Supporting Information

Synthesis and Optimization of K_V7 (KCNQ) Potassium Channel Agonists: The Role of Fluorines in Potency and Selectivity

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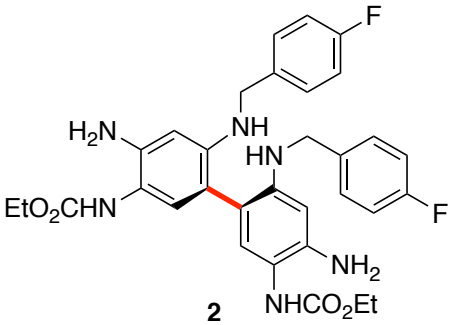
Table of Contents

General Experimental Protocols

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried glassware. Anhydrous tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Anhydrous dichloromethane, toluene and xylene were distilled from CaH_2. 1,4-dioxane, and MeOH, and MeCN were dried over 3 Å molecular sieves unless otherwise noted. Other solvents and reagents were used as obtained from commercial sources without further purification unless noted. Reactions were monitored via TLC using 250 μm pre-coated silica gel 60 F_{254} plates, which were visualized with 254 nm and/or 365 nm UV light. Flash chromatography was performed with SiliCycle silica gel 60 (230-400 mesh). ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker Avance 400, 500 or 600 MHz spectrometers, using the residual solvent as an internal standard. Melting points were obtained using a Laboratory Devices Mel-Temp II with open capillaries and are uncorrected. IR spectra were obtained on a PerkinElmer Spectrum 100 FT-IR. HRMS data were obtained on a Thermo Scientific Exactive Orbitrap LC-MS using heated electrospray ionization (HESI). X-Ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractometer. All screening samples were analyzed by LC-HRMS prior to submission, and passed purity requirements (>95% by UV/ELS detection). LC-HRMS and ELS data were obtained on a Thermo Scientific Exactive Orbitrap LC-HRMS (ESI positive ion mode) coupled to an Agilent Technologies 385-ELSD and a Thermo Scientific Accela HPLC system using a 3.5 μm Waters XTerra C18 column (2.1 x 50 mm; 10 min gradient elution with MeCN/H_2O/MeOH containing 0.1% formic acid at a flow rate of 500 μL/min from 3:92:5 at 0-0.5 min to 93:2:5 at 4.0 min, back to 3:92:5 from 6.0 to 7.5 min).

Metabolic stability in pooled human and male mouse liver microsomes, and bidirectional permeability in the MDCK-MDR1 cell line, were determined at Pharmaron.

Synthesis Procedures and Compound Characterizations



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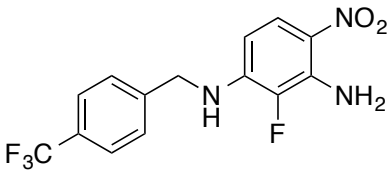
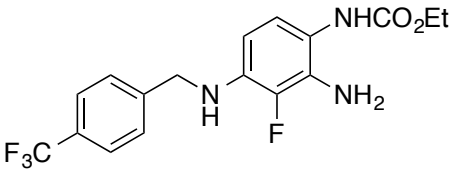
Diethyl (4,4'-diamino-6,6'-bis((4-fluorobenzyl)amino)-[1,1'-biphenyl]-3,3'-diyl)dicarbamate (2). To a solution of retigabine **1** (1.22 g, 4.02 mmol) in CH_2Cl_2 (300 mL) was added (diacetoxyiodo)benzene (0.648 g, 2.01 mmol) in one portion. The reaction mixture was stirred at room temperature for 2 h. The resulting purple solution was quenched with saturated Na_2CO_3, extracted with CH_2Cl_2 (3 x 30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1) to afford **2** as a purple solid (0.334 g, 27%). Recrystallization from CH_2Cl_2/hexanes afford a yellowish solid: Mp 180.2-184.4 °C; IR (ATR) 3355, 1699, 1623, 1509, 1224, 1062, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 (dd, 4 H, *J* = 8.3, 5.5 Hz), 6.94 (t, 4 H, *J* = 8.6 Hz), 6.81 (s, 2 H), 6.13 (brs, 2 H), 5.96 (s, 2 H), 4.21 (s, 4 H), 4.17 (q, 4 H, *J* = 7.0 Hz), 3.92 (brs, 6 H), 1.38-1.09 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9 (d, *J* = 245.1 Hz), 155.6, 145.6, 142.9, 135.2 (d, *J* = 3.0 Hz), 130.1, 128.6 (d, *J* = 8.1 Hz), 115.5 (d, *J* = 21.3 Hz), 114.6, 113.5, 99.3, 61.5, 47.5, 14.7; HRMS (HESI) *m/z* calcd for $C_{32}H_{35}N_6O_4F_2$ $[M+H]^+$ 605.2682, found 605.2682.



2-Fluoro-4-nitro-*N*^{1}-(4-(trifluoromethyl)benzyl)benzene-1,3-diamine (5a). To a stirred solution of 2,3-difluoro-6-nitroaniline **4a** (1.10 g, 6.15 mmol) in dry DMSO (6 mL) was added 4-(trifluoromethyl)benzylamine **3a** (1.00 g, 5.60 mmol) followed by Et_3N (0.94 mL, 6.71 mmol) and I_2 (28 mg, 0.11 mmol). The reaction mixture was heated to 120 °C for

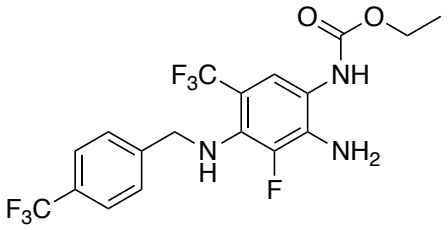
36 h, cooled to room temperature, diluted with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was recrystallized from acetone/hexanes to afford **5a** (1.20 g). The filtrate was concentrated and purified by chromatography on SiO_2 (acetone/hexanes, 1:8 to 1:4 to 1:3, containing Et_3N (1%)) to afford an additional batch of **5a** (0.34 g; total amount 1.54 g, 84%) as a yellow solid: Mp 165.4-166.7 °C; IR (ATR) 3487, 3377, 1629, 1549, 1480, 1411, 1329, 1275, 1236, 1200, 1178, 1154, 1090, 1066, 1016, 787, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, 1 H, *J* = 9.5, 1.0 Hz), 7.63 (d, 2 H, *J* = 8.0 Hz), 7.44 (d, 2 H, *J* = 8.0 Hz), 6.00-6.12 (m, 3 H), 4.94 (brs, 1 H), 4.55 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 144.2 (app d, *J* = 1.0 Hz), 141.5 (d, *J* = 9.0 Hz), 137.6 (d, *J* = 227.0 Hz), 135.8 (d, *J* = 13.0 Hz), 128.8 (q, *J* = 32.0 Hz), 127.6, 125.4 (q, *J* = 4.0 Hz), 124.5 (d, *J* = 4.0 Hz), 124.5 (q, *J* = 269.0 Hz), 122.9 (d, *J* = 2.0 Hz), 100.7 (d, *J* = 4.0 Hz), 45.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s, 3 F), -160.7 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{14}H_{12}N_3O_2F_4$ $[M+H]^+$ 330.0860, found 330.0858.



Ethyl (2-amino-3-fluoro-4-((4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-81). To a solution of **5a** (0.066 g, 0.2 mmol) in MeOH (0.5 mL) was added zinc powder (0.066 g, 1.00 mmol) followed by the dropwise addition of a solution of saturated ammonium chloride (0.19 mL). The reaction mixture was stirred vigorously at room temperature for 5 h and filtered through celite. The celite was washed with EtOAc and the aqueous solution was extracted with EtOAc (3 x 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford 3-fluoro-N^4-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine as a dark red solid that was used in the next step without further purification.

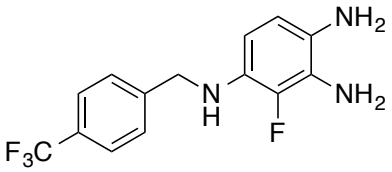
An oven-dried 5-mL round bottomed flask equipped with a magnetic stir bar under argon was charged at 0 °C with 3-fluoro-N^4-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine, CH_2Cl_2 (1 mL) and DIPEA (0.043 mL, 0.25 mmol). Ethyl chloroformate (0.02 mL, 0.20 mmol) was added dropwise via syringe at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and

then for 3 h at room temperature, quenched with water, and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4 to 2:3) to afford a dark red solid that was recrystallized (CH_2Cl_2/hexanes) to give **RL-81** (0.035 g, 47%) as colorless crystals: Mp 171.4-172.2 °C; IR (ATR) 3400, 3338, 3299, 1676, 1644, 1618, 1528, 1489, 1478, 1443, 1323, 1249, 1158, 1113, 1103, 826, 781, 775, 768, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, *J* = 8.0 Hz), 7.46 (d, 2 H, *J* = 8.0 Hz), 6.73 (d, 1 H, *J* = 8.4 Hz), 6.13 (br s, 1 H), 5.99 (t, 1 H, *J* = 8.8 Hz), 4.42 (s, 2 H), 4.33 (br s, 1 H), 4.19 (q, 2 H, *J* = 7.2 Hz), 3.86 (br s, 2 H), 1.29 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 156.0, 146.4, 141.7 (d, J = 227.7 Hz), 135.4, 132.5, 129.3 (q, *J* = 32.0 Hz), 128.5, 126.1 (q, *J* = 3.9 Hz), 125.5 (q, *J* = 271.0 Hz), 122.3, 116.4, 101.3, 61.2, 47.4, 15.0; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.5 (s, 3 F), -156.1 (s ,1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{18}N_3O_2F_4$ $[M+H]^+$ 372.1330, found 372.1327.

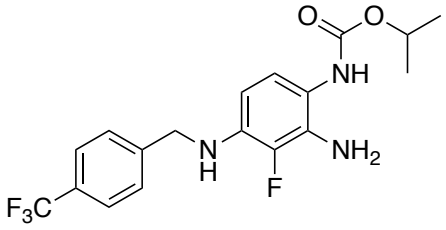


Ethyl (2-amino-3-fluoro-5-(trifluoromethyl)-4-((4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-073). To an oven dried microwave vial fitted with a stir bar was added 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one **6** (0.332 g, 1.05 mmol) and **RL-81** (0.260 g, 0.700 mmol). The vial was evacuated and filled with N_2 (3x), followed by dry CH_3CN (14 mL). The reaction mixture was stirred for 5 h at 85 °C, concentrated in vacuo, and diluted with EtOAc and saturated Na_2CO_3. The aqueous layer was extracted with EtOAc (3 x 5 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4 to 3:7, containing Et_3N(1%)) to afford a yellow oil that was purified by another chromatography on SiO_2 (20 %-25% EtOAc/hexanes, 1:4 to 1:3, containing Et_3N (1%)). A third chromatography on SiO_2 (EtOAc/hexanes, 1:4, containing Et_3N (1%)) of slightly less pure fractions provided an additional batch of product, and the combined fractions were recrystallized from CH_2Cl_2/hexanes to afford **RL-073** (0.052 g, 17%) as a white solid: Mp 107.8 -108.6 °C; IR

(ATR) 3371, 2986, 1703, 1642, 1492, 1324, 1225, 1158, 1108, 1066 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, 2 H, *J* = 8.0 Hz), 7.47 (d, 2 H, *J* = 8.0 Hz), 7.10 (s, 1 H), 6.09 (brs, 1 H), 4.55 (s, 2 H), 4.21 (q, 2 H ,*J* = 7.0 Hz), 4.14 (br s, 3 H), 1.30 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.4, 143.8, 142.8 (d, *J* = 232.6 Hz), 135.8, 133.1 (d, *J* = 9.0 Hz), 129.7 (q, *J* = 32.3 Hz), 127.8, 125.7-125.5 (m), 124.7 (qd, *J* = 269.2, 4.2 Hz), 124.3 (q, *J* = 272.0 Hz) , 120.0, 115.4, 107.6 (d, *J* = 25.8 Hz), 62.0, 50.8 (d, *J* = 9.5 Hz), 14.5; ^{19}F NMR (471 MHz, $CDCl_3$) δ -59.3 (s, 3 F), -62.5 (s, 3 F), -146.1 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{18}H_{17}N_3O_2F_7$ $[M+H]^+$ 440.1204, found 440.1195.

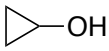


3-Fluoro-*N*^{4}-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine. To a stirred solution of **5a** (0.50 g, 1.52 mmol) in EtOH (5 mL) was added 10% Pd/C (0.082 g, 0.076 mmol) under N_2. The reaction mixture was stirred at room temperature for 4 h under a hydrogen atmosphere (H_2 balloon), and filtered through Celite. The filter cake was washed with CH_2Cl_2, and the combined liquid layers were concentrated in vacuo to afford crude 3-fluoro-*N*^{4}-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.39 g, 86%) as a red solid that was directly used for the next step: ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, *J* = 8.0 Hz), 7.47 (d, 2 H, *J* = 8.0 Hz), 6.35 (dd, 1 H, *J* = 8.4, 2.0 Hz), 5.96 (app t, 1 H, *J* = 8.4 Hz), 4.38 (s, 2 H), 4.01 (br s, 1 H), 3.51 (br s, 2 H), 3.06 (br s, 2 H).



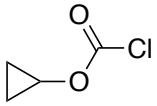
Isopropyl (2-amino-3-fluoro-4-((4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-32). A solution of 3-fluoro-*N*^{4}-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.15 g, 0.50 mmol) in CH_2Cl_2 (10 mL) under argon was charged at 0 °C with diisopropylethylamine (0.10 mL, 0.55 mmol) and

dropwise with a solution of isopropyl chloroformate (1 M in toluene, 0.045 mL, 0.45 mmol). The reaction mixture was stirred for 4 h at 0 °C, and quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 1:1, containing Et_3N (1%)) to afford **RL-32** as a light yellow solid (0.14 g, 73%). Recrystallization from CH_2Cl_2/hexanes afforded **RL-32** (0.102 g) as a colorless solid: Mp 199.6-200.0 °C; IR (ATR) 3415, 3357, 3305, 1679, 1525, 1519, 1478, 1325, 1260, 1158, 1124, 1107, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, *J* = 8.0 Hz), 7.46 (d, 2 H, *J* = 8.4 Hz), 6.73 (d, 1 H, *J* = 8.8 Hz), 6.08 (br s, 1 H), 5.99 (t, 1 H, *J* = 8.8 Hz), 4.97 (sept, 1 H, *J* = 6.0 Hz), 4.43 (d, 2 H, *J* = 5.6 Hz), 4.32 (br s, 1 H), 3.88 (br s, 2 H), 1.28 (d, 6 H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 143.6, 141.4 (d, *J* = 223.0 Hz), 134.9 (d, *J* = 10.0 Hz), 130.8, 129.7 (q, *J* = 32.0 Hz), 127.4, 125.7 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 270.0 Hz), 121.7, 115.6, 101.9, 69.2, 47.5, 22.2; ^{19}F NMR (376 MHz , $CDCl_3$) δ -62.4 (s, 3F), -156.1 (s, 1F); HRMS (HESI) *m/z* calcd for $C_{18}H_{20}N_3O_2F_4$ $[M+H]^+$ 386.1484, found 386.1484.

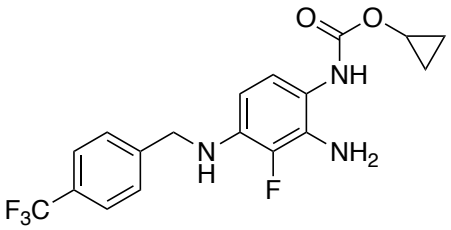


Cyclopropanol.[1] A suspension of cyclopropyl boronic acid (1.00 g, 11.6 mol) in water (8 mL) was treated at 0 °C with NaOH (1.02 g, 25.6 mmol), and stirred for 5 min until a homogeneous solution formed. A solution of 30% aqueous H_2O_2 (6.54 mL, 64.0 mmol) was added dropwise, and stirring was continued for 3 h at 0 °C. The reaction mixture was extracted with Et_2O (3 x 5 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo at 0 °C to afford cyclopropanol (0.36 g, 53%) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 3.52-3.48 (m, 1 H), 0.57-0.46 (m, 4 H). The compound was dissolved in dry CH_2Cl_2 (10 mL) and stored refrigerated over 4 Å molecular sieves for 1 d before usage.

[1] Riggs, J. R.; Nagy, M.; Elsner, J.; Erdman, P.; Cashion, D.; Robinson, D.; Harris, R.; Huang, D.; Tehrani, L.; Deyanat-Yazdi, G.; Narla, R. K.; Peng, X.; Tran, T.; Barnes, L.; Miller, T.; Katz, J.; Tang, Y.; Chen, M.; Moghaddam, M. F.; Bahmanyar, S.; Pagarigan, B.; Delker, S.; LeBrun, L.; Chamberlain, P. P.; Calabrese, A.; Canan, S. S.; Leftheris, K.; Zhu, D.; Boylan, J. F. "The Discovery of a Dual Ttk Protein Kinase/Cdc2-Like Kinase (Clk2) Inhibitor for the Treatment of Triple Negative Breast Cancer Initiated from a Phenotypic Screen." *J. Med. Chem.* **2017**, *60*(21), 8989-9002.



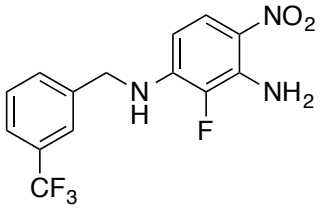
Cyclopropyl carbonochloridate.[2] A solution of cyclopropanol (0.060 g, 1.03 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C, treated with K_2CO_3 (0.43 g, 3.10 mmol) followed by phosgene (20% wt in toluene, 0.54 mL, 1.03 mmol), and stirred vigorously overnight at 0 °C to room temperature. Unreacted phosgene was removed by purging the solution for 30 min with N_2 gas which was then passed through an aqueous KOH trap. The reaction mixture was filtered through anhydrous $MgSO_4$, and concentrated at 0 °C to afford cyclopropyl chloroformate as a colorless oil (~0.3 mL) that was used directly as a toluene solution for the next step (cyclopropyl chloroformate/cyclopropanol = 1:0.19, theoretical concentration = 2.8 M). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41-3.36 (m, 1 H), 0.98-0.82 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 56.2, 5.49.



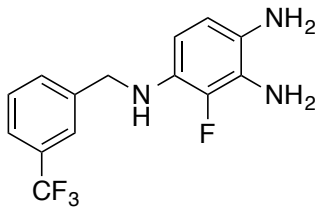
Cyclopropyl (2-amino-3-fluoro-4-((4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-56). A solution of 3-fluoro-*N*^{4}-(4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.07 g, 0.23 mmol) in CH_2Cl_2 (2.5 mL) was treated with diisopropylethylamine (0.045 mL, 0.26 mmol), cooled 0 °C and treated dropwise with cyclopropyl chloroformate (~ 2.8 M in toluene, 0.075 mL). The resulting mixture was stirred overnight at 0 °C to rt. After addition of water, the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by chromatography on SiO_2 (hexanes/EtOAc, 5:1 to 2:1) to afford **RL-56** (0.042 g, 47%) as a light yellow solid: Mp 175.1 - 175.6 °C; IR (ATR) 3314, 2937, 1696, 1523, 1327, 1258, 1163, 1117, 1103, 1066, 826, 764, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, *J* = 8.4 Hz), 7.46 (d, 2 H, *J* = 8.0 Hz), 6.72 (d, 1 H, *J* = 7.6 Hz), 6.15 (br s, 1 H), 5.99 (t, 1 H, *J* = 8.8 Hz), 4.42 (d, 2 H, *J* = 5.6 Hz), 4.33 (brs,

[2] Grabowska, U.; Joensson, D.; Klasson, B.; Wiktelius, D.: Medivir UK Ltd. "Preparation of Cycloalkyl Pyrazole and Imidazole Compounds as Cysteine Protease Inhibitors for Therapy." WO 2012172473 A1 20121220.

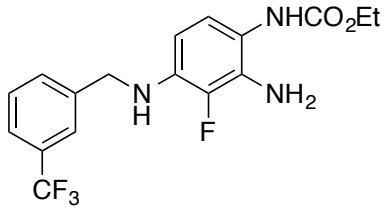
1 H), 4.15-4.10 (m, 1 H), 3.85 (brs, 2 H), 0.72-0.70 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 143.5, 141.3 (d, *J* = 230.0 Hz), 135.0 (d, *J* = 9.0 Hz), 130.8, 129.7 (q, *J* = 32.0 Hz), 127.4, 125.7 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 271.0 Hz), 121.6, 115.2, 101.9, 49.9, 47.5, 5.2; ^{19}F NMR (376 MHz , $CDCl_3$) δ -62.4 (s, 3 F), -156.0 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{18}H_{18}N_3O_2F_4$ [M+H] 384.1330, found 384.1329.



2-Fluoro-4-nitro-*N*^{1}-(3-(trifluoromethyl)benzyl)benzene-1,3-diamine (5b). To a stirred solution of 2,3-difluoro-6-nitroaniline **4a** (0.200 g, 1.11 mmol) in dry DMSO (4.6 mL) were added 3-(trifluoromethyl)benzylamine **3b** (0.195 mL, 1.34 mmol) followed by Et_3N (0.135 g, 1.34 mmol) and I_2 (cat. 2 mg). The reaction mixture was heated to 120 °C for 24 h, cooled to room temperature, diluted with water (25 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:10 to 1:4 to 1:3) to afford **5b** as a yellow solid (0.280 g, 76%): Mp 156.0-157.2 °C; IR (ATR) 3495, 3383, 1627, 1480, 1411, 1275, 1251, 1120, 1070, 798 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, 1 H, *J* = 9.6, 1.6 Hz), 7.59-7.57 (m, 2 H), 7.54-7.47 (m, 2 H), 6.15-6.00 (m, 3 H), 4.93 (brs, 1 H), 4.54 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9 (d, *J* = 9.5 Hz), 138.9, 138.0 (d, *J* = 228.6 Hz), 135.2 (d, *J* = 12.9 Hz), 131.5 (q, *J* = 32.5 Hz), 130.5, 129.6, 125.6 (d, *J* = 3.5 Hz), 124.9 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 272.4 Hz), 124.0 (q, *J* = 3.7 Hz), 123.7 (d, *J* = 2.9 Hz), 100.7 (d, *J* = 2.9 Hz), 46.8; ^{19}F NMR (471 MHz , $CDCl_3$) δ -62.7 (s, 3 F), -160.6 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{14}H_{12}N_3O_2F_4$ $[M+H]^+$ 330.0860, found 330.0858.

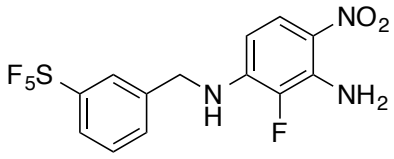


3-Fluoro-*N*^{4}-(3-(trifluoromethyl)benzyl)benzene-1,2,4-triamine. To a stirred solution of **5b** (0.280 g, 0.85 mmol) in MeOH (2 mL) was added zinc powder (0.278 g, 4.25 mmol) followed by the dropwise addition of a solution of saturated aqueous ammonium chloride (0.80 mL). The reaction mixture was stirred vigorously at room temperature overnight, diluted with EtOAc (2 mL) and water (1 mL), and filtered through a pad of Celite. The Celite was washed with EtOAc and the solution was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford crude 3-fluoro-*N*^{4}-(3-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.190 g, 75%) as a dark red solid that was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1 H), 7.56 (d, 1 H, *J* = 7.6 Hz), 7.52 (d, 1 H, *J* = 7.6 Hz), 7.44 (t, 1 H, *J* = 7.6 Hz), 6.37 (dd, 1 H, *J* = 8.4, 2.0 Hz), 5.99 (t, 1 H, *J* = 8.8 Hz), 4.36 (s, 2 H), 3.98 (brs, 1 H), 3.52 (brs, 2 H), 3.10 (brs, 2 H); ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.5 (s, 3 F), -155.8 (s, 1 F).

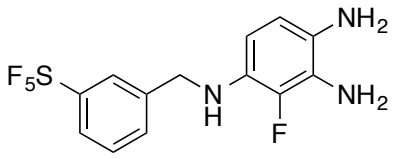


Ethyl (2-amino-3-fluoro-4-((3-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-73). A solution of 3-fluoro-*N*^{4}-(3-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.060 g, 0.20 mmol) under argon in CH_2Cl_2 (1 mL) was charged at 0 °C with diisopropylethylamine (0.043 mL, 0.25 mmol) and dropwise ethyl chloroformate (0.02 mL, 0.20 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and for 3 h at room temperature, then quenched by addition of water. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4 to 2:3) to afford **RL-73** (0.045 g, 60%) as a dark red solid. Recrystallization from CH_2Cl_2/hexanes gave colorless crystals: Mp 129.3-129.7 °C; IR (ATR) 3406, 3290, 1676, 1452, 1329, 1246, 1160, 1113, 1072, 915, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1 H), 7.57-7.51 (m, 2 H), 7.45 (t, 1 H, *J* = 7.6 Hz), 6.74 (dd, 1 H, *J* = 8.4, 1.2 Hz), 6.11 (br s, 1 H), 6.02 (t, 1 H, *J* = 8.8 Hz), 4.41 (d, 2 H, *J* = 5.2 Hz), 4.30 (brs, 1 H), 4.20 (q, 2 H, *J* = 7.2 Hz), 3.86 (brs, 2 H), 1.28 (t, 3 H, *J* = 7.2

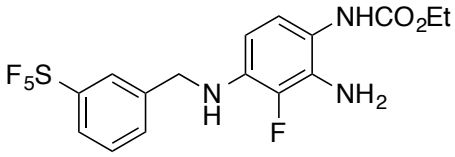
Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 156.0, 143.1, 141.8 (d, *J* = 227.9 Hz), 135.5 (d, *J* = 9.7 Hz), 132.4, 131.8, 130.9 (q, *J* = 31.8 Hz), 130.1, 125.5 (q, *J* = 271.5 Hz), 124.5 (q, *J* = 3.9 Hz), 124.3 (q, *J* = 3.9 Hz), 122.3, 116.5, 101.3, 61.2, 47.4, 15.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6 (s, 3 F), -155.5 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{18}N_3O_2F_4$ $[M+H]^+$ 372.1330, found 372.1328.



2-Fluoro-4-nitro-*N*^{1}-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,3-diamine (5c). A suspension of 2,3-difluoro-6-nitroaniline **4a** (0.500 g, 2.78 mmol) in dry DMSO (5 mL) was treated with 3-(pentafluorosulfanyl)benzylamine **3c** (0. 714 g, 3.06 mmol) followed by Et_3N (0.43 mL, 3.06 mmol) and I_2 (cat. 5 mg). The reaction mixture was heated to 120 °C for 24 h, cooled to room temperature, diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was treated with a small amount of Et_2O (2 mL), sonicated, and filtered, and the filter cake was again washed with Et_2O (3 x 3 mL) to afford **5c** (0.51 g) as a yellow solid. The filtrate was concentrated in vacuo and the residue was purified by chromatography on SiO_2 (acetone/hexanes, 1:10 to 1:4 to 1:3) to afford additional **5c** (0.17 g). The fractions were combined to afford **5c** (0.68 g, 63%) as a yellow solid: Mp 169.5-170.0 °C; IR (ATR) 3495, 3385, 1631, 1549, 1482, 1413, 1286, 1273, 1240, 1206, 1176, 1141, 1105, 1087, 891, 859, 820, 796, 775, 751, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, 1 H, *J* = 9.6, 1.6 Hz), 7.72-7.68 (m, 2 H), 7.50-7.46 (m, 2 H), 6.07 (brs, 2 H), 6.02 (dd, 1 H, *J* = 9.6, 8.0 Hz), 5.00 (brs, 1 H), 4.54 (d, 2 H, *J* =1.5 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 154.8 (app t, *J* = 16.0 Hz), 142.2 (d, *J* = 9.0 Hz), 142.2, 138.5 (d, *J* = 228.0 Hz), 136.7 (d, *J* = 13.0 Hz), 131.6, 130.4, 125.7-125.4 (m), 125.5 (d, *J* = 5.0 Hz), 125.3 (app t, *J* = 5.0 Hz), 123.8 (d, *J* = 2.0 Hz), 101.6 (d, *J* = 3.0 Hz), 46.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ 84.0 (quint, 1 F, *J* = 150.4 Hz), 62.7 (d, 4 F, *J* = 150.4 Hz), -160.4 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{13}H_{12}N_3O_2F_2S$ $[M+H]^+$ 388.0549, found 388.0549.

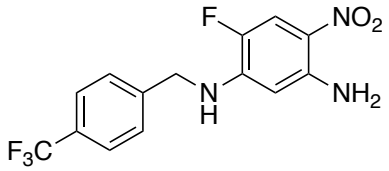


3-Fluoro-*N*^{4}-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,2,4-triamine. A solution of **5c** (0.500 g, 1.29 mmol) in MeOH (4 mL) was treated with zinc powder (0.422 g, 6.45 mmol) followed by dropwise addition of an aqueous solution of saturated ammonium chloride (1.22 mL). The reaction mixture was stirred vigorously at room temperature overnight, and filtered through Celite. The Celite was washed (EtOAc), and the filtrate was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure to afford 3-fluoro-*N*^{4}-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,2,4-triamine (0.390 g, 85%) as a red solid that was used in the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1 H), 7.64 (d, 1 H, *J* = 8.4 Hz), 7.51 (d, 1 H, *J* =7.6 Hz), 7.41 (t, 1 H, *J* = 8.0 Hz), 6.39 (d, 1 H, *J* = 7.6 Hz), 5.98 (t, 1 H, *J* = 8.4 Hz), 4.35 (s, 2 H), 3.32 (br, 5 H).

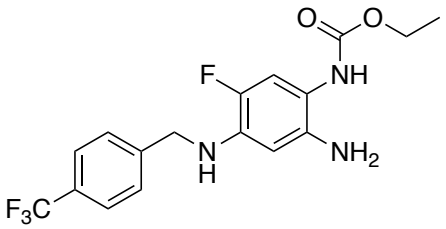


Ethyl (2-amino-3-fluoro-4-((3-(pentafluoro-λ^6-sulfanyl)benzyl)amino)phenyl)carbamate (RL-02). A solution of 3-fluoro-*N*^{4}-(3-(pentafluoro-λ^6-sulfanyl)benzyl)benzene-1,2,4-triamine (0.20 g, 0.56 mmol) in CH_2Cl_2 (3 mL) was treated under argon at 0 °C with diisopropylethylamine (0.12 mL, 0.7 mmol), followed by the dropwise addition of ethyl chloroformate (0.055 mL, 0.56 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, then for 3 h at room temperature, quenched with water and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:3 to 2:3) to afford yellow solid that was recrystallized from CH_2Cl_2/hexanes to afford **RL-02** (0.123 g, 44%) as a colorless solid: Mp 141.3-142.1 °C; IR (ATR) 3420, 3375, 2986, 1689, 1637, 1525, 1484, 1288, 1254, 1241, 829, 816, 787, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1 H), 7.65 (d, 1 H, *J* = 8.0 Hz), 7.50 (d, 1 H, *J* = 7.6 Hz),

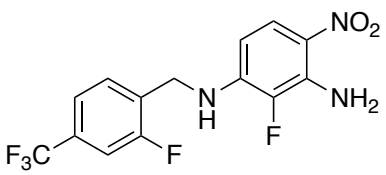
7.42 (t, 1 H, *J* = 8.0 Hz), 6.74 (d, 1 H, *J* = 7.6 Hz), 6.24 (brs, 1 H), 6.00 (t, 1 H, *J* = 8.8 Hz), 4.40 (s, 2 H), 4.19 (q, 2 H, *J* = 7.2 Hz), 3.98 (brs, 3 H), 1.28 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 154.4 (quint, *J* = 17.0 Hz), 141.3 (d, *J* = 232.0 Hz), 140.7, 134.7 (d, *J* = 9.0 Hz), 130.9, 130.3, 129.2, 125.0 (app t, *J* = 5.0 Hz), 124.8 (quint, *J* = 5.0 Hz), 121.7, 115.6, 101.9, 61.7, 47.6, 14.6; ^{19}F NMR (565 MHz, $CDCl_3$) δ 84.5 (quint, 1 F, *J* = 146.9 Hz), 62.8 (d, 4 F, *J* = 146.9 Hz), -155.8 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{16}H_{18}N_3O_2F_6S$ $[M+H]^+$ 430.1018, found 430.1015.



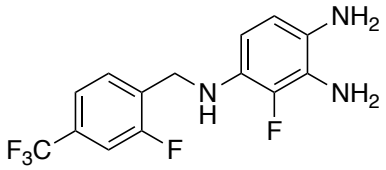
6-Fluoro-4-nitro-*N*^{1}-(4-(trifluoromethyl)benzyl)benzene-1,3-diamine (5d). A 30-mL microwave vial equipped with a magnetic stir bar was charged with 4,5-difluoro-2-nitroaniline **4b** (0.530 g, 2.98 mmol) and 4-(trifluoromethyl)benzylamine **3a** (0.575 g, 3.28 mmol). The vial was evacuated and filled with N_2 (3x). Dry DMSO (3 mL) was added followed by Et_3N (0.42 mL, 2.98 mmol) and I_2 (0.023 g, 0.089 mmol). The vial was sealed and the reaction mixture was heated to 120 °C for 30 h, cooled to room temperature, diluted with water (30 mL), and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (acetone/hexanes, 1:4 to 3:7, containing Et_3N (1%)) to afford **5d** (0.81 g, 82 %) as a yellow solid: Mp 150-151 °C; IR (ATR) 3446, 3323, 1641, 1549, 1397, 1325, 1283, 1251, 1105, 867 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 1 H, *J* = 12.4 Hz), 7.64 (d, 2 H, *J* = 8.0 Hz), 7.44 (d, 2 H, *J* = 8.0 Hz), 6.14 (brs, 2 H), 5.69 (d, 1 H, *J* = 7.6 Hz), 5.12 (brs, 1 H), 4.50 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 143.8 (d, *J* = 14.0 Hz), 143.5 (d, *J* = 235.0 Hz), 141.0, 130.4 (q, *J* = 32.0 Hz), 127.4, 126.1 (q, *J* = 4.0 Hz), 124.1 (q, *J* = 270.0 Hz), 121.6 (d, *J* = 9.0 Hz), 111.1 (d, *J* = 23.0 Hz), 96.1, 46.7; ^{19}F NMR (376 MHz , $CDCl_3$) δ -62.6 (s, 3F), -146.8 (s, 1F); HRMS (HESI) *m/z* calcd for $C_{14}H_{12}N_3O_2F_4$ $[M+H]^+$ 330.0860, found 330.0856.



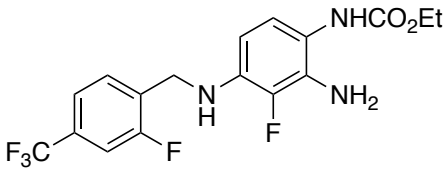
Ethyl (2-amino-5-fluoro-4-((4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-72). A solution of **5d** (0.410 g, 1.25 mmol) in MeOH (4 mL) was charged with zinc powder (0.407 g, 6.23 mmol) followed by dropwise addition of saturated aqueous ammonium chloride solution (1.25 mL). The reaction mixture was stirred vigorously at room temperature for 1 h, filtered through Celite, and the filter cake was washed with EtOAc. The filtrate was treated with saturated aqueous Na_2CO_3 solution, and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting solid was dissolved in CH_2Cl_2 (20 mL), cooled to 0 °C, treated with diisopropylethylamine (0.33 mL, 1.87 mmol) and ethyl chloroformate (0.11 mL, 1.12 mmol). The reaction mixture was stirred for 1 h at 0 °C and then for 3 h at room temperature before saturated aqueous Na_2CO_3 was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 2:3, containing Et_3N (1%)) to afford crude product that was recrystallized (CH_2Cl_2/hexanes) to give **RL-72** (0.112 g. 24 %) as a colorless solid: Mp 174.0-174.4 °C; IR (ATR) 3341, 2971, 1738, 1677, 1540, 1324, 1249, 1123, 1067, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, *J* = 8.0 Hz), 7.45 (d, 2 H, *J* = 8.0 Hz), 6.93 (d, 1 H, *J* = 10.8 Hz), 6.13 (br s, 1 H), 5.93 (d, 1 H, *J* = 8.4 Hz), 4.39 (s, 2 H), 4.19 (q, 2 H, *J* = 7.2 Hz), 3.55 (brs, 2 H), 1.28 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 145.0 (d, *J* = 231.0 Hz), 143.3, 138.0, 135.3, 129.7 (q, *J* = 32.0 Hz), 127.4, 125.8 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 270.0 Hz), 112.8, 100.9, 61.6, 47.5, 14.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4 (s, 3 F), -146.3 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{18}N_3O_2F_4$ $[M+H]^+$ 372.1330, found 372.1326.



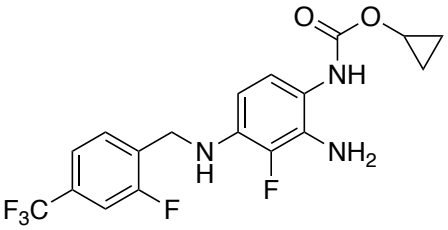
2-Fluoro-*N*^{1}-(2-fluoro-4-(trifluoromethyl)benzyl)-4-nitrobenzene-1,3-diamine (5e). A solution of 2-fluoro-4-(trifluoromethyl)benzylamine **3d** (0.10 g, 0.50 mmol) and 2,3-difluoro-6-nitroaniline **4a** (0.095 g, 0.53 mmol) in dry DMSO (1.0 mL) was treated under argon with Et_3N (0.077 mL, 0.55 mmol) and I_2 (5 mg, 0.02 mmol). The reaction mixture was heated to 120 °C for 30 h, cooled to room temperature, quenched with water (10 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (acetone/hexanes, 1:8 to 1:5 to 1:4, containing Et_3N (0.2%)) to afford **5e** (0.142 g, 81%) as a yellow solid: Mp 153.4-153.6 °C; IR (ATR) 3487, 3379, 1629, 1547, 1478, 1420, 1281, 1238, 1176, 1161, 1115, 1090, 908, 755, 742 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.78 (d, 1 H, *J* = 9.6 Hz), 7.66 (t, 1 H, *J* = 8.0 Hz), 7.54-7.51 (m, 2 H), 6.71 (brs, 2 H), 6.59 (br s, 1 H), 6.24-6.19 (m, 1 H), 4. 74 (d, 2 H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.2 (d, *J* = 247.4 Hz), 142.1 (d, *J* = 9.5 Hz), 138.6 (d, *J* = 228.8 Hz), 136.7 (d, *J* = 13.3 Hz), 131.8 (d, *J* = 14.6 Hz), 131.5 (qd, *J* = 25.1, 8.3 Hz),130.9 (d, *J* = 4.6 Hz), 125.6 (d, *J* = 3.7 Hz), 124.5 (qd, *J* = 271.5, 2.8 Hz), 123.9 (d, *J* = 2.8 Hz), 122.2 (quint, *J* = 3.8 Hz), 113.4 (dq, *J* = 25.1, 3.9 Hz), 101.3 (d, *J* = 3.12 Hz), 40.6 (d, *J* = 4.6 Hz); ^{19}F NMR (376 MHz, acetone-d_6) δ -63.1 (s, 3 F), -117.3 (s, 1 F), -160.5 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{14}H_{11}N_3O_2F_5$ $[M+H]^+$ 348.0766, found 348.0764.



3-Fluoro-*N*^{4}-(2-fluoro-4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine. A solution of **5e** (0.14 g, 0.40 mmol) in MeOH (2 mL) was treated with zinc powder (0.26 g, 4.03 mmol) followed dropwise by saturated aqueous ammonium chloride (0.76 mL). The reaction mixture was stirred vigorously at room temperature for 5 h, and filtered through Celite. The filter cake was washed (CH_2Cl_2), and the filtrate was dried (Na_2SO_4) and concentrated in vacuo to afford crude 3-fluoro-*N*^{4}-(2-fluoro-4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.10 g, 78%) as a red solid that was used in the next step without further purification: HRMS (HESI) *m/z* calcd for $C_{14}H_{13}N_3F_5$ $[M+H]^+$ 318.1024, found 318.1023.

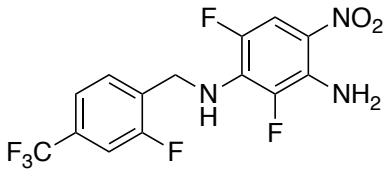


Ethyl (2-amino-3-fluoro-4-((2-fluoro-4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-18). A solution of 3-fluoro-*N*^{4}-(2-fluoro-4-(trifluoromethyl)benzyl)benzene-1,2,4-triamine (0.090 g, 0.28 mmol) in CH_2Cl_2 (6 mL) under argon was treated at 0 °C with diisopropylethylamine (0.06 mL, 0.35 mmol) and dropwise with ethyl chloroformate (0.028 mL, 0.28 mmol). The reaction mixture was stirred for 4 h at 0 °C and quenched with water. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL), and the combined extracts were dried (Na_2SO_4), concentrated in vacuo and purified by chromatography on SiO_2 (hexanes/EtOAc, 5:1 to 4:1 to 3:1) to afford **RL-18** (0.045 g, 41%) as a red solid that was recrystallized (CH_2Cl_2/hexanes) to afford a colorless solid (0.030 g): Mp 170.1-170.7 °C; IR (ATR) 3407, 3331, 3297, 1681, 1646, 1521, 1489, 1428, 1329, 1254, 1217, 1163, 1120, 1081, 1064, 911, 874, 783, 744, 710 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, 1 H, *J* = 8.0 Hz), 7.36 (d, 1 H, *J* = 8.0 Hz), 7.32 (d, 1 H, *J* = 10.0 Hz), 6.74 (d, 1 H, *J* = 8.5 Hz), 6.13 (brs, 1 H), 6.00 (app t, 1 H, *J* = 8.5 Hz), 4.48 (d, 2 H, *J* = 6.5 Hz), 4.32 (brs, 1 H), 4.19 (q, 2 H, *J* = 7.0 Hz), 3.87 (brs, 2 H), 1.29 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4 (d, *J* = 248.2 Hz), 155.5, 141.4 (d, *J* = 232.4 Hz), 134.6 (d, *J* = 9.9 Hz), 131.5 (qd, *J* = 33.4, 8.0 Hz), 131.0, 130.7 (d, *J* = 14.5 Hz), 129.7 (d, *J* = 4.6 Hz), 123.4 (qd, *J* = 272.3, 2.9 Hz), 121.9, 121.3 (quint, *J* = 3.8 Hz), 115.7, 112.9 (dq, *J* = 24.8, 3.9 Hz), 101.8, 61.7, 41.4 (d, *J* = 4.3 Hz), 14.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.6 (s, 3 F), -116.7 (s, 1 F), -156.0 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{17}N_3O_2F_5$ $[M+H]^+$ 390.1235, found 390.1237.



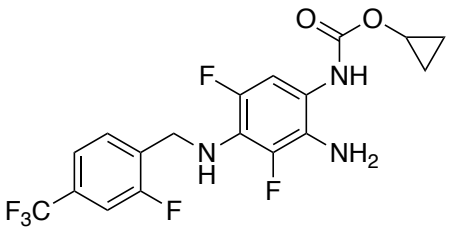
Cyclopropyl (2-amino-3-fluoro-4-((2-fluoro-4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-35). A suspension of **5e** (0.347

g, 1.00 mmol) and zinc powder (0.327 g, 5.00 mmol) in MeOH (10 mL) was treated dropwise with aqueous 5 M ammonium chloride solution (1.00 mL) and stirred vigorously at room temperature for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated, diluted with EtOAc and saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. A solution of the dark red residue in dry CH_2Cl_2 (20 mL) was treated with diisopropylethylamine (0.21 mL, 1.20 mmol) and cyclopropyl chloroformate (0.50 mL, 1.00 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1, containing Et_3N (1%)) to afford a light yellow solid that was recrystallized (CH_2Cl_2/hexanes) to afford **5e** (0.221 g. 55 %) as a colorless solid: Mp 177-178 °C; IR (ATR) 3306, 1689, 1338, 1123 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1 H, *J* = 7.6 Hz), 7.38-7.31 (m, 2 H), 6.73 (d, 1 H, *J* = 7.6 Hz), 6.14 (br s, 1 H), 6.00 (t, 1 H, *J* = 8.8 Hz), 4.47 (d, 2 H, *J* = 5.6 Hz), 4.33 (brs, 1 H), 4.16-4.10 (m, 1 H), 3.86 (brs, 2 H), 0.80-0.60 (m, 4 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.4 (d, *J* = 248.5 Hz), 155.7, 141.4 (d, *J* = 230.8 Hz), 134.6, 131.4 (qd, *J* = 33.5, 8.0 Hz), 130.8, 130.6 (d, *J* = 14.3 Hz), 129.7 (d, *J* = 4.9 Hz), 123.4 (qd, *J* = 272.1, 2.0 Hz), 121.6, 121.5-121.2 (m), 115.5, 112.9 (dm, *J* = 24.8 Hz), 101.8, 49.9, 41.3 (d, *J* = 4.2 Hz), 5.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6 (s, 3 F), -116.7 (s, 1 F), -155.9 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{18}H_{17}N_3O_2F_5$ $[M+H]^+$ 402.1235, found 402.1232.



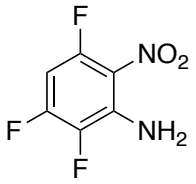
2,6-Difluoro-*N*^{1}-(2-fluoro-4-(trifluoromethyl)benzyl)-4-nitrobenzene-1,3-diamine (5f). A vial containing 2-fluoro-4-(trifluoromethyl)benzylamine **3d** (0.20 g, 1.00 mmol) and 2,3,4-trifluoro-6-nitroaniline **4c** (0.19 g, 1.00 mmol) was evacuated and backfilled with N_2 (3 x). Dry DMSO (2.0 mL) was added, followed by Et_3N (0.15 mL, 1.06 mmol) and I_2 (10 mg, 0.04 mmol). The vial was sealed and the reaction mixture was heated to 120 °C for 30 h, cooled to

room temperature, diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4, containing Et_3N (0.2%)) to afford a yellow solid that was recrystallized from CH_2Cl_2/hexanes to afford **5f** (0.26 g, 71 %) as a bright yellow solid: Mp 108-110 °C; IR (ATR) 3500, 3379, 3088, 1644, 1528, 1509, 1431, 1328, 1256, 1126, 909 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 7.72 (t, 1 H, *J* = 8.0 Hz), 7.65-7.47 (m, 3 H), 6.76 (brs, 2 H), 6.48 (brs, 1 H), 4.87 (d, 2 H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.8 (d, *J* = 247.5 Hz), 143.4 (dd, *J* = 233.0, 9.0 Hz), 139.0 (dd, *J* = 230.0, 7.0 Hz), 136.0 (d, *J* = 14.0 Hz), 133.0 (dd, *J* = 16.00, 10.0 Hz), 132.8 (d, *J* = 13.0 Hz), 131.4 (qd, *J* = 33.0, 8.0 Hz), 130.6 (d, *J* = 5.0 Hz), 124.5 (qd, *J* = 270.0, 3.0 Hz), 122.2 (app quint, *J* = 4 Hz), 121.6 (dd, *J* = 10.0, 5.0 Hz), 113.4 (dq, *J* = 25.0, 4.0 Hz), 107.5 (dd, *J* = 25.0, 2.0 Hz), 42.6 (d, *J* = 4.0 Hz); ^{19}F NMR (376 MHz, acetone-d_6) δ -63.1 (s, 3 F), -118.0 (s, 1 F), -144.7 (d, 1 F, *J* = 3.8 Hz), -155.5 (d, 1 F, *J* = 7.5 Hz); HRMS (HESI) *m/z* calcd for $C_{14}H_{10}N_3O_2F_6$ $[M+H]^+$ 366.0672, found 366.0669.



Cyclopropyl (2-amino-3,5-difluoro-4-((2-fluoro-4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-36). A solution of **5f** (0.365 g, 1.00 mmol) in MeOH (10 mL) was treated with zinc powder (0.327 g, 5.00 mmol) followed by a 5 M aqueous ammonium chloride solution (1.00 mL). The reaction mixture was stirred vigorously at room temperature for 2 h, and filtered through Celite. The filtrate was concentrated in vacuo, and the residue was diluted with EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to yield a dark red residue that was dissolved in dry CH_2Cl_2 (20 mL). After addition of diisopropylethylamine (0.21 mL, 1.20 mmol) and cyclopropyl chloroformate (0.50 mL, 1.00 mmol), the reaction mixture was stirred vigorously at room temperature for 4 h, and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was

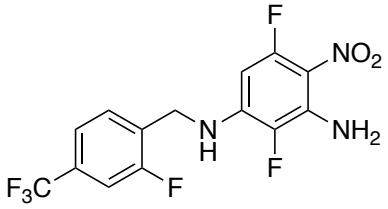
extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1, containing Et_3N (1%)) to afford a pink solid that was recrystallized (CH_2Cl_2/hexanes) twice to afford **RL-36** (0.204 g, 49%) as a light beige solid: Mp 119-120 °C; IR (ATR) 3309, 1702, 1519, 1429, 1329, 1239, 1164, 1124 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, 1 H, *J* = 7.5 Hz), 7.35 (d, 1 H, *J* = 8.0 Hz), 7.29 (d, 1 H, *J* = 10.0 Hz), 6.90 (s, 1 H), 6.40 (brs, 1 H), 4.54 (d, 2 H, *J* = 7.0 Hz), 4.13-4.10 (m, 1 H), 3.97 (brs, 1 H), 3.50 (brs, 2 H), 0.71 (d, 4 H, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6 (d, *J* = 248.5 Hz), 155.1, 146.5 (d, *J* = 232.6 Hz), 143.9 (d, *J* = 229.9 Hz), 131.5 (qd, *J* = 33.3, 8.0 Hz), 131.2 (d, *J* = 14.8 Hz), 130.3 (d, *J* = 4.8 Hz), 125.5, 123.4 (qd, *J* = 272.3, 2.7 Hz), 122.7, 121.2 (quint, *J* = 3.8 Hz), 117.0, 112.9 (dq, *J* = 24.9, 3.8 Hz), 107.2, 50.0, 44.3 (q, *J* = 3.8 Hz), 5.1; ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.7 (s, 3 F), -117.1 (s, 1 F), -139.2 (s, 1 F), -147.1 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{18}H_{16}N_3O_2F_6$ $[M+H]^+$ 420.1141, found 420.1140.



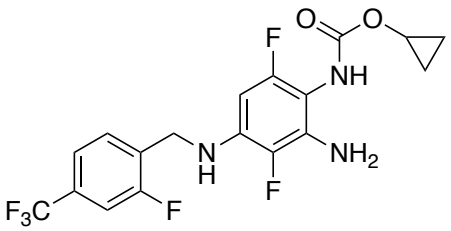
2,3,5-Trifluoro-6-nitroaniline (4d).[3] A sealable vial was flushed with N_2 and filled with 2,3,4,6-tetrafluoronitrobenzene (1.05 g, 5.22 mmol) and Et_2O (20 mL). Aqueous 28% ammonium hydroxide solution (1.60 mL, 11.49 mmol) was added dropwise over 1 h. The reaction mixture was stirred for 1 h at room temperature, quenched with water, and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo, and the residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:19 to 1:9) to afford **4d** (0.884 g, 88%) as a bright yellow solid: Mp 63-65 °C; IR(ATR) 3499, 3389, 3099, 1647, 1594, 1539, 1473, 1354, 1285, 1239, 1108, 1092, 885 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.37 (ddd, 1 H, *J* = 11.4, 10.0, 6.5 Hz), 6.04 (brs, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (ddd, *J* = 261.3, 14.1, 3.6 Hz), 152.2 (ddd, *J* = 256.6, 14.9,

[3] Burdon, J.; Fisher, D.; Parsons, I. W.; Tatlow, J. C. "Aromatic Polyfluoro Compounds Lvii. Nucleophilic Replacement Reactions of 1,2,3,5-Tetrafluoro-4-Nitrobenzene, 1,2,3,5-Tetrafluorodinitrobenzene and 1-Bromo-2,3,4,6-Tetrafluoro-5-Nitrobenzene." *J. Fluorine Chem.* **1981**, *18*, 507-514.

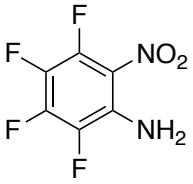
11.4 Hz), 137.0-136.7 (m), 135.0 (dd, *J* = 14.8, 4.8 Hz), 121.9, 93.5 (dd, *J* = 27.4, 23.5 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ, -117.5 (dd, 1 F, *J* = 12.0, 8.9 Hz), -125.7 (dd, 1 F, *J* = 20.8, 8.9 Hz), -161.5 (dd, 1 F, *J* = 20.8, 12.2 Hz); HRMS (HESI) *m/z* calcd for $C_6H_4N_2O_2F_3$ $[M+H]^+$ 193.0225, found 193.0222.



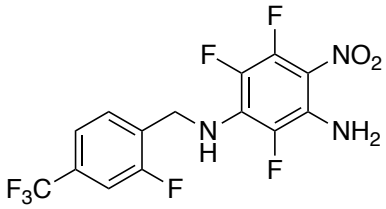
2,5-Difluoro-*N*^{1}-(2-fluoro-4-(trifluoromethyl)benzyl)-4-nitrobenzene-1,3-diamine (5g). An oven-dried sealable vial was charged with 2-fluoro-4-(trifluoromethyl)benzylamine **3d** (0.36 g, 1.87 mmol) and **4d** (0.36 g, 1.087 mmol). The vial was evacuated and backfilled with N_2 (3 x). Dry DMSO (2.0 mL) was added, followed by Et_3N (0.32 mL, 2.25 mmol) and I_2 (24 mg, 0.09 mmol). The vial was sealed and the reaction mixture was heated to 120 °C for 36 h, cooled to room temperature, diluted with water (20 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4, containing Et_3N (0.2%)) to afford a yellow solid that was recrystallized (CH_2Cl_2/hexanes) to afford **5g** (0.38 g, 56 %) as a yellow solid: Mp 149-150 °C; IR (ATR) 3488, 3401, 1637, 1551, 1425, 1270, 1171, 1116, 881, 789 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2 H), 7.36 (d, 1 H, *J* = 10.2 Hz), 5.92 (br s, 2 H), 5.85 (dd, 1 H, *J* = 13.8, 7.2 Hz), 5.02 (brs, 1 H), 4.55 (d, 2 H, *J* = 6.6 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.4 (d, *J* = 247.5 Hz), 156.1 (dd, *J* = 255.0, 1.5 Hz), 139.8 (dd, *J* = 13.9, 10.9 Hz), 135.2 (d, *J* = 13.6 Hz), 134.2 (dd, *J* = 225.0, 2.1 Hz), 132.4 (qd, *J* = 33.0, 8.0 Hz), 129.6 (d, *J* = 4.5 Hz), 128.6 (d, *J* = 15.0 Hz), 123.2 (q, *J* = 271.6 Hz), 121.7 (quint, *J* = 3.6 Hz), 117.2 (d, *J* = 10.0 Hz), 113.4 (dq, *J* = 24.0, 3.8 Hz), 88.7 (d, *J* = 27.0 Hz), 40.8 (d, *J* = 4.5 Hz); ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.8 (s, 3 F), -115.8 (s, 1 F), -116.8 (d, 1 F, *J* = 11.3 Hz), -164.0 (d, 1 F, *J* = 11.3 Hz); HRMS (HESI) *m/z* calcd for $C_{14}H_{10}N_3O_2F_6$ $[M+H]^+$ 366.0672, found 366.0669.



Cyclopropyl (2-amino-3,6-difluoro-4-((2-fluoro-4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-46). A solution of **5g** (0.366 g, 1.00 mmol) in MeOH (10 mL) was treated with zinc powder (0.327 g, 5.00 mmol) followed by 5 M aqueous ammonium chloride solution (1.00 mL, 5.00 mmol) and vigorously stirred at room temperature for 2 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo, and dissolved in EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. A solution of the residue in dry CH_2Cl_2 (20 mL), was treated sequentially with diisopropylethylamine (0.21 mL, 1.20 mmol) and cyclopropyl chloroformate (0.41 mL, 0.90 mmol). The mixture was stirred vigorously at room temperature for 4 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1, containing Et_3N(1%)) to afford a light yellow solid that was recrystallized (CH_2Cl_2/hexanes) to give **RL-46** (0.17 g, 41 %) as a colorless solid: Mp 192-194 °C; IR (ATR) 3302, 1694, 1659, 1541, 1430, 1337, 1271, 1122 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 353 K) δ 7.91 (brs, 1 H), 7.65-7.51 (m, 3 H), 5.92 (br, 1 H), 5.76 (dd, 1 H, *J* = 12.1, 1.6 Hz), 4.71 (br s, 2 H), 4.43 (d, 2 H, *J* = 6.3 Hz), 4.00 (sept, 1 H, *J* = 3.2 Hz), 0.66-0.57 (m, 4 H); ^{13}C NMR (151 MHz, acetone-d_6) 161.3 (d, *J* = 246.8 Hz), 157.9, 157.1 (d, *J* = 236.7 Hz), 137.2 (d, *J* = 231.6 Hz), 136.7-136.2 (m), 135.5 (dd, *J* = 12.1, 5.4 Hz), 132.6 (d, *J* = 14.5 Hz), 131.2 (qd, *J* = 33.0, 8.1 Hz), 131.0 (d, *J* = 4.6 Hz), 124.5 (qd, *J* = 271.6, 2.2 Hz), 122.3 -122.0 (m), 113.3 (dq, *J* = 25.2, 3.9 Hz), 102.7 (dd, *J* = 18.0, 4.4 Hz), 87.8 (d, *J* = 27.3 Hz), 49.8, 41.0 (d, *J* = 4.3 Hz), 5.3; ^{19}F NMR (565 MHz, acetone-d_6) δ -63.0 (s, 3 F), -117.8 (s, 1 F), -127.7 (d, 1 F, *J* = 11.3 Hz), -163.4 (d, 1 F, *J* = 11.3 Hz); HRMS (HESI) *m/z* calcd for $C_{18}H_{16}N_3O_2F_6$ $[M+H]^+$ 420.1141, found 420.1139.

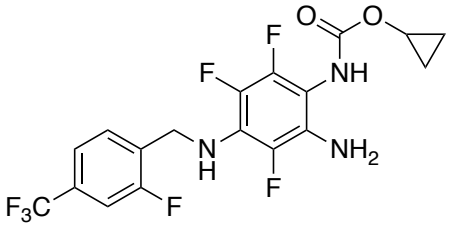


2,3,4,5-Tetrafluoro-6-nitroaniline (4e).[3] To a 3-neck round bottom flask flushed with N_2 were added pentafluoronitrobenzene (0.45 g, 2.01 mmol), Et_2O (10 mL), and 28% aqueous ammonium hydroxide (0.56 mL, 4.01 mmol) dropwise over the course of 4 h. After addition of water, the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:9 to 1:4) to afford 2,3,5,6-tetrafluoro-4-nitroaniline (0.097g, 23%) as a light yellow solid and 2,3,4,5-tetrafluoro-6-nitroaniline (0.24 g, 57%) as a yellow solid: Mp 41-43 °C; IR(ATR) 3494, 3373, 2923, 1668, 1606, 1538, 1519, 1351, 1255, 1121, 998 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (brs); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.9 (dtd, *J* = 262.6, 12.7, 4.7 Hz), 144.3 (ddt, *J* = 260.2, 13.9, 4.5 Hz), 136.3 (ddd, *J* = 243.1, 12.2, 3.7 Hz), 133.3 (dt, *J* = 246.0, 15.1 Hz), 132.3 (d, *J* = 12.9 Hz), 121.2; ^{19}F NMR (471 MHz, $CDCl_3$) δ -144.7 (dt, 1 F, *J* = 22.7, 9.3 Hz), -147.1 (td, 1 F, *J* = 21.3, 8.9 Hz), -160.4 to -160.1 (m, 1 F), -172.1 (td, 1 F, *J* = 22.4, 5.2 Hz); HRMS (HESI) *m/z* calcd for $C_6HN_2O_2F_4$ $[M-H]^-$ 208.9969, found 208.9976.



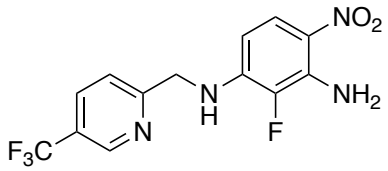
2,5,6-Trifluoro-*N*^{1}-(2-fluoro-4-(trifluoromethyl)benzyl)-4-nitrobenzene-1,3-diamine (5h). To an oven dried sealable vial were added **3d** (0.39 g, 2.00 mmol) and **4e** (0.40 g, 1.90 mmol). The vial was evacuated, backfilled with N_2 (3 x), and dry DMSO (2.0 mL) was added followed by Et_3N (0.32 mL, 2.28 mmol) and I_2 (24 mg, 0.09 mmol). The vial was sealed and the reaction mixture was heated to 120 °C for 42 h, cooled to room temperature, diluted with water (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced

pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4 to 1:3, containing Et_3N (0.2%)) to afford a yellow solid that was recrystallized (CH_2Cl_2/hexanes) to afford **5h** (0.37 g, 51%) as a yellow solid: Mp 119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.40 (m, 2 H), 7.36 (d, 1 H, *J* = 10.0 Hz), 5.86 (br s, 2 H), 4.78 (s, 3 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.5 (d, *J* = 249.0 Hz). 144.2 (ddd, *J* = 258.6, 14,2, 3.0 Hz), 134.1 (dm, *J* = 228.2 Hz), 133.1 (d, *J* = 14.7 Hz), 132.8 (ddd, *J* = 235.2, 16.7, 7.9 Hz), 132.3 (qd, *J* = 33.6, 8.1 Hz), 131.4 (td, *J* = 11.5, 3.8 Hz), 129.9 (d, *J* = 4.1 Hz), 129.7 (d, *J* = 14.2 Hz), 123.2 (qd, *J* = 272.7, 2.1 Hz), 121.9-121.5 (m), 115.9, 113.29 (dq, *J* = 24.6, 3.5 Hz), 43.1 (dd, *J* = 12.7, 4.5 Hz);^{19}F NMR (565 MHz, $CDCl_3$) δ -62.8 (s, 3 F), -116.3 (s, 1 F), -147.1 (dd, 1 F, *J* = 22.6, 5.7 Hz), -160.8 (d, 1 F, *J* = 11.3 Hz), -169.7 (d, 1 F, *J* = 17.0 Hz); HRMS (HESI) *m/z* calcd for $C_{14}H_9N_3O_2F_7$ $[M+H]^+$ 384.0578, found 384.0575.



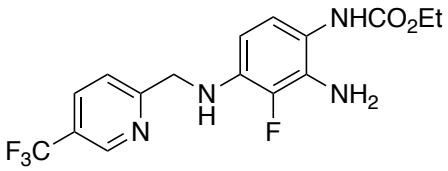
Cyclopropyl (2-amino-3,5,6-trifluoro-4-((2-fluoro-4-(trifluoromethyl)benzyl)amino)phenyl)carbamate (RL-50). A suspension of **5h** (0.383 g, 1.00 mmol) and zinc powder (0.327 g, 5.00 mmol) in MeOH (10 mL) was treated dropwise with 5 M aqueous ammonium chloride solution (1.00 mL) and stirred vigorously at room temperature for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated, and diluted with EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. A solution of the yellow residue in dry CH_2Cl_2 (20 mL) was treated with diisopropylethylamine (0.21 mL, 1.20 mmol), followed by cyclopropyl chloroformate (0.50 mL, 1.00 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h, and quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4 to 3:7, containing Et_3N (1%)) to yield a light yellow solid that was recrystallized from CH_2Cl_2/hexanes to afford

RL-50 (0.089 g. 20 %) as a colorless solid: Mp 126-128 °C; IR (ATR) 3365, 1721, 1514, 1330, 1170, 1127 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 373 K) δ 8.05 (brs, 1 H), 7.66 (t, 1 H, *J* = 7.6 Hz), 7.57-7.37 (m, 2 H), 5.56 (t, 1 H, *J* = 6.8 Hz), 4.57 (d, 2 H, *J* = 6.8 Hz), 4.52 (brs, 2 H), 4.04 (sept, 1 H, *J* = 3.2 Hz), 0.71-0.57 (m, 4 H); ^{13}C NMR (151 MHz, CD_3OD) δ 161.7 (d, *J* = 247.5 Hz), 158.3, 146.2 (ddd, *J* = 238.5, 12.0, 3.0 Hz), 138.9 (d, *J* = 226.9 Hz), 135.3 (d, *J* = 232.2 Hz), 133.6 (d, *J* =14.6 Hz), 132.0 (qd, *J* = 33.2, 8.2 Hz), 131.6 (d, *J* = 14.1 Hz), 131.2 (d, *J* = 4.2 Hz), 126.7 (t, *J* = 11.6 Hz), 124.9 (qd, *J* = 268.5, 2.4 Hz), 122.3-122.0 (m), 113.5 (dq, *J* = 25.4, 3.5 Hz), 104.1-103.8 (m), 50.7, 43.7, 5.5; ^{19}F NMR (565 MHz, CD_3OD) δ -64.1 (s, 3 F), -119.0 (s, 1 F), -153.7 (dd, 1 F, *J* = 20.9, 7.3 Hz), -158.7 (d, 1 F, *J* = 5.7 Hz), -172.0 (d, 1 F, *J* = 21.4 Hz); HRMS (HESI) *m/z* calcd for $C_{18}H_{15}N_3O_2F_7$ $[M+H]^+$ 438.1047, found 438.1044.

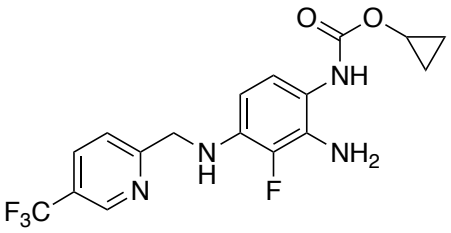


2-Fluoro-4-nitro-*N*^{1}-((5-(trifluoromethyl)pyridin-2-yl)methyl)benzene-1,3-diamine (5i). 2-(Aminomethyl)-5-(trifluoromethyl)pyridine hydrochloride (0.180 g, 0.804 mmol) was neutralized with 1 M NaOH (0.84 mL). The resulting aqueous solution was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo to give a yellowish oil that was dissolved in dry DMSO (1.6 mL) and treated with 2,3-difluoro-6-nitroaniline **4a** (0.144 g, 0.804 mmol) followed by Et_3N (0.12 mL, 0.885 mmol) and I_2 (8 mg, 0.03 mmol, 0.04 equiv). The reaction mixture was heated to 120 °C for 30 h, cooled to room temperature, diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (acetone/hexanes, 1:8 to 1:5 to 1:4, containing Et_3N(0.2%)) to give **5i** (0.20 g, 75 %) as a yellow solid: Mp 138.2-138.5 °C; IR (ATR) 3484, 3370, 1629, 1607, 1551, 1482, 1325, 1282, 1251, 1126, 1077, 1018, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1 H), 7.95-7.87 (m, 2 H), 7.44 (d, 1 H, *J* = 8.4 Hz), 6.10-6.05 (m, 3 H), 5.72 (br s, 1H), 4.66 (d, 2 H, *J* = 5.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 146.5 (q, *J* = 4.0 Hz), 140.7 (d, *J* = 9.0 Hz), 138.1 (d, *J* = 227.0 Hz), 135.3 (d, *J* = 13.0 Hz), 134.2 (q, *J* = 3.5 Hz), 126.0 (q, *J* = 33.0 Hz),

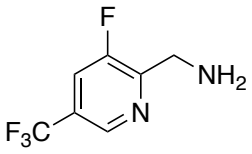
125.6 (d, *J* = 3.0 Hz), 123.7 (d, *J* = 3.0 Hz), 123.5 (q, *J* = 271.0 Hz), 121.3, 100.9 (d, *J* = 3.0 Hz), 47.8; ^{19}F NMR (376 MHz , $CDCl_3$) δ -62.3 (s, 3 F), -160.5 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{13}H_{11}N_4O_2F_4$ $[M+H]^+$ 331.0813, found 331.0811.



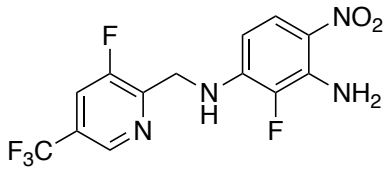
Ethyl (2-amino-3-fluoro-4-(((5-(trifluoromethyl)pyridin-2-yl)methyl)amino)phenyl)carbamate (RL-31). A solution of **5i** (0.165 g, 0.5 mmol) in EtOH (2.5 mL) was treated with 10% Pd/C (0.025 g) under N_2 and stirred at room temperature for 5 h under an atmosphere of H_2 gas (balloon). The reaction mixture was filtered through Celite (CH_2Cl_2), and concentrated in vacuo to afford a brown solid (0.135 g, 0.43 mmol, 90%) that was dissolved in CH_2Cl_2 (8 mL) and treated under argon at 0 °C with diisopropylethylamine (0.08 mL, 0.48 mmol) followed by ethyl chloroformate (0.038 mL, 0.39 mmol) dropwise at 0 °C. The reaction mixture was stirred for 4 h at 0 °C, quenched with water, and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 1:1, in the presence of Et_3N (1%)) to yield a light yellow solid (0.078 g, 43%) that was recrystallized (CH_2Cl_2/hexanes) to afford **RL-31** (0.048 g) as a colorless solid: Mp 153.6-154.2 °C; IR (ATR) 3303, 1685, 1638, 1540, 1532, 1528, 1329, 1260, 1128, 764, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1 H), 7.86 (dd, 1 H, *J* = 8.4, 2.0 Hz), 7.46 (d, 1 H, *J* = 8.4 Hz), 6.72 (d, 1 H, *J* = 8.4 Hz), 6.30 (br s, 1 H), 5.96 (t, 1 H, *J* = 8.8 Hz), 4.85 (br s, 1 H), 4.53 (d, 2 H, *J* = 5.6 Hz), 4.18 (q, 2 H, *J* = 7.2 Hz), 3.88 (brs, 2 H), 1.27 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 155.5, 146.4 (q, *J* = 4.0 Hz), 141.4 (d, *J* = 230.4 Hz), 134.7 (d, *J* = 9.8 Hz), 134.0 (q, *J* = 3.4 Hz), 131.0, 125.3 (q, *J* = 33.0 Hz), 123.6 (q, *J* = 272.2 Hz), 121.7, 121.1, 115.5, 101.8, 61.7, 49.1, 14.7; ^{19}F NMR (376 MHz , $CDCl_3$) δ -62.3 (s, 3 F), -155.8 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{16}H_{17}N_4O_2F_4$ $[M+H]^+$ 373.1282, found 373.1280.



Cyclopropyl (2-amino-3-fluoro-4-(((5-(trifluoromethyl)pyridin-2-yl)methyl)amino)phenyl)carbamate (RL-68). A mixture of **5i** (0.33 g, 1.00 mmol) and zinc powder (0.327 g, 5.00 mmol) in MeOH (10 mL) was treated dropwise with 5 M aqueous ammonium chloride solution (1.00 mL, 5.00 mmol) and stirred vigorously at room temperature for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated, diluted with EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered, concentrated in vacuo. and dissolved in dry CH_2Cl_2 (20 mL). After addition of diisopropylethylamine (0.21 mL, 1.20 mmol) and cyclopropyl chloroformate (0.50 mL, 1.00 mmol), the reaction mixture was stirred vigorously at room temperature for 4 h and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1, containing Et_3N (1%)) to yield a light yellow solid that was recrystallized (CH_2Cl_2/hexanes) to afford **RL-68** (0.089 g, 23%) as a colorless solid: Mp 170-171 °C; IR (ATR) 3308, 1691, 1529, 1327, 1123, 1079, 1020, 768 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 8.81 (s, 1 H), 8.02 (d, 1 H, *J* = 7.8 Hz), 7.60 (d, 1 H, *J* = 7.8 Hz), 6.65 (d, 1 H, *J* = 7.2 Hz), 5.89 (t, 1 H, *J* = 7.8 Hz), 4.53 (s, 2 H), 4.10-3.97 (m, 1 H), 0.87-0.42 (m, 4 H); ^{13}C NMR (151 MHz, CD_3OD) δ 165.9, 158.4, 146.8, 142.4 (d, *J* = 230.2 Hz), 136.0, 135.5, 132.6, 126.3 (q, *J* = 33.0 Hz), 125.2 (q, *J* = 271.9 Hz), 123.0, 122.7, 116.4, 102.2, 50.3, 49.6, 5.5; ^{19}F NMR (565 MHz, CD_3OD) δ -63.7 (s, 3 F), -157.8 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{17}N_4O_2F_4$ $[M+H]^+$ 385.1282, found 385.1280.

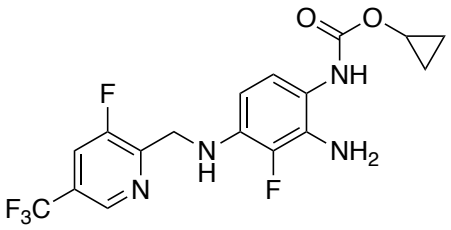


(3-Fluoro-5-(trifluoromethyl)pyridin-2-yl)methanamine (3f). A solution of 3-fluoro-5-(trifluoromethyl)picolinonitrile (2.20 g, 11.57 mmol) in MeOH (20 mL) was treated with 10% Pd/C (0.616 g, 0.579 mmol) and concentrated HCl (1.07 mL, 12.73 mmol) and stirred at room temperature for 15 h under an atmosphere of H_2 (balloon). The reaction mixture was filtered through Celite, and the Celite was washed with MeOH and water. The filtrate was concentrated to remove the MeOH, treated with additional water, and the aqueous solution was extracted with CH_2Cl_2 (3 x 10 mL). The aqueous layer was treated with 1 N NaOH (13 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated in vacuo to afford **3f** as green-blue oil (1.32 g, 59%): IR (ATR) 3377, 2913, 1416, 1333, 1127, 932 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 7.45 (d, 1 H, *J* = 8.8 Hz), 3.96 (s, 2 H), 1.69 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 (d, *J* = 258.0 Hz), 154.3 (d, *J* = 15.0 Hz), 141.8-141.5 (m), 126.3 (qd, *J* = 33.0, 3.0 Hz), 122.6 (qd, *J* = 271.0, 1.0 Hz), 119.7 (dq, *J* = 22.0, 3.5 Hz), 41.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5 (s, 3 F), -126.1 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_7H_7N_2F_4$ $[M+H]^+$ 195.0540, found 195.0540.



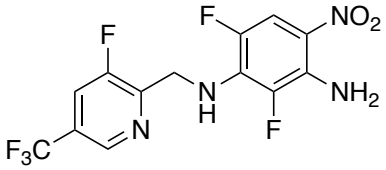
2-Fluoro-*N*^{1}-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)methyl)-4-nitrobenzene-1,3-diamine (5j). An oven-dried sealable vial was charged with **3f** (0.46 g, 2.37 mmol) and 2,3-difluoro-6-nitroaniline **4a** (0.433 g, 2.49 mmol evacuated and backfilled with N_2 (3 x), and treated with dry DMSO (2.5 mL) followed by Et_3N (0.37 mL, 2.61 mmol) and I_2 (0.030 g, 0.118 mmol). The vial was sealed and the reaction mixture was heated to 100 °C for 6 h, cooled to room temperature, diluted with water (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4, containing Et_3N (0.5%)) to afford **5j** (0.37 g, 45%) as a yellow solid: Mp 158.9-161.2 °C; IR (ATR) 3385, 1629, 1483, 1418, 1334, 1278, 1126, 933, 741 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.78 (s, 1 H), 8.07 (d, 1 H, *J* = 9.6 Hz), 7.81 (dd, 1 H, *J* = 9.6, 1.2 Hz), 6.69 (brs, 2 H), 6.50 (brs, 1 H), 6.39 (dd, 1 H, *J* = 9.6, 8.4 Hz), 4.85 (d, 2 H, *J* = 5.4 Hz); ^{13}C NMR

(151 MHz, acetone-d_6) δ 157.7 (d, *J* = 260.0 Hz), 151.1 (d, *J* = 15.3 Hz), 142.5-142.3 (m), 142.2 (d, *J* = 9.5 Hz), 138.7 (d, *J* = 228.2 Hz), 136.6 (d, *J* = 13.2 Hz), 127.5 (qd, *J* = 33.5, 3.5 Hz), 125.6 (d, *J* = 3.7 Hz), 123.9 (q, *J* = 272.2 Hz), 123.8 (d, *J* = 2.9 Hz), 121.5 (dq, *J* = 21.7, 3.6 Hz), 101.8 (d, *J* = 3.0 Hz), 43.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.1 (s, 3 F), -124.7 (s, 1 F), -160.5 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{13}H_{10}N_4O_2F_5$ $[M+H]^+$ 349.0718, found 349.0716.

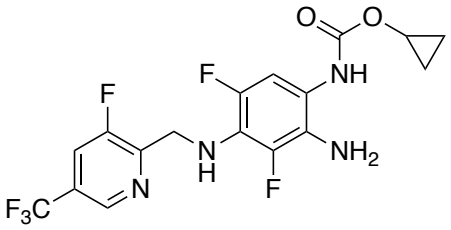


Cyclopropyl (2-amino-3-fluoro-4-(((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)methyl)amino)phenyl)carbamate (RL-96). A solution of **5j** (0.23 g, 0.66 mmol) in MeOH (7 mL) was treated with zinc powder (0.216 g, 3.30 mmol) followed by a 5 M aqueous ammonium chloride solution (0.66 mL, 3.30 mmol). The reaction mixture was stirred vigorously at room temperature for 2h, filtered through Celite, and the filtrate was concentrated, diluted with EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. A solution of the residue in dry CH_2Cl_2 (20 mL) was treated with diisopropylethylamine (0.14 mL, 0.79 mmol) followed by a 1 M solution of cyclopropyl chloroformate in toluene (0.66 mL, 0.66 mmol). The reaction mixture was stirred vigorously at room temperature for 4 h, and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), evaporated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1, containing Et_3N (1%)) to yield a light-yellow solid that was recrystallized (CH_2Cl_2/hexanes) to afford **RL-96** (0.088 g, 33%) as a colorless solid: Mp 162.6-163.5 °C; IR (ATR) 3333, 1701, 1540, 1415, 1331, 1130 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (s, 1 H), 7.63 (d, 1 H, *J* = 8.4 Hz), 6.81 (s, 1 H), 6.27-6.19 (d, 1 H, *J* = 8.4 Hz), 6.15 (br s, 1 H), 5.13 (brs, 1 H), 4.56 (s, 2 H), 4.18-4.08 (m, 1 H), 3.84 (br s, 2 H), 0.80-0.55 (m, 4 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7 (d, *J* = 260.8 Hz), 155.6, 150.3 (d, *J* = 14.9 Hz), 142.0-141.6 (m), 141.8 (d, *J* = 231.8 Hz), 134.7, 130.7, 127.1 (q, *J* = 33.7 Hz), 122.7

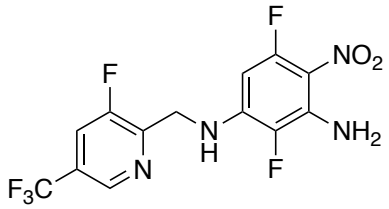
(q, *J* = 272.6 Hz), 121.5, 120.3 (dq, *J* = 21.6, 3.3 Hz), 115.6, 102.3, 49.9, 43.2, 5.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.1 (s, 3 F), -124.9 (s, 1 F), -155.4 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{16}N_4O_2F_5$ $[M+H]^+$ 403.1188, found 403.1185.



2,6-Difluoro-*N*^{1}-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)methyl)-4-nitrobenzene-1,3-diamine (5k). An oven-dried sealable vial was charged with **3f** (0.243 g, 1.25 mmol) and 2,3,4-trifluoro-6-nitroaniline **4c** (0.200 g, 1.04 mmol), evacuated and backfilled with N_2 (3 x), and charged with dry DMSO (2 mL), Et_3N (0.18 mL, 1.25 mmol) and I_2 (0.132 g, 0.520 mmol). The vial was sealed and the reaction mixture was heated to 60 °C for 30 h before cooling to room temperature, diluted with water (20 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 5 mL), dried (Na_2SO_4), filtered, concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4, containing Et_3N (0.2%)) to afford **5k** (0.221 g, 58%) as a yellow solid: Mp 157.6-158.4 °C; IR (ATR) 3314, 1548, 1474, 1412, 1339, 1256, 1136 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.78 (s, 1 H), 8.07 (d, 1 H, *J* = 9.2 Hz), 7.61 (d, 1 H, *J* = 9.2 Hz), 6.76 (brs, 2 H), 6.40 (brs, 1 H), 5.02 (s, 2 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 157.2 (d, *J* = 259.6 Hz), 151.4 (d, *J* = 15.0 Hz), 143.6 (dd, *J* = 231.8, 8.8 Hz), 142.6-142.2 (m), 139.2 (dd, *J* = 230.7, 7.0 Hz), 135.9 (d, *J* = 14.6 Hz), 133.4 (dd, *J* = 15.6, 10.7 Hz), 127.4 (qd, *J* = 33.6, 3.6 Hz), 123.9 (q, *J* = 271.9 Hz), 121.8-121.4 (m), 121.4 (dq, *J* = 22.0, 3.6 Hz), 107.4 (dd, *J* = 24.9, 2.1 Hz), 44.5-44.3 (m); ^{19}F NMR (376 MHz, acetone-d_6) δ -62.1 (s, 3 F), -125.1 (s, 1 F), -143.3 (d, 1 F, *J* = 6.6 Hz), -155.7 (d, 1 F, *J* = 6.6 Hz); HRMS (HESI) *m/z* calcd for $C_{13}H_9N_4O_2F_6$ $[M+H]^+$ 367.0624, found 367.0623.

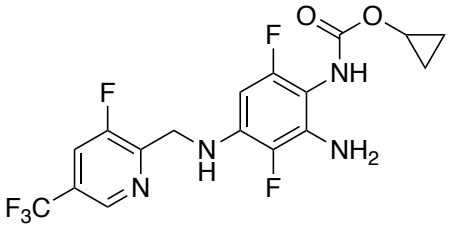


Cyclopropyl (2-amino-3,5-difluoro-4-(((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)methyl)amino)phenyl)carbamate (RL-01). A solution of **5k** (0.220 g, 0.601 mmol) in MeOH (6 mL) was treated with zinc powder (0.196 g, 3.00 mmol) followed by a 5 M aqueous ammonium chloride solution (0.60 mL, 3.00 mmol). The reaction mixture was stirred vigorously at room temperature for 2 h, filtered through Celite, and the filtrate was concentrated in vacuo, diluted with EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. A solution of the residue in dry CH_2Cl_2 (12 mL) was treated with diisopropylethylamine (0.125 mL, 0.721 mmol) followed by cyclopropyl chloroformate (0.43 mL, 0.600 mmol). The reaction mixture was stirred vigorously at room temperature for 4 h, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1, containing Et_3N (1%)) to give a crude product that was recrystallized (CH_2Cl_2/hexanes) to afford **RL-01** (0.093 g, 37%) as a colorless solid: Mp 137-138 °C; IR (ATR) 3366, 1714, 1523, 1336, 1234, 1136 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1 H), 7.60 (d, 1 H, *J* = 9.0 Hz), 6.91 (s, 1 H), 6.46 (s, 1 H), 4.90 (brs, 1 H), 4.71 (s, 2 H), 4.14-4.07 (m, 1 H), 3.42 (brs, 2 H), 0.78-0.60 (m, 4 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.4 (d, *J* = 260.8 Hz), 155.0, 150.7 (d, *J* = 15.6 Hz), 146.6 (d, *J* = 230.7 Hz), 144.0 (d, *J* = 224.2 Hz), 141.9-141.6 (m), 127.0 (qd, *J* = 33.9, 3.0 Hz), 125.4, 123.2, 122.7 (q, *J* = 272.9 Hz), 120.3 (dq, *J* = 21.5, 3.3 Hz), 116.8, 107.1, 50.0, 45.4, 5.2; ^{19}F NMR (565 MHz, $CDCl_3$) δ -62.1 (s, 3 F), -125.2 (s, 1 F), -139.5 (s, 1 F), -147.1 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{15}N_4O_2F_6$ $[M+H]^+$ 421.1094, found 421.1093.



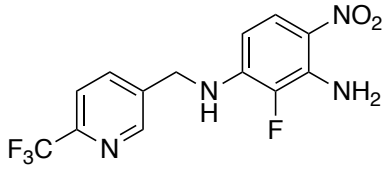
2,5-Difluoro-*N*1-((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)methyl)-4-nitrobenzene-1,3-diamine (5l). An oven-dried sealable vial was charged with **3f** (0.364 g, 1.87 mmol) and 2,3,5-trifluoro-6-nitroaniline **4d** (0.300 g, 1.56 mmol), evacuated and back filled with N_2 (3x),

and charged with dry DMSO (3 mL) followed by Et_3N (0.24 mL, 1.72 mmol) and I_2 (0.198 g, 0.781 mmol). The vial was sealed and the reaction mixture was heated to 60 °C for 30 h, cooled to room temperature, diluted with water (30 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (acetone/hexanes, 1:4, containing Et_3N (0.2%)) to yield a yellow solid that was recrystallized (EtOAc) to afford **5l** (0.21 g, 37%) as yellow powder: Mp 181-182 °C; IR (ATR) 3387, 1639, 1334, 1276, 1137 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1 H), 8.29 (d, 1 H, *J* = 9.2 Hz), 7.39 (brs, 1 H), 6.90 (s, 2 H), 6.22 (dd, 1 H, *J* = 15.2, 7.2 Hz), 4.72 (d, 2 H, *J* = 5.6 Hz); ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.6 (d, *J* = 260.0 Hz), 155.1 (d, *J* = 252.7 Hz), 150.7 (d, *J* = 14.6 Hz), 141.7-141.5 (m), 141.0 (dd, *J* = 10.7, 14.6 Hz), 135.7 (d, *J* = 14.0 Hz), 133.2 (d, *J* = 226.6 Hz), 125.8 (qd, *J* = 33.1, 3.4 Hz), 122.9 (q, *J* = 272.8 Hz), 121.1 (dq, *J* = 21.9, 3.2 Hz), 115.0 (dd, *J* = 10.6, 3.2 Hz), 88.7 (d, *J* = 28.7 Hz), 42.1; ^{19}F NMR (376 MHz, acetone-d_6) δ -60.5 (s, 3 F), -119.1 (d, 1 F, *J* = 11.3 Hz), -123.8 (s, 1 F), -160.6 (d, 1 F, *J* = 11.3 Hz); HRMS (HESI) *m/z* calcd for $C_{13}H_9N_4O_2F_6$ $[M+H]^+$ 367.0624, found 367.0621.



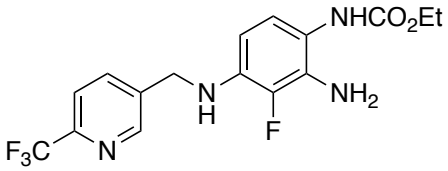
Cyclopropyl (2-amino-3,6-difluoro-4-(((3-fluoro-5-(trifluoromethyl)pyridin-2-yl)methyl)amino)phenyl)carbamate (RL-12). A solution of **5l** (0.200 g, 0.546 mmol) in MeOH (6 mL) was treated with zinc powder (0.179 g, 2.73 mmol) followed by a 5 M aqueous ammonium chloride solution (0.55 mL, 2.73 mmol). The reaction mixture was stirred vigorously at room temperature for 2 h, filtered through Celite, and the filtrate was concentrated, diluted with EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. A solution of the residue in dry CH_2Cl_2 (10 mL) was treated with diisopropylethylamine (0.12 mL, 0.68 mmol) followed by cyclopropyl chloroformate (0.39 mL, 0.546 mmol), stirred vigorously at room temperature for 4 h, and quenched with saturated aqueous $NaHCO_3$. The

aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1, containing Et_3N (1%)) to yield a beige solid that was recrystallized (CH_2Cl_2/hexanes) to afford **RL-12** (0.095 g, 41%) as an off-white solid: Mp 200-202 °C; IR (ATR) 3345, 1695, 1660, 1344, 1278, 1128 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 8.84 (s, 1 H), 8.28 (d, *J* = 9.6 Hz, 1 H), 8.17 (s, 1 H), 6.07 (brs, 1 H), 5.94-5.85 (m, 1 H), 4.94 (s, 2 H), 4.55 (d, *J* = 5.4 Hz, 2 H), 4.03-3.86 (m, 1 H), 0.72-0.38 (m, 4 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 156.7 (d, *J* = 259.5 Hz), 155.7 (d, *J* = 236.1 Hz), 155.5, 151.6 (d, *J* = 14.4 Hz), 141.8-141.4 (m), 135.6 (d, *J* = 225.4 Hz), 135.7-135.3 (m), 134.5, 125.5 (qd, *J* = 33.0, 3.5 Hz), 122.9 (q, *J* = 272.7 Hz), 121.0 (dq, *J* = 22.1, 3.2 Hz), 100.8 (d, *J* = 16.1 Hz), 86.4 (d, *J* = 27.4 Hz), 48.8, 42.7, 4.8; ^{19}F NMR (565 MHz, DMSO-d_6) δ -60.5 (s, 3 F), -124.0 (s, 1 F), -126.3 (d, 1 F, *J* = 11.3 Hz), -160.5 (d, 1 F, *J* = 11.3 Hz); HRMS (HESI) *m/z* calcd for $C_{17}H_{15}N_4O_2F_6$ $[M+H]^+$ 421.1094, found 421.1091.

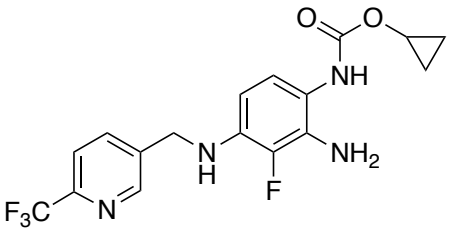


2-Fluoro-4-nitro-*N*^{1}-((6-(trifluoromethyl)pyridin-3-yl)methyl)benzene-1,3-diamine (5m). A solution of 3-(aminomethyl)-6-(trifluoromethyl)pyridine **3g** (0.200 g, 1.08 mmol) and 2,3-difluoro-6-nitroaniline **4a** (0.203 g, 1.13 mmol) in dry DMSO (2 mL) was treated under N_2 with Et_3N (0.16 mL, 1.19 mmol) and I_2 (11 mg, 0.04 mmol). The reaction mixture was heated to 120 °C for 30 h, cooled to room temperature, diluted with water (20 mL), and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (acetone/hexanes, 1:8 to 1:5 to 1:4, containing Et_3N (1%)) to afford **5m** (0.302 g, 85%) as a yellow solid: Mp 151.8-152.2 °C; IR (ATR) 3478, 3364, 1631, 1484, 1335, 1286, 1251, 1178, 1131, 1085 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.81 (s, 1 H), 8.08 (d, 1 H, *J* = 8.0 Hz), 7.82 (d, 1 H, *J* = 8.4 Hz), 7.78-7.75 (m, 1 H), 6.71 (brs, 3 H), 6.27-6.21 (m, 1 H), 4.80 (d, 2 H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 150.2, 147.2 (q, *J* = 34.0 Hz), 142.0 (d, *J* = 9.0 Hz), 139.6, 138.6 (d, *J* = 228.0 Hz), 137.3, 136.7 (d, *J* = 13.0 Hz),

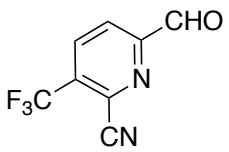
125.6 (d, *J* = 4.0 Hz), 123.9 (d, *J* = 2.0 Hz), 122.8 (q, *J* = 271.0 Hz), 121.2 (q, *J* = 2.7 Hz), 101.5 (d, *J* = 3.3 Hz), 44.2; ^{19}F NMR (376 MHz, acetone-d_6) δ -68.2 (s, 3 F), -160.3 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{13}H_{11}N_4O_2F_4$ $[M+H]^+$ 331.0813, found 331.0811.



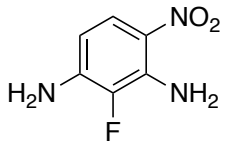
Ethyl (2-amino-3-fluoro-4-(((6-(trifluoromethyl)pyridin-3-yl)methyl)amino)phenyl)carbamate (RL-24). A solution of **5m** (0.28 g, 0.85 mmol) in EtOH (4 mL) was charged with 10% Pd/C (0.046 g) under N_2 and stirred at room temperature for 5 h under an atmosphere of H_2 (ballon). The reaction mixture was filtered through Celite (CH_2Cl_2), and concentrated in vacuo to afford a red orange solid (0.235 g, 0.78 mmol, 92%) that was added under argon at 0 °C to a solution of diisopropylethylamine (0.15 mL, 0.86 mmol) in CH_2Cl_2 (16 mL). Ethyl chloroformate (0.070 mL, 0.70 mmol) was added dropwise via syringe at 0 °C. The resulting mixture was stirred for 4 h at 0 °C, quenched with water, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 1:1 to 1:2, containing Et_3N (1%)) to yield a yellow solid (0.190 g, 65%) that was recrystallized (CH_2Cl_2/hexanes) to afford **RL-24** (0.162 g) as a colorless solid: Mp 149.6-149.9 °C; IR (ATR) 2962, 3312, 3295, 1676, 1521, 1486, 1474, 1454, 1340, 1137, 1130, 1115, 1087, 779, 719, 714 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1 H), 7.86 (d, 1 H, *J* = 8.0 Hz), 7.65 (d, 1 H, *J* = 8.0 Hz), 6.74 (d, 1 H, *J* = 8.5 Hz), 6.13 (brs, 1 H), 5.96 (t, 1 H, *J* = 8.5 Hz), 4.48 (d, 2 H, *J* = 6.0 Hz), 4.35 (brs, 1 H), 4.19 (q, 2 H, *J* = 7.0 Hz), 3.88 (brs, 2 H), 1.29 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 149.1, 147.3 (q, *J* = 34.0 Hz), 141.2 (d, *J* = 231.0 Hz), 138.4, 136.1, 134.4 (d, *J* = 10.0 Hz), 131.0, 121.8, 121.7 (q, *J* = 272.0 Hz), 120.5 (q, *J* = 2.6 Hz), 115.8, 101.7, 61.7, 45.1, 14.6; ^{19}F NMR (471 MHz , $CDCl_3$) δ -67.8 (s, 3 F), -155.7 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{16}H_{17}N_4O_2F_4$ $[M+H]^+$ 373.1282, found 373.1276.



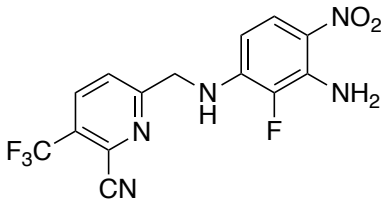
Cyclopropyl (2-amino-3-fluoro-4-(((6-(trifluoromethyl)pyridin-3-yl)methyl)amino)phenyl)carbamate (RL-67). A mixture of **5m** (0.200 g, 0.606 mmol) and zinc powder (0.198 g, 3.03 mmol) in MeOH (7 mL) was treated dropwise with 5 M aqueous ammonium chloride solution (0.61 mL, 3.03 mmol), and stirred vigorously at room temperature for 1 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was diluted with EtOAc and saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc (3 x 10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The dark red residue was dissolved in dry CH_2Cl_2 (12 mL) and treated with diisopropylethylamine (0.13 mL, 0.73 mmol) followed by an 0.8 M solution of cyclopropyl chloroformate in toluene (0.76 mL, 0.61 mmol). The reaction mixture was stirred vigorously at room temperature for 4 h, quenched with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and purified by chromatography on SiO_2 (EtOAc/hexanes, 3:7 to 1:1, containing Et_3N (1%)) to yield a light yellow solid that was recrystallized (CH_2Cl_2/hexanes) to afford **RL-67** (0.064 g, 28%) as a colorless solid: Mp 148-149 °C; IR (ATR) 3345, 1707, 1638, 1527, 1335, 1237, 1134, 1085, 775 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 8.79 (s, 1 H), 8.05 (d, *J* = 7.8 Hz, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.66 (brs, 1 H), 6.73 (s, 1 H), 5.98 (app t, *J* = 8.4 Hz, 1 H), 5.53 (brs, 1 H), 4.59 (d, 2 H), 4.44 (brs, 2 H), 4.10-3.99 (m, 1 H), 0.71-0.52 (m, 4 H); ^{13}C NMR (151 MHz, acetone-d_6) δ 156.3, 150.2, 146.9 (q, *J* = 34.1 Hz), 141.7 (d, *J* = 238.5 Hz), 140.9, 137.2, 135.1, 132.4, 122.9 (q, *J* = 272.9 Hz), 122.4, 121.2-121.0 (m), 116.4, 101.2, 49.6, 45.0, 5.3; ^{19}F NMR (565 MHz, acetone-d_6) δ -68.1 (s, 3 F), -157.6 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{17}N_4O_2F_4$ $[M+H]^+$ 385.1282, found 385.1281.



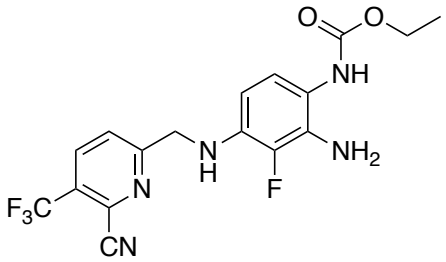
6-Formyl-3-(trifluoromethyl)picolinonitrile (3h). A solution of TBAF (0.45 mL, 0.452 mmol) and 6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(trifluoromethyl)picolinonitrile (0.13 g, 0.411 mmol) in THF (2 mL) was stirred at room temperature for 1 h, and concentrated under reduced pressure. A solution of the crude residue and SeO_2 (0.050 g, 0.452 mmol) in 1,4-dioxane (1 mL) was heated at 110 °C for 8 h, cooled to room temperature, filtered through Celite, and the Celite was washed (CH_2Cl_2). The filtrate was concentrated under reduced pressure and purified by chromatography on SiO_2 (EtOAc/hexanes, 1:10) to afford **3h** (0.031 g, 38%) as light yellow oil: IR (ATR) 1724, 1307, 1141, 1119, 1036, 856, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (d, 1 H, *J* = 0.4 Hz), 8.34 (d, 1 H, *J* = 8.0 Hz), 8.27 (d, 1 H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 155.0, 136.6 (q, *J* = 4.0 Hz), 133.6 (q, *J* = 34.0 Hz), 132.0, 123.9, 121.4 (q, *J* = 273.0 Hz), 113.5; ^{19}F NMR (376 MHz , $CDCl_3$) δ -62.1 (s); HRMS (HESI) *m/z* calcd for $C_8H_4N_2OF_3$ $[M+H]^+$ 201.0270, found 201.0270.



2-Fluoro-4-nitrobenzene-1,3-diamine (4f). A microwave vial containing a solution of 2,3-difluoro-6-nitroaniline (1.00 g, 5.74 mmol) in 1,4-dioxane (5 mL) was treated with 28% aqueous ammonium hydroxide solution (4.00 mL, 28.97 mmol). The vial was sealed and heated at 95 °C for 19 h. The solvent was removed in vacuo, and the residue was diluted with EtOAc, dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by chromatography on SiO_2 (acetone/hexanes, 1:3 to 1:2, containing Et_3N (1%)) to afford **4f** (0.85 g, 89%) as a yellow solid: Mp 174-175.5°C; IR (ATR) 3341, 1631, 1537, 1474, 1411, 1280, 1210, 758 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.71 (dd, 1 H, *J* = 9.6, 1.6 Hz), 6.13 (dd, 1 H, *J* = 9.6, 8.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 143.5 (d, *J* = 10.0 Hz), 138.3 (d, *J* = 13.0 Hz), 138.3 (d, *J* = 226.0 Hz), 124.8, 123.9 (d, *J* = 2.0 Hz), 105.9 (d, *J* = 4.0 Hz); ^{19}F NMR (471 MHz , $CDCl_3$) δ -159.2; HRMS (HESI) *m/z* calcd for $C_6H_7N_3O_2F$ $[M+H]^+$ 172.0517, found 172.0516.



6-(((3-Amino-2-fluoro-4-nitrophenyl)amino)methyl)-3-(trifluoromethyl)picolinonitrile (5n). A mixture of **3h** (0.20 g, 1.00 mmol), **4f** (0.171 g, 1.00 mmol), TsOH (0.017 g, 0.10 mmol) and 4 Å molecular sieves (200 mg) in dry xylene (1 mL) was heated at reflux for 1 h, cooled to room temperature, quenched with MeOH (0.5 mL) and treated with $NaBH_4$ (0.045 g, 1.20 mmol). The reaction mixture was stirred for 30 minutes, filtered, concentrated in vacuo, and the residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 1:4 to 1:1) to afford **5n** (0.11 g, 31%) as a yellow solid: Mp 195-196.5 °C; IR (ATR) 3359, 1636, 1280, 1131, 1039, 834, 757 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.44 (d, 1 H, *J* = 8.4 Hz), 8.04 (d, 1 H, *J* = 8.4 Hz), 7.79 (d, 1 H, *J* = 9.6, 1.6 Hz), 6.75 (brs, 3 H), 6.22 (d, 1 H, *J* = 9.6, 8.4 Hz), 4.91 (d, 2 H, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 165.6, 141.8 (d, *J* = 10.0 Hz), 138.7 (d, *J* = 228.0 Hz), 137.0 (q, *J* = 4.0 Hz), 136.7 (d, *J* = 13.0 Hz), 131.0 (q, *J* = 2.0 Hz), 129.2 (q, *J* = 33.0 Hz), 126.0, 125.8, 123.8 (d, *J* = 3.0 Hz), 123.3 (q, *J* = 271.0 Hz), 115.3, 101.5 (d, *J* = 3.0 Hz), 48.2; ^{19}F NMR (471 MHz , acetone-d_6) δ -62.3 (s, 3 F), -160.3 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{14}H_{10}N_5O_2F_4$ $[M+H]^+$ 356.0765, found 356.0764.



Ethyl (2-amino-4-(((6-cyano-5-(trifluoromethyl)pyridin-2-yl)methyl)amino)-3-fluorophenyl)carbamate (RL-23). A solution of **5n** (0.10 g, 0.28 mmol) in MeOH (2 mL) was treated with zinc powder (0.092 g, 1.41 mmol) followed by 5 M aqueous ammonium chloride solution (0.28 mL). The reaction mixture was stirred vigorously at room temperature for 40 min, treated with diisopropylethylamine (0.49 mL, 2.81 mmol) followed

by ethyl chloroformate (0.13 mL, 1.41 mmol), stirred vigorously at room temperature for 2 h, and filtered through Celite. The filter cake was washed with EtOAc, and the filtrate was diluted with EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography on SiO_2 (EtOAc/hexanes, 2:3 to 3:2, containing Et_3N (1%)) to afford **RL-23** (0.048 g, 43%) as a light yellow solid: Mp 153-154 °C; IR (ATR) 3367, 1690, 1527, 1308, 1227, 1143, 1124, 1038, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, 1 H, *J* = 8.5 Hz), 7.71 (d, 1 H, *J* = 8.0 Hz), 6.72 (d, 1 H, *J* = 8.5 Hz), 6.19 (brs, 1 H), 5.87 (t, 1 H, *J* = 8.8 Hz), 4.59 (s, 2 H), 4.19 (q, 2 H, *J* = 7.0 Hz), 3.98 (brs, 3 H), 1.28 (t, 3 H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 155.5, 141.3 (d, *J* = 230.0 Hz), 135.4 (q, *J* = 5.0 Hz), 134.0 (d, *J* = 10.0 Hz), 131.2 (d, *J* = 12.0 Hz), 130.8 (d, *J* = 2.0 Hz), 129.1 (q, *J* = 34.0 Hz), 124.3, 122.0 (q, *J* = 272.0 Hz), 121.9, 116.0, 114.3, 101.6, 61.8, 48.8, 14.7; ^{19}F NMR (471 MHz , $CDCl_3$) δ -61.7 (s, 3 F), -155.5 (s, 1 F); HRMS (HESI) *m/z* calcd for $C_{17}H_{16}N_5O_2F_4$ $[M+H]^+$ 398.1235, found 398.1231.

Metabolic Stability Properties of Selected Analogs in Liver Microsomes

Table 1. Metabolic Stability of Test Compounds in Pooled Human and Male Mouse Liver Microsomes

Compound ID	Species	*In vitro* $T_{1/2}$ (min)	*In vitro* Cl_{int} (µL/min/mg protein)	Scale-up Cl_{int} (mL/min/kg)
Verapamil	Human	16.36	84.74	106.28
	Mouse	7.82	177.30	780.12
RG	Human	970.06	1.43	1.79
	Mouse	273.86	5.06	22.27
RL-02	Human	270.26	5.13	6.43
	Mouse	50.96	27.20	119.66
RL-12	Human	312.16	4.44	5.57
	Mouse	108.37	12.79	56.28
RL-18	Human	210.91	6.57	8.24
	Mouse	98.01	14.14	62.22
RL-24	Human	405.65	3.42	4.29
	Mouse	275.65	5.03	22.12
RL-32	Human	451.33	3.07	3.85
	Mouse	292.77	4.73	20.83
RL-36	Human	76.41	18.14	22.75
	Mouse	19.05	72.76	320.14
RL-56	Human	127.65	10.86	13.62
	Mouse	83.69	16.56	72.87
RL-73	Human	349.50	3.97	4.97
	Mouse	49.65	27.92	122.83
RL-81	Human	344.48	4.02	5.05
	Mouse	187.02	7.41	32.61

Table 2. Metabolic Stability of Test Compounds in Pooled Human and Male Mouse Liver Microsomes

Compound ID	Species	Assay Format	Remaining Percentage (%)				
			0 min	15 min	30 min	45 min	60 min
Verapamil	Human	With NADPH	100.00	38.60	17.34	11.41	7.66
		Without NADPH	100.00	103.90	101.98	106.44	105.73
	Mouse	With NADPH	100.00	13.63	4.18	1.76	0.93
		Without NADPH	100.00	94.69	90.79	95.87	91.23
RG	Human	With NADPH	100.00	101.32	99.67	99.11	95.84
		Without NADPH	100.00	102.76	98.95	97.46	95.71
	Mouse	With NADPH	100.00	96.17	82.57	82.00	89.57
		Without NADPH	100.00	98.83	103.43	95.02	101.05
RL-02	Human	With NADPH	100.00	105.56	93.93	90.05	89.33
		Without NADPH	100.00	100.24	94.95	102.41	99.29
	Mouse	With NADPH	100.00	83.57	67.72	55.94	44.08
		Without NADPH	100.00	91.07	81.53	72.80	68.39
		Heat-inactivated microsomes without NADPH	100.00	110.71	100.02	98.98	100.40
RL-12	Human	With NADPH	100.00	104.29	95.46	94.46	88.96
		Without NADPH	100.00	98.09	93.08	92.79	91.29
	Mouse	With NADPH	100.00	90.71	82.28	75.60	67.81
		Without NADPH	100.00	101.45	99.47	89.92	92.79
RL-18	Human	With NADPH	100.00	98.78	89.02	89.50	82.11
		Without NADPH	100.00	94.21	87.44	84.60	84.82
	Mouse	With NADPH	100.00	88.68	83.49	73.06	64.83
		Without NADPH	100.00	94.12	91.32	86.67	83.30
RL-24	Human	With NADPH	100.00	95.27	92.42	92.93	89.08
		Without NADPH	100.00	85.65	95.02	96.18	94.72
	Mouse	With NADPH	100.00	97.99	89.91	84.83	89.01
		Without NADPH	100.00	100.37	100.07	100.46	105.64
RL-32	Human	With NADPH	100.00	101.95	95.23	97.27	91.24
		Without NADPH	100.00	101.69	109.34	96.61	105.09
	Mouse	With NADPH	100.00	102.98	96.08	91.09	89.03
		Without NADPH	100.00	109.93	107.09	97.78	103.18
RL-36	Human	With NADPH	100.00	89.48	78.65	67.46	58.33
		Without NADPH	100.00	85.28	77.70	75.44	69.25
		Heat-inactivated microsomes without NADPH	100.00	95.60	102.34	94.75	91.75
	Mouse	With NADPH	100.00	53.18	29.85	17.99	11.23
		Without NADPH	100.00	103.45	94.87	90.81	83.01
RL-56	Human	With NADPH	100.00	95.66	82.58	77.59	73.90
		Without NADPH	100.00	98.57	88.71	87.12	86.61
	Mouse	With NADPH	100.00	89.53	79.20	69.43	61.02
		Without NADPH	100.00	99.47	89.90	89.61	80.20
RL-73	Human	With NADPH	100.00	98.58	96.08	96.83	86.96
		Without NADPH	100.00	95.40	98.26	94.08	96.51
	Mouse	With NADPH	100.00	83.55	65.70	54.72	43.38
		Without NADPH	100.00	87.38	75.33	65.69	53.37
		Heat-inactivated microsomes without NADPH	100.00	103.99	106.78	116.82	95.01
RL-81	Human	With NADPH	100.00	96.86	91.85	88.26	90.09
		Without NADPH	100.00	99.04	96.48	94.79	92.86
	Mouse	With NADPH	100.00	93.27	89.30	83.30	80.14
		Without NADPH	100.00	104.80	98.59	93.88	98.46

Lilly OIDD Screening Materials and Methods

HEK293 cells expressing heteromeric human Kv7.2/3 and Kv7.3/5 channel were obtained from ChanTest Corp./Charles River Laboratories (Cat #s CT6147 and CT6018, respectively). In these cell lines, expression of Kv7.3 is constitutive, whereas expression of Kv7.2 or Kv7.5 is inducible by exposure to tetracycline/doxycycline.

HEK293 cells stably expressing homomeric human Kv7.4 and heteromeric human Kv7.4/5 channels were generated at Lilly Research Laboratories, using the Jump-In™ T-REx™ platform from Invitrogen (Carlsbad, CA).

Unless otherwise specified, all cell culture reagents were obtained from ThermoFischer Scientific (Waltham, MA), and all other reagents were obtained from Sigma-Aldrich (St Louis, MO).

Kv7 Automated Electrophysiology (IonWorks Barracuda) assay

Assay Protocol:

- Starting with a 85-95% confluent T-150 flask of HEK293 cells expressing homomeric or heteromeric Kv7 channel, cells are dissociated using 3 mL Trypsin (0.25%) for 8 min at 37 °C, 5% CO_2.
- Cells are re-suspended in External Buffer at 2.5-3.6M cells/mL and placed in the IonWorks Barracuda™ (IWB, Molecular Devices, Sunnyvale, CA) instrument.
- External Buffer, Intracellular Buffer and cells are placed into the PatchPlate by the instrument.
- Whole cell recording configuration is achieved by perforation of a patch of cell membrane with 0.1 g/L amphotericin.
- Cells are voltage clamped at -80 mV on IWB and current is measured in response to 1 s voltage steps ranging from -80 mV to +40 mV.
- Test compound is added at final concentrations of 10 μM to 0.5 nM in External Buffer and equilibrated for 6 min.
- Current measurements are repeated in the presence of the test compound.
-

Buffers:

- External Buffer: (in mM): NaCl 140, KCl 5, $CaCl_2$ 2, $MgCl_2$ 1.1, HEPES 10, glucose 10, pH 7.4 using NaOH.
- Intracellular Buffer: 90 KGluconate, 40 KCl, 3.2 $MgCl_2$, 3.2 EGTA and 5 HEPES; pH 7.25 using KOH.

Data Analysis:

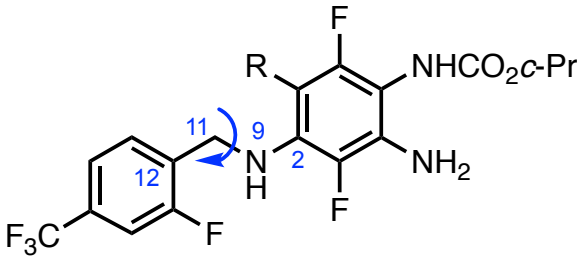
Currents (I) are converted to conductance (G) by the following formula: $G=I/(V-E_K)$, using -84 mV as the reversal potential for potassium (E_K). Conductance values after compound addition are normalized to the pre-compound max conductance (conductance at +40 mV) for the same well. Conductance-voltage (G-V) curves are generated and fit to the Boltzmann equation.

Measure parameters are:

- Conc@2xG(.15): Compound concentration that doubles the conductance at a voltage corresponding to 15% channel activation under control conditions.
- Delta V0.5: Difference in the mid-point of the G-V curve between 10 μM test compound and DMSO control.
- DeltaG@maxconc: Difference in the conductance at +40 mV between 10 μM test compound and DMSO control.
- Max obs DeltaG: Largest fold difference in the conductance at +40 mV between any concentration of test compound and DMSO control.

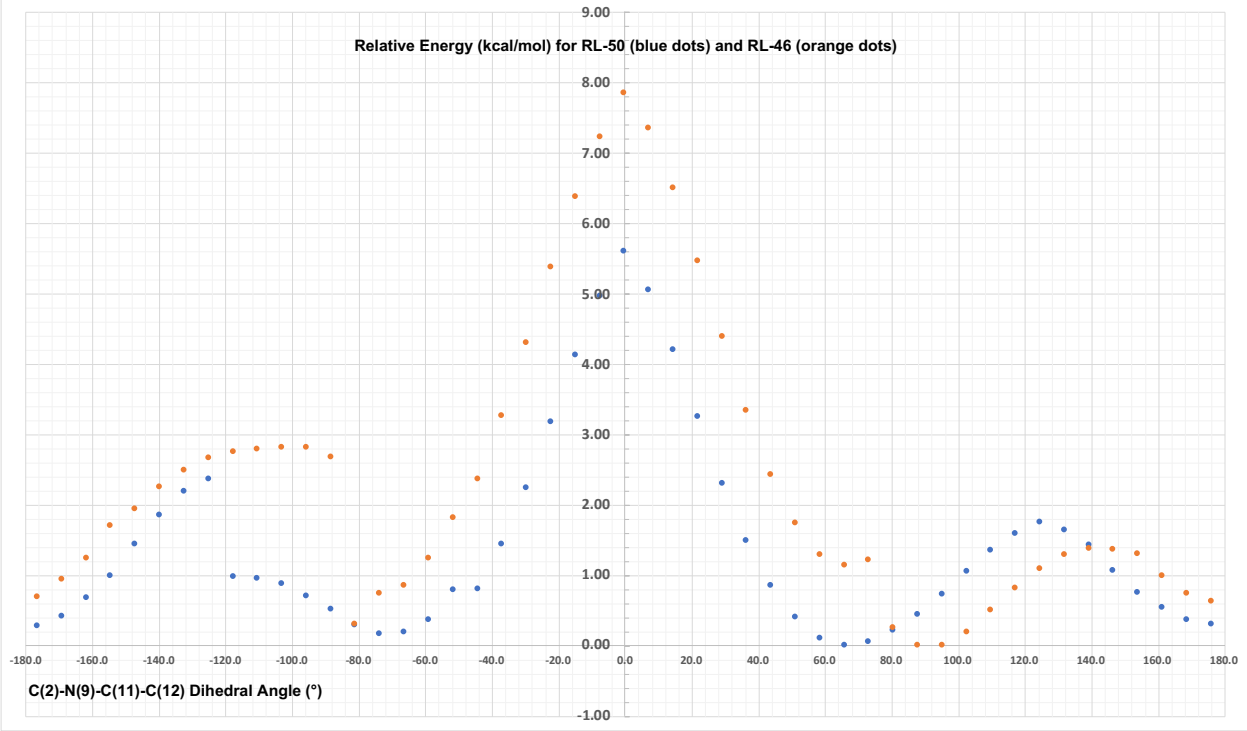
Dihedral Angle Analysis of RL-50 and RL-46

A dihedral angle analysis for **RL-50** and **RL-46** was performed in Spartan 18, Built 1.3.0 (Wavefunction Inc. Irvine, CA) and relative energies (kcal/mol) were plotted as a function of the benzylamine dihedral angle C(2)-N(9)-C(11)-C(12).

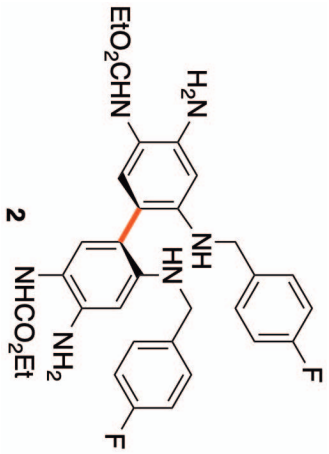


RL-50 (R = F)

RL-46 (R = H)



RL740.013 CDC13 500Mhz



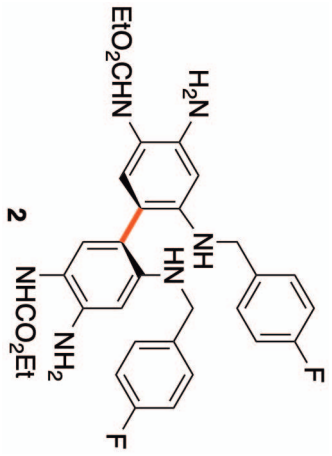
CDCl3

7.260
7.205
7.194
7.189
7.178
6.961
6.944
6.927
6.811
6.132
5.956
4.207
4.187
4.173
4.158
4.144
3.920
1.279
1.270
1.256

4.00
4.08
1.98
1.69
2.16
0.45
3.93
4.58
4.74
6.38

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

RL740.013 CDC13 500Mhz



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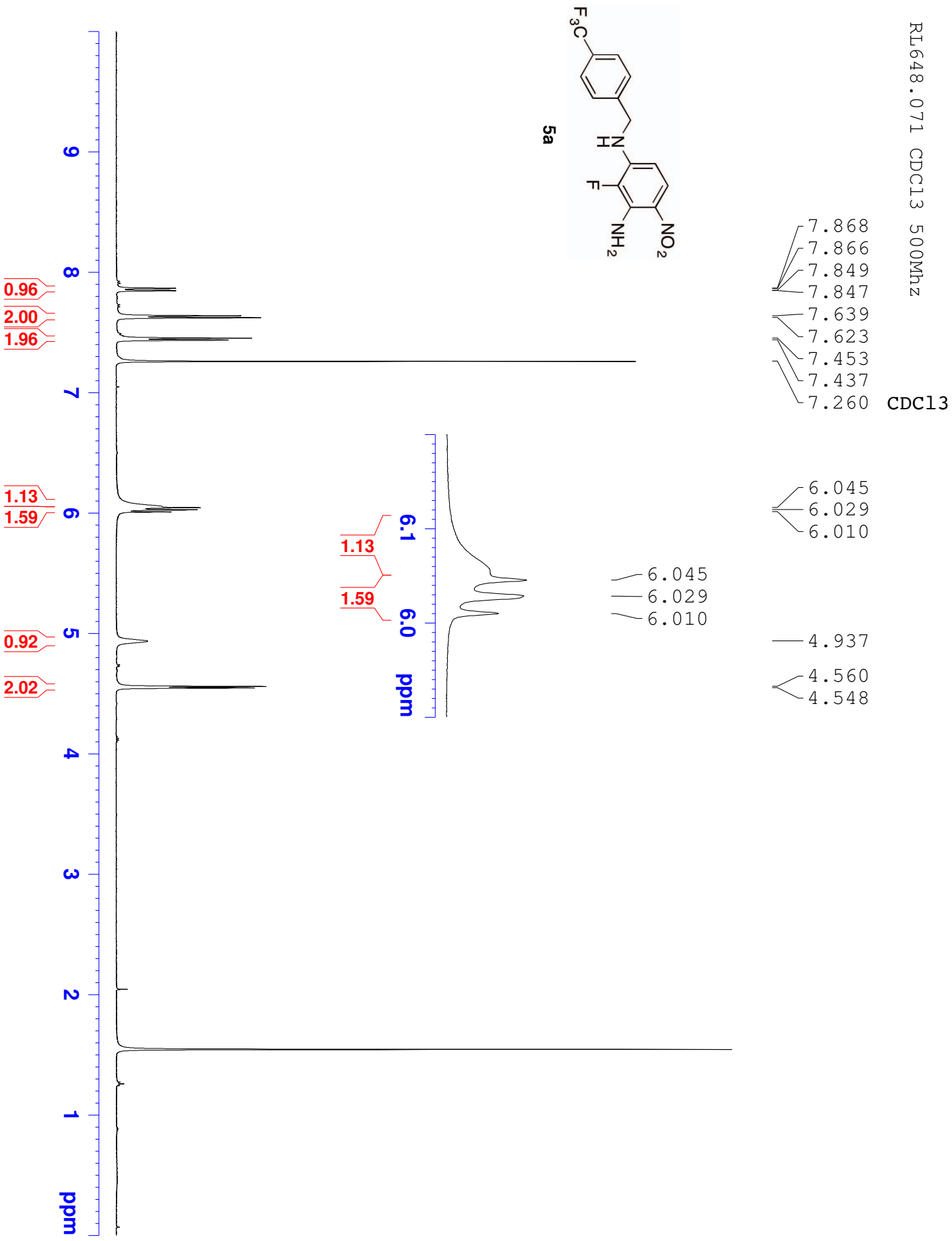
161.05
155.62
145.62
142.88
135.16
135.14
130.14
128.61
128.54
115.60
115.44
114.56
113.48
99.25
77.41
77.16
76.91
CDCl3
61.54
47.48
14.73

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm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F
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NO2
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7.639
7.623
7.453
7.437
7.260
CDCl3
6.045
6.029
6.010
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4.560
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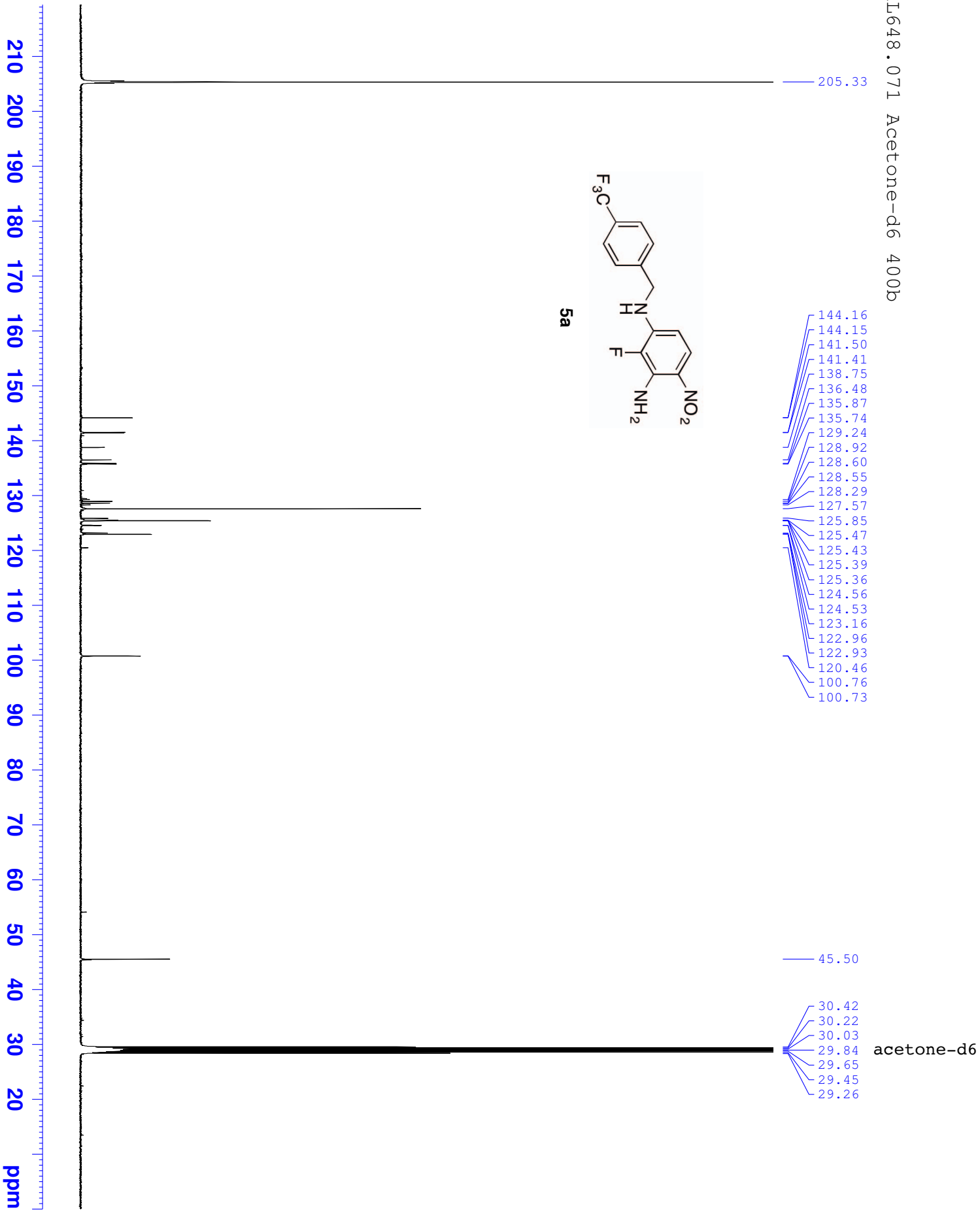
ppm
6.1
6.0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141.41
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128.92
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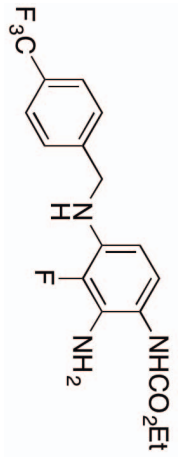
128.29
127.57
125.85
125.47
125.43
125.39
125.36
124.56
124.53
123.16
122.96
122.93
120.46
100.76
100.73
45.50
30.42
30.22
30.03
29.84
29.65
29.45
29.26
acetone-d6
5a
F3C
NH
F
NH2
NO2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

RL648.081 CDC13 400a



RL-81

CDCl3

7.599
7.579
7.472
7.452
7.260

6.738
6.717

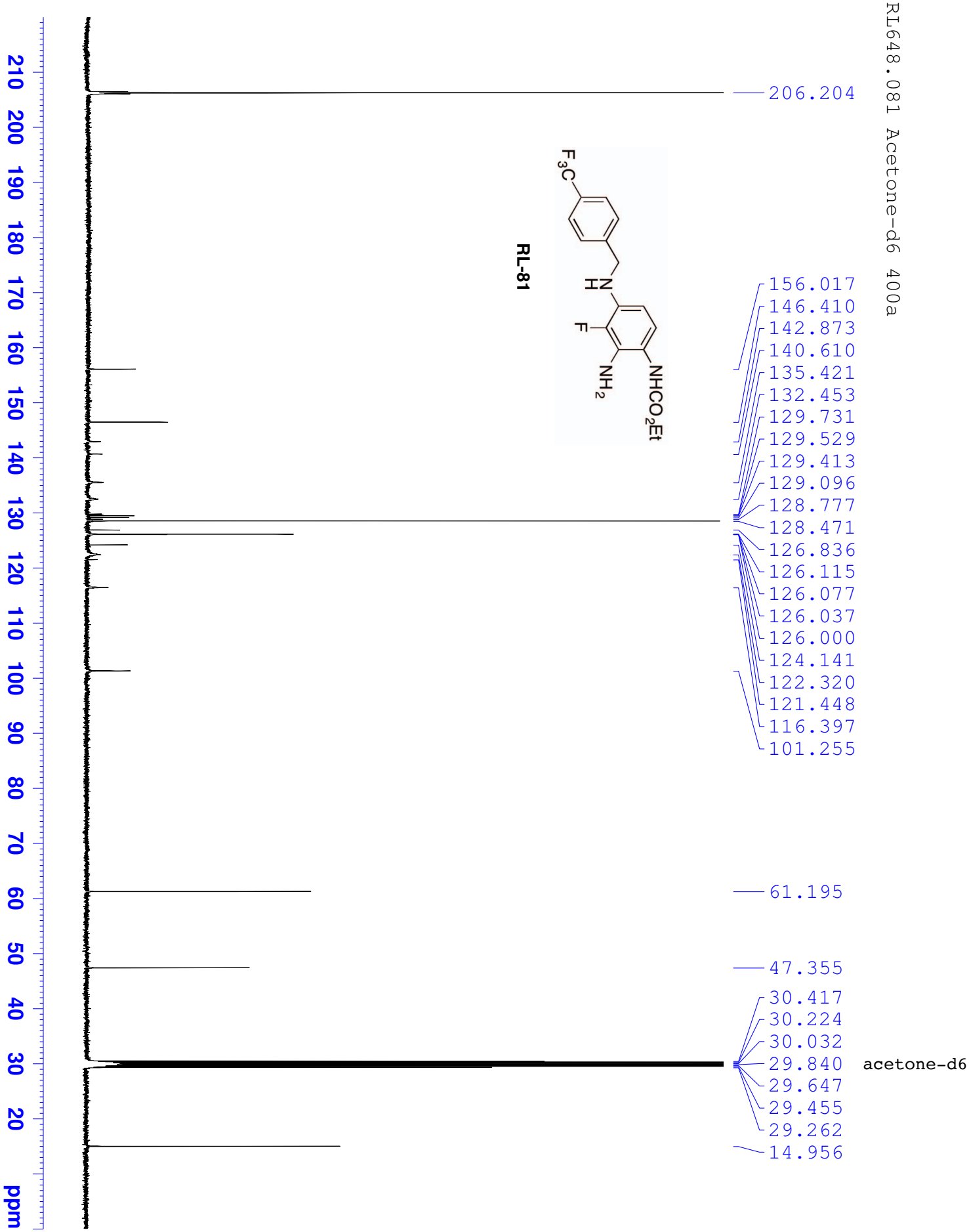
6.128
6.011
5.989
5.967

4.423
4.332
4.220
4.202
4.184
4.167
3.865

1.303
1.286
1.268

2.04
2.01
1.00
0.79
1.10
2.18
0.88
2.15
1.86
3.11

9 8 7 6 5 4 3 2 1 ppm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135.421
132.453
129.731
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129.413
129.096
128.777
128.471
126.836
126.115
126.077
126.037
126.000
124.141
122.320
121.448
116.397
101.255
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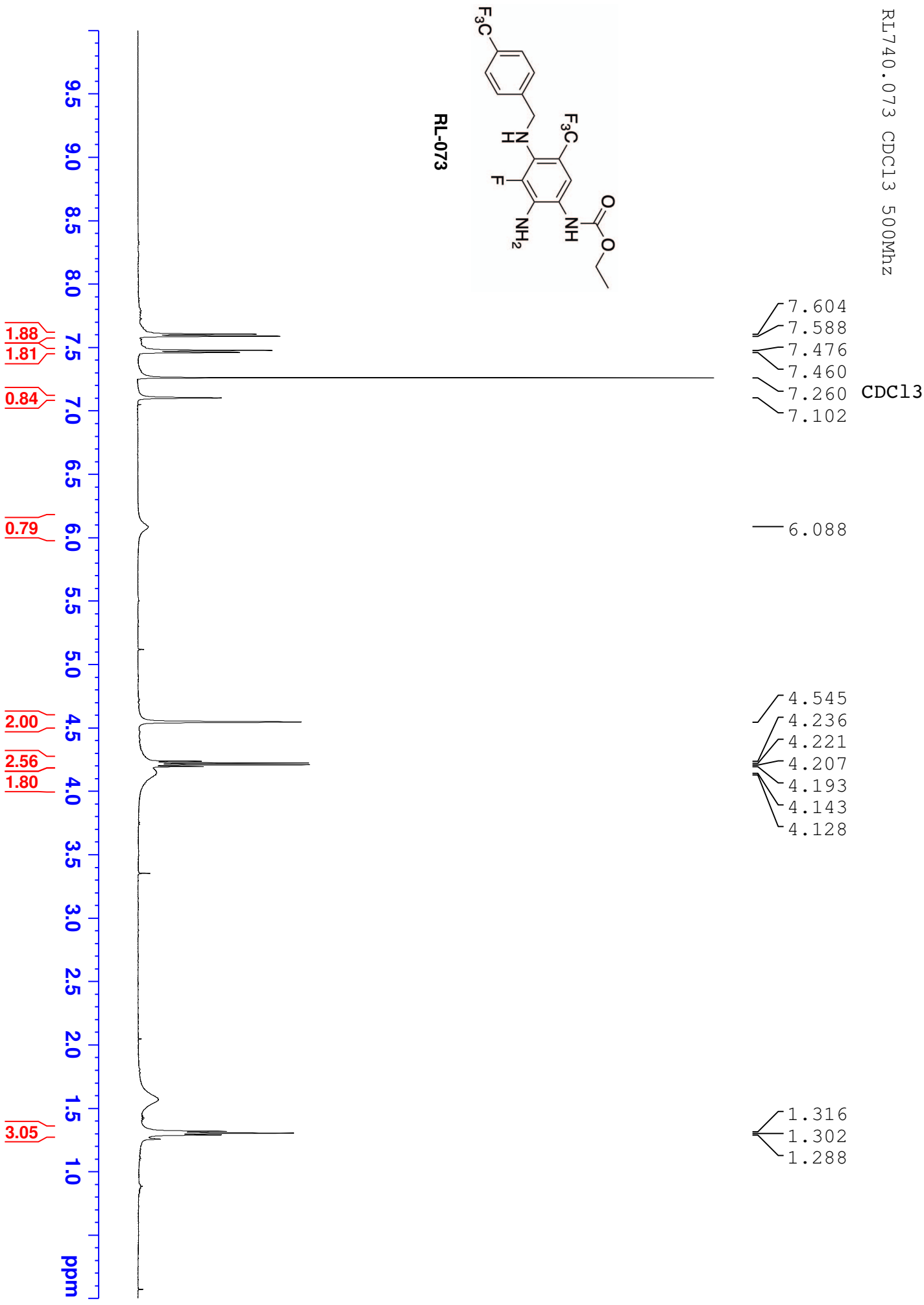
14.956
acetone-d6
ppm


RL740.073 CDCl3 500Mhz
RL-073
F3C
NH
F
NH2
NH
O
O
7.604
7.588
7.476
7.460
7.260
7.102
CDCl3
6.088
4.545
4.236
4.221
4.207
4.193
4.143
4.128
1.316
1.302
1.288
1.88
1.81
0.84
0.79
2.00
2.56
1.80
3.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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5.0
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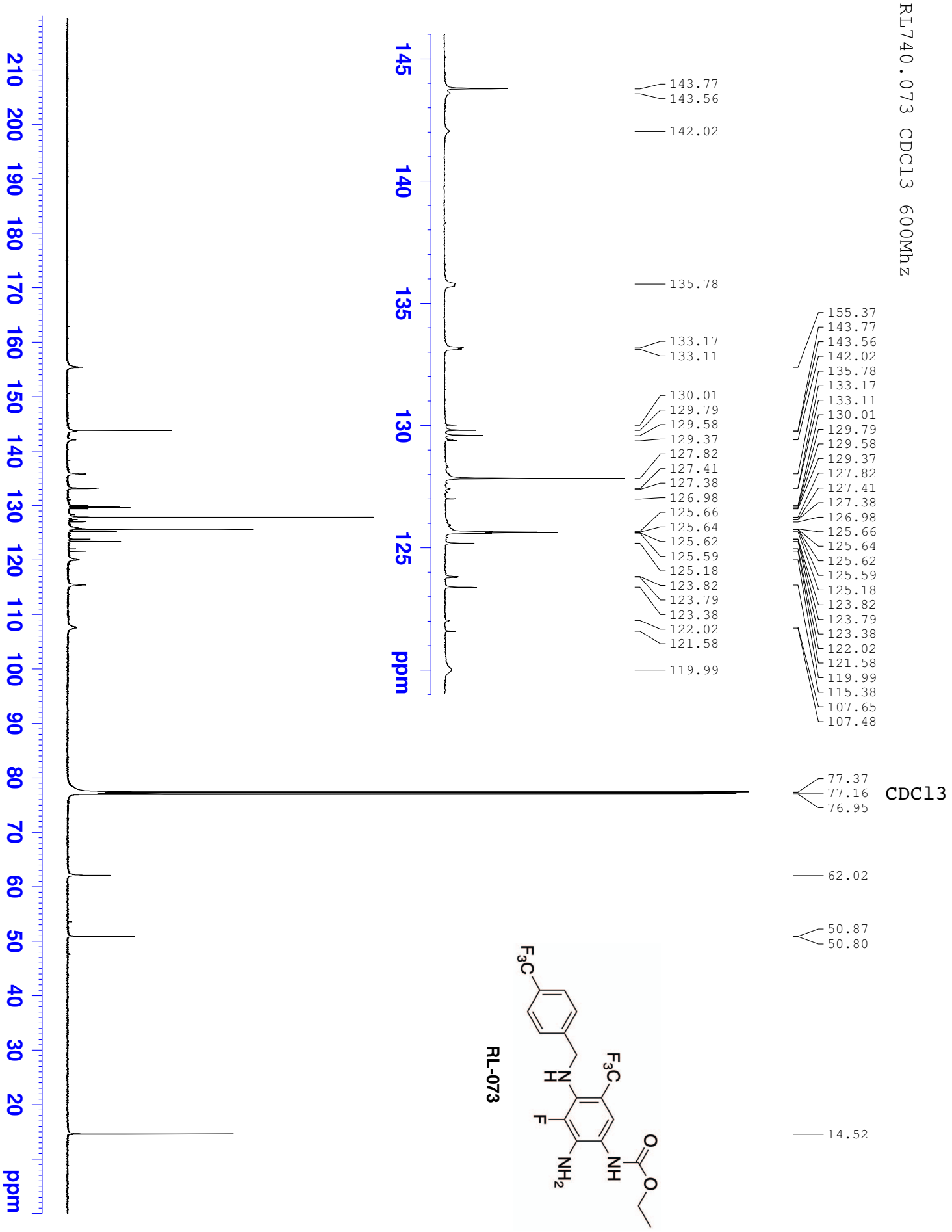
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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143.56
142.02
135.78
133.17
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130.01
129.79
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127.82
127.41
127.38
126.98
125.66
125.64
125.62
125.59
125.18
123.82
123.79
123.38
122.02
121.58
119.99
115.38
107.65
107.48
77.37
77.16
76.95
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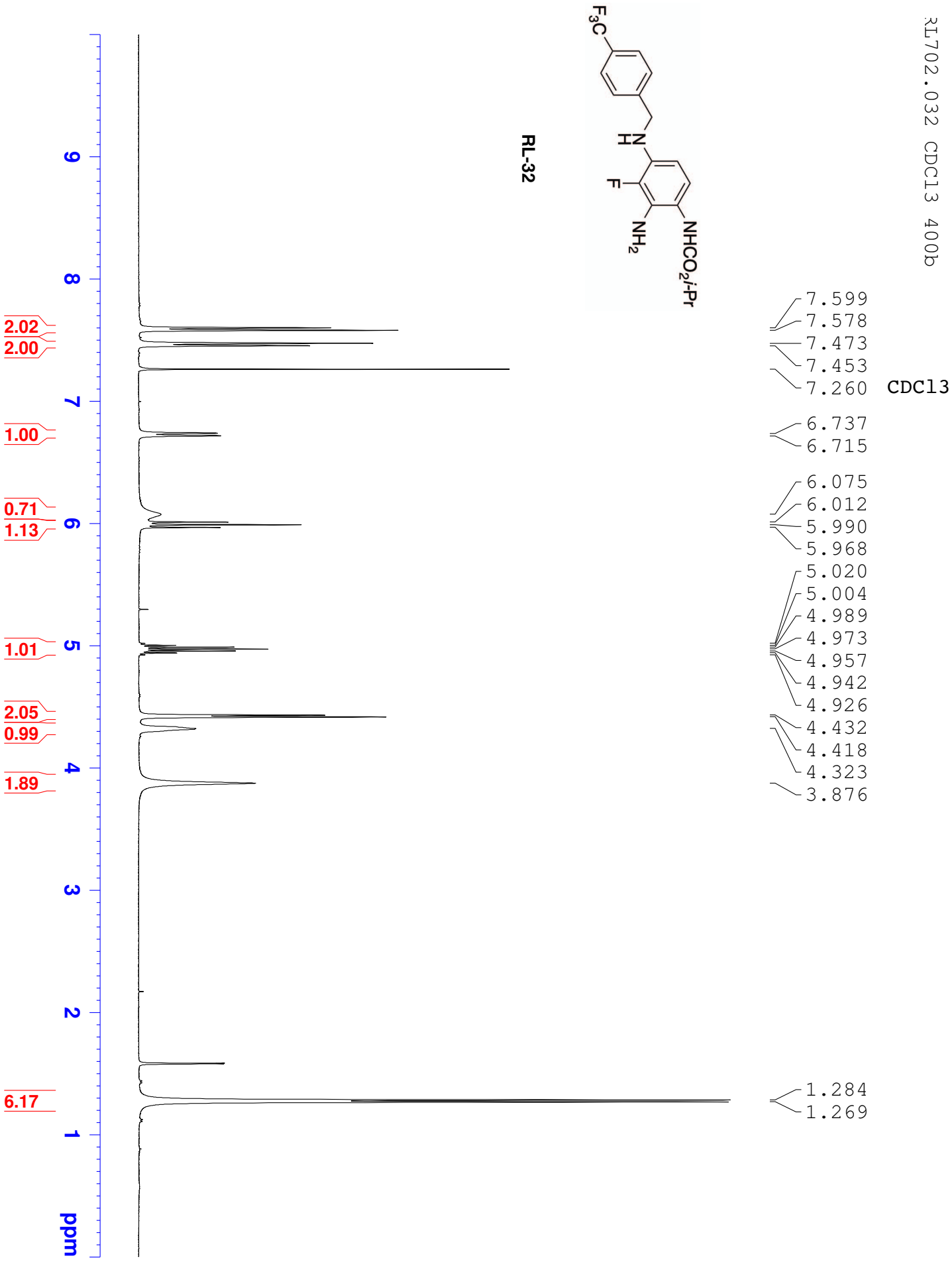
14.52
RL-073
F3C
NH
F
NH2
NH
O
O
ppm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RL-32
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F
NH2
NHCO2i-Pr
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7.578
7.473
7.453
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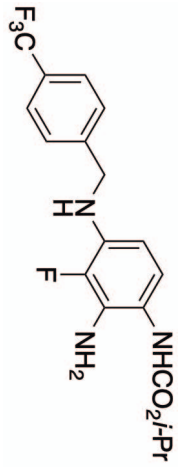
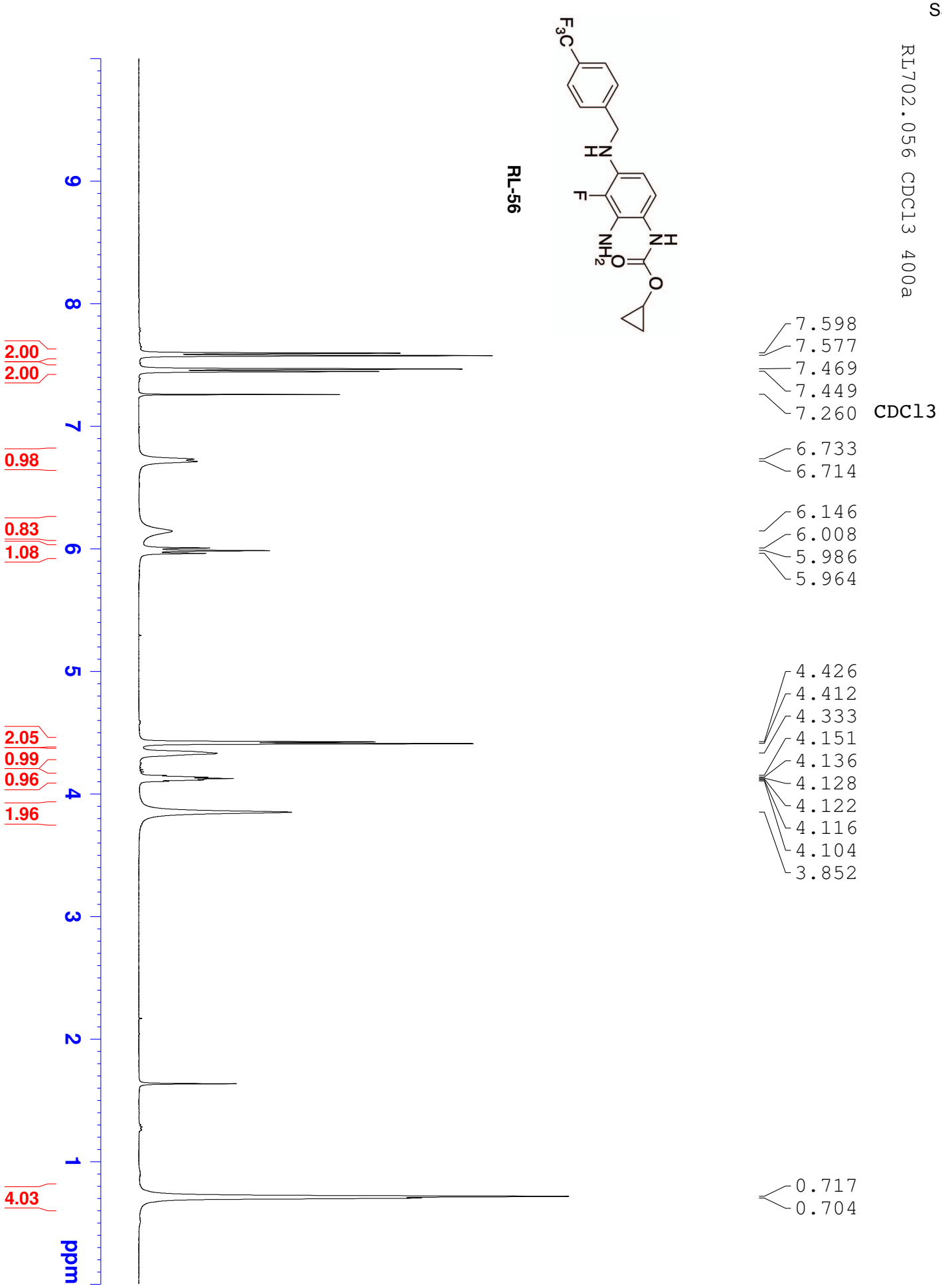
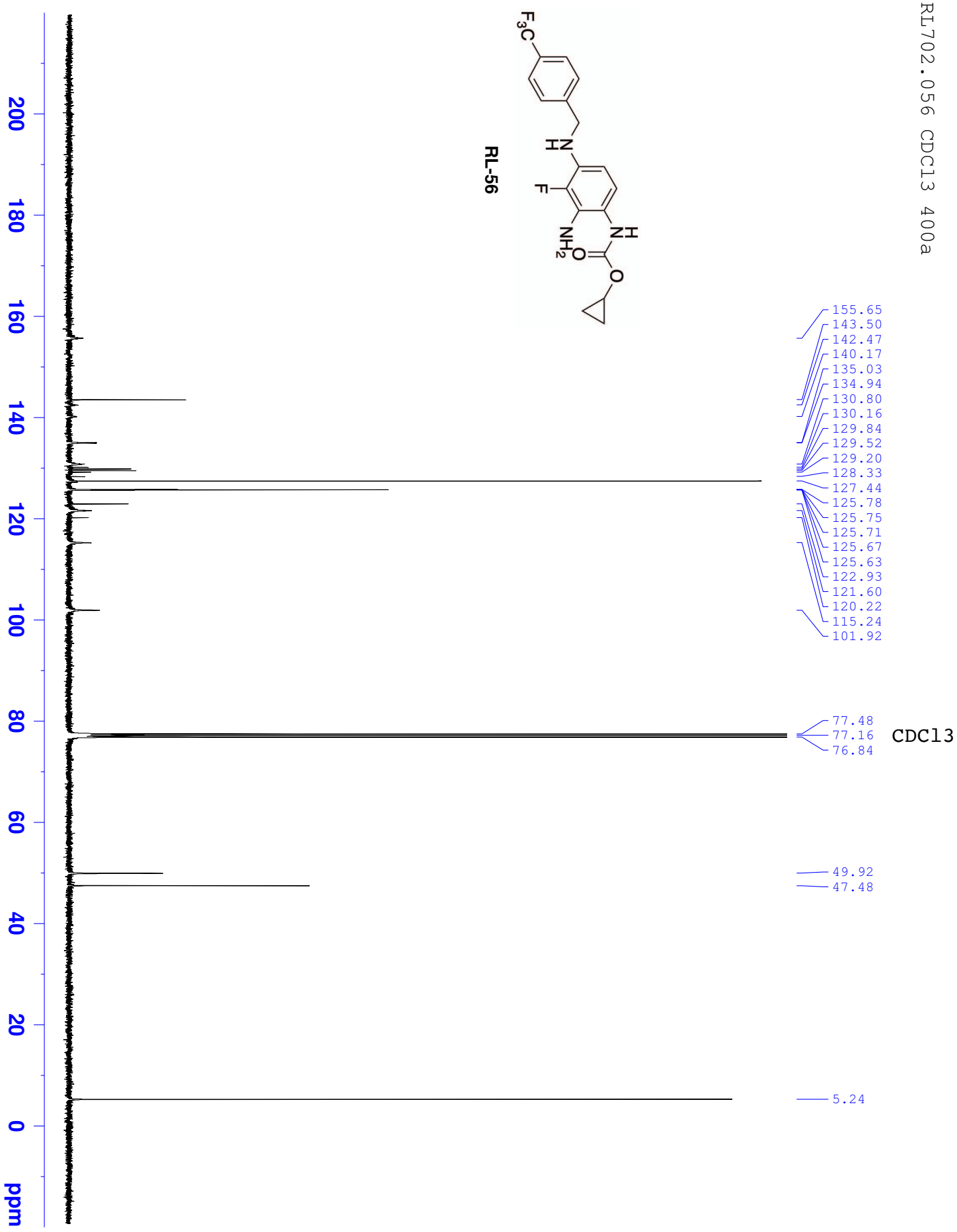
CDCl3
6.737
6.715
6.075
6.012
5.990
5.968
5.020
5.004
4.989
4.973
4.957
4.942
4.926
4.432
4.418
4.323
3.876
1.284
1.269
2.02
2.00
1.00
0.71
1.13
1.01
2.05
0.99
1.89
6.17
ppm

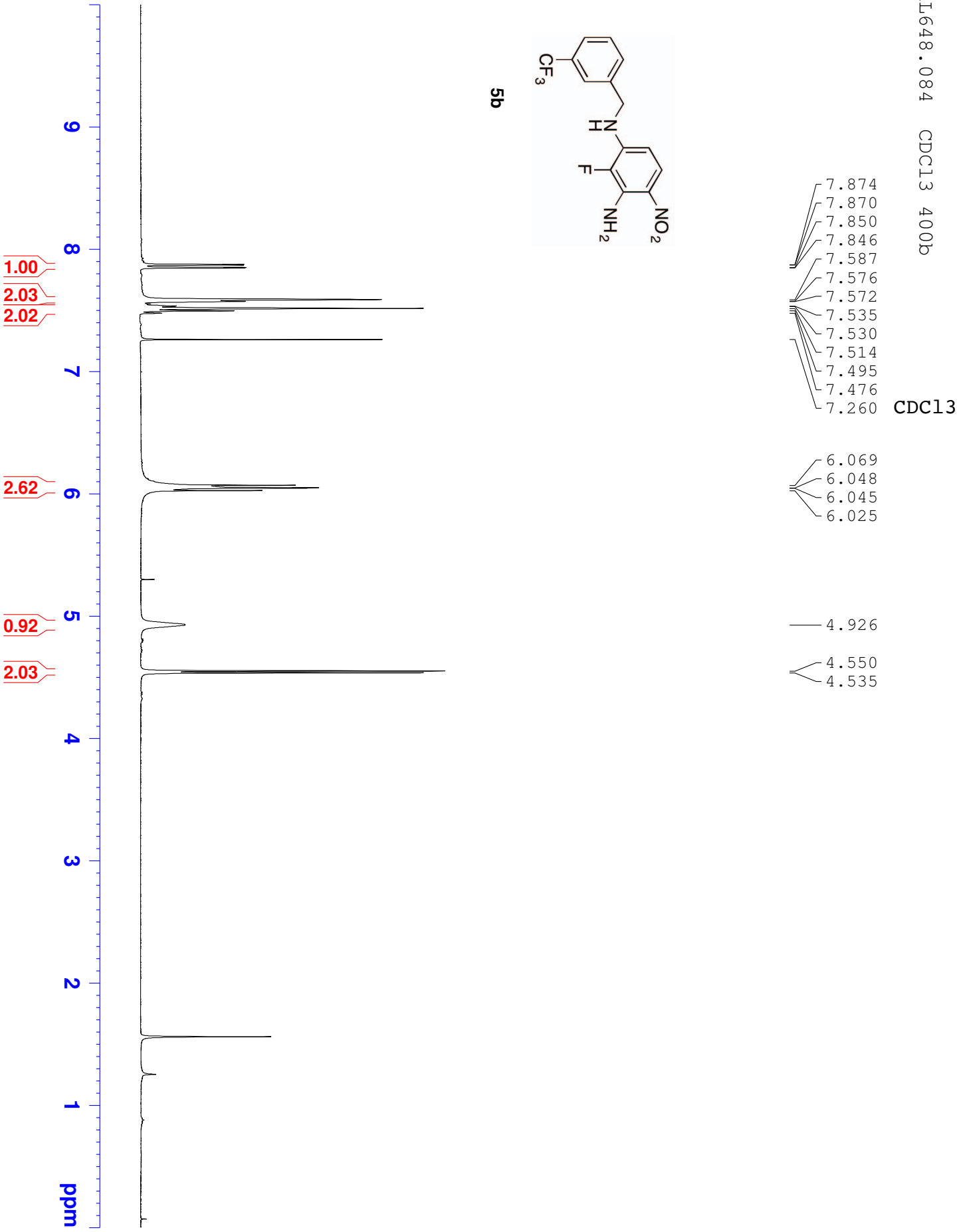
RL702.032 CDC13 400b

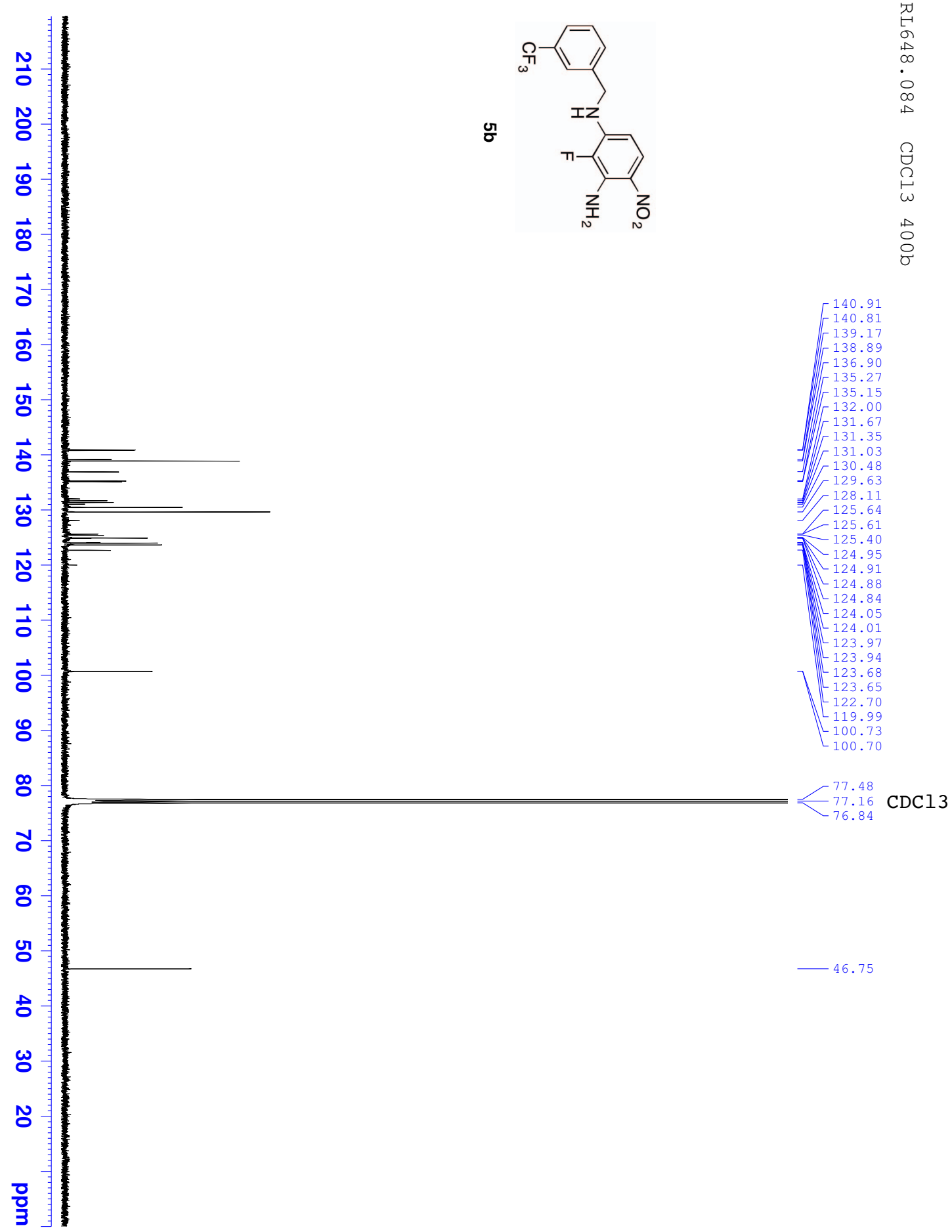


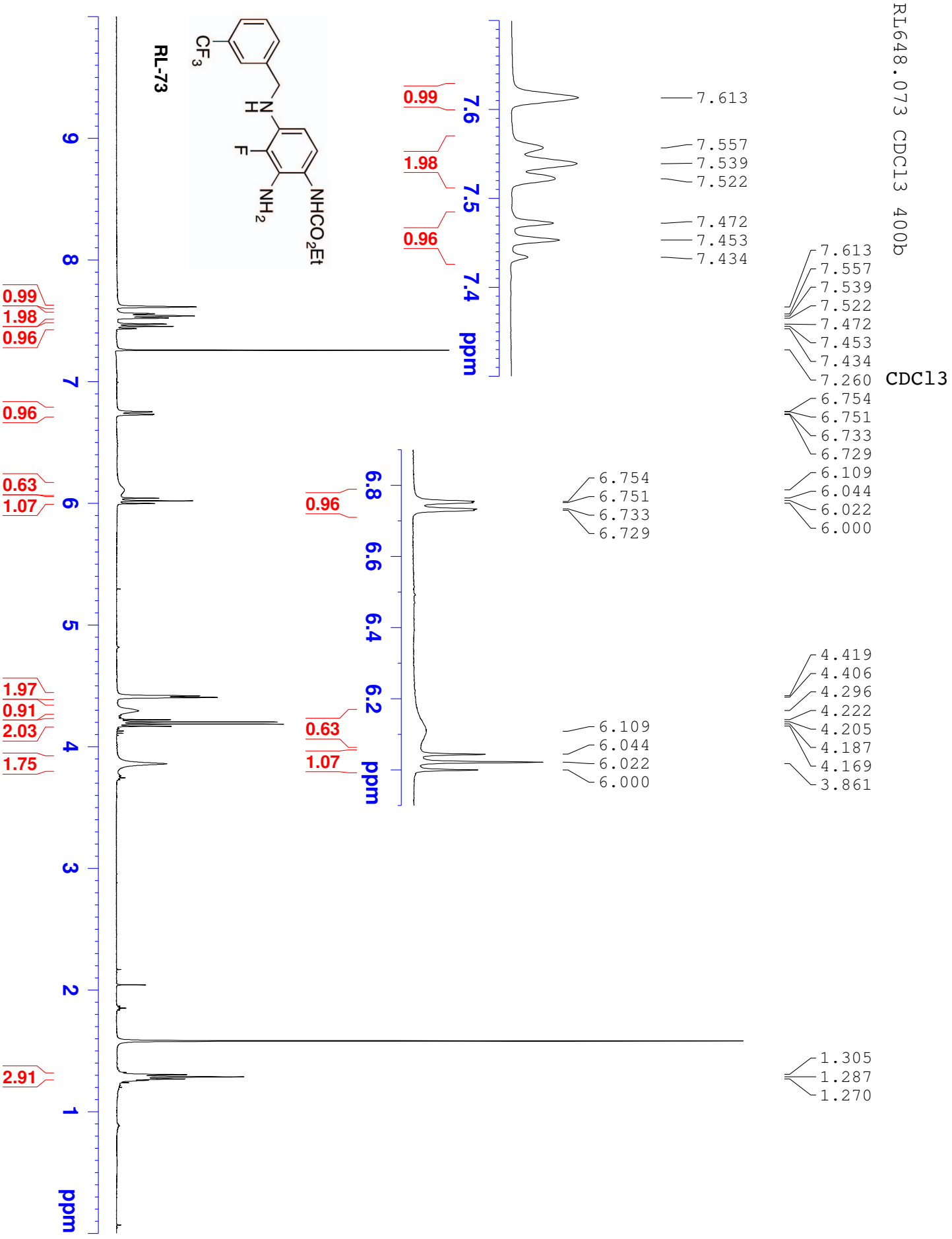
RL-32

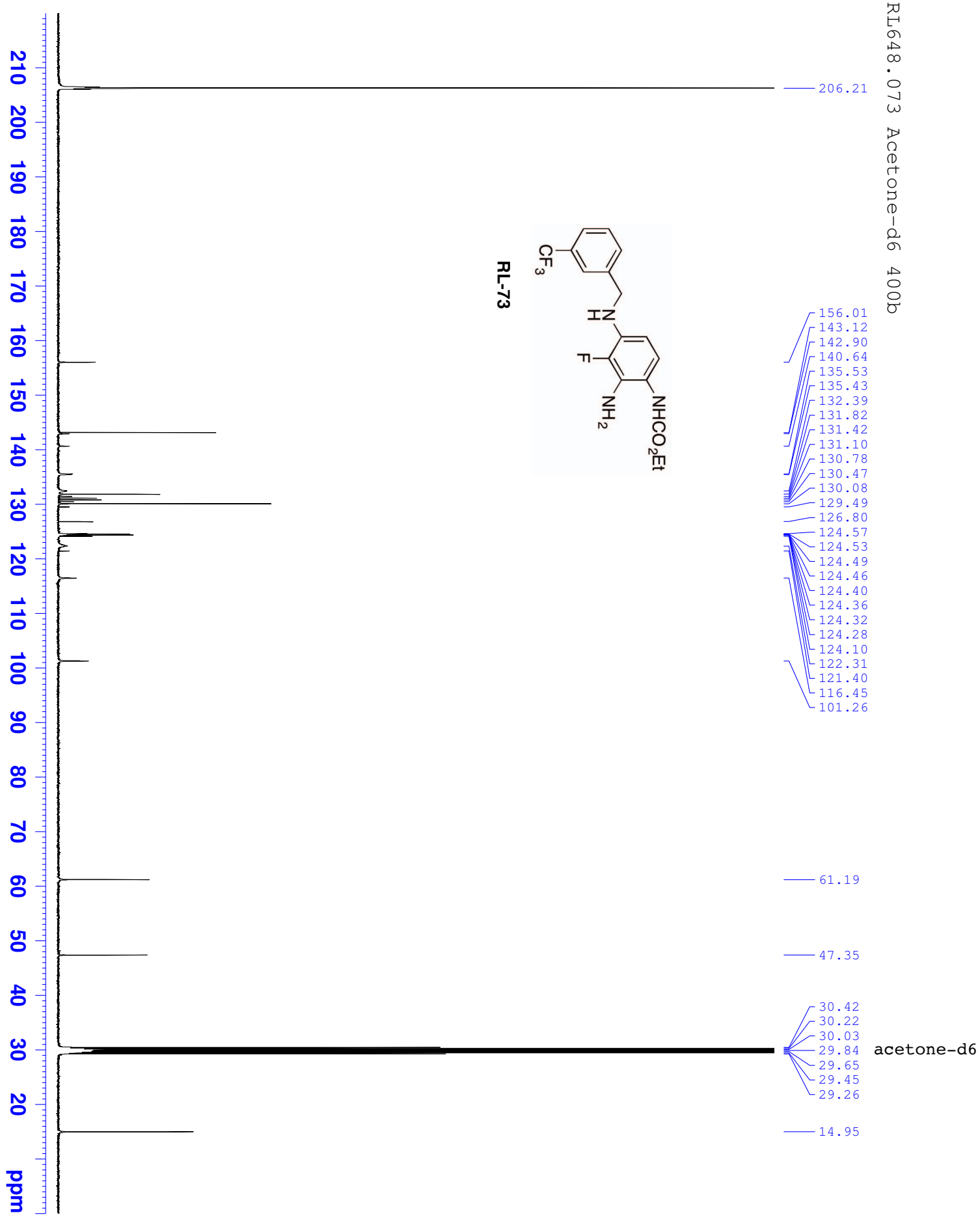

RL702.056 CDCl3 400a
RL-56
CDCl3
7.598
7.577
7.469
7.449
7.260
6.733
6.714
6.146
6.008
5.986
5.964
4.426
4.412
4.333
4.151
4.136
4.128
4.122
4.116
4.104
3.852
0.717
0.704
2.00
2.00
0.98
0.83
1.08
2.05
0.99
0.96
1.96
4.03
ppm

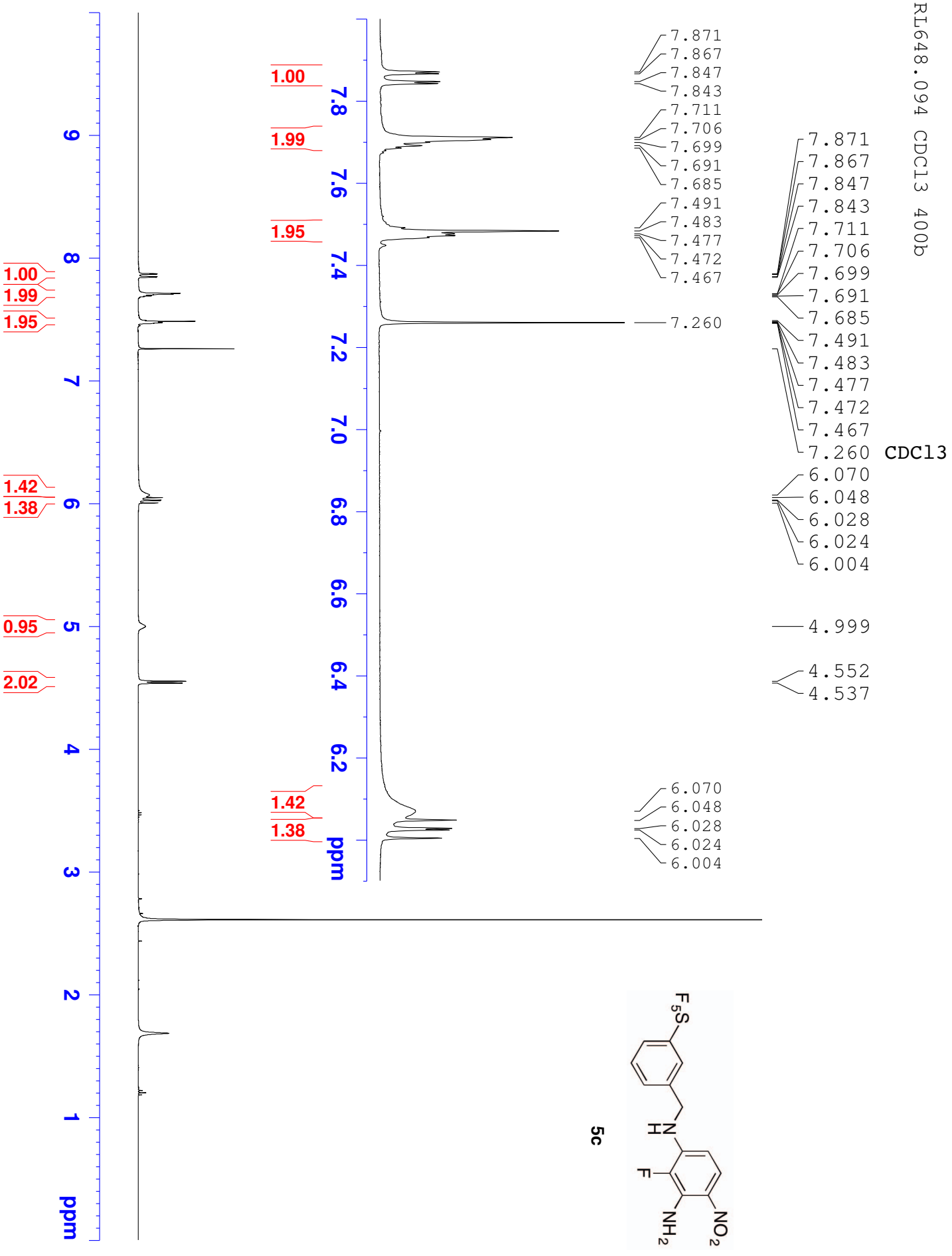

RL702.056 CDCl3 400a
RL-56
155.65
143.50
142.47
140.17
135.03
134.94
130.80
130.16
129.84
129.52
129.20
128.33
127.44
125.78
125.75
125.71
125.67
125.63
122.93
121.60
120.22
115.24
101.92
77.48
77.16
76.84
CDCl3
49.92
47.48
5.24
200
180
160
140
120
100
80
60
40
20
0
ppm


RL648.084 CDCl3 400b
5b
CF3
N
H
F
NH2
NO2
7.874
7.870
7.850
7.846
7.587
7.576
7.572
7.535
7.530
7.514
7.495
7.476
7.260
CDCl3
6.069
6.048
6.045
6.025
4.926
4.550
4.535
1.00
2.03
2.02
2.62
0.92
2.03
9
8
7
6
5
4
3
2
1
ppm

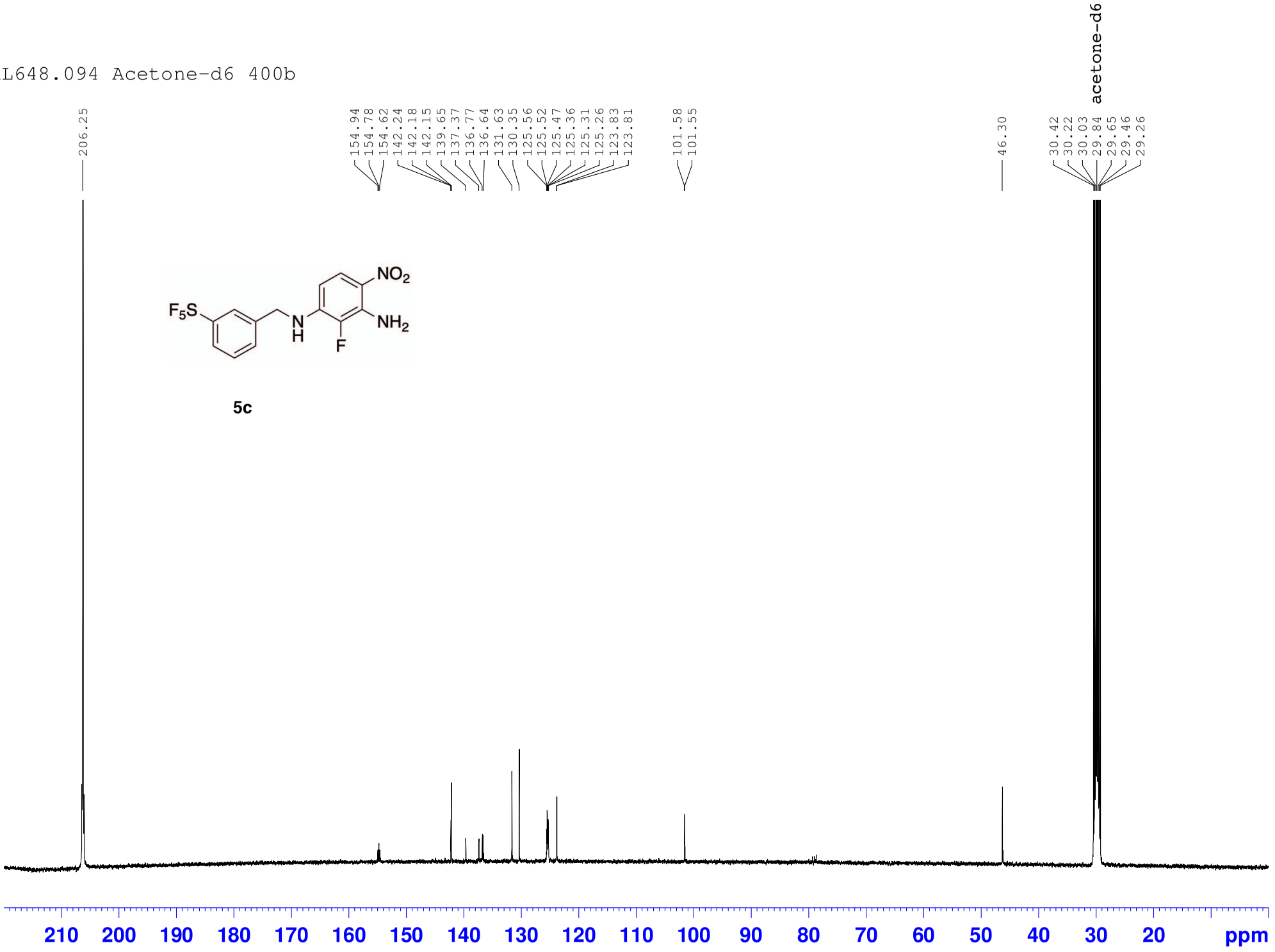

RL648.084 CDCl3 400b
5b
CF3
N
H
F
NH2
NO2
140.91
140.81
139.17
138.89
136.90
135.27
135.15
132.00
131.67
131.35
131.03
130.48
129.63
128.11
125.64
125.61
125.40
124.95
124.91
124.88
124.84
124.05
124.01
123.97
123.94
123.68
123.65
122.70
119.99
100.73
100.70
77.48
77.16
76.84
CDCl3
46.75
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


RL-73
RL648.073 CDCl3 400b
CDCl3
CF3
NH
F
NH2
NHCO2Et
0.99
1.98
0.96
0.96
0.63
1.07
1.97
0.91
2.03
1.75
2.91
0.99
1.98
0.96
0.96
0.63
1.07
ppm
7.613
7.557
7.539
7.522
7.472
7.453
7.434
6.754
6.751
6.733
6.729
6.109
6.044
6.022
6.000
4.419
4.406
4.296
4.222
4.205
4.187
4.169
3.861
1.305
1.287
1.270
7.260

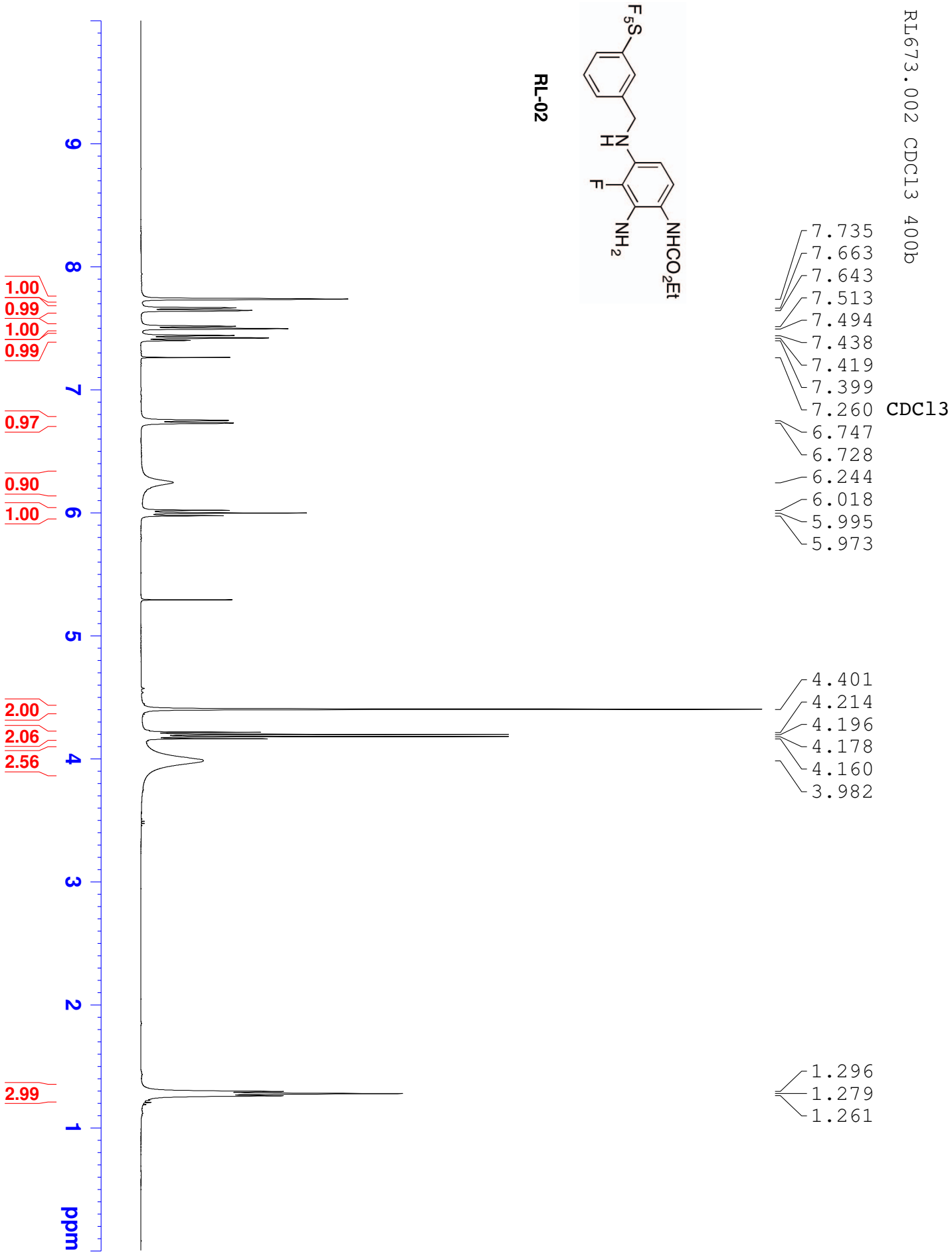

RL648.073 Acetone-d6 400b
RL-73
206.21
156.01
143.12
142.90
140.64
135.53
135.43
132.39
131.82
131.42
131.10
130.78
130.47
130.08
129.49
126.80
124.57
124.53
124.49
124.46
124.40
124.36
124.32
124.28
124.10
122.31
121.40
116.45
101.26
61.19
47.35
30.42
30.22
30.03
29.84
29.65
29.45
29.26
acetone-d6
14.95
ppm

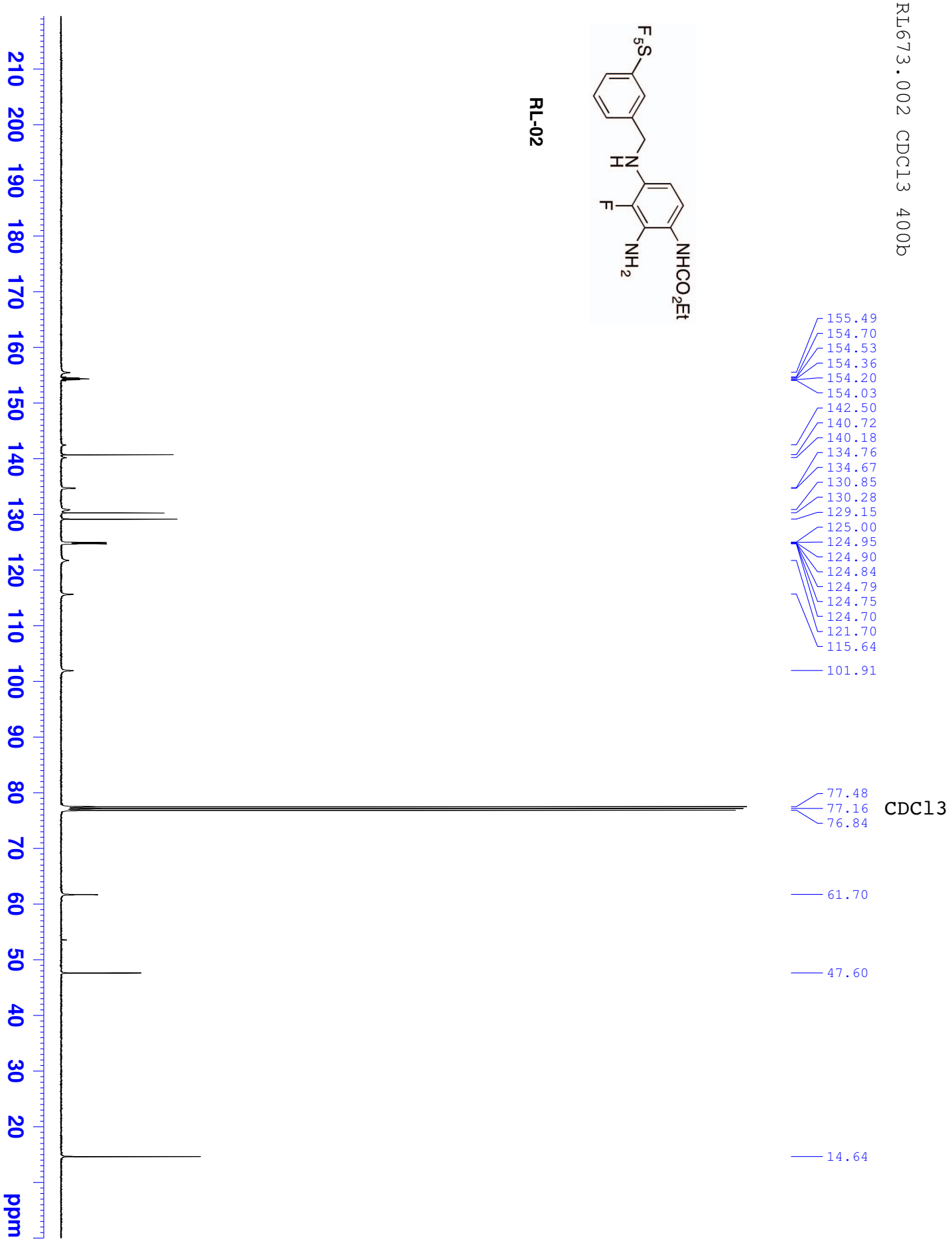

RL648.094 CDCl3 400b
7.871
7.867
7.847
7.843
7.711
7.706
7.699
7.691
7.685
7.491
7.483
7.477
7.472
7.467
7.260
CDCl3
6.070
6.048
6.028
6.024
6.004
4.999
4.552
4.537
1.00
1.99
1.95
1.42
1.38
0.95
2.02
ppm
5c

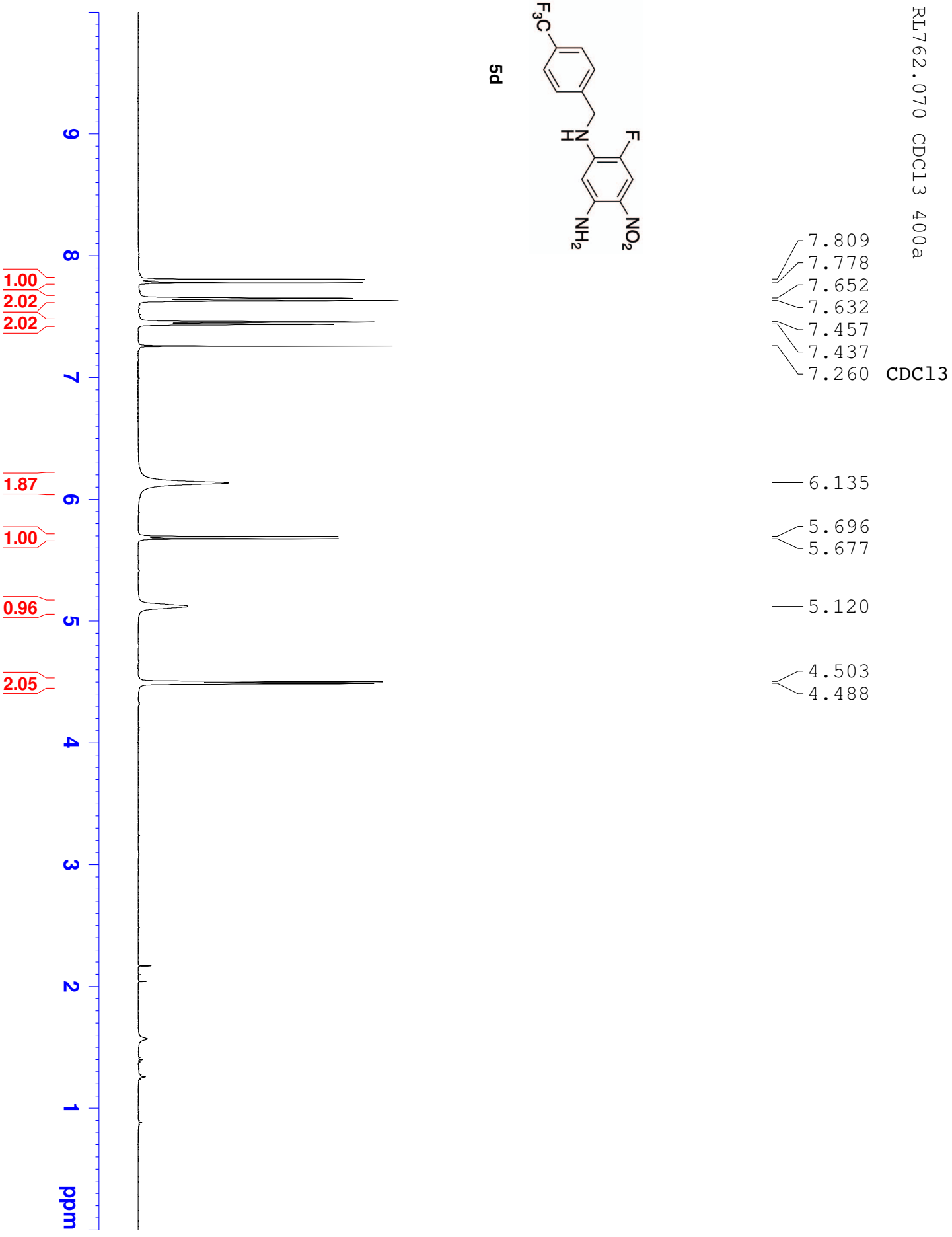
RL648.094 Acetone-d6 400b



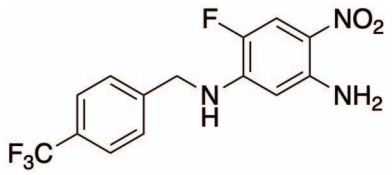
5c


RL673.002 CDC13 400b
RL-02
F5S
NHCO2Et
NH2
F
7.735
7.663
7.643
7.513
7.494
7.438
7.419
7.399
7.260 CDCl3
6.747
6.728
6.244
6.018
5.995
5.973
4.401
4.214
4.196
4.178
4.160
3.982
1.296
1.279
1.261
1.00
0.99
1.00
0.99
0.97
0.90
1.00
2.00
2.06
2.56
2.99
ppm


RL673.002 CDC13 400b
RL-02
F5S
NH
F
NH2
NHCO2Et
155.49
154.70
154.53
154.36
154.20
154.03
142.50
140.72
140.18
134.76
134.67
130.85
130.28
129.15
125.00
124.95
124.90
124.84
124.79
124.75
124.70
121.70
115.64
101.91
77.48
77.16
76.84
CDCl3
61.70
47.60
14.64
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

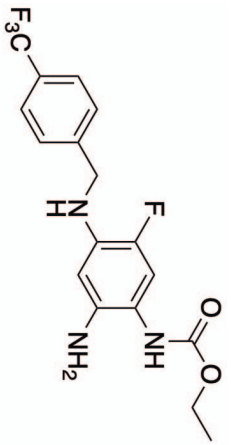

RL762.070 CDCl3 400a
5d
F3C
N
H
F
NH2
NO2
7.809
7.778
7.652
7.632
7.457
7.437
7.260
CDCl3
6.135
5.696
5.677
5.120
4.503
4.488
1.00
2.02
2.02
1.87
1.00
0.96
2.05
9
8
7
6
5
4
3
2
1
ppm

RL760.070 CDCl3 400b



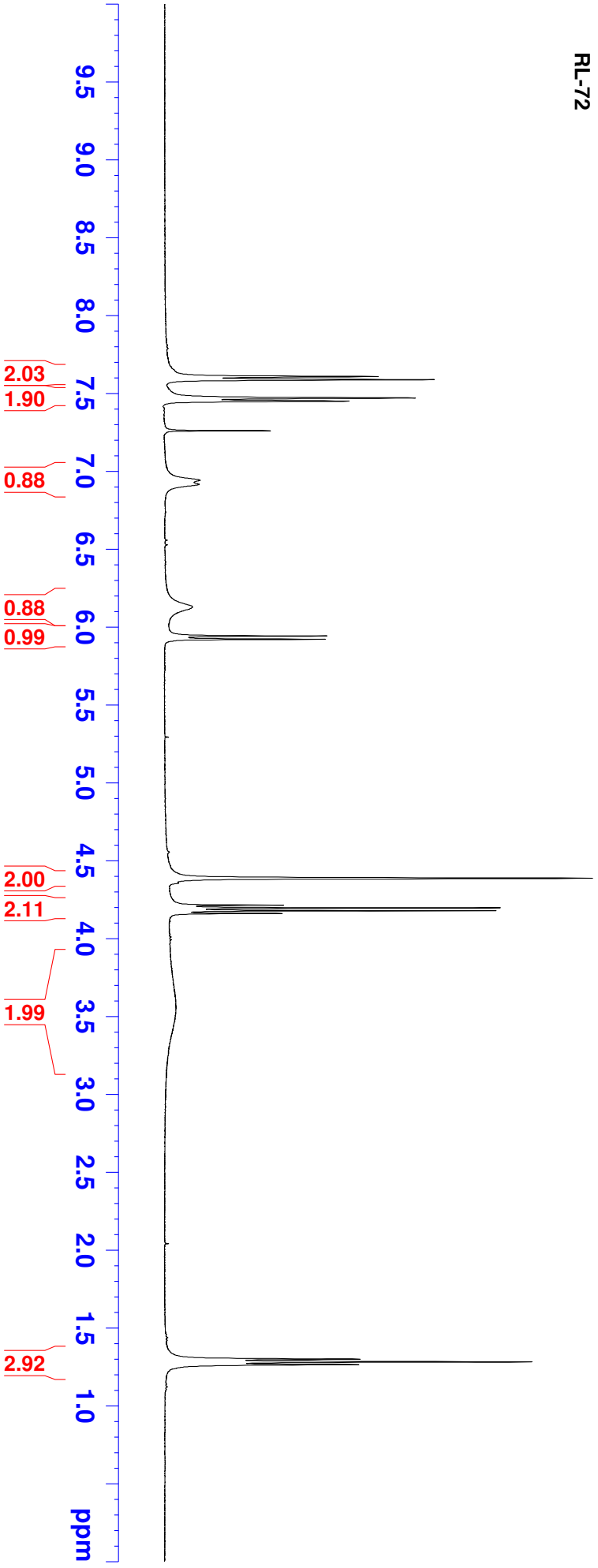
5d

RL762.072 CDC13 400b

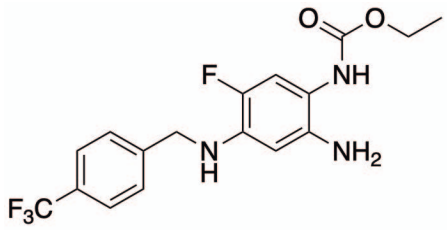


RL-72

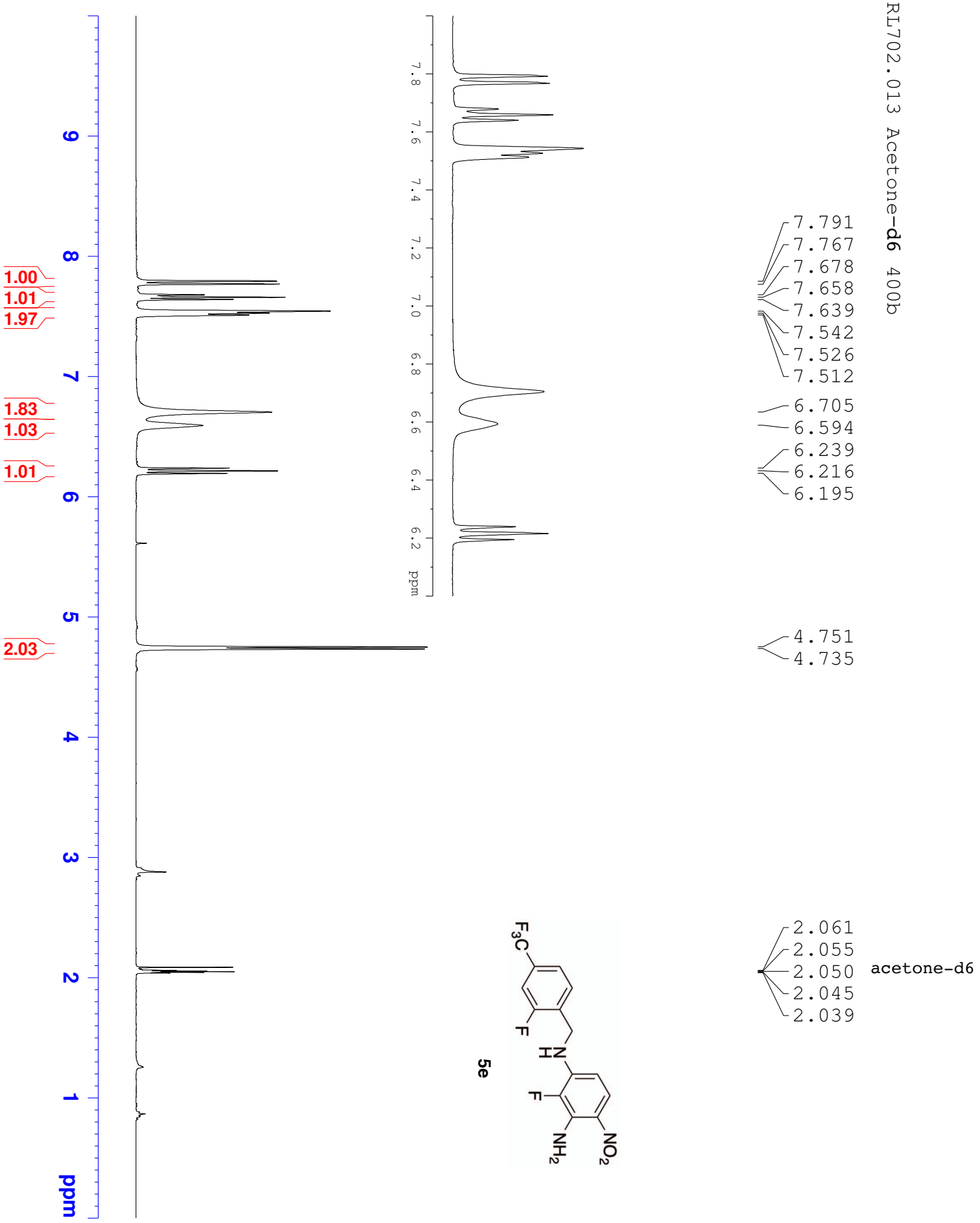
7.605
7.585
7.468
7.448
7.260 CDCl3
6.942
6.915
6.127
5.942
5.921
4.386
4.214
4.196
4.178
4.160
3.550
1.299
1.281
1.264



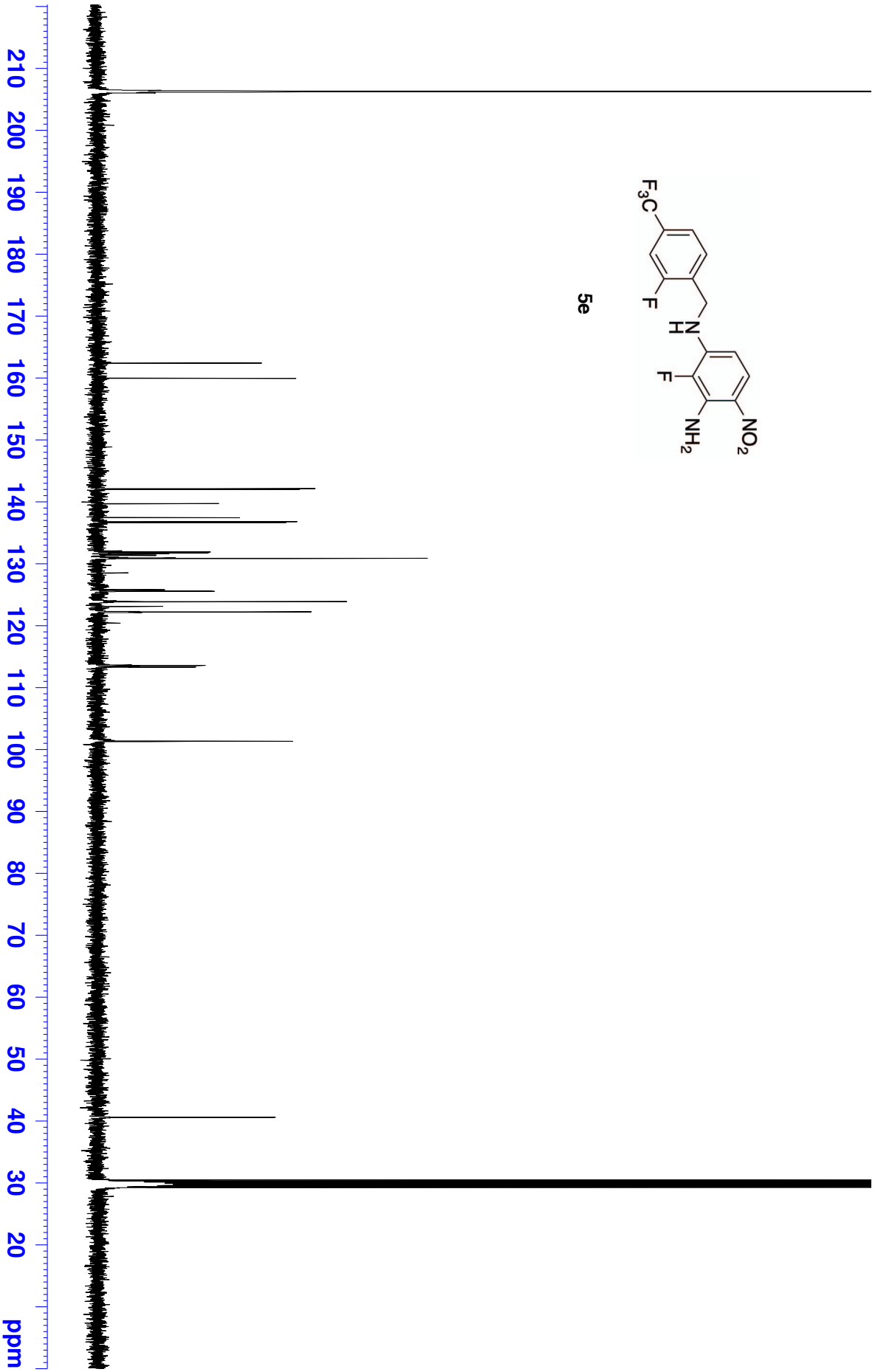
RL762.072 CDCl3 400b

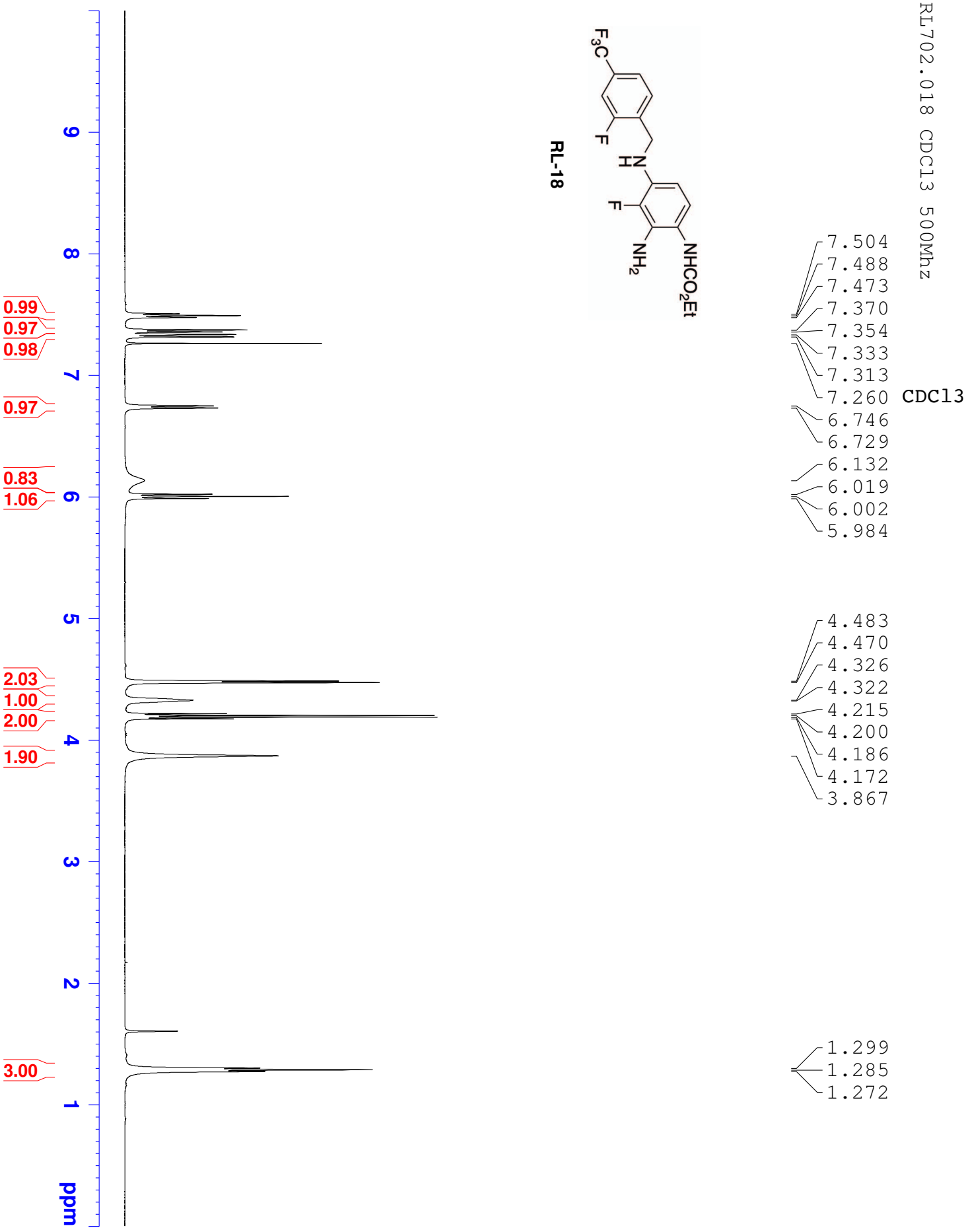


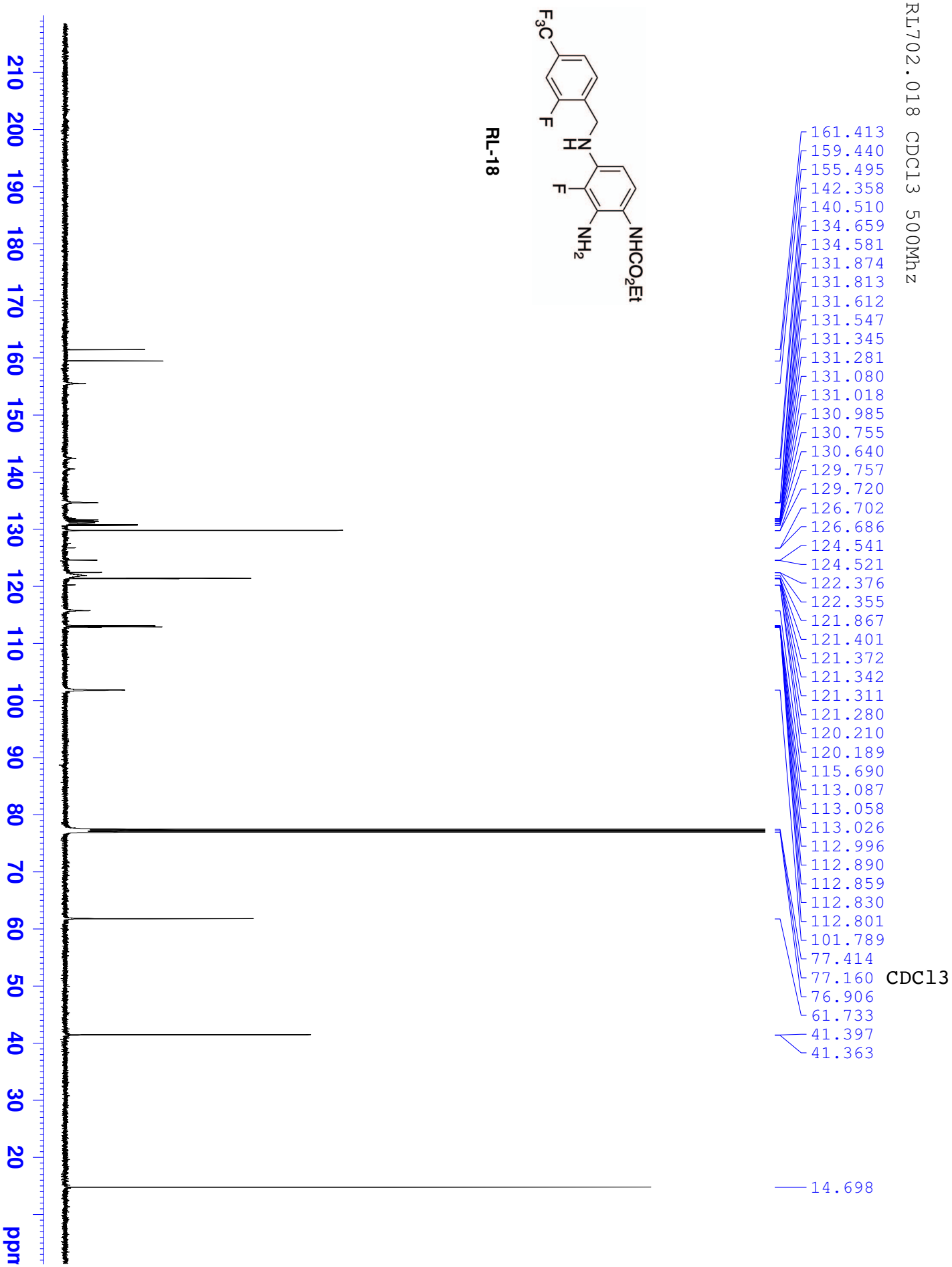
RL-72

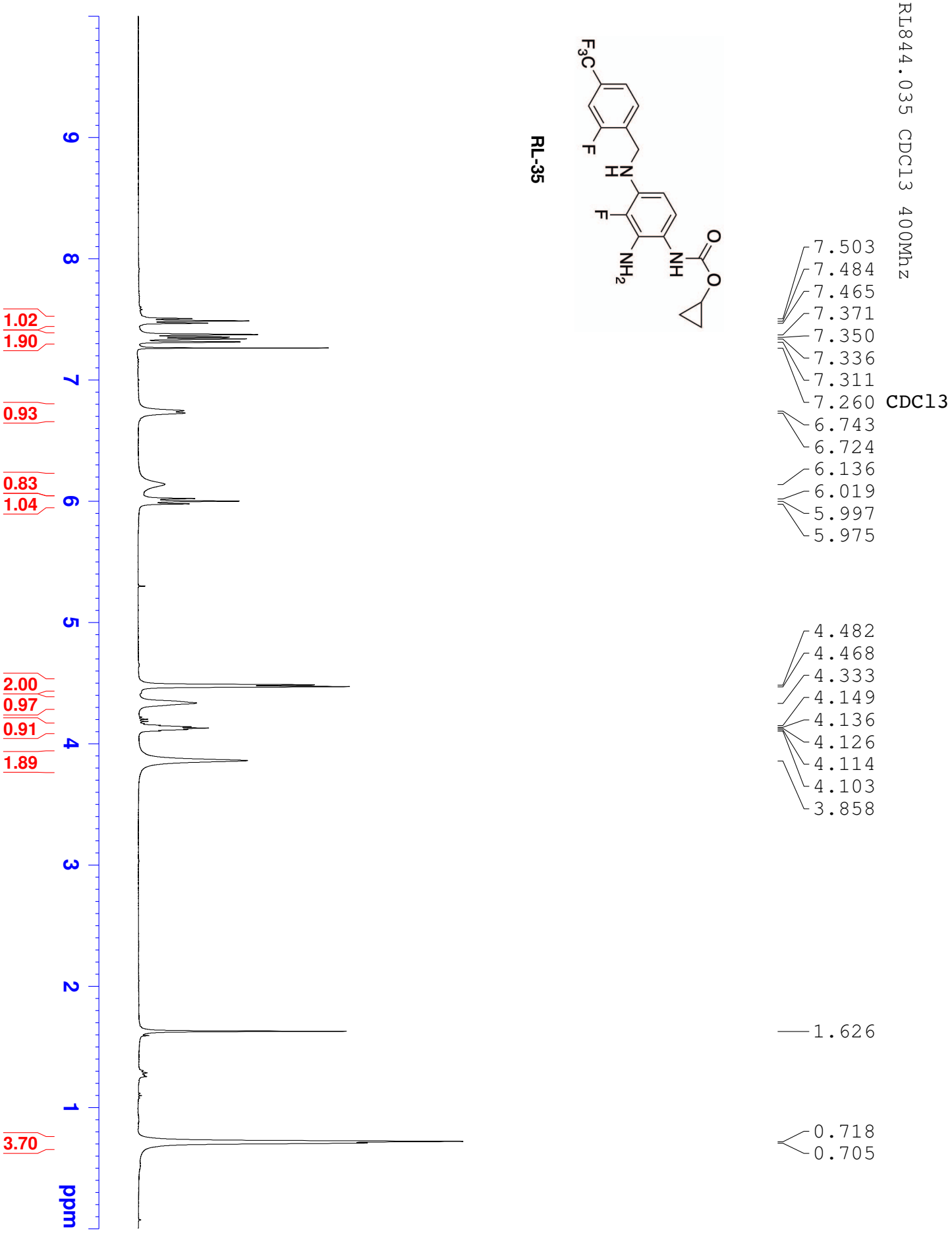

RL702.013 Acetone-d6 400b
7.791
7.767
7.678
7.658
7.639
7.542
7.526
7.512
6.705
6.594
6.239
6.216
6.195
4.751
4.735
2.061
2.055
2.050
2.045
2.039
acetone-d6
1.00
1.01
1.97
1.83
1.03
1.01
2.03
ppm
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
ppm
F3C
F
N
H
F
NH2
NO2
5e

RL702.013 Acetone-**d6** 400b

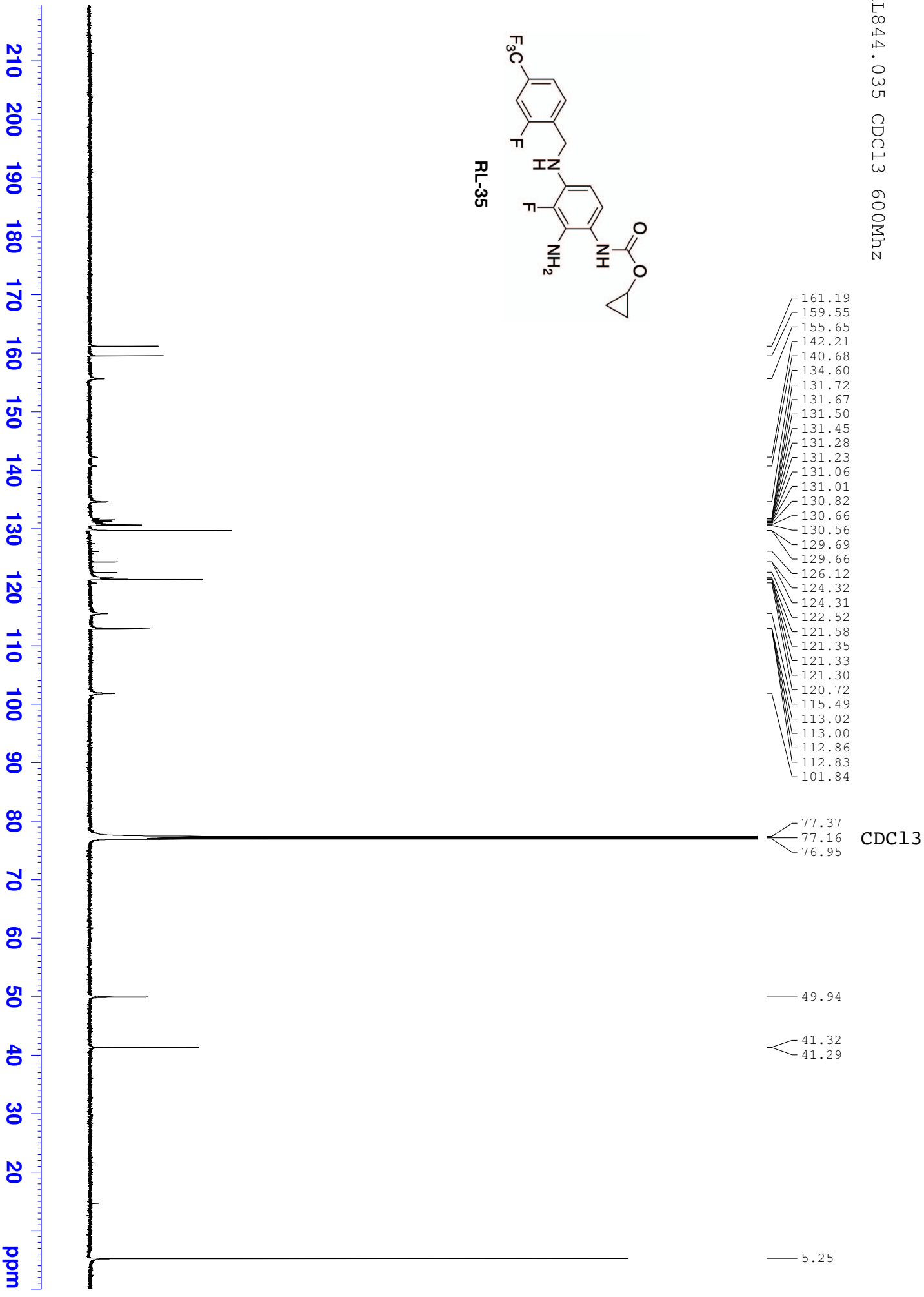


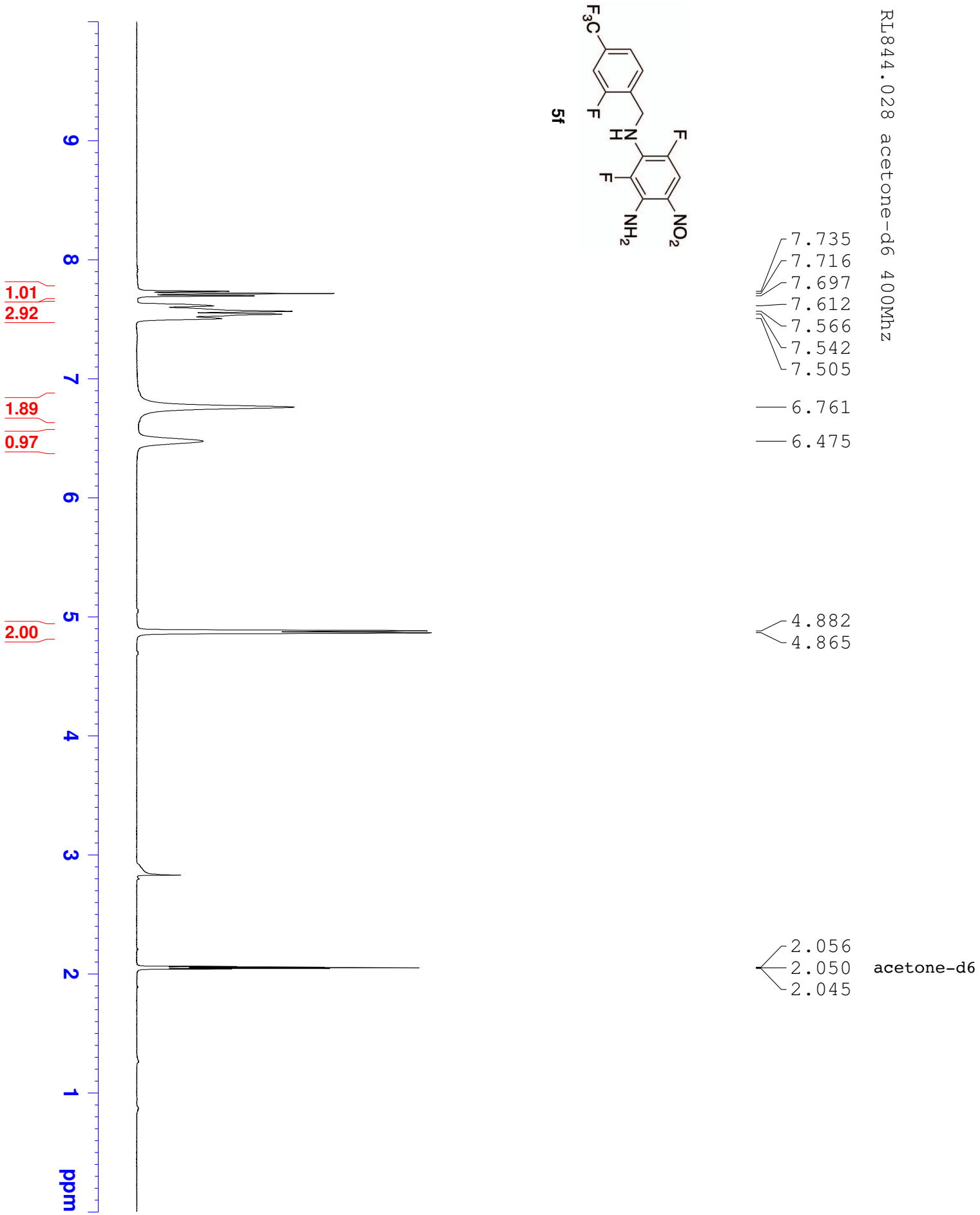

RL702.018 CDCl3 500Mhz
RL-18
F3C
F
N
H
F
NH2
NHCO2Et
7.504
7.488
7.473
7.370
7.354
7.333
7.313
7.260
CDCl3
6.746
6.729
6.132
6.019
6.002
5.984
4.483
4.470
4.326
4.322
4.215
4.200
4.186
4.172
3.867
1.299
1.285
1.272
0.99
0.97
0.98
0.97
0.83
1.06
2.03
1.00
2.00
1.90
3.00
ppm

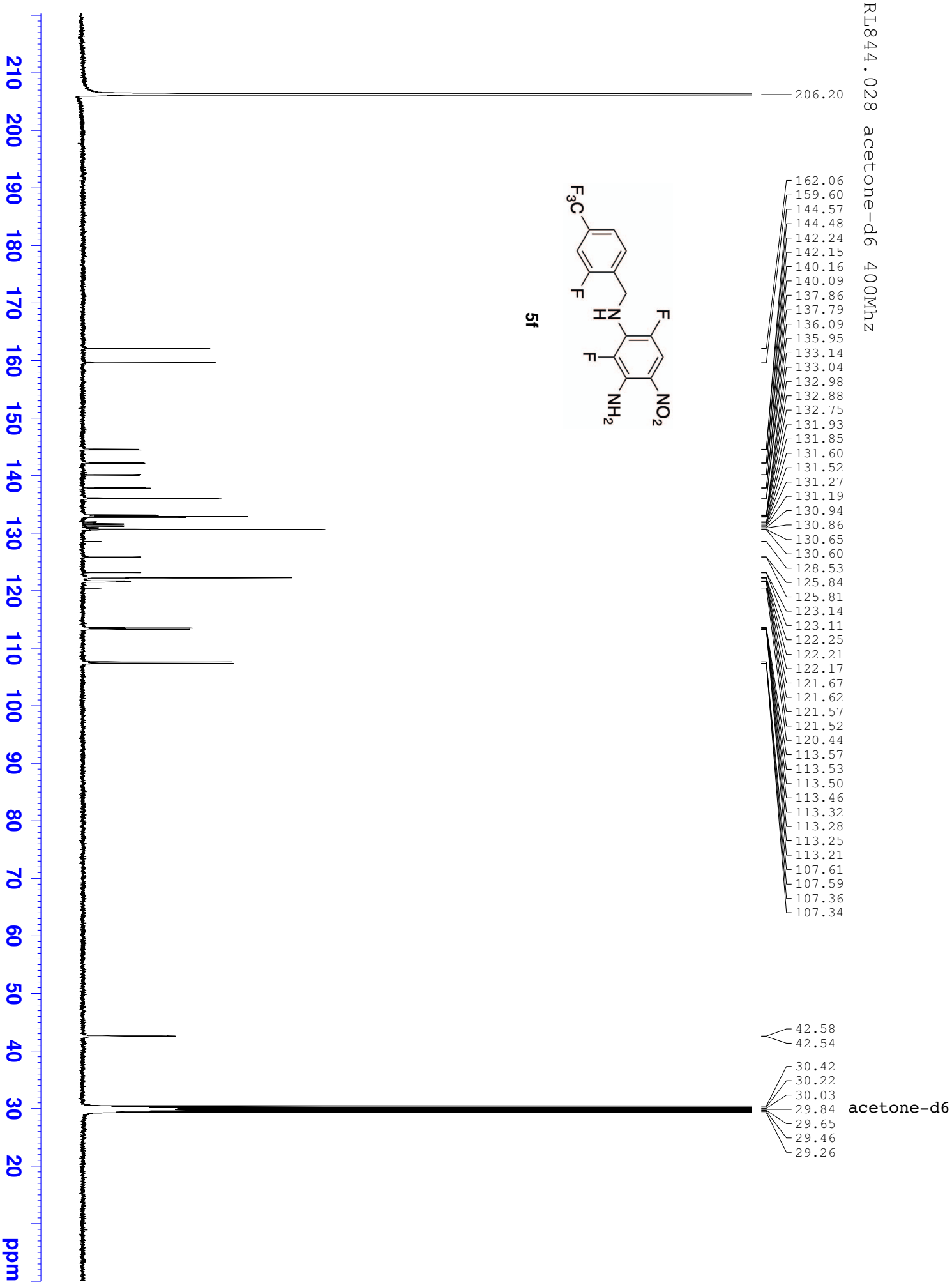

RL702.018 CDCl3 500Mhz
RL-18
F3C
F
N
H
F
NH2
NHCO2Et
161.413
159.440
155.495
142.358
140.510
134.659
134.581
131.874
131.813
131.612
131.547
131.345
131.281
131.080
131.018
130.985
130.755
130.640
129.757
129.720
126.702
126.686
124.541
124.521
122.376
122.355
121.867
121.401
121.372
121.342
121.311
121.280
120.210
120.189
115.690
113.087
113.058
113.026
112.996
112.890
112.859
112.830
112.801
101.789
77.414
77.160
76.906
61.733
41.397
41.363
14.698
CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


RL844.035 CDCl3 400Mhz
RL-35
F3C
F
N
H
F
NH2
NH
O
O
7.503
7.484
7.465
7.371
7.350
7.336
7.311
7.260 CDCl3
6.743
6.724
6.136
6.019
5.997
5.975
4.482
4.468
4.333
4.149
4.136
4.126
4.114
4.103
3.858
1.626
0.718
0.705
1.02
1.90
0.93
0.83
1.04
2.00
0.97
0.91
1.89
3.70
9
8
7
6
5
4
3
2
1
ppm

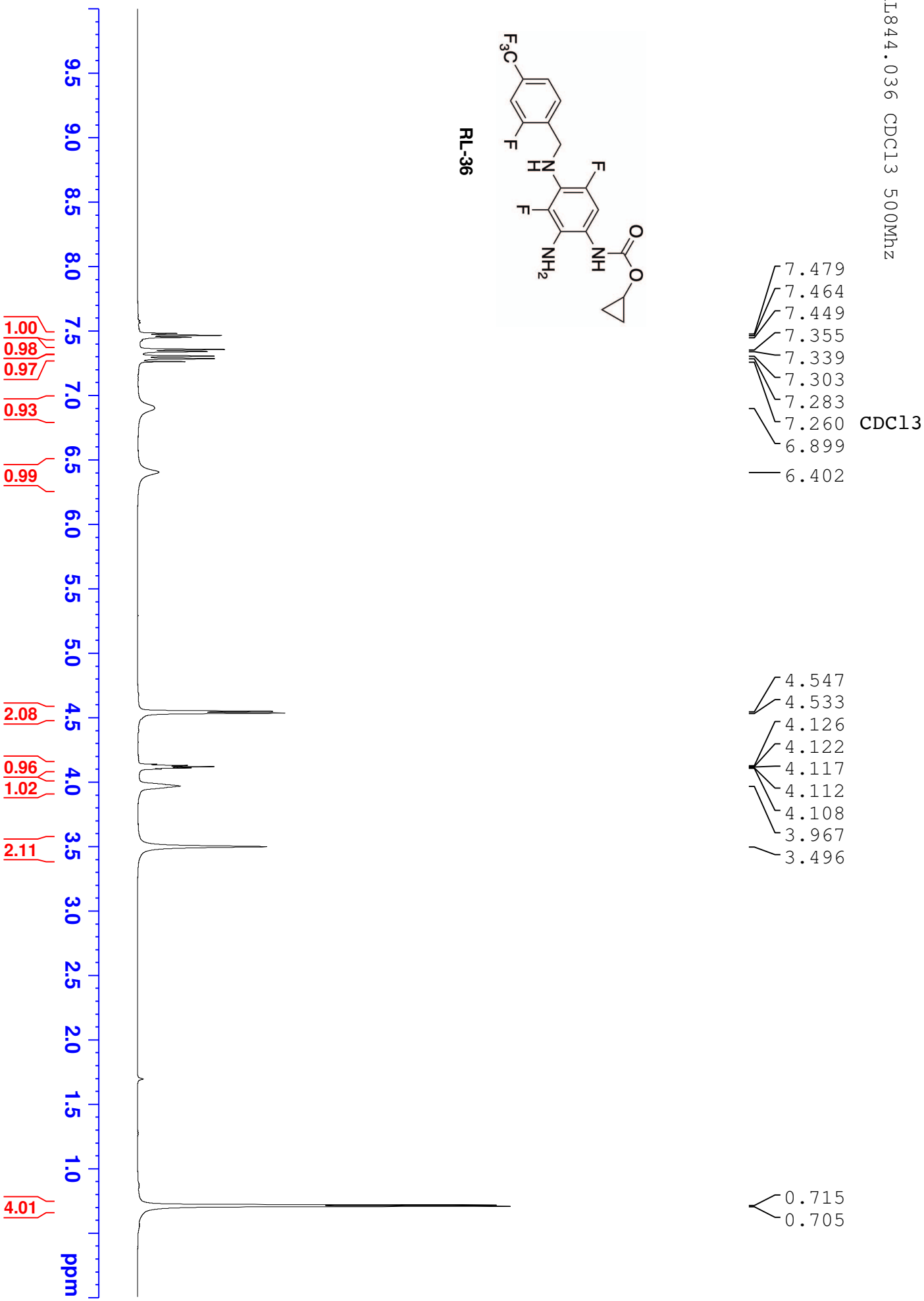
RL844.035 CDCl3 600Mhz

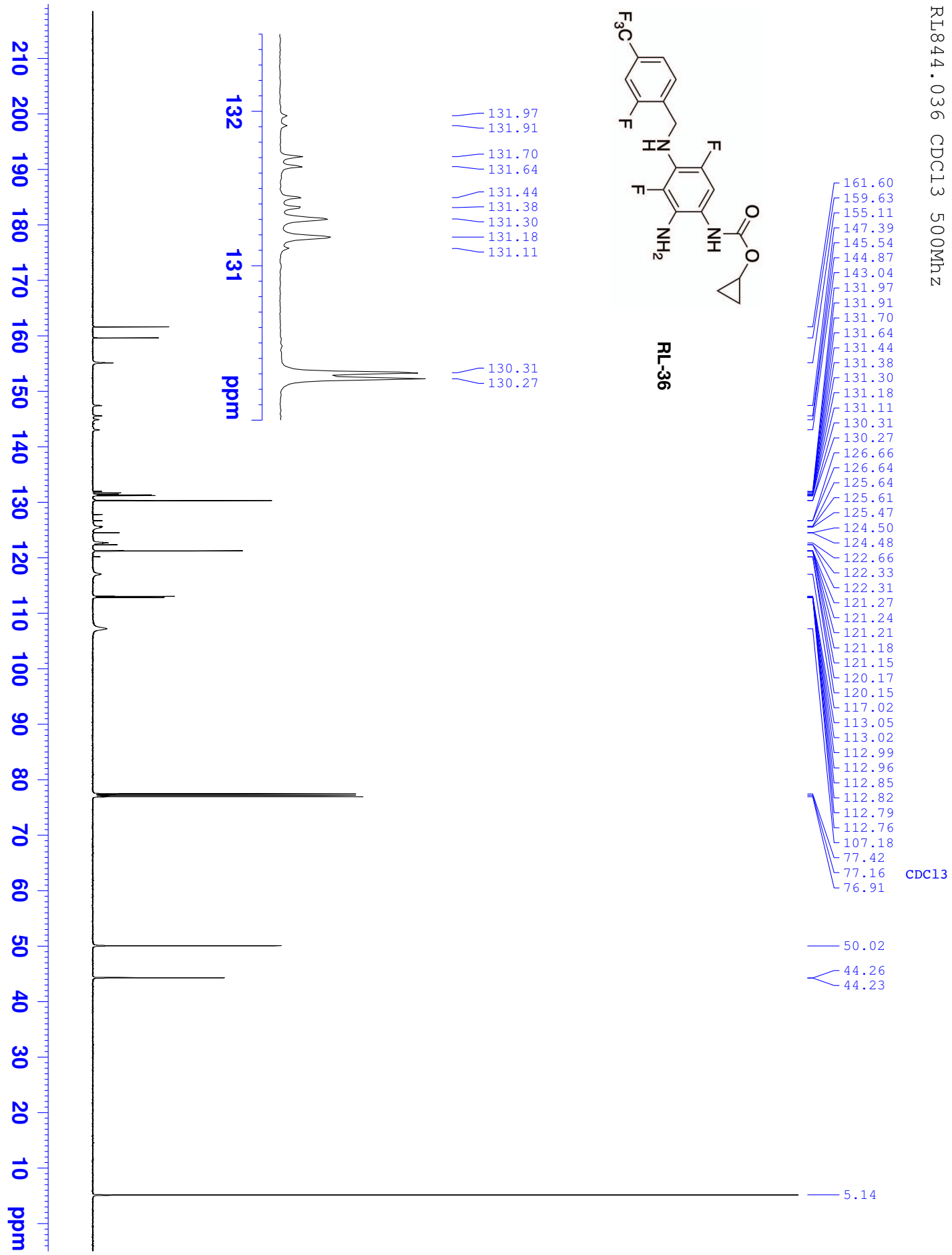



RL844.028 acetone-d6 400Mhz
5f
F3C
F
NH
F
F
NH2
NO2
7.735
7.716
7.697
7.612
7.566
7.542
7.505
6.761
6.475
4.882
4.865
2.056
2.050
2.045
acetone-d6
1.01
2.92
1.89
0.97
2.00
9
8
7
6
5
4
3
2
1
ppm


RL844.028 acetone-d6 400Mhz
206.20
162.06
159.60
144.57
144.48
142.24
142.15
140.16
140.09
137.86
137.79
136.09
135.95
133.14
133.04
132.98
132.88
132.75
131.93
131.85
131.60
131.52
131.27
131.19
130.94
130.86
130.65
130.60
128.53
125.84
125.81
123.14
123.11
122.25
122.21
122.17
121.67
121.62
121.57
121.52
120.44
113.57
113.53
113.50
113.46
113.32
113.28
113.25
113.21
107.61
107.59
107.36
107.34
42.58
42.54
30.42
30.22
30.03
29.84
29.65
29.46
29.26
acetone-d6
5f
F3C
F
N
H
F
NH2
NO2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

RL844.036 CDC13 500Mhz

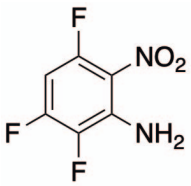



RL844.036 CDCl3 500Mhz
RL-36
CDCl3
161.60
159.63
155.11
147.39
145.54
144.87
143.04
131.97
131.91
131.70
131.64
131.44
131.38
131.30
131.18
131.11
130.31
130.27
126.66
126.64
125.64
125.61
125.47
124.50
124.48
122.66
122.33
122.31
121.27
121.24
121.21
121.18
121.15
120.17
120.15
117.02
113.05
113.02
112.99
112.96
112.85
112.82
112.79
112.76
107.18
77.42
77.16
76.91
50.02
44.26
44.23
5.14
132
131
ppm
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

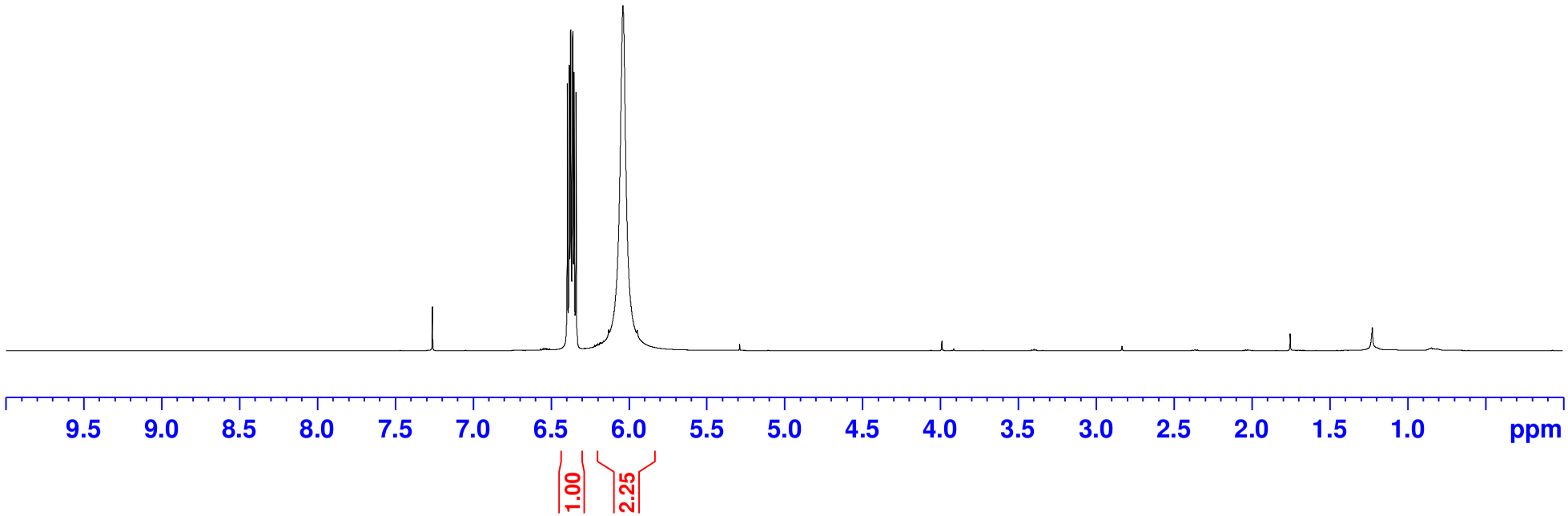
RL844.040 CDCl3 500Mhz

CDCl3

7.260
6.394
6.380
6.374
6.371
6.360
6.358
6.351
6.338
6.036



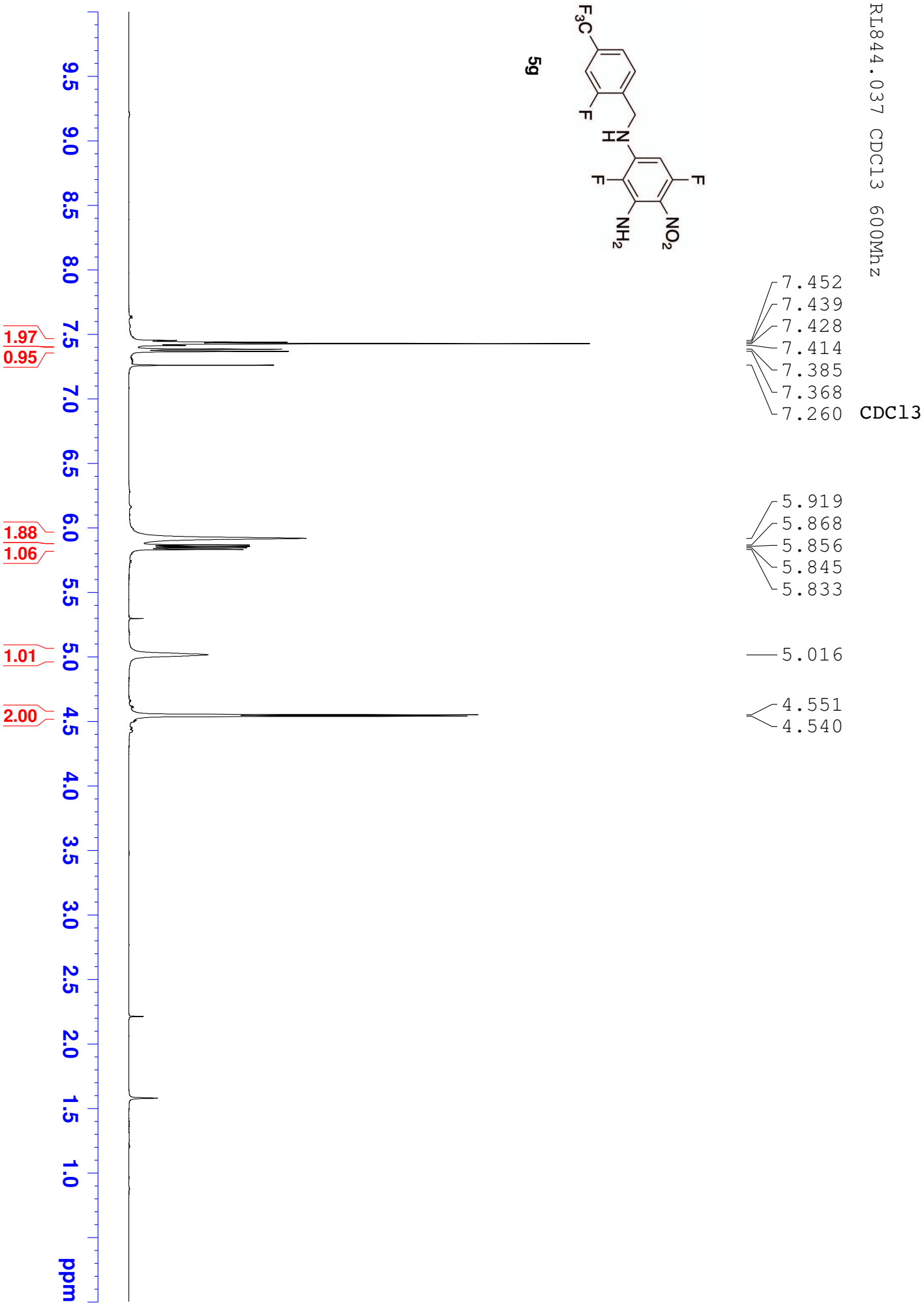
4d



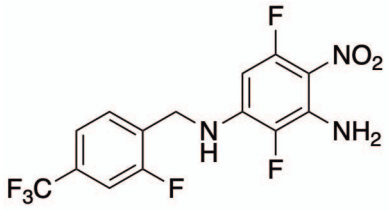
RL844.040 CDCl3 500Mhz

155.03
155.00
154.92
154.89
153.30
153.21
153.18
153.09
152.95
152.92
152.84
152.81
151.26
151.17
151.14
151.05
136.96
136.93
136.90
136.84
136.80
135.05
135.01
134.93
134.90
121.90
93.74
93.56
93.53
93.34
77.41
77.16
76.91
CDCl3

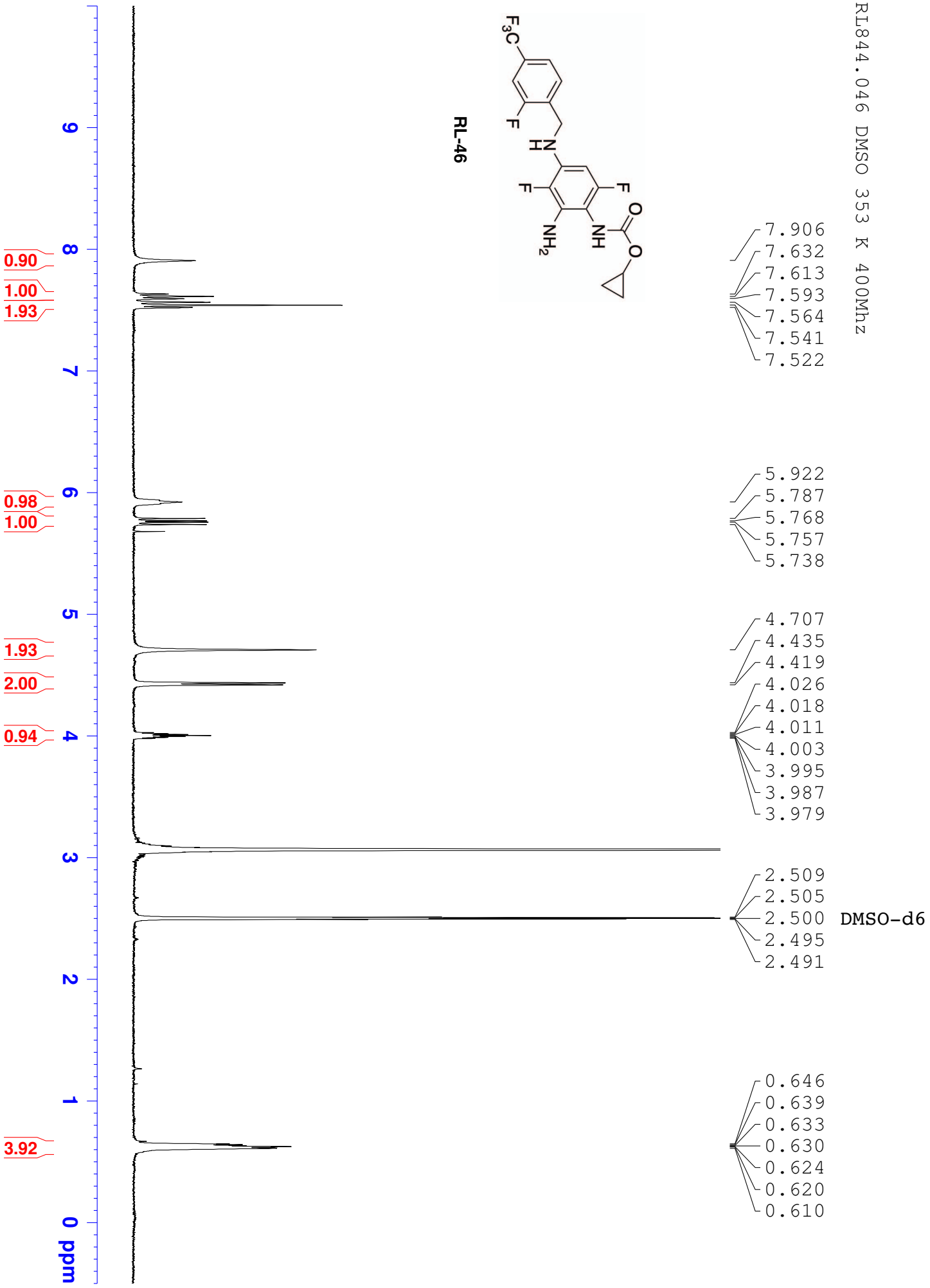
4d


RL844.037 CDCl3 600Mhz
5g
F3C
F
H
N
F
F
NH2
NO2
7.452
7.439
7.428
7.414
7.385
7.368
7.260
CDCl3
5.919
5.868
5.856
5.845
5.833
5.016
4.551
4.540
1.97
0.95
1.88
1.06
1.01
2.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

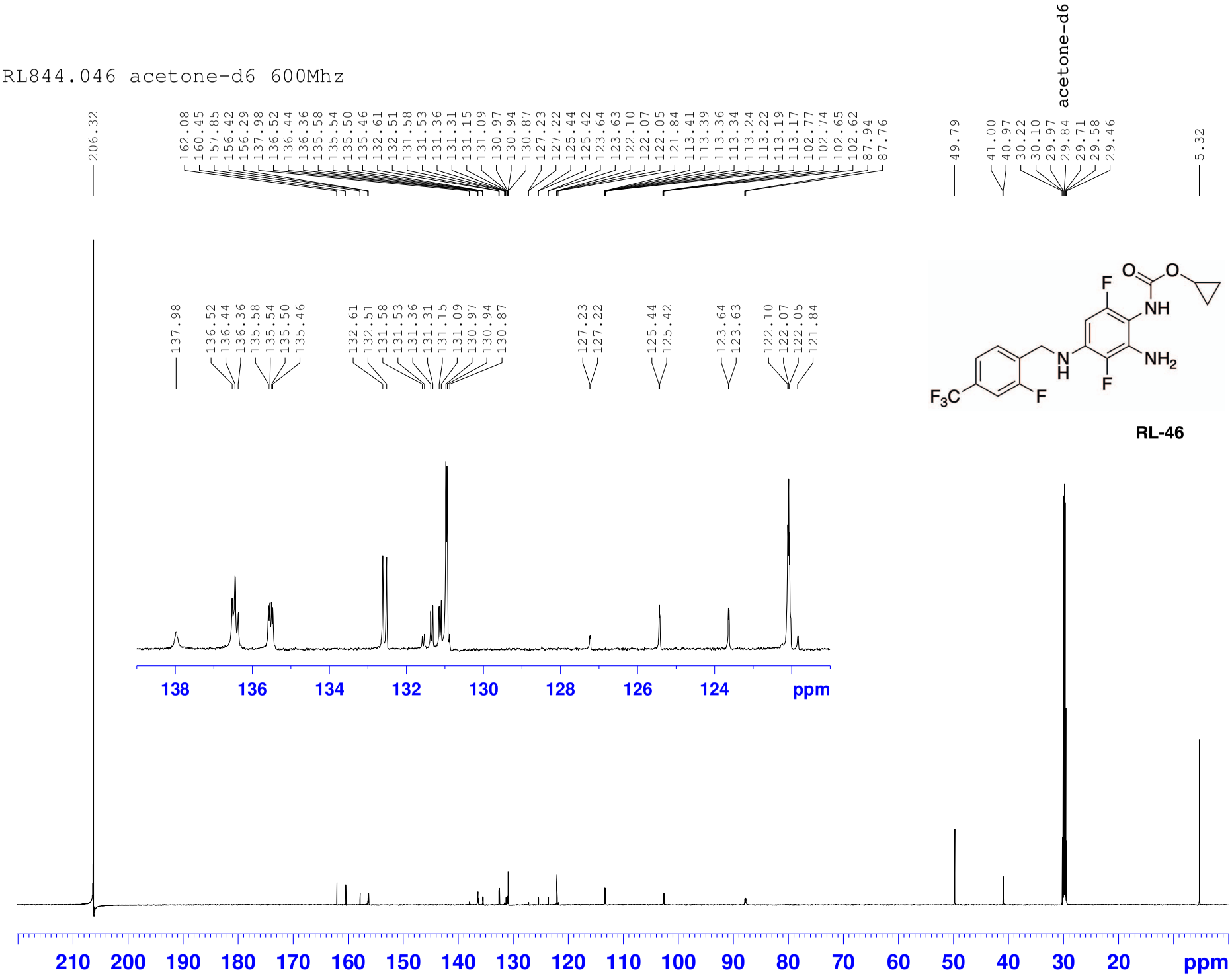
RL844.037 CDCl3 600MHz



5g


RL844.046 DMSO 353 K 400Mhz
RL-46
7.906
7.632
7.613
7.593
7.564
7.541
7.522
5.922
5.787
5.768
5.757
5.738
4.707
4.435
4.419
4.026
4.018
4.011
4.003
3.995
3.987
3.979
2.509
2.505
2.500
2.495
2.491
DMSO-d6
0.646
0.639
0.633
0.630
0.624
0.620
0.610
0.90
1.00
1.93
0.98
1.00
1.93
2.00
0.94
3.92
9
8
7
6
5
4
3
2
1
0 ppm

RL844.046 acetone-d6 600Mhz

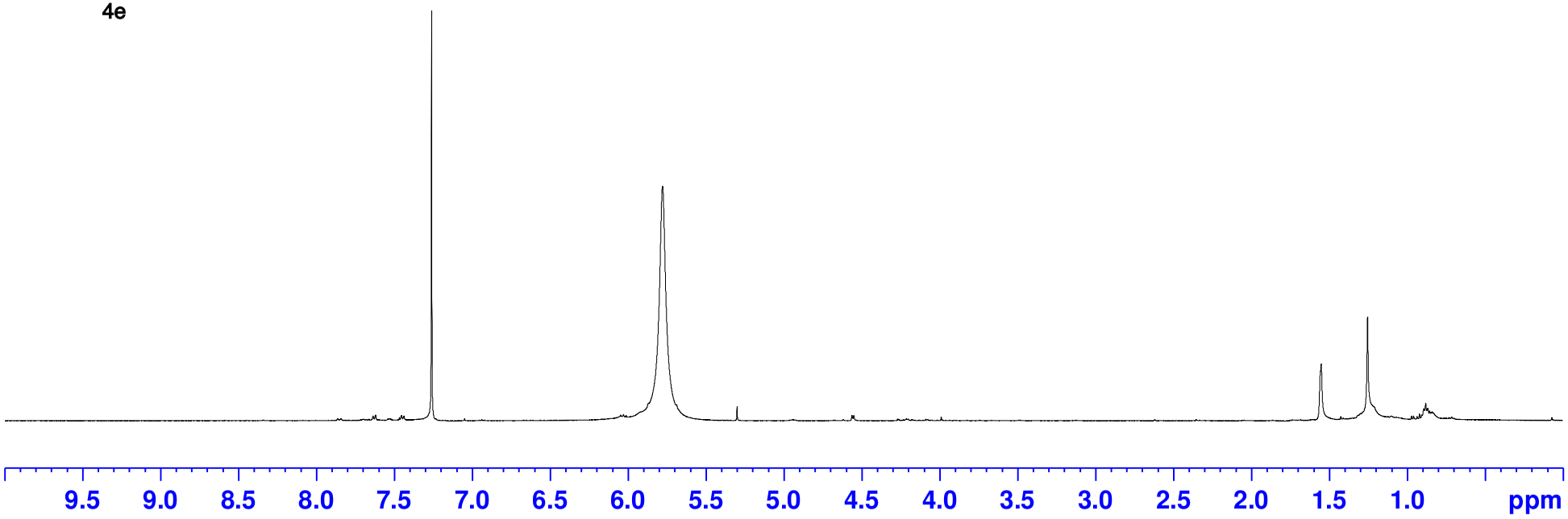


RL844.038 CDCl3 500Mhz

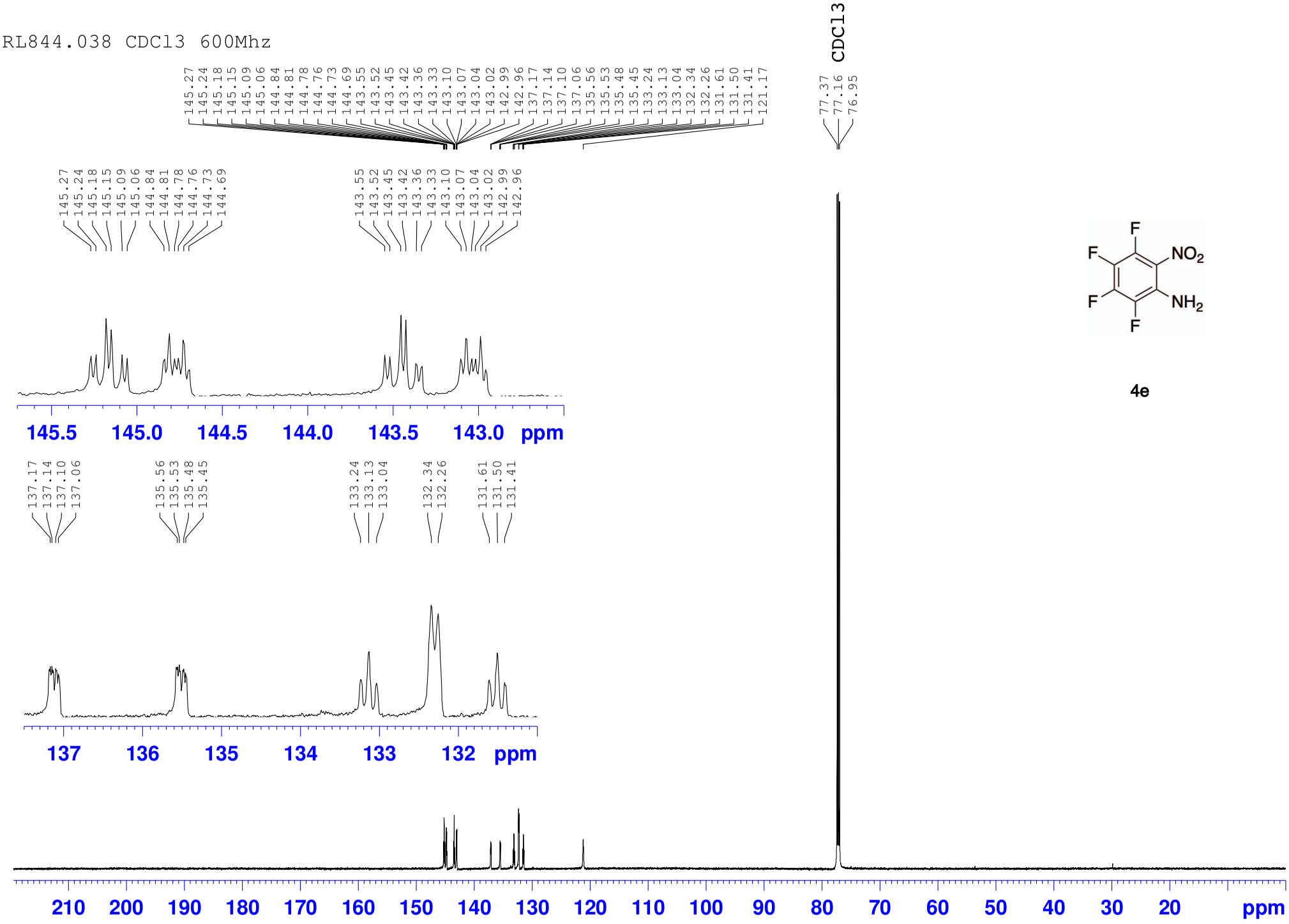
7.260 CDCl3

5.777

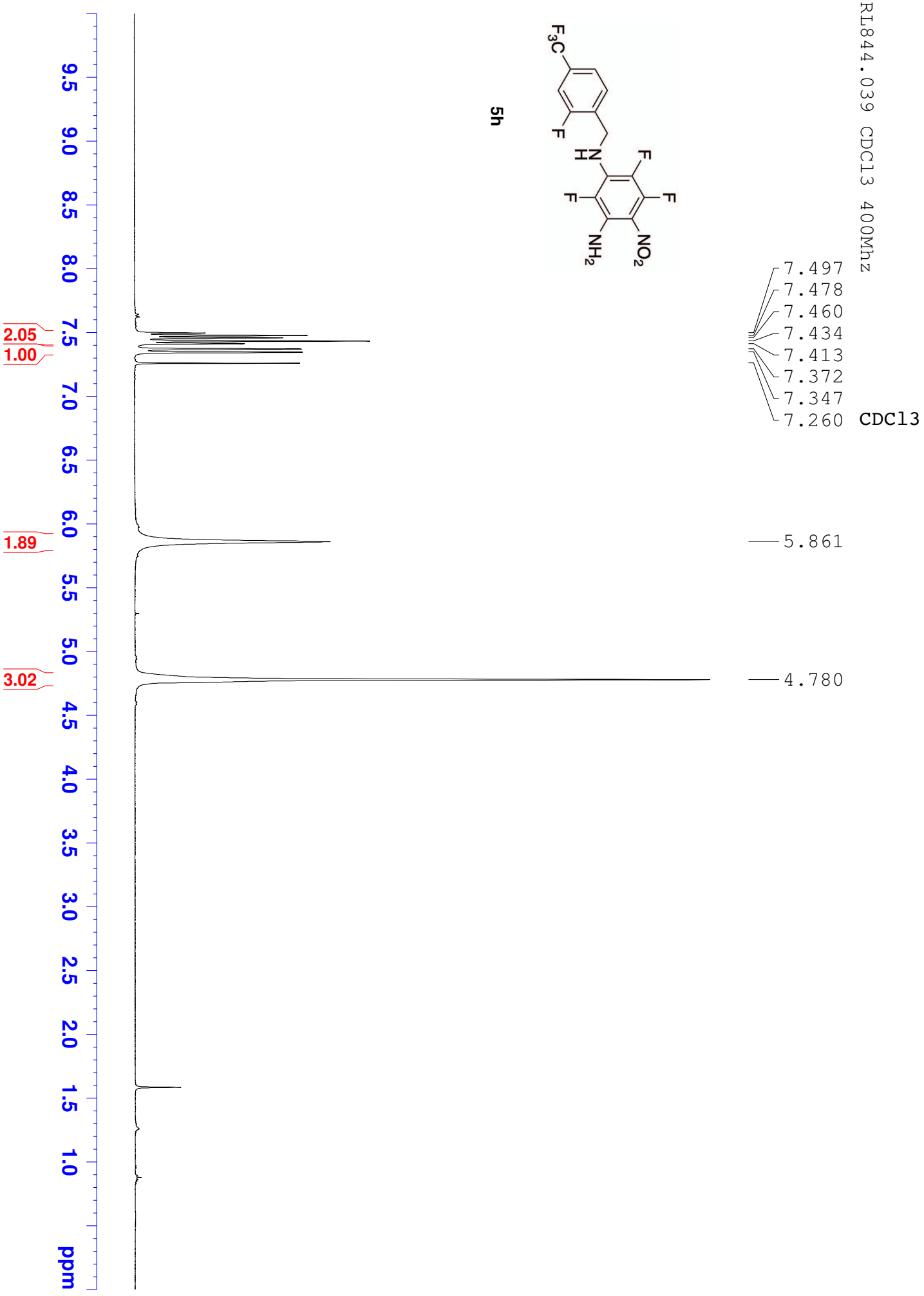
4e



RL844.038 CDCl3 600Mhz

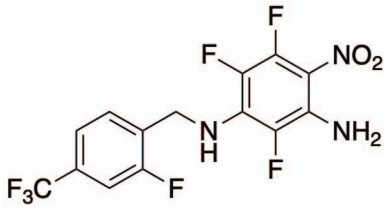


4e

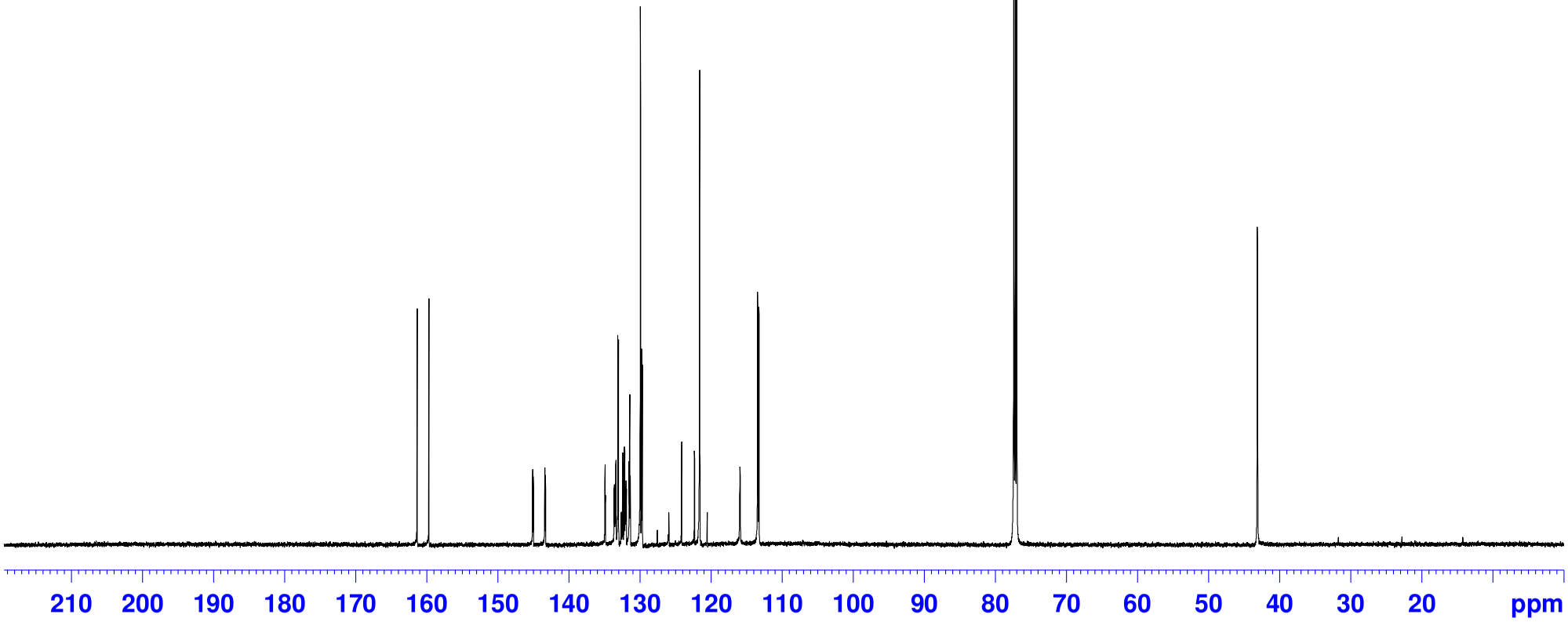

RL844.039 CDCl3 400Mhz
5h
F3C
F
N
H
F
F
NH2
NO2
7.497
7.478
7.460
7.434
7.413
7.372
7.347
7.260
CDCl3
5.861
4.780
2.05
1.00
1.89
3.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

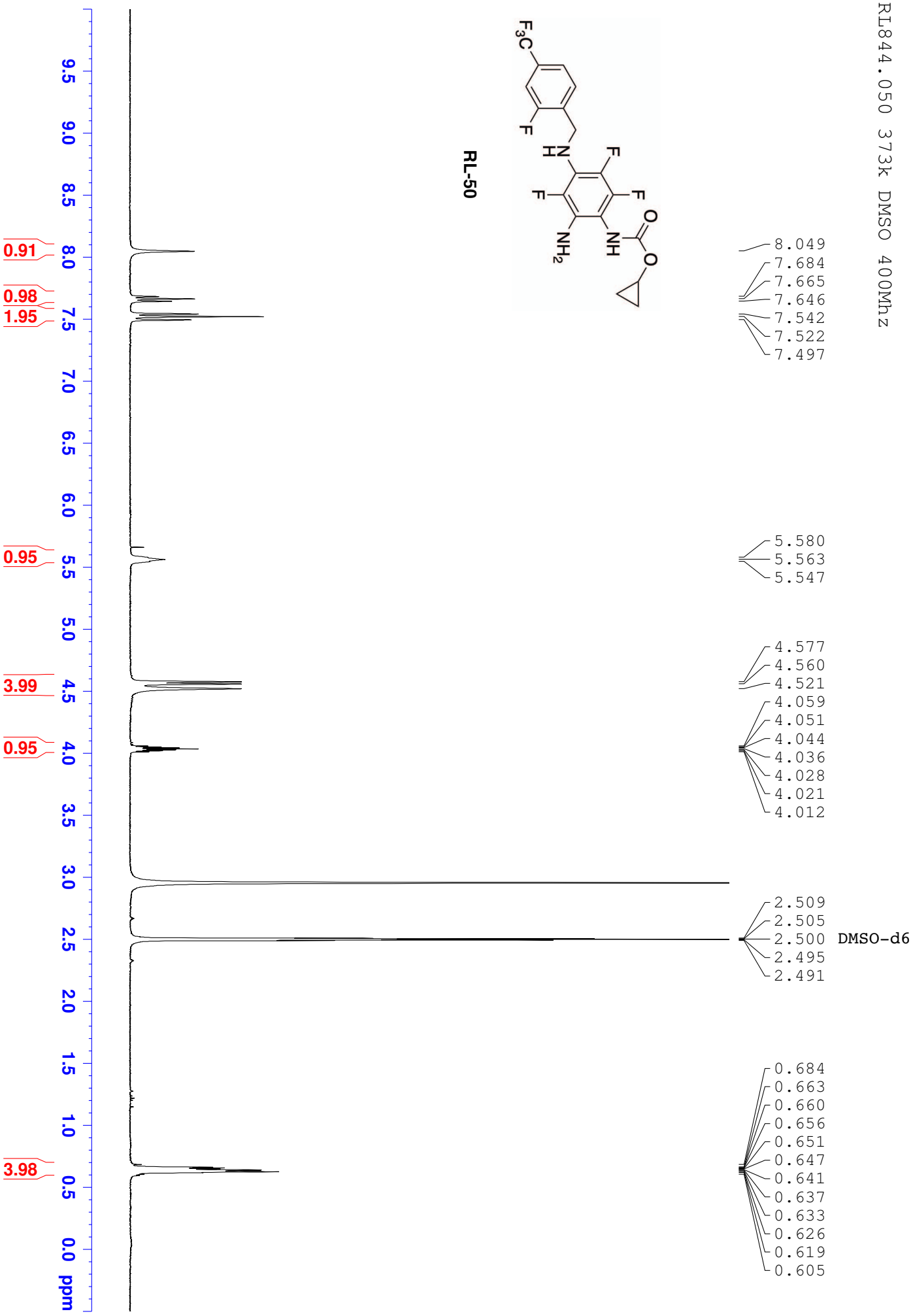
RL844.039 CDCl3 600MHz

161.33
159.68
145.10
145.08
145.00
144.98
143.39
143.36
143.29
143.27
134.92
134.89
134.86
133.63
133.57
133.51
133.46
133.40
133.38
133.35
133.09
133.00
132.64
132.59
132.42
132.37
132.20
132.14
132.07
132.02
131.96
131.92
131.91
131.51
131.49
131.44
131.41
131.36
131.34
129.94
129.91
129.74
129.64
125.93
125.92
124.13
122.33
122.31
121.61
121.59
121.57
121.54
120.52
115.91
113.42
113.40
113.37
113.26
113.23
113.21
77.37
77.16 CDCl3
76.95
43.14
43.11
43.09
43.06



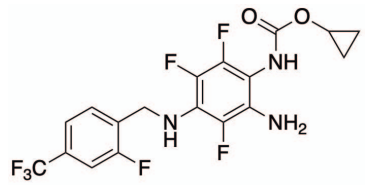
5h




RL844.050 373k DMSO 400Mhz
RL-50
F3C
F
N
H
F
F
NH2
NH
O
O
8.049
7.684
7.665
7.646
7.542
7.522
7.497
5.580
5.563
5.547
4.577
4.560
4.521
4.059
4.051
4.044
4.036
4.028
4.021
4.012
2.509
2.505
2.500
2.495
2.491
DMSO-d6
0.684
0.663
0.660
0.656
0.651
0.647
0.641
0.637
0.633
0.626
0.619
0.605
0.91
0.98
1.95
0.95
3.99
0.95
3.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

S88

RL844.050 CD3OD 600Mhz



RL-50

CD3OD

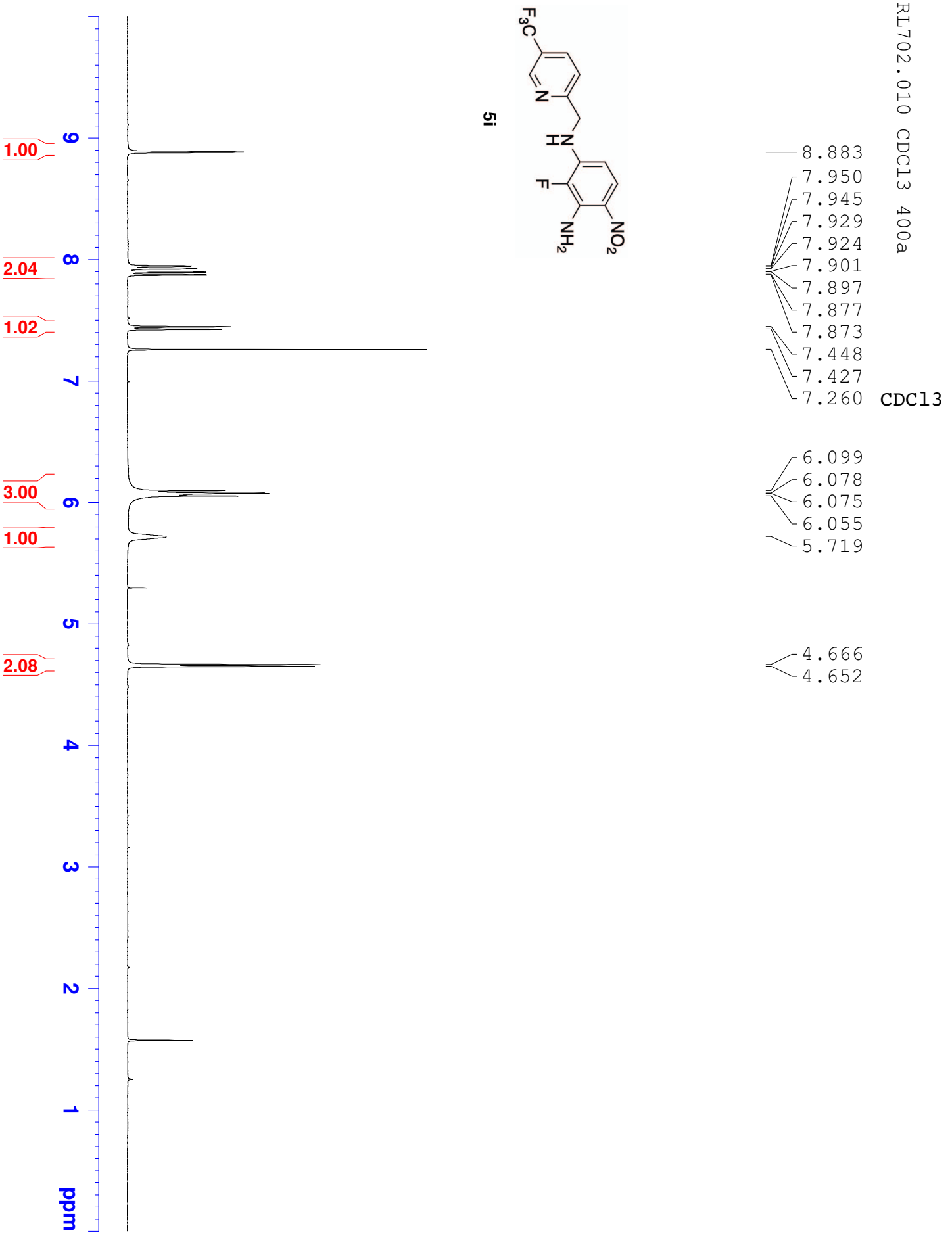
162.47 160.83 158.27 147.03 147.01 146.94 146.92 145.44 145.42 145.36 145.34 139.65 138.15 136.10 134.57 133.61 133.51 132.34 132.28 132.12 132.06 131.90 131.84 131.68 131.58 131.17 131.14 127.60 126.82 126.74 126.67 125.80 125.78 124.00 123.99 122.19 122.15 122.12 122.10 113.57 113.54 113.52 113.50 113.40 113.38 113.35 113.33 104.04 104.00 103.96 103.91 50.74 49.43 49.28 49.14 49.00 48.86 48.72 48.58 43.74 5.51

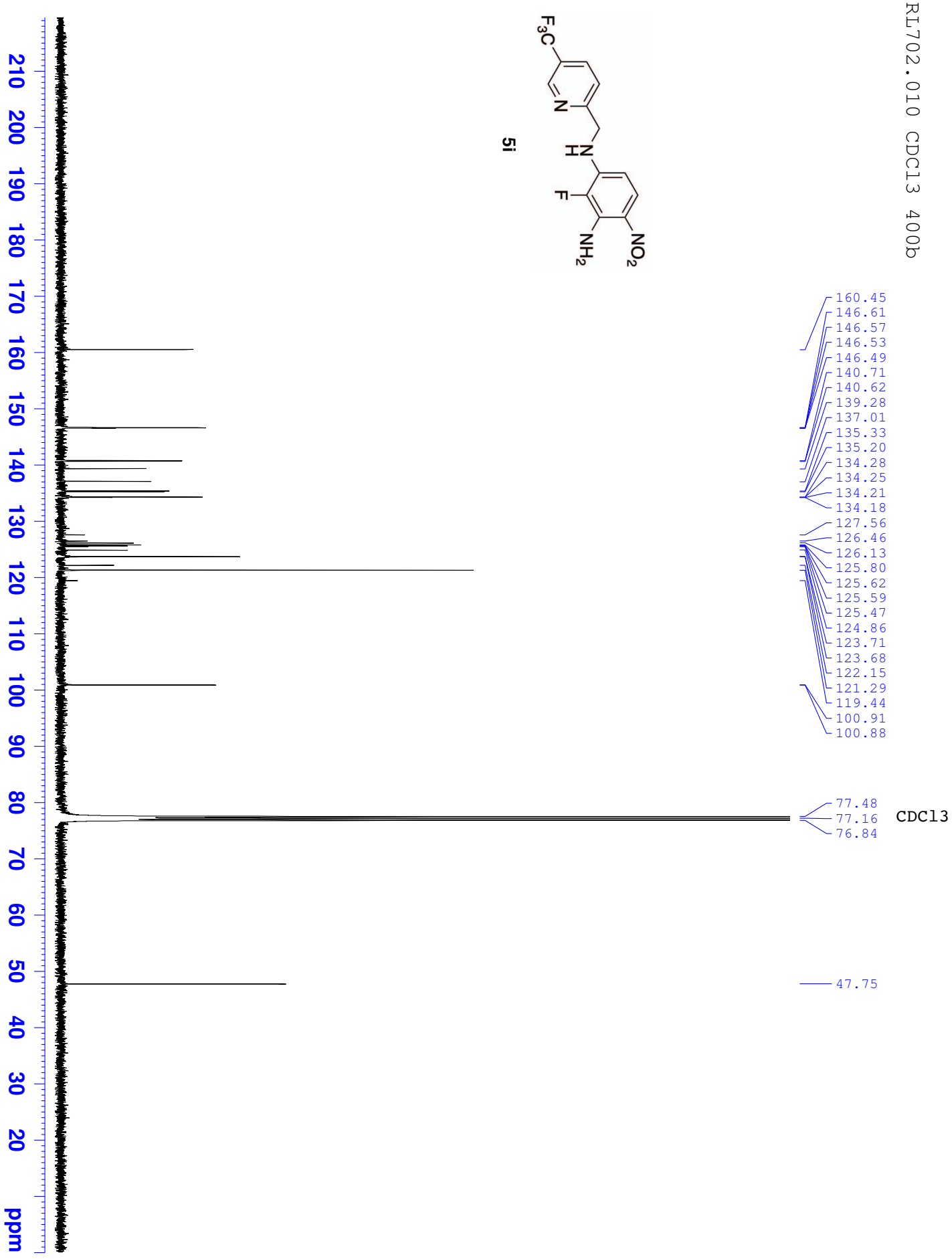
147 146 ppm

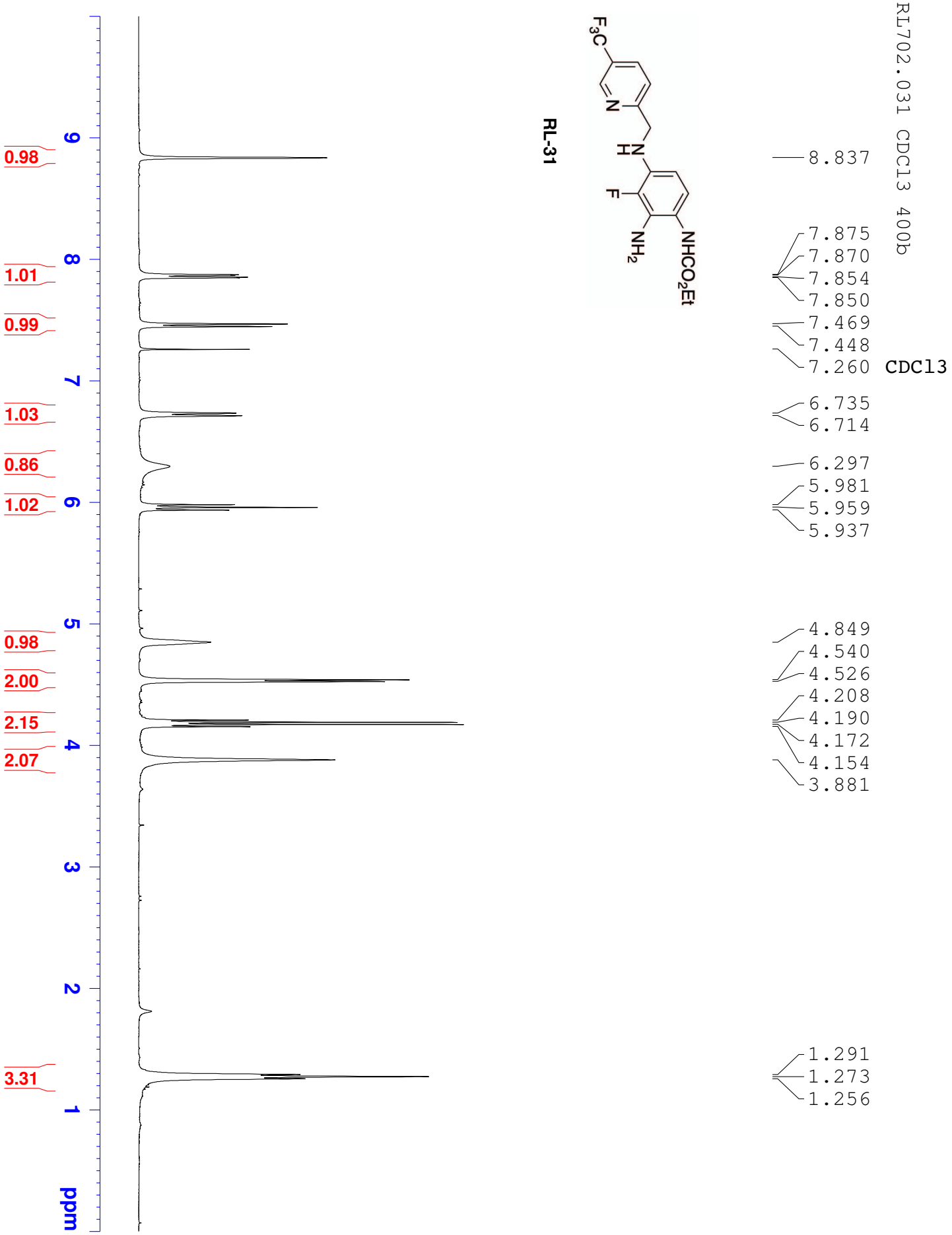
113.5 ppm

138 136 134 132 130 128 126 124 ppm

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

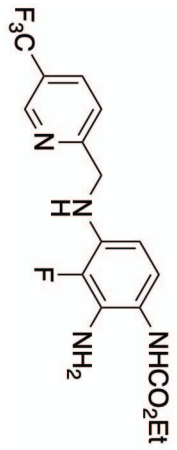

RL702.010 CDC13 400a
8.883
7.950
7.945
7.929
7.924
7.901
7.897
7.877
7.873
7.448
7.427
7.260
CDCl3
6.099
6.078
6.075
6.055
5.719
4.666
4.652
5i
F3C
N
H
F
NH2
NO2
1.00
2.04
1.02
3.00
1.00
2.08
9
8
7
6
5
4
3
2
1
ppm


RL702.010 CDC13 400b
5i
160.45
146.61
146.57
146.53
146.49
140.71
140.62
139.28
137.01
135.33
135.20
134.28
134.25
134.21
134.18
127.56
126.46
126.13
125.80
125.62
125.59
125.47
124.86
123.71
123.68
122.15
121.29
119.44
100.91
100.88
77.48
77.16
76.84
CDCl3
47.75
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


RL702.031 CDC13 400b
RL-31
F3C
N
H
F
NH2
NHCO2Et
8.837
7.875
7.870
7.854
7.850
7.469
7.448
7.260
CDC13
6.735
6.714
6.297
5.981
5.959
5.937
4.849
4.540
4.526
4.208
4.190
4.172
4.154
3.881
1.291
1.273
1.256
0.98
1.01
0.99
1.03
0.86
1.02
0.98
2.00
2.15
2.07
3.31
9
8
7
6
5
4
3
2
1
ppm

RL702.031 CDC13 400b

RL-31



162.91
155.49
146.41
146.37
146.33
146.29
142.51
140.22
134.71
134.61
134.02
133.98
133.95
133.92
131.03
127.71
125.84
125.51
125.18
125.00
124.86
122.29
121.74
121.12
119.59
115.52
101.82

77.48
77.16 CDCl3
76.84

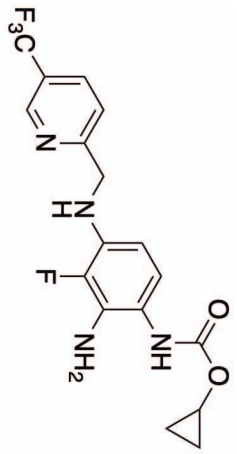
61.67

49.06

14.66

200 180 160 140 120 100 80 60 40 20 0 ppm

RL844.068 CD3OD 600Mhz



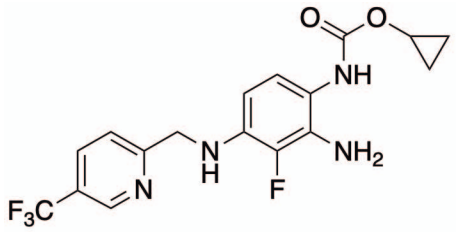
RL-68

8.812
8.029
8.016
7.603
7.590
6.659
6.647
5.900
5.886
5.873
4.532
4.037
3.310 CD3OD
0.693
0.680

1.00
1.01
1.02
1.00
1.04
2.13
0.95
4.09

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

RL844.068 CD3OD 600Mhz



RL-68

165.90
158.39
146.77
143.18
141.66
135.96
135.47
132.59
127.83
126.57
126.35
126.14
126.02
125.92
124.23
123.02
122.70
122.43
116.37
102.16
CD3OD
50.32
49.55
49.43
49.28
49.14
49.00
48.86
48.72
48.58
5.52

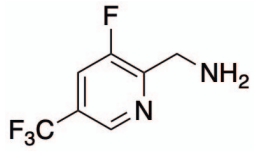
136 134 132 130 128 126 124 122 120 118 ppm

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

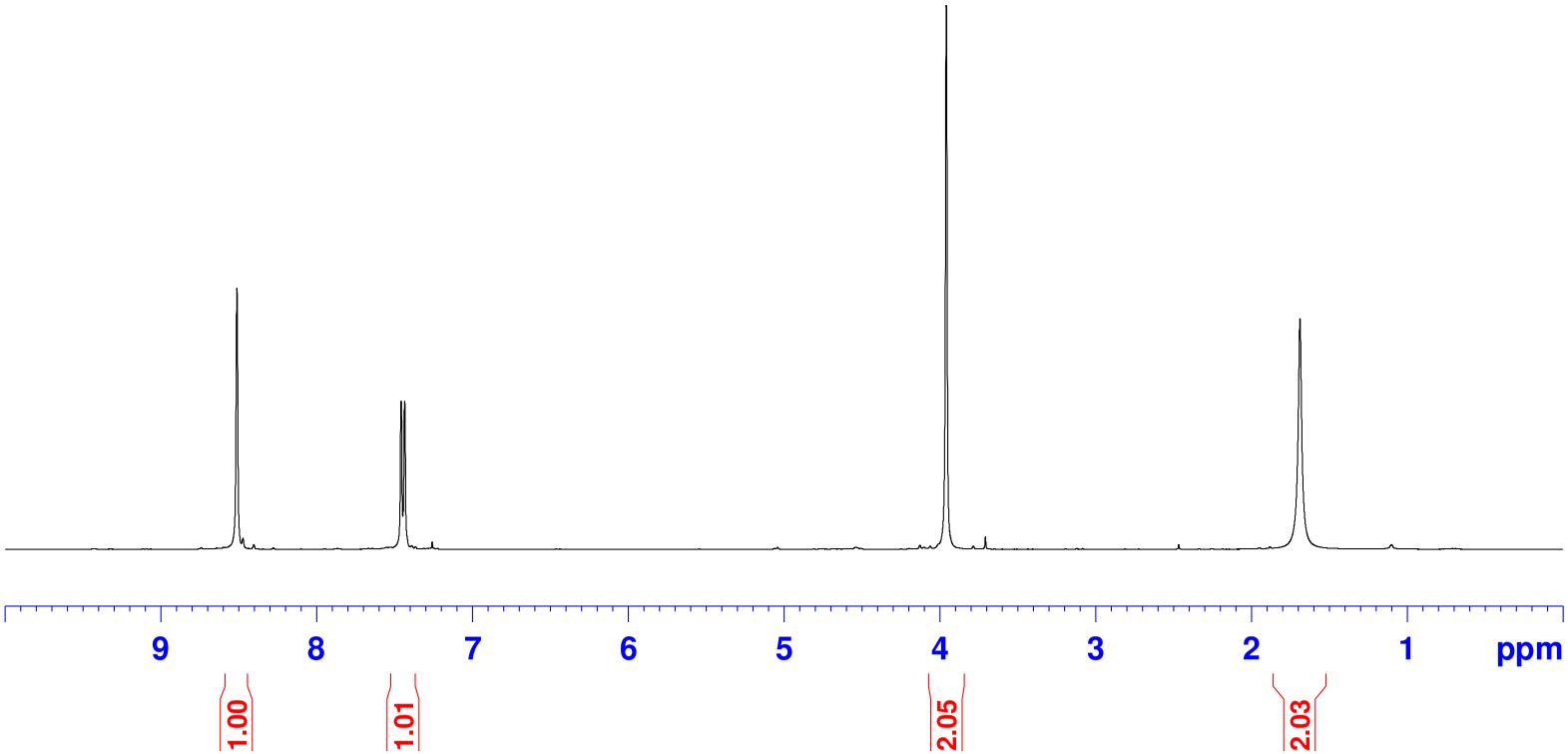
RL844.091 CDCl3 400a

CDCl3

8.514
7.460
7.438
7.260
3.960
1.689



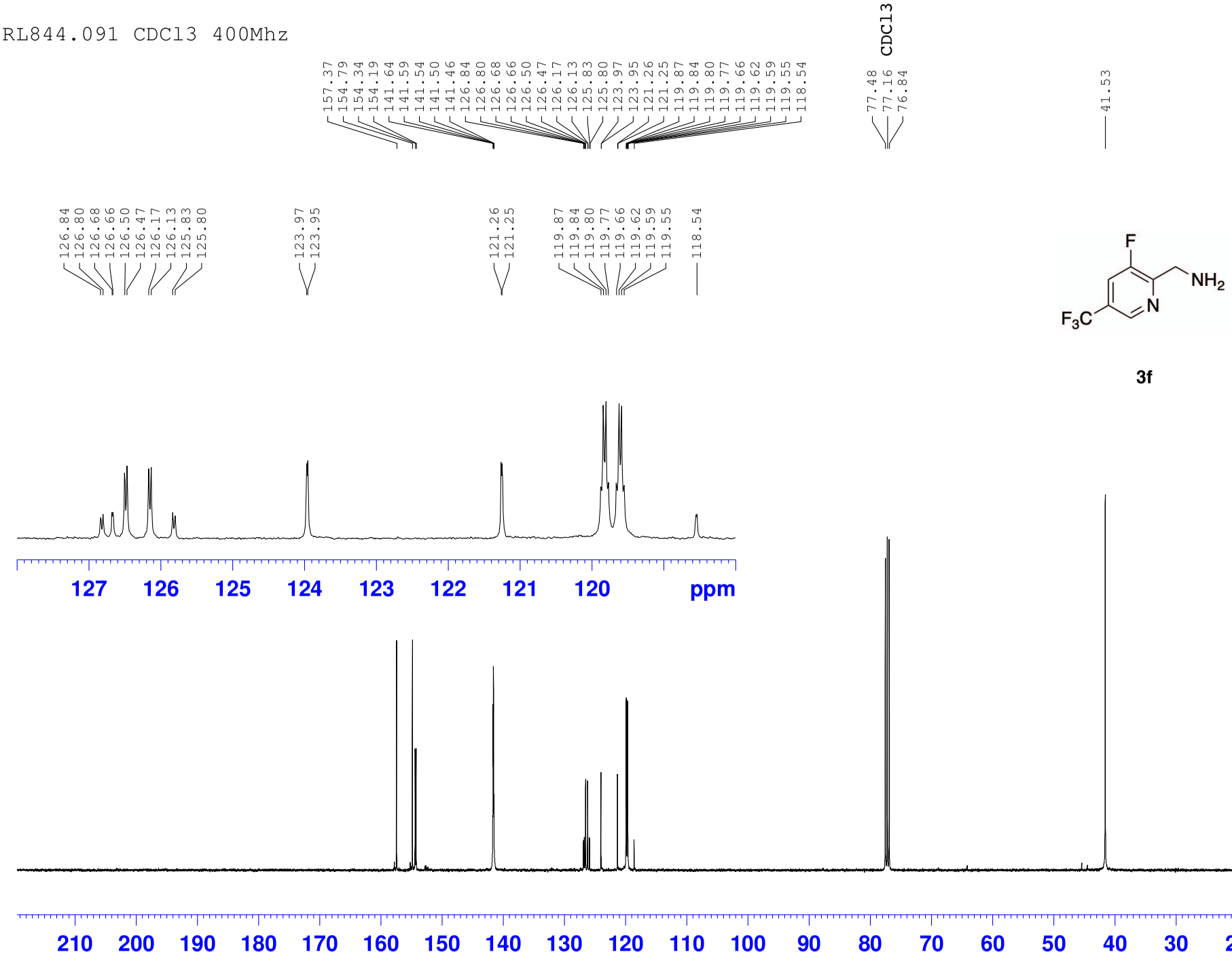
3f

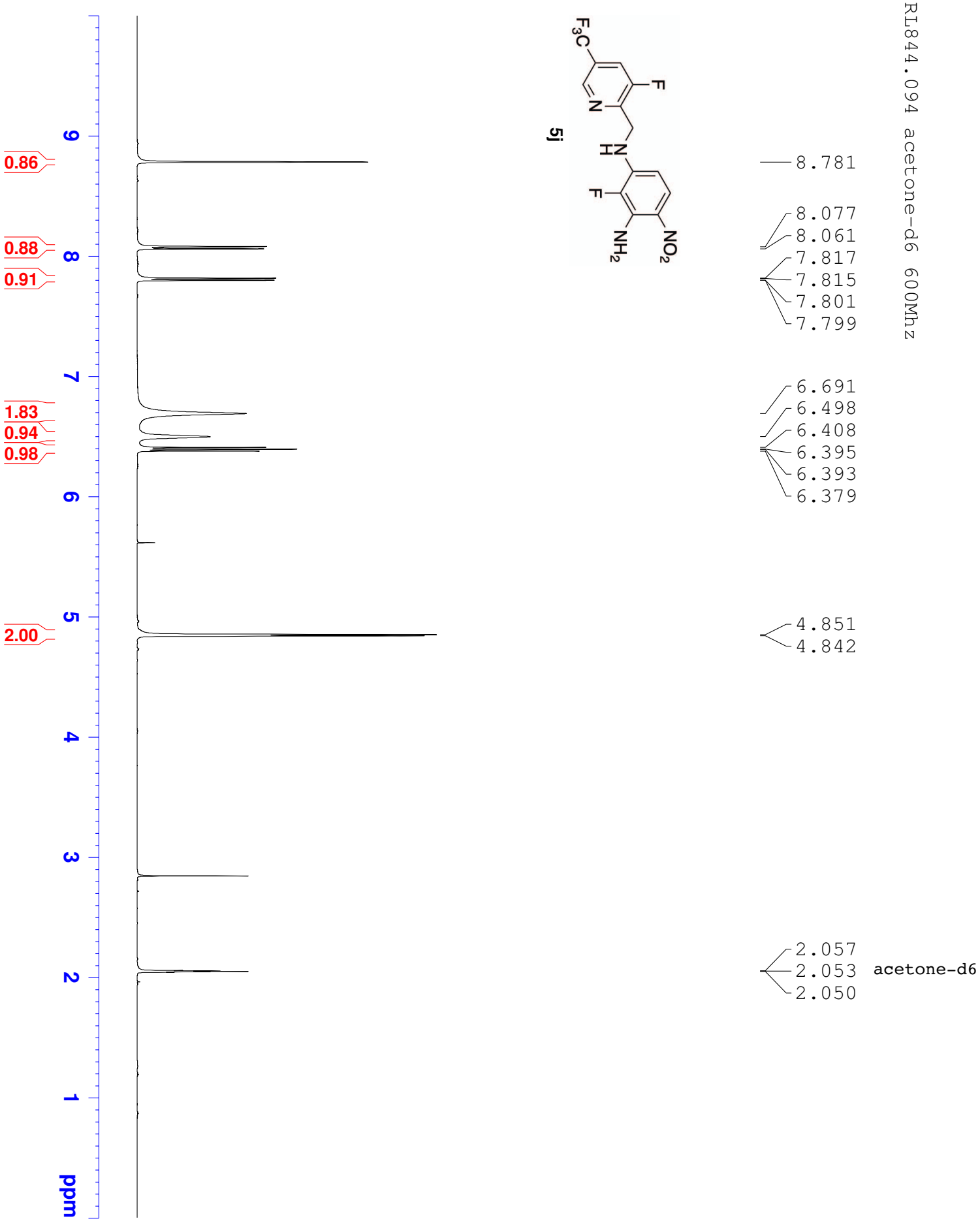


NAME	RL844.091_2
EXPNO	10
PROCNO	1
Date_	20180630
Time	14.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	8012.820 Hz
FIDRES	0.122266 Hz
AQ	4.0894966 sec
RG	16
DW	62.400 usec
DE	6.50 usec
TE	88.9 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	400.1324710 MHz
NUC1	1H
P1	14.50 usec
SI	65536
SF	400.1300103 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

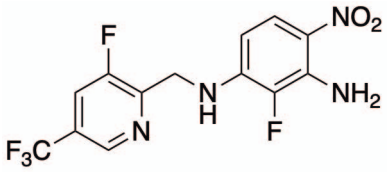
S96

RL844.091 CDCl3 400Mhz




RL844.094 acetone-d6 600Mhz
5j
8.781
8.077
8.061
7.817
7.815
7.801
7.799
6.691
6.498
6.408
6.395
6.393
6.379
4.851
4.842
2.057
2.053
2.050
acetone-d6
0.86
0.88
0.91
1.83
0.94
0.98
2.00
ppm

RL844.094 acetone-d6 600Mhz



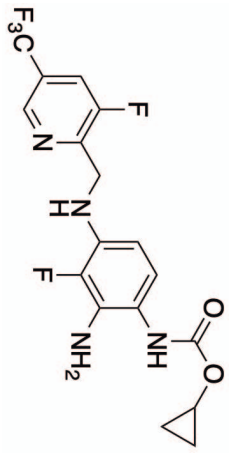
5j

206.21
158.60
156.88
151.19
151.09
142.47
142.44
142.41
142.38
142.35
142.20
142.13
139.42
137.91
136.68
136.59
127.88
127.86
127.66
127.64
127.44
127.42
127.22
127.20
126.56
125.60
125.58
124.76
123.80
123.78
122.95
121.65
121.62
121.60
121.58
121.50
121.48
121.46
121.15
101.81
101.79
43.11
30.22
30.10
29.97
29.84
29.71
29.58
29.45
acetone-d6

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

RL844.096 CDC13 600Mhz

RL-96



8.693

7.634
7.620

7.260 CDCl3

6.813

6.242
6.228
6.215
6.151

5.129

4.562

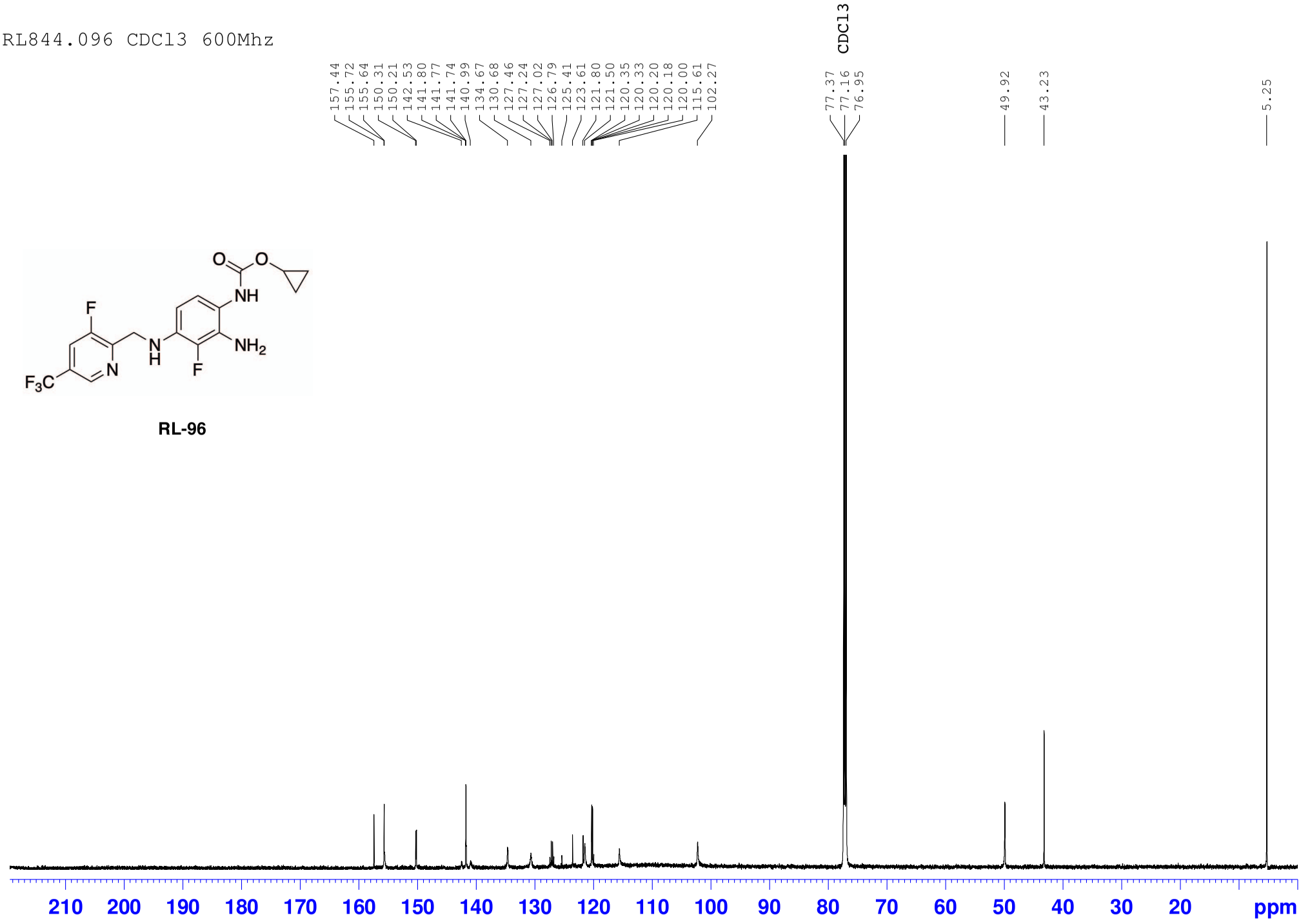
4.137
4.132

3.844

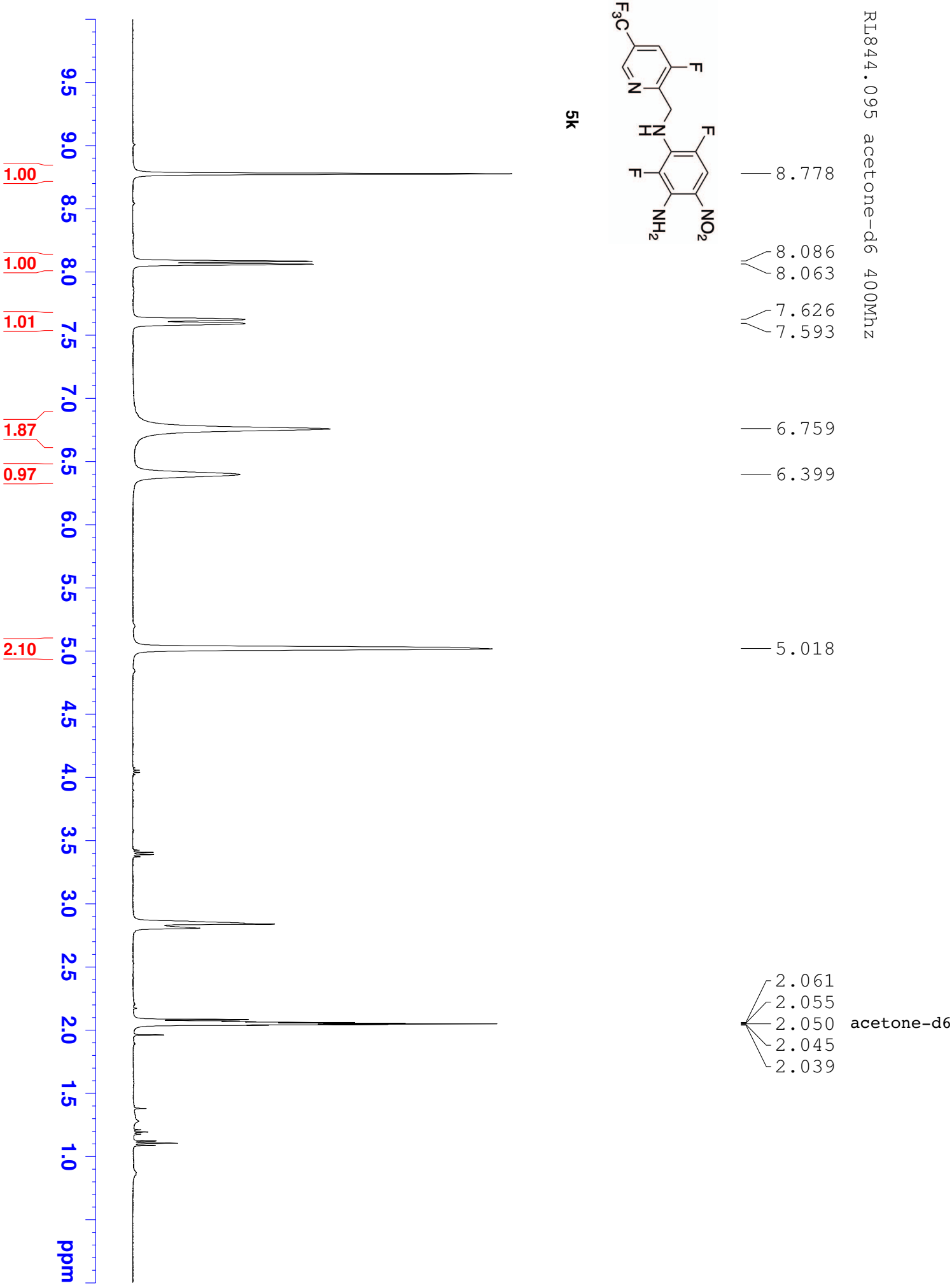
0.719
0.710

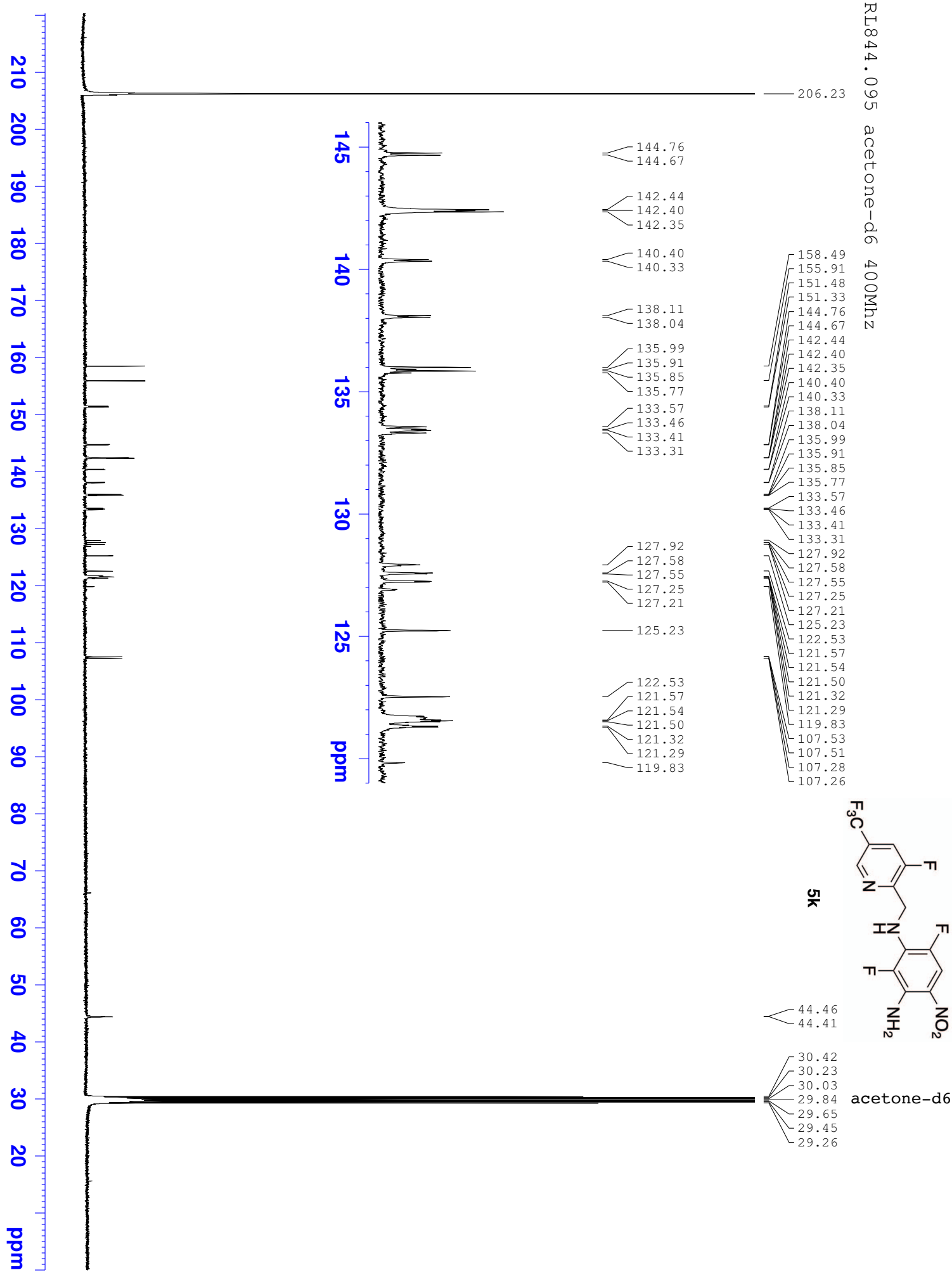
S100

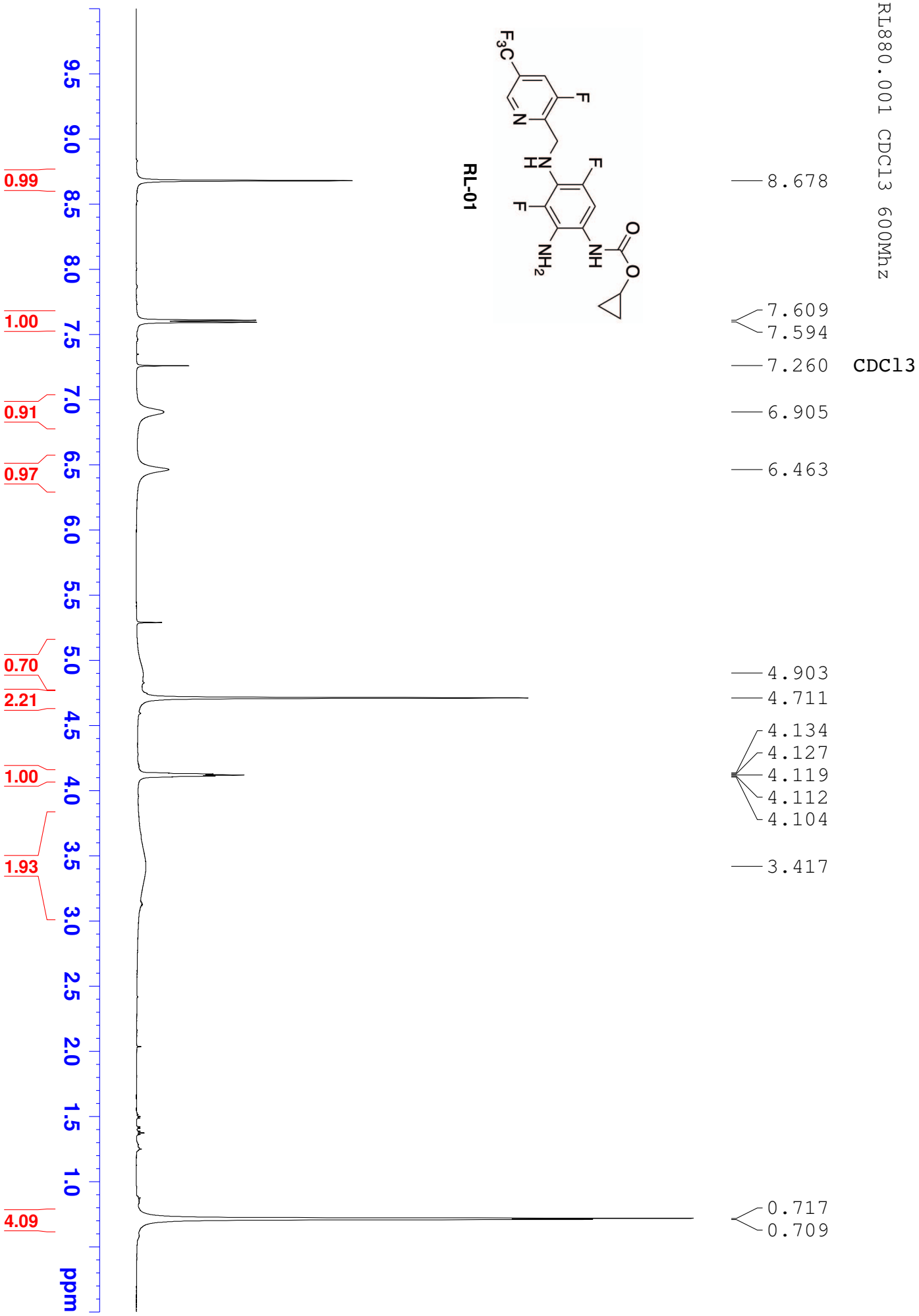
RL844.096 CDCl3 600Mhz

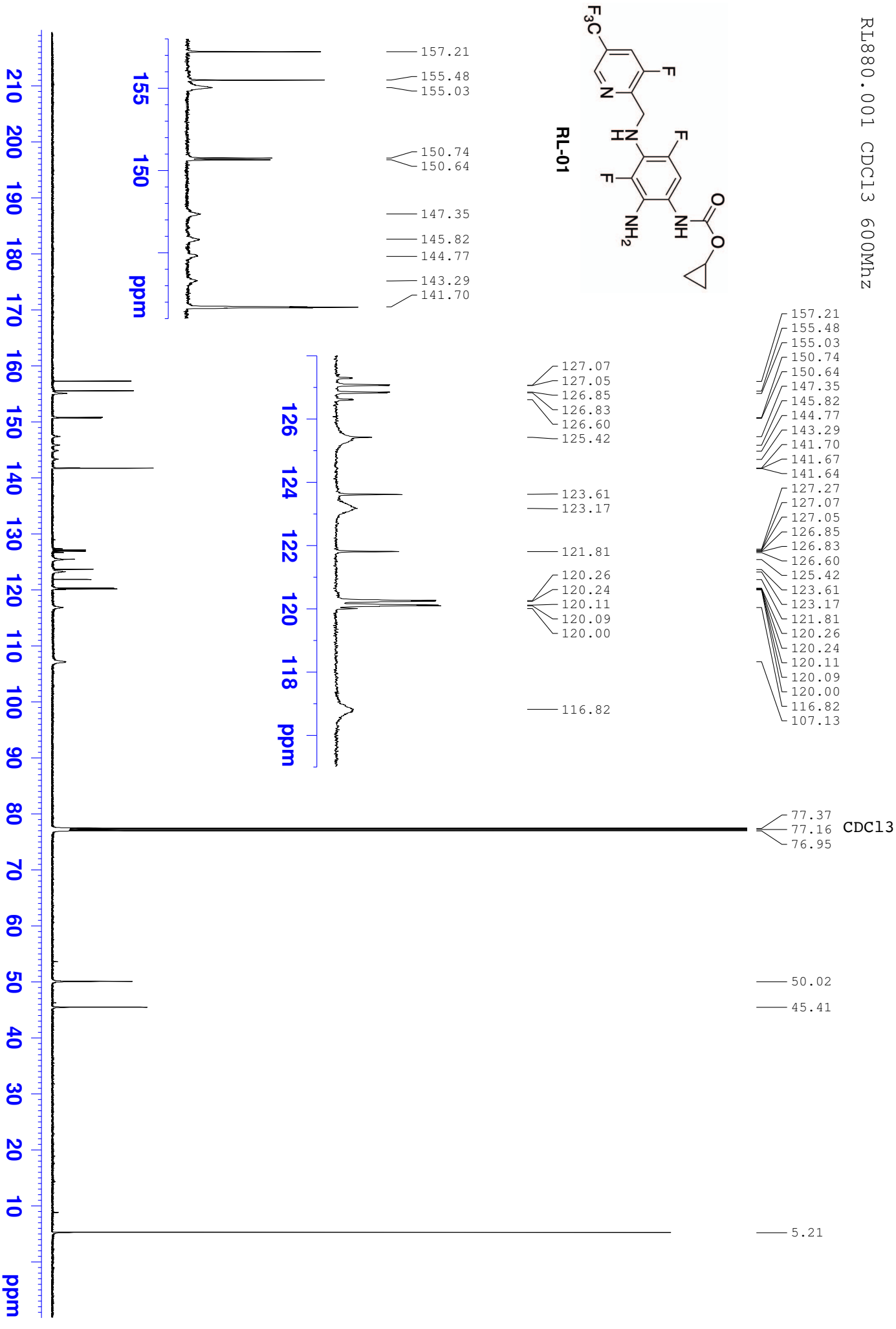


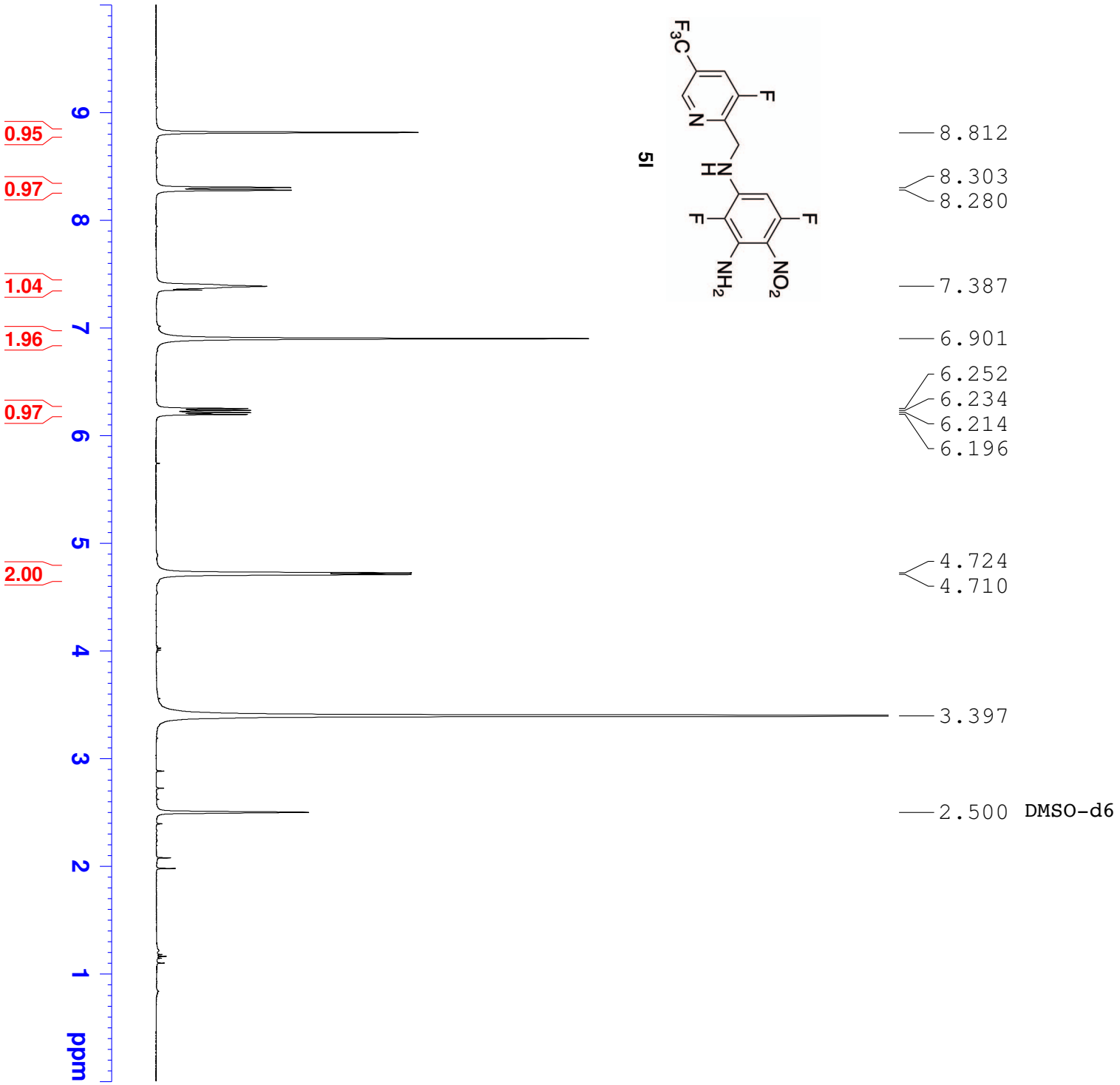
RL-96


RL844.095 acetone-d6 400Mhz
5k
8.778
8.086
8.063
7.626
7.593
6.759
6.399
5.018
2.061
2.055
2.050
2.045
2.039
acetone-d6
1.00
1.00
1.01
1.87
0.97
2.10
ppm


RL844.095 acetone-d6 400Mhz
206.23
144.76
144.67
142.44
142.40
142.35
140.40
140.33
138.11
138.04
135.99
135.91
135.85
135.77
133.57
133.46
133.41
133.31
127.92
127.58
127.55
127.25
127.21
125.23
122.53
121.57
121.54
121.50
121.32
121.29
119.83
158.49
155.91
151.48
151.33
144.76
144.67
142.44
142.40
142.35
140.40
140.33
138.11
138.04
135.99
135.91
135.85
135.77
133.57
133.46
133.41
133.31
127.92
127.58
127.55
127.25
127.21
125.23
122.53
121.57
121.54
121.50
121.32
121.29
119.83
107.53
107.51
107.28
107.26
44.46
44.41
30.42
30.23
30.03
29.84
29.65
29.45
29.26
acetone-d6
5k
F3C
F
N
H
F
F
NH2
NO2
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
145
140
135
130
125
ppm

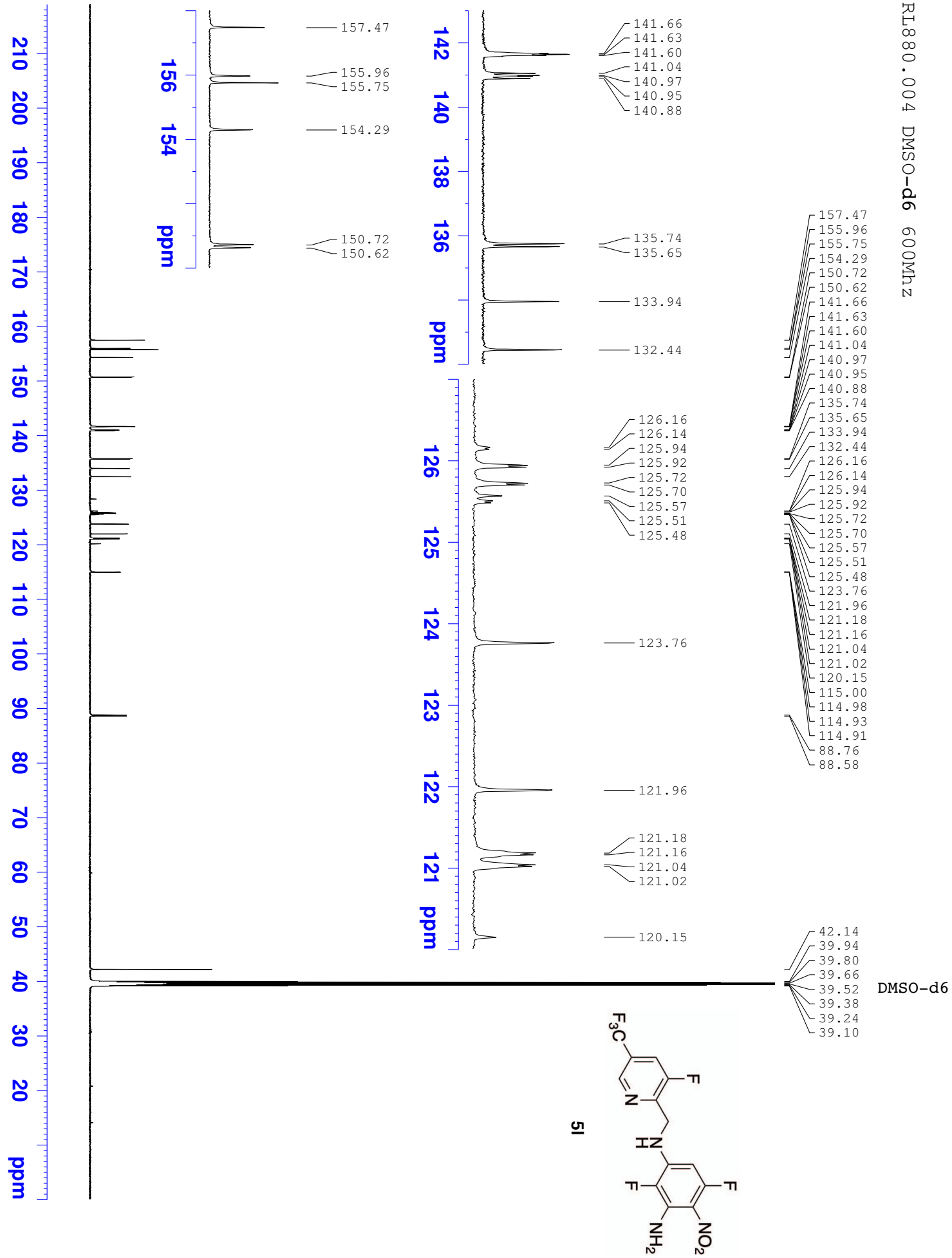

RL880.001 CDCl3 600Mhz
RL-01
8.678
7.609
7.594
7.260
CDCl3
6.905
6.463
4.903
4.711
4.134
4.127
4.119
4.112
4.104
3.417
0.717
0.709
0.99
1.00
0.91
0.97
0.70
2.21
1.00
1.93
4.09
ppm


RL880.001 CDCl3 600Mhz
RL-01
157.21
155.48
155.03
150.74
150.64
147.35
145.82
144.77
143.29
141.70
127.07
127.05
126.85
126.83
126.60
125.42
123.61
123.17
121.81
120.26
120.24
120.11
120.09
120.00
116.82
157.21
155.48
155.03
150.74
150.64
147.35
145.82
144.77
143.29
141.70
141.67
141.64
127.27
127.07
127.05
126.85
126.83
126.60
125.42
123.61
123.17
121.81
120.26
120.24
120.11
120.09
120.00
116.82
107.13
77.37
77.16
76.95
CDCl3
50.02
45.41
5.21
ppm
155
150
126
124
122
120
118
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10




```
NAME                 RL880.004
EXPNO                       10
PROCNO                       1
Date_                 20180714
Time                     15.21
INSTRUM                   spect
PROBHD     5 mm PABBO BB-
PULPROG                   zg30
TD                       65536
SOLVENT                  DMSO
NS                          16
DS                           2
SWH                 8012.820 Hz
FIDRES              0.122266 Hz
AQ                  4.0894966 sec
RG                          57
DW                  62.400 usec
DE                   6.50 usec
TE                  -2673.8 K
D1                  1.0000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1                400.1324710 MHz
NUC1                        1H
P1                  14.50 usec
SI                       65536
SF                  400.1300035 MHz
WDW                         EM
SSB                          0
LB                    0.30 Hz
GB                           0
PC                        1.00
```


RL880.004 DMSO-d6 600Mhz
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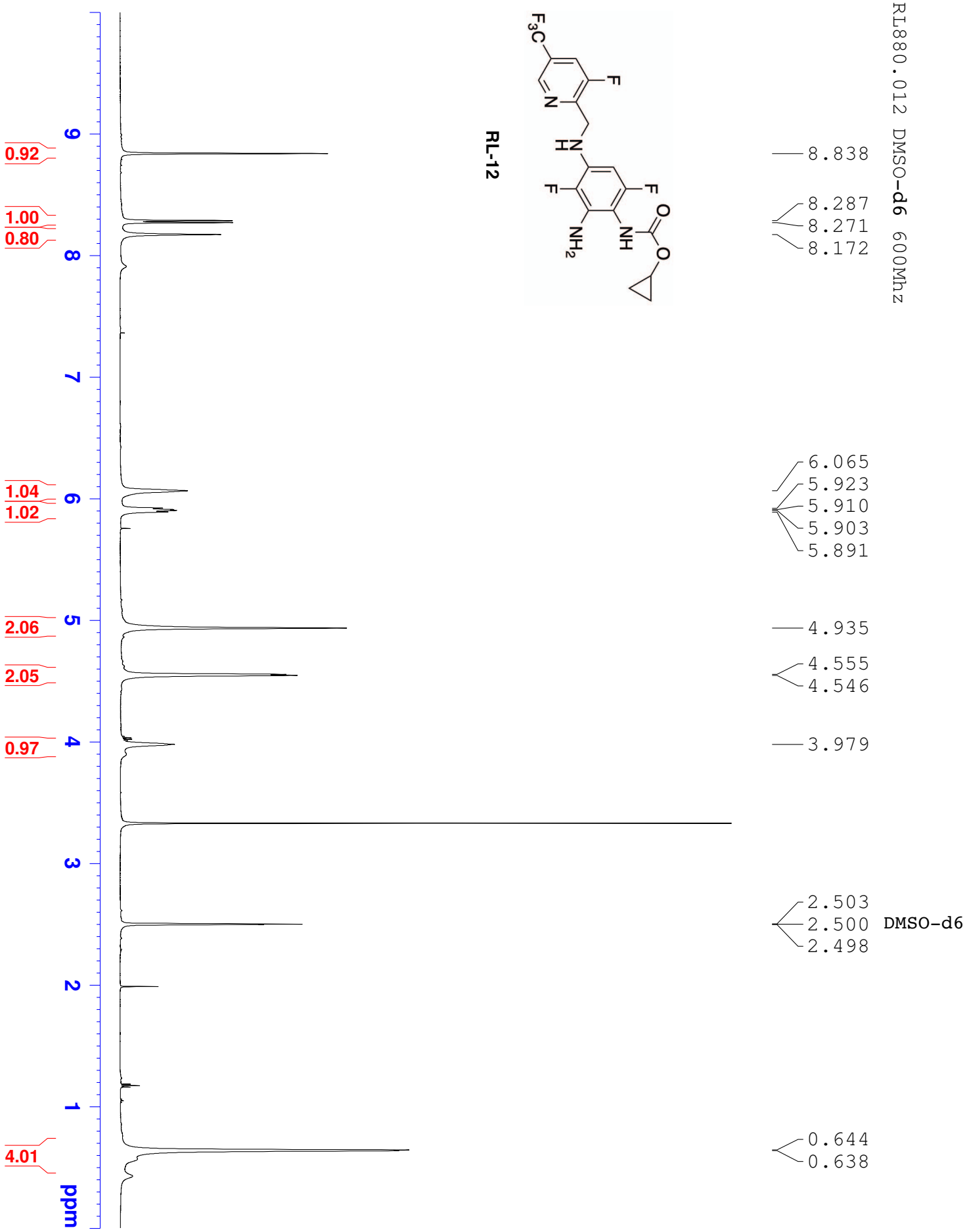
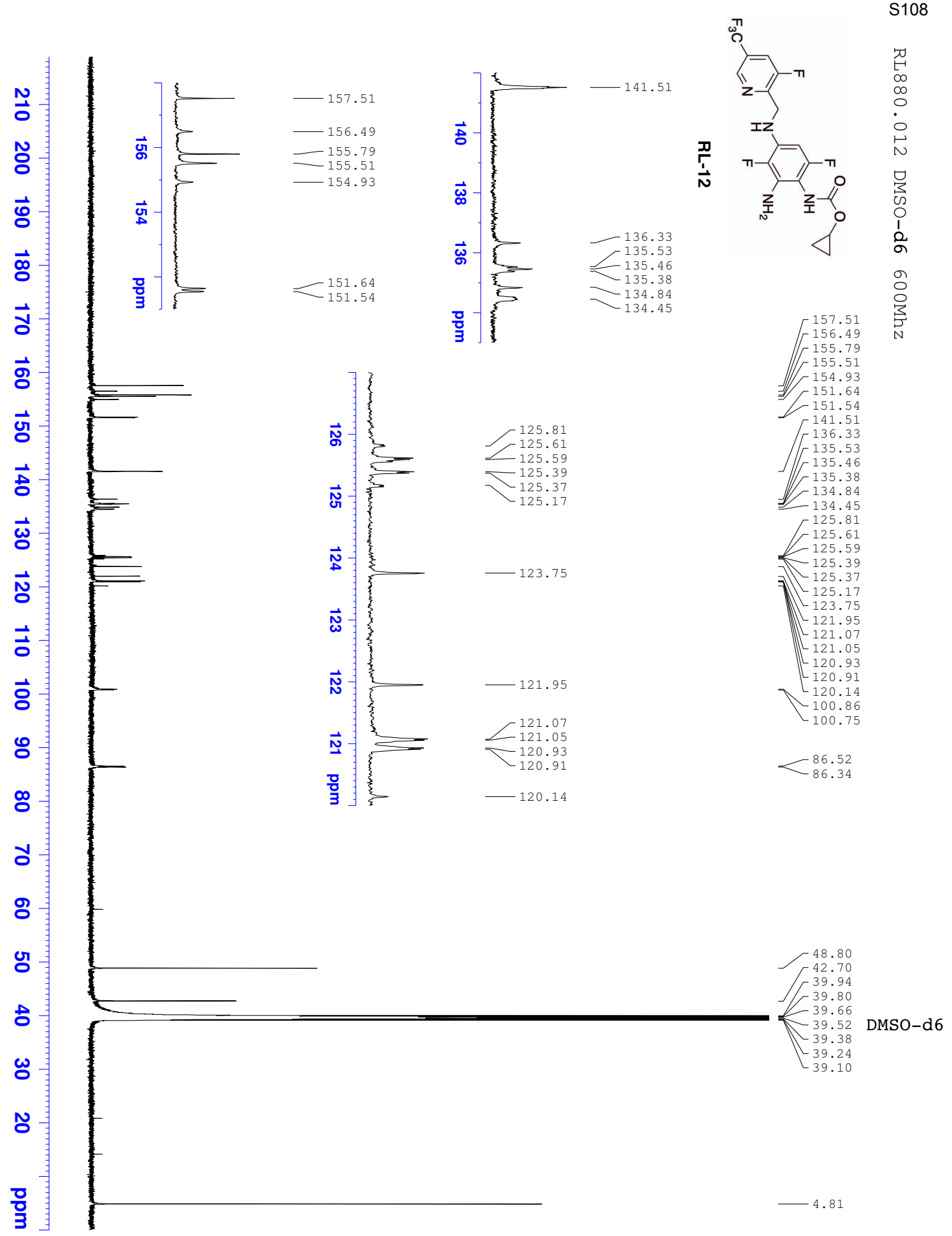
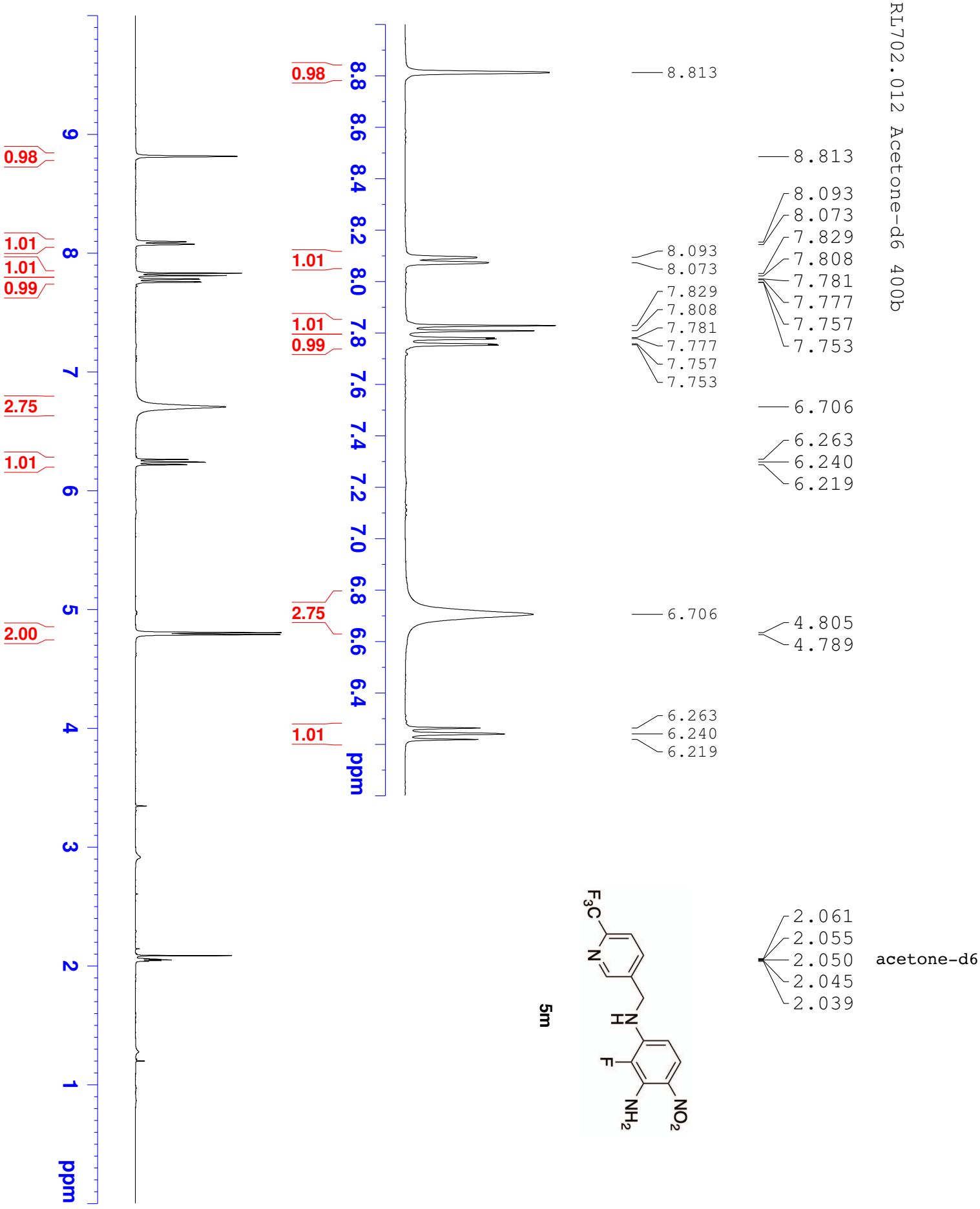
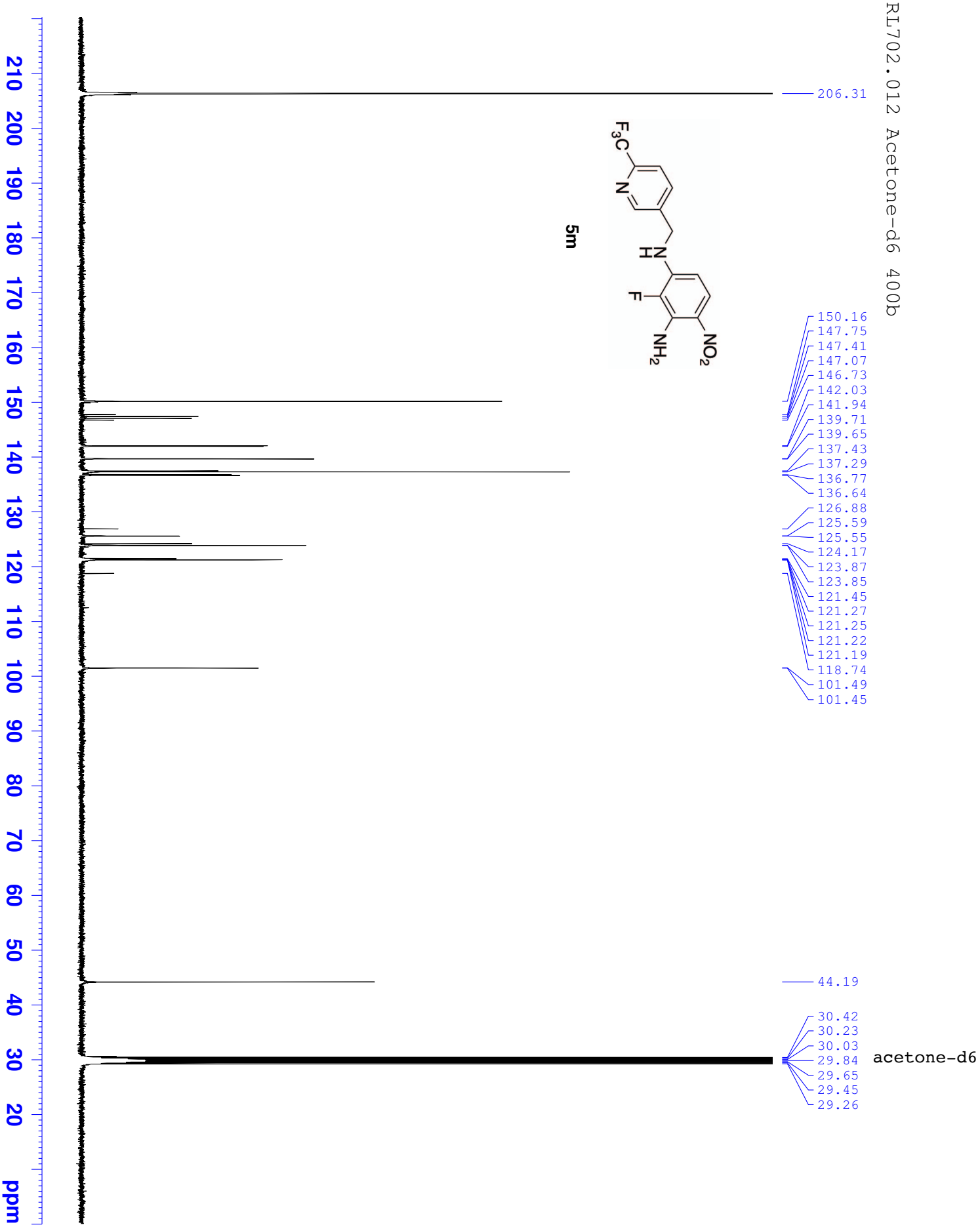
155.96
155.75
154.29
150.72
150.62
141.66
141.63
141.60
141.04
140.97
140.95
140.88
135.74
135.65
133.94
132.44
126.16
126.14
125.94
125.92
125.72
125.70
125.57
125.51
125.48
123.76
121.96
121.18
121.16
121.04
121.02
120.15
42.14
39.94
39.80
39.66
39.52
39.38
39.24
39.10
DMSO-d6
5l
ppm

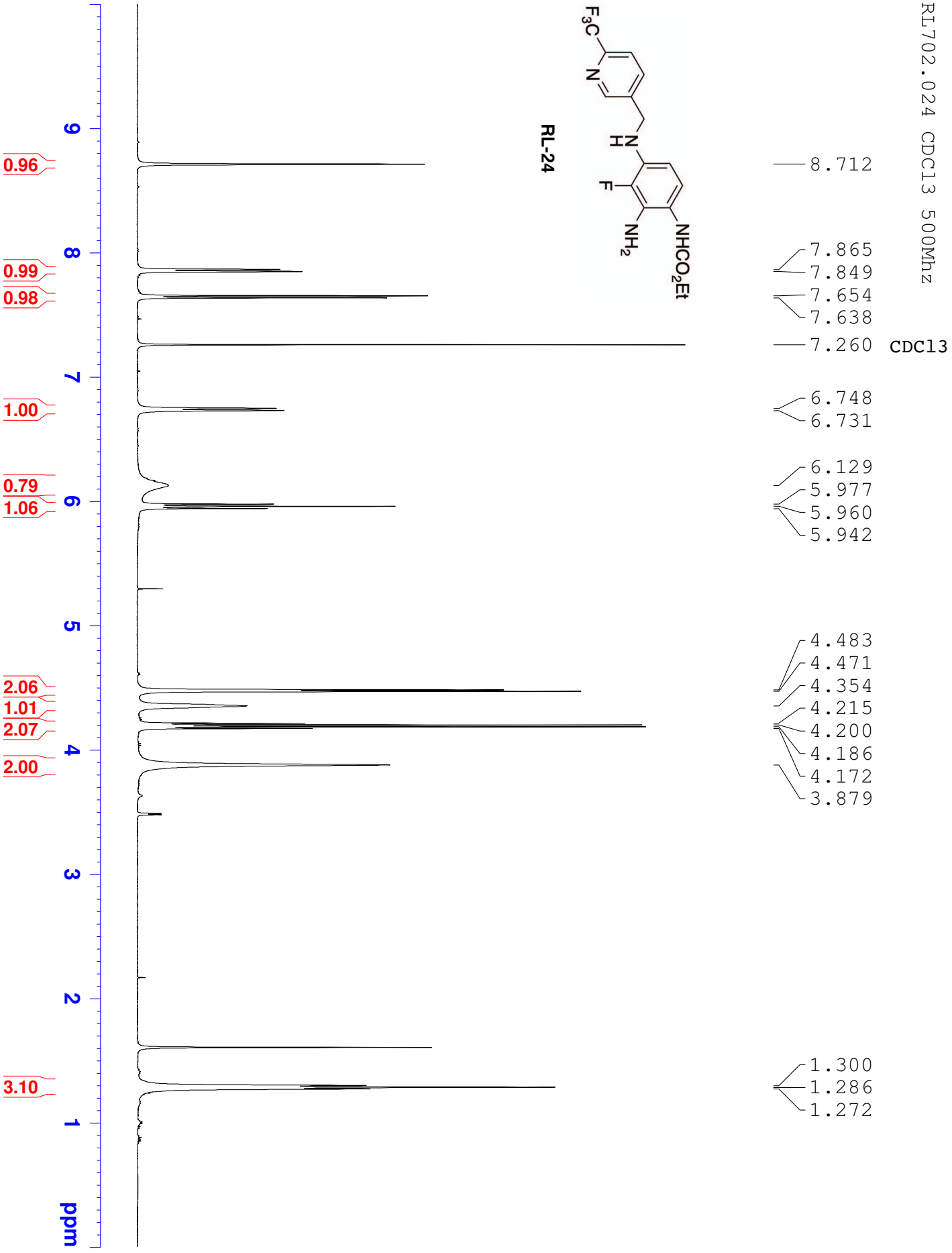

RL880.012 DMSO-d6 600Mhz
RL-12
8.838
8.287
8.271
8.172
6.065
5.923
5.910
5.903
5.891
4.935
4.555
4.546
3.979
2.503
2.500
2.498
DMSO-d6
0.644
0.638
0.92
1.00
0.80
1.04
1.02
2.06
2.05
0.97
4.01
ppm

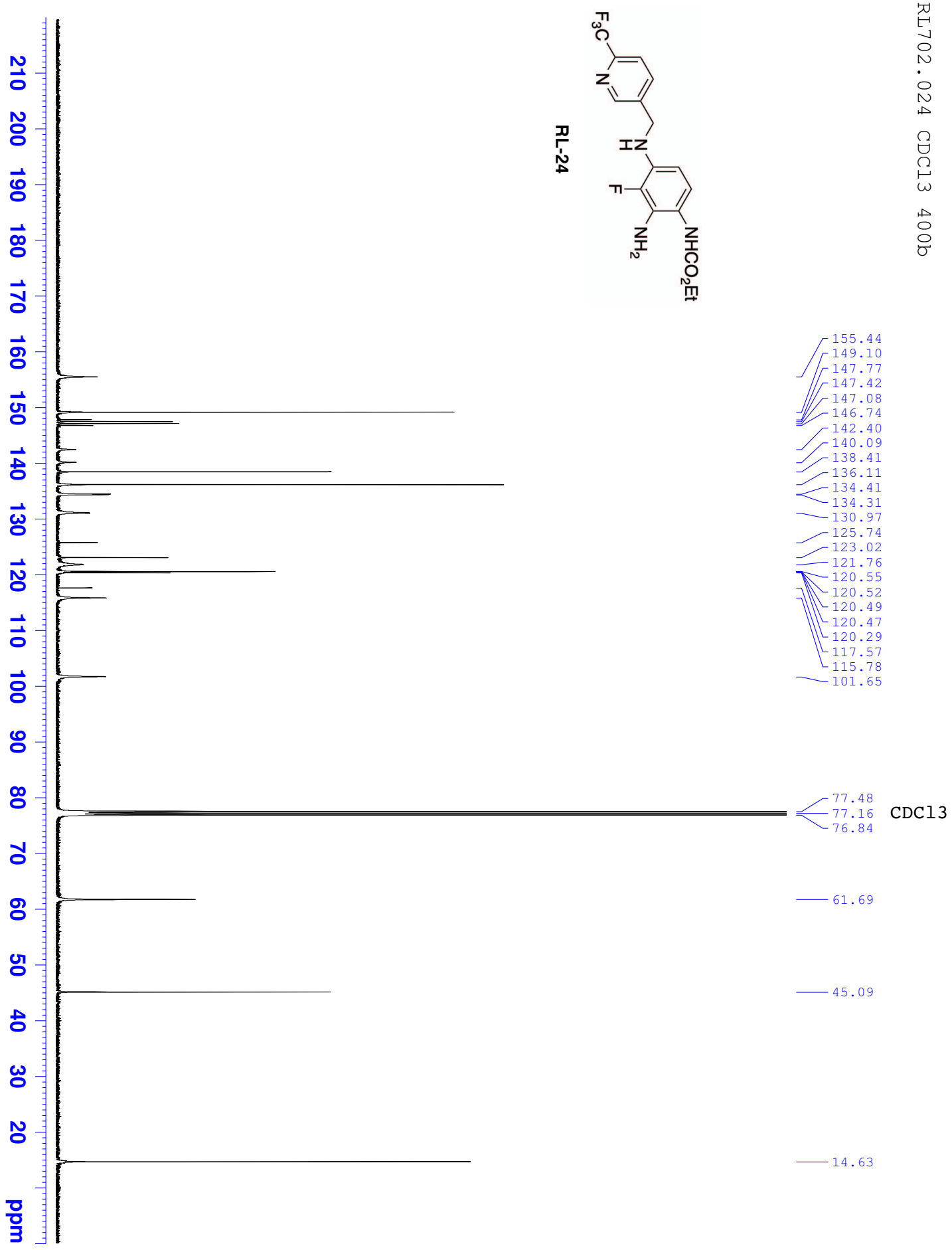

RL880.012 DMSO-d6 600Mhz
RL-12
DMSO-d6
157.51
156.49
155.79
155.51
154.93
151.64
151.54
141.51
136.33
135.53
135.46
135.38
134.84
134.45
125.81
125.61
125.59
125.39
125.37
125.17
123.75
121.95
121.07
121.05
120.93
120.91
120.14
100.86
100.75
86.52
86.34
48.80
42.70
39.94
39.80
39.66
39.52
39.38
39.24
39.10
4.81
ppm

RL702.012 Acetone-d6 400b

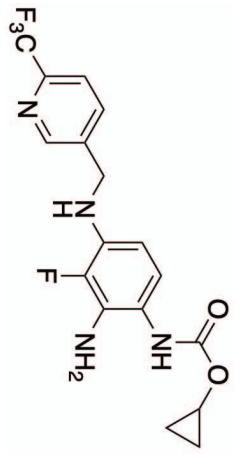



RL702.012 Acetone-d6 400b
206.31
150.16
147.75
147.41
147.07
146.73
142.03
141.94
139.71
139.65
137.43
137.29
136.77
136.64
126.88
125.59
125.55
124.17
123.87
123.85
121.45
121.27
121.25
121.22
121.19
118.74
101.49
101.45
44.19
30.42
30.23
30.03
29.84
29.65
29.45
29.26
acetone-d6
5m
F3C
N
H
F
NH2
NO2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

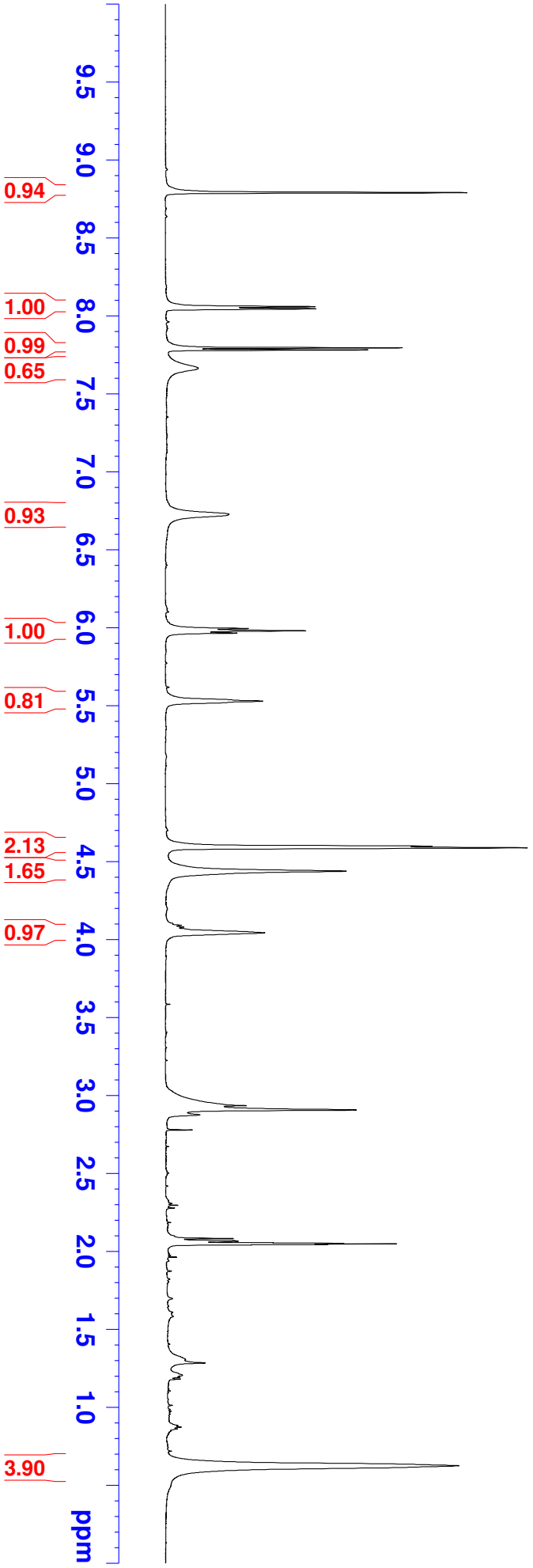

RL702.024 CDCl3 500Mhz
RL-24
8.712
7.865
7.849
7.654
7.638
7.260
CDCl3
6.748
6.731
6.129
5.977
5.960
5.942
4.483
4.471
4.354
4.215
4.200
4.186
4.172
3.879
1.300
1.286
1.272
0.96
0.99
0.98
1.00
0.79
1.06
2.06
1.01
2.07
2.00
3.10
ppm


RL702.024 CDCl3 400b
RL-24
F3C
N
H
N
F
NH2
NHCO2Et
155.44
149.10
147.77
147.42
147.08
146.74
142.40
140.09
138.41
136.11
134.41
134.31
130.97
125.74
123.02
121.76
120.55
120.52
120.49
120.47
120.29
117.57
115.78
101.65
77.48
77.16
76.84
CDCl3
61.69
45.09
14.63
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

RL844.067 acetone-d6 600Mhz



RL-67



8.790
8.058
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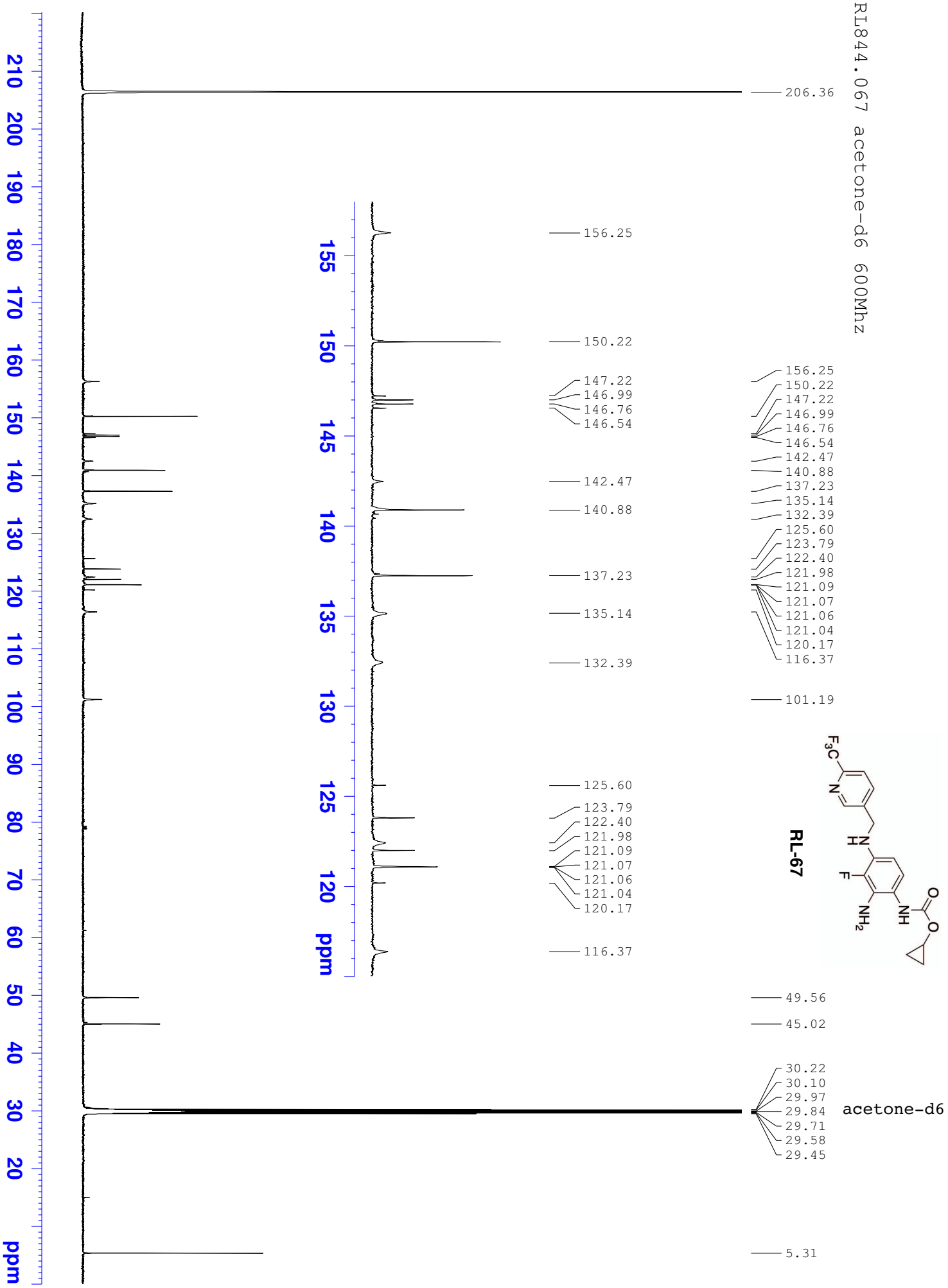
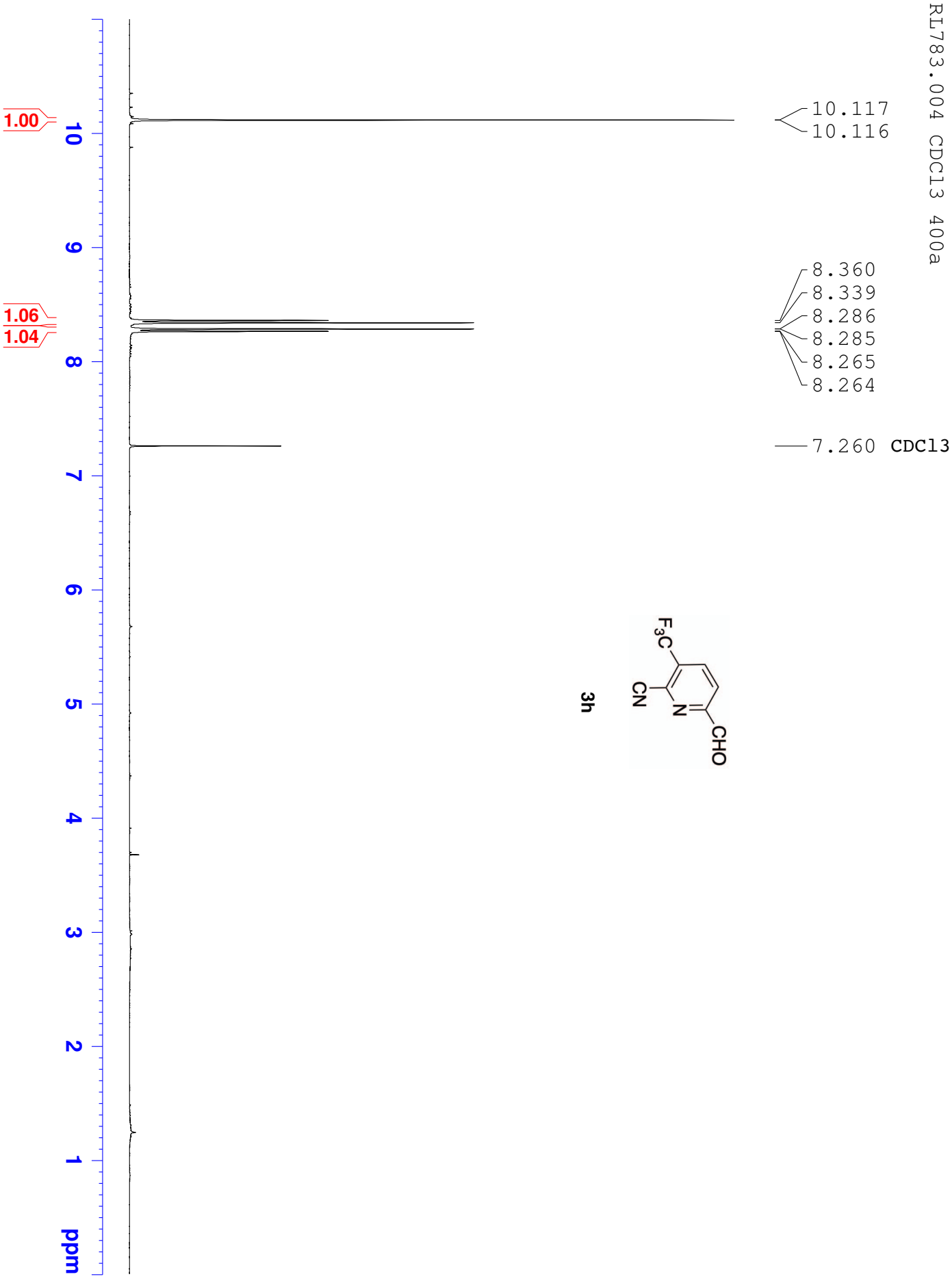
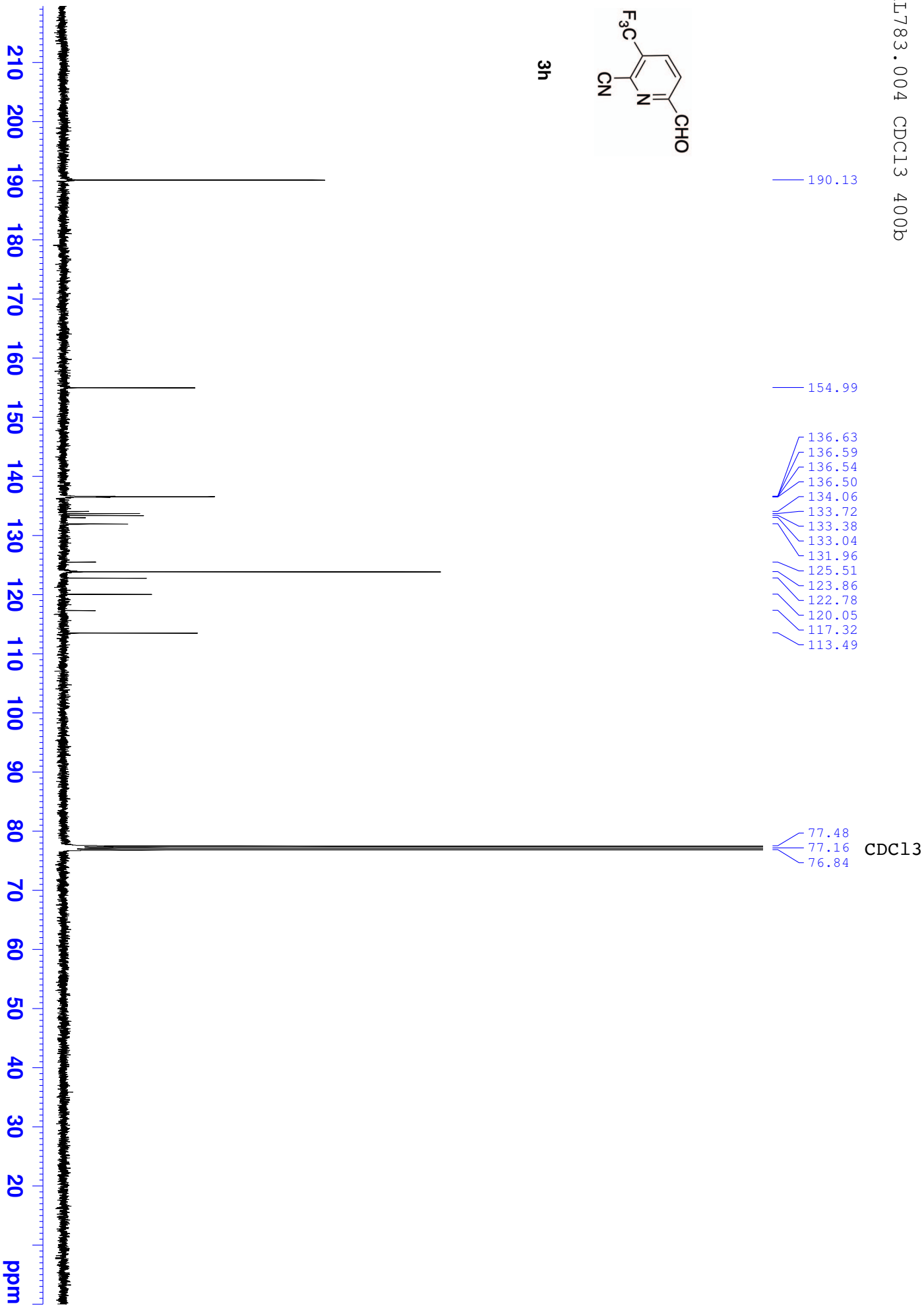
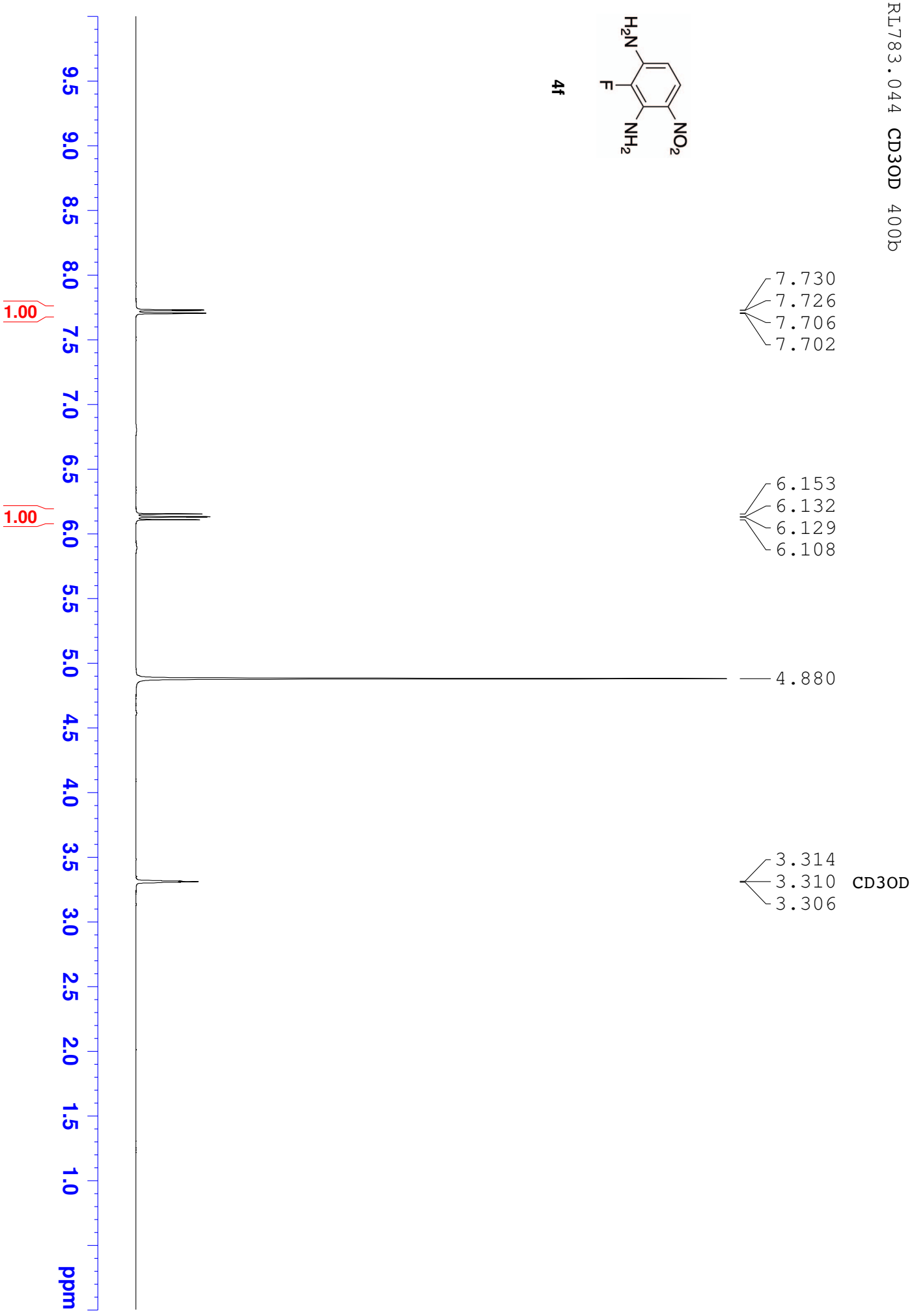
7.794
7.781
7.664
6.727
5.994
5.979
5.965
5.529
4.598
4.588
4.438
4.048
4.043
4.032
4.029
2.057
2.054
2.050 acetone-d6
2.047
2.043
0.640
0.627
0.618
0.513

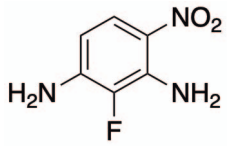

RL844.067 acetone-d6 600Mhz
206.36
156.25
150.22
147.22
146.99
146.76
146.54
142.47
140.88
137.23
135.14
132.39
125.60
123.79
122.40
121.98
121.09
121.07
121.06
121.04
120.17
116.37
101.19
49.56
45.02
30.22
30.10
29.97
29.84
29.71
29.58
29.45
acetone-d6
5.31
RL-67
ppm


RL783.004 CDC13 400a
10.117
10.116
8.360
8.339
8.286
8.285
8.265
8.264
7.260 CDCl3
1.00
1.06
1.04
10
9
8
7
6
5
4
3
2
1
ppm
F3C
CN
N
CHO
3h


RL783.004 CDCl3 400b
3h
F3C
CN
N
CHO
190.13
154.99
136.63
136.59
136.54
136.50
134.06
133.72
133.38
133.04
131.96
125.51
123.86
122.78
120.05
117.32
113.49
77.48
77.16
76.84
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


RL783.044 CD3OD 400b
4f
7.730
7.726
7.706
7.702
6.153
6.132
6.129
6.108
4.880
3.314
3.310
3.306
CD3OD
1.00
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

RL783.044 **CD3OD** 400b

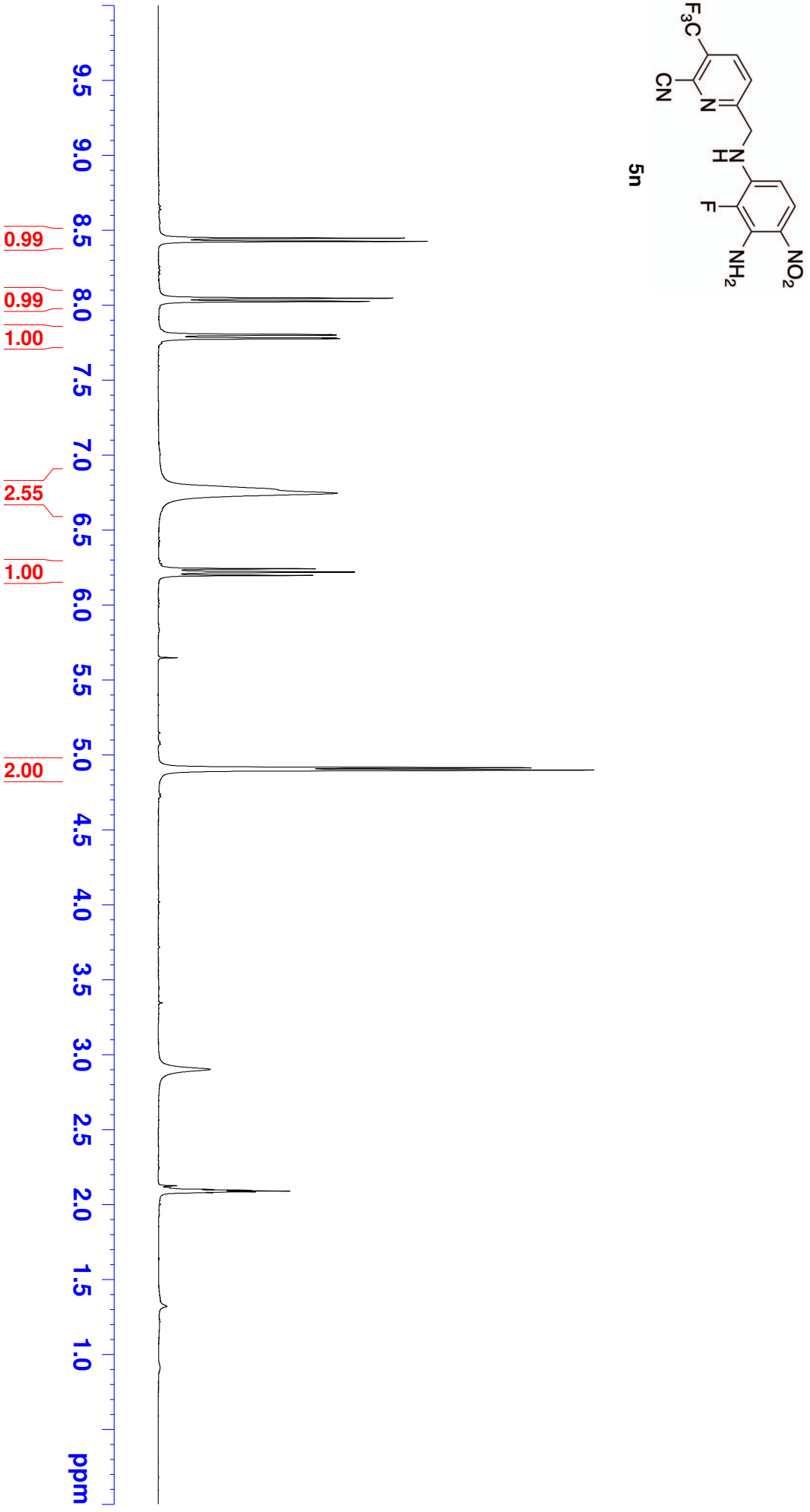


4f

143.54
143.44
139.42
138.41
138.28
137.16
124.83
123.90
123.88
105.90
105.86
CD3OD
49.64
49.42
49.21
49.00
48.79
48.57
48.36

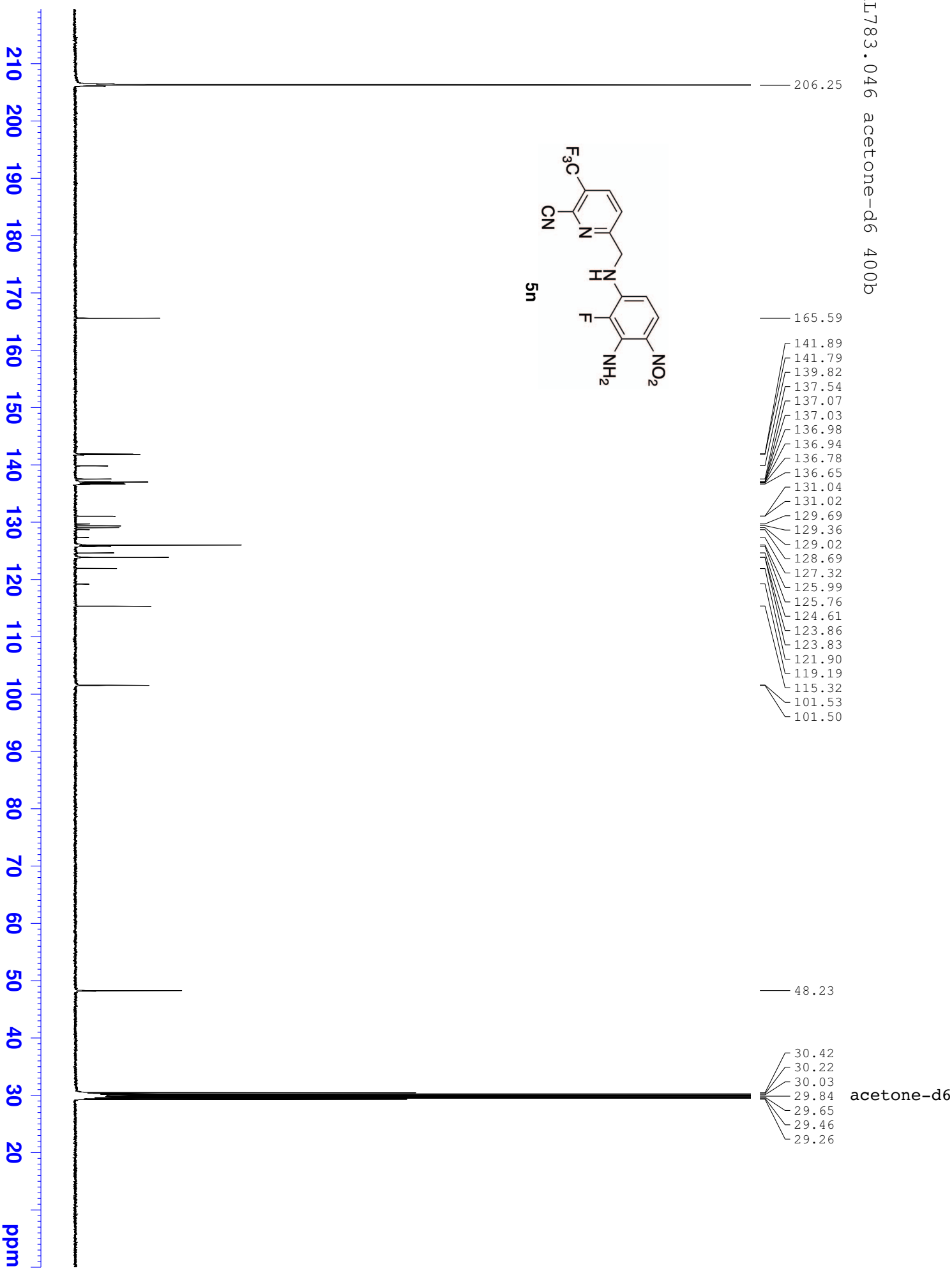
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

RL783.046 acetone-d6 400b



5n

8.448
8.427
8.047
8.026
7.805
7.801
7.781
7.777
6.746
6.242
6.221
6.218
6.198
4.914
4.899
2.902
2.101
2.095
2.090 acetone-d6
2.085
2.079


RL783.046 acetone-d6 400b
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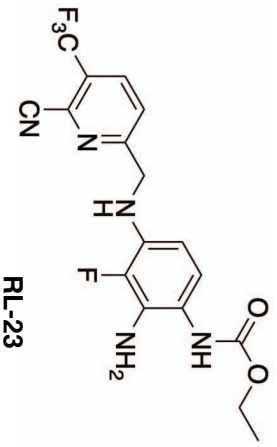
165.59
141.89
141.79
139.82
137.54
137.07
137.03
136.98
136.94
136.78
136.65
131.04
131.02
129.69
129.36
129.02
128.69
127.32
125.99
125.76
124.61
123.86
123.83
121.90
119.19
115.32
101.53
101.50
48.23
30.42
30.22
30.03
29.84
29.65
29.46
29.26
acetone-d6
5n
F3C
CN
N
H
F
NH2
NO2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

RL783.023 CDC13 500Mhz



RL-23

8.037
8.020
7.713
7.697

7.260 CDCl3

6.730
6.713

6.192
5.882
5.865
5.847

4.587
4.207
4.193
4.178
4.164
3.980

1.295
1.281
1.267

0.94
0.94
0.96
0.89
0.97
2.00
0.39
2.23
1.71
3.04

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0

ppm

RL783.023 CDCl3 400a

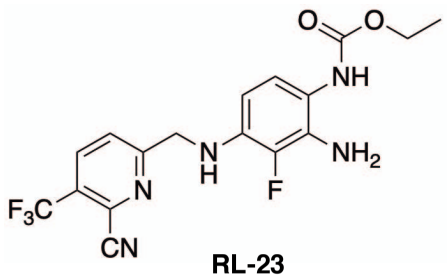
164.89
155.46
142.46
140.16
135.45
135.40
135.37
135.32
134.06
133.96
131.23
131.11
130.81
130.79
129.59
129.25
128.91
128.57
126.05
124.31
123.33
121.91
120.61
117.89
116.00
114.31
101.58

CDCl3
77.48
77.16
76.84

61.75

48.82

14.66



RL-23