Support Information

# Cascade Knoevenagel and Aza-Wittig Reactions for the Synthesis of Substituted Quinolines and Quinolin-4-ols

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**Content**

## 1. General information

Chemicals and solvents were purchased from Sigma and Oakwood. $^{1}$H-NMR (400 MHz) and $^{13}$C-NMR spectra (101 MHz) were recorded on Agilent NMR spectrometers. Chemical shifts were reported in parts per million (ppm), Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). LC-MS were performed on an Agilent 2100 LC with a 6130 quadrupole MS spectrometers. A C18 column (5.0 μm, 6.0 x 50 mm) was used for the separation. The mobile phases were MeOH and $H_2O$ both containing 0.05% $CF_3CO_2H$. A linear gradient from 25:75 (v/v) MeOH/water to 100% MeOH over 7.0 min at a flow rate of 0.7 mL/min was used as a mobile phase. UV detections were conducted at 210 nm, 254 nm and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). Final products were purified were performed on YAMAZEN AI-580 flash column system with Agela silica gel columns (230-400 μm mesh).

## 2. General procedure for one-pot synthesis

General procedure 1 for the synthesis of **4**, **8**, **12** and **16**. To a solution of 2-azidobenzaldehyde **1** (0.50 mmol), compound **2**, **6**, **10** or **14** (0.55 mmol), $Et_3N$ (0.50 mmol) and $Ph_3P$ (0.6mmol) in 2.5 mL of $CH_3CN$ was heated at 95 $^{o}$C for 12 h. The reaction mixture upon the completion of the reaction as monitored by LC-MS. The reaction mixture was concentrated and washed with plenty of $Et_2O$ or separated on a YAMAZEN AI-580 flash column to afford purified targets.

General procedure 2 for the synthesis of **5**, **9**, **17** and **18**. To a solution of 2-azidobenzaldehyde **1** (0.50 mmol), compound **3**, **7**, **15** or Cyclic 1,3-dicarbonyl (0.55 mmol), $Et_3N$ (0.50 mmol) and $Ph_3P$ (0.6mmol) in 2.5 mL of $CH_3CN$ was heated at 95 $^{o}$C for 12 h. The reaction mixture upon the completion of the reaction as monitored by LC-MS. The reaction mixture was concentrated and separated on a YAMAZEN AI-580 flash column to afford purified targets.

General procedure 3 for the synthesis of **13**. To a solution of 2-azidobenzaldehyde **1** (0.50 mmol), compound **11** (0.55 mmol), LiOH (0.60 mmol) and $Ph_3P$ (0.6mmol) in 2.5 mL of $CH_3CN$ was heated at 95 $^{o}$C for 6 h. The reaction mixture upon the completion of the reaction as monitored by LC-MS. The reaction mixture was concentrated and separated on a YAMAZEN AI-580 flash column to afford purified products **13**.

## 3. Characterization of products

*Ethyl 4-hydroxy-2-methylquinoline-3-carboxylate (**4a**):* white solid (90% yield). $^{1}$H NMR (400 MHz, DMSO) δ 11.84 (s, 1H), 8.03 (dd, J = 8.1, 1.5 Hz, 1H), 7.64 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.31 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).$^{13}$C NMR (101 MHz, DMSO) δ 173.8, 167.2, 149.3, 139.6, 132.6, 125.5, 125.0, 124.1, 118.4, 115.2, 60.7, 18.6, 14.6. HRMS (ESI-TOF,

*m/z*): $[M+H]^+$ calcd. for $C_{13}H_{14}NO_3$ 232.0974, found: 232.0977.

*(4-hydroxy-2-phenylquinolin-3-yl)(phenyl)methanone (**4b**):* white solid (91% yield). $^1H$ NMR (400 MHz, DMSO) δ 12.12 (s, 1H), 8.10 – 8.05 (m, 1H), 7.79 – 7.68 (m, 4H), 7.56 – 7.49 (m, 1H), 7.47 – 7.34 (m, 8H).$^{13}C$ NMR (101 MHz, DMSO) δ 196.2, 175.5, 150.1, 140.6, 138.5, 134.3, 133.4, 132.8, 130.3, 129.4, 129.1, 129.0, 128.9, 125.3, 124.3, 120.7, 119.5. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{22}H_{16}NO_2$ 326.1181, found: 326.1177.

*Ethyl 8-hydroxy-6-methyl-[1,3]dioxolo[4,5-g]quinoline-7-carboxylate (**4c**):* white solid (77% yield). $^1H$ NMR (400 MHz, DMSO) δ 11.89 – 11.57 (m, 1H), 7.34 – 7.30 (m, 1H), 6.95 – 6.90 (m, 1H), 6.12 (s, 2H), 4.24 – 4.14 (m, 2H), 2.34 – 2.28 (m, 3H), 1.28 – 1.19 (m, 3H).$^{13}C$ NMR (101 MHz, DMSO) δ 206.9, 172.6, 167.3, 151.8, 147.5, 145.8, 136.6, 120.4, 114.6, 102.5, 102.0, 97.1, 60.6, 31.1, 18.3, 14.6. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{14}H_{14}NO_5$ 276.0872, found: 276.0874.

*Ethyl 6-bromo-4-hydroxy-2-methylquinoline-3-carboxylate (**4d**):* white solid (89% yield). $^1H$ NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.80 (dd, J = 8.8, 2.4 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H).$^{13}C$ NMR (101 MHz, DMSO) δ 172.5, 166.8, 149.9, 138.5, 135.4, 127.6, 126.5, 121.1, 116.8, 115.5, 60.9, 18.6, 14.6.HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{13}H_{13}BrNO_3$ 310.0079, found: 310.0081.

*Ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate (**4e**):* white solid (85% yield). $^1H$ NMR (400 MHz, DMSO) δ 12.02 (s, 1H), 7.99 – 7.93 (m, 1H), 7.69 (dd, J = 8.8, 2.5 Hz, 1H), 7.58 – 7.52 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.37 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).$^{13}C$ NMR (101 MHz, DMSO) δ 172.6, 166.9, 149.9, 138.3, 132.8, 128.7, 126.1, 124.4, 121.0, 115.4, 60.8, 18.7, 14.6. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{13}H_{13}ClNO_3$ 266.0584, found: 266.0582.

*Isopropyl 4-hydroxy-2-methylquinoline-3-carboxylate (**4f**):* white solid (87% yield). $^1H$ NMR (400 MHz, DMSO) δ 11.80 (s, 1H), 8.05 – 7.98 (m, 1H), 7.64 (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.52 – 7.47 (m, 1H), 7.34 – 7.28 (m, 1H), 5.05 (dq, J = 12.6, 6.3 Hz, 1H), 2.36 (s, 3H), 1.25 (d, J = 6.3 Hz, 6H).$^{13}C$ NMR (101 MHz, DMSO) δ 173.8, 166.6, 148.8, 139.6, 132.6, 125.4, 125.0, 124.0, 118.4, 115.6, 68.1, 22.1, 18.4. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{14}H_{16}NO_3$ 246.1130, found: 246.1132.

*Ethyl 4-hydroxy-2-phenylquinoline-3-carboxylate (**4g**):* white solid (80% yield). $^1H$ NMR (400 MHz, DMSO) δ 12.05 (s, 1H), 8.12 – 8.08 (m, 1H), 7.71 – 7.64 (m, 2H), 7.58 – 7.50 (m, 5H), 7.37 (ddd, J = 14.5, 7.3, 4.3 Hz, 1H), 3.94 (q, J = 7.1 Hz, 2H), 0.89 (t, J = 7.1 Hz, 3H).$^{13}C$ NMR (101 MHz, DMSO) δ 174.0, 166.7, 150.0, 140.2, 134.4, 132.8, 130.6, 129.0, 128.6, 125.4, 125.1, 124.4, 119.4, 115.9, 60.6, 14.1. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{18}H_{16}NO_3$ 294.1130, found: 294.1127.

*Ethyl 6-chloro-4-hydroxy-2-phenylquinoline-3-carboxylate (**4h**):* white solid (77% yield). $^1H$ NMR (400 MHz, $CDCl_3$) δ 13.57 (s, 1H), 8.20 (t, J = 1.5 Hz, 1H), 7.63 – 7.58 (m, 4H), 7.53 (ddd, J = 6.8, 4.0, 1.3 Hz, 1H), 7.46 – 7.39 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 0.89 (t, J

= 7.1 Hz, 3H).$^{13}$C NMR (101 MHz, $CDCl_3$) δ 200.5, 169.2, 160.1, 146.9, 140.4, 133.6, 131.7, 129.4, 128.4, 128.0, 127.7, 123.1, 119.0, 102.9, 61.9, 13.5. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{18}H_{15}ClNO_3$ 328.0740, found: 328.0736.

*Ethyl 4-hydroxy-2-propylquinoline-3-carboxylate (**4i**):* white solid (88% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 8.32 (dd, J = 8.2, 1.3 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.59 (ddd, J = 8.4, 7.1, 1.4 Hz, 1H), 7.37 – 7.28 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.87 – 2.74 (m, 2H), 1.85 – 1.70 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H)..$^{13}$C NMR (101 MHz, $CDCl_3$) δ 175.7, 167.4, 154.5, 139.8, 132.3, 125.4, 125.1, 124.3, 118.9, 115.0, 61.0, 34.9, 23.0, 14.1, 13.8. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{15}H_{18}NO_3$ 260.1287, found: 260.1291.

*Ethyl 2-ethyl-4-hydroxyquinoline-3-carboxylate (**4j**):* white solid (83% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 8.33 (dd, J = 8.1, 1.1 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.66 – 7.53 (m, 1H), 7.33 (t, J = 7.3 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.96 – 2.80 (m, 2H), 1.42 – 1.29 (m, 3H), 1.29 – 1.18 (m, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 175.7, 167.4, 155.7, 139.8, 132.3, 125.5, 124.3, 118.8, 61.1, 26.7, 14.1, 13.8. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{14}H_{16}NO_3$ 246.1130, found: 246.1127.

*Ethyl 2-cyclopropyl-4-hydroxyquinoline-3-carboxylate(**4k**):* white solid (83% yield). $^1$H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 8.00 (dd, J = 8.1, 1.5 Hz, 1H), 7.70 – 7.57 (m, 2H), 7.30 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.11 – 1.99 (m, 1H), 1.29 – 1.23 (m, 3H), 1.04 (dd, J = 5.3, 4.6 Hz, 4H).$^{13}$C NMR (101 MHz, DMSO) δ 173.6, 167.4, 152.2, 139.7, 132.5, 125.2, 124.9, 124.0, 118.8, 116.8, 60.9, 14.6, 13.4, 8.1. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{15}H_{16}NO_3$ 258.1130, found: 258.1132.

*Ethyl 4-hydroxy-2-(thiophen-2-yl)quinoline-3-carboxylate (**4l**):* white solid (81% yield). $^1$H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 8.08 (dt, J = 8.1, 1.1 Hz, 1H), 7.91 – 7.87 (m, 1H), 7.72 – 7.68 (m, 2H), 7.54 (dt, J = 4.8, 2.4 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.26 (dd, J = 5.0, 3.6 Hz, 1H), 4.11 – 4.05 (m, 2H), 1.07 (t, J = 7.1 Hz, 3H).$^{13}$C NMR (101 MHz, DMSO) δ 174.0, 166.7, 142.3, 140.1, 133.8, 133.1, 130.7, 130.6, 128.3, 125.3, 124.9, 124.6, 119.3, 116.4, 61.1, 49.0, 14.2.HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{16}H_{14}NO_3S$ 300.0694, found: 300.0700.

*Ethyl 2-methylquinoline-3-carboxylate (**5a**):* white solid (89% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.07 – 7.97 (m, 1H), 7.89 – 7.81 (m, 1H), 7.80 – 7.70 (m, 1H), 7.55 – 7.47 (m, 1H), 4.47 – 4.36 (m, 2H), 2.98 (s, 3H), 1.47 – 1.39 (m, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 166.5, 158.4, 148.6, 139.8, 131.6, 128.5, 128.4, 126.5, 125.7, 123.9, 61.4, 25.7, 14.3. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{13}H_{14}NO_2$ 216.1025, found: 216.1022.

*Ethyl 6-bromo-2-phenylquinoline-3-carboxylate (**5b**):* white solid (88% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.48 (m, 1H), 8.09 – 8.00 (m, 2H), 7.90 – 7.81 (m, 1H), 7.66 – 7.58 (m, 2H), 7.51 – 7.40 (m, 3H), 4.24 – 4.14 (m, 2H), 1.07 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 167.6, 158.4, 146.9, 140.3, 137.8, 134.9, 131.2, 130.1, 128.8, 128.5, 128.2, 126.9, 126.4, 121.1, 61.7, 13.7. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for

$C_{18}H_{15}BrNO_2$ 356.0286, found: 356.0290.

*Ethyl 2-isopropylquinoline-3-carboxylate (**5c**):* colorless oil (79% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 0.6 Hz, 1H), 8.06 (ddd, J = 8.5, 1.8, 0.8 Hz, 1H), 7.82 (dt, J = 8.8, 4.4 Hz, 1H), 7.75 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.51 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 3.95 (tt, J = 13.5, 6.8 Hz, 1H), 1.48 – 1.42 (t, J= 7.1 3H), 1.41 – 1.36 (d, J = 6.9, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 165.7, 148.6, 138.9, 131.0, 129.0, 128.1, 126.3, 125.4, 124.2, 61.4, 50.8, 32.9, 22.3, 14.3, HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{15}H_{18}NO_2$ 244.1318, found: 244.1321.

*Phenyl(2-phenylquinolin-3-yl)methanone (**5d**):* white solid (79% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 0.6 Hz, 1H), 8.25 (ddd, J = 8.5, 1.8, 0.8 Hz, 1H), 7.90 (dt, J = 8.4, 2.5 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.74 – 7.68 (m, 2H), 7.66 – 7.59 (m, 3H), 7.53 – 7.45 (m, 2H), 7.34 – 7.26 (m, 4H). $^{13}$CMR (101 MHz, $CDCl_3$) δ 196.9, 157.4, 148.3, 139.7, 137.6, 137.0, 133.3, 132.8, 132.4, 132.1, 132.0, 131.2, 129.9, 129.7, 129.2, 128.8, 128.7, 128.5, 128.4, 128.4, 128.4, 128.1, 127.3, 127.1, 125.8. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{22}H_{16}NO$ 310.1232, found: 310.1319.

*Ethyl 4-hydroxy-2-(trifluoromethyl)quinoline-3-carboxylate (**8a**):* white solid (87% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 12.93 (s, 1H), 8.37 (ddd, J = 8.3, 1.5, 0.6 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.91 – 7.84 (m, 1H), 7.68 (t, J = 7.4 Hz, 1H), 4.52 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 169.5, 169.4, 168.3, 147.1, 133.3, 129.8, 128.4, 123.5, 122.3, 120.9, 63.0, 13.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.38. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{13}H_{11}F_3NO_3$ 286.0691, found: 286.0688.

*Ethyl 6-chloro-4-hydroxy-2-(trifluoromethyl)quinoline-3-carboxylate (**8b**):* white solid (89% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 12.93 (s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 8.04 (d, J = 8.9 Hz, 1H), 7.80 (dd, J = 8.9, 2.4 Hz, 1H), 4.53 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 169.2, 167.4, 145.5, 134.6, 134.1, 131.4, 122.6, 122.3, 121.4, 119.6, 116.9, 63.3, 13.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.46. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{13}H_{10}ClF_3NO_3$ 320.0301, found: 320.0305.

*Ethyl 6-bromo-4-hydroxy-2-(trifluoromethyl)quinoline-3-carboxylate (**8c**):* white solid (87% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, J = 2.0, 0.6 Hz, 1H), 7.98 – 7.90 (m, 2H), 4.53 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 169.4, 167.3, 145.7, 136.7, 131.4, 126.0, 122.7, 122.3, 121.8, 119.6, 63.3, 13.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.49. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{13}H_{10}BrF_3NO_3$ 363.9796, found: 363.9800.

*Ethyl 4-hydroxy-7-methoxy-2-(trifluoromethyl)quinoline-3-carboxylate (**8d**):* white solid (73% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 12.88 (s, 1H), 8.26 – 8.19 (m, 1H), 7.41 (d, J = 2.5 Hz, 1H), 7.29 – 7.23 (m, 1H), 4.50 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 169.5, 167.9, 163.8, 149.5, 124.8, 122.5, 121.0, 119.8, 114.9, 108.3, 100.7, 62.8, 55.8, 13.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.40. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{14}H_{13}F_3NO_4$ 316.0797, found: 316.0801.

*Ethyl 8-hydroxy-6-(trifluoromethyl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxylate* ***(8e)****:* white solid (82% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 12.65 (s, 1H), 7.58 – 7.52 (m, 1H), 7.39 – 7.34 (m, 1H), 6.17 (s, 2H), 4.50 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 169.5, 166.4, 153.5, 149.3, 146.0, 122.6, 119.0, 116.9, 106.7, 102.4, 101.5, 99.1, 62.8, 13.5. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.09. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{14}H_{11}F_3NO_5$ 330.0589, found: 330.0593.

*Ethyl 4-hydroxy-2-(perfluoroethyl)quinoline-3-carboxylate* ***(8f)****:* white solid (80% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, J = 8.3, 0.9 Hz, 1H), 8.01 (t, J = 14.2 Hz, 1H), 7.90 – 7.78 (m, 1H), 7.66 (t, J = 7.3 Hz, 1H), 4.55 – 4.48 (m, 2H), 1.46 (q, J = 7.3 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 169.1, 167.8, 133.0, 129.4, 128.3, 123.4, 120.6, 119.9, 117.6, 113.0, 112.0, 62.8, 51.0, 12.9. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -78.99, -107.46. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{14}H_{11}F_5NO_3$ 336.0659, found: 336.0662.

*Ethyl 6-chloro-4-hydroxy-2-(perfluoroethyl)quinoline-3-carboxylate* ***(8g)****:* white solid (82% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 12.73 (s, 1H), 8.31 (d, J = 2.3 Hz, 1H), 7.98 (d, J = 8.9 Hz, 1H), 7.78 (dd, J = 8.9, 2.3 Hz, 1H), 4.53 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 168.8, 167.2, 144.9, 134.7, 133.9, 131.4, 122.5, 121.3, 120.2, 117.3, 112.0, 111.7, 63.2, 13.6. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -78.97, -107.42. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{14}H_{10}ClF_5NO_3$ 370.0269, found: 370.0266.

*Ethyl 6-chloro-2-(difluoromethyl)-4-hydroxyquinoline-3-carboxylate* ***(8h)****:* white solid (85% yield). $^{1}$H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.79 (dd, J = 8.9, 2.5 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).$^{13}$CMR (101 MHz, DMSO) δ 172.2, 164.8, 133.7, 130.1, 126.9, 124.4, 122.2, 114.1, 112.7, 110.4, 61.6, 30.8, 14.4. $^{19}$F NMR (376 MHz, DMSO) δ -117.80, -117.94. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{12}H_{10}ClF_2NO_3$ 301.0317, found: 301.0321.

*Ethyl 2-(trifluoromethyl)quinoline-3-carboxylate* ***(9a)****:* white solid (86% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.74 (dd, J = 8.0, 7.2 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 165.5, 147.0, 140.1, 132.3, 130.1, 129.5, 128.1, 124.2, 119.8, 116.6, 106.3, 62.5, 13.9.$^{19}$F NMR (376 MHz, $CDCl_3$) δ -63.91. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{13}H_{11}F_3NO_2$ 270.0742, found: 270.0739.

*Ethyl 6-bromo-2-(trifluoromethyl)quinoline-3-carboxylate* ***(9b)****:* white solid (90% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.14 – 8.09 (m, 2H), 7.96 (ddd, J = 9.0, 2.1, 1.0 Hz, 1H), 4.47 (qd, J = 7.2, 0.9 Hz, 2H), 1.43 (td, J = 7.2, 0.8 Hz, 3H). $^{13}$CMR (101 MHz, $CDCl_3$) δ 165.1, 145.4, 138.9, 135.9, 131.7, 130.1, 128.5, 124.9, 124.0, 122.0, 119.4, 62.7, 13.9.$^{19}$F NMR (376 MHz, $CDCl_3$) δ -64.06. HRMS (ESI-TOF*, m/z*): $[M+H]^+$ calcd. for $C_{13}H_{10}BrF_3NO_2$ 347.9847, found: 347.9847.

*Methyl 2-(trifluoromethyl)quinoline-3-carboxylate* ***(9c)****:* white solid (87% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.99 – 7.87 (m, 2H), 7.74 (dd, J = 8.1, 7.1 Hz, 1H), 4.01 (d, J = 1.0 Hz, 3H). $^{13}$CMR (101 MHz, $CDCl_3$) δ 165.8, 146.9,

140.2, 132.4, 130.1, 129.6, 128.2, 127.4, 123.7, 122.3, 119.7, 53.1.$^{19}$F NMR (376 MHz, $CDCl_3$) δ -64.25. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{12}H_9F_3NO_2$ 256.0585, found: 256.0588.

*Methyl 2-(difluoromethyl)quinoline-3-carboxylate (**9d**):* white solid (86% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.27 (d, J = 8.5 Hz, 1H), 7.99 – 7.85 (m, 2H), 7.73 – 7.66 (m, 1H), 4.02 (d, J = 0.9 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 165.4, 148.1, 140.9, 132.6, 130.1, 128.8, 128.5, 127.1, 113.6, 111.2, 108.8, 52.9.$^{19}$F NMR (376 MHz, $CDCl_3$) -118.44, -118.58. HRMS (ESI-TOF, *m/z*): $[M+H]^+$calcd. for $C_{12}H_{10}F_2NO_2$ 238.0680, found: 238.0676.

*Ethyl 2-(difluoromethyl)quinoline-3-carboxylate (**9e**):* white solid (88% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, J = 0.7 Hz, 1H), 8.26 (dd, J = 8.5, 0.4 Hz, 1H), 7.95 (dd, J = 8.2, 1.2 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.72 – 7.64 (m, 1H), 4.48 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 165.0, 148.0, 140.8, 132.4, 130.0, 128.8, 128.5, 128.4, 127.2, 113.7, 111.3, 62.1, 14.1.$^{19}$F NMR (376 MHz, $CDCl_3$) -118.25, -118.40. HRMS (ESI-TOF, *m/z*): $[M+H]^+$calcd. for $C_{13}H_{12}F_2NO_2$ 252.0836, found: 252.0840.

*Ethyl 6-(difluoromethyl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxylate (**9f**):* white solid (70% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.65 – 8.60 (m, 1H), 7.53 – 7.47 (m, 1H), 7.14 (s, 1H), 6.18 (s, 2H), 4.45 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 165.2, 153.3, 149.7, 147.1, 138.8, 124.8, 113.5, 111.1, 108.7, 106.3, 103.0, 102.4, 61.9, 14.2.$^{19}$F NMR (376 MHz, $CDCl_3$) -117.81, -117.95. HRMS (ESI-TOF, *m/z*): $[M+H]^+$calcd. for $C_{14}H_{12}F_2NO_4$ 296.0734, found: 296.0729.

*Ethyl 6-(difluoromethyl)-[1,3]dioxolo[4,5-g]quinoline-7-carboxylate (**9g**):* white solid (90% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.16 – 8.07 (m, 2H), 7.98 – 7.92 (m, 1H), 4.04 – 4.00 (m, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 165.1, 150.8, 146.6, 139.8, 136.0, 131.6, 130.4, 128.2, 123.1, 113.4, 111.0, 53.0. $^{19}$F NMR (376 MHz, $CDCl_3$) -118.63, -118.77. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{13}H_{11}BrF_2NO_2$ 329.9941, found: 329.9936.

*Ethyl 2-(perfluoroethyl)quinoline-3-carboxylate (**9h**):* colorless oil (77% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.97 – 7.84 (m, 2H), 7.72 (t, J = 7.6 Hz, 1H), 4.46 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 166.1, 146.6, 139.2, 132.1, 130.2, 129.6, 128.0, 127.1, 125.5, 120.9, 120.5, 117.7, 62.5, 13.9. $^{19}$F NMR (376 MHz, $CDCl_3$) -80.28, -108.88. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{14}H_{11}F_5NO_2$ 320.0710, found: 320.0707.

*Ethyl 6-chloro-2-(perfluoroethyl)quinoline-3-carboxylate (**9i**):* white solid (73% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.14 (t, J = 7.5 Hz, 1H), 7.92 (d, J = 2.3 Hz, 1H), 7.84 – 7.78 (m, 1H), 4.47 (q, J = 7.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 165.7, 145.0, 144.6, 138.2, 135.8, 133.1, 131.7, 127.7, 126.5, 120.2, 117.3, 111.7, 62.7, 13.9.$^{19}$F NMR (376 MHz, $CDCl_3$) -80.33, -109.03. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{14}H_{10}ClF_5NO_2$ 354.0320, found: 354.0317.

*Phenyl(2-(trifluoromethyl)quinolin-3-yl)methanone (**9j**)*: white solid (70% yield). $^1$H NMR

(400 MHz, $CDCl_3$) δ 8.32 – 8.25 (m, 2H), 7.94 – 7.88 (m, 2H), 7.83 (dd, J = 8.4, 1.2 Hz, 2H), 7.75 (dd, J = 8.1, 7.1 Hz, 1H), 7.65 (ddd, J = 8.8, 2.5, 1.2 Hz, 1H), 7.49 (td, J = 7.5, 1.2 Hz, 2H). $^{13}$CMR (101 MHz, $CDCl_3$) δ 193.5, 146.8, 144.6, 137.3, 136.3, 134.2, 131.9, 130.7, 130.2, 130.2, 129.6, 128.7, 127.9, 127.3, 122.5, 119.8.$^{19}$F NMR (376 MHz, $CDCl_3$) -62.80. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{17}H_{11}F_3NO$ 302.0793, found: 302.0796.

*6-Bromo-2-(4-bromophenyl)-3-fluoroquinoline (**12a**)*: white solid (69% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.91 (m, 4H), 7.81 – 7.71 (m, 2H), 7.70 – 7.60 (m, 2H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 156.7, 154.0, 143.7, 134.2, 132.5, 131.8, 131.2, 130.8, 129.4, 128.8, 128.7, 124.5, 121.7, 119.1, 118.9.$^{19}$F NMR (376 MHz, $CDCl_3$) -122.64, 122.67. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{15}H_9Br_2FN$ 378.9008, found: 378.9012.

*6-Bromo-2-(4-bromophenyl)-3-fluoroquinoline (**13a**)*: white solid (69% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 1H), 8.18 – 8.12 (m, 1H), 8.08 – 8.02 (m, 2H), 7.84 – 7.79 (m, 2H), 7.76 – 7.70 (m, 1H), 7.67 – 7.61 (m, 2H), 7.53 (ddd, J = 8.1, 5.7, 1.2 Hz, 1H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 156.0, 148.2, 138.5, 136.9, 131.9, 129.8, 129.7, 129.1, 127.5, 127.2, 126.5, 123.9, 118.5. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{15}H_{11}BrN$ 284.0075, found: 284.0079.

*(E)-2-Styrylquinoline (**13b**)*: white solid (81% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.77 (dd, J = 9.8, 7.2 Hz, 1H), 7.73 – 7.62 (m, 5H), 7.56 – 7.46 (m, 2H), 7.43 – 7.38 (m, 2H), 7.35 – 7.30 (m, 1H). $^{13}$CMR (101 MHz, $CDCl_3$) δ 156.0, 148.3, 136.5, 136.3, 134.4, 132.5, 132.4, 132.1, 132.0, 129.7, 129.2, 128.8, 128.7, 128.6, 127.5, 127.3, 127.2, 126.1, 119.2. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{17}H_{14}N$ 232.1126, found: 232.1130.

*(E)-2-(4-Methylstyryl)quinoline (**13c**)*: white solid (78% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 16.9, 8.6 Hz, 2H), 7.77 (d, J = 8.1 Hz, 1H), 7.73 – 7.63 (m, 3H), 7.54 (d, J = 7.9 Hz, 2H), 7.48 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.36 (d, J = 16.3 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 2.38 (s, 3H). $^{13}$CMR (101 MHz, $CDCl_3$) δ 156.2, 148.3, 138.7, 137.5, 136.2, 134.4, 133.7, 129.7, 129.5, 129.2, 128.7, 128.0, 127.5, 127.3, 127.2, 126.0, 119.2. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{18}H_{16}N$ 246.1283, found: 246.1279.

*6-Bromo-2-propylquinoline (**13d**)*: white solid (80% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, J = 16.9, 8.6 Hz, 2H), 7.77 (d, J = 8.1 Hz, 1H), 7.73 – 7.63 (m, 3H), 7.54 (d, J = 7.9 Hz, 2H), 7.48 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.36 (d, J = 16.3 Hz, 1H), 7.21 (d, J = 7.8 Hz, 2H), 2.38 (s, 3H). $^{13}$CMR (101 MHz, $CDCl_3$) δ 163.3, 146.3, 135.3, 134.7, 132.8, 130.4, 129.5, 122.2, 119.4, 41.1, 23.1, 13.9.HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{12}H_{13}BrN$ 250.0231, found: 250.0226.

*6-Bromo-2-(trifluoromethyl)quinoline (**13e**)*: white solid (77% yield). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.6 Hz, 1H), 8.08 (dd, J = 8.9, 3.3 Hz, 2H), 7.88 (dd, J = 9.0, 2.2 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 148.5, 145.7, 137.1, 134.4, 131.7, 129.8, 129.7, 122.9, 117.7, 117.7. $^{19}$F NMR (376 MHz, $CDCl_3$) -67.65. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{10}H_6BrF_3N$ 275.9636, found: 275.9640.

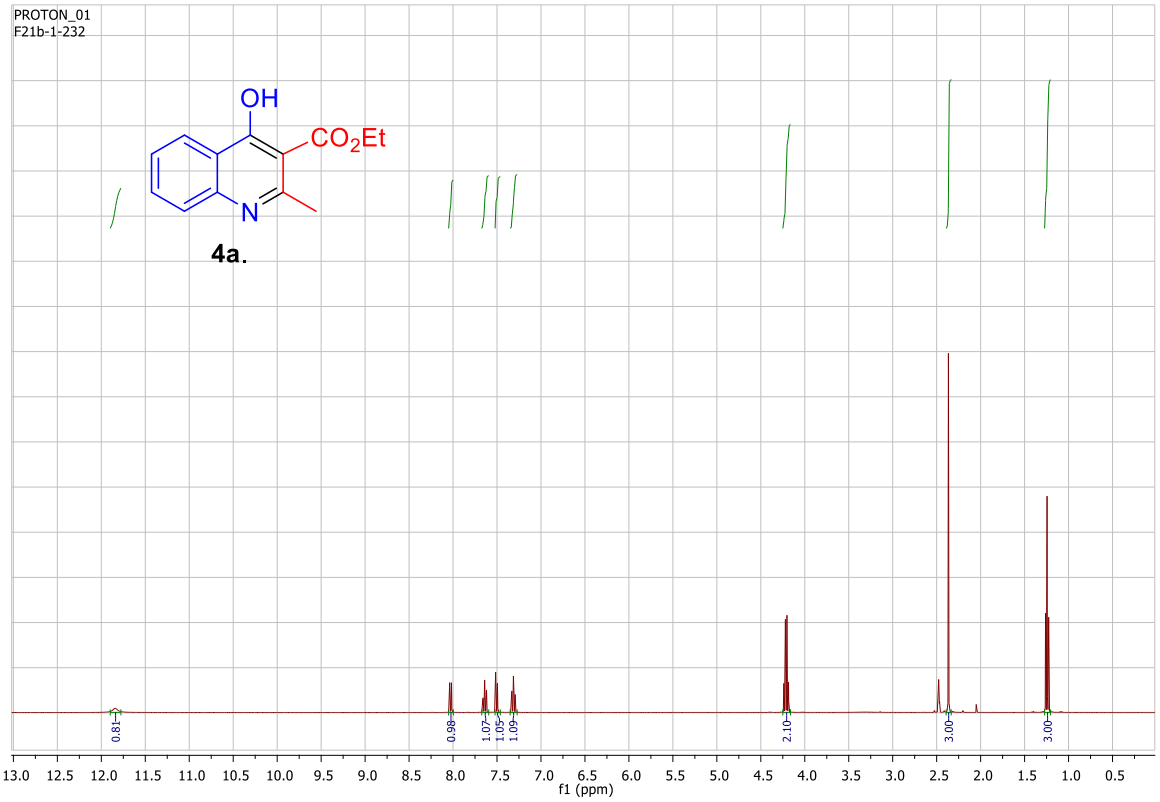
*6-Bromo-2-(difluoromethyl)quinoline (**13f**)*: white solid (73% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.6 Hz, 1H), 8.03 (dd, J = 16.6, 5.5 Hz, 2H), 7.84 (dd, J = 9.0, 2.2 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1H), 6.75 (t, J = 55.2 Hz, 1H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 153.1, 145.7, 136.8, 133.9, 131.4, 129.6, 122.1, 117.7, 117.7, 114.4. $^{19}$F NMR (376 MHz, $CDCl_3$) -114.45, -114.60. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{10}H_6BrF_3N$ 257.9730, found: 275.9727.

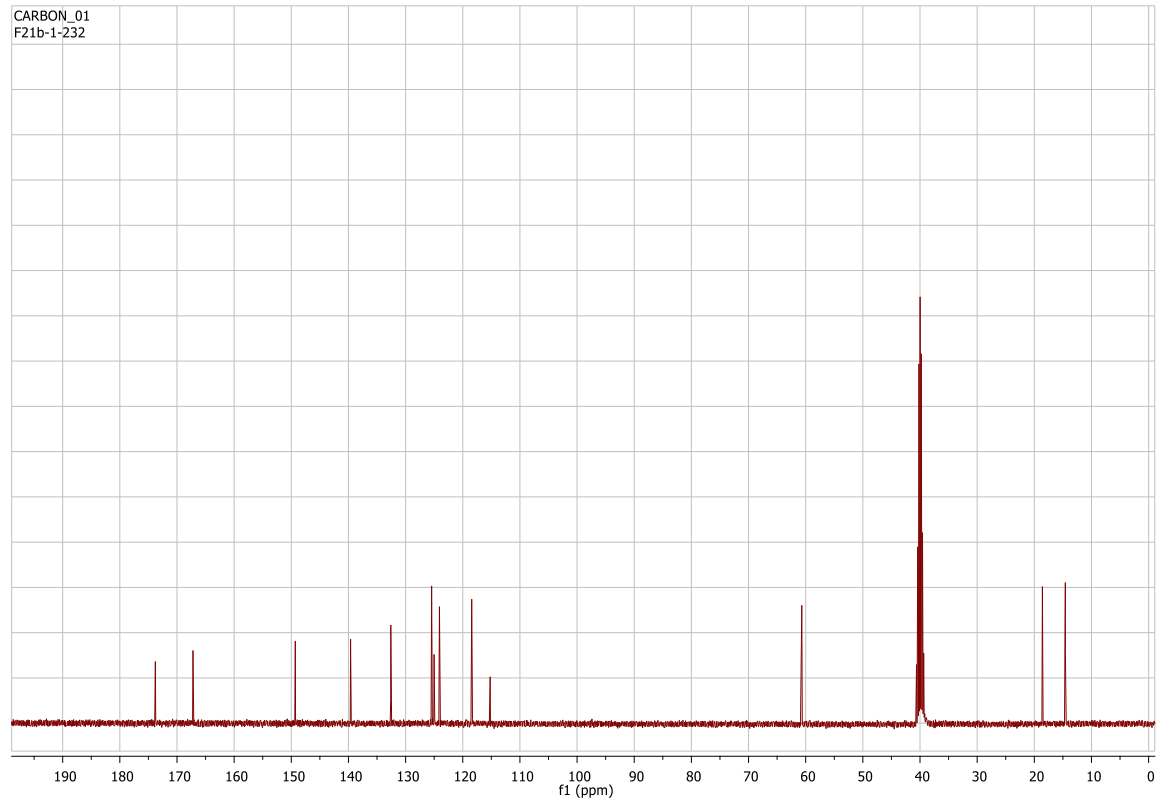
*Diethyl (2-methylquinolin-3-yl)phosphonate (**17a**)*: white solid (79% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 16.3 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.85 (dd, J = 8.1, 0.5 Hz, 1H), 7.77 (ddd, J = 9.6, 7.0, 1.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 4.29 – 4.06 (m, 4H), 2.92 (s, 3H), 1.34 (dt, J = 5.0, 3.8 Hz, 6H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 158.9, 148.8, 144.7, 131.8, 128.4, 126.6, 125.2, 122.2, 120.3, 62.5, 62.4, 25.1, 16.3, 16.3. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{14}H_{19}NO_3P$ 280.1103, found: 280.1099.

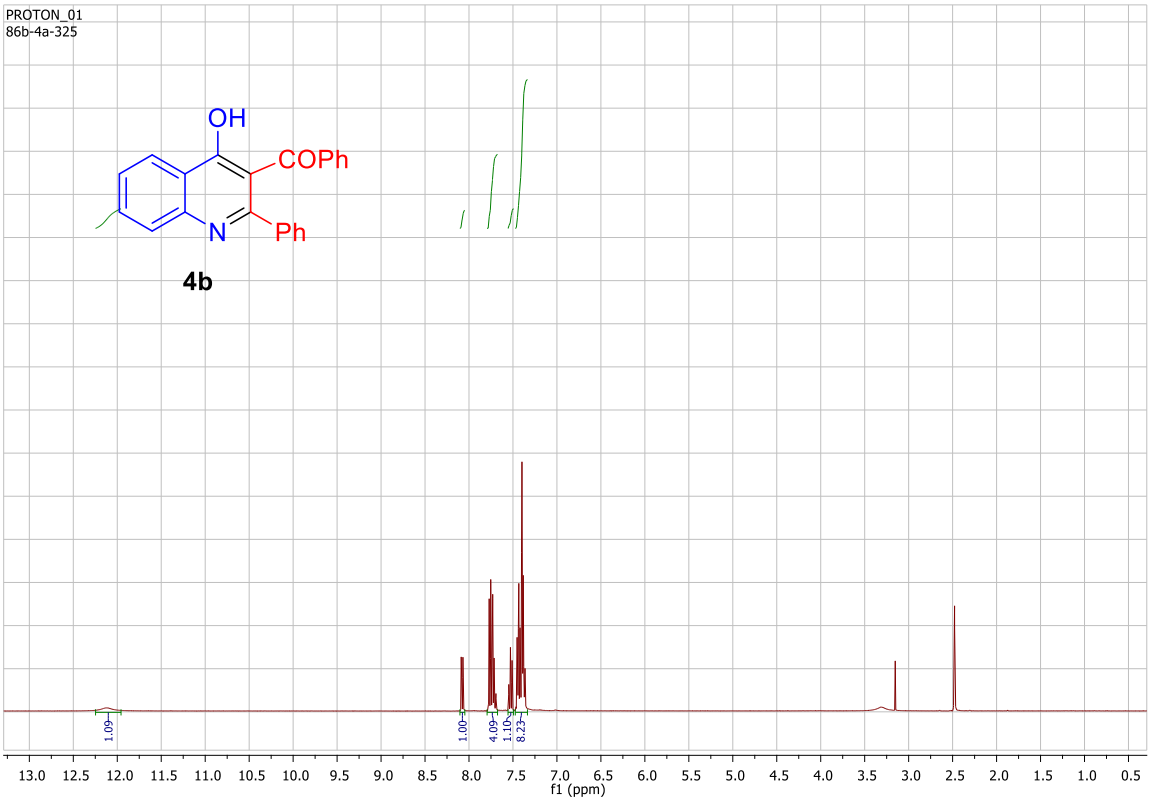
*11H-Indeno[1,2-b]quinolin-11-one (**18a**)*: white solid (80% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.15 – 8.06 (m, 2H), 7.90 – 7.80 (m, 2H), 7.79 – 7.72 (m, 1H), 7.71 – 7.64 (m, 1H), 7.56 – 7.48 (m, 2H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 190.9, 162.1, 150.6, 143.9, 137.5, 135.6, 132.5, 132.1, 131.6, 130.5, 129.8, 127.7, 127.2, 127.1, 124.2, 121.8. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{16}H_{10}NO$ 232.0762, found: 232.0759.

*6H-Chromeno[4,3-b]quinolin-6-one (**18b**)*: off-white solid (69% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.36 – 8.30 (m, 1H), 8.13 – 8.04 (m, 2H), 7.94 – 7.85 (m, 1H), 7.83 – 7.76 (m, 1H), 7.64 – 7.57 (m, 2H), 7.44 – 7.38 (m, 1H).$^{13}$CMR (101 MHz, $CDCl_3$) δ 178.1, 157.5, 156.2, 149.4, 140.0, 136.1, 133.5, 129.6, 128.1, 127.0, 126.4, 126.2, 124.4, 120.9, 118.4, 116.5. HRMS (ESI-TOF, *m/z*): $[M+H]^+$ calcd. for $C_{16}H_{10}NO_2$ 248.0712, found: 248.0716.

## 4. NMR Spectra of Products

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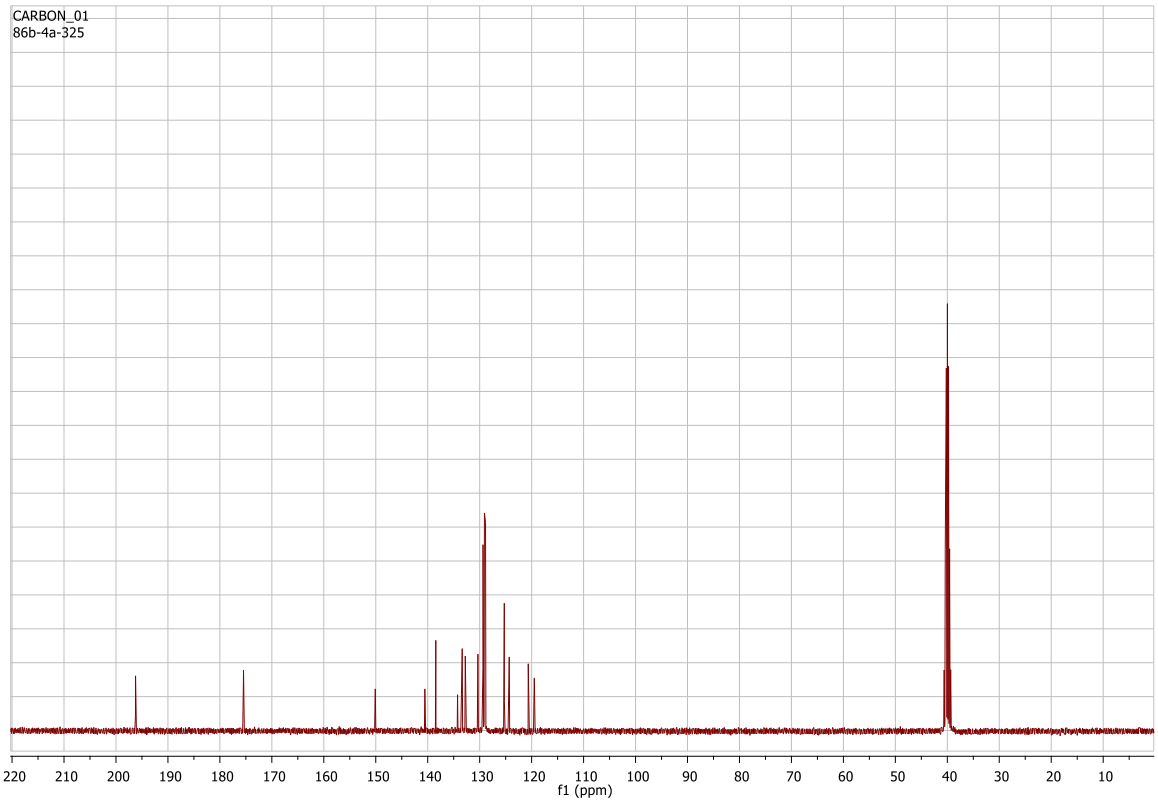
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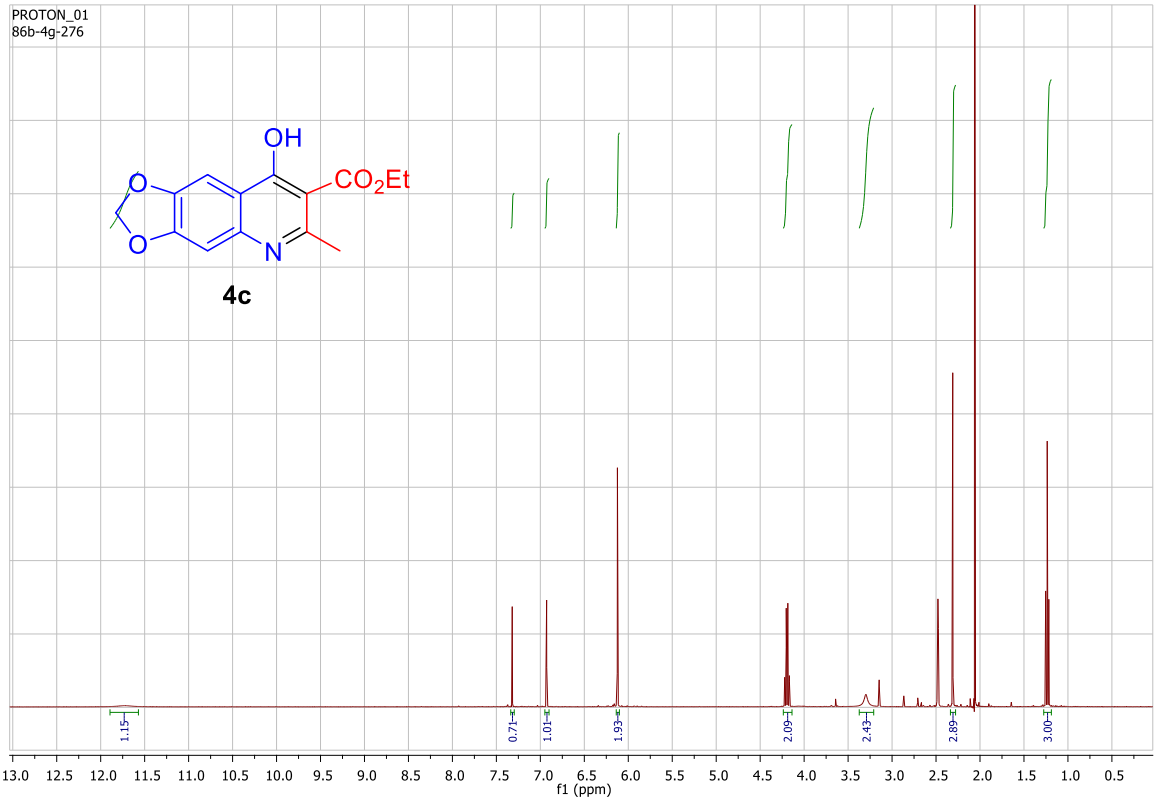
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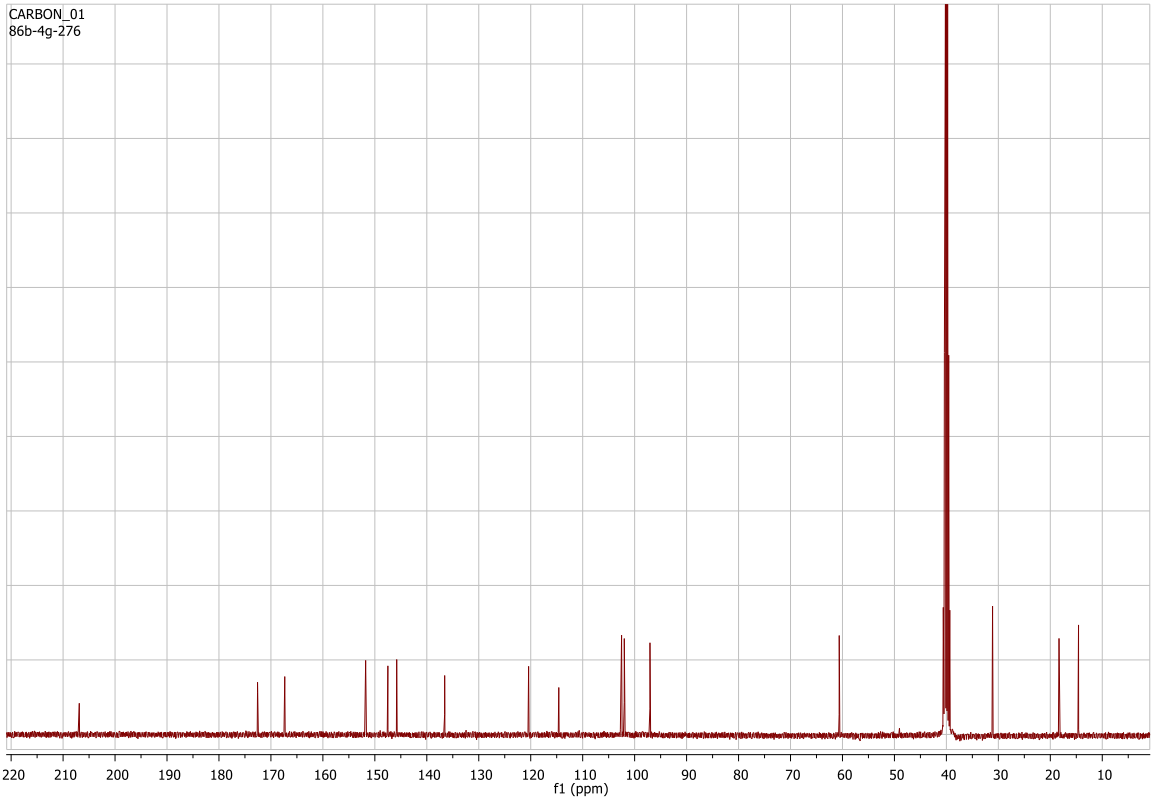
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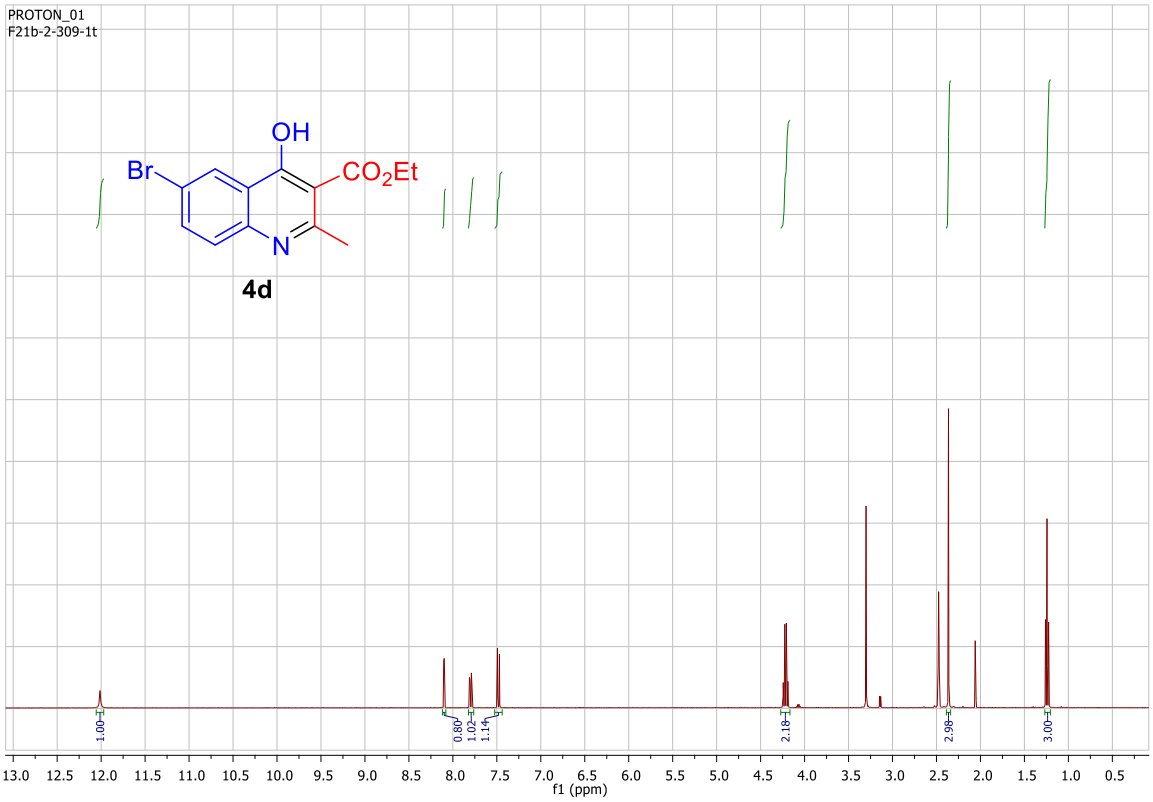
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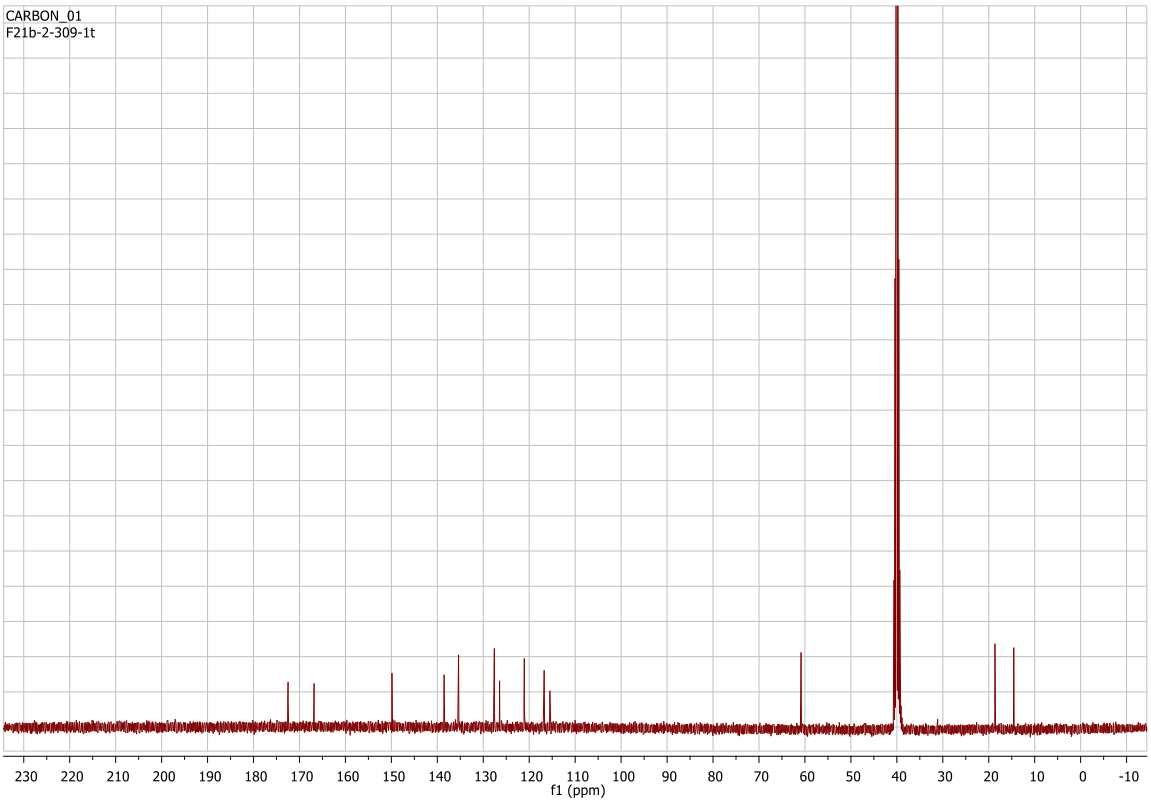
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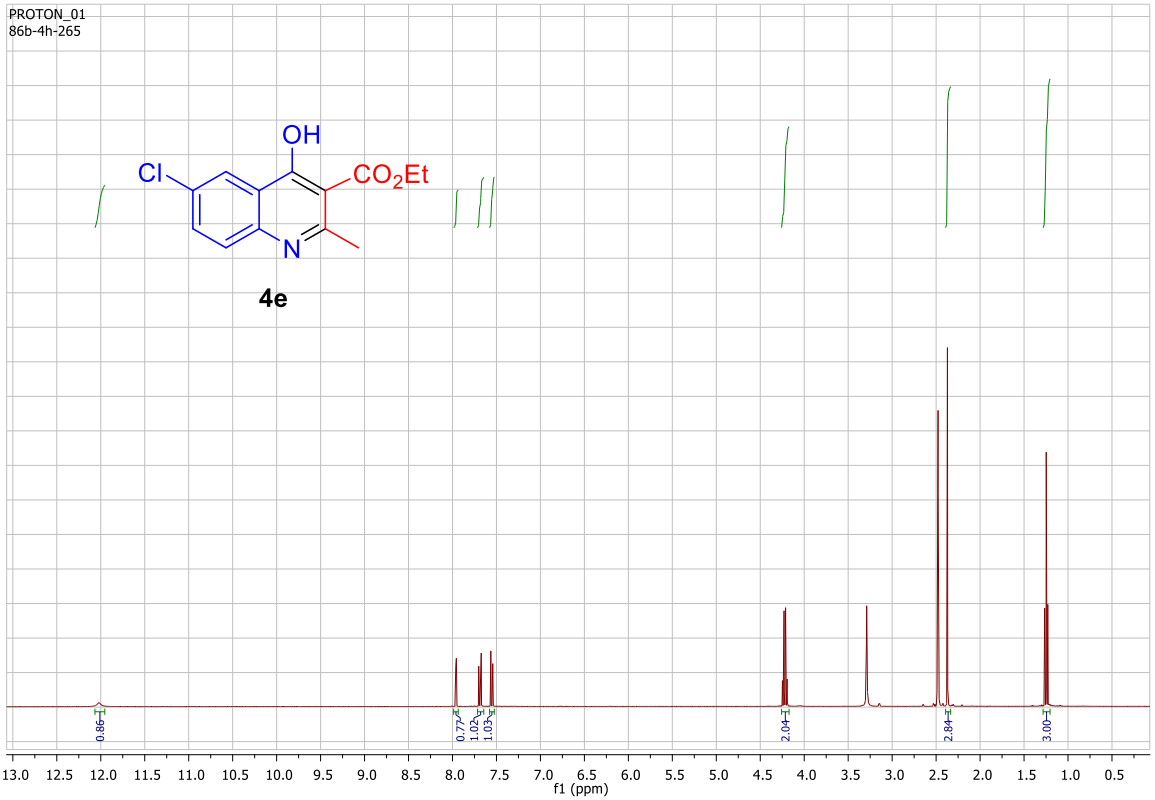
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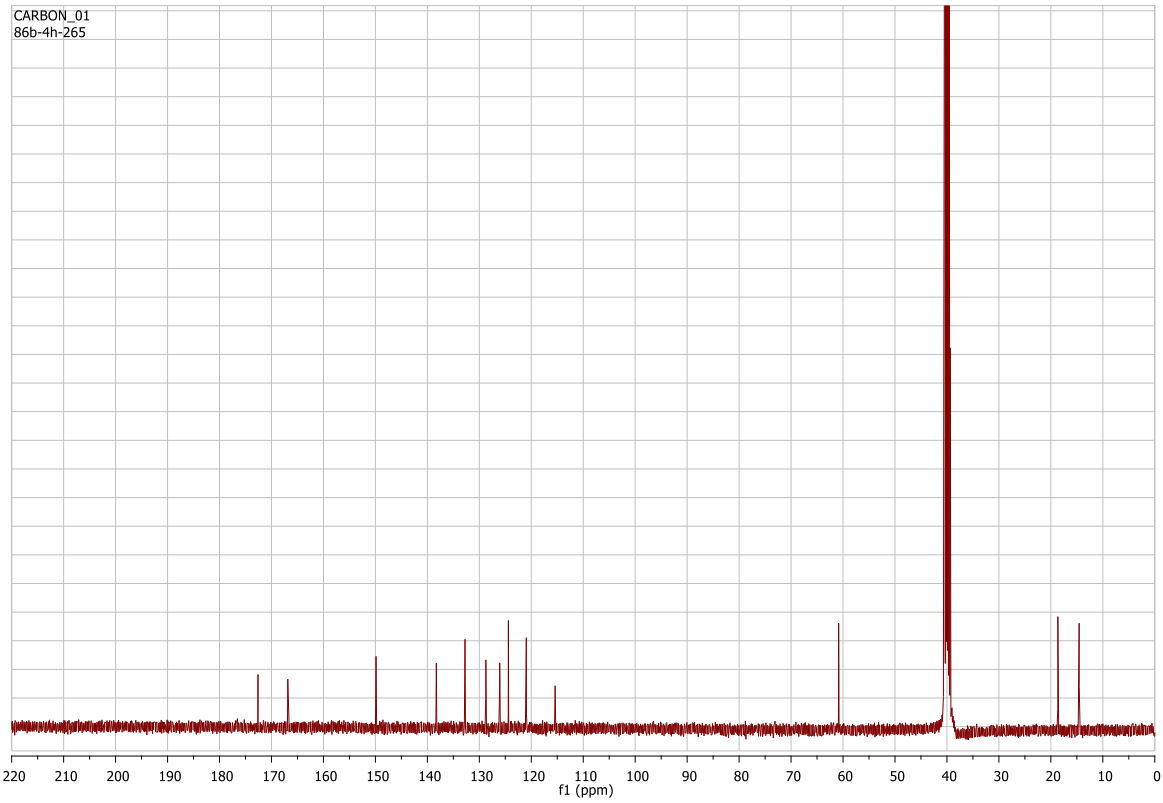
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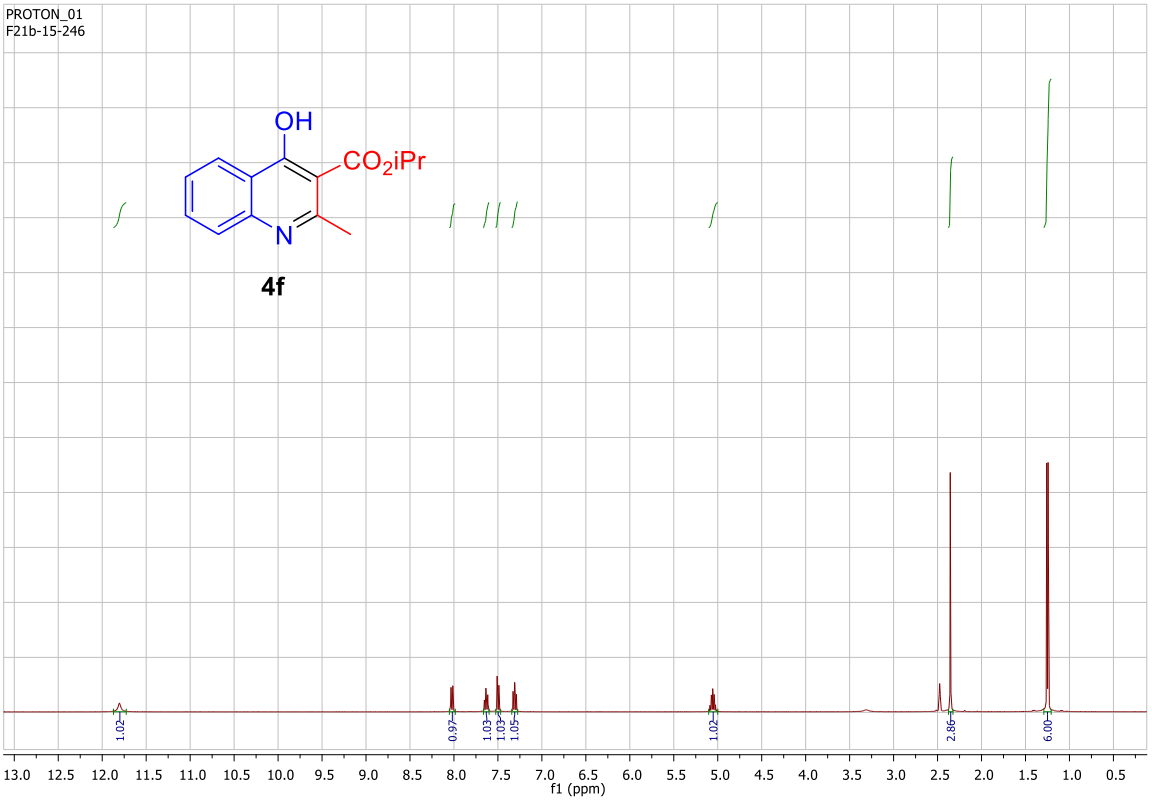
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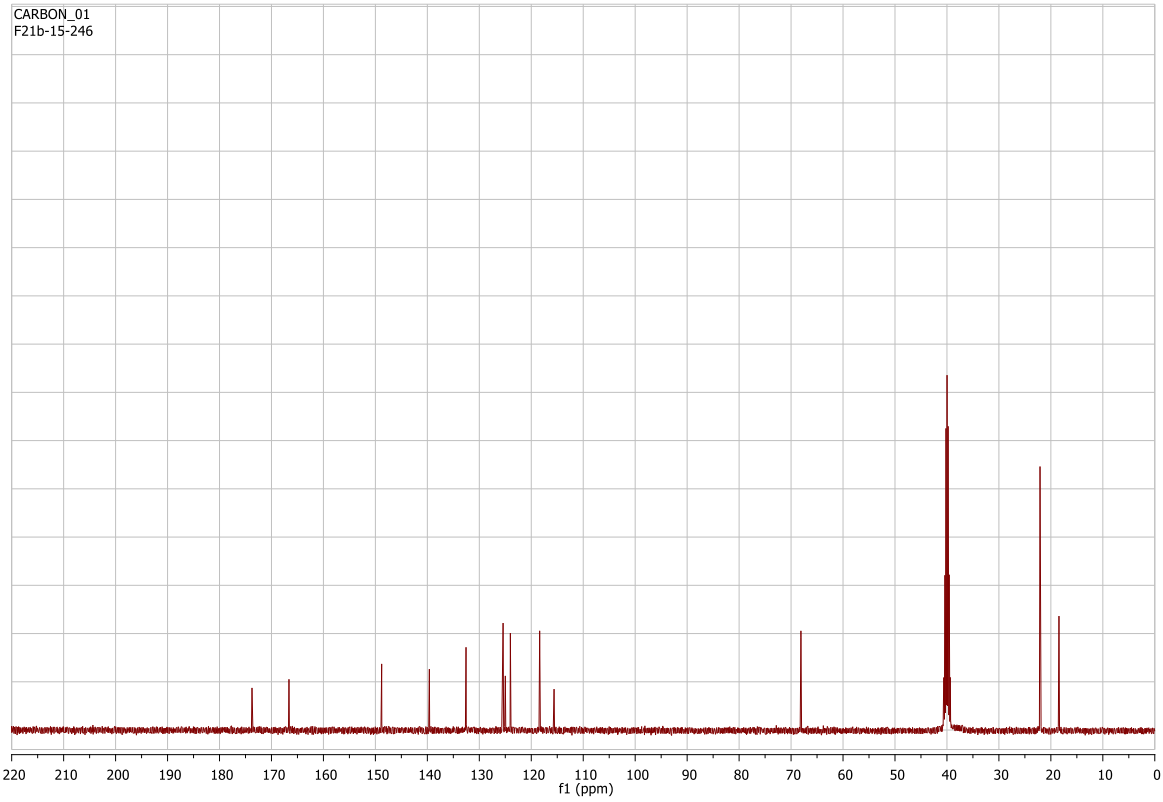
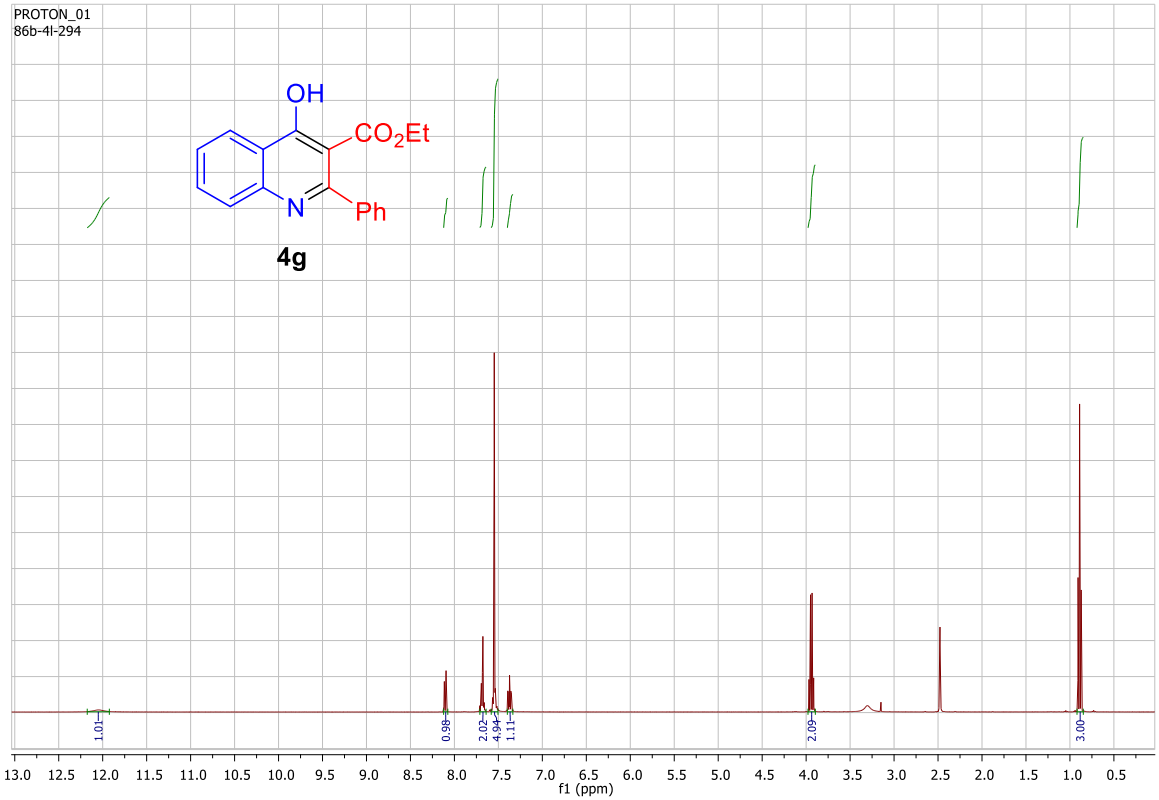
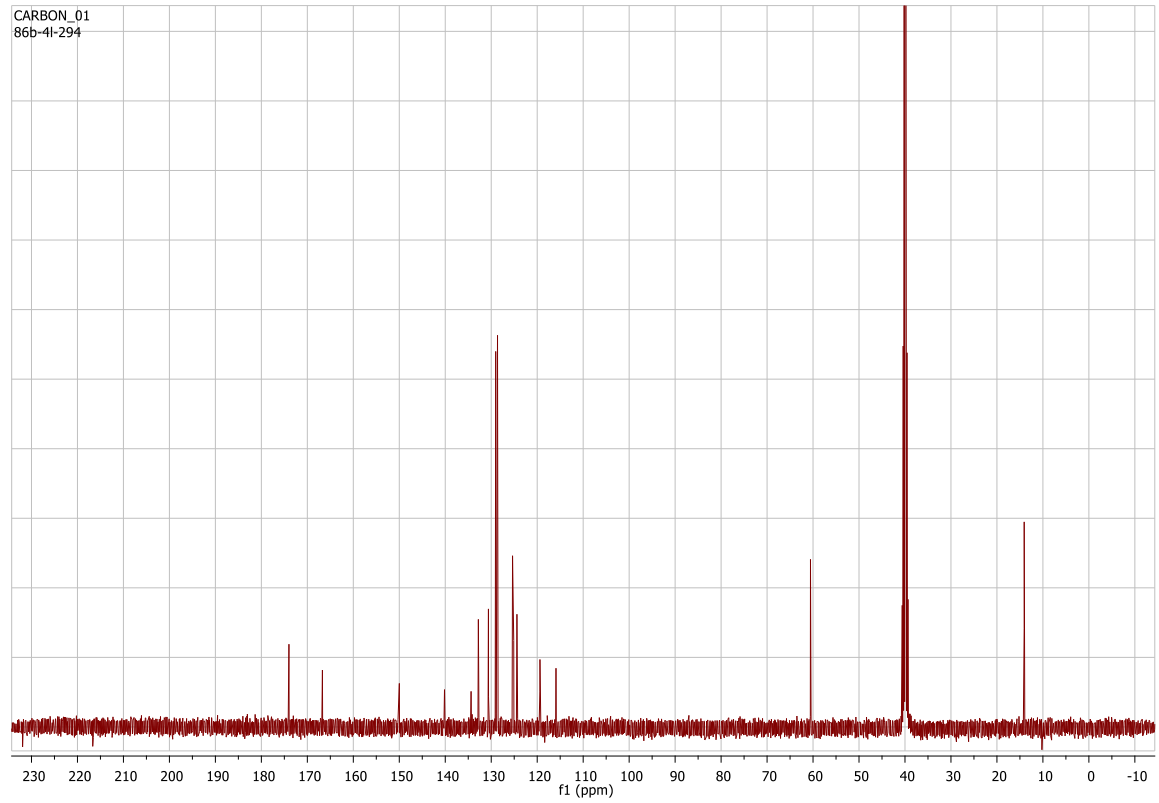
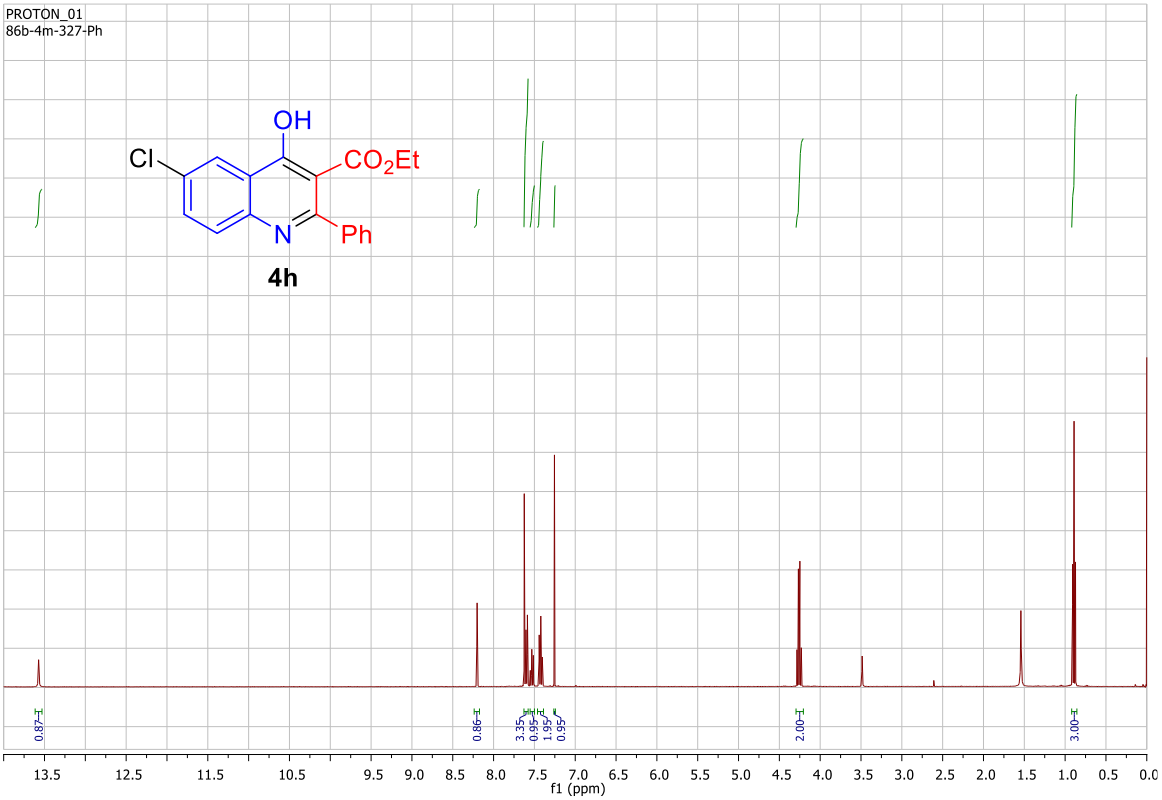
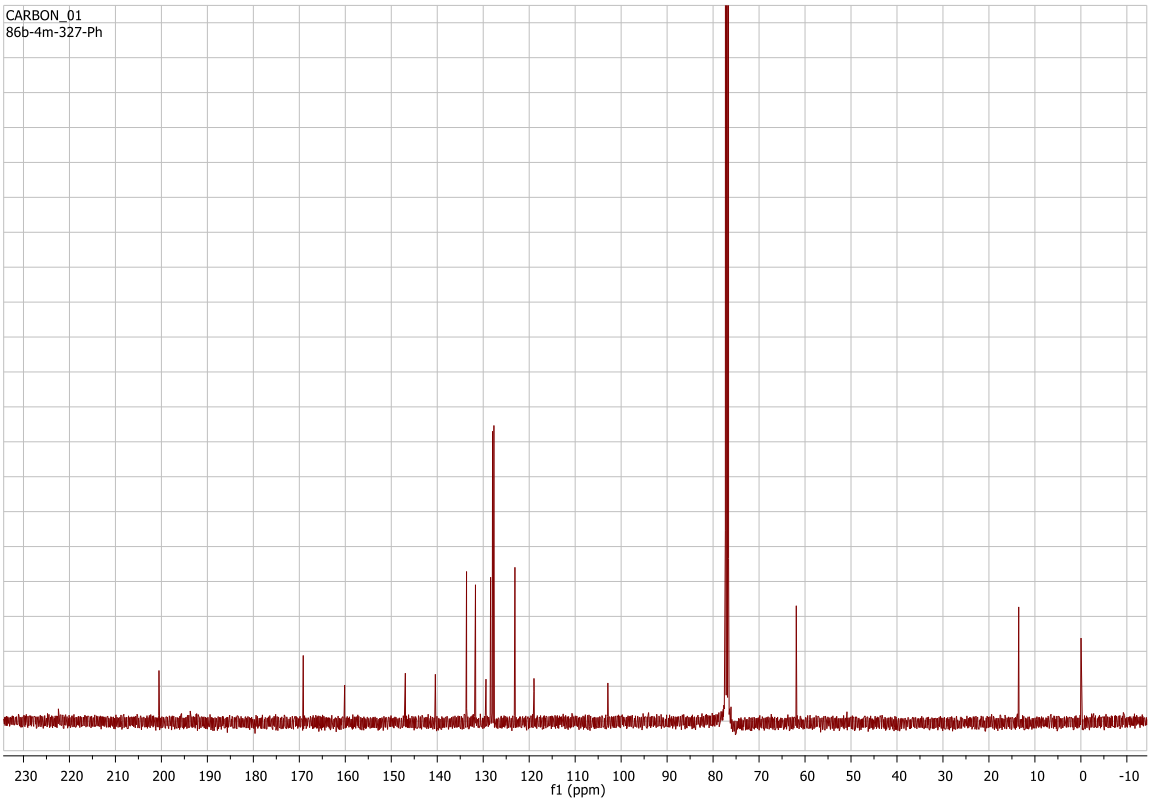
1.02
2.86
6.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

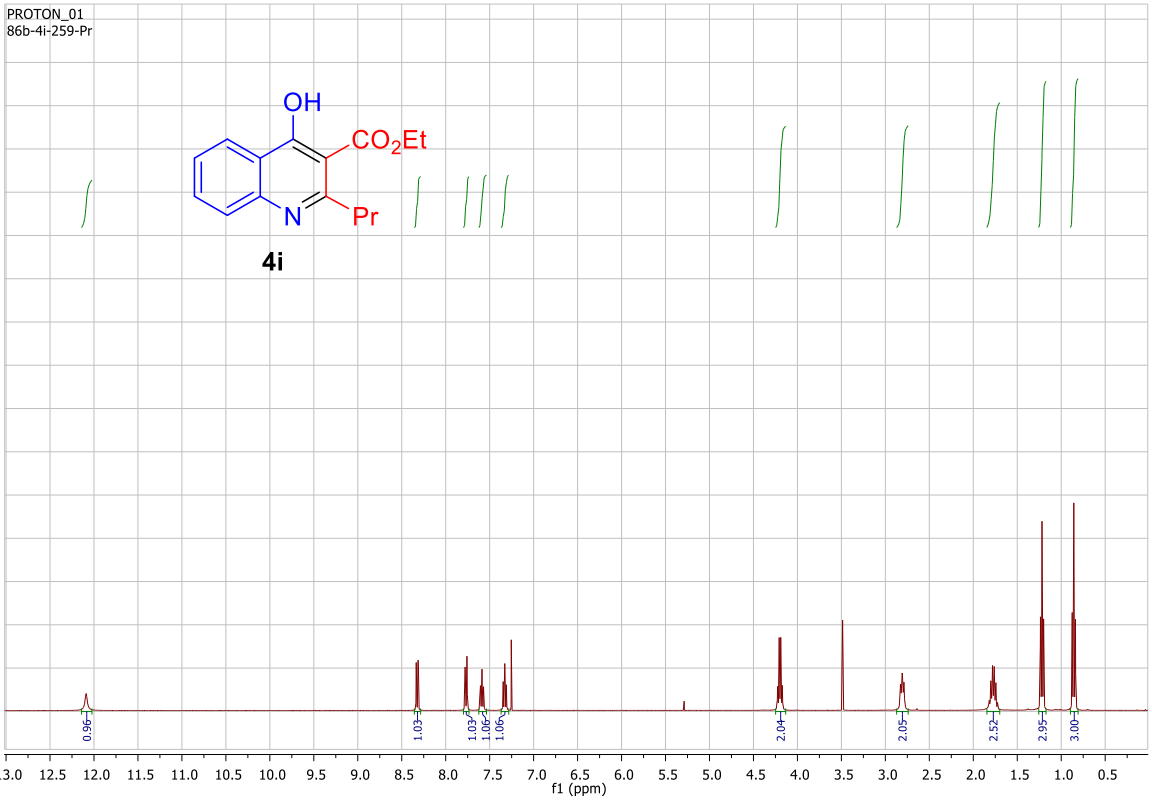

CARBON_01
F21b-15-246
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

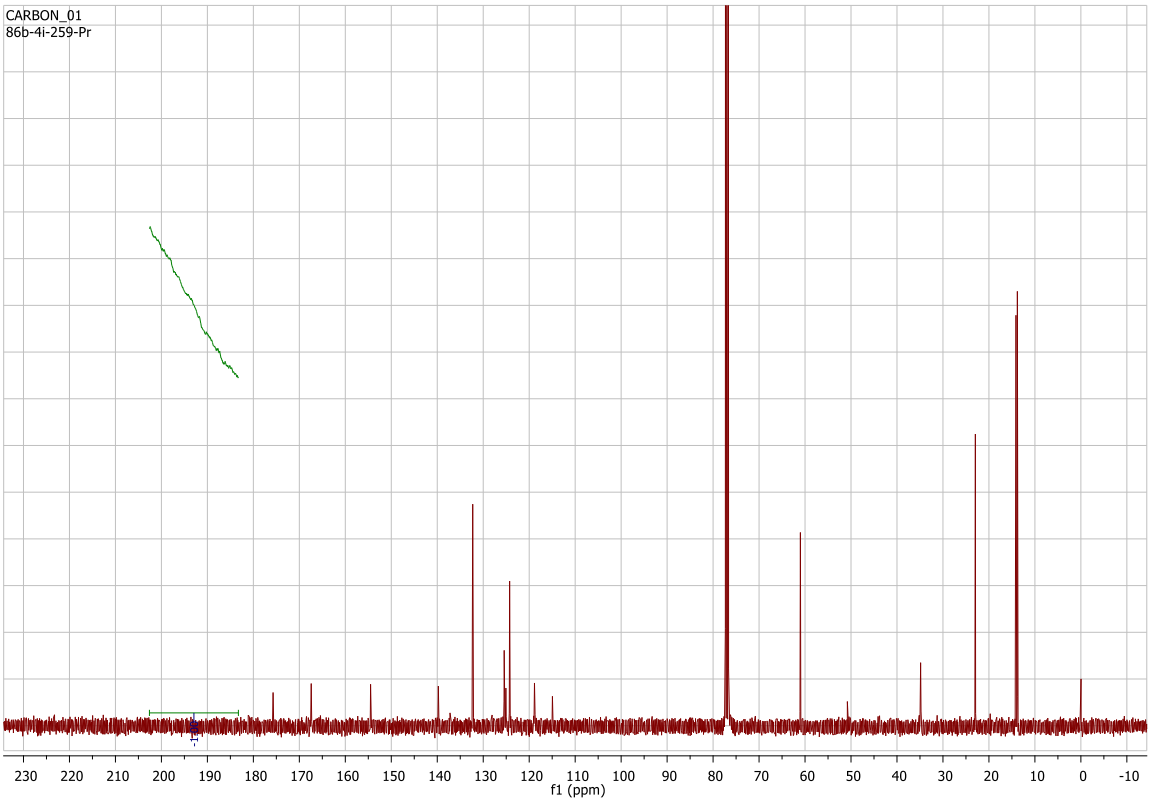

PROTON_01
86b-4l-294
OH
CO2Et
N
Ph
4g
1.01
0.98
2.02
4.94
1.11
2.09
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

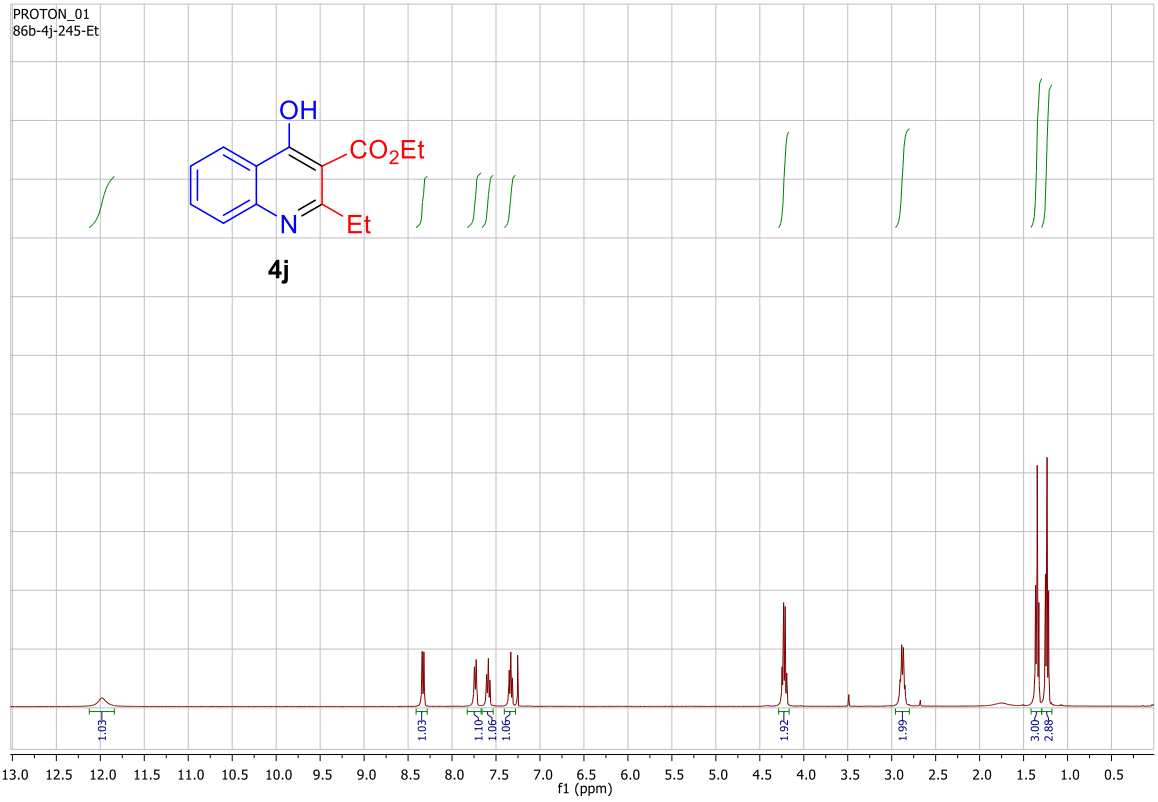

CARBON_01
86b-4l-294
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

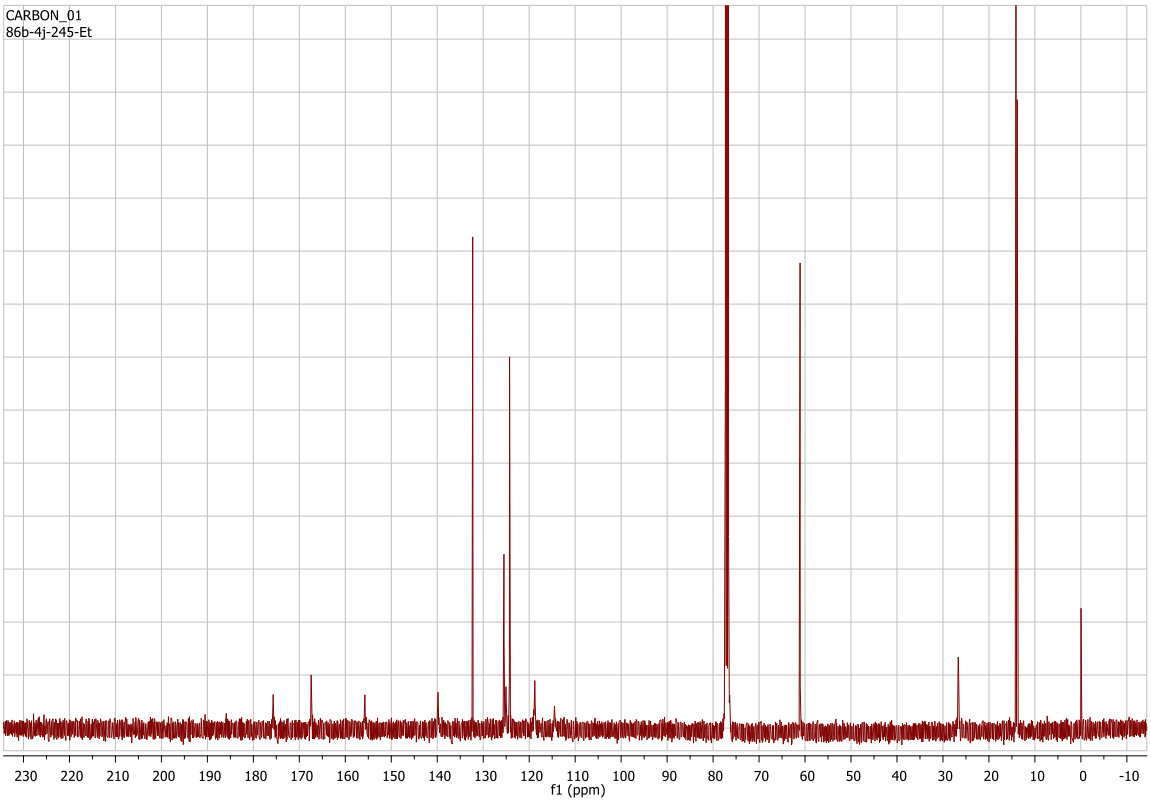

PROTON_01
86b-4m-327-Ph
OH
Cl
CO2Et
N
Ph
4h
0.87
0.86
3.35
0.95
1.95
0.95
2.00
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

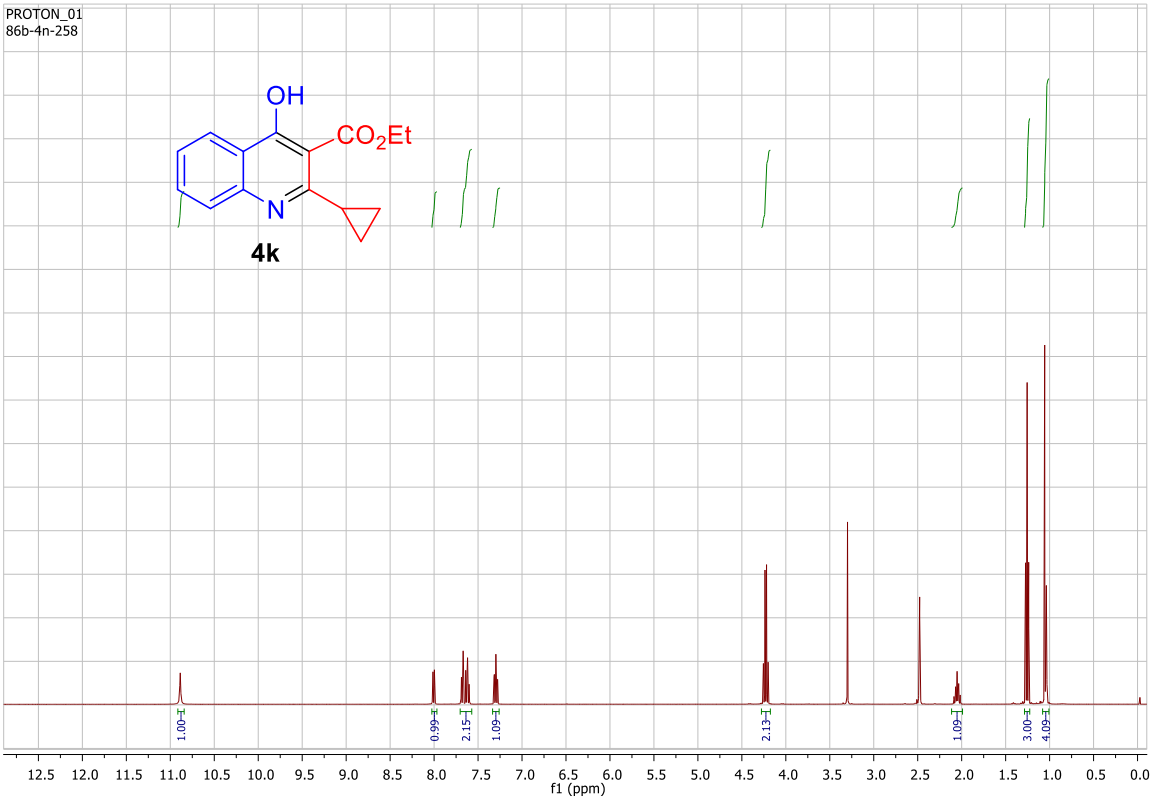

CARBON_01
86b-4m-327-Ph
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

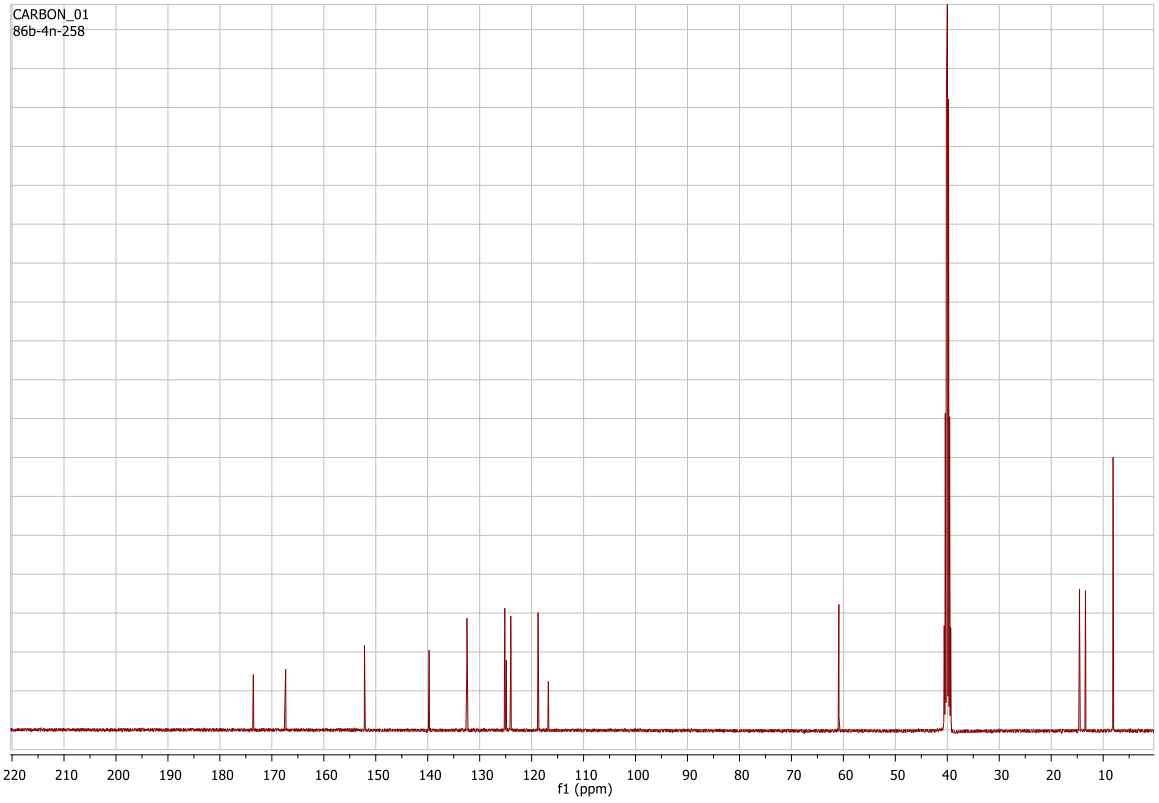

PROTON_01
86b-4i-259-Pr
OH
CO2Et
N
Pr
4i
0.96
1.03
1.03
1.06
1.06
2.04
2.05
2.52
2.95
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

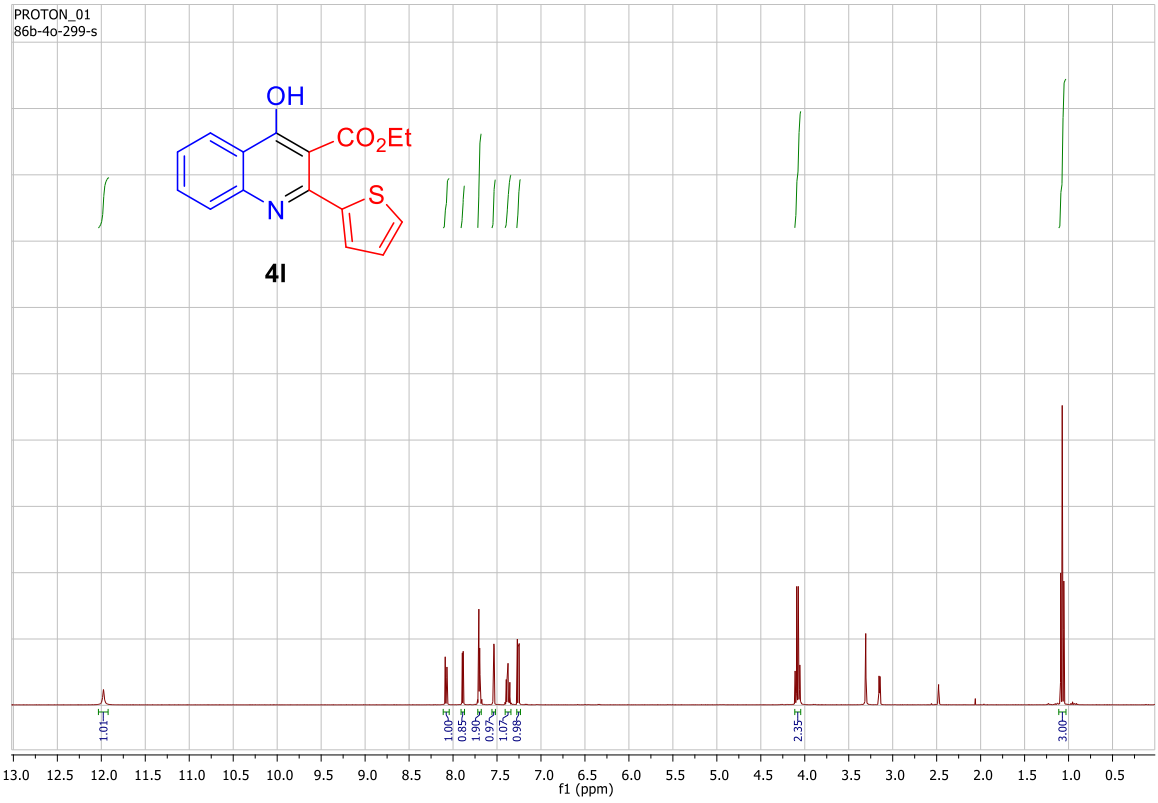

CARBON_01
86b-4i-259-Pr
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

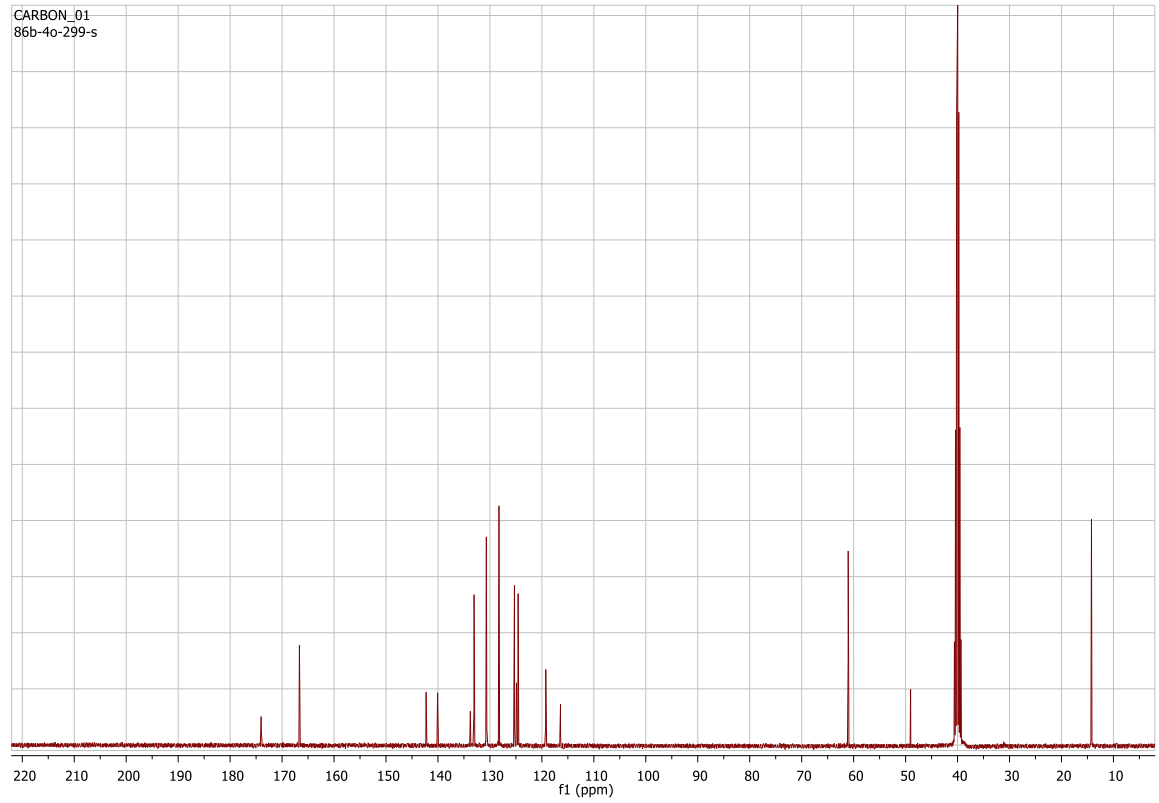

PROTON_01
86b-4j-245-Et
OH
CO2Et
N
Et
4j
1.03
1.03
1.10
1.06
1.06
1.92
1.99
3.00
2.88
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

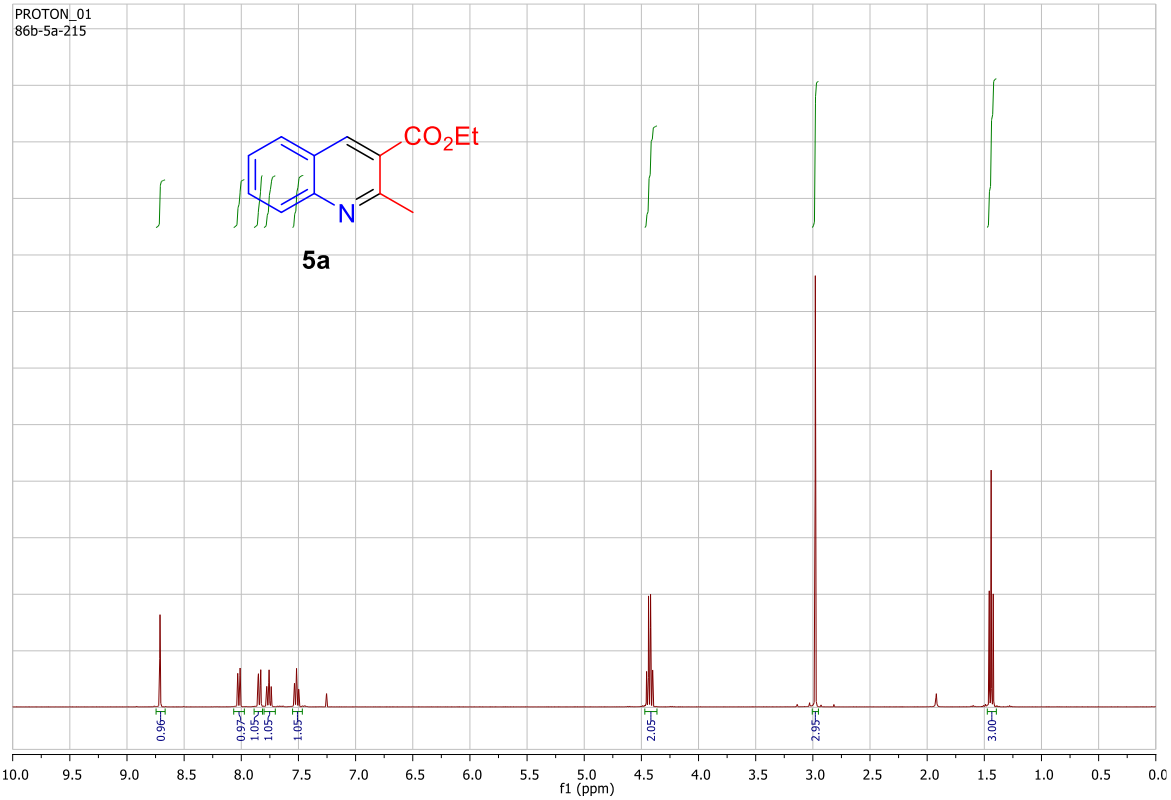

CARBON_01
86b-4j-245-Et
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

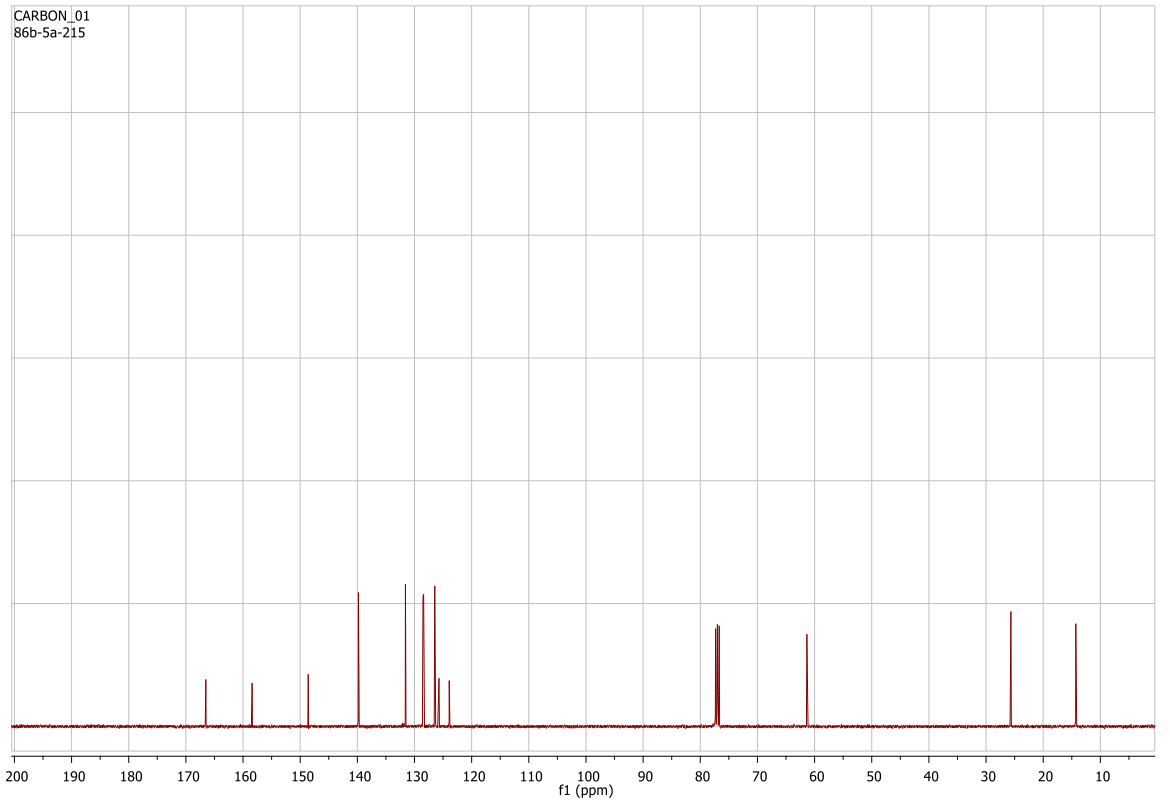

PROTON_01
86b-4n-258
OH
CO2Et
N
4k
1.00
0.99
2.15
1.09
2.13
1.09
3.00
4.09
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

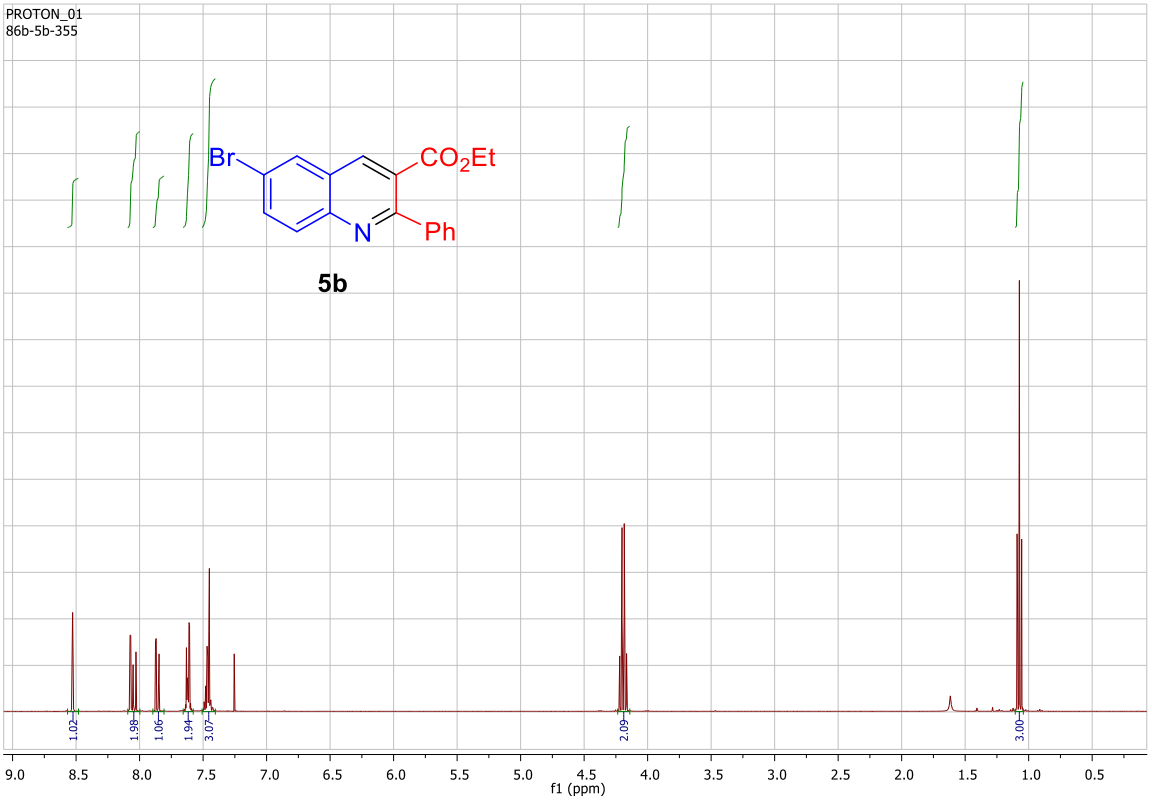

CARBON_01
86b-4n-258
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

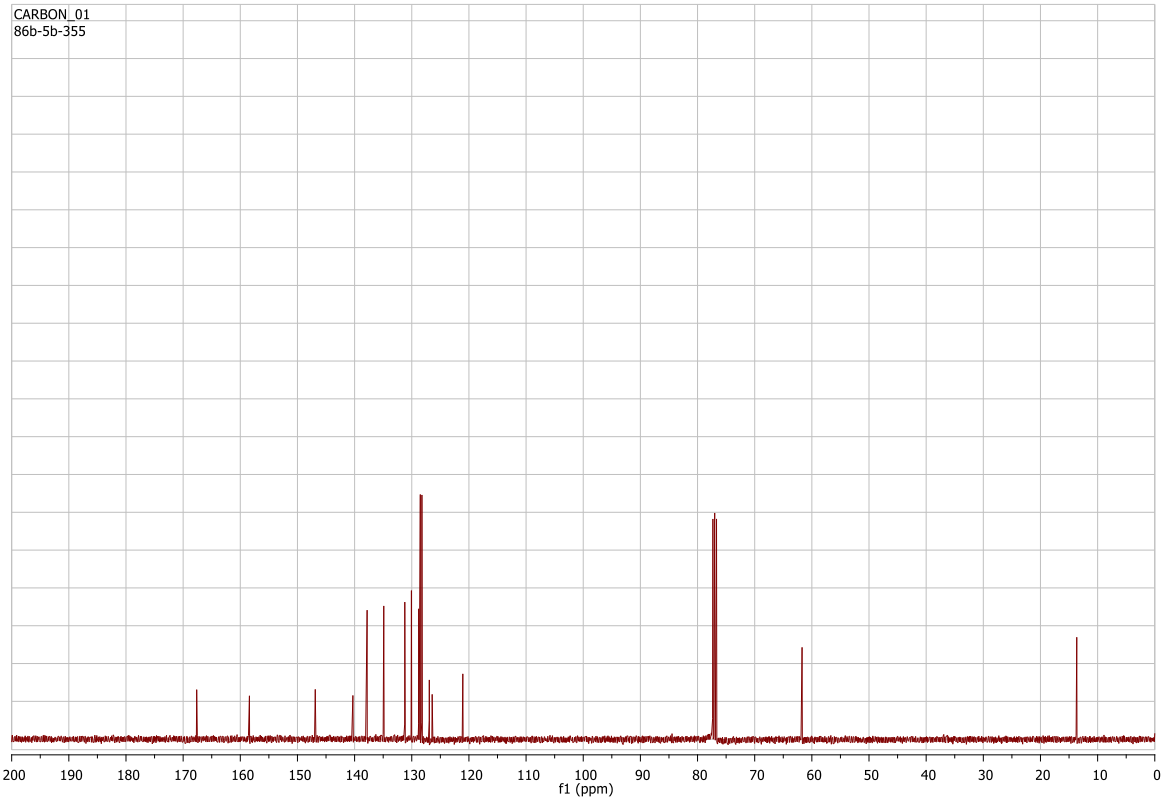

PROTON_01
86b-4o-299-s
OH
CO2Et
N
S
4l
1.01
1.00
0.85
1.90
0.97
1.07
0.98
2.35
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

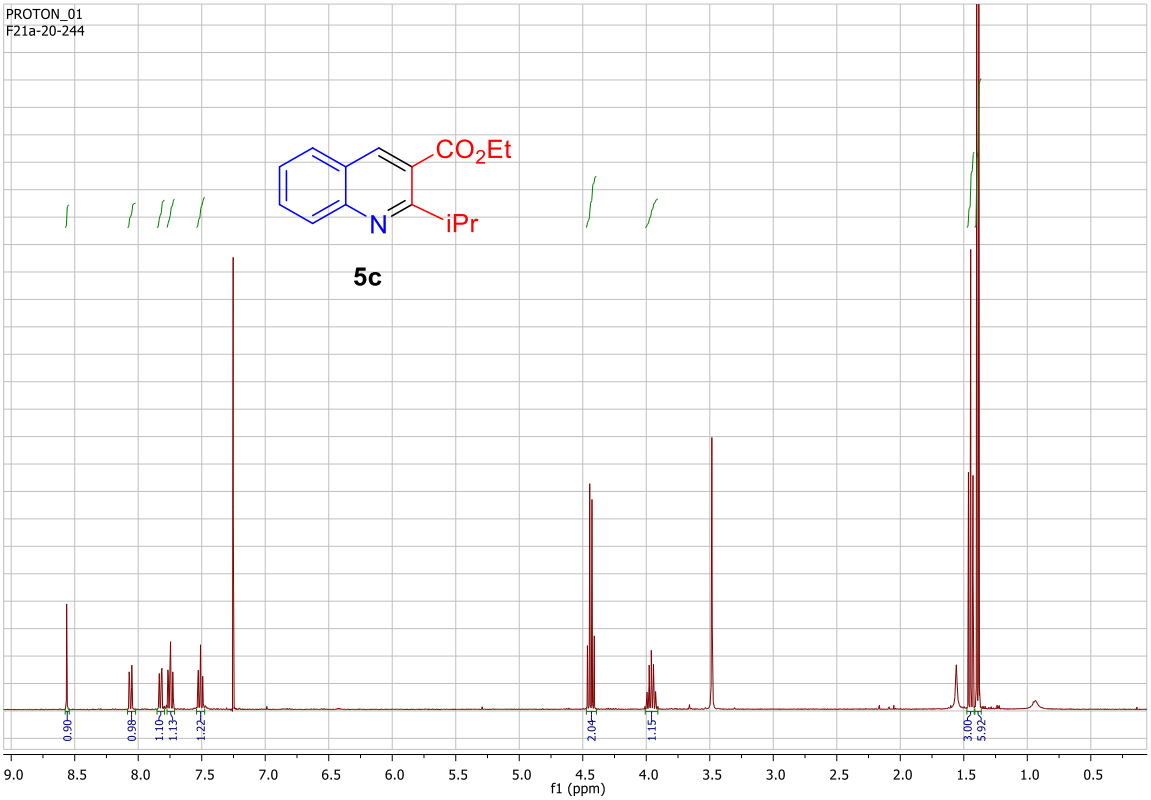

CARBON_01
86b-4o-299-s
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

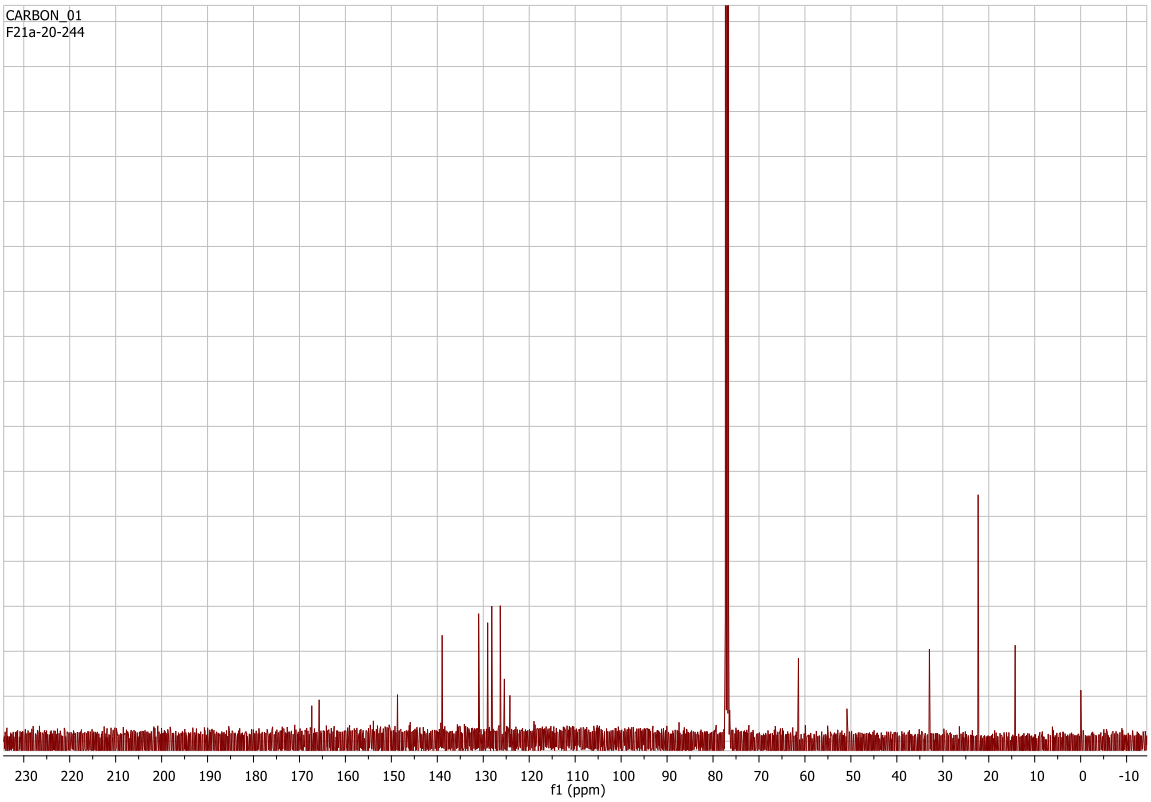

PROTON_01
86b-5a-215
CO2Et
N
5a
0.96
0.97
1.05
1.05
1.05
2.05
2.95
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

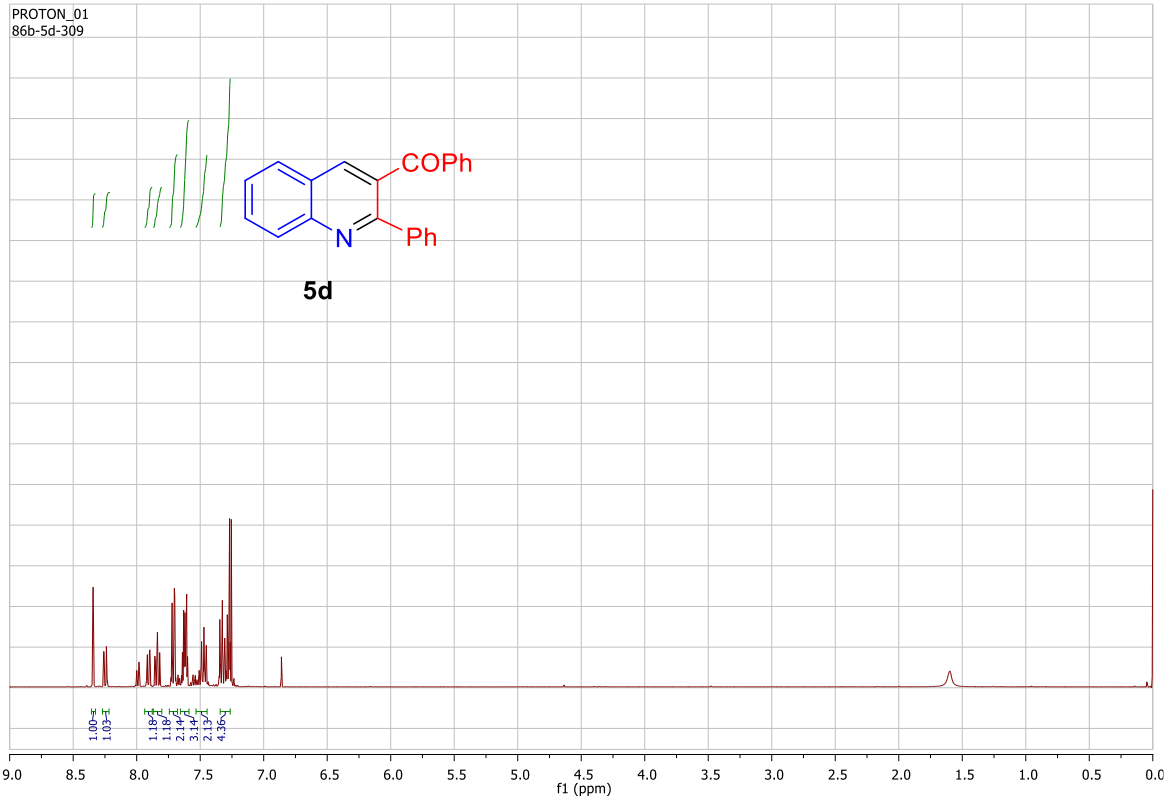

CARBON_01
86b-5a-215
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

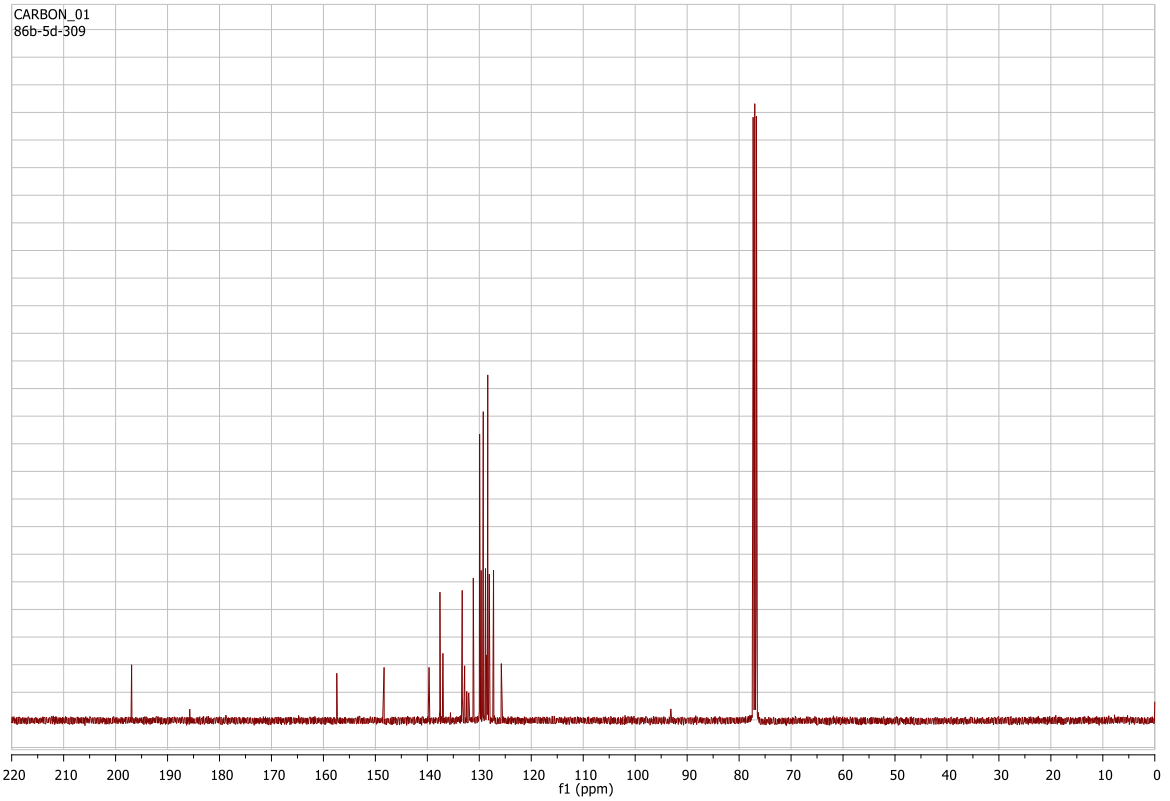

PROTON_01
86b-5b-355
Br
CO2Et
N
Ph
5b
1.02
1.98
1.06
1.94
3.07
2.09
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

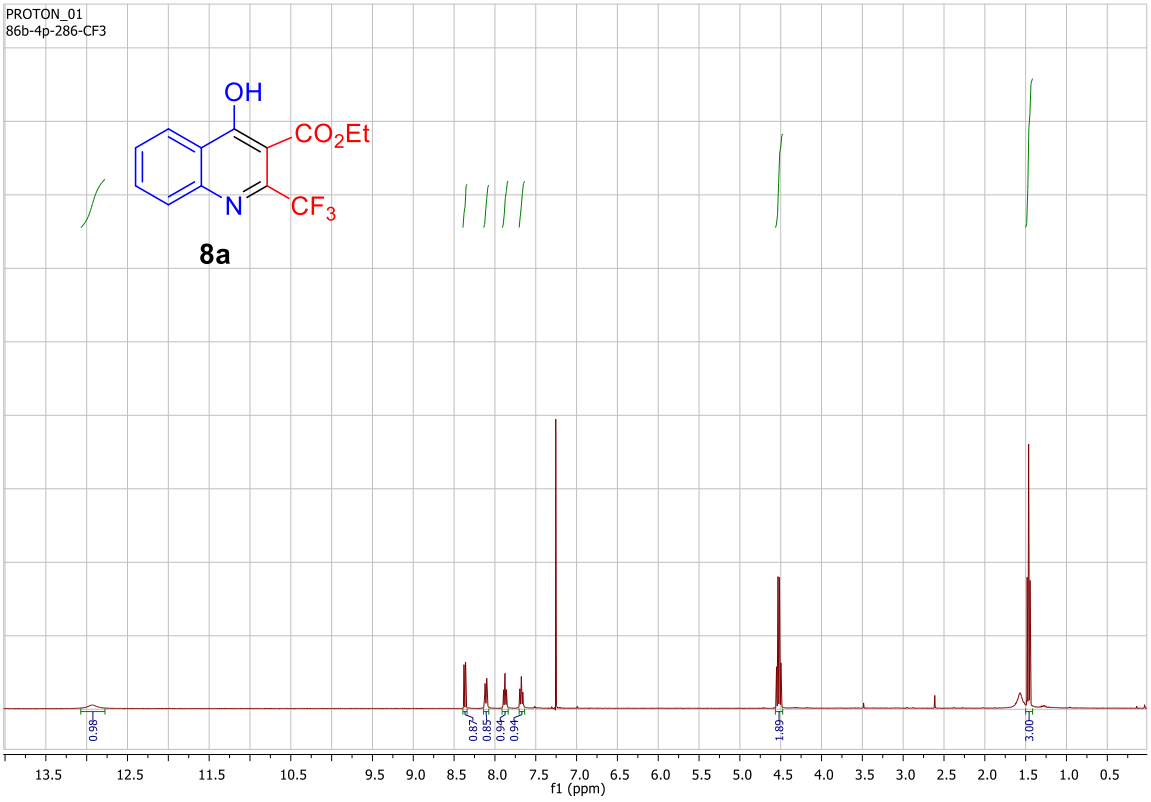

CARBON_01
86b-5b-355
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

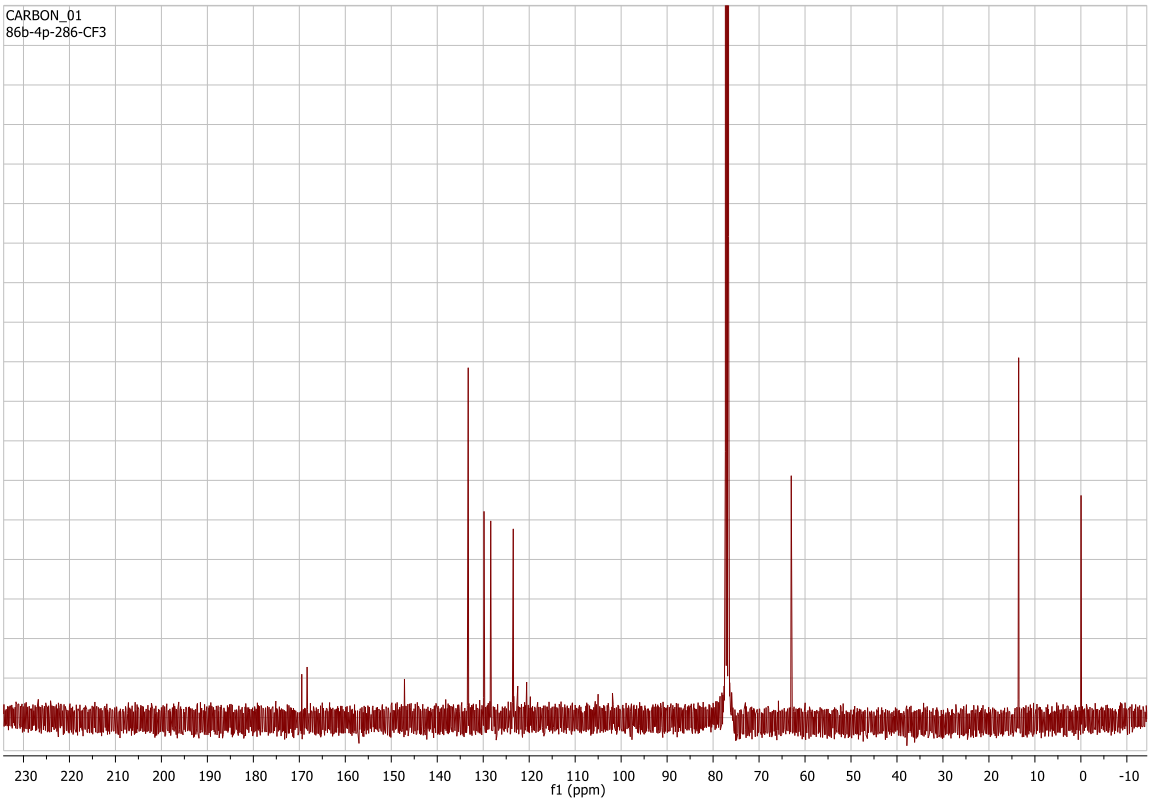

PROTON_01
F21a-20-244
CO2Et
N
iPr
5c
0.90
0.98
1.10
1.19
1.22
2.04
1.15
3.00
5.92
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

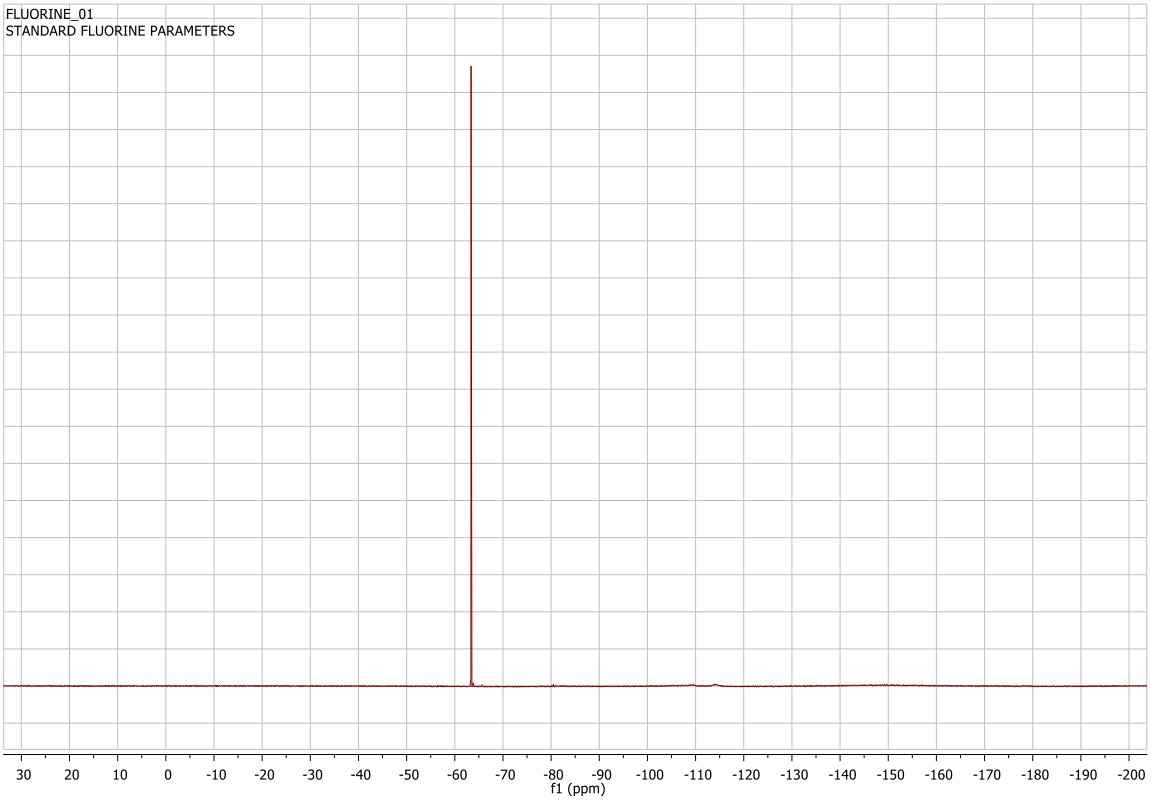

CARBON_01
F21a-20-244
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

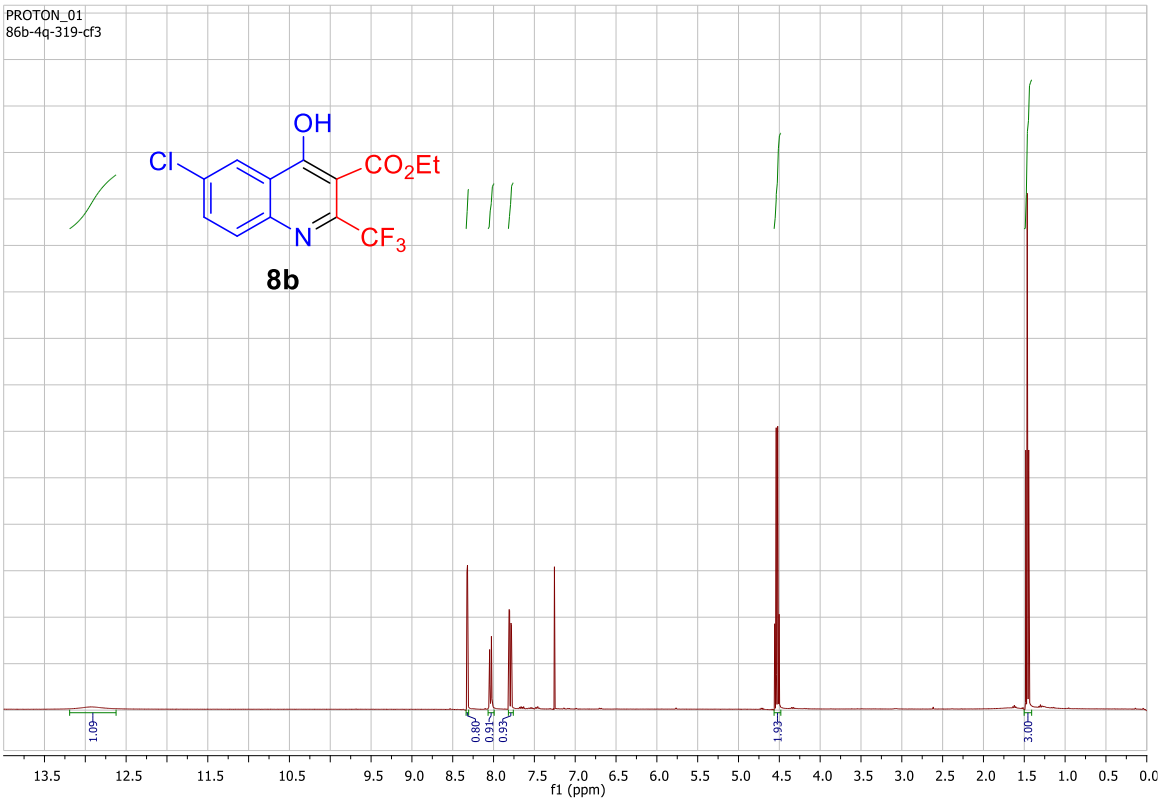

PROTON_01
86b-5d-309
COPh
Ph
N
5d
1.00
1.03
1.18
1.18
2.14
3.14
2.13
4.36
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

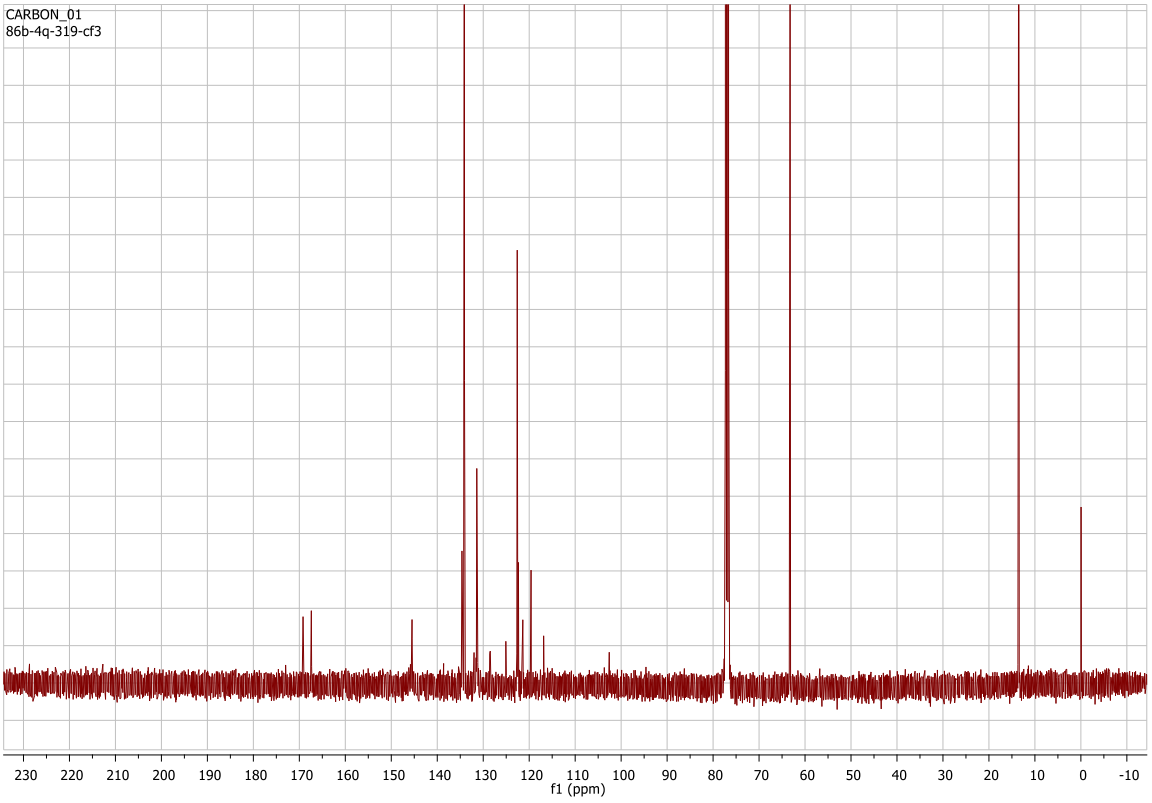

CARBON_01
86b-5d-309
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

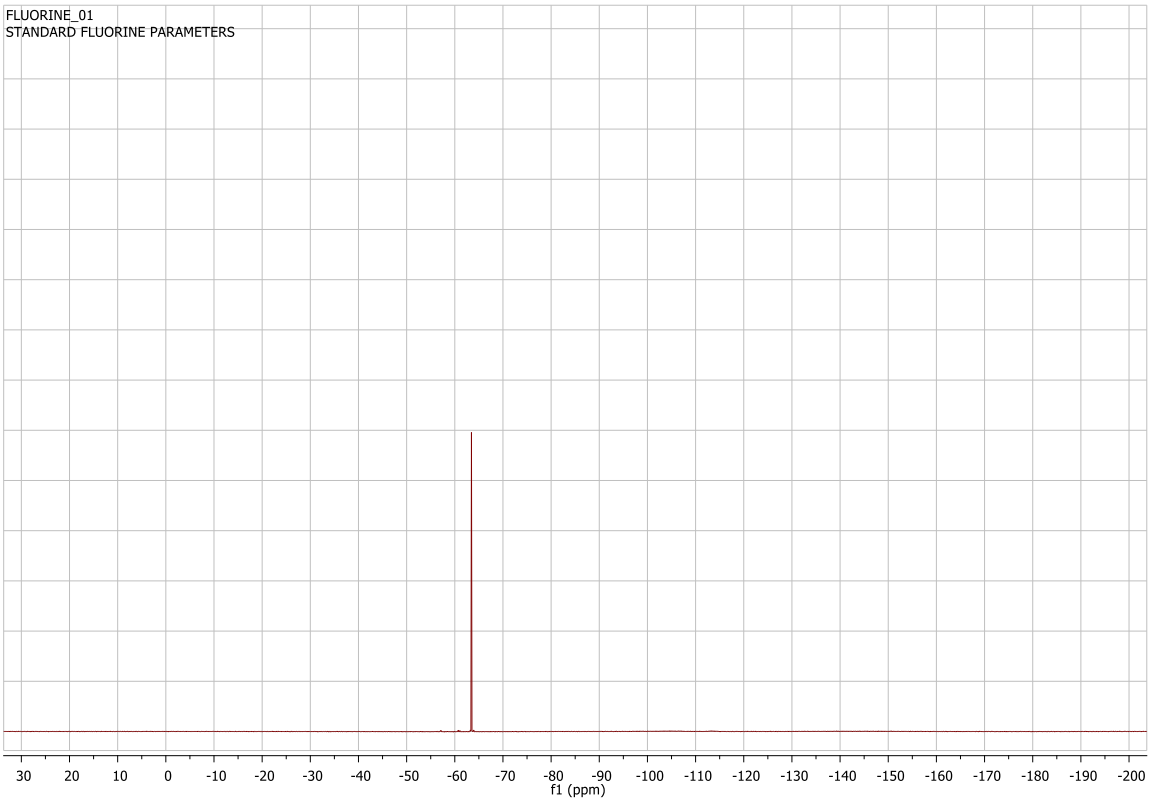

PROTON_01
86b-4p-286-CF3
OH
CO2Et
N
CF3
8a
0.98
0.87
0.85
0.94
0.94
1.89
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

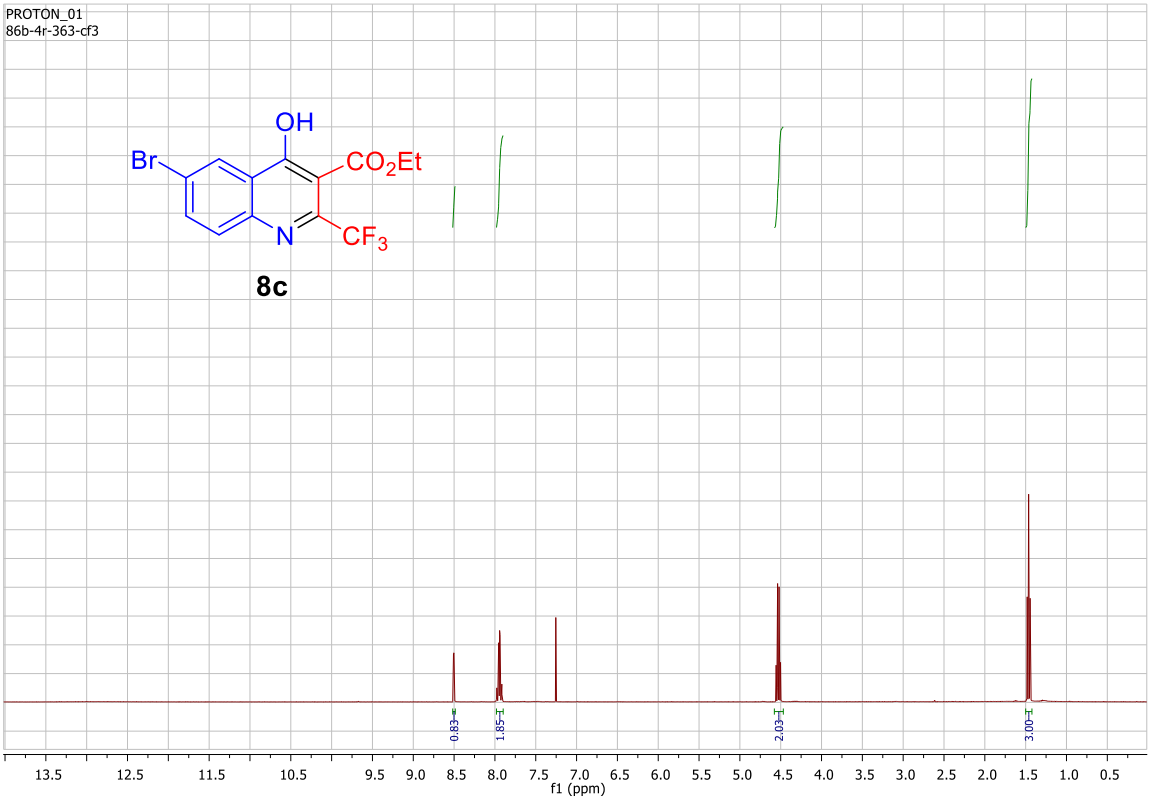

CARBON_01
86b-4p-286-CF3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

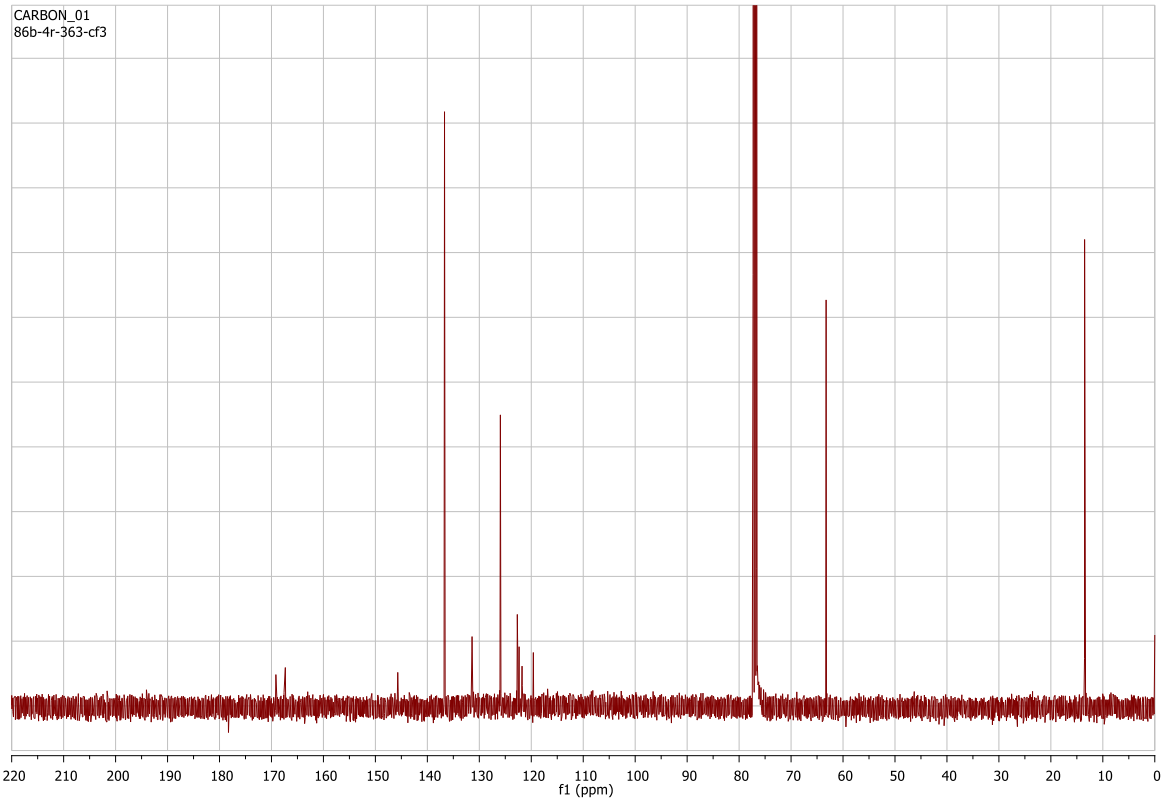

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

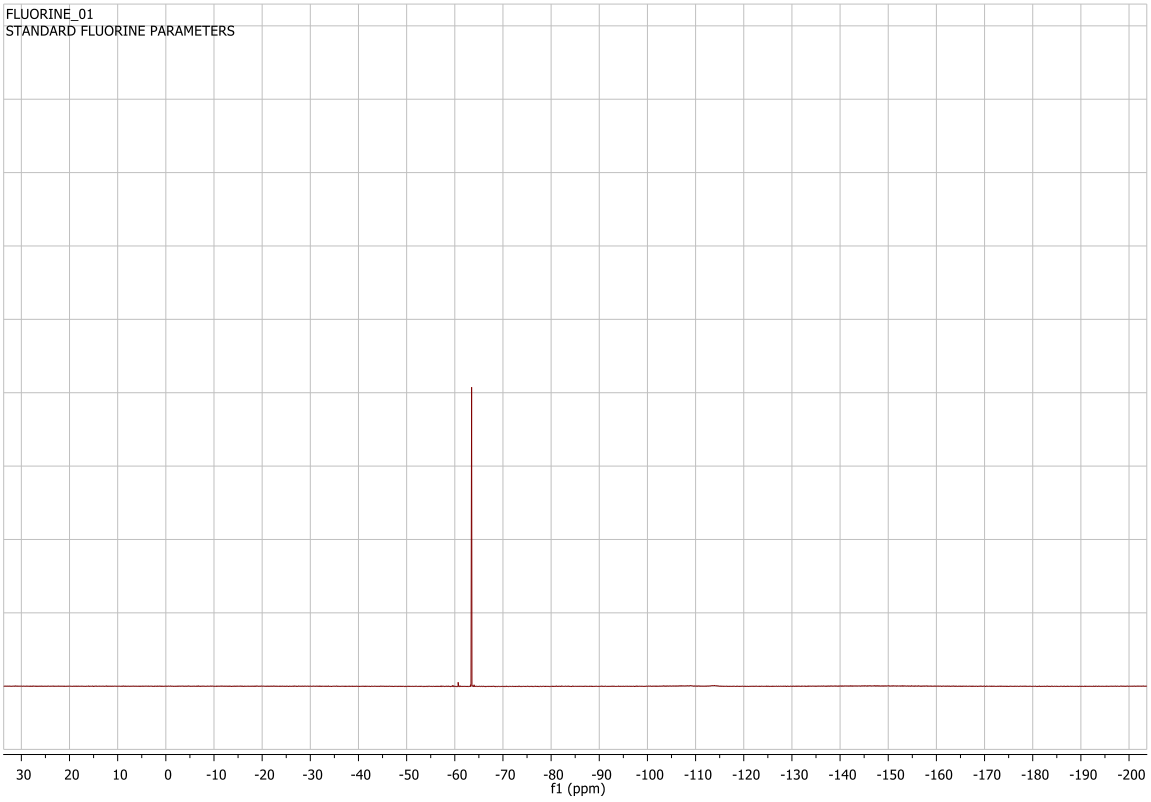

PROTON_01
86b-4q-319-cf3
OH
Cl
CO2Et
N
CF3
8b
1.09
0.80
0.91
0.93
1.93
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

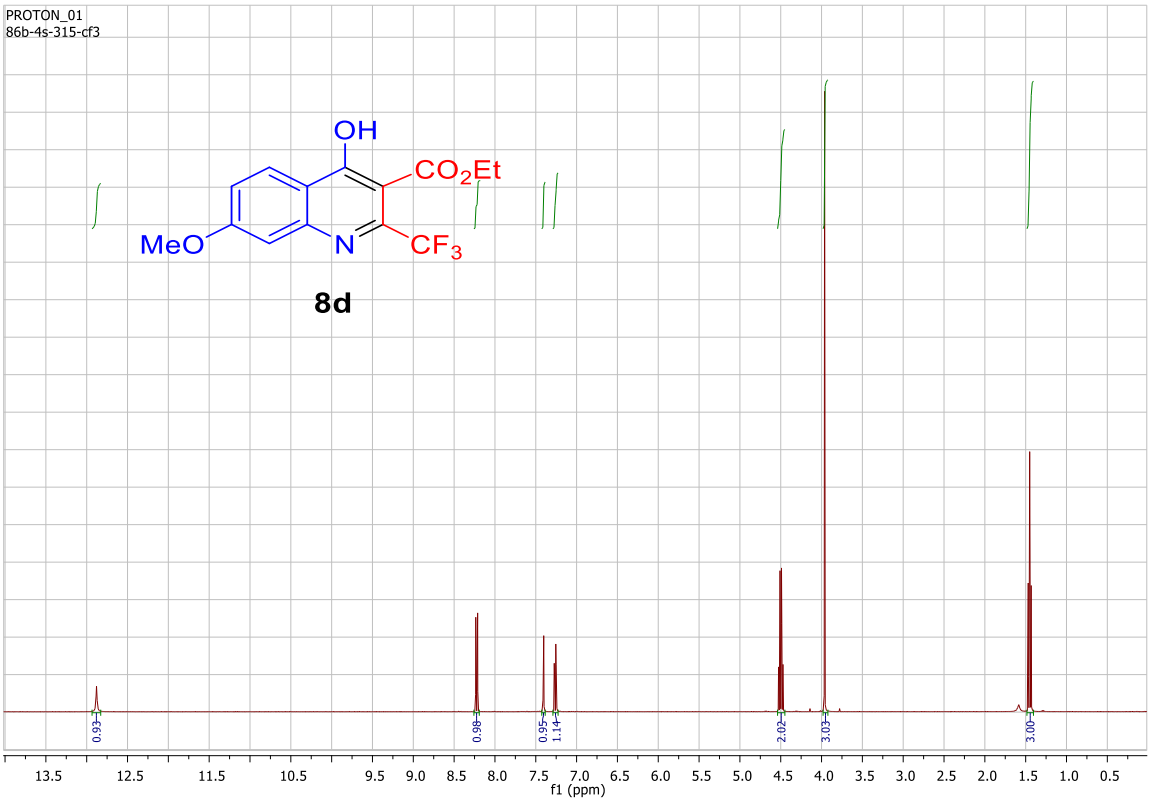

CARBON_01
86b-4q-319-cf3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

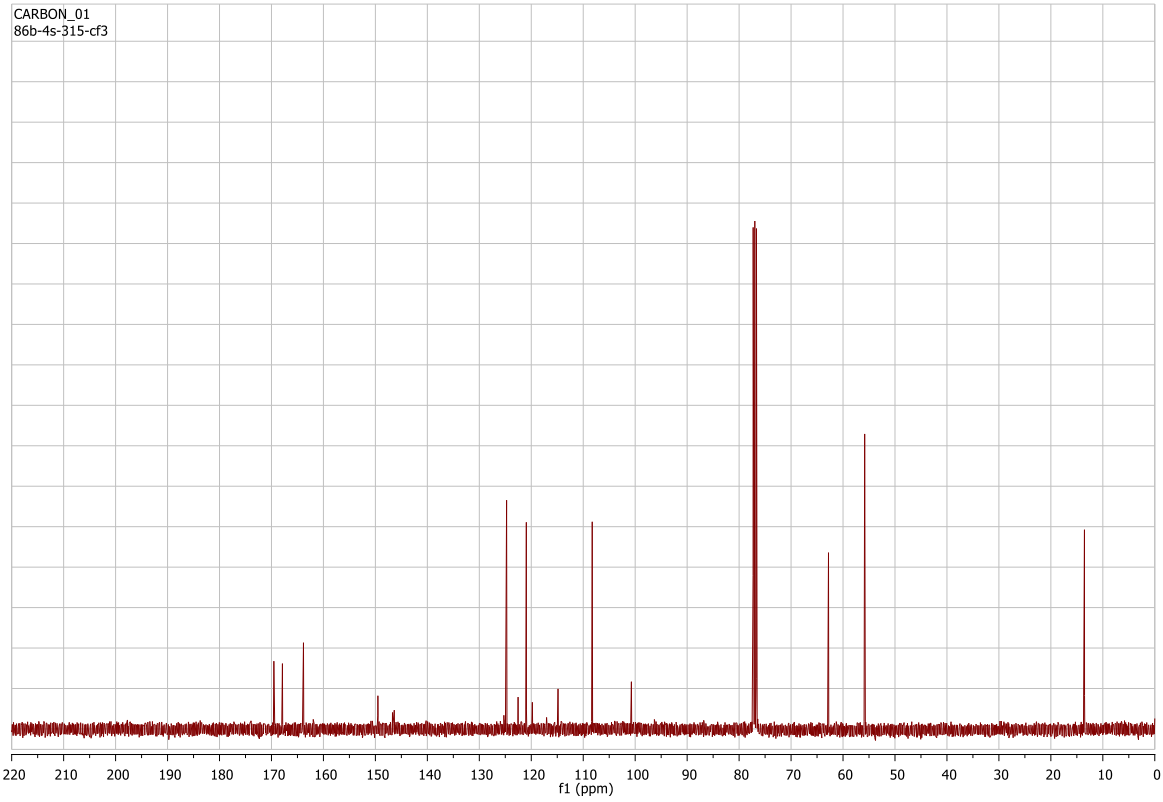

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

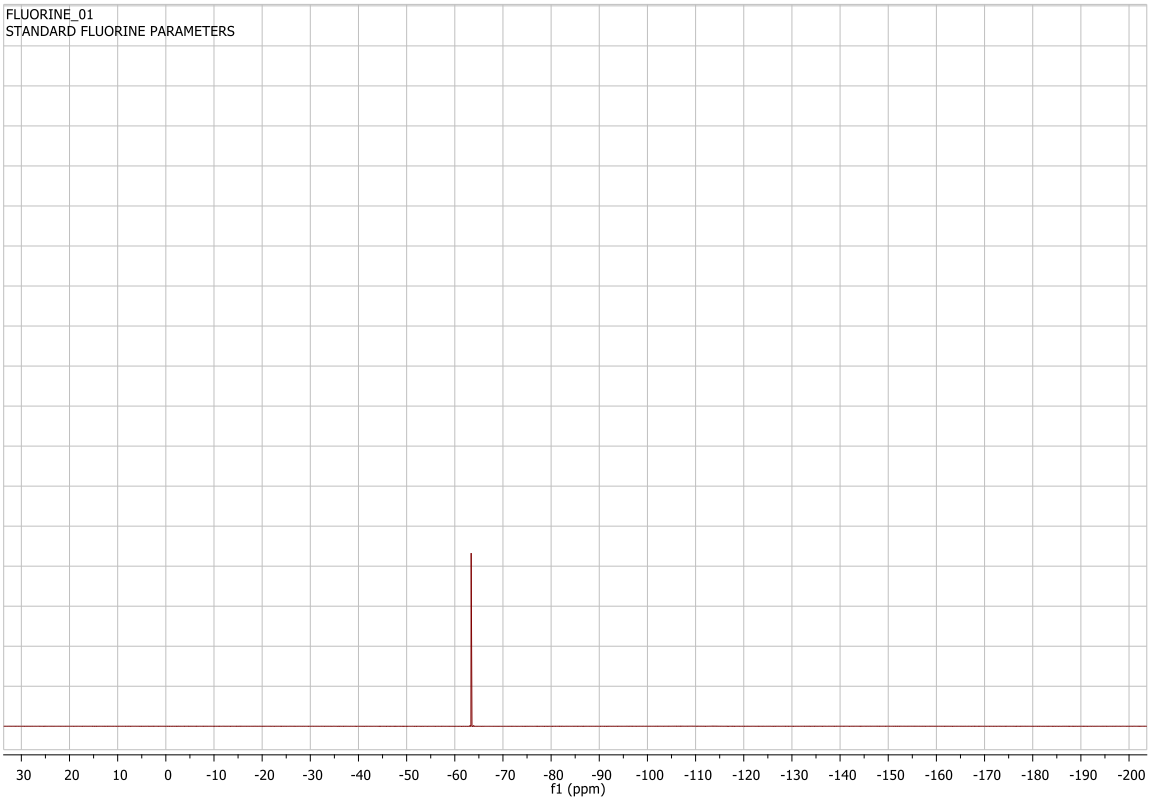

PROTON_01
86b-4r-363-cf3
OH
Br
CO2Et
N
CF3
8c
0.83
1.85
2.03
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

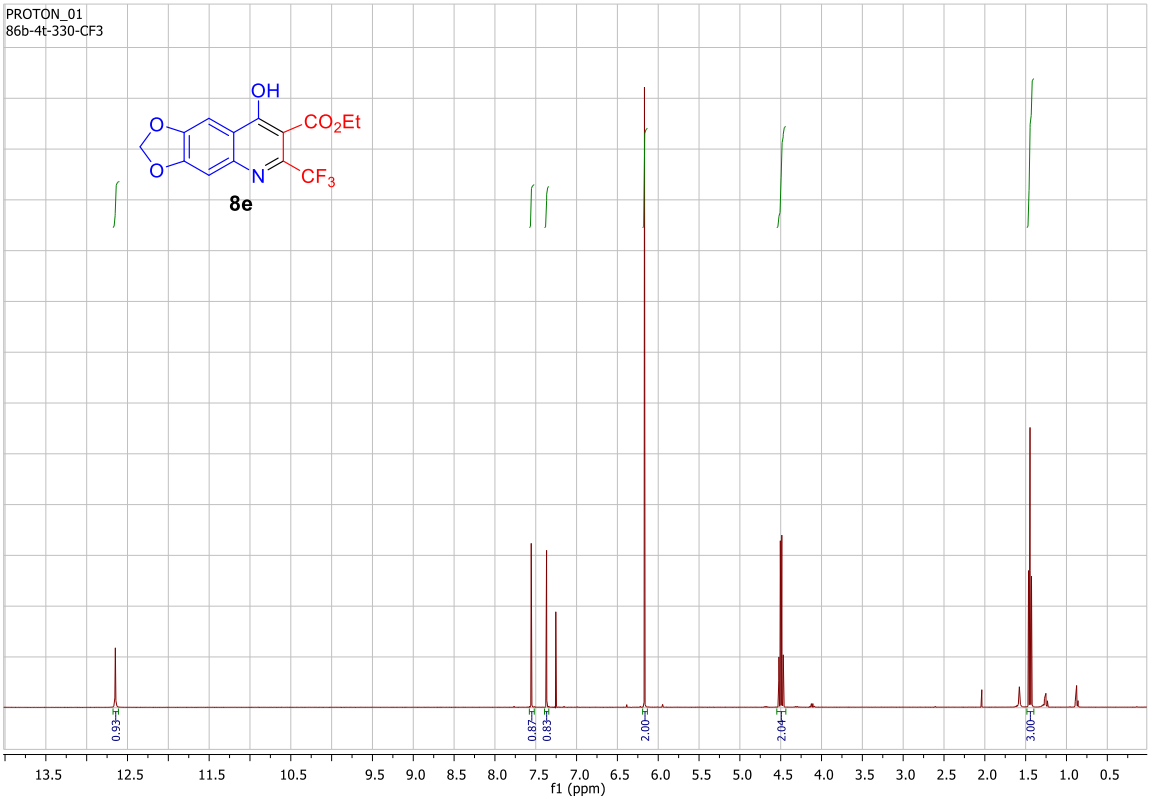

CARBON_01
86b-4r-363-cf3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

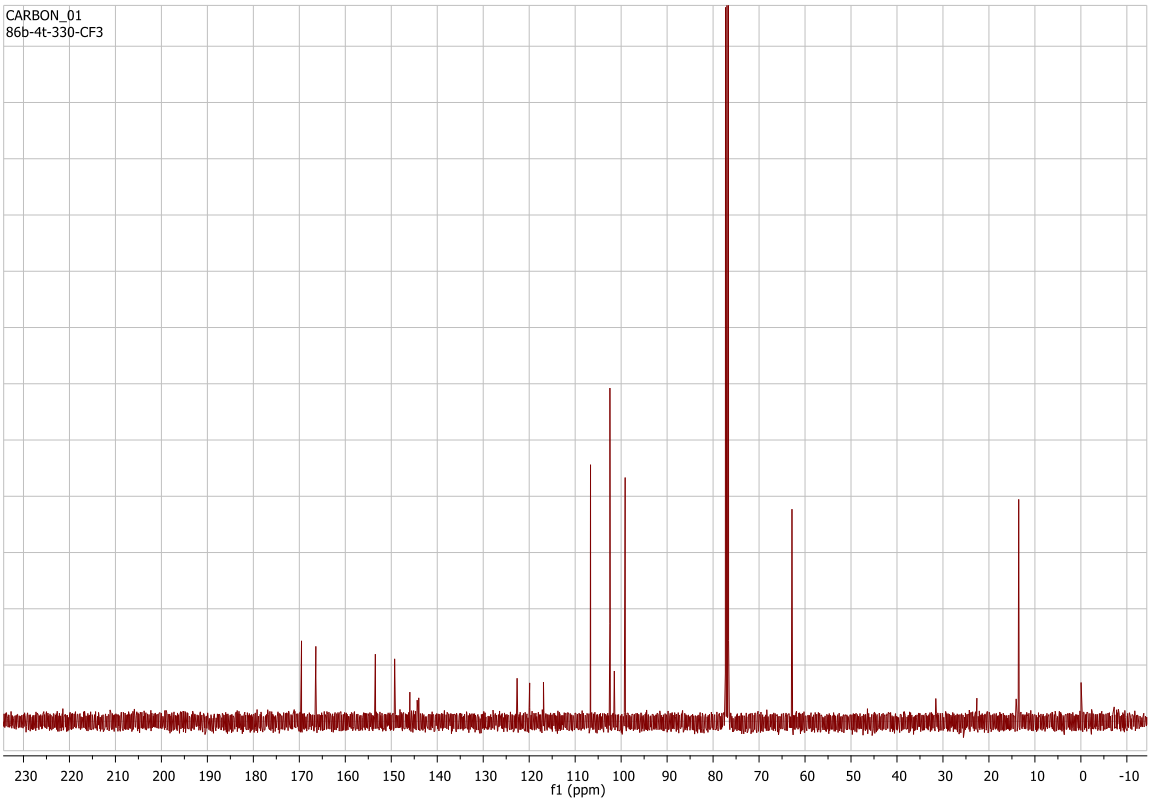

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

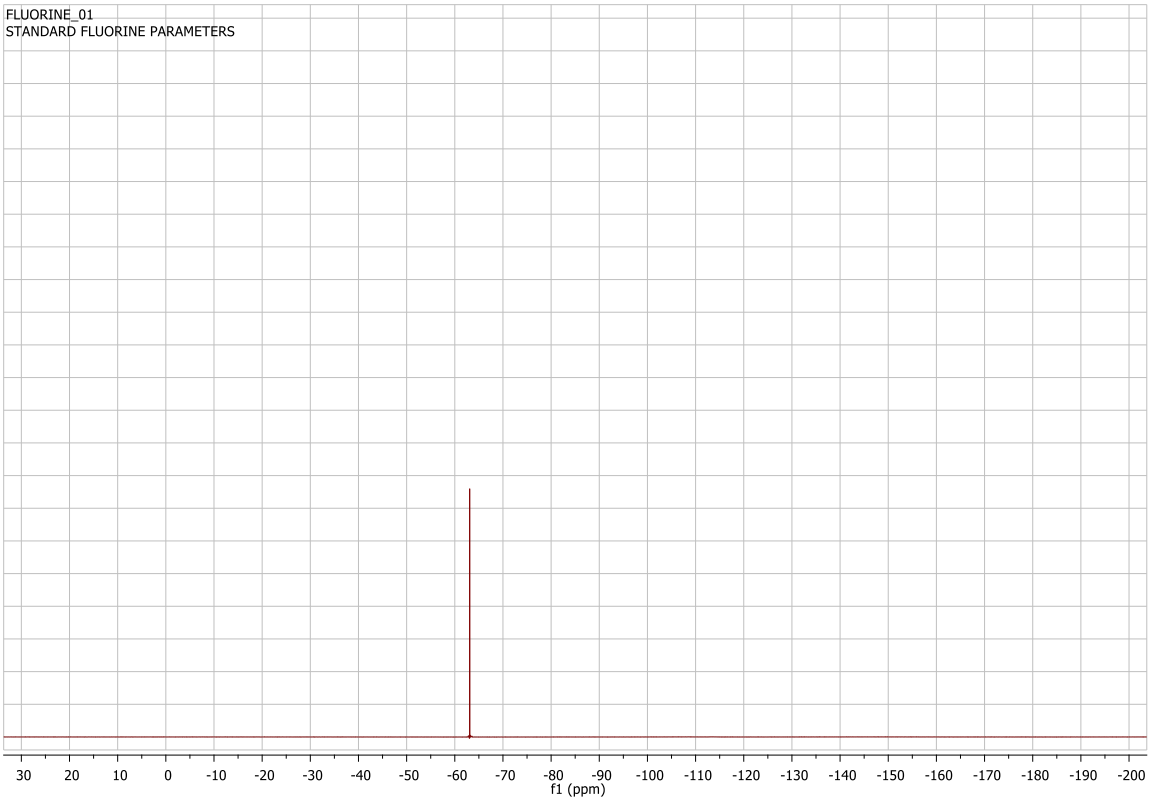

PROTON_01
86b-4s-315-cf3
OH
CO2Et
MeO
N
CF3
8d
0.93
0.98
0.95
1.14
2.02
3.03
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

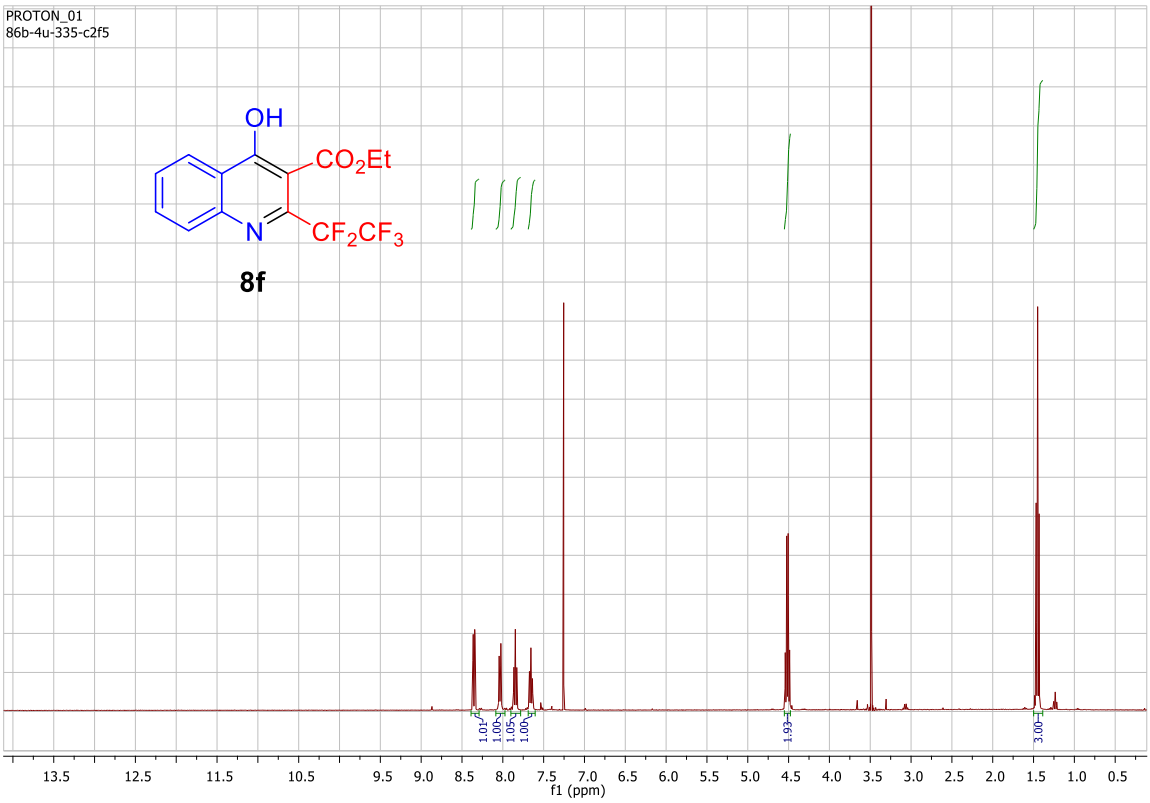

CARBON_01
86b-4s-315-cf3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

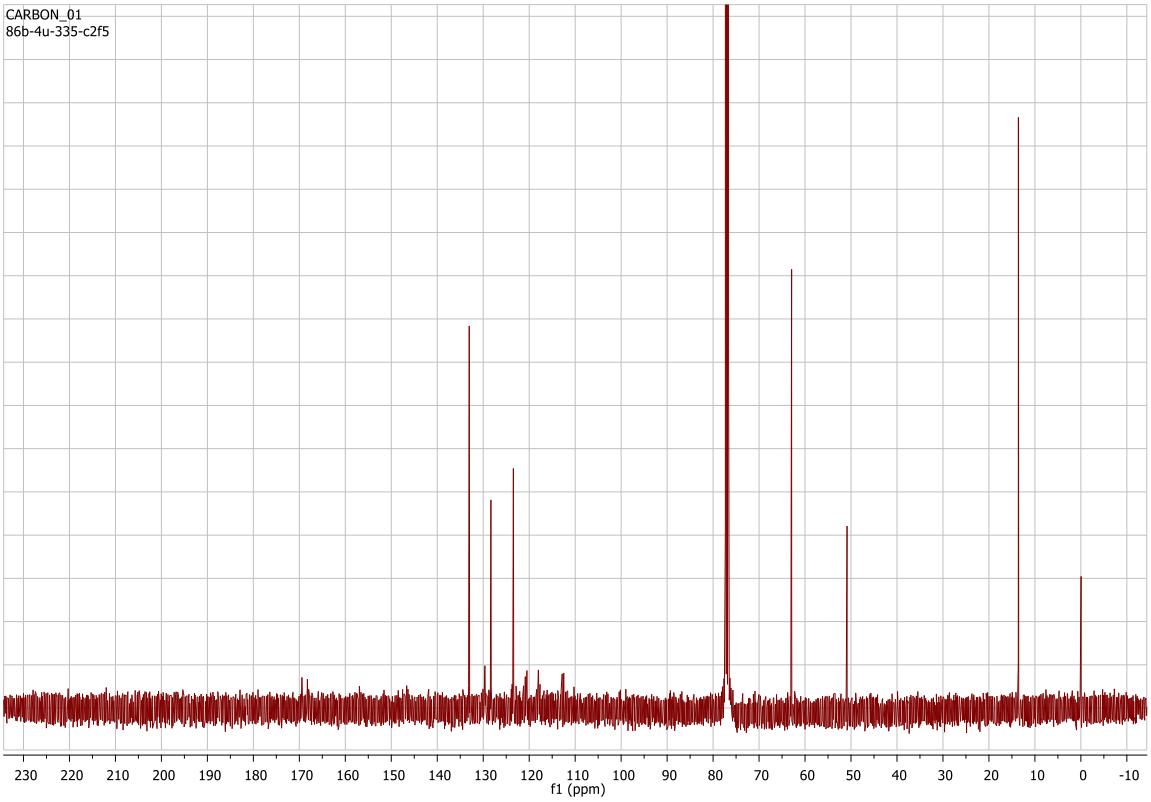

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

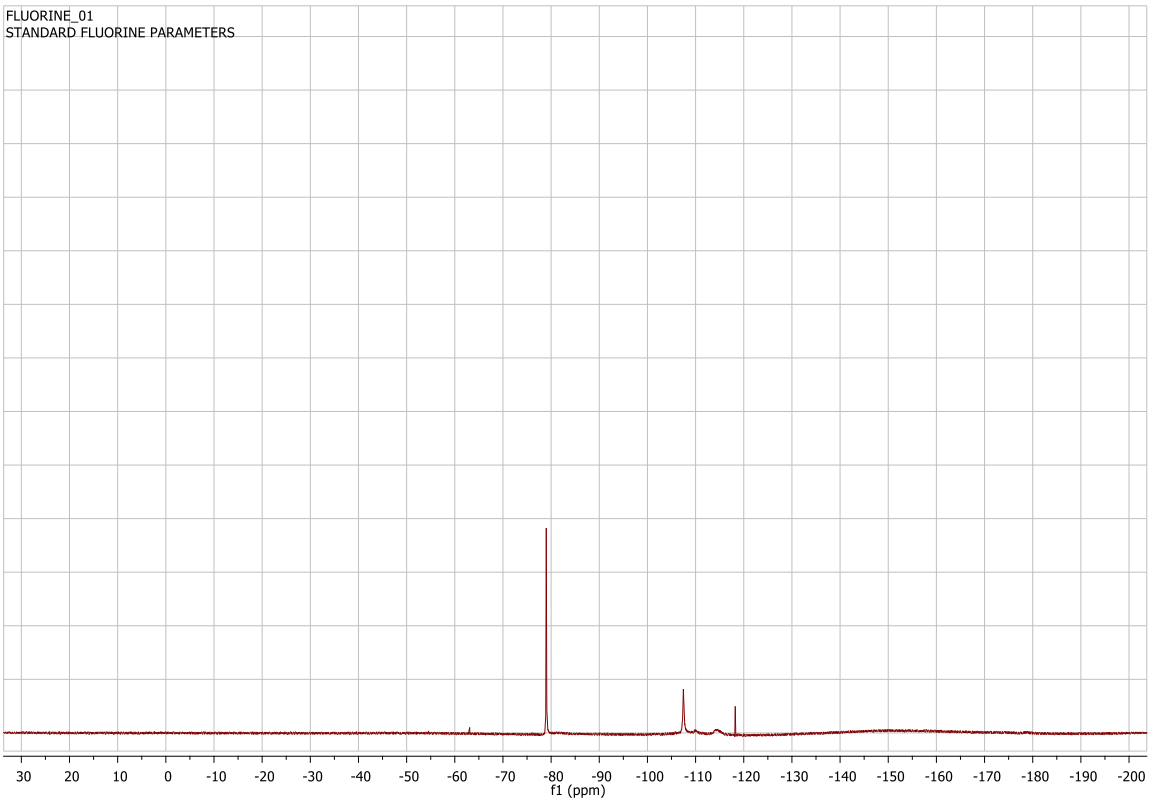

PROTON_01
86b-4t-330-CF3
OH
$CO_2Et$
O
O
N
$CF_3$
8e
0.93
0.87
0.83
2.00
2.04
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

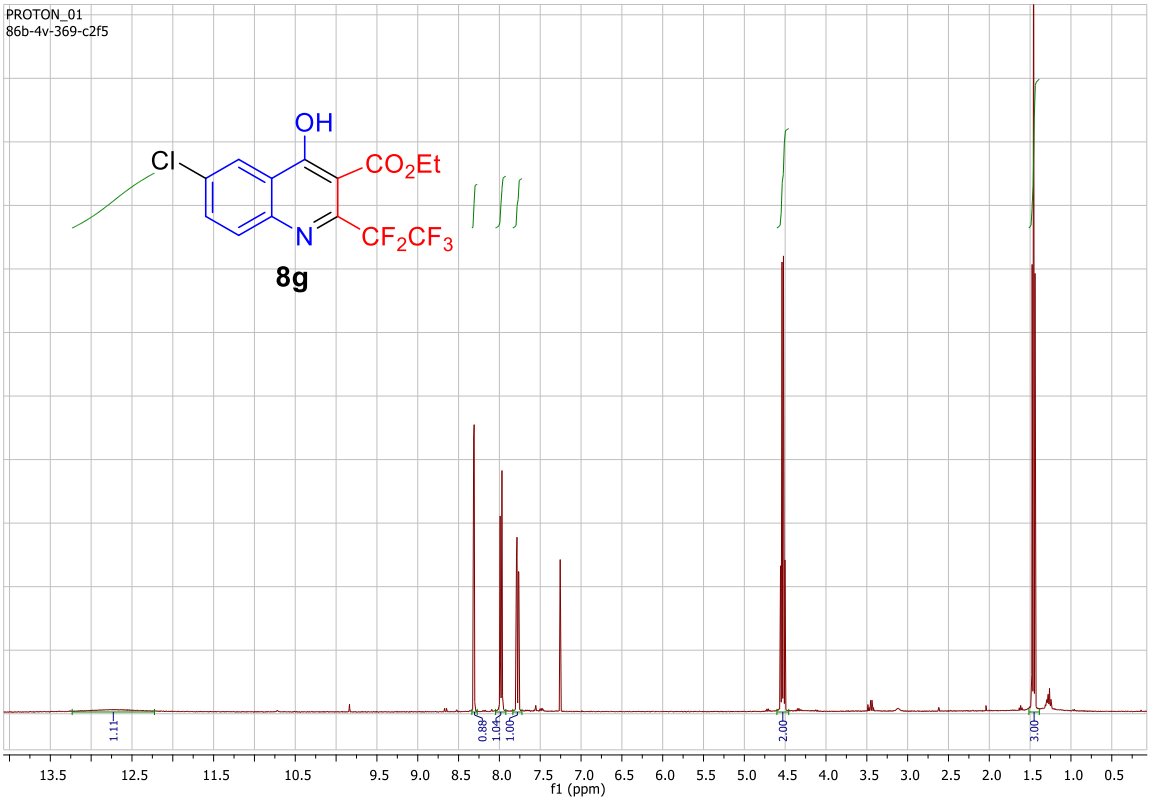

CARBON_01
86b-4t-330-CF3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

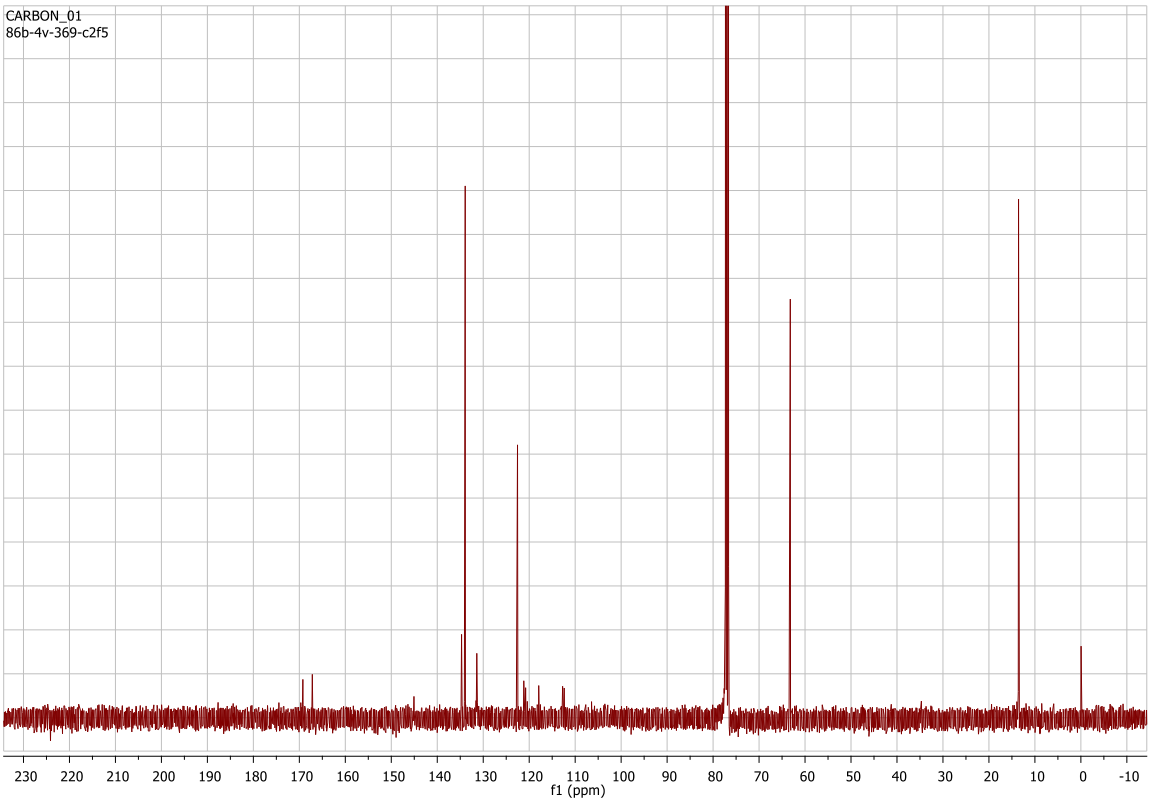

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

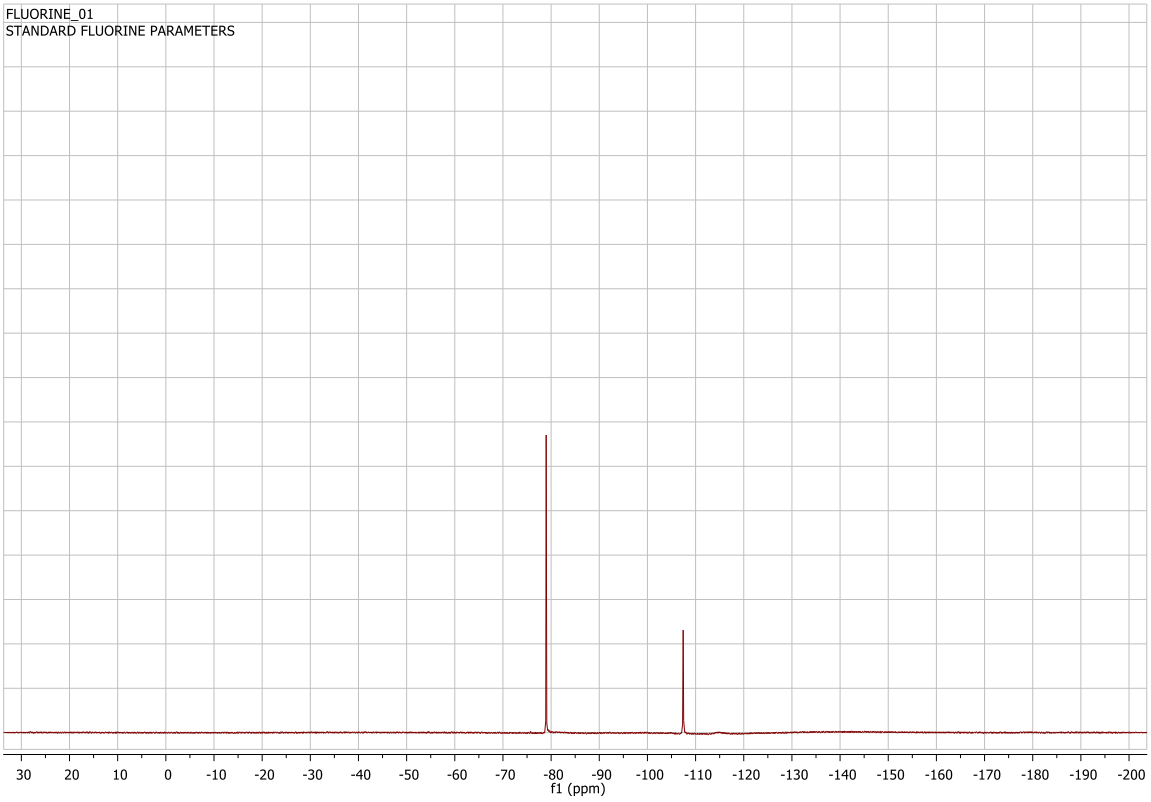

PROTON_01
86b-4u-335-c2f5
OH
CO2Et
N
CF2CF3
8f
1.01
1.00
1.05
1.00
1.93
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

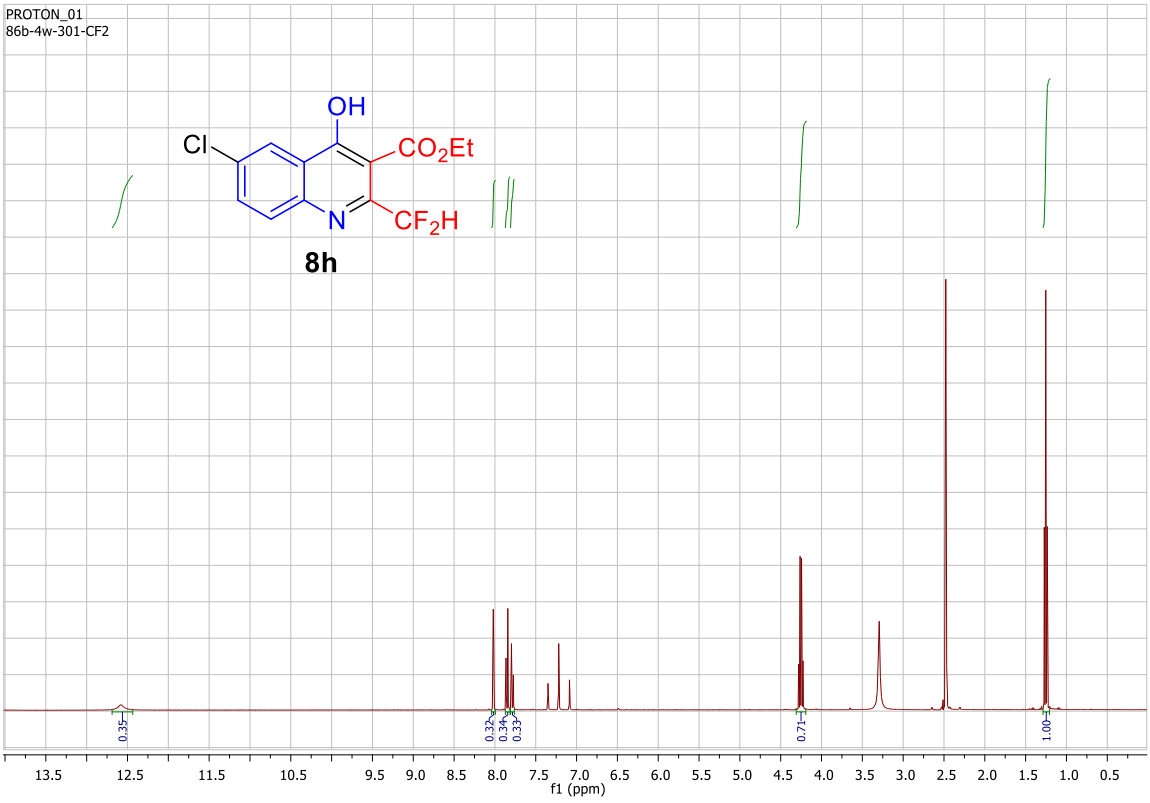

CARBON_01
86b-4u-335-c2f5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

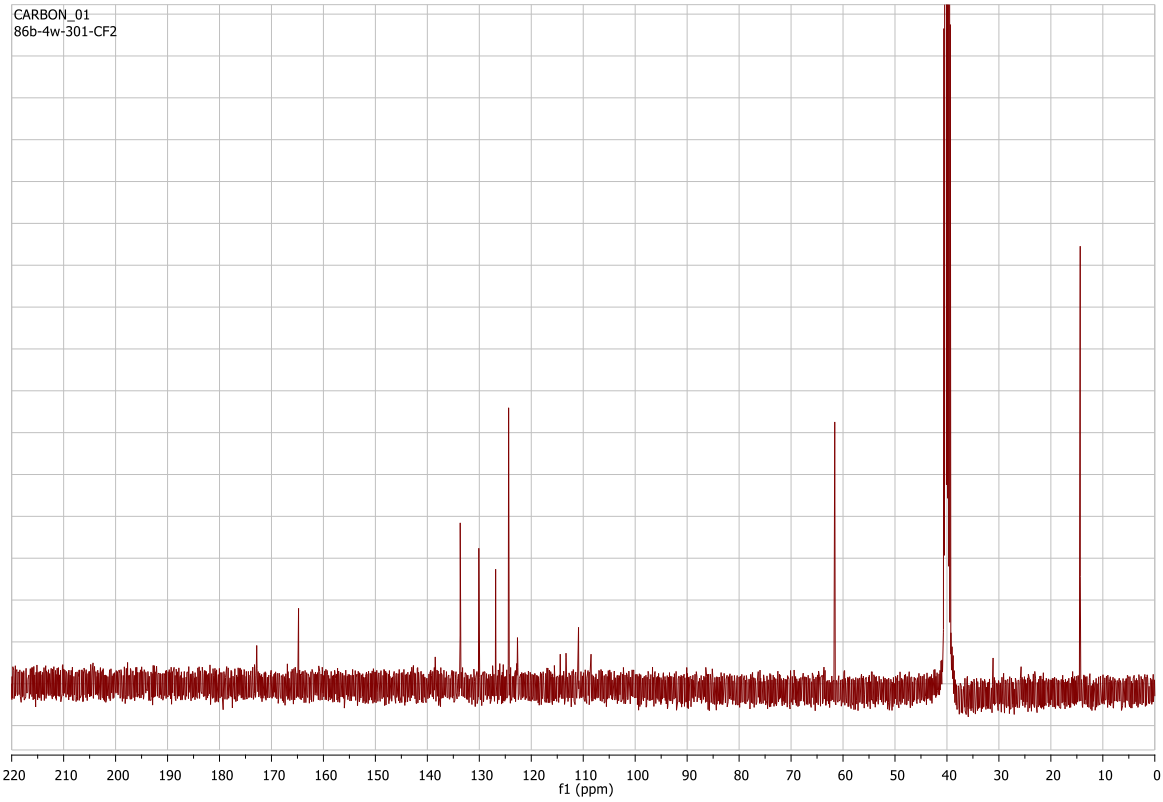

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

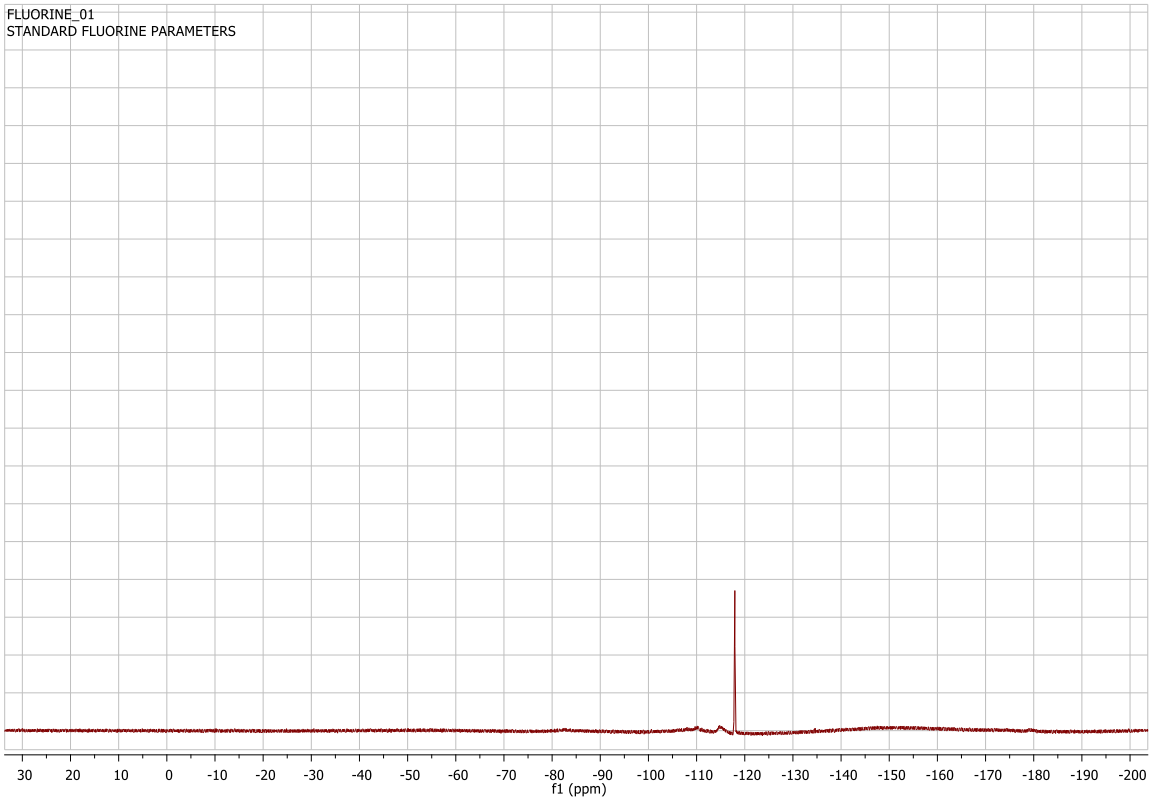

PROTON_01
86b-4v-369-c2f5
OH
Cl
CO2Et
N
CF2CF3
8g
1.11
0.88
1.04
1.00
2.00
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

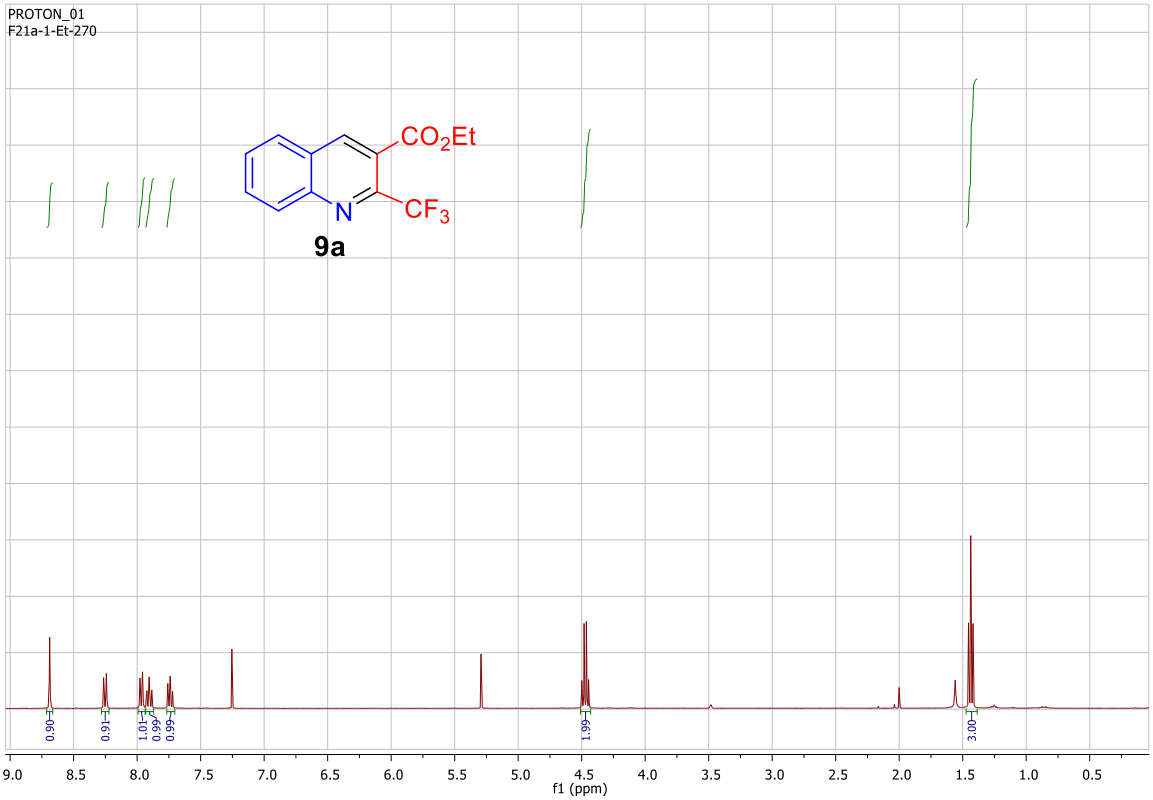

CARBON_01
86b-4v-369-c2f5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

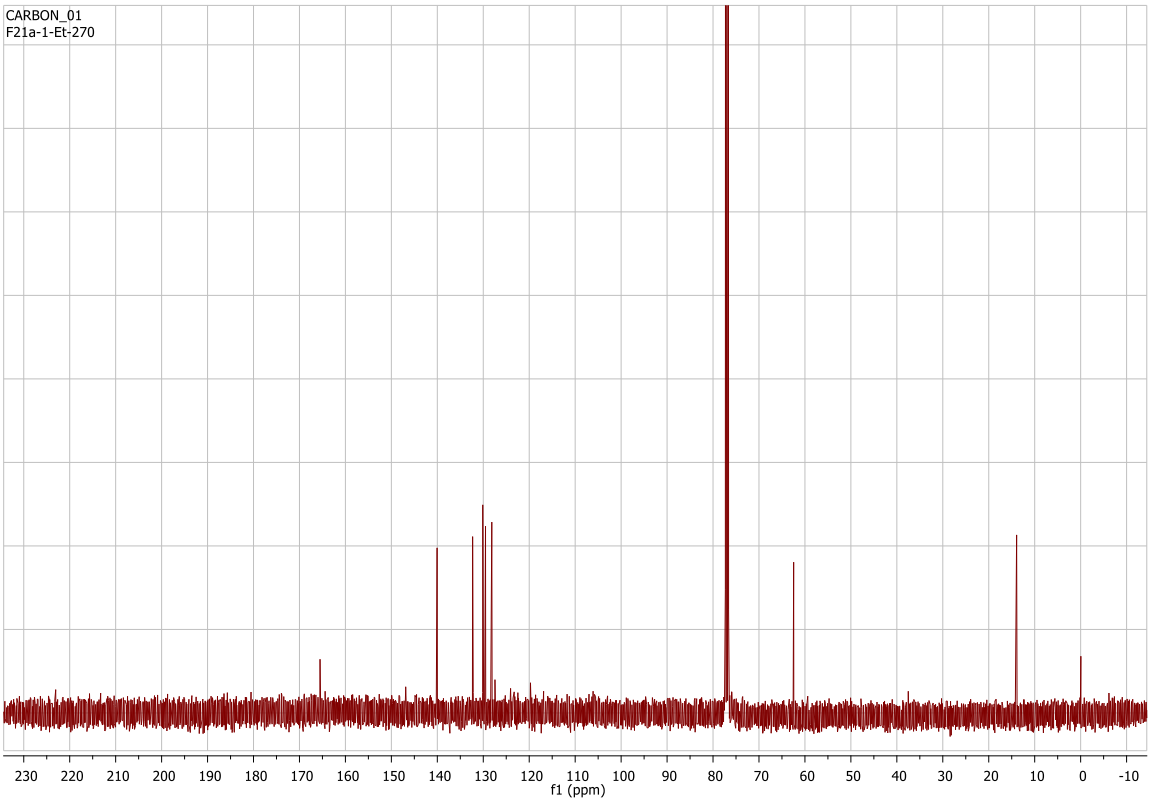

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

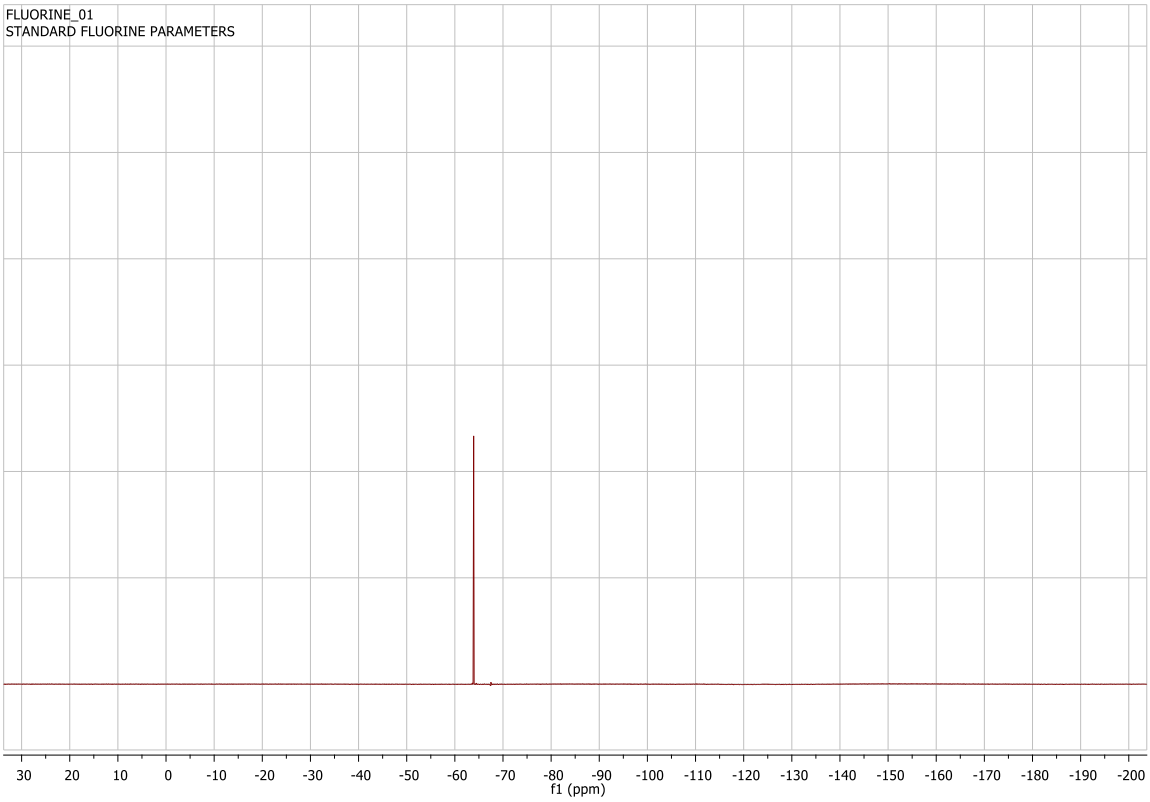

PROTON_01
86b-4w-301-CF2
OH
Cl
CO2Et
N
CF2H
8h
0.35
0.32
0.34
0.33
0.71
1.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

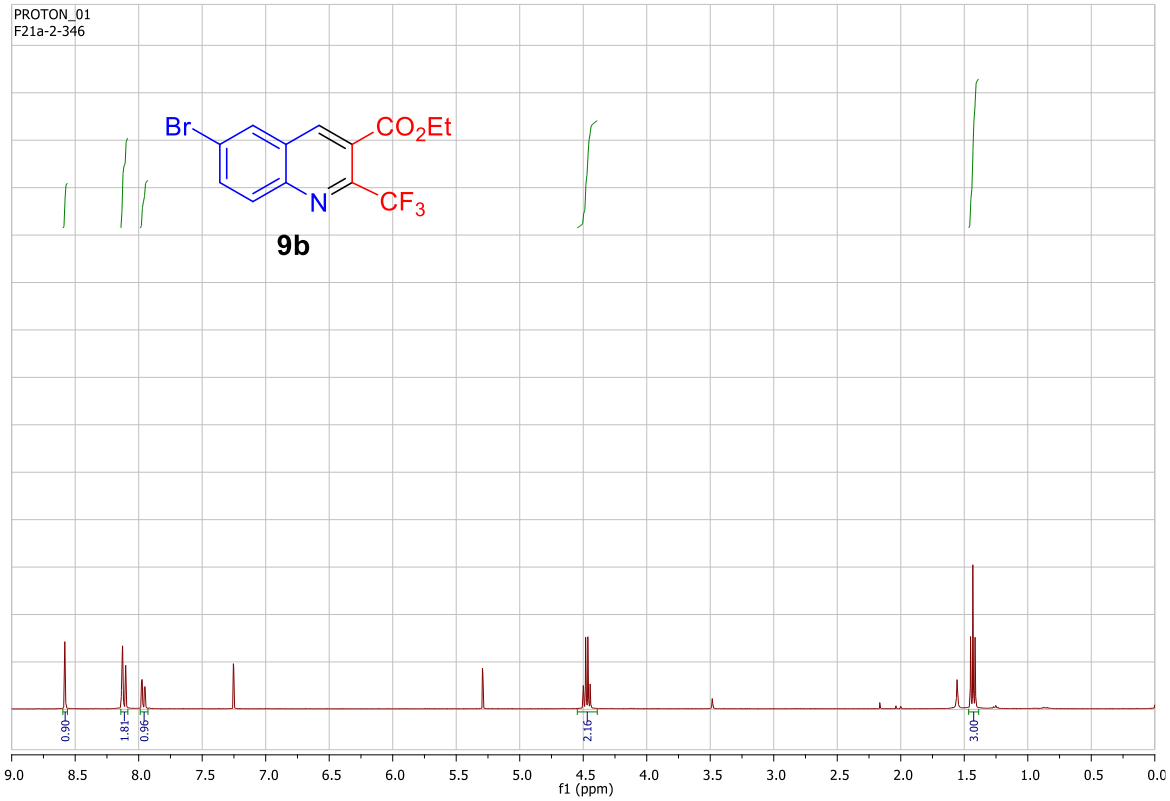

CARBON_01
86b-4w-301-CF2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

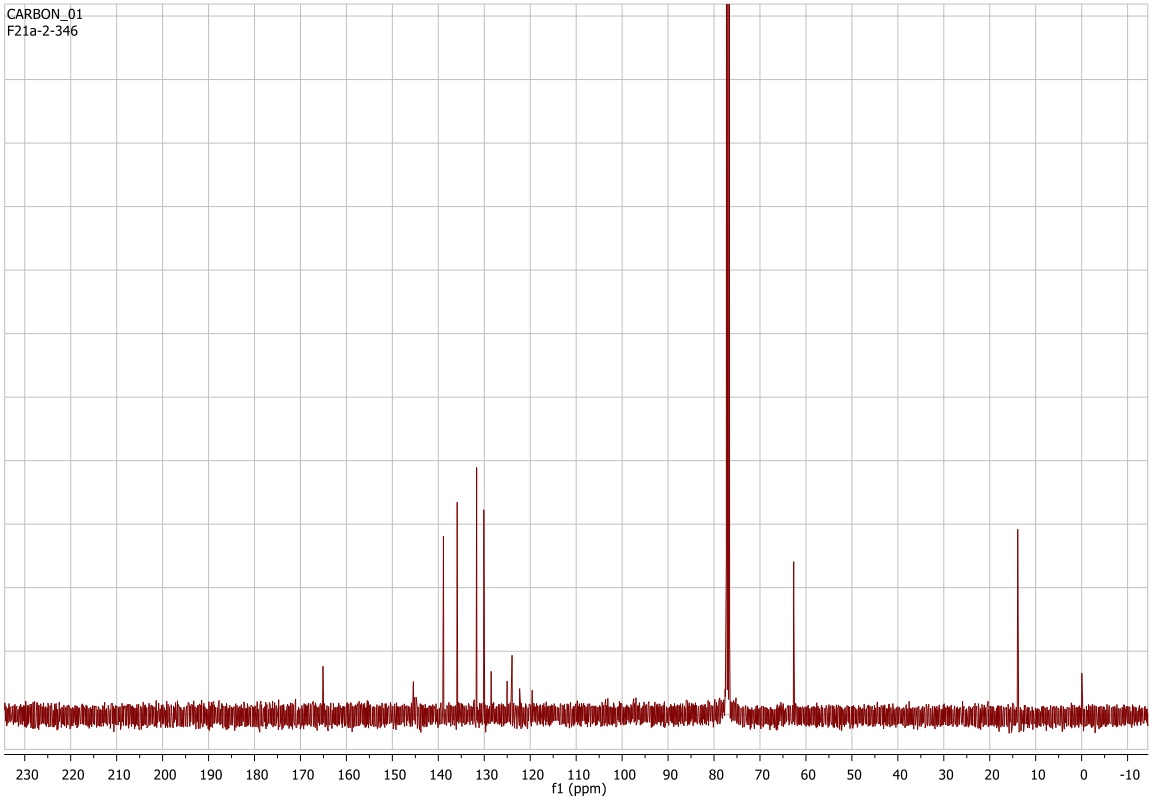

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

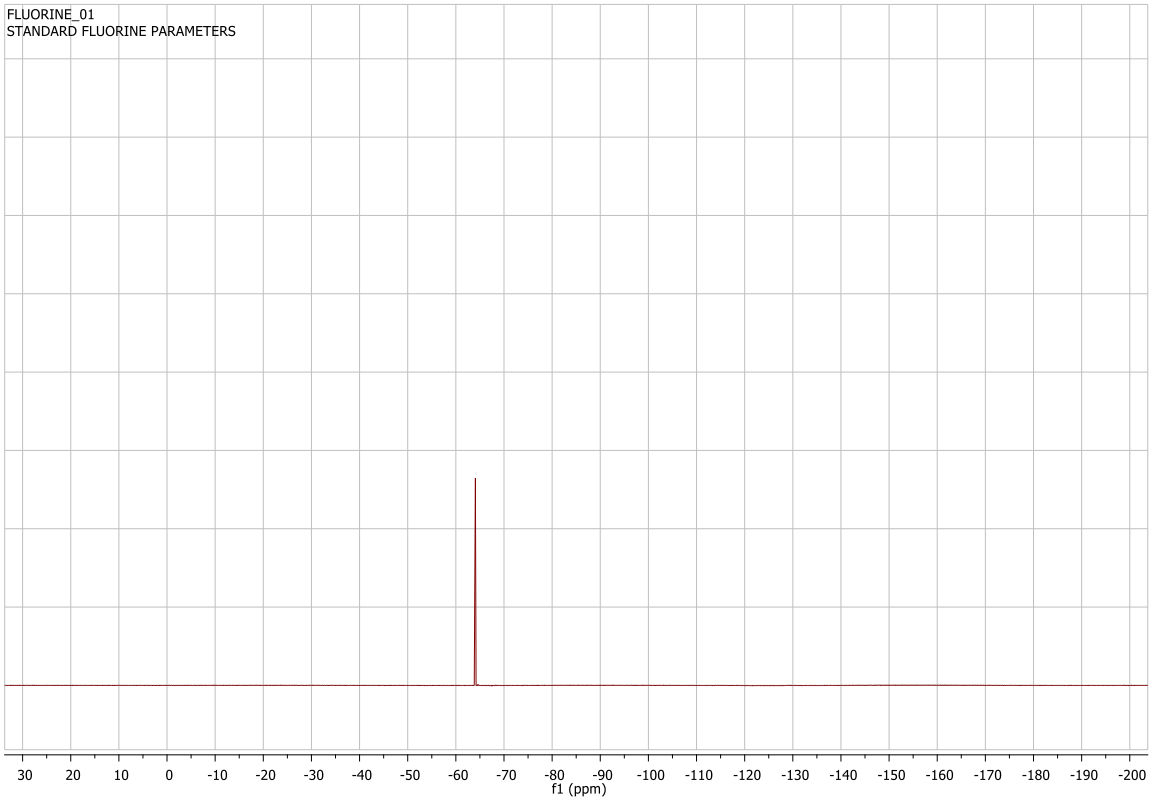

PROTON_01
F21a-1-Et-270
CO2Et
CF3
N
9a
0.90
0.91
1.01
0.99
0.99
1.99
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

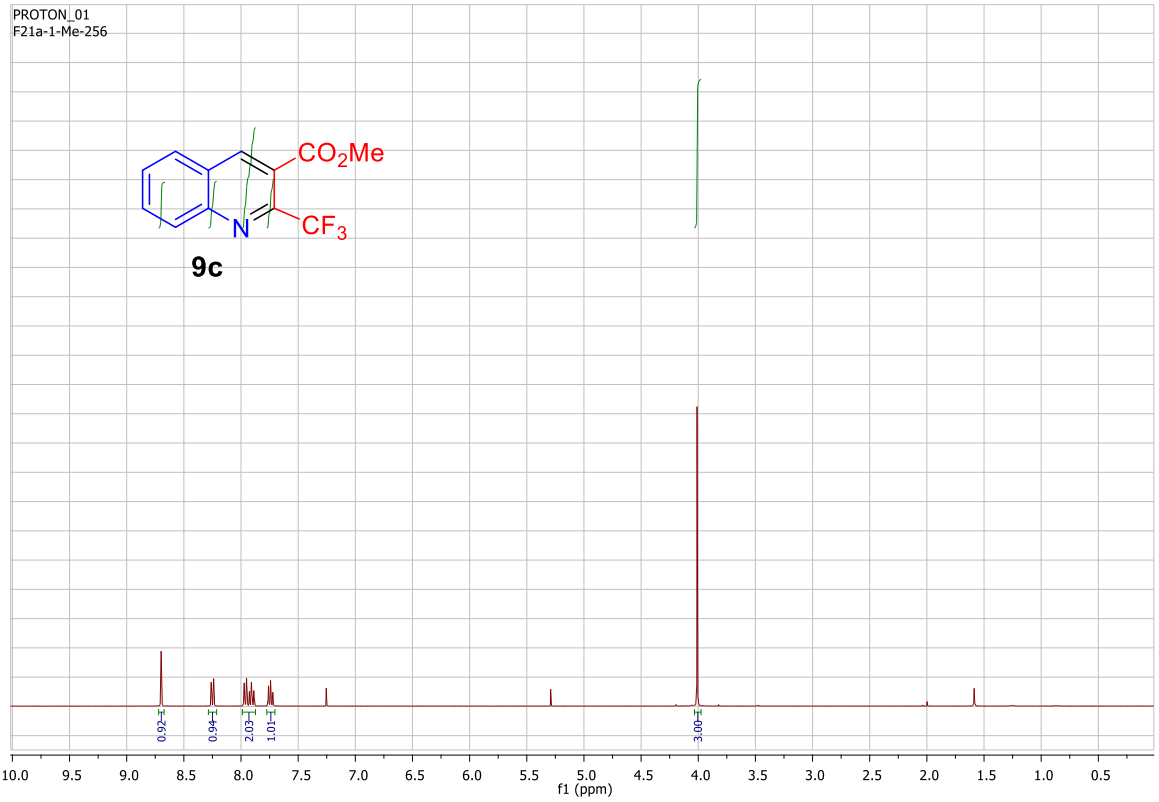

CARBON_01
F21a-1-Et-270
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

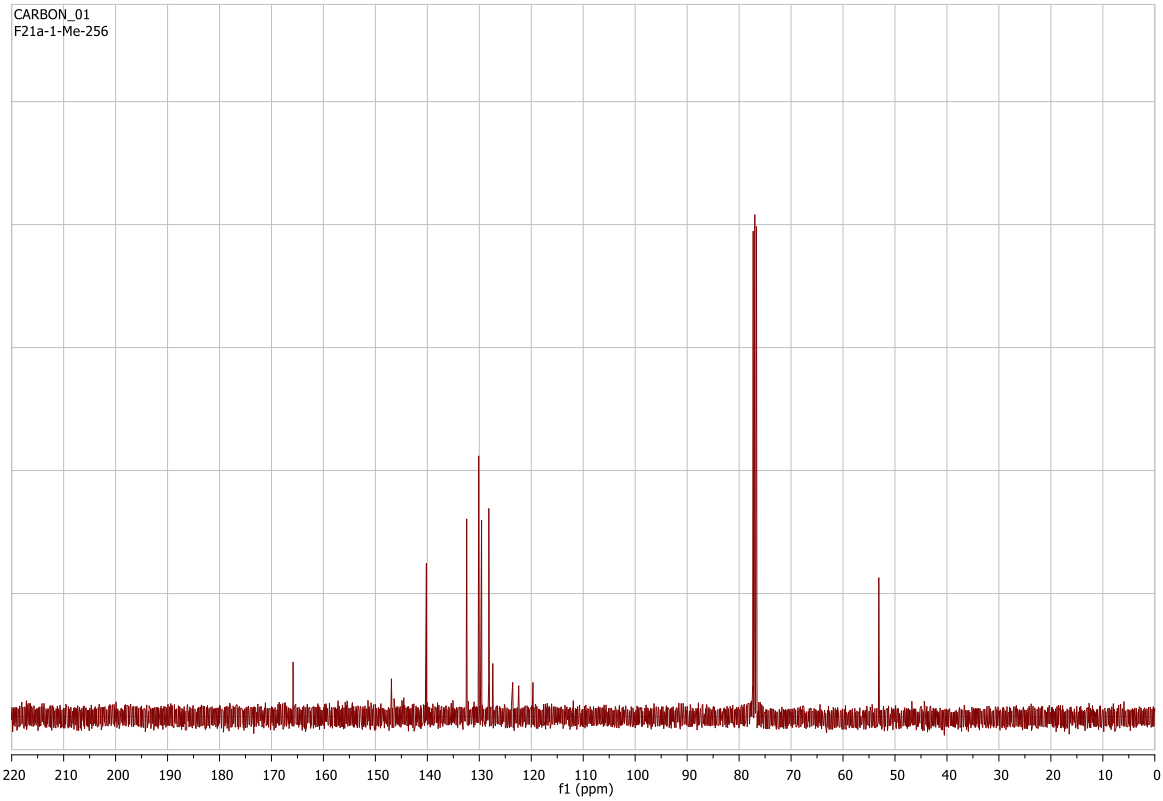

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

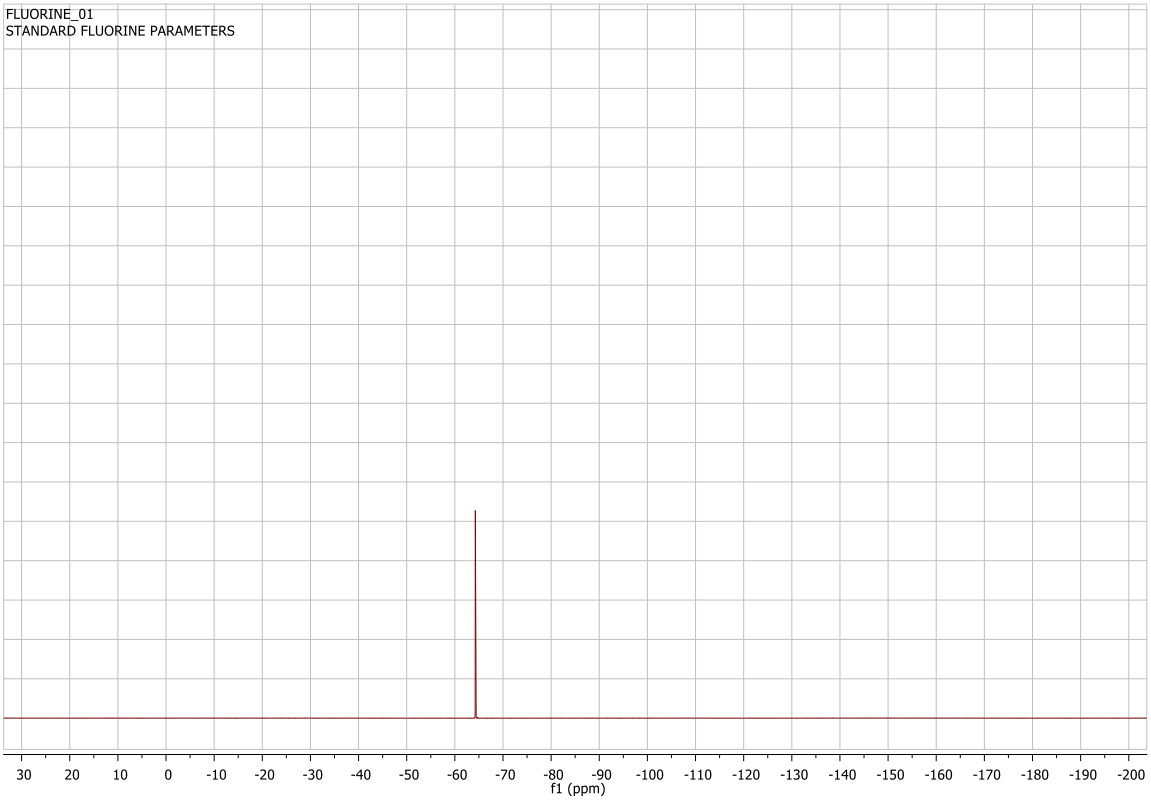

PROTON_01
F21a-2-346
Br
CO2Et
N
CF3
9b
0.90
1.81
0.96
2.16
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

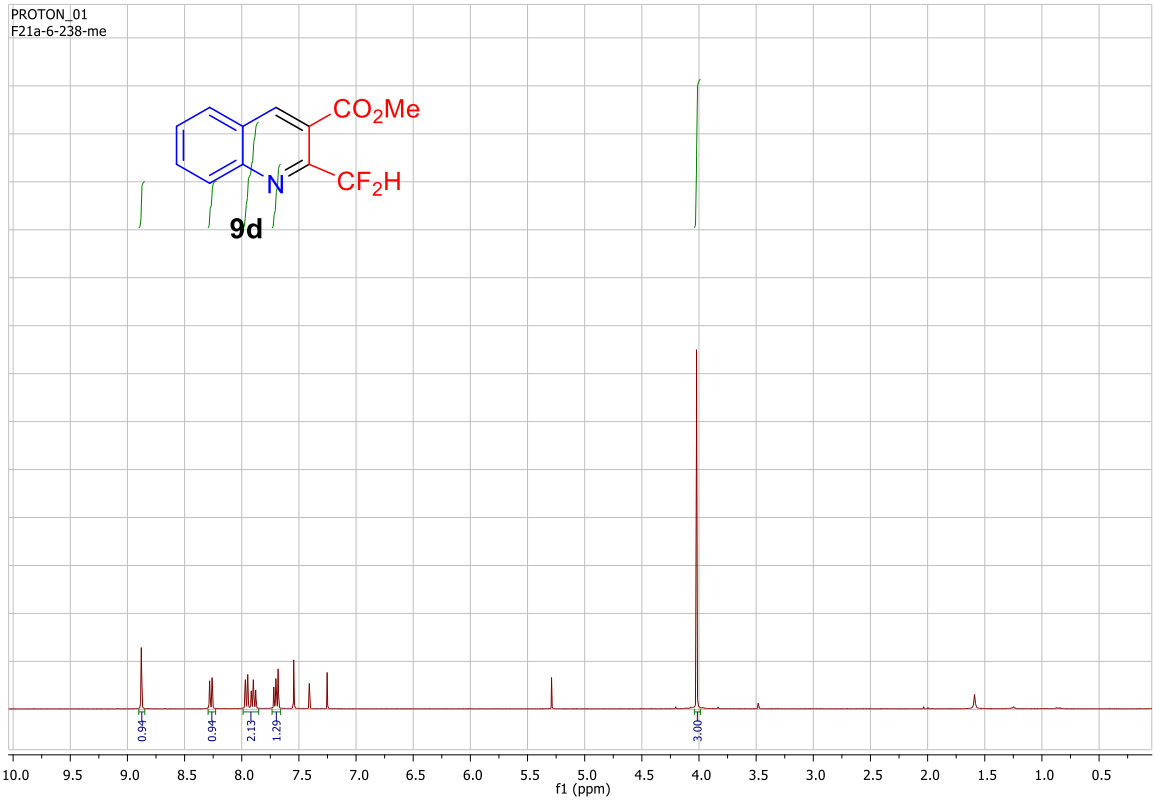

CARBON_01
F21a-2-346
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

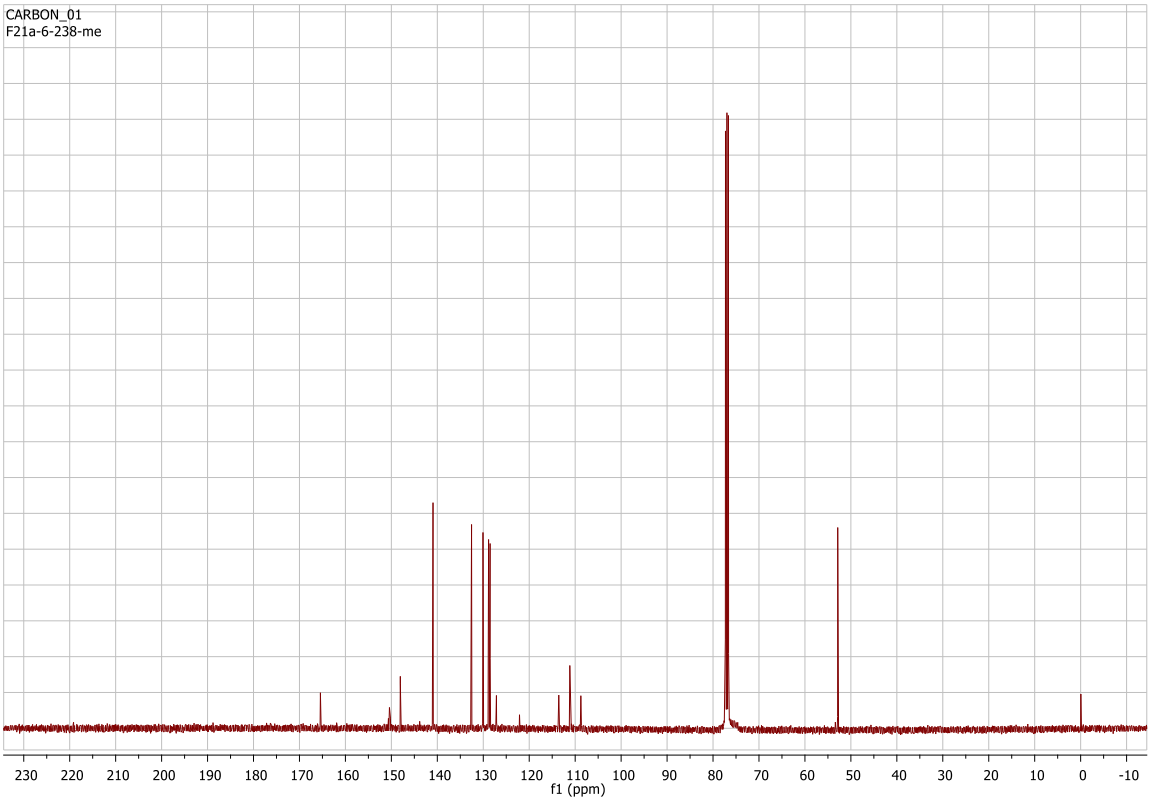

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

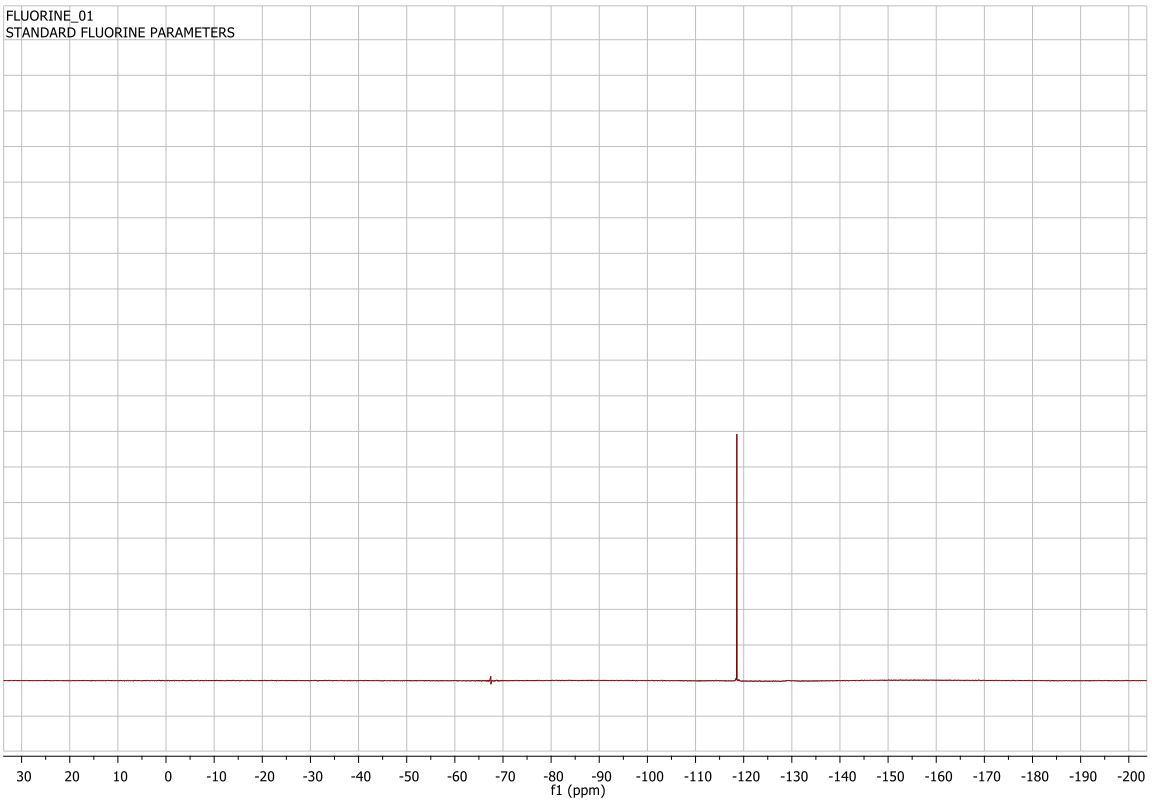

PROTON_01
F21a-1-Me-256
CO2Me
CF3
N
9c
0.92
0.94
2.03
1.01
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

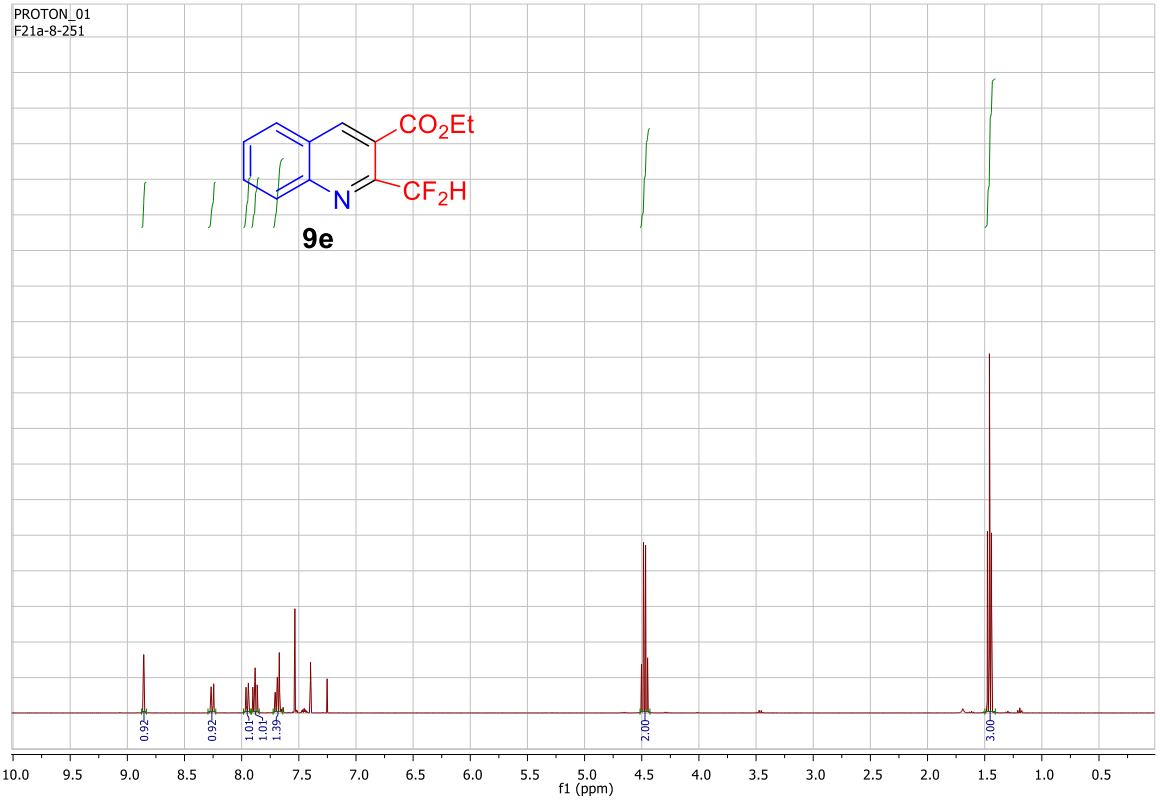

CARBON_01
F21a-1-Me-256
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

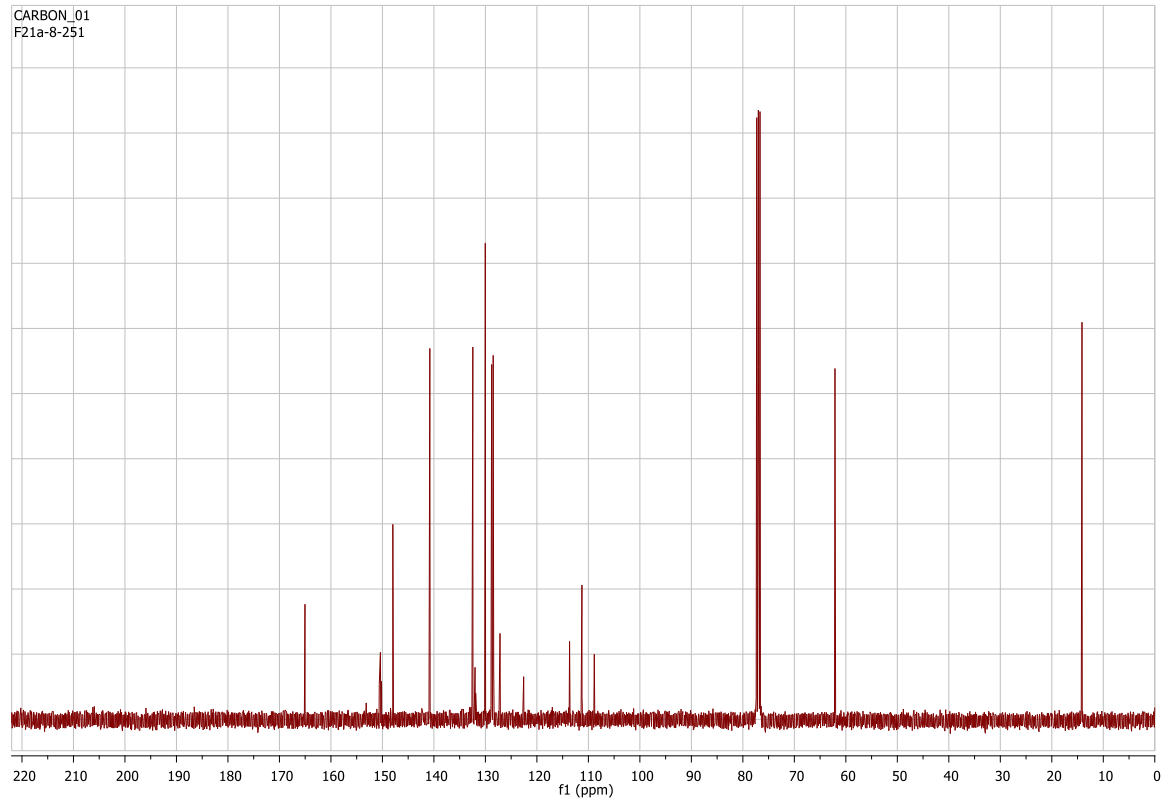

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

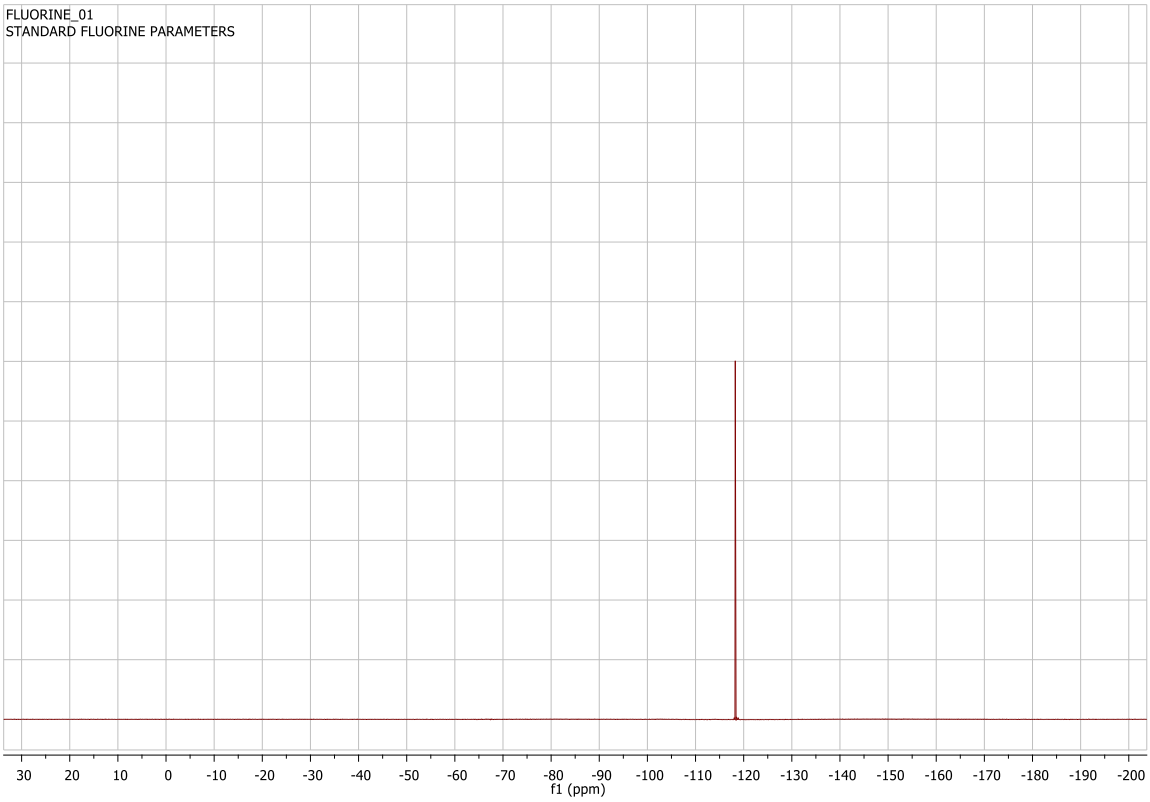

PROTON_01
F21a-6-238-me
CO2Me
CF2H
N
9d
0.94
0.94
2.13
1.29
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

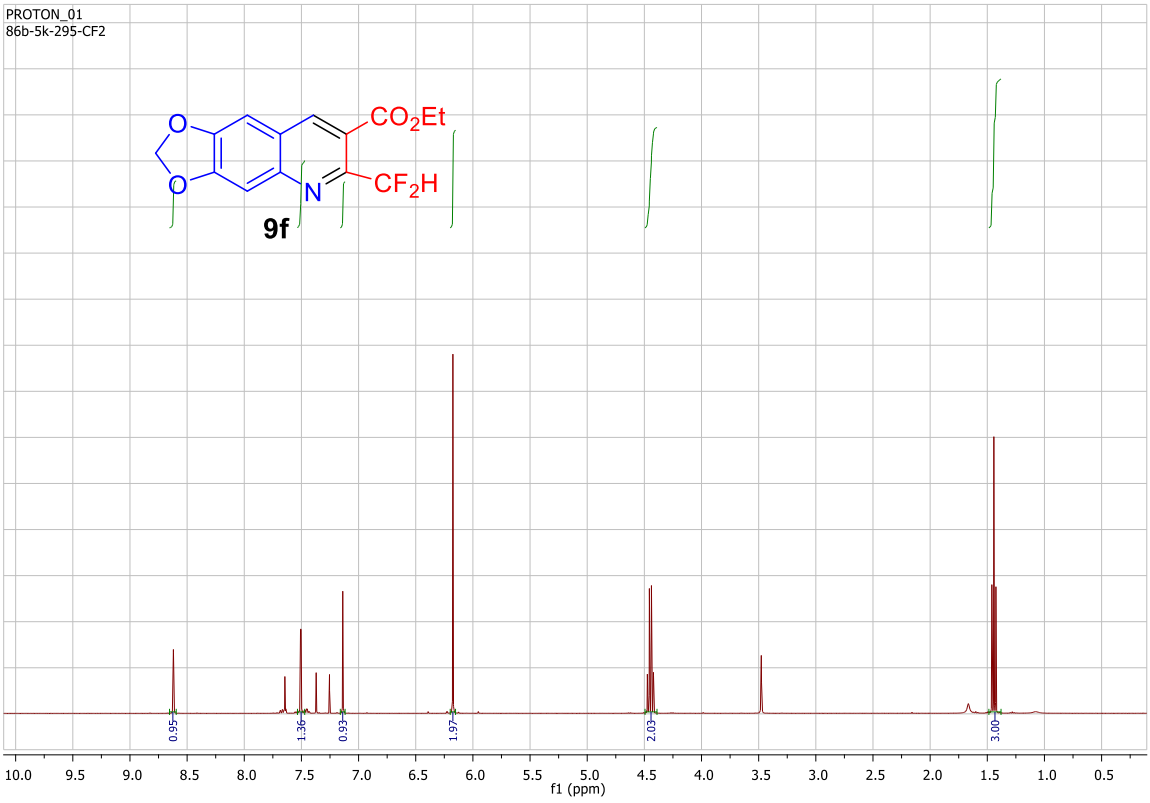

CARBON_01
F21a-6-238-me
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

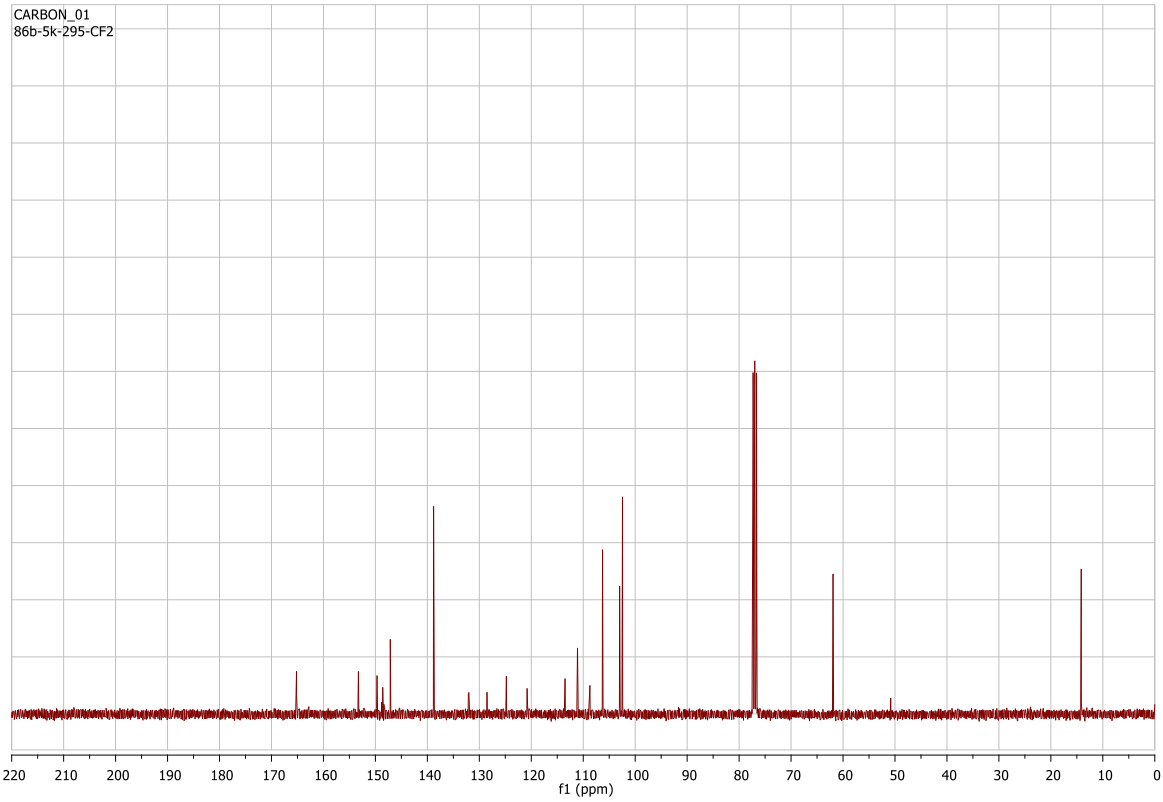

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

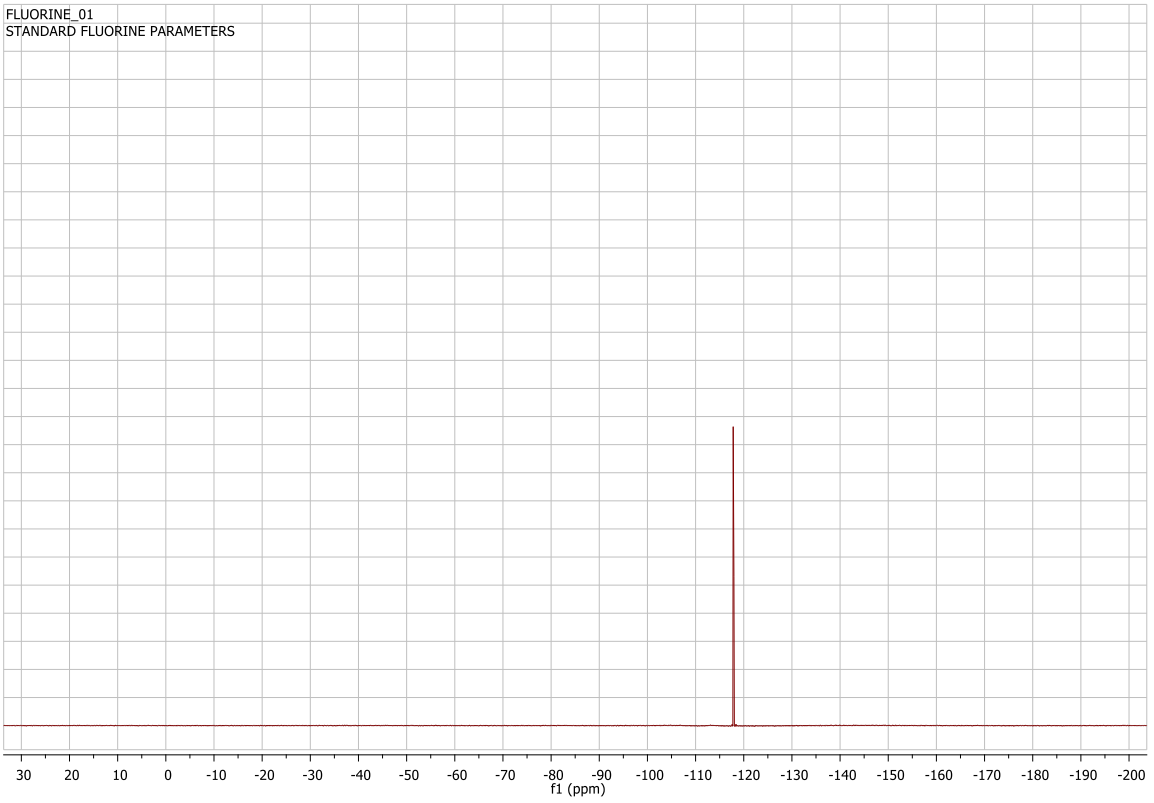

PROTON_01
F21a-8-251
CO2Et
CF2H
N
9e
0.92
0.92
1.01
1.01
1.39
2.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

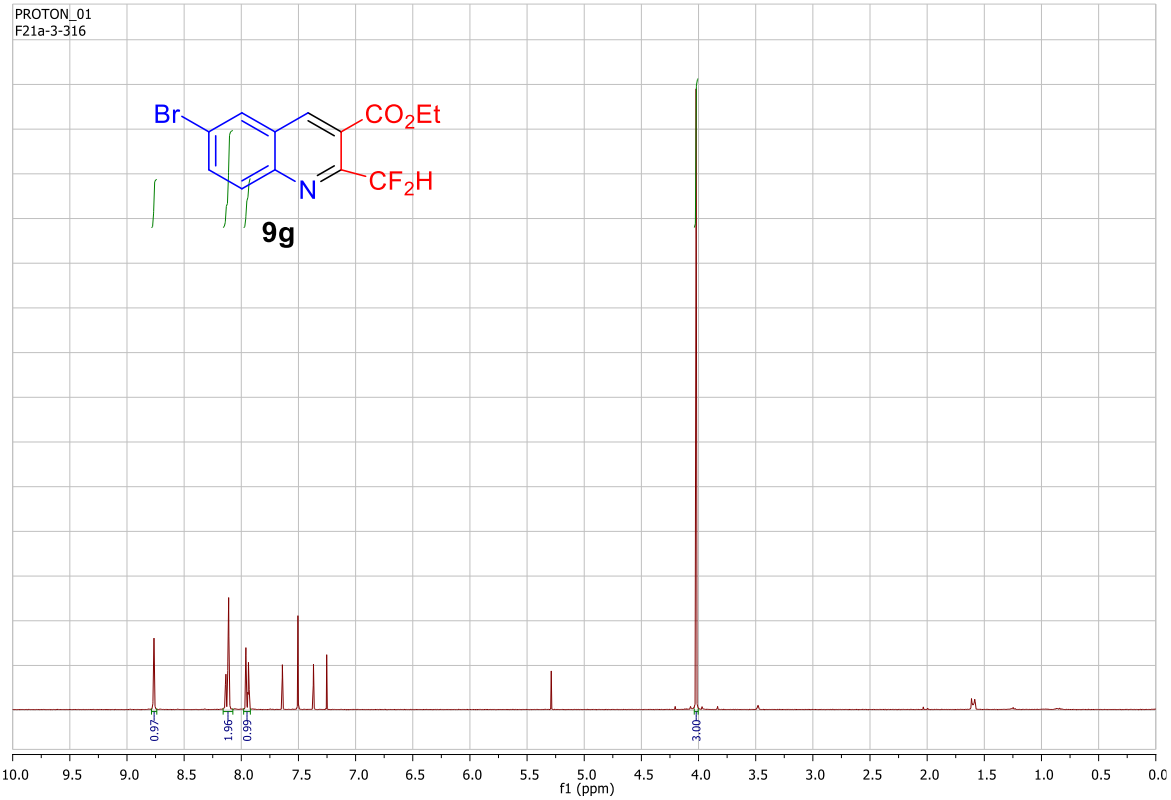

CARBON_01
F21a-8-251
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

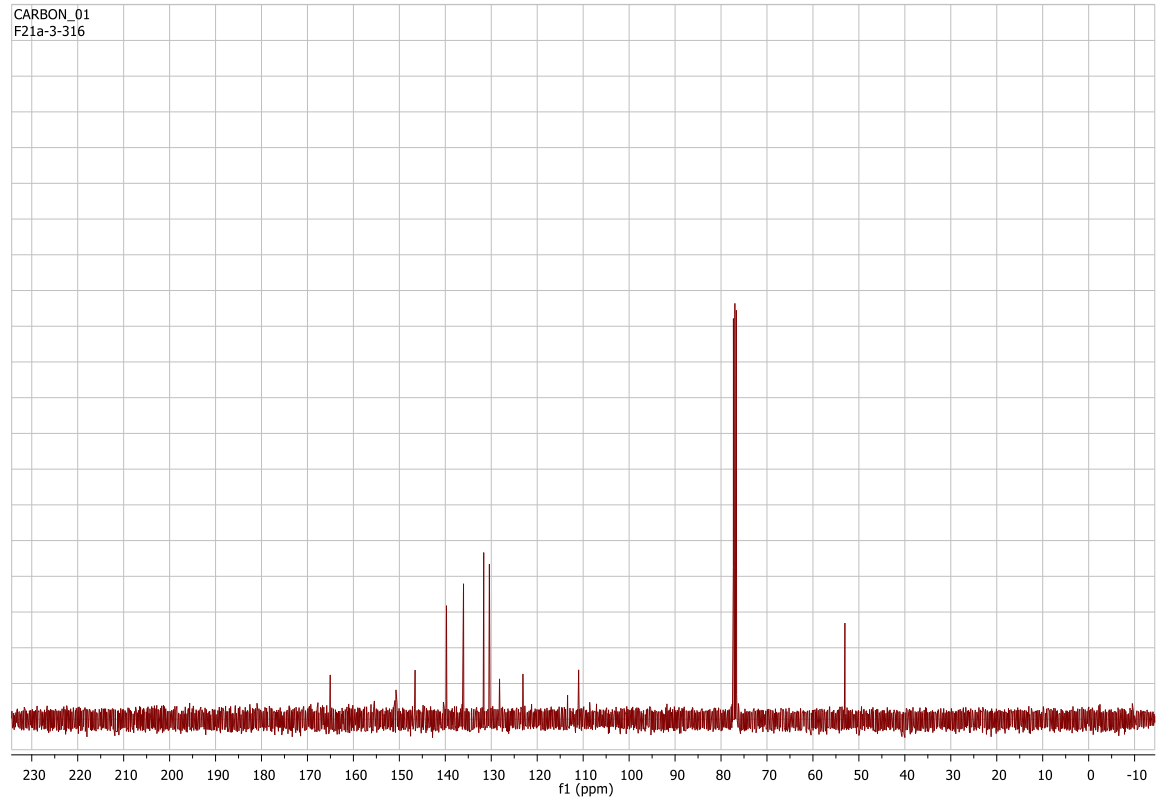

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

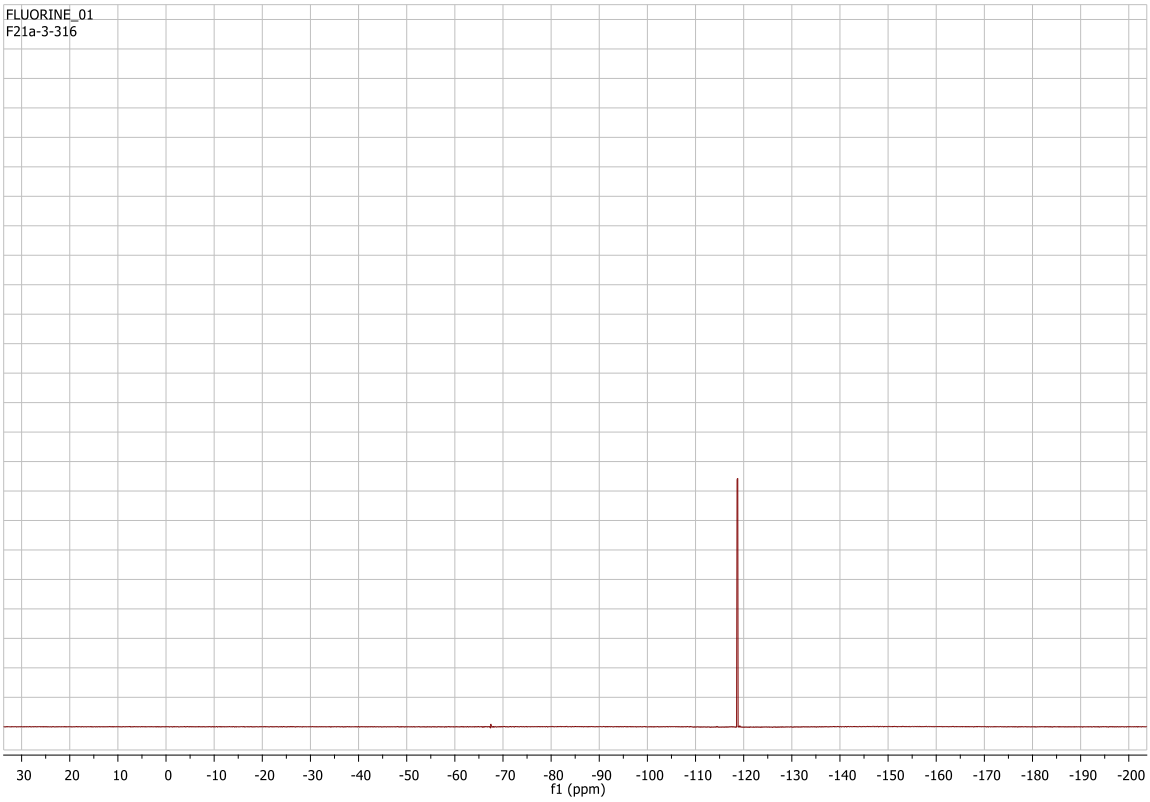

PROTON_01
86b-5k-295-CF2
O
O
N
CO2Et
CF2H
9f
0.95
1.36
0.93
1.97
2.03
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

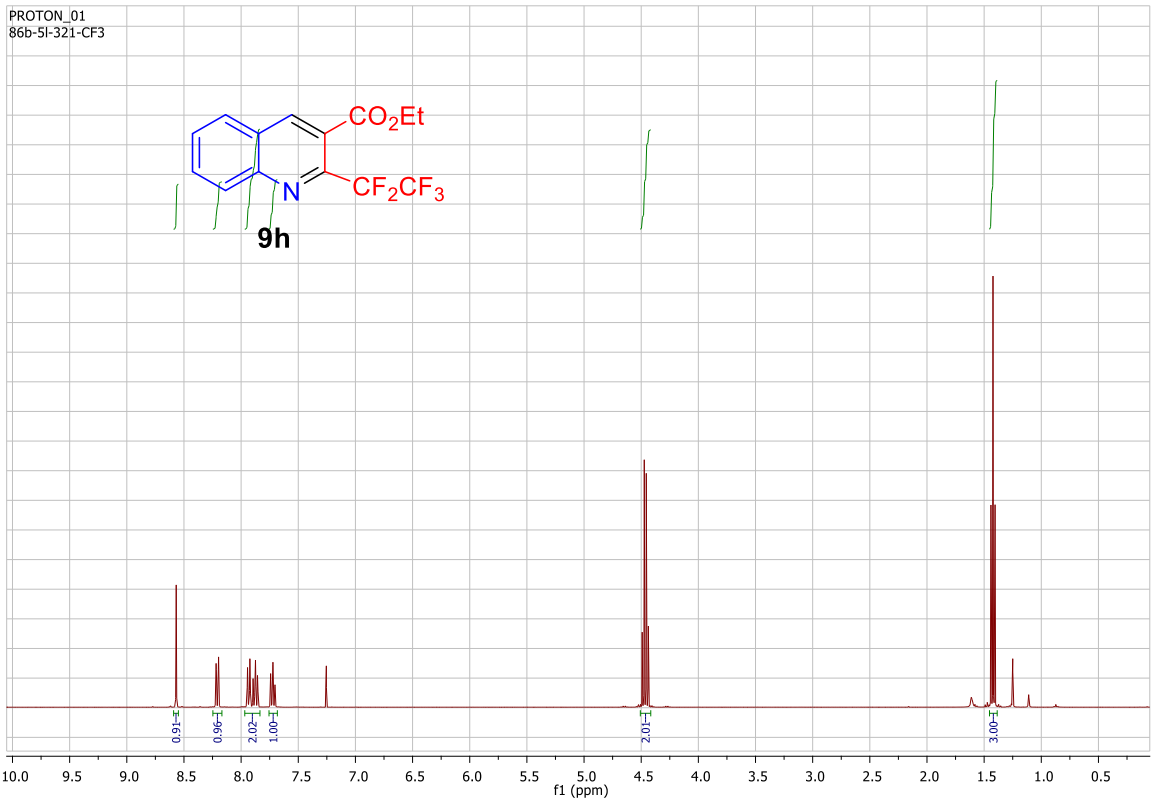

CARBON_01
86b-5k-295-CF2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

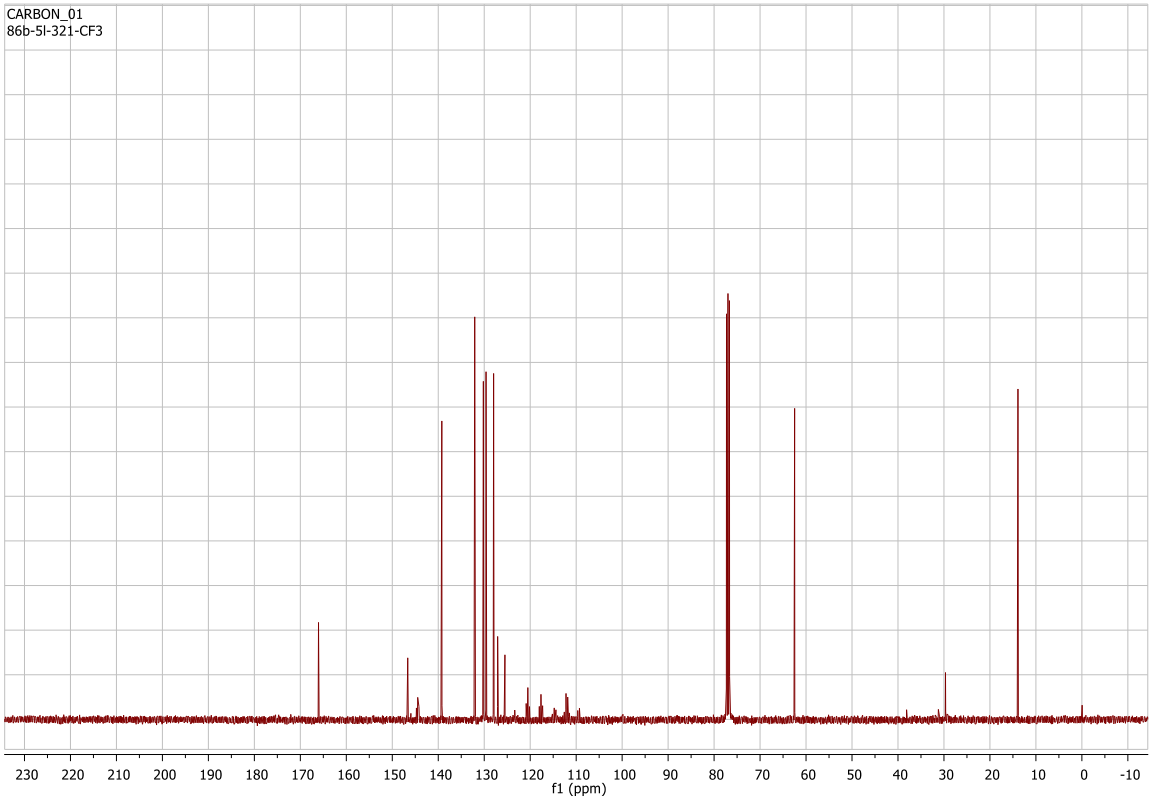

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

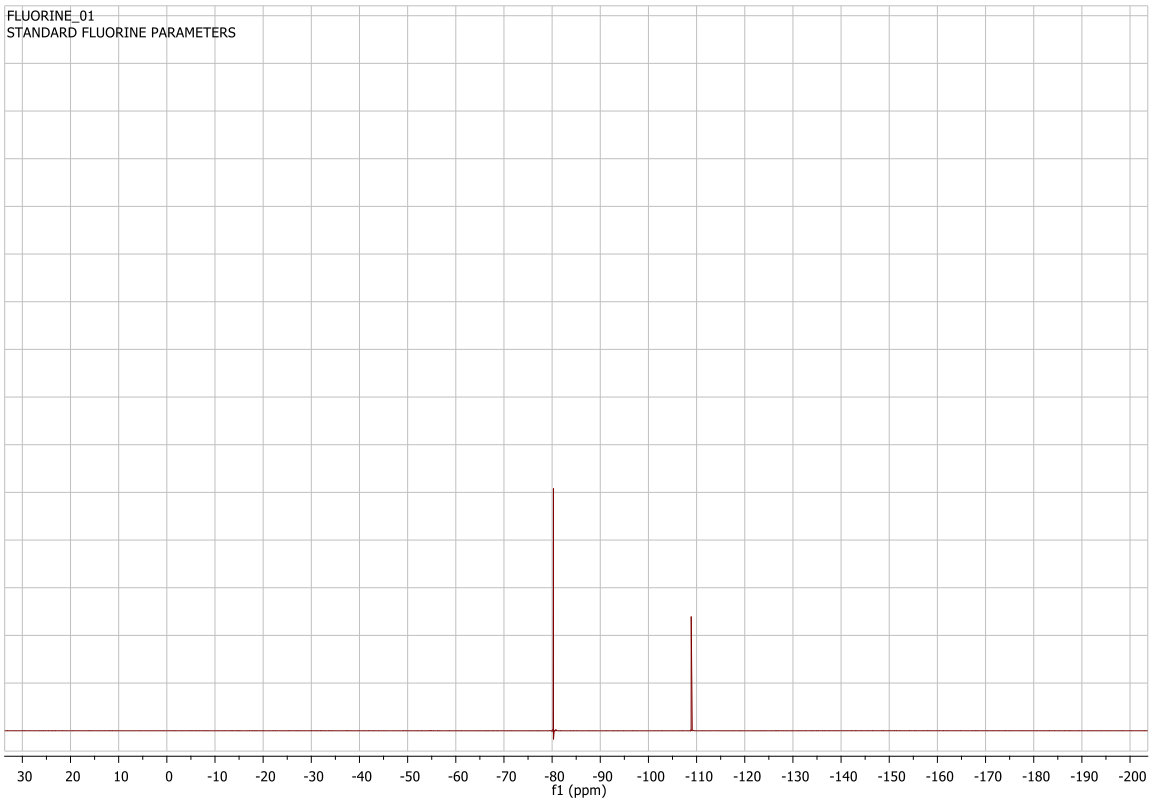

PROTON_01
F21a-3-316
Br
CO2Et
CF2H
N
9g
0.97
1.96
0.99
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

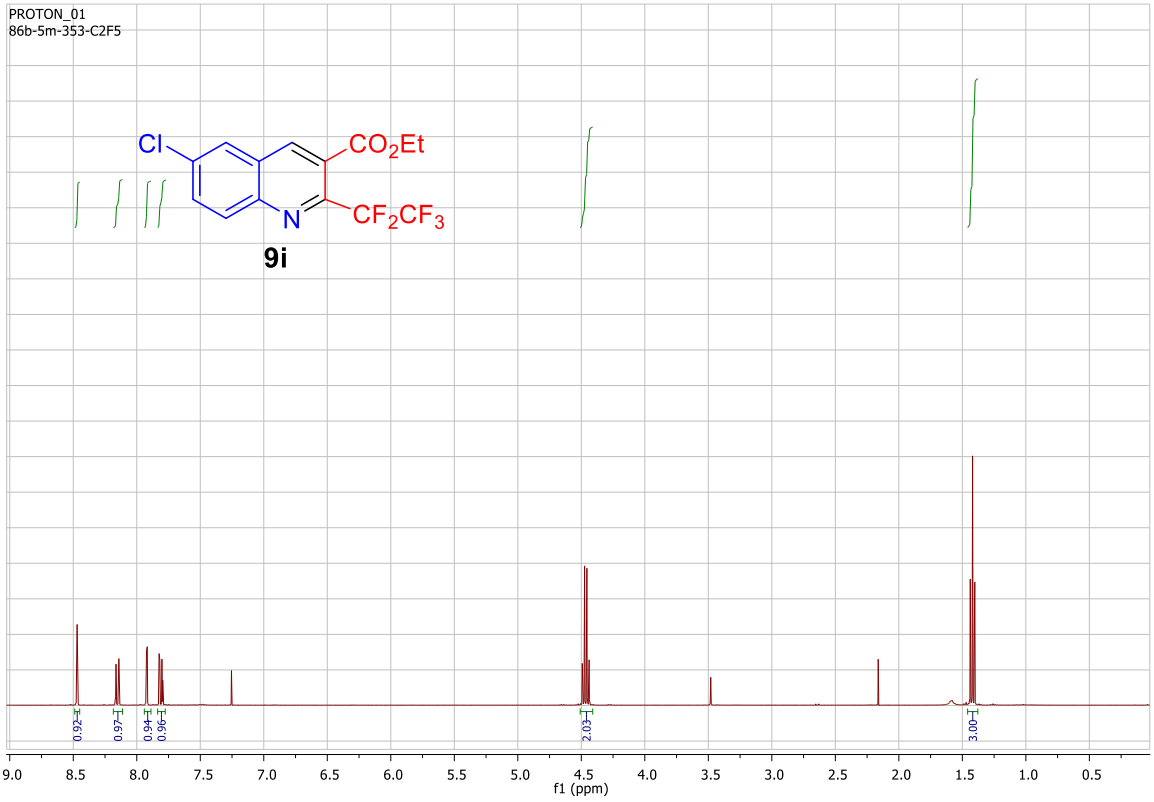

CARBON_01
F21a-3-316
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

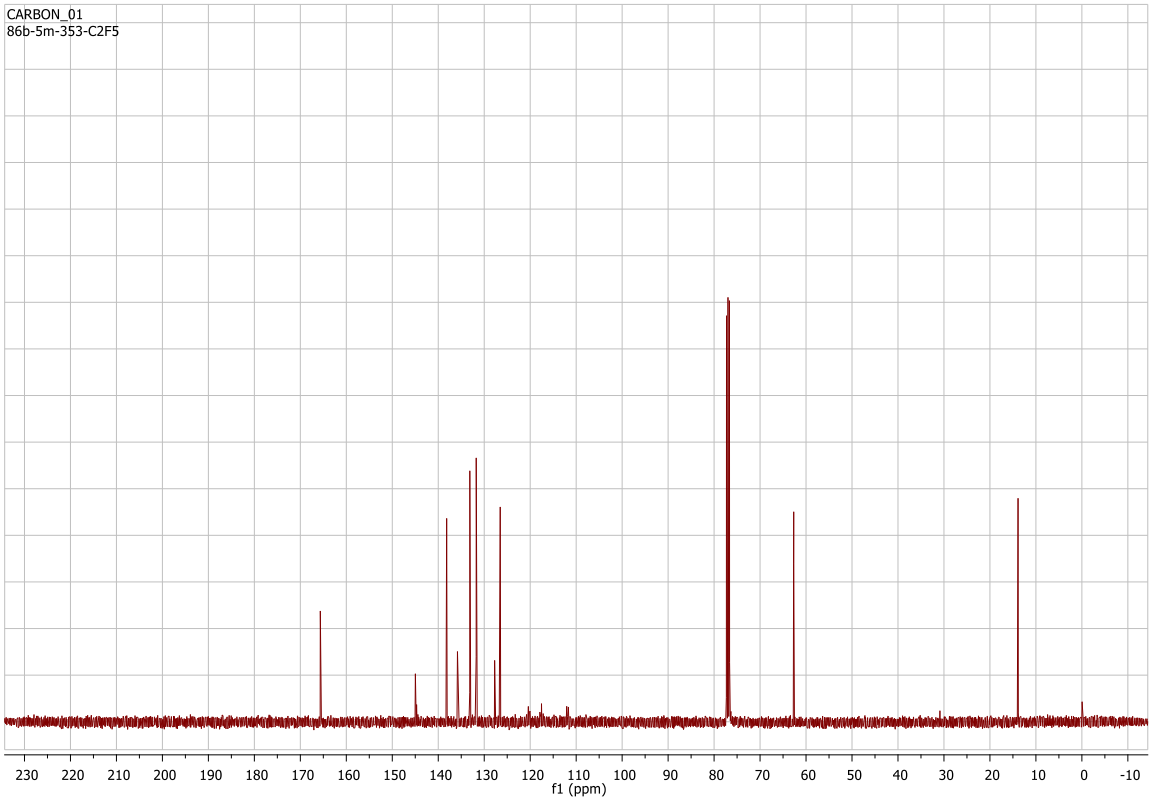

FLUORINE_01
F21a-3-316
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

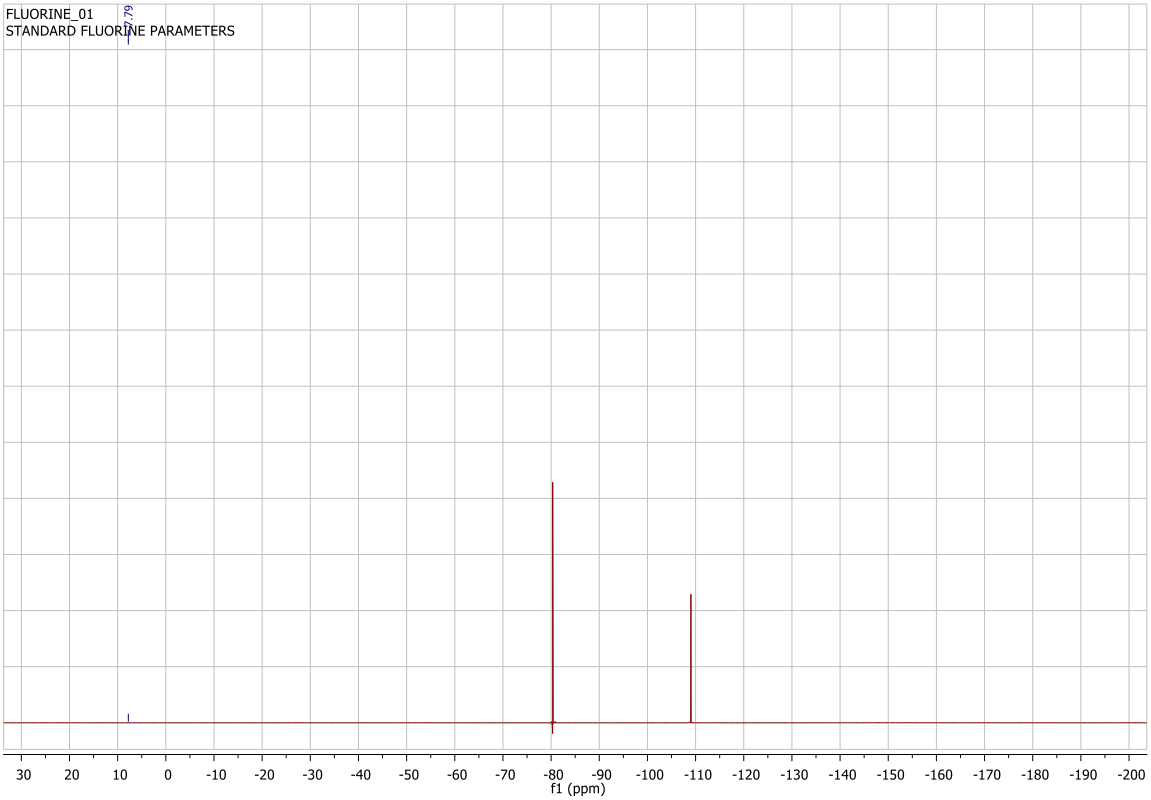

PROTON_01
86b-5l-321-CF3
CO2Et
CF2CF3
N
9h
0.91
0.96
2.02
1.00
2.01
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

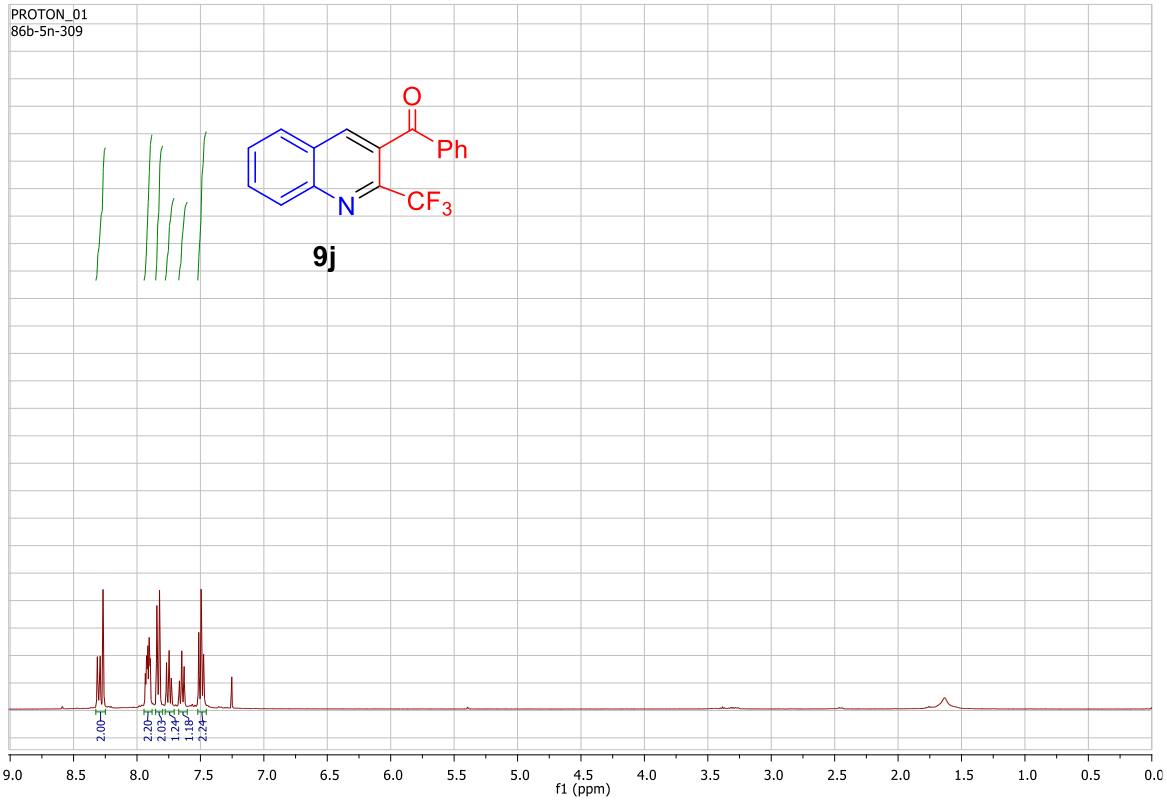

CARBON_01
86b-5l-321-CF3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

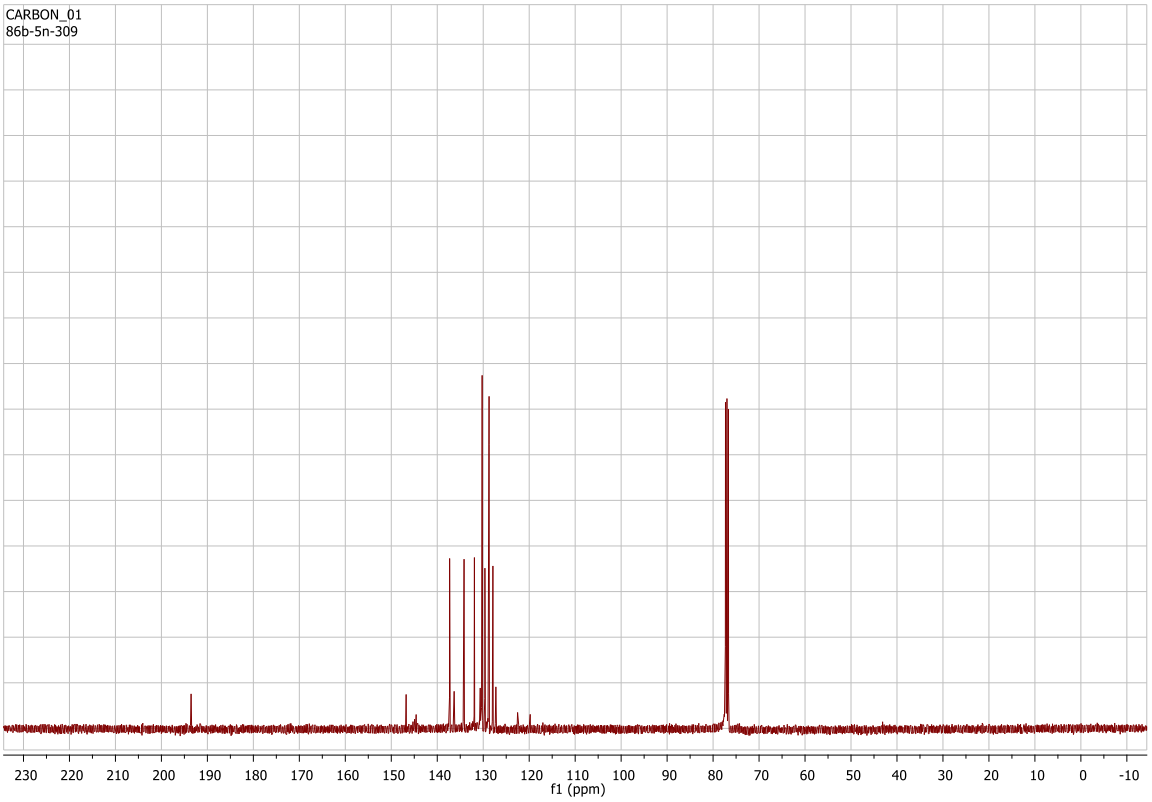

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

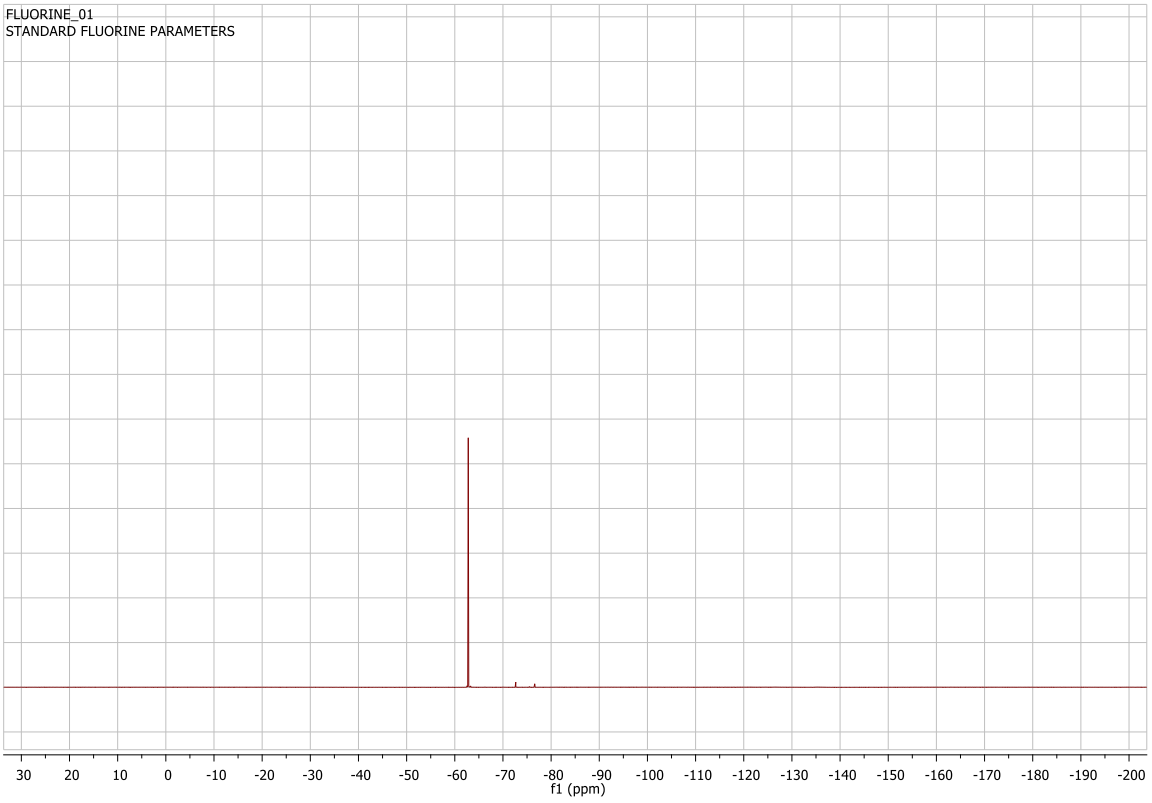

PROTON_01
86b-5m-353-C2F5
Cl
$CO_2Et$
N
$CF_2CF_3$
9i
0.92
0.97
0.94
0.96
2.03
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

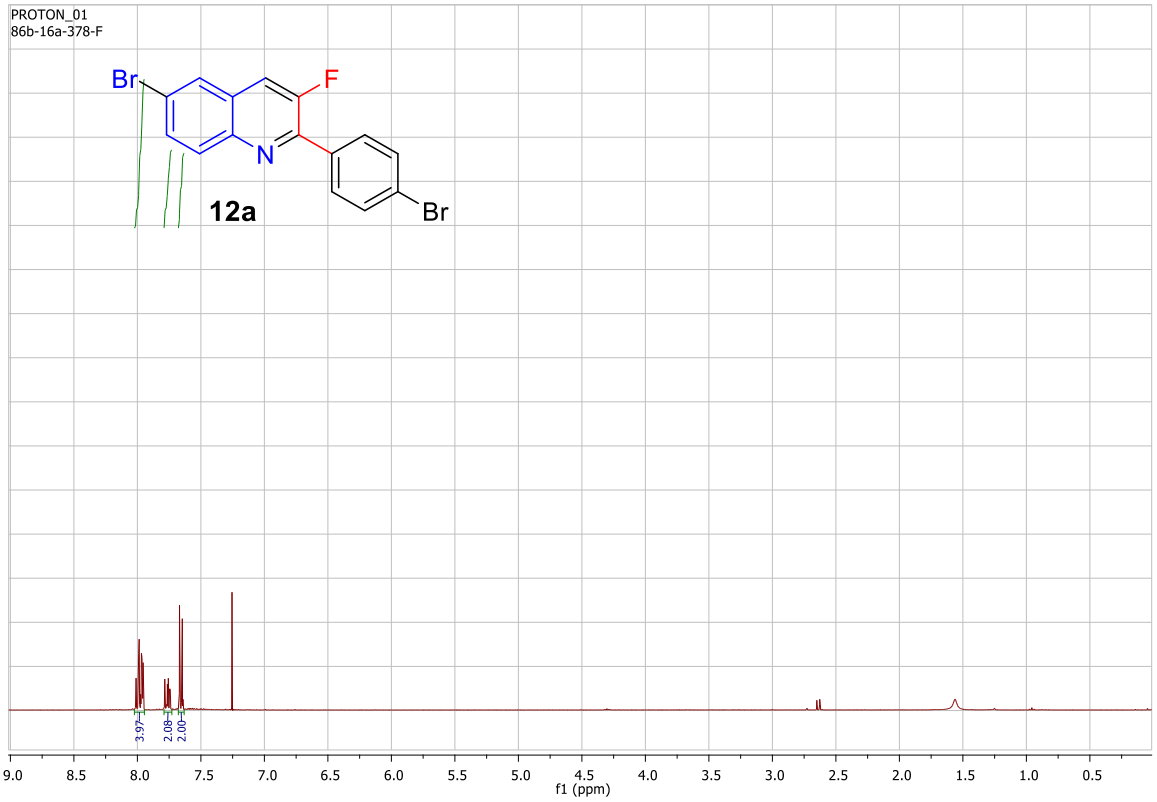

CARBON_01
86b-5m-353-C2F5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

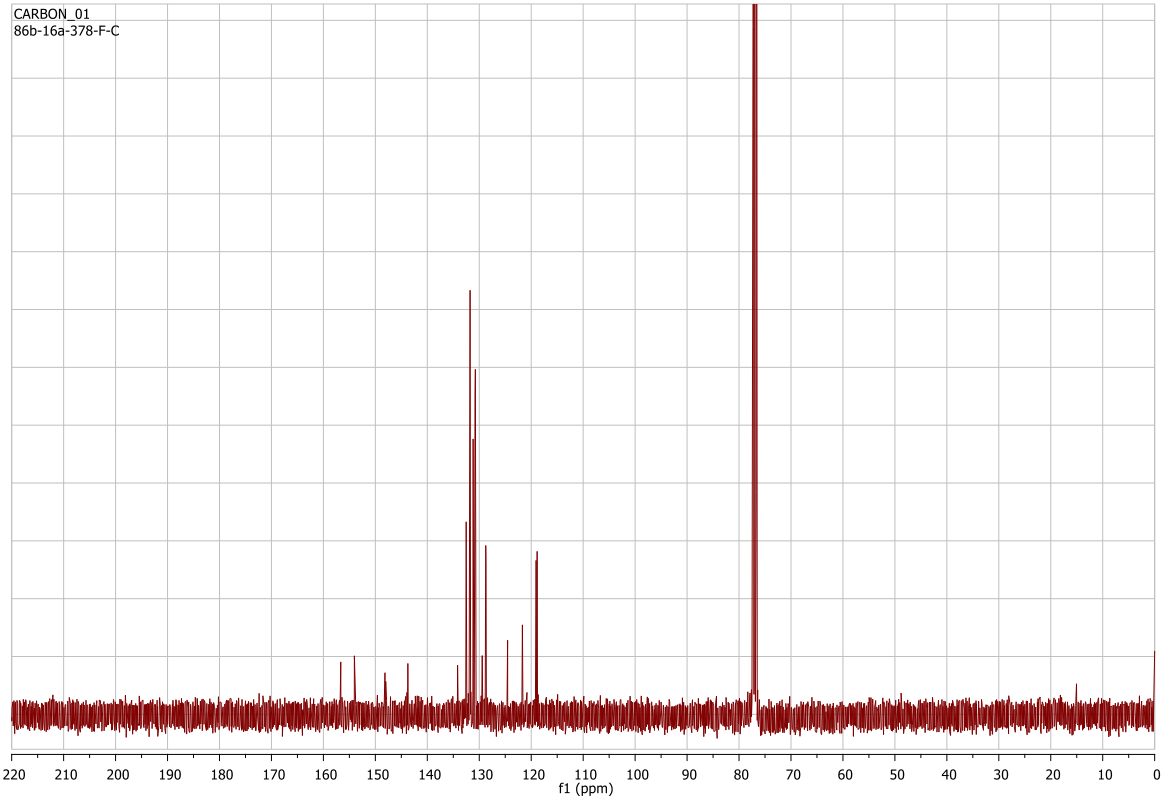

FLUORINE_01
STANDARD FLUORINE PARAMETERS
-62.79
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

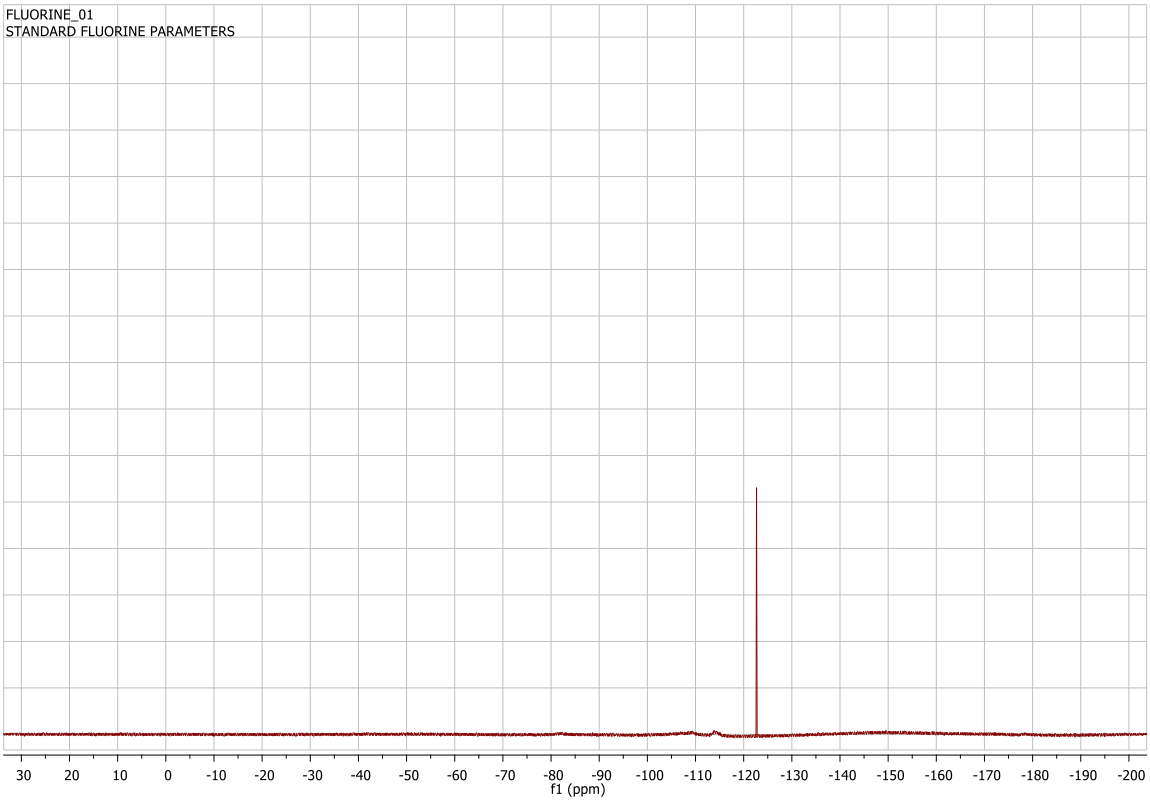

PROTON_01
86b-5n-309
O
Ph
N
CF3
9j
2.00
2.20
2.03
1.24
1.18
2.24
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

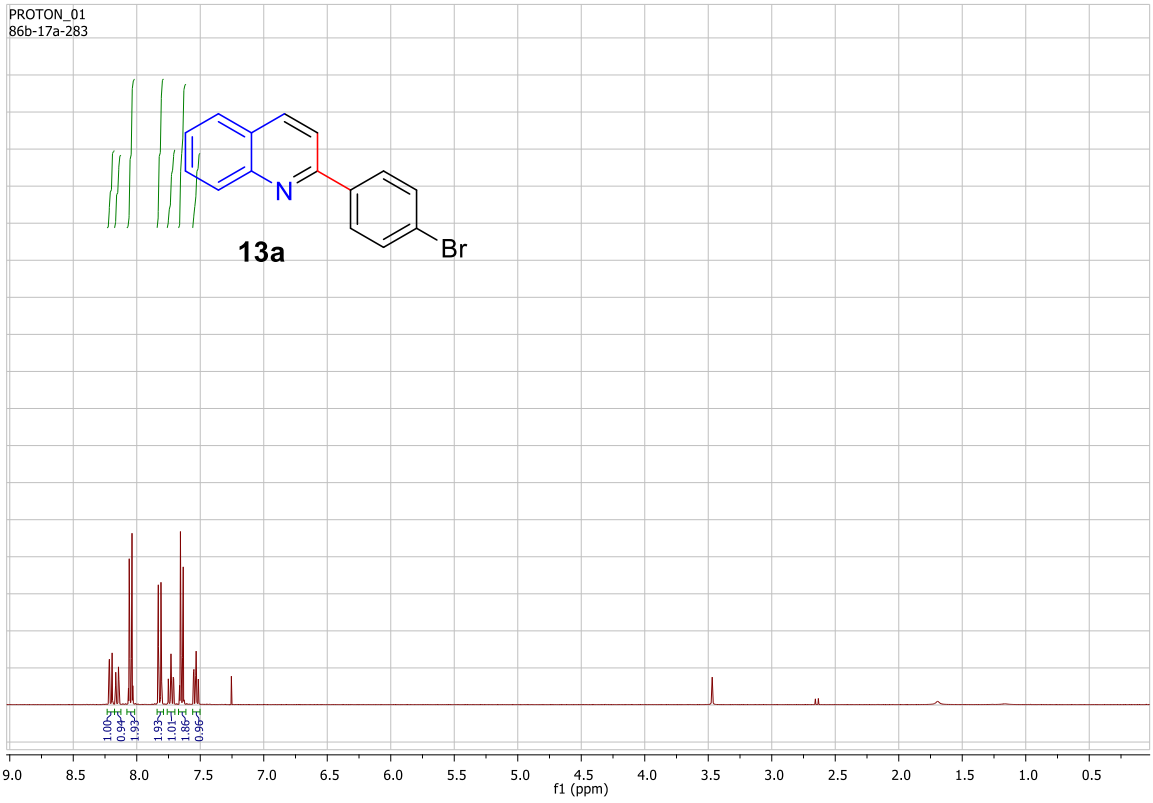

CARBON_01
86b-5n-309
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

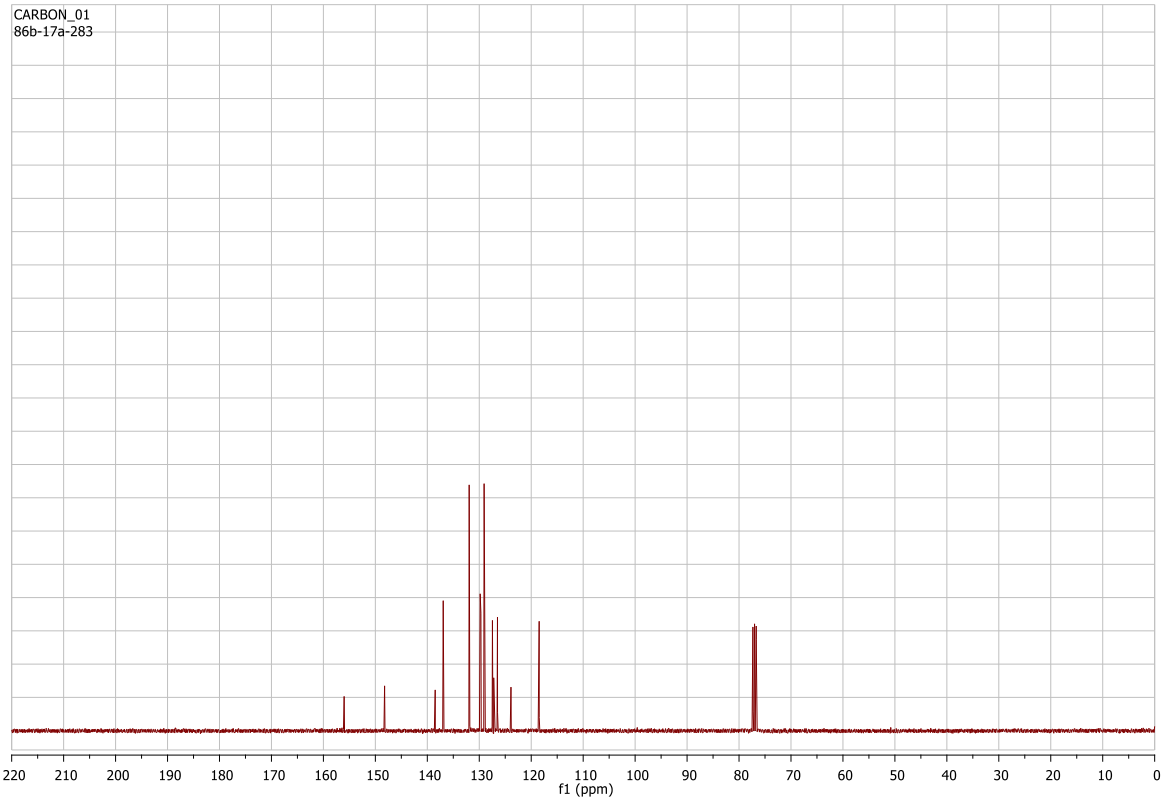

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

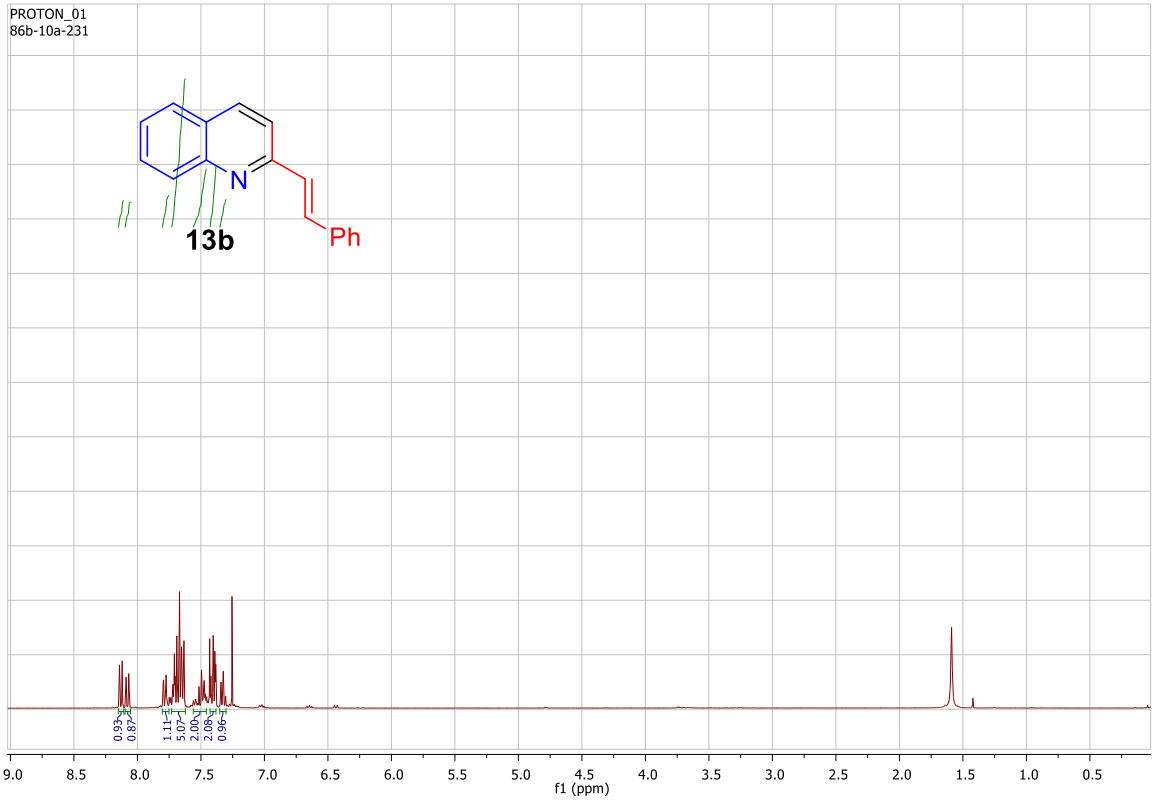

PROTON_01
86b-16a-378-F
Br
F
N
12a
Br
3.97
2.08
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

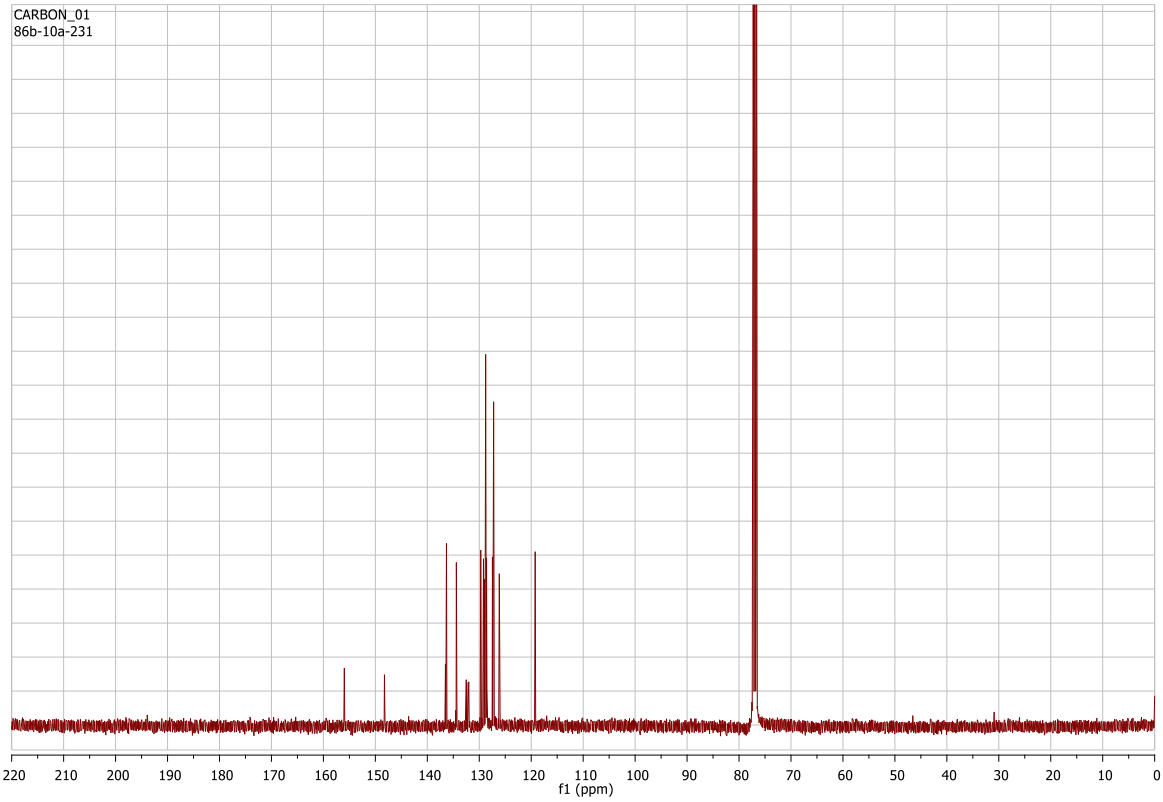

CARBON_01
86b-16a-378-F-C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

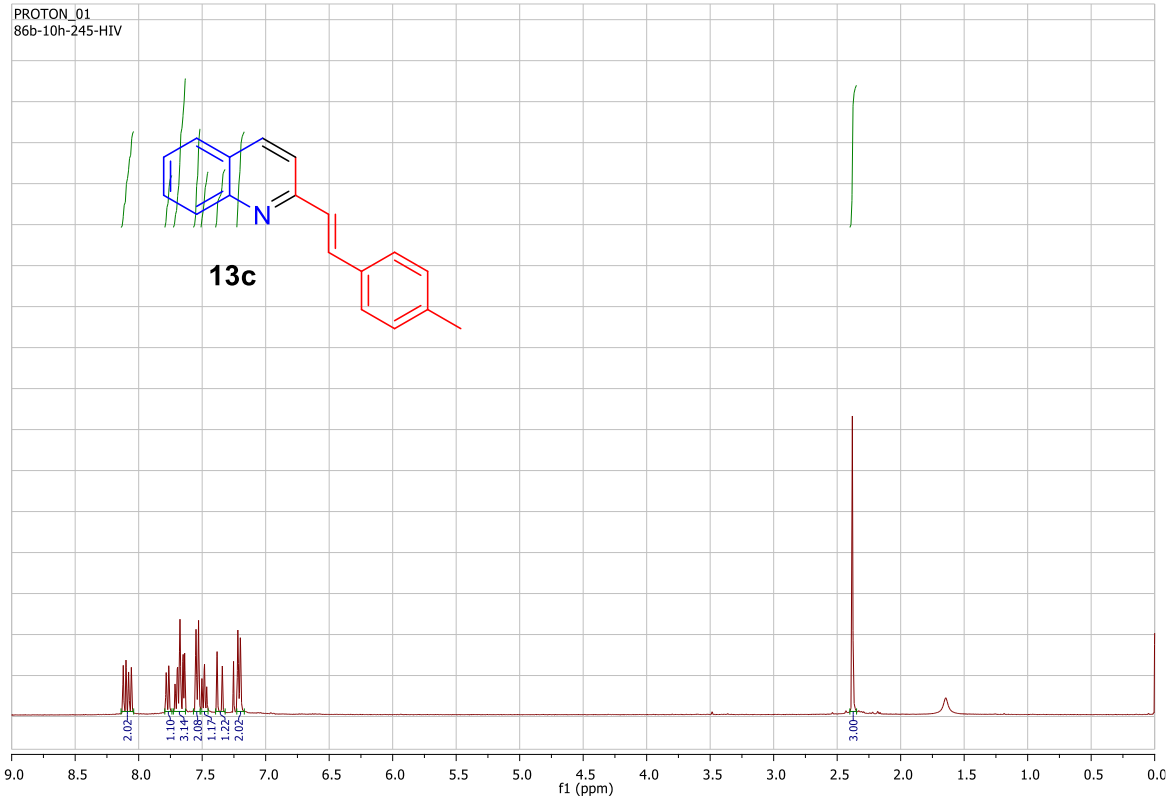

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

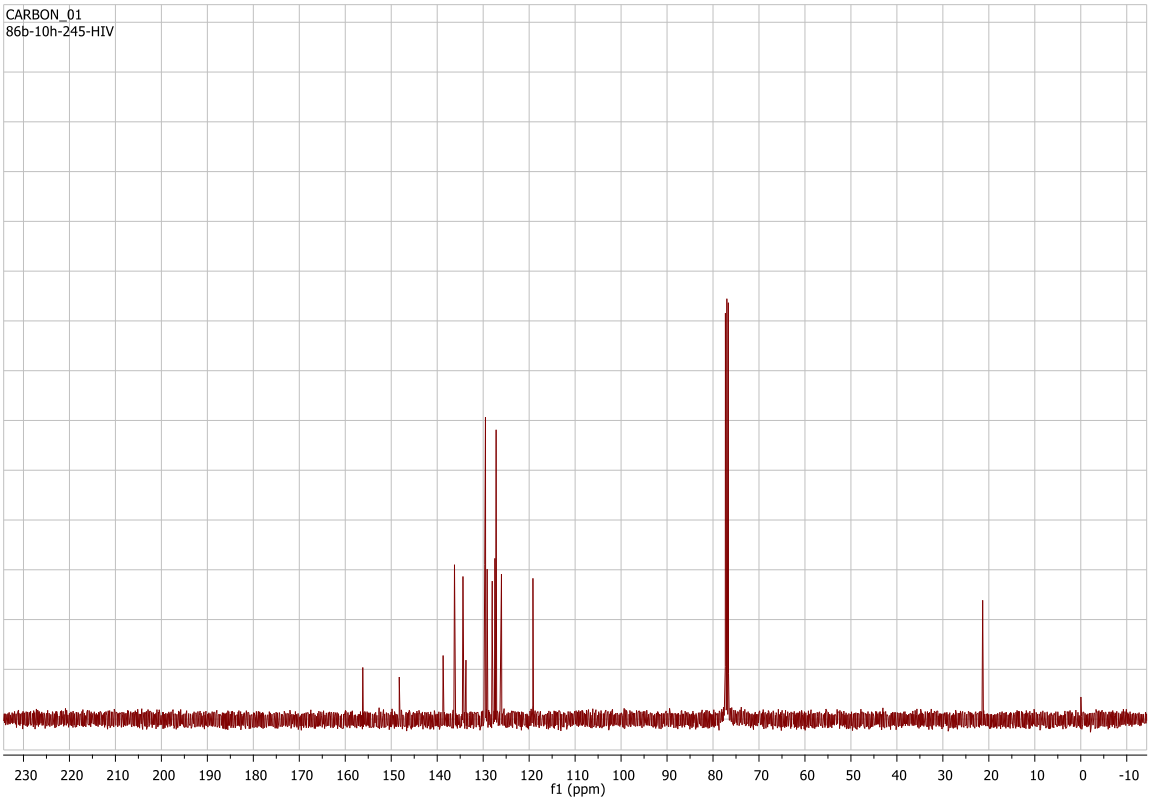

PROTON_01
86b-17a-283
N
Br
13a
1.00
0.94
1.93
1.93
1.01
1.86
0.96
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

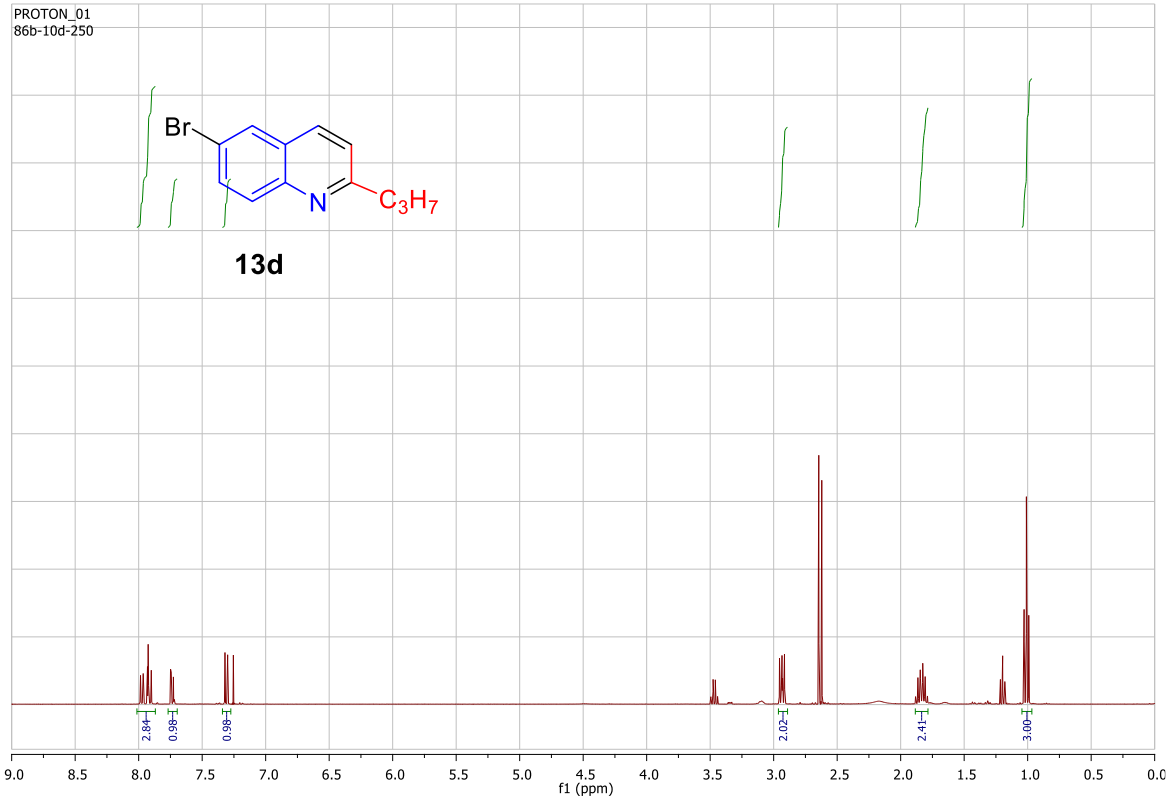

CARBON_01
86b-17a-283
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

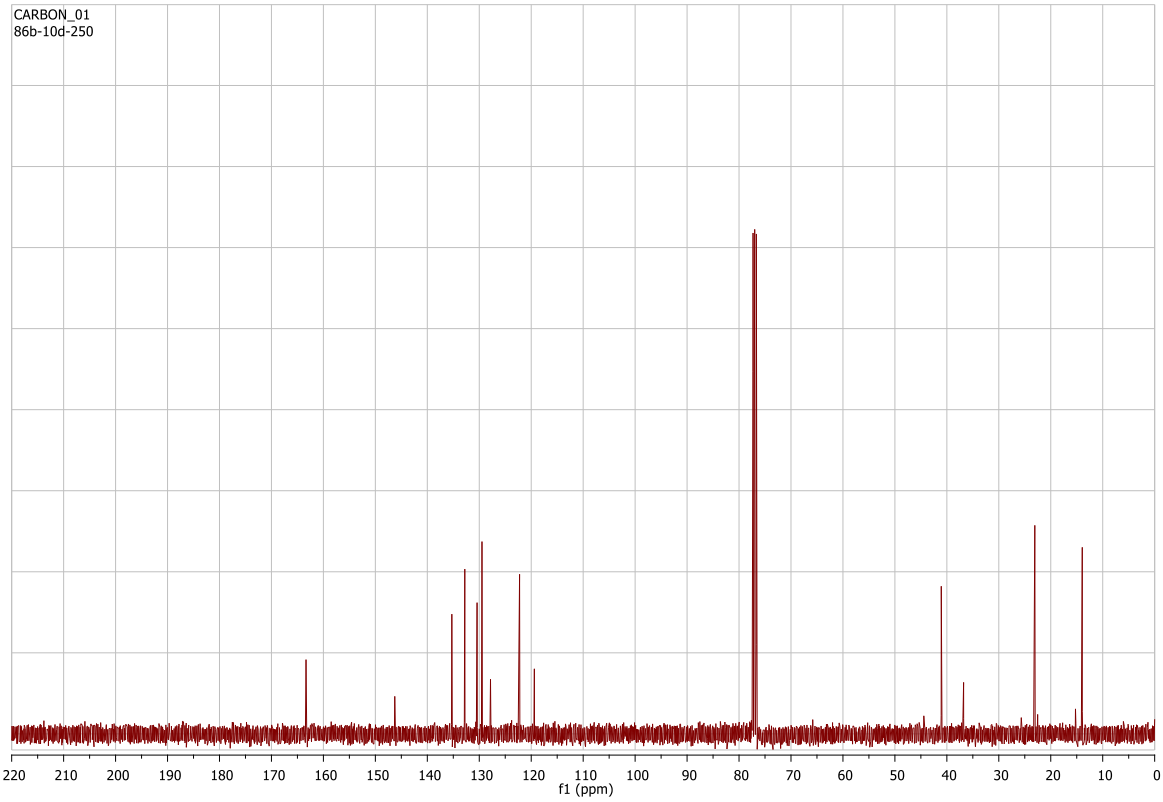

PROTON_01
86b-10a-231
N
Ph
13b
0.93
0.87
1.11
5.07
2.00
2.08
0.96
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

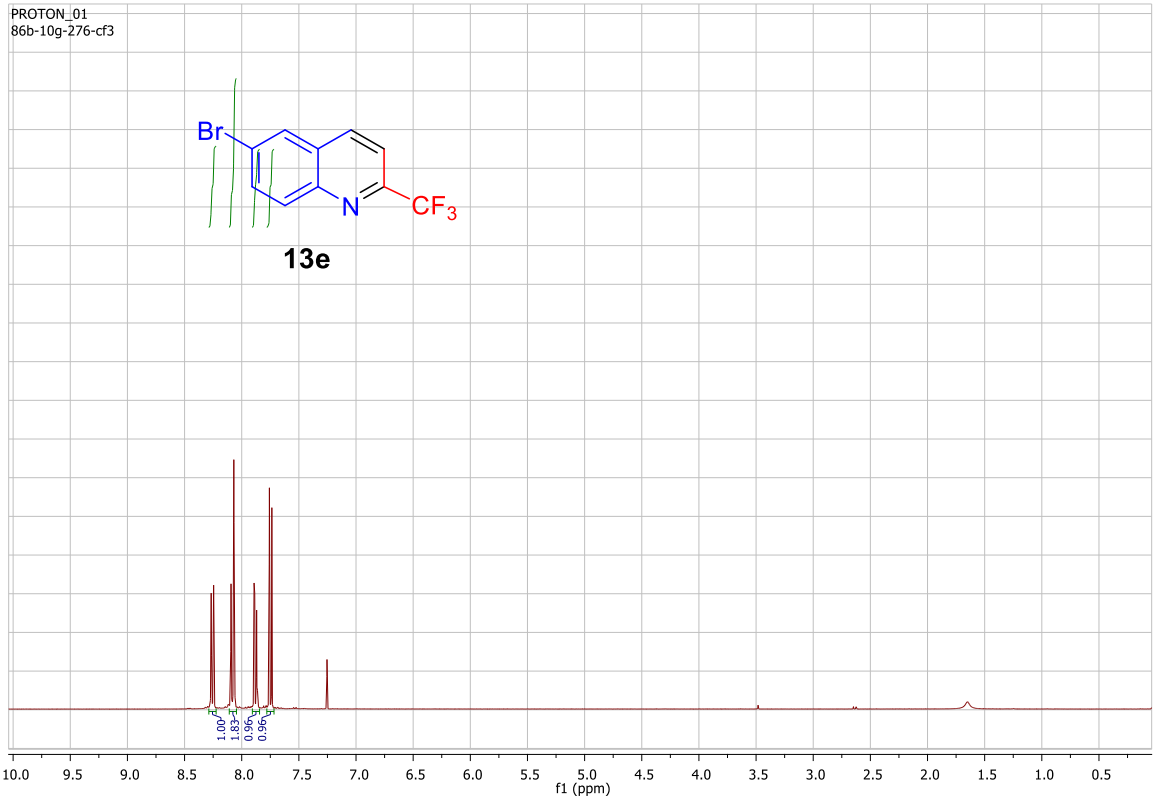

CARBON_01
86b-10a-231
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


PROTON_01
86b-10h-245-HIV
N
13c
2.02
1.10
3.14
2.08
1.17
1.22
2.02
3.00
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)

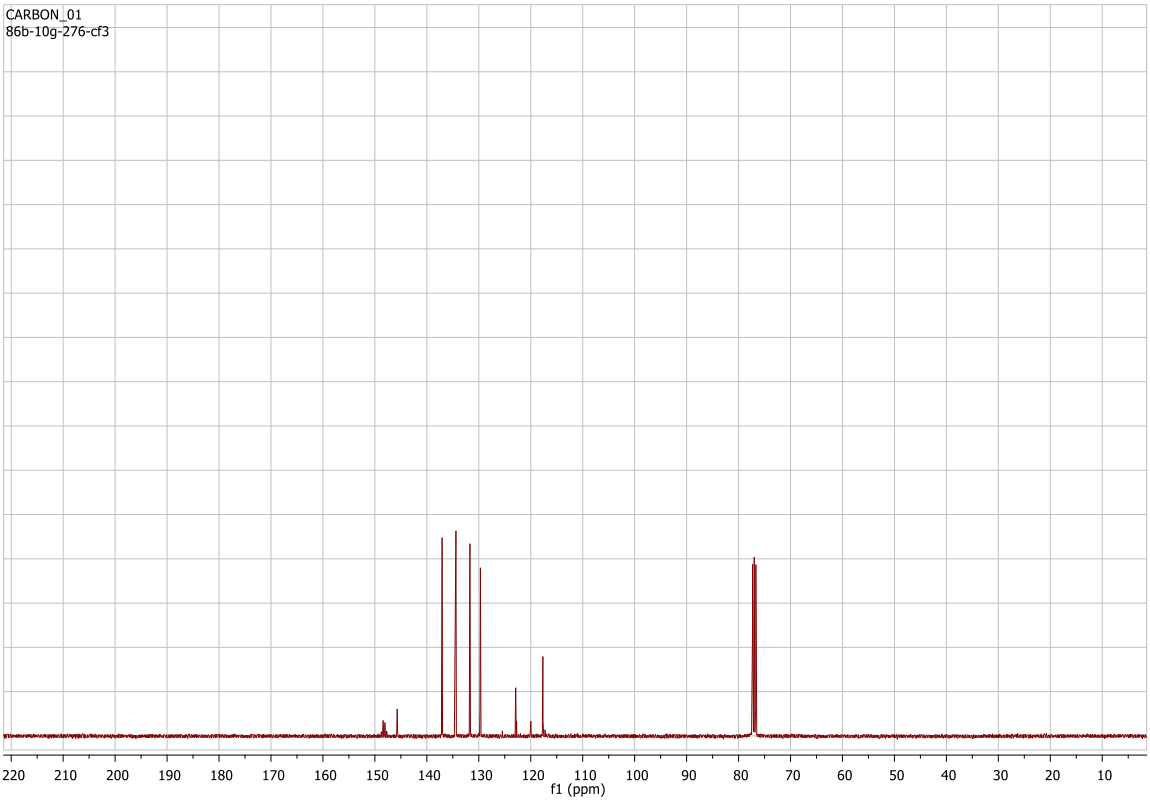

CARBON_01
86b-10h-245-HIV
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

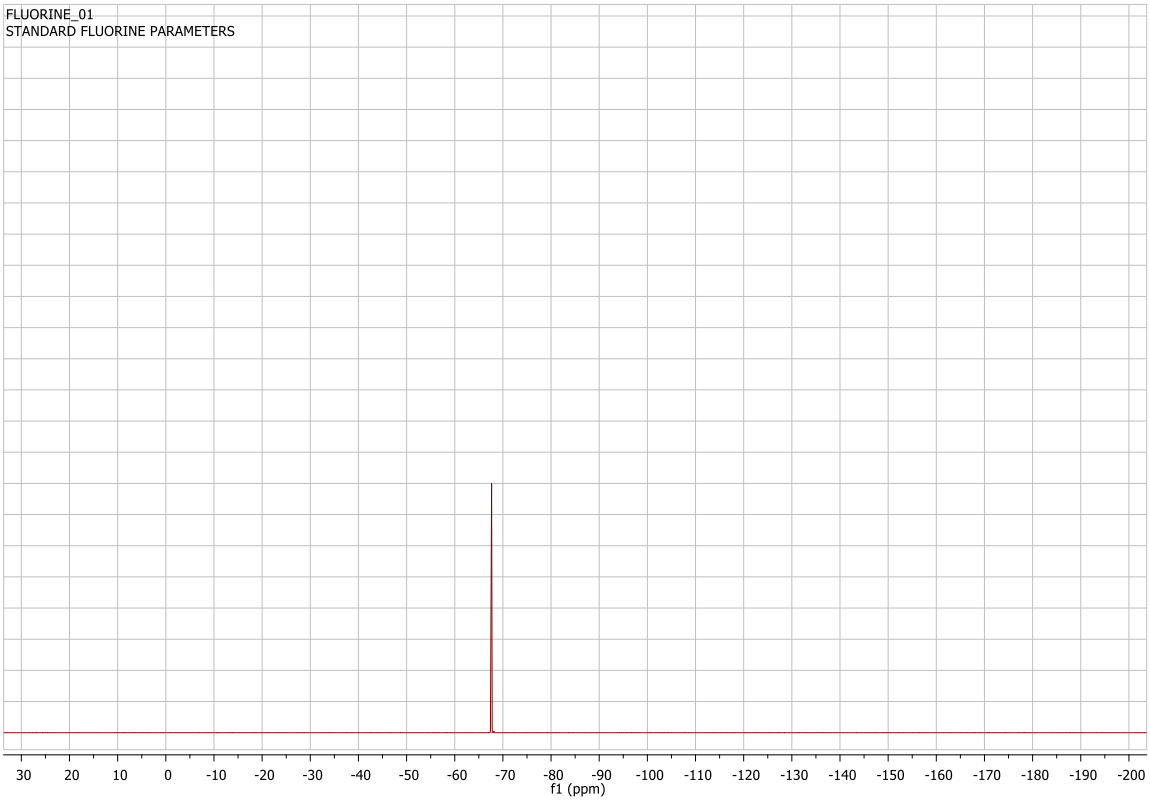

PROTON_01
86b-10d-250
Br
N
$C_3H_7$
13d
2.84
0.98
0.98
2.02
2.41
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

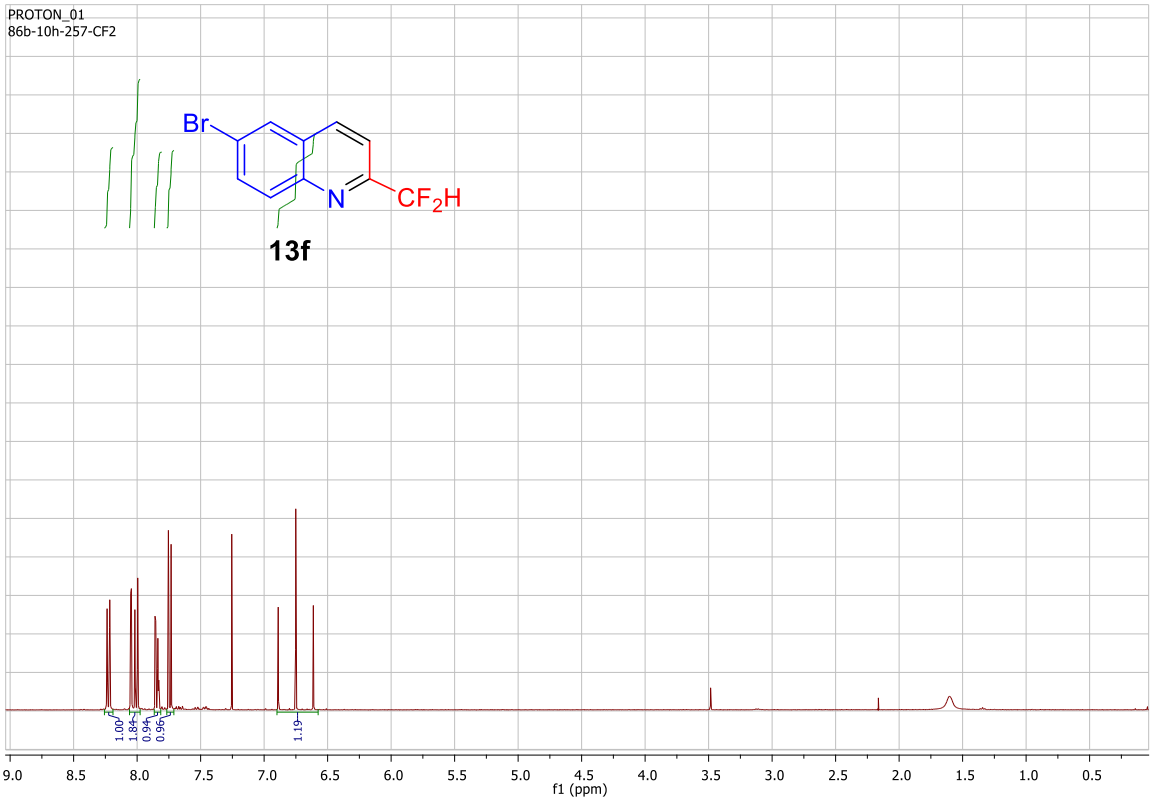

CARBON_01
86b-10d-250
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

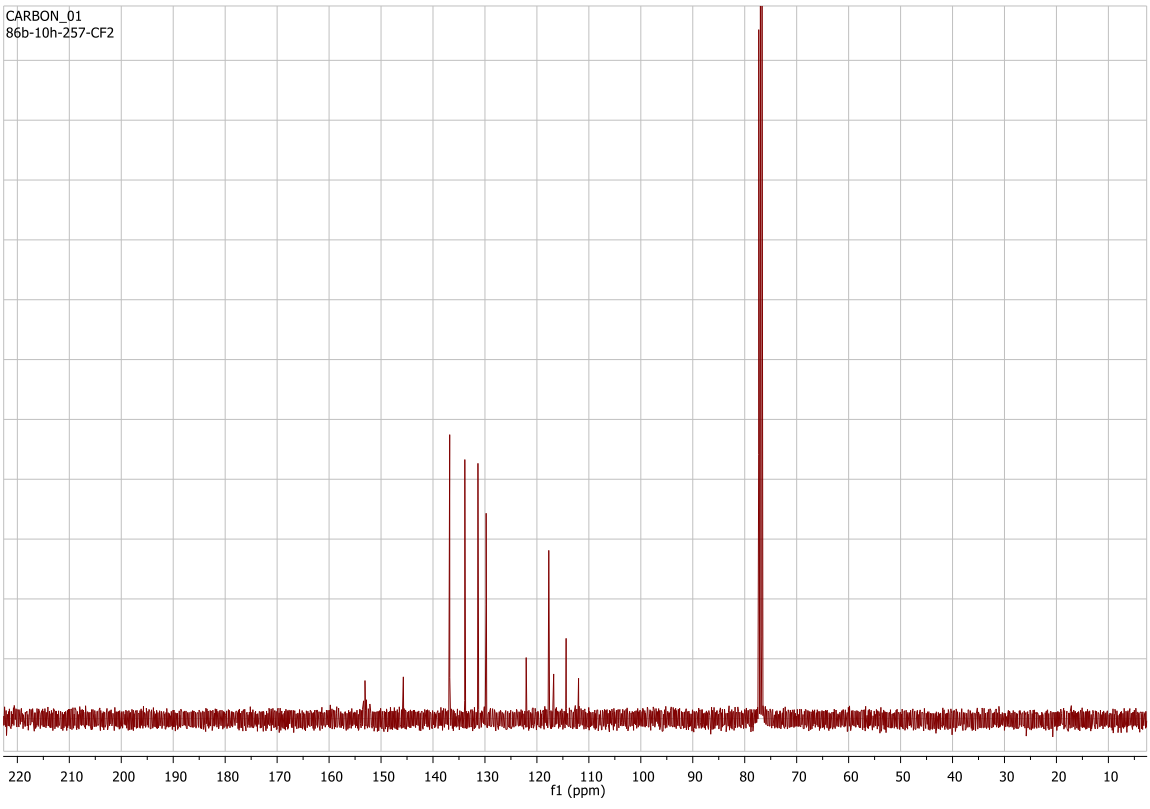

PROTON_01
86b-10g-276-cf3
Br
N
CF3
1.00
1.83
0.96
0.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

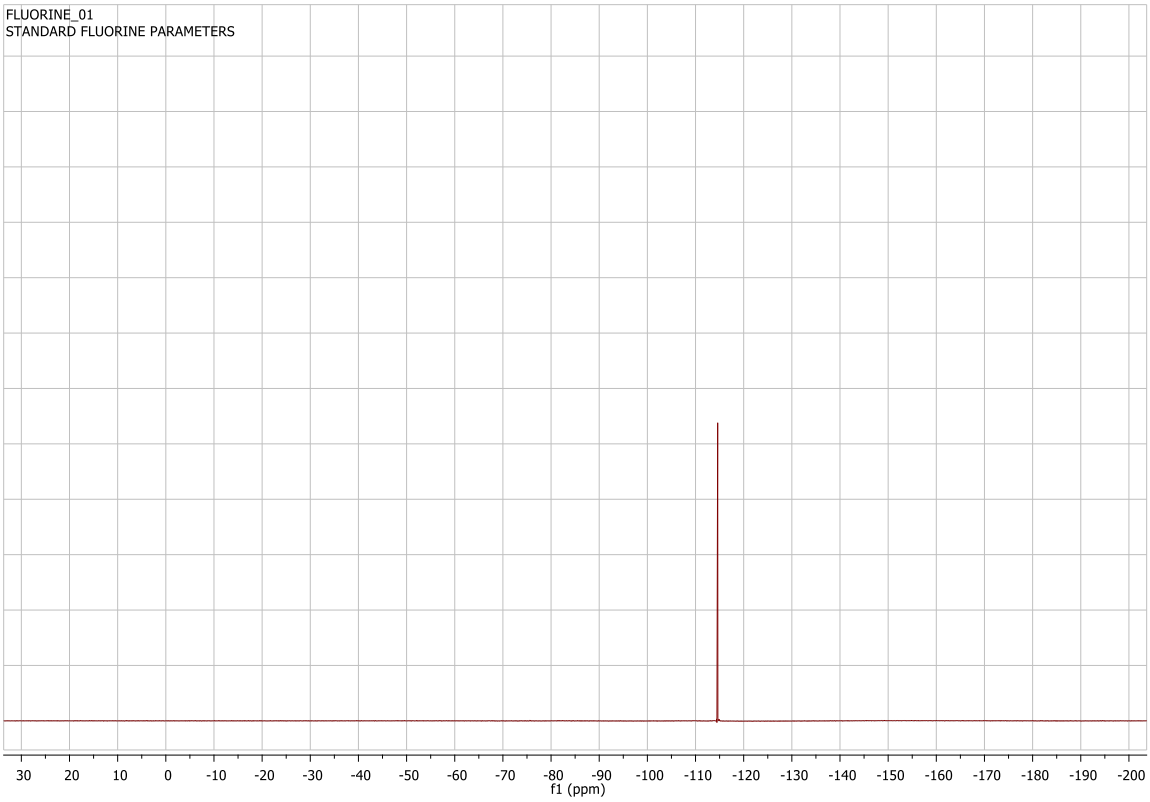
**13e**

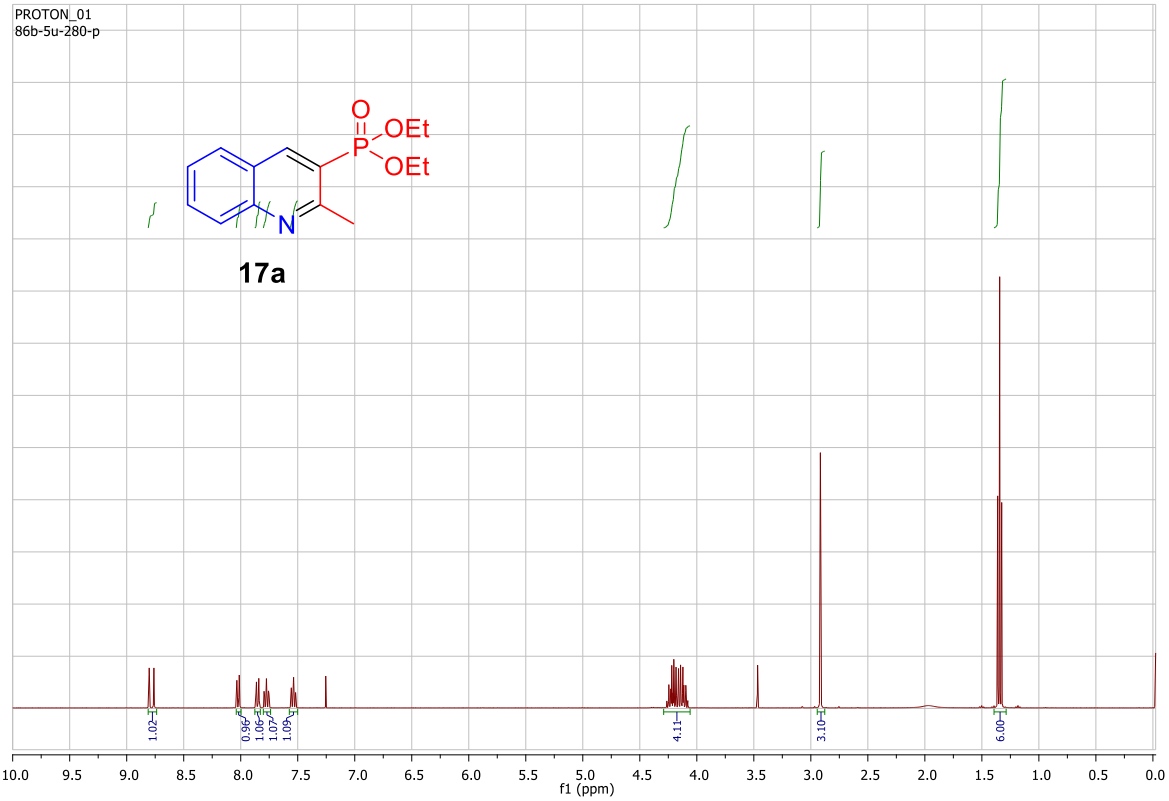

CARBON_01
86b-10g-276-cf3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

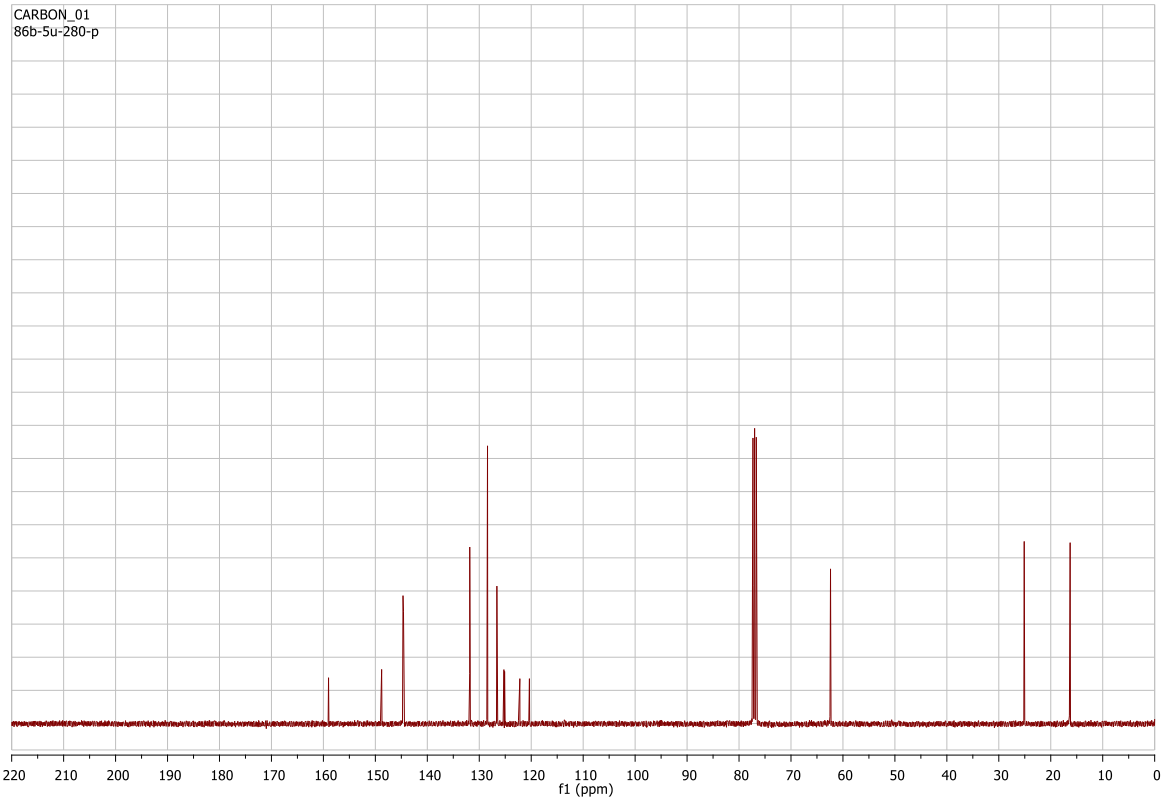

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

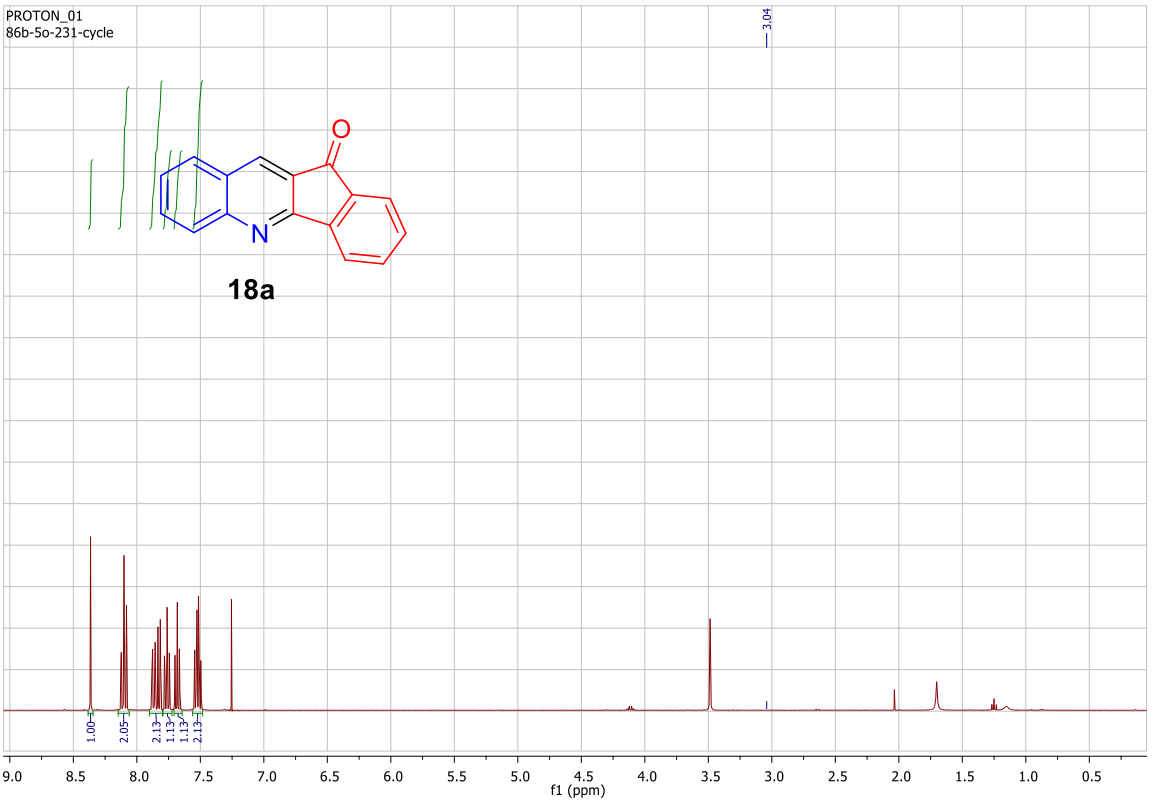

PROTON_01
86b-10h-257-CF2
Br
N
CF2H
13f
1.00
1.84
0.94
0.96
1.19
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

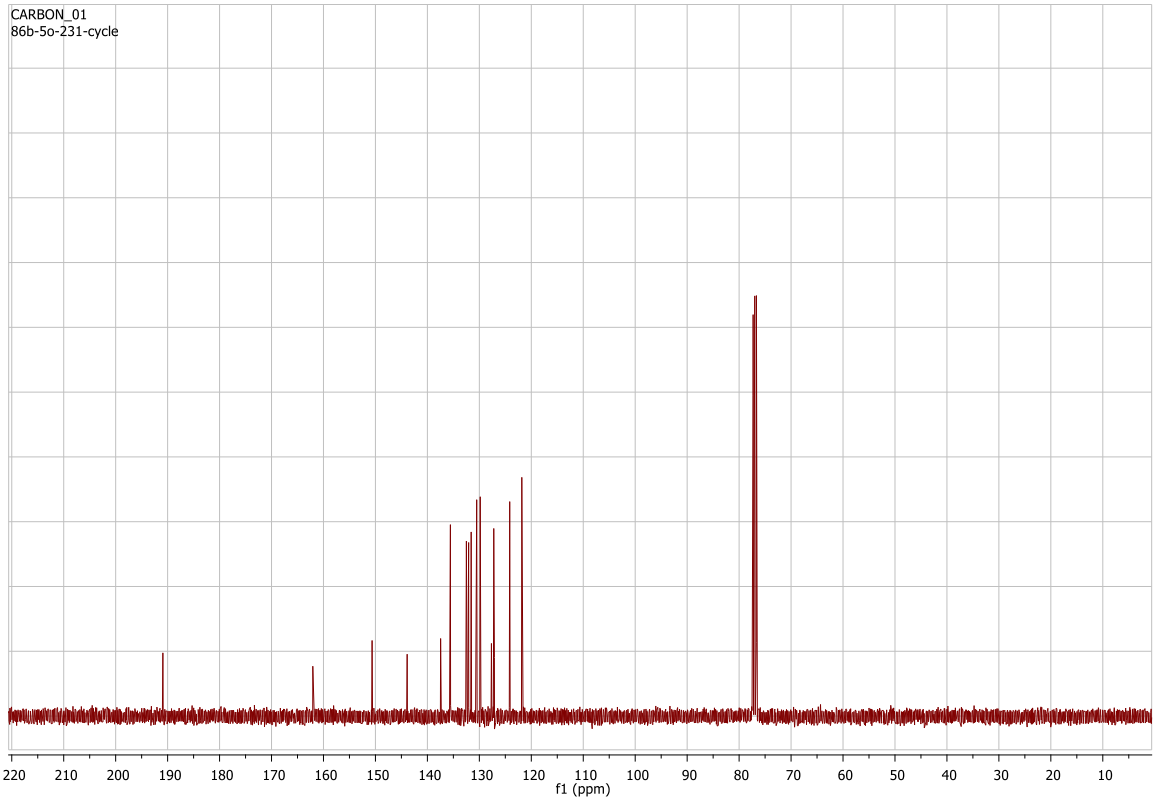

CARBON_01
86b-10h-257-CF2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

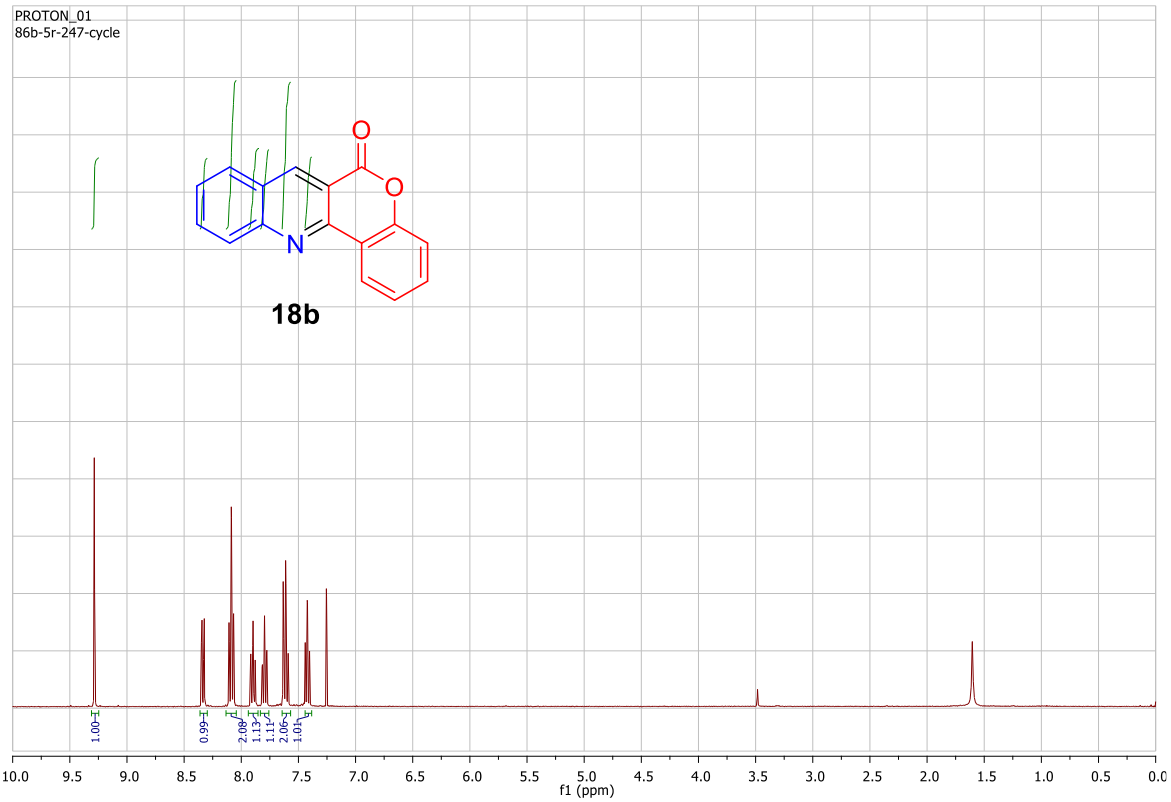

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


PROTON_01
86b-5u-280-p
O
OEt
P
OEt
N
17a
1.02
0.96
1.06
1.07
1.09
4.11
3.10
6.00
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)

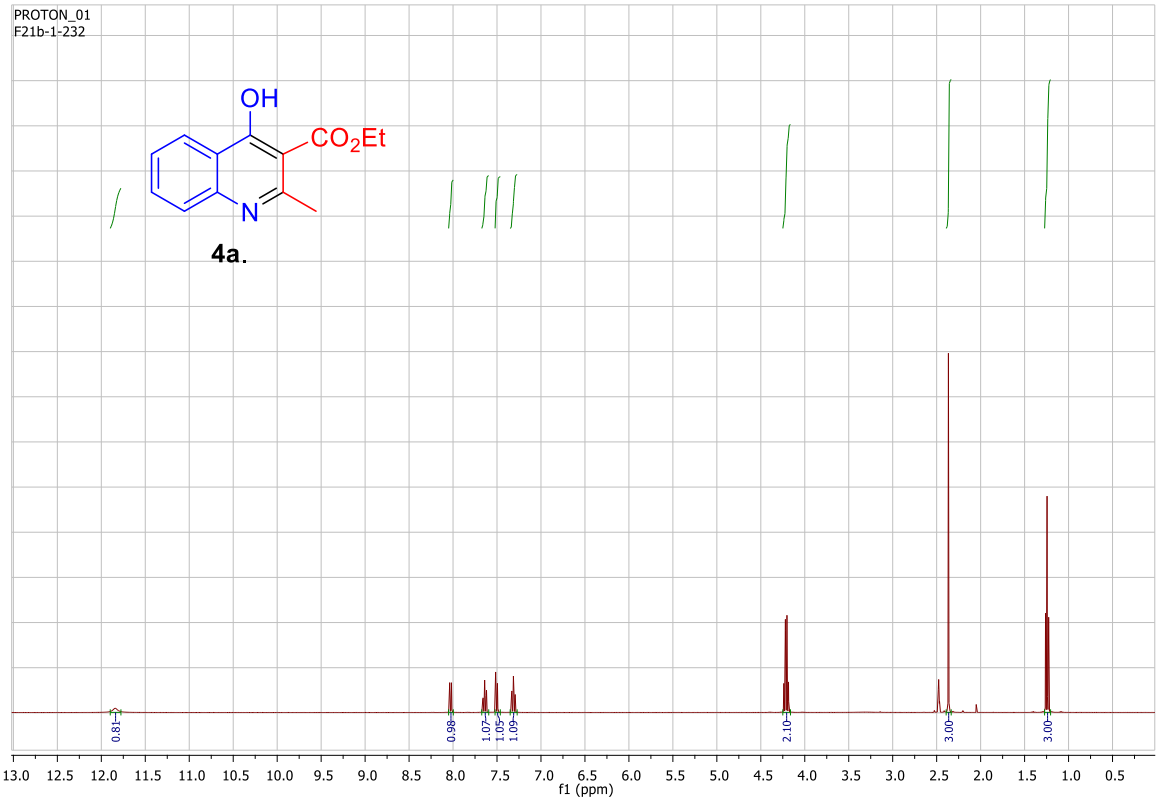

CARBON_01
86b-5u-280-p
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

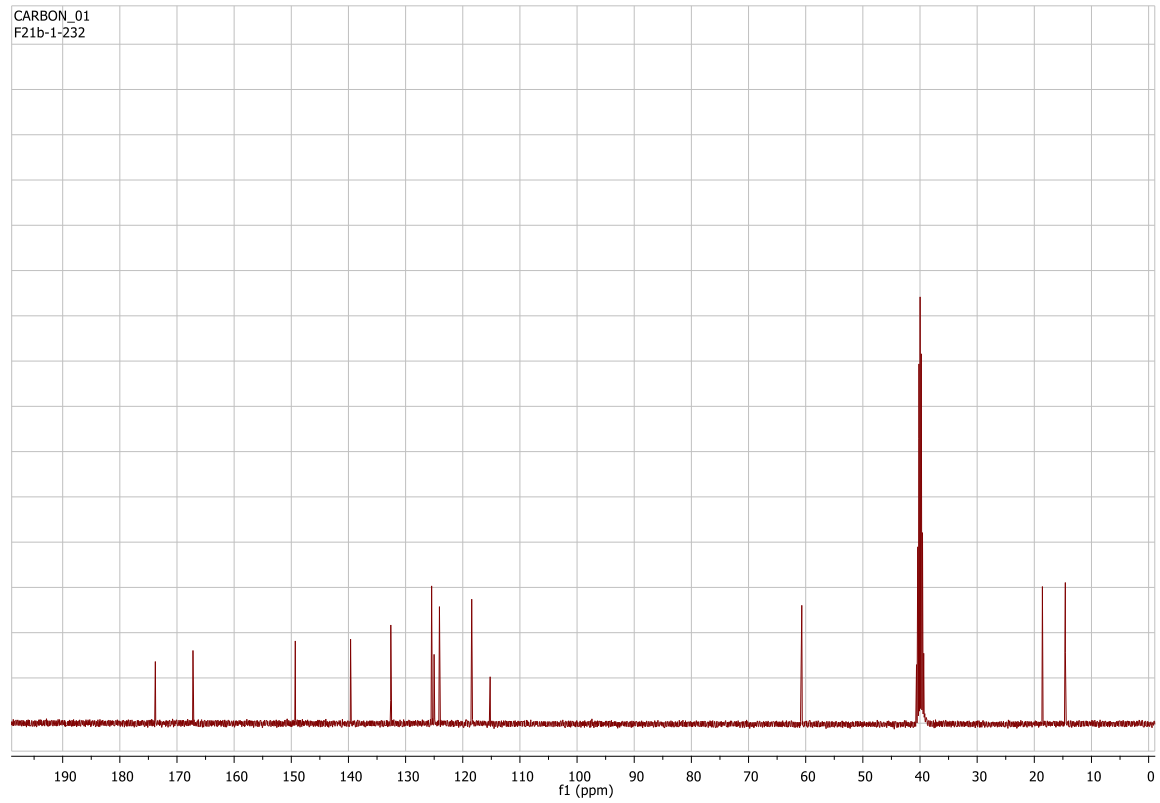

PROTON_01
86b-5o-231-cycle
3.04
O
N
18a
1.00
2.05
2.13
1.13
1.13
2.13
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

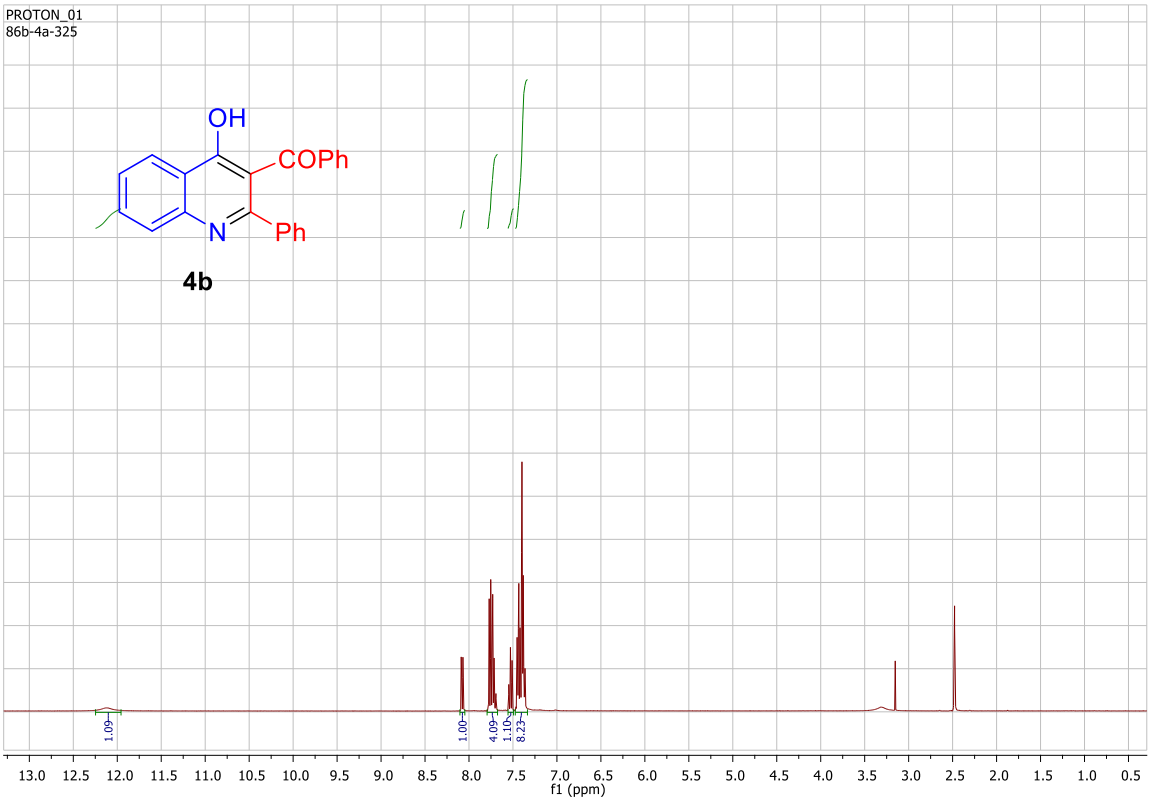

CARBON_01
86b-5o-231-cycle
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

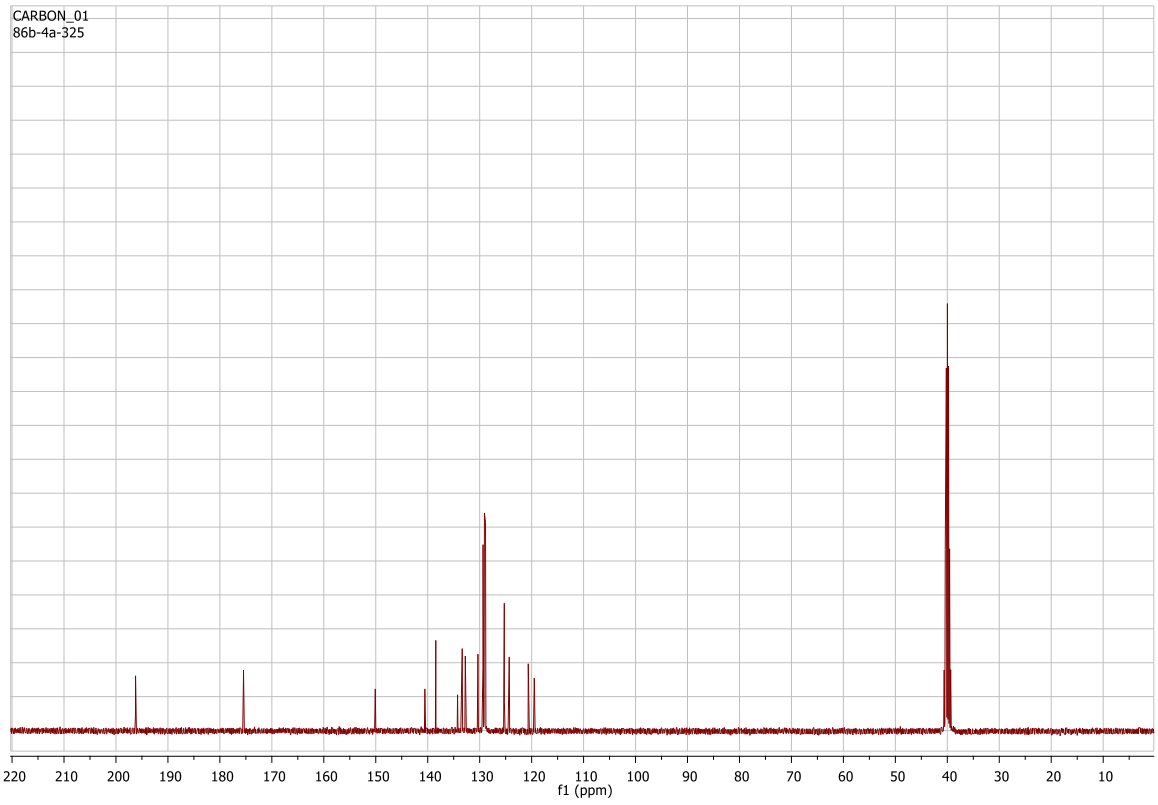

PROTON_01
86b-5r-247-cycle
O
O
N
18b
1.00
0.99
2.08
1.13
1.11
2.06
1.01
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

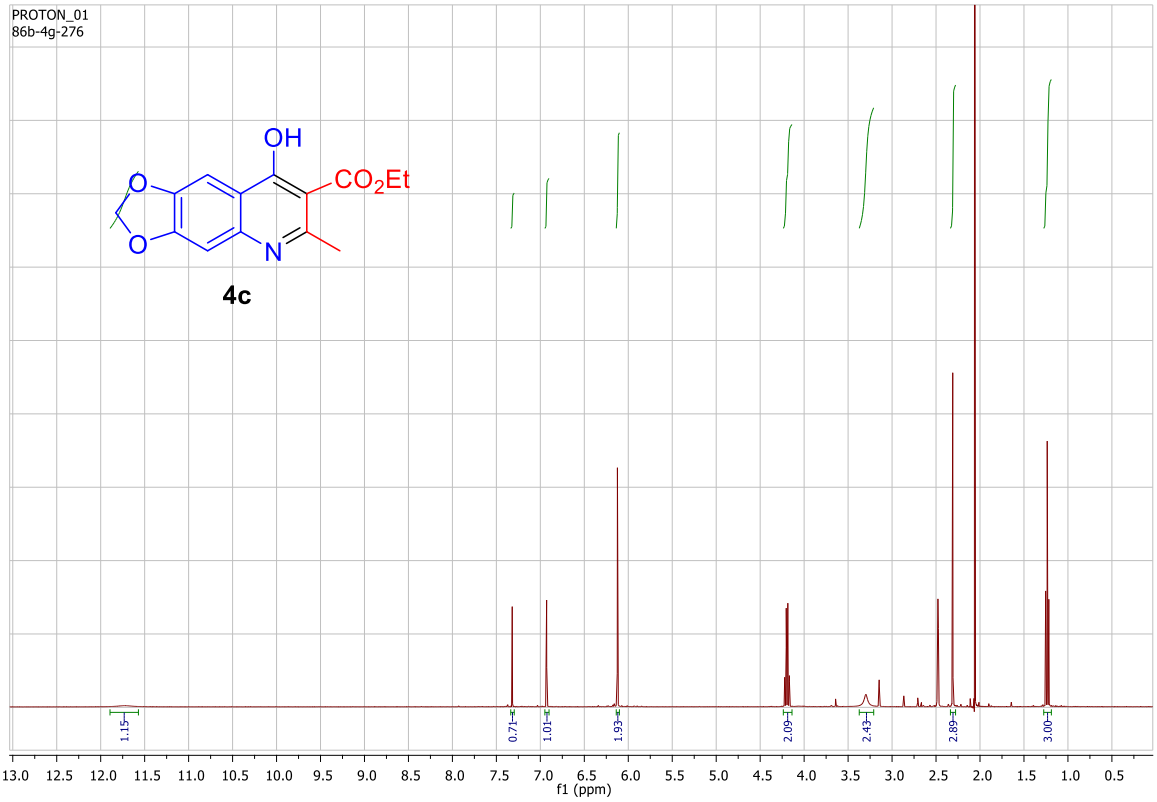
## 5. NMR Spectra of Products

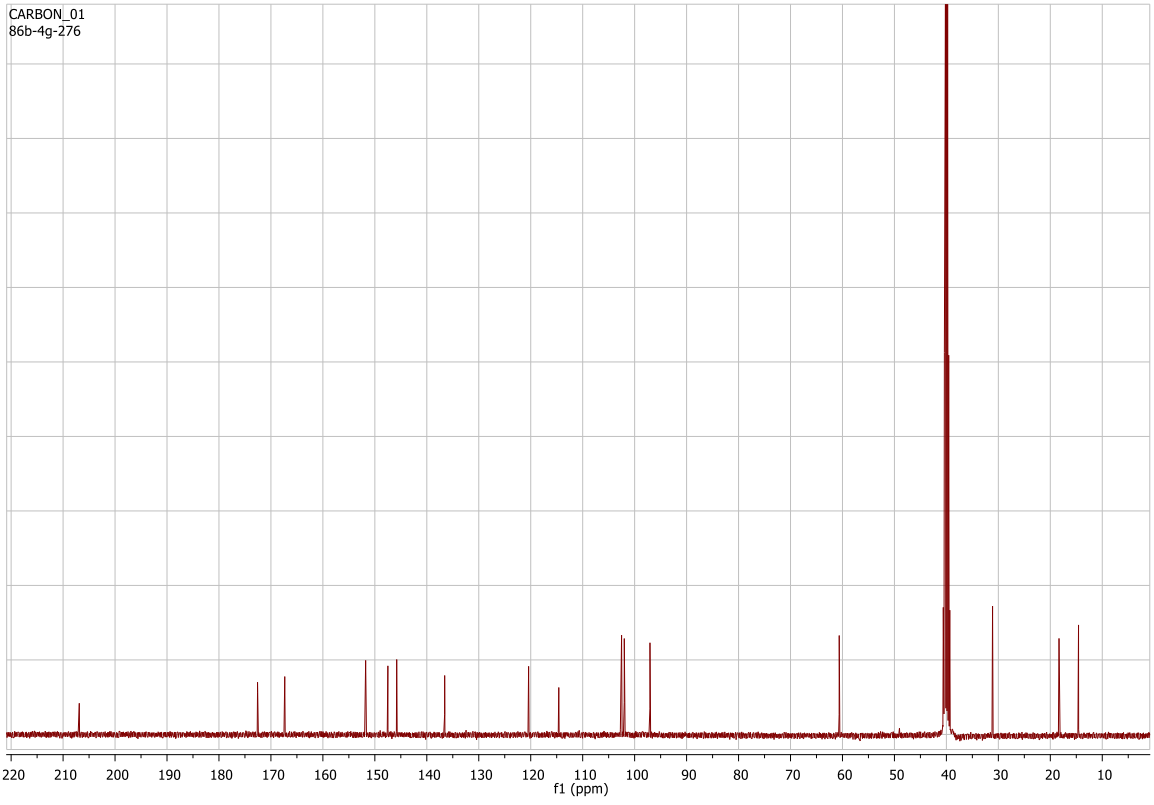


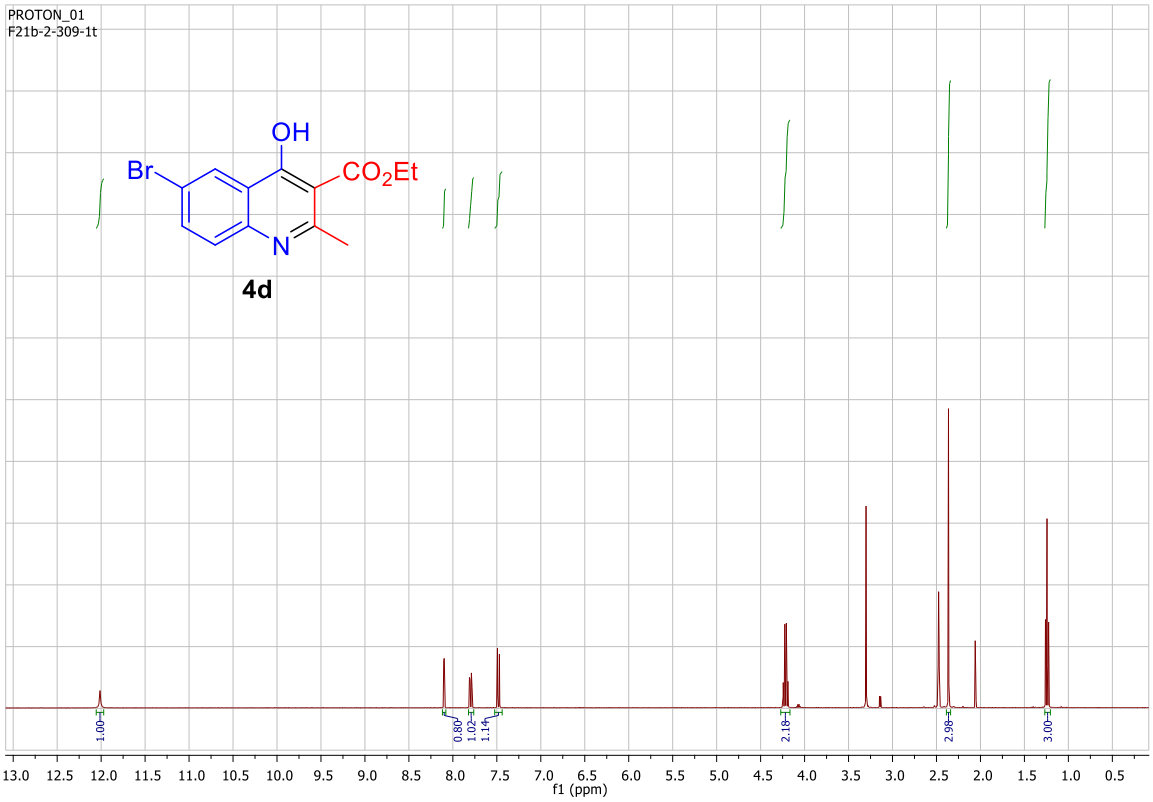



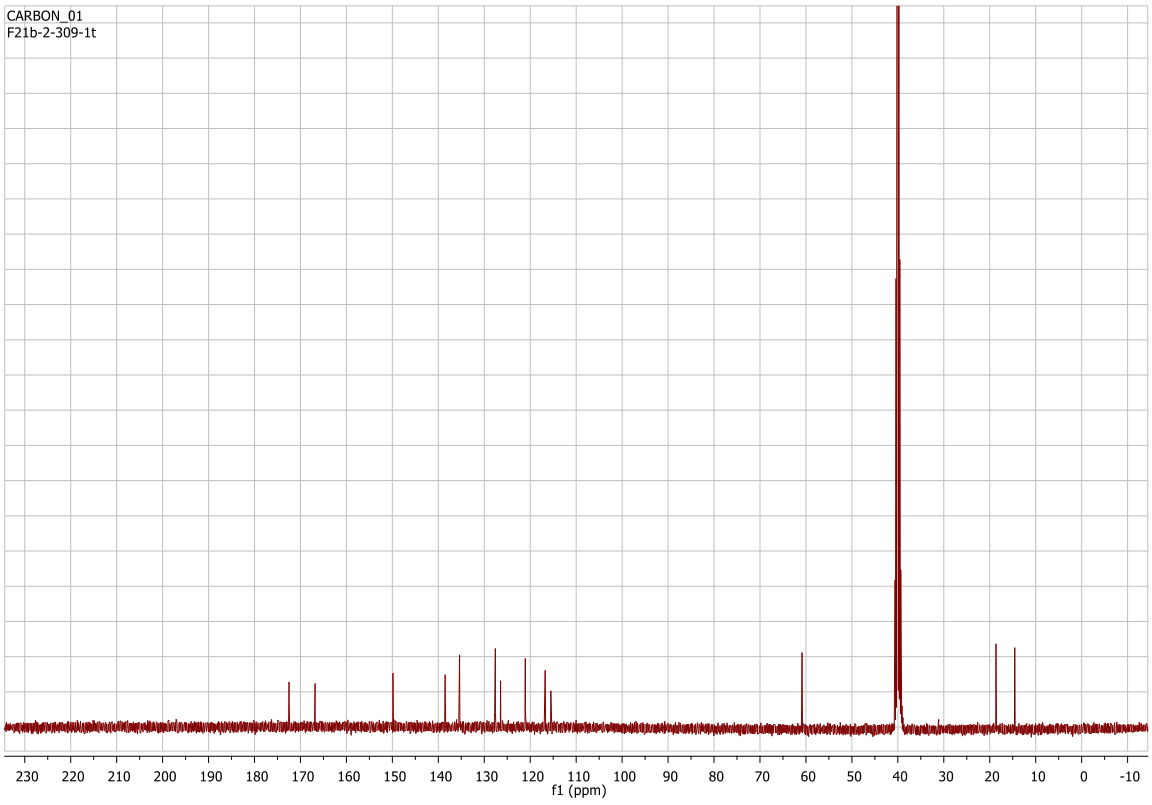

PROTON_01
86b-4a-325
OH
COPh
N
Ph
4b
1.09
1.00
4.09
1.10
8.23
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

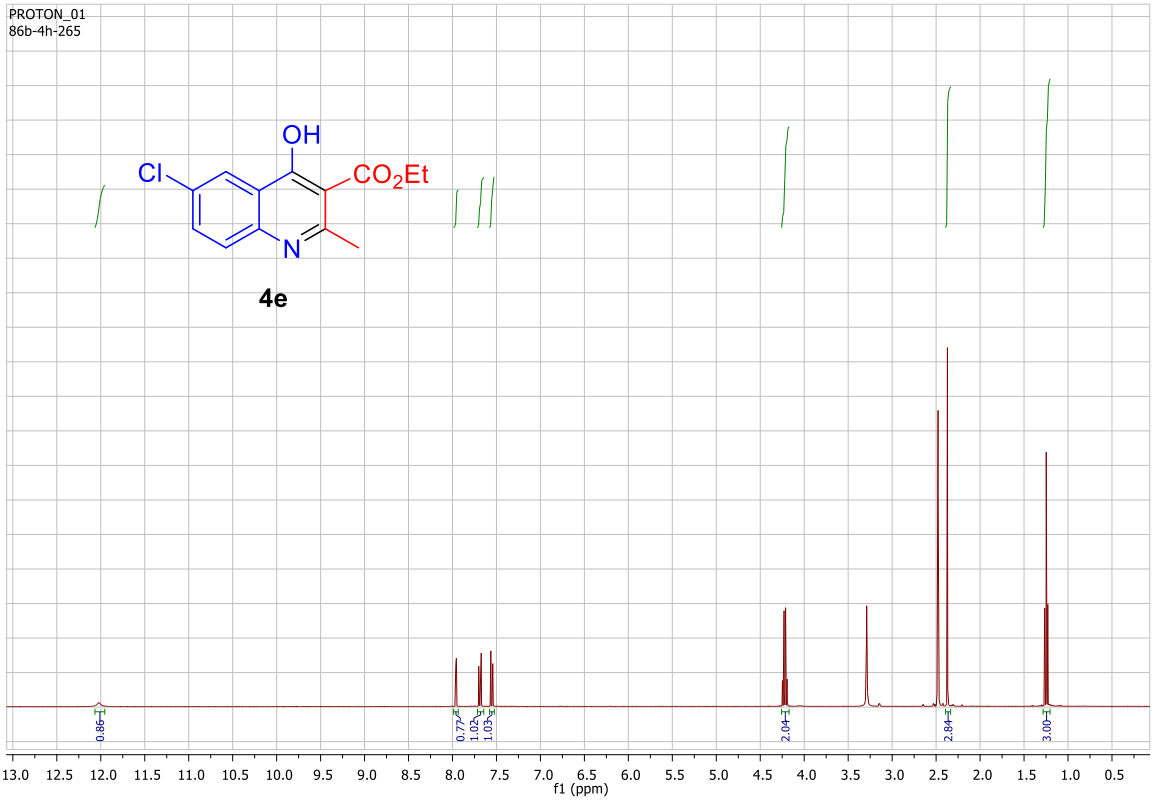

CARBON_01
86b-4a-325
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

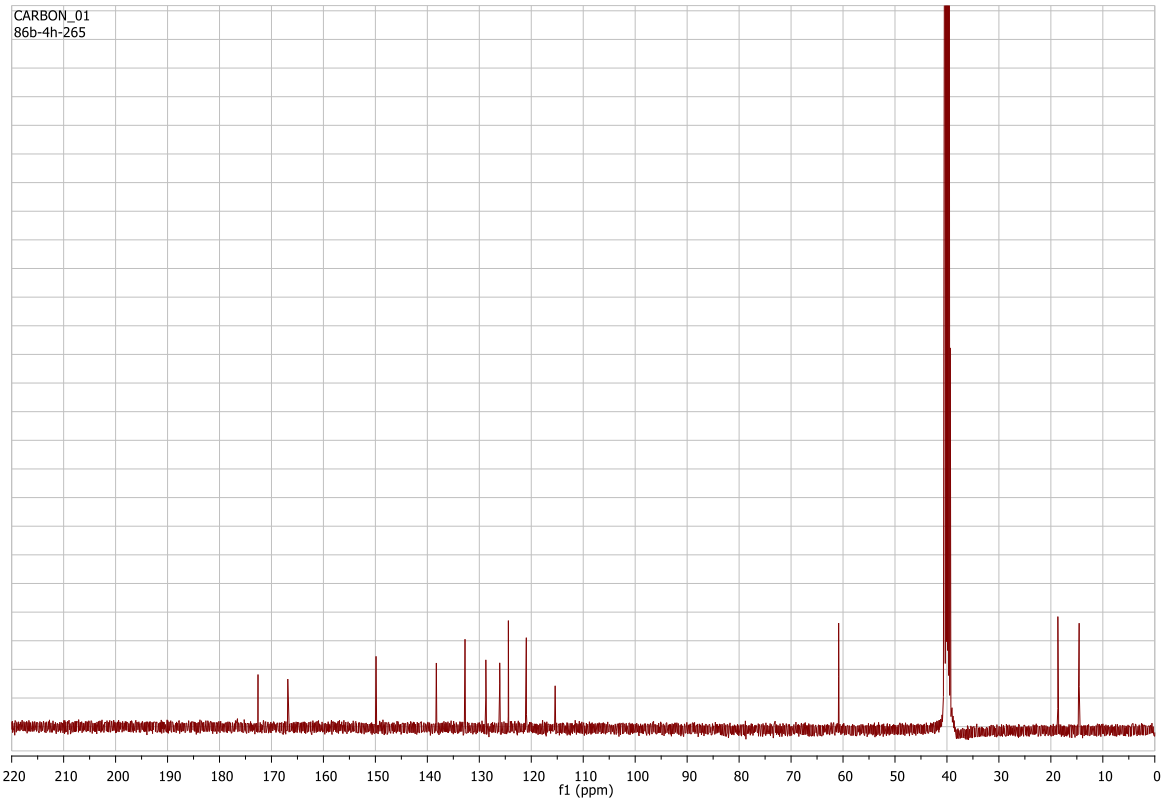

PROTON_01
86b-4g-276
OH
CO2Et
O
O
N
4c
1.15
0.71
1.01
1.93
2.09
2.43
2.89
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

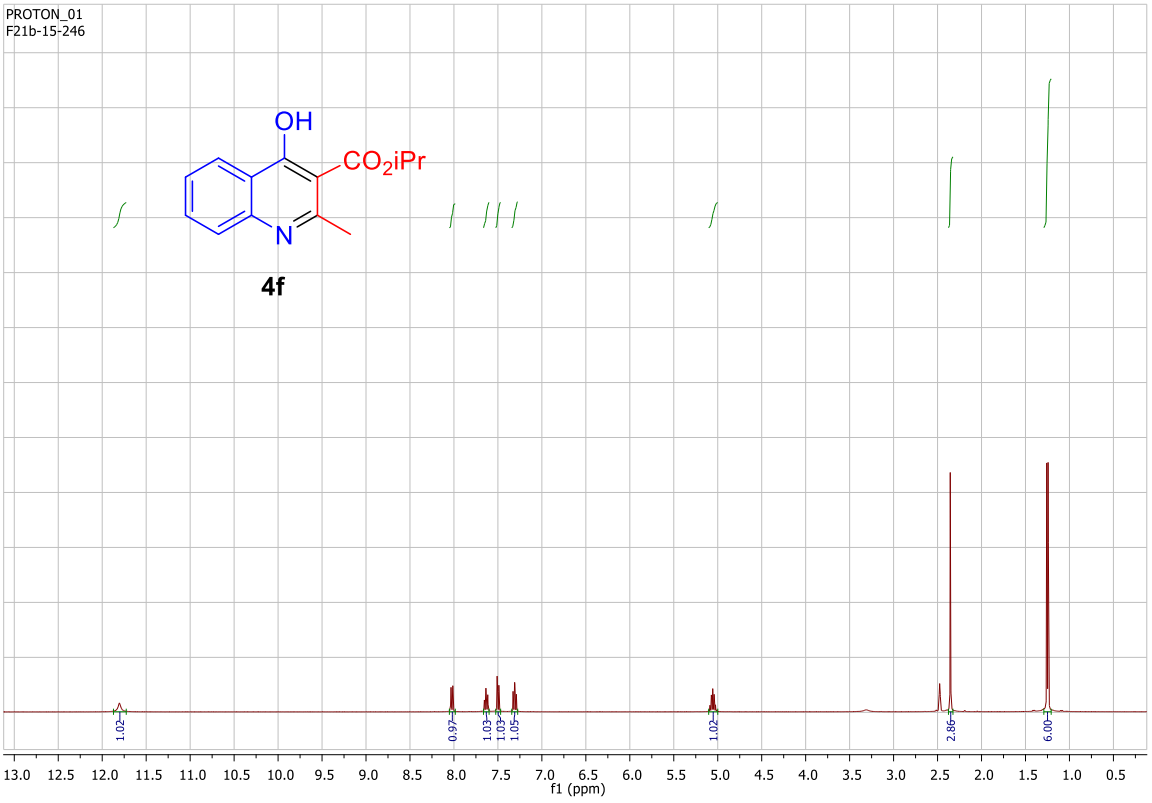

CARBON_01
86b-4g-276
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

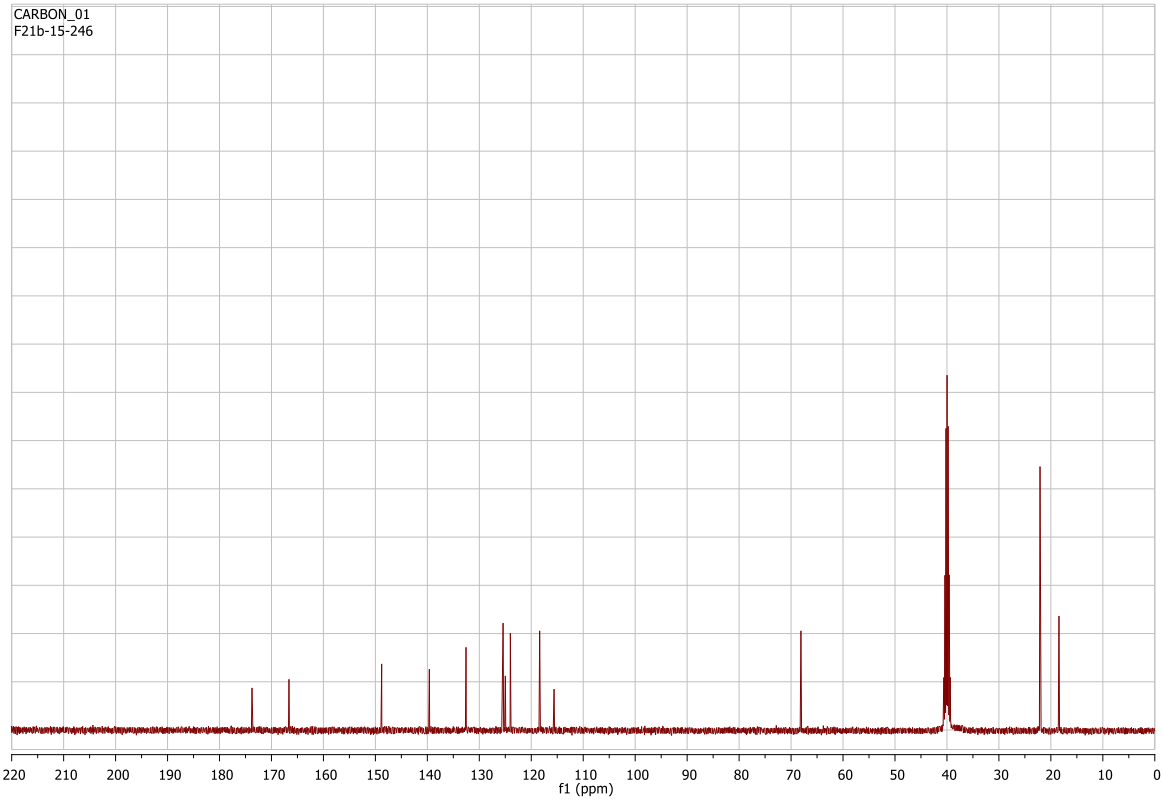

PROTON_01
F21b-2-309-1t
OH
Br
CO2Et
N
4d
1.00
0.80
1.02
1.14
2.18
2.98
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

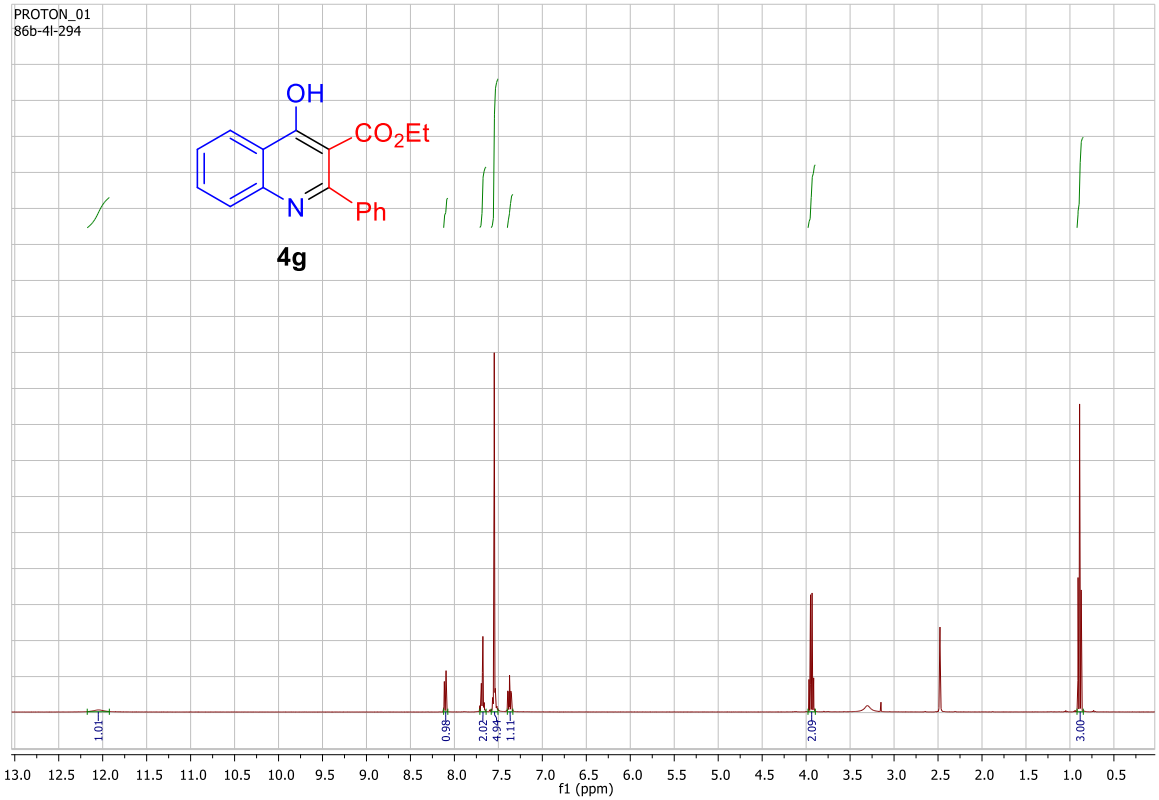

CARBON_01
F21b-2-309-1t
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

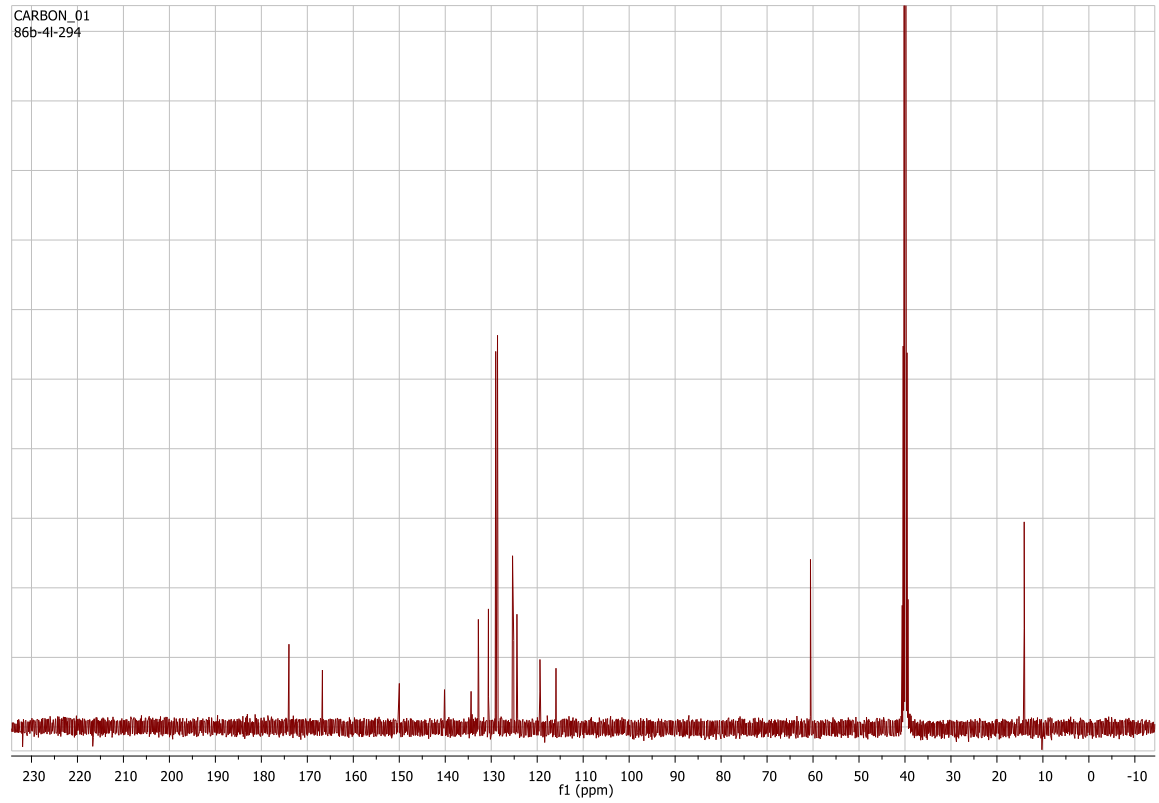

PROTON_01
86b-4h-265
OH
Cl
CO2Et
N
4e
0.86
0.77
1.02
1.05
2.04
2.84
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

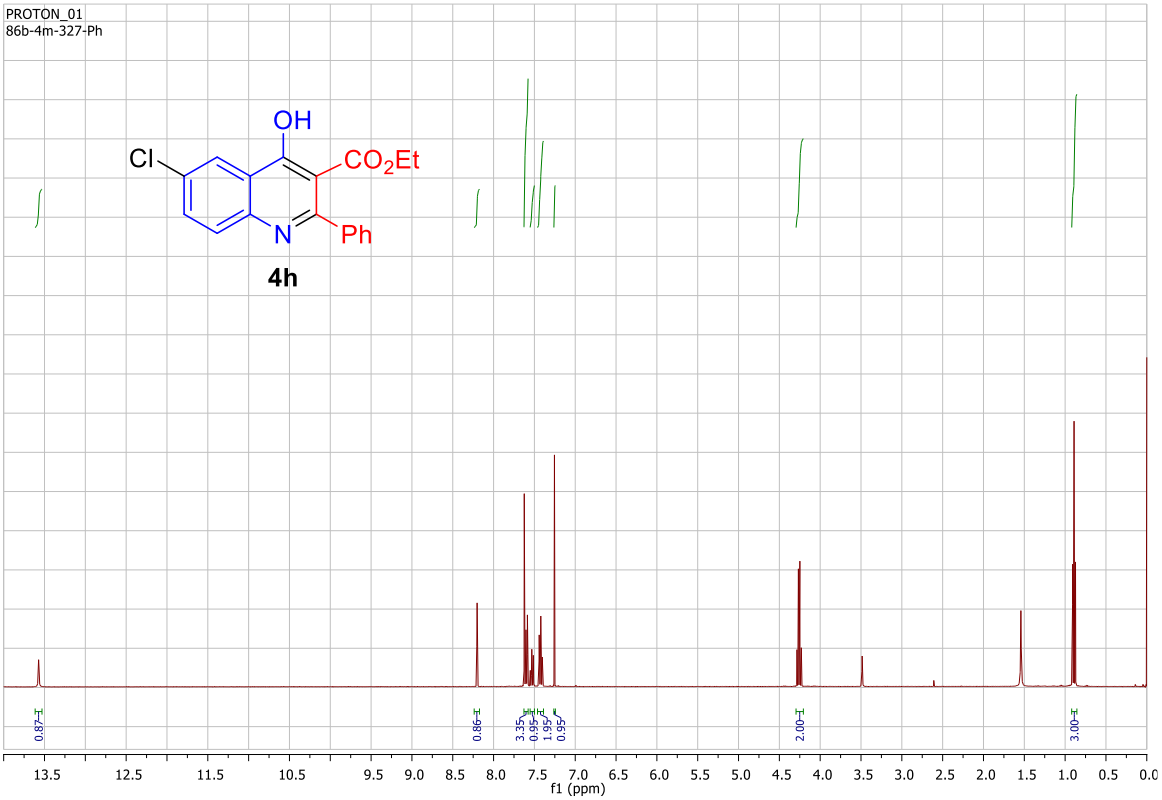

CARBON_01
86b-4h-265
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

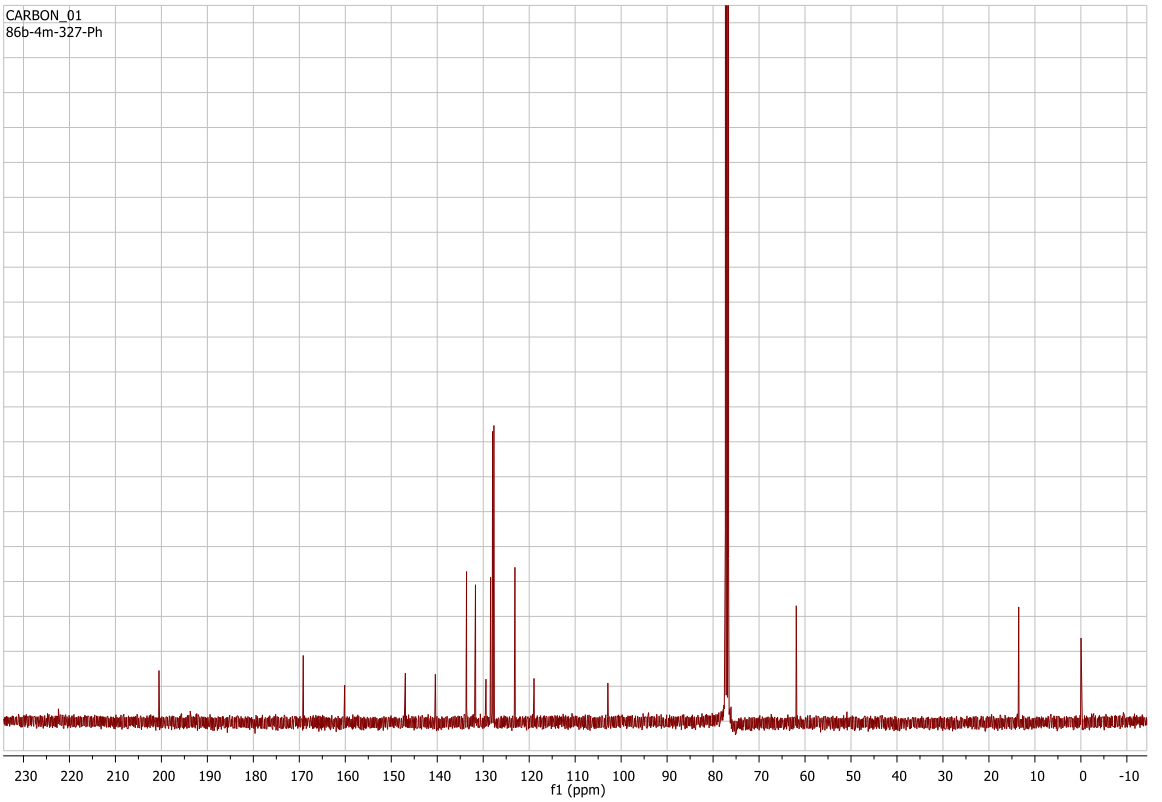

PROTON_01
F21b-15-246
OH
CO2iPr
N
4f
1.02
0.97
1.03
1.03
1.05
1.02
2.86
6.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

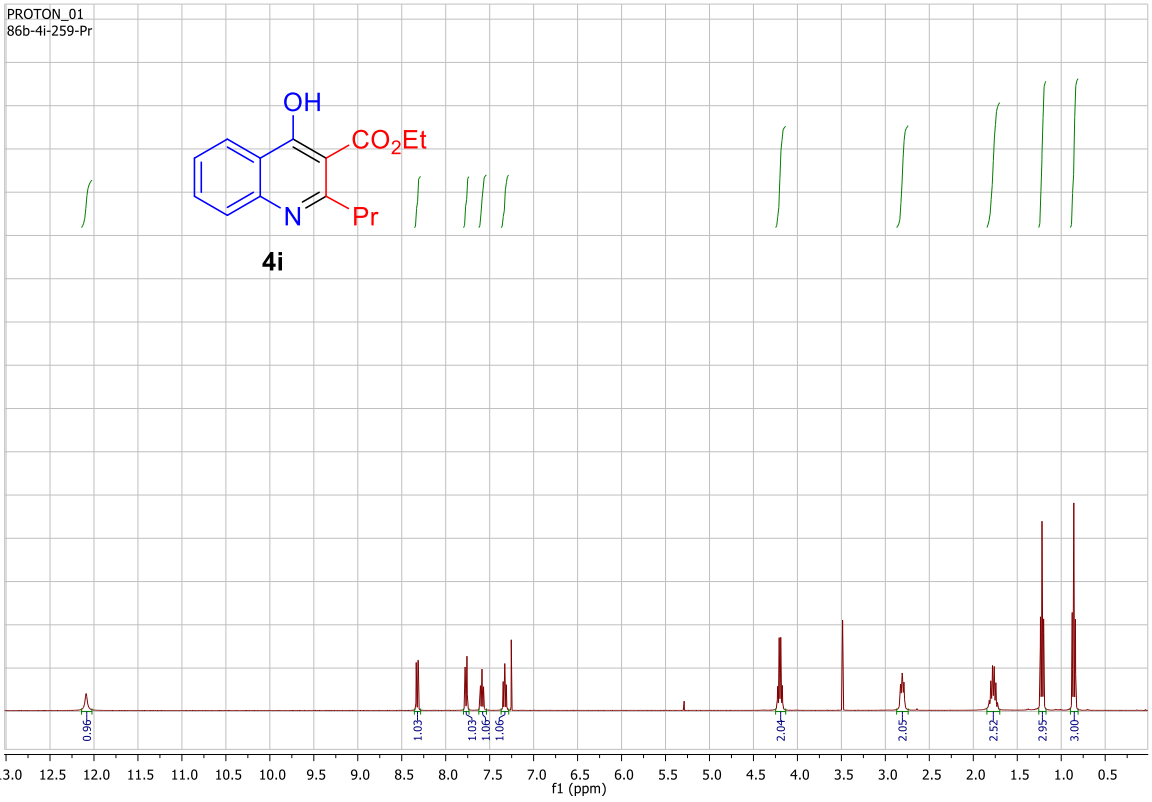

CARBON_01
F21b-15-246
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

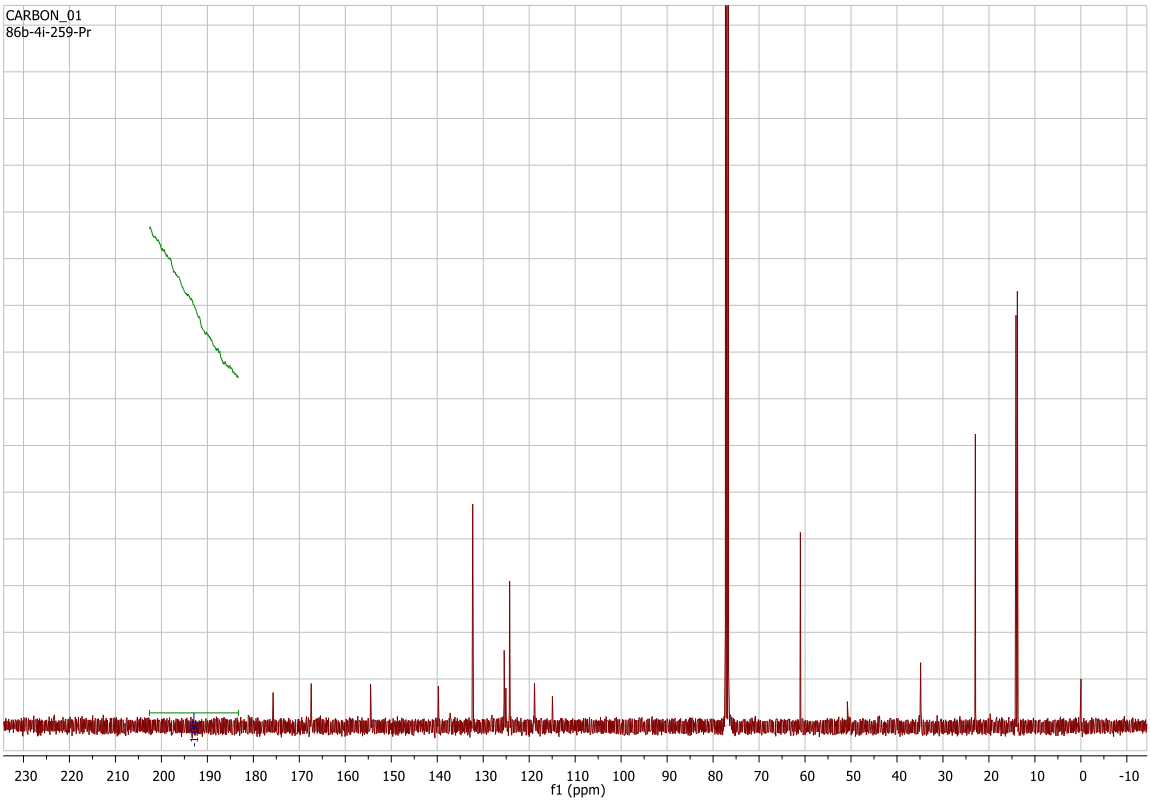

PROTON_01
86b-4l-294
OH
CO2Et
N
Ph
4g
1.01
0.98
2.02
4.94
1.11
2.09
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

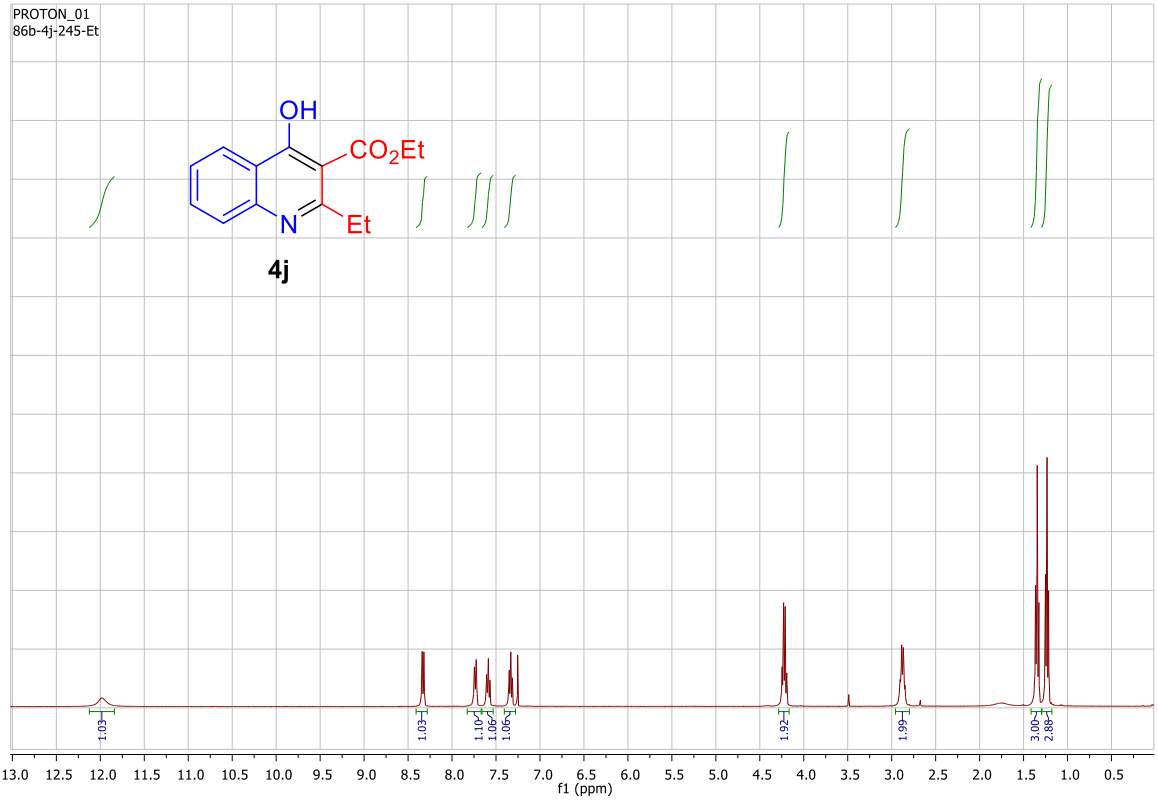

CARBON_01
86b-4l-294
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

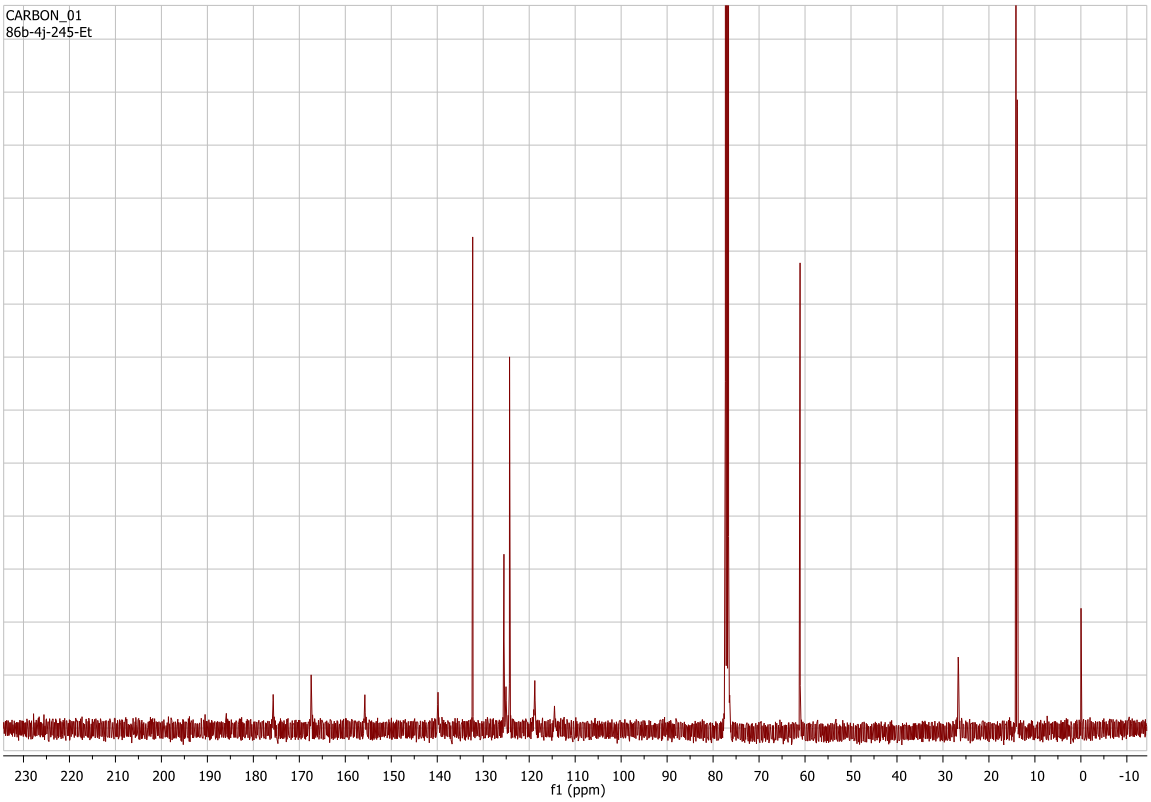

PROTON_01
86b-4m-327-Ph
OH
Cl
CO2Et
N
Ph
4h
0.87
0.86
3.35
0.95
1.95
0.95
2.00
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

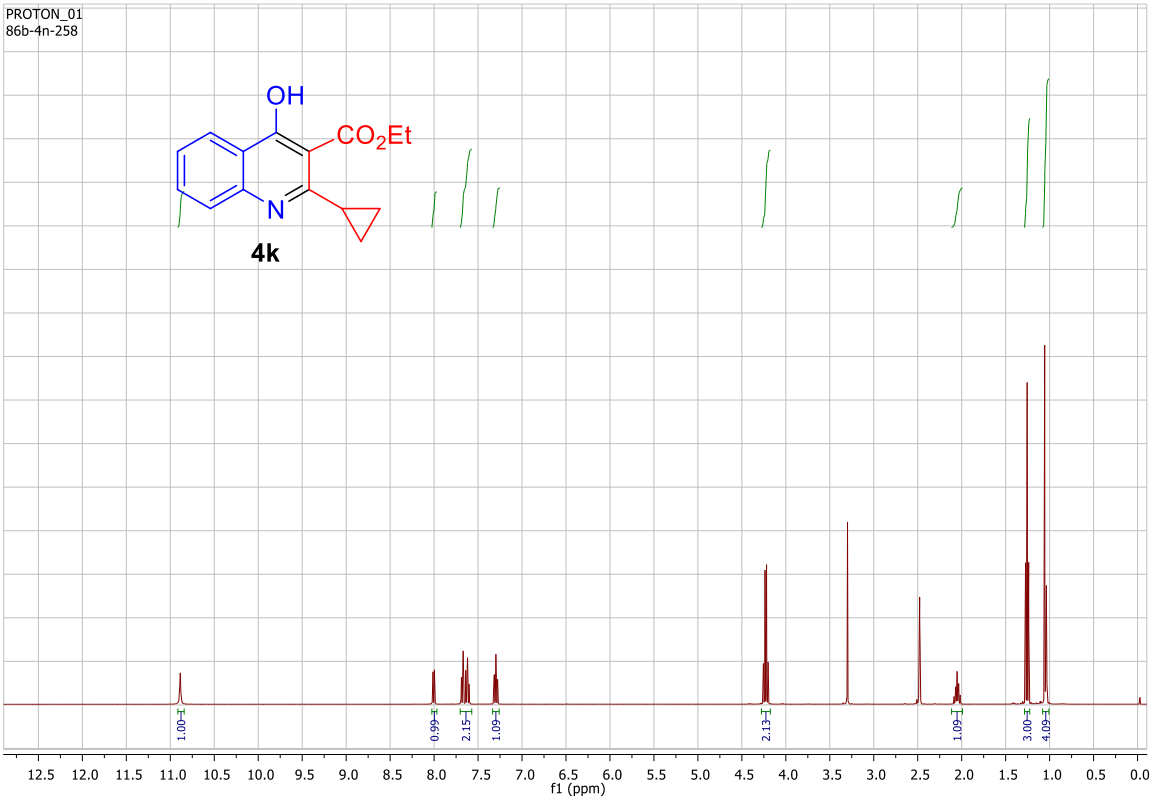

CARBON_01
86b-4m-327-Ph
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

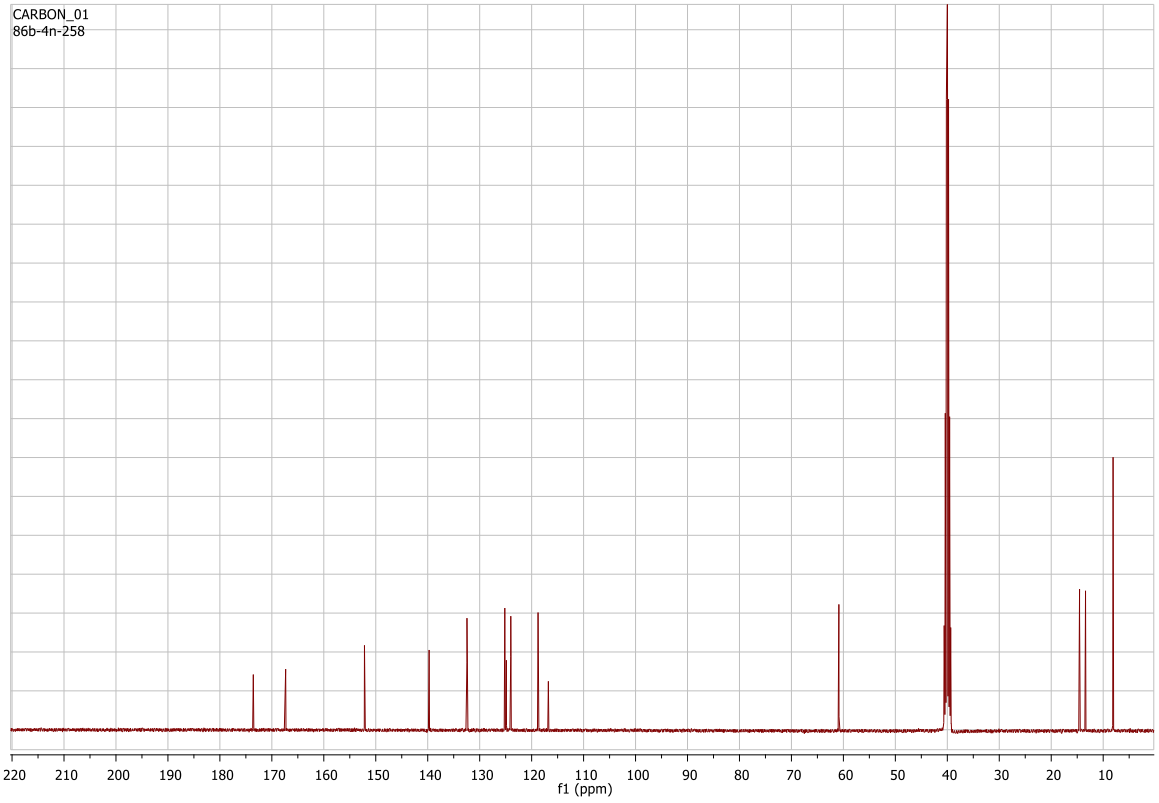

PROTON_01
86b-4i-259-Pr
OH
CO2Et
N
Pr
4i
0.96
1.03
1.03
1.06
1.06
2.04
2.05
2.52
2.95
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

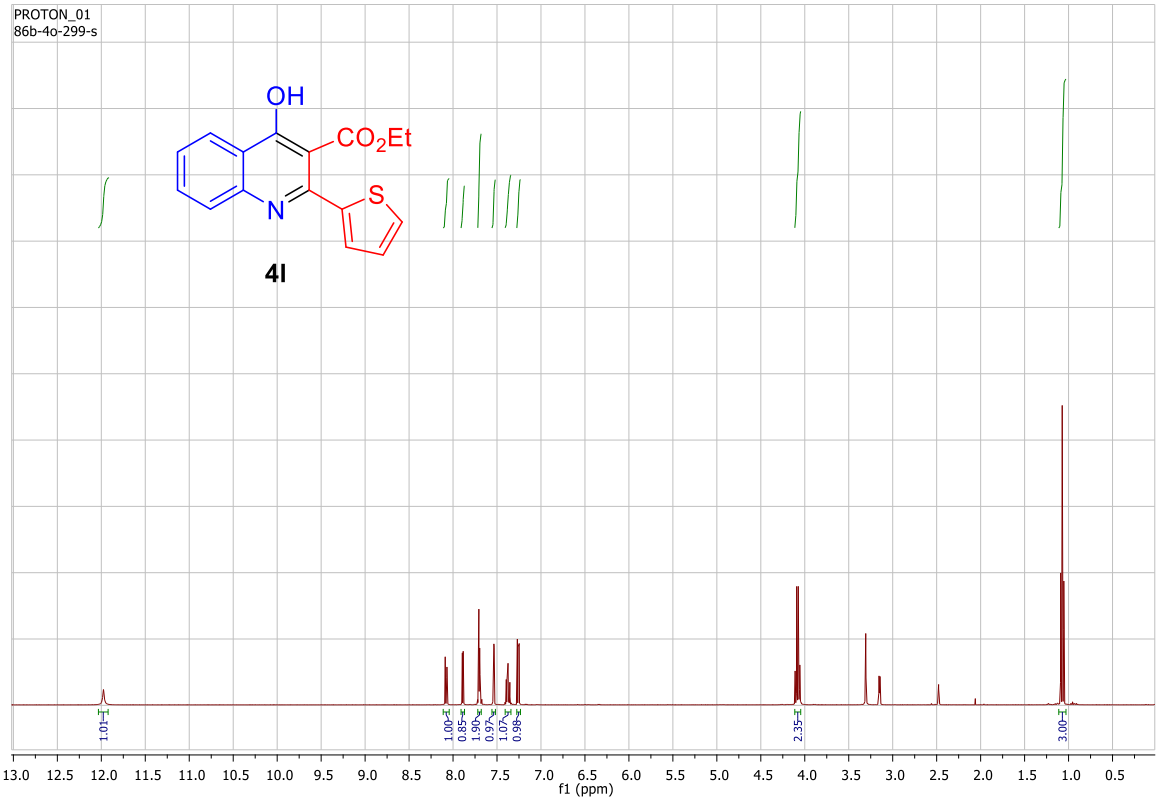

CARBON_01
86b-4i-259-Pr
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

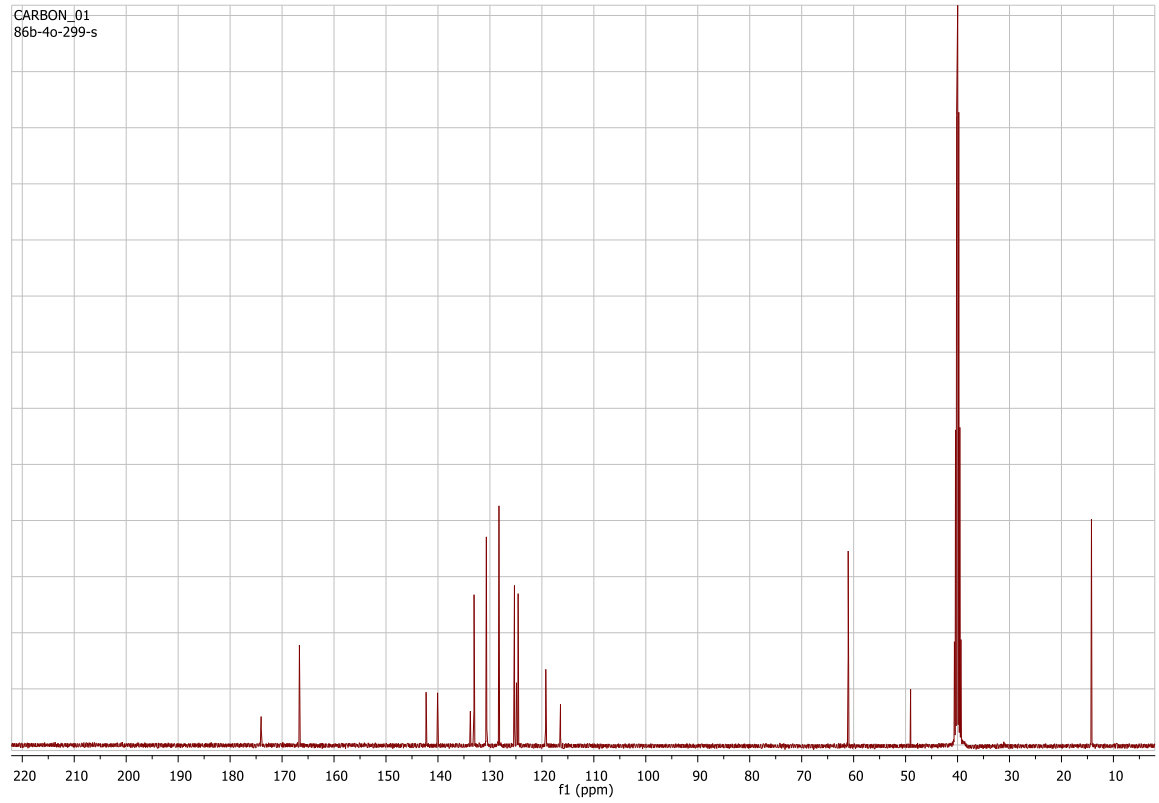

PROTON_01
86b-4j-245-Et
OH
CO2Et
N
Et
4j
1.03
1.03
1.10
1.06
1.06
1.92
1.99
3.00
2.88
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

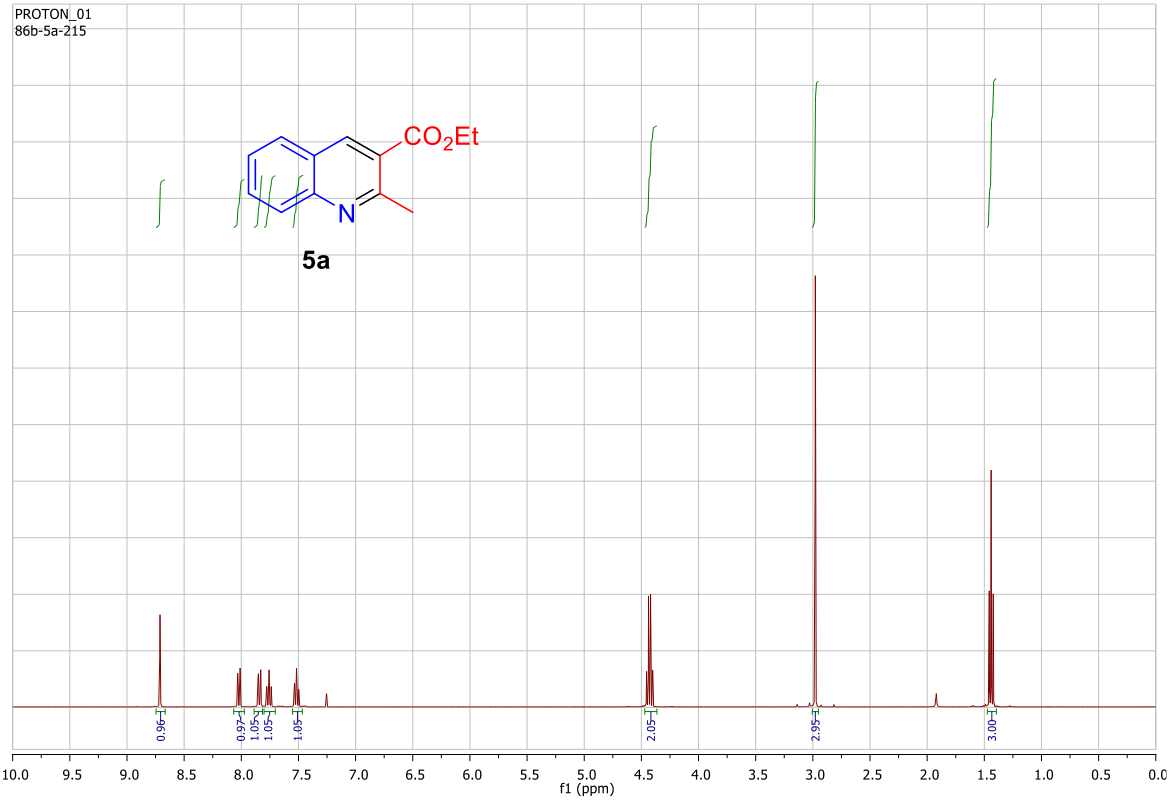

CARBON_01
86b-4j-245-Et
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

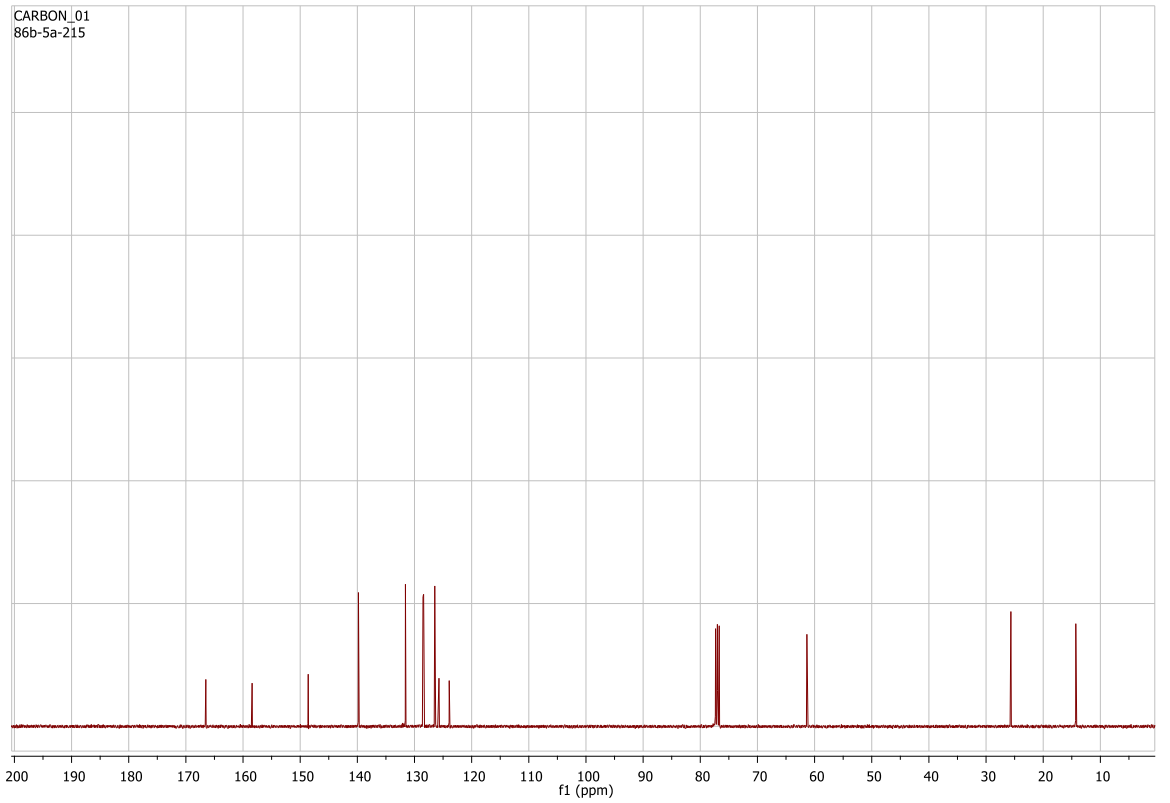

PROTON_01
86b-4n-258
OH
CO2Et
N
4k
1.00
0.99
2.15
1.09
2.13
1.09
3.00
4.09
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

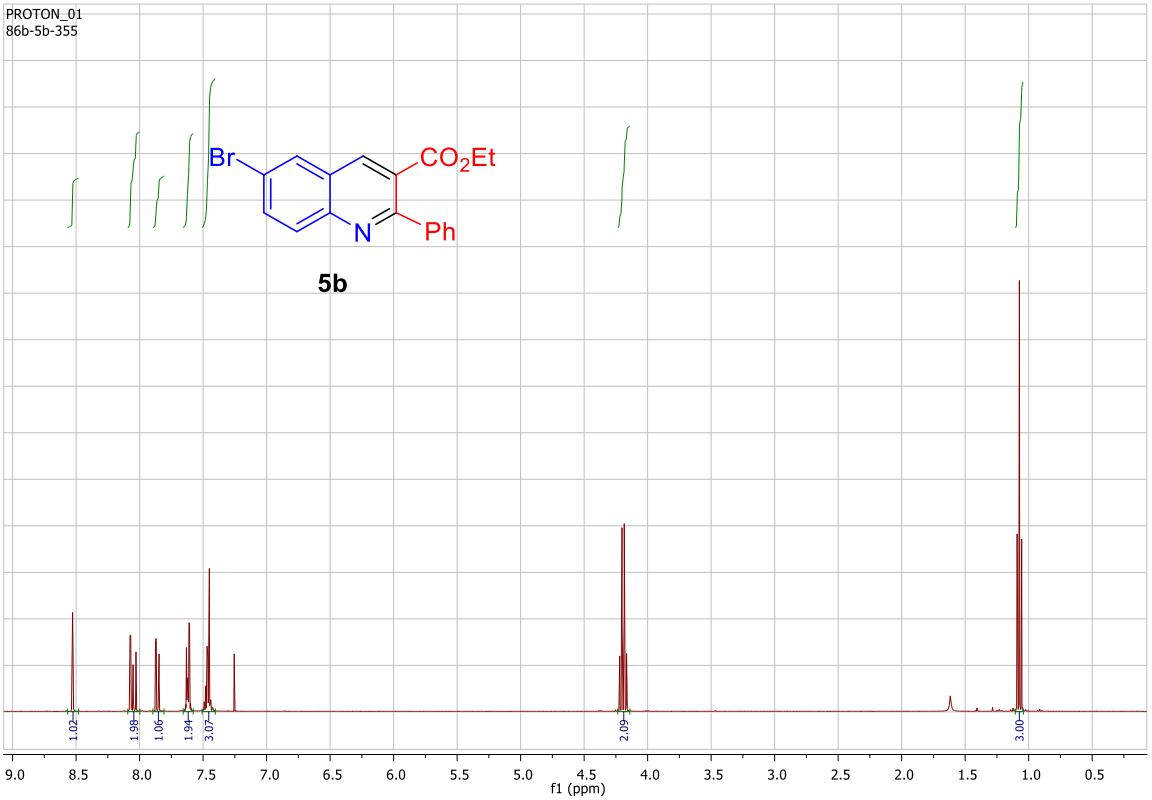

CARBON_01
86b-4n-258
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

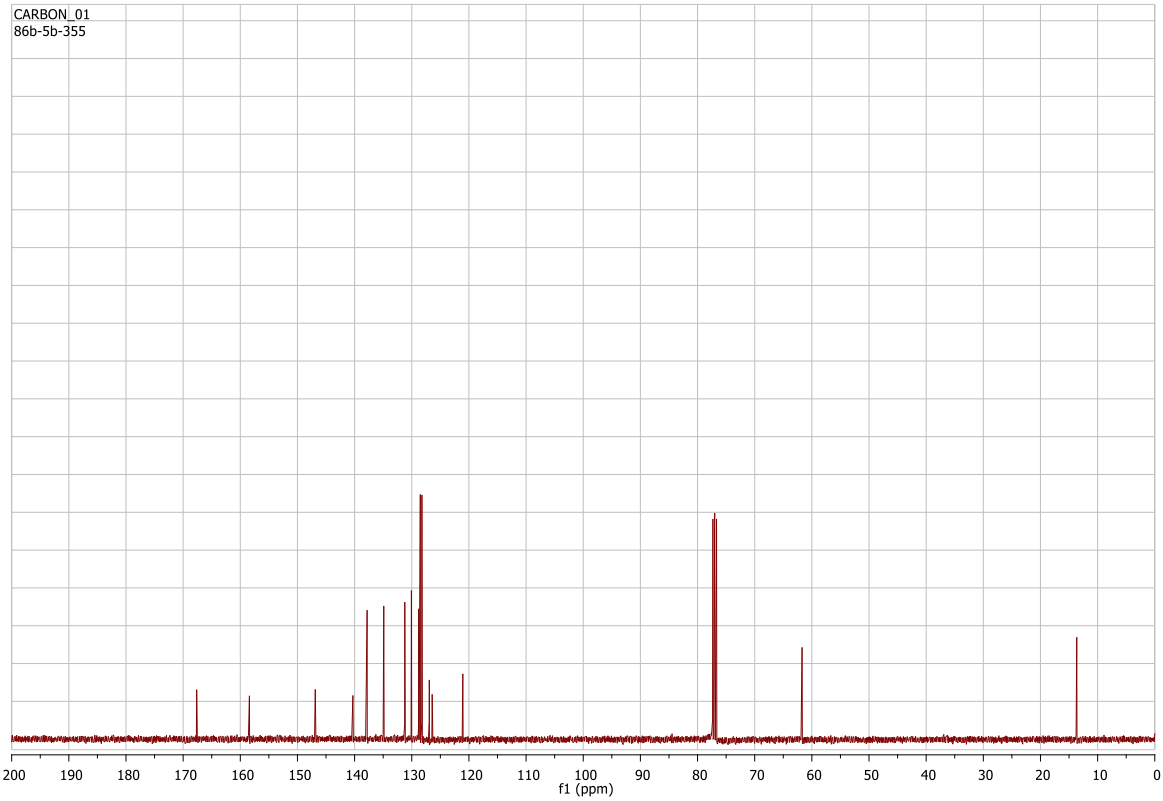

PROTON_01
86b-4o-299-s
OH
CO2Et
S
N
4l
1.01
1.00
0.85
1.90
0.97
1.07
0.98
2.35
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

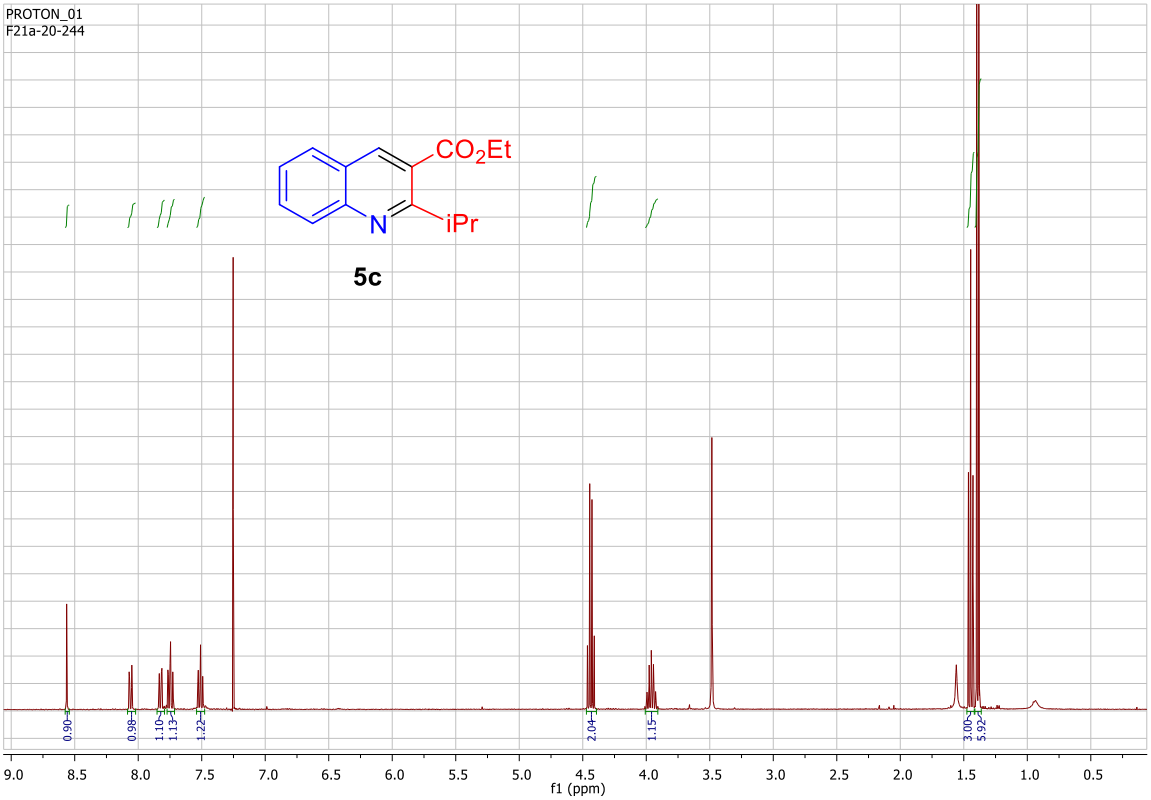

CARBON_01
86b-4o-299-s
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

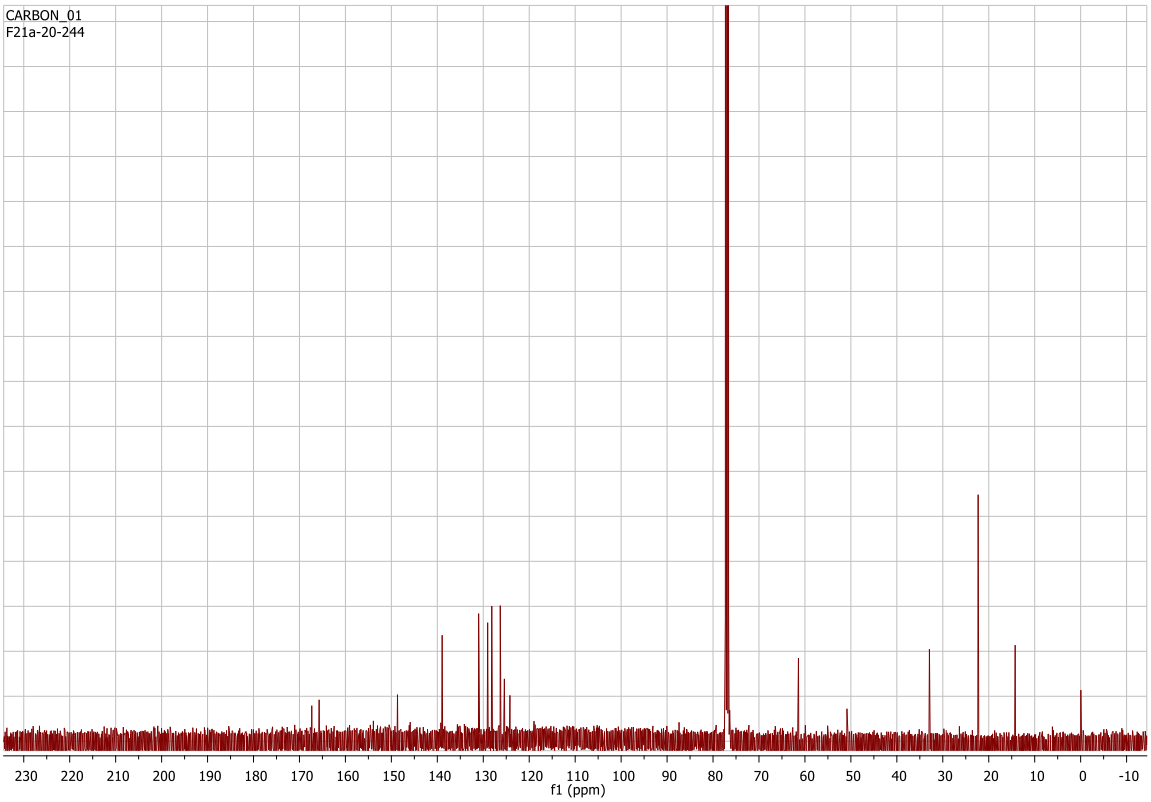

PROTON_01
86b-5a-215
CO2Et
N
5a
0.96
0.97
1.05
1.05
1.05
2.05
2.95
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

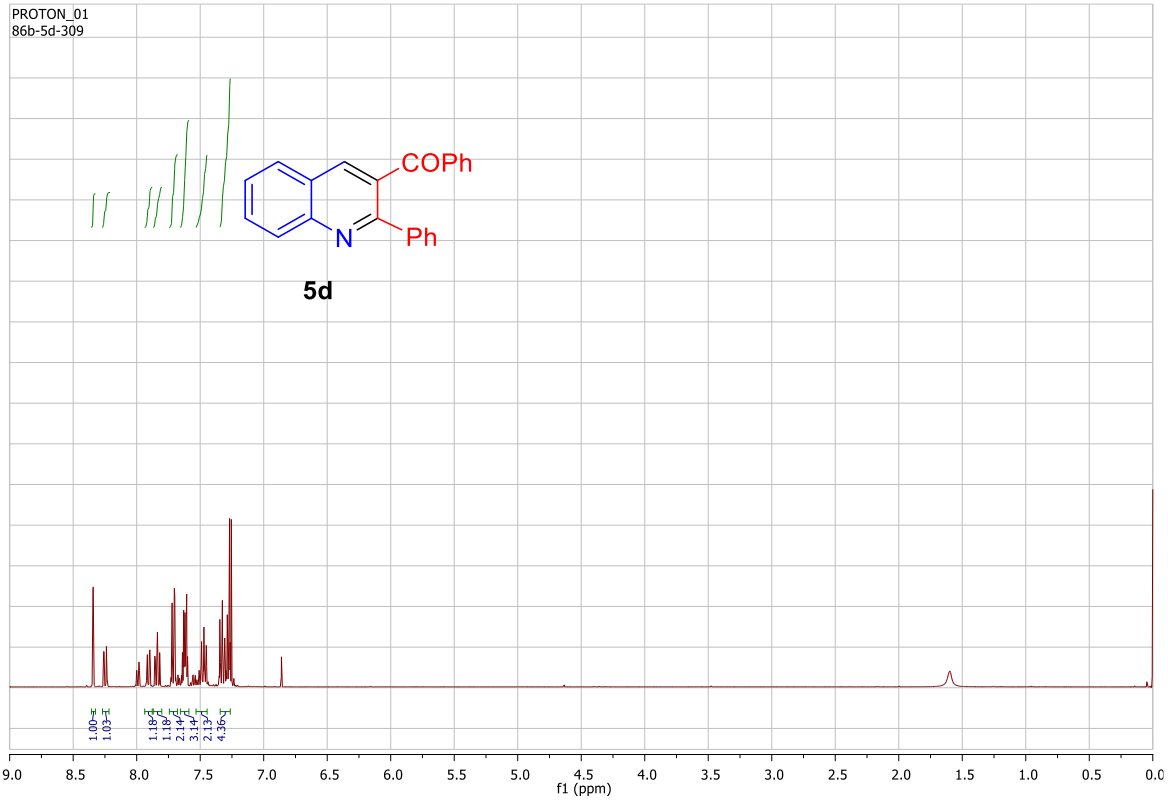

CARBON_01
86b-5a-215
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

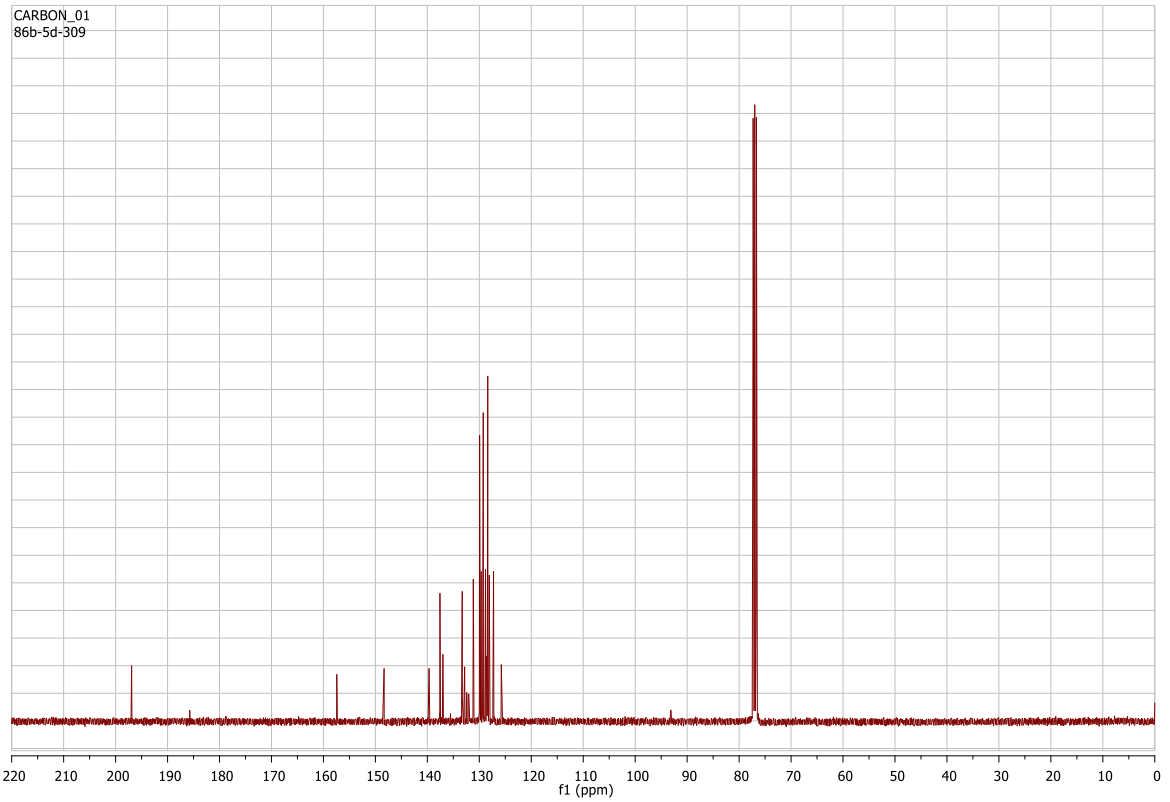

PROTON_01
86b-5b-355
Br
CO2Et
N
Ph
5b
1.02
1.98
1.06
1.94
3.07
2.09
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

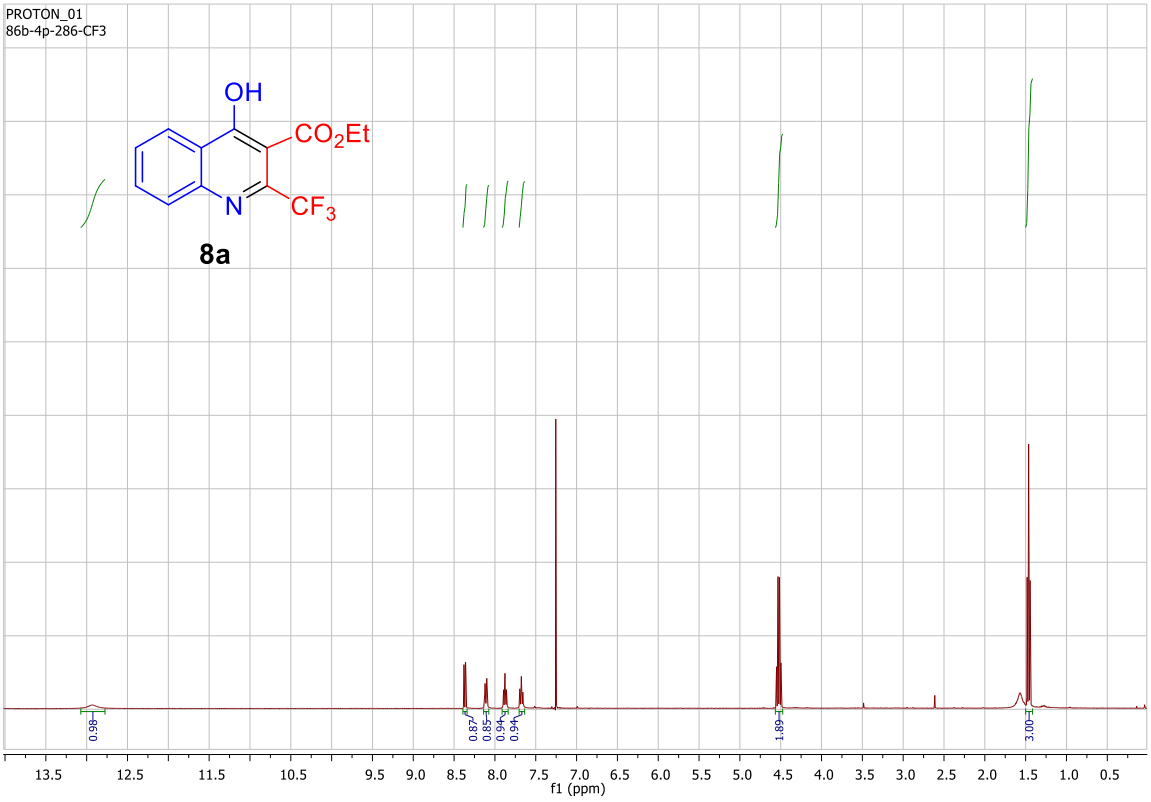

CARBON_01
86b-5b-355
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

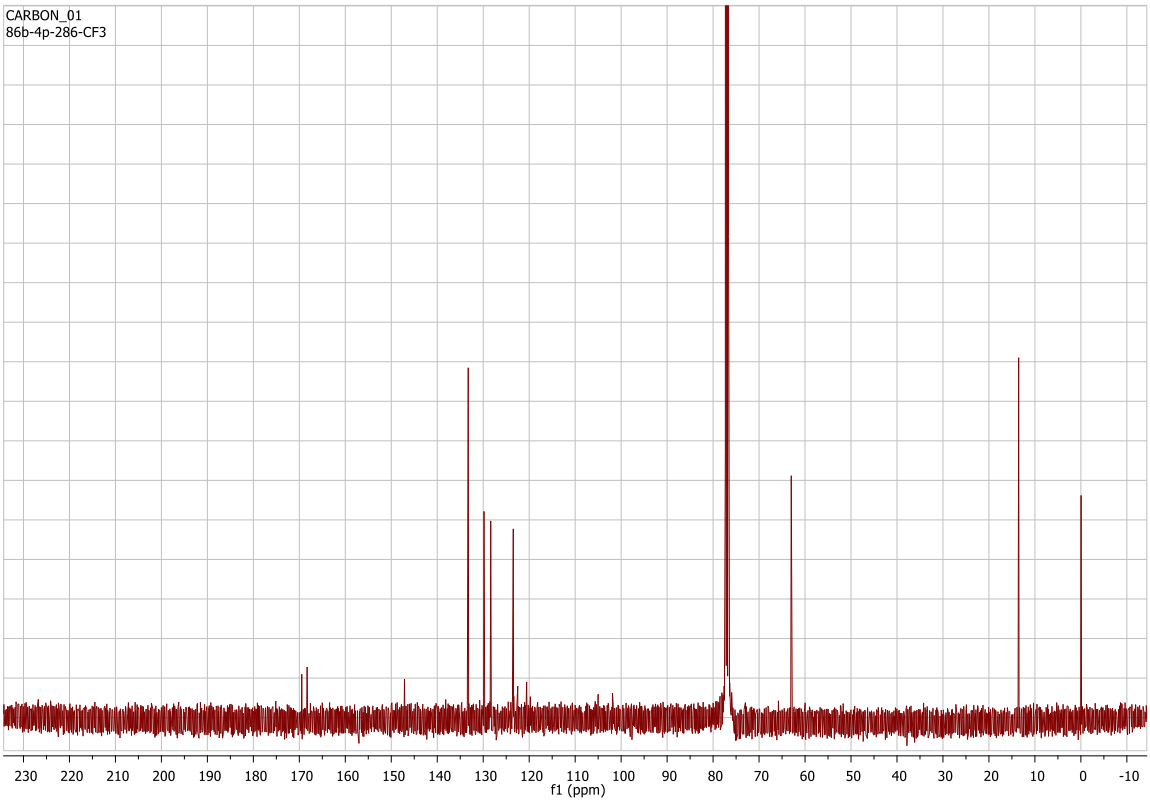

PROTON_01
F21a-20-244
CO2Et
N
iPr
5c
0.90
0.98
1.10
1.19
1.22
2.04
1.15
3.00
5.92
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

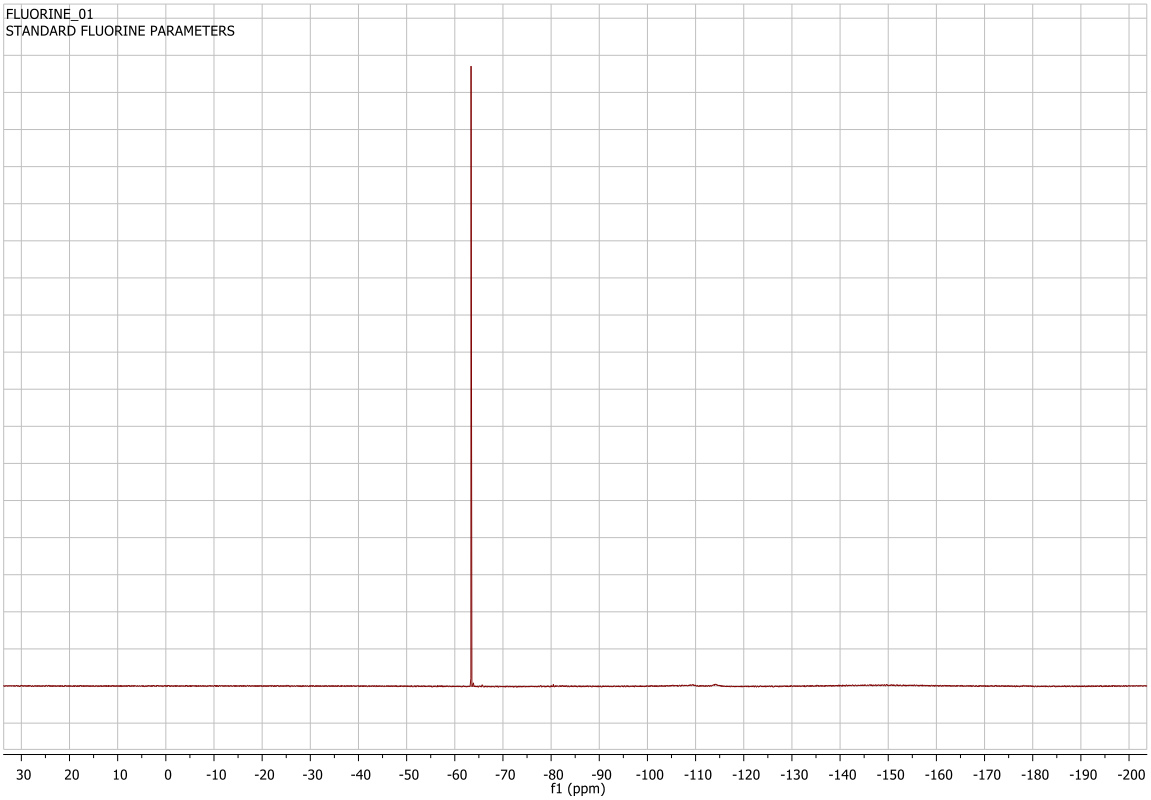

CARBON_01
F21a-20-244
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

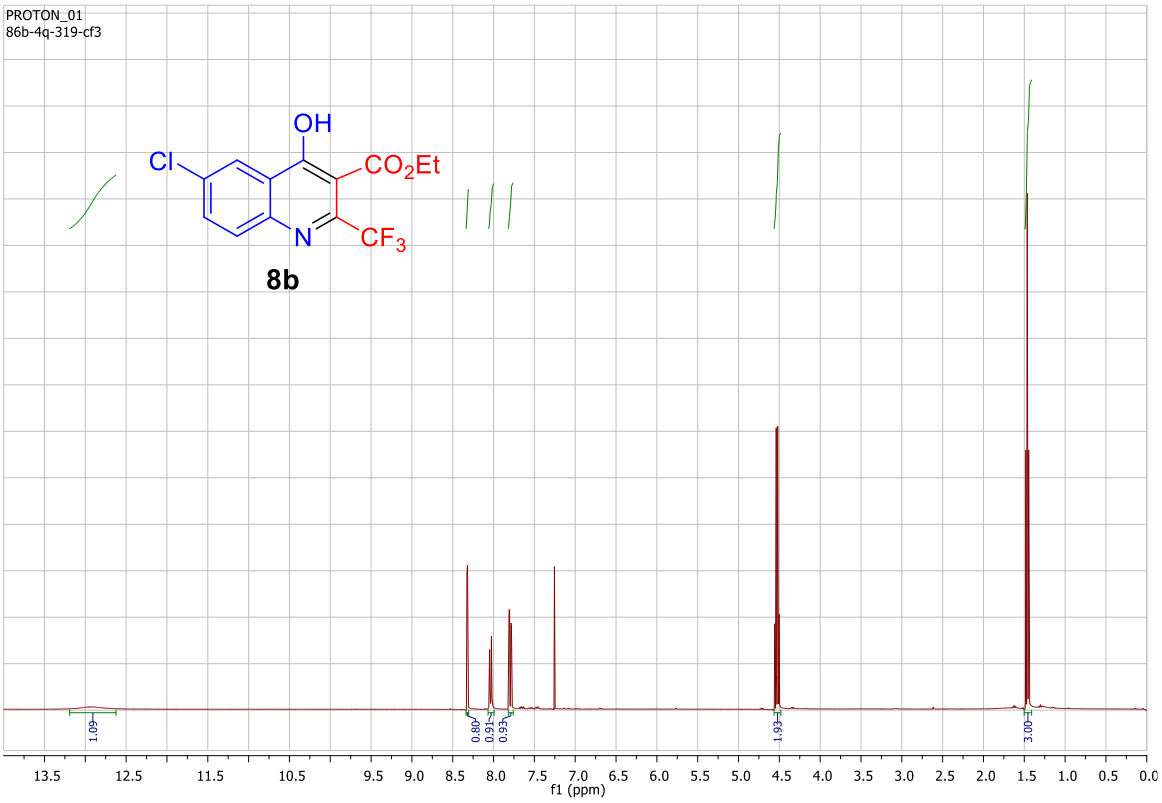

PROTON_01
86b-5d-309
COPh
Ph
N
5d
1.00
1.03
1.18
1.18
2.14
3.14
2.13
4.36
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

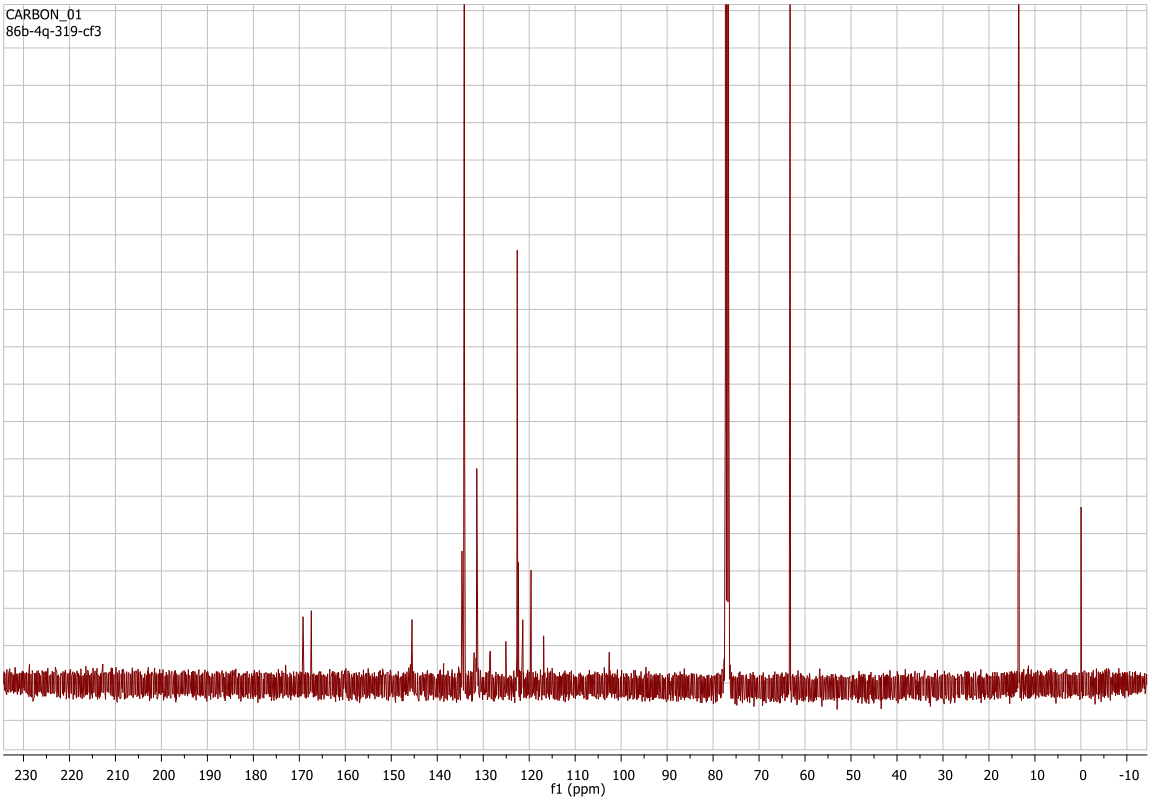

CARBON_01
86b-5d-309
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

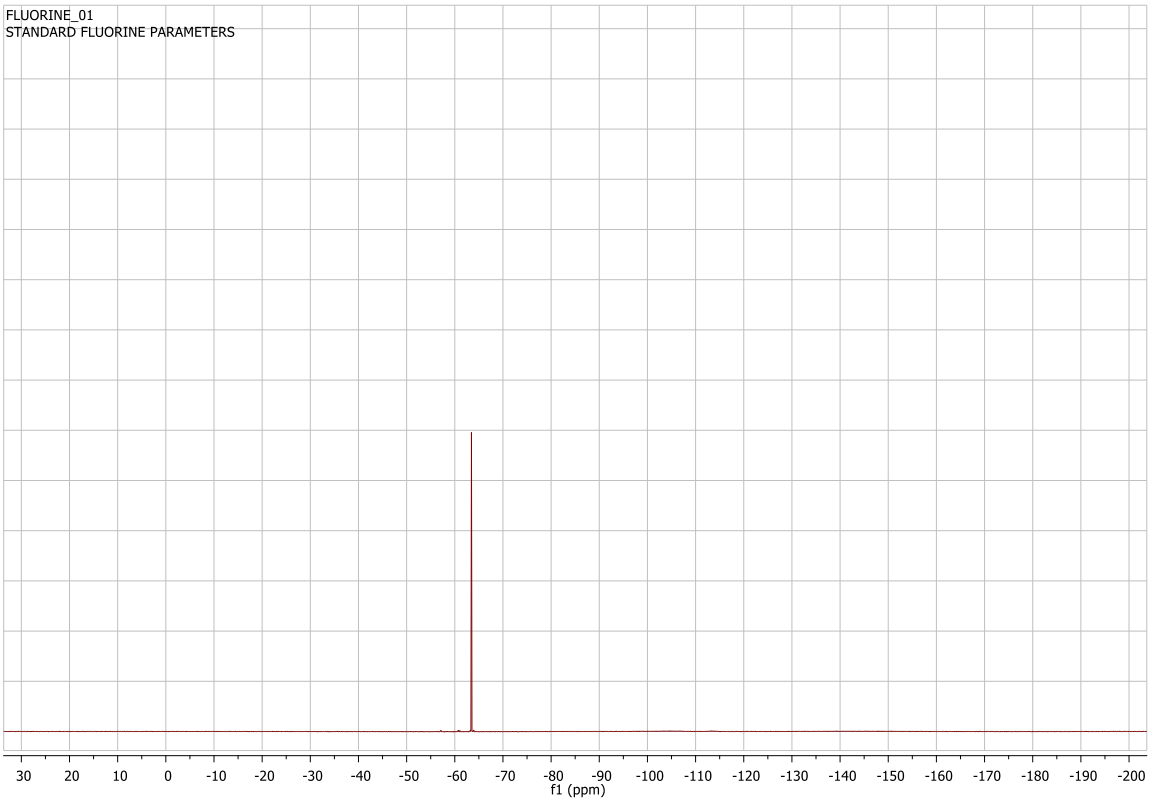

PROTON_01
86b-4p-286-CF3
OH
CO2Et
N
CF3
8a
0.98
0.87
0.85
0.94
0.94
1.89
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

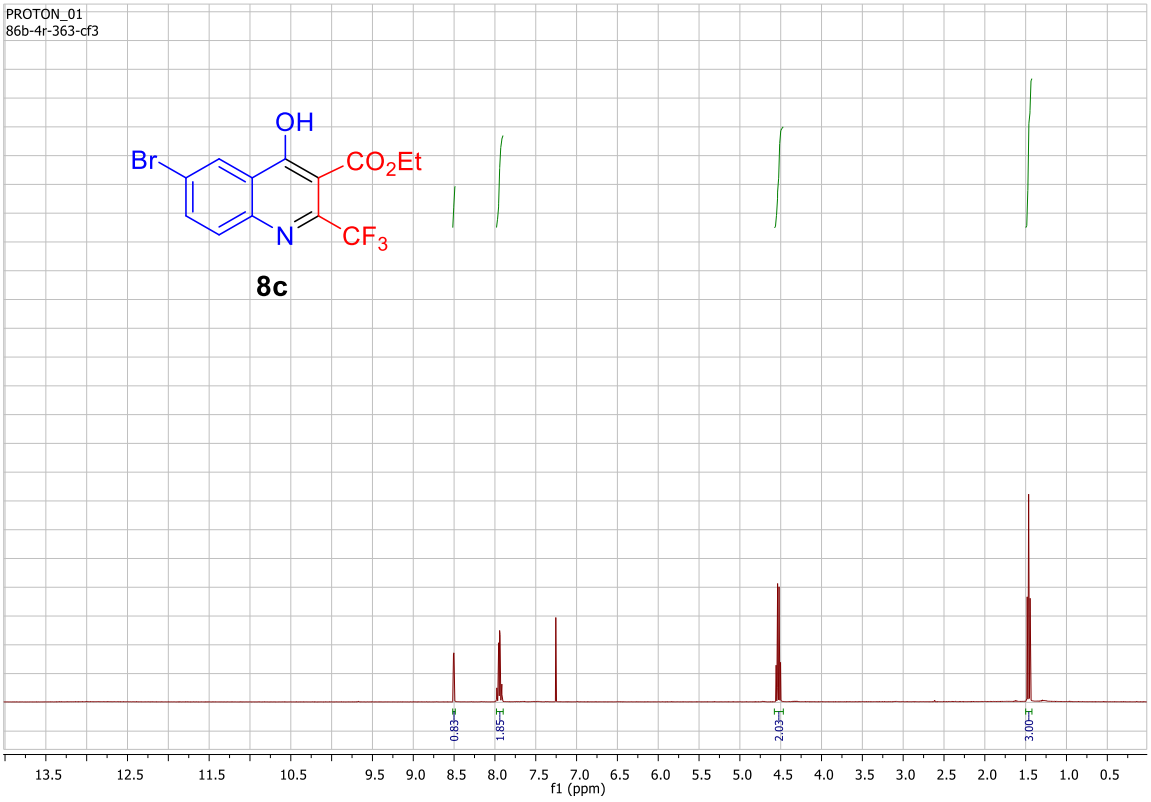

CARBON_01
86b-4p-286-CF3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

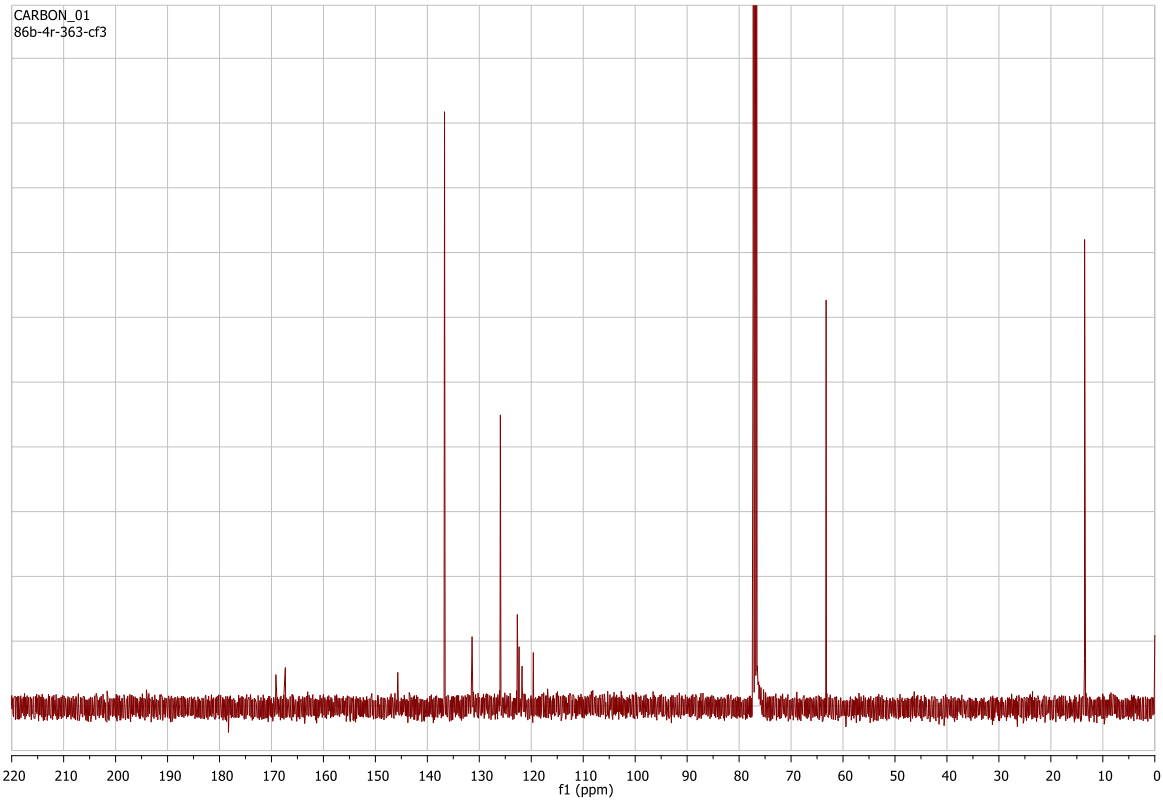

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

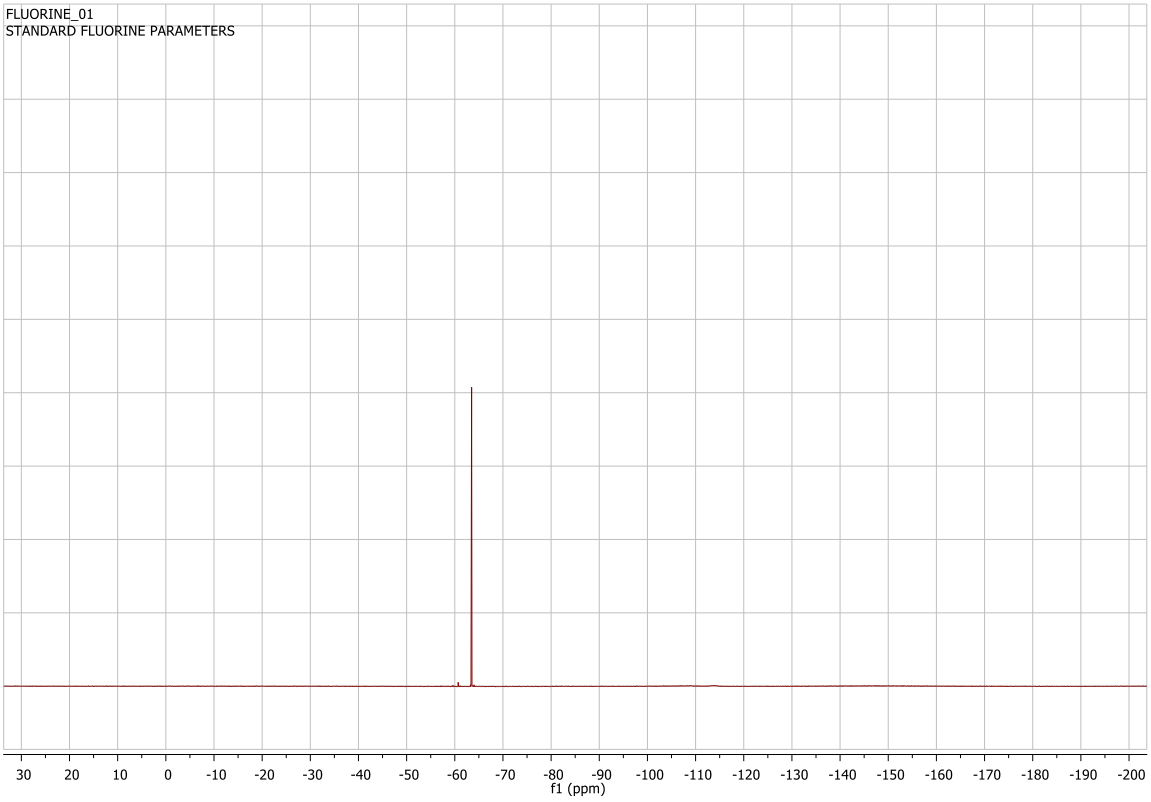

PROTON_01
86b-4q-319-cf3
OH
Cl
CO2Et
N
CF3
8b
1.09
0.80
0.91
0.93
1.93
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

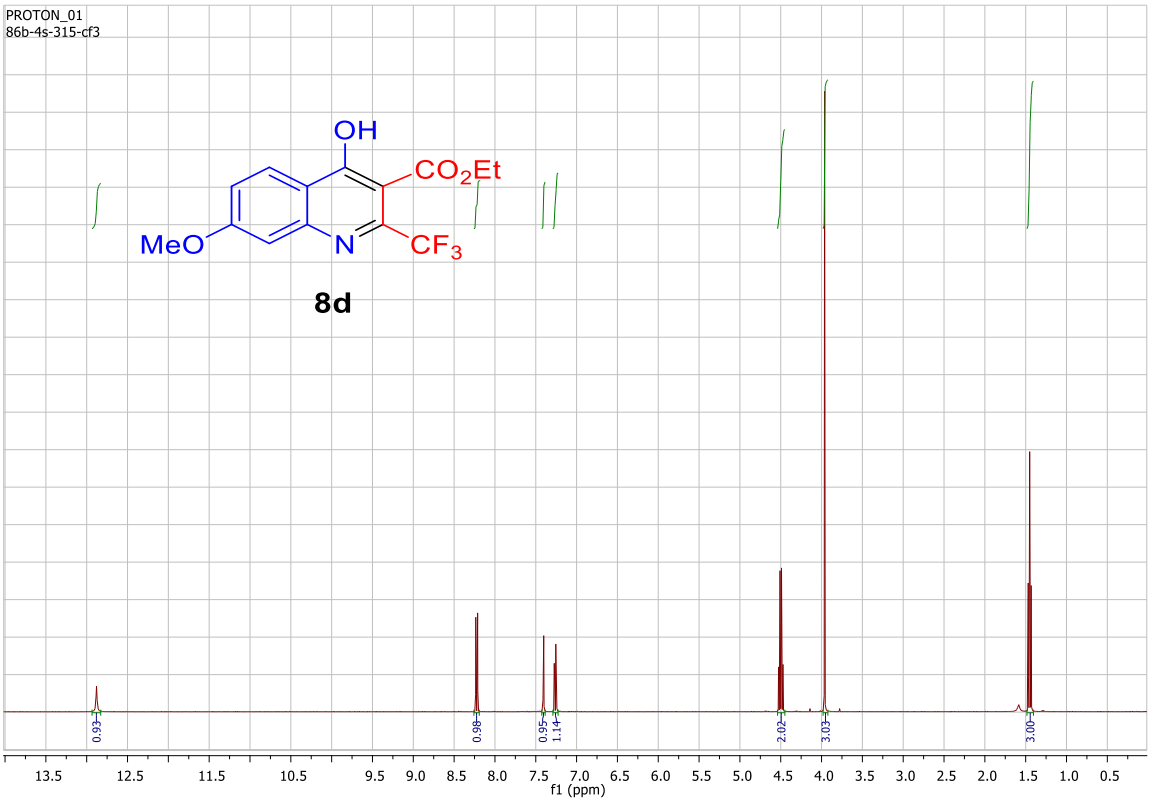

CARBON_01
86b-4q-319-cf3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

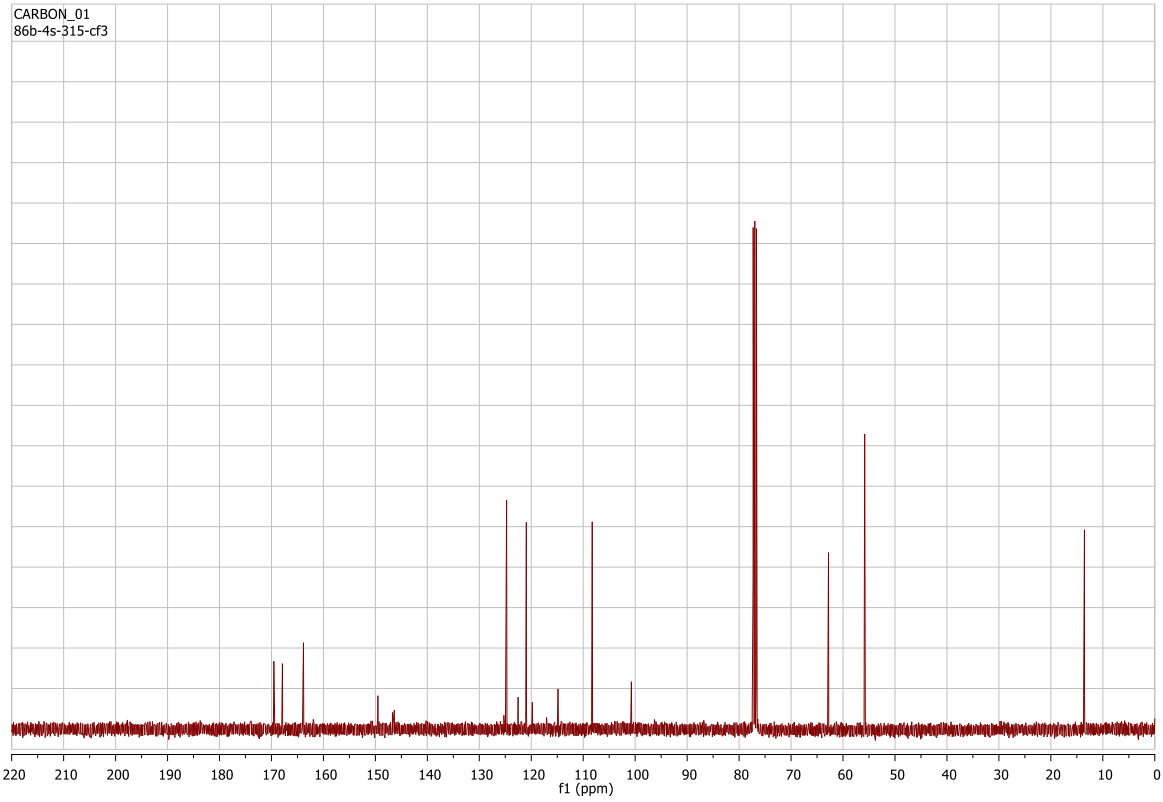

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

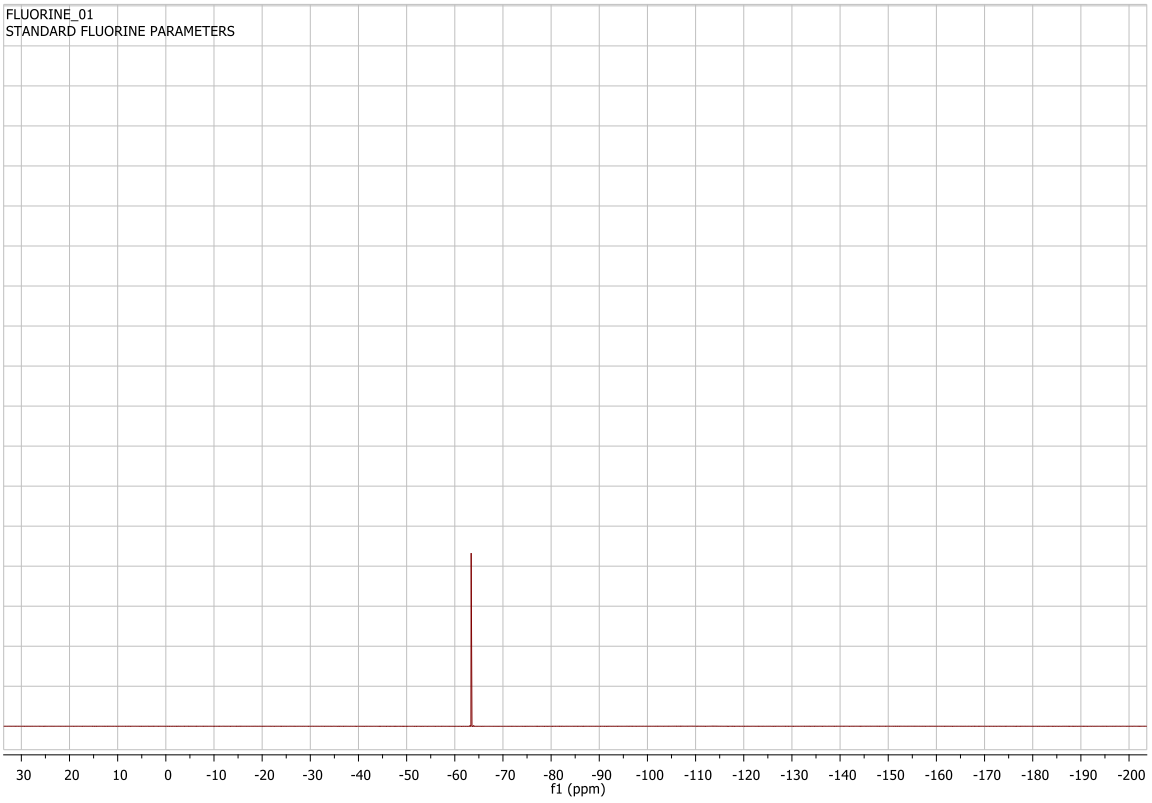

PROTON_01
86b-4r-363-cf3
OH
Br
CO2Et
N
CF3
8c
0.83
1.85
2.03
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

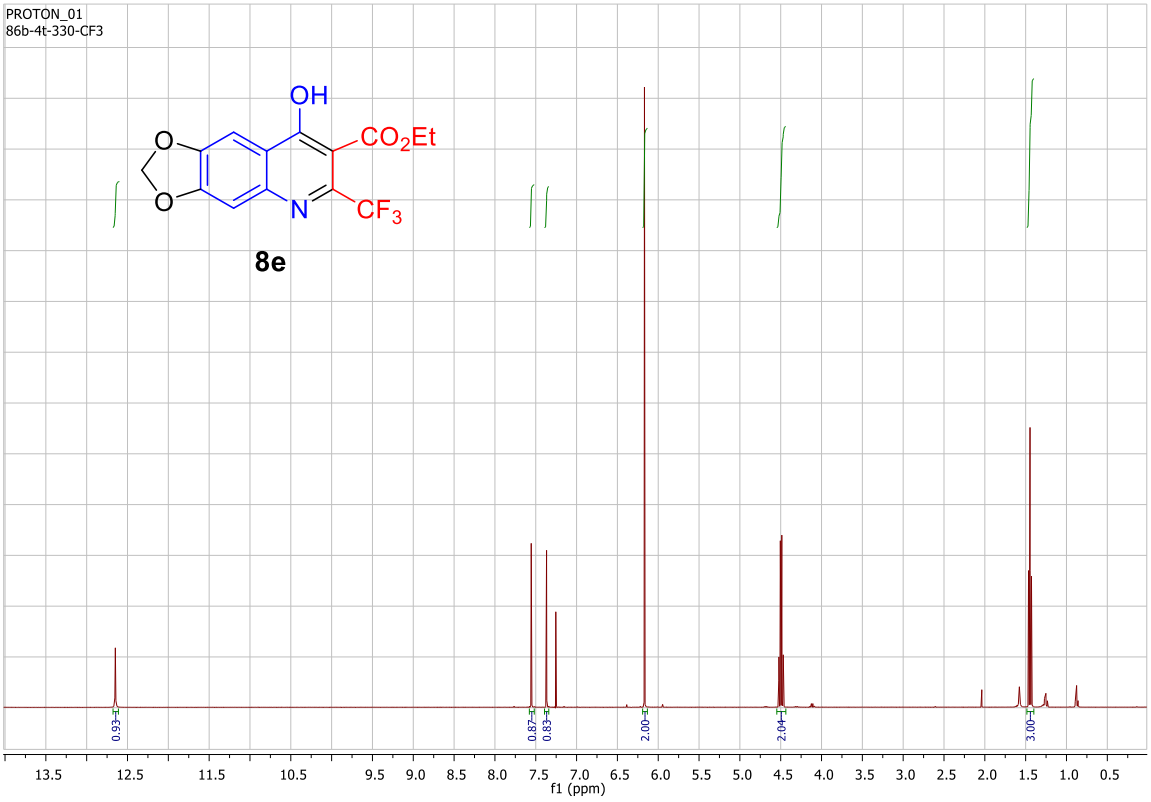

CARBON_01
86b-4r-363-cf3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

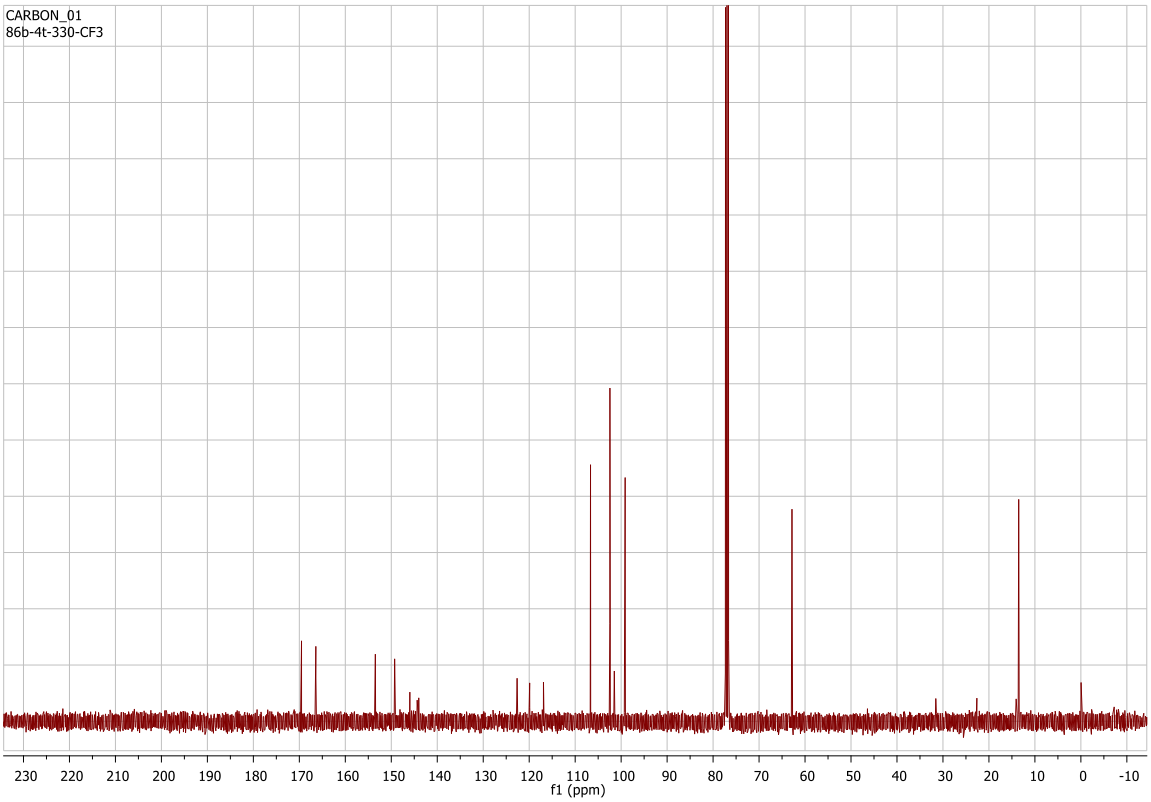

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

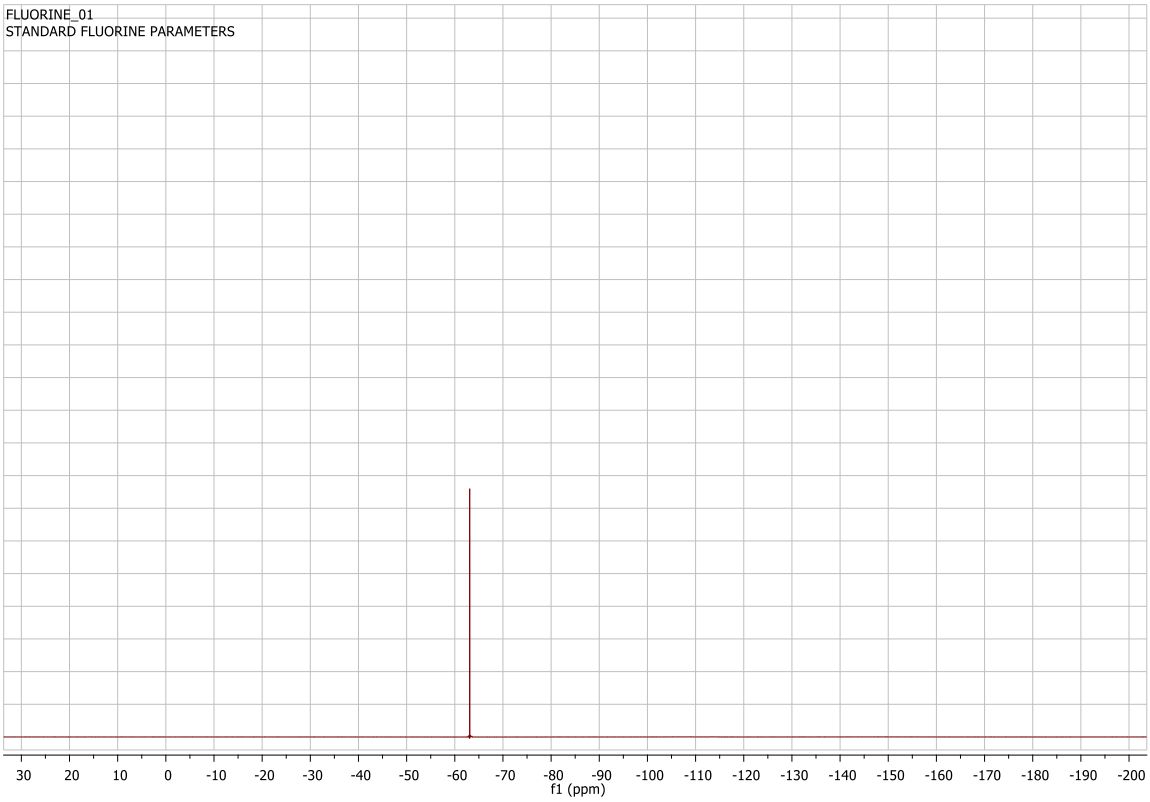

PROTON_01
86b-4s-315-cf3
OH
CO2Et
MeO
N
CF3
8d
0.93
0.98
0.95
1.14
2.02
3.03
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

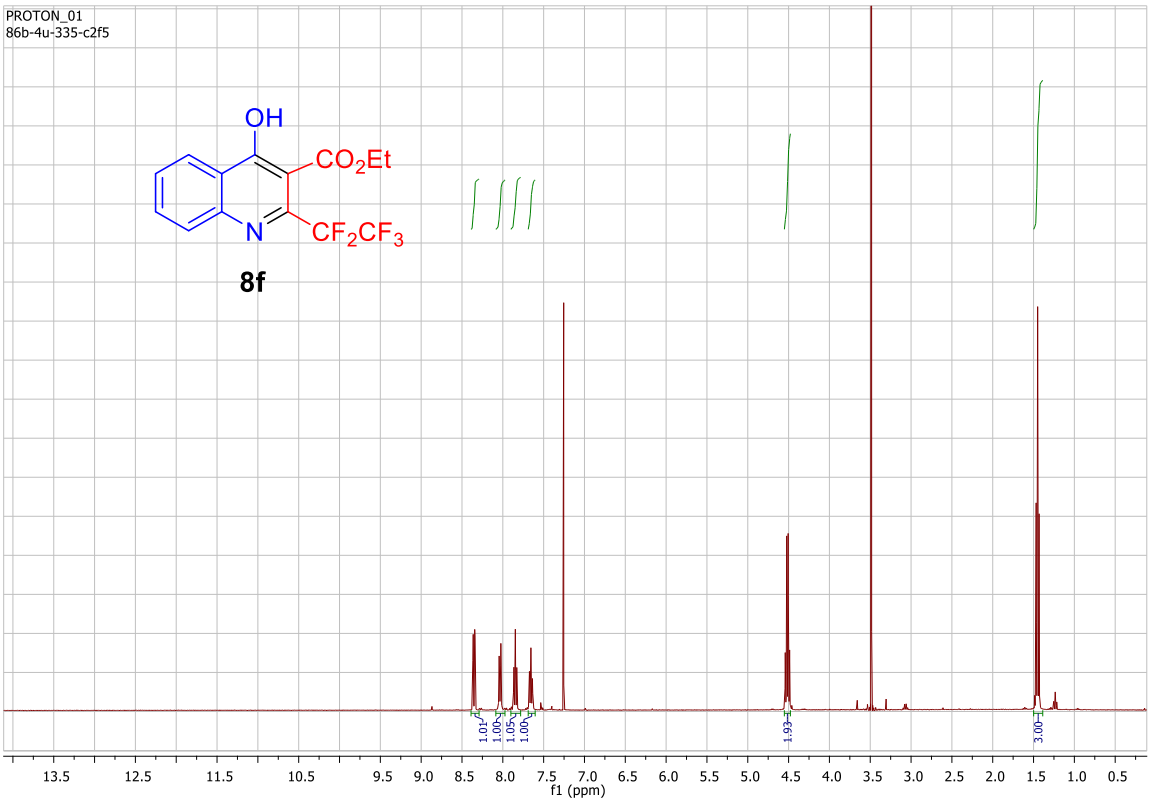

CARBON_01
86b-4s-315-cf3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

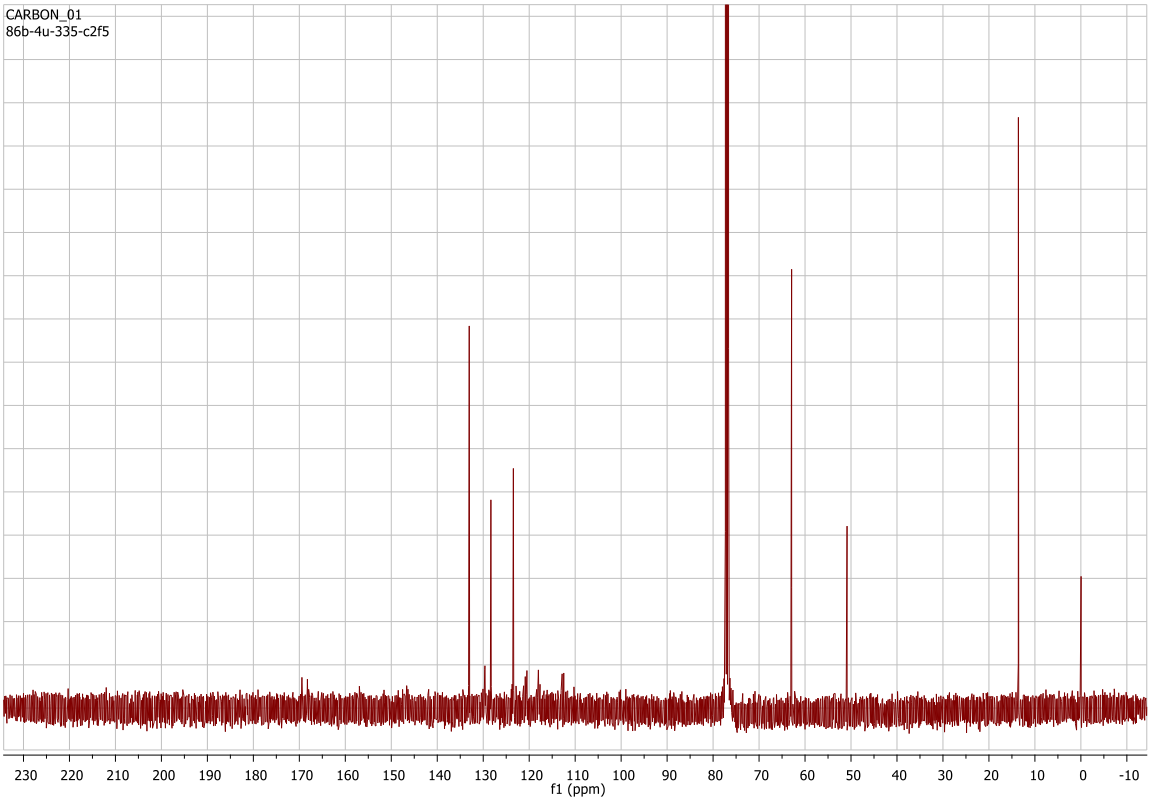

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

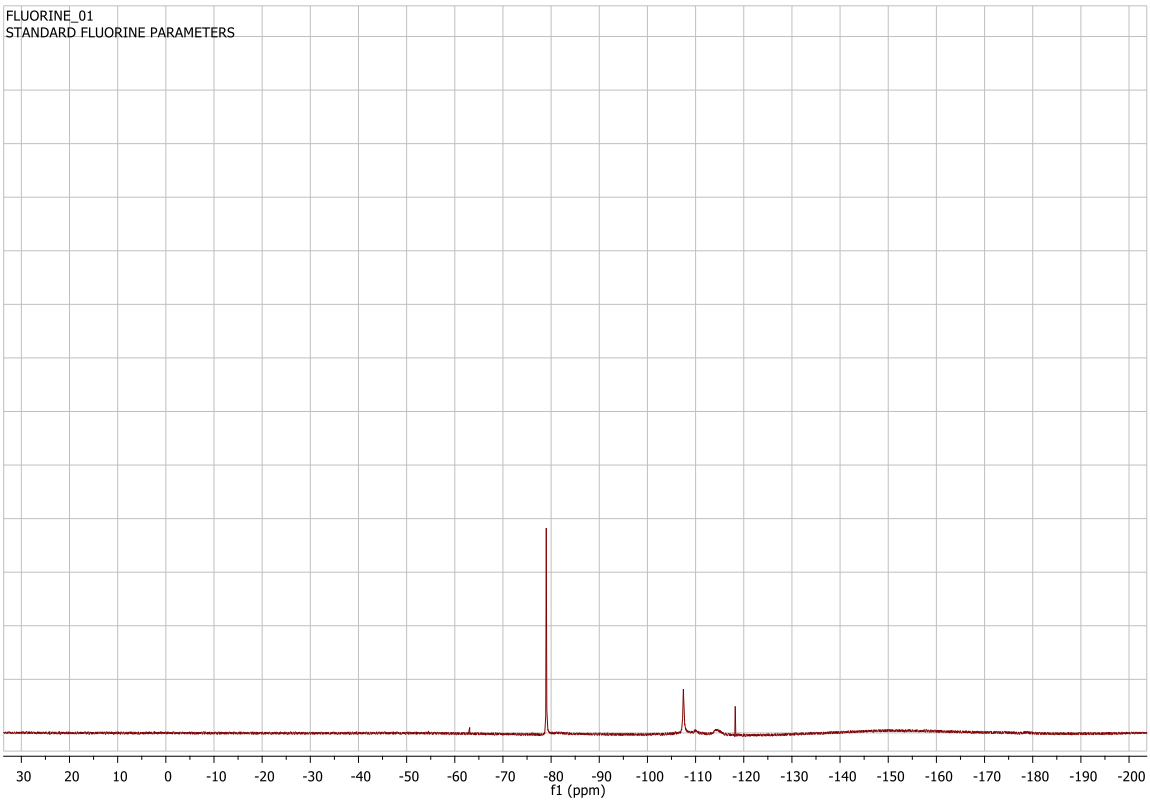

PROTON_01
86b-4t-330-CF3
OH
CO2Et
CF3
N
O
O
8e
0.93
0.87
0.83
2.00
2.04
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

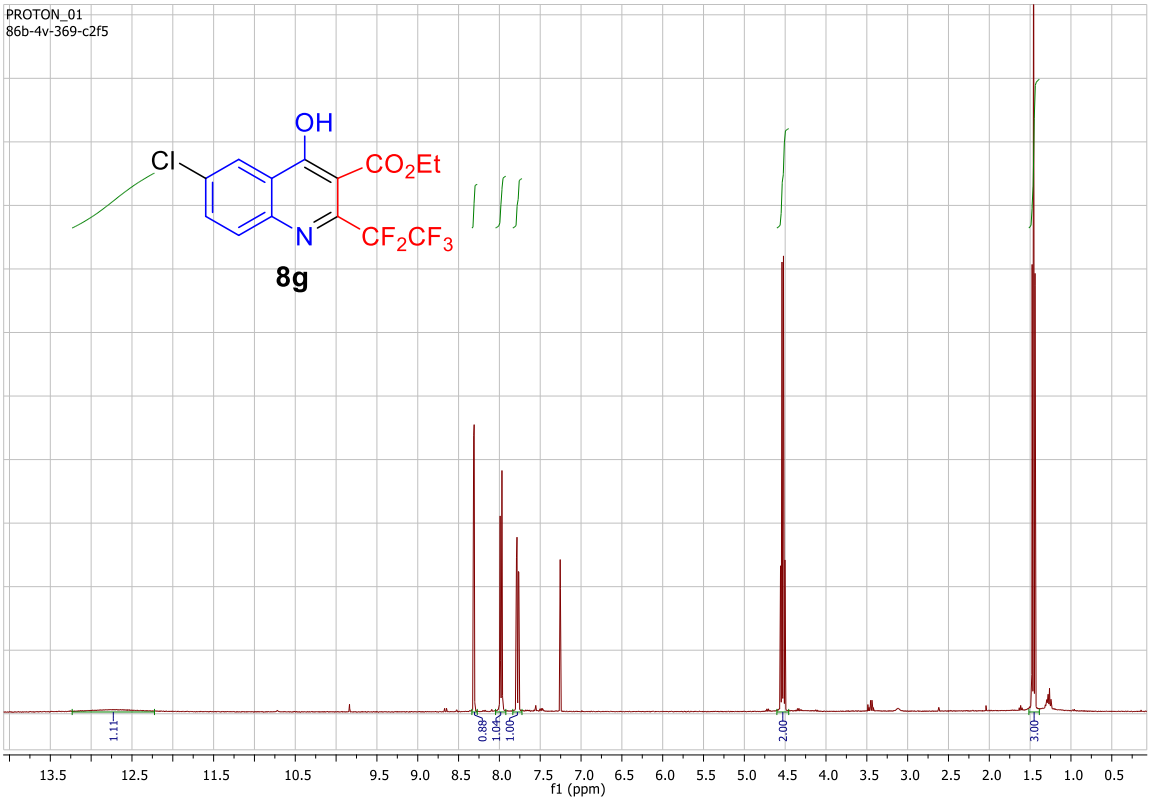

CARBON_01
86b-4t-330-CF3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

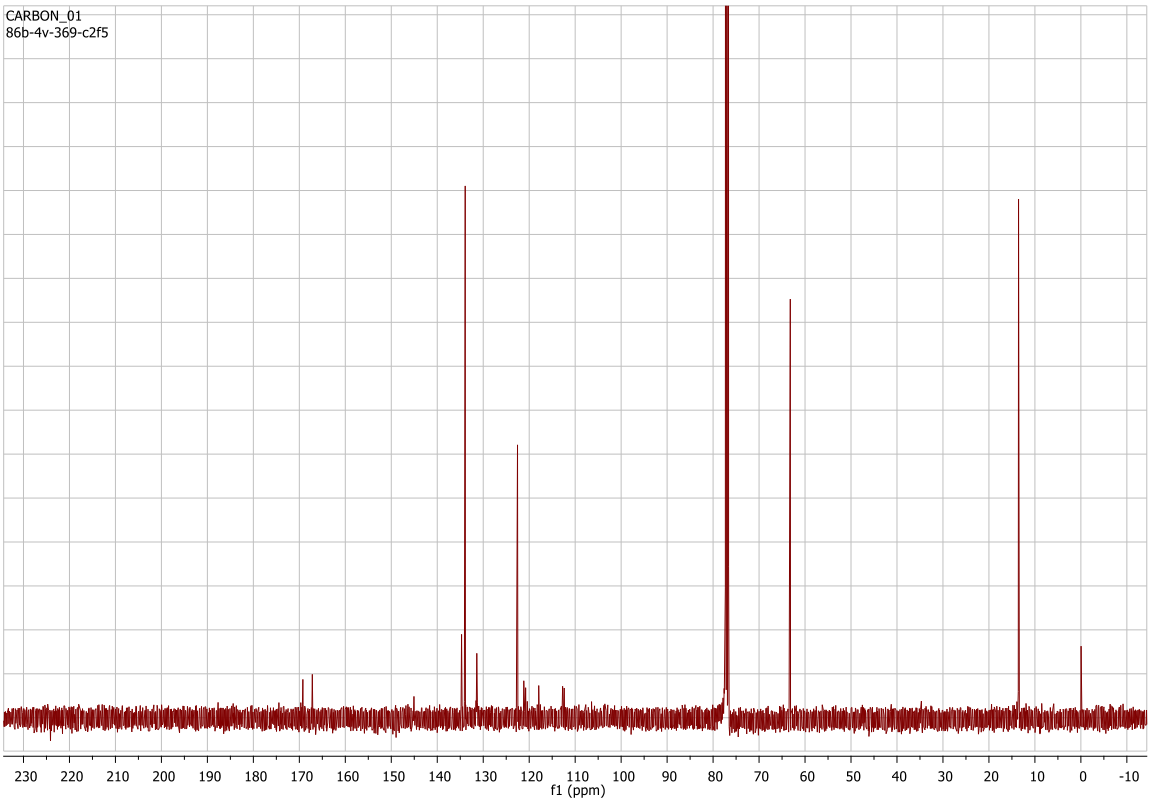

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

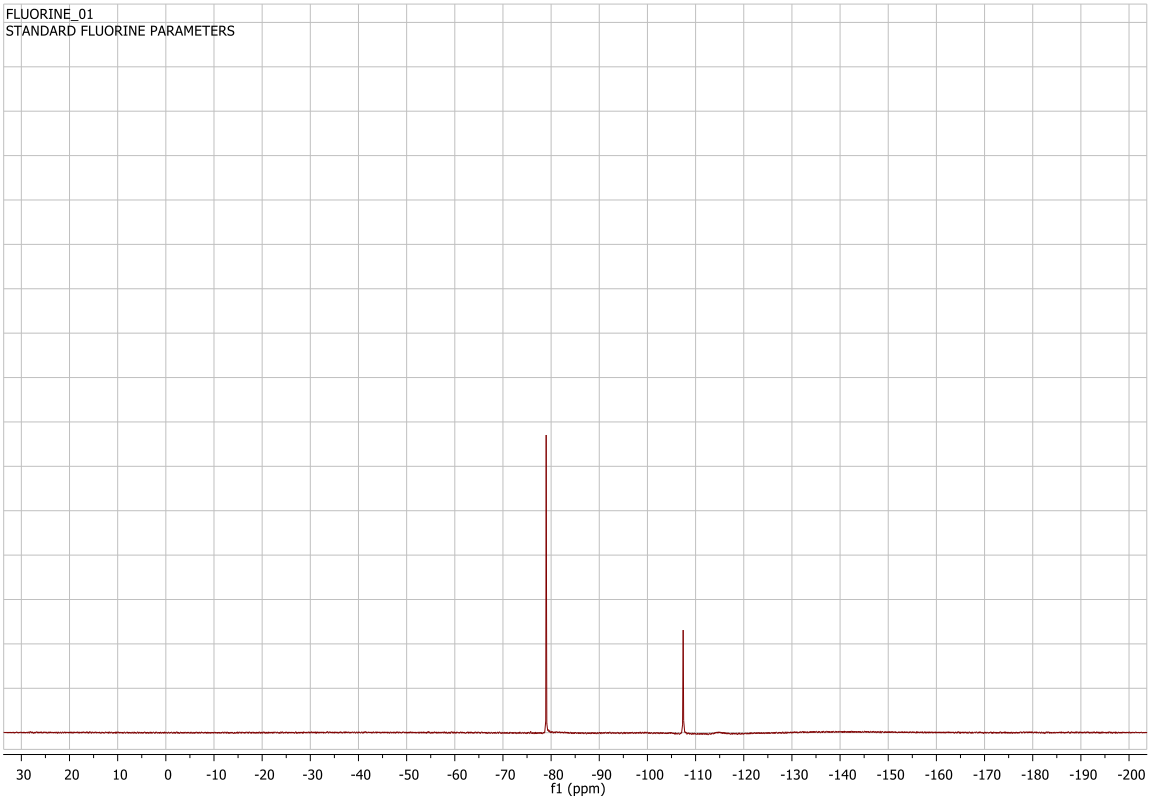

PROTON_01
86b-4u-335-c2f5
OH
CO2Et
N
CF2CF3
8f
1.01
1.00
1.05
1.00
1.93
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

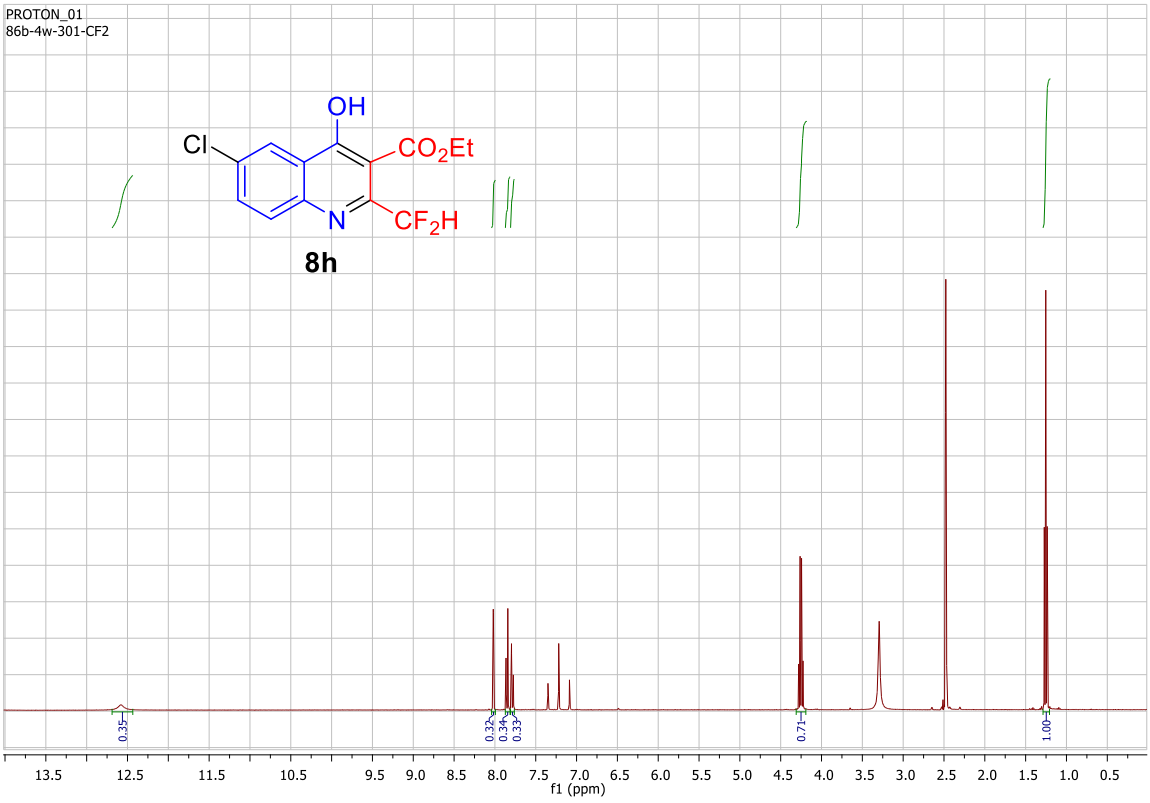

CARBON_01
86b-4u-335-c2f5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

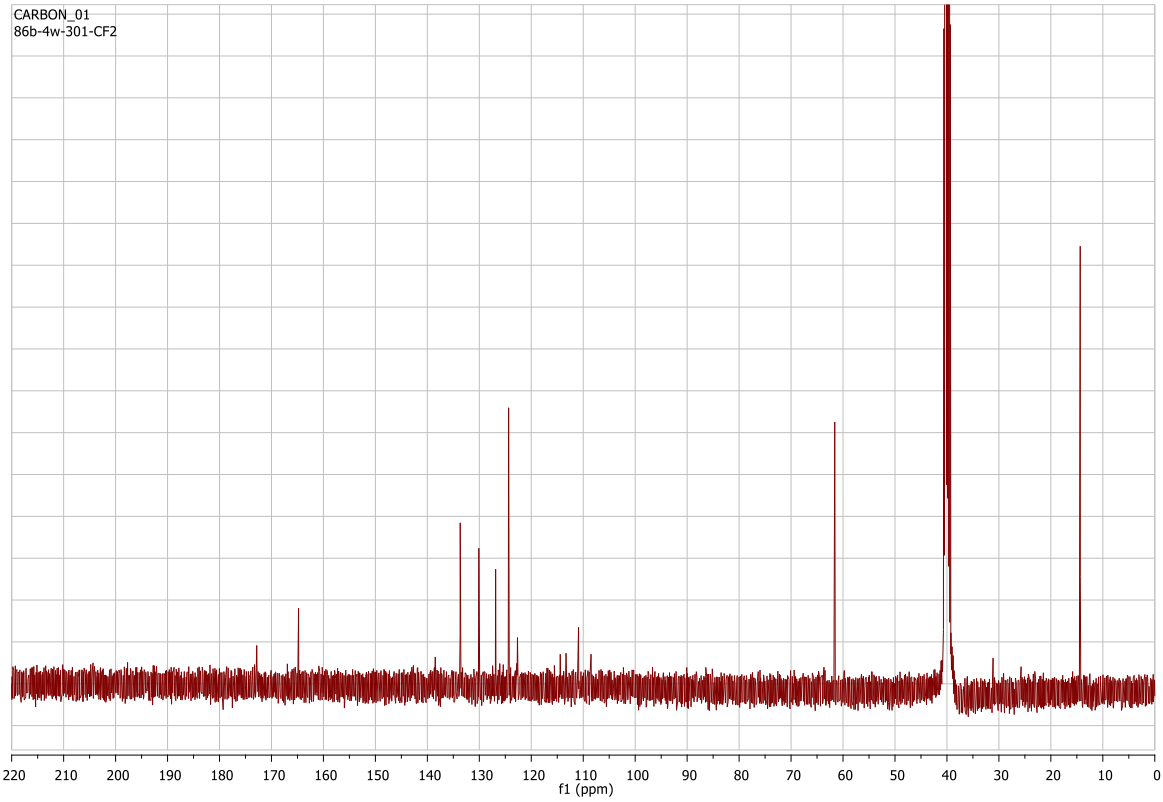

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

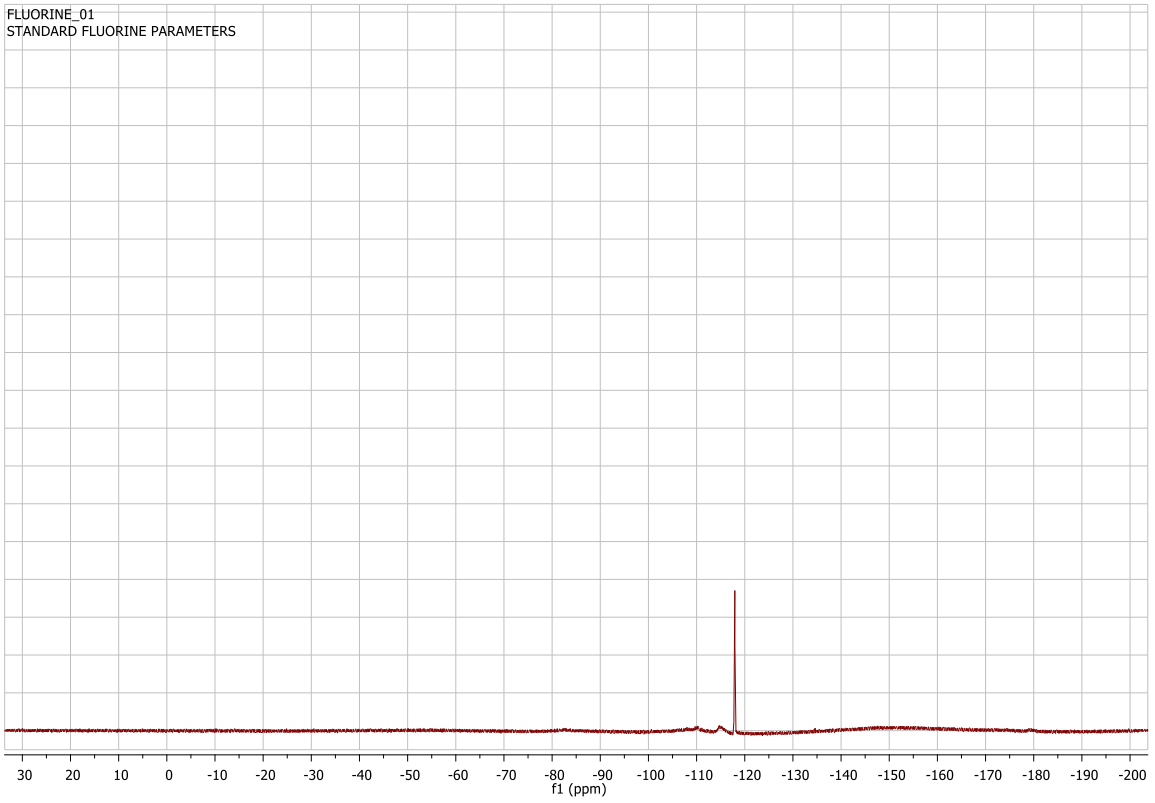

PROTON_01
86b-4v-369-c2f5
OH
Cl
CO2Et
N
CF2CF3
8g
1.11
0.88
1.04
1.00
2.00
3.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

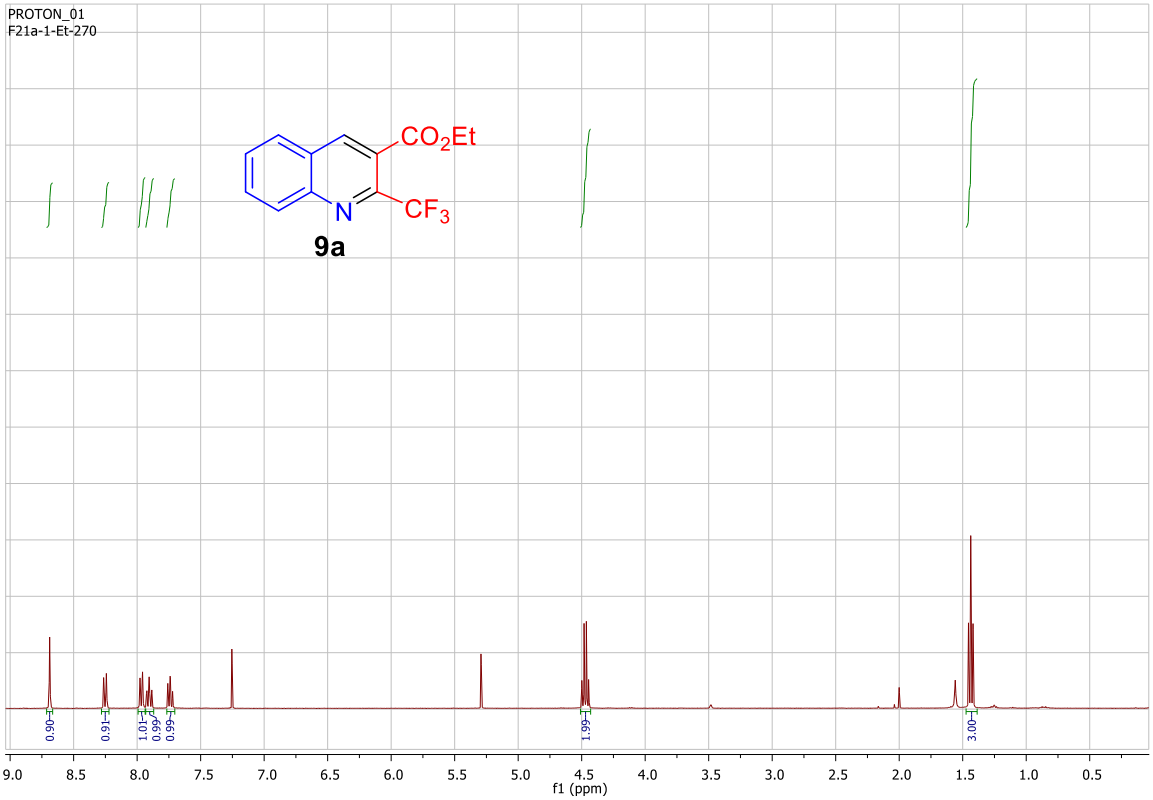

CARBON_01
86b-4v-369-c2f5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

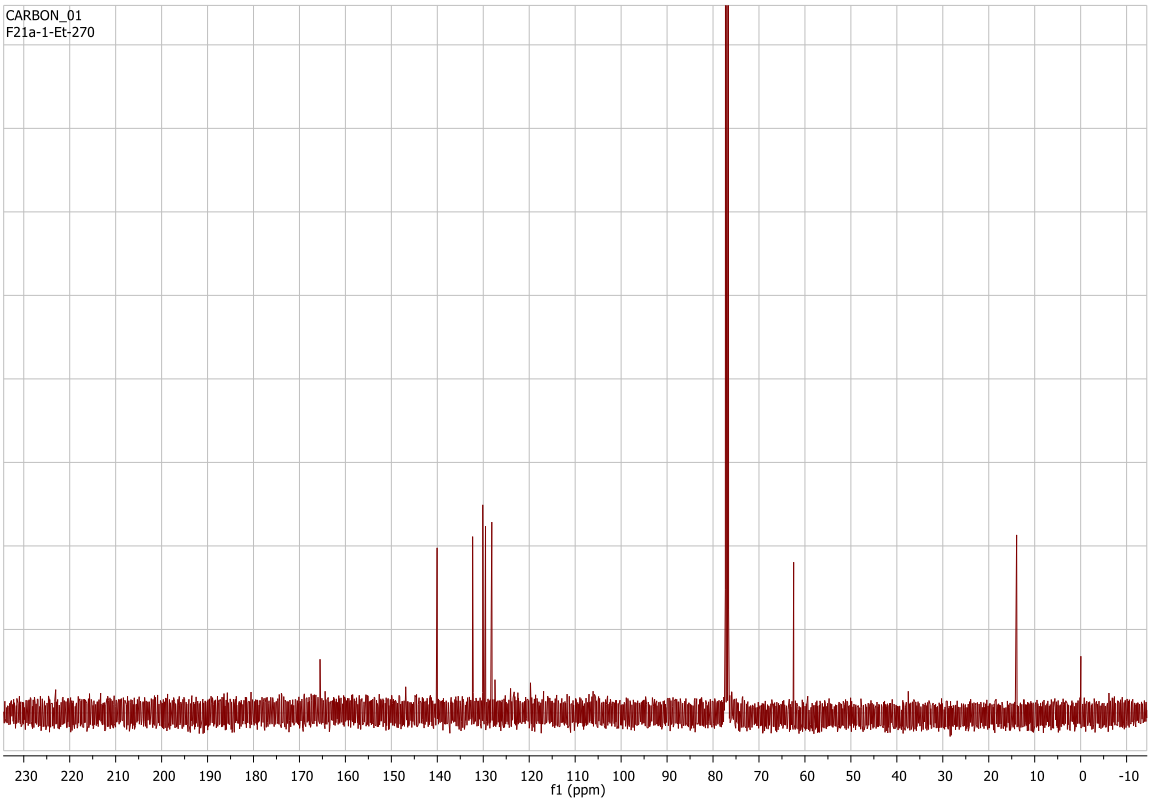

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

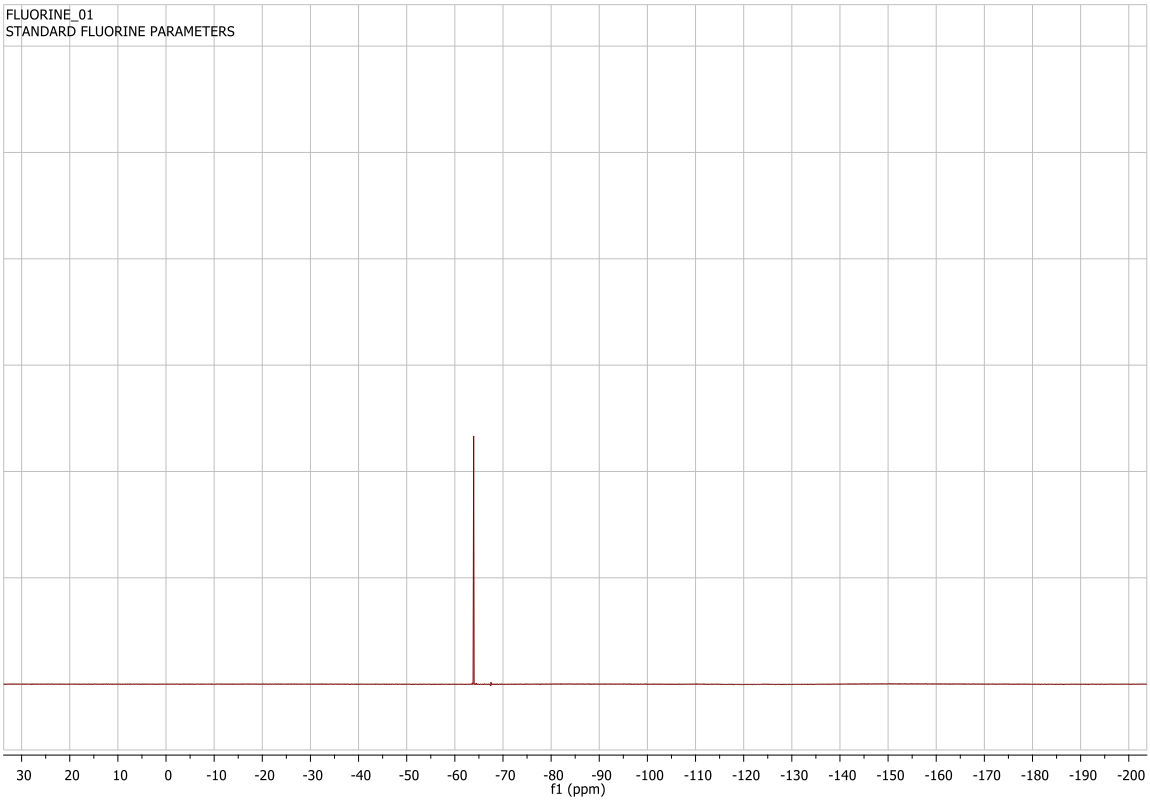

PROTON_01
86b-4w-301-CF2
OH
Cl
CO2Et
N
CF2H
8h
0.35
0.32
0.34
0.33
0.71
1.00
13.5 12.5 11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

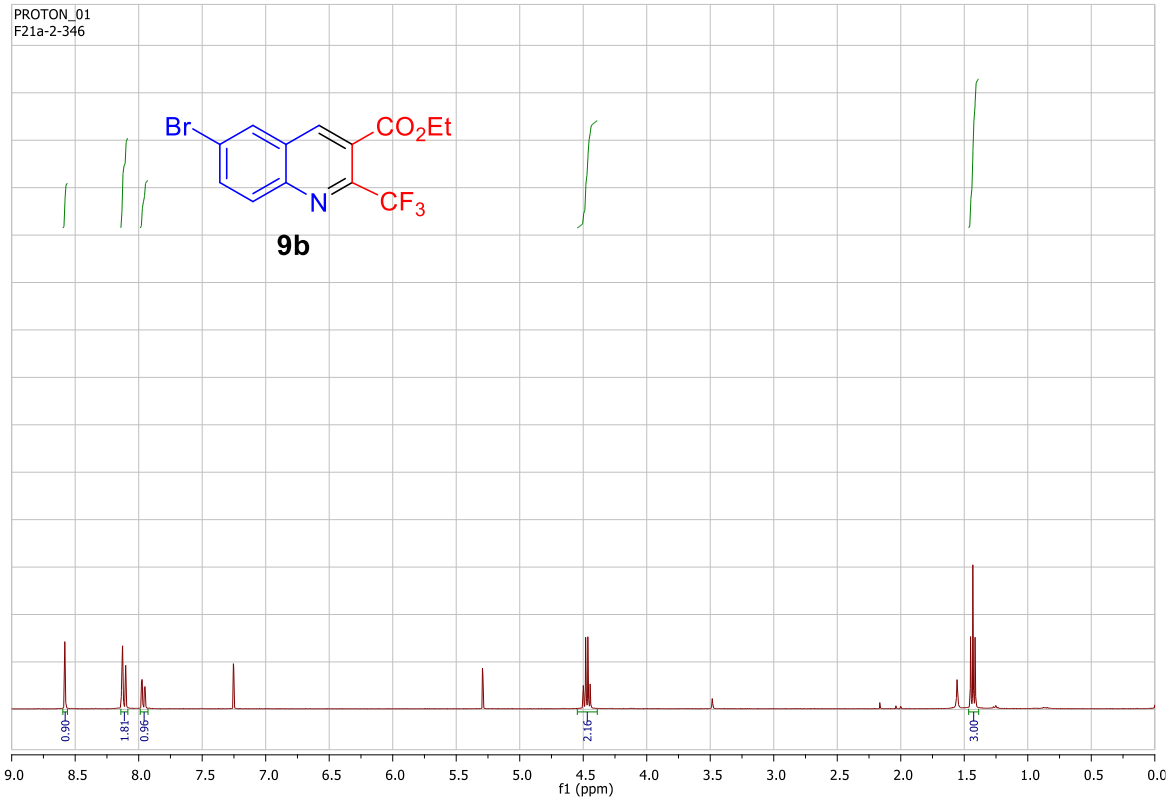

CARBON_01
86b-4w-301-CF2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

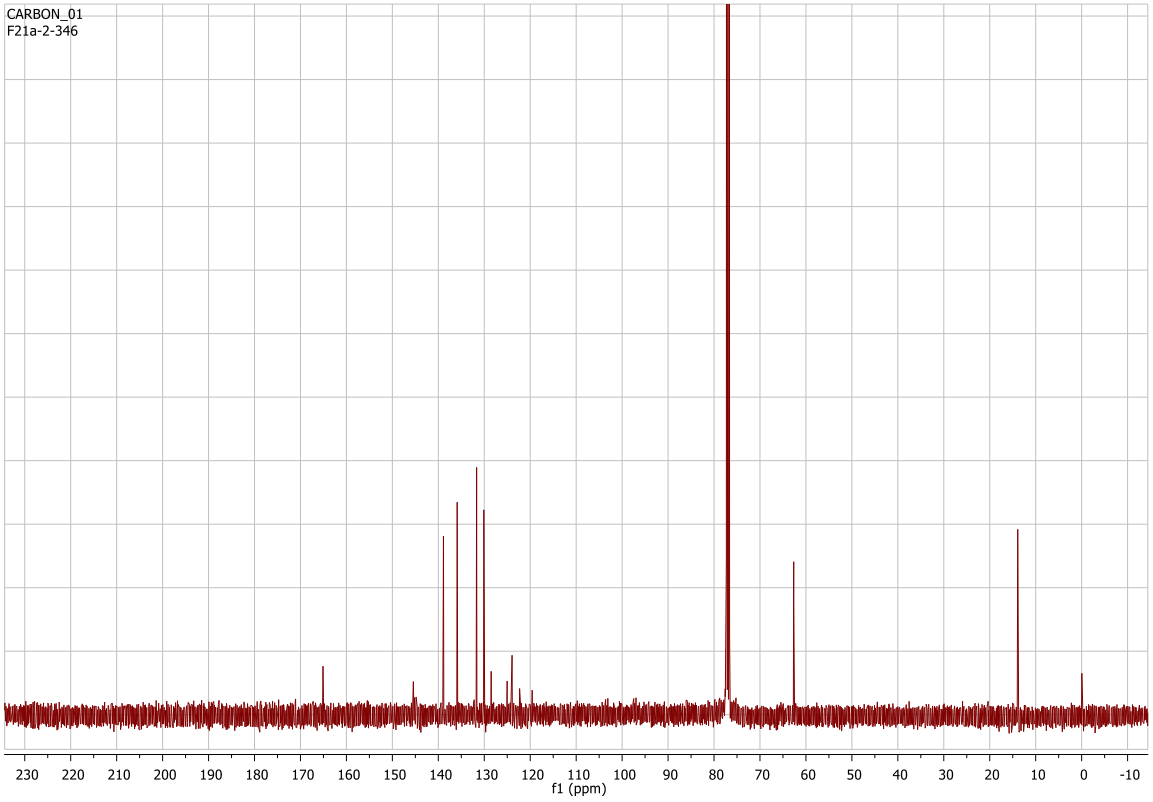

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

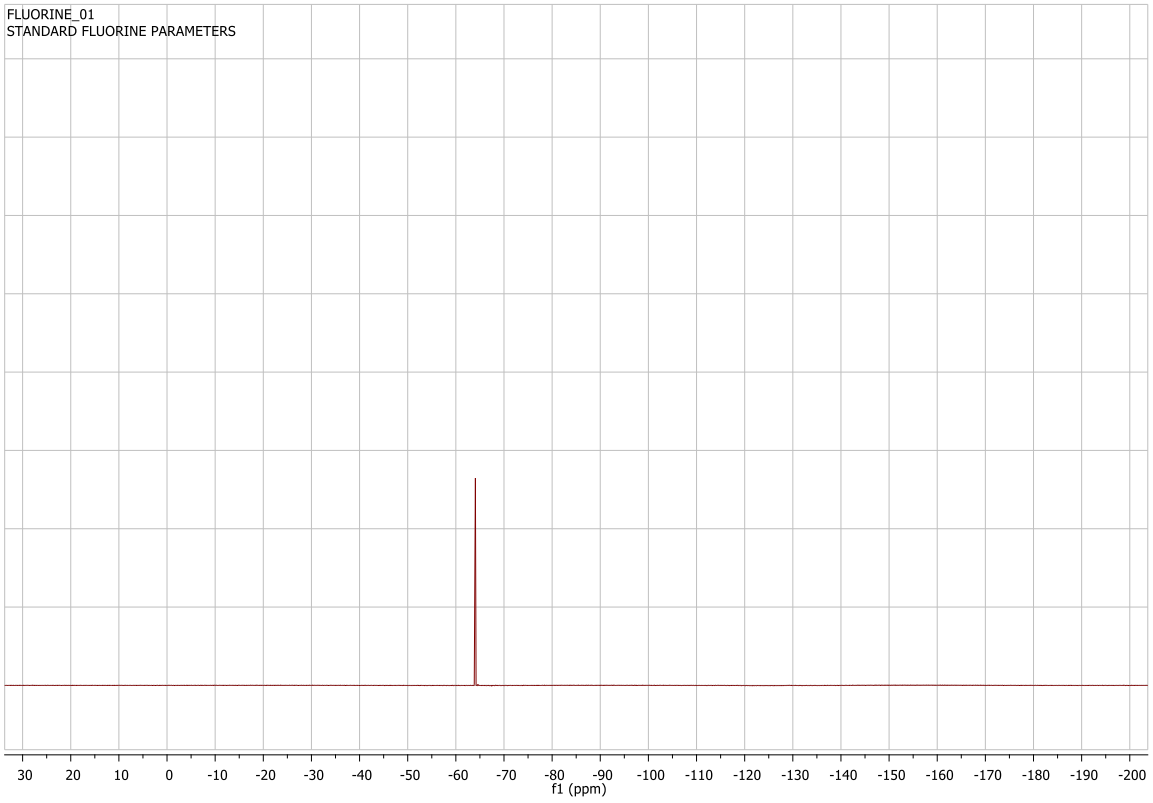

PROTON_01
F21a-1-Et-270
$CO_2Et$
$CF_3$
N
9a
0.90
0.91
1.01
0.99
0.99
1.99
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

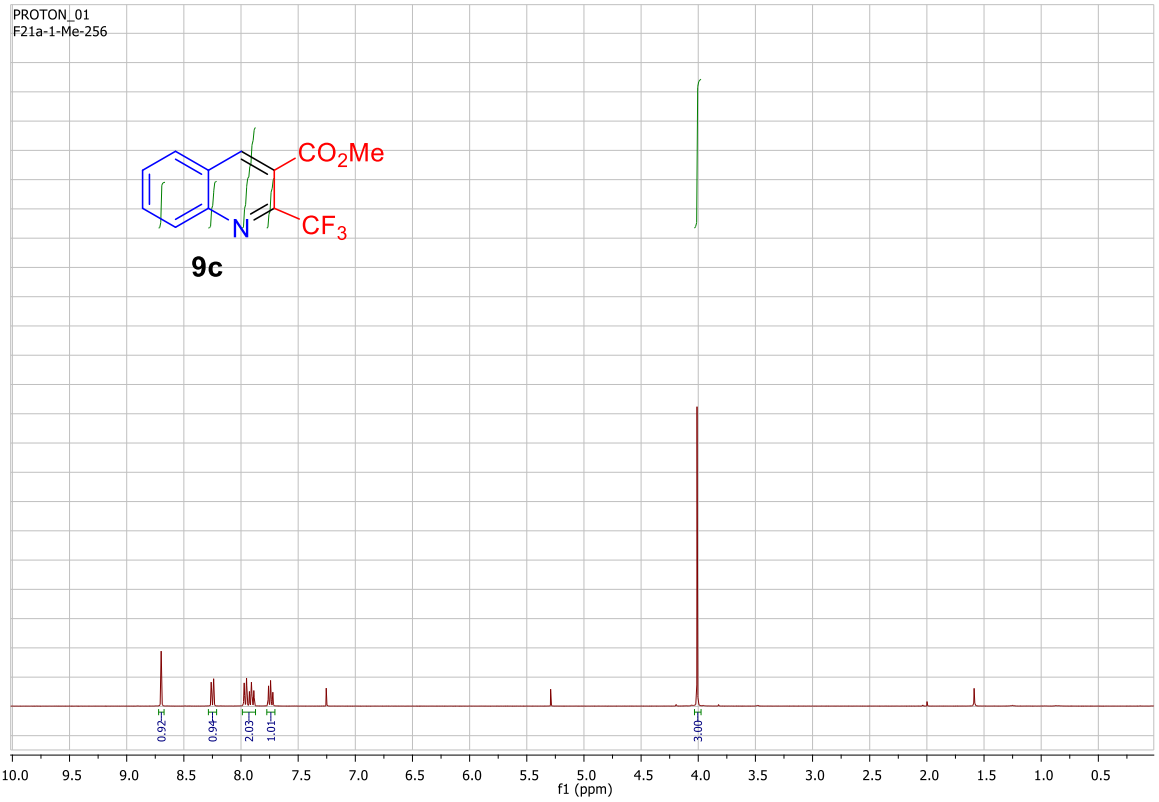

CARBON_01
F21a-1-Et-270
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

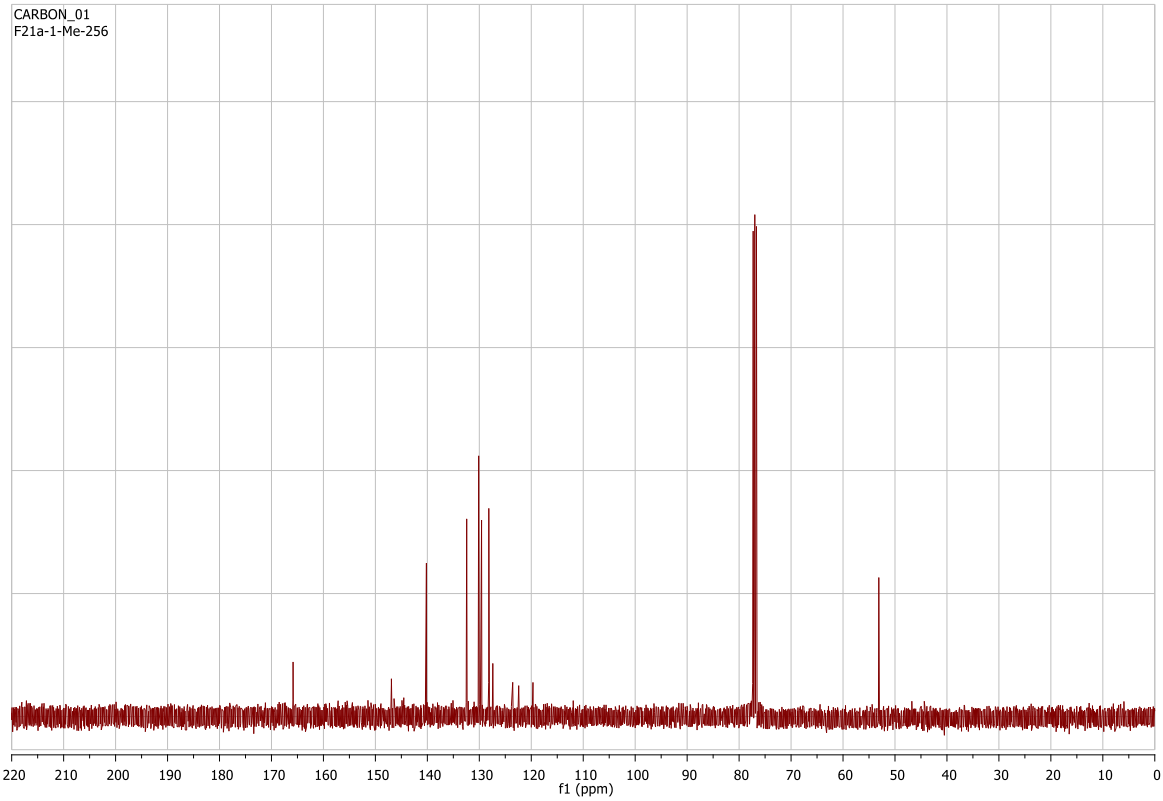

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

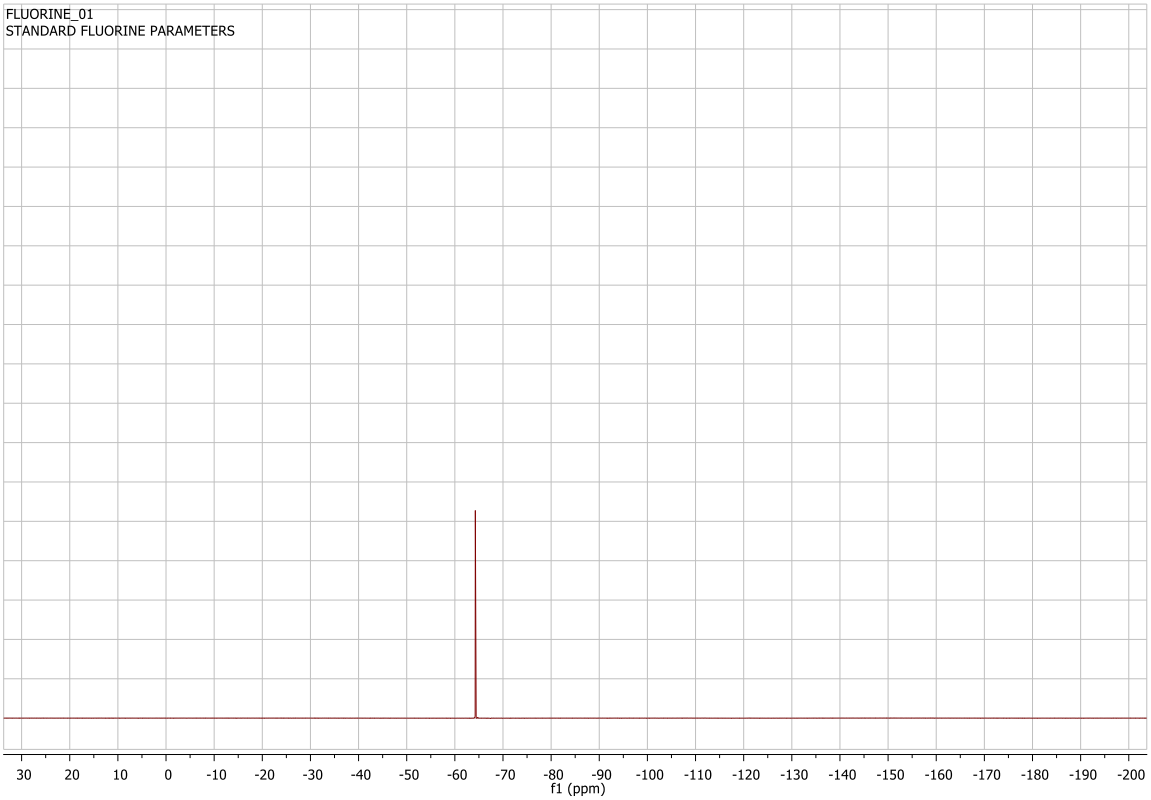

PROTON_01
F21a-2-346
Br
CO2Et
N
CF3
9b
0.90
1.81
0.96
2.16
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

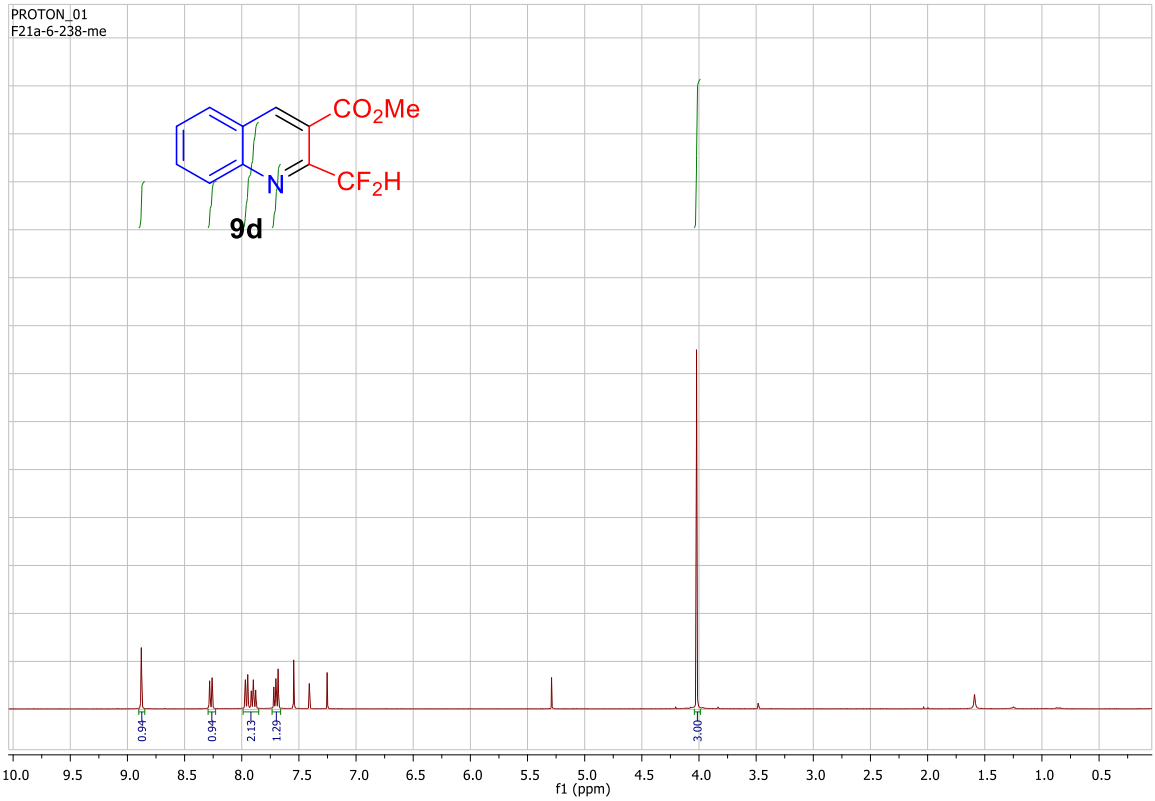

CARBON_01
F21a-2-346
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

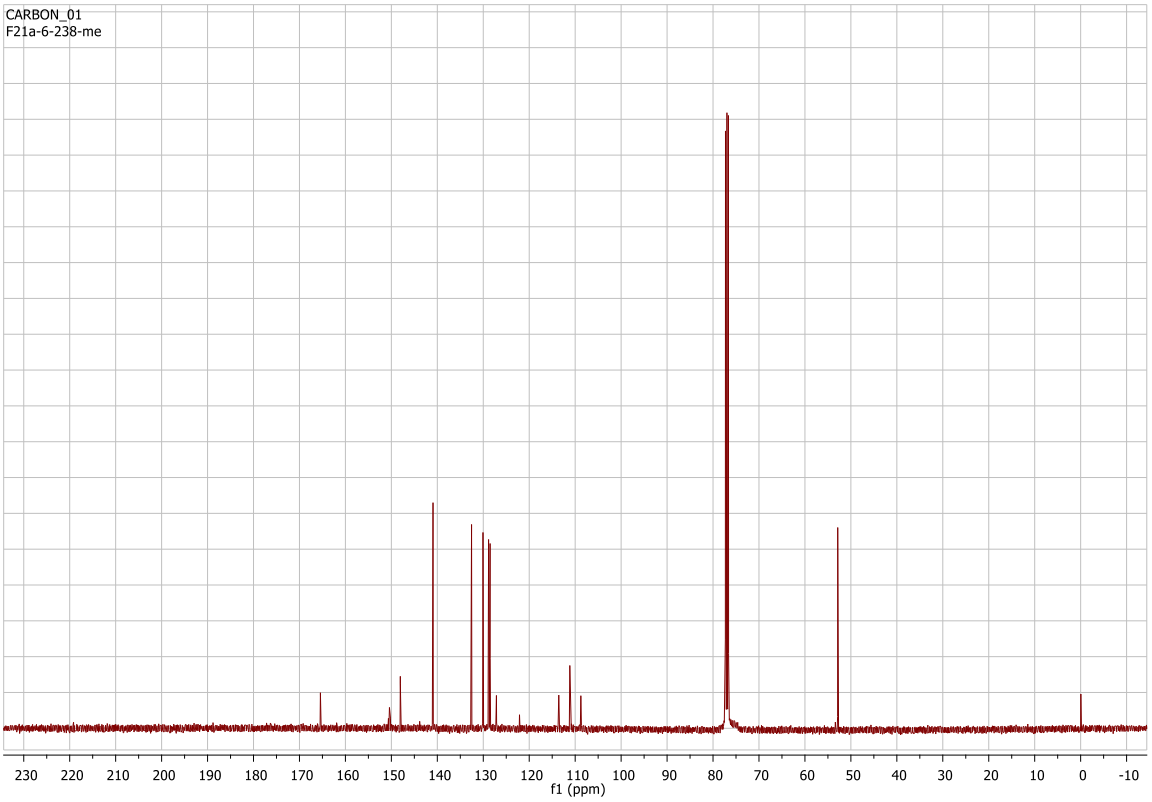

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

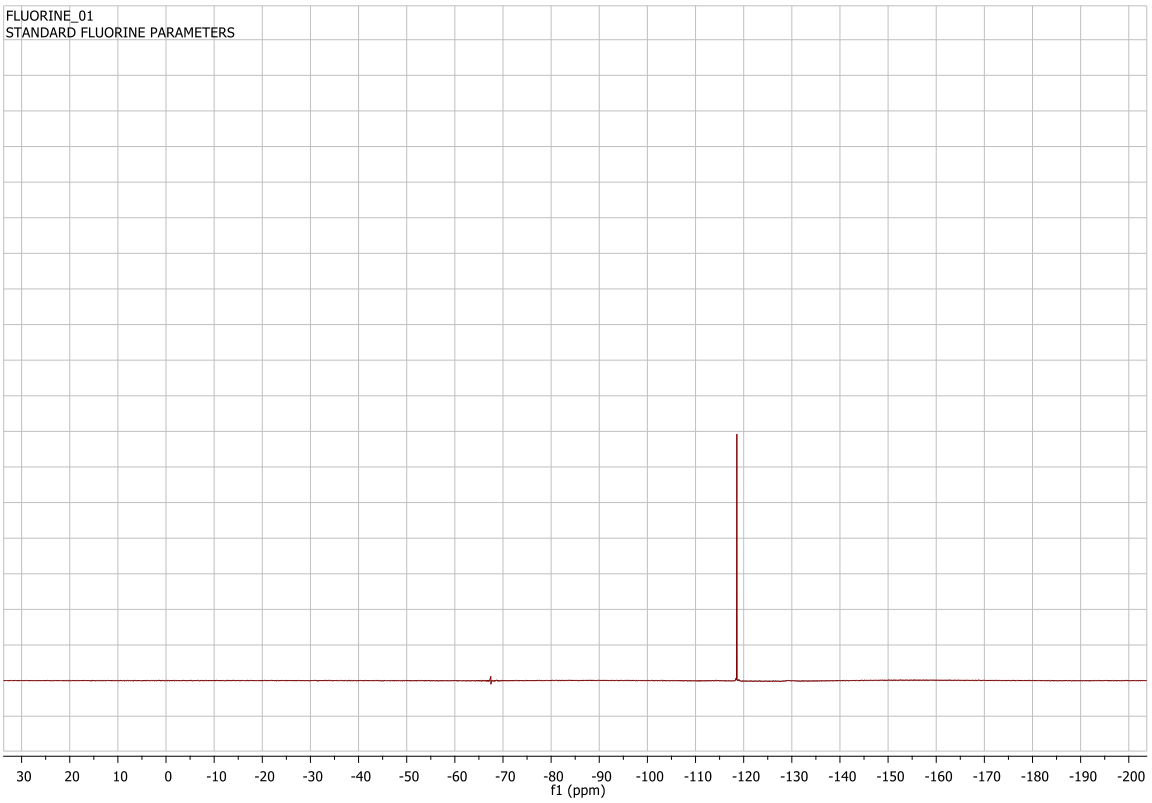

PROTON_01
F21a-1-Me-256
CO2Me
CF3
N
9c
0.92
0.94
2.03
1.01
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

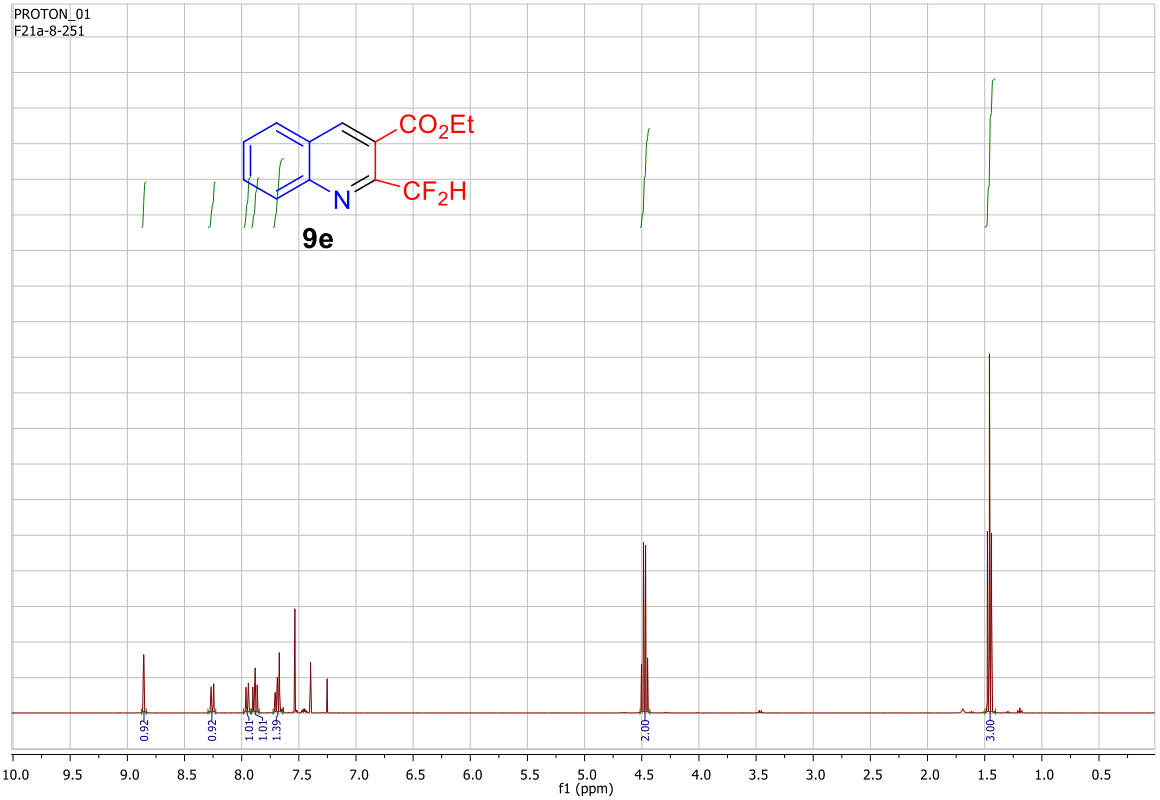

CARBON_01
F21a-1-Me-256
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

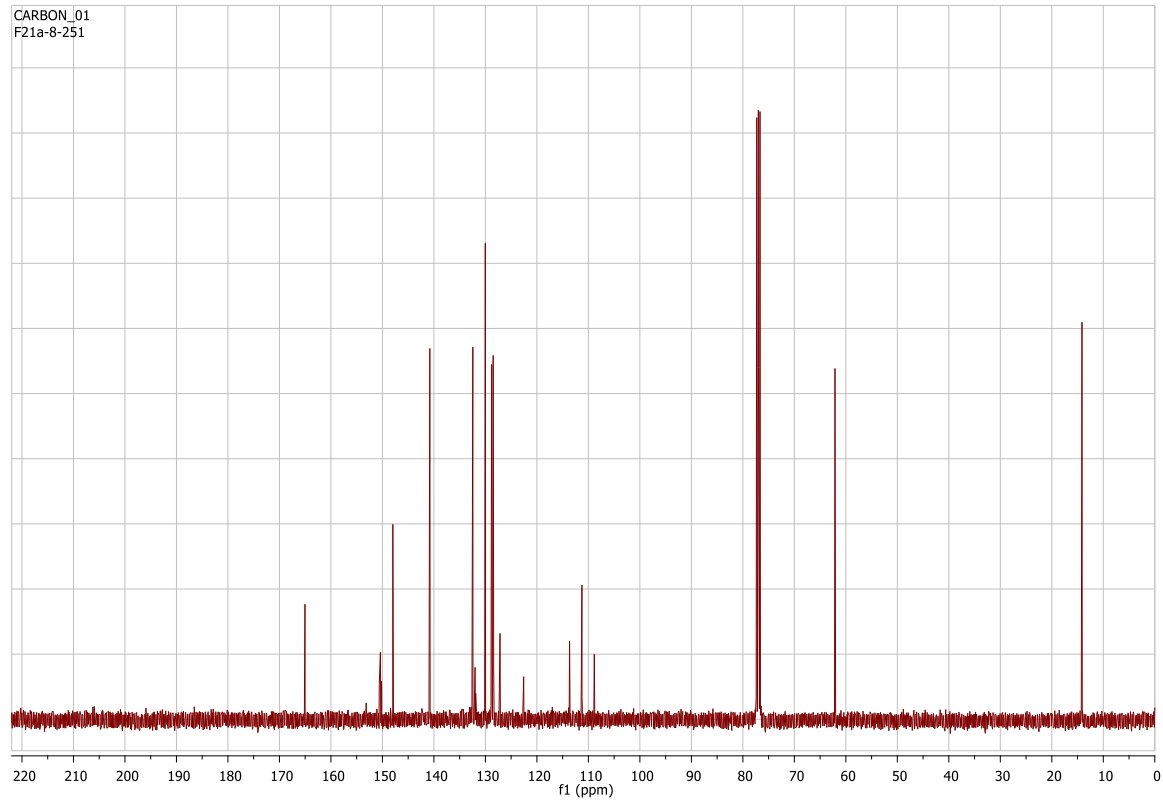

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

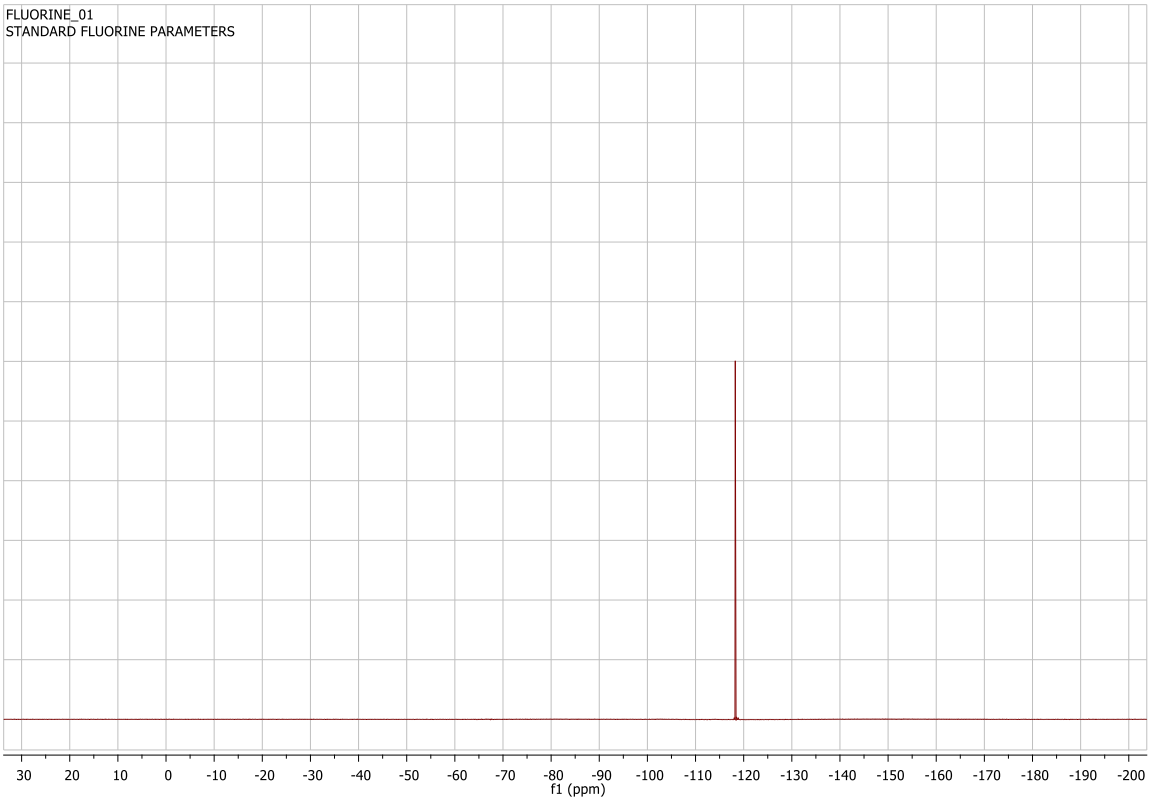

PROTON_01
F21a-6-238-me
CO2Me
CF2H
N
9d
0.94
0.94
2.13
1.29
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

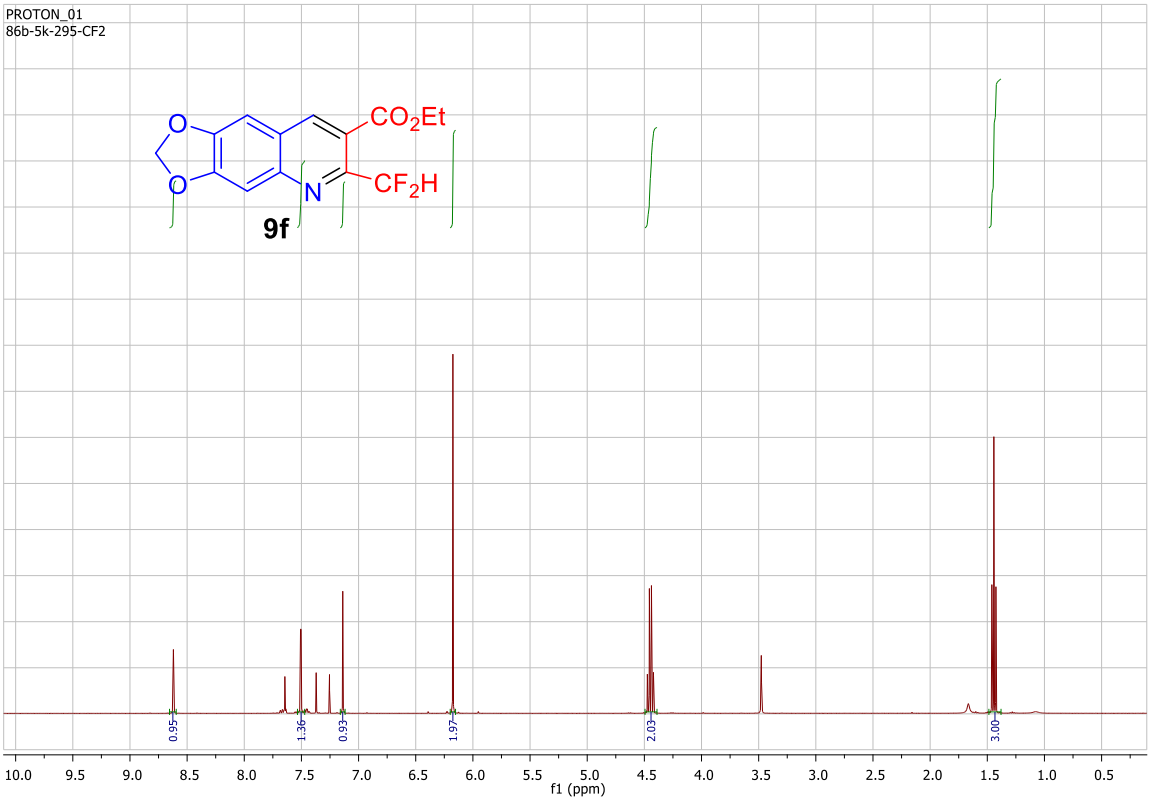

CARBON_01
F21a-6-238-me
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

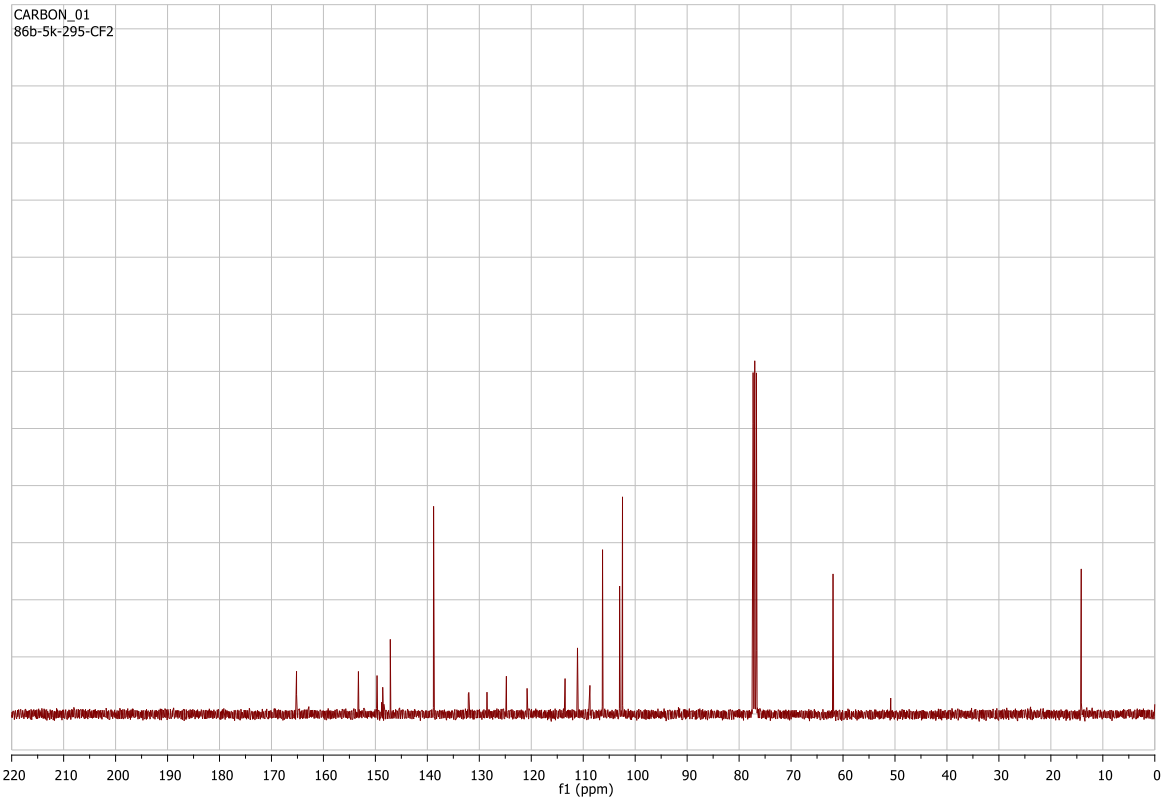

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

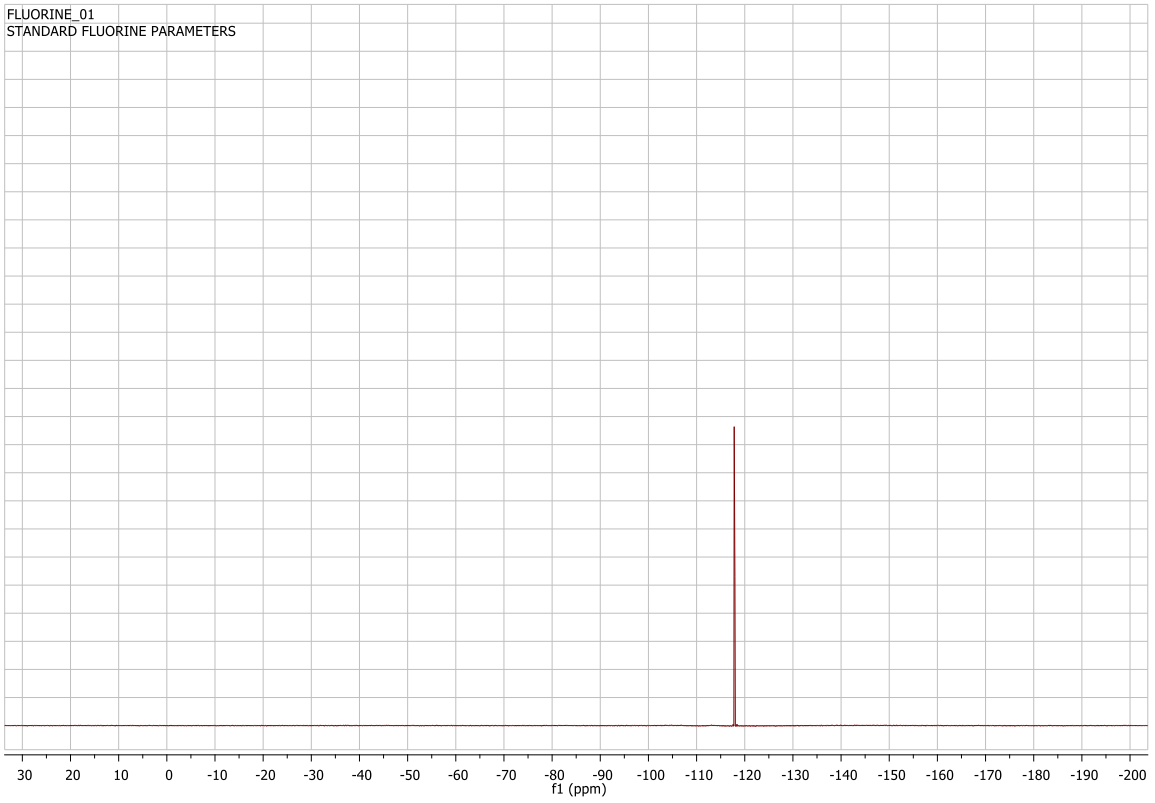

PROTON_01
F21a-8-251
CO2Et
CF2H
N
9e
0.92
0.92
1.01
1.01
1.39
2.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

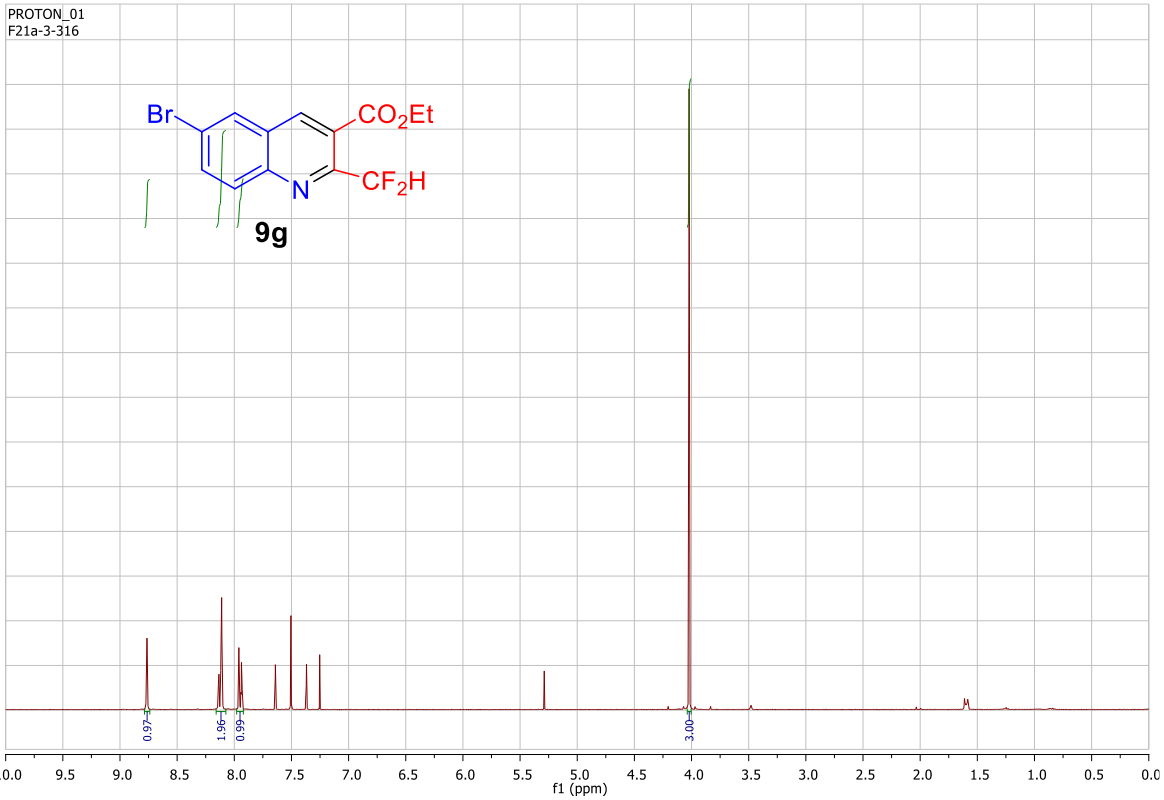

CARBON_01
F21a-8-251
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

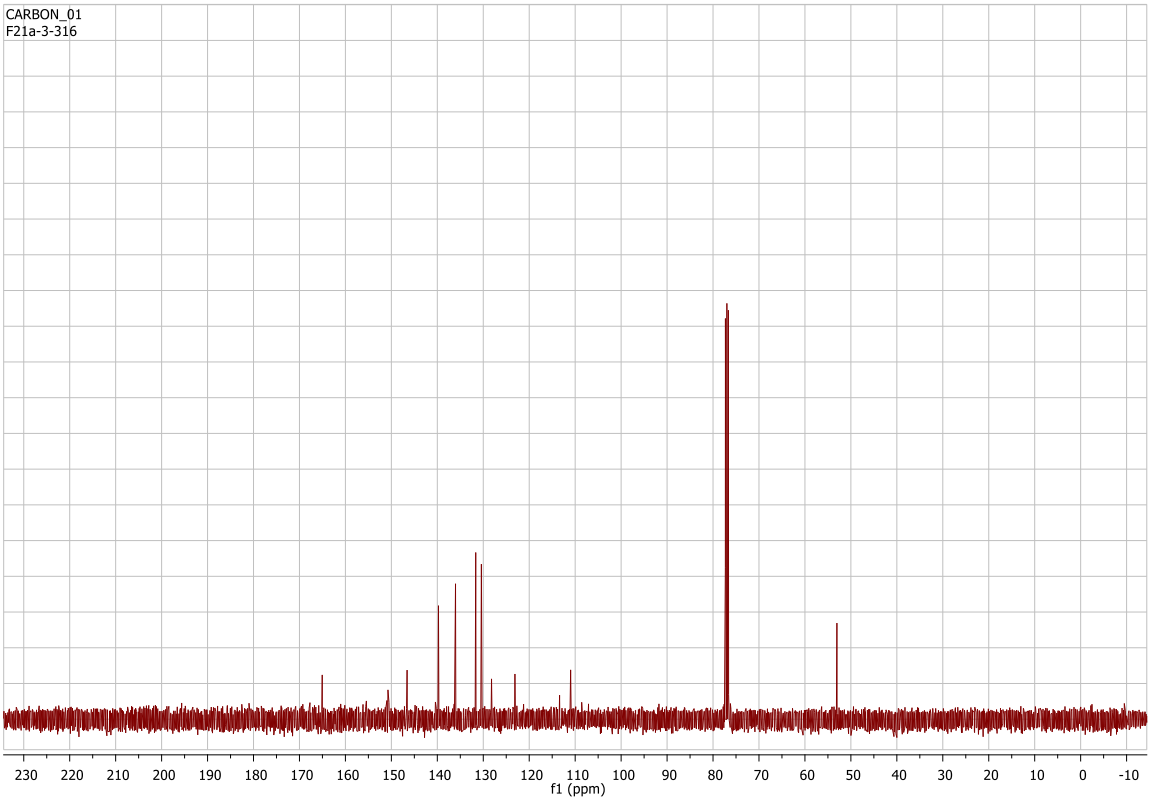

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

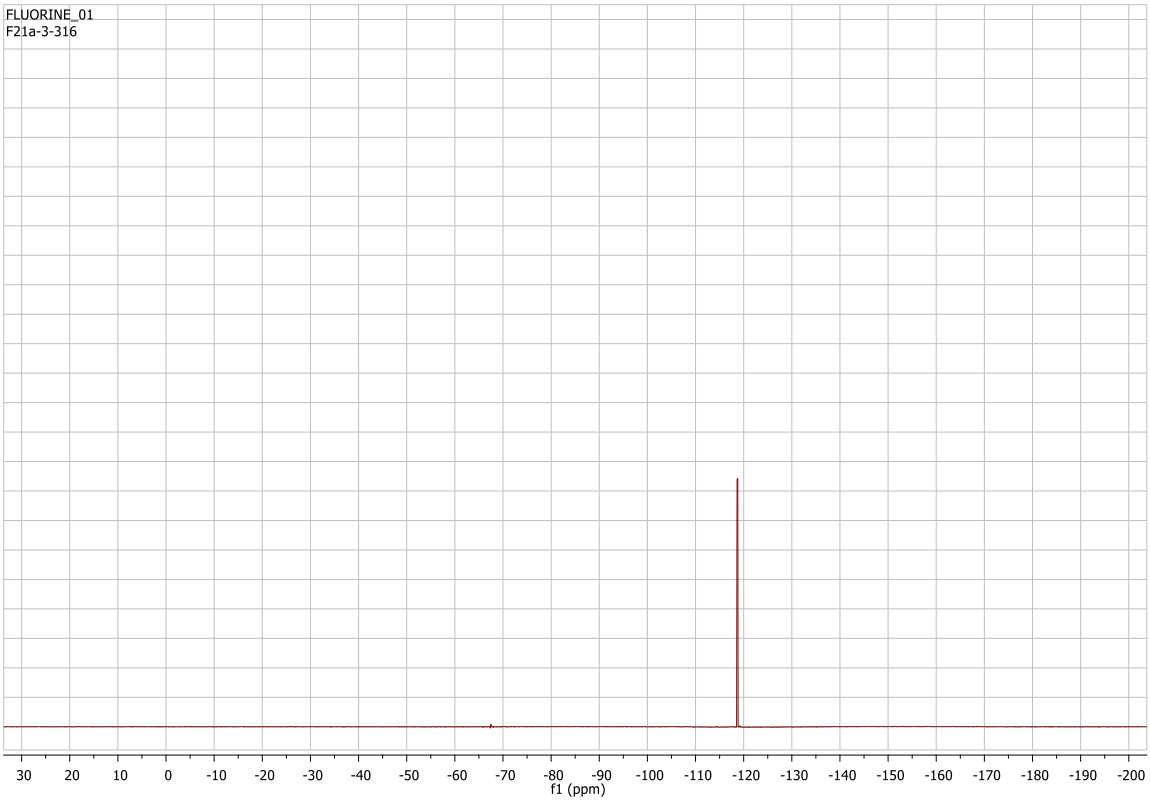

PROTON_01
86b-5k-295-CF2
O
O
N
CO2Et
CF2H
9f
0.95
1.36
0.93
1.97
2.03
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

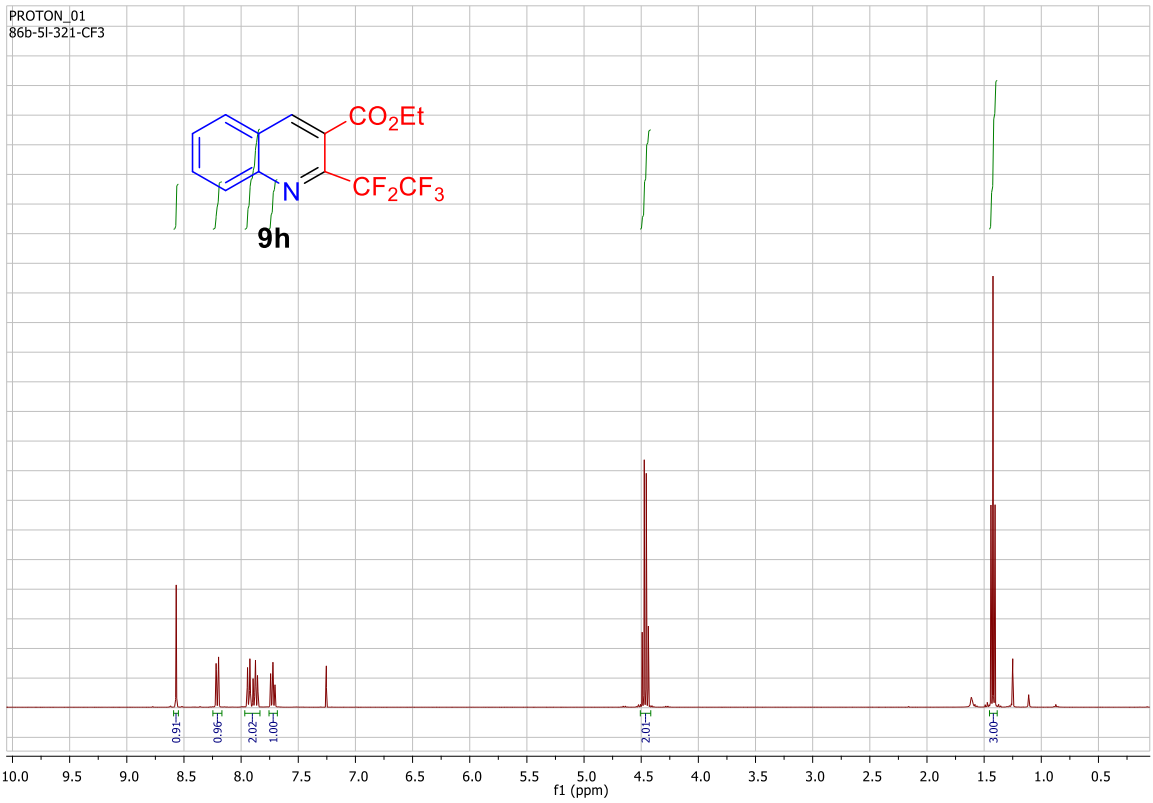

CARBON_01
86b-5k-295-CF2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

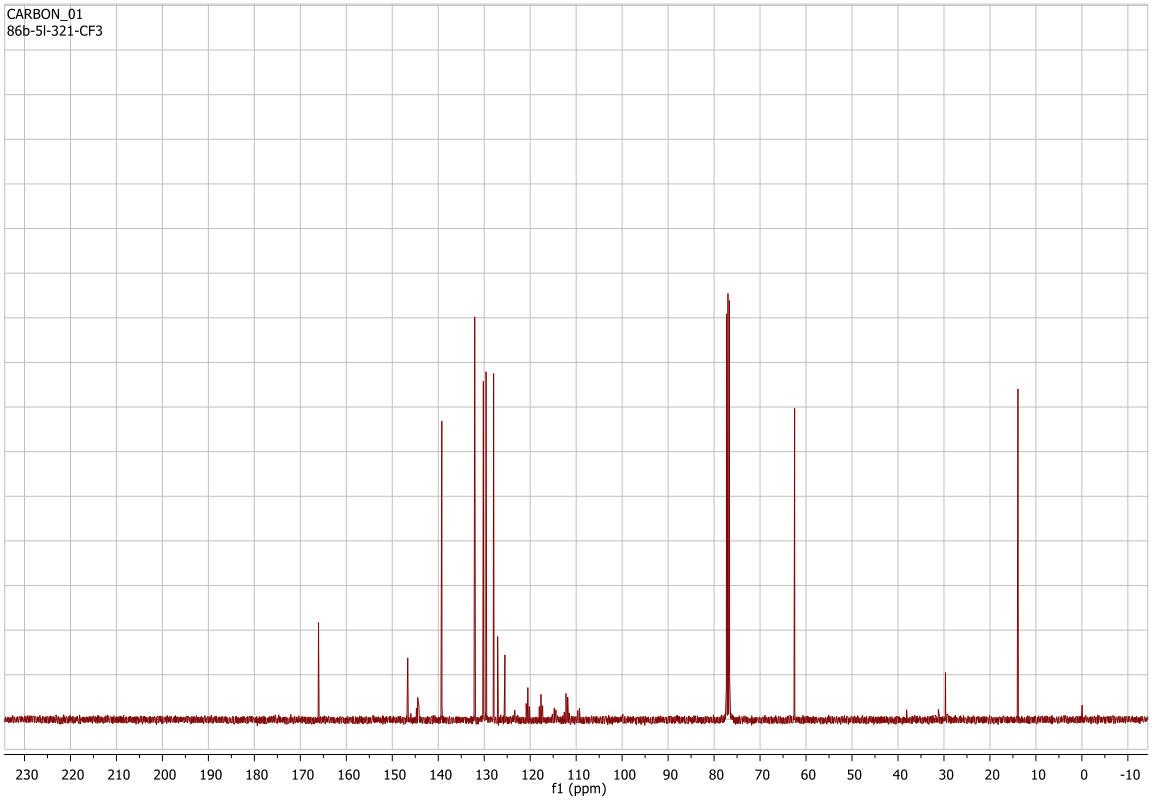

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

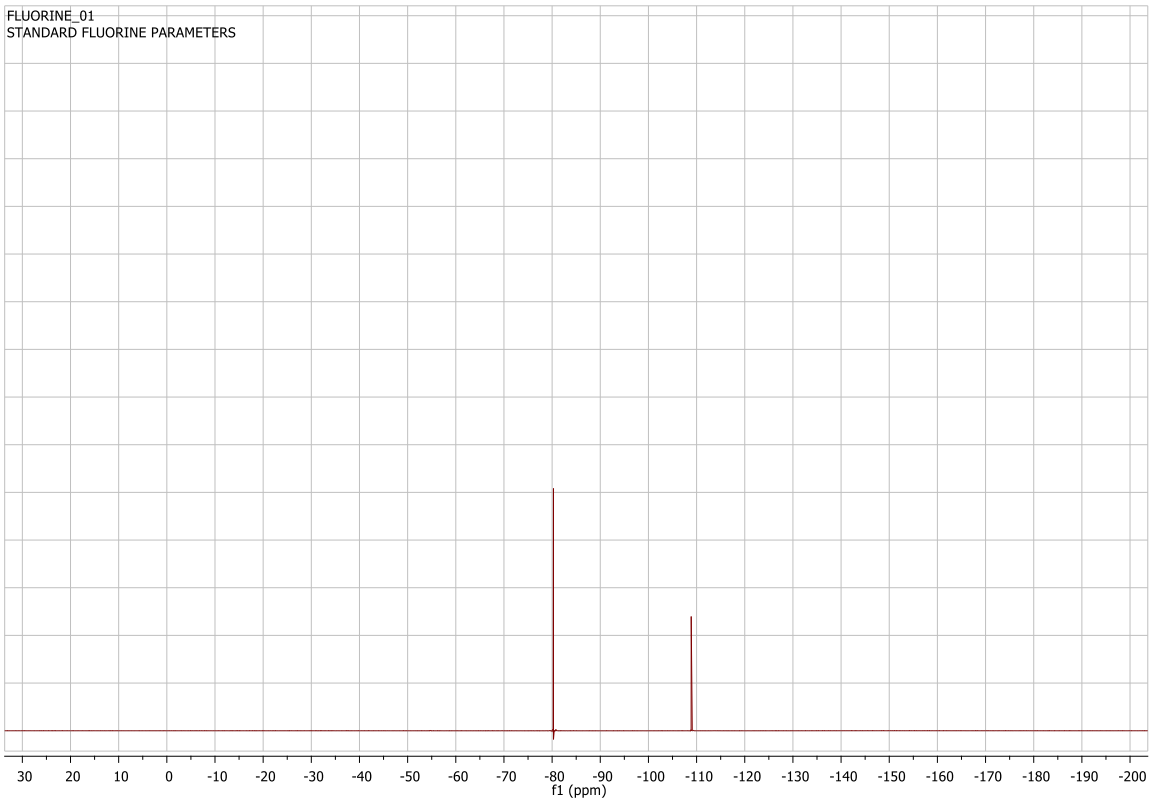

PROTON_01
F21a-3-316
Br
CO2Et
CF2H
N
9g
0.97
1.96
0.99
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

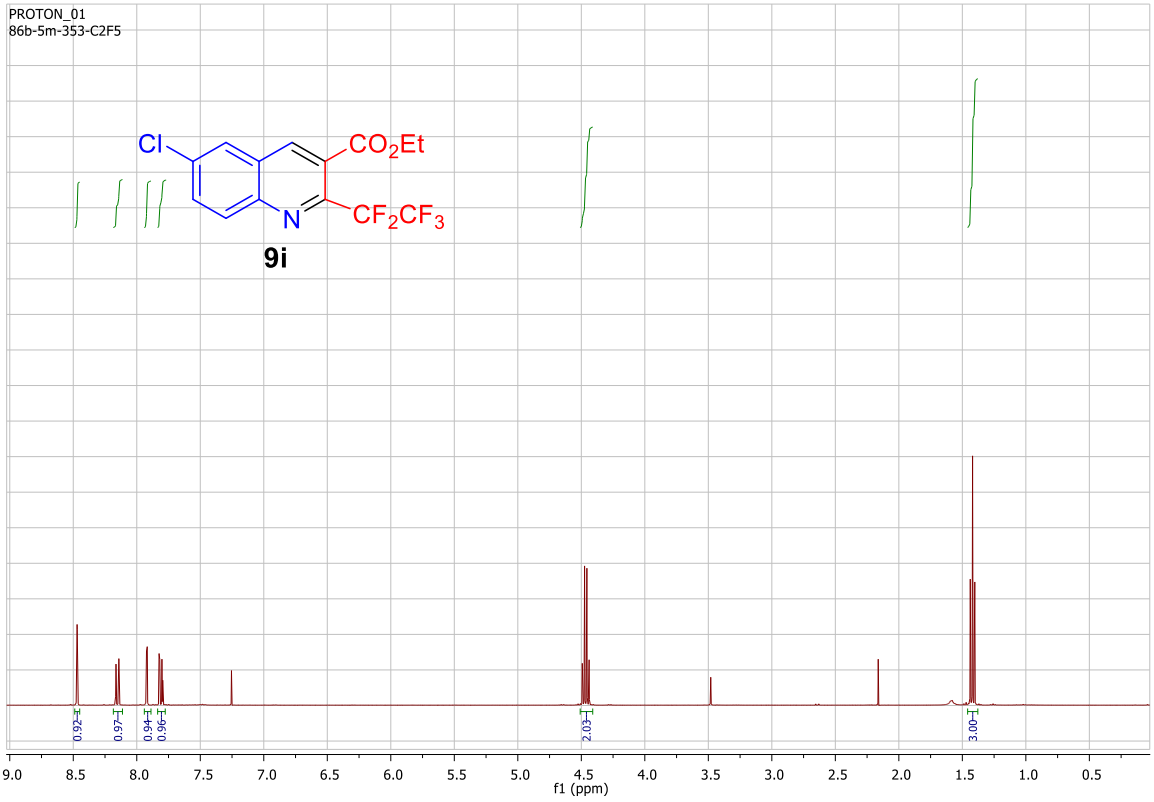

CARBON_01
F21a-3-316
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

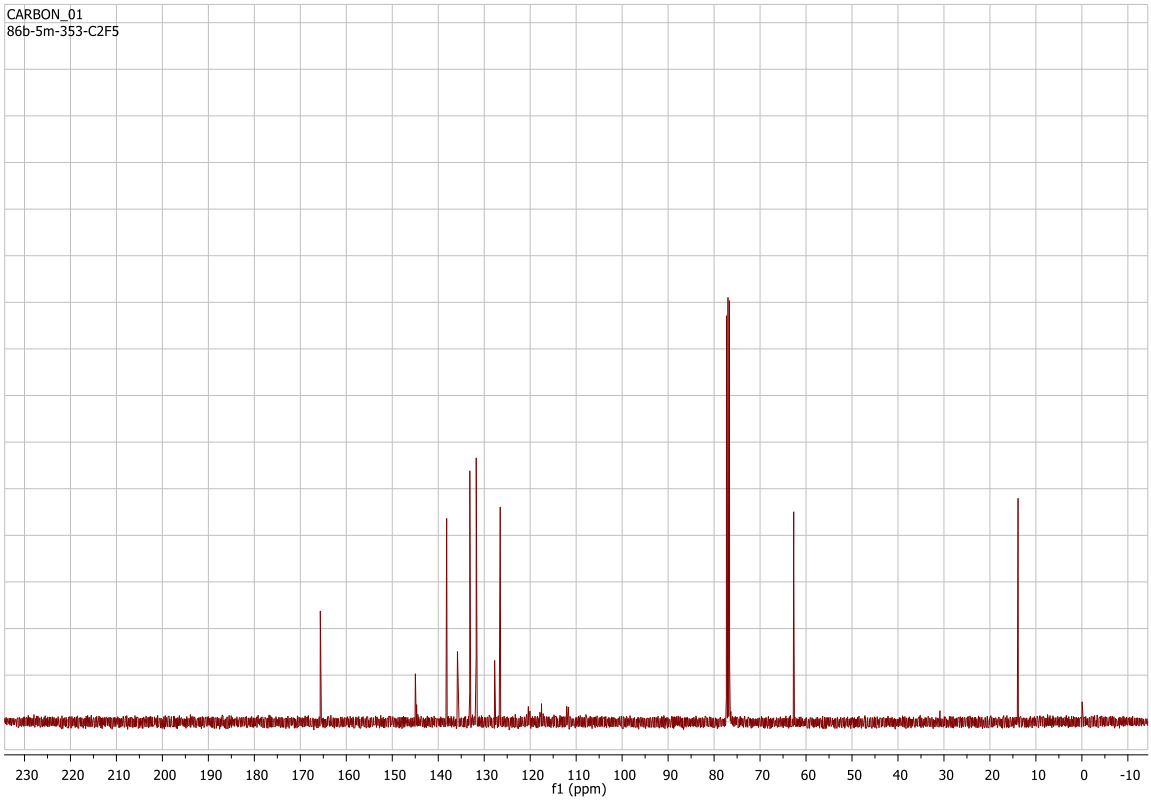

FLUORINE_01
F21a-3-316
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

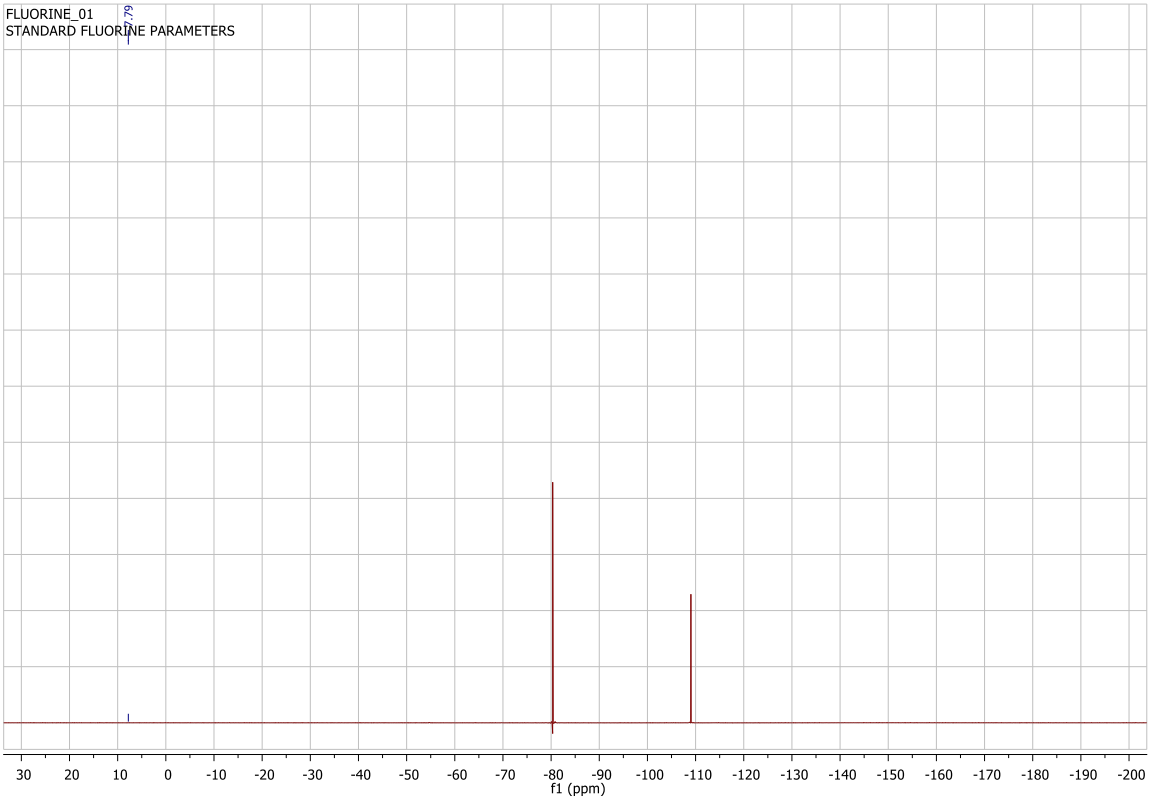

PROTON_01
86b-5l-321-CF3
$CO_2Et$
$CF_2CF_3$
N
9h
0.91
0.96
2.02
1.00
2.01
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

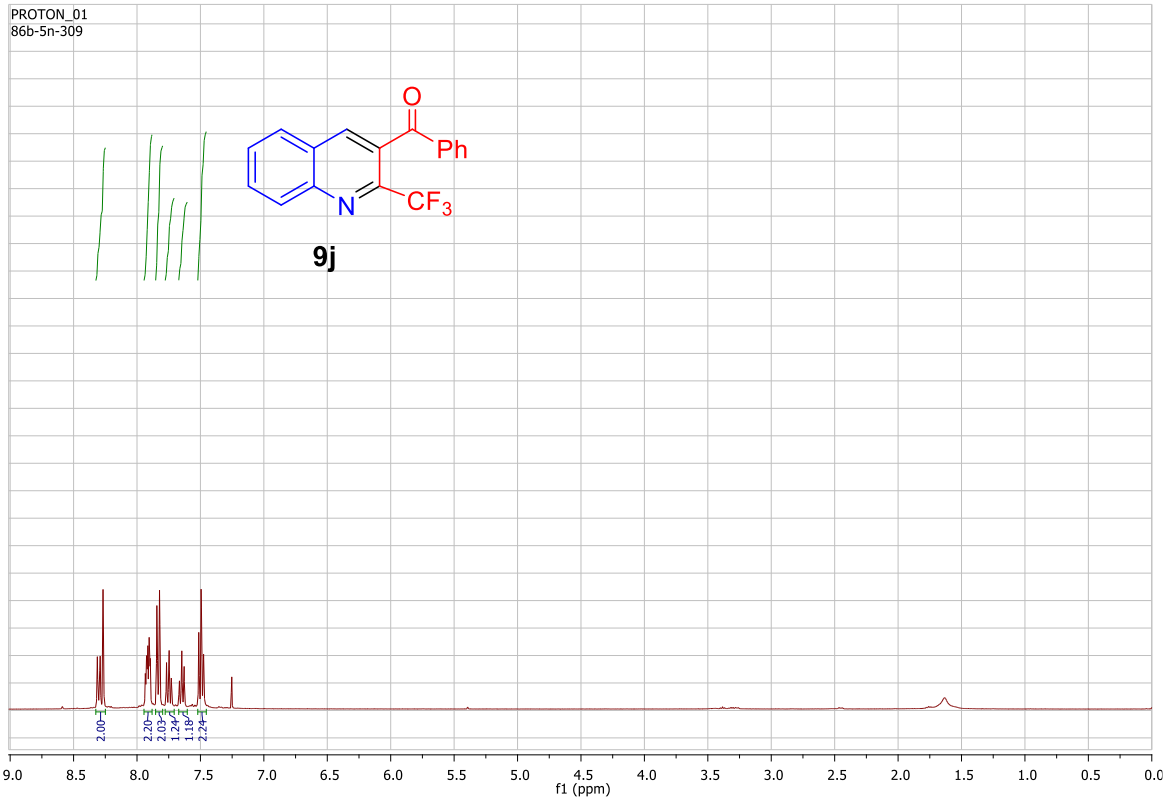

CARBON_01
86b-5l-321-CF3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

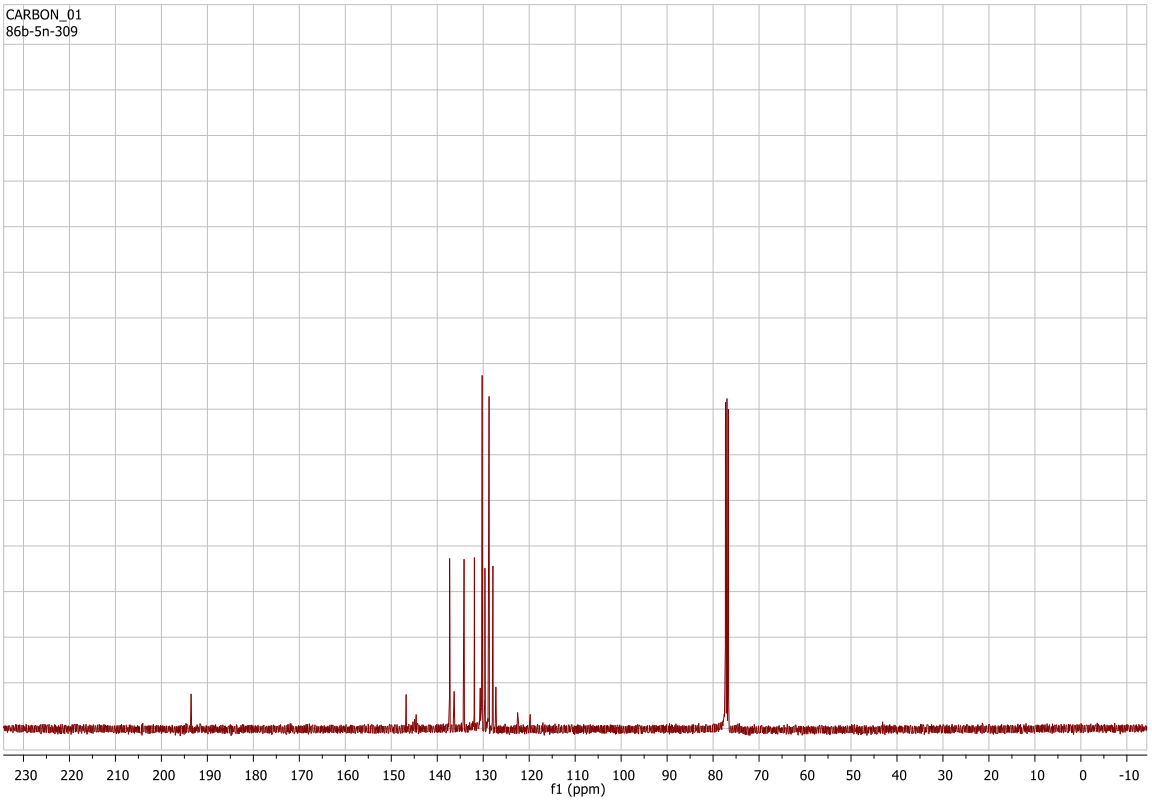

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

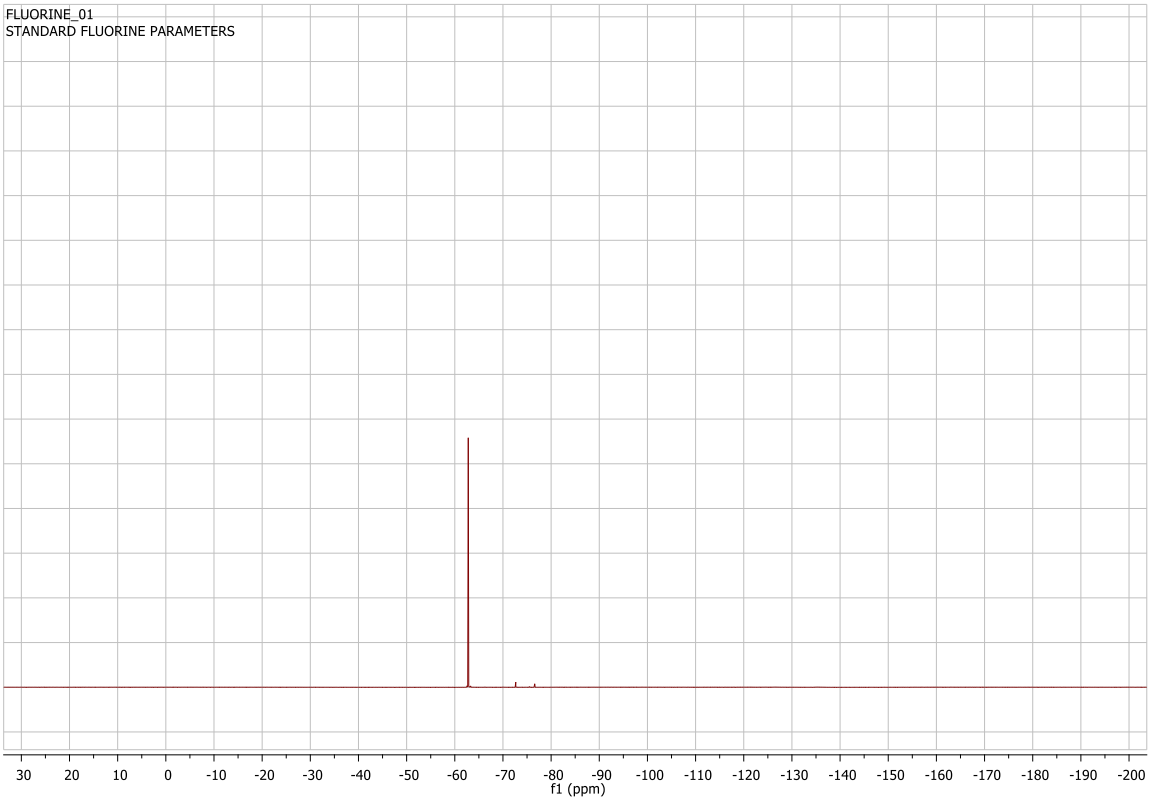

PROTON_01
86b-5m-353-C2F5
Cl
$CO_2Et$
N
$CF_2CF_3$
9i
0.92
0.97
0.94
0.96
2.03
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

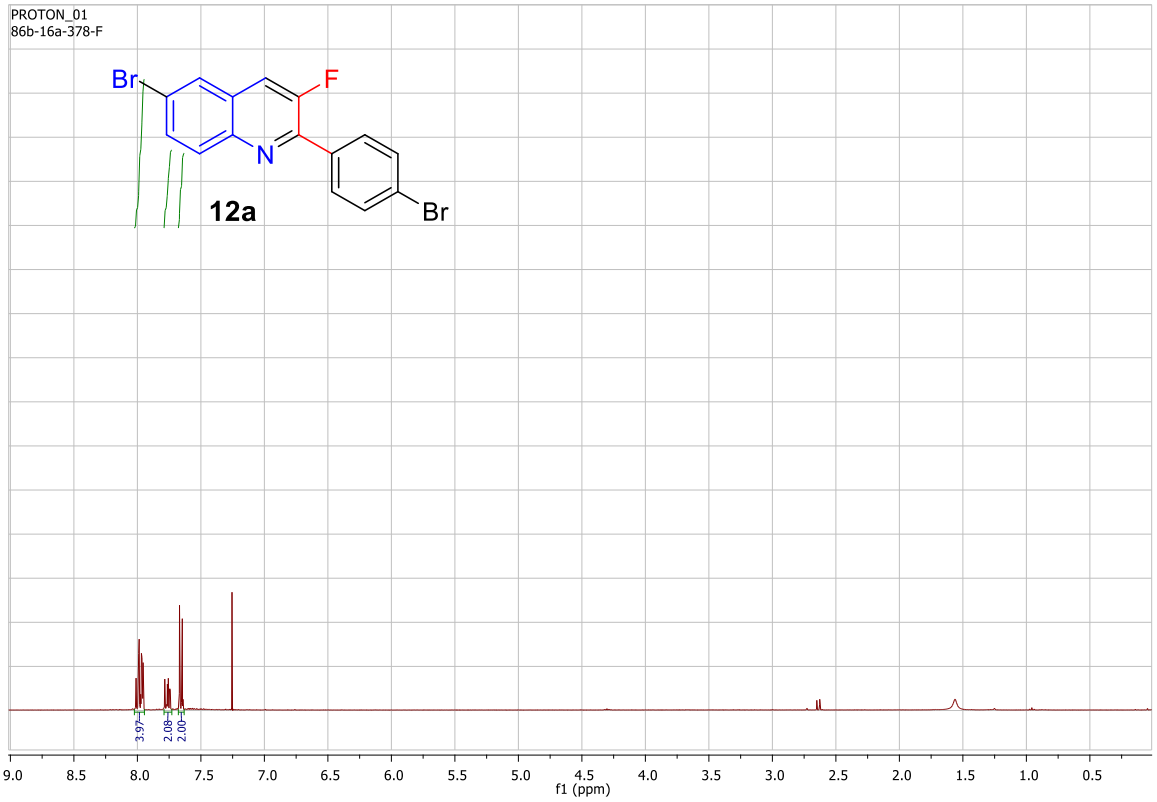

CARBON_01
86b-5m-353-C2F5
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

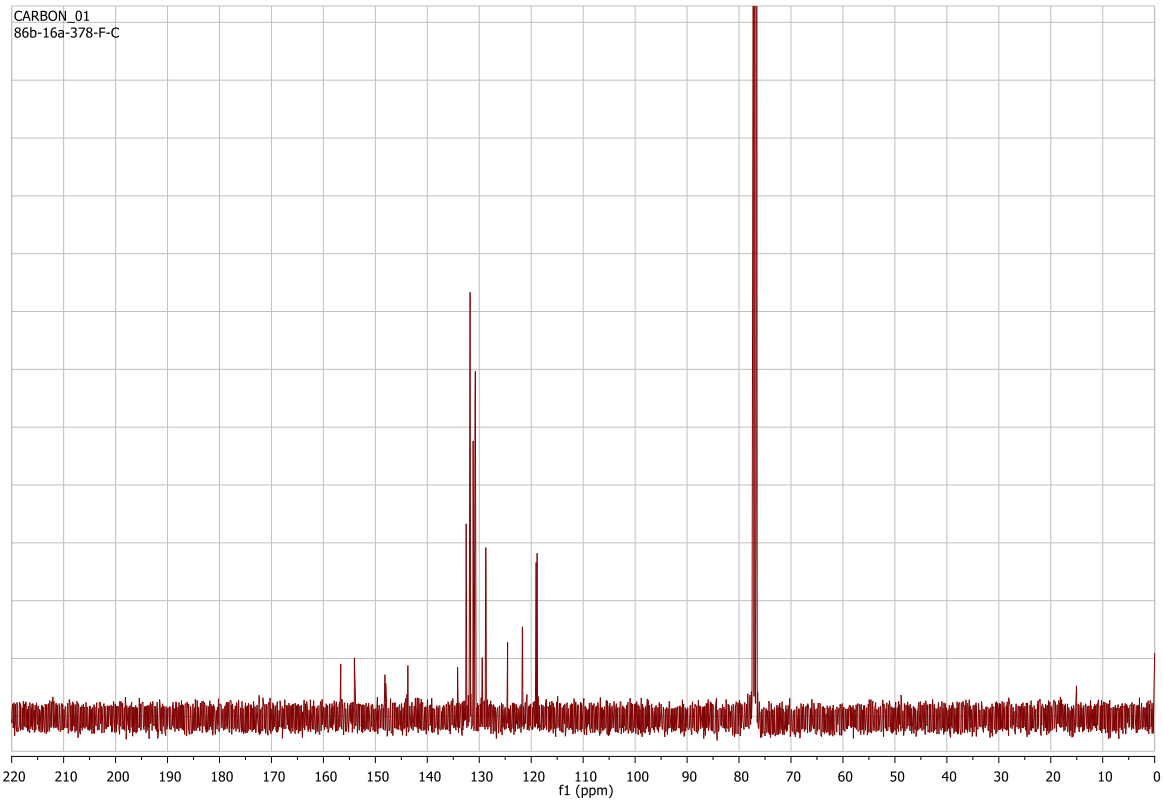

FLUORINE_01
STANDARD FLUORINE PARAMETERS
-77.79
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

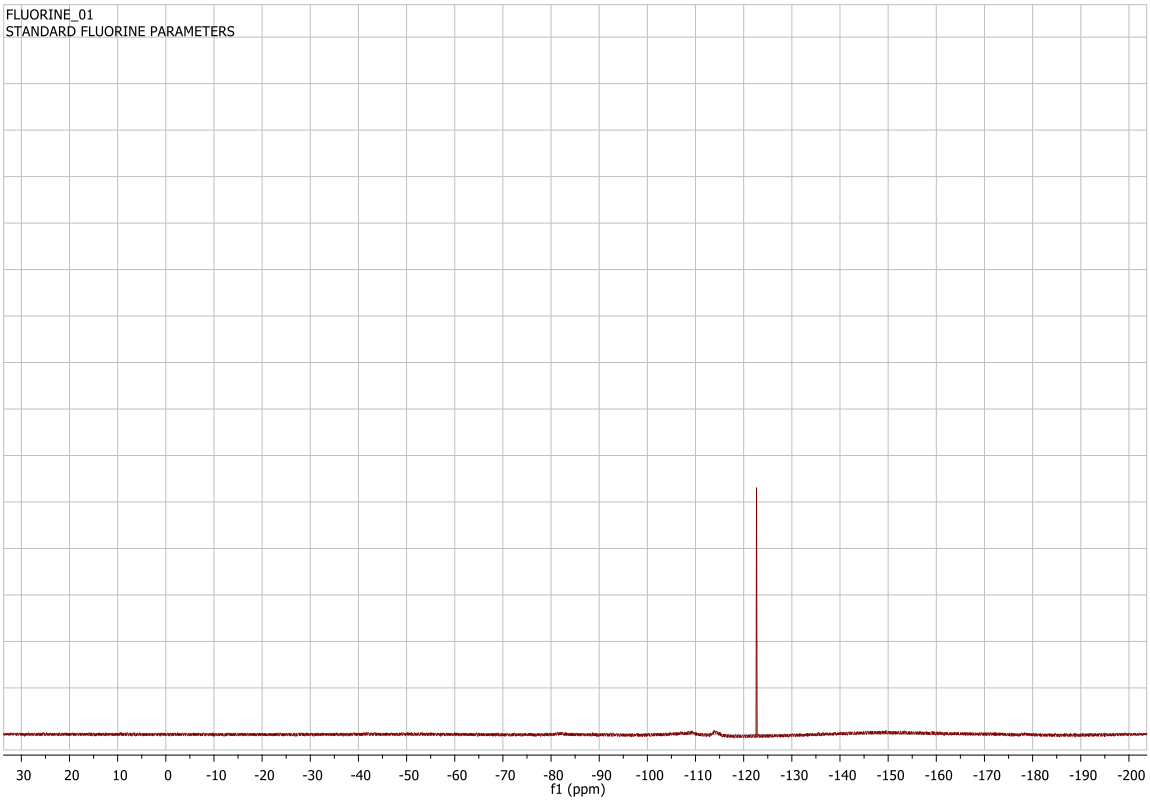

PROTON_01
86b-5n-309
O
Ph
N
CF3
9j
2.00
2.20
2.03
1.24
1.18
2.24
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

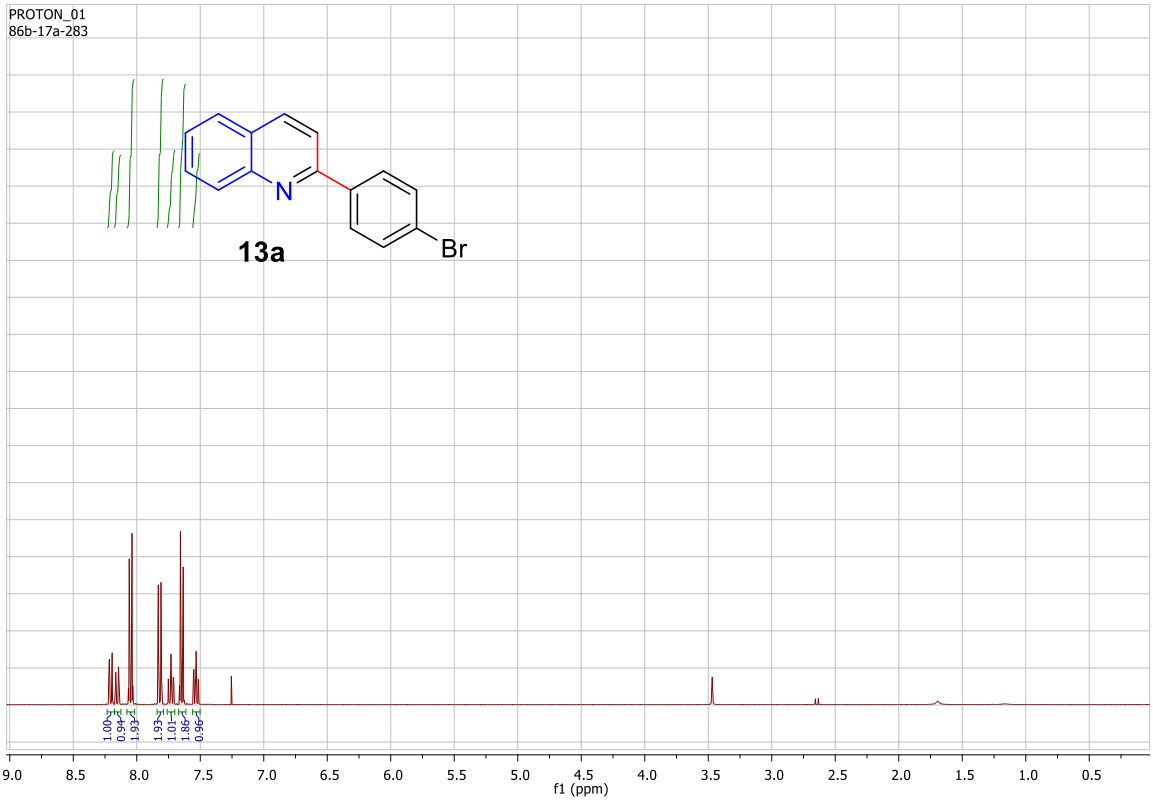

CARBON_01
86b-5n-309
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

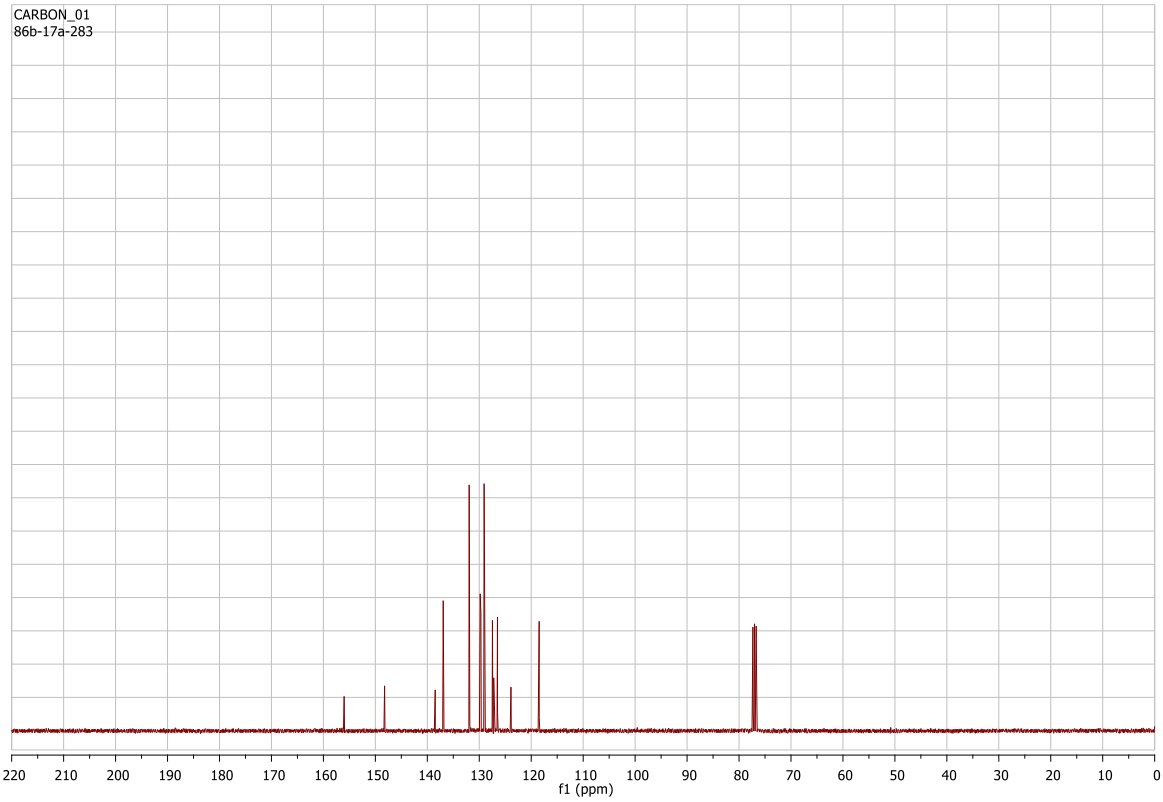

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

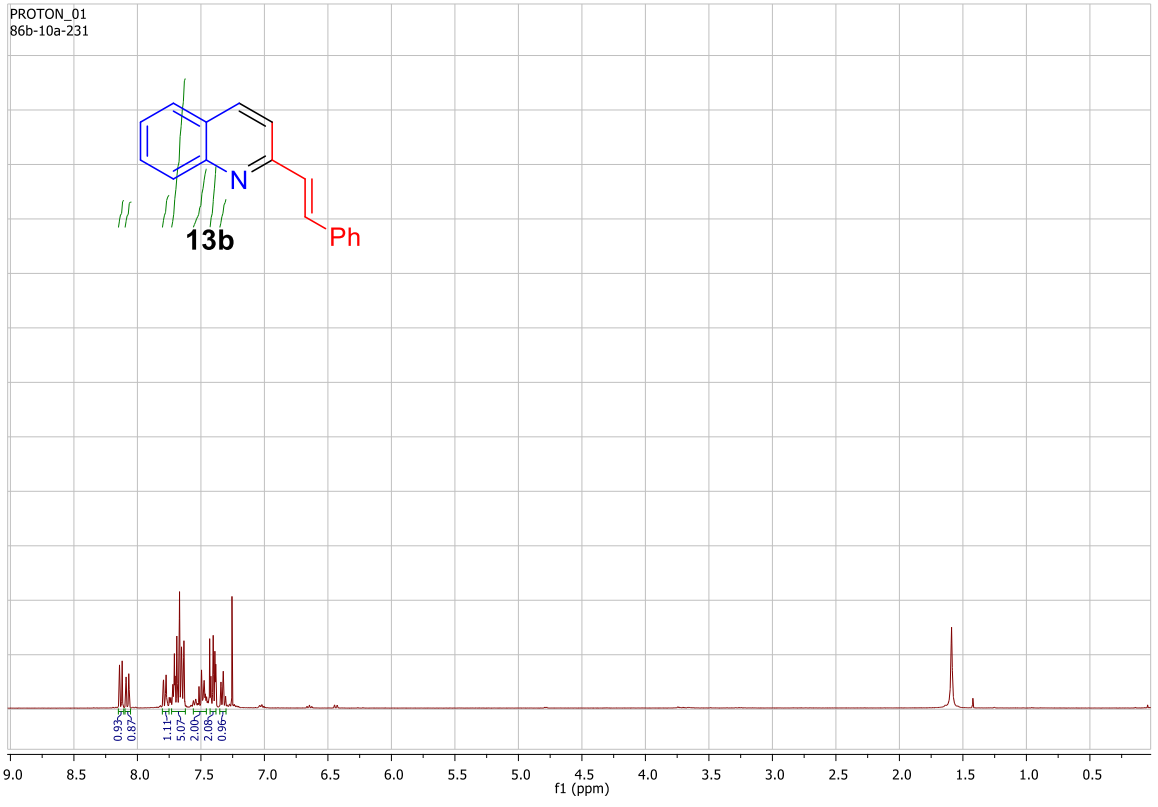

PROTON_01
86b-16a-378-F
Br
F
N
12a
Br
3.97
2.08
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

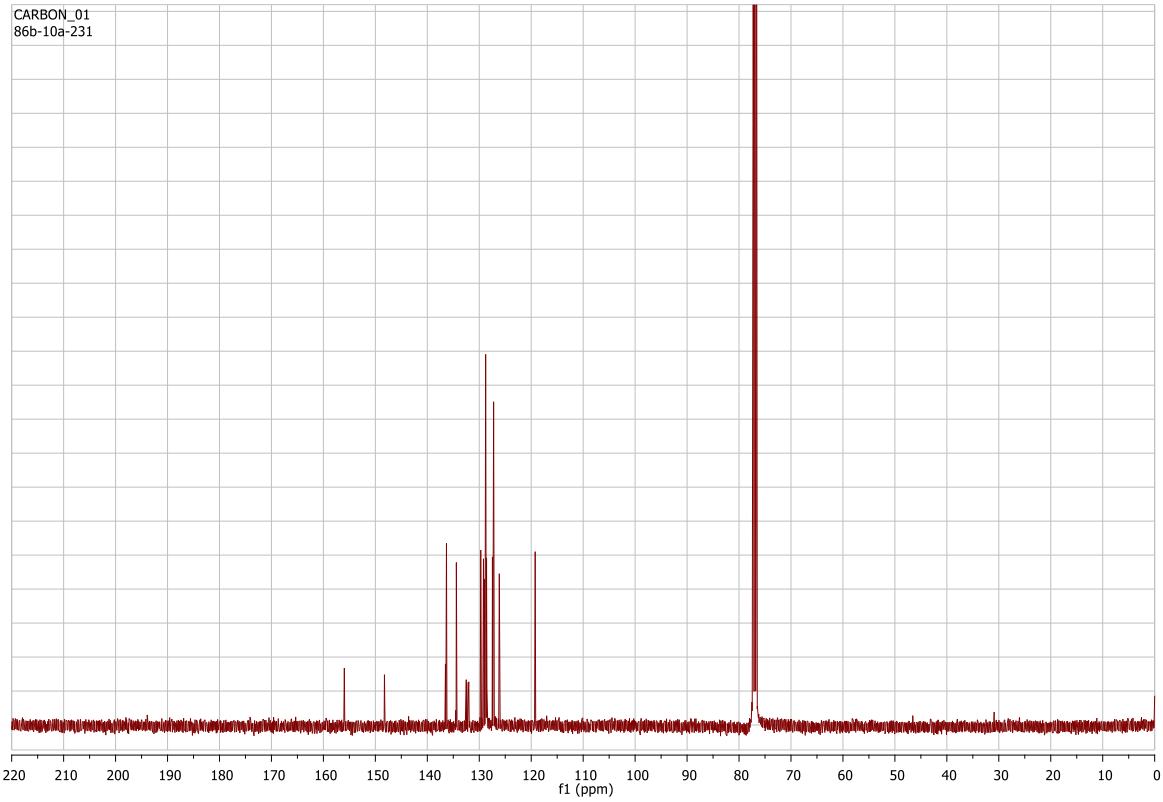

CARBON_01
86b-16a-378-F-C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

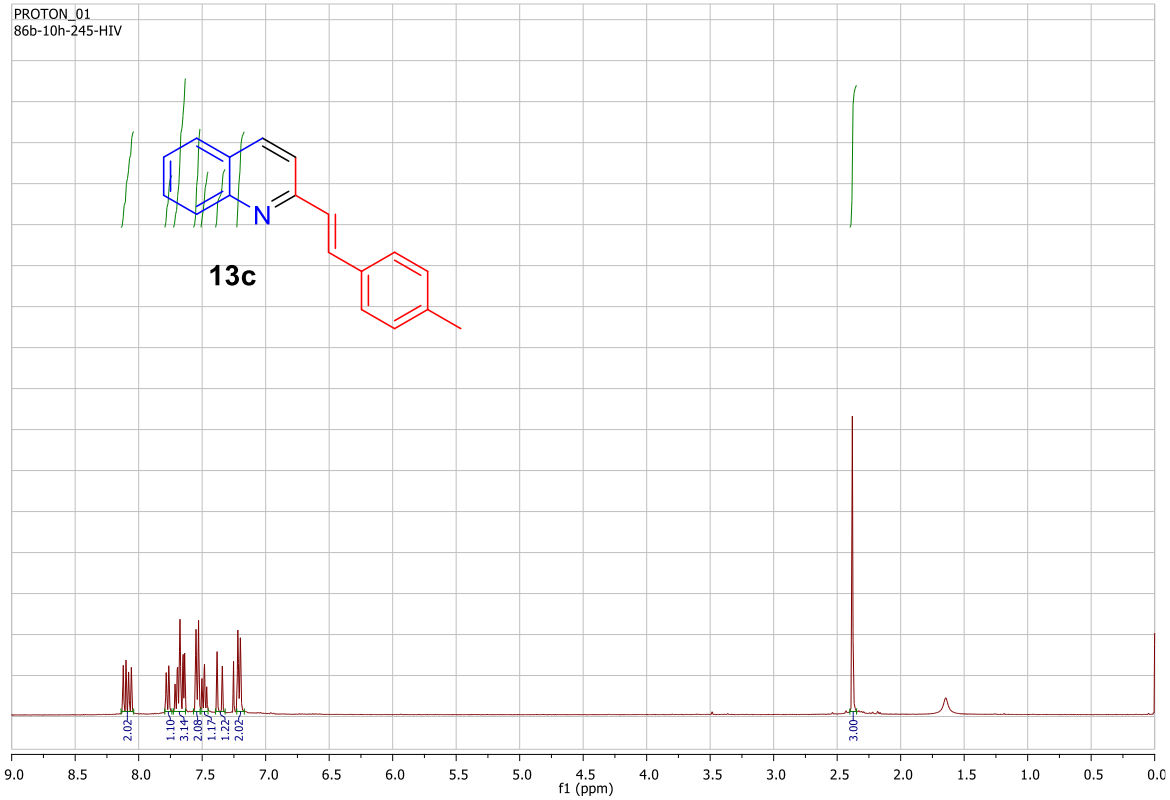

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

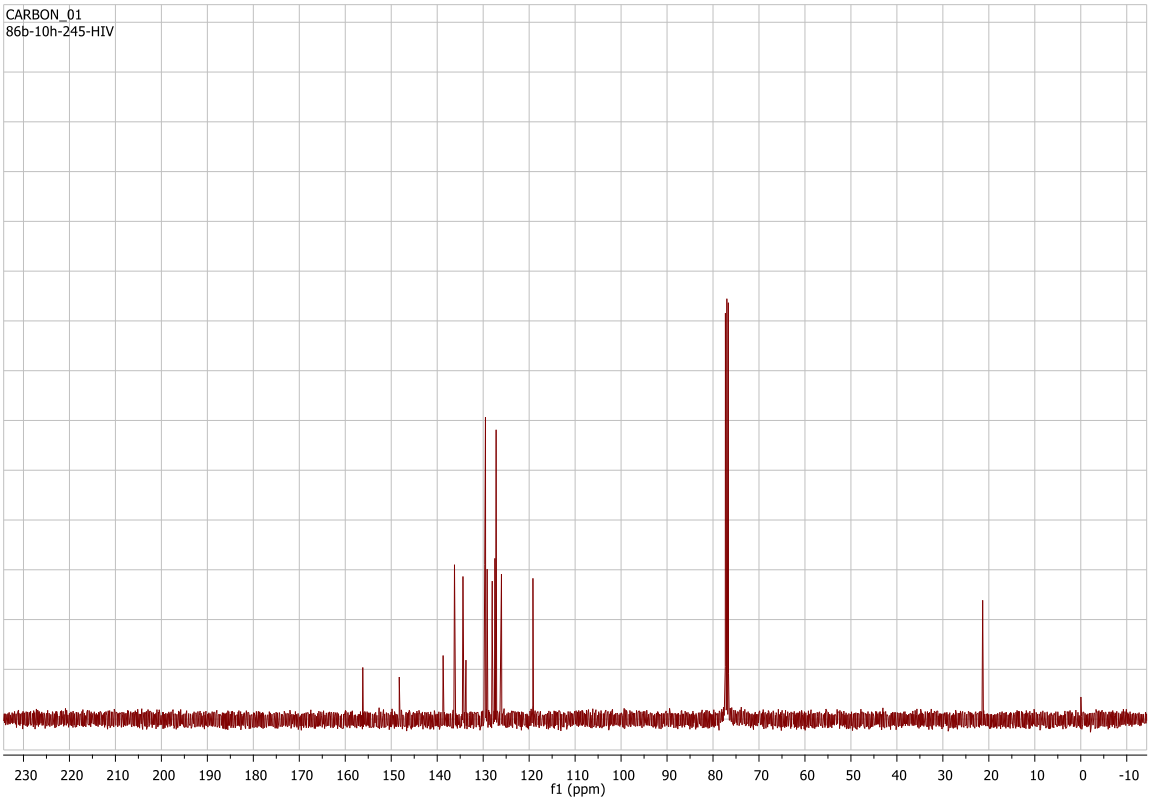

PROTON_01
86b-17a-283
N
Br
13a
1.00
0.94
1.93
1.93
1.01
1.86
0.96
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

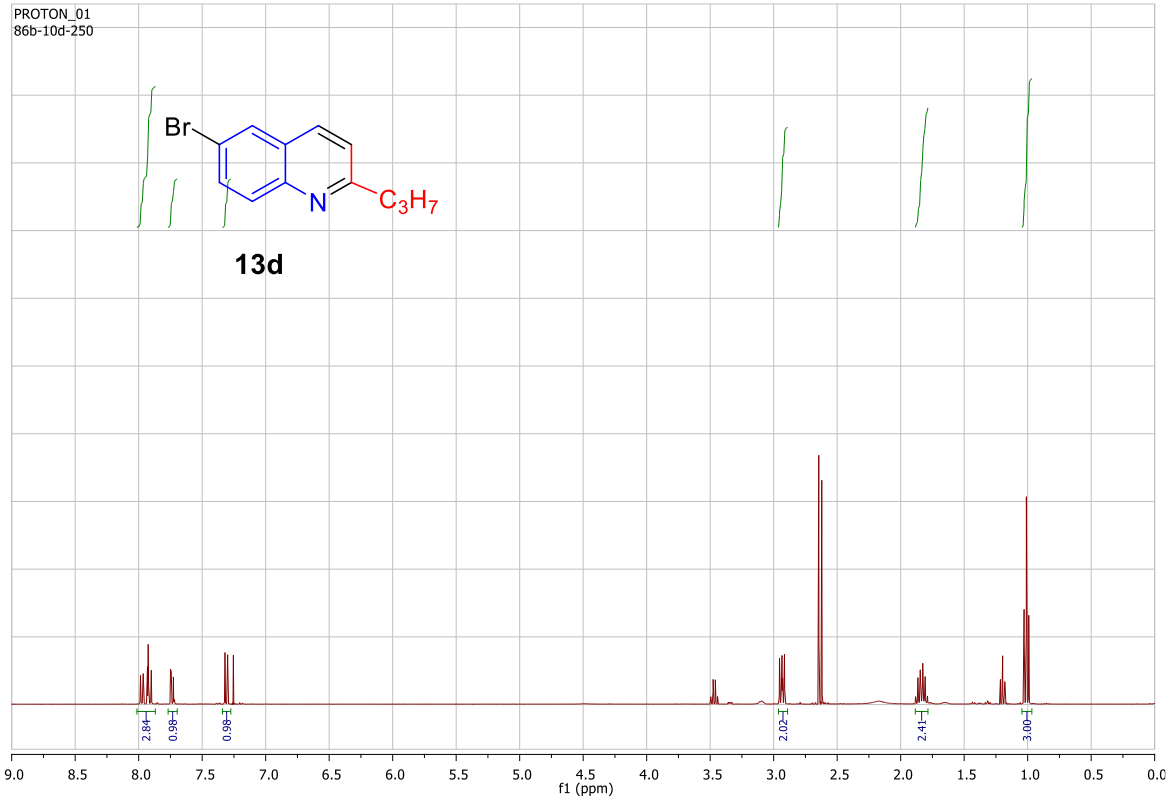

CARBON_01
86b-17a-283
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

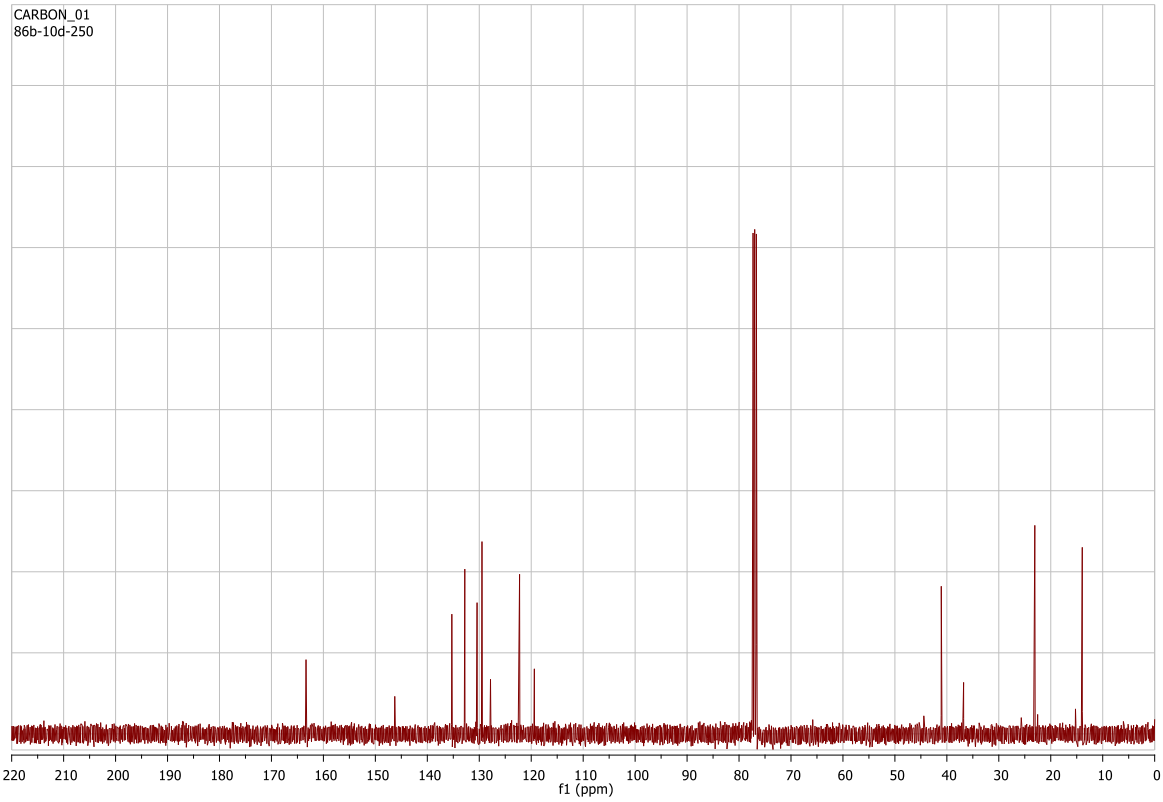

PROTON_01
86b-10a-231
N
Ph
13b
0.93
0.87
1.11
5.07
2.00
2.08
0.96
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

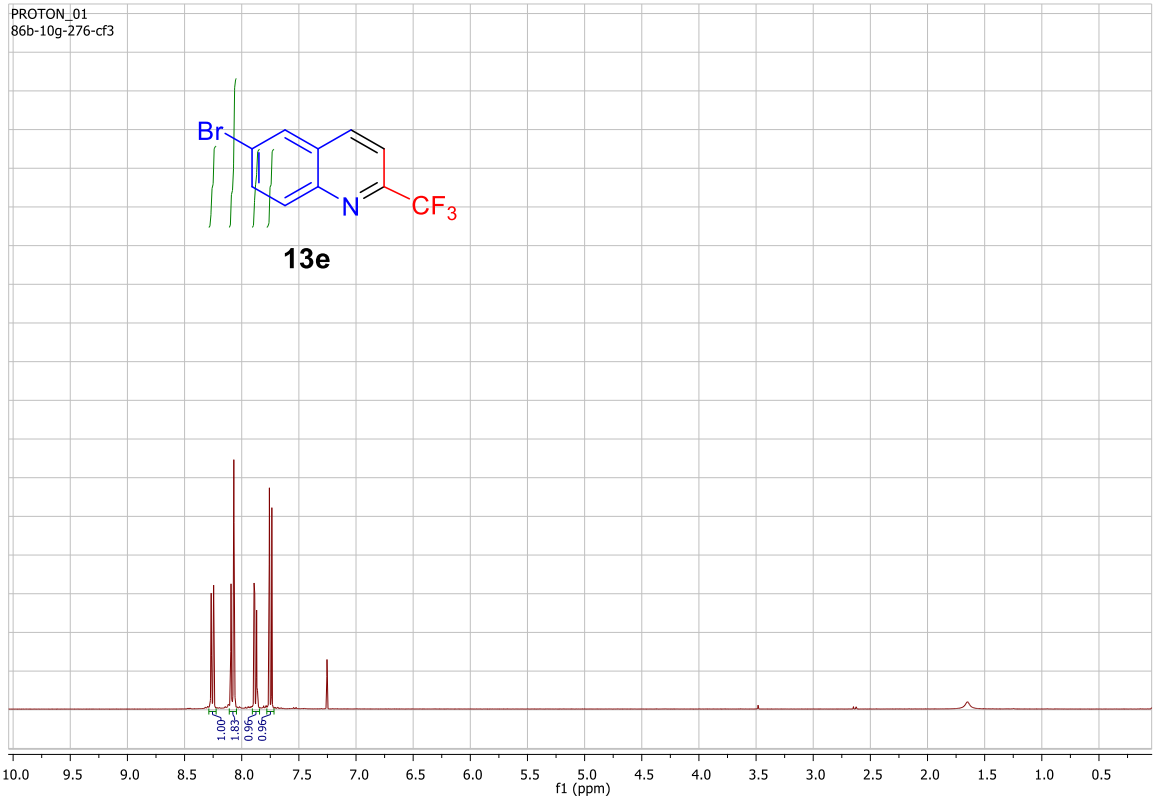

CARBON_01
86b-10a-231
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


PROTON_01
86b-10h-245-HIV
N
13c
2.02
1.10
3.14
2.08
1.17
1.22
2.02
3.00
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)

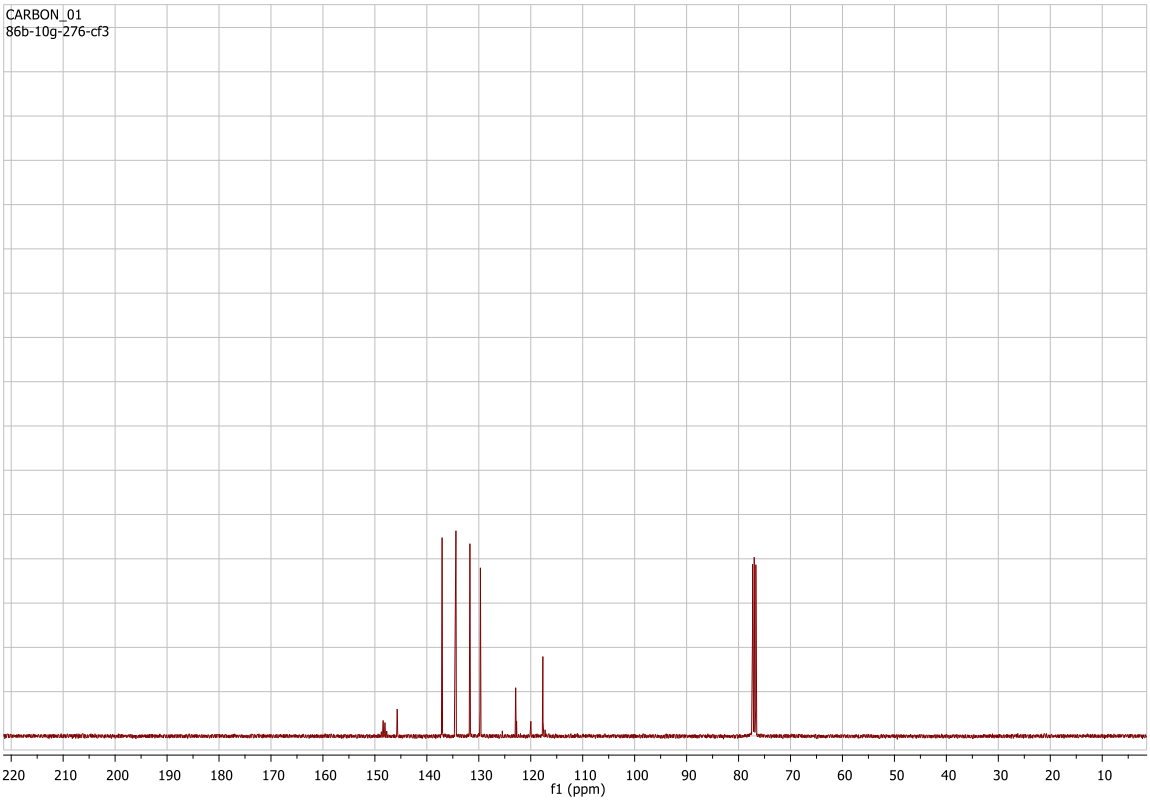

CARBON_01
86b-10h-245-HIV
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

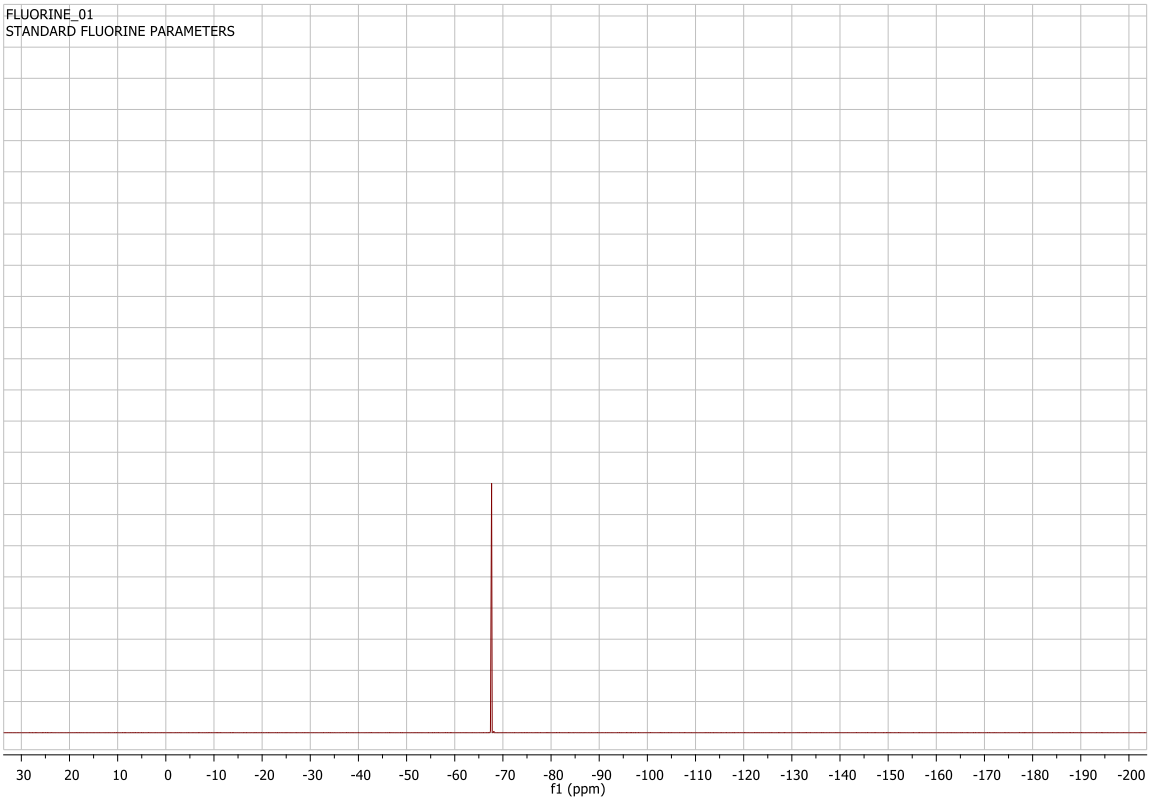

PROTON_01
86b-10d-250
Br
N
$C_3H_7$
13d
2.84
0.98
0.98
2.02
2.41
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

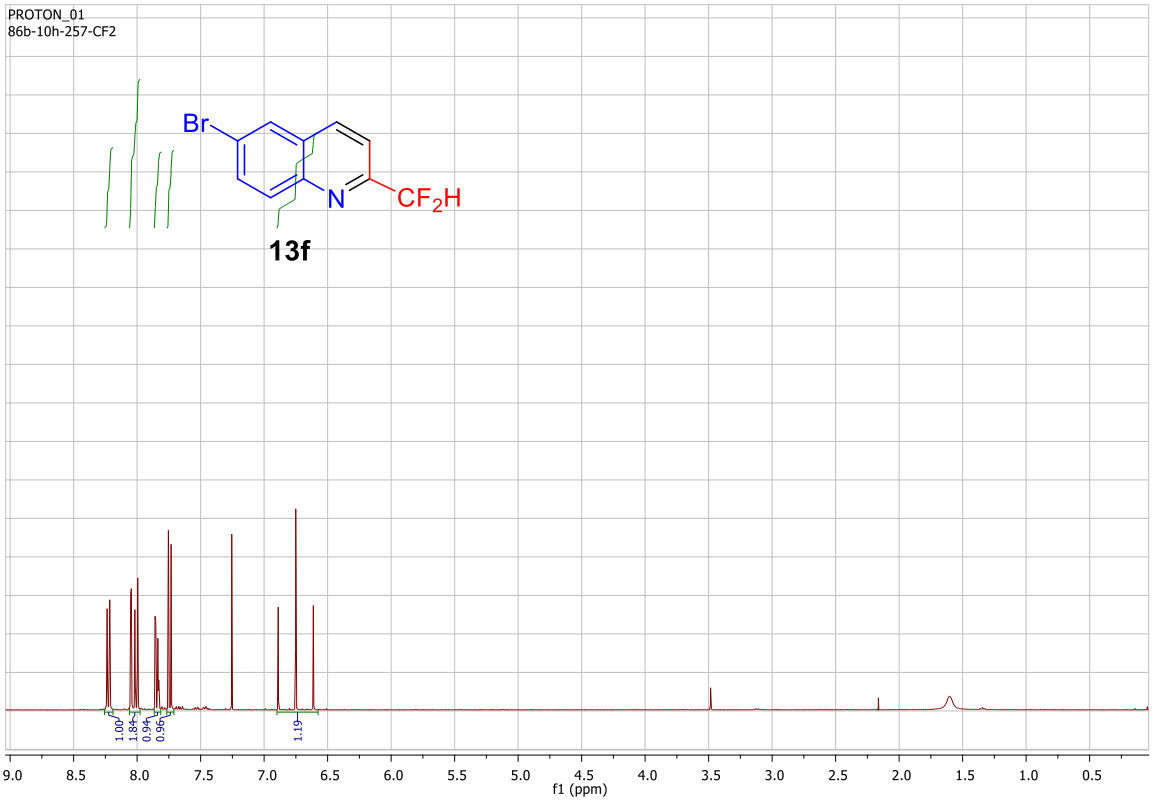

CARBON_01
86b-10d-250
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

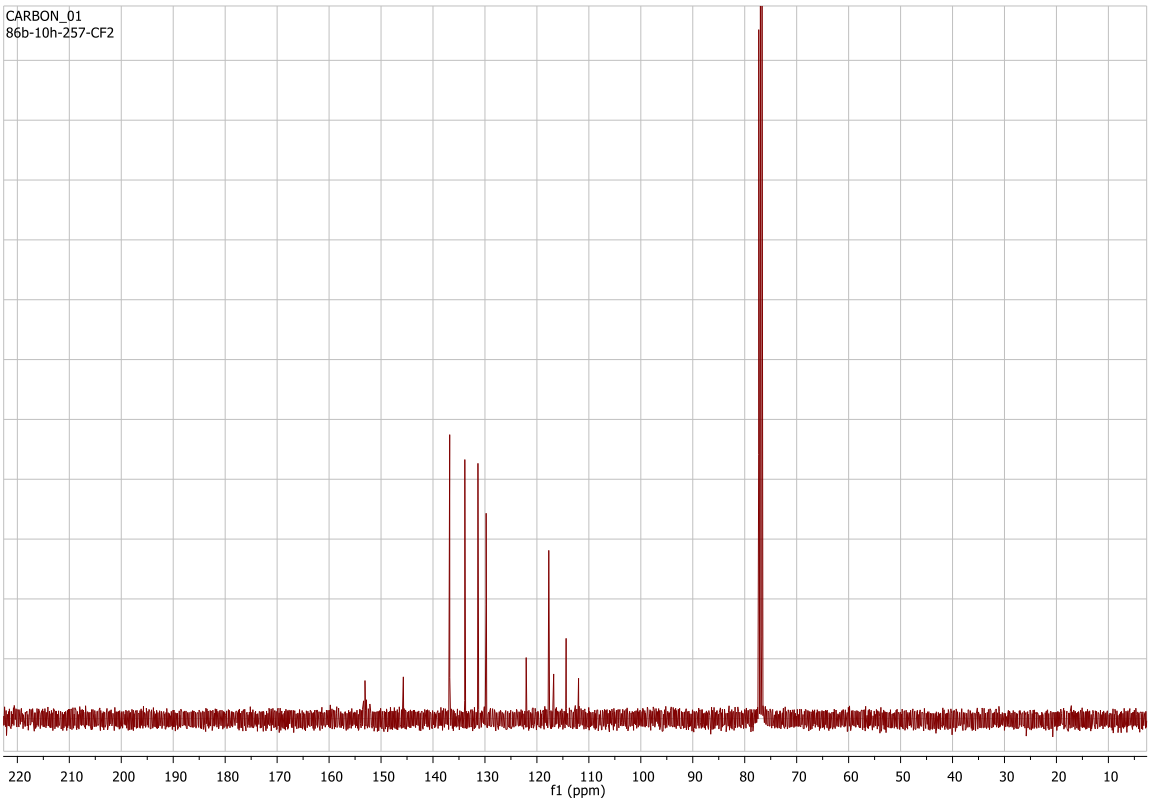

PROTON_01
86b-10g-276-cf3
Br
N
CF3
1.00
1.83
0.96
0.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

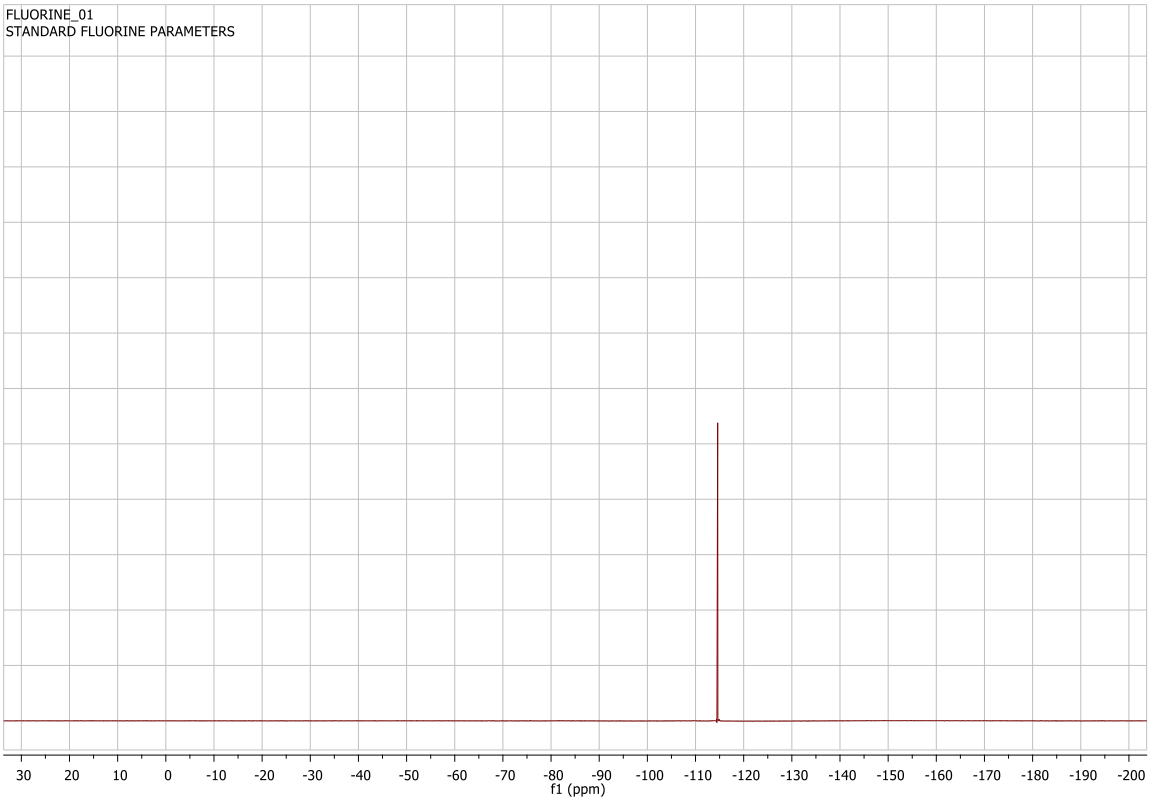
**13e**

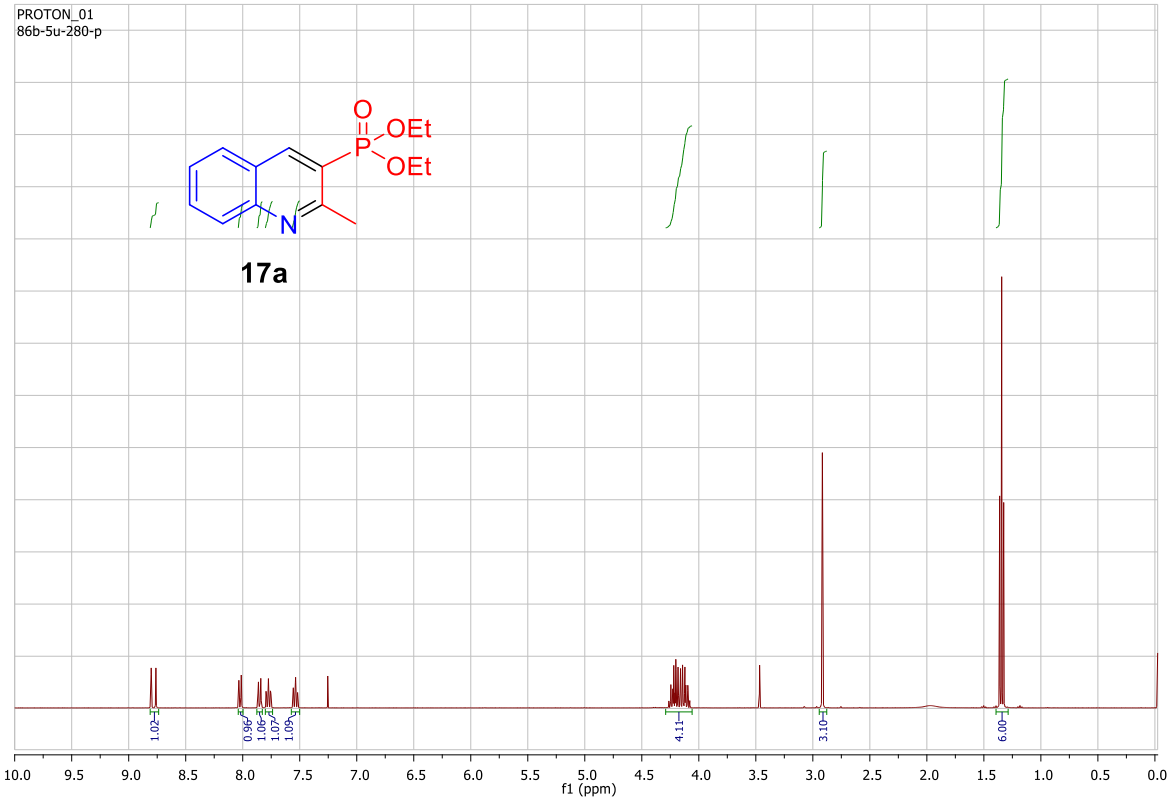

CARBON_01
86b-10g-276-cf3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

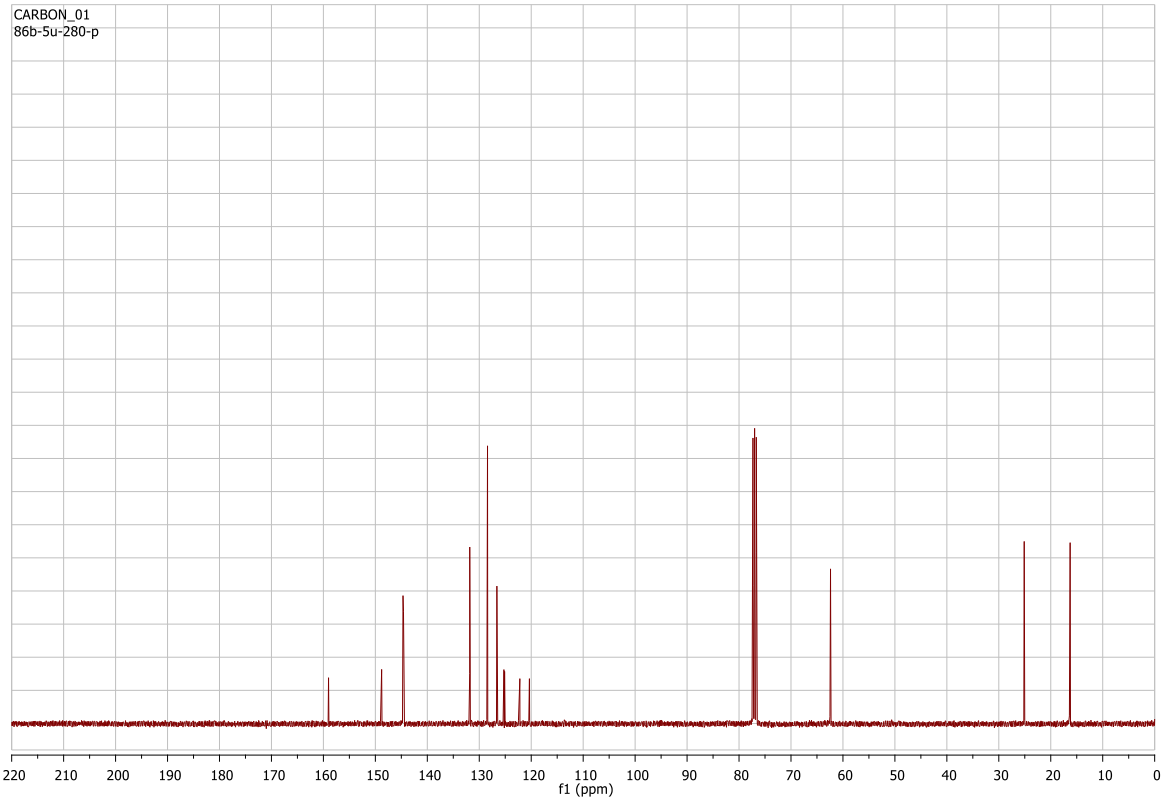

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

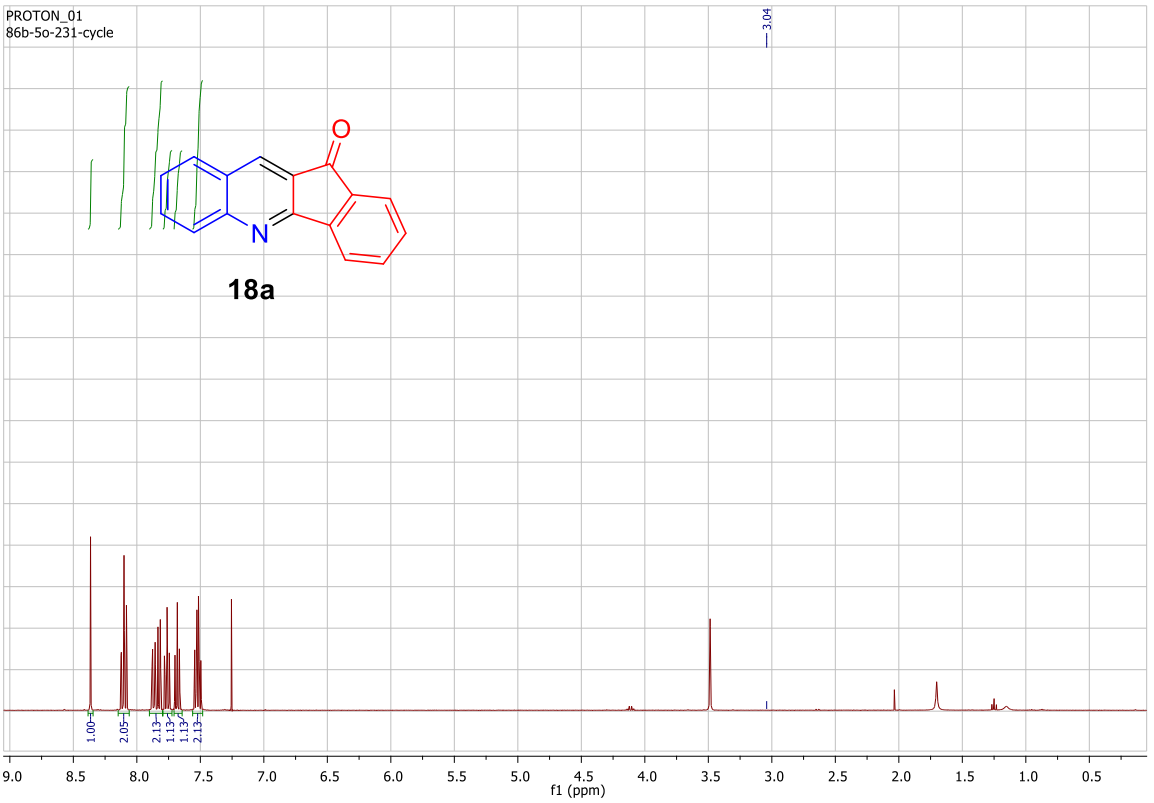

PROTON_01
86b-10h-257-CF2
Br
N
CF2H
13f
1.00
1.84
0.94
0.96
1.19
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

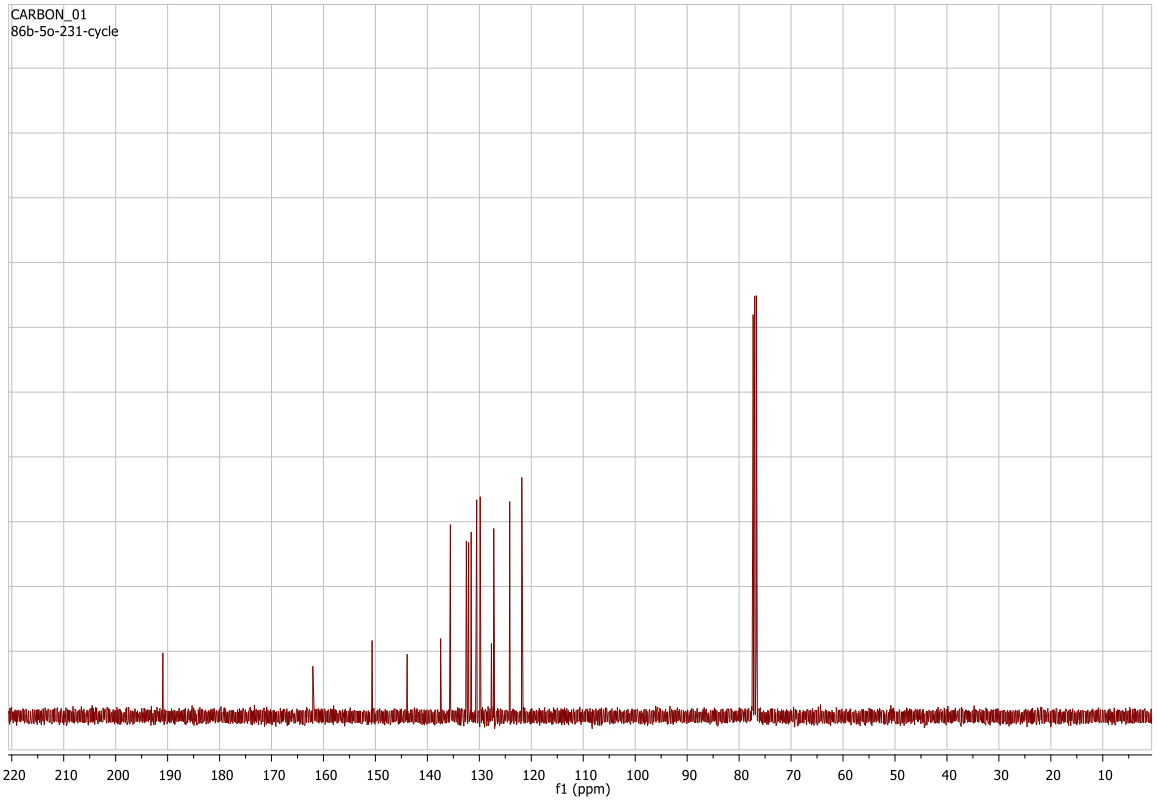

CARBON_01
86b-10h-257-CF2
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

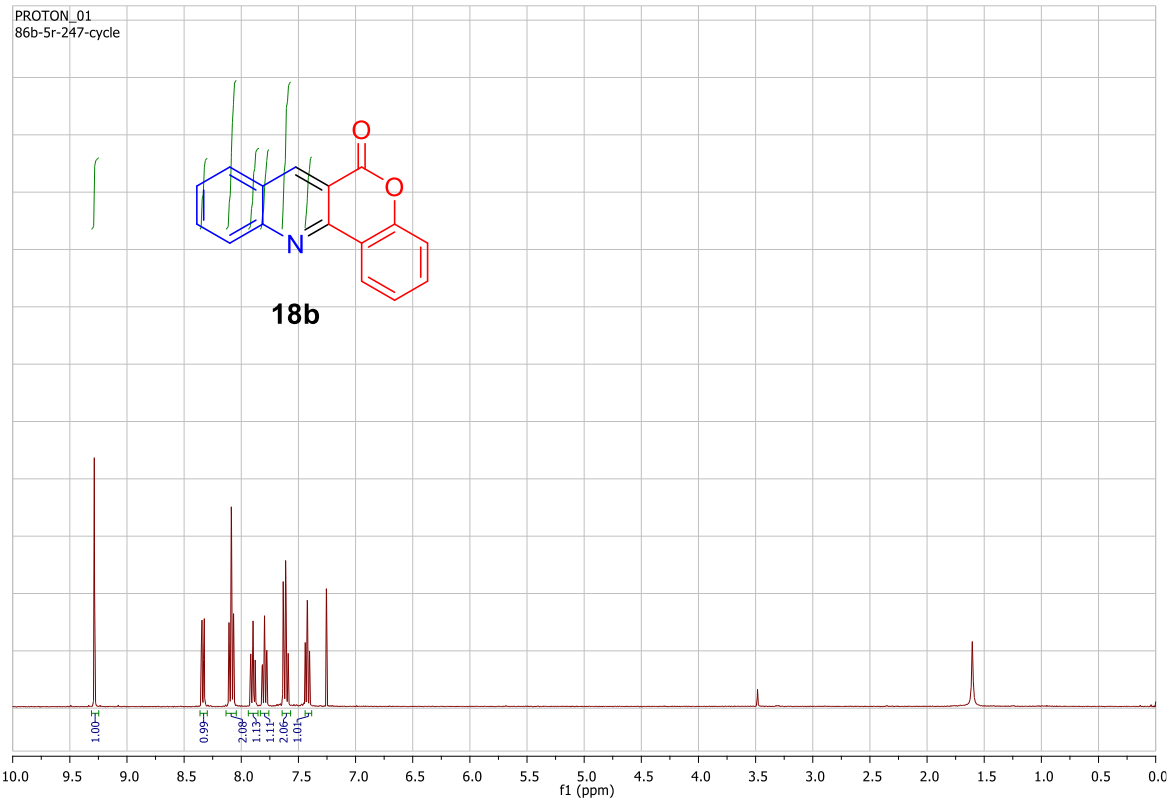

FLUORINE_01
STANDARD FLUORINE PARAMETERS
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

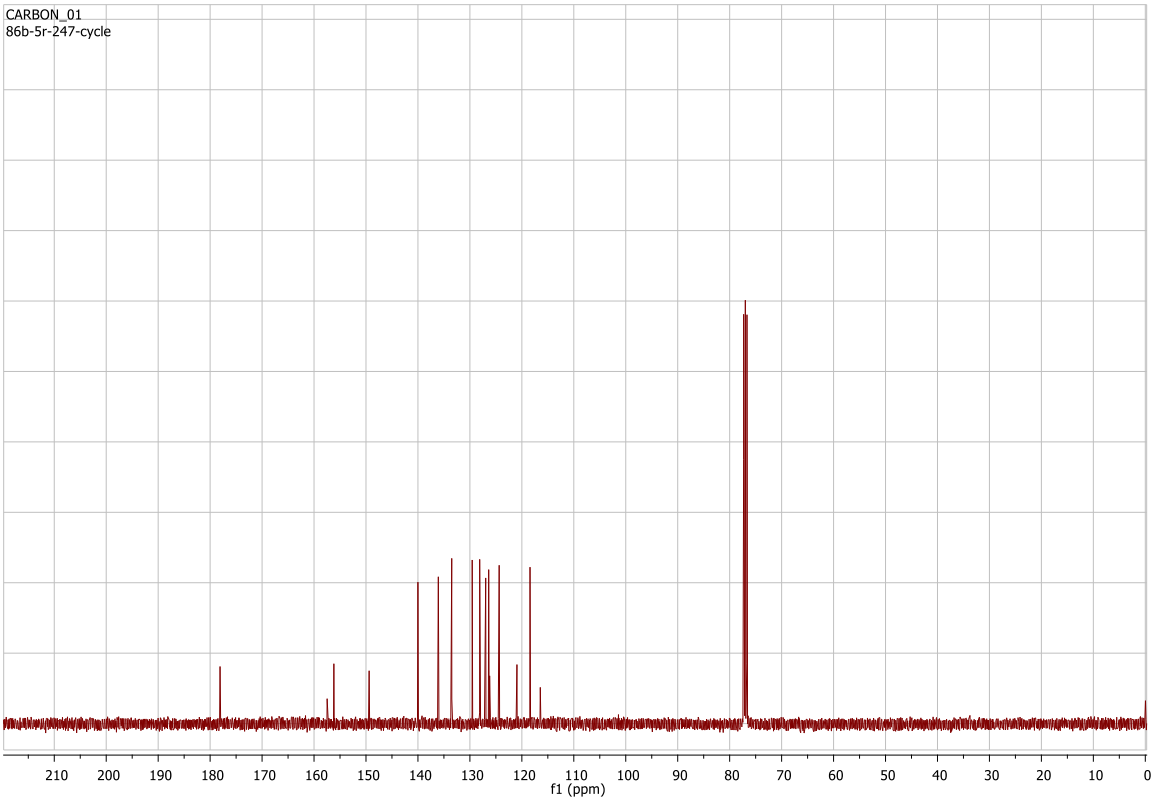

PROTON_01
86b-5u-280-p
O
OEt
P
OEt
N
17a
1.02
0.96
1.06
1.07
1.09
4.11
3.10
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CARBON_01
86b-5u-280-p
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


PROTON_01
86b-5o-231-cycle
3.04
O
N
18a
1.00
2.05
2.13
1.13
1.13
2.13
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)


CARBON_01
86b-5o-231-cycle
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


PROTON_01
86b-5r-247-cycle
O
O
N
18b
1.00
0.99
2.08
1.13
1.11
2.06
1.01
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)


CARBON_01
86b-5r-247-cycle
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

**5. Green chemistry metrics analysis**

The following formulae were used for calculating Atom Economy (AE), Atom Efficiency (AEf), Carbon Efficiency (CE), Reaction Mass Efficiency (RME), Optimum Efficiency (OE), Mass Productivity (MP), Mass Intensity (MI) and Process Mass Intensity (PMI), E factor, Solvent and Water Intensity (SI and WI).[5-13]

$$\mathbf{AE} = \frac{\mathbf{Molecular\ weight\ of\ product}}{\mathbf{Total\ molecular\ weight\ of\ reactants}} \mathbf{X\ 100}$$

$$\mathbf{AEf} = \mathbf{AE\ X\ yield}\%$$

$$\mathbf{CE} = \frac{\mathbf{Amount\ of\ carbon\ in\ the\ product}}{\mathbf{Total\ carbon\ present\ in\ reactants}} \mathbf{X\ 100}$$

$$\mathbf{RME} = \frac{\mathbf{Mass\ of\ isolated\ \ product}}{\mathbf{Total\ mass\ of\ reactants}} \mathbf{X\ 100}$$

$$\mathbf{OE} = \frac{\mathbf{RME}}{\mathbf{AE}} \mathbf{X\ 100}$$

$$\mathbf{MI} = \frac{\mathbf{Total\ mass\ of\ input\ material\ in\ a\ process\ or\ process\ step}}{\mathbf{Mass\ of\ product}}$$

$$\mathbf{PMI} = \frac{\mathbf{Total\ mass\ of\ input\ material\ in\ the\ whole\ process}}{\mathbf{Mass\ of\ product}}$$

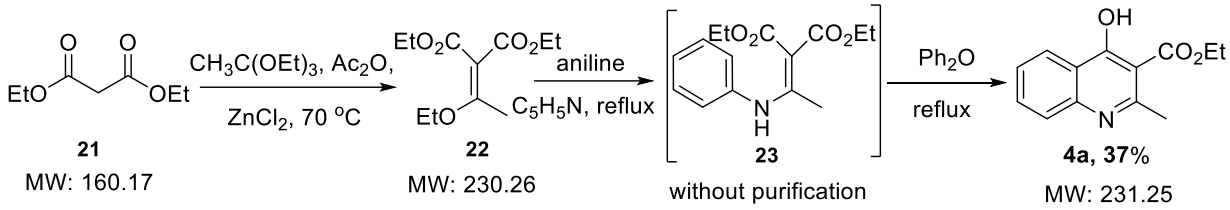
$$\mathbf{MP} = \frac{\mathbf{1}}{\mathbf{PMI}} \mathbf{X\ 100}$$

$$\mathbf{E\ Factor} = \mathbf{PMI} - \mathbf{1}$$

$$\mathbf{SI} = \frac{\mathbf{Total\ mass\ of\ solvents\ excl.water\ in\ the\ whole\ process}}{\mathbf{Mass\ of\ product}}$$

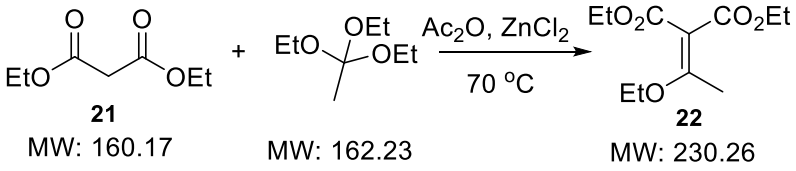
$$\mathbf{WI} = \frac{\mathbf{Total\ mass\ of\ water\ used\ in\ the\ whole\ process}}{\mathbf{Mass\ of\ product}}$$

**5.1. Published synthetic method - Process A** (I. P. J. Hoglund, S. Silver, M. T. Engstrom, H. Salo, A. Tauber, H. K. Kyyronen, P. Saarenketo, A. M. Hoffren, K. Kokko, K. Pohjanoksa, J. Sallinen, J. M. Savola, S. Wurster and O. A. Kallatsa, *J. Med. Chem*., 2006, **49**, 6351-6363)




This is a three-step synthesis, but only two separation steps. Reported procedures for the synthesis of compound **4a** do not always contain all the required information; therefore, some realistic assumptions were used where appropriate and are italicized in the calculations given below. Drying agents, when used, were not included in the calculations.

**Step 1: Synthesis of diethyl 2-(1-ethoxyethylidene)malonate (22)**




Experimental procedure: A solution of 21 (1.59 mL, 10.5 mmol), triethylorthoacetate (5.61 mL, 30.6 mmol), $Ac_2O$ (35 μL, 0.32 mmol), and $ZnCl_2$ (0.4 mg, cat.) was heated in a reaction vessel equipped with a distillation bridge and a thermometer. At a vapor temperature of 70 °C, side products formed in the reaction and started to distill out. $Ac_2O$ (35 μL) was added three times every 30 min. After 4 h of heating, the reaction mixture was allowed to cool to room temperature. The reaction mixture was evaporated gently under reduced pressure to remove low-volatile starting materials and side products. The residue was purified by flash chromatography (hexane/EtOAc= 3:1, *total 85mL*) to obtain 1.70 g (70%) of **22** as a yellowish oil.

Materials used for metrics calculations: compound 21 (1.26 g, 10.5 mmol), triethylorthoacetate (4.95 g, 30.6 mmol), $Ac_2O$ (0.25 g, 2.46 mmol), $ZnCl_2$ (0.4 mg, 0.003 mmol), hexane/EtOAc(85 mL, 62.00 g), compound 22 (1.70g, 7.38 mmol).

$$\mathbf{AE}\ \ (\mathbf{22}) = \frac{\mathbf{230.26}}{\mathbf{120.17 + 162.03}} \times\ \ \mathbf{100} = \mathbf{81.54}$$

$$\mathbf{AEf}\ \ (\mathbf{22}) = \frac{\mathbf{81.54}}{\mathbf{100}} \times\ \ \mathbf{70} = \mathbf{57.08}$$

$$\mathbf{CE}\ \ (\mathbf{22}) = \frac{\mathbf{11}\ \ \times \mathbf{30.60}}{\mathbf{7}\ \times\ \mathbf{10.5} + \mathbf{8}\ \times\ \mathbf{30.60}} \times\ \ \mathbf{100} = \mathbf{25.51}$$

$$\mathbf{RME}\ \ (\mathbf{22}) = \frac{\mathbf{1.7}}{\mathbf{1.26 + 4.95}} \times\ \ \mathbf{100} = \mathbf{27.30}$$

$$\mathbf{OE}\ \ (\mathbf{22}) = \frac{\mathbf{27.30}}{\mathbf{81.54}} \times\ \ \mathbf{100} = \mathbf{33.48}$$

$$\mathbf{MI}\ \ (\mathbf{22}) = \frac{\mathbf{1.26 + 4.97 + 0.25 + 0.0004 + 62.00}}{\mathbf{1.7}} = \mathbf{40.29}$$

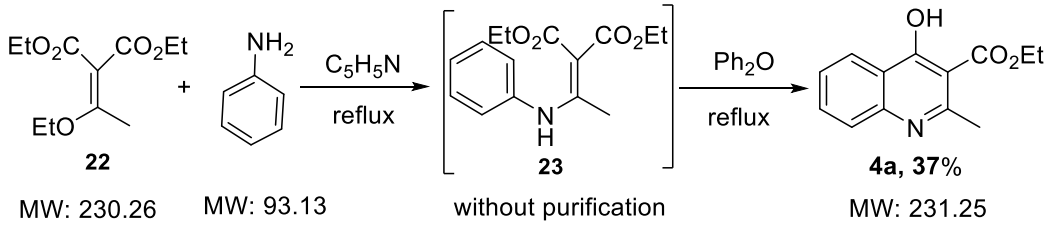
$$\mathbf{MP}\ \ (\mathbf{22}) = \frac{\mathbf{100}}{\mathbf{40.29}} = \mathbf{2.48}$$

$$\mathbf{E\ Factor}\ \ (\mathbf{22}) = \mathbf{40.29} - \mathbf{1} = \mathbf{39.29}$$

$$\mathbf{SI}\ \ (\mathbf{22}) = \frac{\mathbf{62.00}}{\mathbf{1.7}} = \mathbf{36.48}$$

$$\mathbf{WI}\ \ (\mathbf{22}) = \frac{\mathbf{0}}{\mathbf{1.7}} = \mathbf{0}$$

**Steps 2&3: Synthesis of ethyl 4-hydroxy-2-methylquinoline-3-carboxylate (4a)**




Experimental procedure: A solution of compound **22** (2.76 g, 12 mmol) and aniline (1.09 mL, 12 mmol) in pyridine (20 mL) was refluxed for 2 h. The reaction mixture was evaporated in vacuo and the residue was mixed with $Ph_2O$ (10 ml) and again refluxed for 1 h. $Et_2O$ (10 mL) was added to the cooled reaction mixture. The formed precipitate was filtered and washed with plenty of $Et_2O$ (*assuming use of 5 mL*), to afford 1.03 g (37%) of compound **4a** as colorless crystals.

Materials used for metrics calculations: compound 22 (2.76 g, 12 mmol), aniline (1.11 g, 12 mmol), pyridine (20 mL, 19.56g), $Et_2O$ (15 mL, 10.50 g), $Ph_2O$ (10 mL, 10.73 g), compound **4a** (1.03g, 4.45 mmol).

$$\mathbf{AE\ (4a)} = \frac{\mathbf{231.25}}{\mathbf{230.26 + 93.13}} \times \mathbf{100} = \mathbf{71.51}$$

$$\mathbf{AEf\ (4a)} = \frac{\mathbf{71.51}}{\mathbf{100}} \times\ \mathbf{37} = \mathbf{26.46}$$

$$\mathbf{CE\ (4a)} = \frac{\mathbf{13}\ \times\ \mathbf{4.45}}{\mathbf{11}\ \times\ \mathbf{12} + \mathbf{6} \times \mathbf{12}} \times\ \mathbf{100} = \mathbf{28.41}$$

$$\mathbf{RME\ (4a)} = \frac{\mathbf{1.03}}{\mathbf{2.76 + 1.11}} \times\ \mathbf{100} = \mathbf{26.57}$$

$$\mathbf{OE\ (4a)} = \frac{\mathbf{26.57}}{\mathbf{71.51}}\mathbf{X}\ \mathbf{100} = \mathbf{37.15}$$

$$\mathbf{MI\ (4a)} = \frac{\mathbf{2.76 + 1.11 + 19.56 + 10.73 + 10.5}}{\mathbf{1.03}} = \mathbf{148.76}$$

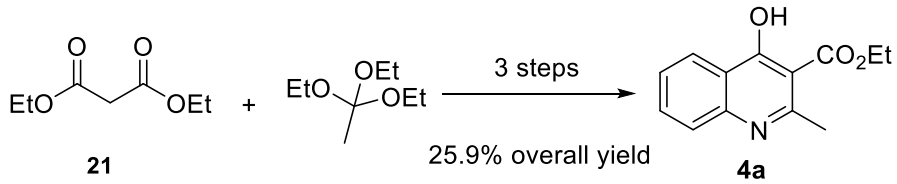
$$\mathbf{MP\ (4a)} = \frac{\mathbf{100}}{\mathbf{148.75}} =\ \mathbf{0.67}$$

$$\mathbf{E\ Factor\ (4a)} = \mathbf{43.37 - 1} = \mathbf{147.76}$$

$$\mathbf{SI\ (4a)} = \frac{\mathbf{19.56 + 10.73 + 10.5}}{\mathbf{1.03}} = \mathbf{40.48}$$

$$\mathbf{WI\ (4a)} = \frac{\mathbf{0}}{\mathbf{1.03}} = \mathbf{0}$$

**Cumulative metrics for compound 4a:**




**21** MW: 160.17 MW: 162.23 **4a** MW: 231.25

$$\mathbf{AE\ (4a\ cumulative)} = \frac{\mathbf{231.25}}{\mathbf{160.17 + 162.23 + 93.13}} \times \mathbf{100} = \mathbf{56}$$

$$\mathbf{AEf\ (4a\ cumulative)} = \frac{\mathbf{61.32}}{\mathbf{100}} \times \mathbf{25.9} = \mathbf{16}$$

$$\mathbf{CE\ (4a\ cumulative)} = \frac{\mathbf{13}\ \times\ \mathbf{4.45}}{(\mathbf{7}\ \times\ \mathbf{10.5} + \mathbf{8}\ \times\ \mathbf{30.60}) \times \frac{\mathbf{12}}{\mathbf{7.38}}\ + \mathbf{6} \times \mathbf{11.96}} \times\ \mathbf{100}$$

$$= \mathbf{10}$$

$$\mathbf{RME\ (4a\ cumulative)} = \frac{\mathbf{1.03}}{\frac{\mathbf{2.76}}{\mathbf{0.273}} + \mathbf{1.11}} \times\ \mathbf{100} = \mathbf{9.0}$$

$$\mathbf{OE(4a\ cumulative)} = \frac{\mathbf{9}}{\mathbf{56}}\mathbf{X}\ \mathbf{100} = \mathbf{16}$$

$$\mathbf{MI\ (4a\ cumulative)} = \frac{\mathbf{2.76 \times 40.29 + 1.11 + 19.56 + 10.73 + 10.5}}{\mathbf{1.03}} = \mathbf{149}$$

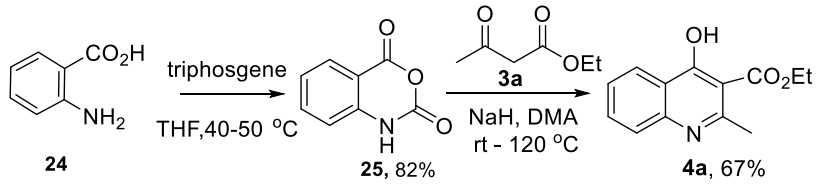
$$\textbf{MP}\ \ (\textbf{4a cumulative}) = \frac{\mathbf{100}}{\mathbf{149}} = \ \ \mathbf{0.7}$$

$$\textbf{E Factor}\ \ (\textbf{4a cumulative}) = \mathbf{149 - 1 = 148}$$

$$\textbf{SI}\ \ (\textbf{4a cumulative}) = \frac{\mathbf{62.0}\ \ \times \frac{\mathbf{12}}{\mathbf{7.38}} + \mathbf{19.56} + \mathbf{10.73} + \mathbf{10.5}}{\mathbf{1.03}} = \mathbf{138}$$

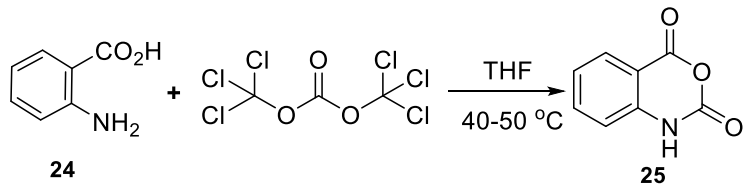
$$\textbf{WI}\ \ (\textbf{4a cumulative}) = \frac{\mathbf{0}}{\mathbf{1.03}} = \mathbf{0}$$

**5.2. Published synthetic method - Process B** (V. Goncalves, J. A. Brannigan, D. Whalley, K. H. Ansell, B. Saxty, A. A. Holder, A. J. Wilkinson, E. W. Tate and R. J. Leatherbarrow, *J. Med. Chem*., 2012, **55**, 3578-3582)




This is a two-step synthesis. Reported procedures for the synthesis of compound **4a** do not always contain all the required information; therefore, some realistic assumptions were used where appropriate and are italicized in the calculations given below. Drying agents, when used, were not included in the calculations.

**Step 1: Synthesis of 2*H*-benzo[d][1,3]oxazine-2,4(1*H*)-dione (25)**




Experimental procedures, A mixture of **24** (0.84 g, 6.1 mmol) and triphosgene (2.67g, 9.0 mmol) in dry THF (2 mL) was heated at 40-50 °C for 3 hr. the solution was concentrated and n-hexane(6 mL) was added. The title compound **25** was obtained as a beige solid (1.0 g, 82%)

Materials used for metrics calculations: compound **24** (0.84g, 6.1 mmol), triphosgene (2.67g,

2.0 mmol), THF (2 mL, 1.78g), n-hexane (6 mL, 4.03g), compound **25** (0.82g, 5.00 mmol).

$$\mathbf{AE}\ (\mathbf{25}) = \frac{\mathbf{163.13}}{\mathbf{137.14 + 296.73}} \times\ \mathbf{100 = 37.60}$$

$$\mathbf{AEf}\ (\mathbf{25}) = \frac{\mathbf{37.60}}{\mathbf{100}} \times\ \mathbf{82 = 58}$$

$$\mathbf{CE}\ (\mathbf{25}) = \frac{\mathbf{8\ \times\ 5}}{\mathbf{3 \times 9 + 7\ \times 6.1}} \times\ \mathbf{100 = 57.41}$$

$$\mathbf{RME}\ (\mathbf{25}) = \frac{\mathbf{0.82}}{\mathbf{2.67 + 0.84}} \times\ \mathbf{100 = 23.27}$$

$$\mathbf{OE}\ (\mathbf{25}) = \frac{\mathbf{23.27}}{\mathbf{37.60}} \times\ \mathbf{100 = 61.88}$$

$$\mathbf{MI}\ (\mathbf{25}) = \frac{\mathbf{4.032 + 1.78 + 2.67 + 0.84}}{\mathbf{0.82}} = \mathbf{11.37}$$

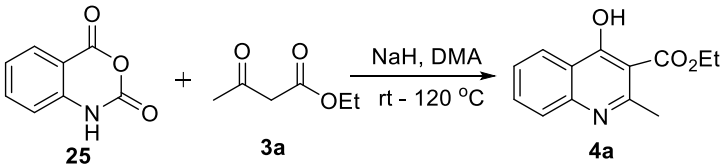
$$\mathbf{MP}\ (\mathbf{25}) = \frac{\mathbf{100}}{\mathbf{11.37}} = \mathbf{8.80}$$

$$\mathbf{E\ Factor}\ (\mathbf{25}) = \mathbf{11.37 - 1 = 10.37}$$

$$\mathbf{SI}\ (\mathbf{25}) = \frac{\mathbf{4.032 + 1.78}}{\mathbf{0.82}} = \mathbf{87.55}$$

$$\mathbf{WI}\ (\mathbf{25}) = \frac{\mathbf{0}}{\mathbf{0.82}} = \mathbf{0}$$

**Step 2: Synthesis of ethyl 4-hydroxy-2-methylquinoline-3-carboxylate (4a)**




**25** MW: 163.13 + **3a** MW: 130.14 → **4a** MW: 231.25

Experimental procedures*:* Ethylacetoacetate **3a** (6.50 g, 50 mmol) was dissolved in 100 mL of *N*,*N*-dimethylacetamide and sodium hydride (1.20 g, 50 mmol) was added portionwise under stirring over 10 min. To this solution was added a mixture of isatoic anhydride **25** (9.79 g, 60 mmol) and *N*,*N*-dimethylacetamide (75 mL) followed by stirring at 120 °C for 20 min. The solution was concentrated under reduced pressure, followed by addition of water (500 mL). The suspension was submitted to ultrasonic waves and the resulting precipitate was collected by filtration, washed with water and dried. Compound 4a as an off-white powder (7.80 g, 67%).

Materials used for metrics calculations: Ethylacetoacetate **3a** (6.50 g, 50 mmol), N, N-dimethylacetamide (175 mL, 163.97g), sodium hydride (1.20 g, 50 mmol), compound **25**

(9.79 g, 60 mmol), water (500 mL, 500g), compound **4a** (7.8g, 33.73 mmol).

$$\mathbf{AE}\ (\mathbf{4a}) = \frac{\mathbf{231.25}}{\mathbf{163.13 + 130.14}} \times \mathbf{100} = \mathbf{78.85}$$

$$\mathbf{AEf}\ (\mathbf{4a}) = \frac{\mathbf{78.85}}{\mathbf{100}} \times\ \mathbf{67} = \mathbf{52.83}$$

$$\mathbf{CE}\ (\mathbf{4a}) = \frac{\mathbf{13}\ \times \mathbf{33.73}}{\mathbf{6}\ \times\ \mathbf{50} + \mathbf{8} \times \mathbf{60}} \times\ \mathbf{100} = \mathbf{56.22}$$

$$\mathbf{RME}\ (\mathbf{4a}) = \frac{\mathbf{7.8}}{\mathbf{6.50 + 9.79}} \times\ \mathbf{100} = \mathbf{47.87}$$

$$\mathbf{OE}\ (\mathbf{4a}) = \frac{\mathbf{47.87}}{\mathbf{78.85}}\mathbf{X}\ \mathbf{100} = \mathbf{60.71}$$

$$\mathbf{MI}\ (\mathbf{4a}) = \frac{\mathbf{500 + 1.2 + 163.97 + 9.79 + 6.5}}{\mathbf{7.8}} = \mathbf{87.37}$$

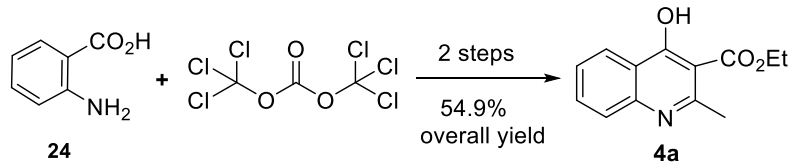
$$\mathbf{MP}\ (\mathbf{4a}) = \frac{\mathbf{100}}{\mathbf{87.37}} = \mathbf{1.14}$$

$$\mathbf{E\ Factor}\ (\mathbf{4a}) = \mathbf{87.37 - 1} = \mathbf{86.37}$$

$$\mathbf{SI}\ (\mathbf{4a}) = \frac{\mathbf{163.98}}{\mathbf{7.8}} = \mathbf{21.02}$$

$$\mathbf{WI}\ (\mathbf{4a}) = \frac{\mathbf{500}}{\mathbf{7.8}} = \mathbf{64.10}$$

**Cumulative metrics for compound 4a:**




**24** MW: 137.14 | MW: 296.73 | **4a** MW: 231.25

$$\mathbf{AE}\ (\mathbf{4a\ cumulative}) = \frac{\mathbf{231.25}}{\mathbf{137.14}\ \mathbf{+ 296.73 + 130.14}} \times\ \mathbf{100} = \mathbf{41}$$

$$\mathbf{AEf}\ (\mathbf{4a\ cumulative}) = \frac{\mathbf{41.00}}{\mathbf{100}} \times\ \mathbf{54.9} = \mathbf{23}$$

$$\mathbf{CE}\ (\mathbf{4a\ cumulative}) = \frac{\mathbf{13}\ \times\ \mathbf{33.73}}{(\mathbf{3} \times \mathbf{9} + \mathbf{7}\ \times \mathbf{6.1}) \times \frac{\mathbf{60}}{\mathbf{5.0}}\ + \mathbf{6} \times \mathbf{50}} \times\ \mathbf{100} = \mathbf{39}$$

$$\mathbf{RME}\ (\mathbf{4a\ cumulative}) = \frac{\mathbf{7.8}}{\frac{\mathbf{9.79}}{\mathbf{0.2327}}\ + \mathbf{6.50}} \times\ \mathbf{100} = \mathbf{16}$$

$$\mathbf{OE}\ (\mathbf{4a\ cumulative}) = \frac{\mathbf{16}}{\mathbf{41}} \times\ \mathbf{100} = \mathbf{39}$$

$$\mathbf{PMI}\ (\mathbf{4a\ cumulative}) = \frac{\mathbf{9.79 \times 11.37 + 6.5 + 163.97 + 1.2 + 500}}{\mathbf{7.8}} = \mathbf{100}$$

$$\mathbf{MP\ \ (4a\ \ cumulative)} = \frac{\mathbf{100}}{\mathbf{100.38}} = \mathbf{1.0}$$

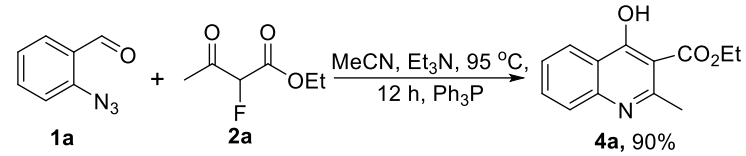
$$\mathbf{E\ Factor\ \ (4a\ \ cumulative)} = \mathbf{100 - 1 = 99}$$

$$\mathbf{SI\ \ (4a\ \ cumulative)} = \frac{\mathbf{5.812 \times \frac{60}{5.0} + 163.98}}{\mathbf{7.8}} = \mathbf{30}$$

$$\mathbf{WI\ \ (4a\ \ cumulative)} = \frac{\mathbf{500}}{\mathbf{7.8}} = \mathbf{64}$$

### 5.3. Current Method, Process C (4a as an example)

#### 5.3.1. One-pot process




**1a** MW: 147.14 **2a** MW: 148.13 **4a,** 90% MW: 231.25

This is a one-pot synthesis with only one step of separation for the final product.

General procedure for the synthesis of **4a.** To a solution of 2-azidobenzaldehyde **1a** (73.5 mg, 0.50 mmol), compound **2a** (82 mg, 0.55 mmol), $Et_3N$ (60.6 mg, 0.5 mmol) and $Ph_3P$ (157.8mg, 0.6mmol) in 2.5 mL of $CH_3CN$ was heated at 95 °C for 12 h. The reaction mixture upon the completion of the reaction as monitored by LC-MS. The reaction mixture was concentrated and washed with plenty of $Et_2O$ (*assuming use of total 2.0 mL*) for three times, afford 103.5 mg (90 %) of compound **4a**.

Materials used for metrics calculations: 2-azidobenzaldehyde **1a** (73.5 mg, 0.50 mmol), compound **2a** (82 mg, 0.55 mmol), $Et_3N$ (60.6 mg, 0.5 mmol) and $Ph_3P$ (157.8mg, 0.6mmol), $CH_3CN$ (2.5 mL, 1965 mg), $Et_2O$ (2.0 mL, 1400 mg), and compound **4a** (103.5 mg, 0.45 mmol).

$$\mathbf{AE\ \ (4a)} = \frac{\mathbf{231.25}}{\mathbf{147.14 + 148.13}} \times\ \ \mathbf{100 = 78}$$

$$\mathbf{AEf\ \ (4a)} = \frac{\mathbf{78}}{\mathbf{100}} \times\ \ \mathbf{90 = 70}$$

$$\mathbf{CE\ \ (4a)} = \frac{\mathbf{13\ \ \times\ \ 0.45}}{\mathbf{7\ \ \times 0.5 + 6\ \ \times 0.55}}\mathbf{X\ \ 100 = 86}$$

$$\mathbf{RME\ \ (4a)} = \frac{\mathbf{103.5}}{\mathbf{82 + 73.5}} \times\ \ \mathbf{100 = 67}$$

$$\mathbf{OE}\ \ (\mathbf{4a}) = \frac{\mathbf{66.56}}{\mathbf{78.32}} \times\ \ \mathbf{100} = \mathbf{85}$$

$$\mathbf{PMI}\ \ (\mathbf{4a}) = \frac{\mathbf{73.5} + \mathbf{82} + \mathbf{1965} + \mathbf{1400} + \mathbf{60.6} + \mathbf{157.8}}{\mathbf{103.5}} = \mathbf{36}$$

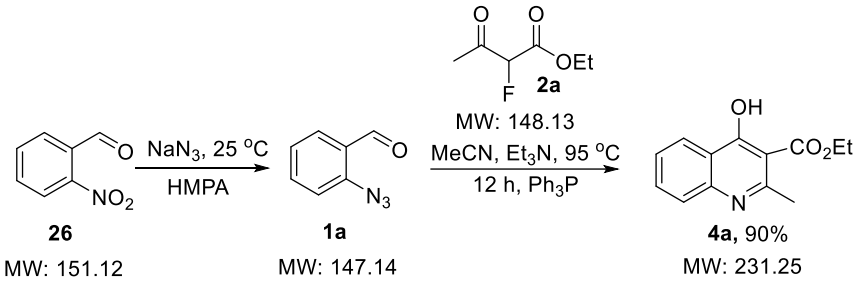
$$\mathbf{MP}\ \ (\mathbf{4a}) = \frac{\mathbf{100}}{\mathbf{36.12}} = \mathbf{2.8}$$

$$\mathbf{E\ Factor}\ \ (\mathbf{4a}) = \mathbf{36.12} - \mathbf{1} = \mathbf{35}$$

$$\mathbf{SI}\ \ (\mathbf{4a}) = \frac{\mathbf{1965} + \mathbf{1400} + \mathbf{60.6}}{\mathbf{103.5}} = \mathbf{33}$$

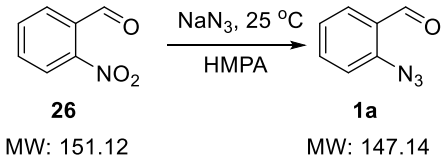
$$\mathbf{WI}\ \ (\mathbf{4a}) = \frac{\mathbf{0}}{\mathbf{103.5}} = \mathbf{0}$$

### 5.3.2 Two-step process (including the synthesis of 2-azidobenzaldehyde)




This is a two-step synthesis. Reported procedures for the synthesis of compound **4a** do not always contain all the required information; therefore, some realistic assumptions were used where appropriate and are italicized in the calculations given below. Drying agents, when used, were not included in the calculations.

**Step 1: Synthesis of 2-azidobenzaldehyde (1a)**




Experimental procedure: A mixture of **26** (1.51 g, 10 mmol) and $NaN_3$ (1.30g, 20 mmol) in HMPA (15 mL) was stirred at 25 °C for 36 hr. The reaction mixture was poured onto water (30 mL) and then stirred at 0-5 °C, the crude product was filtrated and afforded off-yellow solid 1a (1.47g, 100%)

Materials used for metrics calculations: compound **26** (1.51g, 10 mmol), $NaN_3$ (1.30g, 20 mmol), HMPA (15 mL, 15.45g), water (30 mL, 30g), compound **1a** (1.47 g,10 mmol).

$$\mathbf{AE}\ \ (\mathbf{1a}) = \frac{\mathbf{147.14}}{\mathbf{151.12 + 65}} \times\ \ \mathbf{100 = 68.08}$$

$$\mathbf{AEf}\ \ (\mathbf{1a}) = \frac{\mathbf{68.08}}{\mathbf{100}} \times\ \ \mathbf{100 = 68.08}$$

$$\mathbf{CE}\ \ (\mathbf{1a}) = \frac{\mathbf{7} \times\ \mathbf{10}}{\mathbf{7 \times 10}} \times\ \ \mathbf{100 = 100}$$

$$\mathbf{RME}\ \ (\mathbf{1a}) = \frac{\mathbf{1.47}}{\mathbf{1.51 + 1.30}} \times\ \ \mathbf{100 = 52.31}$$

$$\mathbf{OE}\ \ (\mathbf{1a}) = \frac{\mathbf{52.31}}{\mathbf{68.08}} \times\ \ \mathbf{100 = 76.84}$$

$$\mathbf{MI}\ \ (\mathbf{1a}) = \frac{\mathbf{1.51 + 1.30 + 15.45 + 30}}{\mathbf{1.47}} = \mathbf{32.83}$$

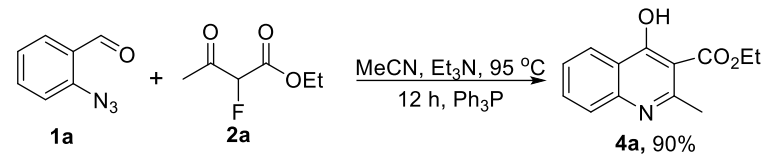
$$\mathbf{MP}\ \ (\mathbf{1a}) = \frac{\mathbf{100}}{\mathbf{32.83}} = \mathbf{3.05}$$

$$\mathbf{E\ Factor}\ \ (\mathbf{1a}) = \mathbf{32.83 - 1 = 31.83}$$

$$\mathbf{SI}\ \ (\mathbf{1a}) = \frac{\mathbf{15.45}}{\mathbf{1.47}} = \mathbf{10.51}$$

$$\mathbf{WI}\ \ (\mathbf{1a}) = \frac{\mathbf{30}}{\mathbf{1.47}} = \mathbf{20.41}$$

**Step 2: Synthesis of ethyl 4-hydroxy-2-methylquinoline-3-carboxylate (4a)**




**1a** MW: 147.14 **2a** MW: 148.13 **4a,** 90% MW: 231.25

General procedure for the synthesis of **4a.** To a solution of 2-azidobenzaldehyde **1a** (73.5 mg, 0.50 mmol), compound **2a** (82 mg, 0.55 mmol), $Et_3N$ (60.6 mg, 0.5 mmol) and $Ph_3P$ (157.8mg, 0.6mmol) in 2.5 mL of $CH_3CN$ was heated at 95 °C for 12 h. The reaction mixture upon the completion of the reaction as monitored by LC-MS. The reaction mixture was concentrated and washed with plenty of $Et_2O$ (*assuming use of total 2.0 mL*) for three times, afford 103.5 mg (90 %) of compound **4a**.

Materials used for metrics calculations: 2-azidobenzaldehyde **1a** (73.5 mg, 0.50 mmol), compound **2a** (82 mg, 0.55 mmol), $Et_3N$ (60.6 mg, 0.5 mmol) and $Ph_3P$ (157.8mg, 0.6mmol), $CH_3CN$ (2.5 mL, 1965 mg), $Et_2O$ (2.0 mL, 1400 mg), and compound **4a** (103.5 mg, 0.45 mmol).

$$\mathbf{AE\ (4a)} = \frac{\mathbf{231.25}}{\mathbf{147.14 + 148.13}} \times\ \mathbf{100 = 78}$$

$$\mathbf{AEf\ (4a)} = \frac{\mathbf{78}}{\mathbf{100}} \times\ \mathbf{90 = 70}$$

$$\mathbf{CE\ (4a)} = \frac{\mathbf{13\ \times\ 0.45}}{\mathbf{7\ \times 0.5 + 6\ \times 0.55}} \mathbf{X\ 100 = 86}$$

$$\mathbf{RME\ (4a)} = \frac{\mathbf{103.5}}{\mathbf{82 + 73.5}} \times\ \mathbf{100 = 67}$$

$$\mathbf{OE\ (4a)} = \frac{\mathbf{66.56}}{\mathbf{78.32}} \times\ \mathbf{100 = 85}$$

$$\mathbf{PMI\ (4a)} = \frac{\mathbf{73.5 + 82 + 1965 + 1400 + 60.6 + 157.8}}{\mathbf{103.5}} = \mathbf{36}$$

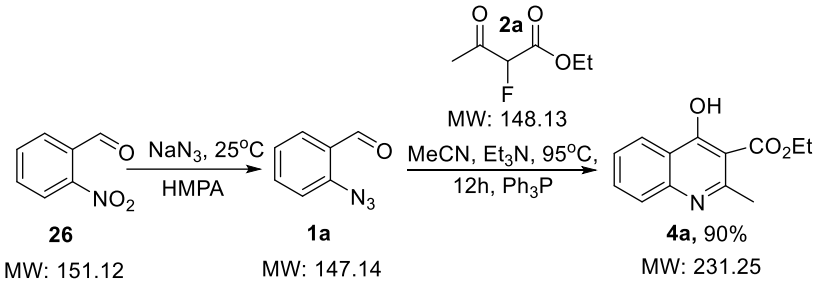
$$\mathbf{MP\ (4a)} = \frac{\mathbf{100}}{\mathbf{36.12}} = \mathbf{2.8}$$

$$\mathbf{E\ Factor\ (4a) = 36.12 - 1 = 35}$$

$$\mathbf{SI\ (4a)} = \frac{\mathbf{1965 + 1400 + 60.6}}{\mathbf{103.5}} = \mathbf{33}$$

$$\mathbf{WI\ (4a)} = \frac{\mathbf{0}}{\mathbf{103.5}} = \mathbf{0}$$

**Cumulative metrics for compound 4a:**




$$\mathbf{AE\ (4a\ cumulative)} = \frac{\mathbf{231.25}}{\mathbf{151.12\ \ + 65 + 148.13}} \times\ \mathbf{100 = 63.5}$$

$$\mathbf{AEf\ (4a\ cumulative)} = \frac{\mathbf{41.00}}{\mathbf{100}} \times\ \mathbf{90 = 57}$$

$$\mathbf{CE\ (4a\ cumulative)} = \frac{\mathbf{13\ \times\ 0.45}}{\mathbf{7 \times 0.5\ \ + 6 \times 0.55}} \times\ \mathbf{100 = 86}$$

$$\mathbf{RME\ (4a\ cumulative)} = \frac{\mathbf{103.5}}{\dfrac{\mathbf{73.5}}{\mathbf{0.5231}}\ \mathbf{+ 82}} \times\ \mathbf{100 = 47}$$

$$\mathbf{OE\ (4a\ cumulative)} = \frac{\mathbf{47}}{\mathbf{63.5}} \times\ \mathbf{100 = 74}$$

$$\mathbf{PMI\ (4a\ cumulative)} = \frac{\mathbf{73.5 \times 33 + 82 + 1965 + 1400 + 60.6 + 157.8}}{\mathbf{103.5}} = \mathbf{59}$$

$$\mathbf{MP\ (4a\ cumulative)} = \frac{\mathbf{100}}{\mathbf{59}} = \mathbf{1.7}$$

$$\textbf{E Factor (4a cumulative)} = 59 - 1 = 58$$

$$\textbf{SI (4a cumulative)} = \frac{15450 \times \frac{0.5}{10} + 1965 + 1400 + 60.6}{103.5} = 41$$

$$\textbf{WI (4a cumulative)} = \frac{30000 \times \frac{0.5}{10}}{103.5} = 14.5$$

## 6. References


1) D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.,* 2002, **4**, 521–527.

2) C. Jiménez-González, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.

3) J. J. Song, R. P. Frutos, T. Tampone and C. H. Senanayake, in *Comprehensive Chirality, Volume 9: Industrial Applications of Asymmetric Synthesis*, eds. E. M. Carreira, H. Yamamoto, Elsevier Science, Amsterdam, 2012, pp. 46–72.

4) N. J. Willis, C. A. Fisher, C. M. Alder, A. Harsanyi, L. Shukla, J. P. Adams and G. Sandford, *Green Chem.*, 2016, **18**, 1313–1318.

5) F. Roschangar, R. A. Sheldon and C. H. Senanayake, *Green Chem.,* 2015, **17**, 752–768.

6) C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111–3121.