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Synthesis of new analgesics based on 4-isopropyl-1-phenyl-3-(trifluoromethyl)pyrazol-5-one

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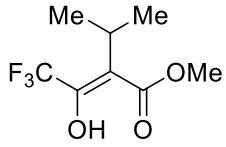
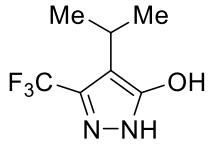
Experimental

Chemical part

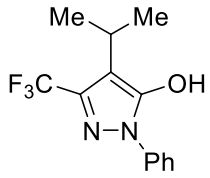
All solvents, chemicals, and reagents were obtained commercially and used without purification. Melting points were measured in open capillaries on a Stuart SMP30 melting point apparatus and were uncorrected. The IR spectra were recorded on Perkin Elmer Spectrum Two using frustrated total internal reflection accessory with diamond crystal. The ^{1}H and ^{19}F NMR spectra were registered on a Bruker DRX-400 (400 or 376 MHz, respectively) or on a Bruker Avance^{III} 500 (500 or 470 MHz, respectively). The ^{13}C NMR spectra were recorded on a Bruker Avance^{III} 500 (125 MHz). The internal standard is $SiMe_4$ (for ^{1}H and ^{13}C NMR spectra) and C_6F_6 (for ^{19}F NMR spectra, δ –162.9 ppm). The microanalyses (C, H, N) were carried out on a PerkinElmer PE 2400 series II elemental analyzer. The column chromatography was performed on Silica gel 60 (0.062-0.2 mm).



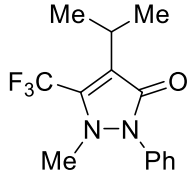
Methyl (2*Z*)-4,4,4-trifluoro-3-hydroxy-2-isopropylbut-2-enoate (3). A mixture of methyl trifluoroacetate **1** (32 g, 0.25 mol) and methyl isovalerate **2** (29.5 g, 0.25 mol) was slowly added to a stirred mixture of NaH (60% dispersion in mineral oil, 10 g, 0.25 mol) in absolute DME (300 ml) at room temperature. The resulting mixture was refluxed for 40 h. The solvent was removed *in vacuo*, the residue was treated with 10% of HCl (200 ml) and extracted with hexane (2x150 ml). The organic lay was dried over Na_2SO_4. Then the solvent was removed in *vacuo* and the residue was distilled to give compound **3** as light-yellow oil (bp 45–48 °C / 15 Torr). Yield 34.5 g (65%). The NMR spectra are identical to the literature data [G. Simchen, A. Schmidt, *Synthesis*. 1997, 117].



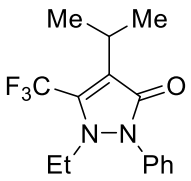
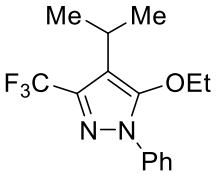
4-(Propan-2-yl)-3-(trifluoromethyl)-1*H*-pyrazol-5-ol (4). A mixture of oxoester **3** (212 mg, 10 mmol) and hydrazine hydrate (50 mg, 10 mmol) in methanol (30 ml) was refluxed for 3 h. After cooling, the solvent was removed in *vacuo* and the residue was purified by the column chromatography. Yield 140 mg (72%), white powder, mp 87-88 °C (eluent–CH_2Cl_2:EtOAc 3:1). IR: ν 3389, 3356 (OH, NH); 1605, 1537, 1505, 1445, 1443 (C=C, C=N); 1249-1131 (CF) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.28 (d, 6H, 2Me, J = 7.0 Hz); 3.01 (sept, 1H, CH, J = 7.0 Hz); 9.57 (br. s, 2H, NH and OH). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 21.54 (2C); 23.13; 112.29; 119.98 (q, CF_3, J = 269.4 Hz); 119.98 (q, C–CF_3, J = 38.2 Hz); 161.12. ^{19}F NMR (470 MHz, $CDCl_3$, δ, ppm): 101.14 (s, CF_3). Anal. calcd. for $C_7H_9F_3N_2O$. C, 43.30; H, 4.67; N, 14.43. Found: C, 43.44; H, 4.58; N, 14.50.



4-Isopropyl-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5-ol (6). A mixture of oxoester **3** (10.6 g, 50 mmol) and phenylhydrazine (5.4 g, 10 mmol) in a glacial acetic acid (100 ml) was refluxed for 20 h. After cooling, cold water (100 ml) was added and the precipitate was filtered off. Yield 9.95 g (74%), off-white powder, mp 134–135 °C. IR: ν 2971 (OH, NH); 1603, 1506, 1478, 1456 (C=C, C=N); 1236-1116 (CF) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ,ppm): a mixture of **enol:keto** isomers (54:46), 1.05, 1.23 (both d, 6H, 2Me, *J* = 6.9 Hz **keto**); 1.05, 1.29 (d, 6H, 2Me, *J* = 7.0 Hz **enol**); 2.55-2.66 (m, 1H, CH **keto**); 3.01 (sept, 1H, CH, *J* = 7.0 Hz **enol**); 3.51 (br. s, 1H, CH*cycl* **keto**); 6.04 (br. s, 1H, OH **enol**) 7.25-7.28, 7.33-7.36, 7.41-7.44, 7.54-7.55, 7.80-7.81 (all m, 5H, Ph both isomers). ^{19}F NMR (470 MHz, $CDCl_3$, δ, ppm): 95.84 (s, CF_3 **keto**); 100.29 (s, CF_3 **enol**). ^{1}H NMR (500 MHz, DMSO-d_6, δ, ppm): 1.25 (d, 6H, 2Me, *J* = 6.2 Hz); 3.00-3.02 (m, 1H, CH); 7.40-7.41, 7.51-7.52, 7.66-7.68 (all m, 5H, Ph); 10.89 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 22.02 (2C); 22.70; 108.37; 121.99 (q, CF_3, *J* = 269.1 Hz); 122.86; 127.35; 129.07; 137.40 (q, C–CF_3, *J* = 35.8 Hz); 137.74; 149.54. ^{19}F NMR (470 MHz, DMSO-d_6, δ, ppm): 102.82 (s, CF_3). Anal. calcd. for $C_{13}H_{12}F_3N_2O$. C, 57.99; H, 4.49; N, 10.40. Found: C, 57.85; H, 4.52; N, 10.53.

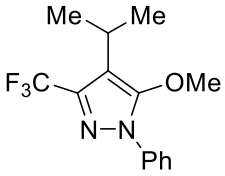


4-Isopropyl-1-methyl-2-phenyl-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one (8a). Dimethyl sulfate (630 mg, 5 mmol) was added to pyrazole **6** (269 mg, 1 mmol). The flask was immersed in the oil bath and heated at 100-110 °C for 12 h. After cooling, diethyl ether (30 ml) was added, the resulting precipitate was isolated and washed with 10% sodium hydroxide. The residue was purified by column chromatography. Yield 110 mg (39%), tawny powder, mp 170 °C dec. (eluent – CH_2Cl_2). IR: ν 1674 (C=O); 1623, 1603, 1494, 1454 (C=C); 1223-1130 (CF) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6+CCl_4, δ, ppm): 1.28 (d, 6H, 2Me, *J* = 10.0 Hz); 3.05 (s+m, 4H, NMe and CH); 7.33-7.35, 7.41-7.43, 7.49-7.53 (all m, 5H, Ph). ^{13}C NMR (125 MHz, DMSO-d_6, δ, ppm): 20.03 (2C); 23.90; 38.29 (q, NMe, *J* 1.85 Hz); 120.21 (q, CF_3, *J* = 272.6 Hz); 122.45 (q, =C_{cycl}, *J* 1.85 Hz); 124.14; 127.32; 129.27; 133.08; 139.74 (q, C–CF_3, *J* = 36.0 Hz); 161.63. ^{19}F NMR (376 MHz, DMSO-d_6+CCl_4, δ, ppm): 103.64 (s, CF_3). Anal. calcd. for $C_{14}H_{15}F_3N_2O$. C, 59.15; H, 5.32; N, 9.85. Found: C, 59.23; H, 5.61; N, 9.91.

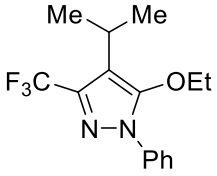



A mixture of 1-ethyl-4-isopropyl-2-phenyl-5-trifluoromethyl-1,2-dihydro-3*H*-pyrazol-3-one (8b) and 5-ethoxy-4-isopropyl-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (9b) - 1:1. The reaction was performed similarly to synthesis of compound **8a** from pyrazole **6** (269 mg, 1 mmol) and diethyl sulfate (770 mg, 5 mmol). Yield 95 mg (32%), tawny oil (eluent – $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.83 (t, 3H, $OCH_2\underline{Me}$, *J* = 7.0 Hz **8b**); 1.25 (t, 3H, $OCH_2\underline{Me}$, *J* = 7.1 Hz **9b**); 1.32 (d, 6H, 2Me, *J* = 7.1 Hz **9b**); 1.35 (d, 6H, 2Me, *J* = 7.0 Hz **8b**); 3.06 (sept, 1H, CH, *J* = 7.1 Hz **9b**); 3.06 (sept, 1H, CH, *J* = 7.0 Hz **8b**); 3.65 (q, 2H, $NC\underline{H_2}Me$, *J* = 7.0 Hz **8b**); 3.81 (q, 2H, $OC\underline{H_2}Me$, *J* = 7.1 Hz **9b**); 7.31-7.38, 7.45-7.48, 7.67-7.69 (all m, 5H, Ph **8b+9b**). ^{19}F NMR (470 MHz, $CDCl_3$, δ, ppm): 100.43 (s, 3F, CF_3 **9b**); 102.46 (s, 3F, CF_3 **8b**).

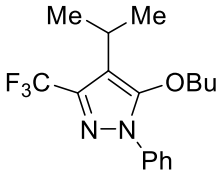
The synthesis of compounds 9a-g (*general procedure*). A mixture of 807 mg (3 mmol) of pyrazole **6**, 3.3 mmol of the corresponding dialkyl sulfate or alkyl halide, and 621 mg (4.5 mmol) of K_2CO_3 in 30 ml of acetonitrile was refluxed until the staring reagents completely disappeared. After cooling, a reaction mass was diluted with water and extracted with $CHCl_3$ (2×15 ml). The organic layer was dried over Na_2SO_4 and the solvent was evaporated to give products **9a-g**.



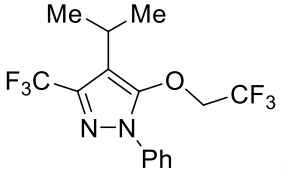
4-Isopropyl-5-methoxy-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (9a). Obtained from pyrazole **6** and dimethyl sulfate. Yield 596 mg (70%), light-yellow oil (eluent – CH_2Cl_2). IR: ν 1598, 1575, 1501, 1472, 1457 (C=C, C=N); 1150-1117 (CF) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.32 (d, 6H, 2Me, *J* = 7.1 Hz); 3.07 (sept, 1H, CH, *J* = 7.1 Hz); 3.65 (s, 3H, OMe); 7.35-7.39, 7.45-7.49, 7.67-7.70 (all m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 22.56 (2C); 23.51; 62.35; 113.44; 121.66 (q, CF_3, *J* = 269.7 Hz); 122.90; 127.85; 129.29; 137.93; 139.18 (q, $\underline{C}–CF_3$, *J* = 36.7 Hz); 152.00. ^{19}F NMR (376 MHz, $CDCl_3$, δ, м.д.): 100.28 (s, CF_3). Anal. calcd. for $C_{14}H_{15}F_3N_2O$. C, 59.15; H, 5.32; N, 9.85. Found: C, 59.33; H, 5.51; N, 9.74.



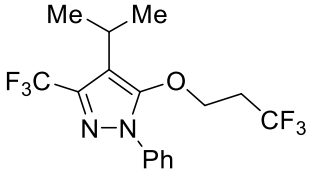
5-Ethoxy-4-isopropyl-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (9b). Obtained from pyrazole **6** and diethyl sulfate. Yield 643 mg (72%), light-yellow oil (eluent – $CHCl_3$). IR: ν 1598, 1573, 1501, 1468, 1446(C=C, C=N); 1152-1118 (CF) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.25 (t, 3H, $OCH_2\underline{Me}$, *J* = 7.1 Hz); 1.32 (d, 6H, 2Me, *J* = 7.1 Hz); 3.08 (sept, 1H, CH, *J* = 7.1 Hz); 3.81 (q, 2H, $OC\underline{H_2}Me$, *J* = 7.1 Hz); 7.35-7.38, 7.45-7.48, 7.67-7.69 (all m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 15.12; 22.53 (2C); 23.52; 71.55; 113.51; 121.71 (q, CF_3, *J* = 269.5 Hz); 123.03; 127.80; 129.18; 138.12; 139.17 (q, $\underline{C}–CF_3$, *J* = 36.6 Hz); 151.10. ^{19}F NMR (470 MHz, $CDCl_3$, δ, ppm): 100.43 (s, CF_3). Anal. calcd. for $C_{15}H_{17}F_3N_2O$. C, 60.40; H, 5.74; N, 9.39.Found: C, 60.56; H, 5.65; N, 9.45.



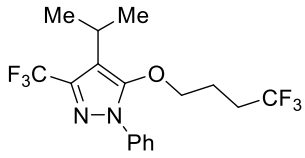
5-Butoxy-4-isopropyl-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (9c). Obtained from pyrazole **6** and dibutyl sulfate. Yield 694 mg (71%), light-yellow oil (eluent – $CHCl_3$). IR: ν 1598, 1573, 1503, 1468, 1446 (C=C, C=N); 1152-1119 (CF) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.85 (t, 3H, $O(CH_2)_3\underline{Me}$, *J* = 7.4 Hz); 1.31 (d, 6H, 2Me, *J* = 7.1 Hz); 1.29-1.38, 1.56-1.63 (both m, 4H, $OCH_2(C\underline{H_2})_2Me$); 3.06 (sept, 1H, CH, *J* = 7.1 Hz); 3.73 (t, 2H, $OC\underline{H_2}(CH_2)_2Me$, *J* = 6.5 Hz); 7.36-7.38, 7.44-7.48, 7.66-7.68 (all m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 13.62; 18.86; 22.56 (2C); 23.52; 31.66; 75.58; 113.39; 121.72 (q, CF_3, *J* = 269.3 Hz); 123.21; 127.85; 129.15; 138.06; 139.18 (q, $\underline{C}–CF_3$, *J* = 36.8 Hz); 151.31. ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): 100.46 (s, CF_3). Anal. calcd. for $C_{17}H_{21}F_3N_2O$. C, 62.56; H, 6.49; N, 5.58. Found: C, 62.67; H, 6.60; N, 5.39.



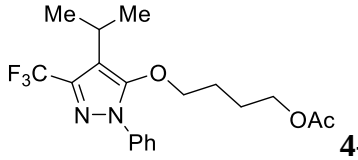
4-Isopropyl-1-phenyl-5-(2,2,2-trifluoroethoxy)-3-trifluoromethyl-1*H*-pyrazole (9d). Obtained from pyrazole **6** and 1,1,1-trifluoro-2-iodoethane. Yield 665 mg (63%), light-yellow oil (eluent – $CHCl_3$). IR: ν 1598, 1577, 1504, 1469, 1448 (C=C, C=N); 1154-1122 (CF) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.33 (d, 6H, 2Me, *J* = 7.1 Hz); 3.09 (sept, 1H, CH, *J* = 7.1 Hz); 4.02 (q, 2H, $OC\underline{H_2}CF_3$, *J* = 8.0 Hz); 7.40-7.44, 7.48-7.52, 7.64-7.66 (all m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 22.35 (2C); 23.41; 70.38 (q, $O\underline{C}H_2CF_3$, *J* = 35.9 Hz); 114.30; 121.39 (q, CF_{3cycl}, *J* = 269.7 Hz); 122.03 (q, CF_3, *J* = 257.1 Hz); 123.18; 128.60; 129.57; 137.14; 139.50 (q, $\underline{C}–CF_3$, *J* = 37.1 Hz); 148.62. ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): 87.50 (t, 3F, CF_3, *J* 8.0 Hz); 100.32 (s, 3F, CF_{3cycl}). Anal. calcd. for $C_{15}H_{14}F_6N_2O$. C, 51.14; H, 4.01; N, 7.95. Found: C, 51.32; H, 4.03; N, 7.84.



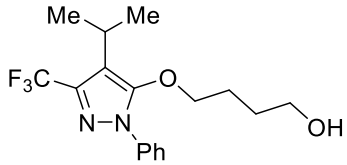
4-Isopropyl-1-phenyl-3-trifluoromethyl-5-(3,3,3-trifluoropropoxy)-1*H*-pyrazole (9e). Obtained from pyrazole **6** and 1,1,1-trifluoro-3-iodopropane. Yield 714 mg (65%), light-yellow oil (eluent – $CHCl_3$). IR: ν 1598, 1575, 1502, 1469, 1448 (C=C, C=N); 1152-1121 (CF) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.32 (d, 6H, 2Me, *J* = 7.1 Hz); 2.44 (qt, 4H, $OCH_2C\underline{H_2}CF_3$, *J* = 10.4, 6.4 Hz); 3.07 (sept, 1H, CH, *J* = 7.1 Hz); 3.92 (t, 2H, $OC\underline{H_2}CH_2CF_3$), *J* = 6.4 Hz); 7.39-7.42, 7.47-7.50, 7.64-7.65 (вall m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 22.49 (2C); 23.48; 34.29 (q, $OCH_2\underline{C}H_2CF_3$, *J* = 29.7 Hz); 67.86 (q, $O\underline{C}H_2CH_2CF_3$, *J* = 3.4 Hz); 113.90; 121.57 (q, $CF_{3\ cycl}$, *J* = 269.6 Hz); 122.64; 125.35 (q, CF_3, *J* = 276.7 Hz); 128.32; 129.40; 137.63; 139.37 (q, $\underline{C}–CF_3$, *J* = 36.9 Hz); 150.14. ^{19}F NMR (470 MHz, $CDCl_3$, δ, ppm): 97.09 (t, 3F, CF_3, *J* 10.4 Hz); 100.33 (s, 3F, $CF_{3\ cycl}$). Anal. calcd. for $C_{16}H_{16}F_6N_2O$. C, 52.46; H, 4.40; N, 7.65. Found: C, 52.68; H, 4.55; N, 7.53.



4-Isopropyl-1-phenyl-5-(4,4,4-trifluorobutoxy)-3-trifluoromethyl-1*H*-pyrazole (9f). Obtained from pyrazole **6** and 1,1,1-trifluoro-4-iodobutane. Yield 787 mg (69%), light-yellow oil (eluent – $CHCl_3$). IR: ν 1598, 1574, 1503, 1469, 1448 (C=C, C=N); 1151-1120 (CF) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.31 (d, 6H, 2Me, *J* = 7.1 Hz); 1.83-1.89, 2.08-2.18 (both m, 4H, $OCH_2(C\underline{H_2})_2CF_3$); 3.08 (sept, 1H, CH, *J* = 7.1 Hz); 3.78 (t, 2H, $OC\underline{H_2}(CH_2)_2CF_3$), *J* = 6.1 Hz); 7.39-7.42, 7.47-7.50, 7.61-7.63 (all m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 22.49 (q, $OCH_2\underline{C}H_2CH_2CF_3$, *J* = 3.1 Hz); 22.60 (2C); 23.53; 30.40 (q, $OCH_2CH_2\underline{C}H_2CF_3$, *J* = 29.4 Hz); 73.78; 113.54; 121.62 (q, $CF_{3\ cycl}$, *J* = 269.7 Hz); 123.55; 126.71 (q, CF_3, *J* = 276.2 Hz); 128.33; 129.31; 137.74; 139.33 (q, $\underline{C}–CF_3$, *J* = 36.7 Hz); 150.61. ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): 95.23 (t, 3F, CF_3, *J* 10.7 Hz); 100.41 (s, 3F, $CF_{3\ cycl}$). Anal. calcd. for $C_{17}H_{18}F_6N_2O$. C, 53.69; H, 4.77; N, 7.37. Found: C, 53.54; H, 4.82; N, 7.49.



4-[(4-Isopropyl-1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-yl)oxy]butyl acetate (9g). Obtained from pyrazole **6** and 4-bromobutyl acetate. Yield 852 mg (74%), light-yellow oil (eluent – $CHCl_3$). IR: ν 1739 (C=O); 1597, 1573, 1503, 1469, 1446 (C=C, C=N); 1152-1119 (CF) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.32 (d, 6H, 2Me, *J* = 7.0 Hz); 1.67-1.68 (m, 4H, $OCH_2(C\underline{H_2})_2CH_2OAc$); 2.03 (s, 3H, OAc); 3.06 (sept, 1H, CH, *J* = 7.0 Hz); 3.76, 4.01 (both t, 4H, $OC\underline{H_2}(CH_2)_2C\underline{H_2}OAc$, *J* = 5.8, 6.0 Hz); 7.36-7.40, 7.45-7.49, 7.64-7.66 (all m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 20.88; 22.59 (2C); 23.51; 25.01; 26.27; 63.71; 75.15; 113.42; 121.65 (q, CF_3, *J* = 269.6 Hz); 123.32; 128.02; 129.21; 137.90; 139.21 (q, $\underline{C}–CF_3$, *J* = 36.7 Hz); 151.02; 170.98. ^{19}F NMR (376 MHz, $CDCl_3$, δ, ppm): 100.42 (s, CF_3). Anal. calcd. for $C_{19}H_{23}F_3N_2O_3$. C, 59.37; H, 6.03; N, 7.29. Found: C, 59.45; H, 6.01; N, 7.40.



4-[4-Isopropyl-1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-yl)oxy]butan-1-ol (9h). Hydrogen chloride was bubbled into solution of pyrazole derivative **9g** (384 mg, 1 mol) in methanol (10 ml) at the room temperature for 1 h. The solvent was evaporated, and the residue was purified by the column chromatography. Yield 274 mg (80%), light-yellow oil (eluent – $CHCl_3$). IR: ν 3390 (OH); 1597, 1573, 1502, 1469, 1446 (C=C, C=N); 1152-1119 (CF) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.32 (d, 6H, 2Me, *J* = 7.1 Hz); 1.55-1.61, 1.67-1.73 (both m, 5H, $OCH_2(C\underline{H_2})_2CH_2O\underline{H}$); 3.06 (sept, 1H, CH, *J* = 7.1 Hz); 3.57, 3.76 (both t, 4H, $OC\underline{H_2}(CH_2)_2C\underline{H_2}OH$, *J* = 6.3, 6.3 Hz); 7.35-7.38, 7.45-7.48, 7.64-7.65 (all m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 22.57 (2C); 23.50; 26.12; 28.81; 62.20; 75.55; 113.41; 121.66 (q, CF_3, *J* = 269.6 Hz); 123.33; 127.97; 129.18; 137.93; 139.19 (q, $\underline{C}–CF_3$, *J* = 36.7 Hz); 151.12. ^{19}F NMR (470 MHz, $CDCl_3$, δ, ppm): 100.49 (s, CF_3). Anal. calcd. for $C_{17}H_{21}F_3N_2O_2$. C, 59.64; H, 6.18; N, 8.18. Found: C, 59.53; H, 6.12; N, 8.34.

Biological part

Laboratory animals (Sprague Dawley rats and CD-mice) were obtained from the Nursery for laboratory Animals "Pushino" at the M.M. Shemyakin and Yu.A. Ovchinnikov Institute of Bioorganic Chemistry RAS, Russia). The animals were housed at natural light cycle and otherwise in a controlled environment, in propylene cages (Bioscape, Germany), on standard bedding (Zolotoi Kot, Russia), supplied with feed for conventional laboratory rodents (BioPro, Russia) according to a schedule and water *ad libitum*.

Animal care and all the procedures were performed by professional staff according to Russian Federation Law №61-FZ March 24, 2010 On Circulation of Medicines, guidelines for preclinical study of medicinal products [Mironov, A.N. Guidelines for Preclinical Study of Medicinal Products. Part One (In Russian); Grif&Ko, Moscow: 2012; Vogel, H.G. Drug Discovery and Evaluation; Springer-Verlag, Berlin, Heidelberg, New York, USA: 2008] and in accordance with approved Regulations for Care and Use of Laboratory Animals of the Research and Educational Center for Applied Chemical and Biological Research at the Perm National Research Polytechnic University.

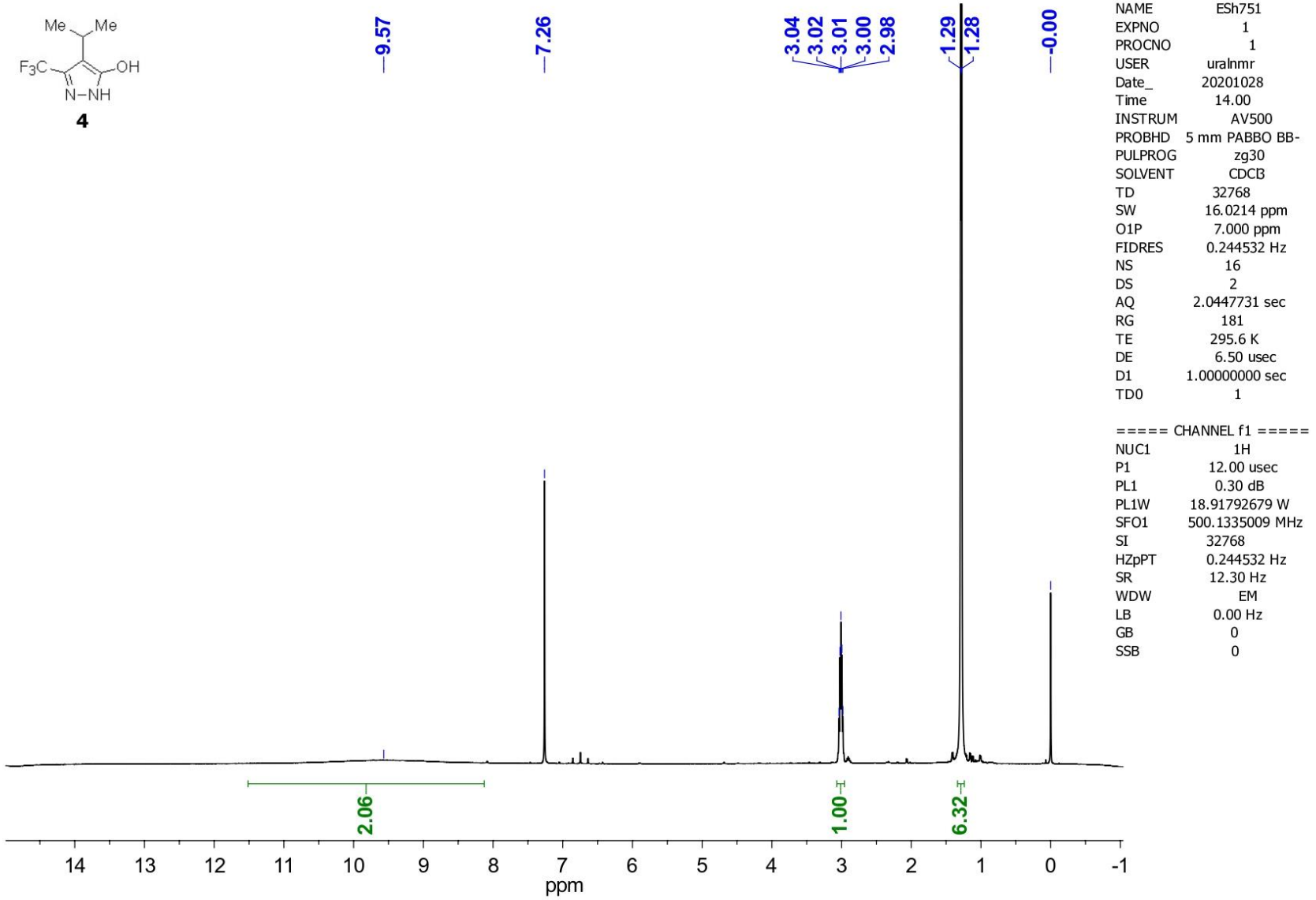
Acute toxicity evaluation

The toxicity evaluation was performed on CD-1 mice. The procedure was based on OECD recommendations and guidelines for pre-clinical study of medicinal products [Mironov, A.N. Guidelines for Preclinical Study of Medicinal Products. Part One (In Russian); Grif&Ko, Moscow: 2012; OECD Guideline 423: Acute oral toxicity. Paris: OECD 1996]. The tested compounds in 1% starch mucus were injected intraperitoneally to three mice. Then, animals were observed during 14 days, the number of deaths was counted and % of viability calculated.

The Hot plate test

The hot plate test was conducted according to established guidelines [Mironov, A.N. Guidelines for Preclinical Study of Medicinal Products. Part One (In Russian); Grif&Ko, Moscow: 2012; Vogel, H.G. Drug Discovery and Evaluation; Springer-Verlag, Berlin, Heidelberg, New York, USA: 2008] on Sprague-Dawley rats (3 male and 3 female rodents per group). The compounds were intraperitoneally administered in the form of suspensions in 1% starch mucus. Negative control group animals received vehicle only (1% starch mucus). Analgin (metamizole sodium, PAO Biosynthesis, Sun Pharma, Penza, Russia, 15 mg/kg in 1% starch mucus solution) was used as reference drug. One and two hours after the injection, rats were placed on an electrically heated to 50 ºC plate (Hot plate 60200 series, TSE-systems, Germany) in a Plexiglas cylindrical restrainer (19 cm diameter x 30 cm). The nociceptive response time was measured by observing the appearance of rats' movements (e.g. jumping, hind paws licking or shaking). Maximal cutoff time was set as 30 seconds regardless of the response in order to preclude skin damaging.

Difference between the values of the latency period for the treated (experimental) and control groups of animals were considered significant at $p \leq 0.05$. Analgesic activity was expressed as an increase (in percent) in the response time to nociceptive stimulation in the group of animals that received the substance, compared with the control group of animals, and was calculated only for those substances which significantly increased the latency period, according to the formula: $AA=((t_{tr}-t_{nc})\times 100)/t_c$, where t_{tr} is the response time to nociceptive stimulation in the group of animals that received the substance or reference drug, t_c is the response time to nociceptive stimulation in animals of the control group.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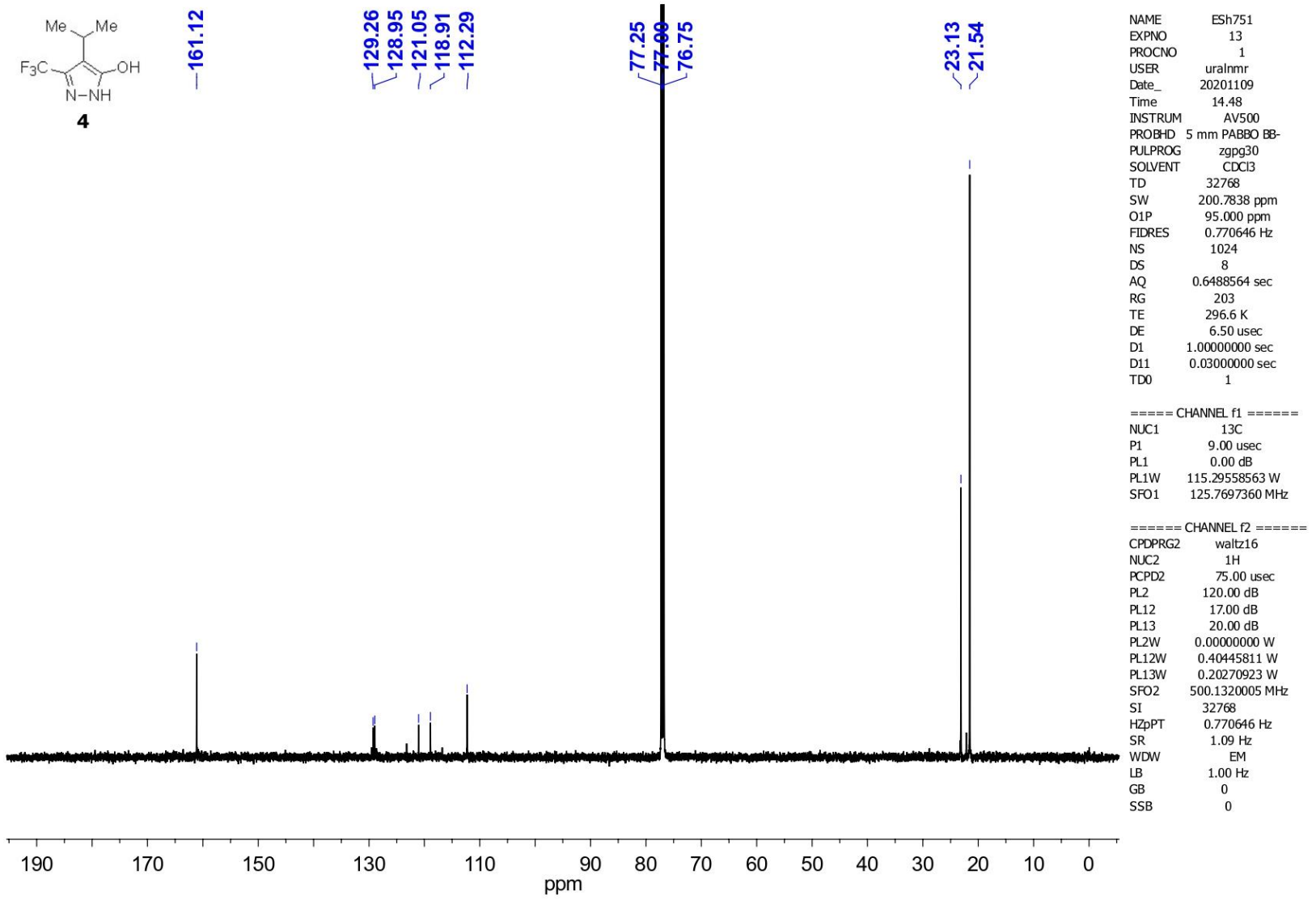
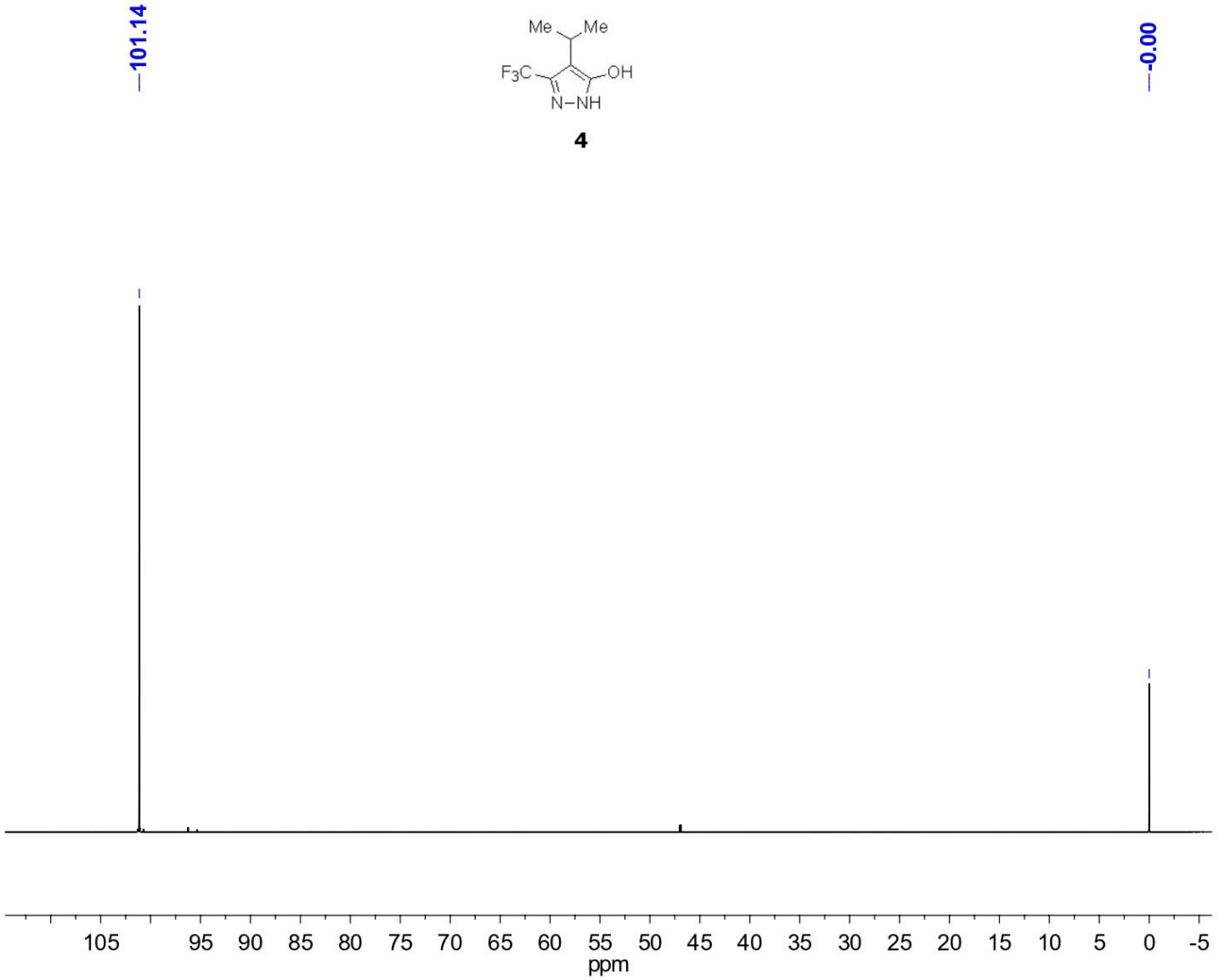
Me
F3C
OH
N–NH
4
9.57
7.26
3.04
3.02
3.01
3.00
2.98
1.29
1.28
0.00
2.06
1.00
6.32
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
NAME ESh751
EXPNO 1
PROCNO 1
USER uralnmr
Date_ 20201028
Time 14.00
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zg30
SOLVENT CDCl3
TD 32768
SW 16.0214 ppm
O1P 7.000 ppm
FIDRES 0.244532 Hz
NS 16
DS 2
AQ 2.0447731 sec
RG 181
TE 295.6 K
DE 6.50 usec
D1 1.00000000 sec
TD0 1
===== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.30 dB
PL1W 18.91792679 W
SFO1 500.1335009 MHz
SI 32768
HZpPT 0.244532 Hz
SR 12.30 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0



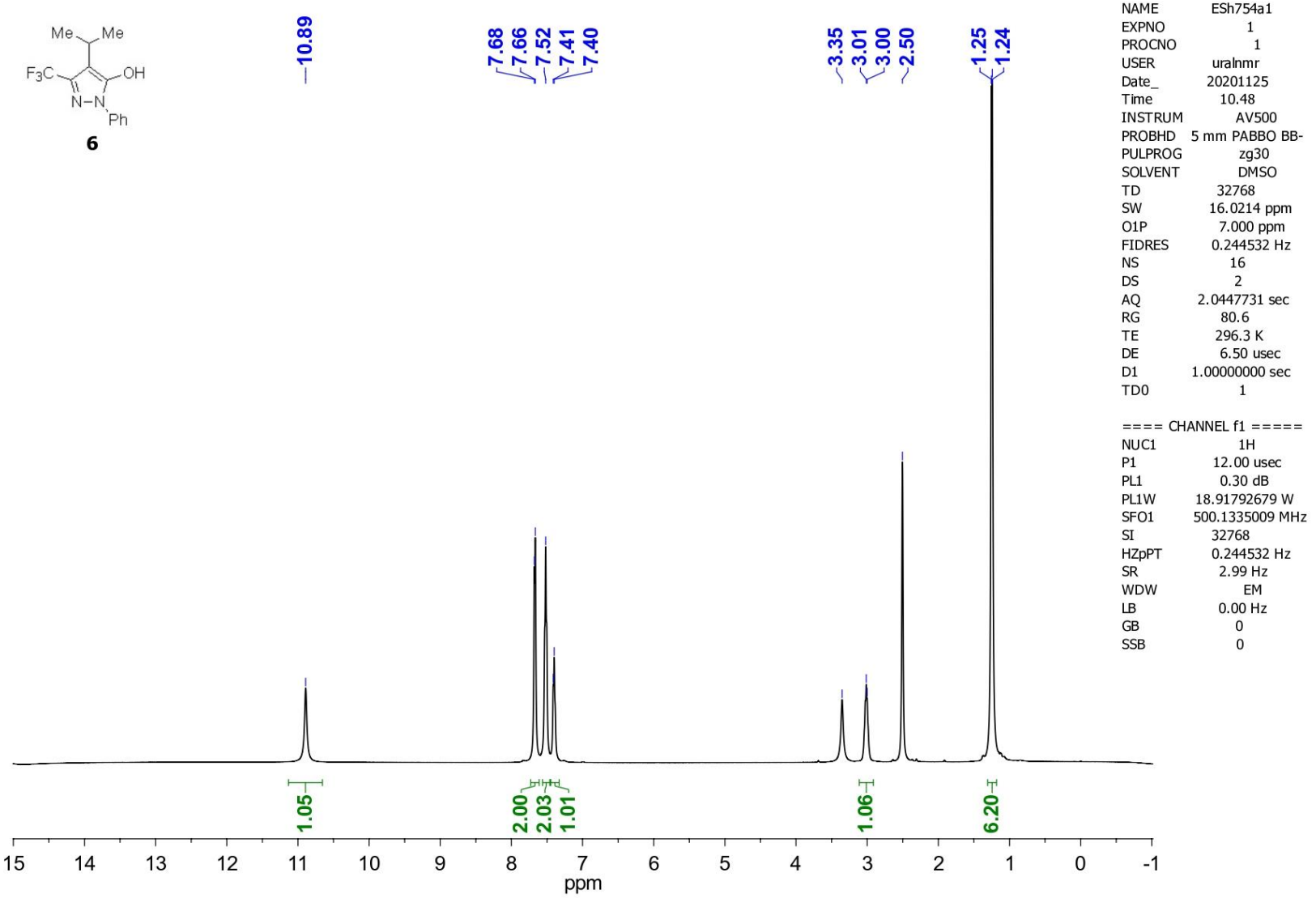
NAME	ESh751
EXPNO	13
PROCNO	1
USER	uralnmr
Date_	20201109
Time	14.48
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
SOLVENT	CDCl3
TD	32768
SW	200.7838 ppm
O1P	95.000 ppm
FIDRES	0.770646 Hz
NS	1024
DS	8
AQ	0.6488564 sec
RG	203
TE	296.6 K
DE	6.50 usec
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
===== CHANNEL f1 ======	
NUC1	13C
P1	9.00 usec
PL1	0.00 dB
PL1W	115.29558563 W
SFO1	125.7697360 MHz
====== CHANNEL f2 ======	
CPDPRG2	waltz16
NUC2	1H
PCPD2	75.00 usec
PL2	120.00 dB
PL12	17.00 dB
PL13	20.00 dB
PL2W	0.00000000 W
PL12W	0.40445811 W
PL13W	0.20270923 W
SFO2	500.1320005 MHz
SI	32768
HZpPT	0.770646 Hz
SR	1.09 Hz
WDW	EM
LB	1.00 Hz
GB	0
SSB	0



NAME	ESh751
EXPNO	19
PROCNO	1
USER	urahmr
Date_	20201028
Time	14.03
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zg30
SOLVENT	CDCl3
TD	131072
SW	120.7506 ppm
O1P	55.000 ppm
FIDRES	0.433488 Hz
NS	16
DS	2
AQ	1.1534836 sec
RG	203
TE	295.7 K
DE	6.50 usec
D1	1.00000000 sec
TD0	1

==== CHANNEL f1 =====

NUC1	19F
P1	15.50 usec
PL1	-5.00 dB
PL1W	46.07103729 W
SFO1	470.5417584 MHz
SI	131072
HZpPT	0.433488 Hz
SR	398.61 Hz
WDW	EM
LB	0.00 Hz
GB	0
SSB	0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OH
N–N
Ph
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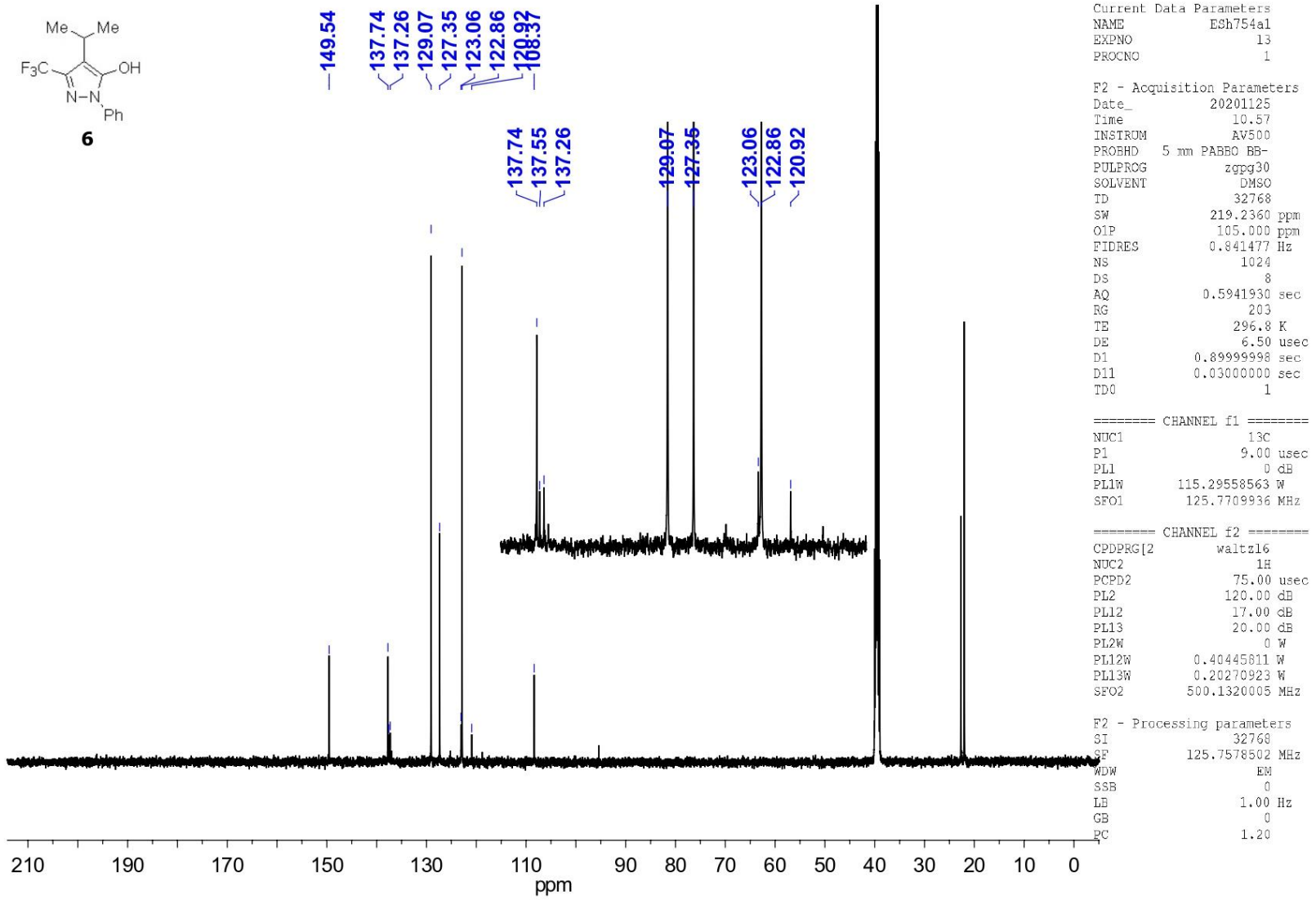
7.68
7.66
7.52
7.41
7.40
3.35
3.01
3.00
2.50
1.25
1.24
1.05
2.00
2.03
1.01
1.06
6.20
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
ppm
NAME ESh754a1
EXPNO 1
PROCNO 1
USER uralnmr
Date_ 20201125
Time 10.48
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zg30
SOLVENT DMSO
TD 32768
SW 16.0214 ppm
O1P 7.000 ppm
FIDRES 0.244532 Hz
NS 16
DS 2
AQ 2.0447731 sec
RG 80.6
TE 296.3 K
DE 6.50 usec
D1 1.00000000 sec
TD0 1
==== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.30 dB
PL1W 18.91792679 W
SFO1 500.1335009 MHz
SI 32768
HZpPT 0.244532 Hz
SR 2.99 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0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F3C
OH
N–N
Ph
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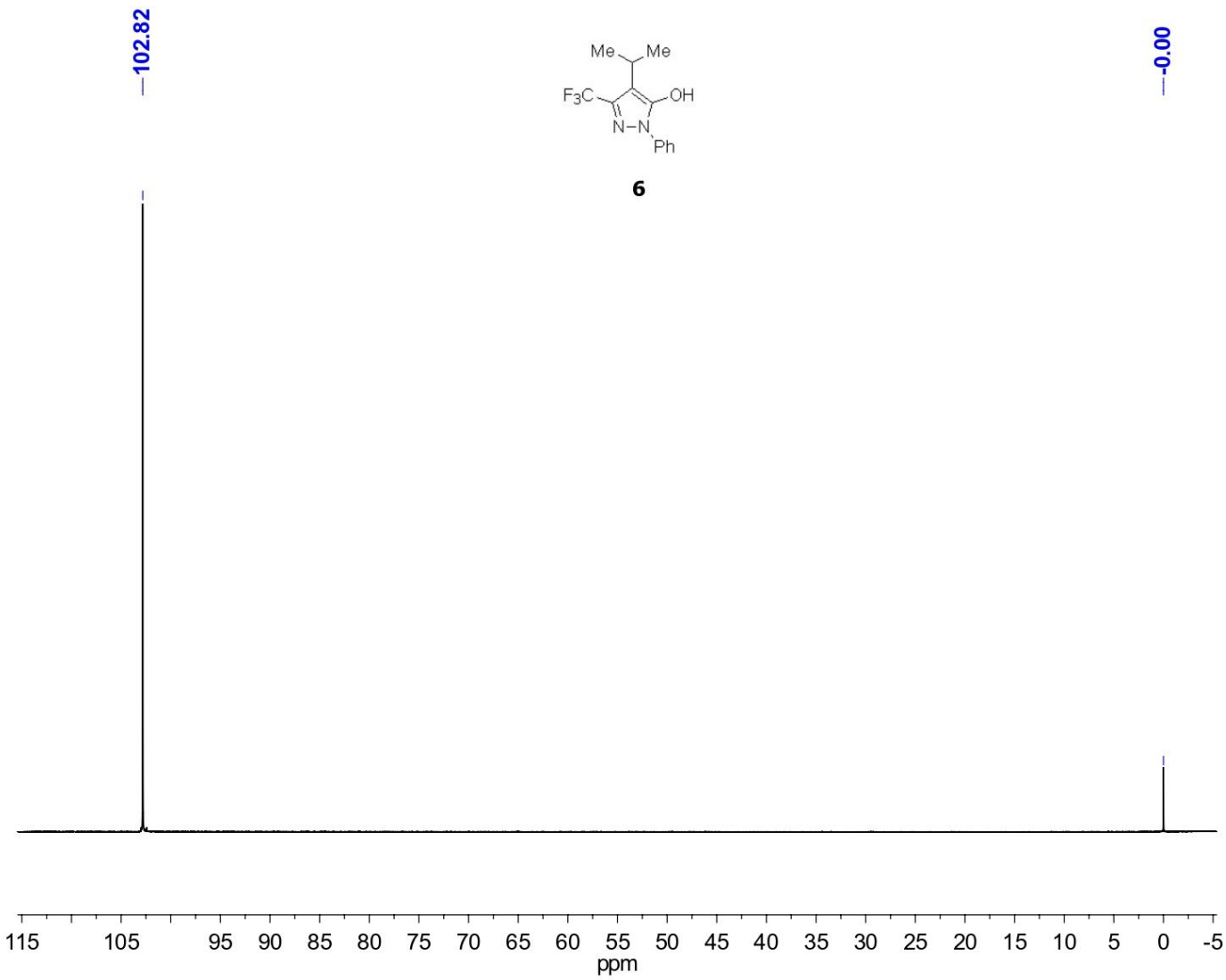
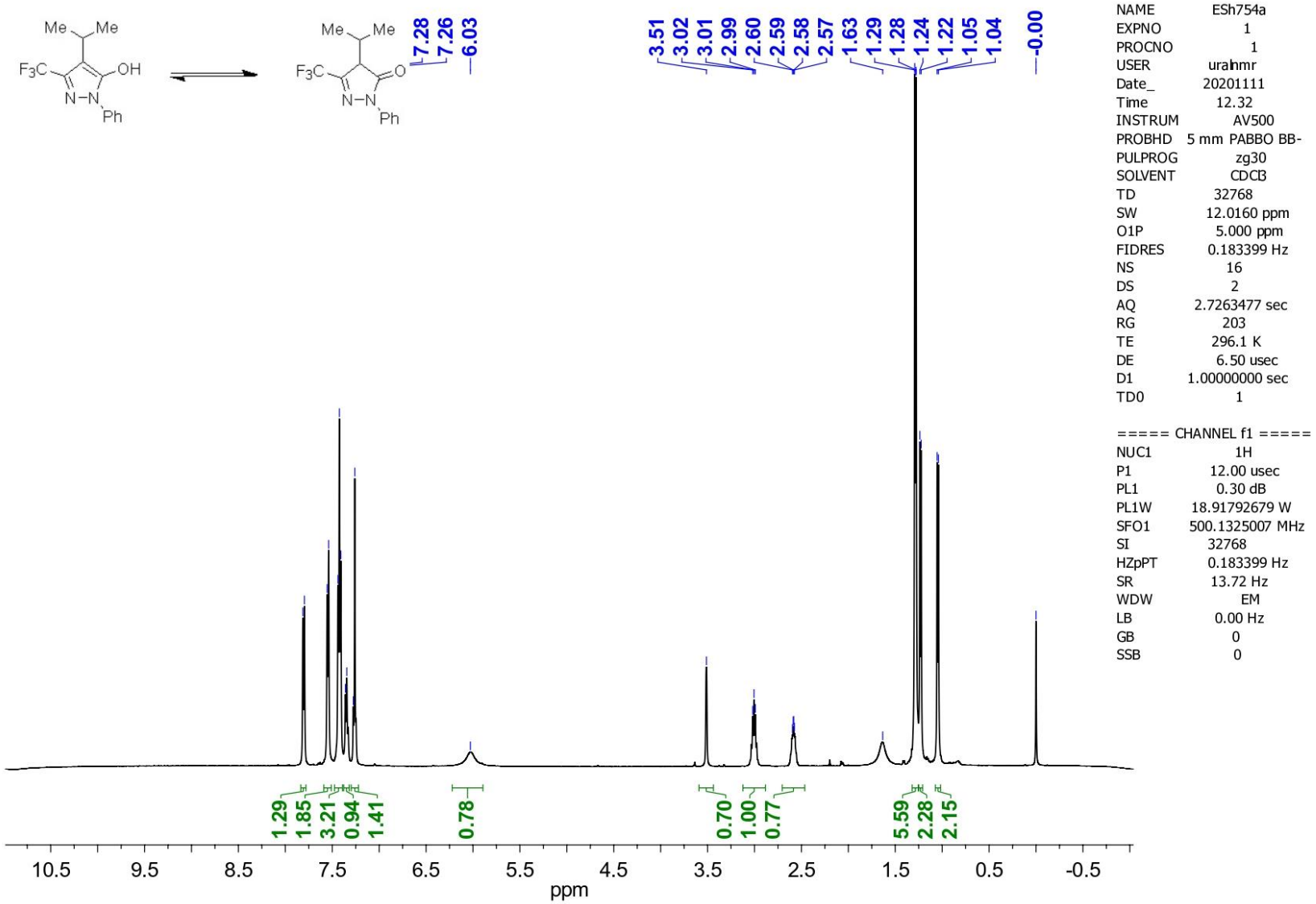
137.26
129.07
127.35
123.06
122.86
120.92
108.37
137.74
137.55
137.26
129.07
127.35
123.06
122.86
120.92
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
ppm
Current Data Parameters
NAME ESh754a1
EXPNO 13
PROCNO 1
F2 - Acquisition Parameters
Date_ 20201125
Time 10.57
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
SOLVENT DMSO
TD 32768
SW 219.2360 ppm
O1P 105.000 ppm
FIDRES 0.841477 Hz
NS 1024
DS 8
AQ 0.5941930 sec
RG 203
TE 296.8 K
DE 6.50 usec
D1 0.89999998 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.00 usec
PL1 0 dB
PL1W 115.29558563 W
SFO1 125.7709936 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 75.00 usec
PL2 120.00 dB
PL12 17.00 dB
PL13 20.00 dB
PL2W 0 W
PL12W 0.40445811 W
PL13W 0.20270923 W
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7578502 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.20



NAME	ESh754a1
EXPNO	19
PROCNO	1
USER	uralnmr
Date_	20201125
Time	10.53
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zg30
SOLVENT	DMSO
TD	131072
SW	120.7506 ppm
O1P	55.000 ppm
FIDRES	0.433488 Hz
NS	8
DS	2
AQ	1.1534836 sec
RG	203
TE	296.3 K
DE	6.50 usec
D1	1.00000000 sec
TD0	1
==== CHANNEL f1 =====	
NUC1	19F
P1	15.50 usec
PL1	-5.00 dB
PL1W	46.07103729 W
SFO1	470.5417584 MHz
SI	131072
HZpPT	0.433488 Hz
SR	-12.29 Hz
WDW	EM
LB	0.00 Hz
GB	0
SSB	0


Me
Me
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OH
N–N
Ph
Me
Me
F3C
O
N–N
Ph
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7.26
6.03
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3.02
3.01
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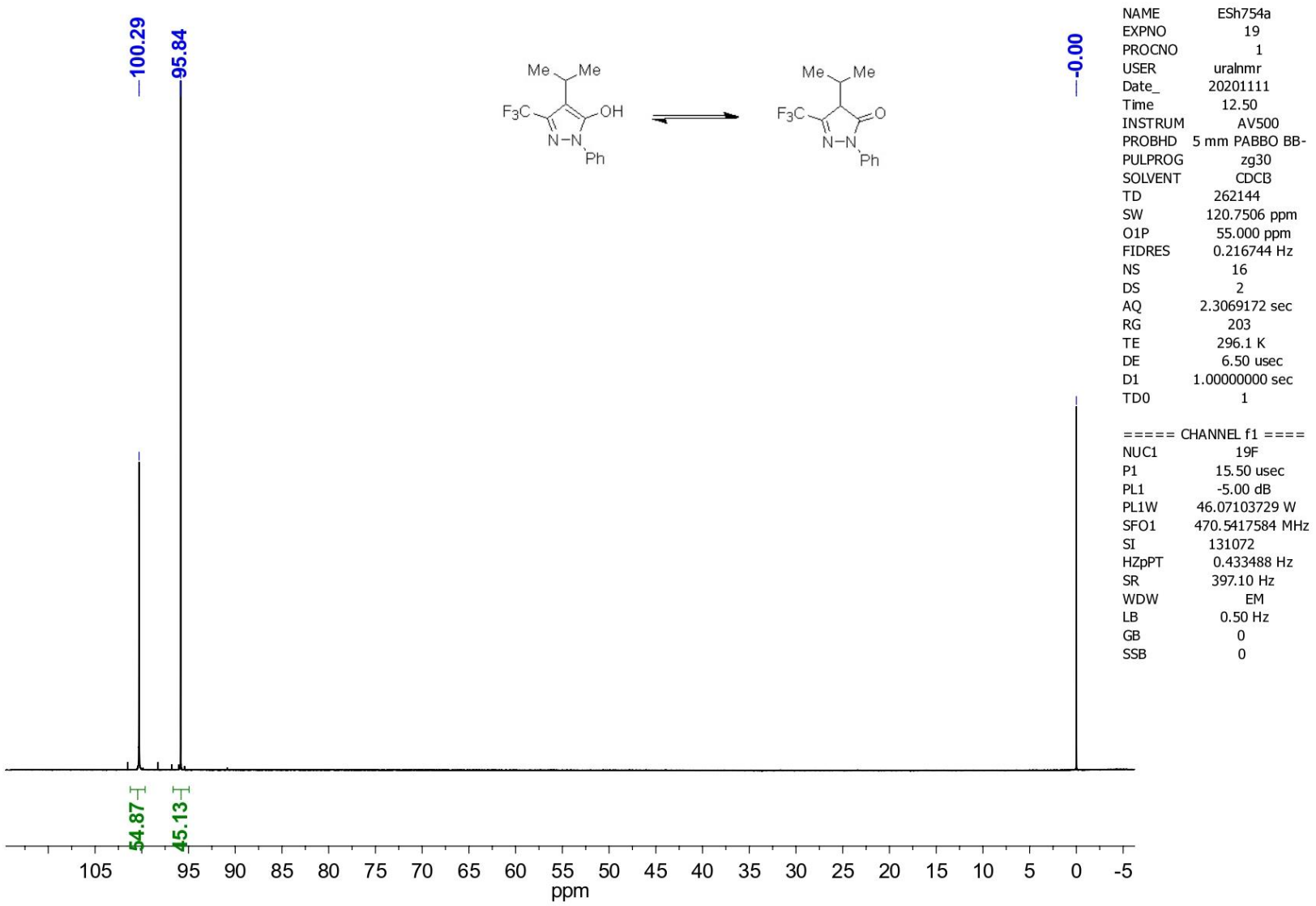
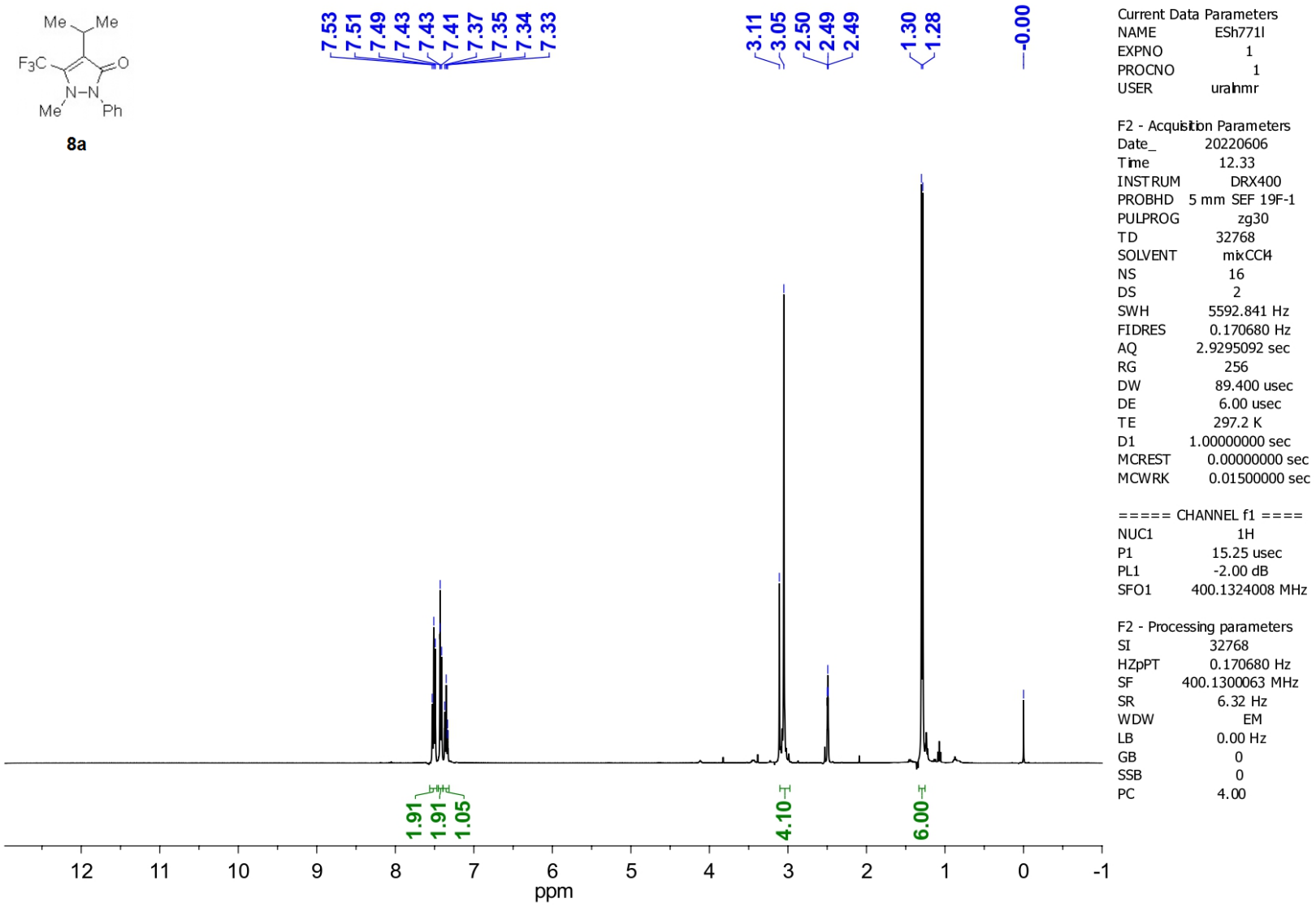
2.59
2.58
2.57
1.63
1.29
1.28
1.24
1.22
1.05
1.04
0.00
1.29
1.85
3.21
0.94
1.41
0.78
0.70
1.00
0.77
5.59
2.28
2.15
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
ppm
NAME ESh754a
EXPNO 1
PROCNO 1
USER urahmr
Date_ 20201111
Time 12.32
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zg30
SOLVENT CDCl3
TD 32768
SW 12.0160 ppm
O1P 5.000 ppm
FIDRES 0.183399 Hz
NS 16
DS 2
AQ 2.7263477 sec
RG 203
TE 296.1 K
DE 6.50 usec
D1 1.00000000 sec
TD0 1
===== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.30 dB
PL1W 18.91792679 W
SFO1 500.1325007 MHz
SI 32768
HZpPT 0.183399 Hz
SR 13.72 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0



NAME	ESh754a
EXPNO	19
PROCNO	1
USER	uralnmr
Date_	20201111
Time	12.50
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zg30
SOLVENT	CDCl3
TD	262144
SW	120.7506 ppm
O1P	55.000 ppm
FIDRES	0.216744 Hz
NS	16
DS	2
AQ	2.3069172 sec
RG	203
TE	296.1 K
DE	6.50 usec
D1	1.00000000 sec
TD0	1
===== CHANNEL f1 ====	
NUC1	19F
P1	15.50 usec
PL1	-5.00 dB
PL1W	46.07103729 W
SFO1	470.5417584 MHz
SI	131072
HZpPT	0.433488 Hz
SR	397.10 Hz
WDW	EM
LB	0.50 Hz
GB	0
SSB	0

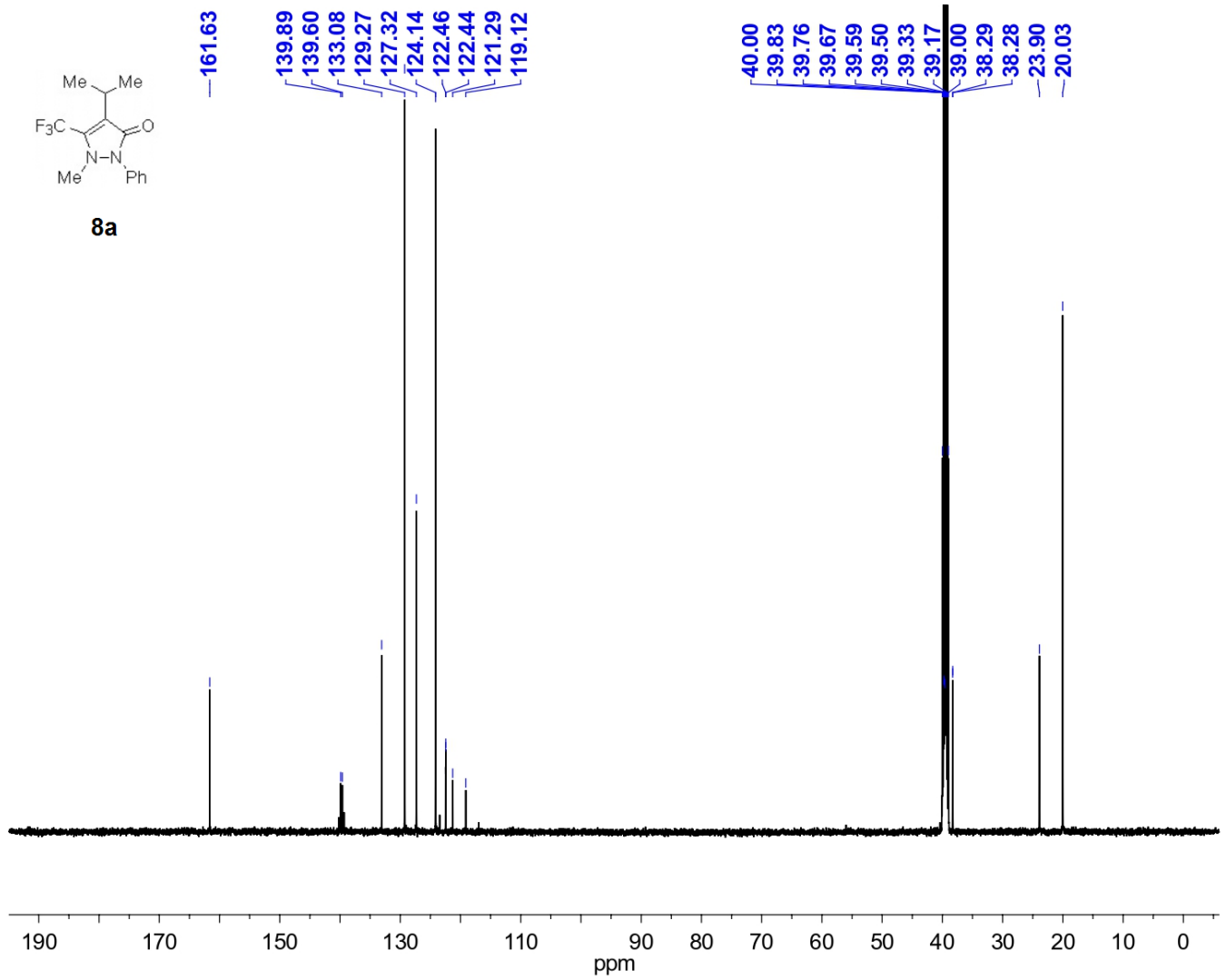


Current Data Parameters
NAME ESh771l
EXPNO 1
PROCNO 1
USER uralnmr

F2 - Acquisition Parameters
Date_ 20220606
Time 12.33
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 32768
SOLVENT mixCCl4
NS 16
DS 2
SWH 5592.841 Hz
FIDRES 0.170680 Hz
AQ 2.9295092 sec
RG 256
DW 89.400 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 ====
NUC1 1H
P1 15.25 usec
PL1 -2.00 dB
SFO1 400.1324008 MHz

F2 - Processing parameters
SI 32768
HZpPT 0.170680 Hz
SF 400.1300063 MHz
SR 6.32 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 4.00



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EXPNO	13
PROCNO	1
USER	uralnmr
Date_	20220623
Time	16.16
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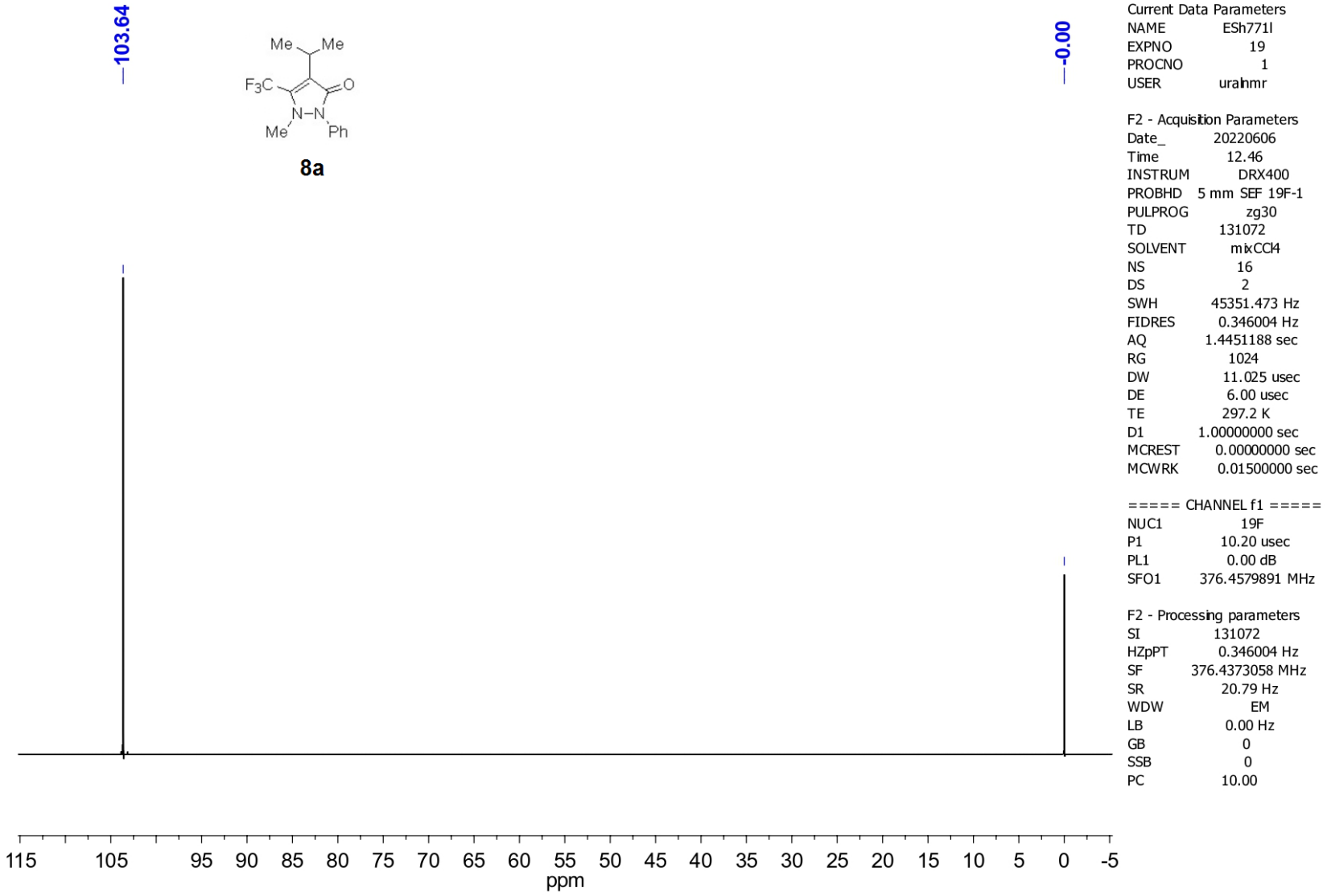
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
SOLVENT	DMSO
TD	65536
SW	200.7838 ppm
O1P	95.000 ppm
FIDRES	0.385323 Hz
NS	2048
DS	8
AQ	1.2976629 sec
RG	203
TE	296.0 K
DE	6.50 usec
D1	1.00000000 sec
D11	0.03000000 sec
TD0	2
===== CHANNEL f1 ======	
NUC1	13C
P1	10.00 usec
PL1	0.00 dB
PL1W	115.29558563 W
SFO1	125.7697360 MHz
====== CHANNEL f2 =====	
CPDPRG2	waltz16
NUC2	1H
PCPD2	75.00 usec
PL2	120.00 dB
PL12	16.30 dB
PL13	19.30 dB
PL2W	0.00000000 W
PL12W	0.47519693 W
PL13W	0.23816262 W
SFO2	500.1320005 MHz
SI	65536
HZpPT	0.385323 Hz
SR	62.74 Hz
WDW	EM
LB	1.00 Hz
GB	0
SSB	0

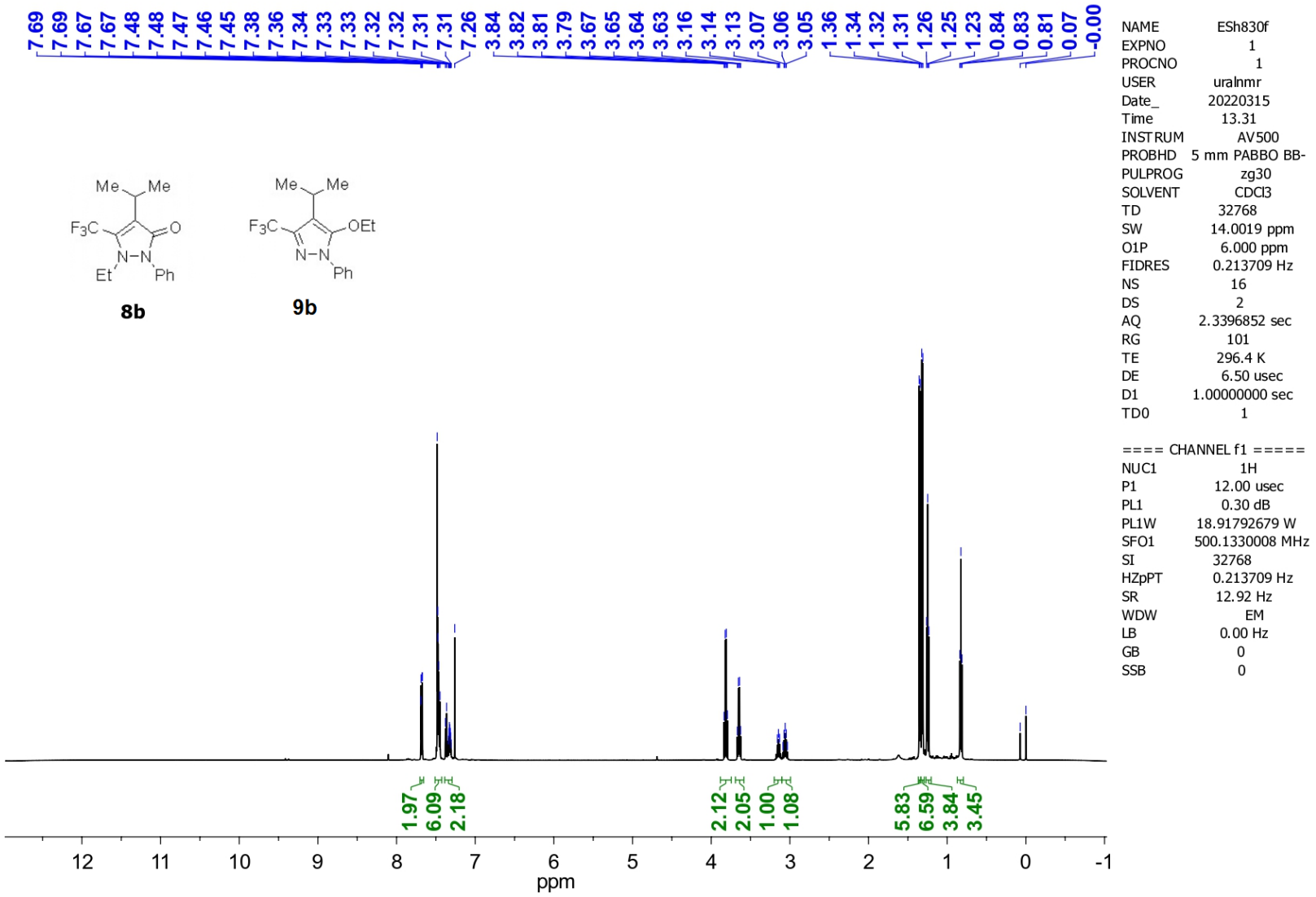


Current Data Parameters
NAME ESh771l
EXPNO 19
PROCNO 1
USER uralnmr

F2 - Acquisition Parameters
Date_ 20220606
Time 12.46
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 131072
SOLVENT mixCCl4
NS 16
DS 2
SWH 45351.473 Hz
FIDRES 0.346004 Hz
AQ 1.4451188 sec
RG 1024
DW 11.025 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

===== CHANNEL f1 =====
NUC1 19F
P1 10.20 usec
PL1 0.00 dB
SFO1 376.4579891 MHz

F2 - Processing parameters
SI 131072
HZpPT 0.346004 Hz
SF 376.4373058 MHz
SR 20.79 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 10.00



NAME	ESh830f
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PROCNO	1
USER	uralnmr
Date_	20220315
Time	13.31
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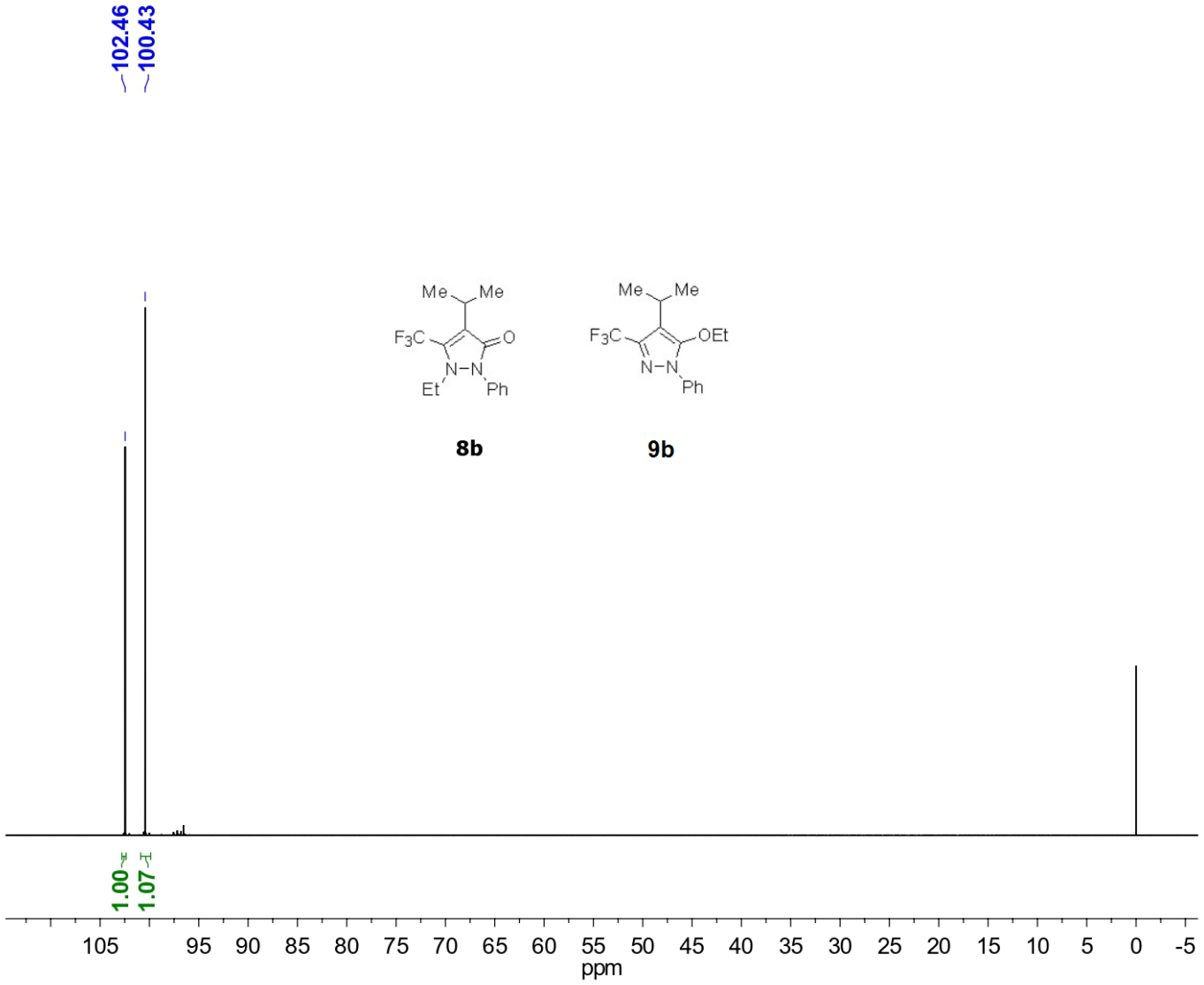
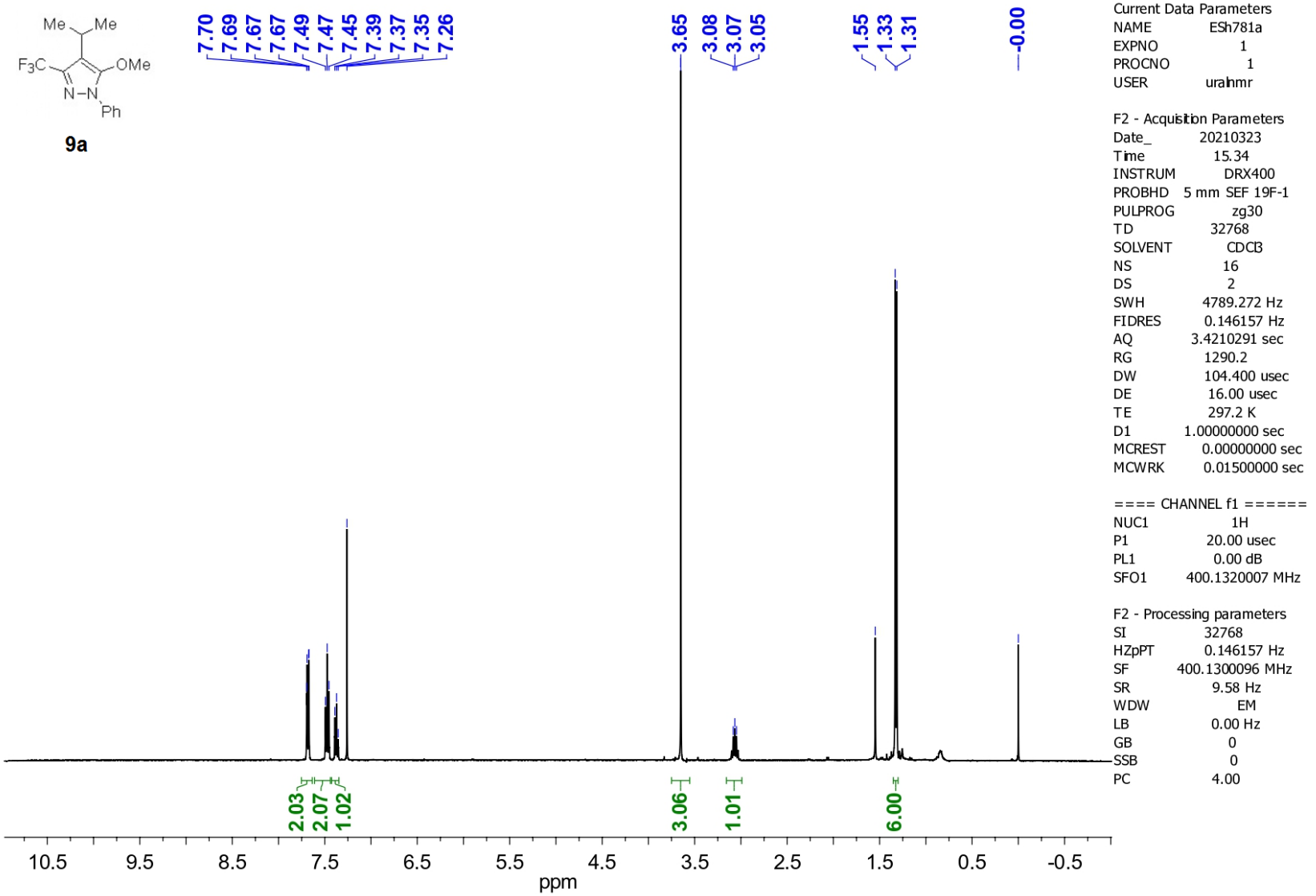
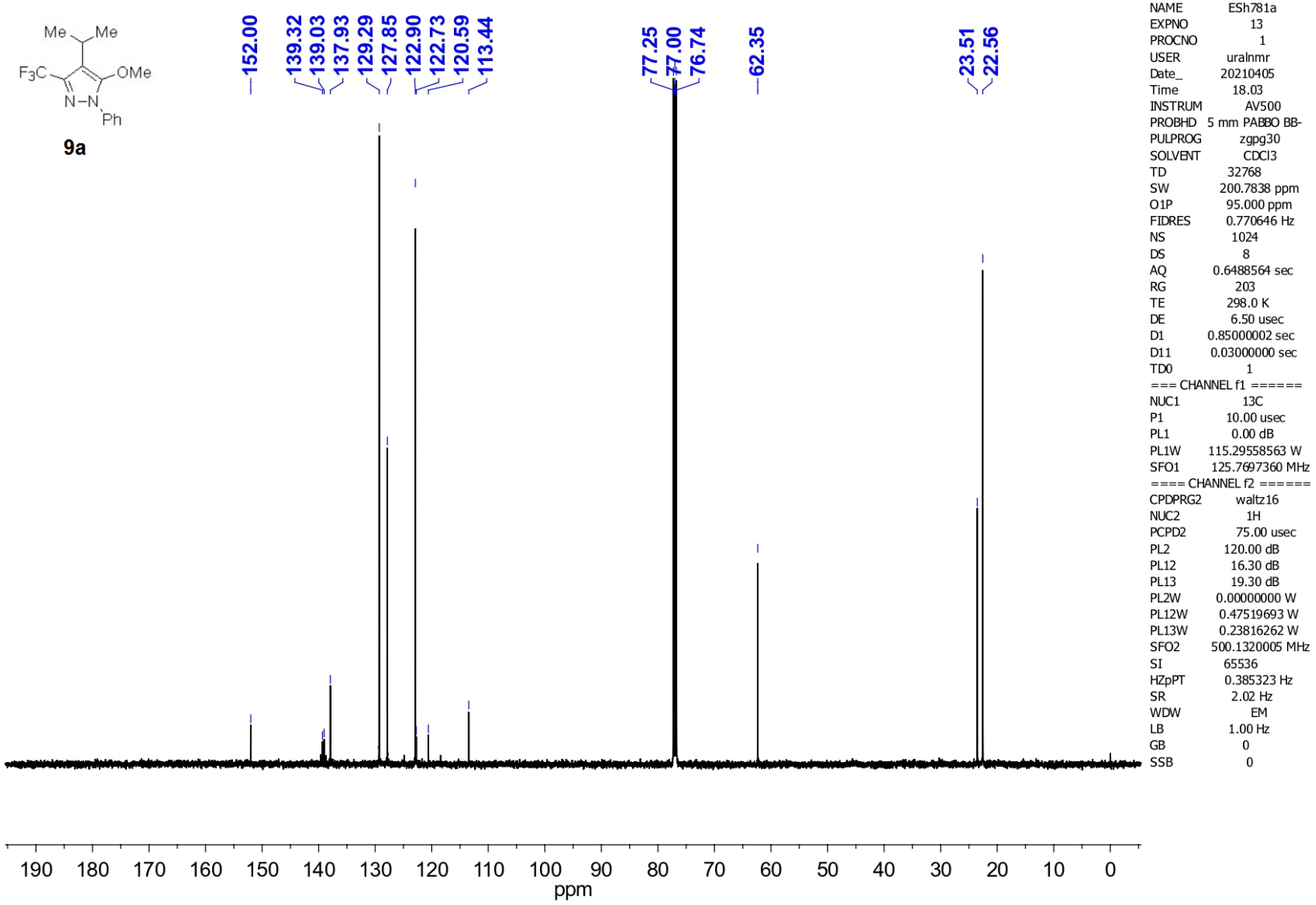
PROBHD	5 mm PABBO BB-
PULPROG	zg30
SOLVENT	CDCl3
TD	32768
SW	14.0019 ppm
O1P	6.000 ppm
FIDRES	0.213709 Hz
NS	16
DS	2
AQ	2.3396852 sec
RG	101
TE	296.4 K
DE	6.50 usec
D1	1.00000000 sec
TD0	1
==== CHANNEL f1 =====	
NUC1	1H
P1	12.00 usec
PL1	0.30 dB
PL1W	18.91792679 W
SFO1	500.1330008 MHz
SI	32768
HZpPT	0.213709 Hz
SR	12.92 Hz
WDW	EM
LB	0.00 Hz
GB	0
SSB	0

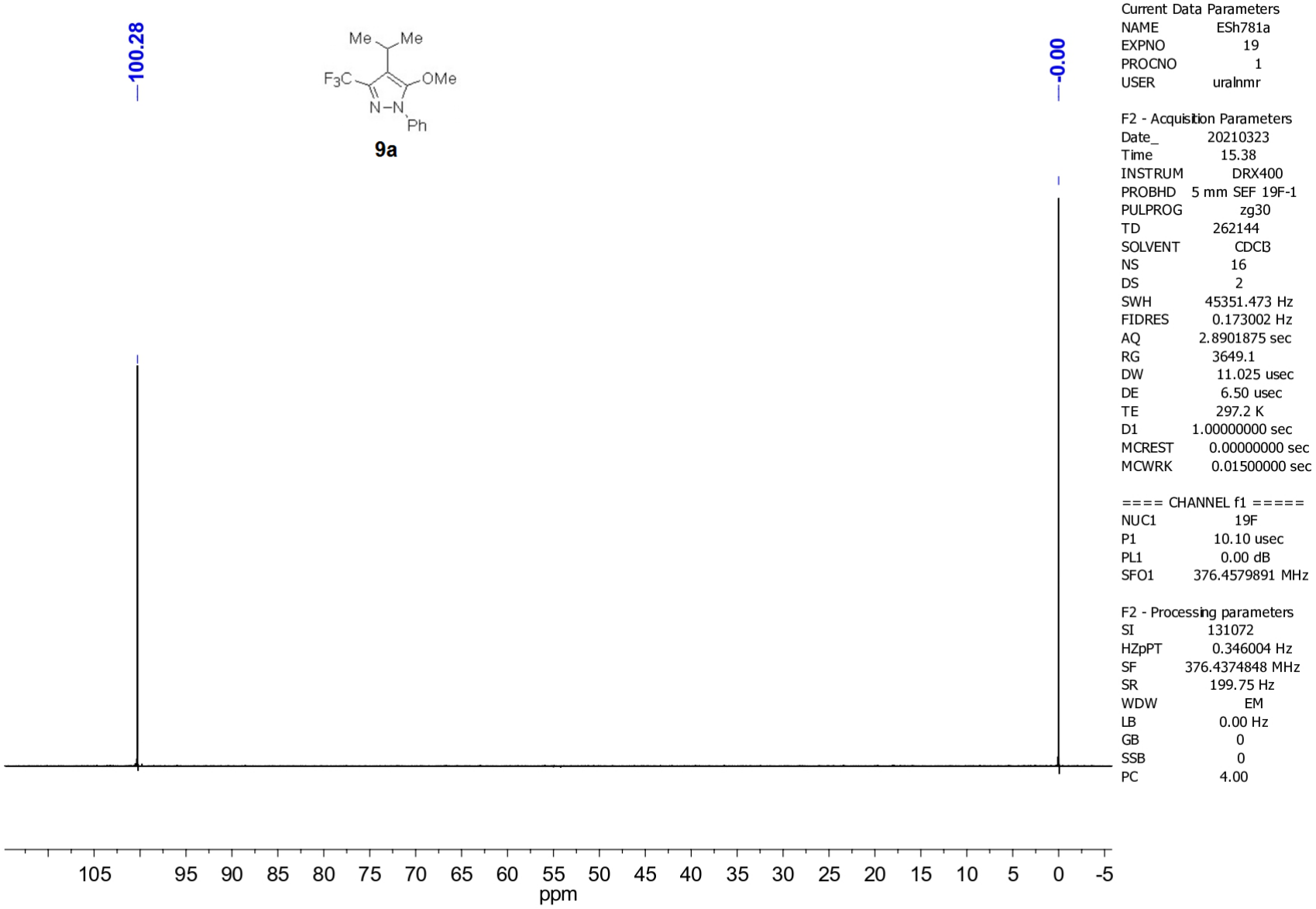


NAME	ESh830f
EXPNO	19
PROCNO	1
USER	uralnmr
Date_	20220315
Time	13.34
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zg30
SOLVENT	CDCl3
TD	131072
SW	120.7506 ppm
O1P	55.000 ppm
FIDRES	0.433488 Hz
NS	8
DS	2
AQ	1.1534836 sec
RG	203
TE	296.5 K
DE	6.50 usec
D1	1.00000000 sec
TD0	1

===== CHANNEL f1 ======	
NUC1	19F
P1	15.50 usec
PL1	-5.00 dB
PL1W	46.07103729 W
SFO1	470.5417584 MHz
SI	131072
HZpPT	0.433488 Hz
SR	395.02 Hz
WDW	EM
LB	0.00 Hz
GB	0
SSB	0


Me
Me
F3C
OMe
N–N
Ph
9a
7.70
7.69
7.67
7.67
7.49
7.47
7.45
7.39
7.37
7.35
7.26
3.65
3.08
3.07
3.05
1.55
1.33
1.31
0.00
2.03
2.07
1.02
3.06
1.01
6.00
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
ppm
Current Data Parameters
NAME ESh781a
EXPNO 1
PROCNO 1
USER uralnmr
F2 - Acquisition Parameters
Date_ 20210323
Time 15.34
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 1290.2
DW 104.400 usec
DE 16.00 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
==== CHANNEL f1 ======
NUC1 1H
P1 20.00 usec
PL1 0.00 dB
SFO1 400.1320007 MHz
F2 - Processing parameters
SI 32768
HZpPT 0.146157 Hz
SF 400.1300096 MHz
SR 9.58 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 4.00


Me
Me
F3C
OMe
N–N
Ph
9a
152.00
139.32
139.03
137.93
129.29
127.85
122.90
122.73
120.59
113.44
77.25
77.00
76.74
62.35
23.51
22.56
NAME ESh781a
EXPNO 13
PROCNO 1
USER uralnmr
Date_ 20210405
Time 18.03
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
SOLVENT CDCl3
TD 32768
SW 200.7838 ppm
O1P 95.000 ppm
FIDRES 0.770646 Hz
NS 1024
DS 8
AQ 0.6488564 sec
RG 203
TE 298.0 K
DE 6.50 usec
D1 0.85000002 sec
D11 0.03000000 sec
TD0 1
=== CHANNEL f1 ======
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
PL1W 115.29558563 W
SFO1 125.7697360 MHz
==== CHANNEL f2 ======
CPDPRG2 waltz16
NUC2 1H
PCPD2 75.00 usec
PL2 120.00 dB
PL12 16.30 dB
PL13 19.30 dB
PL2W 0.00000000 W
PL12W 0.47519693 W
PL13W 0.23816262 W
SFO2 500.1320005 MHz
SI 65536
HZpPT 0.385323 Hz
SR 2.02 Hz
WDW EM
LB 1.00 Hz
GB 0
SSB 0
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

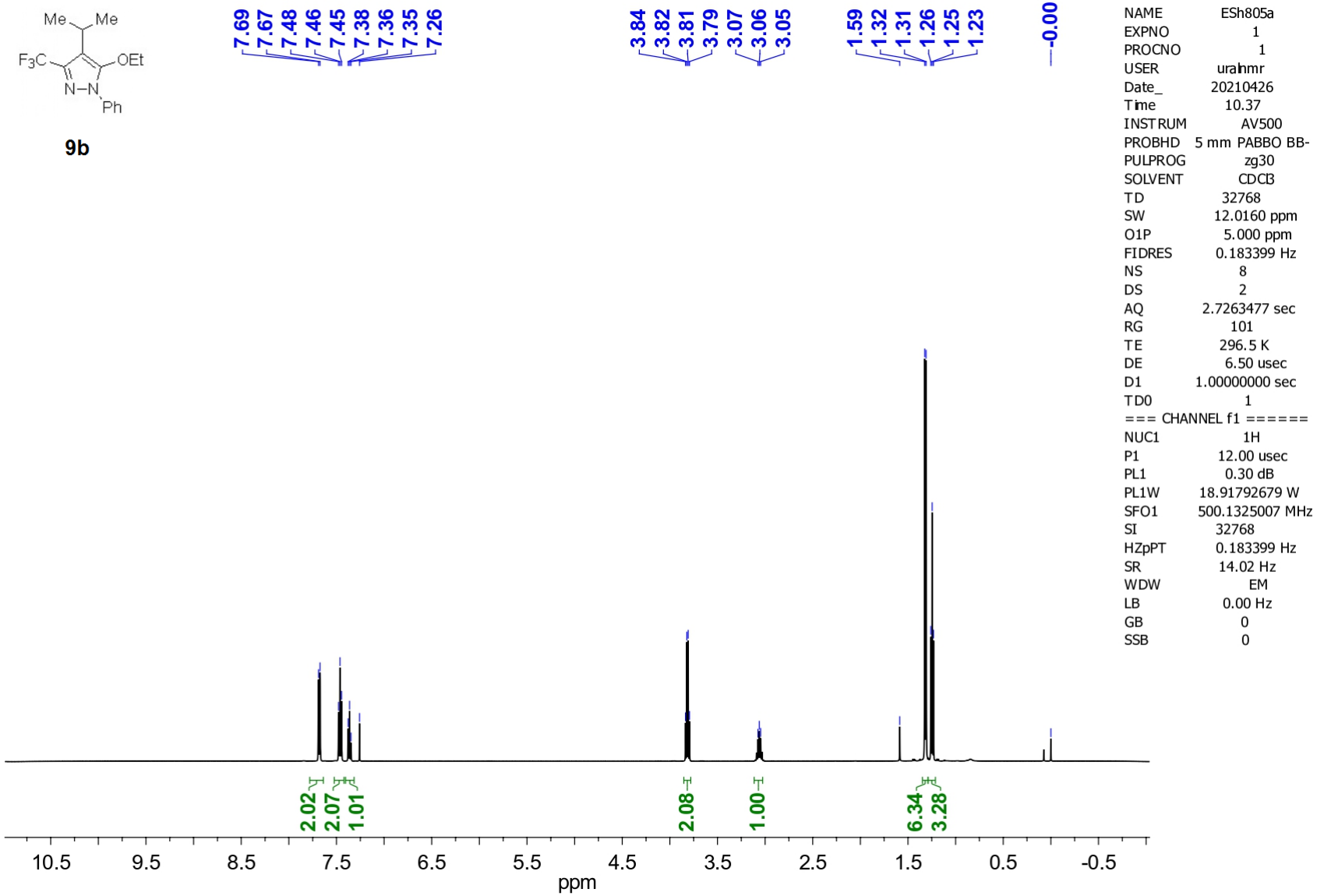


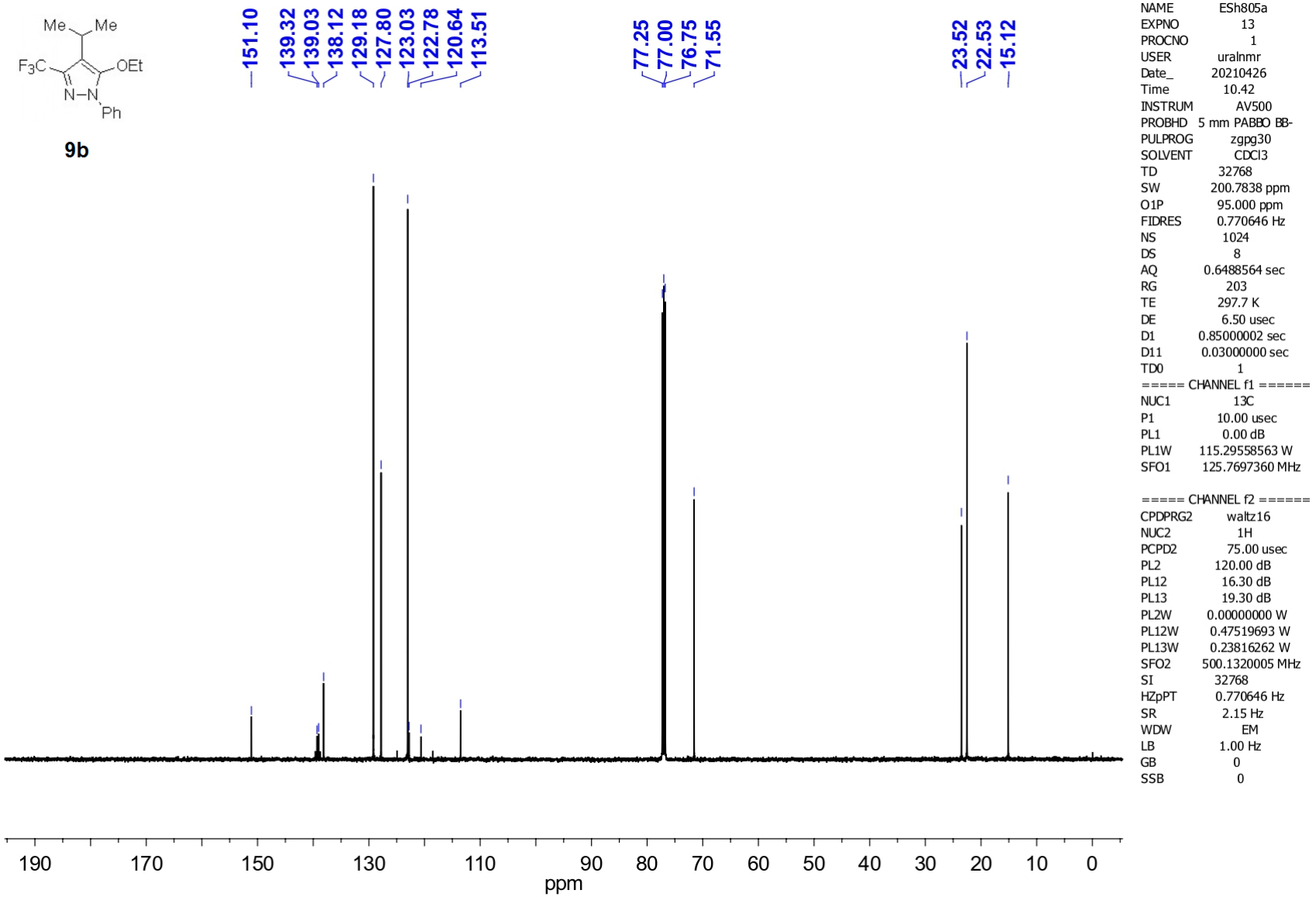
Current Data Parameters
NAME ESh781a
EXPNO 19
PROCNO 1
USER uralnmr

F2 - Acquisition Parameters
Date_ 20210323
Time 15.38
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 262144
SOLVENT CDCl3
NS 16
DS 2
SWH 45351.473 Hz
FIDRES 0.173002 Hz
AQ 2.8901875 sec
RG 3649.1
DW 11.025 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

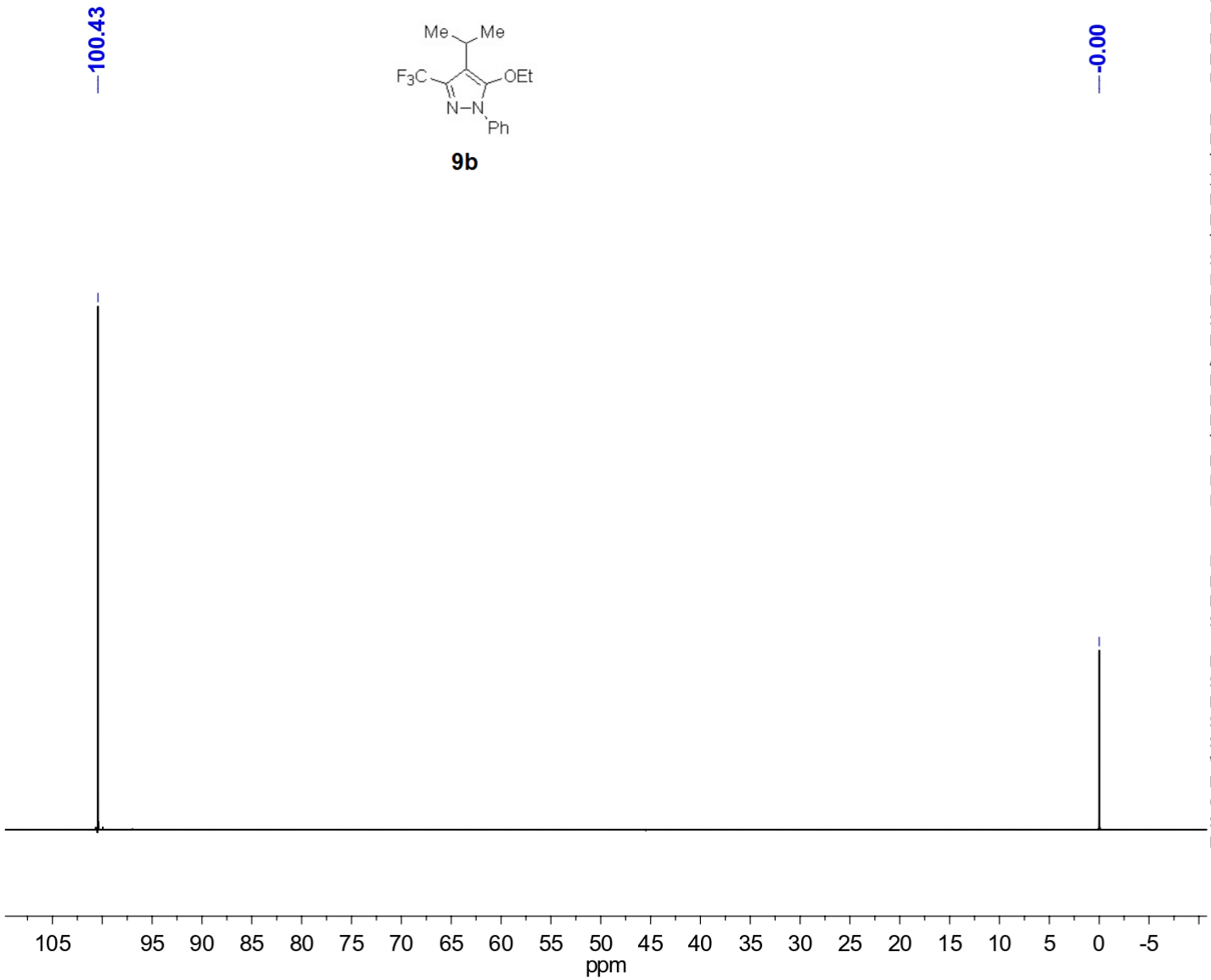
==== CHANNEL f1 =====
NUC1 19F
P1 10.10 usec
PL1 0.00 dB
SFO1 376.4579891 MHz

F2 - Processing parameters
SI 131072
HZpPT 0.346004 Hz
SF 376.4374848 MHz
SR 199.75 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 4.00


Me
Me
F3C
OEt
N–N
Ph
9b
7.69
7.67
7.48
7.46
7.45
7.38
7.36
7.35
7.26
3.84
3.82
3.81
3.79
3.07
3.06
3.05
1.59
1.32
1.31
1.26
1.25
1.23
-0.00
NAME ESh805a
EXPNO 1
PROCNO 1
USER uralhmr
Date_ 20210426
Time 10.37
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zg30
SOLVENT CDCl3
TD 32768
SW 12.0160 ppm
O1P 5.000 ppm
FIDRES 0.183399 Hz
NS 8
DS 2
AQ 2.7263477 sec
RG 101
TE 296.5 K
DE 6.50 usec
D1 1.00000000 sec
TD0 1
=== CHANNEL f1 ======
NUC1 1H
P1 12.00 usec
PL1 0.30 dB
PL1W 18.91792679 W
SFO1 500.1325007 MHz
SI 32768
HZpPT 0.183399 Hz
SR 14.02 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
2.02
2.07
1.01
2.08
1.00
6.34
3.28
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
ppm



NAME	ESh805a
EXPNO	13
PROCNO	1
USER	uralnmr
Date_	20210426
Time	10.42
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
SOLVENT	CDCl3
TD	32768
SW	200.7838 ppm
O1P	95.000 ppm
FIDRES	0.770646 Hz
NS	1024
DS	8
AQ	0.6488564 sec
RG	203
TE	297.7 K
DE	6.50 usec
D1	0.85000002 sec
D11	0.03000000 sec
TD0	1
===== CHANNEL f1 ======	
NUC1	13C
P1	10.00 usec
PL1	0.00 dB
PL1W	115.29558563 W
SFO1	125.7697360 MHz
===== CHANNEL f2 ======	
CPDPRG2	waltz16
NUC2	1H
PCPD2	75.00 usec
PL2	120.00 dB
PL12	16.30 dB
PL13	19.30 dB
PL2W	0.00000000 W
PL12W	0.47519693 W
PL13W	0.23816262 W
SFO2	500.1320005 MHz
SI	32768
HZpPT	0.770646 Hz
SR	2.15 Hz
WDW	EM
LB	1.00 Hz
GB	0
SSB	0

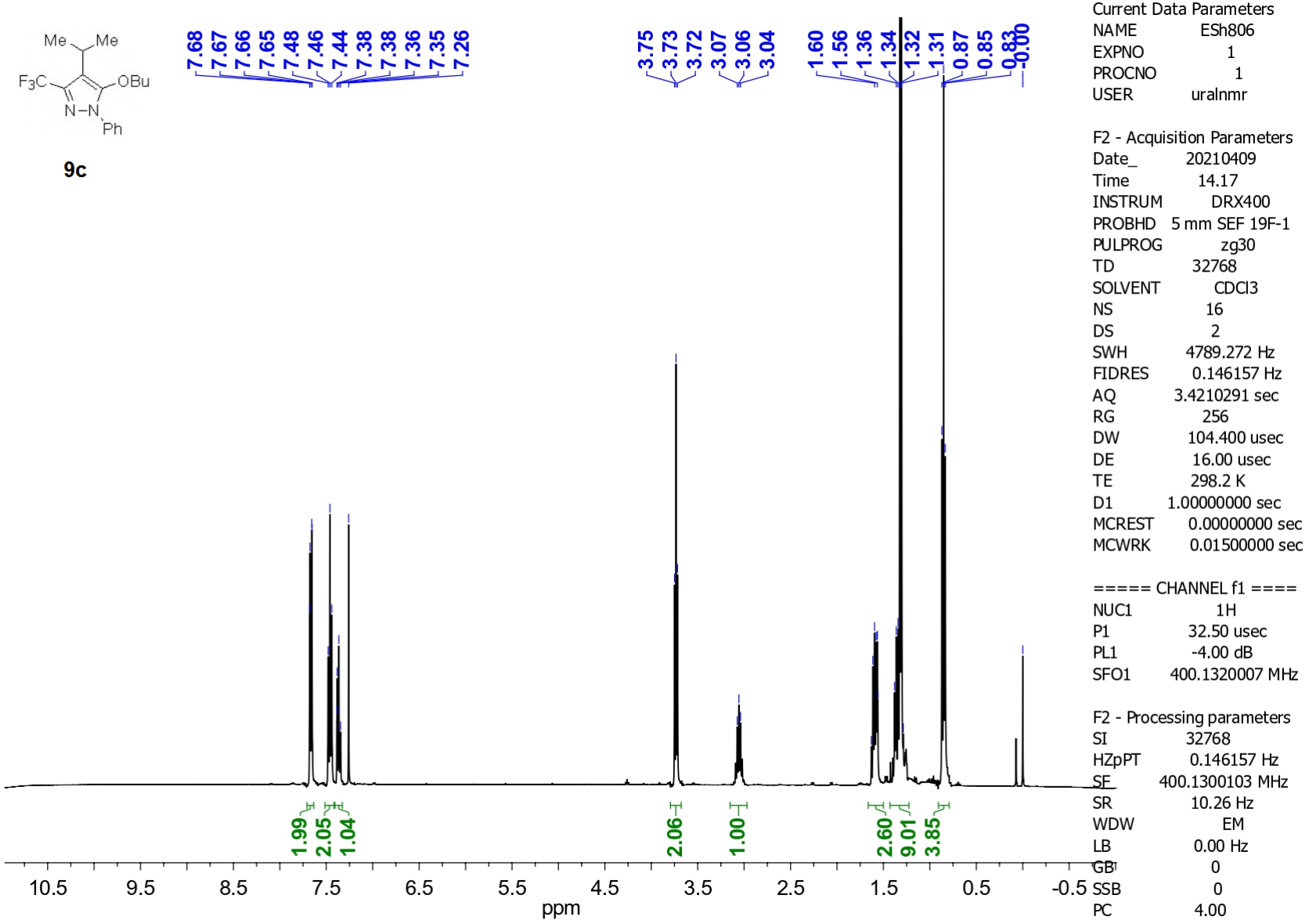


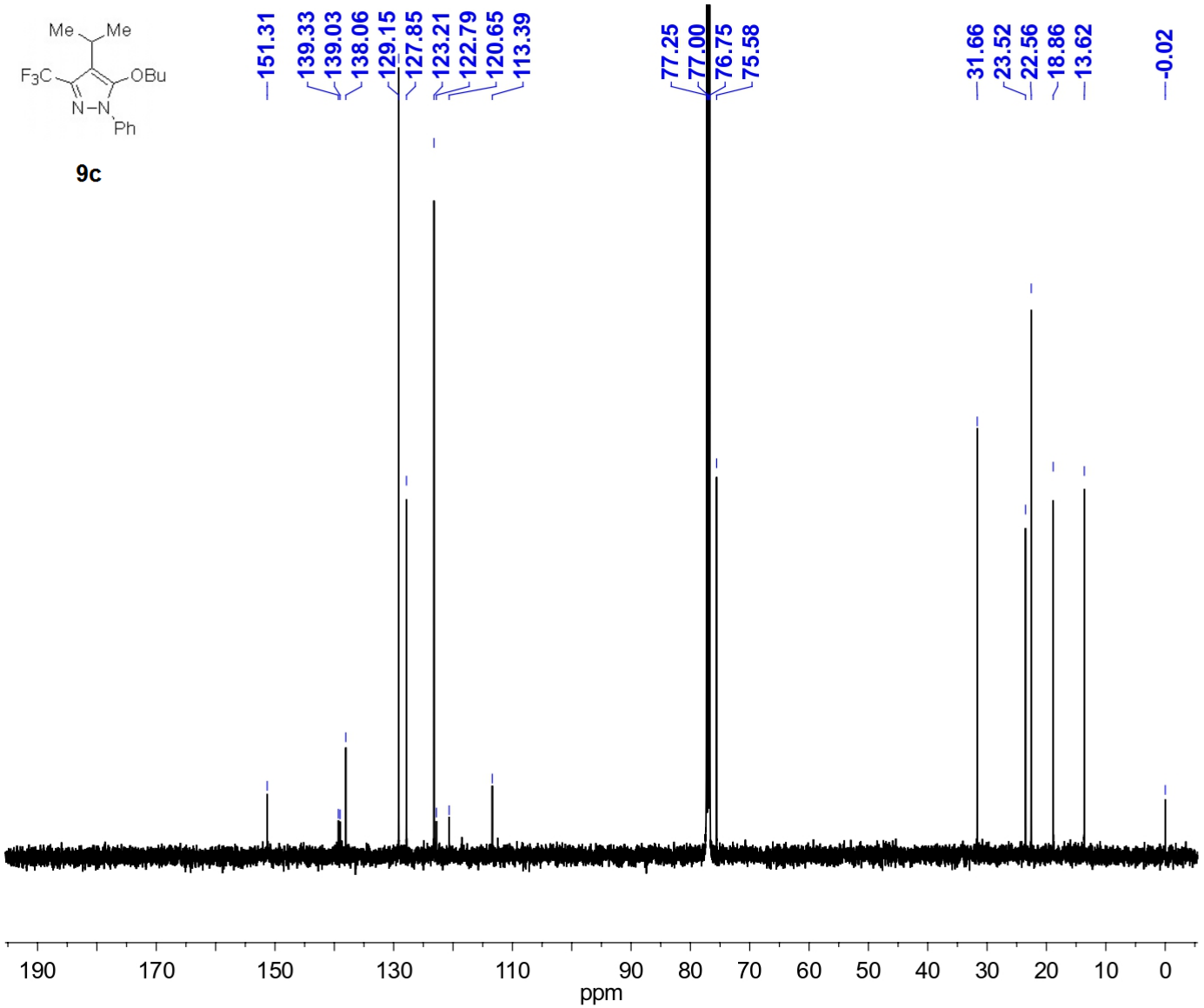
Current Data Parameters
NAME ESh805
EXPNO 19
PROCNO 1
USER uralnmr

F2 - Acquisition Parameters
Date_ 20210406
Time 16.02
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 131072
SOLVENT CDCl3
NS 16
DS 2
SWH 45351.473 Hz
FIDRES 0.346004 Hz
AQ 1.4451188 sec
RG 4597.6
DW 11.025 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

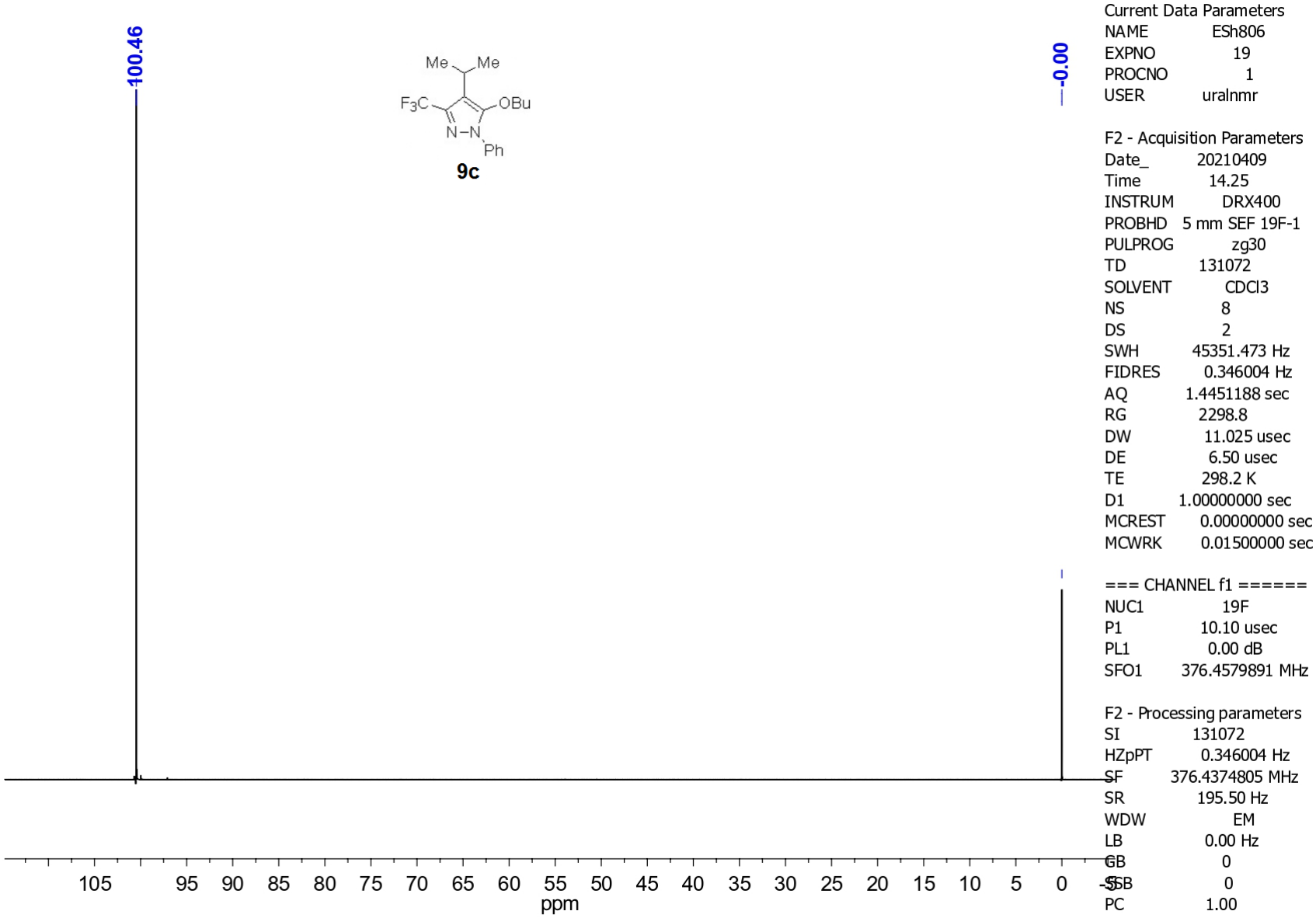
===== CHANNEL f1 ======
NUC1 19F
P1 10.10 usec
PL1 0.00 dB
SFO1 376.4561069 MHz

F2 - Processing parameters
SI 131072
HZpPT 0.346004 Hz
SF 376.4374830 MHz
SR 198.04 Hz
WDW EM
LB 0.20 Hz
GB 0
SSB 0
PC 1.00


Me
Me
F3C
OBu
N–N
Ph
9c
7.68
7.67
7.66
7.65
7.48
7.46
7.44
7.38
7.38
7.36
7.35
7.26
3.75
3.73
3.72
3.07
3.06
3.04
1.60
1.56
1.36
1.34
1.32
1.31
0.87
0.85
0.83
0.00
1.99
2.05
1.04
2.06
1.00
2.60
9.01
3.85
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
ppm
Current Data Parameters
NAME ESh806
EXPNO 1
PROCNO 1
USER uralnmr
F2 - Acquisition Parameters
Date_ 20210409
Time 14.17
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 256
DW 104.400 usec
DE 16.00 usec
TE 298.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
===== CHANNEL f1 ====
NUC1 1H
P1 32.50 usec
PL1 -4.00 dB
SFO1 400.1320007 MHz
F2 - Processing parameters
SI 32768
HZpPT 0.146157 Hz
SF 400.1300103 MHz
SR 10.26 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 4.00



NAME	ESh806a
EXPNO	13
PROCNO	1
USER	uralnmr
Date_	20210426
Time	16.57
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
SOLVENT	CDCl3
TD	32768
SW	200.7838 ppm
O1P	95.000 ppm
FIDRES	0.770646 Hz
NS	3072
DS	8
AQ	0.6488564 sec
RG	203
TE	298.1 K
DE	6.50 usec
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
==== CHANNEL f1 ======	
NUC1	13C
P1	10.00 usec
PL1	0.00 dB
PL1W	115.29558563 W
SFO1	125.7697360 MHz
===== CHANNEL f2 =====	
CPDPRG2	waltz16
NUC2	1H
PCPD2	75.00 usec
PL2	120.00 dB
PL12	16.30 dB
PL13	19.30 dB
PL2W	0.00000000 W
PL12W	0.47519693 W
PL13W	0.23816262 W
SFO2	500.1320005 MHz
SI	32768
HZpPT	0.770646 Hz
SR	1.02 Hz
WDW	EM
LB	1.00 Hz
GB	0
SSB	0

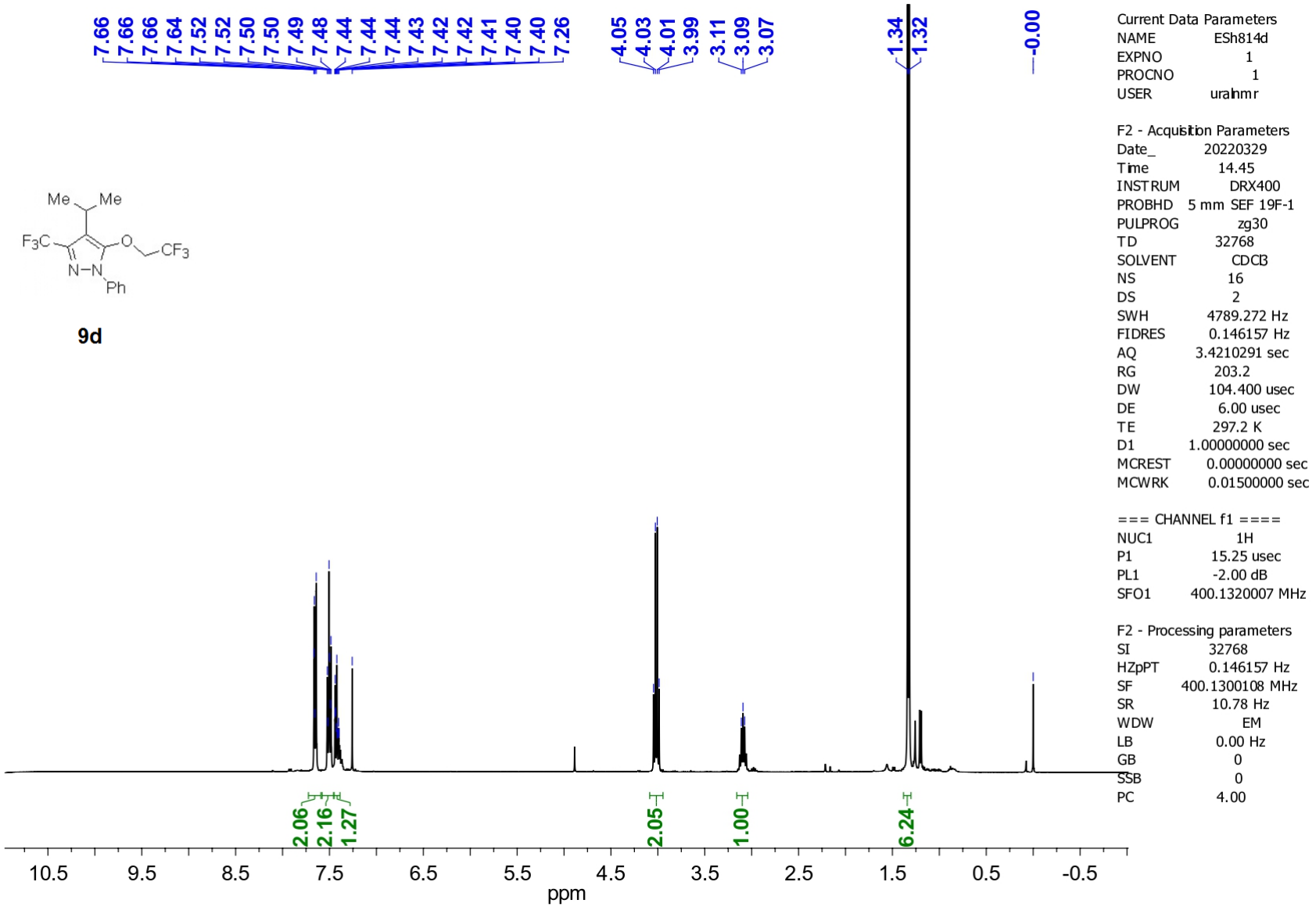


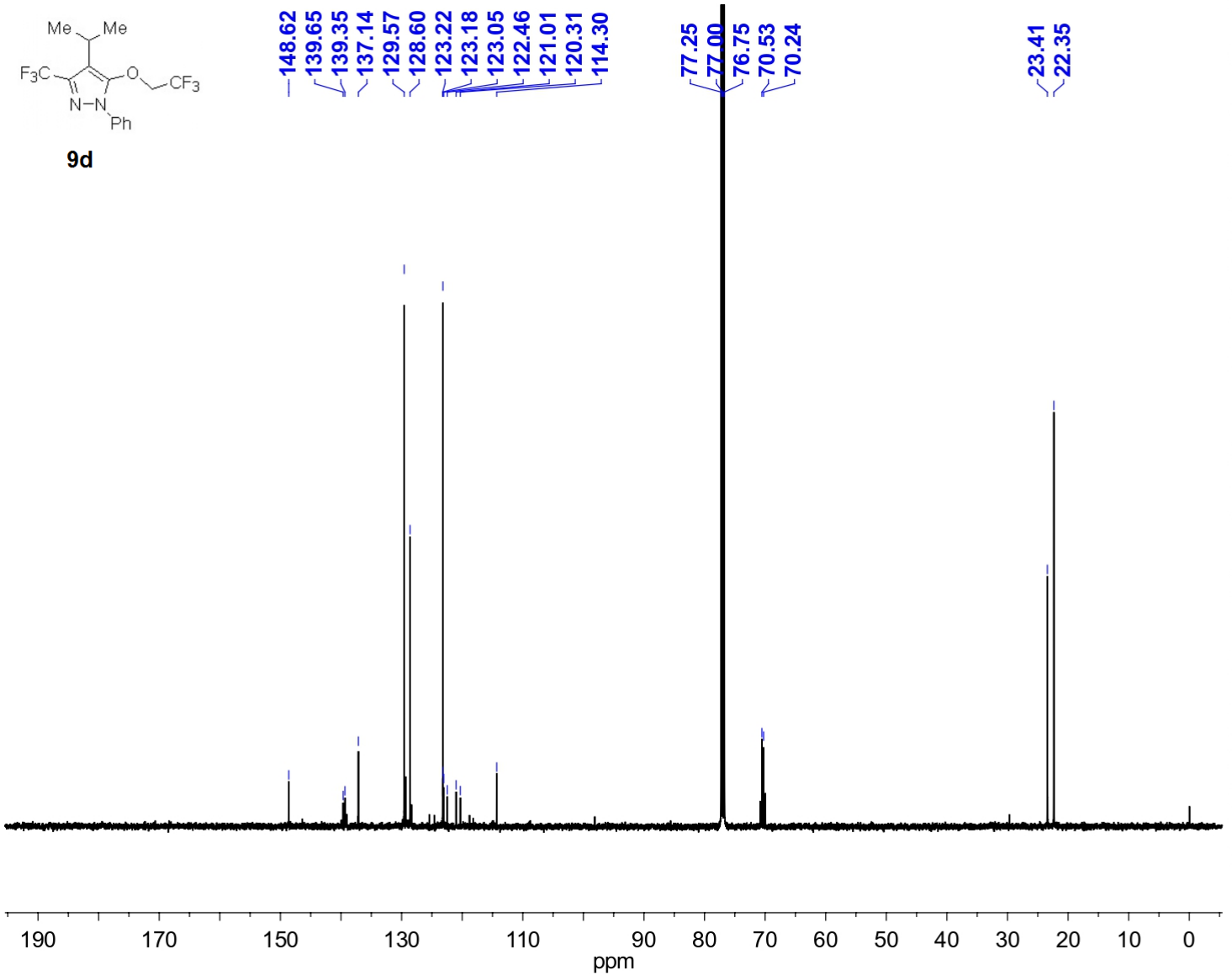
Current Data Parameters
NAME ESh806
EXPNO 19
PROCNO 1
USER uralnmr

F2 - Acquisition Parameters
Date_ 20210409
Time 14.25
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 131072
SOLVENT CDCl3
NS 8
DS 2
SWH 45351.473 Hz
FIDRES 0.346004 Hz
AQ 1.4451188 sec
RG 2298.8
DW 11.025 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

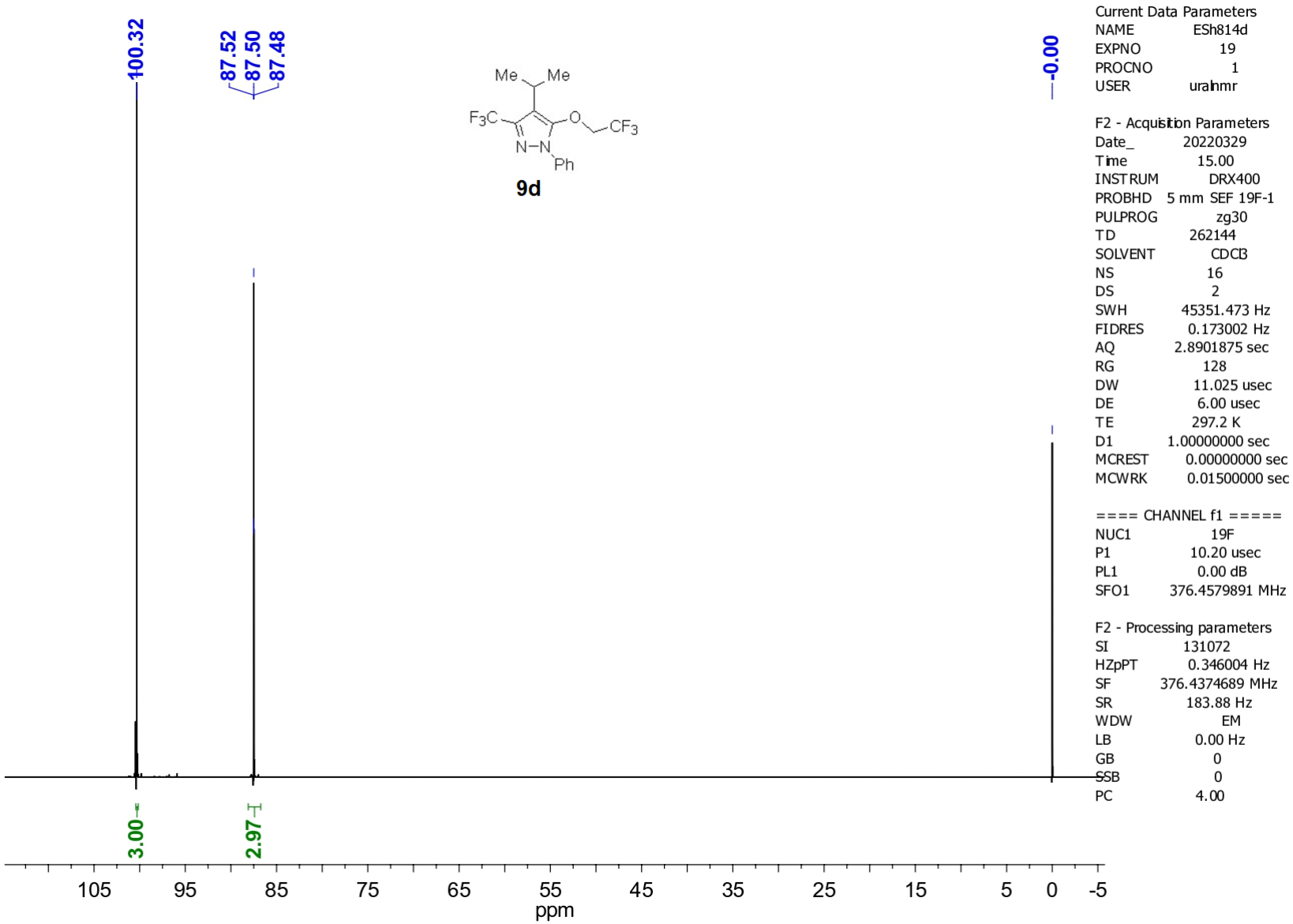
=== CHANNEL f1 ======
NUC1 19F
P1 10.10 usec
PL1 0.00 dB
SFO1 376.4579891 MHz

F2 - Processing parameters
SI 131072
HZpPT 0.346004 Hz
SF 376.4374805 MHz
SR 195.50 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 1.00


7.66
7.66
7.66
7.64
7.52
7.52
7.50
7.50
7.49
7.48
7.44
7.44
7.44
7.43
7.42
7.42
7.41
7.40
7.40
7.26
4.05
4.03
4.01
3.99
3.11
3.09
3.07
1.34
1.32
-0.00
Me
Me
F3C
O
CF3
N–N
Ph
9d
2.06
2.16
1.27
2.05
1.00
6.24
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
ppm
Current Data Parameters
NAME ESh814d
EXPNO 1
PROCNO 1
USER uralnmr
F2 - Acquisition Parameters
Date_ 20220329
Time 14.45
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 203.2
DW 104.400 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
=== CHANNEL f1 ====
NUC1 1H
P1 15.25 usec
PL1 -2.00 dB
SFO1 400.1320007 MHz
F2 - Processing parameters
SI 32768
HZpPT 0.146157 Hz
SF 400.1300108 MHz
SR 10.78 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 4.00



NAME	ESh814d
EXPNO	13
PROCNO	1
USER	uralnmr
Date_	20220419
Time	9.19
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
SOLVENT	CDCl3
TD	32768
SW	200.7838 ppm
O1P	95.000 ppm
FIDRES	0.770646 Hz
NS	1024
DS	8
AQ	0.6488564 sec
RG	203
TE	296.7 K
DE	6.50 usec
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
===== CHANNEL f1 =====	
NUC1	13C
P1	10.00 usec
PL1	0.00 dB
PL1W	115.29558563 W
SFO1	125.7697360 MHz
===== CHANNEL f2 =====	
CPDPRG2	waltz16
NUC2	1H
PCPD2	75.00 usec
PL2	120.00 dB
PL12	16.30 dB
PL13	19.30 dB
PL2W	0.00000000 W
PL12W	0.47519693 W
PL13W	0.23816262 W
SFO2	500.1320005 MHz
SI	32768
HZpPT	0.770646 Hz
SR	1.48 Hz
WDW	EM
LB	1.00 Hz
GB	0
SSB	0

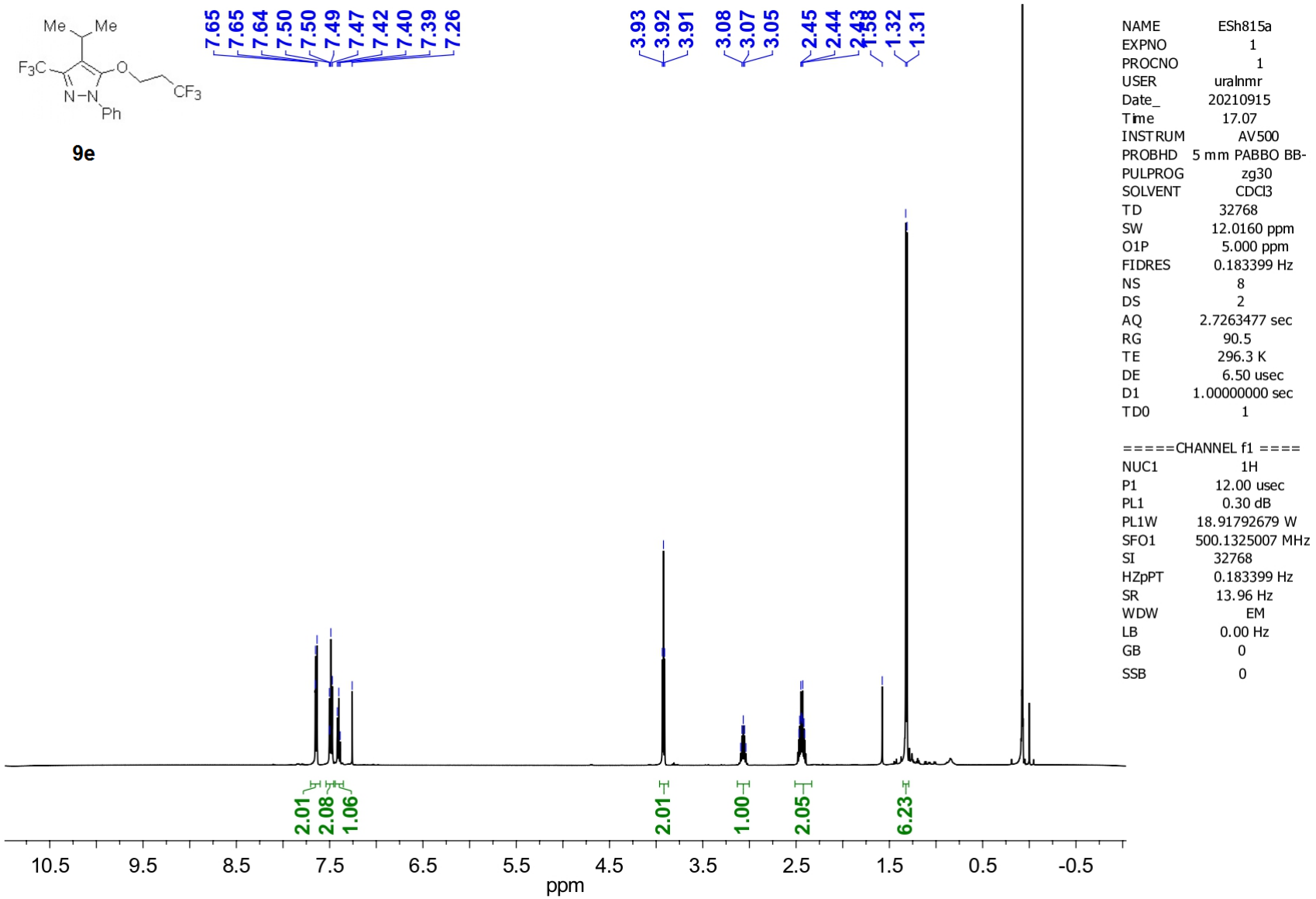


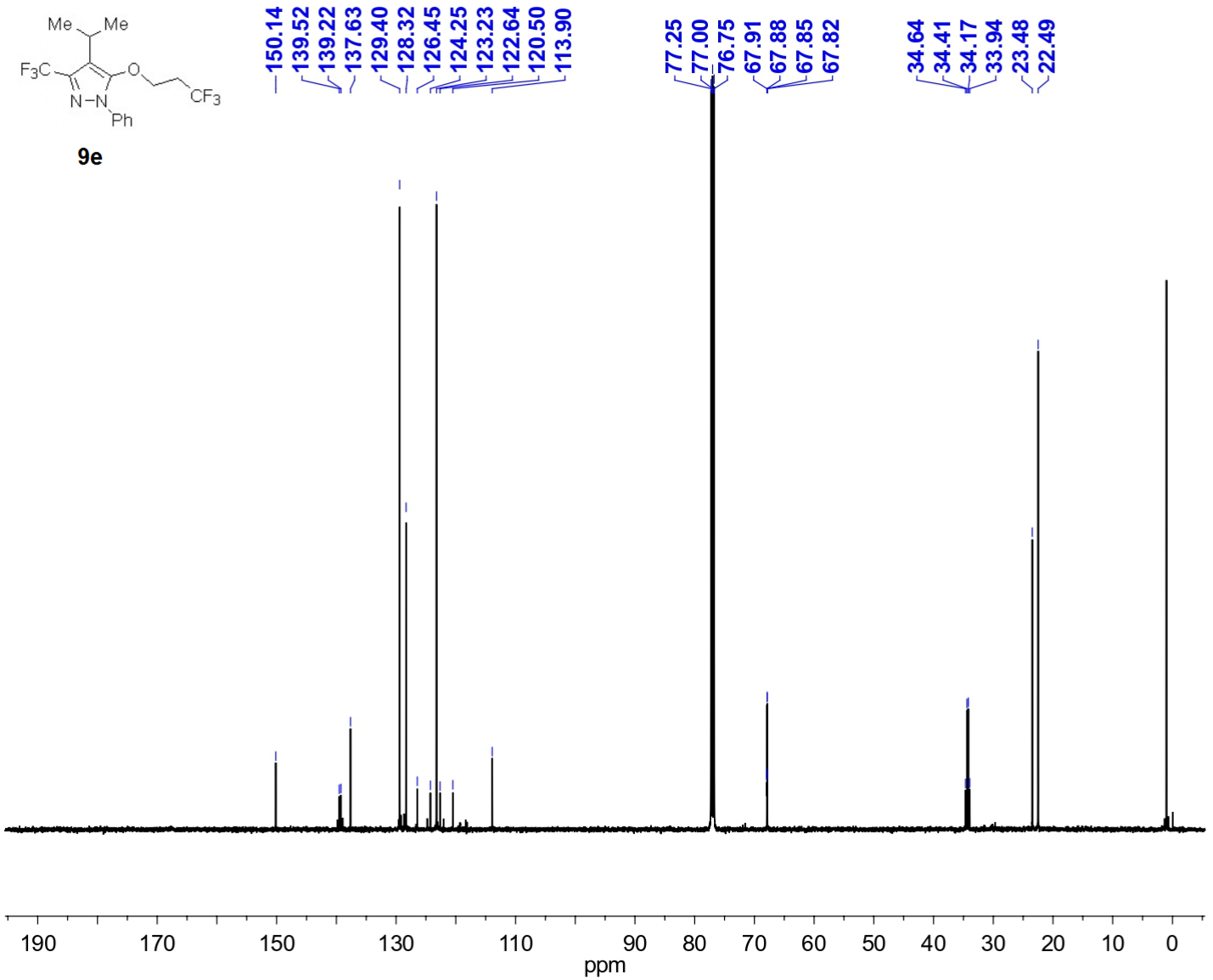
Current Data Parameters
NAME ESh814d
EXPNO 19
PROCNO 1
USER uralhmr

F2 - Acquisition Parameters
Date_ 20220329
Time 15.00
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 262144
SOLVENT CDCl3
NS 16
DS 2
SWH 45351.473 Hz
FIDRES 0.173002 Hz
AQ 2.8901875 sec
RG 128
DW 11.025 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

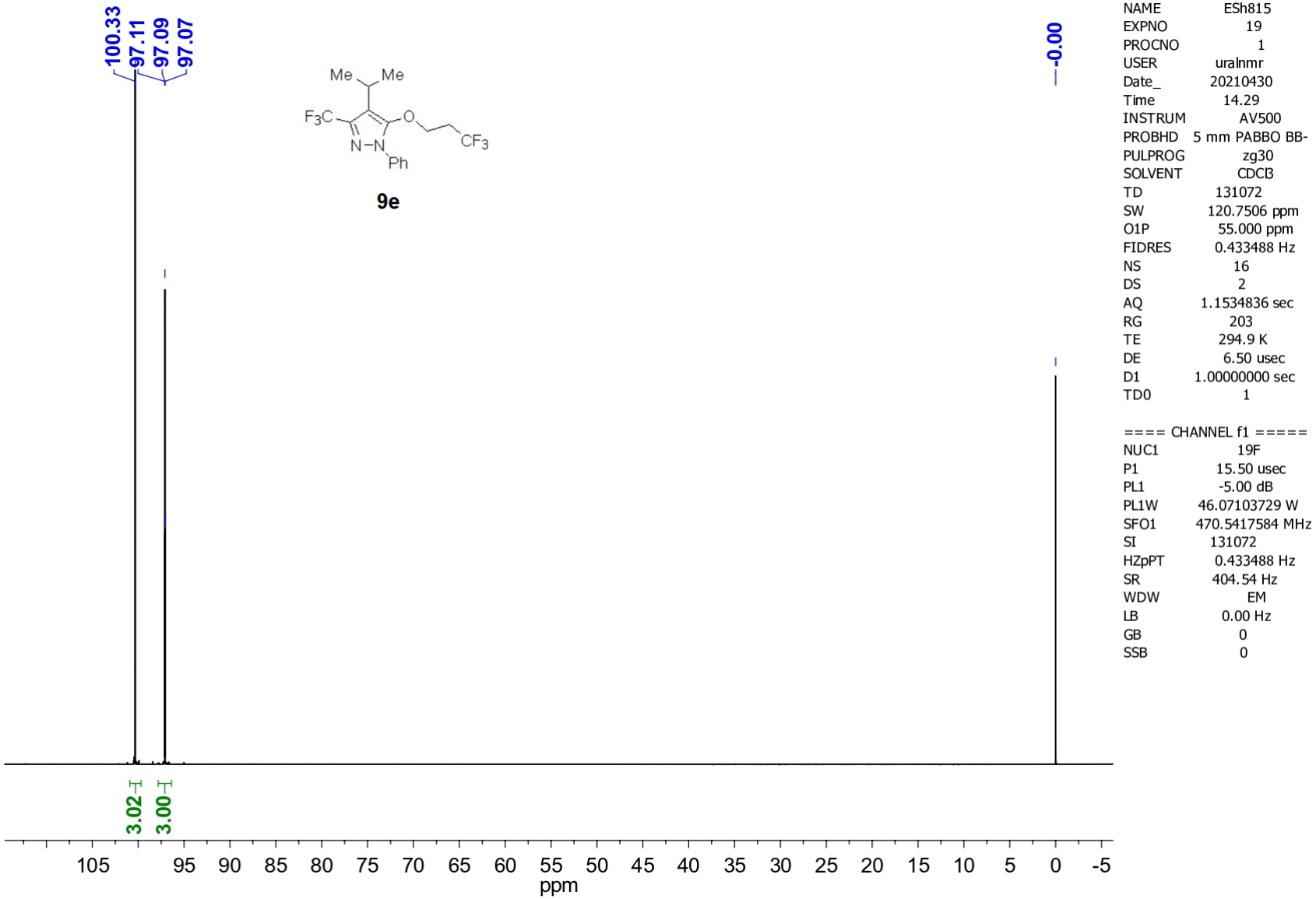
==== CHANNEL f1 =====
NUC1 19F
P1 10.20 usec
PL1 0.00 dB
SFO1 376.4579891 MHz

F2 - Processing parameters
SI 131072
HZpPT 0.346004 Hz
SF 376.4374689 MHz
SR 183.88 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 4.00


Me
Me
F3C
O
CF3
N–N
Ph
9e
7.65
7.65
7.64
7.50
7.50
7.49
7.47
7.42
7.40
7.39
7.26
3.93
3.92
3.91
3.08
3.07
3.05
2.45
2.44
1.58
1.32
1.31
2.01
2.08
1.06
2.01
1.00
2.05
6.23
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
ppm
NAME ESh815a
EXPNO 1
PROCNO 1
USER uralnmr
Date_ 20210915
Time 17.07
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zg30
SOLVENT CDCl3
TD 32768
SW 12.0160 ppm
O1P 5.000 ppm
FIDRES 0.183399 Hz
NS 8
DS 2
AQ 2.7263477 sec
RG 90.5
TE 296.3 K
DE 6.50 usec
D1 1.00000000 sec
TD0 1
=====CHANNEL f1 ====
NUC1 1H
P1 12.00 usec
PL1 0.30 dB
PL1W 18.91792679 W
SFO1 500.1325007 MHz
SI 32768
HZpPT 0.183399 Hz
SR 13.96 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0

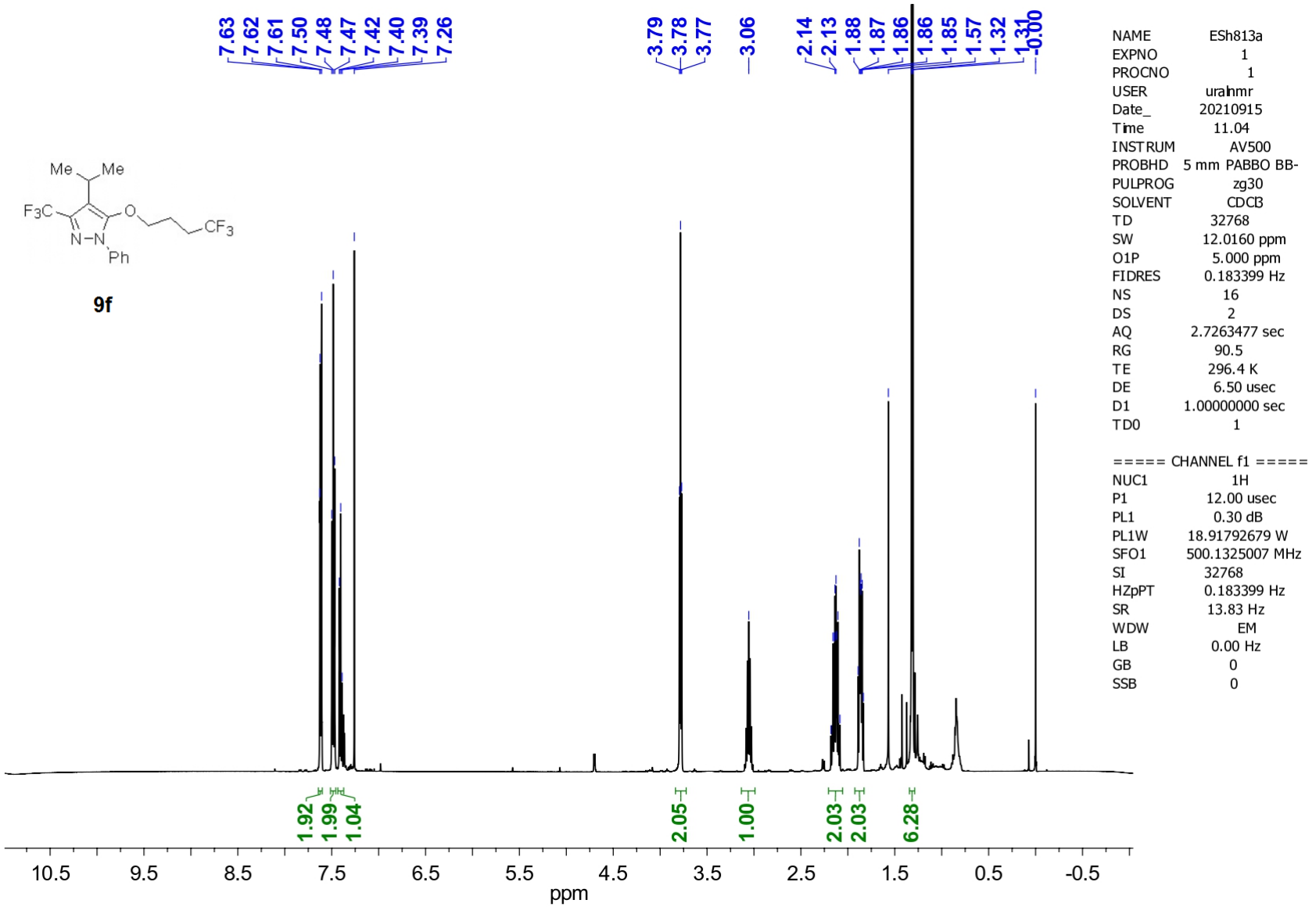


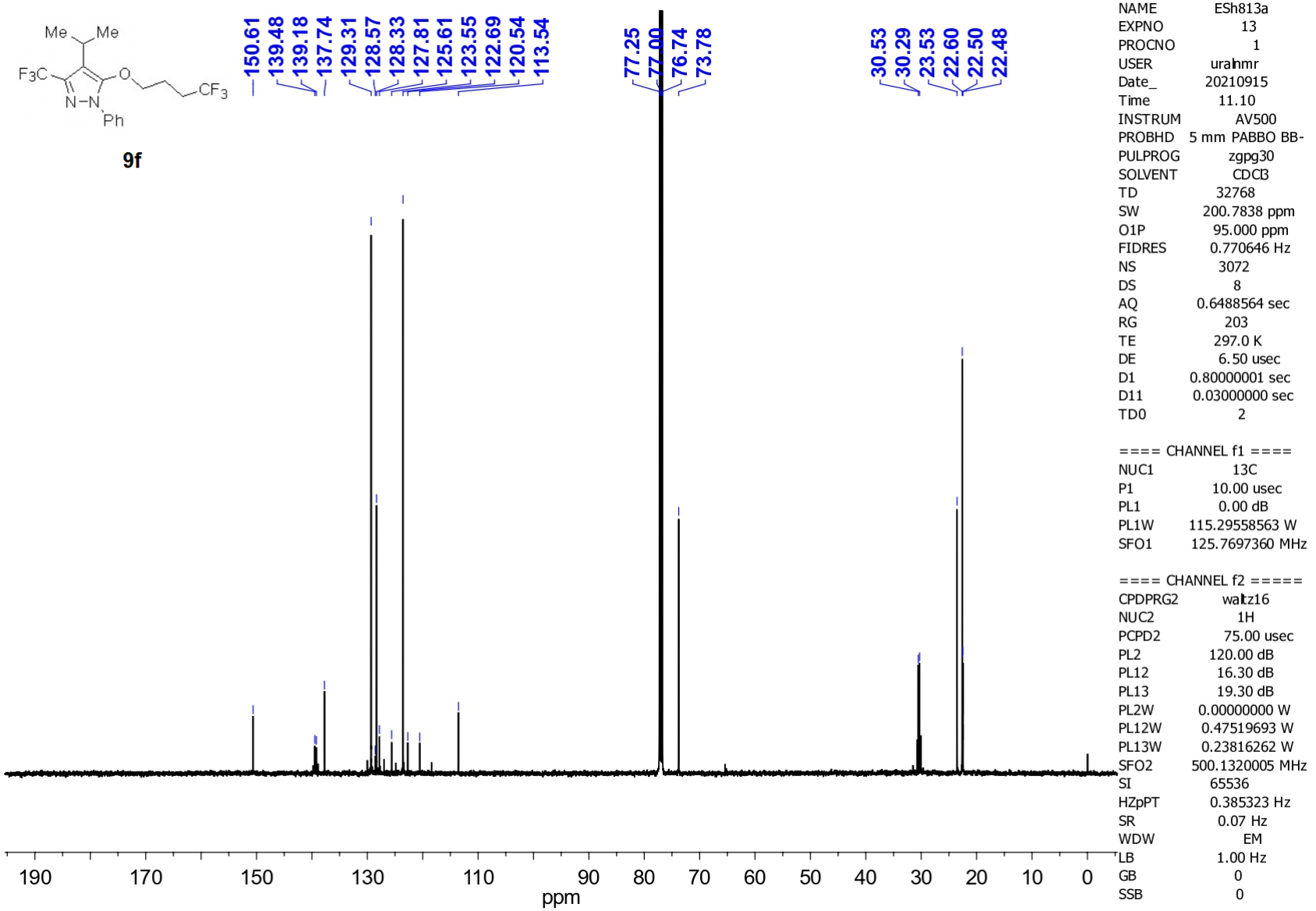
NAME	ESh815a
EXPNO	13
PROCNO	1
USER	uralnmr
Date_	20210915
Time	17.45
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
SOLVENT	CDCl3
TD	65536
SW	200.7838 ppm
O1P	95.000 ppm
FIDRES	0.385323 Hz
NS	2048
DS	8
AQ	1.2976629 sec
RG	203
TE	298.1 K
DE	6.50 usec
D1	0.80000001 sec
D11	0.03000000 sec
TD0	2
====== CHANNEL f1 ======	
NUC1	13C
P1	10.00 usec
PL1	0.00 dB
PL1W	115.29558563 W
SFO1	125.7697360 MHz
====== CHANNEL f2 ======	
CPDPRG2	waltz16
NUC2	1H
PCPD2	75.00 usec
PL2	120.00 dB
PL12	16.30 dB
PL13	19.30 dB
PL2W	0.00000000 W
PL12W	0.47519693 W
PL13W	0.23816262 W
SFO2	500.1320005 MHz
SI	65536
HZpPT	0.385323 Hz
SR	-0.64 Hz
WDW	EM
LB	1.00 Hz
GB	0
SSB	0



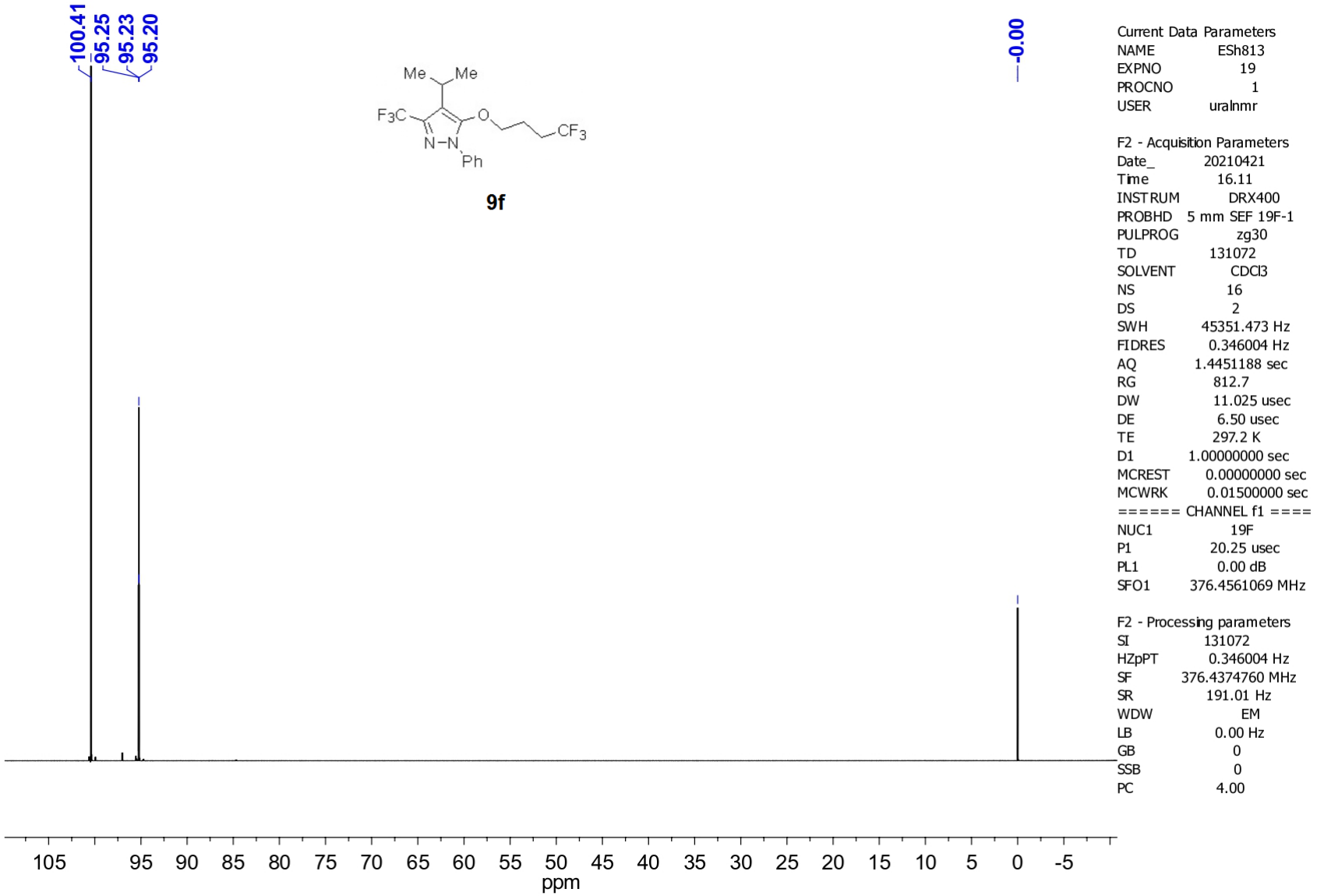
NAME ESh815
EXPNO 19
PROCNO 1
USER uralnmr
Date_ 20210430
Time 14.29
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zg30
SOLVENT CDCl3
TD 131072
SW 120.7506 ppm
O1P 55.000 ppm
FIDRES 0.433488 Hz
NS 16
DS 2
AQ 1.1534836 sec
RG 203
TE 294.9 K
DE 6.50 usec
D1 1.00000000 sec
TD0 1

==== CHANNEL f1 =====
NUC1 19F
P1 15.50 usec
PL1 -5.00 dB
PL1W 46.07103729 W
SFO1 470.5417584 MHz
SI 131072
HZpPT 0.433488 Hz
SR 404.54 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0


7.63
7.62
7.61
7.50
7.48
7.47
7.42
7.40
7.39
7.26
3.79
3.78
3.77
3.06
2.14
2.13
1.88
1.87
1.86
1.86
1.85
1.57
1.32
1.31
0.00
Me
Me
F3C
O
CF3
N–N
Ph
9f
NAME ESh813a
EXPNO 1
PROCNO 1
USER uralnmr
Date_ 20210915
Time 11.04
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zg30
SOLVENT CDCl3
TD 32768
SW 12.0160 ppm
O1P 5.000 ppm
FIDRES 0.183399 Hz
NS 16
DS 2
AQ 2.7263477 sec
RG 90.5
TE 296.4 K
DE 6.50 usec
D1 1.00000000 sec
TD0 1
===== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.30 dB
PL1W 18.91792679 W
SFO1 500.1325007 MHz
SI 32768
HZpPT 0.183399 Hz
SR 13.83 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
1.92
1.99
1.04
2.05
1.00
2.03
2.03
6.28
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
ppm



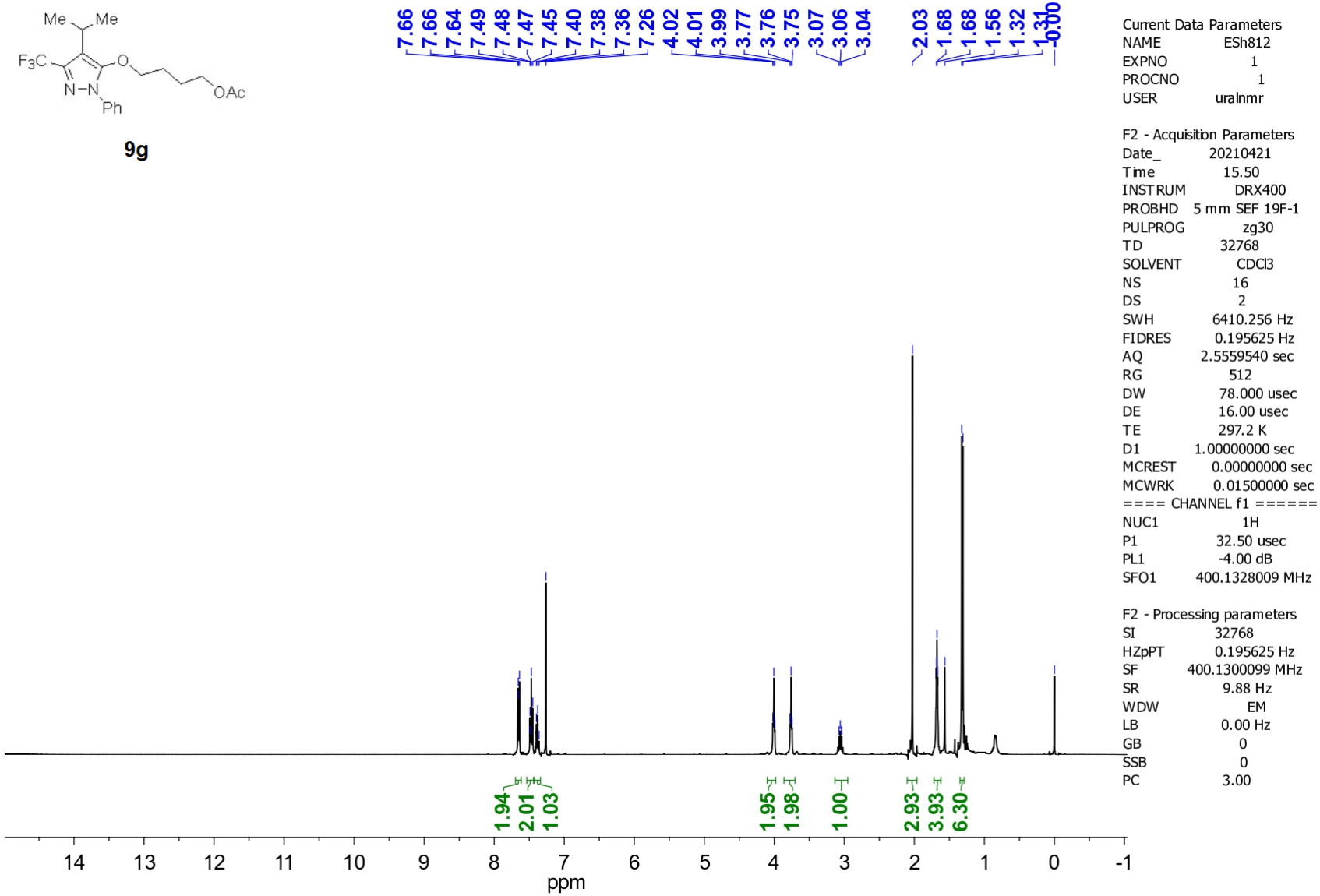
NAME	ESh813a
EXPNO	13
PROCNO	1
USER	urahmr
Date_	20210915
Time	11.10
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
SOLVENT	CDCl3
TD	32768
SW	200.7838 ppm
O1P	95.000 ppm
FIDRES	0.770646 Hz
NS	3072
DS	8
AQ	0.6488564 sec
RG	203
TE	297.0 K
DE	6.50 usec
D1	0.80000001 sec
D11	0.03000000 sec
TD0	2
==== CHANNEL f1 ====	
NUC1	13C
P1	10.00 usec
PL1	0.00 dB
PL1W	115.29558563 W
SFO1	125.7697360 MHz
==== CHANNEL f2 =====	
CPDPRG2	waltz16
NUC2	1H
PCPD2	75.00 usec
PL2	120.00 dB
PL12	16.30 dB
PL13	19.30 dB
PL2W	0.00000000 W
PL12W	0.47519693 W
PL13W	0.23816262 W
SFO2	500.1320005 MHz
SI	65536
HZpPT	0.385323 Hz
SR	0.07 Hz
WDW	EM
LB	1.00 Hz
GB	0
SSB	0

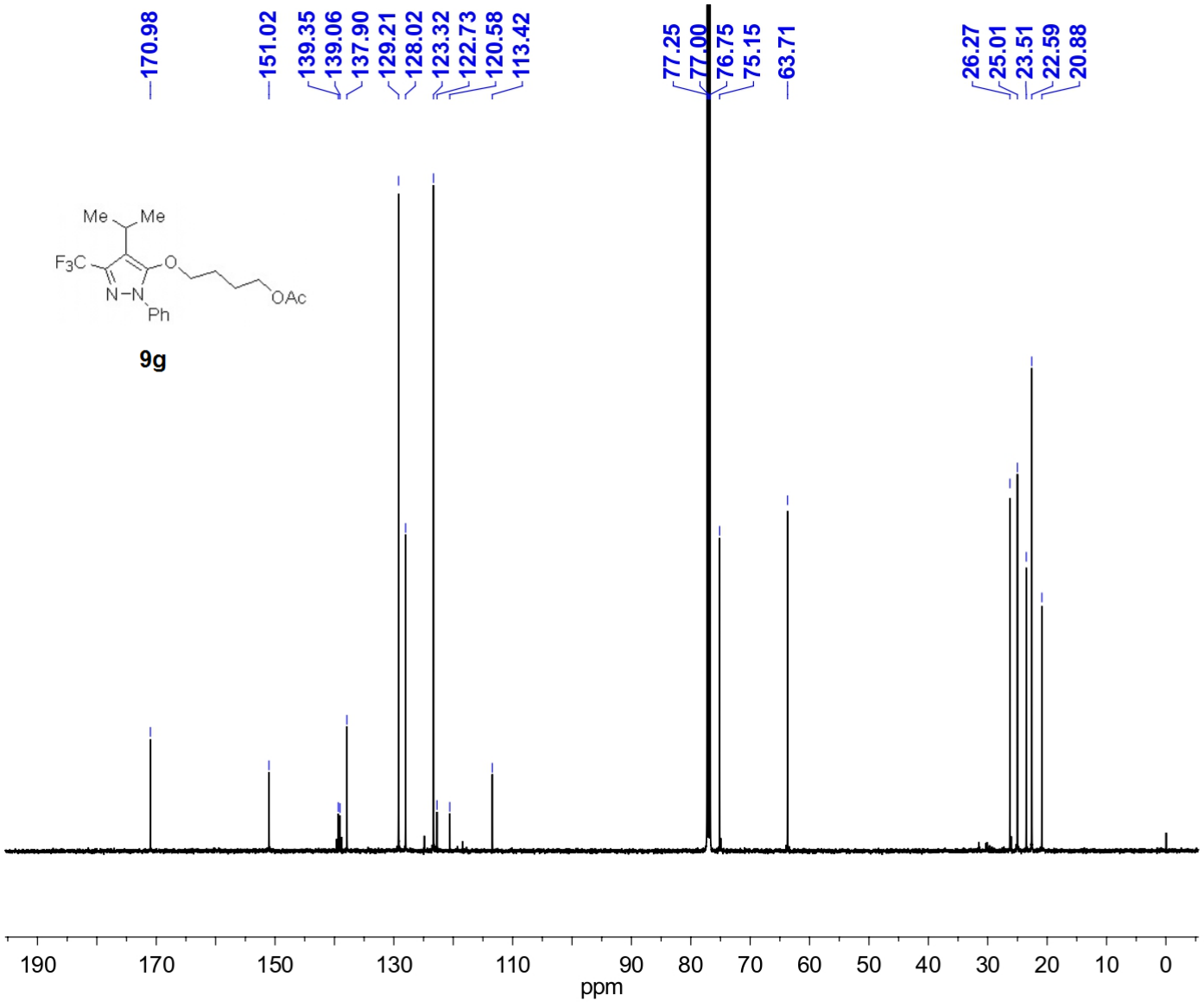


Current Data Parameters
NAME ESh813
EXPNO 19
PROCNO 1
USER uralnmr

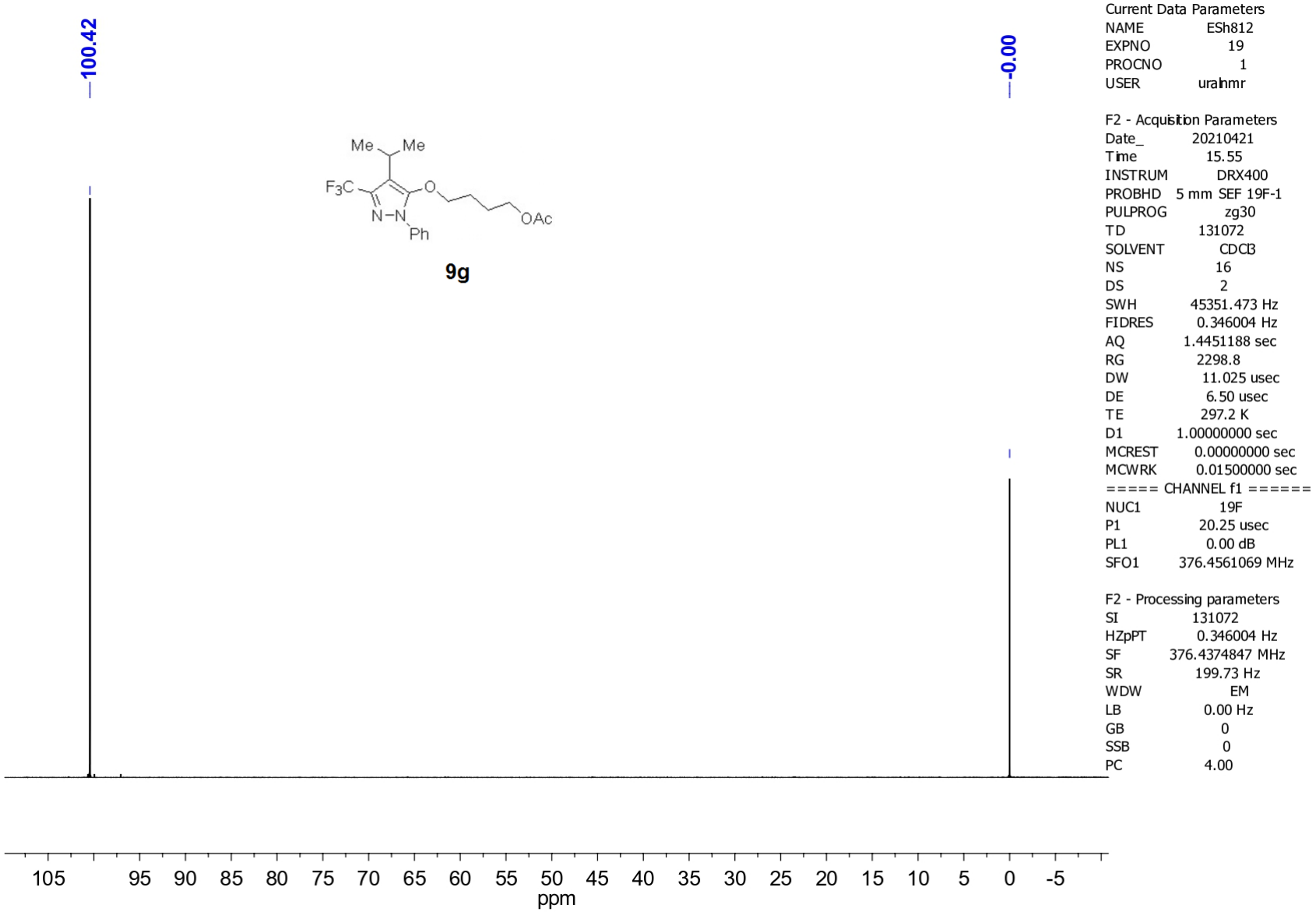
F2 - Acquisition Parameters
Date_ 20210421
Time 16.11
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 131072
SOLVENT CDCl3
NS 16
DS 2
SWH 45351.473 Hz
FIDRES 0.346004 Hz
AQ 1.4451188 sec
RG 812.7
DW 11.025 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
====== CHANNEL f1 ====
NUC1 19F
P1 20.25 usec
PL1 0.00 dB
SFO1 376.4561069 MHz

F2 - Processing parameters
SI 131072
HZpPT 0.346004 Hz
SF 376.4374760 MHz
SR 191.01 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 4.00


Me
Me
F3C
O
N–N
Ph
OAc
9g
7.66
7.66
7.64
7.49
7.48
7.47
7.45
7.40
7.38
7.36
7.26
4.02
4.01
3.99
3.77
3.76
3.75
3.07
3.06
3.04
2.03
1.68
1.68
1.56
1.32
1.31
0.00
1.94
2.01
1.03
1.95
1.98
1.00
2.93
3.93
6.30
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
Current Data Parameters
NAME ESh812
EXPNO 1
PROCNO 1
USER uralnmr
F2 - Acquisition Parameters
Date_ 20210421
Time 15.50
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5559540 sec
RG 512
DW 78.000 usec
DE 16.00 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
==== CHANNEL f1 ======
NUC1 1H
P1 32.50 usec
PL1 -4.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 32768
HZpPT 0.195625 Hz
SF 400.1300099 MHz
SR 9.88 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 3.00



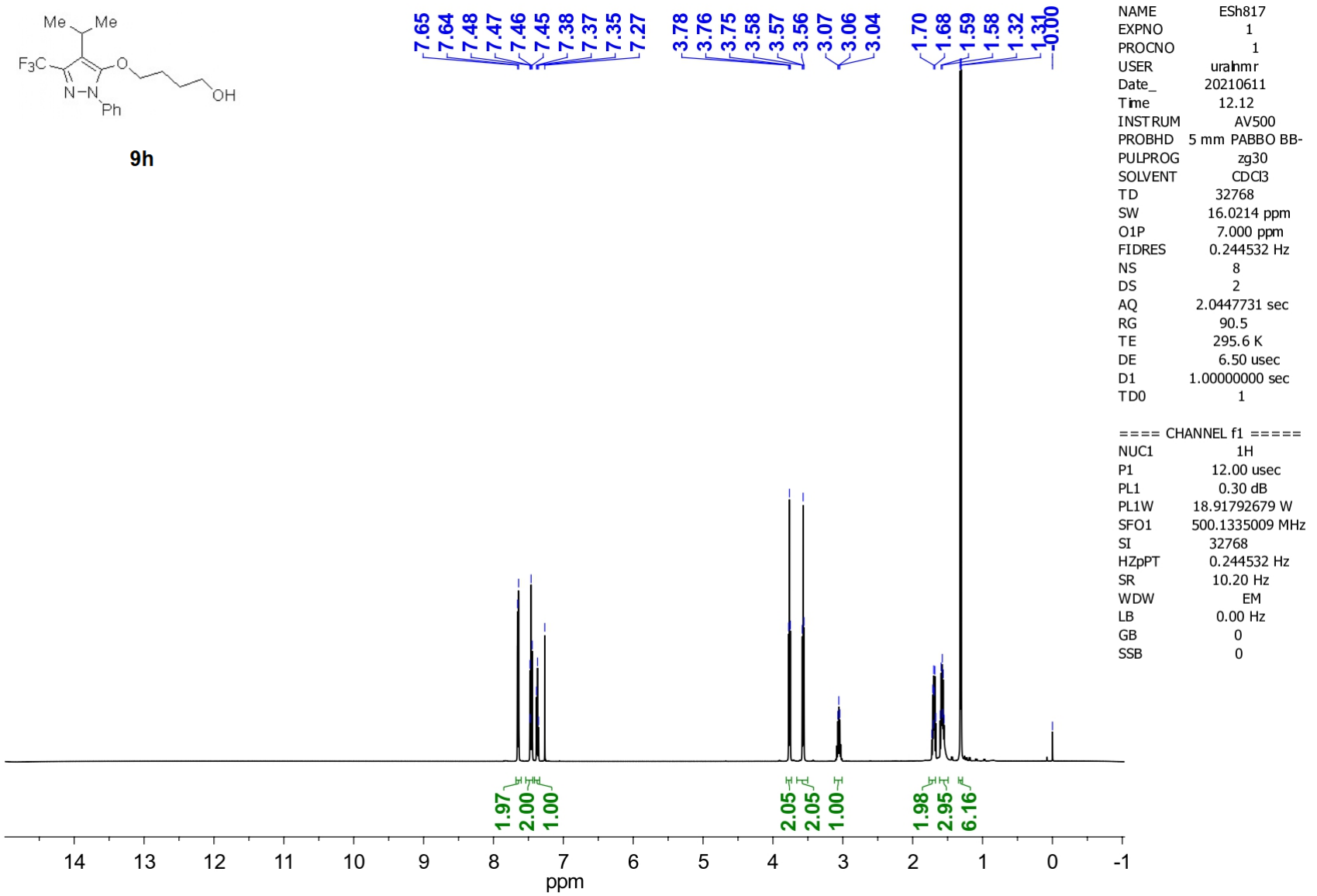
NAME	ESh812
EXPNO	13
PROCNO	1
USER	uralnmr
Date_	20210517
Time	10.36
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
SOLVENT	CDCl3
TD	65536
SW	200.7838 ppm
O1P	95.000 ppm
FIDRES	0.385323 Hz
NS	4096
DS	8
AQ	1.2976629 sec
RG	203
TE	295.9 K
DE	6.50 usec
D1	0.69999999 sec
D11	0.03000000 sec
TD0	4
===== CHANNEL f1 ======	
NUC1	13C
P1	10.00 usec
PL1	0.00 dB
PL1W	115.29558563 W
SFO1	125.7697360 MHz
===== CHANNEL f2 ======	
CPDPRG2	waltz16
NUC2	1H
PCPD2	75.00 usec
PL2	120.00 dB
PL12	16.30 dB
PL13	19.30 dB
PL2W	0.00000000 W
PL12W	0.47519693 W
PL13W	0.23816262 W
SFO2	500.1320005 MHz
SI	65536
HZpPT	0.385323 Hz
SR	3.24 Hz
WDW	EM
LB	1.00 Hz
GB	0
SSB	0

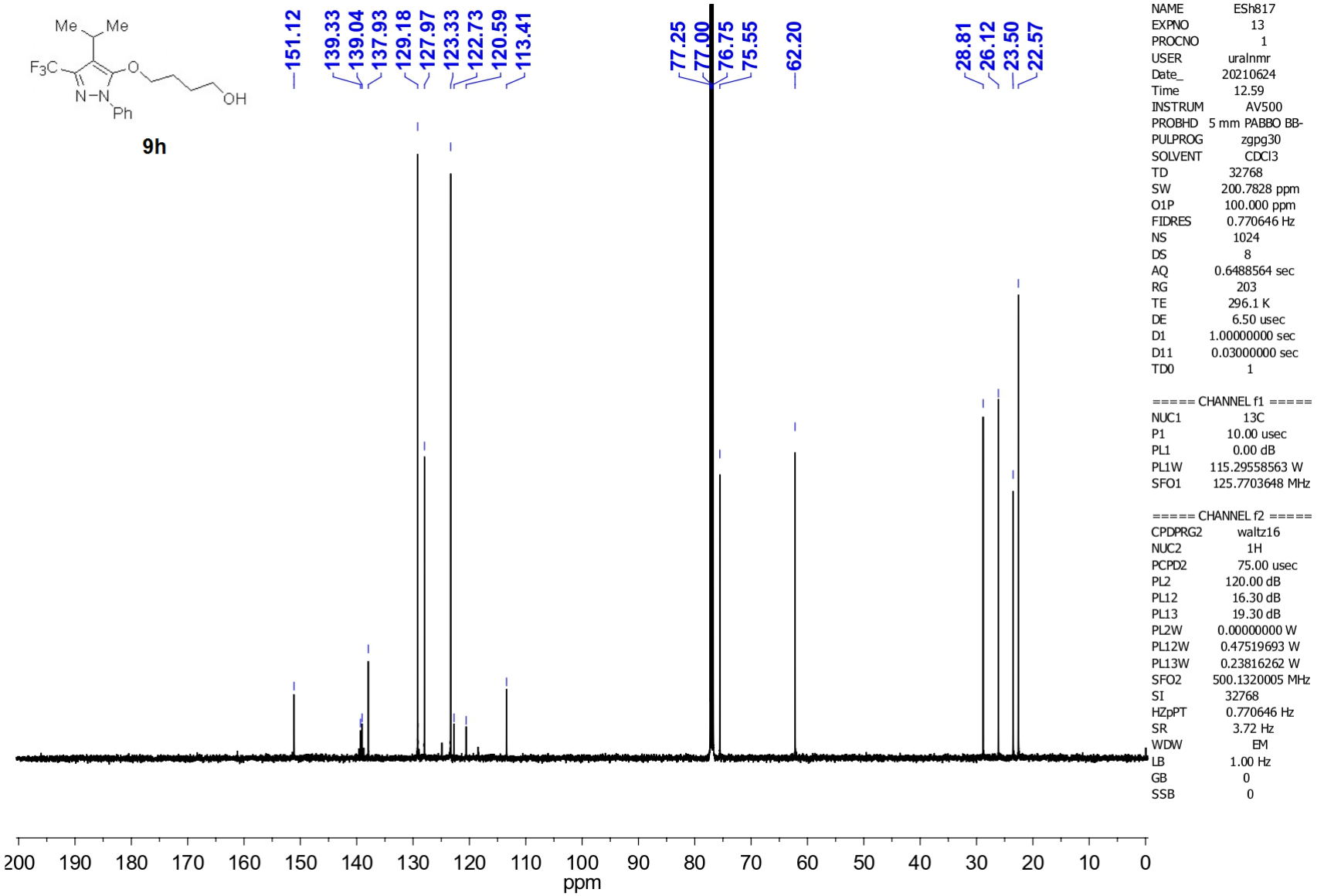


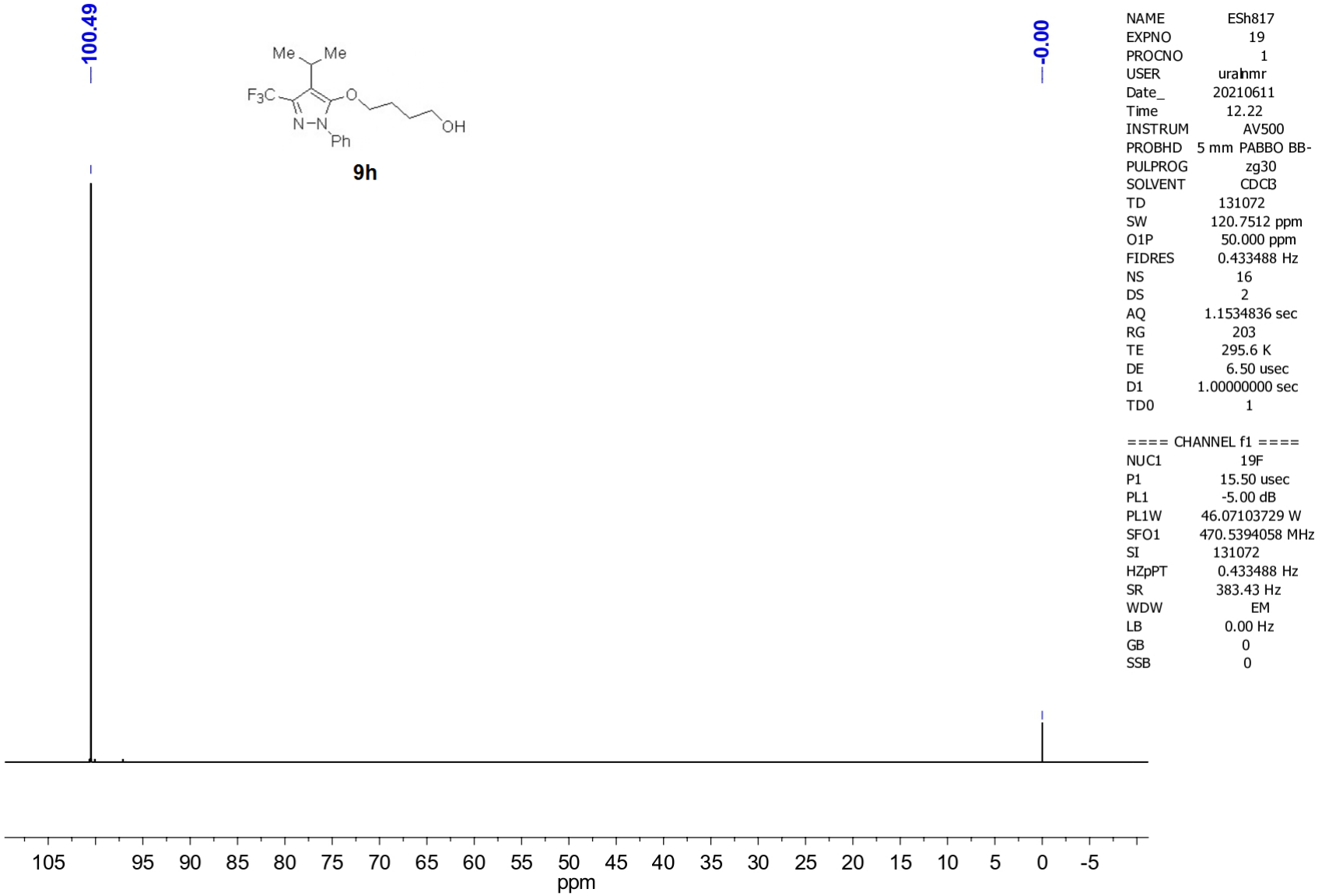
Current Data Parameters
NAME ESh812
EXPNO 19
PROCNO 1
USER urahmr

F2 - Acquisition Parameters
Date_ 20210421
Time 15.55
INSTRUM DRX400
PROBHD 5 mm SEF 19F-1
PULPROG zg30
TD 131072
SOLVENT CDCl3
NS 16
DS 2
SWH 45351.473 Hz
FIDRES 0.346004 Hz
AQ 1.4451188 sec
RG 2298.8
DW 11.025 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
===== CHANNEL f1 ======
NUC1 19F
P1 20.25 usec
PL1 0.00 dB
SFO1 376.4561069 MHz

F2 - Processing parameters
SI 131072
HZpPT 0.346004 Hz
SF 376.4374847 MHz
SR 199.73 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0
PC 4.00


Me
Me
F3C
O
N–N
Ph
OH
9h
7.65
7.64
7.48
7.47
7.46
7.45
7.38
7.37
7.35
7.27
3.78
3.76
3.75
3.58
3.57
3.56
3.07
3.06
3.04
1.70
1.68
1.59
1.58
1.32
1.31
0.00
1.97
2.00
1.00
2.05
2.05
1.00
1.98
2.95
6.16
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
NAME ESh817
EXPNO 1
PROCNO 1
USER uralnmr
Date_ 20210611
Time 12.12
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zg30
SOLVENT CDCl3
TD 32768
SW 16.0214 ppm
O1P 7.000 ppm
FIDRES 0.244532 Hz
NS 8
DS 2
AQ 2.0447731 sec
RG 90.5
TE 295.6 K
DE 6.50 usec
D1 1.00000000 sec
TD0 1
==== CHANNEL f1 =====
NUC1 1H
P1 12.00 usec
PL1 0.30 dB
PL1W 18.91792679 W
SFO1 500.1335009 MHz
SI 32768
HZpPT 0.244532 Hz
SR 10.20 Hz
WDW EM
LB 0.00 Hz
GB 0
SSB 0


Me
Me
F3C
O
N–N
Ph
OH
9h
151.12
139.33
139.04
137.93
129.18
127.97
123.33
122.73
120.59
113.41
77.25
77.00
76.75
75.55
62.20
28.81
26.12
23.50
22.57
NAME ESh817
EXPNO 13
PROCNO 1
USER uralnmr
Date_ 20210624
Time 12.59
INSTRUM AV500
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
SOLVENT CDCl3
TD 32768
SW 200.7828 ppm
O1P 100.000 ppm
FIDRES 0.770646 Hz
NS 1024
DS 8
AQ 0.6488564 sec
RG 203
TE 296.1 K
DE 6.50 usec
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
===== CHANNEL f1 =====
NUC1 13C
P1 10.00 usec
PL1 0.00 dB
PL1W 115.29558563 W
SFO1 125.7703648 MHz
===== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 75.00 usec
PL2 120.00 dB
PL12 16.30 dB
PL13 19.30 dB
PL2W 0.00000000 W
PL12W 0.47519693 W
PL13W 0.23816262 W
SFO2 500.1320005 MHz
SI 32768
HZpPT 0.770646 Hz
SR 3.72 Hz
WDW EM
LB 1.00 Hz
GB 0
SSB 0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm



NAME	ESh817
EXPNO	19
PROCNO	1
USER	urahmr
Date_	20210611
Time	12.22
INSTRUM	AV500
PROBHD	5 mm PABBO BB-
PULPROG	zg30
SOLVENT	CDCl3
TD	131072
SW	120.7512 ppm
O1P	50.000 ppm
FIDRES	0.433488 Hz
NS	16
DS	2
AQ	1.1534836 sec
RG	203
TE	295.6 K
DE	6.50 usec
D1	1.00000000 sec
TD0	1
==== CHANNEL f1 ====	
NUC1	19F
P1	15.50 usec
PL1	-5.00 dB
PL1W	46.07103729 W
SFO1	470.5394058 MHz
SI	131072
HZpPT	0.433488 Hz
SR	383.43 Hz
WDW	EM
LB	0.00 Hz
GB	0
SSB	0