Overcoming Limitations in Decarboxylative Arylation via Ag-Ni Electrocatalysis

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Supporting Materials

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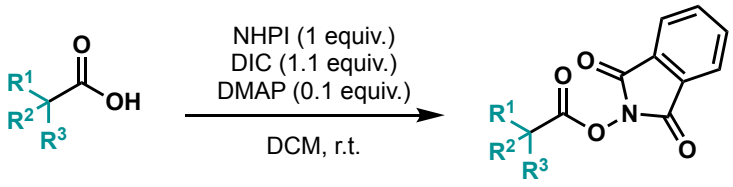
General Experimental Information

All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. All electrochemical experiments were conducted with commercially available ElectraSyn 2.0 and standard equipment unless otherwise stated. The RVC electrodes were purchased from commercial RVC block (purchased from ULTRAMET, 100 ppi, 14.40" x 13.86" x 8"). Optical rotations were recorded using an Anton Paar MCP100 polarimeter. Reagents were either purchased at the highest commercial quality and used without further purification, unless otherwise stated or donated by our industrial collaborators. Yields refer to chromatographically and spectroscopically (^{1}H NMR or LCMS) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F254), using UV light as the visualizing agent and/or p-anisaldehyde, I_2, ninhydrin, $KMnO_4$, dragendorff, DNP and heat as a developing agent. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043 – 0.063 mm). NMR spectra were recorded on Bruker DRX600, DRX-500 and AMX-400 instruments and were calibrated using residual undeuterated solvents as an internal reference (chloroform-d: ^{1}H NMR δ = 7.26 ppm, ^{13}C NMR δ = 77.16 ppm, dimethyl sulfoxide-d6: ^{1}H NMR δ = 2.50 ppm, ^{13}C NMR δ = 39.52 ppm, methanol-d4 ^{1}H NMR δ = 3.31 ppm, ^{13}C NMR δ = 49.00 ppm). The following abbreviations are used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) reflection experiments.

General Procedure 1: Synthesis of NHPI Redox Active Esters

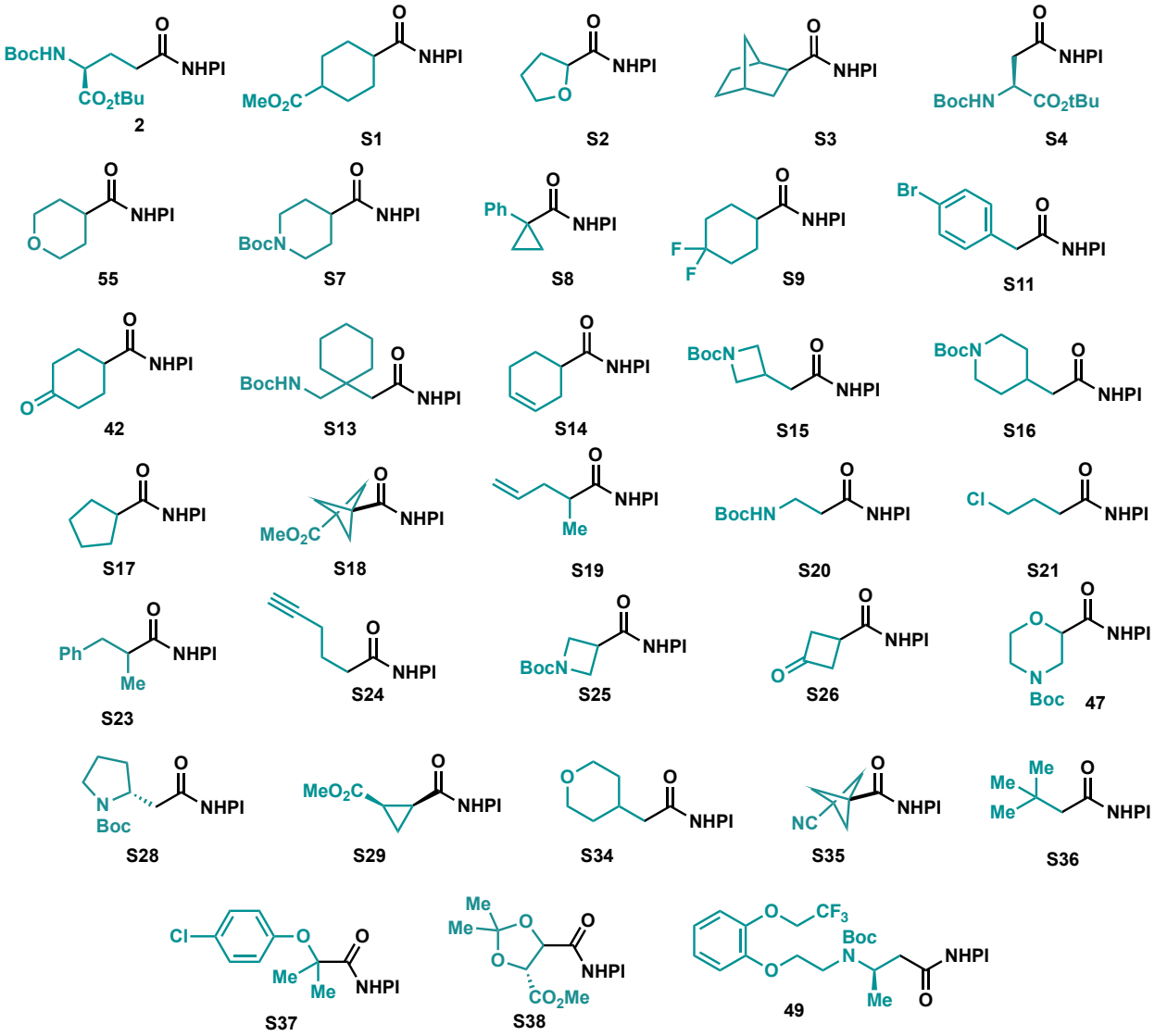


To a stirring solution of carboxylic acid (1.0 equiv.), *N*-hydroxyphthalimide (1.0 equiv.), and 4-dimethylaminopyridine (0.1 equiv.) in anhydrous DCM (0.3 M), DIC (1.1 equiv.) was added via syringe. The reaction mixture was vigorously stirred until complete (monitored by TLC, 0.5 h – 2 h). Upon completion, the mixture was concentrated and was directly purified via silica gel column chromatography to afford the activated ester.

Redox-active esters shown below **2**,[1] **S1**,[2] **S2**,[3] **S3**,[4] **S4**,[1] **43**,[5] **S7**,[6] **S8**, **S18**,[7] **S9**, **S11**,[8] **41**,[9] **S13**,[10] **S14**,[11] **S15**,[12] **S16**,[13] **S18**,[14] **S19**,[15] **S20**,[16] **S21**, **S23**,[17] **S24**, **S28**,[18] **S25**, **45**,[19] **S26**,[20] **S29**,[21] **S34**,[22] **S35**,[23] **S36**,[24] **S37**,[25] **S38**,[26] and **48**[27] have previously been reported in the literature. Please see these references for characterization. For newly reported redox active esters, HRMS failed to detect the target mass due to instability of the NHPI ester motif.

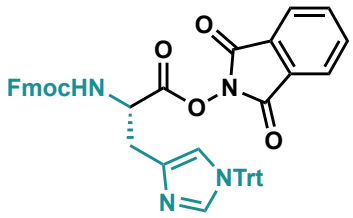
Table S1 – Known NHPI Redox Active Esters

Known NHPI-Redox Active Esters



General Supporting Information for NHPI Redox Active Esters

Compound S5



Following the General Procedure 1 with N^{α}-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-N^{t}-trityl-L-histidine (12.4 g, 20 mmol), *N*-hydroxyphthalimide (4.08 g, 25 mmol), DMAP (244 mg, 2 mmol) and DIC (3.4 mL, 22 mmol) in DCM (200 mL) at rt for 2 h afforded 12.6 g (88%) of the title compound after purification by column chromatography (hexanes to 1:1 hexanes/ethyl acetate).

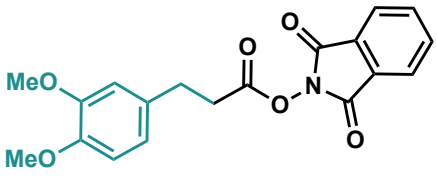
Physical State: Yellow solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85 – 7.76 (m, 3H), 7.73 (d, *J* = 7.7 Hz, 3H), 7.65 – 7.57 (m, 3H), 7.49 (s, 1H), 7.40 – 7.30 (m, 4H), 7.28 (d, *J* = 7.2 Hz, 4H), 7.25 (d, *J* = 6.5 Hz, 4H), 7.09 (d, *J* = 7.6 Hz, 7H), 6.96 (s, 1H), 5.04 (q, *J* = 6.1 Hz, 1H), 4.40 – 4.12 (m, 3H), 3.35 (qd, *J* = 14.9, 5.7 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.3, 165.3, 161.4, 156.1, 144.1, 144.0, 142.1, 141.3, 138.7, 134.9, 134.8, 133.9, 129.9, 129.8, 129.6, 129.0, 128.6, 128.4, 128.3, 128.2, 127.7, 127.2, 127.2, 125.6, 125.5, 124.1, 123.2, 121.2, 119.9, 75.9, 67.6, 53.2, 47.2, 29.9.

TLC: R_f = 0.31 (1:1 hexanes/ethyl acetate)

Compound S6



Following the General Procedure 1 with 3-(3,4-dimethoxyphenyl)propanoic acid (2.0 g, 9.5 mmol), *N*-hydroxyphthalimide (1.55 g, 9.5 mmol), DMAP (116 mg, 0.95 mmol) and DIC (1.64 mL, 10.5 mmol) in DCM (30 mL) at rt for 2 h afforded 1.82 g (54%) of the title compound after purification by column chromatography (gradient elution, hexanes to 4:1 hexanes/ethyl acetate).

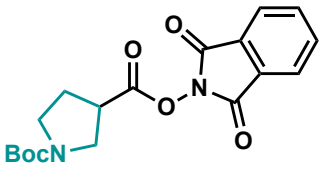
Physical State: Yellow solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.85 – 6.77 (m, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.06 (t, *J* = 7.7 Hz, 2H), 2.97 (t, *J* = 7.8 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.1, 162.0, 149.2, 147.9, 134.9, 131.9, 129.1, 124.1, 120.3, 111.7, 111.5, 56.1, 56.0, 33.2, 30.4.

TLC: R_f = 0.60 (1:1 hexanes/ethyl acetate)

Compound S10



Following the General Procedure 1 with 1-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid (2.15 g, 10 mmol), *N*-hydroxyphthalimide (1.63 g, 10 mmol), DMAP (122 mg, 1 mmol) and DIC (1.72 mL, 11 mmol) in DCM (50 mL) at rt for 2 h afforded 2.35 g (65%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

Physical State: White solid

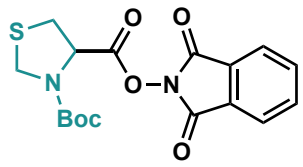
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.84 – 3.35 (m, 5H), 2.35 (s, 2H), 1.47 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): *Major Rotamer* δ 169.8, 161.9, 154.2, 135.0, 129.0, 124.2, 80.0, 48.0, 45.0, 40.8, 29.5, 29.6.

Minor Rotamer δ 169.8, 161.9, 154.2, 135.0, 129.0, 124.2, 80.0, 47.7, 45.3, 39.9, 29.5, 29.6.

TLC: R_f = 0.43 (1:1 hexanes/ethyl acetate)

Compound S12



Following the General Procedure 1 with 3-(*tert*-butoxycarbonyl)thiazolidine-4-carboxylic acid (2.00 g, 8.58 mmol), *N*-hydroxyphthalimide (1.40 g, 8.58 mmol), DMAP (105 mg, 0.86 mmol) and DIC (1.48 mL, 9.44 mmol) in DCM (40 mL) at rt for 2 h afforded 2.19 g (67%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

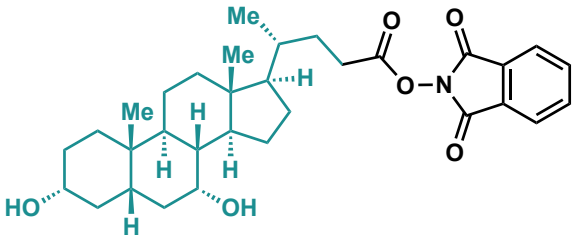
Physical State: White solid

^{1}H NMR (600 MHz, MeOD): δ 7.97 – 7.86 (m, 4H), 5.25 – 5.05 (m, 1H), 4.62 (d, *J* = 9.2 Hz, 1H), 4.58 – 4.45 (m, 1H), 3.72 – 3.53 (m, 1H), 3.46 (dd, *J* = 12.3, 3.9 Hz, 1H), 1.51 (s, 9H).

^{13}C NMR (151 MHz, MeOD): δ 169.2, 163.0, 154.5, 136.4, 130.1, 125.0, 83.5, 61.1, 50.1, 35.7, 28.3.

TLC: R_f = 0.73 (1:1 hexanes/ethyl acetate)

Compound S22



Following the General Procedure 1 with chenodeoxycholic acid (5.00 g, 12.7 mmol), *N*-hydroxyphthalimide (2.07 g, 12.7 mmol), DMAP (155 mg, 1.27 mmol) and DCC (2.89 g, 12.7 mmol) in DCM (60 mL) at rt for 6 h afforded 4.94 g (72%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

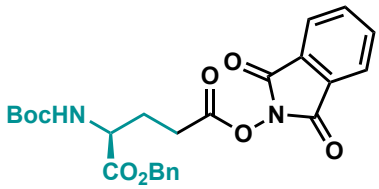
Physical State: White solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (s, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 3.85 (q, *J* = 3.1 Hz, 1H), 3.46 (ddd, *J* = 11.1, 6.7, 4.4 Hz, 1H), 2.71 (ddd, *J* = 16.0, 9.5, 5.2 Hz, 1H), 2.59 (ddd, *J* = 16.0, 9.1, 7.0 Hz, 1H), 2.21 (td, *J* = 13.0, 11.2 Hz, 1H), 2.02 – 1.88 (m, 4H), 1.88 – 1.78 (m, 2H), 1.76 – 1.44 (m, 9H), 1.43 – 1.06 (m, 9H), 1.03 – 0.94 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.91 (s, 3H), 0.69 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.2, 162.1, 134.9, 129.1, 124.1, 72.2, 68.7, 55.9, 42.9, 41.6, 40.0, 39.8, 39.6, 35.5, 35.4, 35.2, 34.7, 33.0, 30.8, 30.8, 28.3, 28.2, 23.9, 22.9, 20.7, 18.4, 11.9.

TLC: R_f = 0.62 (ethyl acetate)

Compound 39



Following the General Procedure 1 with *N*-(*tert*-Butoxycarbonyl)-L-glutamic acid 1-benzyl ester (10.0 g, 29.6 mmol), *N*-hydroxyphthalimide (4.83 g, 29.6 mmol), DMAP (361.6 mg, 2.96 mmol) and DIC (5.1 mL, 32.6 mmol) in DCM (180 mL) at rt for 2 h afforded 12.6 g (88%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

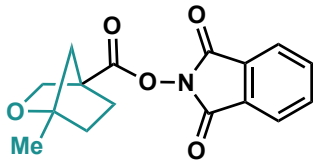
Physical State: White crystalline solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.41 – 7.31 (m, 5H), 5.22 (s, 2H), 5.20 (br s, 1H), 4.45 (s, 1H), 2.78 (ddd, *J* = 17.0, 9.5, 6.2 Hz, 1H), 2.70 (ddd, *J* = 17.0, 9.5, 5.9 Hz, 1H), 2.36 (s, 1H), 2.12 (dddd, *J* = 14.2, 9.5, 8.3, 5.9 Hz, 1H), 1.44 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7, 169.0, 161.9, 155.5, 135.2, 134.9, 129.0, 128.8, 128.7, 128.5, 124.2, 80.4, 67.6, 52.8, 28.4, 27.8, 27.5.

TLC: R_f = 0.45 (1:1 hexanes/ethyl acetate)

Compound S27



Following the General Procedure 1 with 1-methyl-2-oxabicyclo[2.2.1]heptane-4-carboxylic acid (1.5 g, 9.6 mmol), *N*-hydroxyphthalimide (1.57 g, 9.6 mmol), (117 mg, 0.96 mmol) and DIC (1.65 mL, 10.56 mmol) in DCM (50 mL) at rt for 2 h afforded 1.99 g (69%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

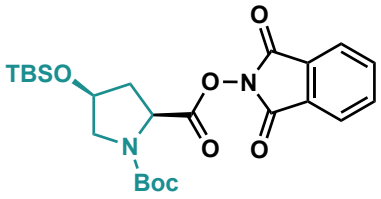
Physical State: White solid

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.3, 3.2 Hz, 2H), 7.79 (dd, *J* = 5.3, 3.2 Hz, 2H), 4.20 (dd, *J* = 6.9, 3.6 Hz, 1H), 3.96 (d, *J* = 6.9 Hz, 1H), 2.32 (tdd, *J* = 11.9, 5.8, 3.5 Hz, 1H), 2.15 (dddd, *J* = 9.5, 7.2, 5.2, 2.7 Hz, 1H), 2.12 – 2.08 (m, 1H), 2.04 (d, *J* = 9.8 Hz, 1H), 1.83 (ddd, *J* = 14.7, 8.6, 3.6 Hz, 2H), 1.46 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.24, 161.96, 134.97, 129.09, 124.17, 85.96, 74.75, 52.06, 46.42, 36.63, 33.20, 18.92.

TLC: R_f = 0.58 (1:1 ethyl acetate/hexanes)

Compound S30



Following the General Procedure 1 with (4*S*)-1-(*tert*-butoxycarbonyl)-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylic acid (100 mg, 0.29 mmol), *N*-hydroxyphthalimide (47.3 mg, 0.29 mmol), DMAP (4 mg, 0.03 mmol) and DIC (0.05 mL, 0.32 mmol) in DCM (1 mL) at rt for 2 h afforded 1.99 g (69%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

Physical State: White solid

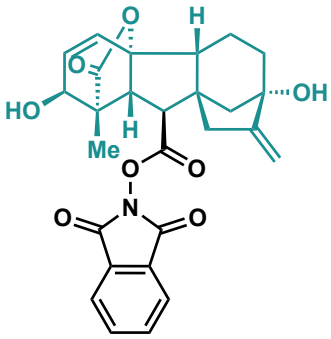
^{1}H NMR (600 MHz, $CDCl_3$): *Major Rotamer* δ 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.64 (dd, *J* = 9.2, 4.9 Hz, 1H), 4.48 – 4.36 (m, 1H), 3.70 (dd, *J* = 11.0, 5.5 Hz, 1H) 3.40 (ddd, *J* = 10.9, 4.2, 0.9 Hz, 1H) 2.58 (ddd, *J* = 12.8, 9.2, 5.3 Hz, 1H), 2.36 (dt, *J* = 13.0, 4.7 Hz, 1H), 1.50 (s, 9H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

Minor Rotamer δ 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 4.70 (dd, *J* = 9.0, 5.5 Hz, 1H), 4.48 – 4.36 (m, 1H), 3.64 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.32 (dd, *J* = 10.8, 4.7 Hz, 1H), 2.58 (ddd, *J* = 12.8, 9.2, 5.3 Hz, 1H), 2.36 (dt, *J* = 13.0, 4.7 Hz, 1H), 1.47 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.5, 161.7, 153.6, 134.8, 129.1, 124.0, 81.3, 69.8, 55.9, 54.1, 39.6, 28.2, 25.8, 18.1 -4.8, -4.9.

TLC: R_f = 0.91 (1:1 ethyl acetate/hexanes)

Compound S31



Following the General Procedure 1 with gibberellic acid (1 g, 2.88 mmol), *N*-hydroxyphthalimide (470 mg, 2.88 mmol), DMAP (35 mg, 0.29 mmol) and DCC (656 mg, 3.18 mmol) in THF (14 mL) at rt for 3 h afforded 1.06 g (72%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

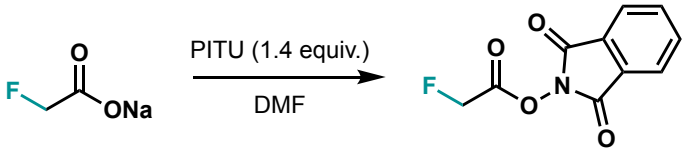
Physical State: Pale yellow solid

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.34 (d, *J* = 9.3 Hz, 1H), 5.93 (dd, *J* = 9.3, 3.7 Hz, 1H), 5.35 (s, 1H), 5.07 (s, 1H), 4.22 (dd, *J* = 6.7, 3.8 Hz, 1H), 3.30 (d, *J* = 10.9 Hz, 1H), 3.15 (d, *J* = 11.0 Hz, 1H), 2.81 (d, *J* = 15.7 Hz, 1H), 2.29 (d, *J* = 15.5 Hz, 1H), 2.14 (dd, *J* = 11.5, 7.1 Hz, 2H), 2.07 – 1.91 (m, 3H), 1.90 – 1.79 (m, 2H), 1.71 (d, *J* = 8.7 Hz, 2H), 1.42 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 178.1, 168.9, 161.9, 156.8, 135.1, 132.7, 132.7, 128.9, 124.2, 108.1, 90.4, 78.3, 69.8, 53.7, 53.5, 51.6, 50.9, 48.3, 44.7, 42.9, 38.0, 17.1, 14.5.

TLC: R_f = 0.58 (1:3 hexanes/ethyl acetate)

Compound S32



To a stirring solution of sodium 2-fluoroacetate (1.0 g, 10 mmol. 1.0 equiv.) in DMF (10 mL) was added 2-(1,3-dioxoisoindolin-2-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate (5.7 g, 14 mmol, 1.4 equiv.). The contents were allowed to stir until complete (measure by TLC). Upon completion, the reaction mixture was diluted in ethyl acetate. The organic material was washed with water (3 x 20 mL) followed by brine (20 ml). The organics were dried over magnesium sulfate, filtered and concentrated to afford a pale yellow paste. The residue was purified via column chromatography (hexanes to 1:1 hexanes/ethyl acetate) to afford **S32** as a white solid (1.23 g, 55% yield). *Note*: this compound was stored in a refrigerator to prevent decomposition.

Physical State: White solid

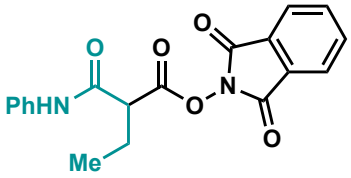
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (dd, J = 5.5, 3.1 Hz, 2H), 7.82 (dd, J = 5.5, 3.1 Hz, 2H), 5.28 (d, J_{HF} = 46.3 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 164.39 (d, J_{CF} = 22.9 Hz), 161.47, 135.23, 128.86, 124.40, 76.08 (d, J_{CF} = 186.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -236.73.

TLC: R_f = 0.28 (1:1 hexanes/ethyl acetate)

Compound S33



Following the General Procedure 1 with 2-(phenylcarbamoyl)butanoic acid (2.07 g, 10 mmol), *N*-hydroxyphthalimide (1.63 g, 10 mmol), DMAP (122 mg, 1 mmol) and DIC (1.7 mL, 11 mmol) in DCM (40 mL) at rt for 3 h afforded 321 mg (91%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

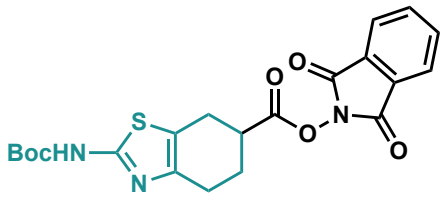
Physical State: White solid

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (br, 1H), 7.93 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.83 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.39 – 7.31 (m, 2H), 7.15 (tt, *J* = 7.3, 1.2 Hz, 1H), 3.73 (dd, *J* = 8.6, 5.8 Hz, 1H), 2.35 – 2.14 (m, 2H), 1.18 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.46, 164.05, 161.99, 137.51, 135.30, 129.19, 128.91, 125.10, 124.46, 120.62, 52.65, 24.30, 11.79.

TLC: R_f = 0.44 (1:1 hexanes/ethyl acetate)

Compound 52



Following the General Procedure 1 with 2-((*tert*-butoxycarbonyl)amino)-4,5,6,7-tetrahydrobenzo[*d*]thiazole-6-carboxylic acid (450 mg, 1.51 mmol), *N*-hydroxyphthalimide (242.3 mg, 1.51 mmol), DMAP (18.5 mg, 0.15 mmol) and DCC (342.4 mg, 1.66 mmol) in THF (6 mL) at rt for 3 h afforded 342 mg (inseparable 5:1 mixture of **52** and DCC-urea byproduct, 46% yield of desired compound, 91 wt/wt%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). This compound was used in the subsequent step without further purification.

Physical State: White solid

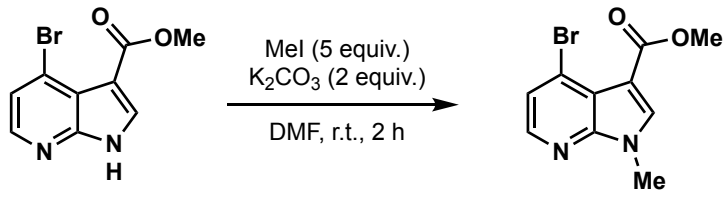
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.26 – 3.05 (m, 3H), 2.96 (dt, *J* = 16.8, 4.7 Hz, 1H), 2.79 (ddd, *J* = 16.8, 10.0, 5.6 Hz, 1H), 2.45 (dq, *J* = 9.8, 3.2 Hz, 1H), 2.15 (tdd, *J* = 10.6, 8.3, 5.2 Hz, 1H), 1.54 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.0, 162.0, 159.2, 152.6, 143.5, 135.0, 129.1, 124.2, 118.8, 82.7, 38.0, 28.4, 25.4, 25.1.

TLC: R_f = 0.26 (1:1 hexanes/ethyl acetate)

Synthesis of Other Starting Materials

Compound 56



To a stirring solution of methyl 4-bromo-1*H*-pyrrolo[2,3-*b*]pyridine-3-carboxylate (1.00 g, 3.92 mmol, 1.0 equiv.) and potassium carbonate (1.08 g, 7.84 mmol, 2.0 equiv.) in DMF (10 mL) was added methyl iodide (1.22 mL, 19.60 mmol, 5.0 equiv.). The resulting suspension was allowed to stir vigorously at room temperature for 3 hours. Upon completion (monitored by LCMS), the reaction mixture was diluted with water (10 mL). The organic material was extracted (3 x 20 mL) with ethyl acetate. The combined organic material was washed with brine, dried over Mg_2SO_4 and concentrated to afford an orange residue. The crude material was purified via silica gel column chromatography (25 – 50% ethyl acetate/hexanes) to afford **56** as a light orange solid (713 mg, 68% yield).

Physical State: Light orange solid

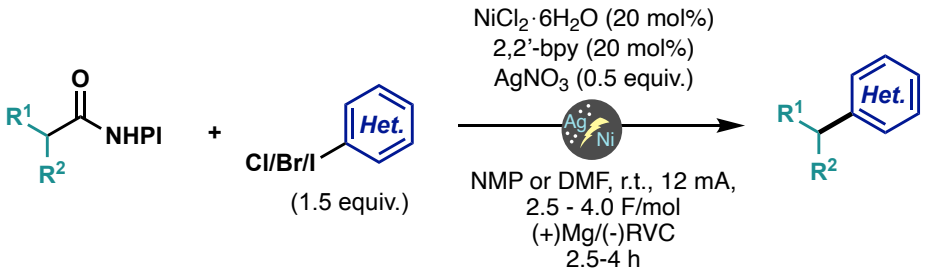
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (d, *J* = 5.1 Hz, 1H), 7.98 (s, 1H), 7.45 (d, *J* = 5.1 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.7, 148.9, 143.8, 136.9, 125.6, 123.5, 118.9, 106.3, 51.5, 32.3.

HRMS (ESI-TOF): calculated for $C_{10}H_9BrN_2O_2$ $[M+H]^+$: 268.9926, found: 268. 9931.

TLC: R_f = 0.56 (1:1 ethyl acetate/hexanes)

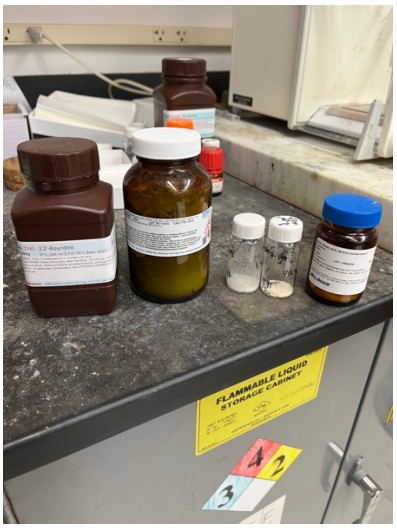
General Procedure 2: Ag-Ni Electrocatalytic Decarboxylative Arylation (0.4 mmol scale)

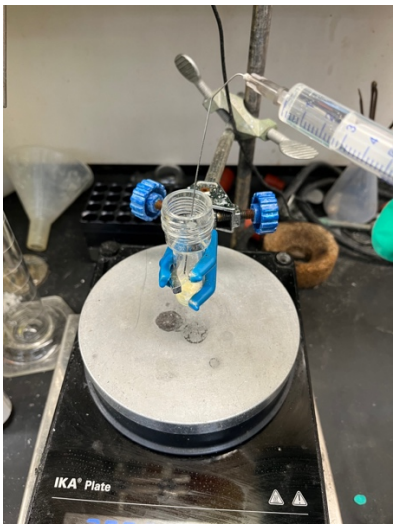


To an oven dried 5 mL ElectraSyn 2.0 vial, redox active ester (RAE) (0.4 mmol, 1 equiv.), aryl halide (0.6 mmol, 1.5 equiv.), $NiCl_2 \cdot 6H_2O$ (19.0 mg, 0.08 mmol, 0.2 equiv.), and 2,2′-bypridine (12.5 mg, 0.08 mmol, 0.2 equiv.) were all directly added as solids/oils. Anhydrous NMP or DMF was then added (3 mL) via syringe. The contents of the vial were allowed to stir until all solids were dissolved (roughly 10 minutes. See picture below). $AgNO_3$ (34.0 mg, 0.20 mmol, 0.5 equiv.) was then added to the reaction mixture directly as a solid. The vial was closed with an ElectraSyn 2.0 vial cap with a magnesium sacrificial anode and a 100 ppi RVC cathode (3 mm x 7 mm x 51 mm). The vial was then placed on an IKA ElectraSyn 2.0 stir plate and electrolysis was set to 12 mA, 0.4 mmol, 2.5 to 4.0 F/mol providing 5.4 A/m2 current density. The reaction underwent the programmed electrolysis open to air. After completion of the reaction, the reaction was transferred to a separatory funnel, the electrodes were rinsed with ethyl acetate (5 mL) and sat'd. aq. $NaHCO_3$ (10 mL) (note: water can be used instead if substrate is sensitive) was *slowly* added. The aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organics were washed successively with distilled water (2 X 10 mL) then brine (1 X 10 mL), then dried over magnesium sulfate before being filtered and concentrated via rotary evaporation. The crude oily solid was purified *via* silica gel chromatography to afford the desired product.

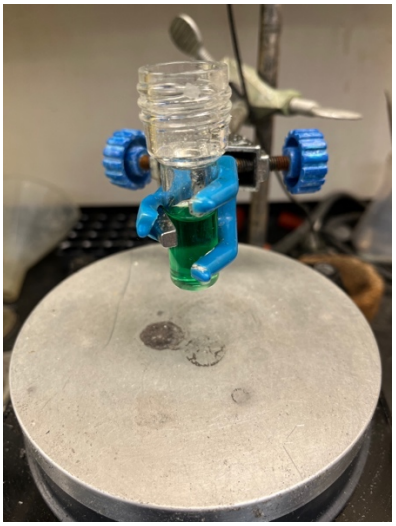
Note: It is important to start the reaction immediately after the addition of $AgNO_3$. If the $AgNO_3$ sits too long before the electrolysis begins, the yield will be diminished.

Visual Guide for General Procedure 2

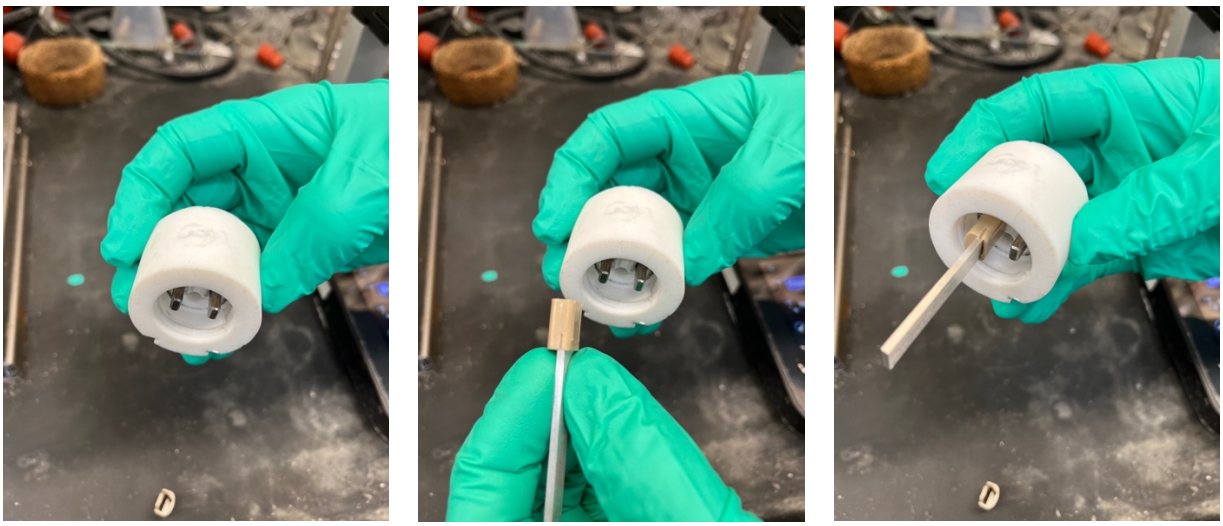


Left: Reagents for the Ag-Ni Electrocatalytic DCC. **Center:** Nickel, ligand, arene and RAE weighed out in an Electrasyn 2.0 vial. **Right:** Addition of NMP to the Electrasyn 2.0 vial.

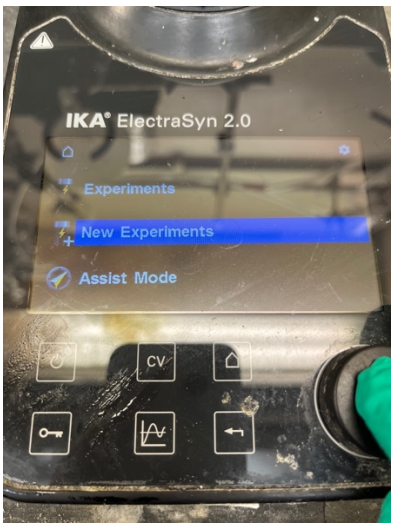


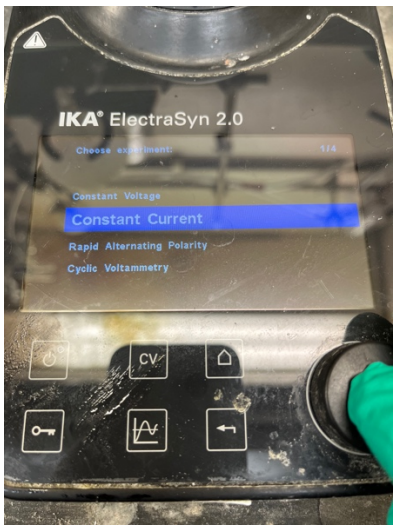
Left: Solution of nickel, ligand, RAE and arene after stirring for 10 minutes. **Center:** (optional) removal of the screwcap on the Electrasyn 2.0 **Right:** (optional) removed screwcap on the Electrasyn 2.0 vial.

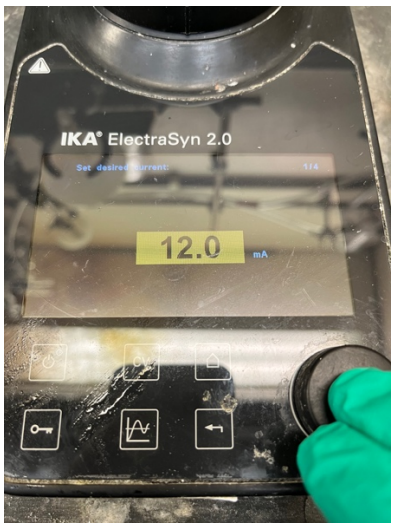


Left: Electrasyn 2.0 Cap without electrodes. **Center:** Insertion of the Mg anode on the left side of the cap. **Right:** Attached Mg electrode.

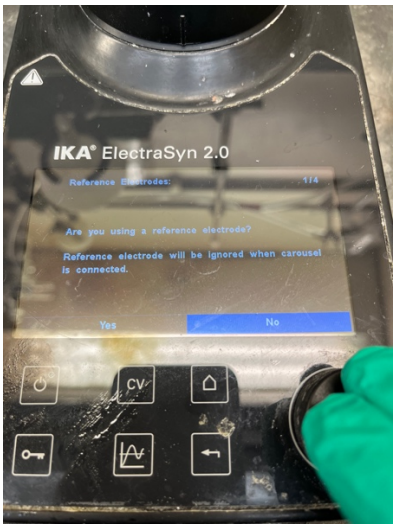
Left: Assembly of the RVC electrode. **Center:** Insertion RVC electrode into the beige clip. **Right:** Attached RVC electrode on the right of the cap.

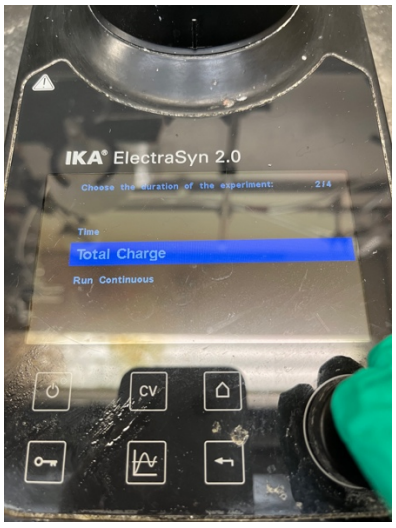


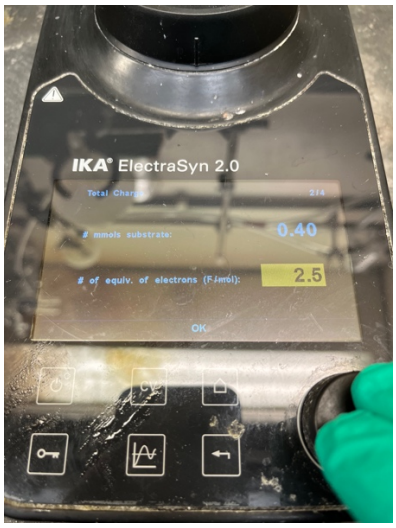




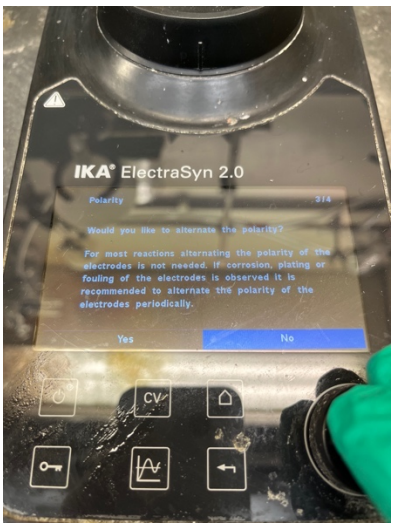
Left: Select “New Experiments”. **Center:** Select “Constant Current”. **Right:** Set the current to 12 mA

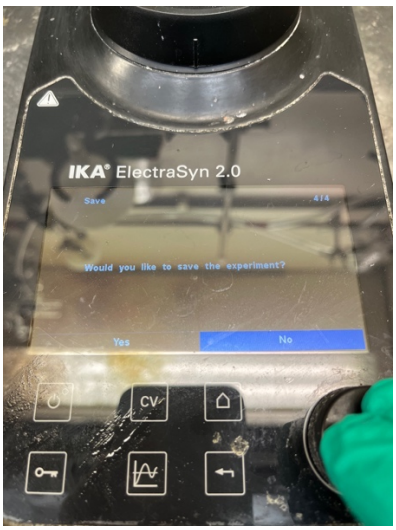




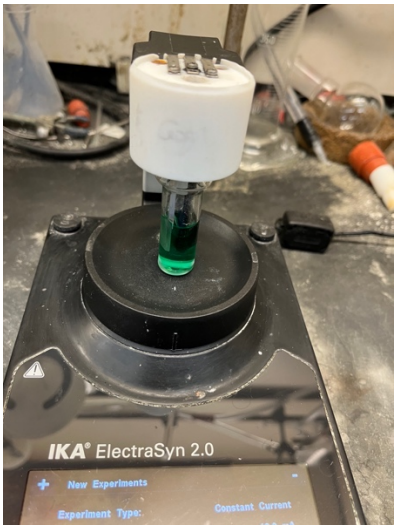


Left: Select “No” when prompted about a reference electrode. **Center:** Select “Total Charge”. **Right:** Set the scale to 0.4 mmol and the “equivalents of electrons” to 2.5 F/mol

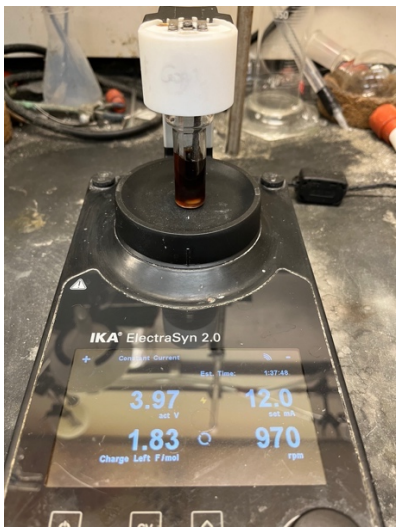




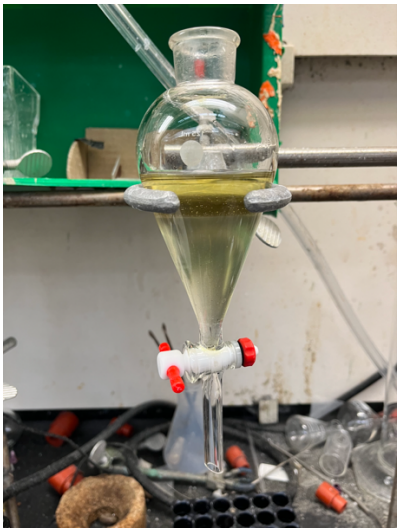
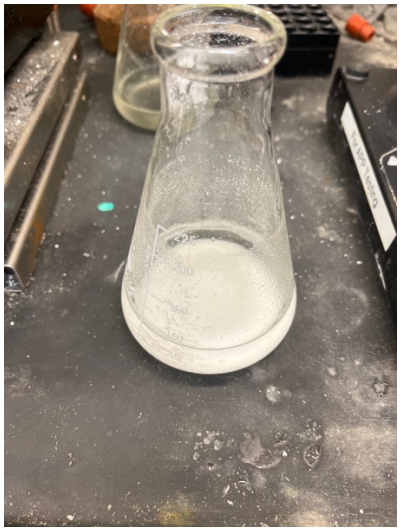
Left: Select “No” when prompted about alternating polarity. **Center:** Select “No” when asked to save experiment. **Right:** Addition of silver nitrate to the homogenous reaction solution.

Left: Attachment of the cap to the Electrasyn 2.0 vial. **Center:** Attached vial to the Electrasyn 2.0. **Right:** Start of the reaction.

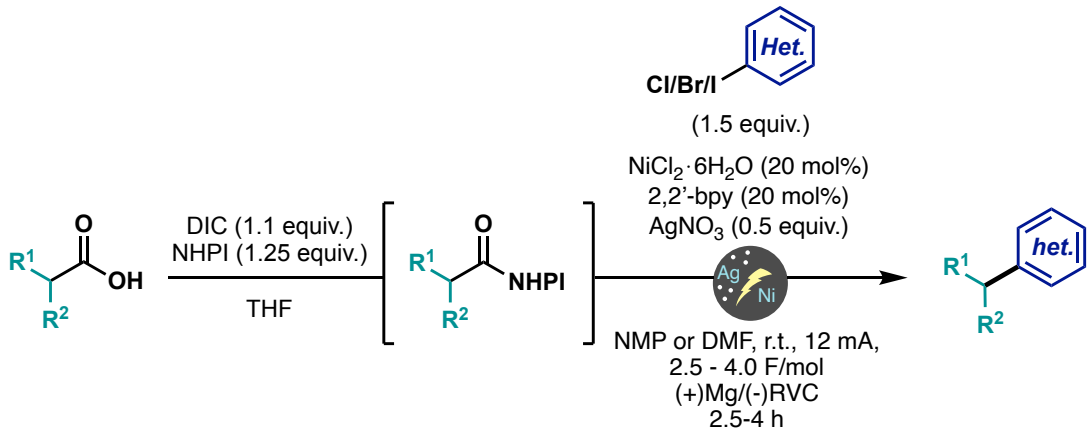


Left: Heterogenous suspension observed at the start of the reaction. **Center:** Return to homogeneity after 0.5 F/mol has passed. **Right:** Reaction mixture after the first 0.5 F/mol

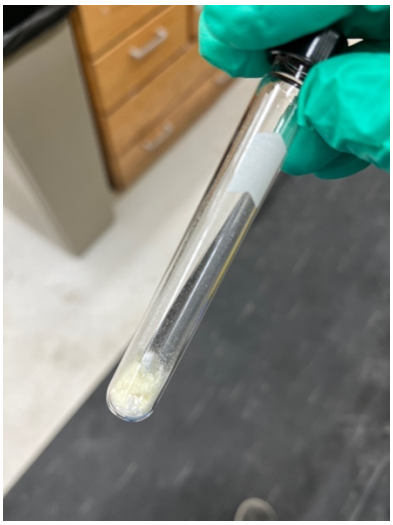
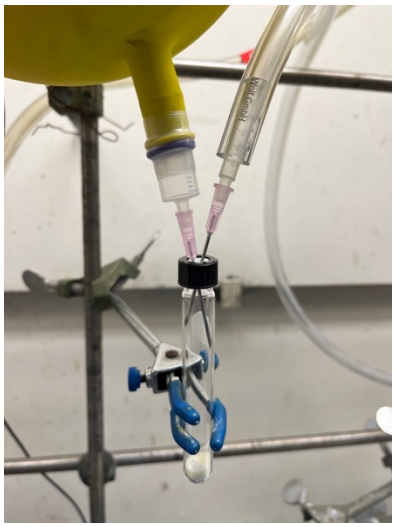
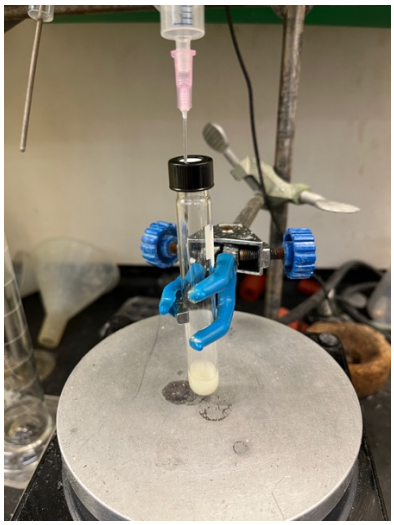
Left: Reaction mixture upon completion. **Center:** Crude reaction mixture partitioned between ethyl acetate in sat'd sodium bicarbonate. **Right:** Combined organic fractions dried over magnesium sulfate.

General Procedure 3: In Situ Ag-Ni Electrocatalytic Decarboxylative Arylation (0.4 mmol scale)

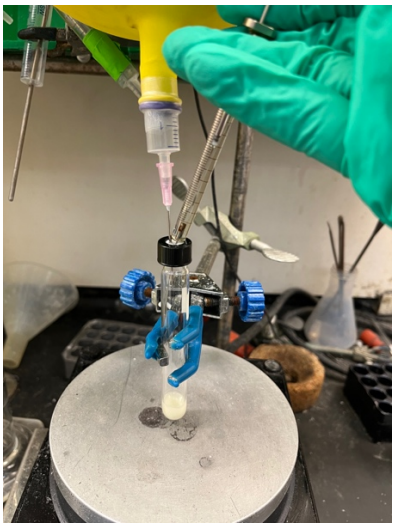
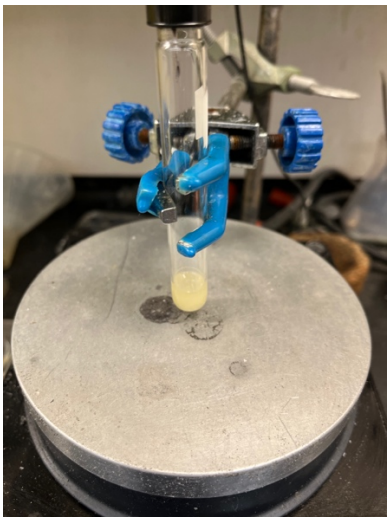
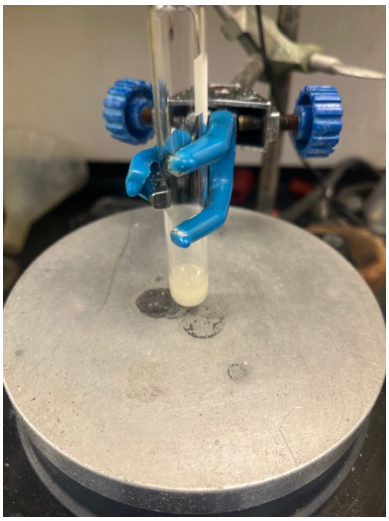


An oven-dried culture tube equipped with stir bar was charged with carboxylic acid (0.4 mmol, 1 equiv.) and N-hydroxyphthalimide (NHPI) (81.6 mg, 0.50 mmol, 1.25 equiv.). The tube was sealed and purged with argon. The contents of the flask were diluted in anhydrous inhibitor-free THF (0.50 mL). To this solution, DIC (69 µL, 0.44 mmol, 1.1 equiv.) was added and the reaction was allowed to stir at room temperature until complete formation of redox active ester (1-3 hours, by TLC) and a white solid was observed. To a separate culture tube containing a stir bar was added $NiCl_2 \cdot 6H_2O$ (19 mg, 0.08 mmol, 0.2 equiv.), 2,2'-bipyridine (12.5 mg, 0.08 mmol, 0.20 equiv.) and aryl halide (0.6 mmol, 1.5 equiv.). This tube was evacuated and backfilled three times with argon before the addition of anhydrous NMP or DMF (2.5 mL). This solution was allowed to stir for 20 minutes and a homogeneous, dark green solution developed. This green solution was transferred via syringe into the flask containing the in situ activated ester (white suspension). This green suspension (~ 3 mL) was added to a 5 mL ElectraSyn 2.0 vial under argon containing a magnesium anode, 100 ppi RVC cathode (3 mm x 7 mm x 51 mm), $AgNO_3$ (34 mg, 0.2 mmol, 0.5 equiv.) and stir bar. After addition electrolysis was immediately started. The electrochemical reaction was performed using an ElectraSyn 2.0 constant current conditions with the settings as follows: 12 mA, 0.4 mmol, 2.5 to 4.0 F/mol providing 5.4 A/m^2 current density. After completion of the reaction, the reaction was transferred to a separatory funnel, the electrodes were rinsed with ethyl acetate (5 mL) and water (10 mL) was slowly added. The aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organics were washed successively with distilled water (2 X 10 mL) then brine (1 X 10 mL), then dried over magnesium sulfate before being filtered and concentrated via rotary evaporation. The crude oily solid was purified silica gel chromatography.

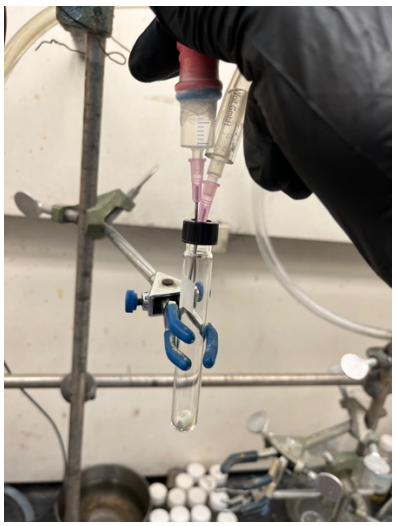
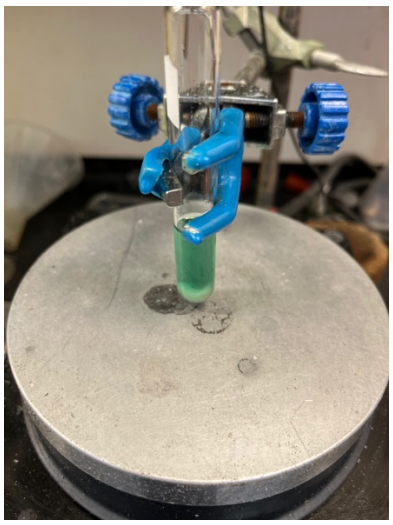
Visual Guide

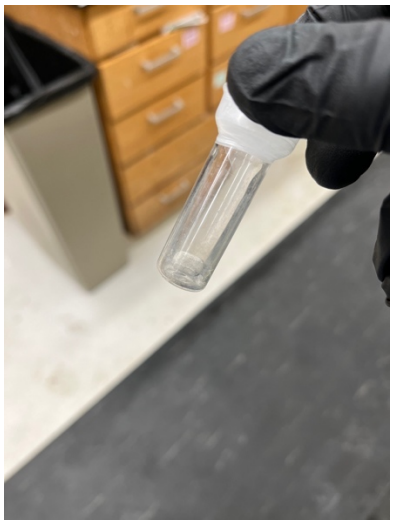
Left: Carboxylic acid and NHPI weighed in a culture tube equipped with stir bar. **Center:** Vacuum and argon purging cycles . **Right:** Carboxylic acid and NHPI dissolved in THF.

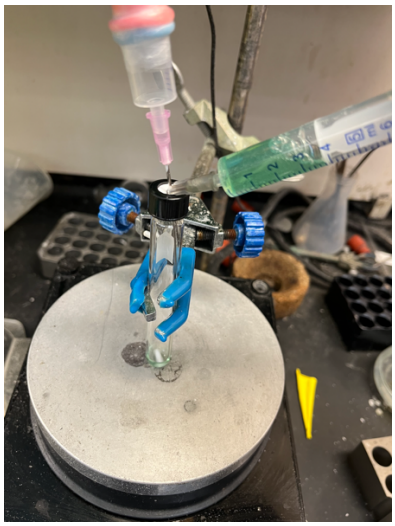




Left: Addition of DIC to the reaction mixture. **Center:** In situ activation after 2 minutes (yellow). **Right:** In situ activation after 1 hour (heterogenous white).

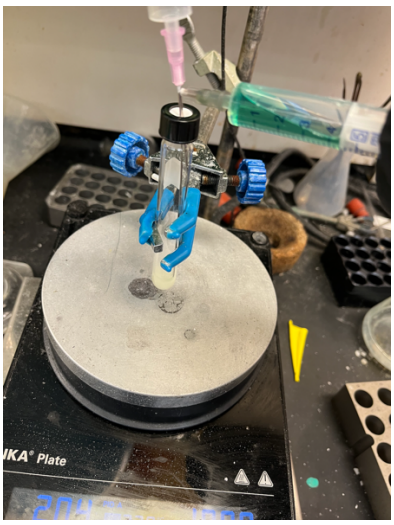




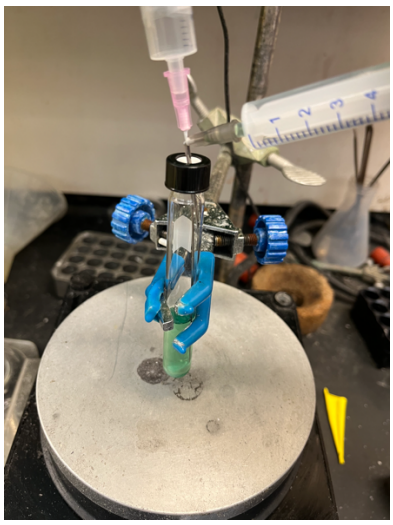
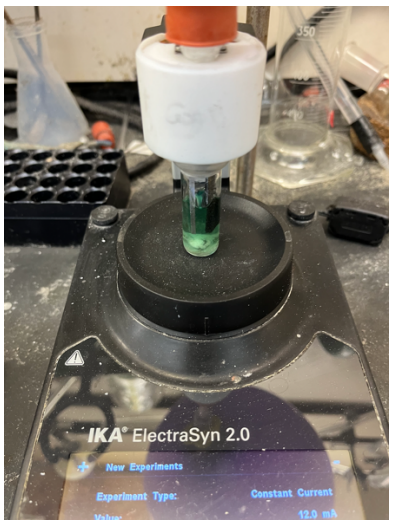
Left: Nickel, ligand and aryl halide weighed out in a culture tube. **Center:** Vacuum and argon purging of the reagents for catalyst solution. **Right:** Catalyst solution stirring in NMP



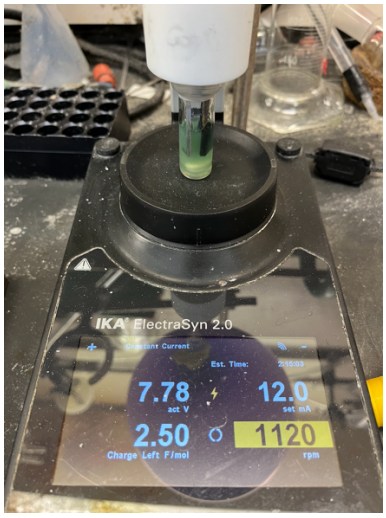


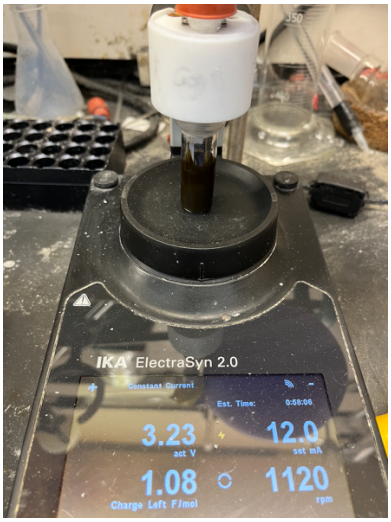
Left: Silver nitrate weighed out in a 5 mL Electrasyn vial. **Center:** Vacuum and purging of the Electrasyn vial with argon. **Right:** Transfer of of the catalyst solution via syringe to the in situ RAE synthesis.

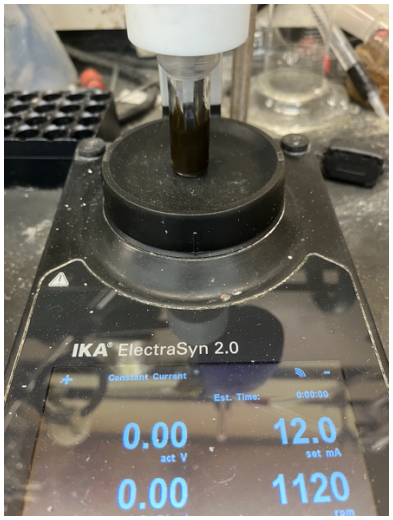


Left: Addition of the catalyst solution to the in situ RAE synthesis. **Center:** Combined catalyst and RAE solutions. **Right:** Combined solution added to the Electrasyn vial with silver before electrolysis.



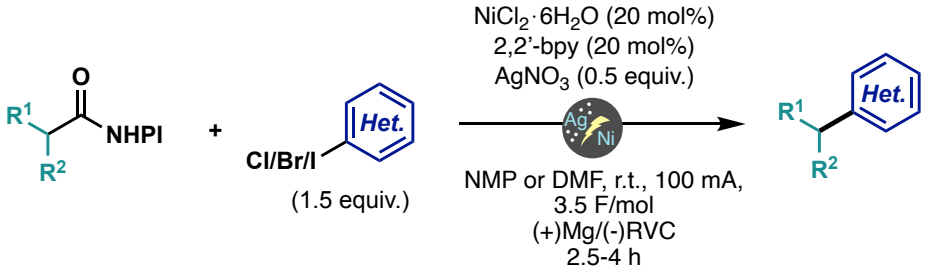




Left: Reaction mixture at the start of the electrolysis. **Center:** Reaction mixture halfway through electrolysis. **Right:** Reaction mixture at the end of electrolysis.

See visual guide for Procedure 2 for work up

General Procedure 4: Ag-Ni Electrocatalytic Decarboxylative Arylation (5 mmol scale)



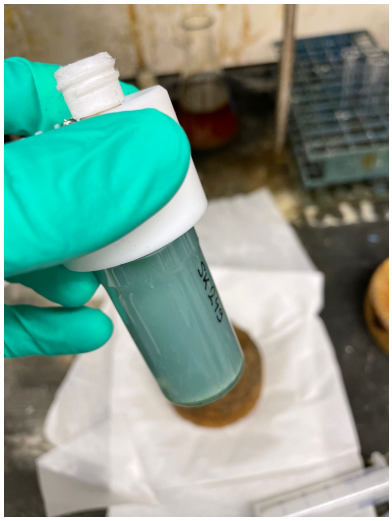
To an oven dried 20 mL ElectraSyn 2.0 vial, redox active ester (RAE) (5 mmol, 1 equiv.), aryl halide (7.5 mmol, 1.5 equiv.), $NiCl_2 \cdot 6H_2O$ (237.8 mg, 1.0 mmol, 0.2 equiv.), and 2,2′-bypridine (156 mg, 1 mmol, 0.2 equiv.) were all directly added as solids/oils. Anhydrous NMP or DMF was then added (18 mL) via syringe. The contents of the vial were allowed to stir until all solids were dissolved (roughly 10 minutes. See picture below). $AgNO_3$ (424 mg, 2.5 mmol, 0.5 equiv.) was then added to the reaction mixture directly as a solid. The vial was equipped with an ElectraSyn 2.0 vial cap with a magnesium sacrificial anode and a cylindrical 100 ppi RVC cathode (9 mm diameter, 40 mm length). The RVC electrode was prepared following a literature procedure.[28] The vial was then placed on an IKA ElectraSyn 2.0 stir plate and electrolysis was set to 100 mA, 5.0 mmol, 3.5 F/mol providing 10.6 A/m^2 current density. The reaction underwent the programmed electrolysis open to air. After completion of the reaction, the reaction was transferred to a separatory funnel, the electrodes were rinsed with ethyl acetate (30 mL) and saturated. aq. $NaHCO_3$ (20 mL) (note: water can be used instead if substrate is sensitive) was *slowly* added. The aqueous layer was extracted with ethyl acetate (3 X 20 mL). The combined organics were washed successively with distilled water (2 X 20 mL) then brine (1 X 20 mL), then dried over magnesium sulfate before being filtered and concentrated via rotary evaporation. The crude oily solid was purified *via* silica gel chromatography to afford the desired product.

Visual Guide



Left: 20 mL Electrasyn Cap with magnesium sacrificial electrode and large RVC electrode with IKA trident. **Center:** Electrodes secured on the 20 mL IKA Electrasyn cap. **Right:** RAE, aryl halide, nickel catalyst and ligand weighed into the vial.

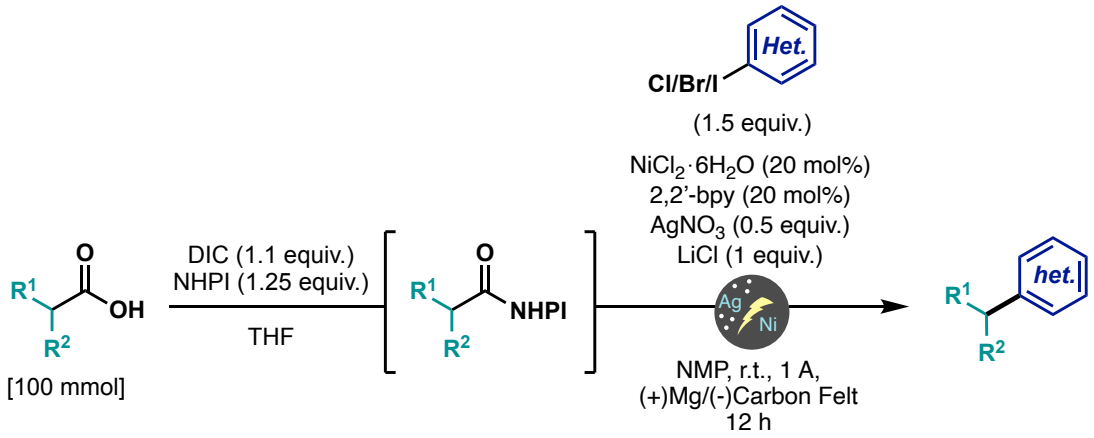




Left: Addition of NMP to the reaction mixture. **Center:** Reaction mixture dissolved in NMP. **Right:** Reaction mixture after the addition of silver nitrate.

Left: Reaction mixture at the outset of electrolysis. **Center:** Reaction mixture after 0.5 F/mol. **Right:** Reaction mixture at the end of electrolysis.

General Procedure 5: Ag-Ni Electrocatalytic Decarboxylative Arylation in Recirculating Flow (100 mmol)



Making the flow cell components

Except for the magnesium and carbon felt electrodes, all flow cell components were custom built using accessible materials and according to the cut diagrams listed in a separate document. The magnesium anode (1mm, AZ31, Amazon) was hand-cut using a small straight-edge blade to be 8.0 cm wide by 20.0c m long. A 1.5 x 5.0 cm notch was cut into the left and ride sides of the top of the magnesium electrode to create a tab for wire connections and to easily slide the electrode between the screw holes of the rest of the flow assembly. Immediately prior to assembling the reactor, the magnesium anode surface was cleaned using 3M HCl, scrubbed with a sponge, and rinsed with water followed by acetone. The carbon felt cathode (3 mm, PAN Polyacrylonitrile, CERA Materials) was cut to 8.0 x 15.0 cm with scissors.

Flow Reactor Assembly

The flow cell was assembled by first laying the front plate flat with bolts (8 x M8-1.25 x 120 mm, stainless steel, Amazon) inserted and protruding upward. Gaskets, electrodes, flow cell and faceplate were all added according to the additional supplementary files and initially secured loosely with nuts. To prevent leaking, Teflon tape was added to each bolt, prior to tightening with a 7/32nd size Allen key. A Peristaltic pump (Part No. VSH-A603150R, ANKO®) equipped with Norprene® tubing (I.D. 9.5 mm, Part No. T63-N1R50, ANKO®) was installed and secured onto the flow cell inlet using adapters. To ensure a proper hold, additional tubing was added at the inlet and outlet of the flow cell. The flow cell outlet tubing (I.D. 9.5 mm, vinyl) was connected in a similar fashion. Two polypropylene tubes (O.D 9.5 mm) were inserted into the opposite ends of

the Norprene® and vinyl tubing, through two rubber septa and capped onto the reaction vessel. All tubing connections were secured with plastic hose clamps where possible.

A 3-neck round bottom flask was used as the recirculator vessel. The third neck of the round bottom flask was capped with a stopper. The power supply (Model No. KA3005D, KORAD®) was attached to each of the electrodes via Alligator clips; red to the magnesium anode (+) and black to the stainless-steel support (carbon felt cathode (-)). Prior to running the reactor with substrate, leak tests were performed at varying flow rates. Leaking was prevented by strongly hand-tightening the bolts and adding Teflon tape where possible. The assembled flow system was rinsed with = N-methyl-2-pyrrolidinone.

Running the Reaction

An oven-dried round bottom flask equipped with stir bar was charged with carboxylic acid (100 mmol, 1 equiv.) and N-hydroxyphthalimide (NHPI) (20.4 g, 125 mmol, 1.25 equiv.). The contents of the flask were diluted in anhydrous inhibitor-free THF (125 mL). To this solution, DIC (17 mL, 110 mmol, 1.1 equiv.) was added dropwise and the reaction was allowed to stir at room temperature until complete formation of redox active ester (3 hours, by TLC).

To the three-necked round bottom flask employed for the flow reservoir $NiCl_2 \cdot 6H_2O$ (4.75 g, 20 mmol, 0.2 equiv.), 2,2'-bipyridine (3.12 g, 20 mmol, 0.20 equiv.), lithium chloride (4.24 g, 100mmol, 1 equiv.), aryl halide (150 mmol, 1.5 equiv.) and NMP (625 mL) were added. This solution was allowed to stir for 20 minutes resulting in a homogeneous, dark green solution.

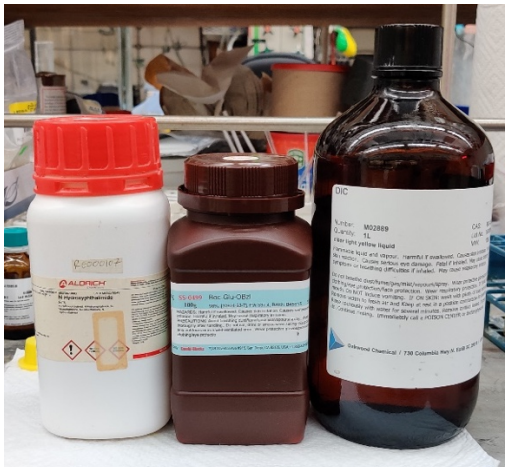
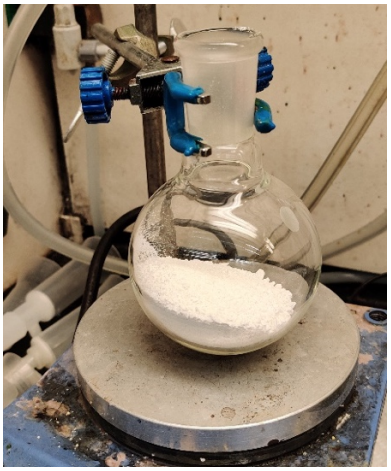
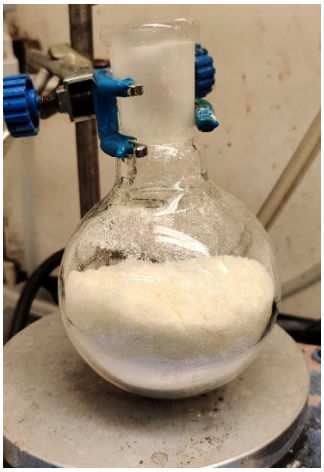
The solution containing the in situ activated ester (white suspension) was filtered directly into the flask containing the green solution while continuously stirring to remove excess insoluble urea, which was rinsed with dry THF (3 x 5 mL). Once all the filtrate was added, the round bottom flask was capped and the pump was turned on (40RPM, ~680mL/min, CCW). To the flask, silver nitrate (8.49 g, 50 mmol, 0.5 equiv.) was added.

The power source was turned on with a constant 1 A current.

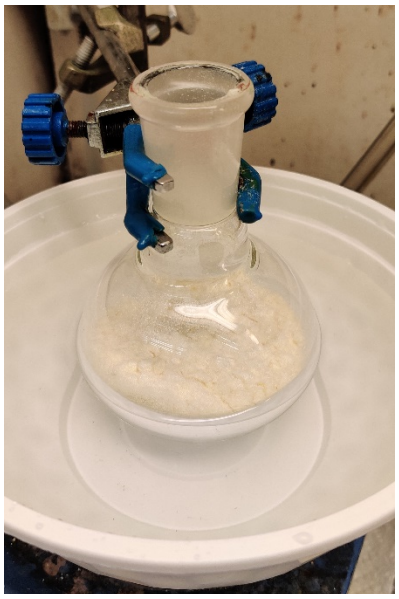
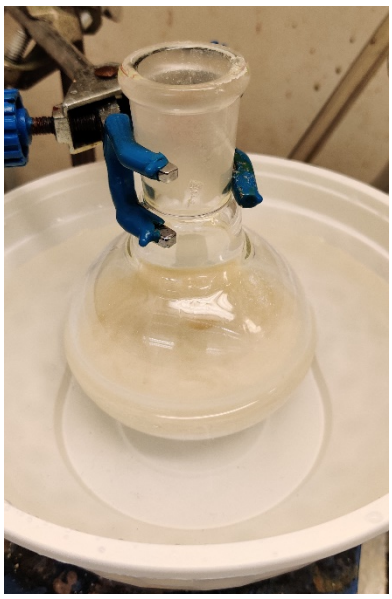
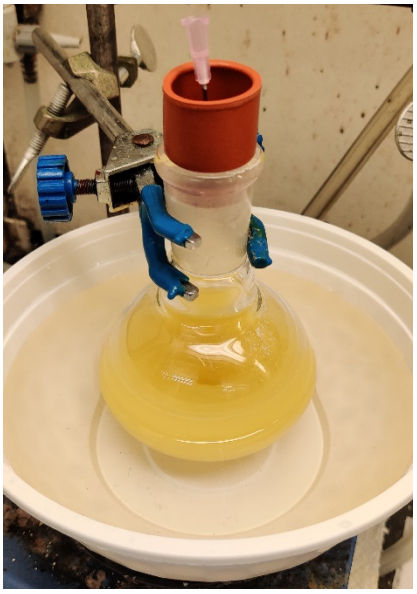
After completion of the reaction, the flow direction was reversed to ensure all liquid was removed from the cell before then removing the reaction mixture. Once removing the reaction mixture, fresh NMP was used to rinse the system before disassembling the cell. Both the consumed magnesium electrode and carbon felt were disposed. All remaining components were rinsed with acetone and left to air dry.

The reaction was divided into three equal portions and individually transferred to a 1 L separatory funnel. Water (250 mL) and diethyl ether (250 mL) were added to the funnel. The aqueous phase was extracted three times for each portion. The organic phase for all three portions were combined and concentrated to ~500 mL. The resulting solution was washed with brine (3 x 200 mL) to remove the residual NMP then dried over magnesium sulfate before being filtered and concentrated via rotary evaporation. The crude oil was purified silica gel chromatography.

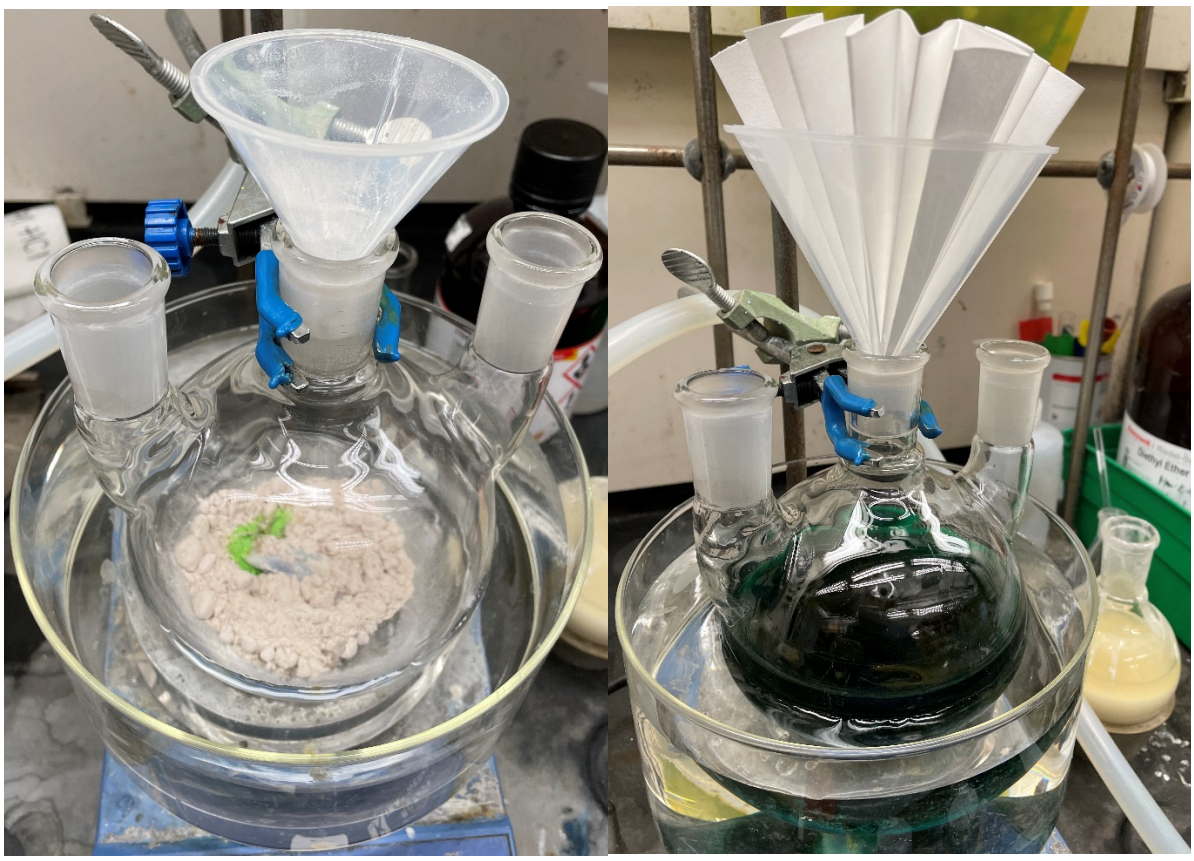
Visual Guide for Recirculating Flow Scale Up

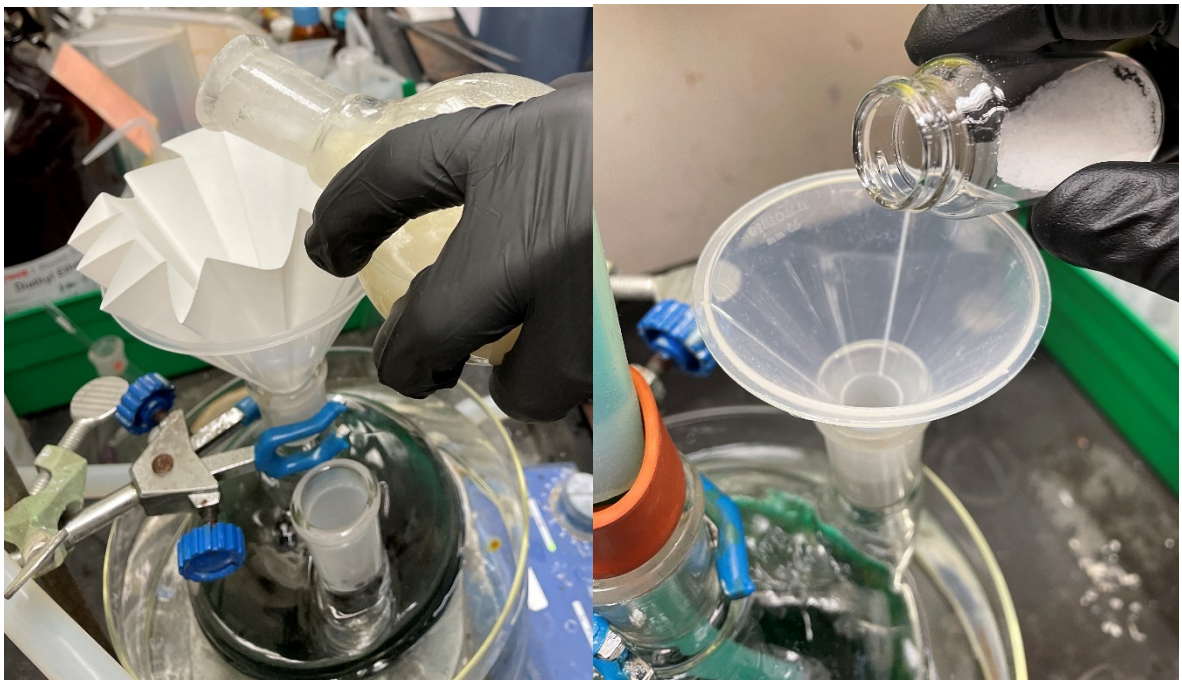
Left: Reagents for the *in situ* RAE synthesis. **Center:** Carboxylic acid added into the flask. **Right:** NHPI added into the flask

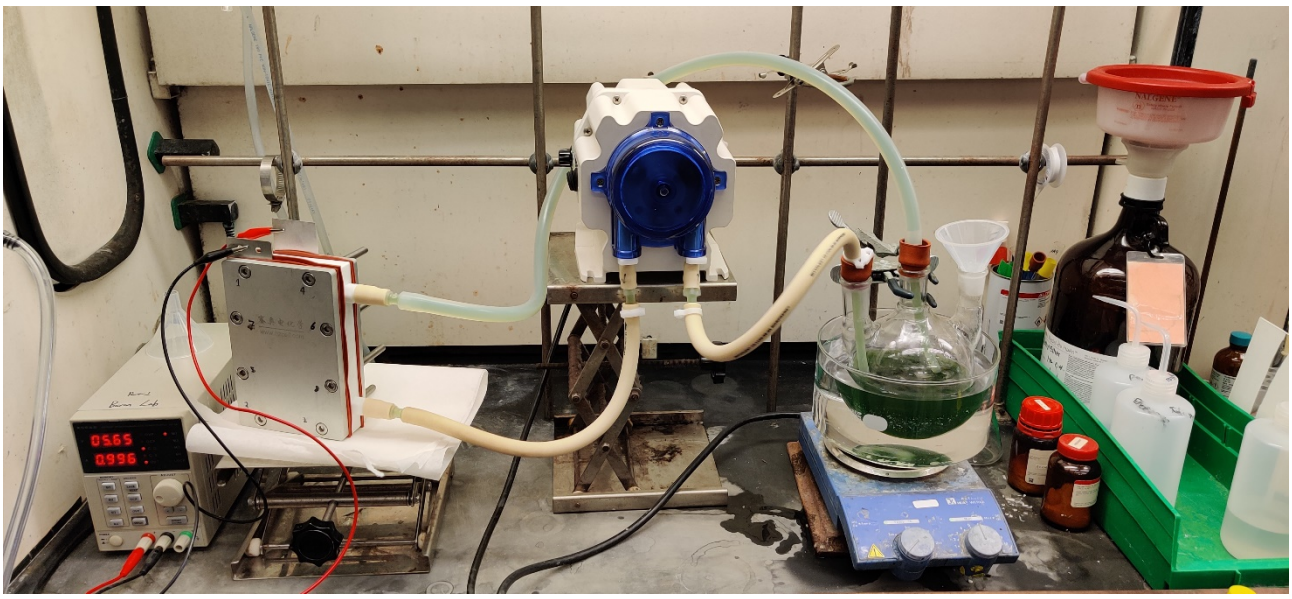
Left: Flask submerged into a water bath **Center:** THF is added (125 mL). **Right:** Reaction Mixture after DIC addition.



Left: 1L, Three-necked round bottom flask charged with aryl iodide, $NiCl_2 \cdot 6H_2O$, 2,2'-bipyridine and LiCl, submerged in a water bath. **Right:** After addition of NMP (625 mL).

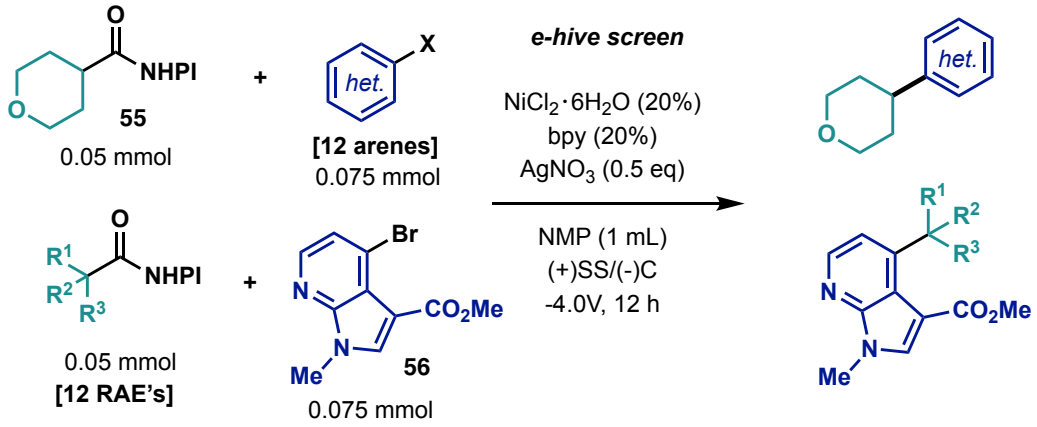


Left: After 3 hours, the RAE solution is transferred to the catalyst solution with a paper filter. **Right:** $AgNO_3$ is added into the flask.



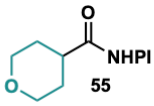
Electrolysis of the reaction mixture.

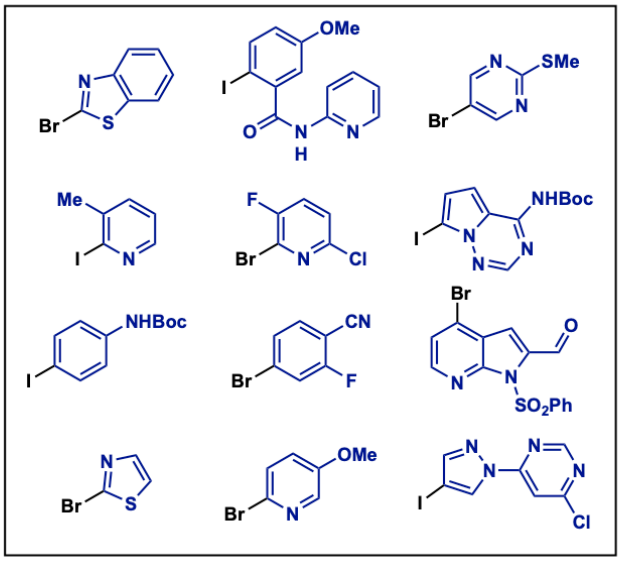
Parallel Synthesis in IKA E-Hive



The following screen was performed using the IKA E-hive attachment for the Electrasyn 2.0. 24 (6 X 4) 0.05 mmol scale reactions were run in parallel. 12 of which were run where **55** (13.7 mg, 0.05 mmol, 1 equiv.) was screened against the 12 different arenes (0.075 mmol, 1.5 eqiuv). The other 12 were run where **56** (20.2 mg, 0.075 mmol, 1.5 equiv) were screened against 12 different RAE's (0.050 mmol, 1 equiv.). These experiments are described in the tables below.

Table S2: Arene screen against 55





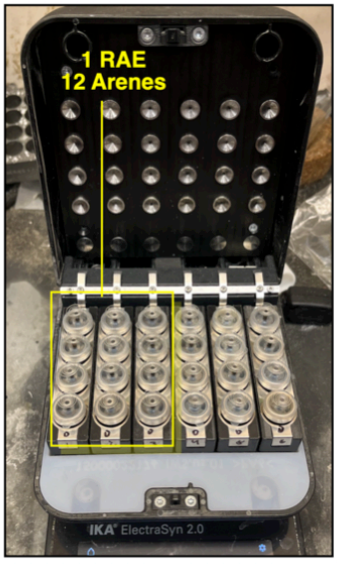
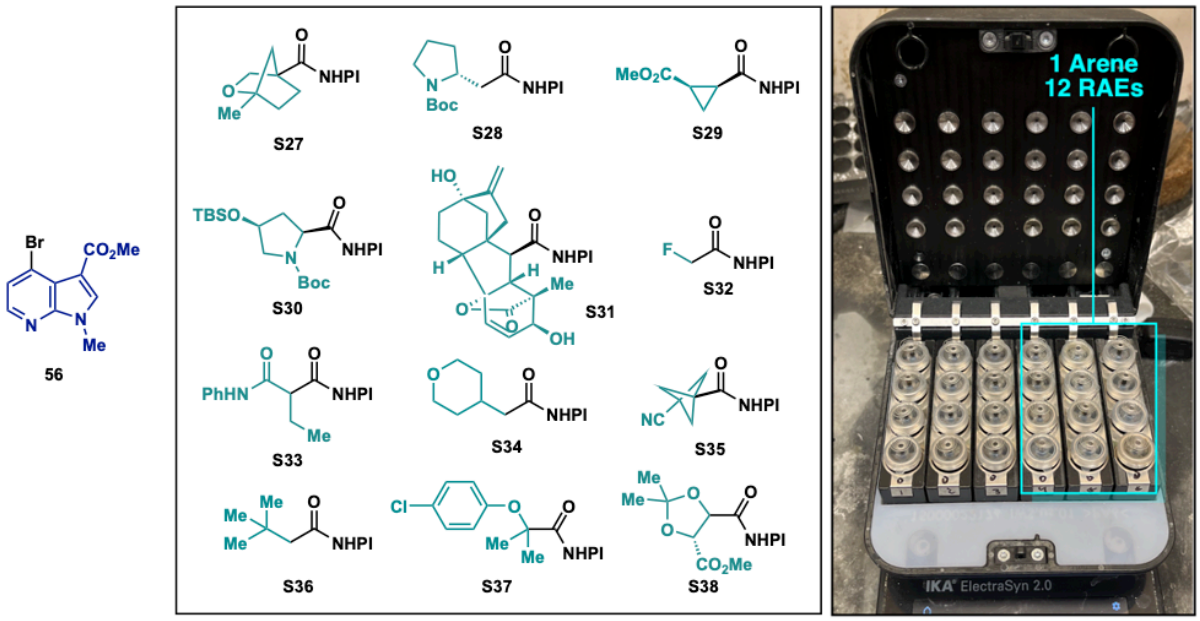


Table S3: RAE screen against 56



Procedure

To 24 stainless steel IKA E-hive vials equipped with stir bar was added silver nitrate (4.25 mg, 0.025 mmol, 0.5 equiv.). To 12 of these vials, 2-bromobenzo[*d*]thiazole (16.1 mg, 0.075 mmol, 1.5 equiv), 2-iodo-5-methoxy-*N*-(pyridin-2-yl)benzamide (26.6 mg, 0.075 mmol, 1.5 equiv.), 5-bromo-2-(methylthio)pyrimidine (15.4 mg, 0.075 mmol, 1.5 equiv.), 2-iodo-3-methylpyridine (16.4 mg, 0.075 mmol, 1.5 equiv.), 2-bromo-6-chloro-3-fluoropyridine (15.7 mg, 0.075 mmol, 1.5 equiv.), *tert*-butyl (7-iodopyrrolo[2,1-*f*][1,2,4]triazin-4-yl)carbamate (27 mg, 0.075 mmol, 1.5 equiv.), *tert*-butyl (4-iodophenyl)carbamate (23.9 mg, 0.075 mmol, 1.5 equiv.), 4-bromo-2-fluorobenzonitrile (15.0 mg, 0.075 mmol, 1.5 equiv.), 4-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbaldehyde (27.4 mg, 0.075 mmol, 1.5 equiv.), 2-bromothiazole (12.3 mg, 0.075 mmol, 1.5 equiv.), 2-bromo-5-methoxypyridine (14.0 mg, 0.075 mmol, 1.5 equiv.), 4-chloro-6-(4-iodo-1*H*-pyrazol-1-yl)pyrimidine (23 mg, 0.075 mmol, 1.5 equiv.) respectively. These 12 vials constitute the arene screen.

Next, the remaining 12 vials were charged with **S27** (15.1 mg, 0.050 mmol, 1.0 equiv.), **S28** (18.7 mg, 0.050 mmol, 1,0 equiv.), **S29** (14.5 mg, 0.050 mmol, 1.0 equiv.), **S30** (24.5 mg, 0.050 mmol, 1.0 equiv.), **S31** (24.6 mg, 0.050 mmol, 1.0 equiv.), **S32** (11.2 mg, 0.050 mmol, 1.0 equiv.), **S33** (17.6 mg, 0.050 mmol, 1.0 equiv.), **S34** (14.5 mg, 0.050 mmol, 1.0 equiv.), **S35** (14.1

mg, 0.050 mmol, 1.0 equiv.), **S36** (13.1 mg, 0.050 mmol, 1.0 equiv.), **S37** (18.0 mg, 0.050, 1.0 equiv.), **S38** (17.5 mg, 0.050 mmol, 1.0 equiv.) respectively. These 12 vials constitute the RAE screen.

A large culture tube equipped with stir bar was charged with **55** (179.4 mg, 0.65 mmol), $NiCl_2 \cdot 6H_2O$ (31.2 mg, 0.13 mmol) and 2,2'-bipyridine (20.8 mg, 0.13 mmol). Anhydrous NMP (13 mL) was added, and the contents were allowed to stir until homogenous. A second large culture tube was charged with **56** (262.37 mg, 0.65 mmol), $NiCl_2 \cdot 6H_2O$ (31.2 mg, 0.13 mmol) and 2,2'-bipyridine (20.8 mg, 0.13 mmol). Anhydrous NMP (13 mL) was added, and the contents were allowed to stir until homogenous.

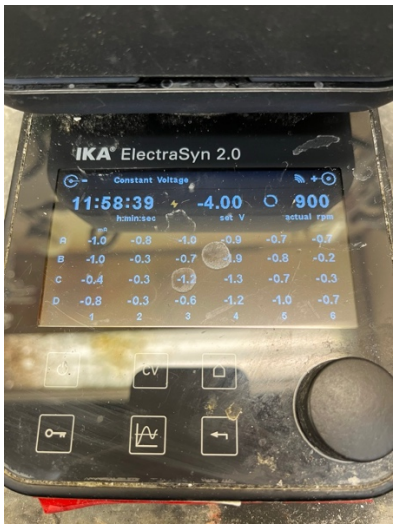
The 24 IKA E-hive vials were placed within the IKA E-hive. 1 mL of the solution containing **55** was added directly to each of the 12 vials of the arene screen. 1 mL of the solution containing **56** was added directly to each of the 12 vials of the RAE screen. Each vial was sealed with a rubber E-hive cap equipped with a commercial graphite cathode. The E-hive was closed and the electrochemical reactions were performed using ElectraSyn 2.0 continuous constant potential conditions with the settings as follows: -4.0 V for 12 hours (the resulting current for each vial ranged from 0.5 mA to 3 mA on average). Upon completion, the rubber caps were removed, and the graphite cathode was washed with ethyl acetate. HPLC/MS was then used to detect product formation. Each reaction mixture was diluted in ethyl acetate, filtered, and concentrated to afford a crude oily solid. Purification and isolation of compounds **57 – 80** was achieved through parallel mass-guided preparative HPLC.

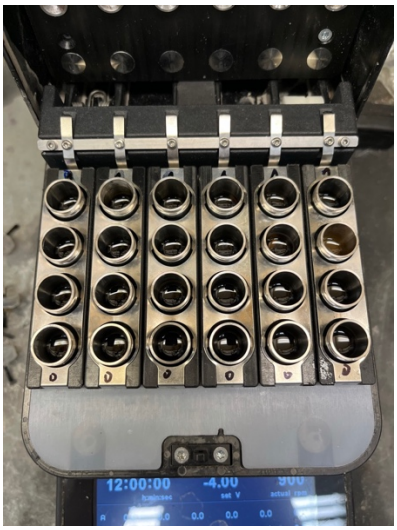
Visual Guide for Parallel Synthesis in E-Hive

Left: E-hive vials all containing silver nitrate. The left 12 contain the varying arenes and the right 12 contain the varying RAE's. **Center:** Stock solutions of nickel, ligand and either **55** or **56**. **Right:** Addition of the appropriate stock solution to the E-hive vials.

Left: E-hive with all reactants present. **Center:** Attachment of the E-hive cap containing the graphite cathode. **Right:** Fully assembled E-hive vial.

Left: E-hive prior to the start of the electrolysis. **Center:** Closed E-hive. **Right:** Electrochemical parameters for the E-hive (-4.0V applied potential for 12 h).





Left: Current at the outset of the E-hive screen. **Right:** Contents of the E-hive vials after electrolysis.

FAQ's

Q: How can the Mg sacrificial electrodes be used multiple times?

A: The Mg electrodes are washed with HCl 3M, water, and acetone. The surface of the electrode is then scraped with a blade.

Q: What are the criteria to decide the reaction solvent?

A: Usually, DMF was employed when high potential with NMP was observed (<10V with electrasyn 2.0 potentiostat). Generally, fused rings, pyrimidines, pyrazines and pyridazines perform better when DMF was used as solvent.

Q: What if the reaction did not go to full conversion?

A: If RAE is not fully consumed after 2.5 F, the electrolysis can be continued until 4 F.

Q: Why is the $AgNO_3$ added just before the electrolysis?

A: As soon as $AgNO_3$ is added into the reaction mixture, the photolabile, insoluble salt AgCl is generating, and a white suspension is formed. It is essential for the correct deposition of the Ag nanoparticles to initiate the electrolysis maximum after 3 minutes from the addition of the salt.

Q: Is the reaction water sensitive?

A: The reaction is not water sensitive, as hydrated reagents and technical solvents could be employed.

Q: Is the reaction air sensitive?

A: The reaction with premade RAEs generally provided only around 5% higher yields when carried out under inert atmosphere. However, when the *in-situ* generation of the RAE is carried out, the reaction resulted to be more sensitive to air, leading to 10% yield difference.

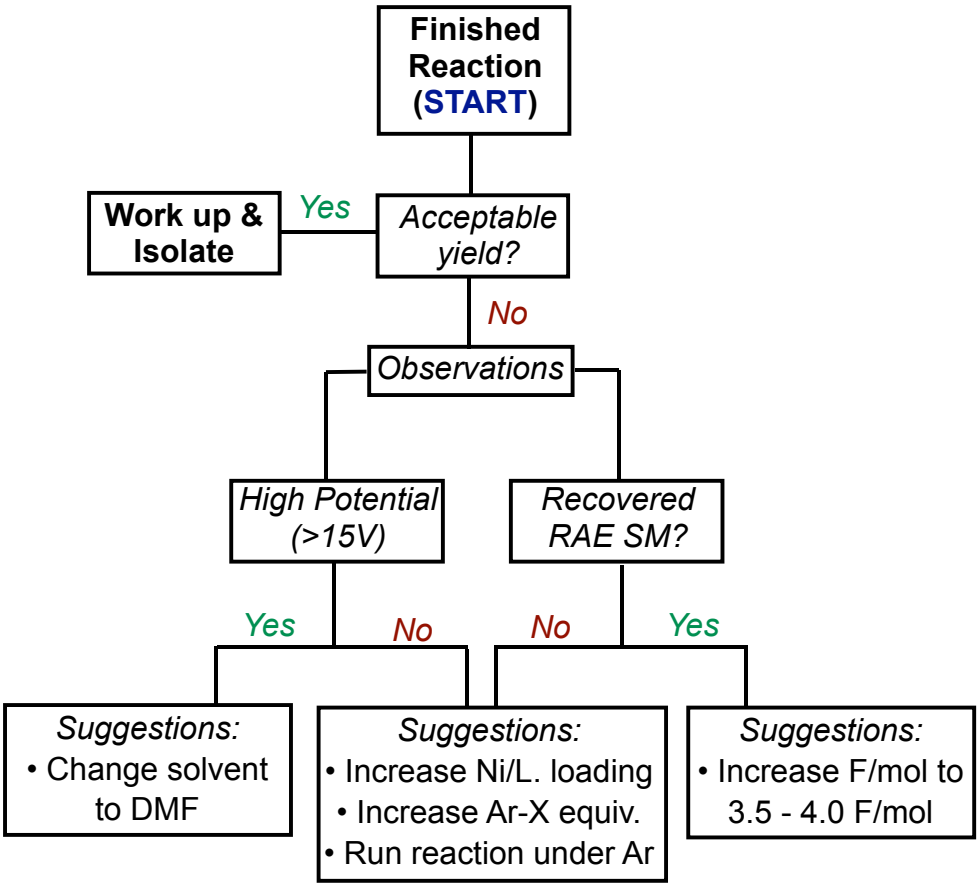
Q: Can the reaction be run more concentrated or diluted?

A: The optimization screening revealed that the protocol is not particularly sensitive to concentration. However, it is highly recommended to adjust the current parameter accordingly (*e.g.* half the concentration, half the current).

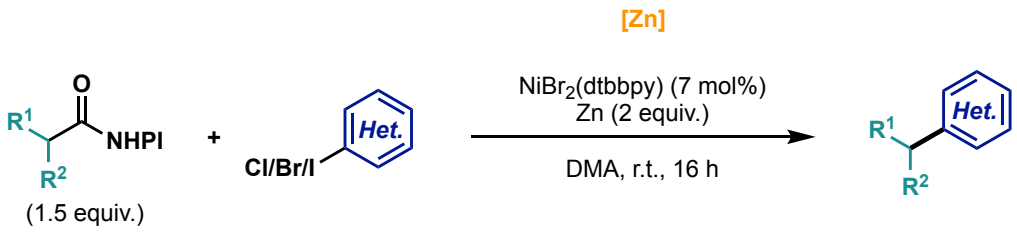
Q: What are the typical side products of the reaction?

A: Regarding the RAE, hydrolysis is the most common side product observed. Regarding the halides, dehalogenation is the most common side product observed.

Troubleshooting Guide

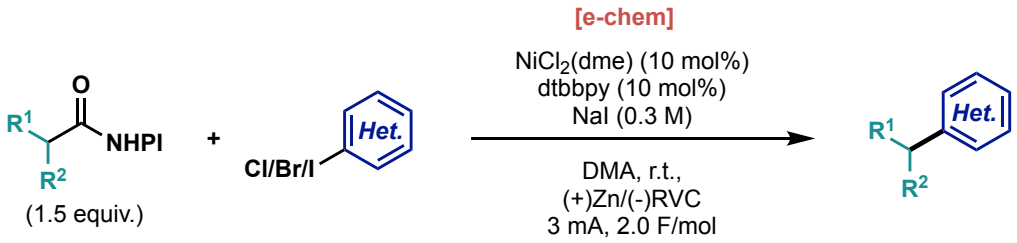


Zinc Mediated DCC Control



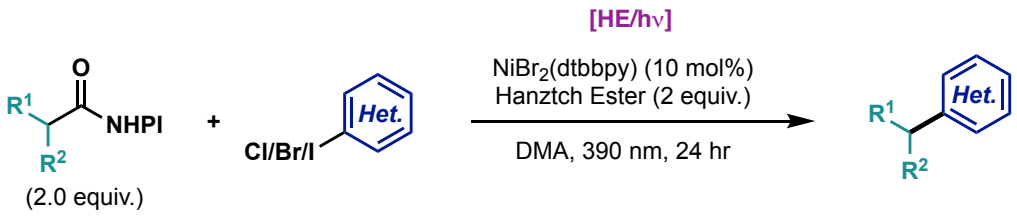
The reaction was performed in accordance with literature procedure on 0.4 mmol scale of aryl halide.[29] Upon completion, the reaction mixture was then diluted with ethyl acetate (3 mL) the mixture was filtered over celite, and an aliquot was analyzed via ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Electrochemically Mediated DCC Control



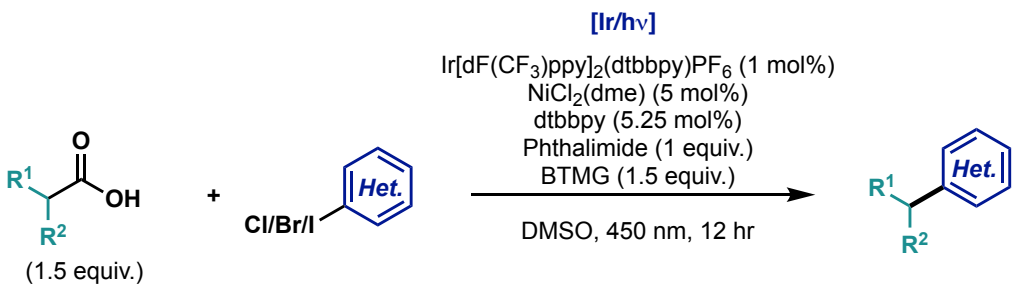
The reaction was performed in accordance with literature procedure on 0.375 mmol scale of aryl halide.[30] After the Upon completion the reaction mixture was diluted with ethyl acetate (3 mL). The mixture was filtered over celite, and an aliquot was analyzed via ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Reductive Photochemical DCC Control



The reaction was performed in accordance with literature procedure on 0.25 mmol scale of aryl halide.[31] A BMS-PR-390 photoreactor was used as the light source.[32] Upon completion the reaction mixtures were worked up according to the literature procedure. The crude material was purified via preparative Reverse Phase chromatography with the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5 µm particles; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation.

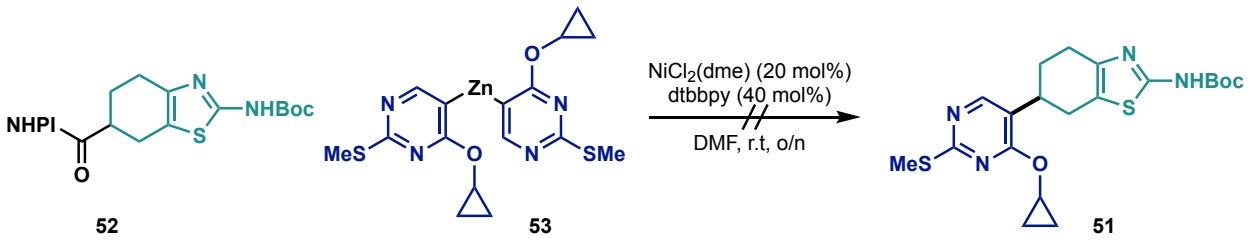
Oxidative Photochemical Activation DCC Control



The reaction was performed in accordance with literature procedure.[33] A BMS-PR-450 photoreactor was used as the light source.[32] Upon completion the reaction mixtures were worked up according to the literature procedure. The crude material was purified via preparative Reverse Phase chromatography with the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5 µm particles; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation.

Prior Attempts at Accessing 51

Negishi-DCC



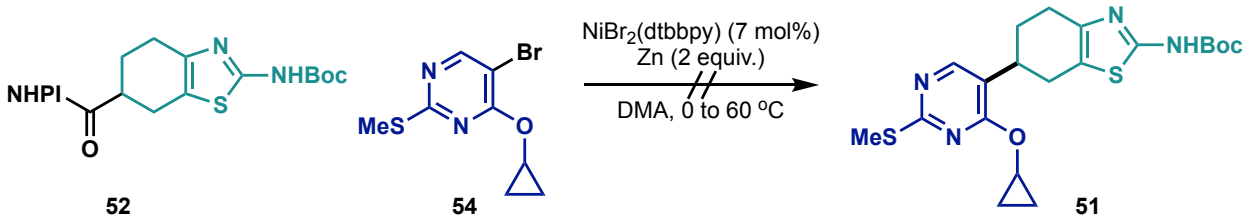
*Preparation of **53***

iPrMgCl LiCl complex (0.49 mL of a 1.3 M solution in THF; 0.632 mmol, 1.1 equiv.) was added to a solution of 5-bromo-4-cyclopropoxy-2-(methylthio)pyrimidine (150 mg, 0.57 mmol, 1 equiv.) in anhydrous THF (5 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h, after which $ZnCl_2$ (63 mL of a 1.0 M solution in Et_2O, 1.1 equiv.) was added. The reaction mixture was stirred at RT for 20 min to give a solution of the bis(4-cyclopropoxy-2-(methylthio)pyrimidin-5-yl)zinc (246 mg, 0.575 mmol) in THF; this reagent was used in the next reaction directly.

Coupling reaction

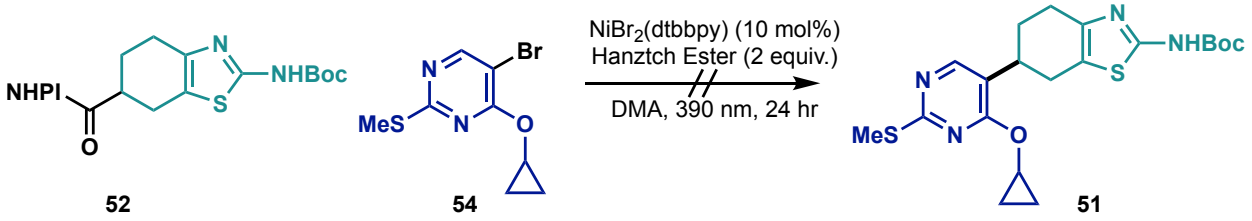
The reaction was performed in accordance with a literature procedure.[34] A 10 mL flask was charged with $NiCl_2$(dme) (9.71 mg, 0.044 mmol, 0.2 equiv.), 4,4'-di-tert-butyl-2,2'-dipyridyl (24 mg, 0.088 mmol, 0.4 equiv.), and **52** (98 mg, 0.221 mmol, 1 equiv.), then was sparged with N_2. Anhydrous DMF (10 mL) was added, and the reaction mixture was stirred for 2 min prior to the addition of **53** (236 mg, 0.552 mmol, 2.5 equiv.) (from the previous reaction) in one portion in THF. The resulting mixture was stirred at RT overnight. At this point LC-MS did not show the presence of the desired product. The reaction was quenched and discarded.

Zn-Mediated DCC



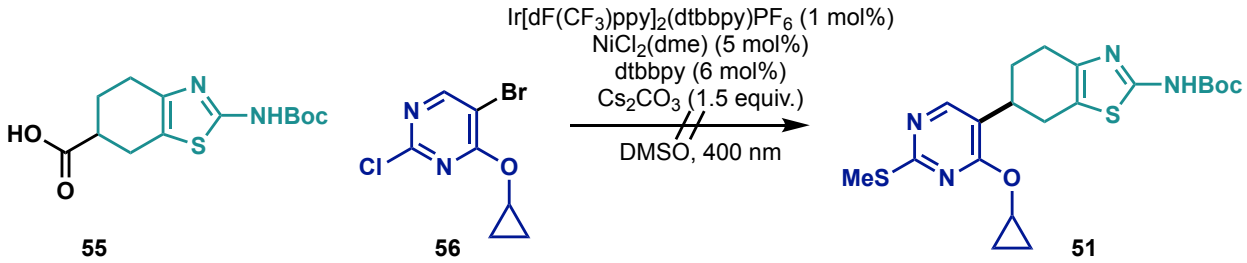
The reaction was performed in accordance with a literature procedure.[29] To an oven-dried flask with a Teflon-coated stir-bar was added $NiBr_2$(dtbbpy) (5.9 mg, 0.012 mmol, 0.07 equiv.), **52** (115 mg, 0.258 mmol, 1.5 equiv.), **54** (45 mg, 0.172 mmol, 1 equiv.), Zinc (22.5 mg, 0.345 mmol, 2 equiv.), and DMA (1 mL). The flask was degassed under N_2 3 times and then stirred at rt for 18 hours. LC-MS only showed trace amount of product. The reaction was further stirred at 60 °C for 18 hours. LC-MS still only showed trace amount of product. The reaction quenched and discarded.

Reductive Photochemical Activation



The reaction was performed in accordance with a literature procedure.[31] To an 8 mL vial equipped with a magnetic stir bar and a rubber septum was added $NiBr_2$(dtbpy) (7.1 mg, 0.015 mmol, 0.1 equiv.), Hantzsch-ester (73.7 mg, 0.291 mmol, 2 equiv.), **52** (97 mg, 0.218 mmol, 1.5 equiv.), **54** (38 mg, 0.146 mmol, 1 equiv.), and DMA (3 mL). The vial was evacuated three times via an inlet needle then purged with argon. The reaction mixture was irradiated for 24 h with two Kessil PR160-purple LED lamps (30 W High Luminous DEX 2100 LED, λmax = 390 nm). LC-MS only showed trace amount of product. The reaction was quenched and discarded.

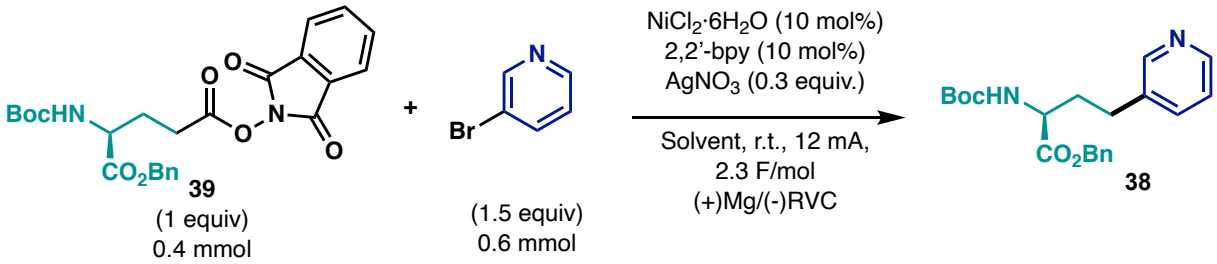
Oxidative Photochemical Activation



The reaction was performed in accordance with a literature procedure.[35] An oven-dried vial was charged with **56** (25 mg, 0.100 mmol, 1 equiv.) (4,4'-Di-t-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-kN)phenyl-kC]iridium(III) hexafluorophosphate (2.5 mg, 0.002 mmol, 0.02 equiv.), 4,4'-Di-tert-butyl-2,2'-dipyridyl (1.6 mg, 0.006 mmol), $NiCl_2$(dme) complex (1 mg, 0.005 mmol, 0.05 equiv.), Cs_2CO_3 (49 mg, 0.15 mmol, 1.5 equiv.), and DMSO (1.5 mL). The reaction mixture was degassed by sparging with N_2 for 10 min, then was stirred in a photoreactor (400 nm light source, 100% intensity, 1000 rpm stirring and 10000 rpm fan speed) for 3 days at RT. At this point, an LC-MS analysis of the reaction mixture did not show any presence of the desired product. The reaction was quenched and discarded.

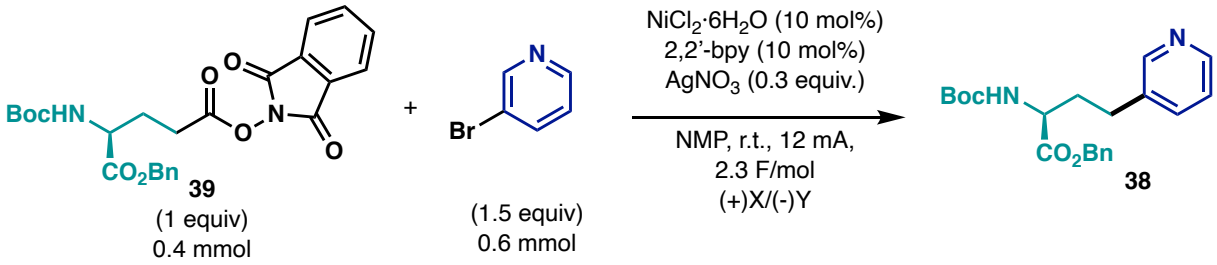
Optimization of the Ag-Ni Electrocatalytic Decarboxylative Arylation

Table S4: Solvent Screen



entry	solvent	%yield (^{1}H-NMR)
1	DMF	16
2	DMA	8
3	NMP	29
4	MeCN	8
5	DMF/THF (4:1)	24
6	DCM	NR
7	NMP/THF (4:1)	25
8	DMI	21

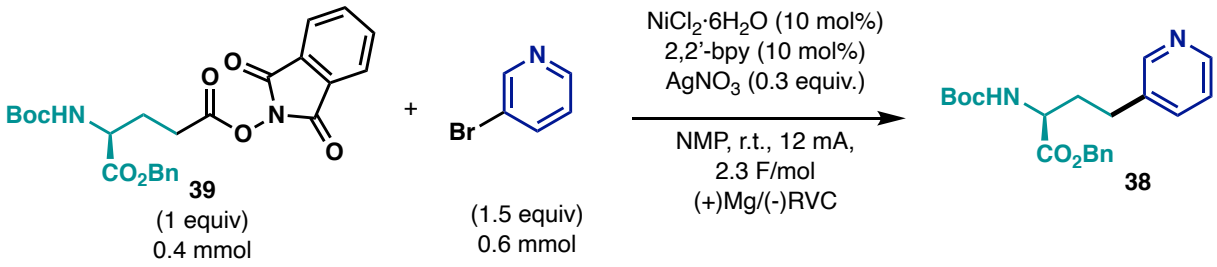
Table S5: Electrode Screen



entry	cathode	Anode	%yield (^{1}H-NMR)
1	RVC	Mg	30
2	RVC	Zn	10
3	RVC	Al[a]	37
4	C	Mg	3
5	C	Zn	11
6	C	Al[a]	3

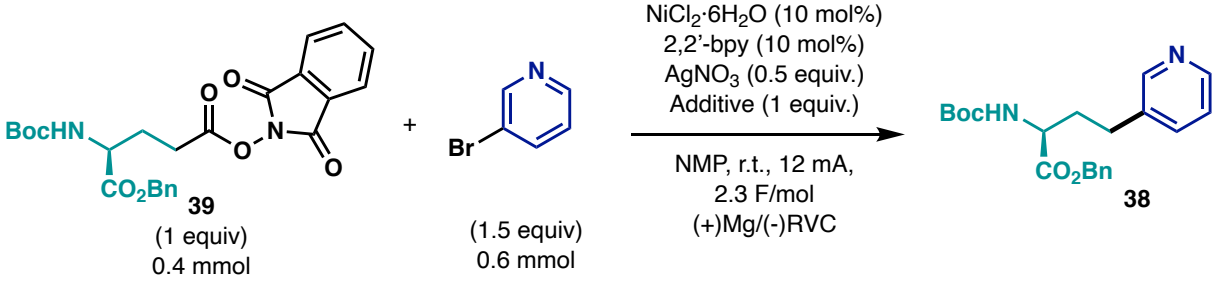
[a] High cell resistance, NaI (0.3 equiv.) added.

Table S6: Silver Loading and F/mol



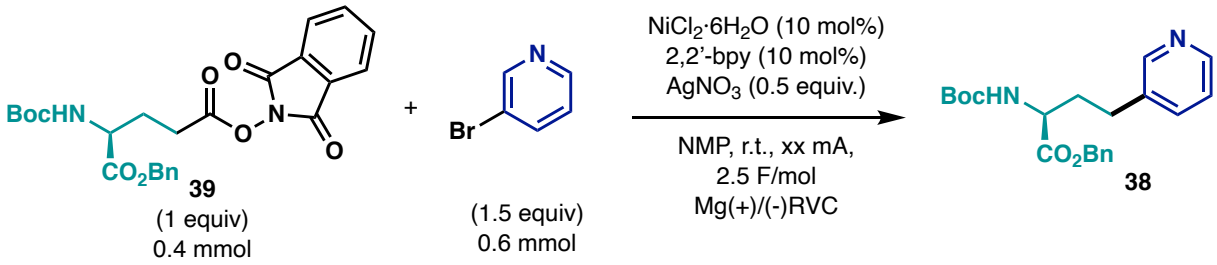
entry	equiv. $AgNO_3$	F/mol	%yield (^{1}H-NMR)
0	0	2.0	5
1	0.1	2.1	5
2	0.2	2.2	13
3	0.3	2.3	29
4	0.4	2.4	36
5	0.5	2.5	43
6	0.6	2.6	39
7	0.7	2.7	41

Table S7: Additive Screen



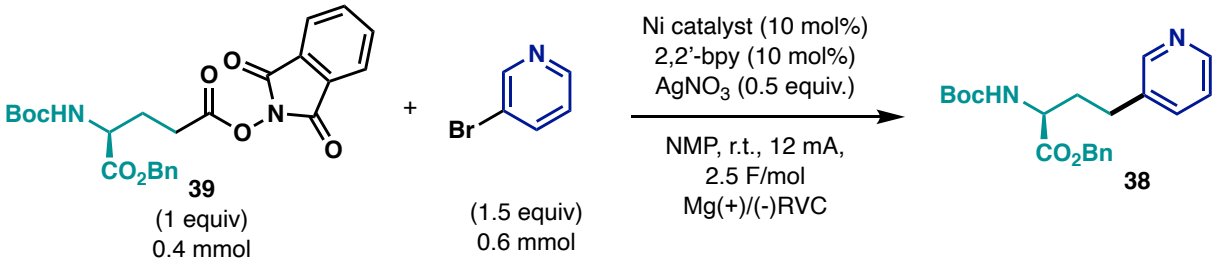
entry	Additive	%yield (^{1}H-NMR)
1	None	43
2	HFIP	12
3	AcOH	27
4	TFA	26
5	Et_3N	19
6	NaOAc	18
7	$NaHCO_3$	38
8	Na_2CO_3	39
9	KH_2PO_4	33
10	K_2HPO_4	34
11	K_3PO_4	33
12	BTMG	0
13	Phtalimide	34

Table S8: Electrochemical Parameters and Concentration



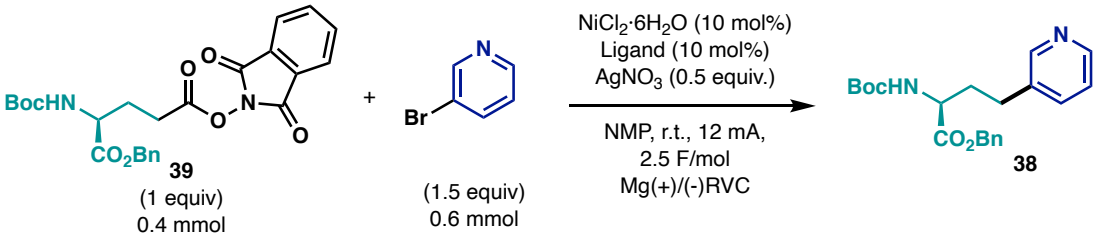
entry	scale	current	concentration	current/mmol	current density (A/m^2)	%yield (^{1}H-NMR)
1	0.2 mmol	12 mA	0.07 M	60	5.4	34
2	0.2 mmol	6 mA	0.07 M	30	2.7	44
3	0.4 mmol	12 mA	0.13 M	30	5.4	43
4	0.4 mmol	6 mA	0.13 M	15	2.7	44
5	0.4 mmol	18 mA	0.13 M	45	8.1	43
6	0.6 mmol	12 mA	0.20 M	20	5.4	36
7	0.6 mmol	18 mA	0.20 M	30	8.1	38

Table S9: Nickel Source Screen



entry	metal source	%yield (^{1}H-NMR)
1	$NiCl_2·6H_2O$	43
2	$NiCl_2$(dme)	39
3	$NiBr_2$(dme)	37
4	$NiBr_2(PPh_3)_2$	15
5	$Ni(NO_3)_2·6H_2O$	24

Table S10: Ligand Screen



entry	ligand	%yield (^{1}H-NMR)
1	L1	43
2	L2	21
3	L3	18
4	L4	33
5	L5	8
6	L6	9
7	L7	30
8	L8	37
9	L9	2
10	L10	0
11	L11	0
12	L12	1
13	L13	0
14	L14	0
15	L15	0
16	L16	0
17	L1 + L15	17

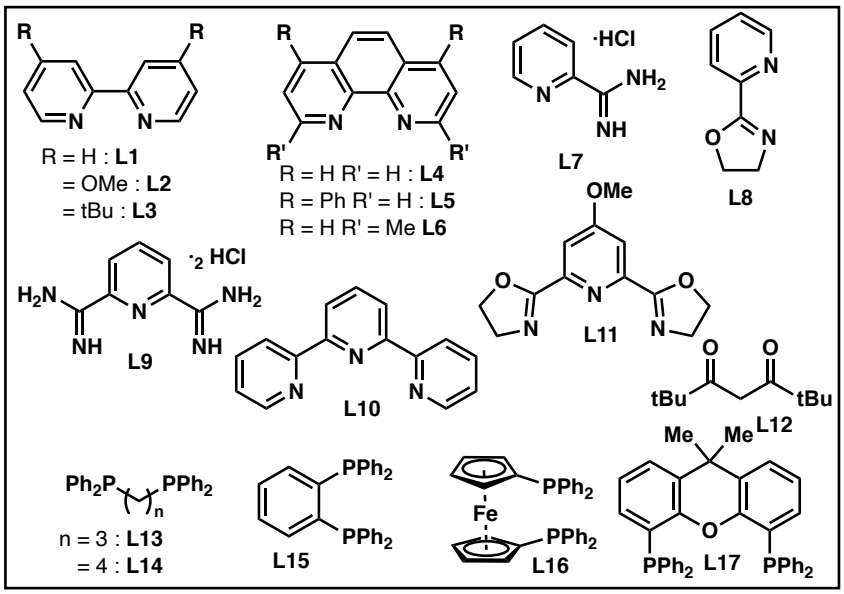
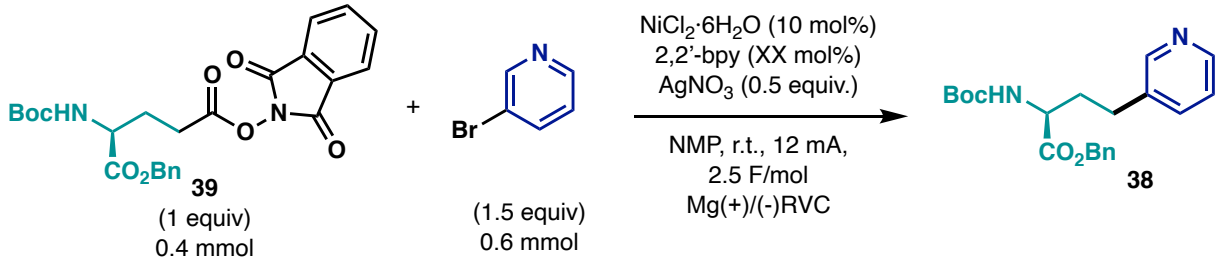
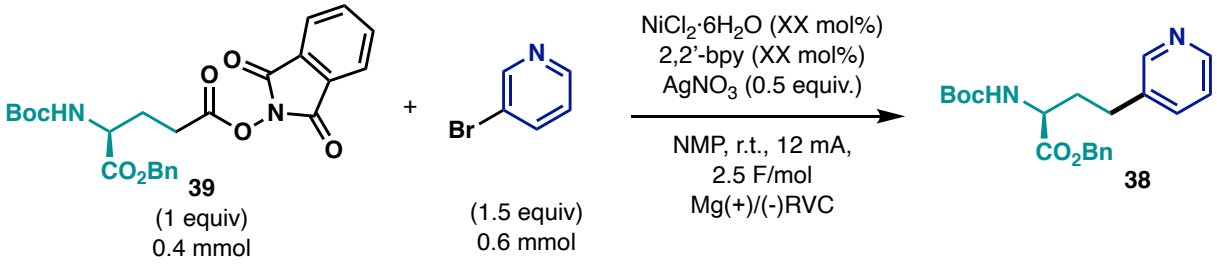


Table S11: Ligand Stoichiometry



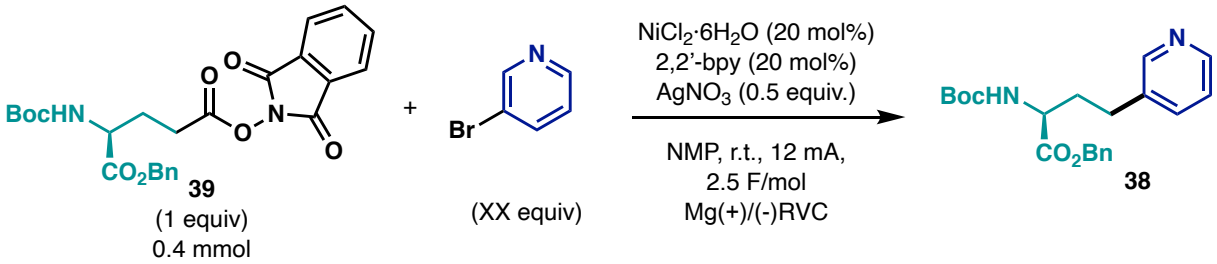
entry	ligand mol %	%yield (^{1}H-NMR)
1	10	43
2	20	10
3	30	0

Table S12: Catalyst Loading



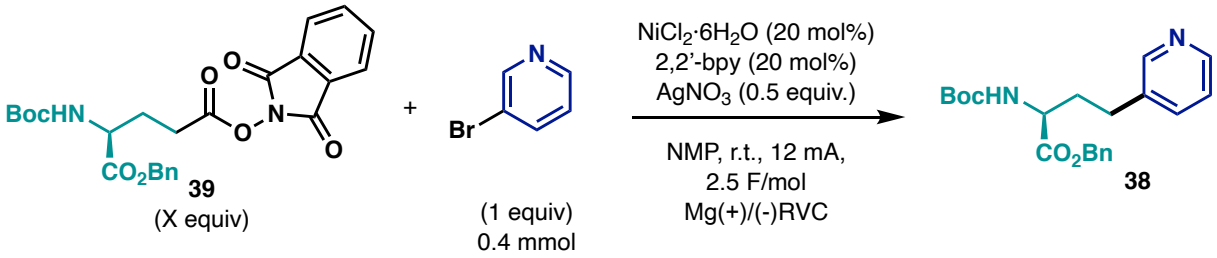
entry	Ni/L mol %	%yield (^{1}H-NMR)
1	5	28
2	10	43
3	12	38
4	15	45
5	20	50
6	30	48

Table S13: Arene Stoichiometry



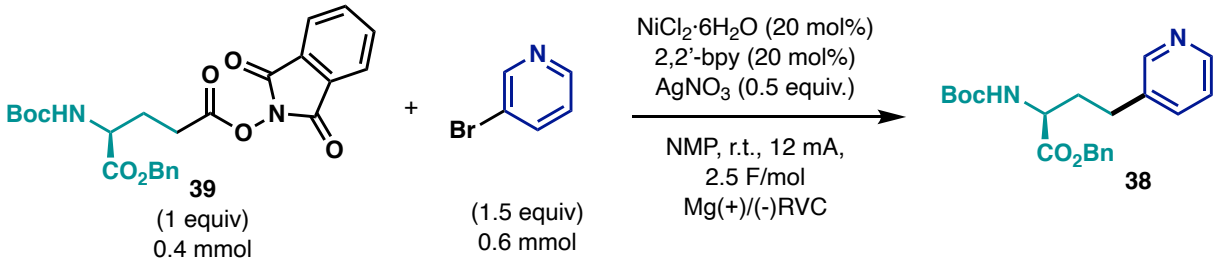
entry	Equiv. Ar-X	%yield (^{1}H-NMR)
1	1.00	42
2	1.25	46
3	1.50	50
4	2.00	50

Table S14: RAE Stoichiometry



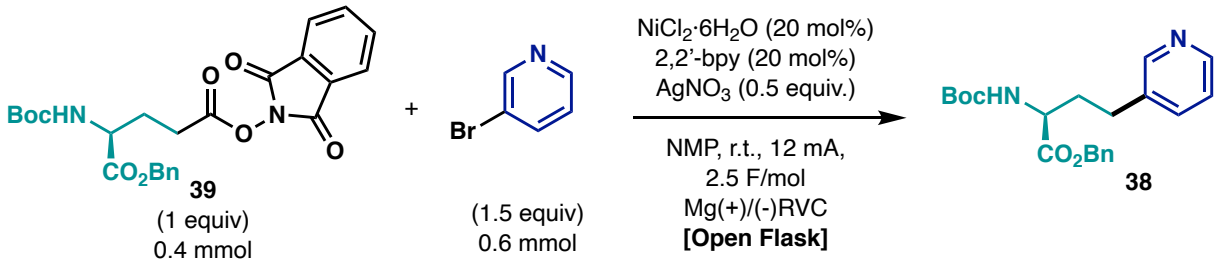
entry	Equiv. RAE	%yield (^{1}H-NMR)
1	1.00	42
2	1.50	43
3	2.00	40

Table S15: Control Study (Under Argon)



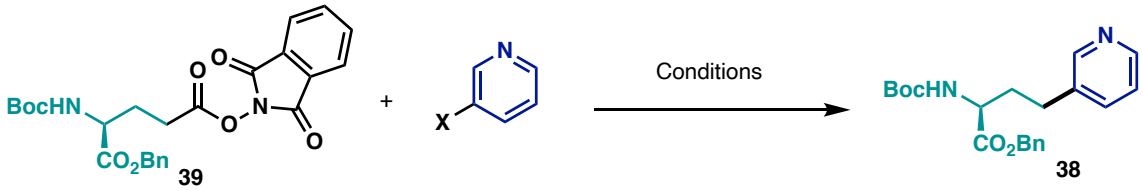
entry	Modification	%yield (^{1}H-NMR)
1	none	50 (50 iso.)
2	Ar-I instead of Ar-Br	63
3	No $AgNO_3$ (Br)	24
4	No $AgNO_3$ (I)	24
5	No Nickel	0
6	No Ligand	27
7	No Electricity (16 h, RT)	12
8	Under Air	45
9	Zinc (2 equiv.), No Electricity	0

Table S16: Control Study (Open Flask)



entry	Modification	%yield (^{1}H-NMR)
1	none	45
2	Technical grade solvent	45
3	Ar-I instead of Ar-Br	62
4	No $AgNO_3$ with Ar-Br	15
5	No $AgNO_3$ with Ar-I	19
6	No Nickel	0
7	No Ligand	28
8	No Electricity (16 h, RT)	0
9	Zinc (2 equiv.), No Electricity	0

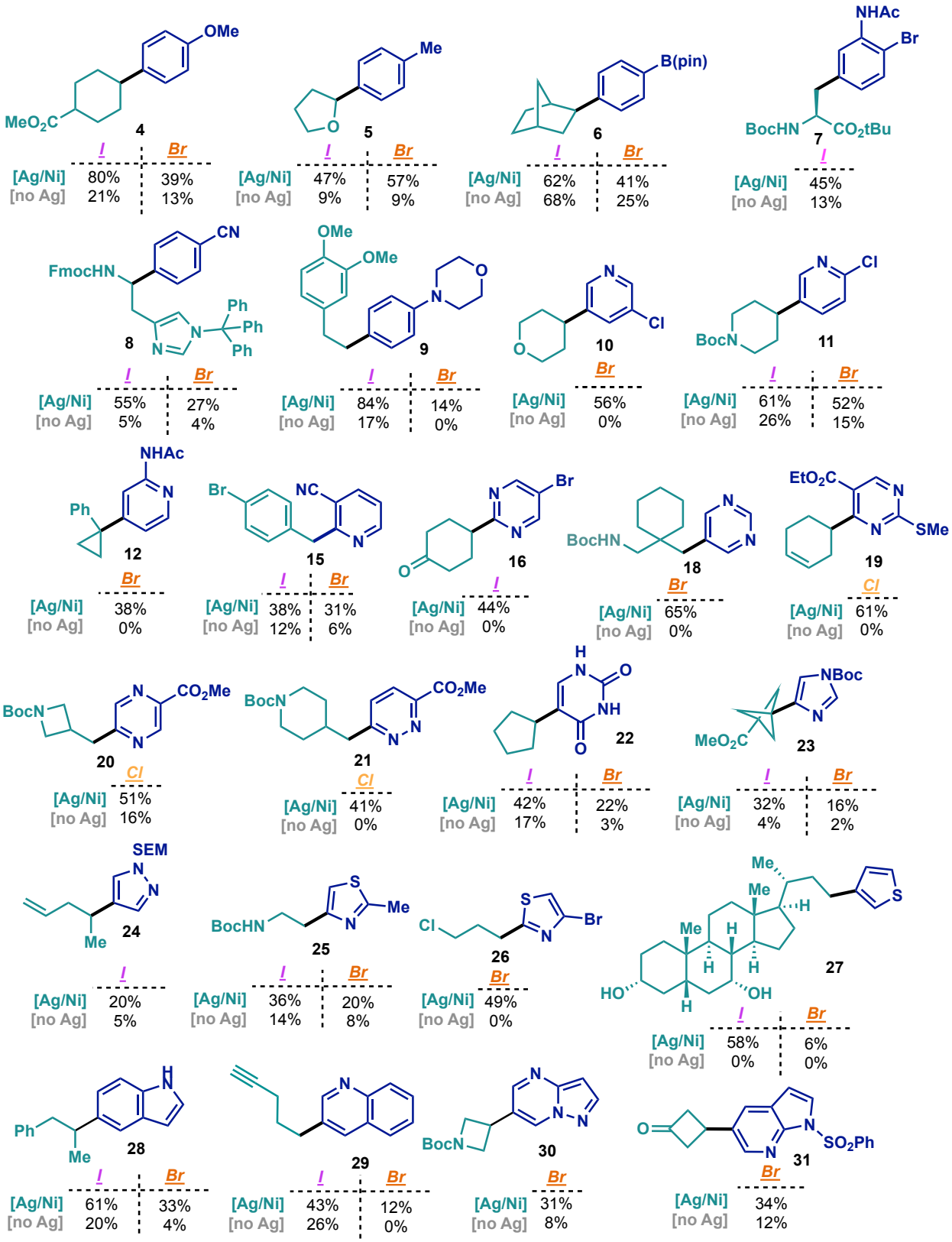
Table S17: State of the Art Comparisons with Existing Methods to Access 38



entry	equiv. RAE	equiv. Arene	conditions	reference	%yield (isolated)
1	1.5	1.0	$NiBr_2$(diglyme) (7%) dtbbpy (7%) Zn (2 equiv.) DMA, r.t., o/n	**[Zn]** *J. Am. Chem. Soc.* **2016**, *138*, 5016 - 5019	X = **I** : N.D. = **Br** : N.D.
2	1.5	1.0	$NiCl_2$(dme) (10%) dtbbpy (10%) NaI (0.2 M) DMA (+)Zn/(-)RVC 3 mA, 2.0 F/mol	**[e-chem]** *Org Lett*, **2019** *21,* 816 - 820	X = **I** : N.D. = **Br** : N.D.
3	2.0	1.0	$NiBr_2$(dtbbpy) (10 mol%) Hanztch Ester (2 equiv.) DMA, 390 nm, 24 hr	**[HE/hν]** *Chem. Sci.* **2021**, *12*, 5450 - 5457	X = **I** : 32% = **Br** : 26%
4	1.5 (free acid used)	1.0	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol%) $NiCl_2$(dme) (5 mol%) dtbbpy (5.25 mol%) Phthalimide (1 equiv.) BTMG (1.5 equiv.) DMSO, 450 nm, 12 hr	**[Ir/hν]** *Science,* **2022**, *376* 532 - 539	X = **I** : 2% = **Br** : 11%
5	1.0	1.5	$NiCl_2 \cdot 6H_2O$ (20 mol%) 2,2'-bpy (20 mol%) $AgNO_3$ (0.5 equiv.) NMP, r.t., 12 mA, 2.5 F/mol Mg(+)/(-)RVC **[Open Flask]**	**[Ag/Ni]** This work	X = **I** : 63% = **Br** : 45%

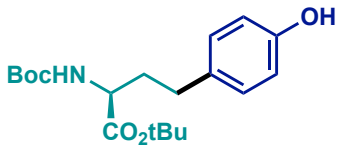
N.D = Not detected.

Table S18: Comparison of Substrates with and without Silver



Procedures and Characterization of Ag-Ni Electrocatalytic Decarboxylative Arylation Products

Compound 1



Following the General Procedure 2 with **2** (179.4 mg, 0.4 mmol) and 4-iodophenol (132.0 mg, 0.6 mmol) or 4-bromophenol (103.8 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 71.0 mg (51%) and 11.2 mg (8%) respectively of the title compound after purification by column chromatography (2:1 hexanes/ethyl acetate).

Flow

Following the General Procedure 5 with (*S*)-5-(*tert*-butoxy)-4-((*tert*-butoxycarbonyl)amino)-5-oxopentanoic acid (30.3 g, 100 mmol) and 4-iodophenol (33.0 g, 150 mmol) in NMP (625 mL) for 4.5 F/mol afforded 15.0 g (43%) of the title compound after purification by column chromatography (3:1 hexanes/ethyl acetate).

Physical State: White Solid

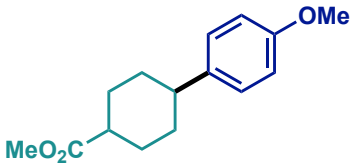
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.02 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 7.9 Hz, 2H), 5.26 (s, 1H), 5.10 (d, *J* = 8.3 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 1H), 2.65 – 2.49 (m, 2H), 2.08 – 1.98 (m, 1H), 1.86 (dt, *J* = 13.1, 6.5 Hz, 1H), 1.47 (s, 9H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.1, 155.6, 154.2, 133.2, 129.6, 115.5, 82.1, 80.0, 54.0, 35.2, 30.8, 28.5, 28.2.

HRMS (ESI-TOF): calculated for $C_{19}H_{29}NO_5$ $[M+H]^+$: 352.2124 found: 352.2115.

TLC: R_f = 0.40 (2:1 hexanes/ethyl acetate)

Compound 4



Following the General Procedure 2 with **S1** (132.5 mg, 0.4 mmol) and 4-iodoanisole (140.4 mg, 0.6 mmol) or 4-bromoanisole (112.0 mg, 0.6 mmol) in NMP (3 mL) for 3.5 F/mol afforded 79.1 mg (80%) and 38.7 mg (39%) respectively of the title compound after purification by column chromatography (15:1 hexanes/ethyl acetate).

Physical State: Colorless oil

d.r.: 1.8:1

^{1}H NMR (600 MHz, $CDCl_3$): *Major diastereomer*: δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.86 – 6.81 (m, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 2.47 (tt, *J* = 12.0, 3.6 Hz, 1H), 2.35 (tt, *J* = 12.2, 3.6 Hz, 1H), 2.09 (dd, 14.1, 3.7 Hz, 2H), 1.95 (dd, 13.8, 3.5 Hz, 2H), 1.61 – 1.54 (m, 2H), 1.44 (qd, *J* = 12.8, 3.2 Hz, 2H).

Minor diastereomer: δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.86 – 6.81 (m, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 2.72 – 2.68 (m, 1H), 2.48 (tt, *J* = 12.0, 3.6 Hz, 1H), 2.26 – 2.20 (m, 2H), 1.78 – 1.72 (m, 2H), 1.68 – 1.61 (m, 4H).

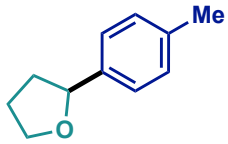
^{13}C NMR (151 MHz, $CDCl_3$): *Major diastereomer*: δ 176.6, 158.0, 139.2, 127.7, 113.9, 55.4, 51.7, 43.1, 42.8, 33.6, 29.5.

Minor diastereomer: δ 175.7, 157.9, 139.4, 127.8, 113.8, 53.6, 51.7, 42.8, 39.0, 30.8, 27.7.

HRMS (ESI-TOF): calculated for $C_{15}H_{21}O_3$ $[M+H]^+$: 249.1491 found: 249.1492.

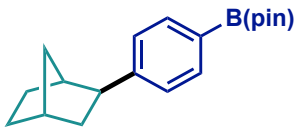
TLC: R_f = 0.69 (4:1 hexanes/ethyl acetate)

Compound 5



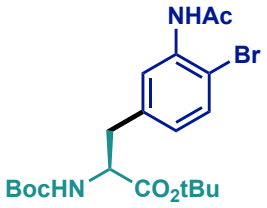
Following the General Procedure 2 with **S2** (105.0 mg, 0.4 mmol) and 4-iodotoluene (130.8 mg, 0.6 mmol) or 4-bromotoluene (102.6 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 30.1 mg (47%) and 36.9 mg (57%) respectively of the title compound after purification by column chromatography (19:1 hexanes/ethyl acetate). The spectroscopic data matched the literature.[36]

Compound 6



Following the General Procedure 2 with **S3** (114.0 mg, 0.4 mmol) and 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (198.0 mg, 0.6 mmol) or 2-(4-bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (169.8 mg, 0.6 mmol) in DMF (3 mL) for 2.5 F/mol afforded 74.0 mg (62%) and 48.9 mg (41%) respectively of the title compound after purification by column chromatography (20:1 hexanes/ethyl acetate). The spectroscopic data matched the literature.[37]

Compound 7



Following the General Procedure 2 with **S4** (173.8 mg, 0.4 mmol) and *N*-(2-bromo-5-iodophenyl)acetamide (203.9 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 82.3 mg (45%) of the title compound after purification by column chromatography (2:1 hexanes/ethyl acetate).

Physical State: White solid

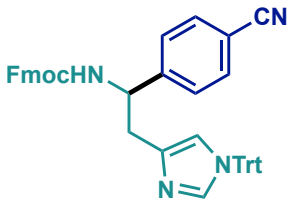
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.56 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 5.02 (d, *J* = 8.1 Hz, 1H), 4.40 (q, *J* = 6.8 Hz, 1H), 3.07 (dd, *J* = 14.1, 5.9 Hz, 1H), 2.95 (dd, *J* = 14.0, 6.4 Hz, 1H), 2.21 (s, 3H), 1.42 (s, 9H), 1.40 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.8, 168.1, 155.1, 137.4, 135.6, 132.0, 126.3, 123.0, 111.5, 82.4, 79.8, 54.7, 38.3, 28.4, 28.1, 25.0.

HRMS (ESI-TOF): calculated for $C_{20}H_{29}BrN_2O_5$ $[M+Na]^+$: 479.1158 found: 479.1152.

TLC: R_f = 0.25 (2:1 hexanes/ethyl acetate)

Compound 8



Following the General Procedure 2 with **S5** (305.9 mg, 0.4 mmol) and 4-iodobenzonitrile (137.4 mg, 0.6 mmol) or 4-bromobenzonitrile (109.2 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 148.9 mg (55%) and 73.1 mg (27%) respectively of the title compound after purification by column chromatography (1:1 hexanes/ethyl acetate).

Physical State: White solid

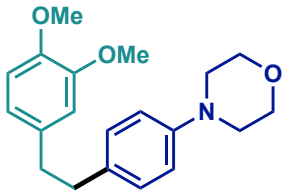
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 6.6 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.46 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (dd, *J* = 6.6, 2.0 Hz, 4H), 7.33 – 7.30 (m, 5H), 7.29 (d, *J* = 1.7 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.02 (d, *J* = 7.7 Hz, 7H), 6.27 (s, 1H), 5.09 (q, *J* = 5.8 Hz, 1H), 4.42 – 4.28 (m, 2H), 4.22 (t, *J* = 7.5 Hz, 1H), 3.16 (dd, *J* = 14.6, 4.7 Hz, 1H), 2.84 (dd, *J* = 14.7, 5.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 156.1, 148.3, 144.2, 144.0, 142.2, 141.4, 138.7, 136.4, 132.1, 129.7, 128.3, 128.2, 127.8, 127.1, 125.3, 120.2, 120.1, 119.1, 110.7, 67.0, 55.2, 47.4, 34.2.

HRMS (ESI-TOF): calculated for $C_{46}H_{36}N_4O_2$ $[M+H]^+$: 677.2917 found: 677.2914.

TLC: R_f = 0.31 (1:1 hexanes/ethyl acetate)

Compound 9



Following the General Procedure 2 with **S6** (142.1 mg, 0.4 mmol) and 4-(4-iodophenyl)morpholine (173.5 mg, 0.6 mmol) or 4-(4-bromophenyl)morpholine (145.3 mg, 0.6 mmol) in NMP (3 mL) for 3.5 F/mol afforded 109.7 mg (84%) and 18.0 mg (14%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 10:1 to 5:1).

Physical State: Pale red solid

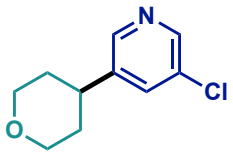
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.11 – 7.06 (m, 2H), 6.87 – 6.83 (m, 2H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.72 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 3.88 – 3.85 (m, 4H), 3.86 (s, 3H), 3.83 (s, 3H), 3.15 – 3.10 (m, 4H), 2.83 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 149.7, 148.8, 147.3, 134,7. 133.6, 129.3, 120.4, 116.0, 112.0, 111.3, 67.1, 56.1, 55.9, 49.9, 37.8, 37.4.

HRMS (ESI-TOF): calculated for $C_{20}H_{25}NO_3$ $[M+H]^+$: 328.1913 found: 328.1912.

TLC: R_f = 0.40 (2:1 hexanes/ethyl acetate)

Compound 10



Following the General Procedure 2 with **55** (110.10 mg, 0.4 mmol) and 3-bromo-5-chloropyridine (115.5 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 44 mg (56%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes:ethyl acetate).

Physical State: Clear colorless oil

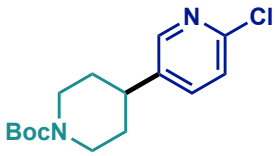
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (d, *J* = 2.3 Hz, 1H), 8.38 (d, *J* = 1.9 Hz, 1H), 7.55 – 7.50 (m, 1H), 4.13 – 4.06 (m, 2H), 3.53 (td, *J* = 11.2, 3.9 Hz, 2H), 2.81 (tt, *J* = 10.7, 5.9 Hz, 1H), 1.87 – 1.76 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 146.9, 146.8, 142.4, 134.1, 132.2, 68.1, 38.9, 33.5.

HRMS (ESI-TOF): calculated for $C_{10}H_{12}ClNO$ $[M+H]^+$: 198.0686, found: 198.0684.

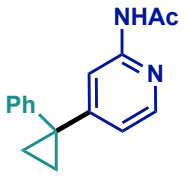
TLC: R_f = 0.33 (1:1 hexanes/ethyl acetate)

Compound 11



Following the General Procedure 2 with **S7** (149.8 mg, 0.4 mmol) and 5-iodo-2chloropyridine (143.7 mg, 0.6 mmol) or 5-bromo-2-chloropyridine (115.5 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 72.3 mg (61%) and 61.6 mg (52%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes:ethyl acetate). The spectroscopic data matched the literature.[38]

Compound 12



Following the General Procedure 2 with **S8** (123.0 mg, 0.4 mmol) and *N*-(4-bromopyridin-2-yl)acetamide (129.0 mg, 0.6 mmol) in NMP (3 mL) for 3.0 F/mol afforded 58.0 mg (38%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 5:1 to 2:1).

Physical State: White solid

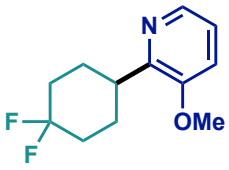
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.03 (br, 1H), 8.04 (d, *J* = 5.4 Hz, 1H), 7.98 (s, 1H), 7.32 (m, 4H), 7.32 – 7.22 (m, 1H), 6.70 (dd, *J* = 5.4, 1.8 Hz, 1H), 2.15 (s, 3H), 1.44 – 1.35 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.02, 158.58, 152.10, 147.15, 143.35, 129.87, 128.74, 128.71, 127.07, 119.22, 111.93, 29.83, 24.81, 17.66.

HRMS (ESI-TOF): calculated for $C_{16}H_{16}N_2O$, $[M+H]^+$: 253.1341, found: 253.1346.

TLC: R_f = 0.20 (1:1 hexanes/ethyl acetate)

Compound 13



Following the General Procedure 2 with **S9** (123.7 mg, 0.4 mmol) and 2-iodo-3-methoxypyridine (141.0 mg, 0.6 mmol) or 2-bromo-3-methoxypyridine (112.8 mg, 0.6 mmol) in NMP (3 mL) for 3.5 F/mol afforded 27.5 mg (30%) and 17.8 mg (20%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes:ethyl acetate).

Physical State: White solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14 (t, *J* = 3.0 Hz, 1H), 7.11 (d, *J* = 3.1 Hz, 2H), 3.84 (s, 3H), 3.23 – 3.15 (m, 1H), 2.27 – 2.15 (m, 2H), 2.06 – 1.95 (m, 2H), 1.94 – 1.78 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 153.6, 153.0, 140.7, 122.0, 116.9, 55.3, 37.3, 34.2, 34.0, 34.0, 33.9, 27.4, 27.3.

^{19}F NMR (471 MHz, $CDCl_3$): δ -91.44 (d, *J* = 234.6 Hz), -101.64 (d, *J* = 234.4 Hz).

HRMS (ESI-TOF): calculated for $C_{12}H_{15}F_2NO$ $[M+H]^+$: 228.1200, found. 228.1205.

TLC: R_f = 0.71 (1:1 hexanes/ethyl acetate)

Compound 14

Following the General Procedure 2 with **S10** (144.2 mg, 0.4 mmol) and 2-iodopyridine (64 µL, 0.6 mmol) or 2-bromopyridine (57 µL, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 46.6 mg (47%) and 51.8 mg (52%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

Physical State: Clear colorless oil

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.54 (d, *J* = 5.1 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.20 – 7.09 (m, 2H), 3.88 – 3.74 (m, 1H), 3.68 – 3.32 (m, 4H), 2.31 – 2.08 (m, 2H), 1.45 (d, *J* = 7.6 Hz, 9H).

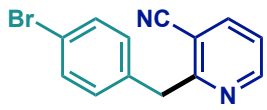
^{13}C NMR (151 MHz, $CDCl_3$): *Major Rotamer* δ 160.9, 154.7, 149.6, 136.7, 122.0, 121.9, 79.3, 51.4, 46.3, 45.8, 31.6, 28.7.

Minor Rotamer: δ 161.1, 154.7, 149.6, 136.7, 122.0, 121.9, 79.3, 51.1, 46.1, 45.5, 32.3, 28.7.

HRMS (ESI-TOF): calculated for $C_{14}H_{20}N_2O_2$ $[M\text{-Boc}+2H]^+$: 149.1079, found: 149.1077.

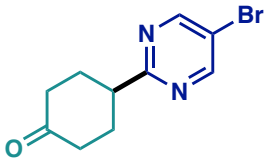
TLC: R_f = 0.43 (1:1 ethyl acetate/hexanes)

Compound 15



Following the General Procedure 2 with **S11** (144.2 mg, 0.4 mmol) and 2-iodonicotinonitrile (138.0 mg, 0.6 mmol) or 2-bromonicotinonitrile (109.8 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 41.1 mg (38%) and 33.9 mg (31%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 10:1 to 6:1). The spectroscopic data matched the literature.[39]

Compound 16



Following the General Procedure 2 with **42** (115.0 mg, 0.4 mmol) and 5-bromo-2-iodopyrimidine (171.0 mg, 0.6 mmol) in DMF (3 mL) for 4.0 F/mol afforded 44.5 mg (44%) of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 5:1 to 3:1).

Physical State: White solid

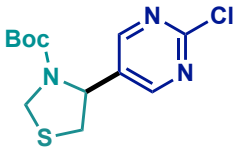
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 2H), 3.33 (tt, *J* = 10.7, 3.7 Hz, 1H), 2.57 – 2.42 (m, 4H), 2.37 – 2.29 (m, 2H), 2.21 – 2.09 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 210.88, 170.62, 157.91, 118.36, 44.34, 40.55, 31.35.

HRMS (ESI-TOF): calculated for $C_{10}H_{11}BrN_2O$, $[M+H]^+$: 255.0133, found: 255.0137.

TLC: R_f = 0.38 (2:1 hexanes/ethyl acetate)

Compound 17



Following the General Procedure 2 with **S12** (151.4 mg, 0.4 mmol) and 2-chloro-5-iodopyrimidine (144.3 mg, 0.6 mmol) in DMF (3 mL) for 2.5 F/mol afforded 30.3 mg (25%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

Physical State: Clear colorless oil

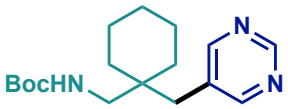
^{1}H NMR (600 MHz, MeOD): δ 8.71 (s, 2H), 5.25 (br s, 1H), 4.64 (br s, 2H), 3.57 (s, 1H), 3.00 (br s, 1H), 1.57 – 1.09 (br m, 9H).

^{13}C NMR (151 MHz, MeOD): δ 161.4, 159.4, 159.4, 159.4, 154.8, 82.7, 60.3, 60.3, 28.5.

HRMS (ESI-TOF): calculated for $C_{12}H_{16}ClN_3O_2S$ $[M+H]^+$: 302.0730, found 302.0728.

TLC: R_f = 0.71 (50% ethyl acetate/hexanes)

Compound 18



Following the General Procedure 2 with **S13** (166.0 mg, 0.4 mmol) and 4-bromopyrimidine (95.0 mg, 0.6 mmol) in NMP (3 mL) for 3.0 F/mol afforded 79.6 mg (65%) of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 2:1 to 1:3).

Physical State: White solid

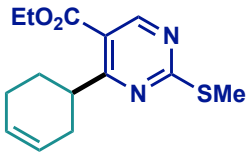
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.53 (s, 2H), 4.54 (br, 1H), 3.03 (d, *J* = 6.5 Hz, 2H), 2.56 (s, 2H), 1.52 (hept, *J* = 7.5 Hz, 4H), 1.45 (s, 9H), 1.33 (dt, *J* = 11.7, 5.2 Hz, 4H), 1.21 (ddd, *J* = 13.5, 8.0, 5.1 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 158.34, 157.07, 156.32, 131.60, 79.70, 45.96, 37.80, 37.68, 32.77, 28.56, 25.96, 21.58.

HRMS (ESI-TOF): calculated for $C_{17}H_{27}N_3O_2$, $[M+H]^+$: 306.2182, found: 306.2190.

TLC: R_f = 0.42 (1:2 hexanes/ethyl acetate)

Compound 19



Following the General Procedure 2 with **S14** (109.0 mg, 0.4 mmol) and ethyl 4-chloro-2-(methylthio)pyrimidine-5-carboxylate (140.0 mg, 0.6 mmol) in DMF (3 mL) for 4.0 F/mol afforded 68.4 mg (61%) of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 20:1 to 15:1).

Physical State: White solid

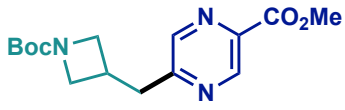
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (s, 1H), 5.82 – 5.70 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.82 (ddt, *J* = 10.8, 7.9, 4.9 Hz, 1H), 2.58 (s, 3H), 2.55 – 2.43 (m, 1H), 2.27 – 2.10 (m, 3H), 1.91 – 1.85 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 175.50, 175.17, 165.31, 159.15, 126.69, 126.43, 118.33, 61.57, 38.72, 30.12, 28.24, 25.72, 14.47, 14.38.

HRMS (ESI-TOF): calculated for $C_{14}H_{18}N_2O_2S$, $[M+H]^+$: 279.1167, found: 279.1171.

TLC: R_f = 0.45 (10:1 hexanes/ethyl acetate)

Compound 20



Following the General Procedure 2 with **S15** (144.0 mg, 0.4 mmol) and methyl 5-chloropyrazine-2-carboxylate (103.5 mg, 0.6 mmol) in NMP (3 mL) for 3.5 F/mol afforded 62.3 mg (51%) of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 2:1 to 1:3).

Physical State: pale yellow solid

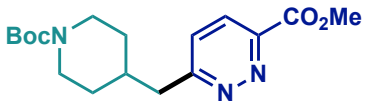
^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (d, *J* = 1.5 Hz, 1H), 8.54 (d, *J* = 1.5 Hz, 1H), 4.06 (t, *J* = 8.4 Hz, 2H), 4.02 (s, 3H), 3.70 (dd, *J* = 8.8, 5.4 Hz, 2H), 3.20 (d, *J* = 7.8 Hz, 2H), 3.04 (pt, *J* = 8.0, 5.4 Hz, 1H), 1.42 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.65, 158.77, 156.47, 145.81, 143.99, 141.34, 79.66, 54.30 (br, low intensity), 53.22, 39.62, 28.54, 28.06.

HRMS (ESI-TOF): calculated for $C_{15}H_{21}N_3O_4$, $[M+H]^+$: 308.1610, found: 308.1613.

TLC: R_f = 0.37 (1:2 hexanes/ethyl acetate)

Compound 21



Following the General Procedure 2 with **S16** (155.0 mg, 0.4 mmol) and methyl 5-chloropyridazine-3-carboxylate (103.5 mg, 0.6 mmol) in DMF (3 mL) for 4.0 F/mol afforded 55.6 mg (41%) of the title compound after purification by column chromatography (gradient elution dichloromethane/methanol from 100:1 to 20:1).

Physical State: pale yellow solid

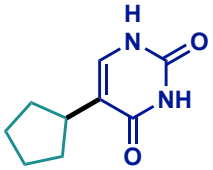
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.6 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 4.08 (m, *J* = 5.5 Hz, 1H), 4.06 (s, 3H), 2.99 (d, *J* = 7.2 Hz, 2H), 2.66 (m, 2H), 2.06 (ddq, *J* = 11.5, 7.7, 3.8 Hz, 1H), 1.61 (d, *J* = 13.2 Hz, 2H), 1.44 (s, 9H), 1.24 (qd, *J* = 12.4, 4.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 164.96, 164.55, 154.96, 150.09, 127.60, 127.49, 79.58, 53.40, 43.81(br, low intensity), 43.20, 36.82, 31.98, 28.61.

HRMS (ESI-TOF): calculated for $C_{17}H_{25}N_3O_4$ $[M\text{-Boc}+2H]^+$: 236.1399, found: 236.1403.

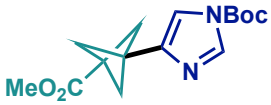
TLC: R_f = 0.33 (2:1 dichloromethane/methanol)

Compound 22



Following the General Procedure 2 with **S17** (103.7 mg, 0.4 mmol) and 5-iodouracil (142.8 mg, 0.6 mmol) or 5-bromouracil (142.8 mg, 0.6 mmol) in NMP (3 mL) for 3.5 F/mol afforded 30.3 mg (42%) and 15.9 mg (22%) respectively of the title compound after purification by column chromatography (ethyl acetate). The spectroscopic data matched the literature.[40]

Compound 23



Following the General Procedure 2 with **S18** (126.1 mg, 0.4 mmol) and tert-butyl 4-iodo-1H-imidazole-1-carboxylate (176.5 mg, 0.6 mmol) or tert-butyl 4-bromo-1H-imidazole-1-carboxylate (148.3 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 37.4 mg (32%) and 18.7 mg (16%) respectively of the title compound after purification by column chromatography (hexanes/ethyl acetate 1:1).

Physical State: White solid

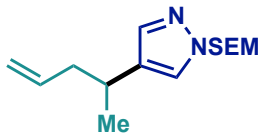
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98 (d, *J* = 1.3 Hz, 1H), 7.12 (d, *J* = 1.3 Hz, 1H), 3.70 (s, 3H), 2.34 (s, 6H), 1.61 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 147.1, 142.1, 137.1, 113.5, 85.8, 53.6, 51.8, 38.5, 36.3, 28.0.

HRMS (ESI-TOF): calculated for $C_{15}H_{20}N_2O_4$ $[M\text{-Boc}+2H]^+$: 193.0977 found: 193.0983.

TLC: R_f = 0.55 (1:1 hexanes/ethyl acetate)

Compound 24



Following the General Procedure 2 with **S19** (103.7 mg, 0.4 mmol) and 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (194.4 mg, 0.6 mmol) in NMP (3 mL) for 3.5 F/mol afforded 21.7 mg (20%) of the title compound after purification by column chromatography (hexanes/ethyl acetate 25:1).

Physical State: Colorless oil.

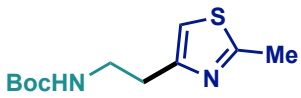
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 (s, 1H), 7.33 (s, 1H), 5.75 (ddt, *J* = 17.1, 10.3, 7.0 Hz, 1H), 5.36 (s, 2H), 5.04 – 4.97 (m, 2H), 3.55 – 3.50 (m, 2H), 2.79 (h, , *J* = 6.9 Hz, 1H), 2.32 (dtt, *J* = 13.6, 6.7, 1,4 Hz, 1H), 2.23 (dtt, *J* = 14.0, 7.2, 1,2 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.90 – 0.86 (m, 2H), –0.03 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.6, 137.0, 128.6, 126.7, 116.4, 80.3, 66.6, 42.7, 29.7, 21.3, 17.9, –1.30.

HRMS (ESI-TOF): calculated for $C_{14}H_{26}N_2OSi$ $[M+H]^+$: 267.1893 found: 267.1895.

TLC: R_f = 0.80 (2:1 hexanes/ethyl acetate)

Compound 25



Following the General Procedure 2 with **S20** (133.7 mg, 0.4 mmol) and 4-iodo-2-methylthiazole (135.0 mg, 0.6 mmol) or 4-bromo-2-methylthiazole (106.8 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 34.9 mg (36%) and 19.0 mg (20%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 10:1 to 4:1).

Physical State: Colorless oil

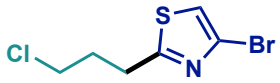
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.97 (s, 1H), 4.91 (br s, 1H), 3.46 (q, *J* = 6.5 Hz, 2H), 2.90 (t, *J* = 6.7 Hz, 2H), 2.69 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.0, 156.0, 154.1, 113.8, 79.3, 40.1, 31.8, 28.6, 19.3.

HRMS (ESI-TOF): calculated for $C_{11}H_{18}N_2O_2S$ $[M+H]^+$: 243.1167 found: 243.1166.

TLC: R_f = 0.24 (1:1 hexanes/ethyl acetate)

Compound 26



Following the General Procedure 2 with **S21** (107.0 mg, 0.4 mmol) and 2,4-dibromothiazole (146.0 mg, 0.6 mmol) in DMF (3 mL) for 3.5 F/mol afforded 47.5 mg (49%) of the title compound after purification by column chromatography (hexanes/ethyl acetate 50:1).

Physical State: Colorless oil

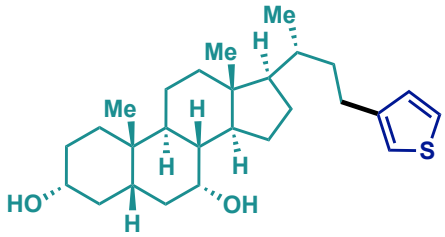
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 1H), 3.62 (t, *J* = 6.3 Hz, 2H), 3.20 – 3.16 (m, 2H), 2.30 – 2.25 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 170.51, 124.74, 116.26, 43.79, 32.10, 30.64.

HRMS (ESI-TOF): calculated for $C_6H_7BrClNS$, $[M+H]^+$: 239.9249, found: 239.9259.

TLC: R_f = 0.38 (10:1 hexanes/ethyl acetate)

Compound 27



Following the General Procedure 2 with **S22** (215.1 mg, 0.4 mmol) and 3-iodothiphene (61 µL, 0.6 mmol) or 3-bromothiophene (56 µL, 0.6 mmol) in DMF (3 mL) for 3.5 F/mol afforded 99.2 mg (58%) with the iodide and 6% NMR yield with the bromide of the title compound after purification of the iodide coupling reaction mixture by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

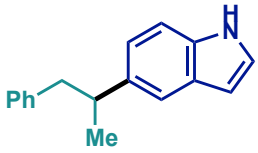
Physical State: White foamy solid

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 4.9, 2.9 Hz, 1H), 6.93 (dd, *J* = 4.9, 1.3 Hz, 1H), 6.91 (dt, *J* = 3.0, 1.1 Hz, 1H), 3.85 (d, *J* = 3.1 Hz, 1H), 3.50 – 3.43 (m, 1H), 2.69 (ddd, *J* = 15.2, 11.0, 4.7 Hz, 1H), 2.51 (ddd, *J* = 14.5, 10.8, 6.1 Hz, 1H), 2.25 – 2.15 (m, 1H), 2.02 – 1.95 (m, 2H), 1.91 (dtd, *J* = 12.9, 9.4, 6.2 Hz, 1H), 1.83 (td, *J* = 12.1, 4.1 Hz, 2H), 1.78 – 1.66 (m, 3H), 1.63 (ddt, *J* = 12.3, 9.5, 4.9 Hz, 2H), 1.54 – 1.42 (m, 4H), 1.42 – 1.23 (m, 7H), 1.23 – 1.18 (m, 2H), 1.18 – 1.07 (m, 1H), 1.02 – 0.97 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 3H), 0.66 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.7, 128.5, 125.2, 119.7, 72.2, 68.7, 56.0, 50.6, 42.9, 41.6, 40.0, 39.8, 39.6, 37.0, 35.7, 35.5, 35.2, 34.7, 33.0, 30.8, 28.4, 27.0, 23.9, 22.9, 20.7, 18.7, 11.9

TLC: R_f = 0.35 (1:1 ethyl acetate/hexanes)

Compound 28



Following the General Procedure 2 with **S23** (123.7 mg, 0.4 mmol) and 5-iodo-1*H*-indole (145.8 mg, 0.6 mmol) or 5-bromo-1*H*-indole (117.6, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 57.3 mg (61%) and 31.0 mg (33%) respectively of the title compound after purification of the iodide coupling reaction mixture by column chromatography (hexanes/ethyl acetate 9:1).

Physical State: Colorless Oil

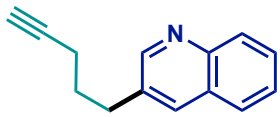
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.32 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.23 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.19 (dd, *J* = 3.1, 2.4 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.14 – 7.11 (m, 2H), 7.07 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.50 (ddd, *J* = 3.0, 2.0, 1.0 Hz, 1H), 3.10 (dq, *J* = 8.6, 6.7 Hz, 1H), 3.03 (dd, *J* = 13.3, 6.2 Hz, 1H), 2.80 (dd, *J* = 13.3, 8.6 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 141.5, 138.9, 134.6, 129.3, 128.2, 128.1, 125.8, 124.4, 121.9, 118.5, 110.9, 102.6, 45.8, 42.0, 21.9.

HRMS (ESI-TOF): calculated for $C_{17}H_{17}N$ $[M+H]^+$: 236.1439 found: 236.1447.

TLC: R_f = 0.45 (4:1 hexanes/ethyl acetate)

Compound 29



Following the General Procedure 2 with **S24** (102.9 mg, 0.4 mmol) and 3-iodo-1,5-naphthyridine (153.0 mg, 0.6 mmol) or 3-bromo-1,5-naphthyridine (124.8, 0.6 mmol) in NMP (3 mL) for 3.5 F/mol afforded 33.9 mg (43%) and 9.1 mg (12%) respectively of the title compound after purification of the iodide coupling reaction mixture by column chromatography (gradient elution, hexanes/ethyl acetate from 10:1 to 6:1).

Physical State: Colorless oil

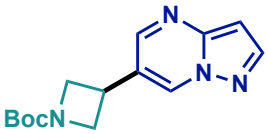
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.80 (d, *J* = 2.3 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.95 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.66 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 2.94 (t, *J* = 7.7 Hz, 2H), 2.27 (td, *J* = 6.9, 2.6 Hz, 2H), 2.04 (t, *J* = .6 Hz, 1H), 1.98 – 1.92 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 152.1, 147.1, 134.6, 134.2, 129.3, 128.9, 128.2, 127.5, 126.8, 83.7, 69.4, 32.0, 29.7, 17.9.

HRMS (ESI-TOF): calculated for $C_{14}H_{13}N$ $[M+H]^+$: 196.1126 found: 196.1127.

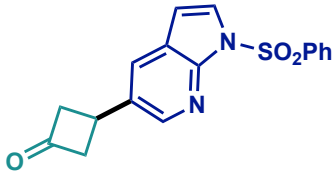
TLC: R_f = 0.52 (2:1 hexanes/ethyl acetate)

Compound 30



Following the General Procedure 2 with **S25** (138.0 mg, 0.4 mmol) and 6-bromopyrazolo[1,5-a]pyrimidine (119.0 mg, 0.6 mmol) in NMP (3 mL) for 3.5 F/mol afforded 34.1 mg (31%) of the title compound after purification by preparative TLC (dichloromethane/methanol 70:1). The spectroscopic data matched the literature.[41]

Compound 31



Following the General Procedure 2 with **S26** (103.7 mg, 0.4 mmol) and 5-bromo-1-(phenylsulfonyl)-1*H*-pyrrolo[2,3-*b*]pyridine (202.3 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 44.6 mg (34%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

Physical State: Clear colorless oil

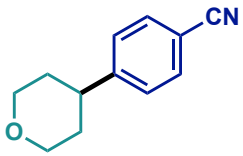
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 2.2 Hz, 1H), 8.22 – 8.17 (m, 2H), 7.79 – 7.77 (m, 1H), 7.75 (d, *J* = 4.0 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 6.58 (dd, *J* = 4.1, 0.8 Hz, 1H), 3.78 (p, *J* = 8.1 Hz, 1H), 3.62 – 3.51 (m, 2H), 3.30 – 3.20 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 205.6, 146.4, 144.3, 138.5, 134.5, 134.2, 129.2, 128.2, 127.4, 127.1, 123.0, 105.3, 55.2, 26.4.

HRMS (ESI-TOF): calculated for $C_{17}H_{14}N_2O_3S$ $[M+H]^+$: 327.0803, found: 327.0806.

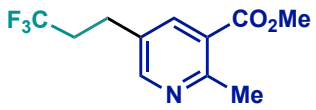
TLC: R_f = 0.16 (3:1 hexanes/ethyl acetate)

Compound 32



Following the General Procedure 3 with tetrahydro-2*H*-pyran-4-carboxylic acid (52.1 mg, 0.4 mmol) and 4-bromobenzonitrile (109.2 mg, 0.6 mmol) in NMP for the electrochemical coupling (2.5 mL) for 2.5 F/mol afforded 46.6 mg (62%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). NMR yield before isolation: 76% using 1,3,5-trimethoxybenzene as an internal standard. The spectroscopic data matched the literature.[42]

Compound 33



Following the General Procedure 3 with 4,4,4-trifluorobutanoic acid (56.8 mg, 0.4 mmol) and methyl 5-iodo-2-methylnicotinate (166.2 mg, 0.6 mmol) in NMP for the electrochemical coupling (2.5 mL) for 2.5 F/mol afforded 32.7 mg (33%) of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 10:1 to 6:1). NMR yield before isolation: 53% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: Colorless oil

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.48 (d, *J* = 2.3 Hz, 1H), 8.04 (d, *J* = 2.4Hz, 1H), 3.93 (s, 3H), 2.92 – 2.89 (m, 2H), 2.81 (s, 3H), 2.46 – 2.36 (m, 2H).

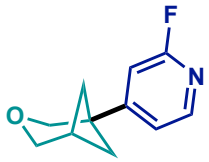
^{13}C NMR (151 MHz, $CDCl_3$): δ 166.9, 158.5, 151.8, 138.2, 131.7, 127.4, 125.3, 52.2, 35.2 (q, *J* = 28.8 Hz), 25.0 (q, *J* = 23.3 Hz), 24.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ 69.14.

HRMS (ESI-TOF): calculated for $C_{11}H_{12}F_3NO_2$ $[M+H]^+$: 248.0898 found: 248.0906.

TLC: R_f = 0.46 (2:1 hexanes/ethyl acetate)

Compound 34



Following the General Procedure 3 with 3-oxabicyclo[3.1.1]heptane-1-carboxylic acid (56.8 mg, 0.4 mmol) and methyl 4-bromo-2-fluoropyridine (105.0 mg, 0.6 mmol) in DMF for the electrochemical coupling (2.5 mL) for 4.0 F/mol afforded 26.4 mg (34%) of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 8:1 to 5:1). NMR yield before isolation: 34% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: Colorless liquid

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 5.2 Hz, 1H), 6.91 – 6.89 (m, 1H), 6.66 – 6.61 (m, 1H), 4.01 (d, J = 2.1 Hz, 2H), 3.89 (s, 2H), 2.49 – 2.42 (m, 1H), 2.24 (td, J = 6.4, 2.6 Hz, 2H), 2.09 (dd, J = 6.3, 2.7 Hz, 2H).

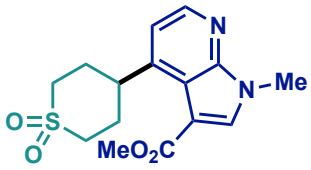
^{13}C NMR (126 MHz, $CDCl_3$): δ 164.21 (d, $^{1}J_{CF}$ = 238.9 Hz), 160.01 (d, $^{3}J_{CF}$ = 7.6 Hz), 147.84 (d, J = 15.3 Hz), 118.68 (d, J_{CF} = 4.3 Hz), 106.57 (d, $^{2}J_{CF}$ = 37.2 Hz), 75.61, 70.31, 46.95 (d, J_{CF} = 2.9 Hz), 35.46, 31.16.

^{19}F NMR (376 MHz, $CDCl_3$): δ -70.61.

HRMS (ESI-TOF): calculated for $C_{11}H_{12}FNO$, $[M+H]^+$: 194.0981, found: 194.0983.

TLC: R_f = 0.45 (4:1 hexanes/ethyl acetate)

Compound 35



Following the General Procedure 3 with tetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide (71.3 mg, 0.4 mmol) and methyl 4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (161.5 mg, 0.6 mmol) in NMP for the electrochemical coupling (2.5 mL) for 2.5 F/mol afforded 55.3 mg (43%) of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 2:1 to 1:2). NMR yield before isolation: 52% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: Colorless solid

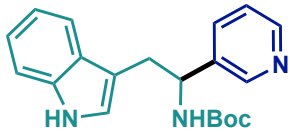
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (d, *J* = 5.0 Hz, 1H), 8.02 (s, 1H), 7.10 (d, *J* = 5.0 Hz, 1H), 4.53 (tt, *J* = 11.9, 3,1 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.40 (td, *J* = 13.9, 3.9 Hz, 2H), 3.20 – 3.13 (m, 2H), 2.43 – 2.36 (m, 2H), 2.36 – 2.29 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 164.7, 148.8, 147.6, 144.7, 137.2, 117.2, 114.8, 105.5, 51.9, 51.6, 38.1, 32.2, 31.0.

HRMS (ESI-TOF): calculated for $C_{15}H_{18}N_2O_4S$ $[M+H]^+$: 323.1066 found: 323.1065.

TLC: R_f = 0.27 (1:2 hexanes/ethyl acetate)

Compound 36



Following the General Procedure 3 with (*tert*-butoxycarbonyl)-*L*-tryptophan (121.7 mg, 0.4 mmol) and 3-iodopyridine (123.0 mg, 0.6 mmol) in NMP for the electrochemical coupling (2.5 mL) for 2.5 F/mol afforded 42.0 mg (31%) of the title compound after purification by column chromatography (gradient elution, dichloromethane to 20:1 dichloromethane/methanol). NMR yield before isolation: 46% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: White foamy solid.

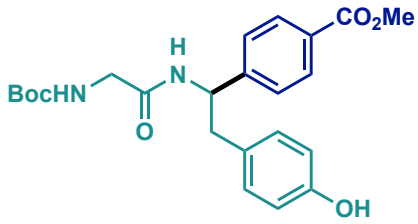
^{1}H NMR (600 MHz, CD_3OD): δ 8.35 (br s, 1H), 8.34 (br s, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.34 (br s, 1H), 7.31 (t, *J* = 8.8 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.91 (s, 1H), 4.96 (t, *J* = 7.7 Hz, 1H), 3.25 (dd, *J* = 14.4, 7.3 Hz, 1H), 3.12 (dd, *J* = 14.4, 7.8 Hz, 1H), 1.39 (s, 9H).

^{13}C NMR (151 MHz, CD_3OD): δ 157.7, 148.6, 148.3, 141.3, 138.0, 136.4, 128.7, 125.0, 124.5, 122.4, 119.8, 119.2, 112.3, 111.6, 80.5, 55.0, 33.7, 28.7.

HRMS (ESI-TOF): calculated for $C_{20}H_{23}N_3O_2$ $[M+H]^+$: 338.1869, found: 338.1872.

TLC: R_f = 0.08 (diethyl ether)

Compound 37



Following the General Procedure 3 with (*tert*-butoxycarbonyl)glycyl-*D*-tyrosine (135.4 mg, 0.4 mmol) and methyl 4-iodobenzoate (157.3 mg, 0.6 mmol) in NMP for the electrochemical coupling (2.5 mL) for 2.5 F/mol afforded 68.8 mg (40%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). NMR yield before isolation: 45% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: Clear amorphous solid.

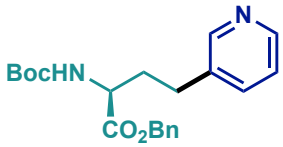
^{1}H NMR (600 MHz, CD_3OD): δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.69 – 6.58 (m, 2H), 5.14 (t, *J* = 7.4 Hz, 1H), 3.89 (s, 3H), 3.72 – 3.56 (m, 2H), 3.02 – 2.93 (m, 2H), 1.44 (s, 9H).

^{13}C NMR (151 MHz, CD_3OD): δ 171.8, 168.4, 158.4, 157.2, 149.1, 131.3, 130.5, 130.1, 129.4, 128.0, 116.1, 80.8, 56.3, 52.6, 44.6, 42.5, 28.7.

HRMS (ESI-TOF): calculated for $C_{23}H_{28}N_2O_6$ $[M+H]^+$: 429.2026, found: 429.2022.

TLC: R_f = 0.11 (1:1 hexanes/ethyl acetate)

Compound 38



Following the General Procedure 2 with **39** (193.0 mg, 0.4 mmol) and 3-iodopyridine (123.0 mg, 0.6 mmol) or 3-bromopyridine (59 µL, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 93 mg (63%) and 67 mg (45%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

BATCH SCALE UP PROCEDURE

Following the General Procedure 4 with **39** (2.41 g, 5.0 mmol) and 3-iodopyridine (1.54 mg, 7.5 mmol) or 3-bromopyridine (732 µL, 7.5 mmol) in NMP (18 mL) for 3.5 F/mol afforded 977 mg (52%) and 745 mg (40%) respectively of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

FLOW

Following the General Procedure 5 with *N*-(*tert*-Butoxycarbonyl)-L-glutamic acid 1-benzyl ester (33.7 g, 100.0 mmol) and 3-iodopyridine (30.8 mg, 150 mmol) in NMP (625 mL) for 4.5 F/mol afforded 18.1 g (49%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate).

Physical State: Pale yellow oil

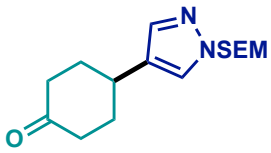
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.44 (d, *J* = 4.8 Hz, 1H), 8.37 (d, *J* = 2.3 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.40 – 7.32 (m, 5H), 7.19 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.12 (d, *J* = 12.3 Hz, 1H), 5.12 (br s, 1H), 4.41 (s, 1H), 2.65 (ddd, *J* = 14.1, 10.5, 6.1 Hz, 1H), 2.57 (td, *J* = 12.5, 5.6 Hz, 1H), 2.21 – 2.08 (m, 1H), 1.94 (dddd, *J* = 13.5, 10.6, 7.6, 5.6 Hz, 1H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.3, 155.4, 150.0, 147.9, 136.2, 136.0, 135.4, 128.8, 128.8, 128.6, 123.5, 80.3, 67.4, 53.3, 34.3, 28.8, 28.5.

HRMS (ESI-TOF): calculated for $C_{21}H_{26}N_2O_4$ $[M+H]^+$: 371.1971, found: 371.1962.

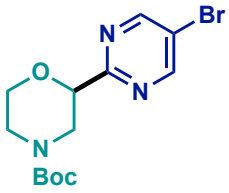
TLC: R_f = 0.20 (1:1 hexanes/ethyl acetate)

Compound 40



Following the General Procedure 2 with **42** (114.9 mg, 0.4 mmol) and 4-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole (194.5 mg, 0.6 mmol) in DMF (3 mL) for 4.0 F/mol afforded 37.0 mg (31%) of the title compound after purification by column chromatography (gradient elution, hexanes/ethyl acetate from 4:1 to 1:1). The spectroscopic data matched the literature.[43]

Compound 44



Following the General Procedure 2 with **47** (114.9 mg, 0.4 mmol) and 5-bromo-2-iodopyrimidine (171.0 mg, 0.6 mmol) in DMF (3 mL) for 4.0 F/mol afforded 38.6 mg (28%) of the title compound after purification by column chromatography (hexanes/ethyl acetate 2:1).

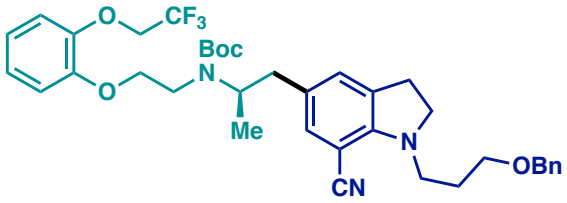
Physical State: White solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.81 (s, 2H), 4.63 (dd, *J* = 10.7, 2.8 Hz, 1H), 4.34 (d, *J* = 70.8 Hz, 1H), 4.10 (d, *J* = 11.2 Hz, 1H), 3.96 (s, 1H), 3.73 (td, *J* = 11.7, 2.9 Hz, 1H), 3.07 (s, 2H), 1.47 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$): δ 164.8, 158.2, 154.7, 119.6, 80.5, 77.9, 67.0, 48.1, 47.1, 44.0, 42.7, 28.5.

HRMS (ESI-TOF): calculated for $C_{13}H_{18}BrN_3O_3$ $[M\text{-}Boc+2H]^+$: 244.0080 found: 244.0073.

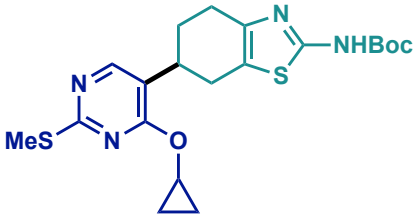
TLC: R_f = 0.55 (1:1 hexanes/ethyl acetate)

Compound 48



Following the General Procedure 2 with **49** (230.9 mg, 0.4 mmol) and 1-(3-(benzyloxy)propyl)-5-bromoindoline-7-carbonitrile (222.6 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 98.8 mg (37%) of the title compound after purification by column chromatography hexanes/ethyl acetate 4:1). The spectroscopic data matched the literature.[27]

Compound 51



Following the General Procedure 2 with **49** (114.9 mg, 91 wt/wt%, 0.36 mmol) and 5-bromo-4-cyclopropoxy-2-(methylthio)pyrimidine (156.7 mg, 0.6 mmol) in NMP (3 mL) for 2.5 F/mol afforded 64.3 mg (41%) of the title compound after purification by column chromatography (hexanes/ethyl acetate 3:1).

Physical State: White Solid

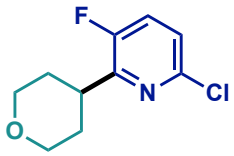
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.11 (s, 1H), 4.44 (tt, *J* = 6.4, 3.1 Hz, 1H), 3.09 (td, *J* = 8.4, 7.6, 4.6 Hz, 1H), 2.94 – 2.87 (m, 1H), 2.84 – 2.69 (m, 3H), 2.55 (s, 3H), 2.00 (dd, *J* = 7.9, 4.8 Hz, 2H), 1.52 (s, 9H), 0.84 – 0.78 (m, 2H), 0.78 – 0.73 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.8, 167.4, 159.0, 154.6, 152.7, 143.9, 120.5, 119.7, 82.5, 51.0, 32.7, 28.4, 28.2, 27.9, 26.0, 14.3, 5.9.

HRMS (ESI-TOF): calculated for $C_{20}H_{26}N_4O_3S_2$ $[M+H]^+$: 435.1525 found: 435.1522.

TLC: R_f = 0.60 (2:1 hexanes/ethyl acetate)

Compound 81



Following the General Procedure 1 (in parallel on carousel with **81 – 86**) with **55** (110.10 mg, 0.4 mmol) and 2-bromo-6-chloro-3-fluoropyridine (126.3 mg, 0.6 mmol) in NMP for the electrochemical coupling (3 mL) for 2.5 F/mol afforded 38.0 mg (44%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). NMR yield before isolation: 51% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: White solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.35 (dd, *J* = 2.1, 0.8 Hz, 1H), 7.38 (dd, *J* = 9.4, 2.0 Hz, 1H), 4.09 (ddt, *J* = 11.6, 4.5, 1.1 Hz, 2H), 3.56 (td, *J* = 12.0, 2.1 Hz, 2H), 3.25 (ttd, *J* = 11.8, 3.8, 1.7 Hz, 1H), 2.03 (dtd, *J* = 13.6, 12.0, 4.4 Hz, 2H), 1.83 – 1.66 (m, 2H).

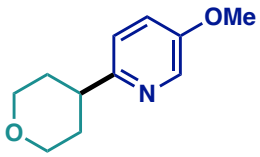
^{13}C NMR (151 MHz, $CDCl_3$): δ 157.4, 155.7, 150.7, 150.6, 144.0, 129.7, 123.3, 123.2, 123.1, 123.1, 68.1, 68.1, 68.0, 68.0, 36.7, 30.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -127.2.

HRMS (ESI-TOF): calculated for $C_{10}H_{11}ClFNO$ $[M+H]^+$: 216.0591 found: 216.0598.

TLC: R_f = 0.58 (3:1 hexanes/ethyl acetate)

Compound 82



Following the General Procedure 1 (in parallel on carousel with **81 – 86**) with **55** (110.10 mg, 0.4 mmol) and 2-bromo-5-methoxypyridine (112.8 mg, 0.6 mmol) in NMP for the electrochemical coupling (3 mL) for 2.5 F/mol afforded 24.5 mg (32%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). NMR yield before isolation: 34% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: Pale yellow oil

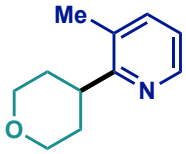
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23 (dd, *J* = 3.0, 0.7 Hz, 1H), 7.15 (dd, *J* = 8.6, 3.0 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 4.11 – 4.04 (m, 2H), 3.83 (s, 3H), 3.58 – 3.48 (m, 2H), 2.94 – 2.85 (m, 1H), 1.84 (ddt, *J* = 9.1, 5.3, 3.8 Hz, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.1, 147.0, 138.0, 130.2, 121.3, 68.4, 39.5, 31.5, 18.7.

HRMS (ESI-TOF): calculated for $C_{11}H_{15}NO_2$ $[M+H]^+$: 194.1181 found: 194.1185.

TLC: R_f = 0.22 (1:1 hexanes/ethyl acetate)

Compound 83



Following the General Procedure 1 (in parallel on carousel with **81 – 86**) with **55** (110.10 mg, 0.4 mmol) and 2-iodo-3-methylpyridine (131.4 mg, 0.6 mmol) in NMP for the electrochemical coupling (3 mL) for 2.5 F/mol afforded 20.2 mg (28%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). NMR yield before isolation: 28% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: Pale yellow oil

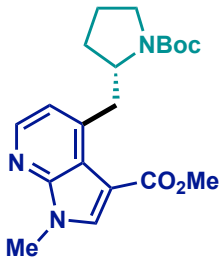
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.42 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.6, 1.8, 0.9 Hz, 1H), 7.02 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.10 (ddt, *J* = 11.6, 4.6, 1.1 Hz, 2H), 3.56 (ddd, *J* = 12.3, 11.3, 2.0 Hz, 2H), 3.09 (tt, *J* = 11.7, 3.7 Hz, 1H), 2.35 (s, 3H), 2.09 (dddd, *J* = 13.7, 12.3, 11.5, 4.4 Hz, 2H), 1.70 – 1.59 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.1, 147.0, 138.0, 130.2, 121.3, 68.4, 39.5, 31.5, 18.7.

HRMS (ESI-TOF): calculated for $C_{11}H_{15}NO$ $[M+H]^+$: 178.1232 found: 178.1237.

TLC: R_f = 0.32 (1:1 hexanes/ethyl acetate)

Compound 84



Following the General with Procedure 1 (in parallel on carousel with **81 – 86**) with **S28** (149.8 mg, 0.4 mmol) and methyl 4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (161.5 mg, 0.6 mmol) in NMP for the electrochemical coupling (3 mL) for 2.5 F/mol afforded 67.8 mg (46%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). NMR yield before isolation: 57% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: Foamy solid.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.25 (dd, *J* = 17.0, 4.8 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 4.8 Hz, 1H), 3.89 (d, *J* = 5.7 Hz, 3H), 3.84 (d, *J* = 6.9 Hz, 3H), 3.55 – 3.25 (m, 4H), 3.20 (qd, *J* = 10.6, 7.1 Hz, 1H), 3.02 (dd, *J* = 10.7, 8.4 Hz, 1H), 2.50 (tt, *J* = 15.3, 8.0 Hz, 1H), 1.84 (dd, *J* = 12.9, 7.6 Hz, 1H), 1.70 – 1.53 (m, 1H), 1.42 (s, 9H).

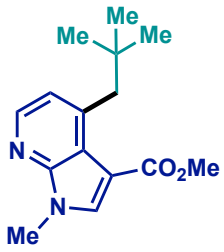
^{13}C NMR (151 MHz, $CDCl_3$): (1:1 mixture of rotamers) *Rotamer 1* δ 164.4, 154.8, 148.9, 144.9, 144.0, 136.6, 119.8, 117.8, 105.9, 79.0, 51.4, 51.3, 45.8, 40.6, 37.8, 32.1, 31.6, 28.7.

Rotamer 2 δ 164.4, 154.7, 148.9, 144.9, 144.0, 136.6, 119.8, 117.7, 105.9, 79.0, 51.4, 50.8, 45.4, 40.0, 37.6, 32.1, 30.6, 28.6.

HRMS (ESI-TOF): calculated for $C_{20}H_{27}N_3O_4$ $[M+Na]^+$: 396.1603 found: 396.1909.

TLC: R_f = 0.29 (1:1 hexanes/ethyl acetate)

Compound 85



Following the General Procedure 1 (in parallel on carousel with **81 – 86**) with **S36** (104.5 mg, 0.4 mmol) and methyl 4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (161.5 mg, 0.6 mmol) in NMP for the electrochemical coupling (3 mL) for 2.5 F/mol afforded 39.8 mg (37%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). NMR yield before isolation: 47% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: clear colorless oil

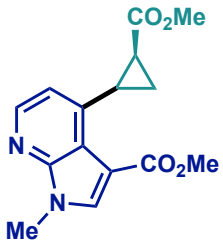
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26 (d, *J* = 4.9 Hz, 1H), 7.95 (s, 1H), 6.96 (d, *J* = 4.9 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.41 (s, 2H), 0.89 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 164.7, 148.8, 144.9, 143.1, 136.8, 121.7, 119.4, 106.7, 51.4, 45.7, 33.1, 32.1, 29.6.

HRMS (ESI-TOF): calculated for $C_{15}H_{20}N_2O_2$ $[M+H]^+$: 261.1603 found: 261.1610.

TLC: R_f = 0.29 (1:1 hexanes/ethyl acetate)

Compound 86



Following the General Procedure 4 with **S29** (115.7 mg, 0.4 mmol) and methyl 4-bromo-1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxylate (161.5 mg, 0.6 mmol) in NMP for the electrochemical coupling (3 mL) for 2.5 F/mol afforded 5.0 mg (5%) of the title compound after purification by column chromatography (gradient elution, hexanes to 1:1 hexanes/ethyl acetate). NMR yield before isolation: 11% using 1,3,5-trimethoxybenzene as an internal standard.

Physical State: White amorphous solid

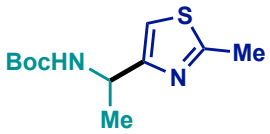
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, *J* = 5.0 Hz, 1H), 7.98 (s, 1H), 6.73 (d, *J* = 5.0 Hz, 1H), 3.98 – 3.93 (m, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 1.92 (ddd, *J* = 8.3, 5.4, 4.4 Hz, 1H), 1.76 (dt, *J* = 9.6, 5.0 Hz, 1H), 1.52 – 1.42 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.6, 164.5, 148.5, 144.4, 144.1, 136.6, 118.6, 113.9, 106.5, 52.1, 52.0, 51.5, 51.5, 32.2, 32.2, 24.9, 24.9, 24.8, 24.7, 16.7, 16.6.

HRMS (ESI-TOF): calculated for $C_{15}H_{16}N_2O_4$ $[M+H]^+$: 289.1188 found: 289.1194.

TLC: R_f = 0.60 (ethyl acetate) Unstable to SiO_2 Cyclopropane opening and decomposition observed.

Compound S34



Following the General Procedure 4 with 1,3-dioxoisoindolin-2-yl (tert-butoxycarbonyl)alaninate (134 mg, 0.4 mmol) and 4-iodo-2-methylthiazole (135 mg, 0.600 mmol), in NMP for the electrochemical coupling (3 mL) for 5.0 F/mol afforded 33.0 mg (34%) of the title compound after purification by reverse phase HPLC.

Physical State: White amorphous solid

^{1}H NMR (400 MHz, DMSO): δ 7.19 (d, *J* = 8.5 Hz, 1H), 7.08 (s, 1H), 4.70 (q, *J* = 7.6 Hz, 1H), 2.61 (s, 3H), 1.38 (s, 9H), 1.33 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, DMSO): δ 164.9, 159.0, 154.8, 112.6, 77.7, 46.7, 28.2, 21.1, 18.7

HRMS (ESI-TOF): calculated for $C_{11}H_{18}N_2O_2S$ $[M+H]^+$: 243.1162 found: 243.1155.

TLC: R_f = 0.53 (1:1 heptane/ethyl acetate)

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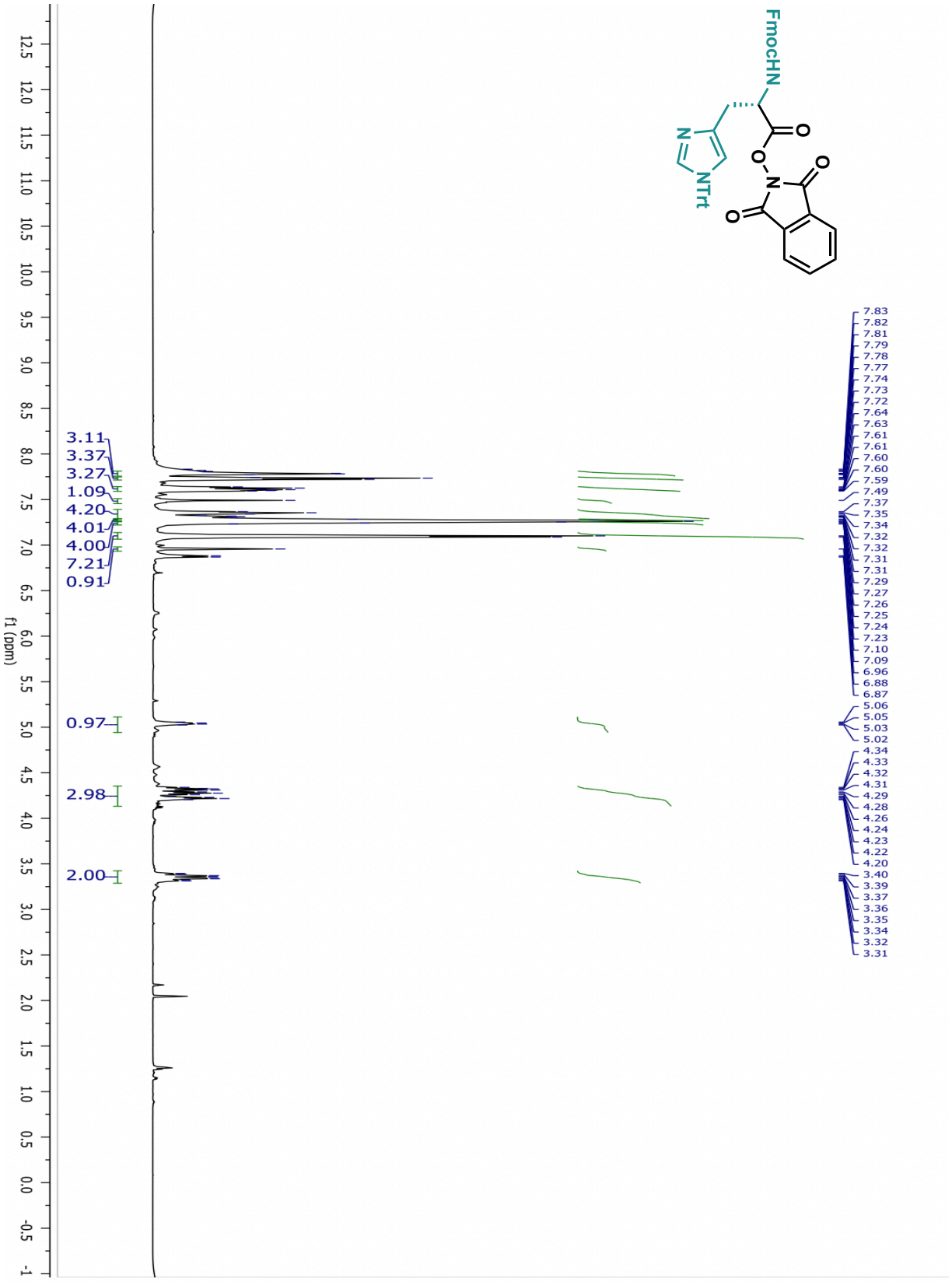
NMR Spectra

Compound S5 ^{1}H-NMR



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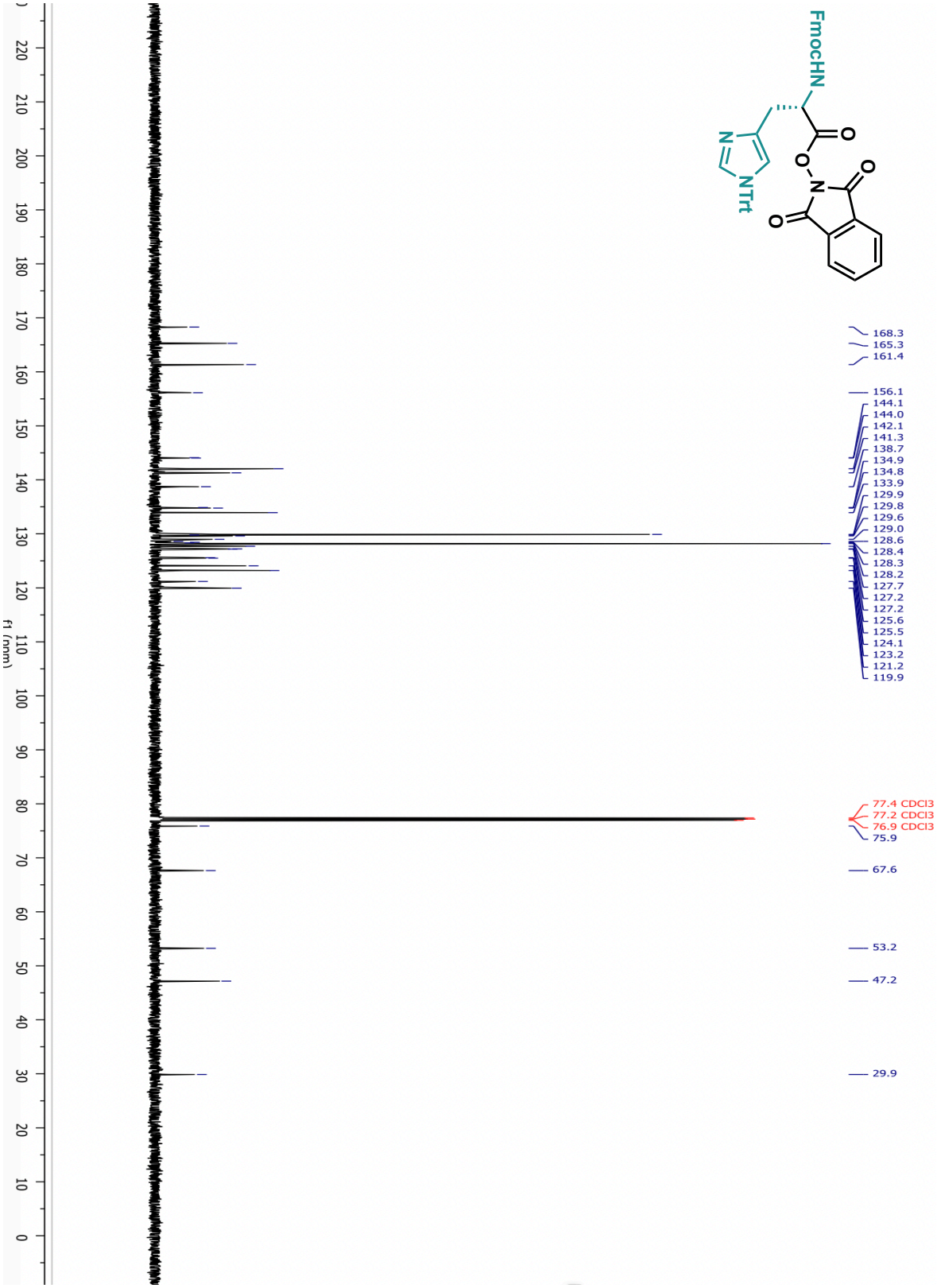

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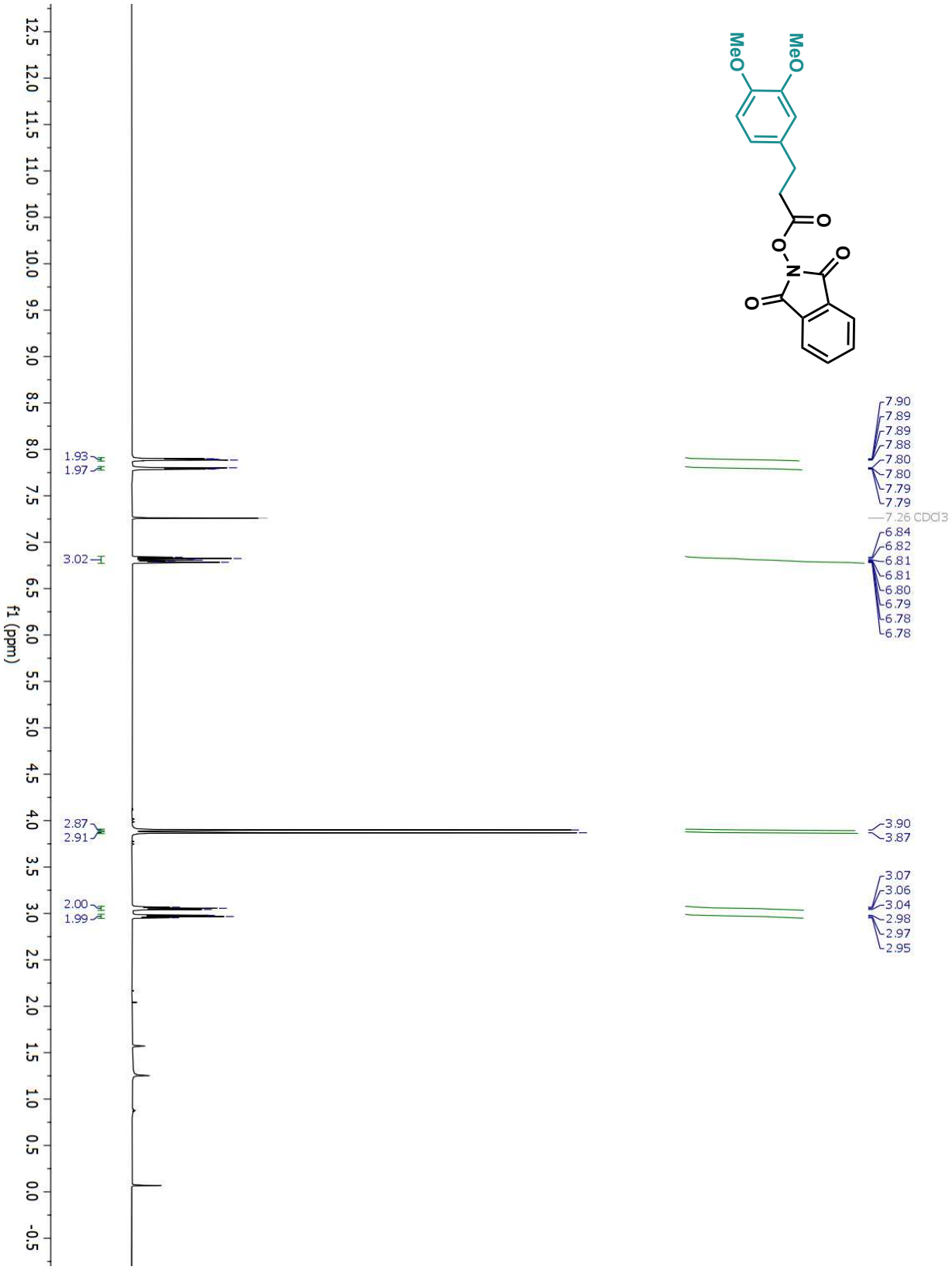

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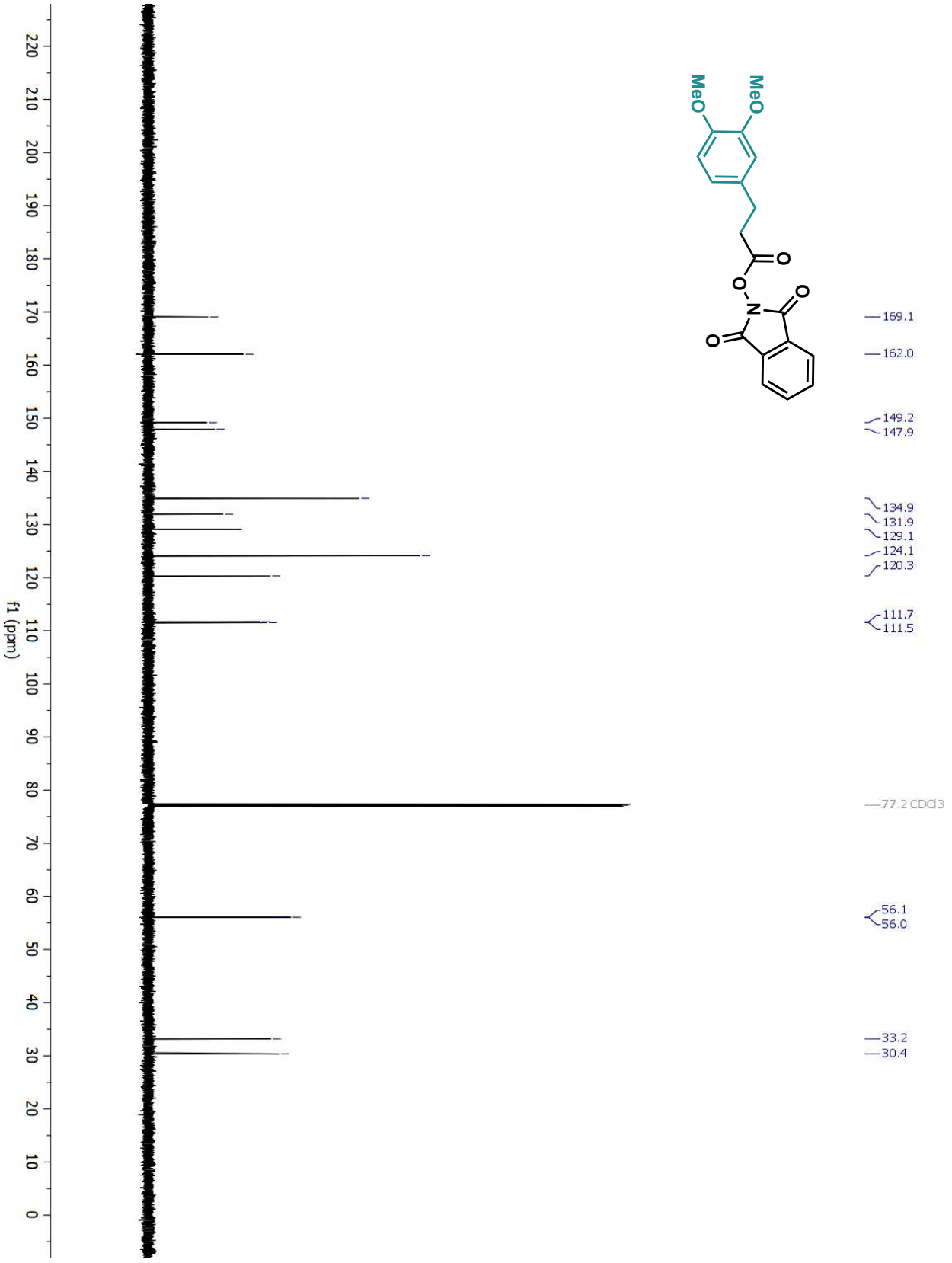

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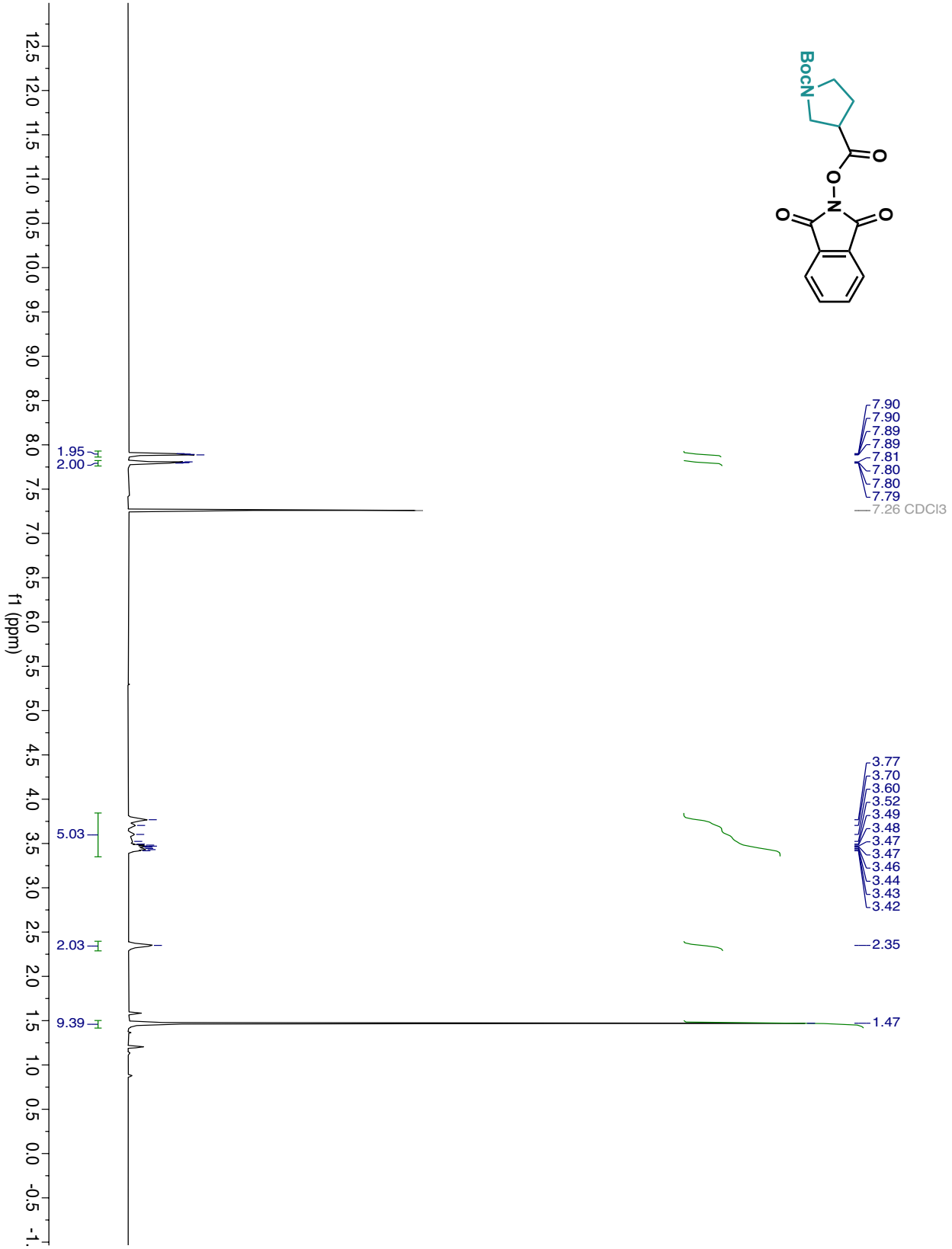

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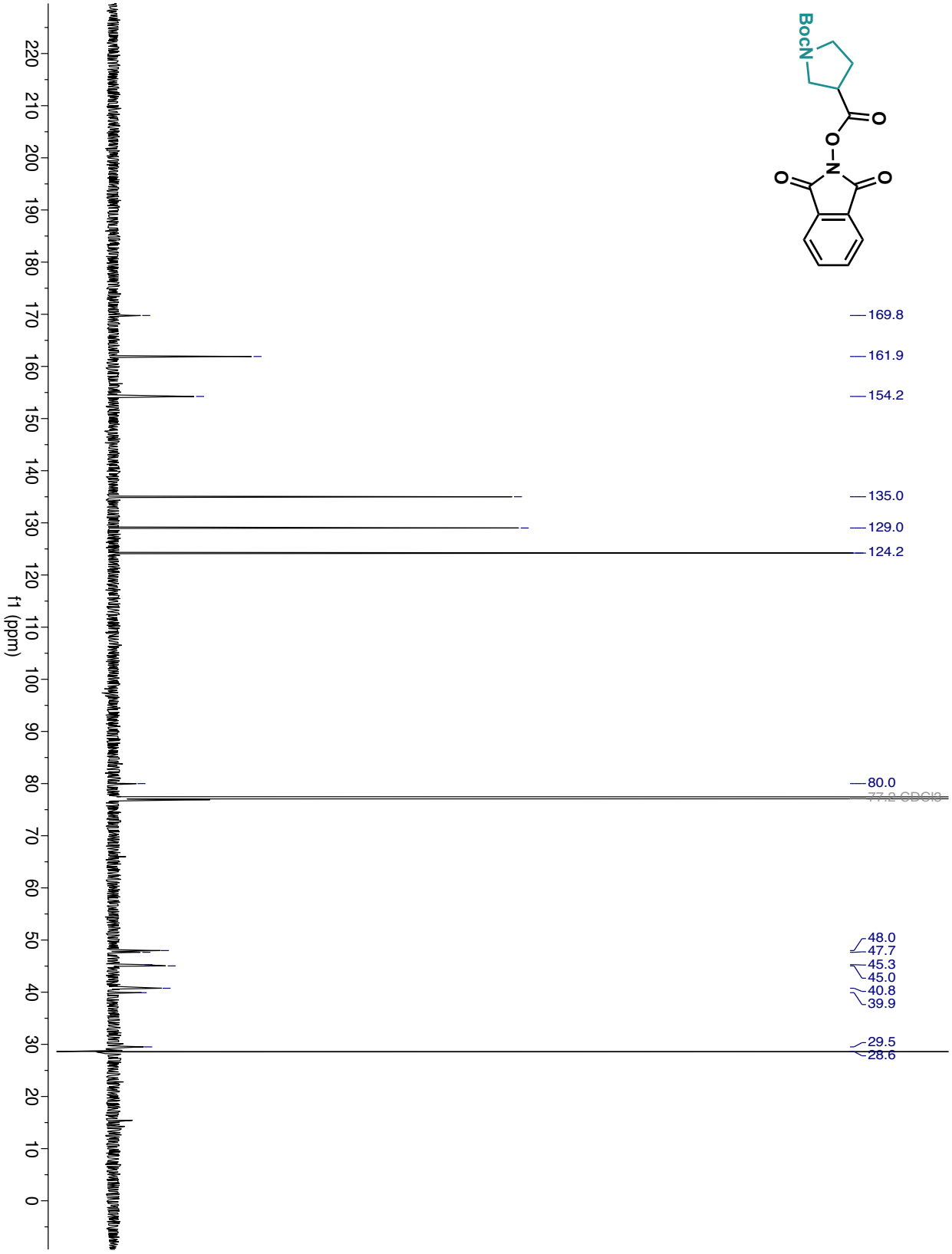

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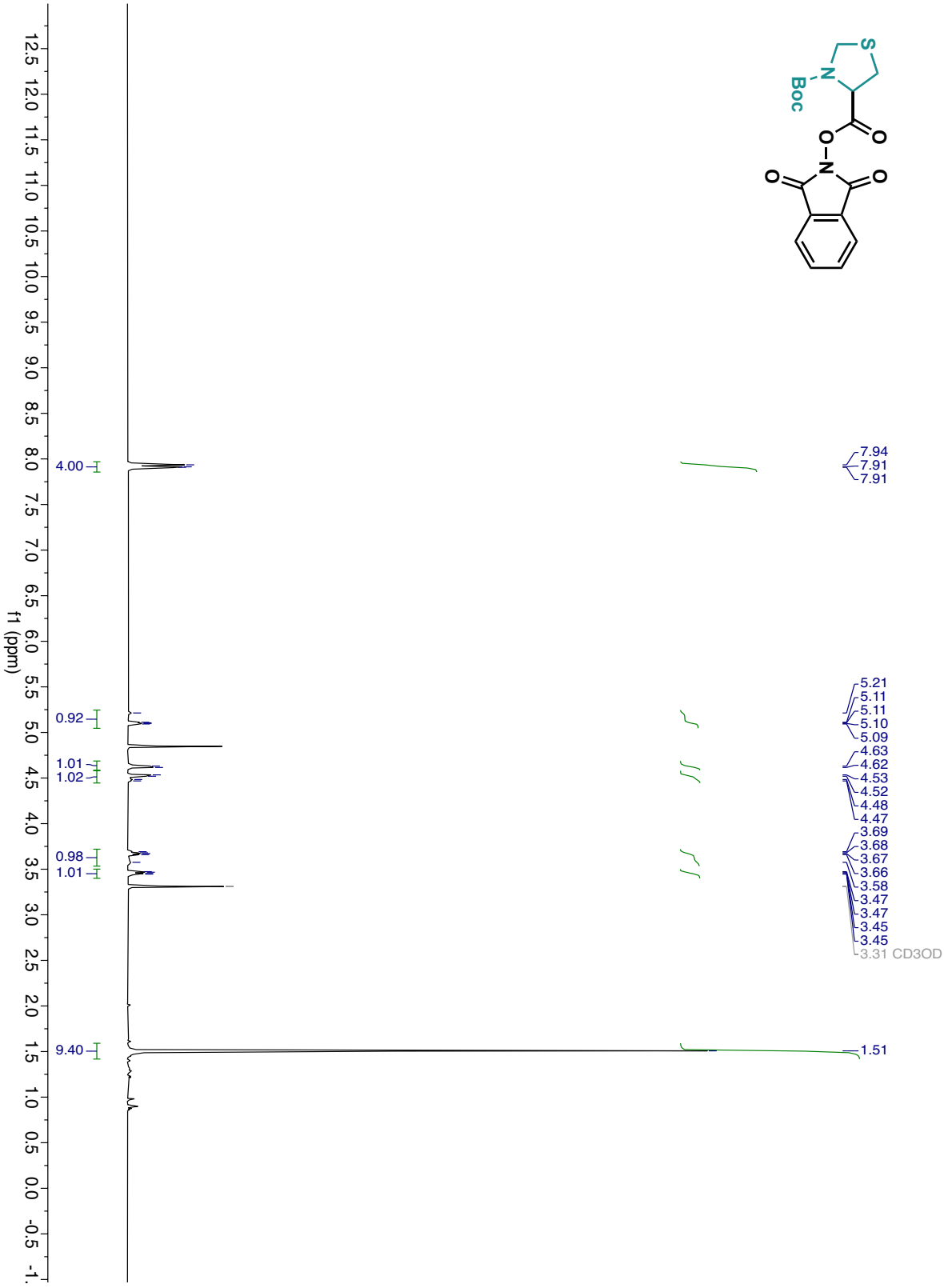

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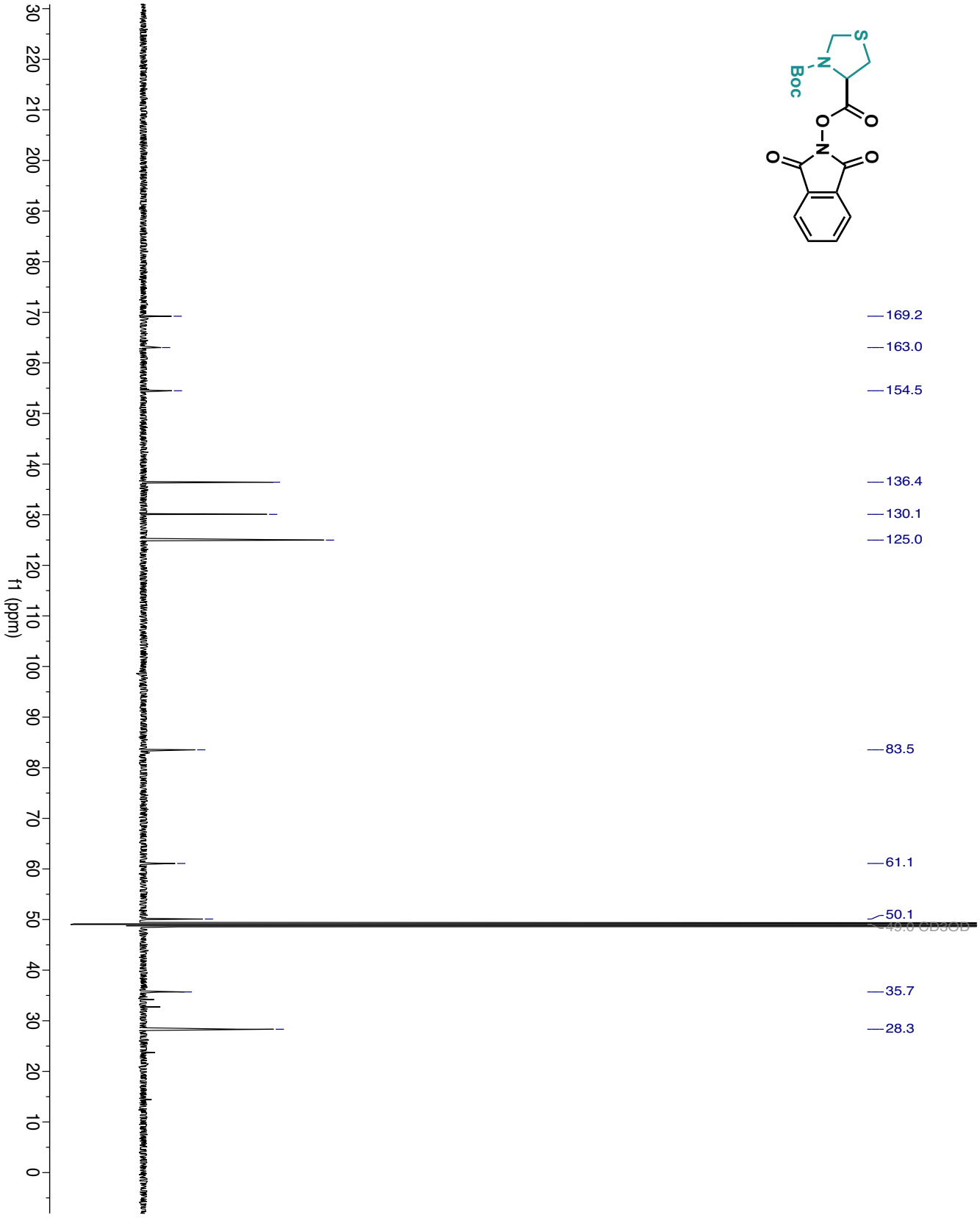

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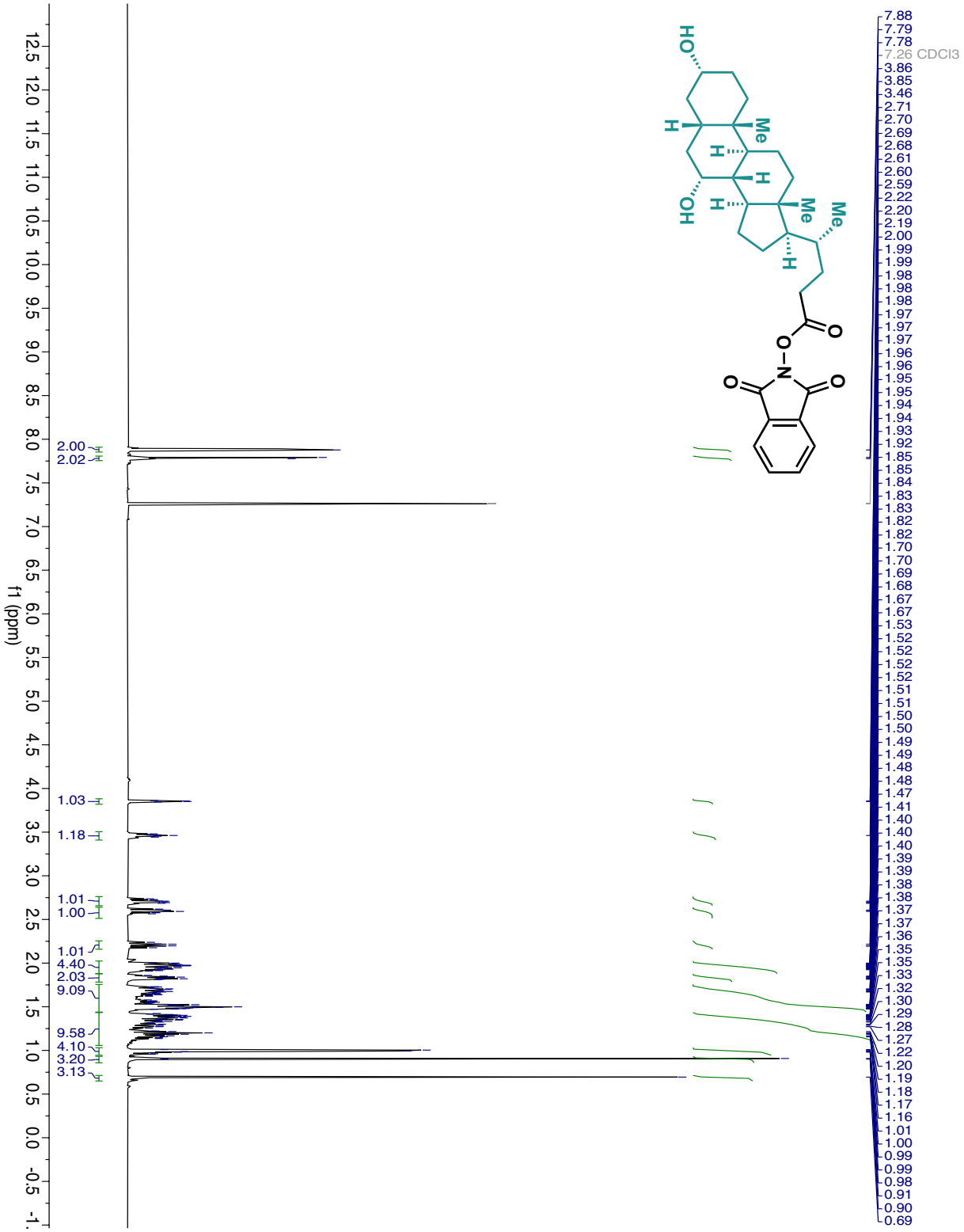

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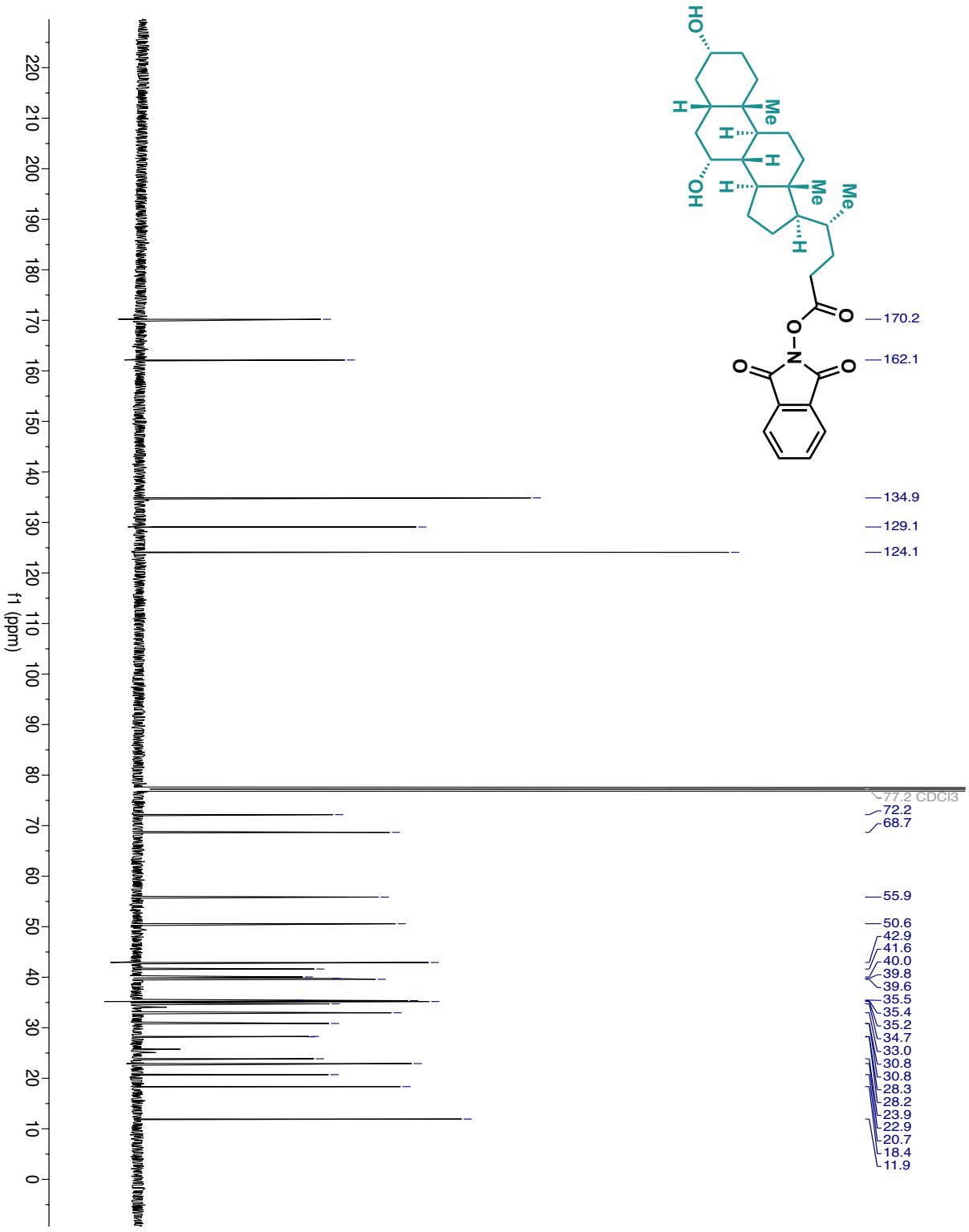

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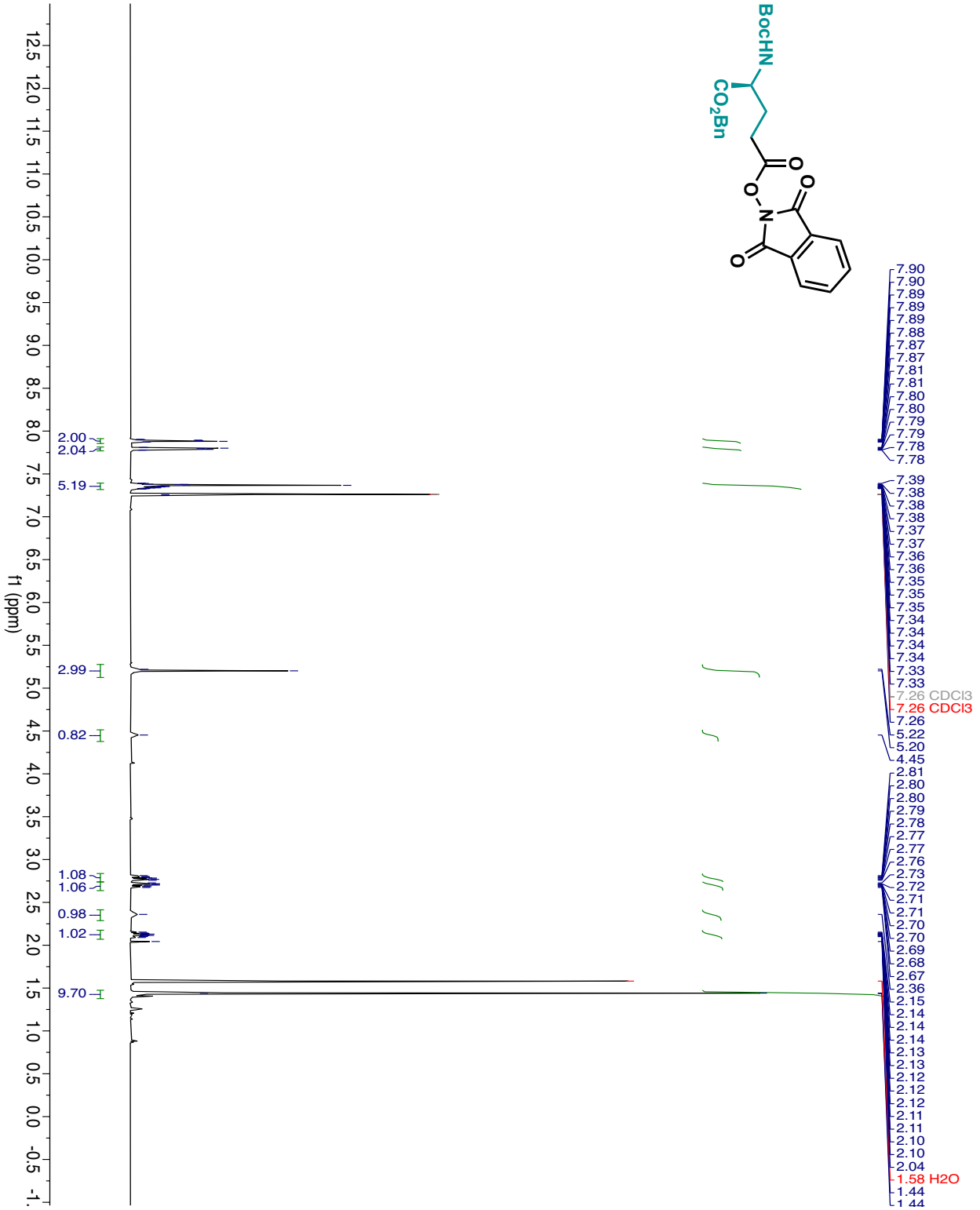

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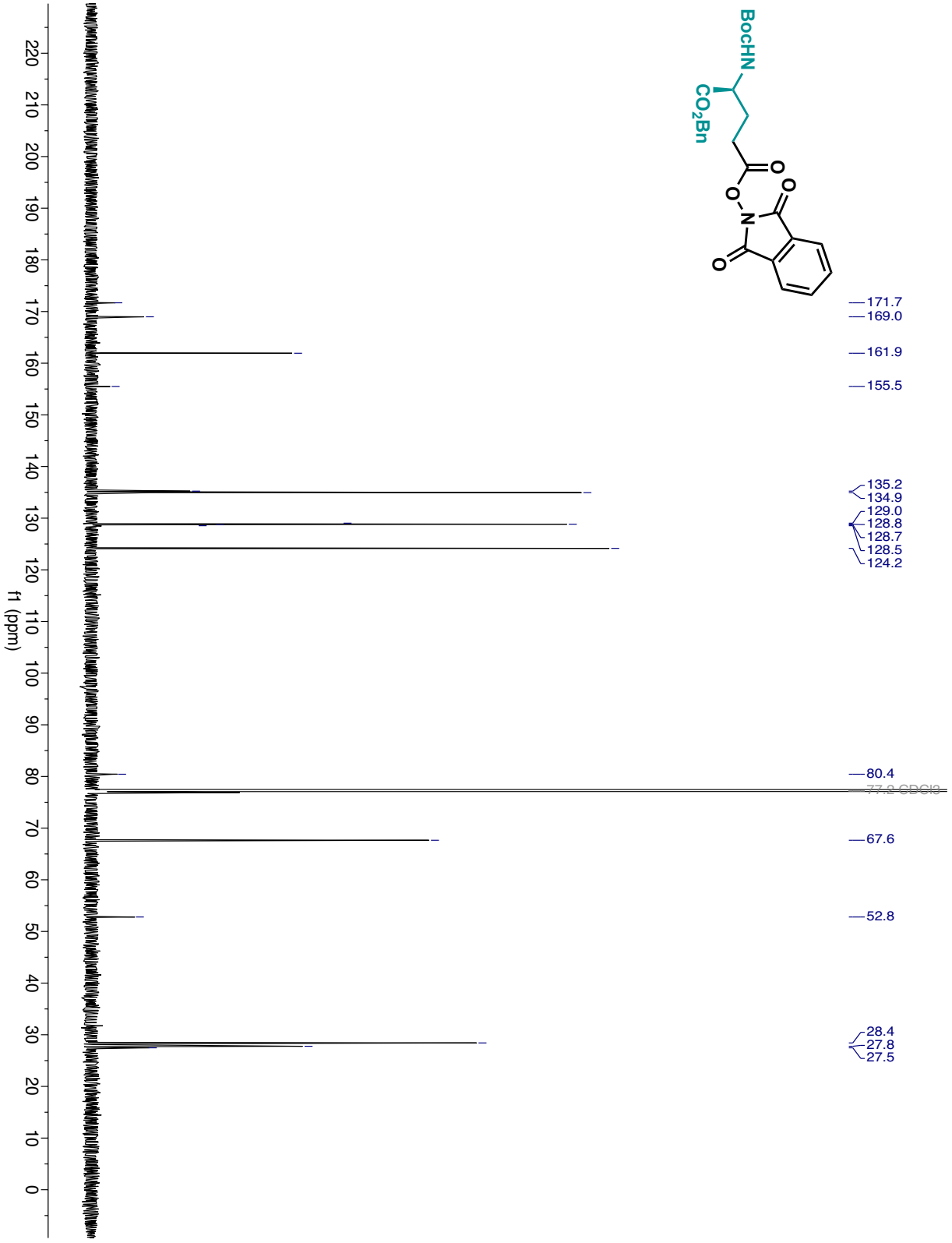

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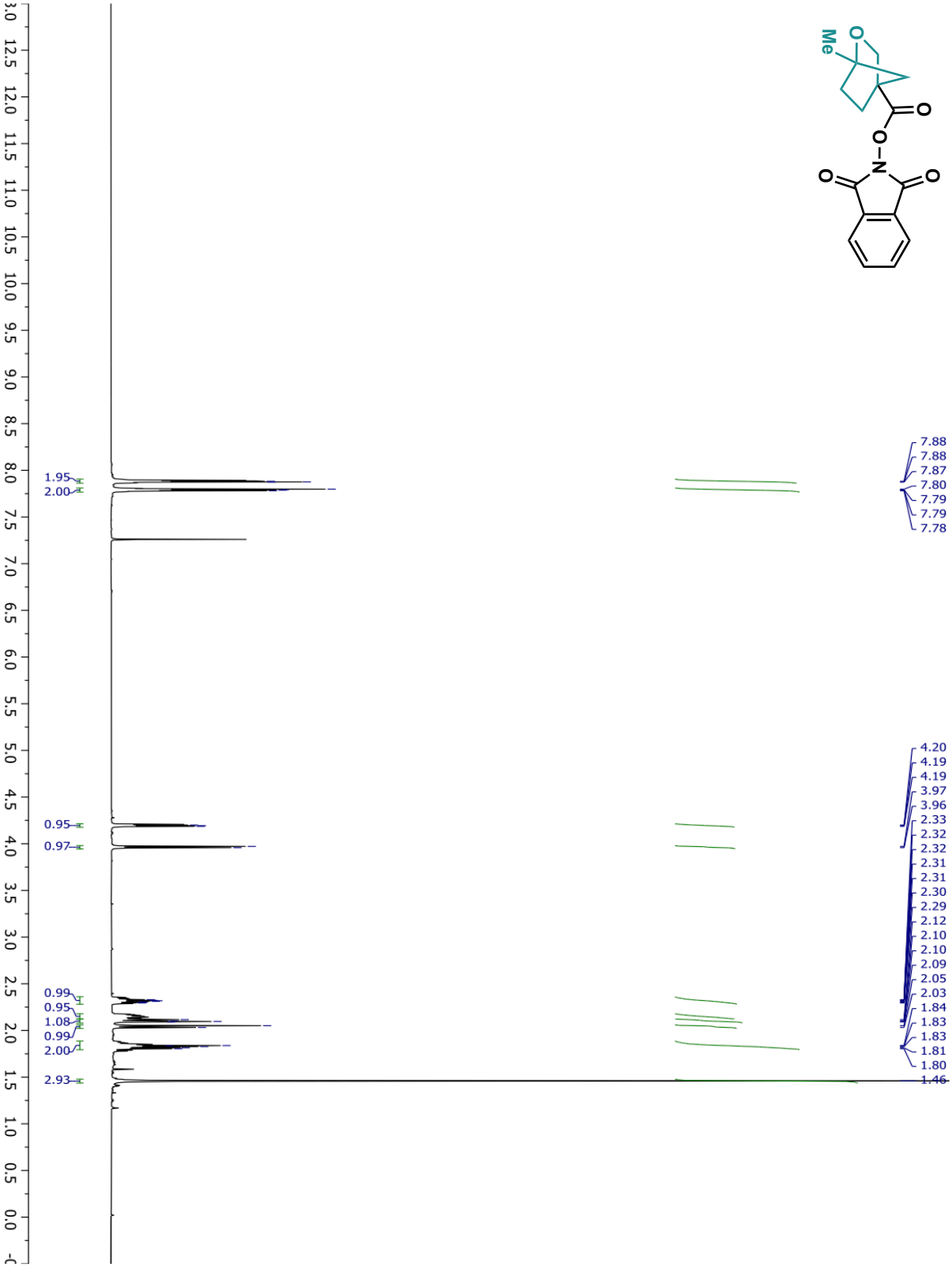

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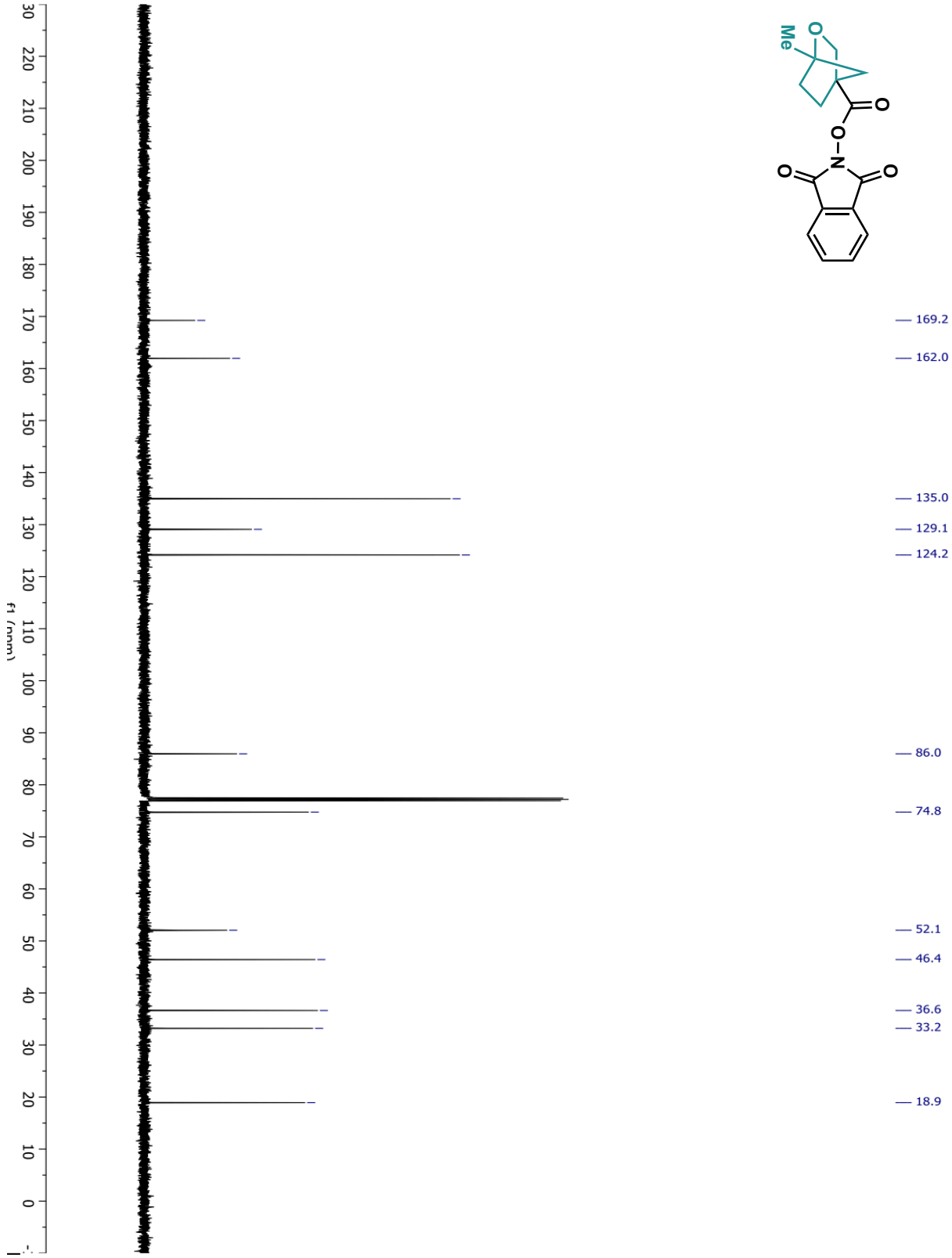

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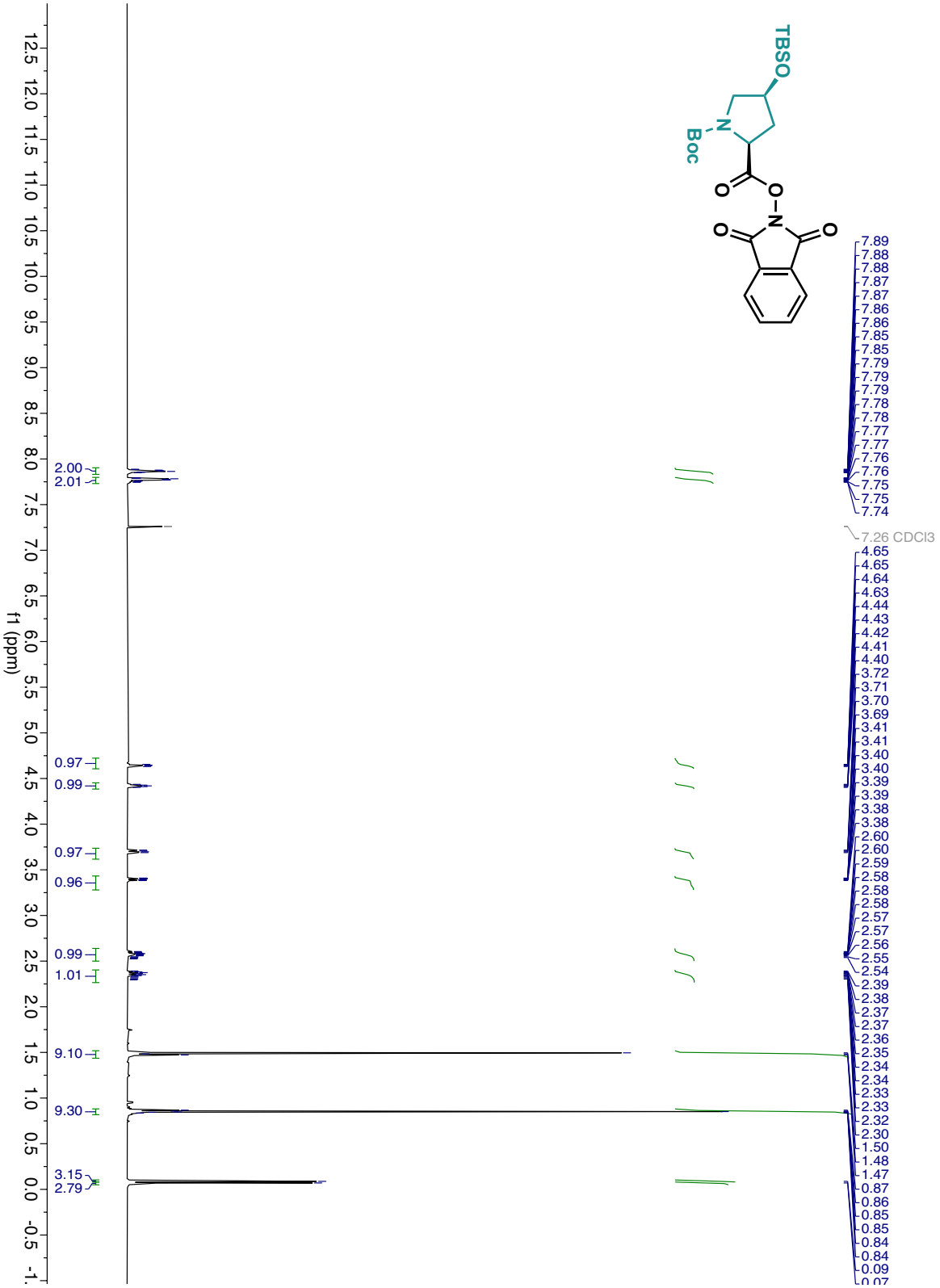

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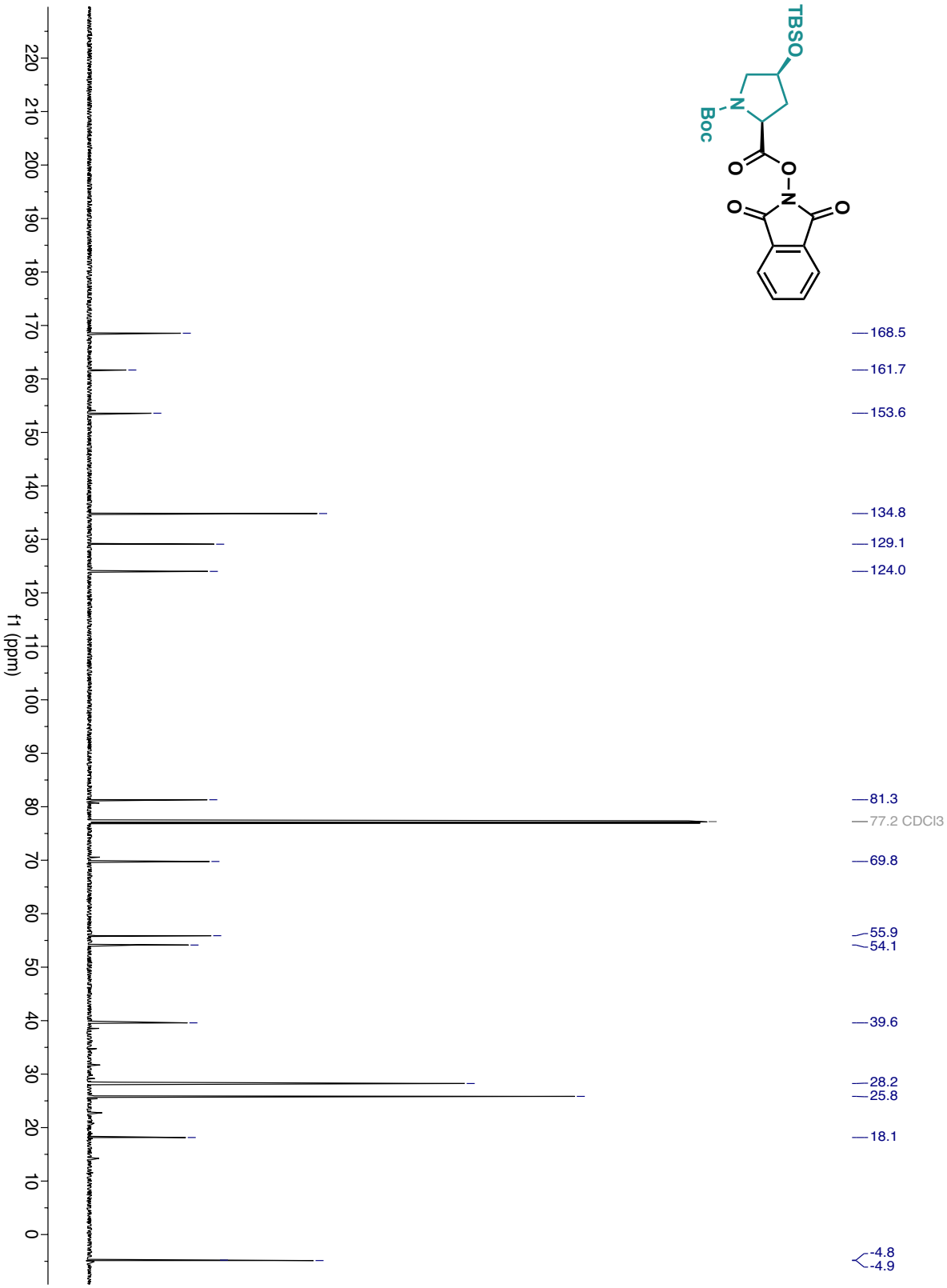

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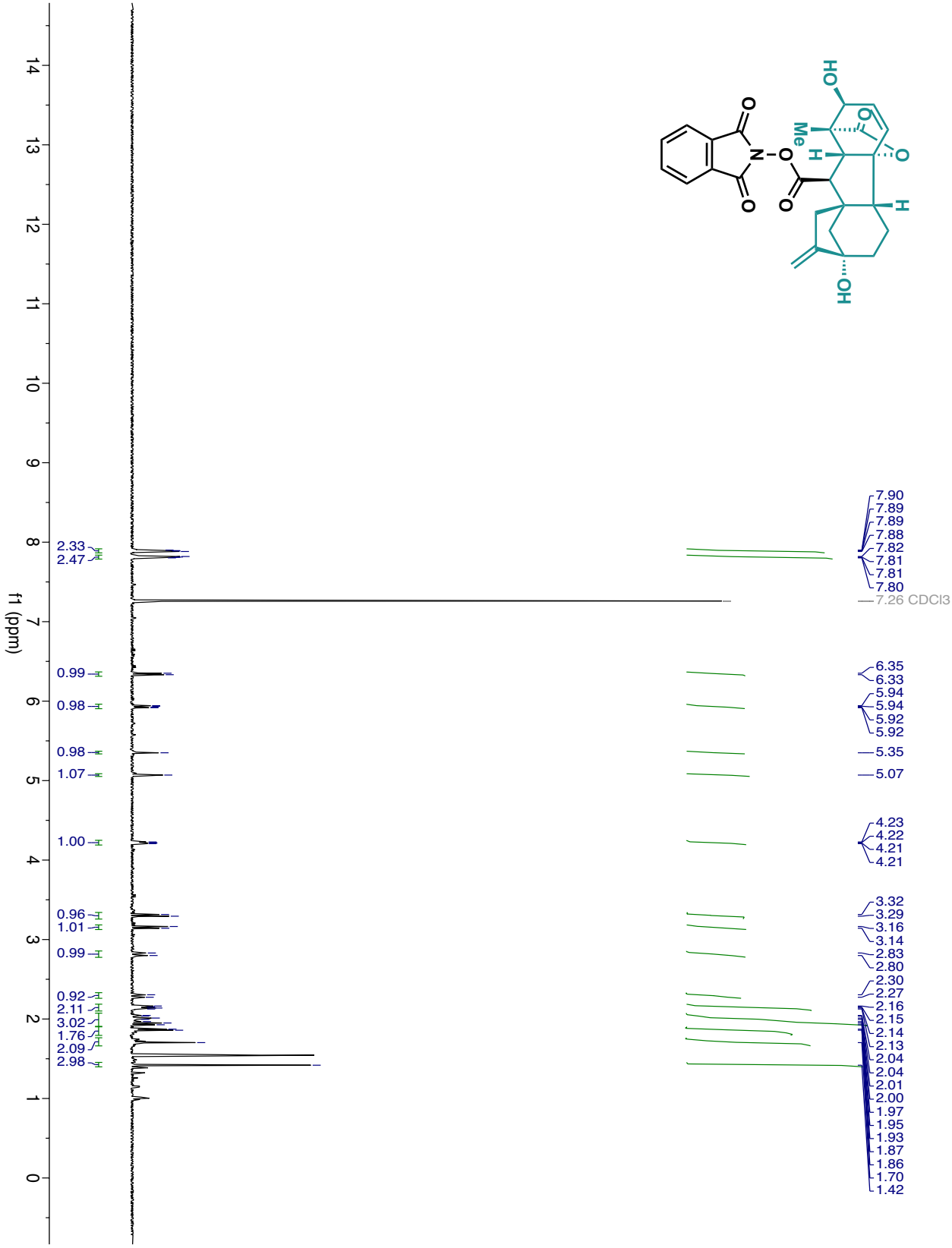

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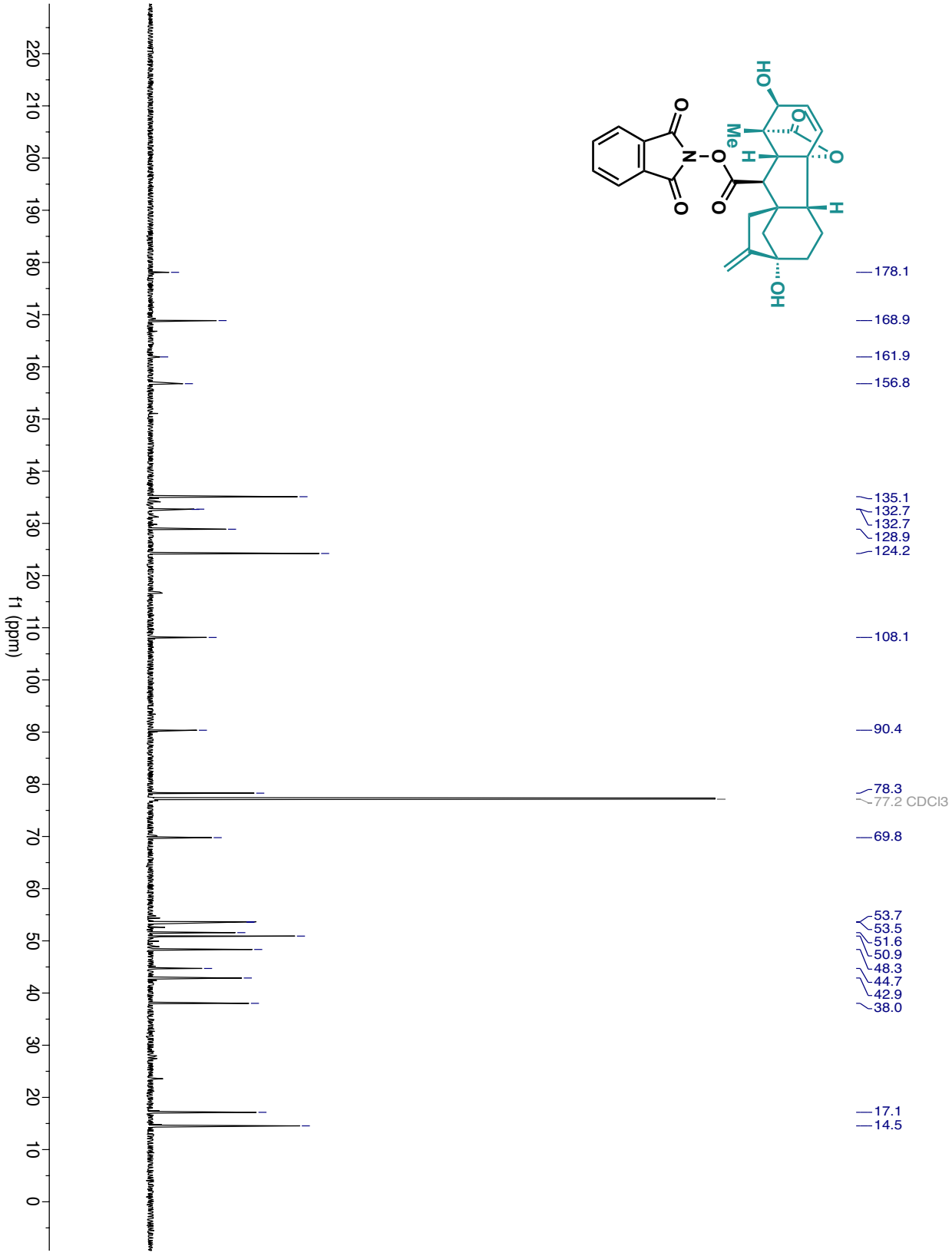

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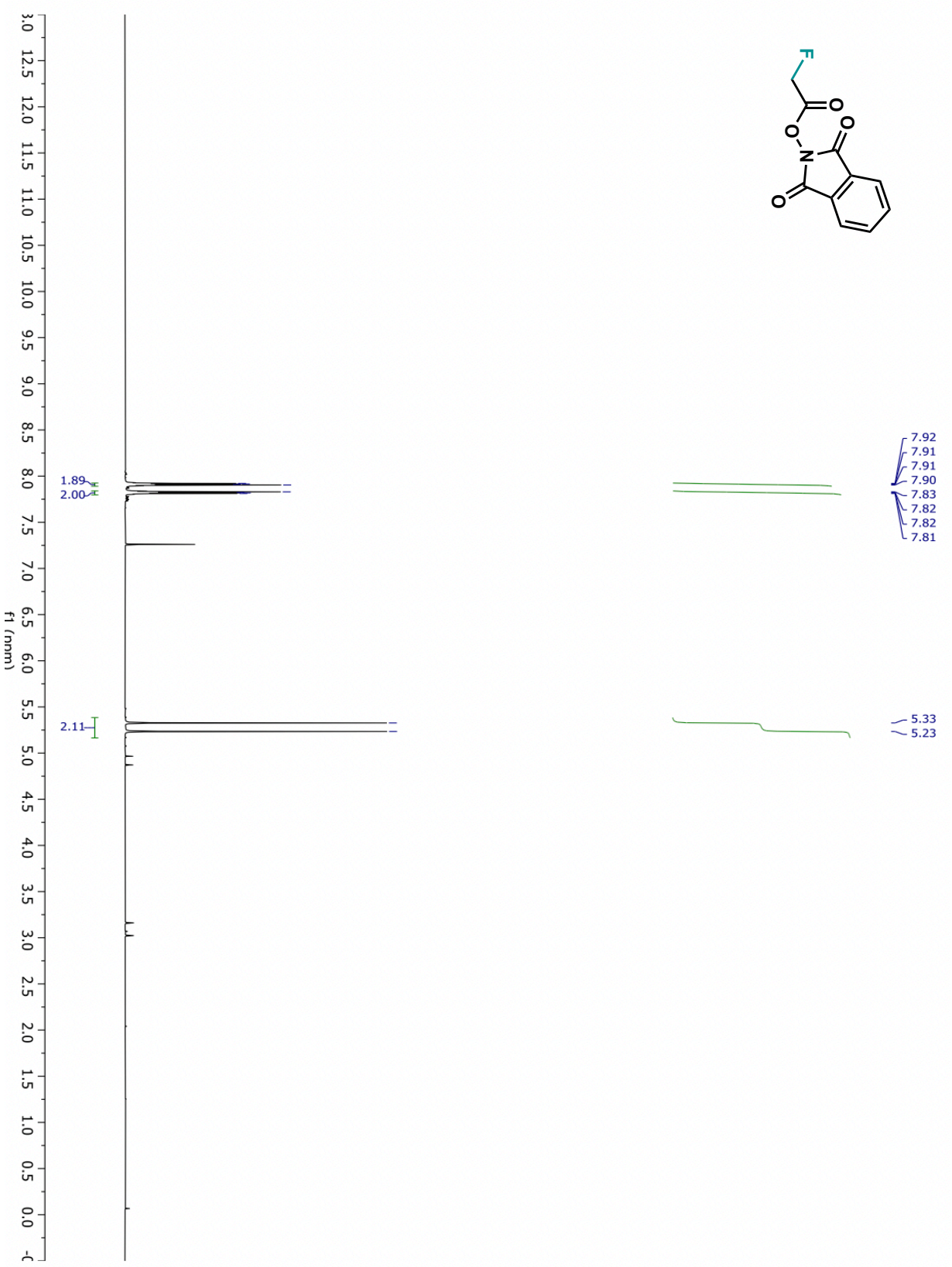

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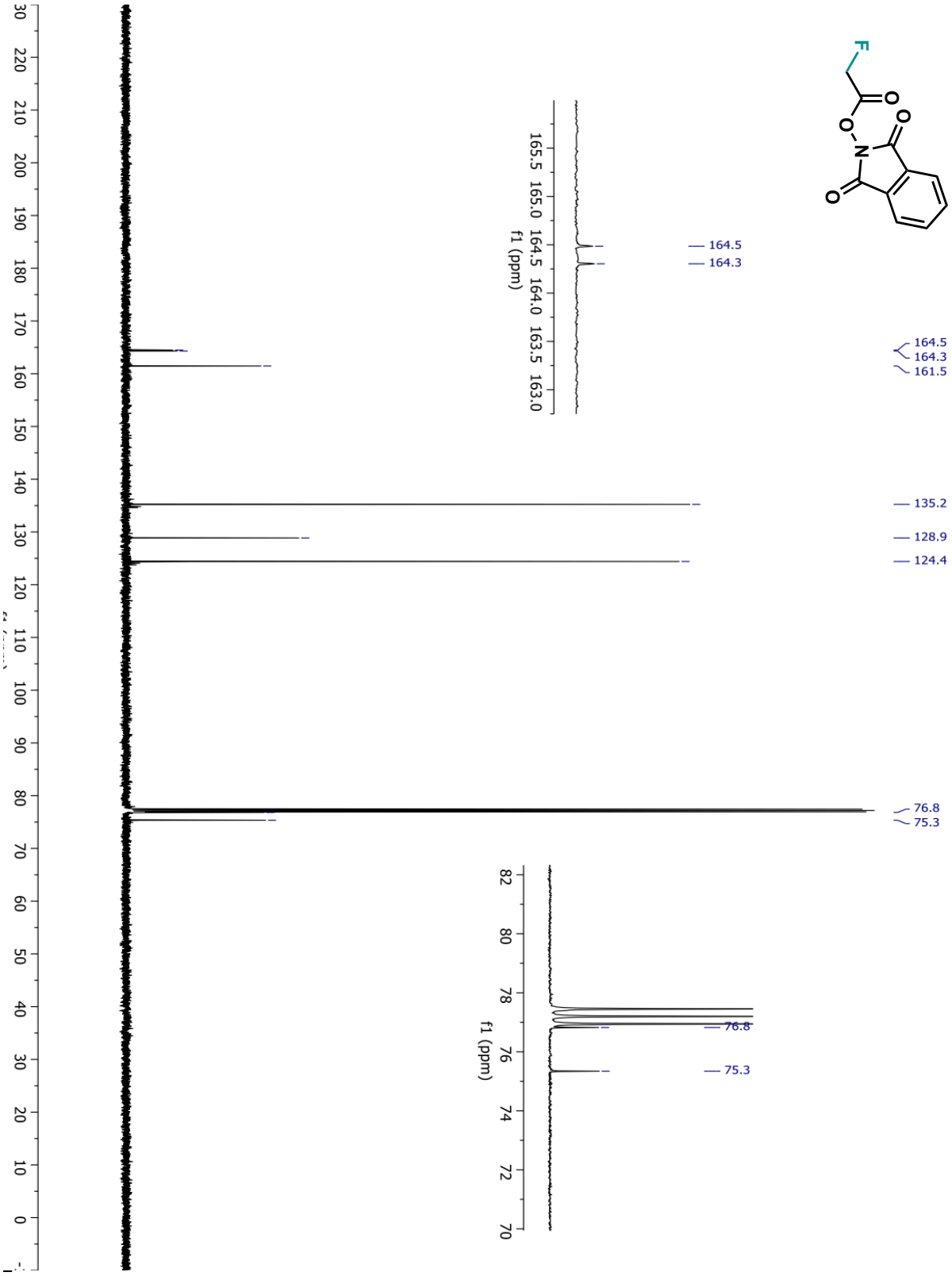
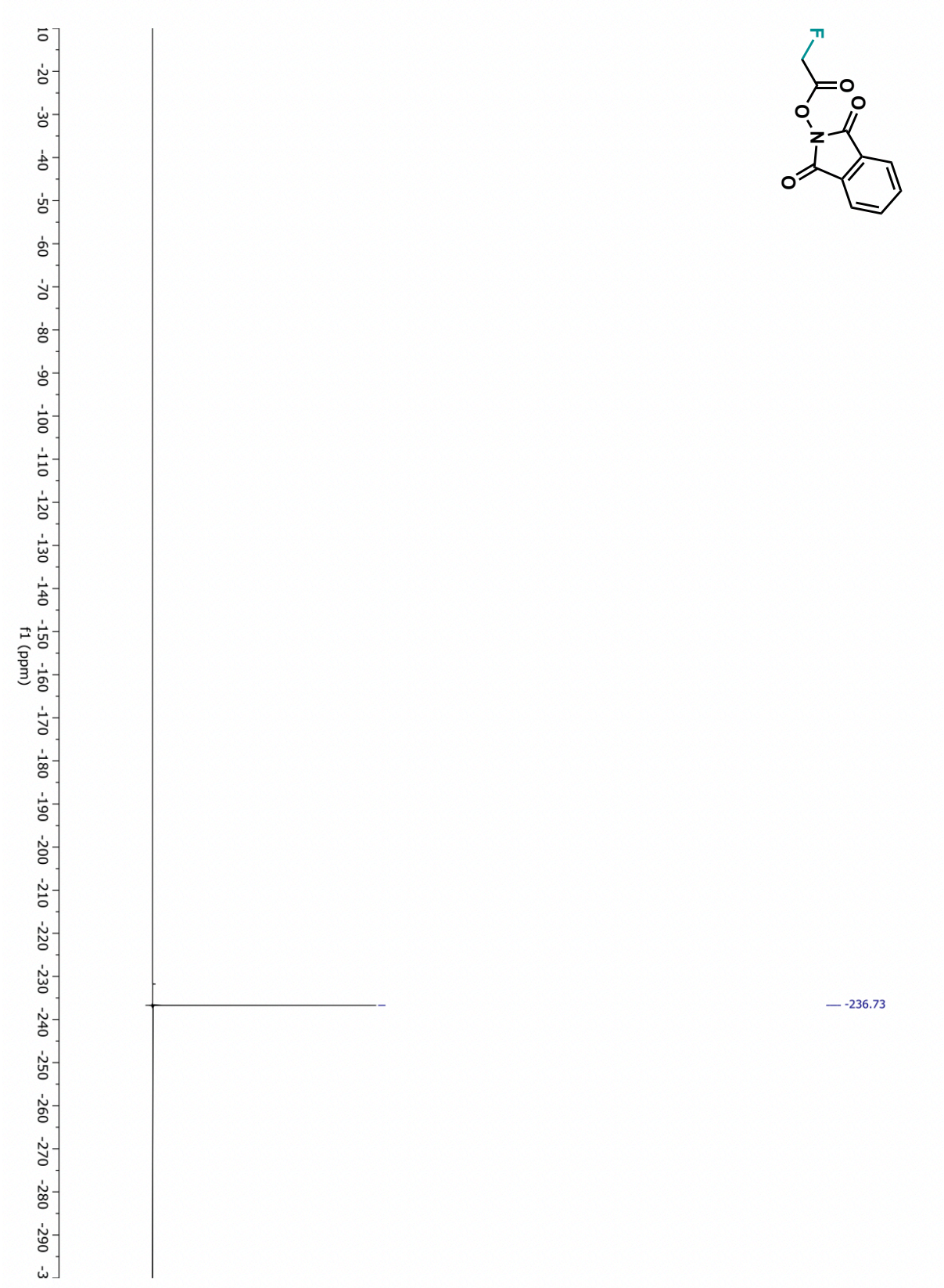


Compound S32 ^{19}F-NMR



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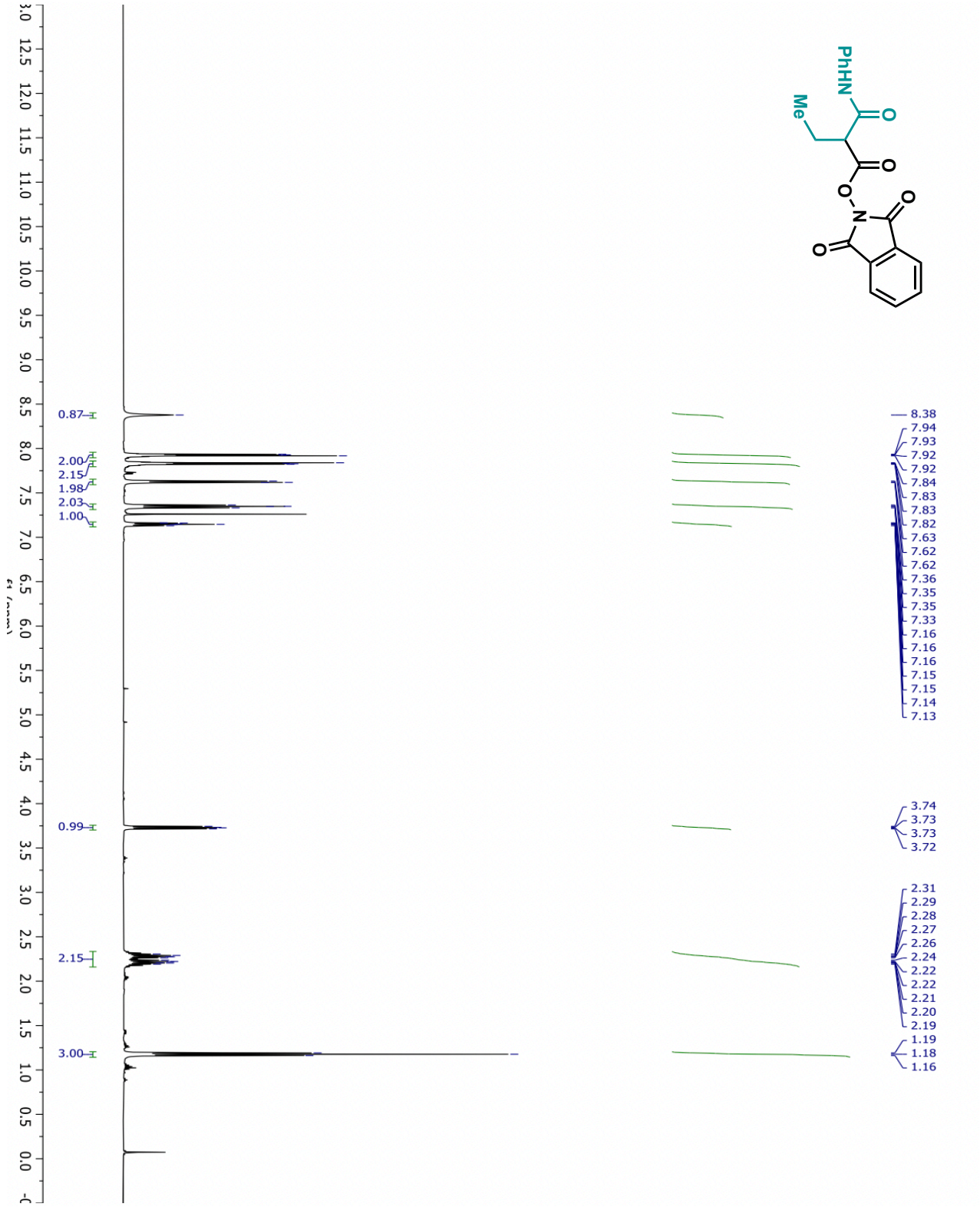

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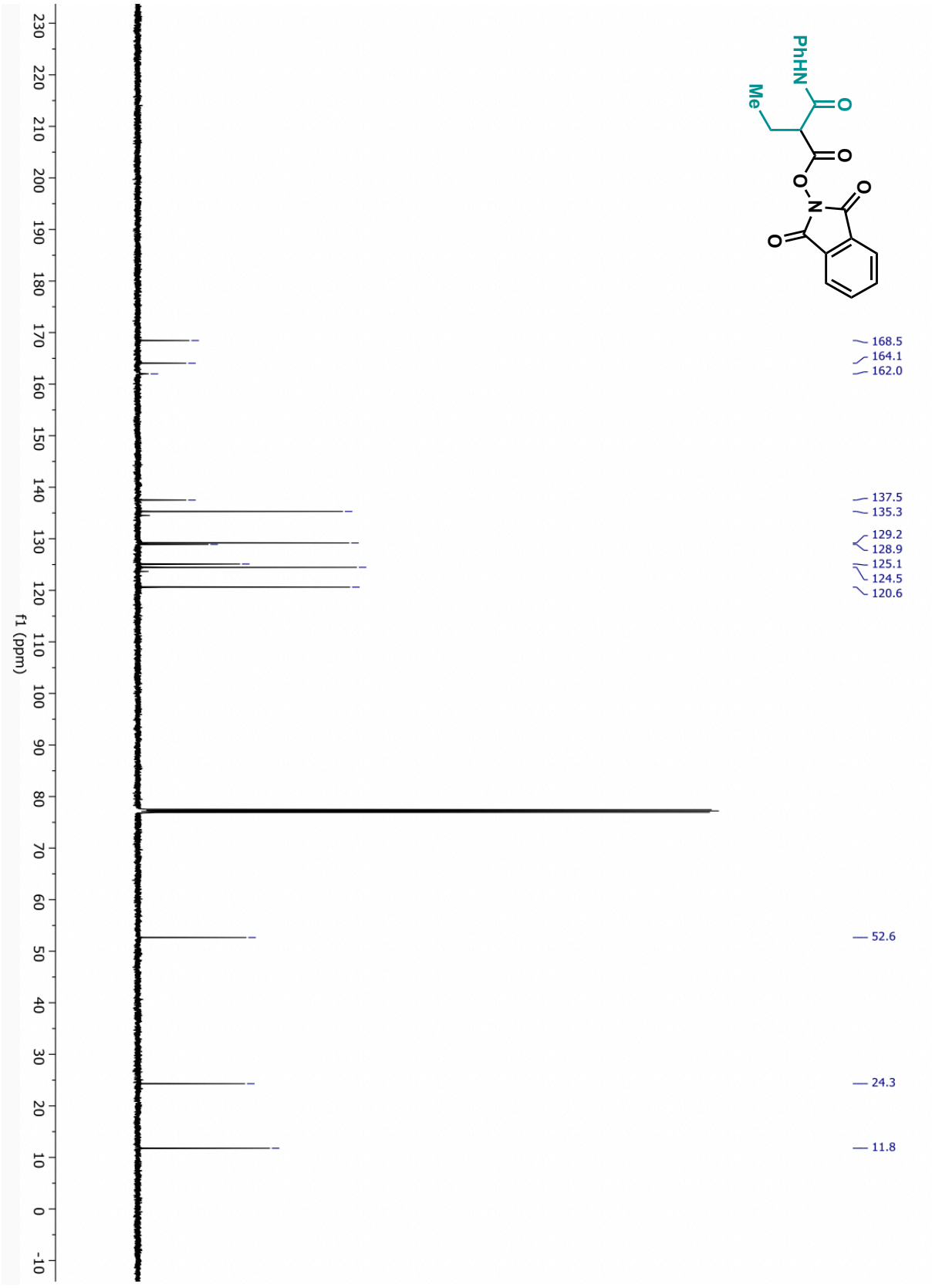

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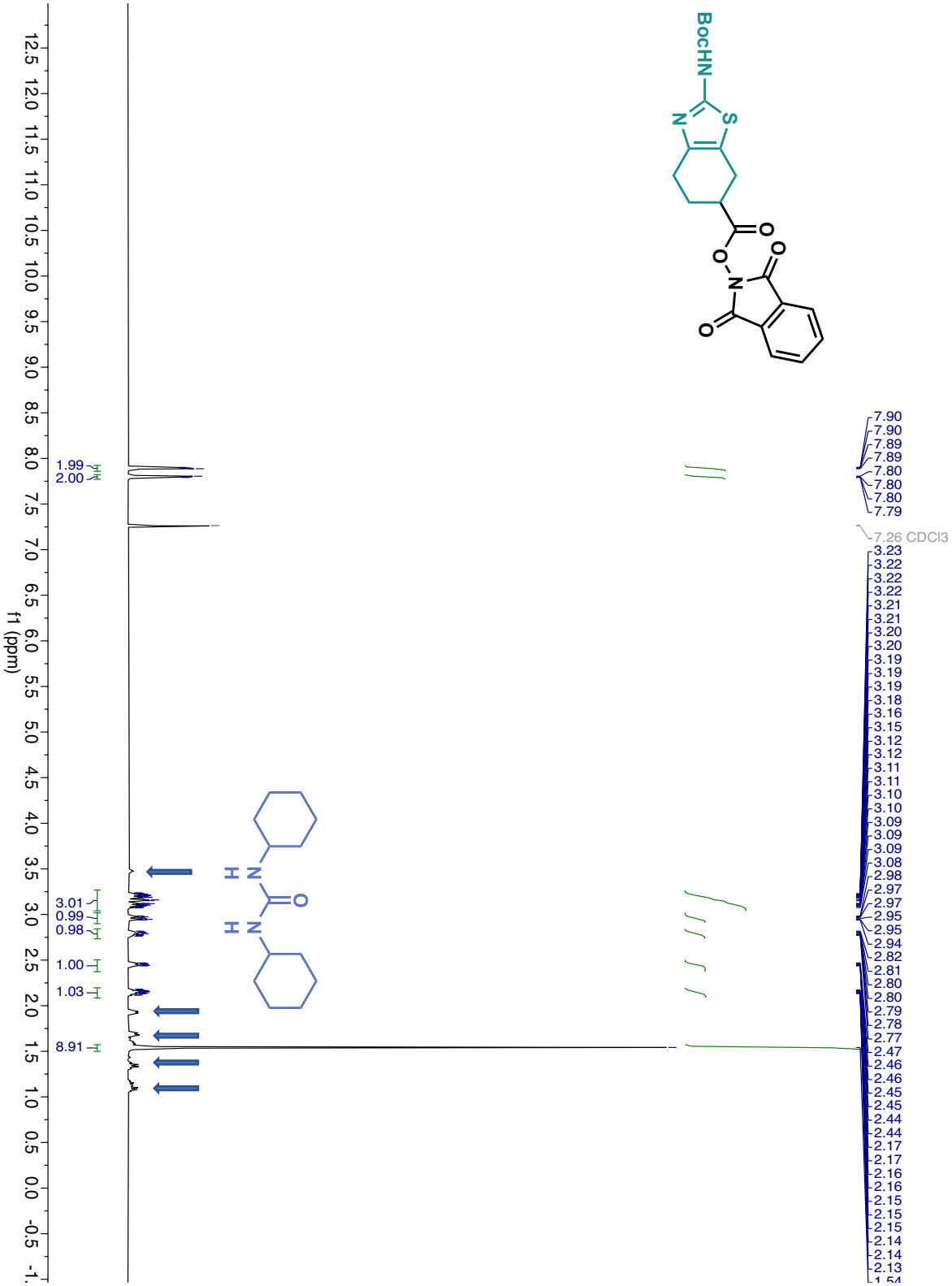

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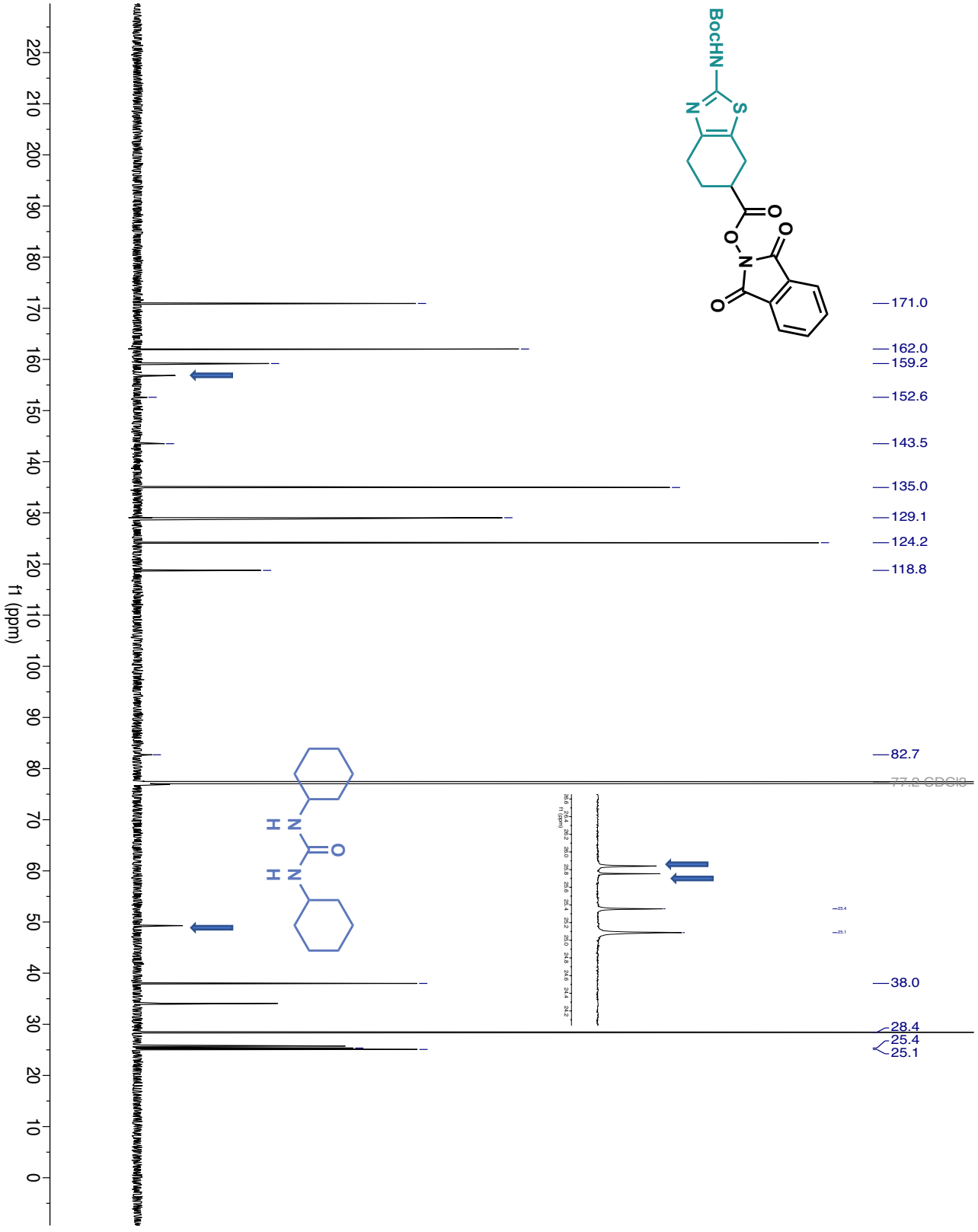

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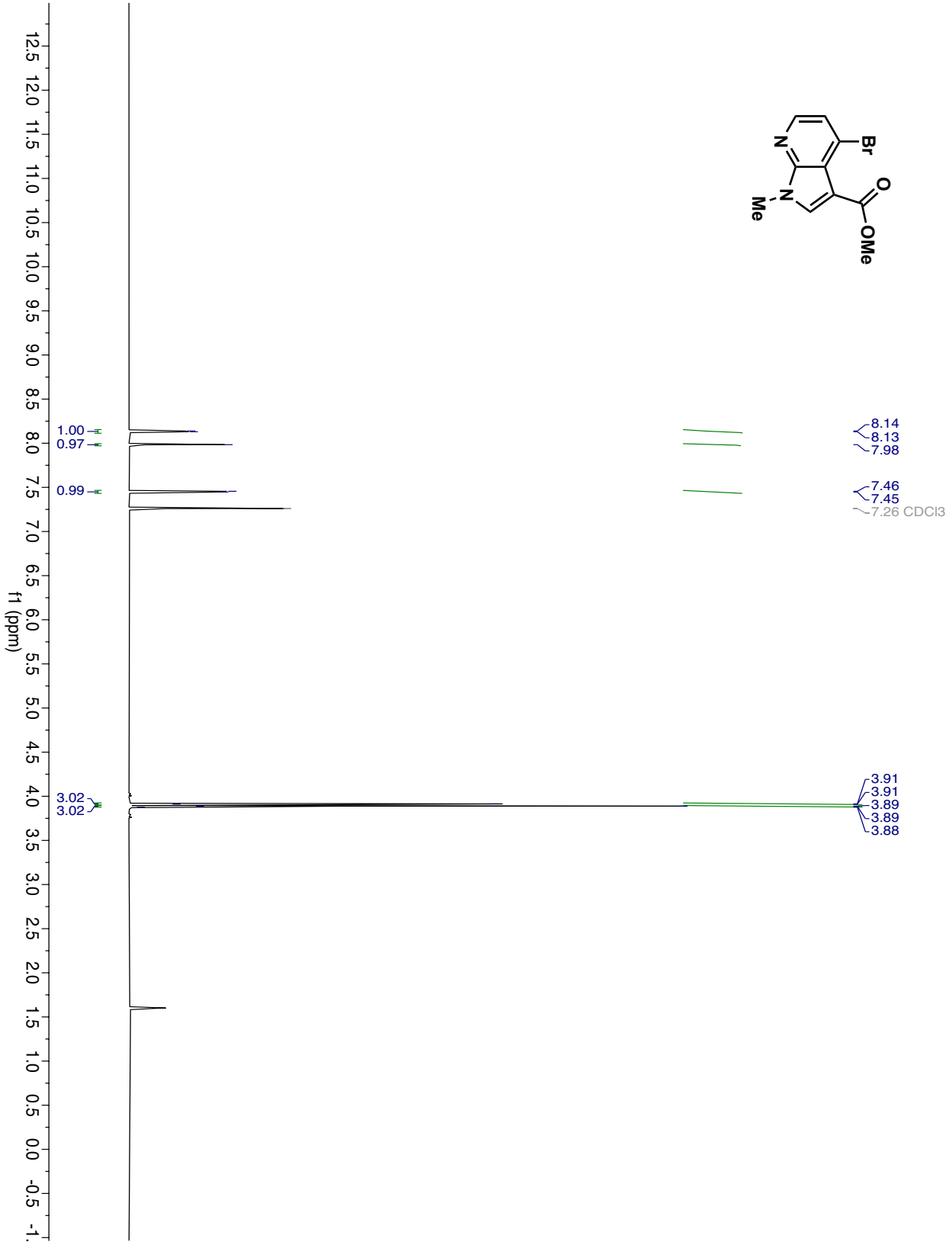

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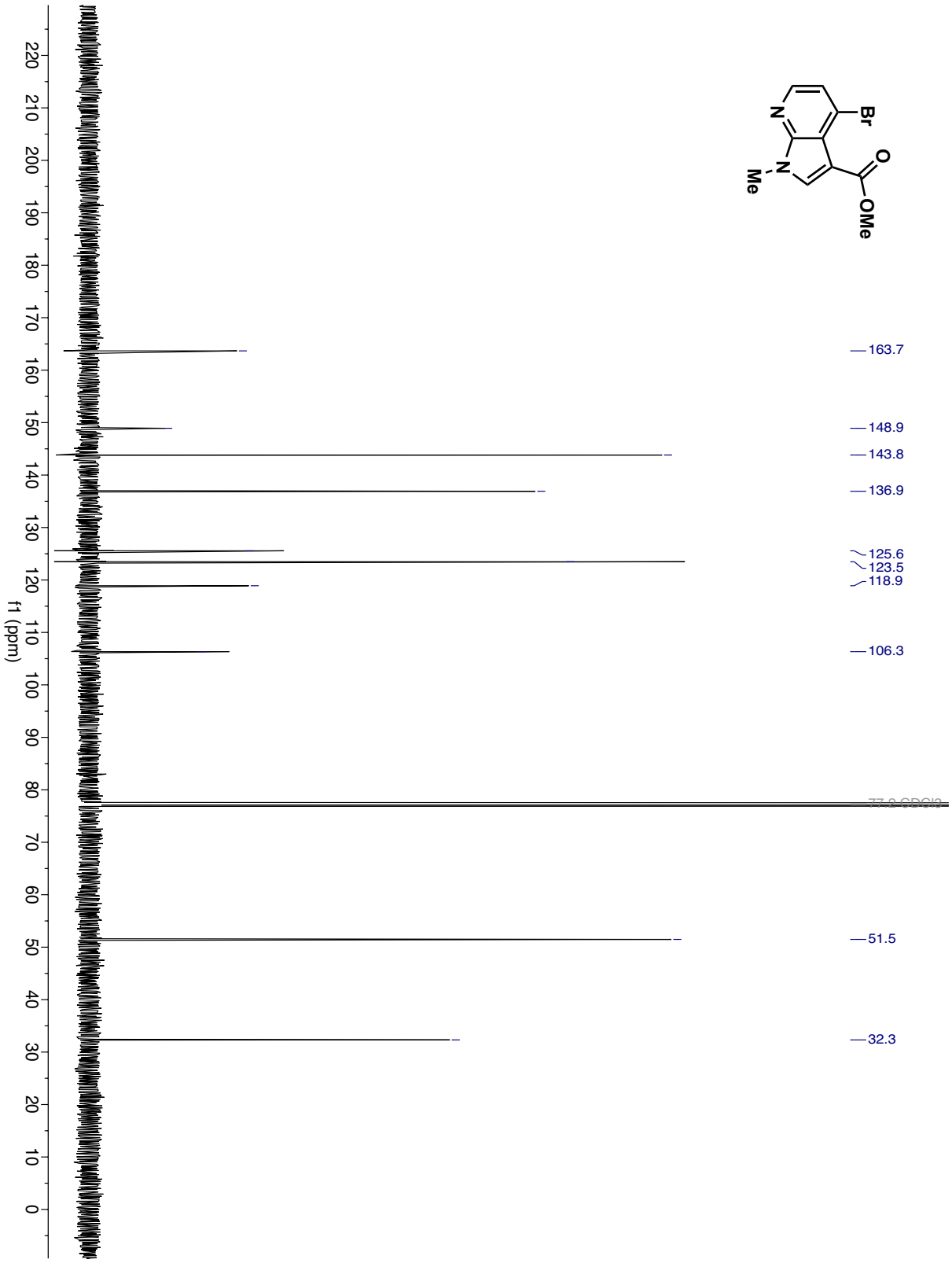

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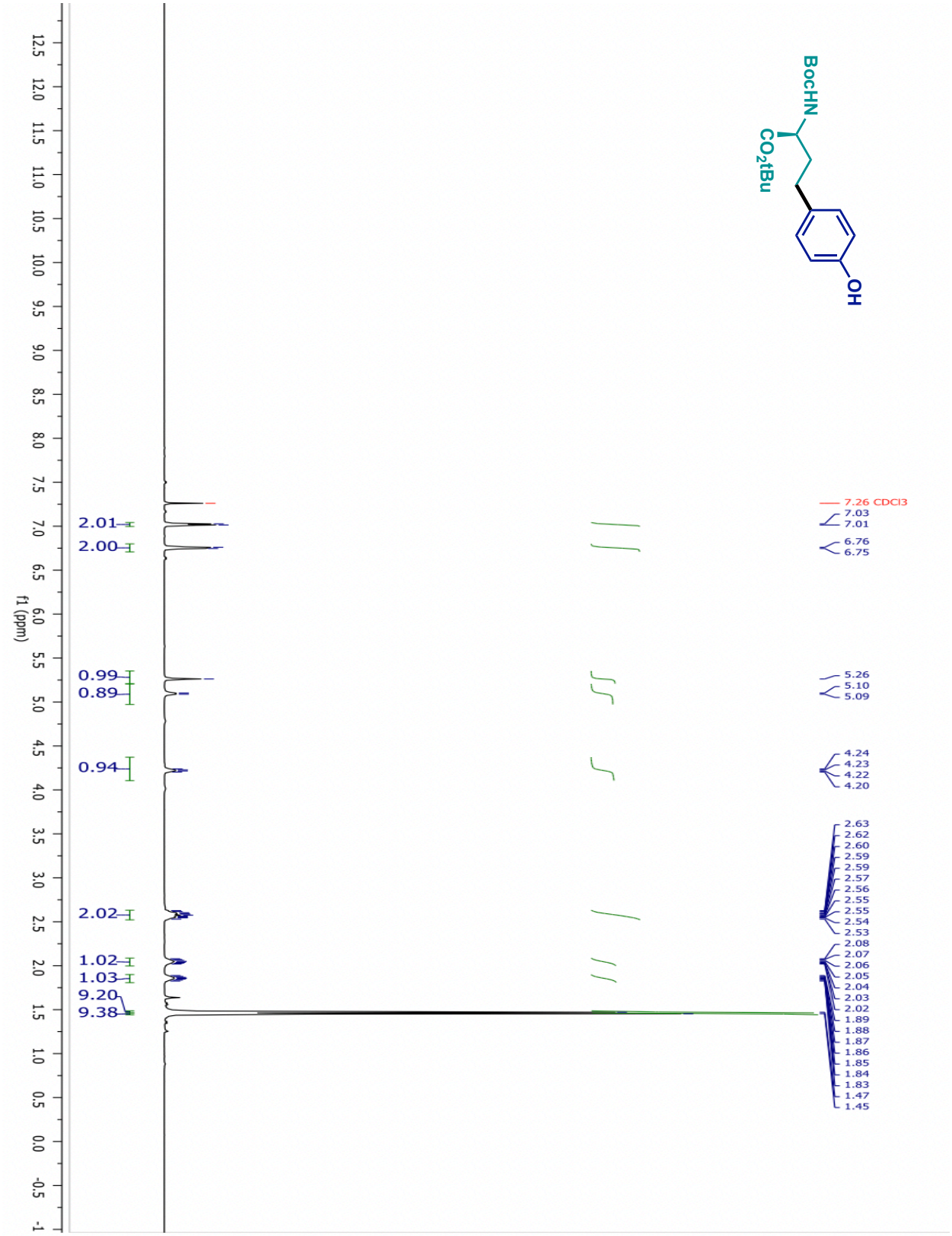

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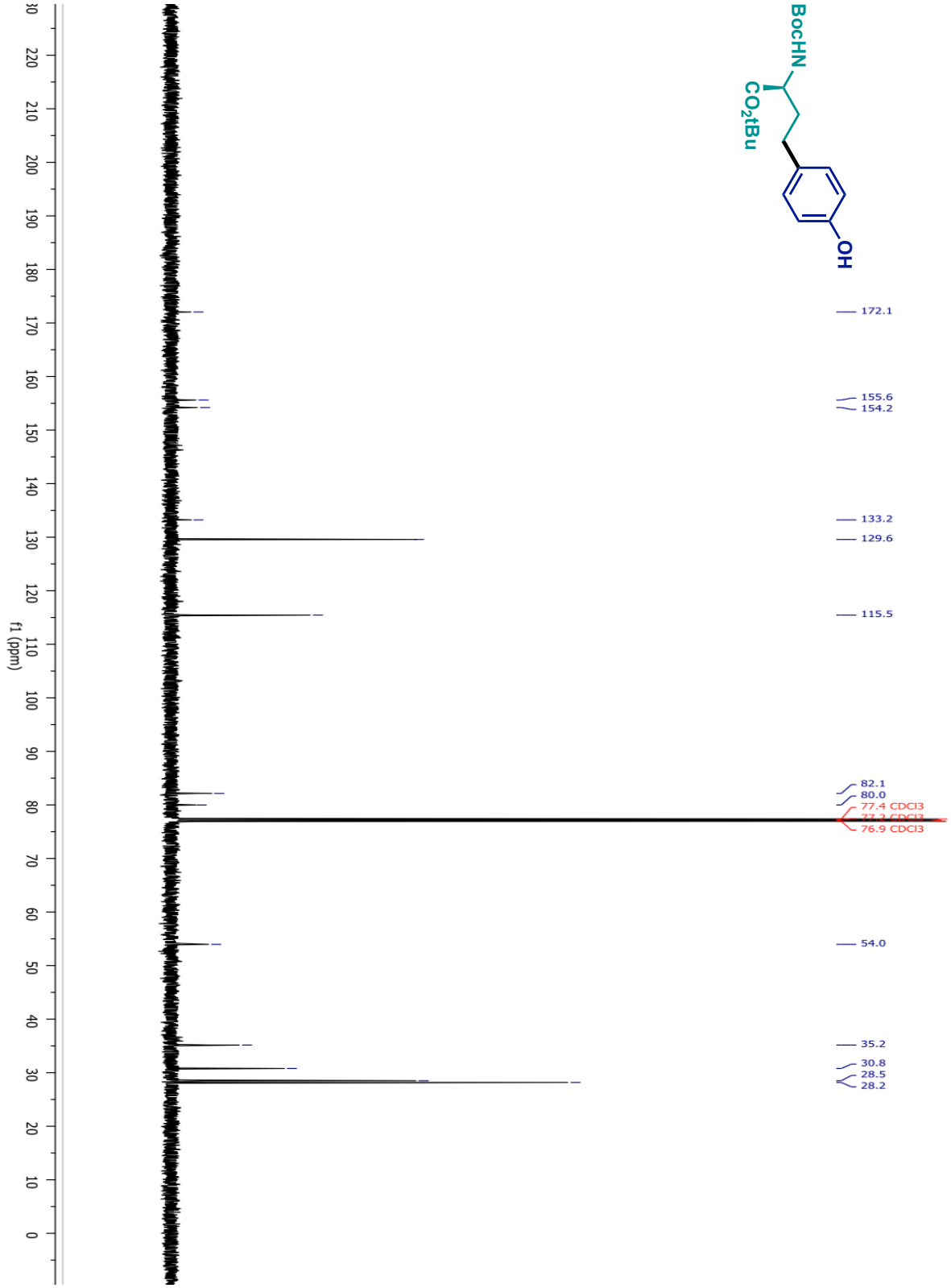

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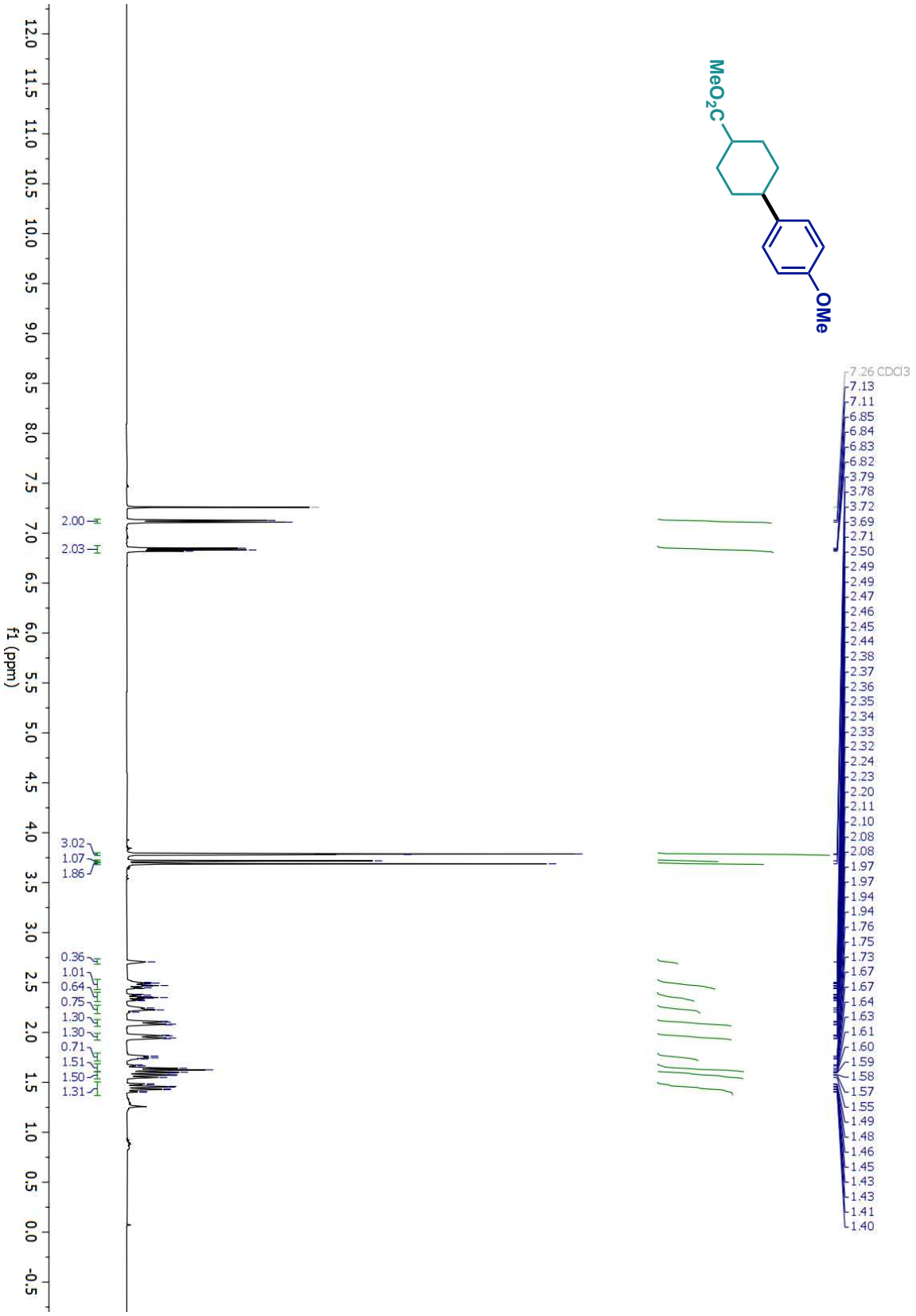

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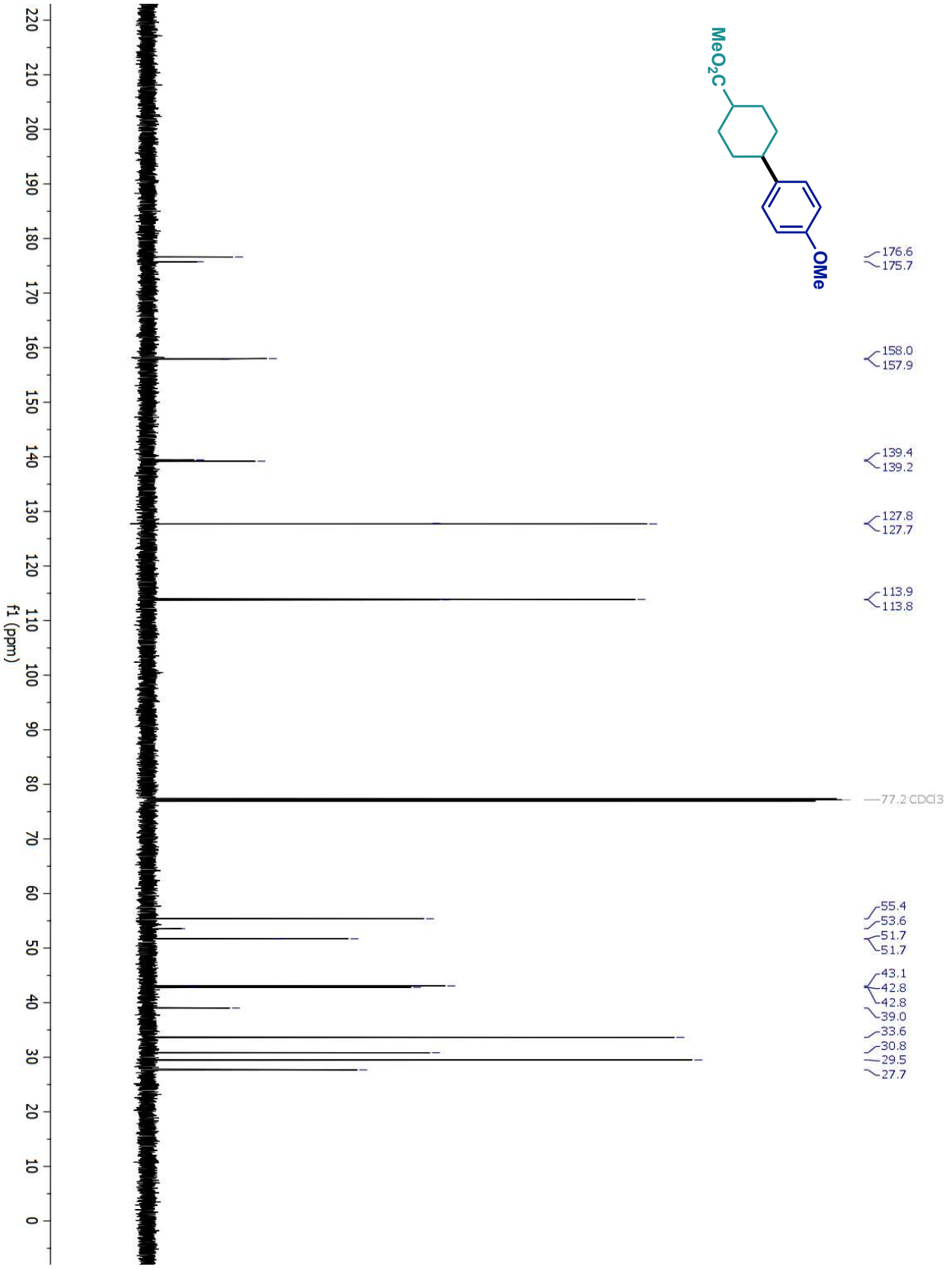

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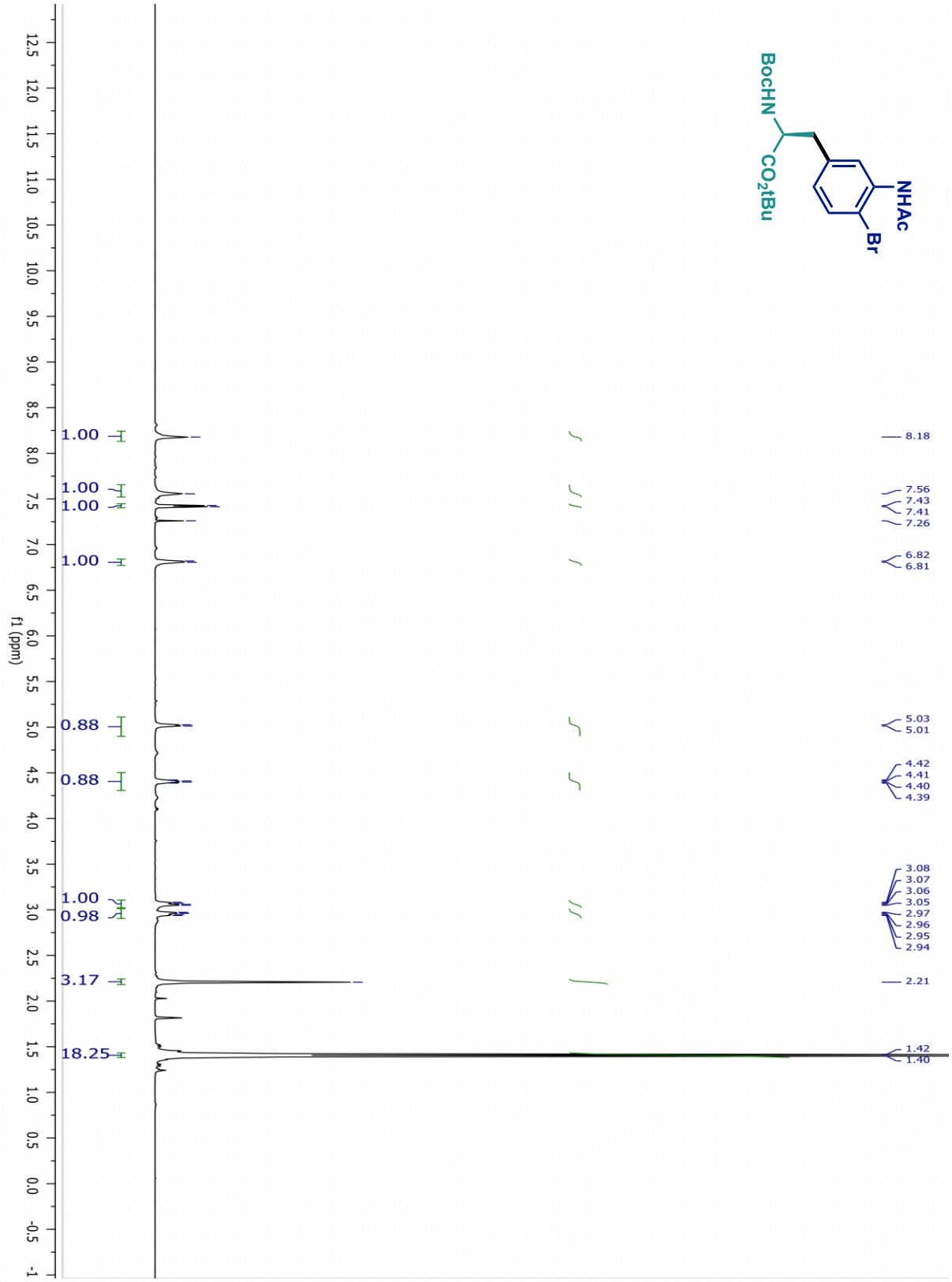

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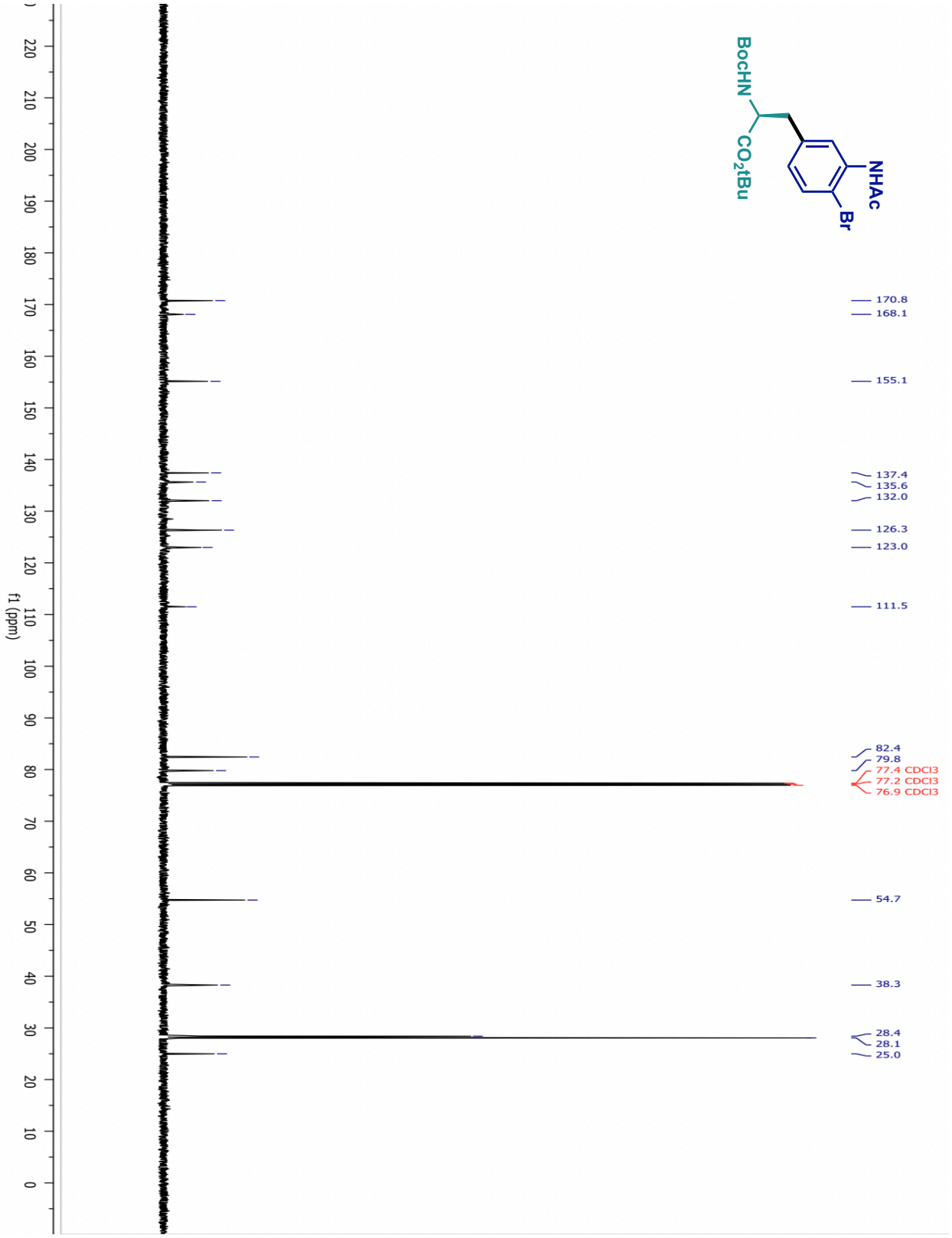

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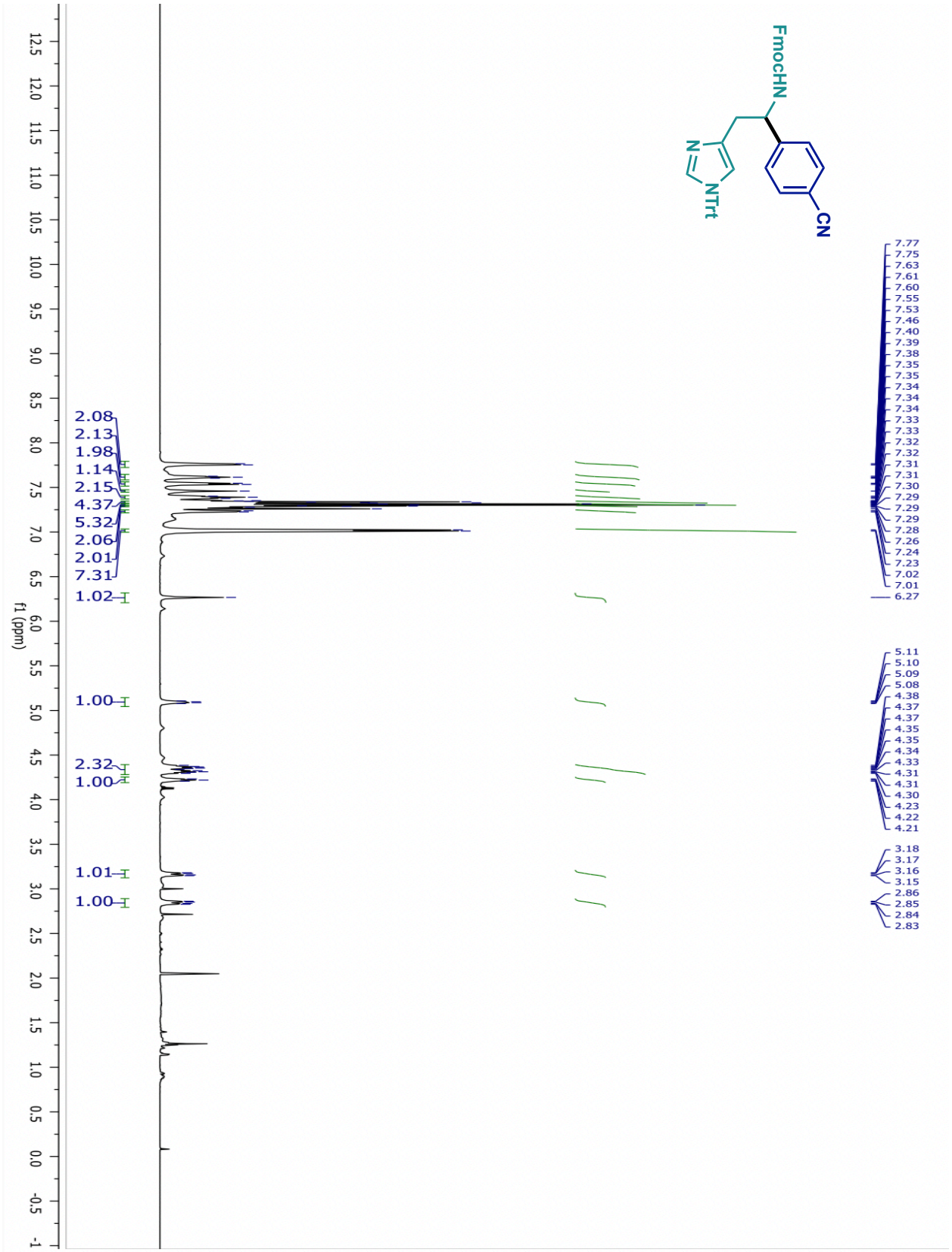

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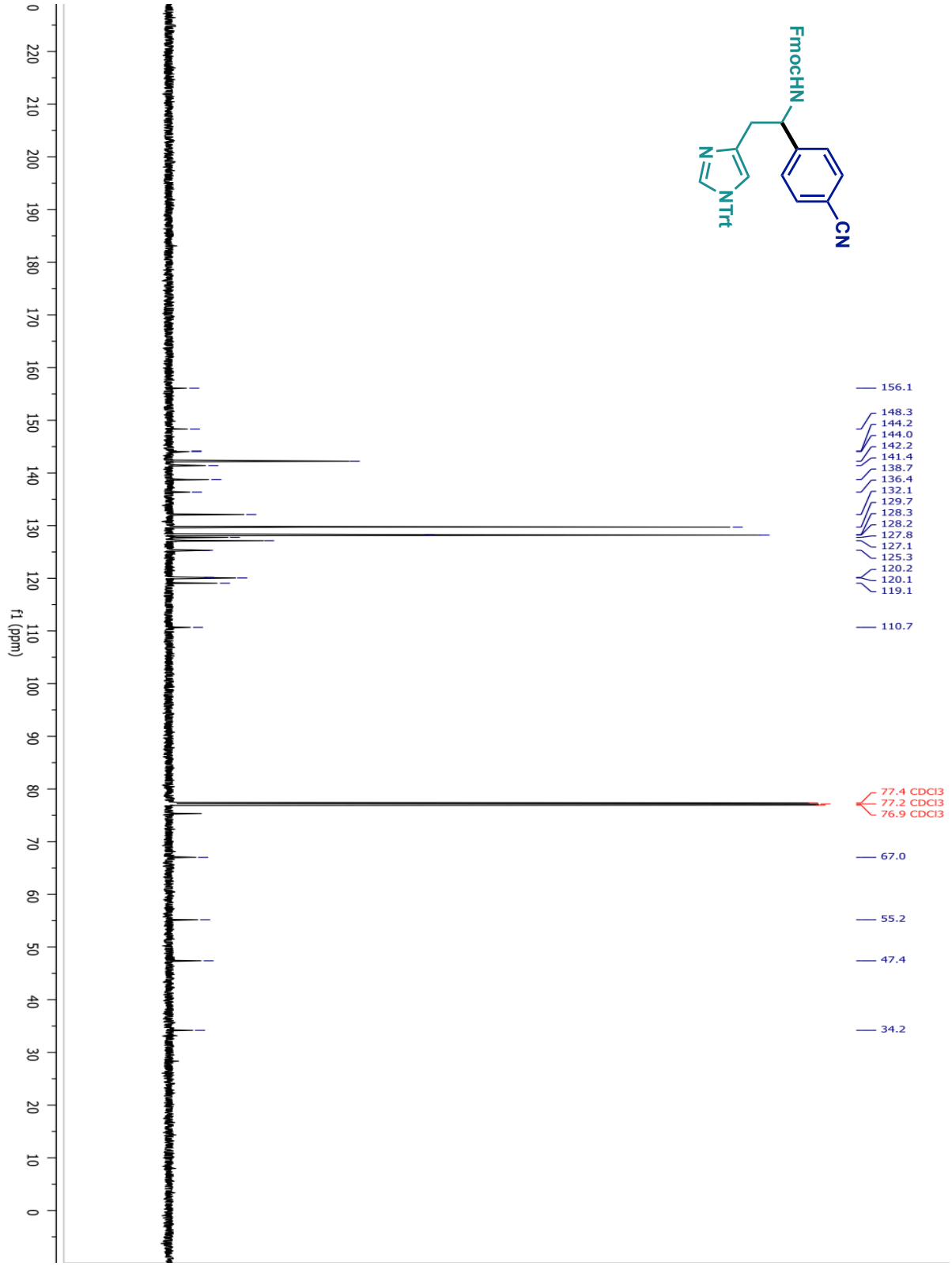

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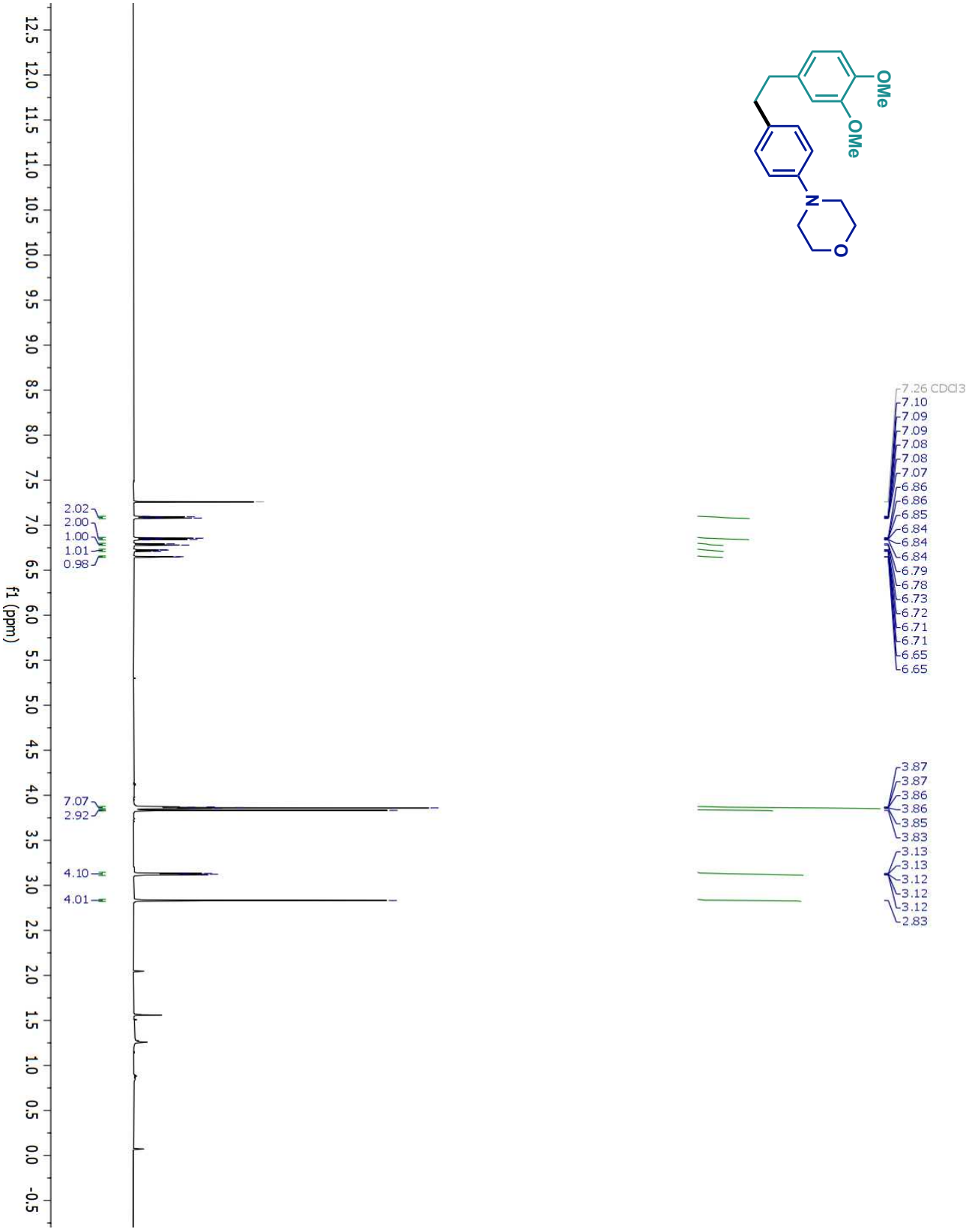

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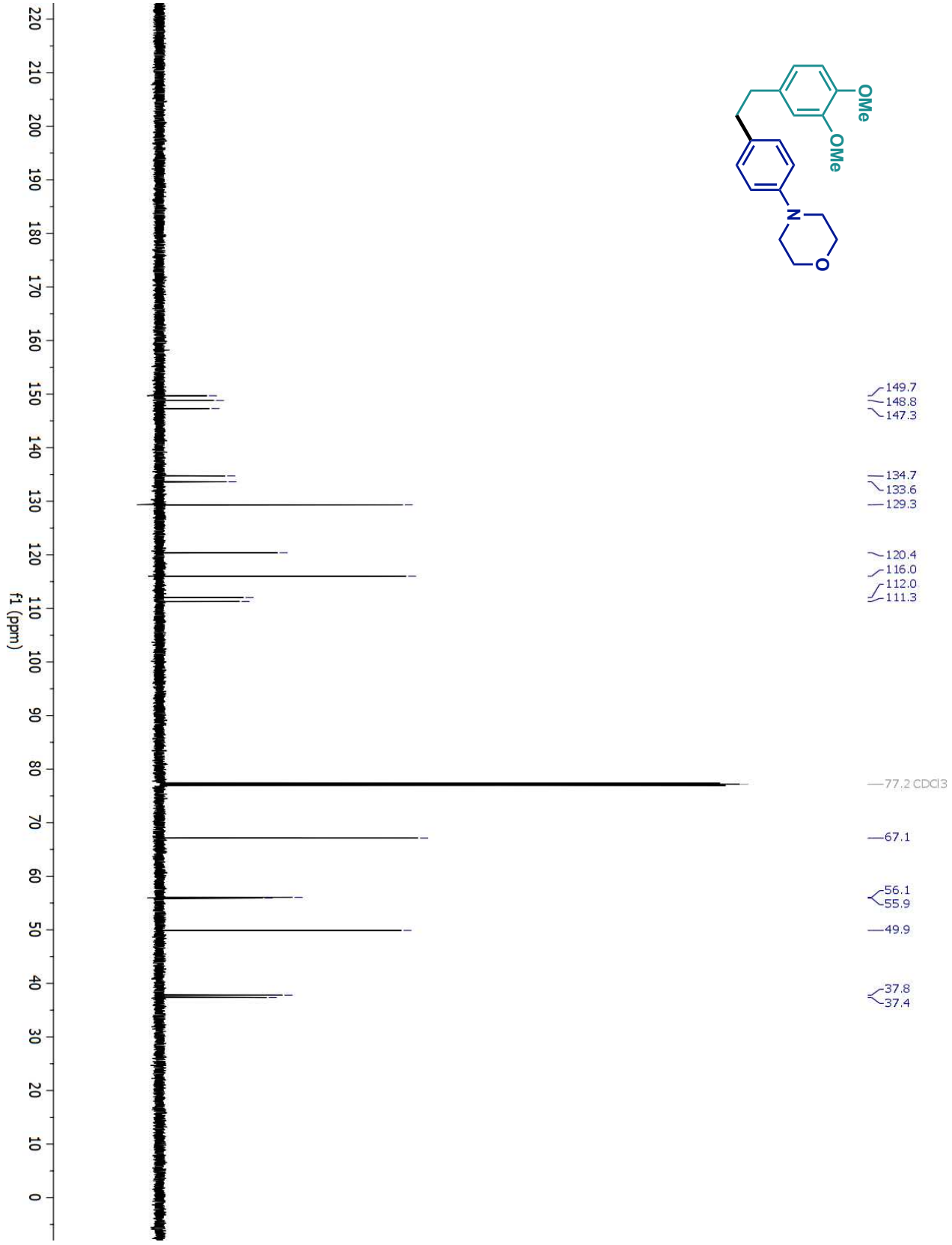

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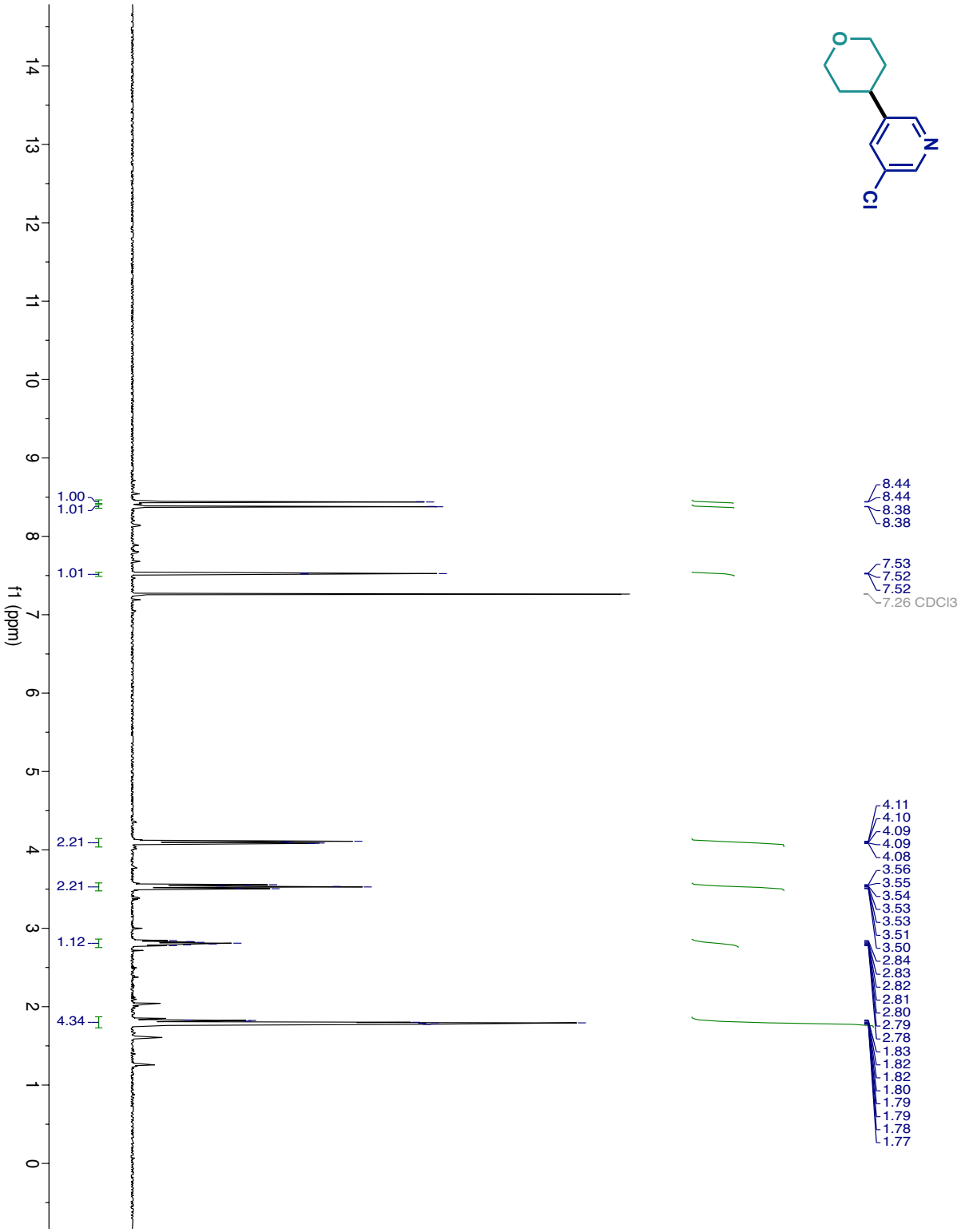

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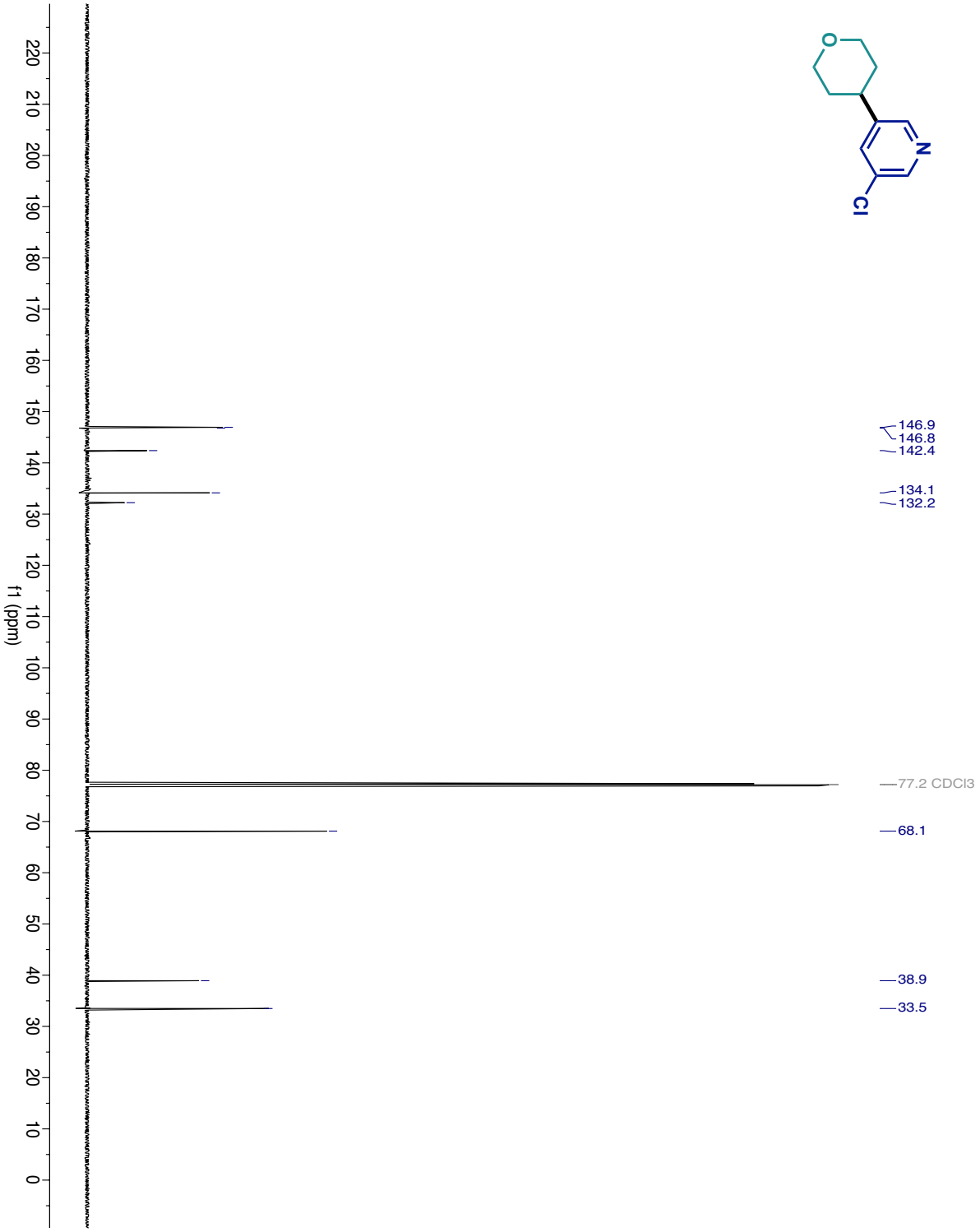

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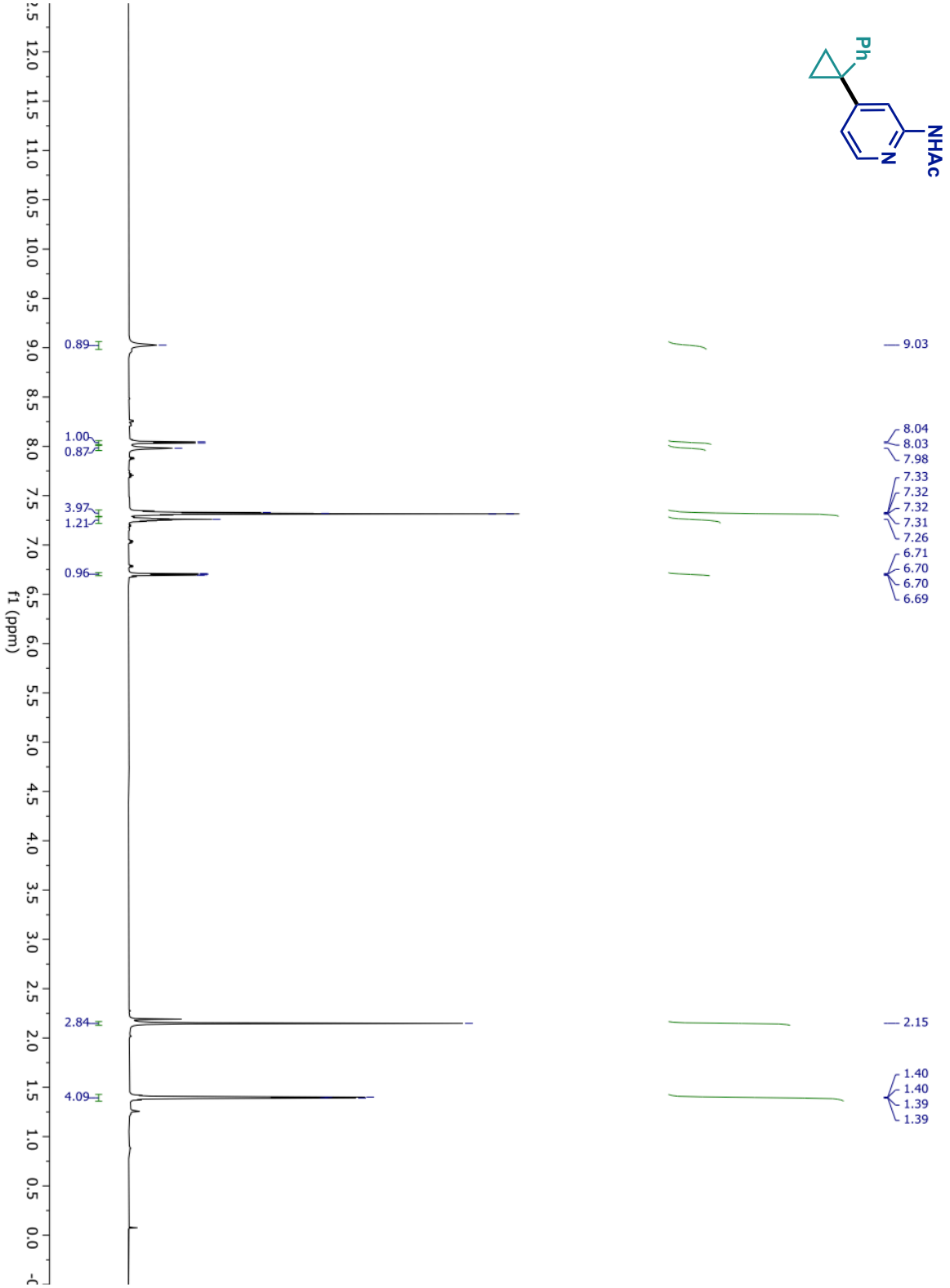

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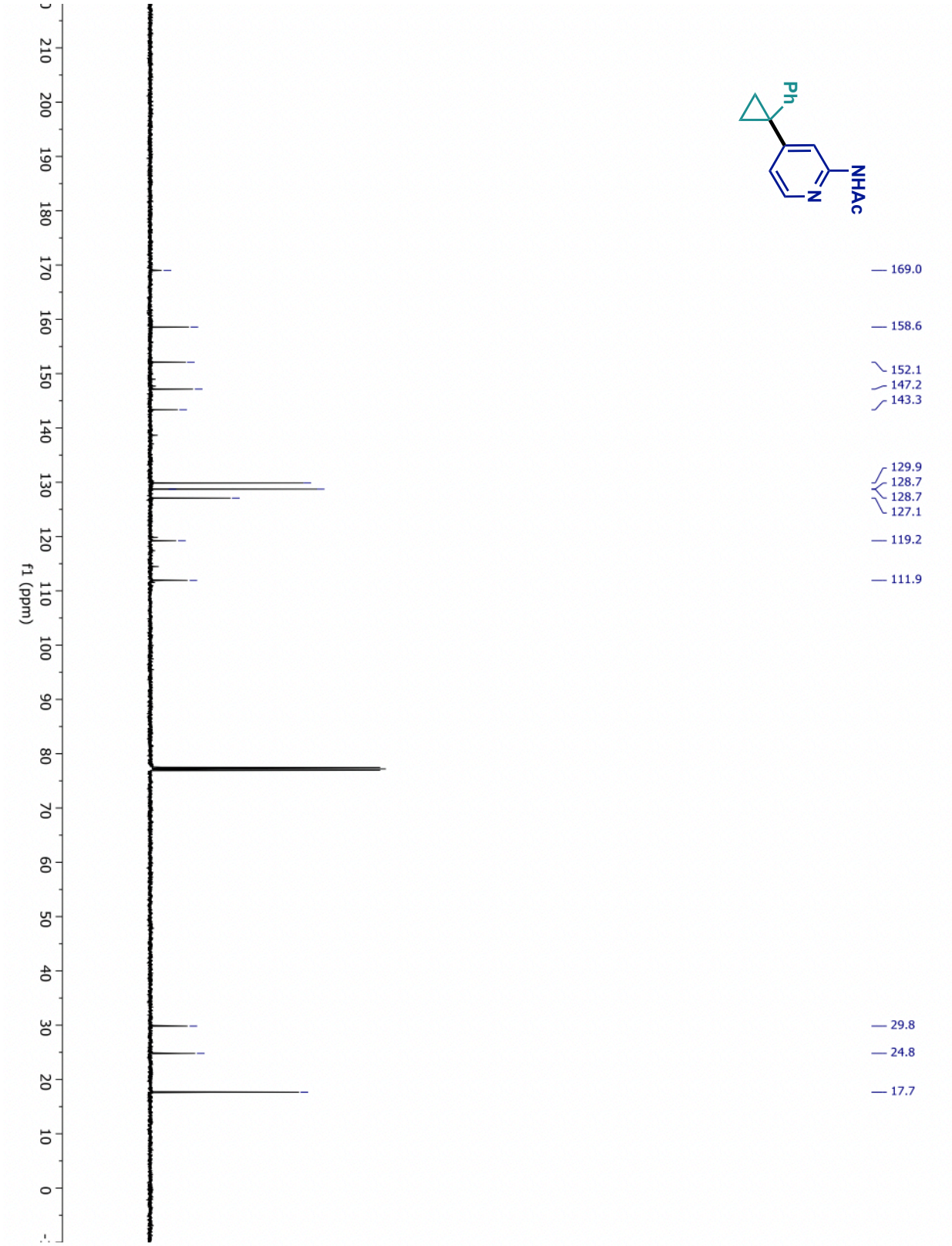

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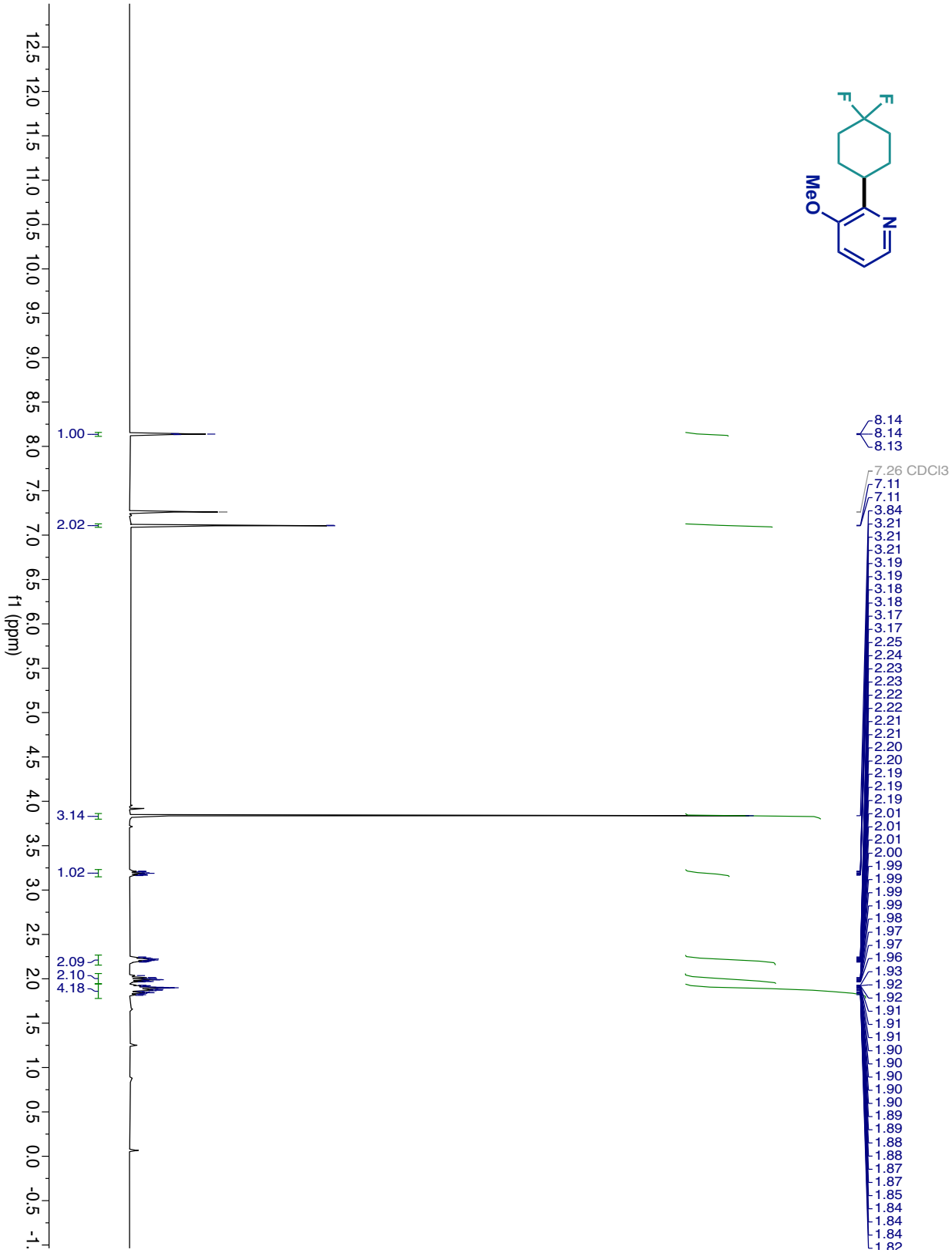

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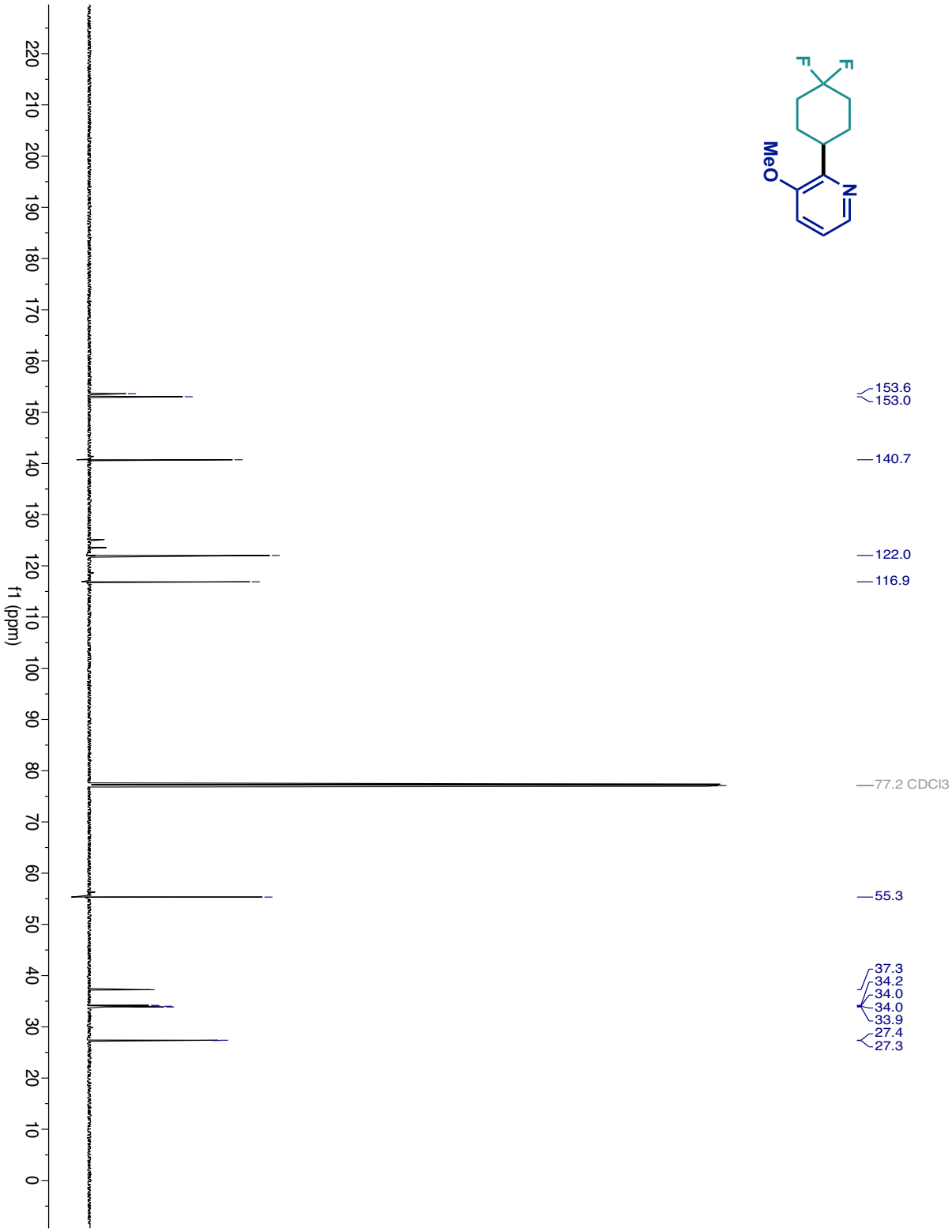

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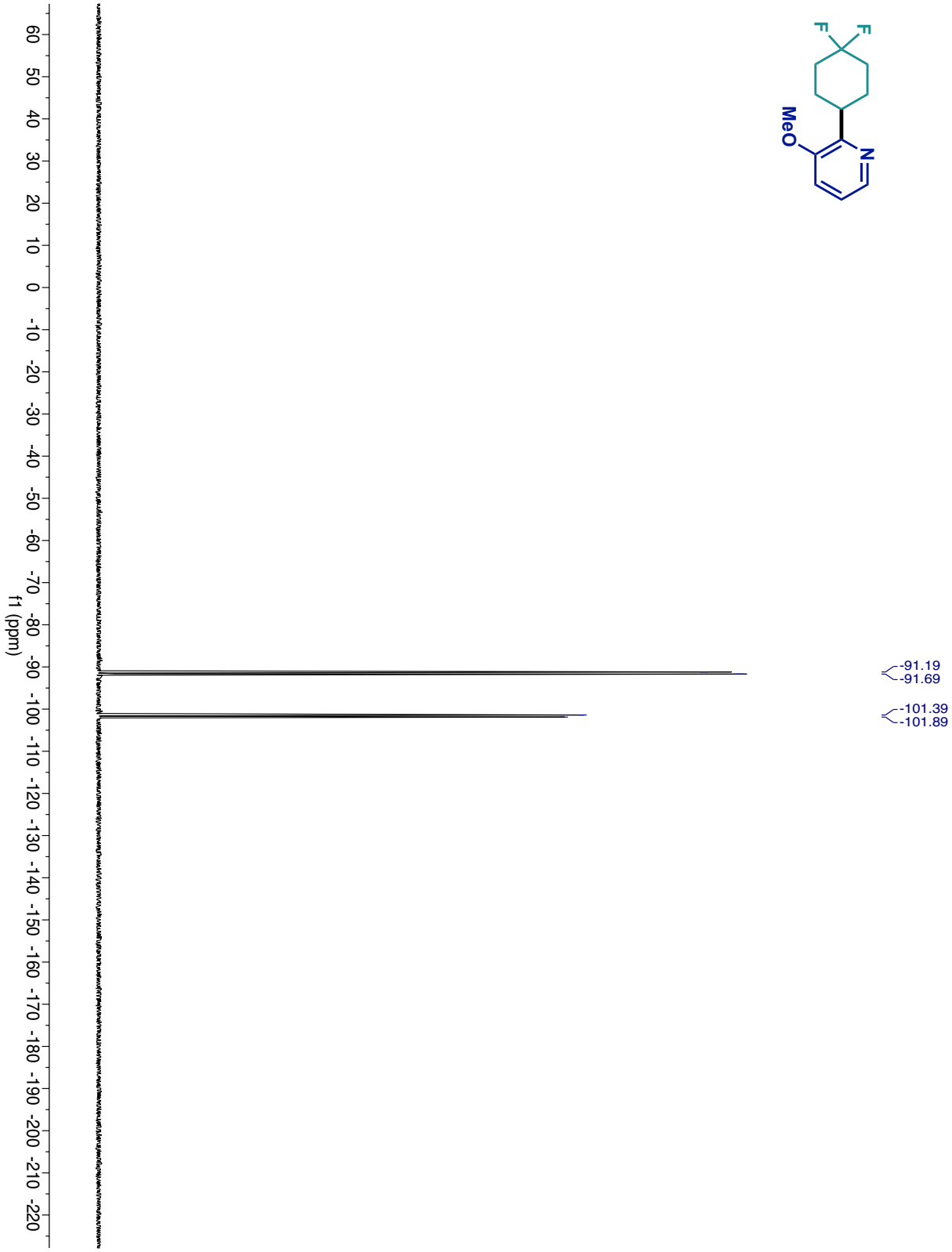

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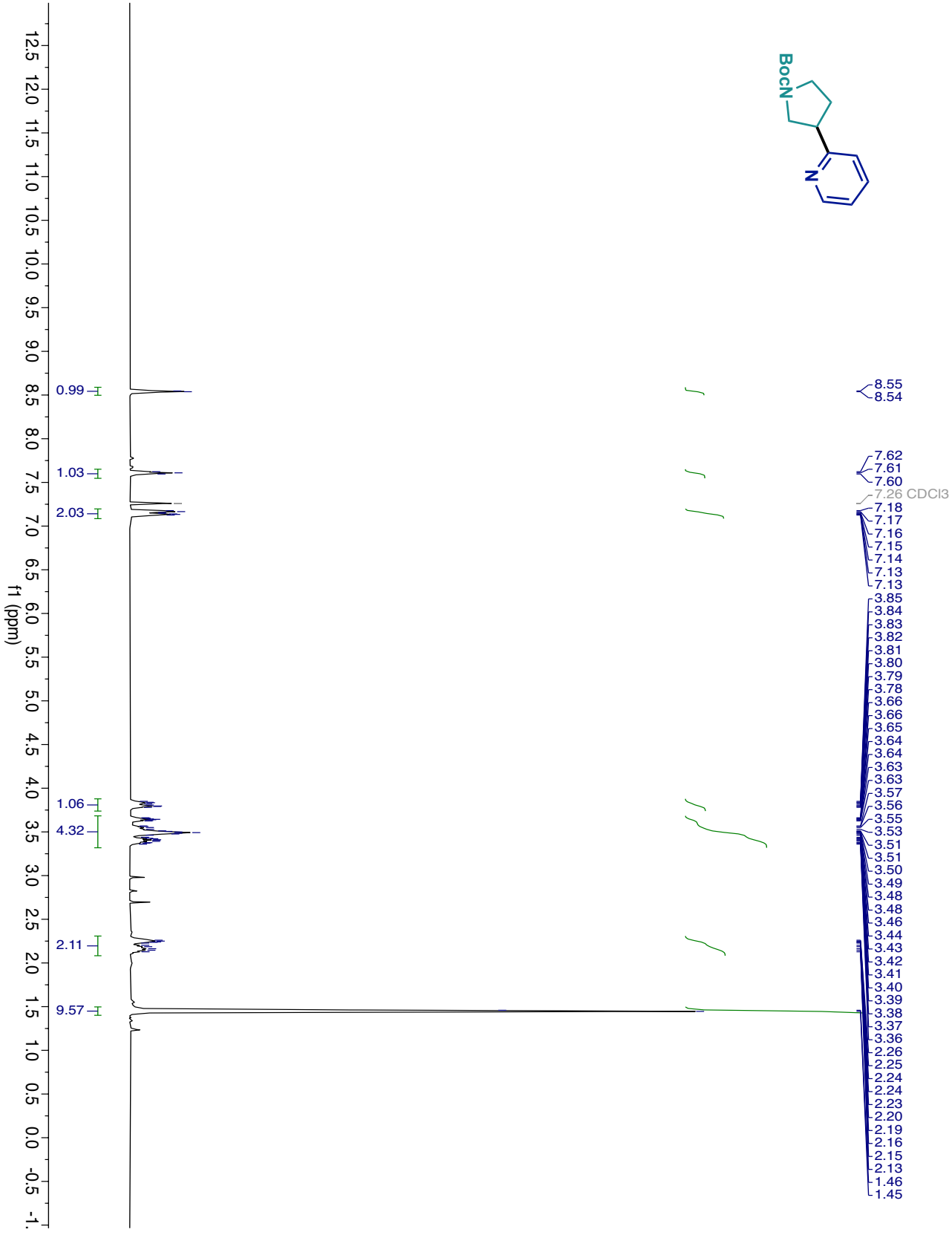
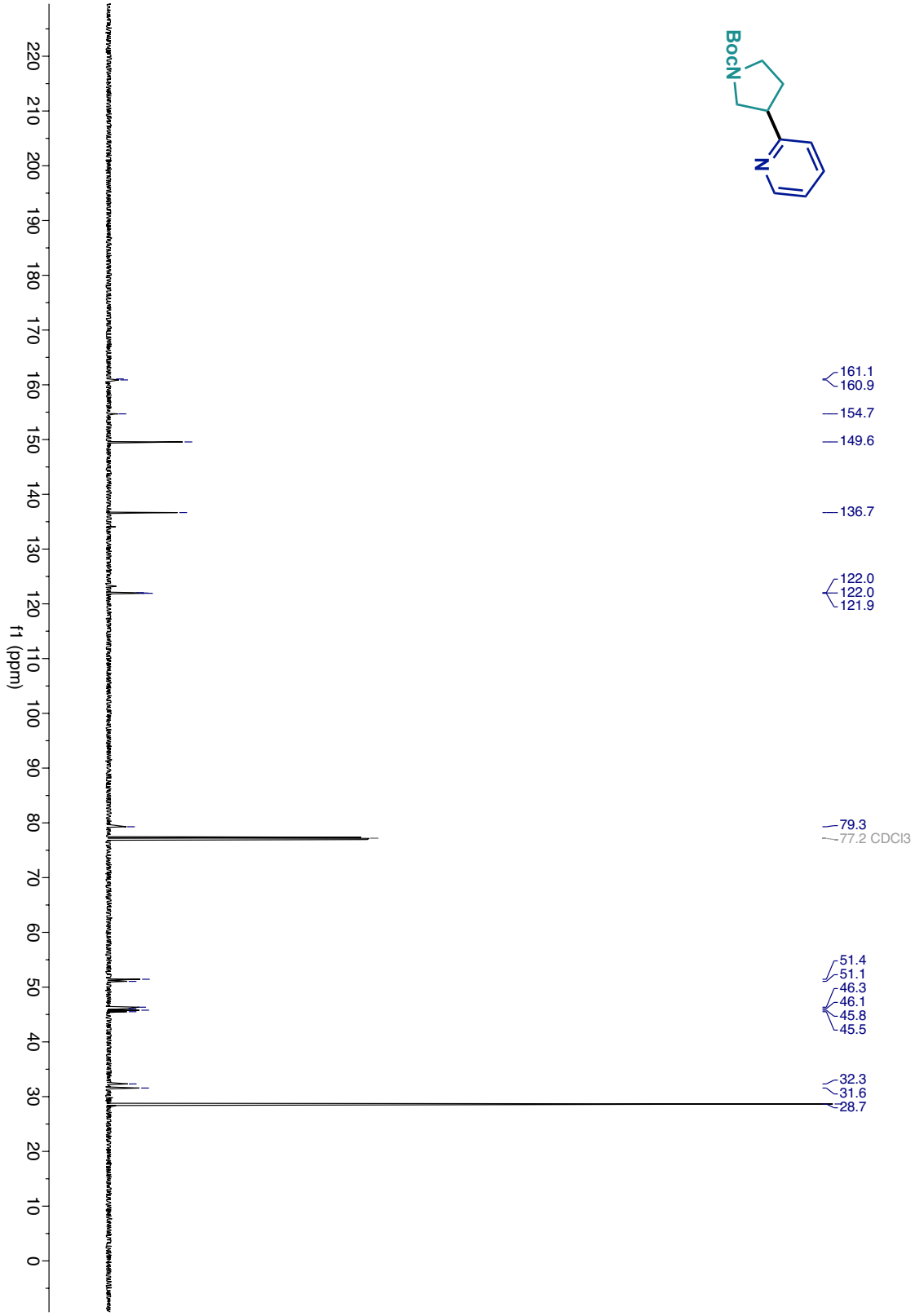
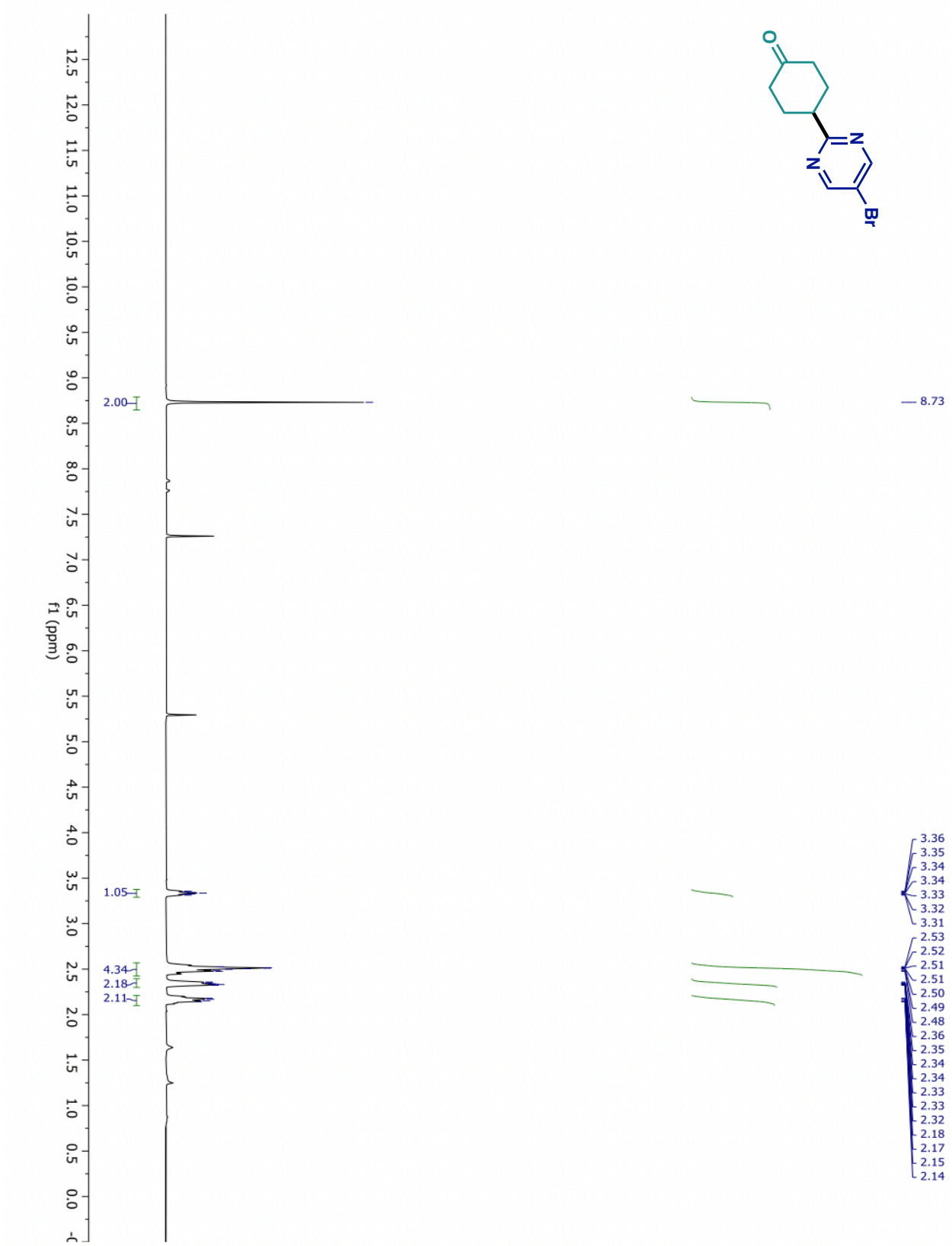


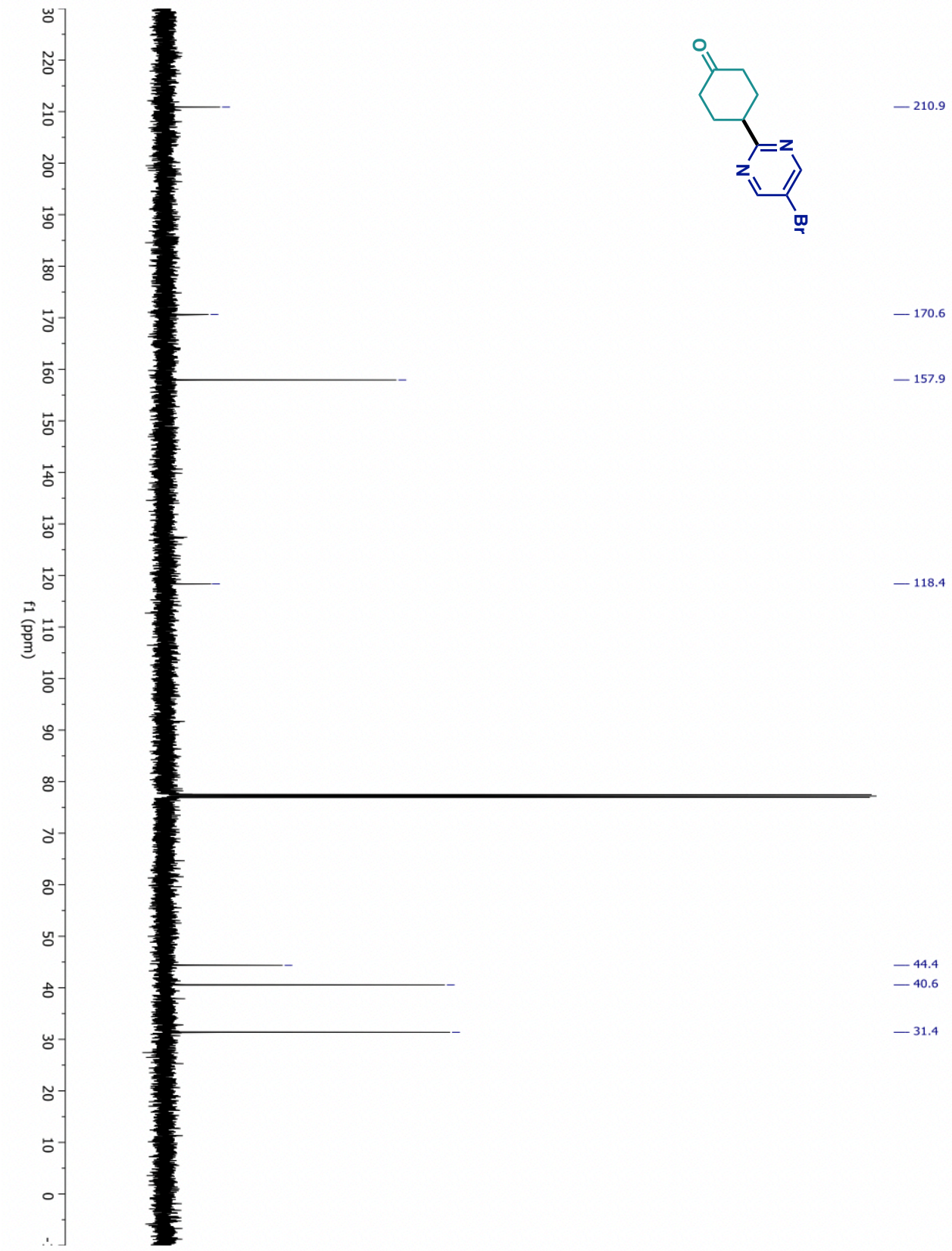
Compound 14 ^{13}C-NMR



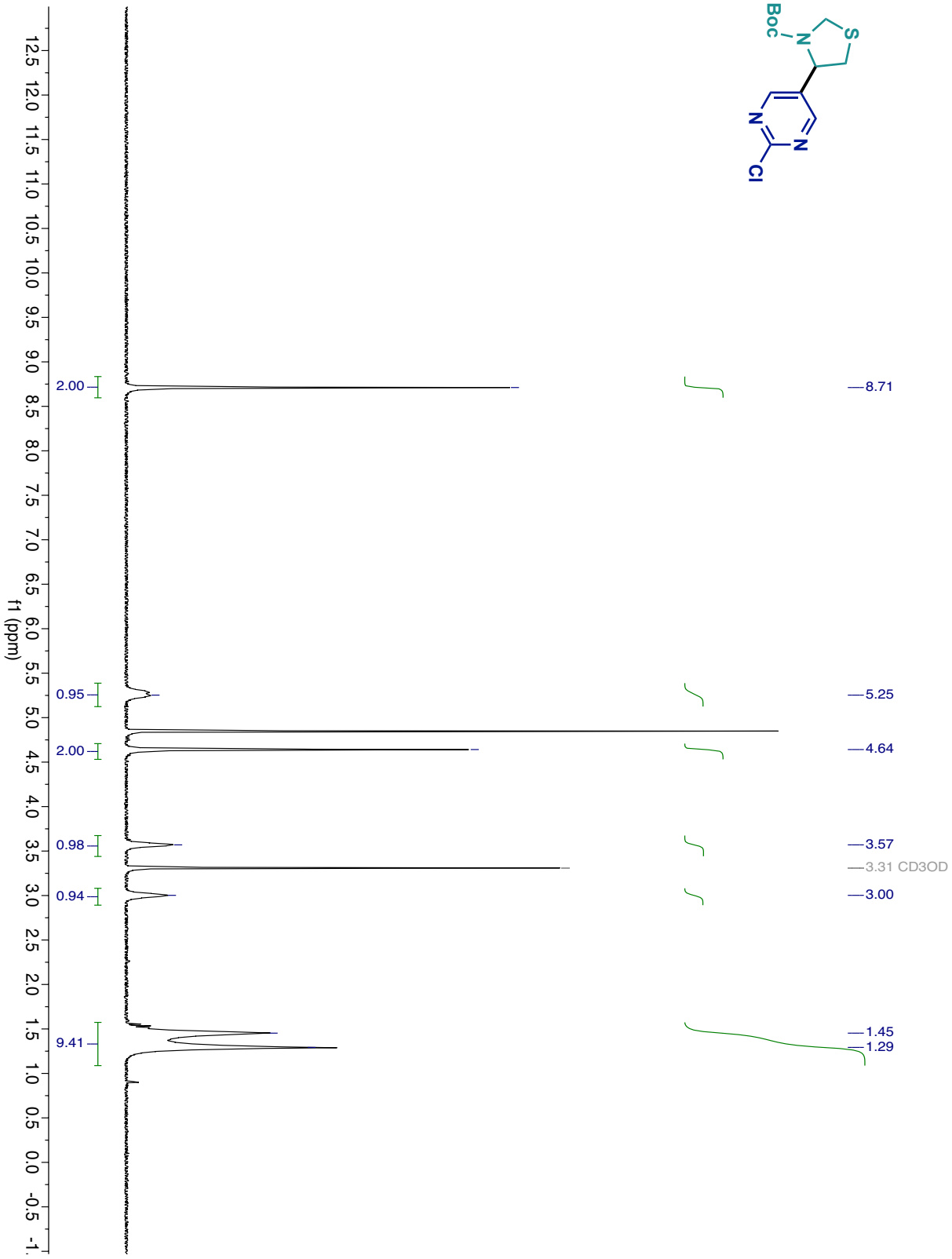
Compound 16 ^{1}H-NMR



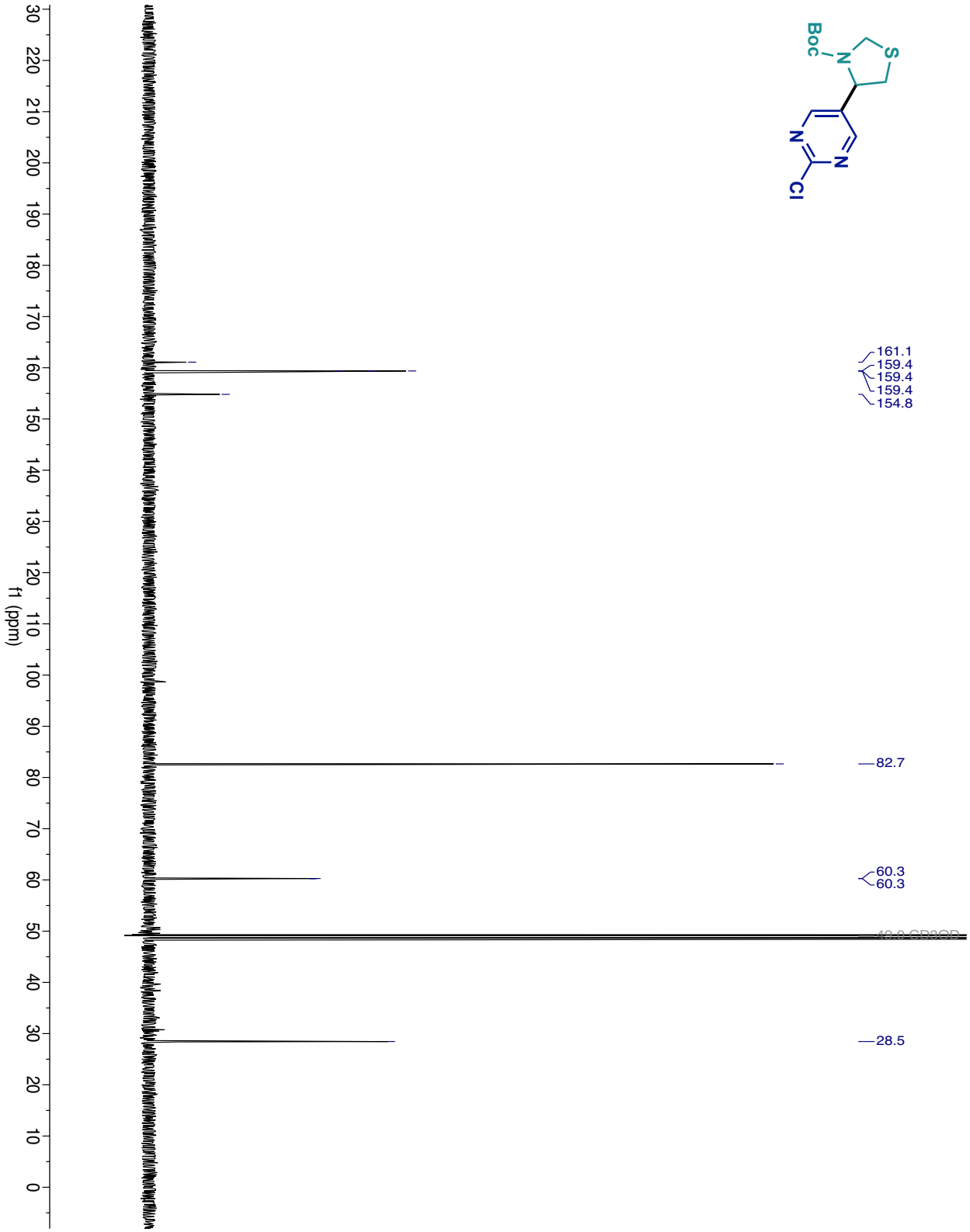
Compound 16 ^{13}C-NMR



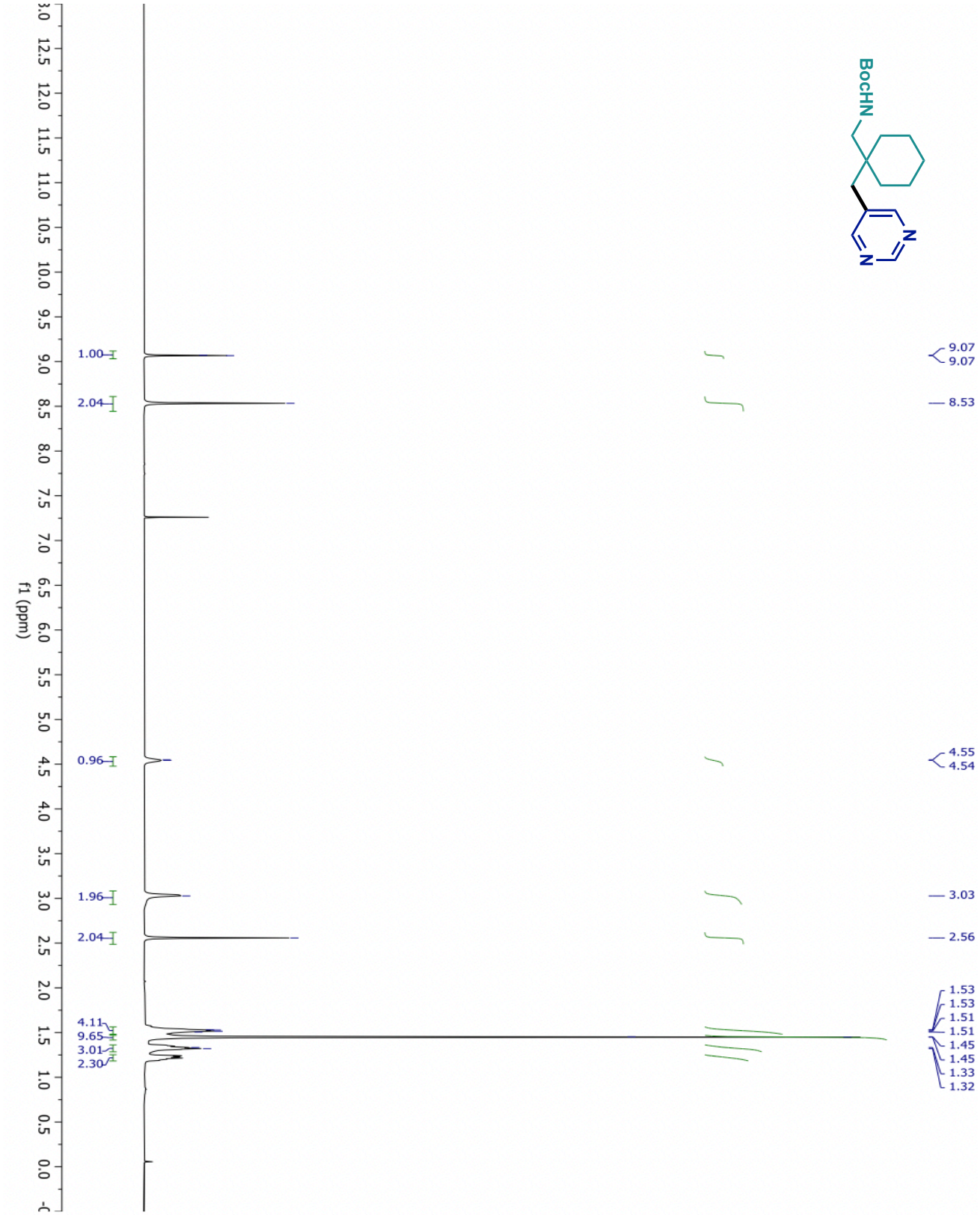
Compound 17 ^{1}H-NMR



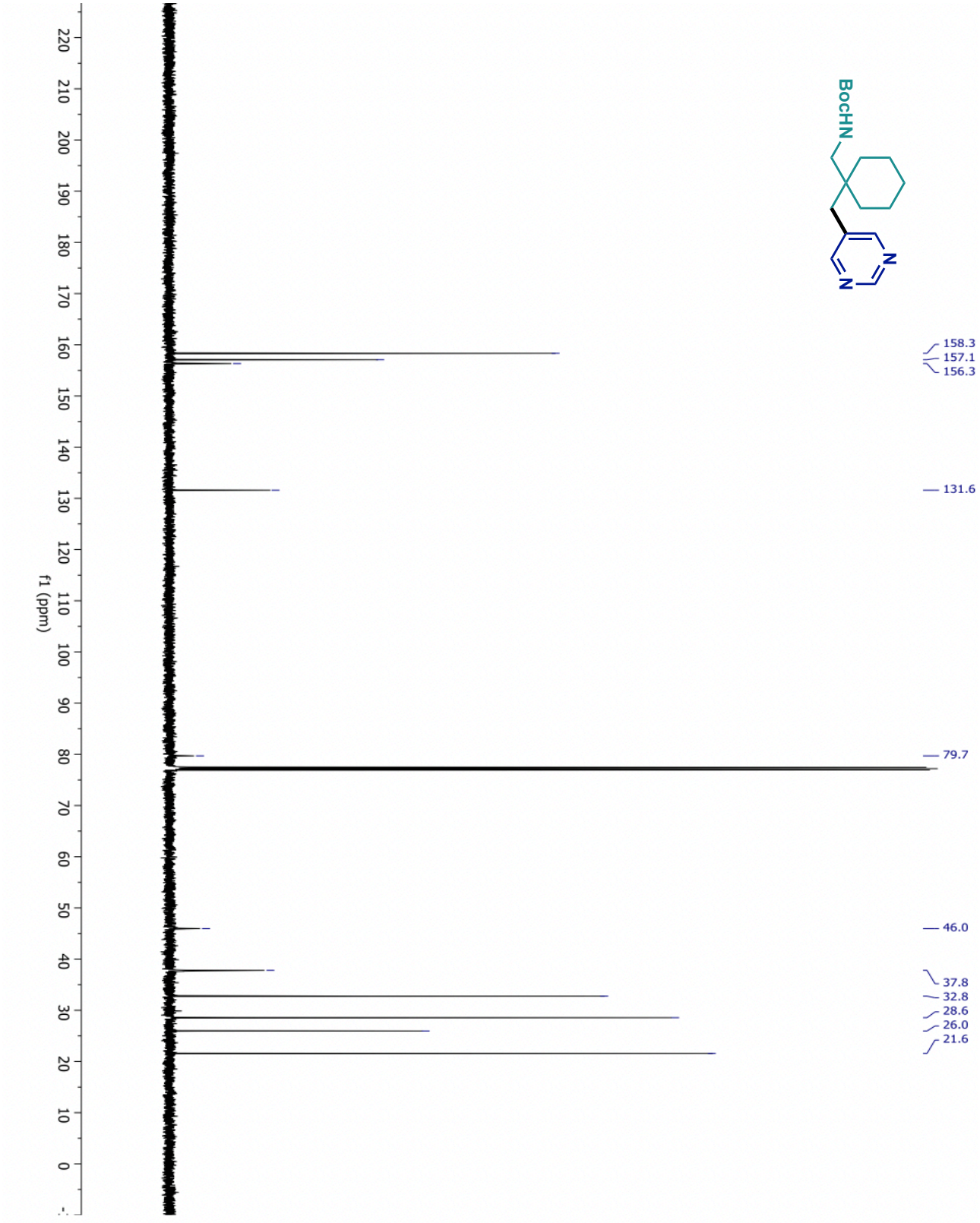
Compound 17 ^{13}C-NMR



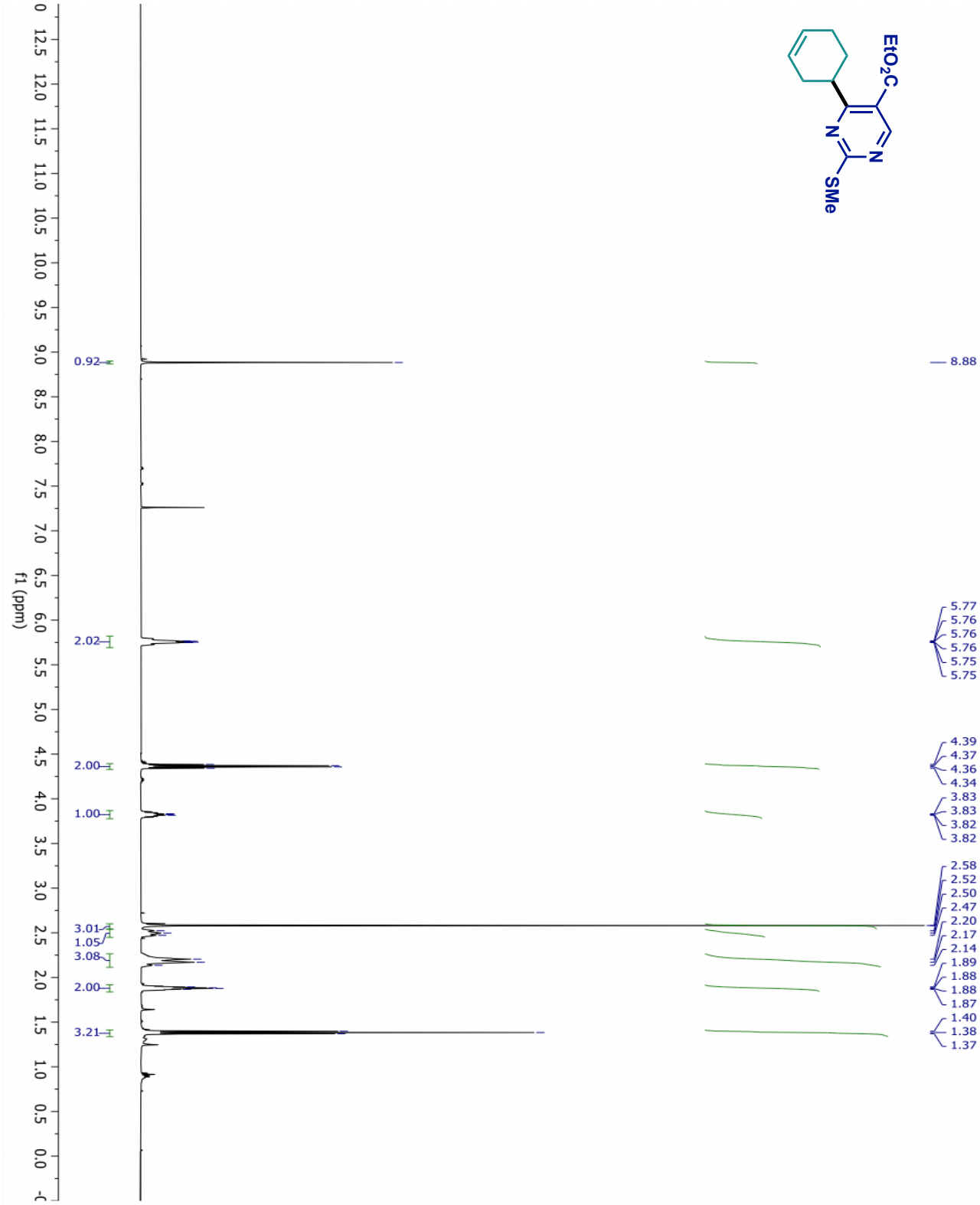
Compound 18 ^{1}H-NMR



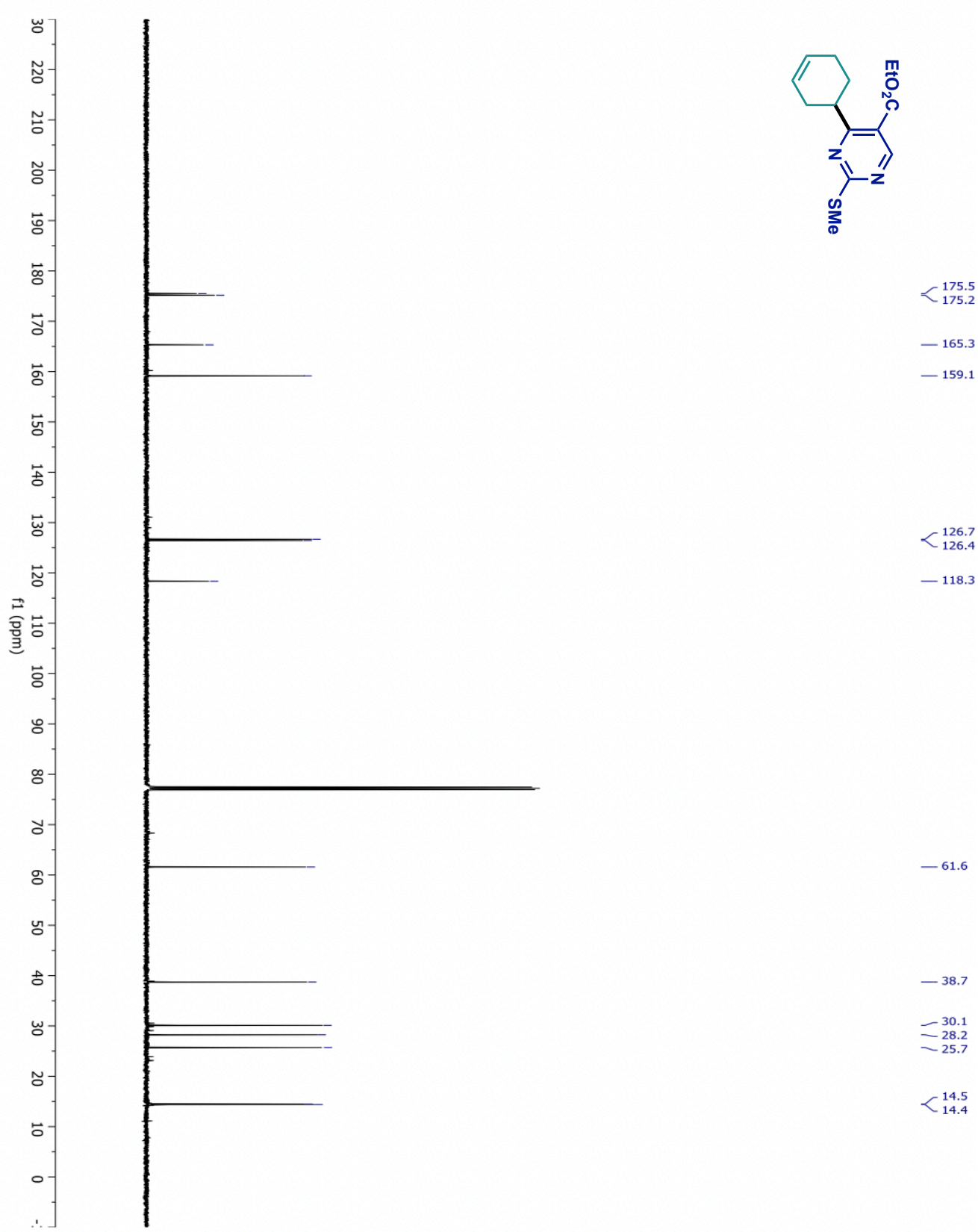
Compound 18 ^{13}C-NMR



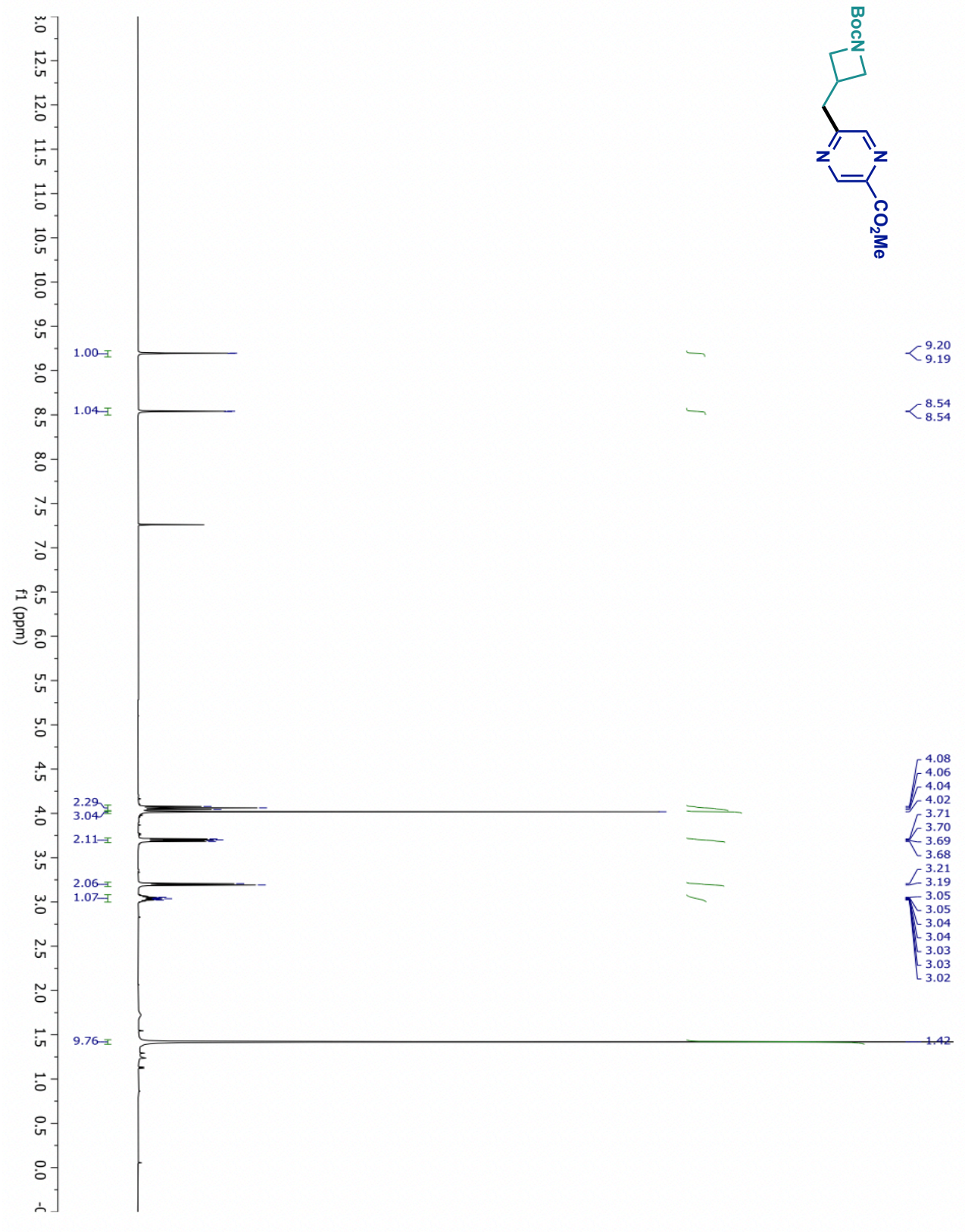
Compound 19 ^{1}H-NMR



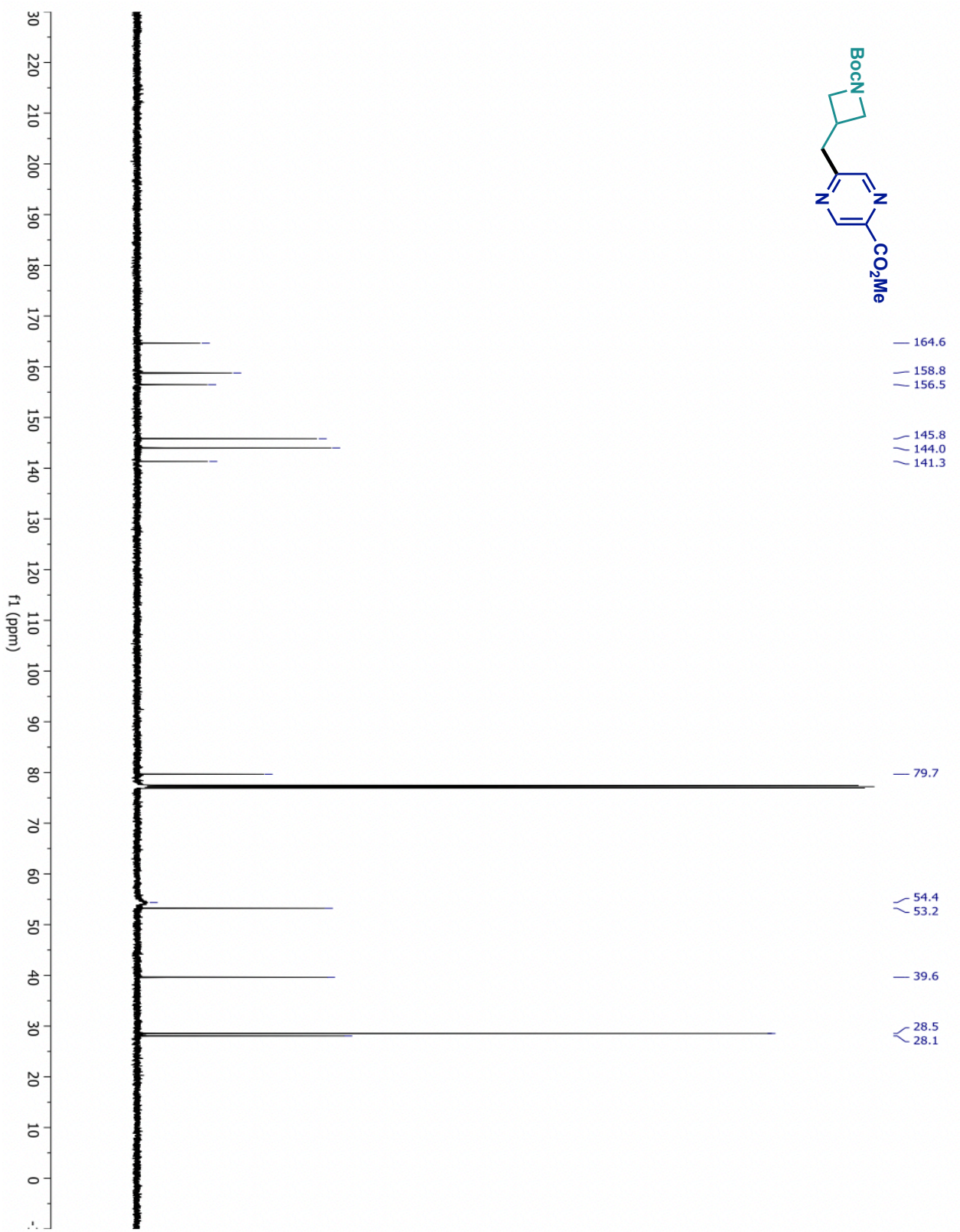
Compound 19 ^{13}C-NMR



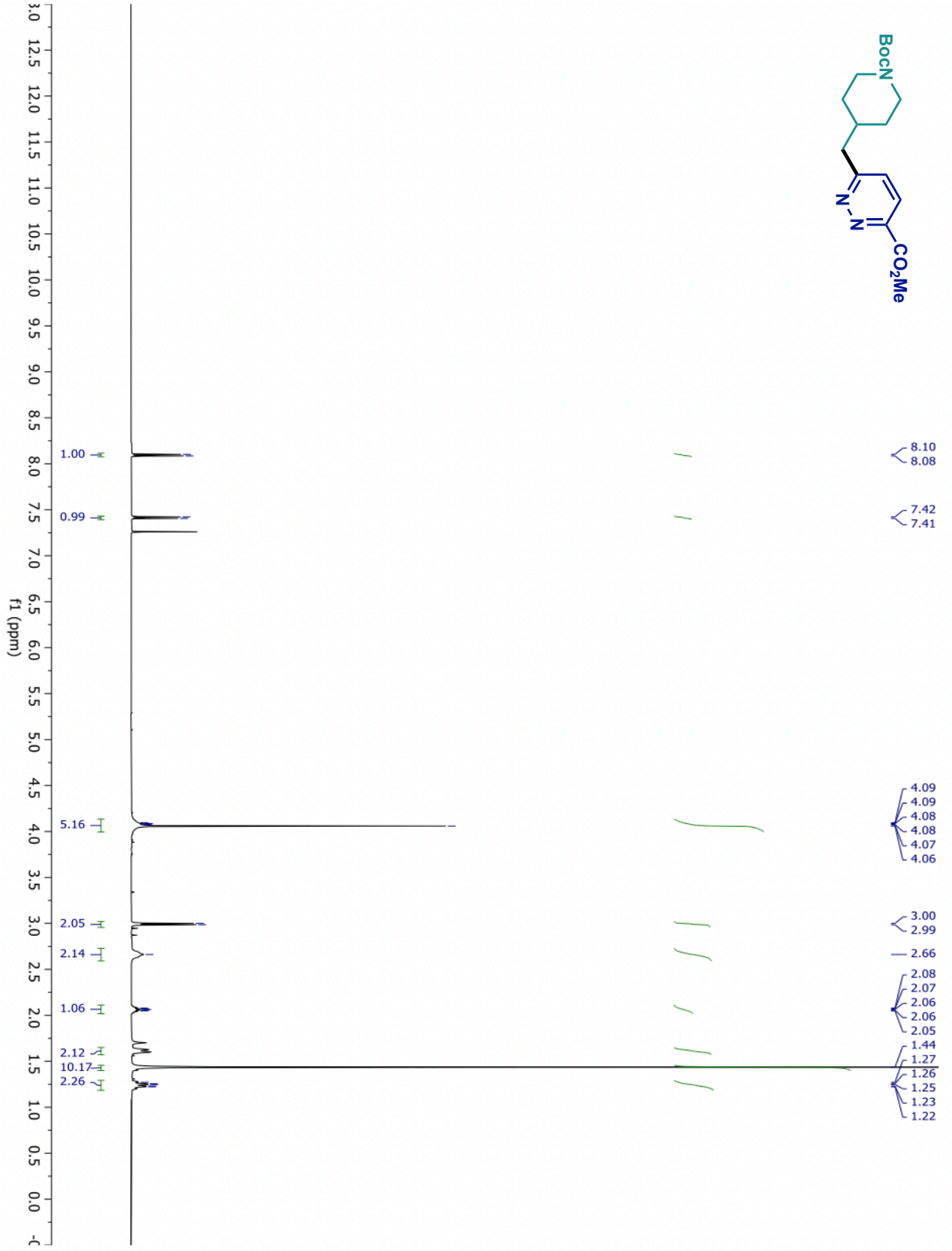
Compound 20 ^{1}H-NMR



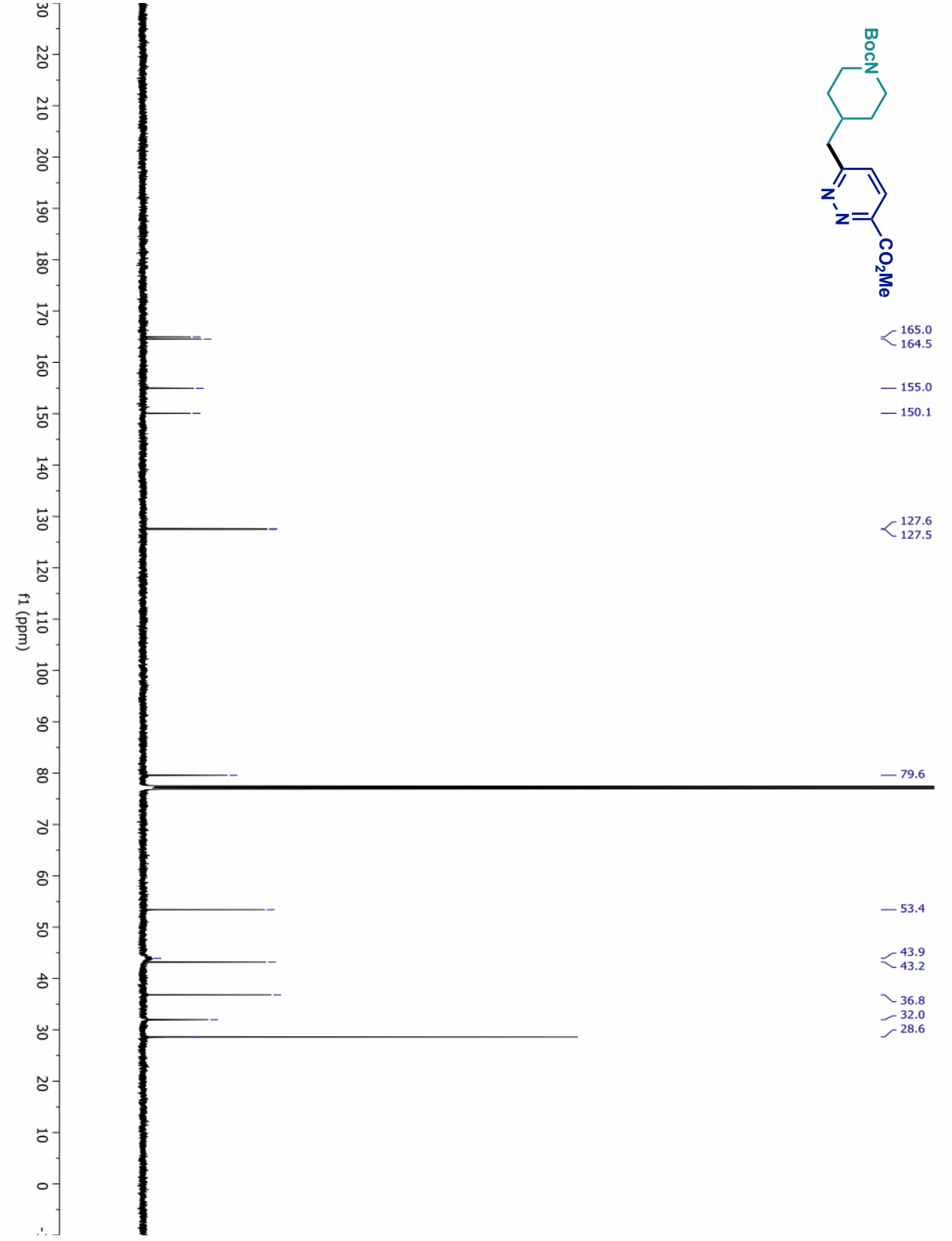
Compound 20 ^{13}C-NMR



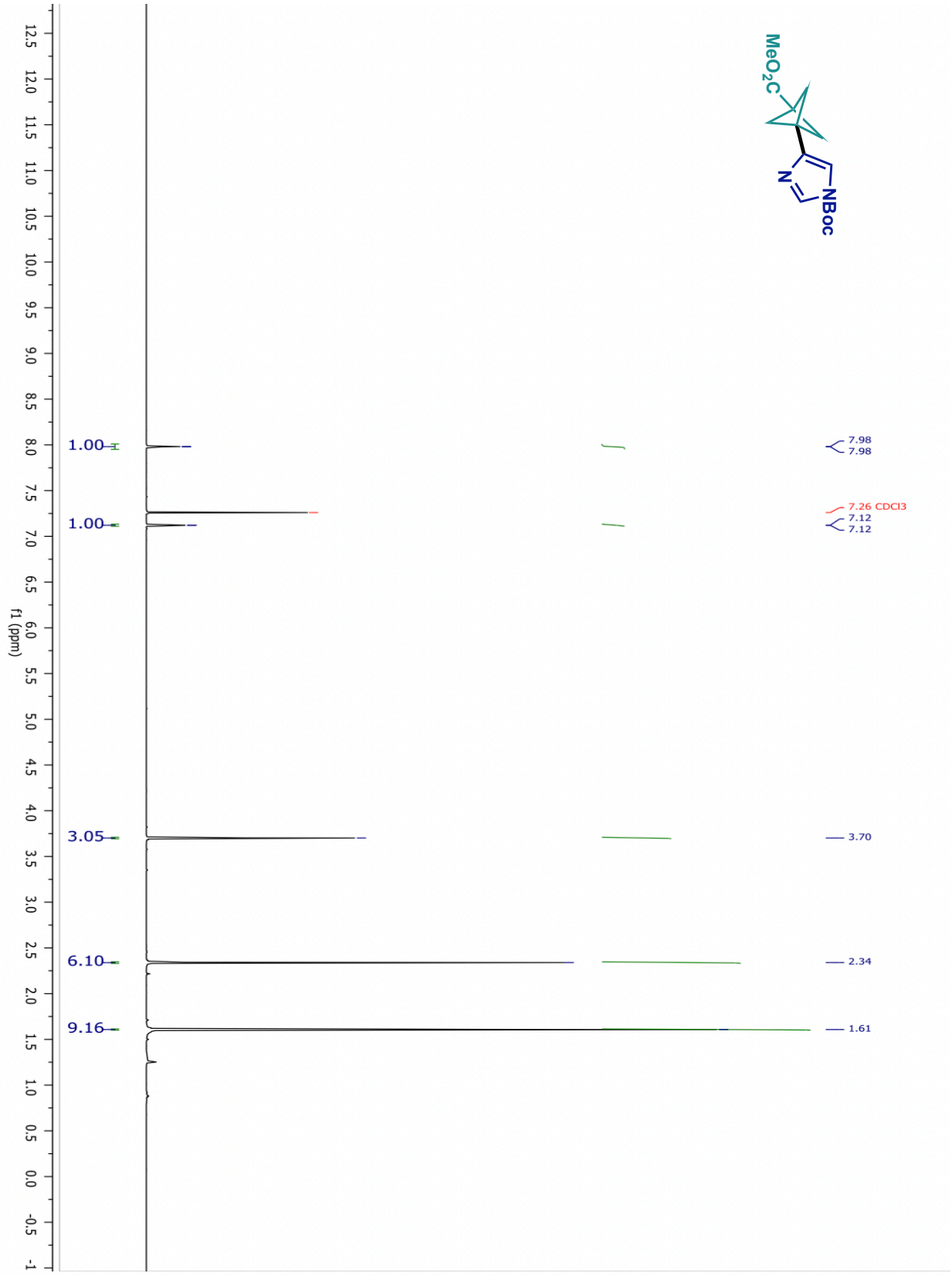
Compound 21 ^{1}H-NMR



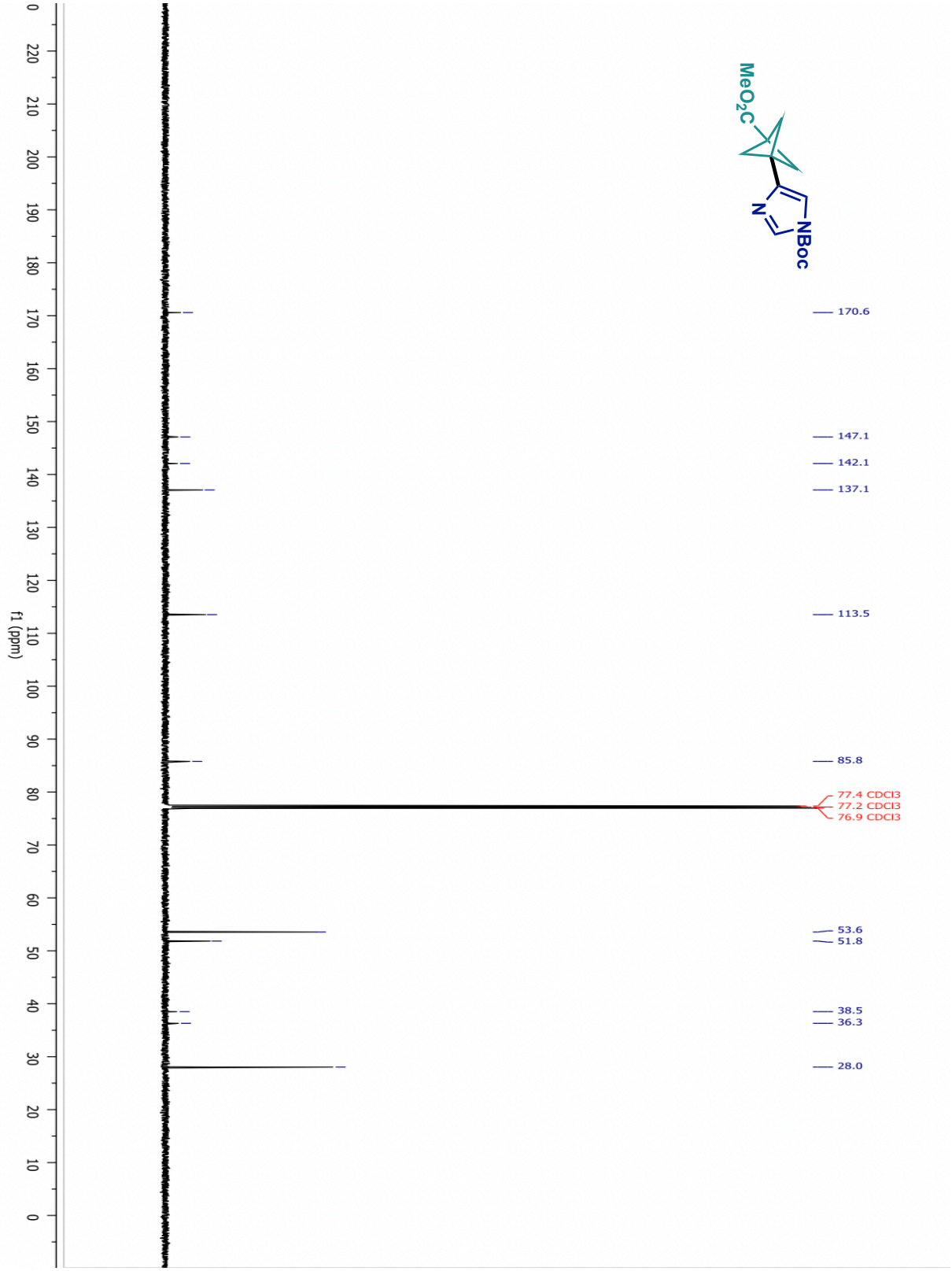
Compound 21 ^{13}C-NMR



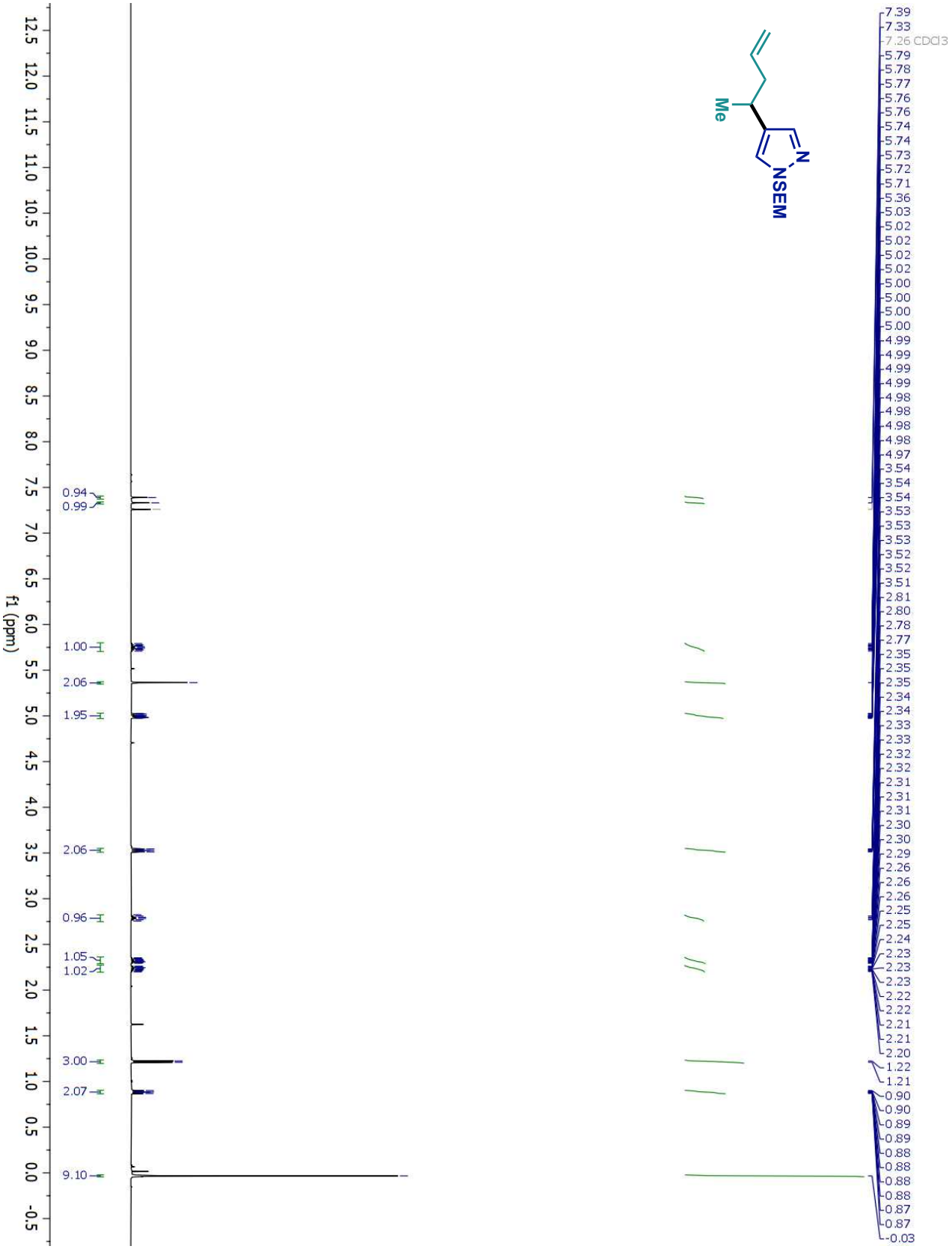
Compound 23 ^{1}H-NMR



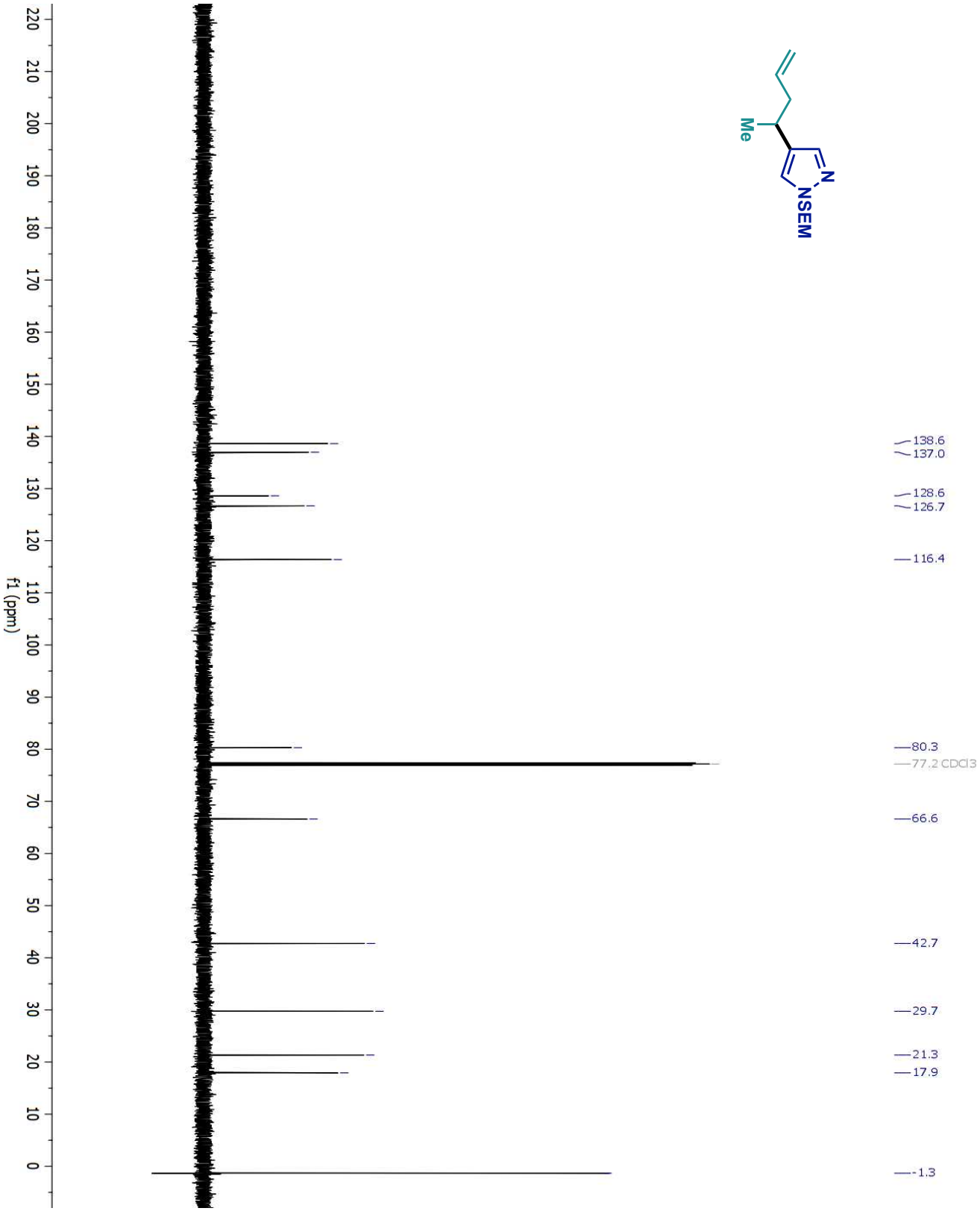
Compound 23 ^{13}C-NMR



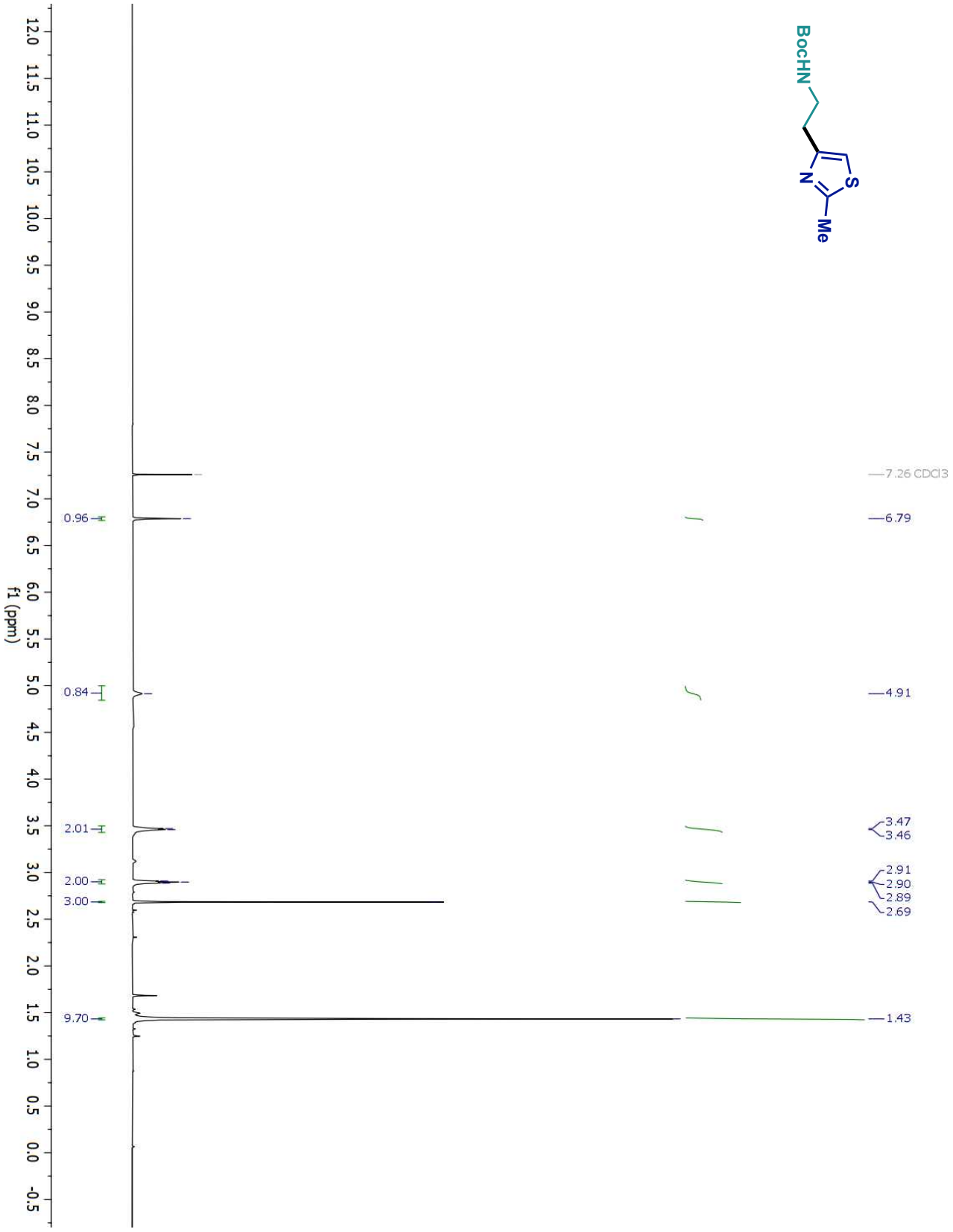
Compound 24 ^{1}H-NMR



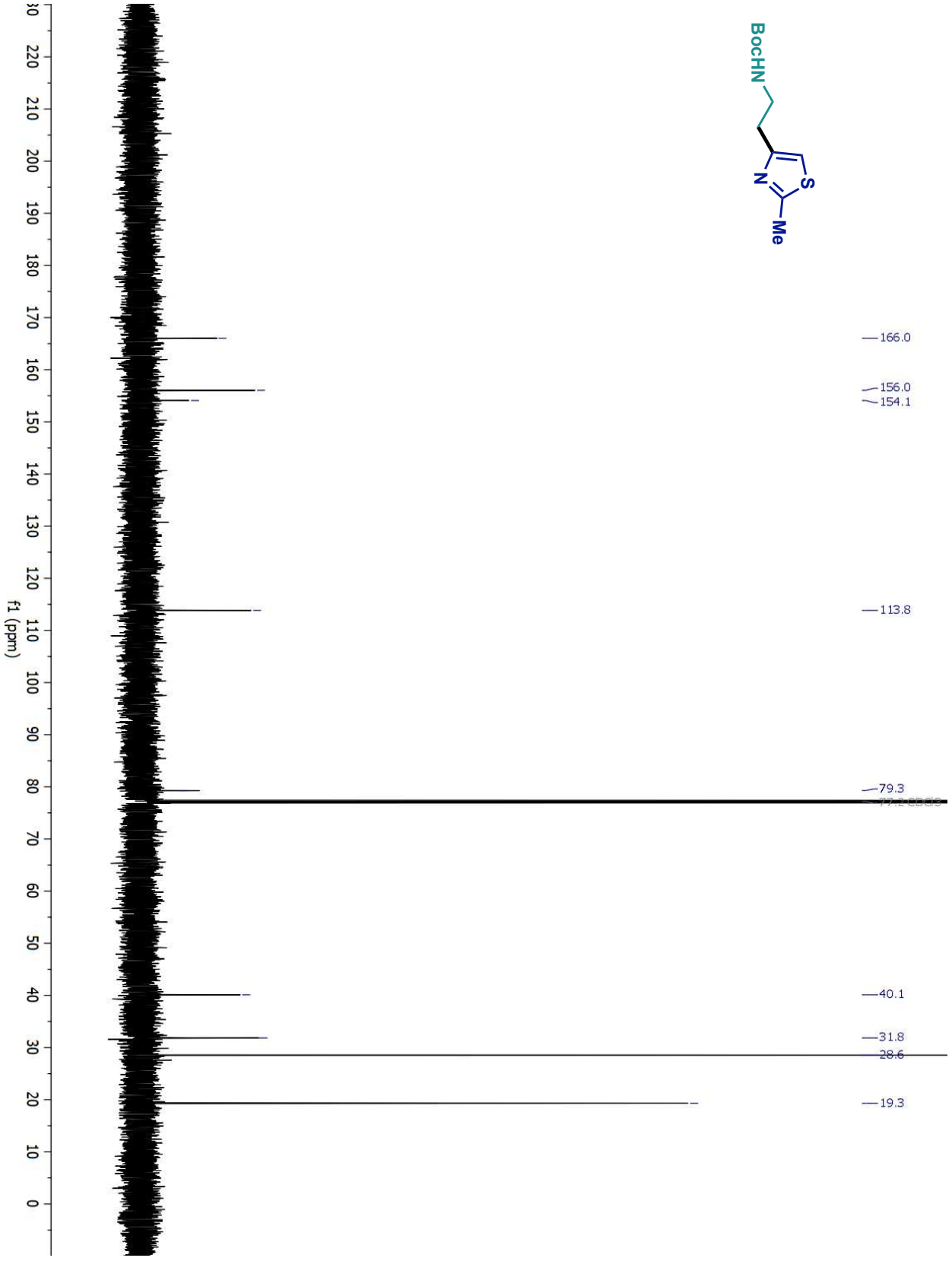
Compound 24 ^{13}C-NMR



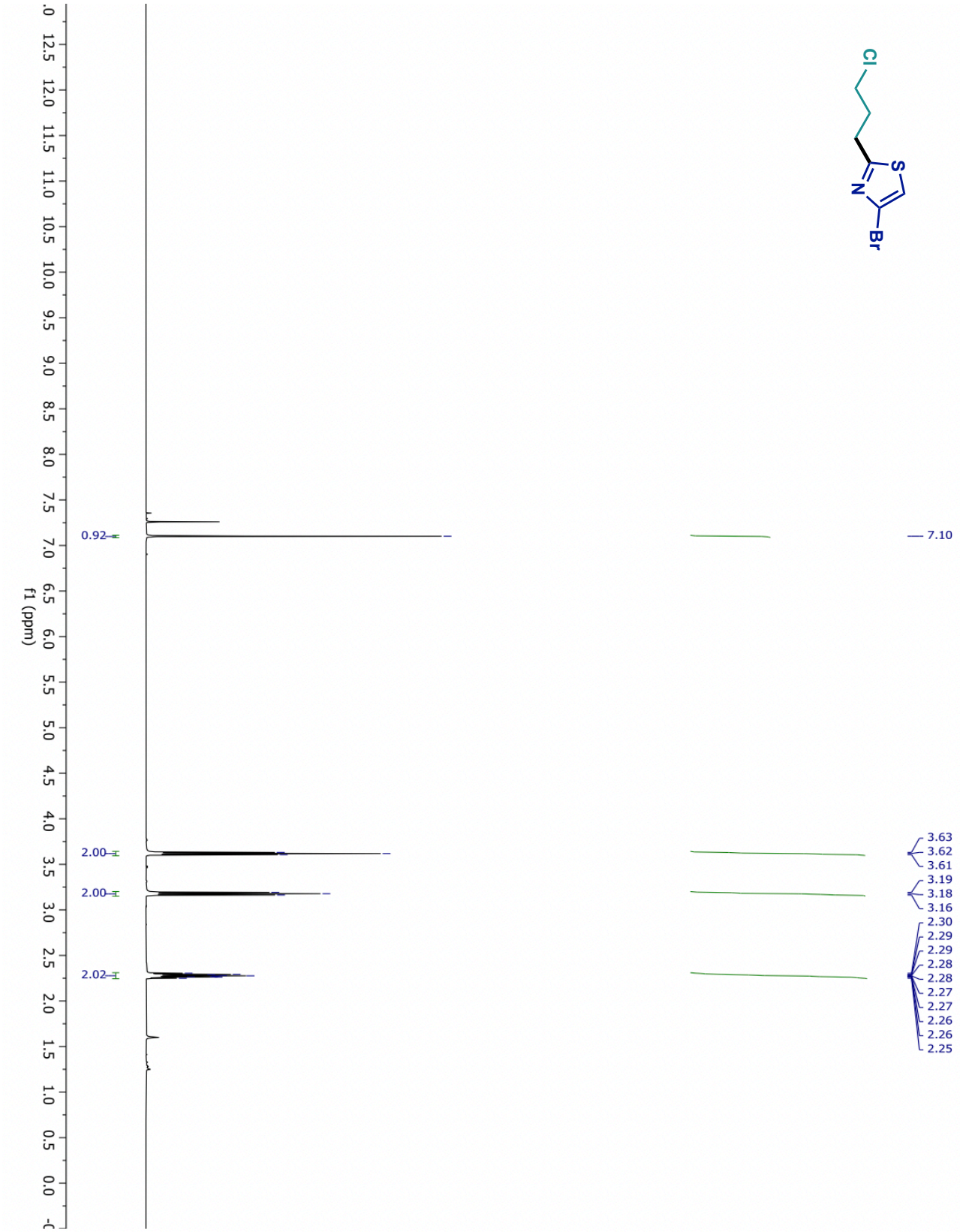
Compound 25 ^{1}H-NMR



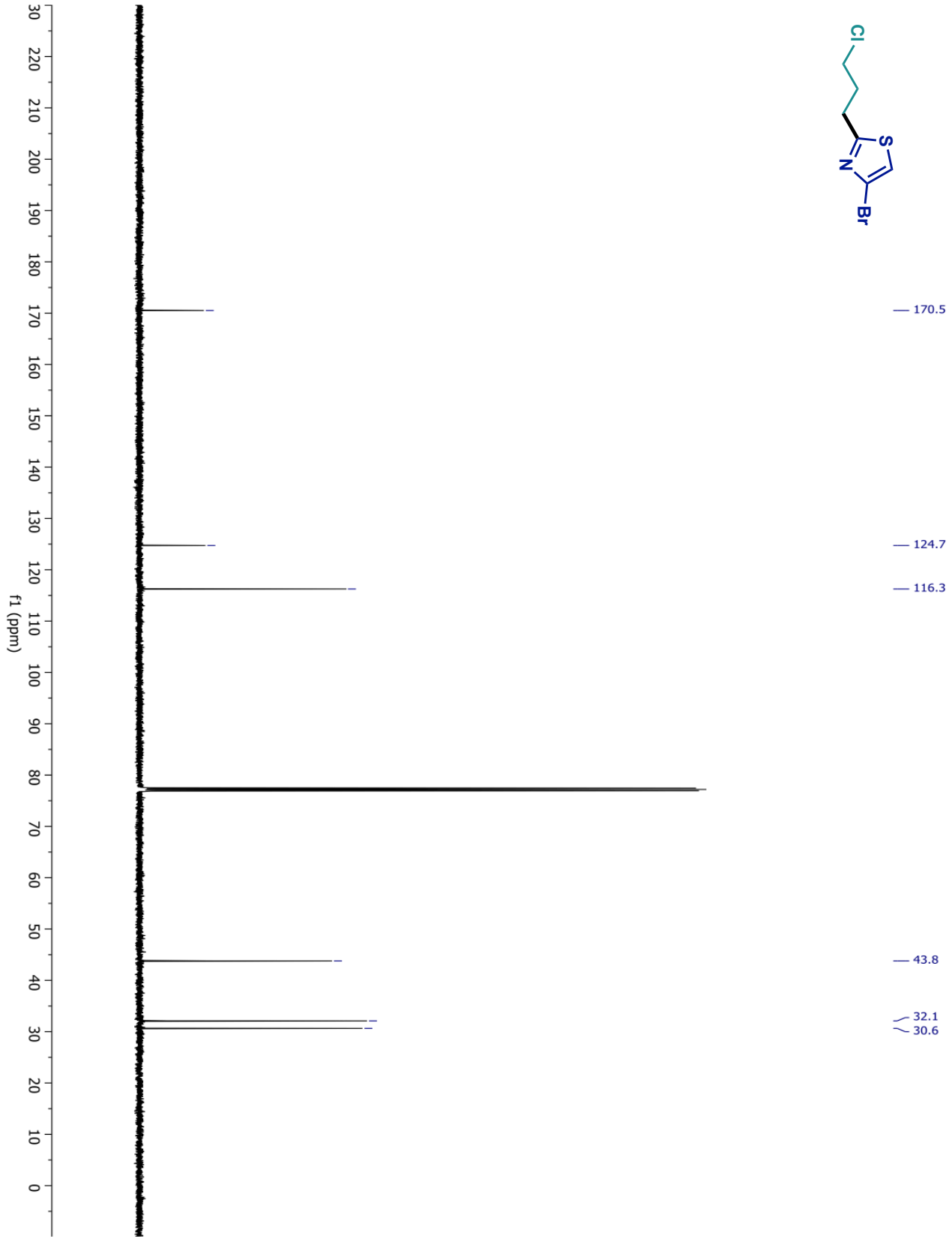
Compound 25 ^{13}C-NMR



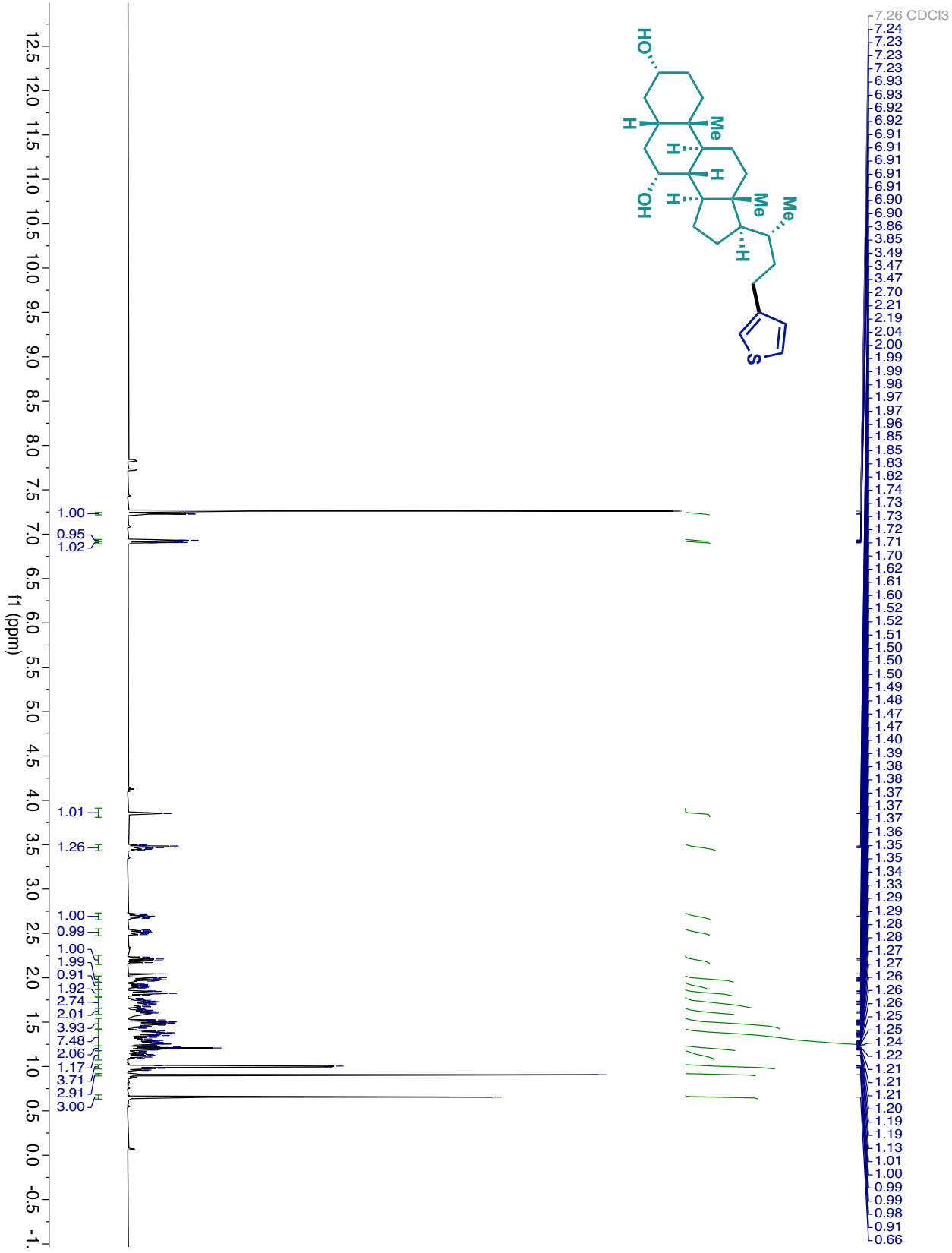
Compound 26 ^{1}H-NMR



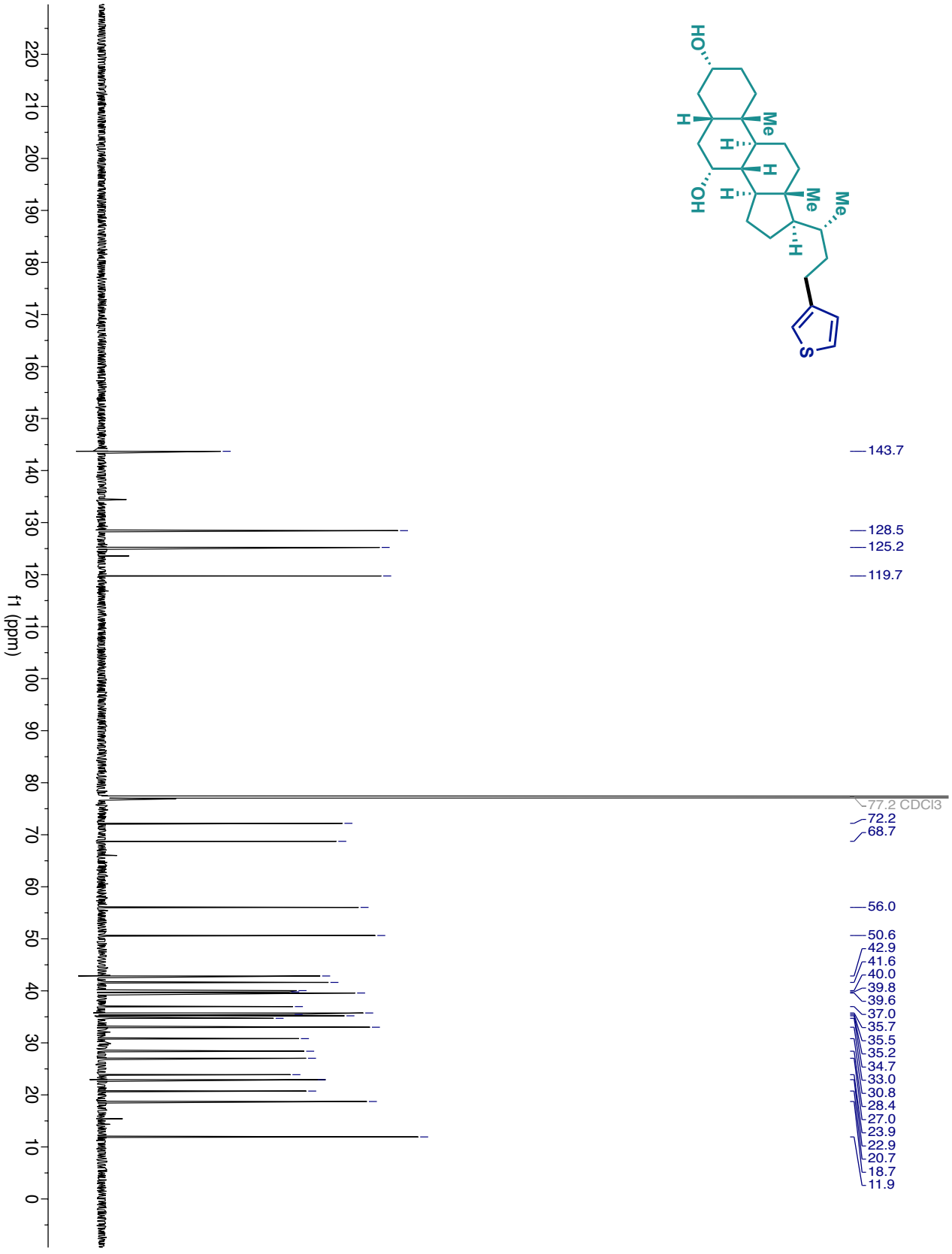
Compound 26 ^{13}C-NMR



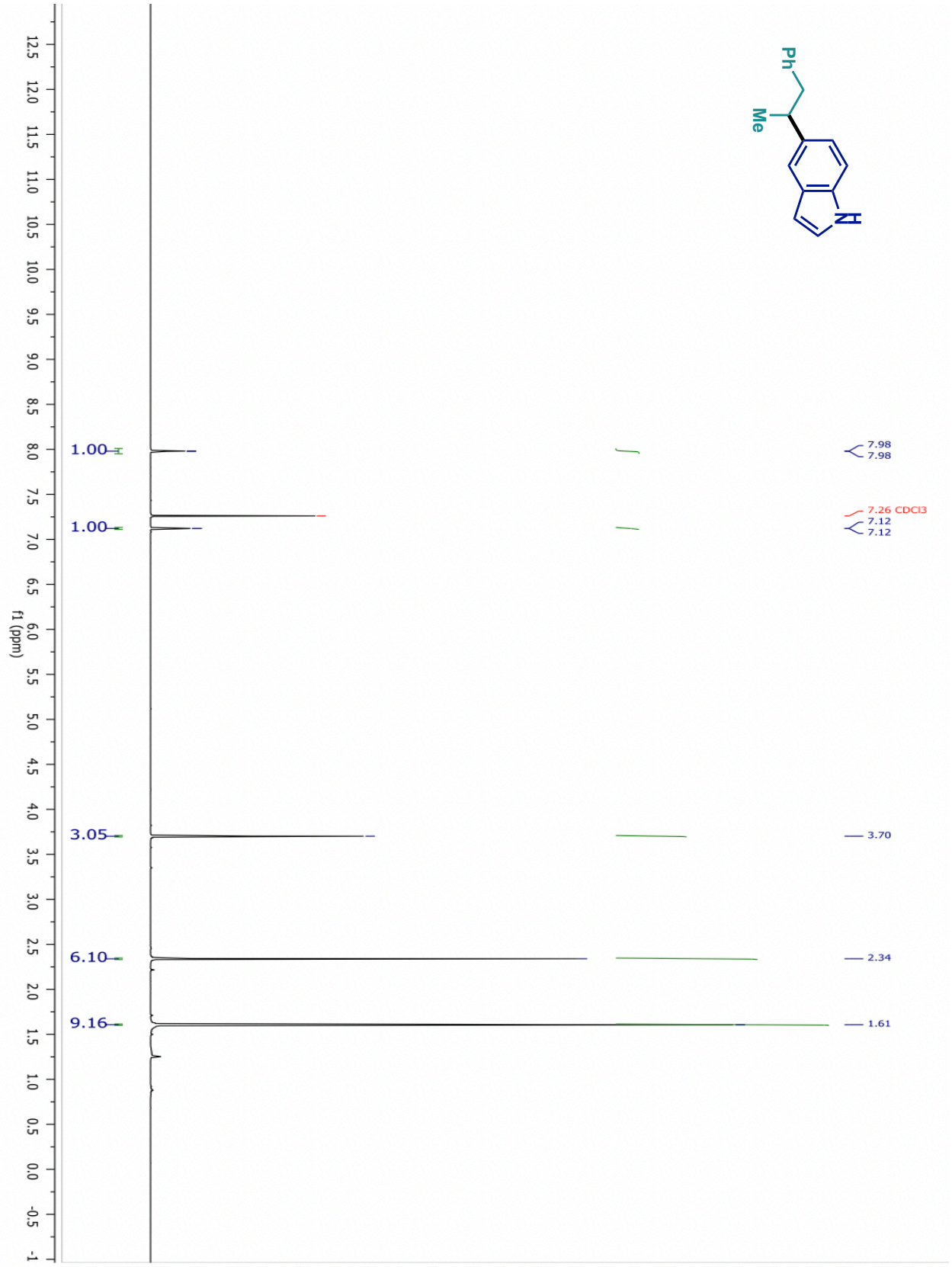
Compound 27 ^{1}H-NMR



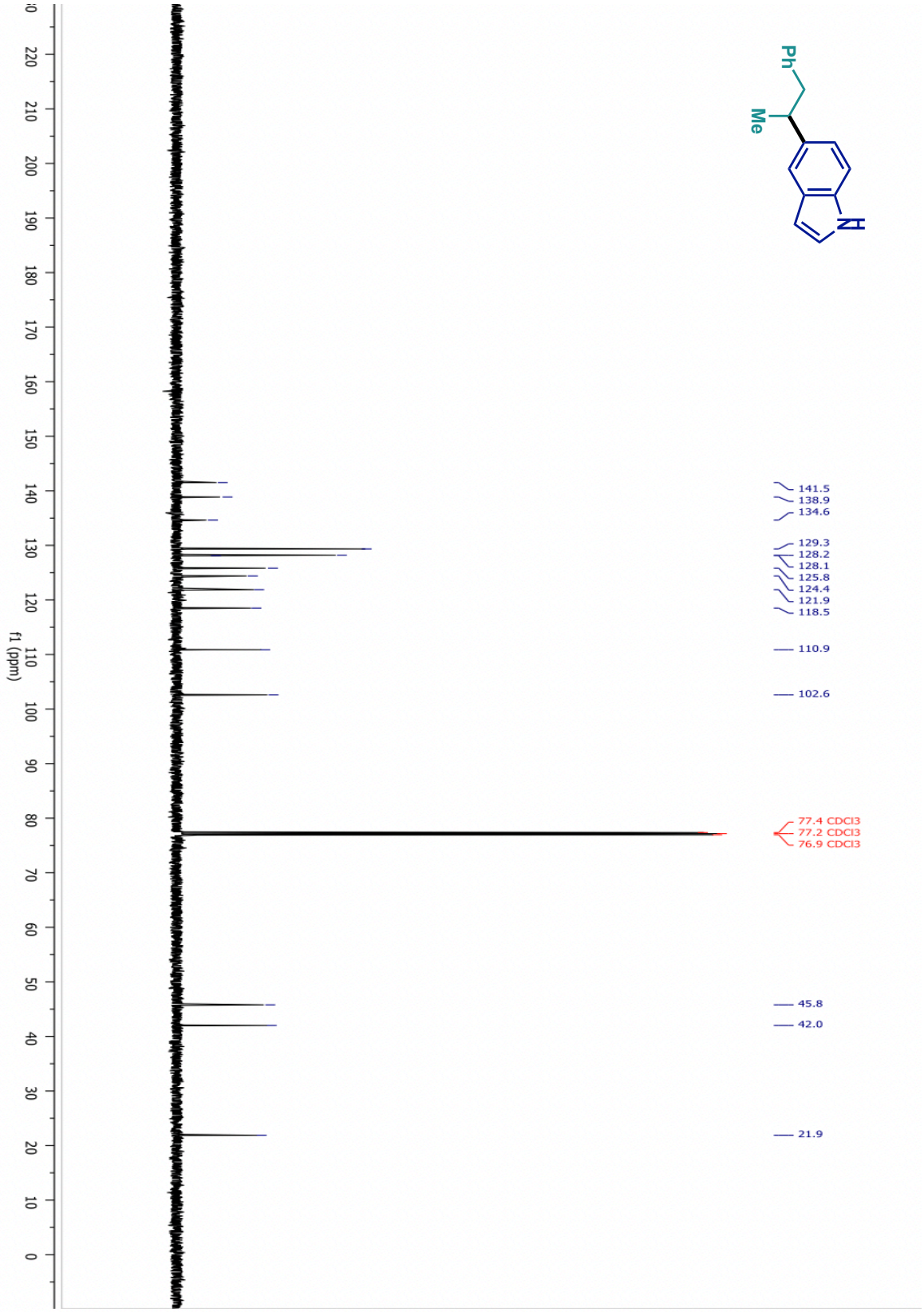
Compound 27 ^{13}C-NMR



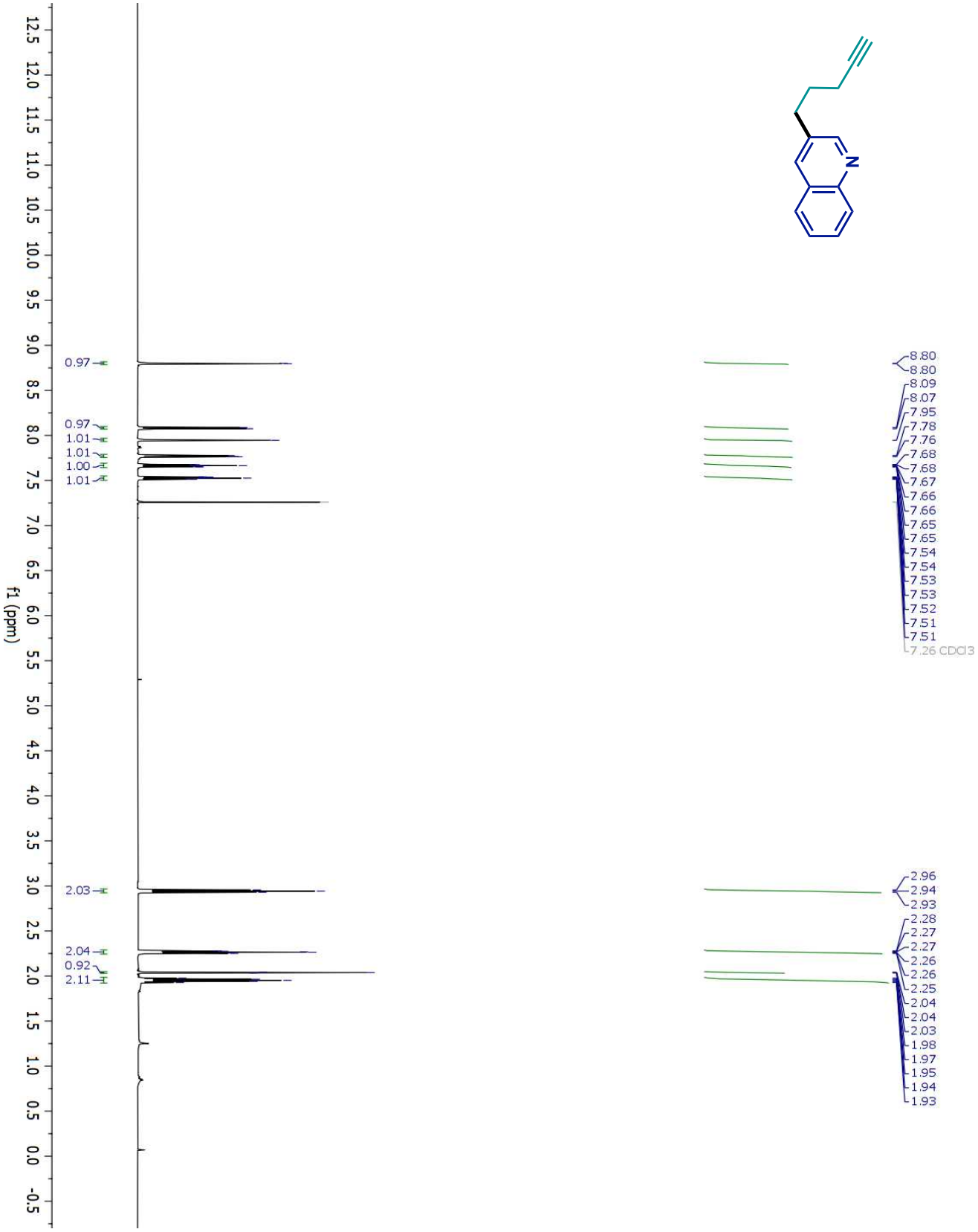
Compound 28 ^{1}H-NMR



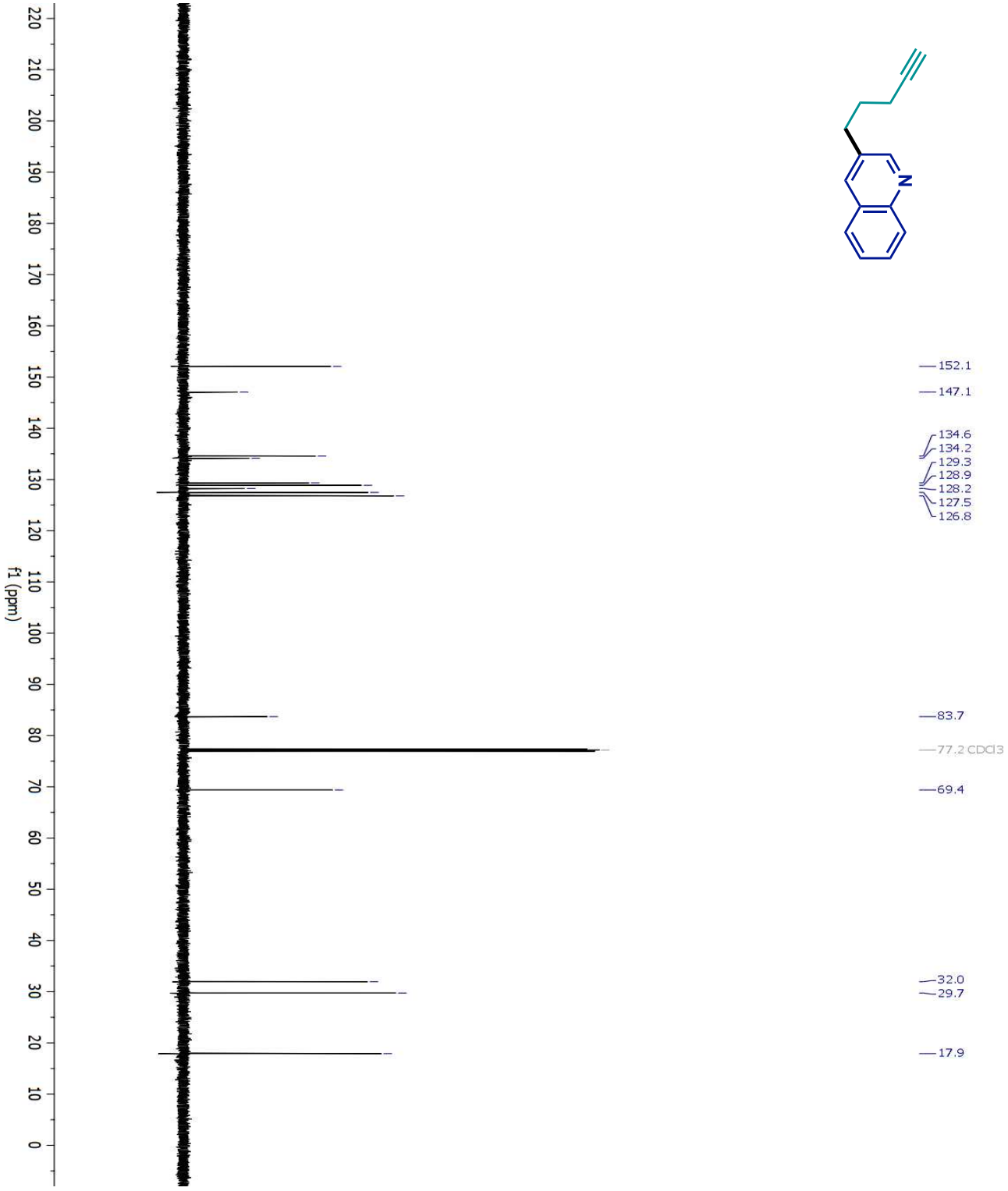
Compound 28 ^{13}C-NMR



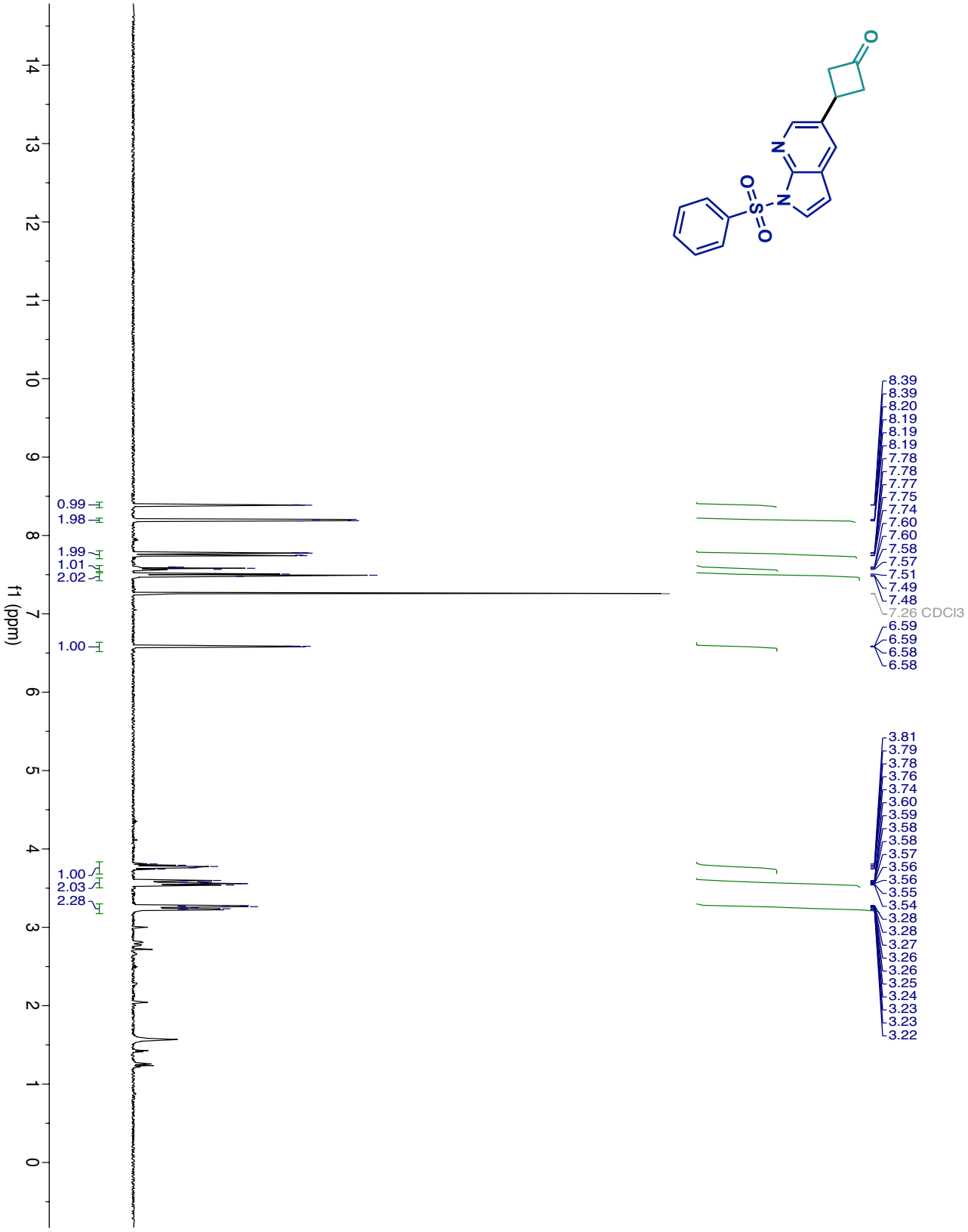
Compound 29 ^{1}H-NMR



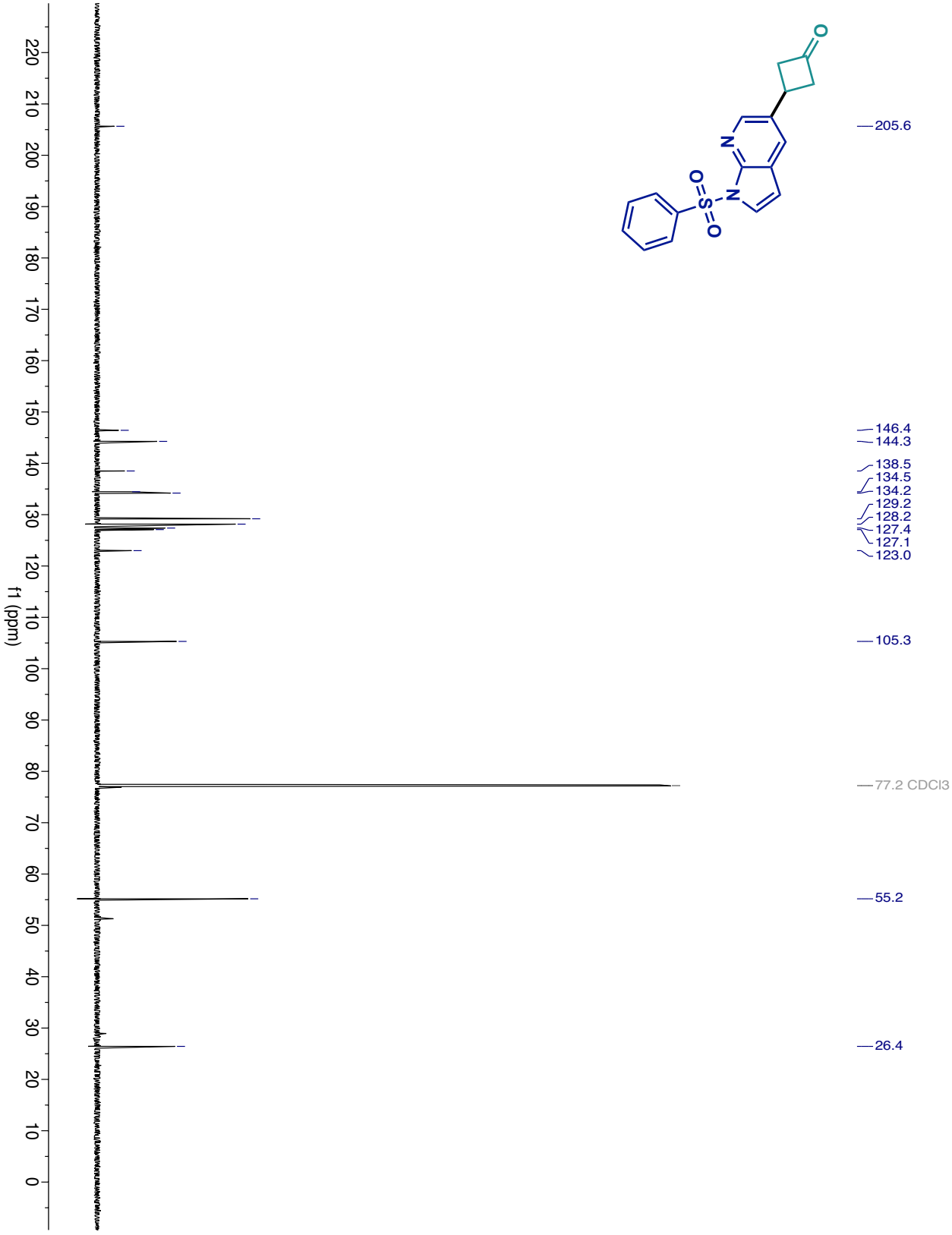
Compound 29 ^{13}C-NMR



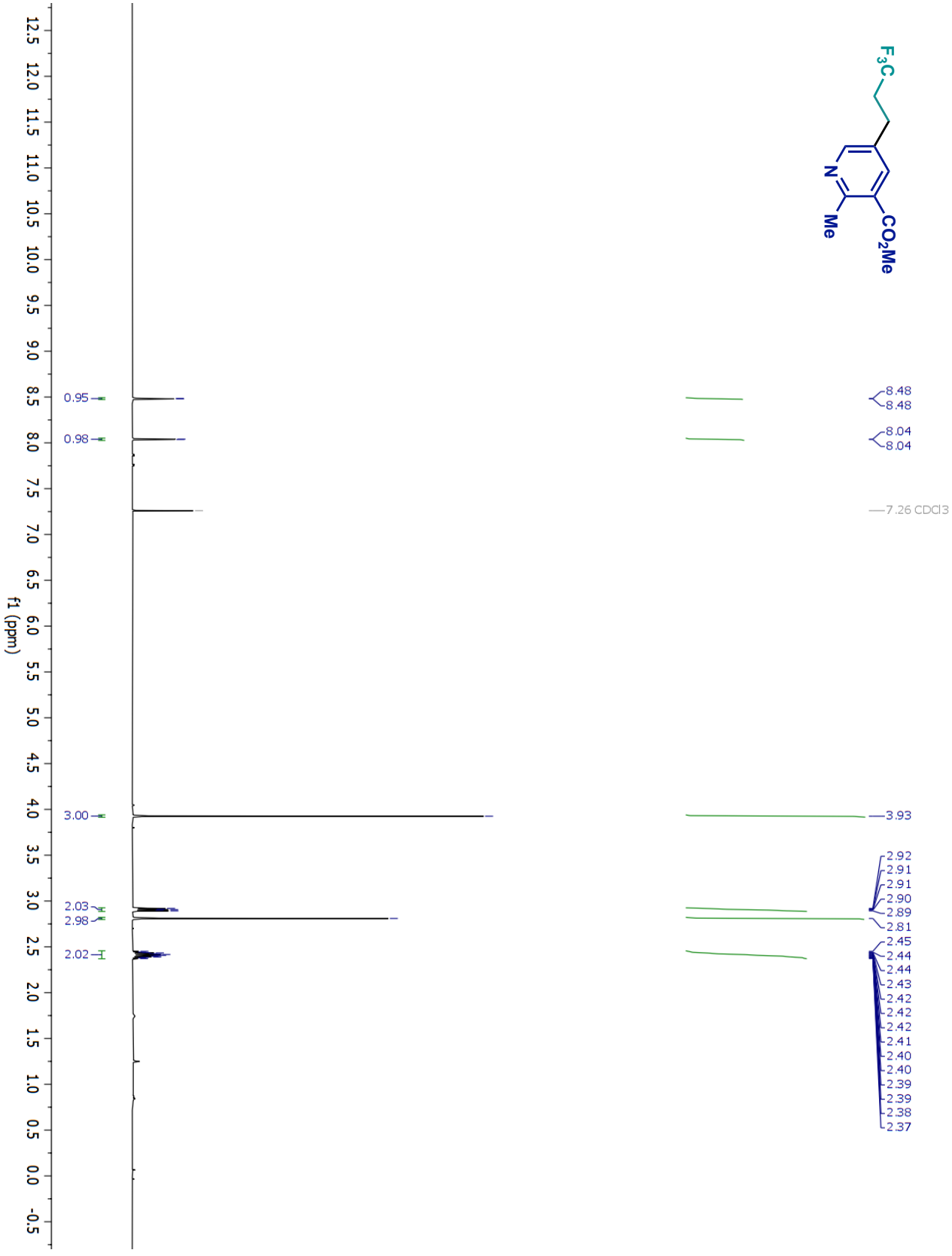
Compound 31 ^{1}H-NMR



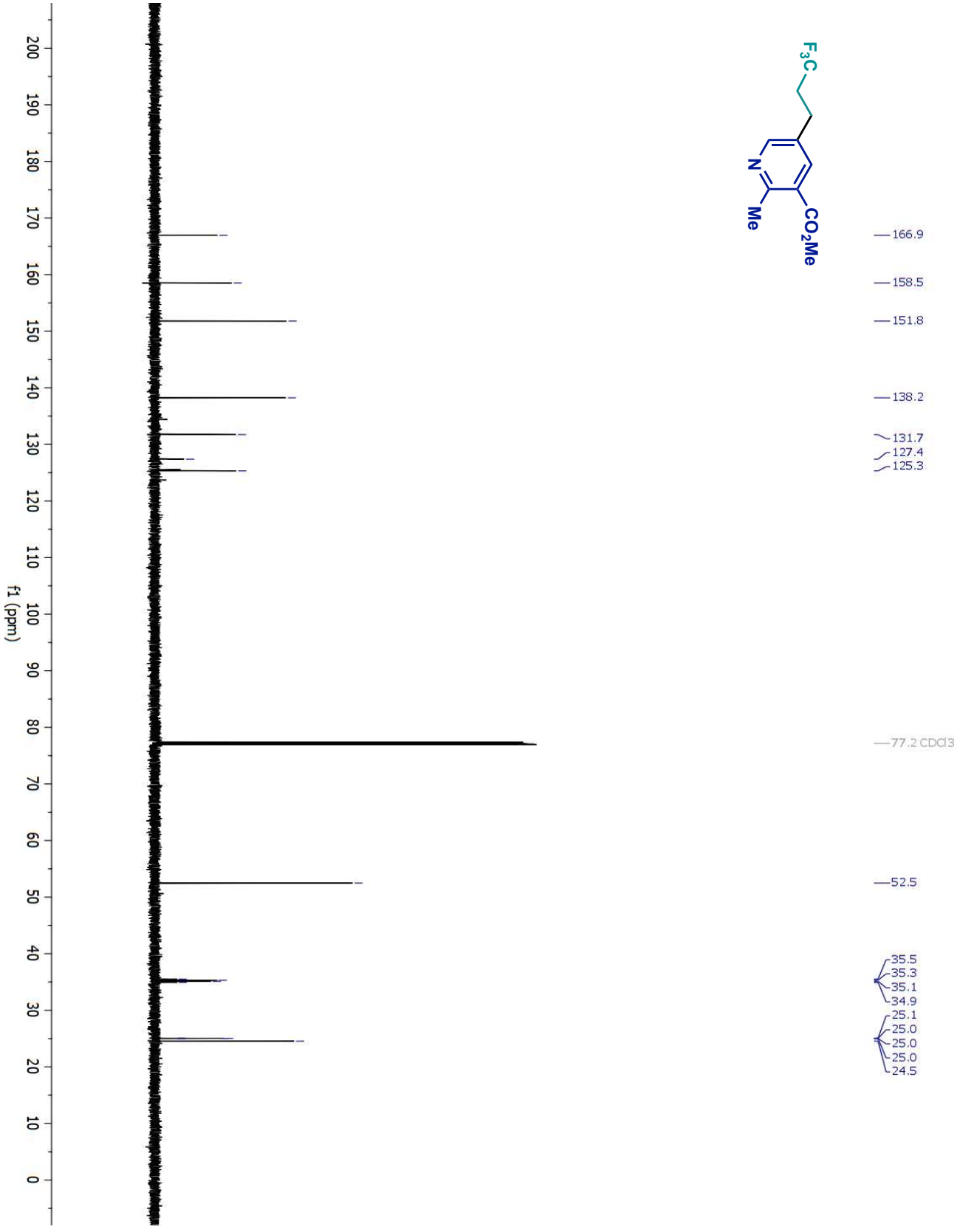
Compound 31 ^{13}C-NMR



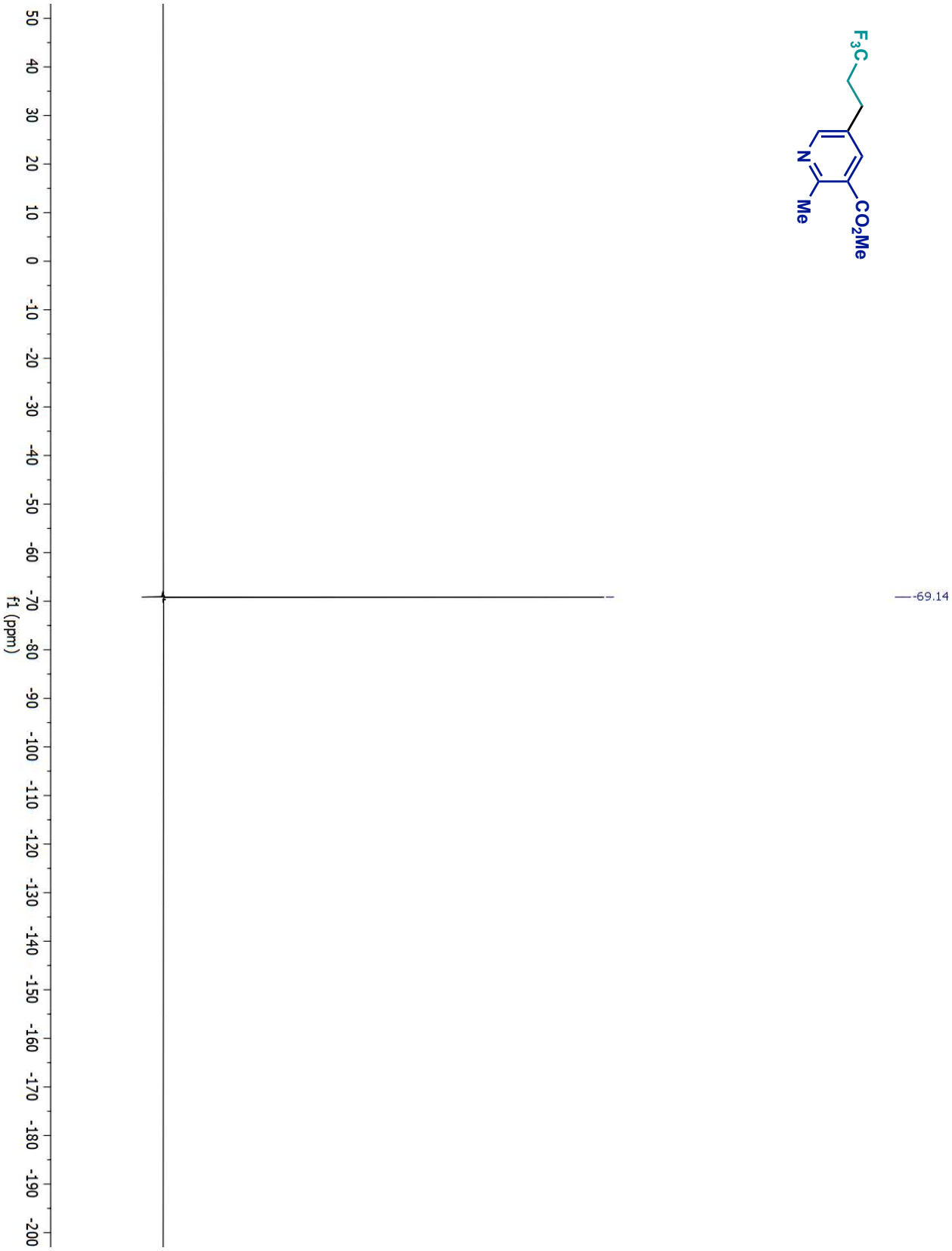
Compound 33 ^{1}H-NMR



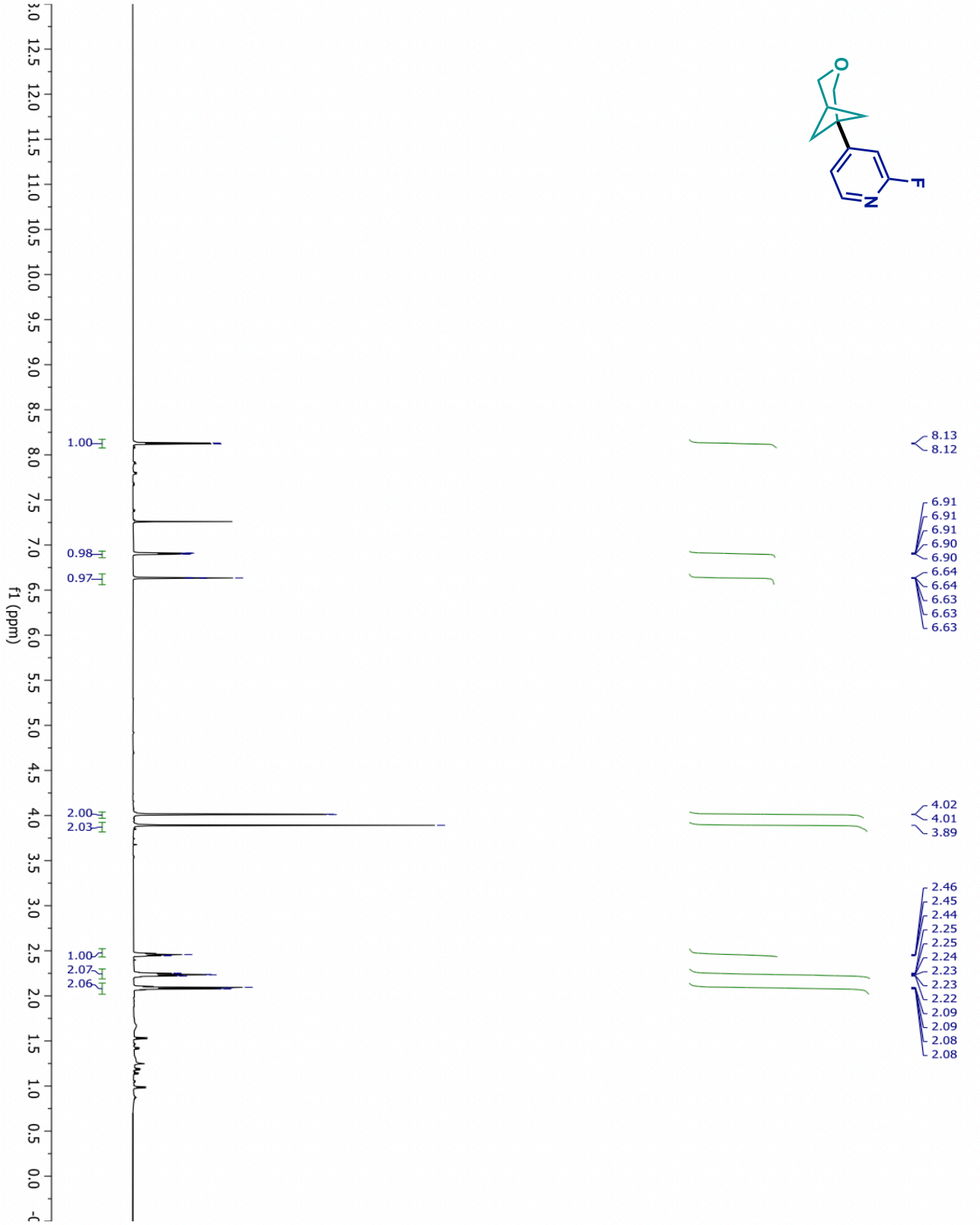
Compound 33 ^{13}C-NMR



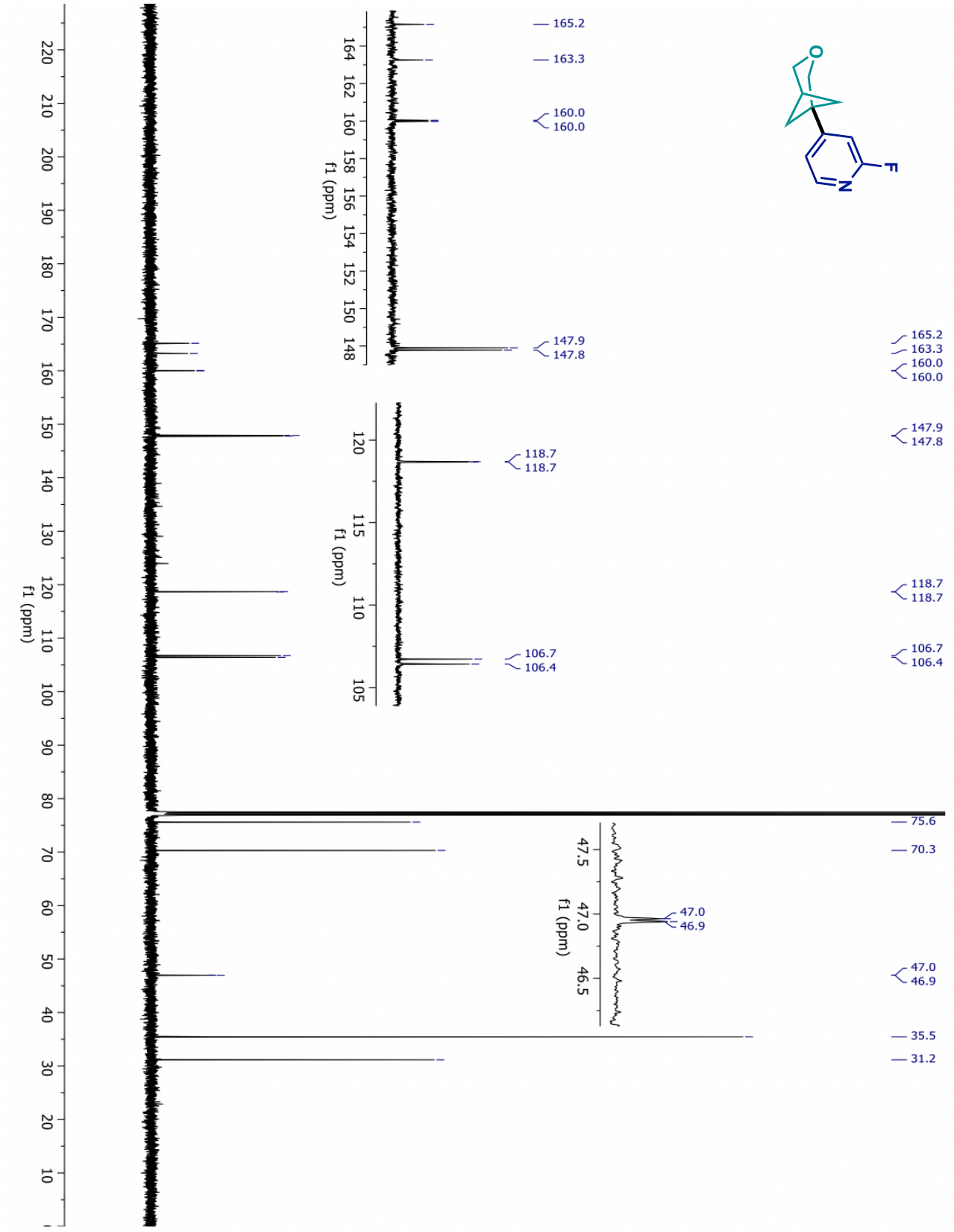
Compound 33 ^{19}F-NMR



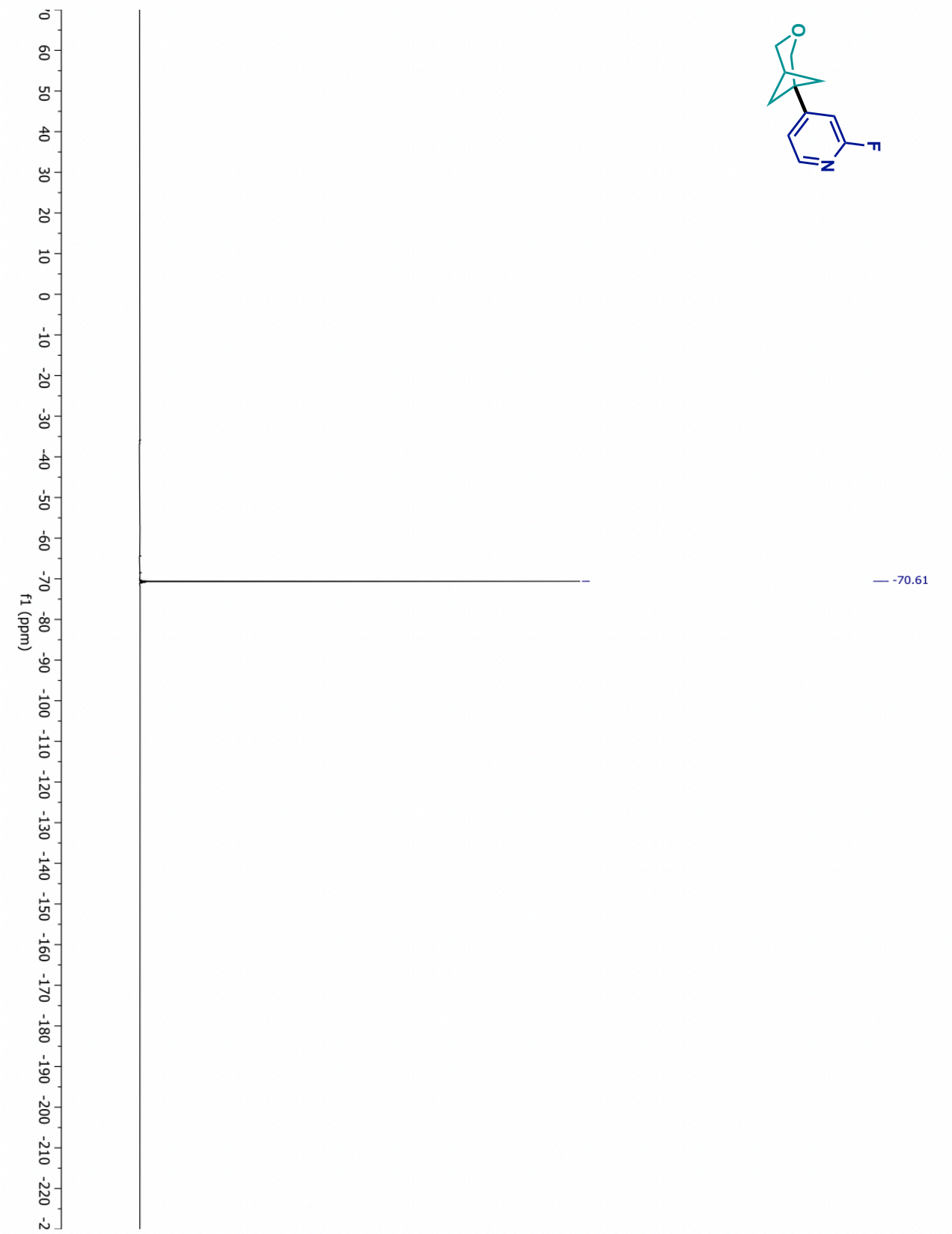
Compound 34 ^{1}H-NMR



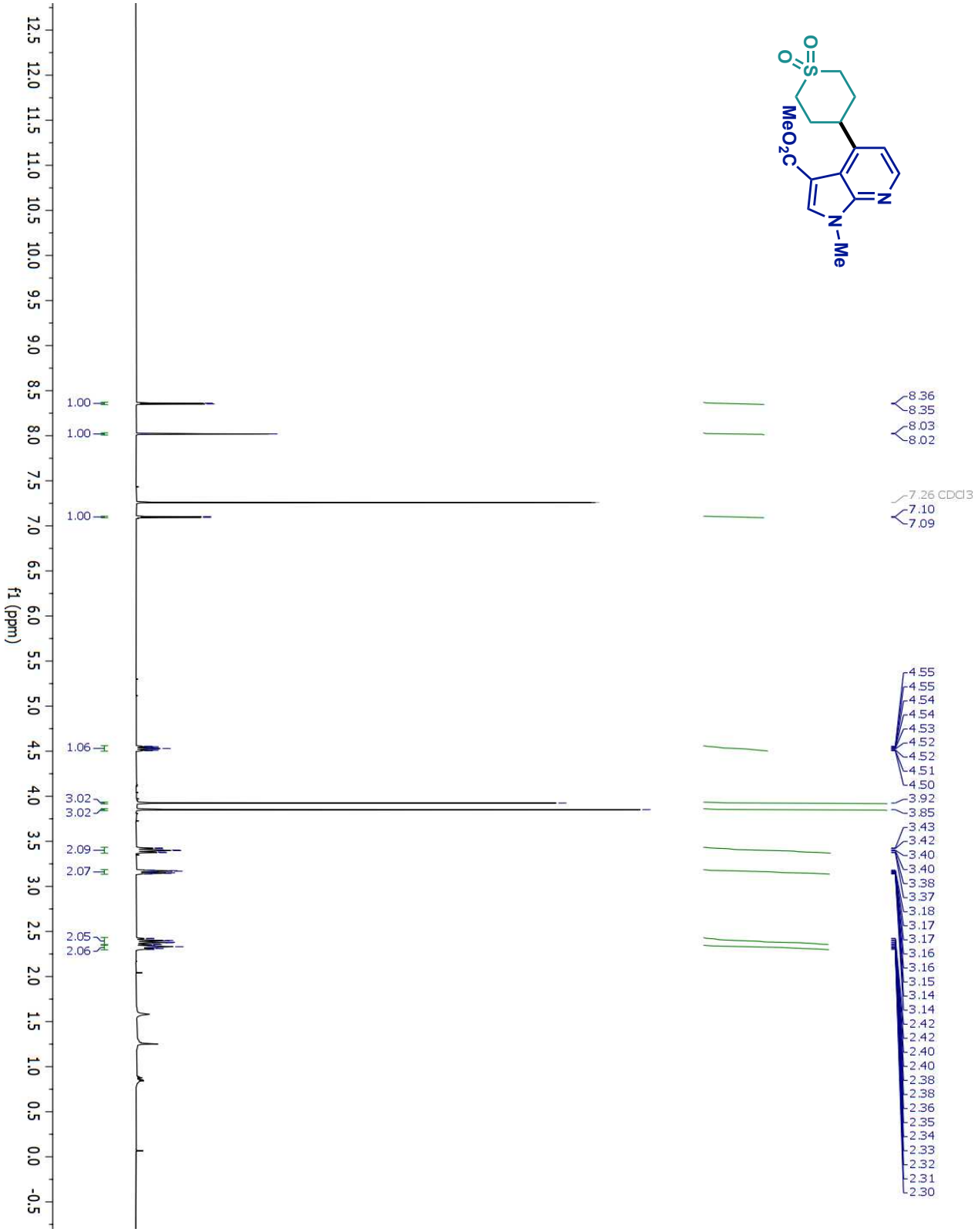
Compound 34 ^{13}C-NMR



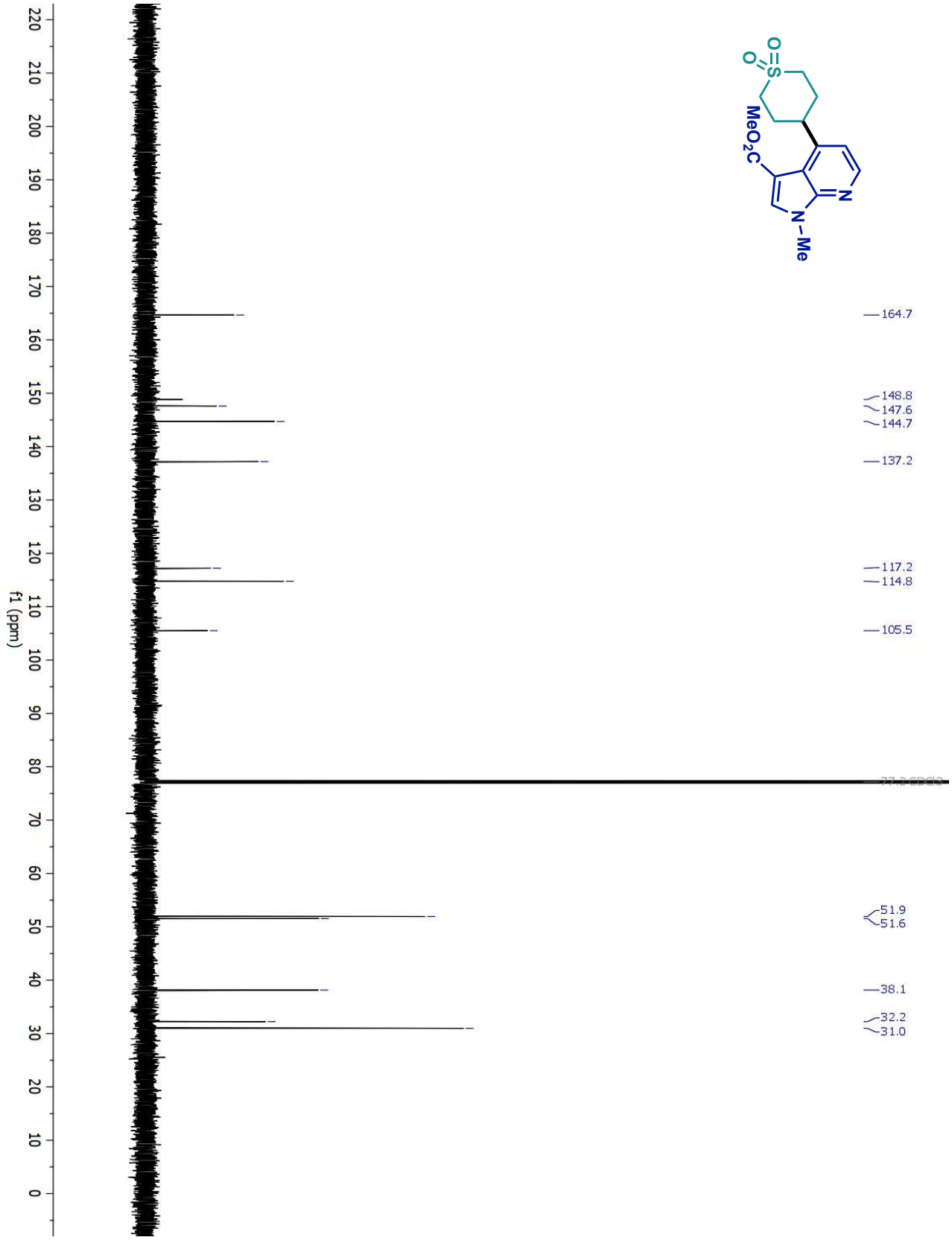
Compound 34 ^{19}F-NMR



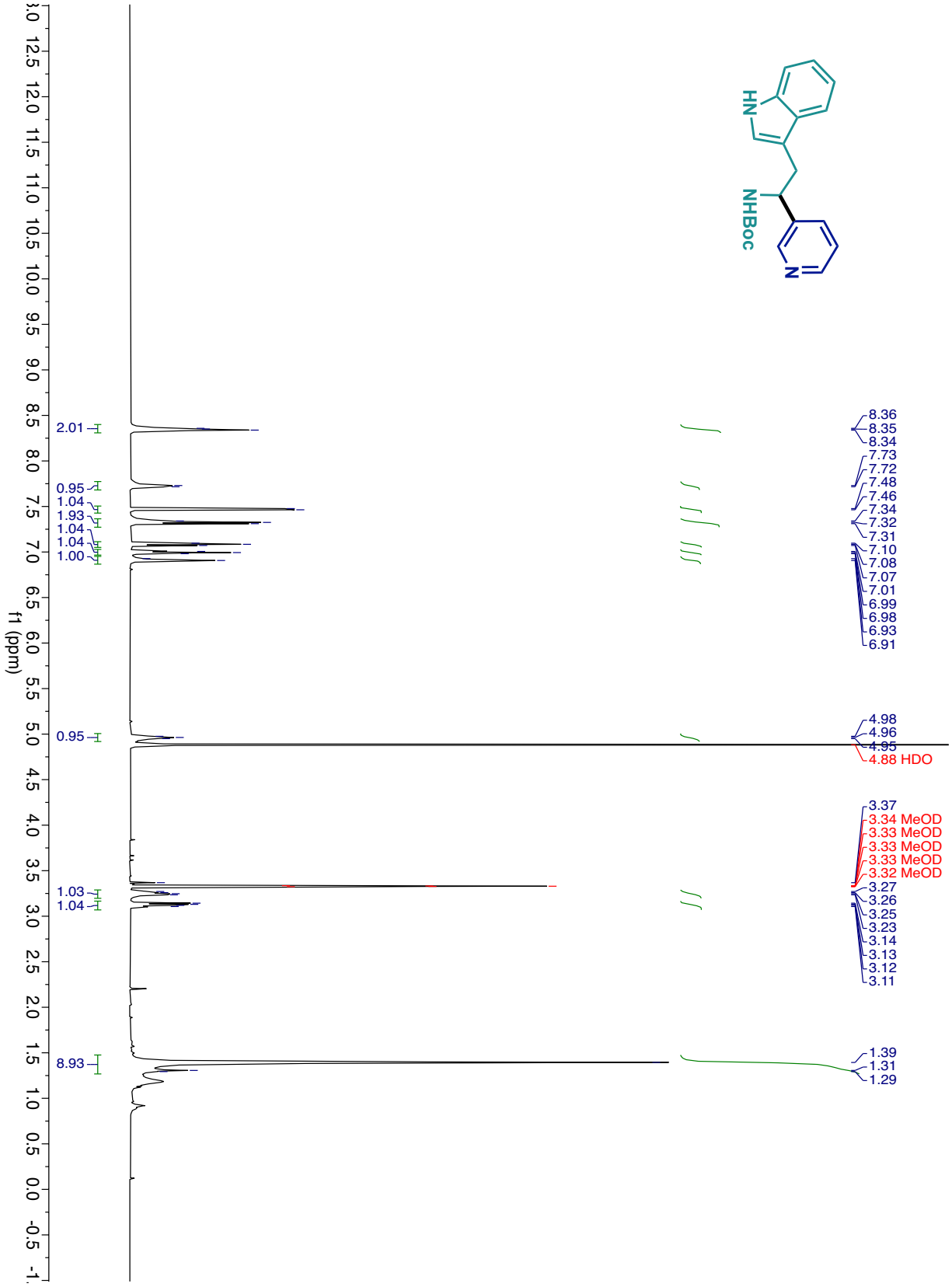
Compound 35 ^{1}H-NMR



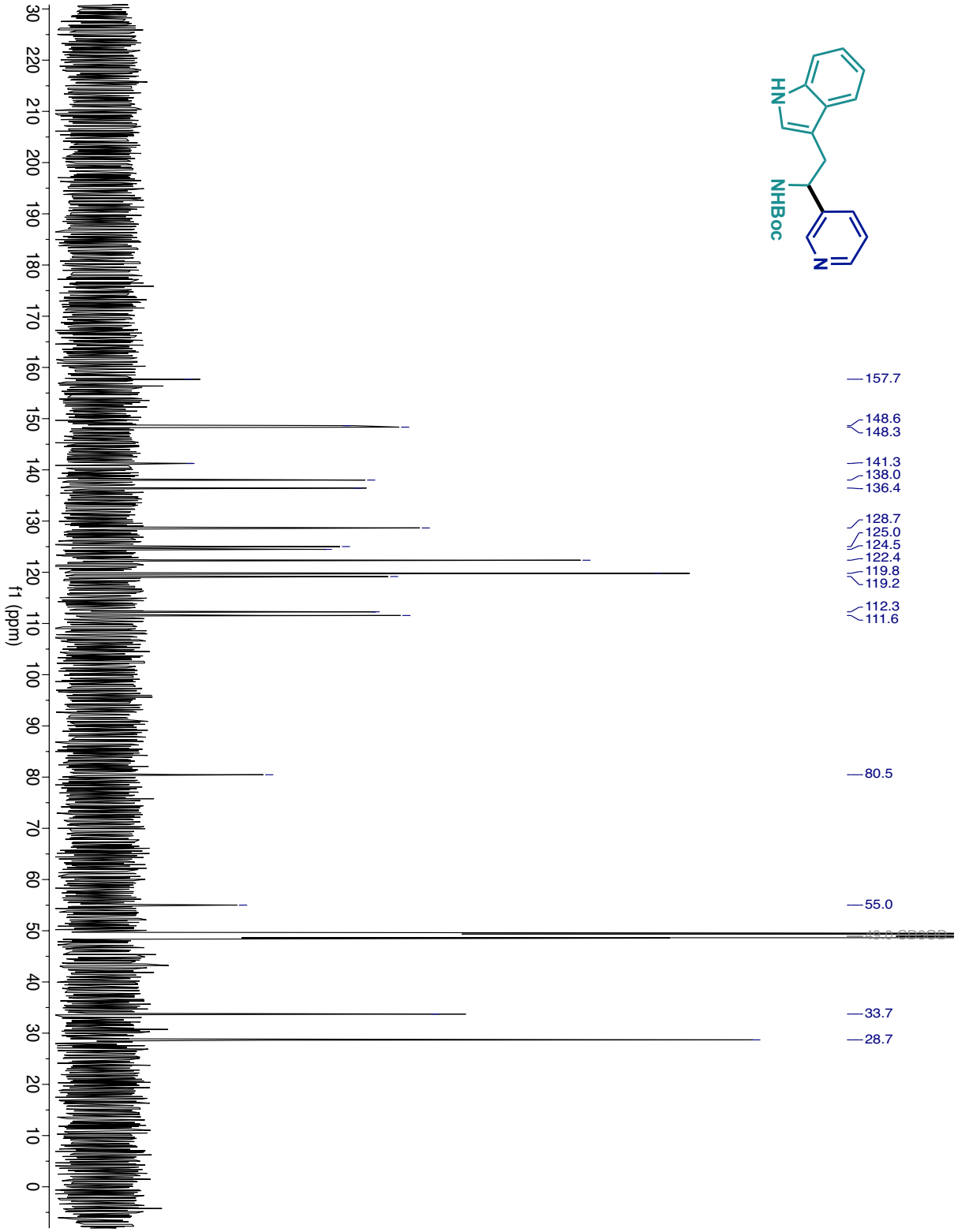
Compound 35 ^{13}C-NMR



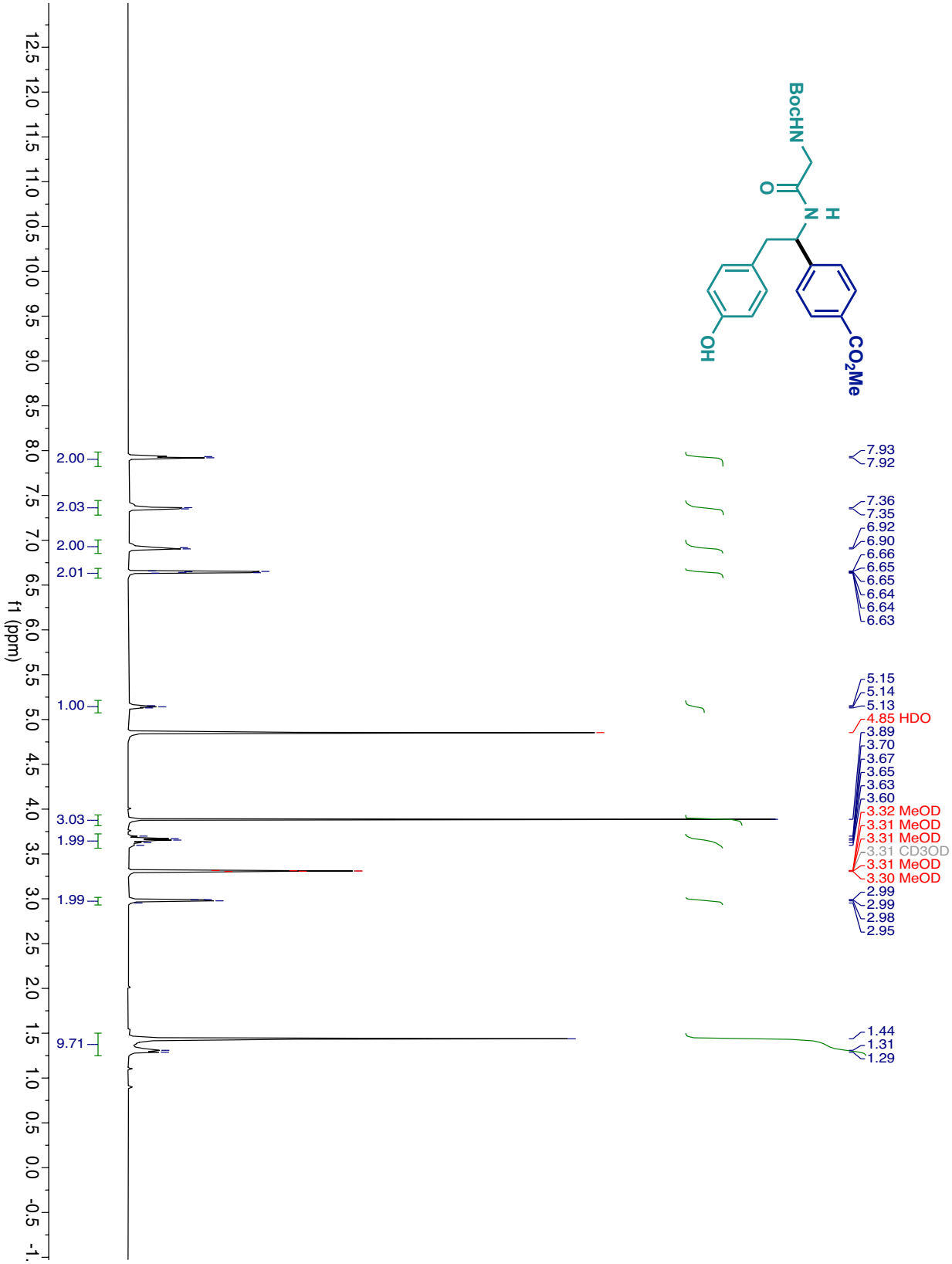
Compound 36 ^{1}H-NMR



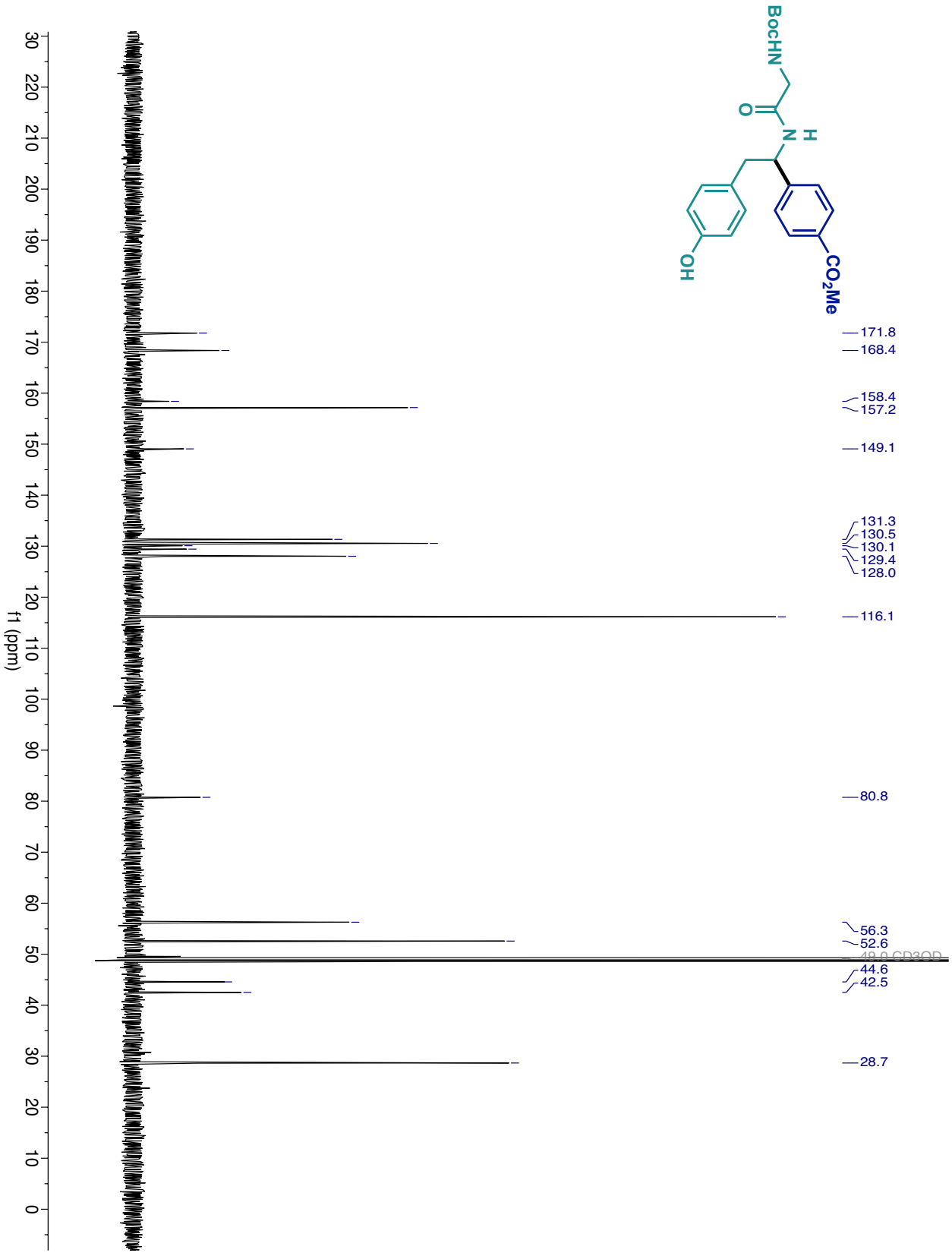
Compound 36 ^{13}C-NMR



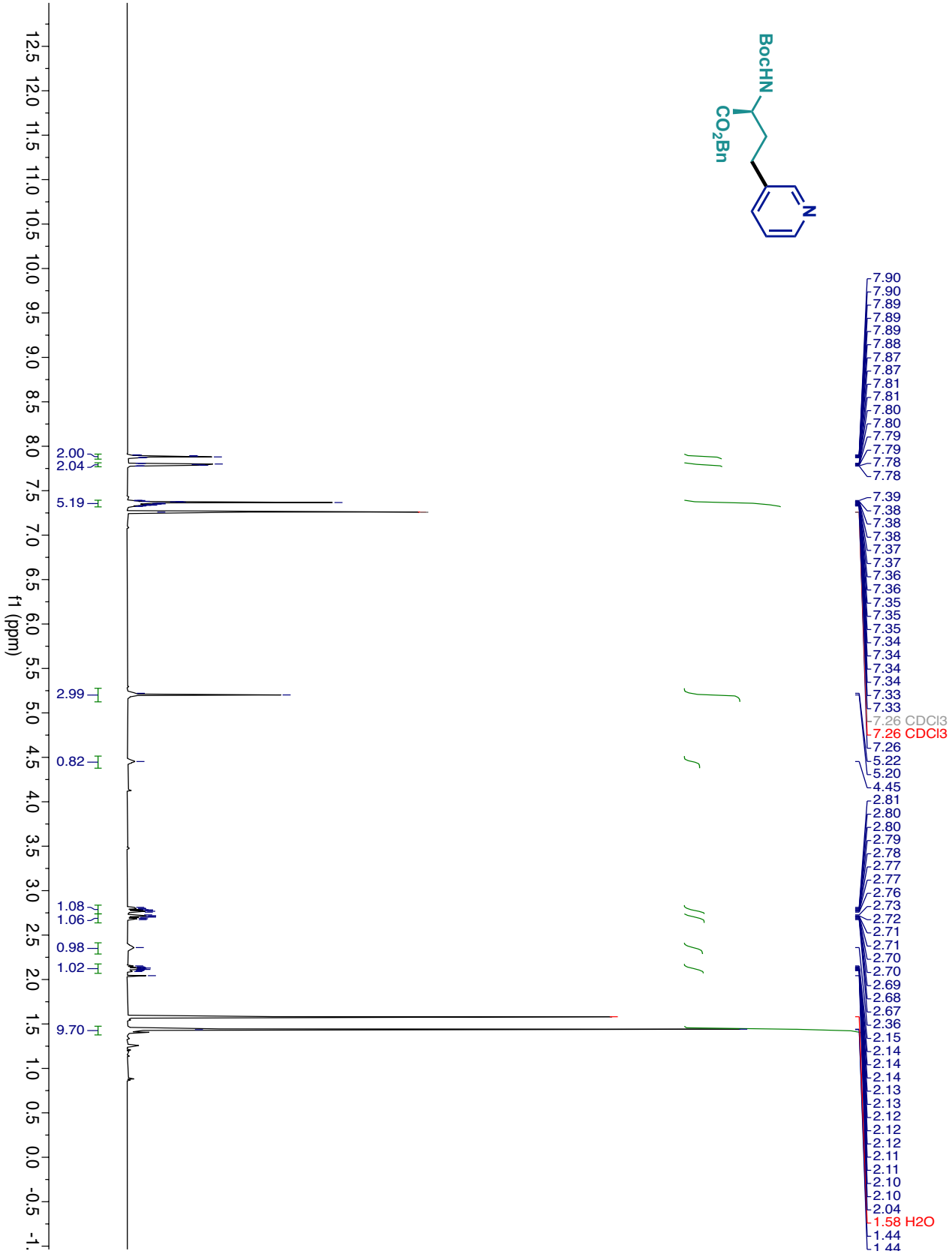
Compound 37 ^{1}H-NMR



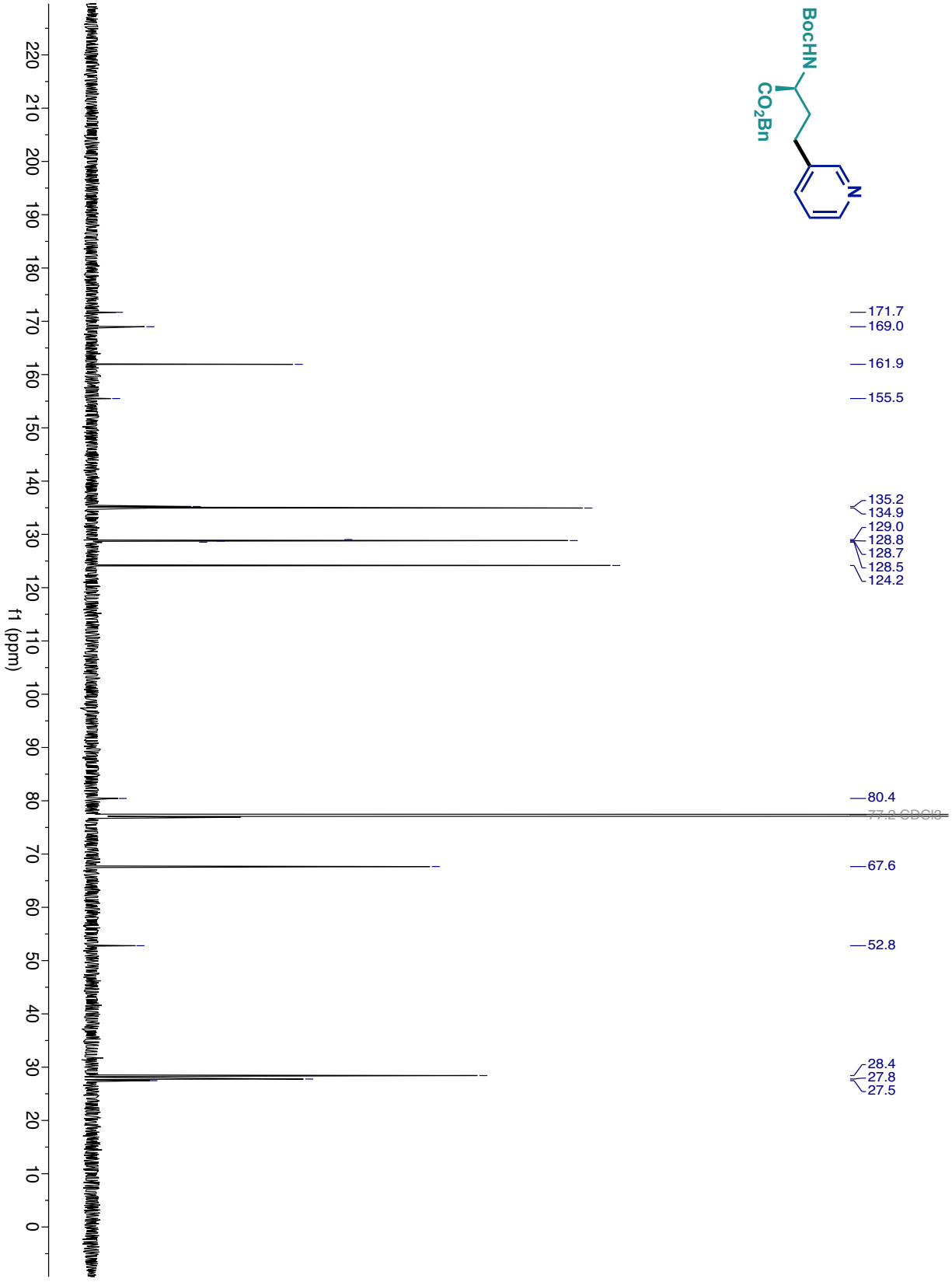
Compound 37 ^{13}C-NMR



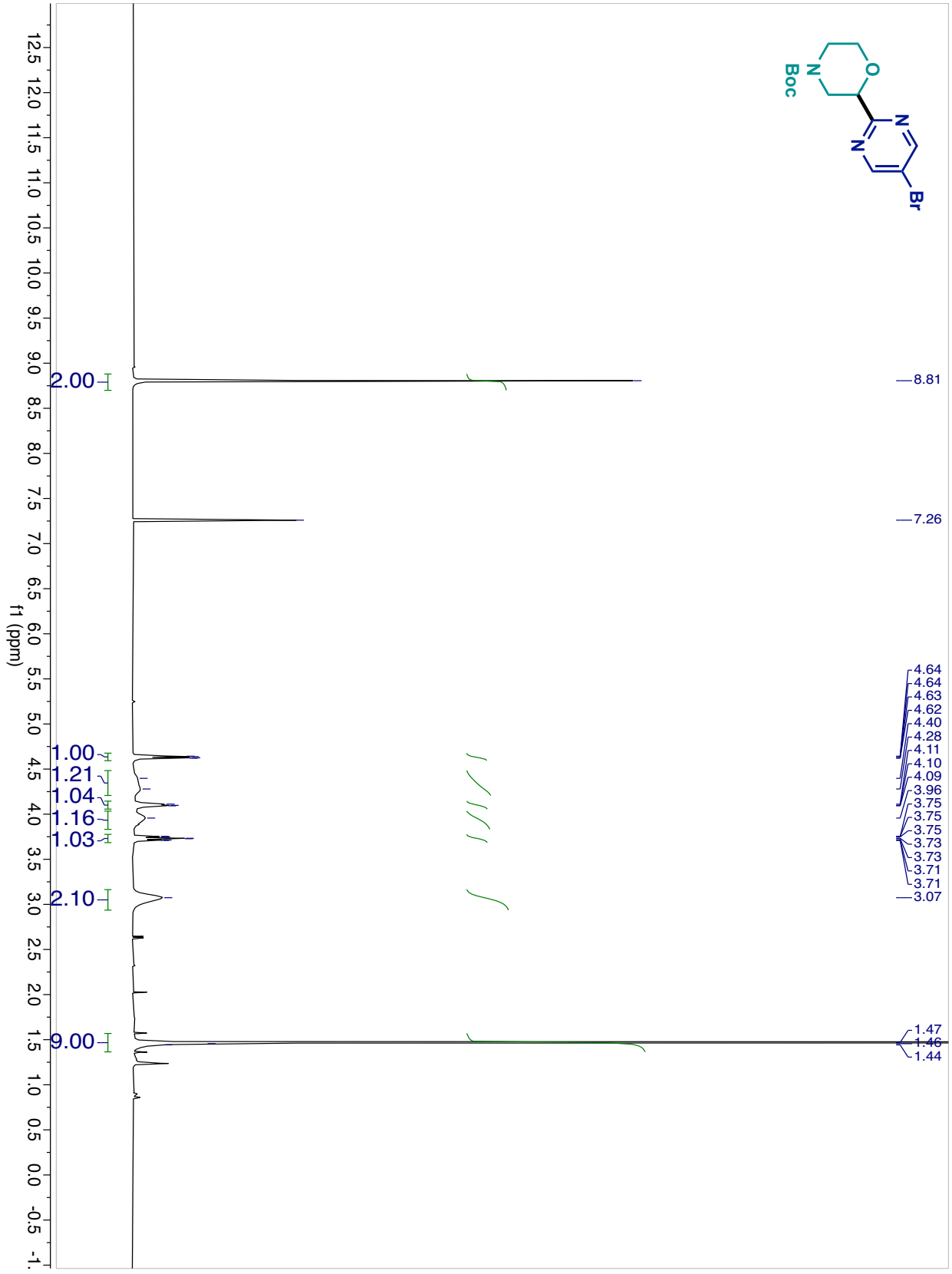
Compound 38 ^{1}H-NMR



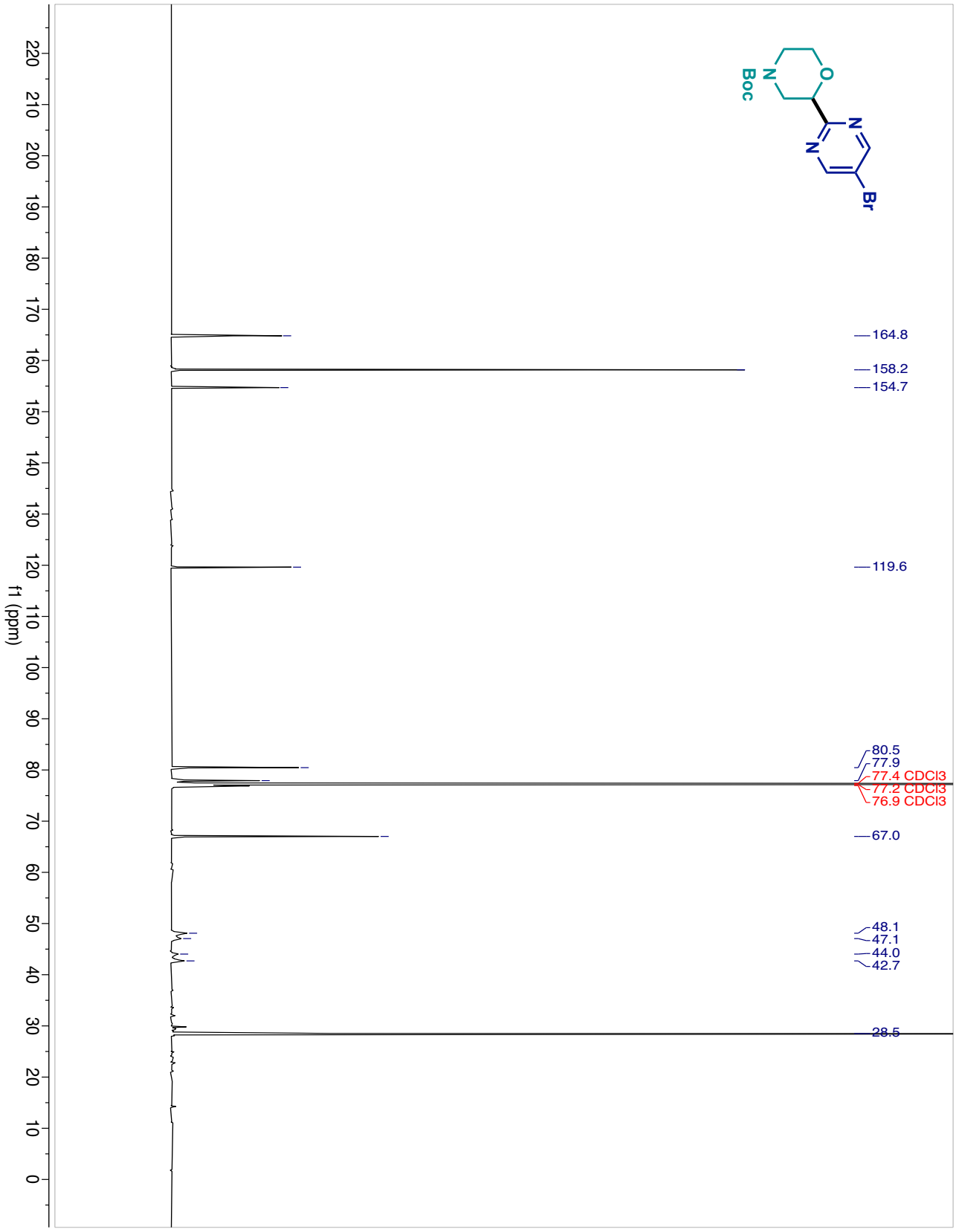
Compound 38 ^{13}C-NMR



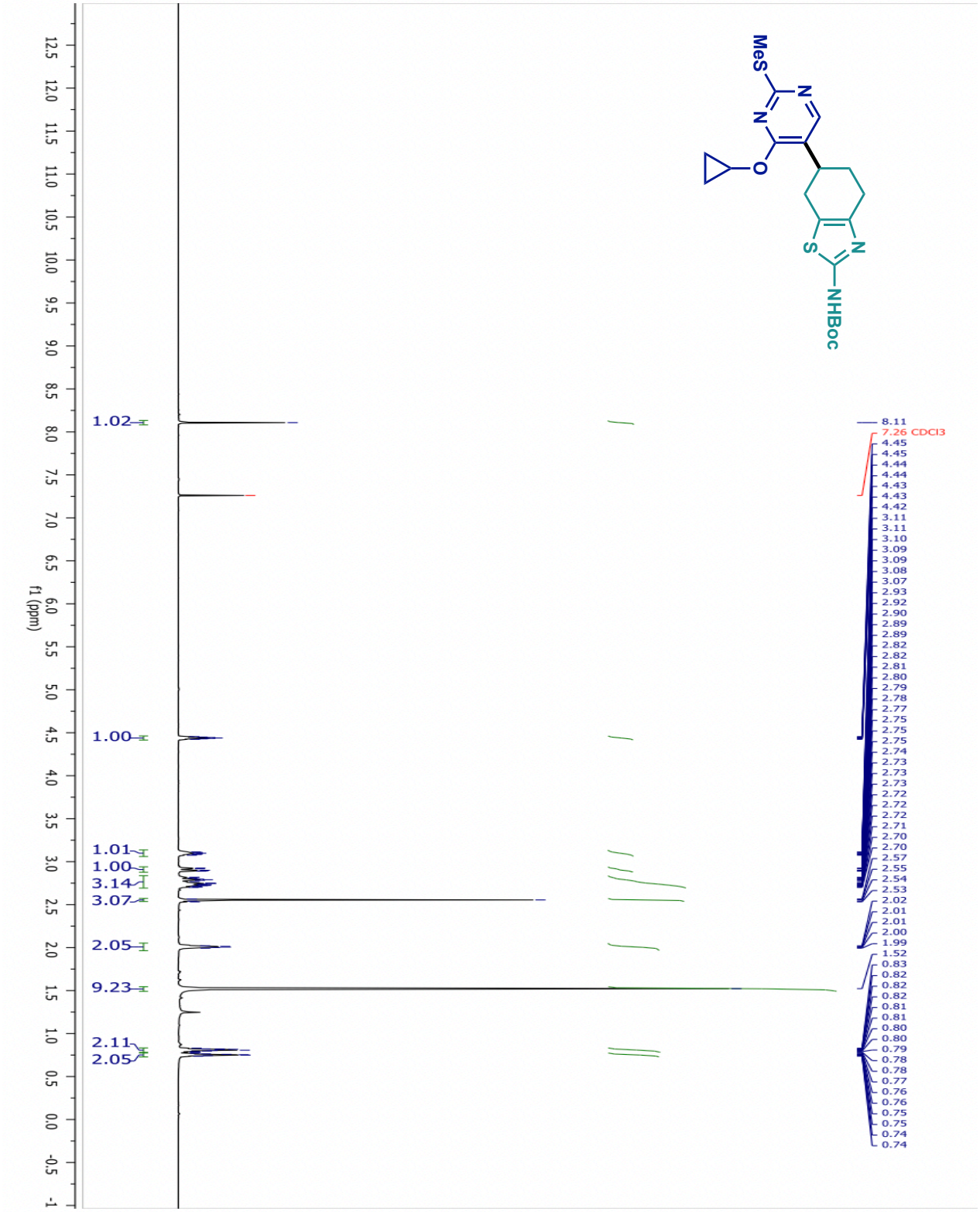
Compound 44 ^{1}H-NMR



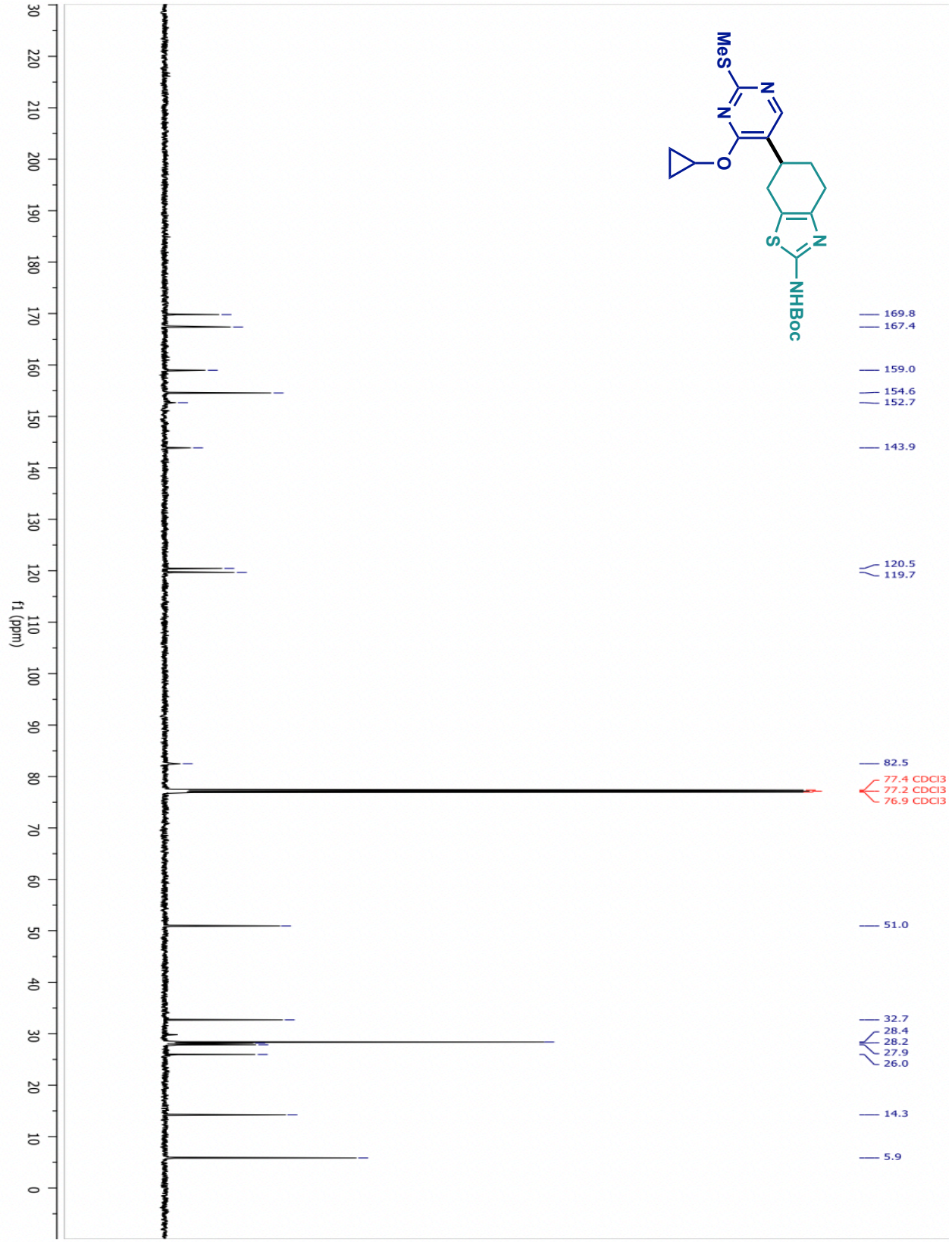
Compound 44 ^{13}C-NMR



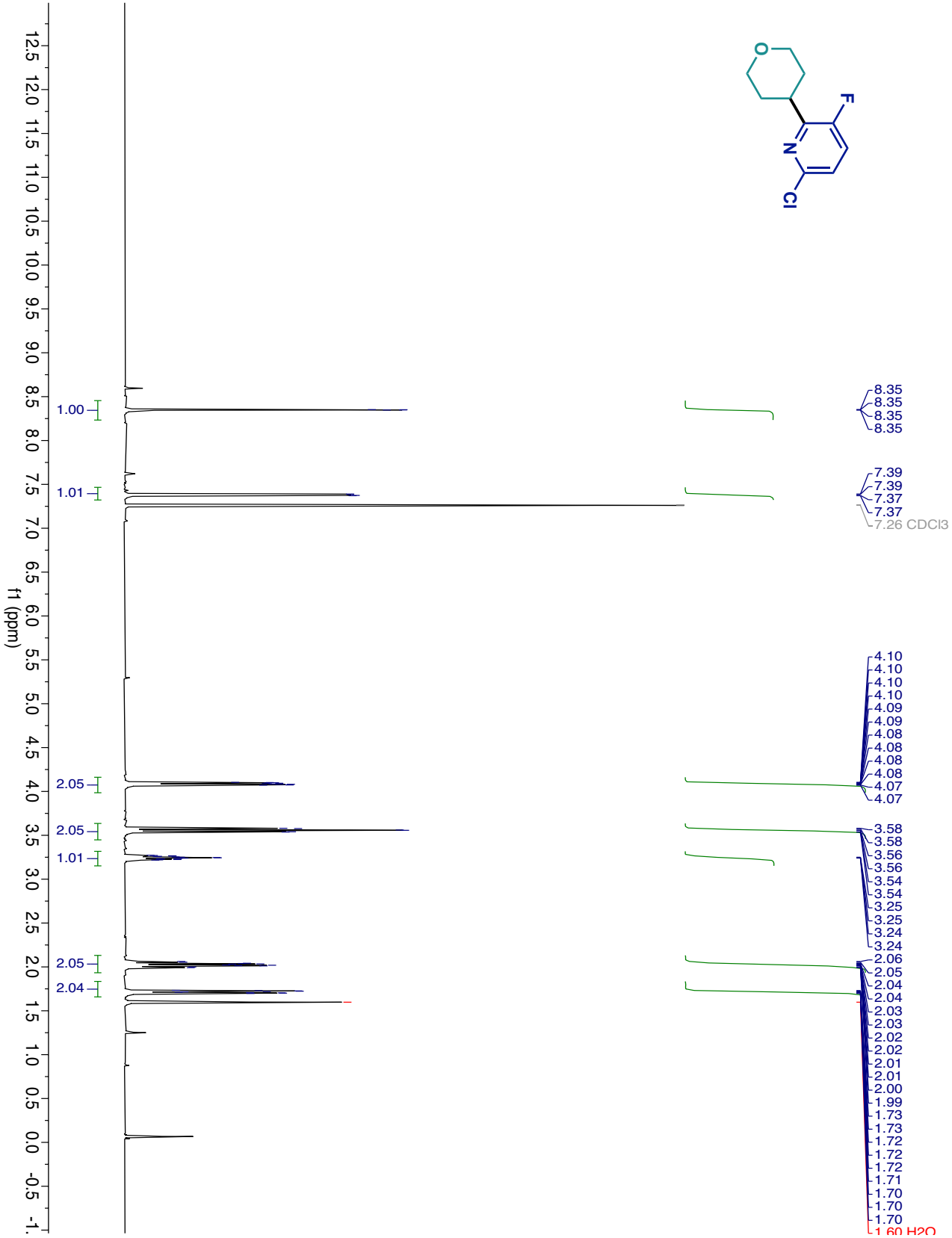
Compound 51 ^{1}H-NMR



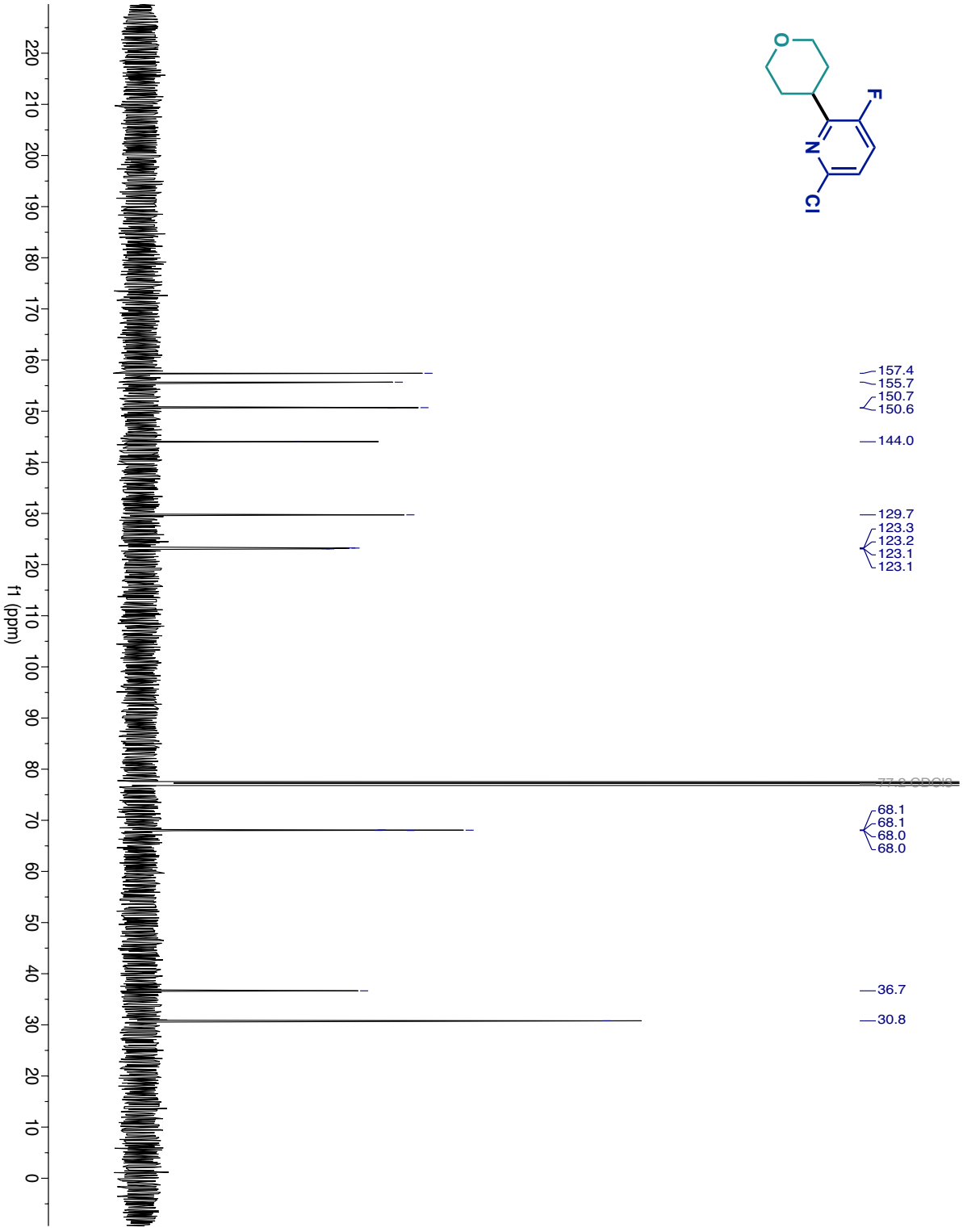
Compound 51 ^{13}C-NMR



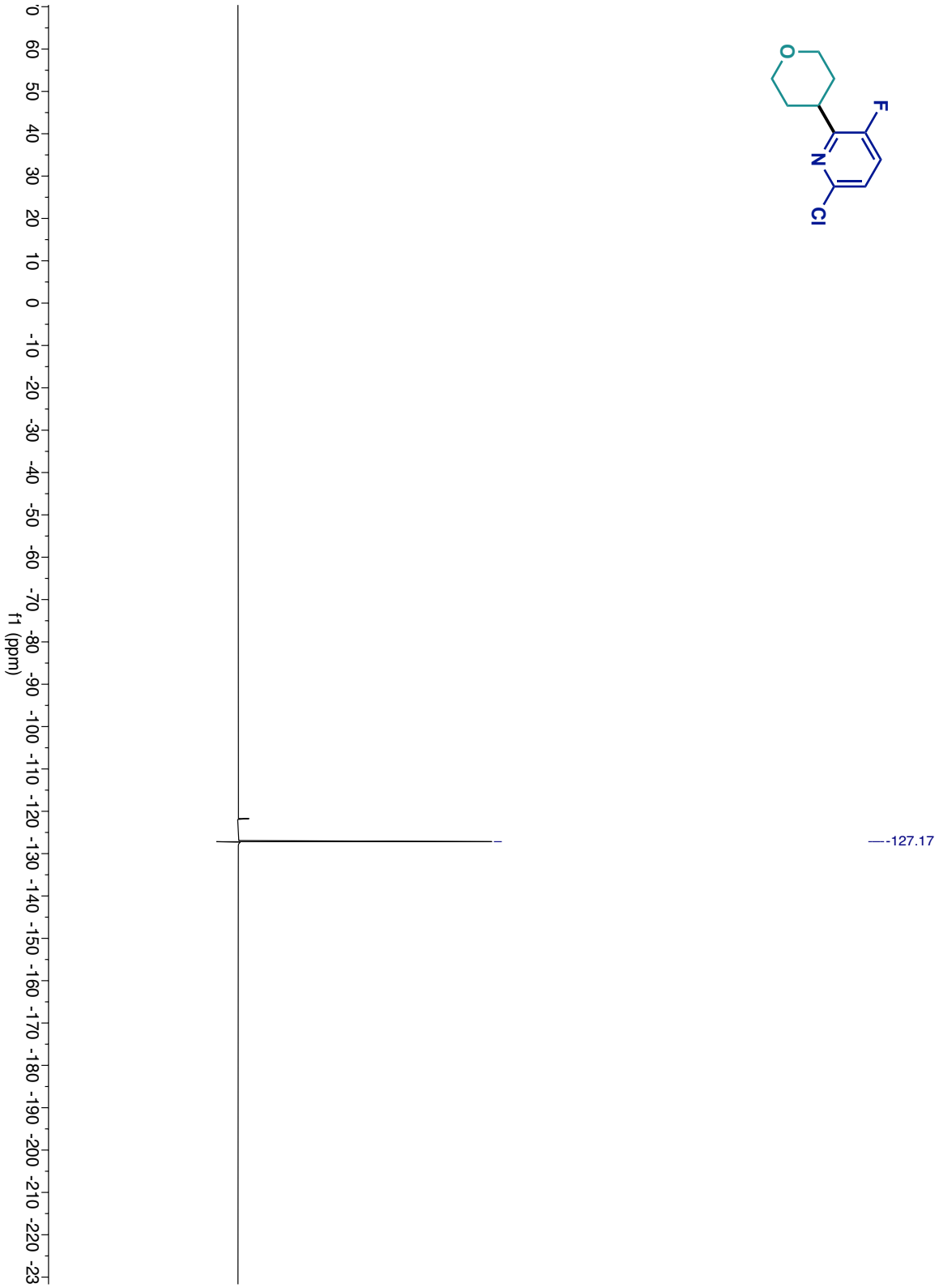
Compound 81 ^{1}H-NMR



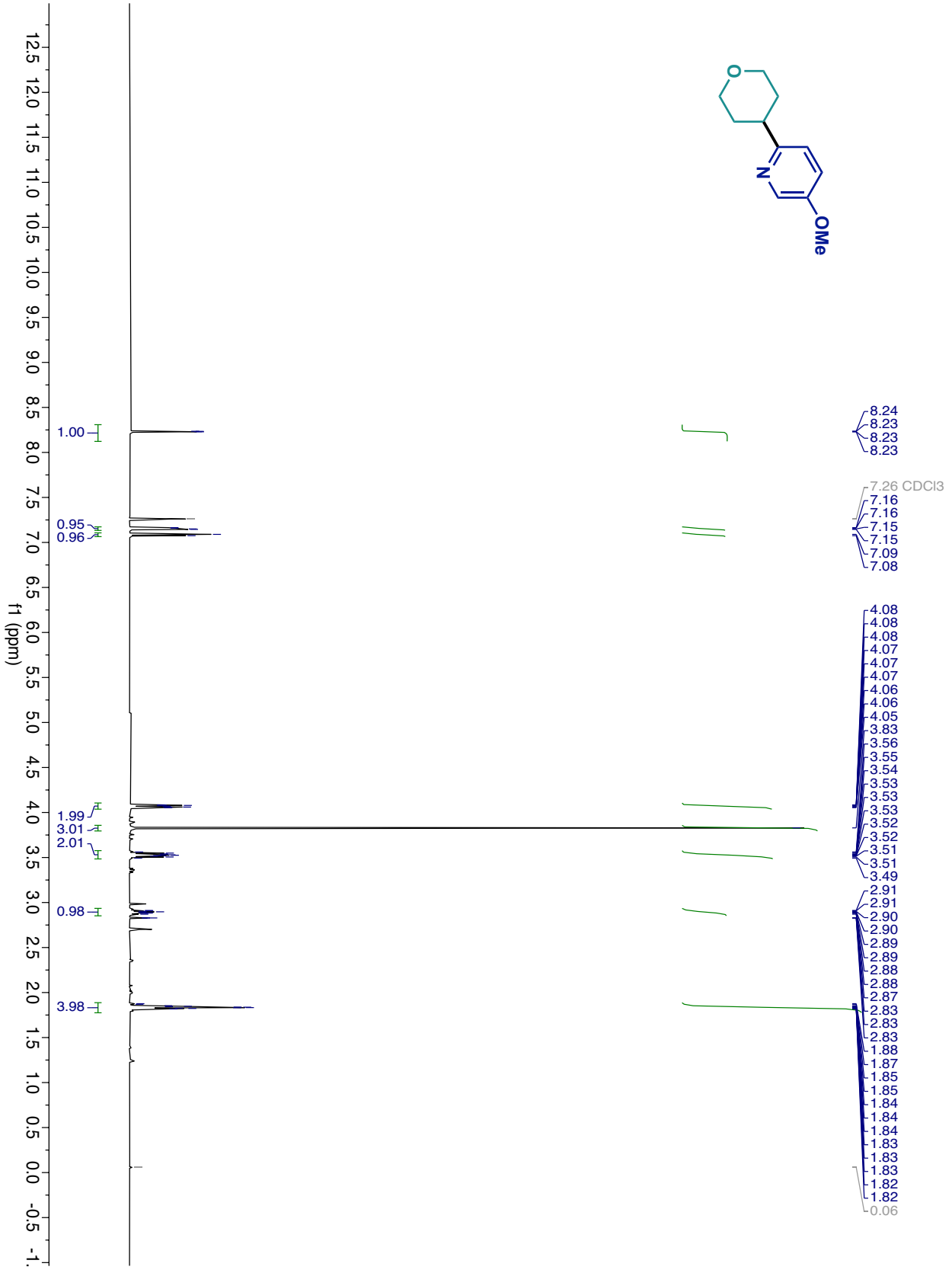
Compound 81 ^{13}C-NMR



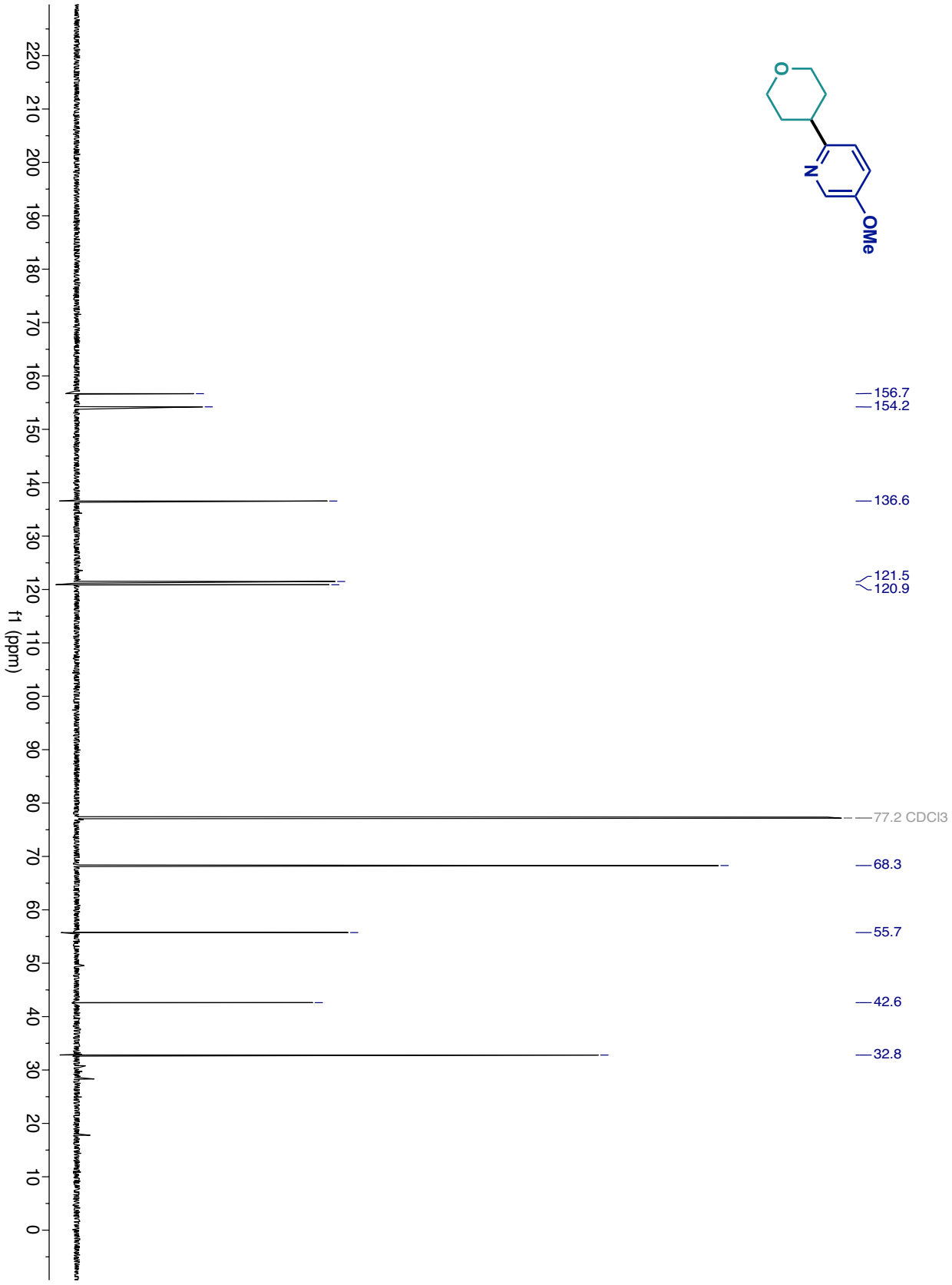
Compound 81 ^{19}F-NMR



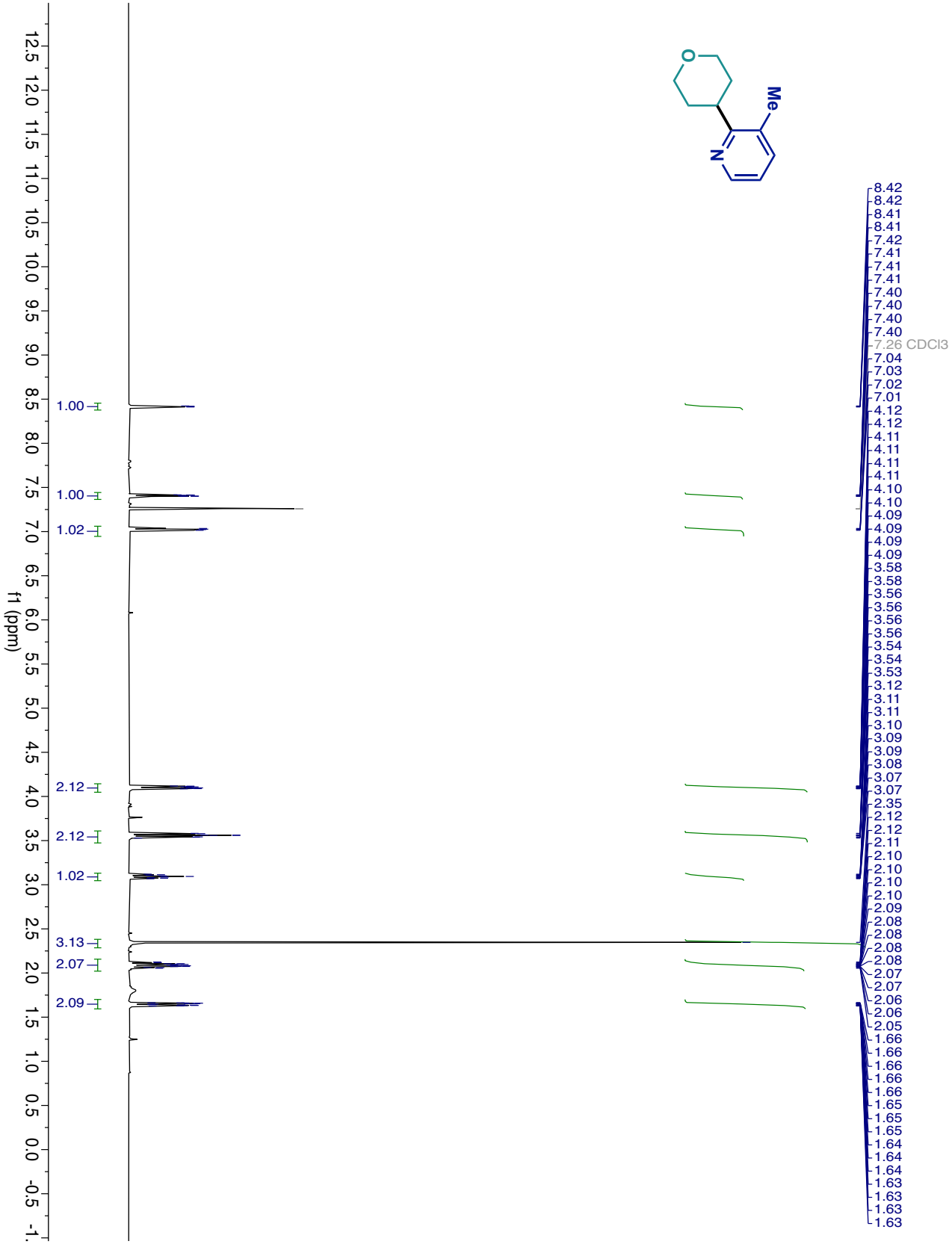
Compound 82 ^{1}H-NMR



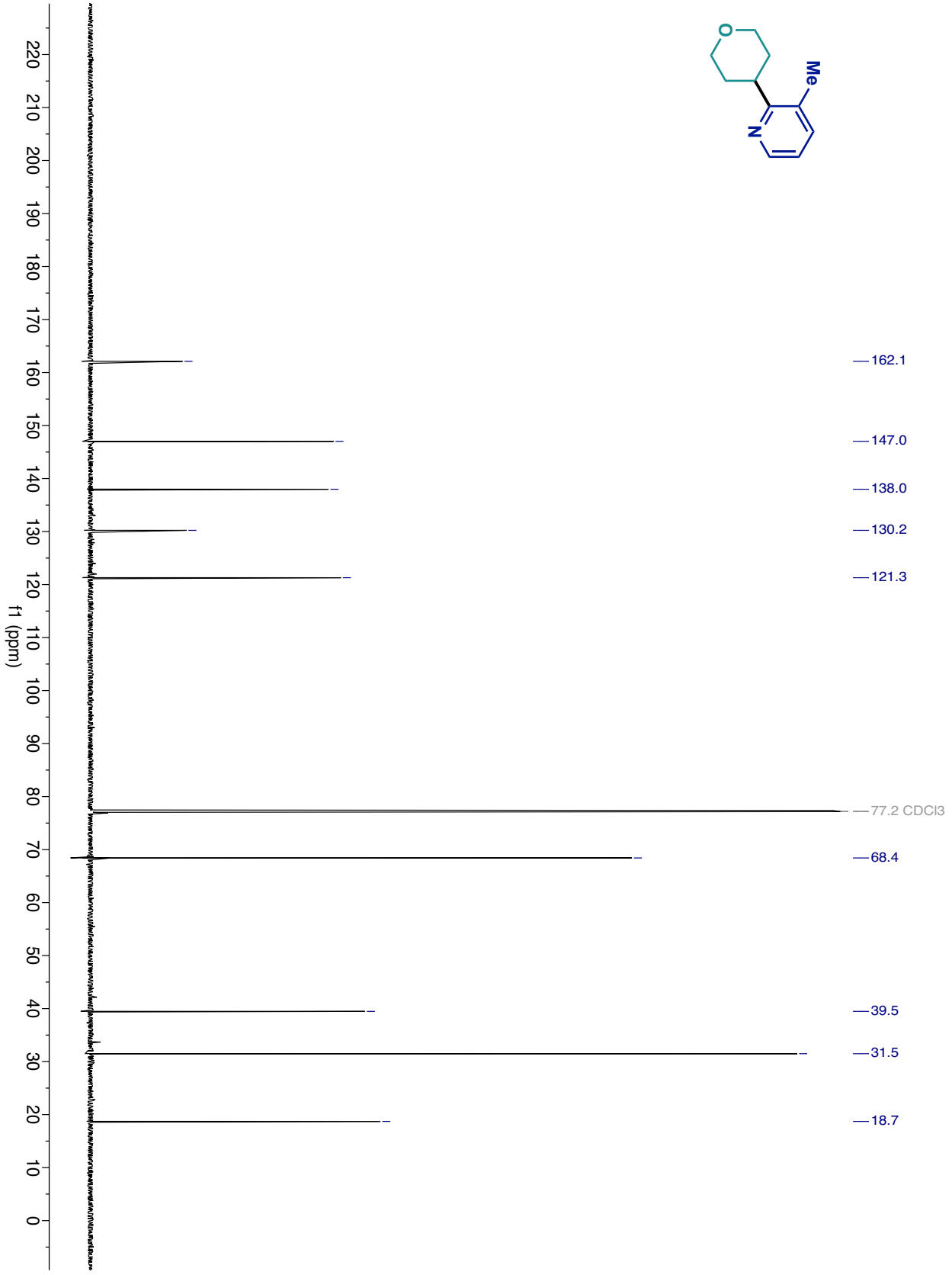
Compound 82 ^{13}C-NMR



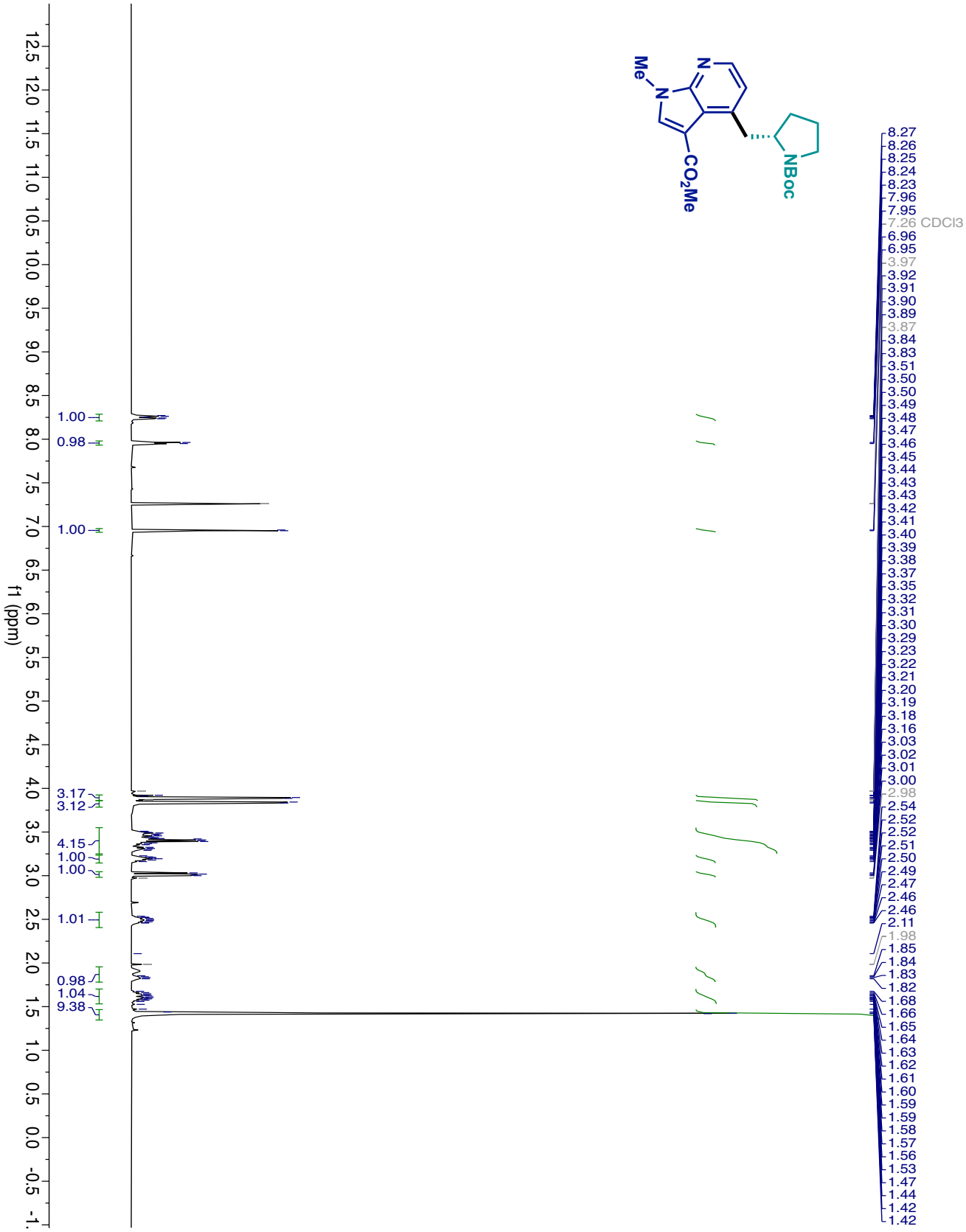
Compound 83 ^{1}H-NMR



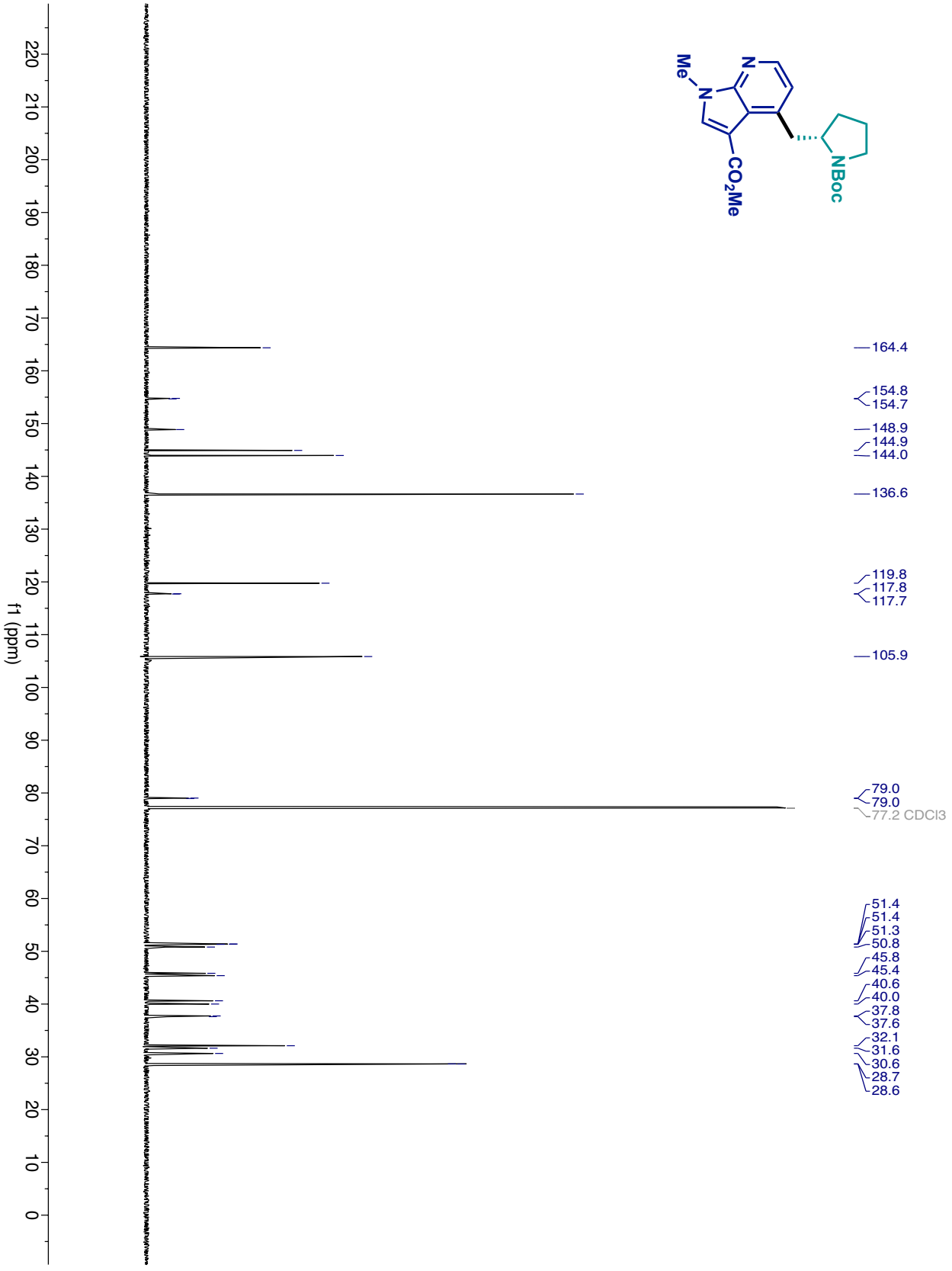
Compound 83 ^{13}C-NMR



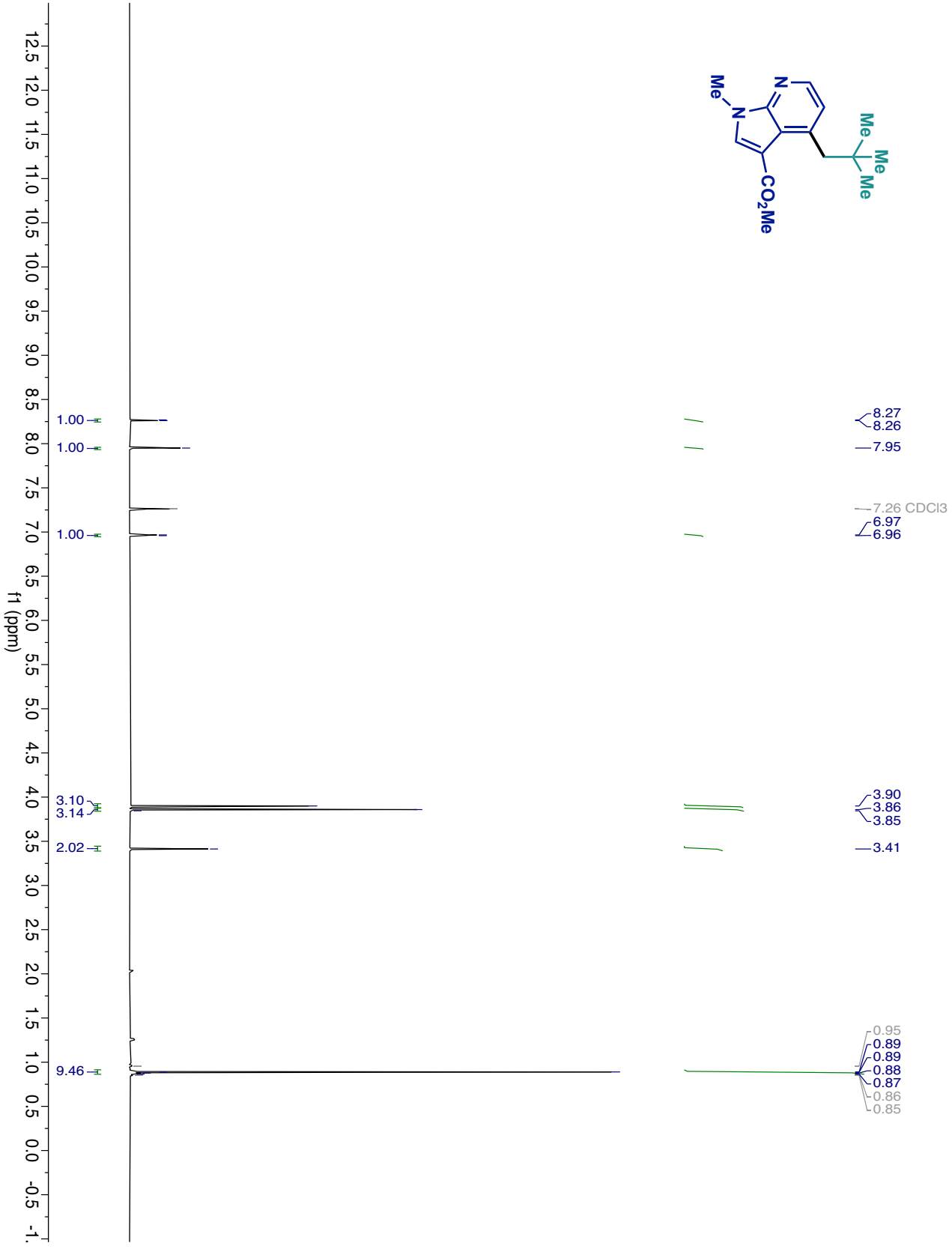
Compound 84 ^{1}H-NMR



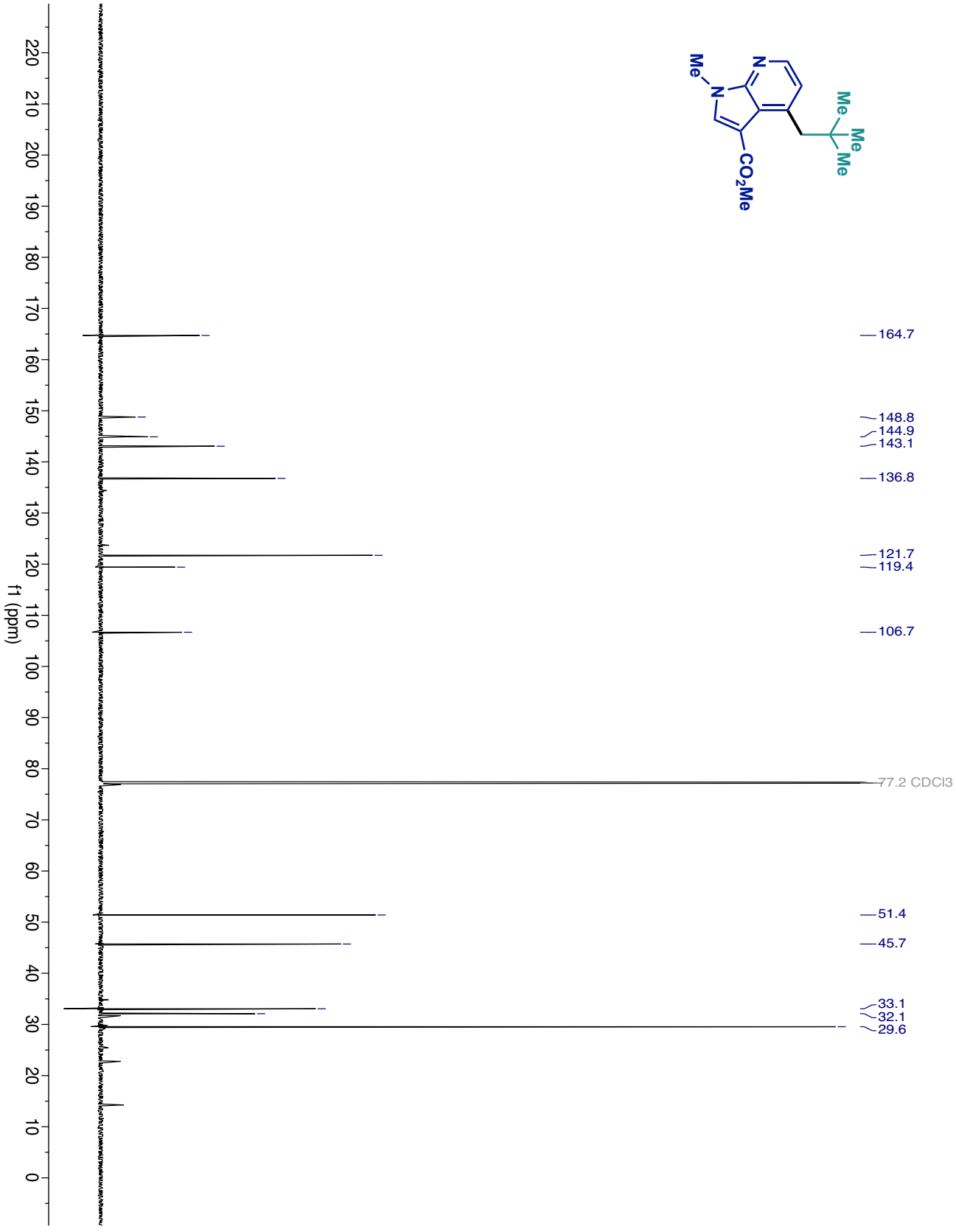
Compound 84 ^{13}C-NMR



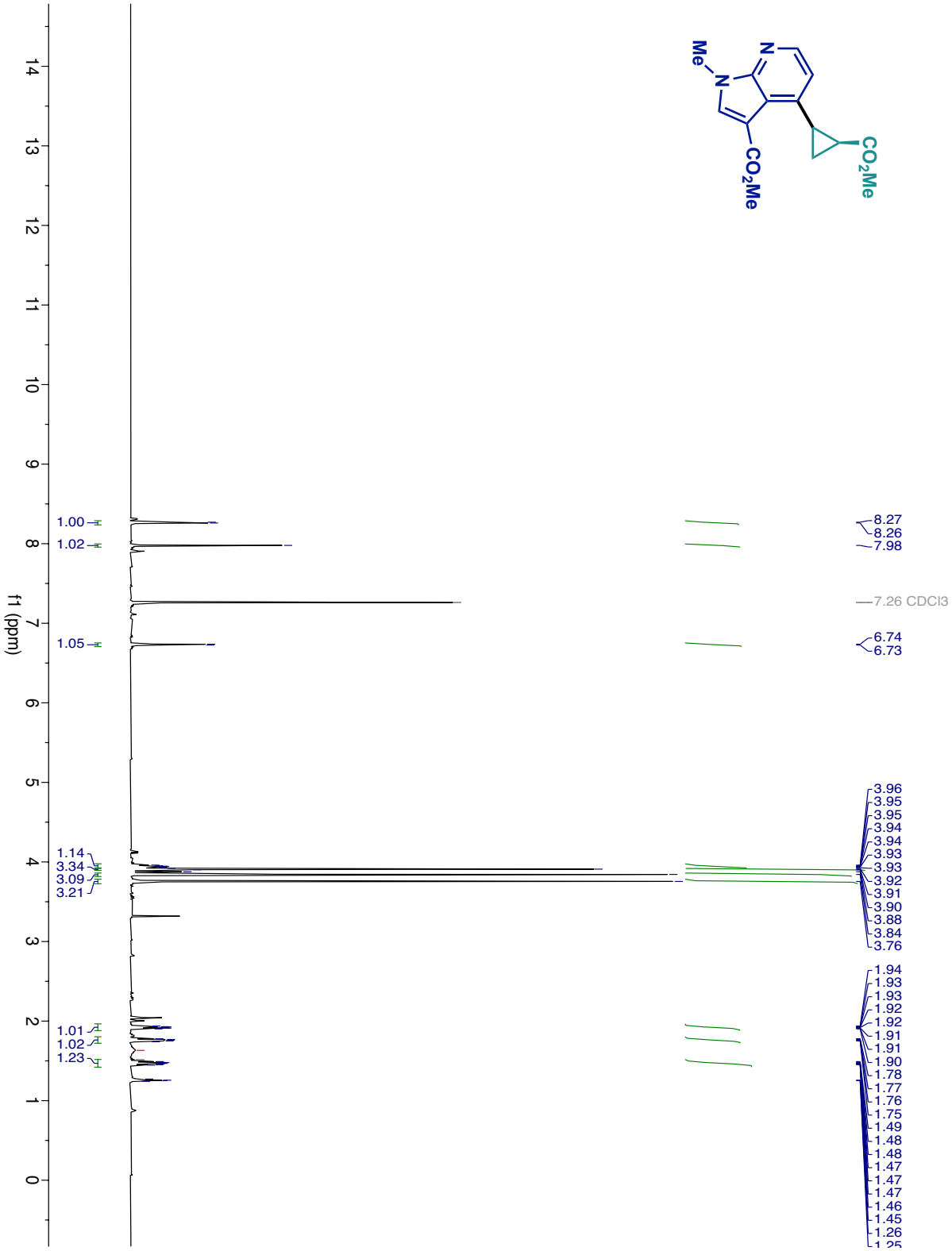
Compound 85 ^{1}H-NMR



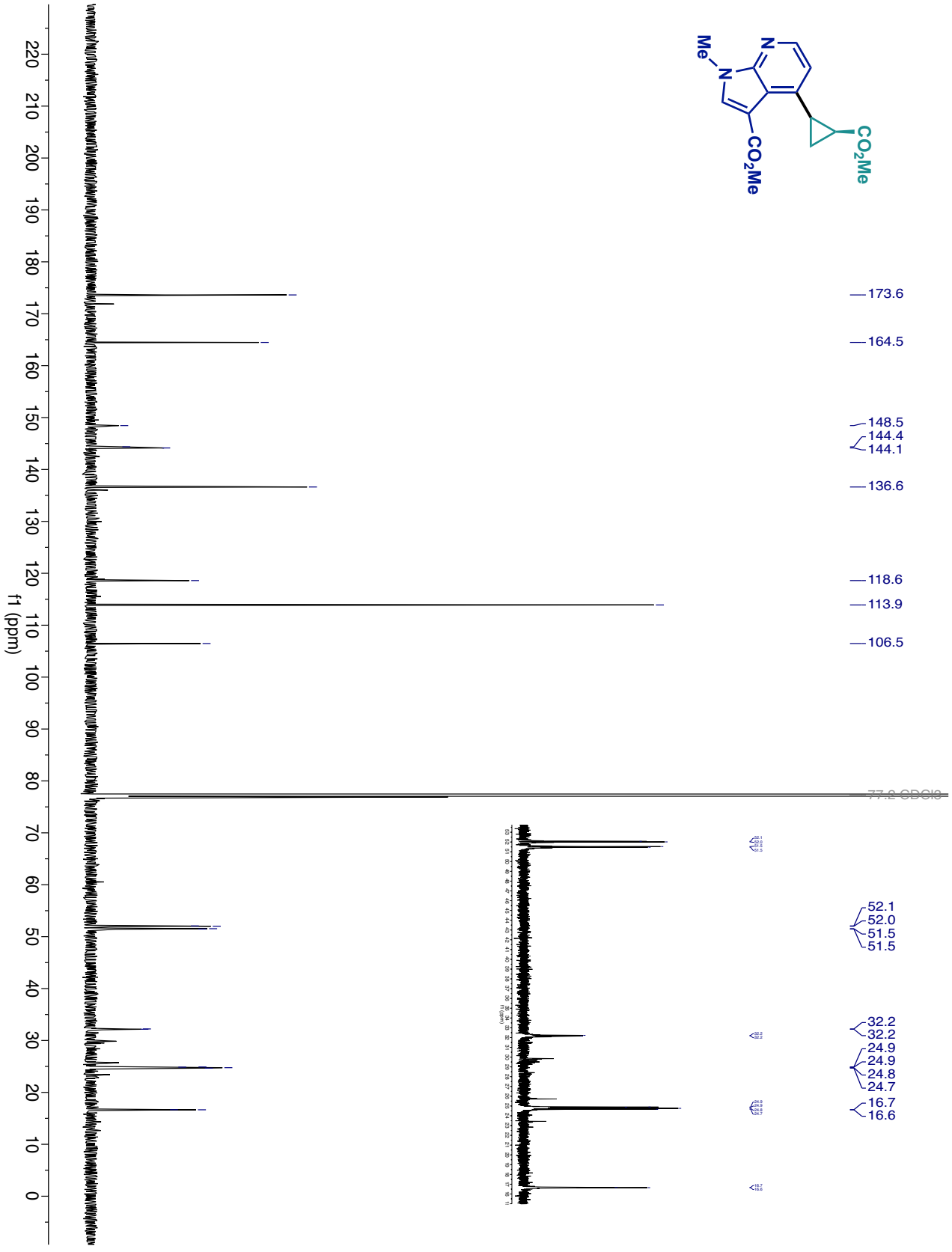
Compound 85 ^{13}C-NMR



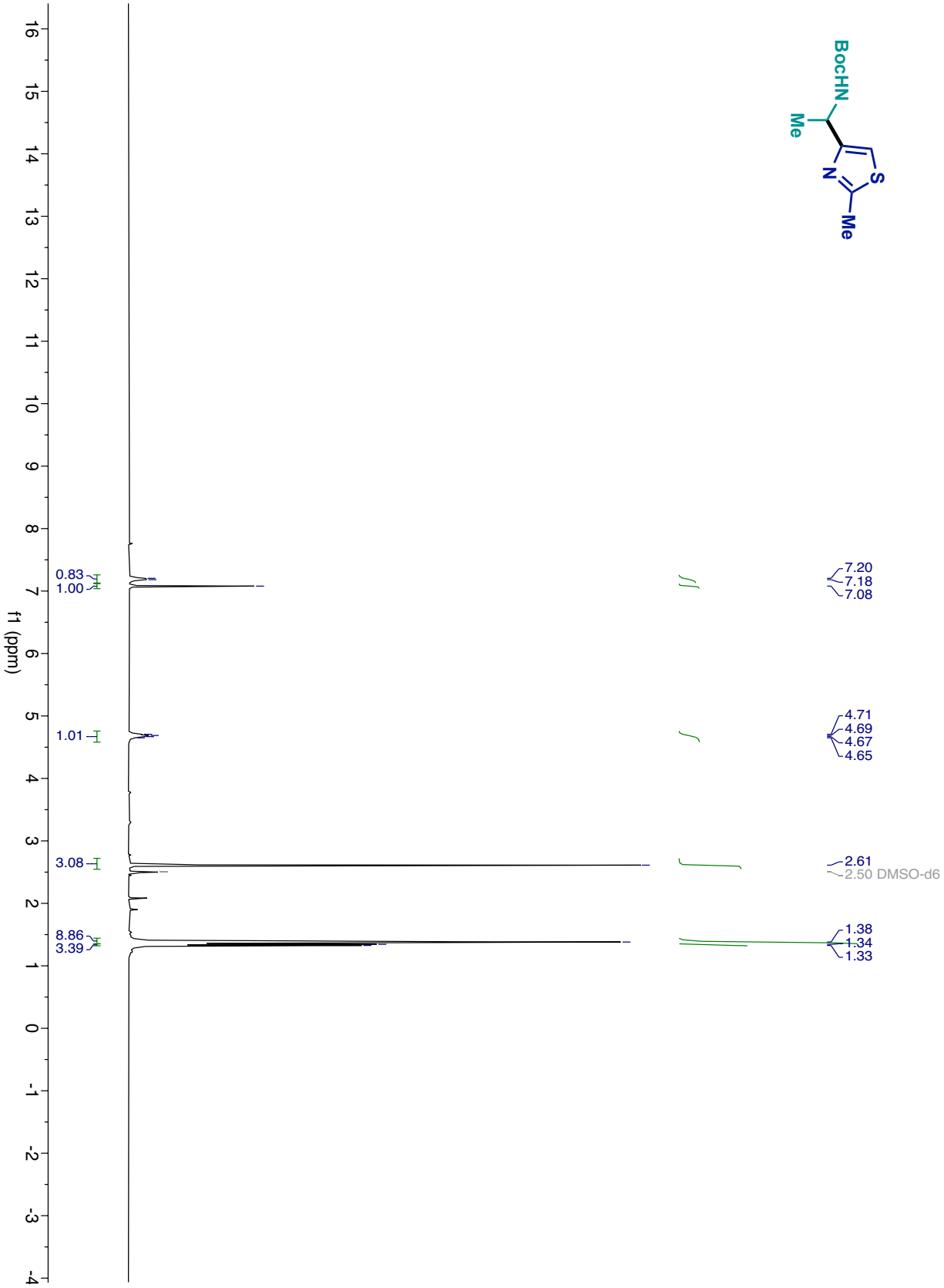
Compound 86 ^{1}H-NMR



Compound 86 ^{13}C-NMR



Compound S34 ^{1}H-NMR



Compound S34 ^{13}C-NMR