Direct Synthesis of Fluorinated Heteroarylether Bioisosteres

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SUPPORTING INFORMATION – PROCEDURES

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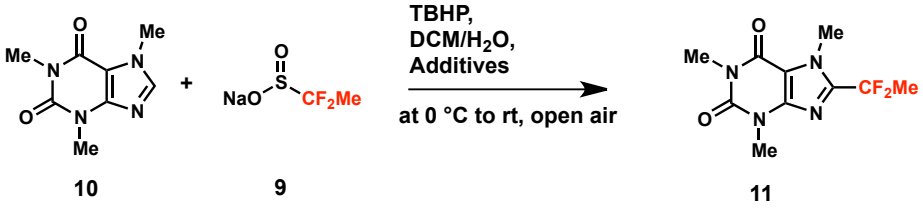
General Experimental Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H-NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and $KMnO_4$ or acidic solution of *p*-anisaldehyde and heat as a developing agent. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm). Preparative HPLC was performed using a Waters Atlantis dC_{18} OBD 10 mm column with dimension 30 x 250 mm, unless otherwise noted. NMR spectra were recorded on Bruker DRX-600, DRX-500, AMX-400, and Varian INOVA-399 instruments and were calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ @ 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR; CH_3OH @ 3.31 ppm ^{1}H NMR, 49.0 ppm ^{13}C NMR; CH_3CN 1.94 ppm ^{1}H NMR, 1.32 ppm ^{13}C NMR). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept= septet, m = multiplet, br = broad. Gas chromatograpy was performed on an Agilent Technologies 7890A instrument using a 30 meter DB-5 column with an internal diameter of 0.250 mm; reaction species were calibrated against tetradecane as an internal standard. In situ reaction calorimetry was performed using an Omnical Insight-CPR-220 calorimeter. High resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-off-flight reflectron experiments. IR experiments were recorded on a Perkin-Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

Optimization of Difluoroethylation on Caffeine



10 **9** **11**

To a solution of caffeine **(10)** (10 mg, 0.05 mmol, 1.0 equiv), sodium difluoroethanesulfinate (DFES-Na) **(9)** (23.0 mg, 0.15 mmol, 3.0 equiv) and Zn salt (0.075 mmol, 1.5 equiv) in DCM (0.2 mL) and H_2O (0.08 mL) was added Brønsted acid (0.05 mmol, 1.0 equiv). The reaction mixture was cooled in ice and TBHP (70% solution in water, 0.035 mL, 0.25 mmol, 5.0 equiv) was added dropwise with vigorous stirring and the stirring was continued at this temperature for 5 min. The reaction was warmed to room temperature and monitored by TLC until completion (24 h). Upon consumption of starting material, the reaction was partitioned between DCM (1.0 mL) and saturated aqueous $NaHCO_3$ (1.0 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 1.0 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuum and NMR analysis of the crude reaction mixture was performed. Then the mixture was purified by column chromatography. The results are listed in Table 1.

Table 1 Optimization of the reaction

Entry	Additive		Conversion (%)[a]
	Brønsted acid	Zinc salt (1.5 eq)	
1	none	none	5
2	TFA (1.0 equiv)	none	30
3	TFA (1.0 equiv)	$ZnCl_2$	43
4	TFA (1.0 equiv)	$ZnSO_3•2H_2O$	24
5	TFA (1.0 equiv)	$Zn(NO_3)_2•6H_2O$	45
6	TFA (1.0 equiv)	$Zn(OTf)_2$	26
7	TFA (1.0 equiv)	$ZnSO_4•7H_2O$	11
8	TFA (1.0 equiv)	$Zn(OAc)_2$	13
9	TFA (1.0 equiv)	ZnF_2	0
10	TFA (1.0 equiv)	$ZnBr_2$	35
11	TFA (1.0 equiv)	ZnI_2	9
12	1M HCl (1.0 equiv)	$ZnCl_2$	29
13	**$TsOH•H_2O$ (1.0 equiv)**	**$ZnCl_2$**	**65 (75)[b]**
14	$TsOH•H_2O$ (1.0 equiv)	none	25
15	none	$ZnCl_2$	49 (56)[c]

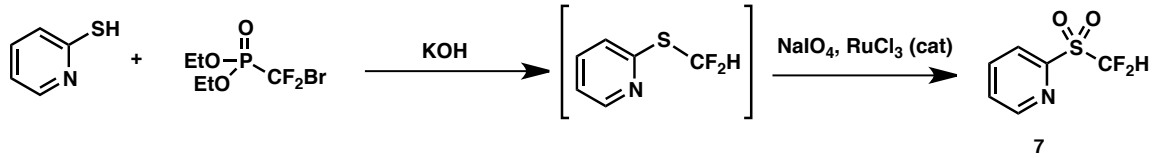
a: reaction ran on 0.05 mmol scale if not indicated
b: conversion on 0.2 mmol scale, isolated yield 71%.
c: conversion on 0.2 mmol scale, isolated yield 56%

Difluoroethylation of Heterocycles: Standard Procedure

To a solution of heterocycle (0.20 mmol, 1.0 equiv), sodium difluoroethanesulfinate (DFES-Na) **(9)**, (91.3 mg, 0.60 mmol, 3.0 equiv) and $ZnCl_2$ (40.9 mg, 0.3 mmol, 1.5 equiv) in DCM (0.8 mL) and H_2O (0.32 mL) was added $TsOH•H_2O$ (38.0 mg, 0.20 mmol, 1.0 equiv). The reaction mixture was cooled using an ice bath and TBHP (70% solution in water, 0.138 mL, 1.0 mmol, 5.0 equiv) was added dropwise with vigorous stirring and the stirring was continued at this temperature for 5 min. The reaction was warmed to room temperature and monitored by TLC until completion. For substrates that do not go to completion in 24 h, a second addition of $ZnCl_2$ (40.9 mg, 0.3 mmol, 1.5 equiv), DFES-Na **(9)** (91.3 mg, 0.60 mmol, 3.0 equiv) and TBHP (0.138 mL, 1.0 mmol, 5.0 equiv) was performed to drive the reaction further. Upon consumption of starting material, the reaction was partitioned between DCM (2.0 mL) and saturated aqueous $NaHCO_3$ (2.0 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 x 2.0 mL). The combined organic layers was dried over Na_2SO_4, concentrated in vacuum and purified with column chromatography.

NOTE: If the addition of TBHP is performed too rapidly, the resulting exotherm can result in reduced yield and selectivity. This is especially important on larger scales, where a syringe pump may be used to add in TBHP. (See gram-scale procedure for substrate **22**)

Synthesis of sodium difluoroethanesulfinate (DFES-Na) (9), $NaSO_2CF_2Me$



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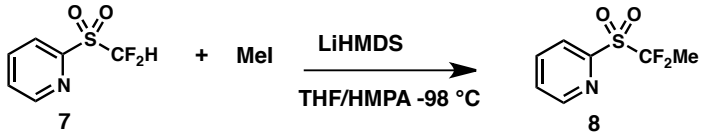
2-(Difluoromethylsulfonyl)pyridine (7, Hu's reagent)

2-(Difluoromethylsulfonyl)pyridine **(7)** was prepared in a new way by adapting a known procedure from a related substrate (Zafrani, Y.; Sod-Moriah, G.; Segall, Y. *Tetrahedron* **2009**, *65*, 5278-5283). KOH (101 g, 1.8 mol, 20 equiv) was added to a round bottom flask containing H_2O (110 mL) at 5 °C in an ice bath under stirring. 2-Mercaptopyridine

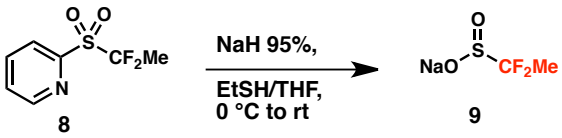
(10.0 g, 90.1 mol, 1.0 equiv) in MeCN (110 mL) was added and the resulting mixture was cooled to –30 °C in a dry ice/acetone bath (reaction temperature monitored internally). Bromodifluoromethyl diethylphosphonate (19.2 mL, 108.1 mmol, 1.2 equiv) was added in one portion *via* syringe (solution appeared yellow). The cooling bath was removed and the reaction mixture was stirred for 30 min. The reaction was monitored by TLC and diluted with CCl_4 (100 mL) upon completion (at which point the mixture appeared dark purple). The layers were separated and the aqueous phase was extracted with CCl_4 (100 mL). The combined organic phase was eluted through silica gel using Et_2O:pentane (1:4). The resulting organic solution was concentrated carefully under vacuum to a volume of ca. 100 mL. MeCN (50 mL), CCl_4 (50 mL), and H_2O (125 mL) were added and the mixture was stirred vigorously. Then $NaIO_4$ (86.7 g, 0.405 mol, 4.5 equiv) and ruthenium trichloride hydrate (18 mg, 0.09 mmol, 0.001 equiv) were added. The reaction was stirred at rt for 14 h, then water (100 mL) and Et_2O (100 mL) were added, the layers were separated, and the resulting reaction mixture was extracted with Et_2O (100 mL × 3). The combined organic phase was washed with saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4, filtered through a thin pad of silica, and concentrated. The crude organic material was recrystallized from DCM resulting in **2** as a colorless solid (12.16 g, 70% yield over two steps). The spectroscopic data for this compound were identical to those reported in the literature: Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444-1447.



2-[(1,1-Difluoroethyl)sulfonyl]pyridine (8)

2-[(1,1-Difluoroethyl)sulfonyl]pyridine **(8)** was prepared using the alkylation procedure of Prakash et al. (see Prakash, G. K. S.; Ni, C.; Wang, F.; Hu, J.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2559-2563). HMPA (22.5 mL) was added under Ar atmosphere to a solution of 2-(difluoromethylsulfonyl)pyridine **(7)** (10.5 g, 54.4 mmol, 1.0 equiv) in

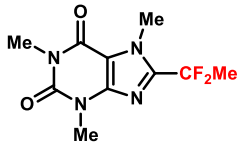
THF (225 mL) in a 1 L 3-neck flask equipped with a stir bar and an internal thermometer. The reaction mixture was cooled to –98 °C (CH_3OH/liquid N_2 bath) and then MeI (16.8 mL) was added. Then, a THF solution of LiHMDS (1 M, 136 mL, 2.5 equiv) was added dropwise over 30 min and the reaction mixture was quenched after 10 min with saturated aqueous NH_4Cl solution (20 mL) at the same temperature. After removal of the cold bath, H_2O (200 mL) was added. The mixture was extracted with EtOAc (3 x 200 mL). The combined organic phase was treated with aqueous LiCl (5%) (3 x 200 mL) to remove HMPA and dried over Na_2SO_4. After the removal of solvents under reduced pressure, 11.26 g of the crude product was obtained and was pure enough to be used directly in the next reaction. An aliquot of crude product was purified by flash column chromatography for analysis (EtOAc/hexanes, from 1:10 to 1:4) to give **8** as a light yellow solid. m.p. = 45 °C; R_f = 0.30 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (qd, J = 4.7 Hz, 0.8 Hz, 1 H), 8.17 – 8.20 (m, 1 H), 8.02 – 8.06 (m, 1 H), 7.67 (ddd, J = 7.9 Hz, 4.7 Hz, 1.1 Hz, 1 H), 2.13 (t, J = 18.6 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 151.0, 138.4, 128.8, 126.5, 124.7 (t, J_{CF} = 285.8 Hz), 17.69 (t, J_{CF} = 21.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –96.0; IR (neat) ν = 1333, 1190, 1169, 1133, 1097, 1077, 954, 896, 790, 745, 679, 581, 561, 504, 475 cm $^{-1}$; HRMS (ESI-TOF) calc'd for $C_7H_8NO_2SF_2$ [M+H$^+$] 208.0238; found 208.0230.



Sodium difluoroethanesulfinate (DFES-Na; 9)

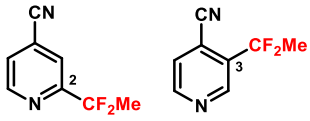
Sodium difluoroethanesulfinate (DFES-Na) **(9)** was prepared using the cleavage procedure of Prakash et al. (see Prakash, G. K. S.; Ni, C.; Wang, F.; Hu, J.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2559-2563). EtSH (17.3 mL) was added slowly into a suspension of NaH (95%) (2.49 g, 103 mmol, 3.0 equiv) in THF (120 ml) at 0 °C under Ar atmosphere *(Caution: EtSH has a strongly disagreeable odor, so it should be handled in a well ventilated hood!)* After stirring at 0 °C for 5 min, a THF (60 mL) solution of 2-[(1,1-difluoroethyl)sulfonyl]pyridine **(8)** (7.155 g, 34.6 mmol, 1.0 equiv) was added. The

flask was sealed with a cap and further wrapped with parafilm. The mixture was stirred at 0 °C for 2 h, then at rt for 10 h. After the removal of solvent under vacuum, the residue was treated with H_2O (20 mL) and neutralized to pH 7 by HCl (1 M), then extracted with Et_2O (20 × 3 mL) to remove 2-(ethylthio)pyridine and EtSH. The aqueous phase was concentrated, and the residue was purified by column chromatography using (MeOH/DCM 1:6 as eluent) resulting in DFES-Na as a white solid (4.102 g, 78% yield). R_f = 0.4 (1:2 MeOH:DCM); m.p. >300 °C; ^{1}H NMR (400 MHz, D_2O) δ 1.67 (t, J = 19.5 Hz, 3 H); ^{13}C NMR (151 MHz, D_2O) δ 128.7 (t, J_{CF} = 277.5 Hz), 14.5 (t, J_{CF} = 22.7 Hz); ^{19}F NMR (376 MHz, D_2O) δ –106.8; IR (neat) ν = 1711, 1383, 1109, 1046, 946, 891, 828, 756, 598, 508, 475, 440 cm^{-1}.



8-(1,1-Difluoroethyl)-1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (11).

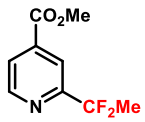
For 0.20 mmol scale, the standard procedure was followed with a reaction time of 38 h (second addition of reagents was performed after 24 h) to provide **11** in 87% yield as a white solid. m.p. = 154–156 °C; R_f = 0.40 (1:40 MeOH:DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (t, J = 1.6 Hz, 3 H), 3.55 (s, 3 H), 3.40 (s, 3 H), 2.15 (t, J = 19.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.8, 151.7, 146.5, 145.4 (t, J_{CF} = 31.7 Hz), 118.4 (t, J_{CF} = 234.5), 109.4, 33.5 (t, J_{CF} = 3.8 Hz), 29.8, 28.2, 23.1 (t, J_{CF} = 24.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –87.5; IR (neat) ν = 1703, 1655, 1547, 1428, 1389, 1341, 1241, 1219, 1174, 1120, 914, 903, 748, 663, 498, cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{10}H_{13}N_4O_2F_2$ [M+H$^+$] 259.1001; found 259.1003.



2-(1,1-Difluoroethyl)isonicotinonitrile (12-C2) and 3-(1,1-difluoroethyl)isonicotinonitrile (12-C3).

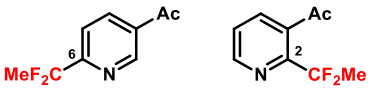
For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **12-C2** and **12-C3** as colorless oils in a combined yield of 74% yield (volatile!). **12-C2**: R_f = 0.8 (1:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84–8.83 (m, 1 H), 7.89 (m, 1 H), 7.62–7.60 (m, 1 H), 2.03 (t, J = 18.8 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.0 (t, J_{CF} = 30.6 Hz), 150.5, 126.4 (t, J_{CF} = 1.3 Hz), 121.8, 121.6 (t, J_{CF} = 4.4 Hz), 120.3 (t, J_{CF} = 238.2 Hz), 116.0, 23.4 (t, J_{CF} = 26.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ – 91.4; IR (neat) ν = 1383, 1306, 1189, 1137, 1114, 1093, 931, 853, 838, 722, 615, 536 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_7N_2F_2$ [M+H$^+$] 169.0572; found 169.0571.

12-C3: R_f = 0.33 (1/3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (br s, 1 H), 8.89 (d, J = 5.2 Hz, 1 H), 7.66–7.64 (m, 1 H), 2.10 (t, J = 18.4, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.1, 146.6 (t, J_{CF} = 8.0 Hz), 134.3 (t, J_{CF} = 27.2 Hz), 126.8, 119.9 (t, J_{CF} = 240.9 Hz), 117.9 (t, J_{CF} = 3.8 Hz), 114.7, 25.6 (t, J_{CF} = 28.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –87.9; IR (neat) ν = 2361, 2339, 1388, 1316, 1269, 1167, 1129, 1100, 934, 916, 844, 799, 558 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_7NF_2$ [M+H$^+$] 169.0572; found 169.0570.



Methyl 2-(1,1-difluoroethyl)isonicotinate (13).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **13** in 92% yield as a colorless oil: R_f = 0.58 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J = 4.8 Hz, 1 H), 8.20 (s, 1 H), 7.92 (d, J = 4.8 Hz, 1 H), 3.98 (s, 3 H), 2.04 (t, J = 18.6 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.1, 156.6 (t, J_{CF} = 30.1 Hz), 150.3, 138.8, 124.1, 120.7 (t, J_{CF} = 239.3 Hz), 119.0 (t, J_{CF} = 4.3 Hz), 53.1, 23.4 (t, J_{CF} = 27.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) –91.2; IR (neat) ν = 2955, 2921, 2852, 1735, 1438, 1414, 1318, 1255, 1186 1132, 927, 764 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_{10}NO_2F_2$ [M+H$^+$] 202.0674; found 202.0683.

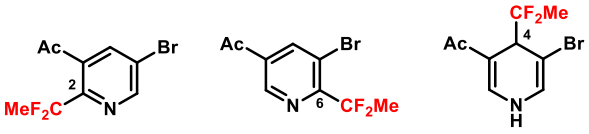


3-Acetyl-2-(1,1-Difluoroethyl)pyridine (14-C2) and 3-acetyl-6-(1,1-difluoroethyl)pyridine (14-C6).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **14-C2** in 8% yield and **14-C6** in 27% yield as colorless oils (35% combined yield).

14-C2: R_f = 0.31 (1:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 8.68 (d, J = 4.0 Hz, 1 H), 7.65 (dd, J = 7.8, 1.5 Hz, 1 H), 7.42 (dd, J = 7.8, 4.8 Hz, 1 H), 2.58 (s, 3 H), 2.07 (t, J = 19.1 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) 202.4, 150.8 (t, J = 30.0 Hz), 149.6, 136.3, 134.7, 124.5, 121.9 (t, J = 239.7 Hz), 31.6, 24.2 (t, J = 27.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) –86.3; IR (neat) ν = 2954, 2923, 2854, 1693, 1593, 1388, 1306, 1266, 1148, 1127, 919, 663 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_9NOF_2$ [M + H$^+$] 186.0725; found 186.0723.

14-C6: R_f = 0.50 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 – 9.17 (m, 1 H), 8.34 (dd, J = 8.1 Hz, 2.2 Hz, 1 H), 7.77 (d, J =8.1 Hz, 1 H), 2.66 (s, 3 H), 2.04 (t, J = 18.7, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.2, 158.9 (t, J_{CF} = 29.9 Hz), 149.5, 137.0, 133.0, 120.7 (t, J_{CF} = 239.3 Hz), 119.6 (t, J_{CF} = 4.13 Hz), 27.1, 23.4 (t, J_{CF} = 27.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –91.6; IR (neat) ν = 2923, 2852, 1692, 1594, 1388, 1306, 1266, 1138, 1127, 1108, 918, 849, 633 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_{10}NOF_2$ [M+H$^+$] 186.0725; found 186.0729.



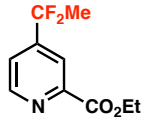
3-Acetyl-5-bromo-2-(1,1-difluoroethyl)pyridine (15-C2), 3-acetyl-5-bromo-6-(1,1-difluoroethyl)pyridine (15-C6) and 3-acetyl-5-bromo-4-(1,1-difluoroethyl)-1,4-dihydropyridine (15-C4)

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **15-C2** in 31% yield and **15-C6** in 9% yield as colorless oils, as well as **15-C4** in 24% yield as a white solid (64% combined yield).

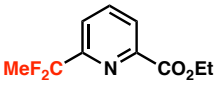
15-C2: R_f = 0.30 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 8.43 (s, 1 H), 2.59 (t, J = 1.0 Hz, 3 H), 2.09 (t, J = 18.7 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 200.9, 154.8, 145.0, 141.5 (t, J_{CF} = 26.9 Hz), 137.5, 121.3 (t, J_{CF} = 242.3 Hz), 118.3, 31.7, 24.7 (t, J_{CF} = 26.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –82.8; IR (neat) ν = 2921, 2852, 1697, 1357, 1267, 1129, 1066, 932, 919, 898, 762, 629, 611, 597, 492 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_9NOF_2Br$ [M+H$^+$] 263.9830; found 263.9833.

15-C6: R_f = 0.35 (1:4 EtOAc:hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.02 (d, J = 1.9 Hz, 1 H), 8.49 (d, J = 1.9 Hz, 1 H), 2.66 (s, 3 H), 2.11 (t, J = 18.9 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.9 155.3 (t, J_{CF} = 29.3 Hz), 146.4, 142.6, 133.9, 121.3 (t, J_{CF} = 241.2 Hz), 118.5, 27.2, 23.1 (t, J_{CF} = 26.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –89.9; IR (neat) ν = 3008, 2927, 1693, 1582, 1493, 1391, 1295, 1213, 1166, 1124, 1038, 914, 663, 567, 504 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_9NOF_2Br$ [M+H$^+$] 263.9830; found 263.9836.

15-C4: m.p. = 122 °C; R_f = 0.23 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 5.4 Hz, 1 H), 6.69 (d, J = 5.4 Hz, 1 H), 6.39 (br s, 1 H), 4.39 (t, J = 12.0 Hz, 1 H), 2.29 (s, 3 H), 1.57 (t, J = 19.0 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.9, 138.0, 127.8, 125.1 (t, J_{CF} = 245.8 Hz), 107.2 (t, J_{CF} = 3.2 Hz), 94.7 (t, J_{CF} = 4.0 Hz), 46.2 (t, J_{CF} = 26.2 Hz), 25.2, 21.7 (t, J_{CF} = 26.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –97.4 (AB system, J_1 = 404.0 Hz, J_2 = 239.0 Hz); IR (neat) ν = 3251, 2360, 1630, 1485, 1343, 1293, 1227, 1018, 986, 916, 861, 652, 633, 547, 520 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_{11}NOF_2Br$ [M+H$^+$] 265.9987; found 265.9993.



16-C4



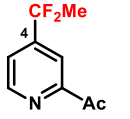
16-C6

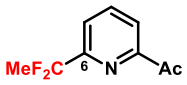
Ethyl 4-(1,1-difluoroethyl)picolinate (16-C4) and ethyl 6-(1,1-difluoroethyl)picolinate (16-C6).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 32 h (second addition of reagents was performed after 16 h) to provide **16-C4** in 56% yield and **16-C6** in 21% yield as colorless oils (78% combined yield).

16-C4: R_f = 0.29 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 4.5 Hz, 1 H), 8.22 (s, 1 H), 7.58 (d, J = 4.5 Hz, 1 H), 4.50 (q, J = 7.1 Hz, 2 H), 1.94 (t, J = 18.3 Hz, 3H), 1.45 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.7, 150.6, 149.1, 147.6 (t, J_{CF} = 28.6 Hz), 122.4 (t, J_{CF} = 5.6 Hz), 120.9 (t, J_{CF} = 5.7 Hz), 120.3 (t, J_{CF} = 239.8 Hz), 62.5, 25.6 (t, J_{CF} = 28.6 Hz), 14.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –91.3; IR (neat) ν = 3732, 3625, 2985, 1718, 1472, 1388, 1366, 1256, 1240, 1018, 995, 859, 754, 695, 461 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{10}H_{12}NO_2F_2$ [M+H$^+$] 216.0831; found 216.0837.

16-C6: R_f = 0.69 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) 8.17 (d, J = 7.8 Hz, 1 H), 7.96 (t, J = 7.8 Hz, 1 H), 7.86–7.80 (m, 1 H), 4.47 (q, J = 7.1 Hz, 2 H), 2.09 (t, J = 18.8 Hz, 3 H), 1.43 (t, J = 7.1 Hz, 3 H);^{13}C NMR (151 MHz, $CDCl_3$) δ 165.0, 155.9 (t, J_{CF} = 30.5 Hz), 148.3, 138.5, 126.3, 122.9 (t, J_{CF} = 3.9 Hz), 121.1 (t, J_{CF} = 238.7 Hz), 62.4, 23.4 (t, J_{CF} = 26.9 Hz), 14.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –90.1; IR (neat) ν = 3602, 2920, 2154, 1933, 1700, 1722, 1672, 1299, 1244, 1139, 129,9 879, 821, 799, 770, 576, 450 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{10}H_{12}NO_2F_2$ [M+H$^+$] 216.0831; found 216.0831.



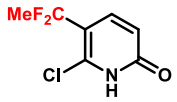


2-acetyl-4-(1,1-difluoroethyl)pyridine (17-C4) and 2-acetyl-6-(1,1-difluoroethyl)pyridine (17-C6).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 48 h (second addition of reagents was performed after 24 h) to provide **17-C4** in 48% yield and **17-C6** in 22% yield as colorless oils (70% combined yield).

17-C4: R_f = 0.63 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, J = 5.0, 0.9 Hz, 1 H), 8.14 (dd, J = 1.9, 0.9 Hz, 1 H), 7.65–7.54 (m, 1 H), 2.75 (s, 3 H), 1.93 (t, J = 18.3 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.5, 154.4, 149.8, 147.4 (t, J_{CF} = 28.5 Hz), 122.5 (t, J_{CF} = 5.5 Hz), 120.4 (t, J_{CF} = 239.5 Hz), 117.5 (t, J_{CF} = 5.7 Hz), 26.0, 25.5 (t, J_{CF} = 28.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –91.1; IR (neat) ν = 2926, 1700, 1607, 1387, 1310, 1177, 1144, 929, 852, 589 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_{10}NOF_2$ [M+H$^+$] 186.0725; found 186.0729.

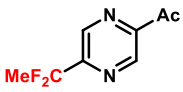
17-C6: R_f = 0.479 (1:2 EtOAc:hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, J = 8.2 Hz, 1 H), 7.96 (t, J = 7.8 Hz, 1 H), 7.86 (d, J = 8.5 Hz, 1 H), 2.74 (s, 3 H), 2.09 (t, J = 18.7 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.7 , 154.8 (t, J_{CF} = 30.6 Hz), 152.9 , 138.3, 123.0, 122.5, 120.5 (t, J_{CF} = 235.1 Hz), 25.7, 22.9 (t, J_{CF} = 27.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –90.1; IR (neat) ν = 3005, 1700, 1605, 1562, 1354, 1310, 1234, 1176, 1145, 927, 853, 563 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_{10}NOF_2$ [M+H$^+$] 186.0725; found 186.0725.



6-Chloro-5-(1,1-difluoroethyl)pyridin-2(1*H*)-one (18).

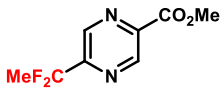
For 0.20 mmol scale, the standard procedure was followed with a reaction time of 40 h (second addition of reagents was performed after 24 h) to provide **18** in 58% yield as a white solid. m.p. = 114 °C; R_f = 0.37 (1:5 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.8 Hz, 1 H), 6.65 (d, J = 7.8 Hz, 1 H), 2.06 (t, J = 18.9 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.0, 143.3, 139.1 (t, J_{CF} = 7.5 Hz), 122.4 (t, J_{CF} = 27.2 Hz), 120.1 (t, J_{CF} = 239.9 Hz), 110.8, 23.6 (t, J_{CF} = 27.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –89.3; IR (neat) ν = 2919, 1651, 1592, 1459, 1286, 1233, 1180, 910, 847, 774, 664, 603, 563,

423 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_7H_7NOF_2Cl$ [M+H^+] 194.0179; found 194.0176.



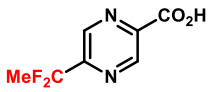
2-Acetyl-5-(1,1-difluoroethyl)pyrazine (19).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **19** in 67% yield as colorless crystals. R_f = 0.80 (1:3 EtOAc:pentane); m.p. = 49–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (d, J = 0.8 Hz, 1 H), 8.98 (d, J = 0.8 Hz, 1 H), 2.74 (s, 3 H), 2.06 (t, J = 18.8 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.8, 153.1 (t, J_{CF} = 30.4 Hz), 148.4, 142.4, 140.3, 120.5 (t, J_{CF} = 237.6 Hz), 26.1, 23.1 (t, J_{CF} = 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –91.7; IR (neat) ν = 1699, 1366, 1391, 1271, 118, 1025, 911, 662, 415 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_9N_2OF_2$ [M+H^+] 187.0677; found 187.0675.



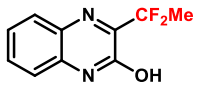
Methyl 5-(1,1-difluoroethyl)pyrazine-2-carboxylate (20).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 42 h (second addition of reagents was performed after 16 h, and third addition of 1.5 equiv of DFES-Na was performed after 32 h) to provide **20** in 55% yield as a white solid. m.p. = 56 °C; R_f = 0.35 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1 H), 9.03 (s, 1 H), 4.06 (s, 3 H), 2.06 (t, J = 18.8 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.9, 153.1 (t, J_{CF} = 30.8 Hz), 145.1, 144.2, 141.1 (t, J_{CF} = 4.6 Hz), 120.4 (t, J_{CF} = 239.4 Hz), 53.5 , 23.1 (t, J_{CF} = 26.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –91.8; IR (neat) ν = 3093, 3012, 2957, 1389, 1341, 1287, 1190, 1103, 962, 813, 770, 735, 643, 428 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_9N_2O_2F_2$ [M+H^+] 203.0627; found 203.0631.



5-(1,1-Difluoroethyl)pyrazine-2-carboxylic acid (21).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **21** in 55% yield as a light yellow solid: m.p. = 110–113°C; R_f = 0.60 (1:3 MeOH:DCM); ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (br s, 1 H), 9.00 (br s, 1 H), 2.06 (t, J = 18.8 Hz, 3 H); ^{13}C NMR (151 MHz, CD_3OD) δ 178.0, 166.1, 154.2 (t, J = 29.8 Hz), 146.3, 141.5, 121.8 (t, J = 238.4 Hz), 23.1 (t, J = 26.6 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –92.7; IR (neat) ν = 1726, 1388, 1298, 1136, 1101, 1035, 918, 831, 814, 722, 408 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_7H_7N_2O_2F_2$ [M+H$^+$] 189.047; found 189.0468.

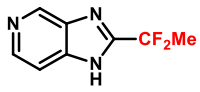


3-(1,1-Difluoroethyl)quinoxalin-2-ol (22).

For 0.20 mmol scale, the standard procedure was followed (2 equiv of DFES-Na was used) with a reaction time of 10 h to provide **22** in 95% yield.

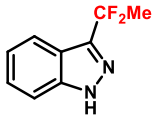
Gram-scale procedure: TsOH•H_2O (1.3 g, 6.84 mmol, 1.0 equiv) was added to an open air, stirred solution of 2-quinoxalinol (1.00 g, 6.84 mmol, 1.0 equiv), DFES-Na (2.6 g, 17.1 mmol, 2.5 equiv) and $ZnCl_2$ (1.16 g, 8.55 mmol, 1.25 equiv) in DCM (27 mL) and H_2O (11 mL) at 0 °C. TBHP (70% solution in H_2O, 4.7 mL, 34.2 mmol, 5.0 equiv) was added slowly with vigorous stirring in three portions over 30 min and stirring was continued at this temperature for 1 h. The ice bath was then removed, and the reaction was warmed to rt and stirred for 24 h with oxygen bubbling into the reaction mixture. The reaction was quenched with aqueous solution of $NaHCO_3$ (125 mL), then extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The crude material was mixed with a minimal amount of silica gel and was purified by column chromatography (gradient from 1:5 to 1:2 EtOAc:hexanes). Removal of the solvent under vacuum provided (**22**) as a white solid (1.28 g, 89% yield). R_f = 0.50 (50% EtOAc in hexanes); m.p. = 172–174 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, J = 7.8 Hz, 1 H), 7.65–7.62 (m, 1 H), 7.46-7.40 (m, 2 H), 2.18 (t, J = 19.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.6, 150.8 (t, J_{CF}= 27.8 Hz), 132.6, 132.3, 131.5, 130.3,

125.0, 119.8 (t, J_{CF} = 239.8 Hz), 116.1, 22.6 (t, J_{CF} = 25.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –94.8; IR (neat) ν = 2382, 1666, 1503, 1485, 1432, 1297, 1224, 1184, 1065, 928, 824, 761, 672, 552, 505, 479 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{10}H_9N_2OF_2$ [M+H$^+$] 211.0677; found 211.0676.



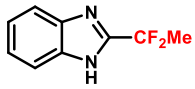
2-(1,1-Difluoroethyl)-1*H*-imidazo[4,5-*c*]pyridine (23).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **23** in 44% yield as white solid. R_f = 0.33 (1:9 MeOH:DCM); m.p. = 193-197°C (decomposed); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.44 (s, 1 H), 8.39 (dt, J = 5.5, 0.8 Hz, 1 H), 7.78 (dt, J = 5.5, 0.9 Hz, 1 H), 2.17 (t, J = 19.0 Hz, 3 H); ^{13}C NMR (151 MHz, acetone-d_6) δ 148.1, 146.0, 142.6 (t, J_{CF} = 31.7 Hz), 141.0, 130.9, 123.2 (t, J_{CF} = 235.6 Hz), 114.9, 23.2 (t, J_{CF} = 26.8 Hz); ^{19}F NMR (376 MHz, acetone-d_6) δ –87.2; IR (neat) ν = 2801, 1481, 1418, 1379, 1253, 1216, 1187, 952, 935, 906, 888, 627, 589, 529, 466 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_8N_3F_2$ [M+H$^+$] 184.0681; found 184.0683.



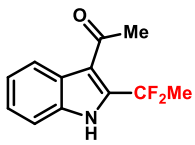
3-(1,1-Difluoroethyl)-1*H*-indazole (24).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **24** in 40% yield as a colorless oil. R_f = 0.60 (1:2 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (br s, 1 H), 7.99–7.96 (m, 1 H), 7.51 (ddd, J = 8.5 Hz, 1.0 Hz, 1.0 Hz, 1 H), 7.44 (ddd, J = 8.5 Hz, 6.8 Hz, 1.0 Hz, 1 H), 7.28–7.24 (m, 1 H), 2.20 (t, J = 18.4 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.1 (t, J_{CF} = 34.7 Hz), 141.2, 127.6, 122.2, 121.4, 120.6 (t, J_{CF} = 230.3 Hz), 119.8, 109.9, 23.7 (t, J_{CF} = 26.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –84.6; IR (neat) ν = 3188, 1498, 1384, 1218, 1118, 1040, 912, 743 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_9N_2F_2$ [M+H$^+$] 183.0728; found 183.0734.



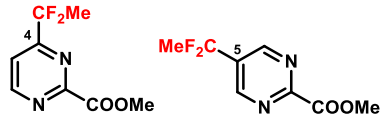
2-(1,1-Difluoroethyl)-1*H*-benzo[*d*]imidazole (25).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **25** in 80% yield as a white solid. m.p. = 190°C (decomposed); R_f = 0.33 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (br s, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.51 (d, J = 7.2 Hz, 1 H), 7.39–7.32 (m, 2 H), 2.22 (t, J = 18.8 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.9 (t, J_{CF} = 32.3 Hz), 142.5, 133.0, 124.9, 123.3, 120.8, 118.0 (t, J_{CF} = 234.3 Hz), 116.6, 23.0 (t, J_{CF} = 25.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –87.4; IR (neat) ν = 2852, 1454, 1314, 1277, 1262, 1126, 1015, 995, 741, 660, 578, 555, 461, 417 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_9N_2F_2$ [M+H$^+$] 183.0728; found 183.0735.



1-[2-(1,1-Difluoroethyl)-1*H*-indol-3-yl]ethanone (26).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 48 h (second addition of reagents was performed after 24 h) to provide **26** in 59% yield as a brown solid. m.p. = 138–139 °C; R_f = 0.50 (1:3 EtOAchexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (br s, 1 H), 8.01–7.99 (m, 1 H), 7.51–7.46 (m, 1 H), 7.37–7.31 (m, 2 H), 2.75 (s, 3 H), 2.24 (t, J = 19.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.2, 137.4 (t, J_{CF} = 30.2 Hz), 133.7, 126.5, 124.3, 123.0, 121.6, 119.8 (t, J_{CF} = 238.7 Hz), 115.4, 112.4, 31.9, 24.6 (t, J_{CF} = 27.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –86.6; IR (neat) ν = 3223, 1636, 1530, 1491, 1422, 1325, 1279, 1210, 1133, 930, 741 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{12}H_{12}F_2NO$ [M+H$^+$] 224.0881; found 224.0883.

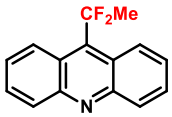


Methyl 4-(1,1-difluoroethyl)pyrimidine-2-carboxylate (27-C4) and methyl 5-(1,1-difluoroethyl)pyrimidine-2-carboxylate (27-C5).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 38 h (Second addition of reagents was performed after 24 h) to provide **27** (**27-C4**:**27-C5** = 10:1) in 74% combined yield as colorless oils.

27-C4: R_f = 0.75 (2:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (br s, 1 H), 7.79 (d, J = 3.2 Hz, 1 H), 4.05 (s, 3 H), 2.05 (t, J = 18.8 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2 (t, J_{CF} = 31.7 Hz), 163.4, 159.6, 156.7, 119.7 (t, J_{CF} = 238.9 Hz), 118.4, 53.8, 22.7 (t, J_{CF} = 26.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –93.2; IR (neat) ν = 1742, 1580, 1385, 1293, 1214, 1163, 929, 770, 608 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_9N_2O_2F_2$ [M+H$^+$] 203.0627; found 203.0633.

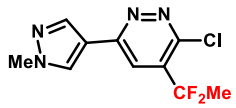
27-C5: R_f = 0.33 (2:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1 H), 4.10 (s, 3 H), 2.10 (t, J = 18.4 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.2, 157.4, 154.9, 133.4 (t, J_{CF} = 26.0 Hz), 119.7 (t, J_{CF} = 240.6 Hz), 54.0, 25.9 (t, J_{CF} = 28.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –89.5; IR (neat) ν = 1739, 1555, 1428, 1328, 1195, 1136, 914, 712, 643 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_8H_9N_2O_2F_2$ [M+H$^+$] 203.0627; found 203.0632.



9-(1,1-Difluoroethyl)acridine (28).

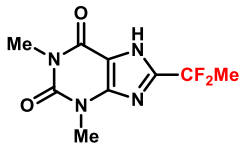
For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **28** in 72% yield as a brown solid. R_f = 0.50 (1:4 EtOAc:hexanes); m.p. = 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48–8.45 (m, 2 H), 8.27 (ddd, J = 9.0 Hz, 1.3 Hz, 0.2 Hz, 2 H), 7.78 (ddd, J = 8.8 Hz, 6.4 Hz, 1.3 Hz, 2 H), 7.59 (ddd, J = 9.0 Hz, 6.4 Hz, 1.2 Hz, 2 H), 2.39 (t, J = 18.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.8, 139.6 (t, J_{CF} = 23.4 Hz), 131.4, 130.4, 127.7, 126.0 (t, J_{CF} = 9.8 Hz), 125.2 (t, J_{CF} = 242.7 Hz), 123.6, 28.3 (t, J_{CF} = 27.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –75.1; IR (neat) ν = 1383, 1199,

1163, 1114, 915, 898, 871, 749, 652, 603, 514, 415 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{15}H_{12}NF_2$ [M+H$^+$] 244.0932; found 244.0933.



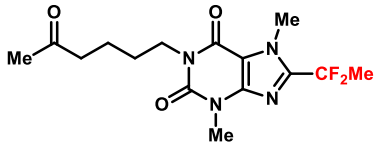
3-Chloro-4-(1,1-difluoroethyl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyridazine (29).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 40 h (Second addition of reagents was performed after 24 h) to provide **29** in 51% yield as a white solid. R_f = 0.25 (1:1 EtOAc:hexanes); m.p. = 157 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 8.03 (s, 1 H), 7.73 (s, 1 H), 4.01 (s, 3 H), 2.10 (t, J = 18.6 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5, 150.1, 138.1, 135.9 (t, J_{CF} = 28.7 Hz), 130.0, 121.1 (t, J_{CF} = 8.2 Hz), 119.0 (t, J_{CF} = 243.3 Hz), 118.7, 39.6, 23.9 (t, J_{CF} = 27.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –92.1; IR (neat) ν = 3012, 3067, 1559, 1512, 1451, 1413, 1387, 1188, 1150, 926, 879, 735, 700, 581, 528, 439, 416 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{10}H_{10}N_4F_2Cl$ [M+H$^+$] 259.0557; found 259.0558.

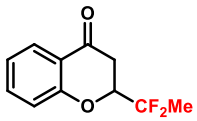


8-(1,1-Difluoroethyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione (30).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 24 h to provide **30** in 90% yield as a white solid: m.p. = 242 ºC (decomposed); R_f = 0.50 (1:40 MeOH:DCM, run two times); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3 H), 3.48 (s, 3 H), 2.13 (t, J = 18.6 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.1, 151.6, 148.5, 147.4 (t, J_{CF} = 33.5 Hz), 117.0 (t, J_{CF} = 236.2 Hz), 107.9, 30.5, 28.6, 23.4 (t, J_{CF} = 23.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –89.1; IR (neat) ν = 2360, 1708, 1648, 1551, 1515, 1453, 1407, 1214, 1056, 994, 790, 762, 747, 509, 495 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_{11}N_4O_2F_2$ [M+H$^+$] 245.0845; found 245.0843.



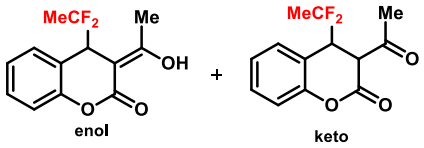
8-(1,1-Difluoroethyl)-3,7-dimethyl-1-(5-oxohexyl)-1*H*-purine-2,6(3*H*,7*H*)-dione (31). For 0.20 mmol scale, the standard procedure was followed with a reaction time of 17 h (second addition of reagents was performed after 14 h) to provide **31** in 45% yield as a white solid: m.p. = 58 °C; R_f = 0.35 (1:1 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (s, 3 H), 4.00 (t, J = 6.9 Hz, 2 H), 3.54 (s, 3 H), 2.49 (t, J = 6.9 Hz, 2 H), 2.25–2.06 (m, 6 H), 1.67–1.63 (m, 4 H);^{13}C NMR (151 MHz, $CDCl_3$) δ 208.8, 155.6, 151.4, 146.5, 145.4 (t, J_{CF} = 31.7 Hz), 118.4 (t, J_{CF} = 234.7 Hz), 109.4, 43.3, 41.1, 33.5 (t, J_{CF} = 3.7 Hz), 30.1, 29.8, 27.5, 23.1 (t, J_{CF} = 25.0 Hz), 21.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –87.5; IR (neat) ν = 2953, 1707, 1664, 1607, 1543, 1215, 1170, 917, 897, 465, 431 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{15}H_{21}N_4O_3F_2$ [M+H$^+$] 343.1576; found 343.1590.



2-(1,1-Difluoroethyl)chroman-4-one (32).

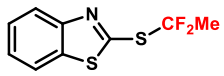
For 0.20 mmol scale, the standard procedure was followed with a reaction time of 34 h (second addition of reagents was performed after 17 h) to provide **32** in 26% yield as a pale yellow solid: m.p. = 56 °C; R_f = 0.23 (1:4 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.84 (m, 1 H), 7.52 (dd, J = 8.1, 7.2, 1 H), 7.12–7.00 (m, 2 H), 4.55 (tdd, J = 13.1, 5.3, 3.8 Hz, 1 H), 3.04–2.78 (m, 2 H), 1.83 (t, J = 19.0 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.4, 160.2, 136.5, 127.2, 122.4, 121.2 (dd, J_{CF} = 243.0 Hz, 238.5 Hz), 120.9, 118.0, 78.0 (dd, J_{CF} = 35.3 Hz, 29.3 Hz), 36.5, 20.2 (t, J_{CF} = 26.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –101.1 (d, J = 255.2 Hz), –105.5 (d, J = 255.2 Hz); IR (neat) ν = 1697, 1604, 1577, 1460. 1392, 1300, 1273, 1139, 1110, 1087, 804, 765, 721, 653, 638, 594, 414 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{11}H_{11}O_2F_2$ [M+H$^+$] 213.0722; found

213.0725.



(*Z*)-4-(1,1-Difluoroethyl)-3-(1-hydroxyethylidene)chroman-2-one (33-enol) and 3-acetyl-4-(1,1-difluoroethyl)chroman-2-one (33-keto).

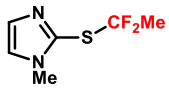
For 0.20 mmol scale, the standard procedure was followed with a reaction time of 38 h (second addition of reagents was performed after 24 h) to provide **33 (enol + keto)** in 83% yield as a pink solid: m.p. = 93 °C (Note: Both major (enol) and minor (keto) peaks are listed for ^{1}H and ^{13}C NMR.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (s, 1 H), 7.40–7.28 (m, 3 H), 7.18 (td, *J* = 7.6, 1.1 Hz, 2 H), 7.12 (d, *J* = 8.2 Hz, 1 H), 7.08 (d, *J* = 8.2 Hz, 1 H), 4.19 (s, 1 H), 4.12 (dd, *J* = 11.4, 9.3 Hz, 2 H), 3.86 (dd, *J* = 20.6, 7.7 Hz, 1 H), 2.31 (s, 1 H), 2.24 (s, 5 H), 1.61 (t, *J* = 18.9 Hz, 2 H), 1.42 (t, *J* = 18.7 Hz, 5 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ; 197.7, 181.0 , 169.6 , 164.2 , 151.0 , 130.7 , 130.4 , 130.1 , 130.1 , 129.9 , 126.6 , 125.2 , 123.3 , 119.2 , 117.5 , 117.2 , 116.6 , 90.6 , 90.6 , 54.4 , 45.2 (t, *J* = 27.3 Hz), 30.4 , 28.2 , 26.1 , 21.5 (t, *J* = 27.0 Hz), 19.8 , 19.8 , 19.6 (t, *J* = 27.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –94.2 (AB system, *J* = 1345.6 Hz, 237.1 Hz, 2 F), –95.3 (AB system, *J* = 1342.8 Hz, 244.8 Hz, 2 F); IR (neat) ν = 2925, 1657, , 1321, 1243, 1216, 1180, 1144, 1108, 953, 923, 754, 724, 618, 524, 466, 418 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{13}H_{13}O_3F_2$ [M+H$^+$] 255.0827; found 255.0830.



2-[(1,1-Difluoroethyl)thio]benzothiazole (34).

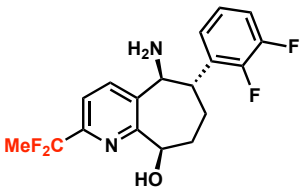
For 0.20 mmol scale, the standard procedure was followed with a reaction time of 5 h to provide **34** in 66% yield as a colorless oil: R_f = 0.53 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (ddd, *J* = 8.3 Hz, 1.1 Hz, 0.5 Hz, 1 H), 7.87 (ddd, *J* = 8.1 Hz, 1.2 Hz, 0.4 Hz, 1 H), 7.51 (ddd, *J* = 8.3 Hz, 7.1 Hz, 1.2 Hz, 1 H), 7.44 (ddd, *J* = 8.1 Hz, 7.1 Hz, 1.1 Hz, 1 H), 2.13 (t, *J* = 17.0 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.8 (t, J_{CF} =

2.6 Hz), 153.9, 138.4, 128.8 (t, J_{CF} = 278.5 Hz), 127.4, 126.8, 124.4, 122.0, 27.4 (t, J_{CF} = 24.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –64.2; IR (neat) ν = 1454, 1417, 1382, 1311, 1238, 1186, 1122, 1078, 989, 932, 877, 756, 726, 707, 679, 660, 607, 547, 519, 461, 421 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_9H_8NS_2F_2$ [M+H$^+$] 232.0061; found 232.0065.



2-[(1,1-Difluoroethyl)thio]-1-methylimidazole (35).

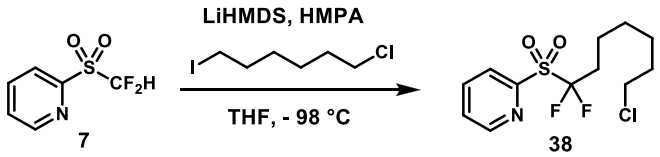
For 0.20 mmol scale, the standard procedure was followed with a reaction time of 5 h to provide **35** in 37% yield as a colorless oil: R_f = 0.15 (1:2 DCM:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 0.8 Hz, 1 H), 7.12 (d, J = 0.8 Hz, 1 H), 3.78 (s, 3 H), 1.95 (t, J = 17.2 Hz, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 133.4, 131.0, 128.6 (t, J_{CF} = 277.5 Hz), 125.1, 34.5, 26.3 (t, J_{CF} = 25.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –65.2; IR (neat) ν = 1457, 1412, 1384, 1281, 1184, 1117, 930, 878, 757, 686, 659, 553, 497, 452, 432, 405 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_6H_9N_2SF_2$ [M+H$^+$] 179.0449; found 179.0446.



(5*S*,6*S*,9R)-5-Amino-2-(1,1-difluoroethyl)-6-(3,4-difluorophenyl)-6,7,8,9-tetrahydro-5*H*-cycloheptapyridin-9-ol (37).

For 0.20 mmol scale, the standard procedure was followed with a reaction time of 22 h to provide **37** in 33% yield as a light yellow solid: R_f = 0.23 (1:1 EtOAc:hexanes); m.p. = 115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H), 7.12–7.07 (m, 2 H), 7.01–6.99 (m, 1 H), 4.99 (dd, J = 11.0 Hz, 2.2 Hz, 1 H), 4.45 (d, J = 9.0 Hz, 1 H), 2.91 (m, 1 H), 2.37–2.28 (m, 2 H), 2.05 (t, J = 18.6 Hz, 3 H), 1.61-1.52 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2, 151.4 (t, J_{CF} = 30.8 Hz), 151.1 (dd, J_{CF} = 249.3, 13.6 Hz), 148.8 (dd, J_{CF} = 246.3, 12.8 Hz), 138.9, 134.8 , 133.3 (d, J_{CF} = 11.2 Hz),

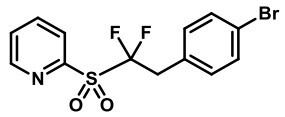
124.8 (dd, J_{CF} = 6.7, 4.4 Hz), 123.9 , 120.8 (t, J_{CF} = 238.3 Hz), 118.6 (t, J_{CF} = 4.1 Hz), 115.9 (d, J_{CF} = 17.1 Hz), 71.2 , 54.2 , 45.4 , 35.7 , 33.5 , 23.4 (t, J_{CF} = 27.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –90.6, –137.2 (d, J = 21.4 Hz), –142.5 (d, J = 21.9 Hz); IR (neat) ν = 3424, 2928, 2853, 1714, 1592, 1484, 1378, 1323, 1289, 1228, 1175, 997, 953, 821, 802, 780 649, 616, 592, 565, 422 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{18}H_{19}N_2OF_4$ [M+H$^+$] 355.1428; found 355.1436.



2-((7-Chloro-1,1-difluoroheptyl)sulfonyl)pyridine (**38**).

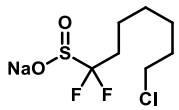
2-((7-Chloro-1,1-difluoroheptyl)sulfonyl)pyridine (**38**) was prepared using the alkylation procedure of Prakash et al. (see Prakash, G. K. S.; Ni, C.; Wang, F.; Hu, J.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2559-2563). HMPA (2.5 mL) was added under Ar atmosphere to a solution of 2-(difluoromethylsulfonyl)pyridine **(7)** (1.12 g, 5.8 mmol, 1.0 equiv) in THF (25 mL) in a 200 mL flask. The reaction mixture was cooled to –98 °C (MeOH/liquid N_2 bath) and 1-chloro-6-iodohexane (2.3 mL, 15.5 mmol, 2.5 equiv) was added. Then a THF solution of LiHMDS (1 M, 17.4 mL, 3.0 equiv) was added dropwise over 10 min and the reaction mixture was kept at –98 °C for 20 min. The reaction was quenched with saturated aqueous NH_4Cl solution (4.5 mL) at the same temperature. After removal of the ice bath, H_2O (30 mL) was added. The mixture was extracted with EtOAc (3 × 35 mL), and the combined organic phase was dried over $MgSO_4$. After the removal of solvents under reduced pressure, the crude product was purified by flash column chromatography (EtOAc:hexane, from 1:10 to 1:4) to give **38** as a colorless oil (1.23 g, 3.94 mmol, 68% yield). R_f = 0.4 (1:2 EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (ddd, J = 4.7, 1.7, 0.9 Hz, 1 H), 8.22–8.11 (m, 1 H), 8.03 (td, J = 7.8, 1.7 Hz, 1 H), 7.66 (ddd, J = 7.7, 4.7, 1.2 Hz, 1 H), 3.52 (t, J = 6.6 Hz, 2 H), 2.47–2.34 (m, 2 H), 1.81–1.74 (m, 2 H), 1.72–1.64 (m, 2 H), 1.52–1.39 (m, 4 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 152.5, 151.0, 138.4, 128.7, 126.5 125.4 (t, J_{CF} = 287.4 Hz), 45.0, 32.4, 30.1 (t, J_{CF} = 19.8 Hz), 28.5, 26.5, 20.8 (t, J_{CF} = 3.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –102.4; IR (neat) ν

= 2924, 2359, 2340, 1345, 1169, 982, 744, 598 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{12}H_{17}NO_2F_2SCl$ [M+H^+] 312.0631; found 312.0634.



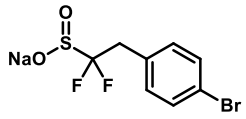
2-((2-(*p*-Bromophenyl)-1,1-difluoroethyl)sulfonyl)pyridine (39)

2-((2-(*p*-Bromophenyl)-1,1-difluoroethyl)sulfonyl)pyridine **(39)** was prepared using the alkylation procedure of Prakash et al. (see Prakash, G. K. S.; Ni, C.; Wang, F.; Hu, J.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2559-2563). HMPA (3 mL) was added under Ar atmosphere to a mixture of 2-(difluoromethylsulfonyl)pyridine **(7)** (760 mg, 3.93 mmol, 1.3 equiv) and 1-bromo-4-(bromomethyl)benzene (746 mg, 3.02 mmol, 1.0 equiv) in THF (33 mL) in a 100 mL flask. The reaction mixture was cooled to –98°C using MeOH/liquid N_2 bath and a THF solution of LiHMDS (1M, 4.5 mL, 1.5 equiv) was added dropwise over 20 min. The reaction mixture was kept at –98 °C for 2 h, then was quenched with saturated aqueous NH_4Cl solution (4.5 mL) at the same temperature. After removal of the cold bath, H_2O (30 mL) was added. The mixture was extracted with EtOAc (3 × 35 mL), and the combined organic phase was dried over $MgSO_4$. After the removal of solvents under reduced pressure, the crude product was purified by flash column chromatography (EtOA:hexanes, from 1:10 to 1:4) to give **(39)** as a white solid (848 mg, 2.36 mmol, 78% yield). The spectroscopic data for this compound were identical to those reported in the literature: Prakash, G. K. S.; Ni, C.; Wang, F.; Hu, J.; Olah, G. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2559–2563.



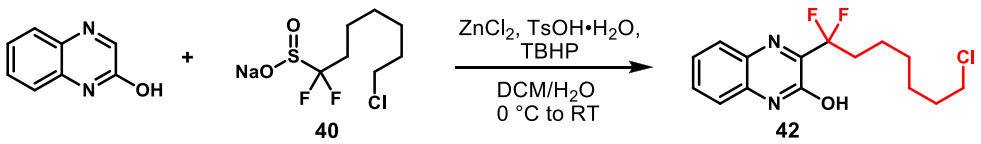
Sodium 7-chloro-1,1-difluoroheptanesulfinate (40)

For 3.75 mmol scale, the same procedure for the preparation of **9** was followed to provide **40** in 85% yield as a white solid: R_f = 0.70 (1:2 MeOH:DCM); m.p. = 150–155 °C; ^{1}H NMR (400 MHz, D_2O) δ 3.63 (t, J = 6.7 Hz, 2 H), 2.07–1.94 (m, 2 H), 1.83–1.76 (m, 2 H), 1.61–1.54 (m, 2 H), 1.51–1.39 (m, 4 H); ^{13}C NMR (151 MHz, D_2O) δ 128.4 (t, J_{CF} = 284.4 Hz), 46.5, 32.5, 28.9 (t, J_{CF} = 20.7 Hz), 28.7 , 26.6 , 21.0 (t, J_{CF} = 4.1 Hz); ^{19}F NMR (376 MHz, D_2O) δ –115.4; IR (neat) ν = 2936, 2857, 1193, 1157, 1072, 1030, 1009, 938, 725, 585 cm^{-1}; elemental analysis calc'd for: $C_7H_{12}O_2F_2NaSCl$ (256.67), calcd: C, 32.76%; H, 4.71%; S, 12.49%; found: C, 32.87%; H, 4.79%; S, 12.74%.



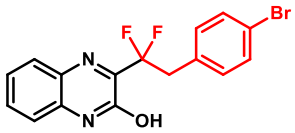
Sodium 2-(4-bromophenyl)-1,1-difluoroethanesulfinate (41)

For 2.5 mmol scale, the same procedure for the preparation of **9** was followed to provide sodium 2-(4-bromophenyl)-1,1-difluoroethanesulfinate **(41)** in 60% yield as a white solid: m.p. > 300 °C; R_f = 0.39 (1:4 MeOH:DCM); ^{1}H NMR (600 MHz, D_2O) δ 7.56 (d, J = 8.4 Hz, 2 H), 7.29 (d, J = 8.1 Hz, 2 H), 3.29 (t, J = 18.9 Hz, 2 H); ^{13}C NMR (151 MHz, D_2O) δ 133.4, 132.3, 131.6, 126.5 (t, J_{CF} = 287.1 Hz), 121.8, 34.1 (t, J_{CF} = 20.8 Hz); ^{19}F NMR (376 MHz, D_2O) δ –114.3. IR (neat) ν = 3409, 2936, 1487, 1428, 1405, 1322, 1222, 1168, 1052, 991, 871, 837, 805, 716, 599, 547, 475 cm^{-1}; elemental analysis calc'd for: $C_8H_6BrF_2NaO_2S$ (305.91), calcd: C, 31.39%; H, 1.97%; S, 10.44%; found: C, 31.63%; H, 2.0%; S, 10.56%.



3-(1,1-Difluoro-6-chloroheptyl)quinoxalin-2-ol (42).

To a solution of 2-quinoxalinol (29.2 mg, 0.20 mmol, 1.0 equiv), sodium 7-chloro-1,1-difluoroheptanesulfinate (**40,** 102.7 mg, 0.40 mmol, 2.0 equiv) and $ZnCl_2$ (27.3 mg, 0.2 mmol, 1.0 equiv) in DCM (0.8 mL) and H_2O (0.32 mL) was added TsOH•H_2O (38.0 mg, 0.20 mmol, 1.0 equiv). The reaction mixture was cooled (ice bath) and TBHP (70% solution in water, 0.138 mL, 1.0 mmol, 5.0 equiv) was added with vigorous stirring and the stirring was continued at this temperature for 5 min. The reaction was warmed to room temperature and monitored by TLC until completion. Upon consumption of the starting material, the reaction was partitioned between DCM (2.0 mL) and saturated aqueous $NaHCO_3$ (2.0 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 2.0 mL). The combined organic layers was dried over Na_2SO_4, concentrated in vacuum and purified with column chromatography to provide **42** in 83% yield as a white solid: R_f = 0.60 (1:1 EtOAc:hexanes); m.p. = 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.2, 1.3 Hz, 1 H), 7.64 (ddd, J = 8.4, 7.2, 1.4 Hz, 1 H), 7.52–7.32 (m, 2 H), 3.52 (t, J = 6.7 Hz, 2 H), 2.59–2.47 (m, 2 H), 1.81–1.74 (m, 2 H), 1.65–1.58 (m, 2 H), 1.52–1.40 (m, 4 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.7, 150.6 (t, J_{CF} = 27.5 Hz), 132.6, 132.1, 131.6, 130.3, 125.0, 120.4 (t, J_{CF} = 244.5 Hz), 116.1, 45.1, 35.0 (t, J_{CF} = 23.9 Hz), 32.5, 28.7, 26.7, 22.0 (t, J_{CF} = 3.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –101.9; IR (neat) ν = 2934, 2853, 1668, 1609, 1161, 1025, 970, 909, 763, 718, 635, 589, 481, 466 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{15}H_{18}N_2OF_2Cl$ [M+H$^+$] 315.1070; found 315.1073.

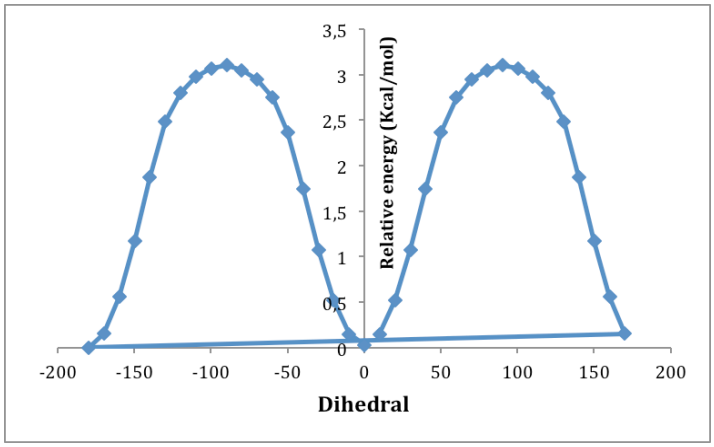


3-(2-(4-Bromophenyl)-1,1-difluoroethyl)quinoxalin-2-ol (43)

To a solution of 2-quinoxalinol (14.6 mg, 0.10 mmol, 1.0 equiv), sodium 2-(4-bromophenyl)-1,1-difluoroethanesulfinate **(41,** 46 mg, 0.14 mmol, 1.5 equiv) and $ZnCl_2$ (20.0 mg, 0.14 mmol, 1.5 equiv) in DCM (0.3 mL) and water (0.12 mL) was added TsOH•H_2O (19.0 mg, 0.10 mmol, 1.0 equiv). The reaction mixture was cooled in ice and TBHP (70% solution in water, 0.068 mL, 0.5 mmol, 5.0 equiv) was added with vigorous

stirring and the stirring was continued at this temperature for 2 h. Then, a second addition of sodium 2-(4-bromophenyl)-1,1-difluoroethanesulfinate **(41)** (46 mg, 0.14 mmol, 1.5 equiv) and TBHP (70% solution in water, 0.068 mL, 0.5 mmol, 5.0 equiv) was performed to drive the reaction further. After 2 h the reaction mixture was warmed to room temperature and upon consumption of the starting material (10–15 min) the reaction was immediately partitioned between EtOAc (2.0 mL) and saturated $NaHCO_3$ (2.0 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 2.0 mL). The combined organic layers was dried over Na_2SO_4, concentrated in vacuum and purified with preparative TLC (1:1 EtOAc:hexane) to provide **43** in 56% yield as a white solid: m.p. = 240 °C; R_f = 0.48 (1:1 EtOAc/hexanes); ^{1}H NMR (600 MHz, acetone-d_6) δ 7.82 (dd, J = 8.1, 1.4 Hz, 1 H), 7.65 (ddd, J = 8.4, 7.3, 1.4 Hz, 1 H), 7.50–7.44 (m, 3 H), 7.38 (ddd, J = 8.4, 7.3, 1.3 Hz, 1 H), 7.30 (d, J = 8.3 Hz, 2 H), 3.86 (t, J = 17.2 Hz, 2 H); ^{13}C NMR (151 MHz, acetone-d_6) δ 153.4, 151.7 (t, J_{CF} = 25.9 Hz), 134.0, 133.6, 133.1, 133.0 (t, J_{CF} = 4.5 Hz), 132.2, 131.7, 130.7, 124.8, 121.8, 119.5 (t, J_{CF} = 245.6 Hz), 116.3, 41.2 (t, J_{CF} = 24.8 Hz); ^{19}F NMR (376 MHz, acetone-d_6) δ –100.1; IR (neat) = 2917, 2836, 1665, 1608, 1565, 1484, 1404, 1337, 1212, 1166, 975, 916, 894, 757, 648, 589, 528 cm^{-1}; HRMS (ESI-TOF) calc'd for $C_{16}H_{11}N_2OF_2Br$ [M+H$^+$] 365.0096; found 365.0101.

Quantum mechanical analysis for anisole



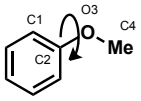
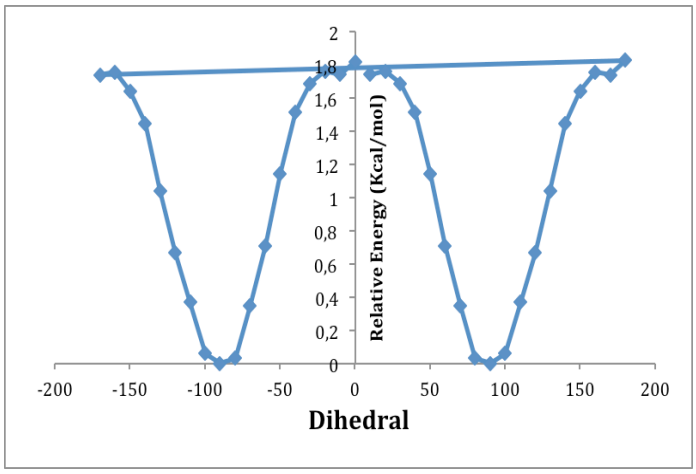


Figure 1: Full QM conformational scan with 10° dihedral increment around C1-C2-O3-C4 of anisole. Minimum energy conformation suggests that the methyl group is in plane

with the benzene ring. B3LYP method with 6-31G** basis set was used for QM calculations.

Quantum mechanical analysis for difluoroethylbenzene



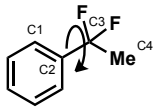


Figure 2: Full conformational scan with 10° dihedral increment around C1-C2-C3-C4 of difluoroethylbenzene. Minimum energy conformation suggests that the methyl group is out of plane (~90^0) with the benzene ring unlike anisole. B3LYP method with 6-31G** basis set was used for QM calculations.

Quantum mechanical electrostatic potential surfaces of anisole and di-fluoroethylbenzene

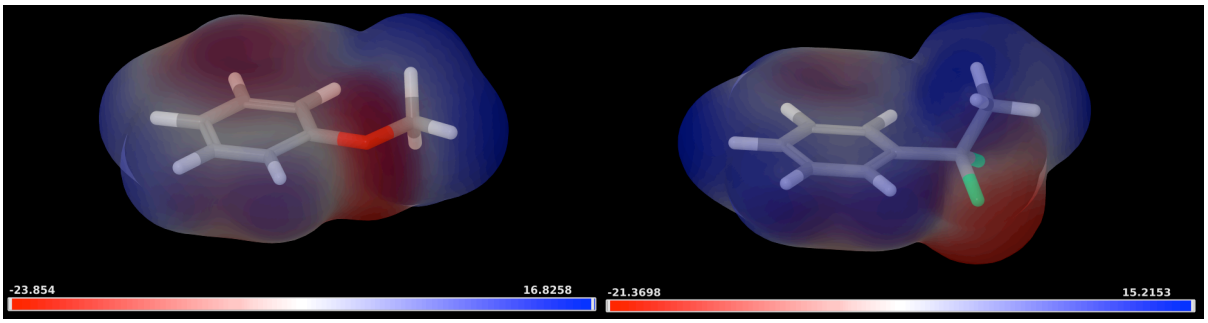
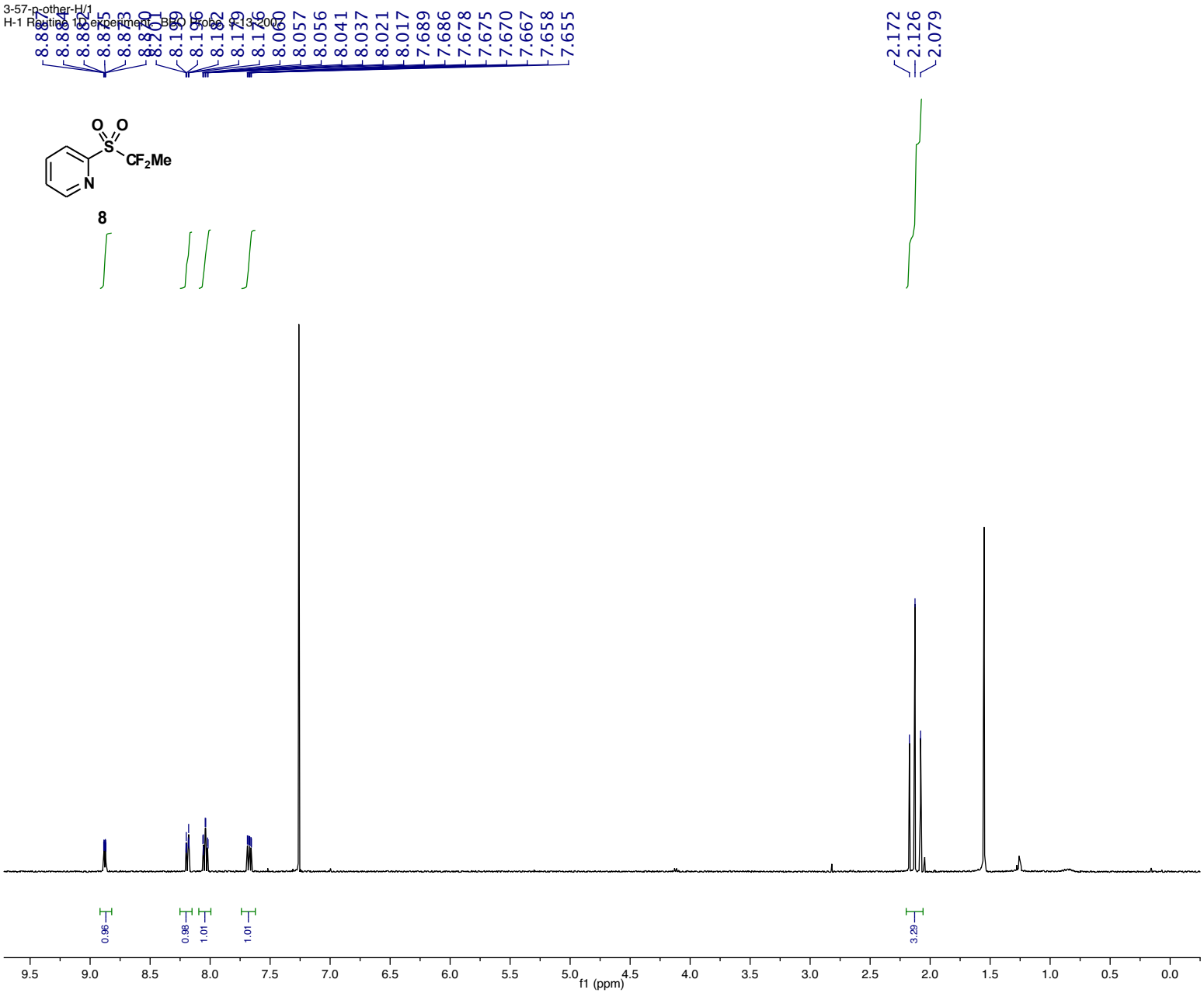
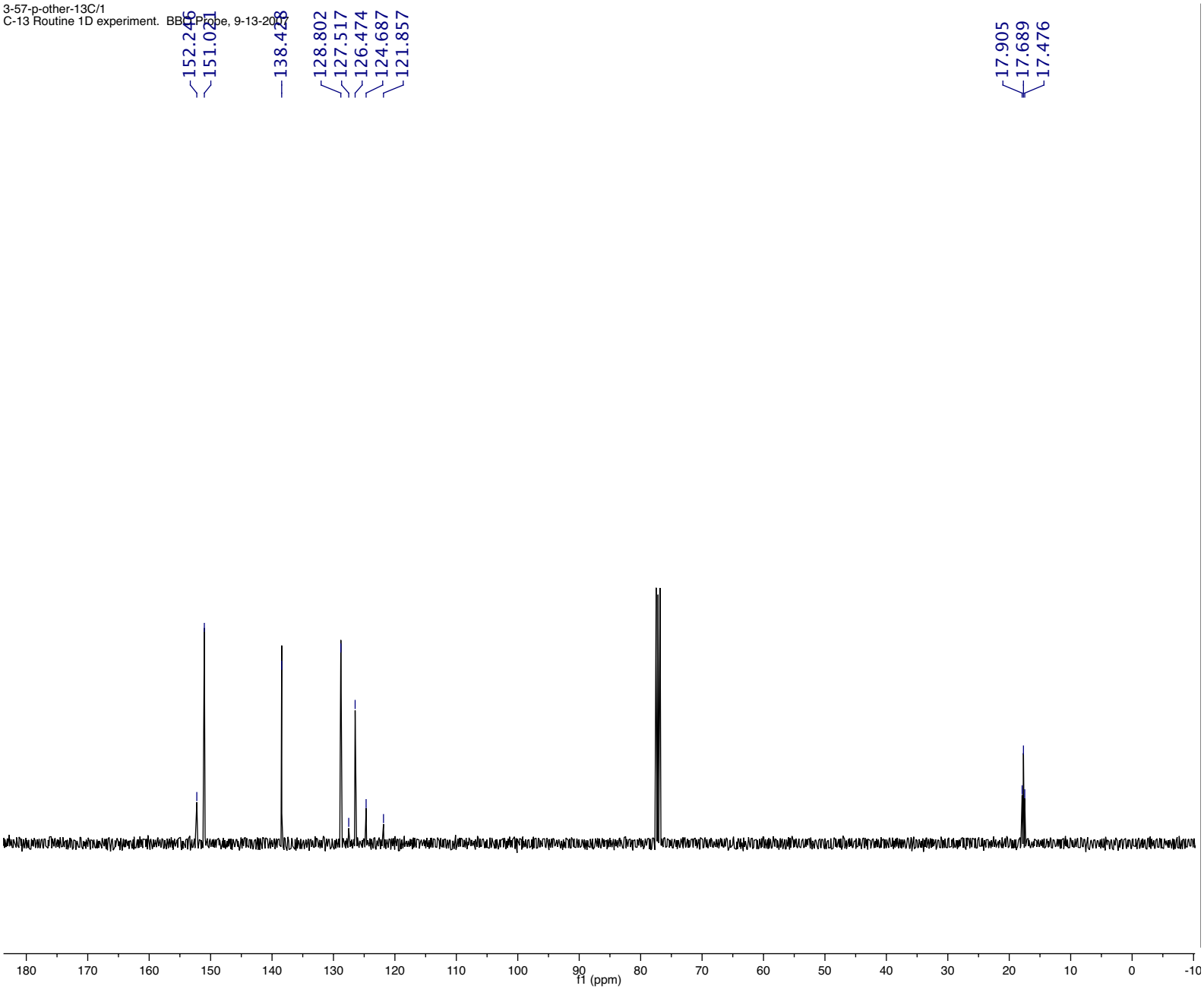
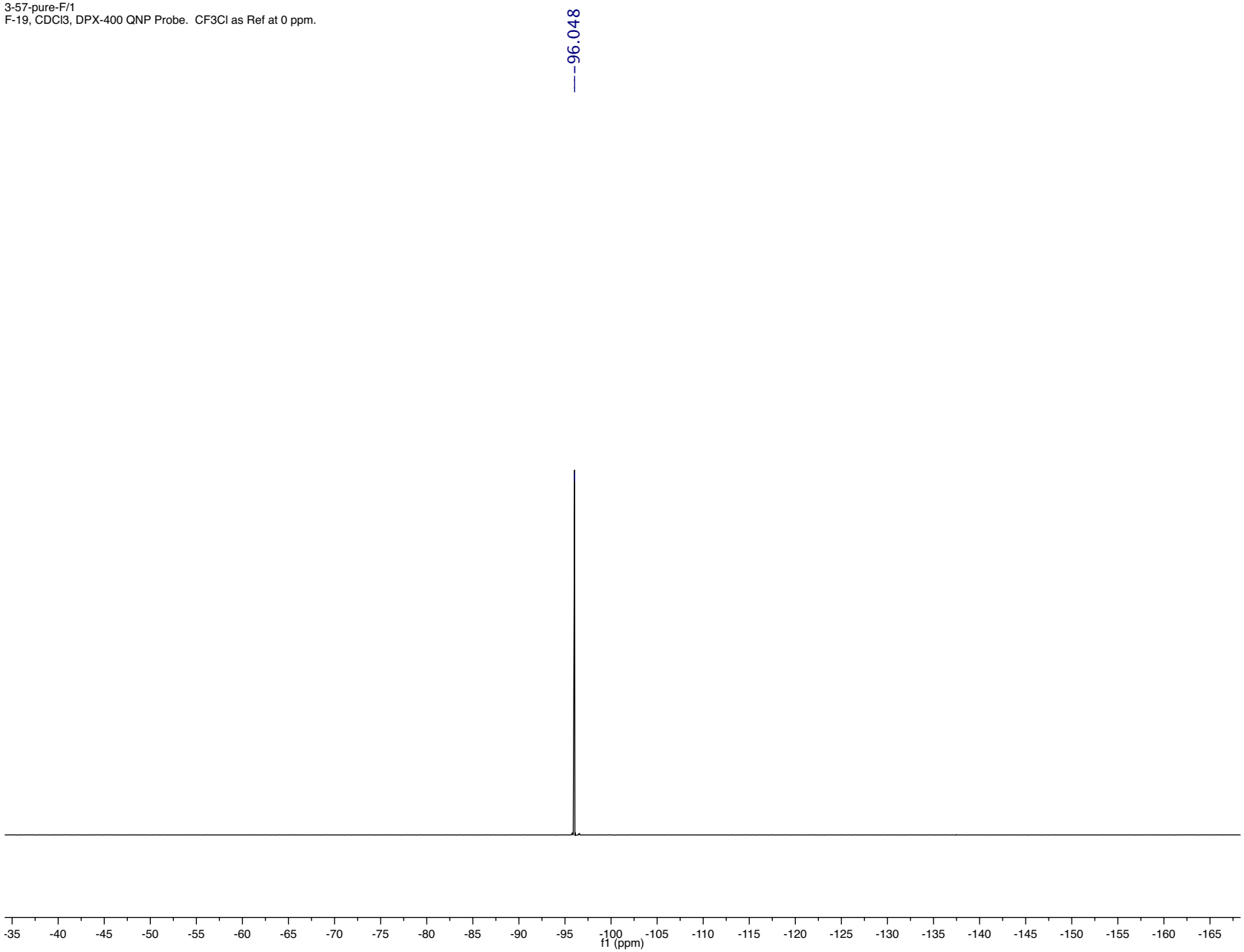


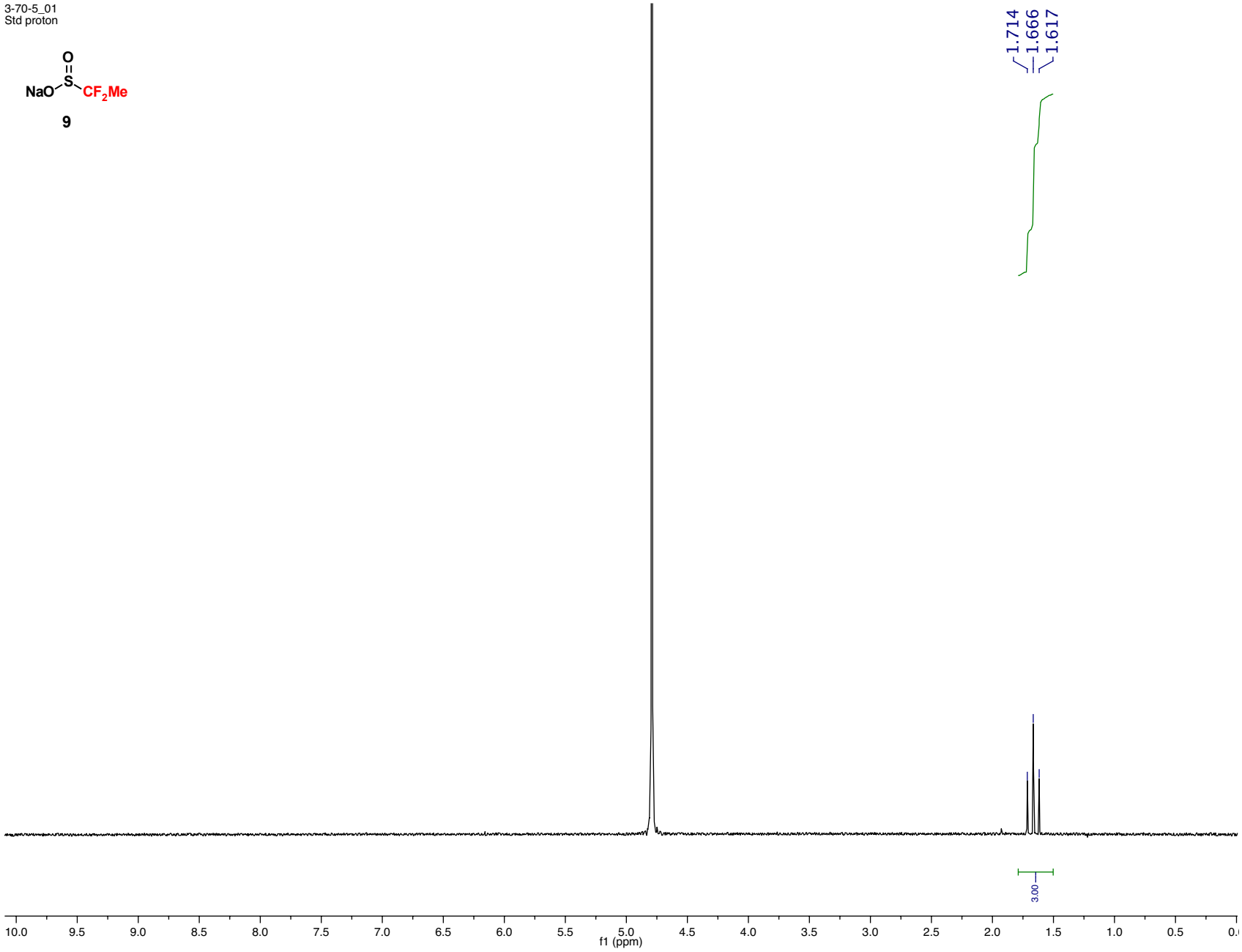
Figure 3: Red represents regions of relatively negative electrostatic potential, while blue represents regions of positive electrostatic potential. Left: Dark red patches observed over the π-system of ring and the methoxy oxygen in anisole. Right: A relatively weaker red patch is observed around the π-system due to the inductive effect of the fluorine atoms in di-fluoroethylbenzene system. The color scale below the images shows the range of electrostatic potential values in au.


3-57-p-other-H/1
H-1 Routine 1D experiment, BBO Probe, 7-13-2007
8.885
8.883
8.880
8.211
8.199
8.196
8.182
8.179
8.176
8.060
8.057
8.056
8.041
8.037
8.021
8.017
7.689
7.686
7.678
7.675
7.670
7.667
7.658
7.655
2.172
2.126
2.079
O
O
S
CF2Me
N
8
0.96
0.98
1.01
1.01
3.29
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)


3-57-p-other-13C/1
C-13 Routine 1D experiment. BBO Probe, 9-13-2013
152.246
151.021
138.428
128.802
127.517
126.474
124.687
121.857
17.905
17.689
17.476
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

3-57-pure-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.




3-70-5_01
Std proton
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S
NaO
CF2Me
9
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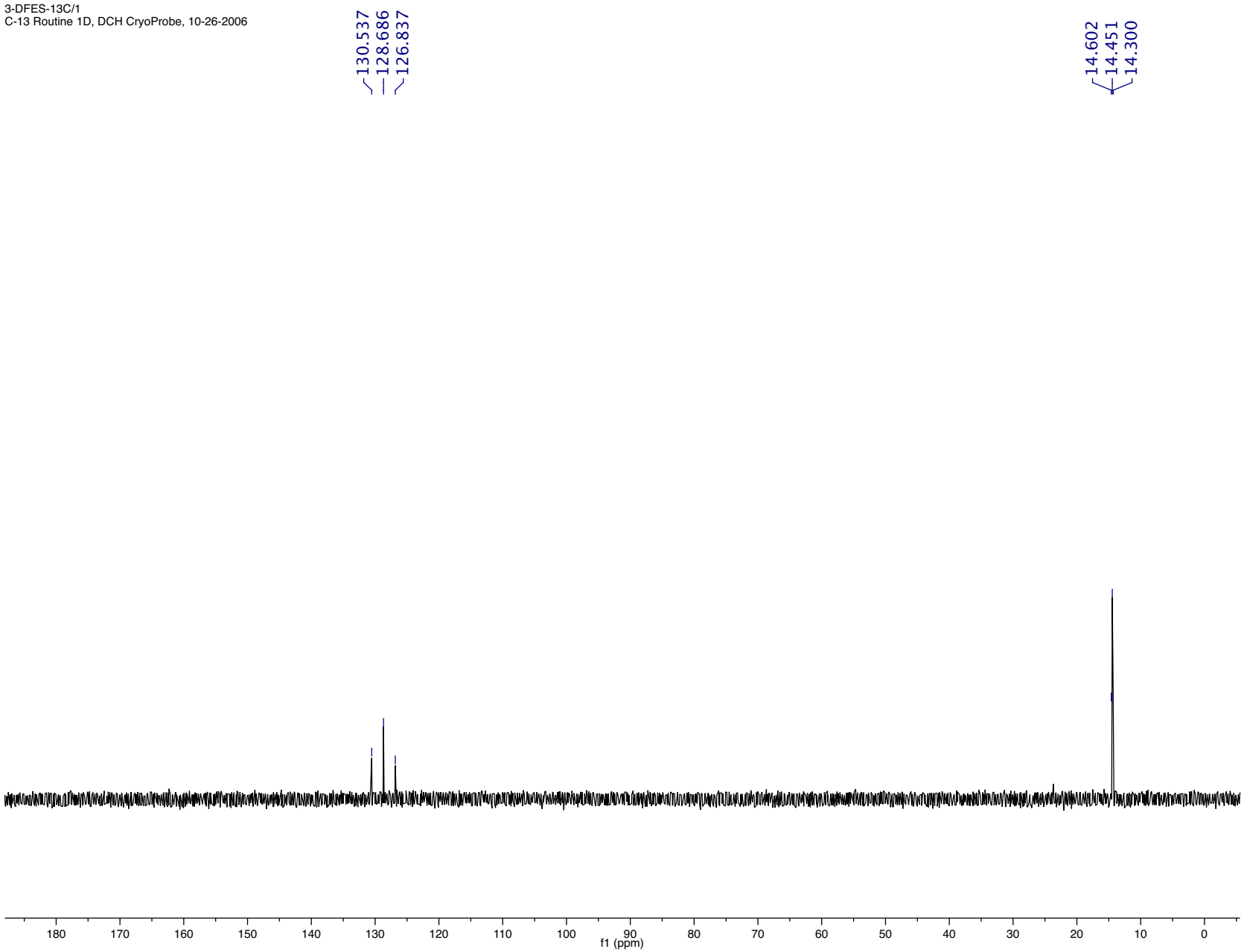
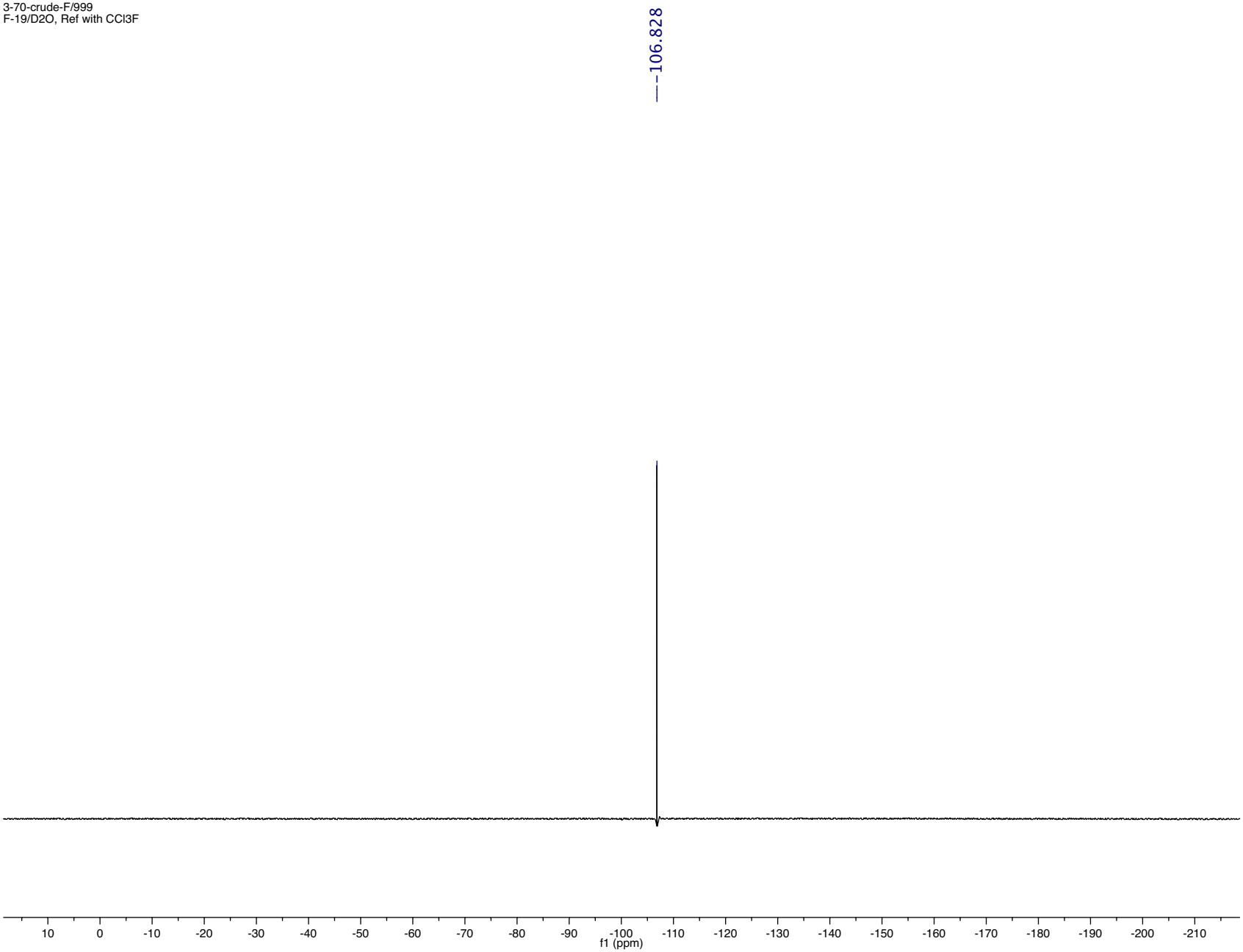
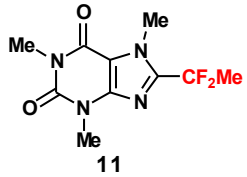
1.666
1.617
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


3-DFES-13C/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
130.537
128.686
126.837
14.602
14.451
14.300
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

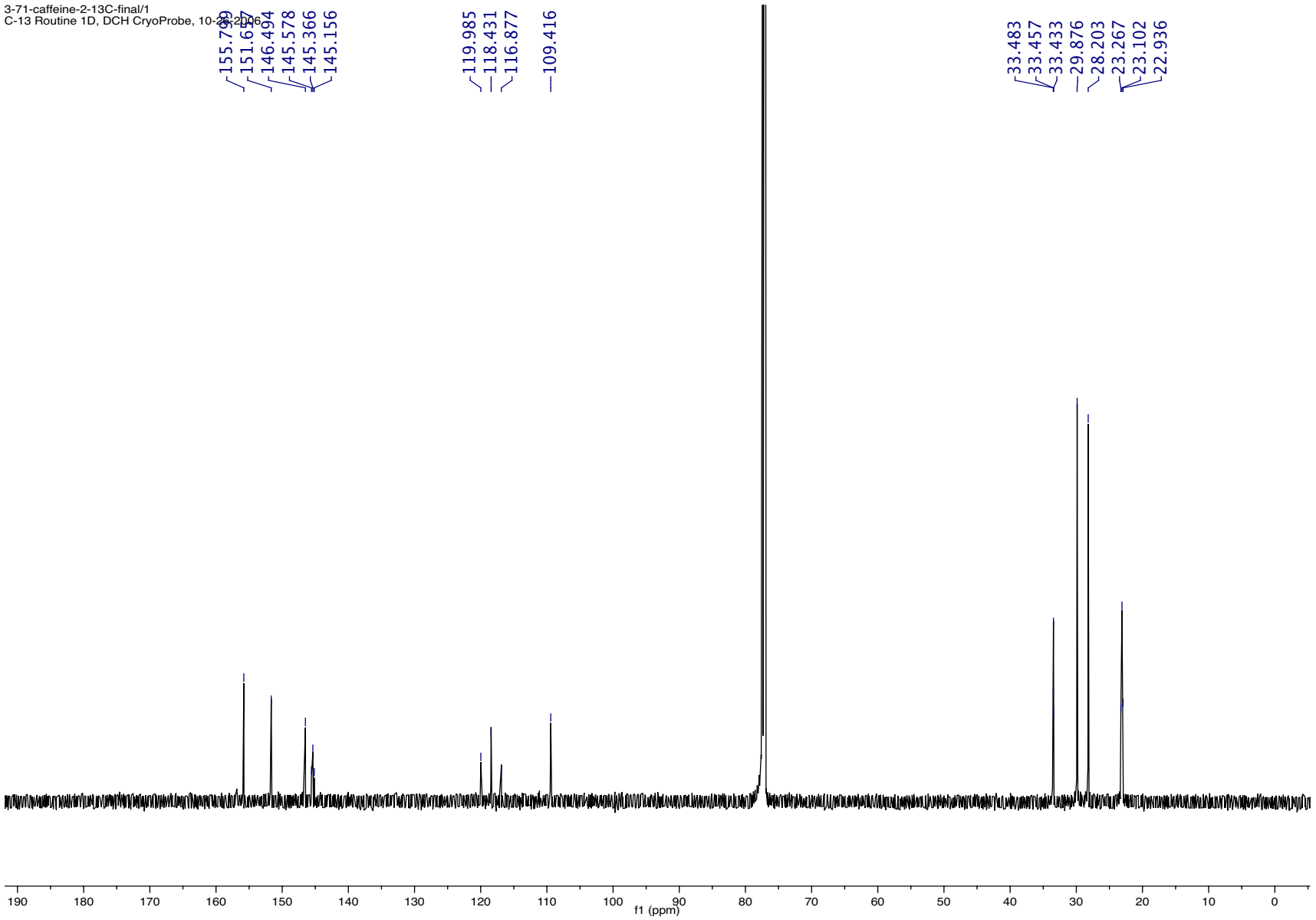
3-70-crude-F/999
F-19/D2O, Ref with CCl3F



3-71-caffeine-2/1
H-1 Routine 1D experiment. BBO Probe, 9-13-2007



11


3-71-caffeine-2-13C-final/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
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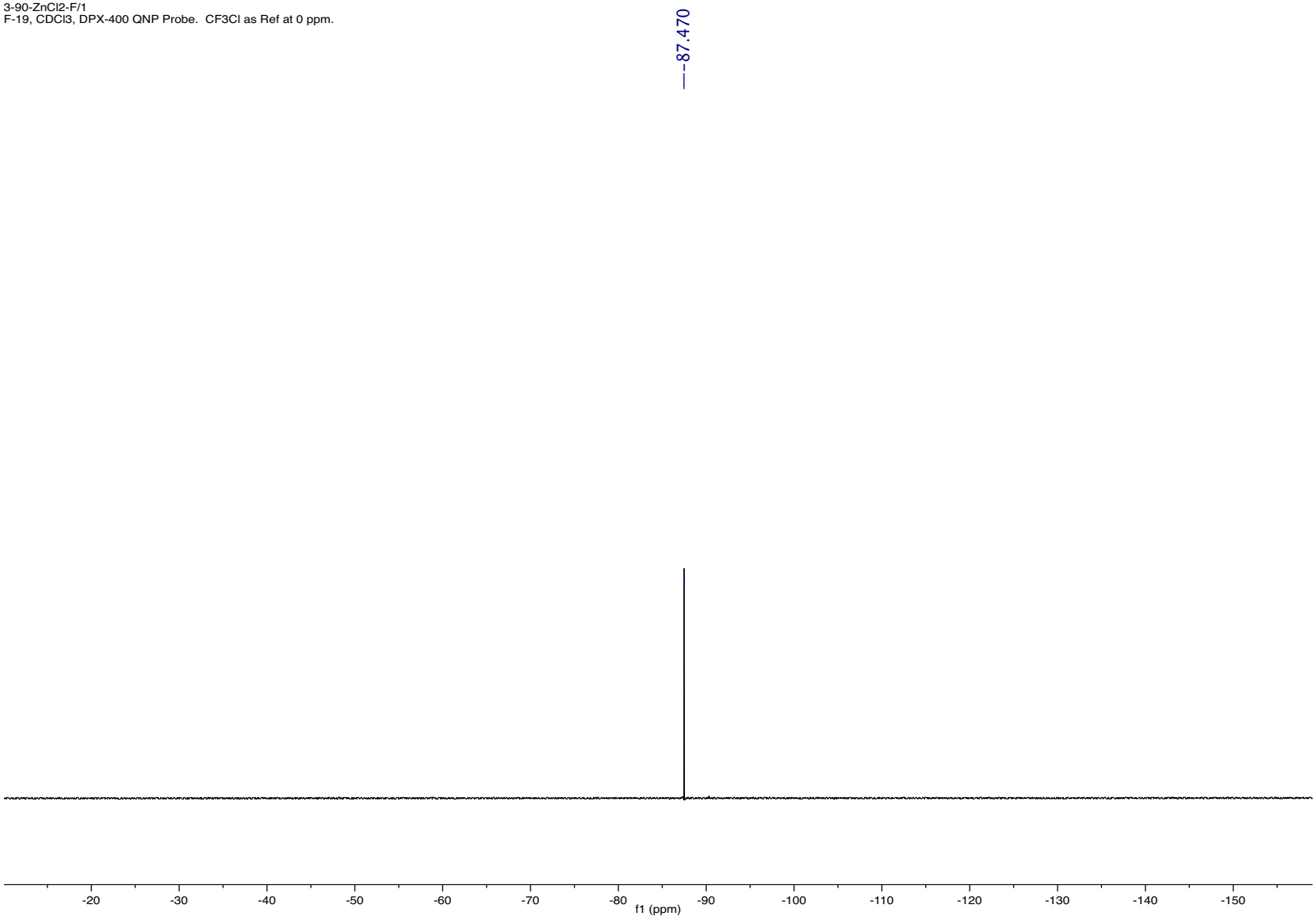
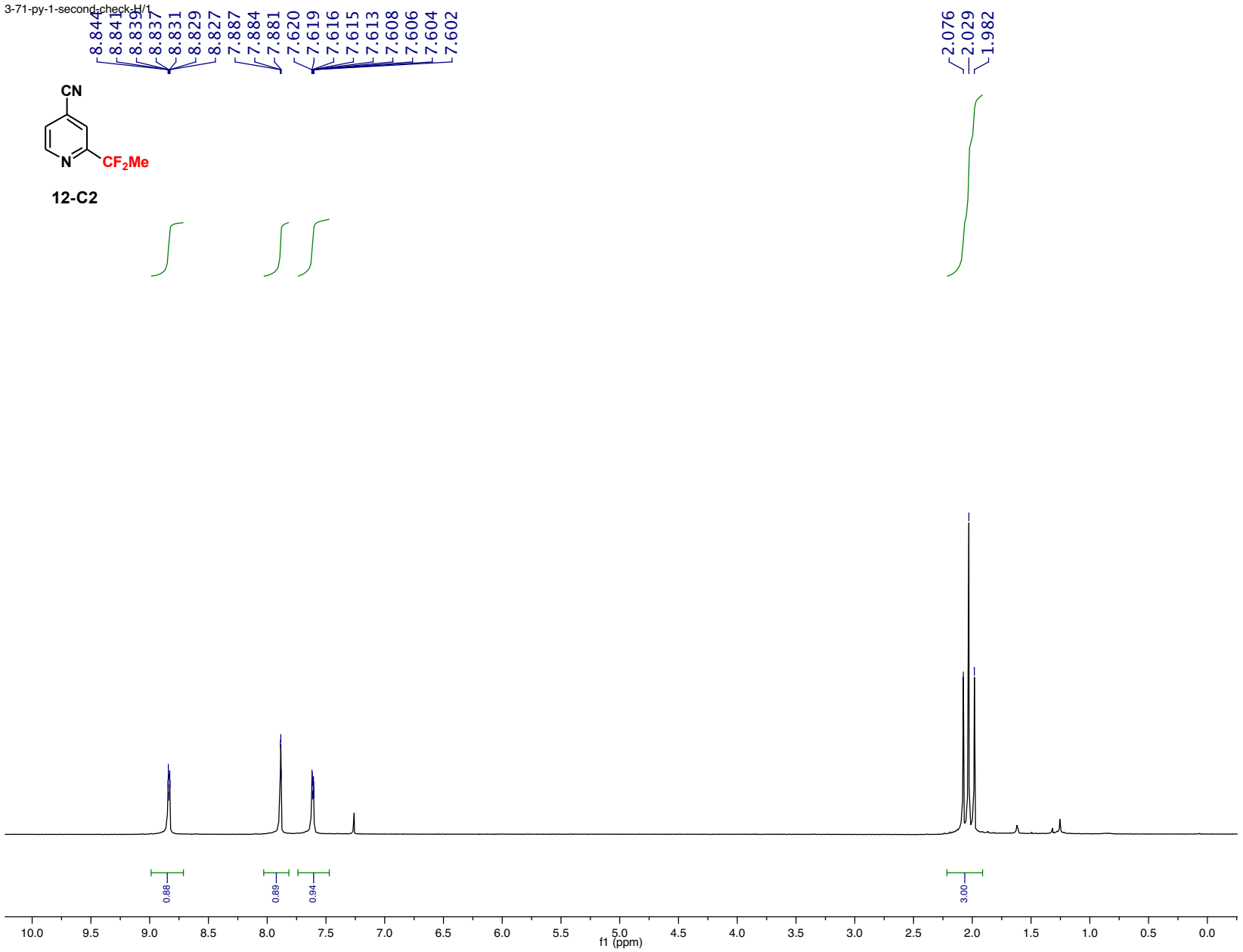
145.578
145.366
145.156
119.985
118.431
116.877
109.416
33.483
33.457
33.433
29.876
28.203
23.267
23.102
22.936
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3-90-ZnCl2-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.




3-71-py-1-second-check-H/1
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8.839
8.837
8.831
8.829
8.827
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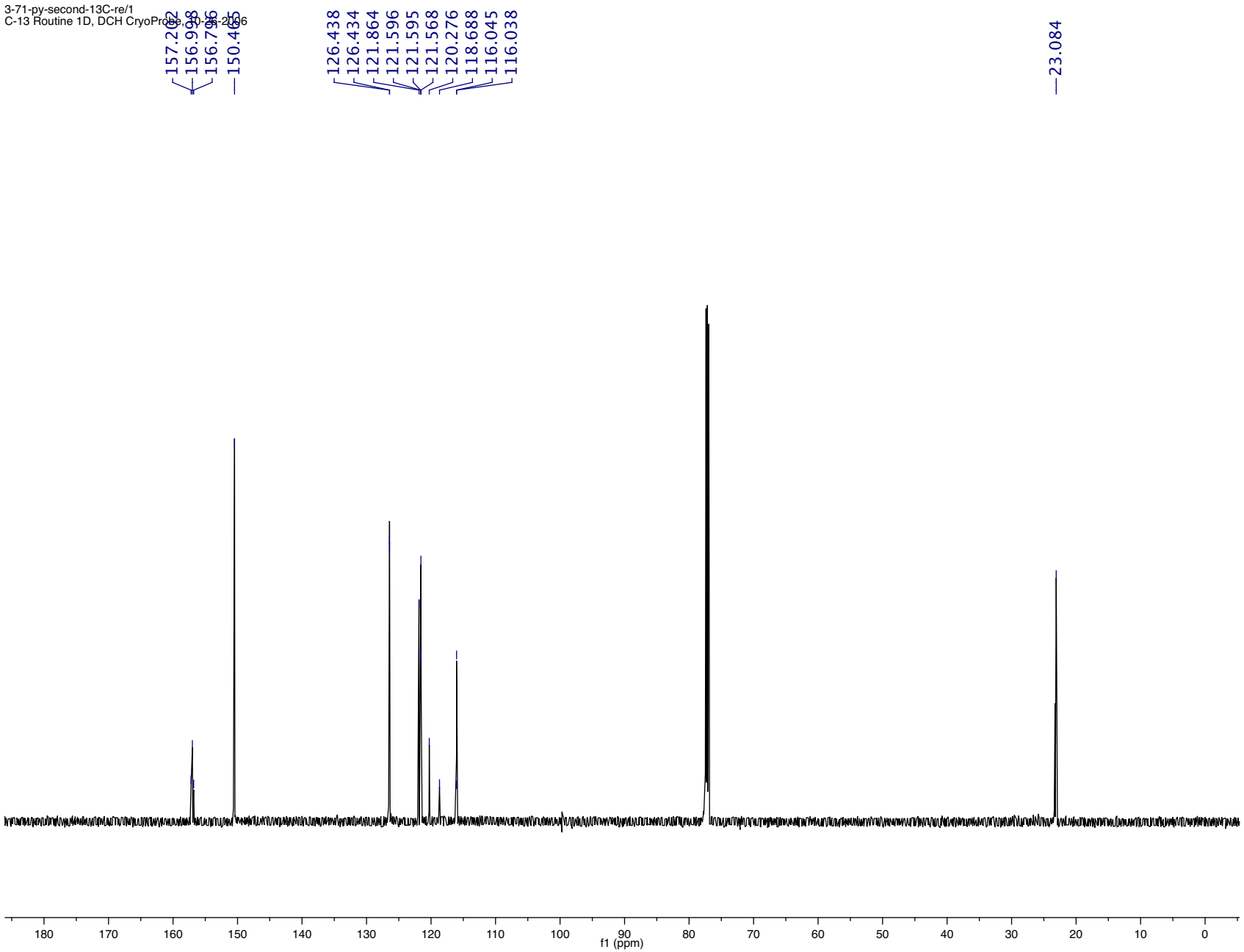
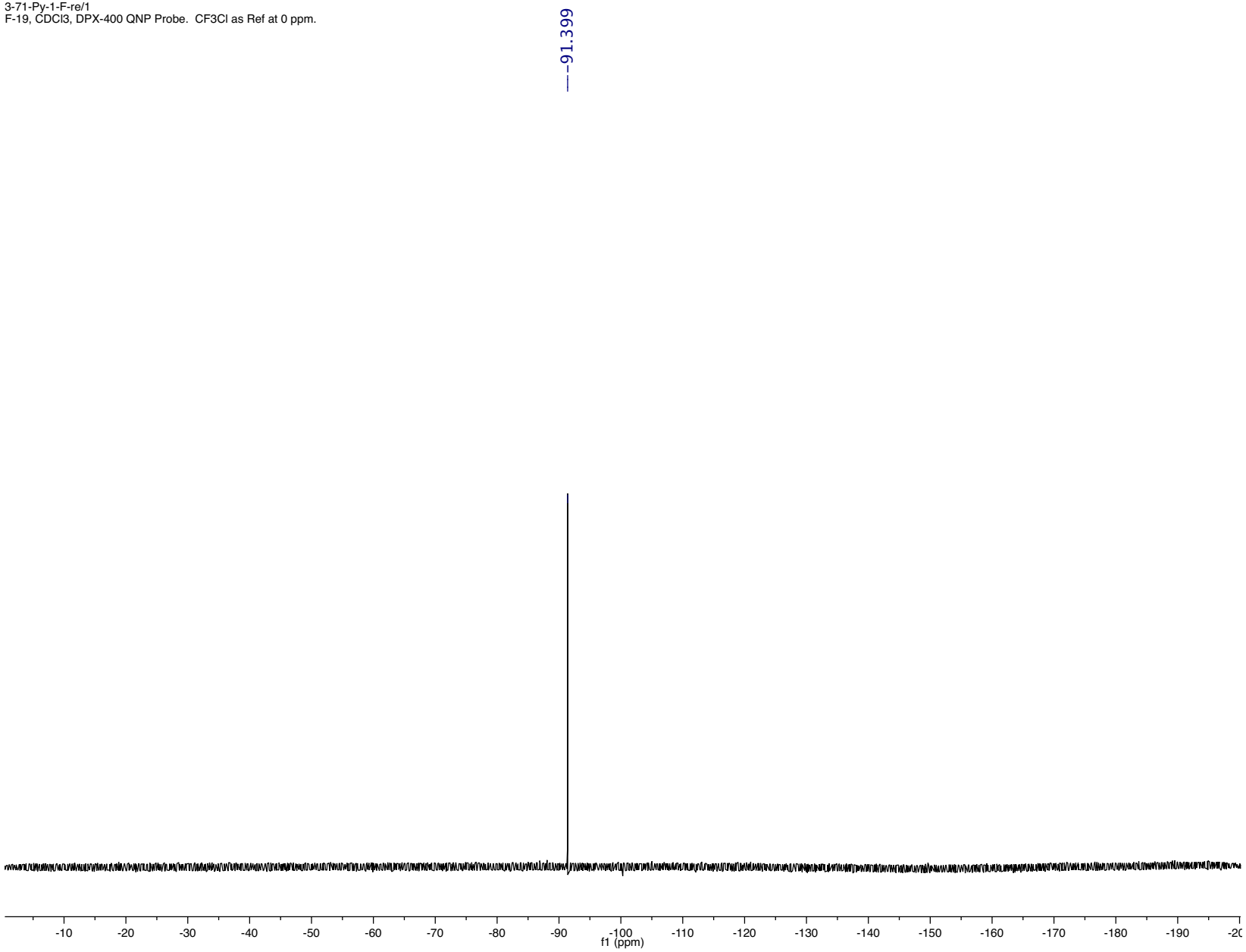
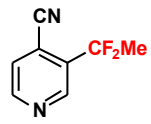
7.619
7.616
7.615
7.613
7.608
7.606
7.604
7.602
2.076
2.029
1.982
CN
N
CF2Me
12-C2
0.88
0.89
0.94
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


3-71-py-second-13C-re/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
157.202
156.998
156.796
150.465
126.438
126.434
121.864
121.596
121.595
121.568
120.276
118.688
116.045
116.038
23.084
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

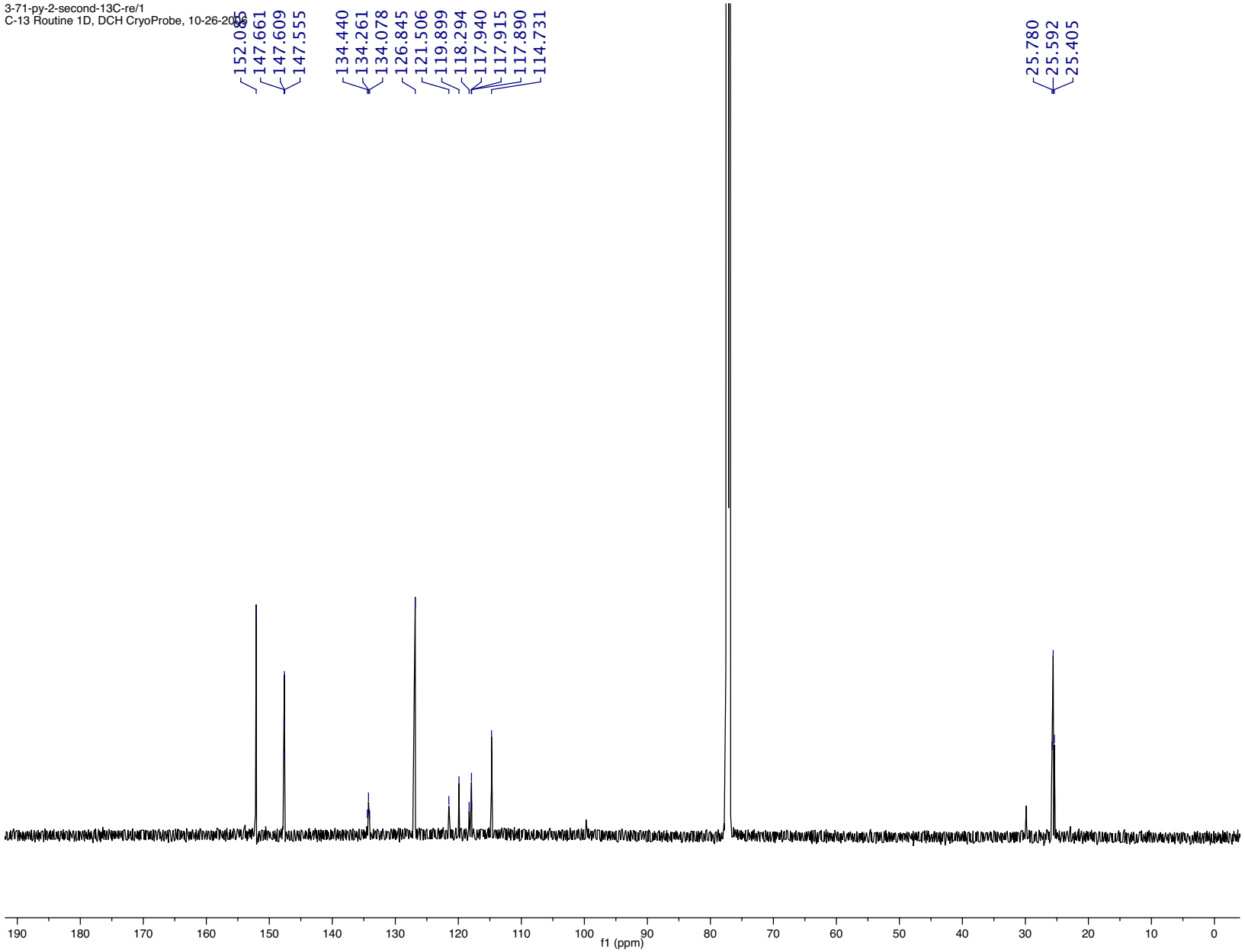
3-71-Py-1-F-re/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.



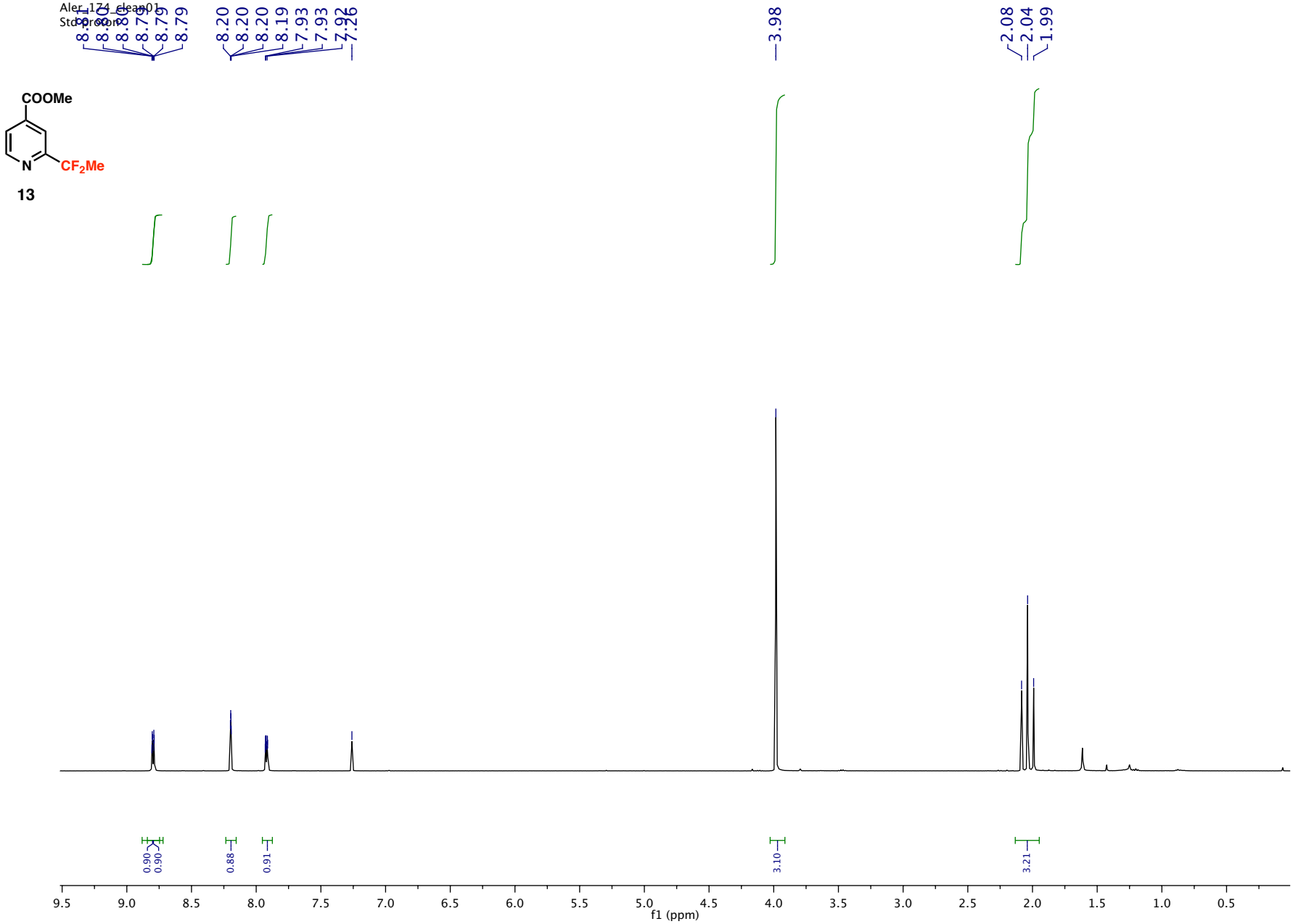
3-71-py-2-second-check-H/1

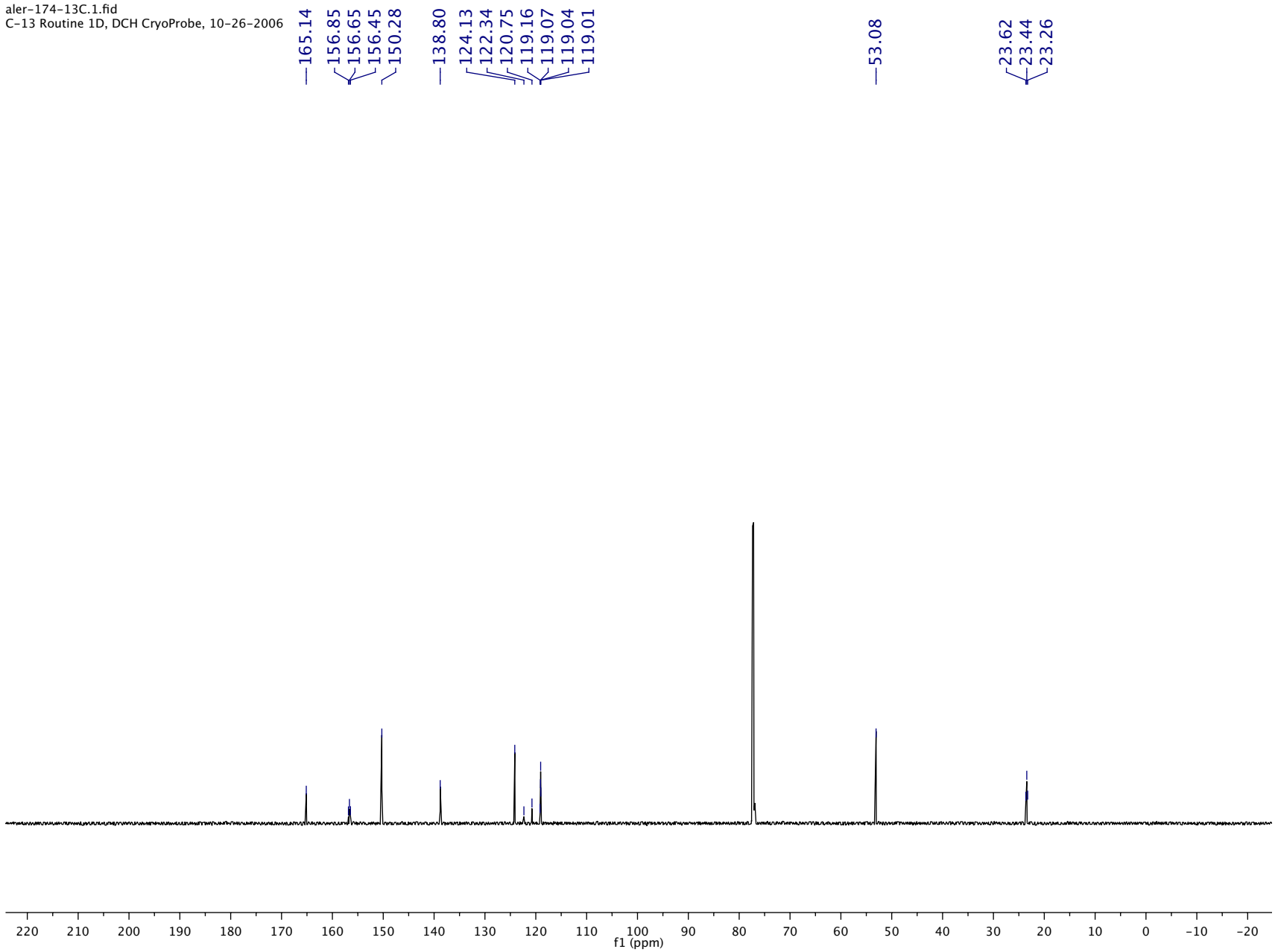


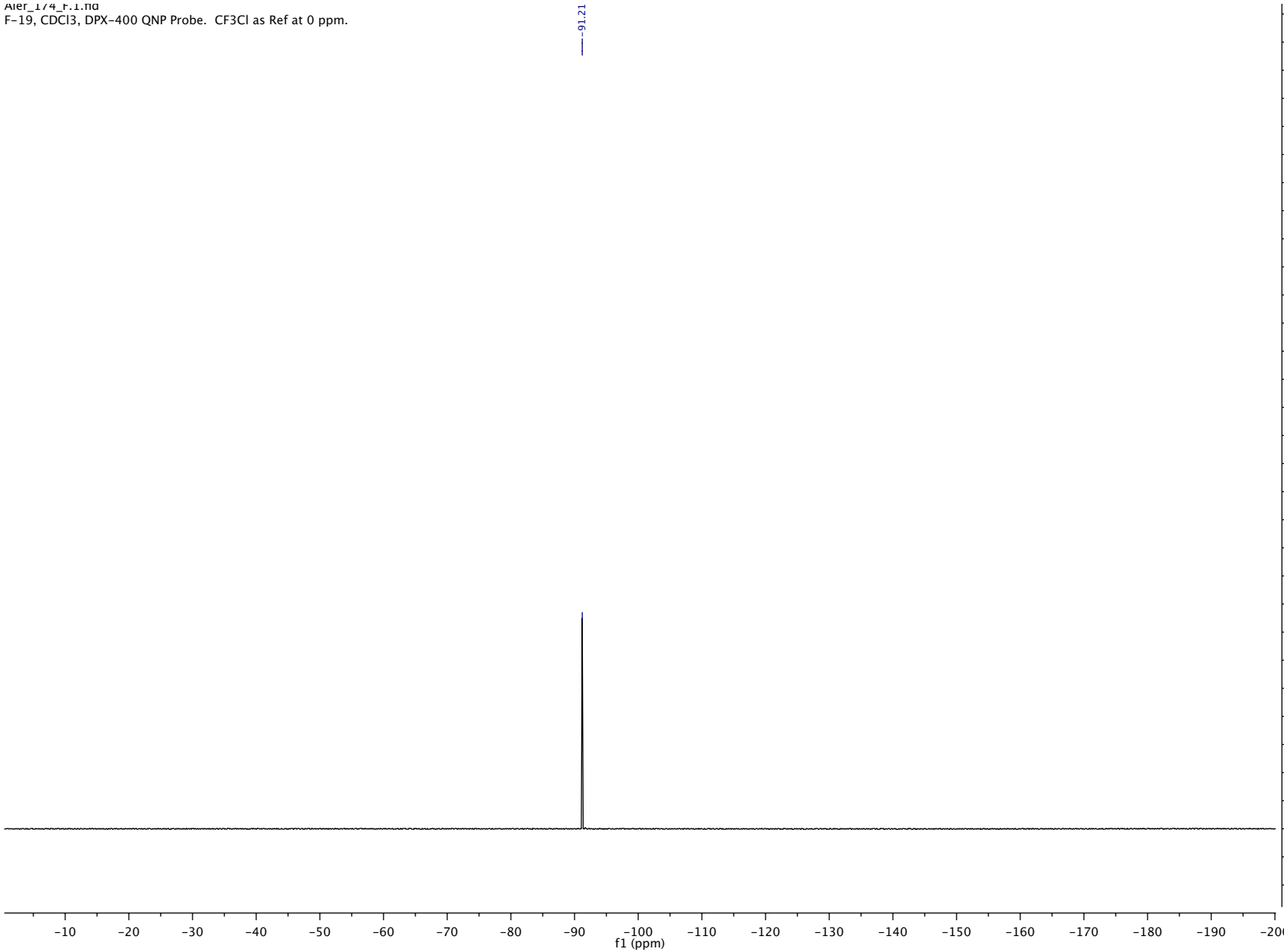
12-C3

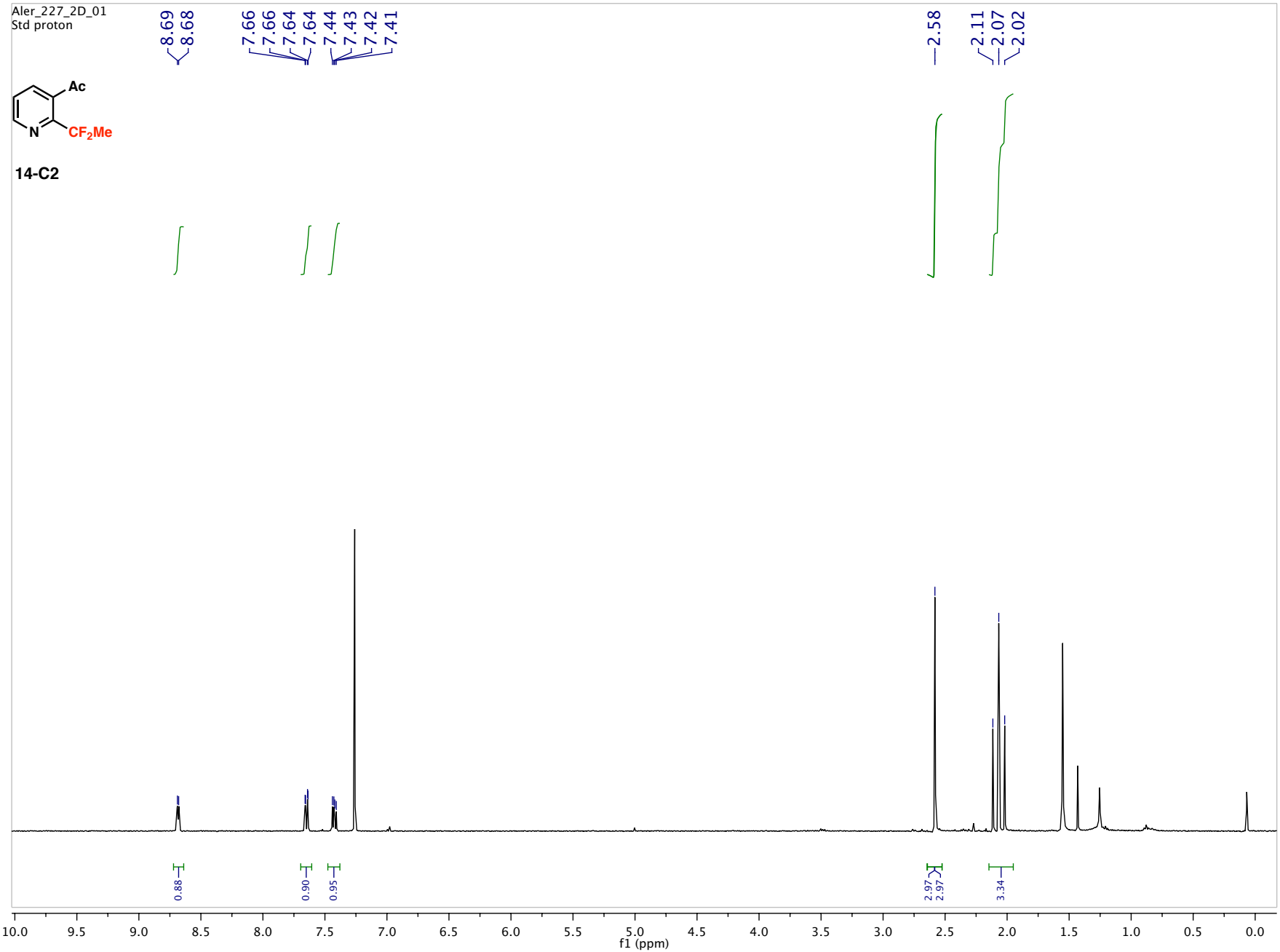

3-71-py-2-second-13C-re/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
152.035
147.661
147.609
147.555
134.440
134.261
134.078
126.845
121.506
119.899
118.294
117.940
117.915
117.890
114.731
25.780
25.592
25.405
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

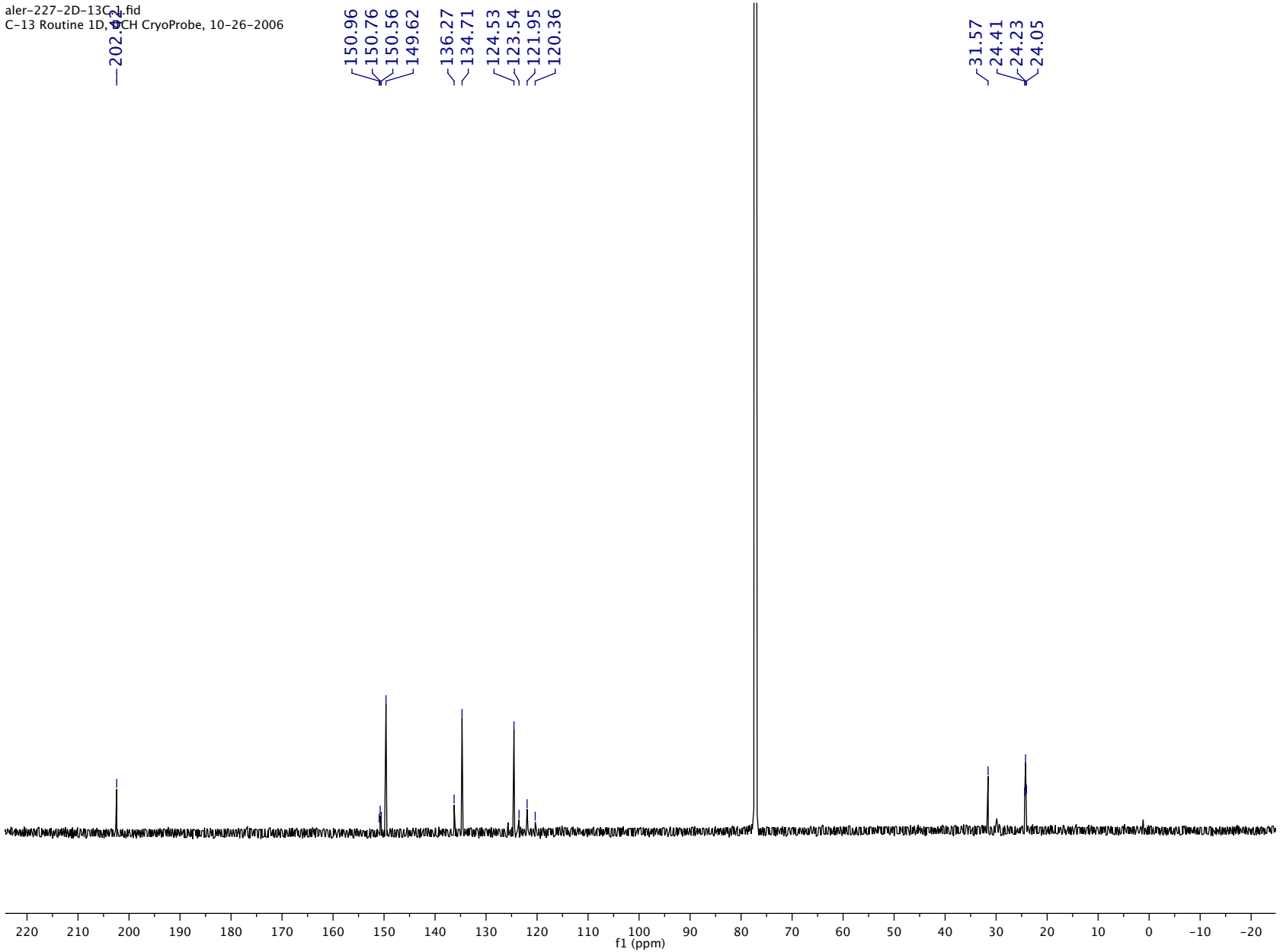
3-71-py-2-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.

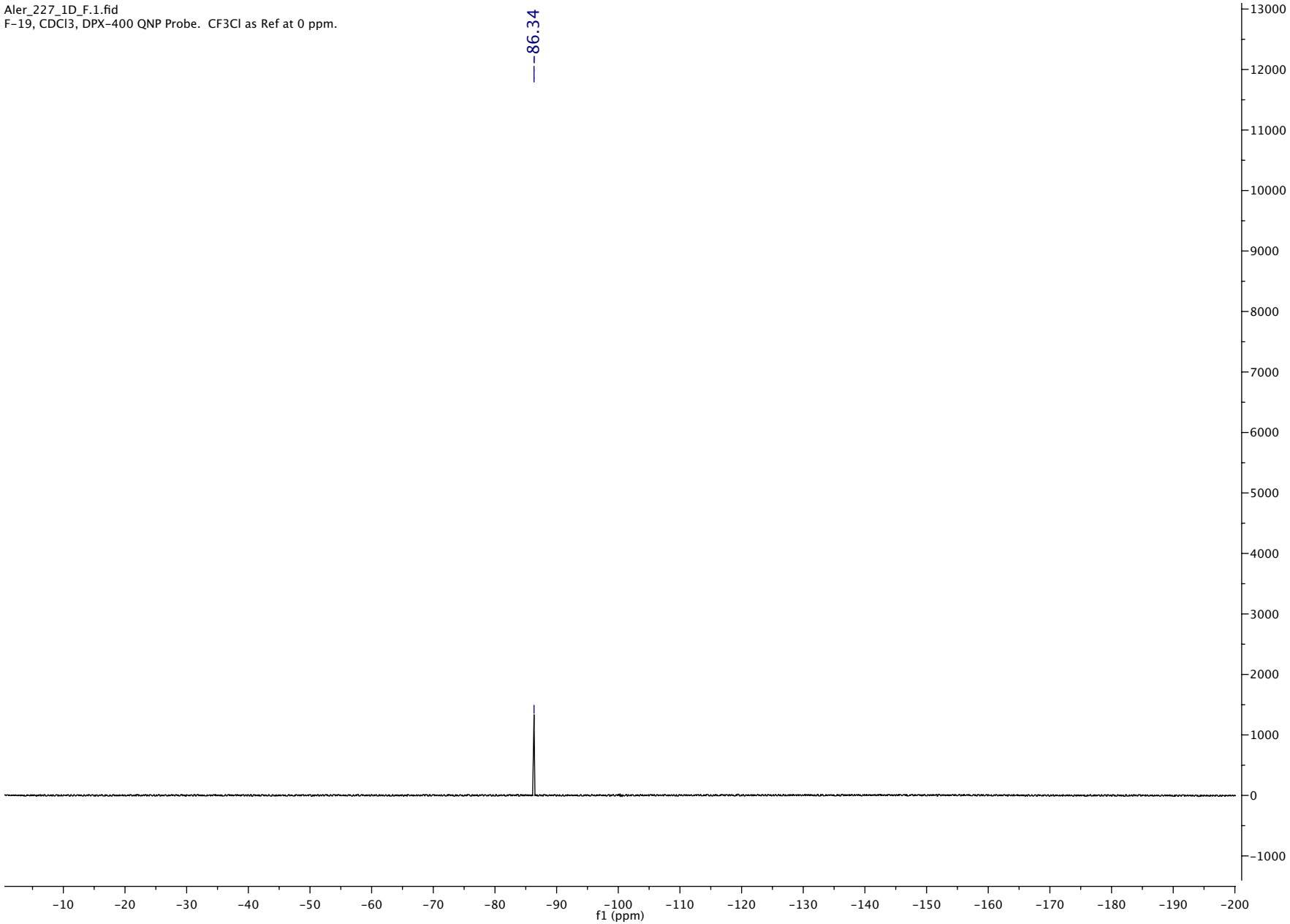

Aler_174_clean01
Std proton
8.80
8.79
8.79
8.79
8.20
8.20
8.20
8.19
7.93
7.93
7.92
7.26
3.98
2.08
2.04
1.99
COOMe
N
CF2Me
13
0.90
0.90
0.88
0.91
3.10
3.21
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

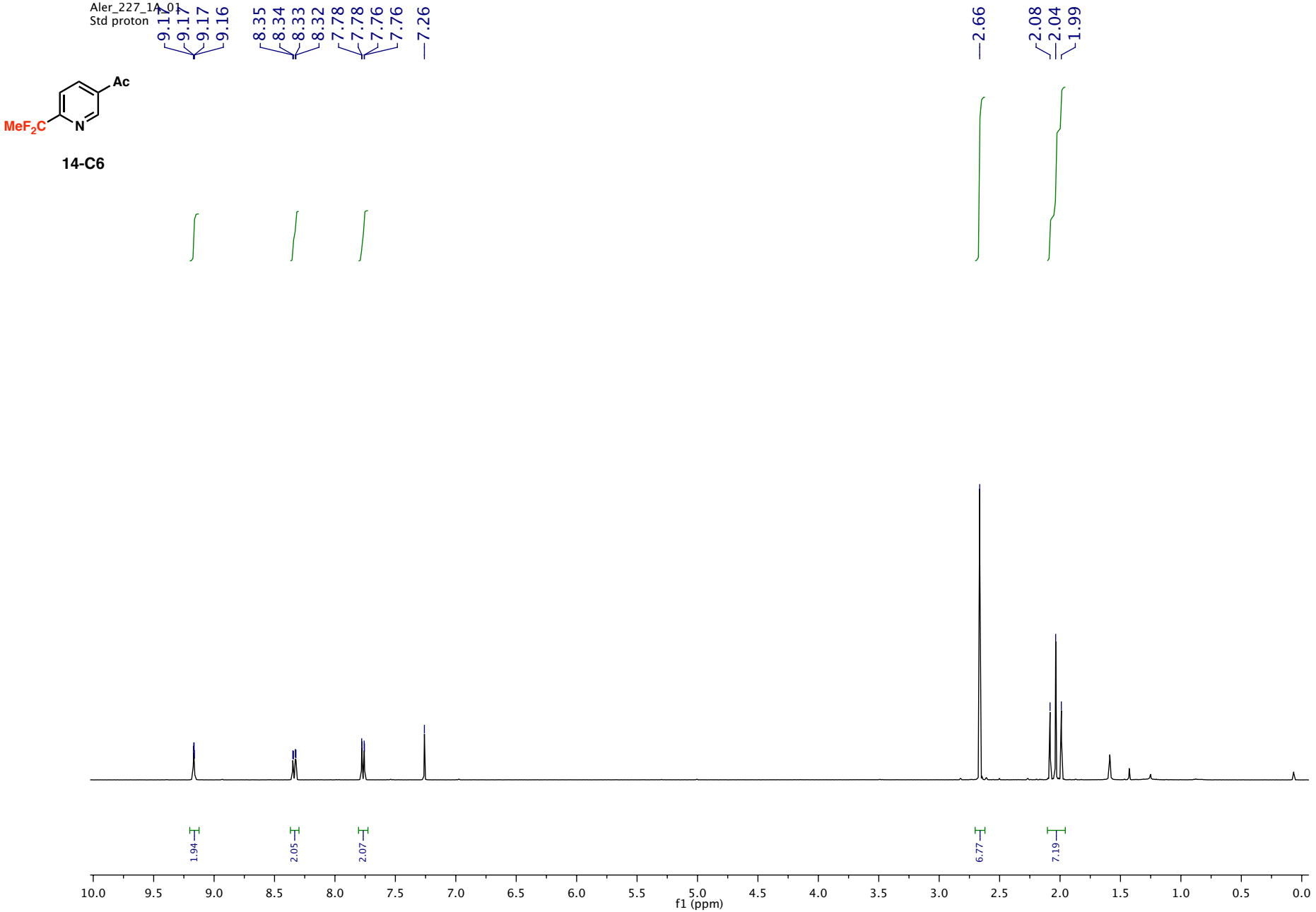

aler-174-13C.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
165.14
156.85
156.65
156.45
150.28
138.80
124.13
122.34
120.75
119.16
119.07
119.04
119.01
53.08
23.62
23.44
23.26
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

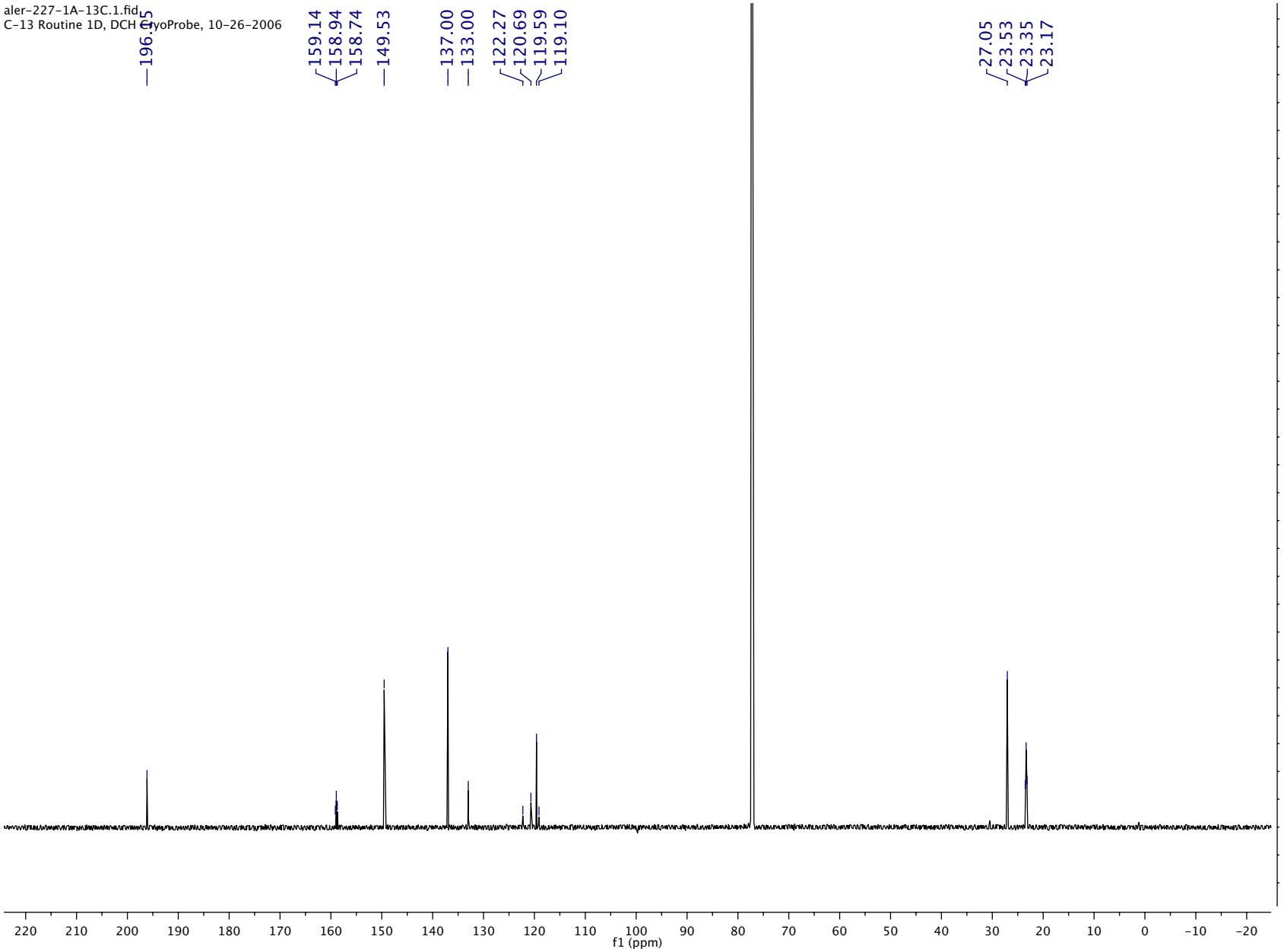

Aler_174_F.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-91.21
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

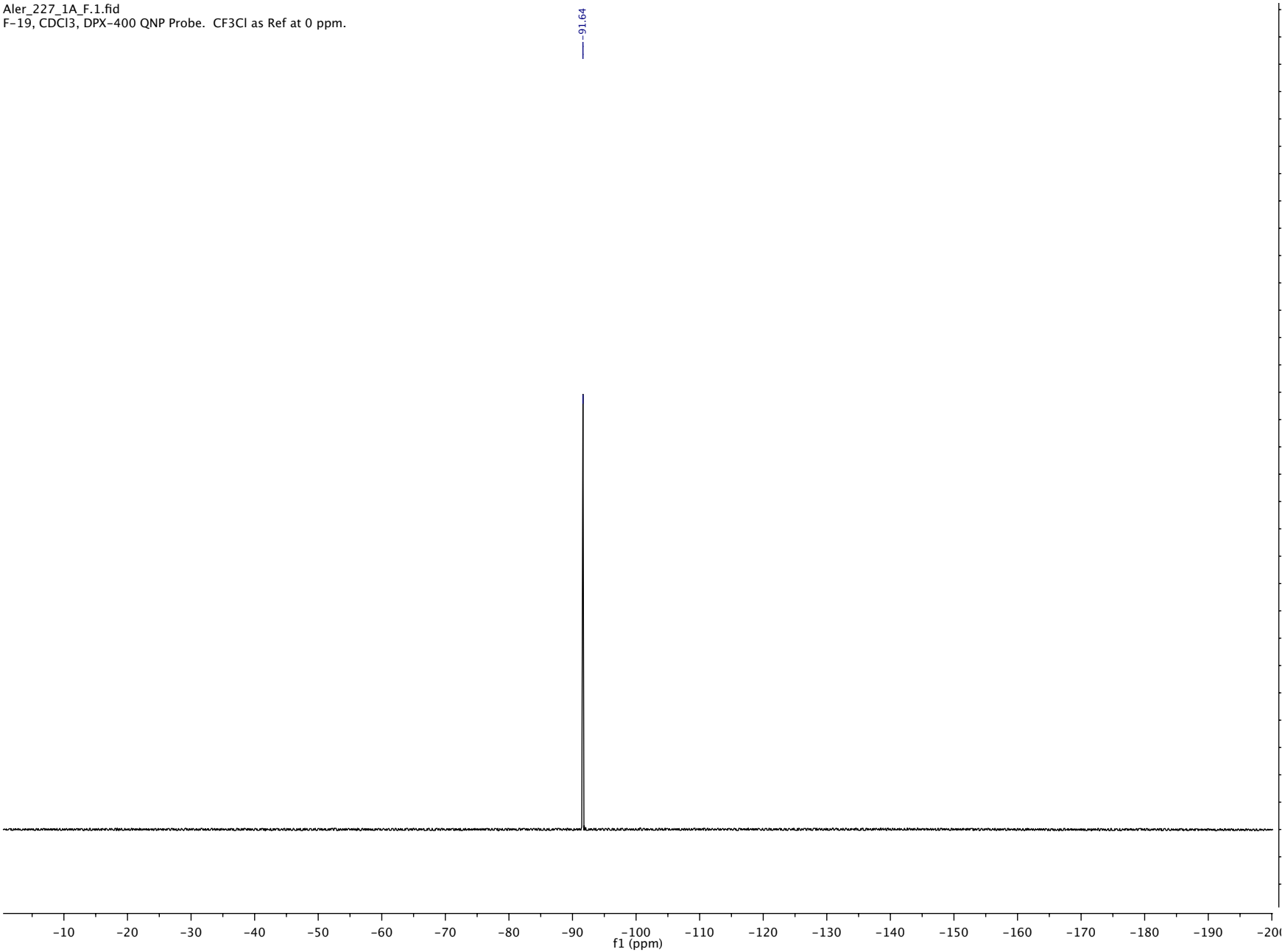

Aler_227_2D_01
Std proton
8.69
8.68
7.66
7.66
7.64
7.64
7.44
7.43
7.42
7.41
2.58
2.11
2.07
2.02
Ac
N
CF2Me
14-C2
0.88
0.90
0.95
2.97
2.97
3.34
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

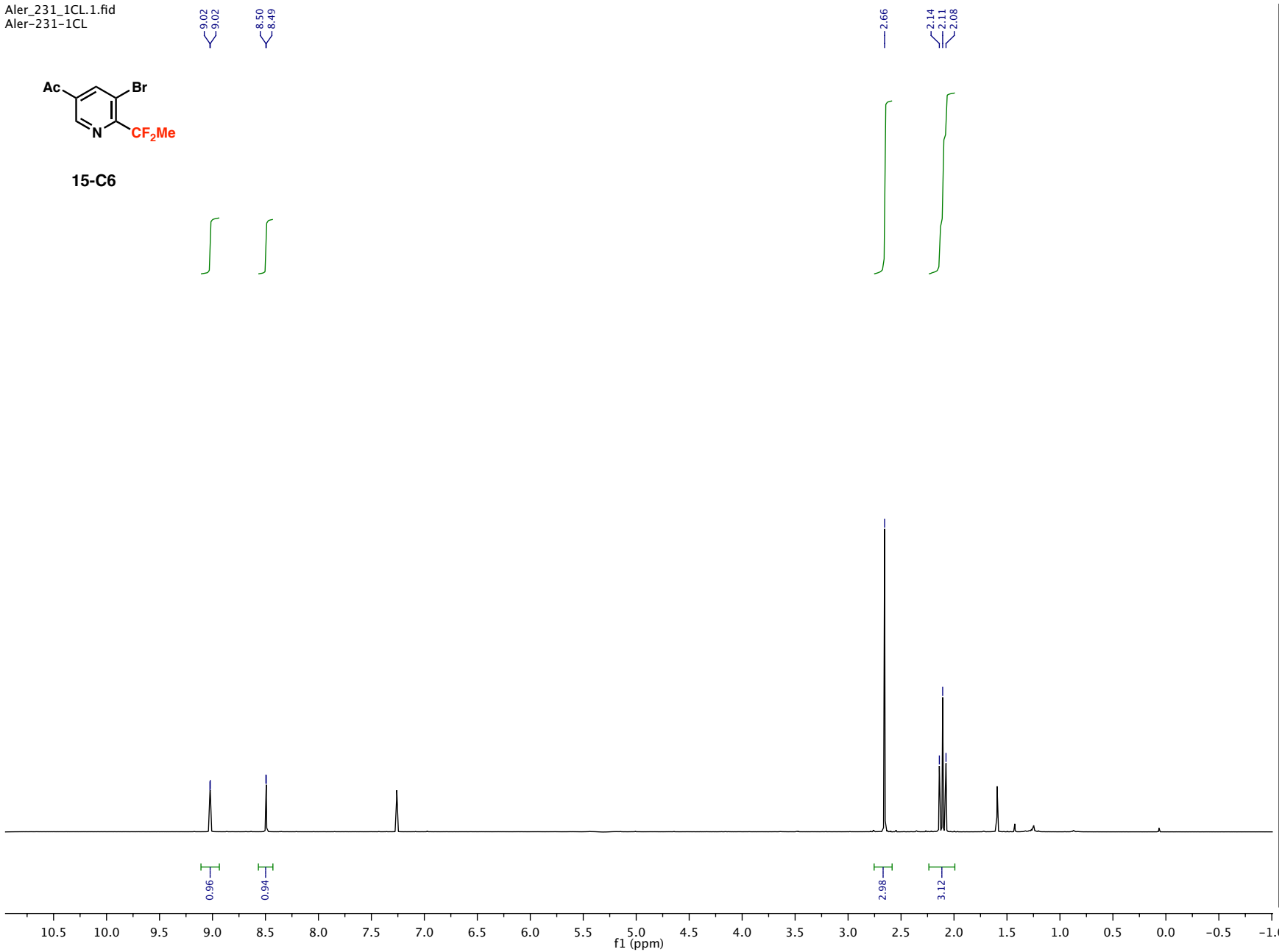

aler-227-2D-13C-1.fid
C-13 Routine 1D, BCH CryoProbe, 10-26-2006
202.24
150.96
150.76
150.56
149.62
136.27
134.71
124.53
123.54
121.95
120.36
31.57
24.41
24.23
24.05
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

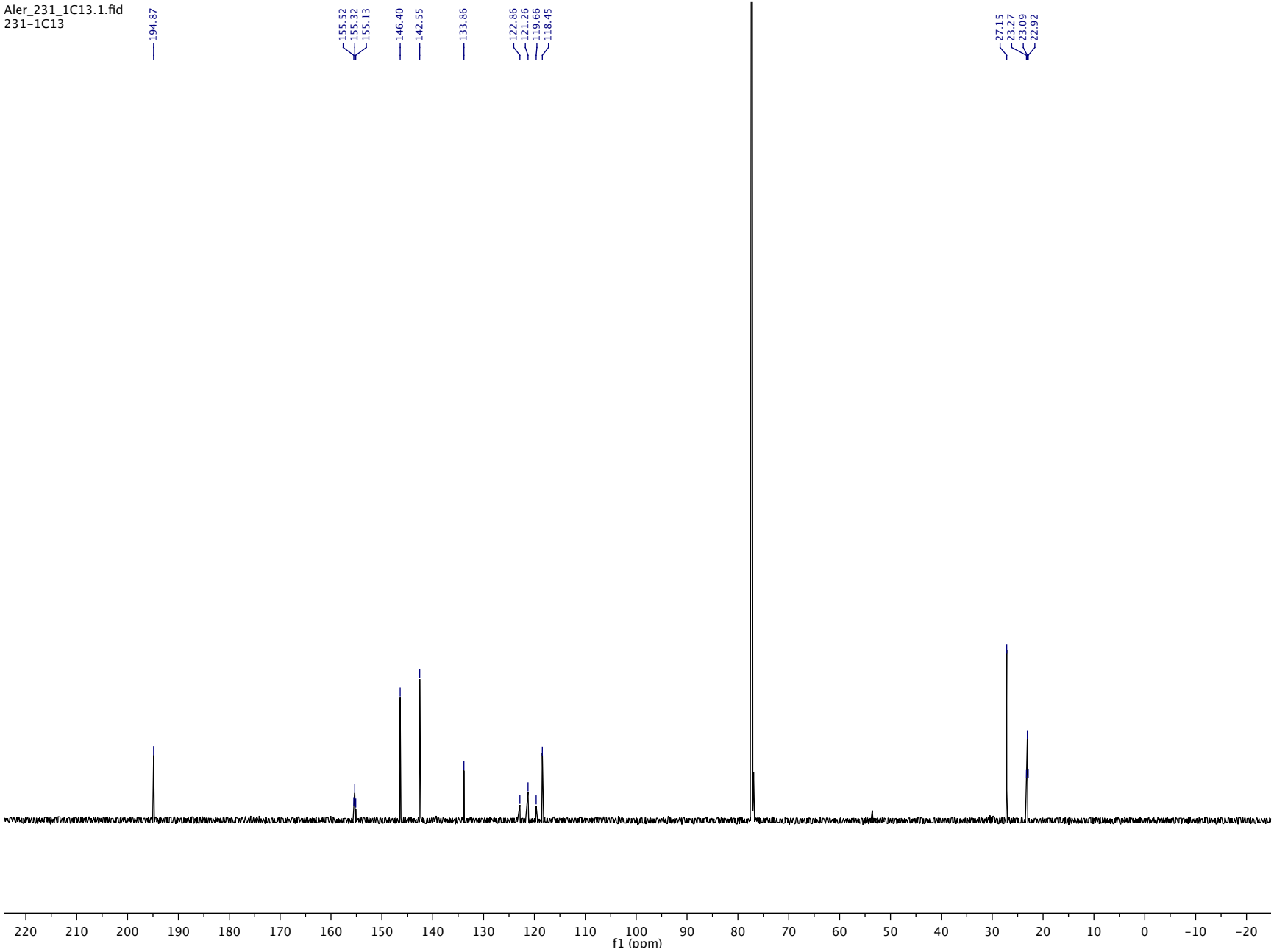

Aler_227_1D_F.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-86.34
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


Aler_227_1A_01
Std proton
9.17
9.17
9.17
9.16
8.35
8.34
8.33
8.32
7.78
7.78
7.76
7.76
7.26
2.66
2.08
2.04
1.99
Ac
MeF2C
N
14-C6
1.94
2.05
2.07
6.77
7.19
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)

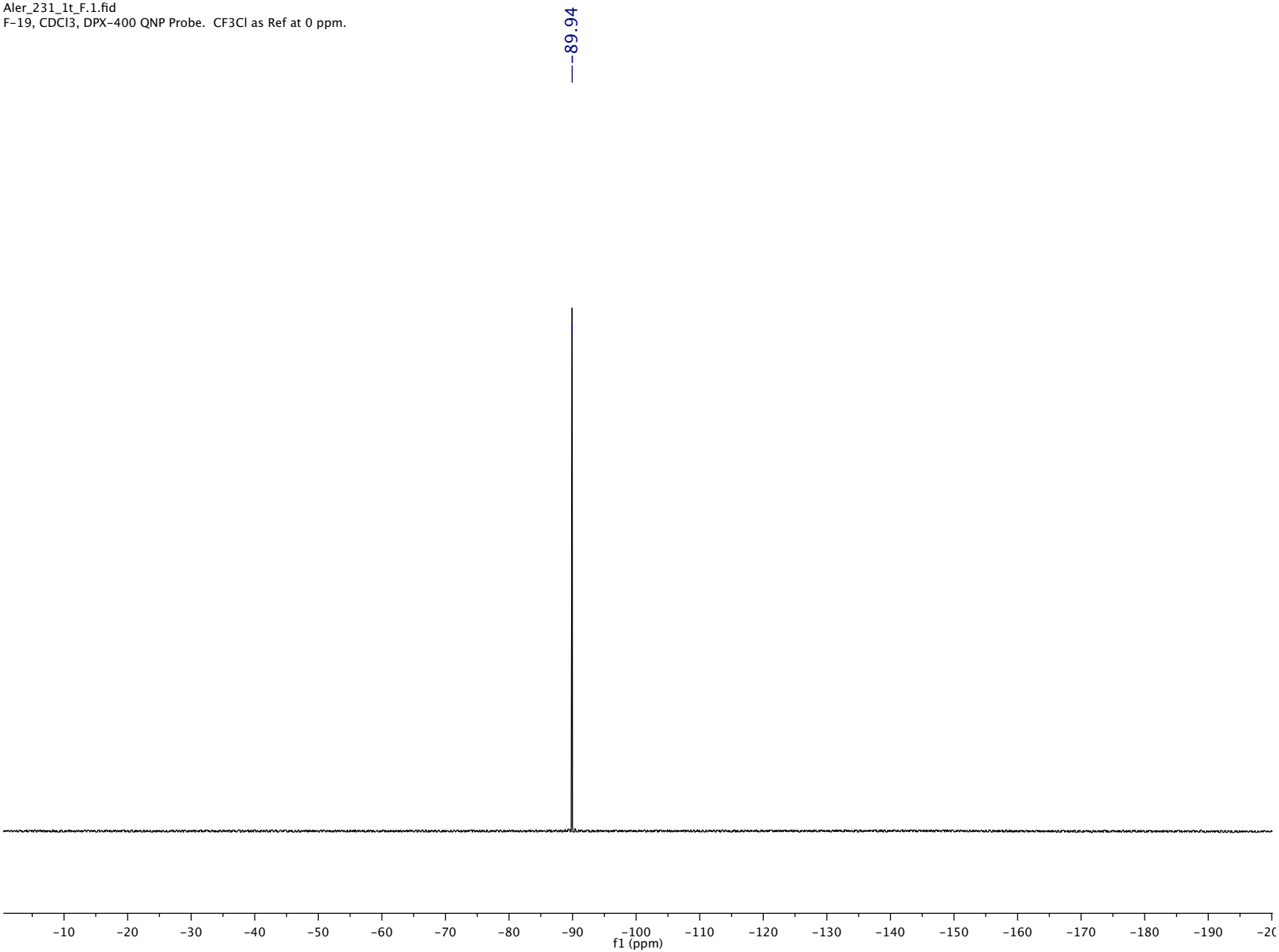

aler-227-1A-13C.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
196.45
159.14
158.94
158.74
149.53
137.00
133.00
122.27
120.69
119.59
119.10
27.05
23.53
23.35
23.17
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

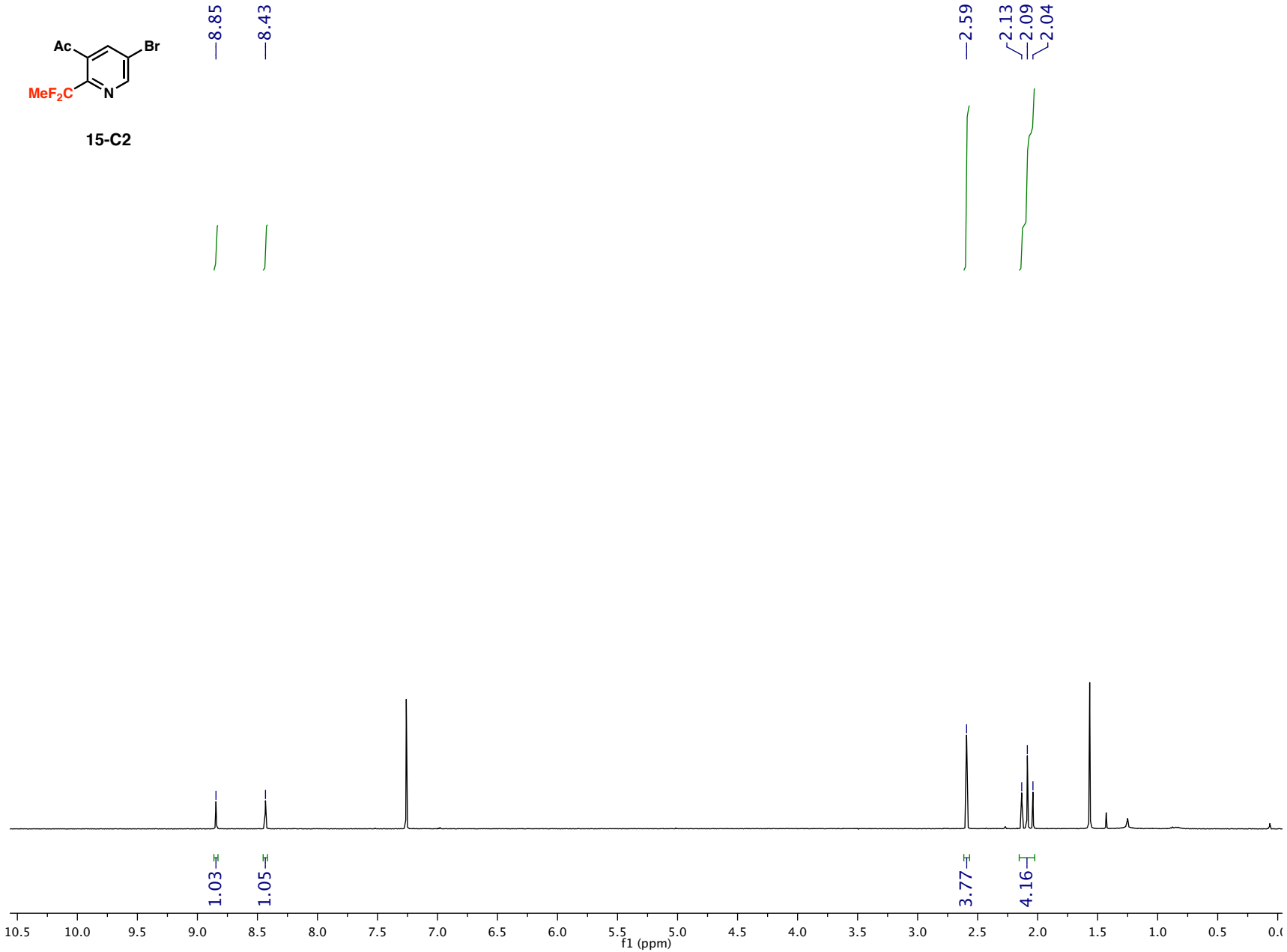

Aler_227_1A_F.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-91.64
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

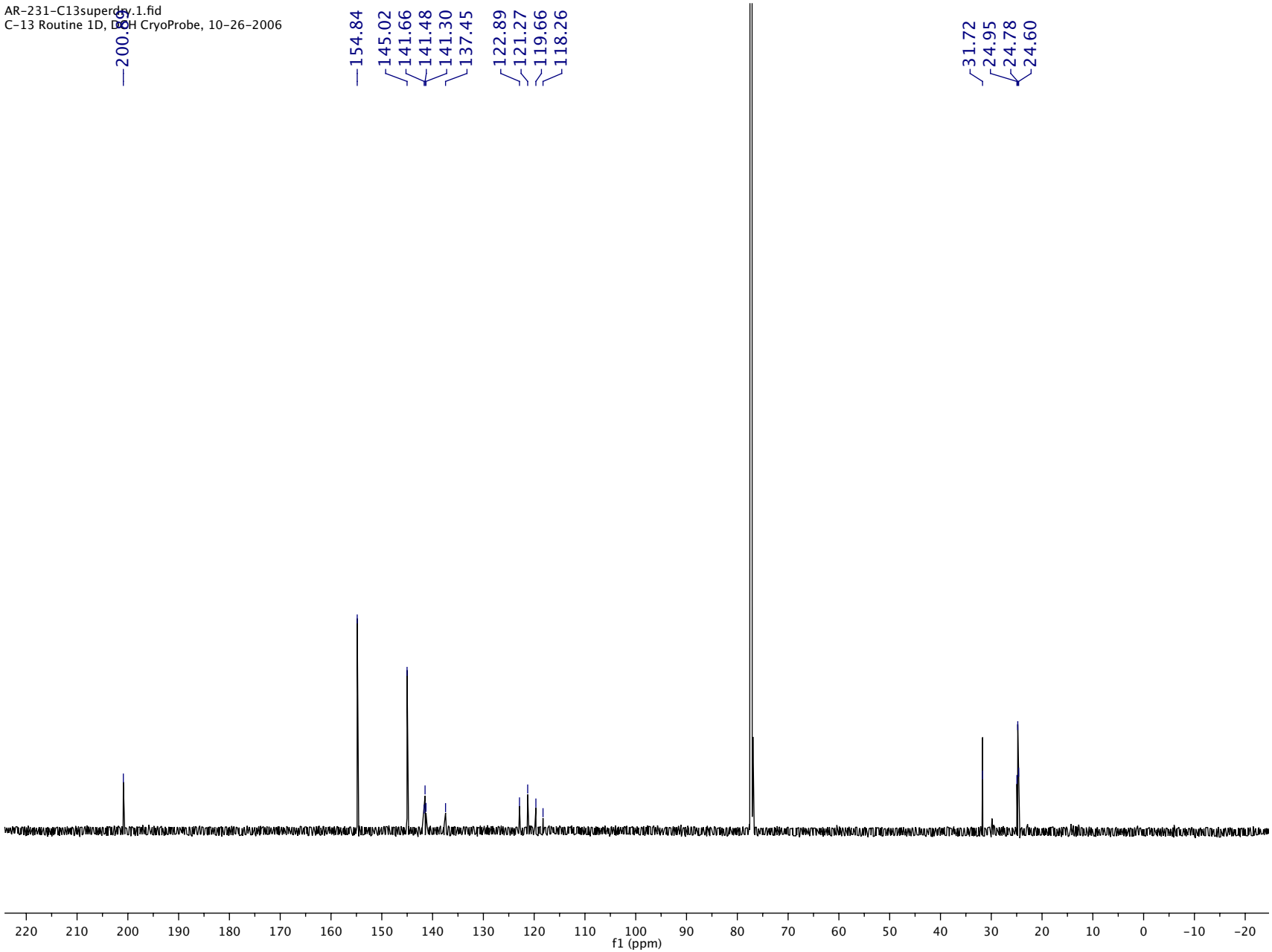

Aler_231_1CL.1.fid
Aler-231-1CL
9.02
9.02
8.50
8.49
2.66
2.14
2.11
2.08
Ac
Br
N
CF2Me
15-C6
0.96
0.94
2.98
3.12
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

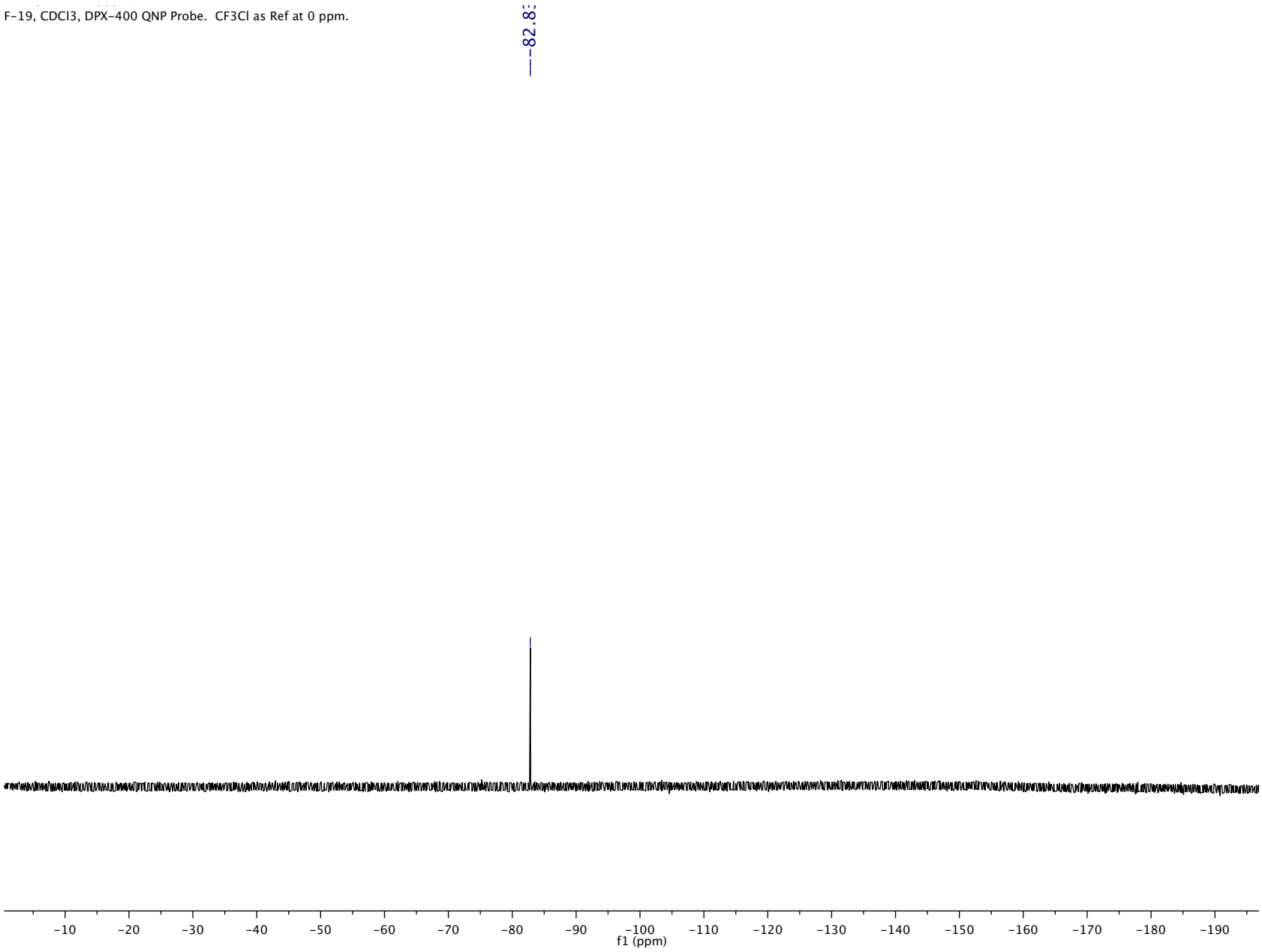

Aler_231_1C13.1.fid
231-1C13
194.87
155.52
155.32
155.13
146.40
142.55
133.86
122.86
121.26
119.66
118.45
27.15
23.27
23.09
22.92
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

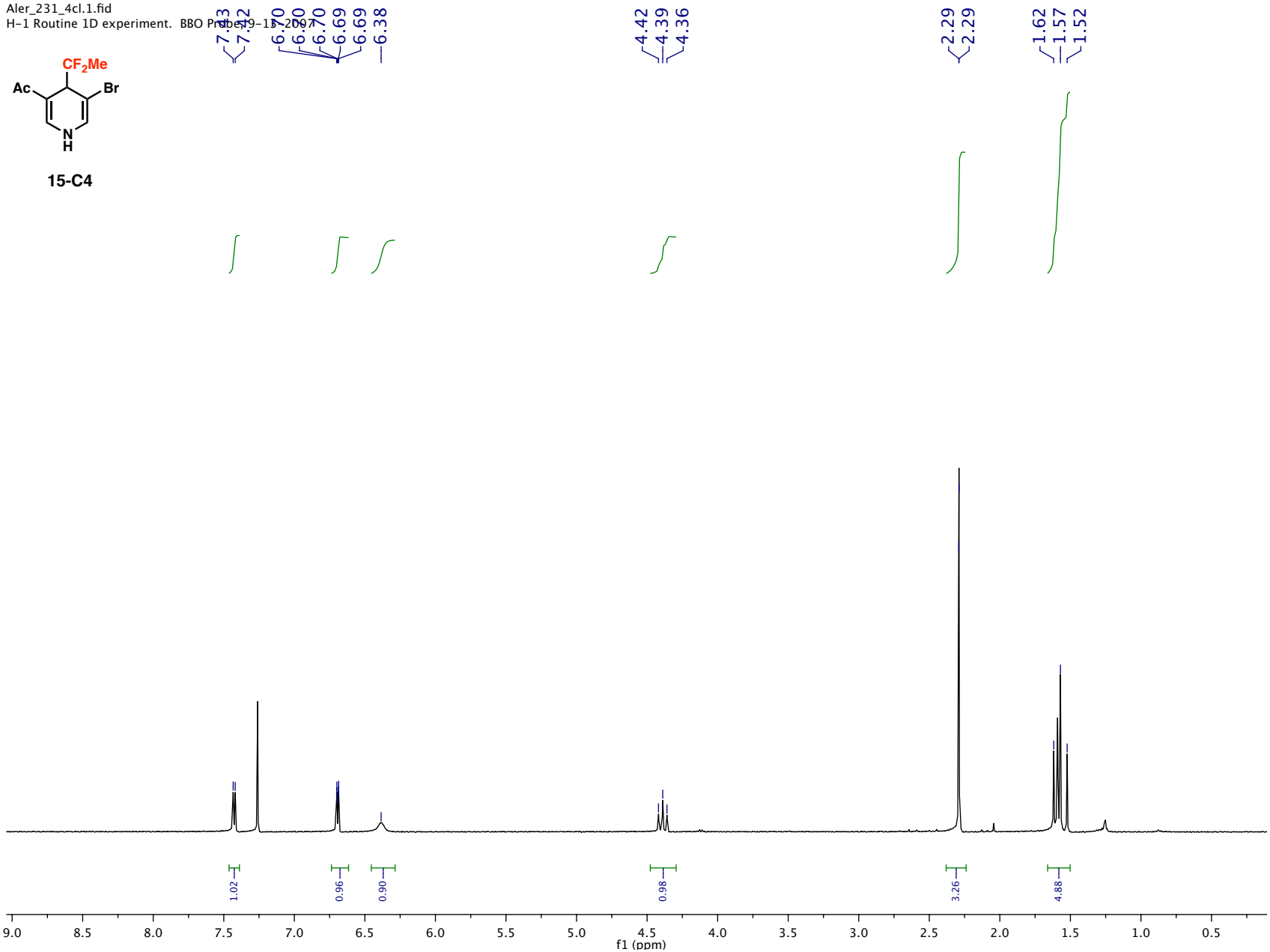
Aler_231_1t_F.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.

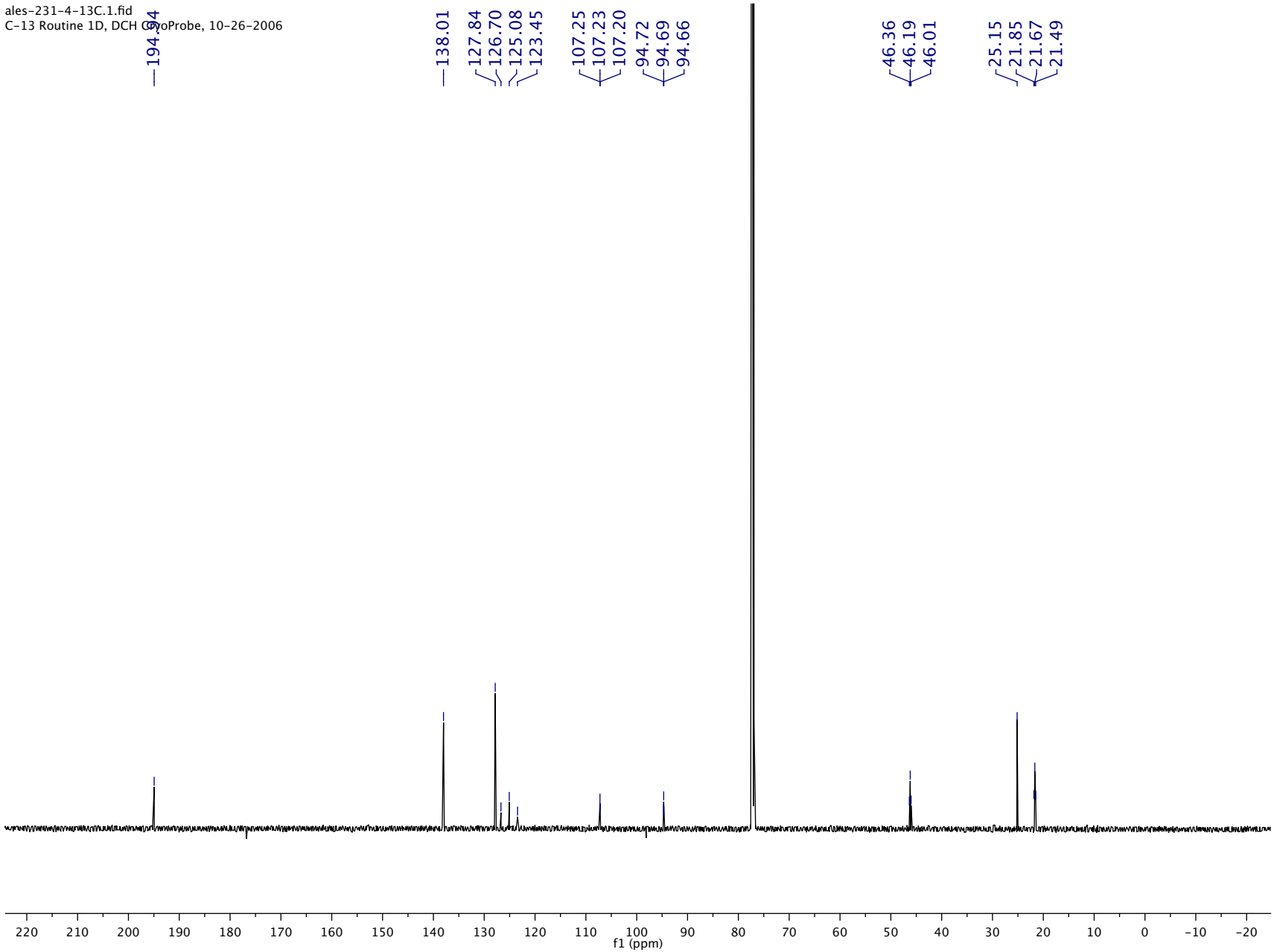


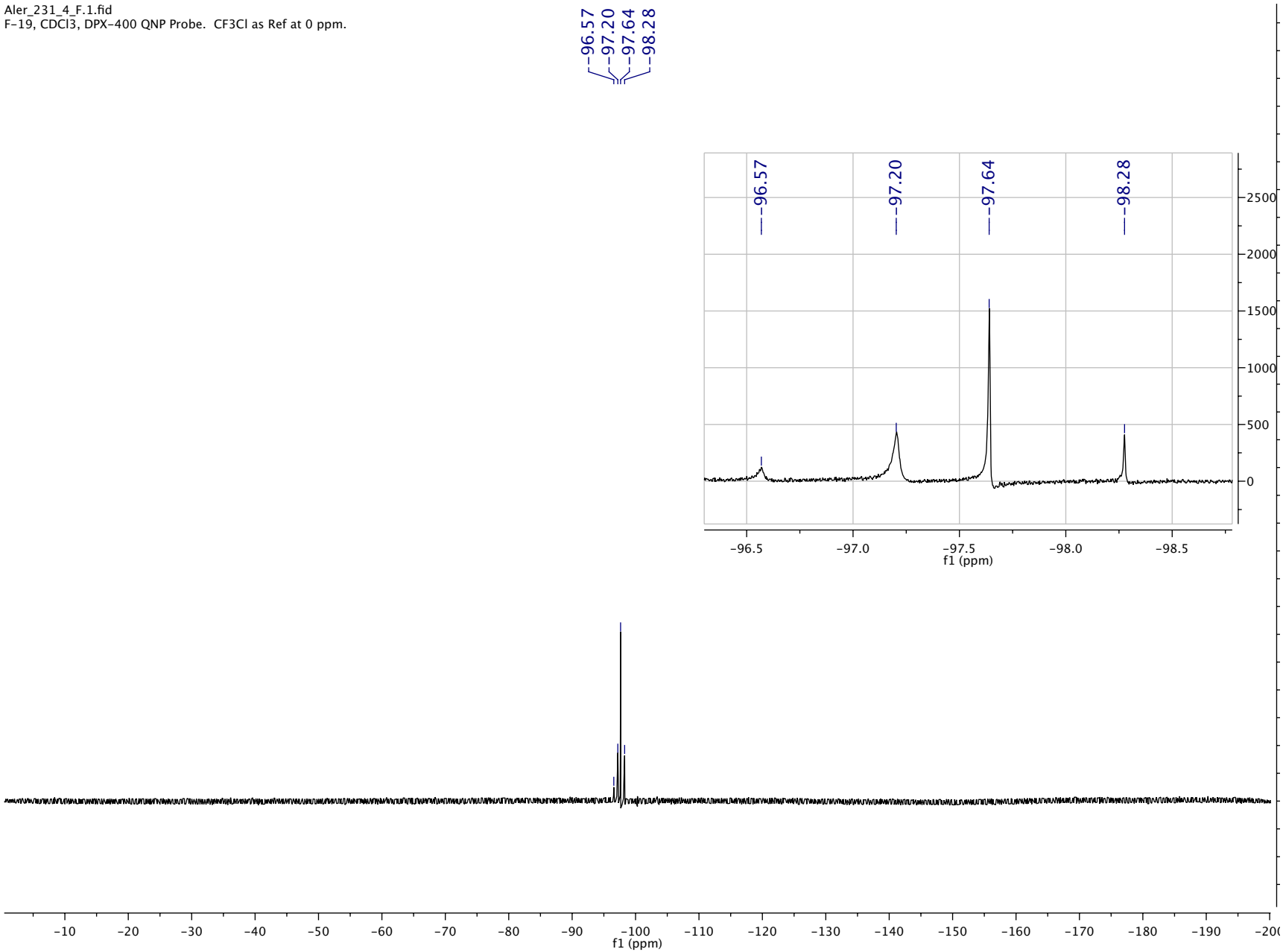

Ac
Br
MeF2C
N
15-C2
8.85
8.43
2.59
2.13
2.09
2.04
1.03
1.05
3.77
4.16
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

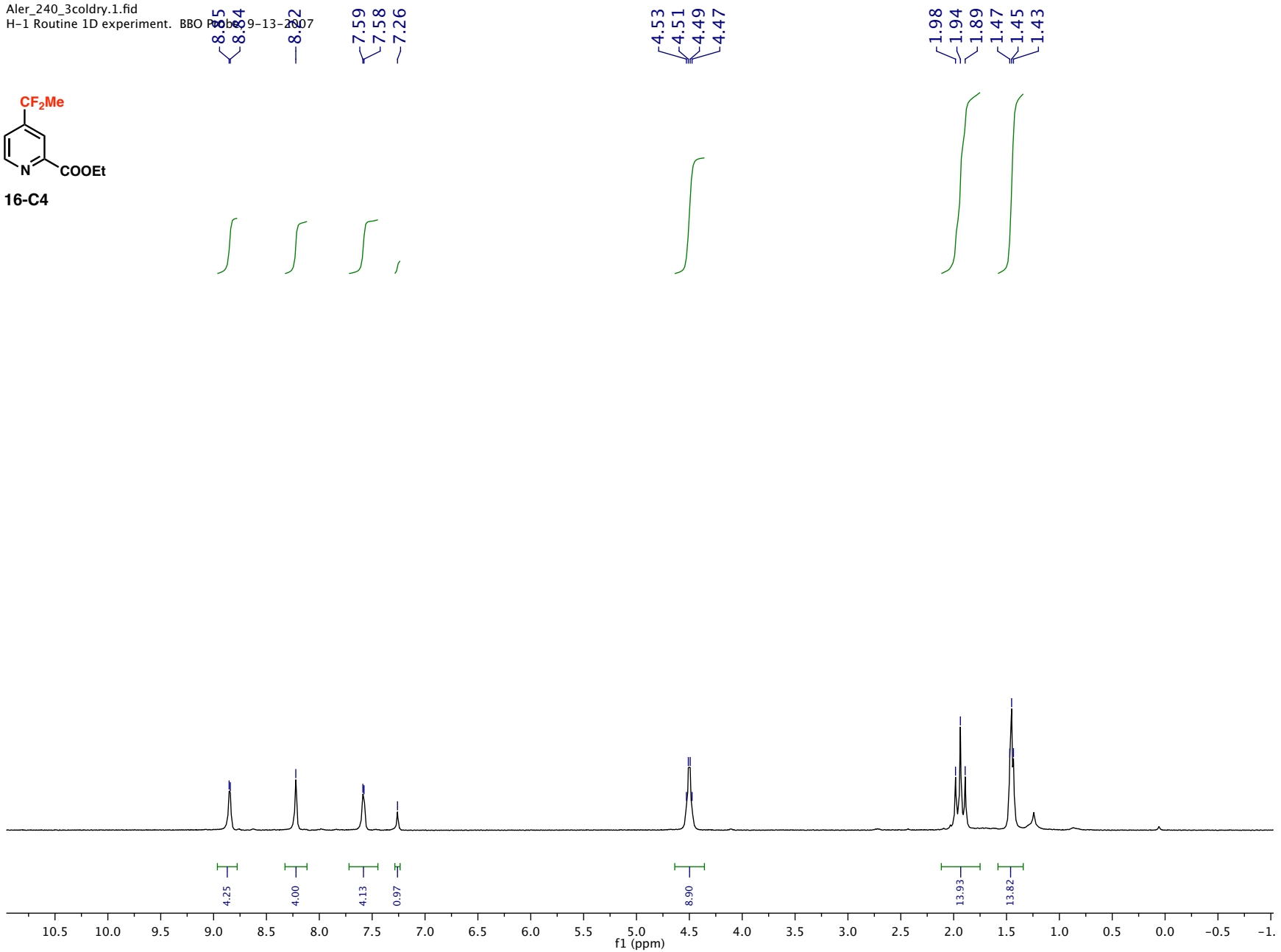

AR-231-C13superdev.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
200.39
154.84
145.02
141.66
141.48
141.30
137.45
122.89
121.27
119.66
118.26
31.72
24.95
24.78
24.60
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

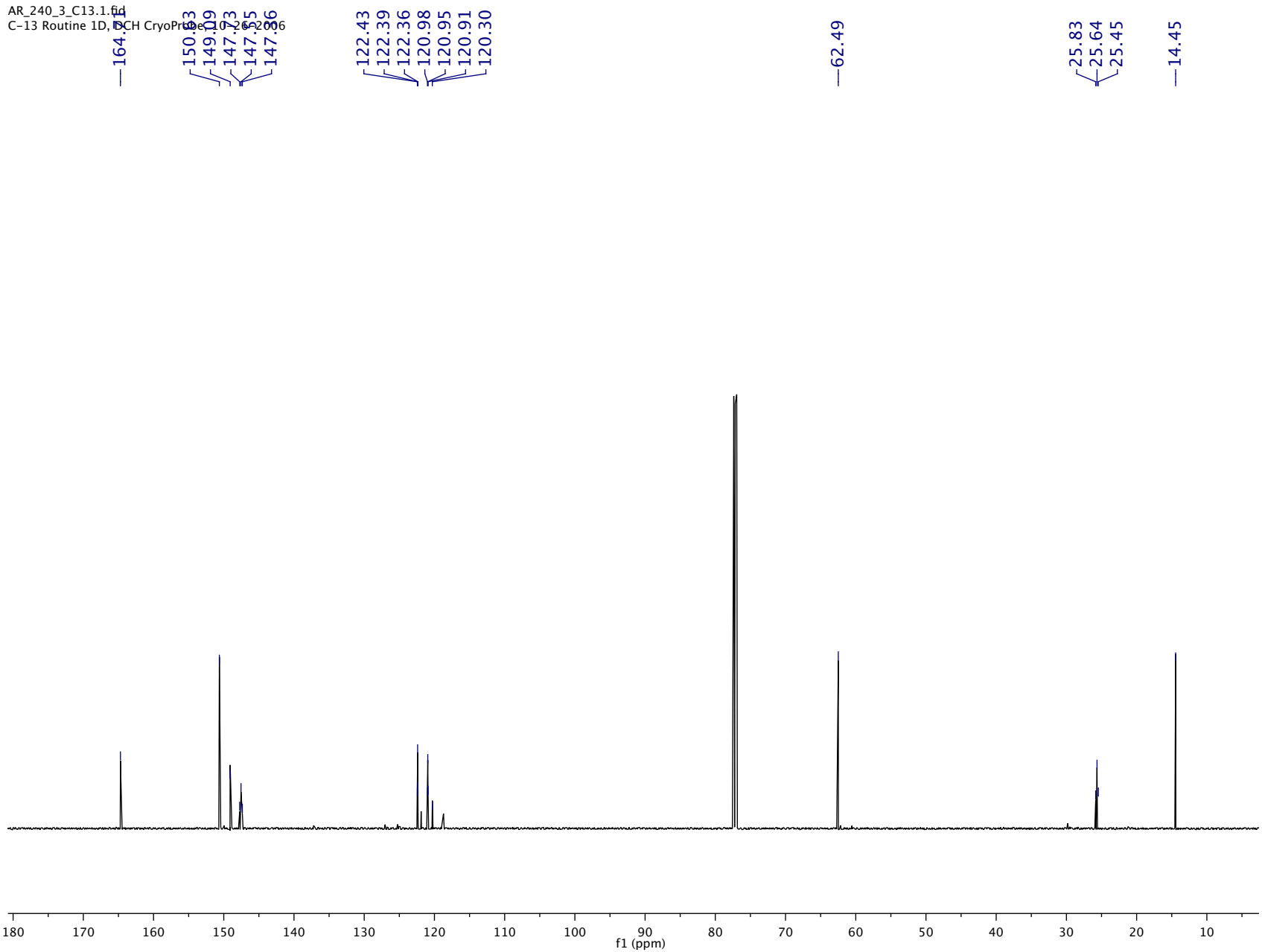

F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-82.83
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

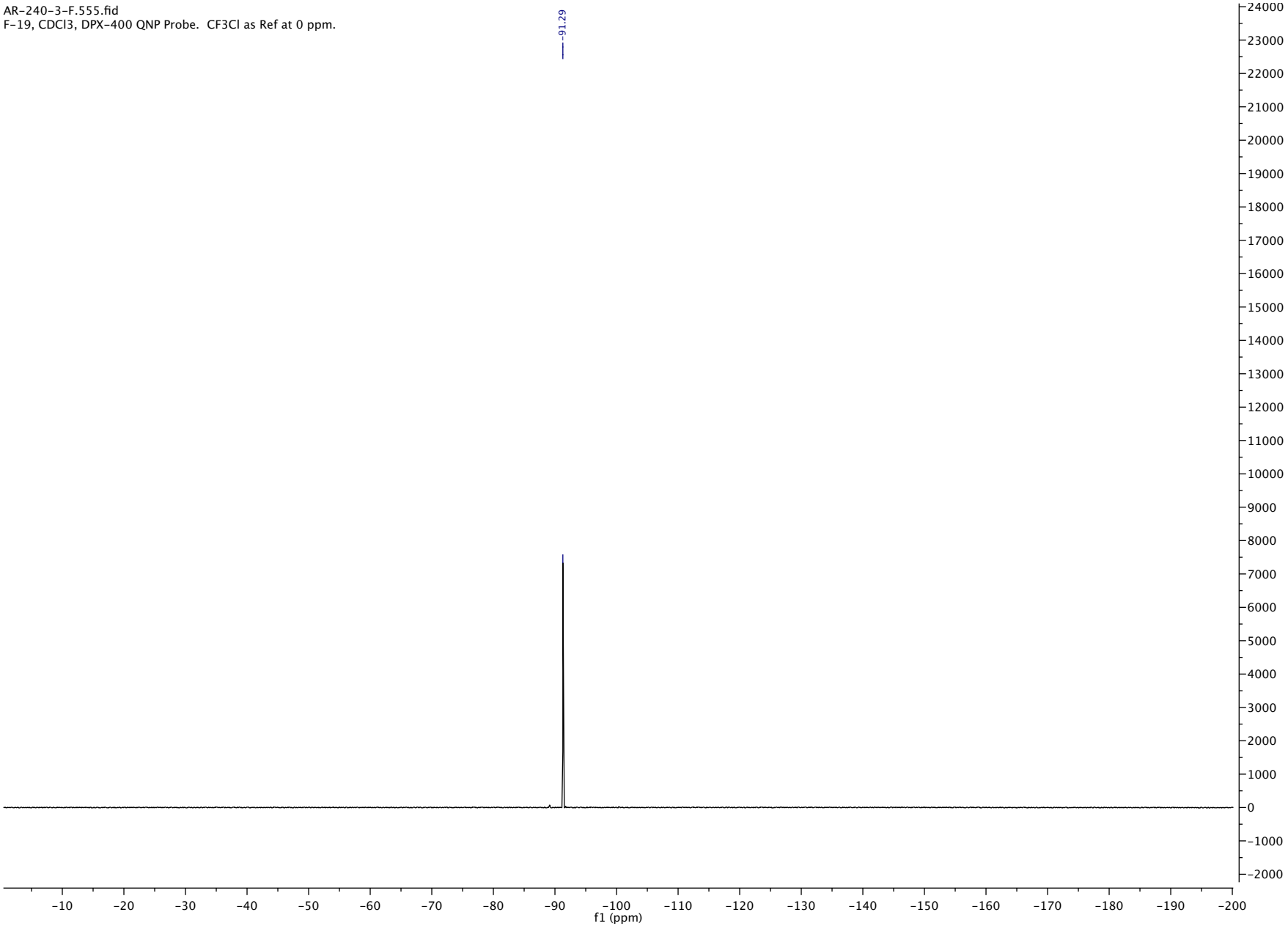

Aler_231_4cl.1.fid
H-1 Routine 1D experiment. BBO Probe 19-13-2007
CF2Me
Ac
Br
N
H
15-C4
7.43
7.42
6.70
6.70
6.70
6.69
6.69
6.38
4.42
4.39
4.36
2.29
2.29
1.62
1.57
1.52
1.02
0.96
0.90
0.98
3.26
4.88
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

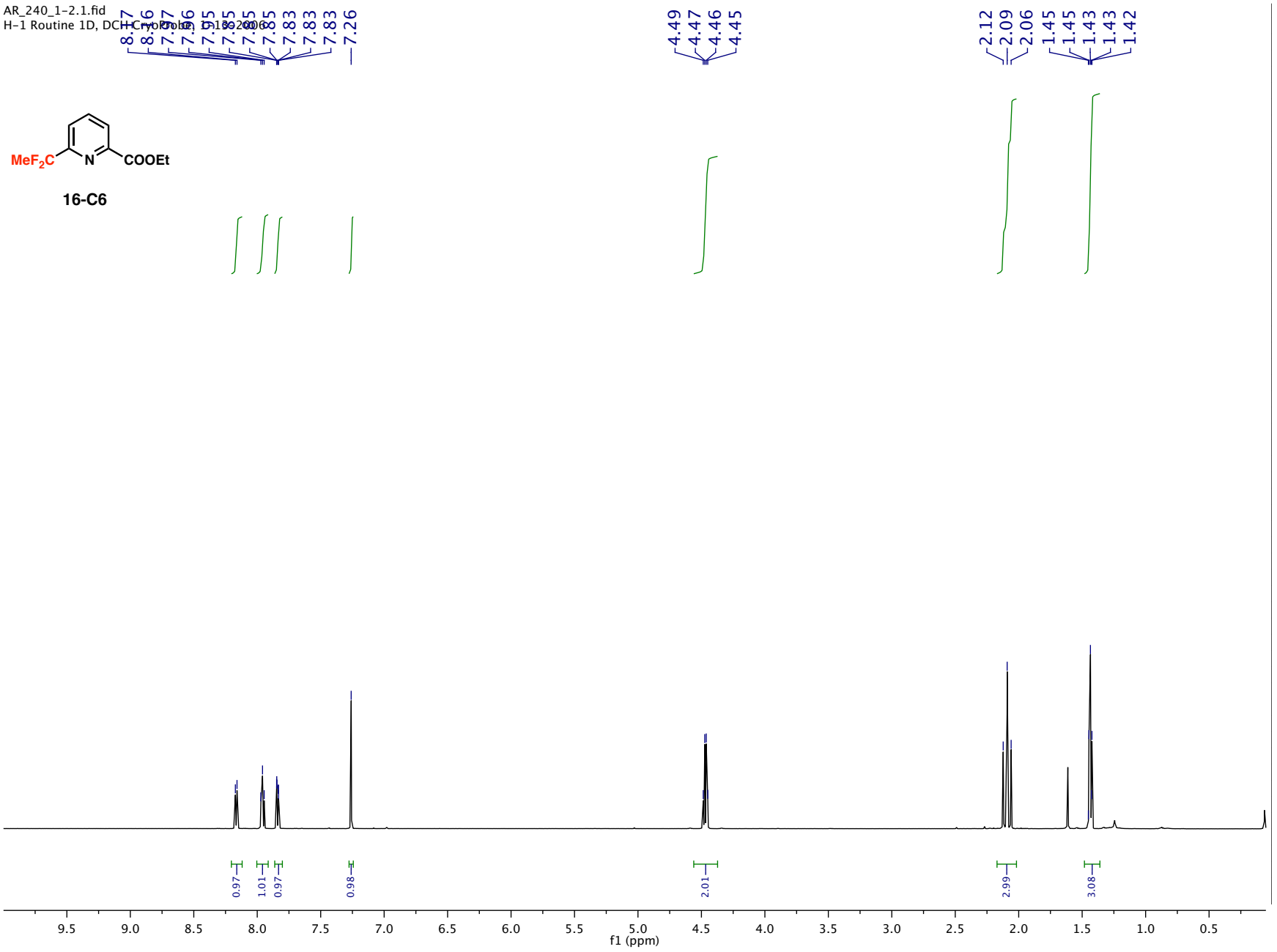

ales-231-4-13C.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
194.94
138.01
127.84
126.70
125.08
123.45
107.25
107.23
107.20
94.72
94.69
94.66
46.36
46.19
46.01
25.15
21.85
21.67
21.49
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

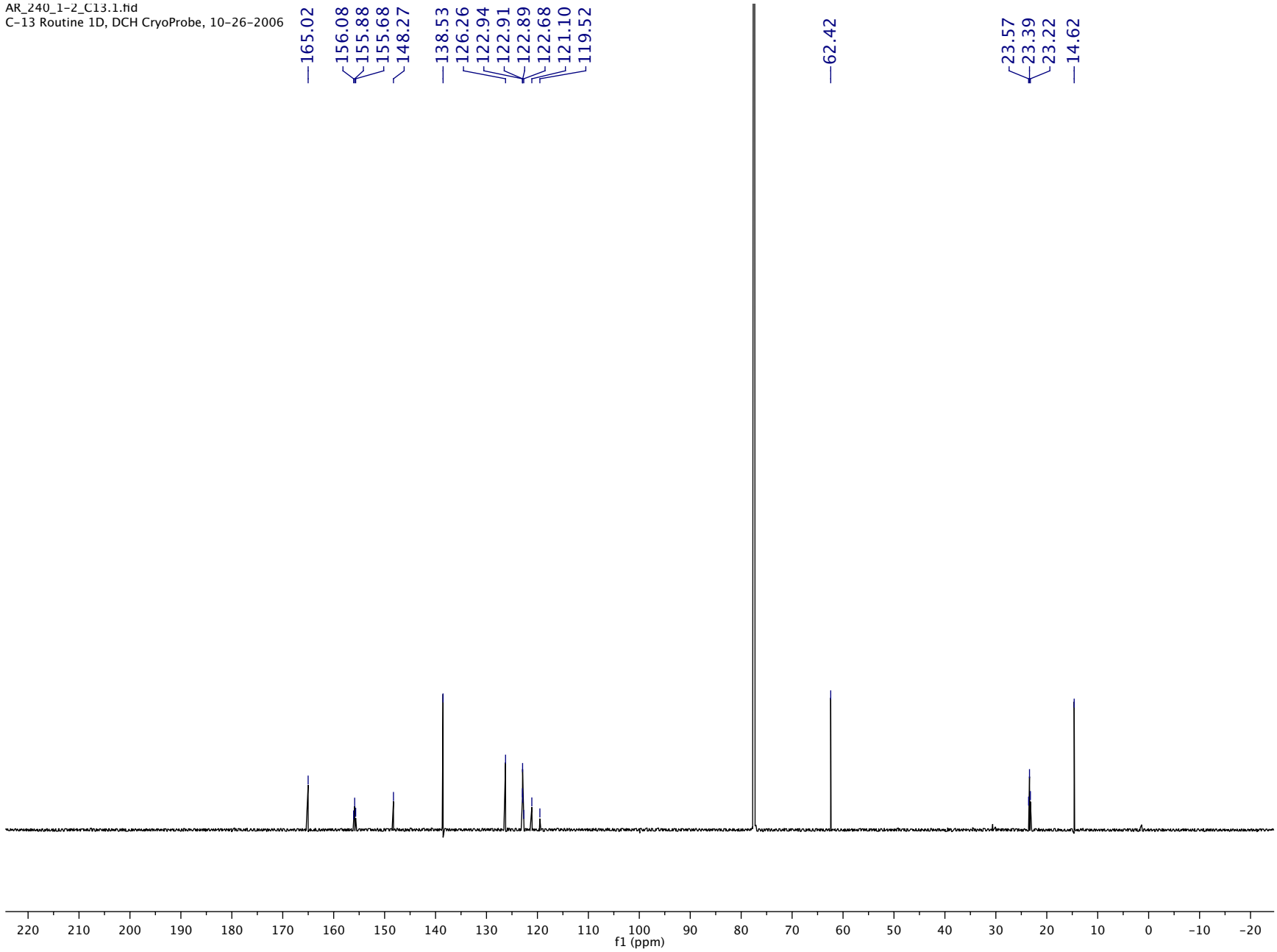

Aler_231_4_F.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-96.57
-97.20
-97.64
-98.28
2500
2000
1500
1000
500
0
-96.5
-97.0
-97.5
-98.0
-98.5
f1 (ppm)
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


Aler_240_3coldry.1.fid
H-1 Routine 1D experiment. BBO Probe 9-13-2007
8.85
8.84
8.22
7.59
7.58
7.26
4.53
4.51
4.49
4.47
1.98
1.94
1.89
1.47
1.45
1.43
CF2Me
N
COOEt
16-C4
4.25
4.00
4.13
0.97
8.90
13.93
13.82
f1 (ppm)


AR_240_3_C13.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
164.14
150.43
149.09
147.73
147.55
147.06
122.43
122.39
122.36
120.98
120.95
120.91
120.30
62.49
25.83
25.64
25.45
14.45
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

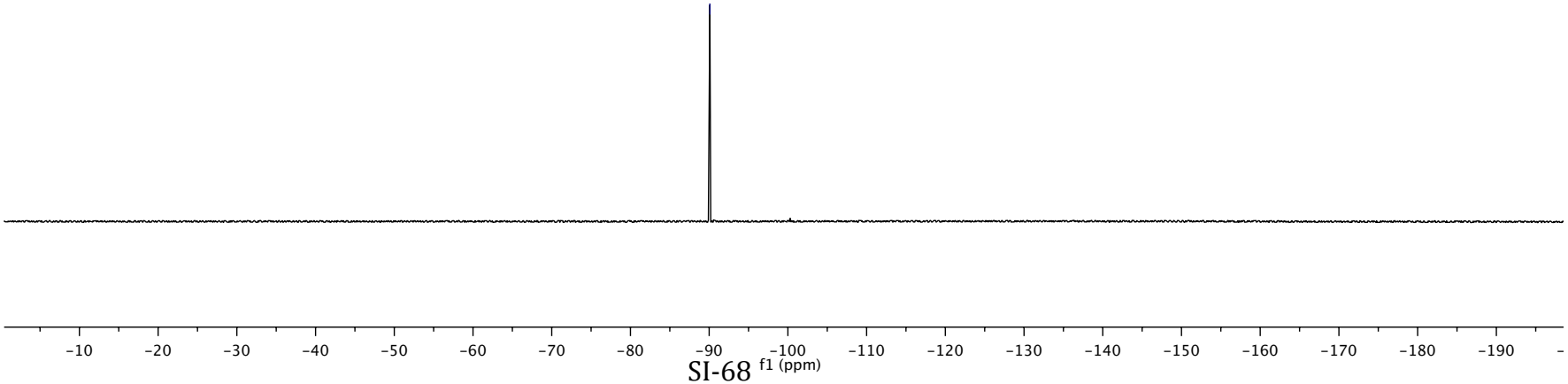

AR-240-3-F.555.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-91.29
f1 (ppm)

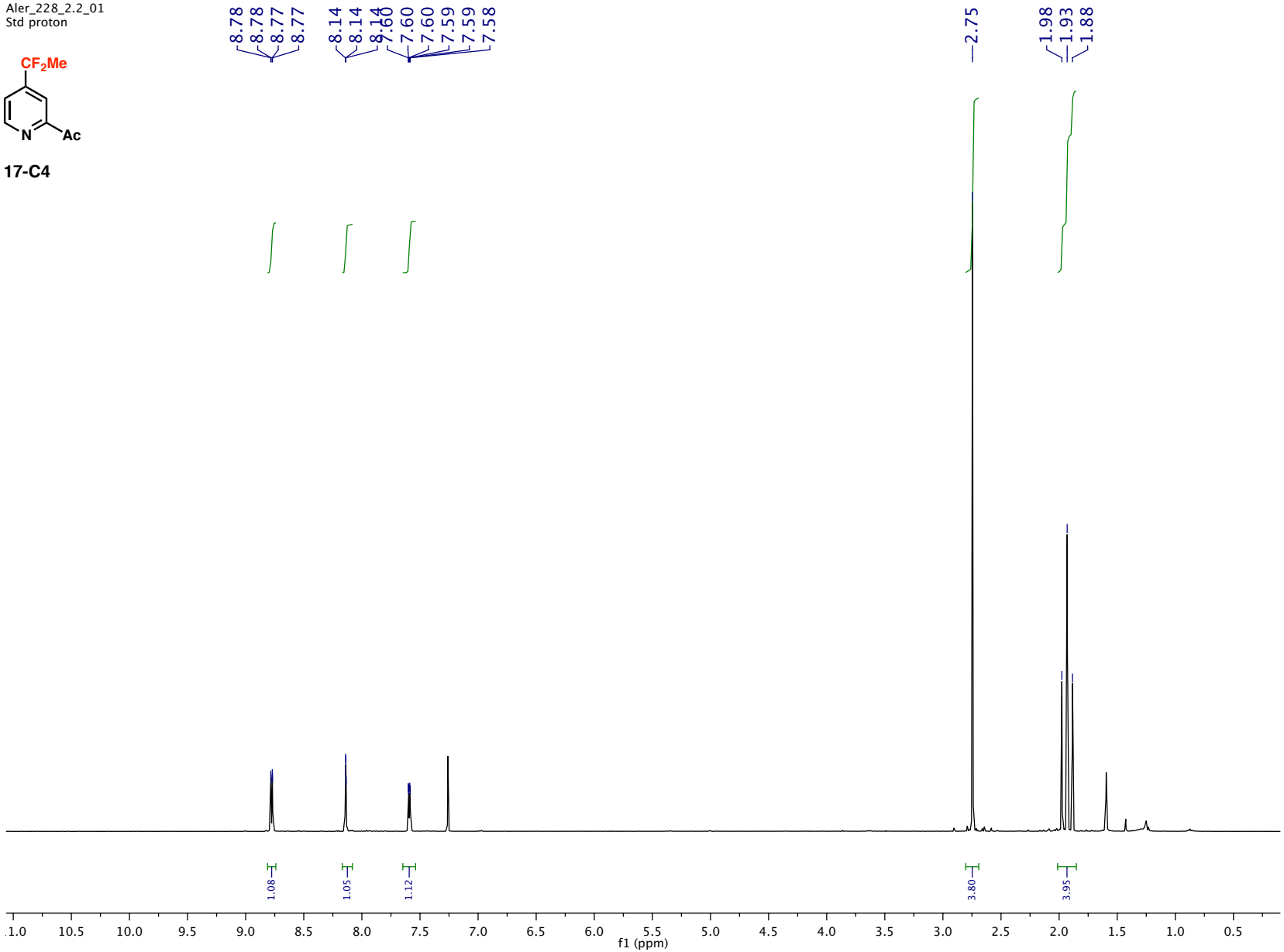

AR_240_1-2.1.fid
H-1 Routine 1D, DCH-Cryoprobe, 1-13-2006
8.87
8.86
7.77
7.76
7.75
7.75
7.65
7.85
7.83
7.83
7.83
7.26
4.49
4.47
4.46
4.45
2.12
2.09
2.06
1.45
1.45
1.43
1.43
1.42
MeF2C
N
COOEt
16-C6
0.97
1.01
0.97
0.98
2.01
2.99
3.08
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

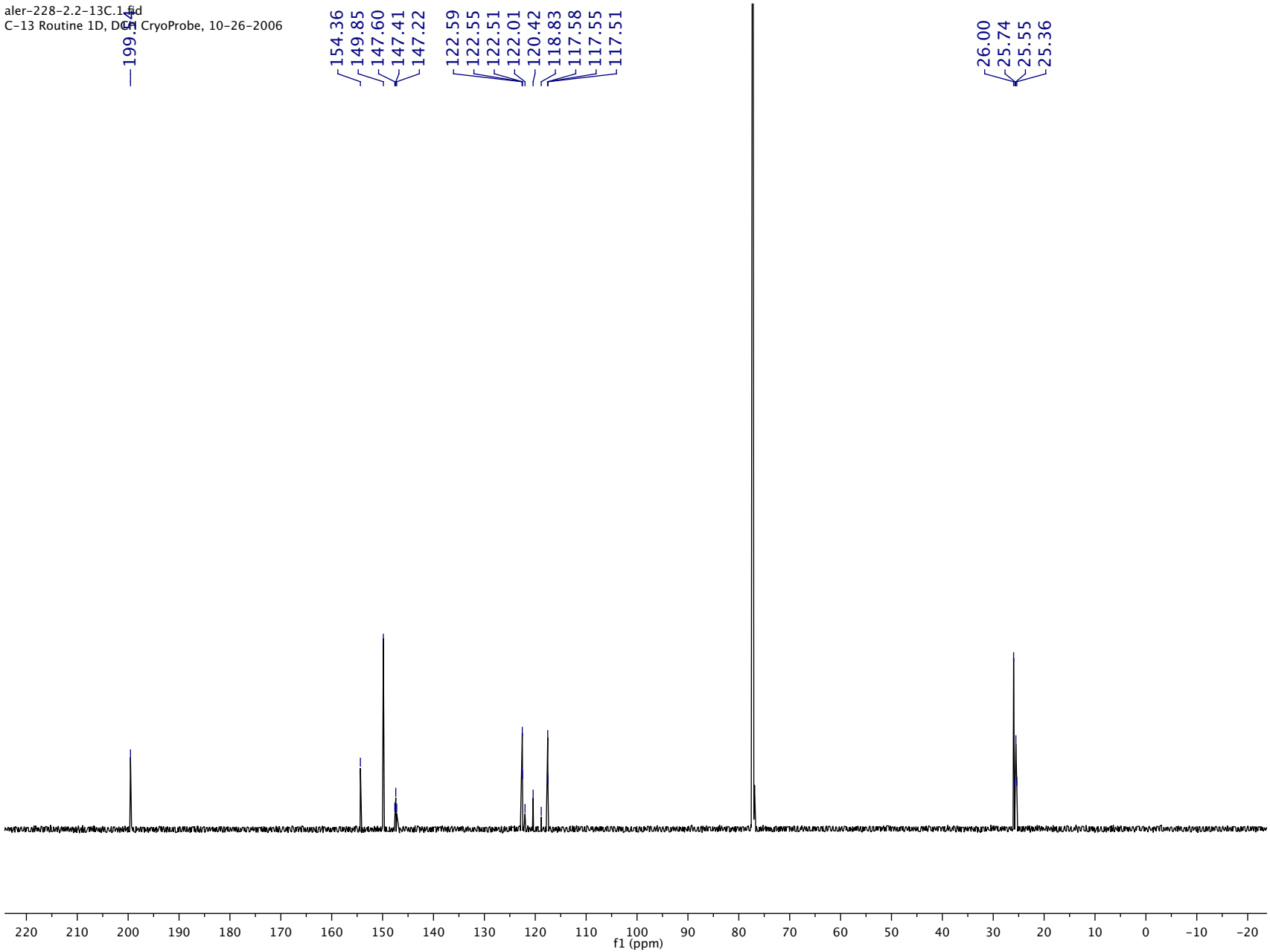

AR_240_1-2_C13.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
165.02
156.08
155.88
155.68
148.27
138.53
126.26
122.94
122.91
122.89
122.68
121.10
119.52
62.42
23.57
23.39
23.22
14.62
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

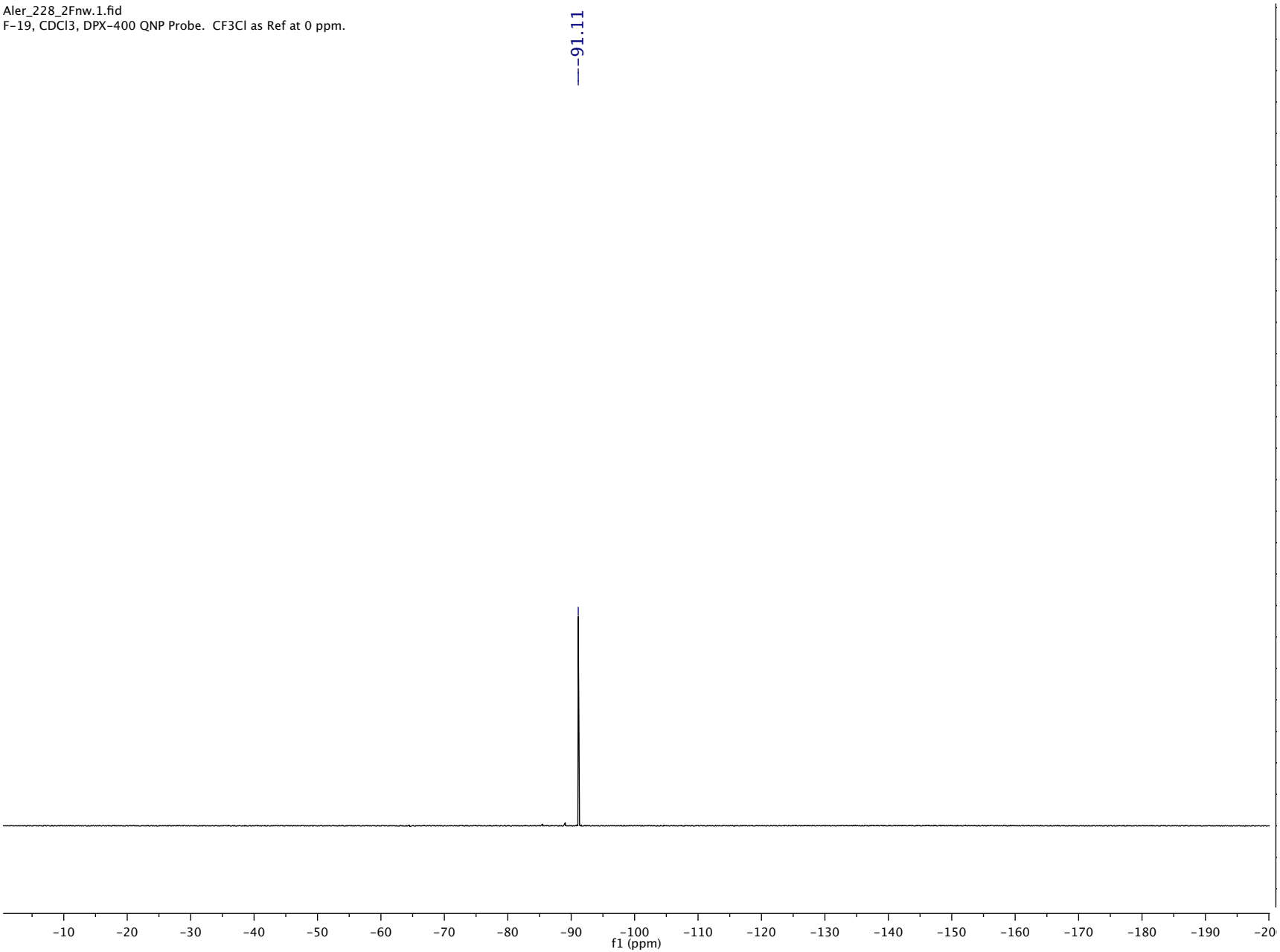
AR-240-1-2-F.555.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.

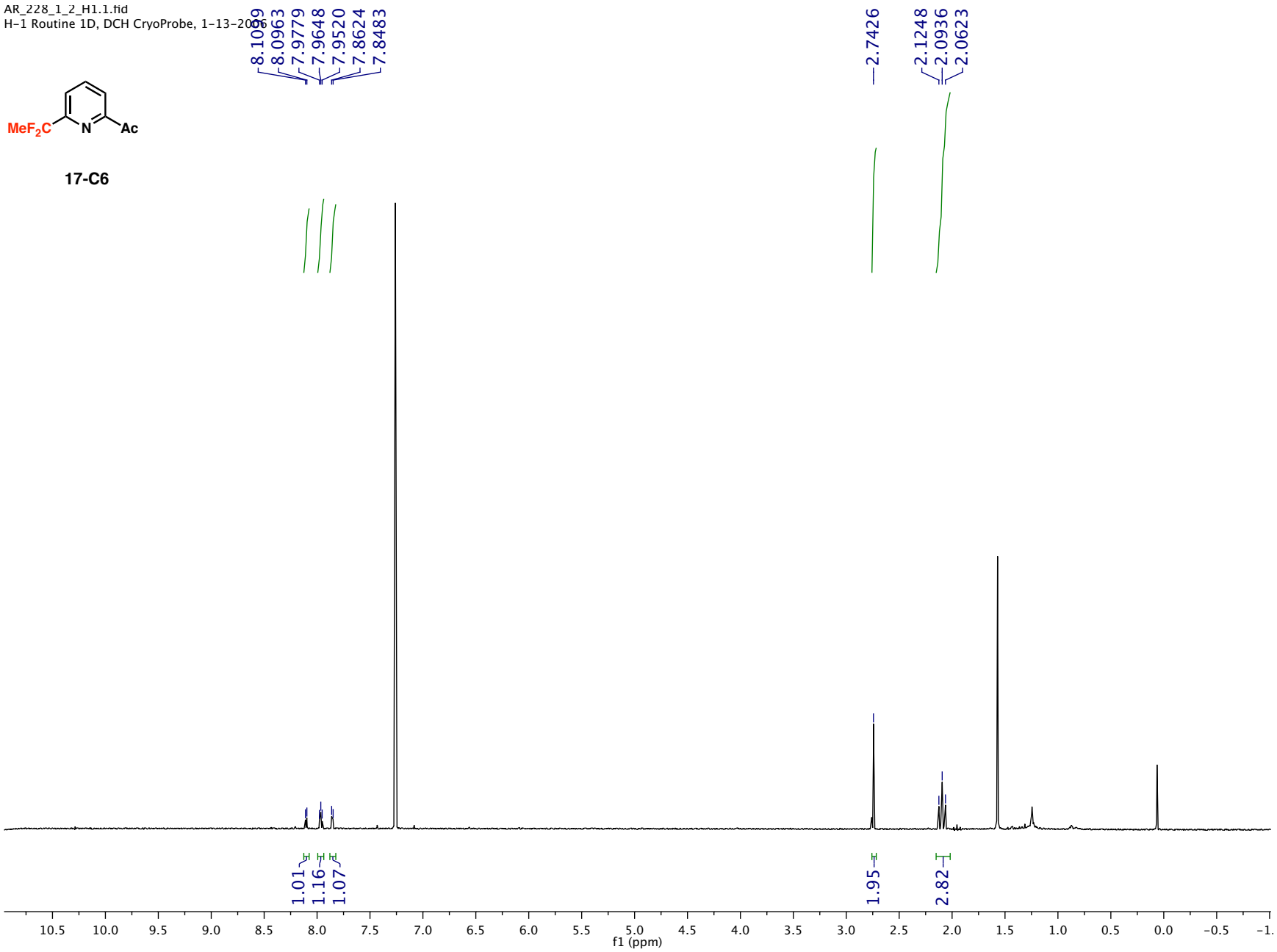
-90.09

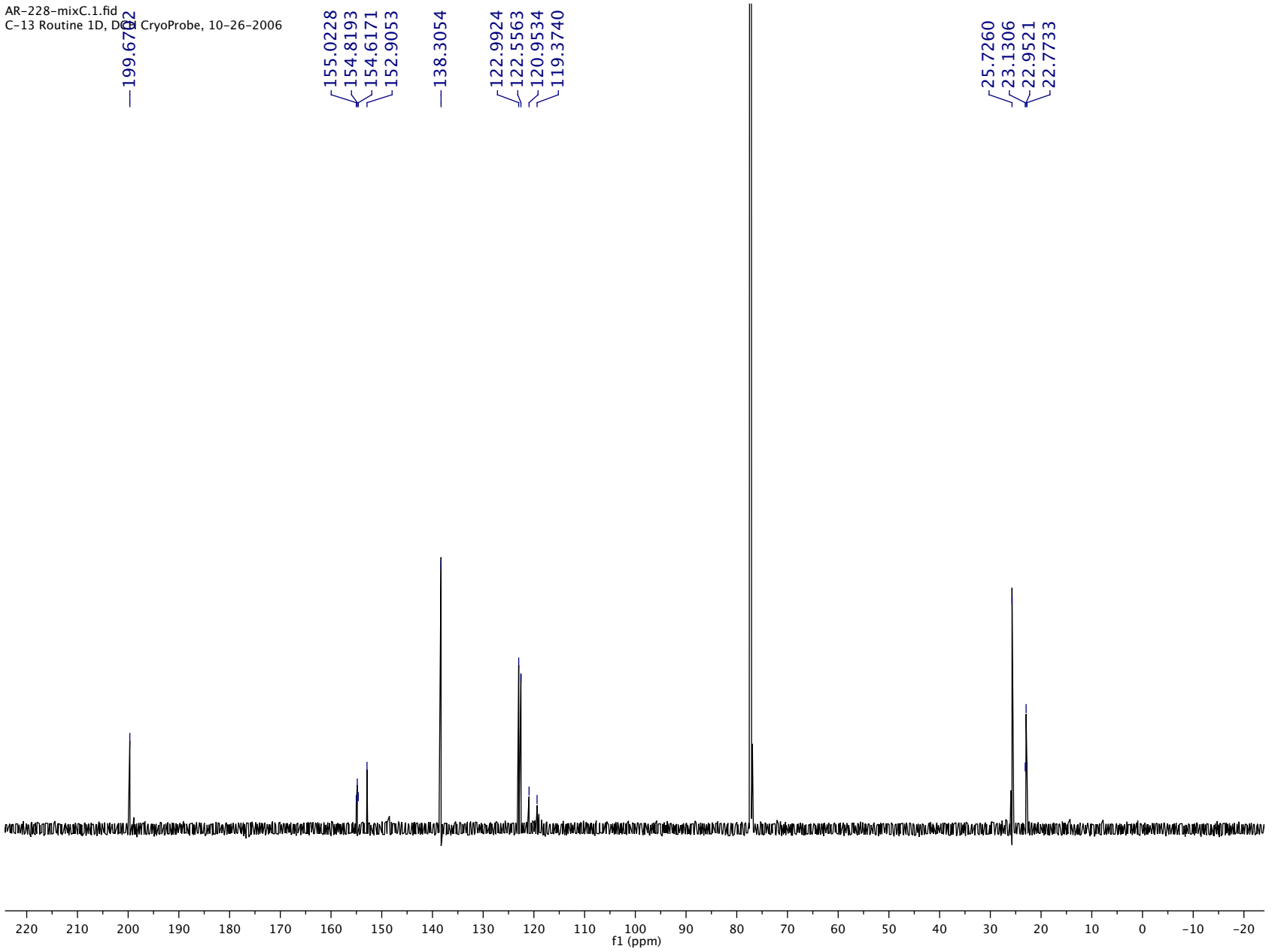


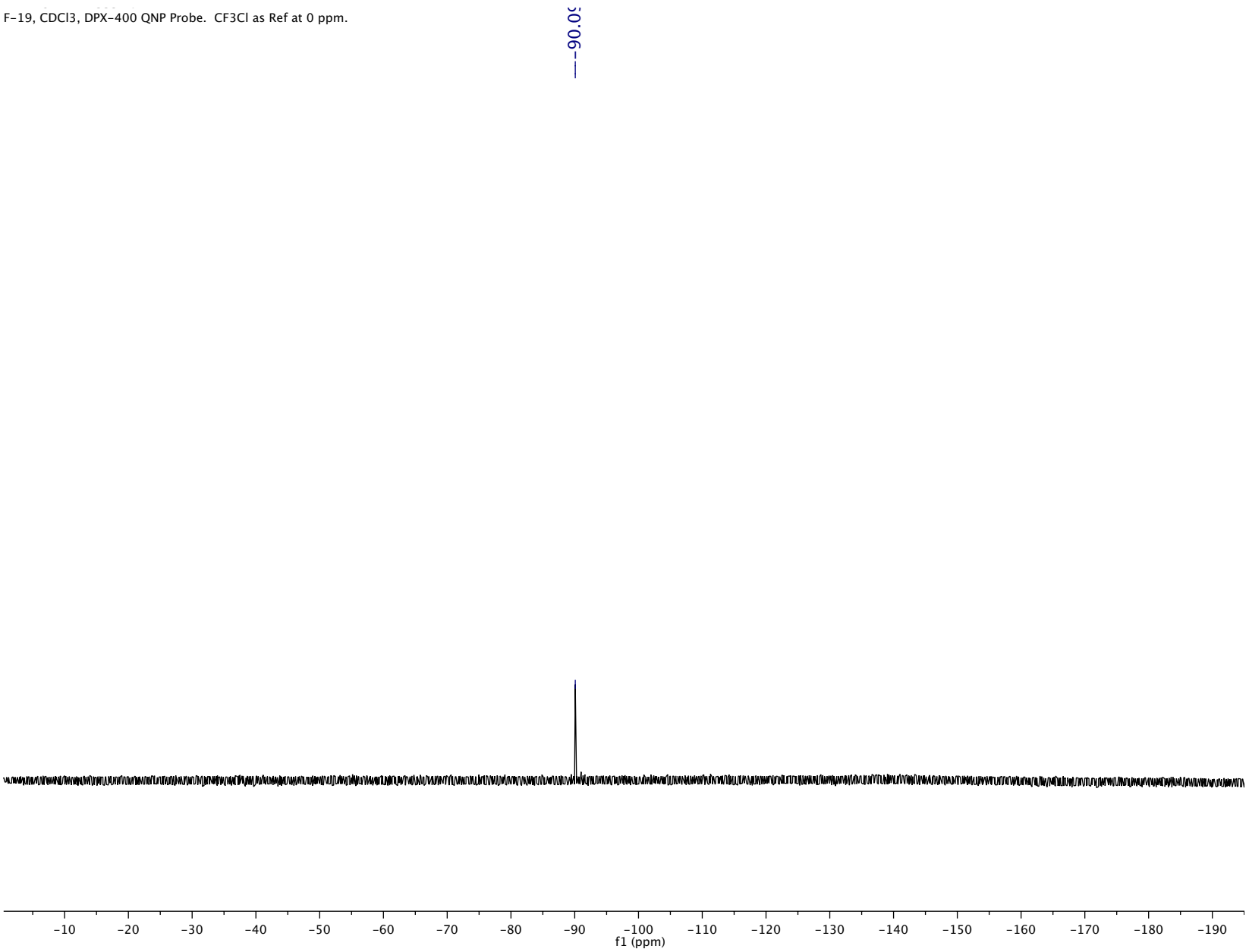

Aler_228_2.2_01
Std proton
CF2Me
N
Ac
17-C4
8.78
8.78
8.77
8.77
8.14
8.14
8.14
8.13
7.60
7.60
7.59
7.59
7.58
2.75
1.98
1.93
1.88
1.08
1.05
1.12
3.80
3.95
f1 (ppm)

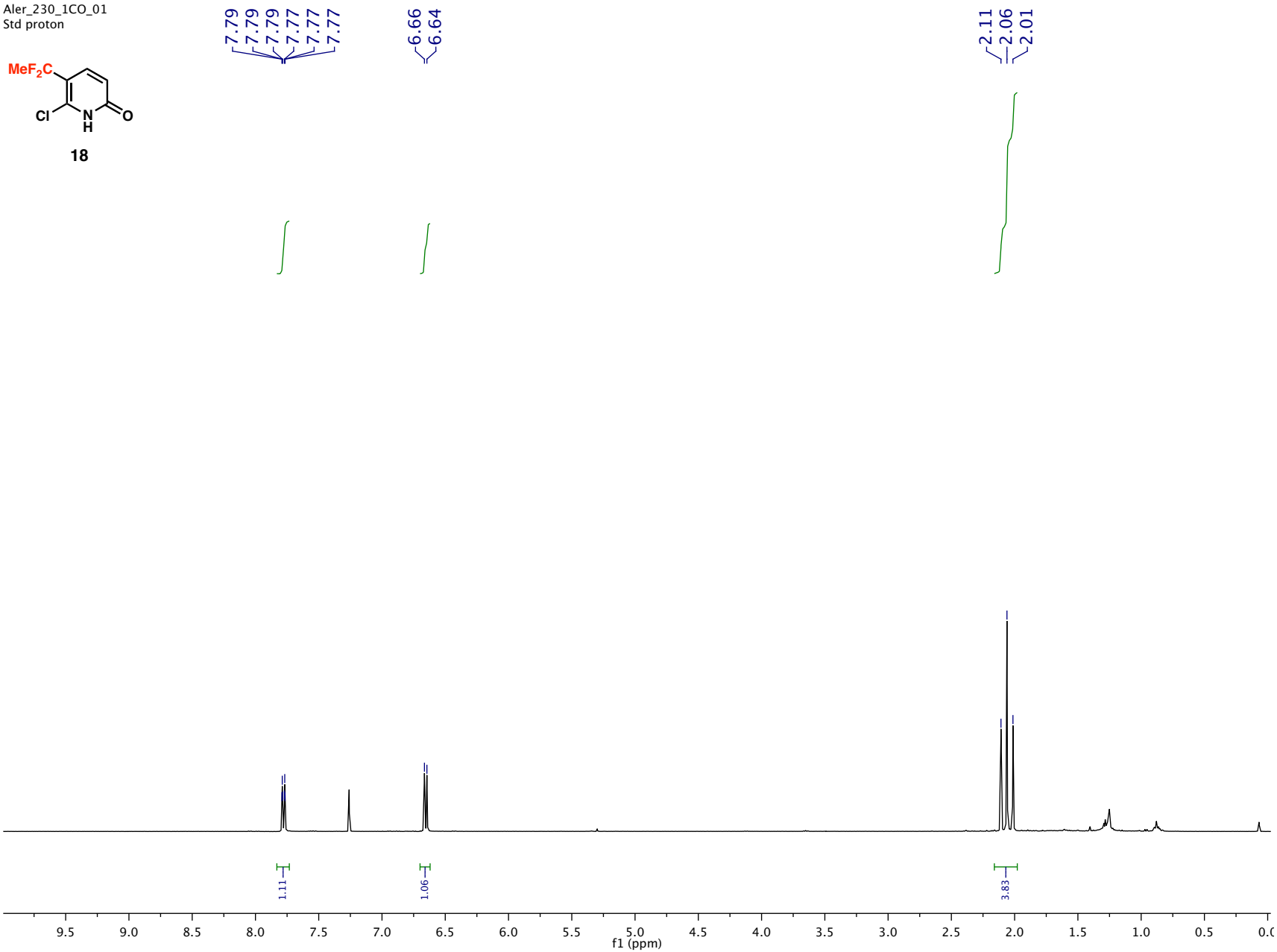

aler-228-2.2-13C.1.fid
C-13 Routine 1D, DCM CryoProbe, 10-26-2006
199.54
154.36
149.85
147.60
147.41
147.22
122.59
122.55
122.51
122.01
120.42
118.83
117.58
117.55
117.51
26.00
25.74
25.55
25.36
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

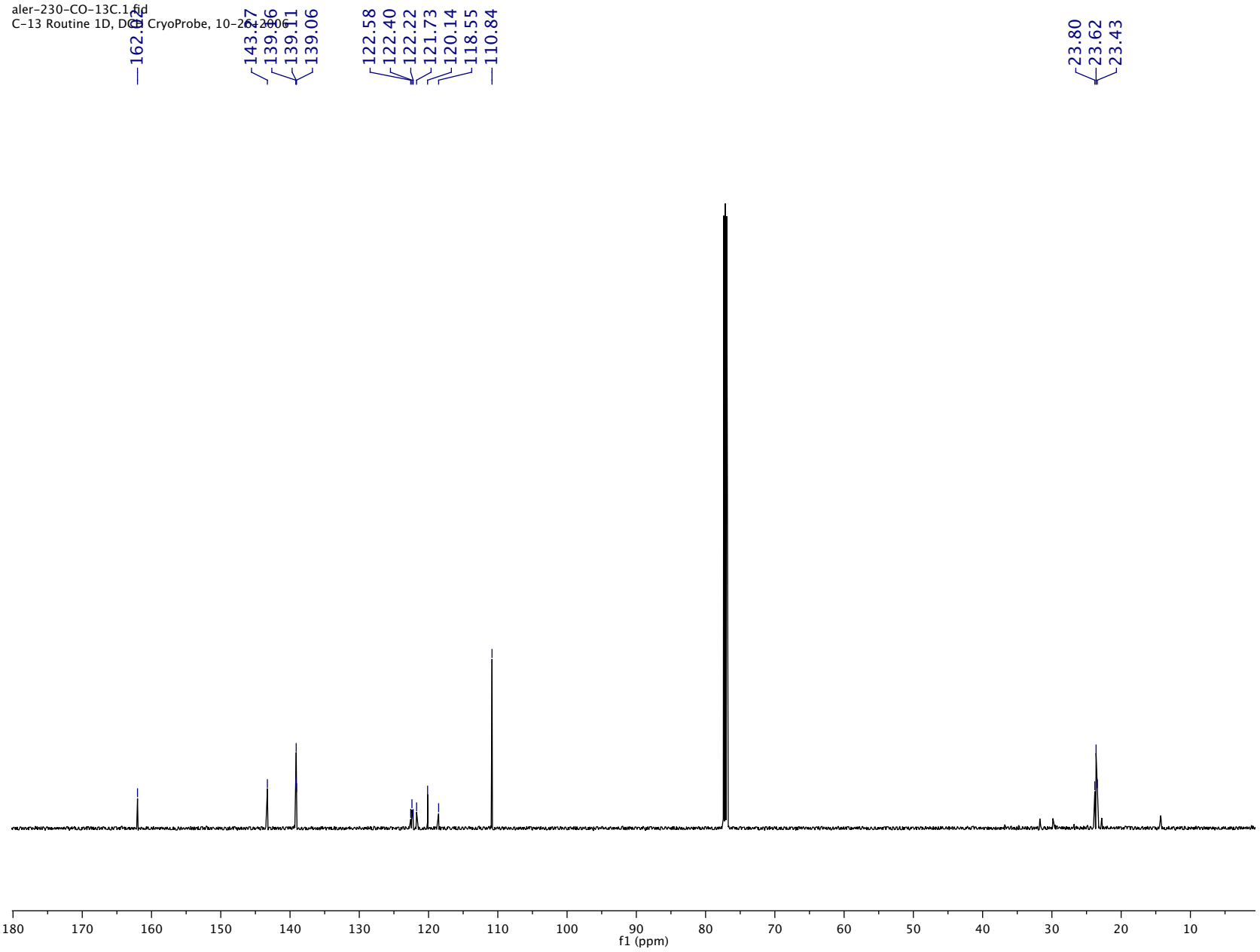

Aler_228_2Fnw.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-91.11
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


AR_228_1_2_H1.1.fid
H-1 Routine 1D, DCH CryoProbe, 1-13-2006
8.1009
8.0963
7.9779
7.9648
7.9520
7.8624
7.8483
2.7426
2.1248
2.0936
2.0623
MeF2C
N
Ac
17-C6
1.01
1.16
1.07
1.95
2.82
f1 (ppm)

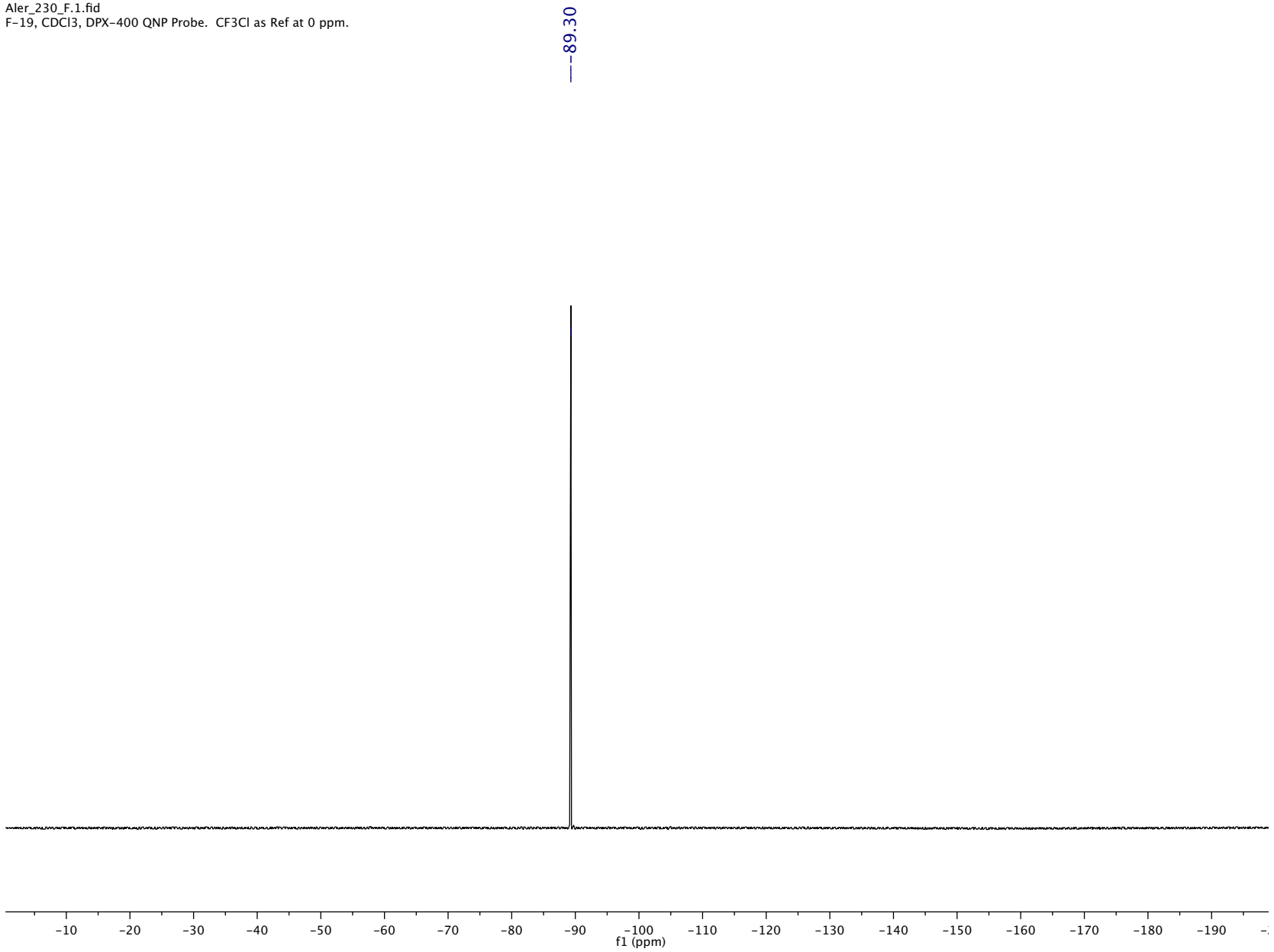

AR-228-mixC.1.fid
C-13 Routine 1D, DCM CryoProbe, 10-26-2006
199.6702
155.0228
154.8193
154.6171
152.9053
138.3054
122.9924
122.5563
120.9534
119.3740
25.7260
23.1306
22.9521
22.7733
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

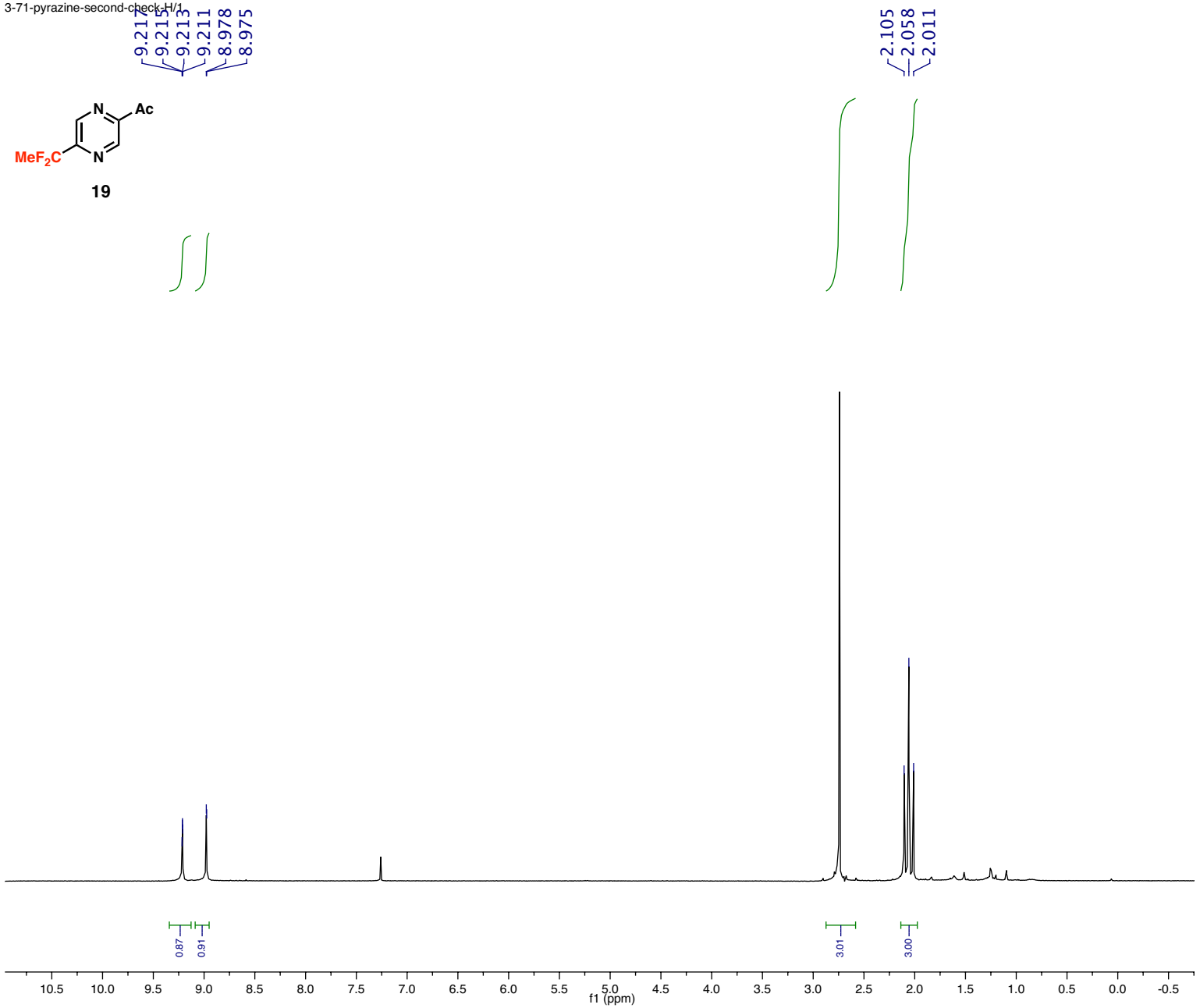

F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-90.0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

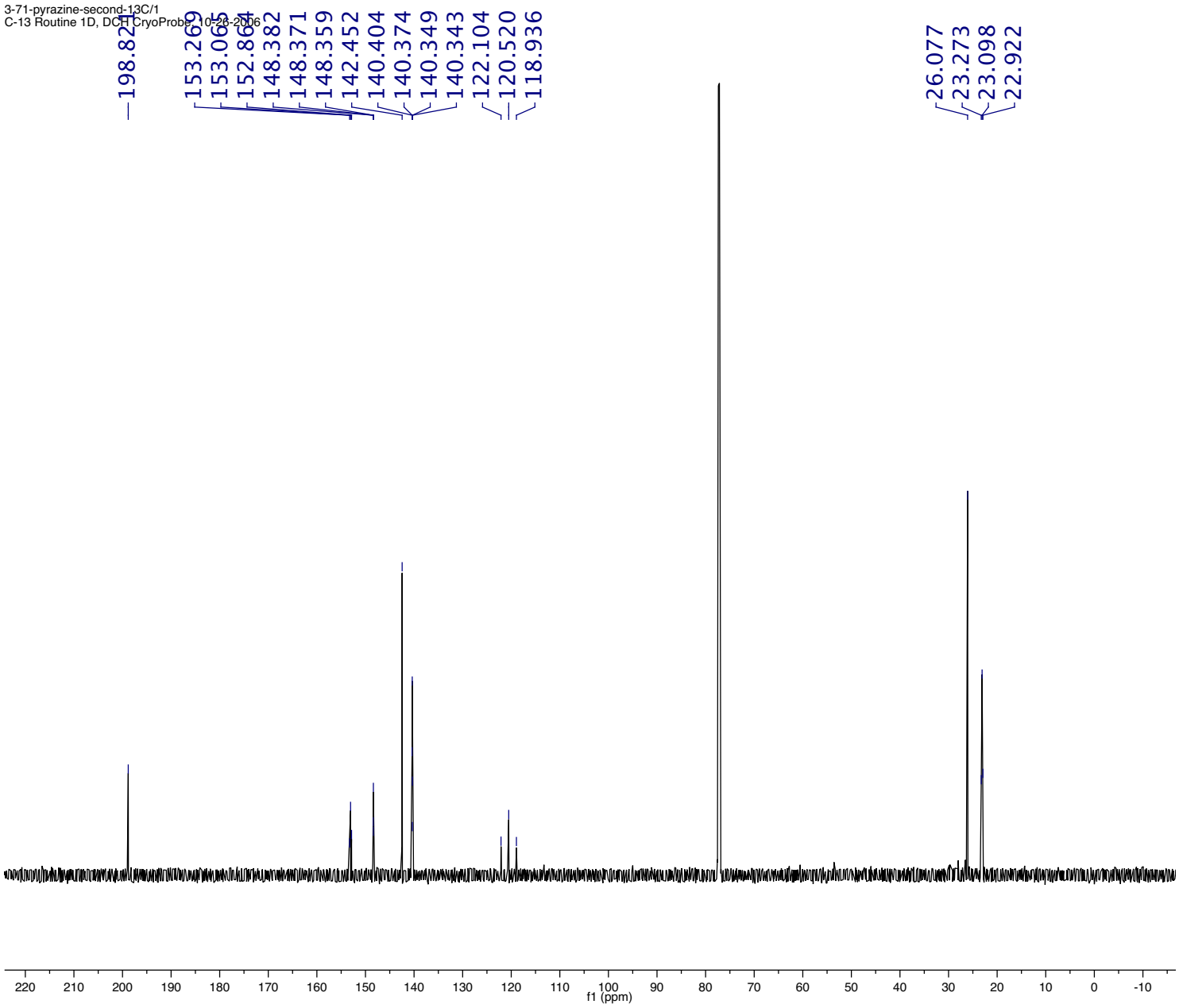

Aler_230_1CO_01
Std proton
MeF2C
Cl
N
H
O
18
7.79
7.79
7.79
7.77
7.77
7.77
6.66
6.64
2.11
2.06
2.01
1.11
1.06
3.83
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

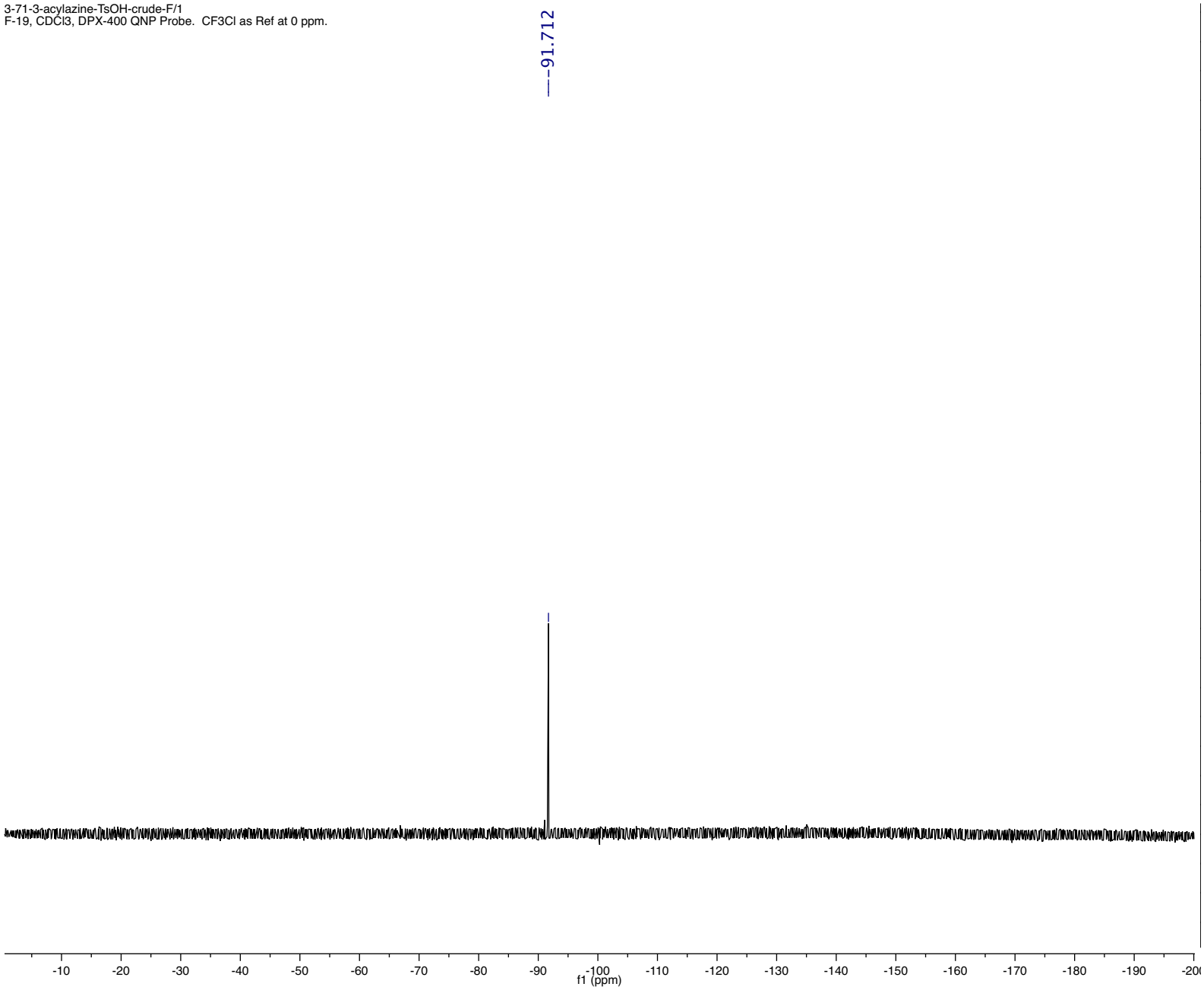

aler-230-CO-13C.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
162.52
143.47
139.46
139.11
139.06
122.58
122.40
122.22
121.73
120.14
118.55
110.84
23.80
23.62
23.43
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

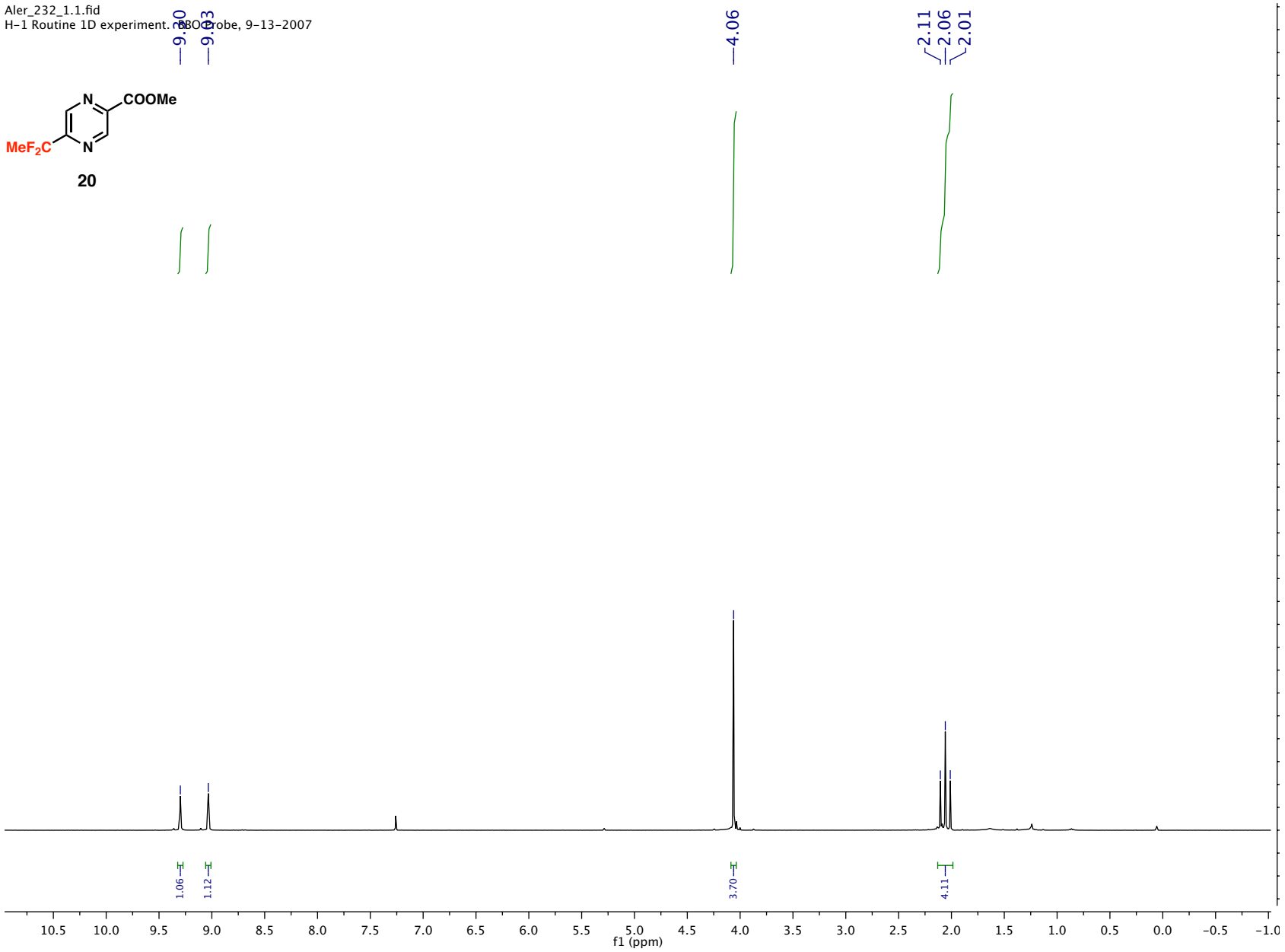
Aler_230_F.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.

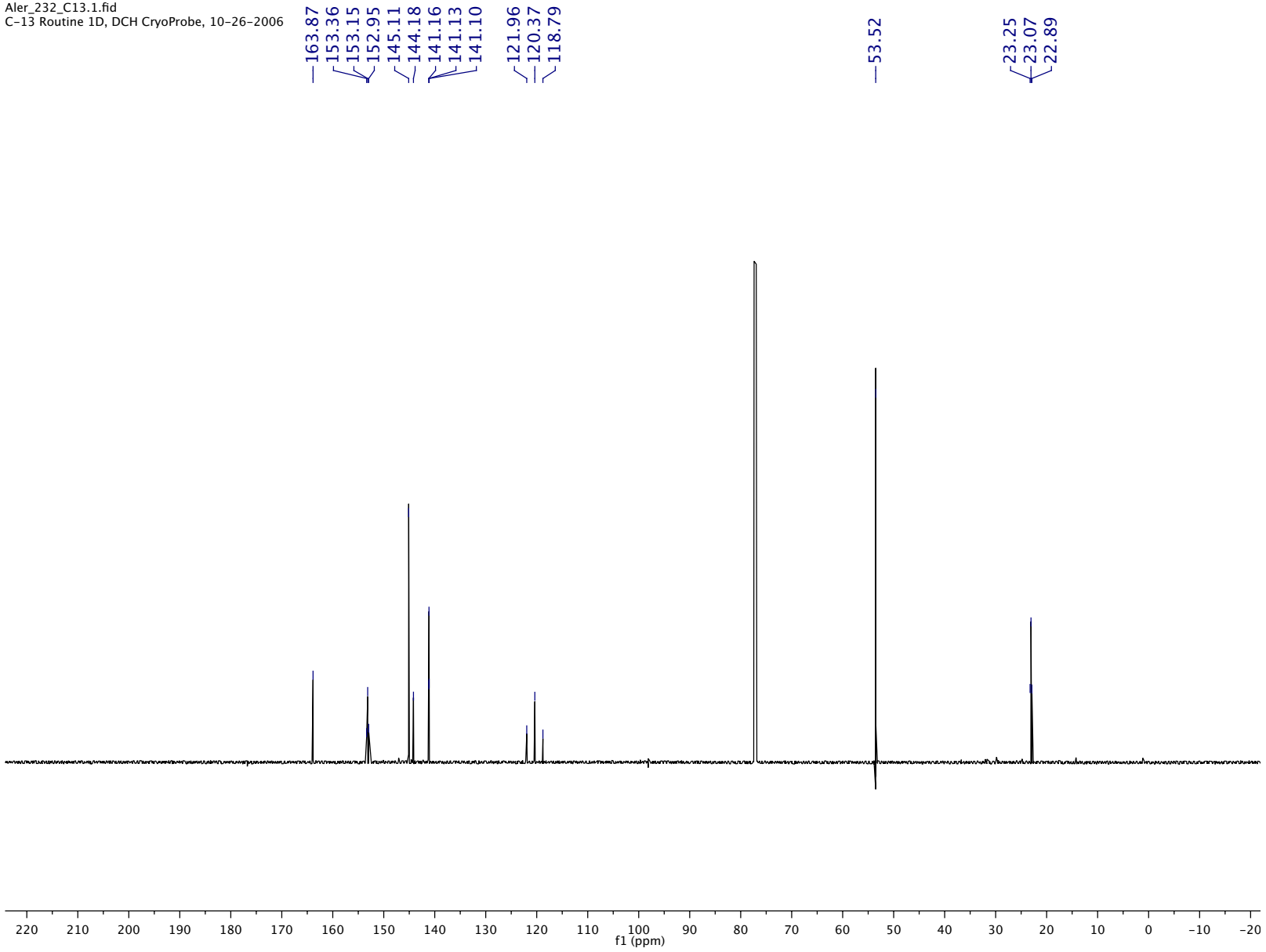


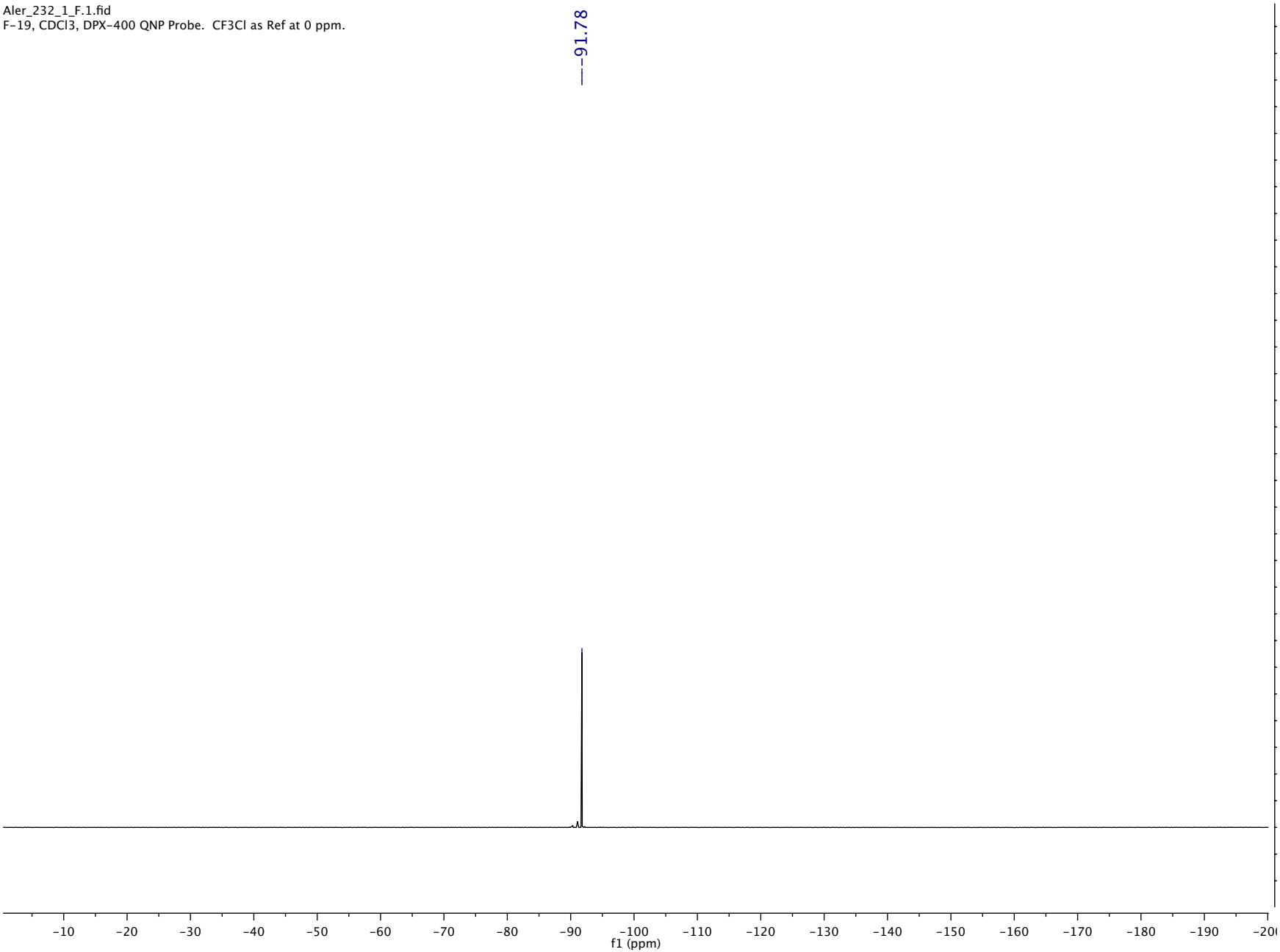

3-71-pyrazine-second-check-H/1
9.217
9.215
9.213
9.211
8.978
8.975
2.105
2.058
2.011
N
Ac
MeF2C
N
19
0.87
0.91
3.01
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

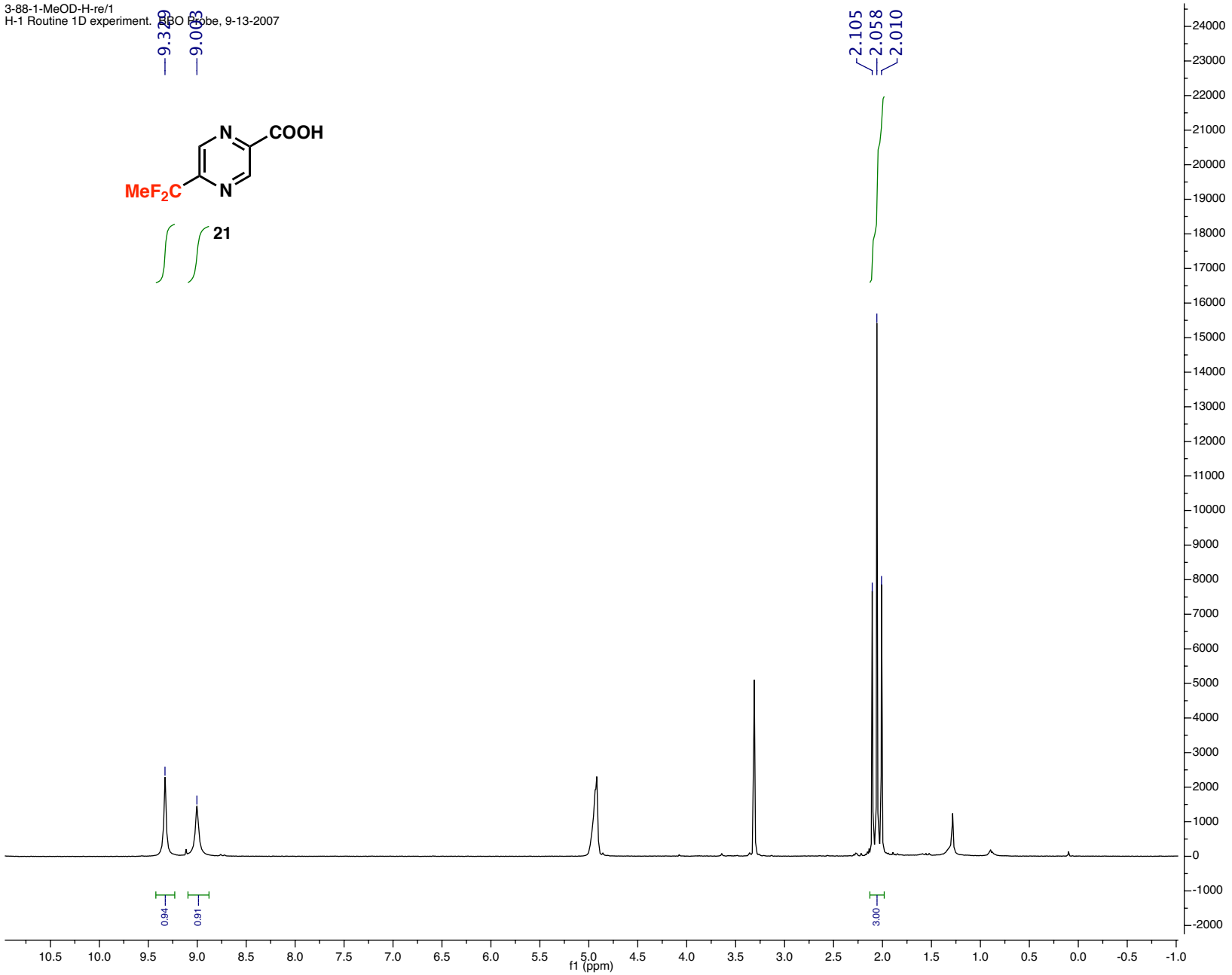

3-71-pyrazine-second-13C/1
C-13 Routine 1D, DCH CryoProbe 10-26-2006
198.822
153.269
153.065
152.864
148.382
148.371
148.359
142.452
140.404
140.374
140.349
140.343
122.104
120.520
118.936
26.077
23.273
23.098
22.922
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

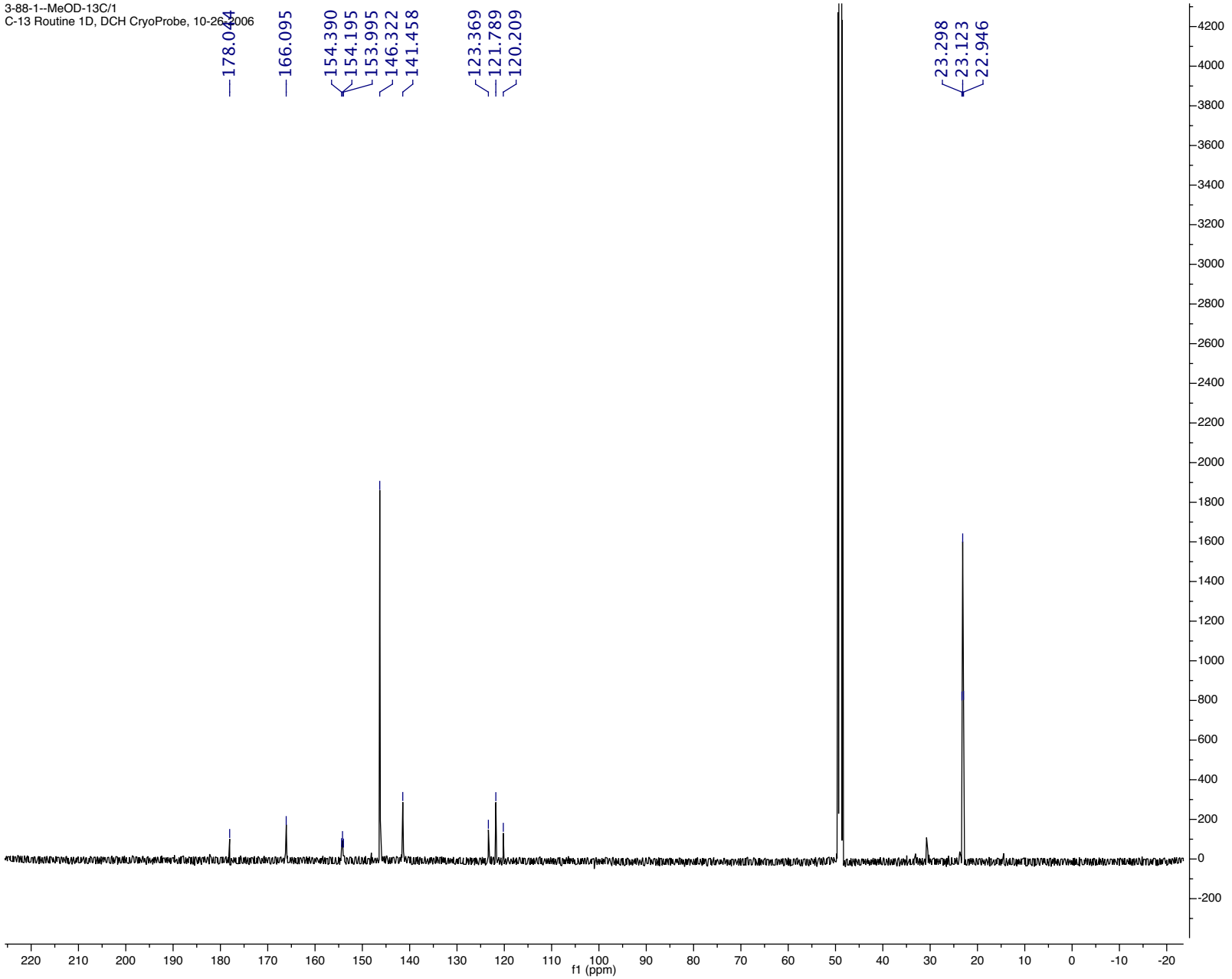

3-71-3-acylazine-TsOH-crude-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-91.712
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

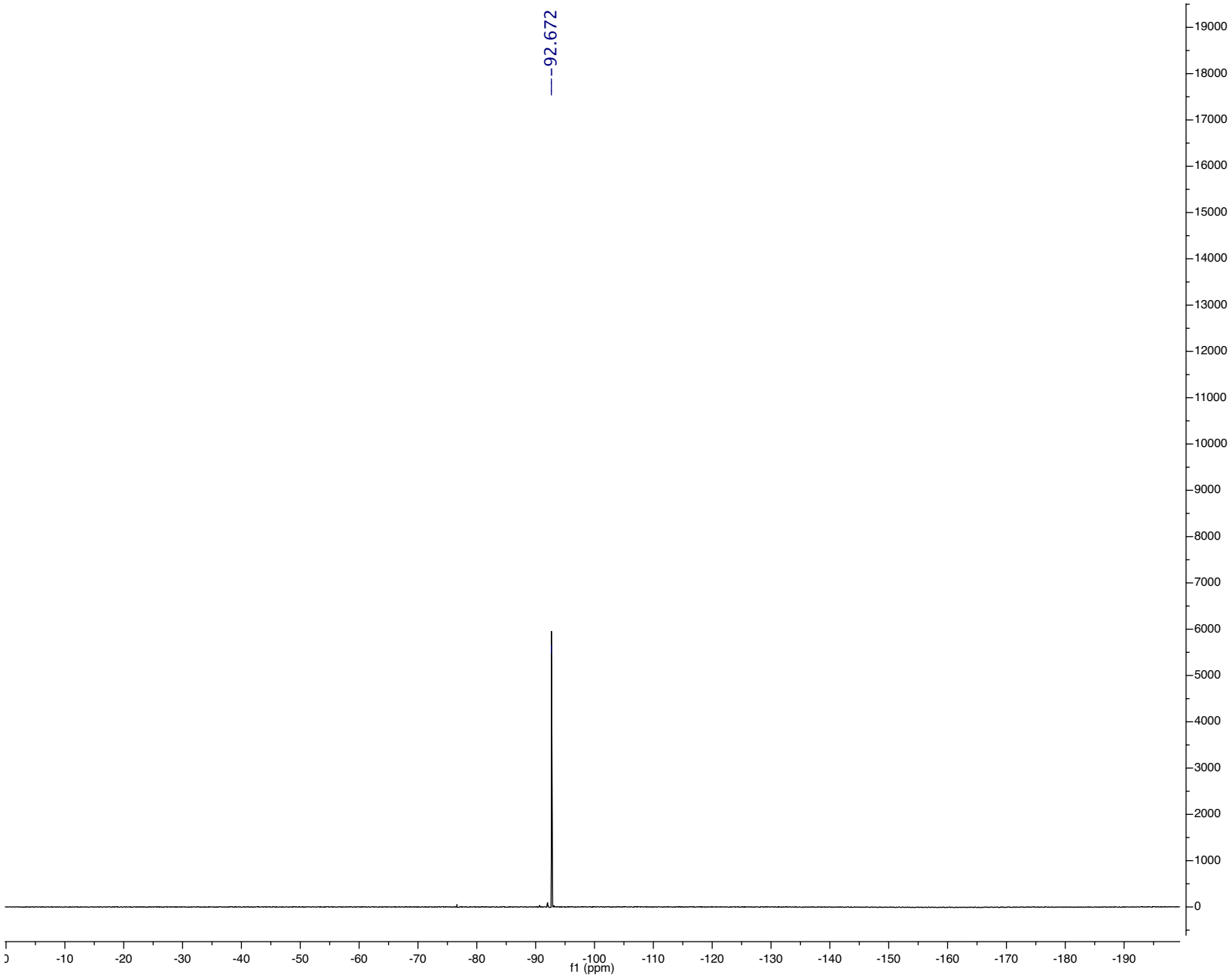

Aler_232_1.1.fid
H-1 Routine 1D experiment, 5BBO Probe, 9-13-2007
9.30
9.03
4.06
2.11
2.06
2.01
N
COOMe
MeF2C
N
20
1.06
1.12
3.70
4.11
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

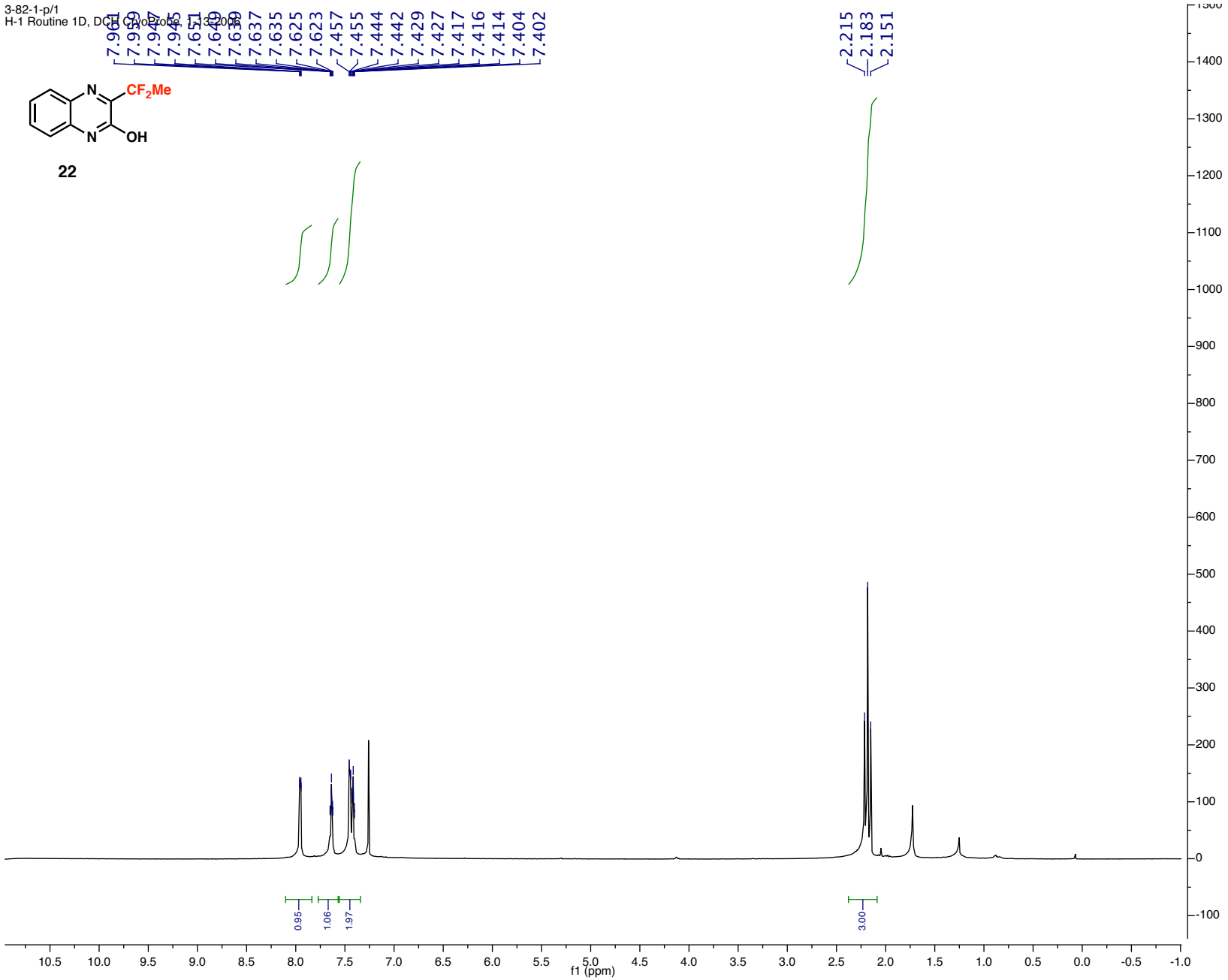

Aler_232_C13.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
163.87
153.36
153.15
152.95
145.11
144.18
141.16
141.13
141.10
121.96
120.37
118.79
53.52
23.25
23.07
22.89
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

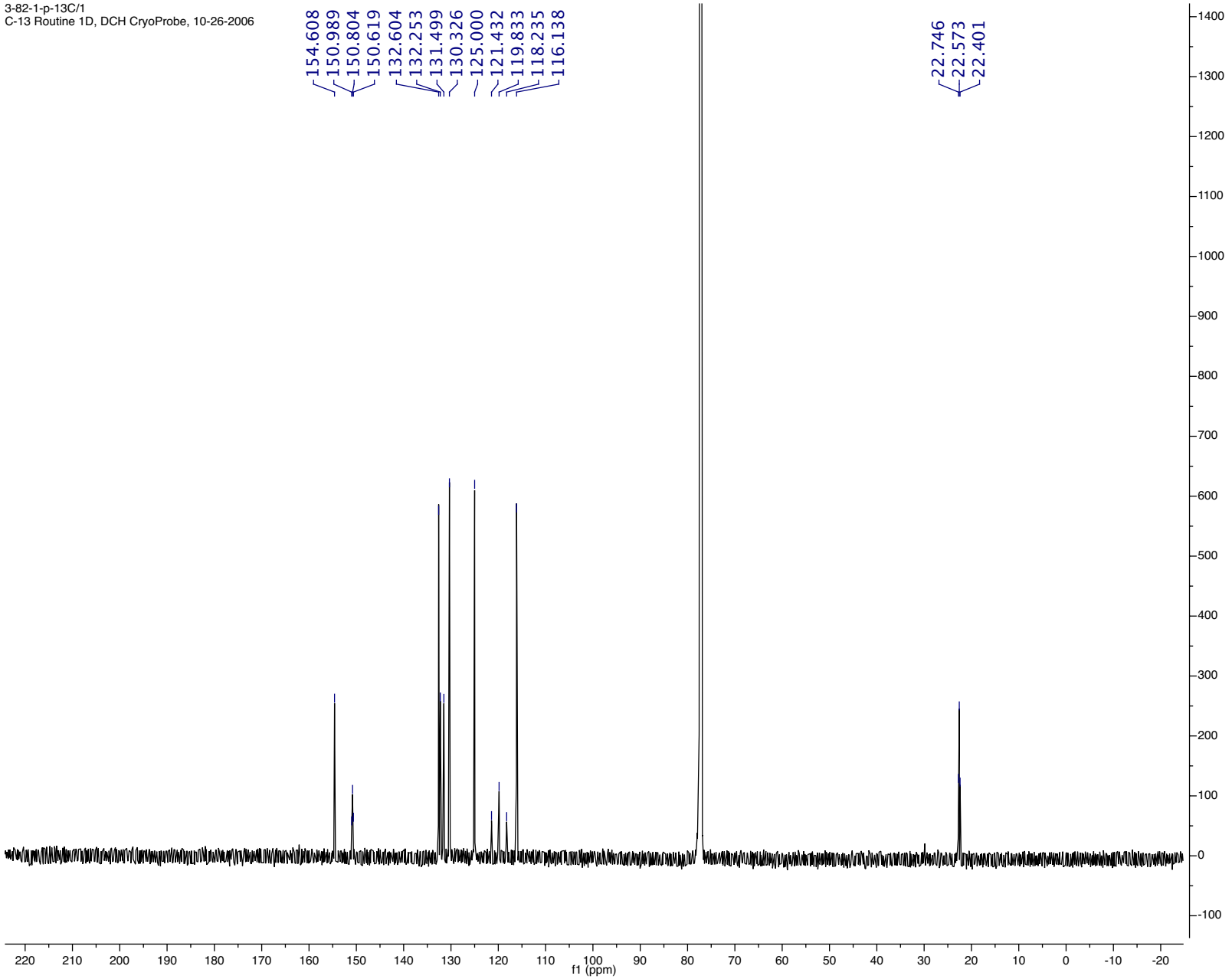

Aler_232_1_F.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-91.78
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

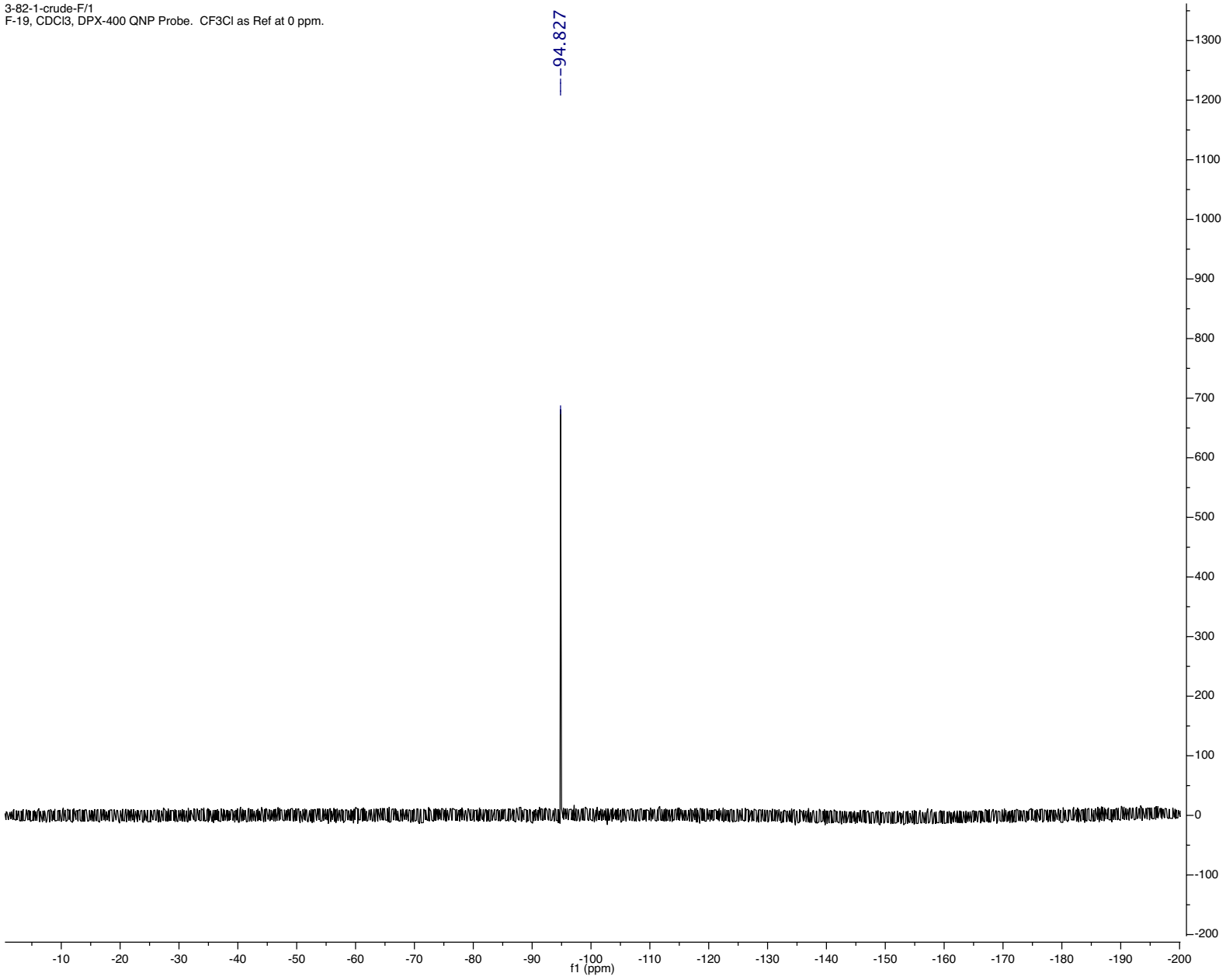

3-88-1-MeOD-H-re/1
H-1 Routine 1D experiment. BBO Probe, 9-13-2007
9.339
9.003
2.105
2.058
2.010
COOH
N
N
MeF2C
21
0.94
0.91
3.00
f1 (ppm)

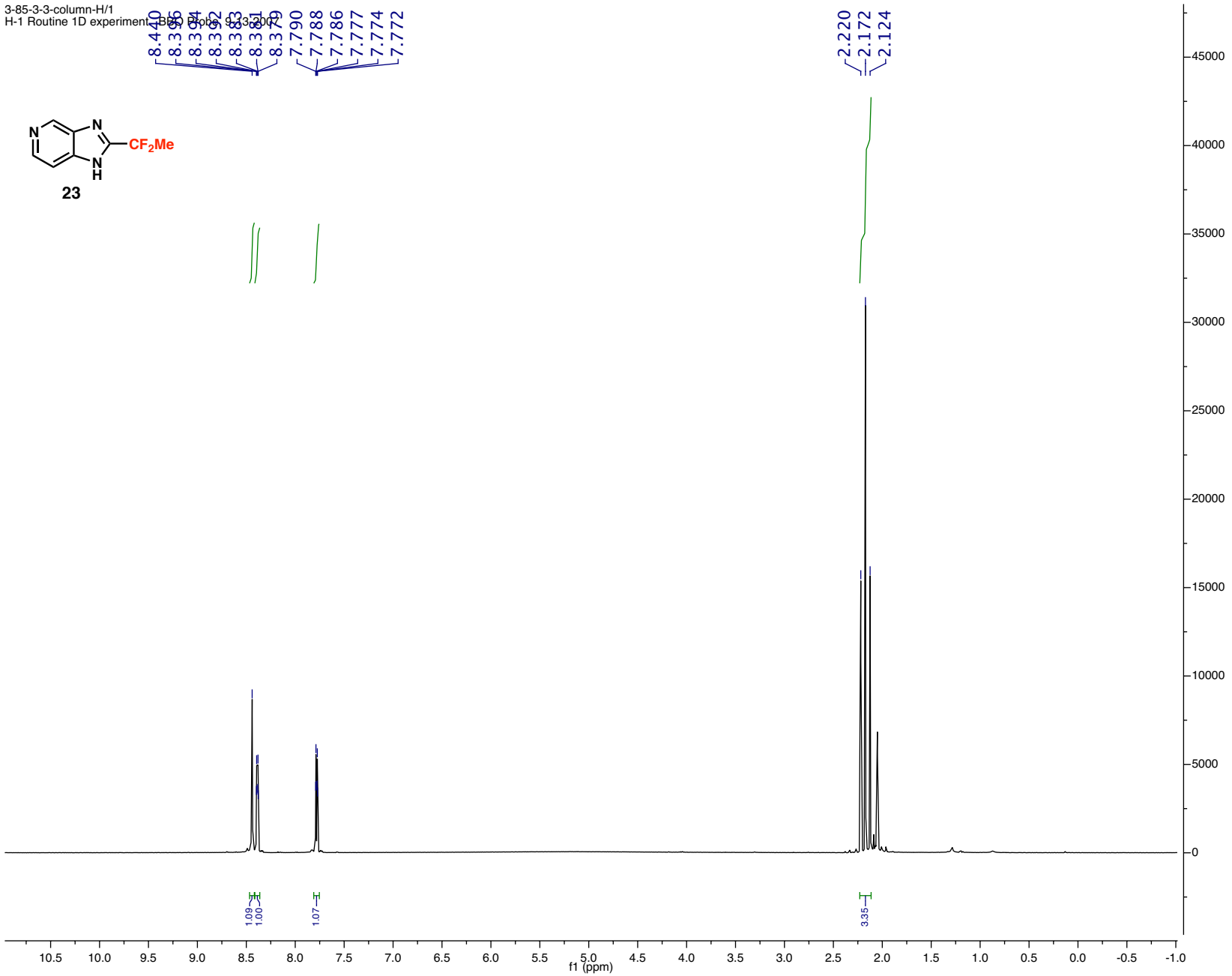

3-88-1--MeOD-13C/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
178.044
166.095
154.390
154.195
153.995
146.322
141.458
123.369
121.789
120.209
23.298
23.123
22.946
f1 (ppm)

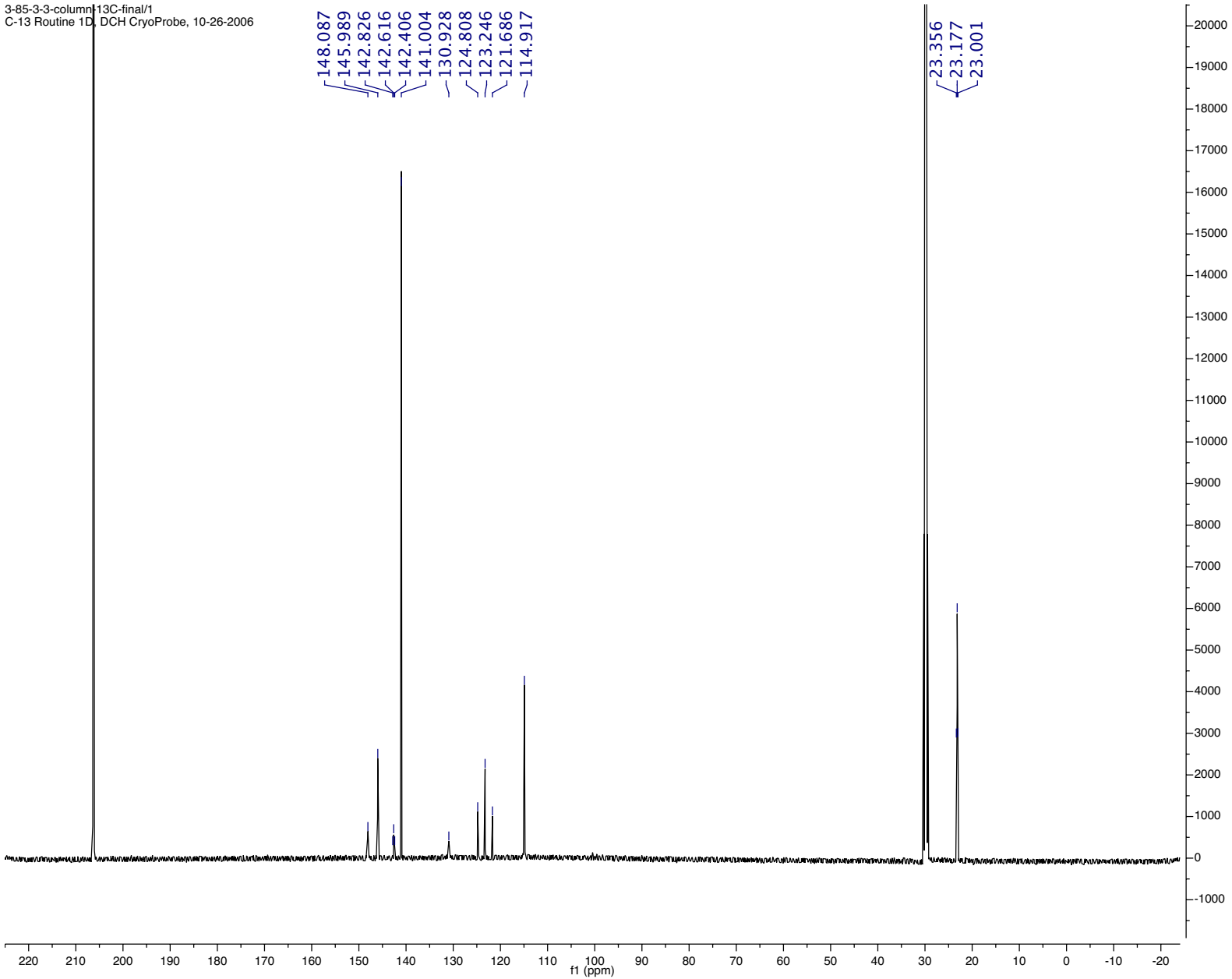

-92.672
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

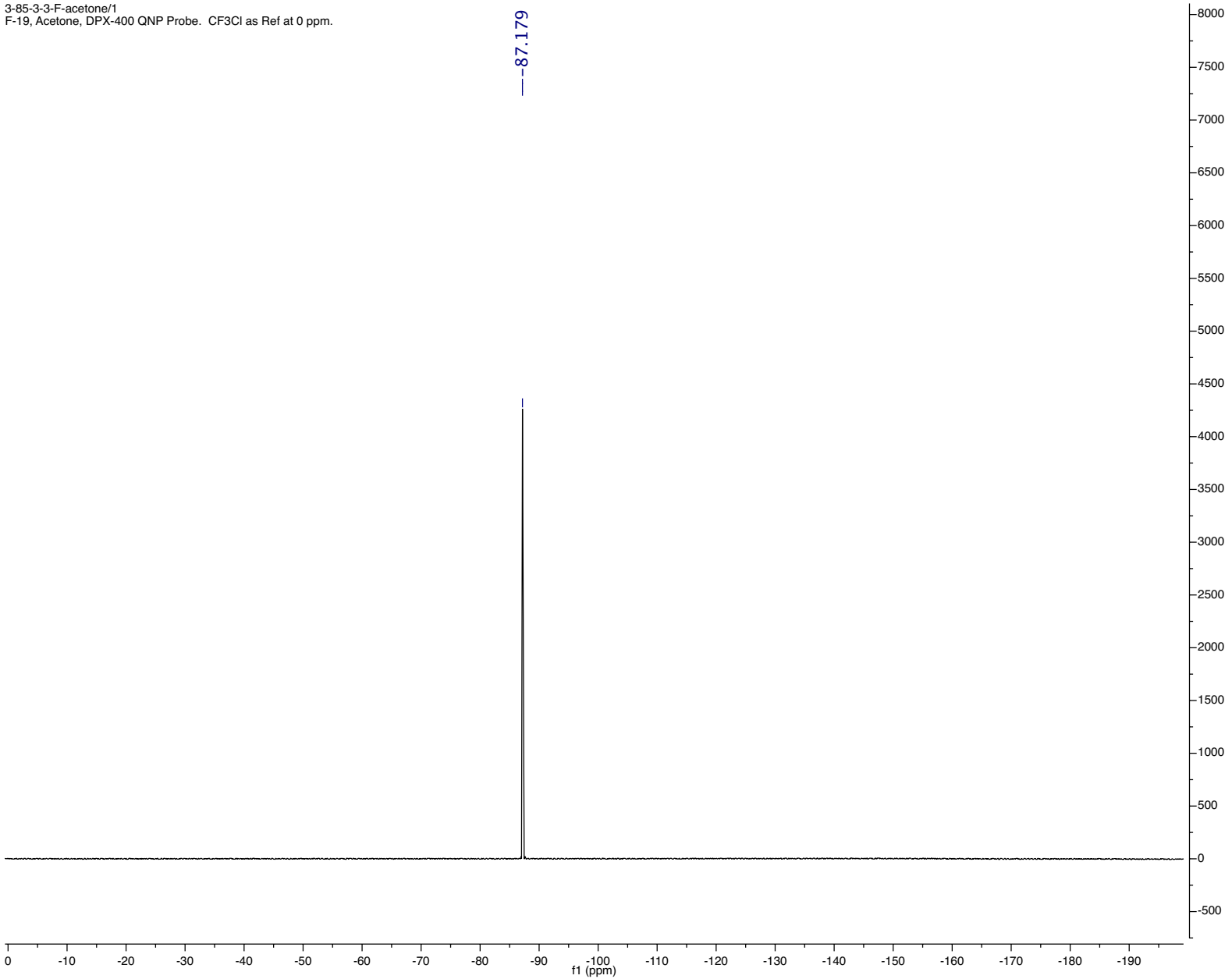

3-82-1-p/1
H-1 Routine 1D, DCH CryoProbe, 1-13-2006
7.961
7.959
7.947
7.945
7.651
7.649
7.639
7.637
7.635
7.625
7.623
7.457
7.455
7.444
7.442
7.429
7.427
7.417
7.416
7.414
7.404
7.402
2.215
2.183
2.151
CF2Me
N
N
OH
22
0.95
1.06
1.97
3.00
f1 (ppm)

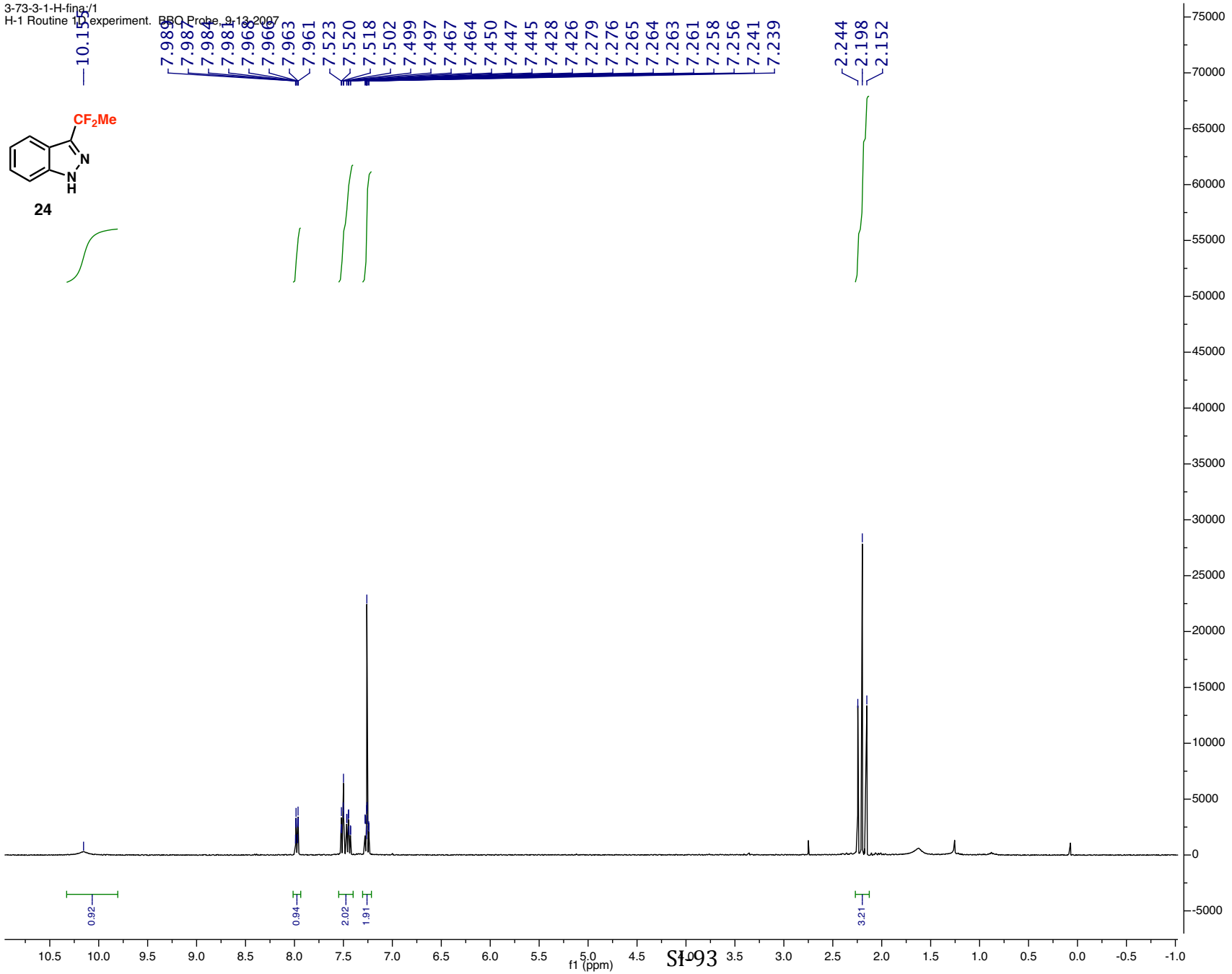

3-82-1-p-13C/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
154.608
150.989
150.804
150.619
132.604
132.253
131.499
130.326
125.000
121.432
119.833
118.235
116.138
22.746
22.573
22.401
f1 (ppm)

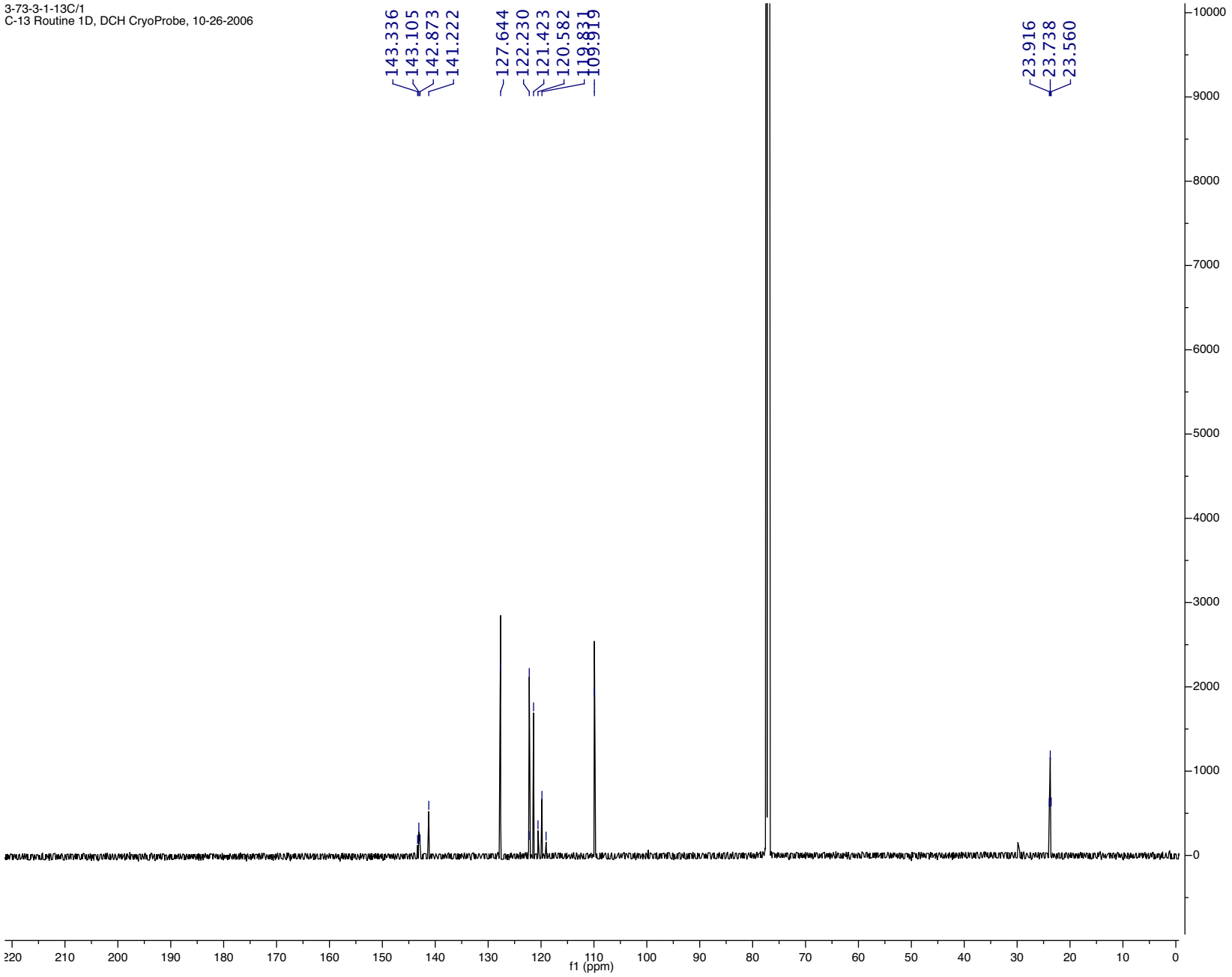

3-82-1-crude-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-94.827
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

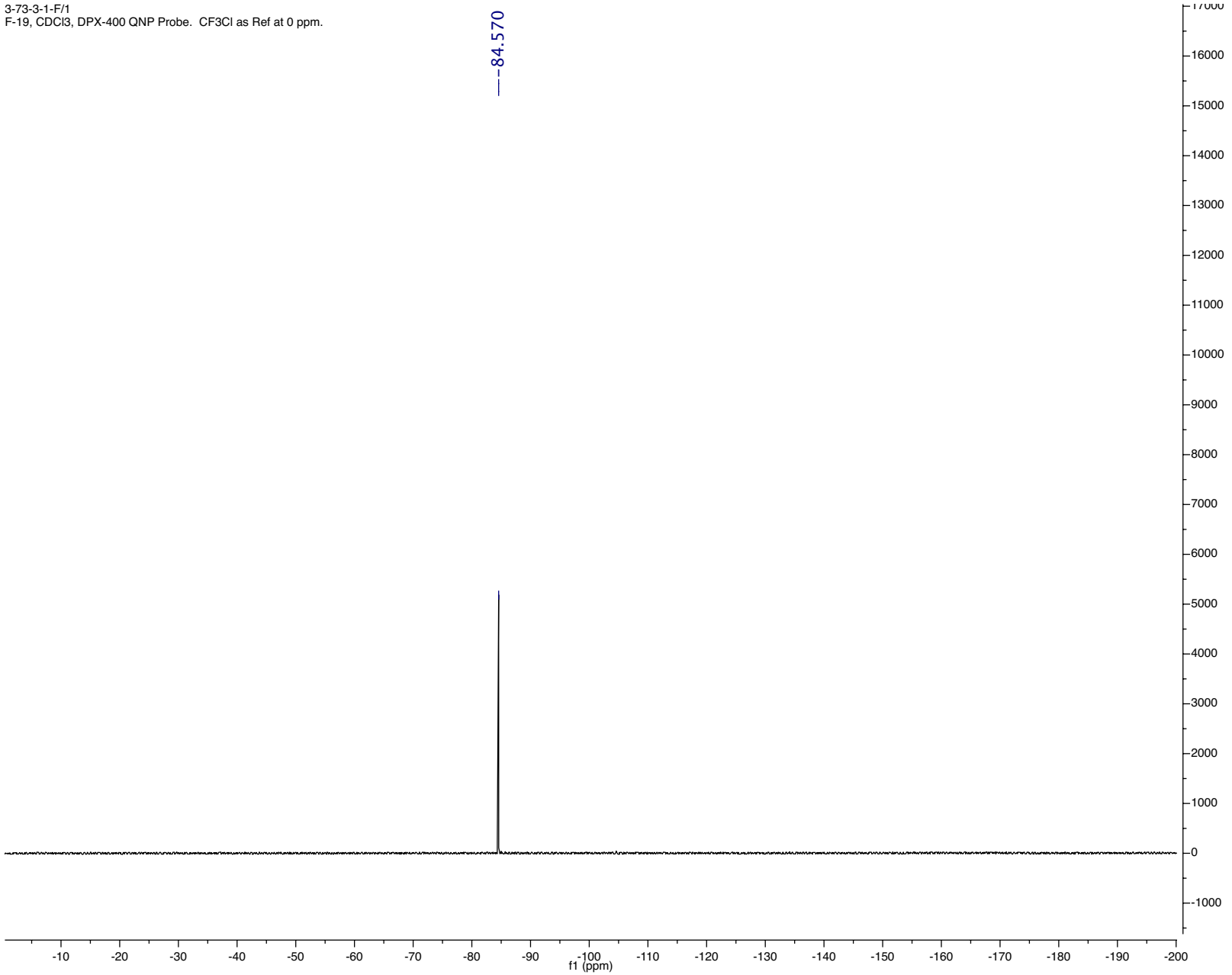

3-85-3-3-column-H/1
H-1 Routine 1D experiment, BBO Probe 9.33.2007
8.470
8.396
8.394
8.392
8.383
8.381
8.379
7.790
7.788
7.786
7.777
7.774
7.772
2.220
2.172
2.124
CF2Me
23
1.09
1.00
1.07
3.35
f1 (ppm)

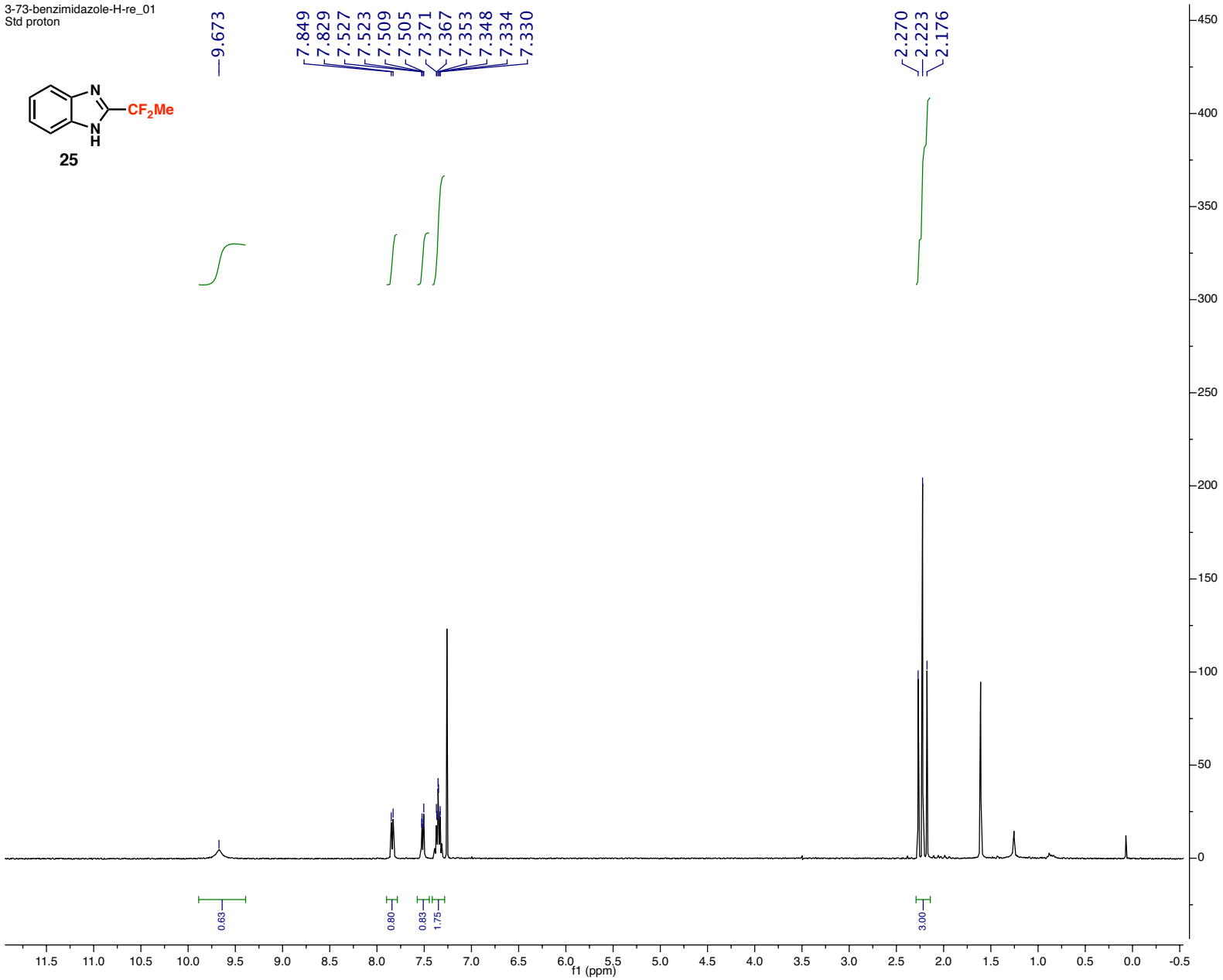

3-85-3-3-column-13C-final/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
148.087
145.989
142.826
142.616
142.406
141.004
130.928
124.808
123.246
121.686
114.917
23.356
23.177
23.001
f1 (ppm)

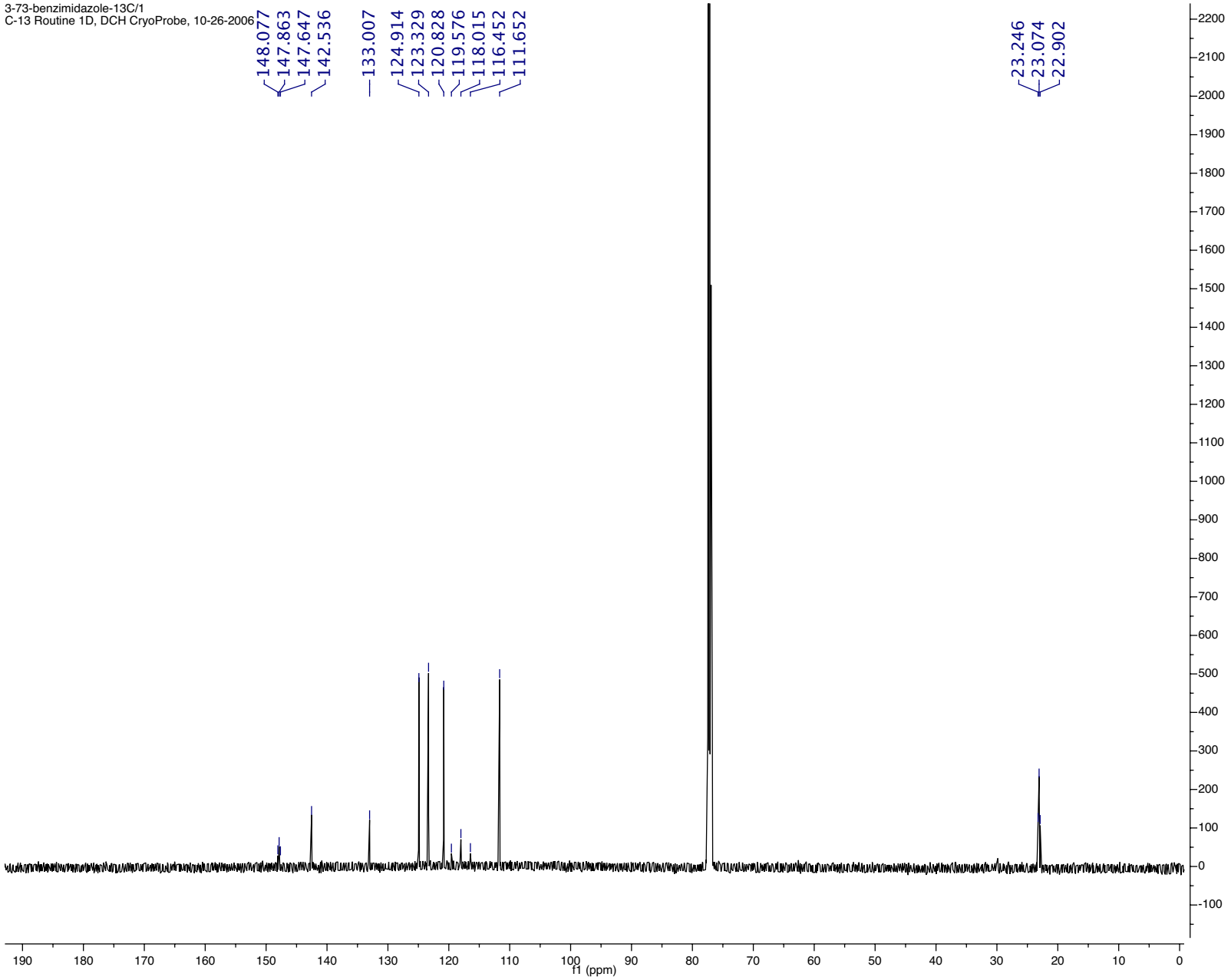

3-85-3-3-F-acetone/1
F-19, Acetone, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-87.179
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

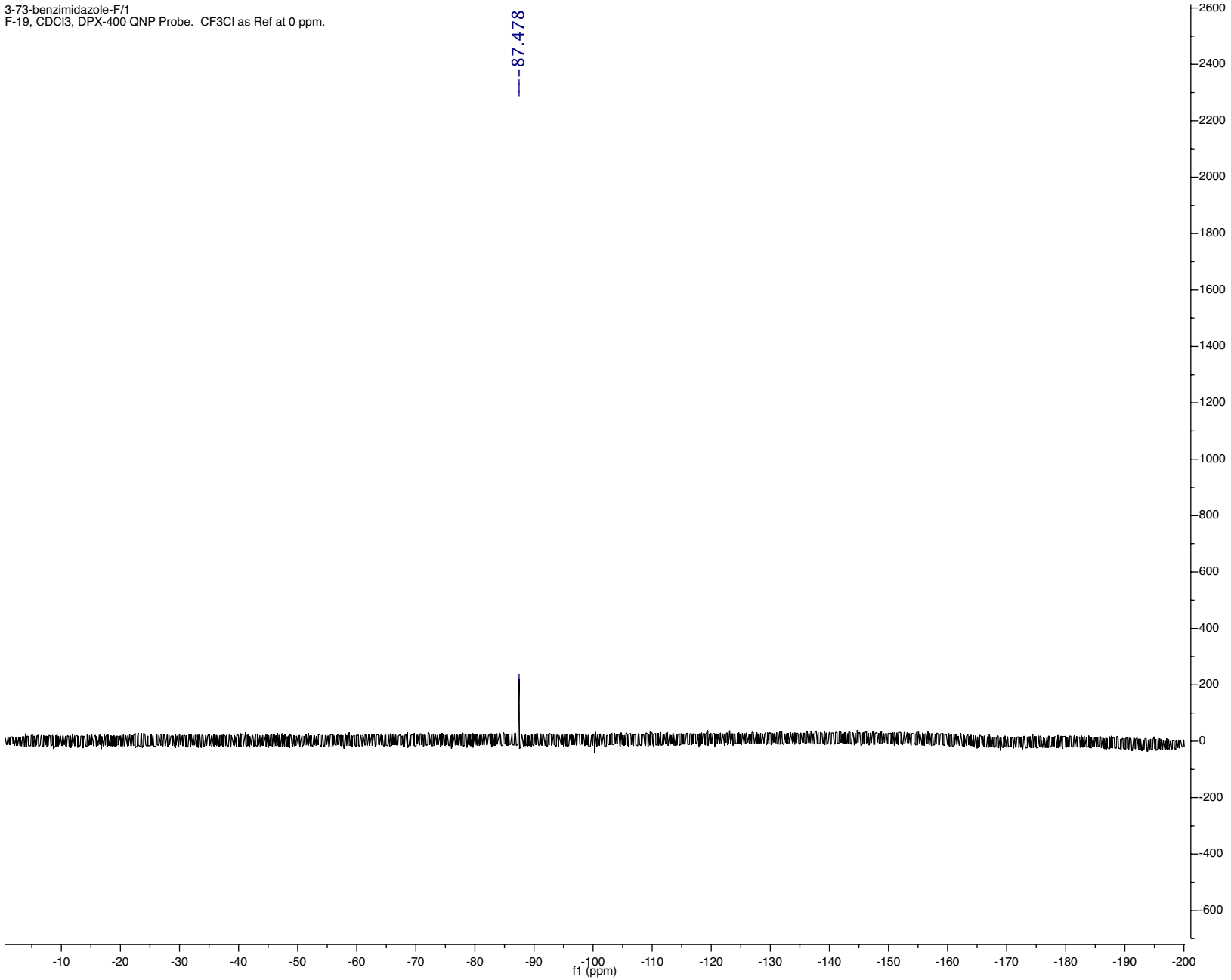

3-73-3-1-H-fina:/1
H-1 Routine 1D experiment. BBO Probe, 9-13-2007
10.152
7.989
7.987
7.984
7.981
7.968
7.966
7.963
7.961
7.523
7.520
7.518
7.502
7.499
7.497
7.467
7.464
7.450
7.447
7.445
7.428
7.426
7.279
7.276
7.265
7.264
7.263
7.261
7.258
7.256
7.241
7.239
2.244
2.198
2.152
CF2Me
N
N
H
24
0.92
0.94
2.02
1.91
3.21
f1 (ppm)

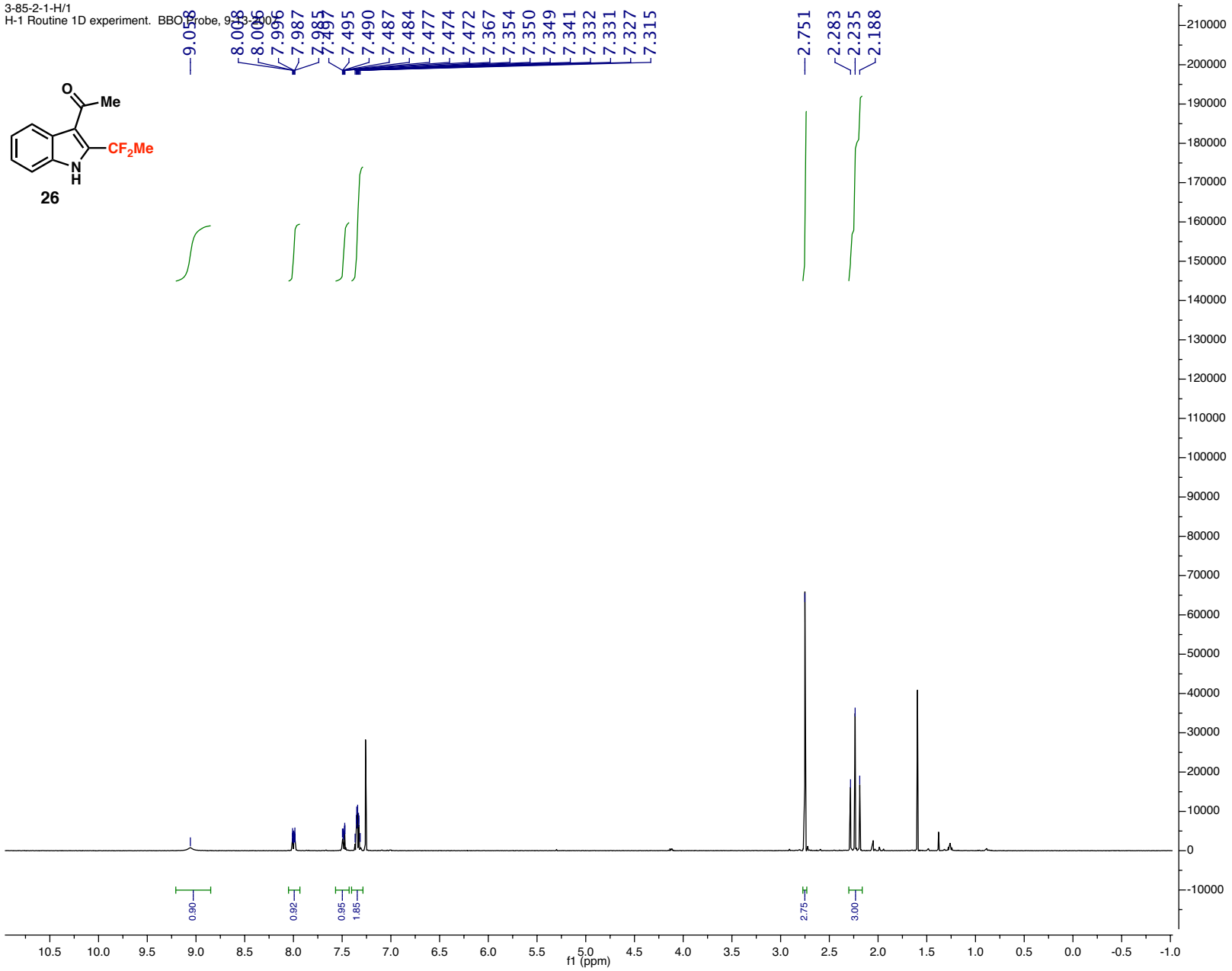

3-73-3-1-13C/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
143.336
143.105
142.873
141.222
127.644
122.230
121.423
120.582
118.831
109.919
23.916
23.738
23.560
f1 (ppm)

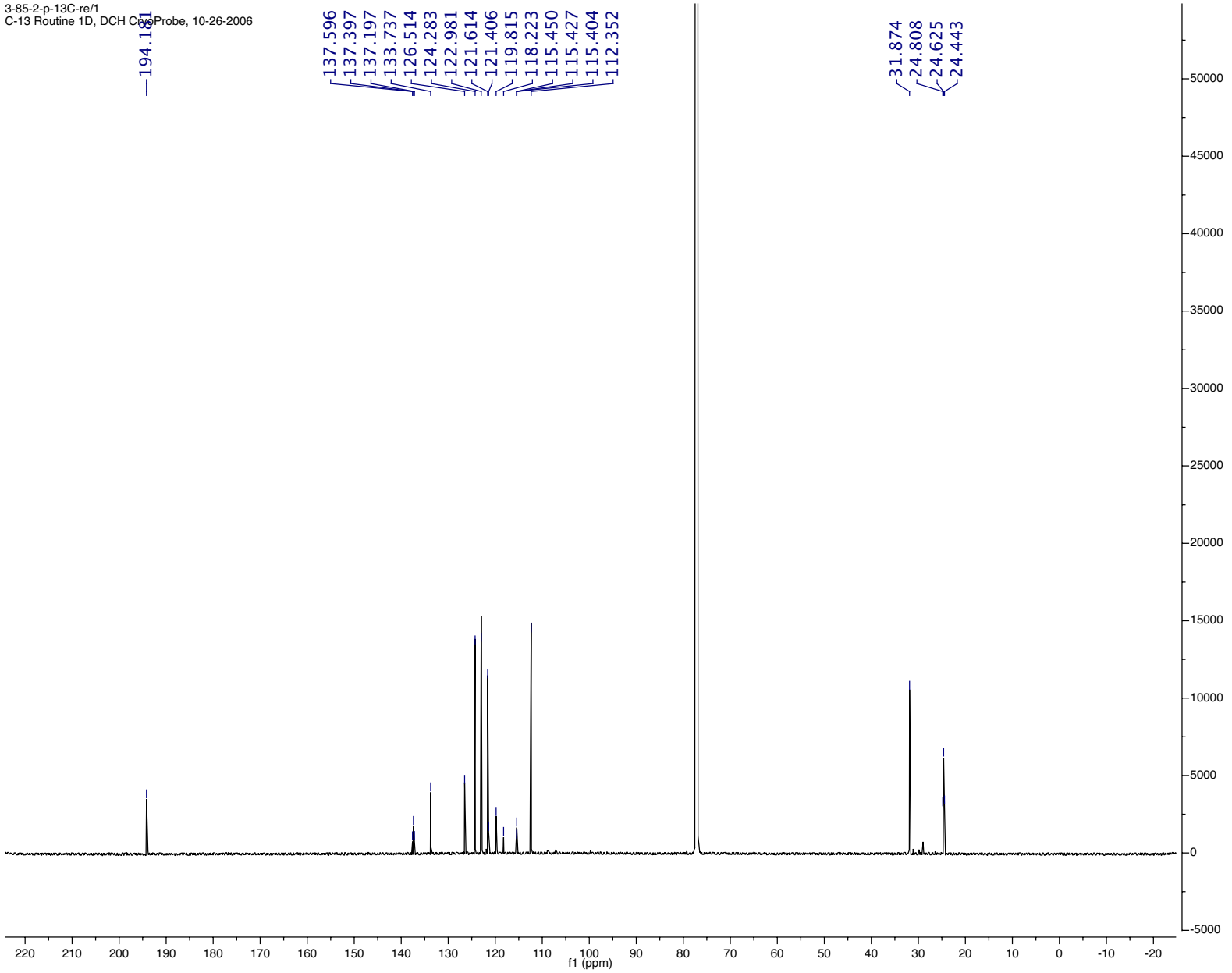

3-73-3-1-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-84.570
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

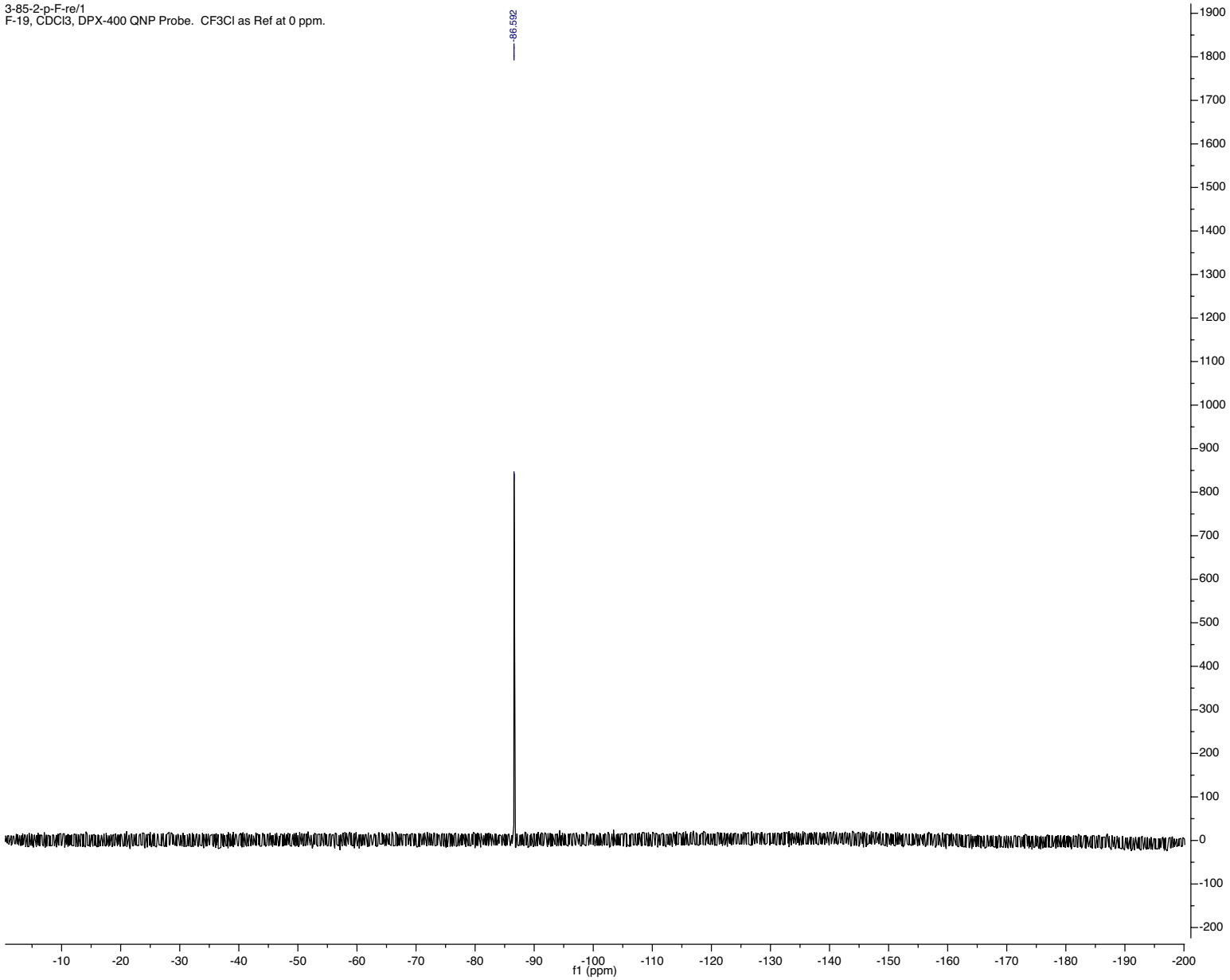

3-73-benzimidazole-H-re_01
Std proton
9.673
7.849
7.829
7.527
7.523
7.509
7.505
7.371
7.367
7.353
7.348
7.334
7.330
2.270
2.223
2.176
CF2Me
25
0.63
0.80
0.83
1.75
3.00
f1 (ppm)

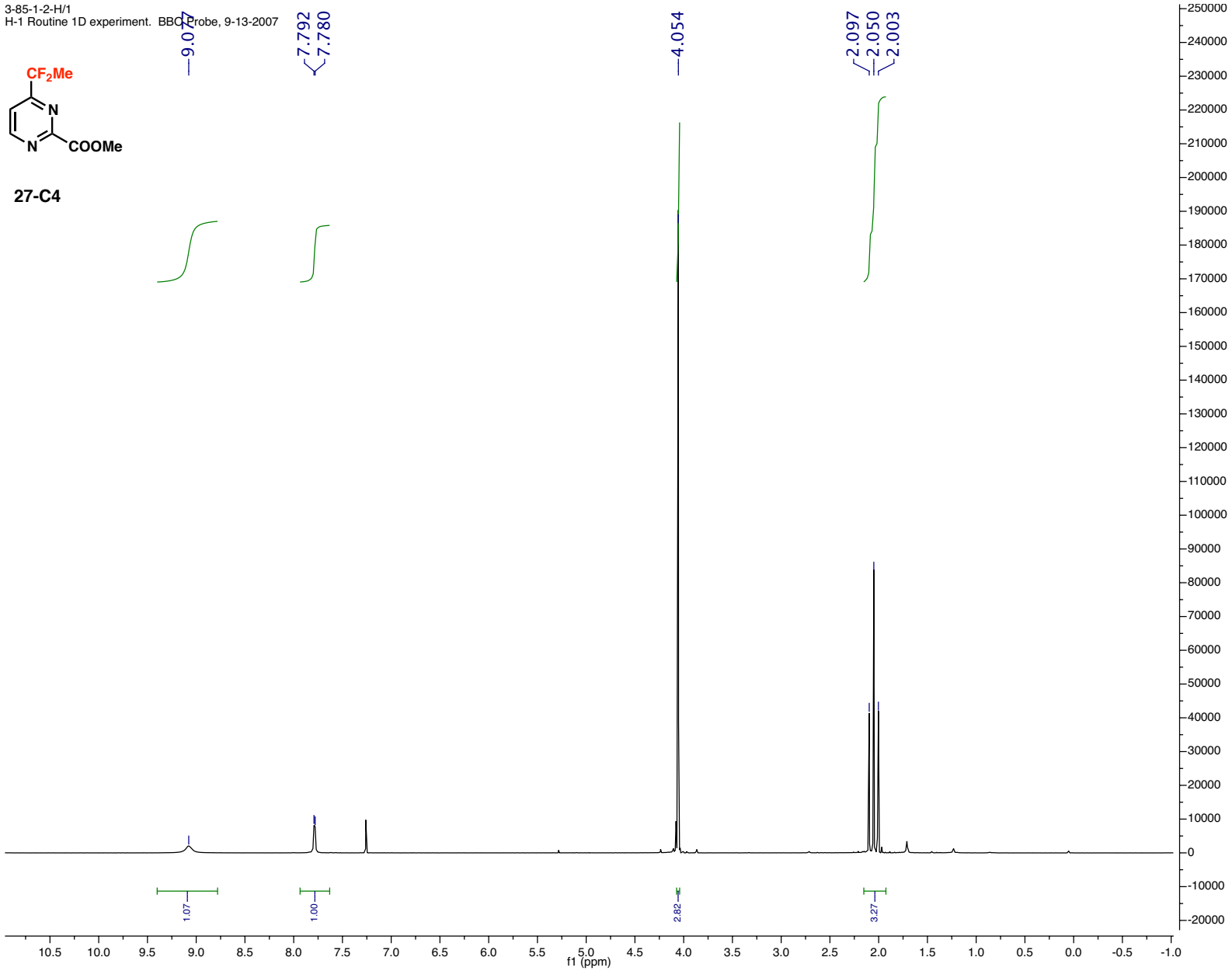

3-73-benzimidazole-13C/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
148.077
147.863
147.647
142.536
133.007
124.914
123.329
120.828
119.576
118.015
116.452
111.652
23.246
23.074
22.902
f1 (ppm)

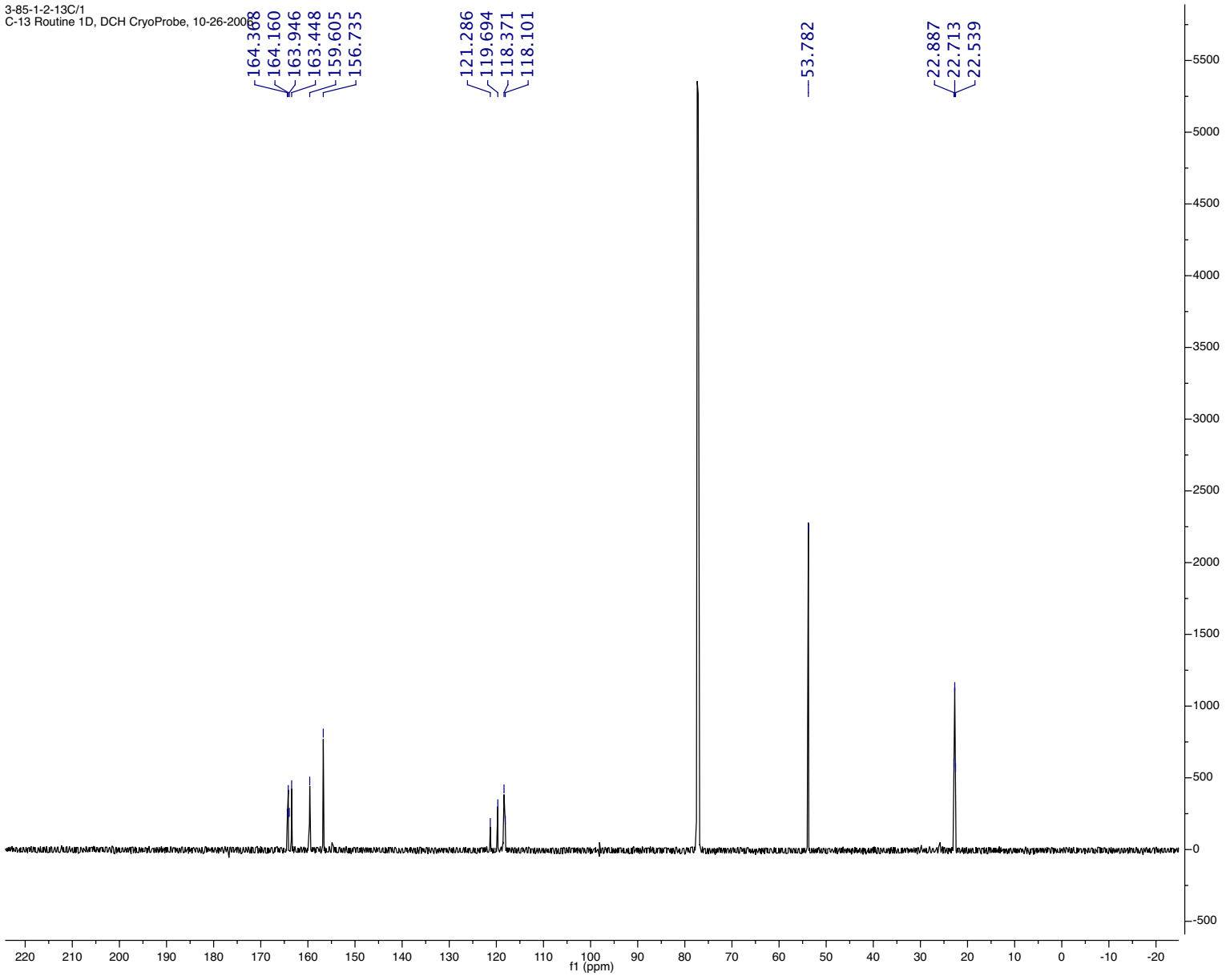

3-73-benzimidazole-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-87.478
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
-600
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

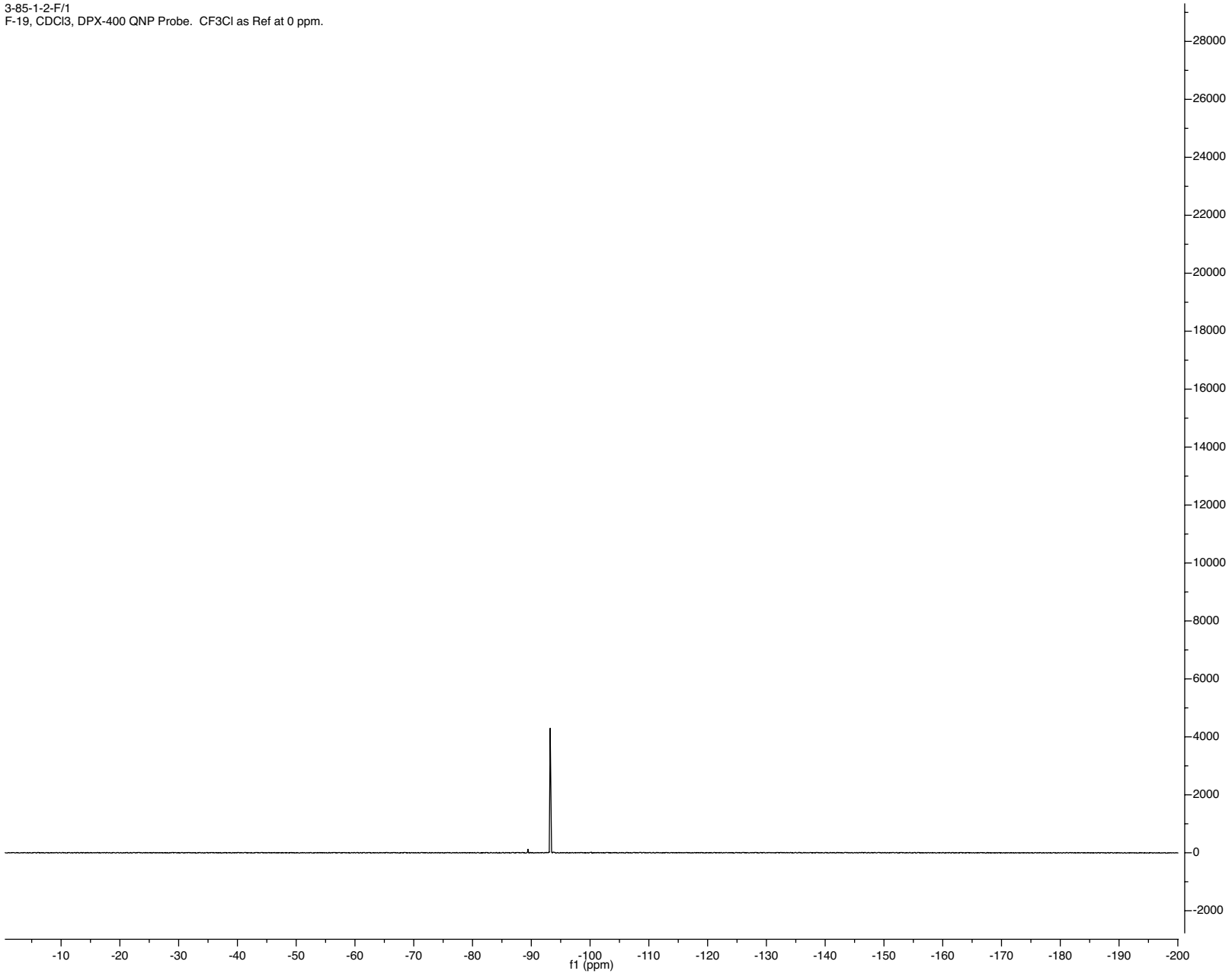

3-85-2-1-H/1
H-1 Routine 1D experiment. BBO Probe, 9/13-200
9.018
8.008
8.006
7.996
7.987
7.985
7.497
7.495
7.490
7.487
7.484
7.477
7.474
7.472
7.367
7.354
7.350
7.349
7.341
7.332
7.331
7.327
7.315
2.751
2.283
2.235
2.188
O
Me
CF2Me
N
H
26
0.90
0.92
0.95
1.85
2.75
3.00
f1 (ppm)

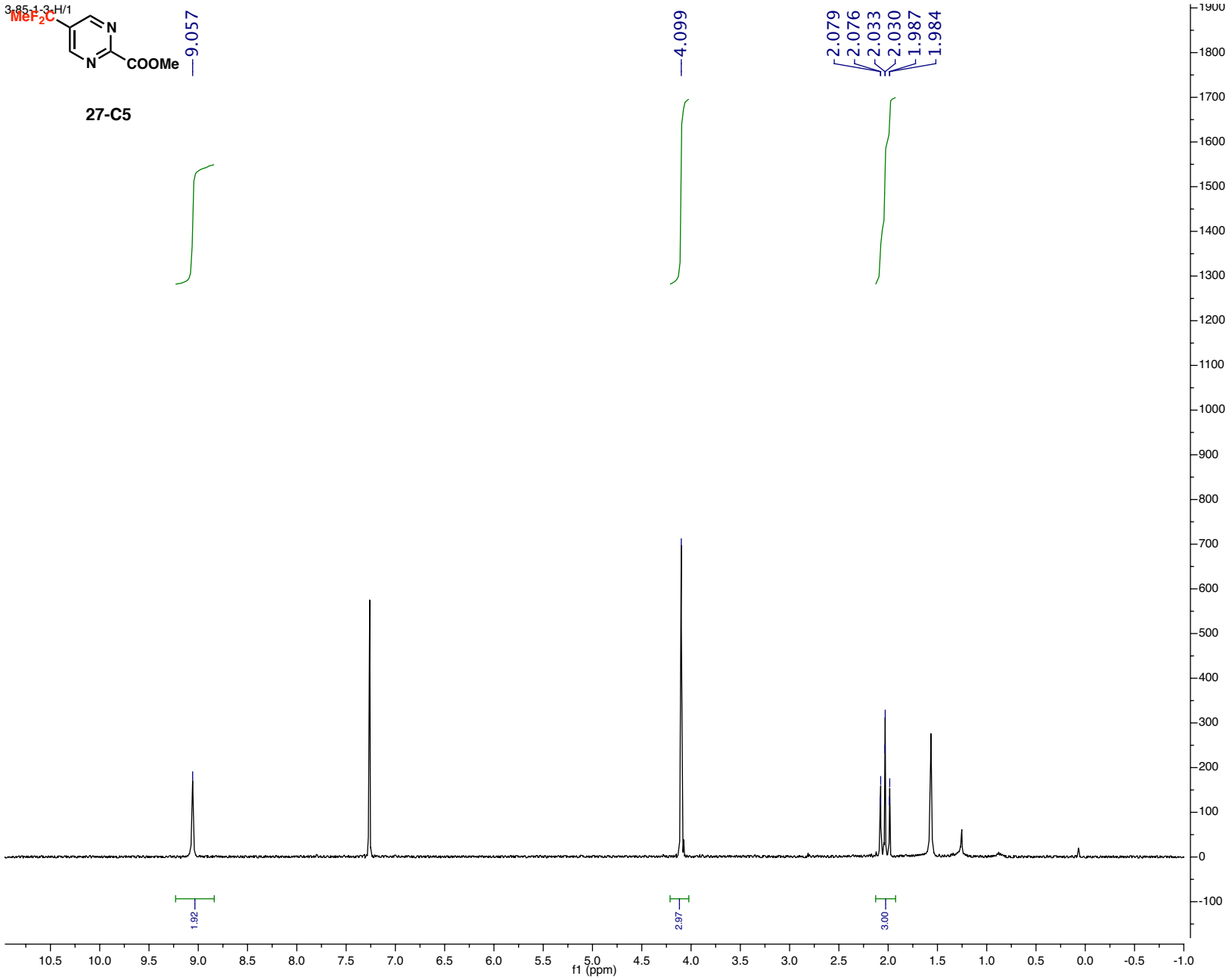

3-85-2-p-13C-re/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
194.181
137.596
137.397
137.197
133.737
126.514
124.283
122.981
121.614
121.406
119.815
118.223
115.450
115.427
115.404
112.352
31.874
24.808
24.625
24.443
f1 (ppm)

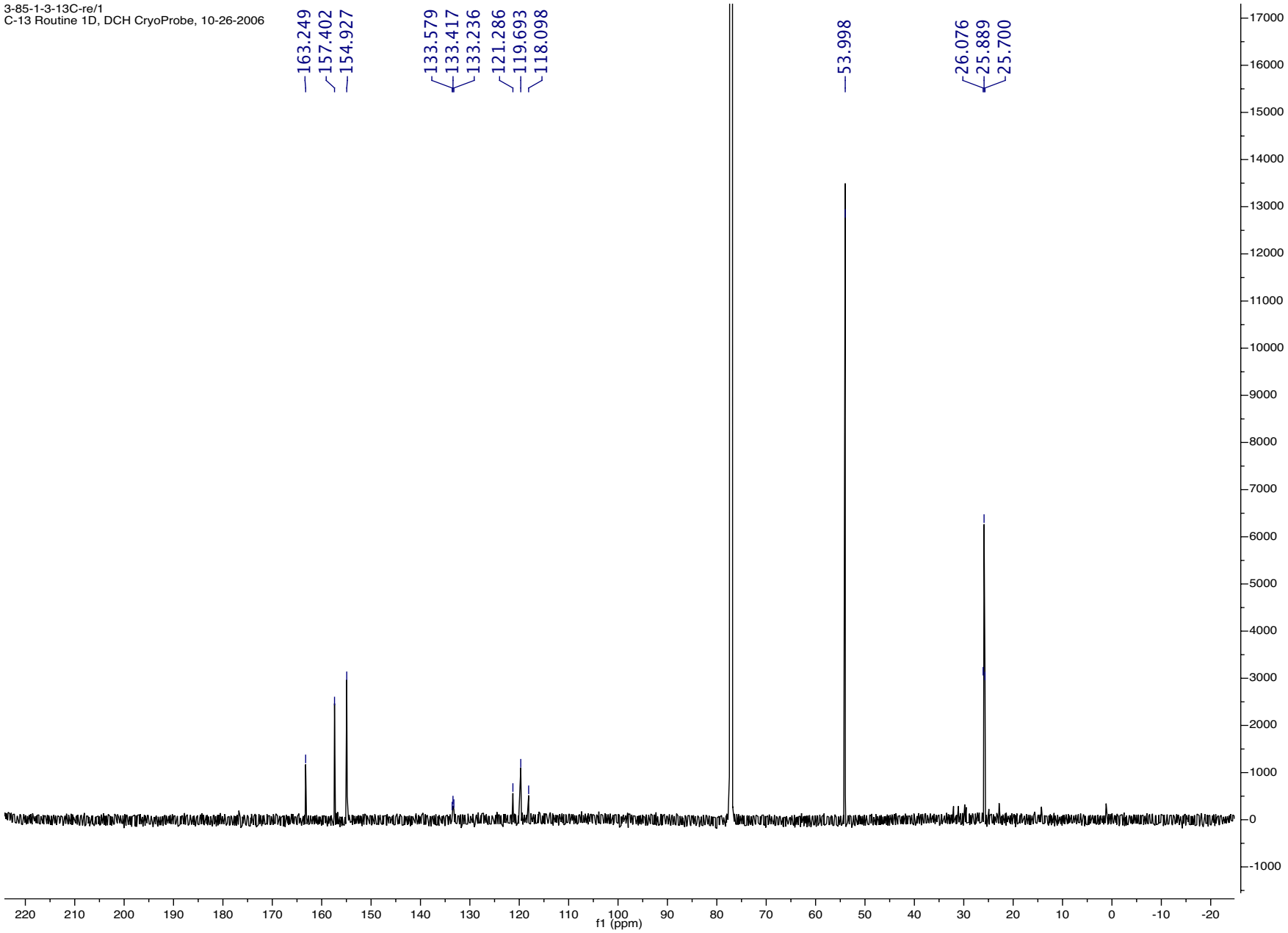

3-85-2-p-F-re/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-86.592
f1 (ppm)

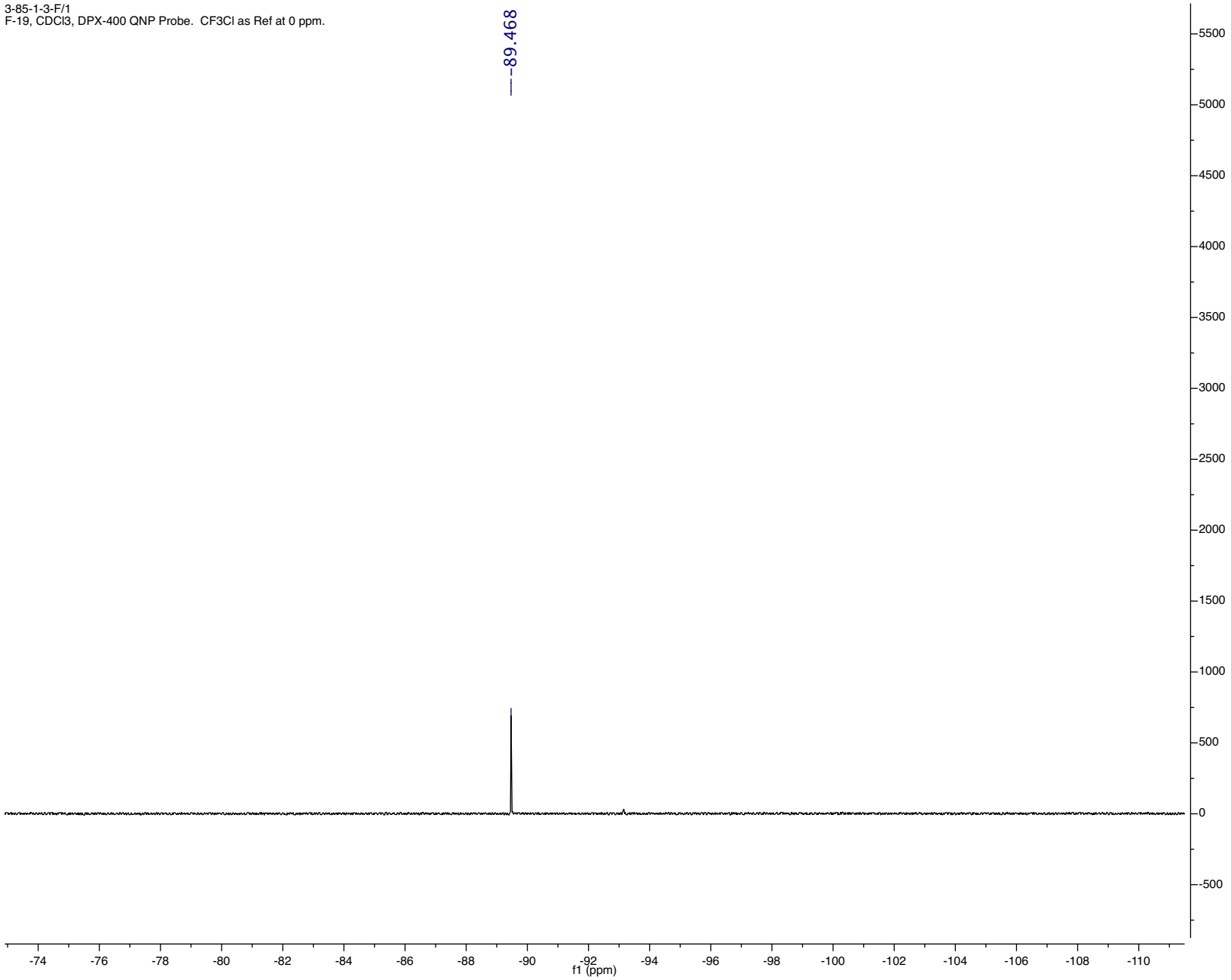

3-85-1-2-H/1
H-1 Routine 1D experiment. BBCI Probe, 9-13-2007
CF2Me
N
N
COOMe
27-C4
9.077
7.792
7.780
4.054
2.097
2.050
2.003
1.07
1.00
2.82
3.27
f1 (ppm)

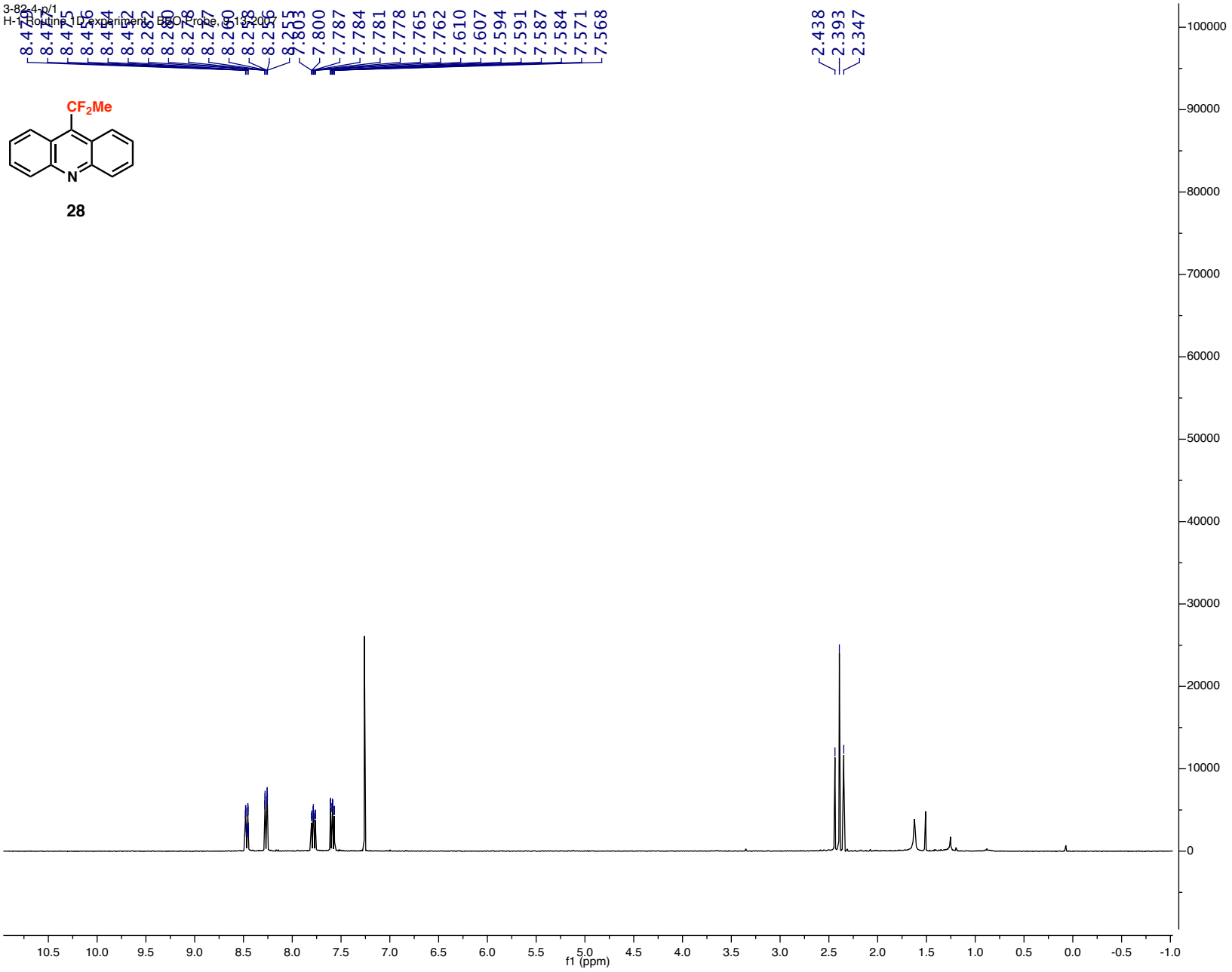

3-85-1-2-13C/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
164.388
164.160
163.946
163.448
159.605
156.735
121.286
119.694
118.371
118.101
53.782
22.887
22.713
22.539
f1 (ppm)

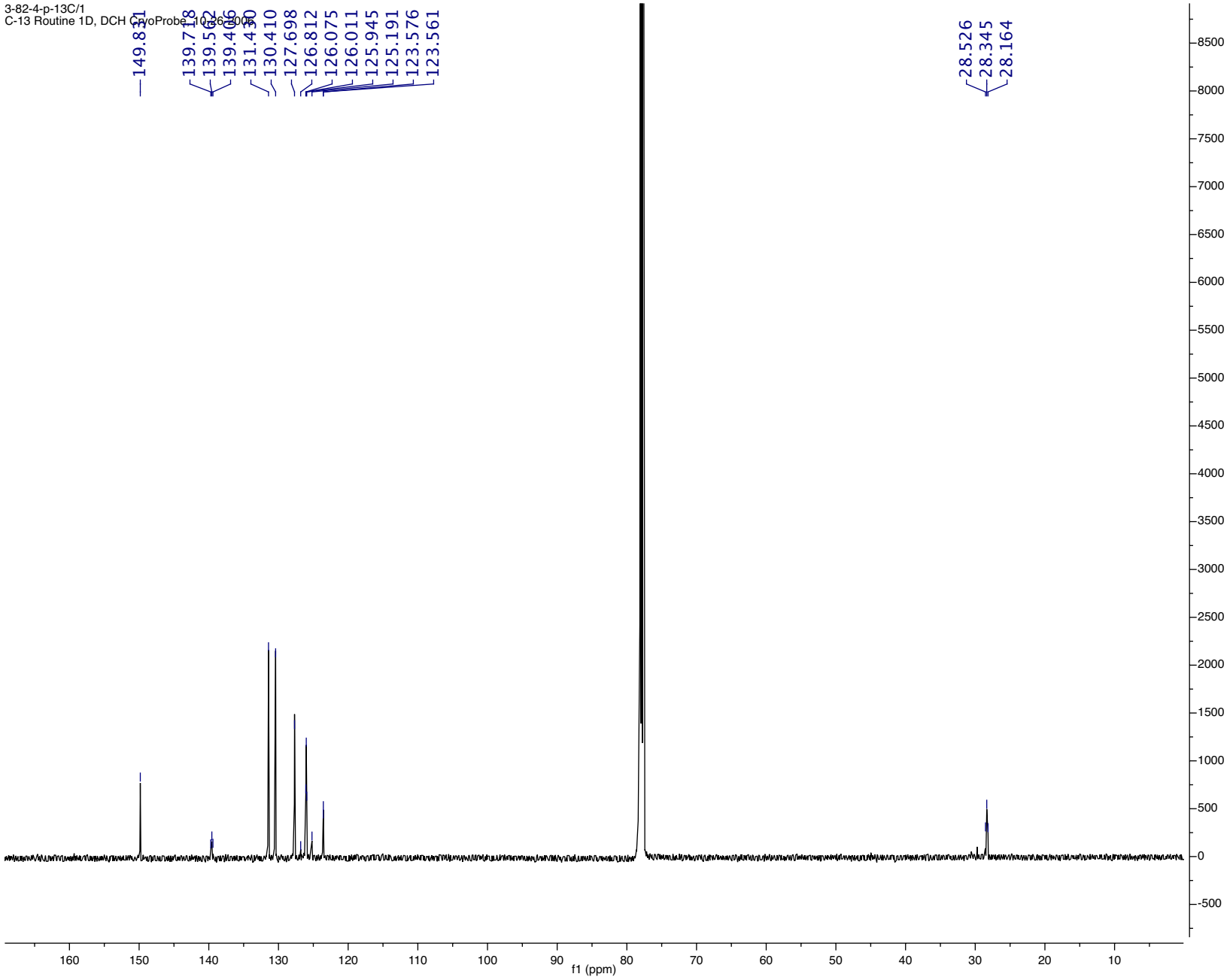

3-85-1-2-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

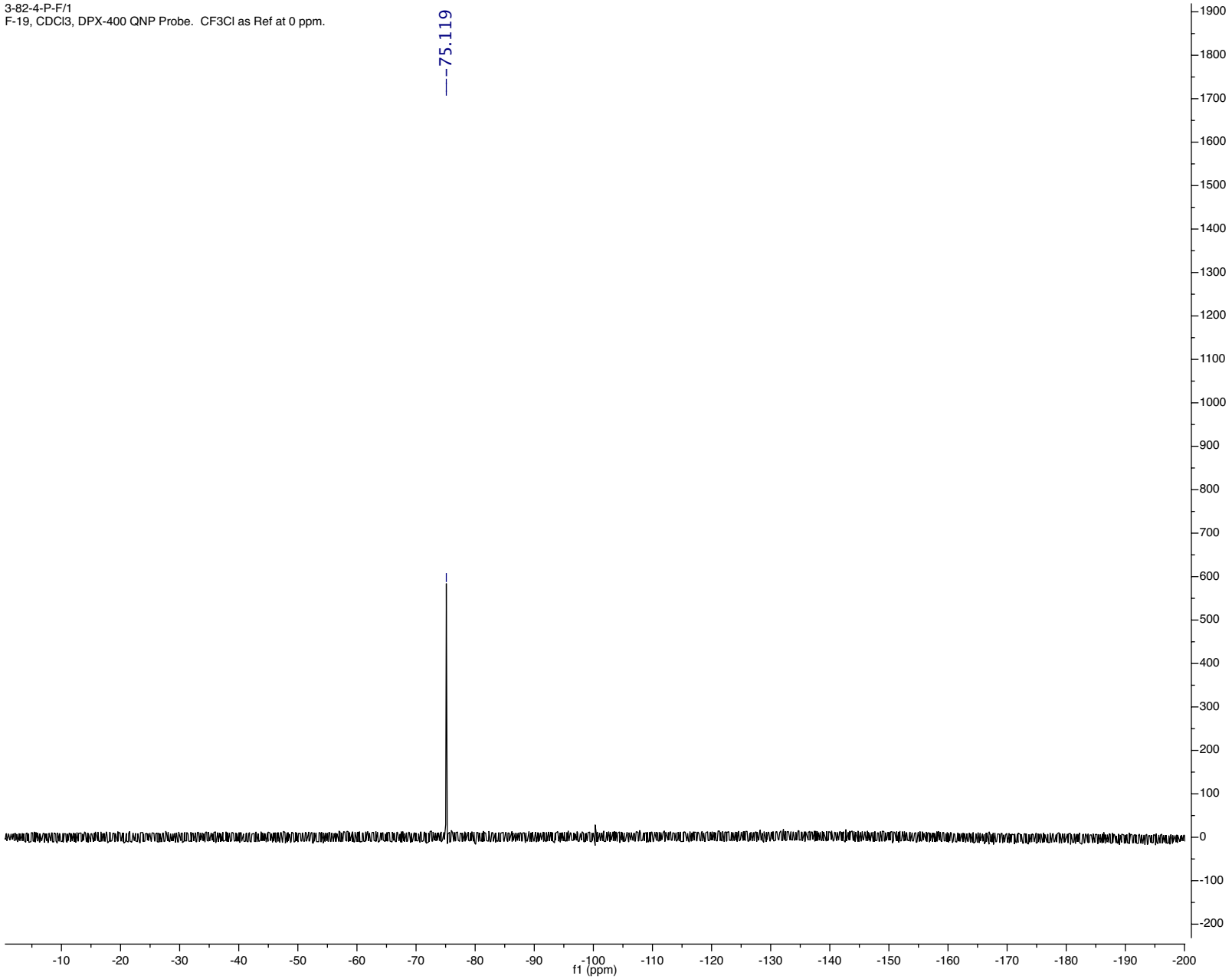

3-85-1-3-H/1
MeF2C
N
N
COOMe
27-C5
9.057
4.099
2.079
2.076
2.033
2.030
1.987
1.984
1.92
2.97
3.00
f1 (ppm)

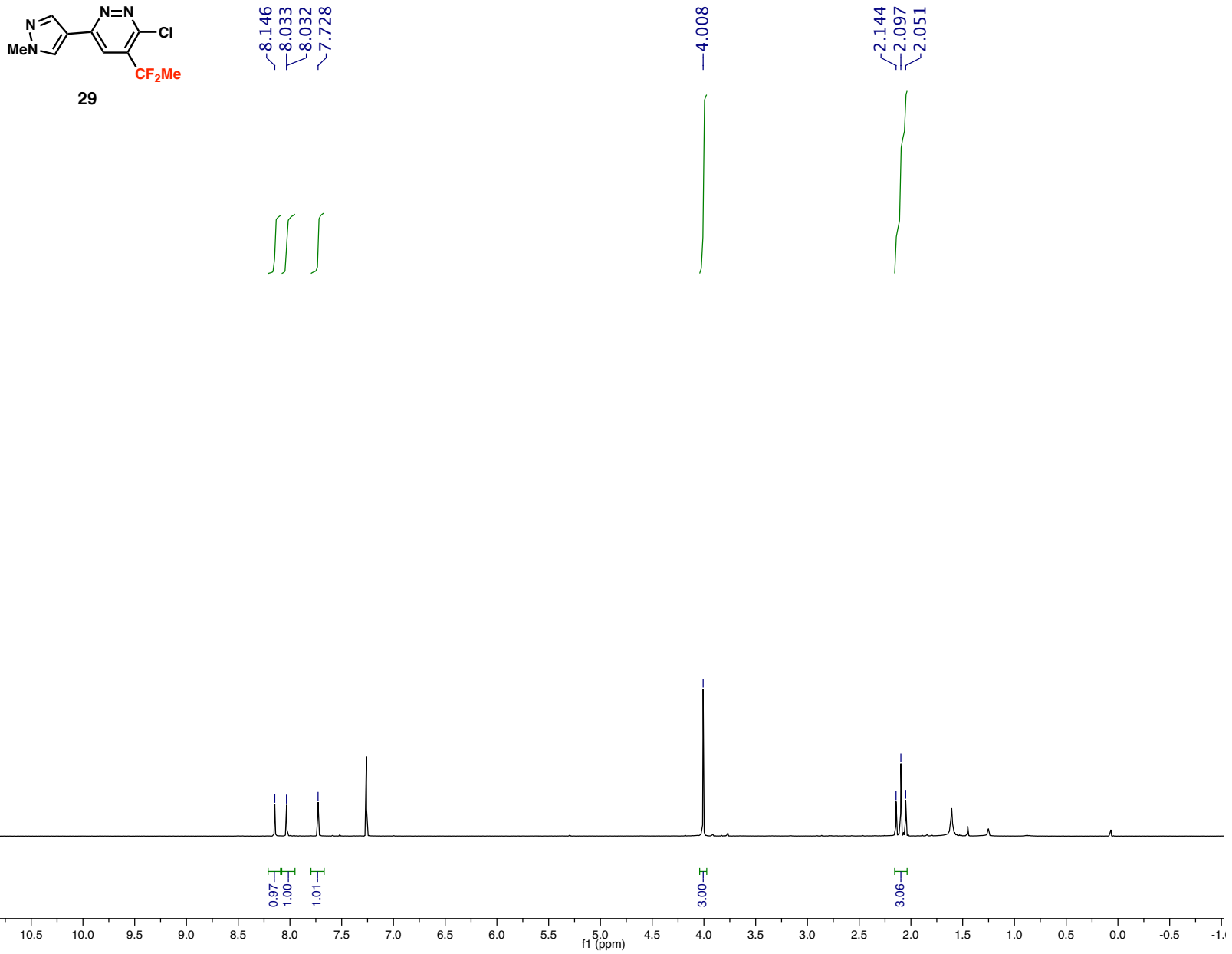

3-85-1-3-13C-re/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
163.249
157.402
154.927
133.579
133.417
133.236
121.286
119.693
118.098
53.998
26.076
25.889
25.700
f1 (ppm)

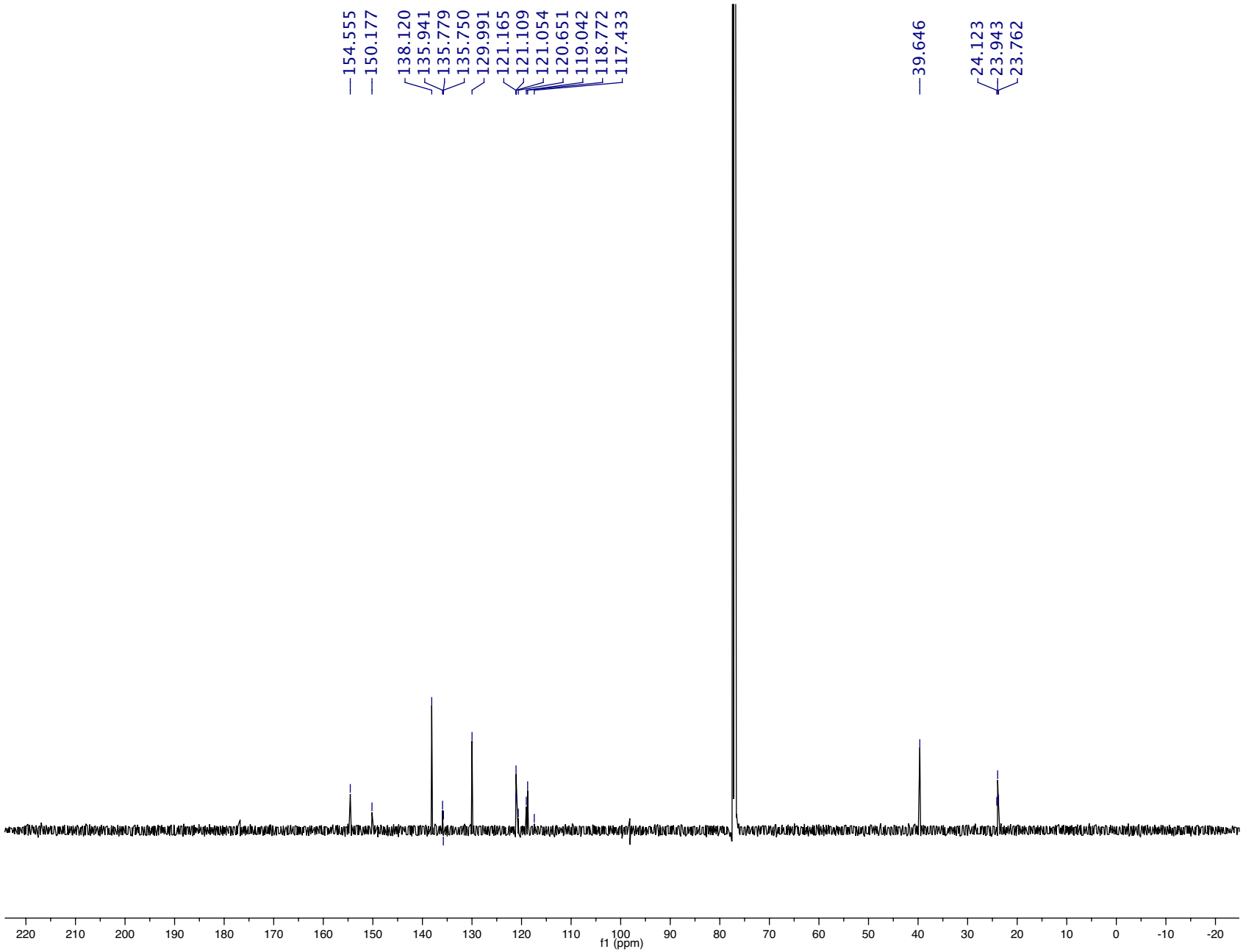

3-85-1-3-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-89.468
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-74
-76
-78
-80
-82
-84
-86
-88
-90
-92
-94
-96
-98
-100
-102
-104
-106
-108
-110
f1 (ppm)

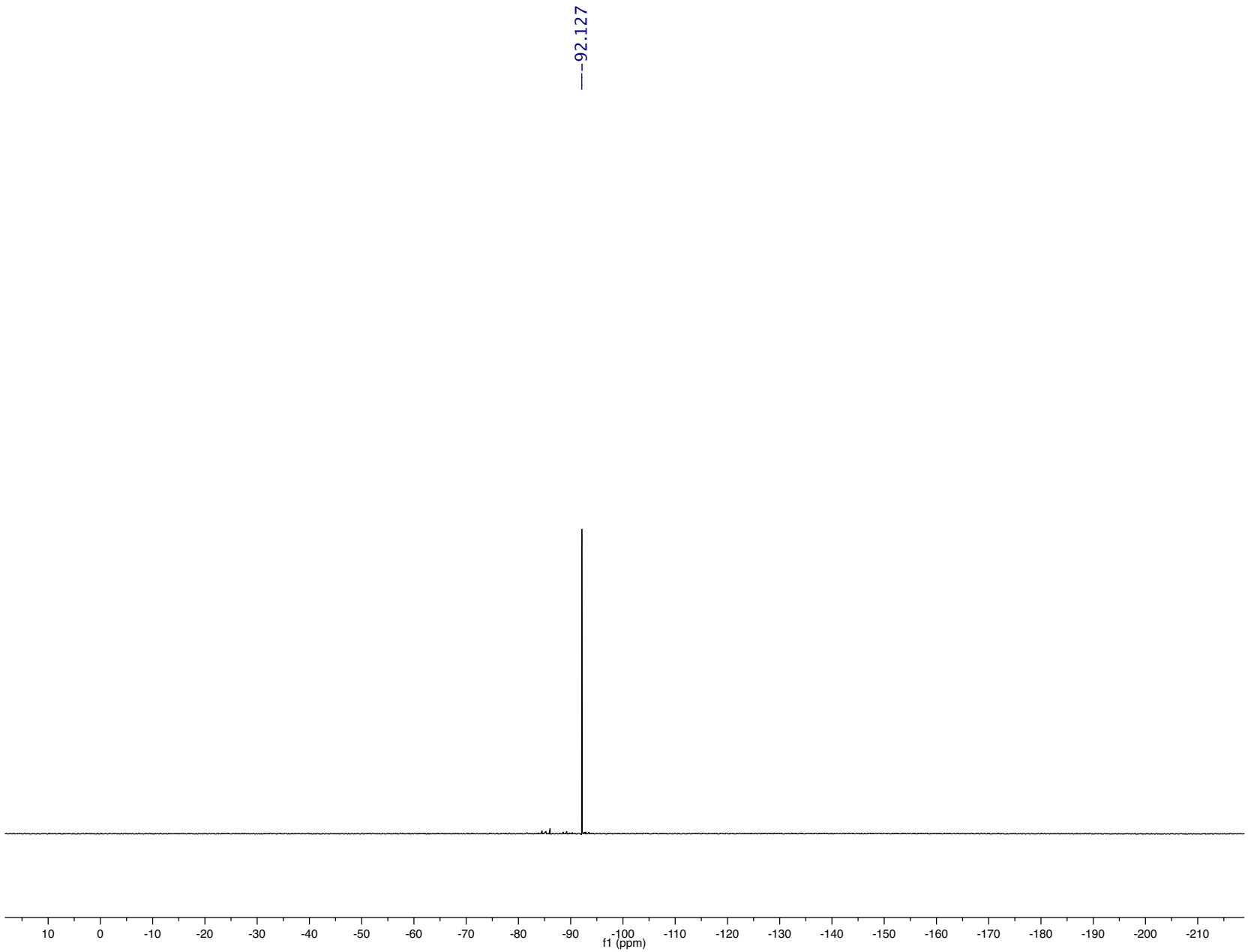

3-82-4-p/1
H-1 Routine 1D experiment, BBO Probe, 5/13/2007
8.465
8.463
8.462
8.222
8.220
8.218
8.217
8.200
8.198
8.196
8.253
7.803
7.800
7.787
7.784
7.781
7.778
7.765
7.762
7.610
7.607
7.594
7.591
7.587
7.584
7.571
7.568
2.438
2.393
2.347
CF2Me
N
28
f1 (ppm)


3-82-4-p-13C/1
C-13 Routine 1D, DCH CryoProbe 10-26-2006
149.831
139.718
139.502
139.406
131.430
130.410
127.698
126.812
126.075
126.011
125.945
125.191
123.576
123.561
28.526
28.345
28.164
f1 (ppm)

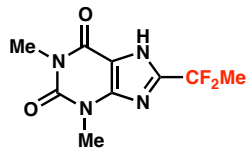

3-82-4-P-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-75.119
f1 (ppm)


N=N
N
MeN
Cl
CF2Me
29
8.146
8.033
8.032
7.728
4.008
2.144
2.097
2.051
0.97
1.00
1.01
3.00
3.06
10.5
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
-0.5
f1 (ppm)

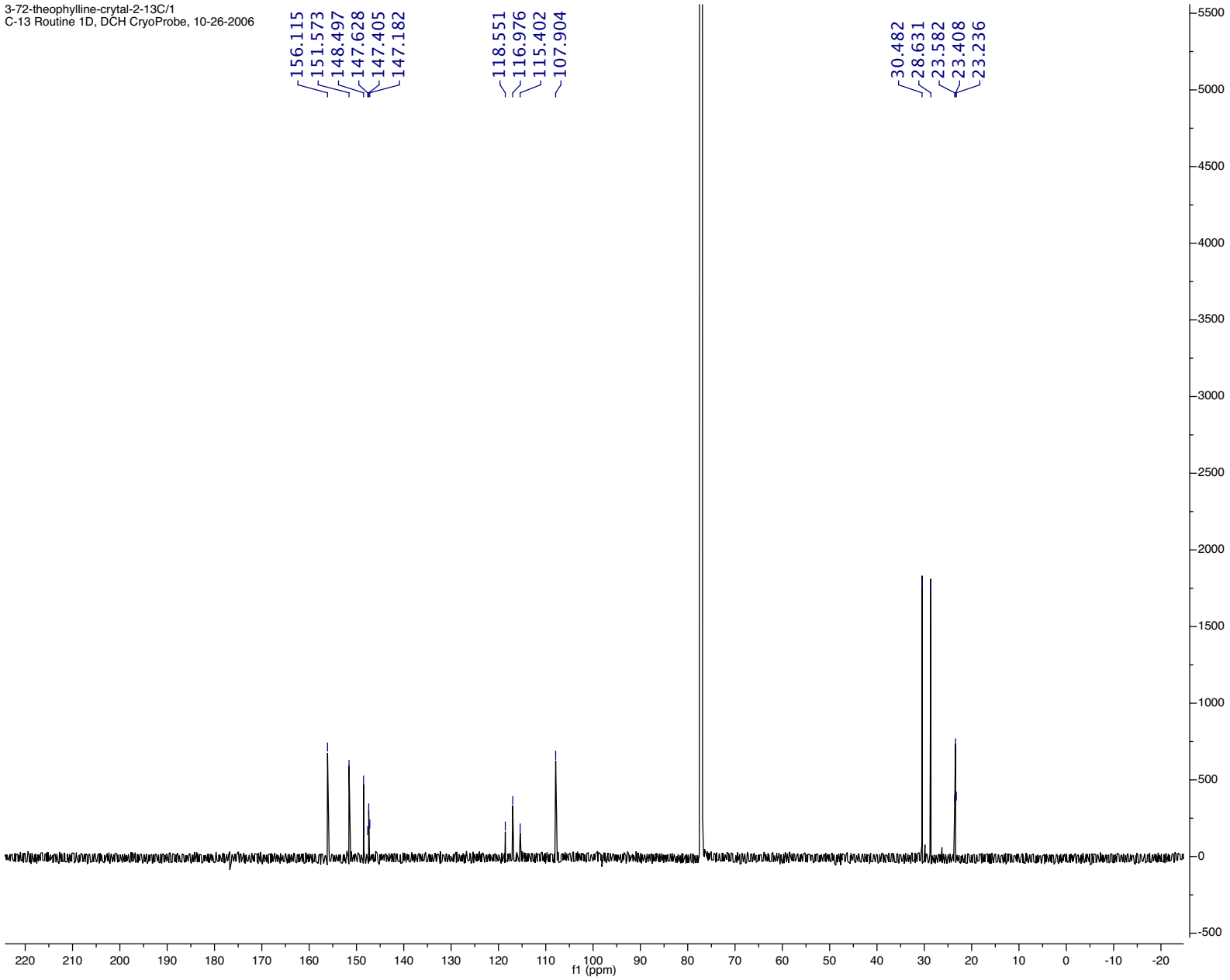

154.555
150.177
138.120
135.941
135.779
135.750
129.991
121.165
121.109
121.054
120.651
119.042
118.772
117.433
39.646
24.123
23.943
23.762
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

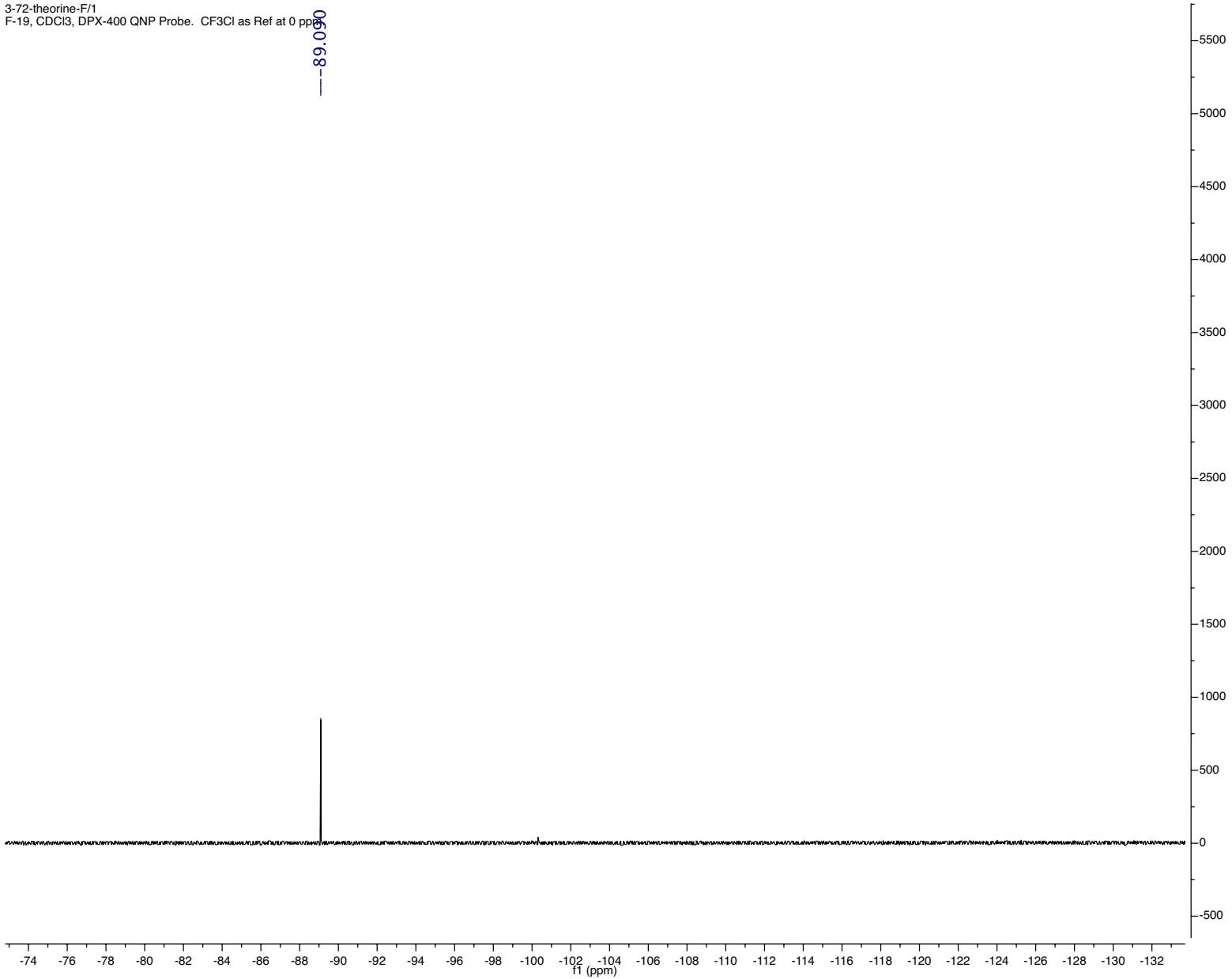

-92.127
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

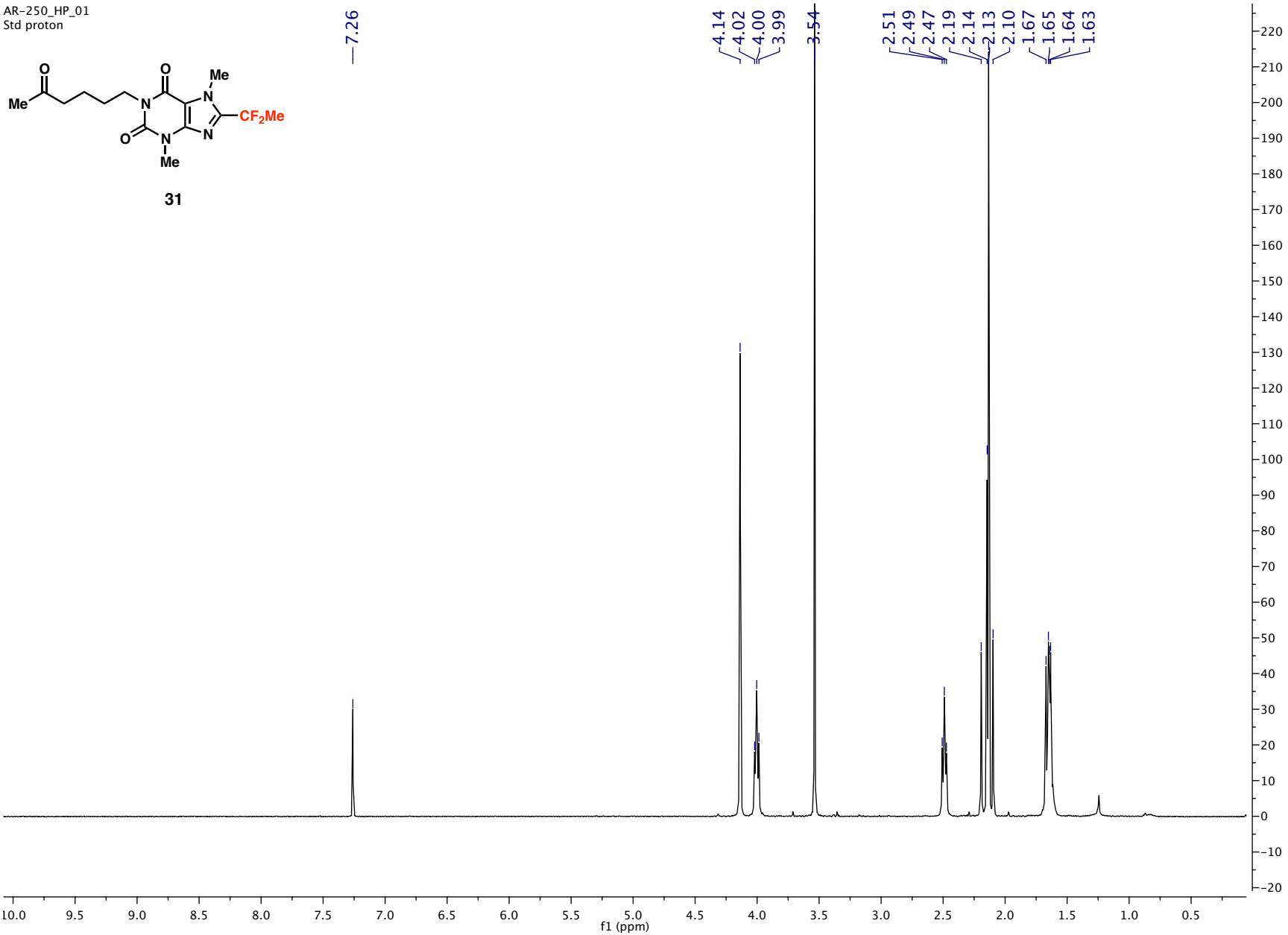
3-72-theoline-H-re_01
Std proton

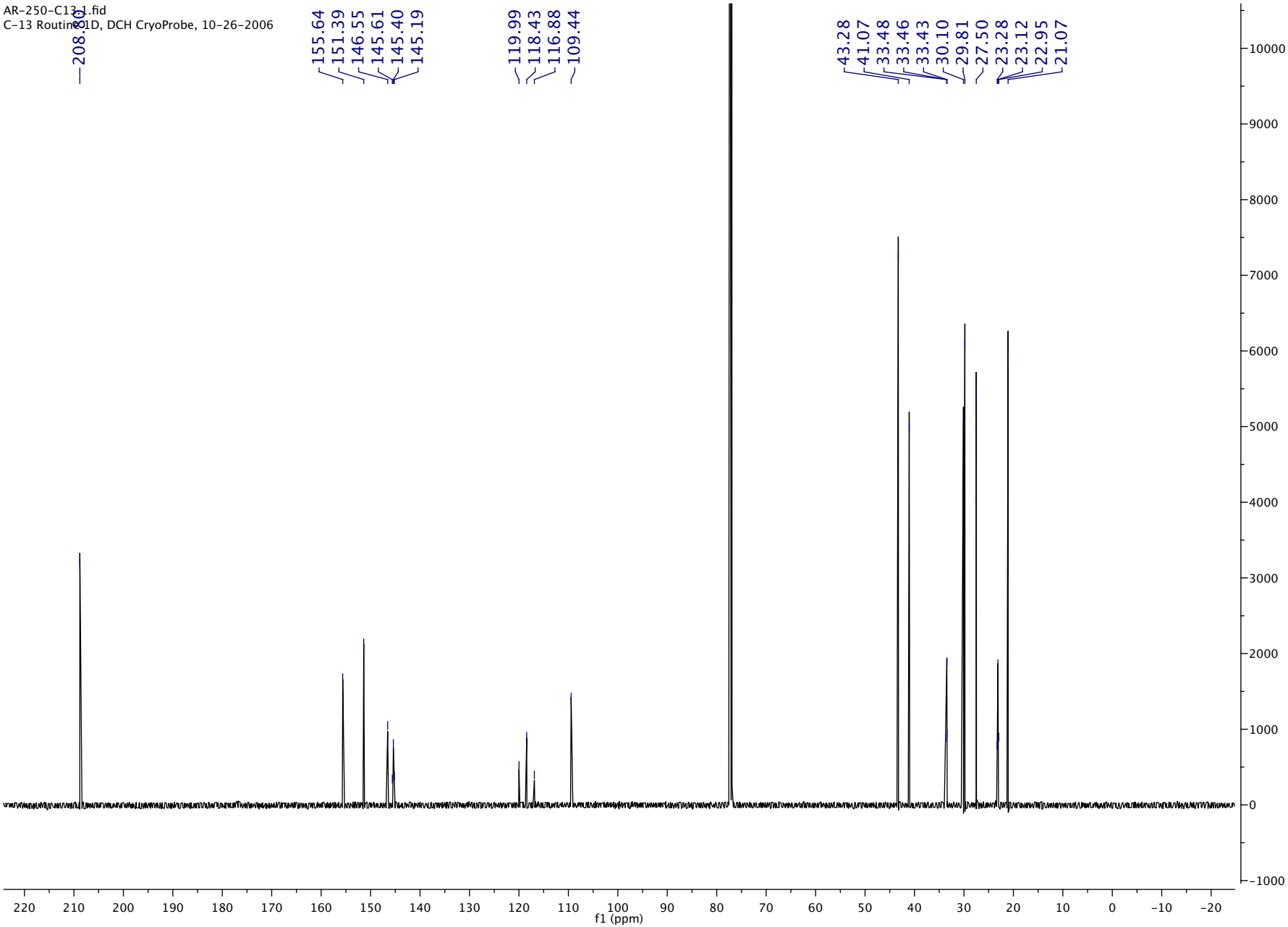


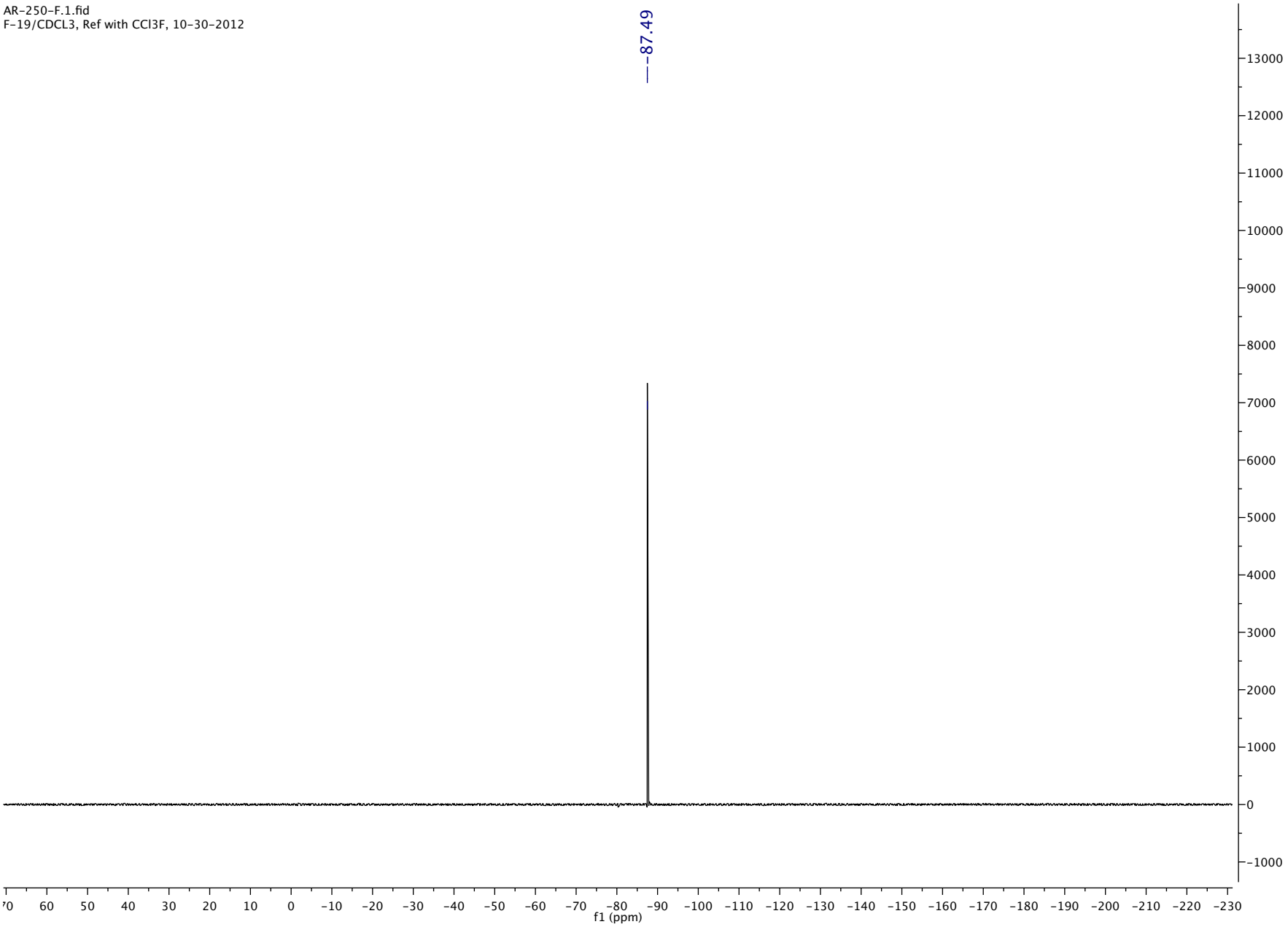
30

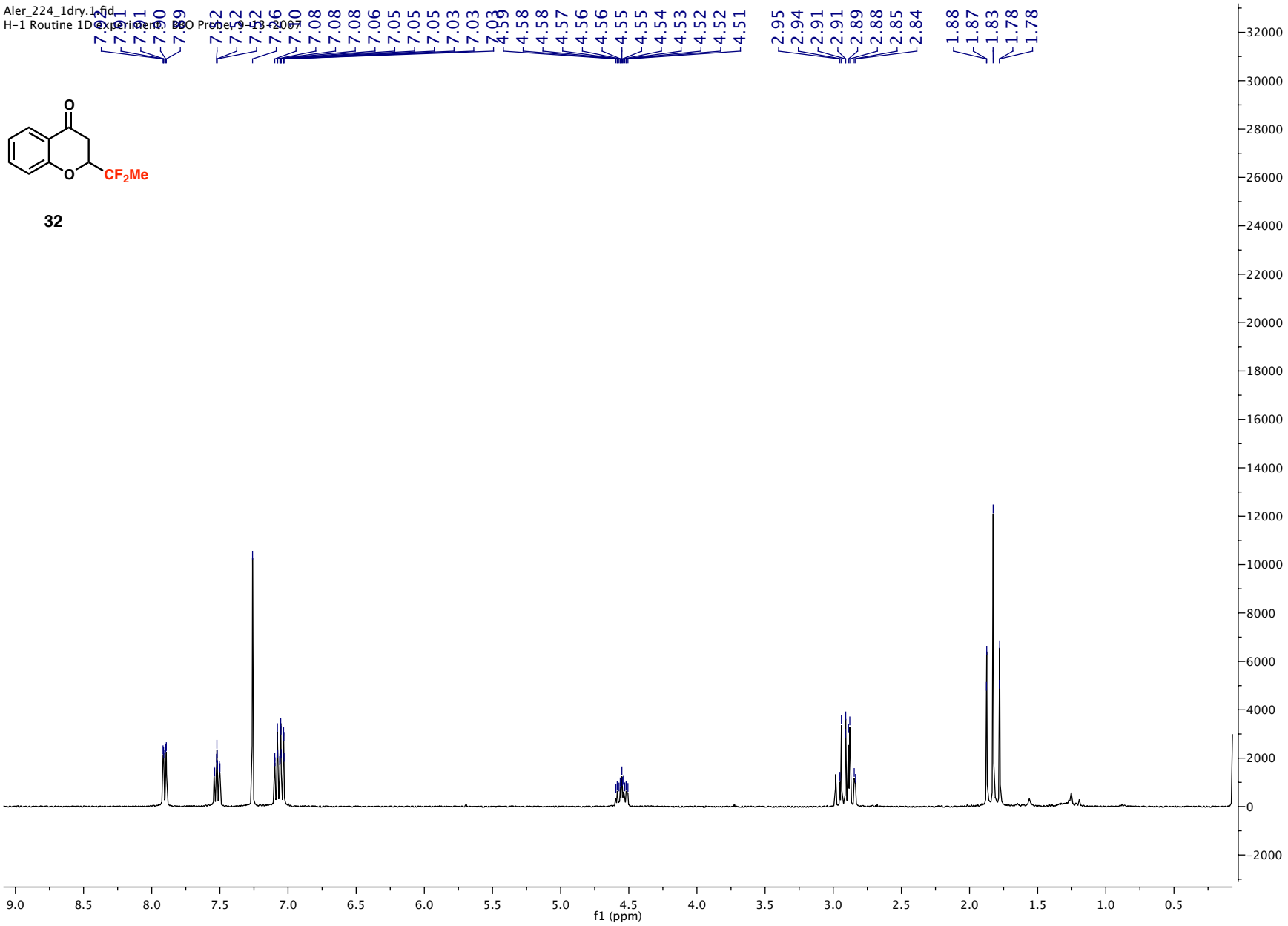

3-72-theophylline-crytal-2-13C/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
156.115
151.573
148.497
147.628
147.405
147.182
118.551
116.976
115.402
107.904
30.482
28.631
23.582
23.408
23.236
f1 (ppm)

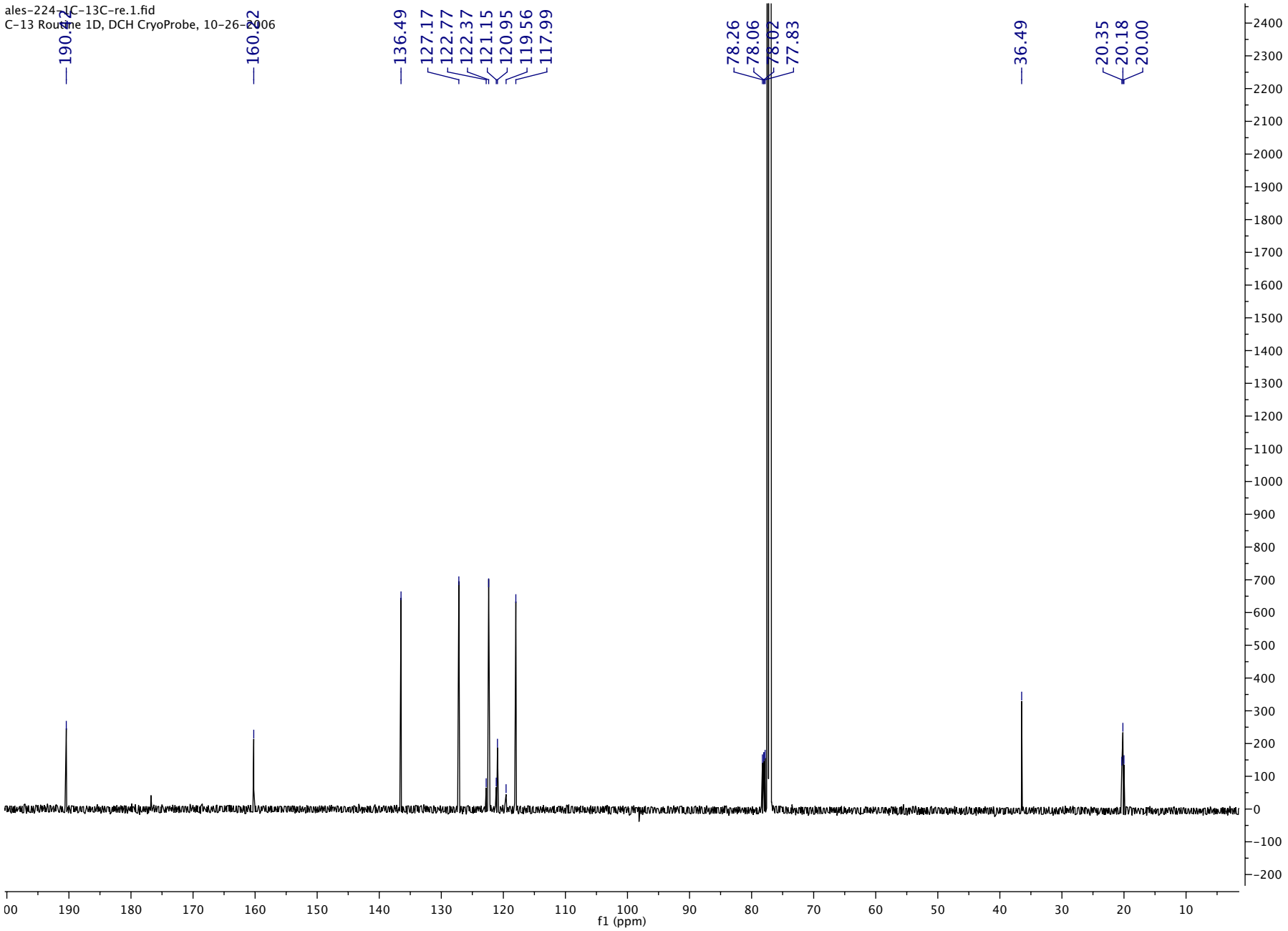

3-72-theorine-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm
-89.090
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-74 -76 -78 -80 -82 -84 -86 -88 -90 -92 -94 -96 -98 -100 -102 -104 -106 -108 -110 -112 -114 -116 -118 -120 -122 -124 -126 -128 -130 -132
f1 (ppm)

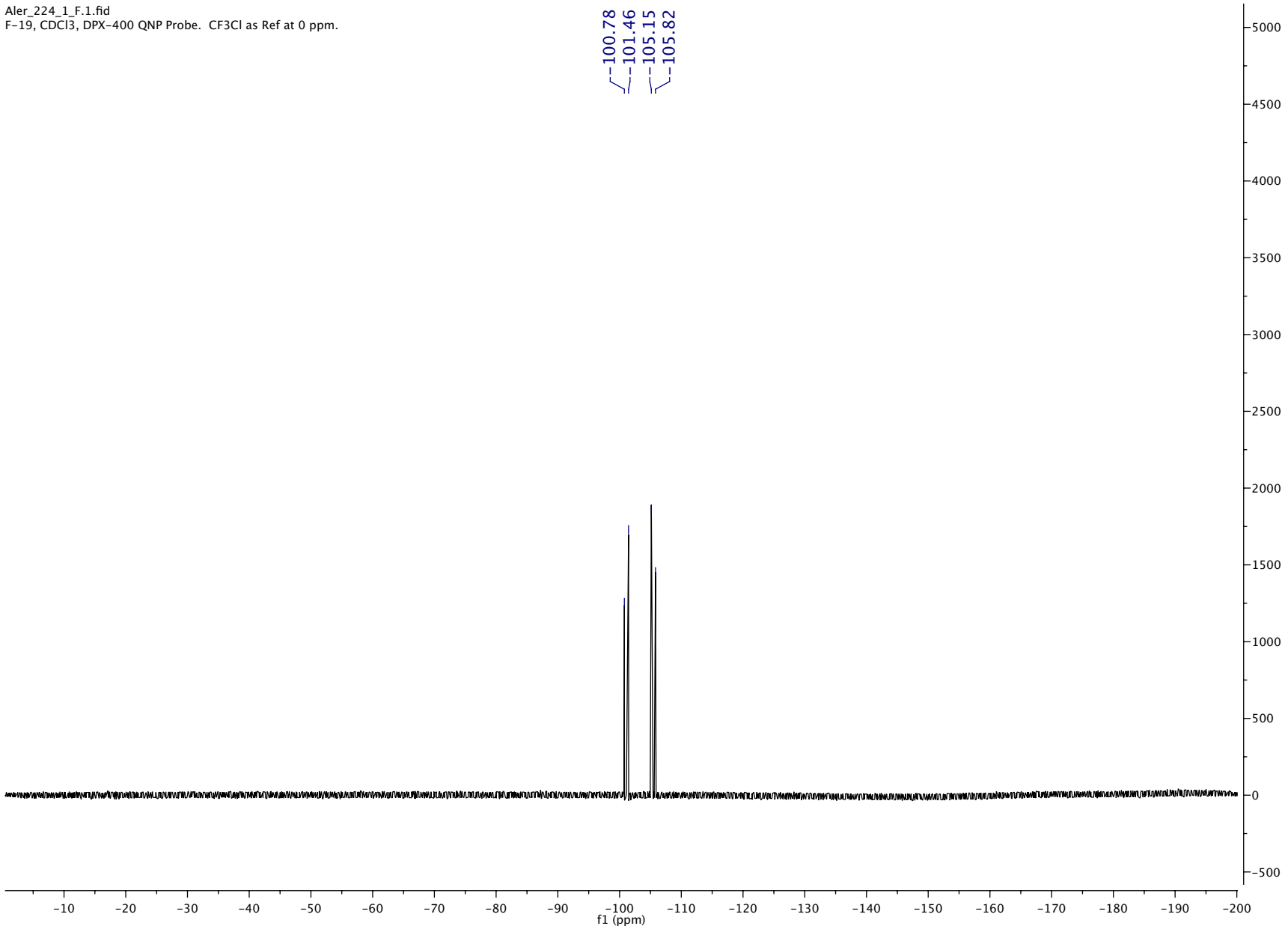

AR-250_HP_01
Std proton
Me
O
O
N
N
Me
N
N
O
N
Me
CF2Me
31
7.26
4.14
4.02
4.00
3.99
3.54
2.51
2.49
2.47
2.19
2.14
2.13
2.10
1.67
1.65
1.64
1.63
f1 (ppm)

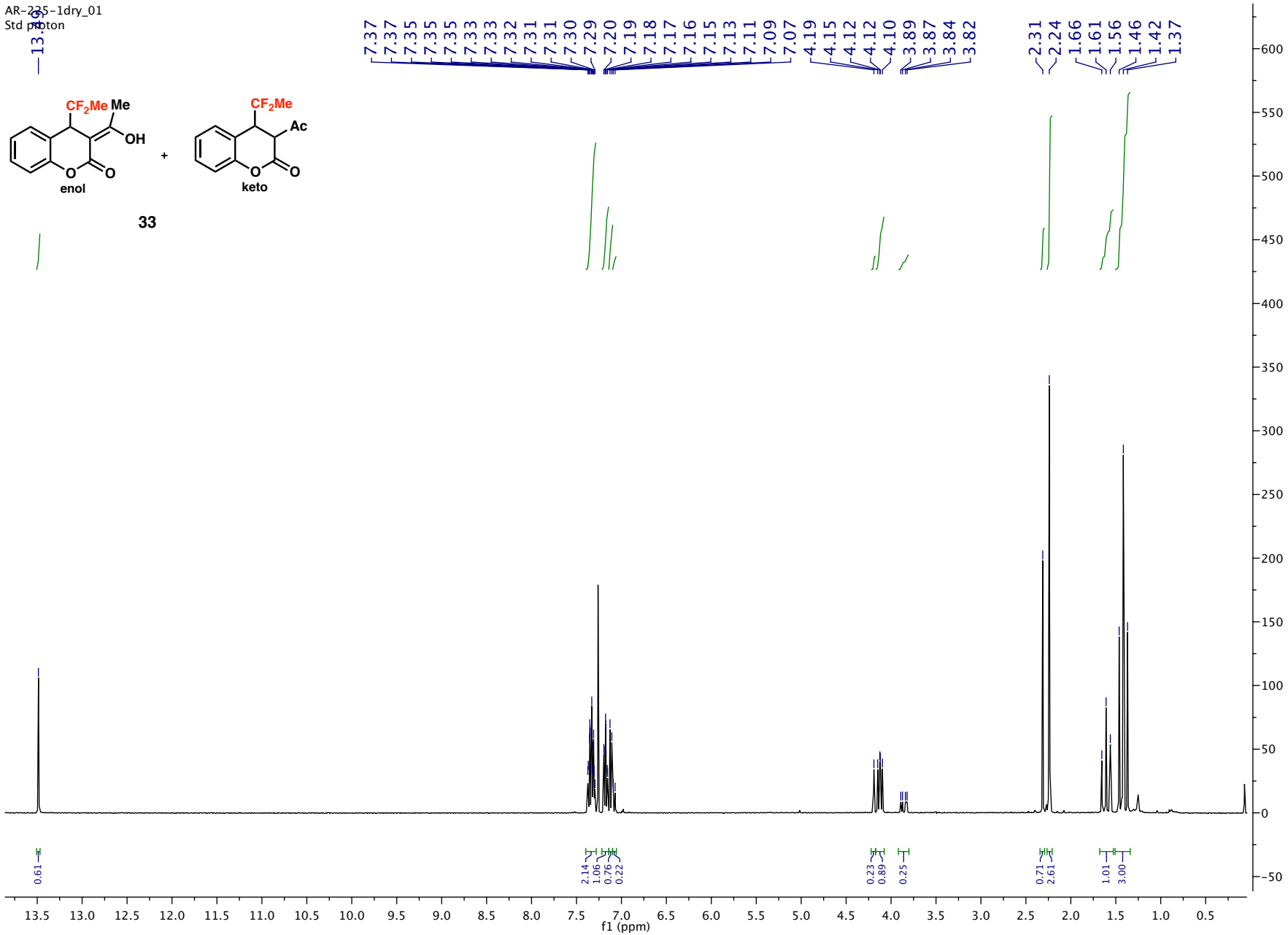

AR-250-C13-1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
208.80
155.64
151.39
146.55
145.61
145.40
145.19
119.99
118.43
116.88
109.44
43.28
41.07
33.48
33.46
33.43
30.10
29.81
27.50
23.28
23.12
22.95
21.07
f1 (ppm)

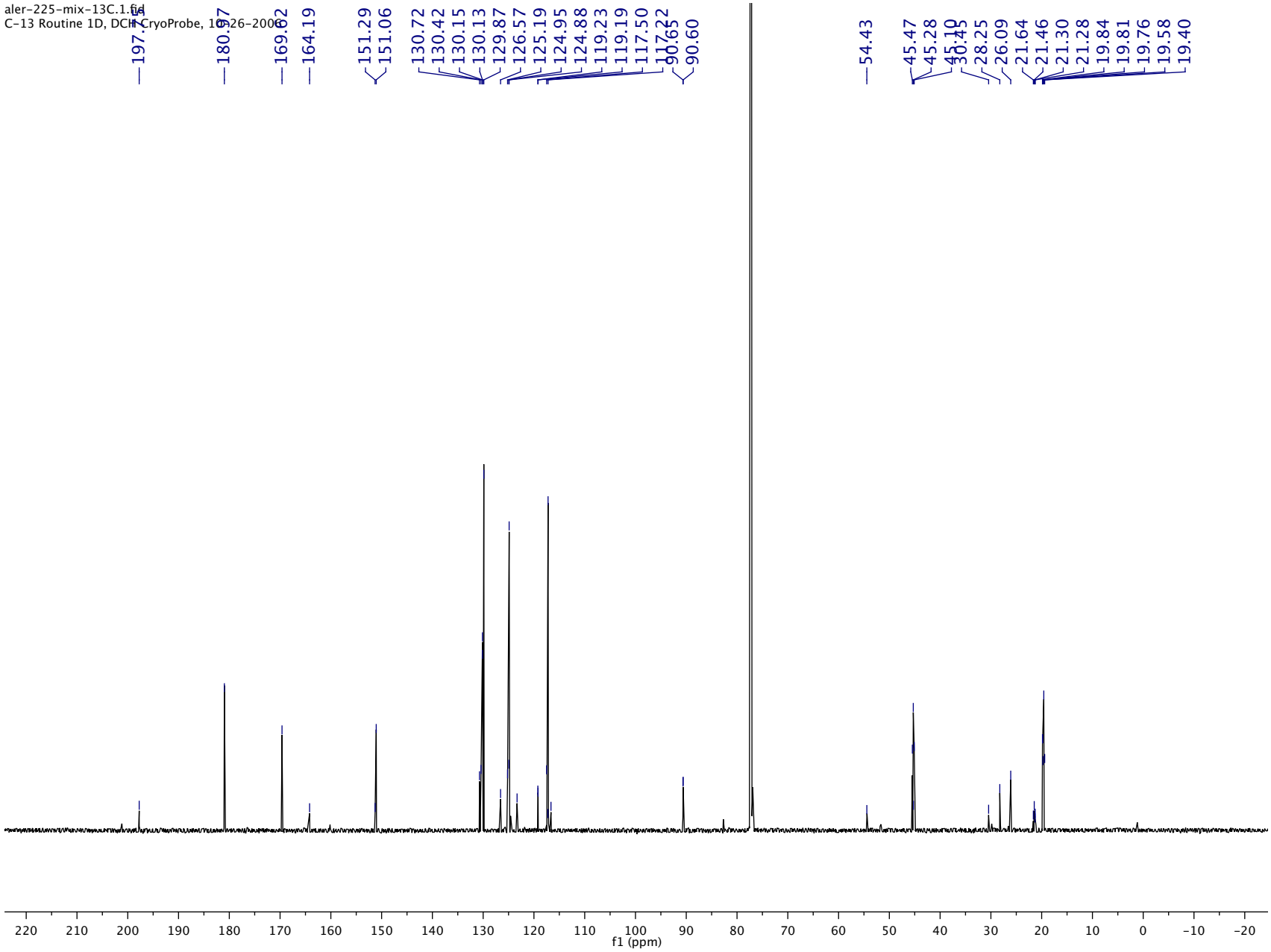

AR-250-F.1.fid
F-19/CDCL3, Ref with CCl3F, 10-30-2012
-87.49
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

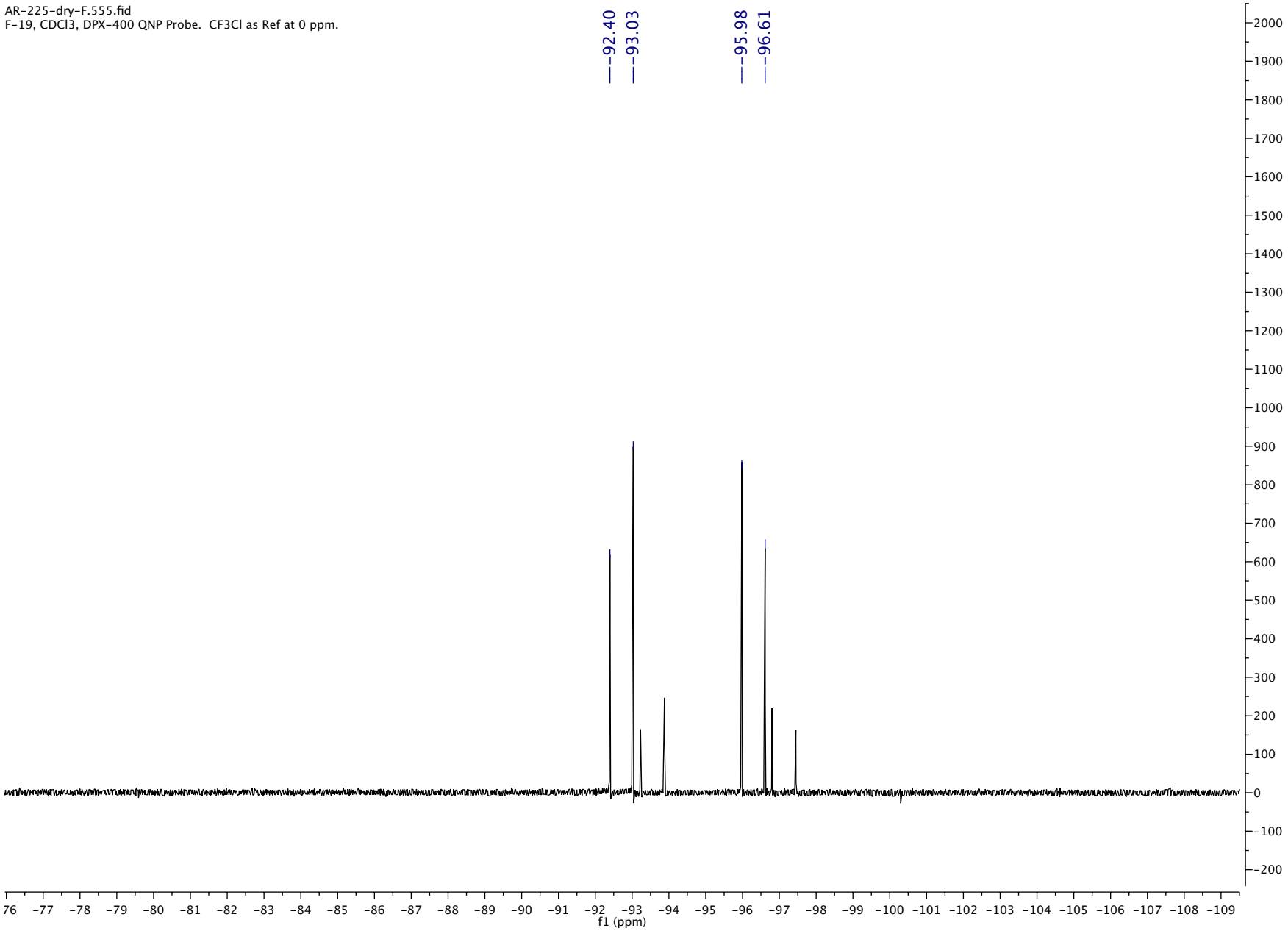

Aler_224_1dry.1.fid
H-1 Routine 1D Experiment, BBO Probe, 9-13-2007
7.31 7.31 7.31 7.30 7.29 7.22 7.22 7.22 7.16 7.10 7.08 7.08 7.08 7.06 7.05 7.05 7.03 7.03 7.03 4.59 4.58 4.58 4.57 4.56 4.56 4.55 4.55 4.54 4.53 4.52 4.52 4.51 2.95 2.94 2.91 2.91 2.89 2.88 2.85 2.84 1.88 1.87 1.83 1.78 1.78
O
O
CF2Me
32
f1 (ppm)

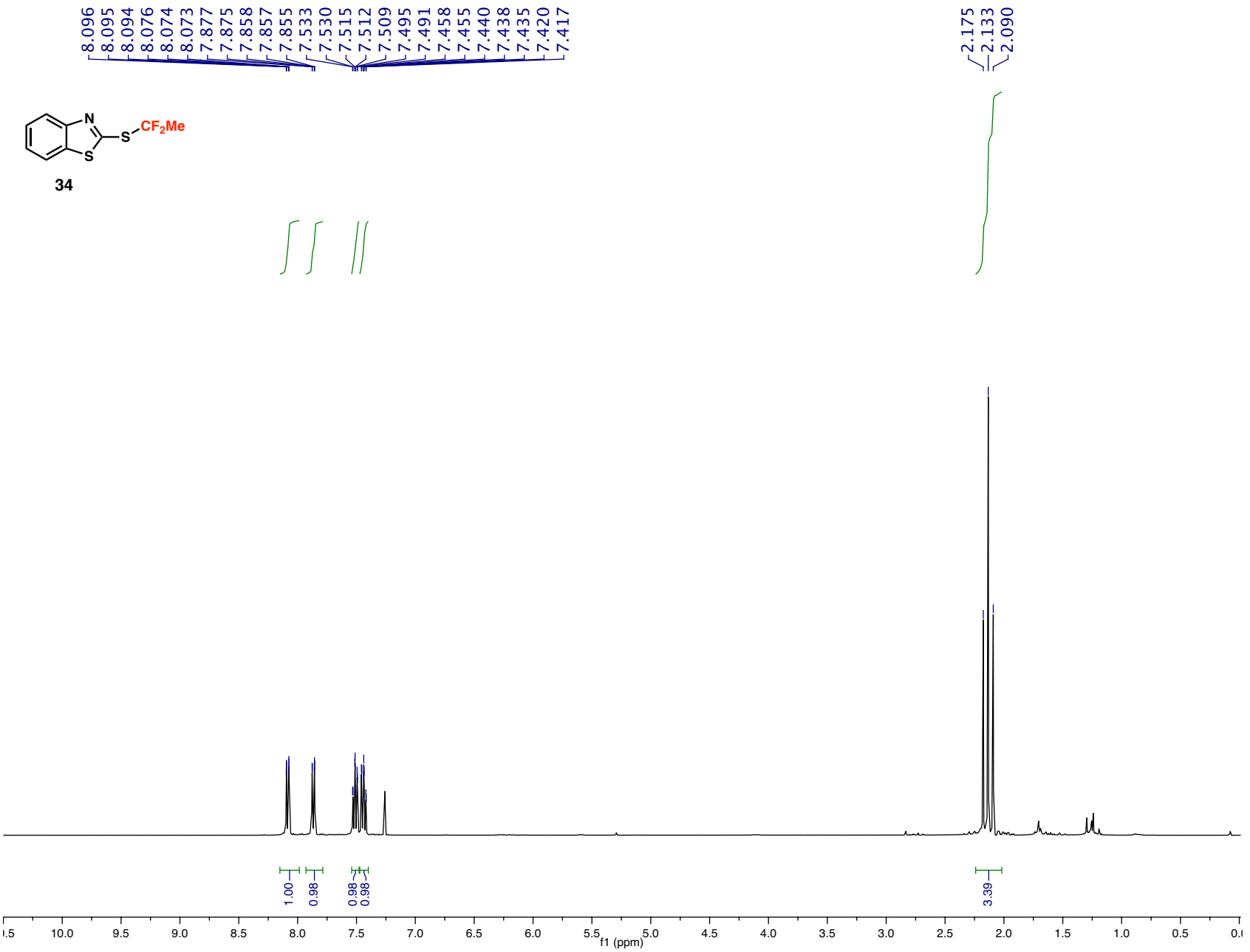

ales-224-1C-13C-re.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
190.74
160.22
136.49
127.17
122.77
122.37
121.15
120.95
119.56
117.99
78.26
78.06
78.02
77.83
36.49
20.35
20.18
20.00
f1 (ppm)

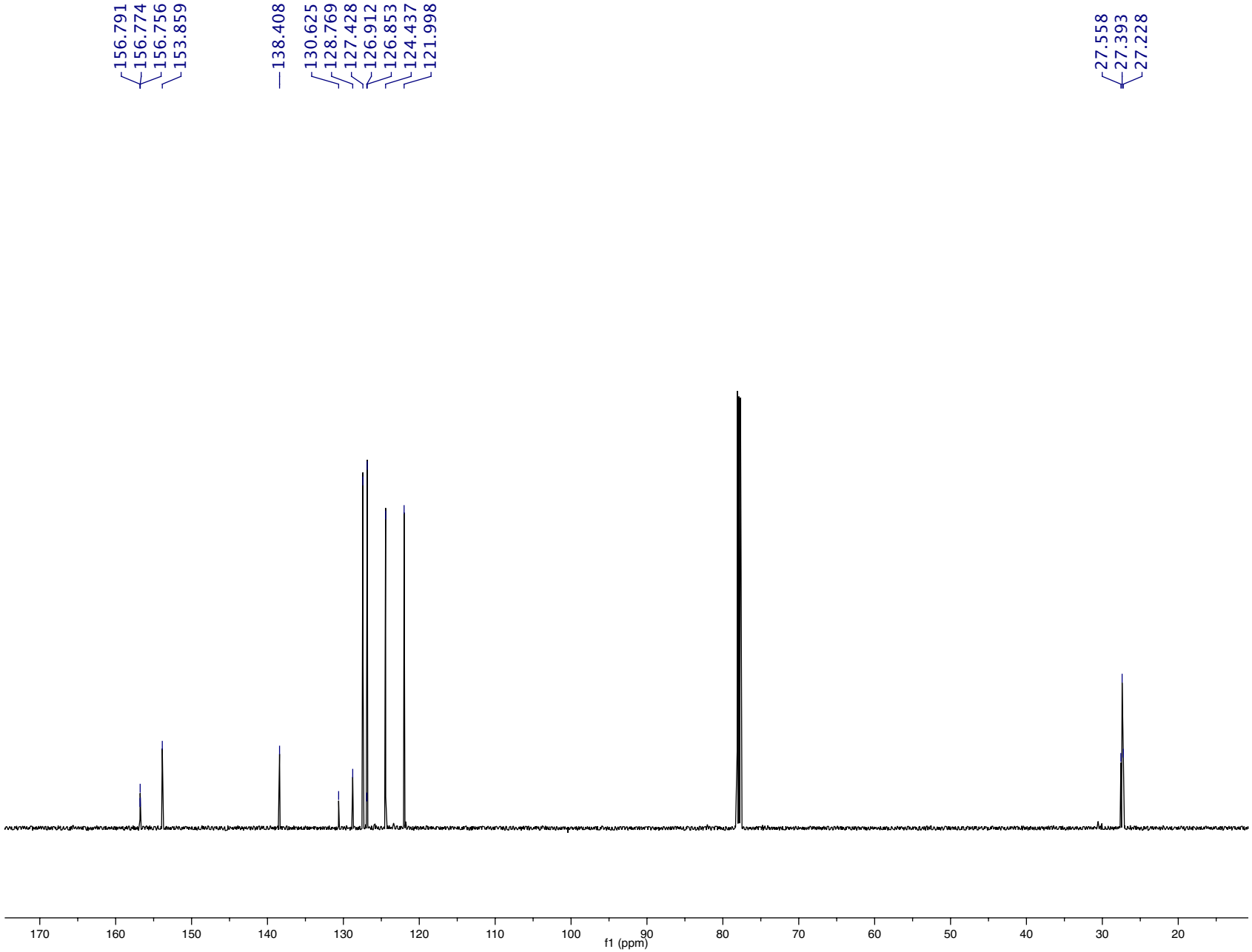

Aler_224_1_F.1.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-100.78
-101.46
-105.15
-105.82
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

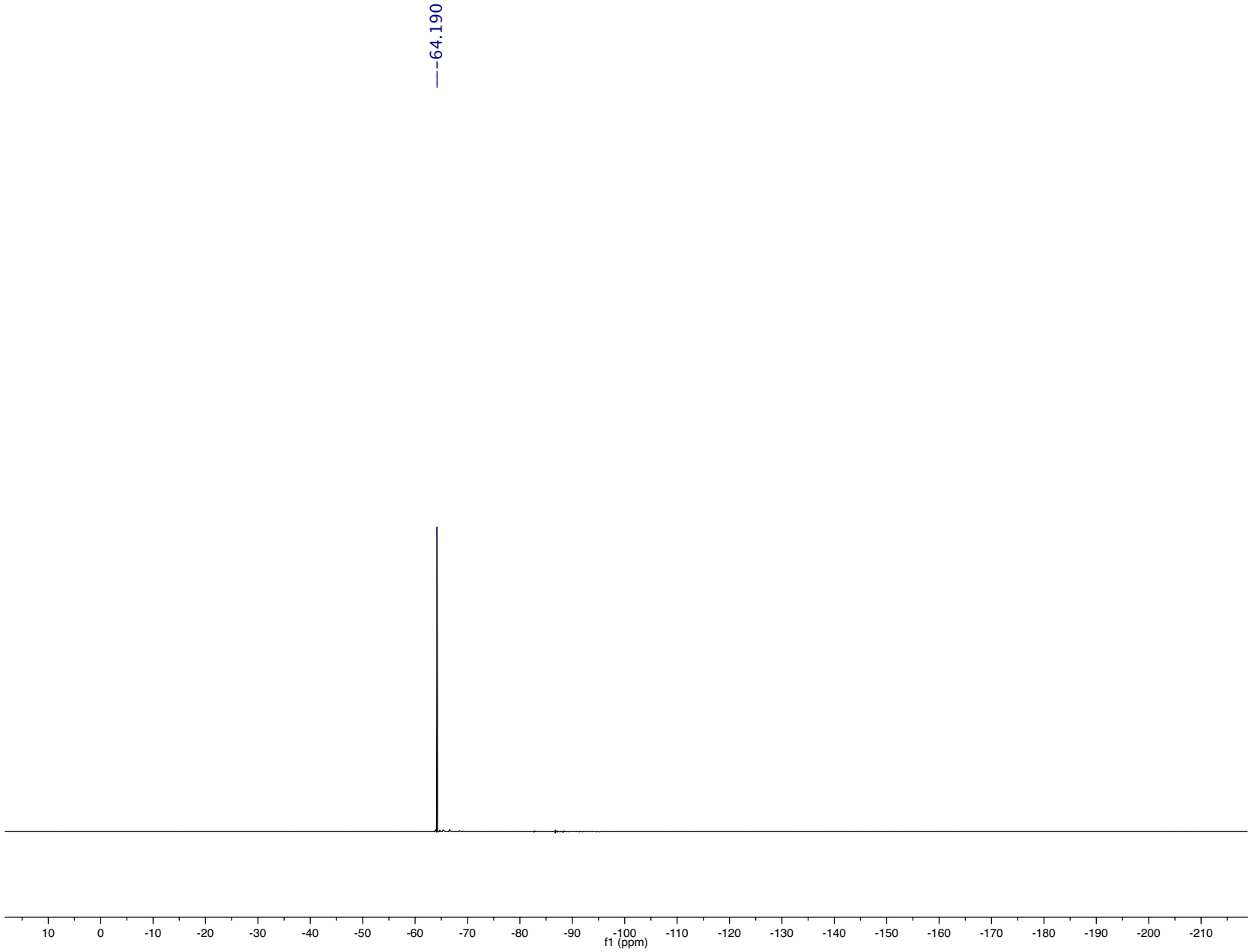

AR-225-1dry_01
Std proton
13.47
7.37 7.37 7.35 7.35 7.35 7.33 7.33 7.32 7.31 7.31 7.30 7.29 7.20 7.19 7.18 7.17 7.16 7.15 7.13 7.11 7.09 7.07
4.19 4.15 4.12 4.12 4.10
3.89 3.87 3.84 3.82
2.31 2.24
1.66 1.61 1.56 1.46 1.42 1.37
CF2Me Me
OH
O O
enol
+
CF2Me
Ac
O O
keto
33
0.61
2.14 1.06 0.76 0.22
0.23 0.89 0.25
0.71 2.61
1.01 3.00
f1 (ppm)


aler-225-mix-13C.1.fid
C-13 Routine 1D, DCM CryoProbe, 10-26-2006
197.76
180.97
169.62
164.19
151.29
151.06
130.72
130.42
130.15
130.13
129.87
126.57
125.19
124.95
124.88
119.23
119.19
117.50
117.22
90.65
90.60
54.43
45.47
45.28
45.10
30.45
28.25
26.09
21.64
21.46
21.30
21.28
19.84
19.81
19.76
19.58
19.40
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


AR-225-dry-F.555.fid
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-92.40
-93.03
-95.98
-96.61
f1 (ppm)


8.096
8.095
8.094
8.076
8.074
8.073
7.877
7.875
7.858
7.857
7.855
7.533
7.530
7.515
7.512
7.509
7.495
7.491
7.458
7.455
7.440
7.438
7.435
7.420
7.417
2.175
2.133
2.090
N
S
S
CF2Me
34
1.00
0.98
0.98
0.98
3.39
f1 (ppm)

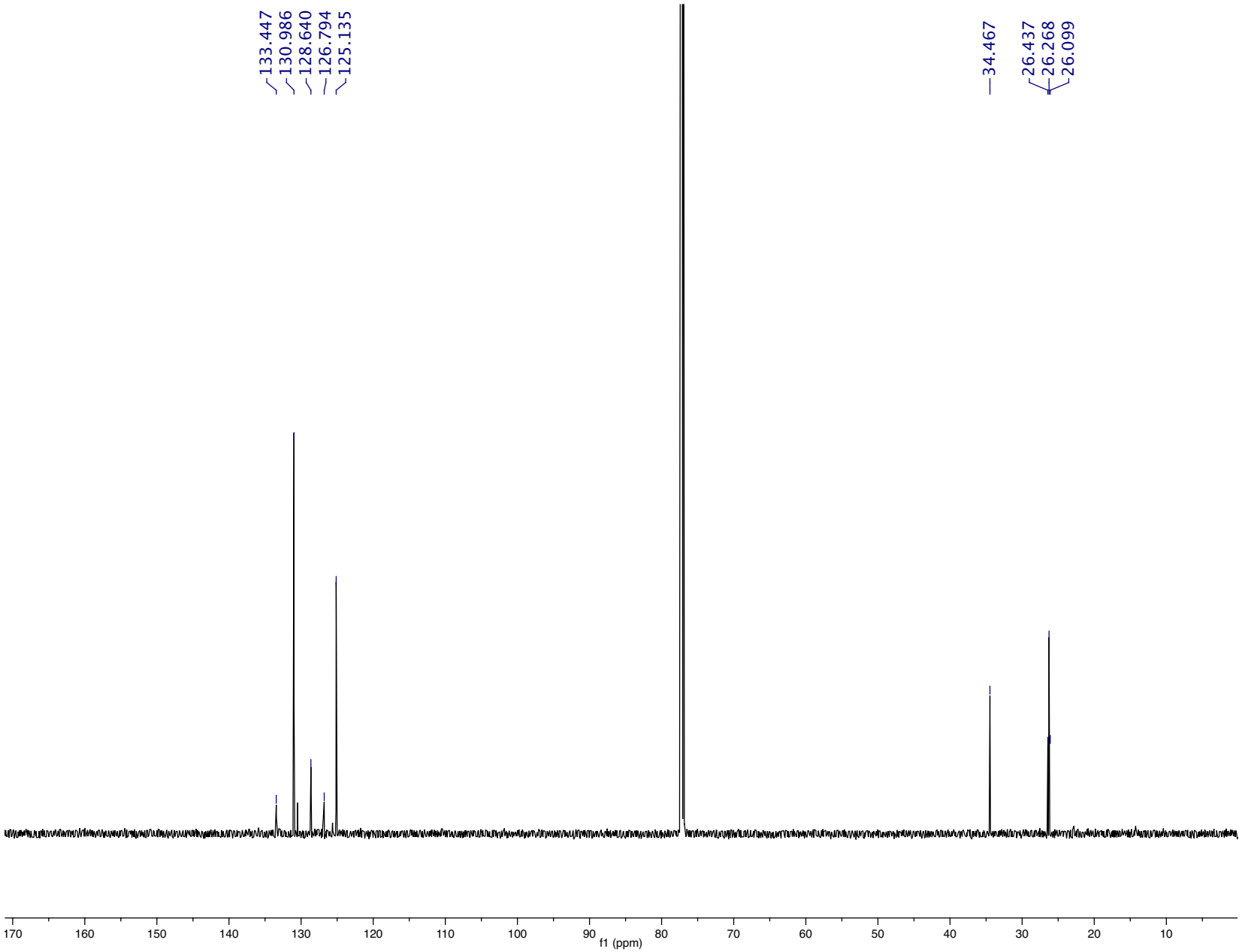

156.791
156.774
156.756
153.859
138.408
130.625
128.769
127.428
126.912
126.853
124.437
121.998
27.558
27.393
27.228
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

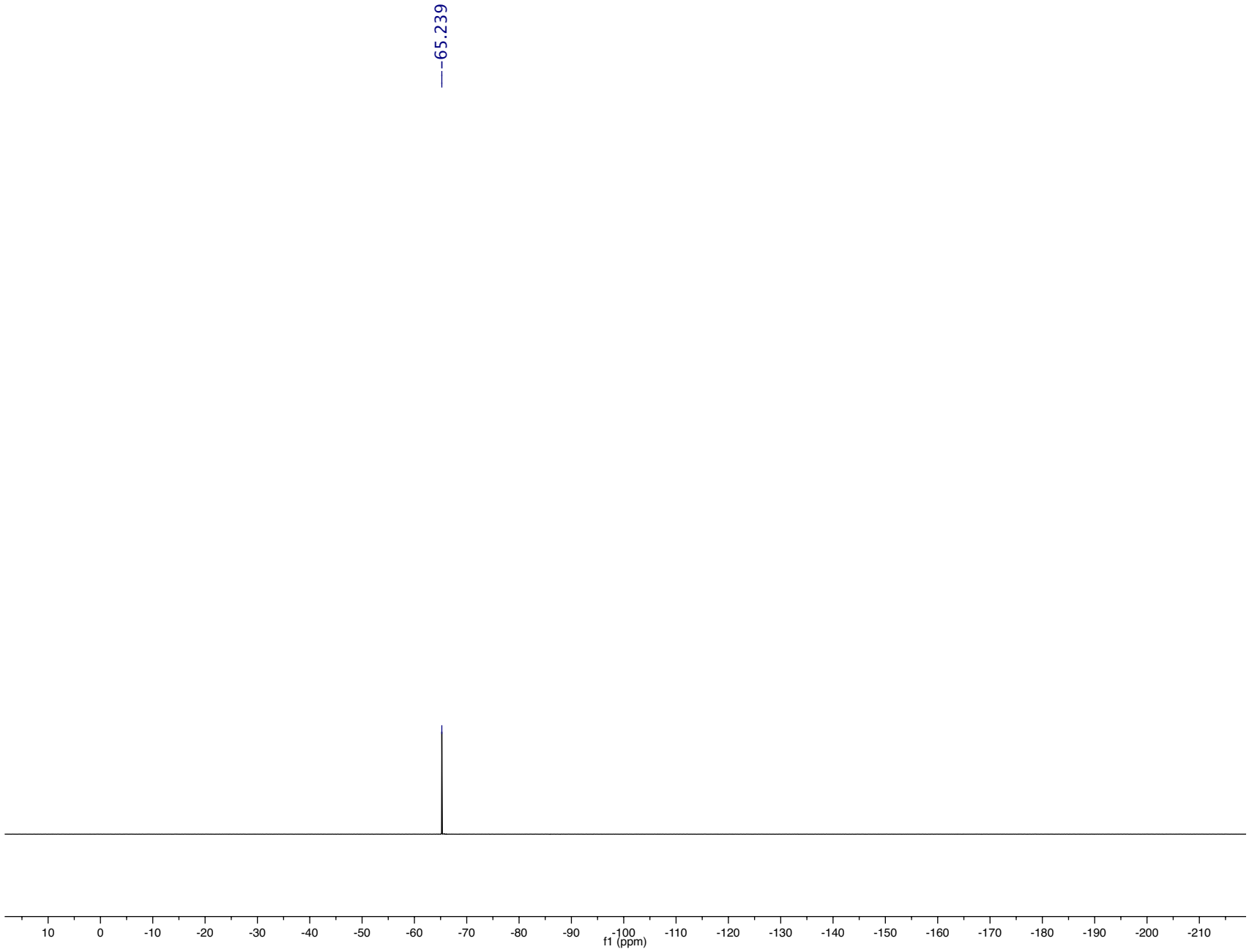

-64.190
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

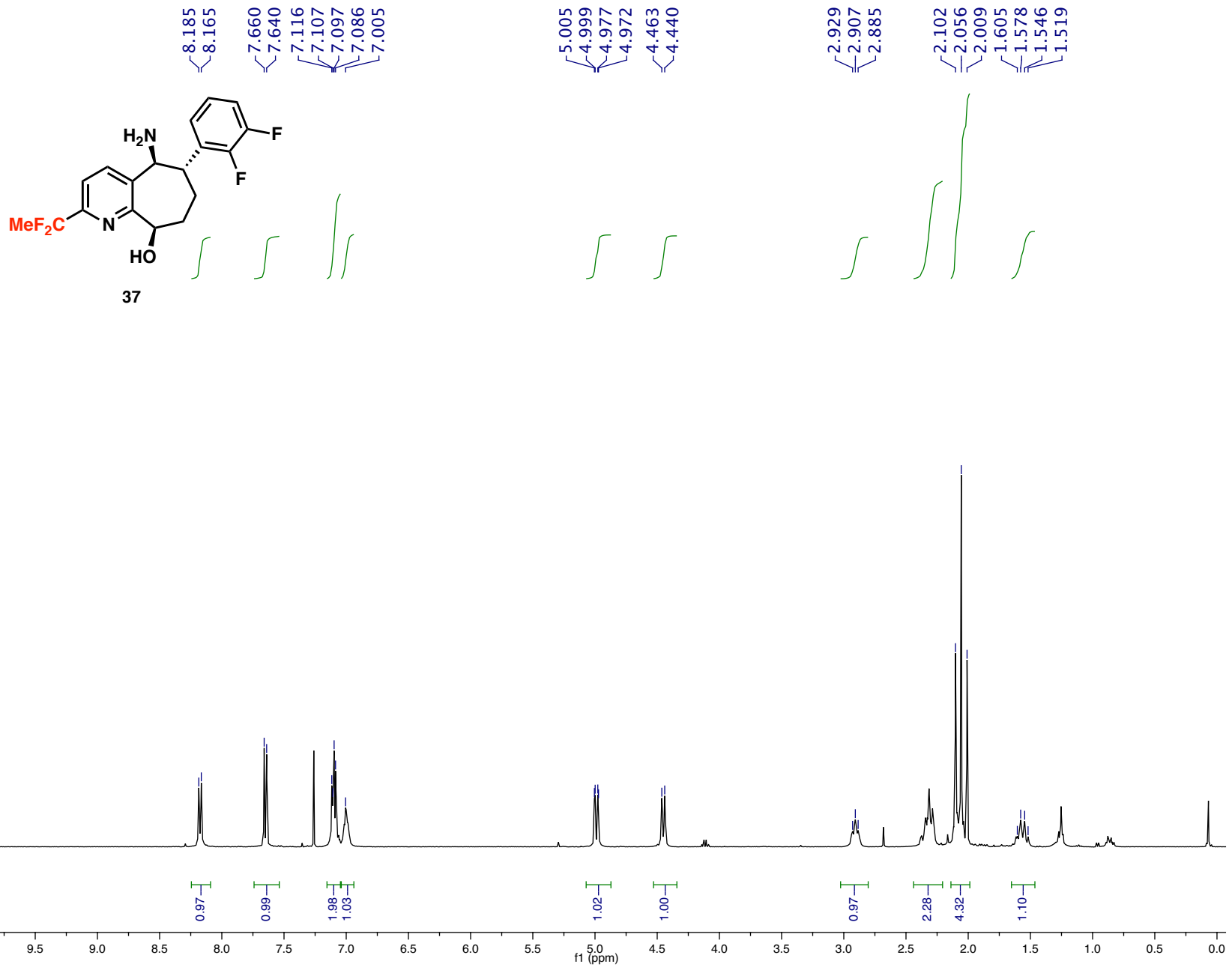

N
S
CF2Me
N
Me

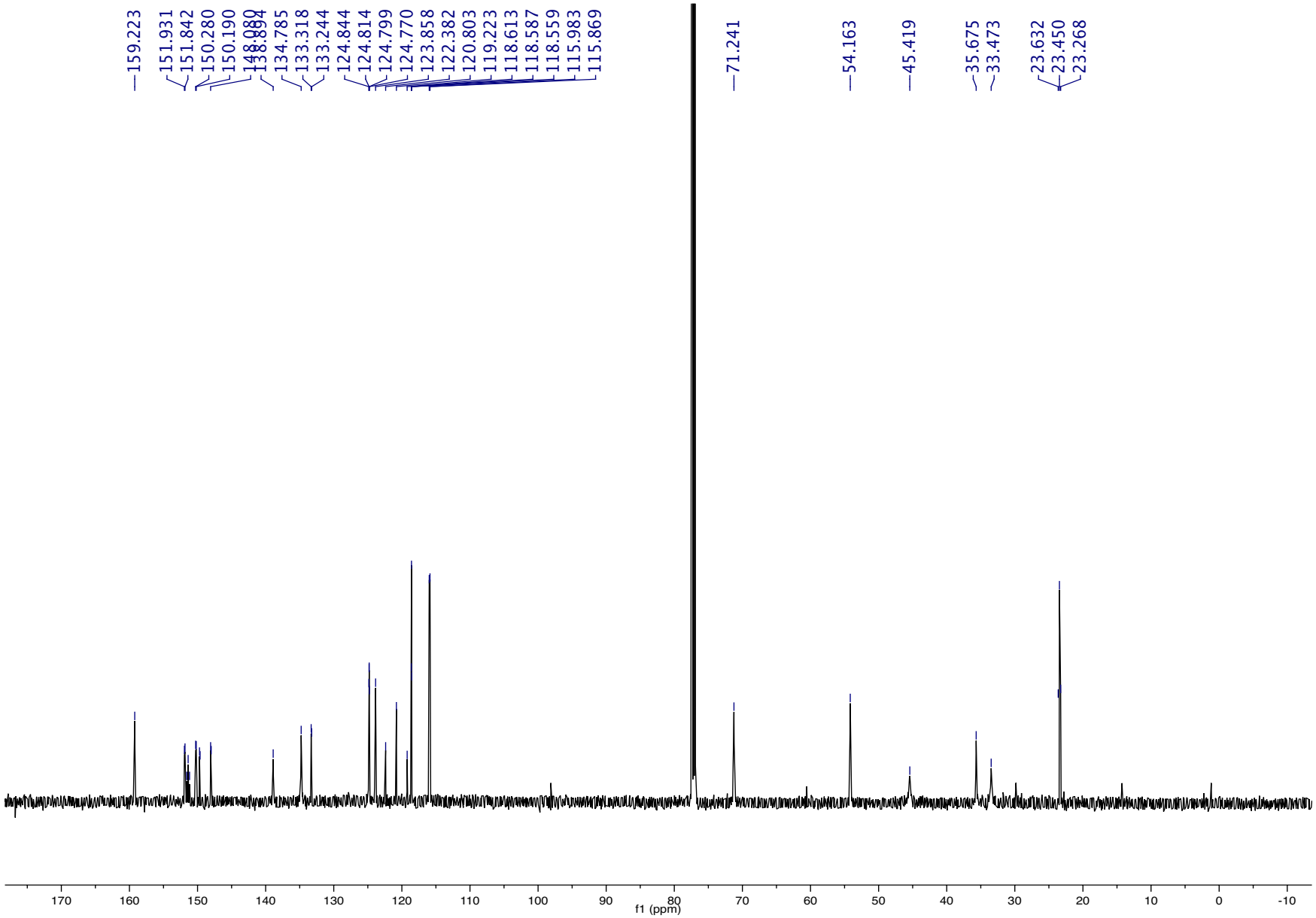
35

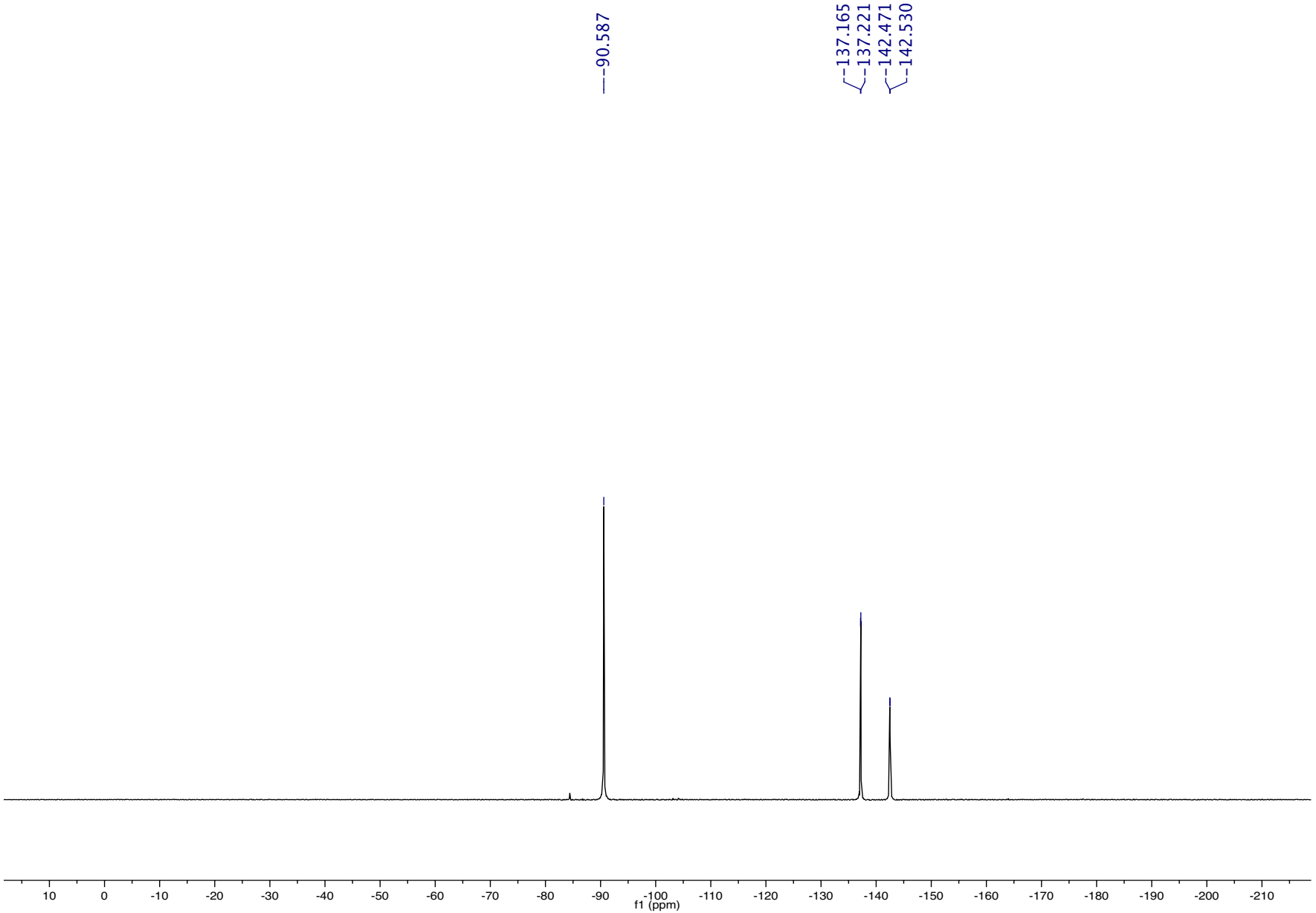
7.206
7.204
7.125
7.123
1.994
1.951
1.908
0.94
0.89
3.00
3.27
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

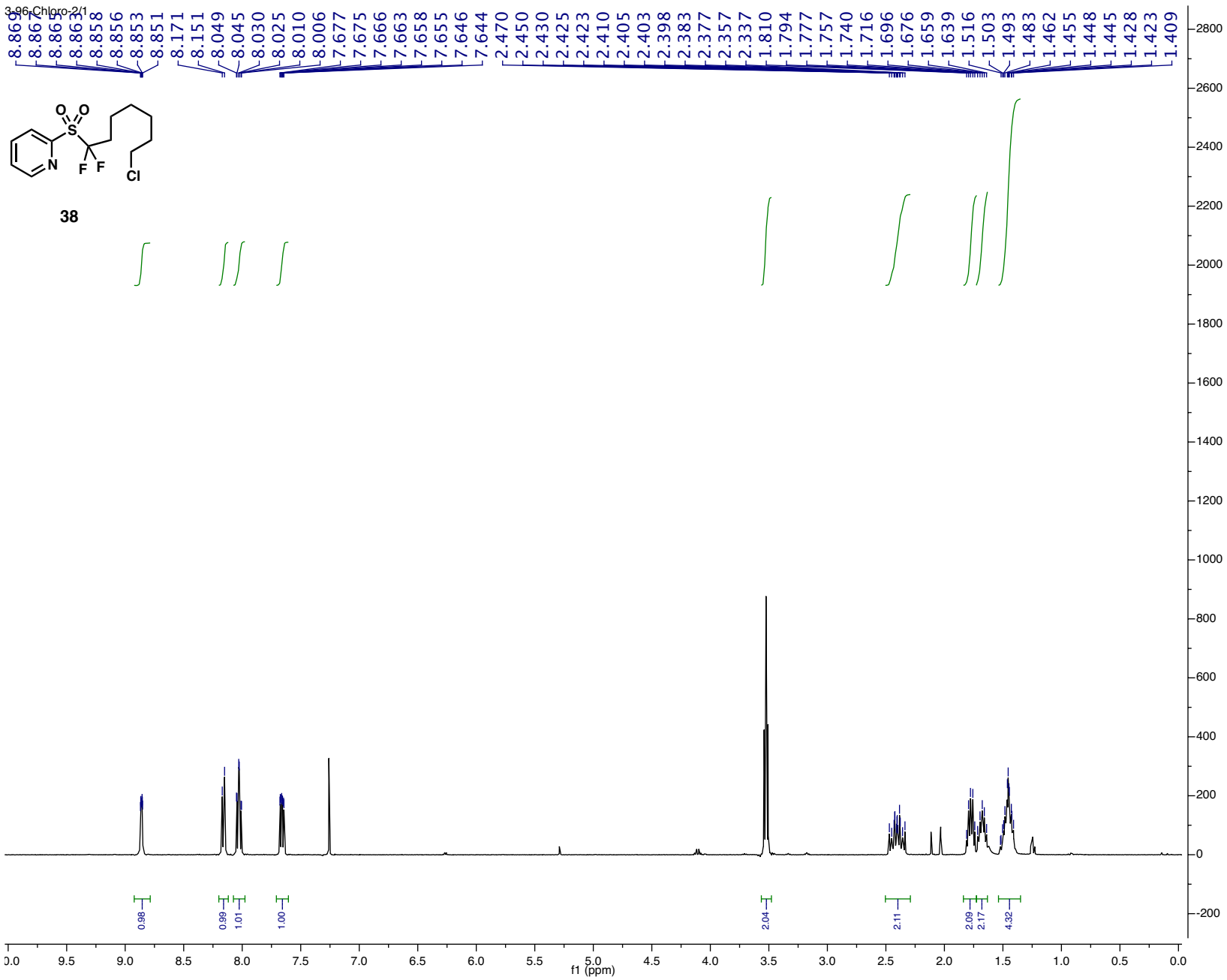

133.447
130.986
128.640
126.794
125.135
34.467
26.437
26.268
26.099
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

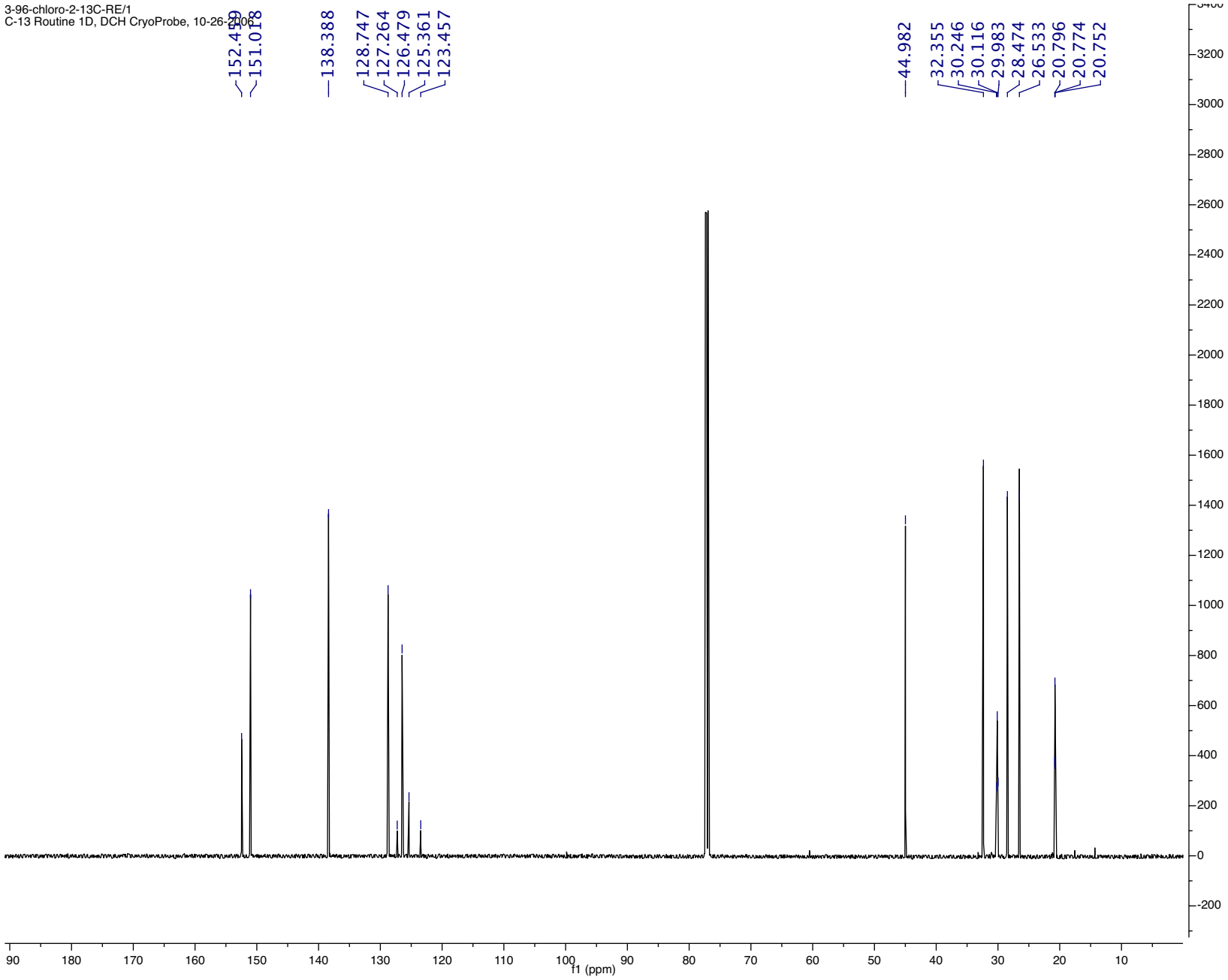

−65.239
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
f1 (ppm)
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210

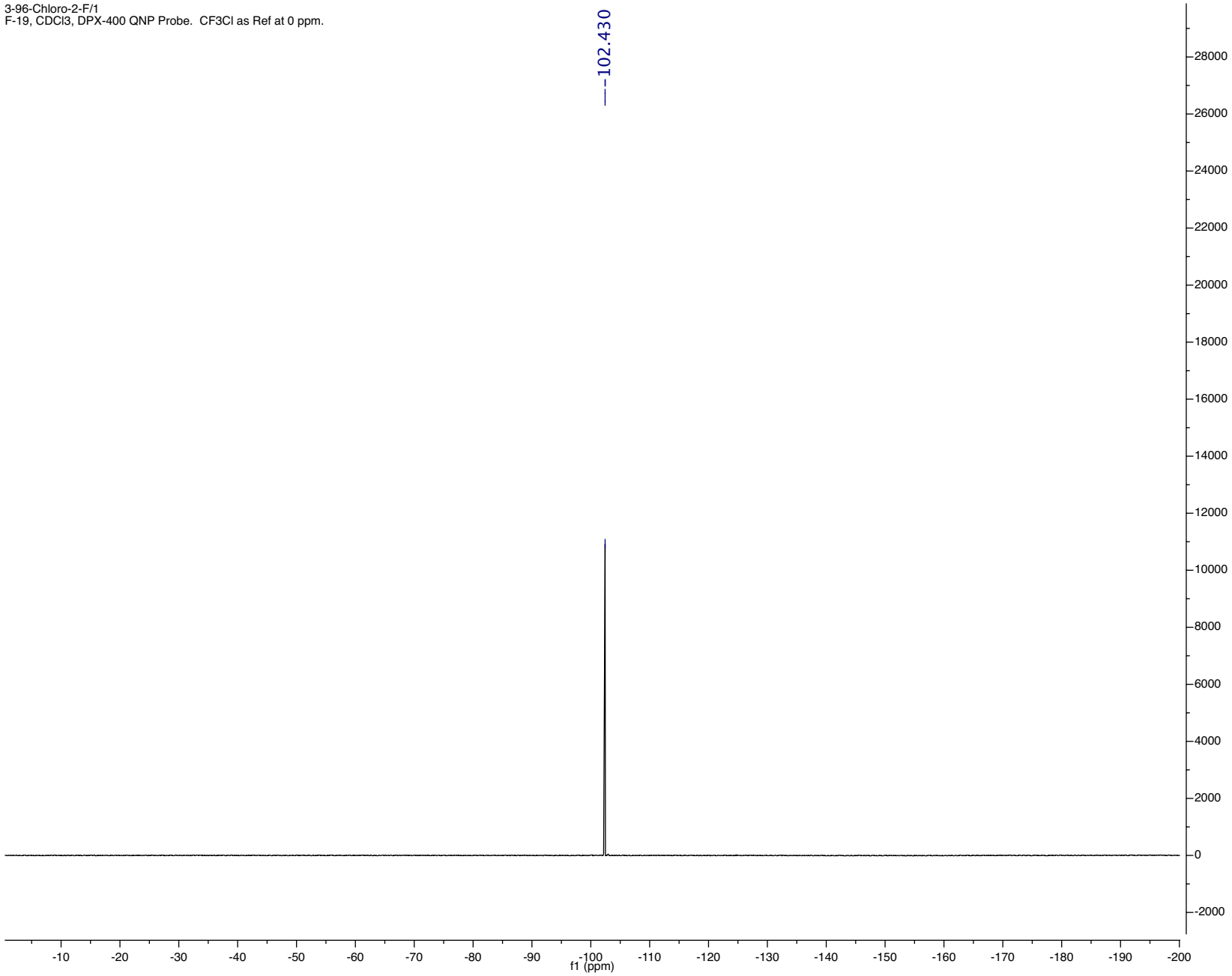

8.185
8.165
7.660
7.640
7.116
7.107
7.097
7.086
7.005
5.005
4.999
4.977
4.972
4.463
4.440
2.929
2.907
2.885
2.102
2.056
2.009
1.605
1.578
1.546
1.519
H2N
F
F
MeF2C
N
HO
37
0.97
0.99
1.98
1.03
1.02
1.00
0.97
2.28
4.32
1.10
f1 (ppm)


159.223
151.931
151.842
150.280
150.190
148.080
138.894
134.785
133.318
133.244
124.844
124.814
124.799
124.770
123.858
122.382
120.803
119.223
118.613
118.587
118.559
115.983
115.869
71.241
54.163
45.419
35.675
33.473
23.632
23.450
23.268
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

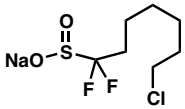

-90.587
-137.165
-137.221
-142.471
-142.530
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


3-96-Chloro-2/1
8.867 8.863 8.858 8.856 8.853 8.851 8.171 8.151 8.049 8.045 8.030 8.025 8.010 8.006 7.677 7.675 7.666 7.663 7.658 7.655 7.646 7.644 2.470 2.450 2.430 2.425 2.423 2.410 2.405 2.403 2.398 2.383 2.377 2.357 2.337 1.810 1.794 1.777 1.757 1.740 1.716 1.696 1.676 1.659 1.639 1.516 1.503 1.493 1.483 1.462 1.455 1.448 1.445 1.428 1.423 1.409
O O S N F F Cl
38
0.98 0.99 1.01 1.00 2.04 2.11 2.09 2.17 4.32
f1 (ppm)

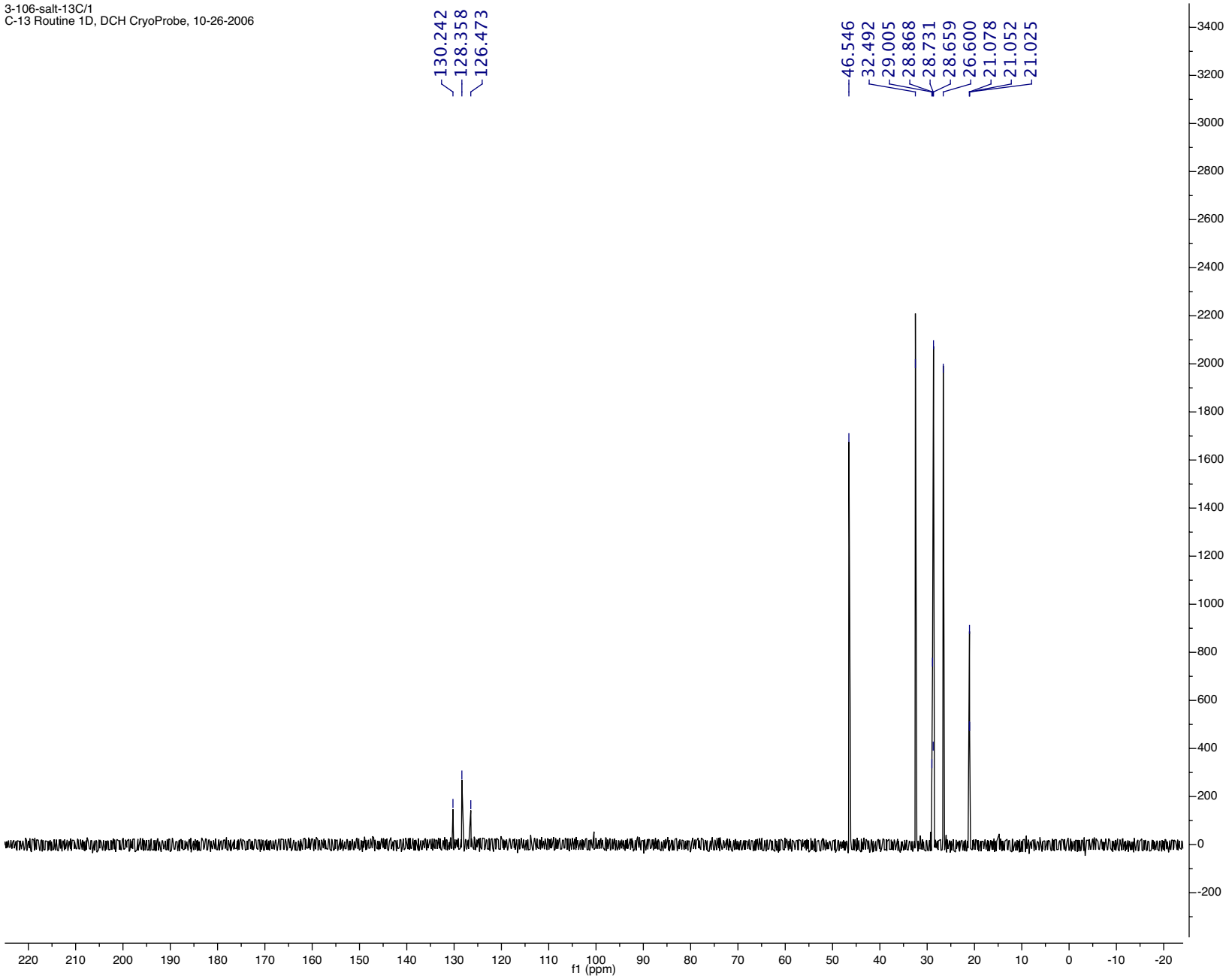

3-96-chloro-2-13C-RE/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2020
152.499
151.018
138.388
128.747
127.264
126.479
125.361
123.457
44.982
32.355
30.246
30.116
29.983
28.474
26.533
20.796
20.774
20.752
f1 (ppm)

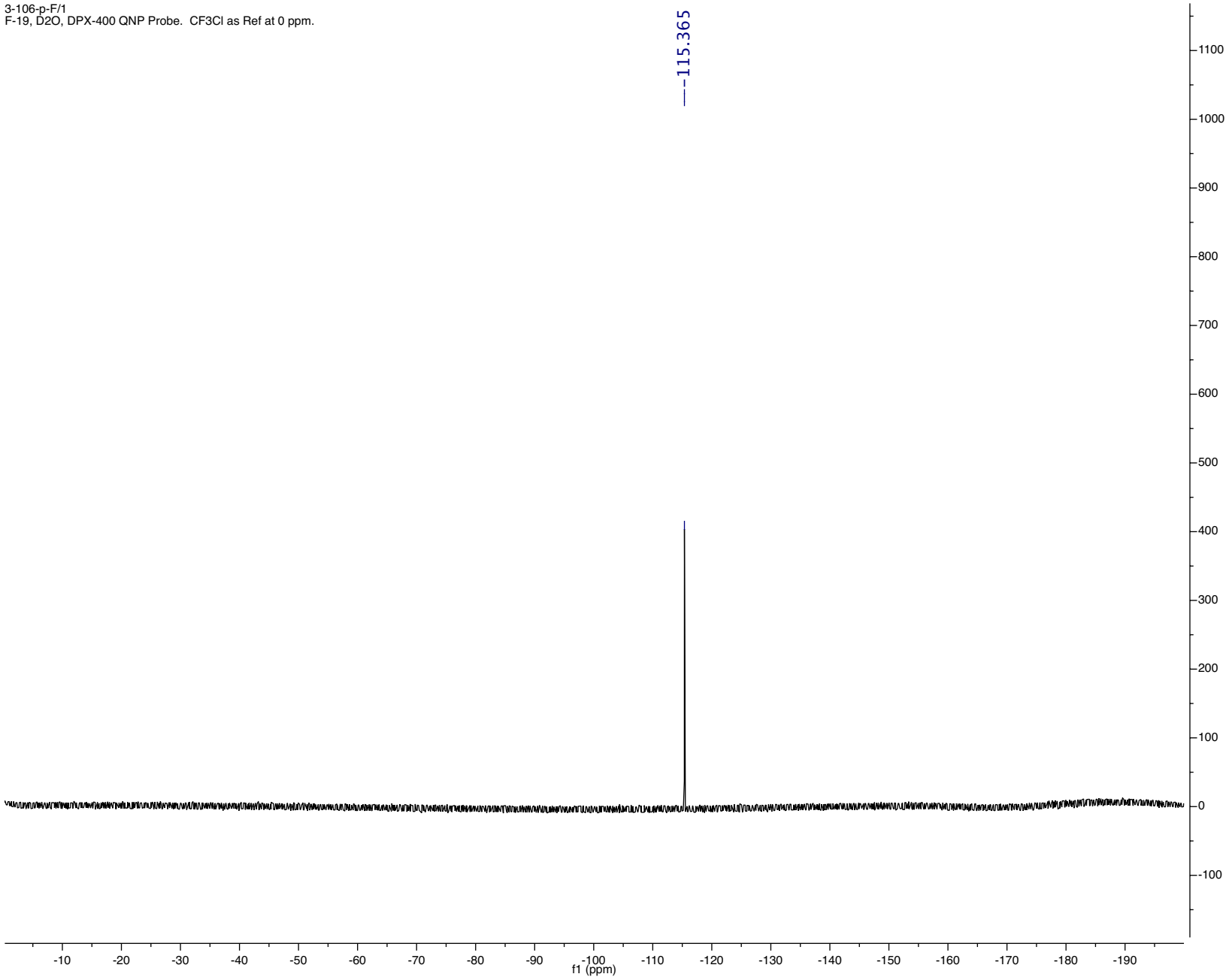

3-96-Chloro-2-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-102.430
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

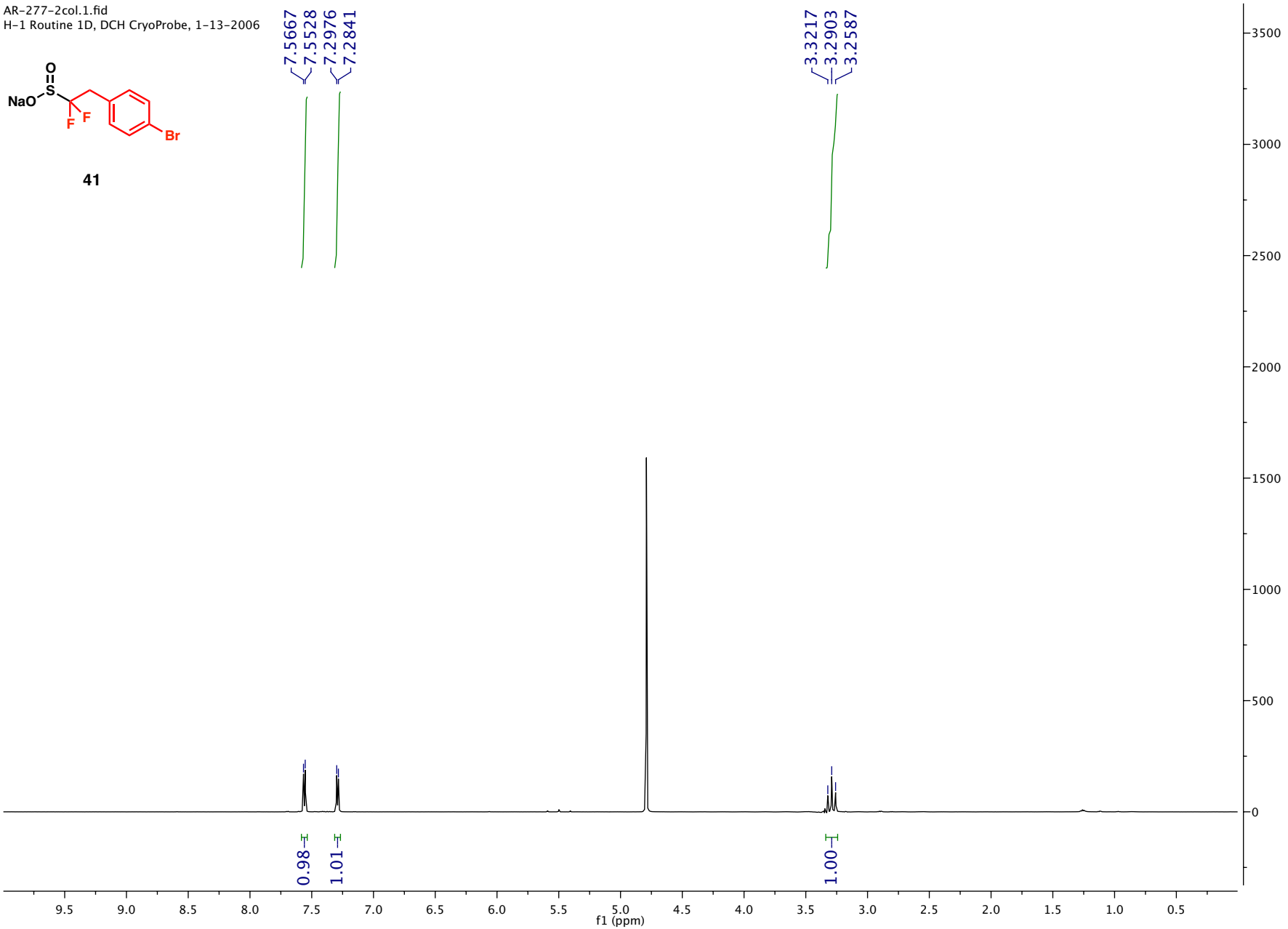
3-106-salt-redisue-2/999
H-1 Routine 1D experiment. BBO Probe, 9-13-2007

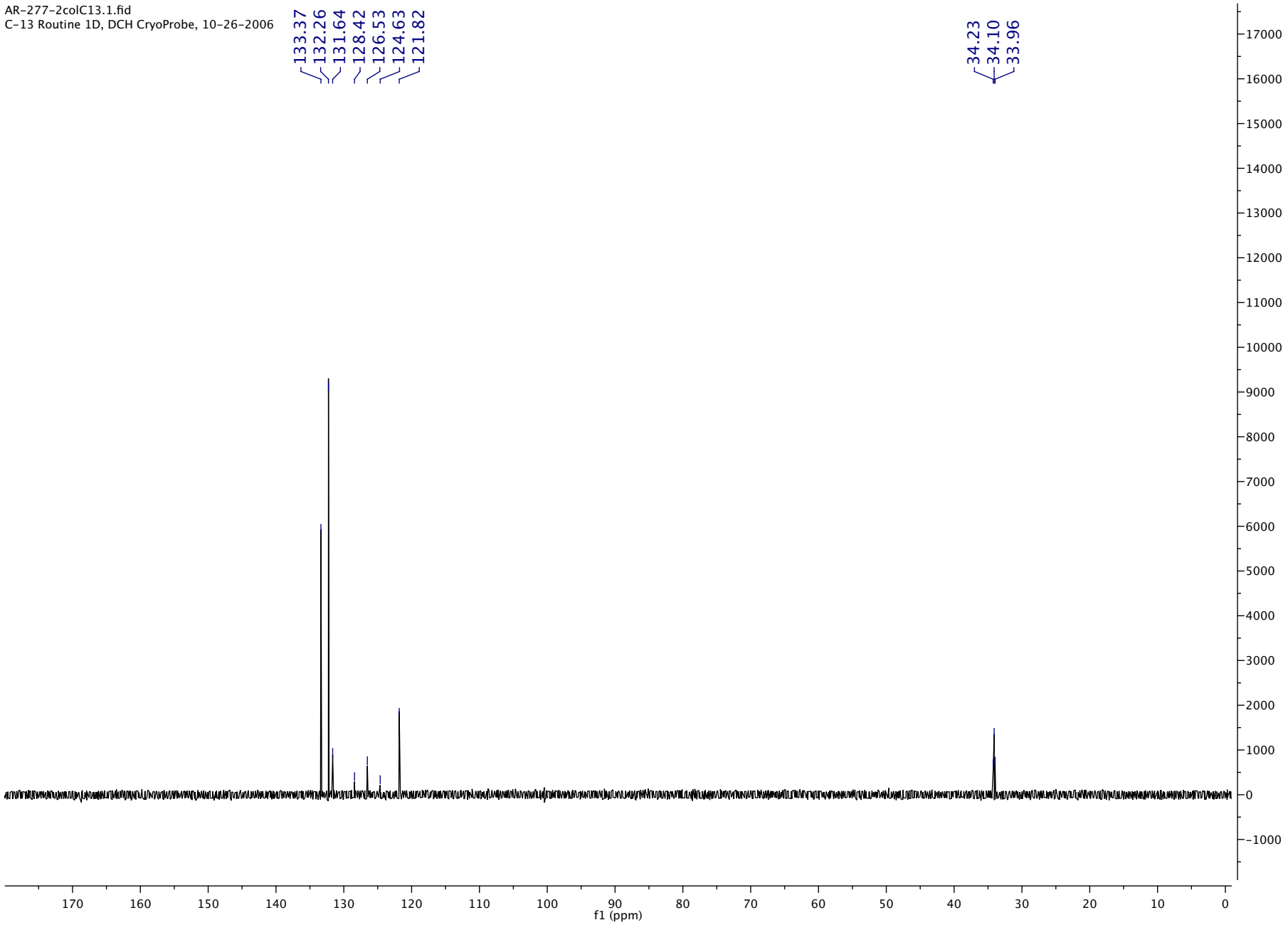


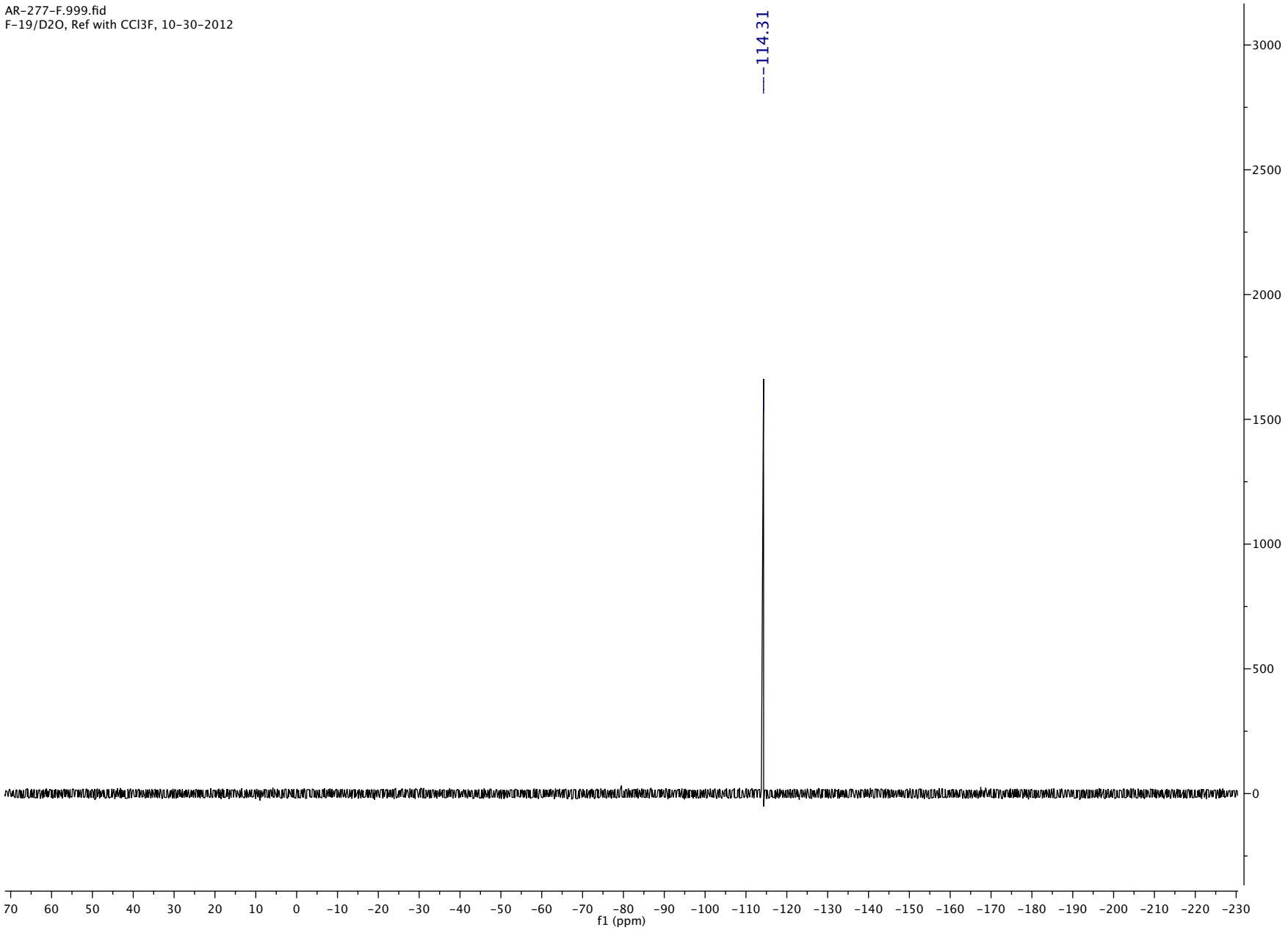
40

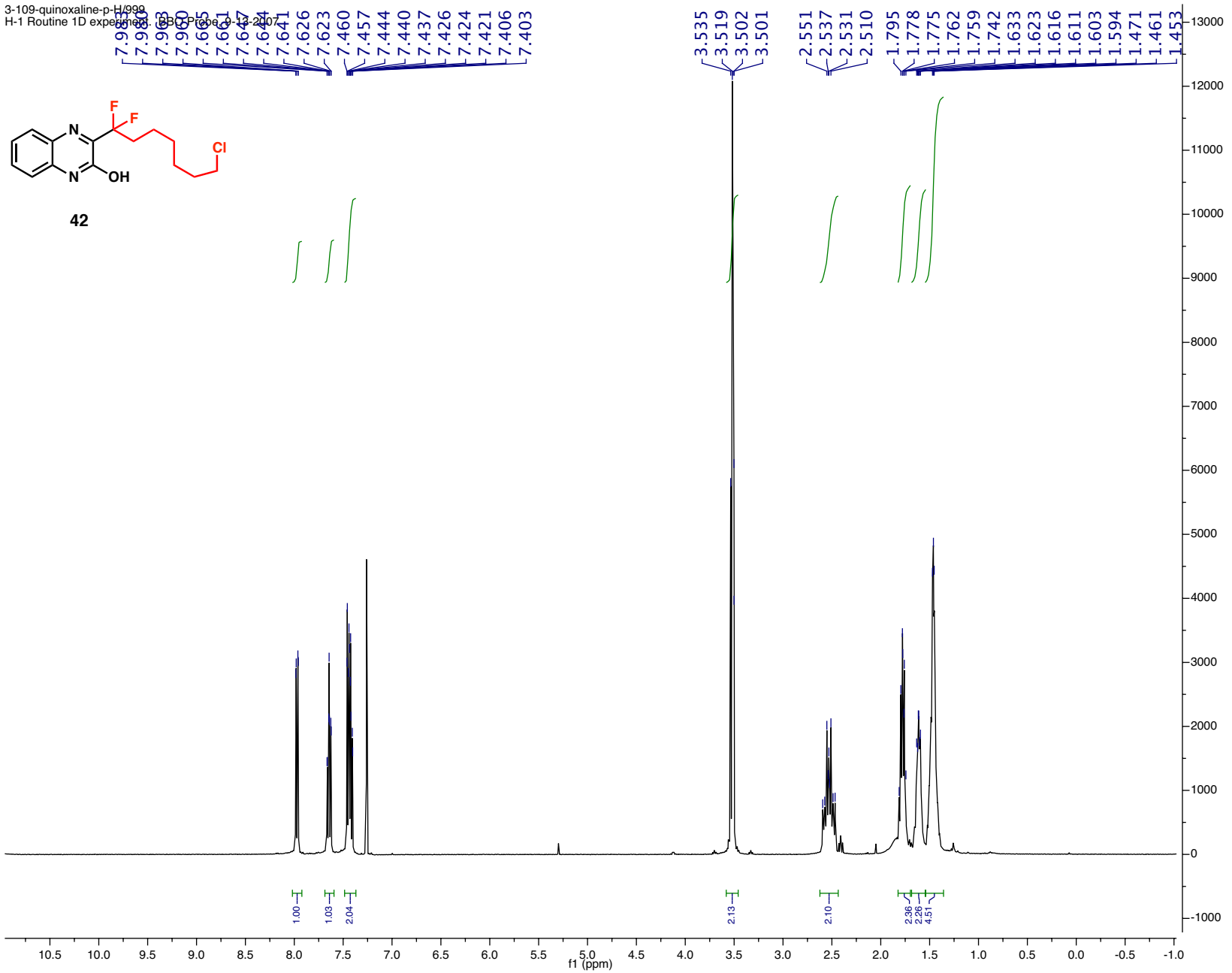

3-106-salt-13C/1
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
130.242
128.358
126.473
46.546
32.492
29.005
28.868
28.731
28.659
26.600
21.078
21.052
21.025
f1 (ppm)

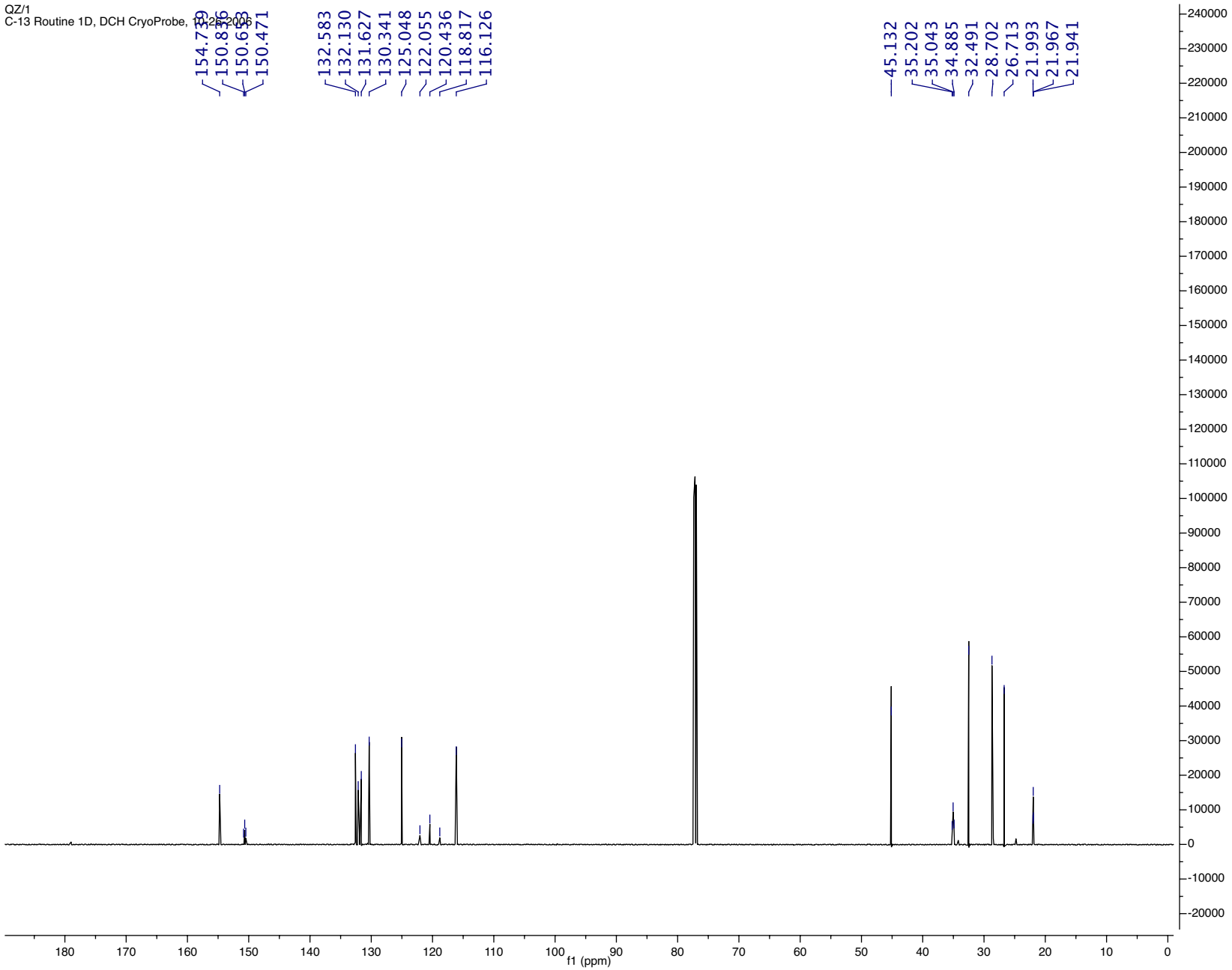

3-106-p-F/1
F-19, D2O, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-115.365
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

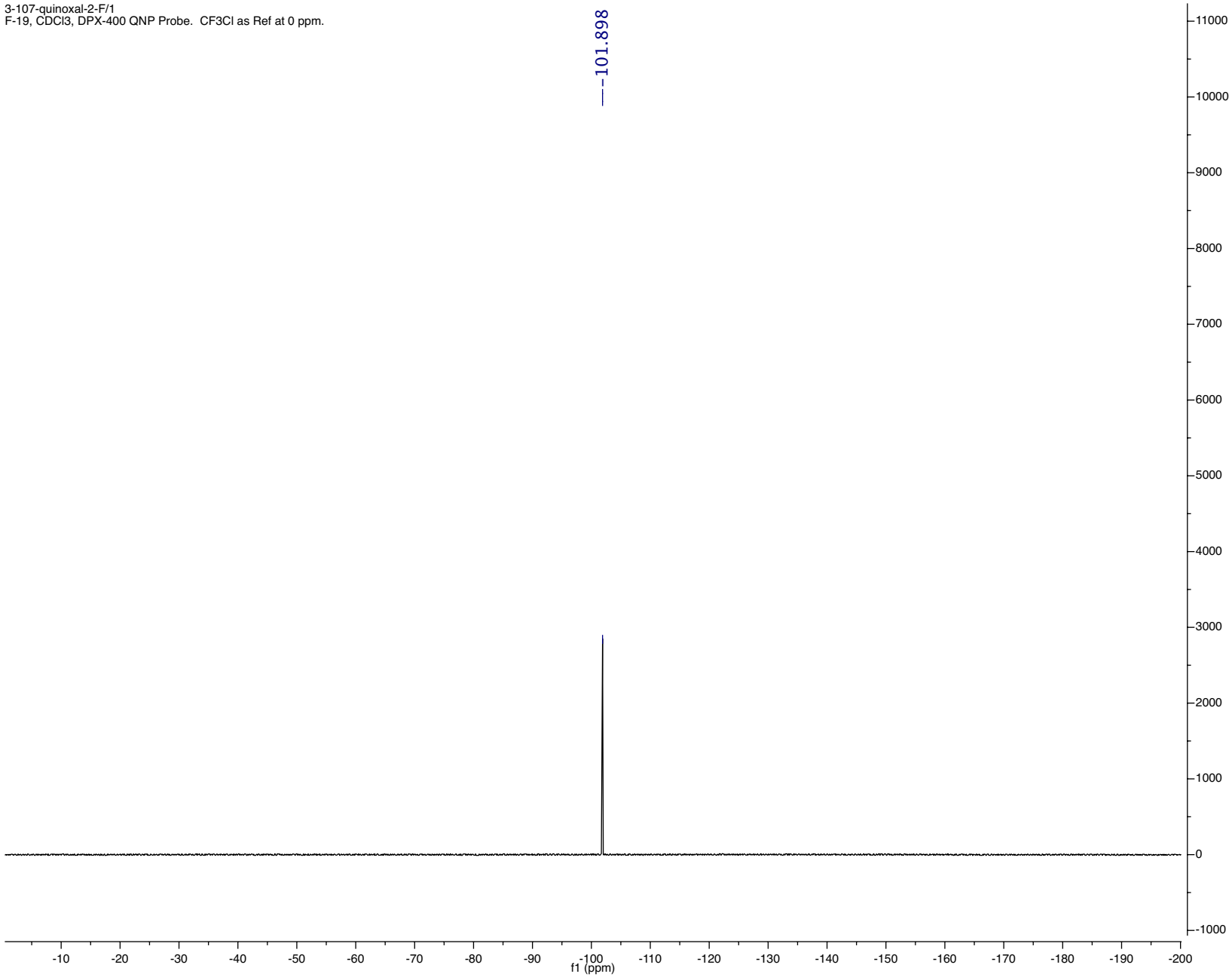

AR-277-2col.1.fid
H-1 Routine 1D, DCH CryoProbe, 1-13-2006
NaO
O
S
F
F
Br
41
7.5667
7.5528
7.2976
7.2841
3.3217
3.2903
3.2587
0.98
1.01
1.00
f1 (ppm)

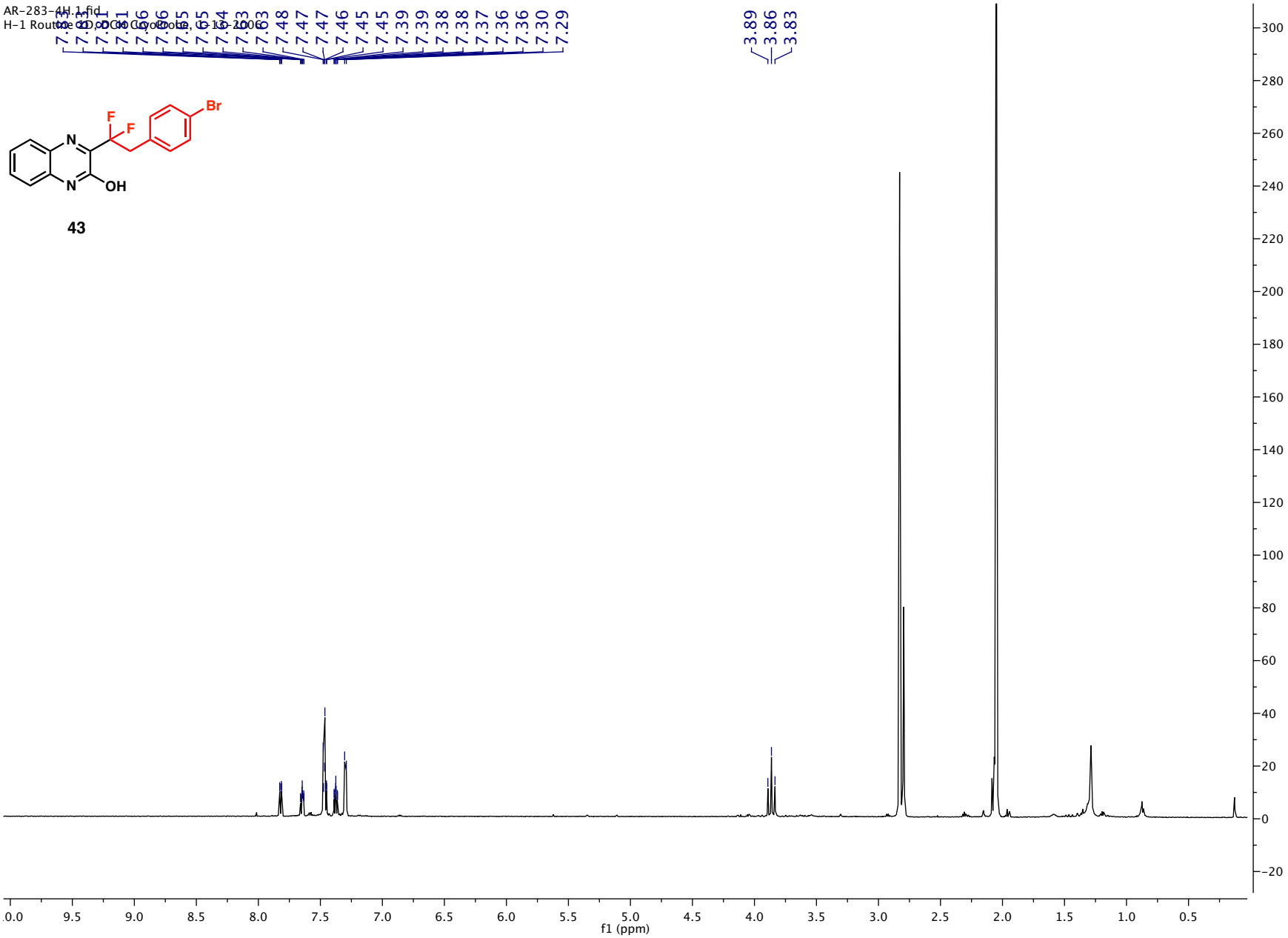

AR-277-2colC13.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
133.37
132.26
131.64
128.42
126.53
124.63
121.82
34.23
34.10
33.96
f1 (ppm)

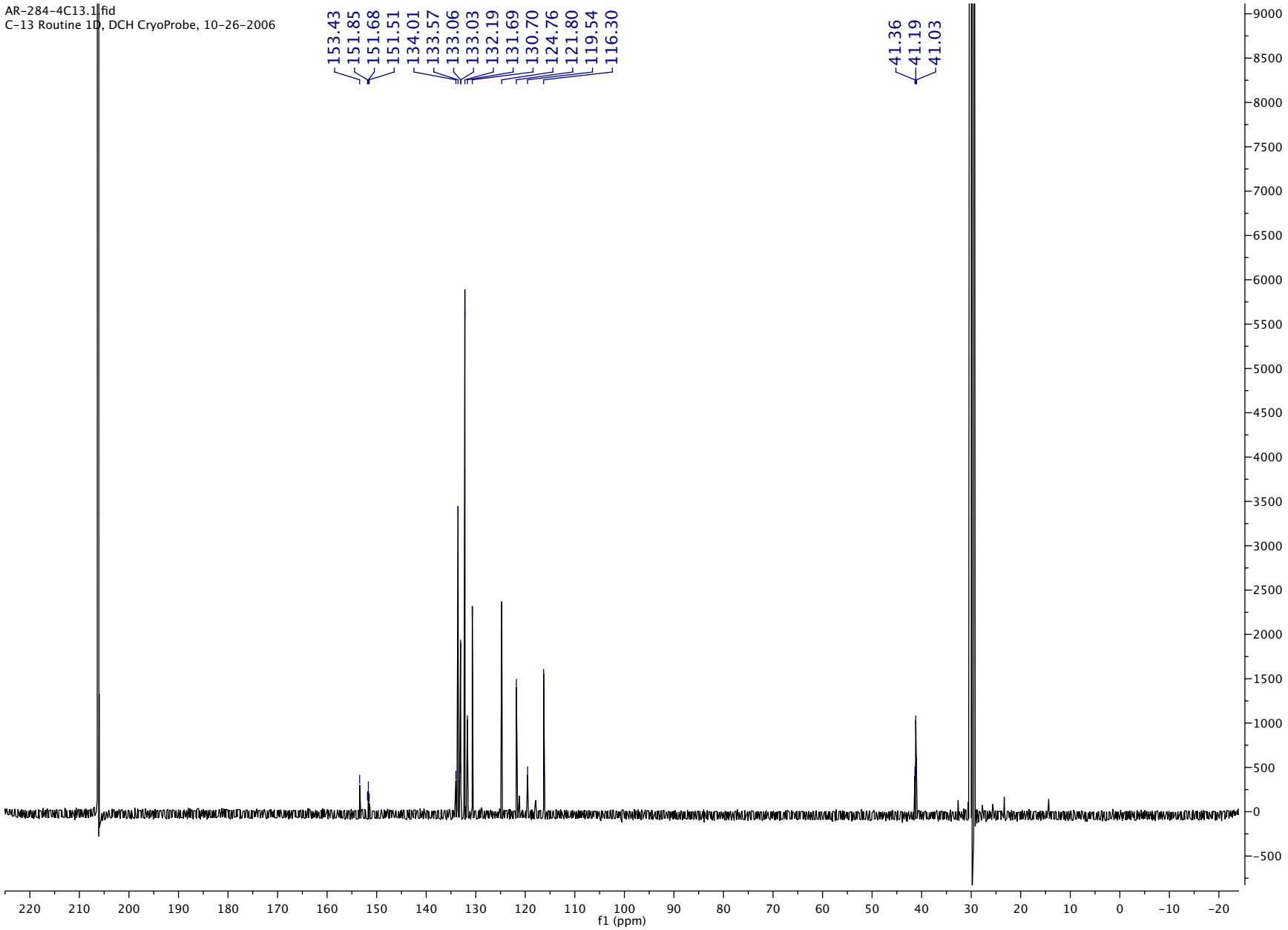

AR-277-F.999.fid
F-19/D2O, Ref with CCl3F, 10-30-2012
-114.31
3000
2500
2000
1500
1000
500
0
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)

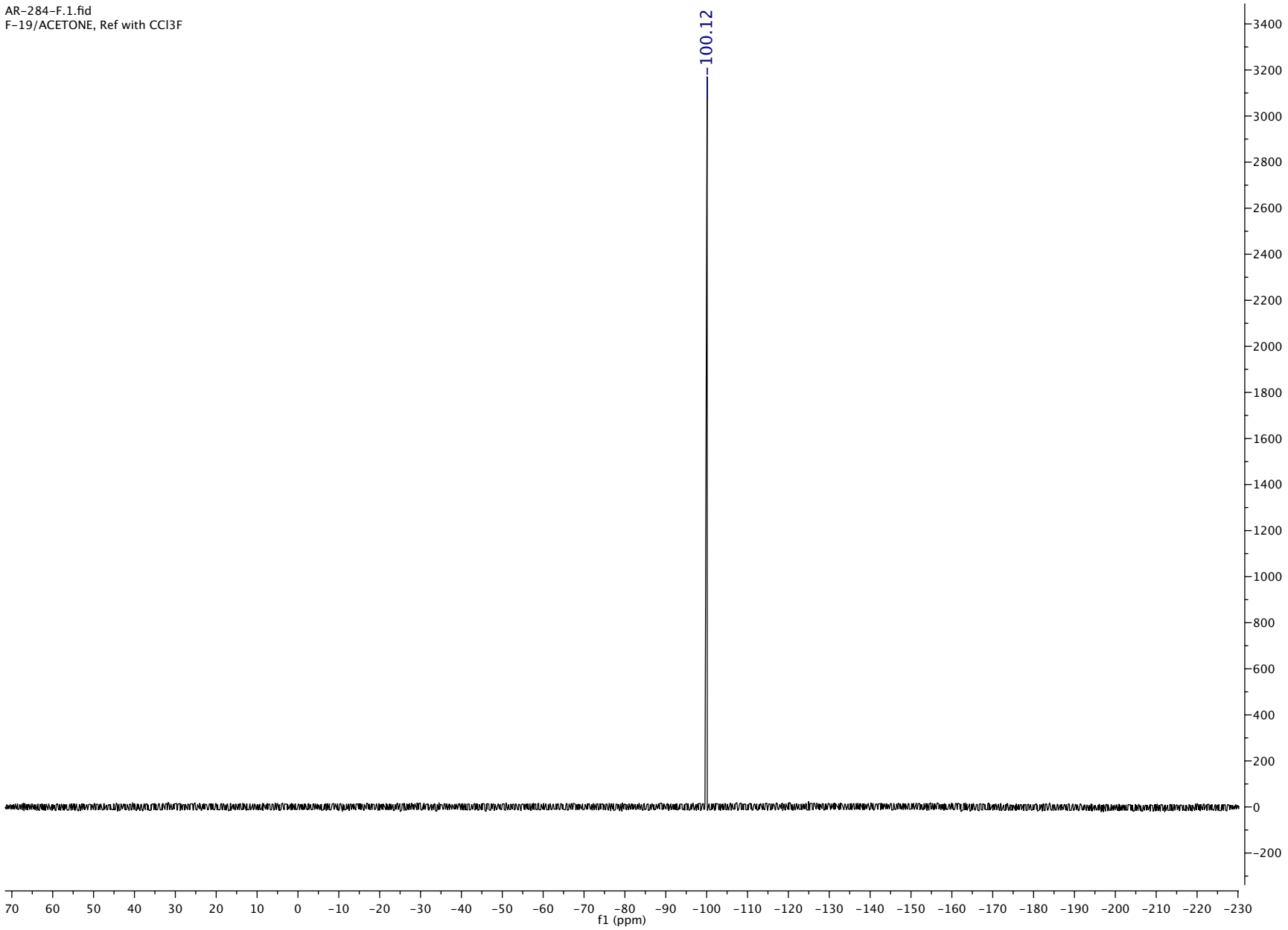

3-109-quinoxaline-p-H/999
H-1 Routine 1D experiment, PABCD Probe, 9-13-2007
7.993
7.990
7.963
7.960
7.655
7.651
7.647
7.644
7.641
7.626
7.623
7.460
7.457
7.444
7.440
7.437
7.426
7.424
7.421
7.406
7.403
3.535
3.519
3.502
3.501
2.551
2.537
2.531
2.510
1.795
1.778
1.775
1.762
1.759
1.742
1.633
1.623
1.616
1.611
1.603
1.594
1.471
1.461
1.453
F
F
N
N
OH
Cl
42
1.00
1.03
2.04
2.13
2.10
2.36
2.26
4.51
f1 (ppm)


QZ/1
C-13 Routine 1D, DCH CryoProbe, 10-25-2006
154.739
150.836
150.633
150.471
132.583
132.130
131.627
130.341
125.048
122.055
120.436
118.817
116.126
45.132
35.202
35.043
34.885
32.491
28.702
26.713
21.993
21.967
21.941
f1 (ppm)


3-107-quinoxal-2-F/1
F-19, CDCl3, DPX-400 QNP Probe. CF3Cl as Ref at 0 ppm.
-101.898
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


AR-283-4H.1.fid
H-1 Routine 1D, CDCl3 Cryoprobe, 6-13-2006
7.71 7.71 7.71 7.71 7.66 7.66 7.65 7.65 7.64 7.63 7.63 7.48 7.47 7.47 7.46 7.45 7.45 7.39 7.39 7.38 7.38 7.37 7.36 7.36 7.30 7.29
3.89 3.86 3.83
F
F
Br
N
N
OH
43
f1 (ppm)


AR-284-4C13.1.fid
C-13 Routine 1D, DCH CryoProbe, 10-26-2006
153.43
151.85
151.68
151.51
134.01
133.57
133.06
133.03
132.19
131.69
130.70
124.76
121.80
119.54
116.30
41.36
41.19
41.03
f1 (ppm)


AR-284-F.1.fid
F-19/ACETONE, Ref with CCl3F
-100.12
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230
f1 (ppm)