Truncated Militarinone Fragments Identified by Total Chemical Synthesis Induce Neurite Outgrowth

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Supporting Information

Experimental Part

1. General Methods and Materials

Reactions involving air or moisture sensitive reagents or intermediates were performed under argon or nitrogen in glassware which had been oven dried, heat gun dried or flame dried *in vacuo*. Concentration under reduced pressure was performed by rotary evaporation at 40 °C (unless otherwise specified). Yields refer to purified, dried and spectroscopically pure compounds.

Reagents were purchased from Sigma-Aldrich, ABCR, Acros or Lancaster and used without further purification unless stated otherwise.

Solvents for work-up and chromatography were distilled from technical quality. Solvents used for chemical transformations were either puriss. quality or dried by filtration through activated aluminium oxide under argon or nitrogen (H_2O content < 10 ppm, *Karl-Fischer* titration) in a PureSolve MD 5 solvent purification system.

Thin layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates (0.25 mm thickness) precoated with fluorescent indicator. The developed plates were examined under UV light and stained with potassium permanganate followed by heating.

Flash chromatography was performed using silica gel 60 (230-240 mesh) from Fluka at 0.3-0.5 bar pressure.

^{1}H and ^{13}C NMR spectra were recorded either using Bruker Avance 400 MHz, Bruker Avance DRX 500 MHz, Varian Gemini 300 MHz or Bruker DPX 400 MHz or Bruker DRX 600 MHz spectrometers at room temperature. Chemical shifts (δ-values) are reported in ppm, spectra were calibrated related to the solvent residual proton chemical shift and the solvent residual carbon chemical shift,[1] multiplicity is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and coupling constant *J* in Hz.

[1] H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512-7515.

IR spectra were recorded using a *Varian 800 FT-IR ATR Spectrometer*. The absorptions are reported in cm^{-1}.

HRMS-ESI were recorded by the Mass spectrometric Service of the University of Bern on Sciex QSTAR Pulsar mass spectrometer or by the Mass spectroscopy Service of EPF Lausanne on MICROMASS (ESI) Q-TOF Ultima API. Fragment ions are given in *m*/*z* using electrospray ionization.

X-ray analyses were performed at low temperature (exact temperature in appendix) using Mo K_a radiation on a Bruker KappaAPEX diffractometer. Integration of the frames and data reduction was carried out using APEX2.[2] The structures were solved by direct methods using SIR92.[3] All non hydrogen atoms were refined by full-matrix least-squares on *F* using CRYSTALS.[4] Hydrogen atoms were placed in calculated positions by means of the "riding" model.

Melting points (M.p.) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected.

Analytical High Performance Liquid Chromatography (HPLC) was performed on a *Dionex Chromatography System* (Interface Chromeleon, ASI 100 automatic sample injector, PDA 100 (USB) PD detector, pump P680, degaser, MSQ-ESI mass spectrometric detector). The flow rate was 1 mL/min and a Phenomenex Gemini 5 µm C18 110A column (250 x 4.6 mm) or a Phenomenex Gemini 5 µm C18 110A column (50 x 4.6 mm) was used.

Semi Preperative High Performance Liquid Chromatography (SP-HPLC) was performed on a *Dionex Chromatography System* (Interface Chromeleon, ASI 100 automatic sample injector, PDA 100 (USB) PD detector, pump P680). The flow rate was 5 mL/min and a Phenomenex Gemini 5 µm C18 110A column (150 x 10 mm) was used.

[2] Bruker Analytical X-ray Systems, Inc., **2006**. *Apex2*, Version 2 User Manual, M86-E01078, Madison, WI.
[3] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Cryst.* **1994**, *27*, 435.
[4] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Cryst.* **2003**, *36*, 1487.

Lyophilisations were performed with a *Christ Freeze Dryer Alpha 1-2 LD plus*.

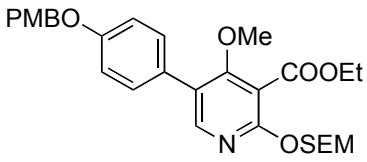
2. Experimental procedures

2.1 General Procedure for Suzuki Coupling Reactions

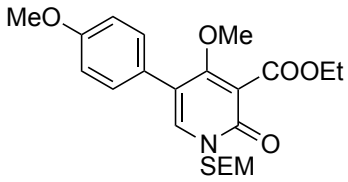
A suspension of ethyl 5-bromo-4-methoxy-2-((2-(trimethylsilyl)ethoxy)methoxy)nicotinate **7**[5] (1.0 eq.) or ethyl 5-bromo-4-methoxy-2-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydropyridine-3-carboxylate **8** [5] (1.0 eq.), $Pd(PPh_3)_4$ (0.1 eq.), K_2CO_3 (3.0 eq.) and boronic acid derivative (1.5 eq.) in degassed (freeze/thaw) DME/H_2O/DMF (9:1:0.5, 1 mL/100 mg 5-bromo-pyridine substrate) was stirred at 60°C under an argon atmosphere. The reaction was monitored by TLC and diluted with EtOAc upon completion. The organic layer was washed with sat. aq. NH_4Cl, brine (2x) and water (1x), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by gradient flash chromatography and dried *in vacuo*.

[5] H. J. Jessen, A. Schumacher, T. Shaw, A. Pfaltz, K. Gademann, *Angew. Chem. Int. Ed.* **2011**, *50*, 4222.

Ethyl -4-methoxy- 5-(4-((4-methoxybenzyl)oxy)phenyl) -2-((2-(trimethylsilyl)ethoxy)methoxy) nicotinate 10[5]: The compound was prepared according to literature procedures. All analytical data were in full agreement with previously published values.[5]

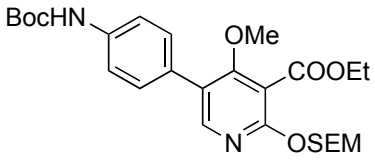


Ethyl 4-methoxy-5- (4-methoxyphenyl)-2-oxo-1- ((2-(trimethylsilyl)ethoxy)methyl)-1,2-dihydropyridine-3- carboxylate 8a: The

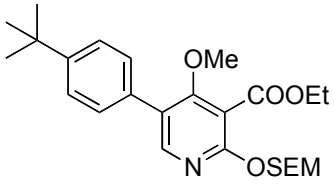


reaction was carried out according to general procedure 2.1. using the following amounts: **8**[5] (428 mg, 1.1 mmol, 1.0 eq.), $Pd(PPh_3)_4$ (122 mg, 0.11 mmol, 0.1 eq.), K_2CO_3 (437 mg, 3.3 mmol, 3.0 eq.), 4-methoxyphenylboronic acid (240 mg, 1.6 mmol, 1.5 eq.). The crude material was purified by flash chromatography (SiO_2, pentane/EtOAc 1:1) to give the product **8c** as a yellow oil (418 mg, 0.97 mmol, 92%). $\boldsymbol{R_f}$ = 0.17 (SiO_2, pentane/Et_2O, 2:1). **FTIR** (neat): $\tilde{\nu}$ = 2954, 2361, 1730, 1653, 1514, 1463, 1392, 1306, 1248, 1207, 1137, 1086, 835, 632 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.33 (s, 1H), 7.30 – 7.27 (m, 2H), 6.96 – 6.90 (m, 2H), 5.33 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 3H), 3.71 – 3.62 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.00 – 0.90 (m, 2H), -0.00 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.1, 163.8, 161.3, 159.5, 135.9, 130.3, 126.2, 116.7, 114.1, 112.1, 76.3, 67.6, 62.1, 59.4, 55.5, 18.2, 14.3, -1.2. **HRMS-ESI** calcd for $C_{22}H36NO_6Si^+$: 343.1993, found 343.1983.

Ethyl-4-methoxy-5-(4-*N*-Boc-phenyl)-2-((2-(trimethylsilyl)ethoxy)methoxy)-nicotinate 8b: The reaction was carried out according to general procedure 2.1. using the following amounts: **7**[5] (400 mg, 984 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (114 mg, 98.4 µmol, 0.1 eq.), K_2CO_3 (408 mg, 2.95 mmol, 3.0 eq.), *tert*-butyl-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carbamate (471 mg, 1.48 mmol, 1.5 eq.). The crude material was purified by flash chromatography (SiO_2, pentane/Et_2O 2:1 + 0.25% TEA) and was obtained as a yellow oil (510 mg, 983 µmol, quant.). $\boldsymbol{R_f}$ = 0.40 (SiO_2, pentane/Et_2O, 2:1). **FTIR** (neat): $\tilde{\nu}$ = 3342, 2954, 1728, 1590, 1526, 1496, 1443, 1400, 1365, 1319, 1231, 1156, 1076, 1050, 913, 836, 652 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.08 (s, 1H), 7.50-7.35 (m, 4H), 6.62 (s, 1H), 5.60 (s, 2H), 4.50-4.30 (m, 2H), 3.75-3.85 (m, 2H), 3.59 (s, 3H), 1.52 (s, 9H), 1.46-1.35(m, 3H), 1.05-0.96 (m, 2H), 0.02 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.5, 163.3, 159.8, 152.8, 149.2, 138.2, 129.7, 129.3, 124.4, 118.7, 110.9, 90.6, 80.9, 67.3, 61.8, 60.7, 28.5, 18.1, 14.4, -1.3. **HRMS-ESI** calcd for $C_{26}H_{39}N_2O_6Si^+$: 519.2521, found 519.2505.

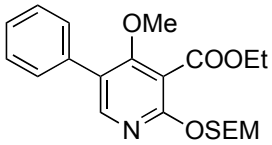


Ethyl-4-methoxy-5-(4-*tert*-butylphenyl)-2-((2-(trimethylsilyl)ethoxy)methoxy) nicotinate 8c: The reaction was carried out according general to general procedure 2.1. using the following amounts: **7**[5] (150 mg, 369 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (42.7 mg, 36.9 µmol, 0.1 eq.), K_2CO_3 (153 mg, 1.11 mmol, 3.0 eq.), 4-*tert*-Butylphenylboronic acid (98.6 mg, 554 µmol, 1.5 eq.). The crude material was purified by flash chromatography (SiO_2, pentane/Et_2O 5:1 + 0.20% TEA) and the product was obtained as a yellow oil (88.6 mg, 193 µmol, 53%). R_f = 0.44 (SiO_2, pentane/Et_2O, 5:1). **FTIR** (neat): $\tilde{\nu}$ = 2955, 2925, 1734, 1590, 1468, 1443, 1364, 1322, 1206, 1074, 914, 836, 656, 624 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.46-7.36 (m, 4H), 5.62 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.83-3.77 (m, 2H), 3.60 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.36 (s, 9H), 1.04 - 0.96 (m, 2H), 0.01 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.6, 163.3, 159.7, 150.8, 149.3, 131.8, 128.7, 125.6, 124.6, 110.7, 90.6, 67.3, 61.7, 60.7, 34.7, 31.4, 18.1, 14.3, -1.3. **HRMS-ESI** calcd for $C_{25}H_{38}NO_5Si^+$: 460.2514, found 460.2500.

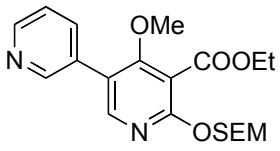


Ethyl-4-methoxy-5-(4-fluorophenyl)-2-((2-(trimethylsilyl)ethoxy)methoxy) nicotinate 8d: The reaction was carried out according general to general procedure 2.1. using the following amounts: **7**[5] (150 mg, 369 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (42.7 mg, 36.9 µmol, 0.1 eq.), K_2CO_3 (153 mg, 1.11 mmol, 3.0 eq.), 4-fluorophenylboronic acid (77.5 mg, 554 µmol, 1.5 eq.). The crude material was purified by flash chromatography (SiO_2, pentane/Et_2O 4:1 +0.25% TEA) and the product was obtained as a yellow oil (40.1 mg, 94.9 µmol, 26%). $\boldsymbol{R_f}$ = 0.42 (SiO_2, pentane/Et_2O, 4:1). FTIR (neat): $\tilde{\nu}$ = 2923, 2852, 1718, 1591, 1468, 1442, 1325, 1248, 1217, 1117, 1049, 978, 913, 841, 757, 695, 647 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.07 (s, 1H), 7.46 - 7.39 (m, 2H), 7.16 - 7.08 (m, 2H), 5.61 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.84 - 3.72 (m, 2H), 3.59 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.20-0.92 (m, 2H), 0.01 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.4, 163.8, 162.6 (d, *J* = 247.3 Hz), 161.4, 149.1, 130.8 (d, *J* = 8.1 Hz), 123.9, 115.7 (d, *J* = 21.5 Hz), 110.7, 90.7, 67.4, 61.9, 60.7, 29.8, 18.2, 14.4, -1.4. **^{19}F-NMR** (367 MHz, $CDCl_3$) δ = -114.6. **HRMS-ESI** calcd for $C_{21}H_{29}FNO_5Si^+$: 422.1749, found 429.1788.

Ethyl-4-methoxy-5-(phenyl)-2-((2-(trimethylsilyl)ethoxy)methoxy) nicotinate 8e: The reaction was carried out according general to general procedure 2.1. using the following amounts: **7**[5] (100 mg, 246 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (28.4 mg, 24.6 µmol, 0.1 eq.), K_2CO_3 (102 mg, 738 µmol, 3.0 eq.), phenylboronic acid (45.0 mg, 369 µmol, 1.5 eq.). The crude material was purified by flash chromatography (SiO_2, pentane/Et_2O 3:1 +0.25% TEA) and the product was obtained as a yellow oil (91.0 mg, 225 µmol, 92%). $\boldsymbol{R_f}$ = 0.56 (SiO_2, Pentane/Et_2O, 3:1). FTIR (neat): $\tilde{\nu}$ = 2992, 2852, 1733, 1589, 1444, 1365, 1321, 1264, 1206, 1060, 983, 912, 835, 700 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.53 - 7.30 (m, 5H), 5.62 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.88 - 3.73 (m, 2H), 3.57 (s, 3H), 1.1 (t, *J* = 7.2 Hz, 3H), 1.03-0.96 (m, 2H), 0.01 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.4, 163.3, 159.9, 149.3, 134.8, 129.1, 128.7, 127.8, 124.7, 110.7, 90.6, 67.3, 61.8, 60.7, 18.1, 14.3, -1.4. **HRMS-ESI** calcd for $C_{21}H_{30}NO_5Si^+$: 404.1888, found 404.1882.

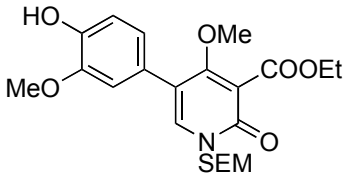


Ethyl-4-methoxy-5-(3-pyridine)-2-((2-(trimethylsilyl)ethoxy)methoxy) nicotinate



8f: The reaction was carried out according general to general procedure 2.1. using the following amounts: **7**[5] (150 mg, 369 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (42.7 mg, 36.9 µmol, 0.1 eq.), K_2CO_3 (153 mg, 1.11 mmol, 3.0 eq.), pyridine-3-boronic acid (68.1 mg, 554 µmol, 1.5 eq.). The crude material was purified by flash chromatography (SiO_2, Et_2O +0.25% TEA) and the product was obtained as a yellow oil (98.7 mg, 244 µmol, 66%). R_f = 0.38 (SiO_2, Et_2O). **FTIR** (neat): $\tilde{\nu}$ = 2920, 2852, 1732, 1586, 1443, 1365, 1266, 1199, 1116, 1065, 993, 910, 836, 714, 666, 627 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.70-8.67 (m, 1H), 8.57 (dd, *J* = 4.8 Hz, *J* = 1.9 Hz, 1H), 8.07 (s, 1H), 7.80-7.73 (m, 1H), 7.32 (dd, *J* = 7.9 Hz, *J* = 1.9 Hz, 1H), 5.59 (s, 2H) 4.40 (q, *J* = 7.1 Hz, 2H), 3.81-3.73 (m, 2H), 3.64 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 0.98-0.93 (m, 2H), -0.02 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.3, 163.0, 160.7, 149.7, 148.9, 148.8, 136.4, 130.6, 123.4, 121.3, 110.1, 90.7, 67.4, 61.9, 60.5, 18.1, 14.1, -1.4. **HRMS-ESI** calcd for $C_{20}H_{29}N_2O_5Si^+$: 405.1840, found 405.1833.

Ethyl-5-(4-hydroxy-3-methoxyphenyl)-4-methoxy-2-oxo-1-((2-(trimethylsilyl) ethoxy) methyl)-1,2-dihydropyridine-3-carboxylate



8g: The reaction was carried out according general to general procedure 2.1. using the following amounts: **8**[(5)] (400 mg, 984 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (114 mg, 98.4 µmol, 0.1 eq.), K_2CO_3 (408 mg, 2.95 mmol, 3.0 eq.), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (369 mg, 1.48 mmol, 1.5 eq.). The crude material was purified by gradient flash chromatography (SiO_2, pentane/Et_2O 1:3 to 0:3 +0.25% TEA) and the product was obtained as a yellow oil (352 mg, 783 µmol, 80%). $\boldsymbol{R_f}$ = 0.38 (SiO_2, Pentane/Et_2O, 1:3). **FTIR** (neat): $\tilde{\nu}$ = 3411, 2953, 1729, 1650, 1515, 1463, 1373, 1246, 1200, 1134, 1084, 1028, 853, 630 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.34 (s, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 6.83 (dd, *J* = 8.1 Hz, *J* = 1.9 Hz, 1H'), 5.78 (s, 1H), 5.33 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.73 (s, 3H), 3.70 - 3.62 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.97-0.91 (m, 2H), 0.00 (s, 9H).**^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.0, 163.9, 161.1, 146.6, 145.7, 136.1, 125.8, 122.1, 117.0, 114.6, 111.9, 67.7, 62.1, 59.5, 56.2, 29.8, 25.0, 18.1, 14.3, -1.3. **HRMS-ESI** calcd for $C_{22}H_{34}NO_6Si^+$: 450.1943, found 450.1930.

Ethyl-4-methoxy-5-(4-pyridine)–2-oxo–1-((2-(trimethylsilyl) ethoxy)methyl)-1,2-dihydropyridine-3-carboxylate 8h: The reaction was carried out according general to general procedure 2.1. using the following amounts: **8**[5] (400 mg, 984 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (114 mg, 98.4 µmol, 0.1 eq.), K_2CO_3 (408 mg, 2.95 mmol, 3.0 eq.), pyridine-4-boronic acid (181 mg, 1.48 mmol, 1.5 eq.). The organic layer was extracted with sat. aq. sodium carbonate solution and the crude material was purified by flash chromatography (SiO_2, DCM/MeOH 25:1 +0.25% TEA) and HPLC (RP18, H_2O/ACN 4:1 to 0:1 in 25 min, 5 mL/min, retention time 3.8 min) and then lyophilised to give a yellow oil (136 mg, 336 µmol, 34%). $\boldsymbol{R_f}$ = 0.14 (SiO_2, DCM/MeOH 25:1 +0.25% TEA). **FTIR** (neat): $\tilde{\nu}$ = 2954, 2897, 1728, 1650, 1592, 1547, 1463, 1393, 1337, 1306, 1206, 1137, 1084, 1021, 832, 610 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.47 (d, *J* = 5.9 Hz, 2H), 7.39 (s, 1H), 7.20 (d, *J* = 5.9 Hz, 2H), 5.22 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.58 - 3.49 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.87 - 0.75 (m, 2H), -0.13 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.1, 162.6, 161.3, 150.1, 142.0, 136.6, 123.7, 114.4, 111.4, 76.4, 67.9, 62.3, 59.3, 18.2, 14.2, -1.3. **HRMS-ESI** calcd for $C_{20}H_{29}N_2O_5Si^+$: 405.1840, found 405.1830.

2-Methoxy-4-(pyridin-3-yl)phenol 13: The reaction was carried out according general to general procedure 2.1. using the following amounts: 3-bromopyridine (100 mg, 633 µmol, 1.0 eq.), $Pd(PPh_3)_4$ (73 mg, 63 µmol, 0.1 eq.), K_2CO_3 (262 mg, 1.90 mmol, 3.0 eq.), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (237 mg, 0.96 mmol, 1.5 eq.). The reaction mixture was diluted with EtOAc, washed twice with brine, dried over sodium sulfate and purified by flash chromatography (SiO_2, Et_2O). The obtained oil was dissolved in DCM and was then extracted three times with sat. aq. sodium bicarbonate solution to remove residual boronic ester. The organic layer was then dried over sodium sulfate and the crude material was further purified by recrystalisation in Et_2O to give a colourless solid (89 mg, 442 µmol, 70%). **M.p.** : 148-150°C, $\boldsymbol{R_f}$ = 0.23 (SiO_2, pentane/EtOAc 4:1). **FTIR** (neat): $\tilde{\nu}$ = 2991, 2943, 1590, 1518, 1465, 1434, 1399, 1366, 1308, 1216, 1185, 1125, 891, 855, 786, 709 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 8.81 (d, *J* = 2.0 Hz, 1H), 8.55 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.85 - 7.80 (m, 1H), 7.34 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.12 - 7.00 (m, 3H), 6.02 (s, 1H), 3.97 (s, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 148.03, 147.89, 147.11, 146.08, 136.69, 134.04, 130.12, 123.51, 120.36, 115.12, 109.61, 56.06. **HRMS-ESI** calcd for $C_{12}H_{12}NO_2^+$: 202.0863, found 202.0863.

2.2 General Procedure for the Deprotection of O-SEM Protected Pyridones

To a stirred solution of *O*-SEM protected pyridone (1.0 eq., 0.05 M in DCM) at rt was added TFA (1.0 eq.) and the reaction was monitored by TLC. Further aliquots of TFA (0.2 eq.) were added until TLC indicated complete conversion. The solvent was removed *in vacuo* and the residue was dissolved in a minimum amount of DCM. To the resulting solution pentane was added until precipitation was observed. The slurry was stored at 4°C over night. The precipitate was collected and washed with cold pentane. Precipitation was repeated if required.

Ethyl 4-methoxy-5-(4-((4-methoxybenzyl)oxy)phenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate 10[5]: The compound was prepared according to literature procedures. All analytical data was in full agreement with the previously published values.

Ethyl 5-(4-((*tert*-butoxycarbonyl)amino)phenyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate 12e: The reaction was carried out according to general procedure 2.2. using the following amounts: **8b** (280 mg, 540 µmol, 1.0 eq.). The product was obtained as a colourless solid (160 mg, 412 µmol, 76 %). **M.p.** : 230-233°C, $\boldsymbol{R_f}$ = 0.25 (SiO_2, DCM/MeOH 15:1). **FTIR** (neat): $\tilde{\nu}$ = 3260, 2979, 1734, 1717, 1715, 1615, 1588, 1533, 1525, 1445, 1391, 1363, 1298, 1235, 1150, 1076, 893, 830 cm^{-1}. **^{1}H-NMR** (400 MHz, $(CD_3)_2SO$) δ = 11.90 (s, 1H), 9.41 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.36 (s, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.57 (s, 1H), 1.48 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $(CD_3)_2SO$) δ = 165.3, 163.6, 160.7, 152.8, 138.8, 135.6, 129.1, 127.3, 118.0, 114.3, 112.7, 79.1, 61.0, 59.4, 28.1, 13.9. **HRMS-ESI** calcd for $C_{20}H_{25}N_2O_6^+$: 389.1713, found 389.1707.

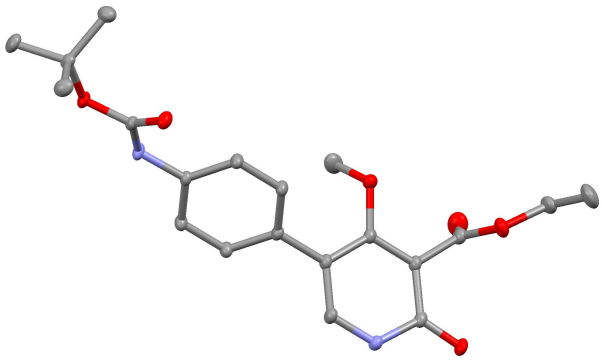
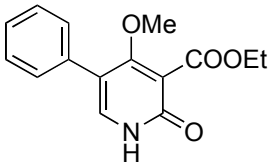


Figure 1 X-ray structure of Ethyl 5-(4-((*tert*-butoxycarbonyl)amino)phenyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate, CCDC 888459.

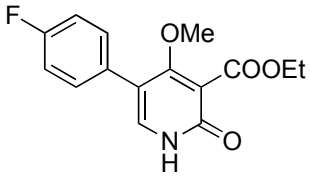
4-(5-(ethoxycarbonyl)-4-methoxy-6-oxo-1,6-dihydropyridin-3-yl)benzenaminium 2,2,2-trifluoroacetate 12f: 12e (86 mg, 0.22 µmol, 1.0 eq.) was dissolved in TFA (2 mL, 50% in DCM) at rt and monitored by TLC. After 3h DCM (5 mL) was added and the solvents were removed *in vacuo*. The crude material was dissolved in DCM and a minimum amount of MeOH and then pentane was added until precipitation began. The mixture was stored in the fridge over night, filtered, dried *in vacuo* which gave **12f** as a colourless crystals (83 mg, 0.21 µmol, 93 %). **M.p.** : 168-171°C, $\boldsymbol{R_f}$ = 0.15 (SiO_2, DCM/MeOH 9:1). **FTIR** (neat): $\tilde{\nu}$ = 2880, 1728, 1678, 1635, 1515, 1470, 1396, 1304, 1169, 1120, 1078, 1012, 832, 795, 709 cm^{-1}. **^{1}H-NMR** (400 MHz, $(CD_3)_2SO$) δ = 7.38 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 186.3, 165.4, 163.5, 160.8 135.7, 129.9, 119.4, 119.3, 114.1, 112.4, 61.1, 59.3, 13.9. **^{19}F-NMR** (367 MHz, $(CD_3)_2SO$) δ = -74.0. **HRMS-ESI** calcd for $C_{15}H_{17}N_2O_4^+$: 289.1188, found 289.1183. For the biological assays, a portion of **12f** was dissolved in EtOAc and extracted two times with NaOH (1M). The aqueous layer was extracted three times with DCM and the combined organic layers were dried over sodium sulfate and the solvent removed in vacuo to give the free base as an off white solid. No ^{19}F signal was observed in the fluorine NMR (see attached spectrum). **1H NMR** (400 MHz, $CDCl_3$) δ = 7.32 (s, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

Ethyl 4-methoxy-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxylate 12a: The



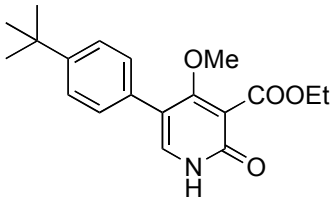
reaction was carried out according to general procedure 2.2. using the following amounts: **8e** (70 mg, 0.17 mmol, 1.0 eq.). The product was obtained as a colourless solid (31 mg, 0.11 mmol, 65 %). **M.p.** : 146-148°C, $\boldsymbol{R_f}$ = 0.48 (SiO_2, DCM/MeOH 15:1). **FTIR** (neat): $\tilde{\nu}$ = 2959, 2921, 2851, 1709, 2362, 1724, 1633, 1546, 1461, 1390, 1292, 1239, 1187, 1075, 1015, 988, 943, 880, 757, 701 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 13.37 (s, 1H), 7.49 -7.30 (m, 6H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ =165.8, 165.5, 164.1 136.1, 133.8, 129.1, 128.7, 127.9, 117.4, 112.5, 62.0, 59.8, 14.3. **HRMS-ESI** calcd for $C_{15}H_{16}FNO_4^+$: 274.1074, found 274.1069.

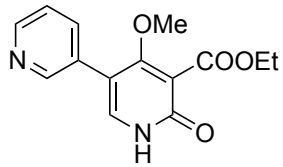
Ethyl 5-(4-fluorophenyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate



12b: The reaction was carried out according to general procedure 2.2. using the following amounts: **8d** (70 mg, 83 µmol, 1.0 eq.). The product was obtained as a colourless solid (13 mg, 45 µmol, 54 %). **M.p.** : 158-159°C, $\boldsymbol{R_f}$ = 0.51 (SiO_2, DCM/MeOH 15:1). **FTIR** (neat): $\tilde{\nu}$ = 2922, 2853, 2362, 1725, 1642, 1512, 1468, 1390, 1301, 1235, 1195, 1161, 1077, 838 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 13.31 (s, 1H), 7.39 (s, 1H), 7.32 (dd, *J* = 8.4, *J* = 5.5 Hz, 2H), 7.10 (dd, *J* = 8.6, *J* = 8.6 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.9, 164.5 (d, *J* = 247.4 Hz), 164.1, 161.4, 135.9, 130.8 (d, *J* = 8.1 Hz), 129.8, 129.7, 116.9, 115.7 (d, *J* = 21.6 Hz), 62.1, 59.7, 14.3. **^{19}F-NMR** (367 MHz, $CDCl_3$) δ = -114.3. **HRMS-ESI** calcd for $C_{15}H_{14}FNO_4^+$: 292.0980, found 292.0974.

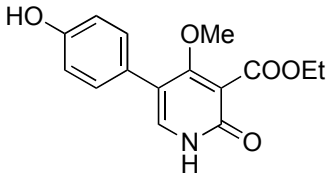
Ethyl 5-(4-(*tert*-butyl)phenyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate 12c: The reaction was carried out according to general procedure 2.2. using the following amounts: **8c** (69 mg, 0.15 mmol, 1.0 eq.). The product was obtained as a colourless solid (40 mg, 0.12 mmol, 81 %). **M.p.** : 240-241°C, $\boldsymbol{R_f}$ = 0.46 (SiO_2, DCM/MeOH 15:1). **FTIR** (neat): $\tilde{\nu}$ = 2962, 2918, 1851, 1722, 1633, 1545, 1472, 1388, 1293, 1242, 1197, 990 ,884, 932, 765, 669, 611 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 13.42 (s, 1H), 7.41 (s, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 4H), 1.34 (s, 9H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.5, 164.0, 160.0, 150.8, 135.9, 130.8, 128.6, 125.6, 117.1, 112.4, 62.0, 59.8, 34.7, 31.4, 14.2. **HRMS-ESI** calcd for $C_{19}H_{24}NO_4^+$: 330.1700, found 330.1696.



5'-(ethoxycarbonyl)-4'-methoxy-6'-oxo-1',6'-dihydro-[3,3'-bipyridin]-1-ium 2,2,2-trifluoroacetate 12h: 

The reaction was carried out according to general procedure 2.2. using the following amounts: **8f** (79 mg, 0.20 mmol, 1.0 eq.). The crude was dissolved in DCM and extracted three times with saturated Na_2CO_3, dried over sodium sulfate to give the product as a yellow oil (34 mg, 0.12 mmol, 63%.). $\boldsymbol{R_f}$ = 0.36 (SiO_2, DCM/MeOH 10:1 + 0.1% TEA). **FTIR** (neat): $\tilde{\nu}$ = 2962, 2918, 1851, 1722, 1633, 1545, 1472, 1388, 1293, 1242, 1197, 990 ,884, 932, 765, 669, 611 cm^{-1}. **^{1}H-NMR** (400 MHz, CD_2Cl_2) δ = 10.90 (s, 1H), 8.85 (s, 1H), 8.72 (m, 1H), 8.19 (m, 1H), 7.73 (m, 1H), 7.59 (s, 1H), 4.35 (q, *J* = 7.0 Hz, 1H,), 3.87 (s, 1H), 1.34 (t, *J* = 7.1 Hz, 1H,). **^{13}C-NMR** (101 MHz, CD_2Cl_2) δ = 166.3, 164.8, 164.6, 150.1, 149.2, 134.0, 130.5, 123.7, 114.1, 112.0, 62.5, 59.9, 30.2, 14.4. **HRMS-ESI** calcd for $C_{14}H_{15}N_2O_4^+$: 275.1026, found 275.1024.

Ethyl 5-(4-hydroxyphenyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate



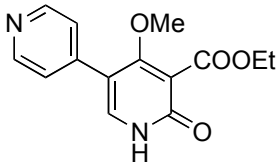
11a: The reaction was carried out according to general procedure 2.2. using the following amounts: **10** (24 mg, 59 µmol, 1.0 eq.). The product was obtained as a colourless solid (17 mg, 59 µmol, quant.). **M.p.** : 234-237°C, $\boldsymbol{R}_f$ = 0.31 (SiO_2, DCM/MeOH 15:1). **FTIR** (neat): $\tilde{\nu}$ = 3269, 2942, 2852 ,1724, 1608, 1512, 1464, 1393, 1304, 1233, 1195, 1176, 1060, 962, 892, 842, 704 cm^{-1}. **^{1}H-NMR** (500 MHz, CD_3OD) δ = 7.35 (s, 1H), 7.22 (d, *J* =8.5 Hz, 2H), 6.83 (d, *J* =8.5 Hz, 2H), 4.35 (q, *J* =7.1 Hz, 2H), 3.65 (s, 3H) 1.36 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (126 MHz, CD_3OD) δ = 167.3, 163.5, 158.6, 136.3, 131.2, 125.9, 119.4, 118.8, 116.5, 114.5, 62.7, 60.4, 14.3. **HRMS-ESI** calcd for $C_{15}H_{16}NO_5^+$: 290.1023, found 290.1018.

2.3 General Procedure for the Deprotection of *N*-SEM Protected Pyridones with TBAF

To a solution of *N*-SEM protected pyridone (1.0 eq., 1 mL dry THF per 10 mg pyridone) under an argon atmosphere was added TBAF (1.2 eq., 1.0 M in THF). The reaction mixture was heated to 60°C and monitored by TLC. Upon completion, the reaction mixture was then allowed to cool to rt and the solvent was removed *in vacuo*. The crude product was purified by gradient flash chromatography.

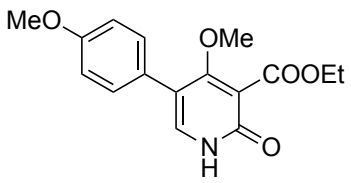
Ethyl 5-(4-hydroxy-3-methoxyphenyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate 12d: The reaction was carried out according to general procedure 2.3 using the following amounts: **8g** (44 mg, 0.98 mmol, 1.0 eq.) and TBAF (0.12 mL, 1M in THF, 0.12 mmol, 1.2 eq.). The crude product was purified by flash chromatography (SiO_2, DCM/MeOH 15:1) to give a colourless solid (22 mg, 0.69 mmol, 70%). **M.p.** : 77-78°C, $\boldsymbol{R_f}$ = 0.17 (SiO_2, DCM/MeOH 12:1). **FTIR** (neat): $\tilde{\nu}$ = 3341, 3130, 2963, 2845, 1730, 1625, 1513, 1467, 1388, 1303, 1253, 1194, 1075, 1029, 884, 823, 700 cm^{-1}. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 13.27 (s, 1H), 7.38 (s, 1H), 6.87 (d, *J* = 8.1 Hz, 1H) 6.82 - 6.78 (m, 2H), 5.67 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 3.90 (s, 3H), 3.70 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (126 MHz, $CDCl_3$) δ =165.9, 165.6, 163.9, 146.6, 145.6, 135.8, 125.7, 122.11, 117.4, 114.7, 113.0, 111.7, 62.1, 59.9, 56.2, 14.3. **HRMS-ESI** calcd for $C_{16}H_{16}NO_6^+$: 320.1134, found 320.1129.

Ethyl 4-methoxy-6-oxo-1,6-dihydro-[3,4'-bipyridine]-5-carboxylate 12g: The



reaction was carried out according to general procedure 2.3 using the following amounts: **8h** (23 mg, 57 µmol, 1.0 eq.) and TBAF (68 µL, 1M in THF, 68 µmol, 1.2 eq.). The crude product was purified by flash chromatography (SiO_2, DCM/MeOH 12:1 + 0.1% TEA) to give a yellow oil (10 mg, 37 µmol, 64%). $\boldsymbol{R_f}$ = 0.22 (SiO_2, DCM/MeOH 12:1 + 0.1% TEA). **FTIR** (neat): $\tilde{\nu}$ = 2922, 2853, 1724, 1631, 1466, 1399, 1260, 1079, 1022, 628 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 13.33 (s, 1H), 8.61 (d, *J* = 5.9 Hz, 2H), 7.51 (s, 1H), 7.40 (d, *J* = 5.9 Hz, 2H), 3.80 (s, H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).**^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 165.7, 164.4, 164.2, 150.1, 142.0, 136.3, 123.6, 114.7, 111.9, 62.3, 59.7, 14.2. **HRMS-ESI** calcd for $C_{14}H_{16}N_2O_4^+$: 275.1110, found 275.1026.

Ethyl 4-methoxy-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate 9a: To **8a** (230 mg, 0.53 mmol, 1.0 eq.) in DMF (1 mL) TBAF (1.60 mL, 1M in THF, 1.06 mmol, 1.2 eq.) was added. The mixture was stirred for 6h at 60°C. The solvents were removed *in vacuo* and the crude material was dissolved in DCM. Upon slow addition of *n*-hexane, the target compound **9a** precipitated from the solution. The colorless solid was filtered and washed with DCM/hexane (1:1; 5 mL), yielding **9a** (87.2 mg, 0.29 mmol, 54%). **M.p.** : 186-188°C. R_f = 0.26 (SiO_2, DCM/MeOH 15:1). **FTIR** (neat): $\tilde{\nu}$ = 2981, 1728, 1637, 1514, 1465, 1393, 1300 , 1245, 1181, 1076, 784 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 13.43 (s, 1H), 7.38 (s, 1H), 7.31 – 7.25 (m, 2H), 6.92 (dd, *J* = 9.2, 2.4 Hz, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.2, 165.8, 164.3, 159.7, 136.1, 130.5, 126.4, 117.3, 114.4, 113.0, 62.2, 60.1, 55.7, 14.6. **HRMS-ESI** calcd for $C_{16}H_{18}NO_5^+$: 304.1179, found 304.1175.



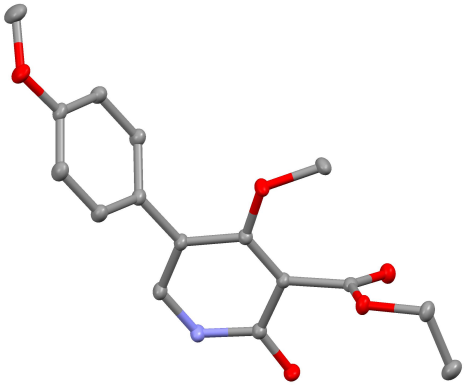


Figure 5.3. X-ray structure of **Polymorph A** CCDC 888460 of Ethyl 4-methoxy-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate.

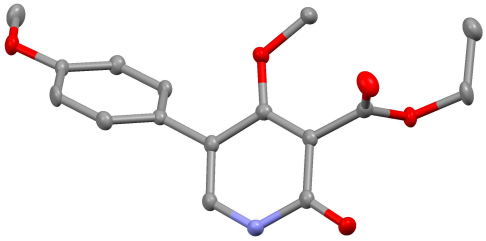


Figure 5.3. X-ray structure of **Polymorph B** CCDC 888461 of Ethyl 4-methoxy-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate.

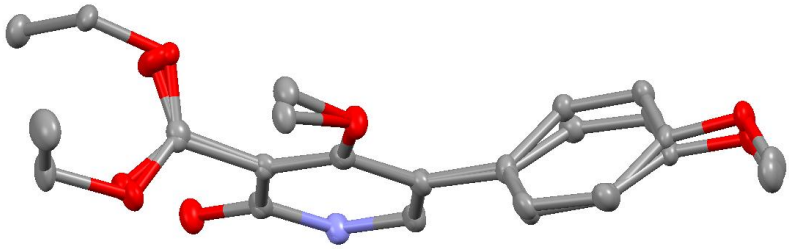
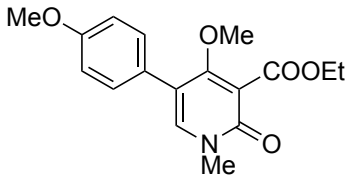


Figure 5.3. Overlay of the X-ray structures of **Polymorph A** (CCDC 888460) and **Polymorph B** (CCDC 888461) of Ethyl 4-methoxy-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate. The ethyl-carboxylate groups on the left site are rotated at about 180°.

Ethyl 4-methoxy-5-(4-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate 9c: To a solution of ethyl 4-methoxy-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **9a** (21 mg, 69 µmol, 1.0 equiv.) in CH_3CN (2 mL) was added potassium carbonate (19 mg, 0.14 mmol, 2.0 equiv.) followed by methyl iodide (49 mg, 0.34 mmol, 5.0 equiv.) . The mixture was stirred 4 hours at 50 °C. The solvents were removed *in vacuo* and the crude material was dissolved in diethyl ether (15 mL). After aqueous extraction (3x5 mL), the organic layer was dried over sodium sulfate and the solvents removed *in vacuo*. Flash chromatography with DCM/MeOH (15:1) yielded **9c** (17 mg, 54 µmol, 77%) as a colorless oil. $\boldsymbol{R_f}$ = 0.40 (SiO_2, DCM/MeOH 20:1). **FTIR** (neat): $\tilde{\nu}$ = 2957, 1725, 1648, 1512, 1513, 1463, 1397, 1358, 1305, 1246, 1207, 1152, 1092, 1023, 836, 631 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 7.28 – 7.24 (m, 2H), 7.20 (s, 1H), 6.94 – 6.89 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.69 (s, 3H), 3.52 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, $CDCl_3$) δ = 166.1, 163.6, 161.2, 159.4, 138.3, 130.3, 126.1, 116.2, 114.1, 112.5, 62.0, 59.5, 55.4, 37.2, 14.3. **HRMS-ESI** calc. for $C_{17}H_{20}NO_5^+$: 318.1336 found: 318.1342.

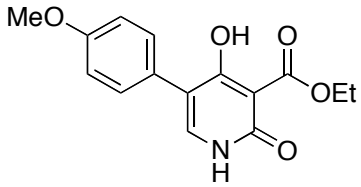


Ethyl 5-(4-hydroxyphenyl)-4-methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate 11c: A 10 mL round bottom flask was charged with flame dried K_2CO_3 (17 mg, 0.12 mmol, 2.0 equiv) and Ethyl 4-methoxy-5-(4-((4-methoxybenzyl)oxy)phenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate **10**^{xy} (25 mg, 60 µmol, 1.0 equiv.). The solids were suspended in Acetonitrile (2 mL) and MeI (43 mg, 0.30 mmol, 5.0 equiv) was added. The reaction mixture was heated to 35°C over night, after which TLC analysis (SiO_2, DCM/MeOH 20:1, R_f= 0.50) indicated complete formation of the product. The solvents were removed *in vacuo*, the residue was taken up in Et_2O (10 mL) and the organic layer was extracted with water (3x5 mL). The layers were separated, and the organic layer was dried over sodium sulfate, filtered and the solvents removed *in vacuo*. The residue was dissolved in DCM containing 2.5% TFA v/v (2 mL). The mixture was stirred 10 minutes at room temperature. The mixture was diluted with a saturated solution of $NaHCO_3$ (10 mL) and extracted with DCM (3x5 mL). The combined organic layers were dried over sodium sulfate and the solvents removed *in vacuo*. Flash chromatography with DCM/MeOH (15:1) yielded **11c** (17 mg, 50 µmol, 83%) as a colorless oil. $\boldsymbol{R_f}$ = 0.50 (SiO_2, DCM/MeOH 15:1). **FTIR** (neat): $\tilde{\nu}$ = 3171, 2950, 1723, 1642, 1577, 1513, 1400, 1269, 1210, 1152, 1090, 1017, 838, 709 cm^{-1}. **^{1}H-NMR** (400 MHz, MeOD) δ = 7.62 (s, 1H), 7.27 – 7.19 (m, 2H), 6.86 – 6.78 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.63 (s, 3H), 3.55 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (101 MHz, MeOD) δ = 167.3, 165.9, 162.7, 158.6, 141.0, 131.3, 125.8, 118.6, 116.4, 114.2, 62.9, 60.5, 37.5, 14.4. **HRMS-ESI** calc. for: $C_{16}H_{18}NO_5^+$: 304.1185 found: 304.1192.

Ethyl 4-hydroxy-5-(4-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate 9d: Ethyl 4-methoxy-5-(4-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate **9c** (14 mg, 0.04 mmol, 1.0 equiv.) was dissolved in THF (1.5 mL). Freshly crystallized LiI (12 mg, 0.09 mmol, 2.0 equiv.) and pyridinium chloride (10 mg, 0.09 mmol, 2.0 equiv.) were added. The reaction mixture was stirred at 60 °C for 16 hours. The solvents were removed *in vacuo* and the residue taken up in ethyl acetate (10 mL). The organic layer was washed with brine (2x 5 mL).The organic layer was dried over sodium sulfate and the solvents removed *in vacuo*. Semipreparative HPLC purification (RP-18, gradient acetonitrile/water) yielded **9d** (3 mg, 0.01 mmol, 24%) as a colorless foam after lyophillization. $\boldsymbol{R_f}$ = 0.45 (SiO_2, DCM/MeOH 10:1). **FTIR** (neat): $\tilde{\nu}$ = 2926, 2361, 1659, 1538, 1412, 1325, 1245, 1178, 1099, 1032, 834, 769, 680, 630 cm^{-1}. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ = 13.94 (s, 1H), 7.41 (s, 1H), 7.35 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.53 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ = 173.1, 172.4, 160.0, 159.4, 142.2, 130.4, 125.0, 114.1, 113.4, 98.7, 62.1, 55.4, 37.6, 14.2. **HRMS-ESI** calc. for: $C_{16}H_{18}NO_5^+$: 304.1185 found: 304.1173.

Ethyl 4-hydroxy-5-(4-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate 11b: Ethyl 5-(4-hydroxyphenyl)-4-methoxy-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate **11a** (20 mg, 0.07 mmol, 1.0 equiv.) was dissolved in THF (2 mL). Freshly crystallized LiI (19 mg, 0.14 mmol, 2.0 equiv.) and pyridinium chloride (16 mg, 0.14 mmol, 2.0 equiv.) were added. The reaction mixture was stirred at 60 °C for 16 hours. The solvents were removed *in vacuo* and the residue was purified by flash chromatography with DCM/MeOH 9:1 to 5:1, yielding **11b** (18 mg, 0.07 mmol, 95%) as a colorless sticky solid. $\boldsymbol{R_f}$ = 0.48 (SiO_2, DCM/MeOH 9:1). **FTIR** (neat): $\tilde{\nu}$ = 3375, 2361, 1672, 1434, 1201, 11361018, 953, 802 cm^{-1}. **^{1}H-NMR** (400 MHz, DMSO-d_6) δ = 13.62 (s, 1H), 11.62 (s, 1H), 9.61 (s, 1H), 7.47 (s, 1H), 7.30-7.18 (m, 2H), 6.84-6.74 (m, 2H), 4.37-4.27 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H). **^{13}C-NMR** (101 MHz, DMSO-d_6) δ = 172.6, 172.0, 159.2, 156.9, 139.6, 130.2, 115.1, 98.4, 61.3, 48.7, 14.2. The quarternary carbon atom at the C (3) position of the pyridone ring could not be observed. **HRMS-ESI** calc. for: $C_{14}H_{14}NO_5^+$: 276.0866 found: 276.0865.

Ethyl 4-hydroxy-5-(4-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate 9b: Ethyl 4-methoxy-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate **9a** (8.0 mg, 0.026 mmol, 1.0 equiv.) was dissolved in degassed THF (1.5 mL). Freshly crystallized LiI (9.8 mg, 0.052 mmol, 2.0 equiv.) and pyridinium chloride (6.1 mg, 0.052 mmol, 2.0 equiv.) were added. The reaction mixture was stirred at 60 °C for 24 hours. The solvents were removed *in vacuo* and the residue taken up in ethyl acetate (10 mL). The organic layer was washed with brine (5 mL) and water (5 mL). The organic layer was dried over sodium sulfate and the solvents removed *in vacuo*. Flash chromatography (SiO_2, DCM:MeOH 30:1) gave the product as a colourless oil. $\boldsymbol{R_f}$ = 0.15 (SiO_2, DCM/MeOH 30:1). **FTIR** (neat): $\tilde{\nu}$ = 2923, 2362, 1678, 1459, 1408, 1250, 1203, 1076, 1032, 839, 765, 630 cm^{-1}. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ = 14.10 (s, 1H), 11.85 (s, 1H), 7.47 (s, 1H), 7.36 (d, *J* = 8.7 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 4.50 (q, *J* = 7.1 Hz, 1H), 3.84 (s, 1H), 1.46 (t, *J* = 7.2 Hz, 2H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ = 174.2, 172.4, 162.2, 159.3, 138.31, 130.2, 130.1, 124.9, 114.4, 113.9, 62.3, 50.1, 14.1. **HRMS-ESI** calc. for: $C_{15}H_{15}NO_5^+$: 289.0950 found: 289.0950.



3. Experimental Conditions of the PC-12 Assay

All experiments were conducted under strictly sterile conditions. Dulbecco's modified eagle medium (DMEM), collagen coated 24-well plates (Becton Dickinson Labware, UK), NGF-7S from murine submaxillary gland, penicillin-streptomycin and Giemsa stain were purchased from Aldrich. TrypLE, horse serum and fetal bovine serum (heat inactivated) were obtained from Invitrogen. PC-12 cells were purchased from ATCC-LGC. The PC-12 assay has been extensively described elsewhere.[6] Briefly, PC-12 cells were cultured in DMEM (10% horse serum, 5% fetal bovine serum, heat inactivated, 200 U/mL Penicillin, 200 mg/mL Streptomycin, 0.005 % β-mercapto ethanol, high glucose + L-Glutamine). Cell aggregates were separated by passage through a 21-gauge needle. Assays were conducted in collagene coated 24-well-plates. Cell suspensions from primary culture (10^5 cells/mL) were preincubated 1 day and then 3 d incubated with the substances. On each plate separate blank measurements with DMSO (0.1%) and with 10 ng/mL NGF were conducted. All assays were performed in triplicate. After incubation cells were fixed with 5% PBS-buffered formaldehyde solution at 0 °C for 1h, stained with giemsa stain (5 min at rt) and washed with PBS three times. Cells from three to five randomly chosen areas were counted and the percentage of neurite positive cells determined (>500 cells per compound). Processes with a length equivalent to one or more diameters of the cell body were regarded as neurites. Significance of the results was examined by ANOVA (Dunnett's posttest) through comparison with blank experiments. ERK-Inhibitor (PD 98059) was obtained from Invitrogen and used as described.

[6] a) I. Dikic, J. Schlessinger, I. Lax, *Curr. Biol.* **1994**, *4*, 702-708, b) H. J. Jessen, D. Barbaras, M. Hamburger, K. Gademann, *Org. Lett.* **2009**, *11*, 3446-3449, c) Y. Obara, T. Aoki, M. Kusano, Y. Ohizumi, *J. Pharmac. Exp. Ther.* **2002**, *301*, 803-811.

4. X-ray Structure Parameters

X-ray parameters of Ethyl 5-(4-((*tert*-butoxycarbonyl)amino)phenyl)-4-methoxy-2-oxo-1,2-dihydropyridine-3-carboxylate 19, CCDC 888459:

formula	$C_{20}H_{24}N_2O_6$
formula weight	388.42
Z, calculated density	4, 1.310 Mg · m^{-3}
F(000)	824
description and size of crystal	colourless plate, 0.03·0.13·0.22 mm^3
absorption coefficient	0.097 mm^{-1}
min/max transmission	0.99 / 1.00
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P 2_1/n
a	12.3996(3) Å
b	8.7715(2) Å
c	18.6699(4) Å
α	90°
β	104.0880(10)°
γ	90°
V	1969.52(8) $Å^3$
min/max Θ	2.249° / 36.364°
number of collected reflections	55114
number of independent refections	9575 (merging r = 0.059)
number of observed reflections	4981 (I>2.0σ(I))
number of refined parameters	253
r	0.0430
rW	0.1019
goodness of fit	1.0758

X-ray parameters of Ethyl 4-methoxy-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate 9a, Polymorph A CCDC 888460:

formula	$C_{16}H_{17}NO_5$
formula weight	303.31
Z, calculated density	2, 1.377 Mg · m^{-3}
F(000)	320
description and size of crystal	colourless block, 0.16·0.21·0.35 mm^3
absorption coefficient	0.103 mm^{-1}
min/max transmission	0.98 / 0.98
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	triclinic, P -1
a	7.2983(2) Å
b	9.2081(3) Å
c	12.3051(5) Å
α	107.988(2)°
β	96.327(2)°
γ	107.4030(10)°
V	731.59(5) Å3
min/max Θ	1.785° / 32.577°
number of collected reflections	18834
number of independent refections	5257 (merging r = 0.028)
number of observed reflections	4090 (I>2.0σ(I))
number of refined parameters	199
r	0.0406
rW	0.0587
goodness of fit	1.0968

X-ray parameters of Ethyl 4-methoxy-5-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate 9a, Polymorph B CCDC 888461:

formula	$C_{16}H_{17}NO_5$
formula weight	303.31
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F(000)	640
description and size of crystal	colourless block, 0.04 · 0.05 · 0.19 mm^3
absorption coefficient	0.103 mm^{-1}
min/max transmission	0.99 / 1.00
temperature	123K
radiation(wavelength)	Mo K_α (λ = 0.71073 Å)
Crystal system, space group	monoclinic, P 21/c
a	11.3216(5) Å
b	7.0251(3) Å
c	18.4969(8) Å
α	90°
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γ	90°
V	1469.47(11) Å3
min/max Θ	1.801° / 30.999°
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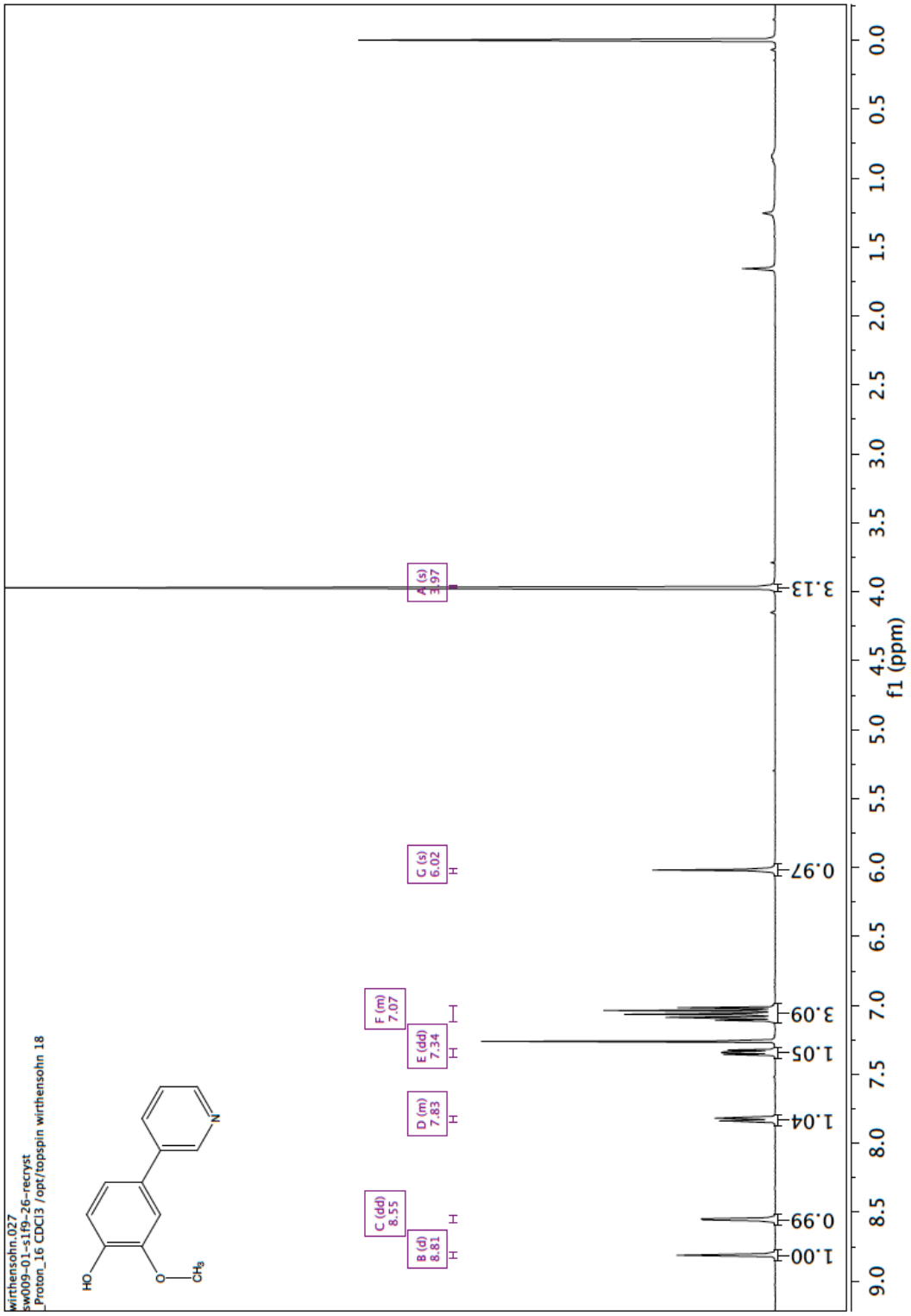
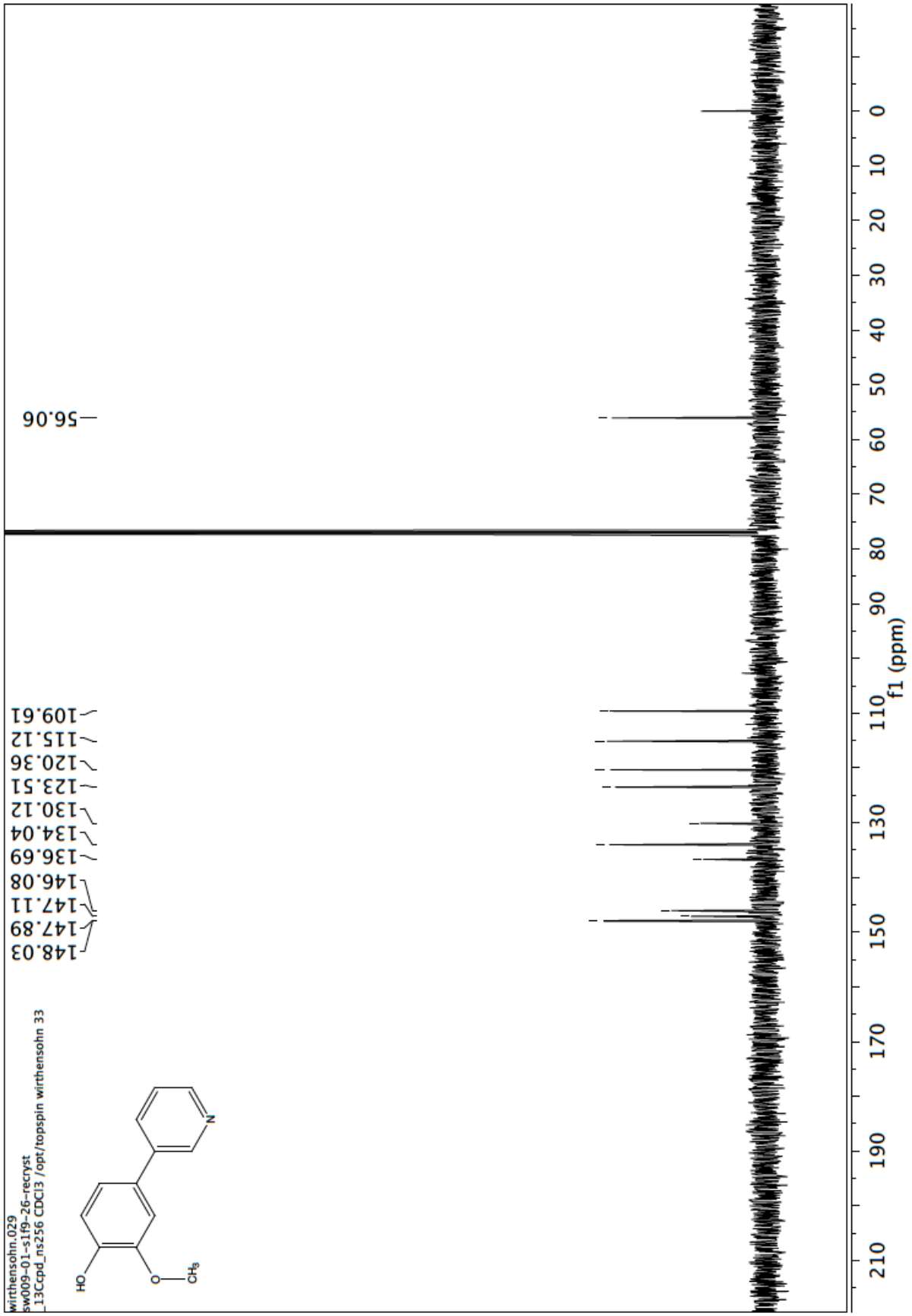
goodness of fit	1.0906

5. NMR Spectra

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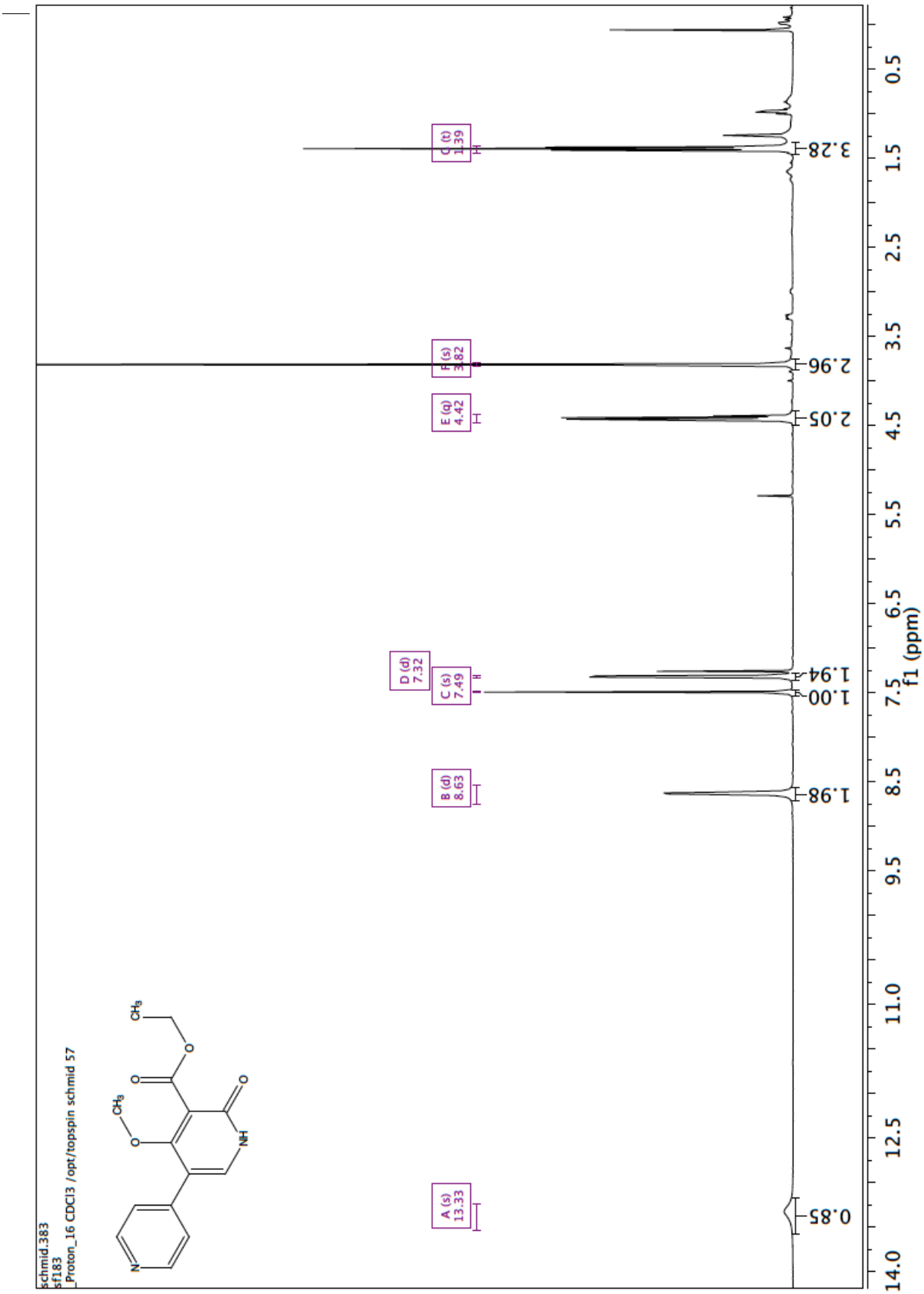
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sf183
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E (q) 4.42
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G (t) 1.39
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1.00
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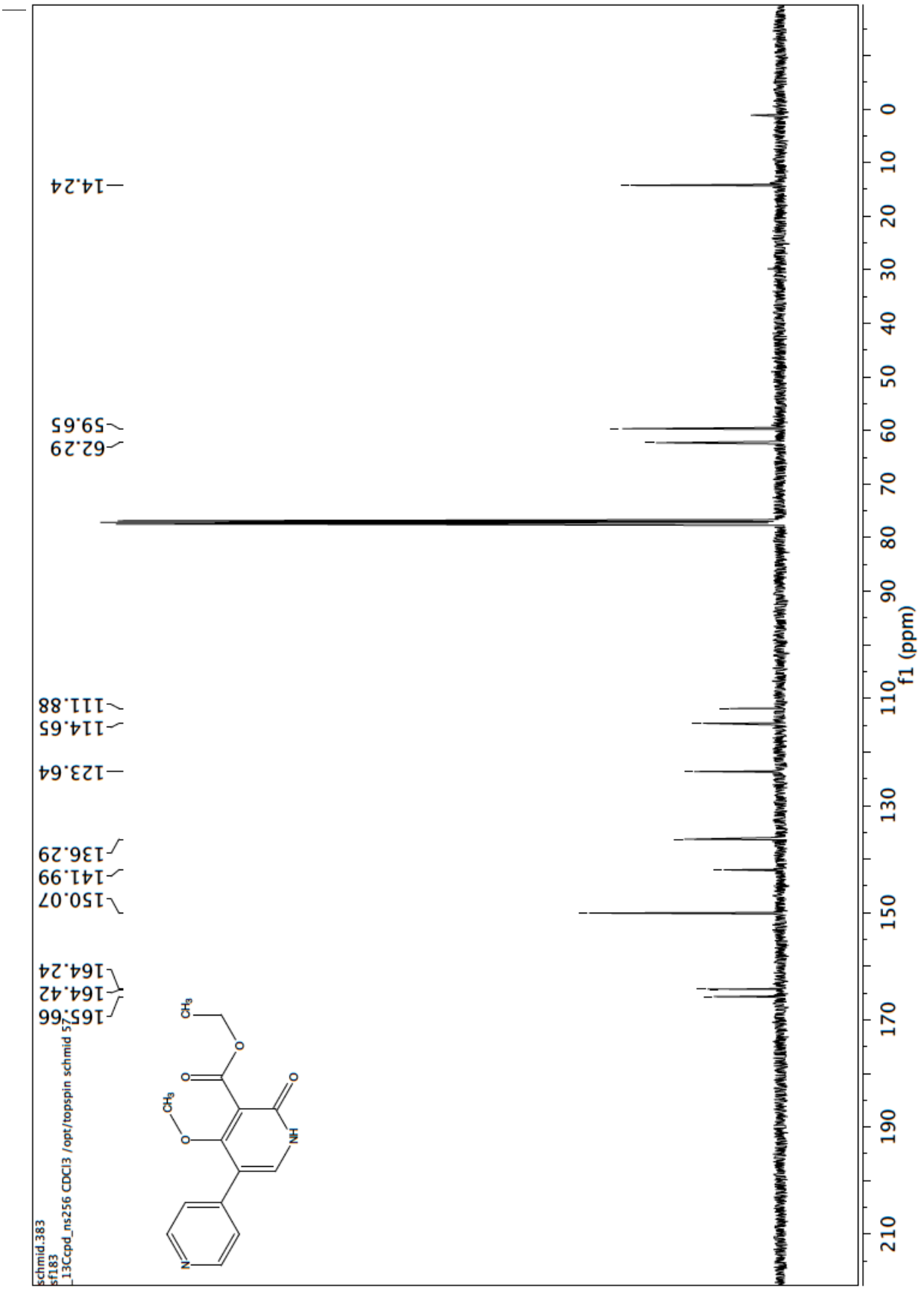
f1 (ppm)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sf183
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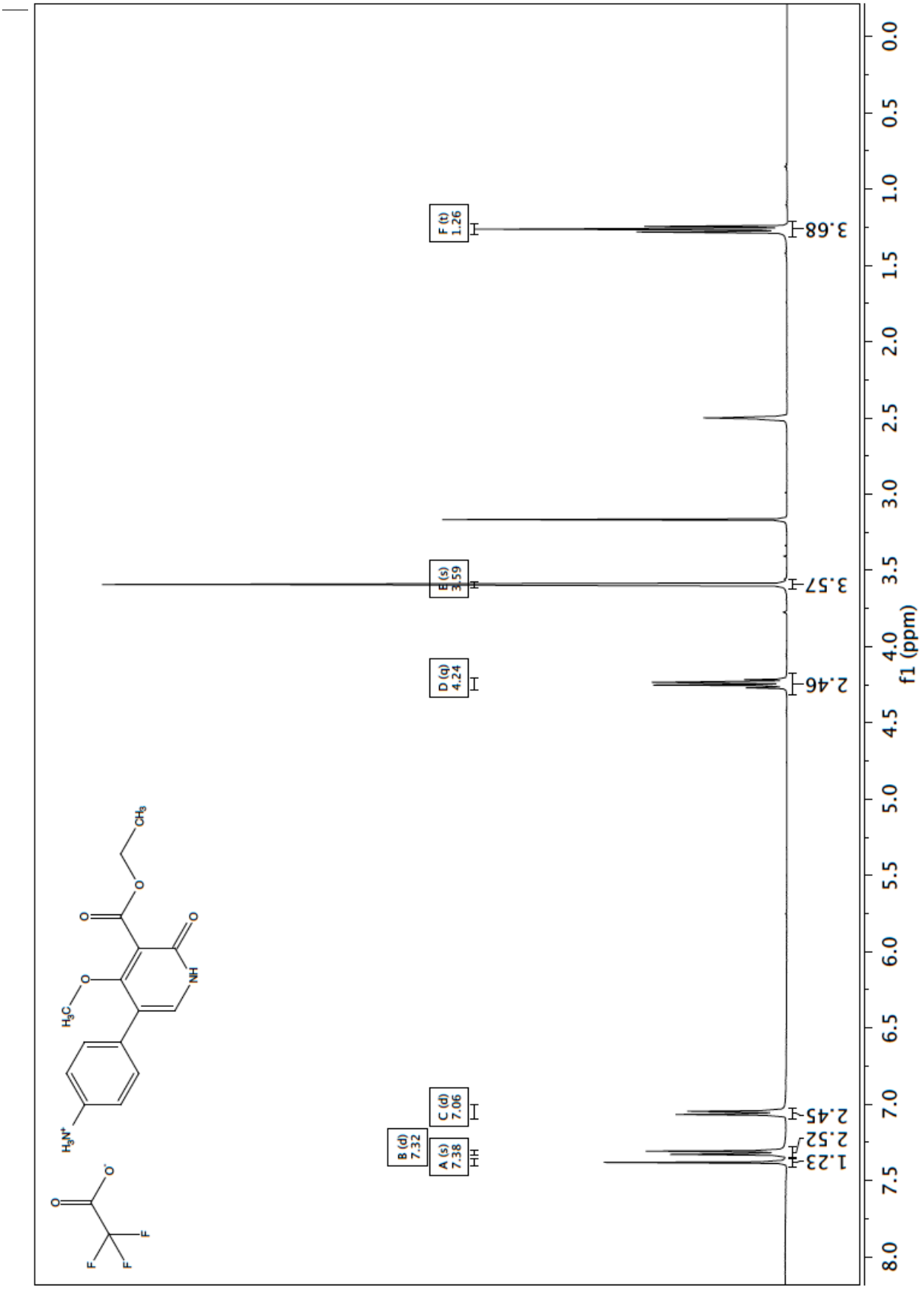
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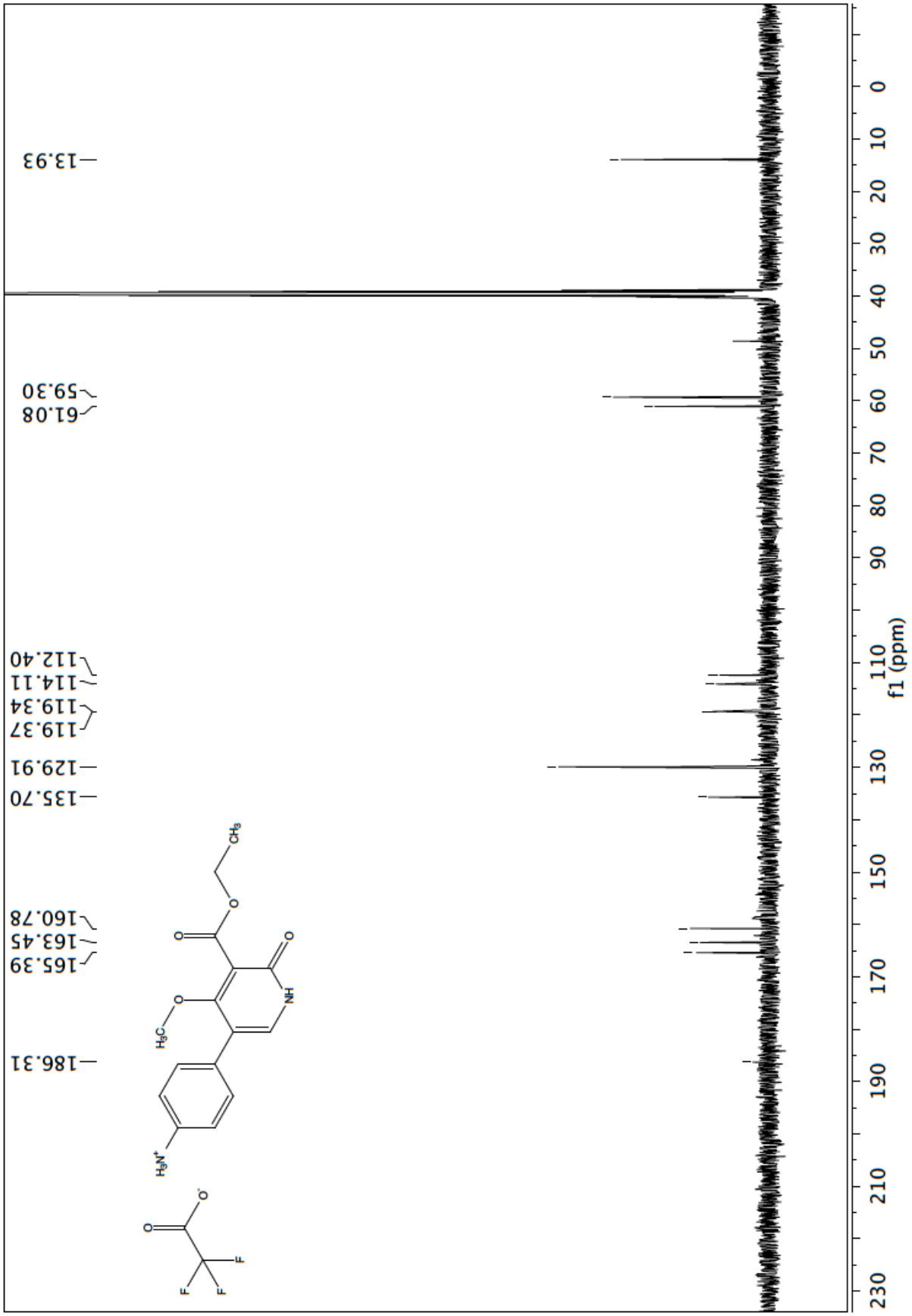
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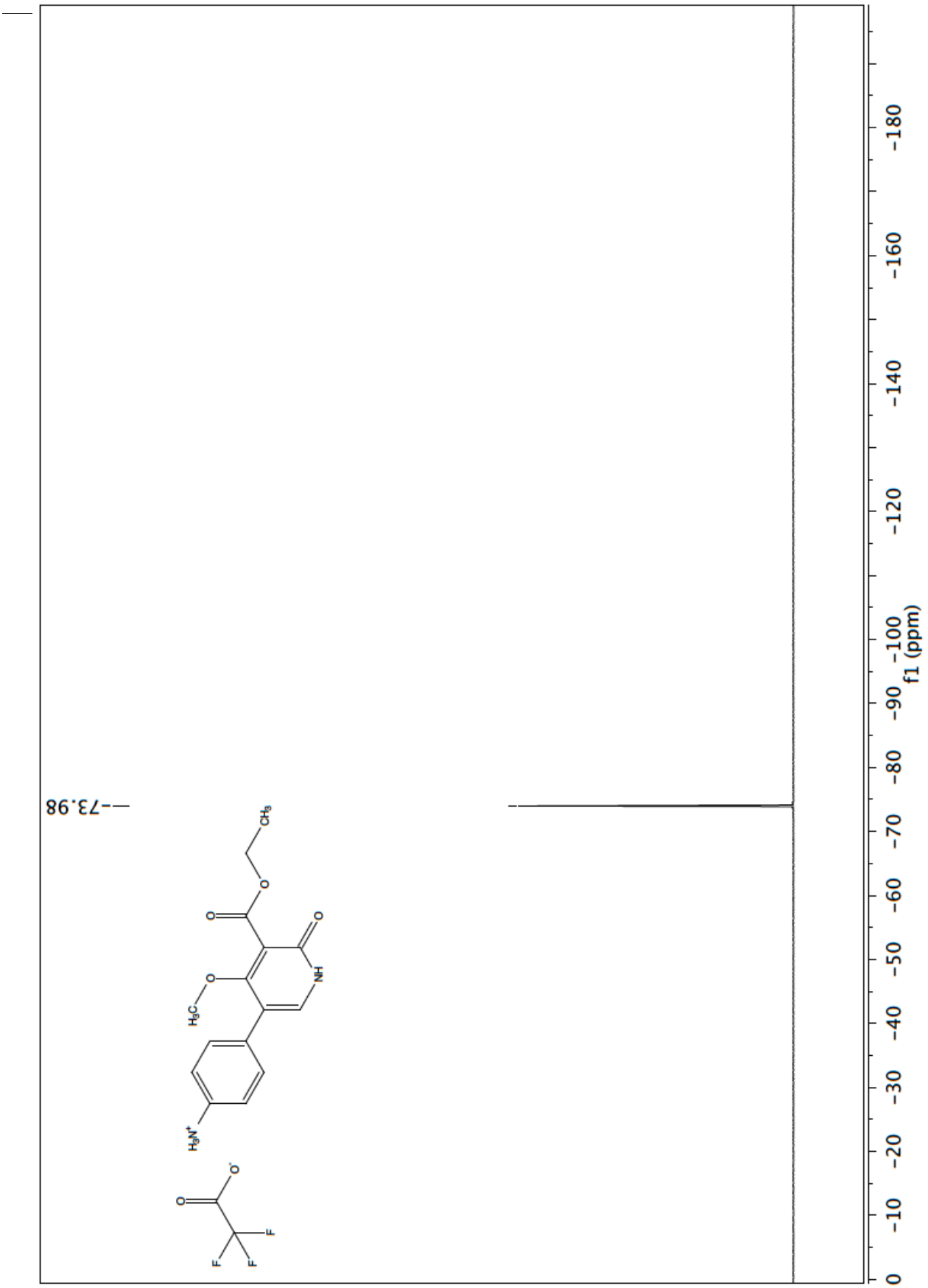
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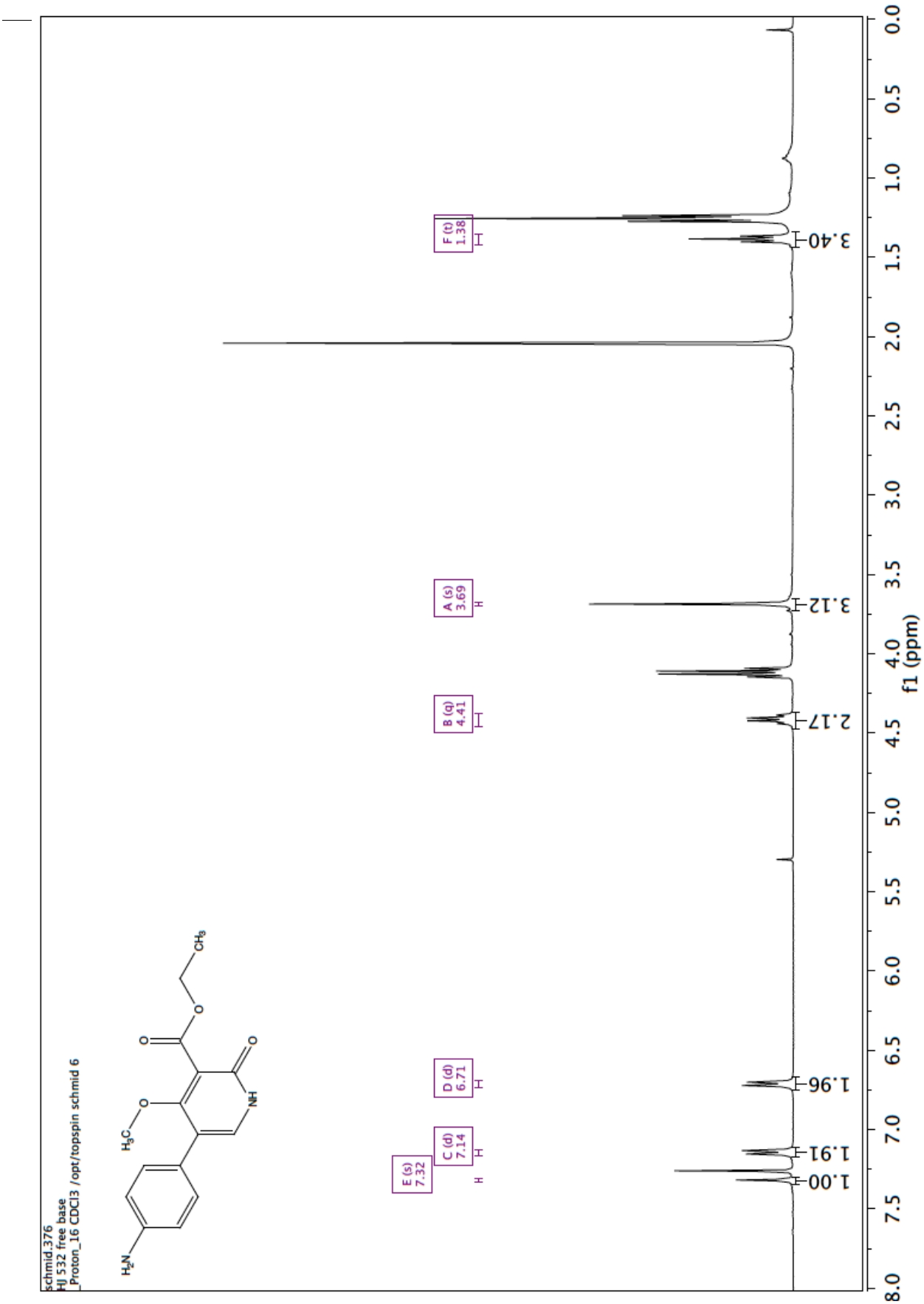
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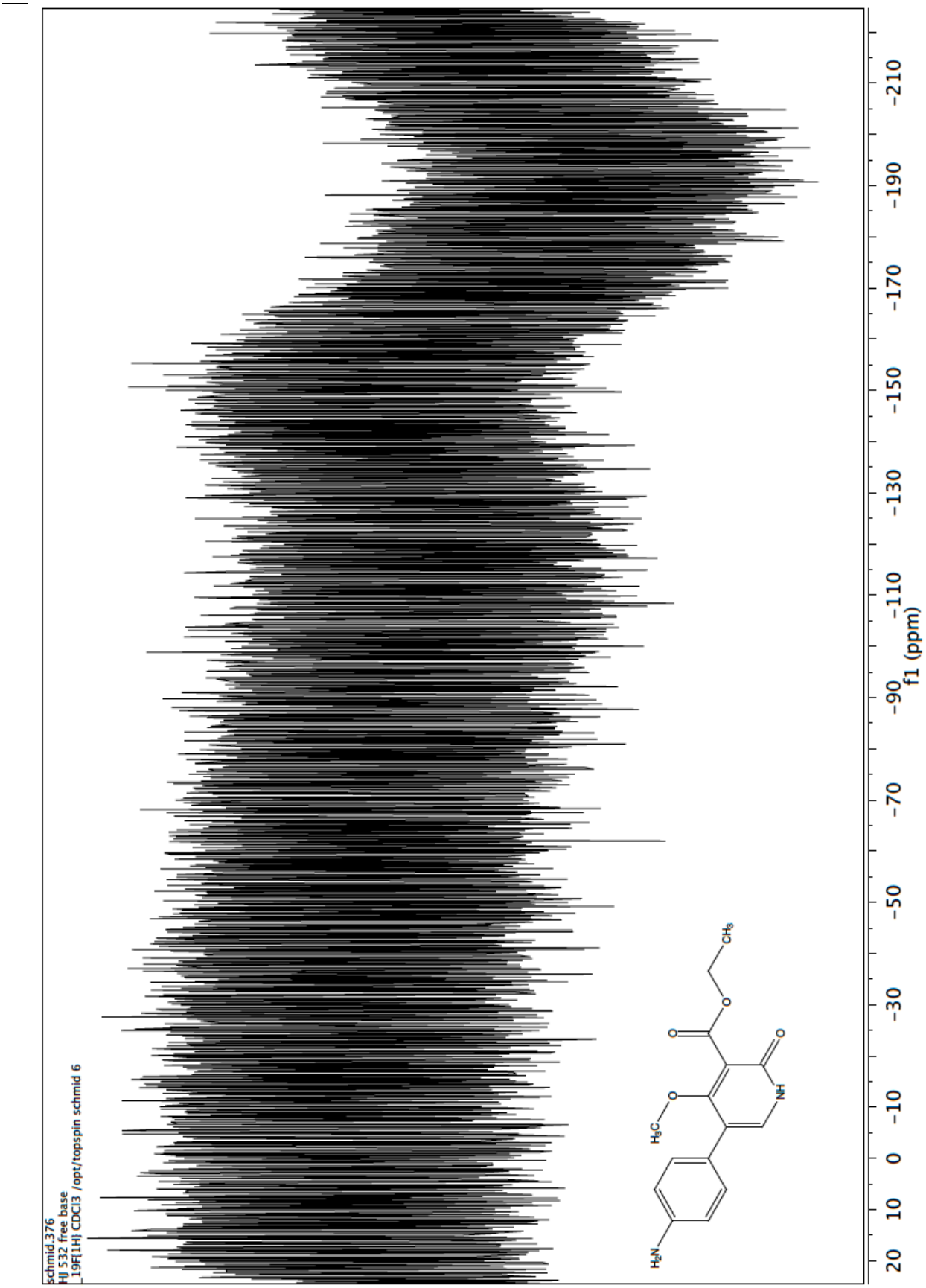
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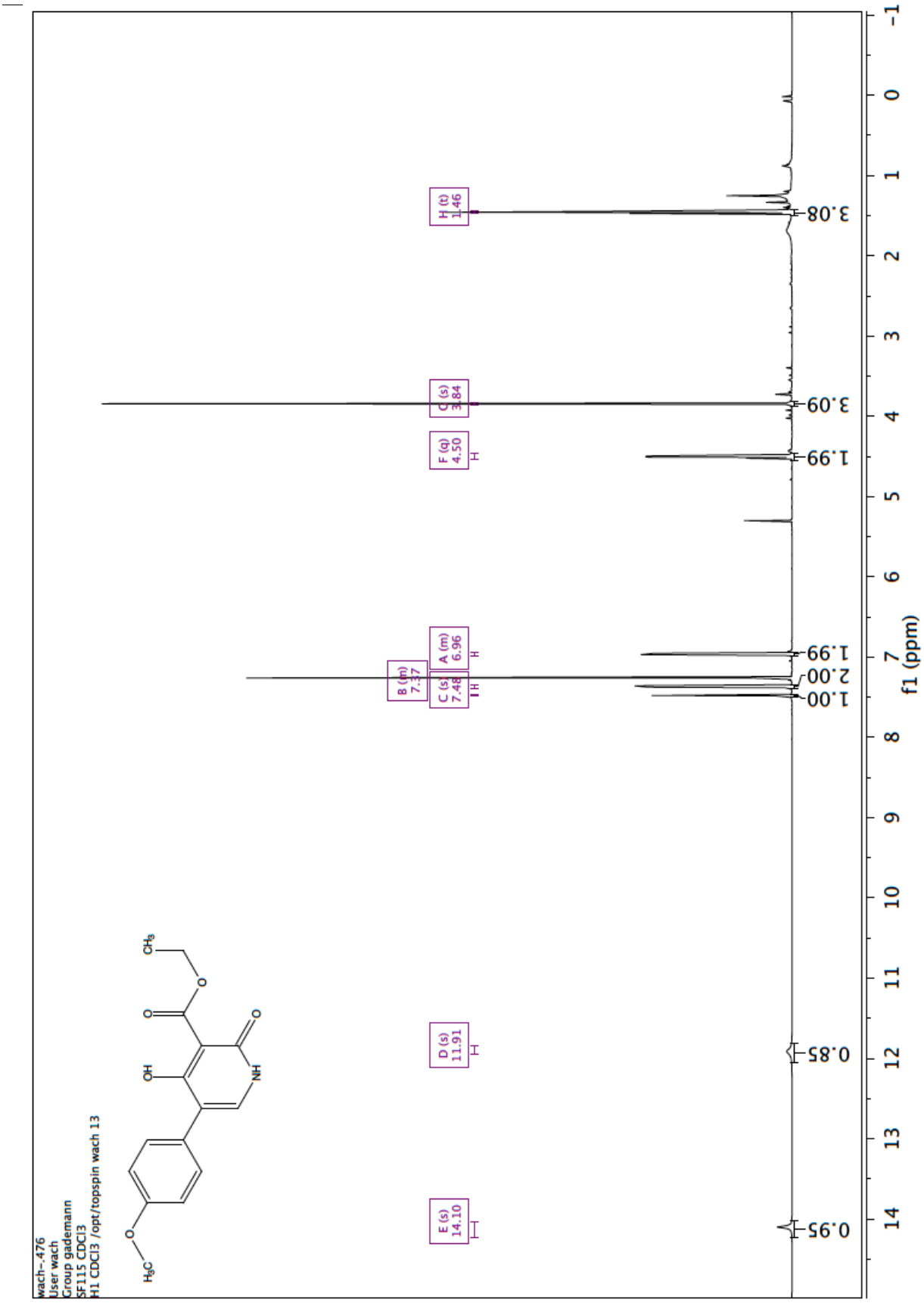
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C (s) 7.48
D (s) 11.91
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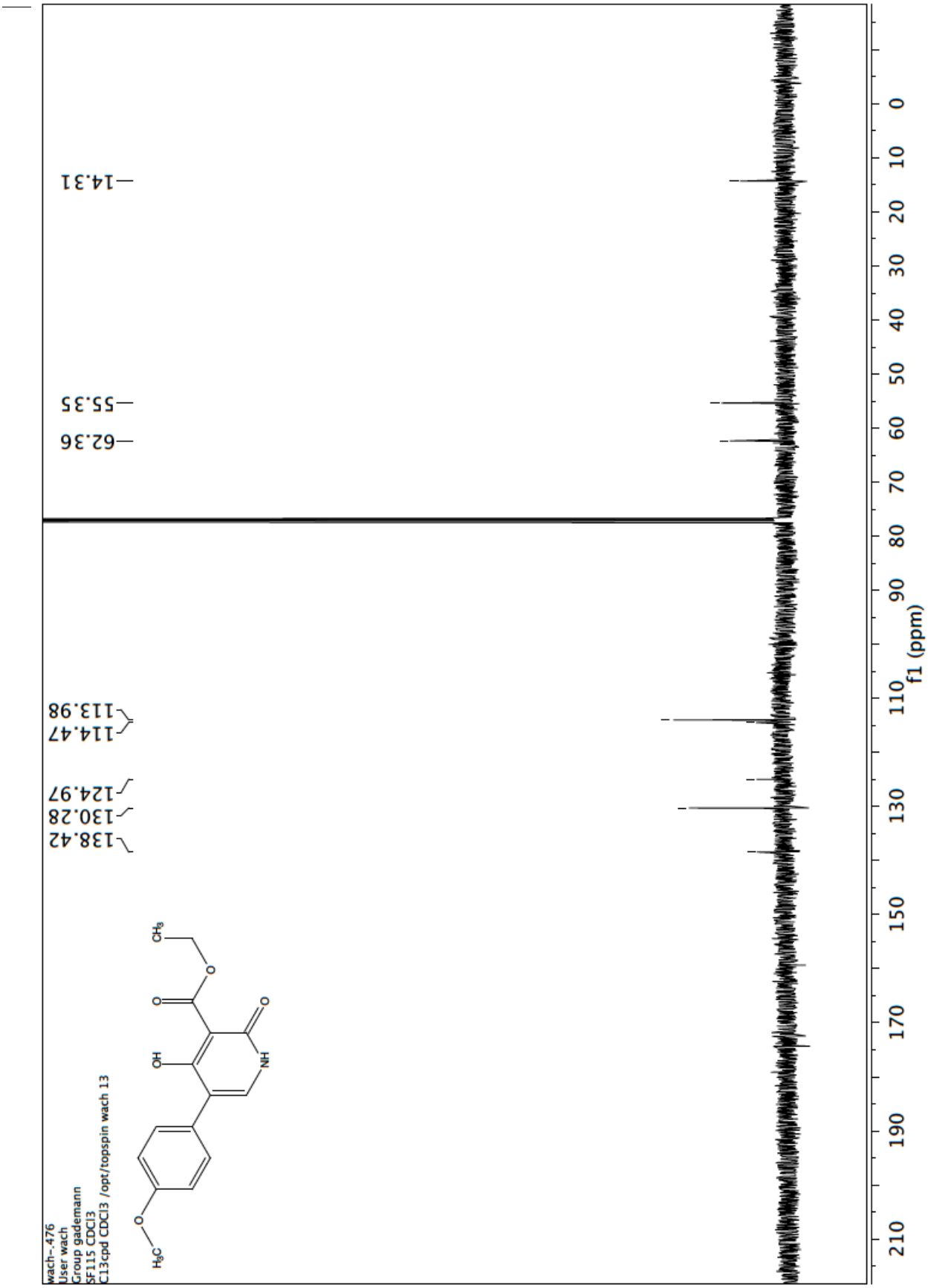
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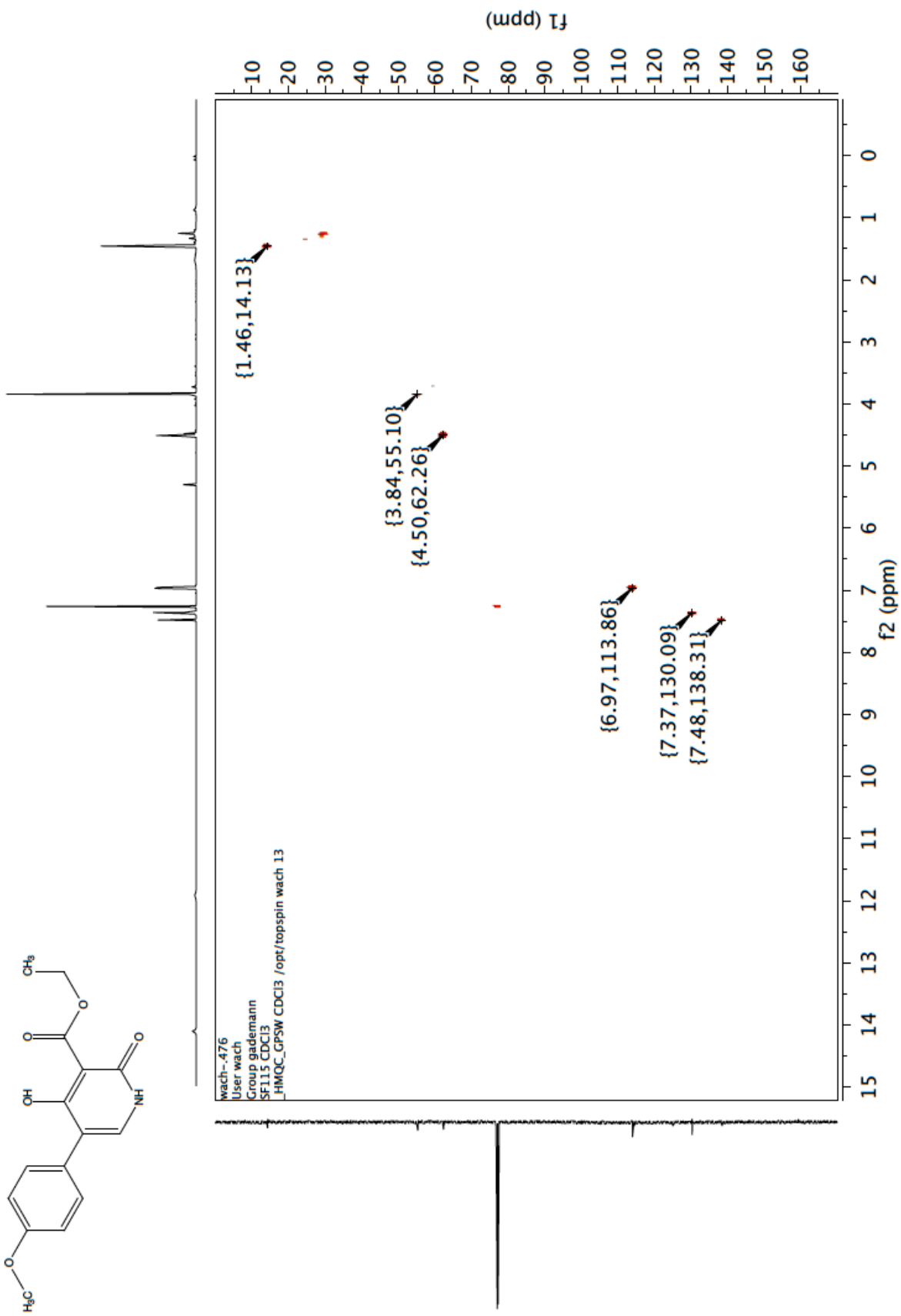
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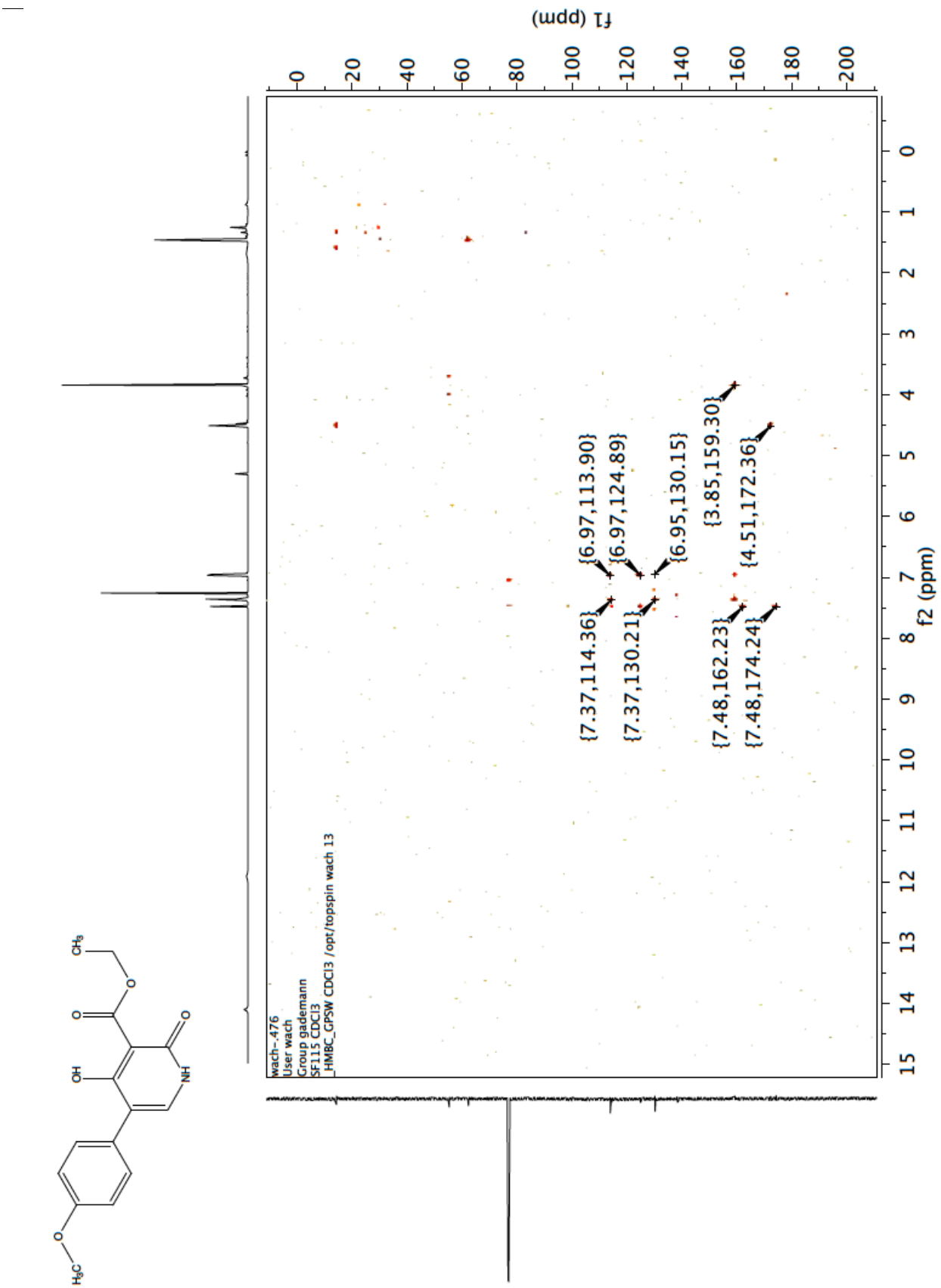
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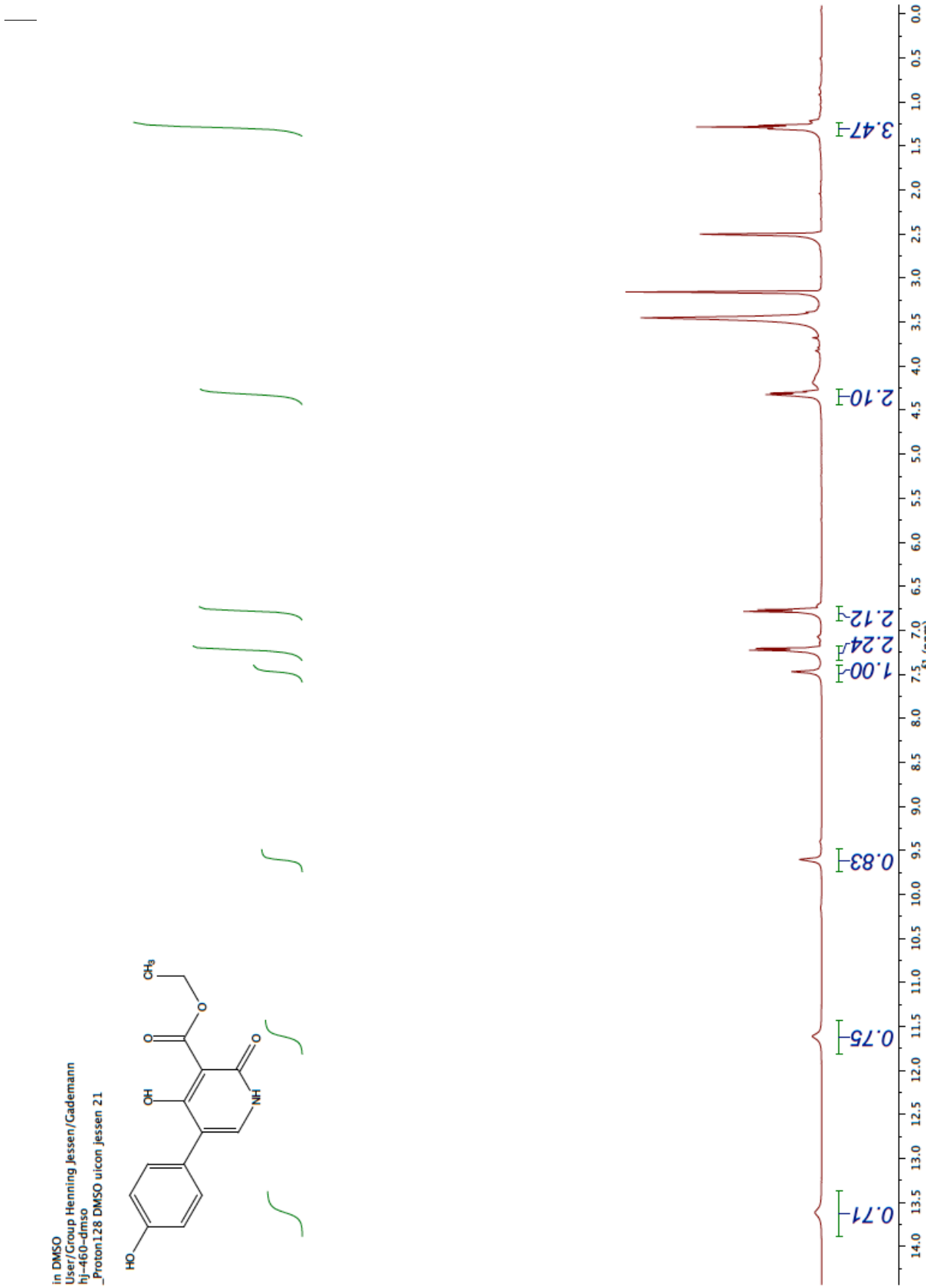
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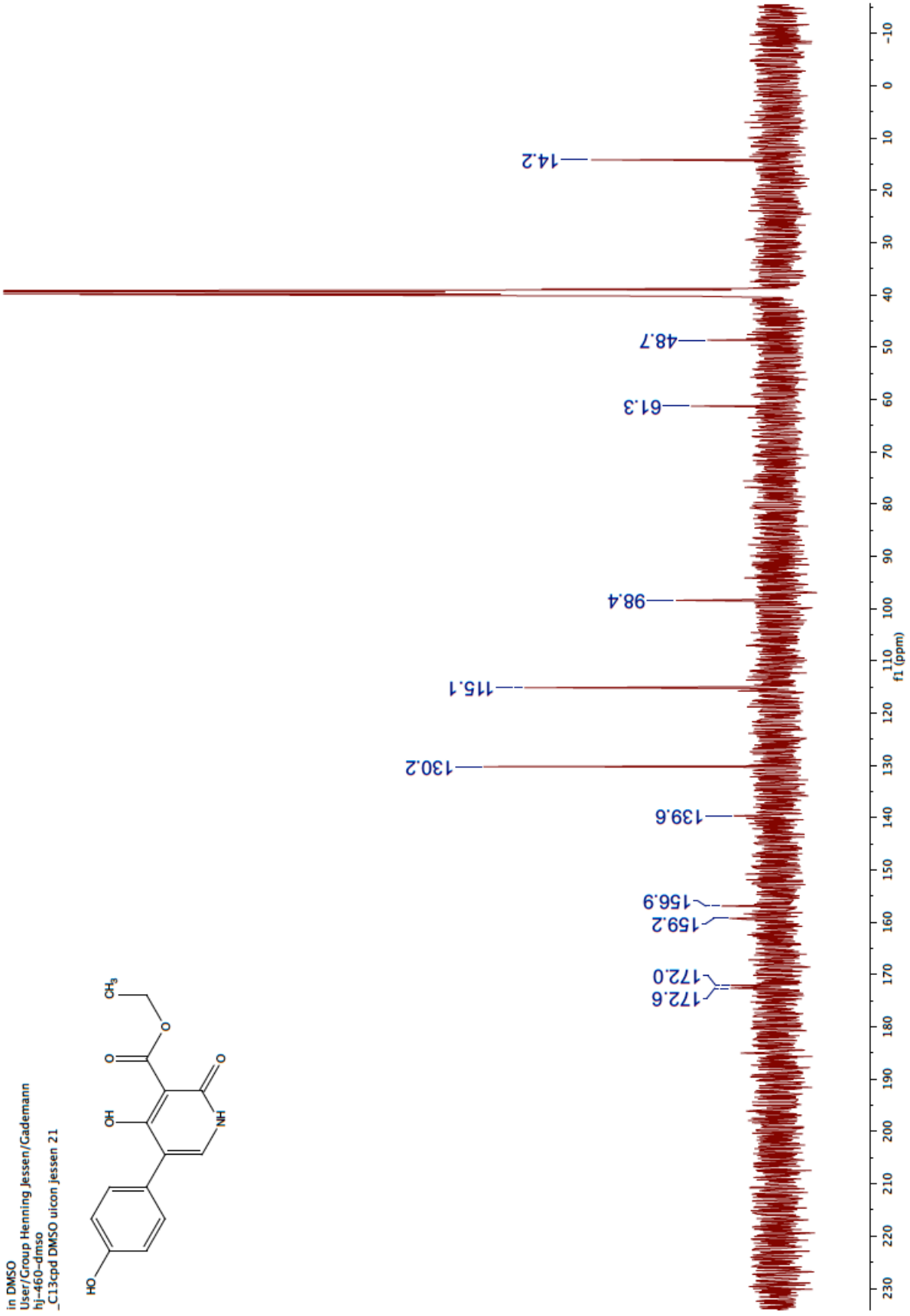
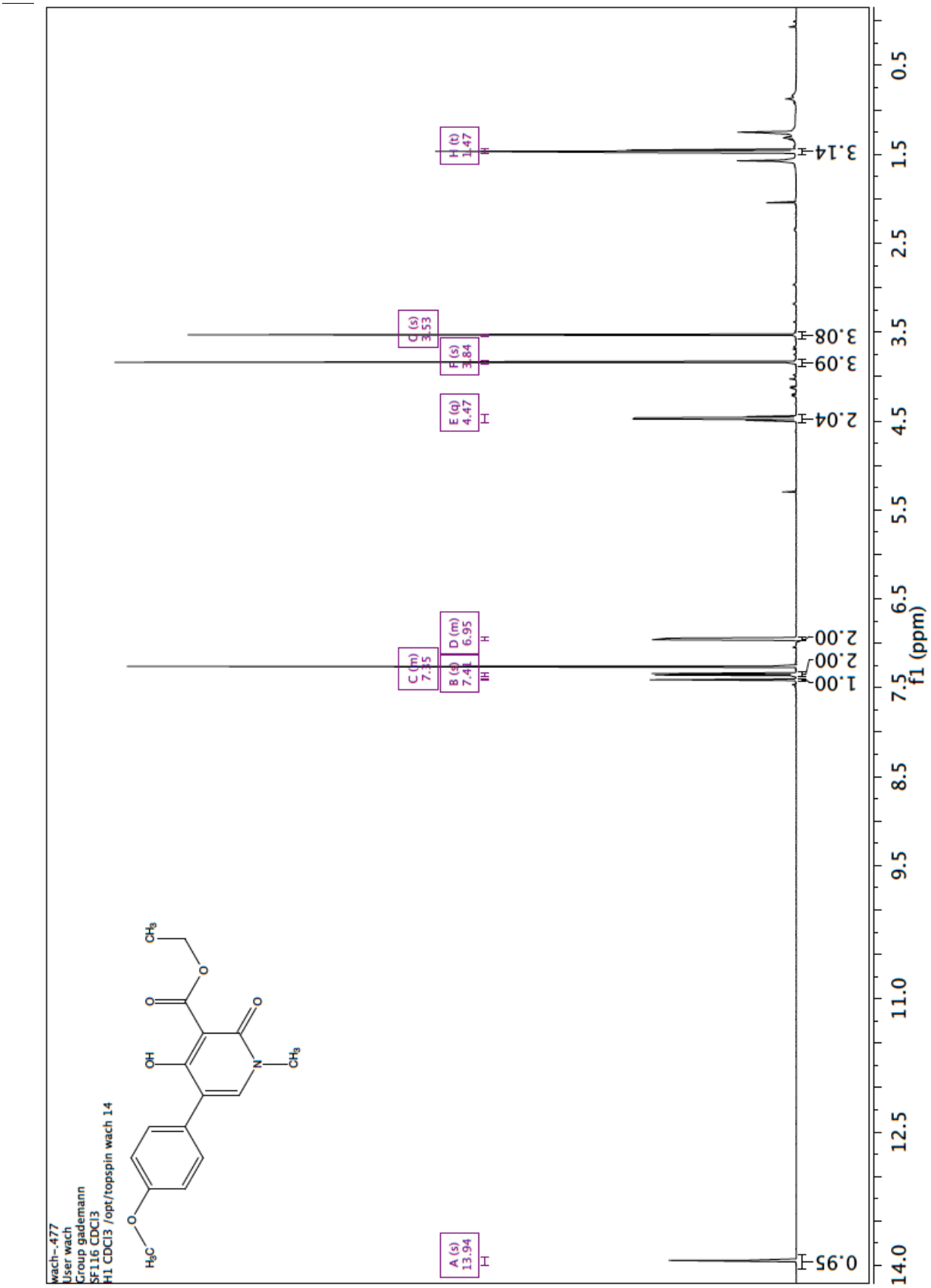
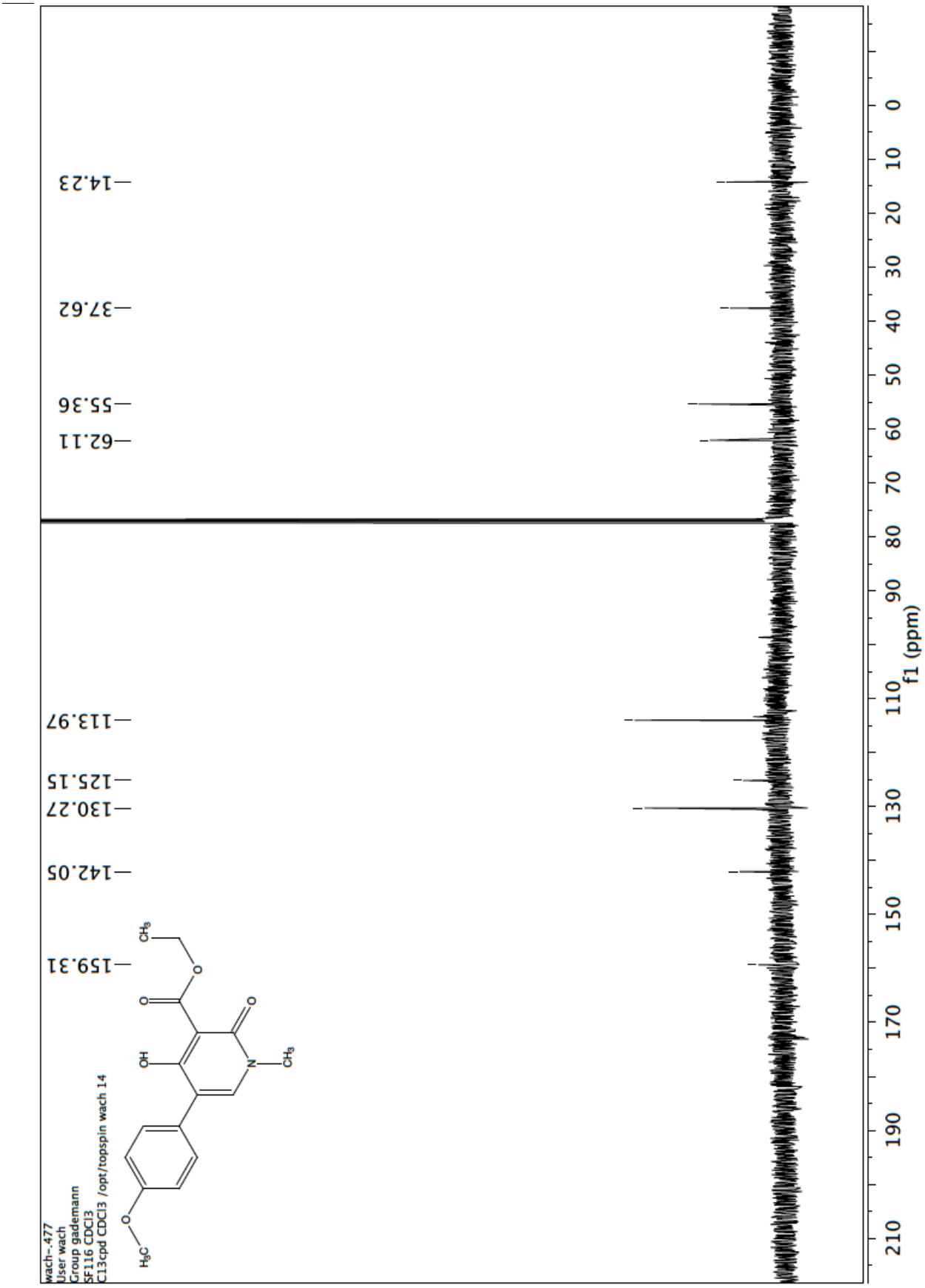
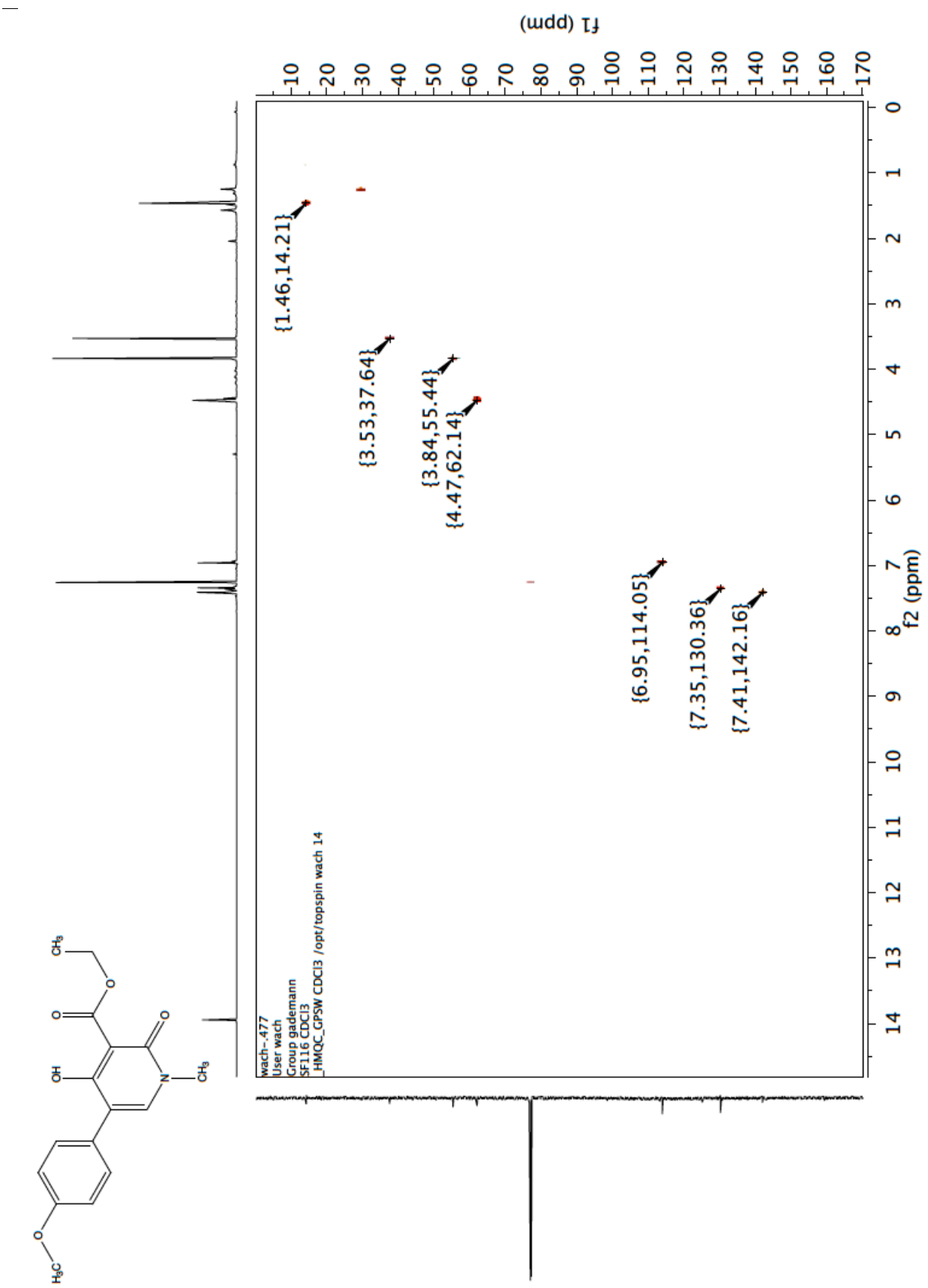
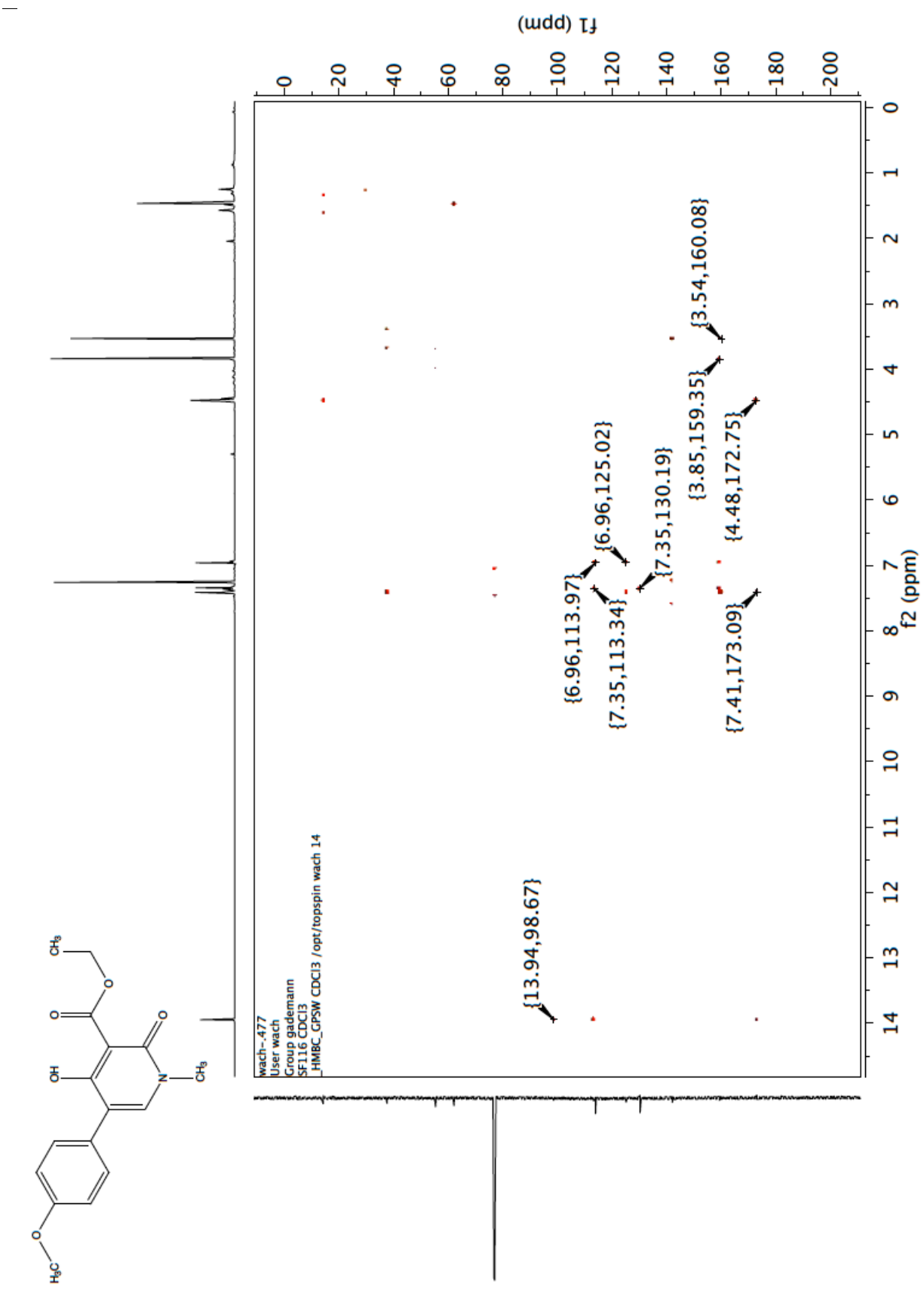
hj-460-dmso
_Proton128 DMSO uicon jessen 21
3.47
2.10
2.12
2.24
1.00
0.83
0.75
0.71

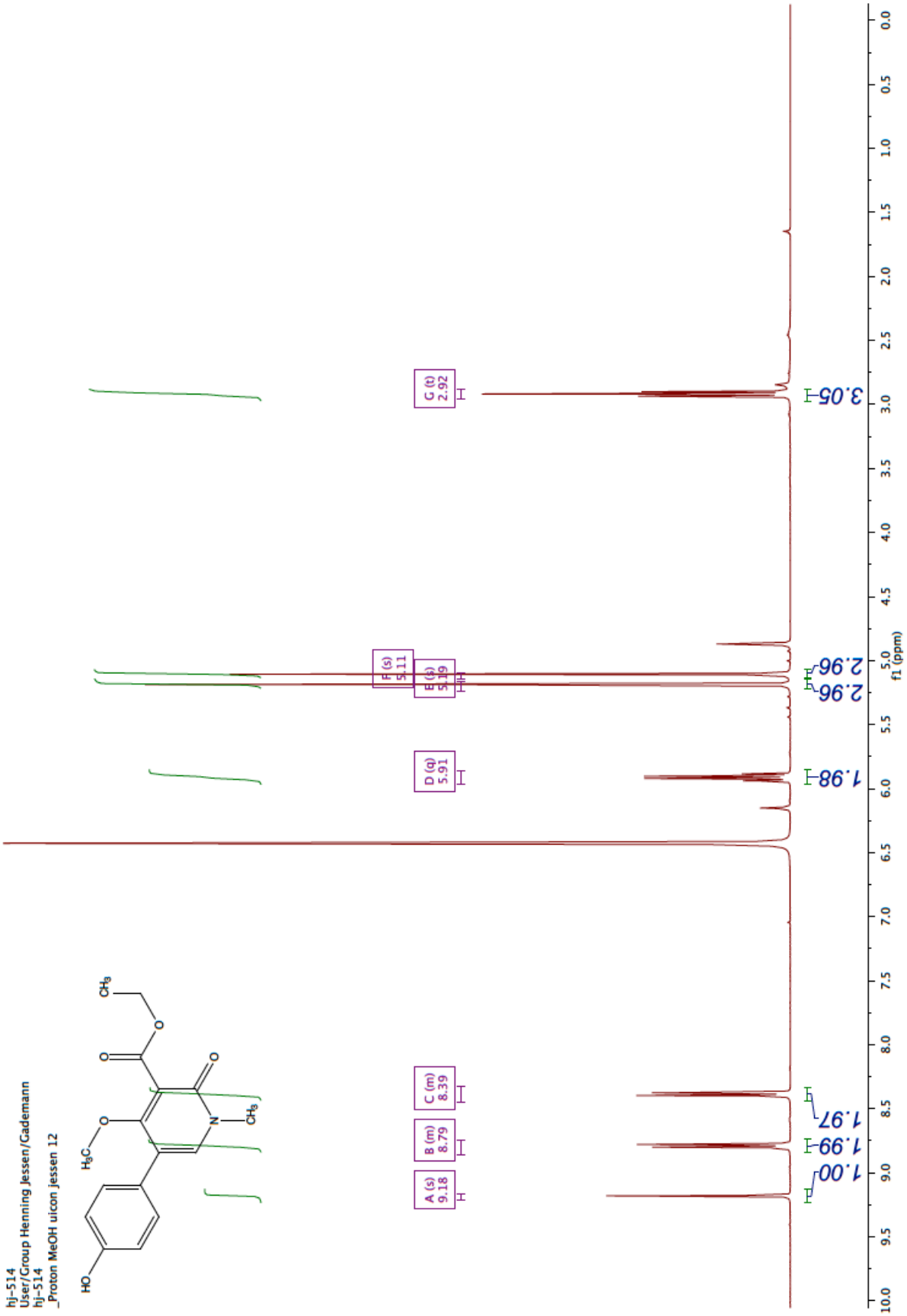

14.2
48.7
61.3
98.4
115.1
130.2
139.6
156.9
159.2
172.0
172.6
f1 (ppm)
in DMSO
User/Group Henning Jessen/Gademann
hj-460-dmso
_C13cpd DMSO uicon jessen 21

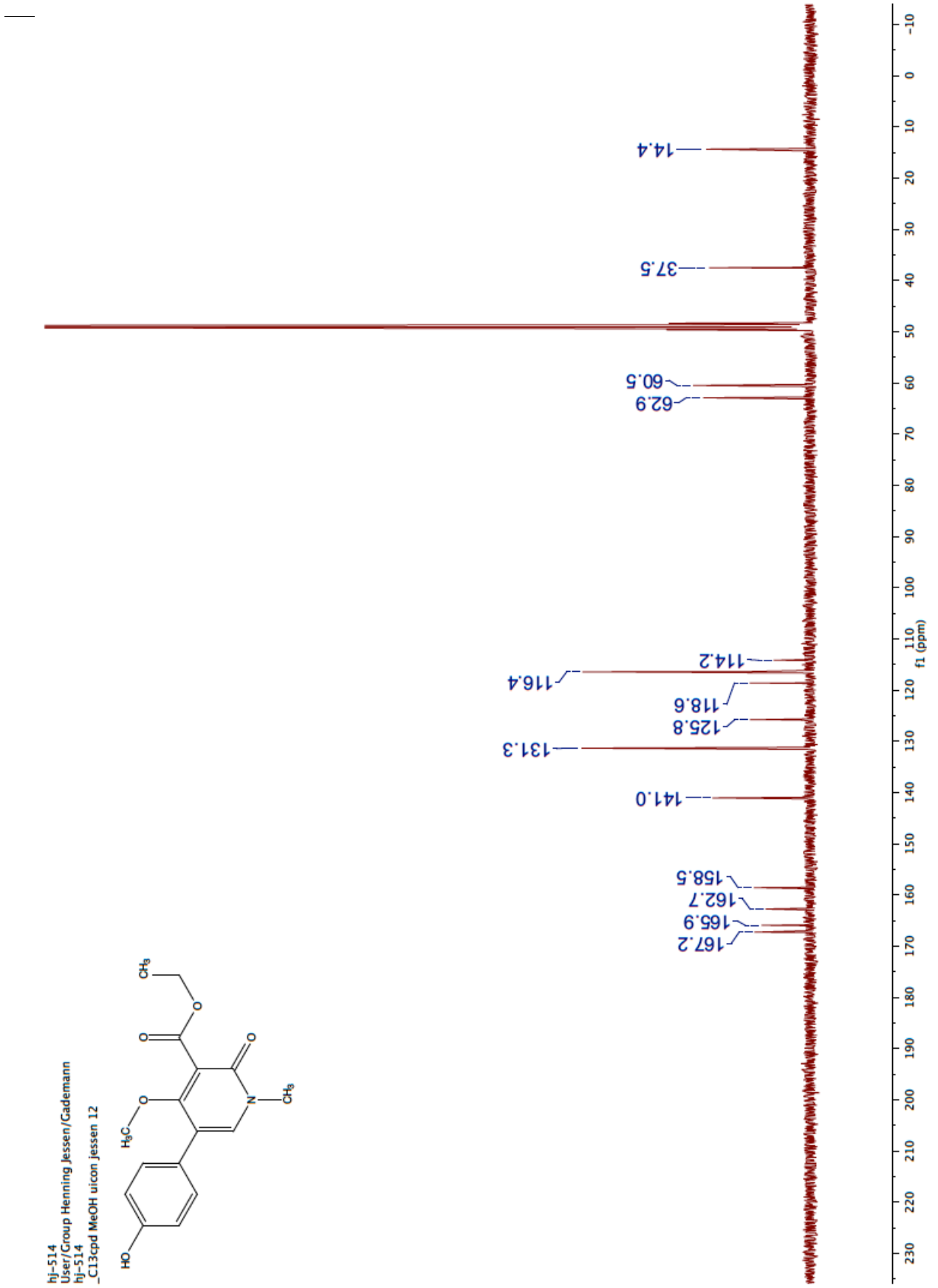


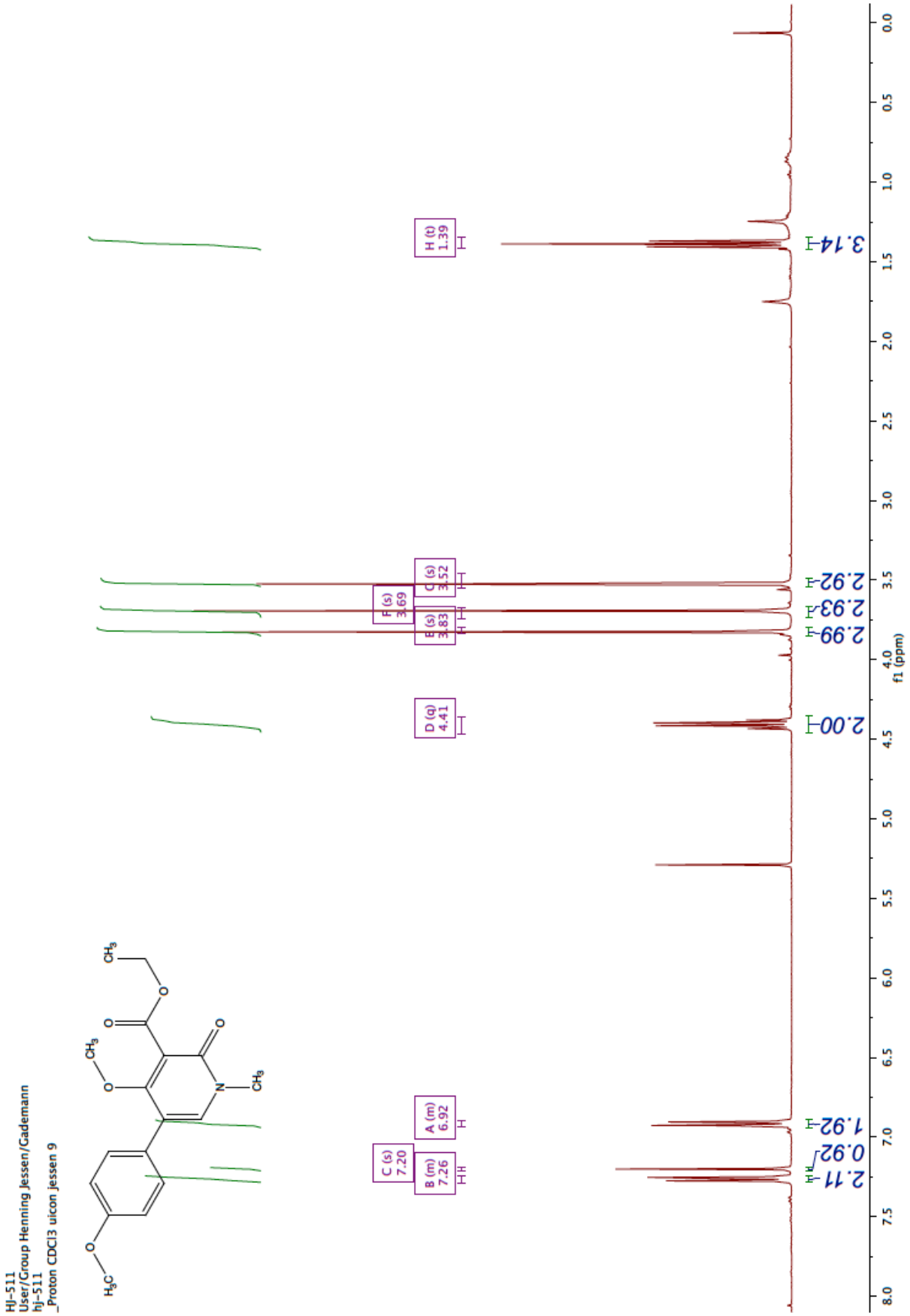

14.23
37.62
55.36
62.11
113.97
125.15
130.27
142.05
159.31
f1 (ppm)
wach-477
User wach
Group gademann
SF116 CDCl3
C13cpd CDCl3 /opt/topspin wach 14

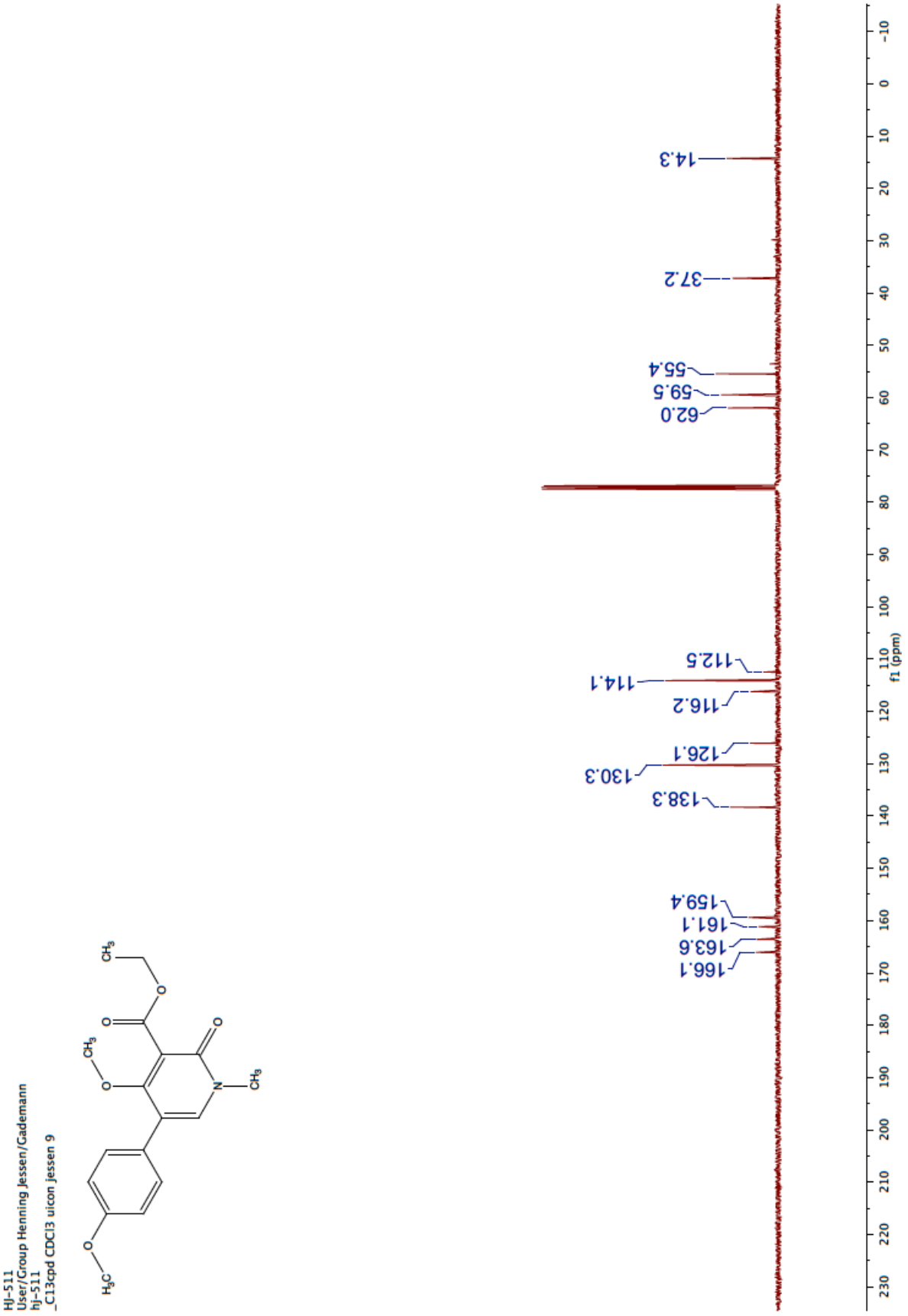

f1 (ppm)
f2 (ppm)
{1.46,14.21}
{3.53,37.64}
{3.84,55.44}
{4.47,62.14}
{6.95,114.05}
{7.35,130.36}
{7.41,142.16}
wach-477
User wach
Group gademann
SF116 CDCl3
_HMQC_GPSW CDCl3 /opt/topspin wach 14
OH
N
O
CH3
H3C

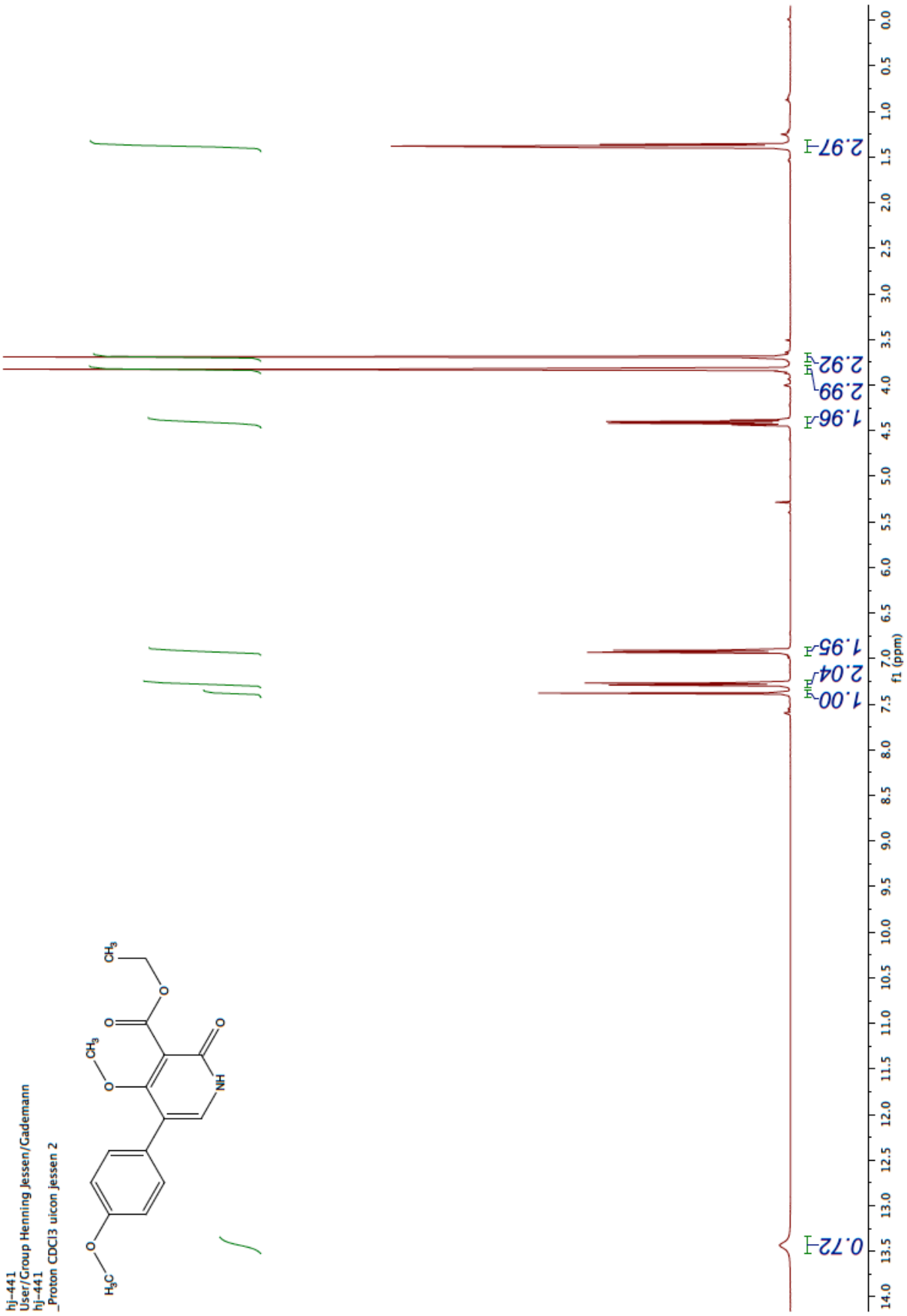

f1 (ppm)
f2 (ppm)
{13.94,98.67}
{6.96,113.97}
{7.35,113.34}
{6.96,125.02}
{7.35,130.19}
{3.85,159.35}
{3.54,160.08}
{4.48,172.75}
{7.41,173.09}
wach-.477
User wach
Group gademann
SF116 CDCl3
_HMBC_GPSW CDCl3 /opt/topspin wach 14

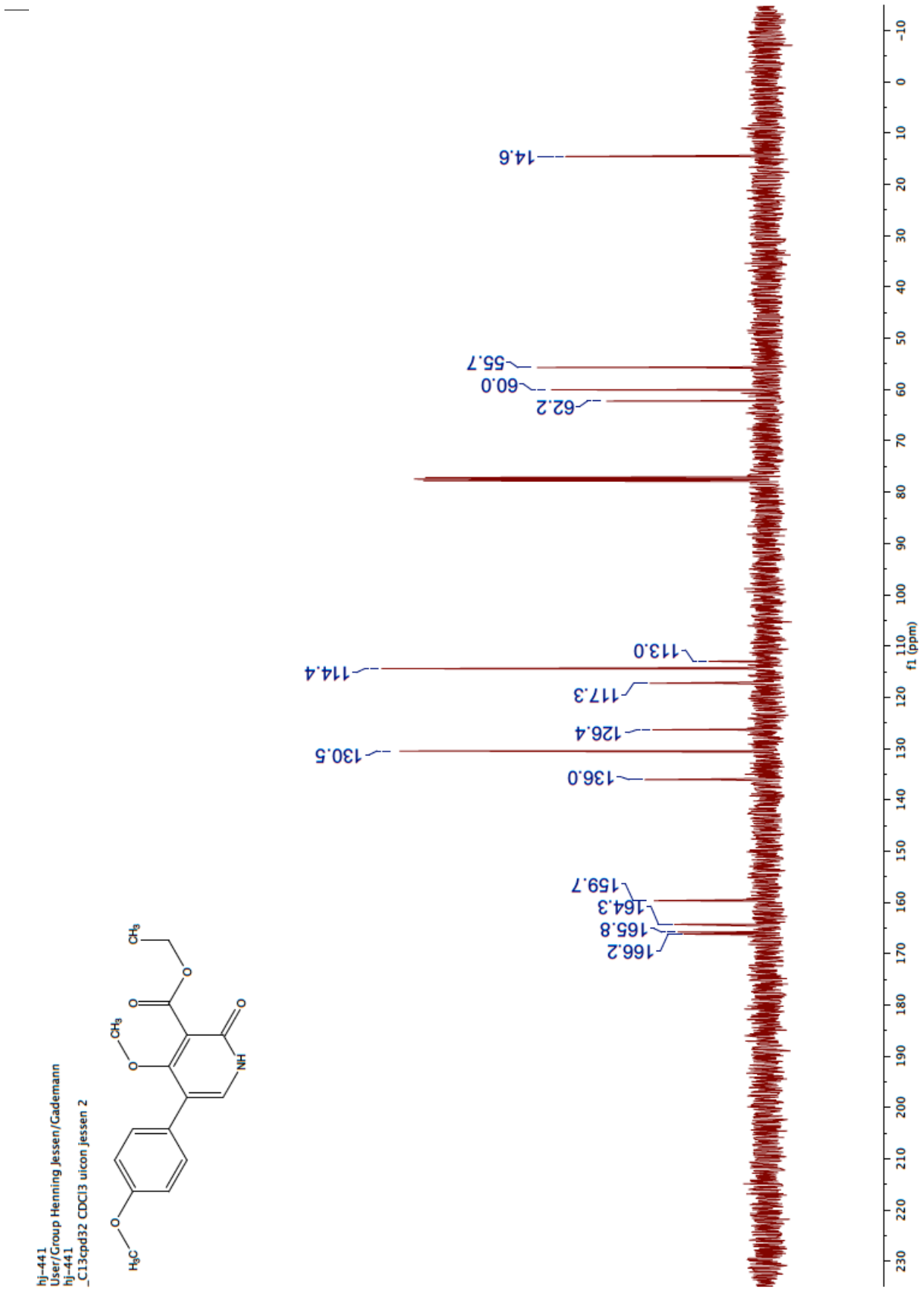

hj-514
User/Group Henning Jessen/Gademann
hj-514
_Proton MeOH uicon jessen 12
A (s) 9.18
B (m) 8.79
C (m) 8.39
D (q) 5.91
E (s) 5.19
F (s) 5.11
G (t) 2.92
1.00
1.99
1.97
1.98
2.96
2.96
3.05
f1 (ppm)

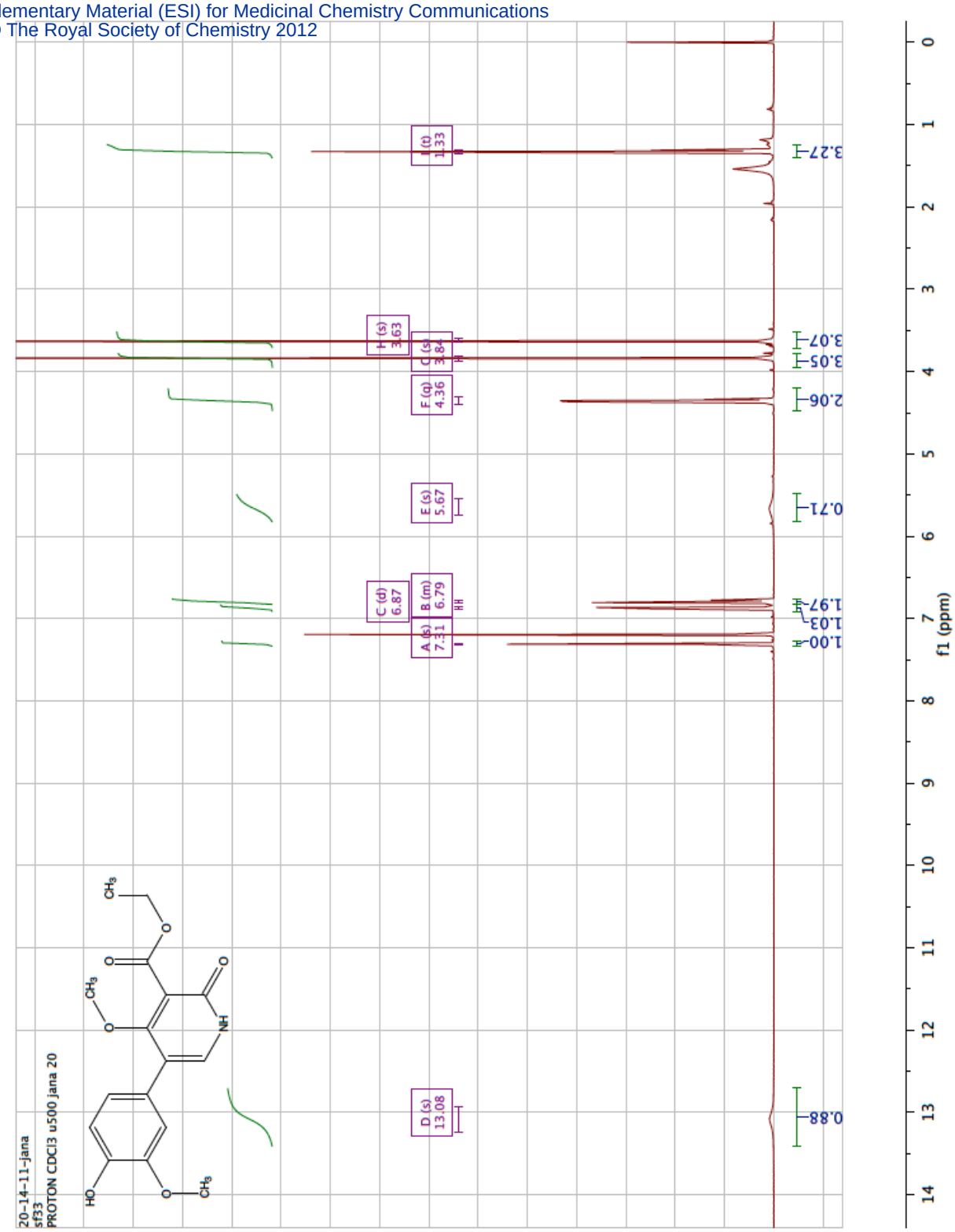

14.4
37.5
60.5
62.9
114.2
116.4
118.6
125.8
131.3
141.0
158.5
162.7
165.9
167.2
f1 (ppm)
hj-514
User/Group Henning Jessen/Gademann
hj-514
_C13cpd MeOH uicon jessen 12

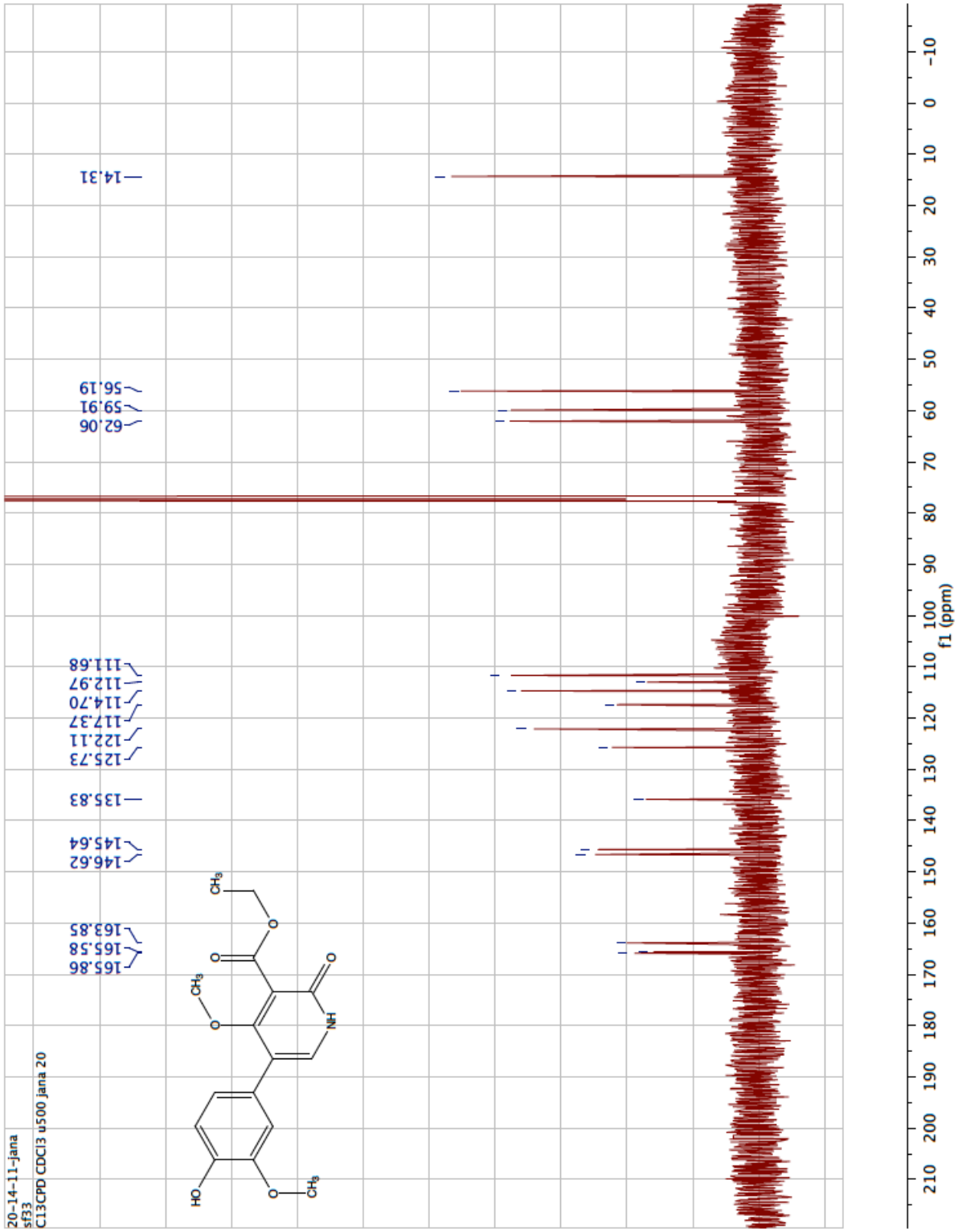

HJ-511
User/Group Henning Jessen/Gademann
hj-511
_Proton CDCl3 uicon jessen 9
H (t) 1.39
G (s) 3.52
F (s) 3.69
E (s) 3.83
D (q) 4.41
C (s) 7.20
B (m) 7.26
A (m) 6.92
3.14
2.92
2.93
2.99
2.00
1.92
0.92
2.11
f1 (ppm)

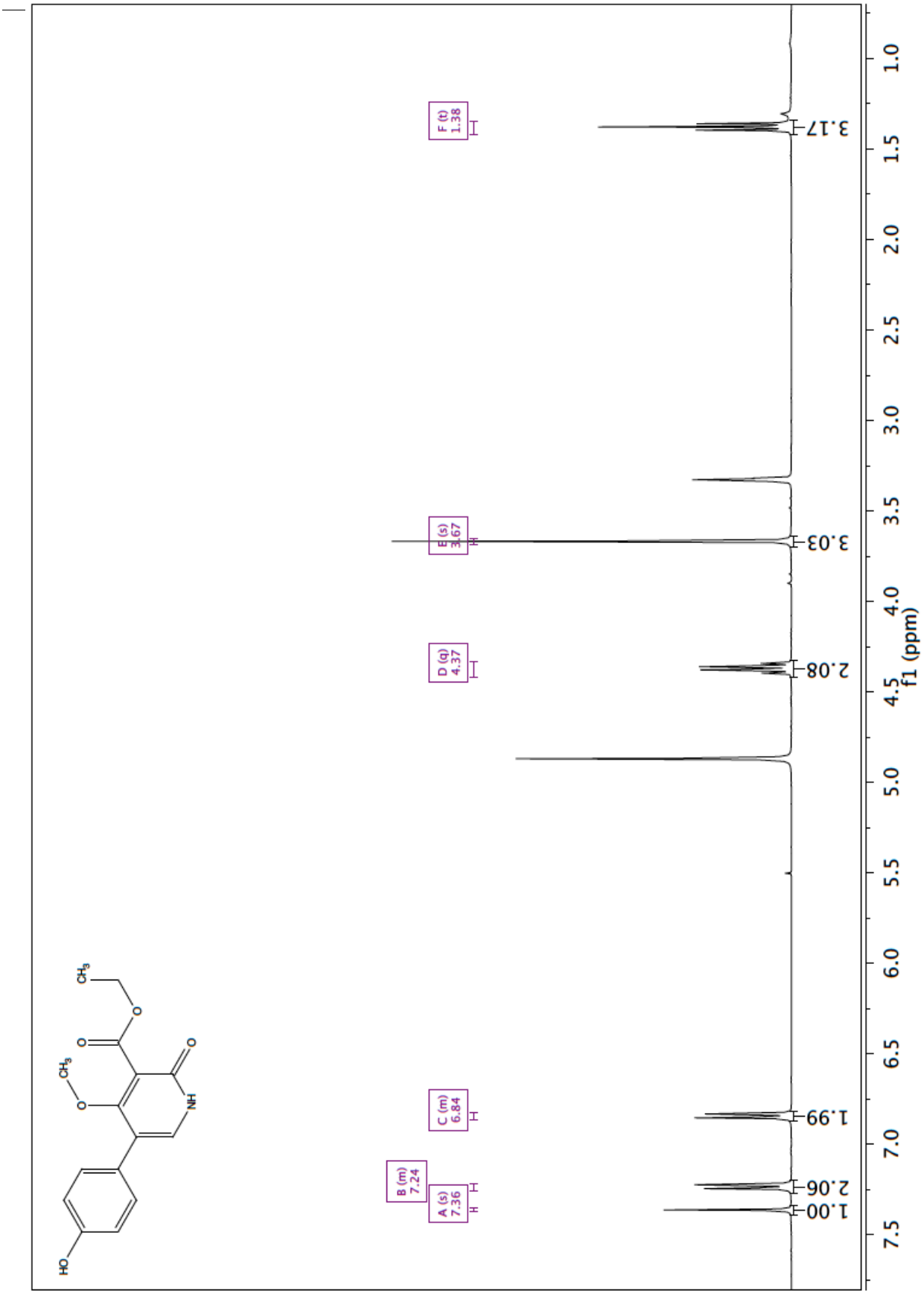

HJ-511
User/Group Henning Jessen/Gademann
hj-511
_C13cpd CDCl3 uicon jessen 9
14.3
37.2
55.4
59.5
62.0
112.5
114.1
116.2
126.1
130.3
138.3
159.4
161.1
163.6
166.1
f1 (ppm)

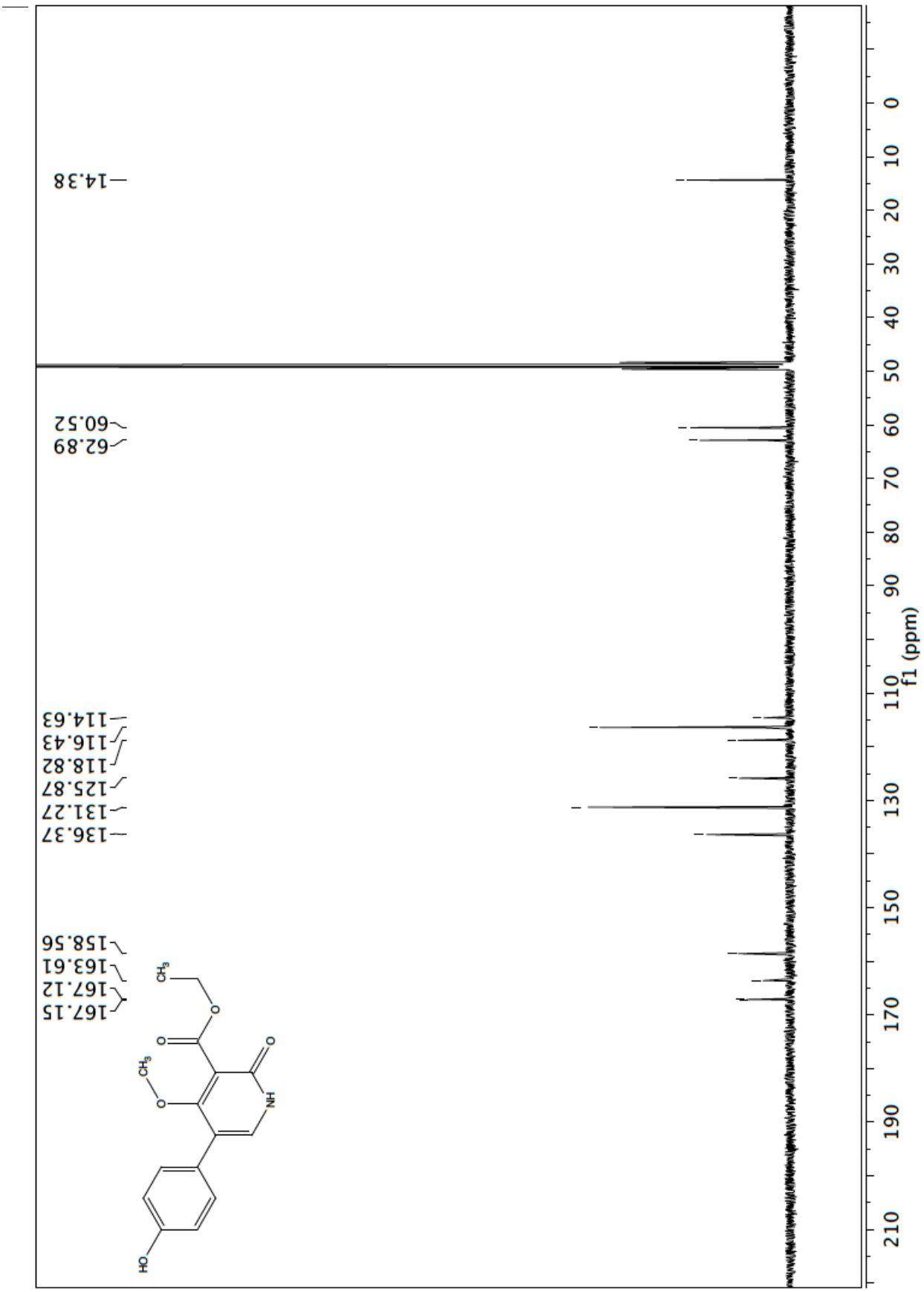

2.97
2.92
2.99
1.96
1.95
2.04
1.00
0.72
f1 (ppm)
hj-441
User/Group Henning Jessen/Gademann
hj-441
_Proton CDCl3 uicon jessen 2

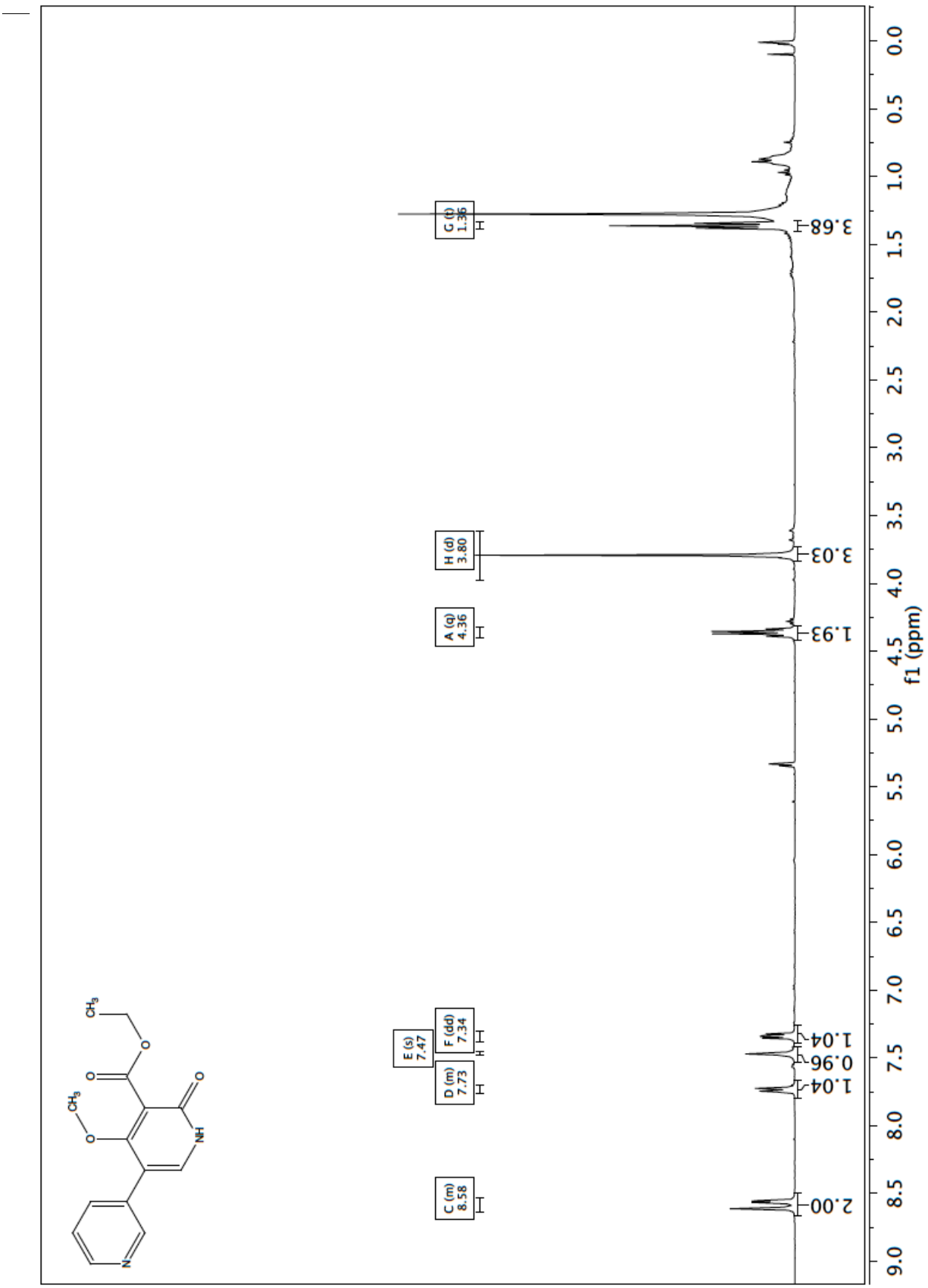

14.6
55.7
60.0
62.2
113.0
114.4
117.3
126.4
130.5
136.0
159.7
164.3
165.8
166.2
f1 (ppm)
hj-441
User/Group Henning Jessen/Gademann
hj-441
_C13cpd32 CDCl3 uicon jessen 2

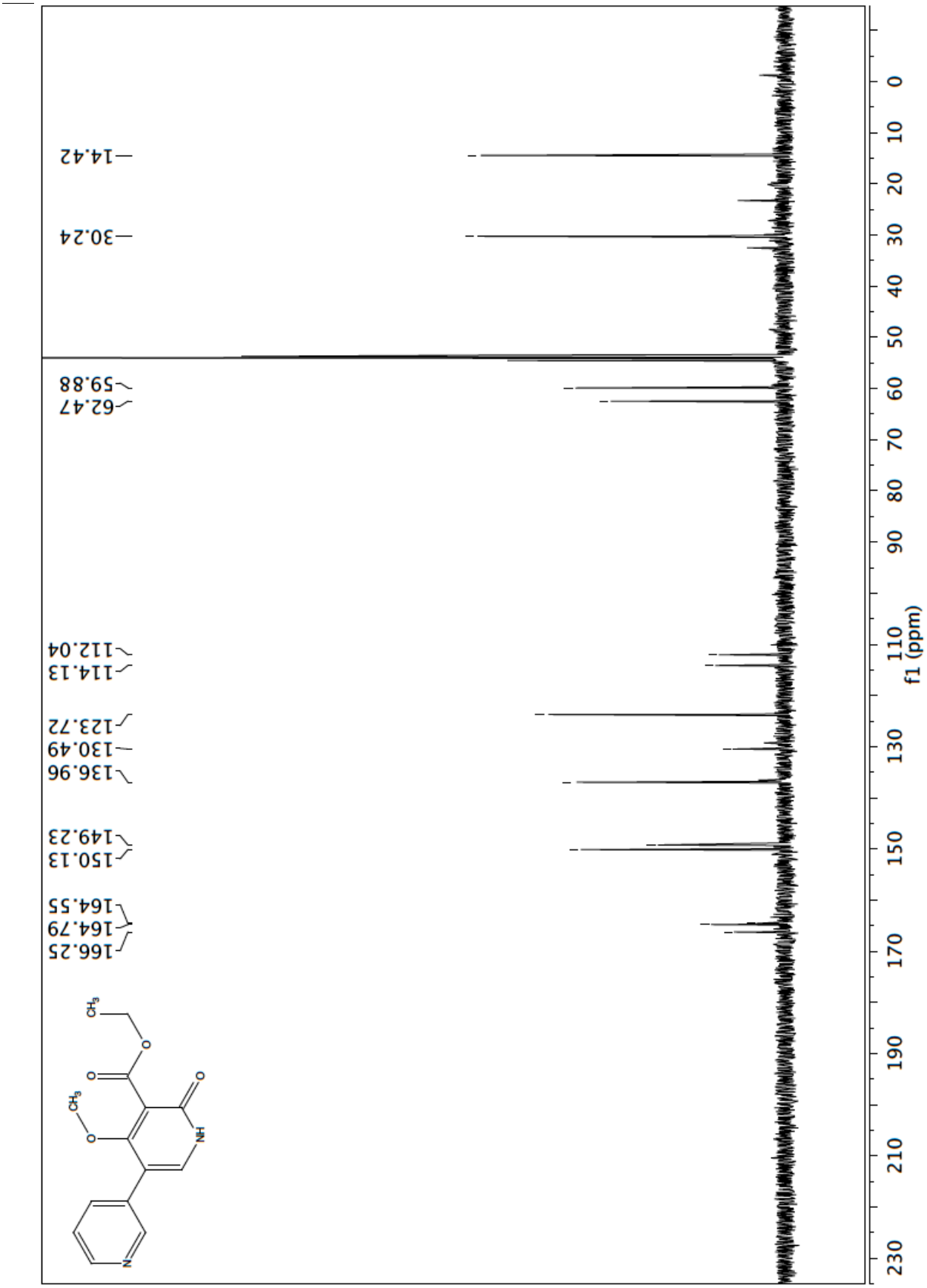


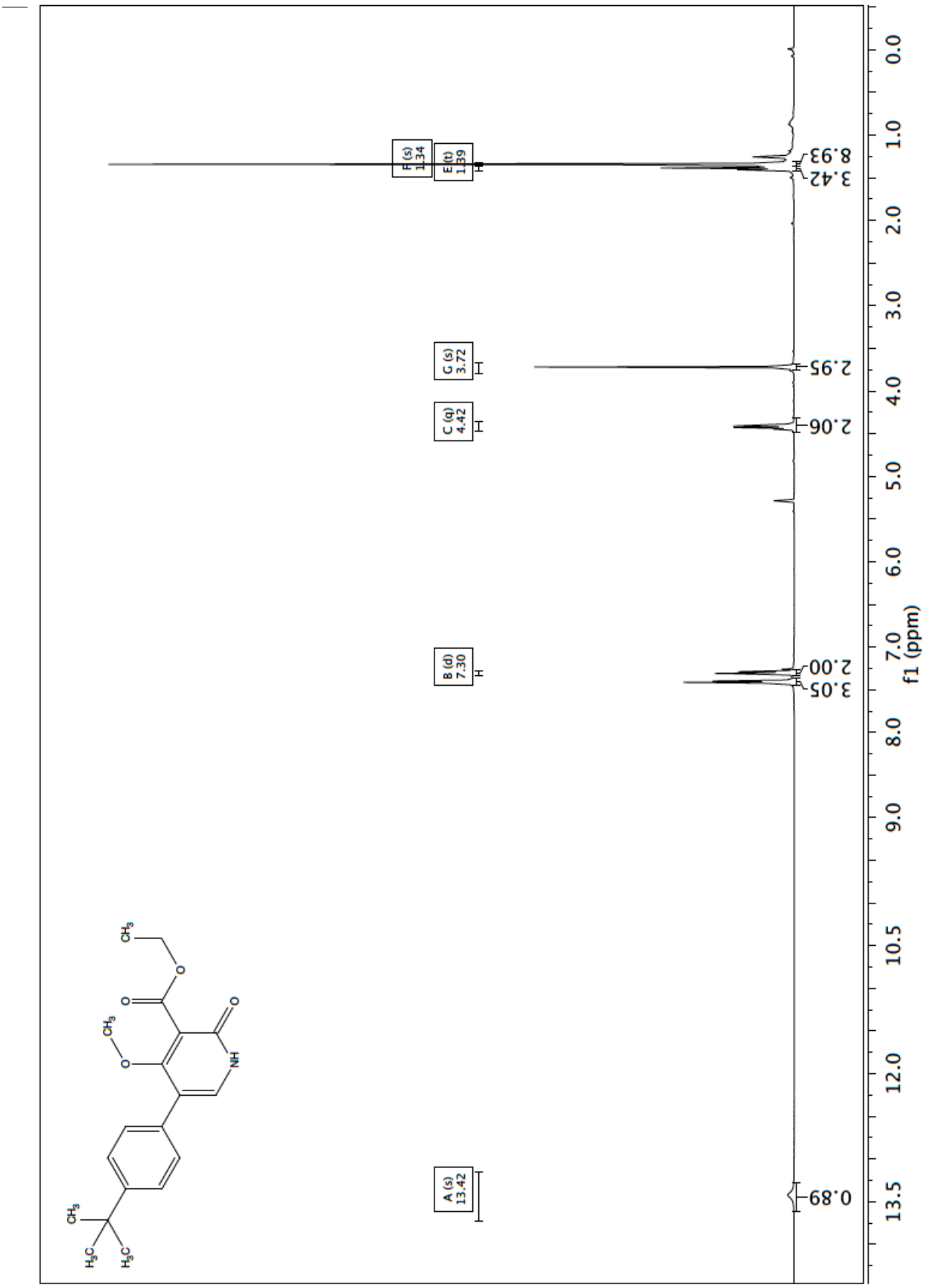

14.31
56.19
59.91
62.06
111.68
112.97
114.70
117.37
122.11
125.73
135.83
145.64
146.62
163.85
165.58
165.86
20-14-11-jana
sf33
C13CPD CDCl3 u500 jana 20
f1 (ppm)

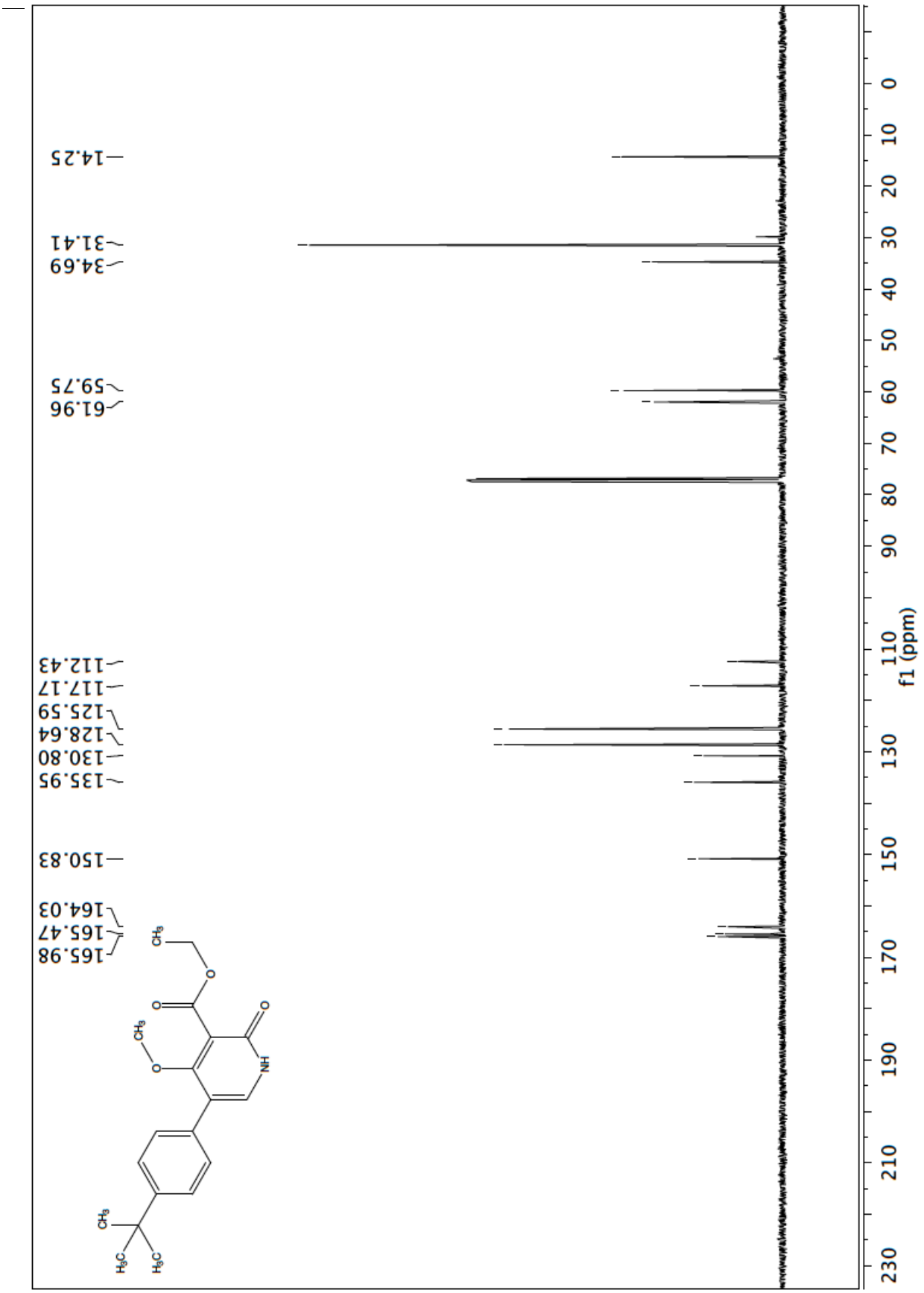

F (t) 1.38
E (s) 3.67
D (q) 4.37
C (m) 6.84
B (m) 7.24
A (s) 7.36
3.17
3.03
2.08
1.99
2.06
1.00
f1 (ppm)

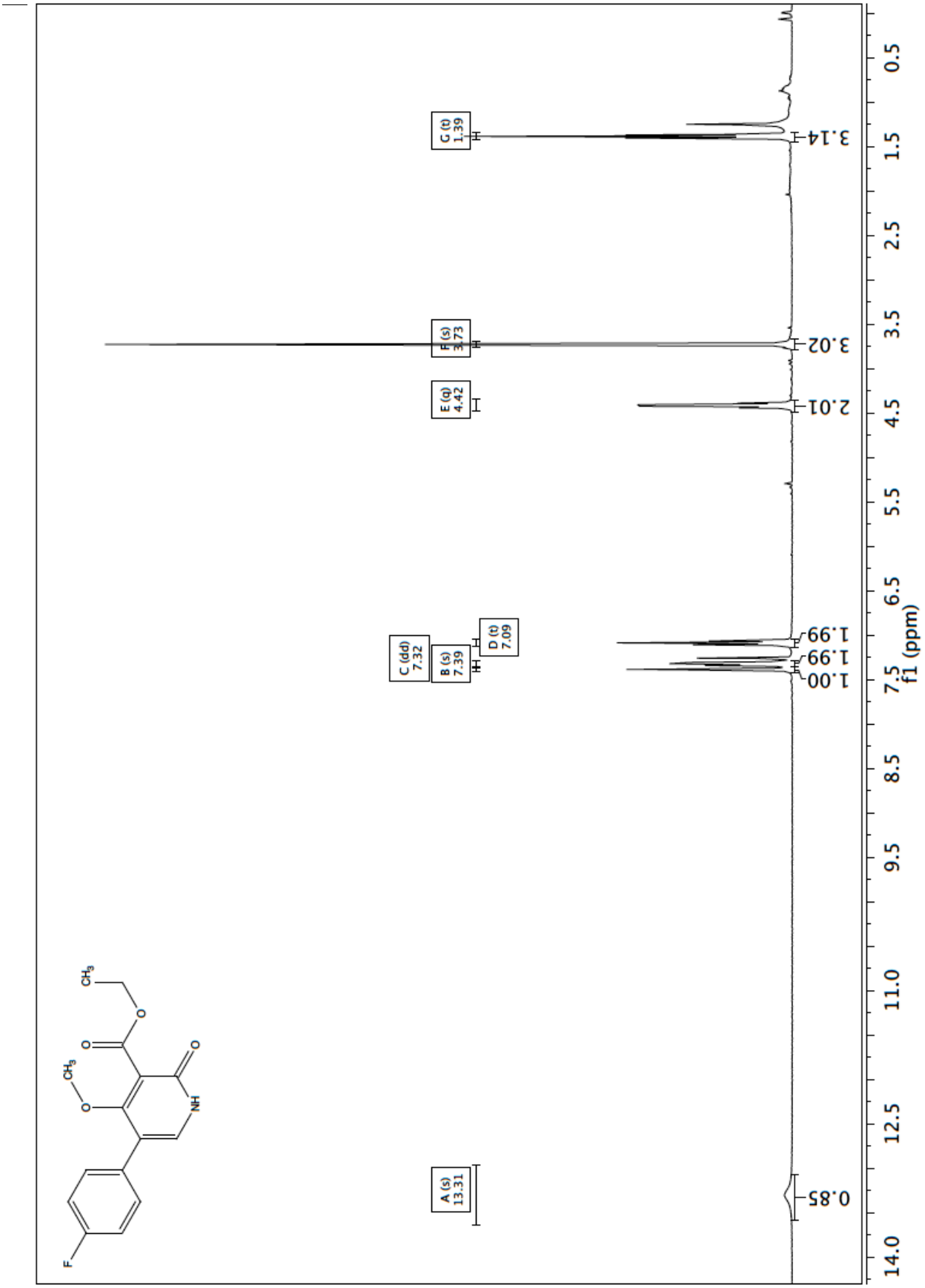

14.38
60.52
62.89
114.63
116.43
118.82
125.87
131.27
136.37
158.56
163.61
167.12
167.15
f1 (ppm)

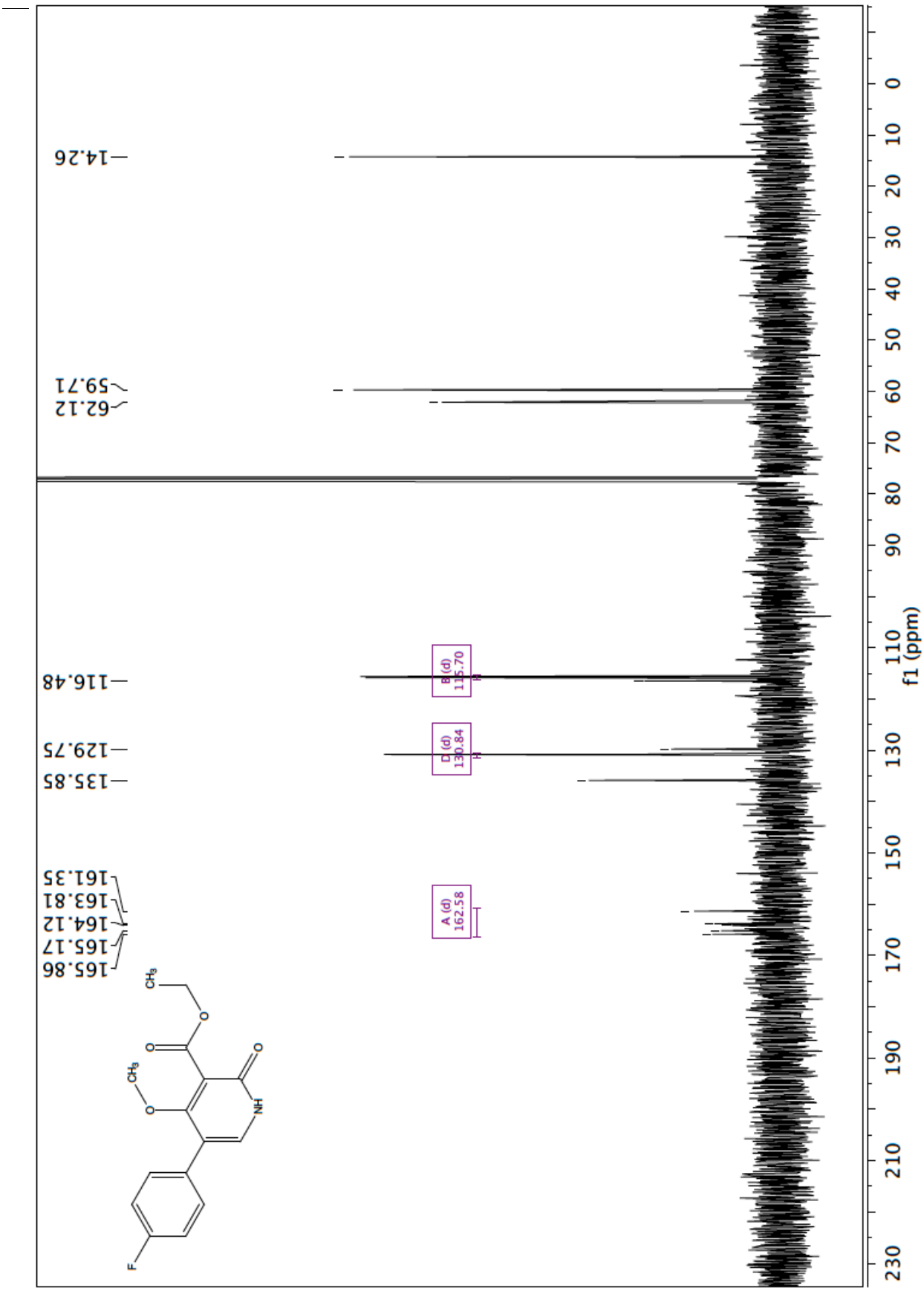

G (t) 1.36
H (d) 3.80
A (q) 4.36
E (s) 7.47
F (dd) 7.34
D (m) 7.73
C (m) 8.58
3.68
3.03
1.93
1.04
0.96
1.04
2.00
f1 (ppm)

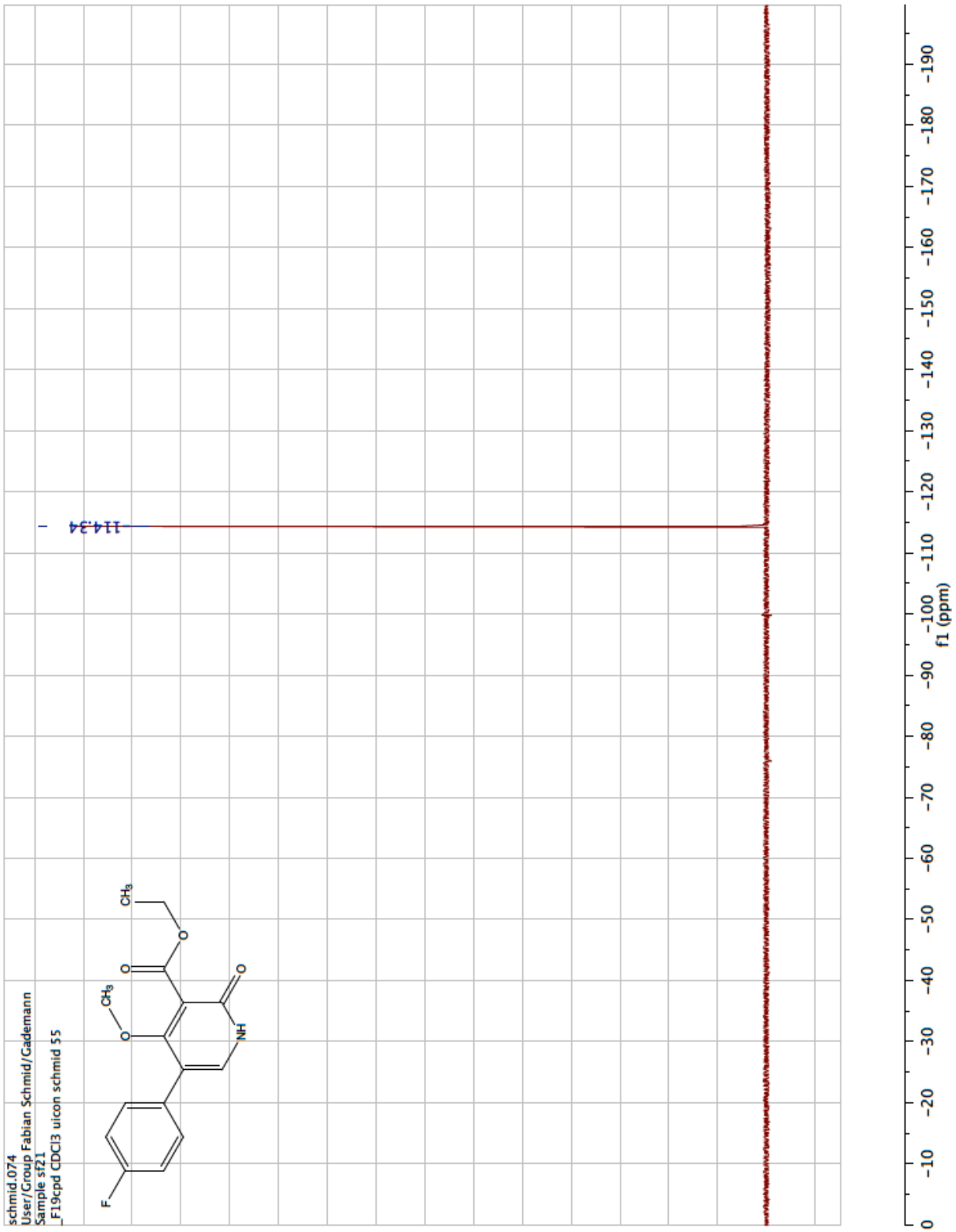

14.42
30.24
59.88
62.47
112.04
114.13
123.72
130.49
136.96
149.23
150.13
164.55
164.79
166.25
f1 (ppm)

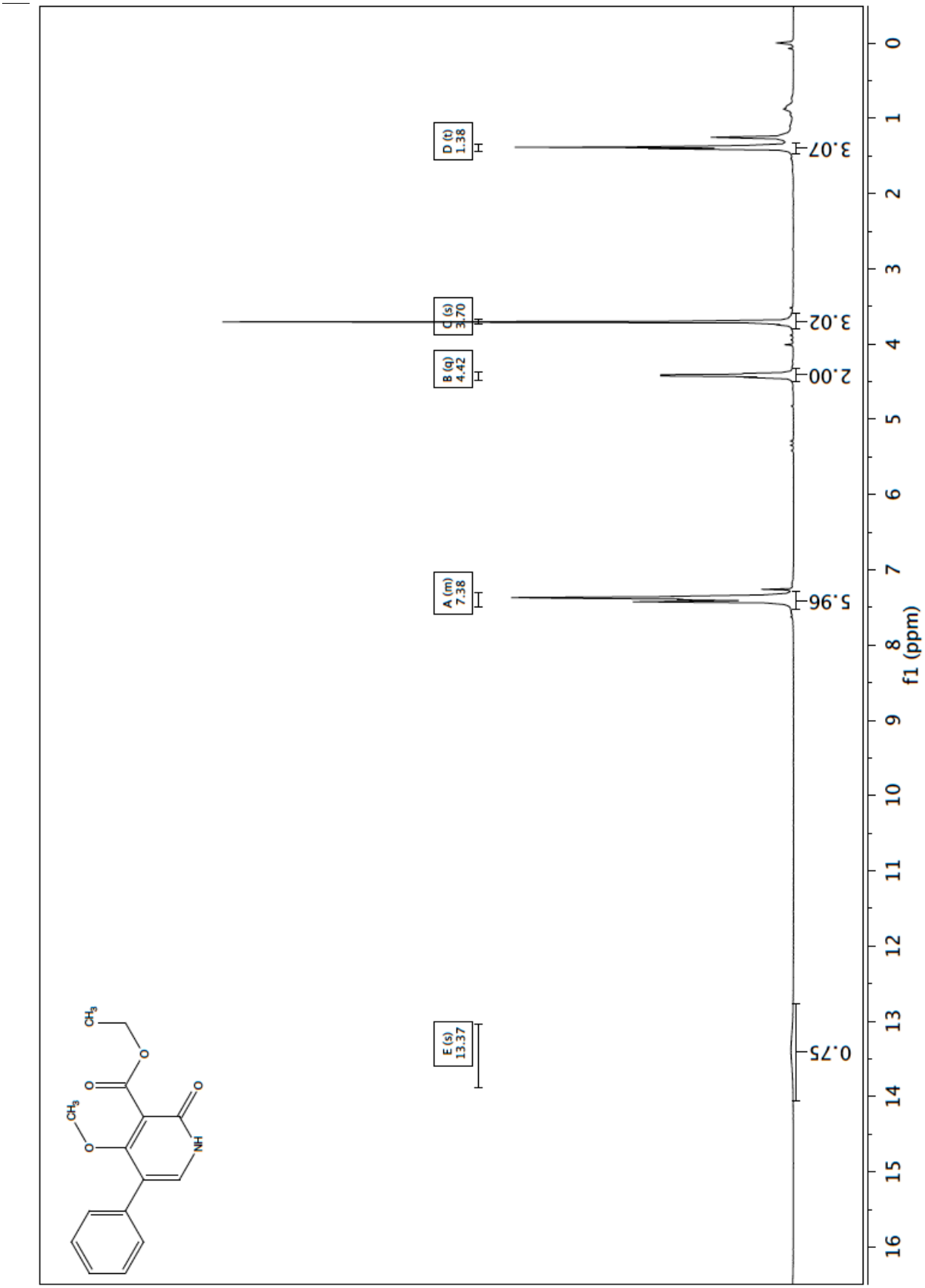


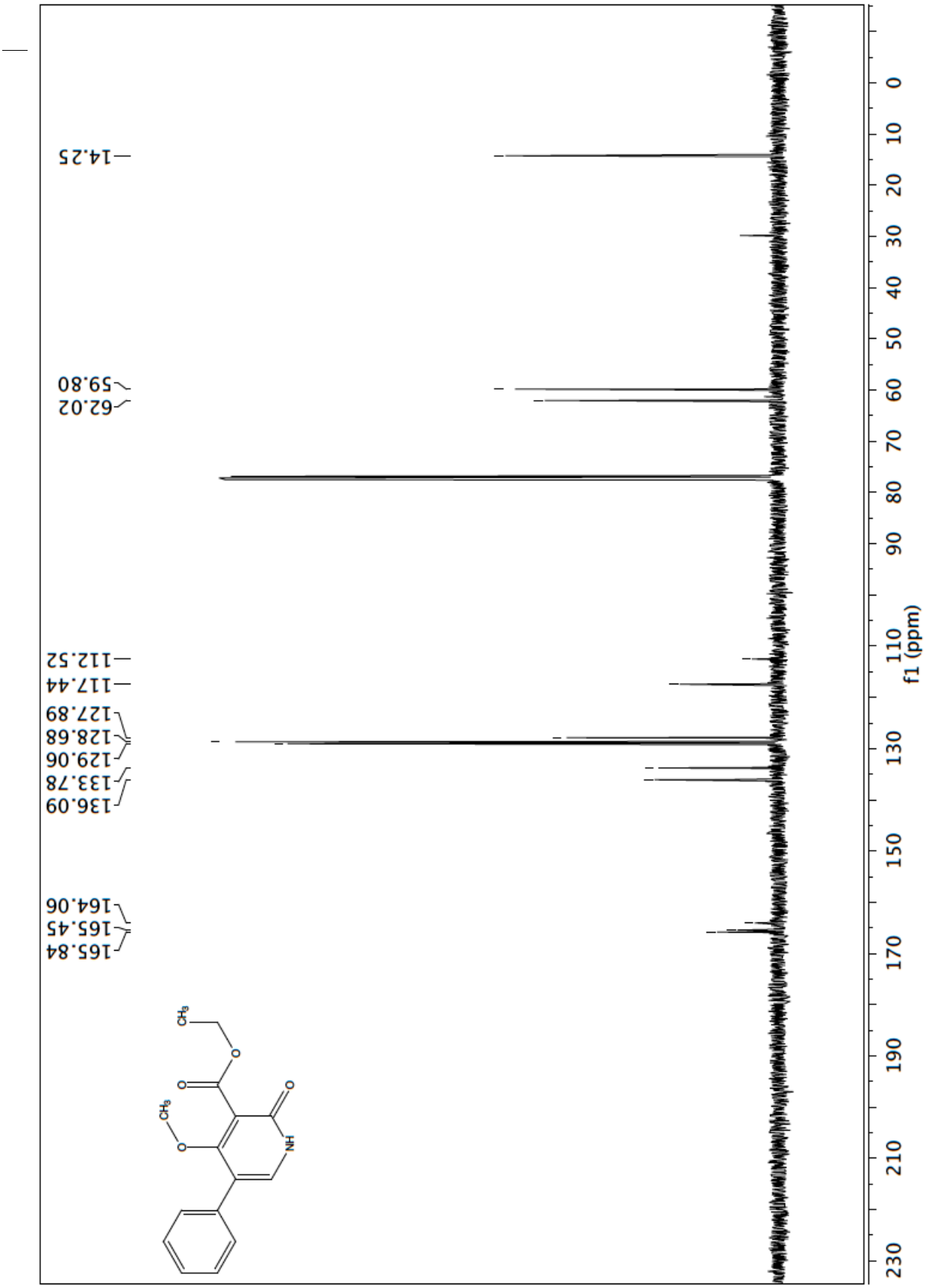


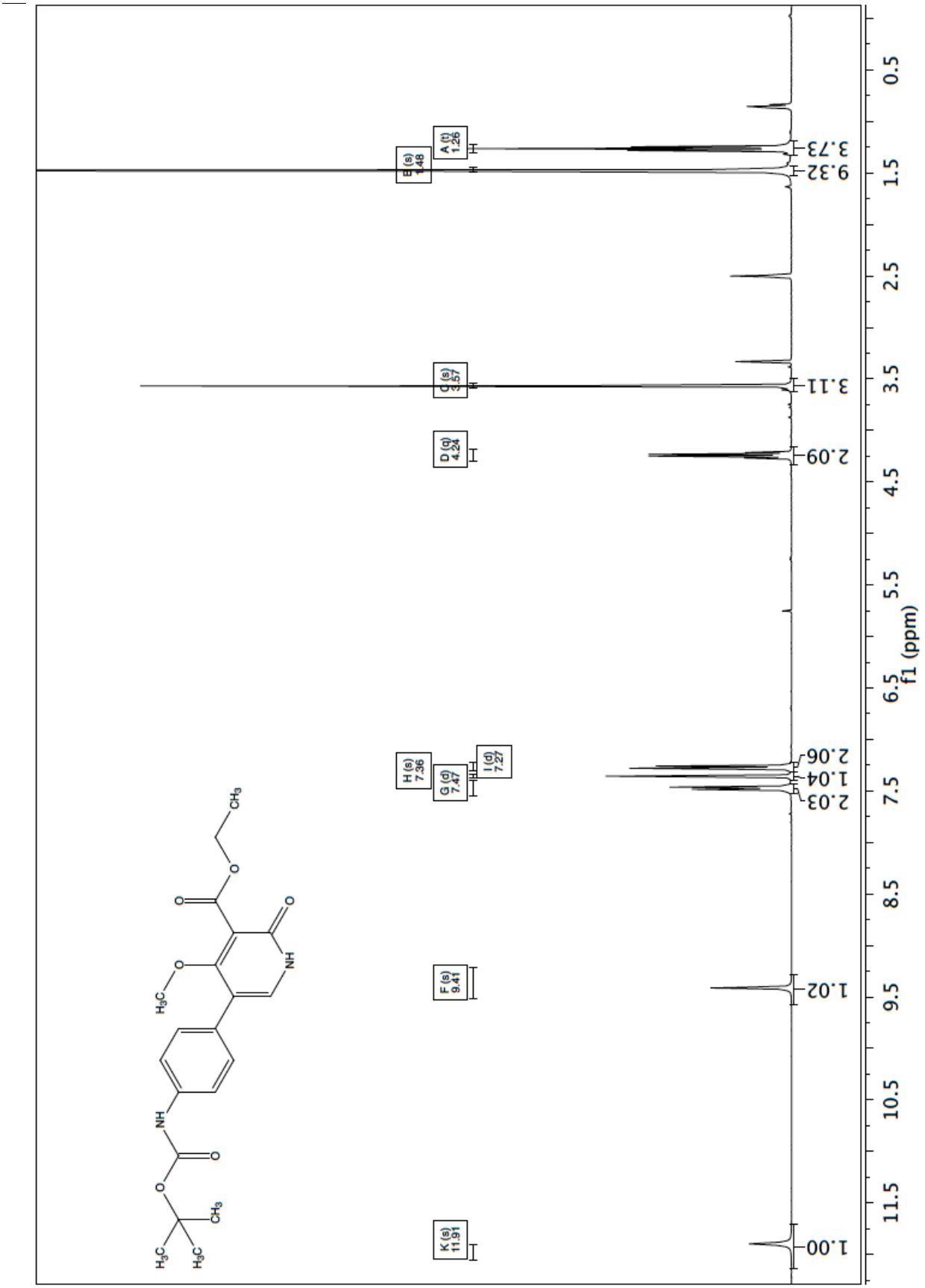

G (t) 1.39
F (s) 3.73
E (q) 4.42
C (dd) 7.32
B (s) 7.39
D (t) 7.09
A (s) 13.31
3.14
3.02
2.01
1.99
1.99
1.00
0.85
f1 (ppm)
0.5
1.5
2.5
3.5
4.5
5.5
6.5
7.5
8.5
9.5
11.0
12.5
14.0
CH3
O
O
O
CH3
O
NH
F

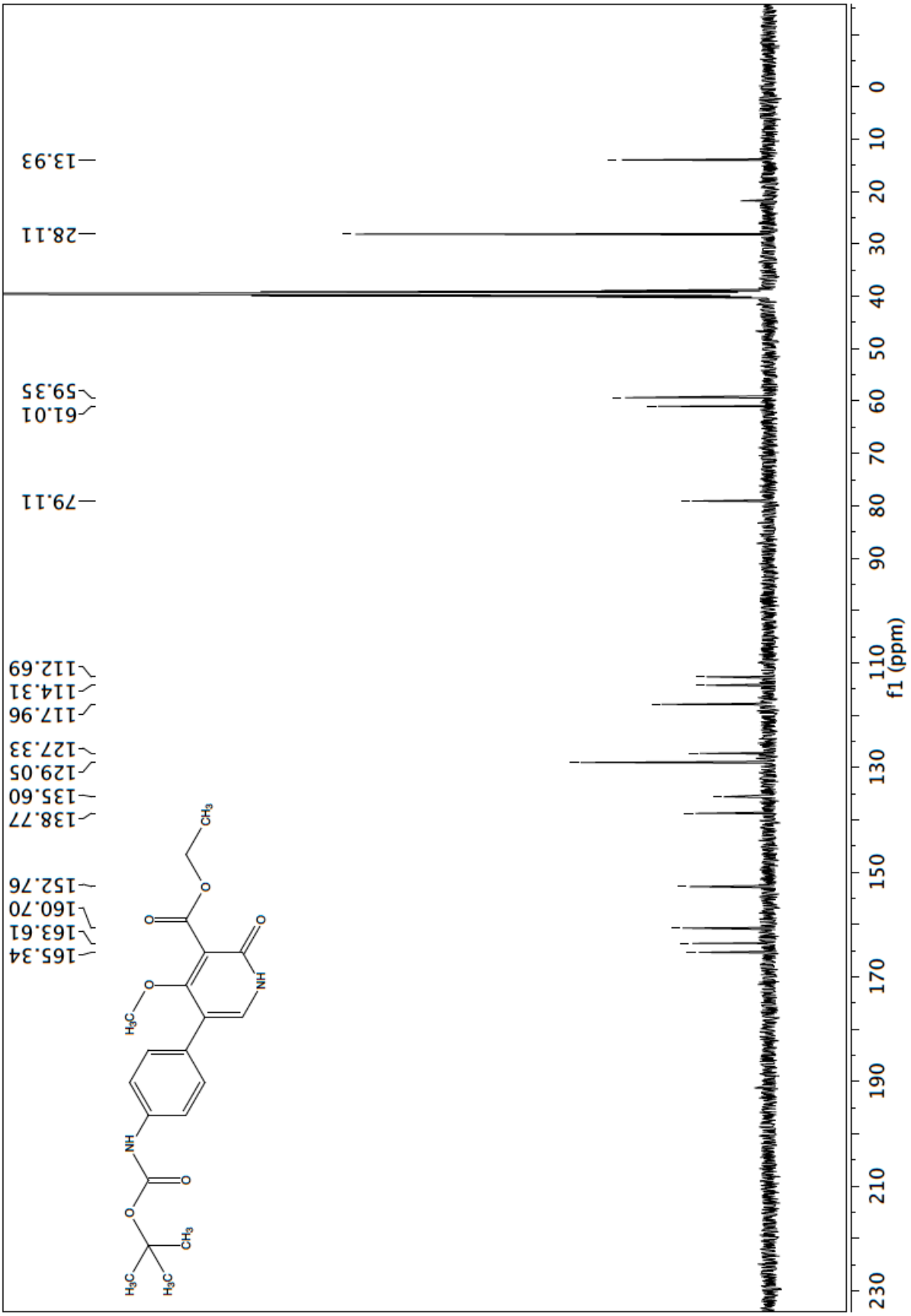


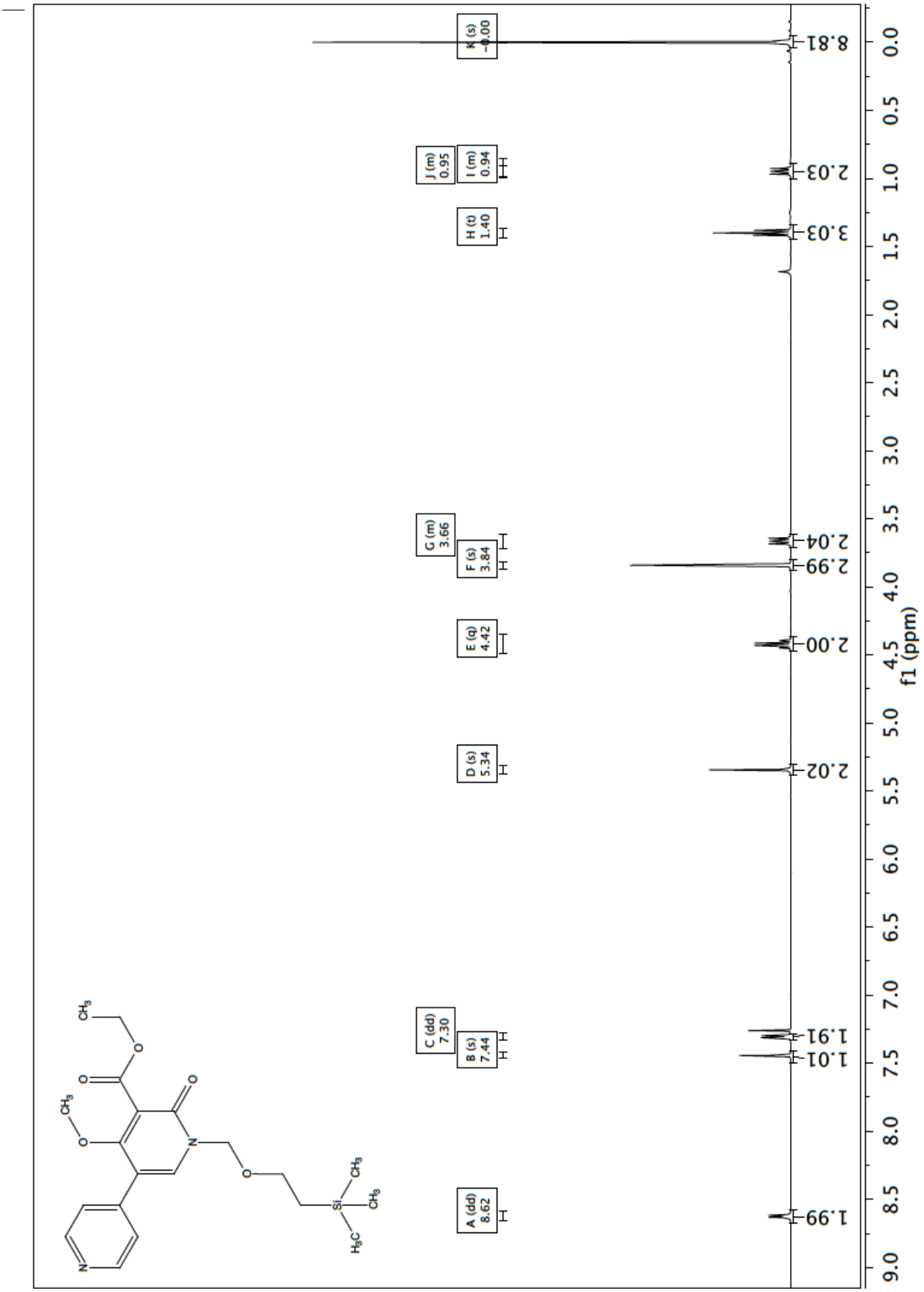


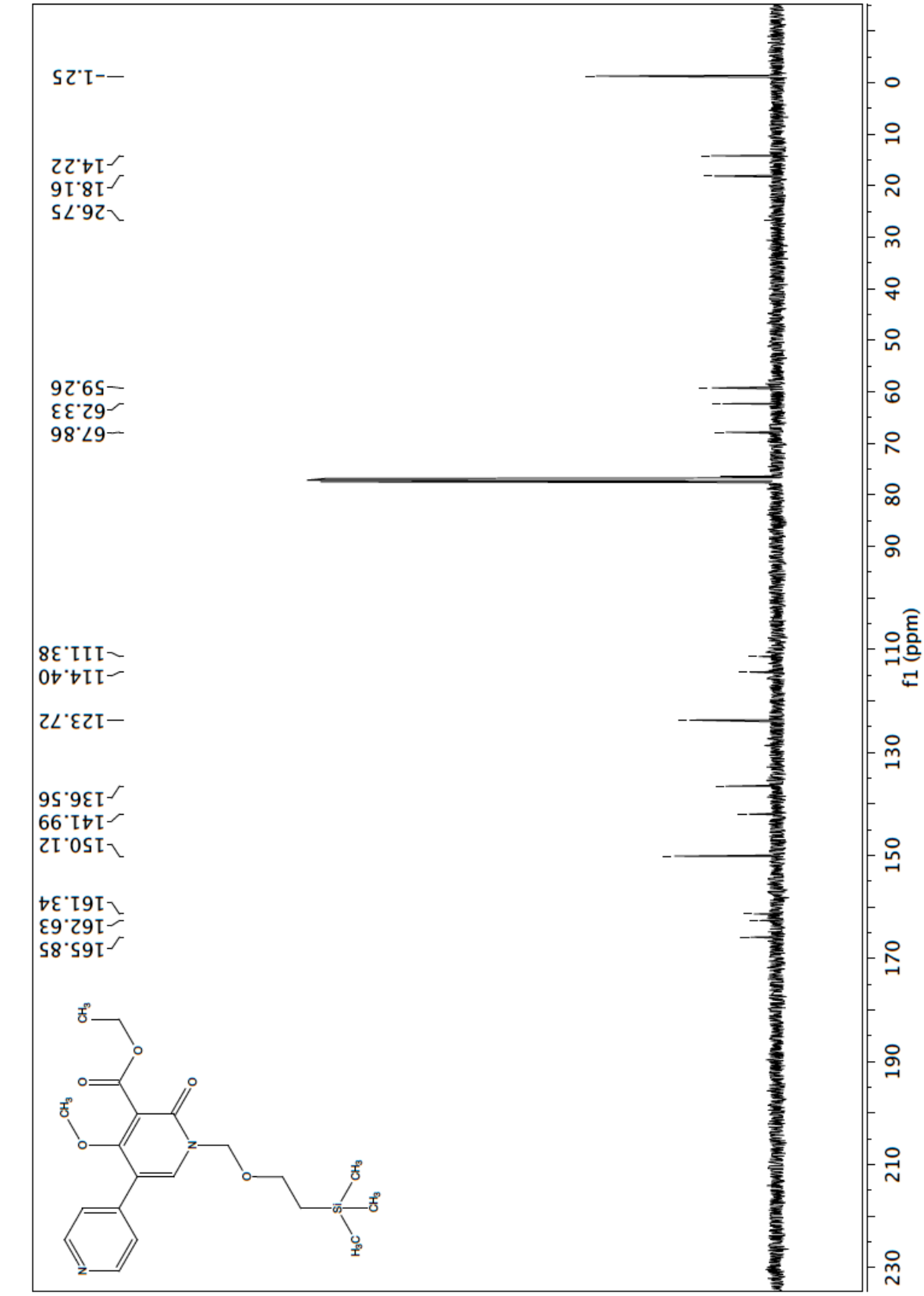

D (t)
1.38
C (s)
3.70
B (q)
4.42
A (m)
7.38
E (s)
13.37
3.07
3.02
2.00
5.96
0.75
f1 (ppm)
NH

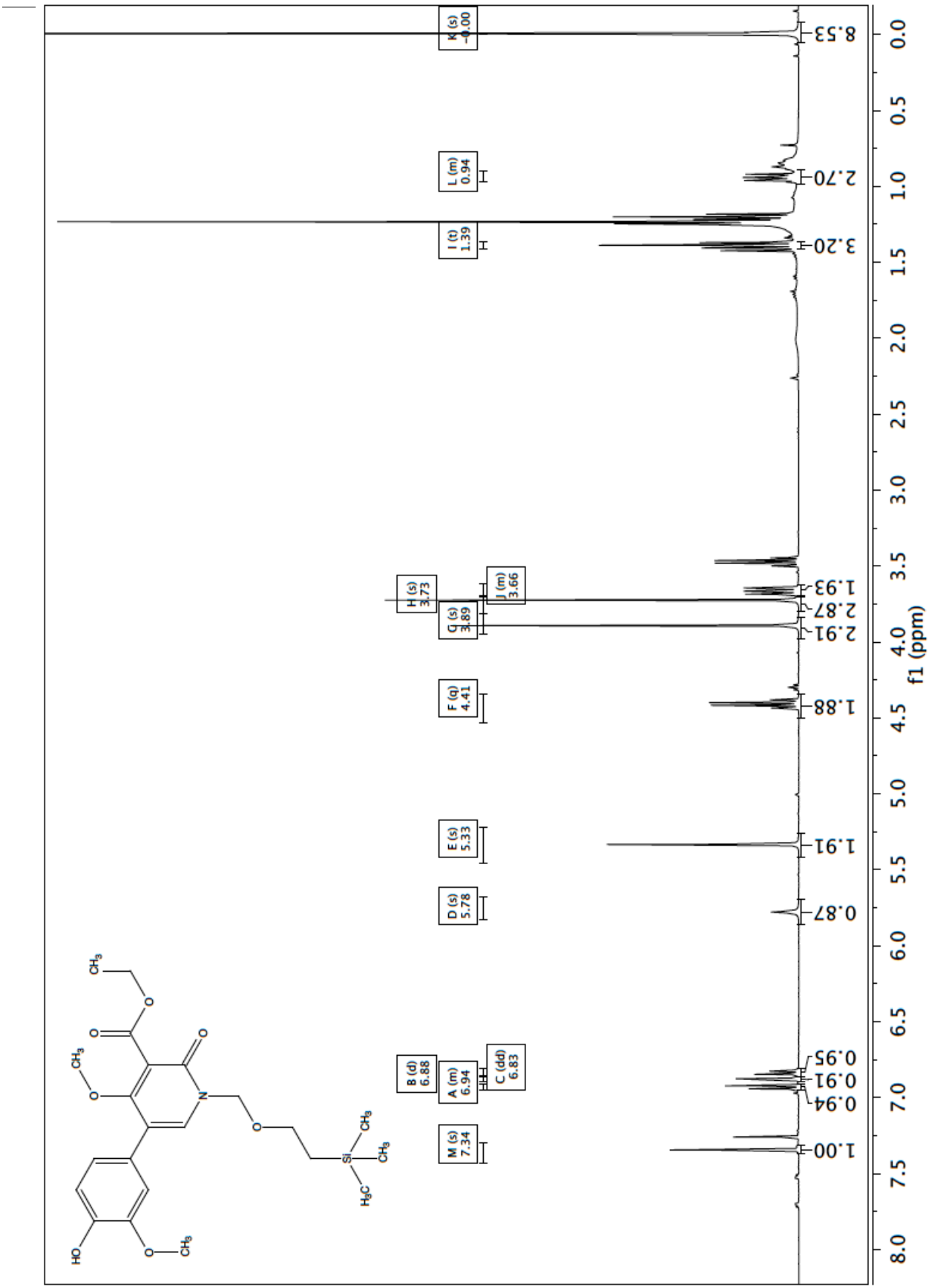

14.25
59.80
62.02
112.52
117.44
127.89
128.68
129.06
133.78
136.09
164.06
165.45
165.84
f1 (ppm)

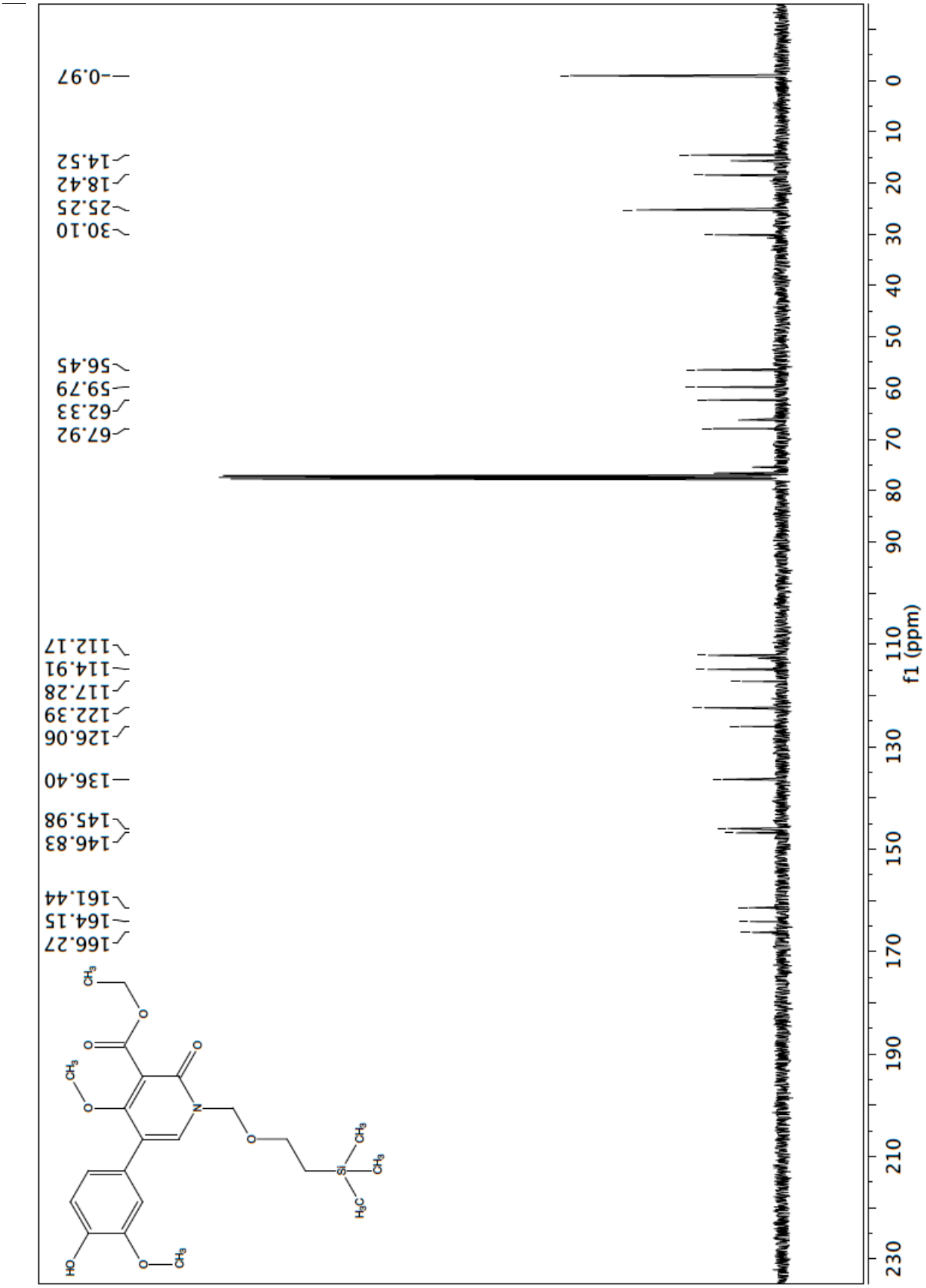

A (t) 1.26
B (s) 1.48
C (s) 3.57
D (q) 4.24
H (s) 7.36
G (d) 7.47
I (d) 7.27
F (s) 9.41
K (s) 11.91
3.73
9.32
3.11
2.09
2.06
1.04
2.03
1.02
1.00
f1 (ppm)

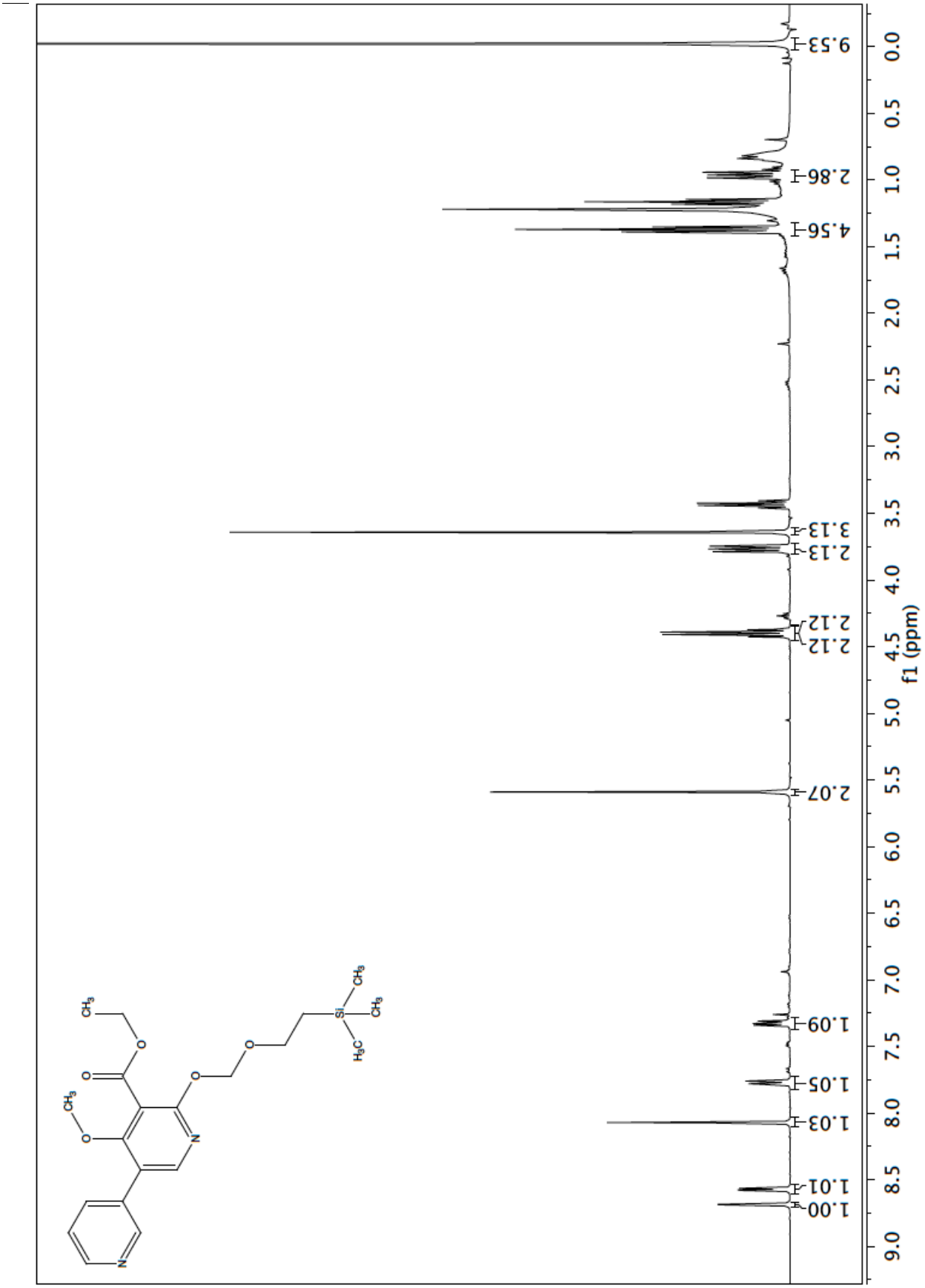

13.93
28.11
59.35
61.01
79.11
112.69
114.31
117.96
127.33
129.05
135.60
138.77
152.76
160.70
163.61
165.34
f1 (ppm)

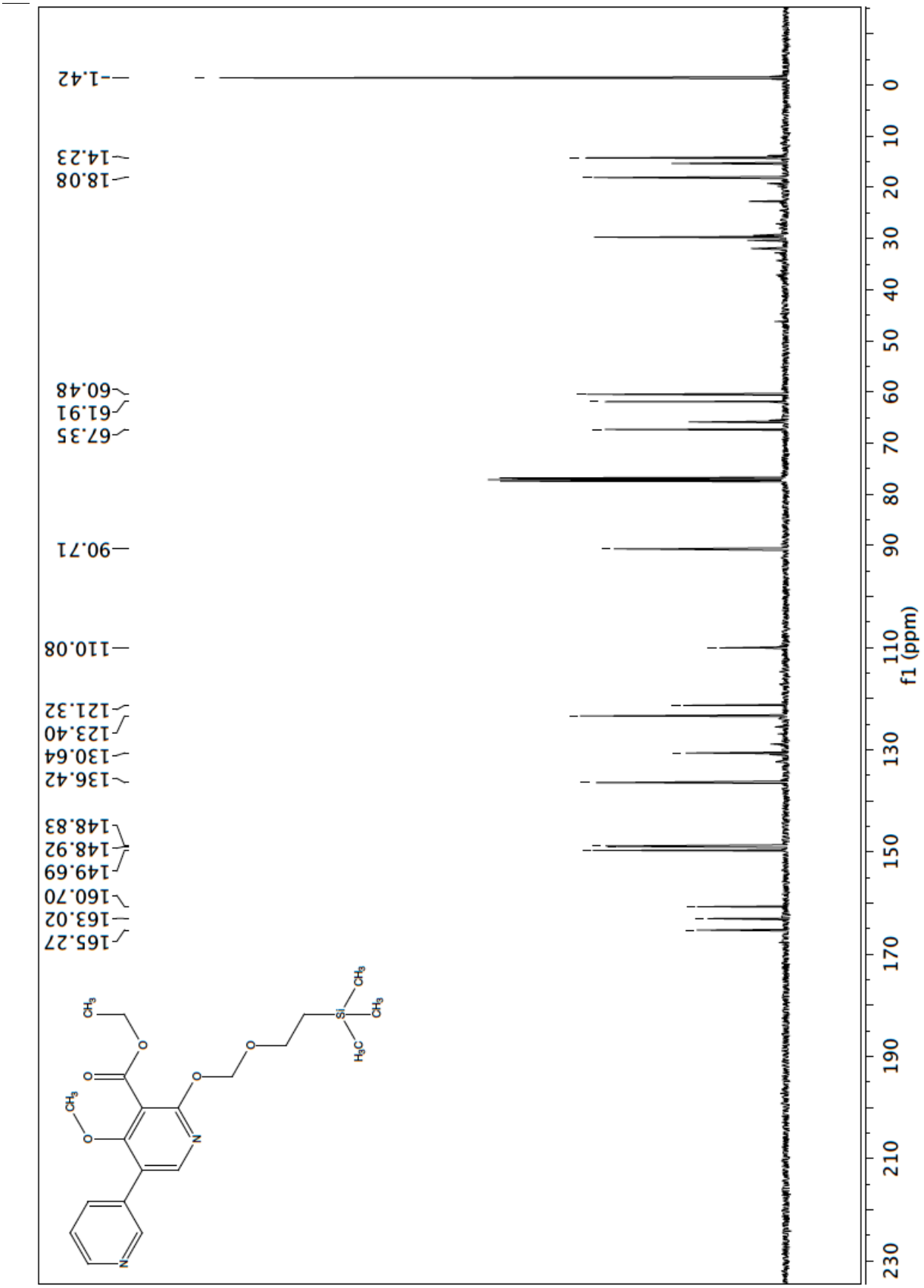

K (s) 8.81
J (m) 0.95
I (m) 0.94
H (t) 1.40
G (m) 3.66
F (s) 3.84
E (q) 4.42
D (s) 5.34
C (dd) 7.30
B (s) 7.44
A (dd) 8.62
8.81
2.03
3.03
2.04
2.99
2.00
2.02
1.91
1.01
1.99
f1 (ppm)

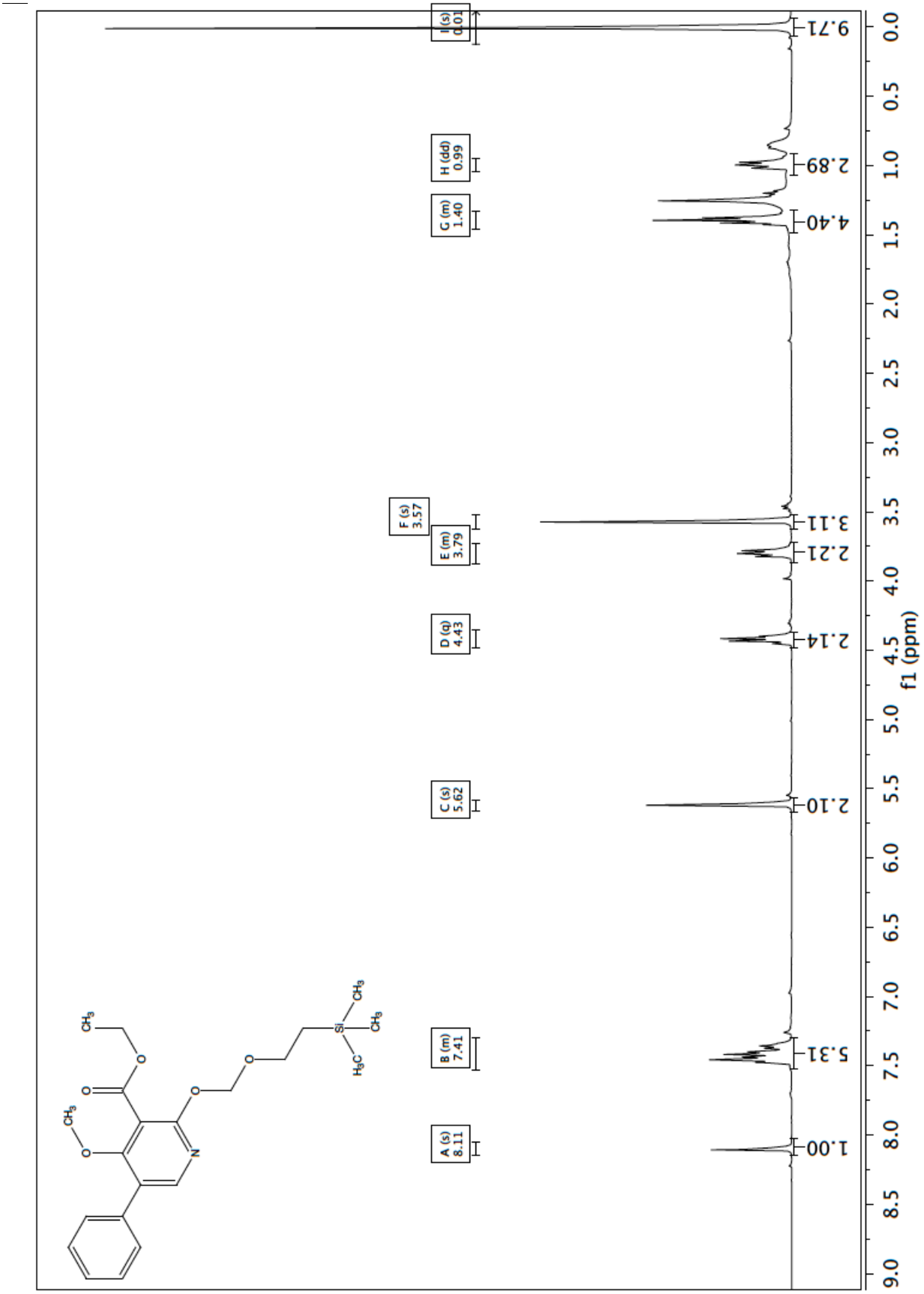


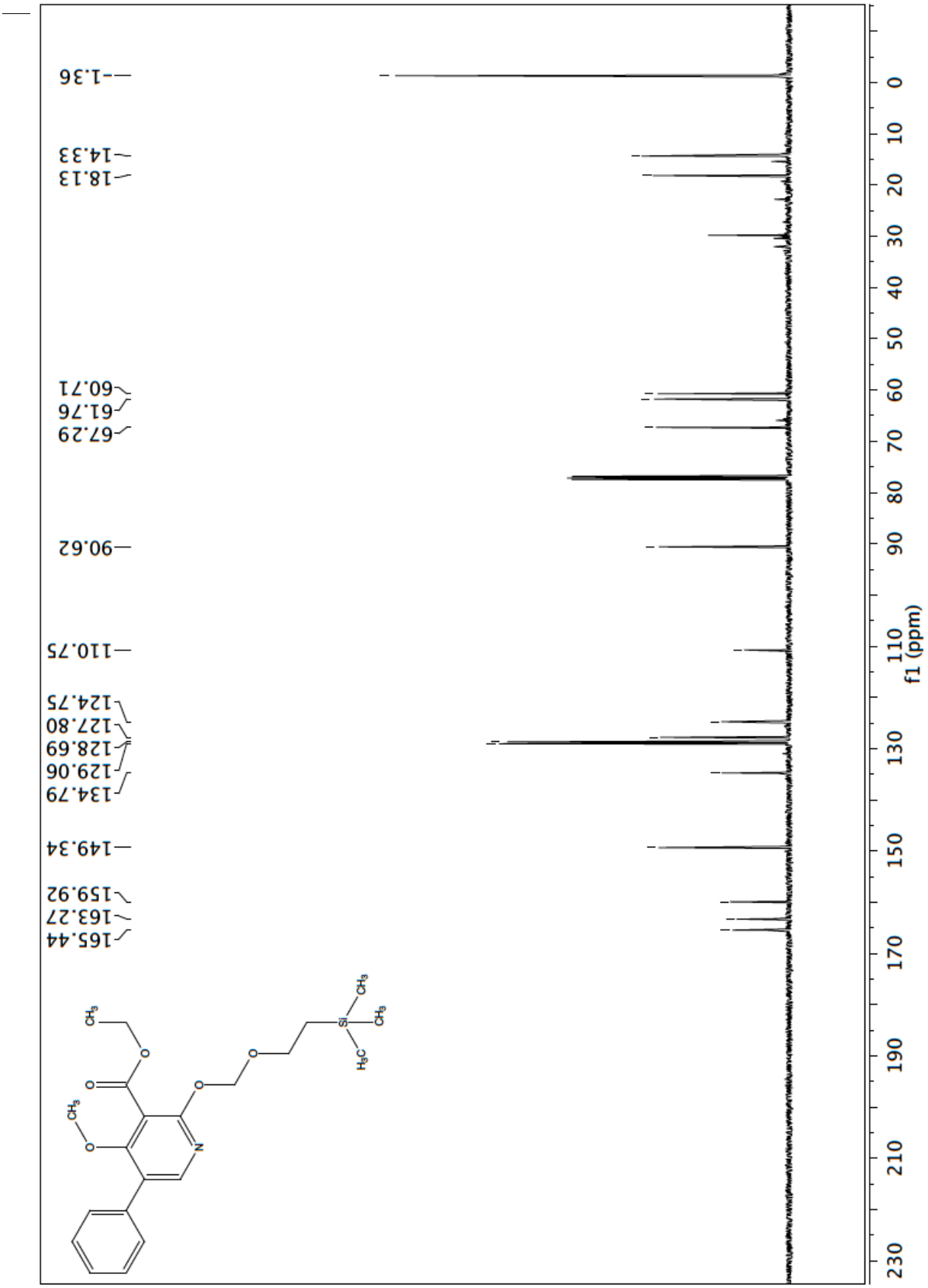

K (s) 9.00
L (m) 0.94
I (t) 1.39
H (s) 3.73
J (m) 3.66
G (s) 3.89
F (q) 4.41
E (s) 5.33
D (s) 5.78
B (d) 6.88
A (m) 6.94
C (dd) 6.83
M (s) 7.34
8.53
2.70
3.20
1.93
2.87
2.91
1.88
1.91
0.87
0.95
0.91
0.94
1.00
f1 (ppm)

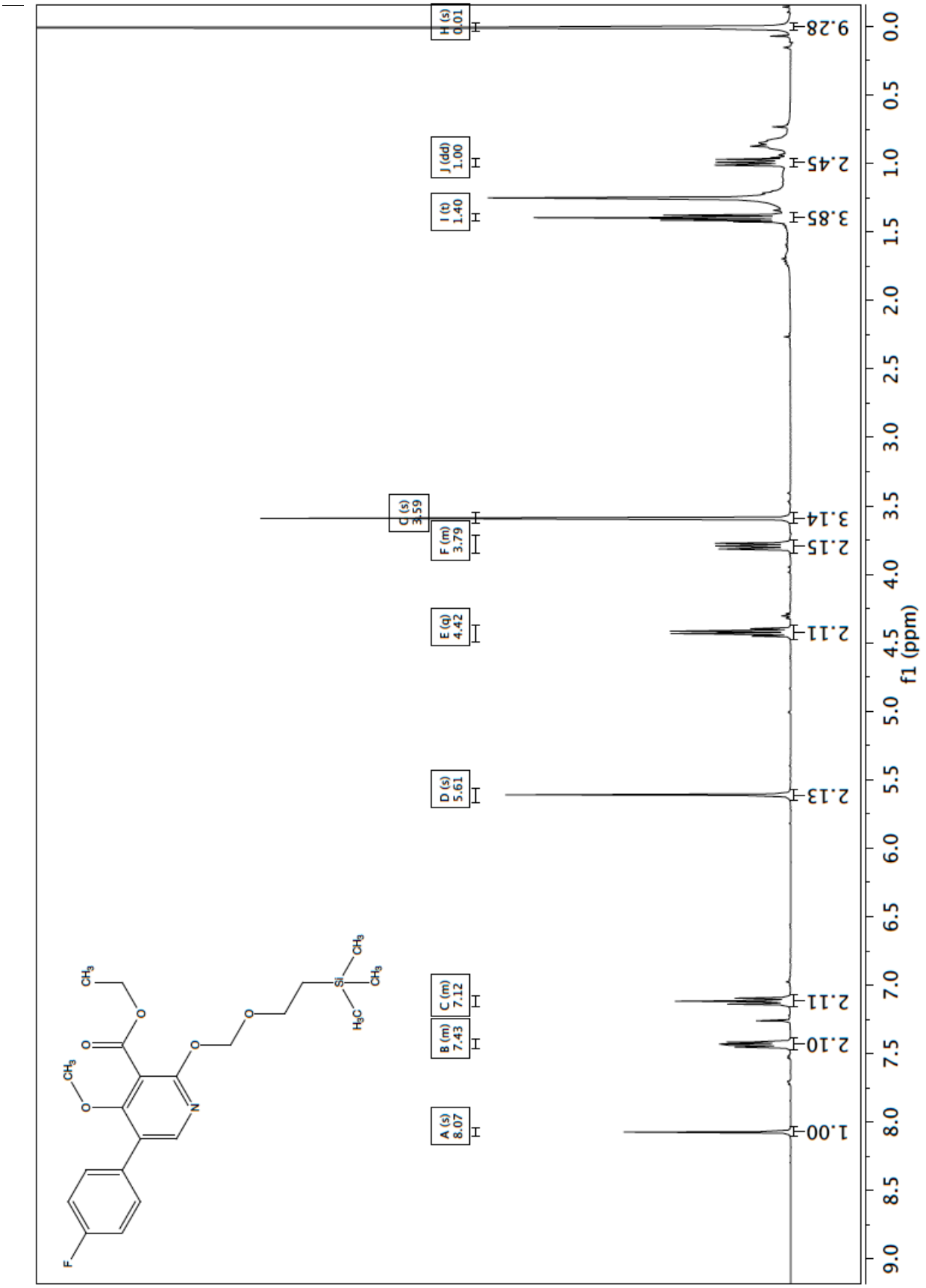

-0.97
14.52
18.42
25.25
30.10
56.45
59.79
62.33
67.92
112.17
114.91
117.28
122.39
126.06
136.40
145.98
146.83
161.44
164.15
166.27
f1 (ppm)

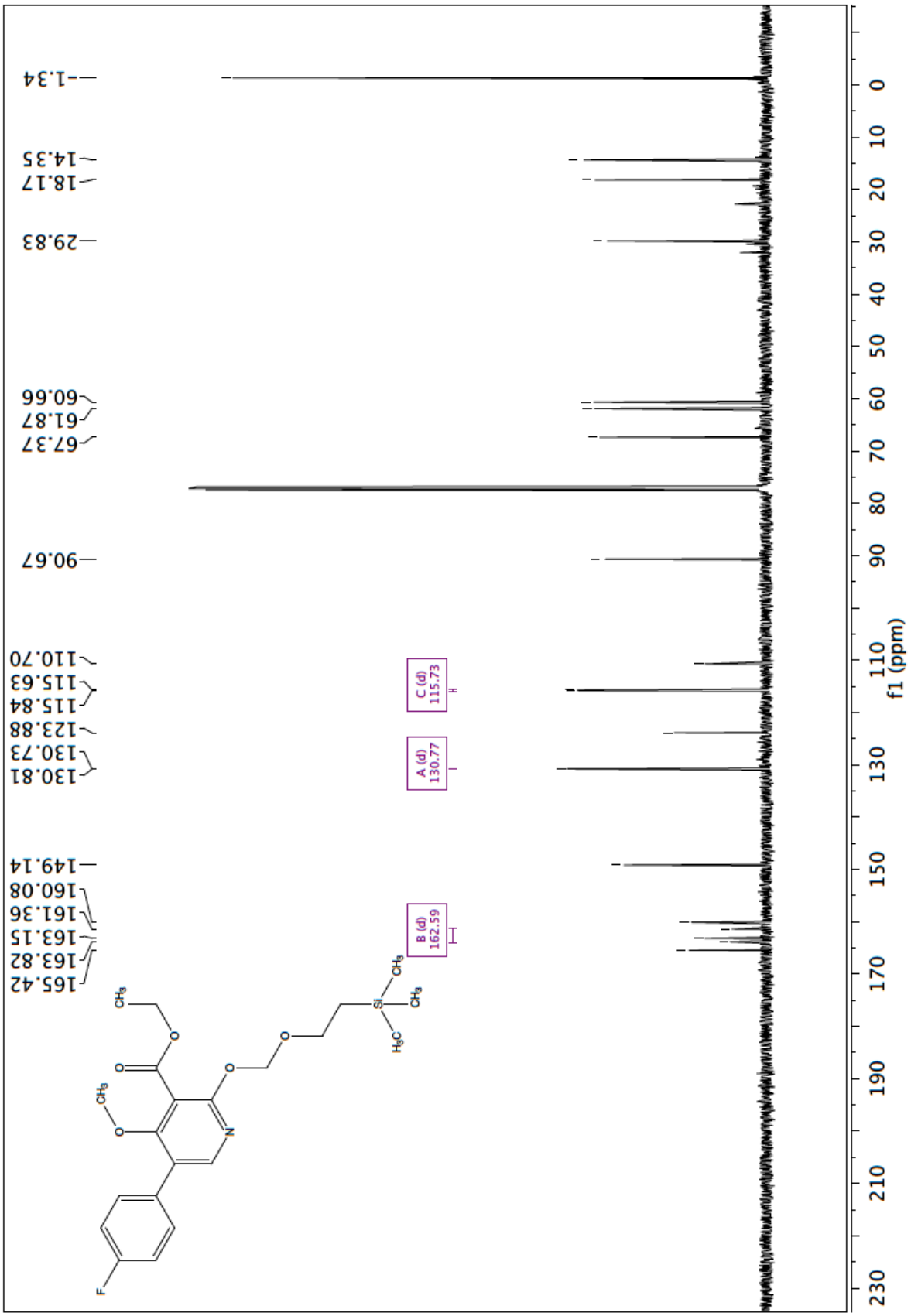

9.53
2.86
4.56
3.13
2.13
2.12
2.12
2.07
1.09
1.05
1.03
1.01
1.00
f1 (ppm)

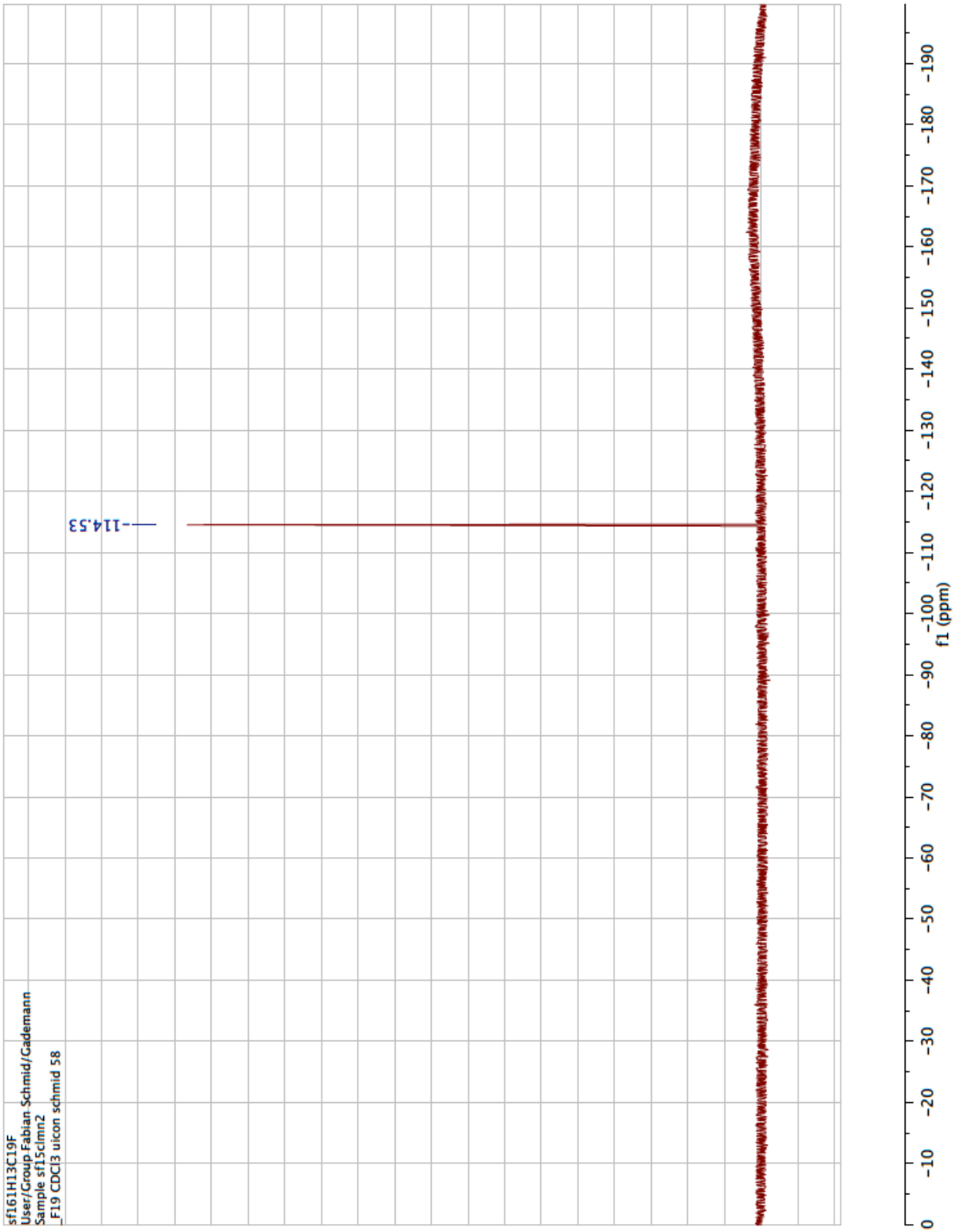

-1.42
14.23
18.08
60.48
61.91
67.35
90.71
110.08
121.32
123.40
130.64
136.42
148.83
148.92
149.69
160.70
163.02
165.27
f1 (ppm)

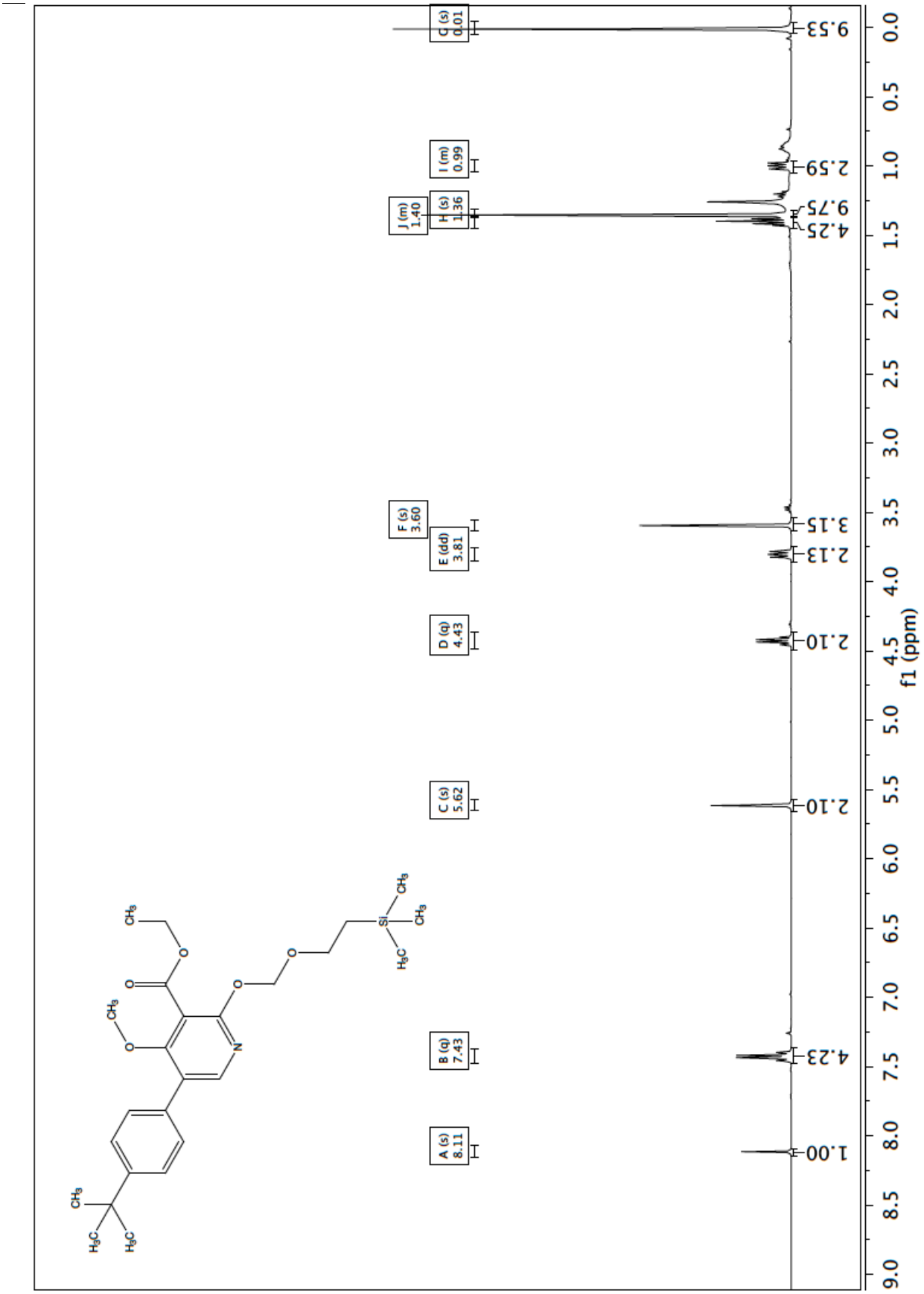


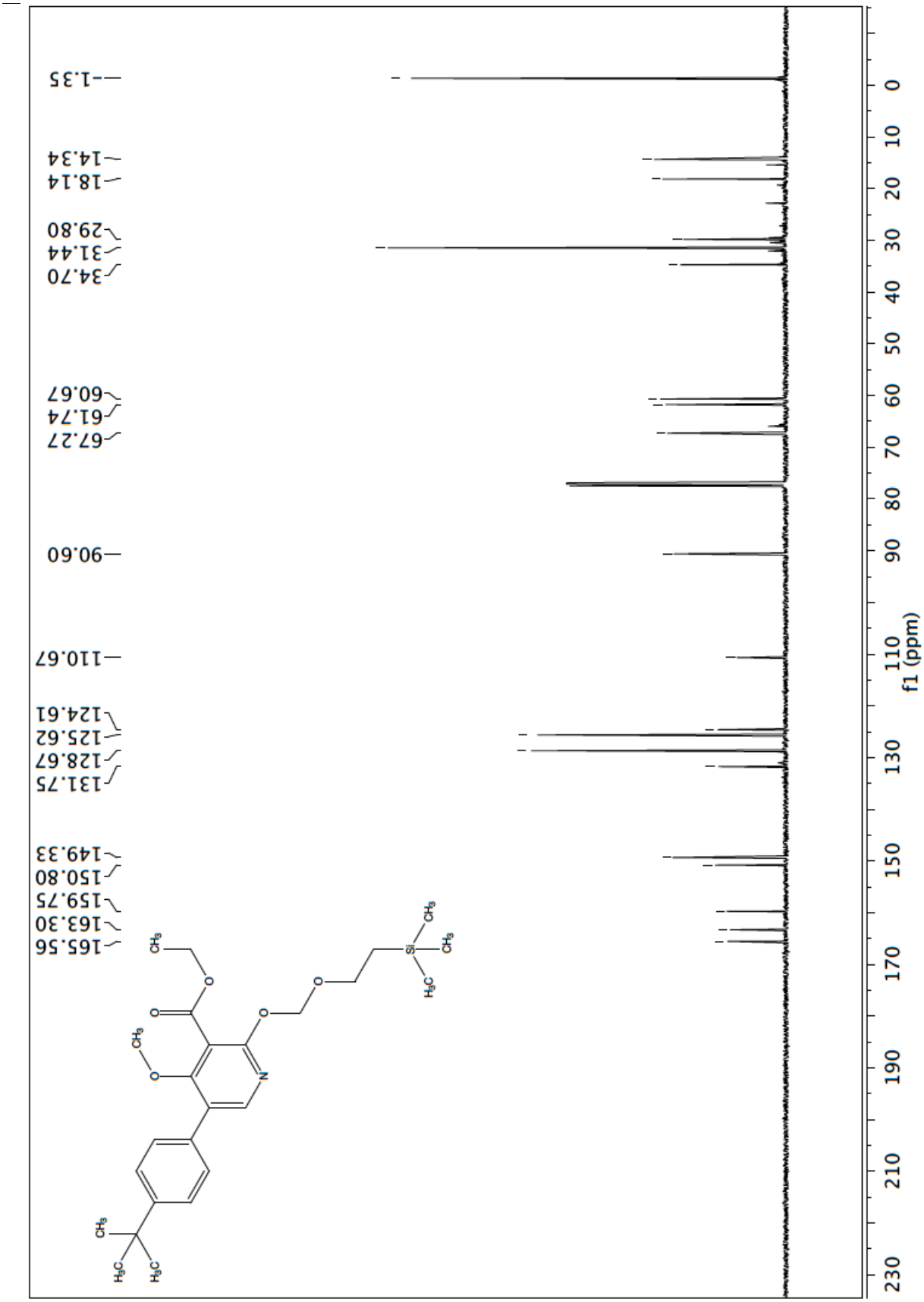

1.36
14.33
18.13
60.71
61.76
67.29
90.62
110.75
124.75
127.80
128.69
129.06
134.79
149.34
159.92
163.27
165.44
f1 (ppm)

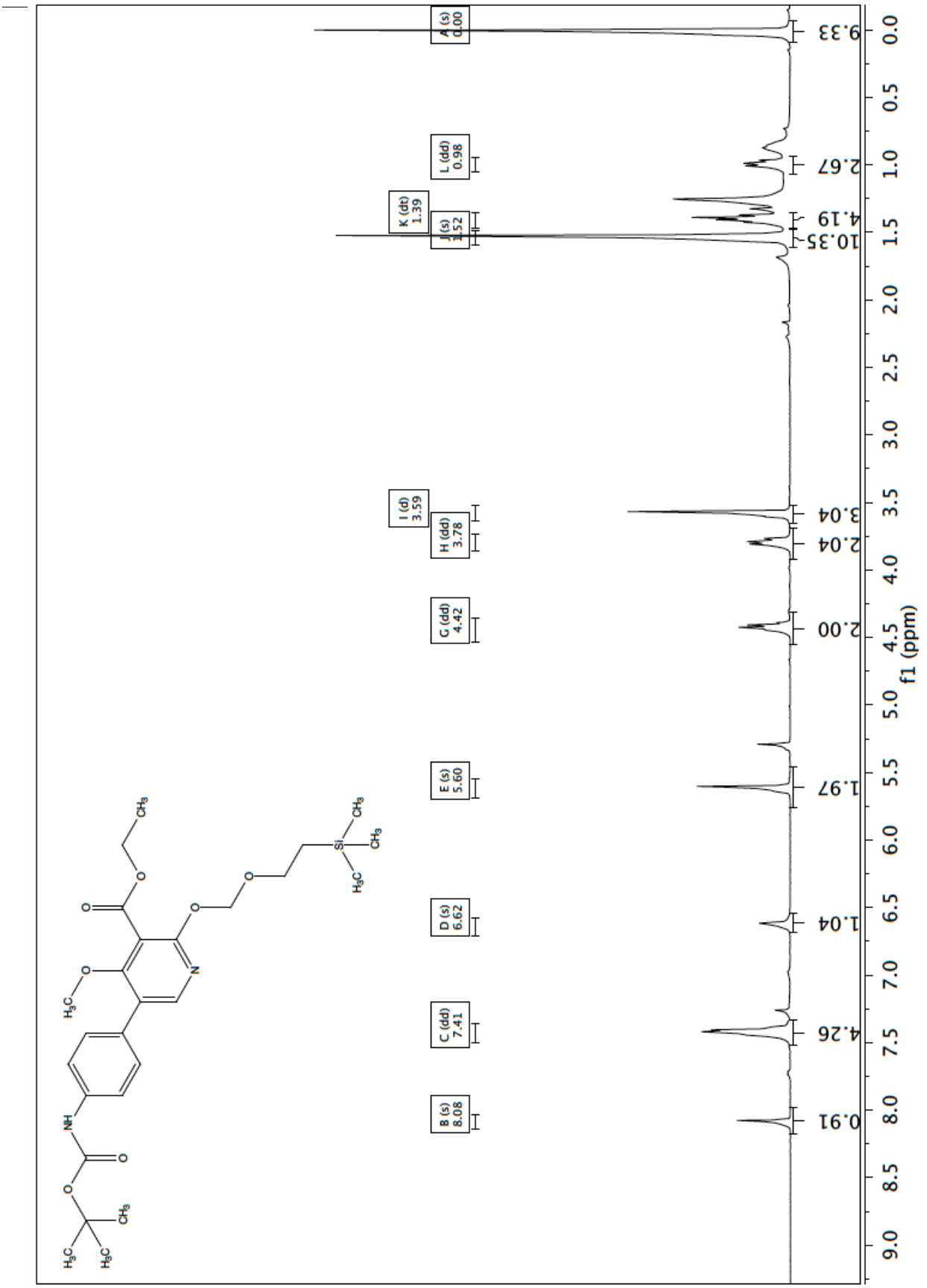

H (s) 0.01
J (dd) 1.00
I (t) 1.40
C (s) 3.59
F (m) 3.79
E (q) 4.42
D (s) 5.61
C (m) 7.12
B (m) 7.43
A (s) 8.07
9.28
2.45
3.85
3.14
2.15
2.11
2.13
2.11
2.10
1.00
f1 (ppm)

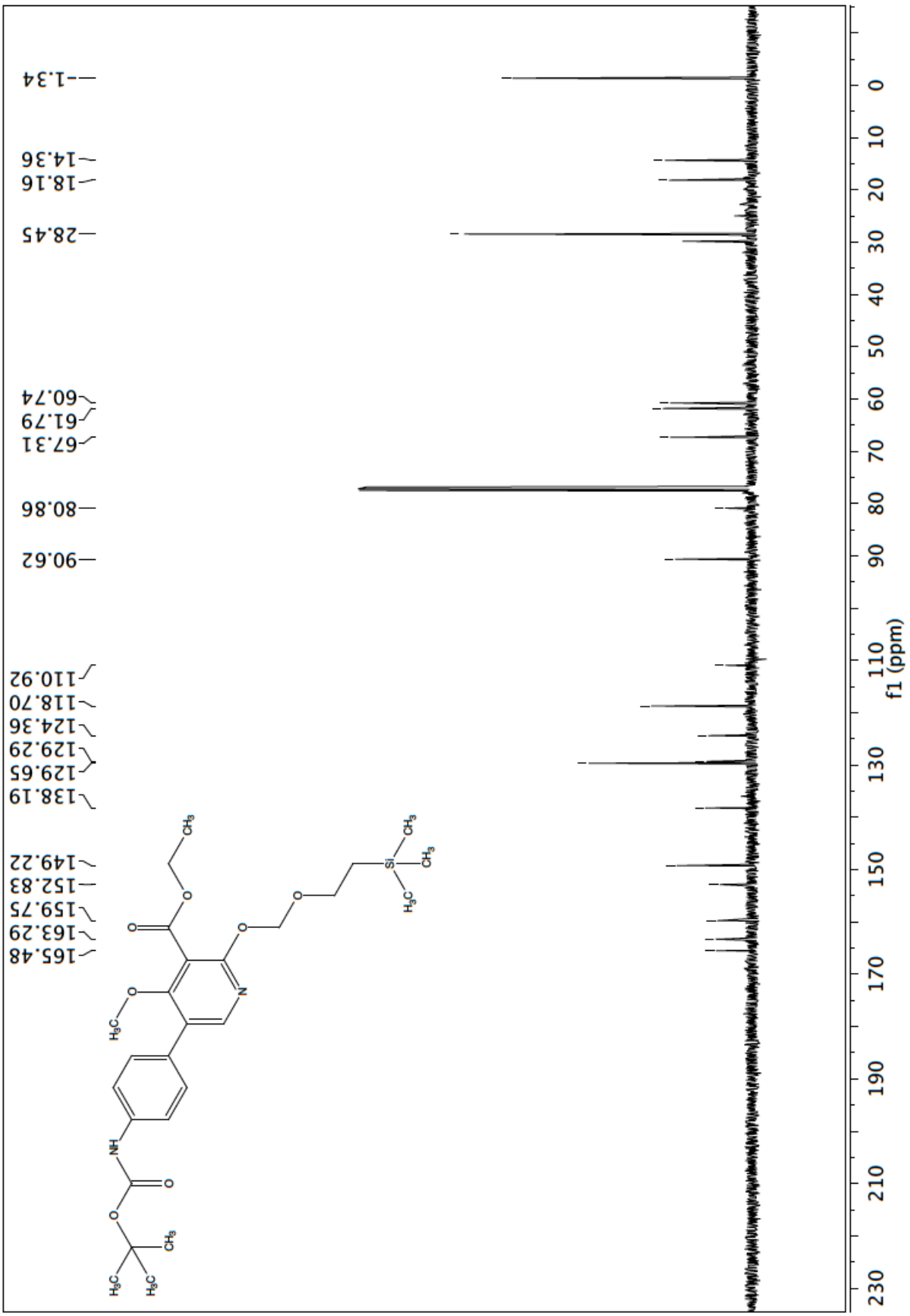


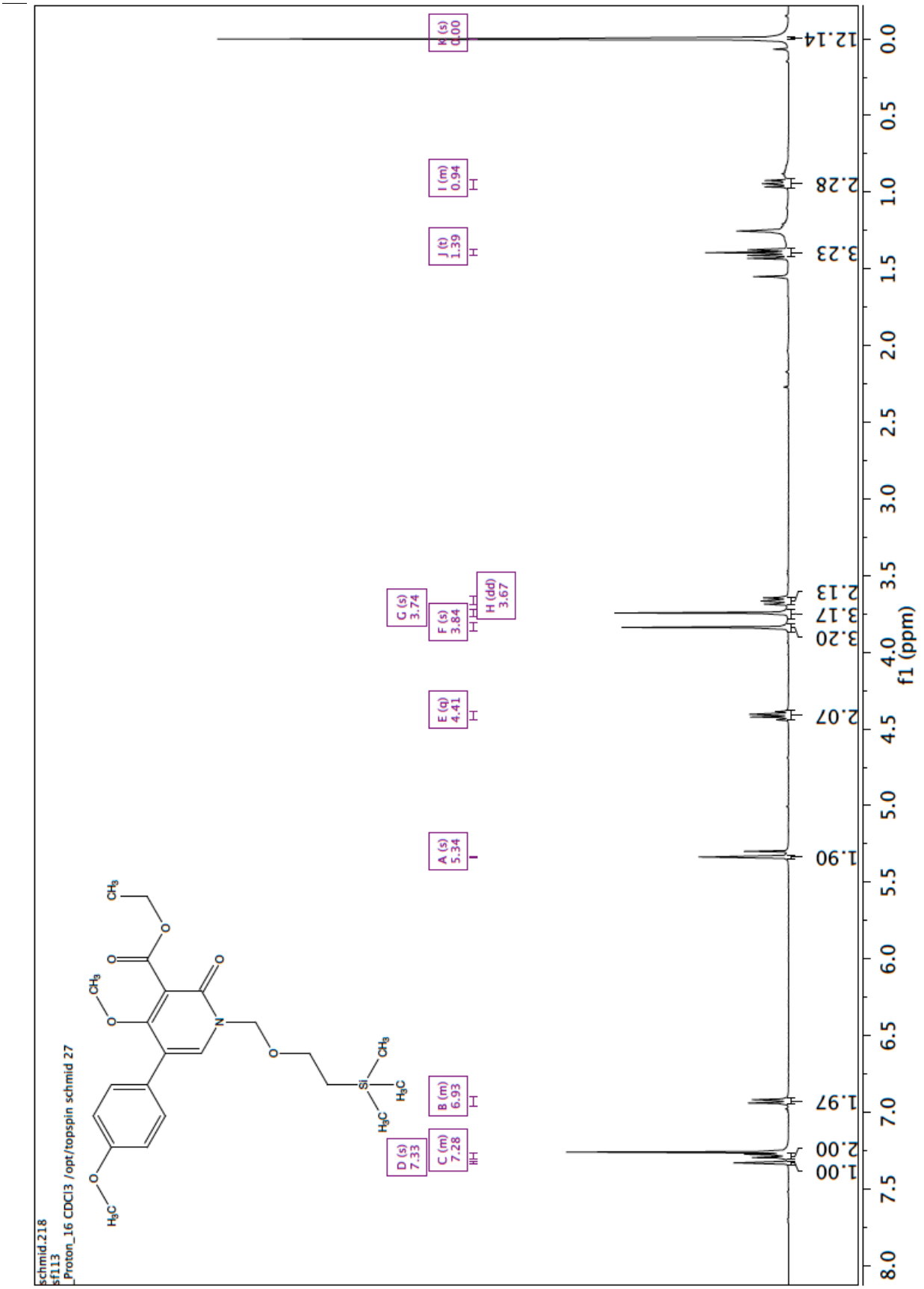


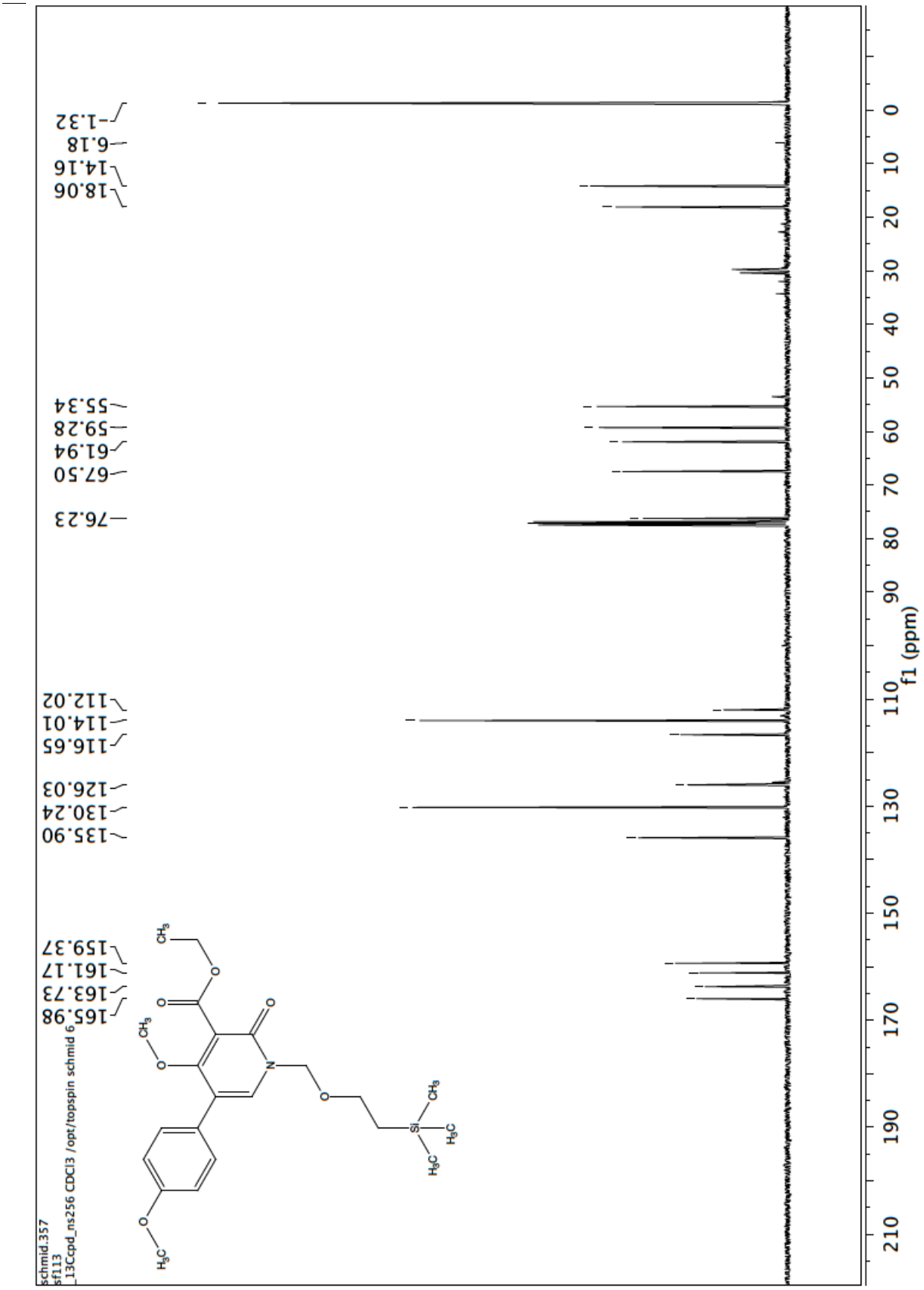

G (s) 0.01
I (m) 0.99
J (m) 1.40
H (s) 1.36
F (s) 3.60
E (dd) 3.81
D (q) 4.43
C (s) 5.62
B (q) 7.43
A (s) 8.11
9.53
2.59
9.75
4.25
3.15
2.13
2.10
2.10
4.23
1.00
f1 (ppm)


-1.35
14.34
18.14
29.80
31.44
34.70
60.67
61.74
67.27
90.60
110.67
124.61
125.62
128.67
131.75
149.33
150.80
159.75
163.30
165.56
f1 (ppm)


A (s) 0.00
L (dd) 0.98
K (dt) 1.39
J (s) 1.52
I (d) 3.59
H (dd) 3.78
G (dd) 4.42
E (s) 5.60
D (s) 6.62
C (dd) 7.41
B (s) 8.08
9.33
2.67
4.19
10.35
3.04
2.04
2.00
1.97
1.04
4.26
0.91
f1 (ppm)

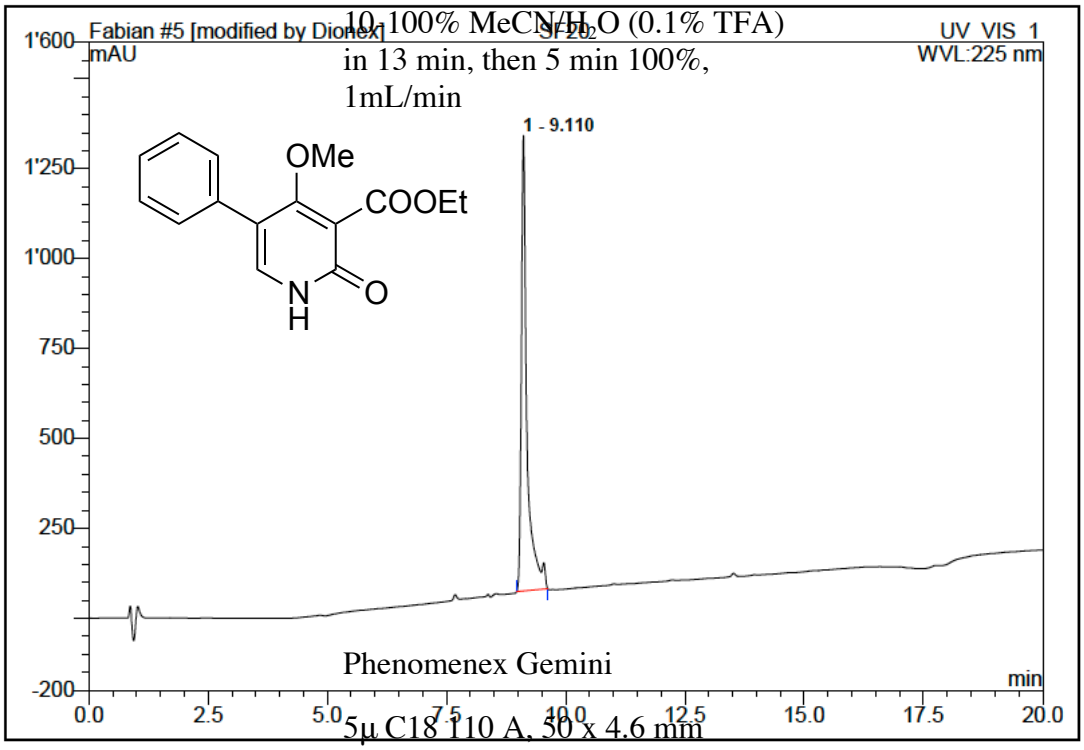

-1.34
14.36
18.16
28.45
60.74
61.79
67.31
80.86
90.62
110.92
118.70
124.36
129.29
129.65
138.19
149.22
152.83
159.75
163.29
165.48
f1 (ppm)


schmid.218
sf113
Proton_16 CDCl3 /opt/topspin schmid 27
K (s) 0.00
I (m) 0.94
J (t) 1.39
G (s) 3.74
F (s) 3.84
H (dd) 3.67
E (q) 4.41
A (s) 5.34
B (m) 6.93
D (s) 7.33
C (m) 7.28
12.14
2.28
3.23
2.13
3.17
3.20
2.07
1.90
1.97
2.00
1.00
f1 (ppm)

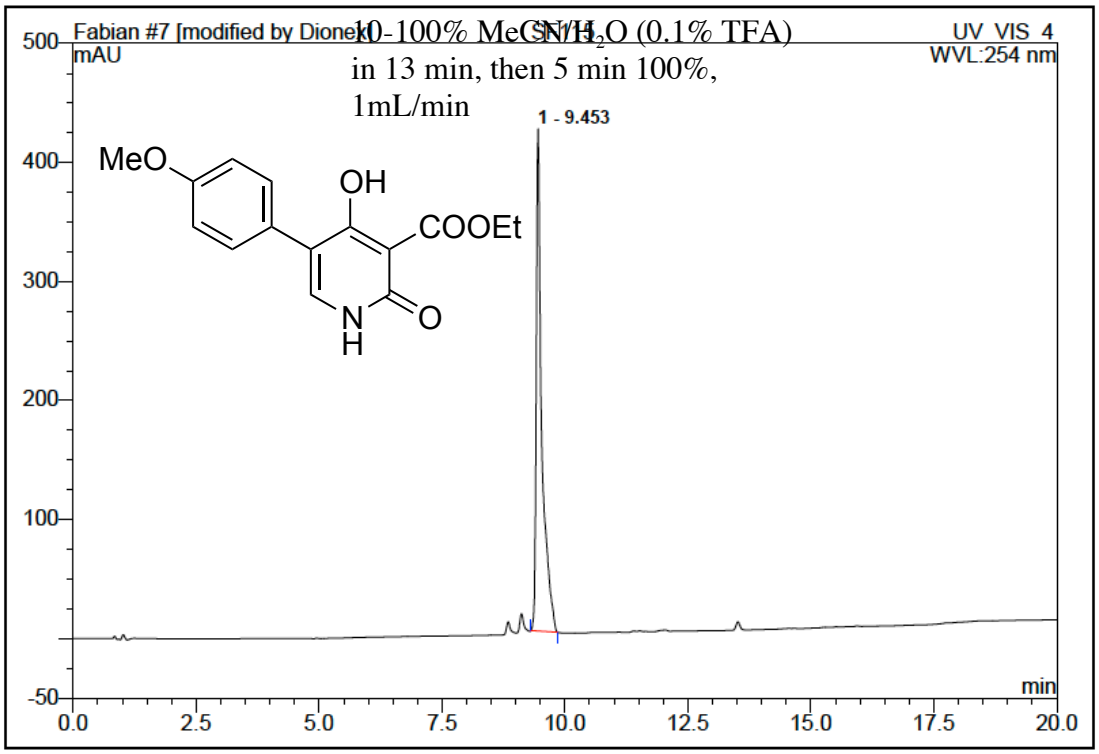

-1.32
6.18
14.16
18.06
55.34
59.28
61.94
67.50
76.23
112.02
114.01
116.65
126.03
130.24
135.90
159.37
161.17
163.73
165.98
f1 (ppm)
schmid.357
sf113
_13Ccpd_ns256 CDCl3 /opt/topspin schmid 6

6. HPLC Traces

Phenomenex Gemini
5µ C18 110 A, 50 x 4.6 mm
10-100% MeCN/H$_2$O (0.1% TFA)
in 13 min, then 5 min 100%,
1mL/min

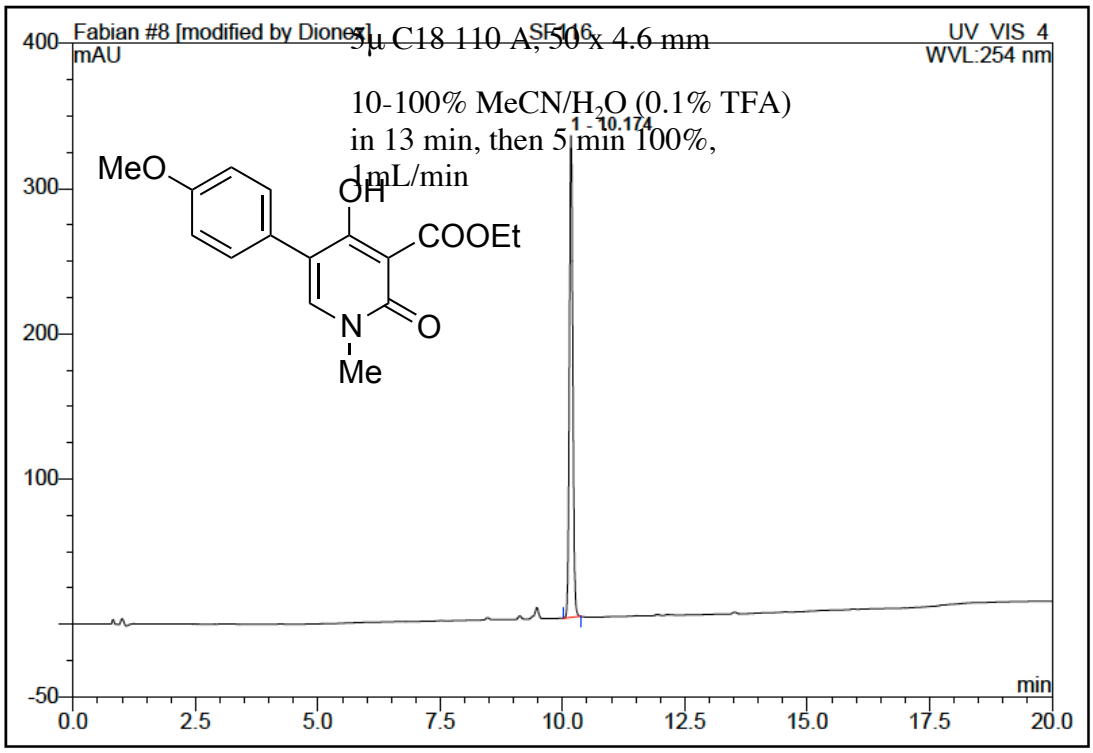


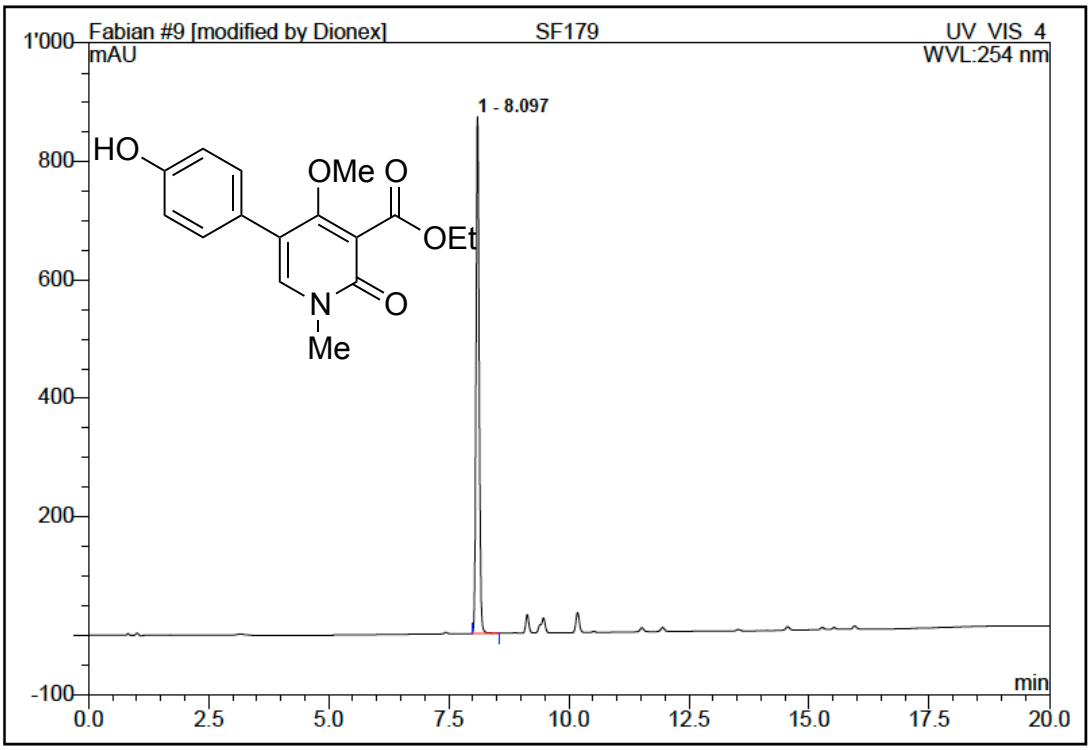
Phenomenex Gemini
5µ C18 110 A, 50 x 4.6 mm
10-100% MeCN/H$_2$O (0.1% TFA)
in 13 min, then 5 min 100%,
1mL/min

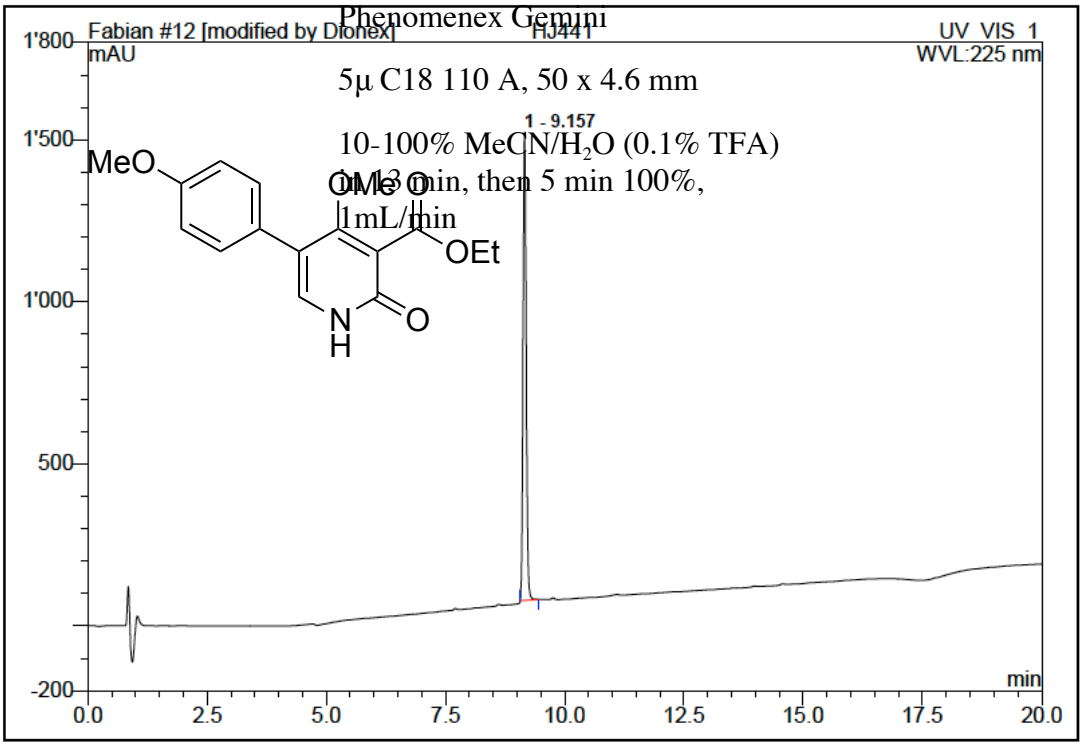


Phenomonex Gemini
~~Phenomenex Gemini~~
5µ C18 110 A, 50 x 4.6 mm

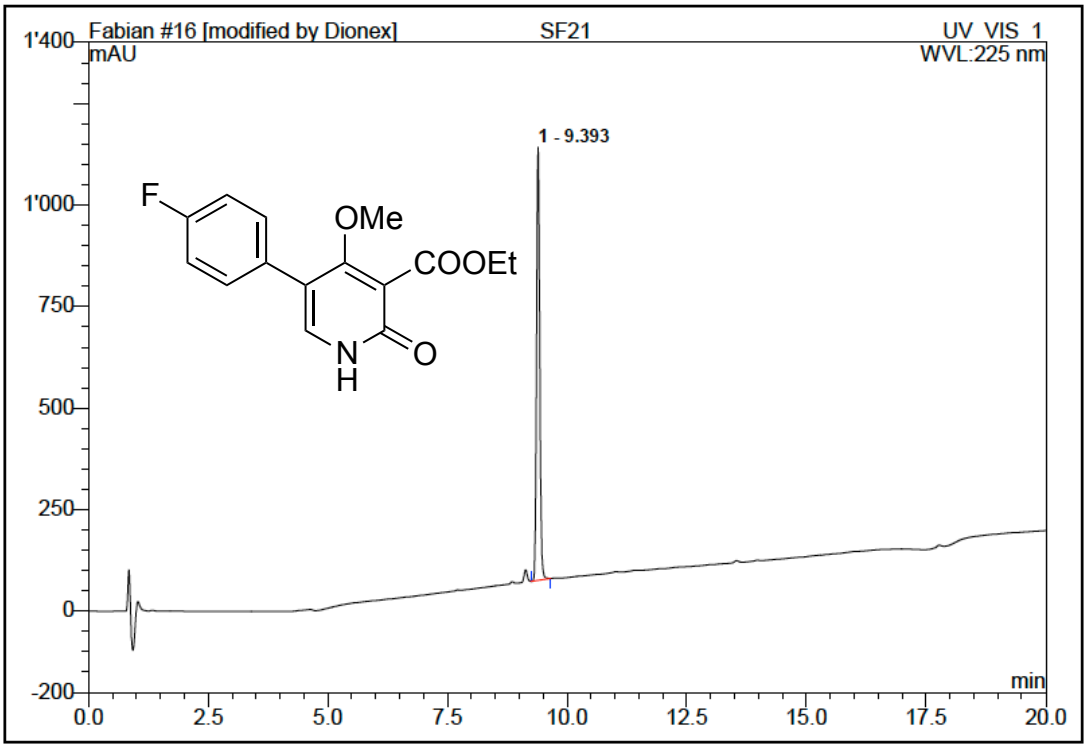
10-100% MeCN/H_2O (0.1% TFA)
in 13 min, then 5 min 100%,
1 mL/min







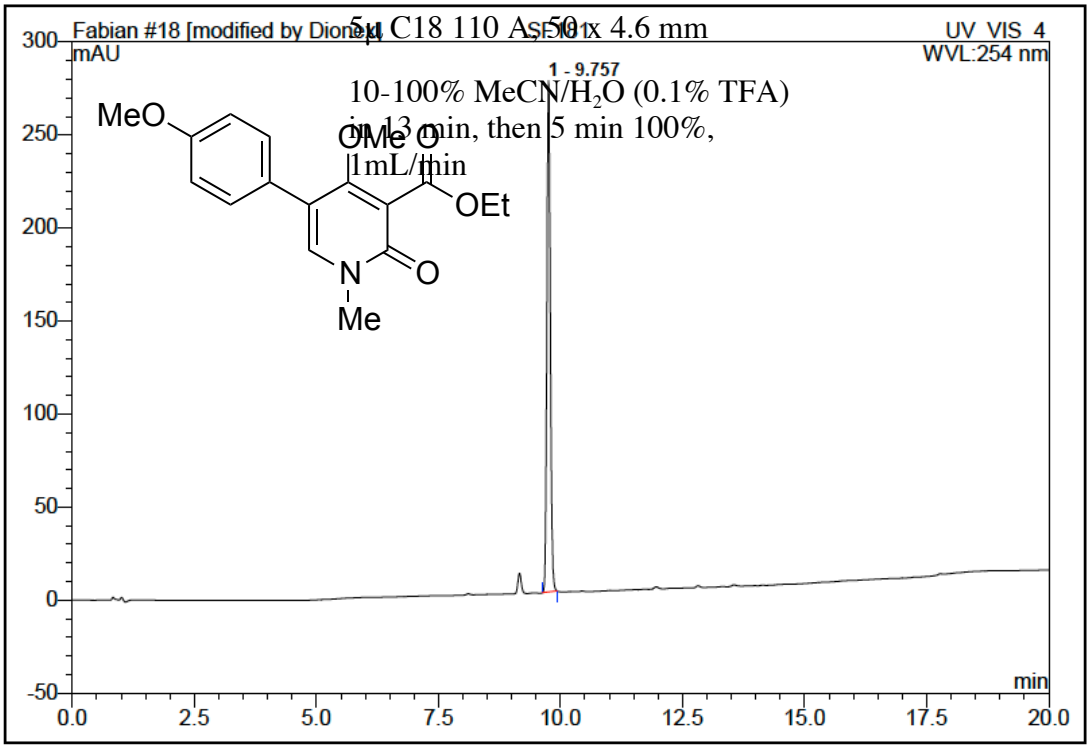
Phenomenex Gemini
5µ C18 110 A, 50 x 4.6 mm
10-100% MeCN/H_2O (0.1% TFA)
0-13 min, then 5 min 100%,
1mL/min

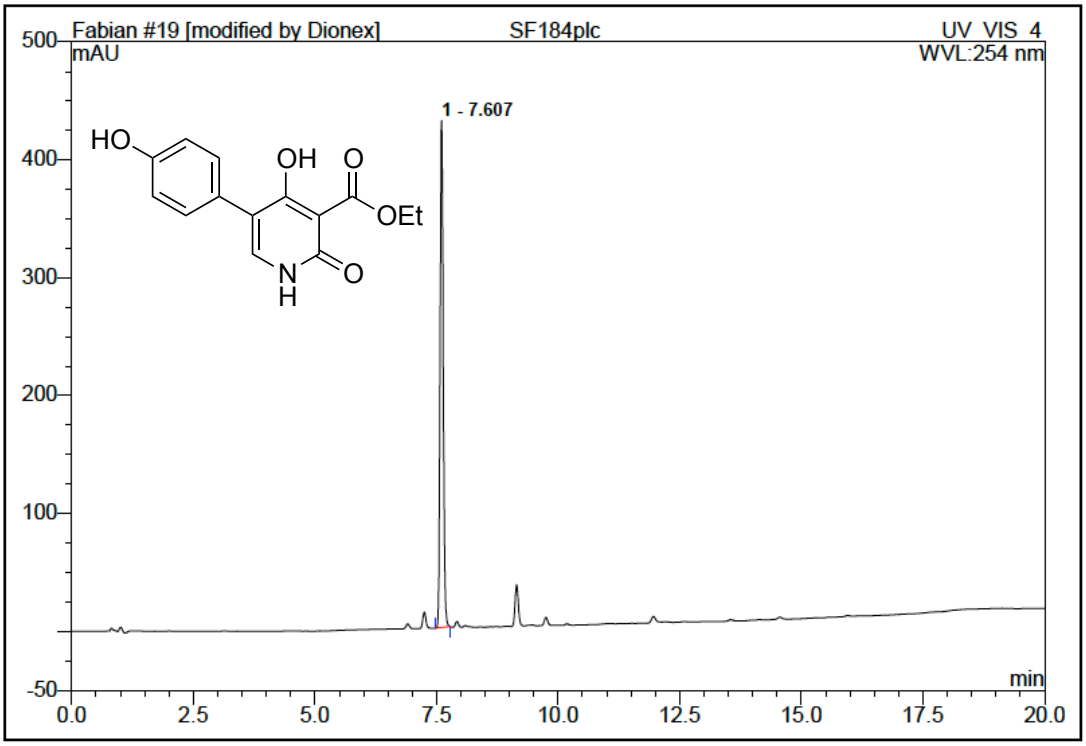


Phenomenex Gemini

5µ C18 110 A, 50 x 4.6 mm

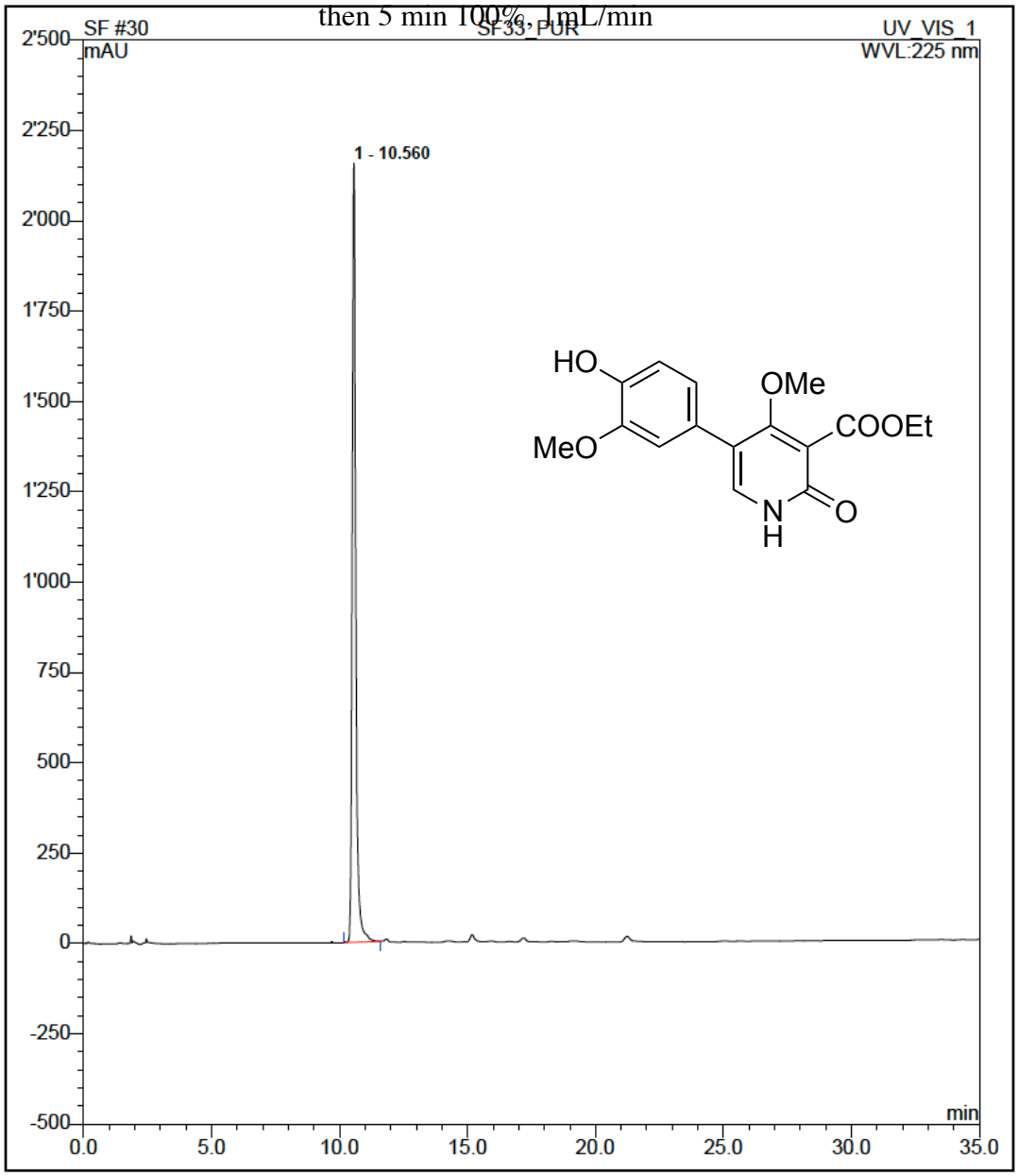
10-100% MeCN/H_2O (0.1% TFA) in 13 min, then 5 min 100%, 1mL/min

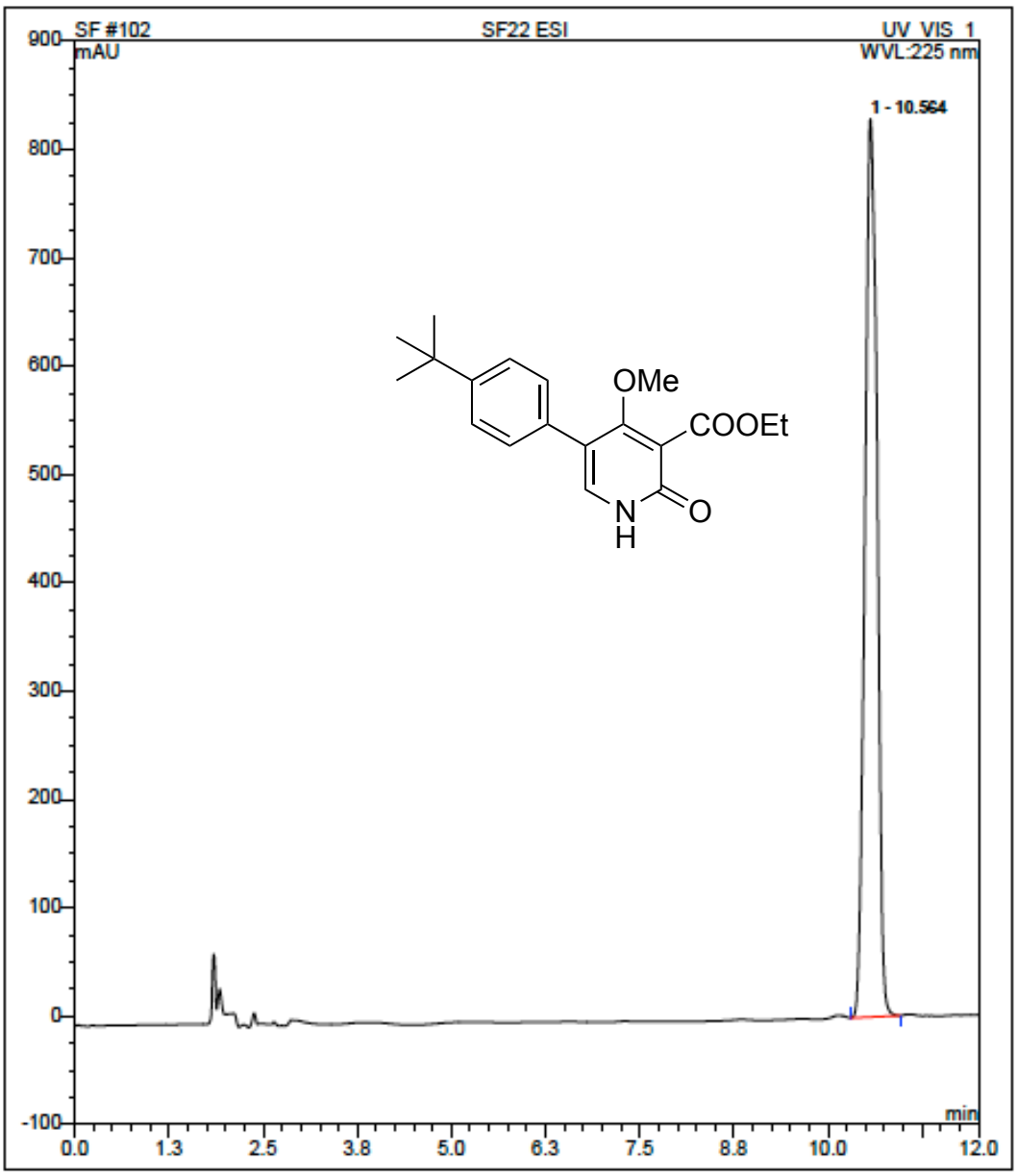


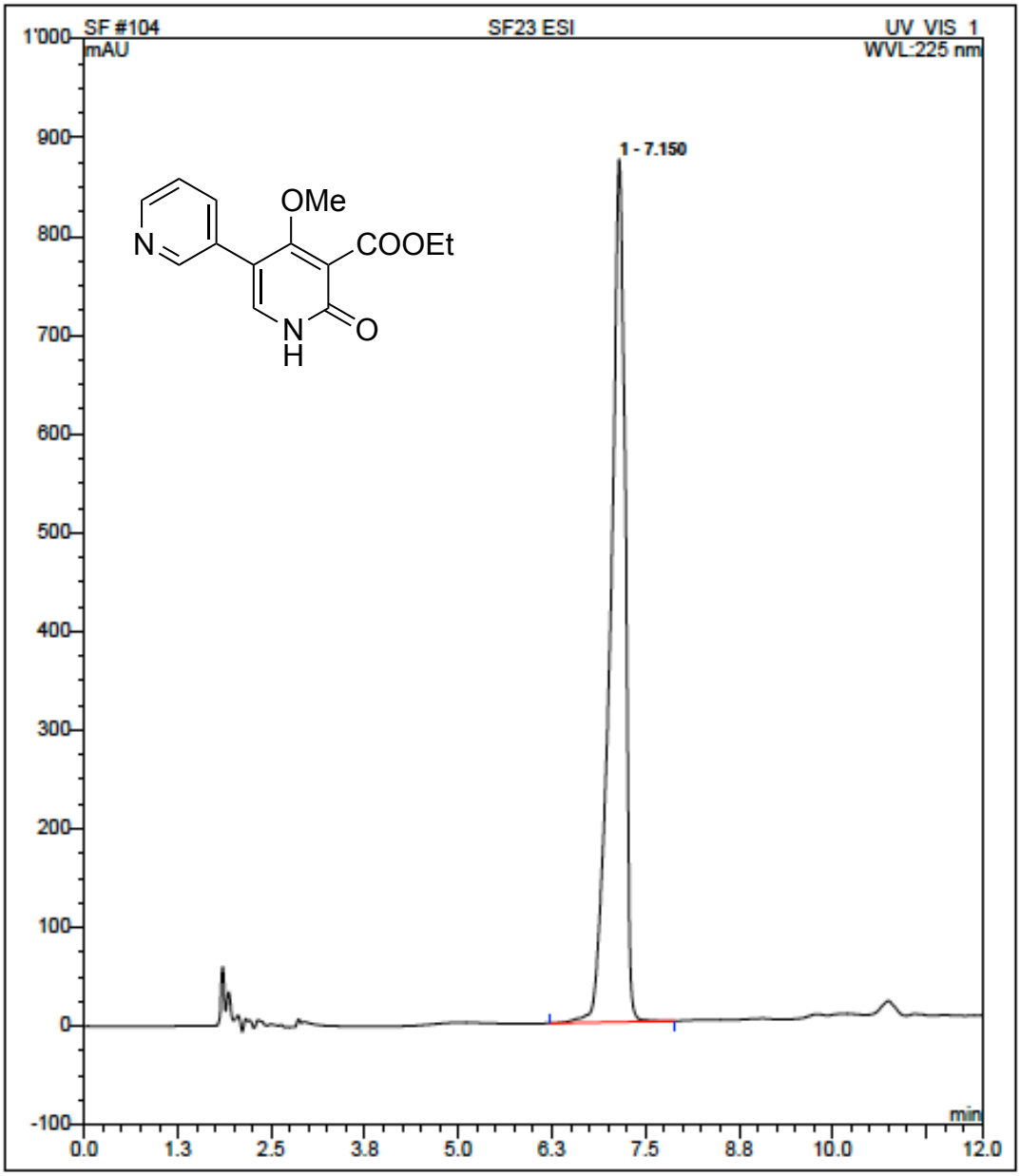


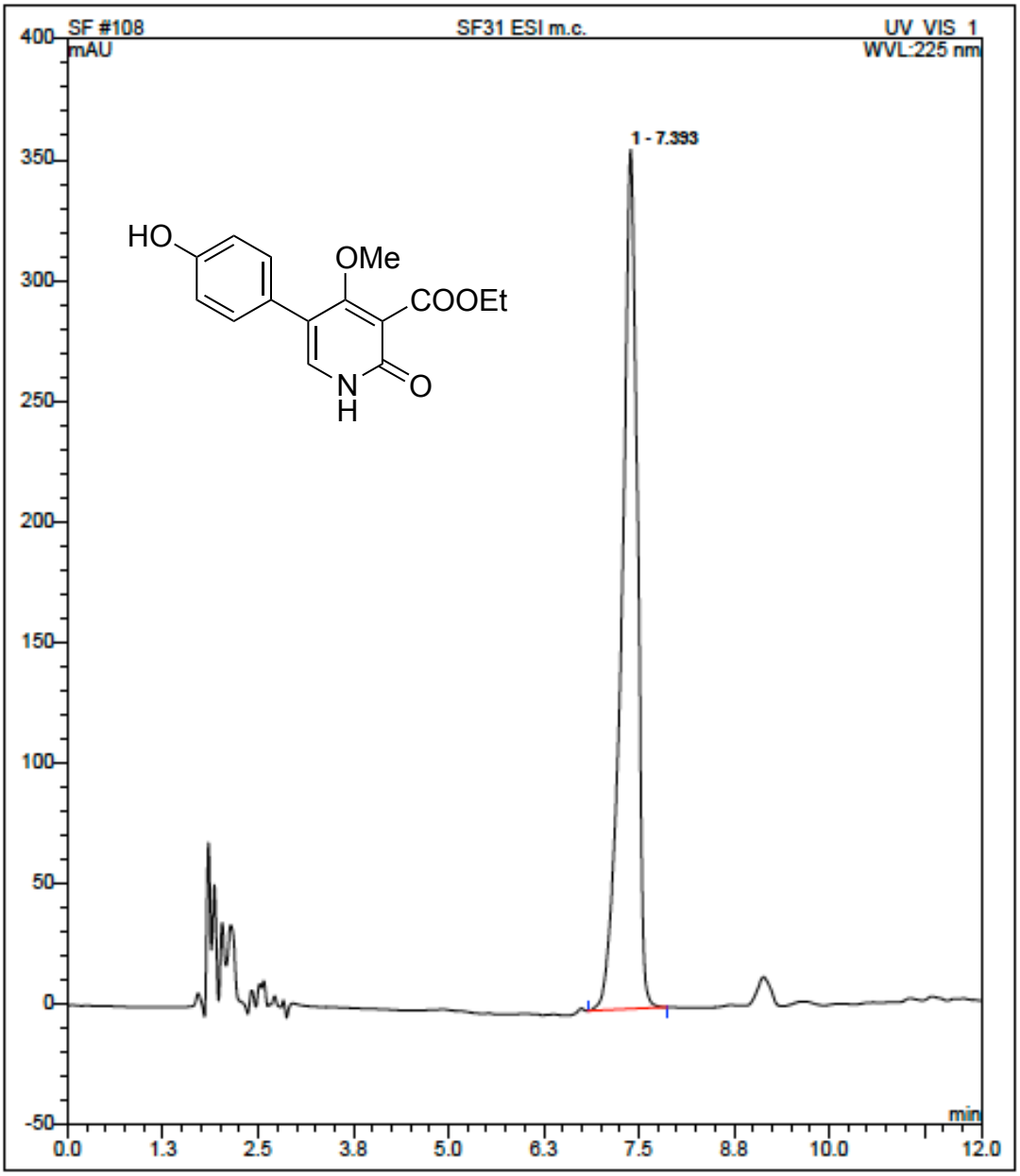
5µ C18 110 A, 250 x 4.6 mm

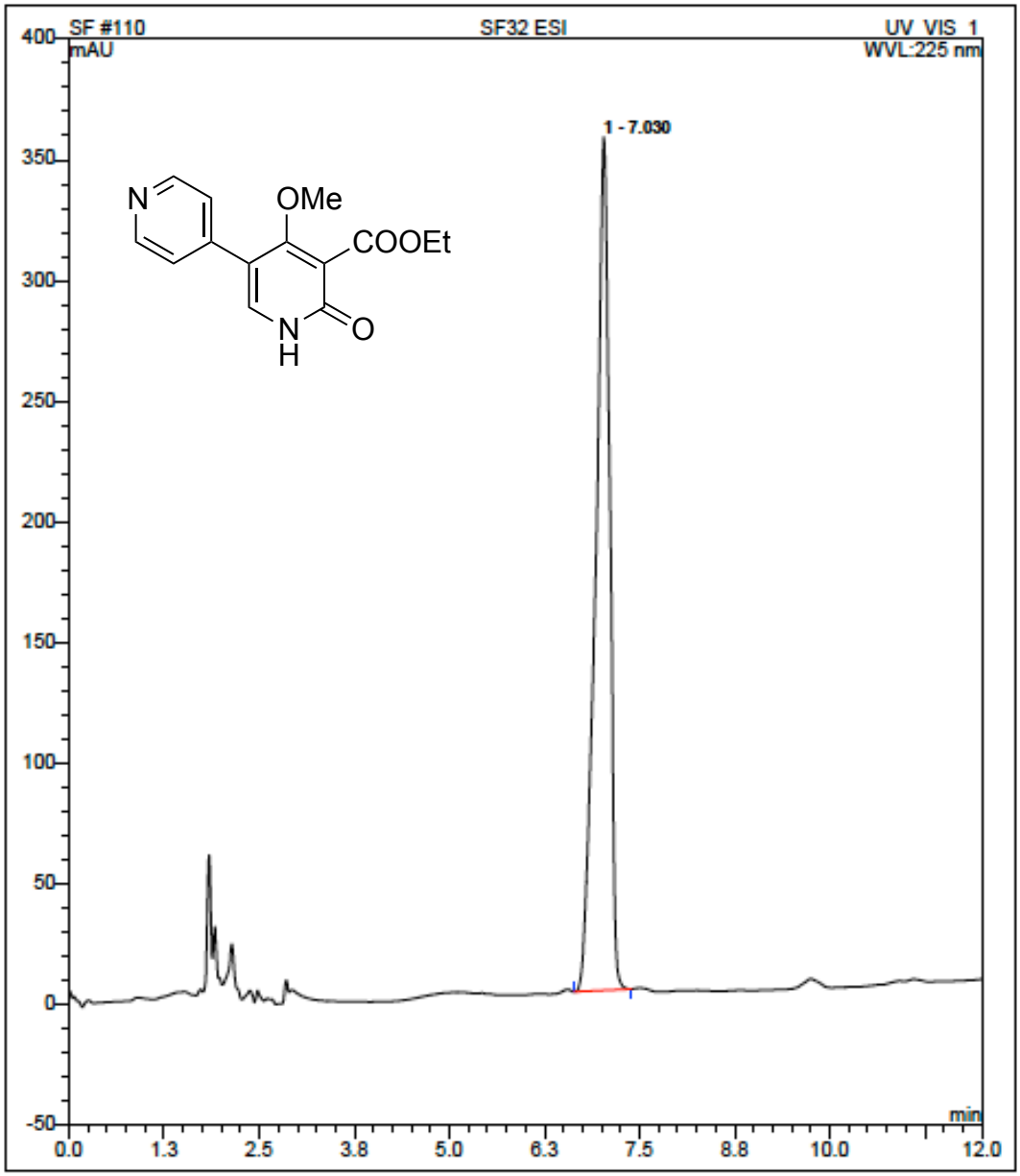
5-100% MeCN/H_2O in 30 min,
then 5 min 100%, 1mL/min

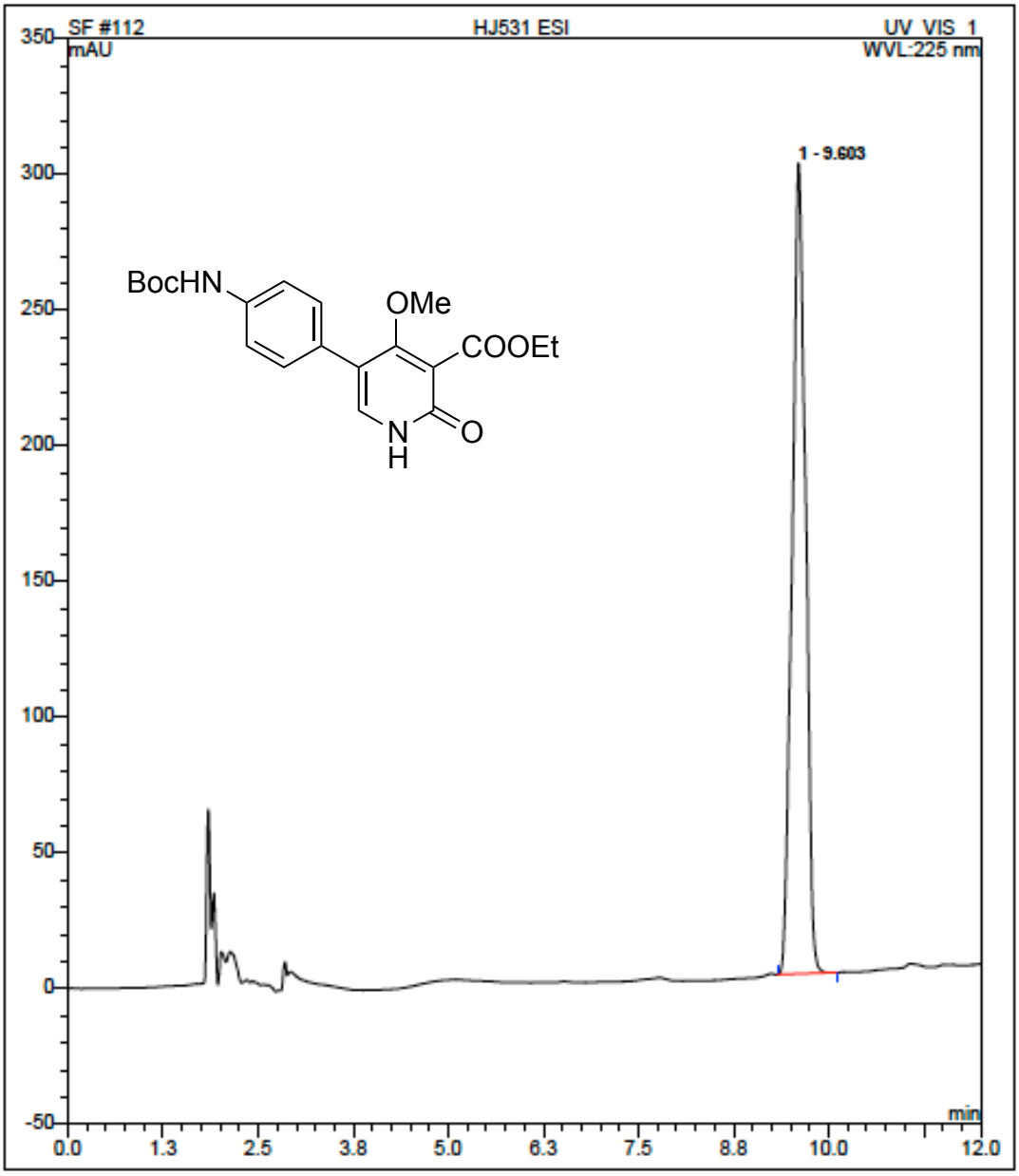


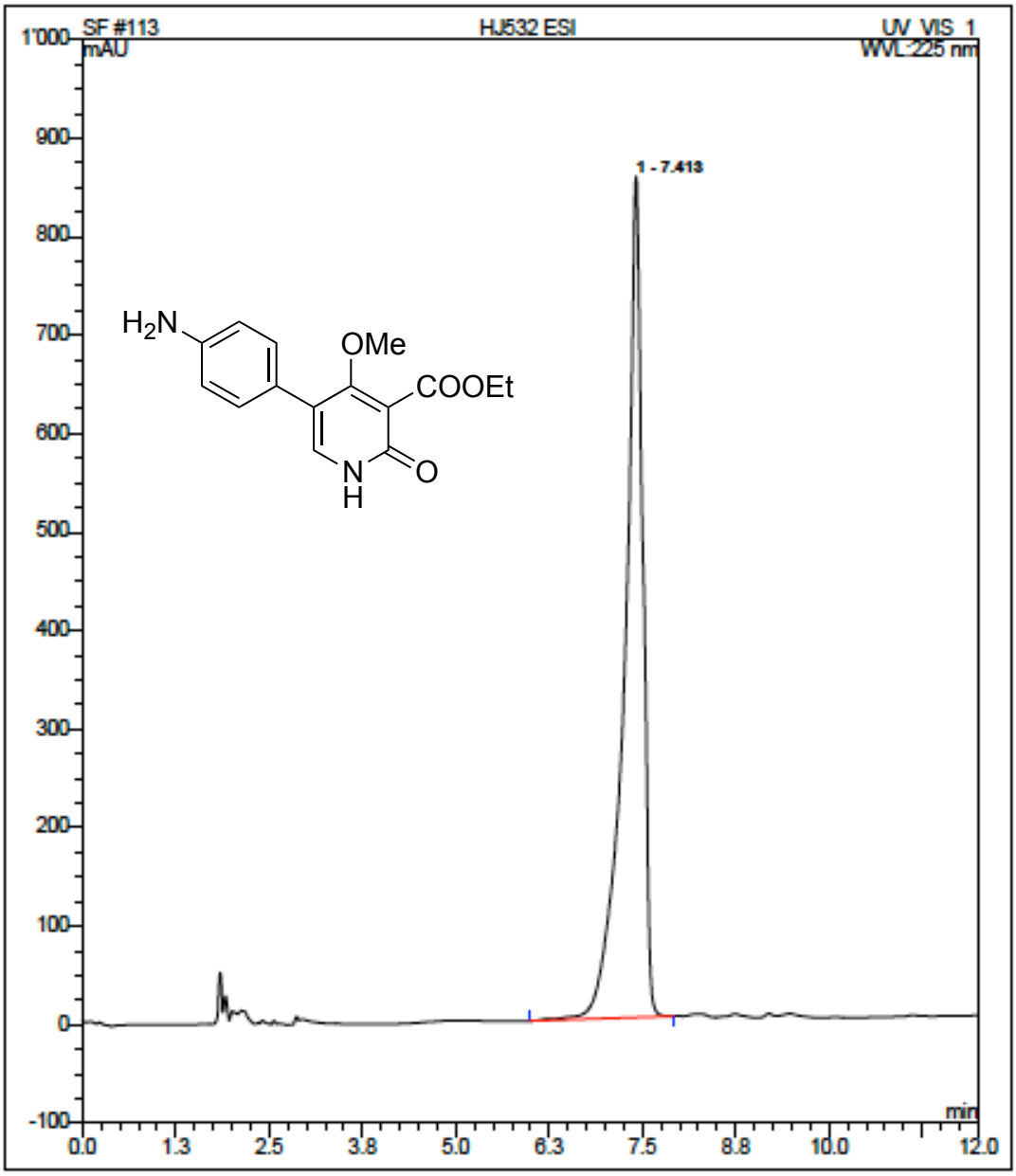

SF #102
SF22 ESI
UV_VIS_1
mAU
WVL:225 nm
1 - 10.564
900
800
700
600
500
400
300
200
100
0
-100
min
0.0
1.3
2.5
3.8
5.0
6.3
7.5
8.8
10.0
12.0
OMe
COOEt
N
H
O

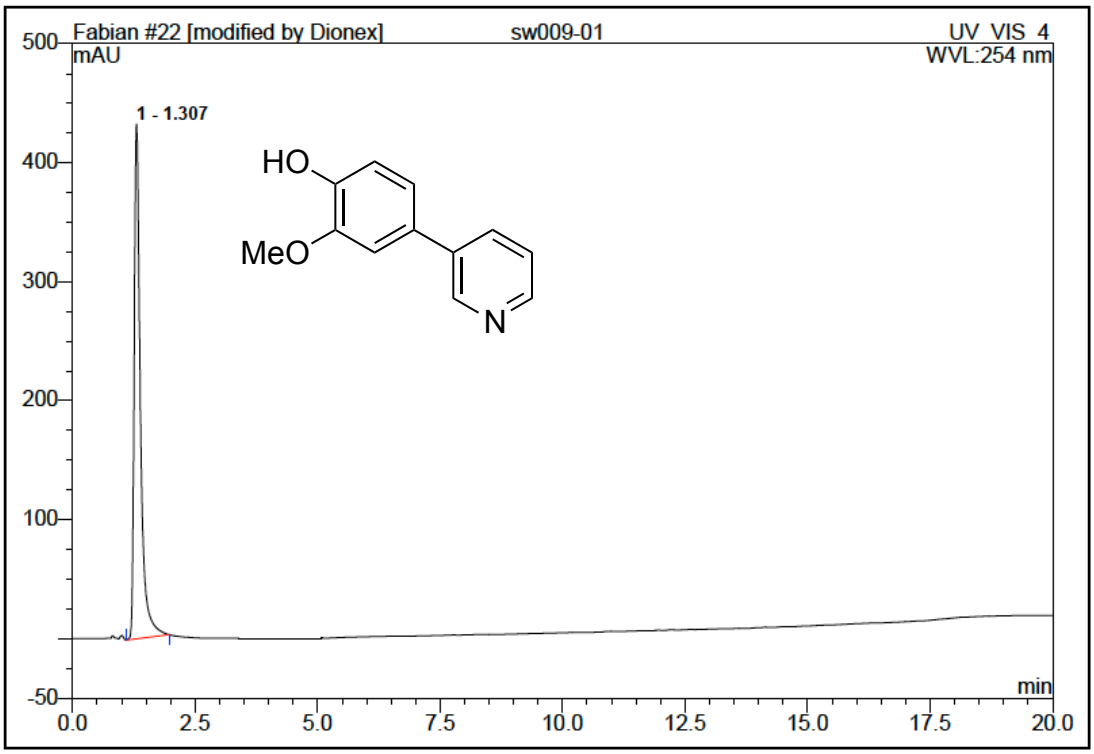





SF #110
mAU
SF32 ESI
UV_VIS_1
WVL:225 nm
1 - 7.030
OMe
COOEt
N
N
H
O
400
350
300
250
200
150
100
50
0
-50
0.0
1.3
2.5
3.8
5.0
6.3
7.5
8.8
10.0
12.0
min




SF #113
HJ532 ESI
UV_VIS_1
mAU
WVL:225 nm
1 - 7.413
H2N
OMe
COOEt
N
H
O
1'000
900
800
700
600
500
400
300
200
100
0
-100
min
0.0
1.3
2.5
3.8
5.0
6.3
7.5
8.8
10.0
12.0


Fabian #22 [modified by Dionex]
sw009-01
UV_VIS_4
mAU
WVL:254 nm
1 - 1.307
HO
MeO
N
500
400
300
200
100
-50
min
0.0
2.5
5.0
7.5
10.0
12.5
15.0
17.5
20.0