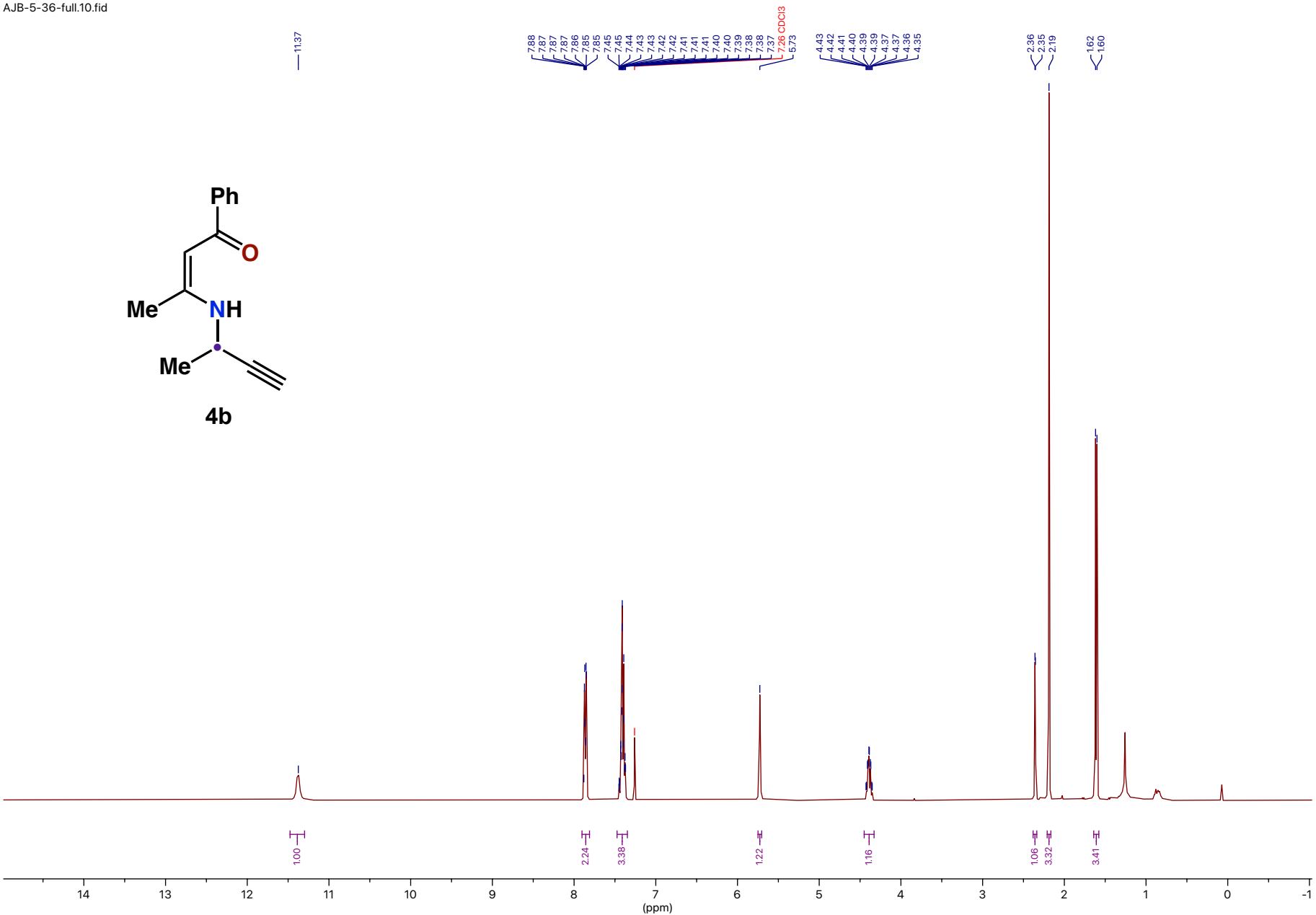
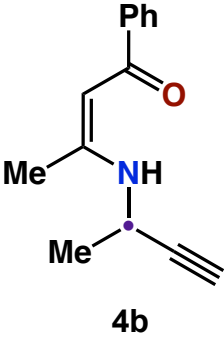
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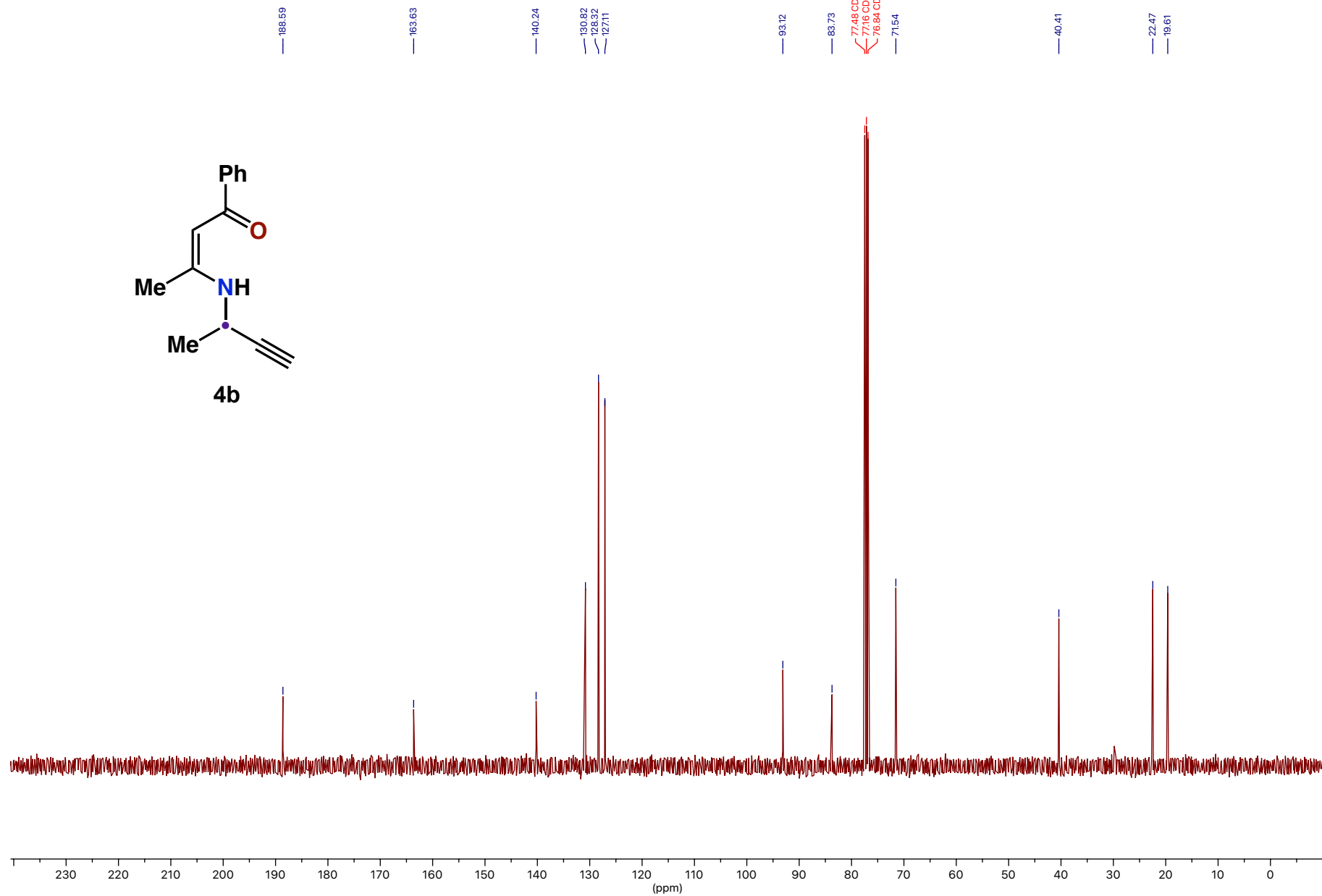
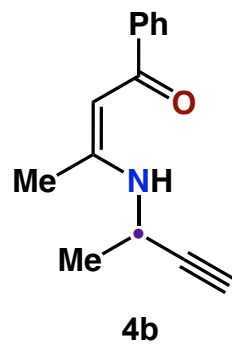


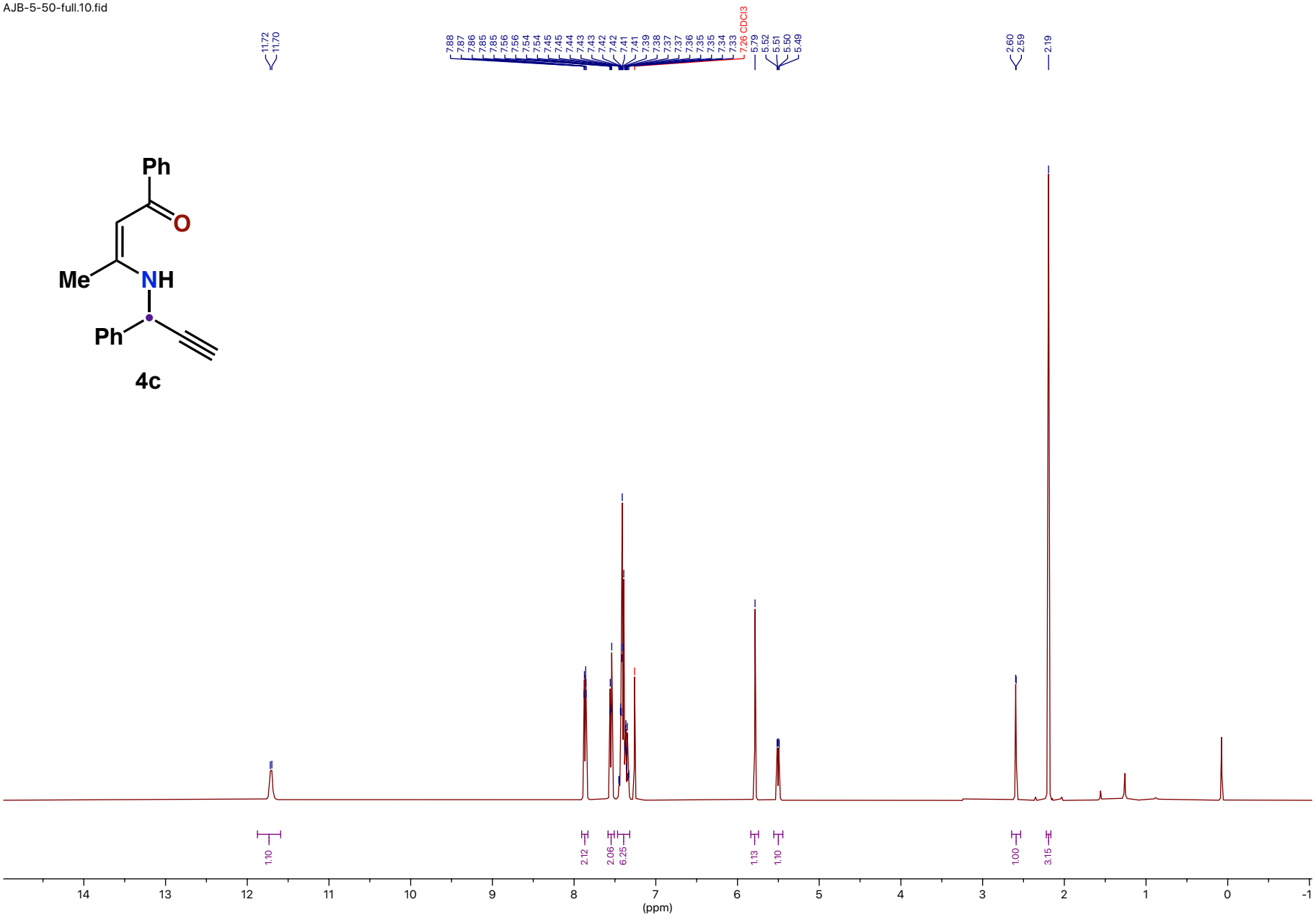


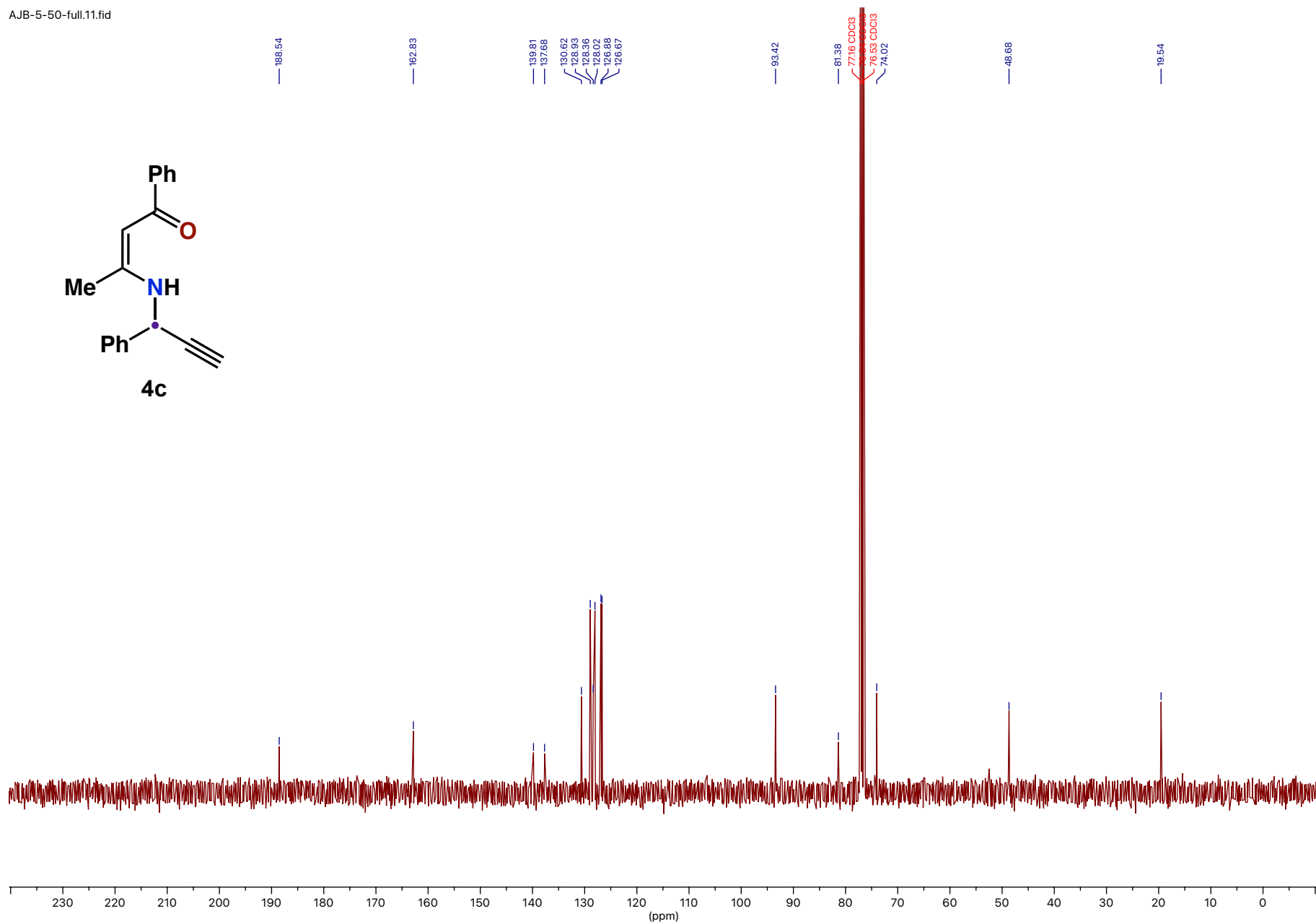
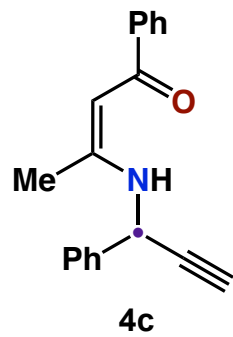
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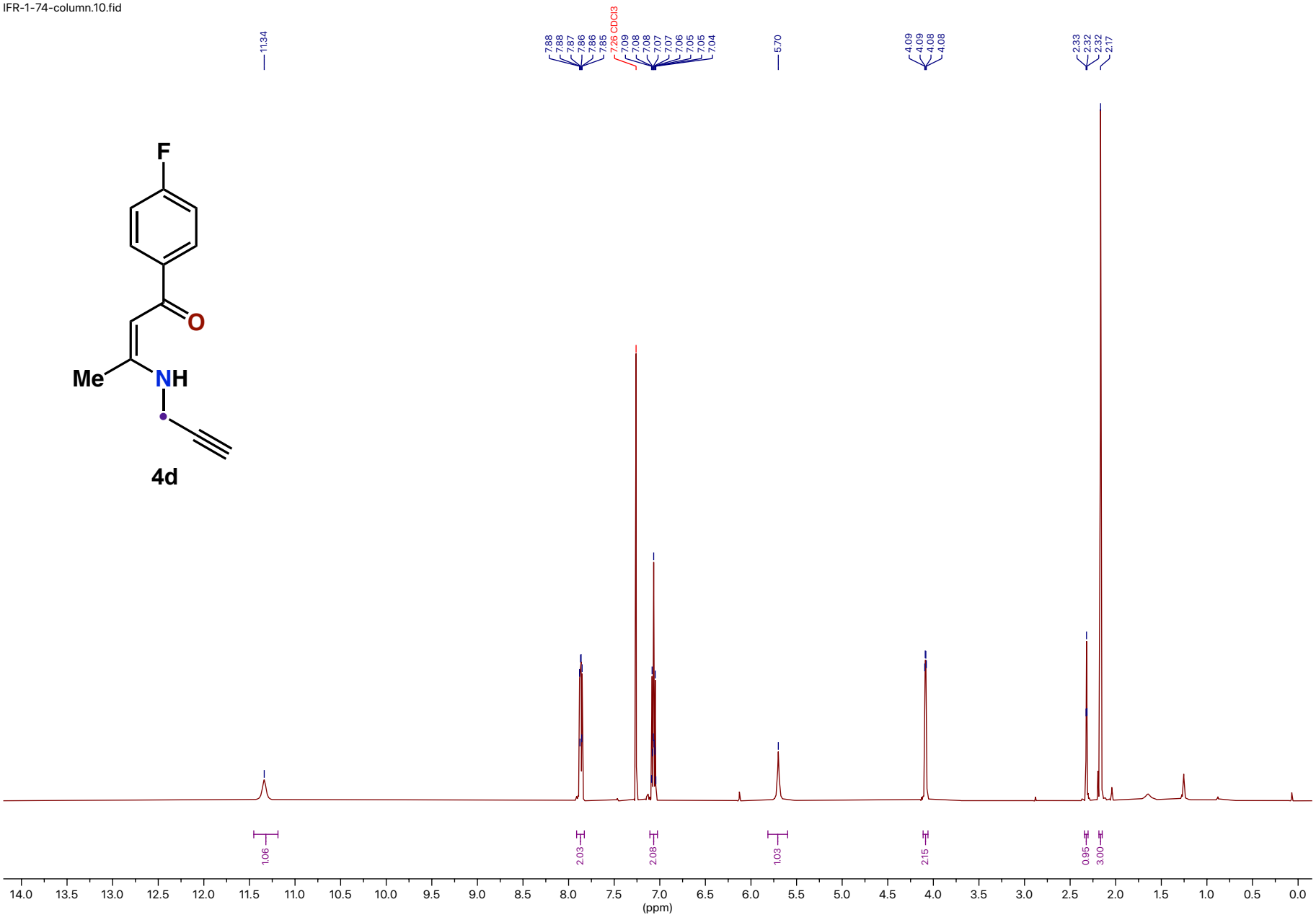


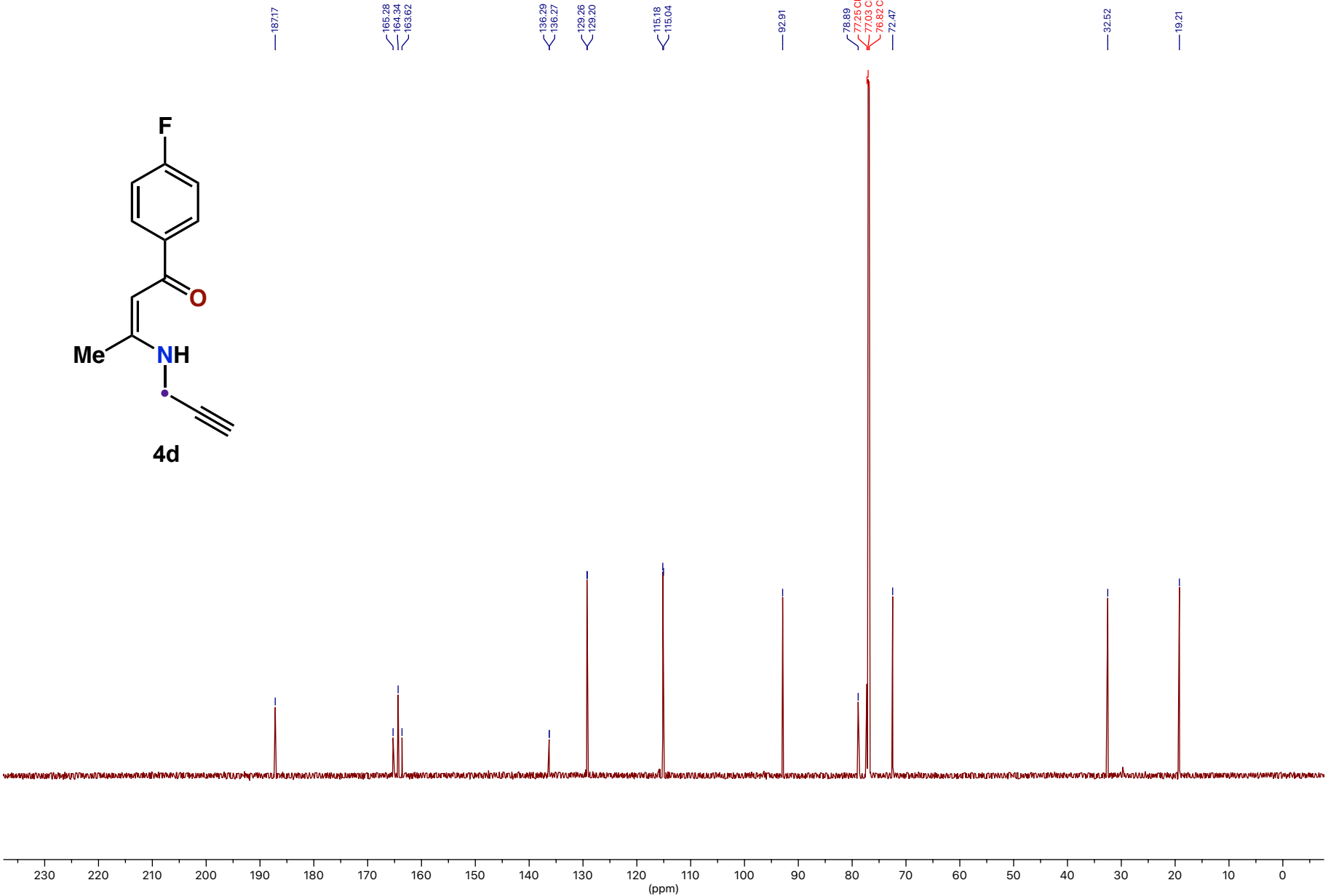


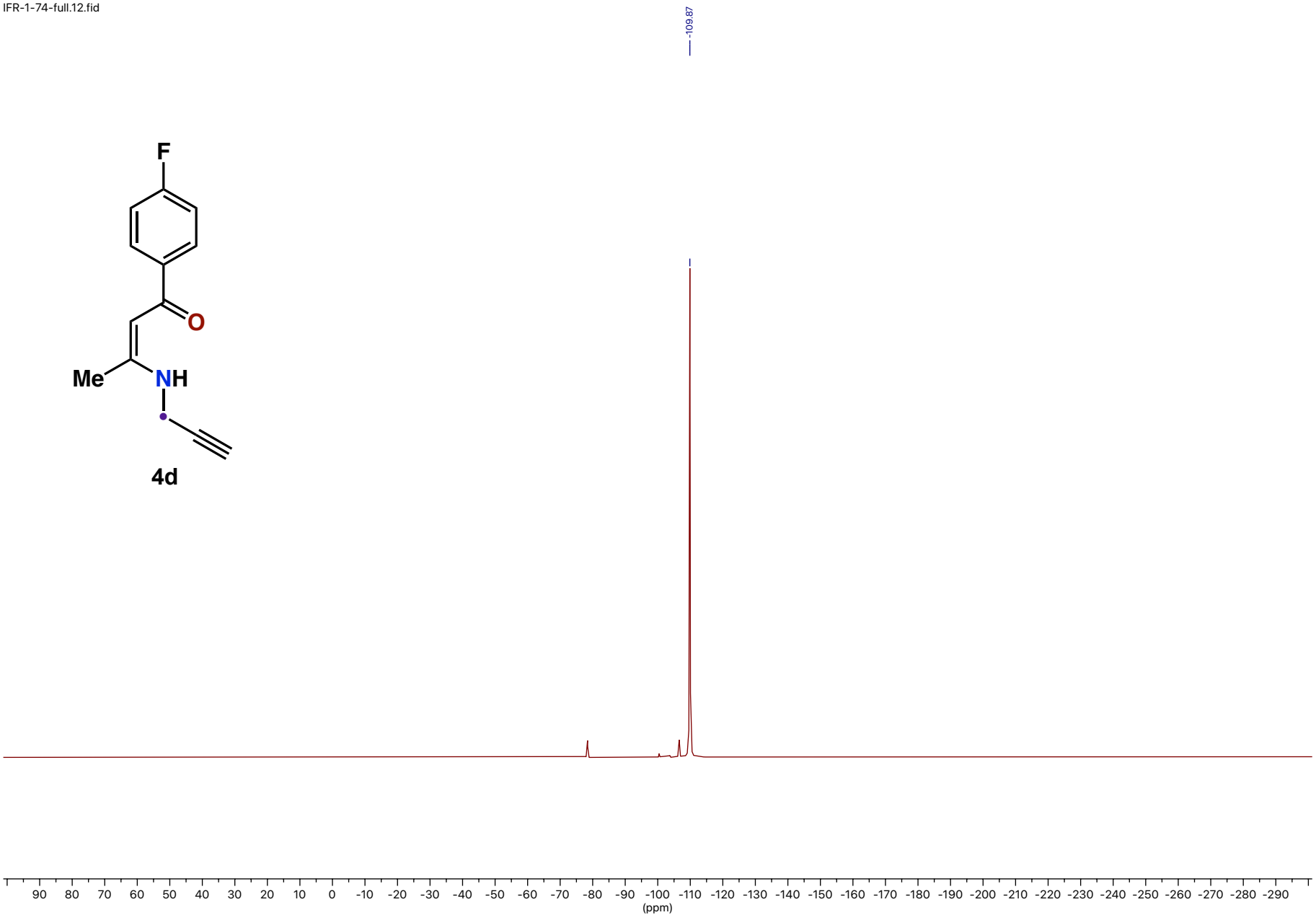
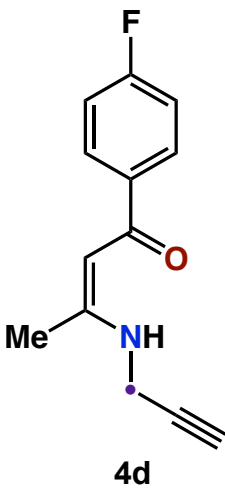


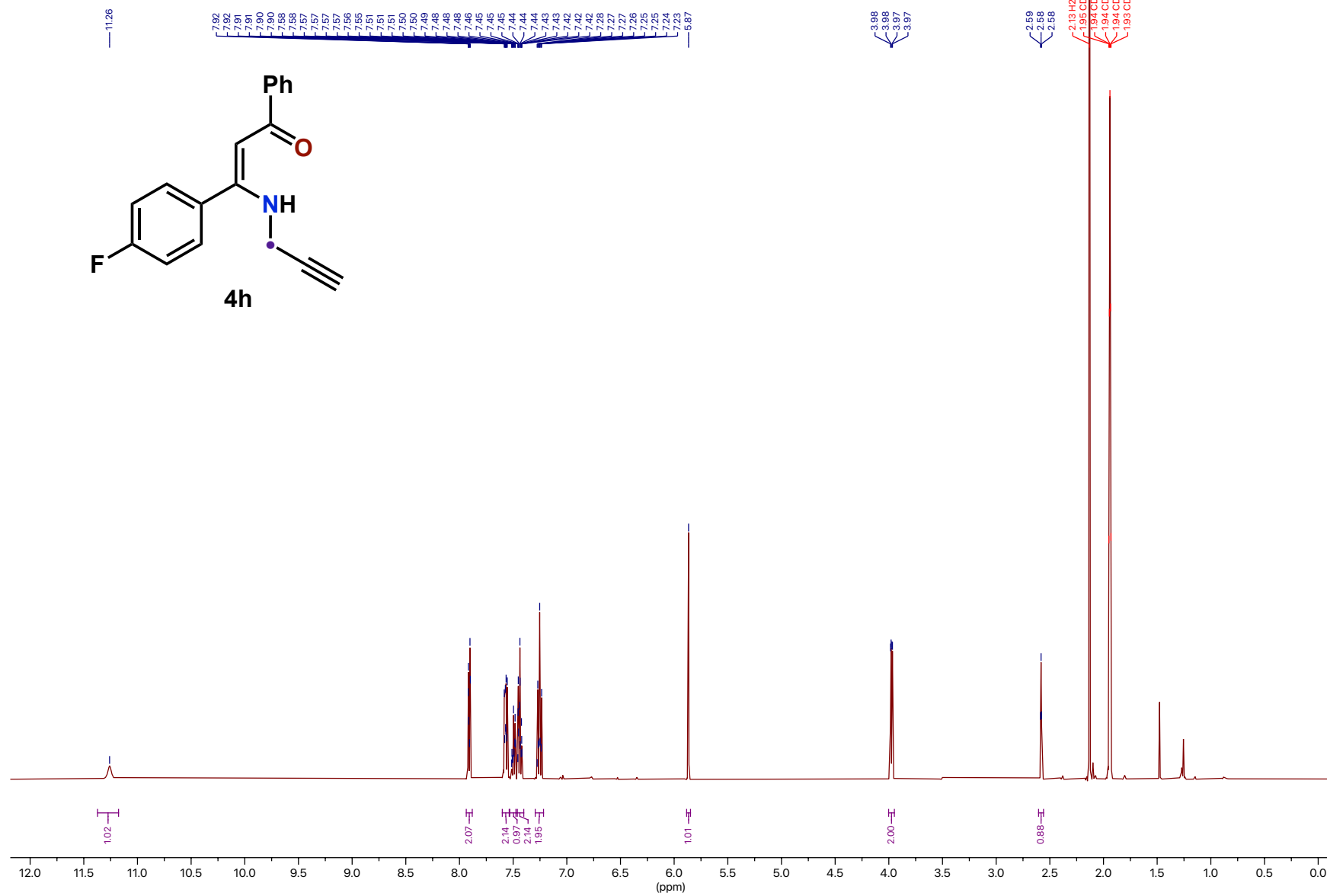


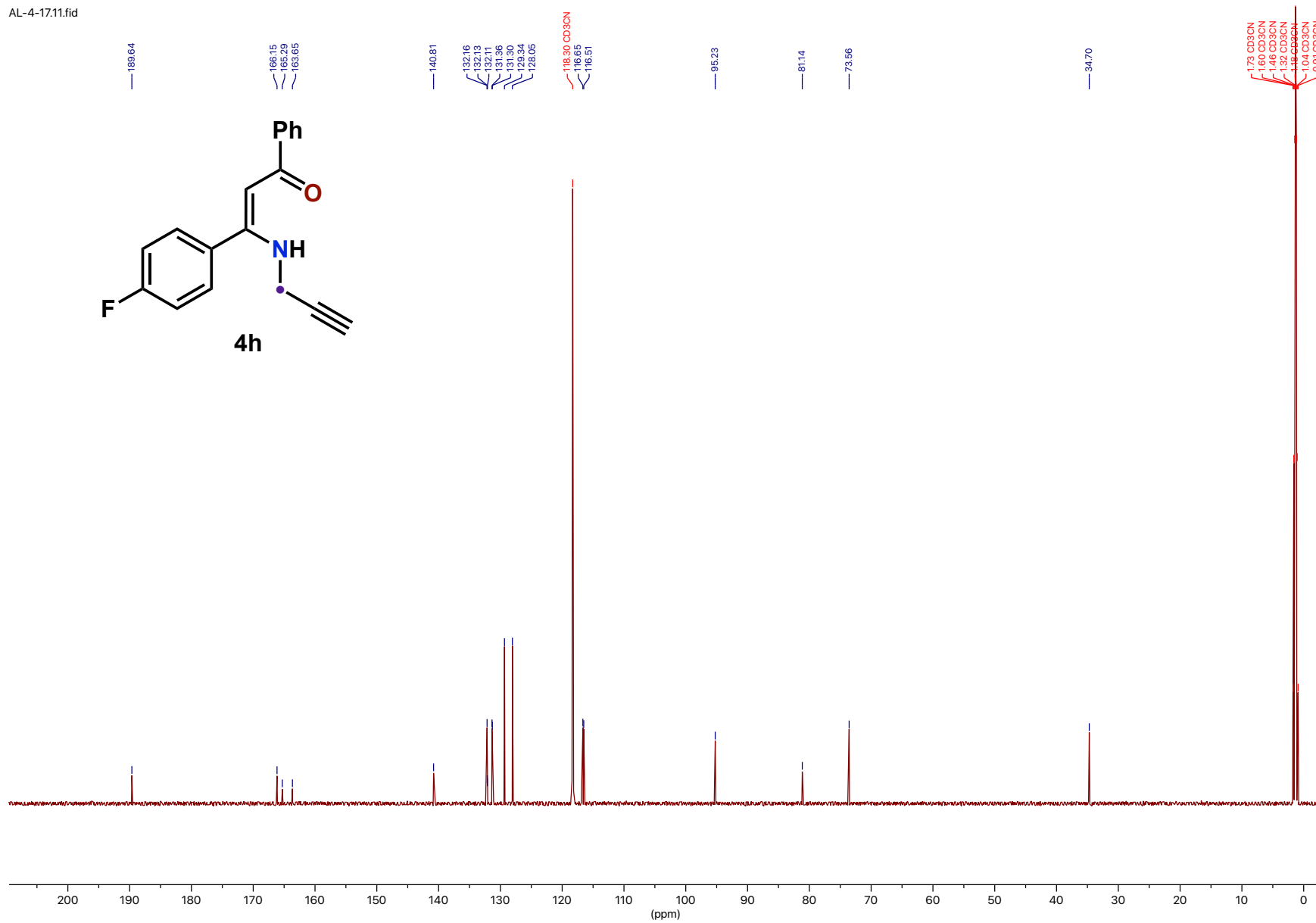


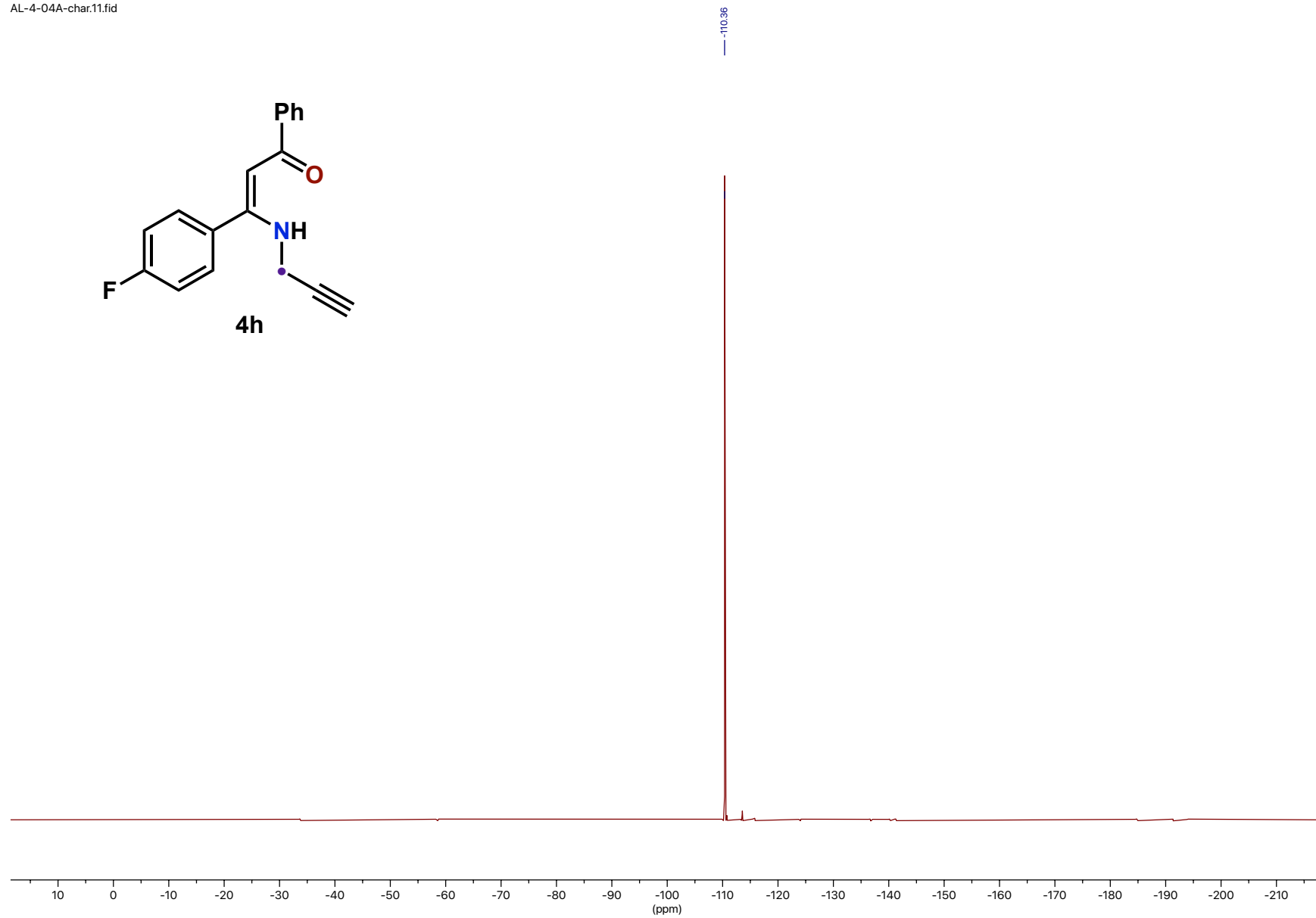
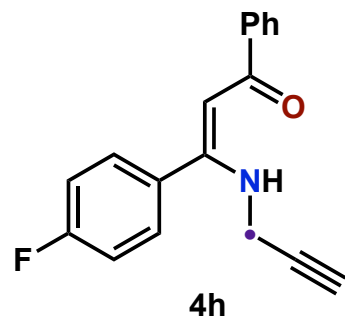


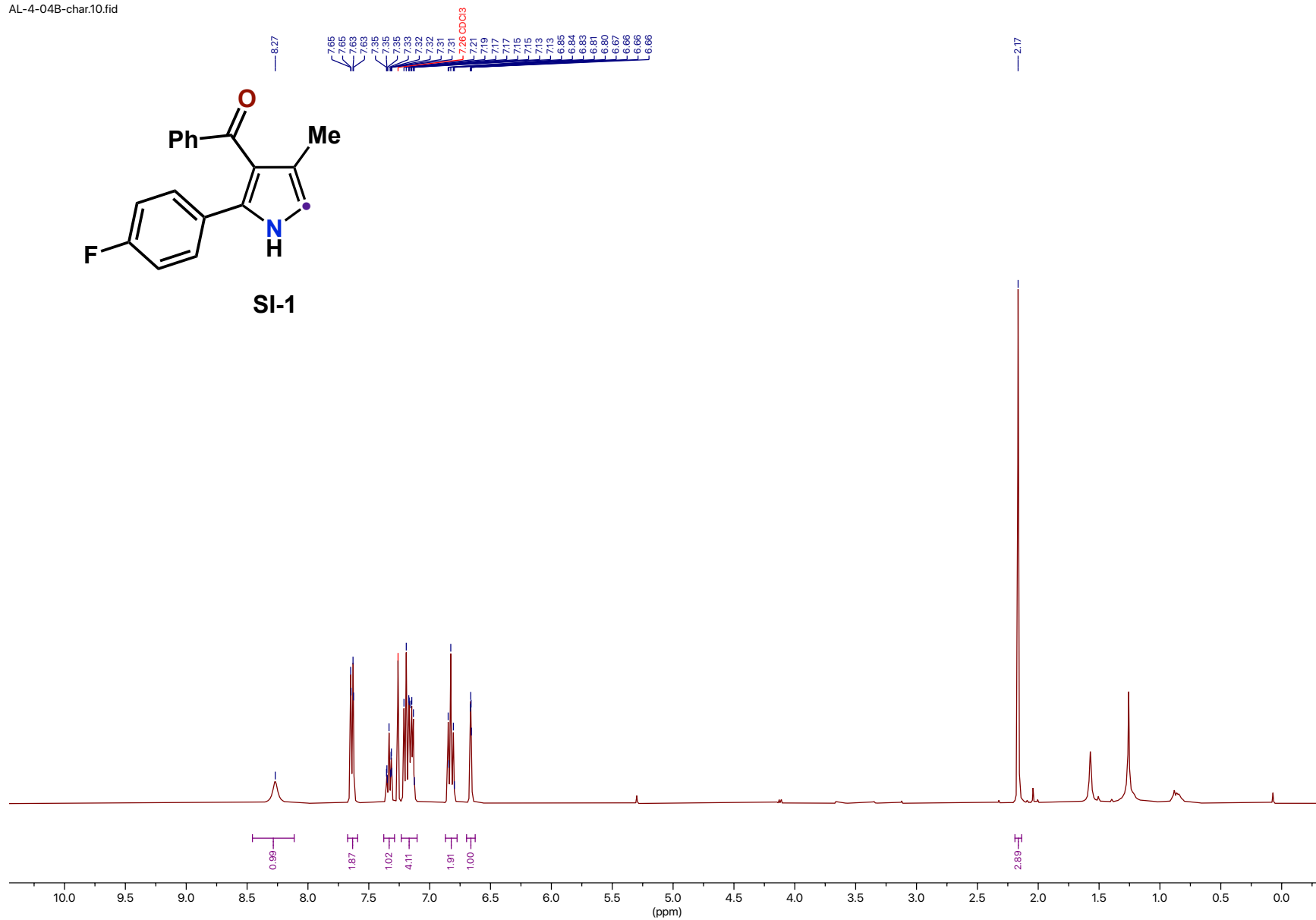


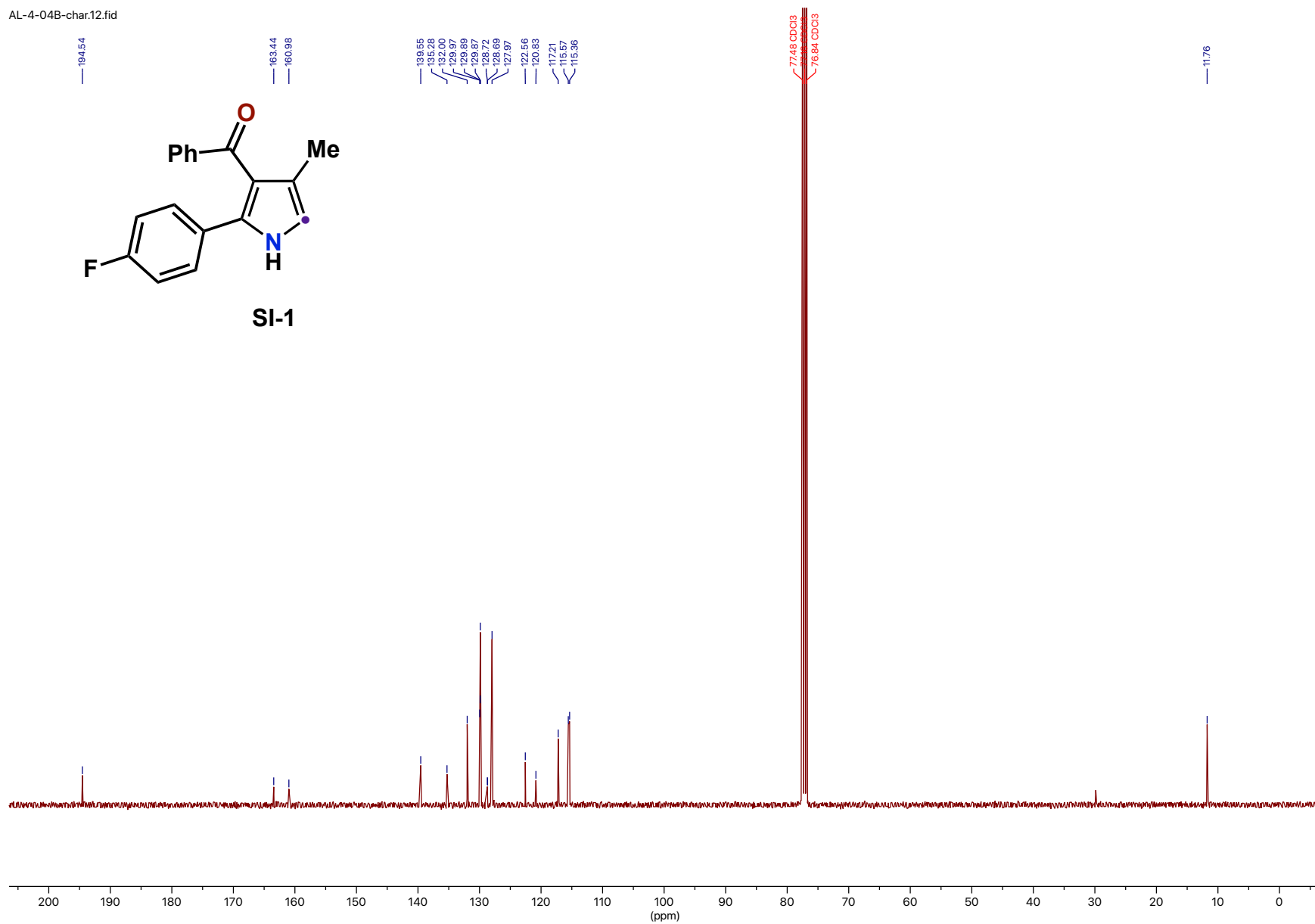












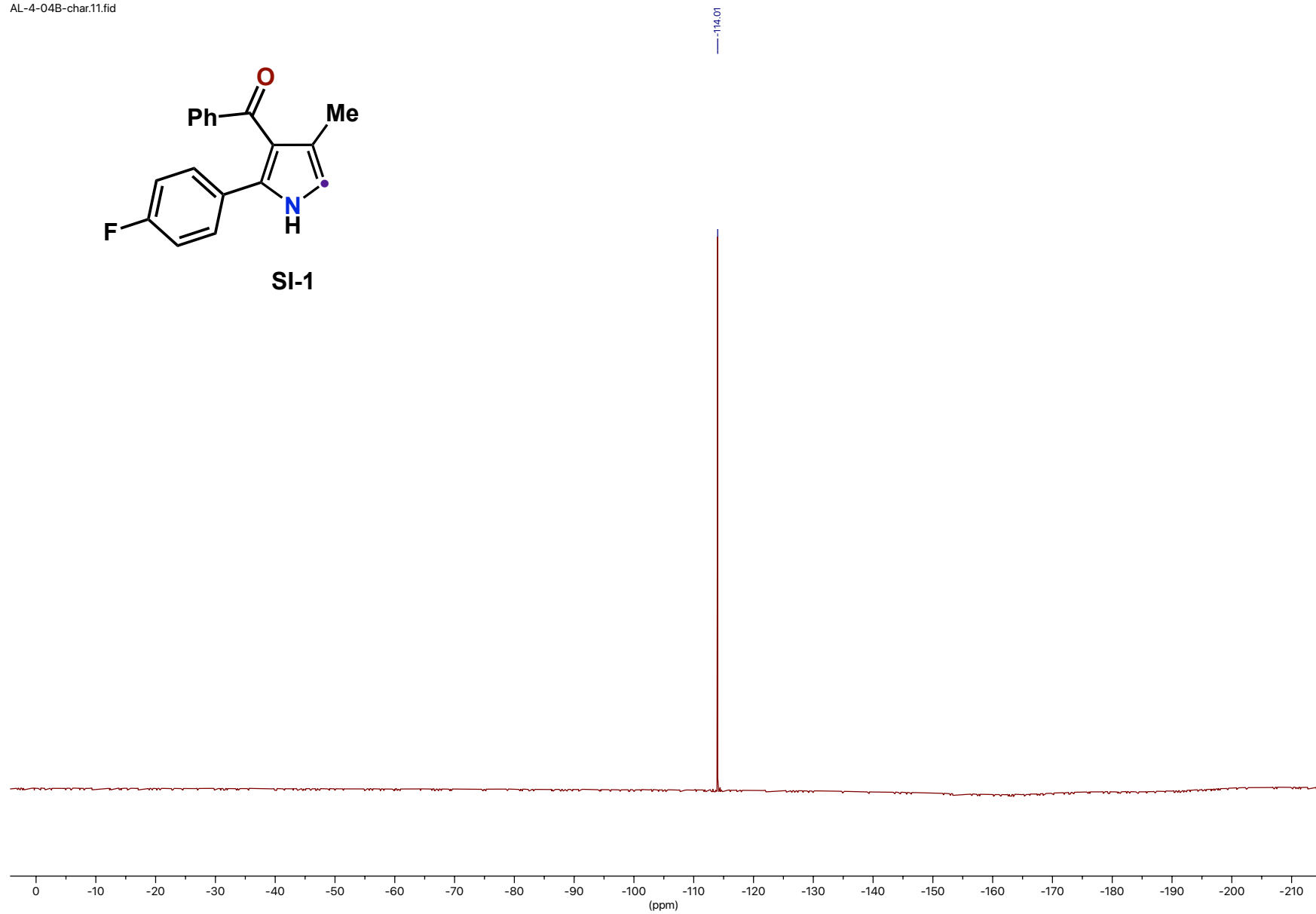
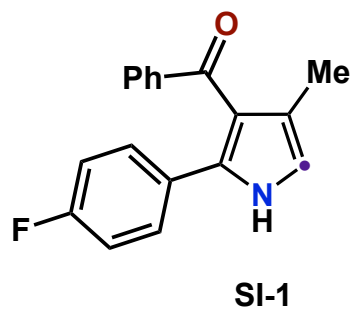
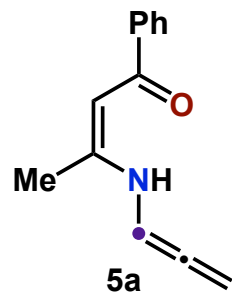
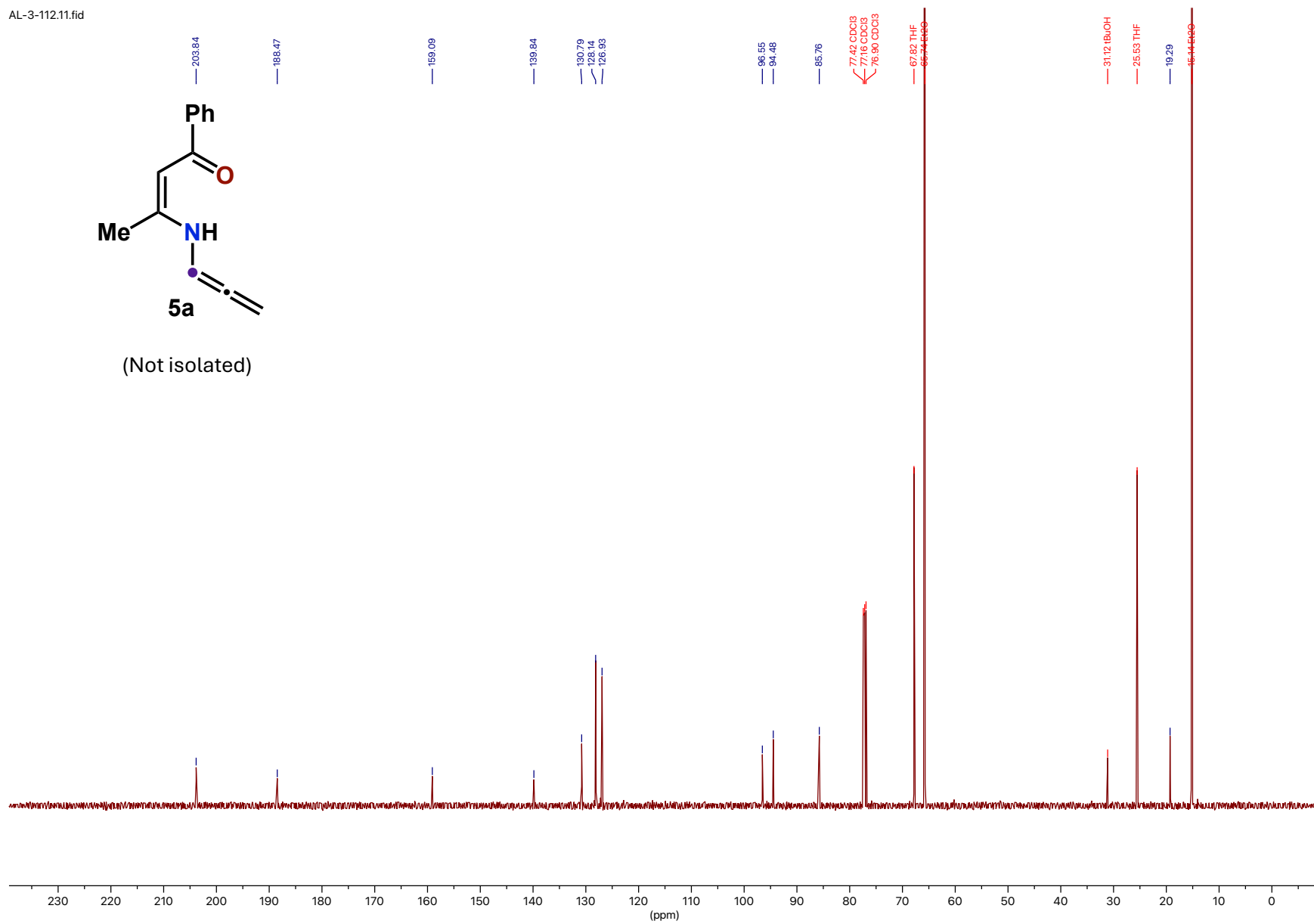


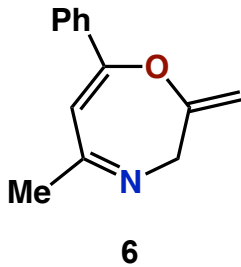
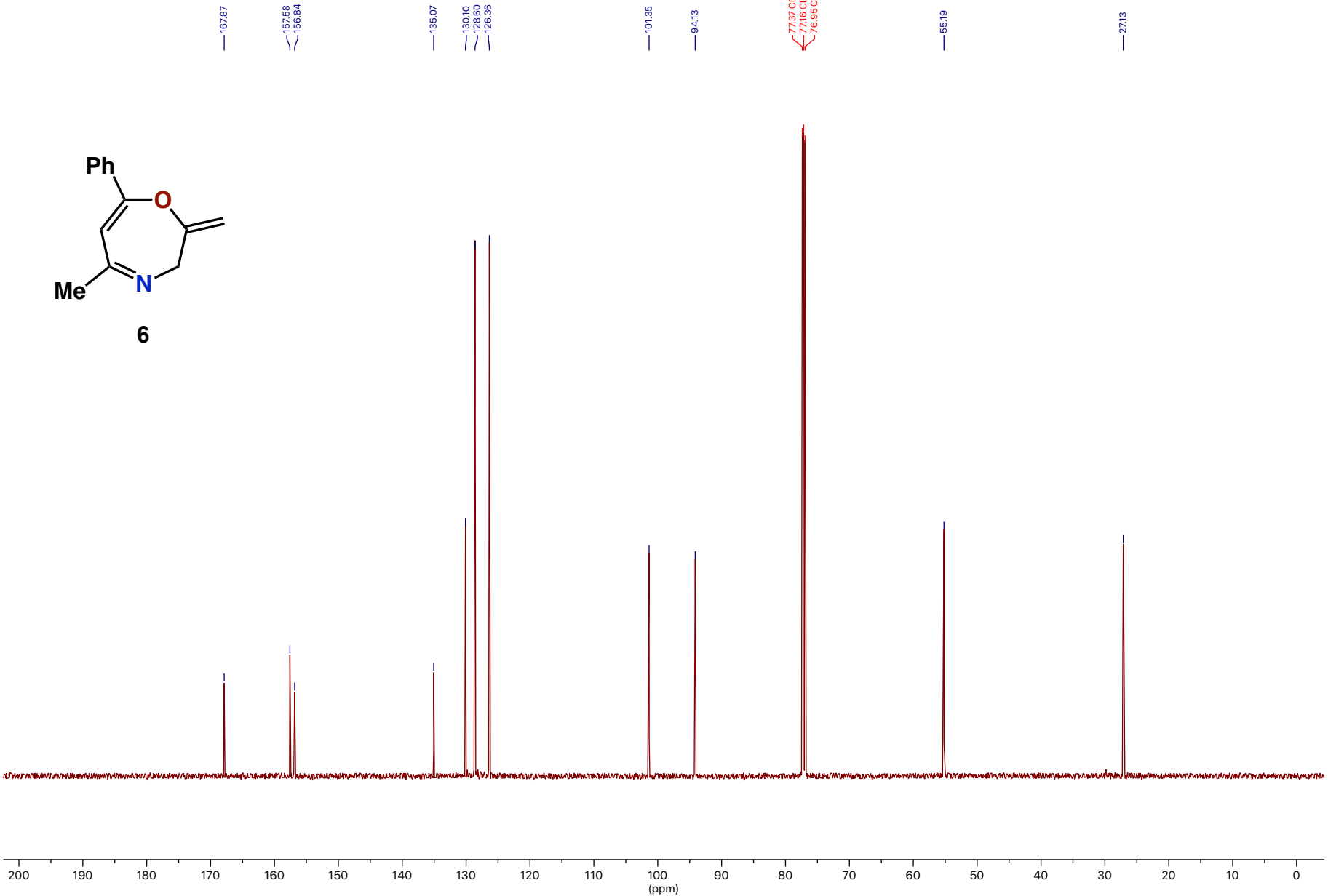
Figure 1: Schematic representation of the 1000 bp DNA region. The top part shows a linear map with 1000 bp scale and various features labeled. The bottom part shows a detailed view of the 1000 bp region with various features labeled.

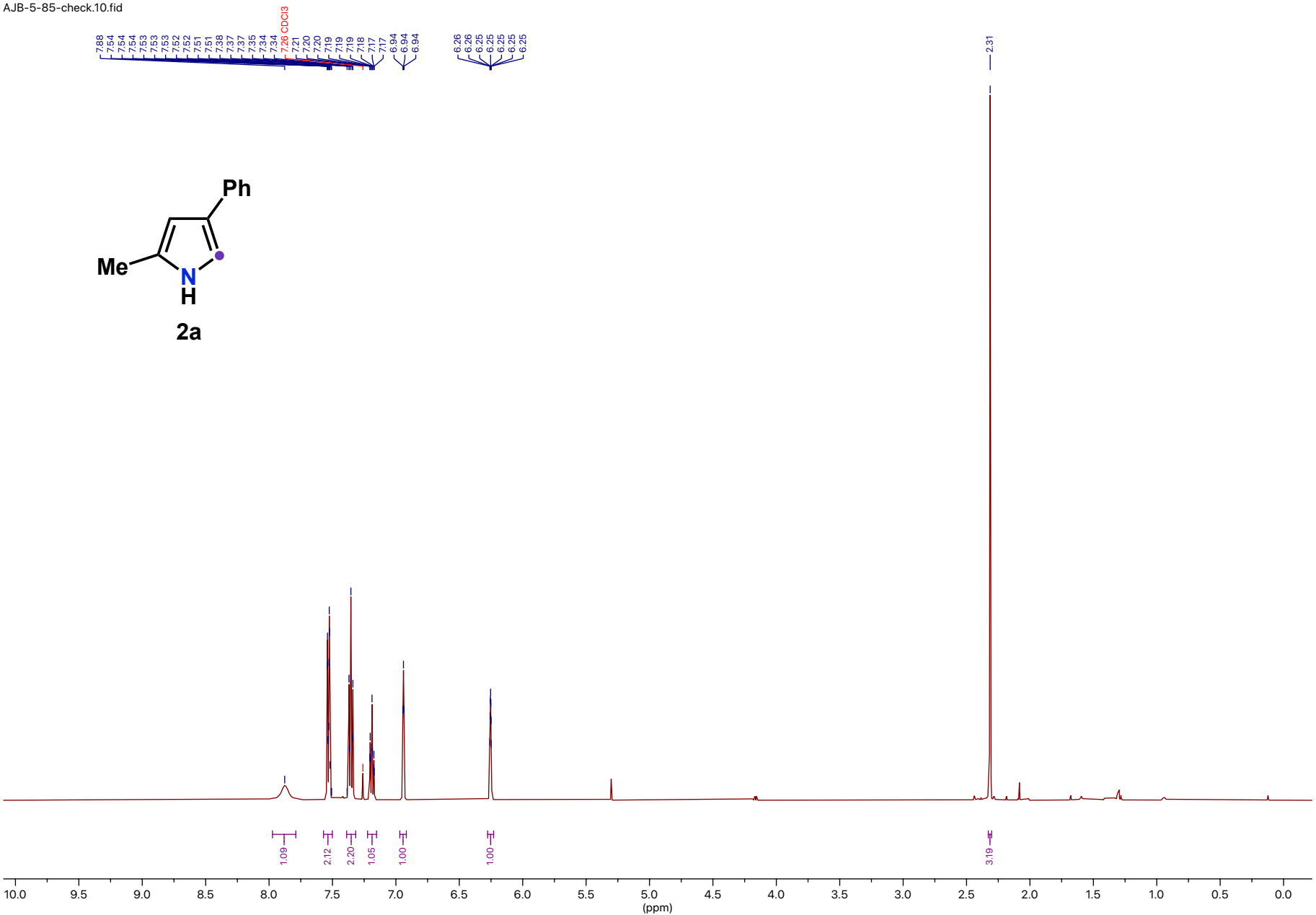
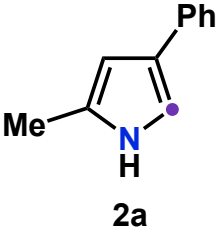


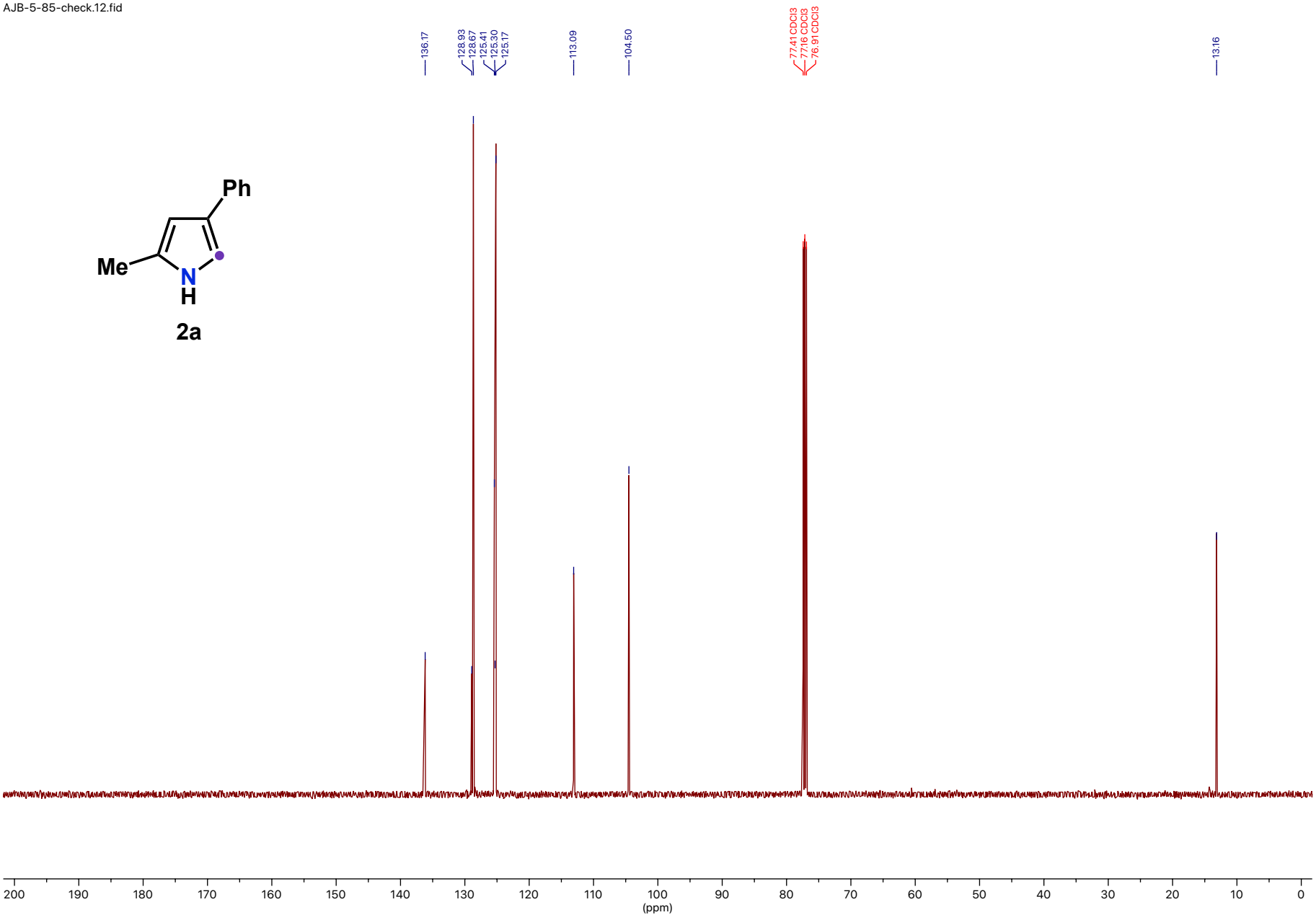
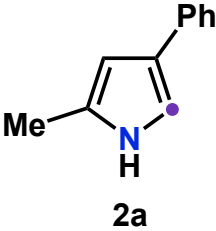


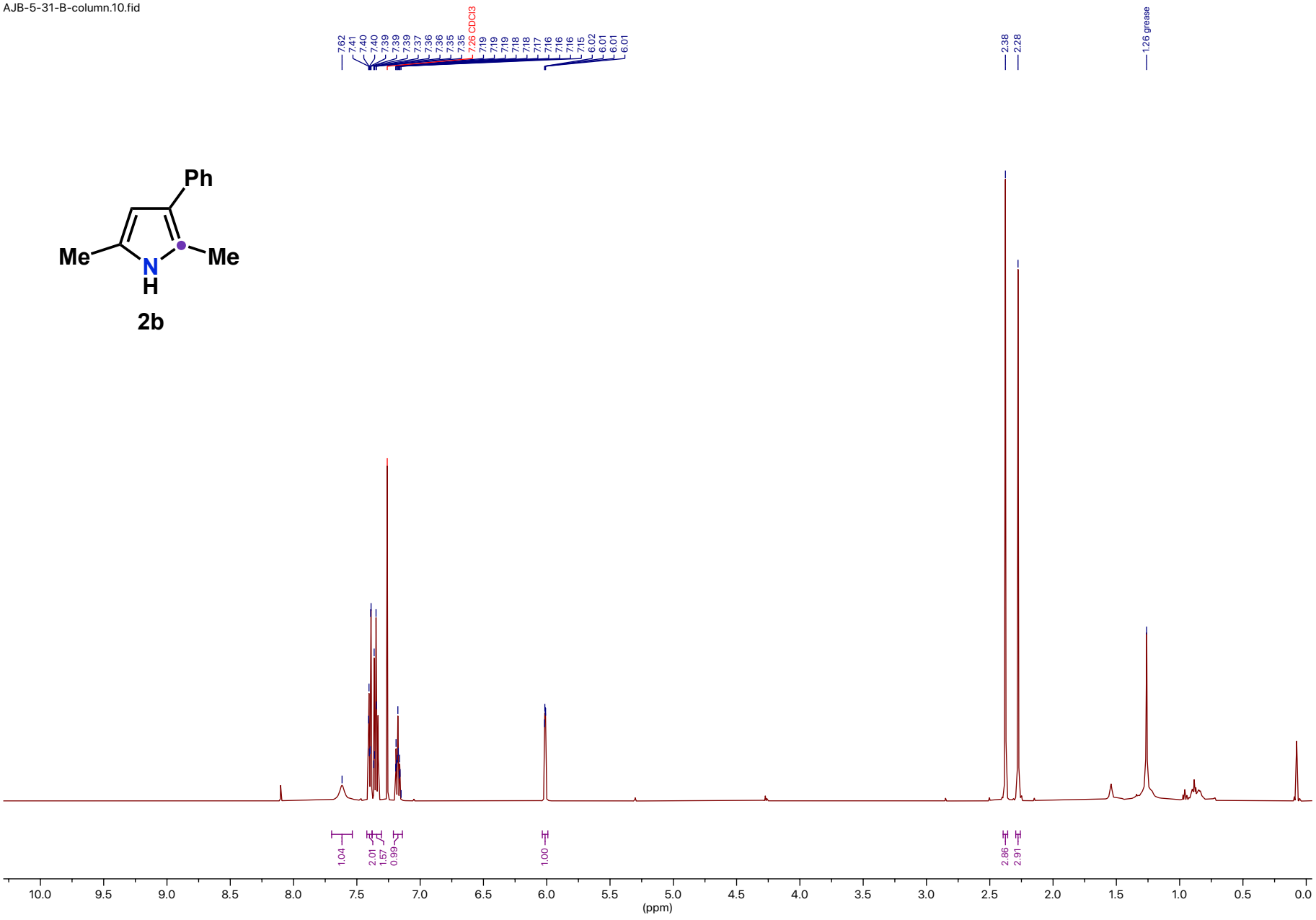
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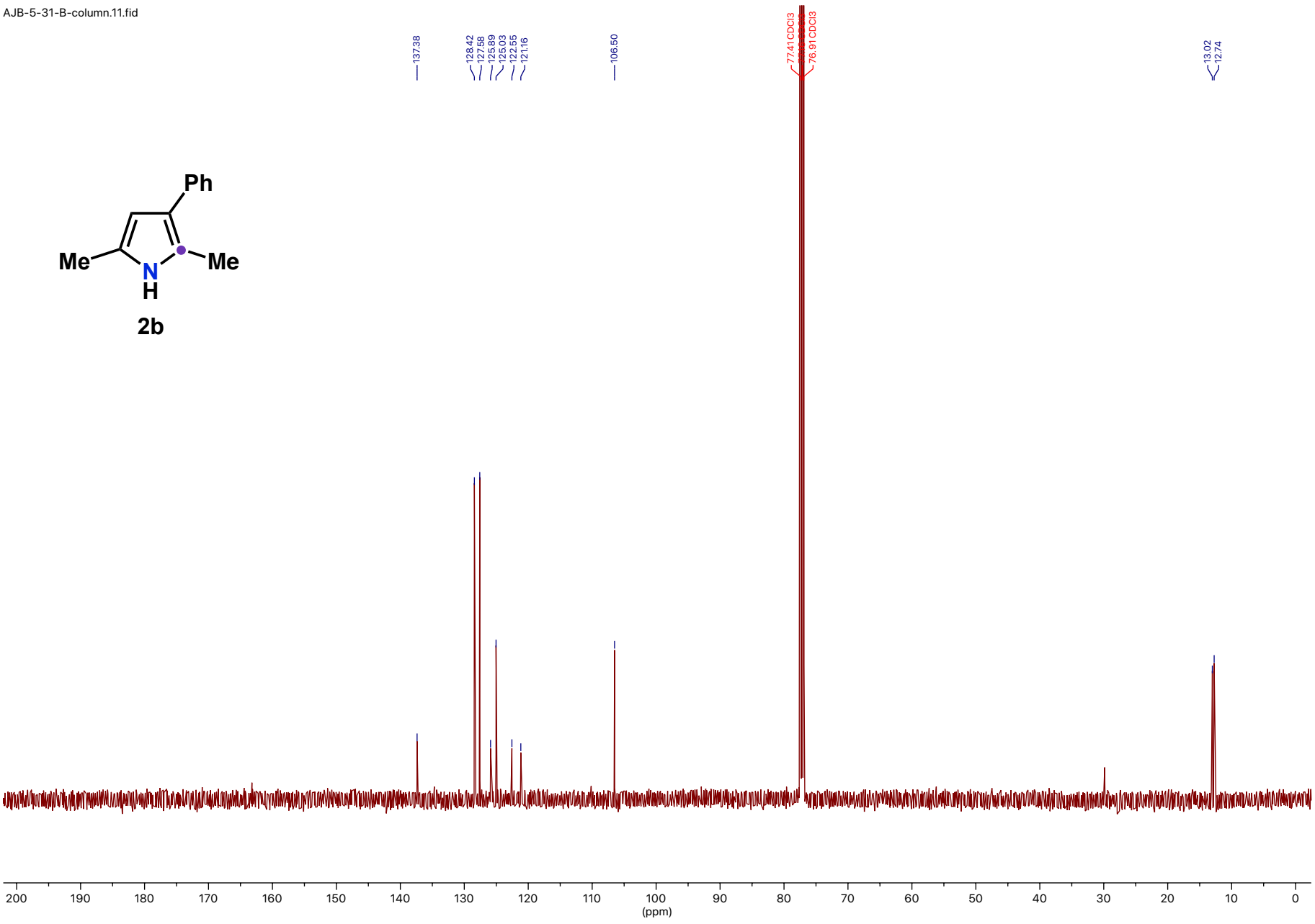
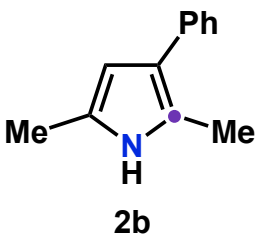


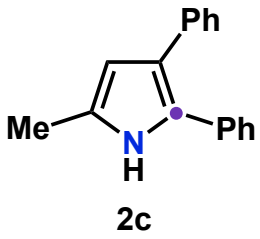
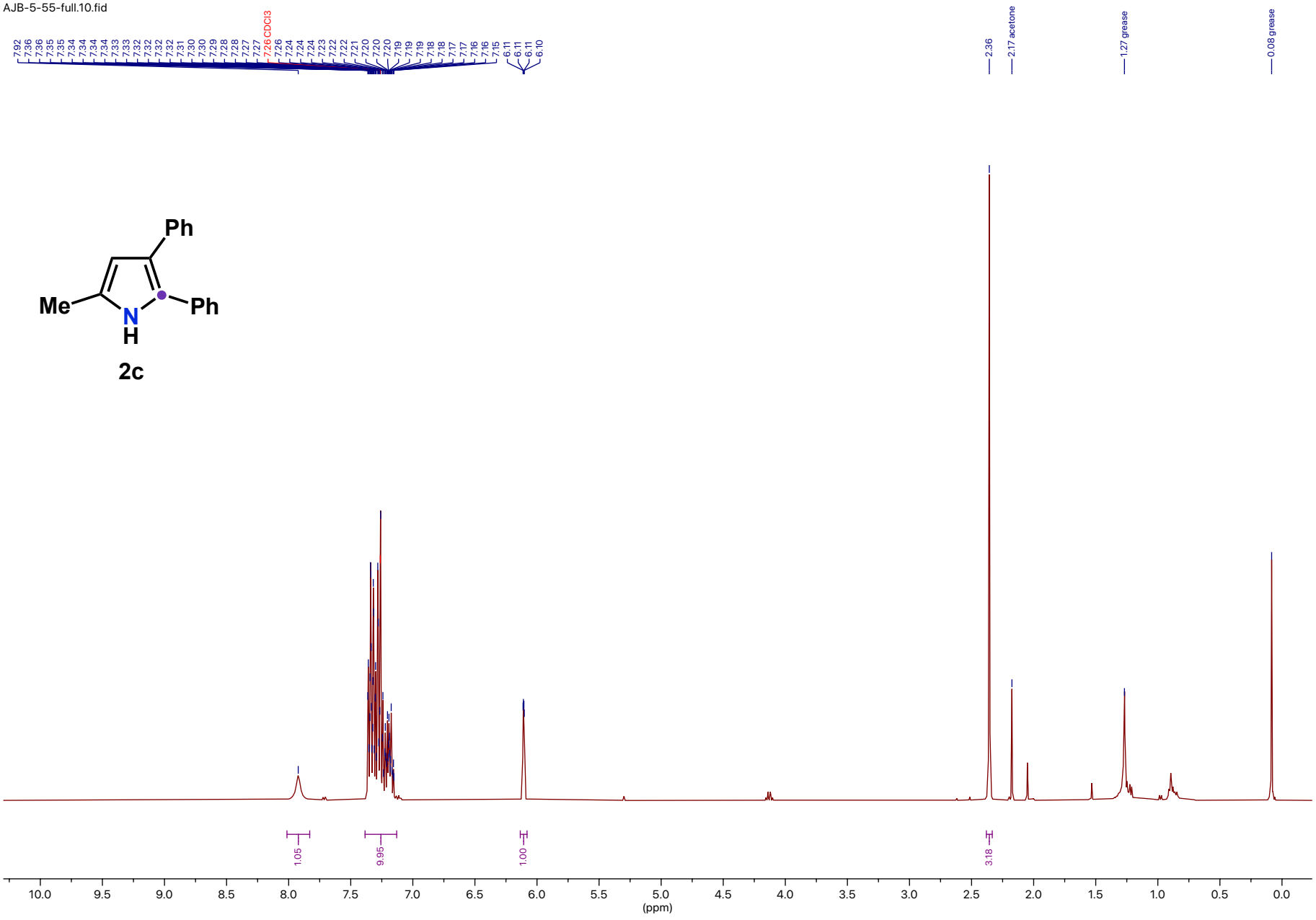


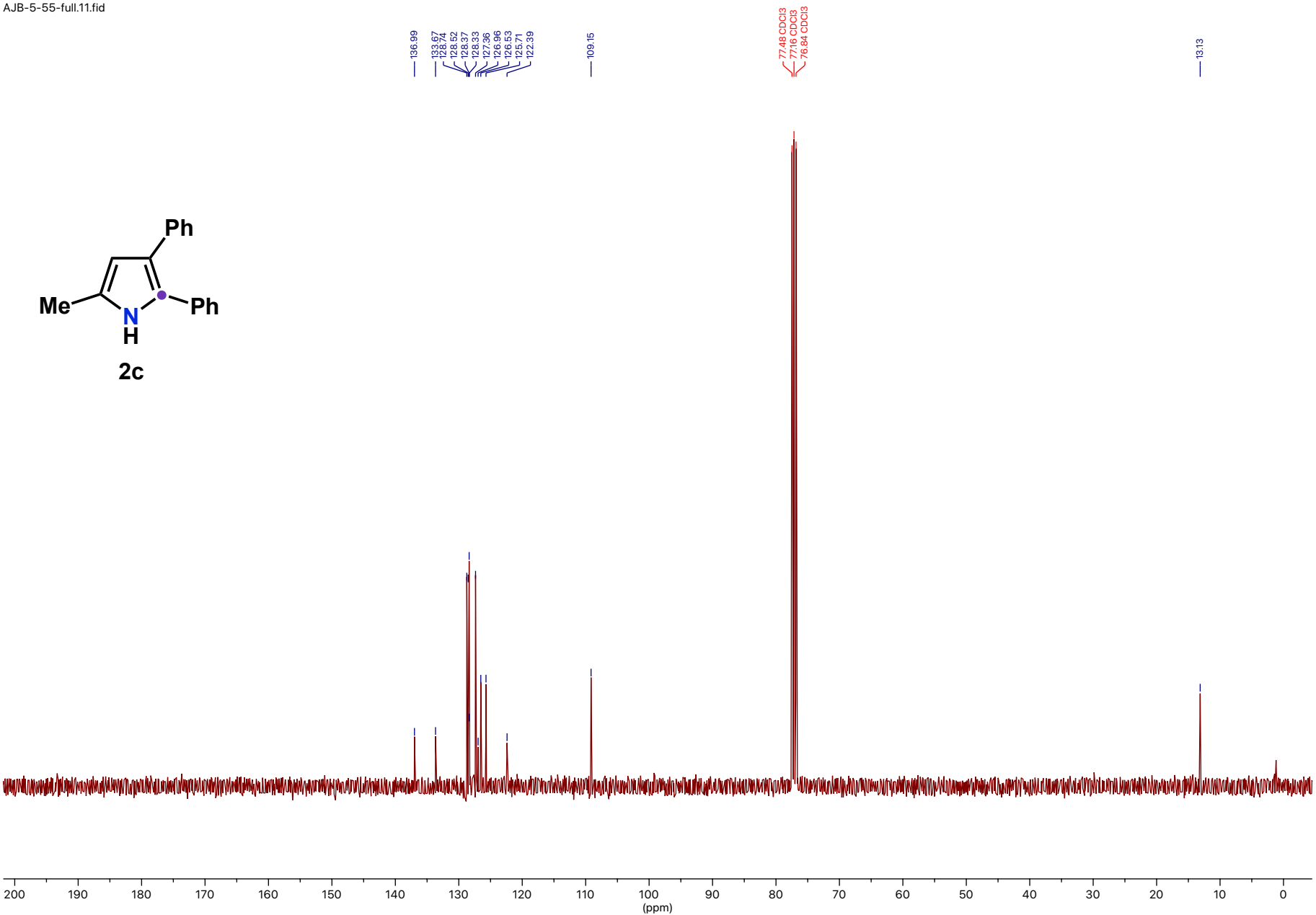


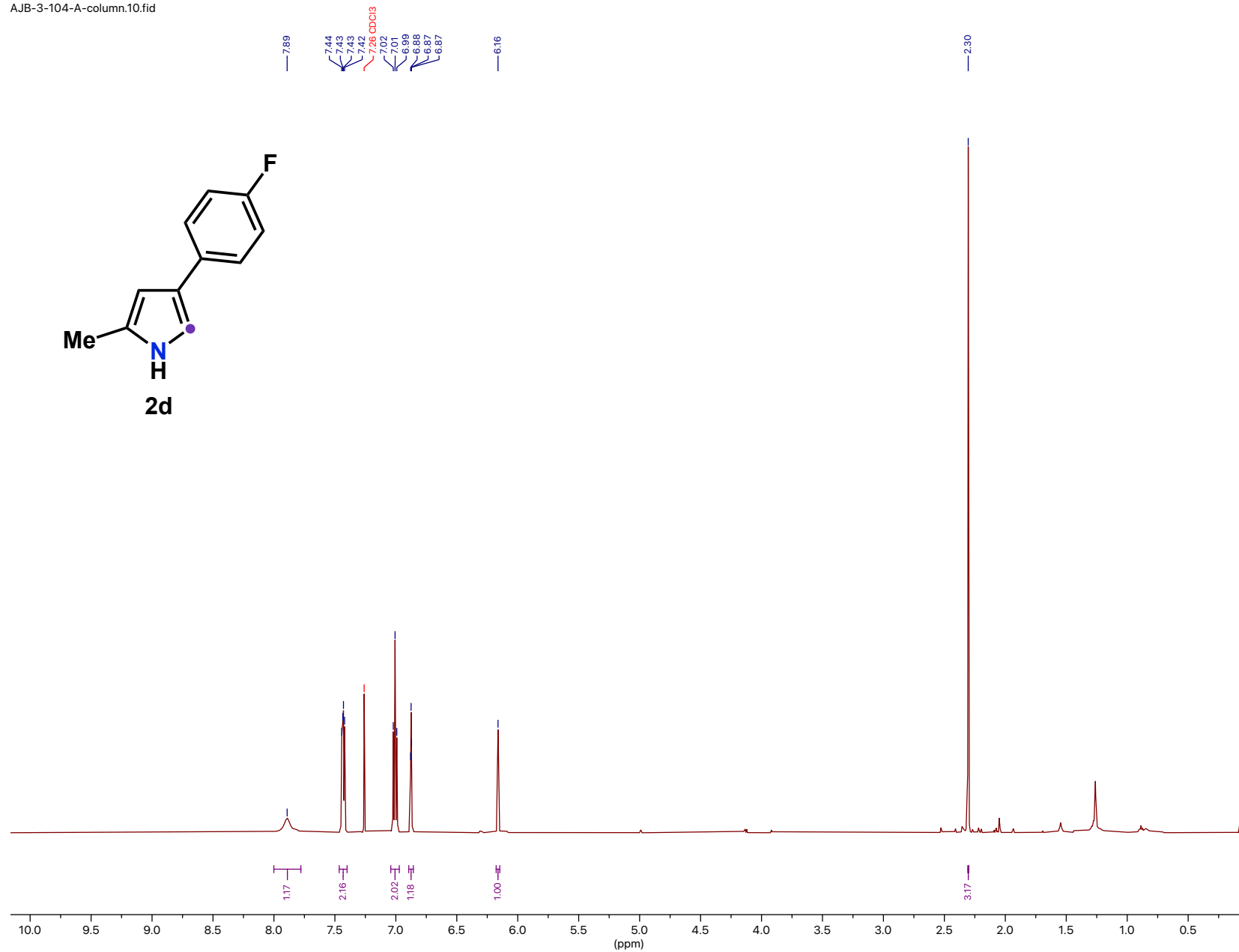


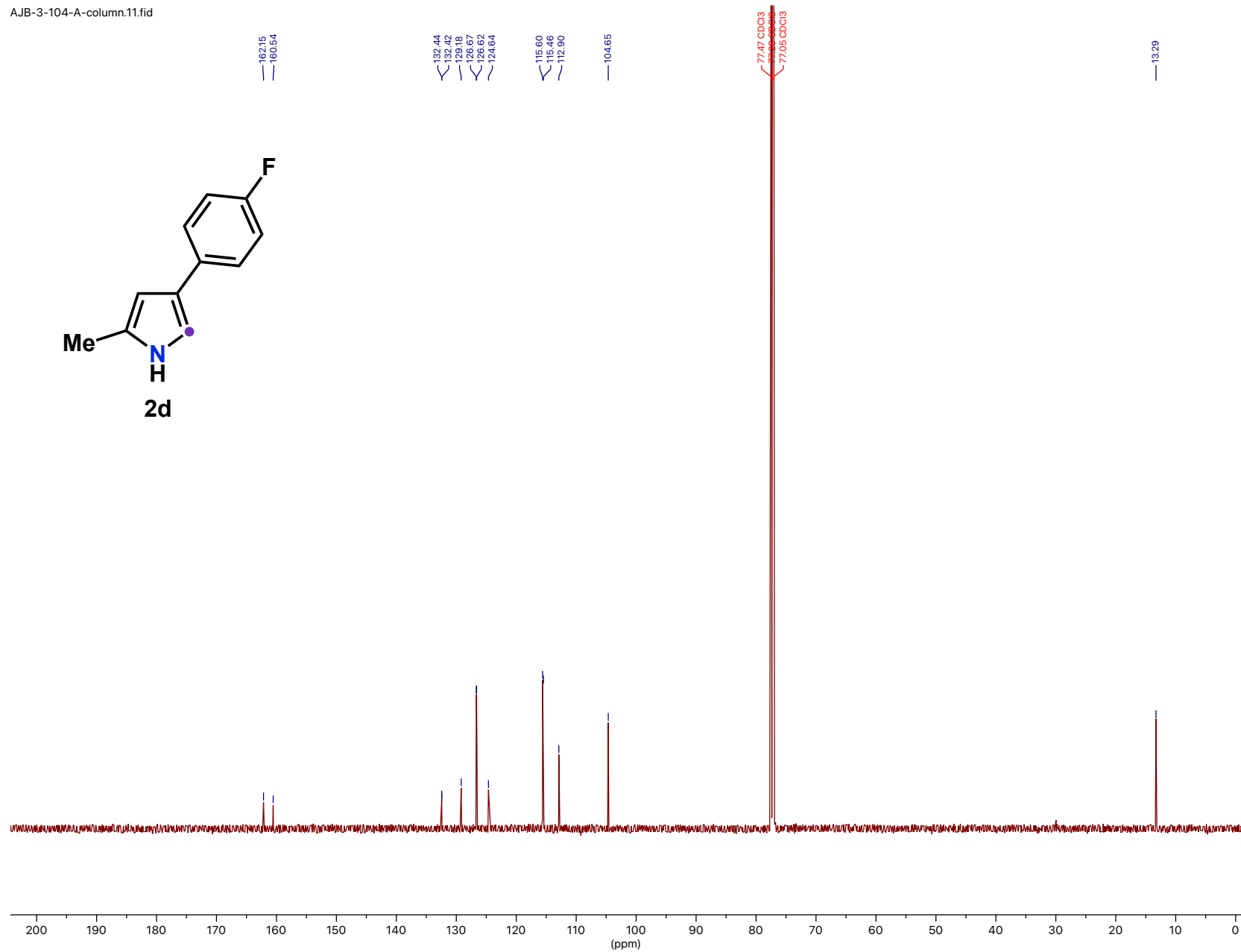
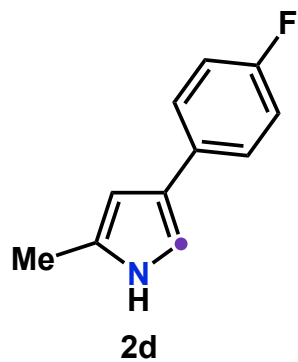


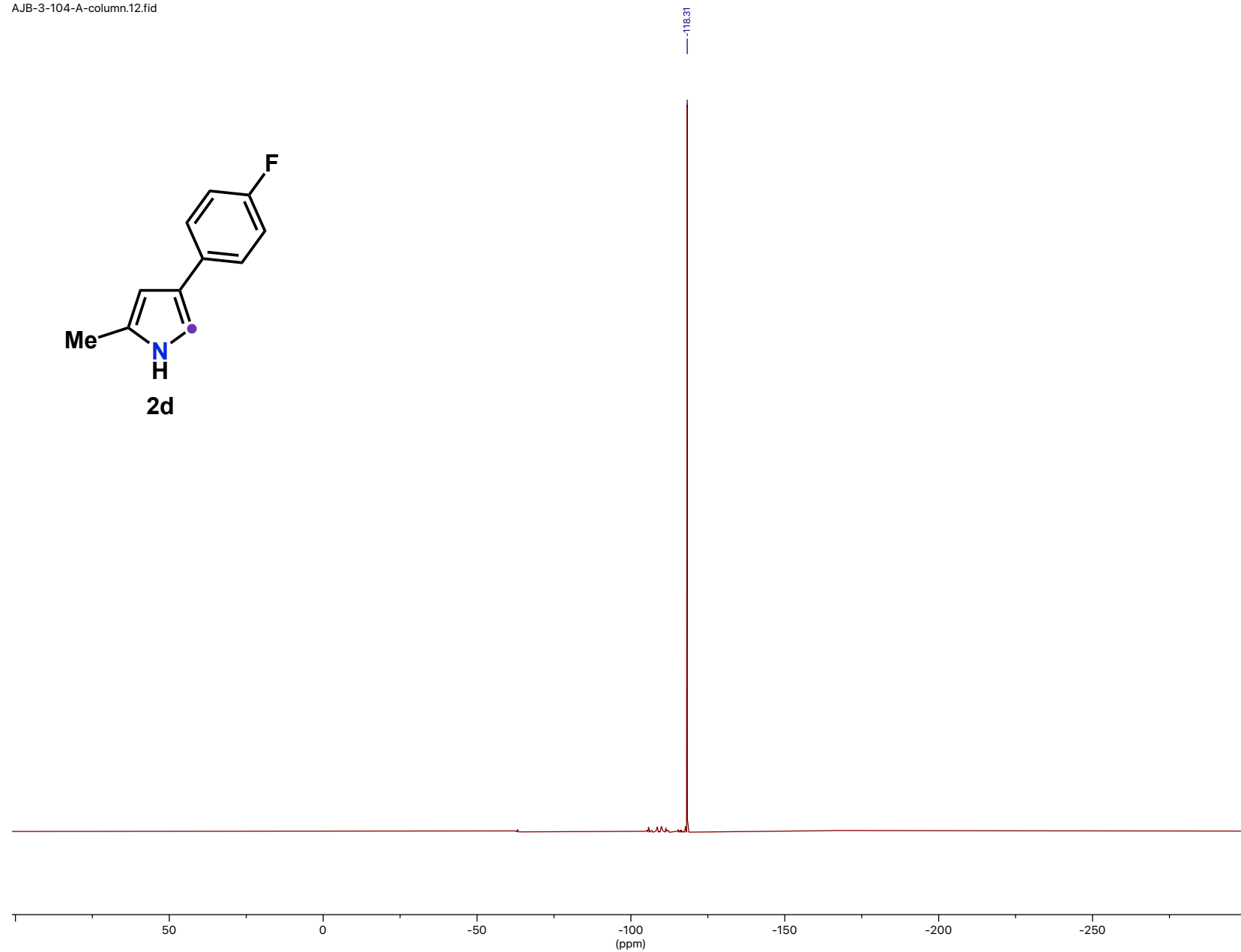
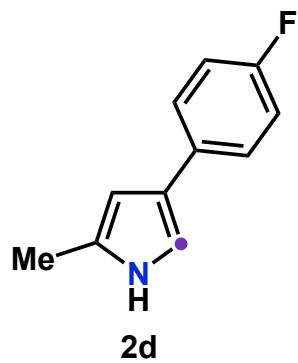


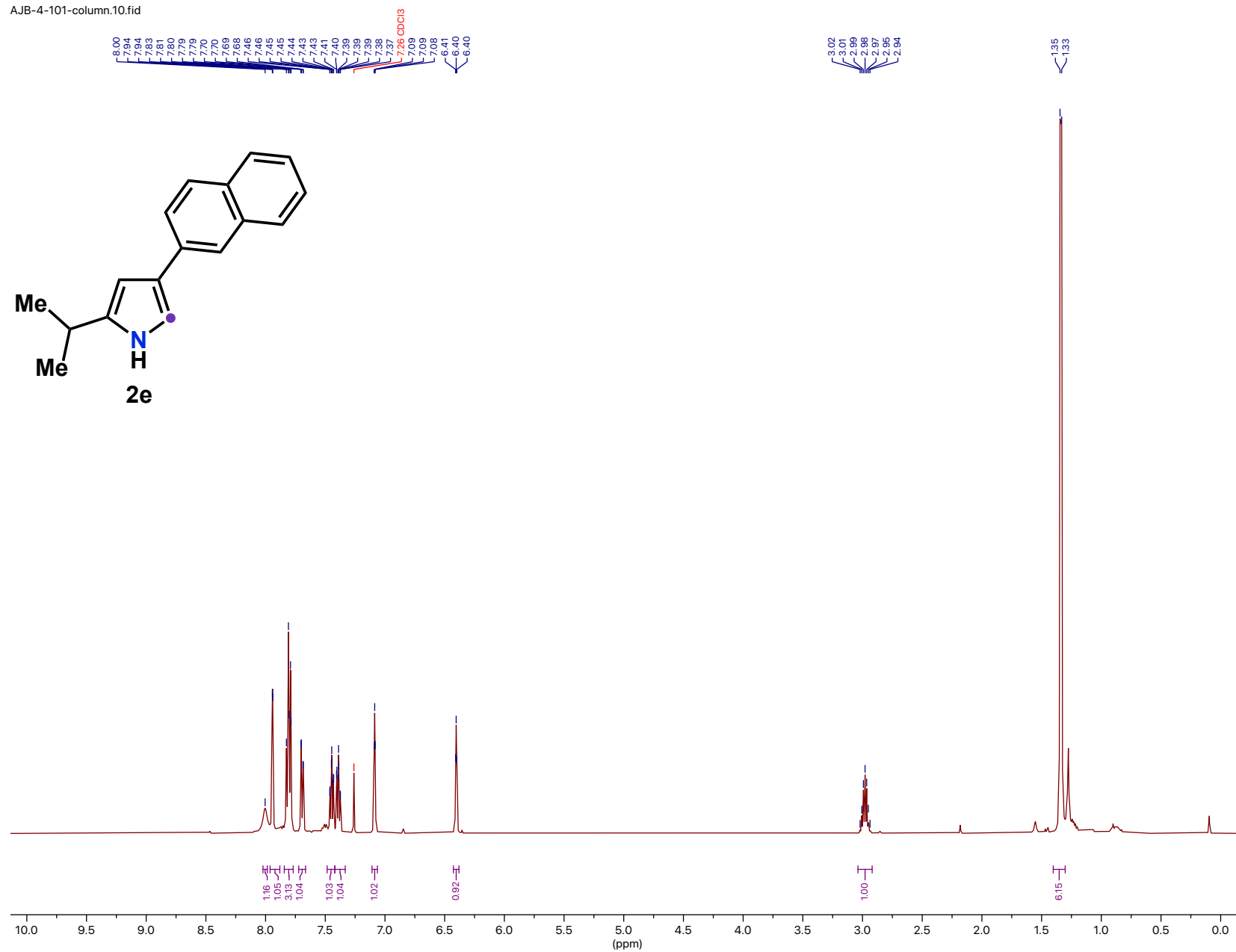
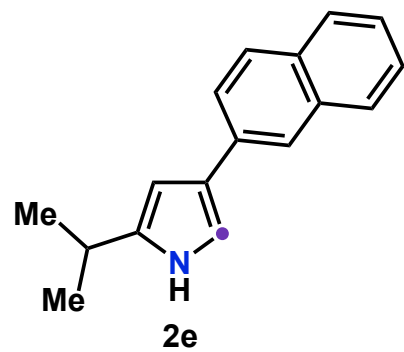


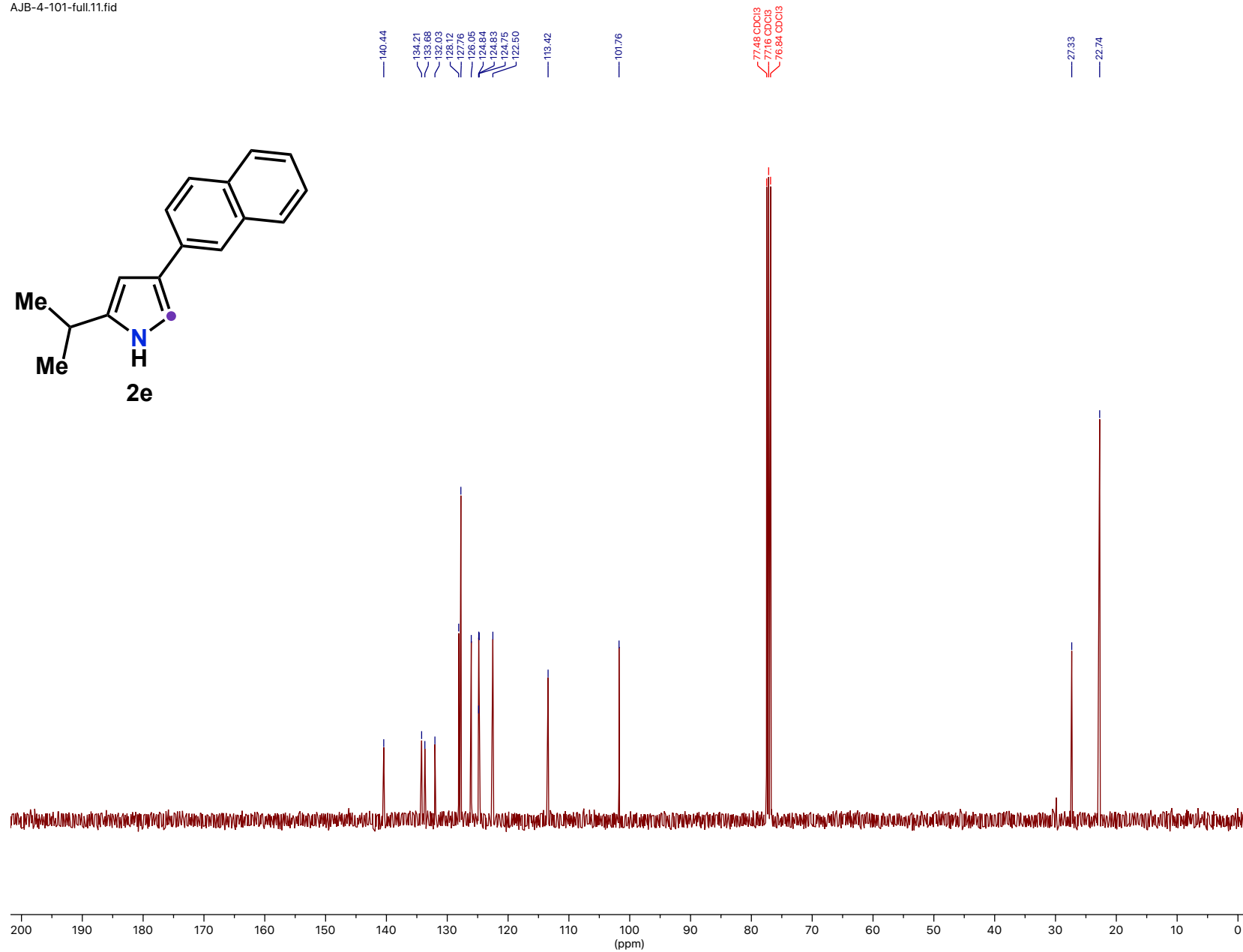
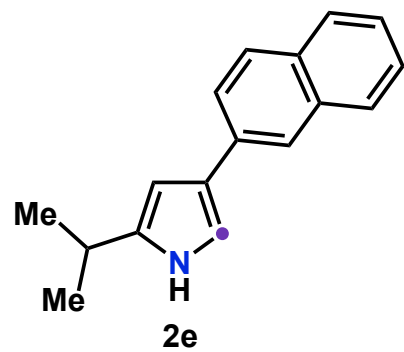


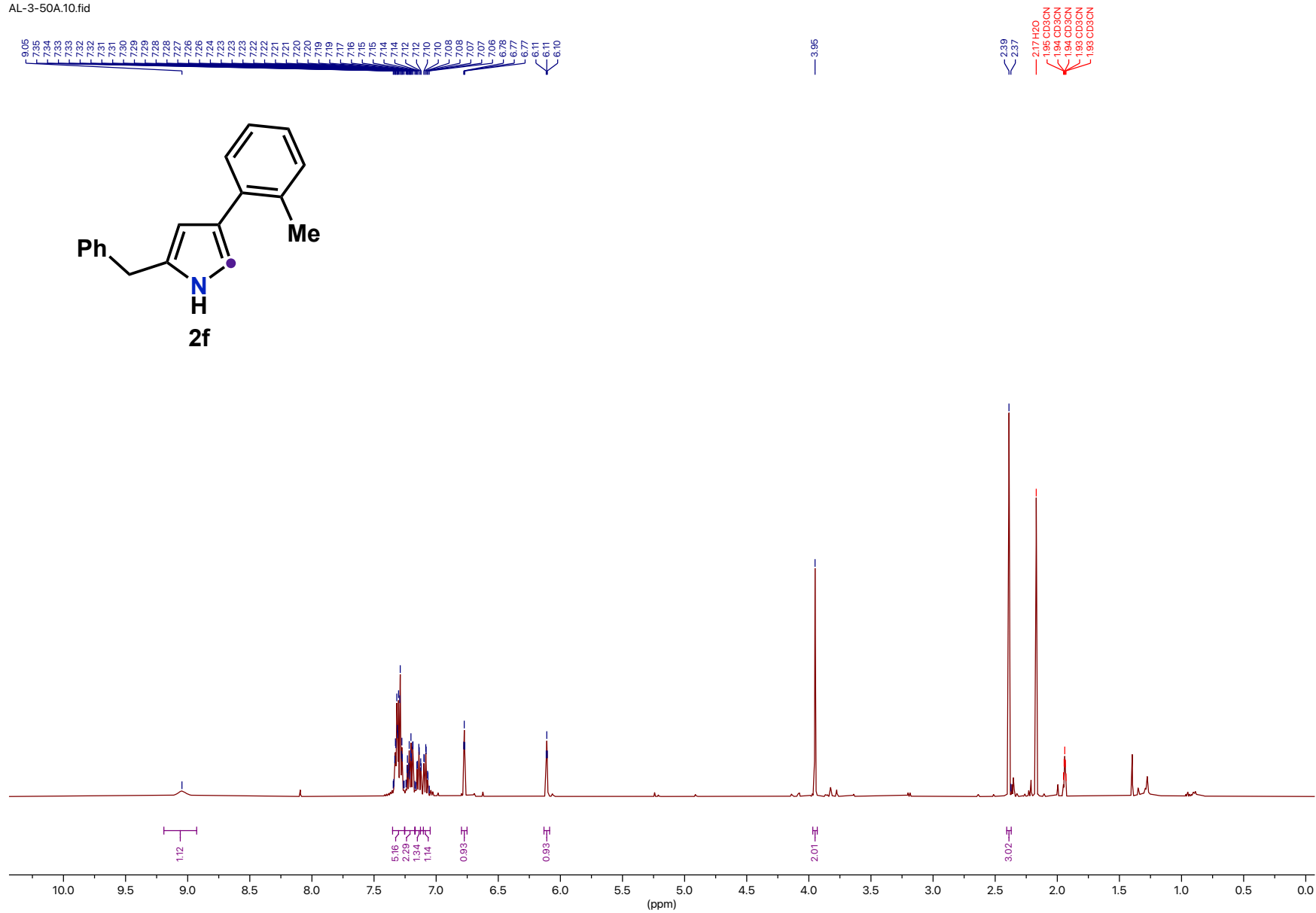


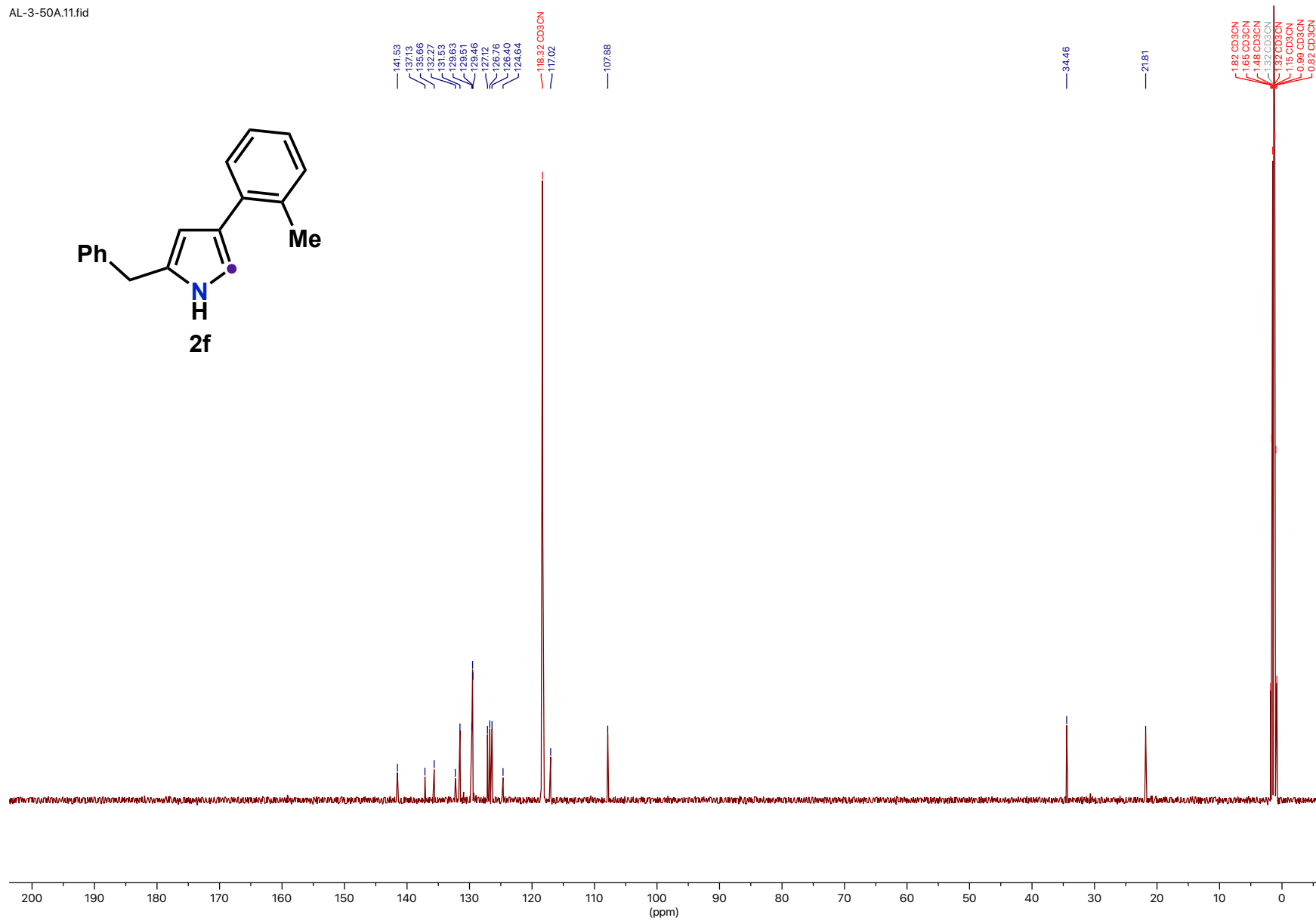


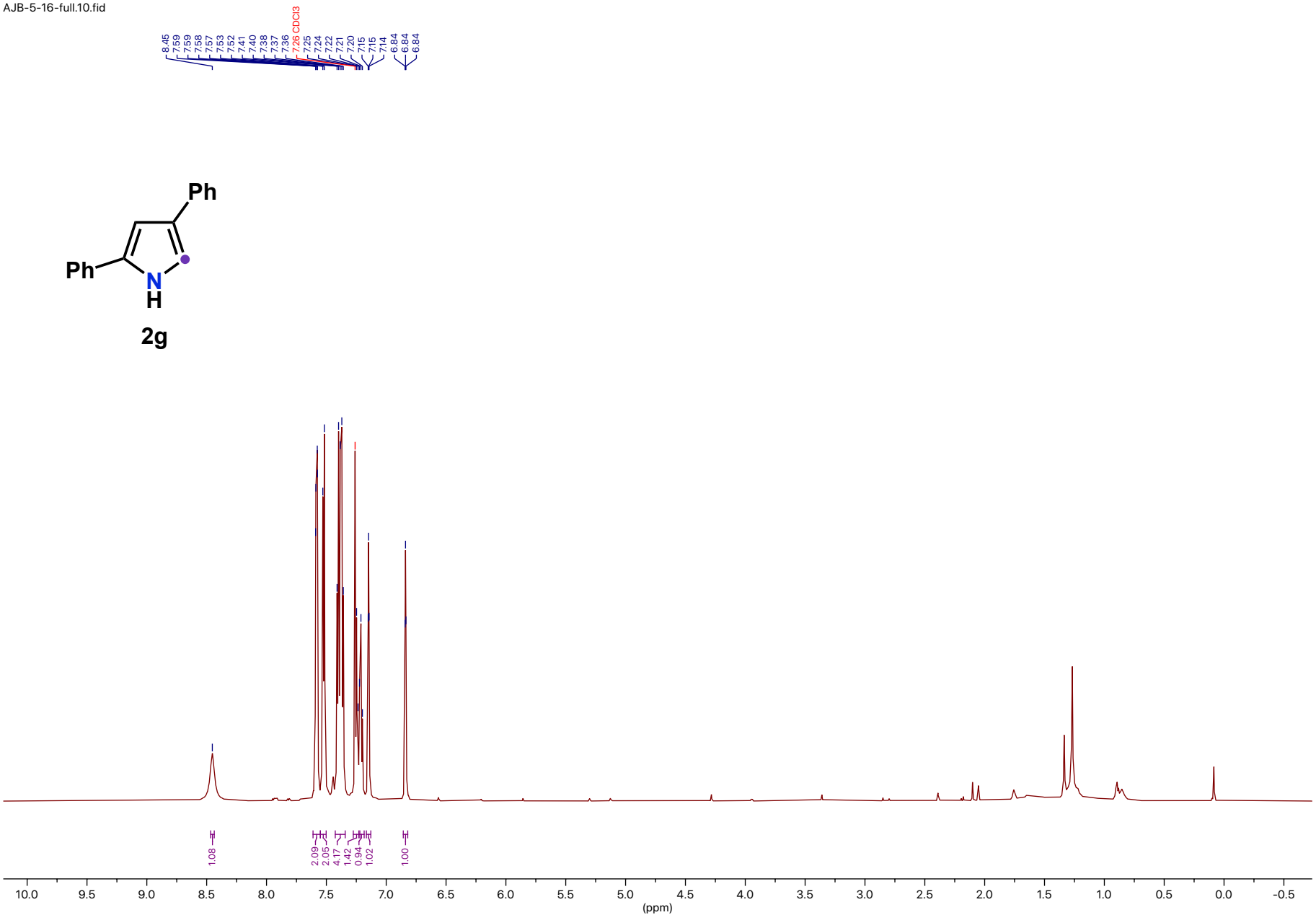


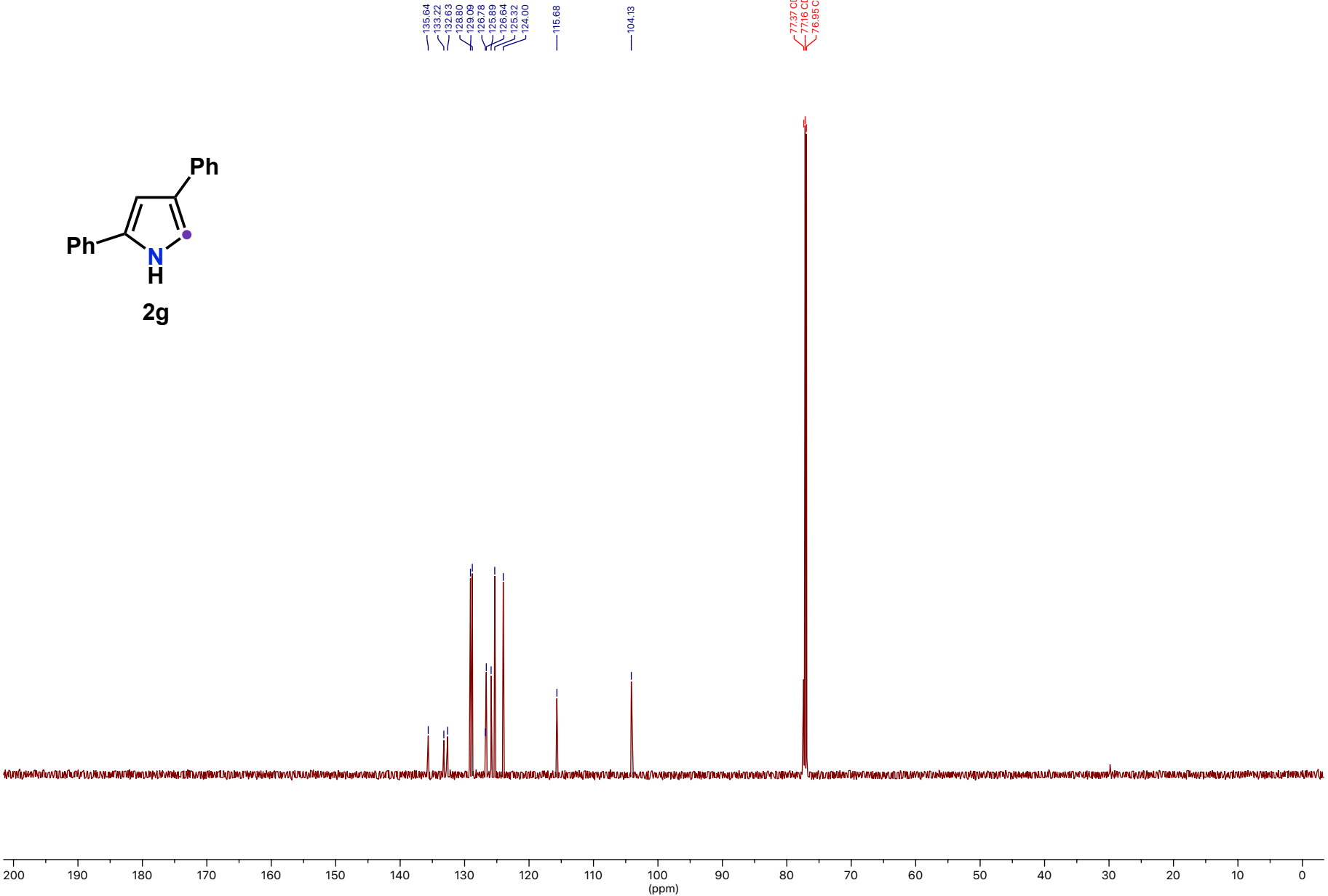


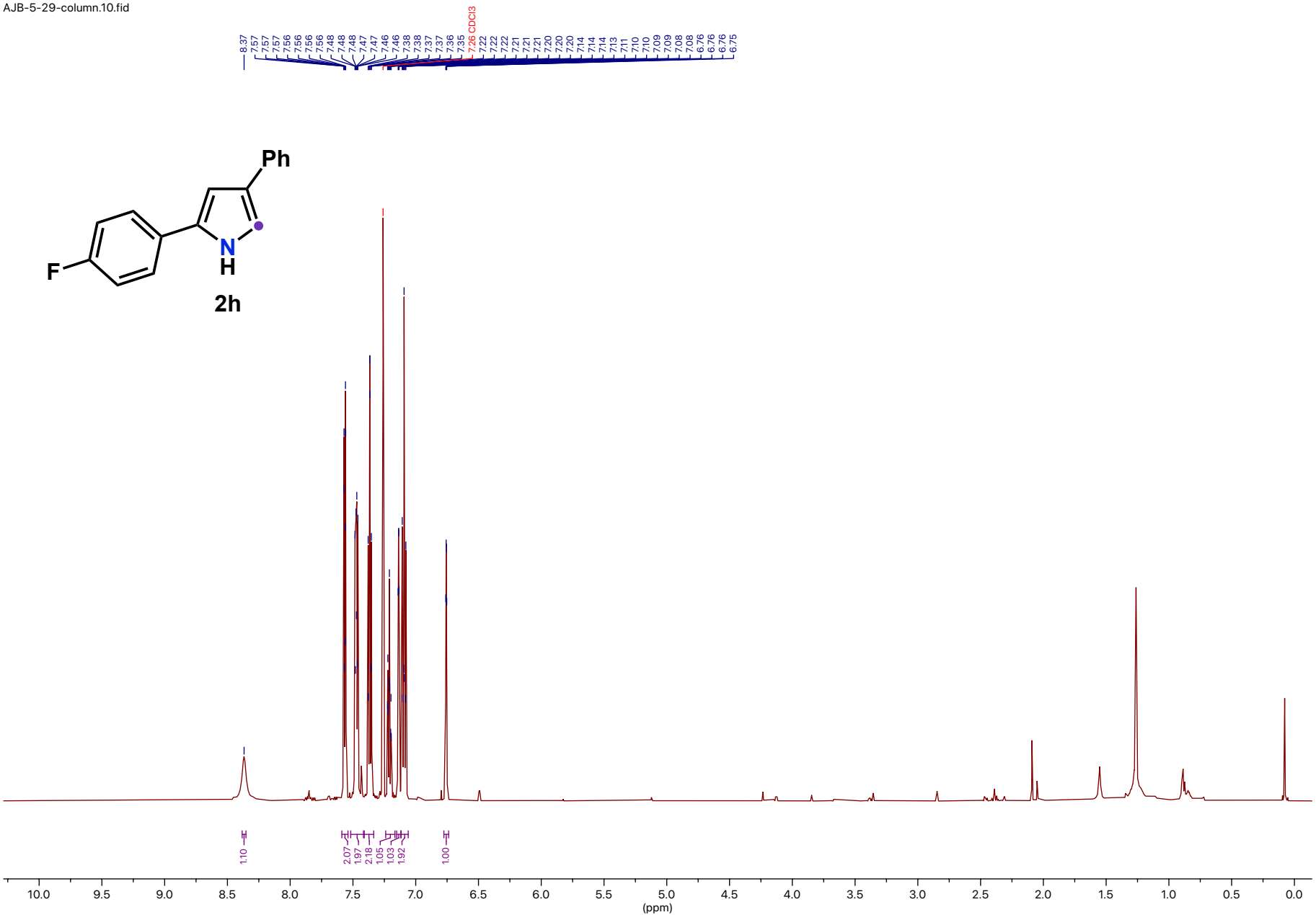


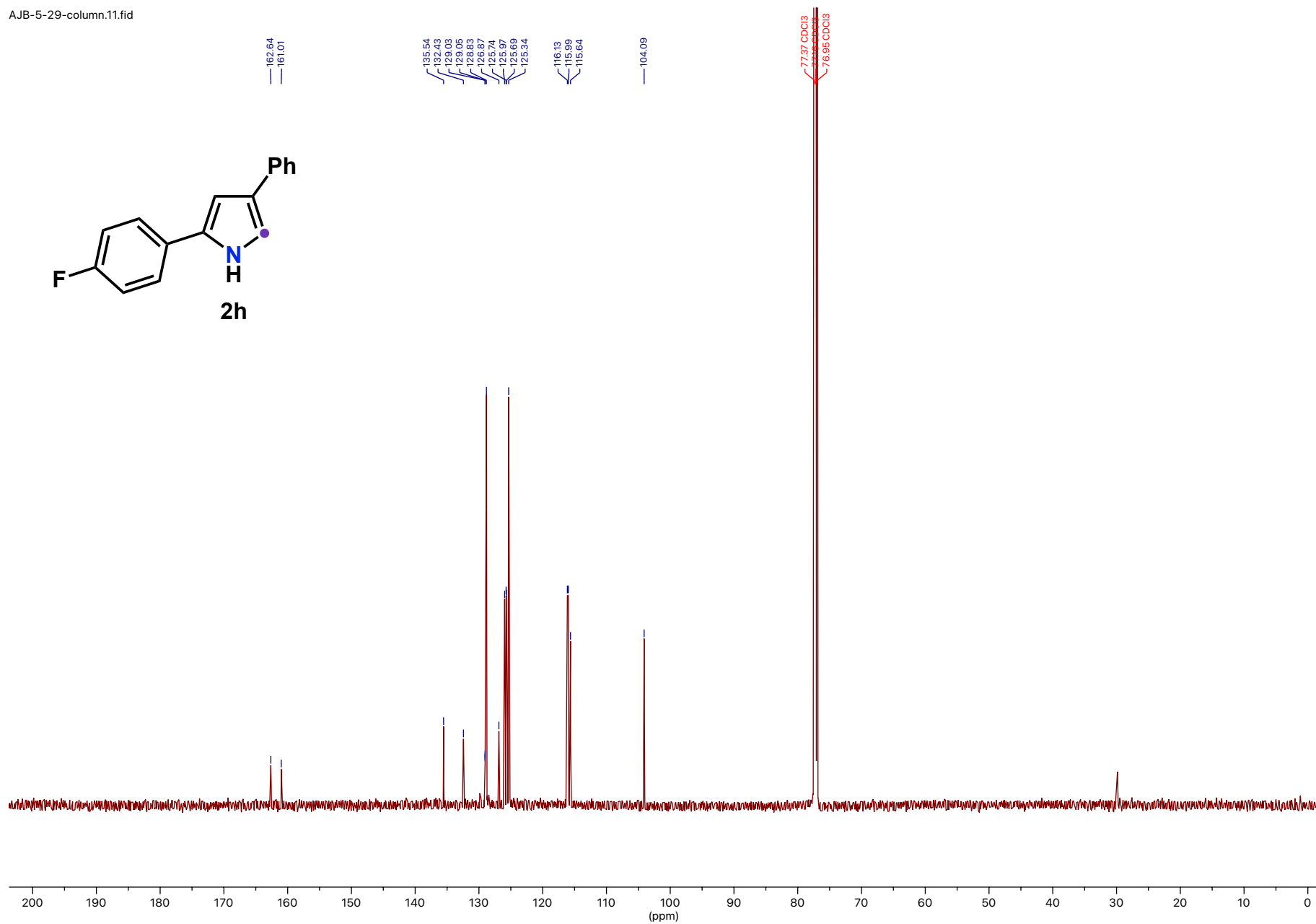
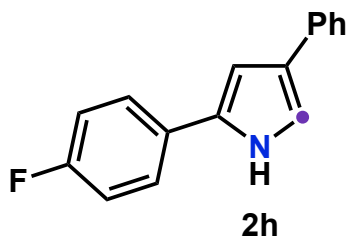


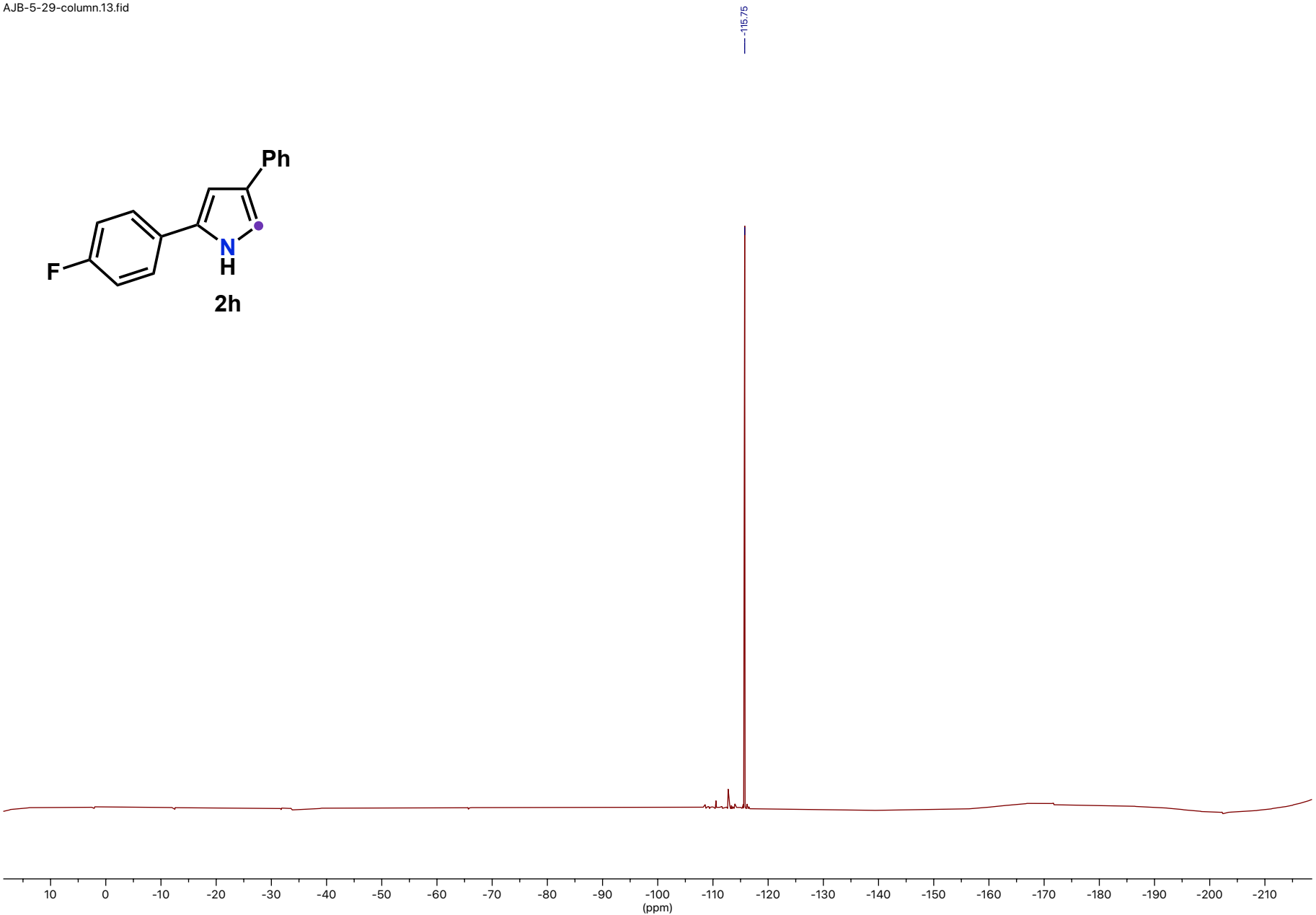
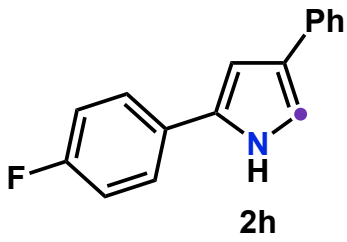


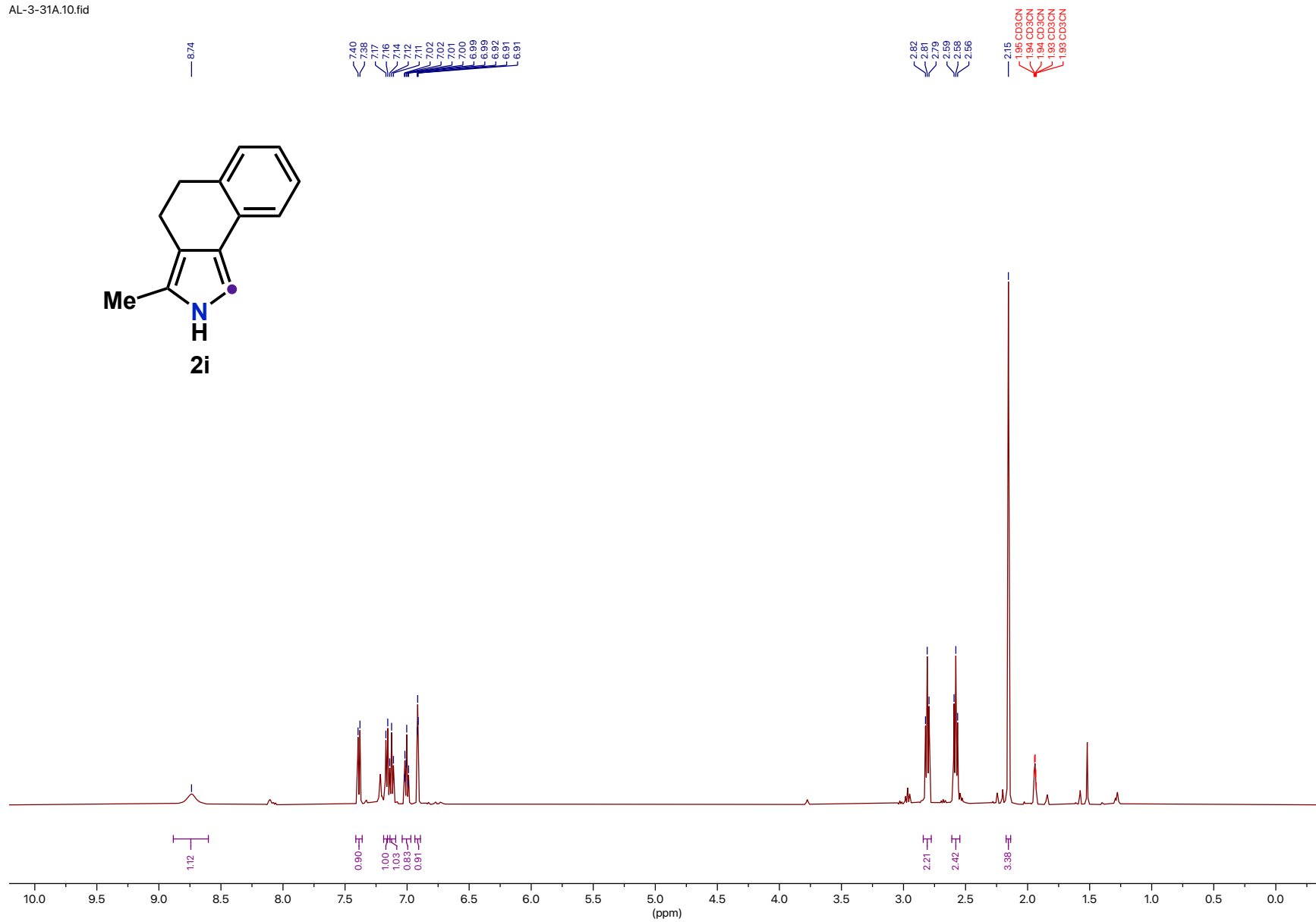


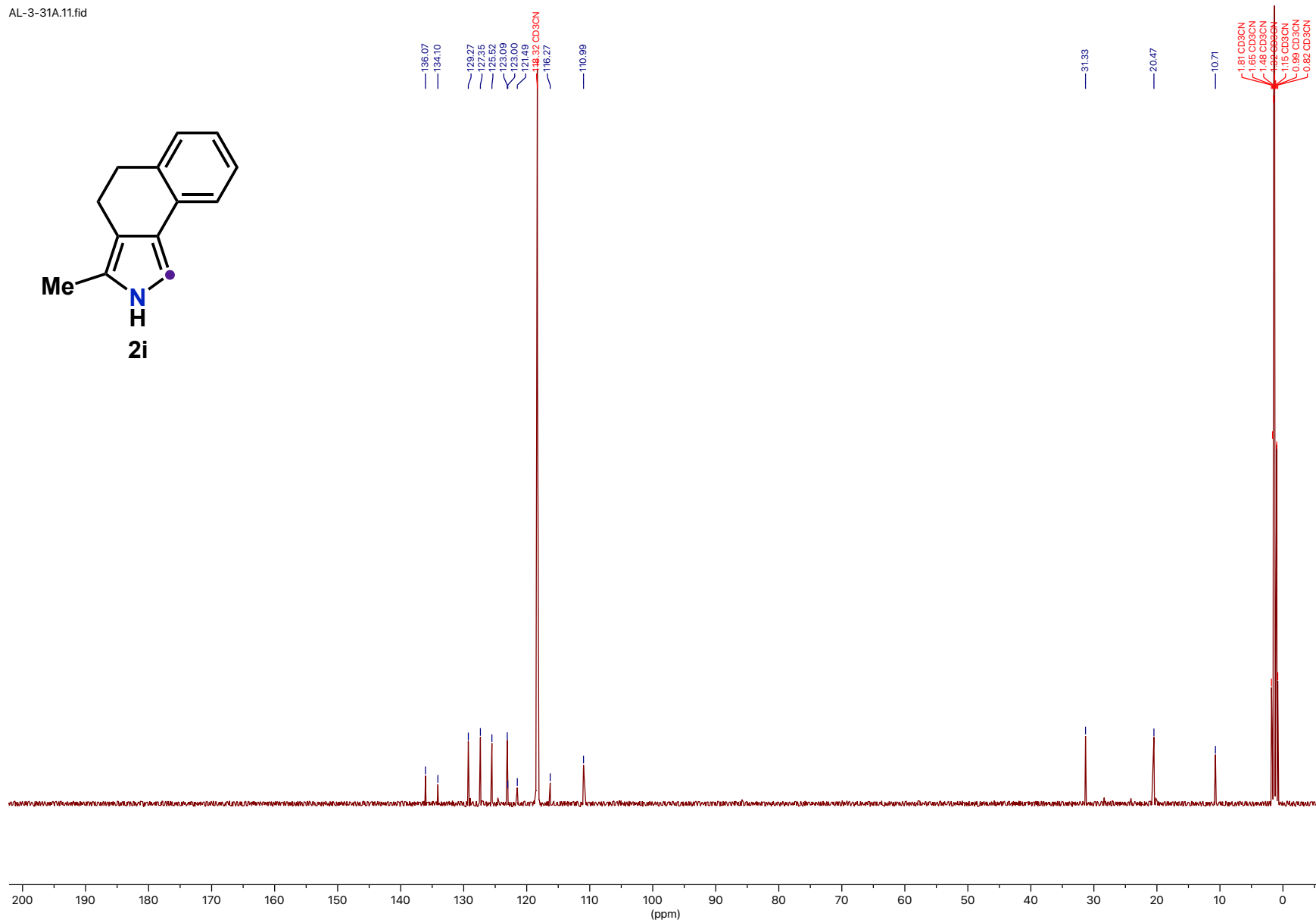
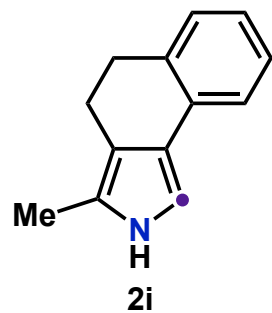


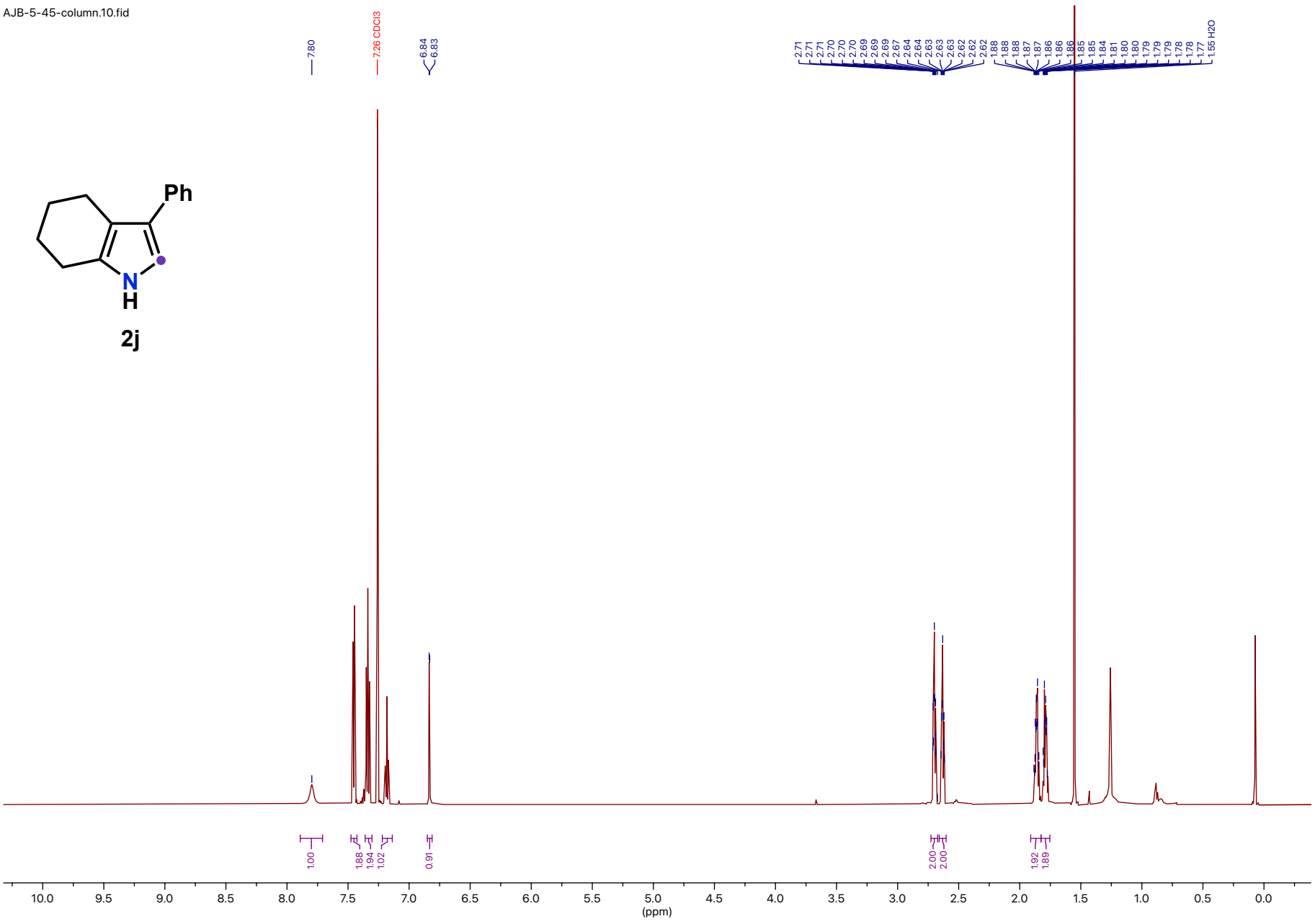


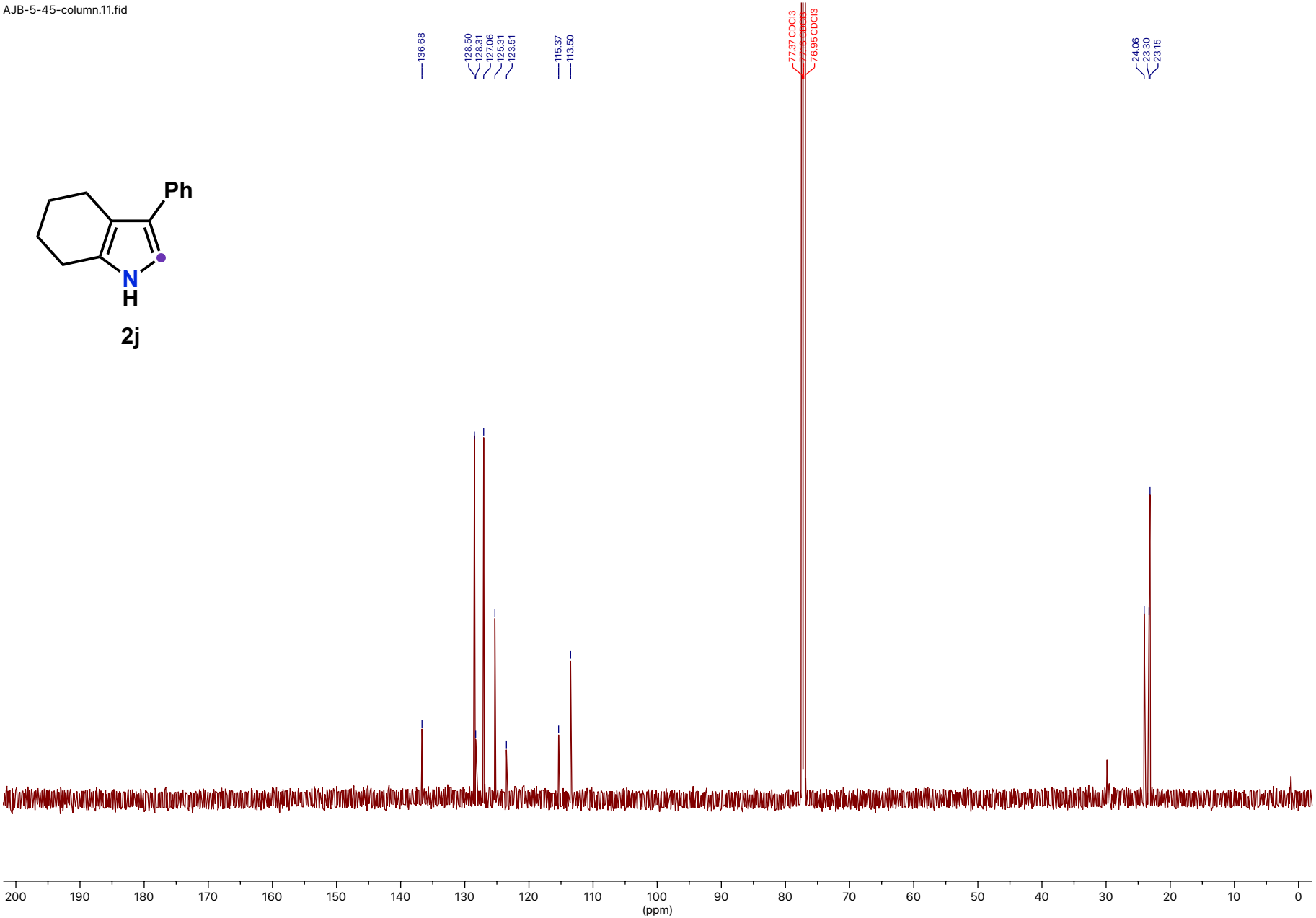


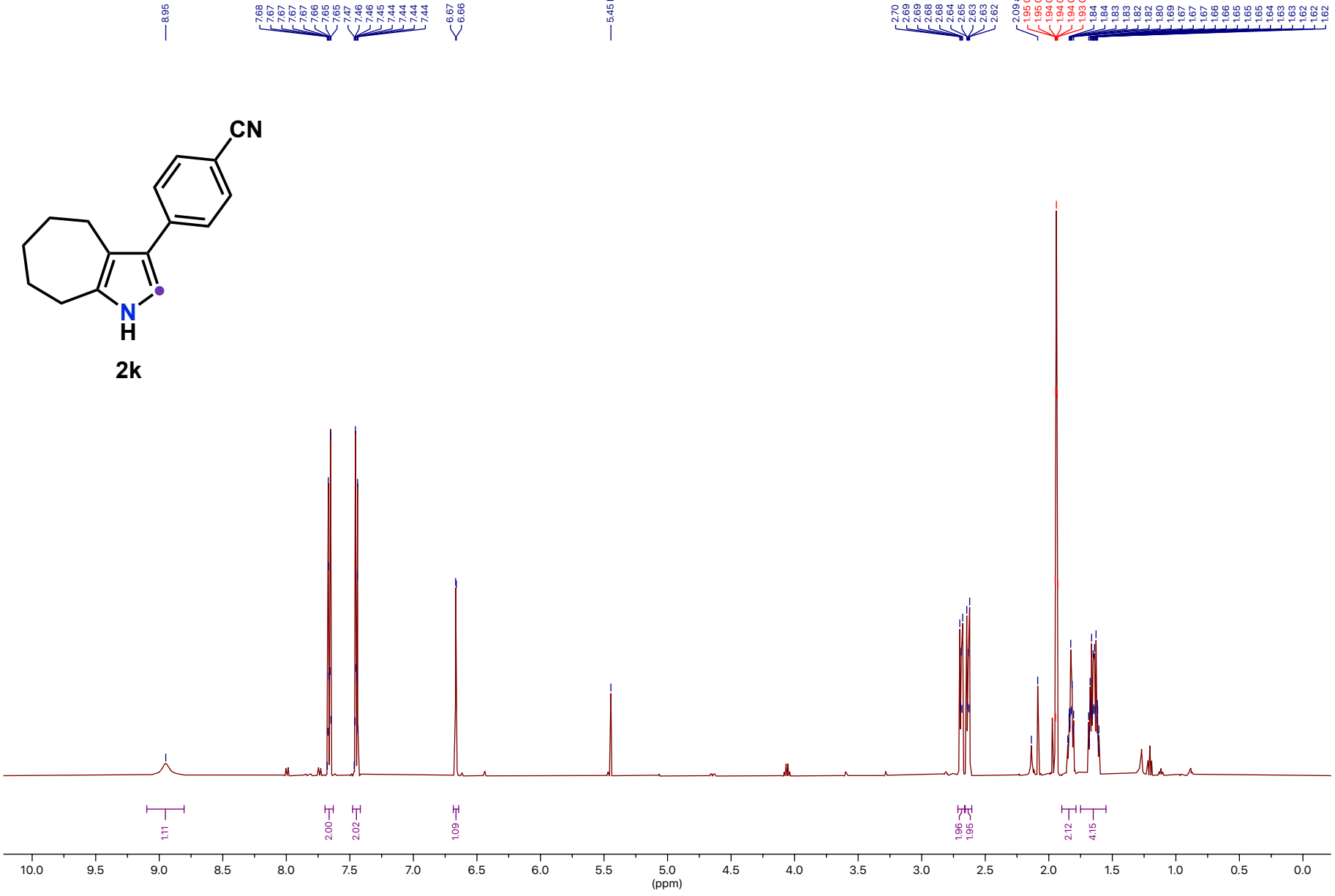


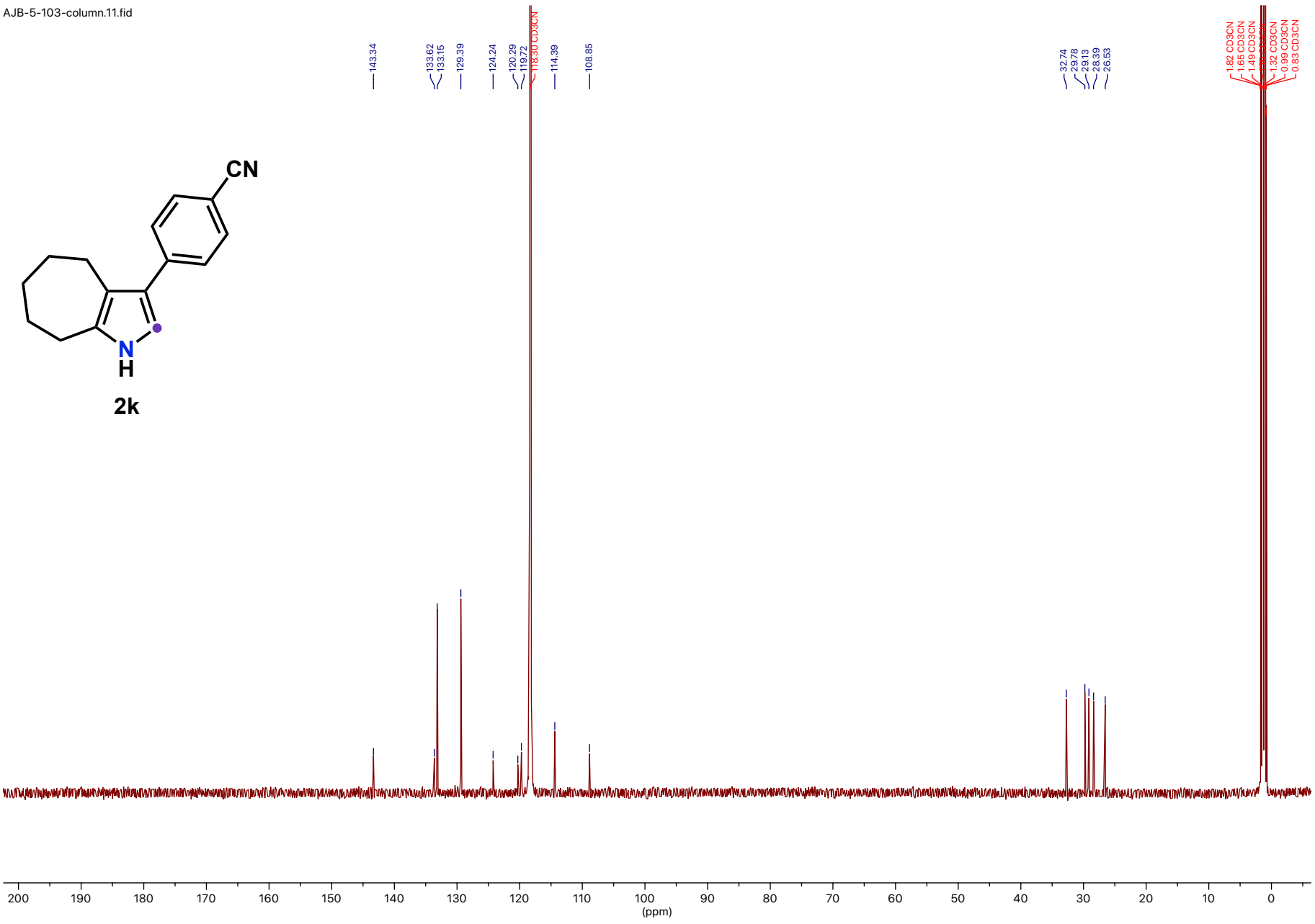


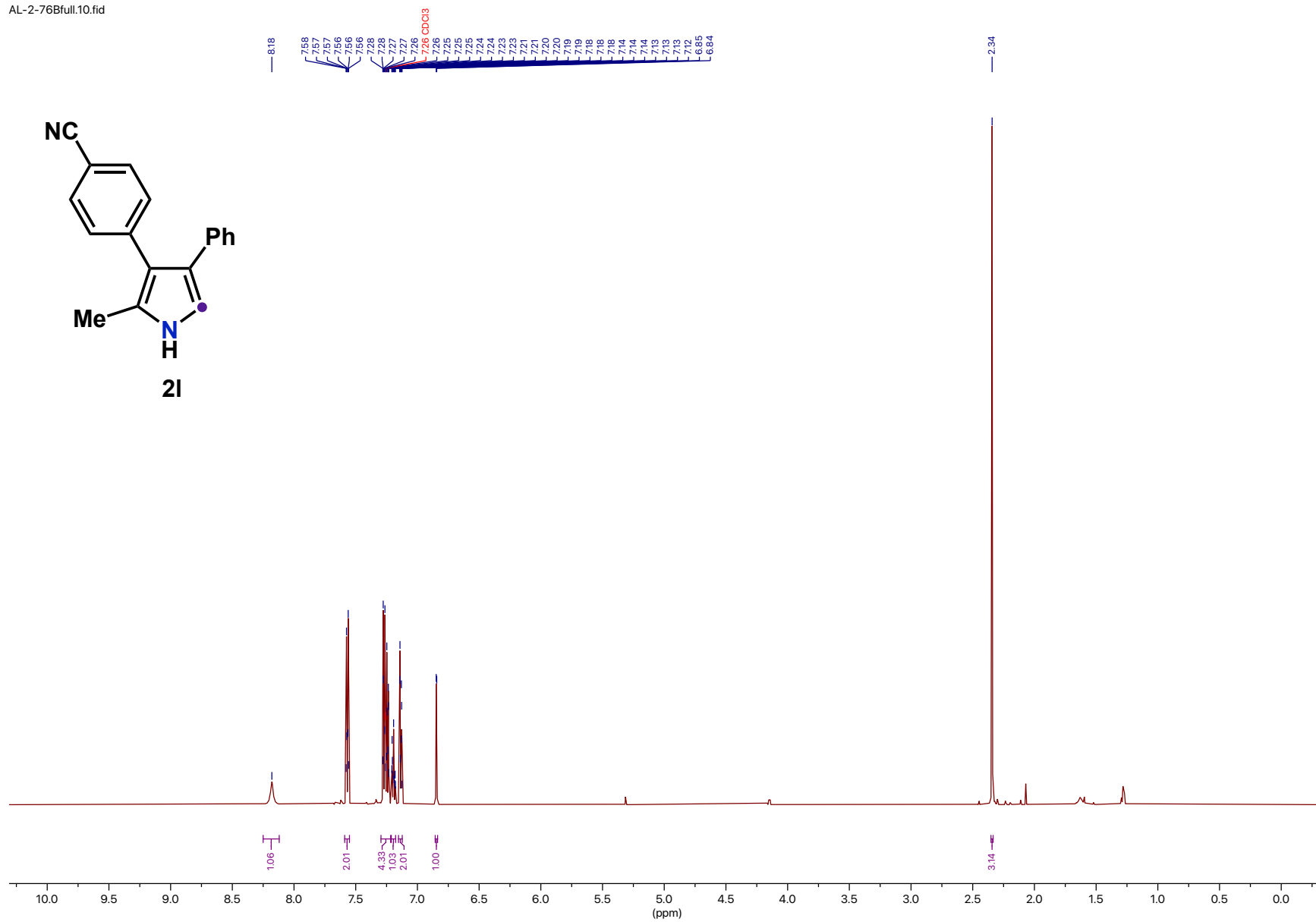




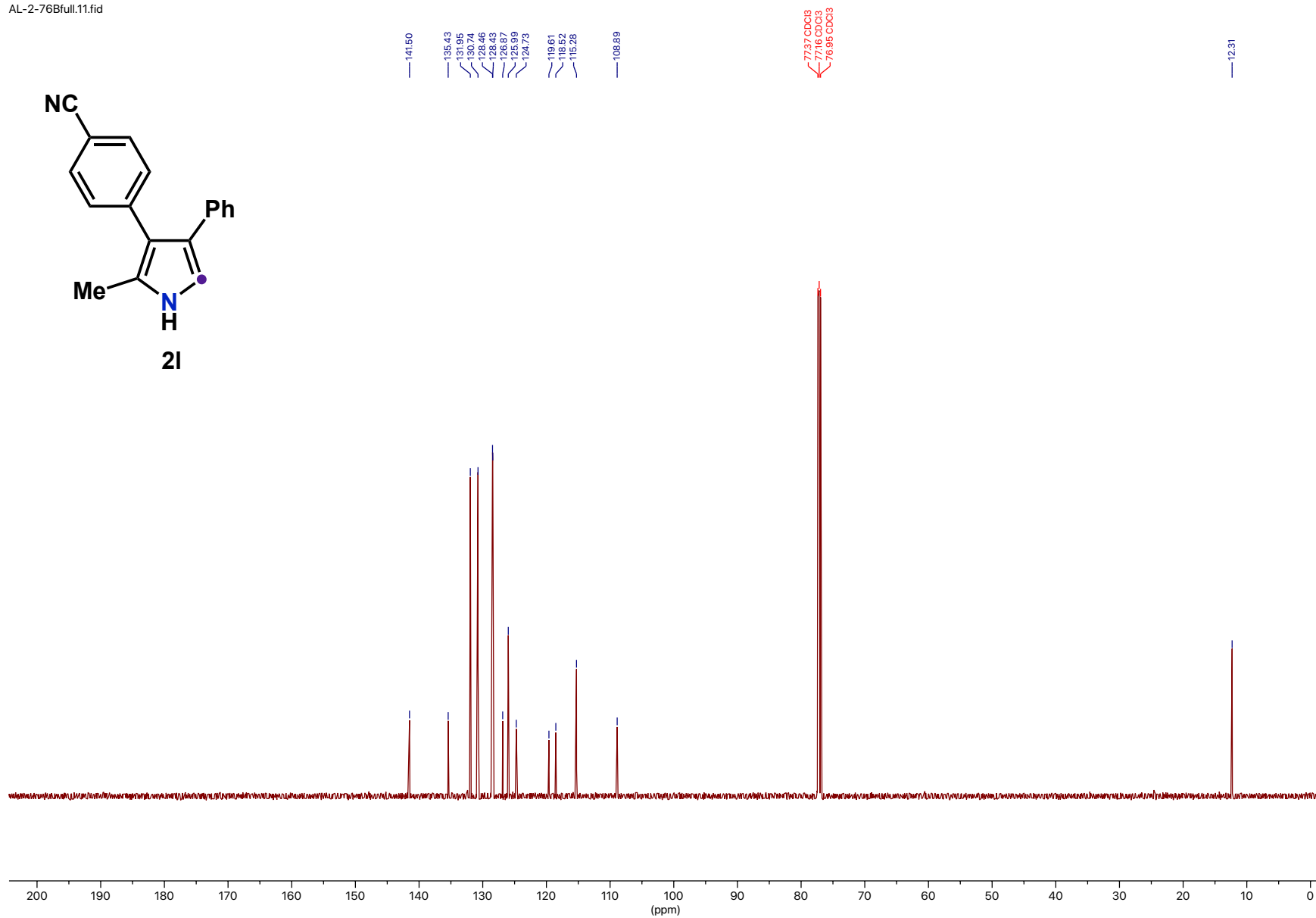
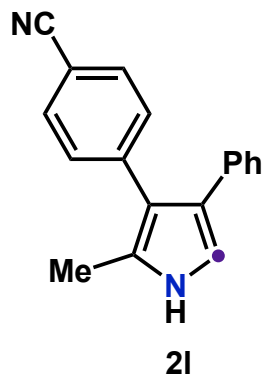


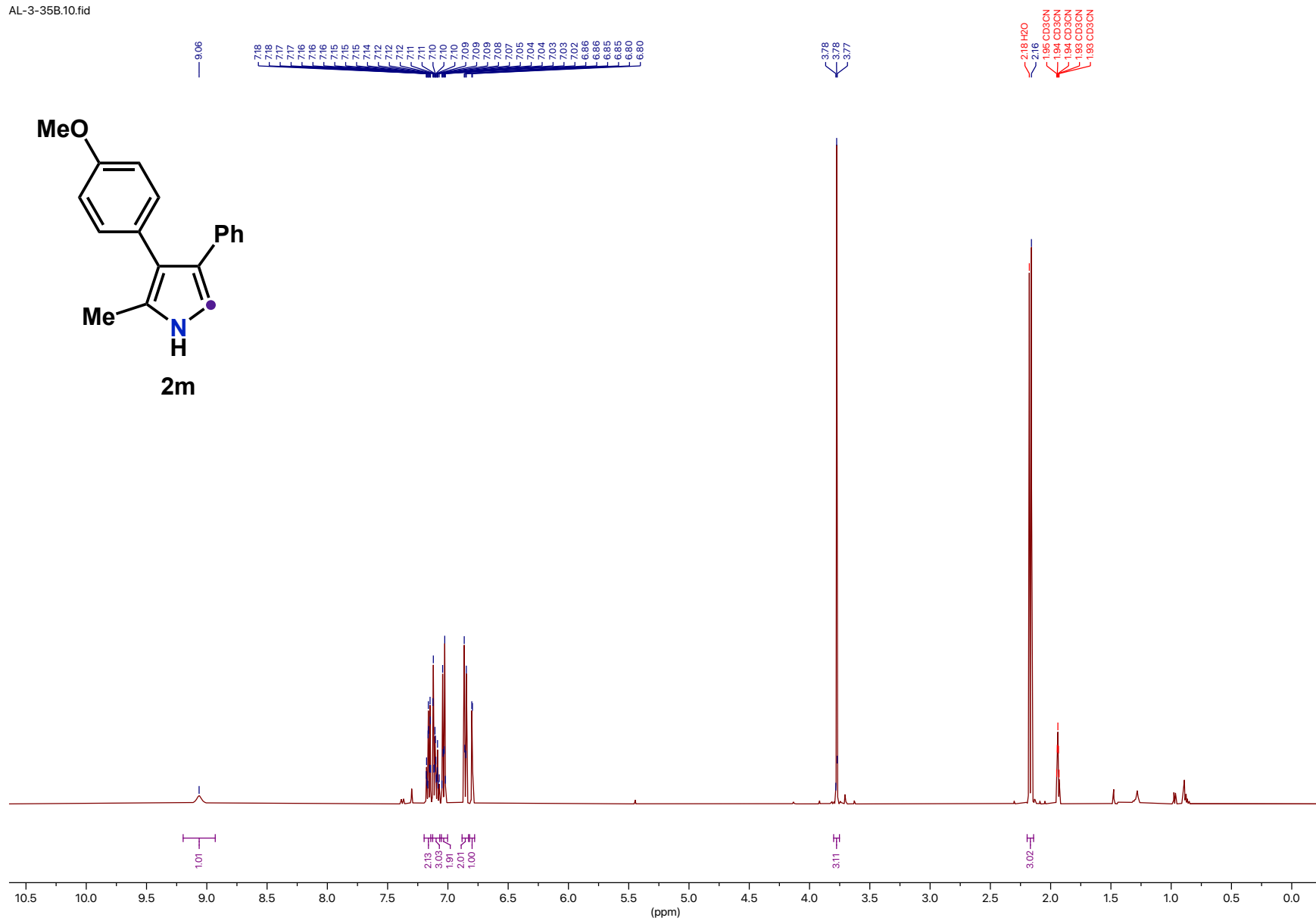


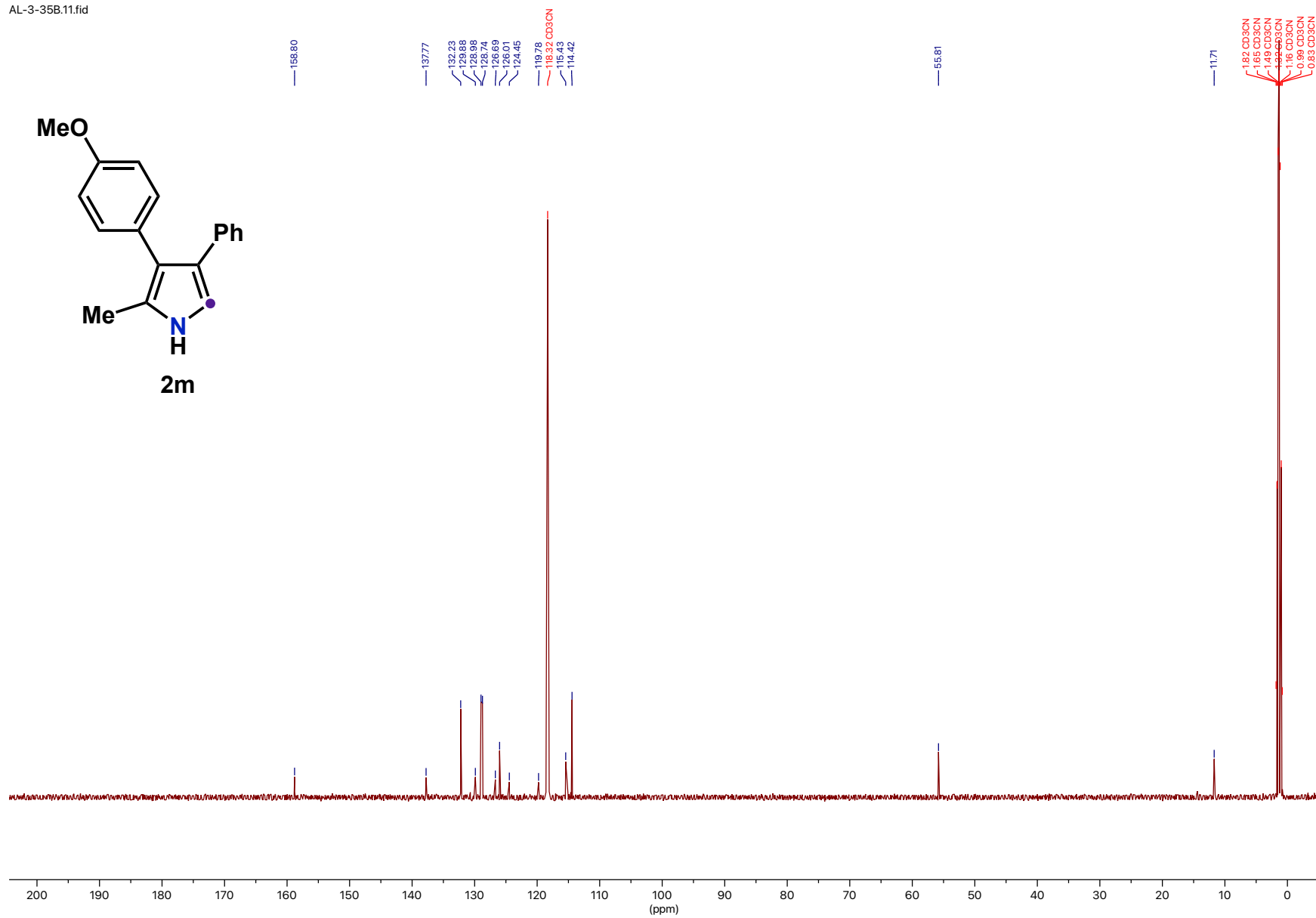


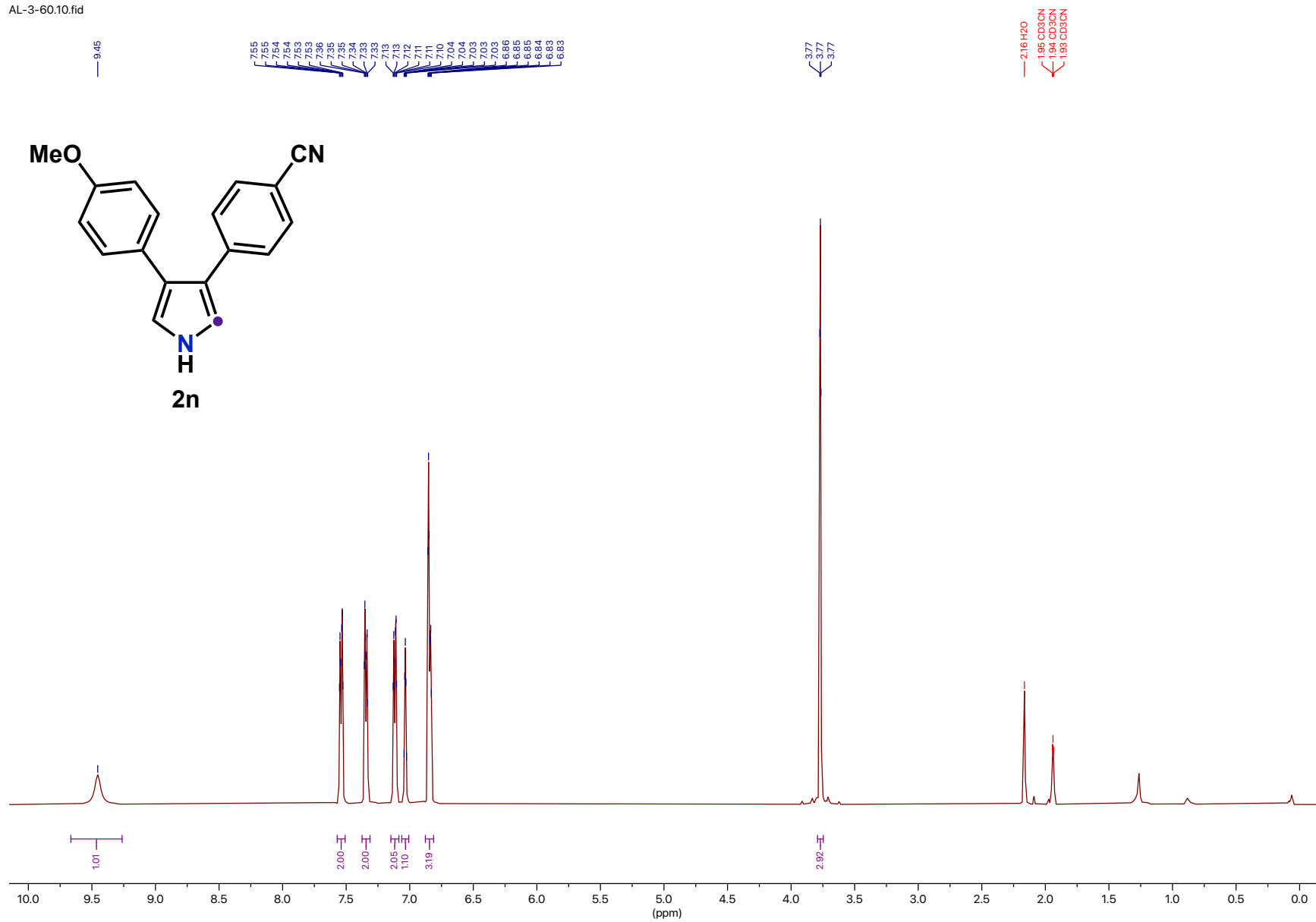


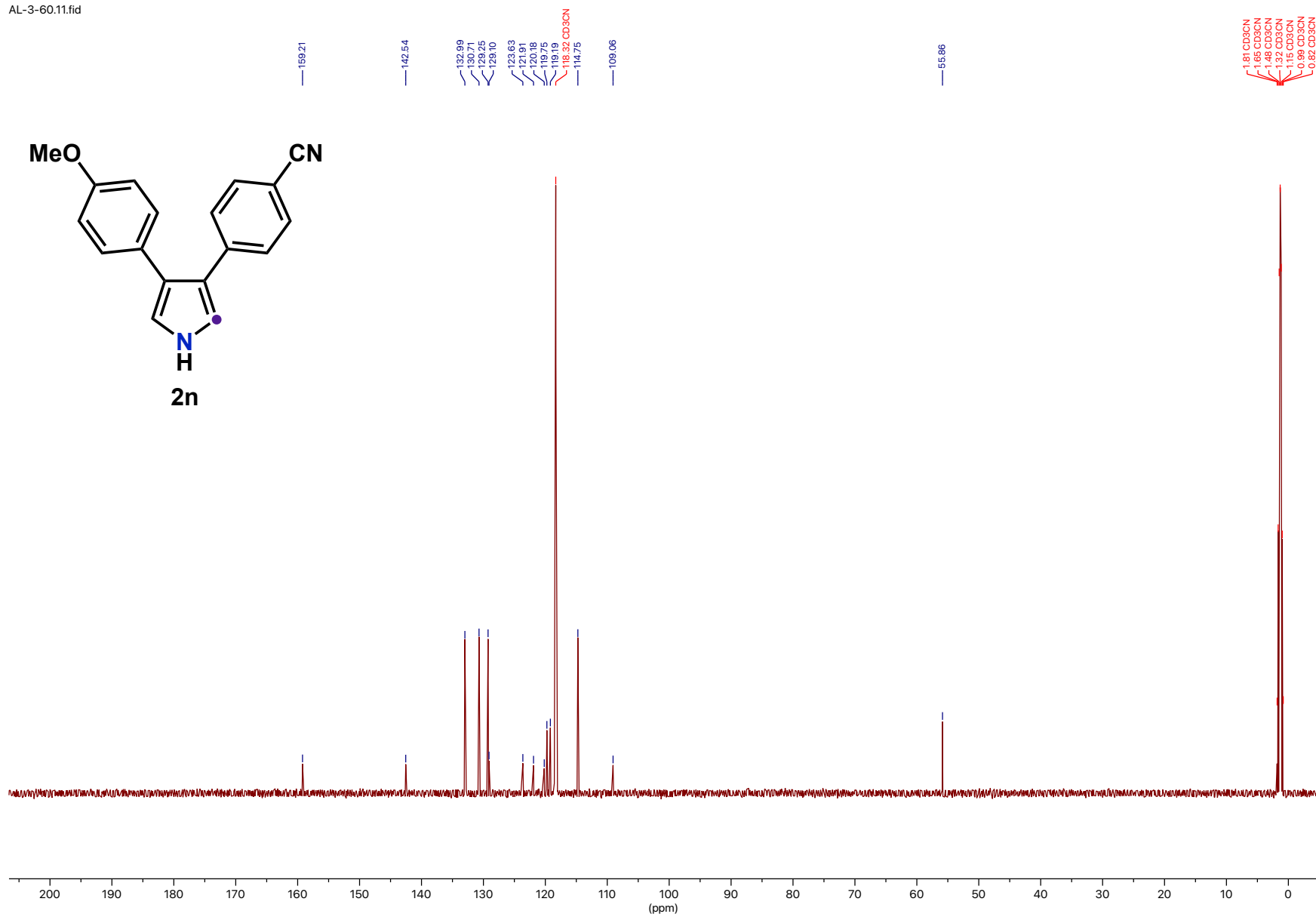
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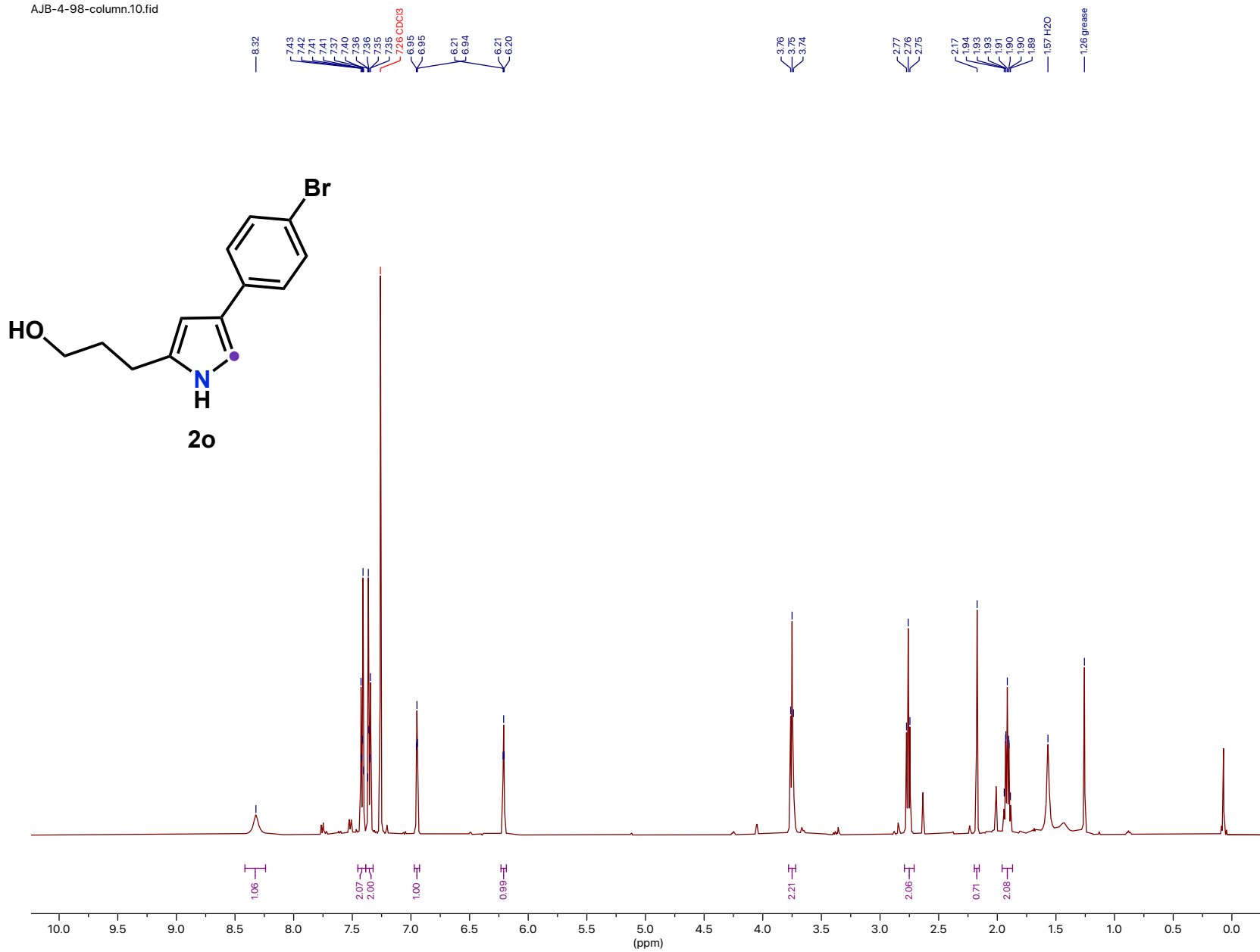


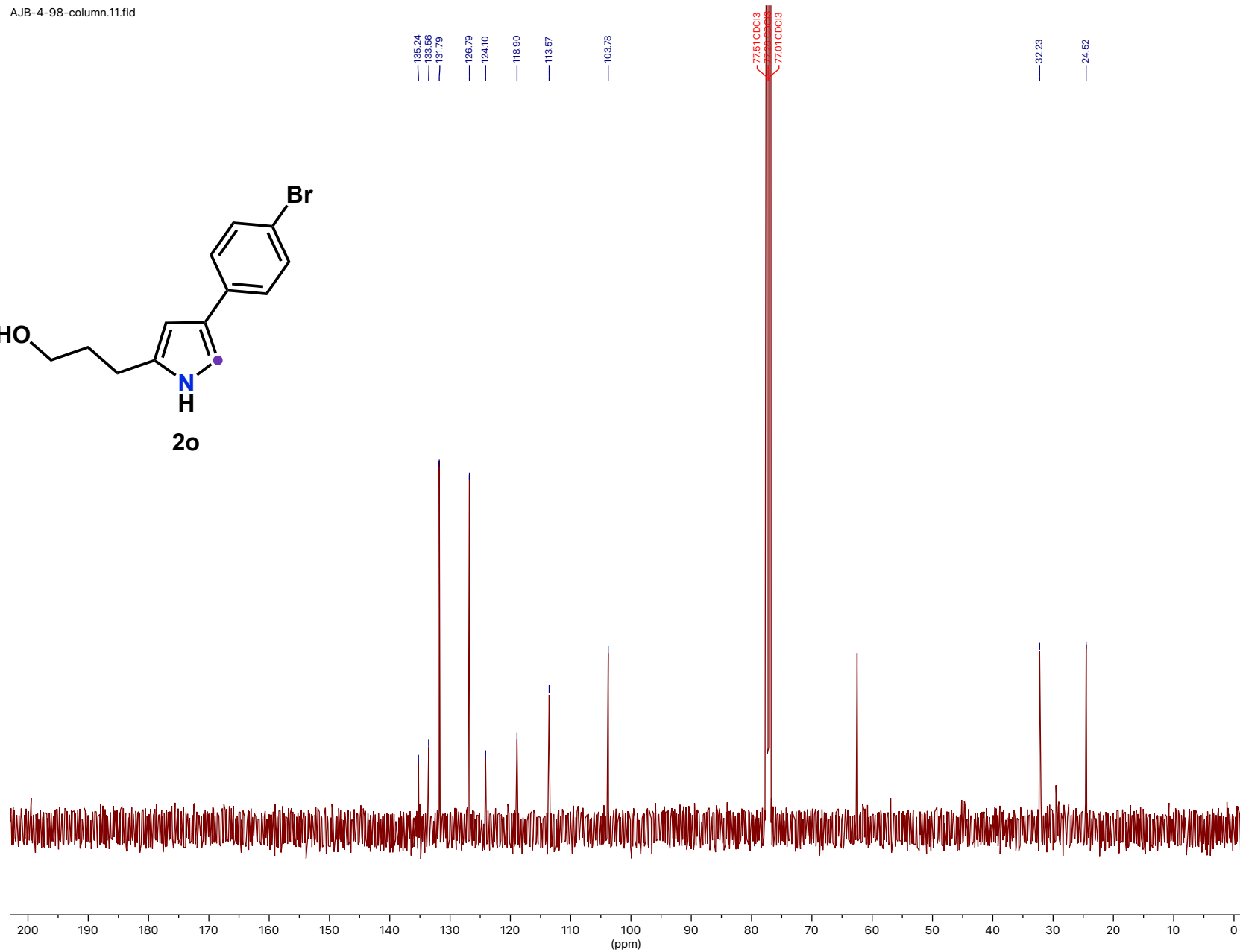
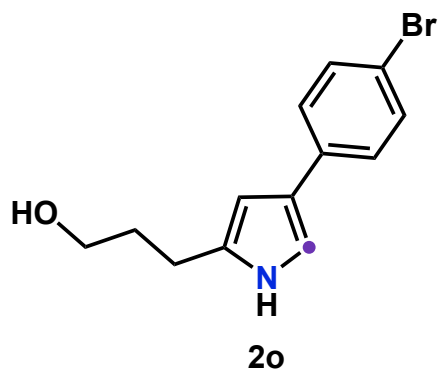


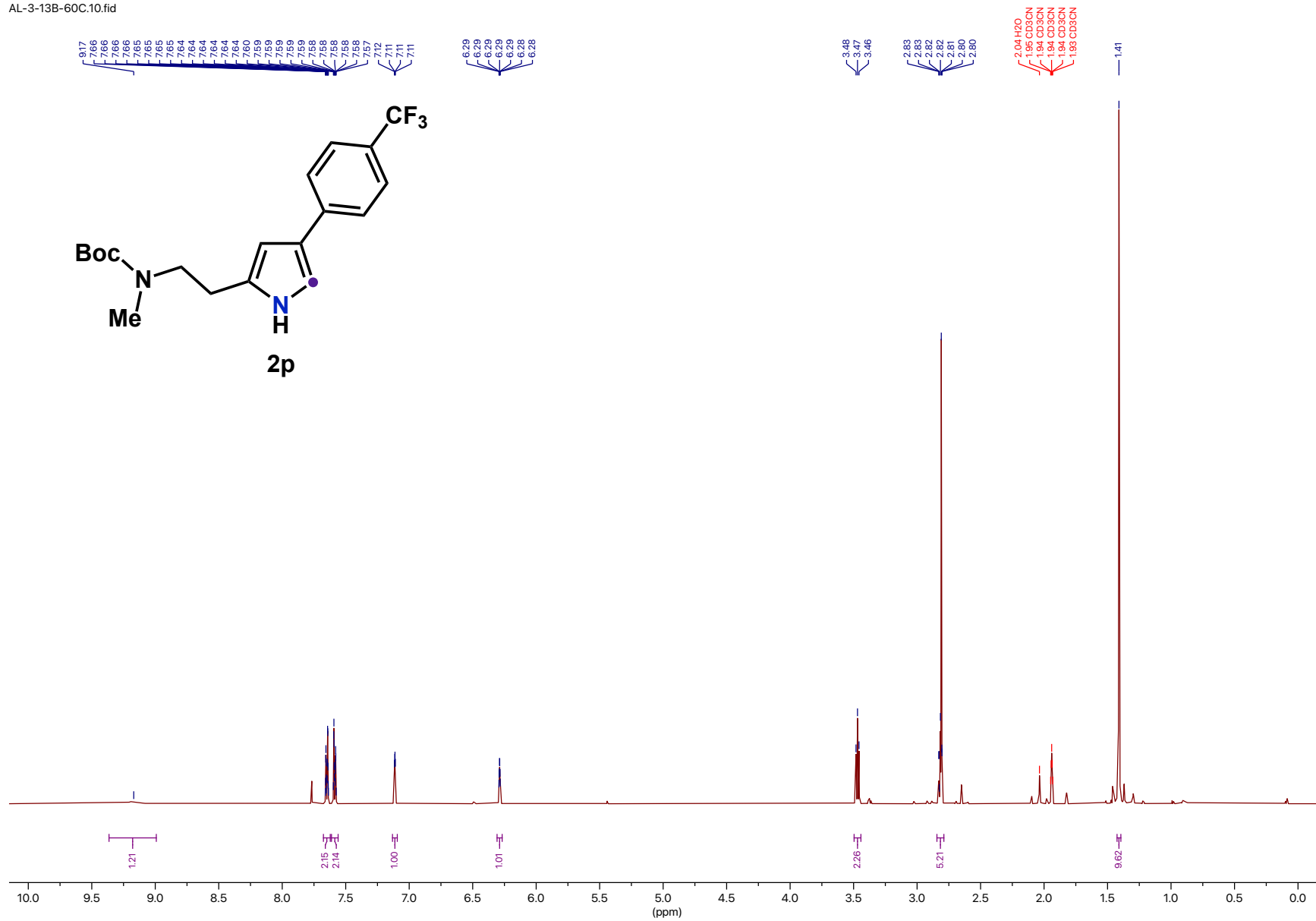


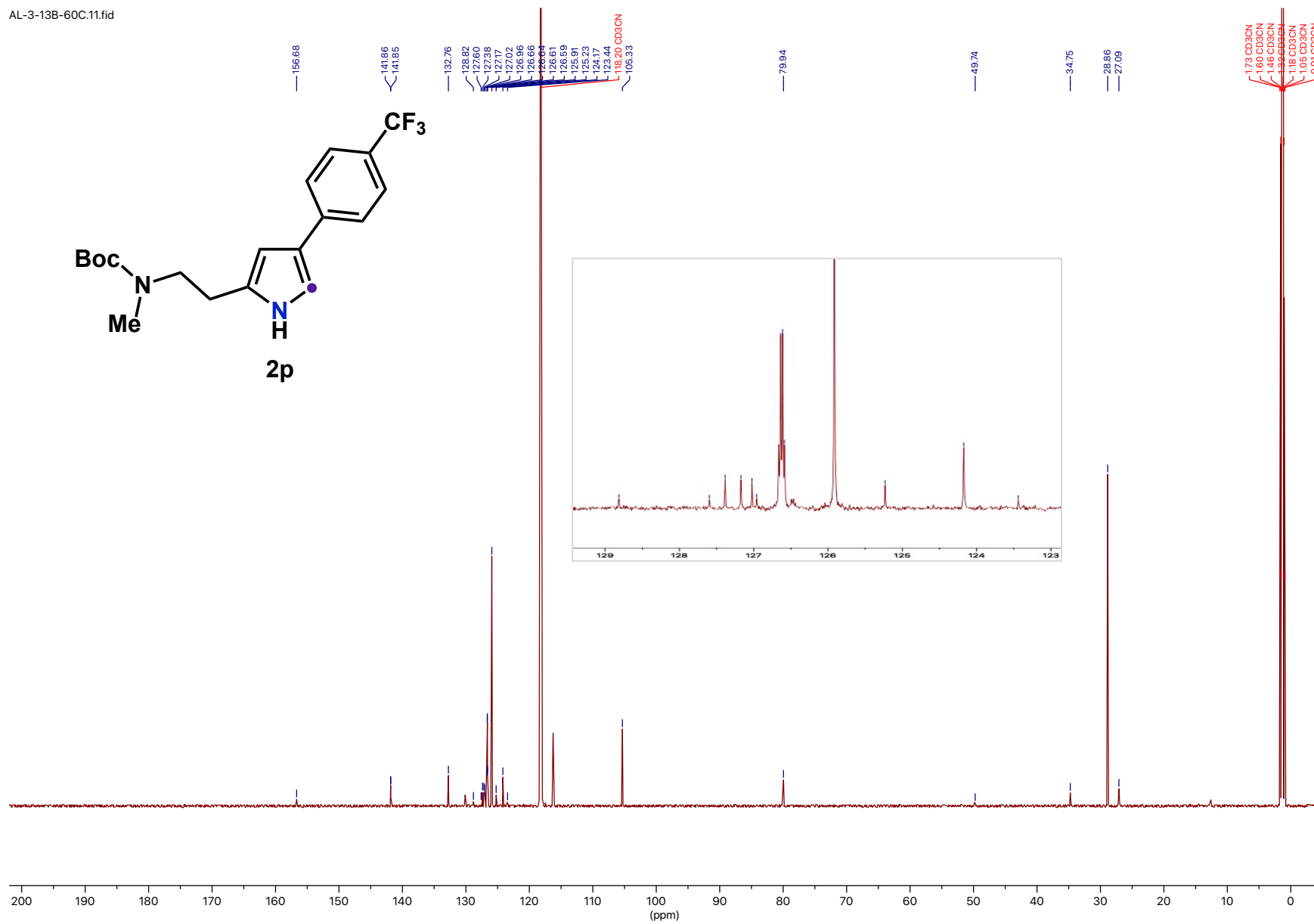


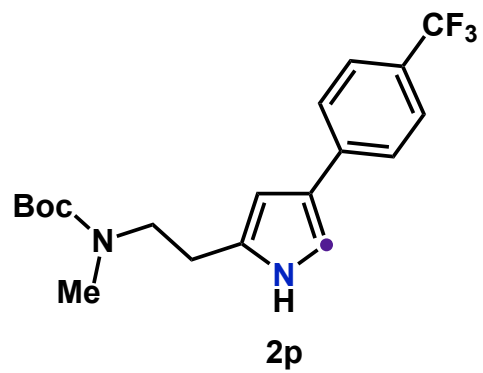




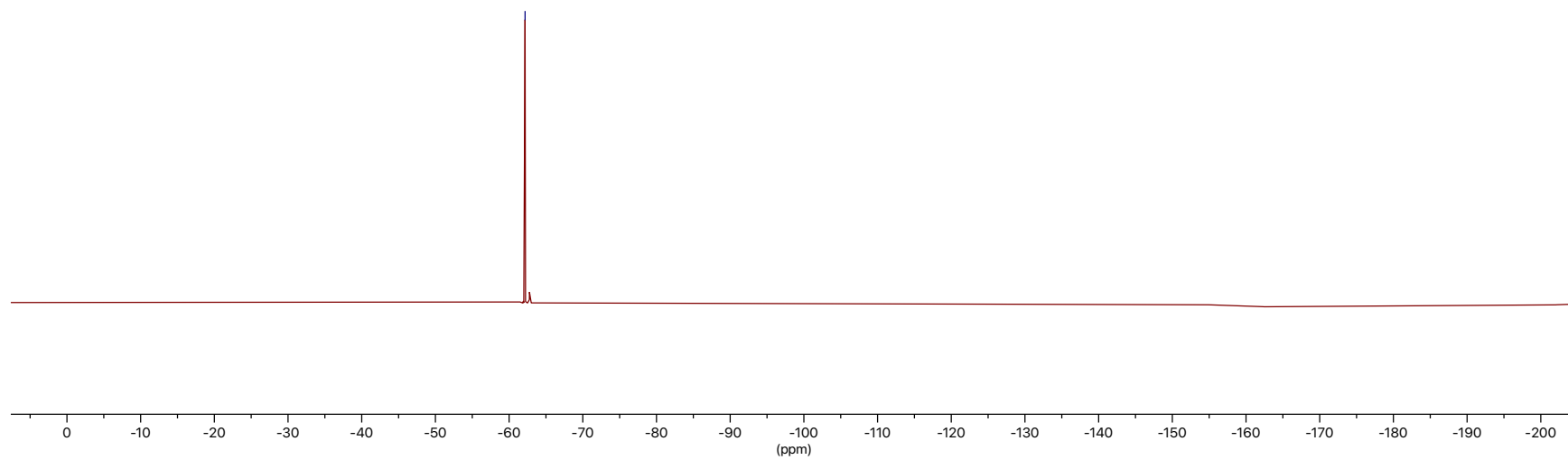


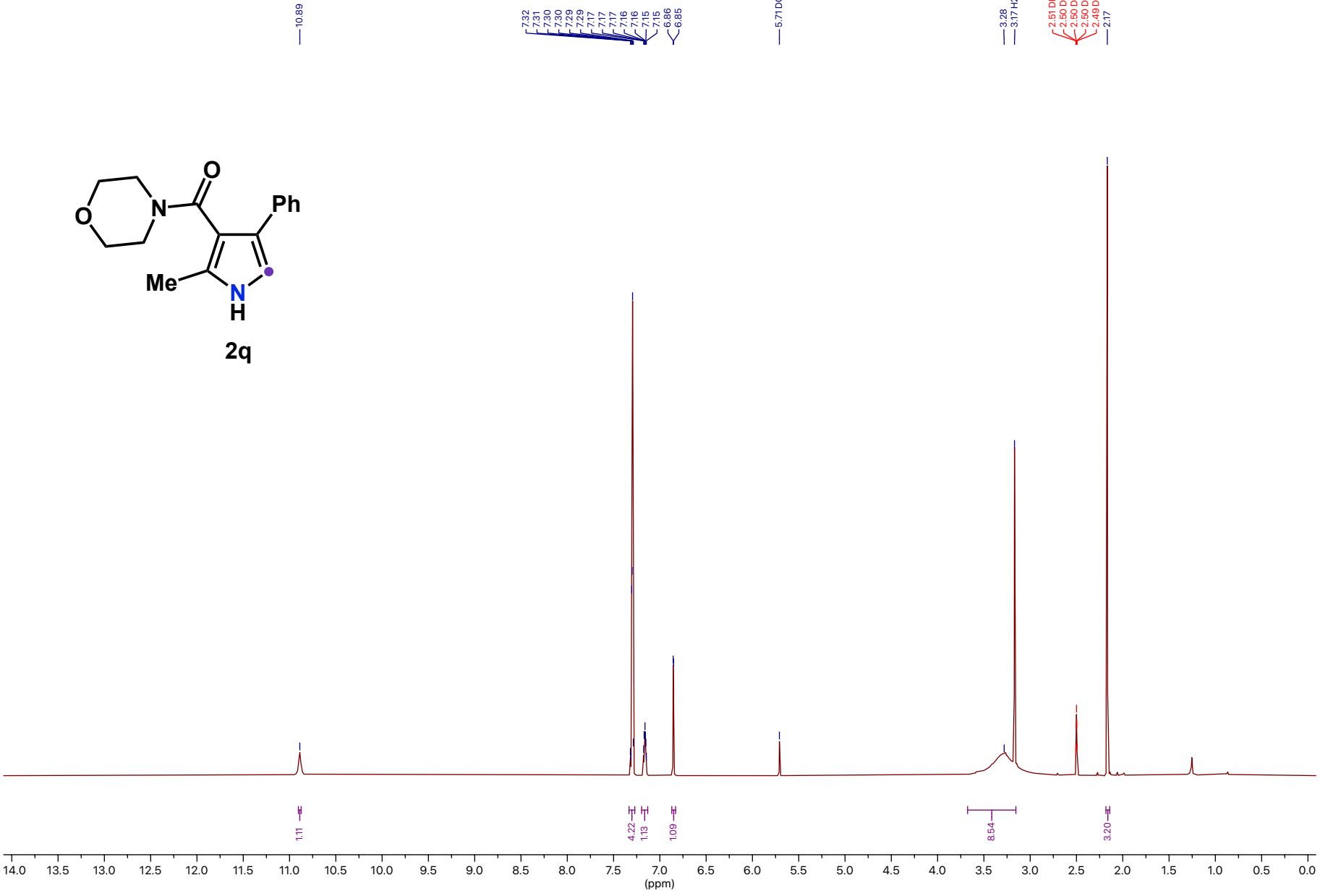


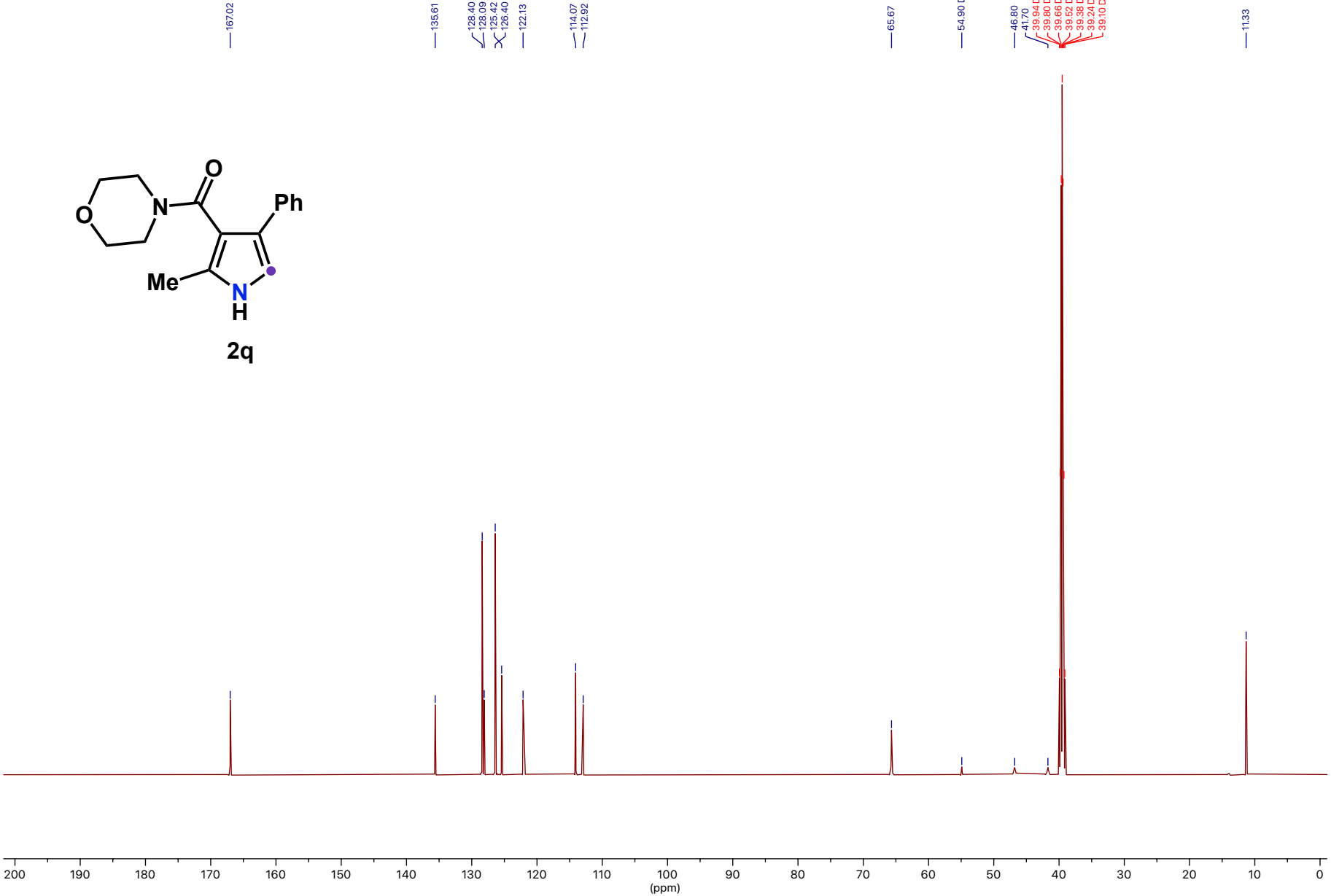


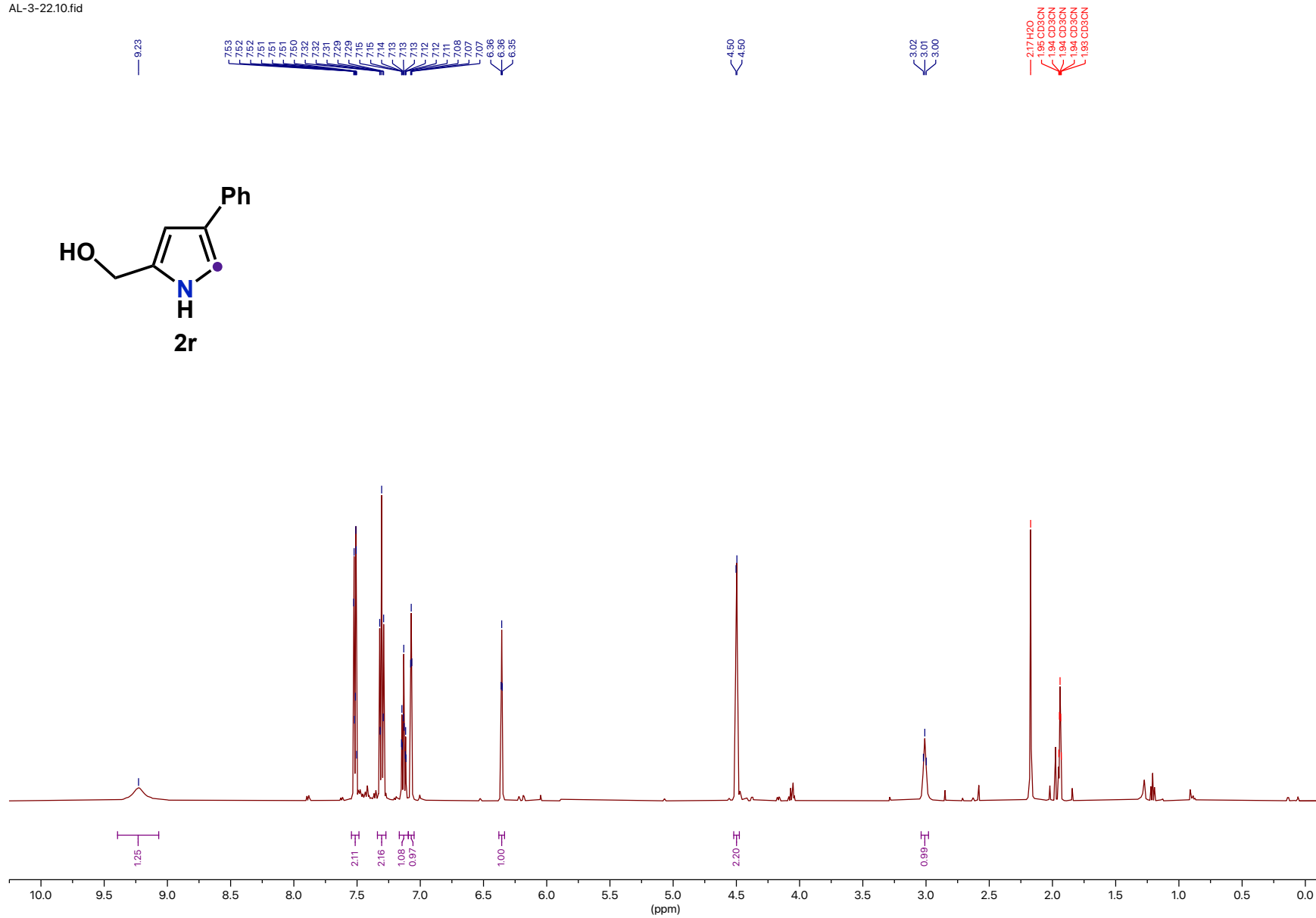


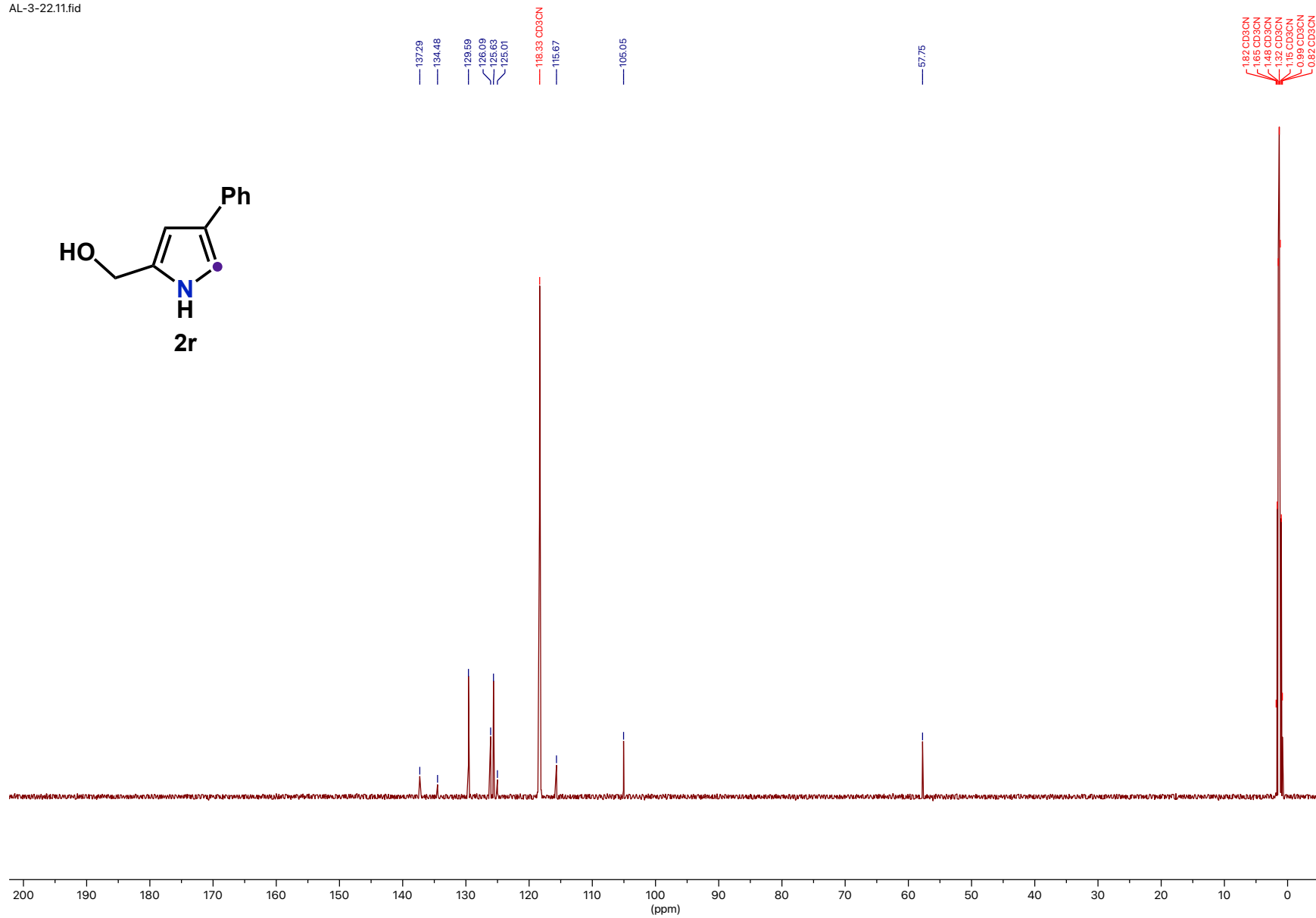
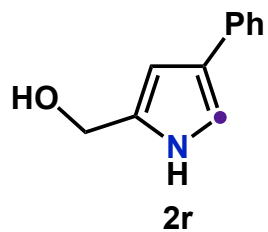
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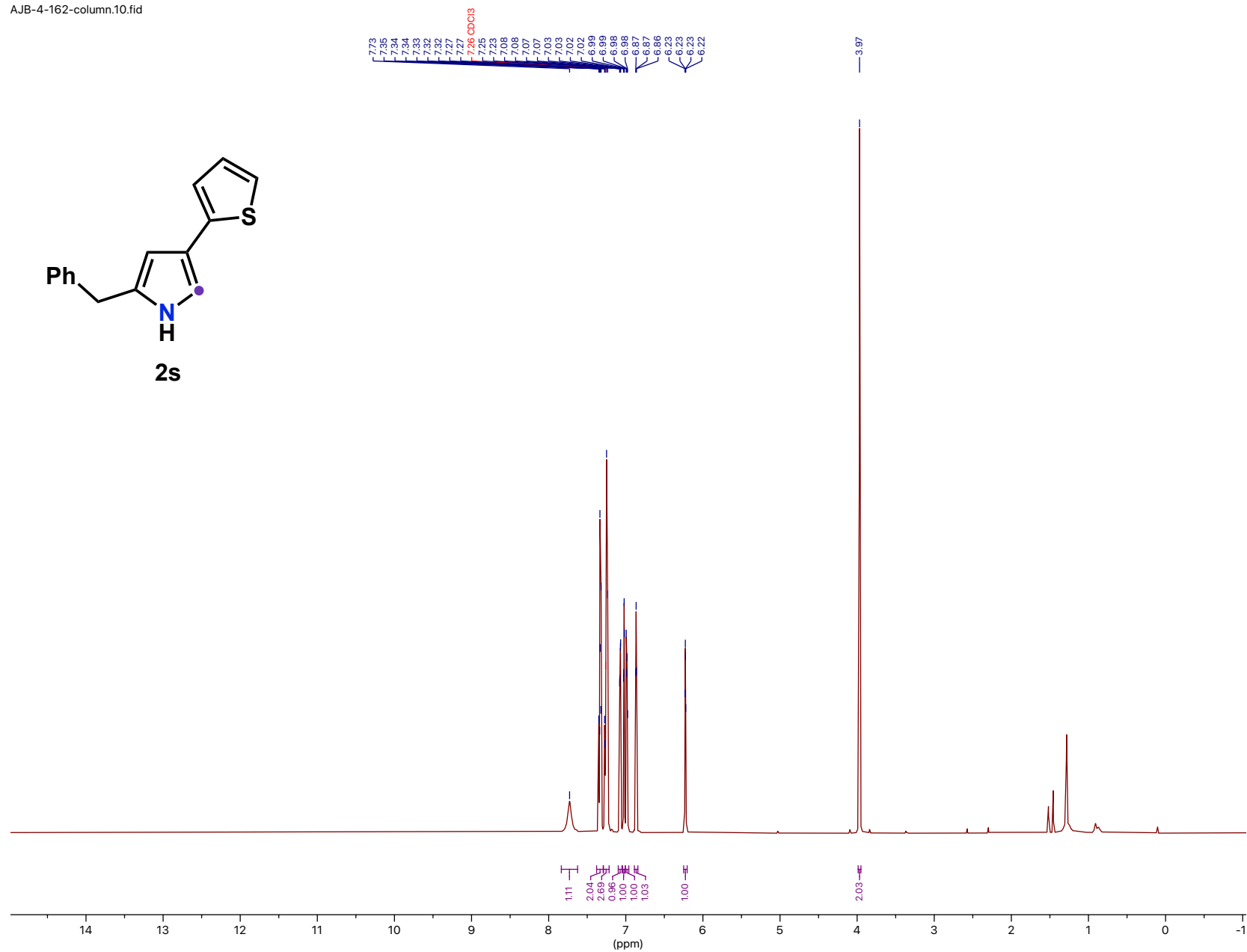
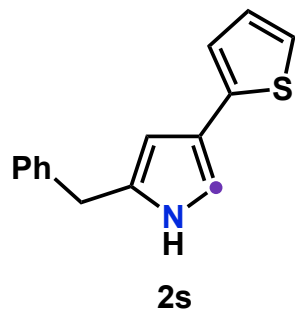


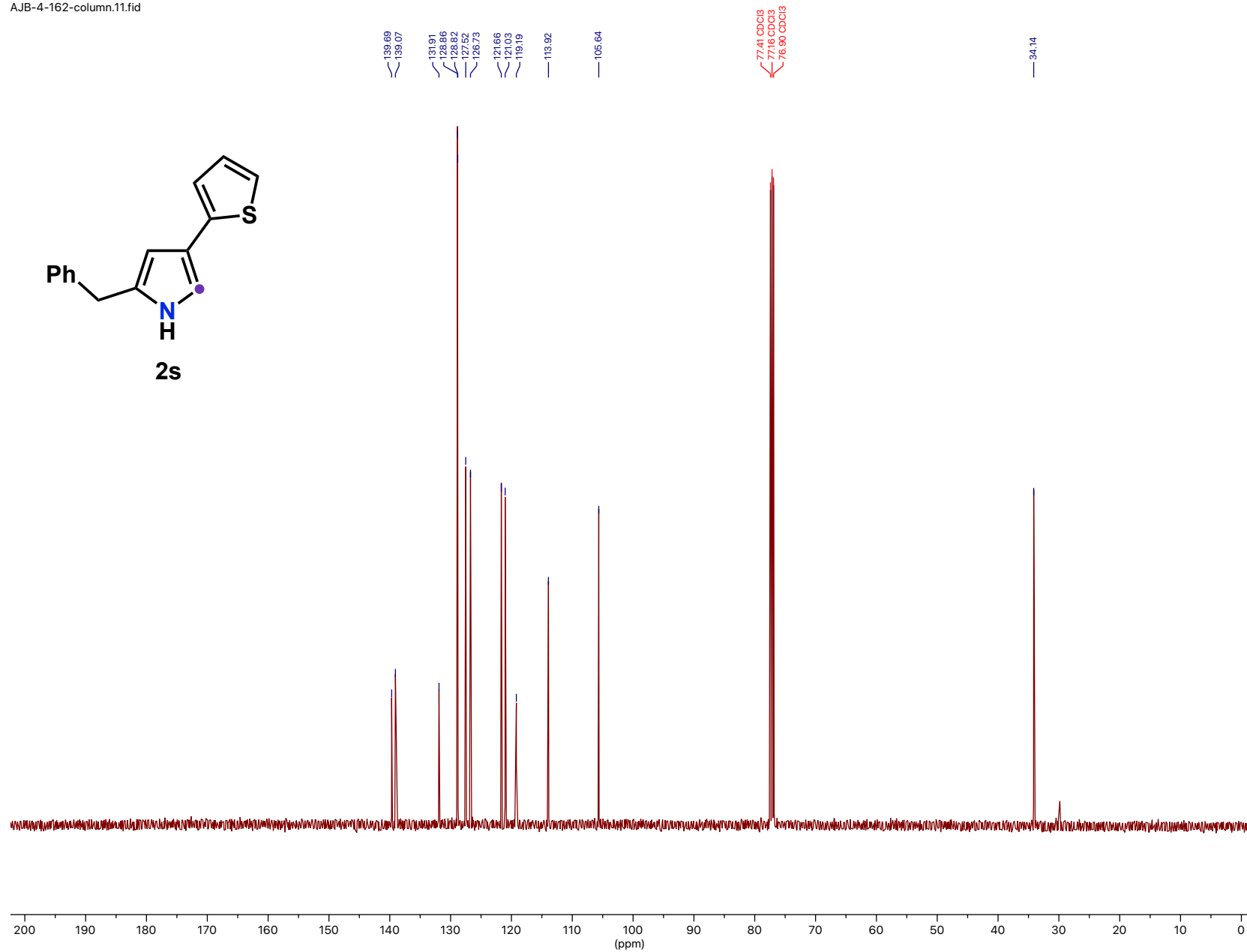


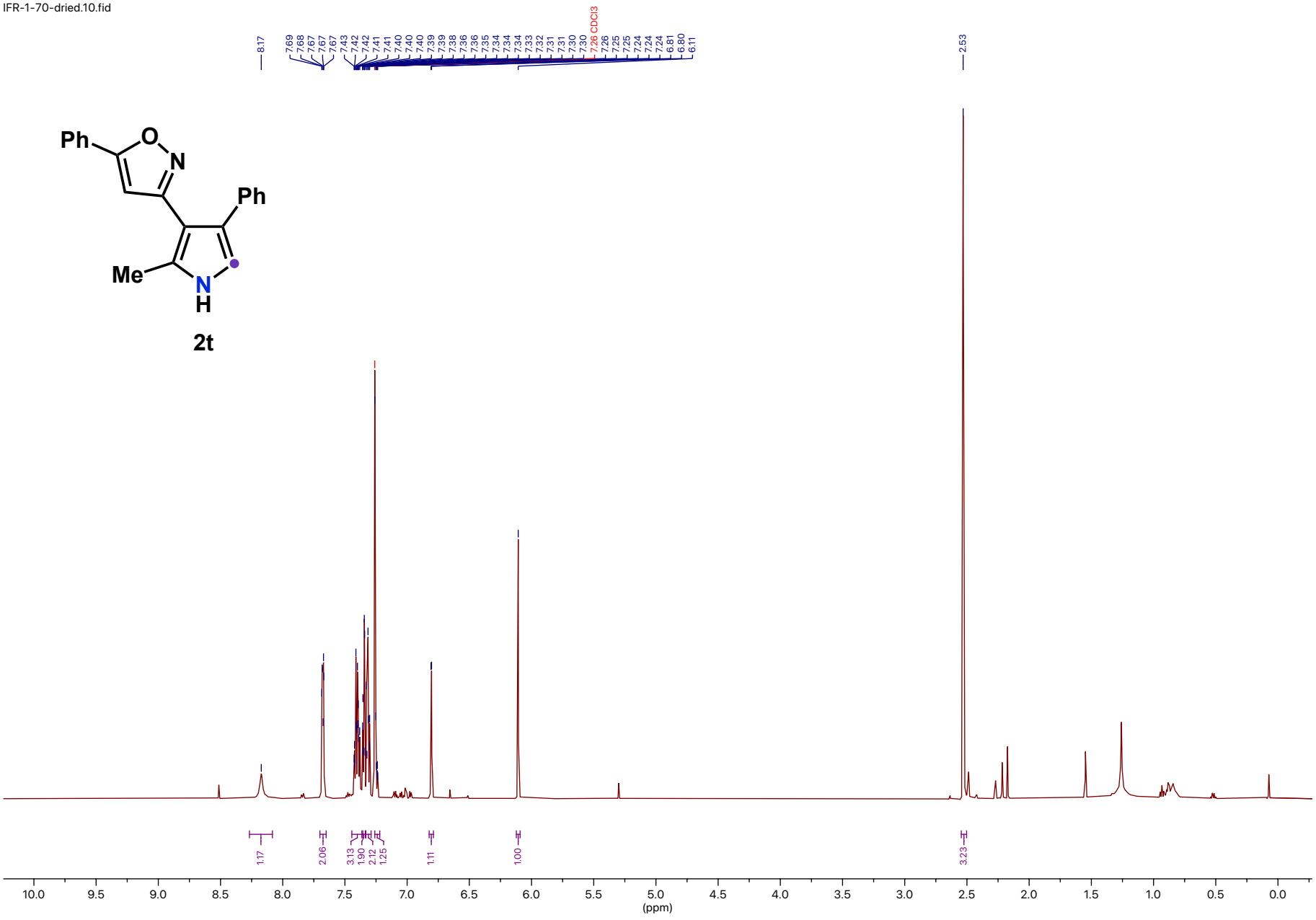


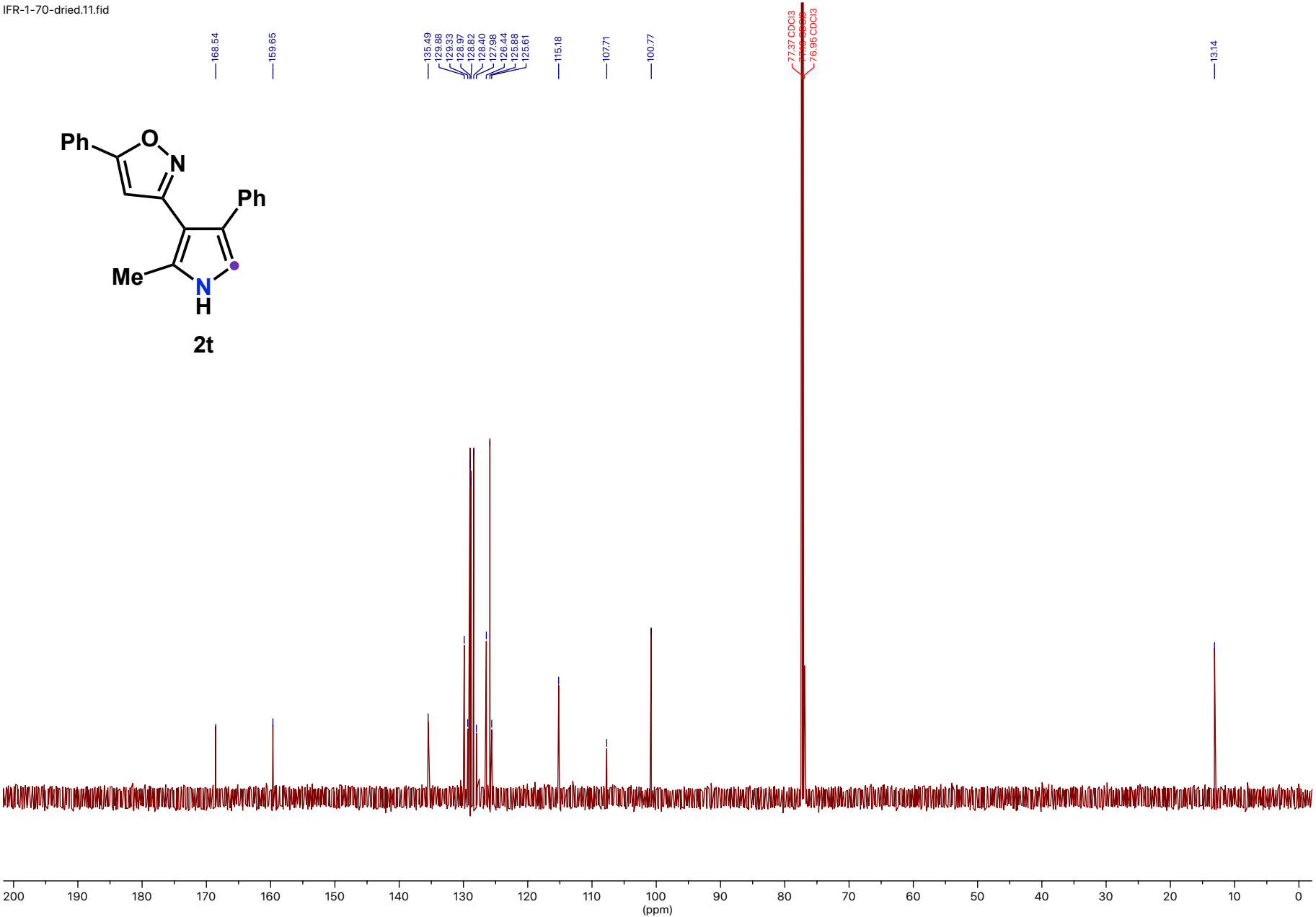
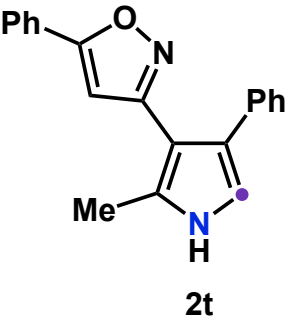


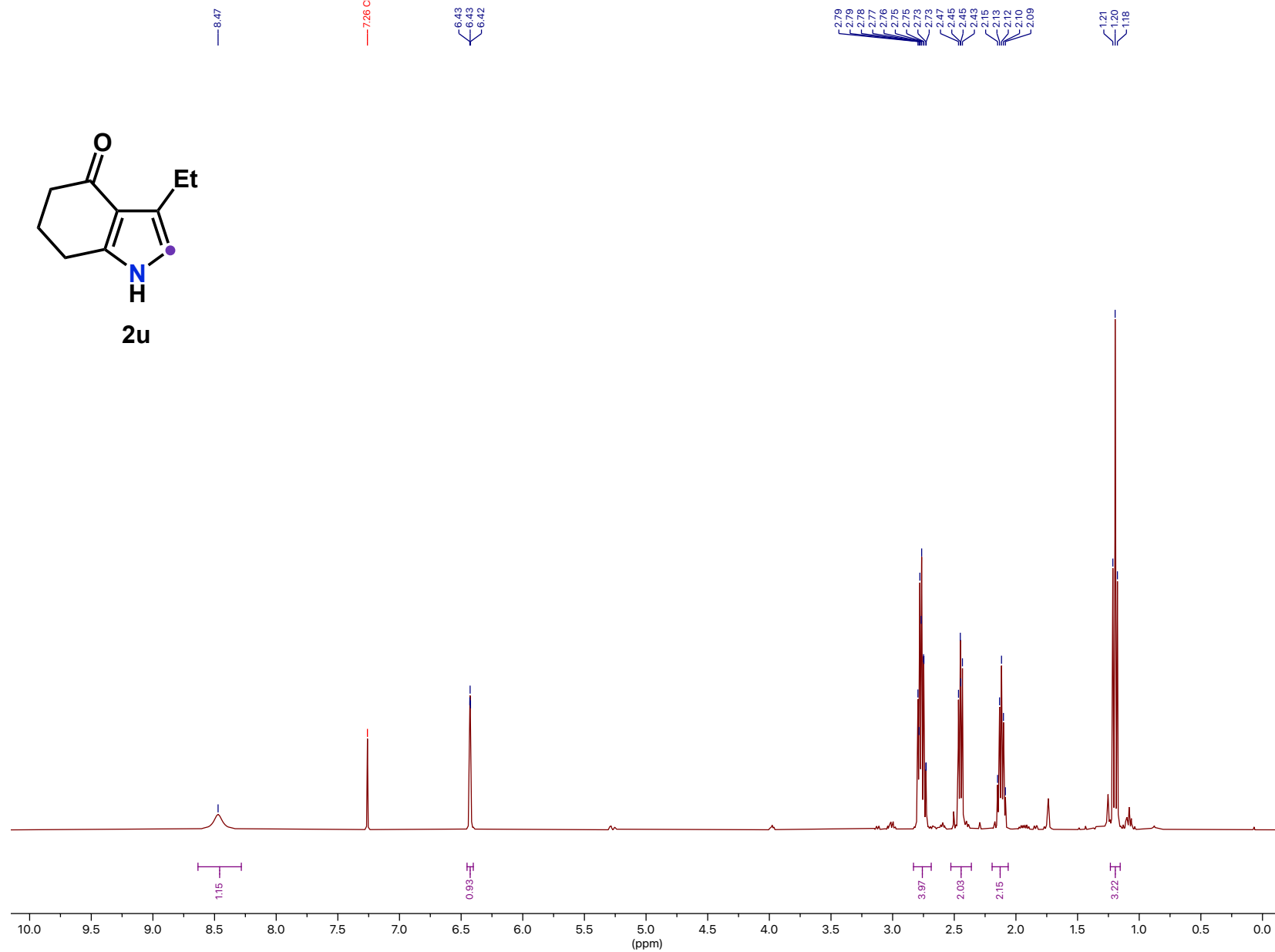


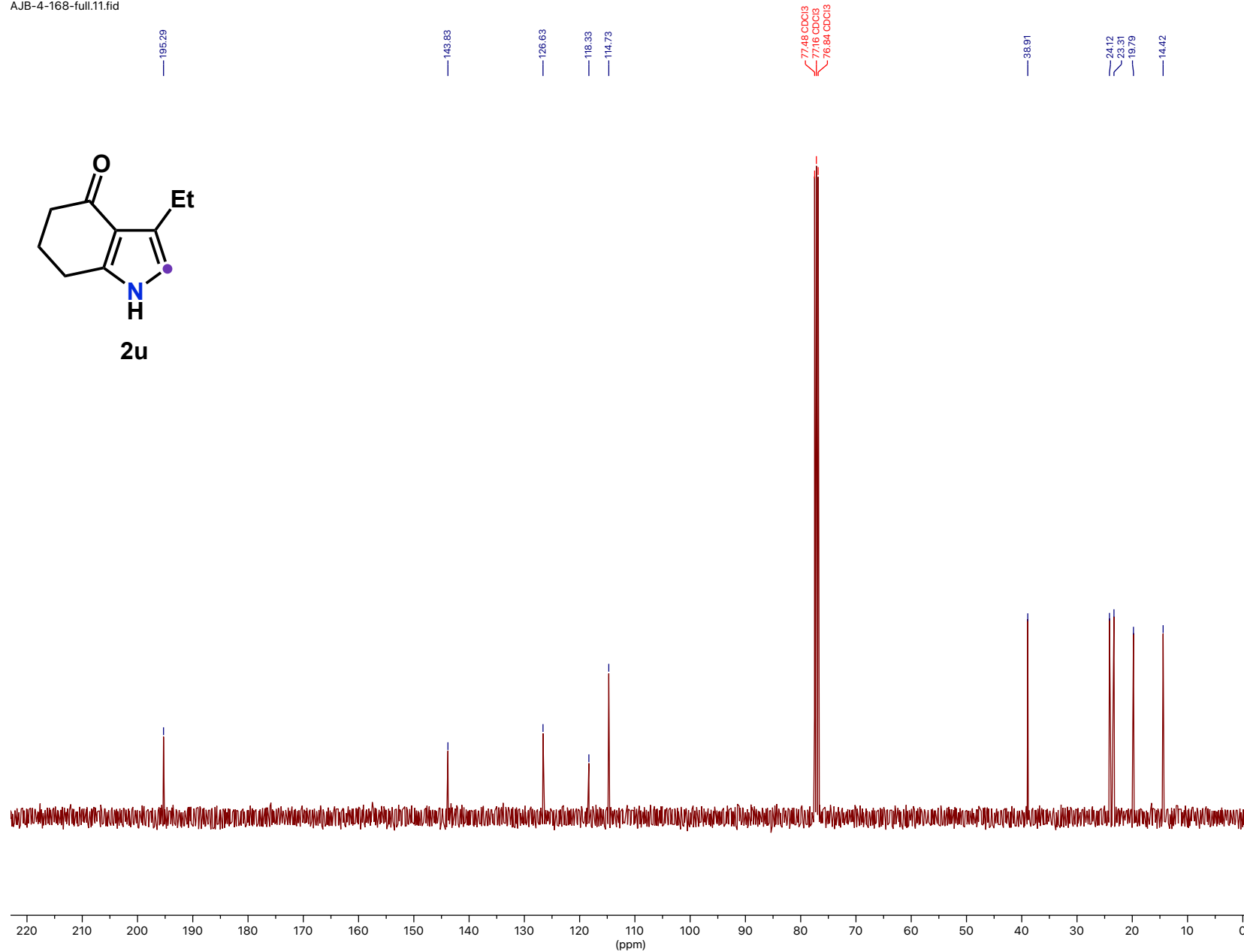
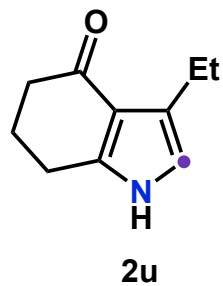


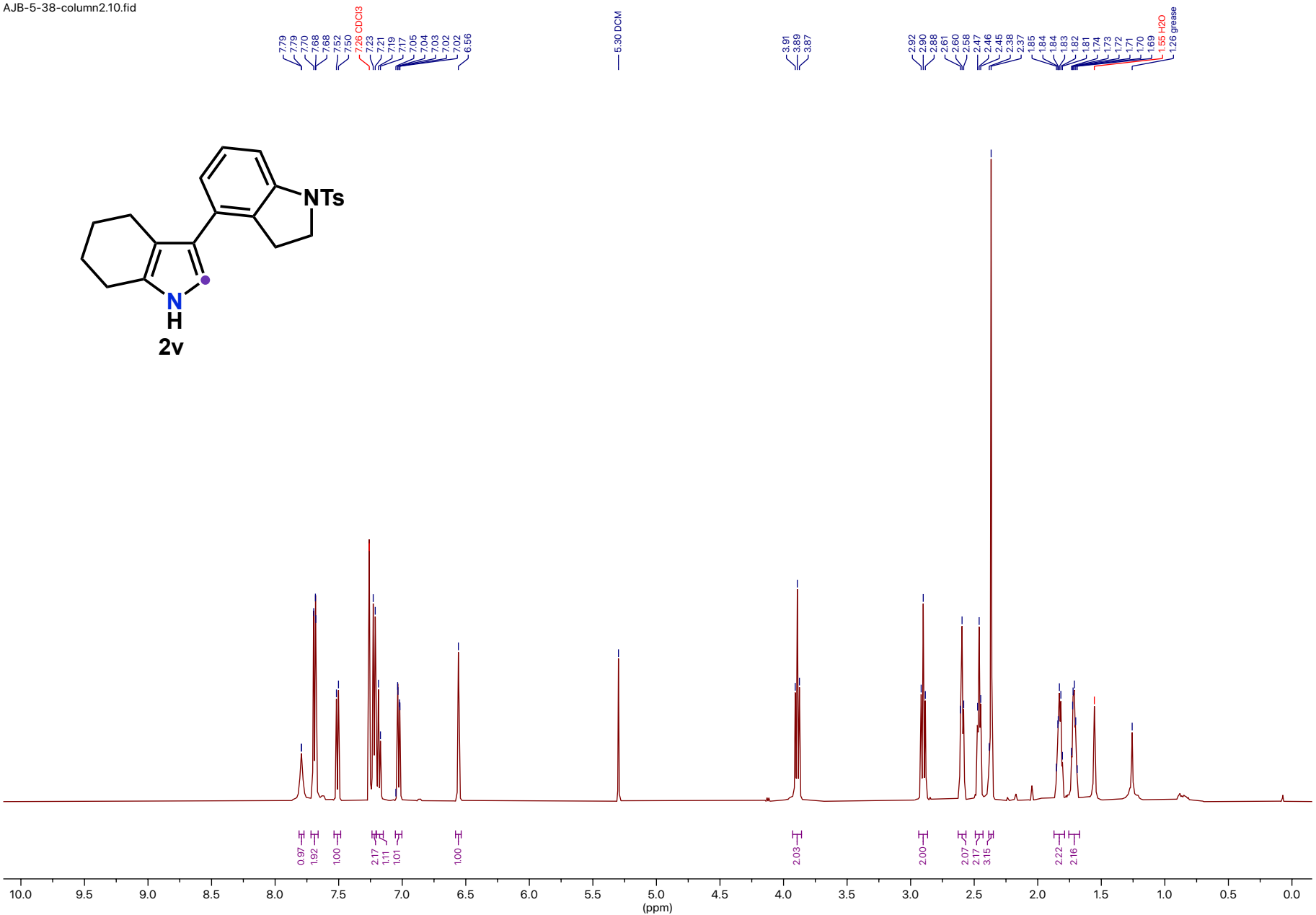


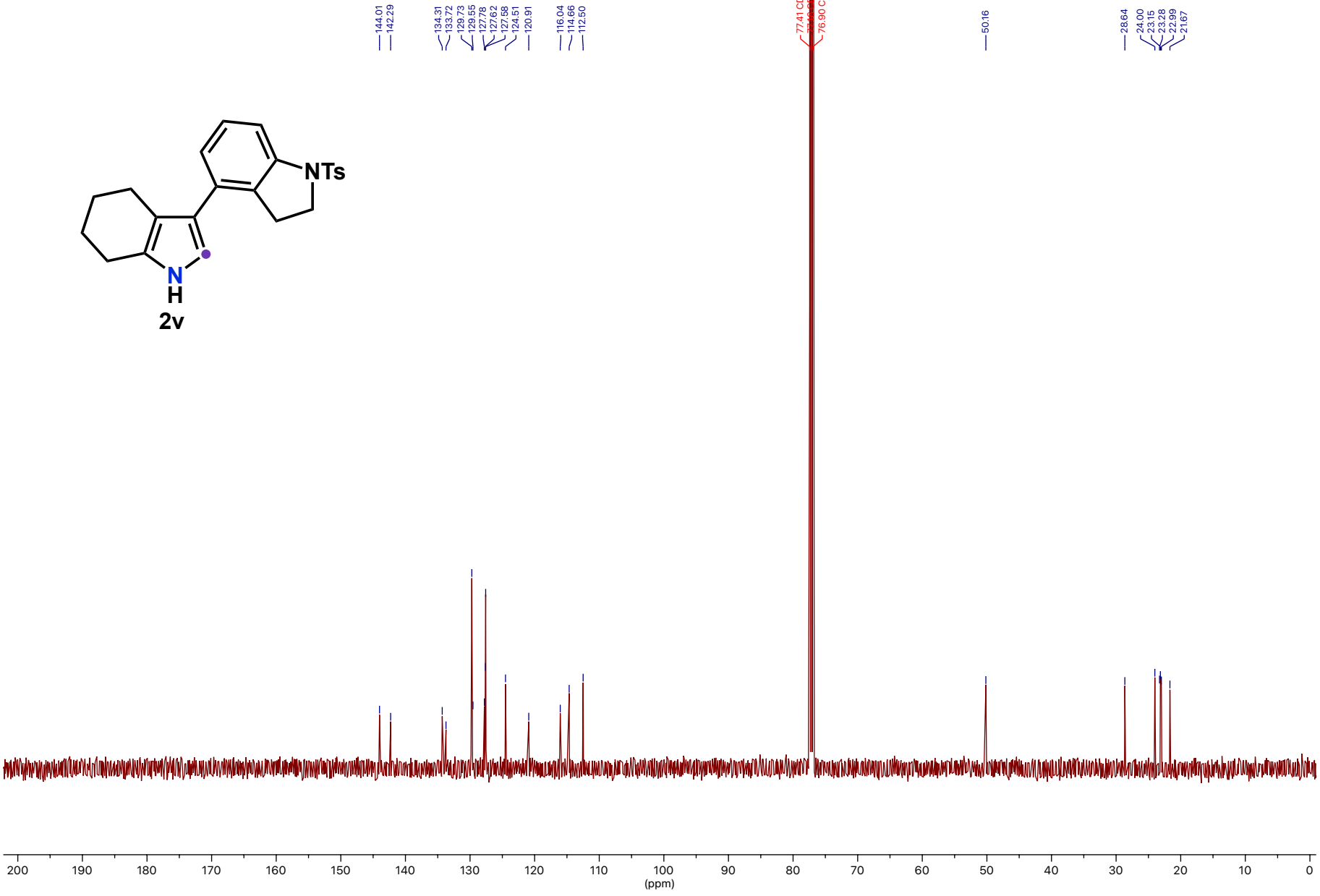


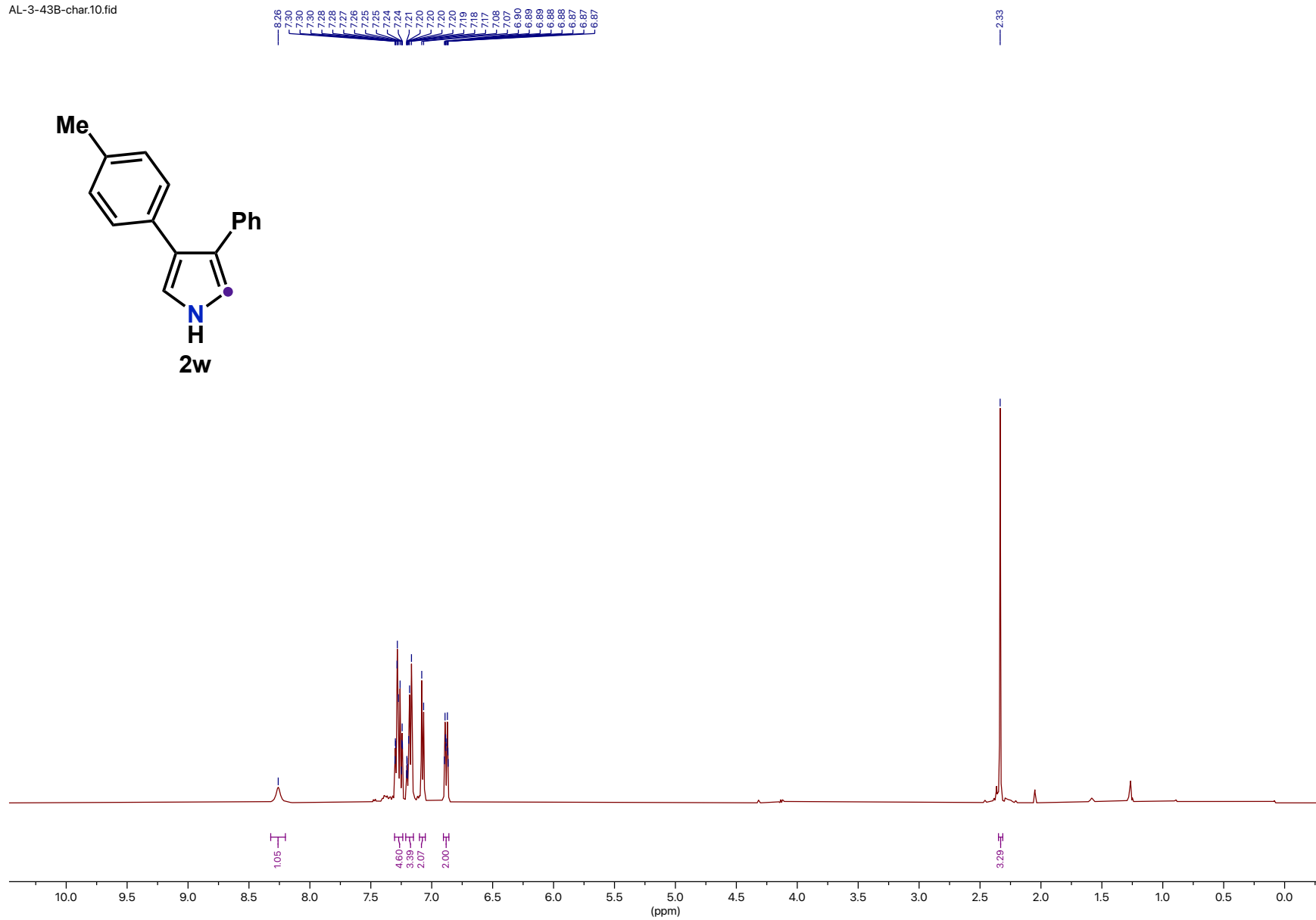


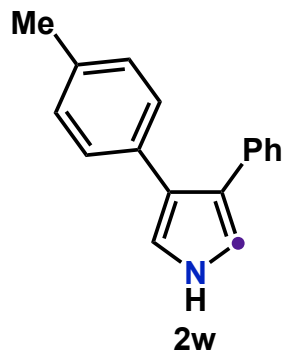








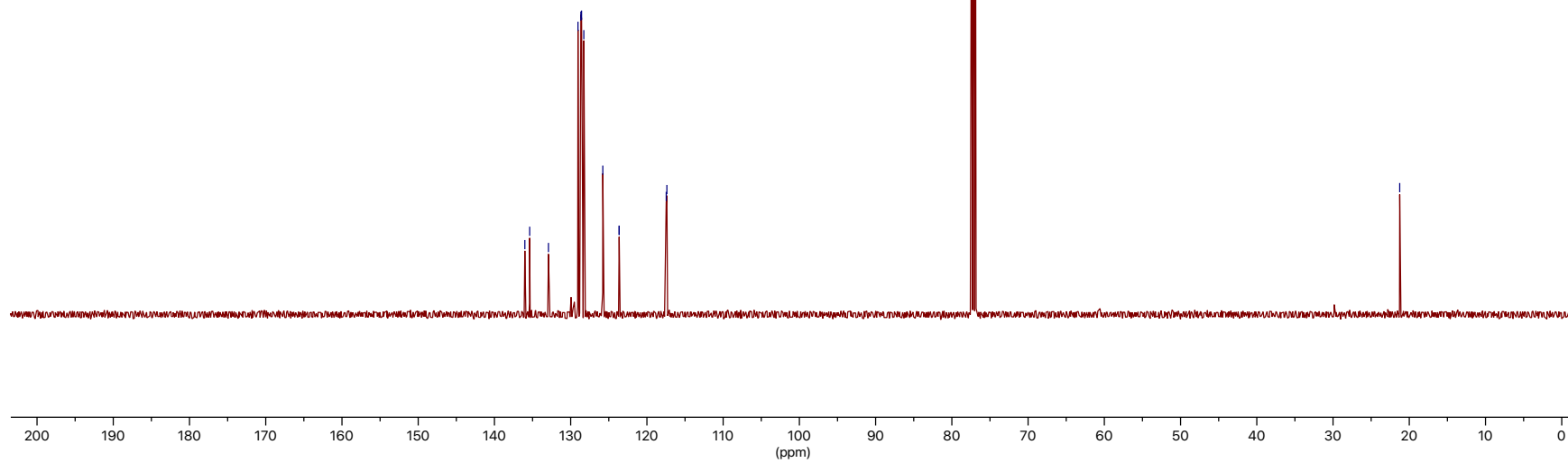


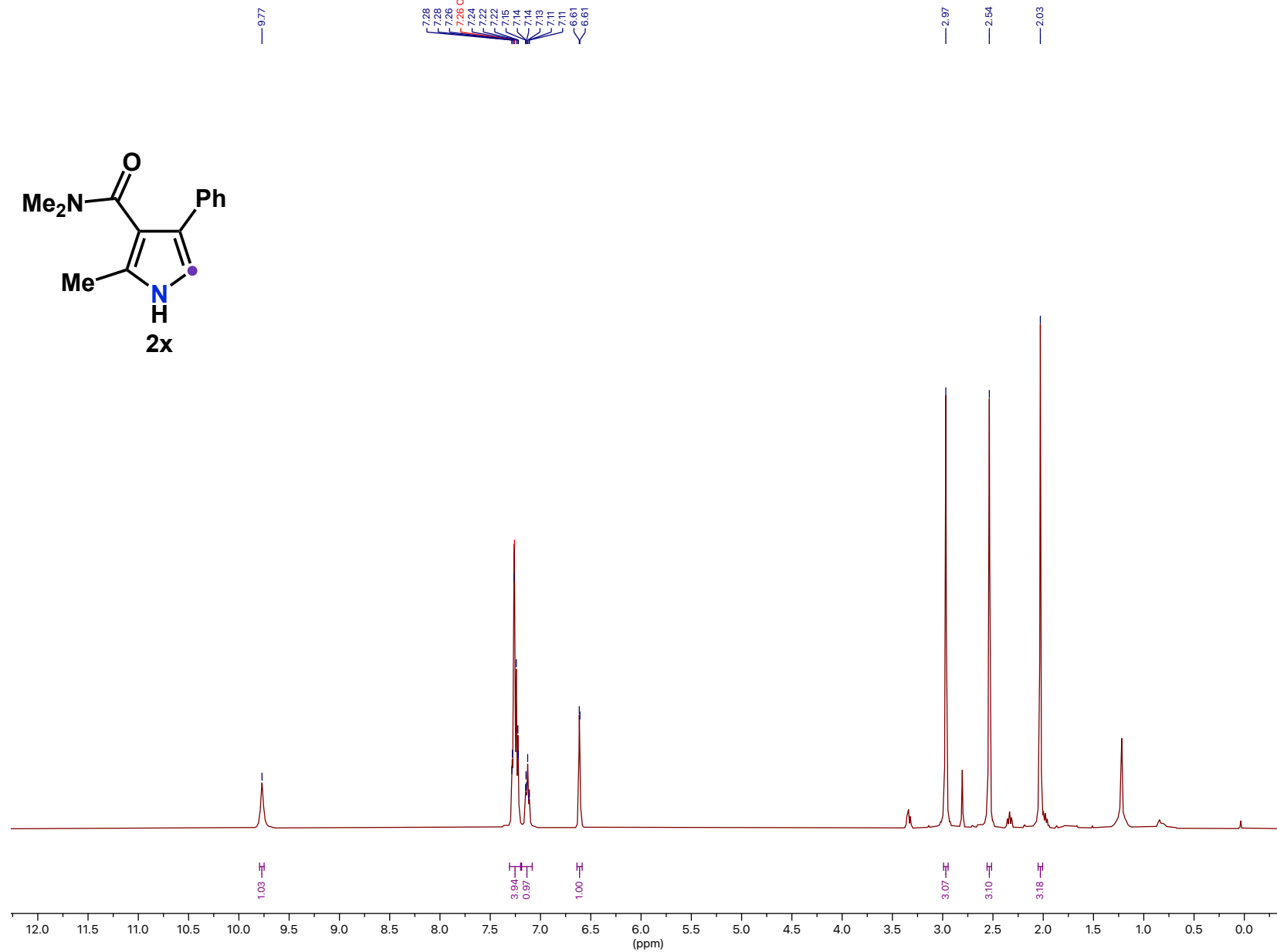


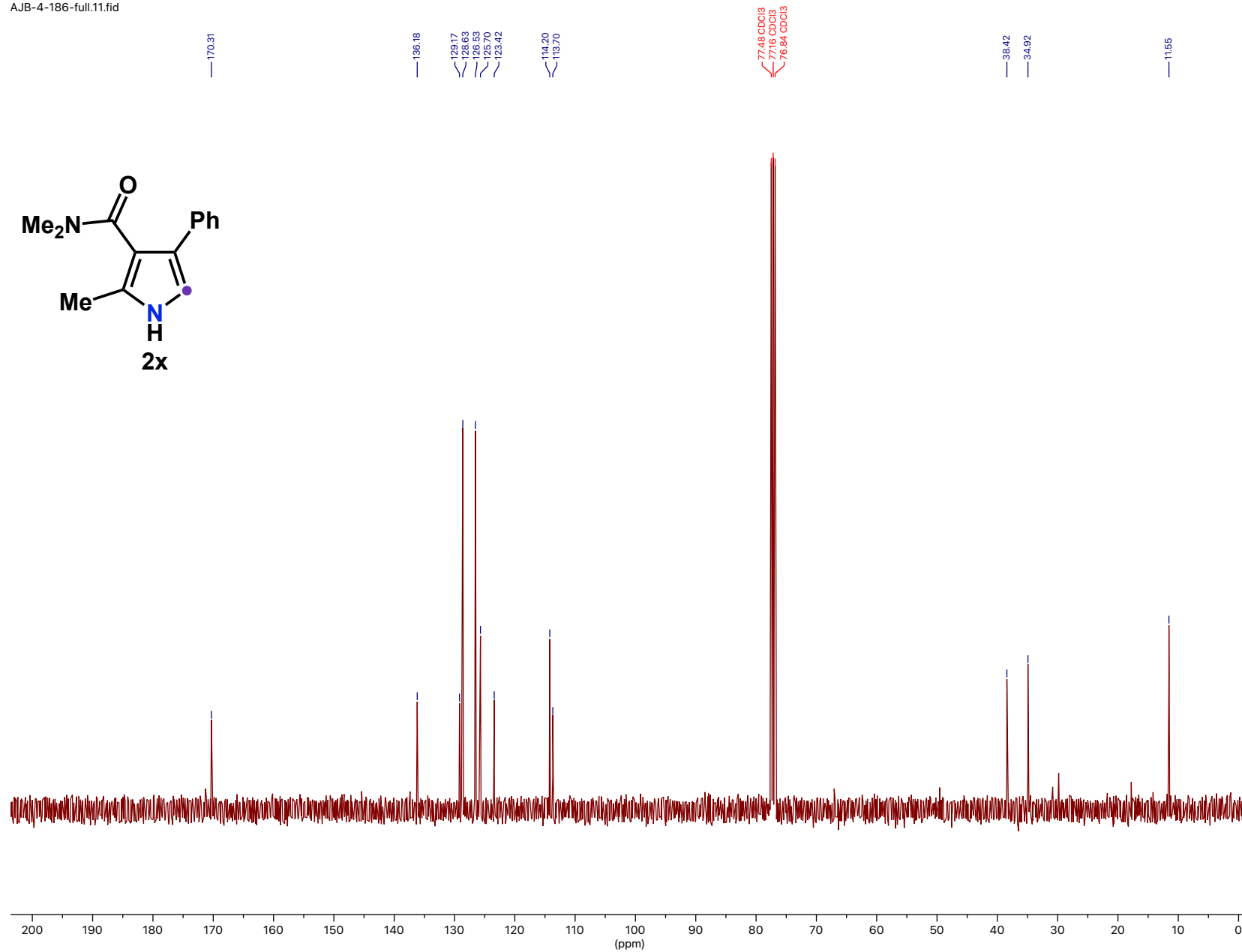
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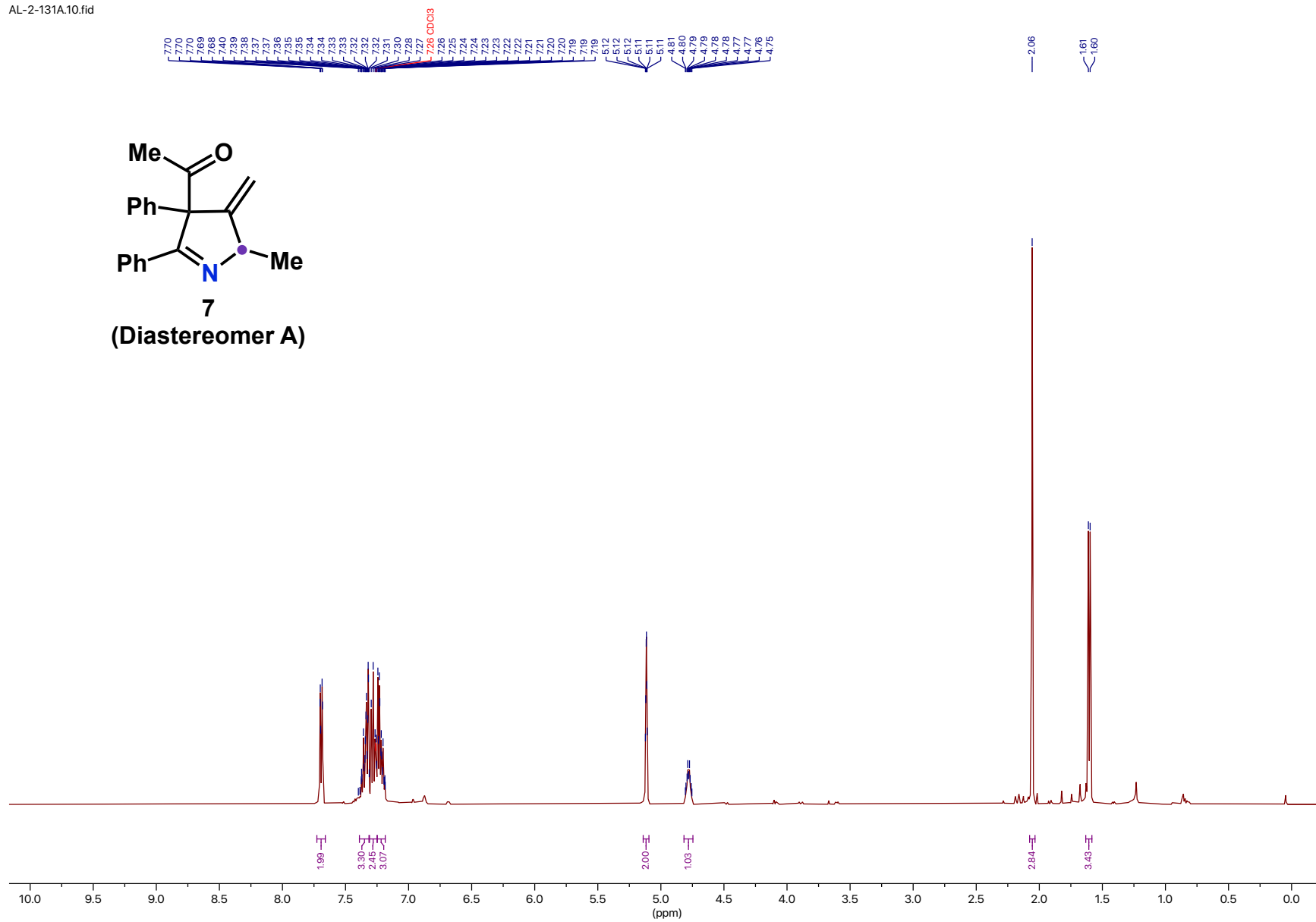
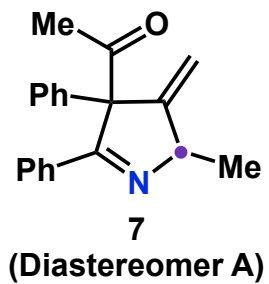
77.41 CDCl₃
77.16 CDCl₃
76.91 CDCl₃

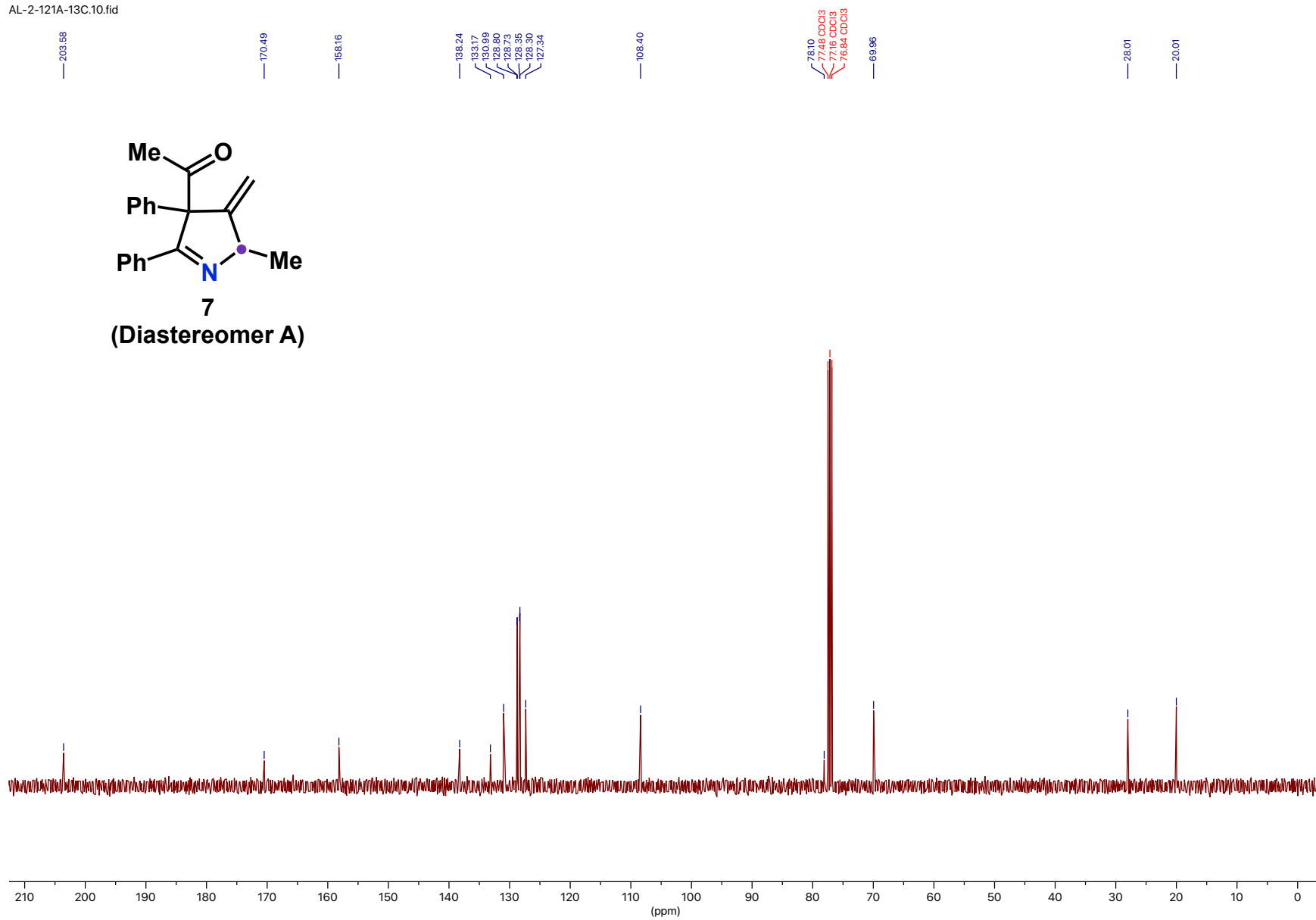
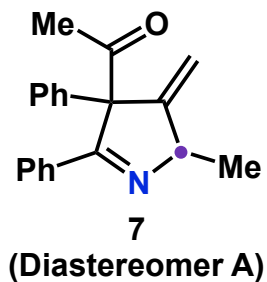
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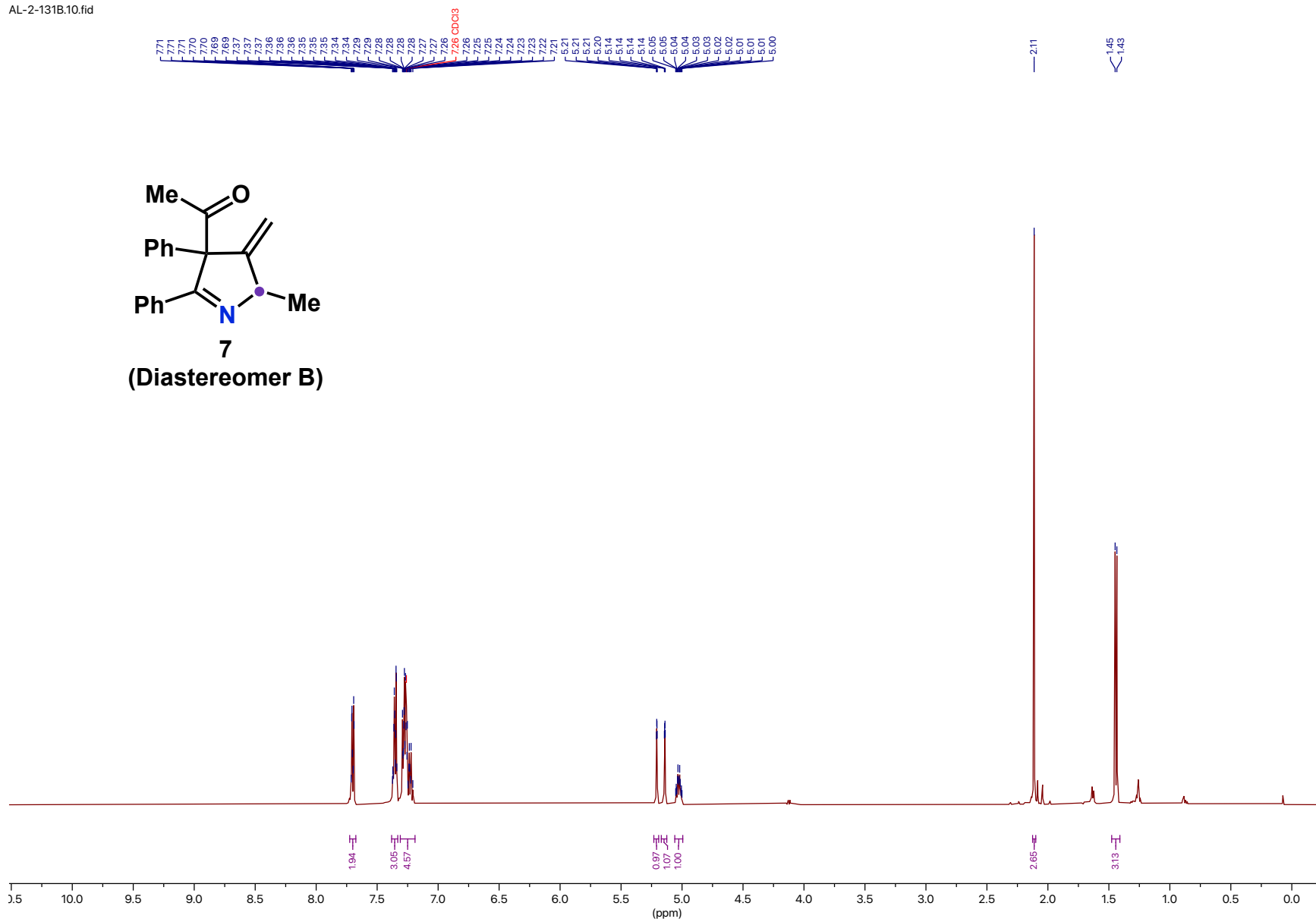
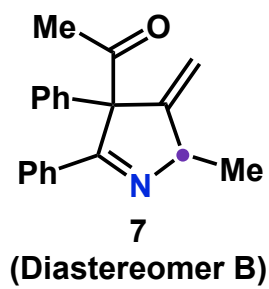












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202.97

170.12

157.66

139.97

133.00

130.84

129.05

128.58

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127.19

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76.04

77.46 CDCl₃

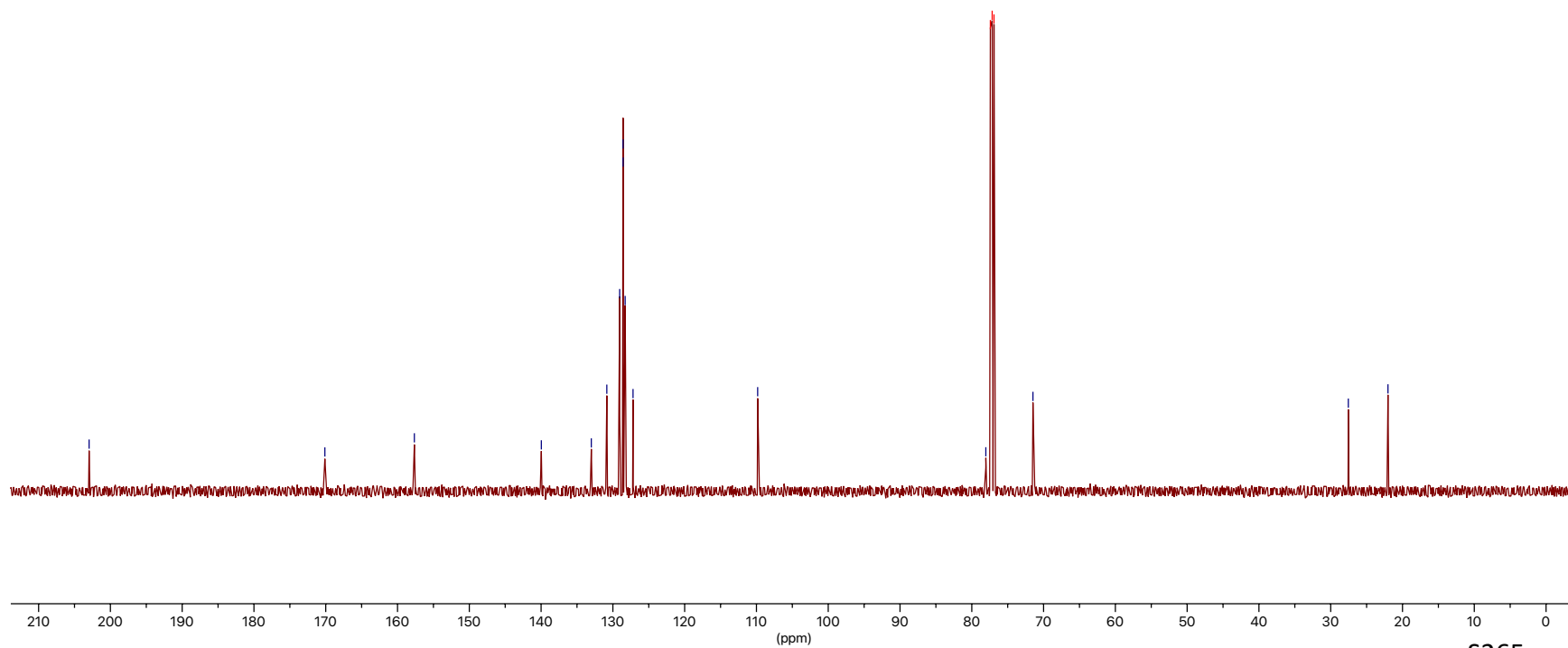
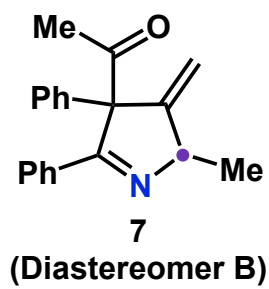
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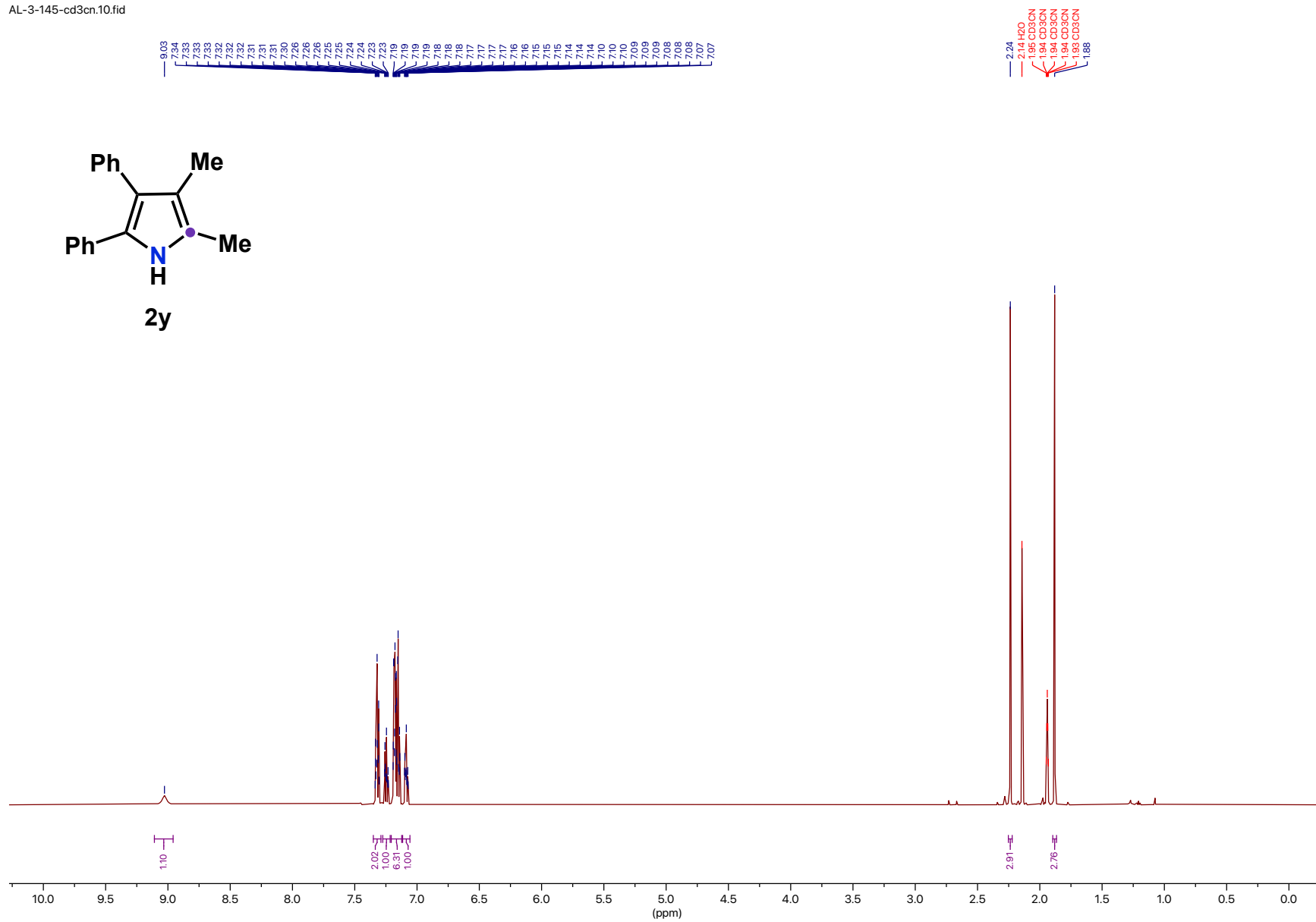
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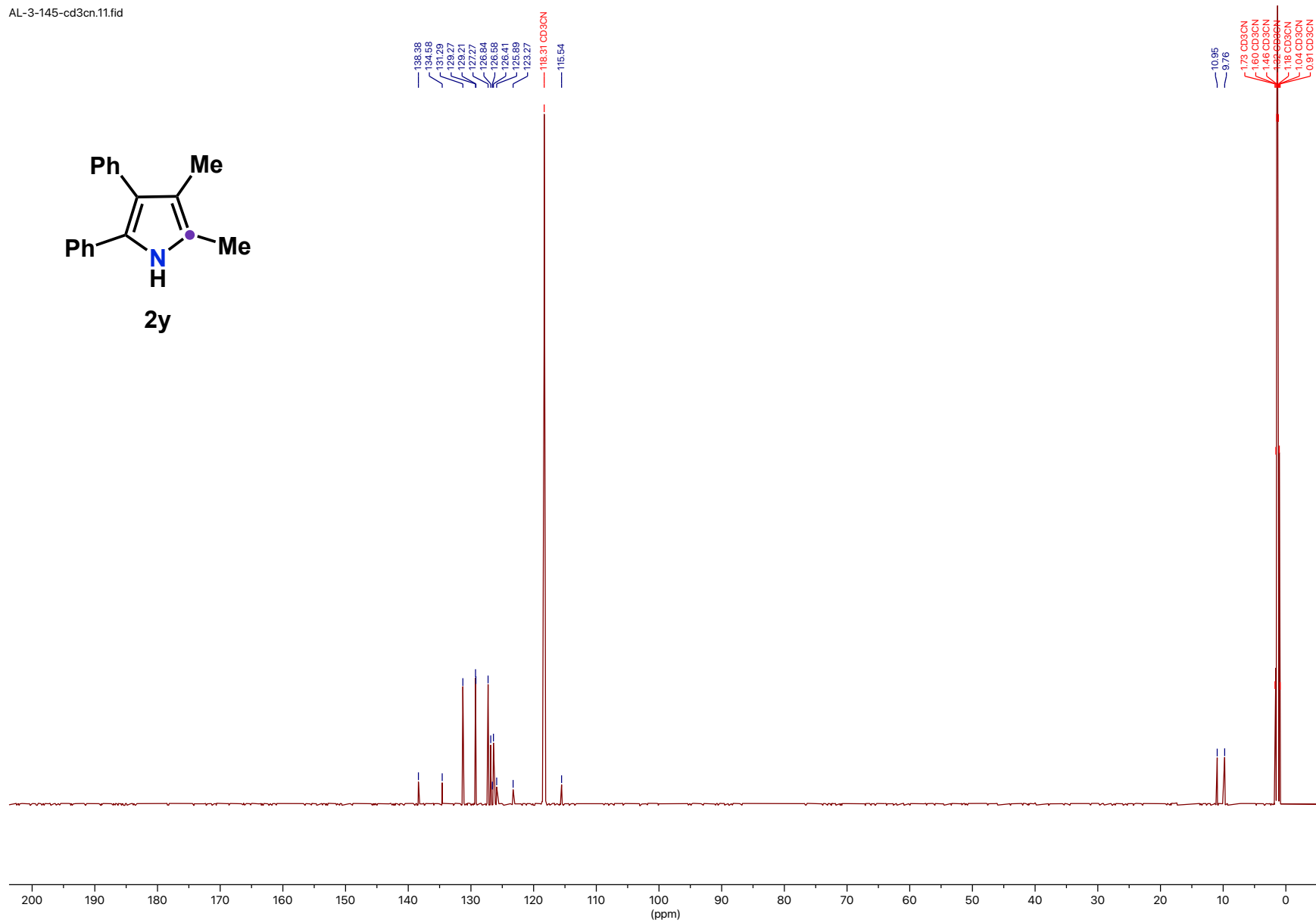
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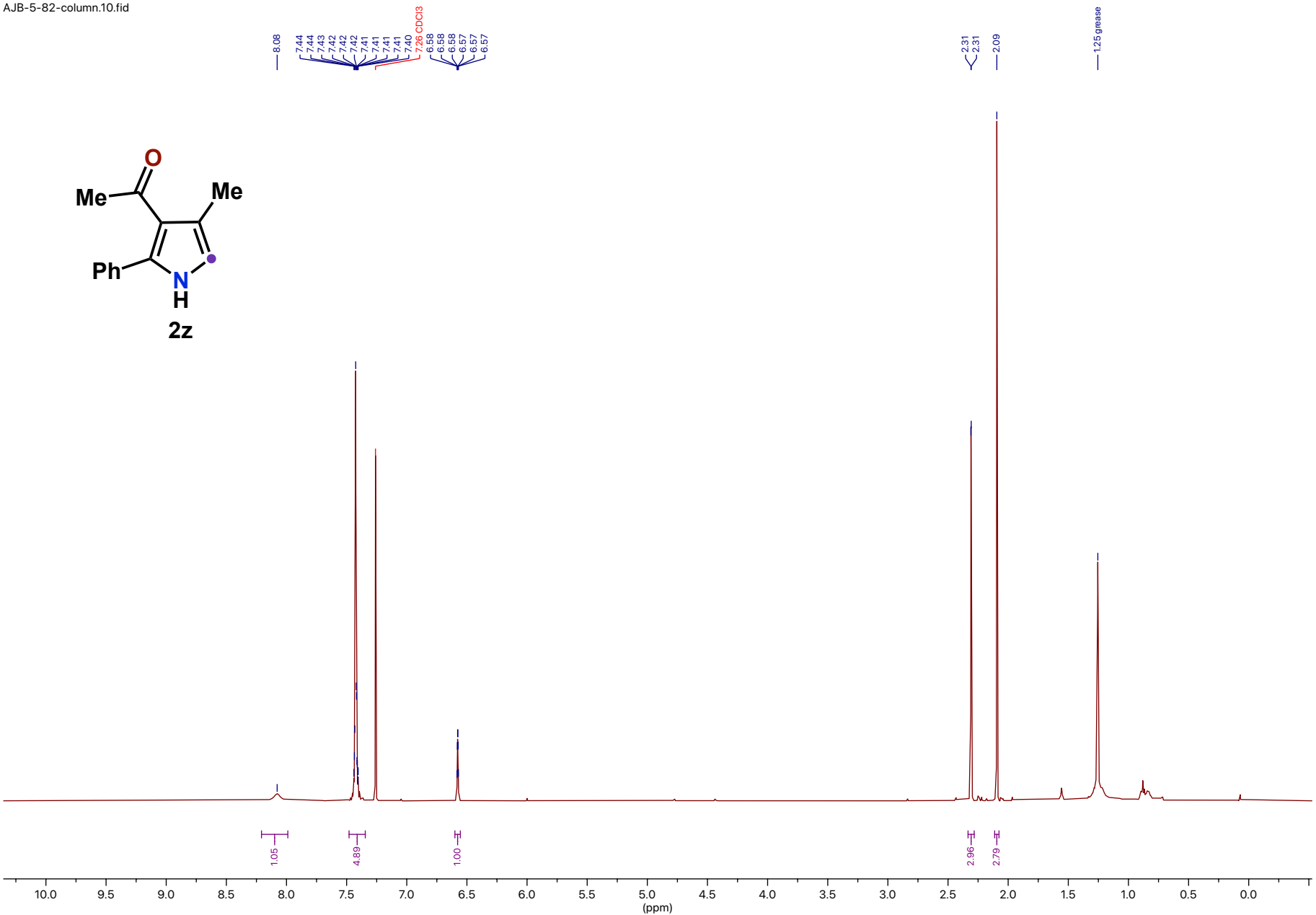
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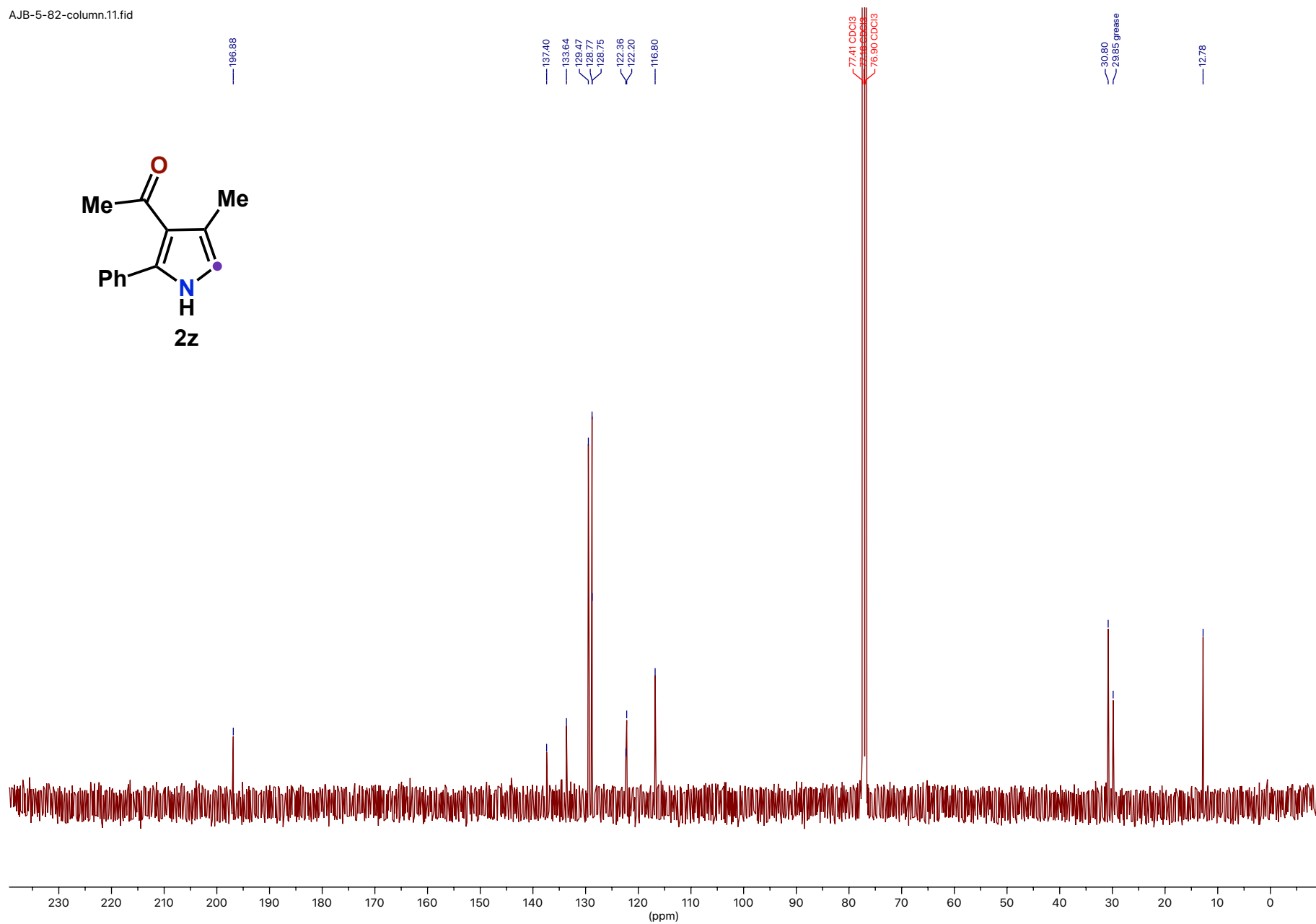
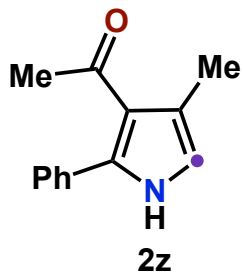
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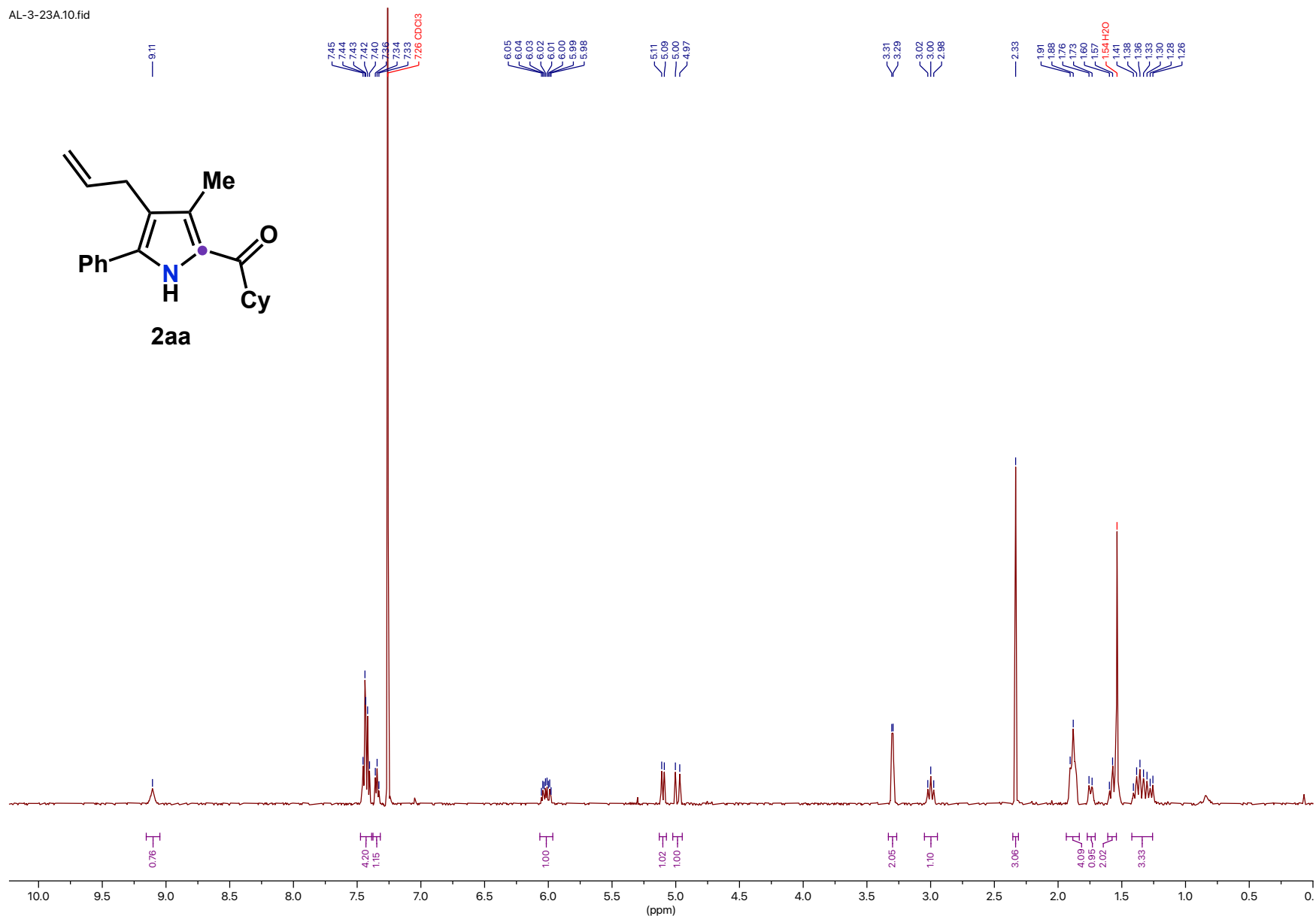




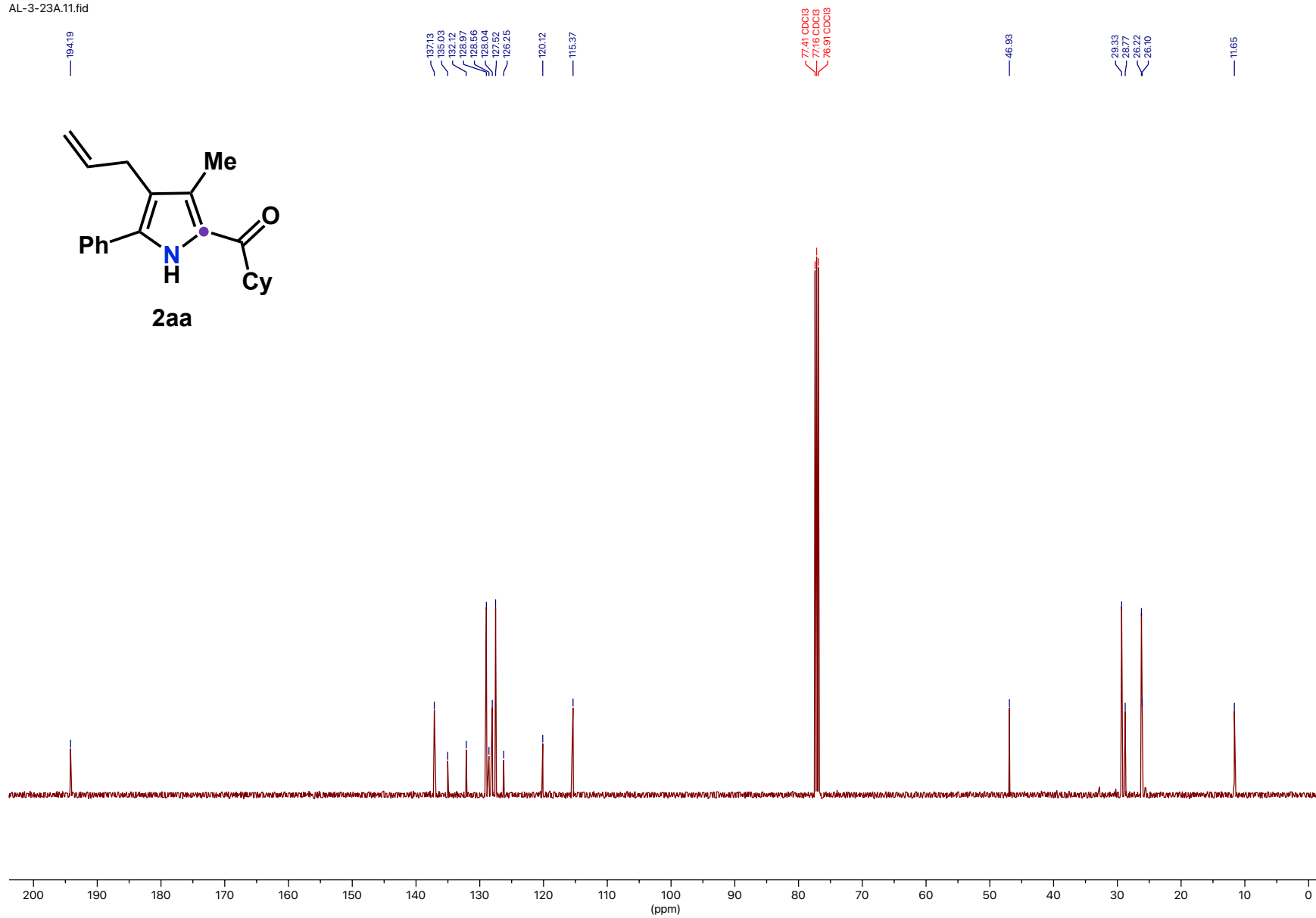
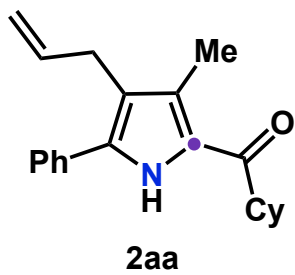


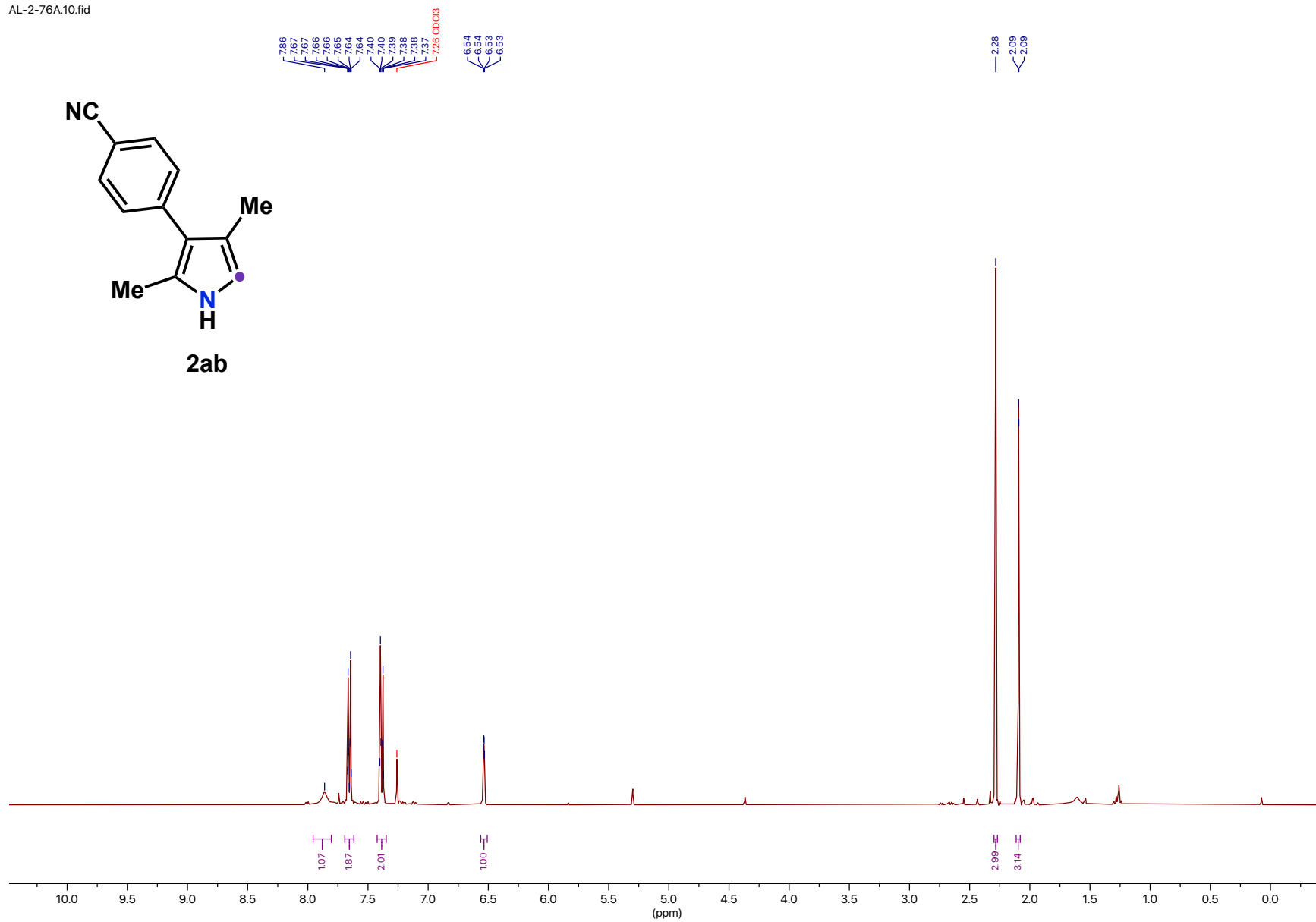


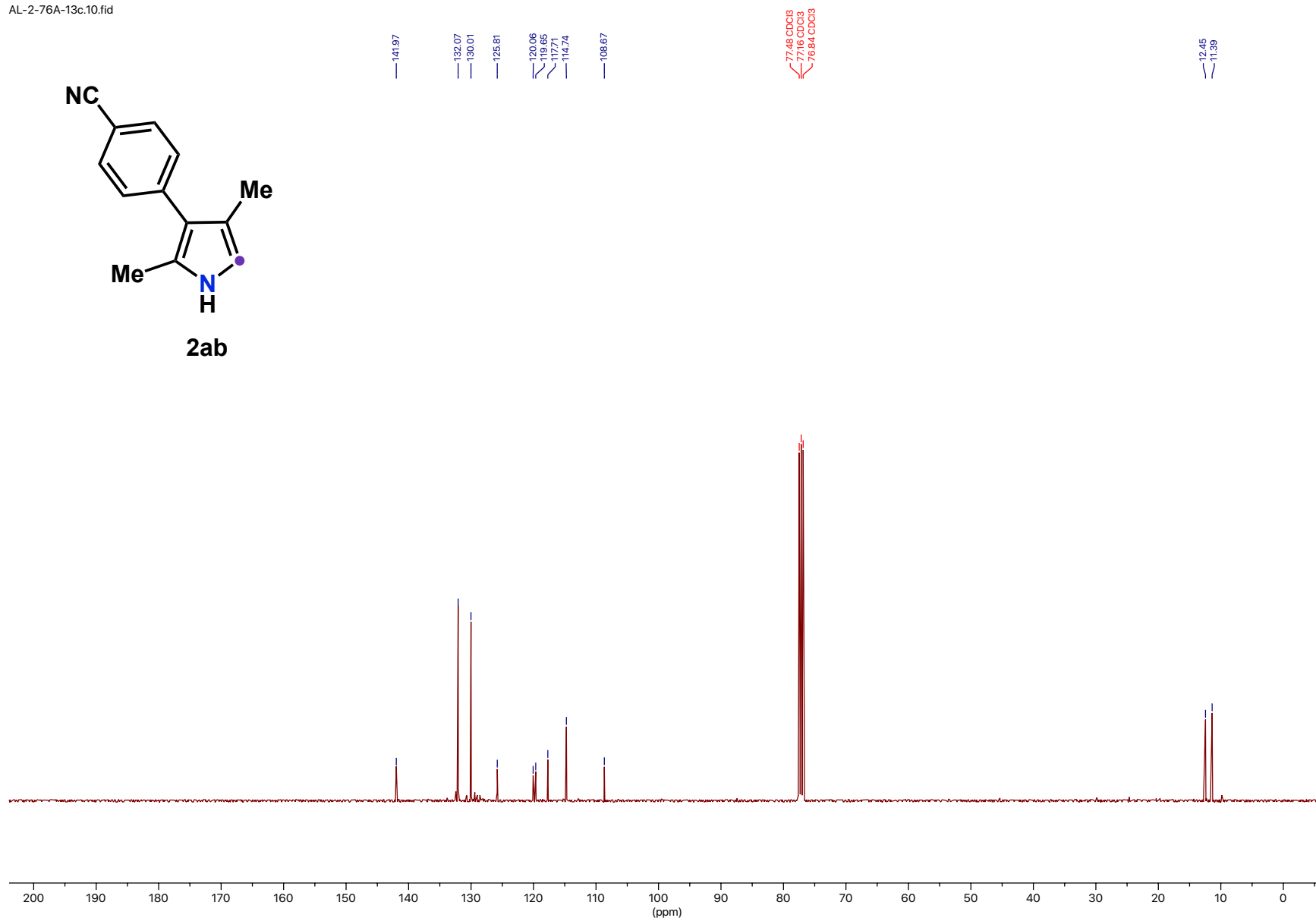
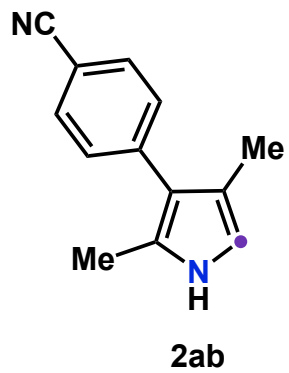


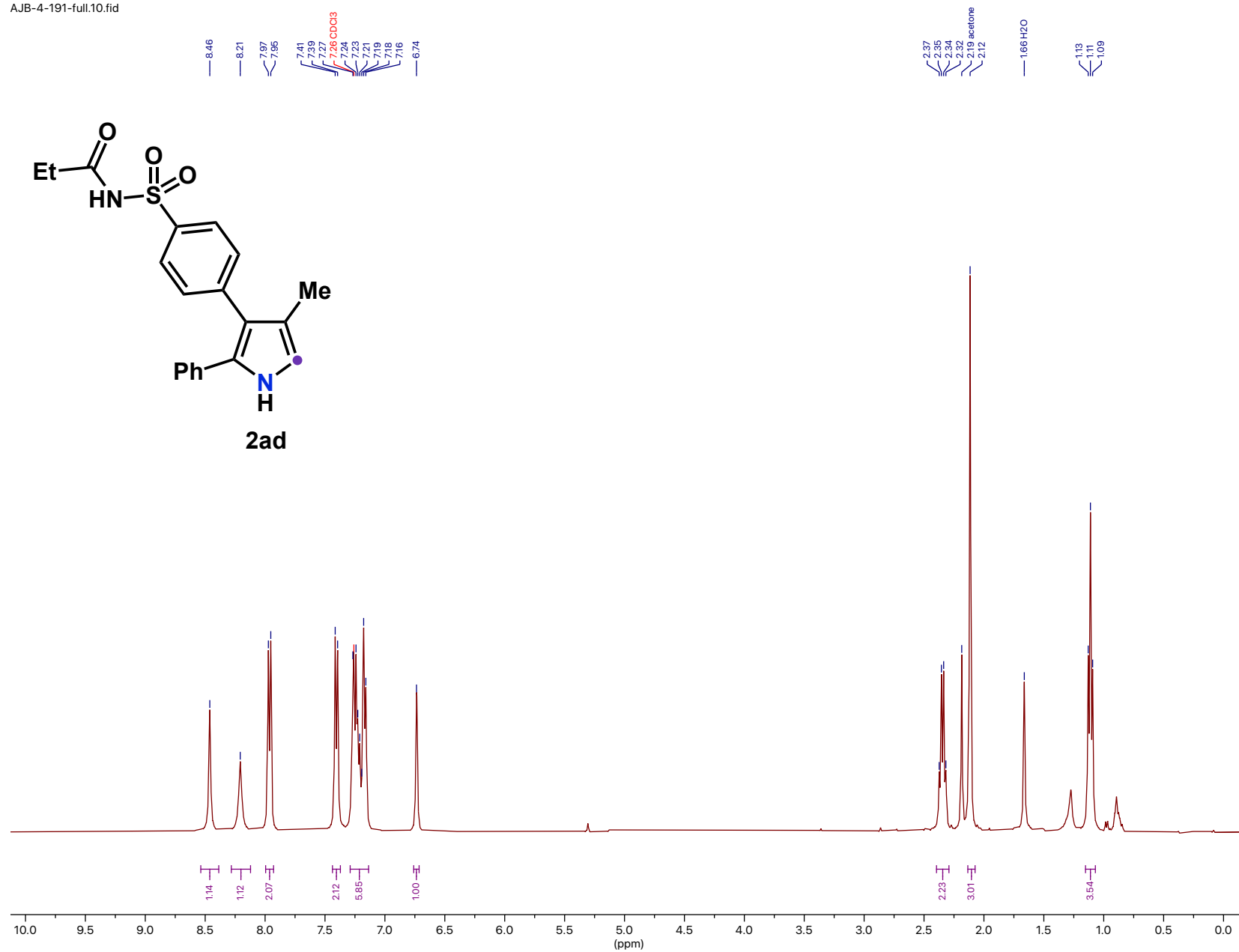


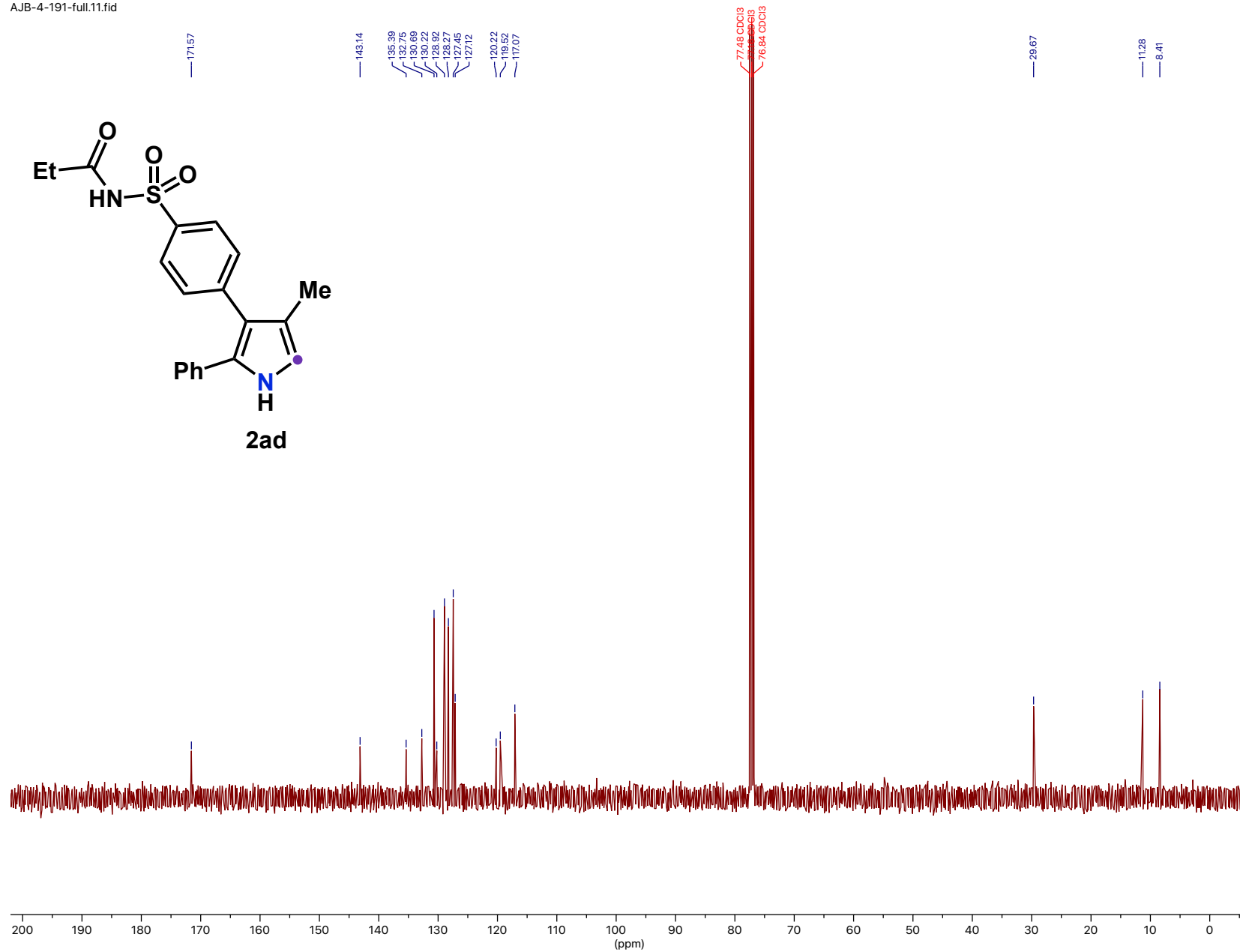
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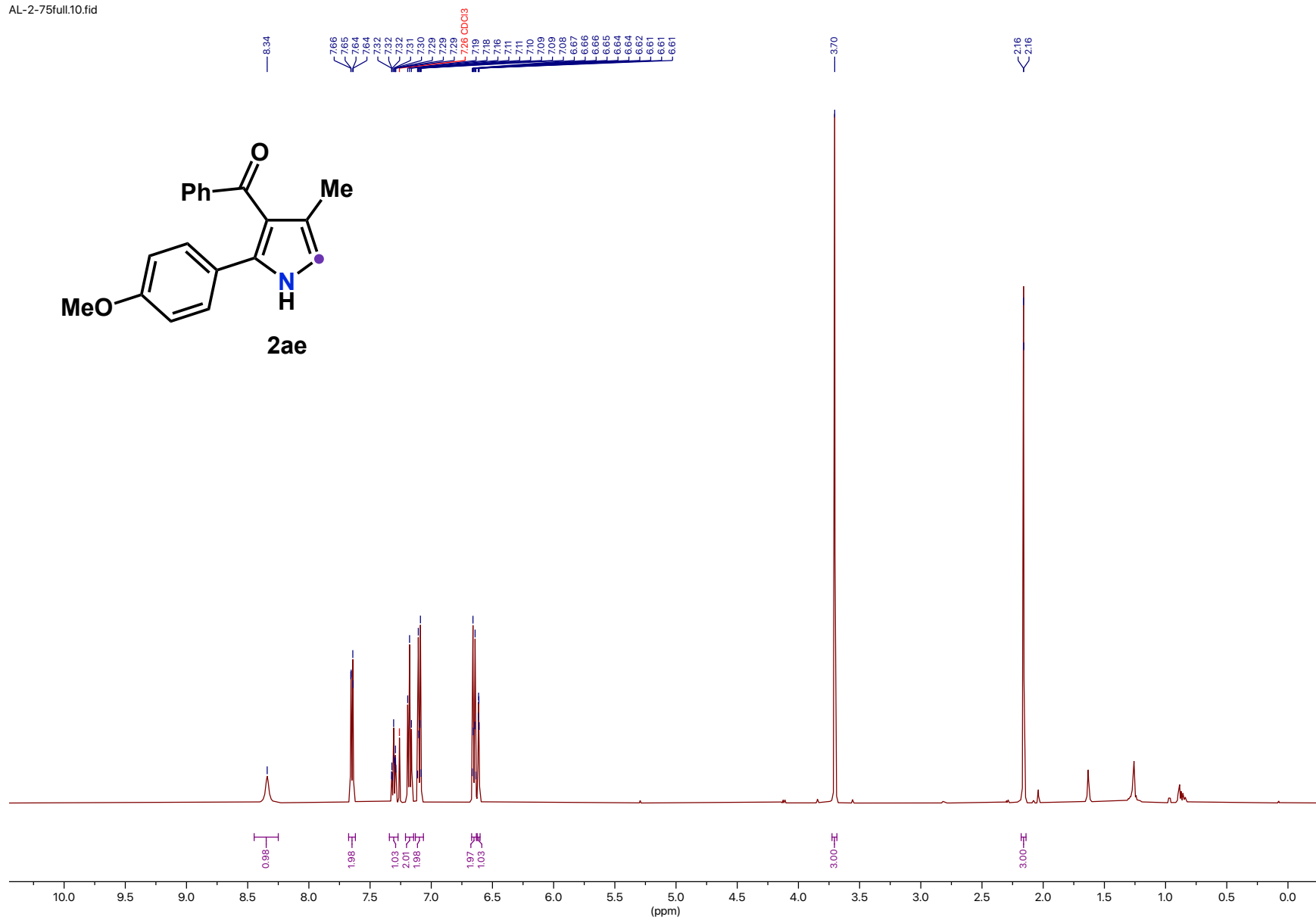




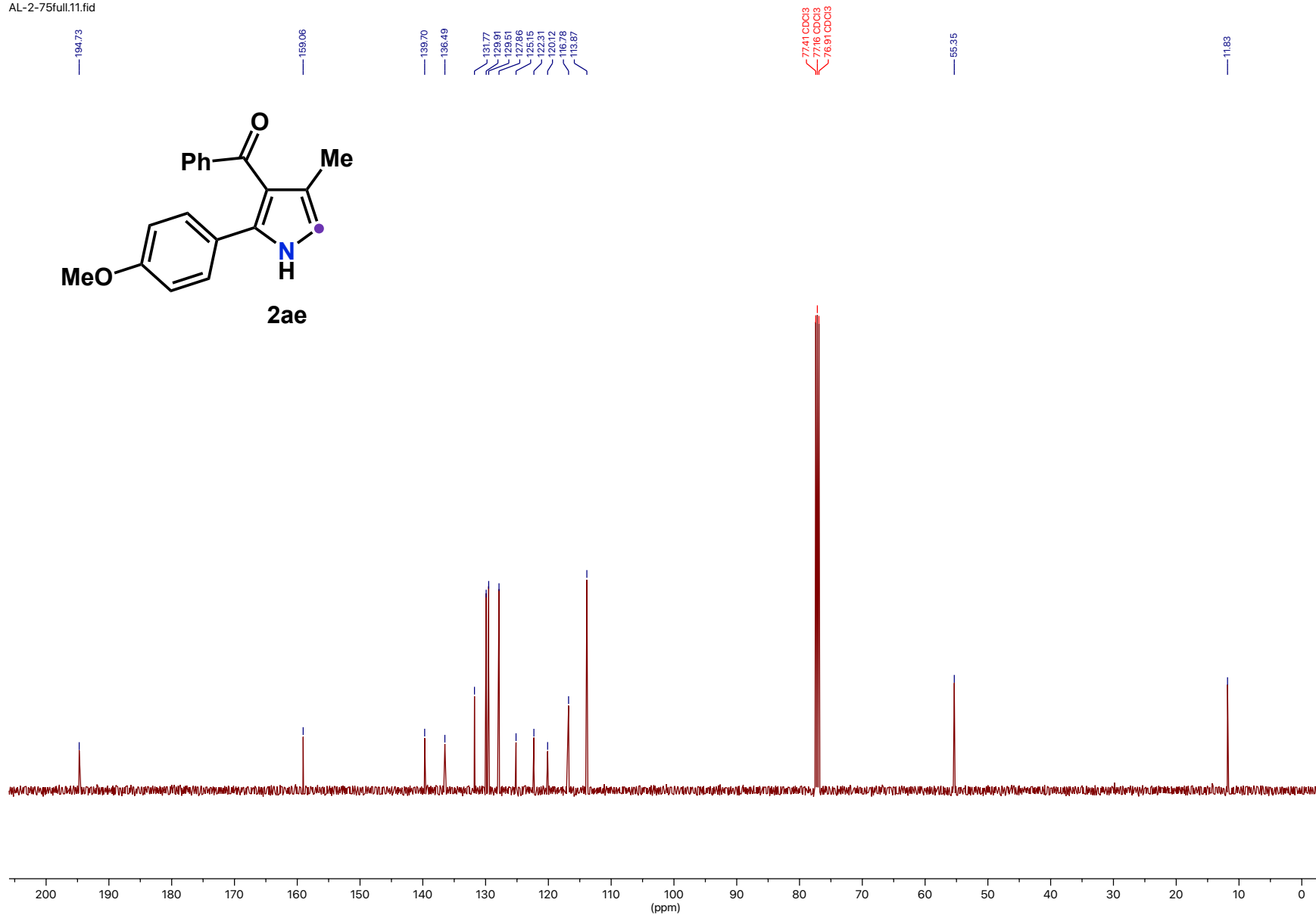
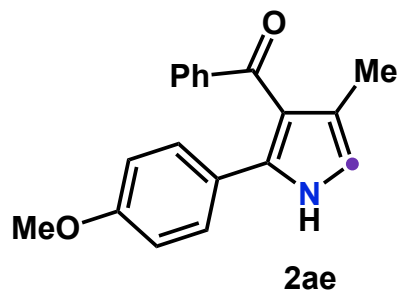


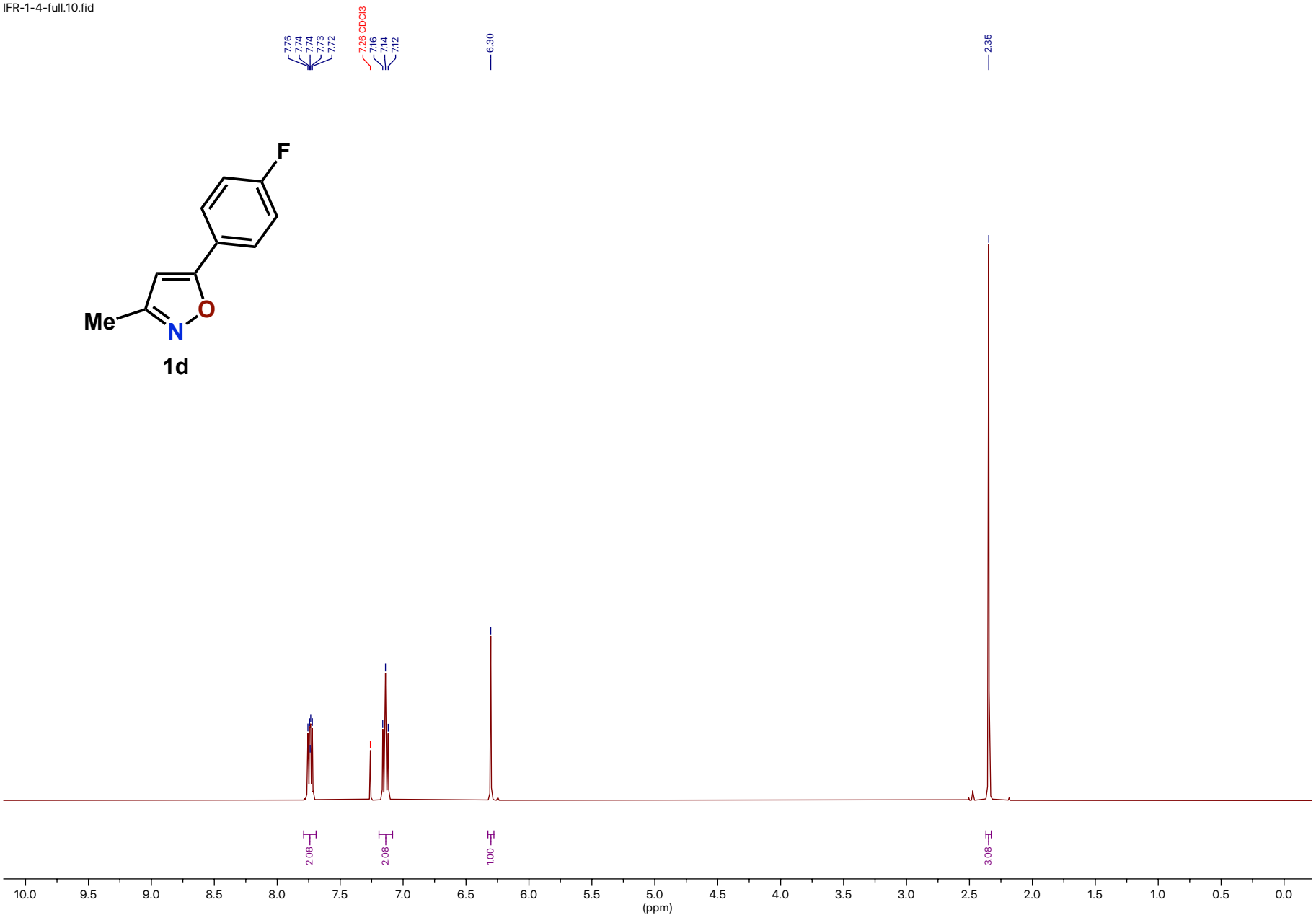


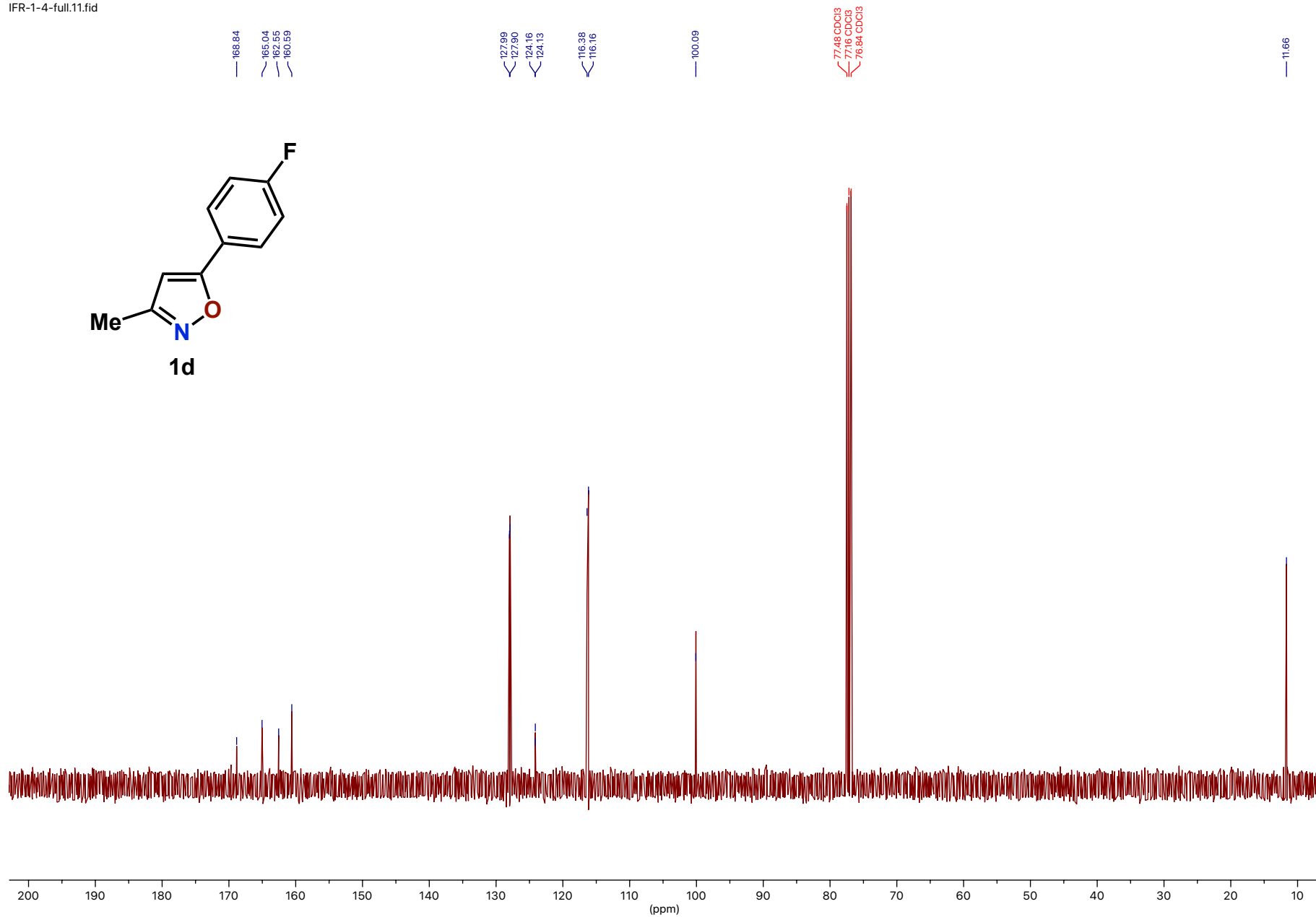
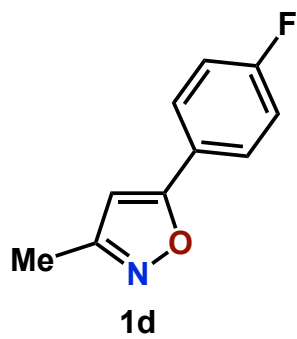


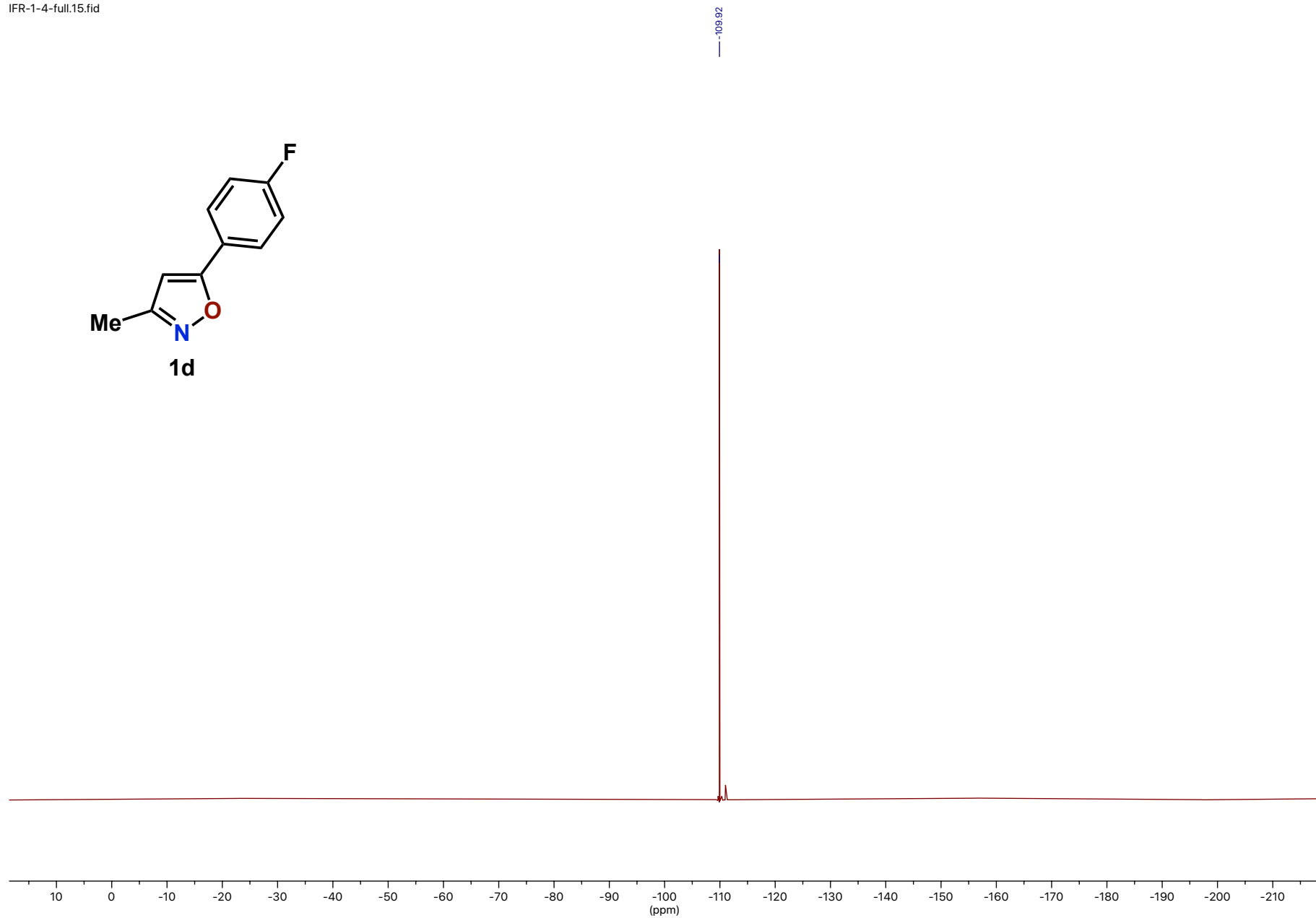
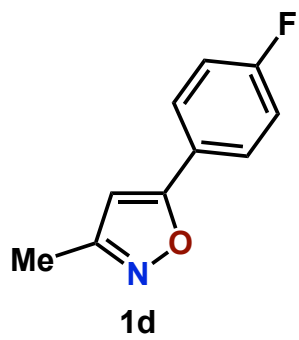


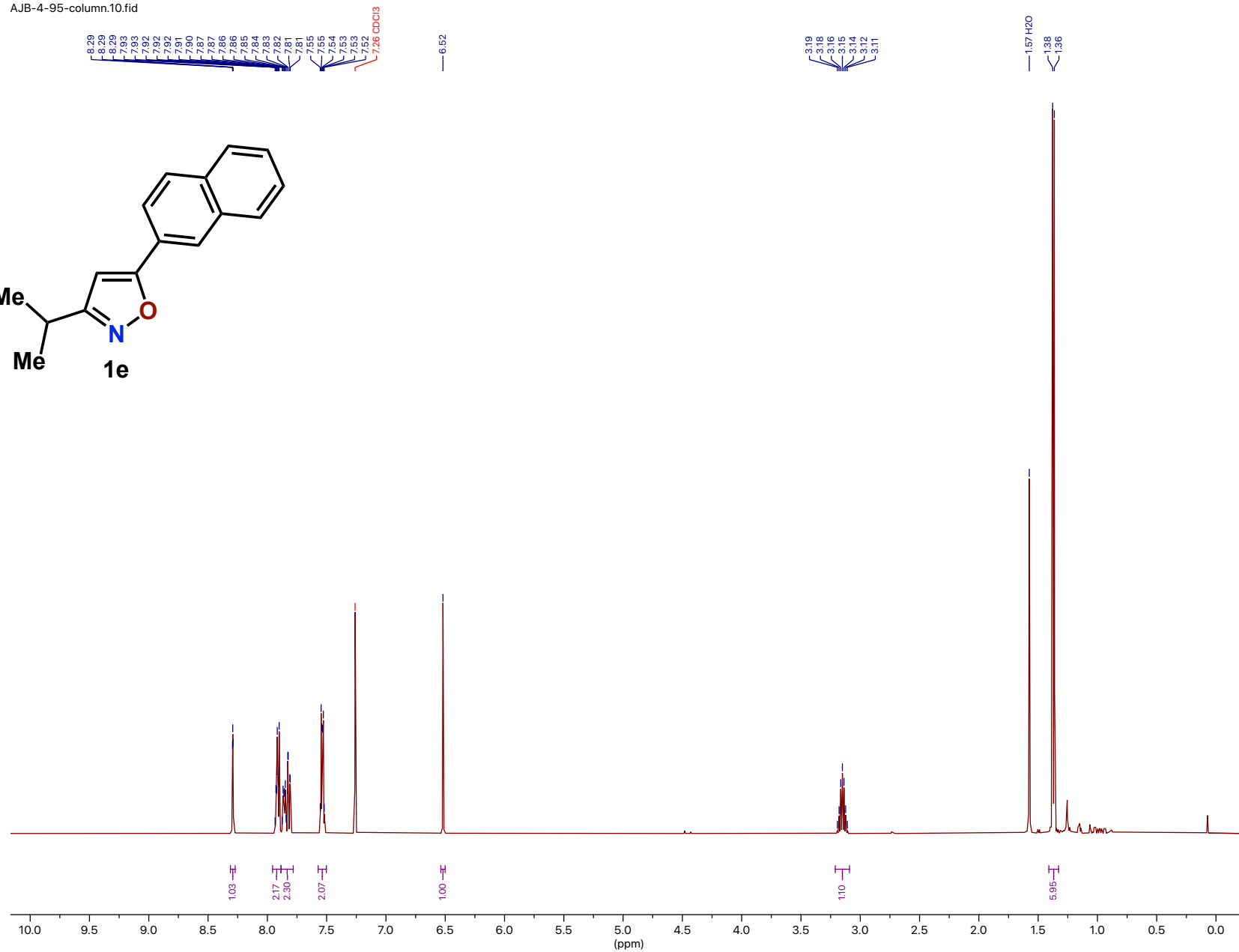
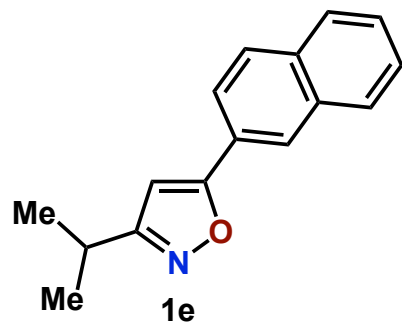
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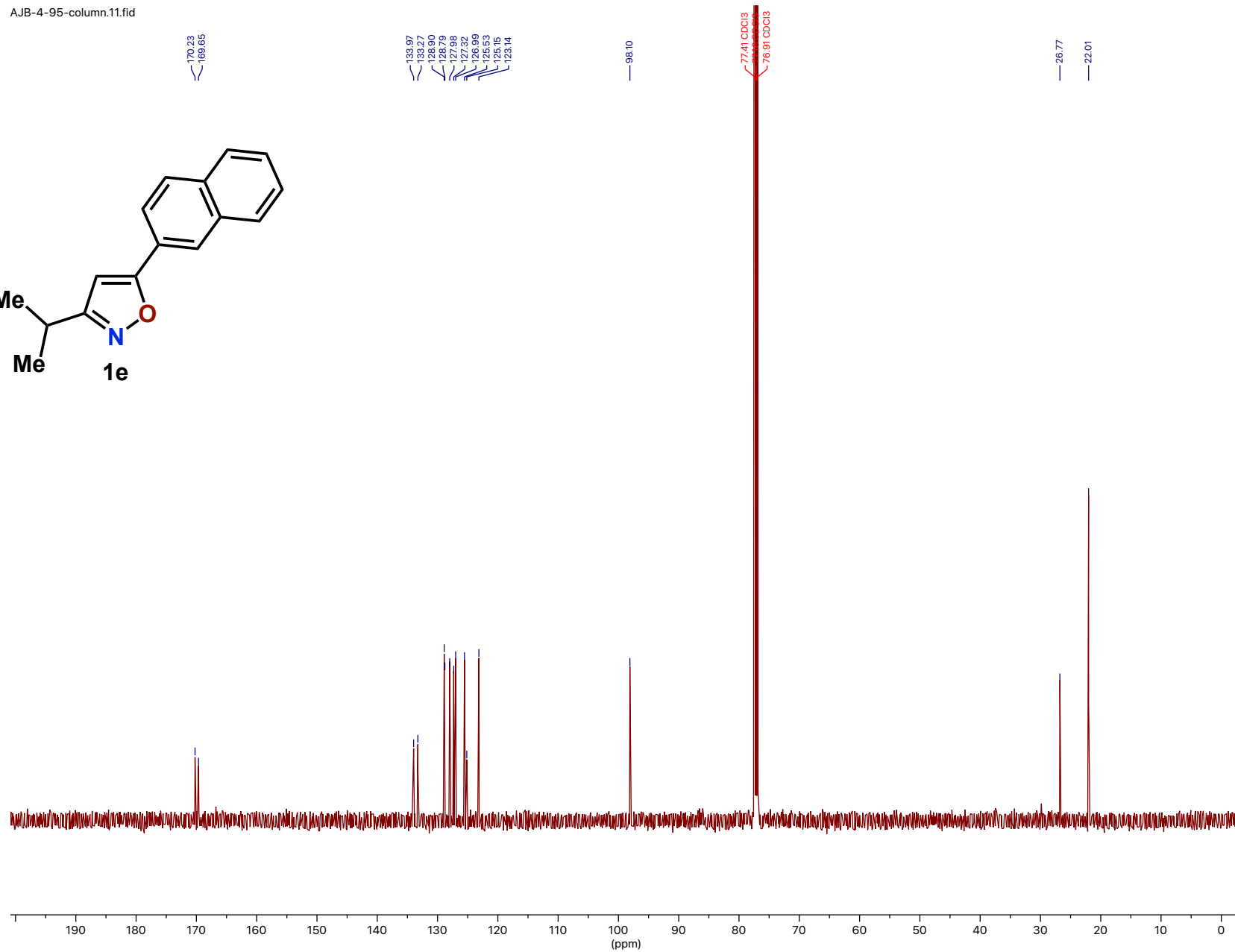
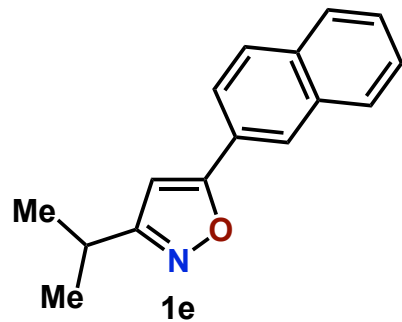


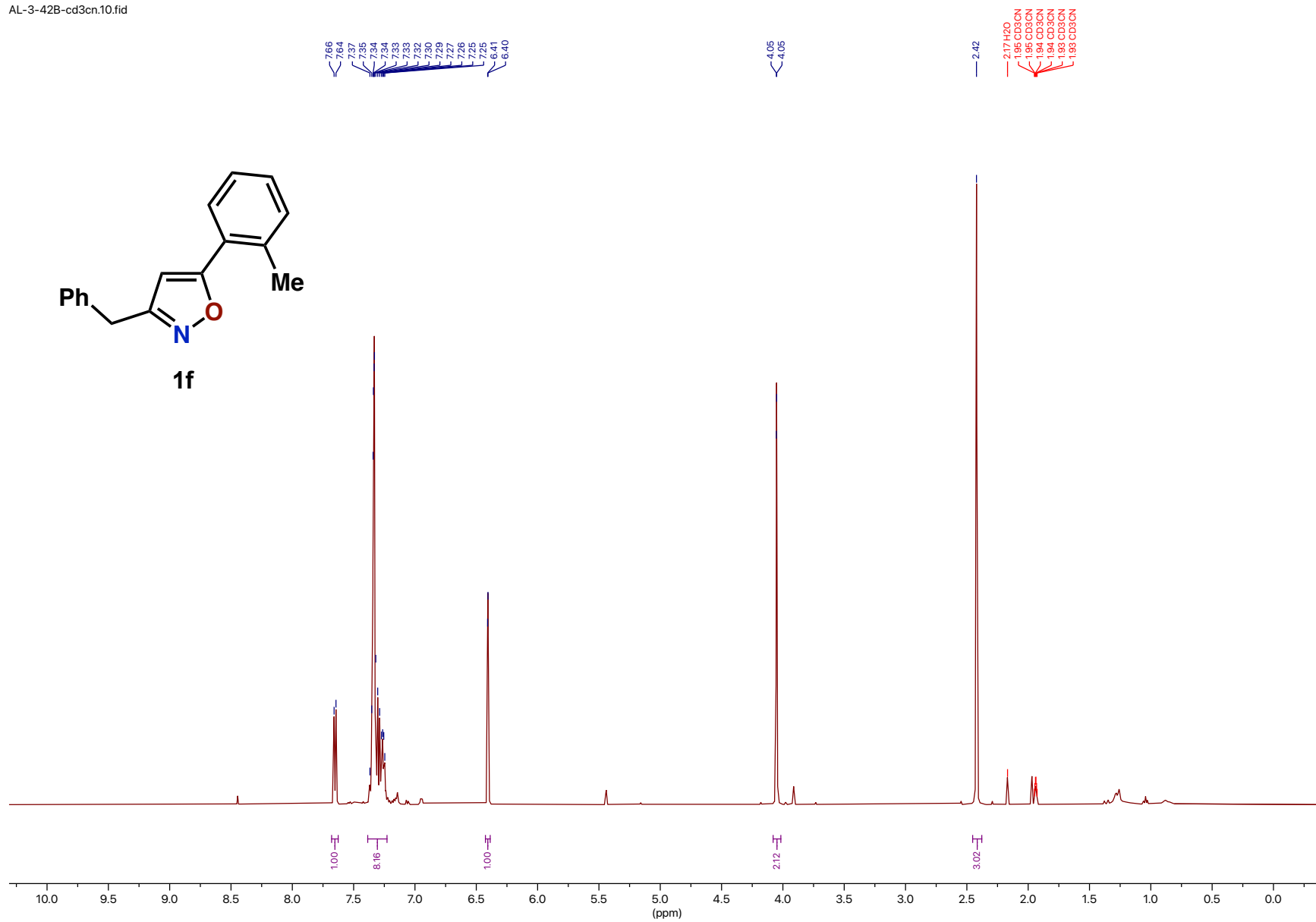


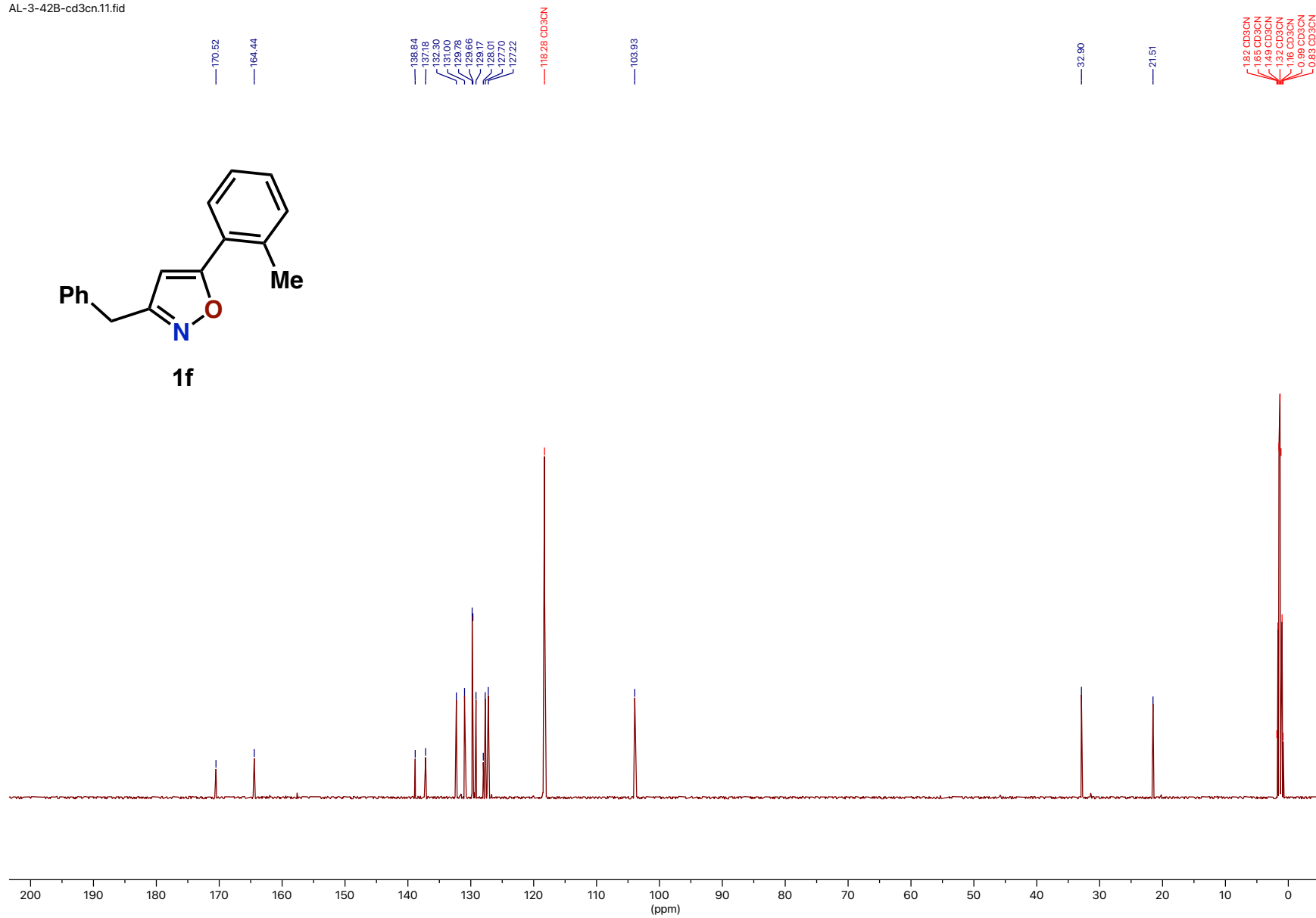
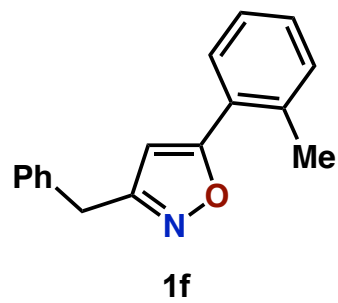


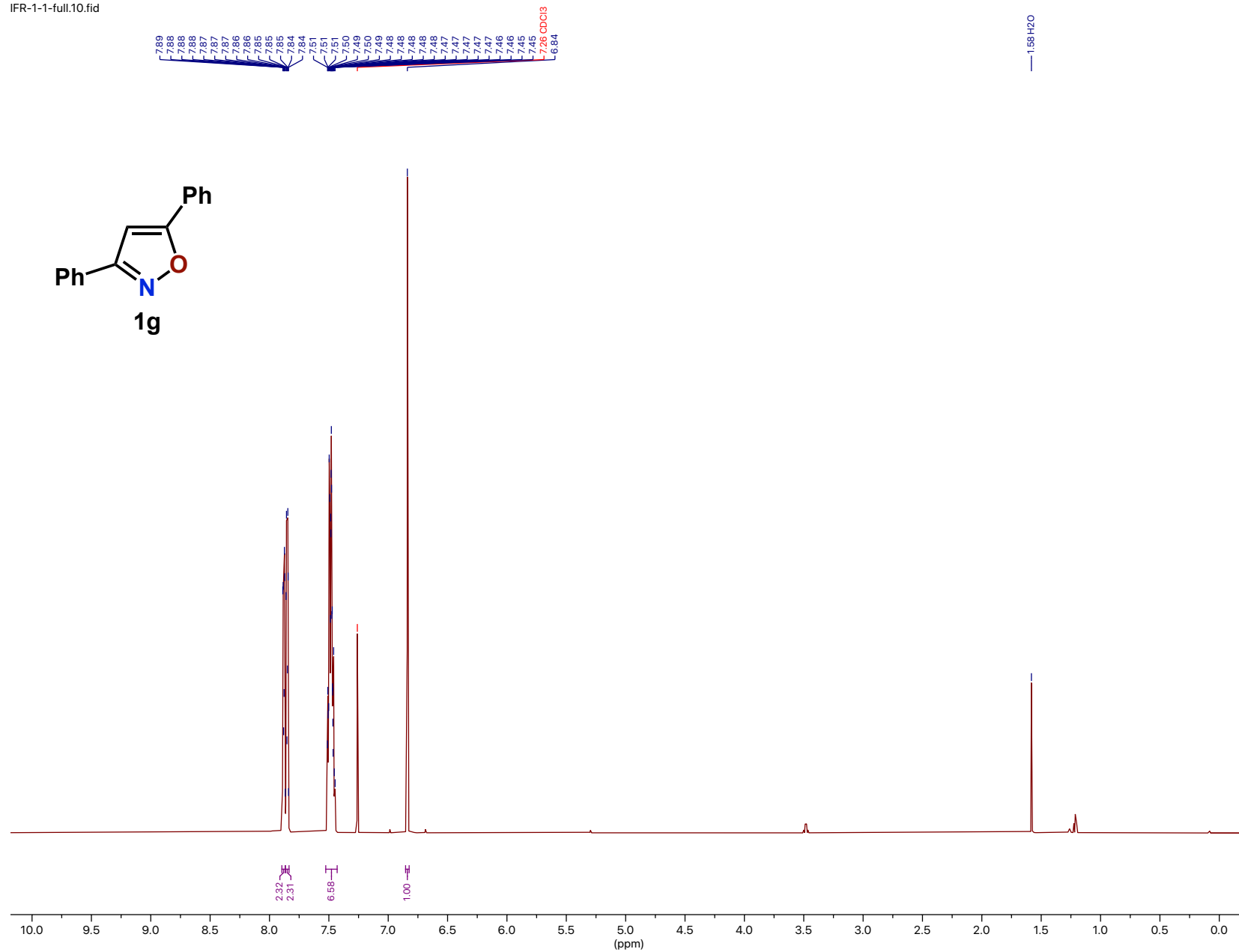


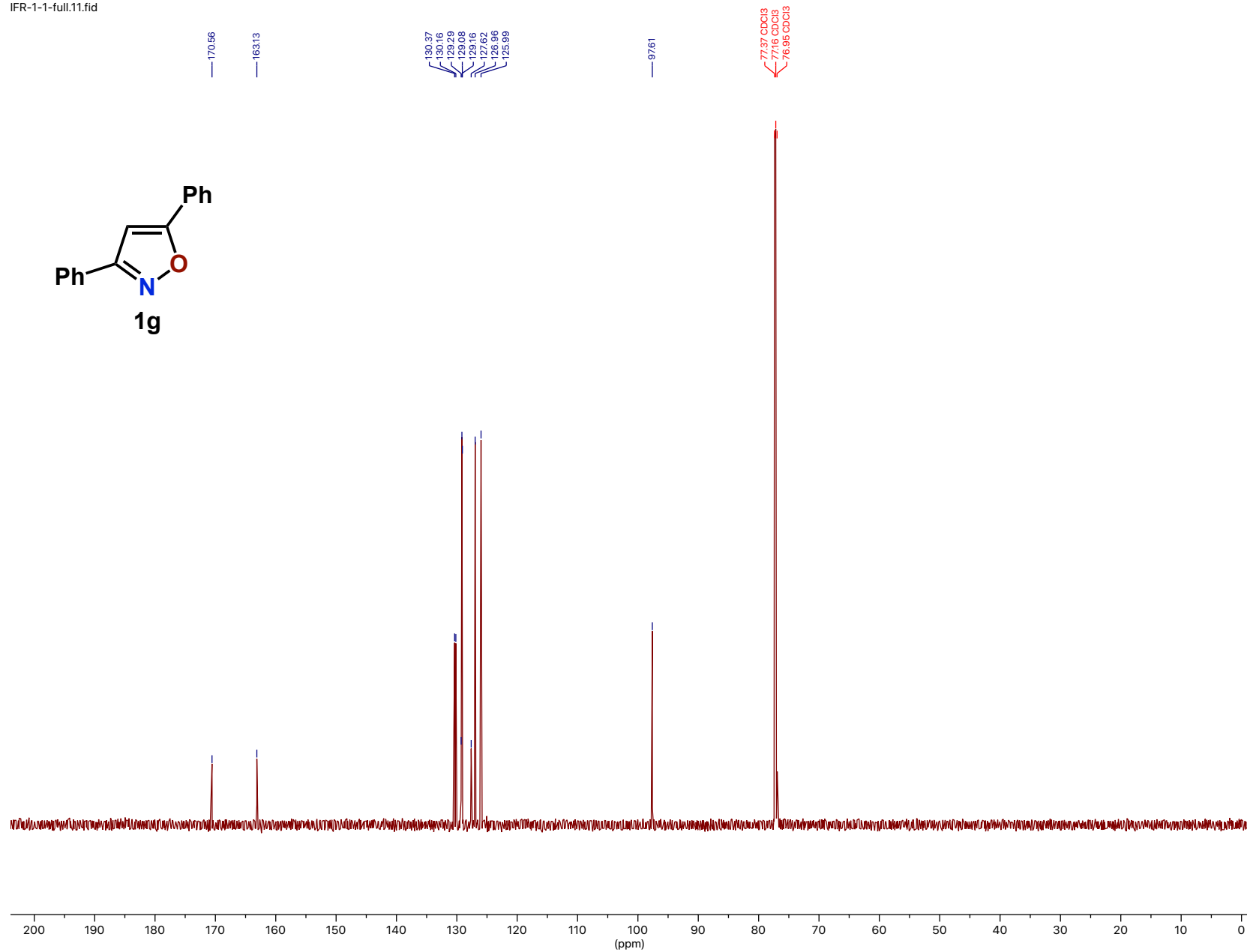


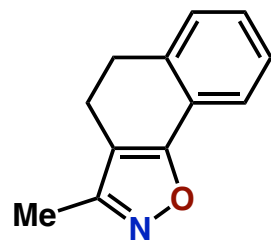




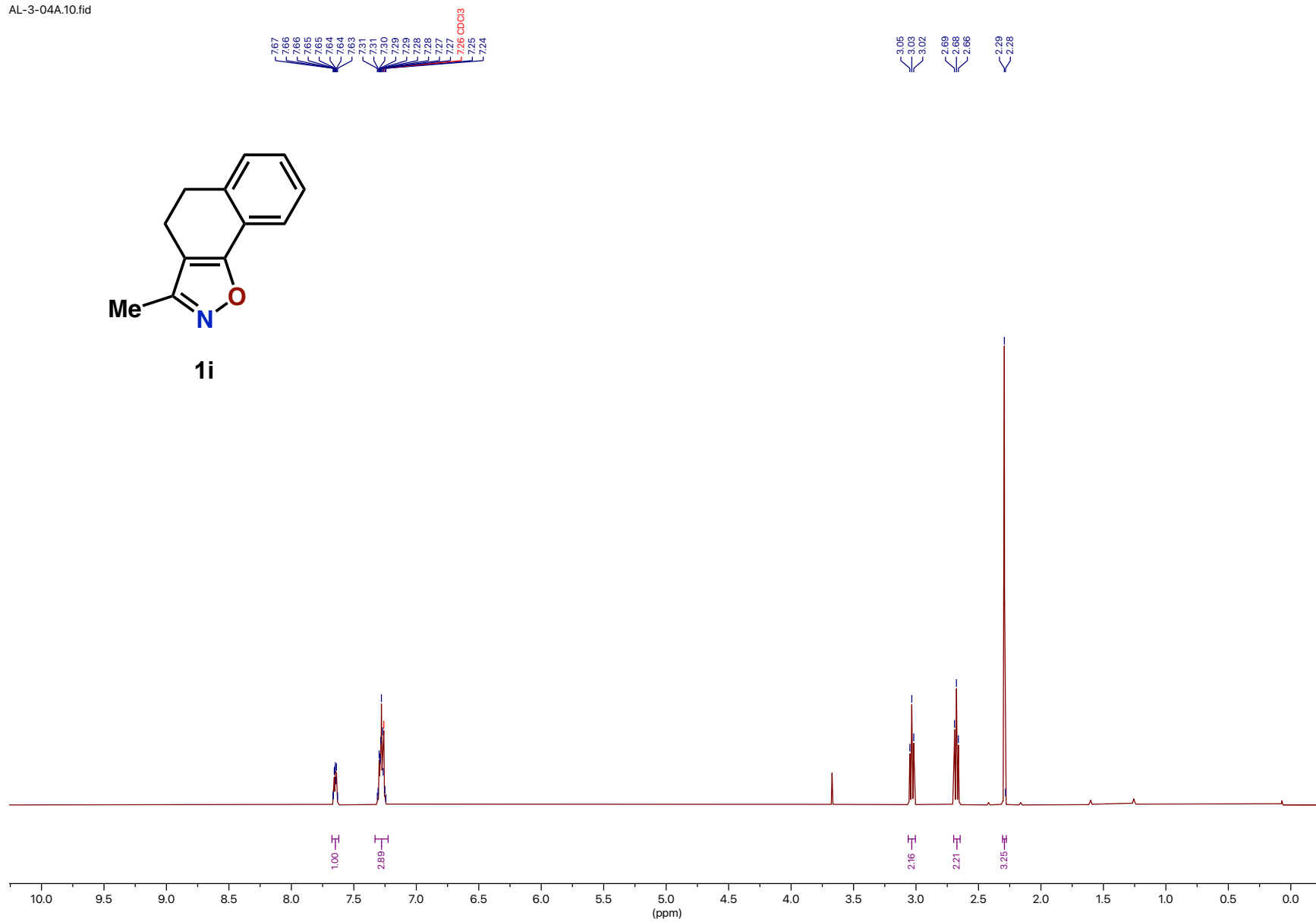


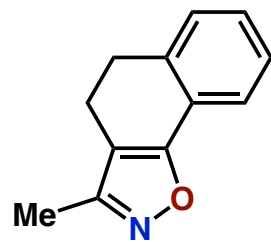




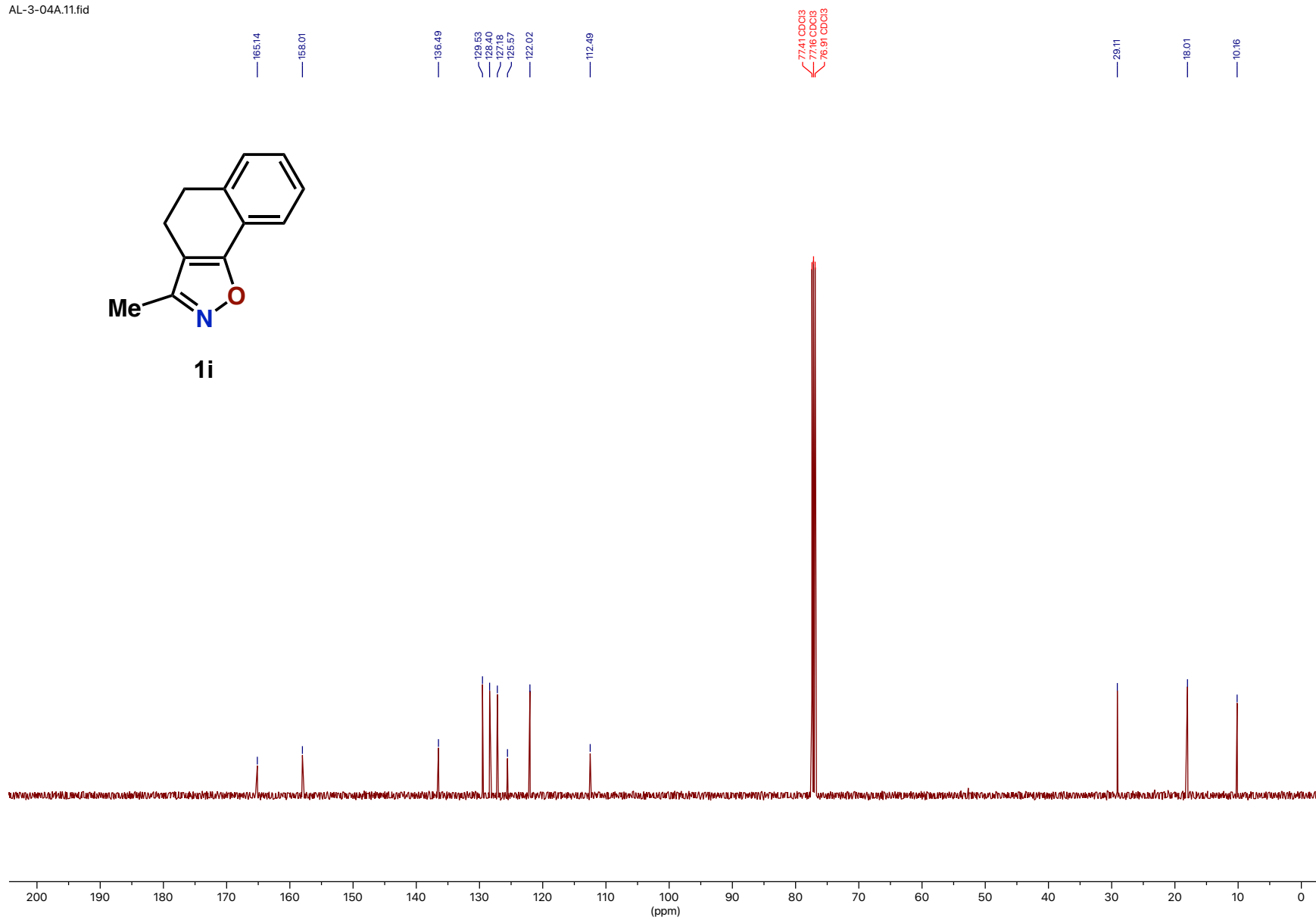


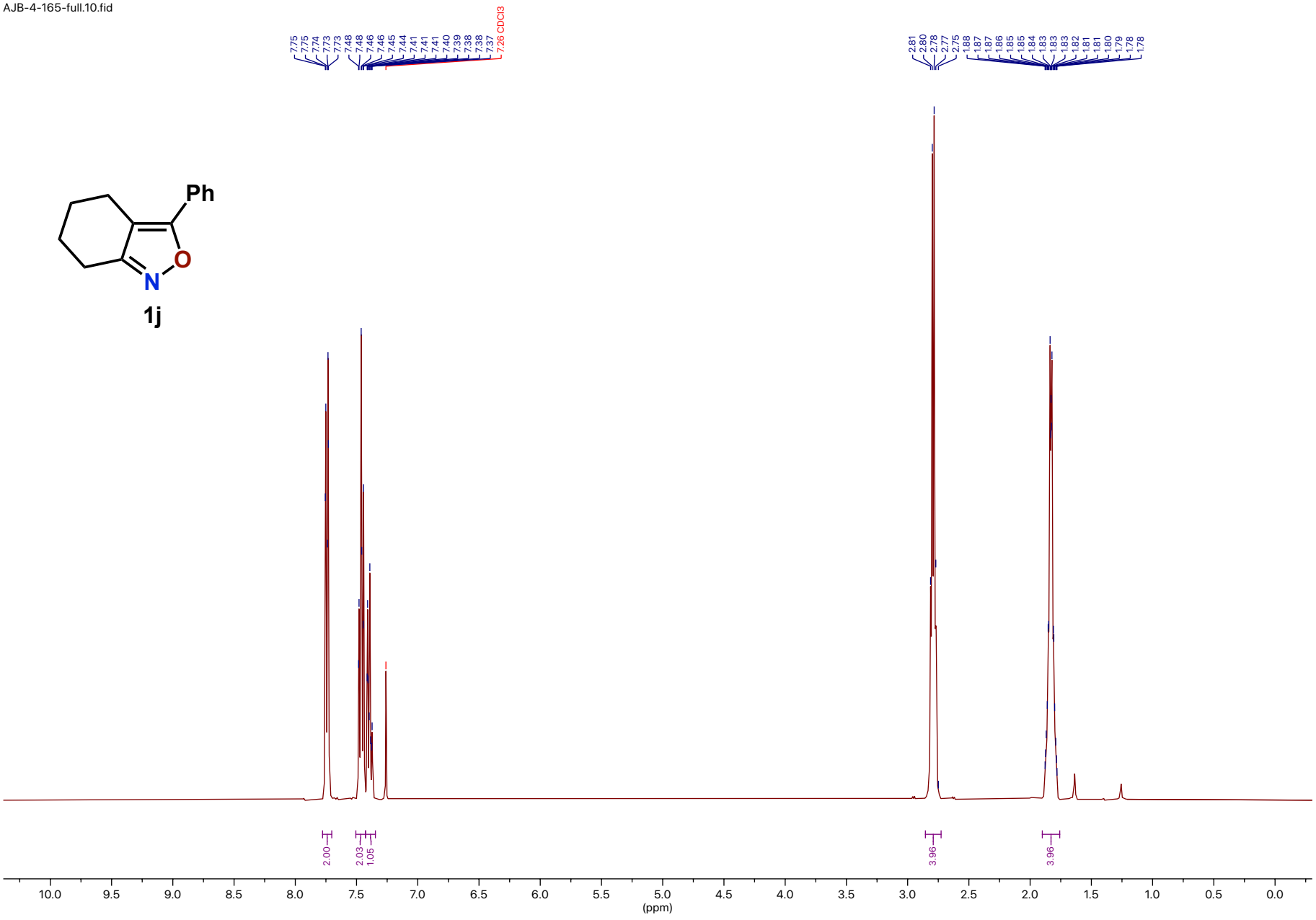
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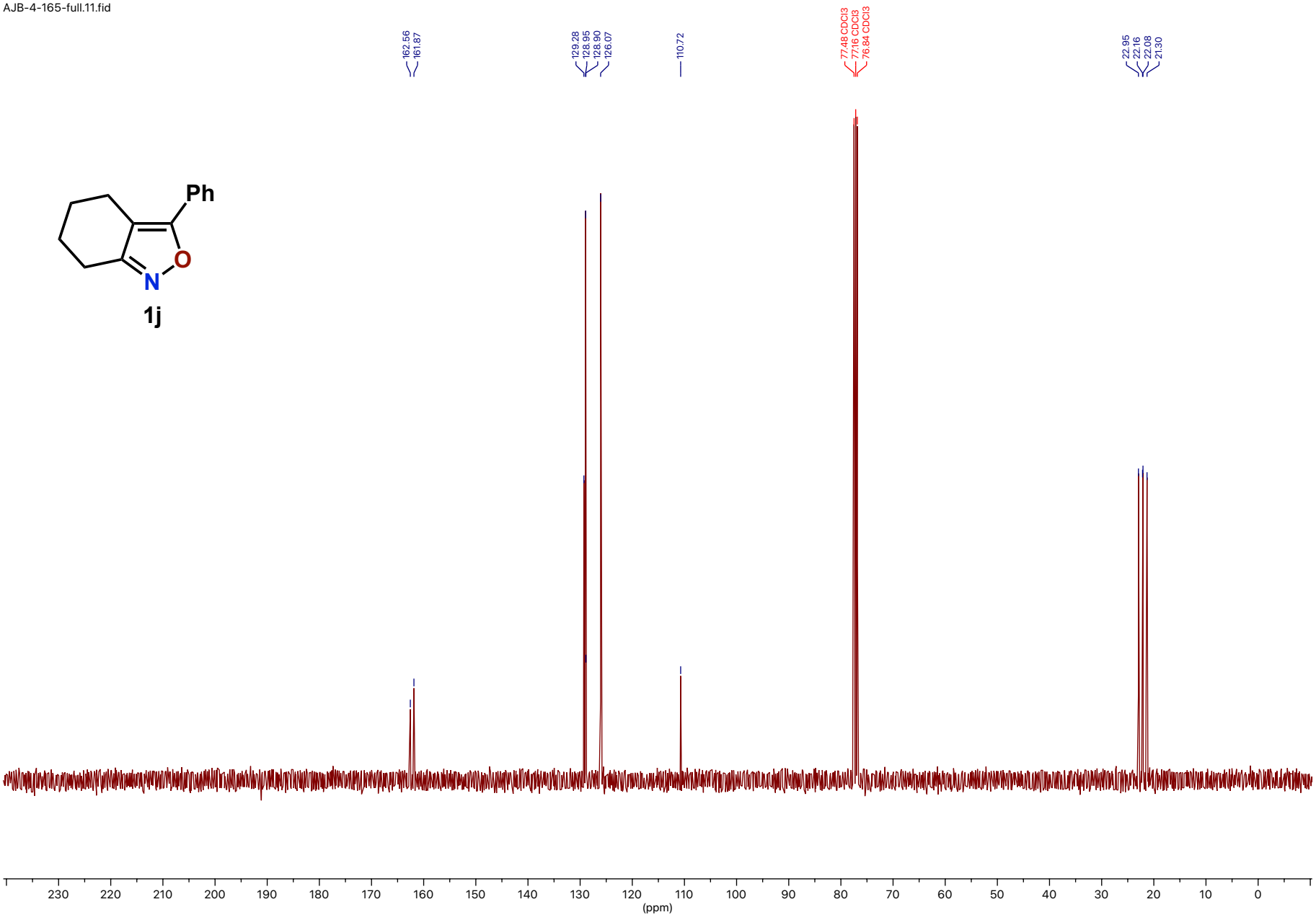
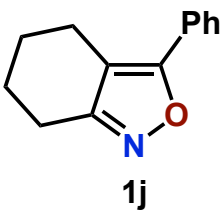


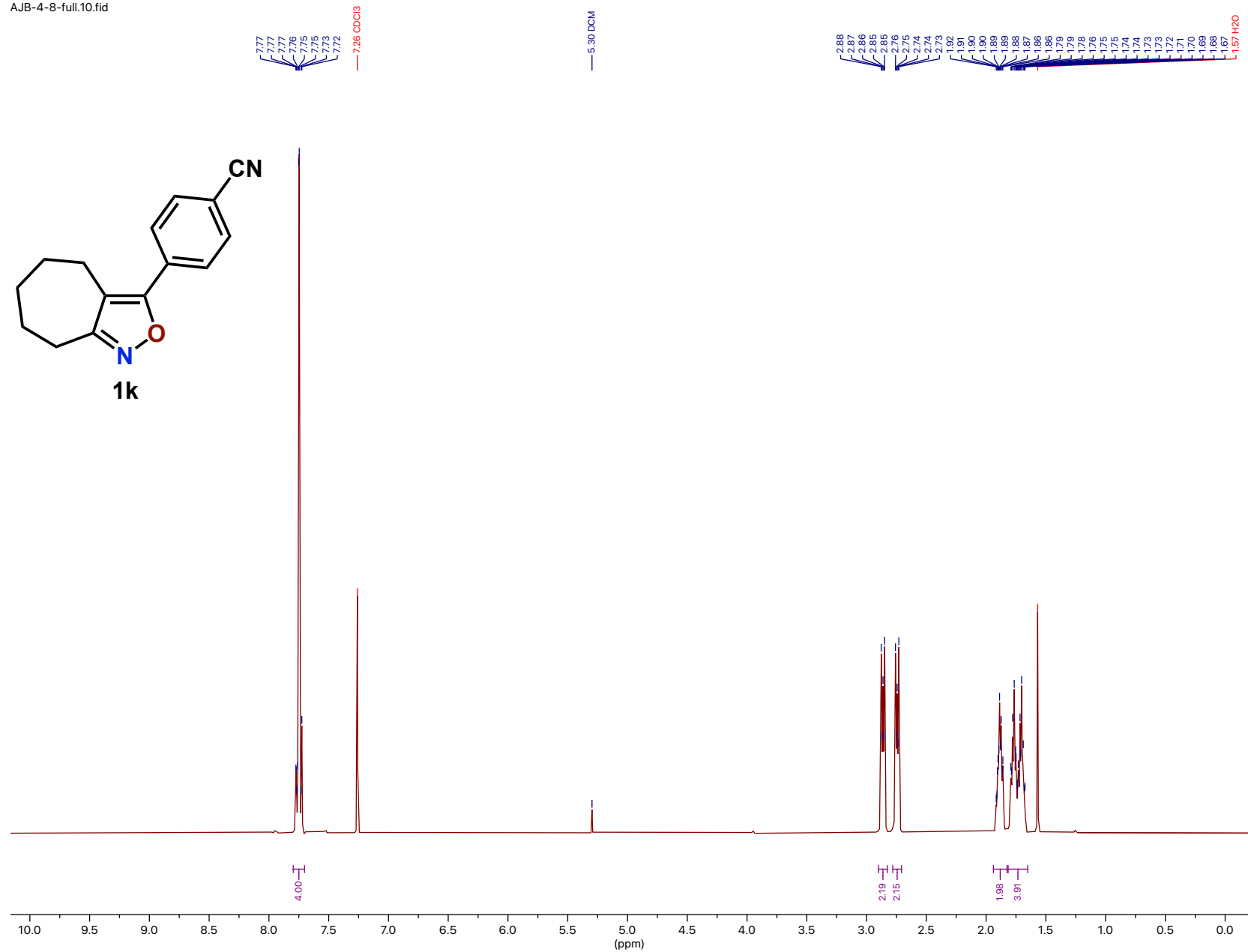


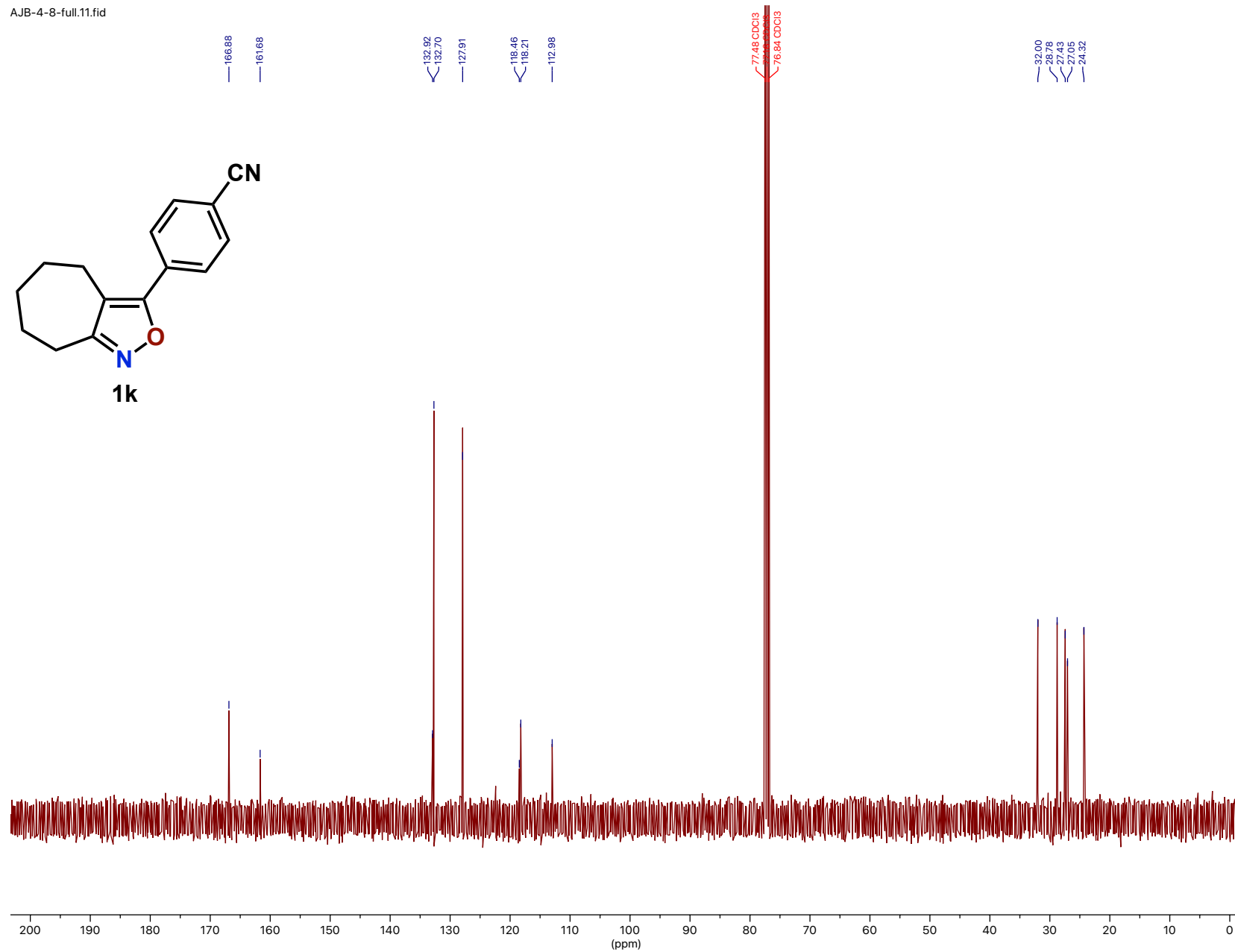
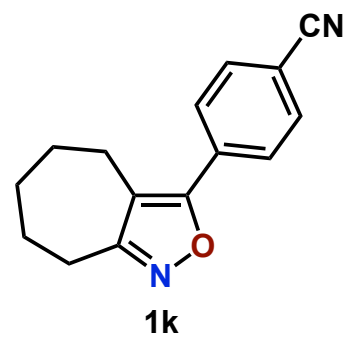
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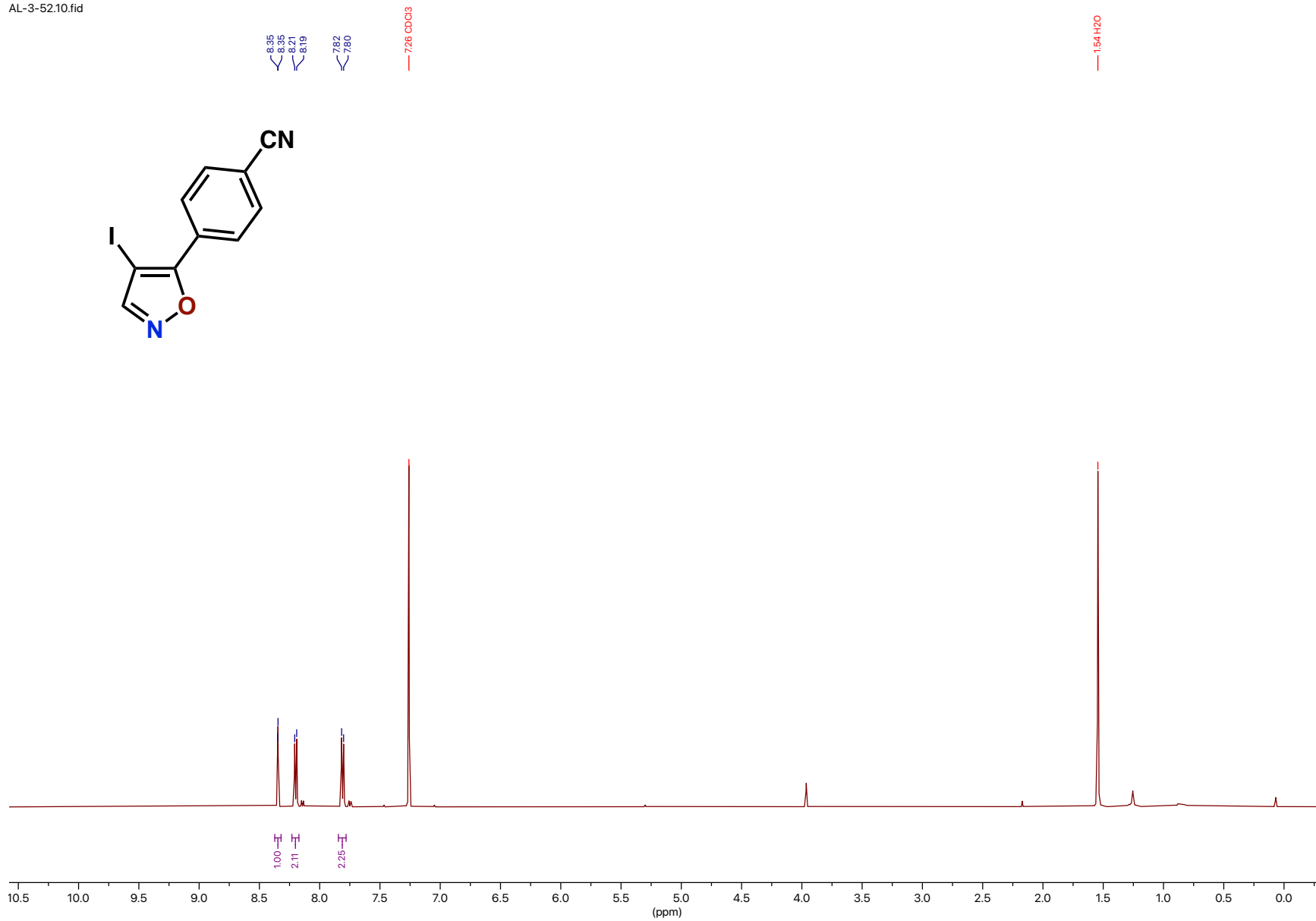


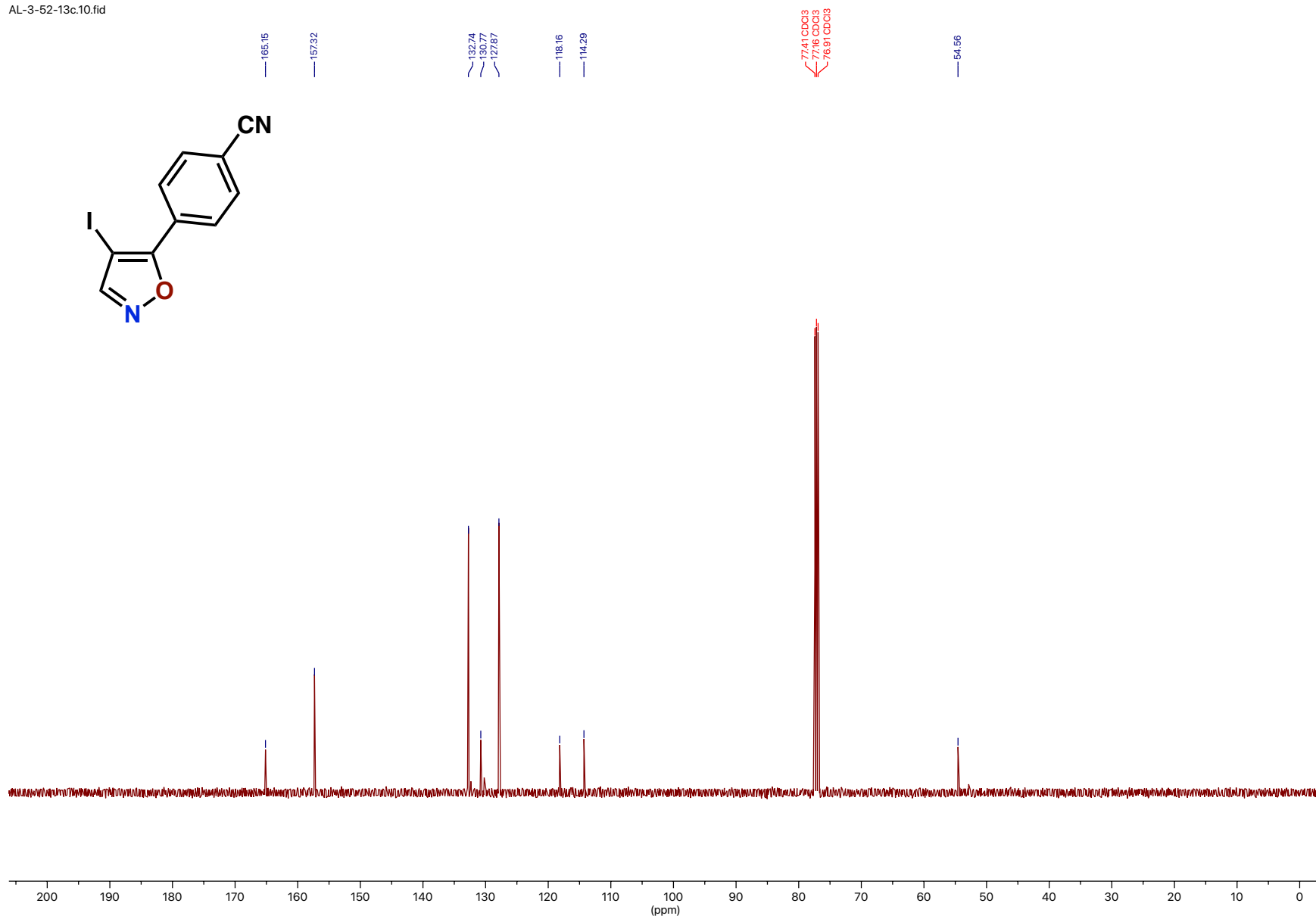


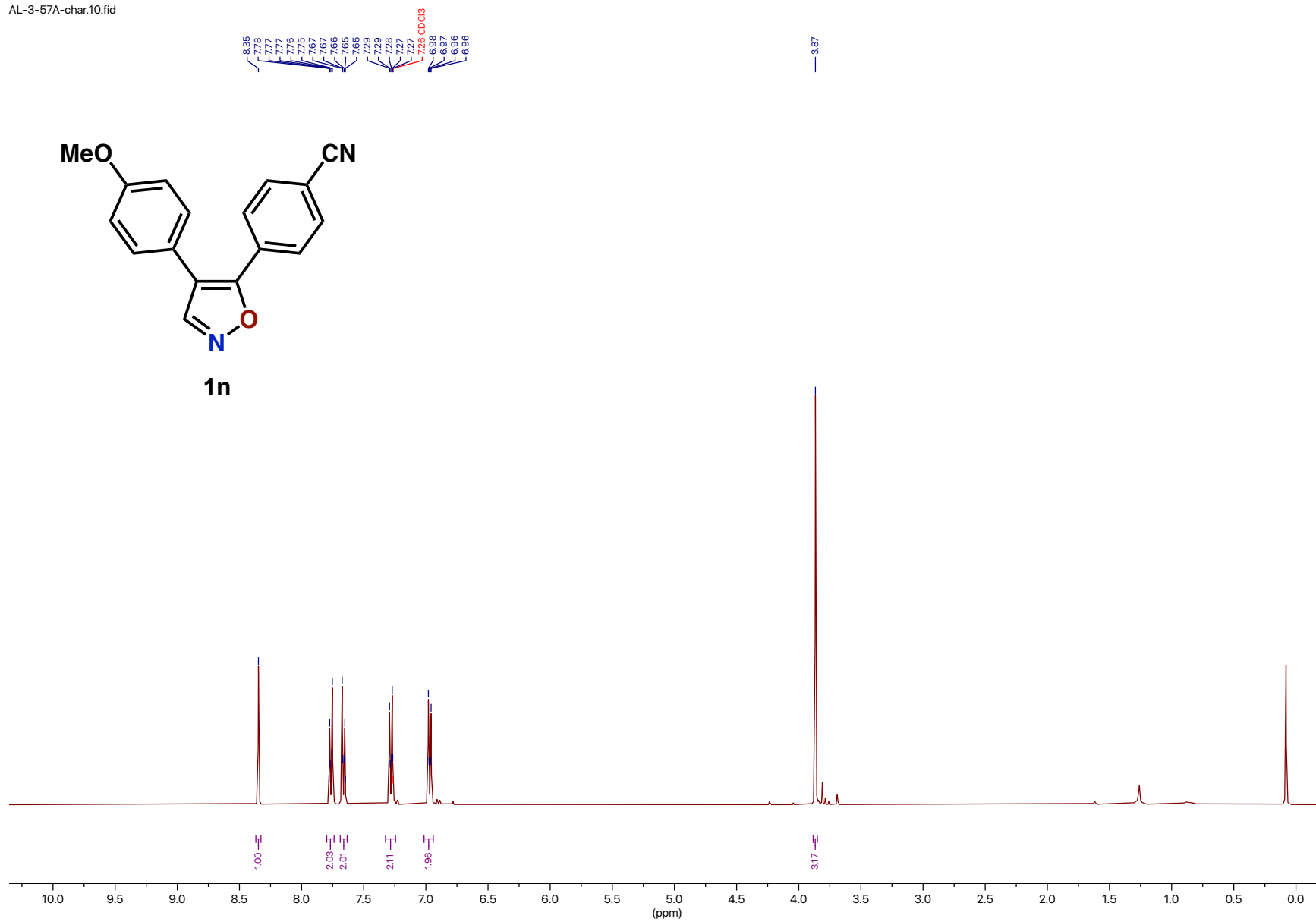


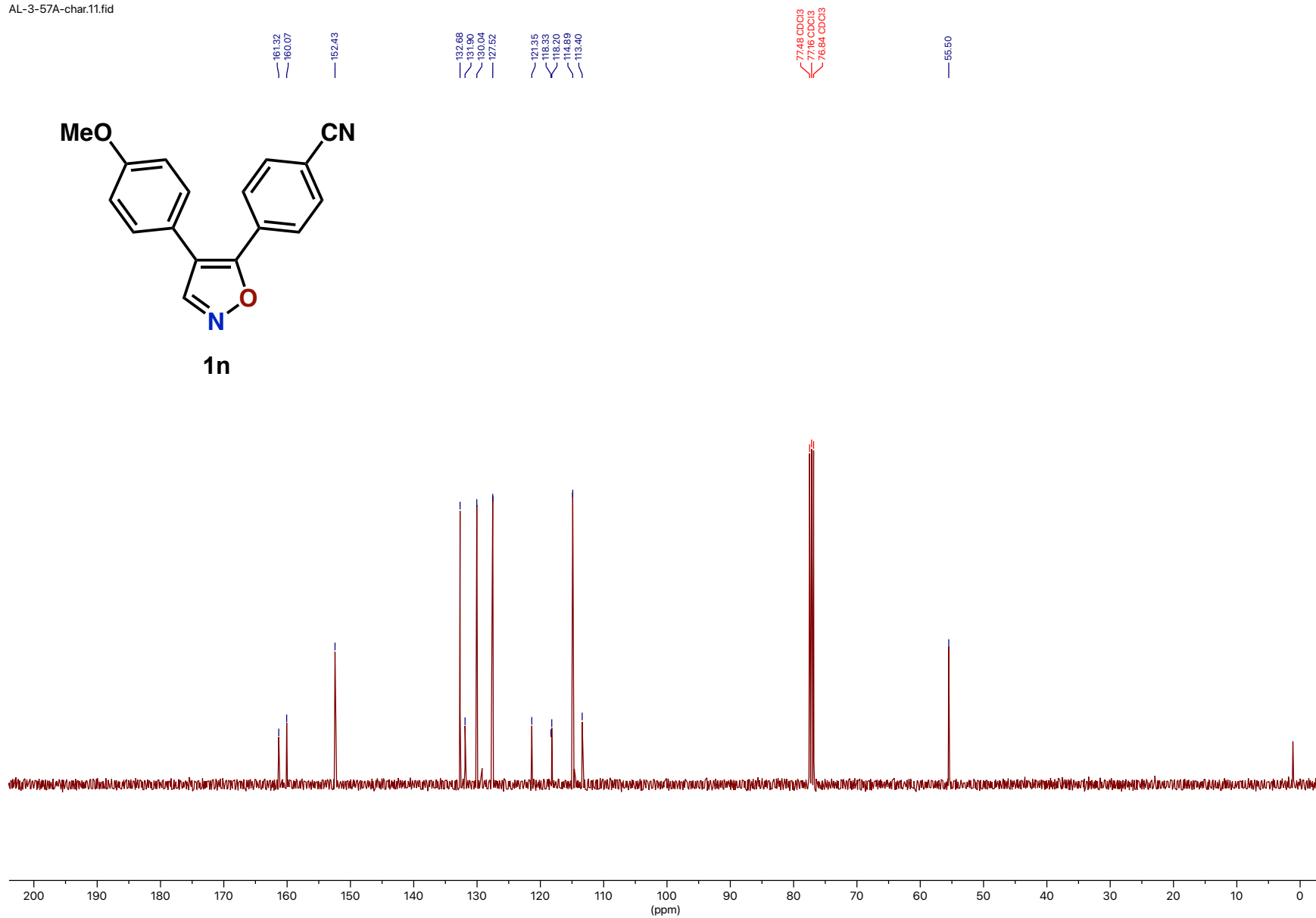
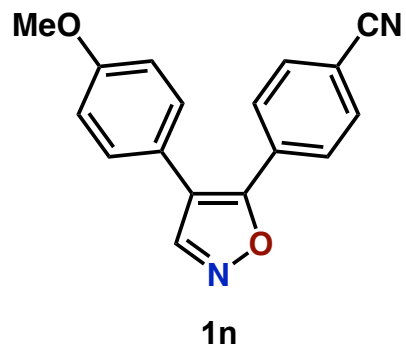


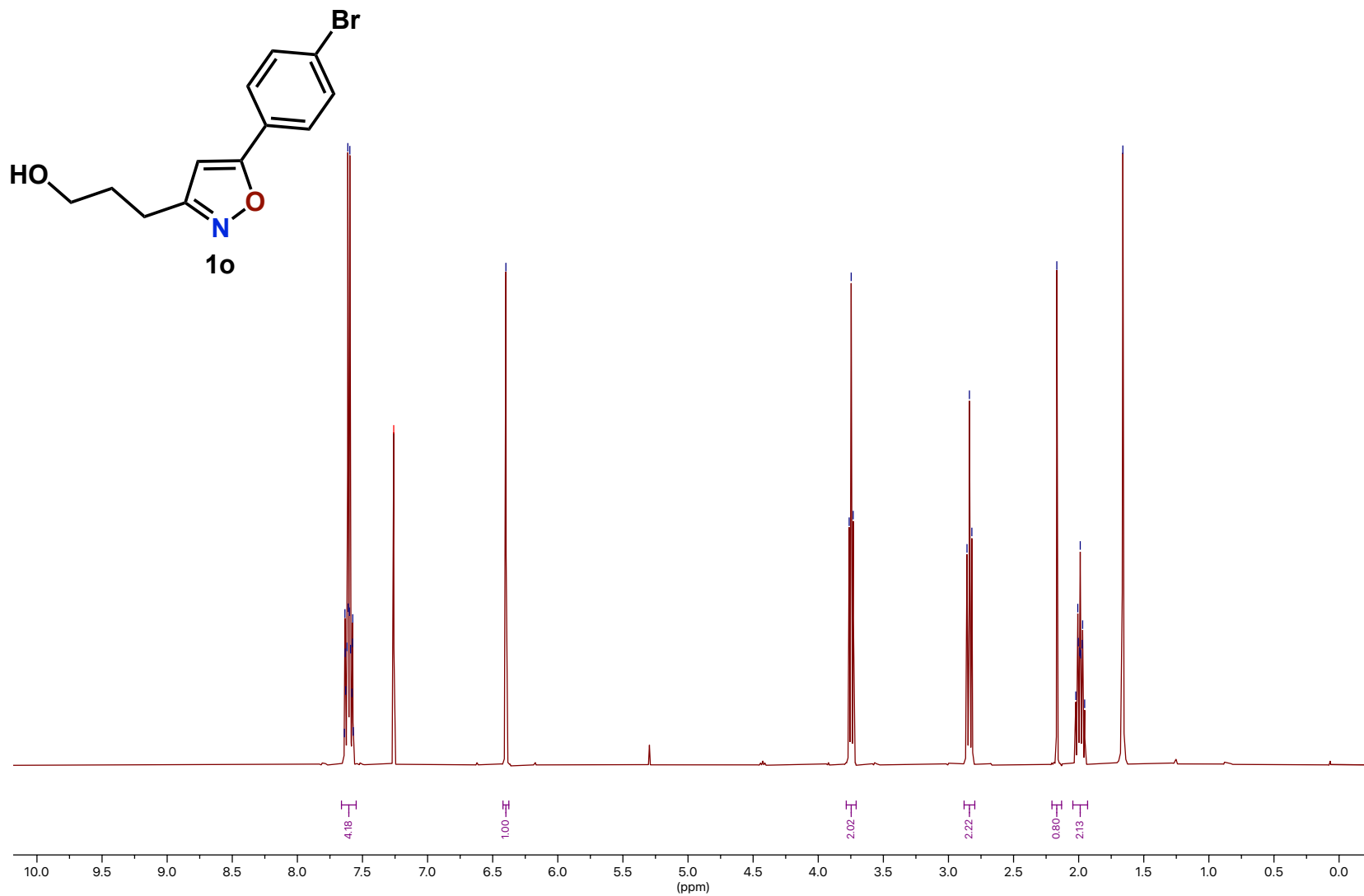


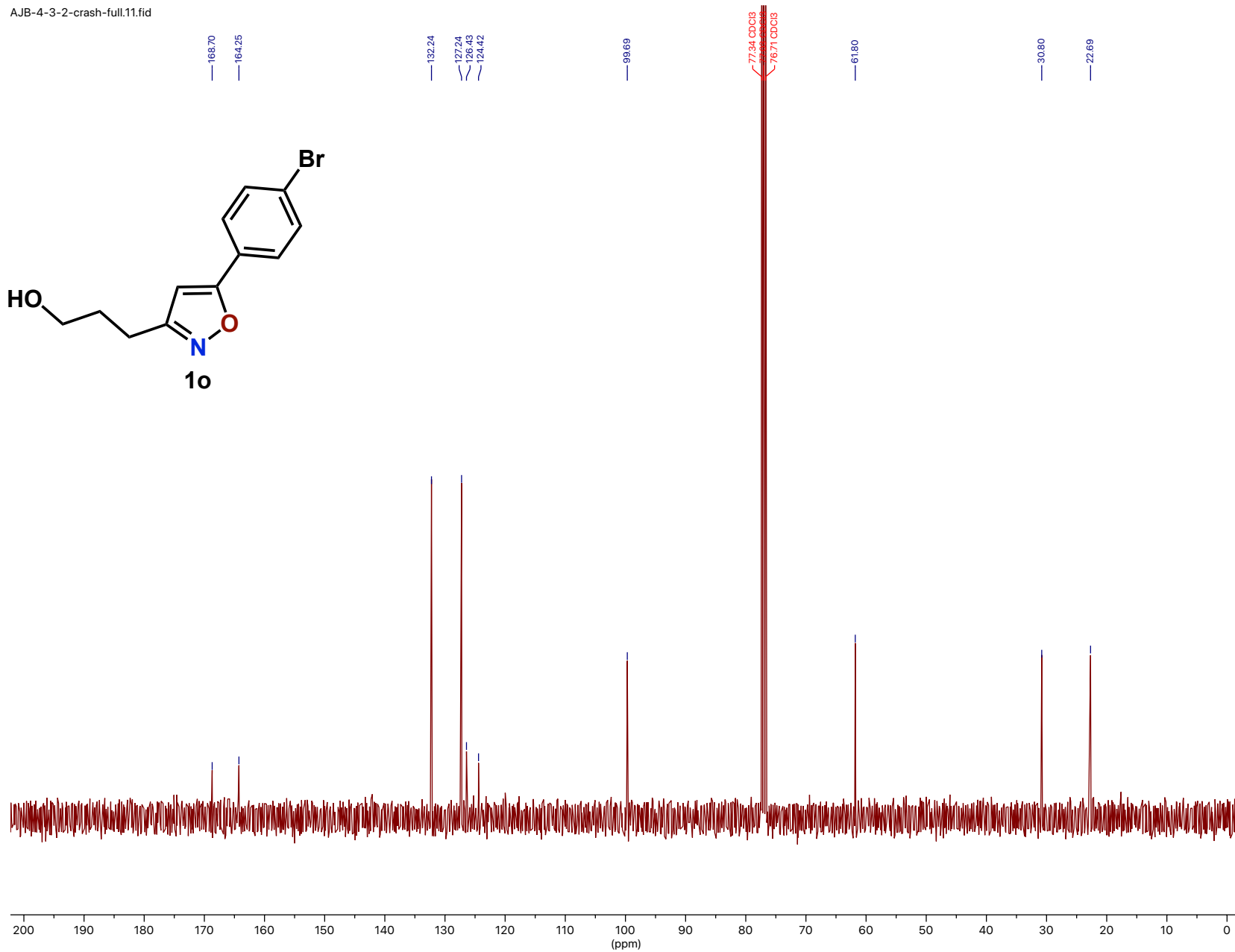
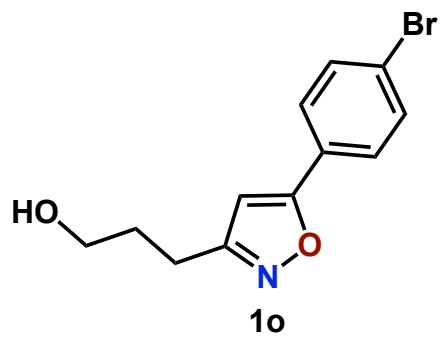


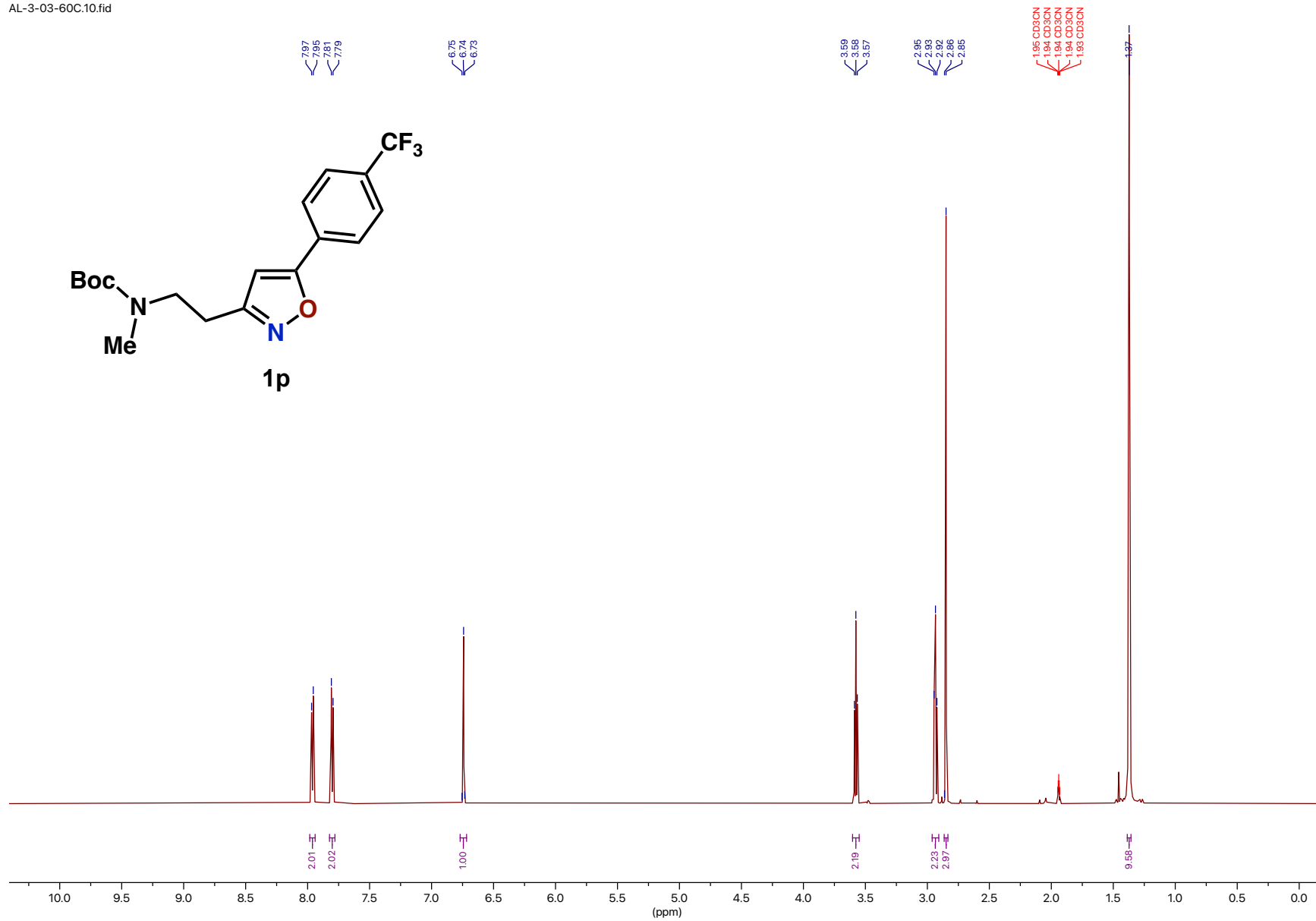


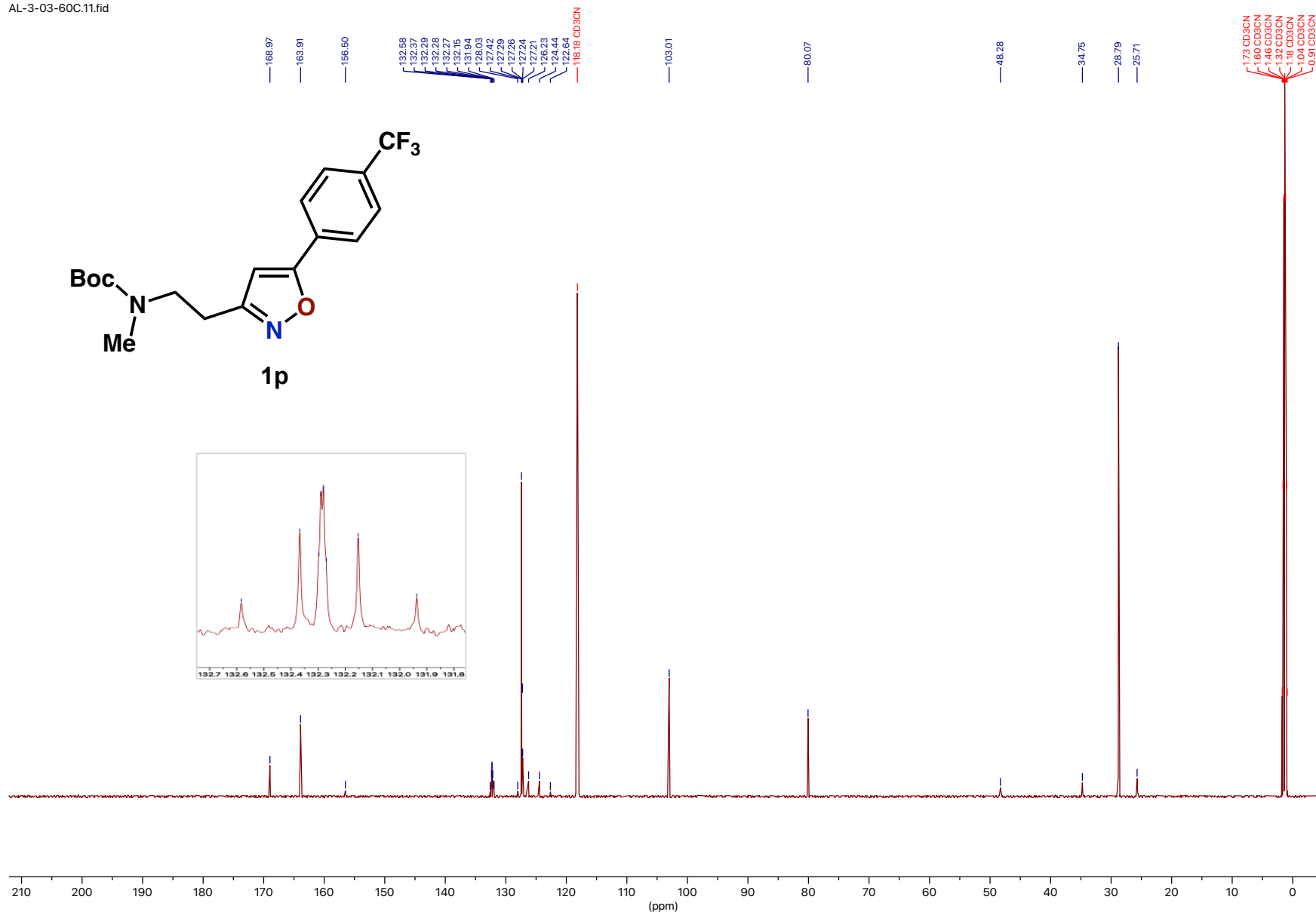


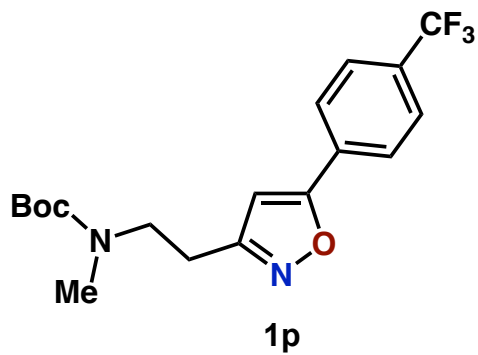




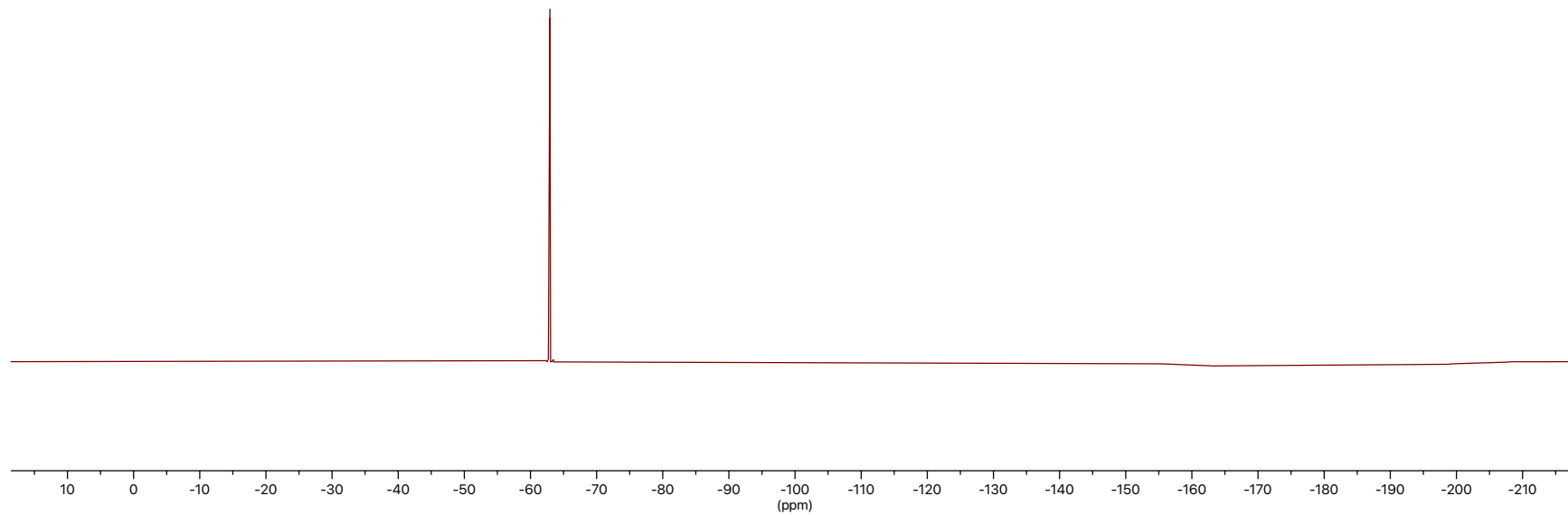


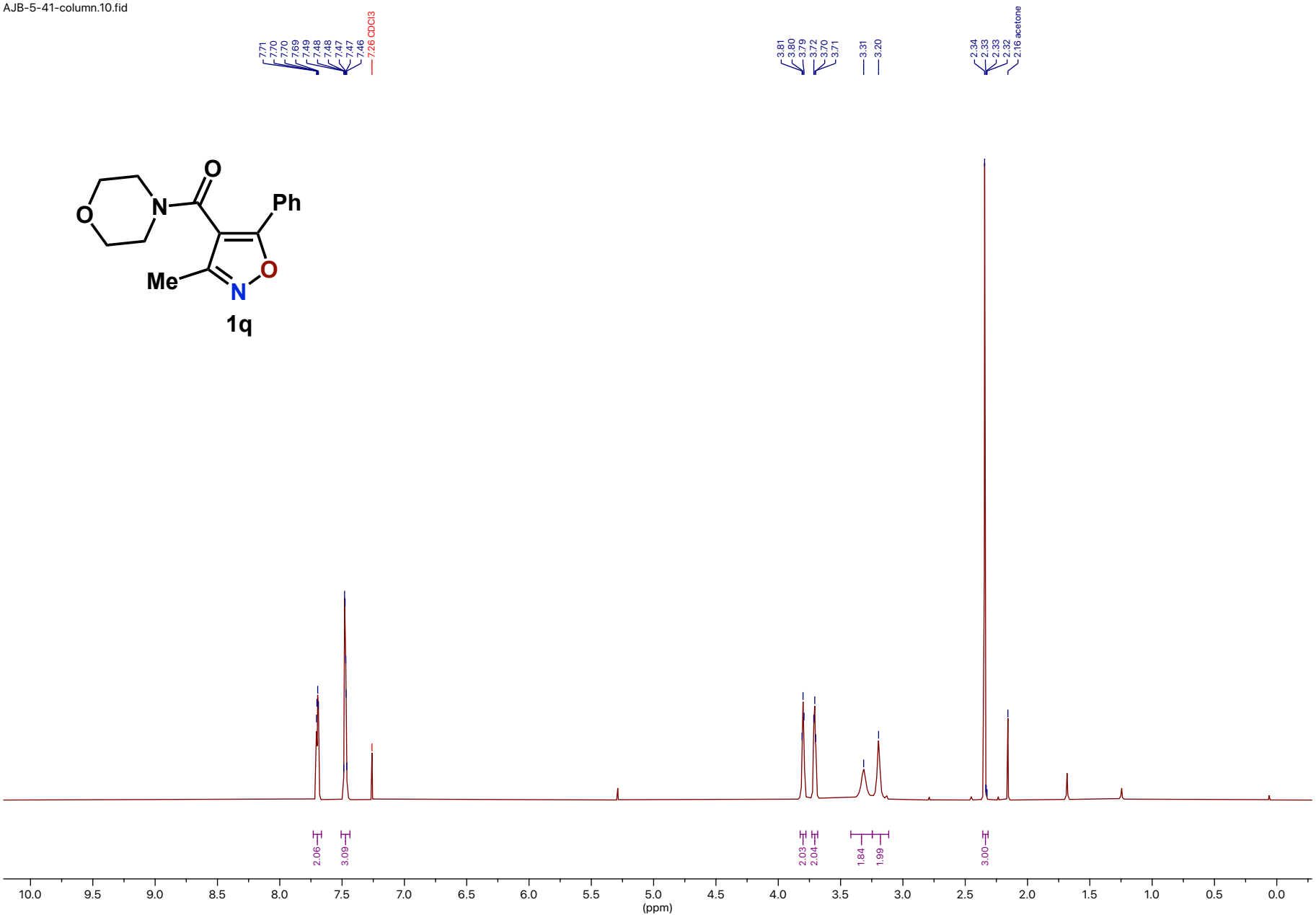


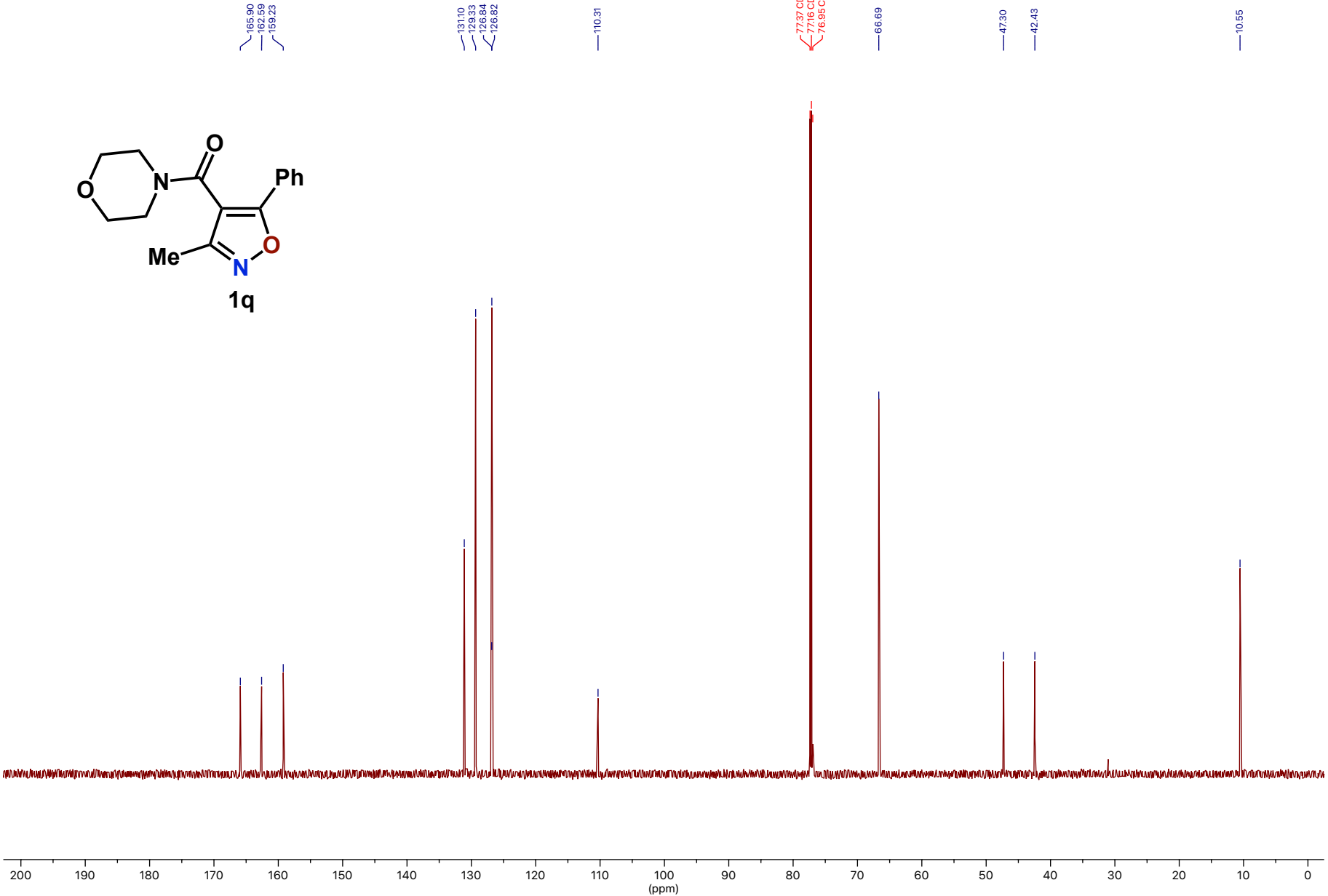




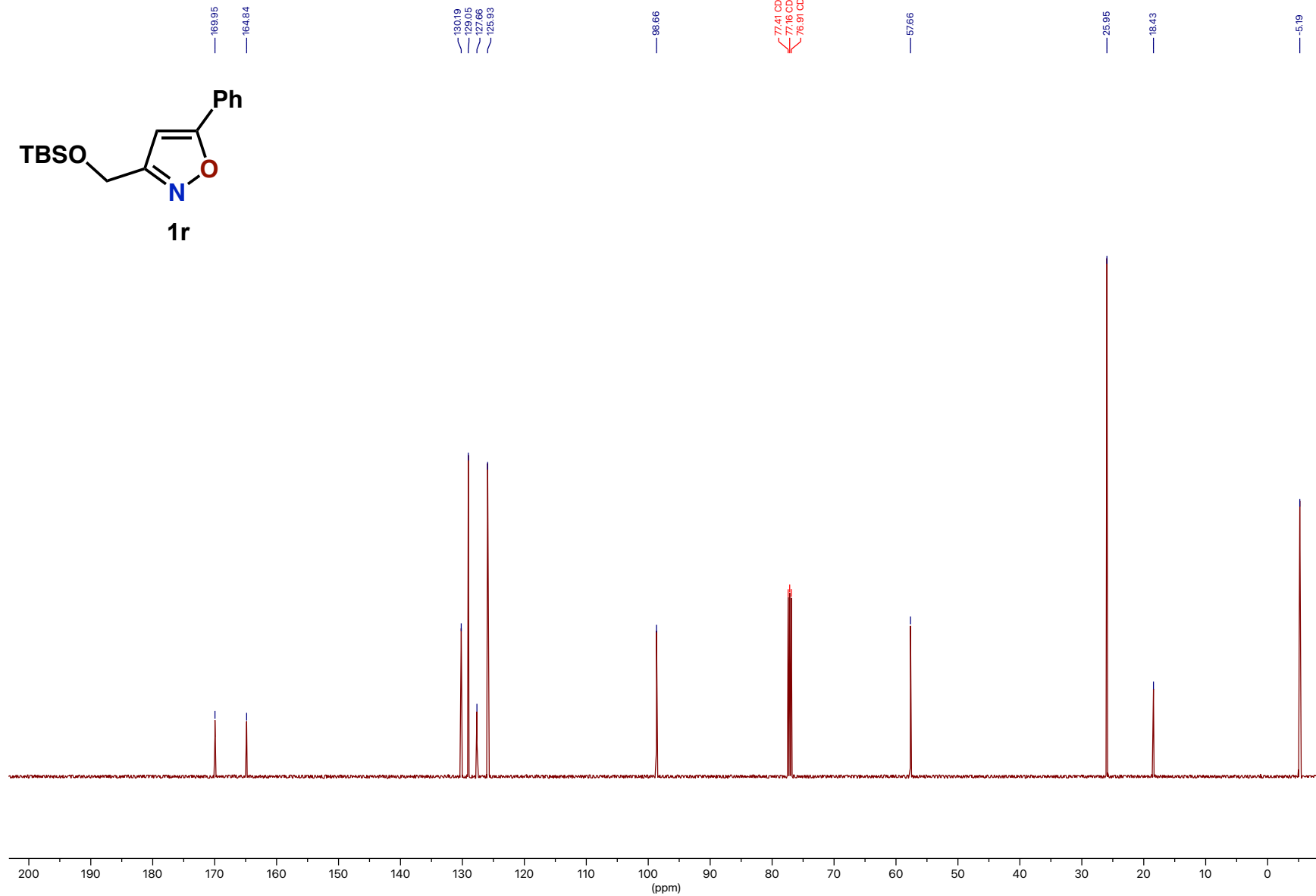
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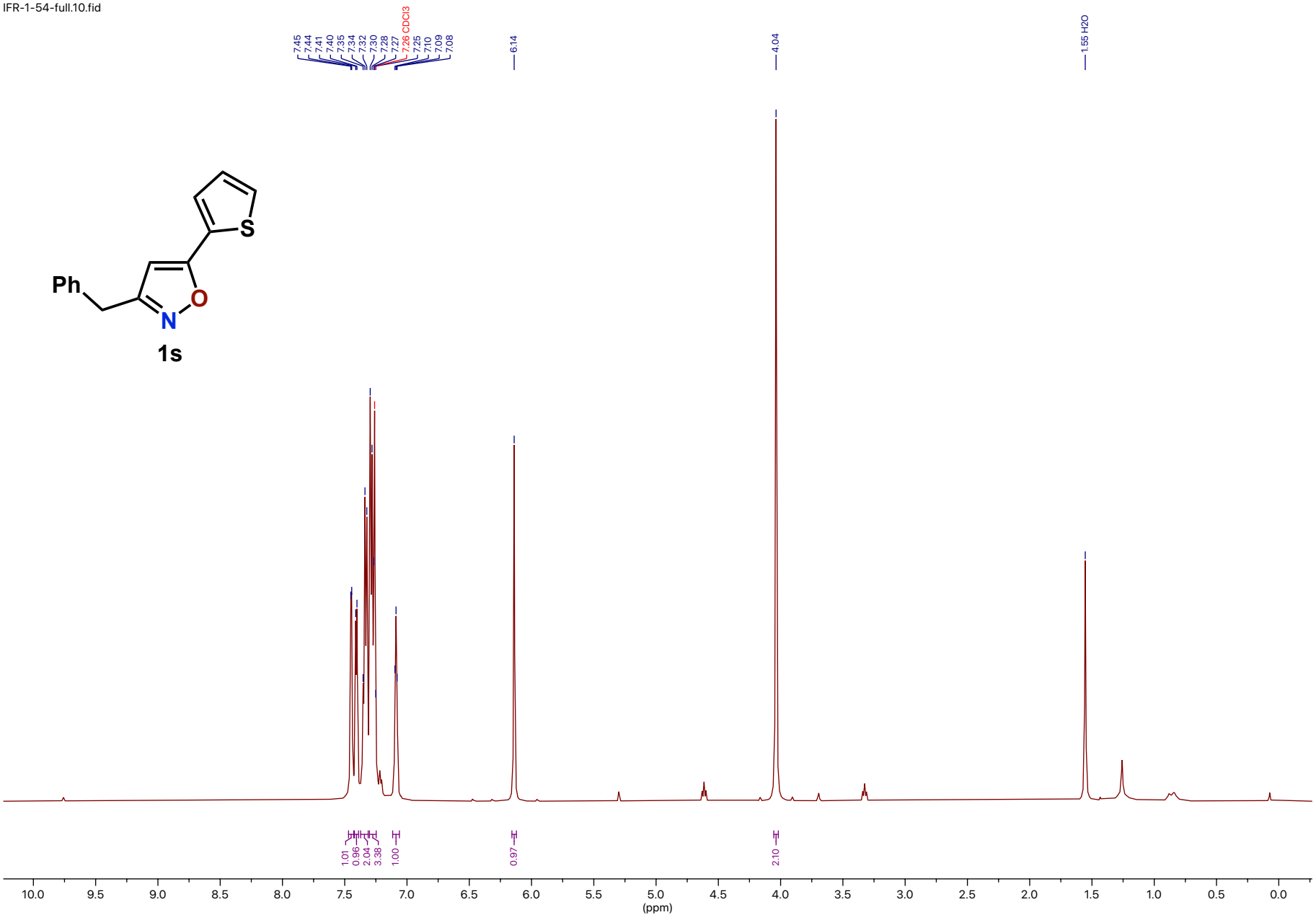


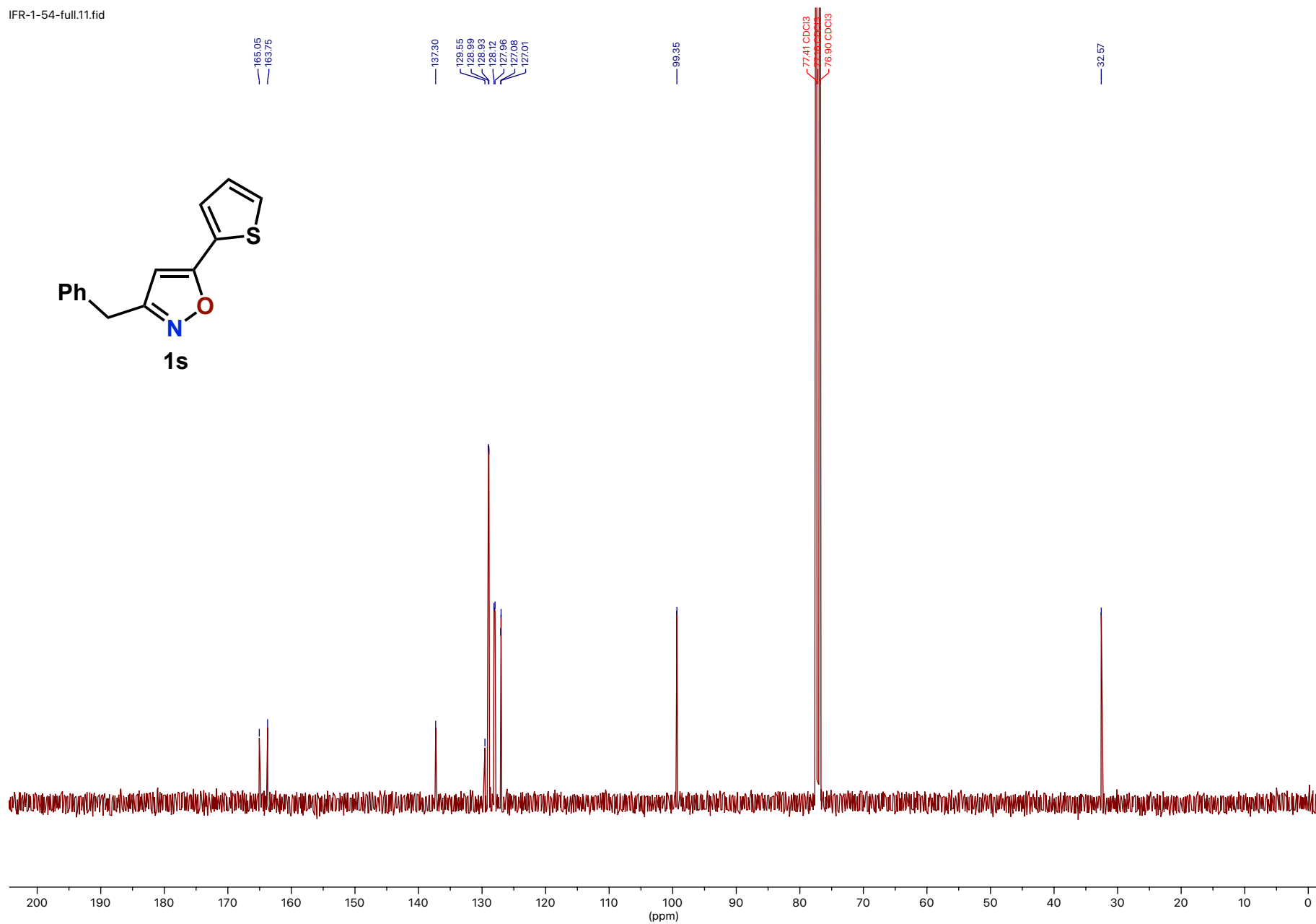
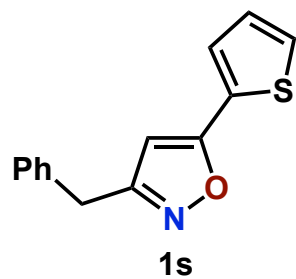


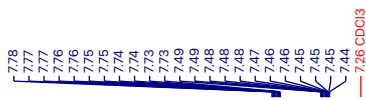
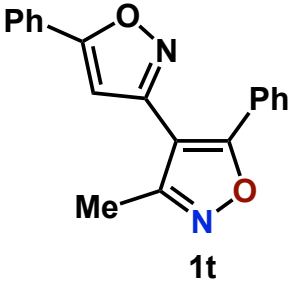
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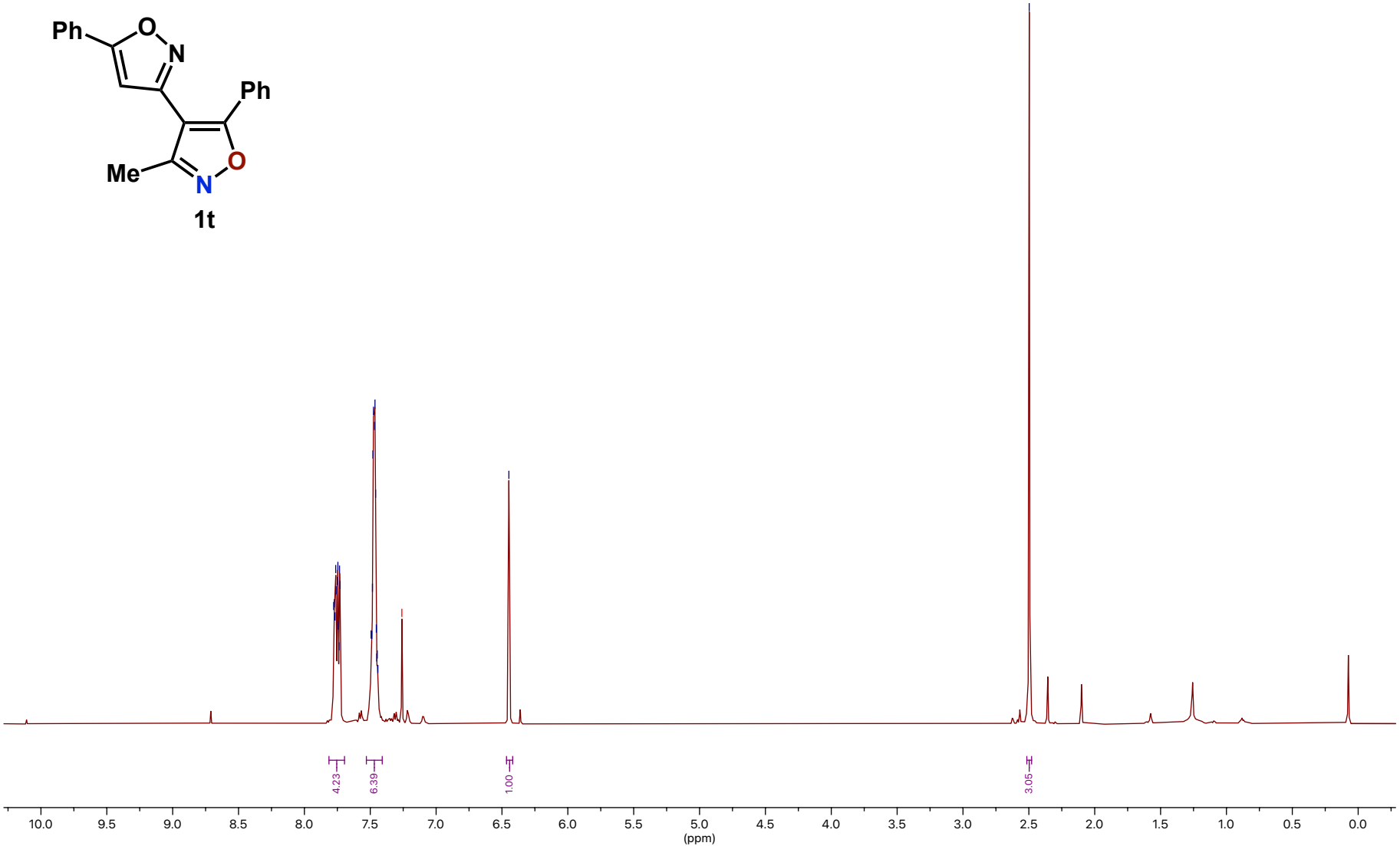


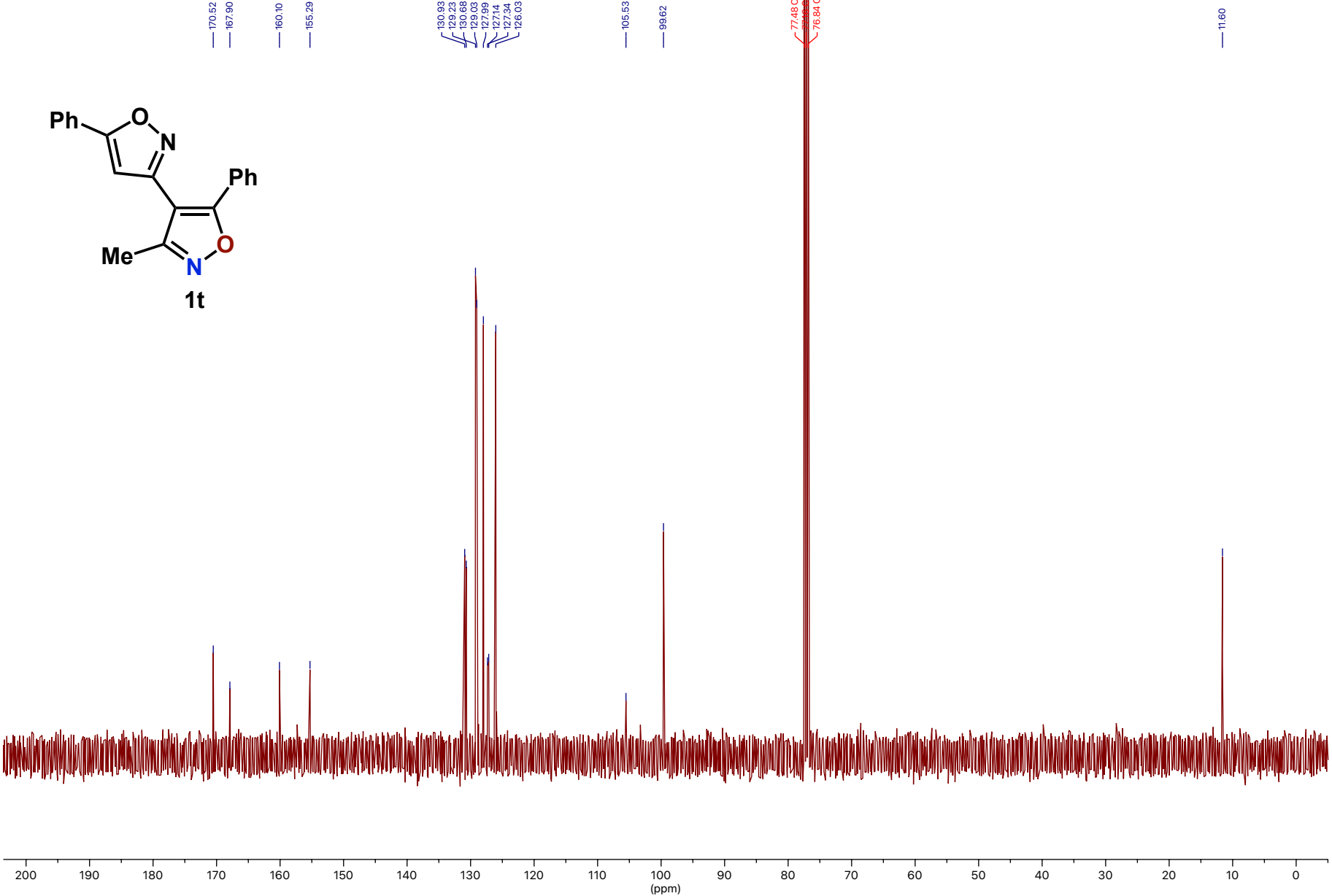
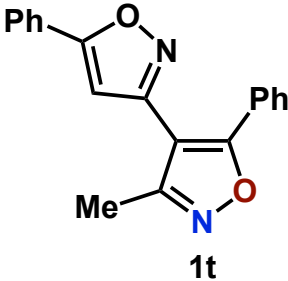


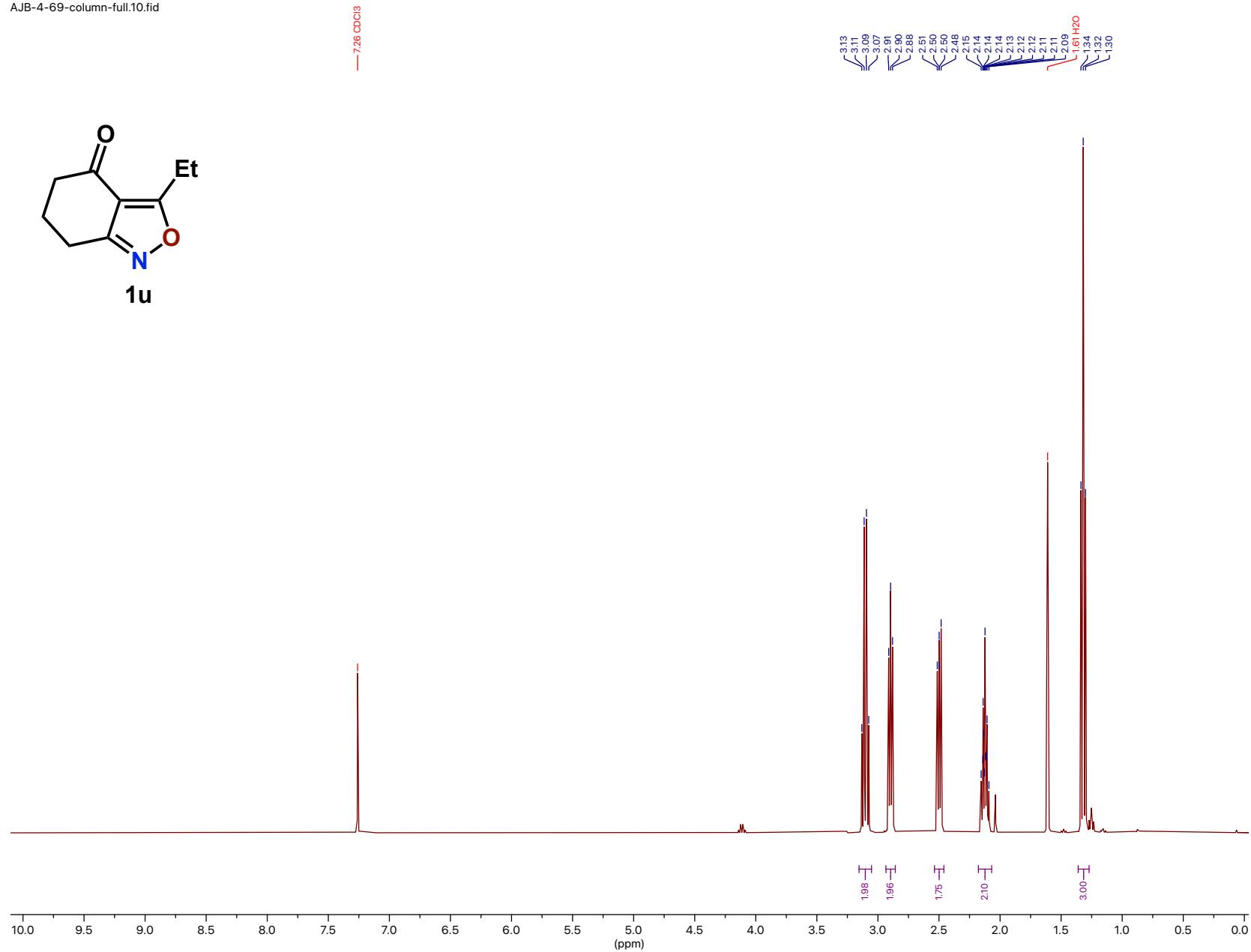
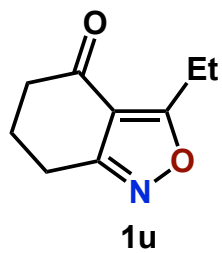


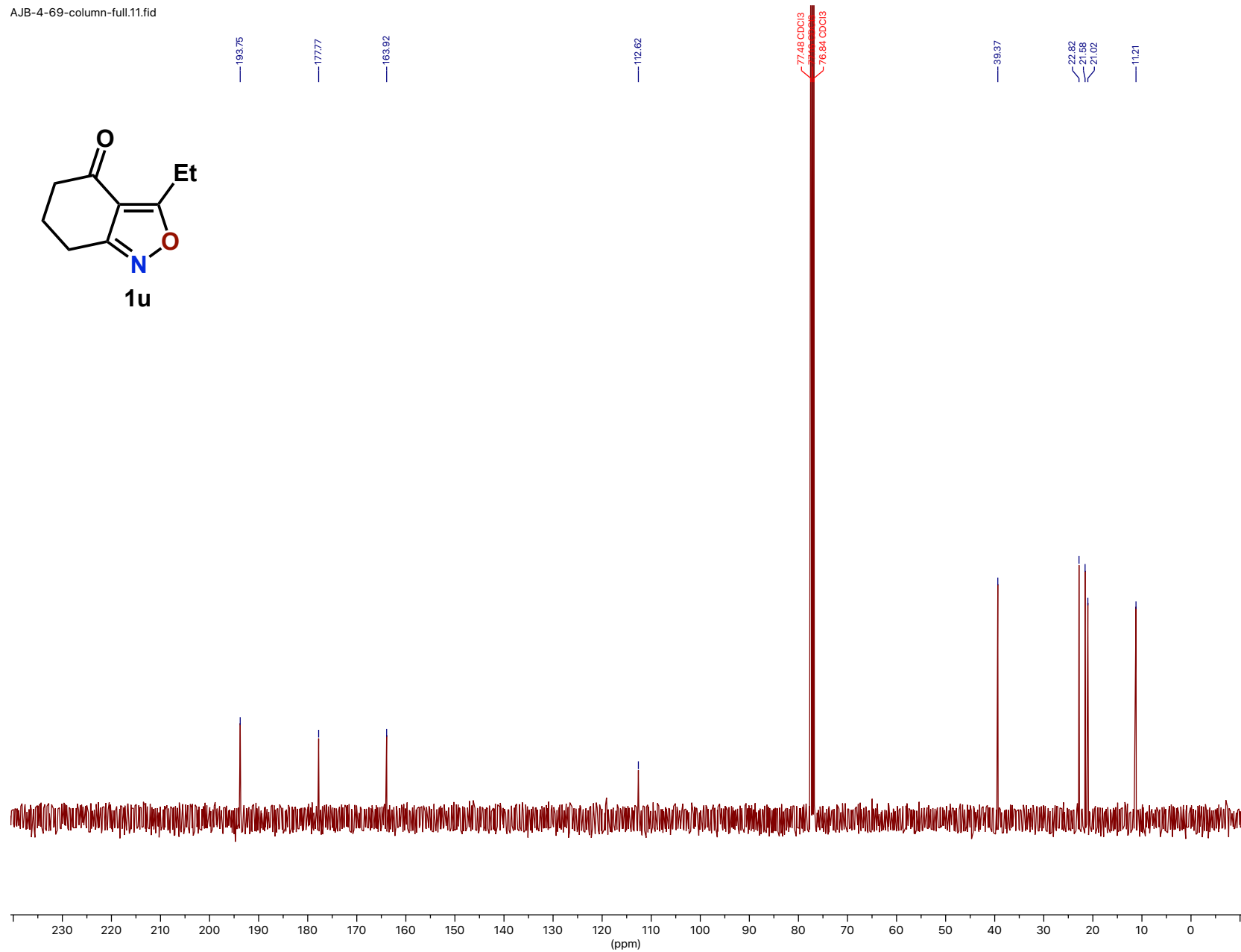
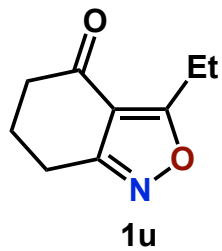
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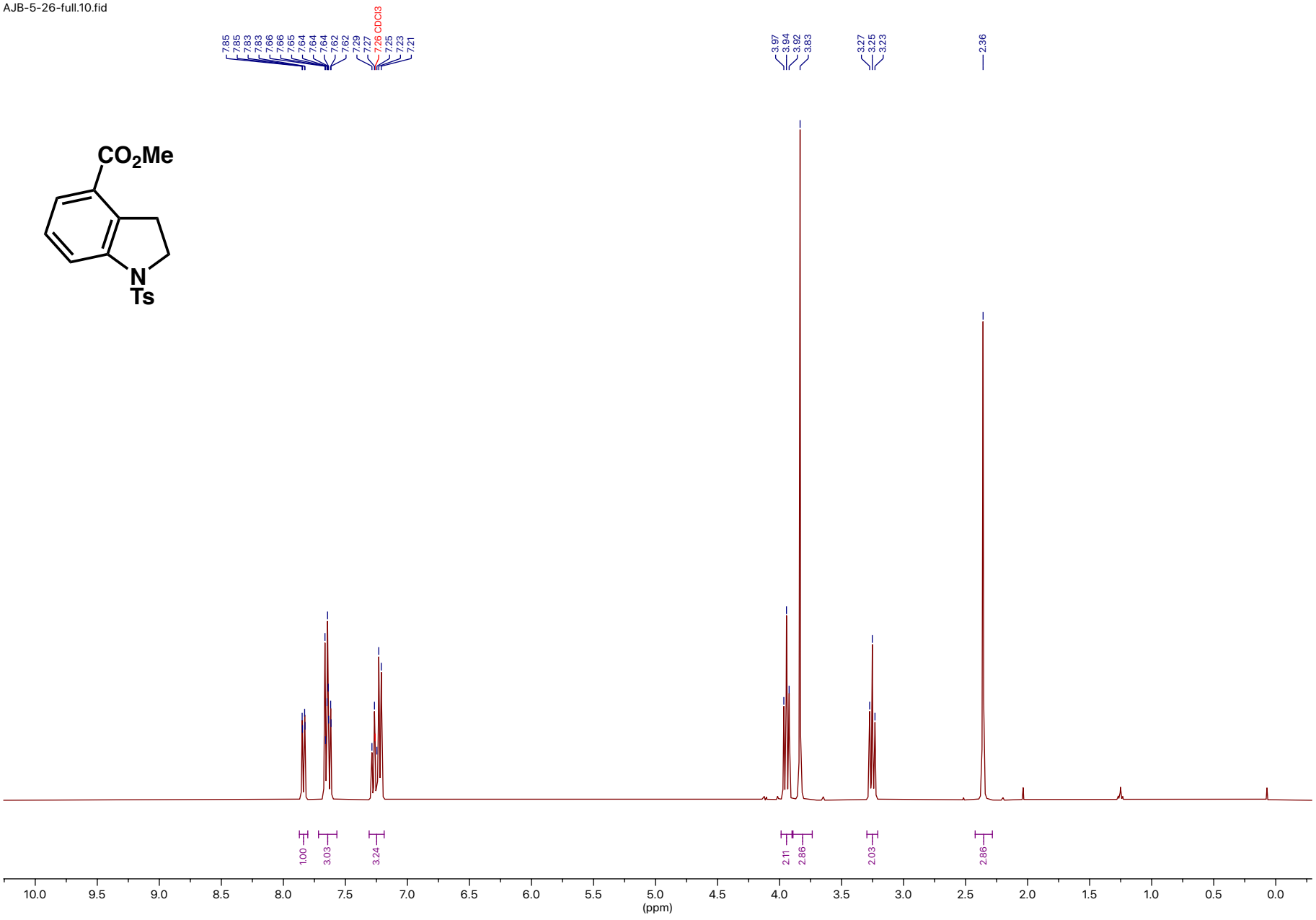
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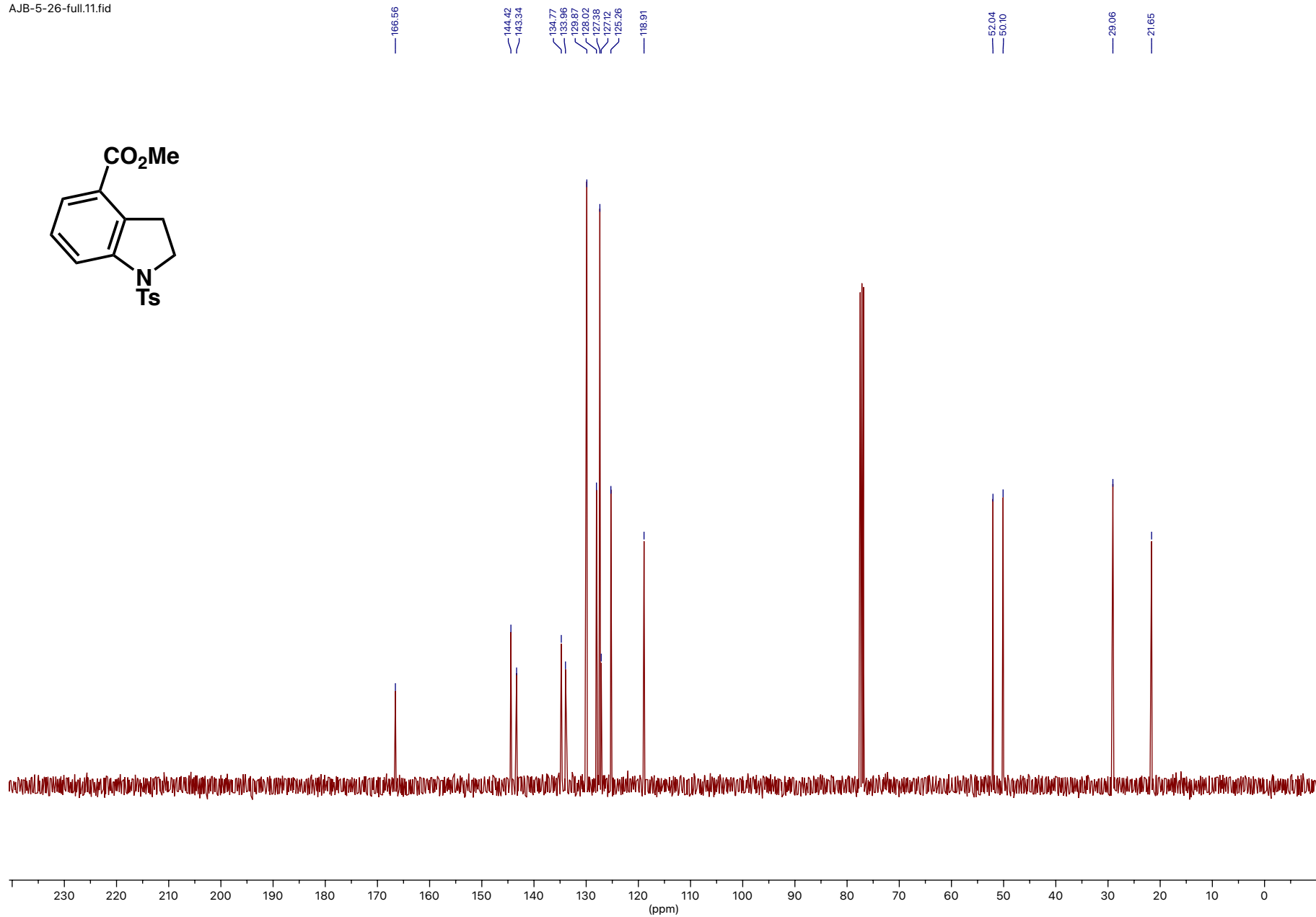
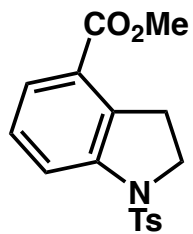


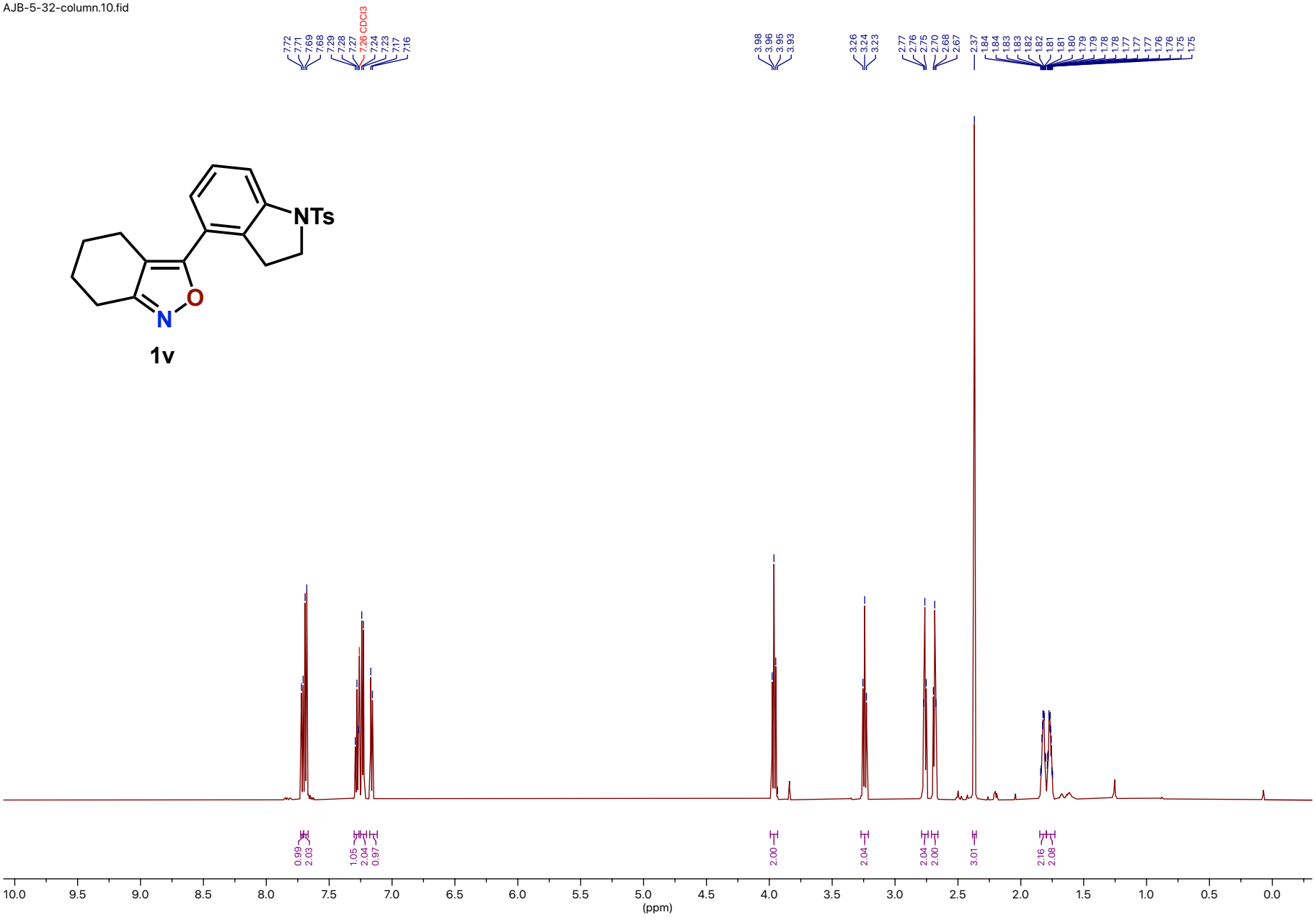


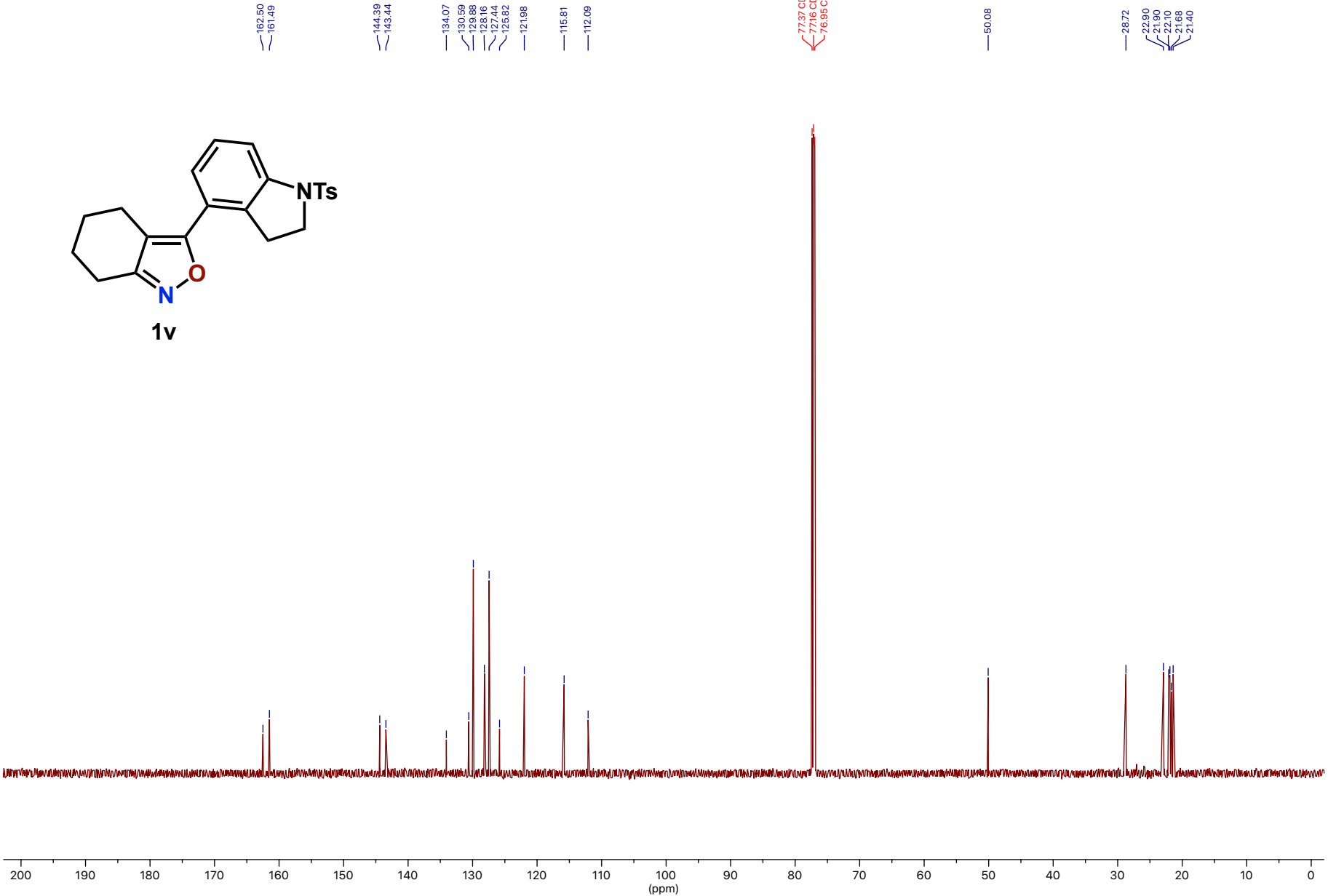


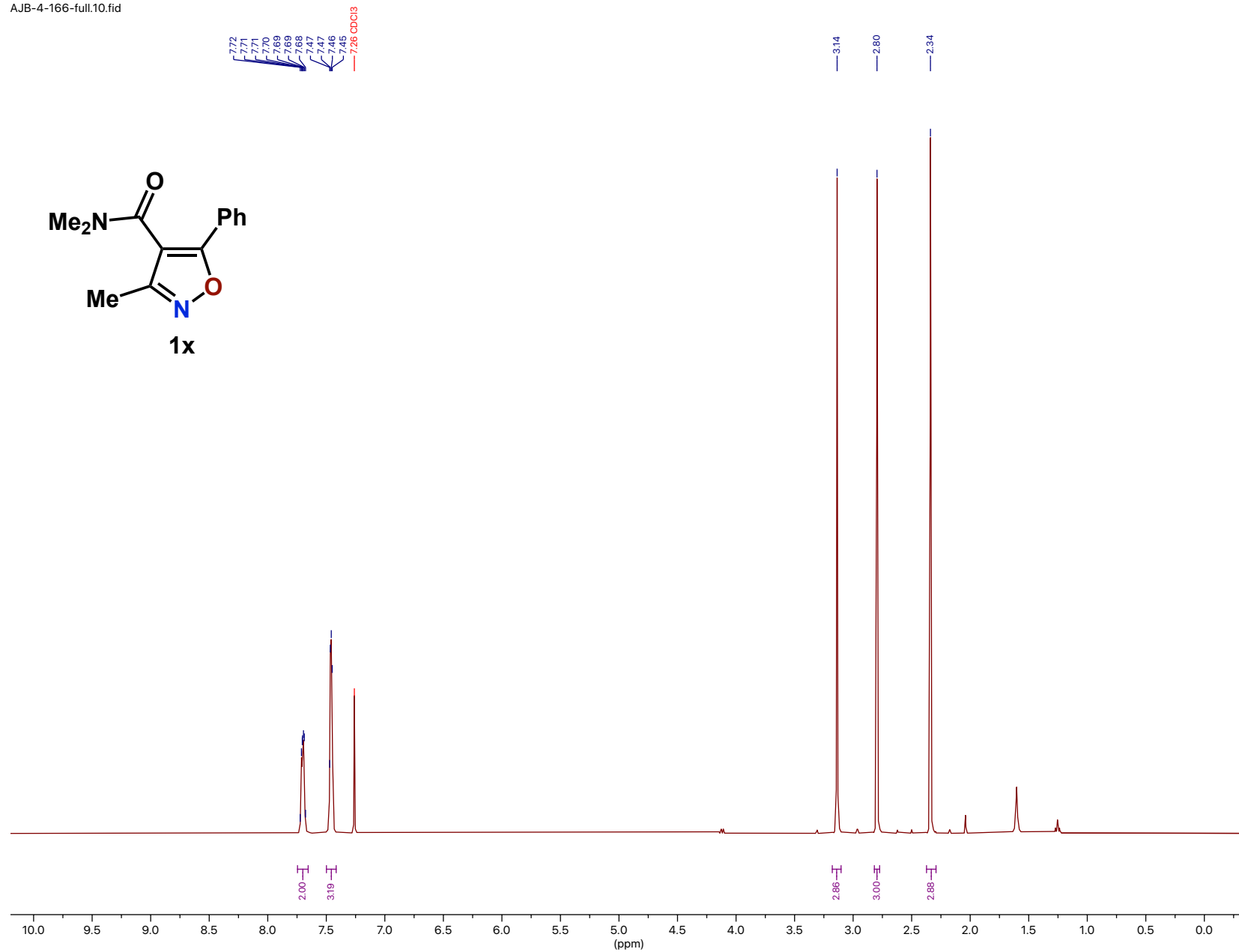


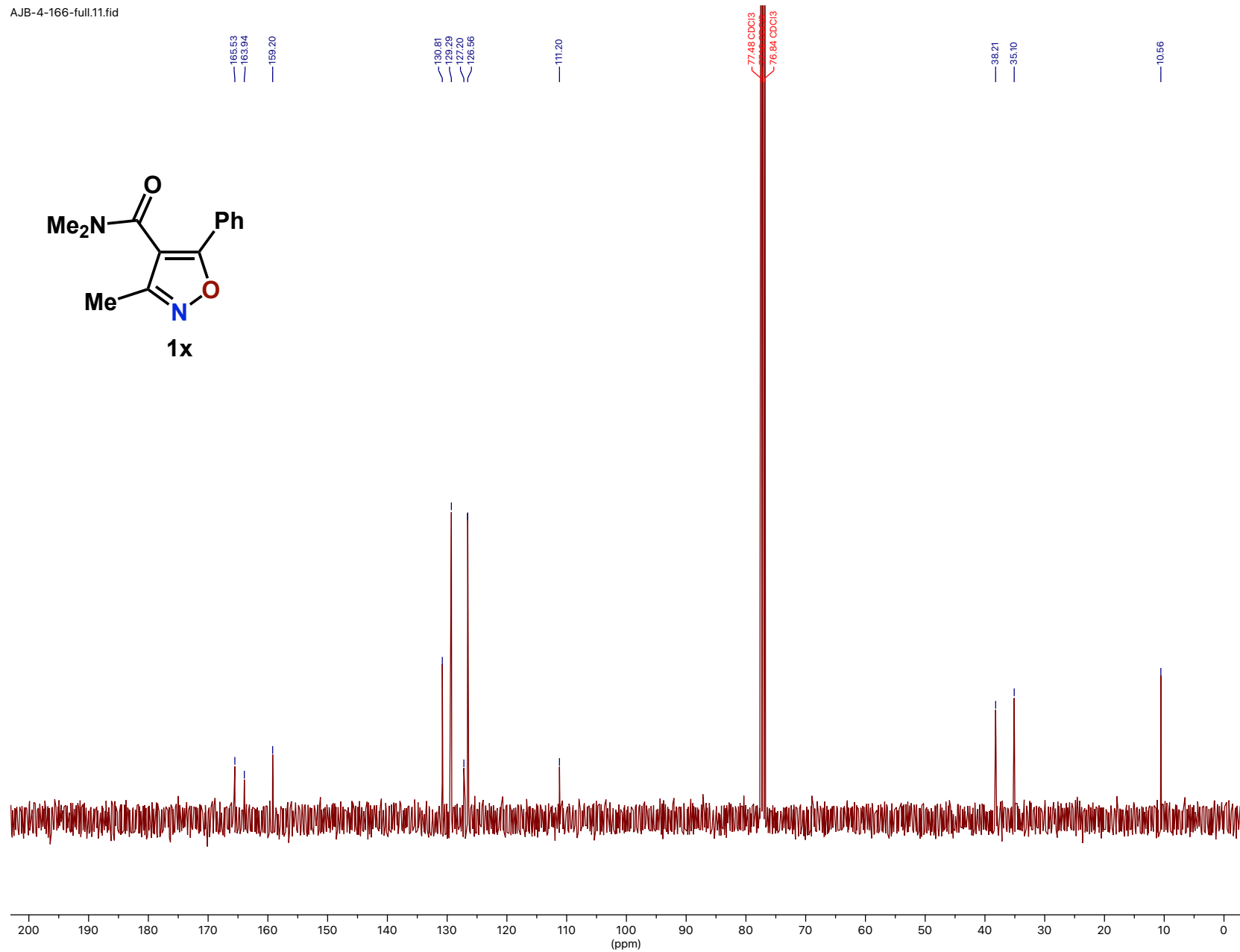


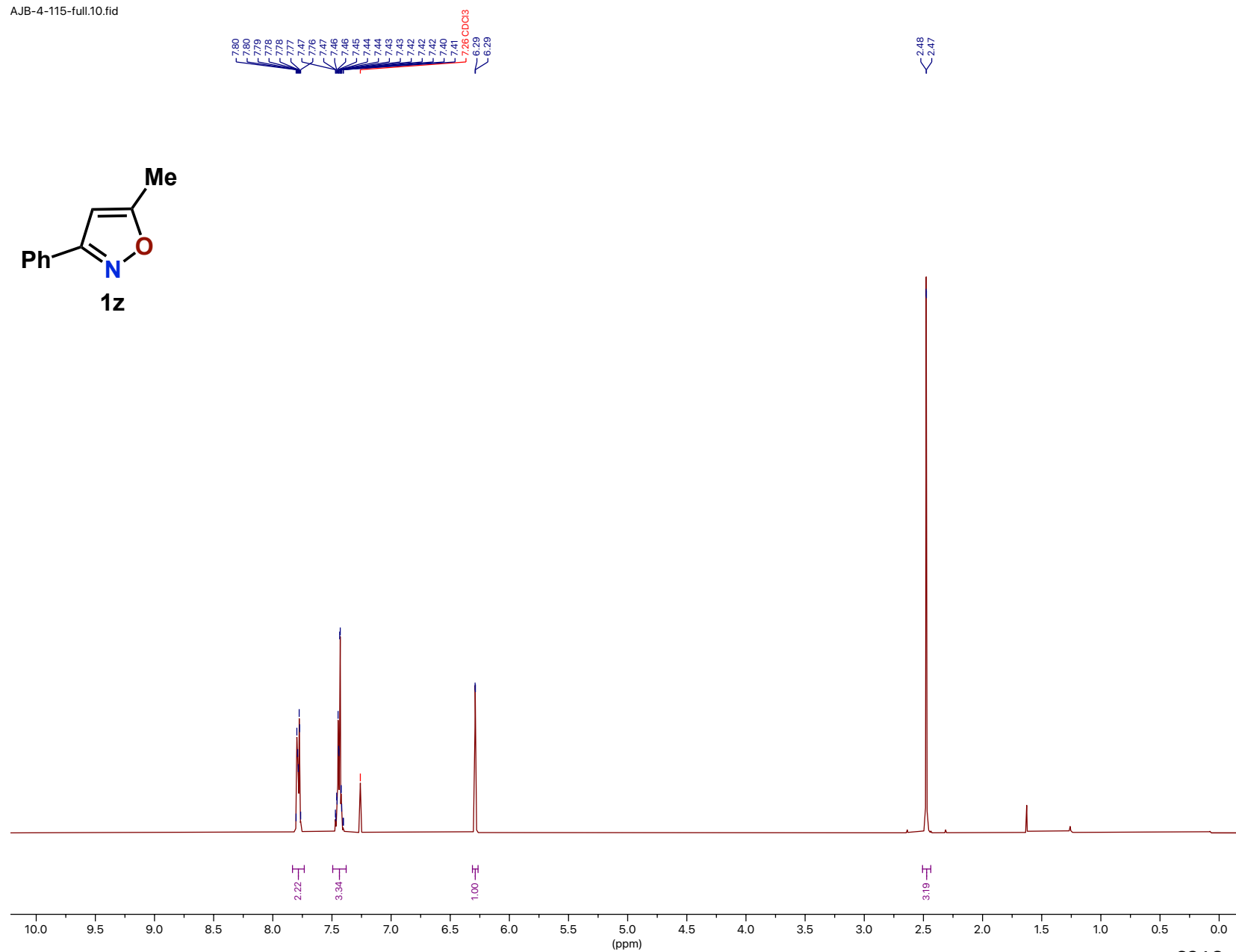
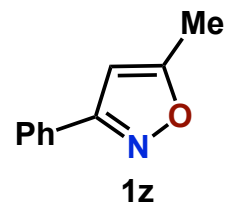


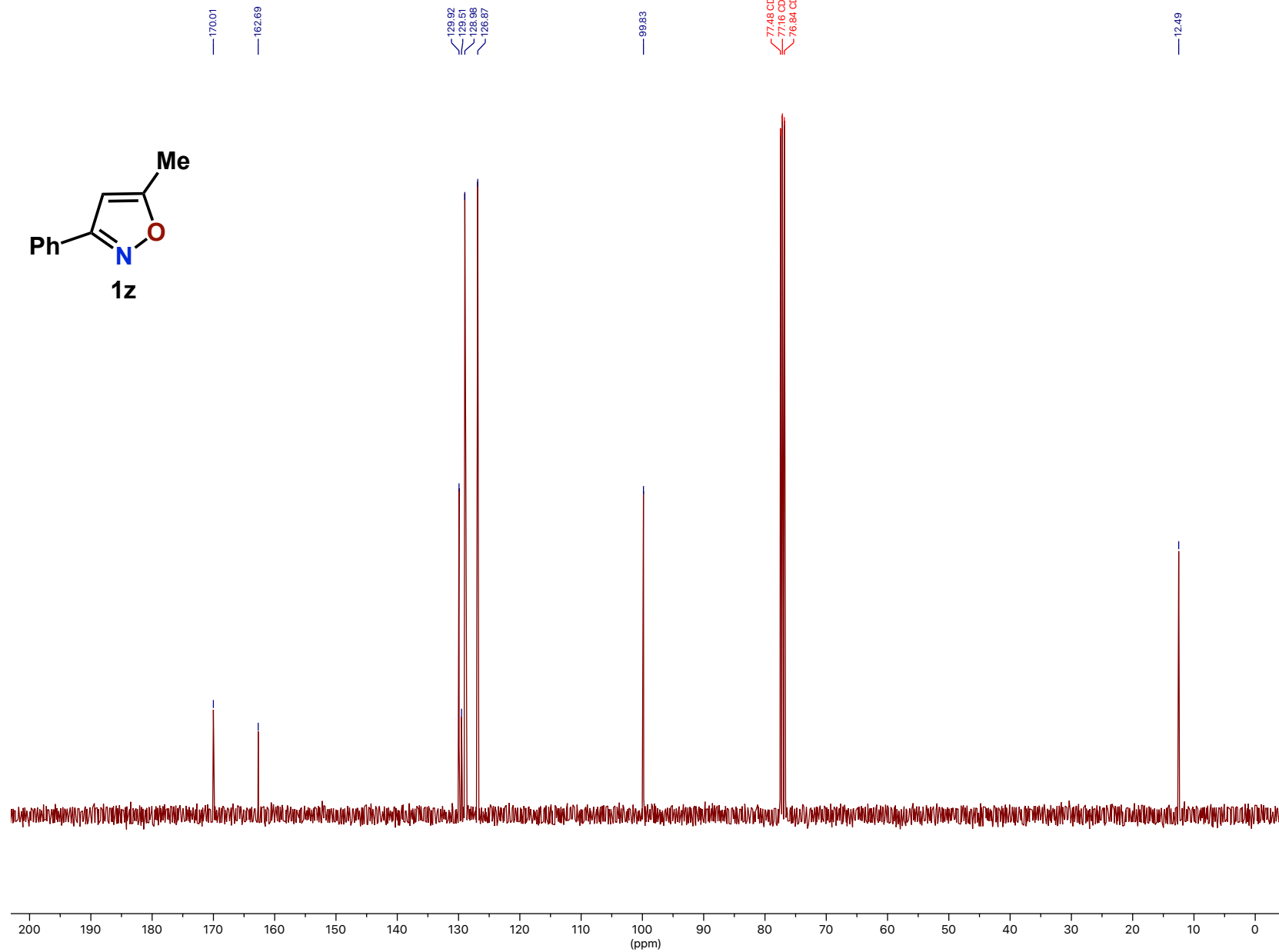


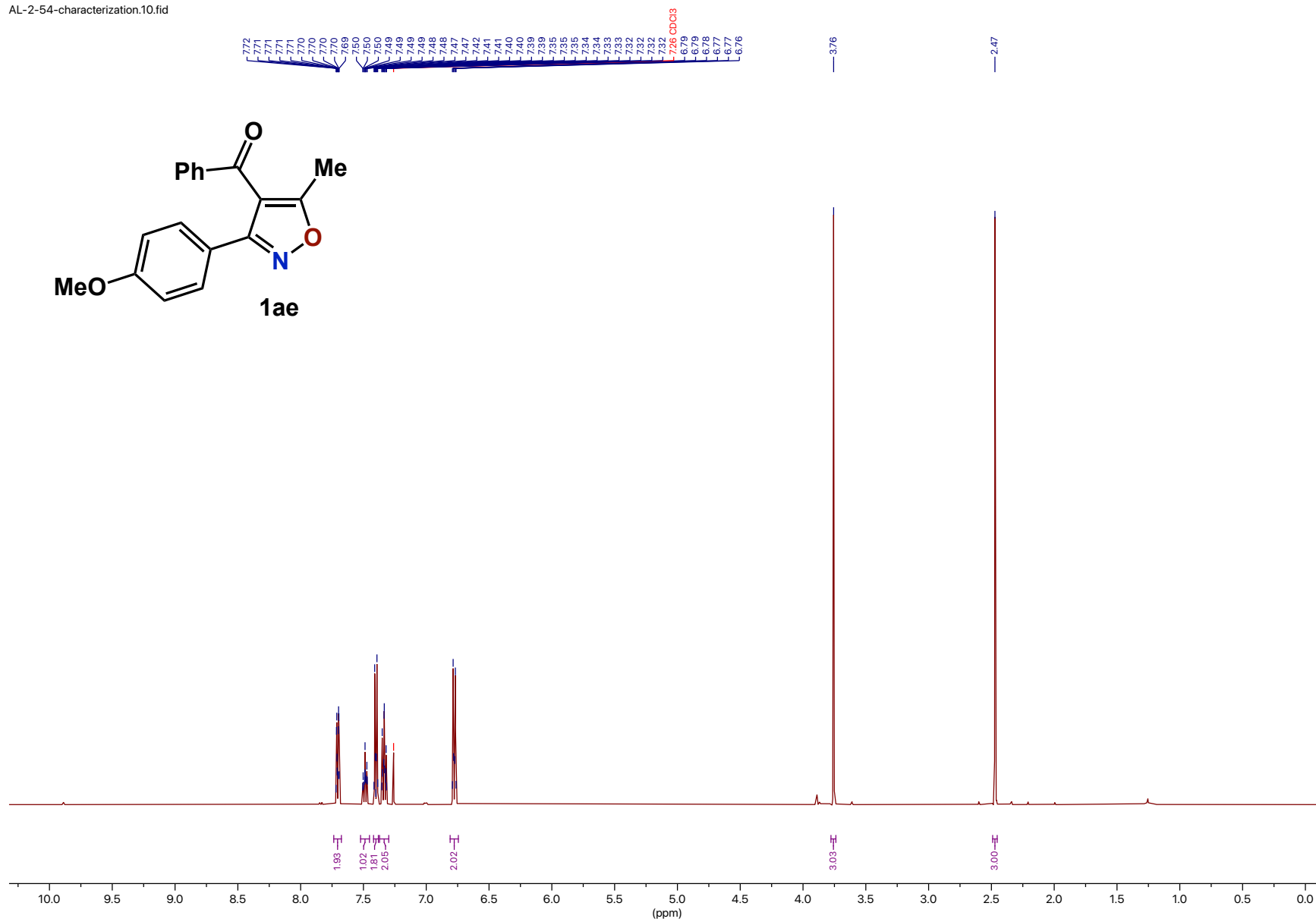


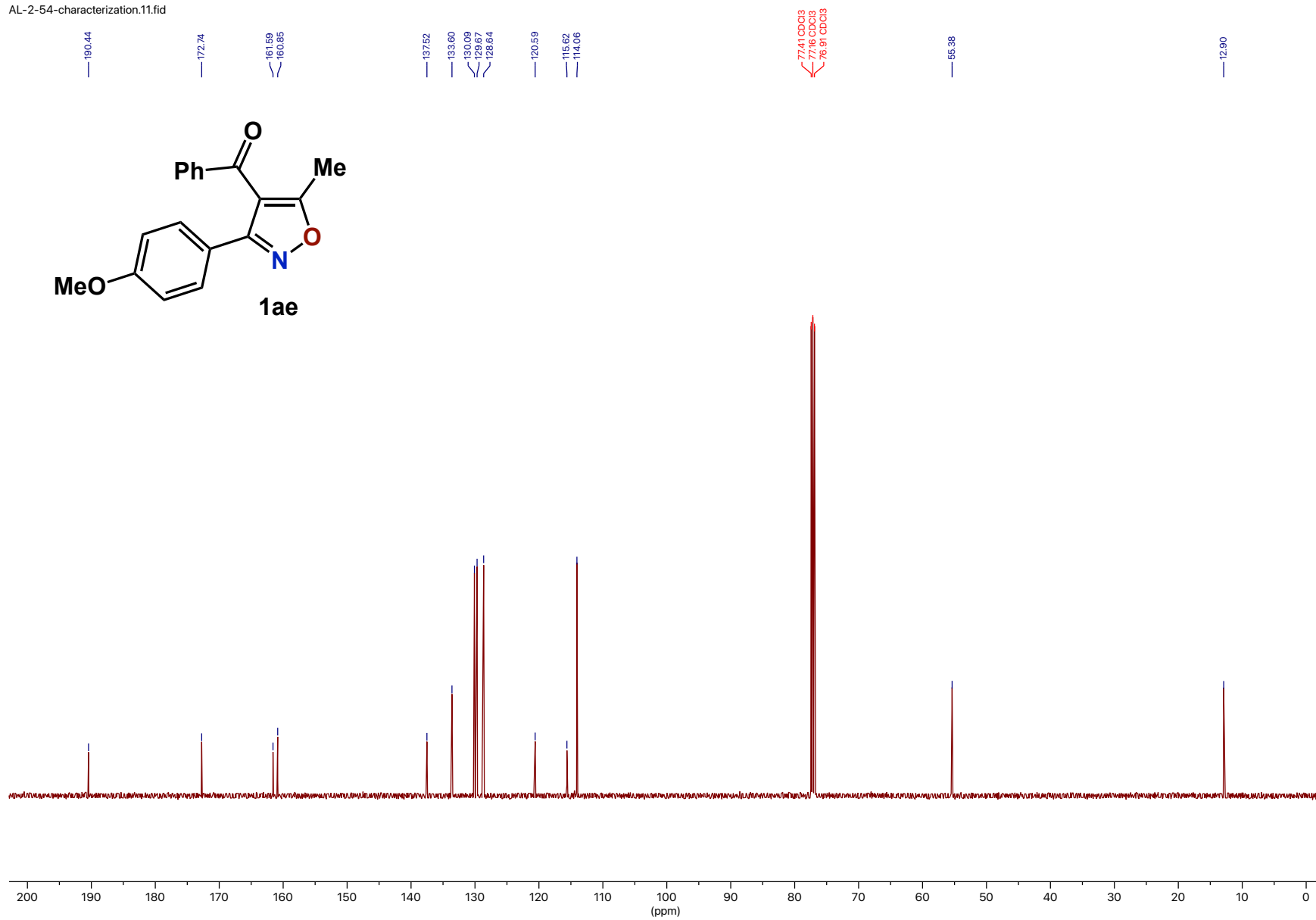
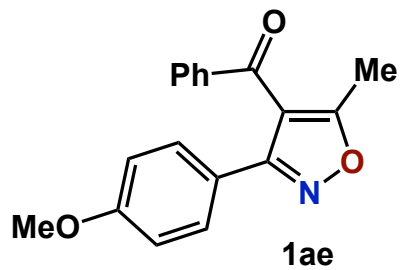


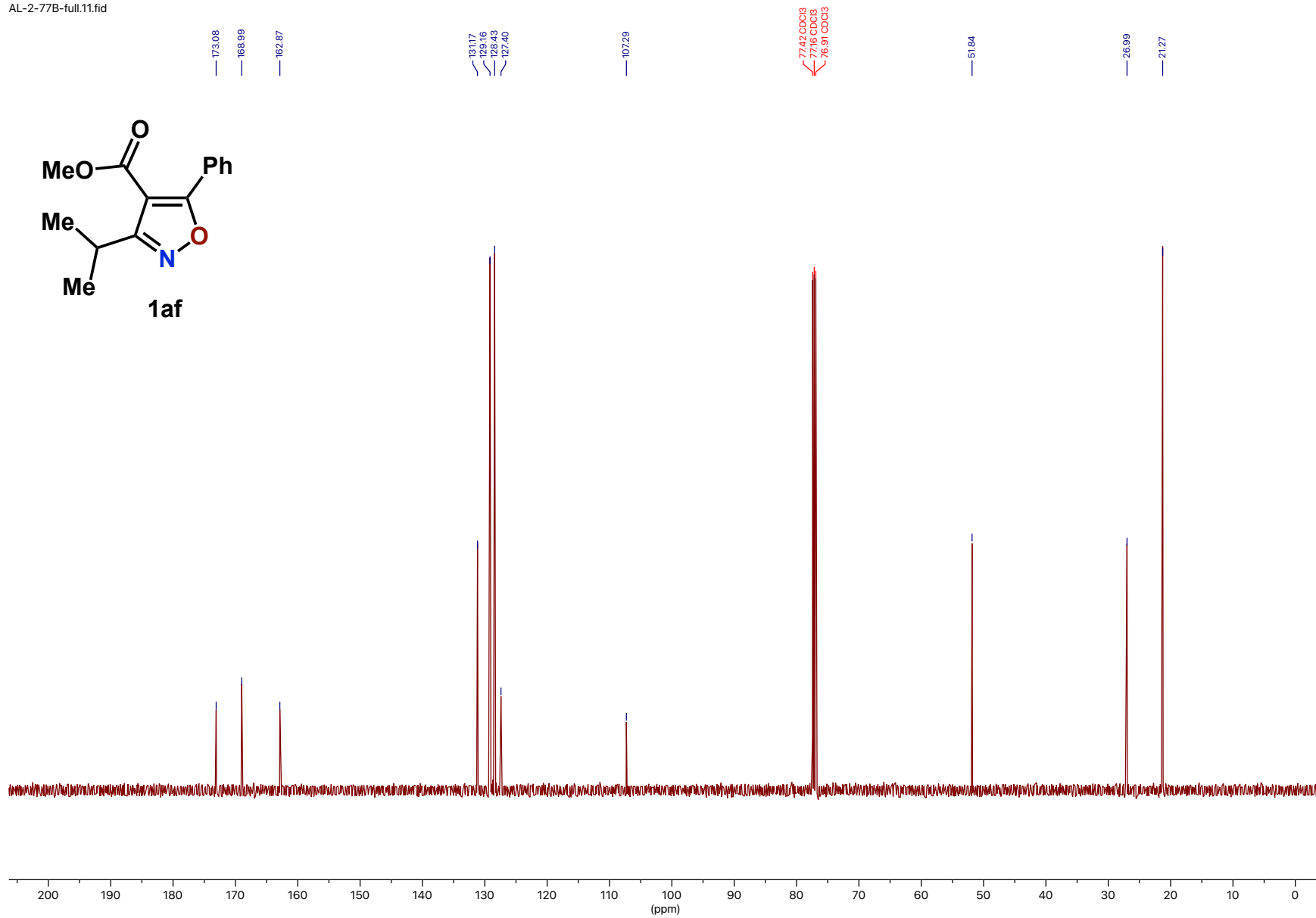


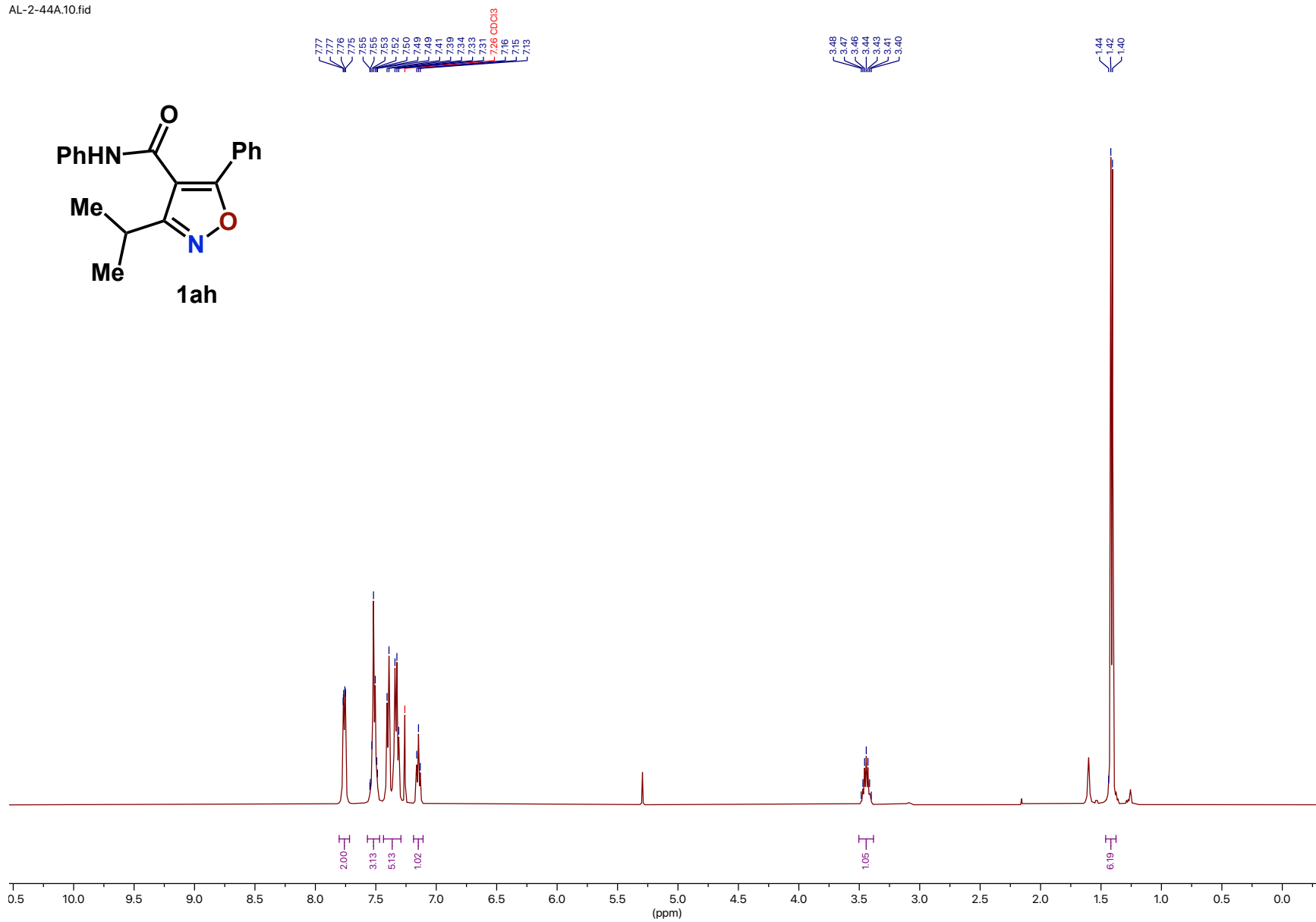
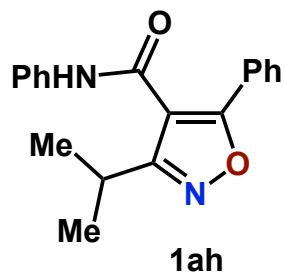




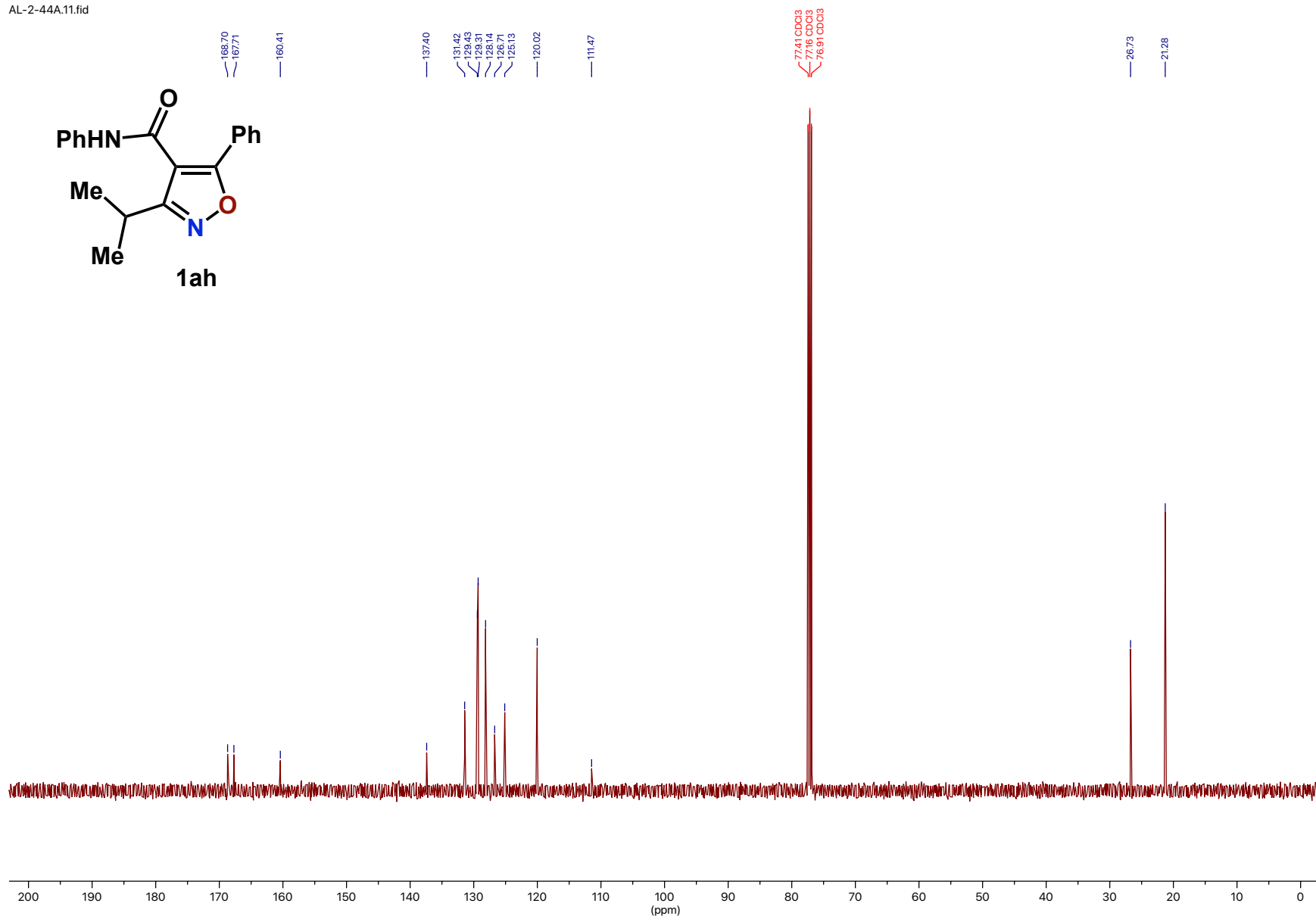
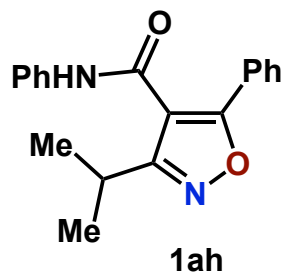








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7.26 CDCl₃

