

Supporting Information

Tetrafluoropyridyl (TFP): A General Phenol Protecting Group Readily Cleaved Under Mild Conditions

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General

All starting materials and reagents were bought from commercial sources and used as received. All reference phenols were purchased from Sigma Aldrich and their NMR spectra recorded as received. All reactions apart from where noted were carried out in air using non-dried solvents or reagents. All flash column chromatography was carried out using silica purchased from Sigma Aldrich using the solvent system noted. ¹H NMR spectra were recorded at 400 and 700 MHz using Bruker Avance III and Varian VNMRS-700 spectrometers. ¹³C NMR spectra were recorded at 101, 151 and 176 MHz using Bruker Avance III, Varian VNMRS-600 and Varian VNMRS-700 spectrometers. ¹⁹F NMR spectra were recorded at 376 MHz using a Bruker Avance III spectrometer. All coupling constants are reported in Hertz (Hz). In cases where it was required 2D NMR techniques were used to confirm compound identity. Chemical shifts are reported in ppm and are referenced to residual solvent peaks; CHCl₃ (¹H 7.26 ppm, ¹³C 77.0 ppm) and CH₃CN (¹H 1.96 ppm, ¹³C 118.3). Mass spectra were

collected on a Waters TQD mass spectrometer and accurate mass spectra were collected on a Waters LCT Premier XE mass spectrometer. Optical rotations were measured with a Jasco P-1020 polarimeter. Melting points were carried out in triplicate and an average of the values taken and reported as a range using a Stuart SMP10 melting point apparatus. Melting points were carried out directly on material purified by flash column chromatography

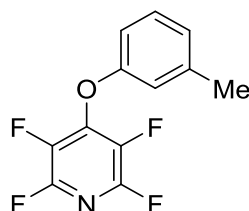
General procedure for the synthesis of tetrafluoropyridyl ethers

To a stirred solution of phenol (1 equiv.) in acetonitrile (20 mL) was added pentafluoropyridine (1.05 equiv.) and potassium carbonate (1.05 equiv.). The reaction mixture was stirred at room temperature for 16 h. After this time the reaction mixture was concentrated under reduced pressure and the resulting residue was purified directly by flash column chromatography.

General procedure for the deprotection of tetrafluoropyridyl ethers

To a stirred solution of TFP ether (1 equiv.) in acetonitrile (5 mL) and water (0.1 mL) was added potassium fluoride (2 equiv.), 18-Crown-6 (3 equiv.) and methyl thioglycolate (10 equiv.). The reaction mixture was stirred for 2 h at 50 °C. After this time the reaction mixture was concentrated under reduced pressure and the resulting residue purified directly by flash column chromatography.

Synthesis of 2,3,5,6-tetrafluoro-4-(*m*-tolylloxy)pyridine 2a



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 4.63 mmol of the corresponding phenol as a white solid (1.16 g) in 97% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.25 (m, 1H, ArH), 7.05 (dt, *J* = 7.6, 0.8, 1H, ArH), 6.91 – 6.85 (m, 2H, ArH), 2.39 (s, 3H, CH₃).

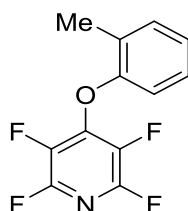
¹³C NMR (176 MHz, Chloroform-*d*) δ 155.80, 145.86 – 144.10 (m), 144.26 – 142.26 (m), 140.46, 138.27 – 136.67 (m), 136.27 – 133.55 (m), 129.66, 125.89, 117.20, 113.53, 21.33.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.63 – -89.17 (m), -152.14 – -156.08 (m).

HRMS ESI⁻ Calculated for $[\text{M}-\text{H}]^- \text{C}_{12}\text{H}_6\text{NOF}_4^- = 256.0386$ Found = 256.0383

MP 39-40 °C

Synthesis of 2,3,5,6-tetrafluoro-4-(*o*-tolylloxy)pyridine 2b



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 4.63 mmol of the corresponding phenol as a clear oil (0.980 g) in 83% yield.

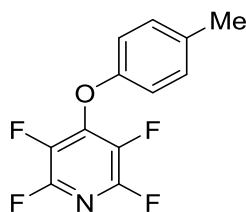
^1H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.28 (m, 1H, ArH), 7.25 – 7.11 (m, 2H, ArH), 6.84 (d, $J = 7.8$ Hz, 1H, ArH), 2.40 (s, 3H, CH_3).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 154.29, 145.15 – 144.98 (m), 144.96 – 144.71 (m), 143.69 – 143.17 (m), 136.73 – 136.39 (m), 135.30 – 134.94 (m), 131.73, 127.99, 127.19, 125.28, 115.75, 15.82.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.13 – -90.17 (m), -154.52 – -156.92 (m).

HRMS ESI⁻ Calculated for $[\text{M}-\text{H}]^- \text{C}_{12}\text{H}_6\text{NOF}_4^- = 256.0386$ Found = 256.0389

Synthesis of 2,3,5,6-tetrafluoro-4-(*p*-tolylloxy)pyridine 2c



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 4.63 mmol of the corresponding phenol as a clear oil (1.13 g) in 95% yield.

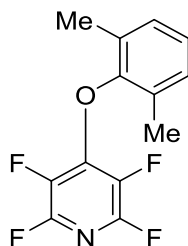
^1H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.11 (m, 2H, ArH), 6.98 (app d, $J = 8.6$, 2H, ArH), 2.38 (s, 3H, CH_3).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 153.78, 145.04 – 144.57 (m), 143.86 – 143.04 (m), 137.16 – 136.45 (m), 135.55 – 135.17 (m), 134.90, 130.38, 116.56, 20.66.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.46 – -89.71 (m), -154.17 – -155.60 (m).

HRMS ESI Calculated for $[\text{M-H}]^- \text{C}_{12}\text{H}_6\text{NOF}_4^- = 256.0386$ Found = 256.0376

Synthesis of 4-(2,6-dimethylphenoxy)-2,3,5,6-tetrafluoropyridine 2d



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 4.09 mmol of the corresponding phenol as a clear oil (0.722 g) in

70% yield.

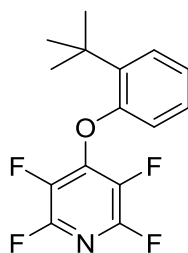
^1H NMR (400 MHz, Chloroform-*d*) δ 7.15 – 7.07 (m, 3H, ArH), 2.25 (s, 6H, CH_3).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 152.29, 145.88 – 145.48 (m), 145.06 – 144.60 (m), 143.82 – 143.31 (m), 135.25 – 134.65 (m), 133.68 – 133.17 (m), 129.19, 129.08, 126.26, 16.03.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -89.33 – -90.11 (m), -159.23 – -160.18 (m).

HRMS ESI Calculated for $[\text{M-H}]^- \text{C}_{13}\text{H}_8\text{NOF}_4^- = 270.0542$ Found = 270.0539

Synthesis of 4-(2-(tert-butyl)phenoxy)-2,3,5,6-tetrafluoropyridine 2e



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 3.33 mmol of the corresponding phenol as a clear oil (0.726 g) in 73% yield.

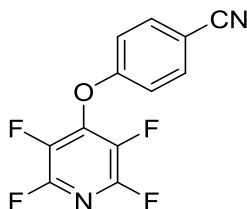
^1H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.44 (m, 1H, ArH), 7.23 – 7.16 (m, 2H, ArH), 6.79 – 6.75 (m, 1H, ArH), 1.48 (s, 9H, CH_3).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 154.80, 145.11 – 144.85 (m), 144.49 – 144.26 (m), 143.75 – 143.43 (m), 139.09, 136.79 – 136.30 (m), 135.52 – 134.92 (m), 127.81, 127.37, 125.07, 116.02, 34.88, 29.91.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.20 – -89.85 (m), -154.13 – -155.13 (m).

HRMS ESI Calculated for $[\text{M-H}]^- \text{C}_{15}\text{H}_{12}\text{NOF}_4^- = 298.0855$ Found = 298.0857

Synthesis of 4-((perfluoropyridin-4-yl)oxy)benzonitrile 2g



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 4.20 mmol of the corresponding phenol as a clear oil (0.991 g) in 88% yield.

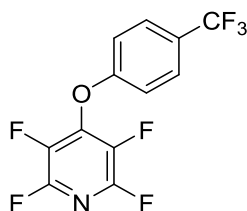
^1H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.71 (m, 2H, ArH), 7.23 – 7.14 (m, 2H, ArH).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 158.30, 145.14 – 144.52 (m), 143.69 – 143.25 (m), 142.84 – 142.53 (m), 137.15 – 136.55 (m), 135.53 – 135.18 (m), 134.49, 117.76, 117.14, 109.07.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -86.57 – -87.49 (m), -152.55 – -154.31 (m).

HRMS ESI Calculated for $[\text{M-H}]^- \text{C}_{12}\text{H}_3\text{N}_2\text{OF}_4^- = 267.0182$ Found = 267.0179

Synthesis of 2,3,5,6-tetrafluoro-4-(4-(trifluoromethyl)phenoxy)pyridine 2h



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 3.08 mmol of the corresponding phenol as a clear oil (0.890 g) in 93% yield.

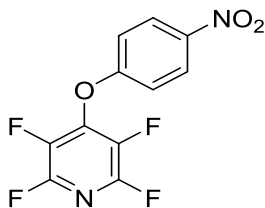
^1H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, $J = 8.4$, 2H, ArH), 7.18 (d, $J = 8.4$, 2H, ArH).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 157.77, 145.07 – 144.67 (m), 143.66 – 143.11 (m), 137.17 – 136.54 (m), 135.73 – 135.15 (m), 128.28 – 127.09 (m), 123.61 (q, $J = 271.9$), 116.64.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.21 (s), -87.19 – -88.83 (m), -153.38 – -154.82 (m).

HRMS ESI Calculated for $[\text{M-H}]^- \text{C}_{12}\text{H}_3\text{NOF}_7^- = 310.0103$ Found = 310.0115

Synthesis of 2,3,5,6-tetrafluoro-4-(4-nitrophenoxy)pyridine 2i



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 3.60 mmol of the corresponding phenol as a white solid (1.01 g) in 97% yield.

^1H NMR (400 MHz, Chloroform-*d*) δ 8.33 (d, $J = 9.2$, 2H, ArH), 7.20 (d, $J = 9.2$, 2H, ArH).

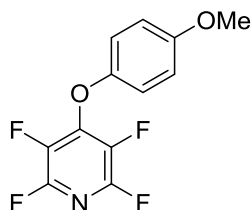
^{13}C NMR (176 MHz, Chloroform-*d*) δ 159.59, 145.01 – 144.75 (m), 144.66, 143.63 – 143.35 (m), 142.76 – 142.51 (m), 137.08 – 136.64 (m), 135.54 – 135.19 (m), 126.19, 116.69.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -85.75 – -87.34 (m), -152.80 – -154.91 (m).

HRMS ESI $^-$ Calculated for $[\text{M}-\text{H}]^- \text{C}_{11}\text{H}_4\text{N}_2\text{O}_3\text{F}_4^- = 287.0080$ Found = 287.0091

MP 84-85 °C

Synthesis of 2,3,5,6-tetrafluoro-4-(4-methoxyphenoxy)pyridine 2j



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 4.03 mmol of the corresponding phenol as a white solid (1.08 g) in 98% yield.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.11 – 6.98 (m, 2H, ArH), 6.95 – 6.83 (m, 2H, ArH), 3.83 (s, 3H, CH_3).

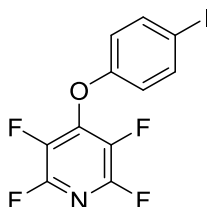
^{13}C NMR (176 MHz, Chloroform-*d*) δ 156.91, 149.64, 145.29 – 145.11 (m), 144.99 – 144.78 (m), 143.70 – 143.34 (m), 136.78 – 136.43 (m), 135.40 – 134.98 (m), 118.18, 114.85, 55.66.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.92 – -89.19 (m), -154.98 – -155.19 (m).

HRMS ESI⁻ Calculated for [M-H]⁻ C₁₂H₆NO₂F₄⁻ = 272.0335 Found = 272.0326

MP 78-79 °C

Synthesis of 2,3,5,6-tetrafluoro-4-(4-iodophenoxy)pyridine 2k



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 2.27 mmol of the corresponding phenol as a white solid (0.835 g) in 99% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 9.0, 2H, ArH), 6.86 (d, *J* = 9.0, 2H, ArH).

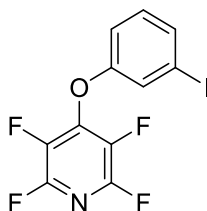
¹³C NMR (176 MHz, Chloroform-*d*) δ 155.62, 144.98 – 144.70 (m), 143.95 – 143.66 (m), 143.57 – 143.31 (m), 138.99, 136.99 – 136.64 (m), 135.46 – 135.15 (m), 118.74, 88.39.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -87.54 – -88.84 (m), -153.20 – -154.50 (m).

HRMS ESI⁻ Calculated for [M-H]⁻ C₁₁H₅NOF₄I⁻ = 367.9196 Found = 367.9203

MP 86-87 °C

Synthesis of 2,3,5,6-tetrafluoro-4-(3-iodophenoxy)pyridine 2l



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 2.27 mmol of the corresponding phenol as a clear oil (0.828 g) in 99% yield.

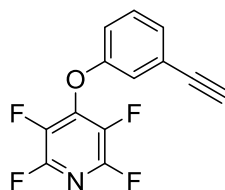
^1H NMR (400 MHz, Chloroform-*d*) δ 7.59 (d, $J = 7.8$, 1H, ArH), 7.44 (t, $J = 2.1$, 1H, ArH), 7.14 (t, $J = 8.1$, 1H, ArH), 7.05 (dd, $J = 8.1, 2.1$, 1H, ArH).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 155.78, 144.96 – 144.69 (m), 143.79 – 143.58 (m), 143.54 – 143.32 (m), 136.96 – 136.70 (m), 135.47 – 135.19 (m), 134.36, 131.27, 125.82, 115.97, 94.14.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -87.45 – -88.23 (m), -153.23 – -154.45 (m).

HRMS ESI Calculated for $[\text{M-H}]^- \text{C}_{11}\text{H}_3\text{NOF}_4\text{I} = 367.9196$ Found = 367.9201

Synthesis of 4-(3-ethynylphenoxy)-2,3,5,6-tetrafluoropyridine 2m



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 2.11 mmol of the corresponding phenol as a clear oil (0.500 g) in 89% yield.

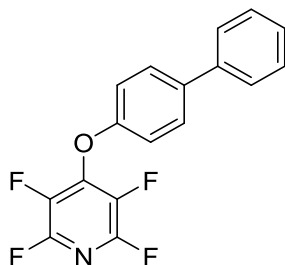
^1H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.35 (m, 2H, ArH), 7.20 – 7.16 (m, 1H, ArH), 7.14 – 7.06 (m, 1H, ArH), 3.15 (s, 1H, CCH).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 155.40, 145.09 – 144.80 (m), 144.03 – 143.77 (m), 143.47 – 143.19 (m), 137.17 – 136.81 (m), 135.46 – 135.10 (m), 130.02, 128.94, 124.12, 119.95, 117.34, 82.06, 78.68.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -87.94 – -88.26 (m), -153.86 – -154.10 (m).

HRMS ESI Calculated for $[M-H]^- C_{13}H_4NOF_4^- = 266.0229$ Found = 266.0225

Synthesis of 4-([1,1'-biphenyl]-4-yloxy)-2,3,5,6-tetrafluoropyridine 2n



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 2.94 mmol of the corresponding phenol as a white solid (0.827 g) in 88% yield.

1H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.55 (m, 4H, ArH), 7.51 – 7.45 (m, 2H, ArH), 7.42 – 7.36 (m, 1H, ArH), 7.15 (d, $J = 8.9$, 2H, ArH).

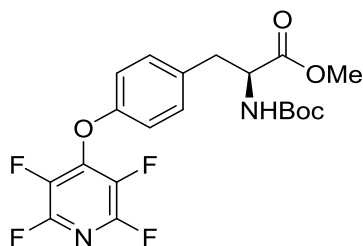
^{13}C NMR (176 MHz, Chloroform-*d*) δ 155.22, 145.05 – 144.70 (m), 144.52 – 144.18 (m), 143.62 – 143.31 (m), 139.80, 138.40, 137.14 – 136.80 (m), 135.62 – 135.24 (m), 128.85, 128.65, 127.50, 126.99, 116.92.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.36 – -88.61 (m), -154.03 – -154.24 (m).

HRMS ESI Calculated for $[M-H]^- C_{17}H_8NOF_4^- = 318.0544$ Found = 318.0542

MP 130-131 °C

Synthesis of methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-((perfluoropyridin-4-yl)oxy)phenyl)propanoate 2o



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 0.68 mmol of the corresponding phenol as a white solid (0.226 g) in 75% yield.

^1H NMR (400 MHz, Chloroform-*d*) δ 7.17 (d, $J = 8.7$, 2H, ArH), 7.01 (d, $J = 8.6$, 2H, ArH), 5.03 (br d, $J = 8.3$, 1H, NH), 4.64 – 4.57 (m, 1H, CH), 3.73 (s, 3H, CH_3), 3.15 (ABX, $J = 13.9$, 5.8, 1H, CH_2), 3.05 (ABX, $J = 13.9$, 6.4, 1H, CH_2), 1.44 (s, 9H, Boc CH_3).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 172.06, 154.93, 154.82, 145.01 – 144.66 (m), 144.50 – 144.27 (m), 143.82 – 143.09 (m), 137.32 – 136.59 (m), 135.68 – 135.13 (m), 133.20, 130.85, 116.72, 80.06, 54.34, 52.26, 37.79, 28.23.

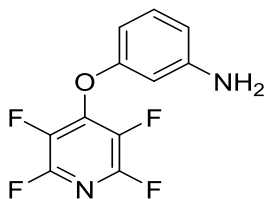
^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.04 – -88.96 (m), -153.31 – -155.42 (m).

HRMS ESI⁺ Calculated for $[\text{M}-\text{H}]^- \text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_5\text{F}_4^- = 443.1230$ Found = 443.1248

MP 105-106 °C

$[\alpha]_D^{27} = +18.14$ (c = 1.0, CH_2Cl_2)

Synthesis of 3-[(2,3,5,6-tetrafluoropyridin-4-yl)oxy]aniline 2p



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 4.59 mmol of the corresponding phenol as a white crystalline solid (1.05 g) in 88% yield.

^1H NMR (700 MHz, Chloroform-*d*) δ 7.13 – 7.08 (m, 1H), 6.52 – 6.47 (m, 1H), 6.39 – 6.35 (m, 1H), 3.79 (br s, 2H).

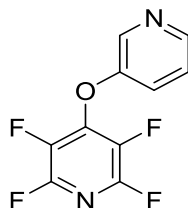
^{13}C NMR (176 MHz, Chloroform-*d*) δ 156.94, 148.21, 144.91 – 144.67 (m), 144.60 – 144.38 (m), 143.54 – 143.26 (m), 137.18 – 136.86 (m), 135.66 – 135.36 (m), 130.56, 111.71, 106.02, 103.22.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.74 – -88.99 (m), -154.25 – -154.46 (m).

HRMS ESI⁺ Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{11}\text{H}_7\text{N}_2\text{OF}_4^+$ = 259.0495 Found = 259.0496

MP 97-98 °C

Synthesis of 2,3,5,6-tetrafluoro-4-(pyridin-3-yloxy)pyridine 2q



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 5.26 mmol of the corresponding phenol as a brown oil (0.624 g) in 49% yield.

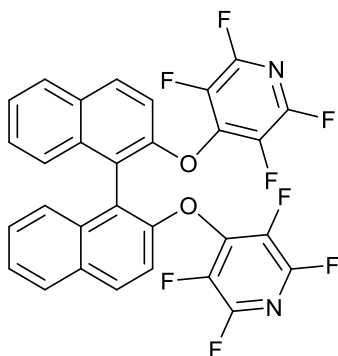
^1H NMR (400 MHz, Chloroform-*d*) δ 8.55 – 8.48 (m, 2H, ArH), 7.44 – 7.34 (m, 2H, ArH).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 152.31, 146.52, 145.00 – 144.68 (m), 143.76 – 143.30 (m), 139.32, 136.90 – 136.50 (m), 135.36 – 134.98 (m), 124.29, 123.90.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -87.05 – -88.31 (m), -153.62 – -154.19 (m).

HRMS ESI⁻ Calculated for $[\text{M}-\text{H}]^-$ $\text{C}_{10}\text{H}_3\text{N}_2\text{OF}_4^-$ = 243.0182 Found = 243.0183

Synthesis of 2,2'-bis((perfluoropyridin-4-yl)oxy)-1,1'-binaphthalene 2r



To a solution of 1,1'-Bi-2-naphthol (0.500 g, 1.75 mmol) in DMF (5 mL) was added pentafluoropyridine (0.592 g, 3.50 mmol) and K_2CO_3 (0.506 g, 3.67 mmol). The reaction mixture was stirred at room temperature for 1 h. After this time the reaction mixture was directly poured into water (100 mL). The resulting precipitant was filtered off and dried under vacuum to give the title compound as a white solid (0.702 g) in 69% yield.

1H NMR (400 MHz, Chloroform-*d*) δ 8.02 (d, $J = 8.9$, 2H, ArH), 7.93 (d, $J = 8.2$, 2H, ArH), 7.54 – 7.44 (m, 4H, ArH), 7.41 – 7.34 (m, 2H, ArH), 7.23 (d, $J = 8.5$, 2H, ArH).

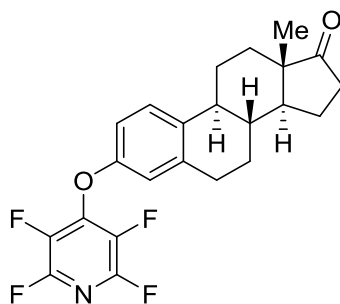
^{13}C NMR (176 MHz, Chloroform-*d*) δ 152.19, 144.66 – 144.40 (m), 144.26 – 143.98 (m), 142.89 – 142.49 (m), 136.07 – 135.57 (m), 134.62 – 133.93 (m), 132.86, 131.22, 130.82, 128.25, 127.74, 126.21, 124.95, 119.33, 117.87.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -89.31 – -90.70 (m), -153.43 – -154.82 (m).

HRMS ESI⁻ Calculated for $[M-H]^-$ $C_{30}H_{11}N_2O_2F_8^- = 583.0693$ Found = 583.0679

MP 210-212 °C

Synthesis of (1S,10R,11S,15S)-15-methyl-5-[(2,3,5,6-tetrafluoropyridin-4-yl)oxy]tetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptadeca-2(7),3,5-trien-14-one 2s



The title compound was synthesised according to the general procedure for the synthesis of tetrafluoropyridyl ethers from 1.85 mmol of estrone with the following modification. Due to the solubility of estrone in MeCN, 1 mL of DMF was added to the reaction mixture and the reaction mixture heated at 70 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (100% hexane to 90% hexane 10% EtOAc). This gave the title compound as a white crystalline solid (0.676 g) in 87% yield.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.6, 1H), 6.86 (dd, *J* = 8.6, 2.7, 1H), 6.80 (d, *J* = 2.7, 1H), 3.06 – 2.86 (m, 2H), 2.61 – 2.49 (m, 1H), 2.46 – 2.39 (m, 1H), 2.35 – 2.26 (m, 1H), 2.24 – 1.97 (m, 4H), 1.73 – 1.42 (m, 7H), 0.95 (s, 3H).

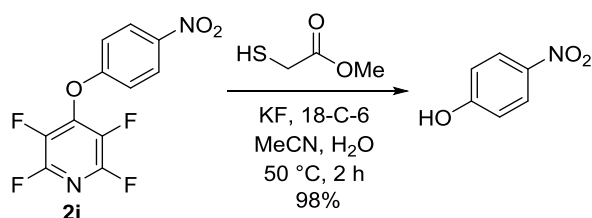
¹³C NMR (176 MHz, Chloroform-*d*) δ 220.51, 153.85, 144.95 – 144.70 (m), 144.68 – 144.48 (m), 143.56 – 143.33 (m), 138.76, 137.08 – 136.83 (m), 136.73, 135.59 – 135.33 (m), 126.87, 116.52, 113.85, 50.38, 47.89, 44.00, 37.98, 35.80, 31.50, 29.45, 26.24, 25.77, 21.55, 13.81.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -88.67 – -88.96 (m), -154.29 – -154.48 (m).

HRMS ESI⁻ Calculated for [M-H]⁻ C₂₃H₂₀NO₂F₄⁻ = 418.1430 Found = 418.1432

MP 153-154 °C

Deprotection of **2i** to 4-nitrophenol



The title compound was synthesised according to the general procedure for the deprotection of tetrafluoropyridyl ethers from 0.22 mmol of compound **1b** as a cream solid (0.030 g) in 98% yield.

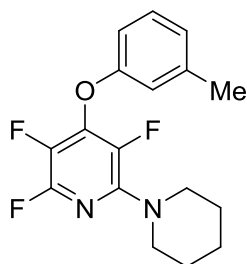
Characterisation data were in agreement with reported literature values.^[1]

$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 8.25 – 8.16 (m, 2H, ArH), 6.99 – 6.92 (m, 2H, ArH).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 161.28, 141.68, 126.30, 115.71.

MS ESI⁻ m/z = 138.1 [M-H]⁻

Synthesis of 2,3,5-trifluoro-4-(3-methylphenoxy)-6-(piperidin-1-yl)pyridine **3**



To a solution of 2,3,5,6-tetrafluoro-4-(*m*-tolylloxy)pyridine (0.100 g, 0.39 mmol) in acetonitrile (10 mL) was added K_2CO_3 (0.113 g, 0.82 mmol) and piperidine (0.070 g, 0.82 mmol). The reaction mixture was heated at reflux for 24 h. After this time the reaction mixture was filtered and concentrated under reduced pressure. The recovered residue was purified by flash column chromatography (100% hexane to 80% hexane 20% EtOAc). This gave the title compound as a clear oil (0.112 g) in 89% yield.

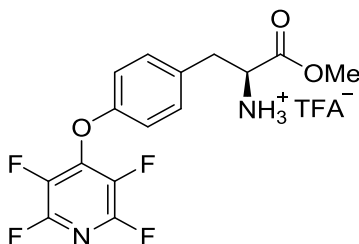
$^1\text{H NMR}$ (400 MHz, Chloroform-*d*) δ 7.24 (t, J = 7.9, 1H, ArH), 6.99 – 6.81 (m, 3H, ArH), 3.47 – 3.36 (m, 4H, CH_2), 2.37 (s, 3H, CH_3), 1.67 (s, 6H, CH_2).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -89.50 (dd, $J = 27.8, 25.1$), -146.38 (dd, $J = 27.8, 3.1$), -165.88 (dd, $J = 25.1, 3.1$).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 156.61, 145.73 (dd, $J = 12.2, 2.5$), 144.42 (dd, $J = 12.2, 2.5$), 143.38 – 143.16 (m), 142.04 – 141.74 (m), 140.07, 139.97 (dd, $J = 6.8, 2.0$), 138.52 (dd, $J = 6.8, 2.0$), 131.93 (d, $J = 32.7$), 130.48 (d, $J = 32.7$), 129.41, 124.65, 116.58, 112.81, 48.56 (d, $J = 5.8$), 25.67, 24.49, 21.35.

HRMS ESI⁺ Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{17}\text{H}_{18}\text{N}_2\text{OF}_3^+$ = 323.1371 Found = 323.1385

Synthesis of methyl (2*S*)-2-amino-3-{4-[(2,3,5,6-tetrafluoropyridin-4-yl)oxy]phenyl}propanoate 4



To a solution of methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-((perfluoropyridin-4-yl)oxy)phenyl)propanoate (0.100 g, 0.26 mmol) in DCM (2 mL) was added TFA (0.5 mL). The reaction mixture was stirred at rt for 2 h. After this time the reaction mixture was concentrated under reduced pressure. This gave the title compound as a colourless crystalline solid (0.112 g) in quantitative yield.

^1H NMR (400 MHz, Chloroform-*d*) δ 8.45 (br s, 3H, NH), 7.24 (d, $J = 8.5$, 2H, ArH), 7.02 (d, $J = 8.5$ Hz, 2H, ArH), 4.26 (t, $J = 6.6$, 1H, CH), 3.71 (s, 3H, CH₃), 3.27 (d, $J = 6.6$, 2H, CH₂).

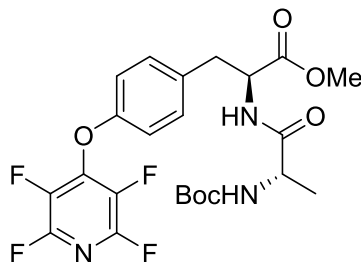
^{13}C NMR (176 MHz, Chloroform-*d*) δ 169.21, 155.46, 144.95 – 144.66 (m), 144.07 – 143.90 (m), 143.58 – 143.30 (m), 136.99 – 136.63 (m), 135.47 – 135.17 (m), 130.94, 130.16, 117.24, 54.11, 53.19, 35.41.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -76.08, -88.42 – -88.64 (m), -154.37 – -154.56 (m).

HRMS ESI⁺ Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_3\text{F}_4^+$ = 345.0862 Found = 345.0878

MP 115-116 °C

Synthesis of methyl (S)-2-((S)-2-((tert-butoxycarbonyl)amino)propanamido)-3-(4-((perfluoropyridin-4-yl)oxy)phenyl)propanoate **5**



To a solution of **3** (0.025 g, 0.068 mmol) in DCM (10 mL) was added PyBOP (0.038 g, 0.074 mmol), DIPEA (0.010 g, 0.074 mmol) and Boc-Ala-OH (0.011 g, 0.068 mmol) and the reaction mixture stirred for 16 h at rt. After this time the reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (100% hexane to 50% hexane 50% EtOAc). This gave the title compound (0.033 g) as a cream solid in 94% yield.

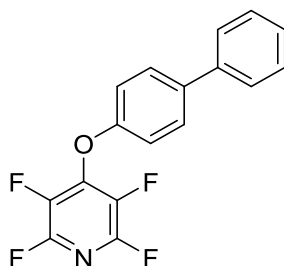
^1H NMR (400 MHz, Chloroform-*d*) δ 7.16 (d, J = 8.6, 2H, ArH), 7.00 (d, J = 8.6, 2H, ArH), 6.60 (br d, J = 7.7, 1H, NH), 4.96 – 4.81 (m, 2H, CH/NH), 4.23 – 4.06 (m, 1H, CH), 3.74 (s, 3H, CH₃), 3.20 (ABX, J = 14.0, 5.9, 1H, CH₂), 3.10 (ABX, J = 14.0, 5.9, 1H, CH₂), 1.46 (s, 9H, CH₃), 1.34 (d, J = 7.1, 3H, CH₃).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 172.20, 171.43, 154.84, 132.91, 130.86, 116.74, 53.08, 52.39, 50.18, 37.21, 28.23, 18.00. Note: at the concentration of the sample which the spectra was recorded the resonances corresponding to the carbons on the fluoropyridine ring were observed but only weakly therefore these have not been reported.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.10 – -88.92 (m), -153.96 – -154.60 (m).

HRMS ESI⁺ Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{23}\text{H}_{26}\text{N}_3\text{O}_6\text{F}_4^+$ = 516.1752 Found = 517.1758

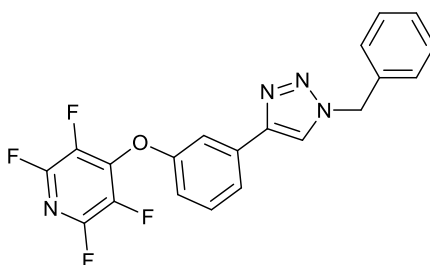
Suzuki-Miyaura Cross Coupling to form 4-([1,1'-biphenyl]-4-yloxy)-2,3,5,6-tetrafluoropyridine **2n**



Under an inert atmosphere, a solution of 2,3,5,6-tetrafluoro-4-(4-iodophenoxy)pyridine (0.100 g, 0.27 mmol) and phenyl boronic acid (0.040 g, 0.33 mmol) in 1,4-dioxane (6 mL) was degassed with bubbling nitrogen for 1 h. At the same time a solution of K_2CO_3 (0.112 g, 0.81 mmol) in H_2O (3 mL) was also degassed with bubbling nitrogen for 1 h. After this time $Pd(PPh_3)_4$ (0.016 g, 5 mol%) was added to the dioxane solution and this was further degassed for 20 min. To the dioxane solution was transferred the K_2CO_3 water solution and the resulting mixture heated at reflux for 5 h. After this time the reaction mixture was concentrated under reduced pressure and the resulting residue purified by flash column chromatography (100% hexane to 90% hexane 10% EtOAc). This gave the title compound as a white solid (0.076 g) in 86% yield.

Characterisation data was in agreement with the values reported above for 4-([1,1'-biphenyl]-4-yloxy)-2,3,5,6-tetrafluoropyridine

Synthesis of 4-[3-(1-benzyl-1H-1,2,3-triazol-4-yl)phenoxy]-2,3,5,6-tetrafluoropyridine **6**



To a solution of **2m** (0.100 g, 0.37 mmol) and benzyl azide (0.049 g, 0.37 mmol) in methanol (10 mL) was added sodium-L-ascorbate (0.015 g, 0.07 mmol) and copper(II) sulfate pentahydrate (0.009 g, 10 mol%). The reaction mixture was heated at 50 °C for 16 hours after which point the reaction mixture

was concentrated under reduced pressure. The residue was purified by flash column chromatography (100% hexane to 100% EtOAc) to give the title compound as a white solid (0.139 g) in 93% yield.

^1H NMR (400 MHz, Acetonitrile- d_3) δ 8.16 (s, 1H, triazole CH), 7.75 (ddd, $J = 7.8, 1.5, 0.9$, 1H, ArH), 7.62 (dd, $J = 2.6, 1.5$, 1H, ArH), 7.51 (app t, $J = 8.0$, 1H, ArH), 7.46 – 7.35 (m, 5H, ArH), 7.17 (dd, $J = 8.3, 2.7$, 1H, ArH), 5.61 (s, 2H, CH_2).

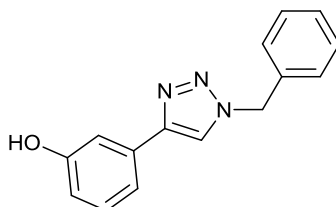
^{13}C NMR (151 MHz, Acetonitrile- d_3) δ 156.39, 146.12, 135.68, 133.26, 130.73, 128.93, 128.42, 128.02, 122.07, 121.54, 115.99, 113.30, 53.66. Note: due to the solubility of the compound the resonances corresponding to the carbons on the fluoropyridine ring were observed but only weakly therefore these have not been reported.

^{19}F NMR (376 MHz, Acetonitrile- d_3) δ -91.32 – -92.21 (m), -156.12 – -156.62 (m).

HRMS ESI $^+$ Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{20}\text{H}_{13}\text{N}_4\text{OF}_4^+$ = 401.1025 Found = 401.1046

MP 166-167 °C

Synthesis of 3-(1-benzyl-1H-1,2,3-triazol-4-yl)phenol 1b



To a solution of 3-hydroxyphenylacetylene (0.100 g, 0.85 mmol) and benzyl azide (0.112 g, 0.85 mmol) in methanol (10 mL) was added sodium-L-ascorbate (0.034 g, 0.17 mmol) and copper(II) sulfate pentahydrate (0.021 g, 10 mol%). The reaction mixture was heated at 50 °C for 3 hours after which point the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography (100% hexane to 100% EtOAc) to give the title compound as a cream solid (0.199 g) in 93% yield.

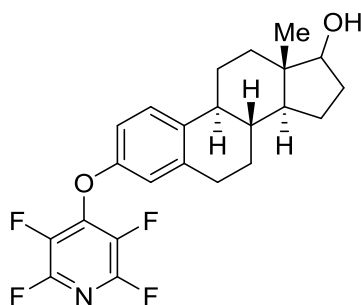
^1H NMR (400 MHz, Acetonitrile- d_3) δ 8.10 (s, 1H, triazole CH), 7.45 – 7.35 (m, 5H, ArH), 7.35 – 7.25 (m, 3H, ArH), 6.84 – 6.78 (m, 1H, ArH), 5.60 (s, 2H, CH_2).

^{13}C NMR (151 MHz, Acetonitrile- d_3) δ 157.31, 147.22, 135.84, 132.30, 130.08, 128.91, 128.35, 127.96, 120.93, 120.92, 114.90, 112.06, 53.59.

HRMS ESI $^+$ Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}^+$ = 252.1137 Found = 252.1152

MP 133-135 $^\circ\text{C}$

Synthesis of (1S,10R,11S,15S)-15-methyl-5-[(2,3,5,6-tetrafluoropyridin-4-yl)oxy]tetracyclo[8.7.0.0 2 ,7.0 11,15]heptadeca-2(7),3,5-trien-14-ol 7



To a solution of **2s** (0.10 g, 0.24 mmol) in THF (10 mL) was added sodium borohydride (0.023 g, 0.60 mmol) and the reaction mixture stirred at rt for 24 h. The reaction mixture was quenched by the addition of water (5 mL) and then concentrated under reduced pressure. The recovered residue was taken up in EtOAc (30 mL) and washed with water (30 mL) and then brine (30 mL). The organic fraction was dried over MgSO_4 , filtered and concentrated under reduced pressure. This gave the title compound as a white crystalline solid (0.091 g) in 90% yield.

^1H NMR (600 MHz, Chloroform- d) δ 7.26 (d, J = 8.6, 1H, ArH), 6.80 (dd, J = 8.6, 2.8, 1H, ArH), 6.74 (d, J = 2.8, 1H, ArH), 3.73 (t, J = 8.5 Hz, 1H, CH), 2.89 – 2.79 (m, 2H, CH_2), 2.34 – 2.27 (m, 1H, CH), 2.25 – 2.17 (m, 1H, CH), 2.16 – 2.08 (m, 1H, CH), 1.96 (dt, J = 12.6, 3.4, 2H, CH_2), 1.92 – 1.86 (m, 1H, CH), 1.75 – 1.65 (m, 1H, CH), 1.55 – 1.16 (m, 8H), 0.78 (s, 3H, CH_3).

^{13}C NMR (151 MHz, Chloroform- d) δ 153.72, 145.09 – 144.80 (m), 144.79 – 144.51 (m), 143.50 – 143.16 (m), 138.98, 137.35, 137.26 – 136.94 (m), 135.52 – 135.17 (m), 126.84, 116.47, 113.68, 81.78, 50.02, 43.98, 43.18, 38.45, 36.61, 30.55, 29.58, 26.93, 26.17, 23.09, 11.02.

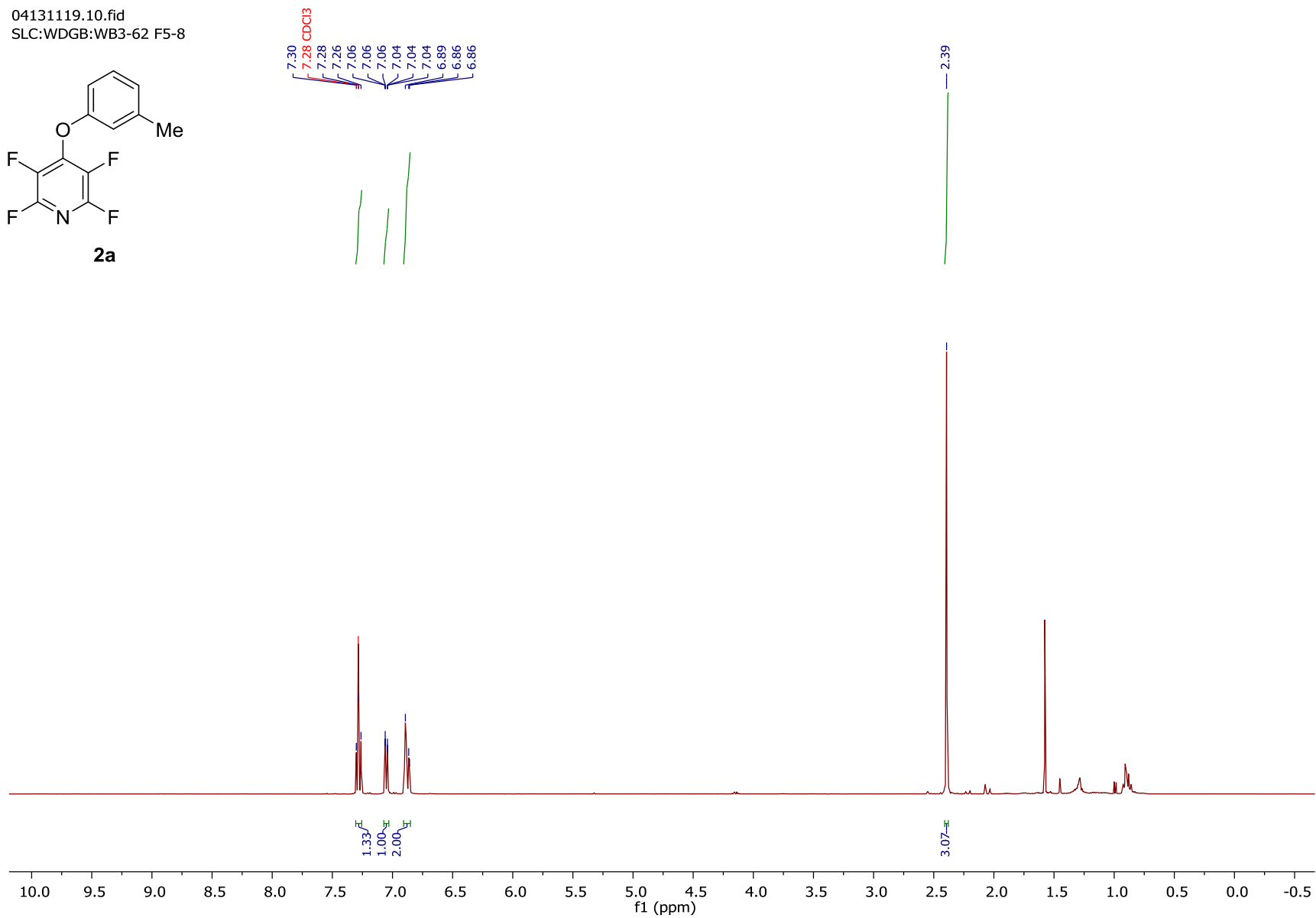
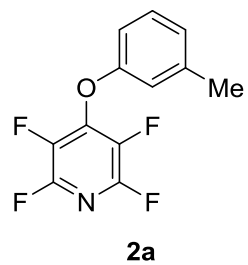
^{19}F NMR (376 MHz, Chloroform- d) δ -88.82 – -89.09 (m), -154.29 – -154.55 (m).

HRMS ESI⁻ Calculated for [M-H]⁻ C₂₃H₂₂NO₂F₄⁻ = 420.1587 Found = 420.1585

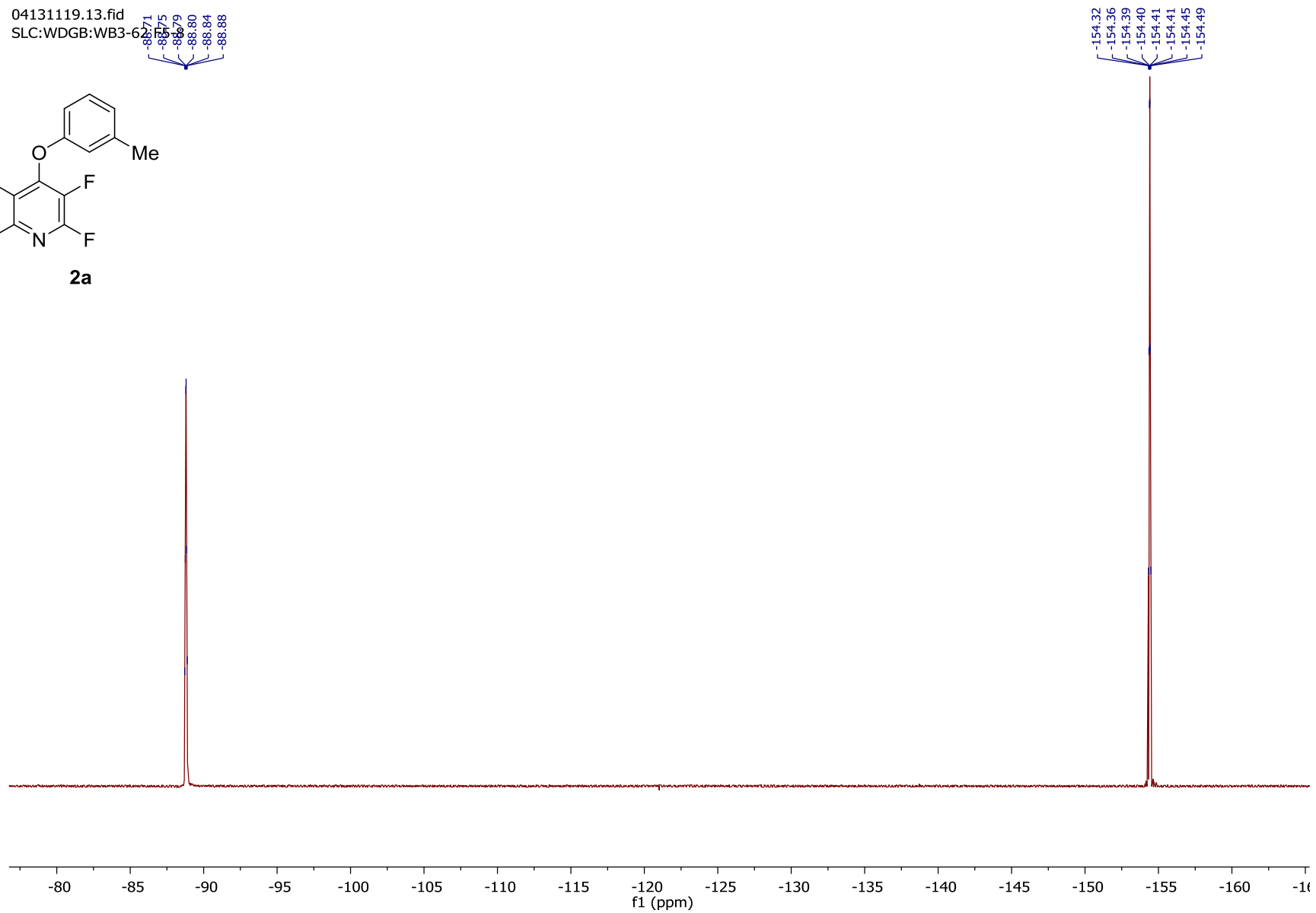
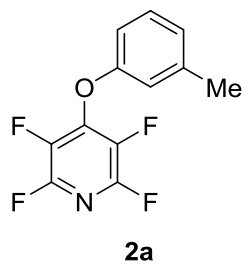
MP 99-101 °C

NMR Data for Synthesised Compounds

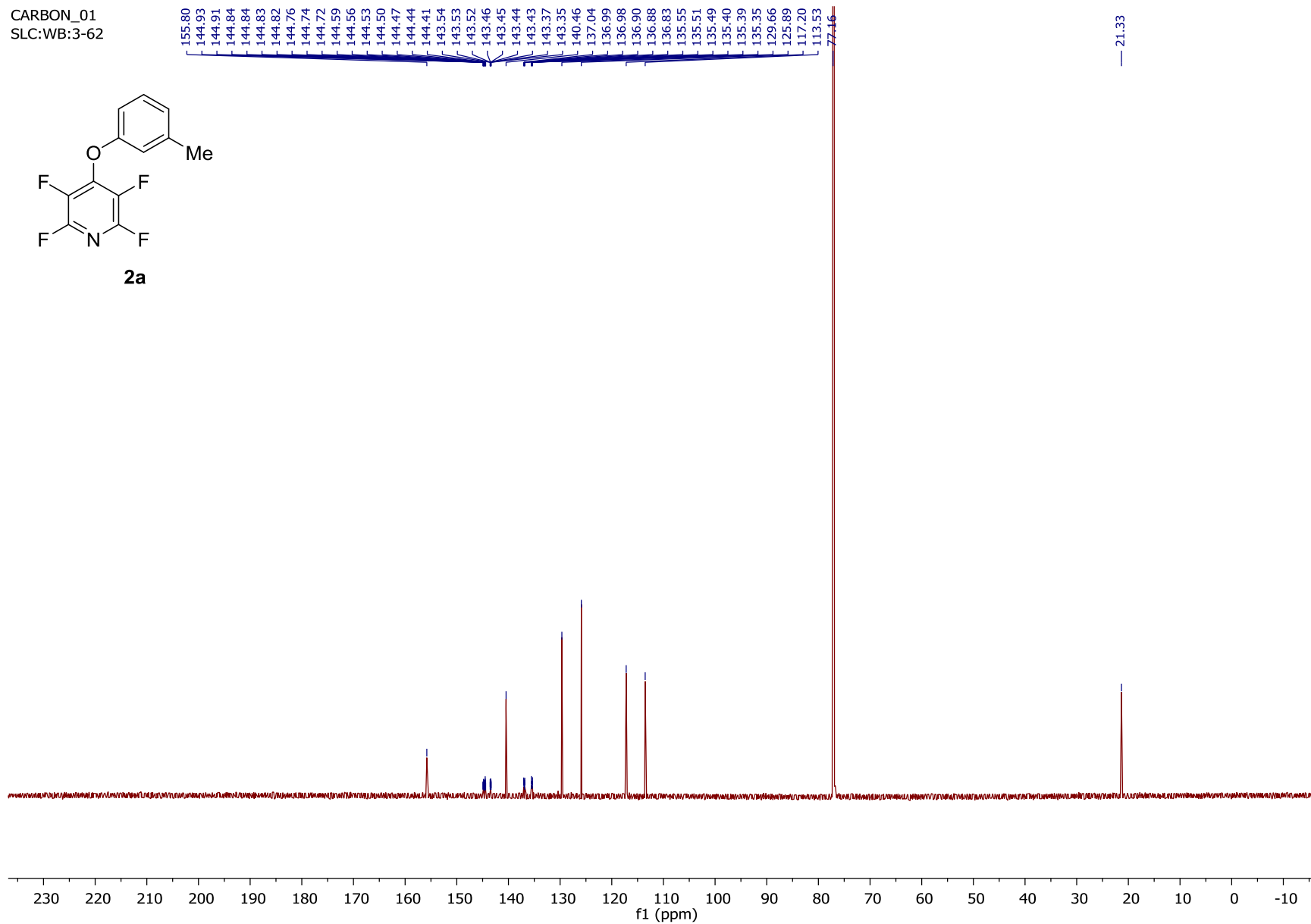
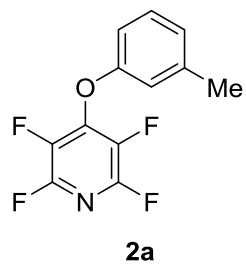
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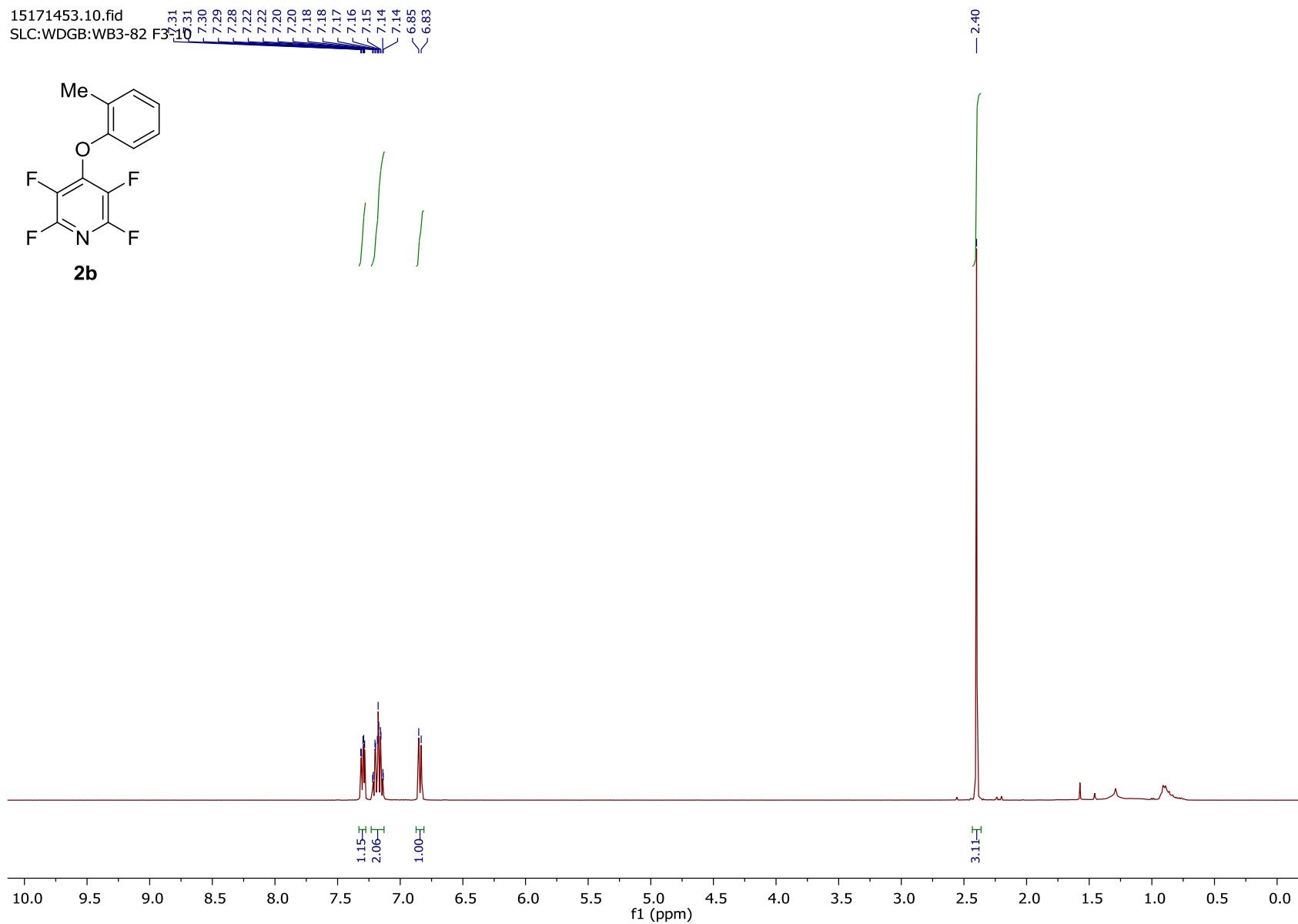
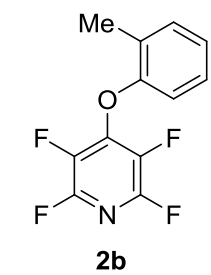


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SLC:WB:3-62

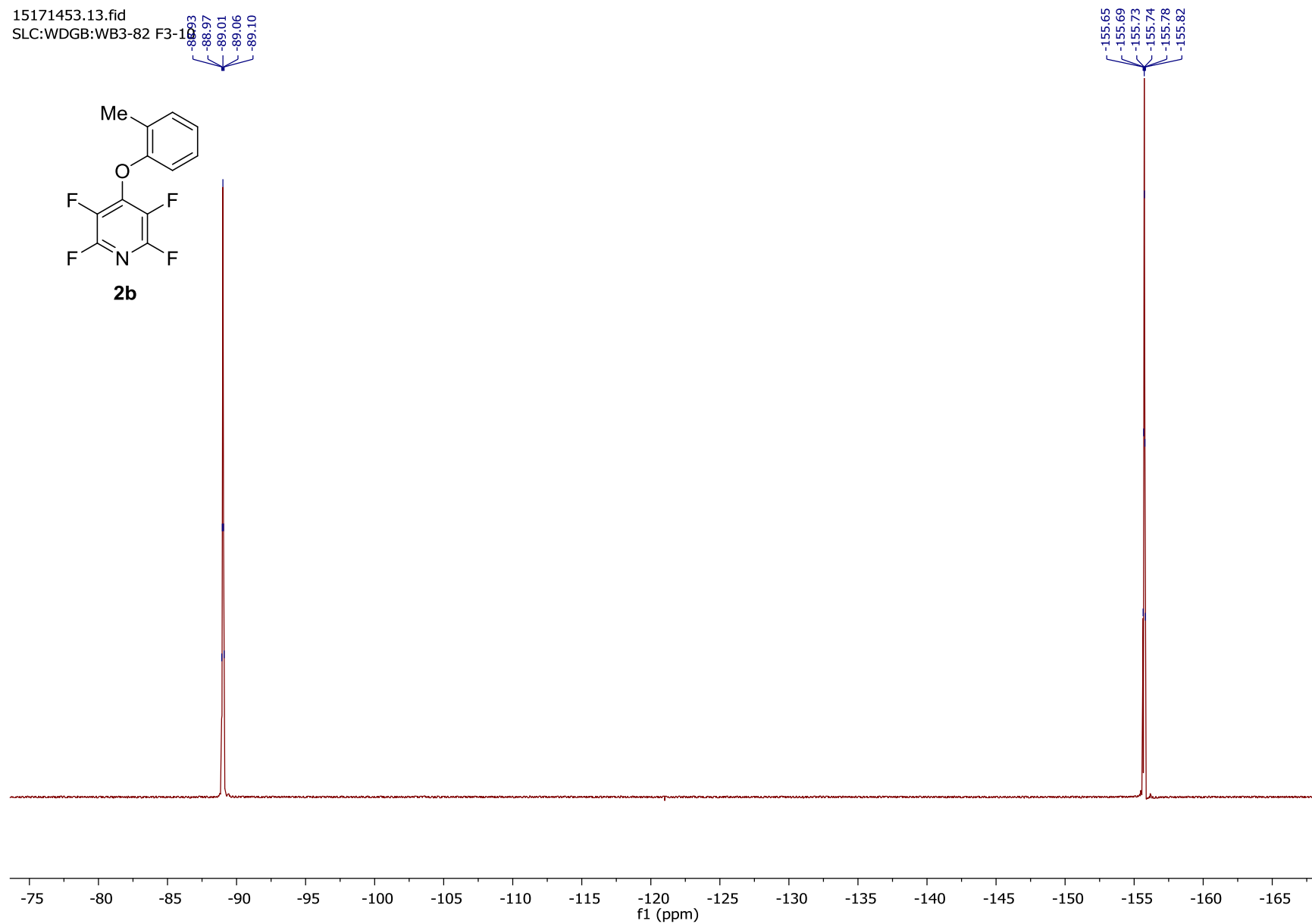
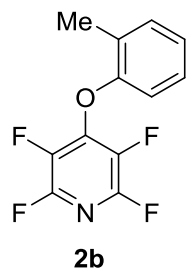


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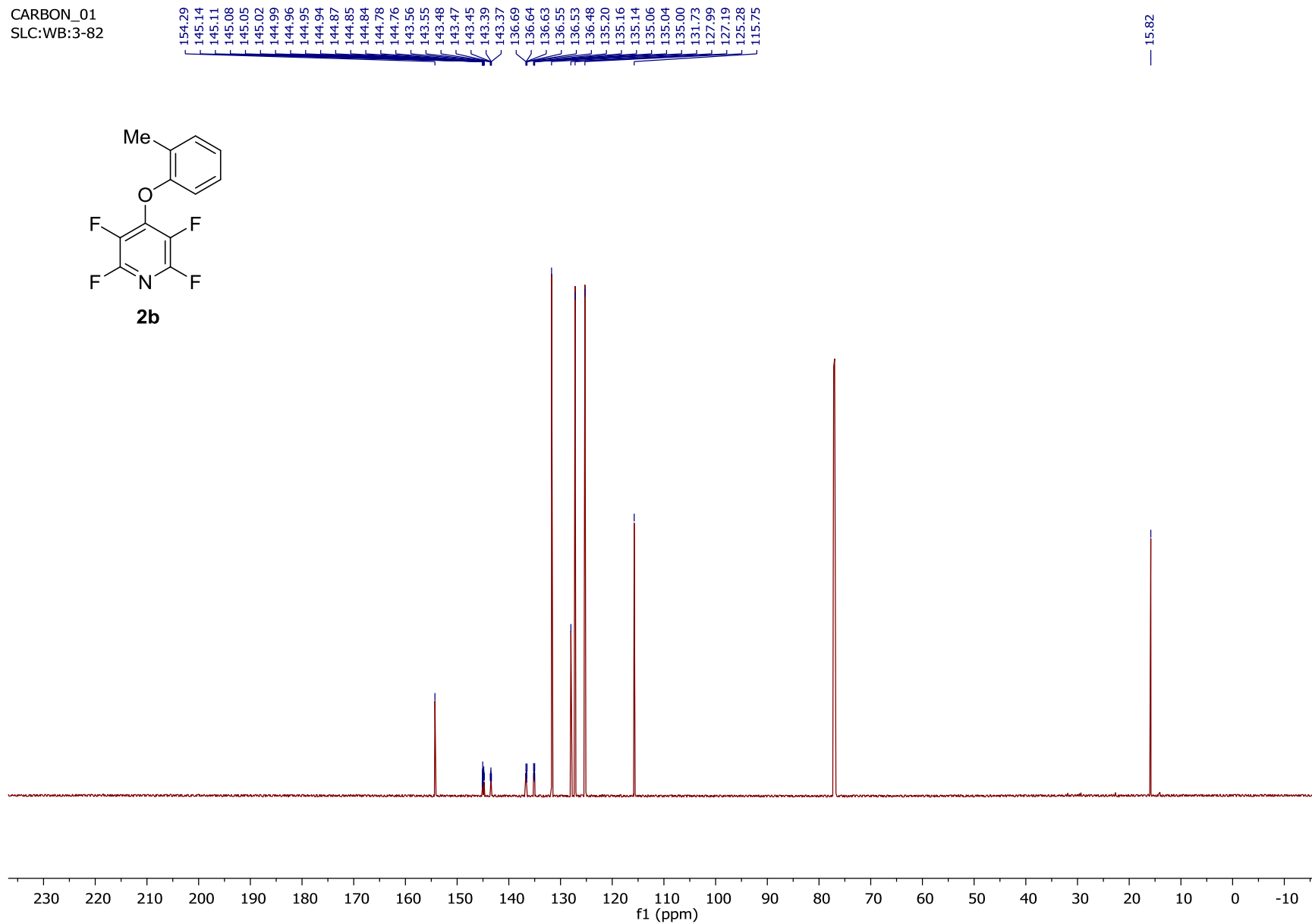
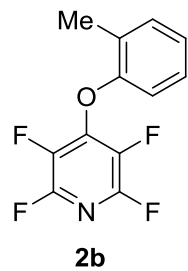
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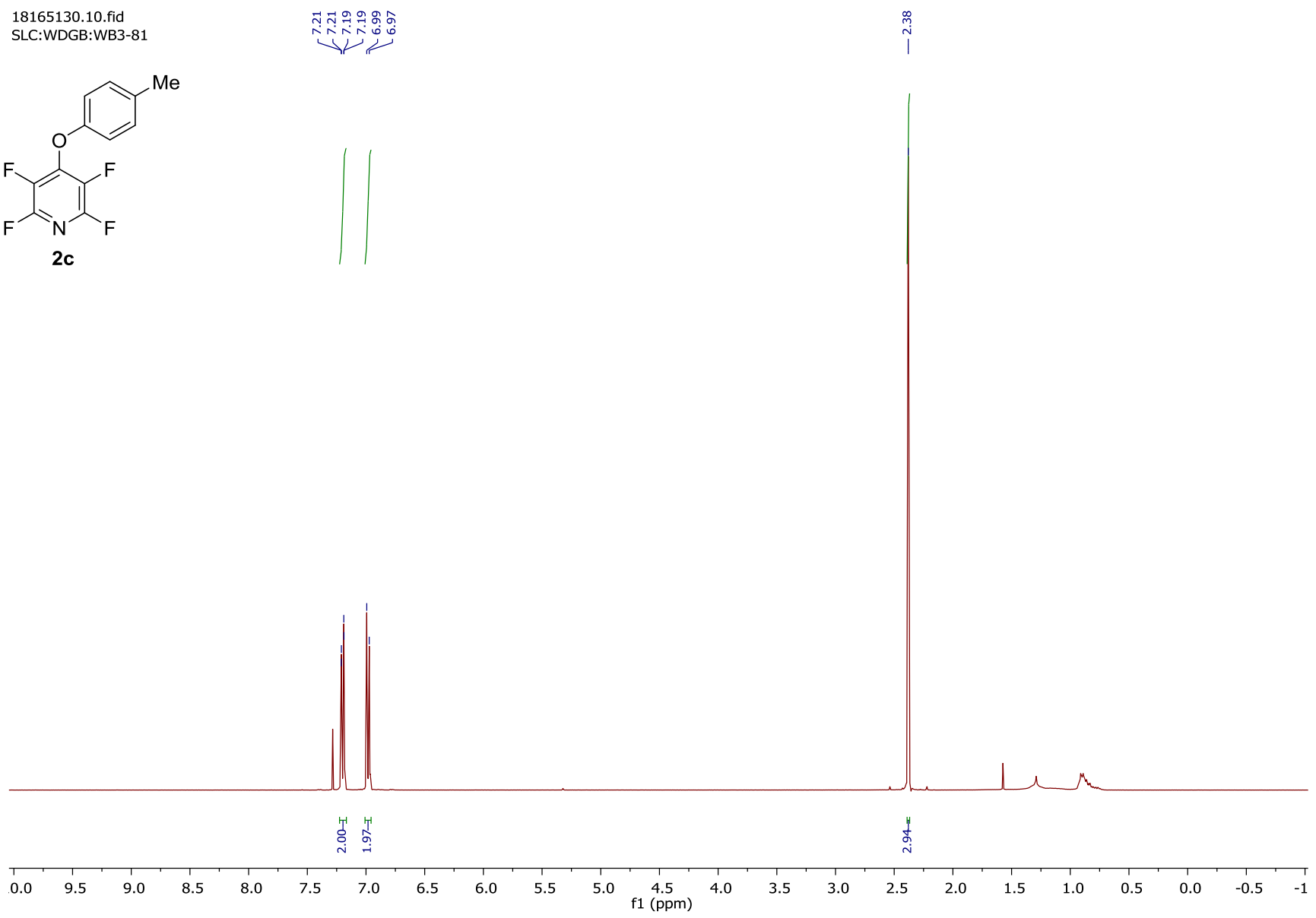
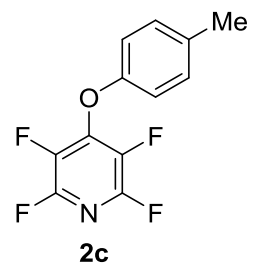
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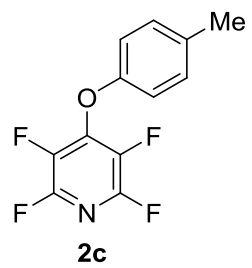
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SLC:WB:3-82



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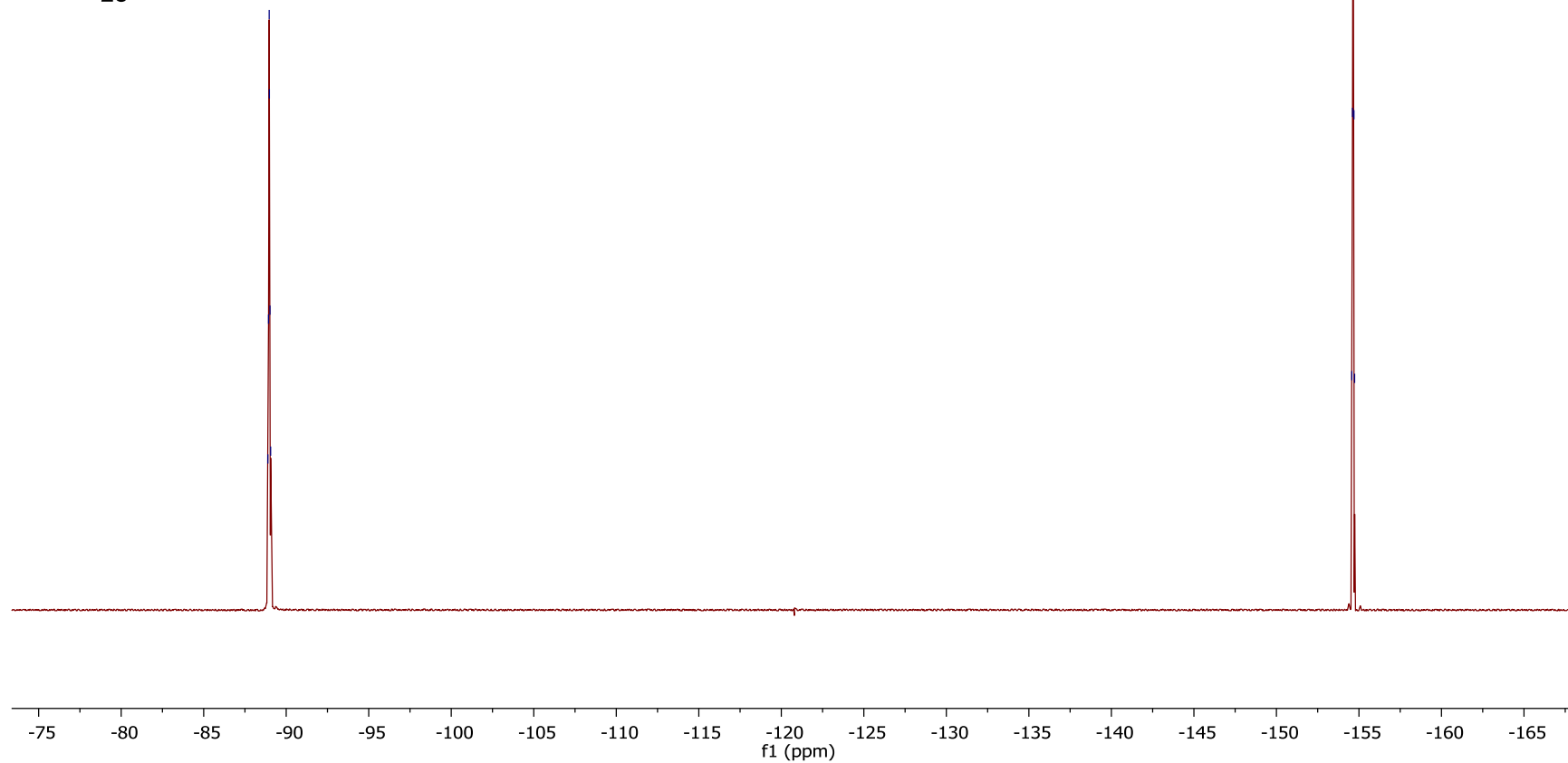


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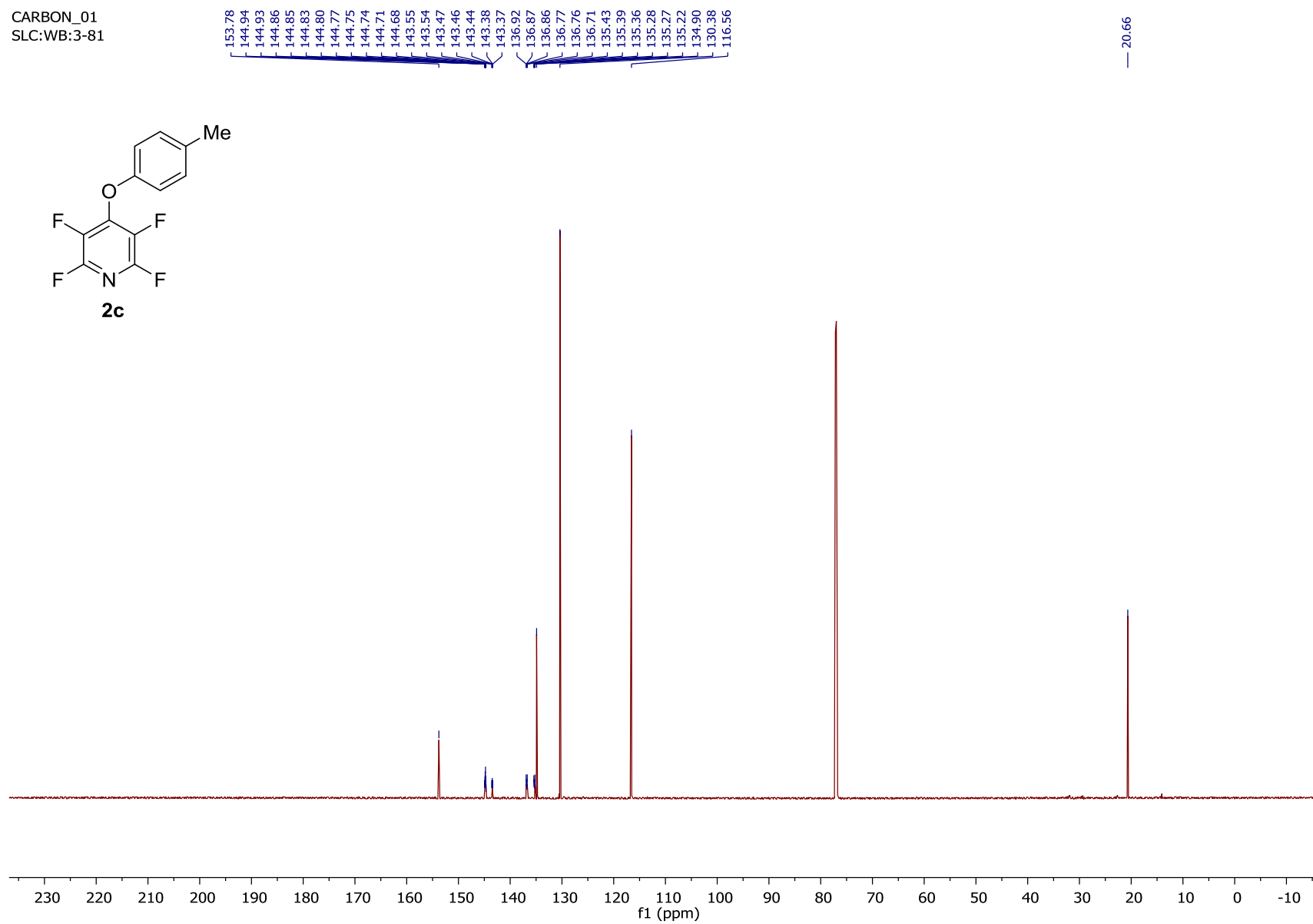
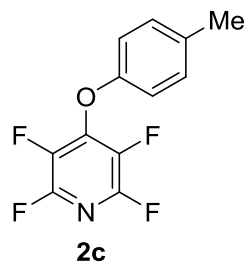


-88.89
-88.93
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-88.98
-89.02
-89.06

-154.57
-154.61
-154.65
-154.66
-154.70
-154.74

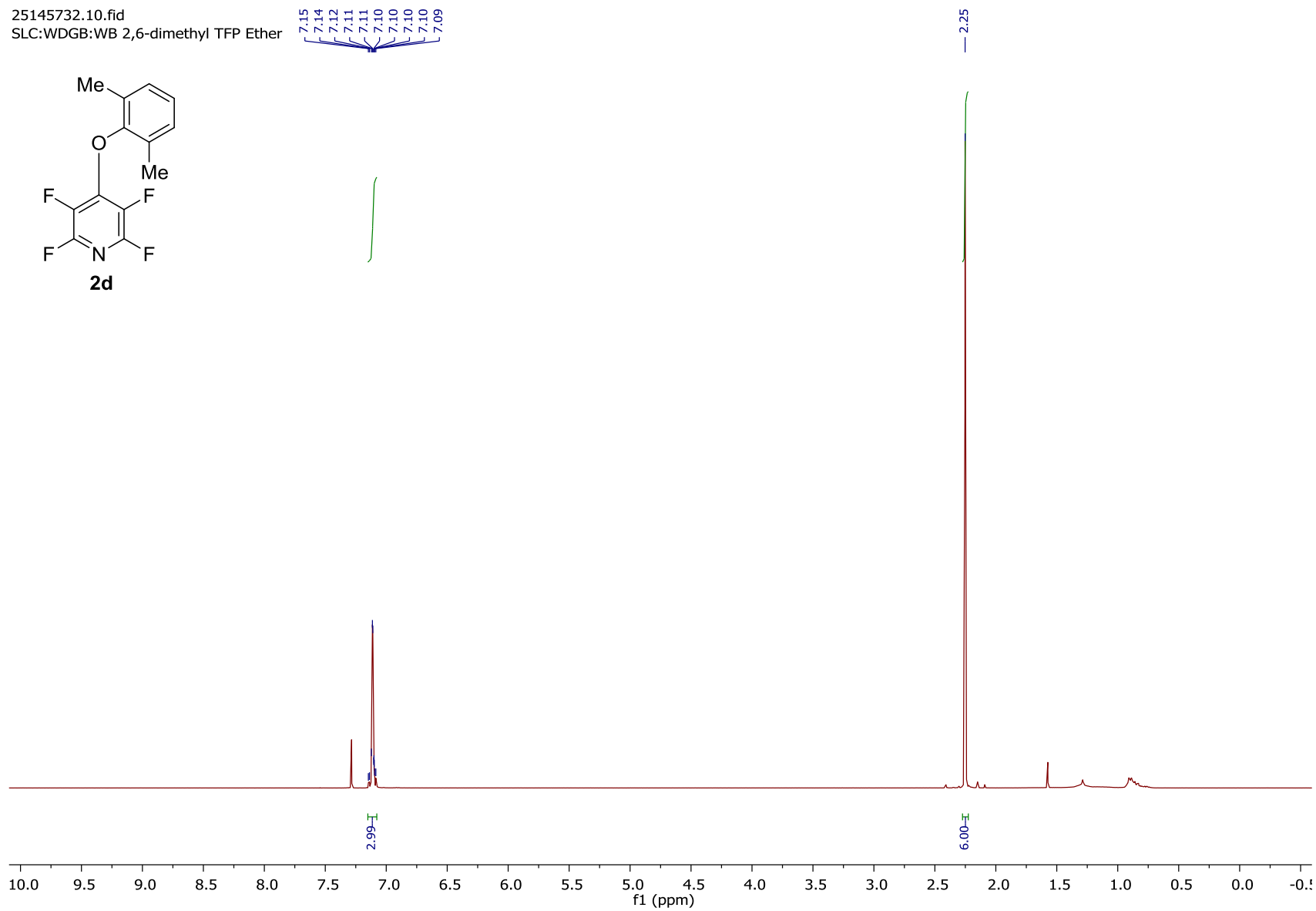
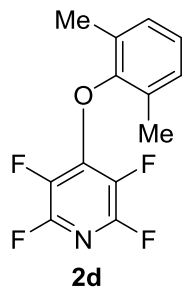


CARBON_01
SLC:WB:3-81

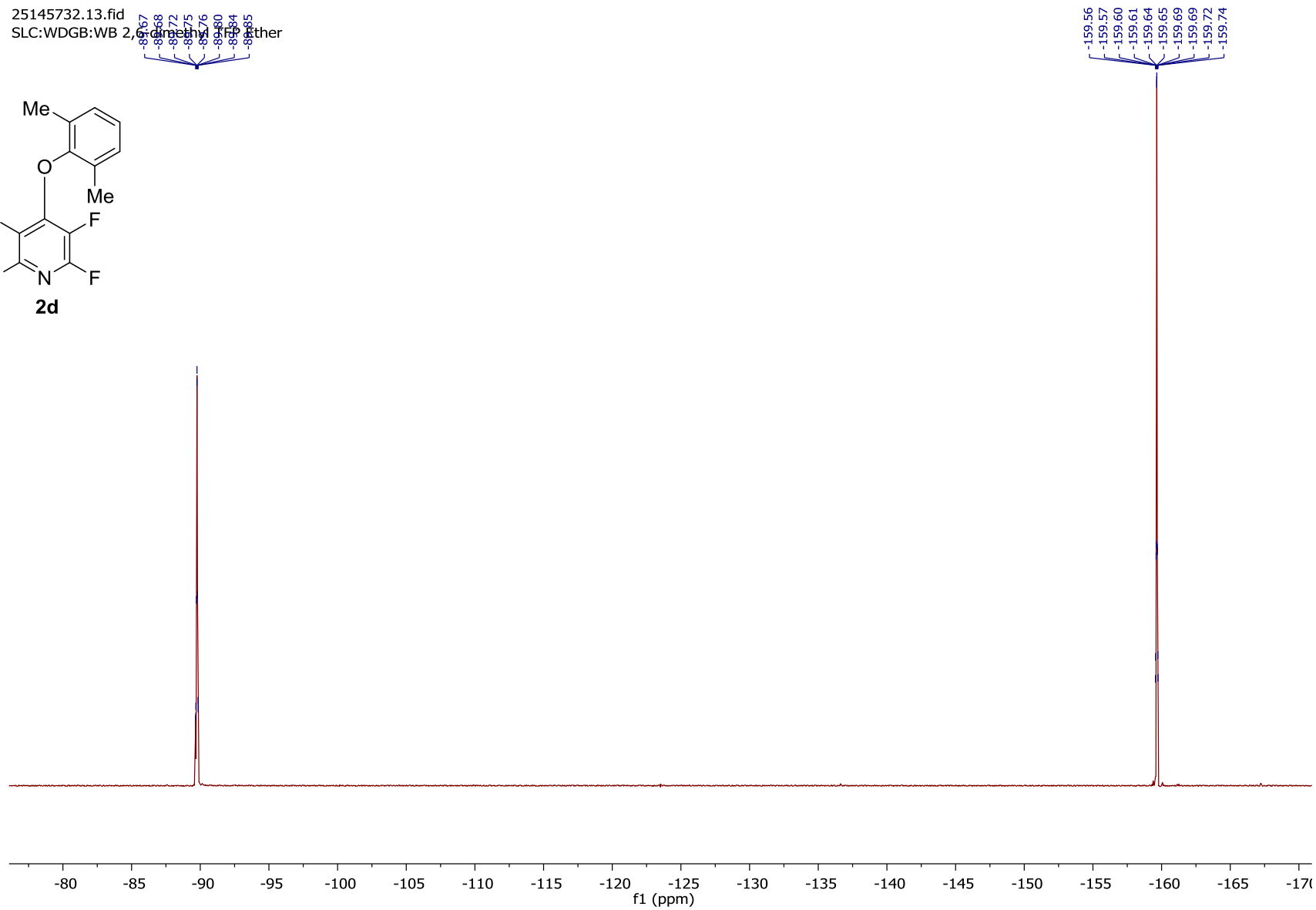
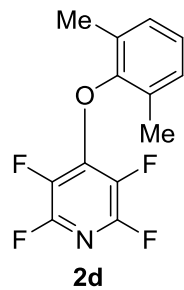


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SLC:WDGB:WB 2,6-dimethyl TFP Ether

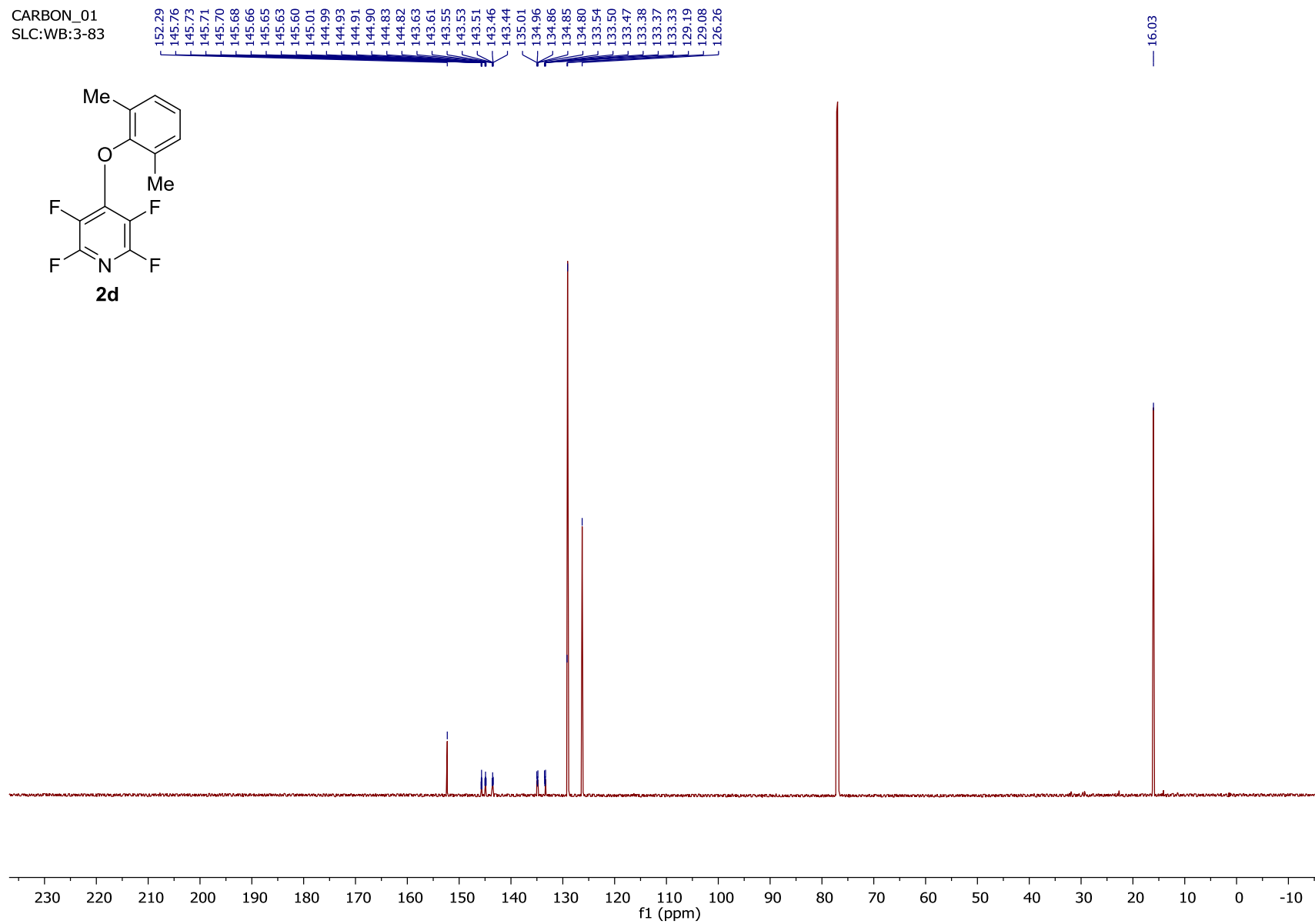
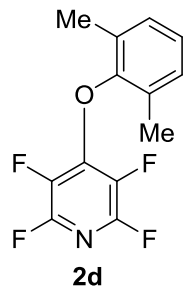
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7.11
7.11
7.10
7.10
7.10
7.09



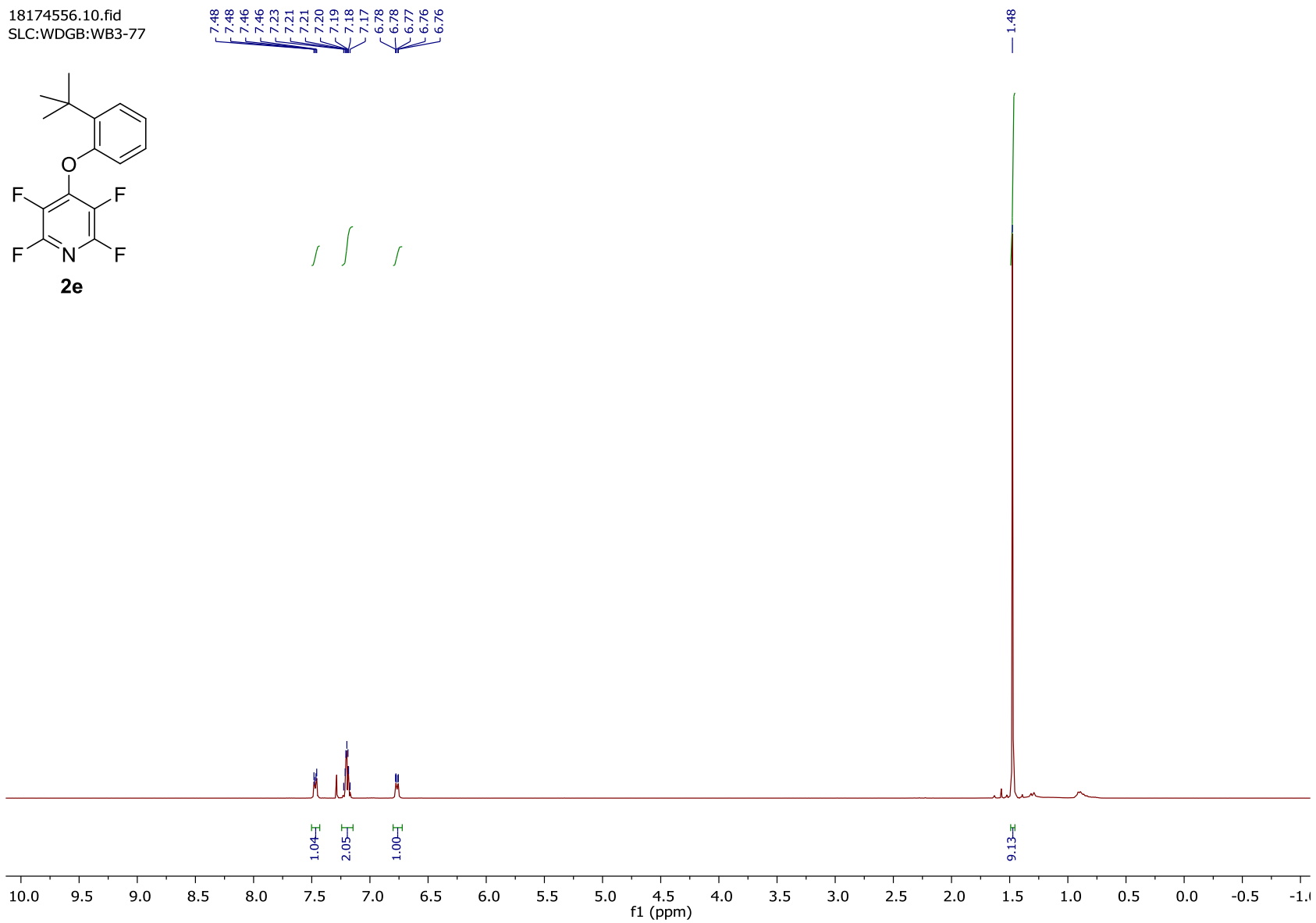
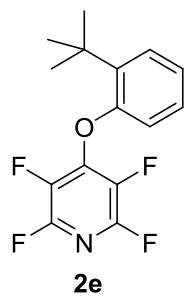
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SLC:WDGB:WB 2,6-dimethyl ether



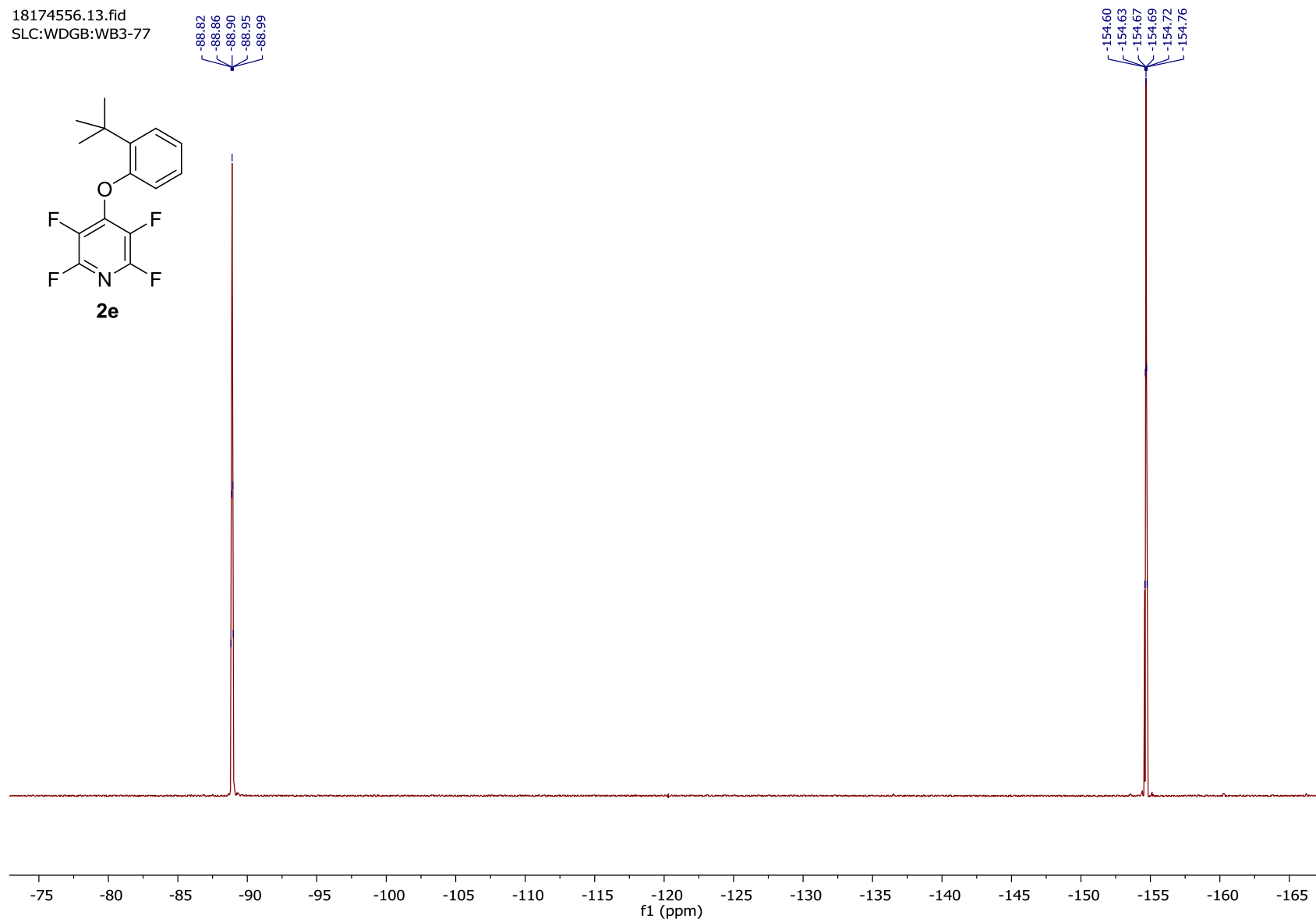
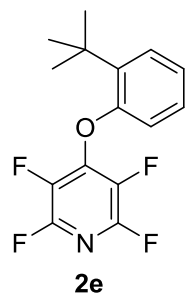
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SLC:WB:3-83



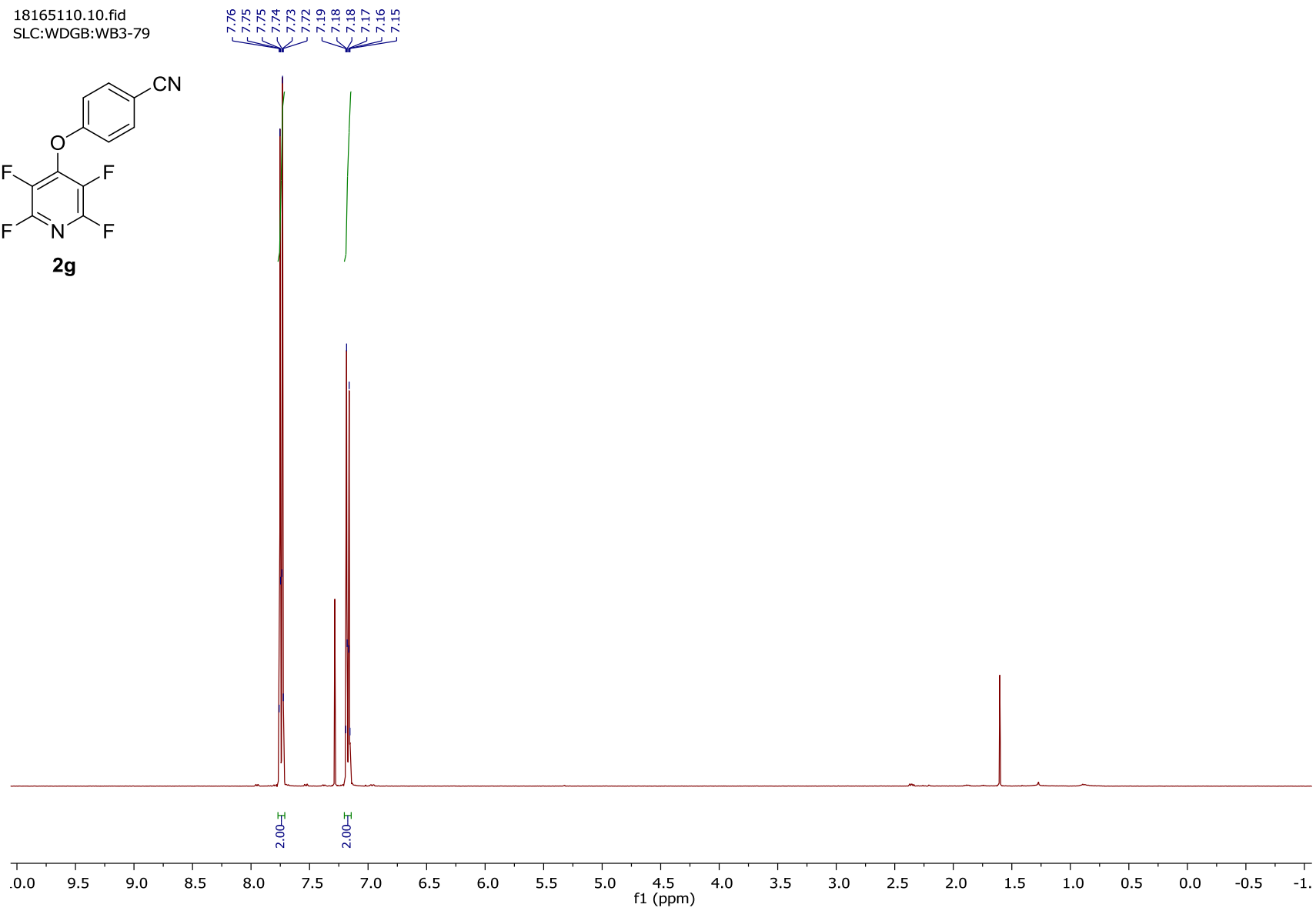
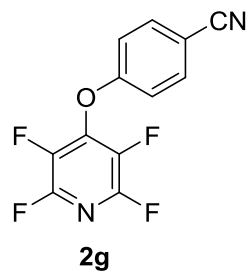
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SLC:WDGB:WB3-77



18174556.13.fid
SLC:WDGB:WB3-77



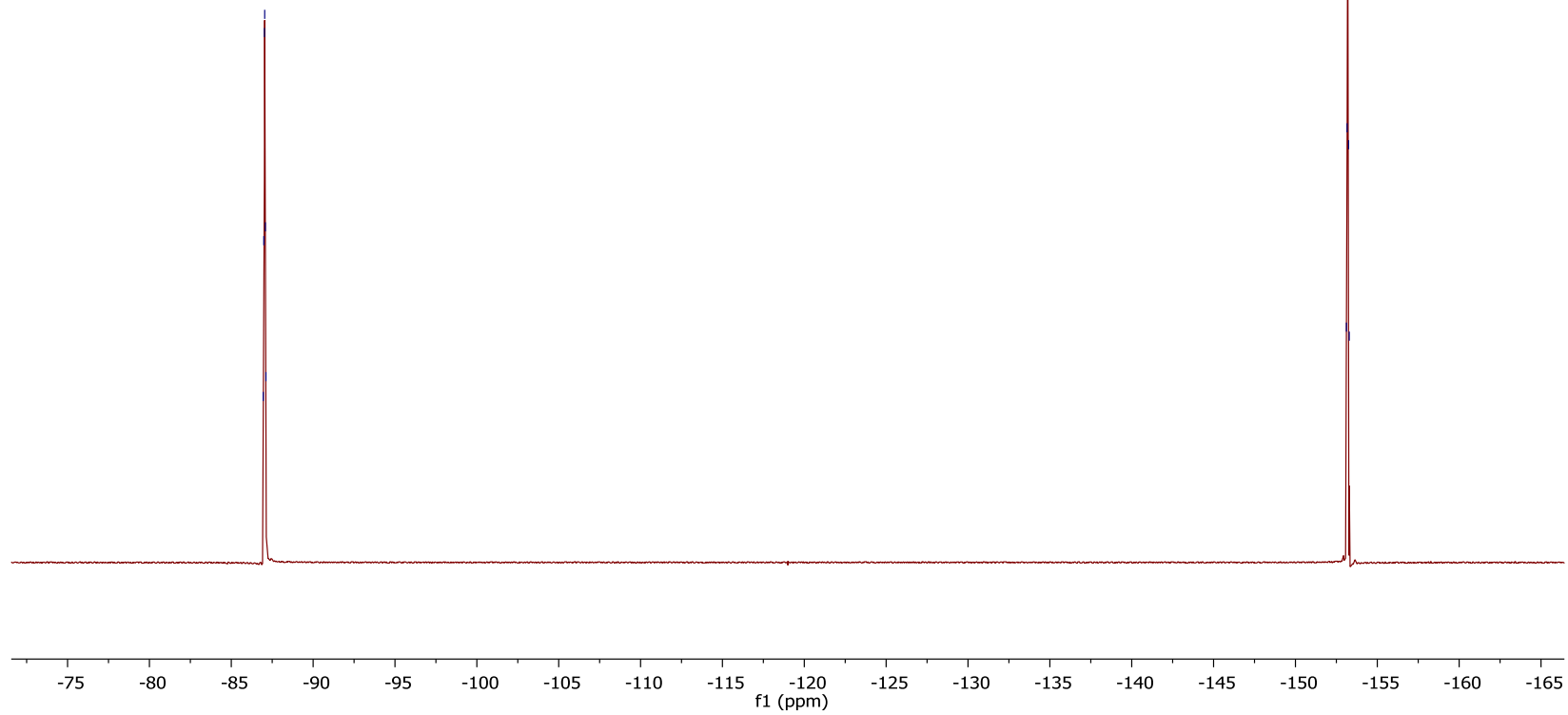
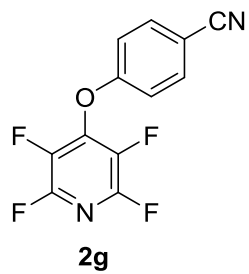
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SLC:WDGB:WB3-79

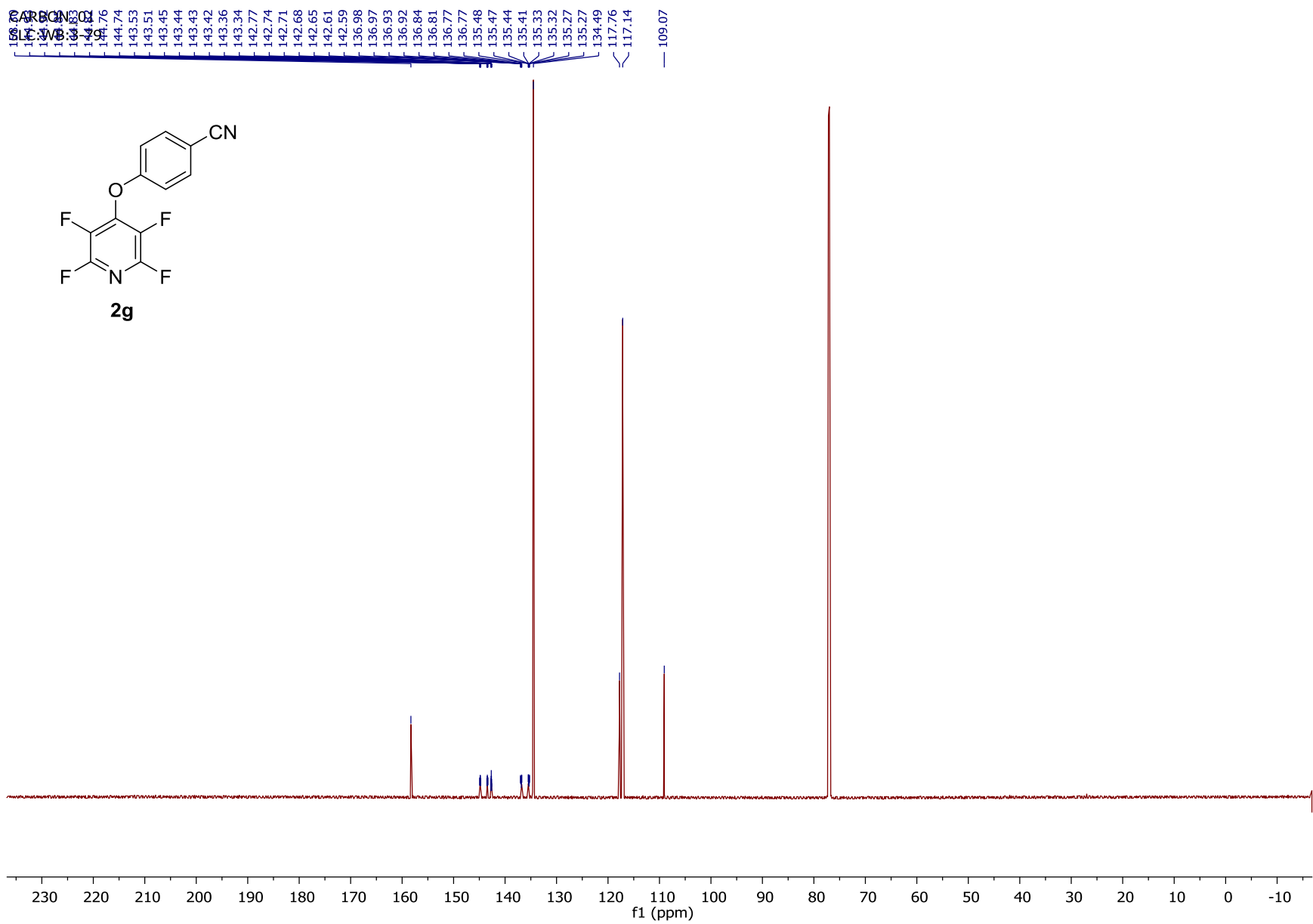


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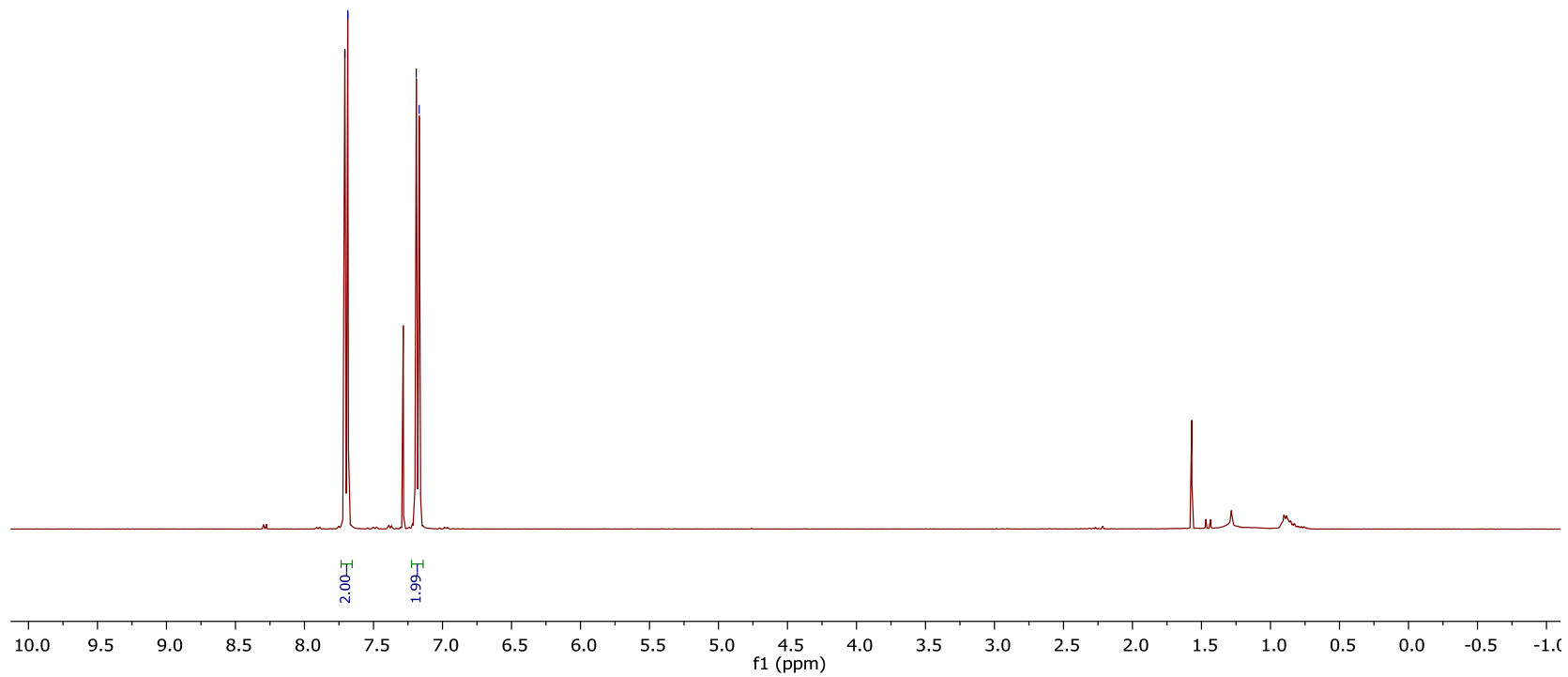
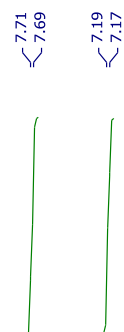
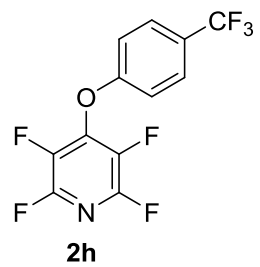
-86.95
-86.99
-87.03
-87.04
-87.08
-87.12

-153.12
-153.16
-153.19
-153.21
-153.25
-153.29

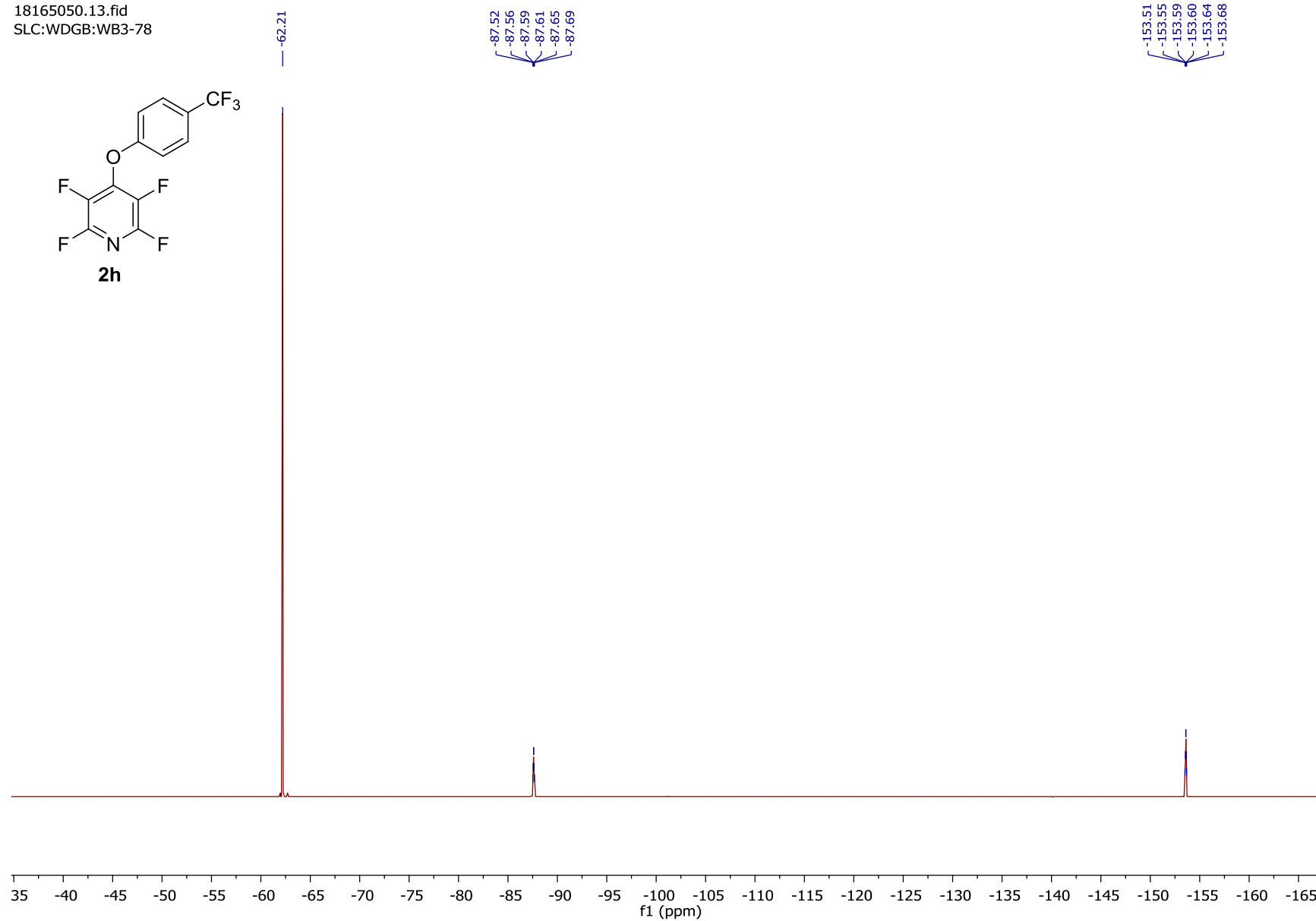
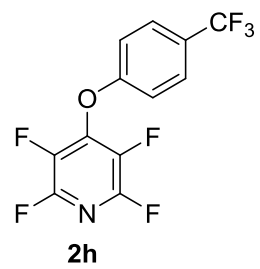




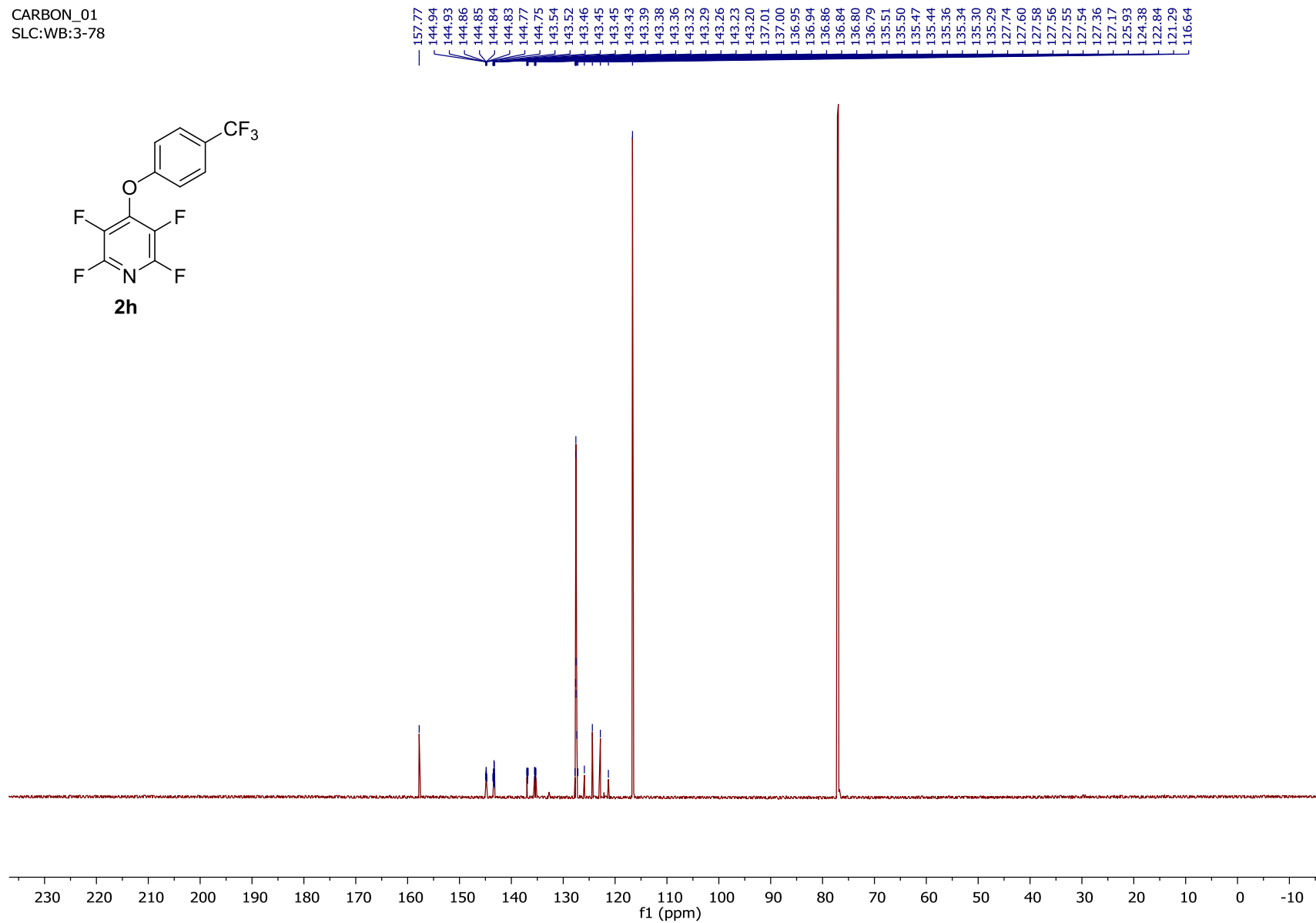
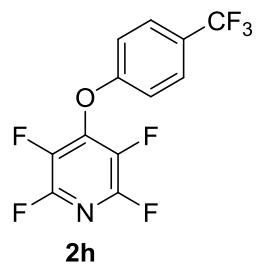
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SLC:WDGB:WB3-78



18165050.13.fid
SLC:WDGB:WB3-78



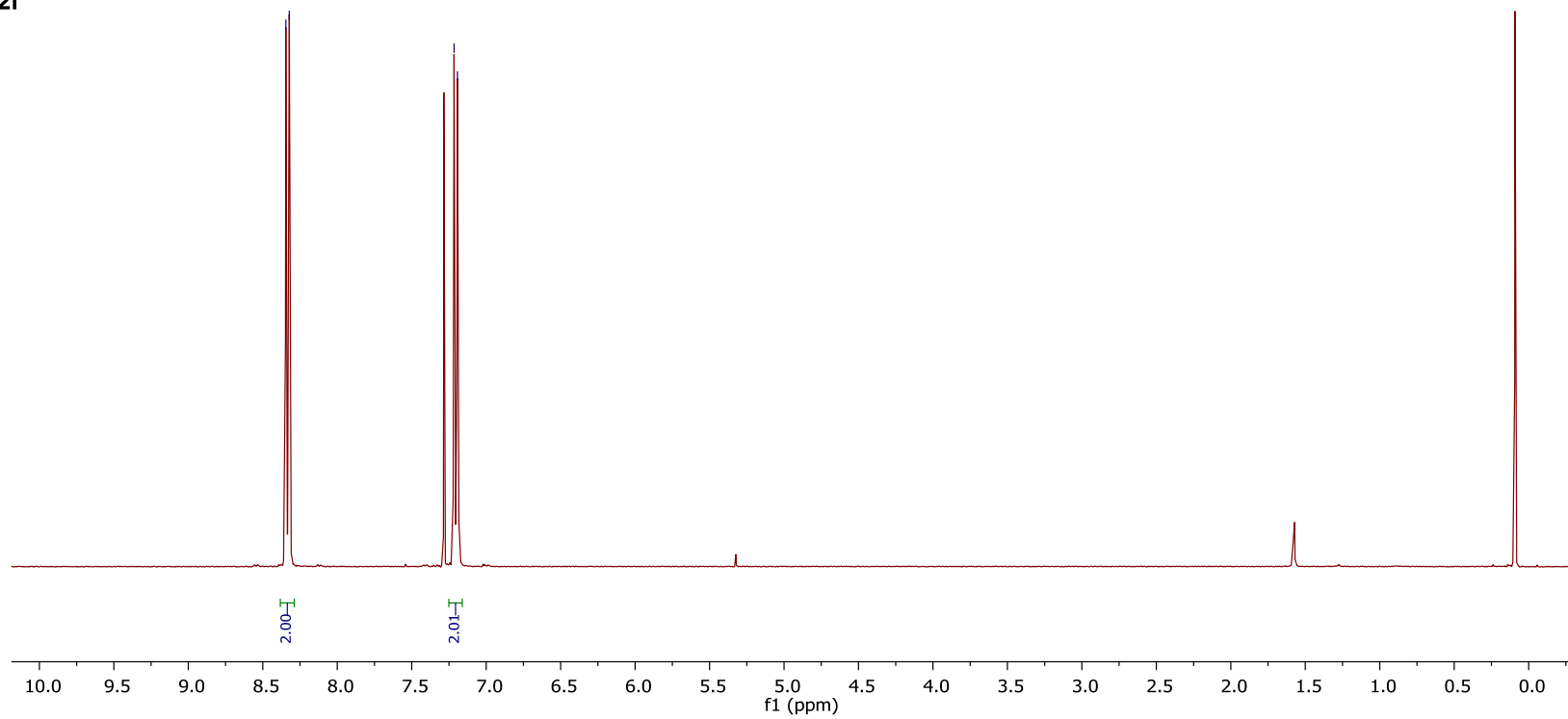
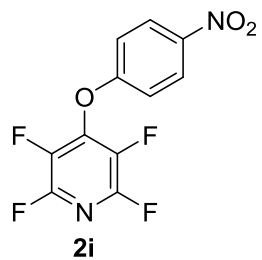
CARBON_01
SLC:WB:3-78



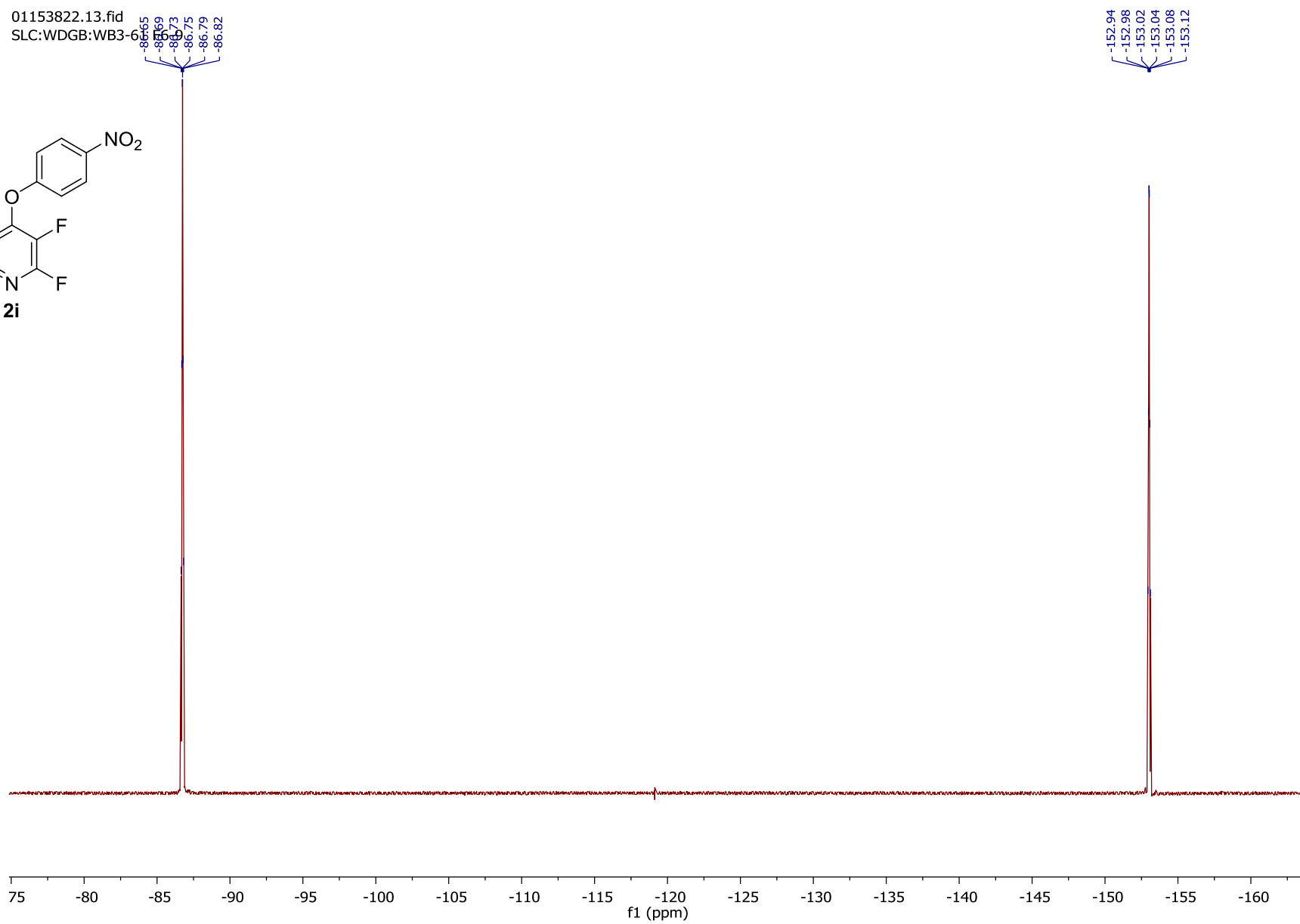
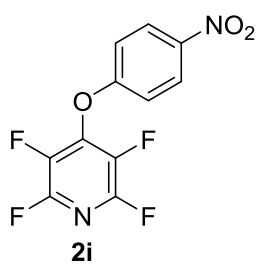
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SLC:WDGB:WB 4-NO2 TFP

8.34
8.32

7.22
7.19

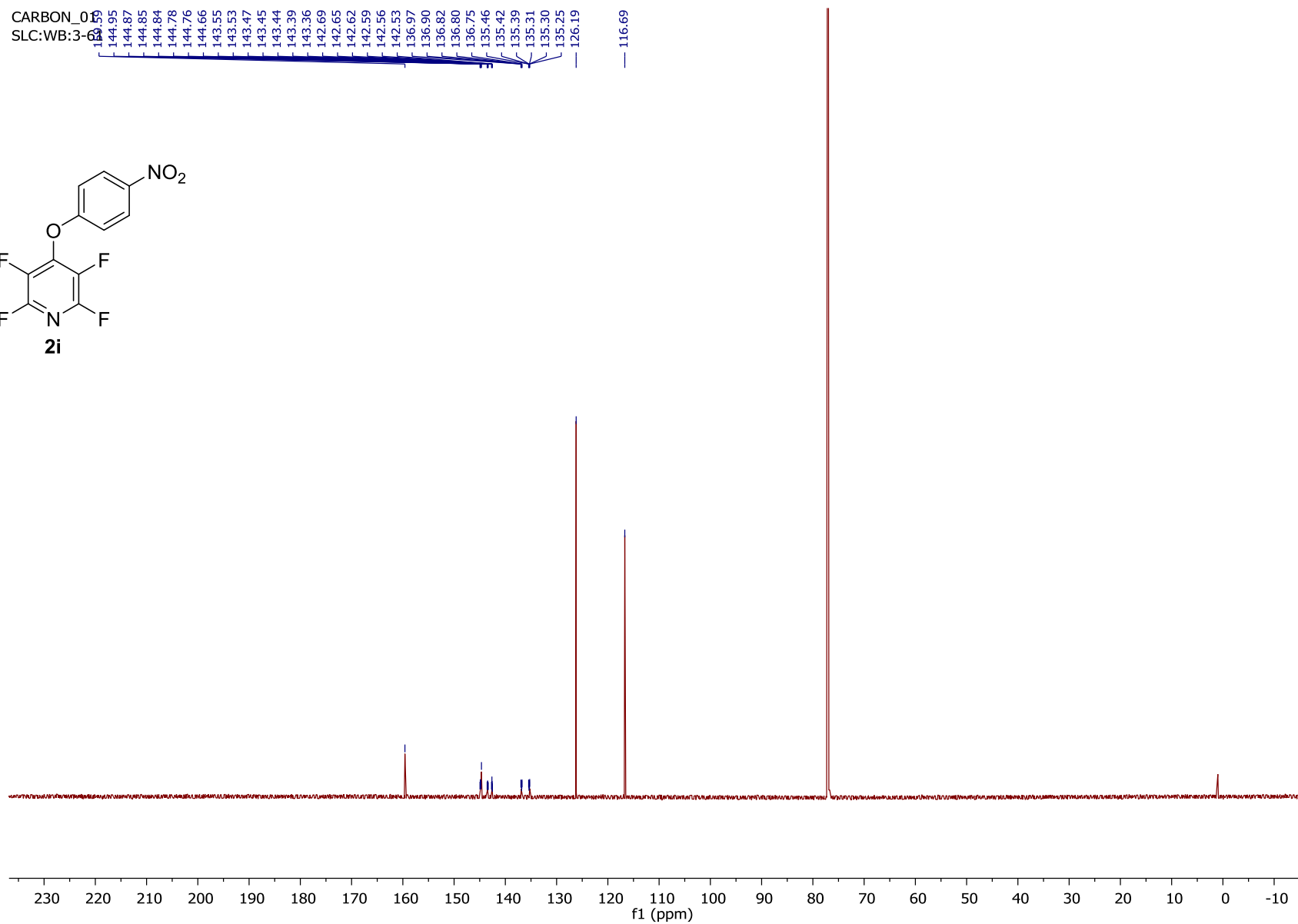
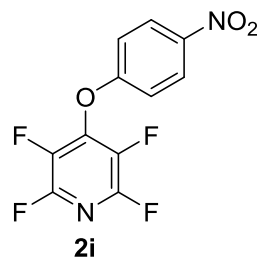


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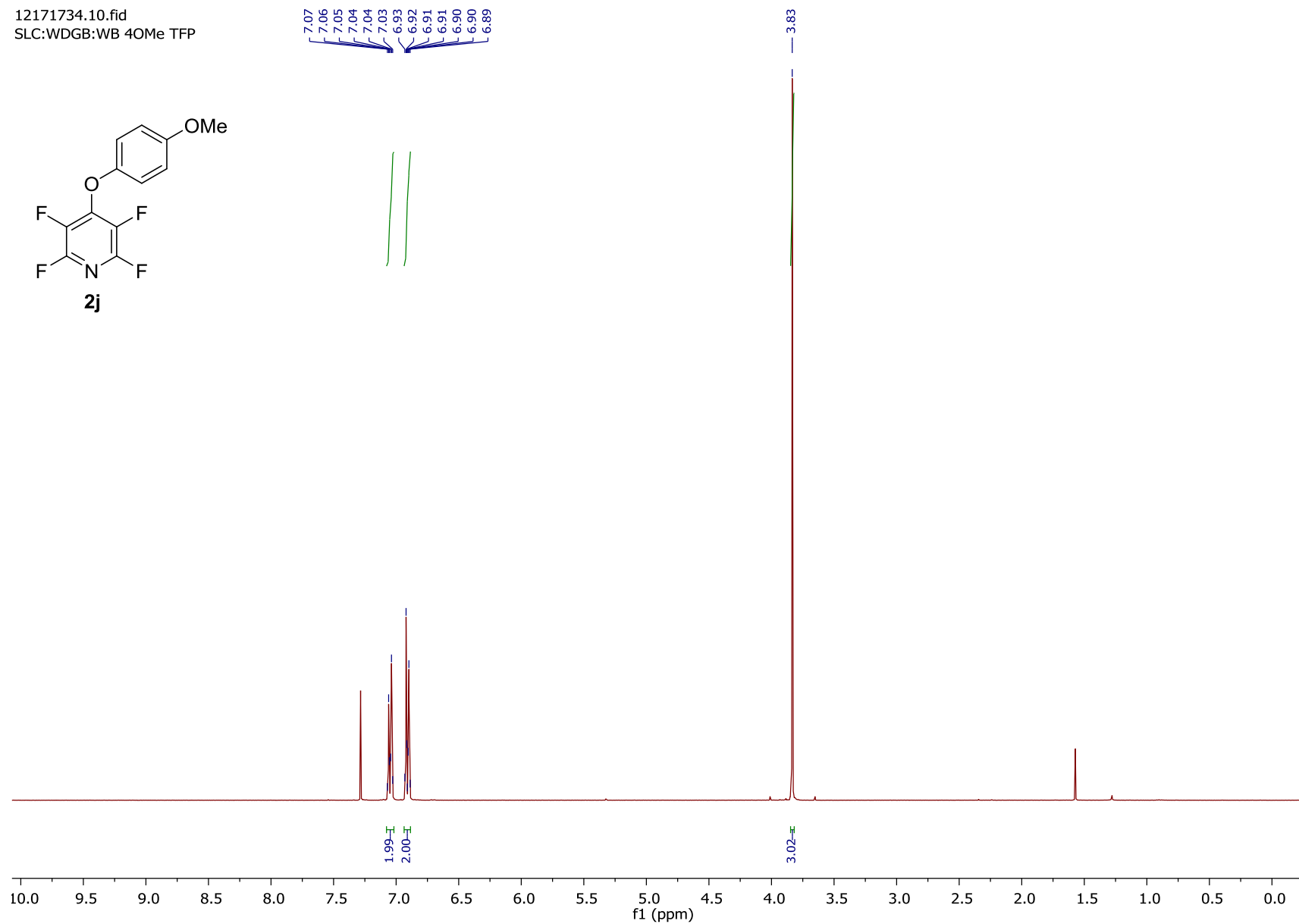
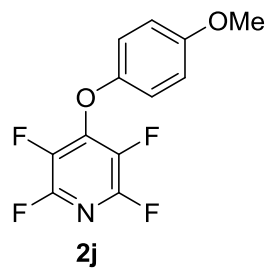


CARBON_01
SLC:WB:3-68

144.95	144.87	144.85	144.84	144.78	144.76	144.66	143.55	143.53	143.47	143.45	143.44	143.39	143.36	142.69	142.65	142.62	142.59	142.56	142.53	136.97	136.90	136.82	136.80	136.75	135.46	135.42	135.39	135.31	135.30	135.25	126.19	116.69
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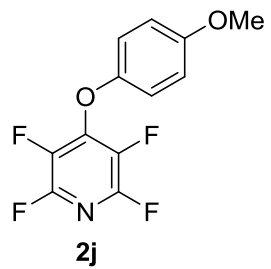


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SLC:WDGB:WB 4OMe TFP

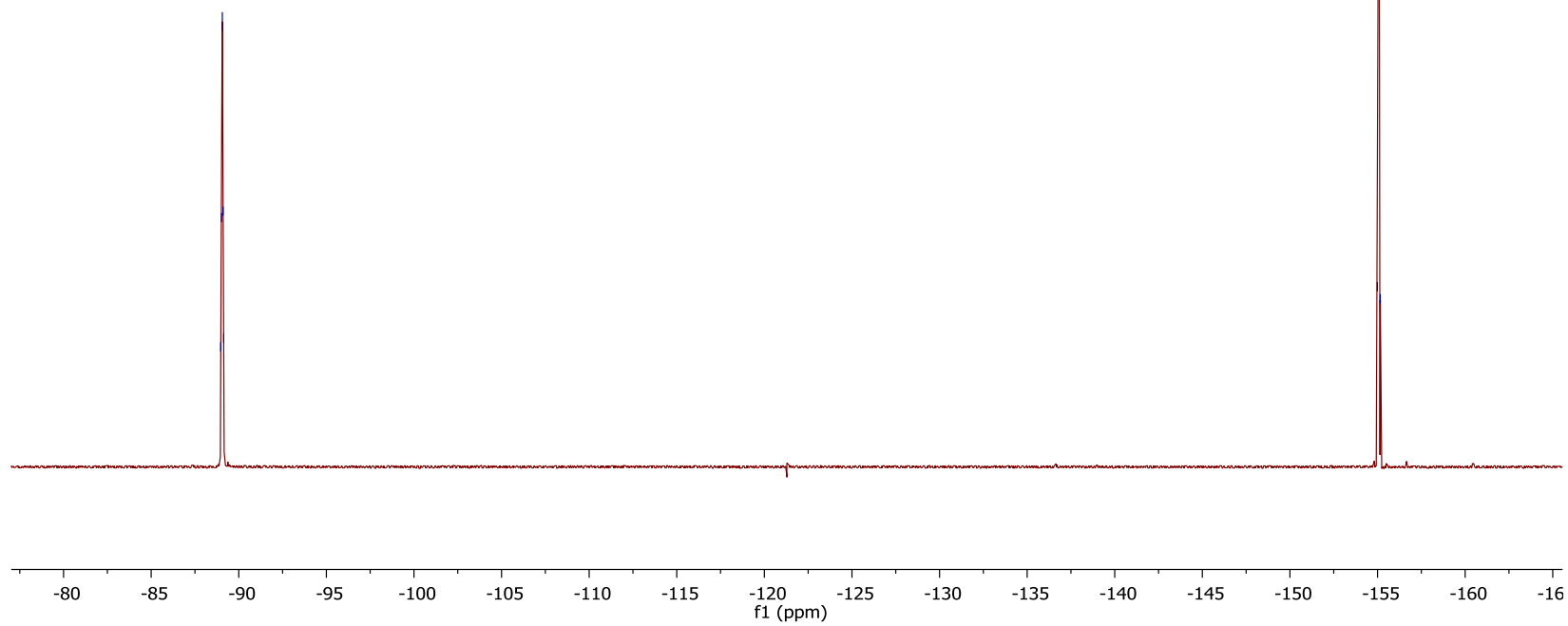


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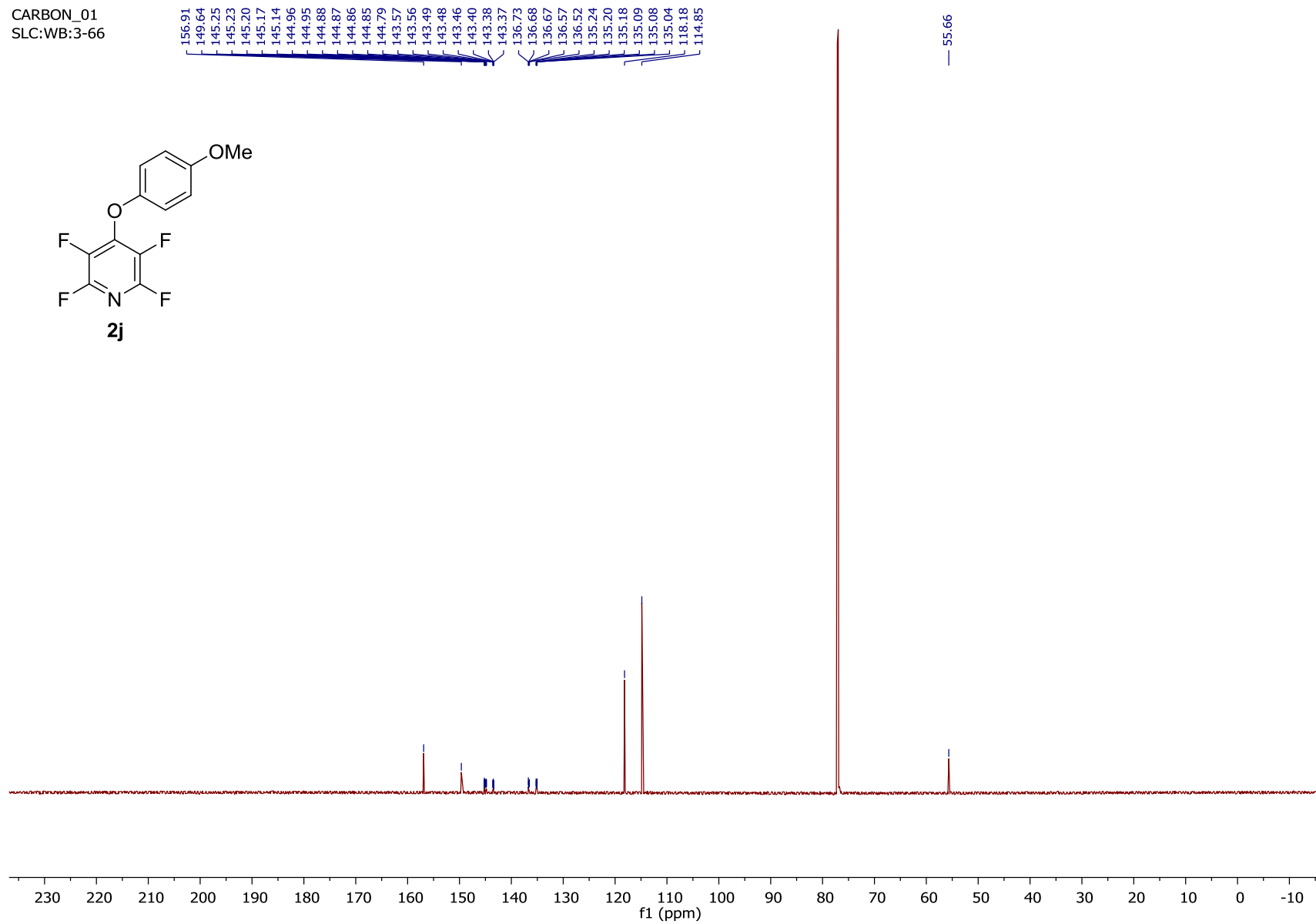
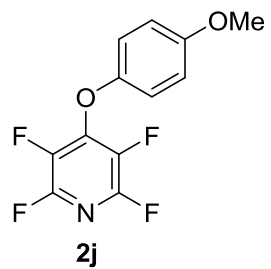
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-89.06
-89.10
-89.14



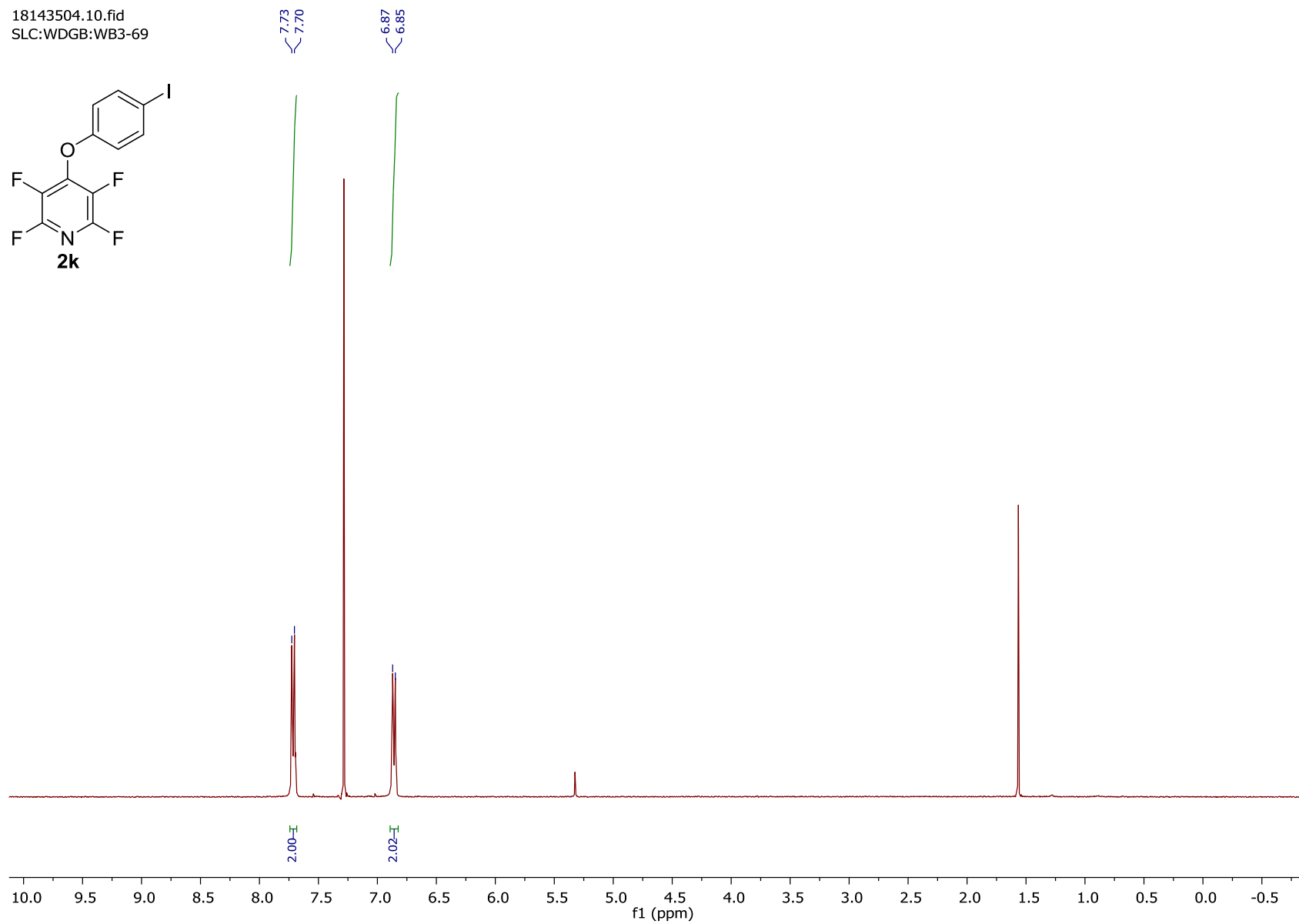
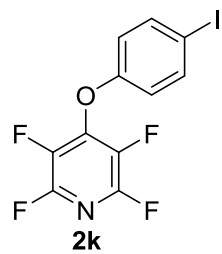
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-155.16



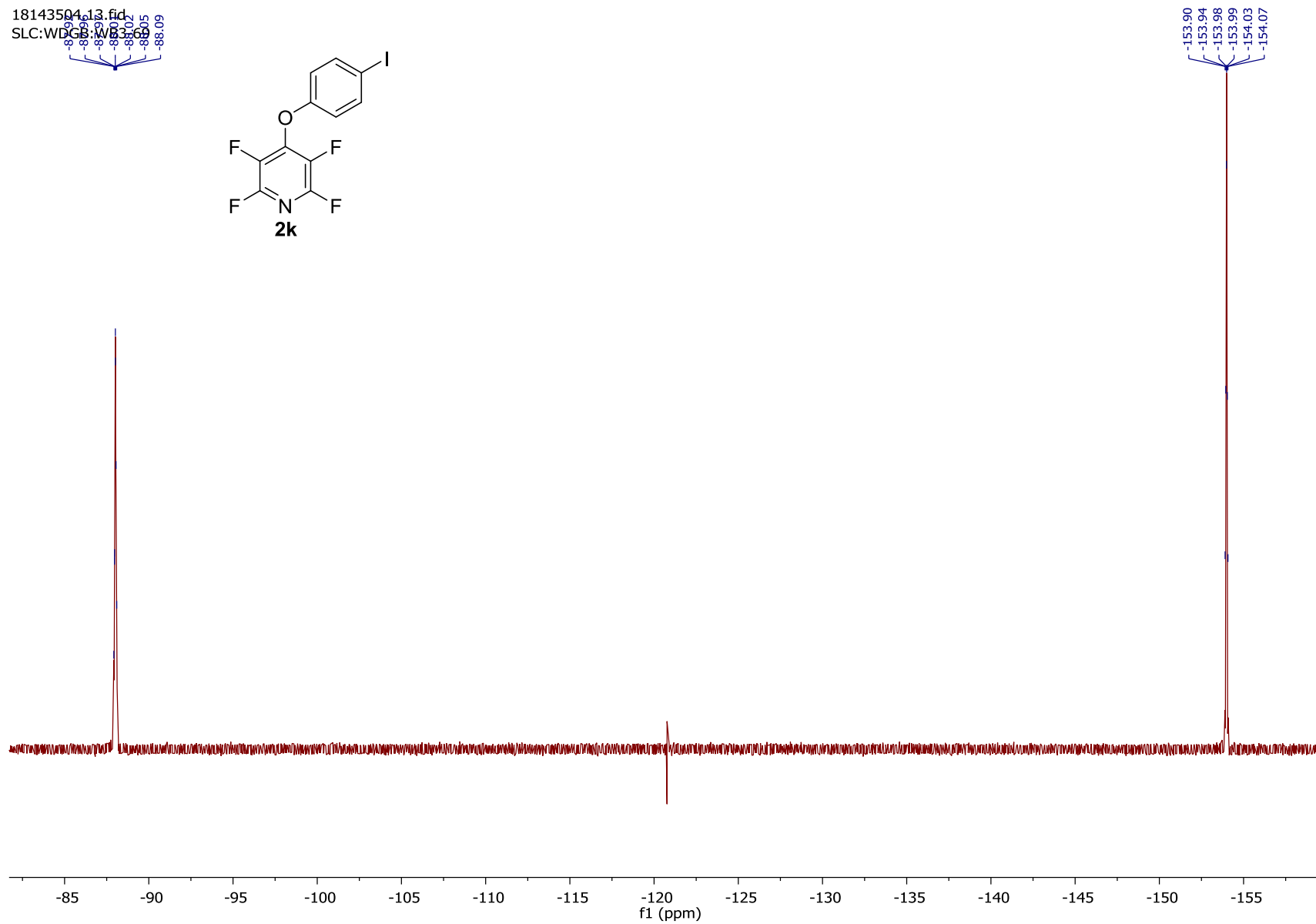
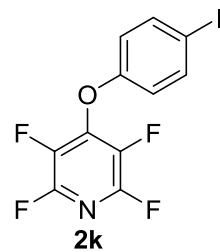
CARBON_01
SLC:WB:3-66



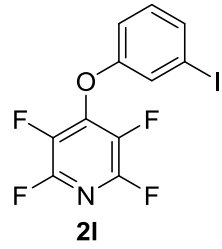
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SLC:WDGB:WB3-69



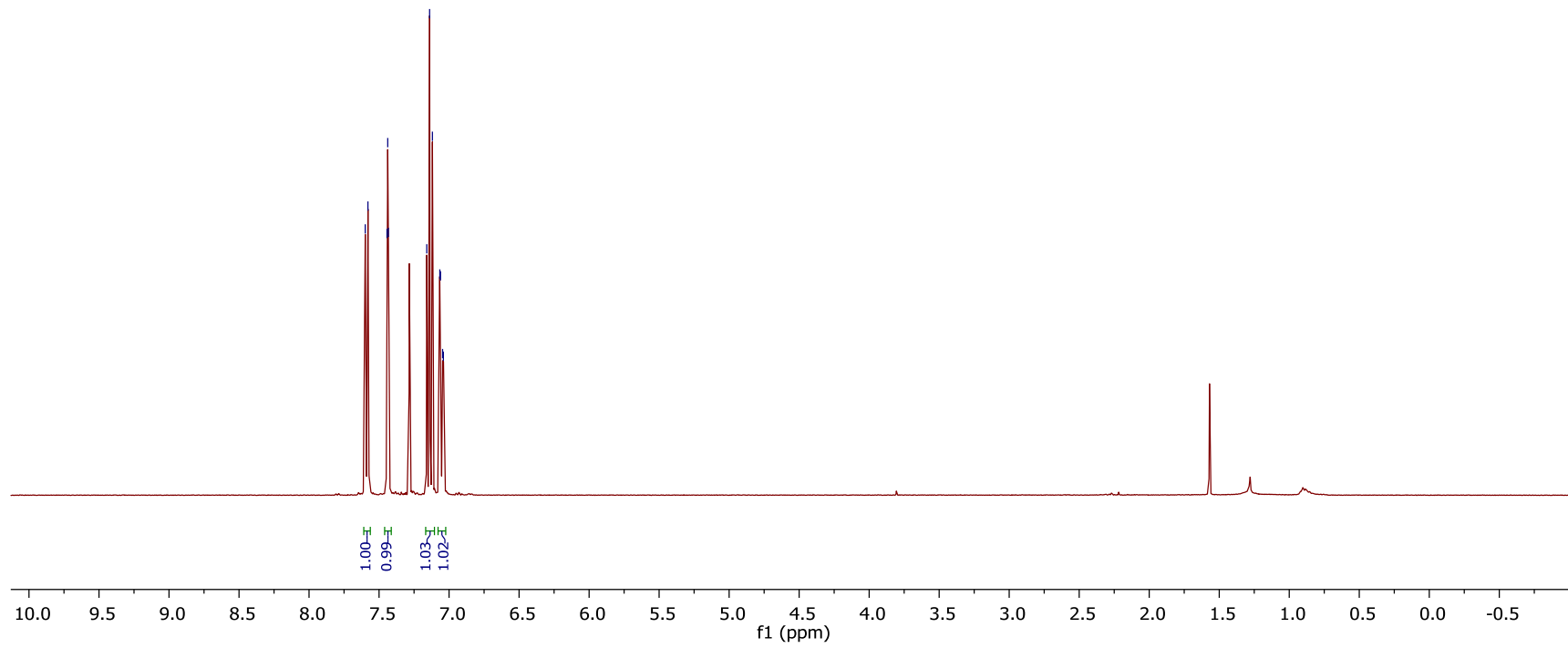
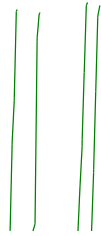
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SLC:WDGB:WB3:66



18143523.10.fid
SLC:WDGB:WB3-71

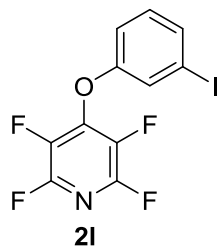


7.60
7.58
7.44
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7.14
7.12
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7.06
7.05
7.04

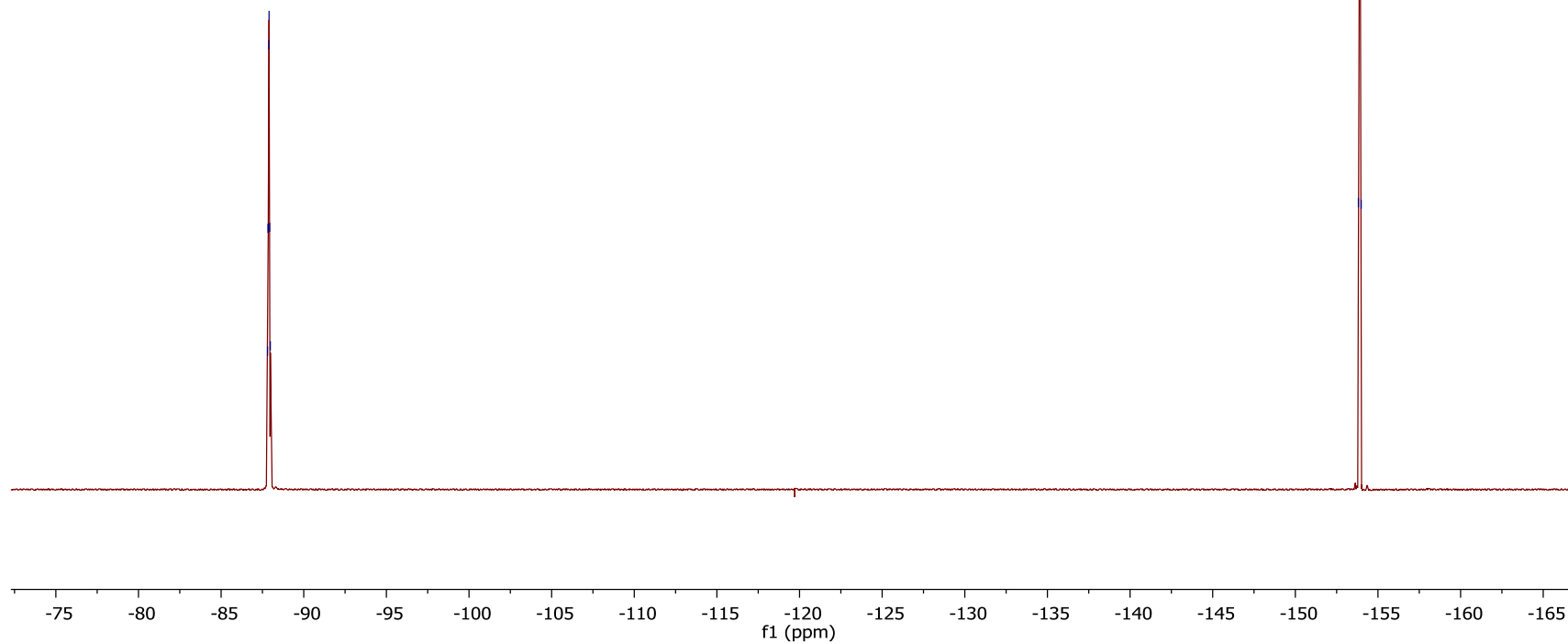


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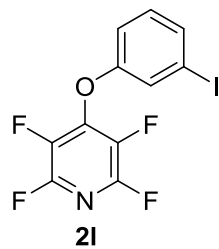
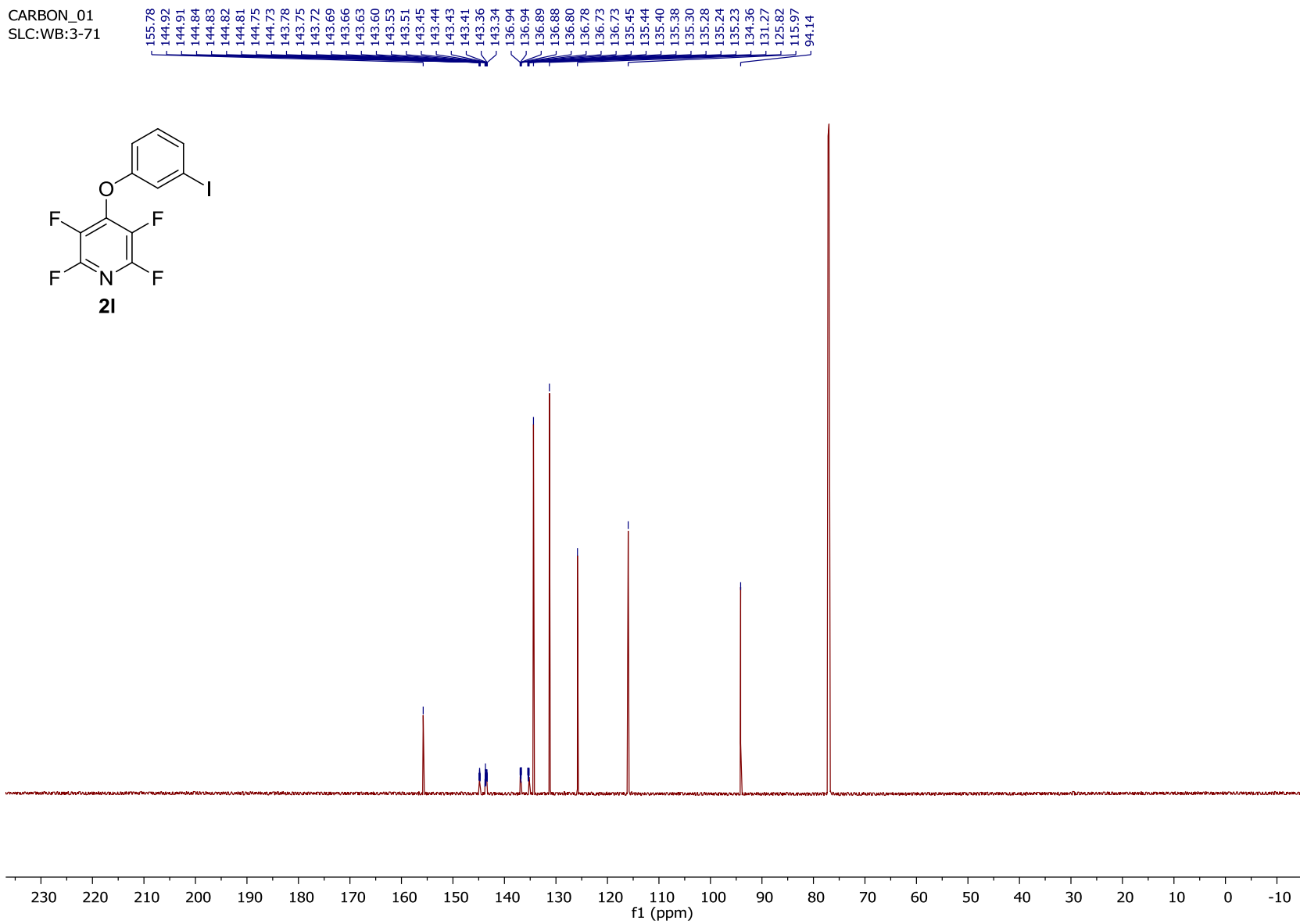
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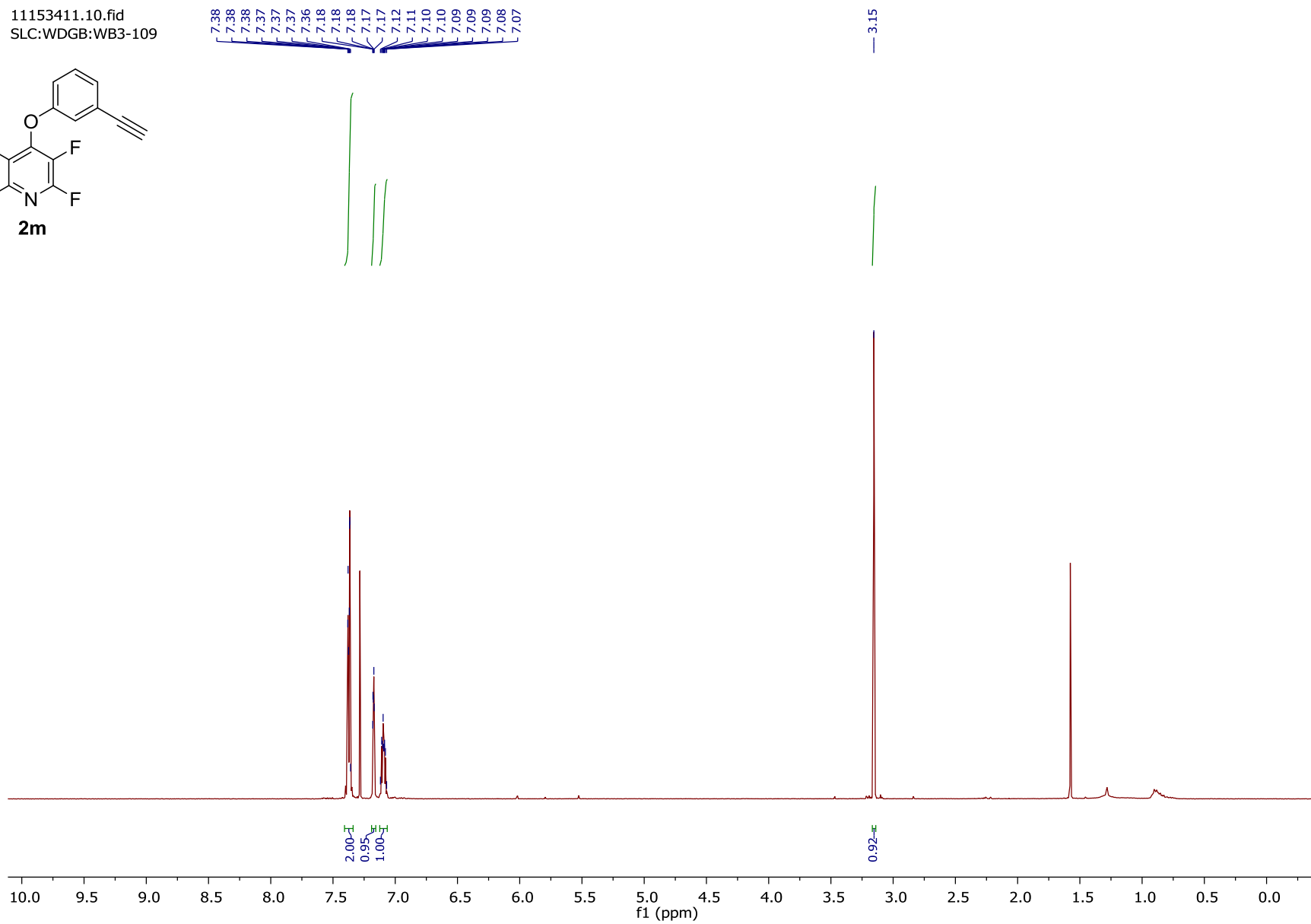
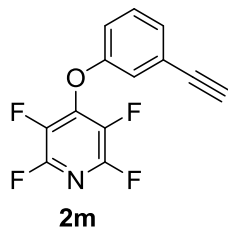
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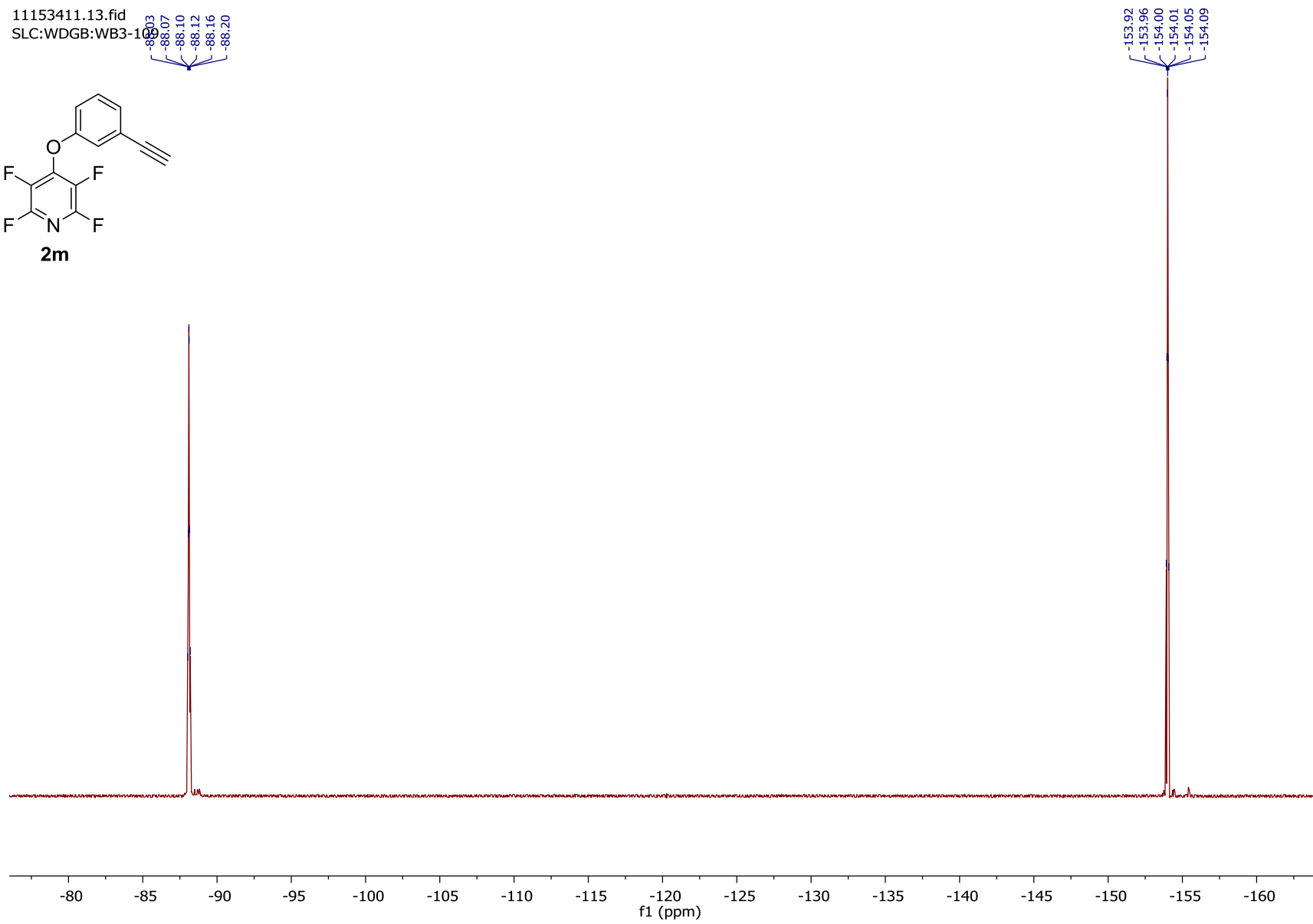
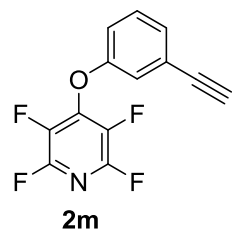
CARBON_01
SLC:WB:3-71



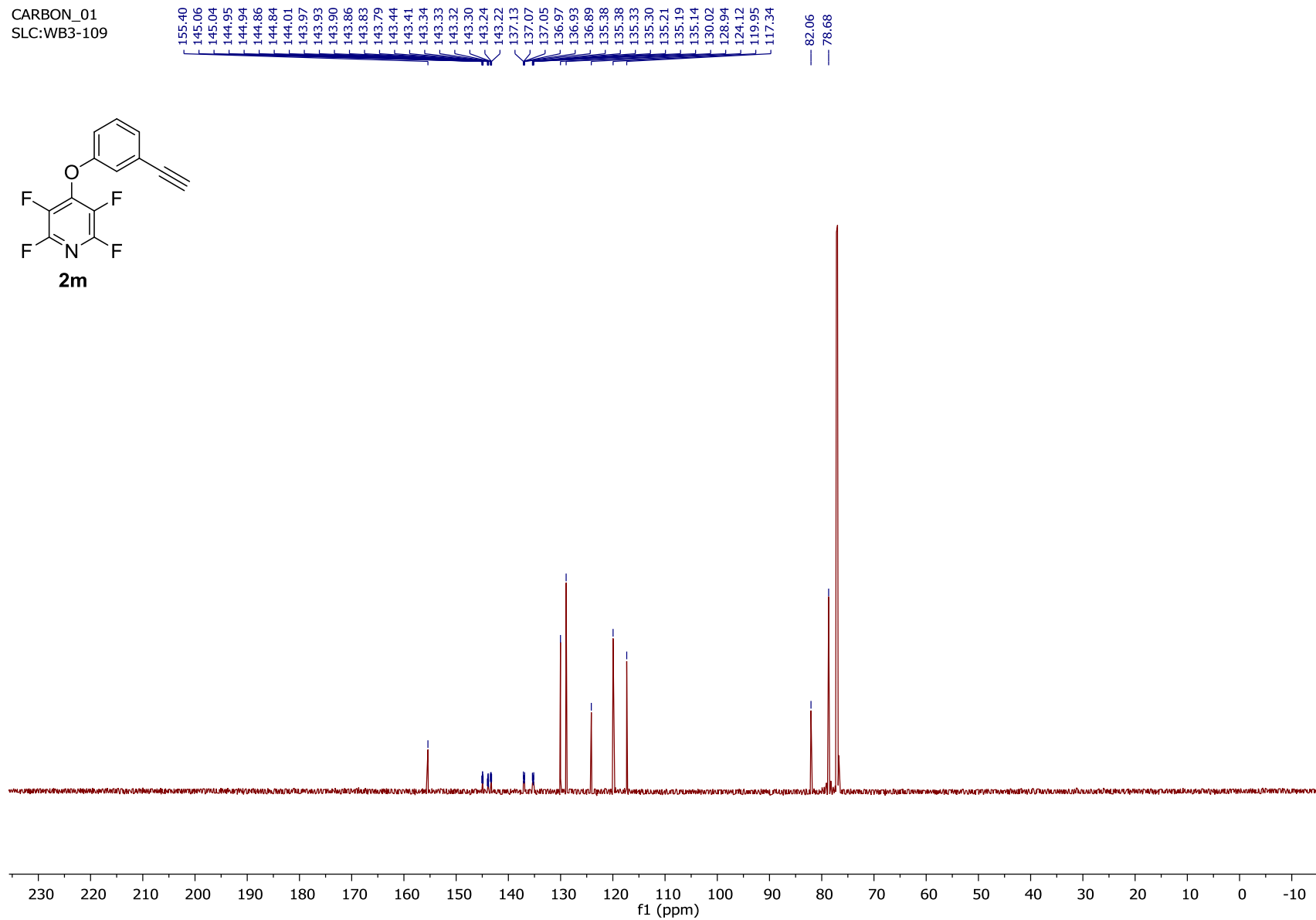
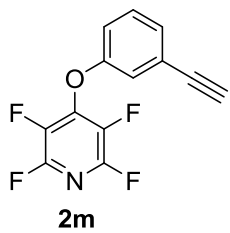
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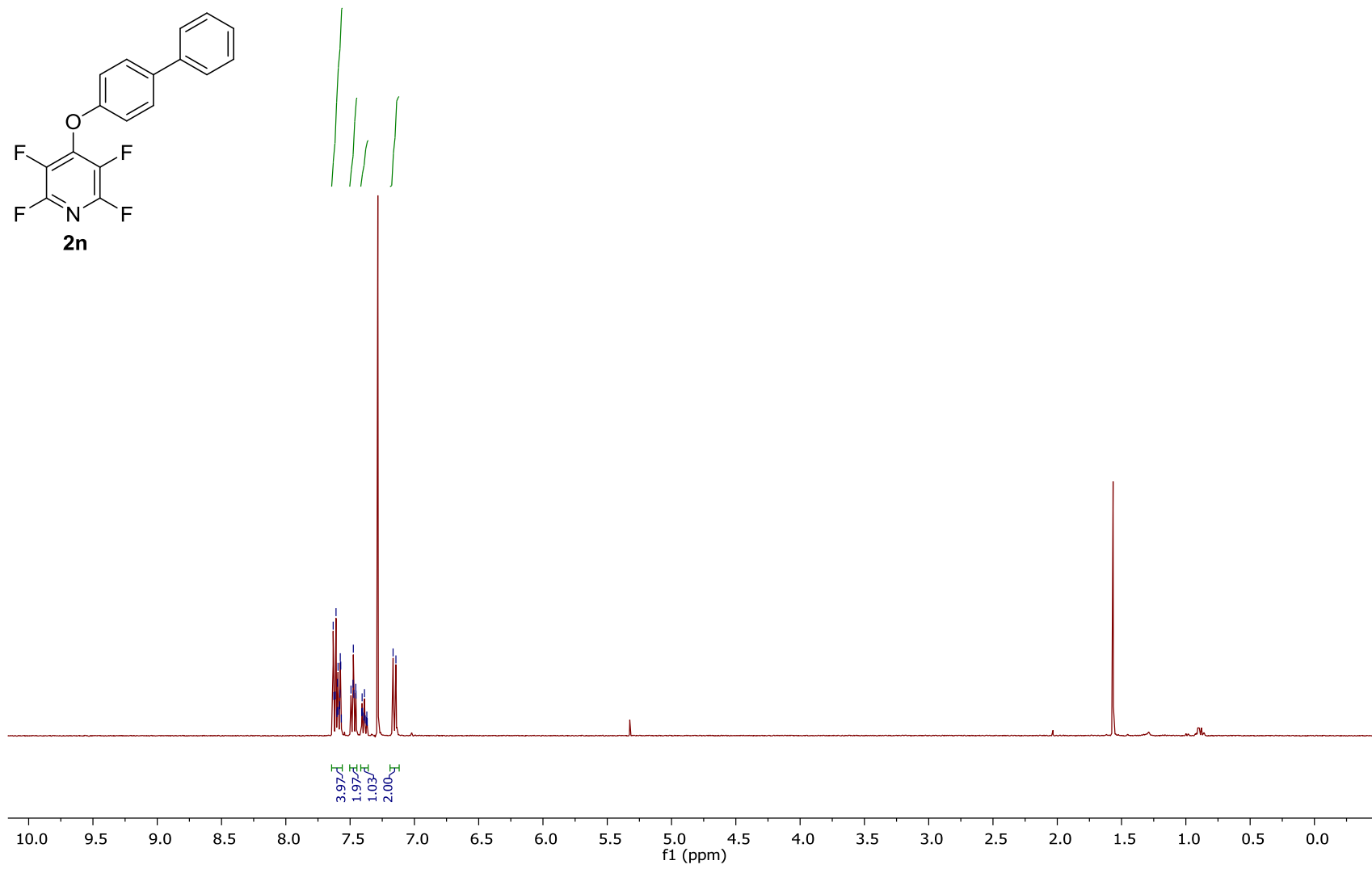
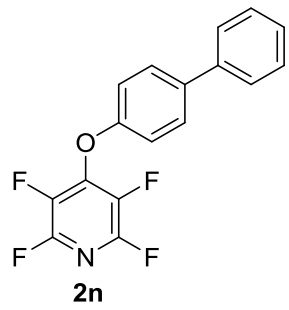
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SLC:WDGB:WB3-10



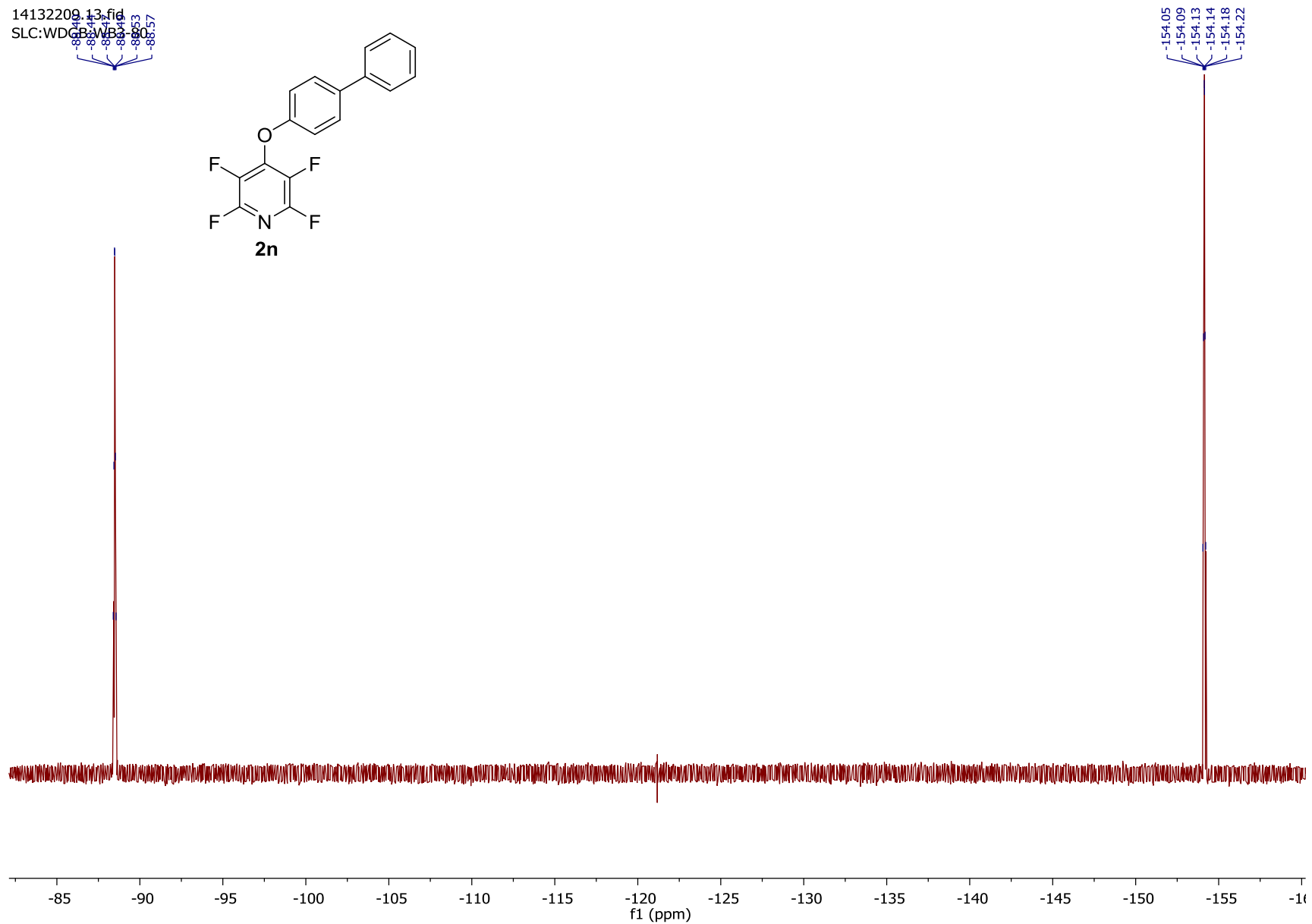
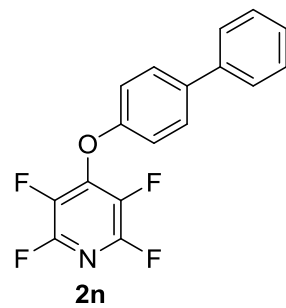
CARBON_01
SLC:WB3-109



14132209.10.f1
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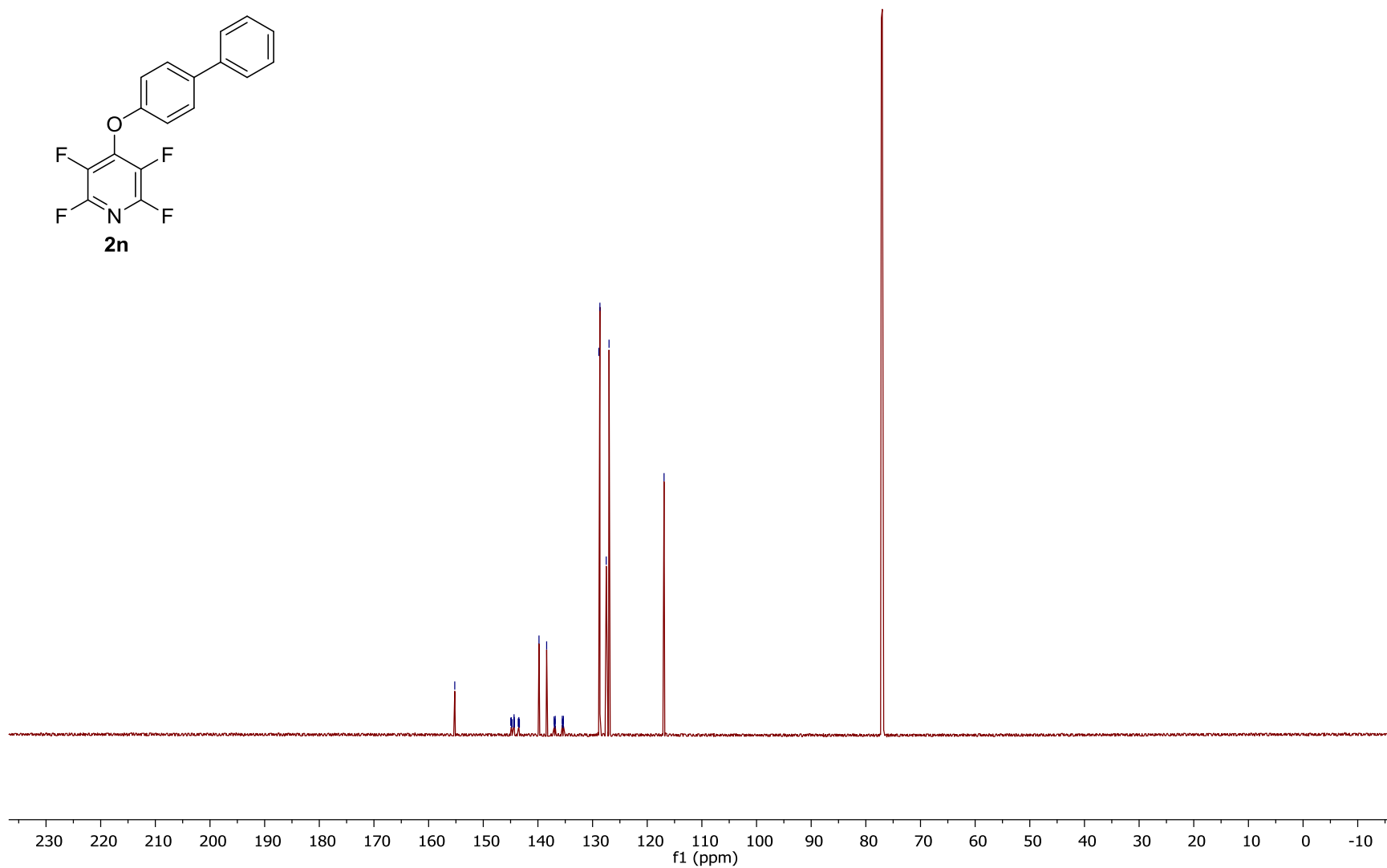
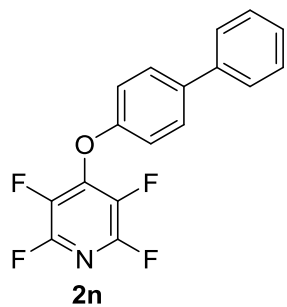


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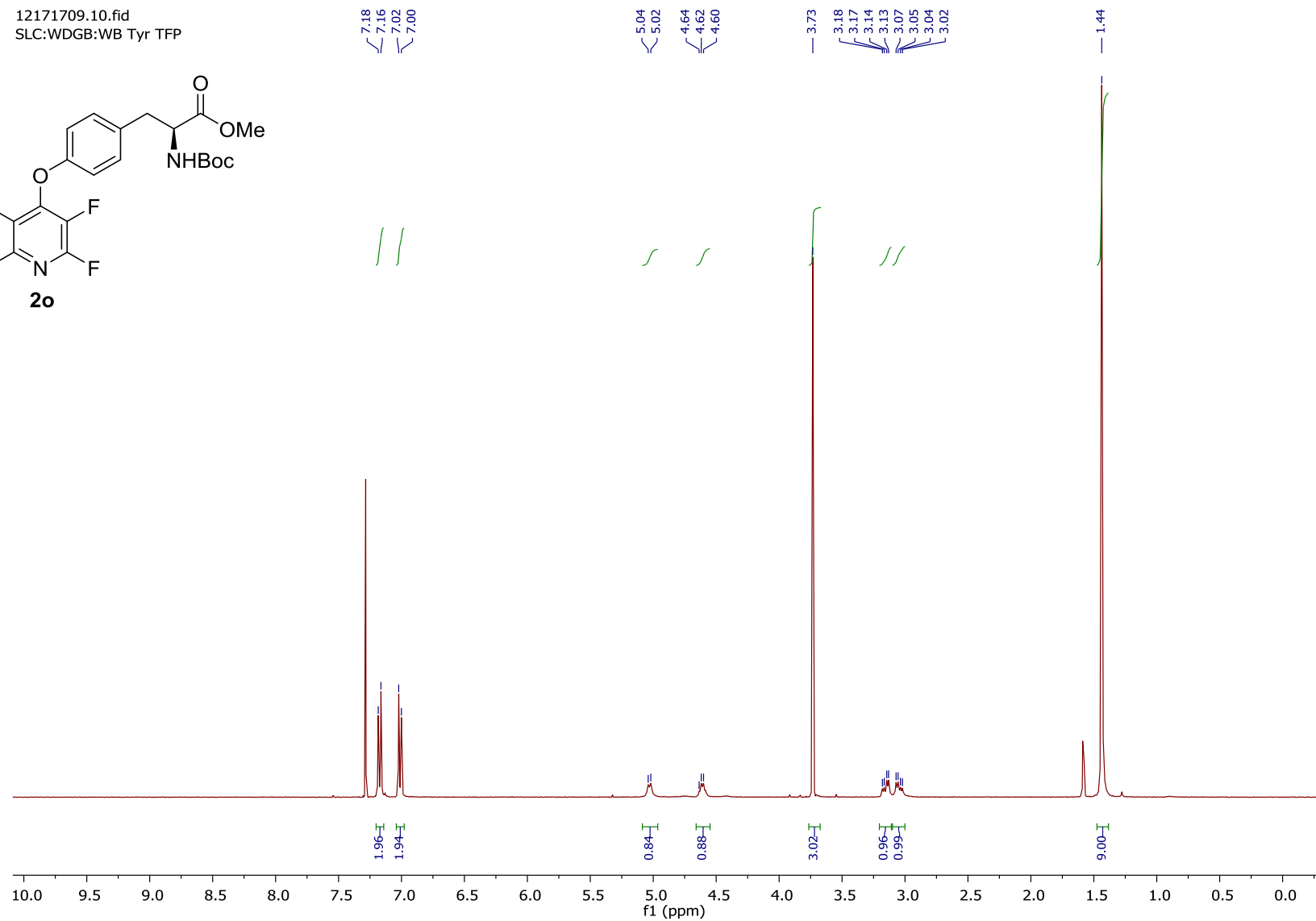
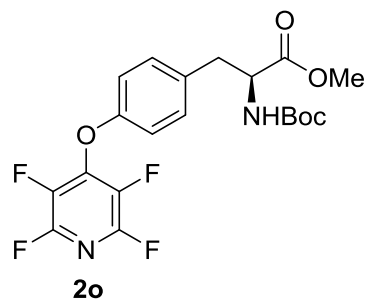


CARBON_01
SLC:WB:3-80

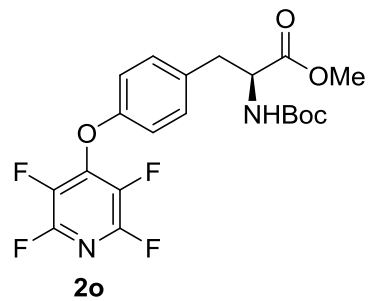
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144.43
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144.37
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144.30
143.58
143.56
143.49
143.46
143.41
143.39
139.80
138.40
137.03
136.99
136.98
136.89
136.87
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135.38
135.34
128.85
128.65
127.50
126.99
116.92



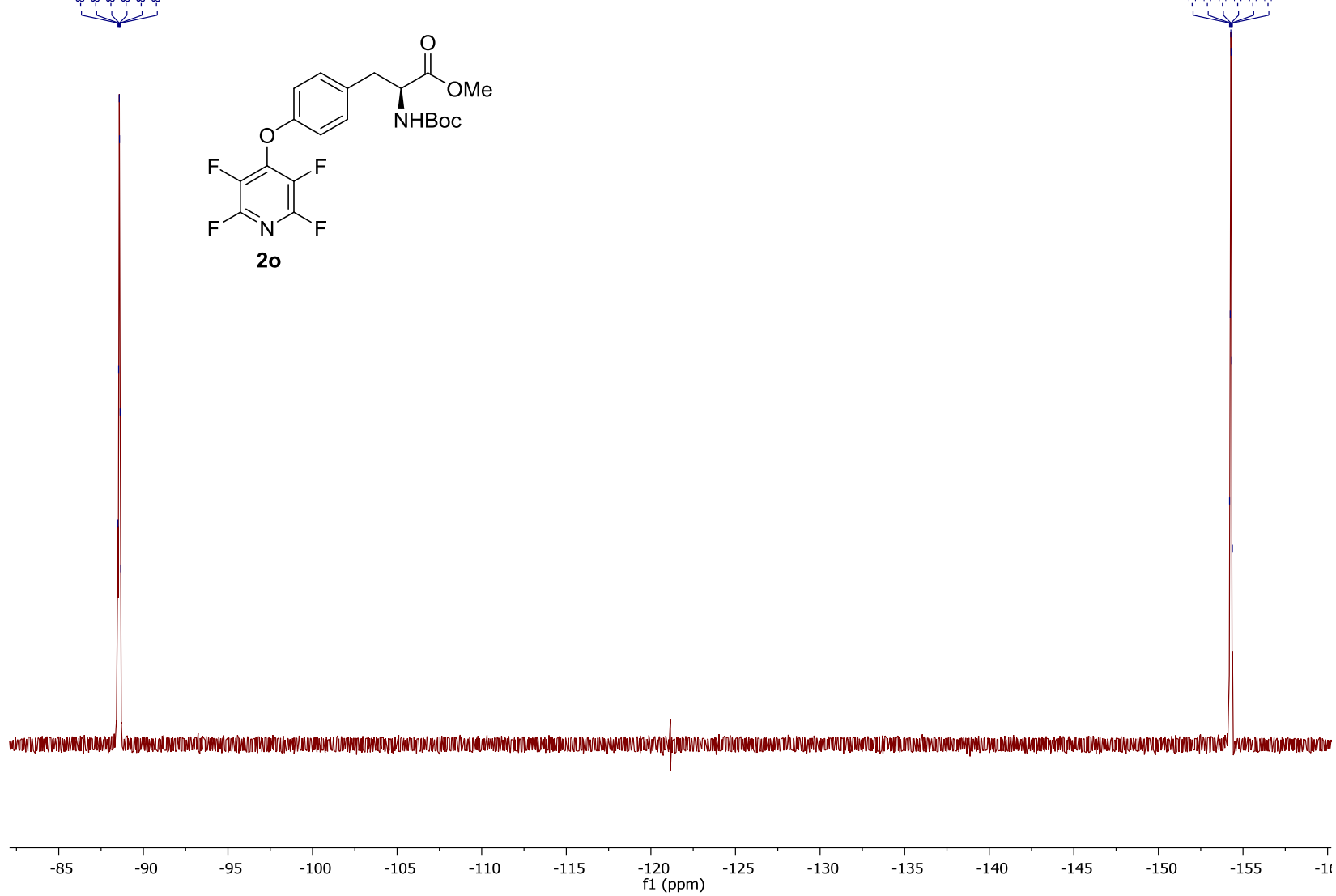
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SLC:WDGB:WB Tyr TFP



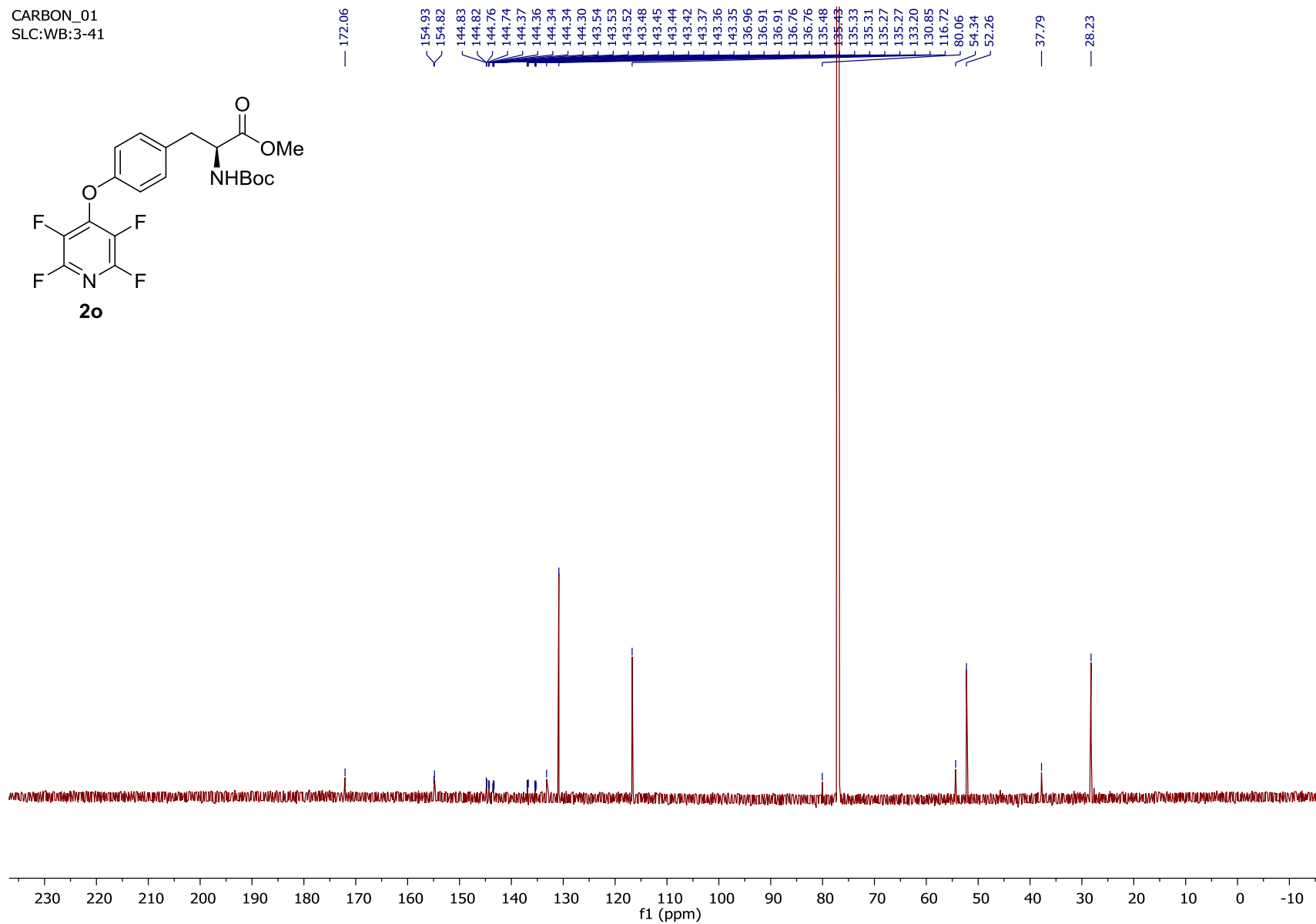
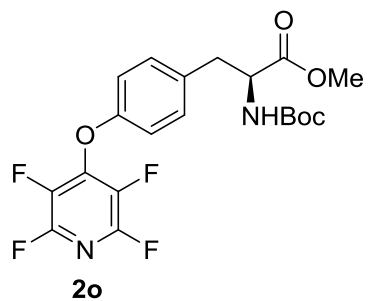
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-88.67



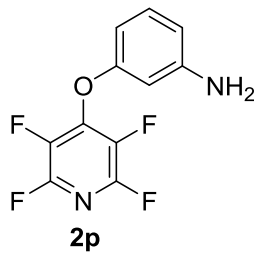
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CARBON_01
SLC:WB:3-41

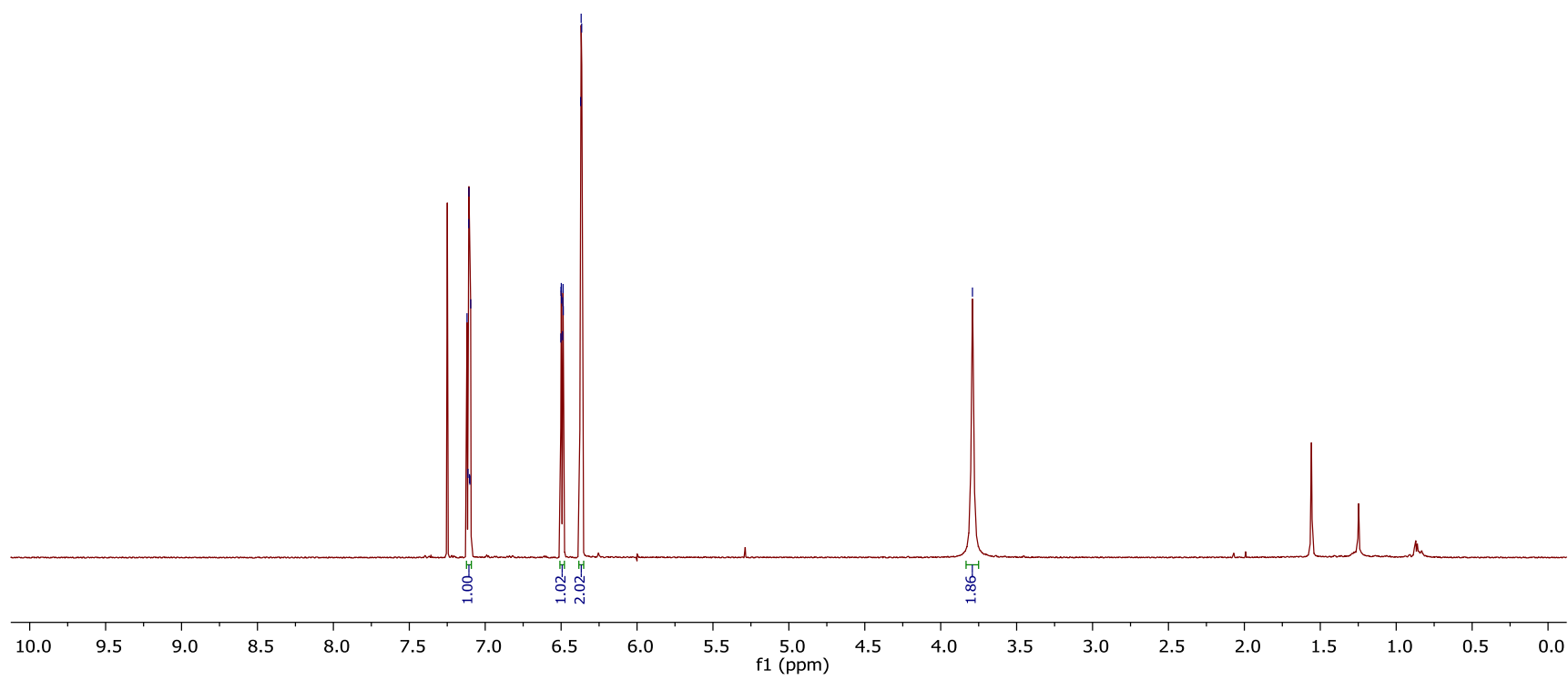


PROTON_01
SLC:WB3-122



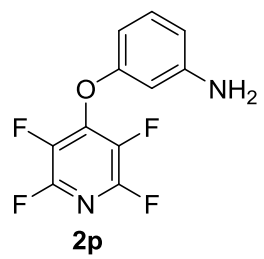
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7.10
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6.50
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6.49
6.49
6.49
6.37
6.36

3.79

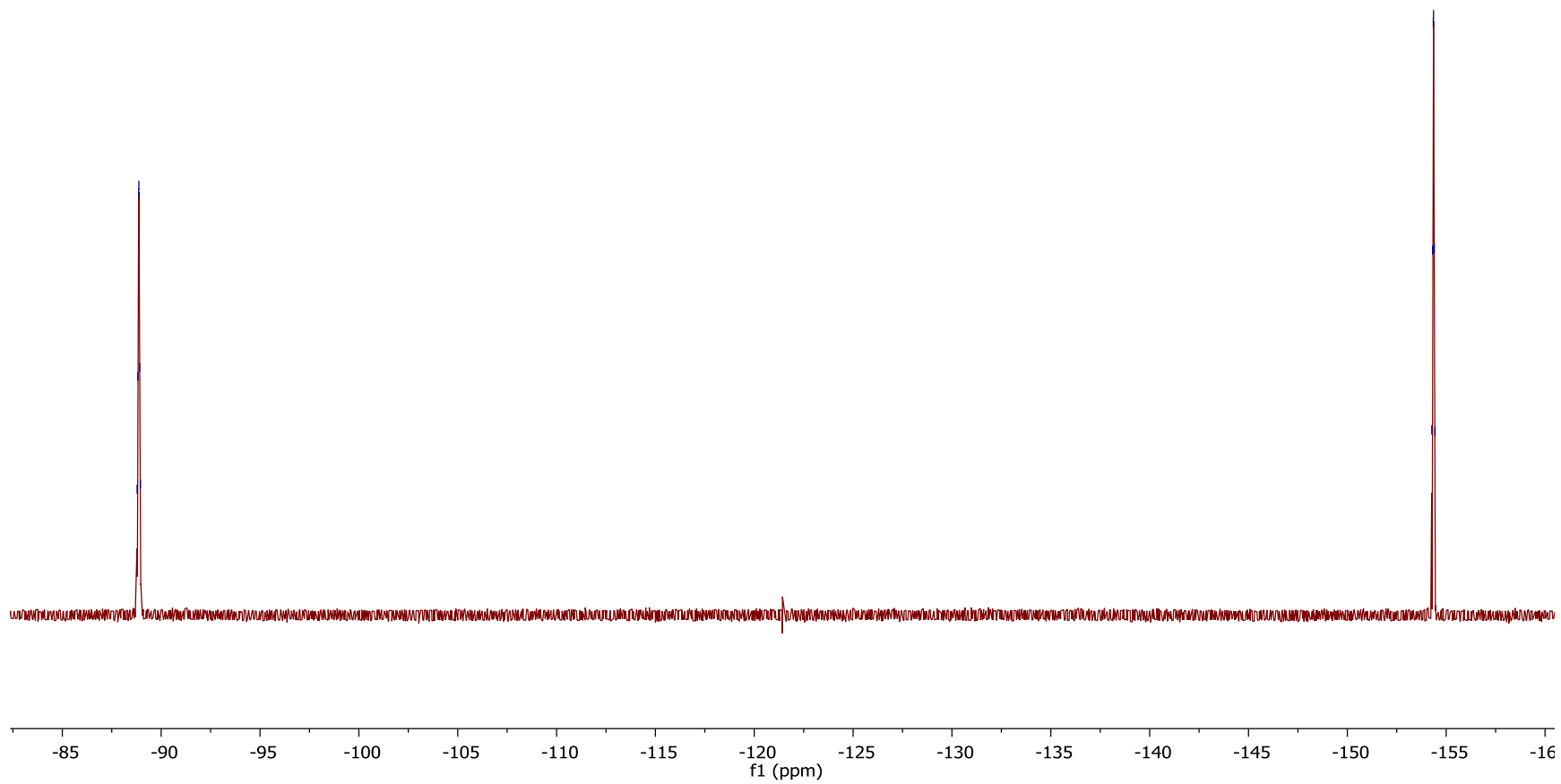


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SLC:WDGBWV22

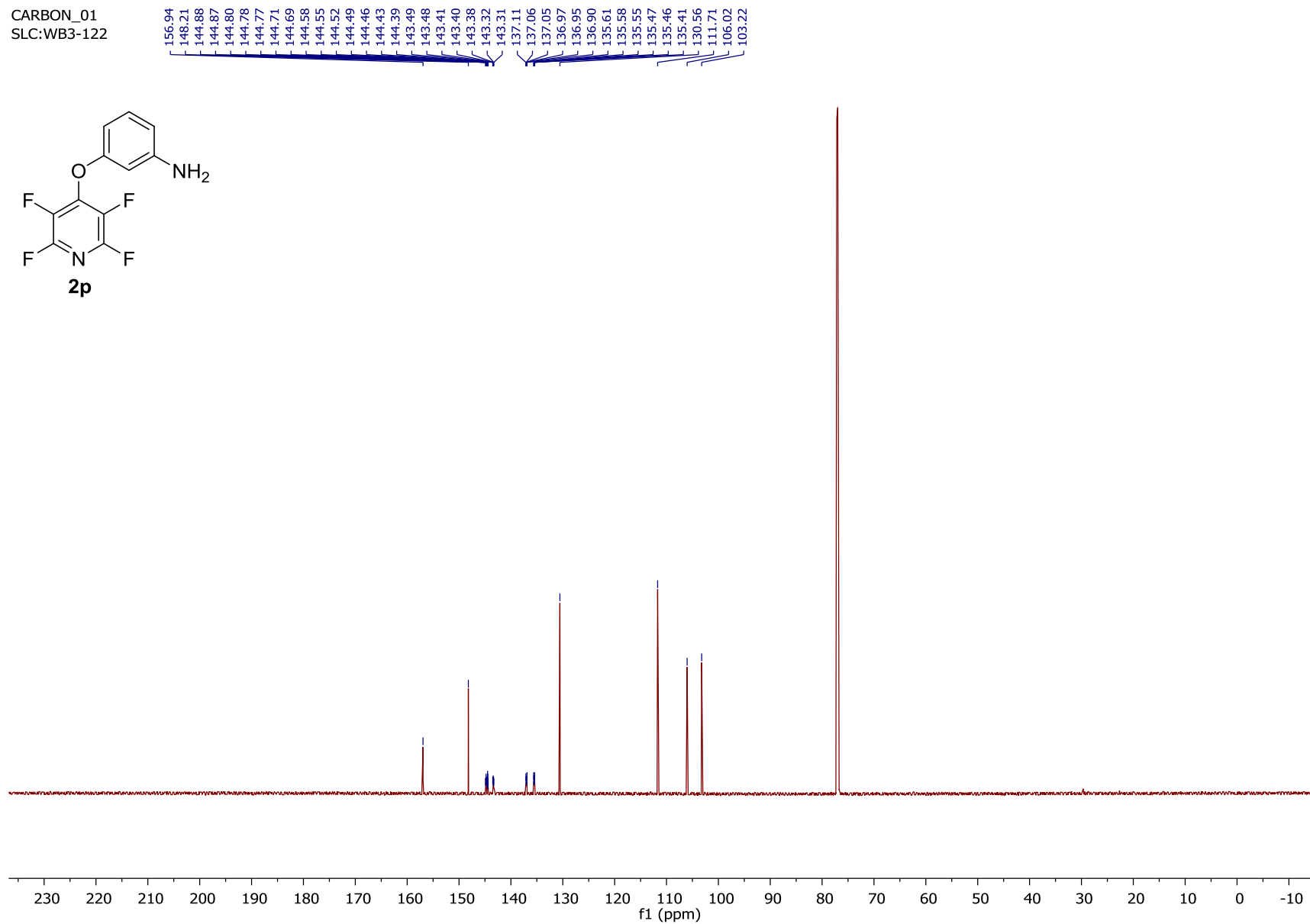
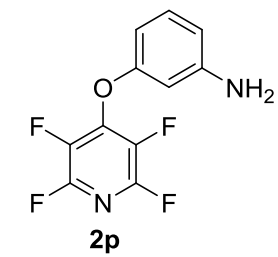
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88.95



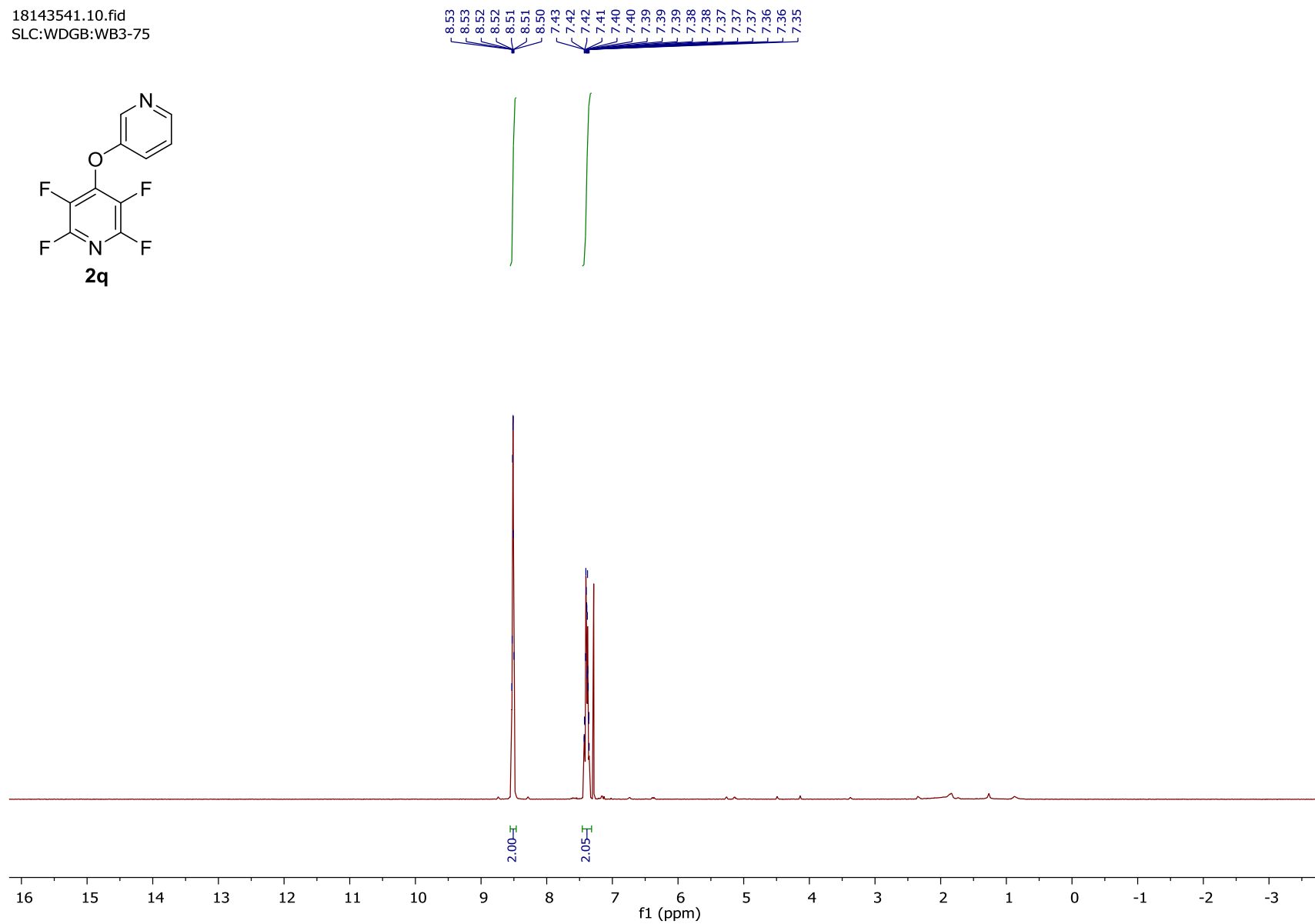
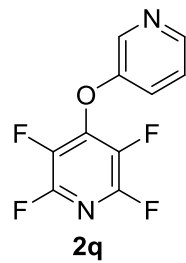
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CARBON_01
SLC:WB3-122



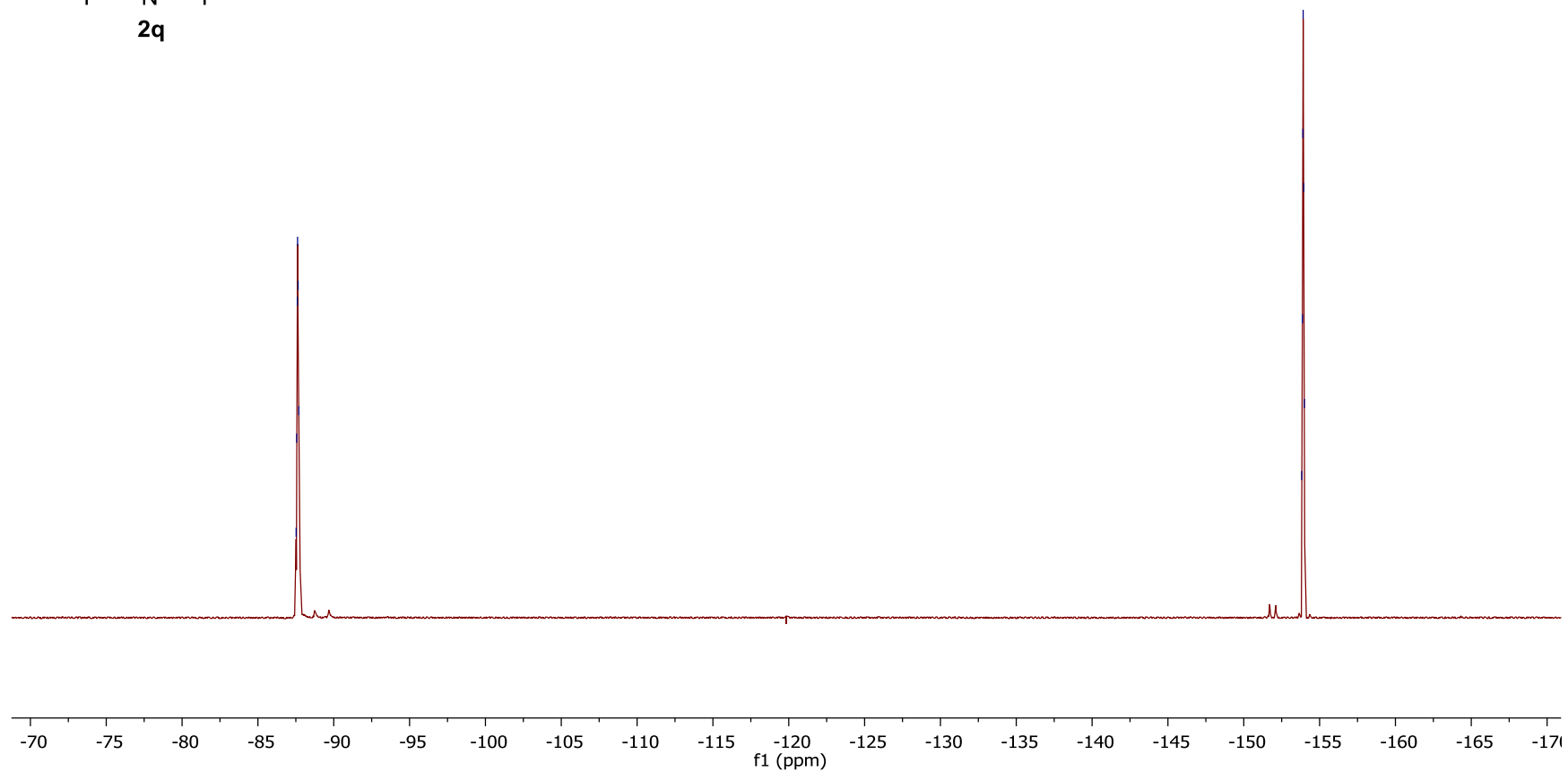
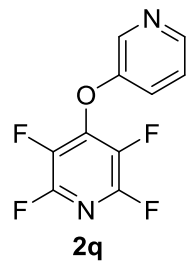
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SLC:WDGB:WB3-75



18143541.13.fid
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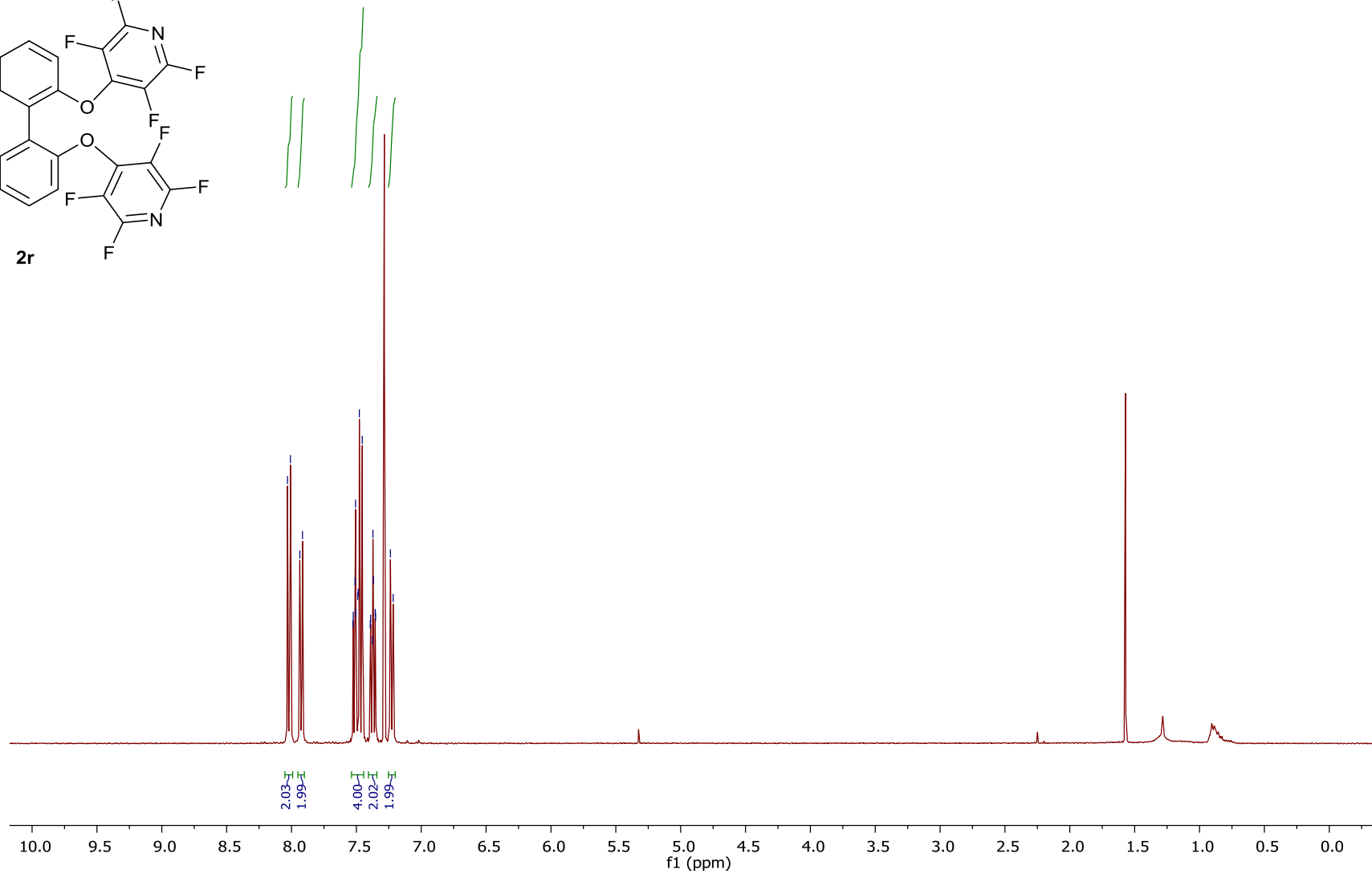
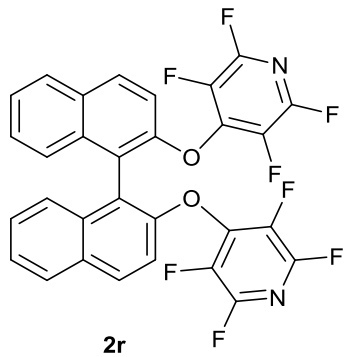
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-153.82
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-153.99



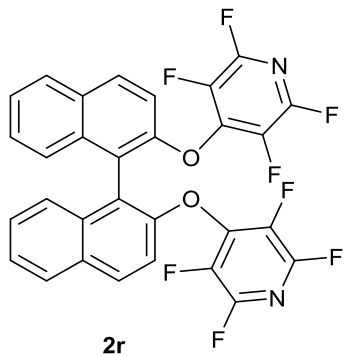
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7.24
7.24
7.22

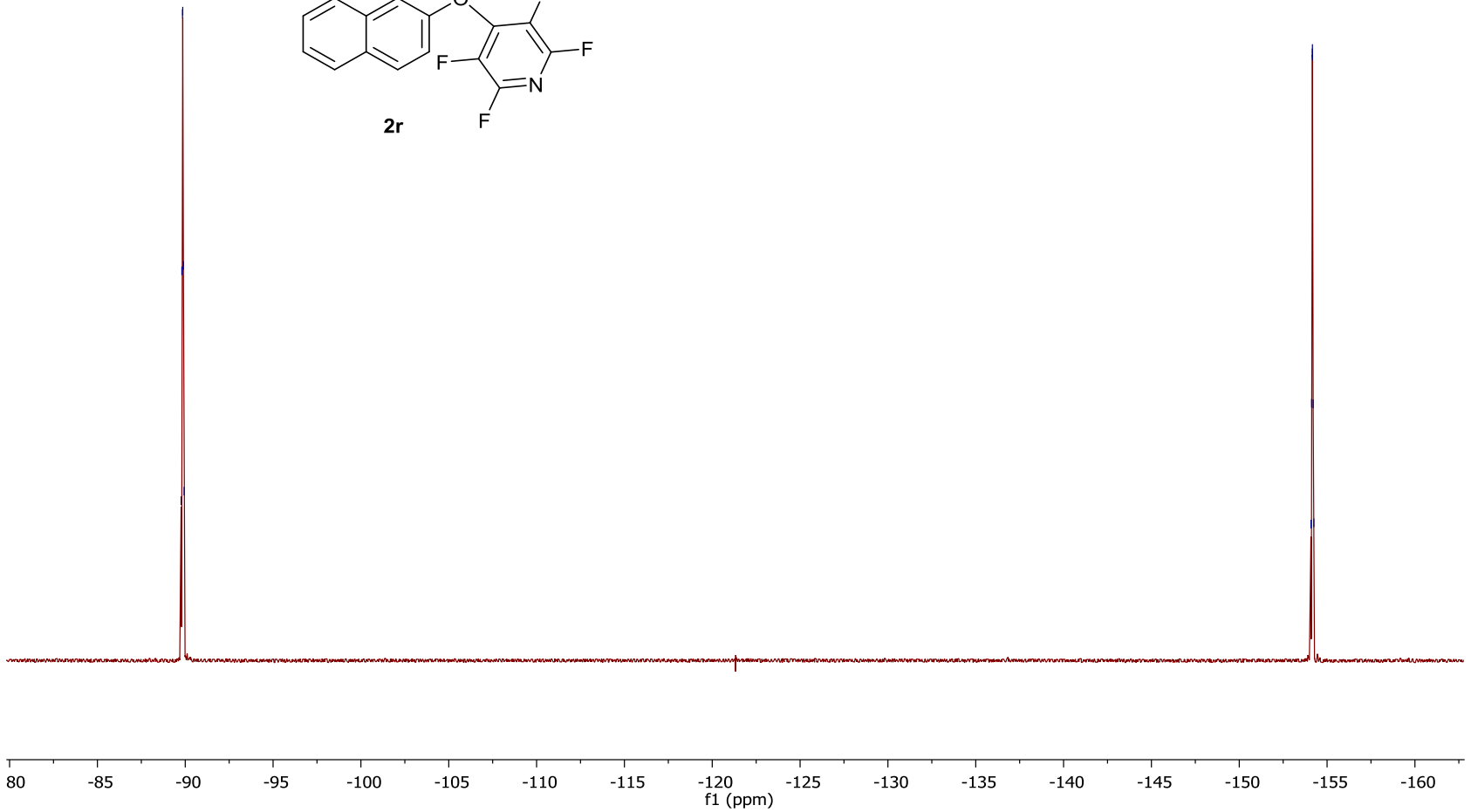


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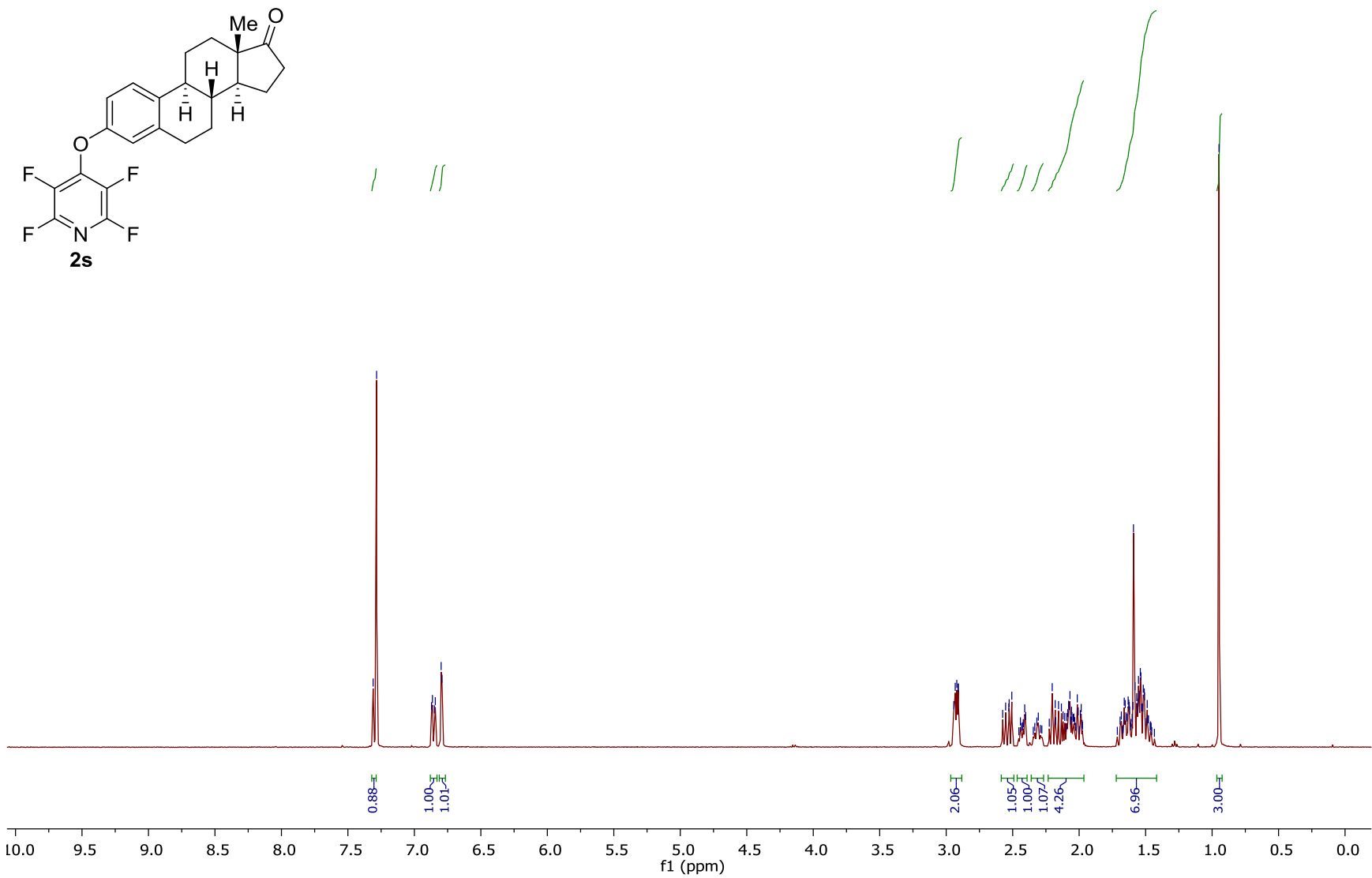
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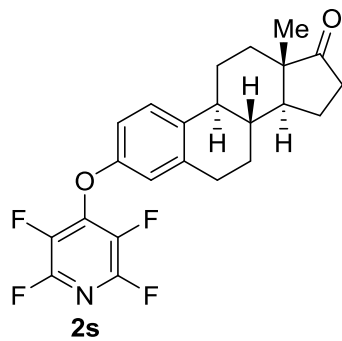


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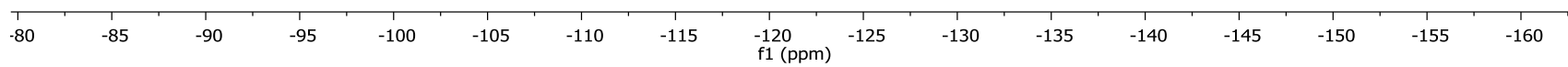


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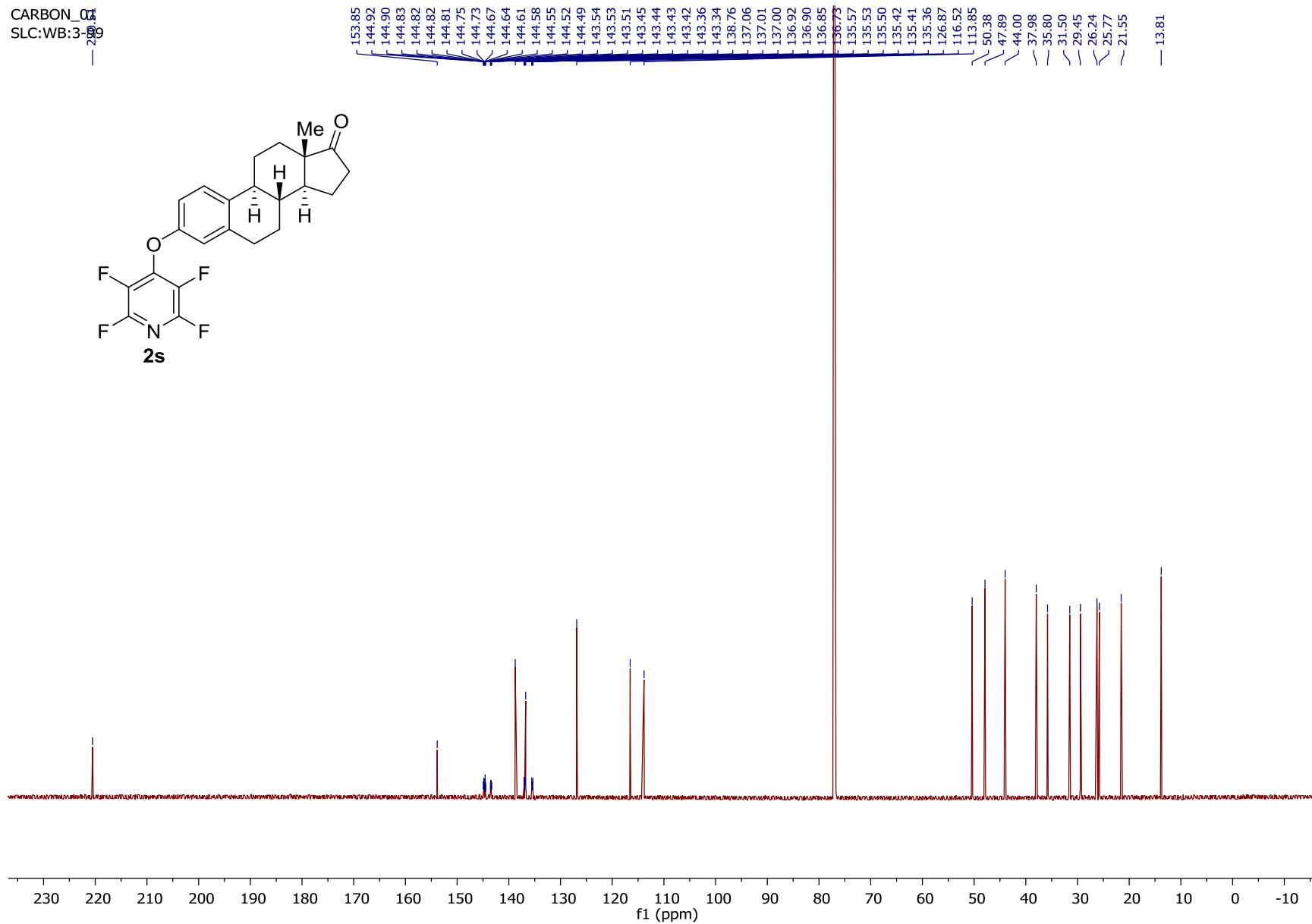
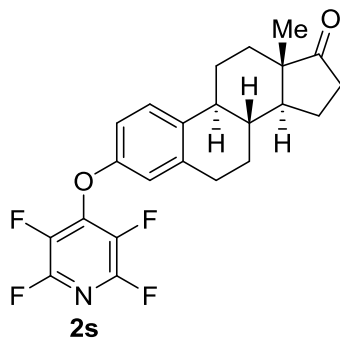
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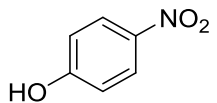
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CARBON_01
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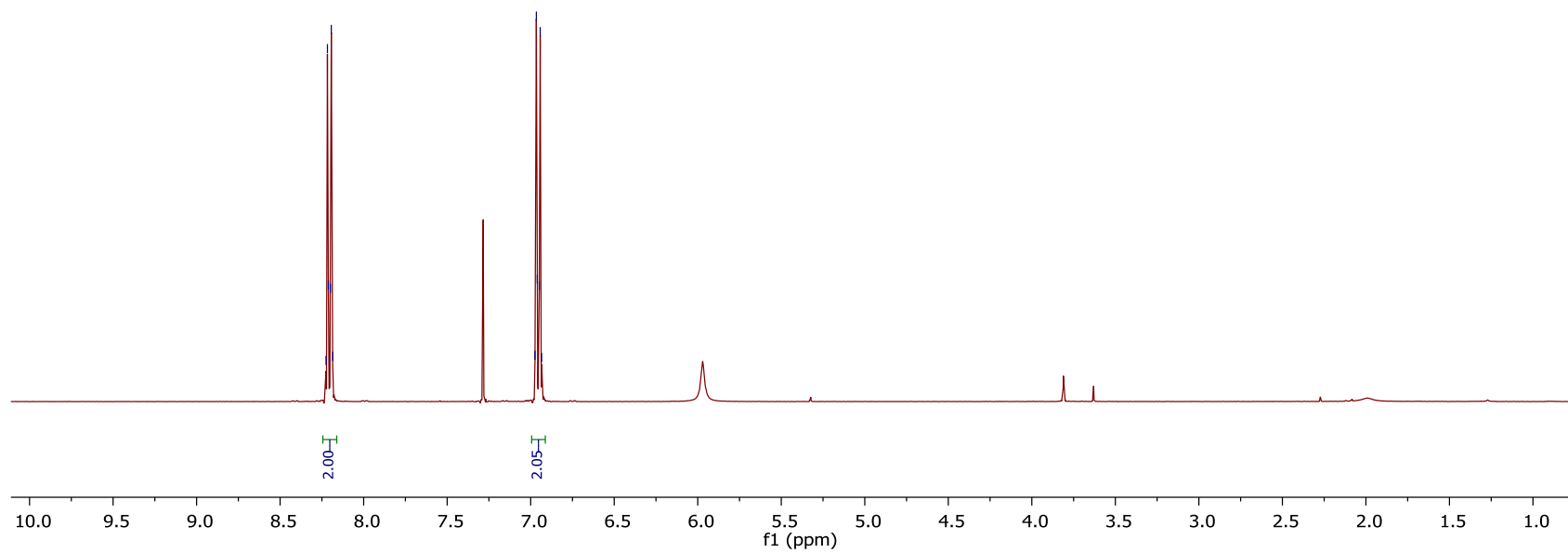


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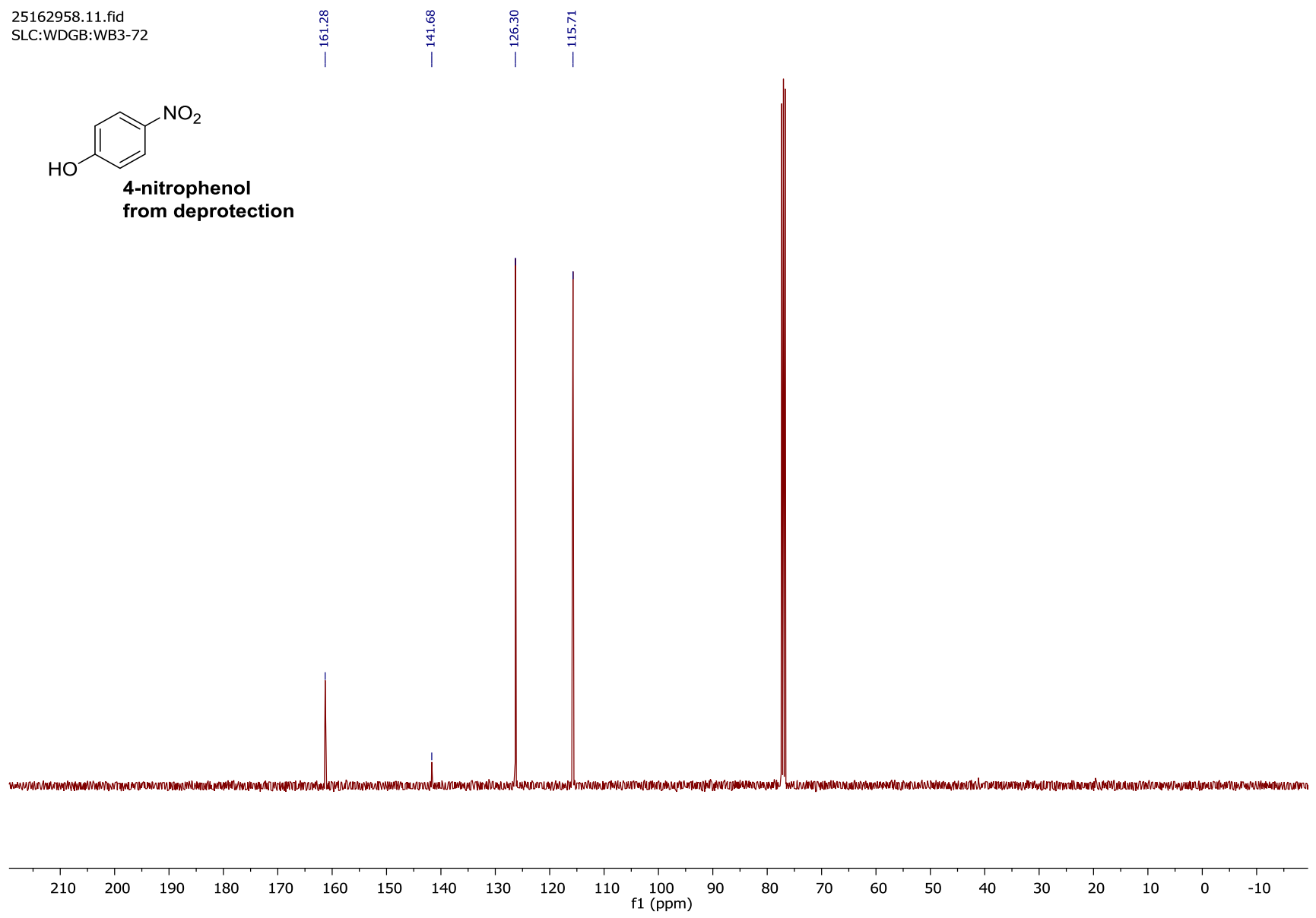
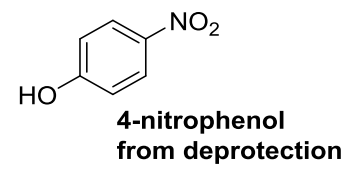


4-nitrophenol
from deprotection

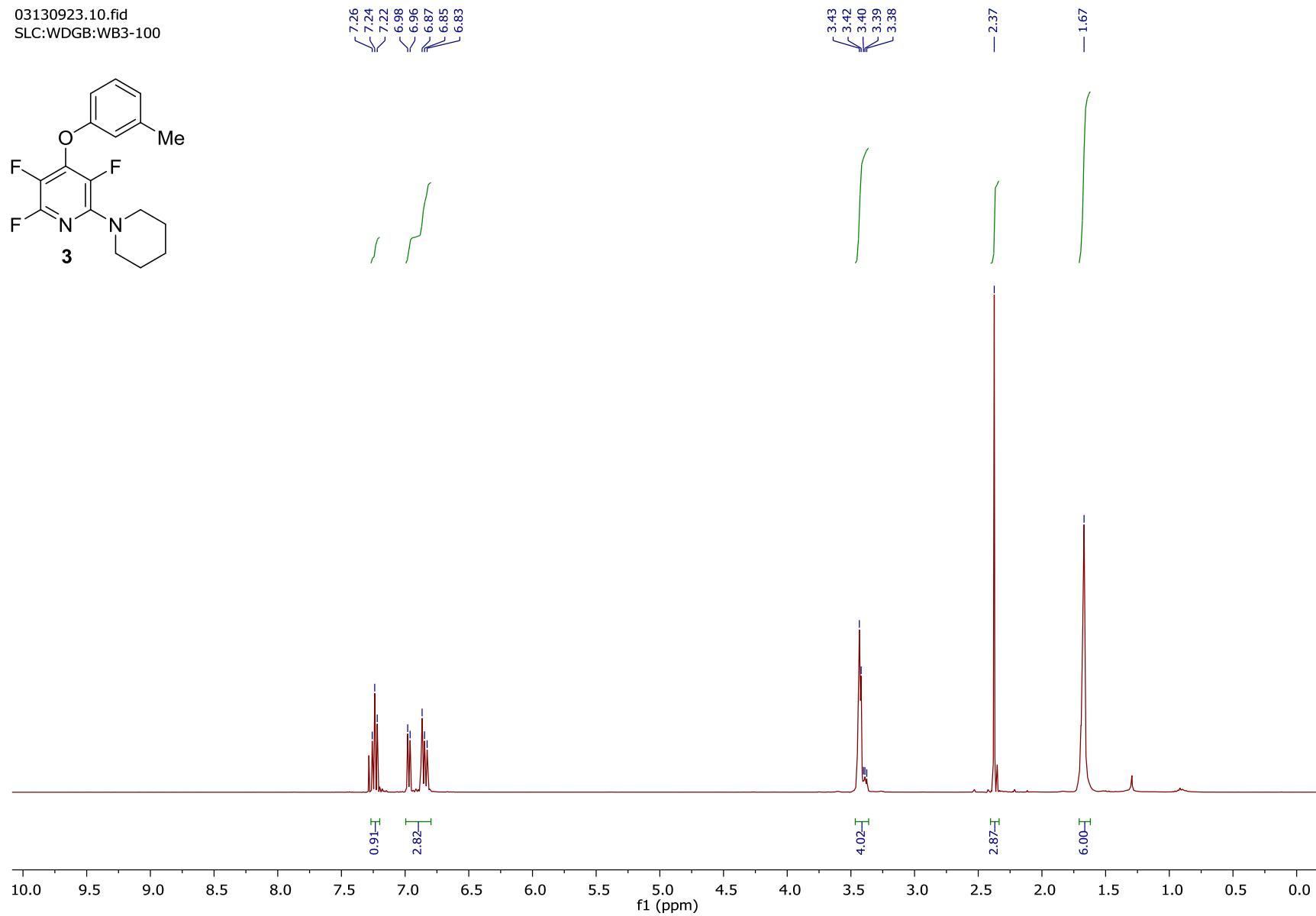
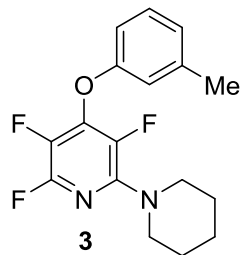
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6.94
6.93



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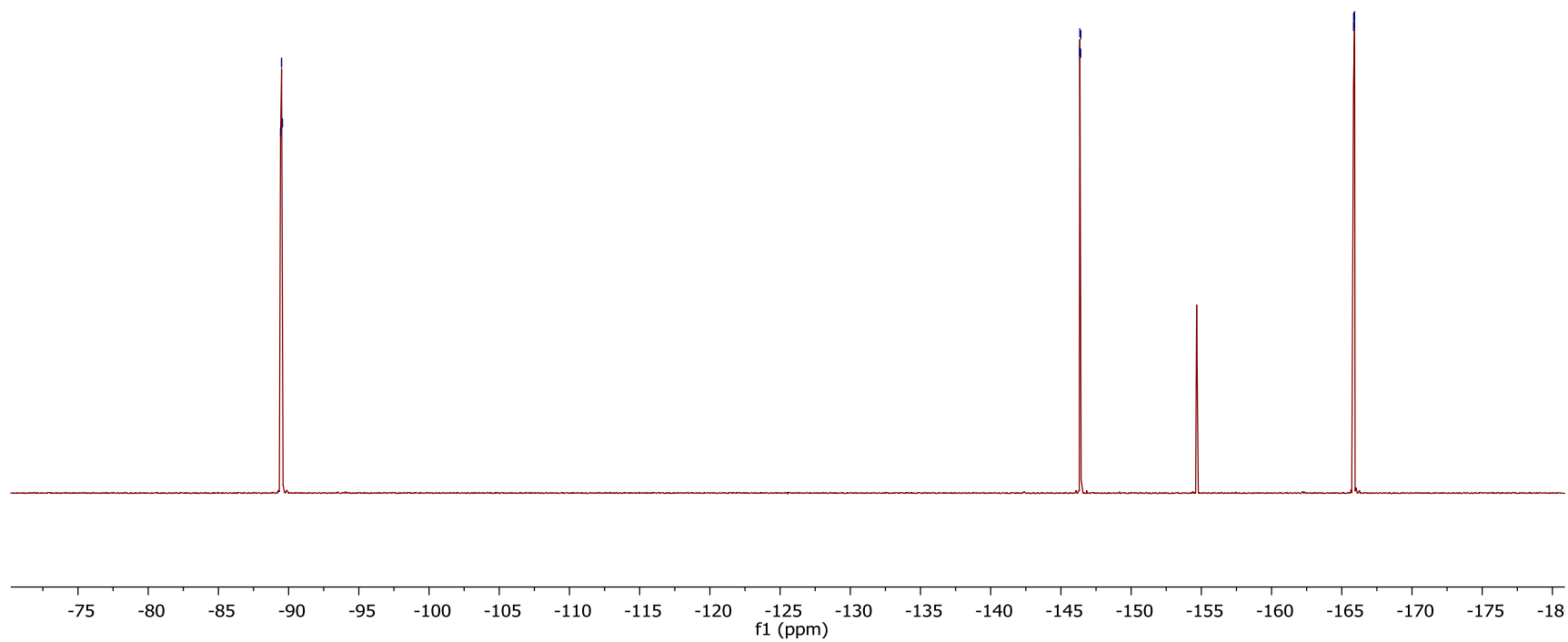
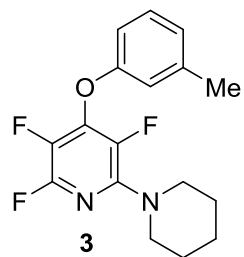


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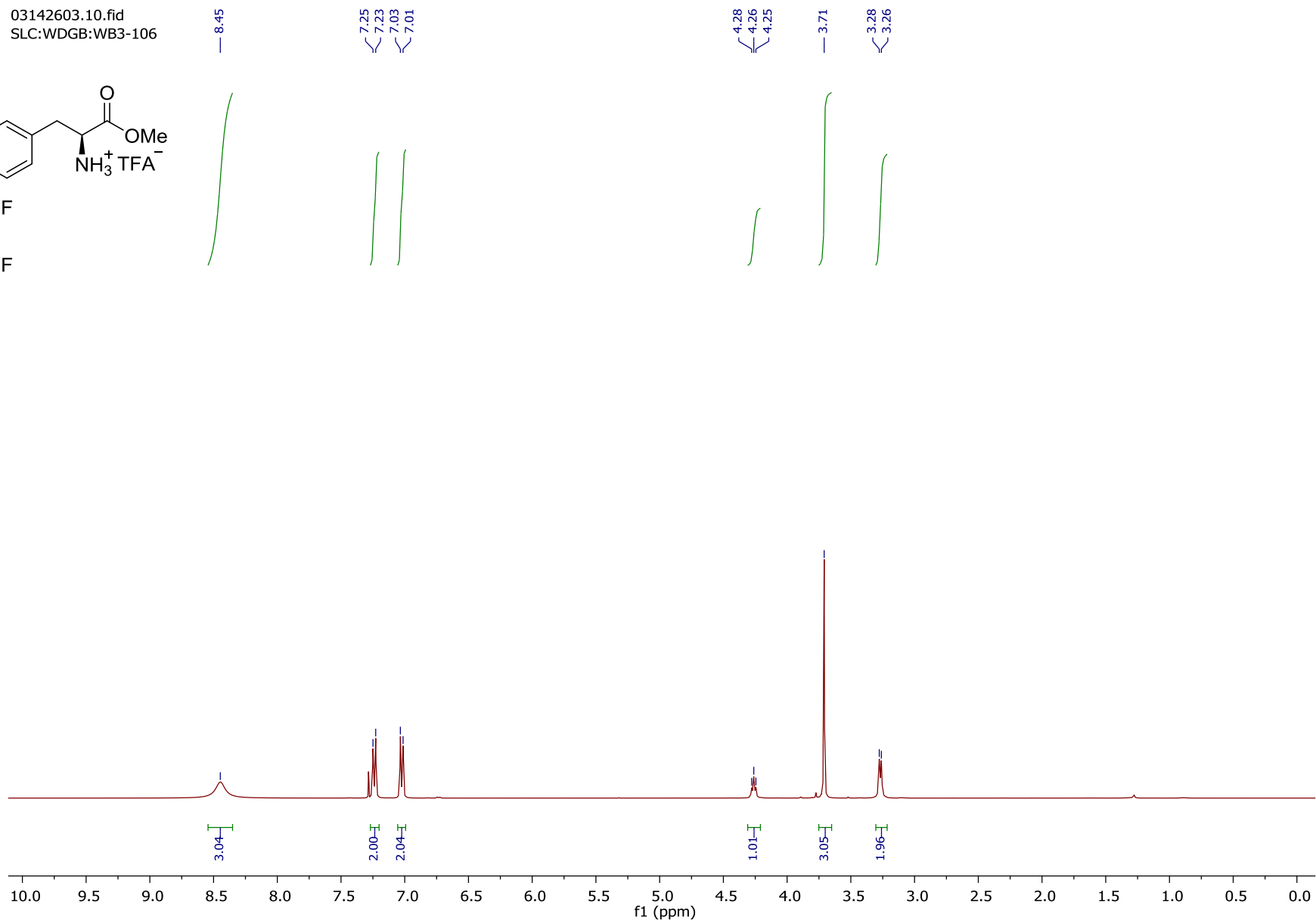
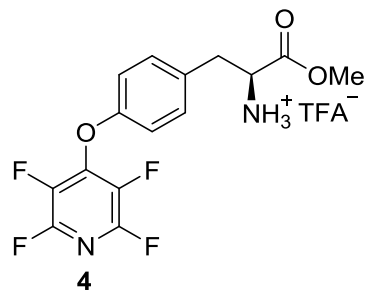
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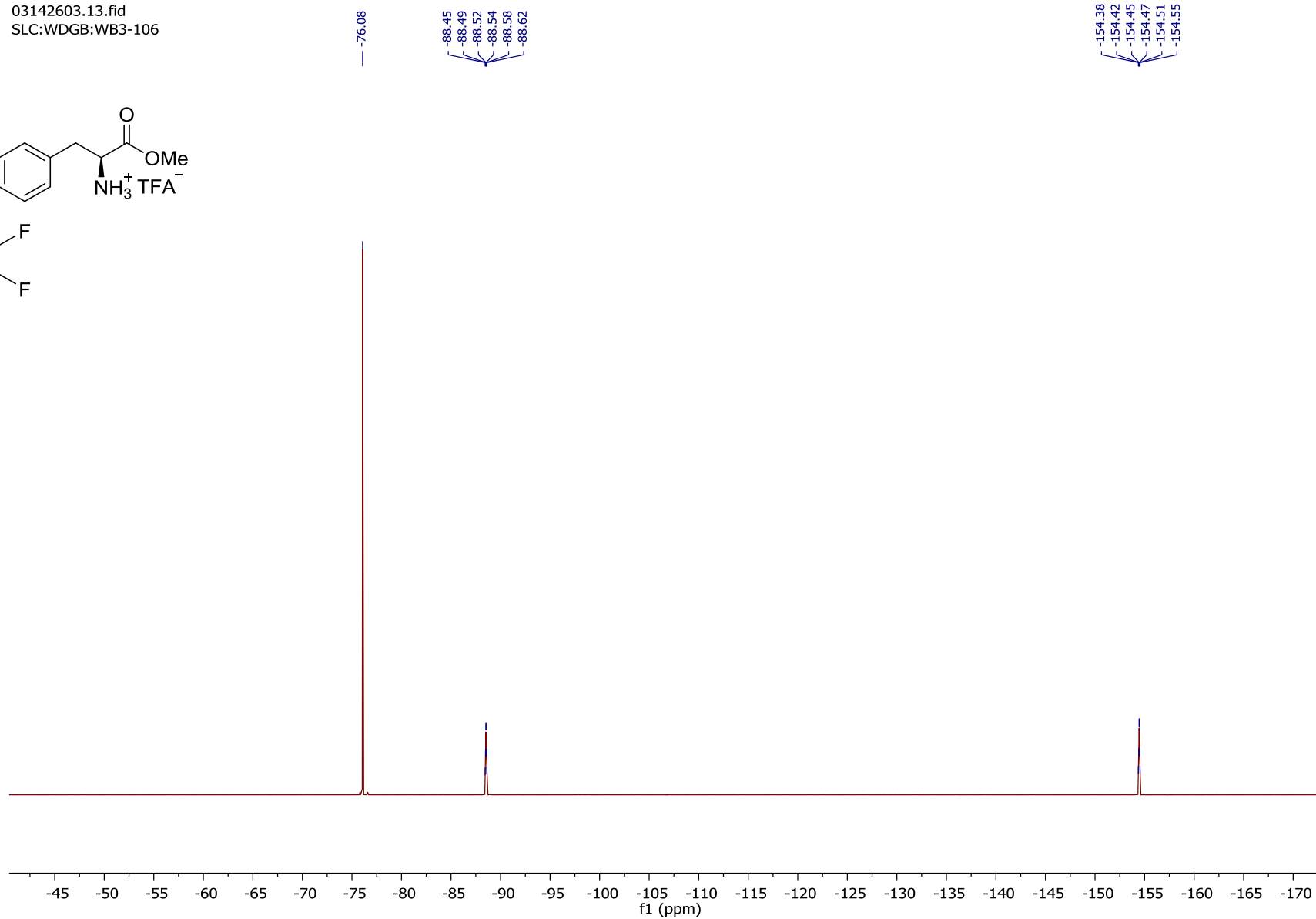
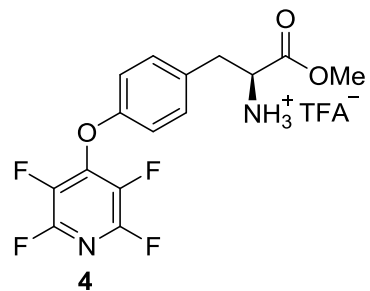
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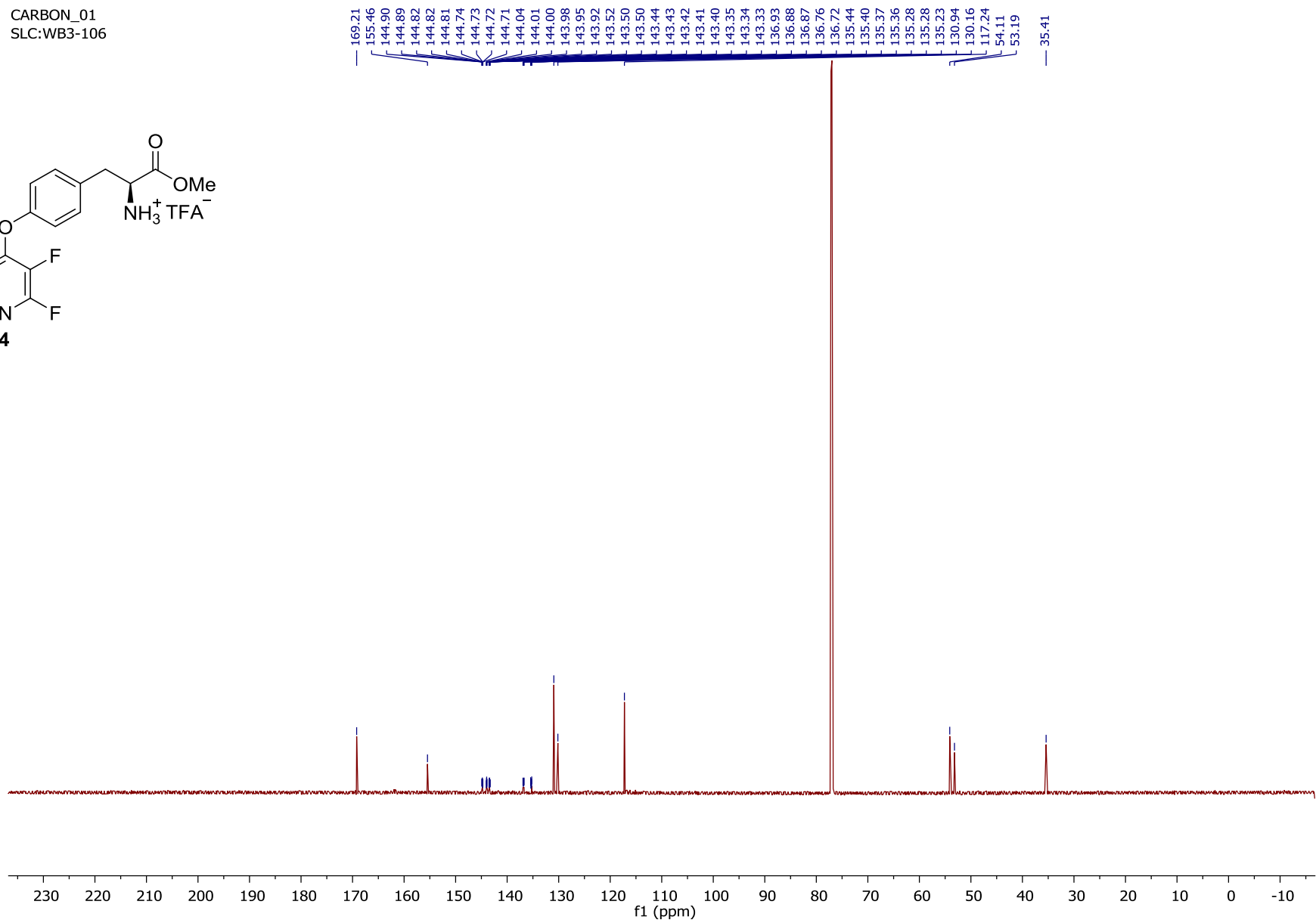
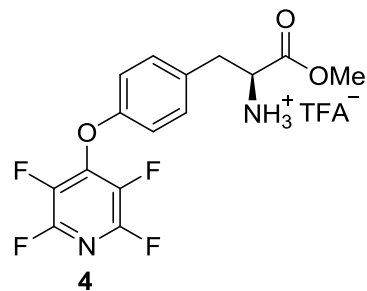
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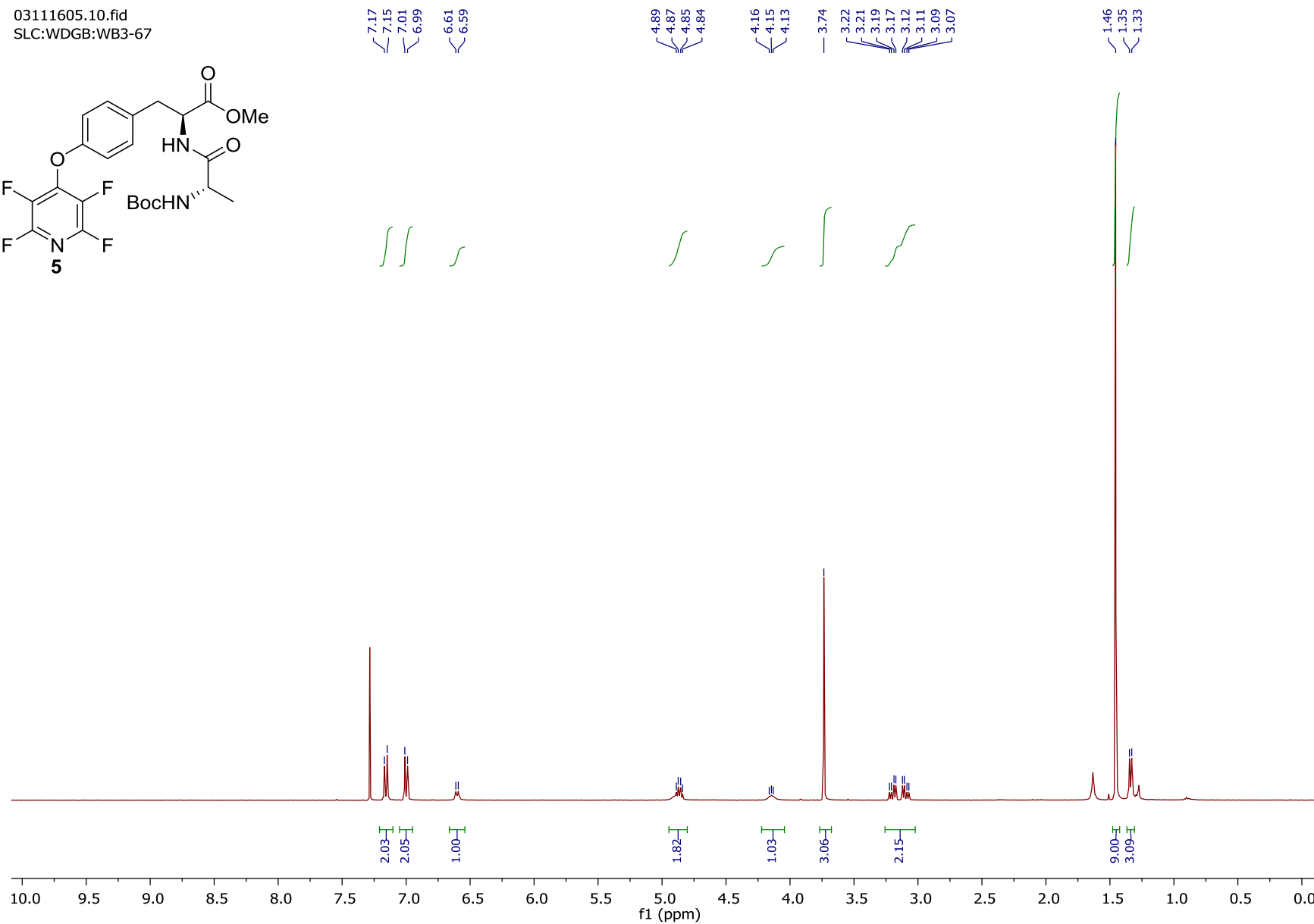
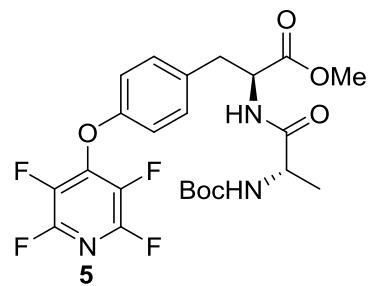
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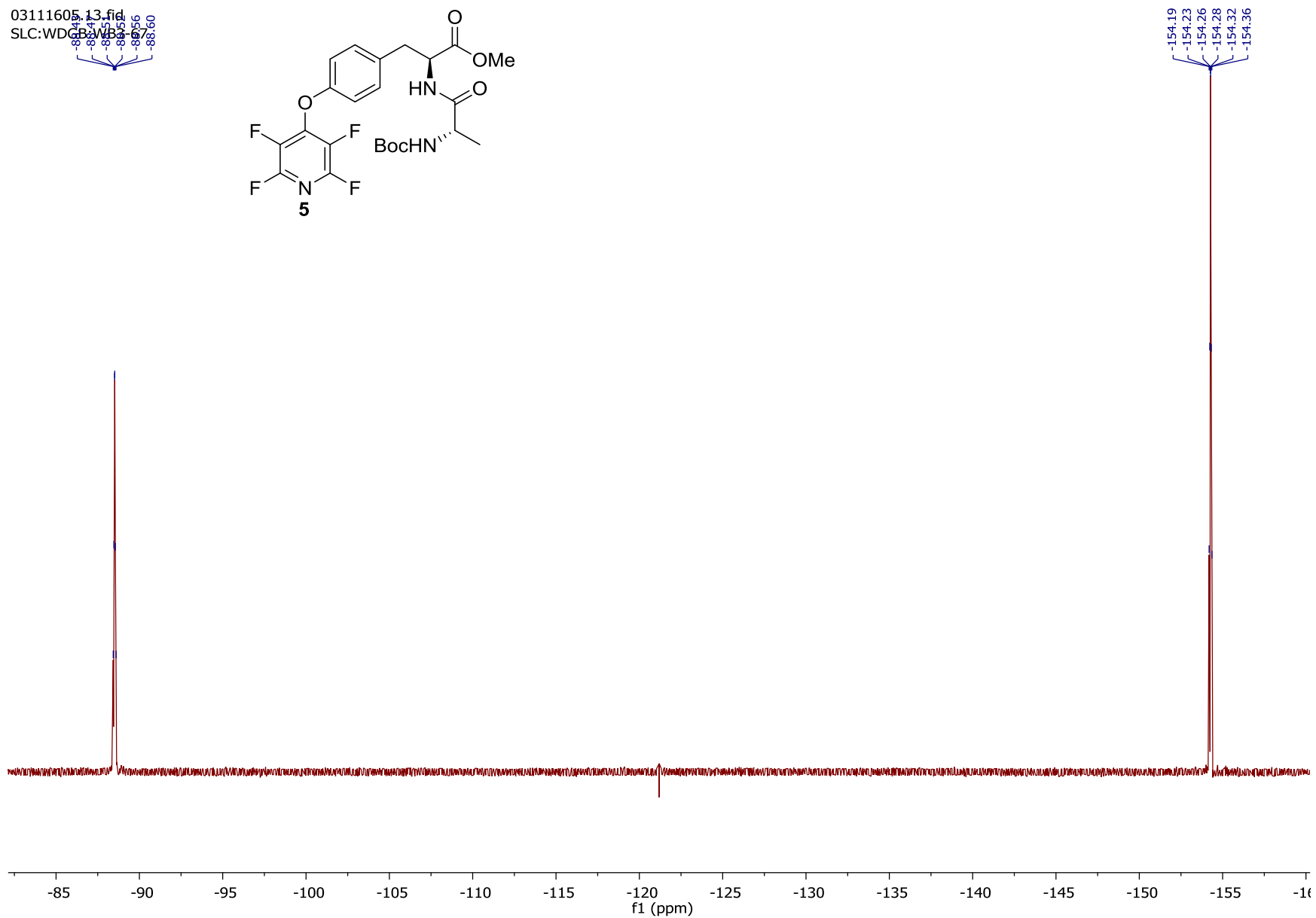
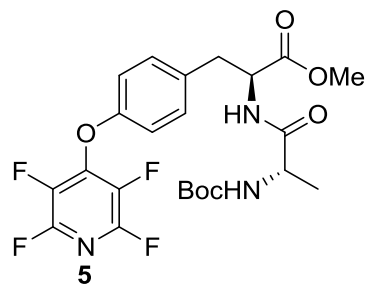
CARBON_01
SLC:WB3-106



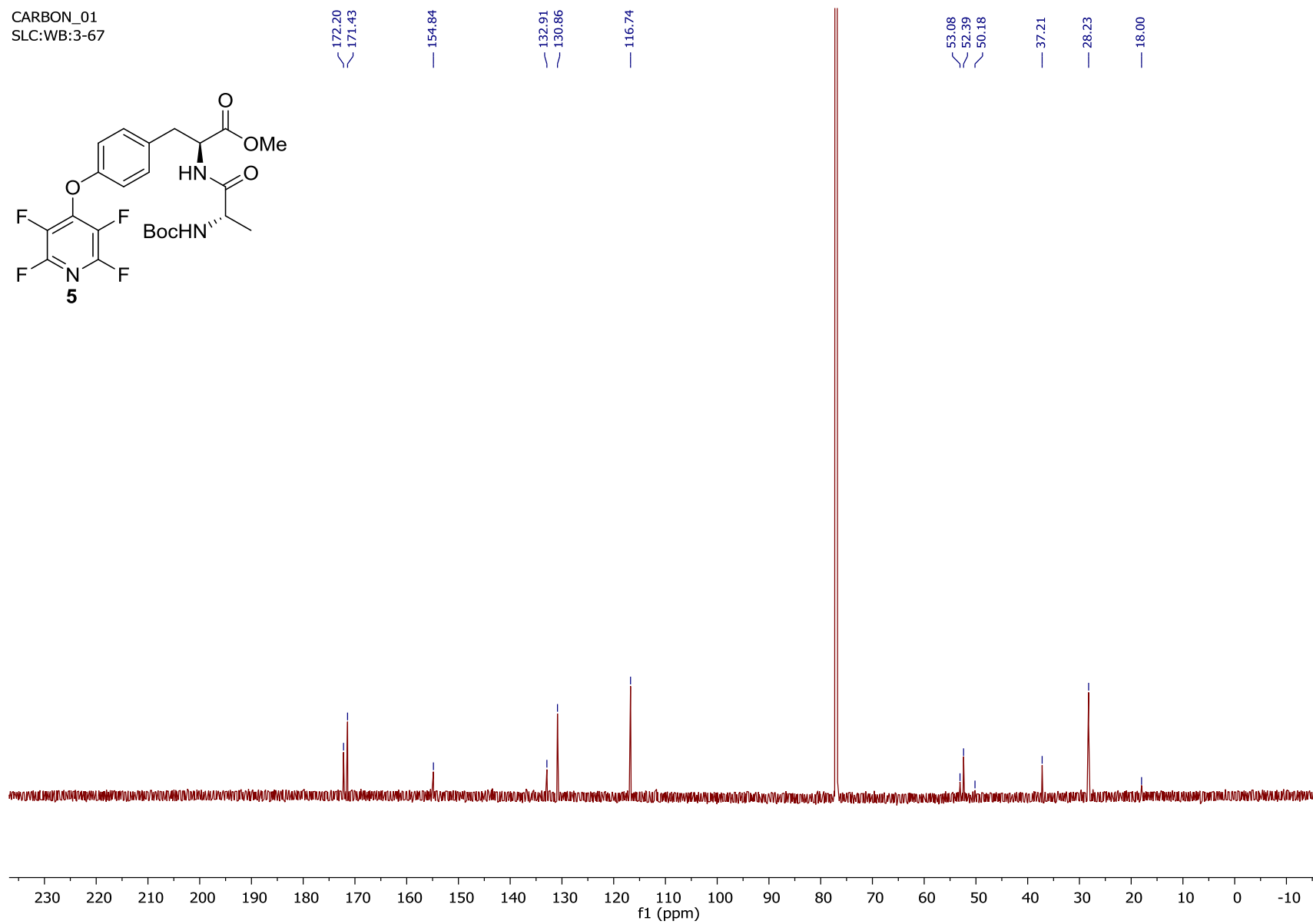
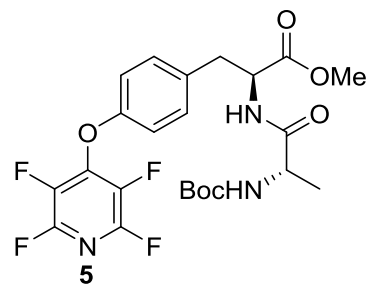
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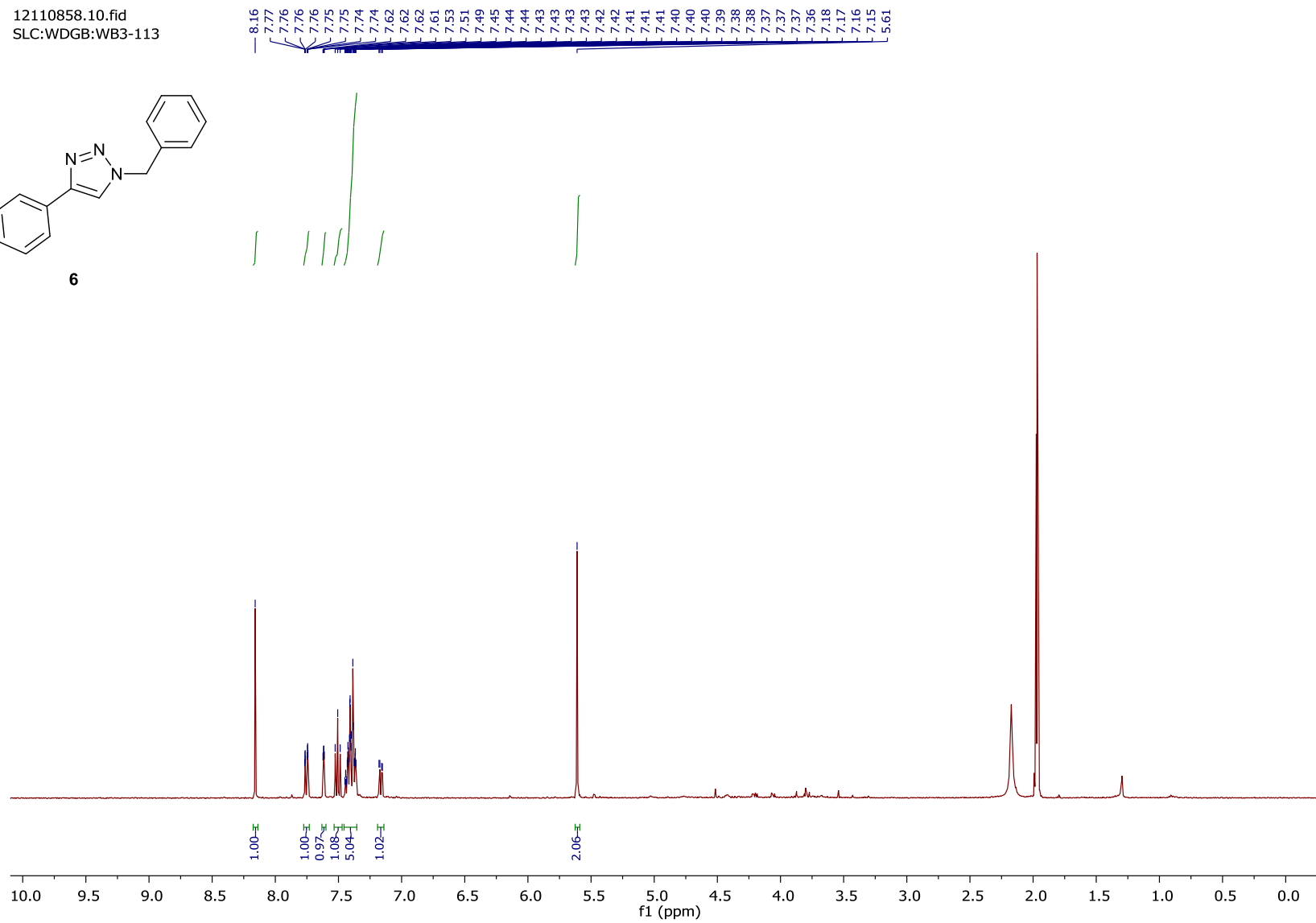
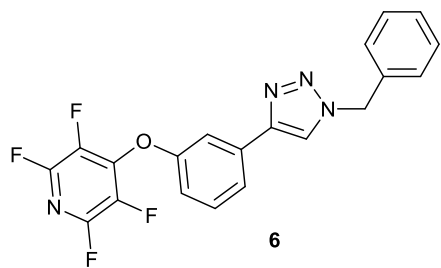
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SLC:WDGBA\WB



CARBON_01
SLC:WB:3-67

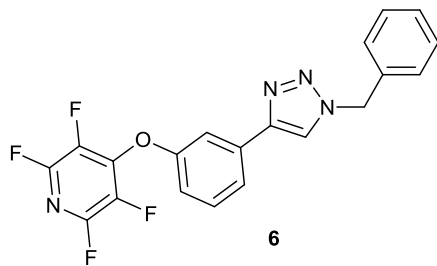


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SLC:WDGB:WB3-113

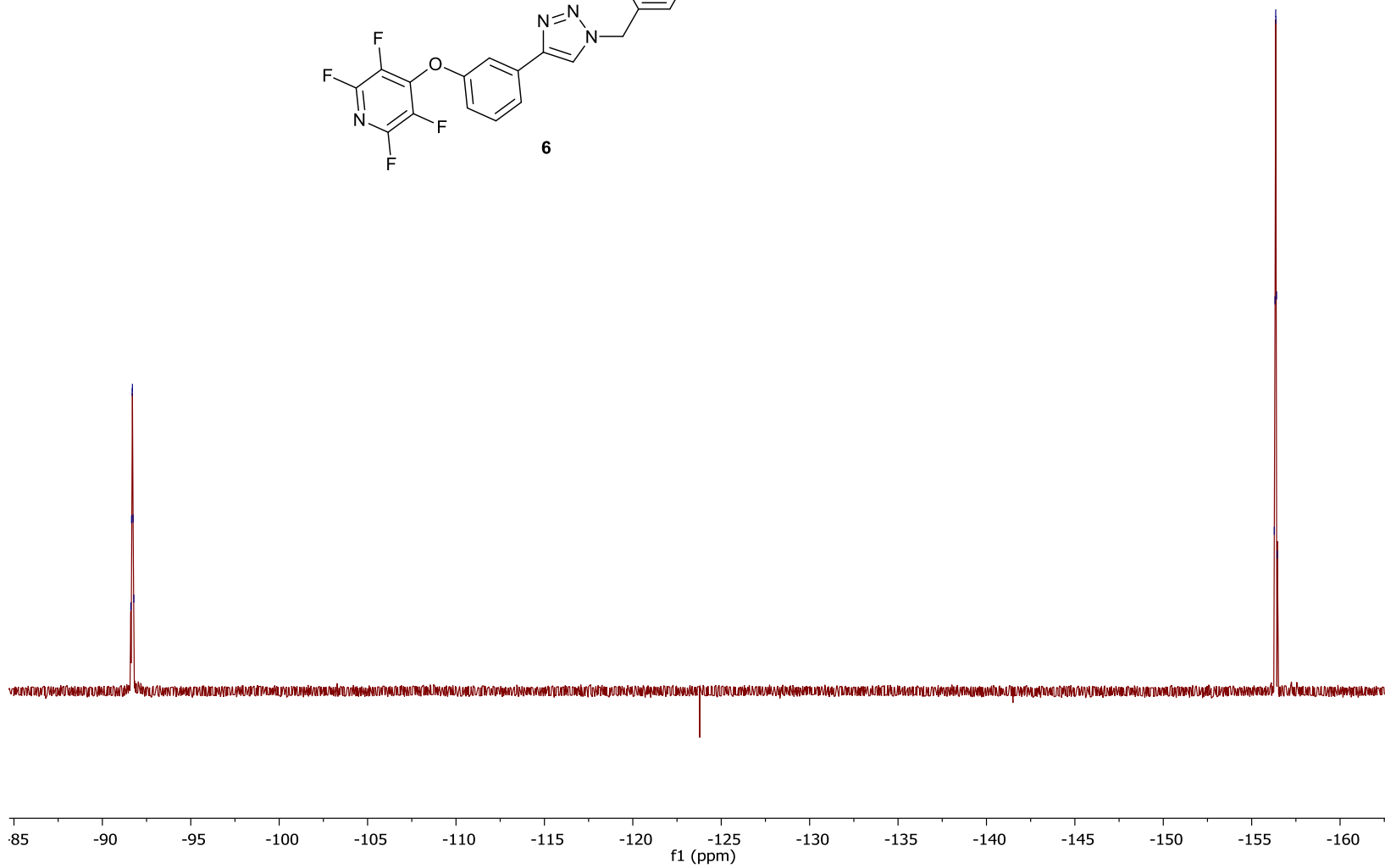


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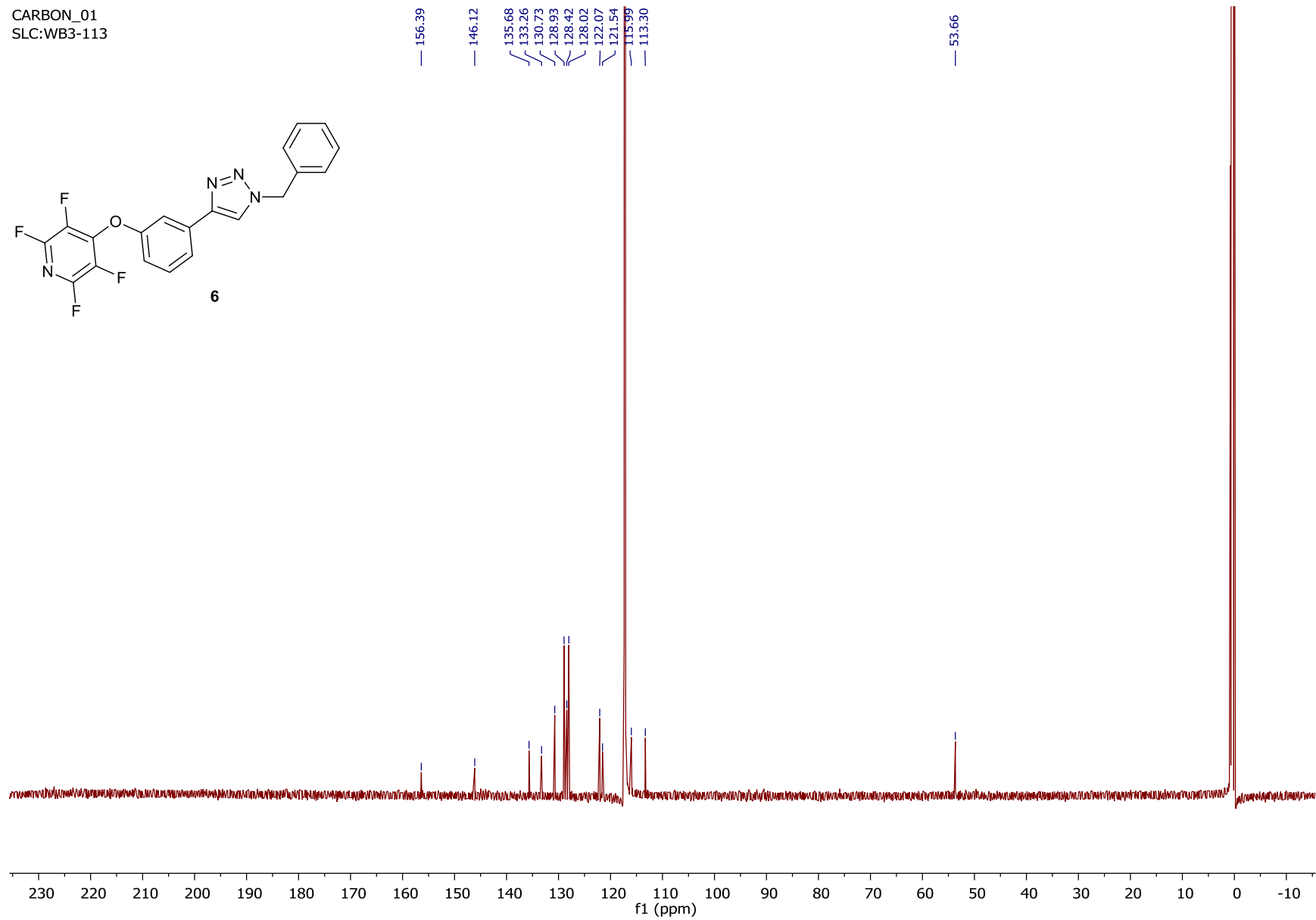
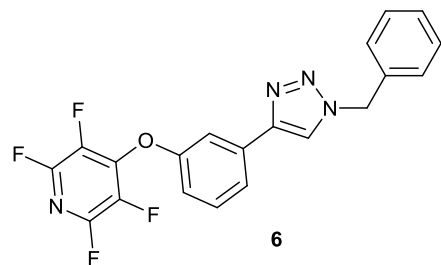
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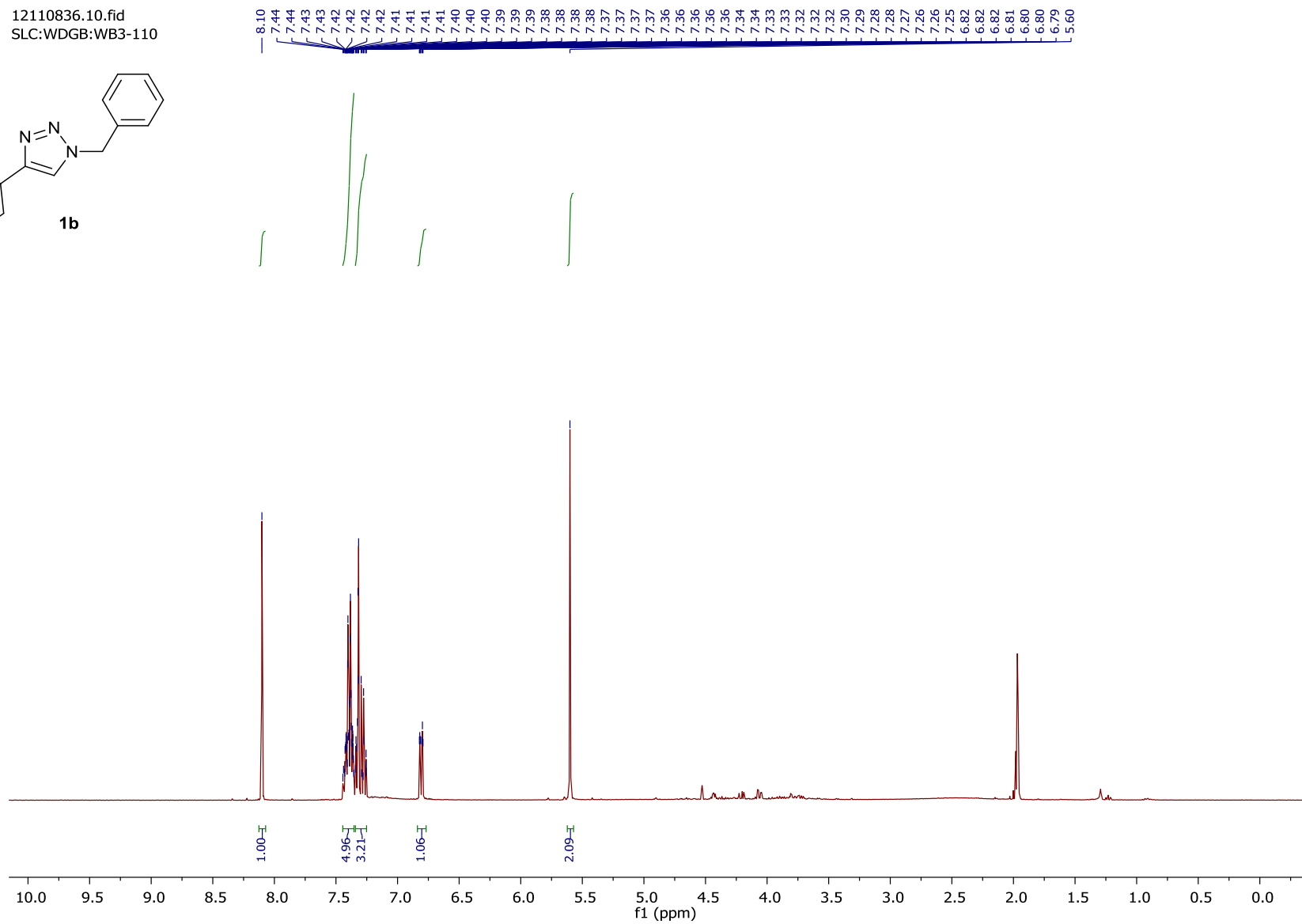
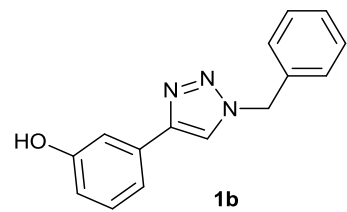
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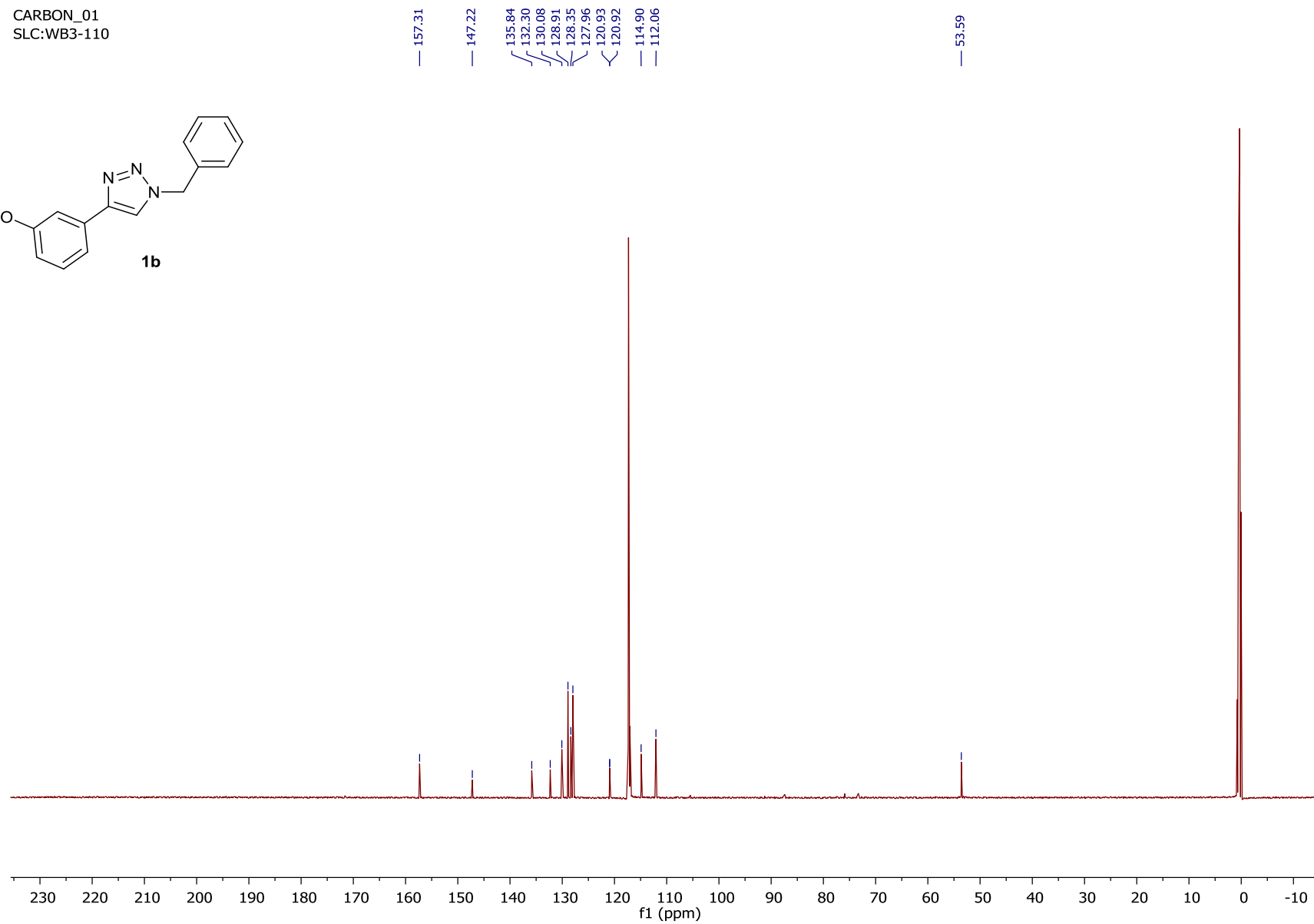
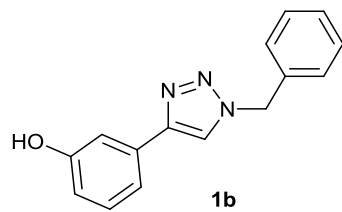
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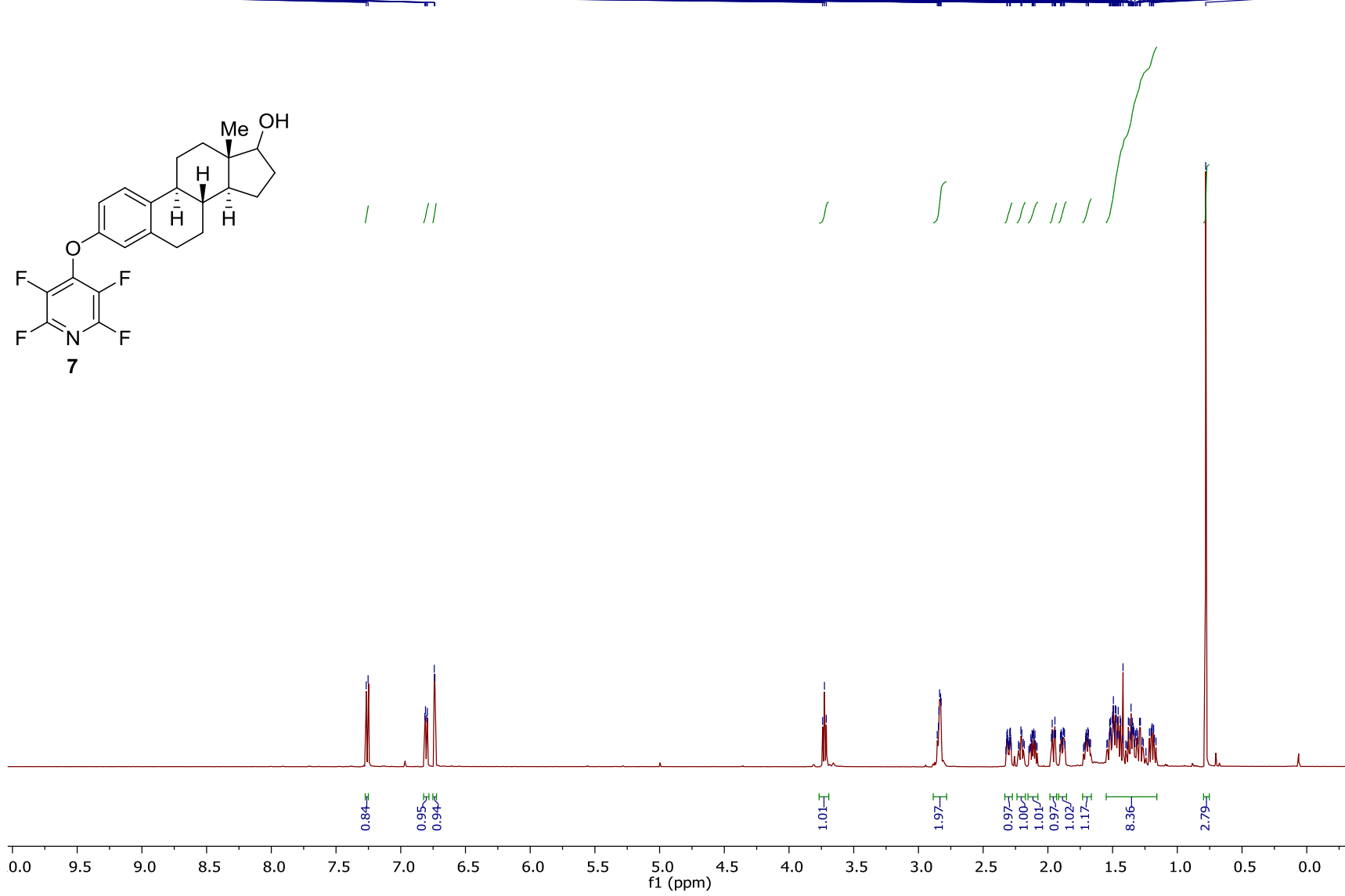
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CARBON_01
SLC:WB3-110



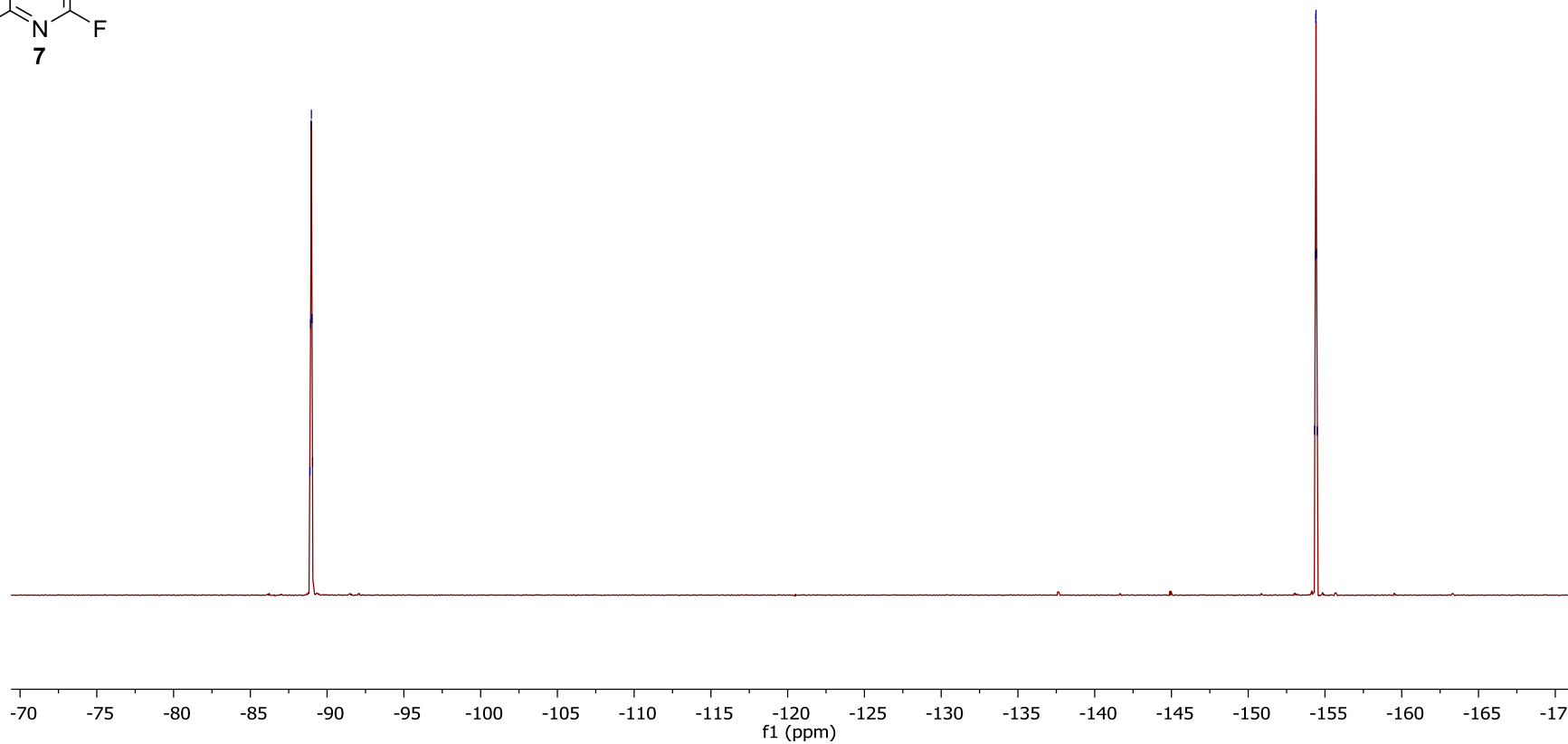
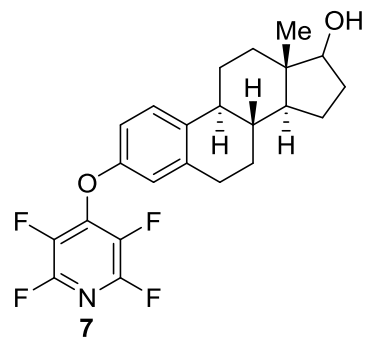
PROTONS
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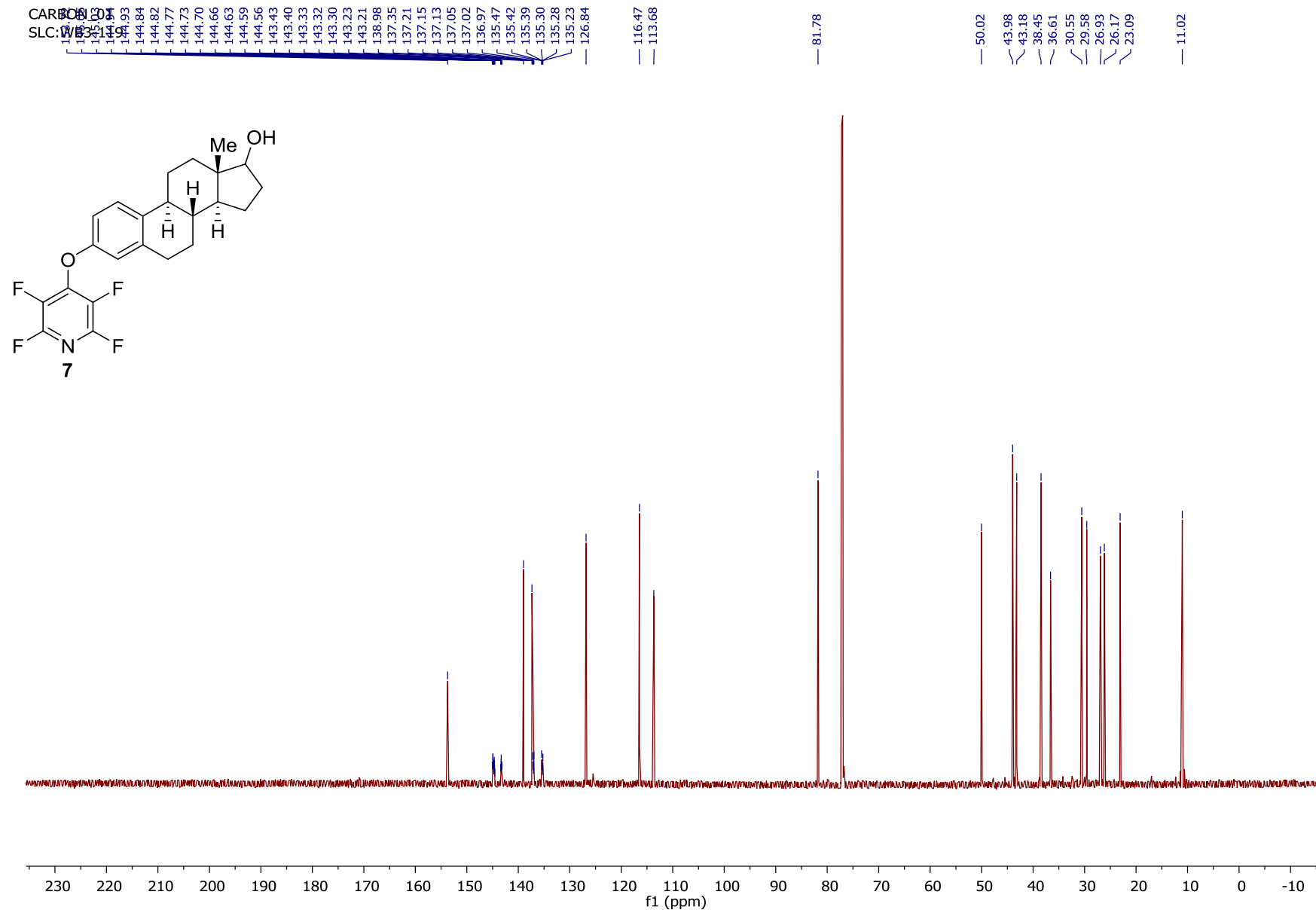


24142808.13.fid
SLC:WDGB:WB3-119

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-89.05

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-154.46
-154.50





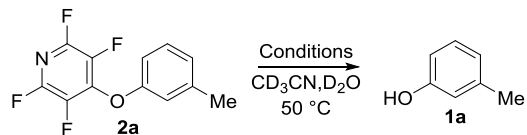
Deprotection Reactions Monitored by NMR

General Procedure for TFP Ether Cleavage monitored by ^1H NMR

To a solution of TFP Ether (0.022 mmol, 1 equiv.) in CD_3CN (0.7 mL) was added KF (0.044 mmol, 2 equiv.), 18-C-6 (0.066 mmol, 3 equiv.) and methyl thioglycolate (0.22 mmol, 10 equiv.) and finally D_2O (0.1 mL). The reaction mixture was gently heated until all components were dissolved. The resulting mixture was transferred to a NMR tube and suspended in a water bath at 50 °C for 1 h. After this time the tube was removed from the water bath and a ^1H NMR spectrum of the reaction mixture recorded. In cases where full conversion was not reached after 1 h the NMR tube was returned to the water bath and heated until full conversion was reached.

Table S1

Table 1: Deprotection condition screening



Entry	Conditions	Time/h	Conversion/%
1	KI (2 equiv.)	24	-
2	KBr (2 equiv.)	24	-
3	KCl (2 equiv.)	24	-
4	KF (2 equiv.)	24	<1
5	KI (2 equiv.), 18-C-6 (3 equiv.)	24	<1
6	KF (2 equiv.), 18-C-6 (3 equiv.)	24	1
7	Nal (2 equiv.), 18-C-6 (3 equiv.)	24	<1
8	KF (2 equiv.), 18-C-6 (3 equiv.), methyl thioglycolate (10 equiv.)	1	78
9	KF (2 equiv.), methyl thioglycolate (10 equiv.)	1	61
10	KF (1 equiv.), 18-C-6 (1 equiv.), methyl thioglycolate (2 equiv.)	1	57
11	Methyl thioglycolate (10 equiv.)	24	<1
12	methyl thioglycolate (10 equiv.), K ₂ CO ₃ (2 equiv.)	24	90

Conversion was determined by ¹H NMR analysis of the reaction mixture (see SI).
All reactions were carried out in a water bath set to 50 °C.

04153718.10.fid
SLC:WDGB:WB3-62 CD3CN 14

25093330.10.fid
SLC:WDGB:WB-Thiol Base 13

17134357.10.fid
SLC:WDGB:WB-Thioglycolate only 12

24152657.10.fid
SLC:WDGB:WB-2eq Thiol 11

27103555.10.fid
SLC:WDGB:WB3-98 NaI 24h 10

17134419.10.fid
SLC:WDGB:WB-Thioglycolate KF 9

27103537.10.fid
SLC:WDGB:WB3-98 KI 18-C-6 8

27103517.10.fid
SLC:WDGB:WB3-98 KF 18-C-6 24h 7

27092316.10.fid
SLC:WDGB:WB3-98 KF 24h 6

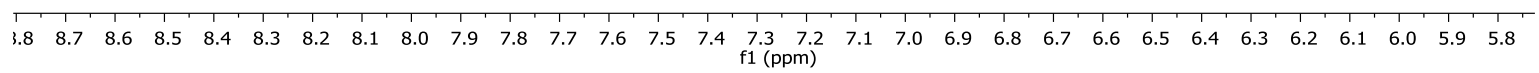
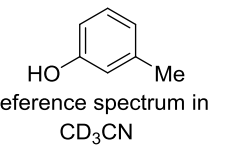
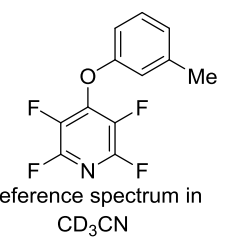
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SLC:WDGB:WB3-98 KCl 24h 5

27092340.10.fid
SLC:WDGB:WB3-98 KBr 24h 4

27092358.10.fid
SLC:WDGB:WB3-98 KI 24h 3

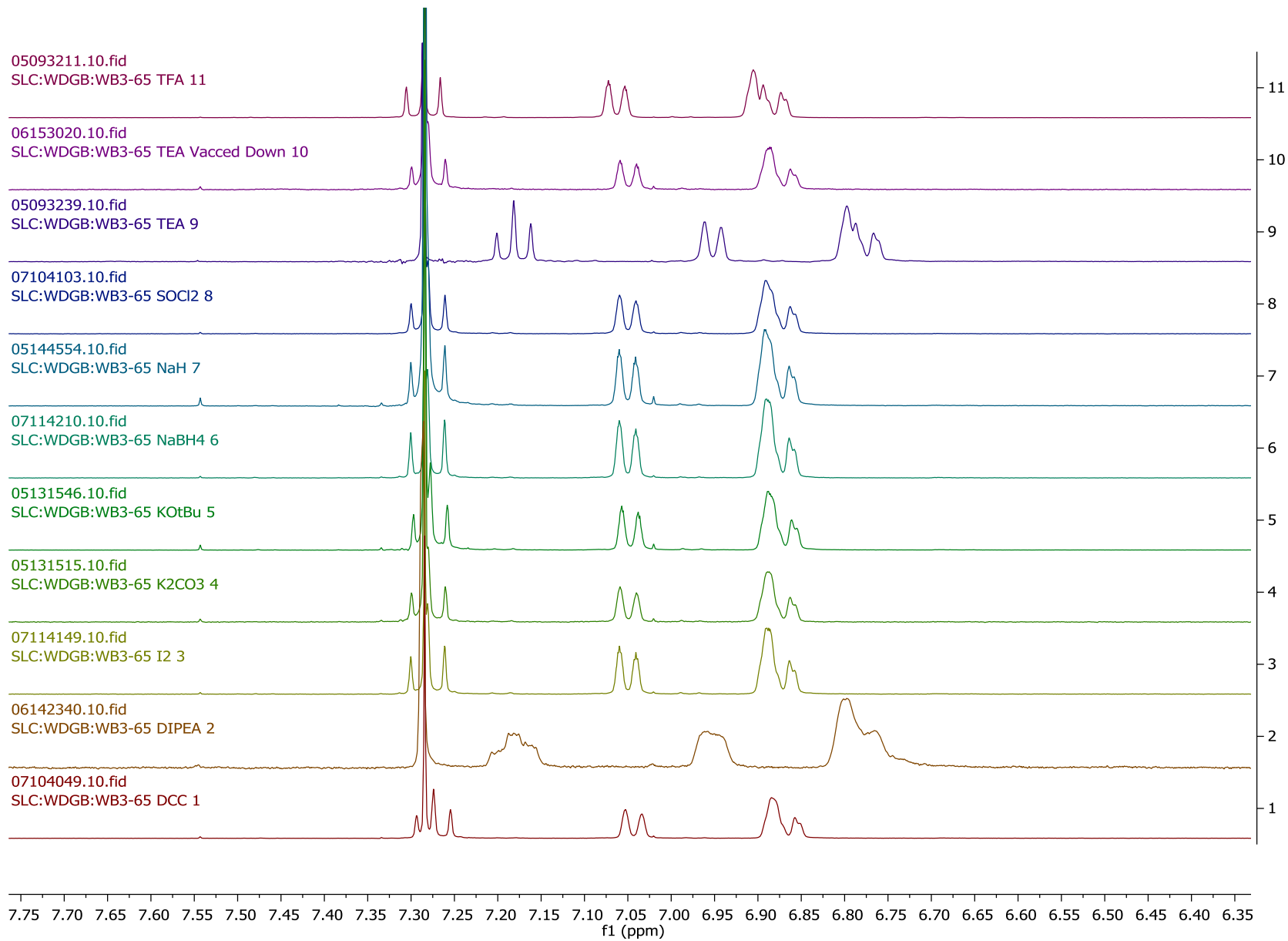
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SLC:WDGB:WB3-88 1h 2

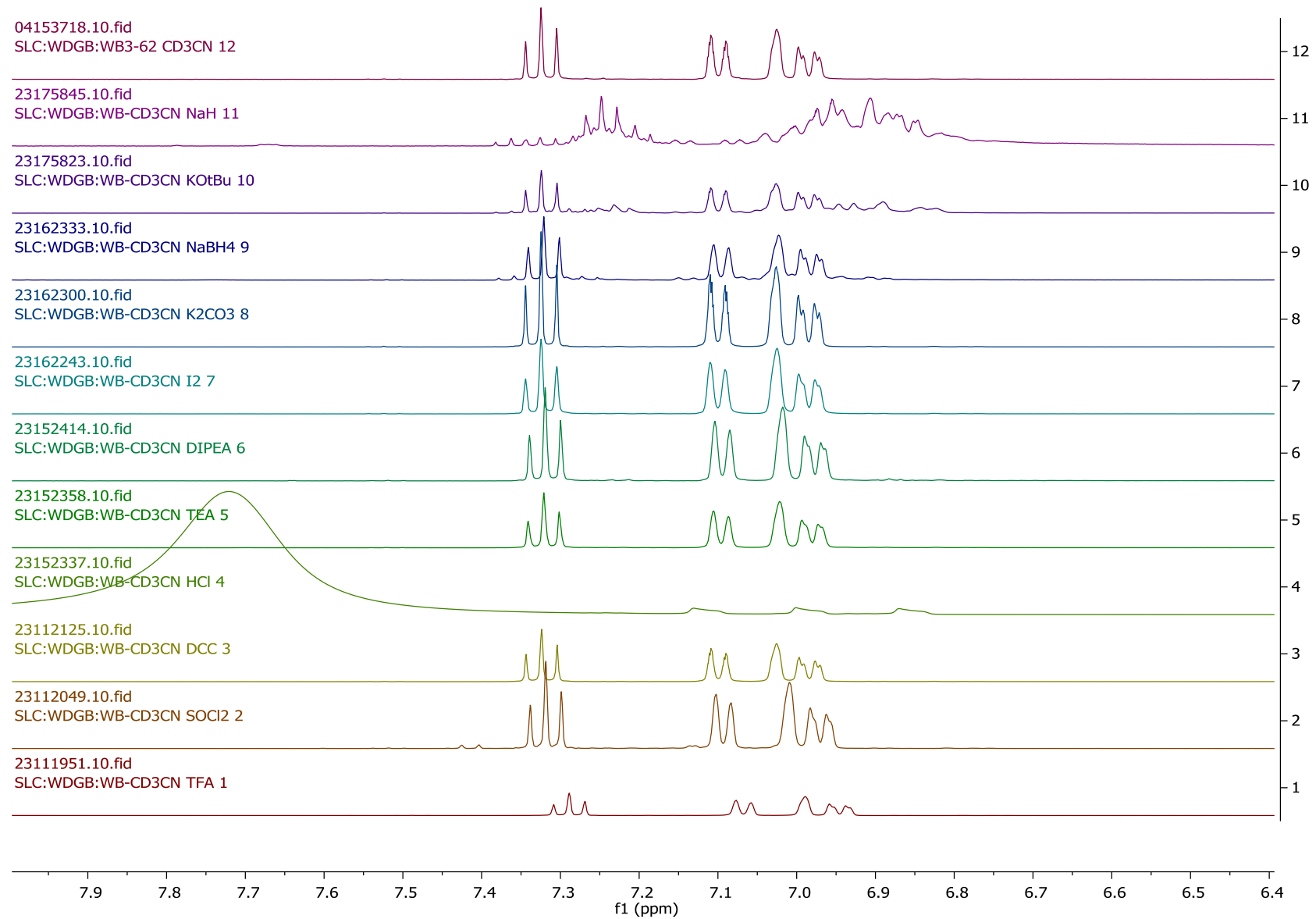
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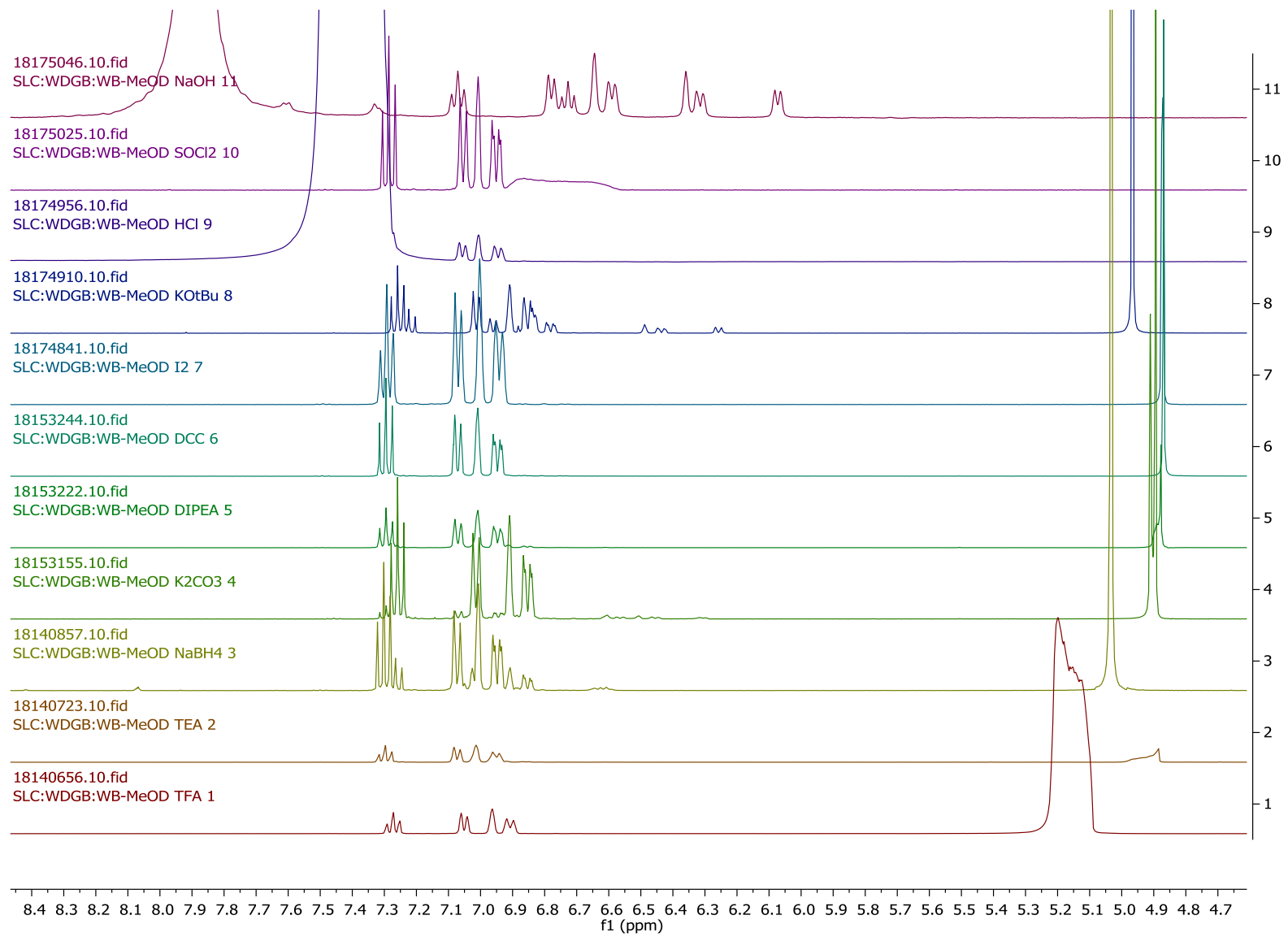


General Procedure for stability testing using ^1H NMR

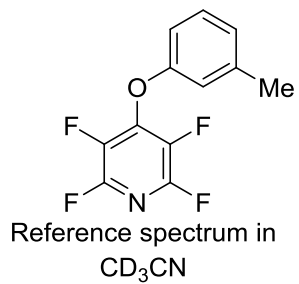
To a solution of TFP ether (10 mg) in deuterated solvent (0.7 mL) was added the desired reagent to be tested. The reaction mixture was transferred to an NMR tube and the reaction mixture left at rt for 24 h. After this time the reaction mixture was analysed by ^1H NMR spectroscopy.



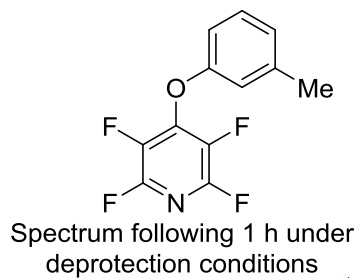




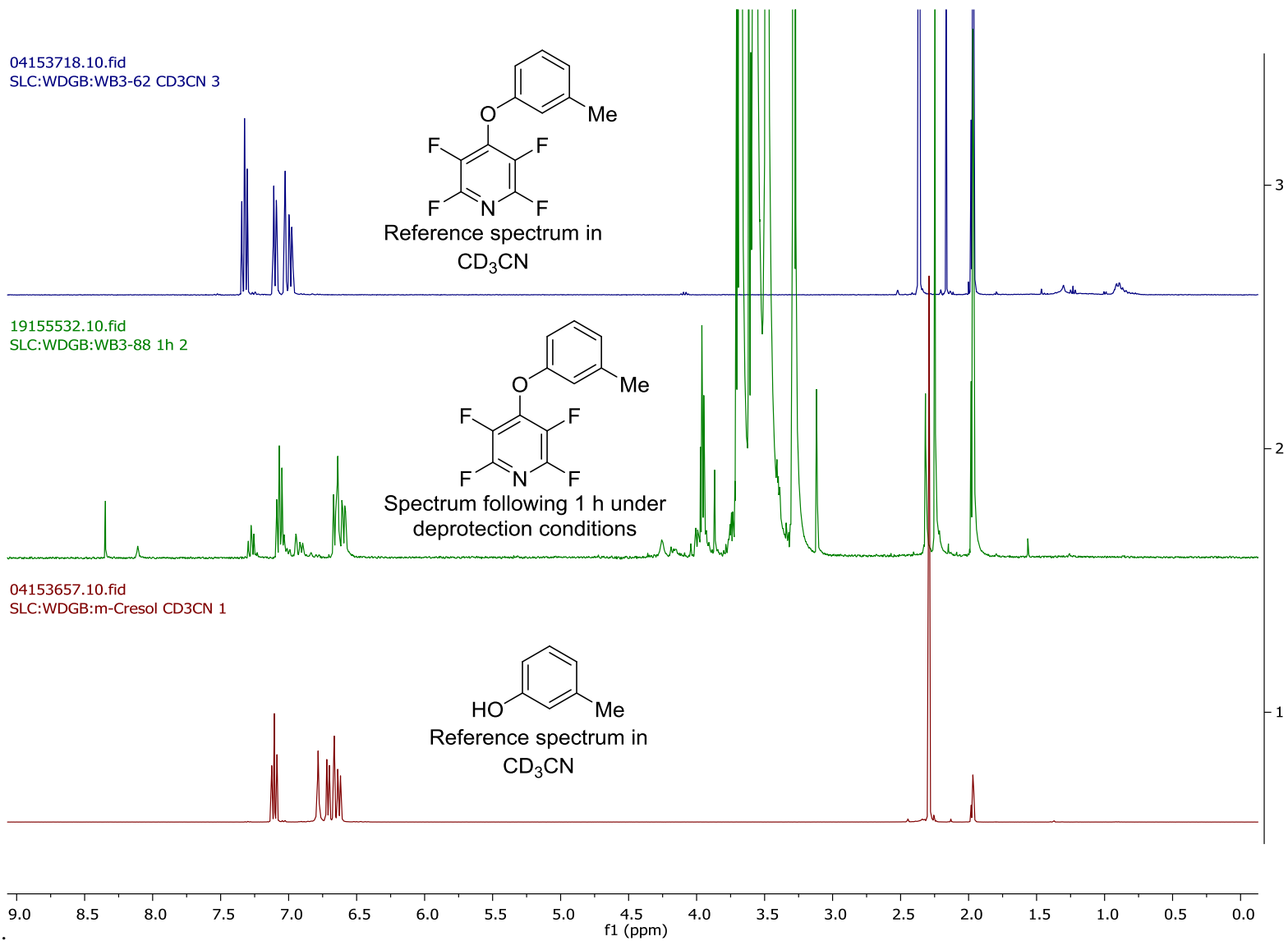
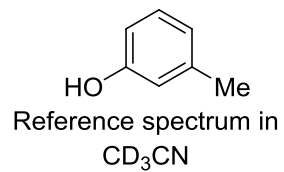
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SLC:WDGB:WB3-62 CD3CN 3



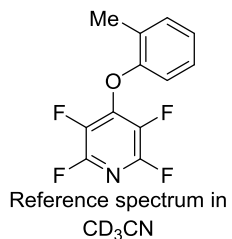
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SLC:WDGB:WB3-88 1h 2



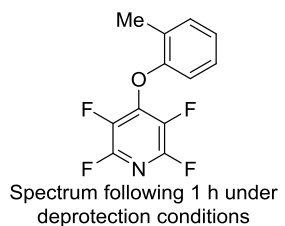
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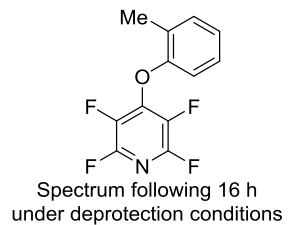
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SLC:WDGB:WB 2MeTFP CD3CN 4



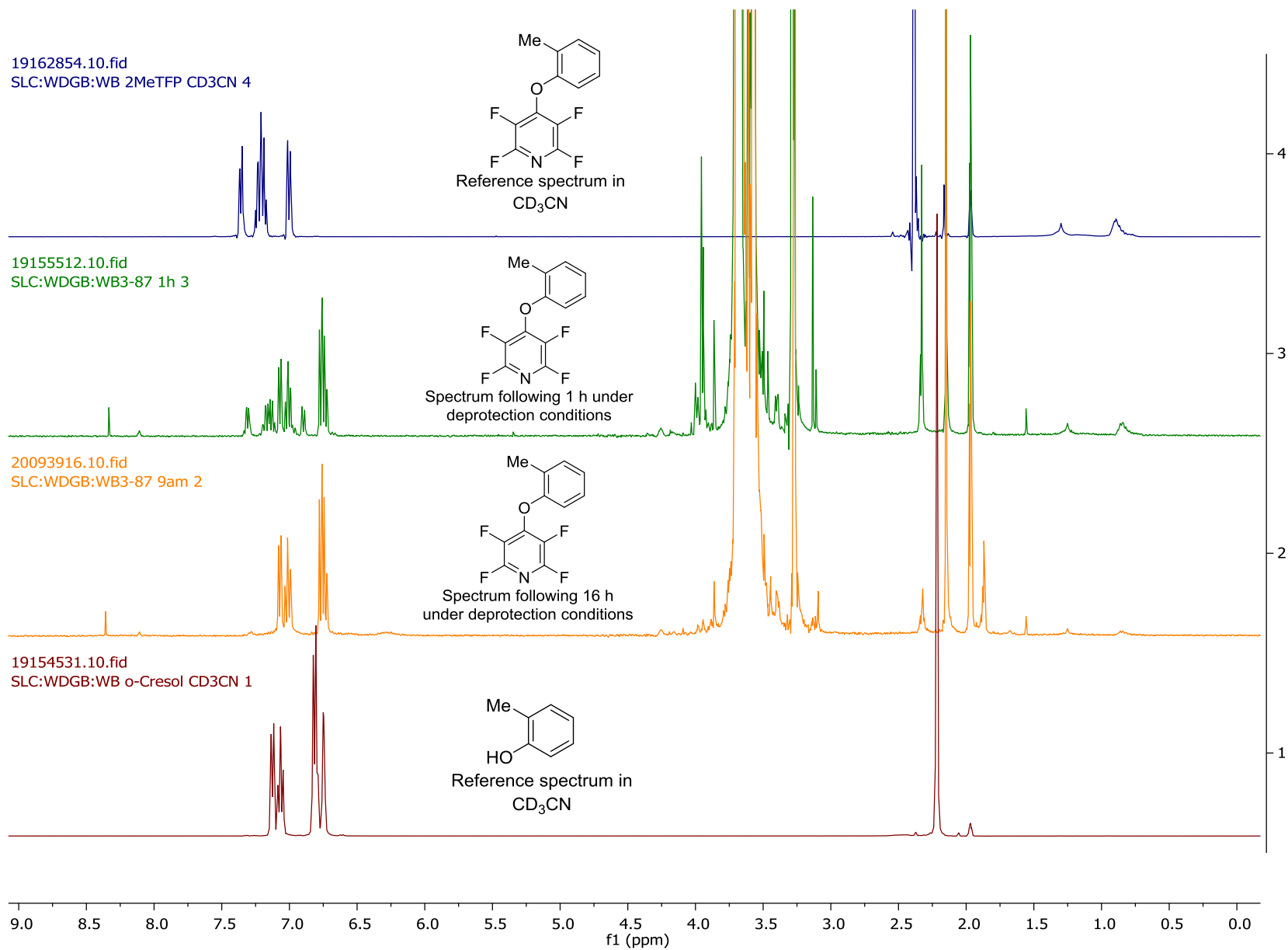
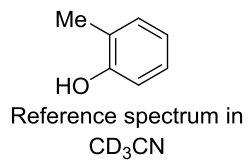
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SLC:WDGB:WB3-87 1h 3



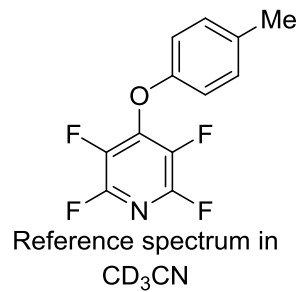
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SLC:WDGB:WB3-87 9am 2



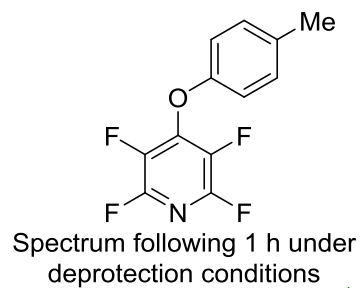
19154531.10.fid
SLC:WDGB:WB o-Cresol CD3CN 1



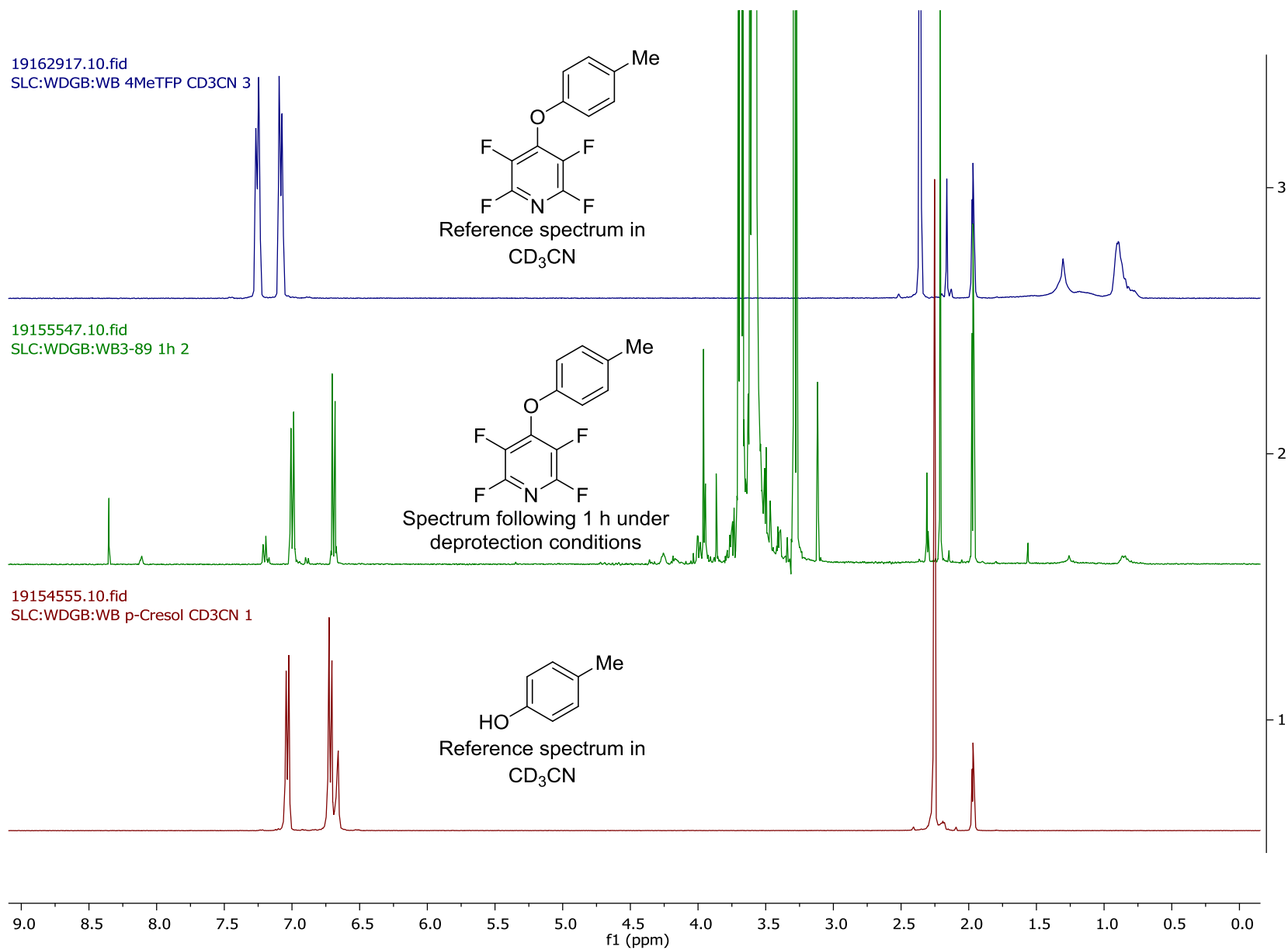
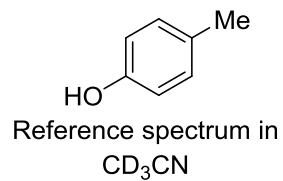
19162917.10.fid
SLC:WDGB:WB 4MeTFP CD3CN 3



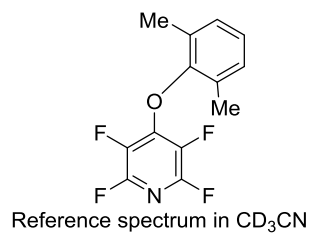
19155547.10.fid
SLC:WDGB:WB3-89 1h 2



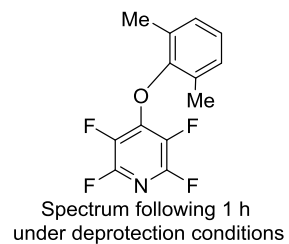
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SLC:WDGB:WB p-Cresol CD3CN 1



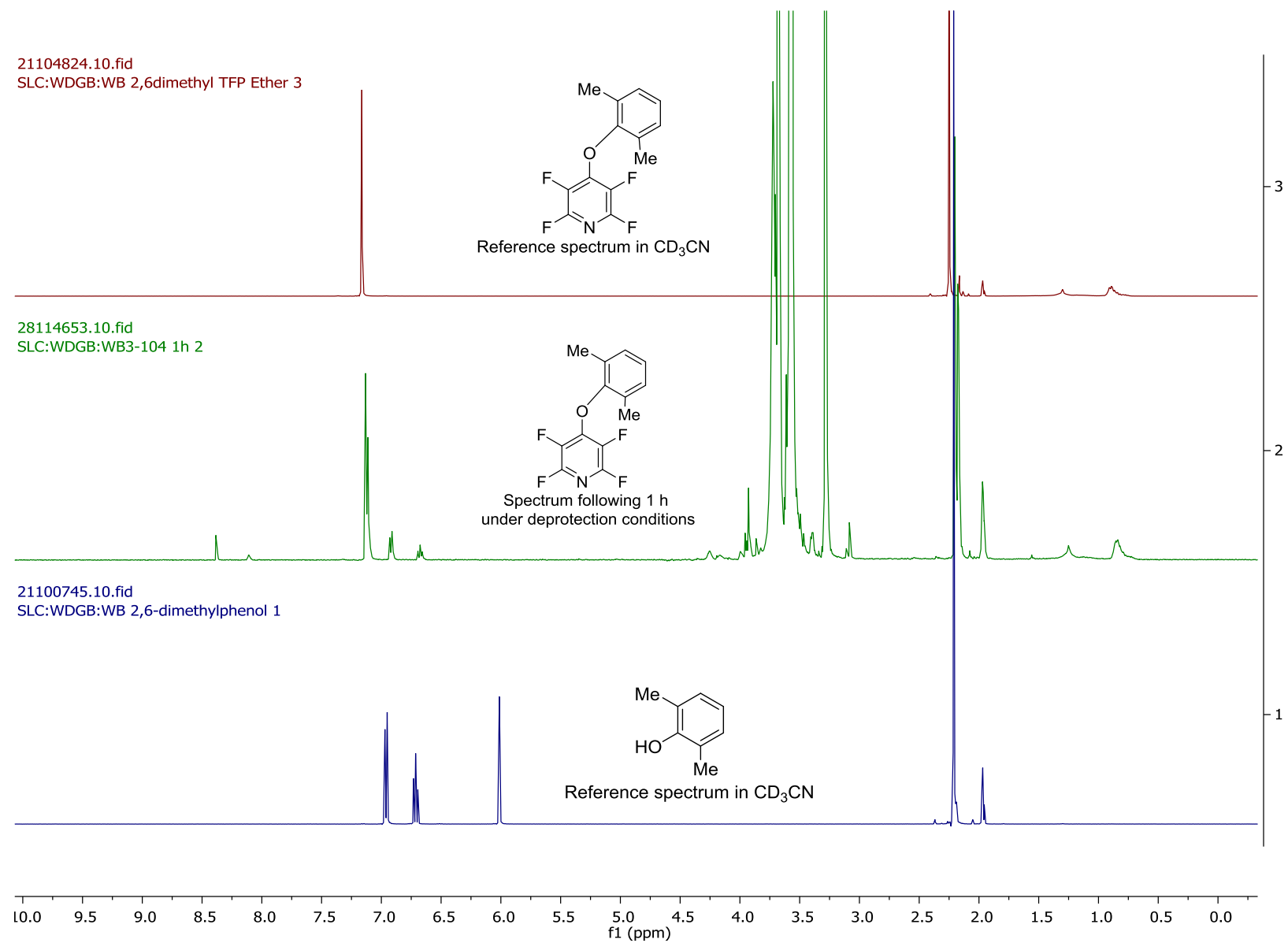
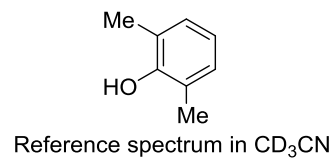
21104824.10.fid
SLC:WDGB:WB 2,6dimethyl TFP Ether 3



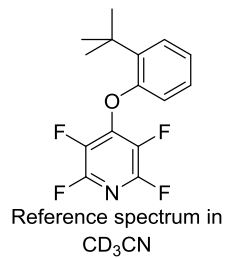
28114653.10.fid
SLC:WDGB:WB3-104 1h 2



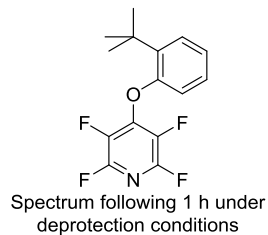
21100745.10.fid
SLC:WDGB:WB 2,6-dimethylphenol 1



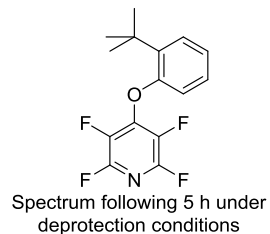
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SLC:WDGB:WB 2tBu TFP Ether 4



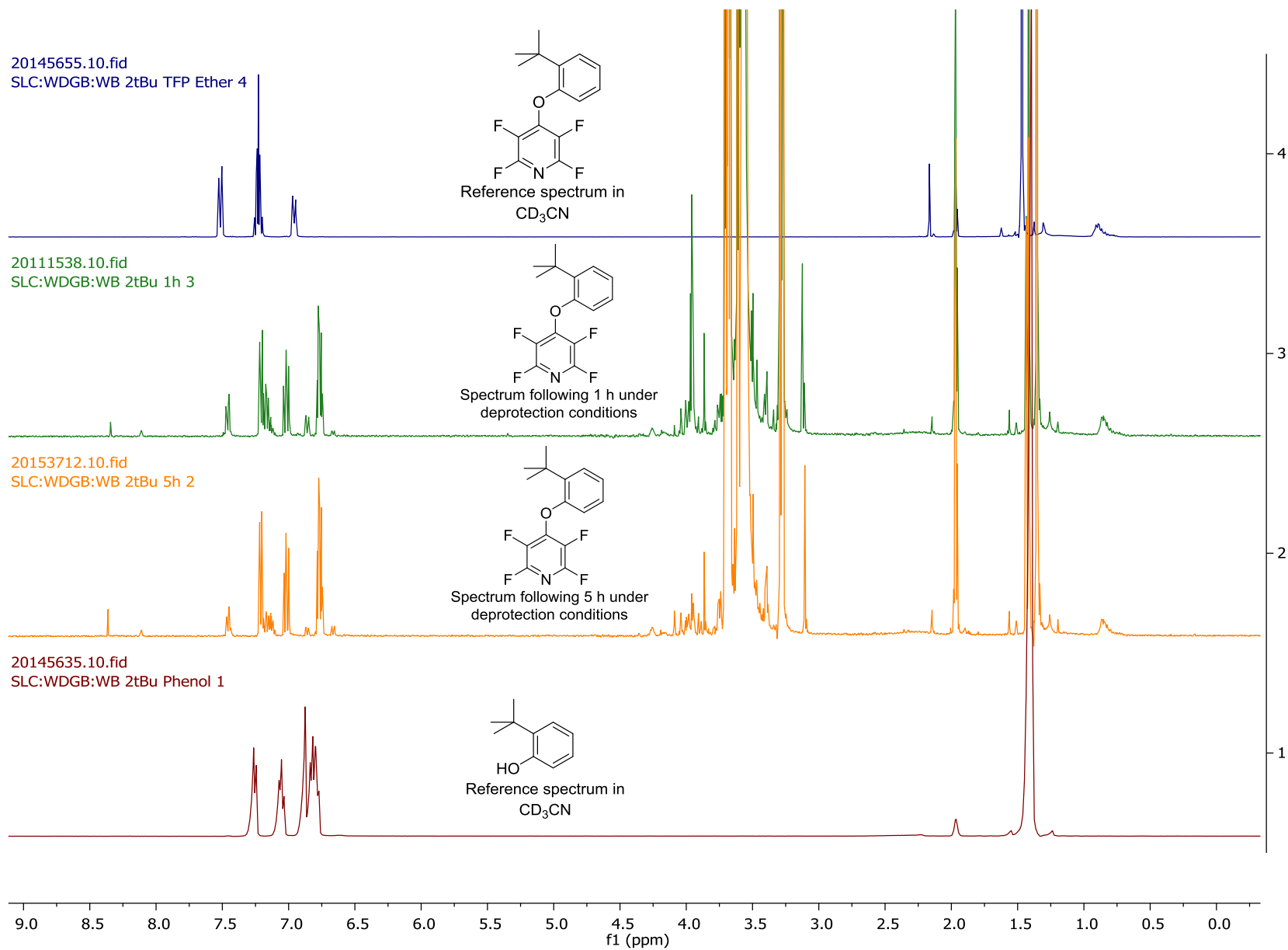
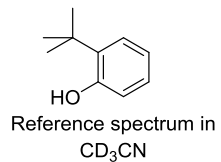
20111538.10.fid
SLC:WDGB:WB 2tBu 1h 3



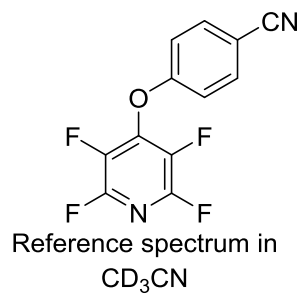
20153712.10.fid
SLC:WDGB:WB 2tBu 5h 2



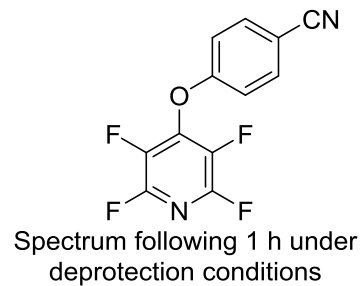
20145635.10.fid
SLC:WDGB:WB 2tBu Phenol 1



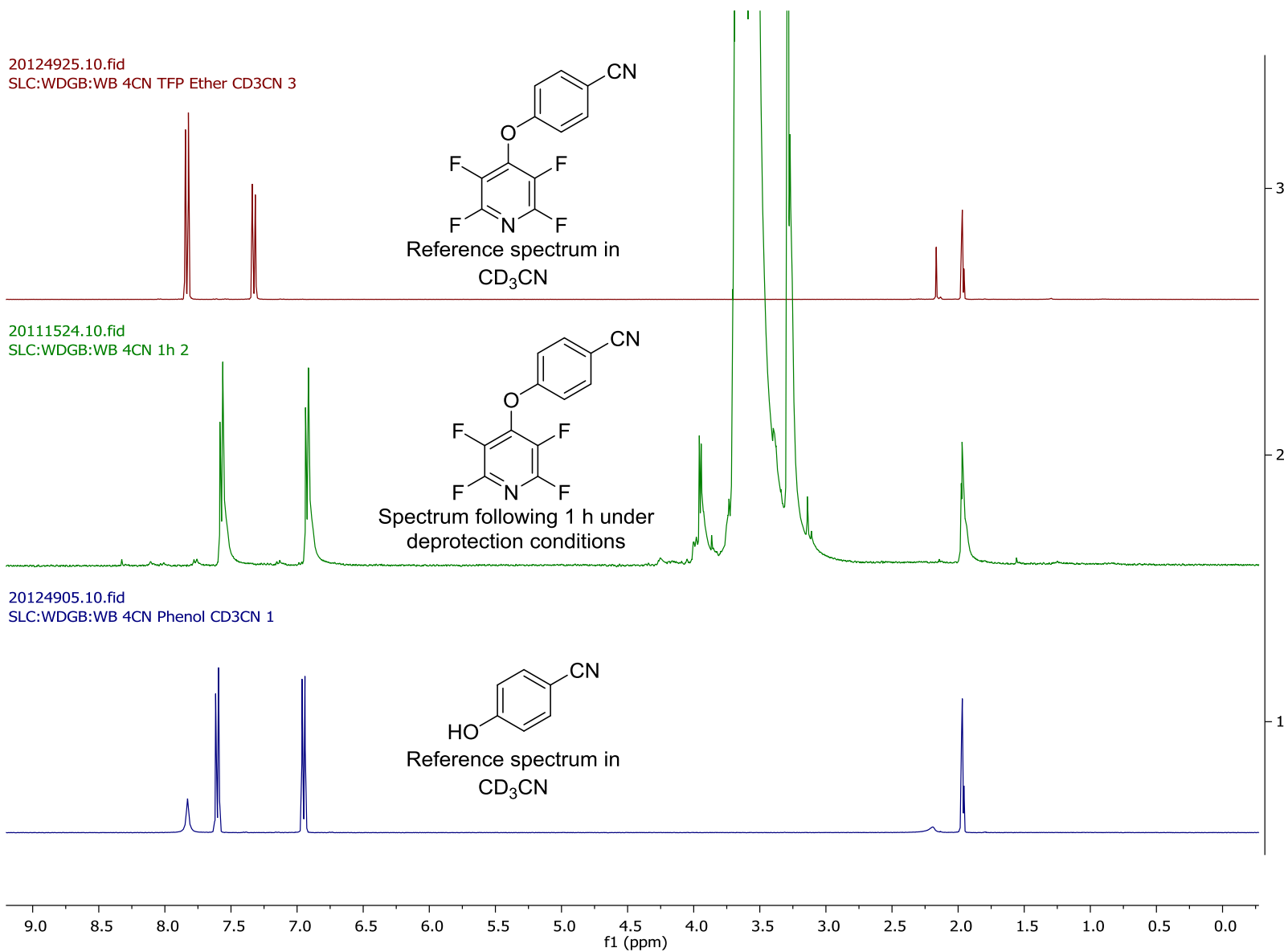
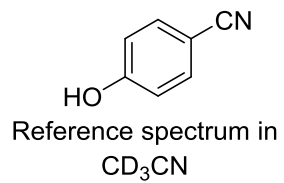
20124925.10.fid
SLC:WDGB:WB 4CN TFP Ether CD3CN 3



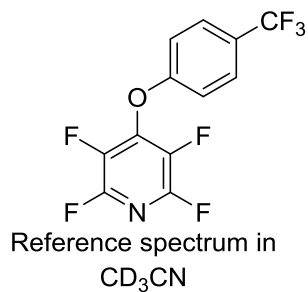
20111524.10.fid
SLC:WDGB:WB 4CN 1h 2



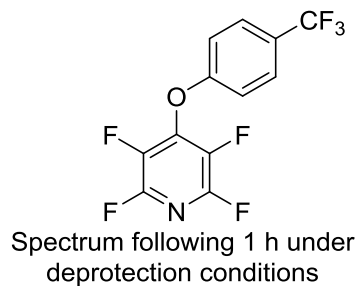
20124905.10.fid
SLC:WDGB:WB 4CN Phenol CD3CN 1



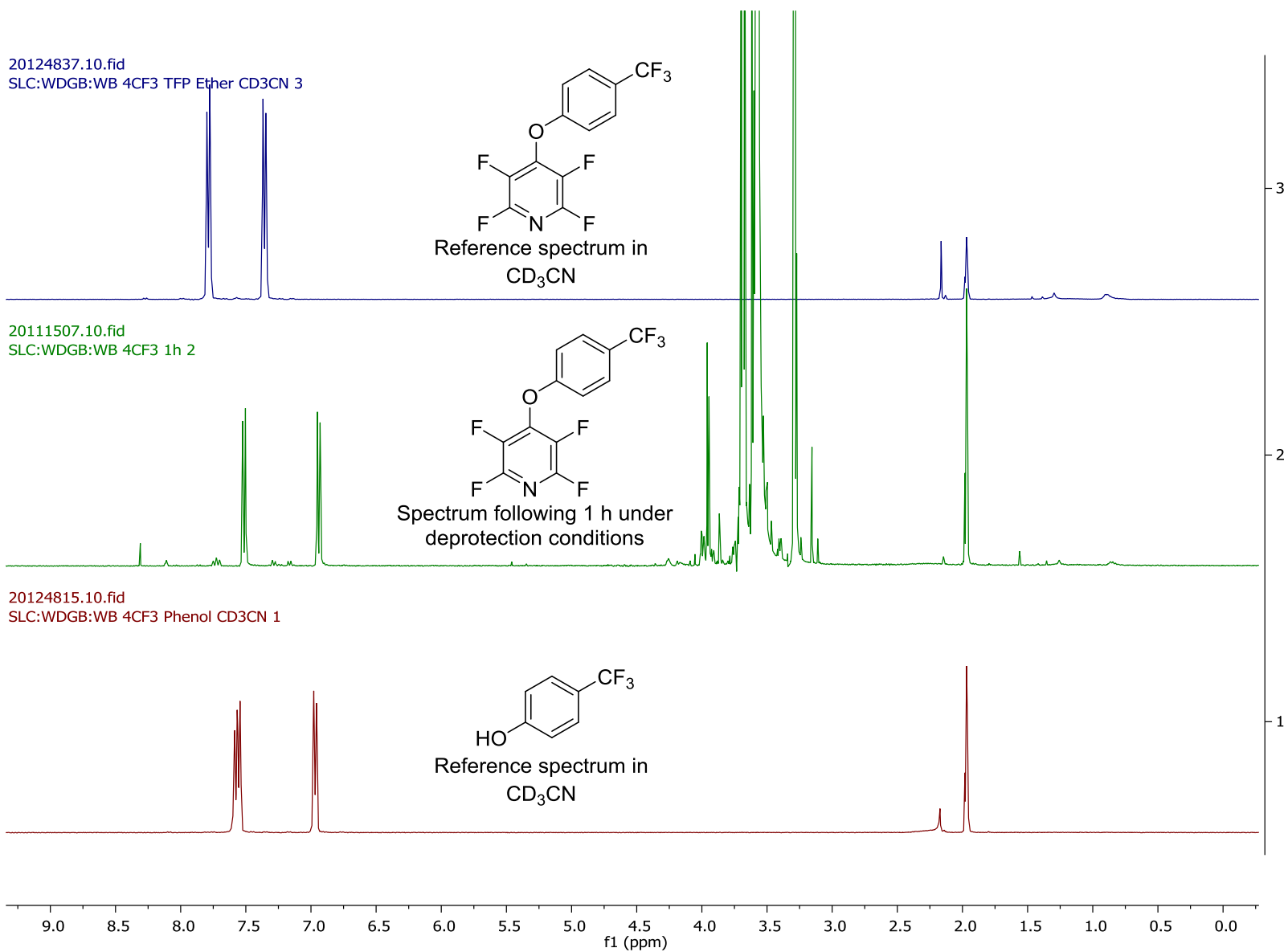
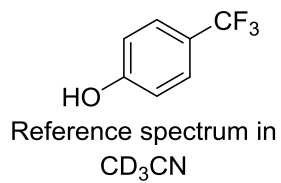
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SLC:WDGB:WB 4CF3 TFP Ether CD3CN 3



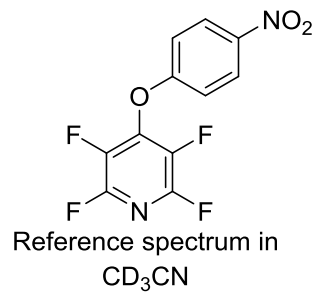
20111507.10.fid
SLC:WDGB:WB 4CF3 1h 2



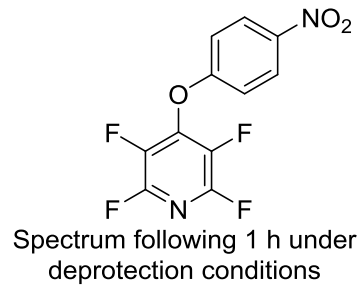
20124815.10.fid
SLC:WDGB:WB 4CF3 Phenol CD3CN 1



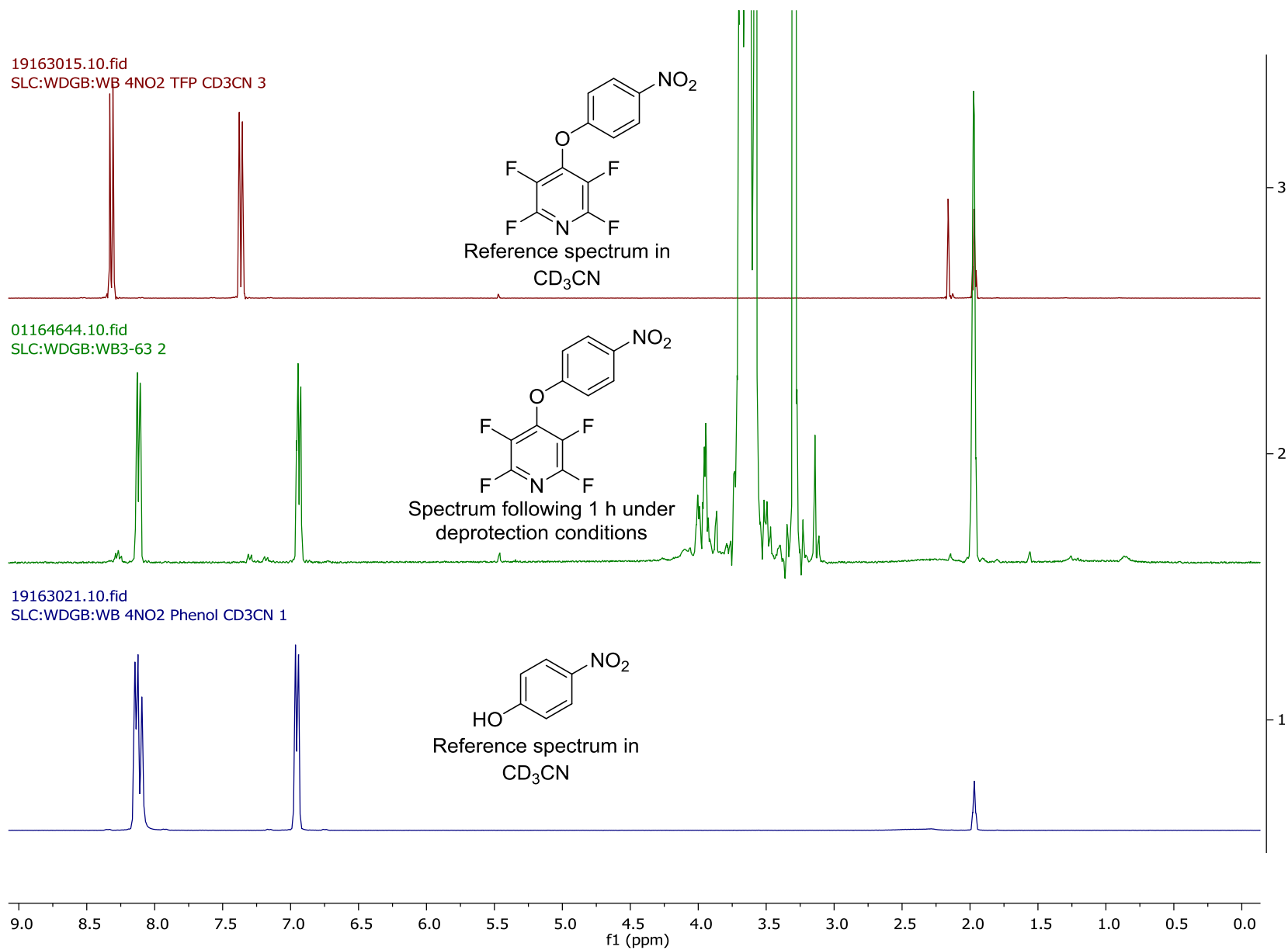
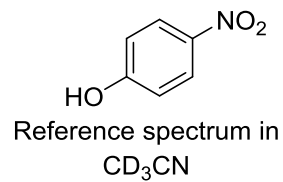
19163015.10.fid
SLC:WDGB:WB 4NO2 TFP CD3CN 3



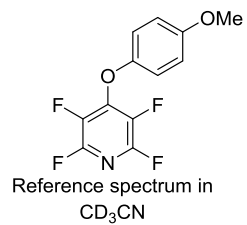
01164644.10.fid
SLC:WDGB:WB3-63 2



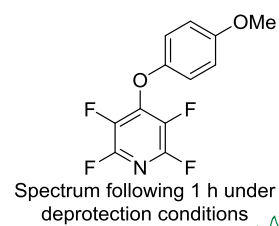
19163021.10.fid
SLC:WDGB:WB 4NO2 Phenol CD3CN 1



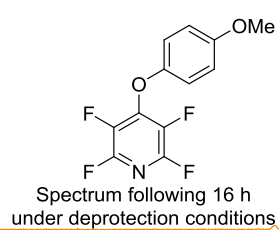
07092108.10.fid
SLC:WDGB:WB3-66 4



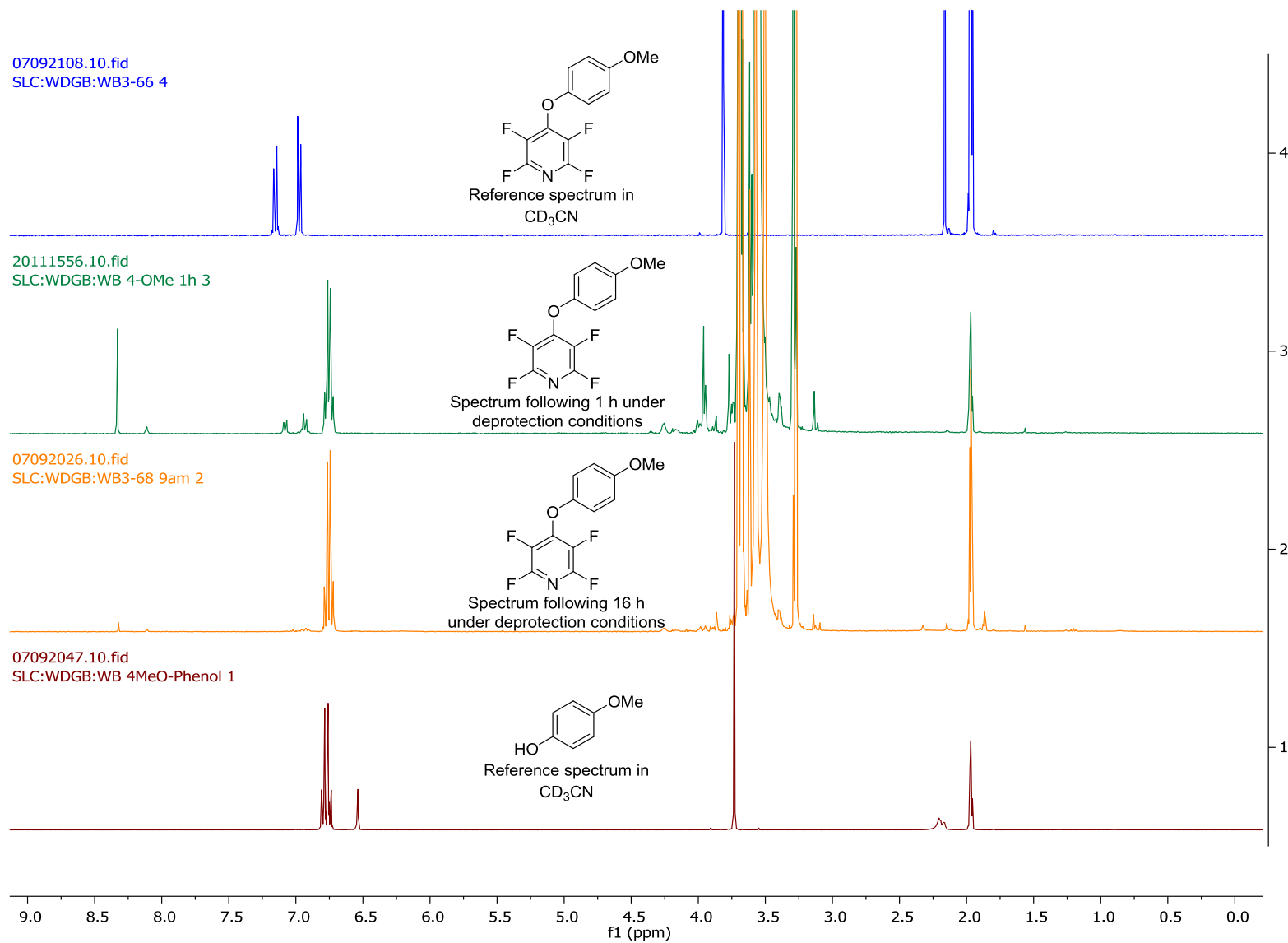
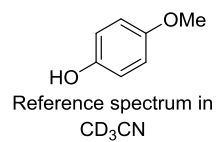
20111556.10.fid
SLC:WDGB:WB 4-OMe 1h 3



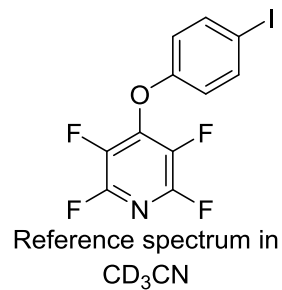
07092026.10.fid
SLC:WDGB:WB3-68 9am 2



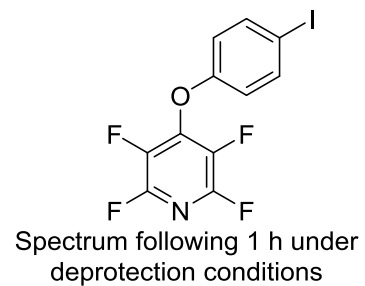
07092047.10.fid
SLC:WDGB:WB 4MeO-Phenol 1



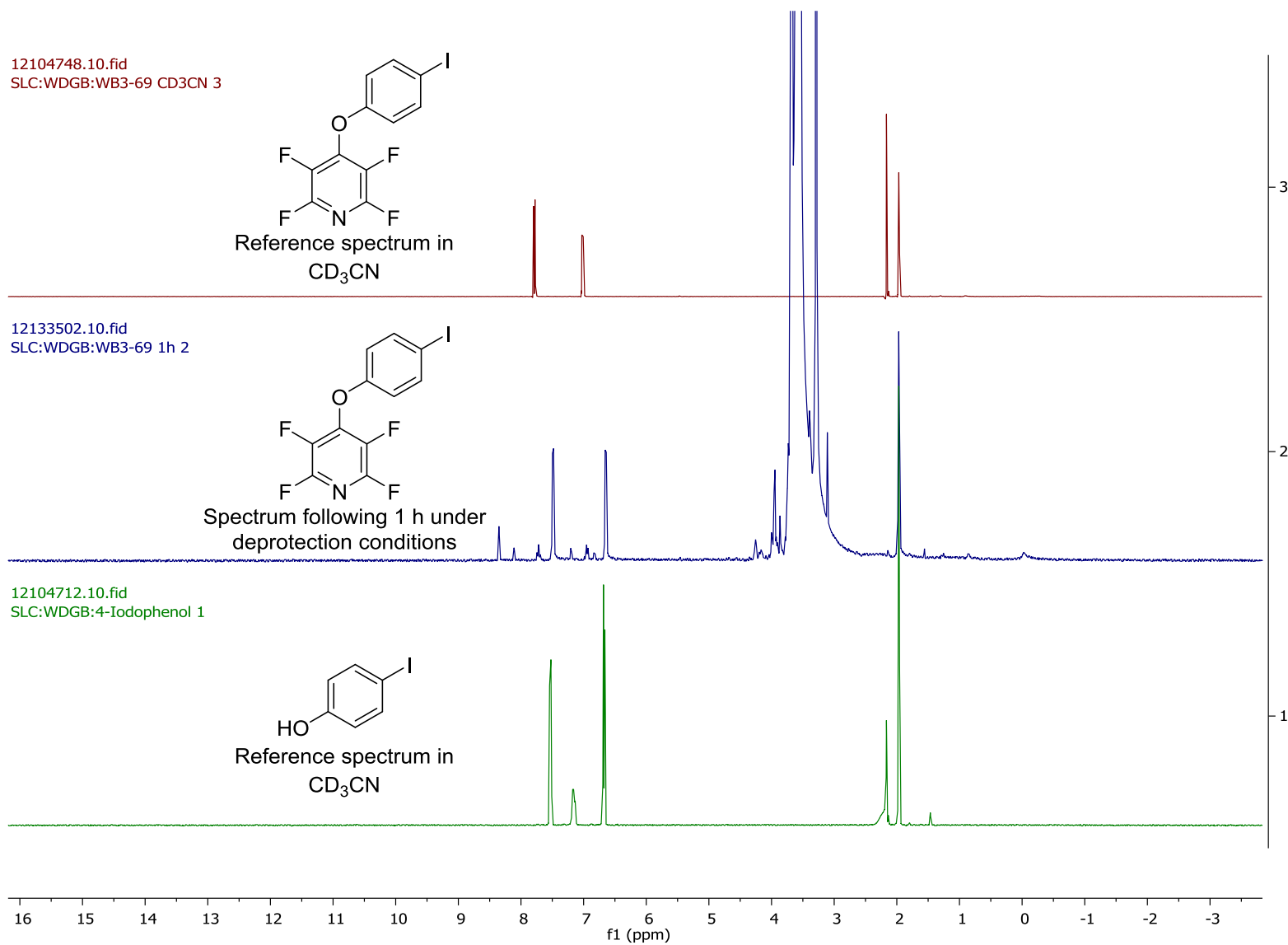
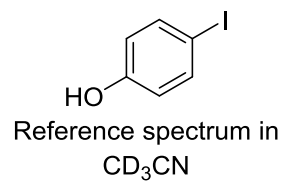
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SLC:WDGB:WB3-69 CD3CN 3



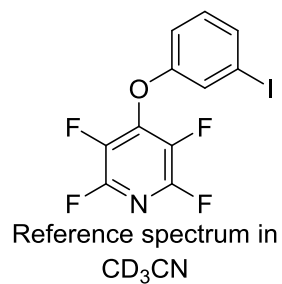
12133502.10.fid
SLC:WDGB:WB3-69 1h 2



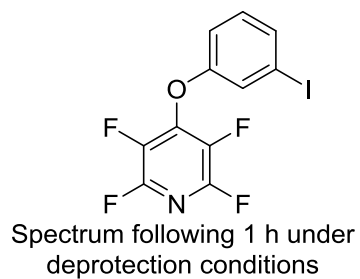
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SLC:WDGB:4-Iodophenol 1



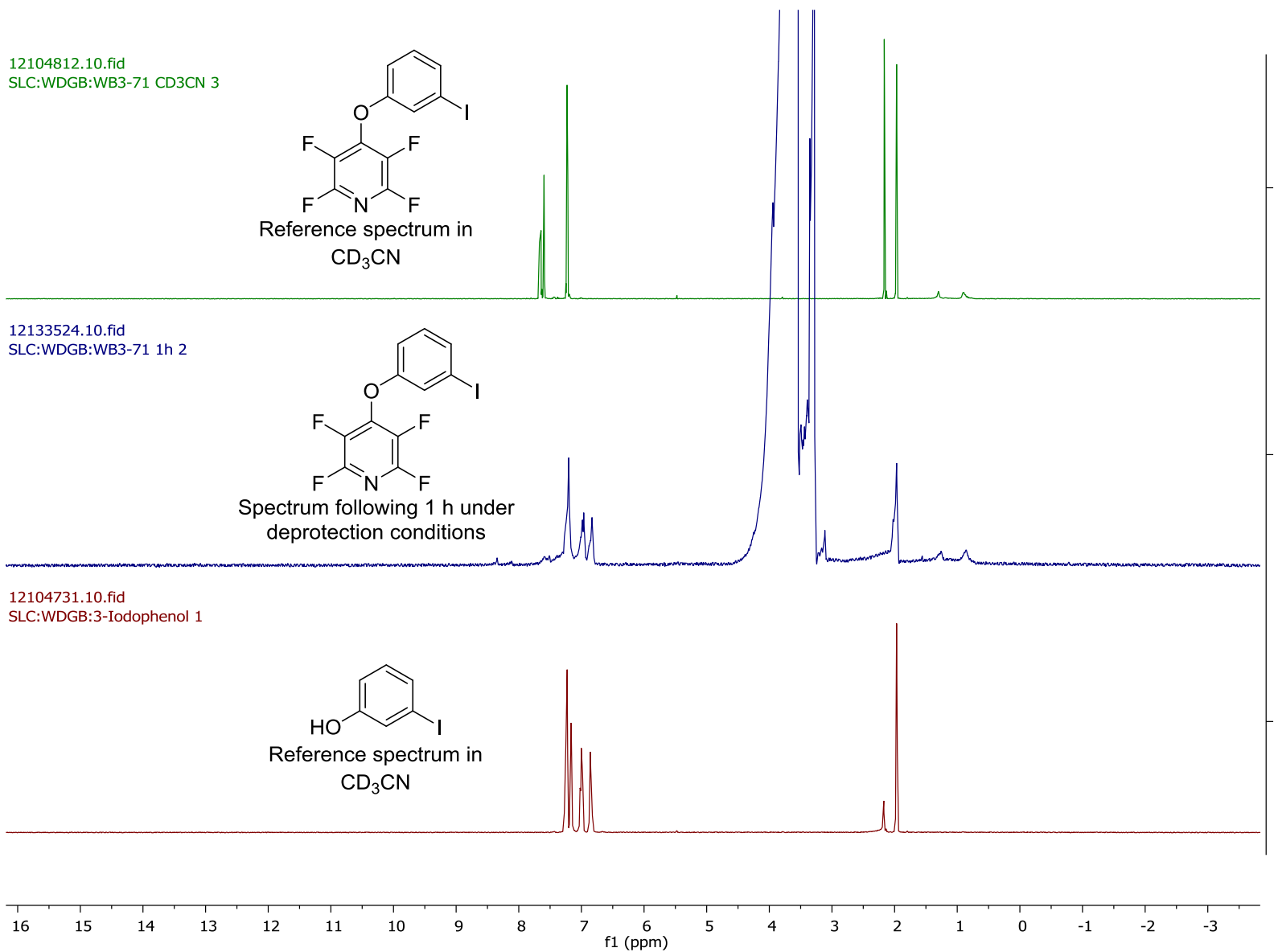
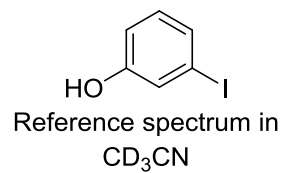
12104812.10.fid
SLC:WDGB:WB3-71 CD3CN 3



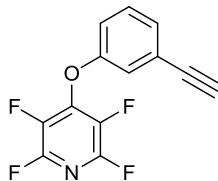
12133524.10.fid
SLC:WDGB:WB3-71 1h 2



12104731.10.fid
SLC:WDGB:3-Iodophenol 1

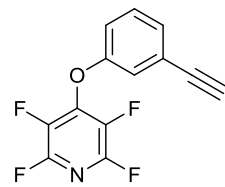


11125027.10.fid
SLC:WDGB:WB3-109 SM 3



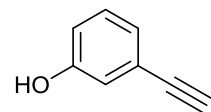
Reference spectrum
in CD₃CN

11133921.10.fid
SLC:WDGB:WB3-111 1H 2

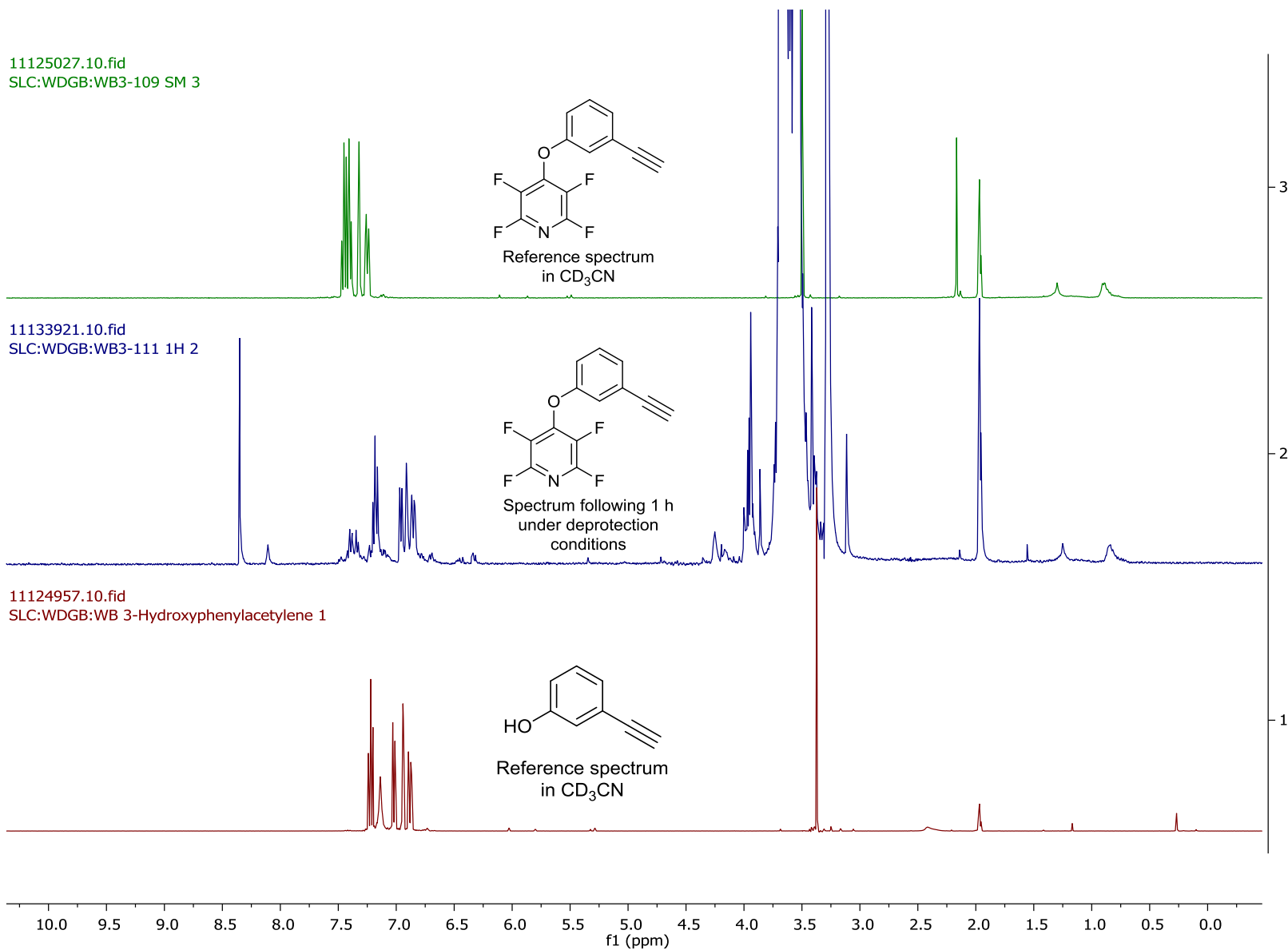


Spectrum following 1 h
under deprotection
conditions

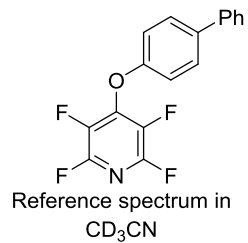
11124957.10.fid
SLC:WDGB:WB 3-Hydroxyphenylacetylene 1



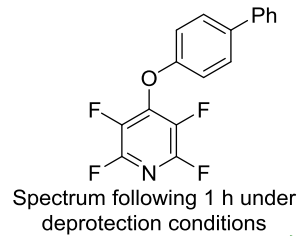
Reference spectrum
in CD₃CN



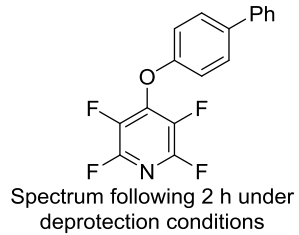
21104809.10.fid
SLC:WDGB:WB 4-Ph TFP Ether 4



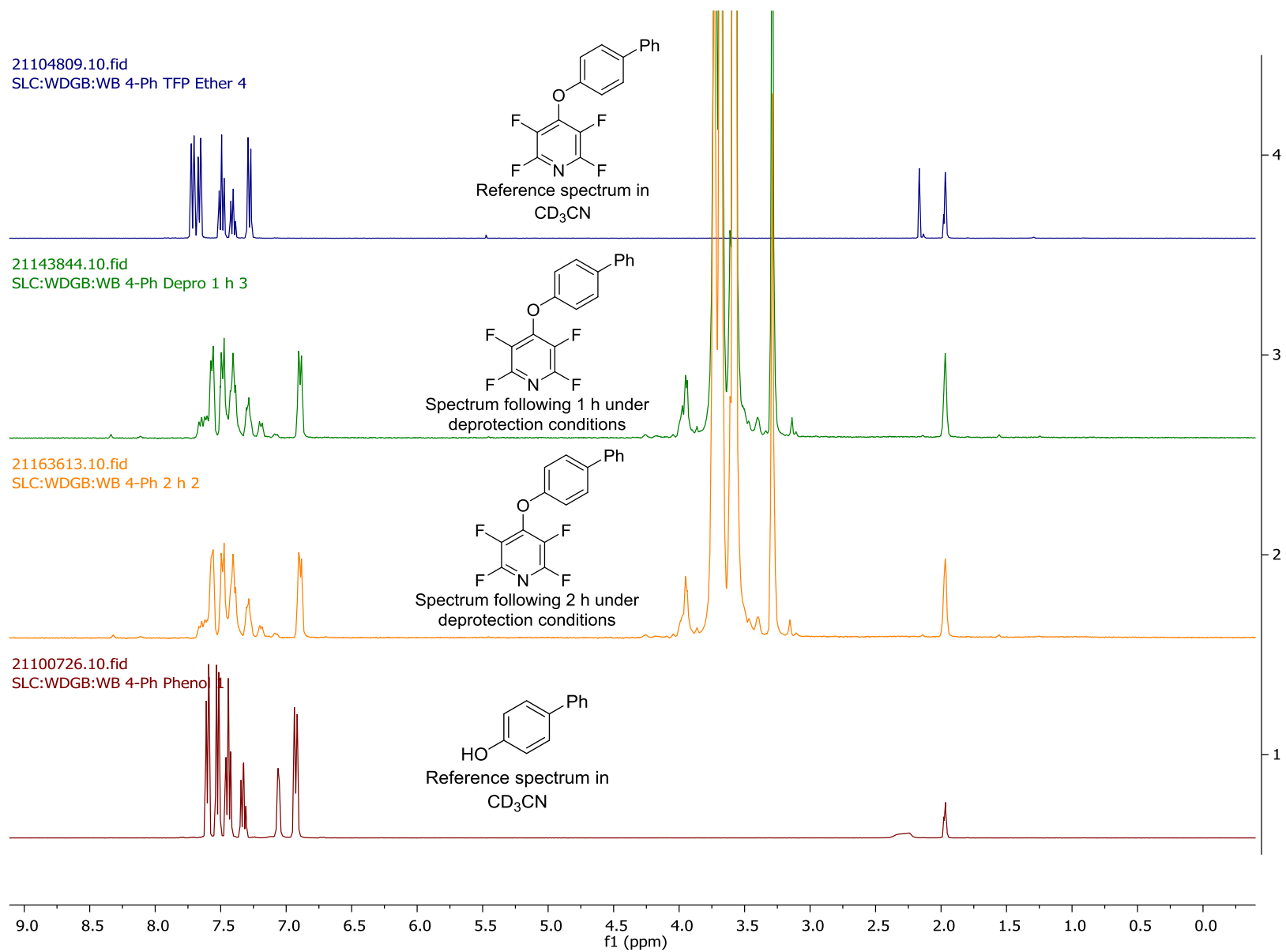
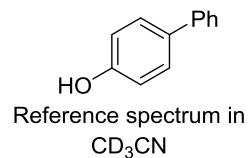
21143844.10.fid
SLC:WDGB:WB 4-Ph Depro 1 h 3

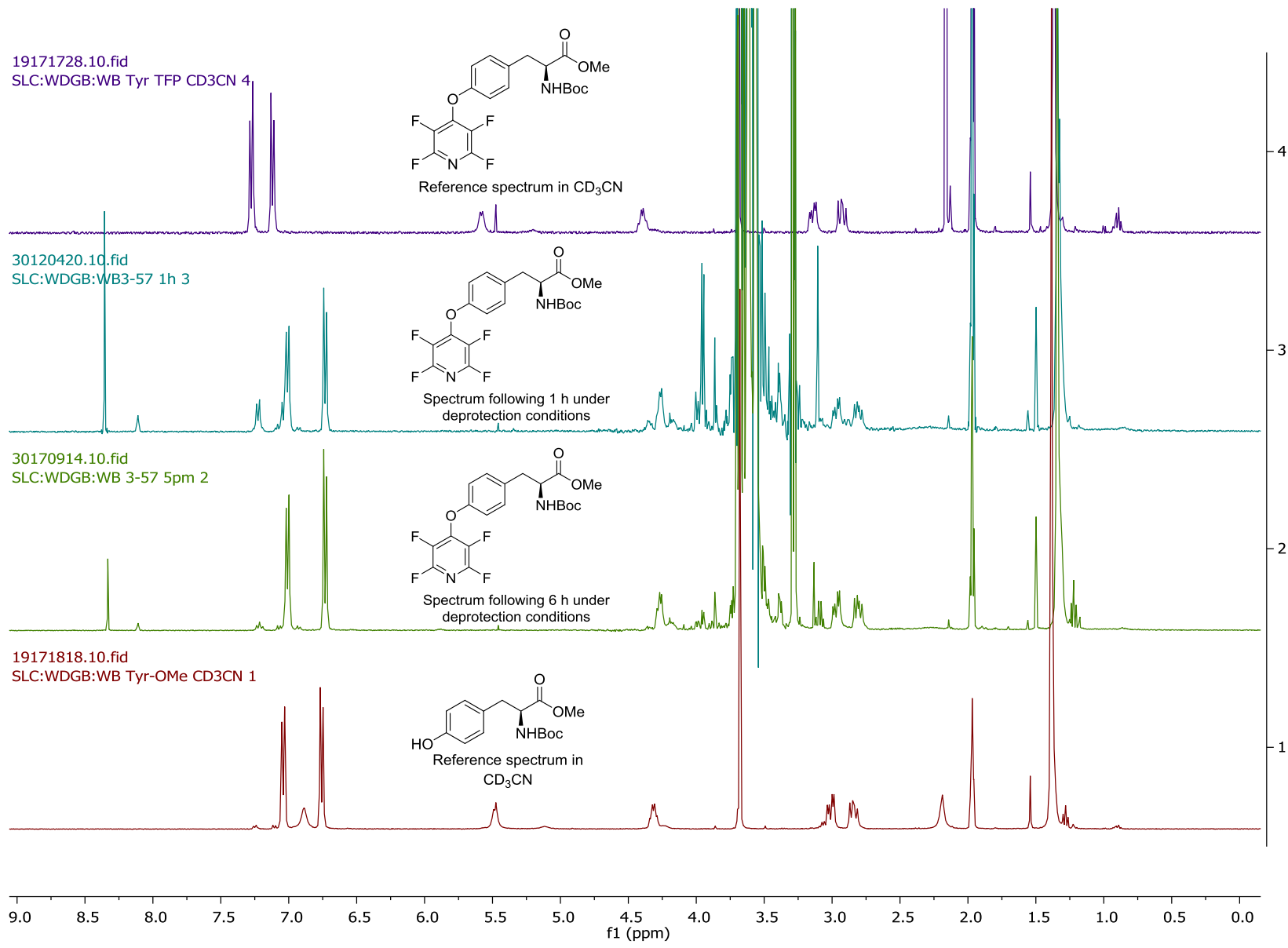


21163613.10.fid
SLC:WDGB:WB 4-Ph 2 h 2

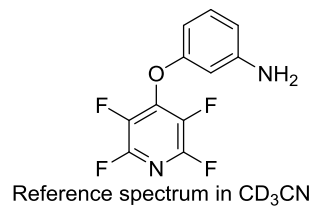


21100726.10.fid
SLC:WDGB:WB 4-Ph Phenol

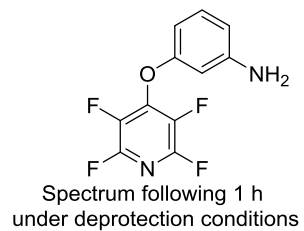




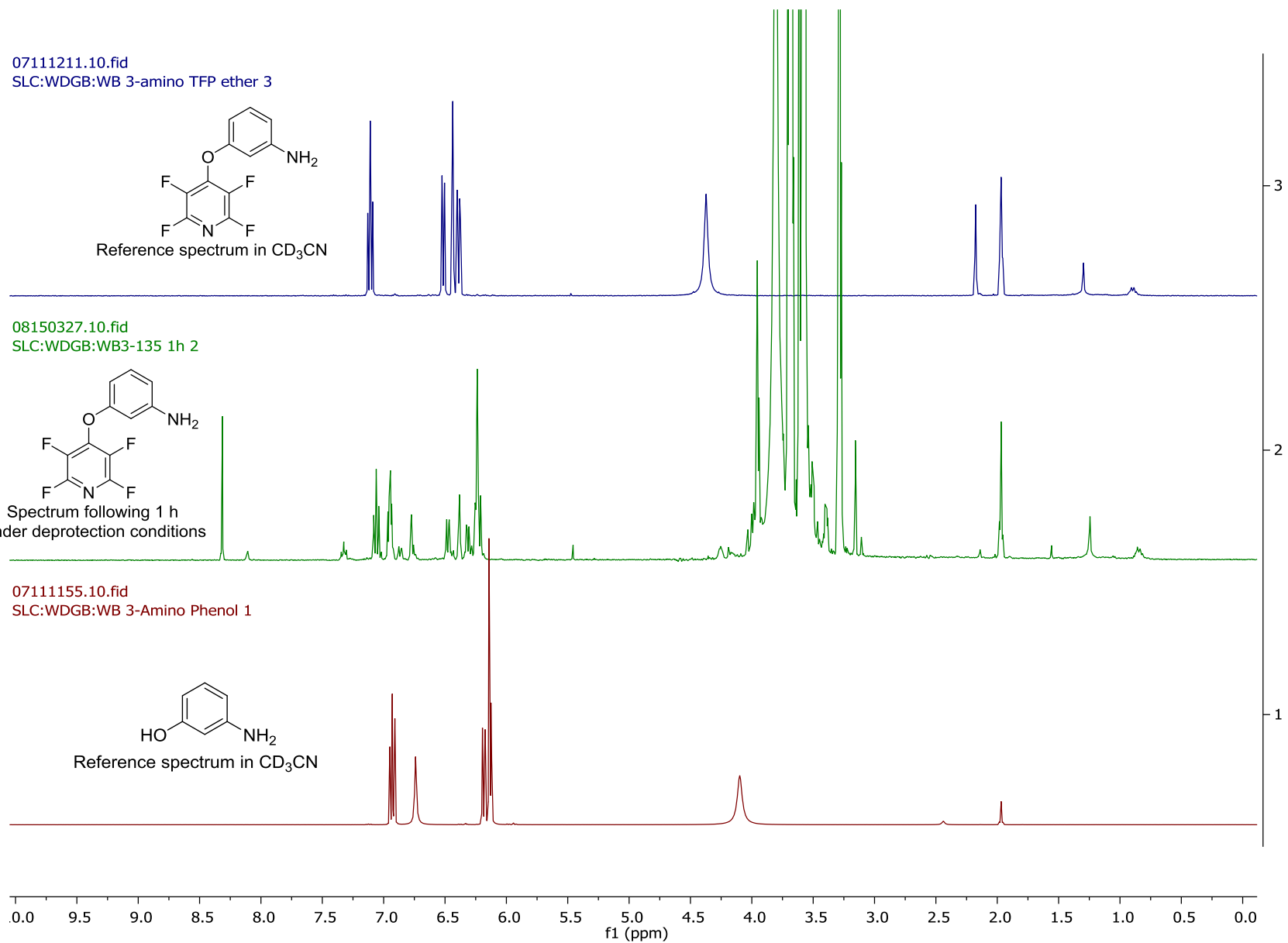
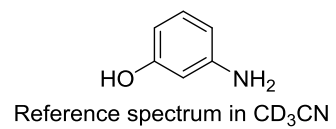
07111211.10.fid
SLC:WDGB:WB 3-amino TFP ether 3



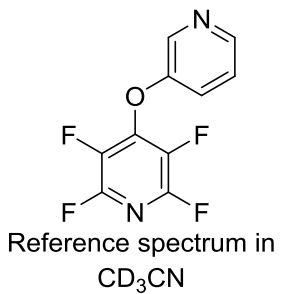
08150327.10.fid
SLC:WDGB:WB3-135 1h 2



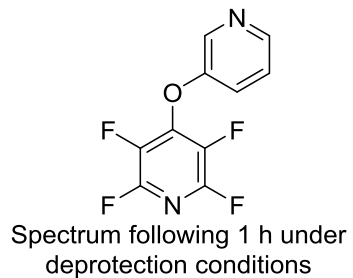
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SLC:WDGB:WB 3-Amino Phenol 1



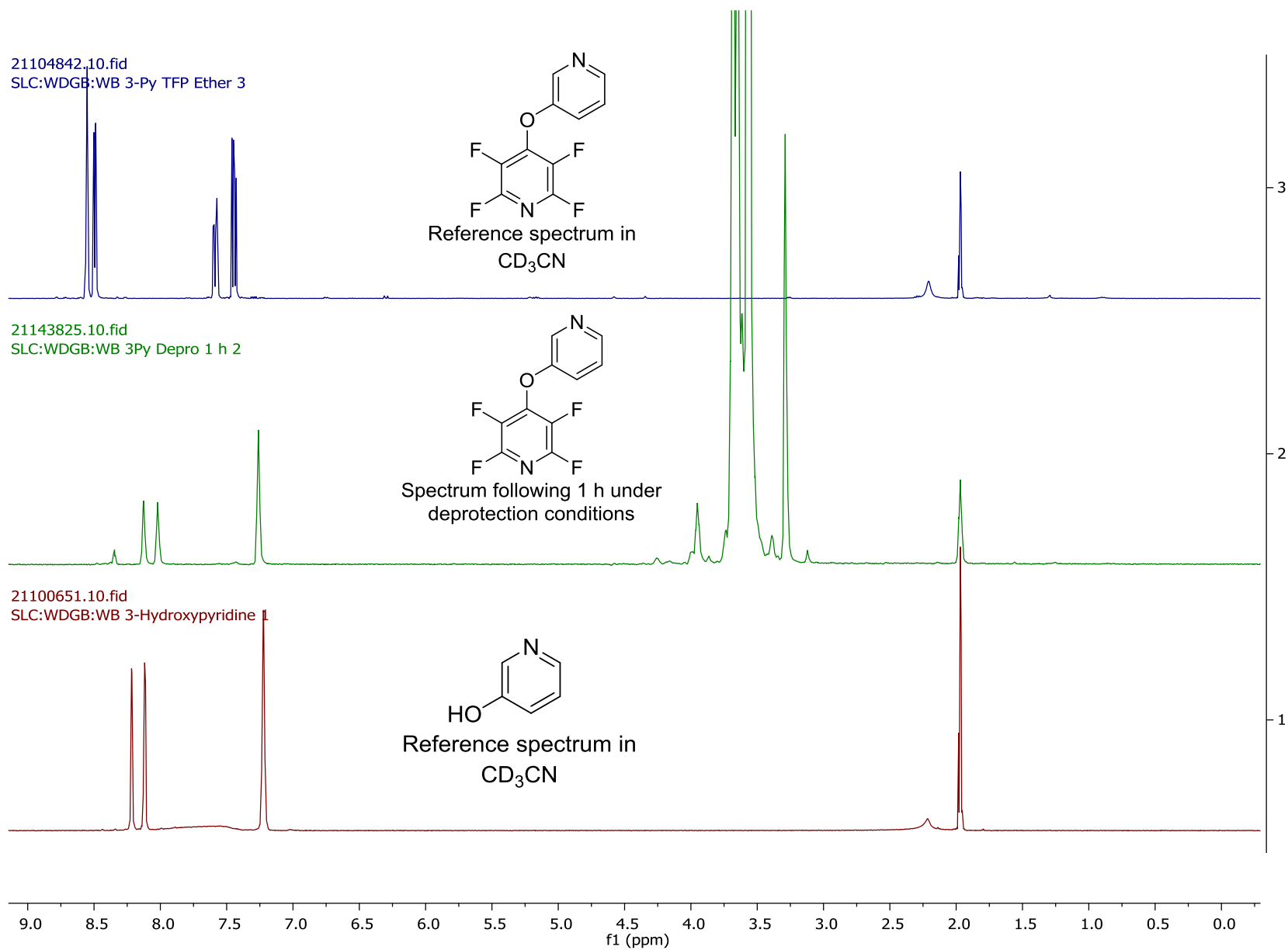
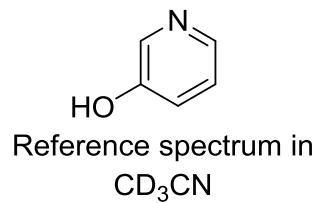
21104842.10.fid
SLC:WDGB:WB 3-Py TFP Ether 3



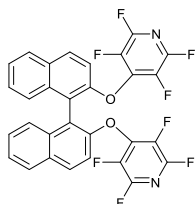
21143825.10.fid
SLC:WDGB:WB 3Py Depro 1 h 2



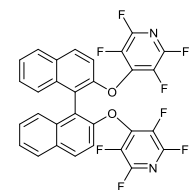
21100651.10.fid
SLC:WDGB:WB 3-Hydroxypyridine



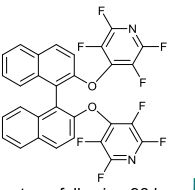
02122522.10.fid
SLC:WDGB:WB BINOL_TFP Ether 4



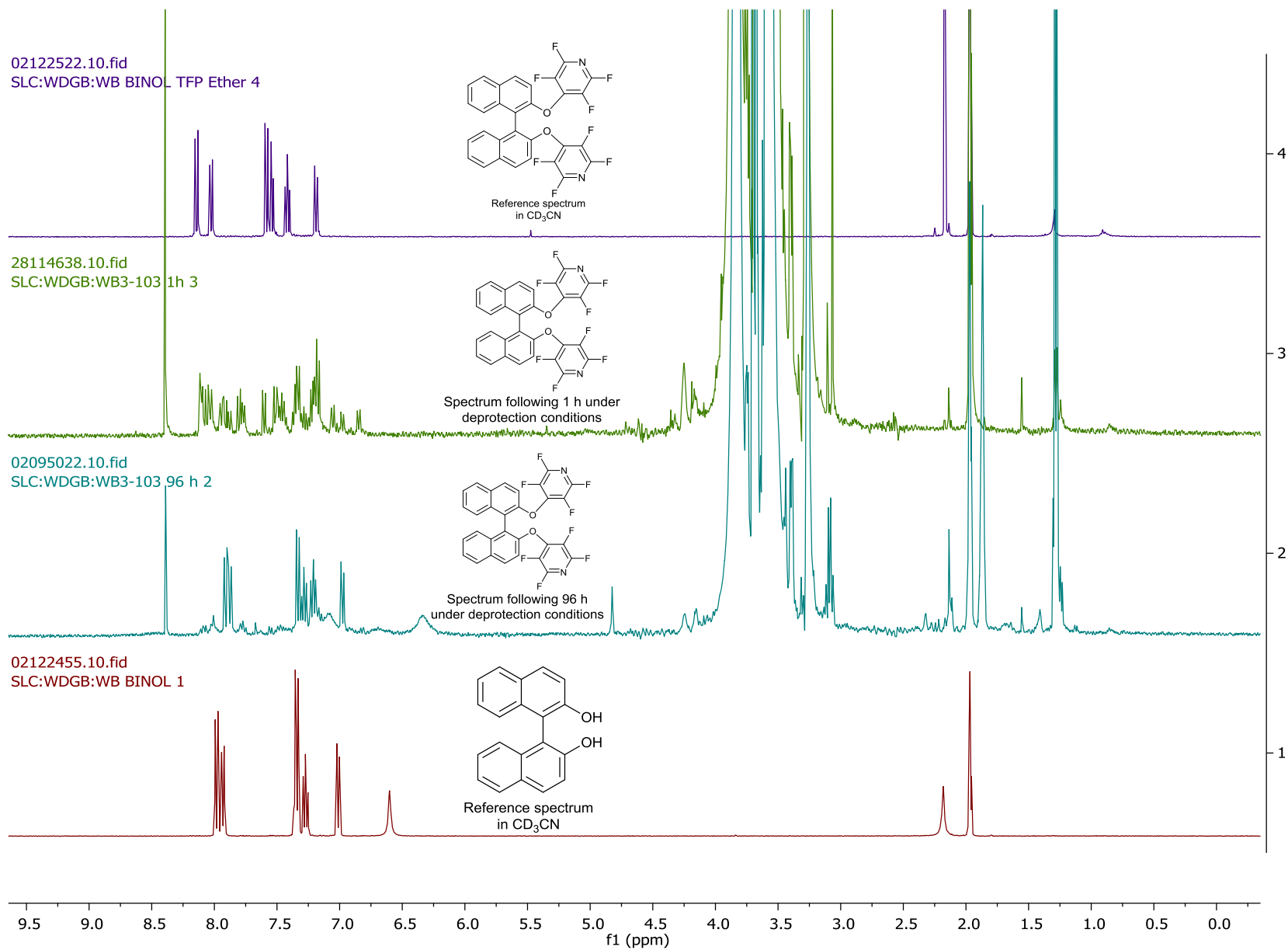
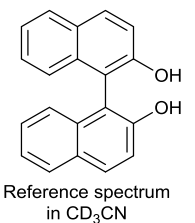
28114638.10.fid
SLC:WDGB:WB3-103 1h 3

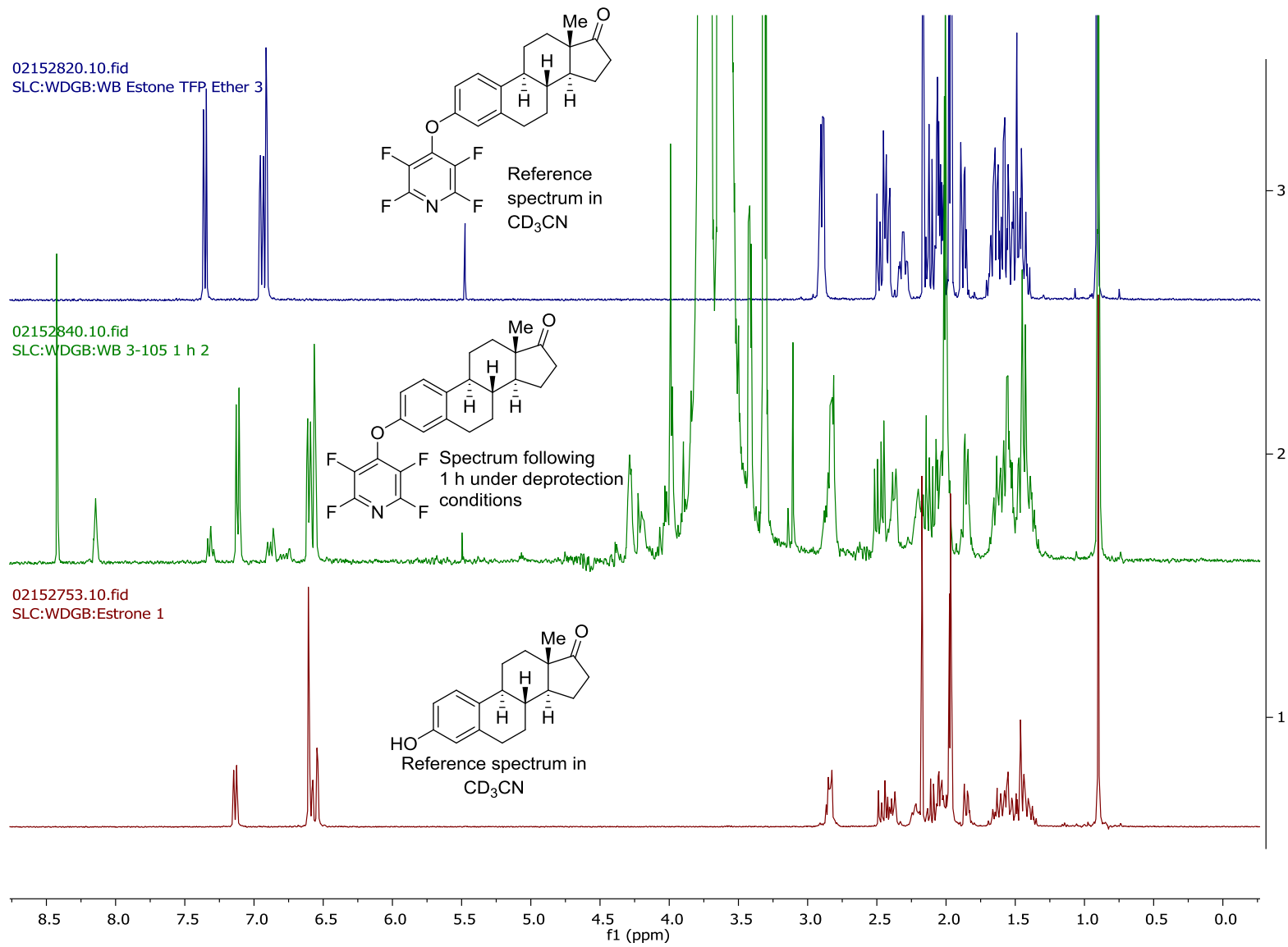


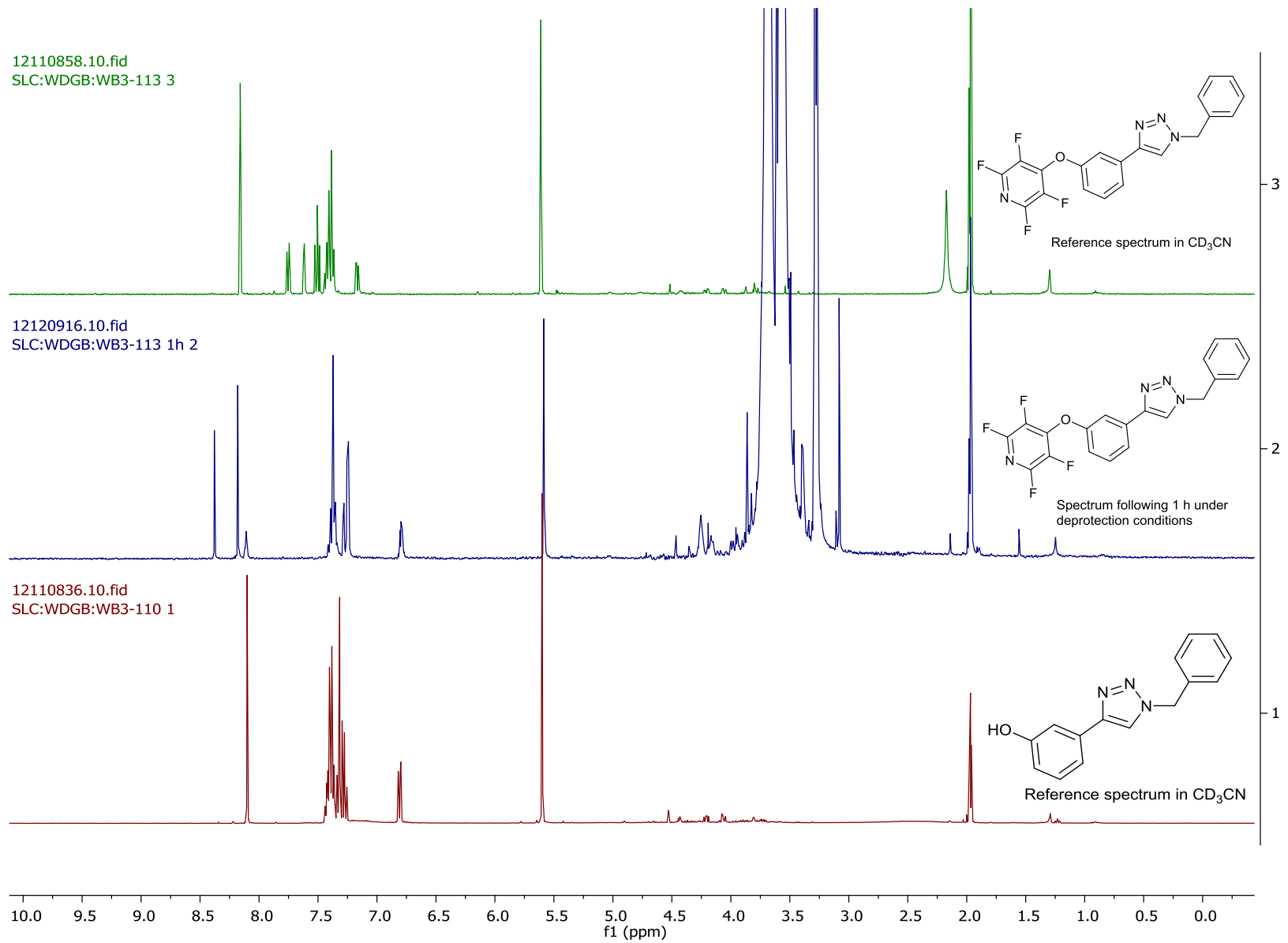
02095022.10.fid
SLC:WDGB:WB3-103 96 h 2



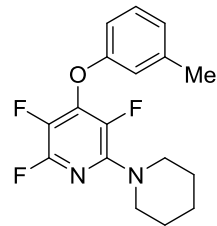
02122455.10.fid
SLC:WDGB:WB BINOL 1





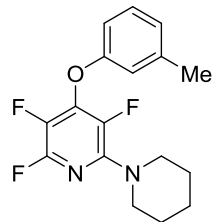


28145750.10.fid
SLC:WDGB:WB3-100 CD3CN 3



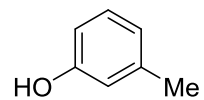
Reference spectrum in CD₃CN

29095508.10.fid
SLC:WDGB:WB3-102 24h 2

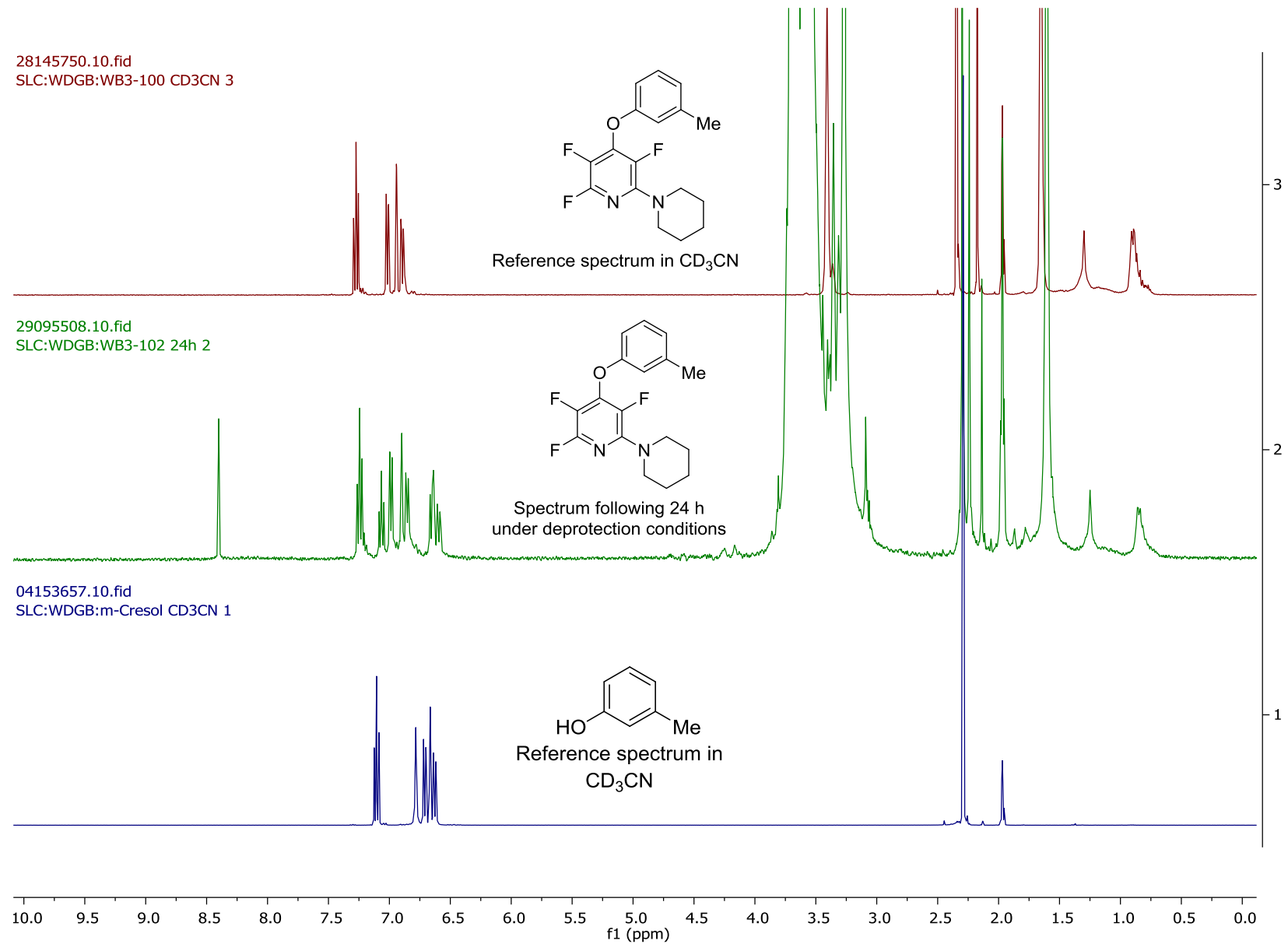


Spectrum following 24 h
under deprotection conditions

04153657.10.fid
SLC:WDGB:m-Cresol CD3CN 1

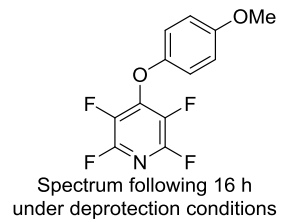


Reference spectrum in
CD₃CN

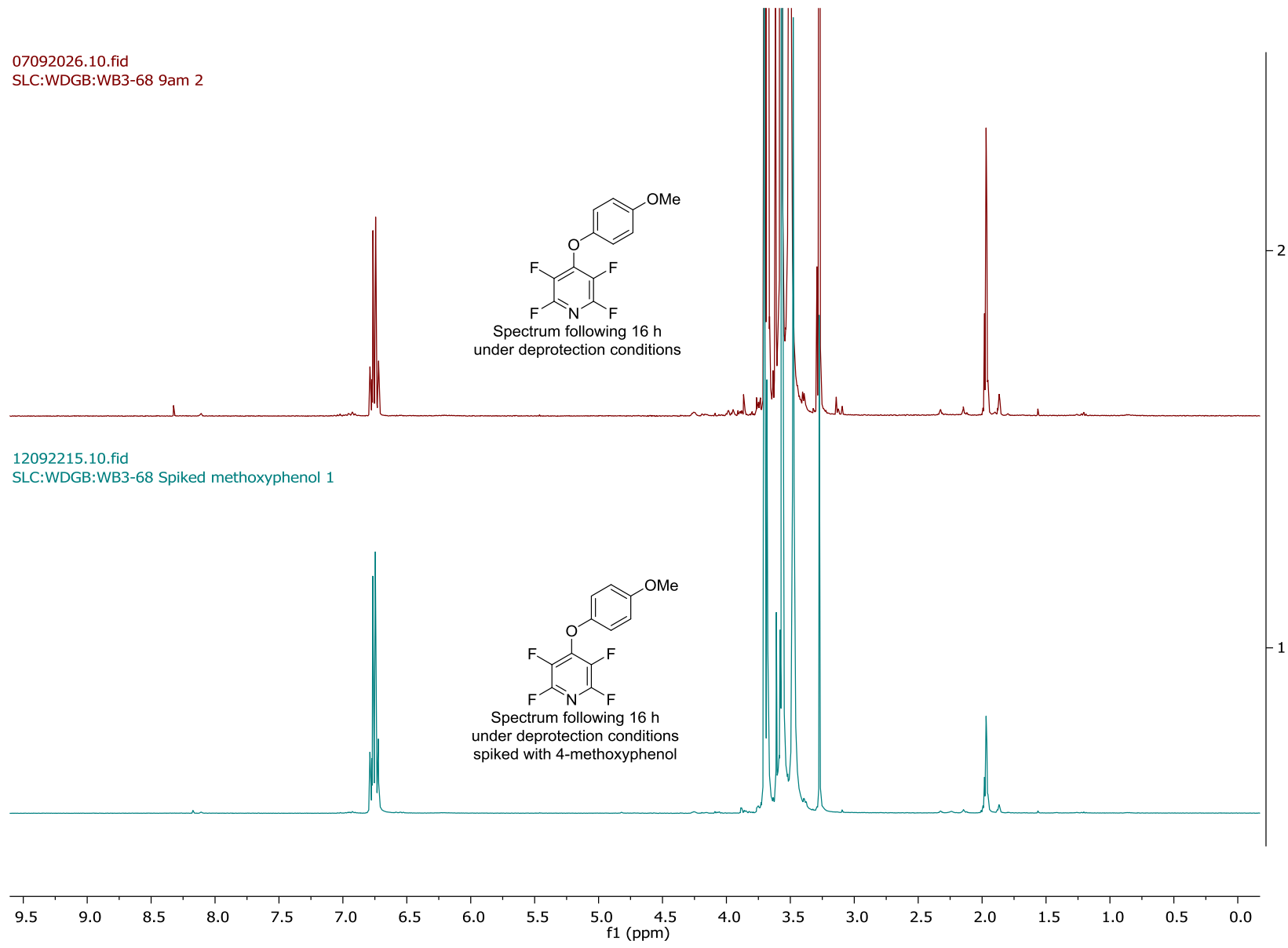
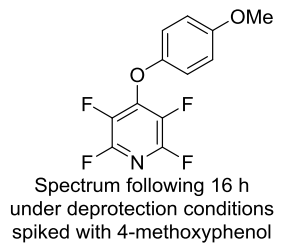


NMR Spiking Experiments

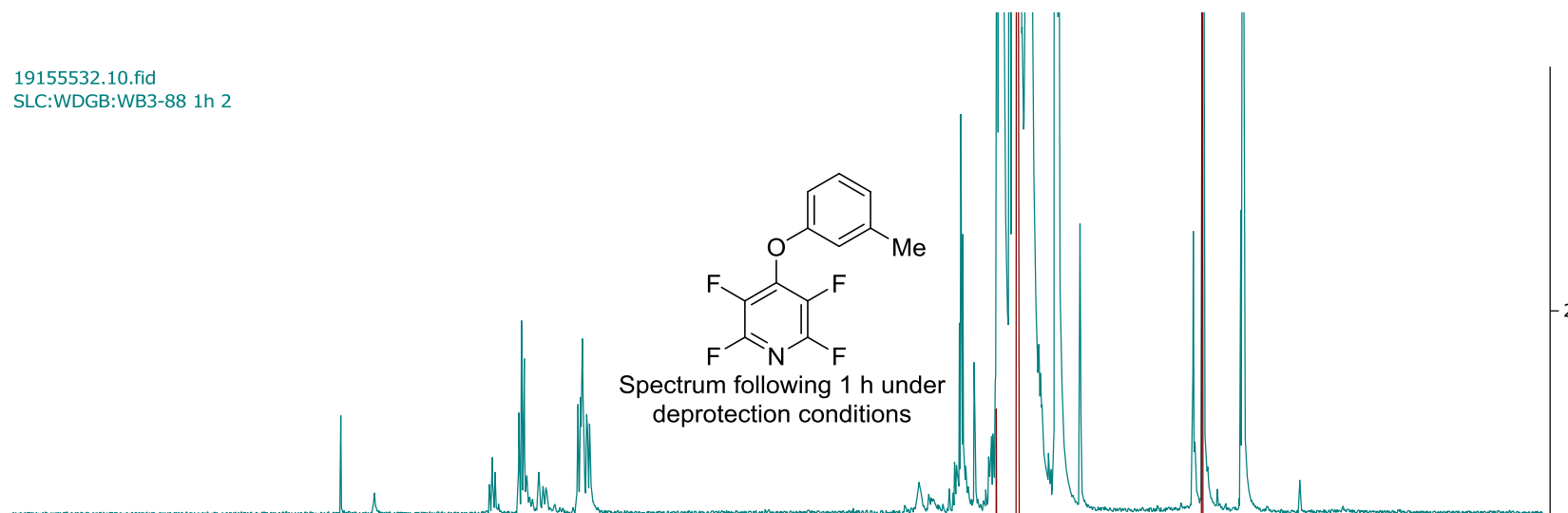
07092026.10.fid
SLC:WDGB:WB3-68 9am 2



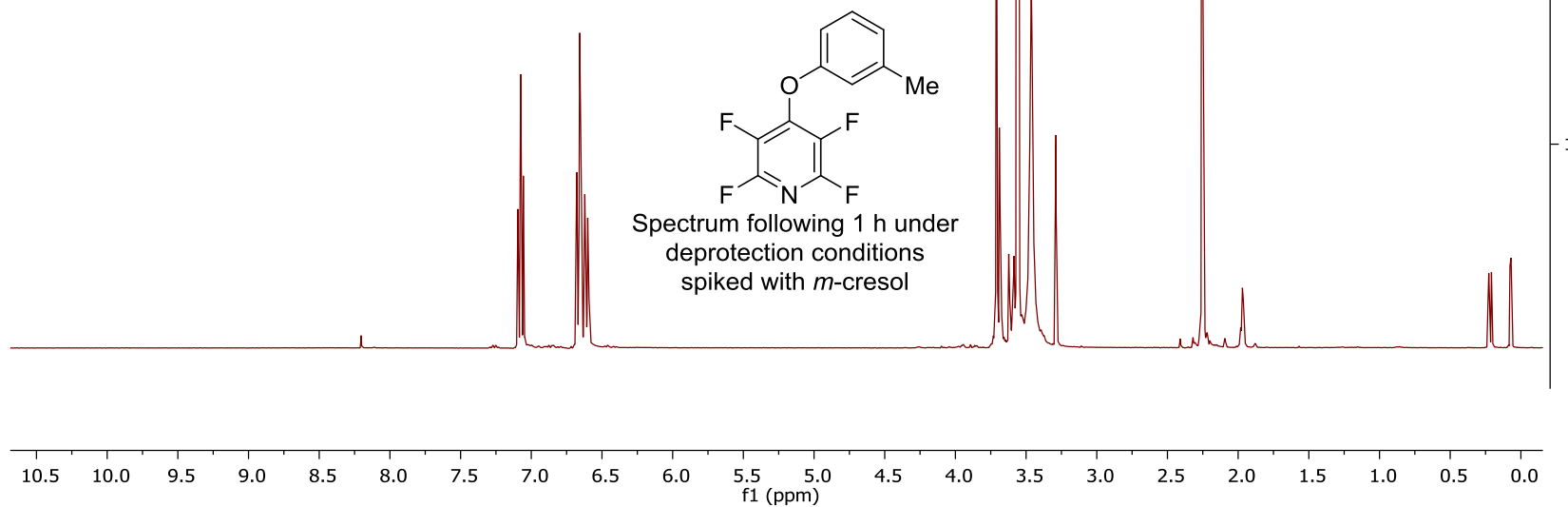
12092215.10.fid
SLC:WDGB:WB3-68 Spiked methoxyphenol 1



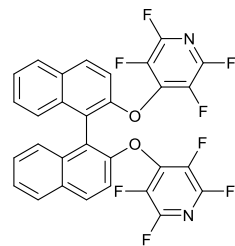
1915532.10.fid
SLC:WDGB:WB3-88 1h 2



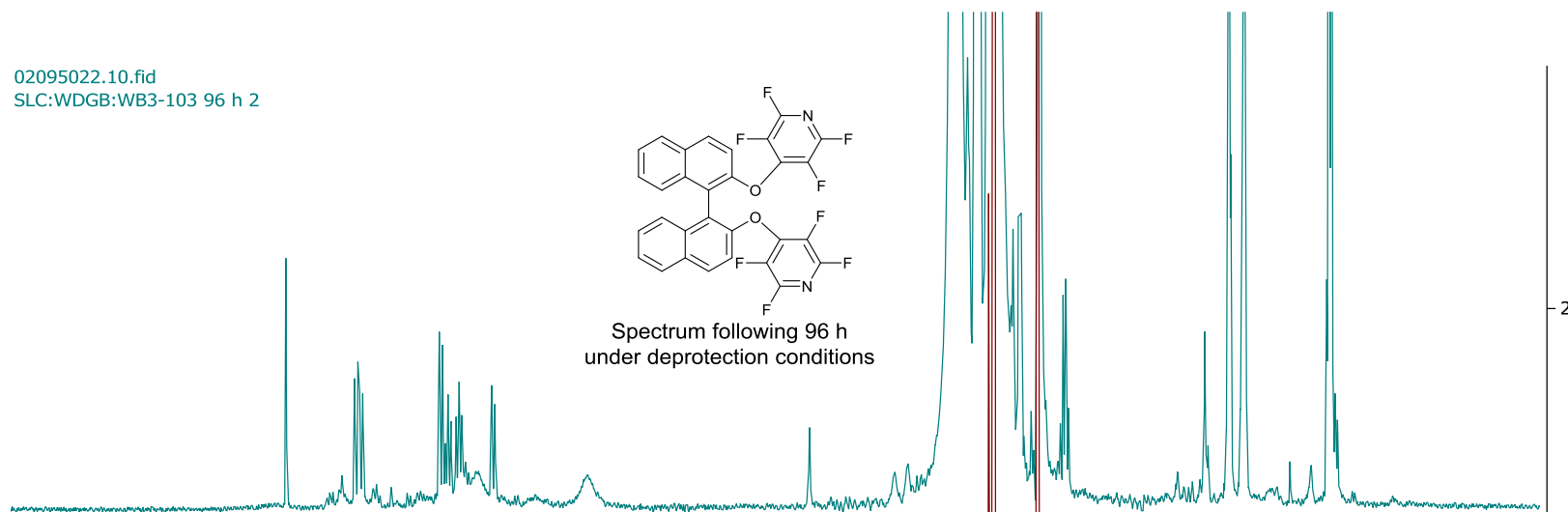
12092258.10.fid
SLC:WDGB:WB3-64 Spiked m-Cresol 1



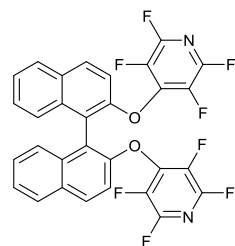
02095022.10.fid
SLC:WDGB:WB3-103 96 h 2



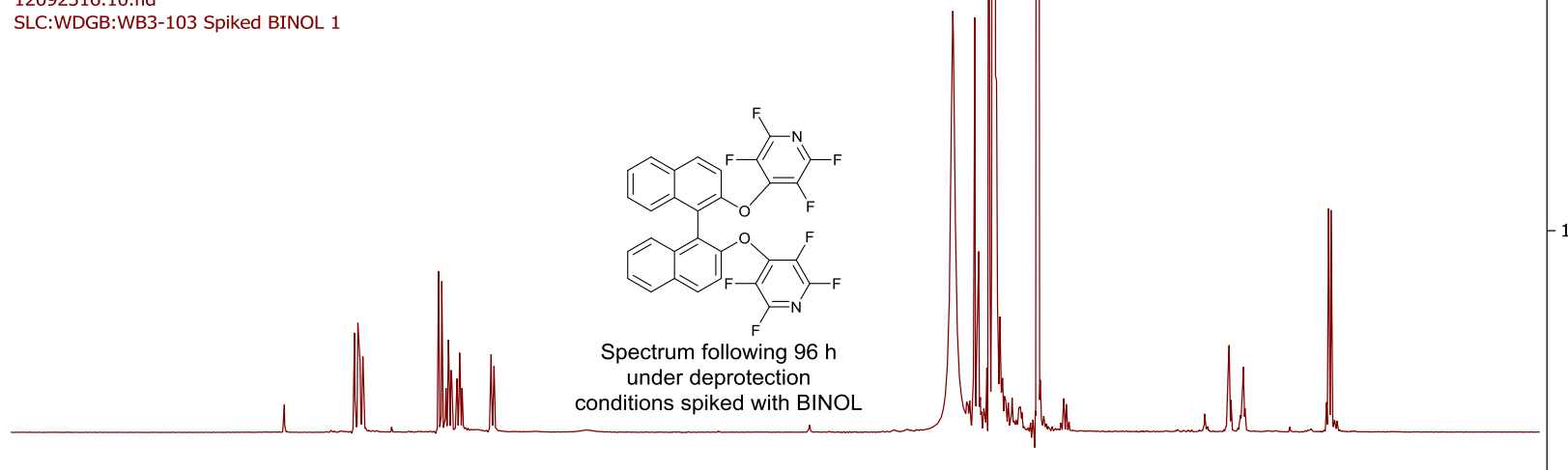
Spectrum following 96 h
under deprotection conditions



12092316.10.fid
SLC:WDGB:WB3-103 Spiked BINOL 1

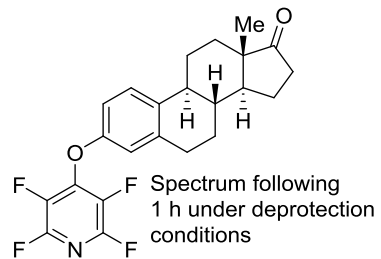


Spectrum following 96 h
under deprotection
conditions spiked with BINOL

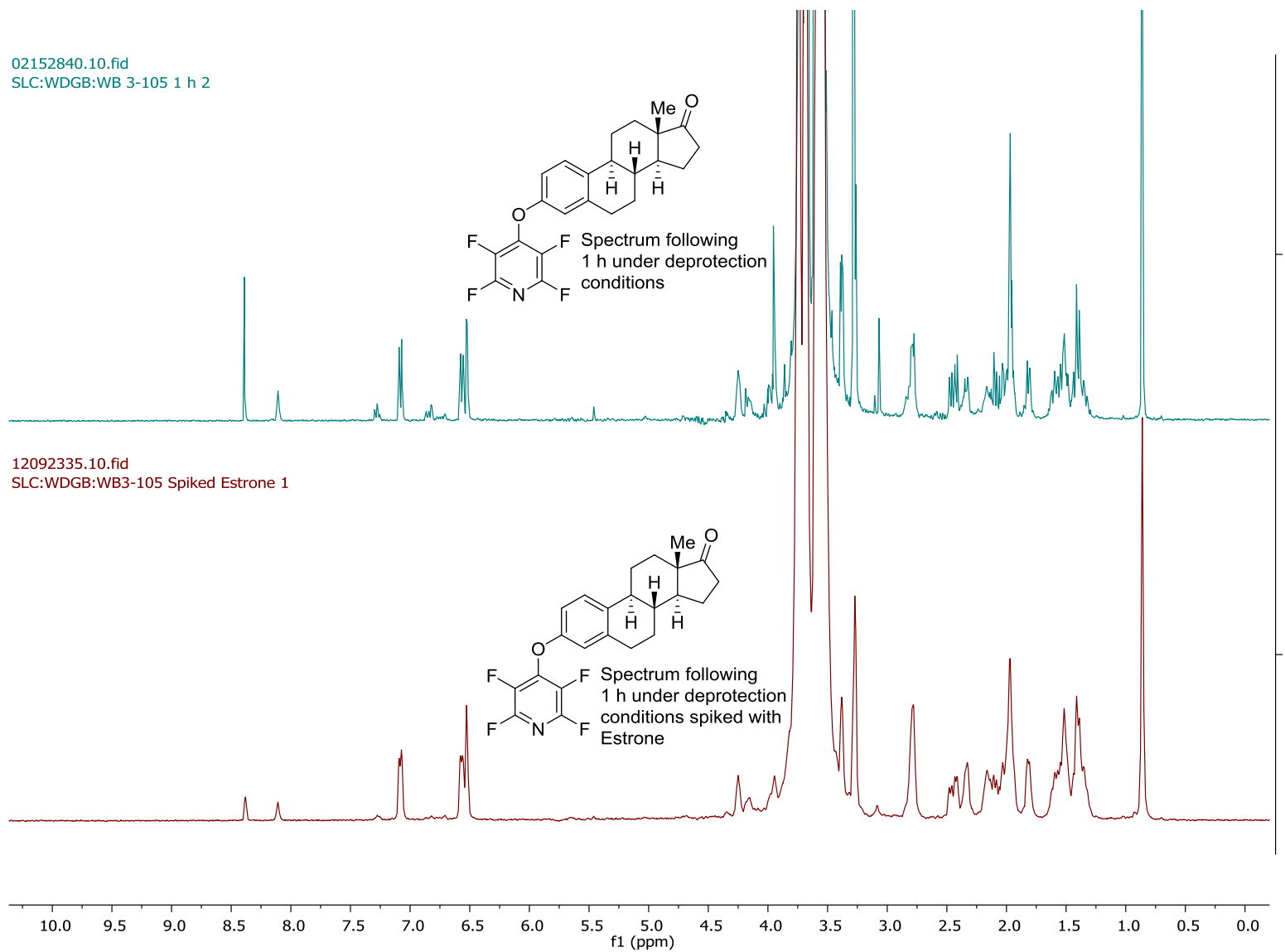
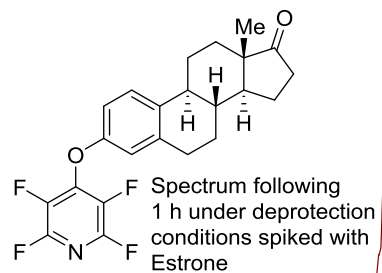


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

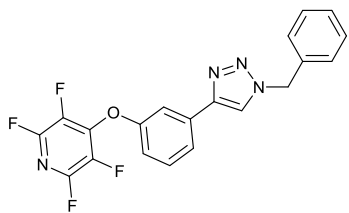
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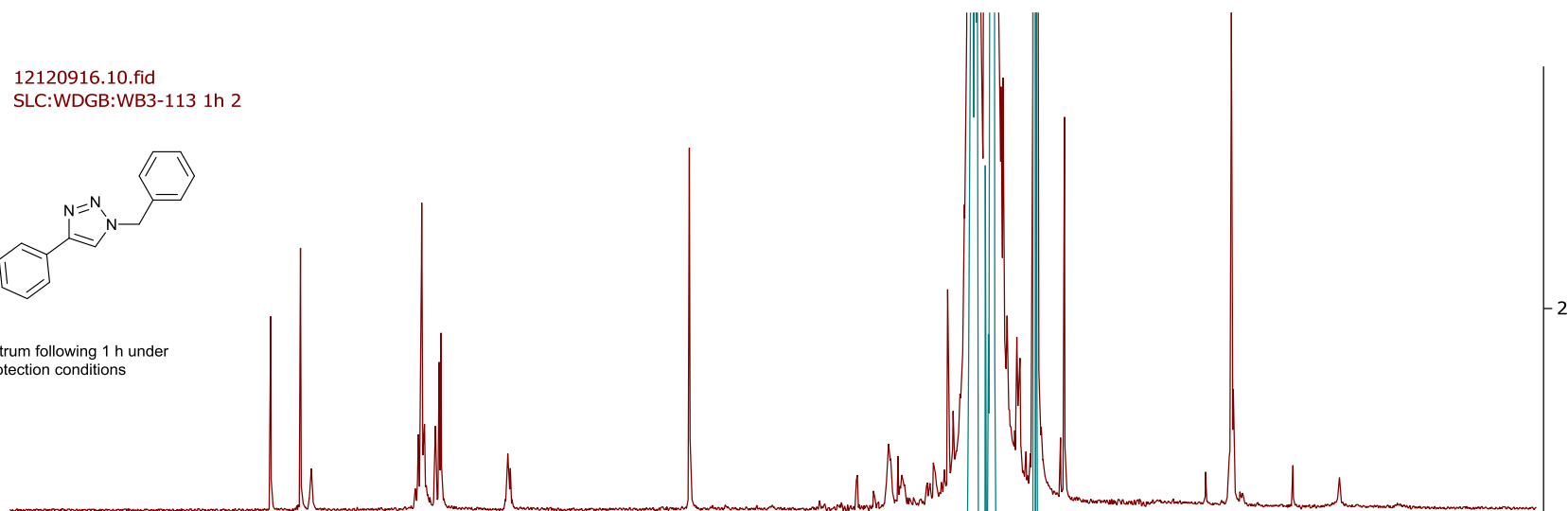
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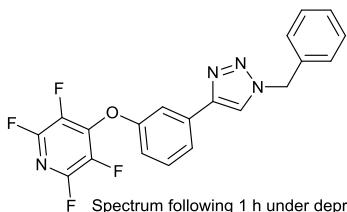
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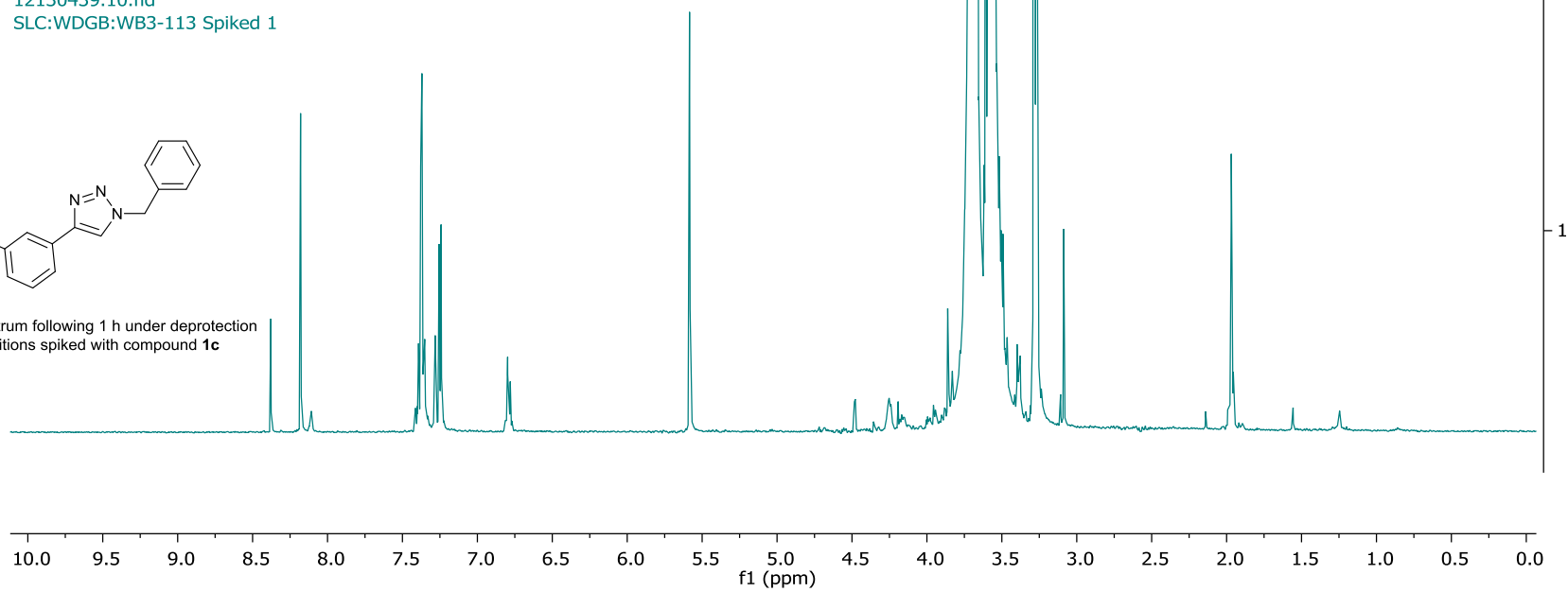
Spectrum following 1 h under
deprotection conditions



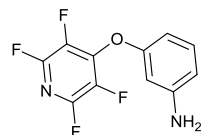
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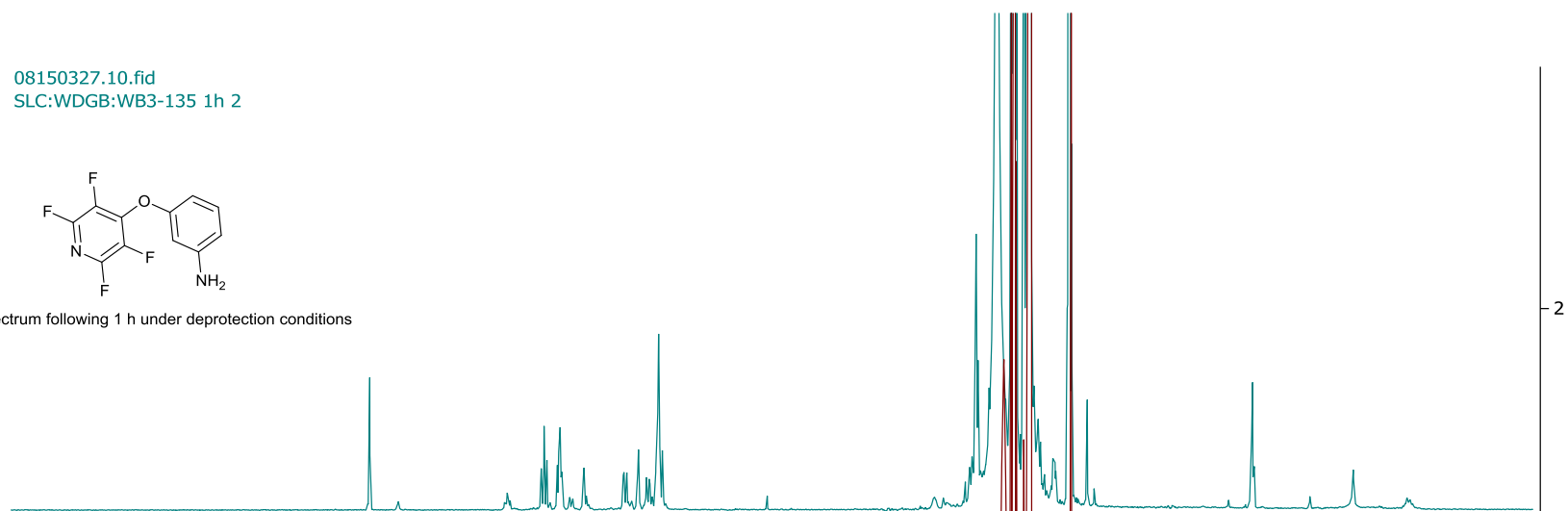
Spectrum following 1 h under deprotection
conditions spiked with compound **1c**



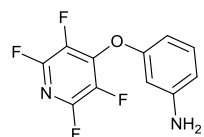
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SLC:WDGB:WB3-135 1h 2



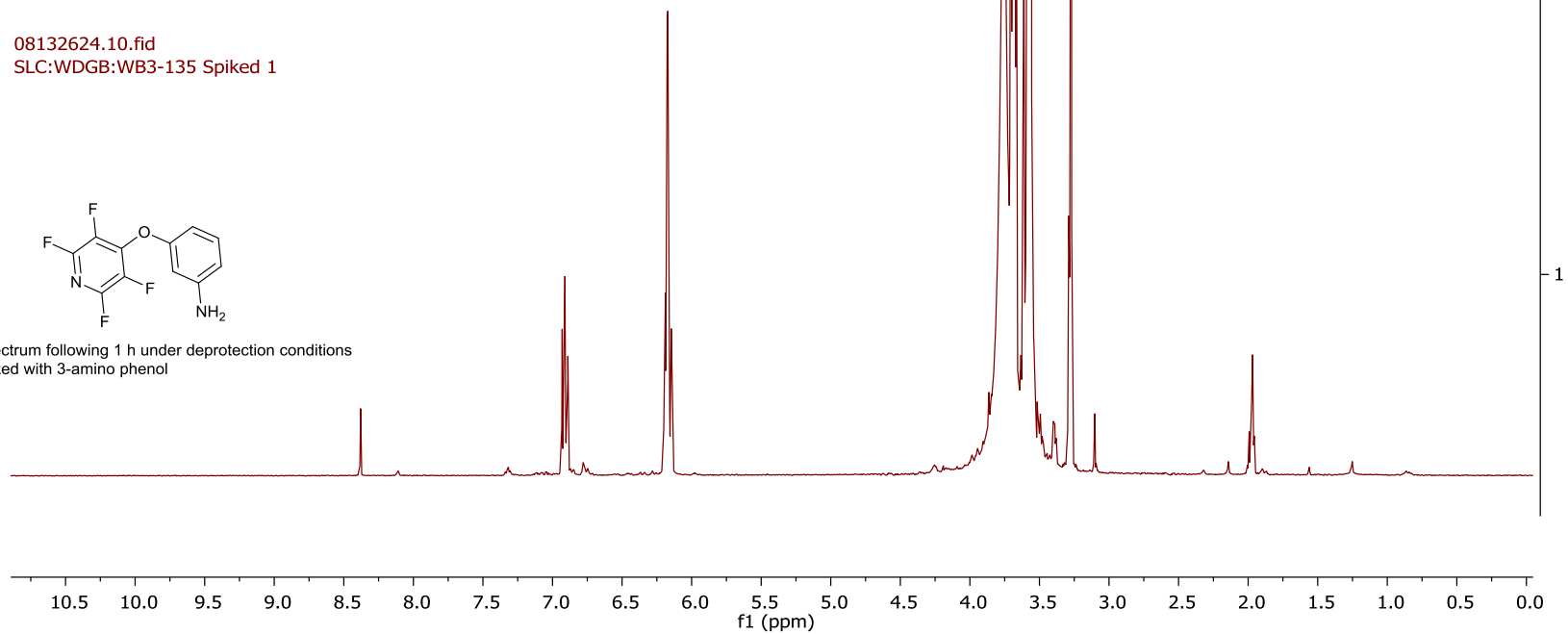
Spectrum following 1 h under deprotection conditions



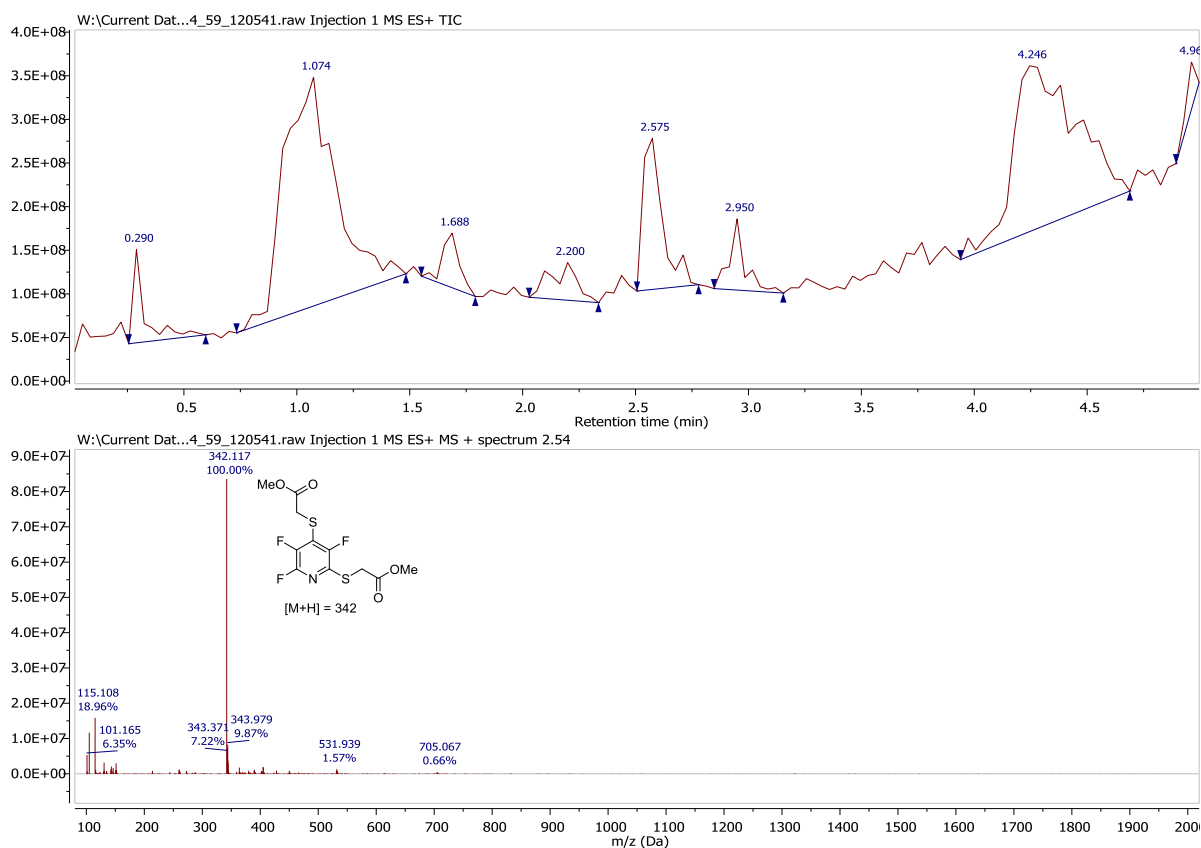
08132624.10.fid
SLC:WDGB:WB3-135 Spiked 1



Spectrum following 1 h under deprotection conditions
spiked with 3-amino phenol



Mass Spectrometry of Reaction Mixture



X-ray Crystallography

The X-ray single crystal data for **2r** and **2i** have been collected using $\lambda\text{MoK}\alpha$ radiation ($\lambda = 0.71073\text{\AA}$) on a Bruker D8Venture diffractometer (Photon100 CMOS detector, $I\mu\text{S}$ -microsource, focusing mirrors) equipped with a Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats at the temperature 120.0(2) K. Both structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using Olex2 [1] and SHELXTL [2] software. All non-hydrogen atoms were refined anisotropically, hydrogen atoms in structure **2r** were refined isotropically, while in the structure **2i** they were placed in the calculated positions and refined in riding mode. Crystal data and parameters of refinement are listed in Table SX. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1856218-

1856219. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

1. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst.* (2009), **42**, 339-341.

2. G.M. Sheldrick, *Acta Cryst.* (2008), **A64**, 112-122

Table S3. Crystal data and structure refinement for 2q and 2i.

Identification code	2r	2i
Empirical formula	C ₃₀ H ₁₂ F ₈ N ₂ O ₂	C ₁₁ H ₄ F ₄ N ₂ O ₃
Formula weight	584.42	288.16
Crystal system	monoclinic	monoclinic
Space group	P2 ₁ /c	P2 ₁ /c
a/Å	13.2804(5)	7.4591(17)
b/Å	8.7572(4)	10.786(3)
c/Å	21.1478(8)	26.797(6)
β/°	106.2235(15)	91.012(6)
Volume/Å ³	2361.53(17)	2155.6(9)
Z	4	8
ρ _{calc} /g/cm ³	1.644	1.776
μ/mm ⁻¹	0.147	0.175
F(000)	1176.0	1152.0
Reflections collected	49176	26864
Independent reflections, R _{int} , Rσ	6565, 0.0333, 0.0211	5207, 0.1252, 0.1388
Data/restraints/parameters	6565/0/427	5207/0/361
Goodness-of-fit on F ²	1.047	1.010
Final R ₁ indexes [I ≥ 2σ (I)]	0.0384	0.0662
Final wR ₂ indexes [all data]	0.1017	0.1393
Largest diff. peak/hole / e Å ⁻³	0.38/-0.25	0.28/-0.36

References

1. Y. Xiao, Y. Xu, H.-S. Cheon and J. Chae, *J. Org. Chem.*, 2013, **78**, 5804-5809.
2. L. Tianfei, S. Xinxin, W. Yaming and S. Qilong, *Angew. Chem. Int. Ed.*, 2012, **51**, 540-543.