Electronic Supplementary Material (ESI) for MedChemComm.

Supporting Information

A Scaffold Merging Approach to Hsp90 C-terminal Inhibition: Synthesis and Evaluation of a Chimeric Library

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Biology Information and Protocols

Cell Culture

The media for each cell line was supplemented with streptomycin (500 µg/mL), penicillin (100 units/mL), and 10% FBS (Corning). MCF7 and SKBR3 cells were maintained in Advanced DMEM/F12 (Gibco) supplemented with L-glutamine (2 mM). PC3-MM2 cells transduced with Luc2/mCherry lentivirus (a gift from George Vielhauer) were maintained in DMEM with 4.5 g/L glucose (Corning 10-013). Cells were grown in a humidified atmosphere (37 °C, 5% CO_2) and passaged when confluent.

Anti-Proliferation Assay

Cells were seeded into clear 96-well plates (2000 cells/well/100 µL media), which were placed in the incubator for 24 h before the addition of compound or vehicle. Test compounds were administered as a solution in DMSO (6 concentrations/compound) for an assay concentration of 1% DMSO. The plates were returned to the incubator for 72 h before cell viability was determined using an MTS/PMS cell proliferation kit (Promega) per the manufacturer's instructions. Absorbance values for cells treated with vehicle were taken as 100% proliferation and values for cells treated with test compounds were normalized to this. EC_{50} values for each experiment performed in triplicate were calculated using Gen5. Values reported are the average of three separate experiments.

Luciferase Refolding Assay

Compound or vehicle was added to wells of a white 96-well plate containing 50 µL media. Test compounds were administered as a 10 mM solution in DMSO for an assay concentration of 100 µM drug and 1% DMSO. PC3-MM2 cells expressing luciferase were grown to confluence, collected, and counted before pelleting 5×10^6 cells. The cell pellet was resuspended in 5 mL media that had been pre-warmed to 50 °C and the suspension was incubated at this temperature until the bioluminescence of luciferase was reduced to 1% of initial counts (1 m). Cells were then added to wells with compound or vehicle for an assay concentration of 50 000 cells/well/100 µL media and the plate was placed in the incubator for 1 h. After 1 h, 100 µL of luciferase substrate reagent (75 mM tricine at pH 7.8, 150 mM KCl, 24 mM MgSO4, 0.3 mM EDTA, 2 mM DTT, 0.313 mM D-luciferin, 0.64 mM coenzyme A, 0.66 mM ATP, 10% Triton-X, 20% glycerol, and 3.5% DMSO) was added to wells and the bioluminescence was measured (0.5 s integration time). RLU values for cells treated with vehicle were taken as 100% refolded and values for cells treated with test compounds were normalized to this. Each experiment was performed in triplicate and values reported are the average

of two separate experiments. Non-heat-treated cells were included in each experiment as an assay control to ensure that heat treatment did not affect cell viability.

Western Blotting

MCF7 cells were seeded into 10 cm dishes and grown to 70% confluence. Compound (administered as a solution in DMSO) or vehicle was diluted into 5 mL fresh media (assay concentration of 1% DMSO) and added to the dishes, which were returned to the incubator for 24 h. Cells were harvested in cold PBS and lysed using MPER (Thermo Scientific) supplemented with protease and phosphatase inhibitors (Roche) per manufacturer's directions. Lysates were clarified at 14 000*g* for 15 m at 4 °C. Protein concentrations were determined using the Pierce BCA protein assay kit per the manufacturer's instructions. Equal amounts of protein (10 µg) were electrophoresed under reducing conditions (10% tris-glycine gels), transferred to PVDF (Millipore Immobilon P), and immunoblotted with the corresponding primary antibody (listed below). Membranes were incubated with an appropriate horseradish peroxidase-labeled secondary antibody, developed with a chemiluminescent substrate (Bio-Rad Clarity), and visualized with autoradiography film (Midsci).

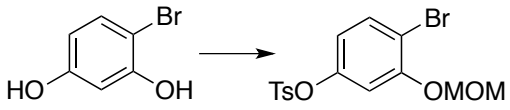
Raf-1: Santa Cruz Biotechnology (sc-133)
Her2: Cell Signaling Technology (2165)
ER-α: Santa Cruz Biotechnology (sc-544)
Cyclin D1: Santa Cruz Biotechnology (sc-753)
Hsp90: Santa Cruz Biotechnology (sc-59577)
Actin: Santa Cruz Biotechnology (sc-1616)
Anti-Rabbit: GE Healthcare Life Sciences (NA934V)
Anti-Mouse: Santa Cruz Biotechnology (sc-2005)

Synthetic Procedures and Characterization

General Information

Reagents and solvents purchased from commercial sources were used without further purification. Where indicated, solvents were dried over anhydrous activated alumina. Reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring unless otherwise noted. TLC analysis was performed on glass backed silica gel plates and visualized by UV light and *p*-anisaldehyde stain. ^{1}H NMR spectra were recorded at 400 (Bruker AVIIIHD 400) or 500 MHz (Bruker AVIII 500) and chemical shifts (δ) are reported in ppm relative to the internal reference ($CDCl_3$, 7.26 ppm). Tabulated ^{1}H NMR data are reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, with coupling constants in Hz. ^{13}C NMR spectra were recorded at 125 MHz (Bruker AVIII 500) and chemical shifts (δ) are reported in ppm relative to the internal reference ($CDCl_3$, 71.16 ppm). Tabulated ^{13}C NMR data are reported as singlets unless noted as follows: d = doublet, q = quartet. HRMS spectra were recorded with an LCT Premier using electrospray ionization and quadrupole time of flight mass analyzer (Waters Micromass). All biologically tested compounds were determined to be >95% pure by ^{1}H and ^{13}C NMR analysis.

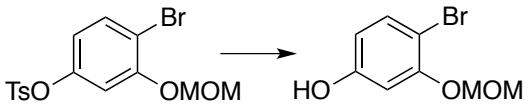
4-bromo-3-(methoxymethoxy)phenyl 4-methylbenzenesulfonate (13):



13

A mixture of 4-bromoresorcinol (15.32 g, 81.1 mmol), 4-toluenesulfonyl chloride (17.07 g, 89.5 mmol, 1.1 eq.), and potassium carbonate (33.81 g, 245 mmol, 3.0 eq.) in acetone (200 mL) was heated at 65 °C. After 24 h, chloromethyl methyl ether (40 mL of 6M solution in dimethoxymethane, 240 mmol, 3.0 eq.) was added to the reaction mixture and stirred for an additional 24 h before the reaction mixture was cooled to rt, filtered, and concentrated under reduced pressure. The resulting residue was dissolved into Et_2O (100 mL) and washed with water (1 x 100 mL) and saturated aqueous NaCl solution (1 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to afford **13** as a colorless amorphous solid (30.64 g, 98%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.45 (s, 3H), 3.43 (s, 3H), 5.10 (s, 2H), 6.57 (dd, *J*=8.7, 2.6 Hz, 1H), 6.77 (d, *J*=2.6 Hz, 1H), 7.29–7.36 (m, 2H), 7.43 (d, *J*=8.7 Hz, 1H), 7.68–7.76 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ= 21.75, 56.39, 95.12, 110.75, 110.96, 116.80, 128.62 (2C), 129.82 (2C), 132.02, 133.39, 145.57, 149.30, 154.26 ppm.

4-bromo-3-(methoxymethoxy)phenol:



13

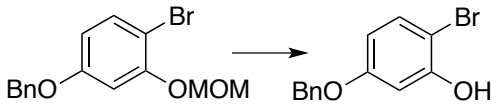
To a solution of **13** (30.64 g, 79.1 mmol) in EtOH (1.0 L) was added 4 M aqueous KOH (100 mL, 400 mmol, 5.0 eq.). The resulting solution was heated at 60 °C for 2 h. After cooling to rt, the reaction mixture was neutralized with 3 M aqueous HCl and concentrated under reduced pressure. The crude residue was dissolved into Et_2O (100 mL) and washed with water (1 x 100 mL) and saturated aqueous NaCl solution (1 x 100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting colorless amorphous solid (18.21 g, 99%) was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$): δ= 3.52 (s, 3H), 5.11 (s, 1H), 5.22 (s, 2H), 6.40 (dd, *J*=2.8, 8.6 Hz, 1H), 6.70 (d, *J*=2.8 Hz, 1H), 7.35 ppm (d, *J*=8.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=56.52, 95.15, 103.38, 104.26, 110.35, 133.57, 154.58, 156.06 ppm.

4-(benzyloxy)-1-bromo-2-(methoxymethoxy)benzene (14):

14

The mono-protected bromo resorcinol obtained above was dissolved into acetone (250 mL) and K_2CO_3 (32.45 g, 235 mmol, 3 eq.) was added to the solution. Benzyl bromide (11 mL, 92.6 mmol, 1.3 eq.) was added slowly to the resulting mixture, which was heated at 65 °C for 20 h. After cooling to rt, the reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to afford **14** as a colorless oil (23.21 g, 92%): ^{1}H NMR (500 MHz, $CDCl_3$): δ= 3.51 (s, 3H), 5.03 (s, 2H), 5.22 (s, 2H), 6.54 (dd, *J*=2.8, 8.8 Hz, 1H), 6.85 (d, *J*=2.8 Hz, 1H), 7.31–7.36 (m, 1H), 7.37–7.44 ppm (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=56.50, 70.44, 95.26, 103.82, 104.32, 109.14, 127.69 (2C), 128.26, 128.75 (2C), 133.30, 136.58, 154.56, 159.23 ppm.

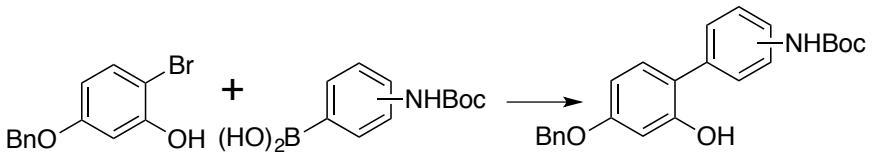
5-(benzyloxy)-2-bromophenol (8):



14 **8**

Bis-protected bromo resorcinol **14** (23.21 g, 71.8 mmol) was dissolved into a 1:1 mixture of MeOH and THF (700 mL). Concentrated HCl (50 mL, 605 mmol, 8.5 eq.) was added slowly to the solution, which was stirred at rt for 40 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved into CH_2Cl_2 (100 mL). The aqueous layer was removed and the organic layer was washed with saturated aqueous NaCl solution (1 x 100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, 3% EtOAc in hexanes) to afford **8** as a light maroon amorphous solid (18.22 g, 91%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=5.03 (s, 2H), 5.48 (s, 1H), 6.49 (dd, *J*=2.9, 8.9 Hz, 1H), 6.68 (d, *J*=2.9 Hz, 1H), 7.29–7.37 (m, 2H), 7.37–7.43 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ= 70.38, 101.31, 102.77, 109.36, 127.59 (2C), 128.26, 128.77 (2C), 132.10, 136.56, 153.08, 159.81 ppm.

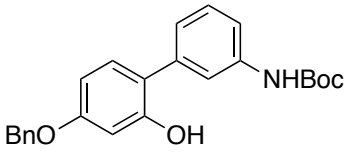
General procedure for Suzuki reaction 1:



8 **9** **15a-b**

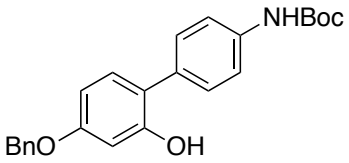
A sealable glass tube was charged with mono-protected bromo resorcinol **8** (6.3 – 16.1 mmol), boronic acid **9** (2.0 eq.), K_2CO_3 (3.0 eq.), and dioxane (0.3 M). The resulting mixture was sparged with Ar for 10 m before the addition of Pd(dppf)Cl_2 (0.05 eq.). After the solution was sparged with Ar for an additional 5 m, the tube was sealed and heated to 85 °C for 12 h. After cooling to rt, the reaction mixture was poured into water and extracted with EtOAc. The organic fractions were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, 10% EtOAc in hexanes) to afford **15**.

***tert*-butyl (4'-(benzyloxy)-2'-hydroxy-[1,1'-biphenyl]-3-yl)carbamate (15a):**



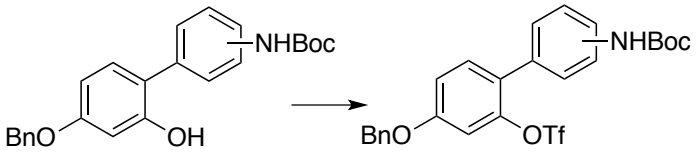
Light brown amorphous solid (2.19 g, 90%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.52 (s, 9H), 5.07 (s, 2H), 5.44 (s, 1H), 6.56 (s, 1H), 6.60–6.64 (m, 2H), 7.09 (dt, *J*=1.5, 7.3 Hz, 1H), 7.13–7.16 (m, 1H), 7.32–7.42 (m, 5H), 7.43–7.46 ppm (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.46 (3C), 70.20, 80.95, 102.37, 107.85, 117.78, 119.26, 120.87, 123.62, 127.63 (2C), 128.13, 128.74 (2C), 130.08, 130.83, 136.99, 137.94, 139.35, 152.82, 153.54, 159.85 ppm.

***tert*-butyl (4'-(benzyloxy)-2'-hydroxy-[1,1'-biphenyl]-4-yl)carbamate (15b):**



Light brown amorphous solid (4.39g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.54 (s, 9H), 5.07 (s, 2H), 5.30 (s, 1H), 6.58 (s, 1H), 6.61–6.64 (m, 2H), 7.10–7.13 (m, 1H), 7.31–7.37 (m, 3H), 7.38–7.42 (m, 2H), 7.43–7.49 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.47 (3C), 70.21, 80.96, 102.34, 107.82, 119.48 (2C), 120.77, 127.62 (2C), 128.12, 128.73 (2C), 129.83 (2C), 130.83, 131.57, 137.00, 137.86, 152.89, 153.55, 159.66 ppm.

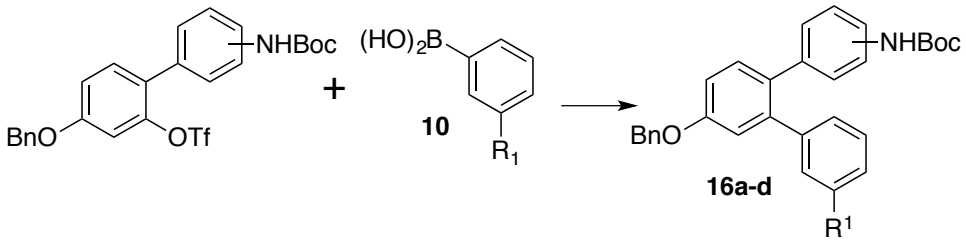
General procedure for Triflation:



15a-b

A microwave vial was charged with biphenyl **15** (2.5 – 4.5 mmol), N-Phenyl-bis(trifluoromethanesulfonimide) (1.5 eq.), K_2CO_3 (4.0 eq.), and anhydrous THF (0.2 M). The vial was sealed and placed in a microwave at 120 °C for 30 m. After cooling to rt, the reaction mixture was poured into water and extracted with EtOAc. The organic fractions were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting light brown residue was used without further purification.

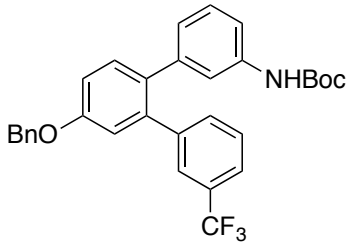
General procedure for Suzuki reaction 2:



A sealable glass tube was charged with the triflate obtained above, boronic acid **10** (1.5 eq.), K_2CO_3 (3.0 eq.), and dioxane (0.3 M). The resulting mixture was sparged with

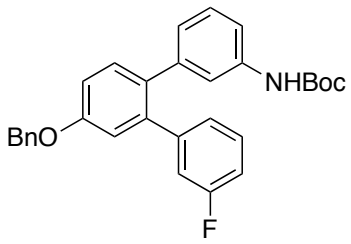
Ar for 10 m before the addition of $Pd_2(dba)_3$ (0.025 eq.) and SPhos (0.1 eq.) (2:1 ligand:Pd ratio). After the solution was sparged with Ar for an additional 5 m, the tube was sealed and heated to 85 °C for 12 h. After cooling to rt, the reaction mixture was poured into water and extracted with CH_2Cl_2. The organic fractions were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to afford **16**.

***tert*-butyl (4'-(benzyloxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)carbamate (16a):**



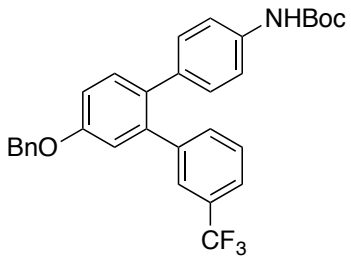
Light brown amorphous solid (2.06 g, 93% over two steps): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.50 (s, 9H), 5.14 (s, 2H), 6.38 (s, 1H), 6.63 (dt, *J*=1.4, 7.6 Hz, 1H), 7.02–7.09 (m, 3H), 7.18 (d, *J*=7.4 Hz, 2H), 7.27–7.31 (m, 2H), 7.35–7.38 (m, 2H), 7.41 (t, *J*=7.4 Hz, 2H), 7.44–7.49 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.45 (3C), 70.35, 80.70, 114.40, 116.64, 116.94, 119.93, 123.51 (q, *J*=3.8 Hz), 124.19 (q, *J*=272.4 Hz), 125.04, 126.52 (q, *J*=3.8 Hz), 127.70 (2C), 128.24, 128.35, 128.59, 128.80 (2C), 130.46 (q, *J*=32.1 Hz), 132.05, 133.30, 133.36, 136.86, 138.28, 140.17, 141.54, 142.13, 152.75, 158.36 ppm.

***tert*-butyl (4'-(benzyloxy)-3''-fluoro-[1,1':2',1''-terphenyl]-3-yl)carbamate (16b):**



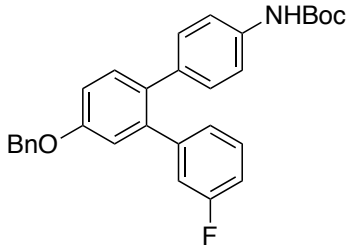
White amorphous solid (0.89 g, 76% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.50 (s, 9H), 5.13 (s, 2H), 6.35 (s, 1H), 6.67 (d, *J*=7.8 Hz, 1H), 6.85–6.93 (m, 3H), 7.00–7.05 (m, 2H), 7.08 (t, *J*=7.9 Hz, 1H), 7.12–7.19 (m, 2H), 7.22–7.30 (m, 1H), 7.31–7.37 (m, 2H), 7.41 (t, *J*=7.3 Hz, 2H), 7.47 ppm (d, *J*=7.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.47 (3C), 70.30, 80.66, 113.66 (d, *J*=21.0 Hz), 114.29, 116.56, 116.69 (d, *J*=21.8 Hz), 116.84, 119.78, 125.01, 125.72 (d, *J*=2.7 Hz), 127.68 (2C), 128.21, 128.56, 128.78 (2C), 129.44 (d, *J*=8.9 Hz), 132.00, 133.24, 136.91, 138.22, 140.48 (d, *J*=1.9 Hz), 141.75, 143.71 (d, *J*=7.8 Hz), 152.78, 158.26, 162.52 ppm (d, *J*=245.4).

***tert*-butyl (4'-(benzyloxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)carbamate (16c):**



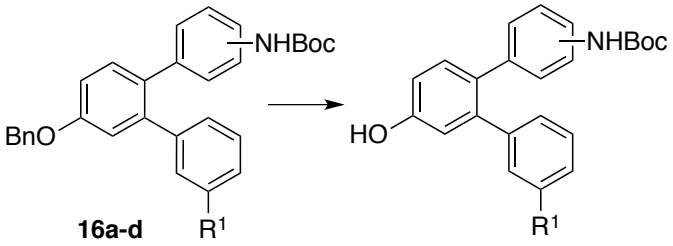
Light brown amorphous solid (1.46 g, 95% over two steps): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.51 (s, 9H), 5.14 (s, 2H), 6.42 (s, 1H), 6.96–6.99 (m, 2H), 7.02–7.07 (m, 2H), 7.20 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=7.8 Hz, 1H), 7.29 (t, *J*=7.6 Hz, 1H), 7.33–7.37 (m, 2H), 7.41 (t, *J*=7.3 Hz, 2H), 7.44–7.49 ppm (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.46 (3C), 70.35, 80.69, 114.49, 116.98, 118.13 (2C), 123.50 (q, *J*=3.8 Hz), 124.19 (q, *J*=272.3 Hz), 126.52 (q, *J*=3.9 Hz), 127.70 (2C), 128.23, 128.38, 128.79 (2C), 130.53 (q, *J*=32.1 Hz), 130.55 (2C), 131.97, 133.16, 133.37, 135.32, 136.89, 136.91, 140.14, 142.30, 152.80, 158.20 ppm.

***tert*-butyl (4'-(benzyloxy)-3''-fluoro-[1,1':2',1''-terphenyl]-4-yl)carbamate (16d):**



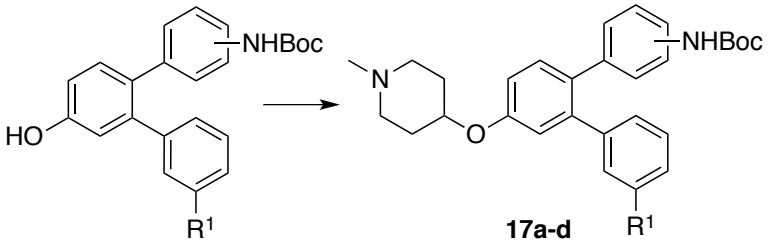
White amorphous solid (0.81 g, 70% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.51 (s, 9H), 5.13 (s, 2H), 6.40 (s, 1H), 6.84–6.92 (m, 3H), 6.98–7.05 (m, 4H), 7.13–7.23 (m, 3H), 7.32 (d, *J*=8.1 Hz, 1H), 7.35 (d, *J*=7.3 Hz, 1H), 7.41 (t, *J*=7.4 Hz, 2H), 7.46 ppm (d, *J*=7.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.48 (3C), 70.31, 80.65, 113.64 (d, *J*=21.1 Hz), 114.38, 116.75 (d, *J*=21.8 Hz), 116.88, 118.07 (2C), 125.74 (d, *J*=2.7 Hz), 127.68 (2C), 128.20, 128.78 (2C), 129.49 (d, *J*=8.4 Hz), 130.46 (2C), 131.89, 133.07, 135.55, 136.83, 136.95, 140.45 (d, *J*=1.9 Hz), 143.86 (d, *J*=7.8 Hz), 152.80, 158.09, 162.53 ppm (d, *J*=245.4 Hz).

General procedure for benzyl deprotection:



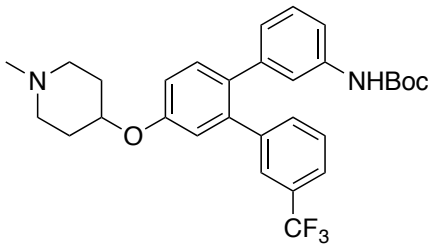
Terphenyl **16** (1.7 – 4.3 mmol) was dissolved into THF (0.1 M) and 10% palladium on carbon (0.1 eq. Pd) was added to the solution. The resulting mixture was sparged with Ar for 10 m and then H_2 for 5 m. Following that, a balloon of H_2 was placed on the reaction flask, which was stirred at rt for 16 h. The reaction mixture was filtered through a pad of celite with EtOAc, concentrated under reduced pressure, and used without further purification.

General procedure for Mitsunobu etherification:



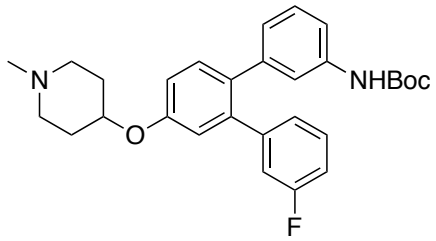
The phenol obtained above (1.4 – 4.1 mmol), 1-methyl-4-hydroxypiperidine (2.0 eq.), and PPh_3 (2.0 eq.) were dissolved into THF (0.6 M). After cooling to 0 °C, DIAD (2.0 eq.) was slowly added to the solution. The reaction mixture was stirred at rt for 48 h and then concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, 0–5% MeOH in CH_2Cl_2) to afford **17**.

***tert*-butyl (4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)carbamate (17a):**



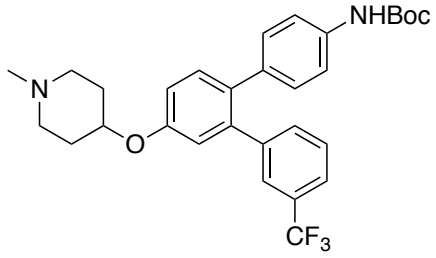
Colorless amorphous solid (1.24 g, 57% over two steps): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.49 (s, 9H), 1.86–1.96 (m, 2H), 2.02–2.10 (m, 2H), 2.32–2.39 (m, 5H), 2.69–2.77 (m, 2H), 4.42 (s, 1H), 6.40 (s, 1H), 6.62 (ddd, *J*=1.1, 1.7, 7.6 Hz, 1H), 6.94–6.98 (m, 2H), 7.06 (t, *J*=7.9 Hz, 1H), 7.15–7.21 (m, 2H), 7.26–7.31 (m, 2H), 7.35 (d, *J*=8.4 Hz, 1H), 7.43–7.48 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.45 (3C), 30.88 (2C), 46.31, 52.66 (2C), 72.18, 80.63, 115.32, 116.59, 118.18, 119.91, 123.49 (q, *J*=3.8 Hz), 124.20 (q, *J*=272.4 Hz), 124.99, 126.50 (q, *J*=4.0 Hz), 128.34, 128.56, 130.44 (q, *J*=32.1 Hz), 132.03, 133.23, 133.31, 138.31, 140.28, 141.56, 142.16, 152.71, 157.01 ppm.

tert-butyl (3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-3-yl)carbamate (17b):



Colorless amorphous solid (0.32 g, 35% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.50 (s, 9H), 1.85–1.97 (m, 2H), 2.01–2.10 (m, 2H), 2.32–2.39 (m, 5H), 2.68–2.77 (m, 2H), 4.40 (s, 1H), 6.38 (s, 1H), 6.67 (d, *J*=7.6 Hz, 1H), 6.85–6.98 (m, 5H), 7.07 (t, *J*=7.9 Hz, 1H), 7.11–7.19 (m, 2H), 7.23 (d, *J*=8.3 Hz, 1H), 7.33 ppm (d, *J*=8.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.48 (3C), 30.89 (2C), 46.32, 52.69 (2C), 72.13, 80.63, 113.63 (d, *J*=21.0 Hz), 115.33, 116.53, 116.69 (d, *J*=21.8 Hz), 118.01, 119.76, 124.97, 125.72 (d, *J*=2.8 Hz), 128.54, 129.42 (d, *J*=8.3 Hz), 132.00, 133.07, 138.23, 140.54 (d, *J*=1.8 Hz), 141.77, 143.75 (d, *J*=7.8 Hz), 152.75, 156.88, 162.52 ppm (d, *J*=245.4 Hz).

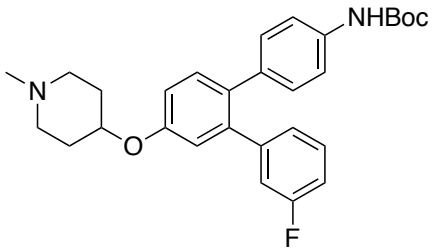
tert-butyl (4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)carbamate (17c):



Colorless amorphous solid (0.75 g, 65% over two steps): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.50 (s, 9H), 1.86–1.95 (m, 2H), 2.02–2.10 (m, 2H), 2.31–2.38 (m, 5H), 2.68–2.76 (m, 2H), 4.41 (s, 1H), 6.46 (s, 1H), 6.93–6.99 (m, 4H), 7.19 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=7.8 Hz, 1H), 7.26–7.30 (m, 1H), 7.32 (d, *J*=8.5 Hz, 1H), 7.43–7.48 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.46 (3C), 30.90 (2C), 46.31, 52.67 (2C), 72.16, 80.66, 115.40,

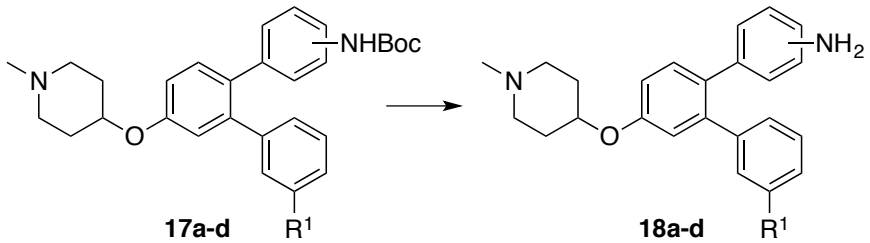
118.14 (2C), 118.21, 123.47 (q, *J*=3.7 Hz), 124.19 (q, *J*=272.4 Hz), 126.50 (q, *J*=3.9 Hz), 128.38, 130.50 (q, *J*=32.2 Hz), 130.53 (2C), 131.94, 133.01, 133.36, 135.33, 136.91, 140.25, 142.33, 152.80, 156.84 ppm.

***tert*-butyl (3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-4-yl)carbamate (17d):**



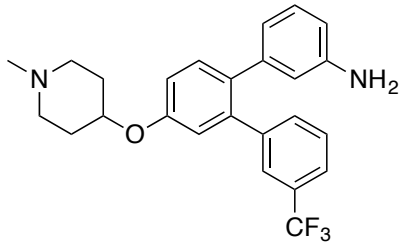
Colorless amorphous solid (0.32 g, 35% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.50 (s, 9H), 1.87–1.98 (m, 2H), 2.04–2.13 (m, 2H), 2.33–2.45 (m, 5H), 2.71–2.80 (m, 2H), 4.42 (s, 1H), 6.41 (s, 1H), 6.84–6.97 (m, 5H), 7.00 (d, *J*=8.4 Hz, 2H), 7.12–7.22 (m, 3H), 7.30 ppm (d, *J*=8.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=28.48 (3C), 30.70 (2C), 46.20, 52.64 (2C), 71.90, 80.67, 113.64 (d, *J*=21.0 Hz), 115.39, 116.74 (d, *J*=21.7 Hz), 118.06, 118.09 (2C), 125.74 (d, *J*=2.7 Hz), 129.49 (d, *J*=8.4 Hz), 130.45 (2C), 131.91, 132.95, 135.54, 136.83, 140.54 (d, *J*=1.9 Hz), 143.87 (d, *J*=7.8 Hz), 152.80, 156.64, 162.54 (d, *J*=245.5 Hz) ppm.

General procedure for boc deprotection:



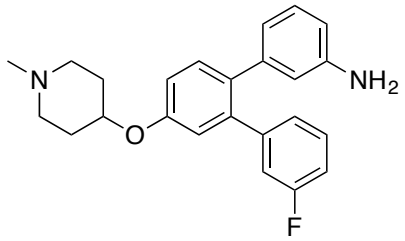
Boc-protected aniline **17** (0.7 – 2.4 mmol) was dissolved into a 10% solution of TFA in CH_2Cl_2 (0.1 M) and stirred at rt. After 12 h, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were concentrated under reduced pressure and the resulting oil was dissolved into CH_2Cl_2 before washing with 3 M NaOH until ^{19}F NMR indicated no remaining TFA salt. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford **18**, which was used without further purification.

4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-amine (18a):



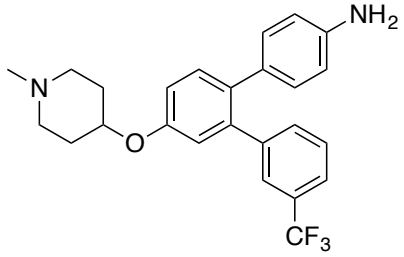
Light yellow amorphous solid (quant.): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.90–1.99 (m, 2H), 2.06–2.13 (m, 2H), 2.39 (s, 3H), 2.47 (s, 2H), 2.74–2.82 (m, 2H), 3.54 (s, 2H), 4.45 (s, 1H), 6.40 (ddd, *J*=1.0, 1.6, 7.6 Hz, 1H), 6.43 (t, *J*=2.0 Hz, 1H), 6.52 (ddd, *J*=1.0, 2.4, 7.9 Hz, 1H), 6.94–6.98 (m, 3H), 7.29– 7.31 (m, 2H), 7.34 (d, *J*=8.7 Hz, 1H), 7.44–7.47 (m, 1H), 7.48 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.52 (2C), 46.04, 52.40 (2C), 71.52, 113.43, 115.14, 116.76, 118.08, 120.75, 123.47 (q, *J*=3.9 Hz), 124.22 (q, *J*=272.4 Hz), 126.44 (q, *J*=3.8 Hz), 128.28, 128.97, 130.36 (q, *J*=32.1 Hz), 131.88, 133.22, 133.85, 140.25, 141.73, 142.26, 146.18, 156.76 ppm.

3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-3-amine (18b):



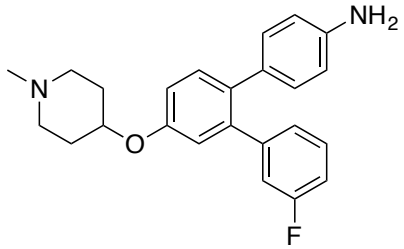
Yellow oil (quant.): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.94–2.06 (m, 2H), 2.13–2.25 (m, 2H), 2.48 (s, 3H), 2.66 (s, 2H), 2.82–2.92 (m, 2H), 3.55 (s, 2H), 4.51 (s, 1H), 6.42–6.47 (m, 2H), 6.52 (d, *J*=8.7 Hz, 1H), 6.85 – 7.00 (m, 6H), 7.17 (q, *J*=7.5, 8.1 Hz, 1H), 7.33 ppm (d, *J*=8.2, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=29.85 (2C), 45.54, 52.04 (2C), 70.38, 113.45, 113.67 (d, *J*=21.0 Hz), 115.06, 116.61 (d, *J*=22.2 Hz), 116.71, 117.97, 120.69, 125.60 (d, *J*=2.8 Hz), 128.92, 129.39 (d, *J*=8.3 Hz), 131.92, 133.98, 140.65 (d, *J*=1.9 Hz), 141.88, 143.77 (d, *J*=7.8 Hz), 146.10, 156.35, 162.50 ppm (d, *J*=245.3 Hz).

4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-amine (18c):



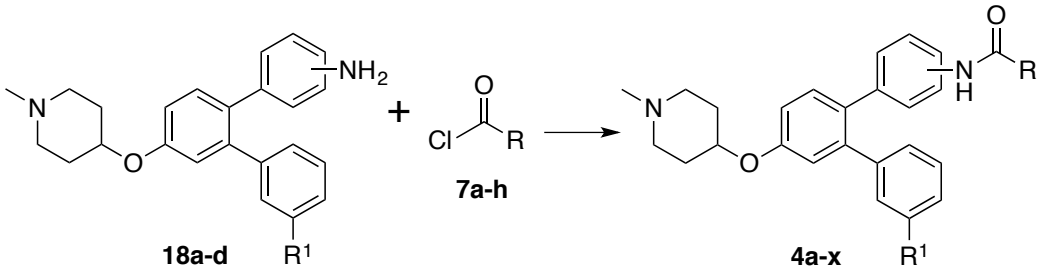
Light yellow amorphous solid (quant.): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.88–1.97 (m, 2H), 2.03–2.10 (m, 2H), 2.33–2.45 (m, 5H), 2.70–2.80 (m, 2H), 3.60 (s, 2H), 4.42 (s, 1H), 6.51–6.55 (m, 2H), 6.81–6.85 (m, 2H), 6.93 (d, *J*=2.6 Hz, 1H), 6.96 (dd, *J*=2.7, 8.4 Hz, 1H), 7.26–7.30 (m, 2H), 7.32 (d, *J*=8.4 Hz, 1H), 7.43–7.46 (m, 1H), 7.47 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.77 (2C), 46.21, 52.60 (2C), 71.88, 114.89 (2C), 115.38, 118.17, 123.29 (q, *J*=3.8 Hz), 124.24 (q, *J*=272.3 Hz), 126.57 (q, *J*=3.8 Hz), 128.30, 130.41 (q, *J*=32.1 Hz), 130.85, 130.91 (2C), 131.84, 133.33, 133.67, 140.08, 142.62, 144.99, 156.46 ppm.

3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-4-amine (18d):



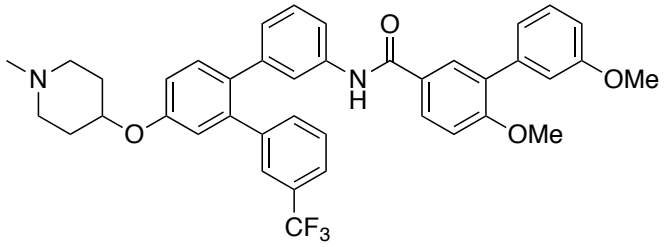
Yellow oil (quant.): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.91–2.02 (m, 2H), 2.08–2.19 (m, 2H), 2.42 (s, 3H), 2.53 (s, 2H), 2.76–2.87 (m, 2H), 3.60 (s, 2H), 4.44 (s, 1H), 6.53 (d, *J*=8.3 Hz, 2H), 6.84 – 6.96 (m, 7H), 7.17 (q, *J*=7.6 Hz, 1H), 7.30 (d, *J*=8.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.31 (2C), 45.87, 52.10 (2C), 71.04, 113.47 (d, *J*=21.0 Hz), 114.90 (2C), 115.32, 116.75 (d, *J*=21.7 Hz), 118.05, 125.71 (d, *J*=2.8 Hz), 129.41 (d, *J*=8.3 Hz), 130.81 (2C), 131.06, 131.83, 133.71, 140.41, 140.42, 144.16 (d, *J*=7.8 Hz), 144.92, 156.13, 162.54 (d, *J*=245.2 Hz).

General procedure for amide coupling reaction:



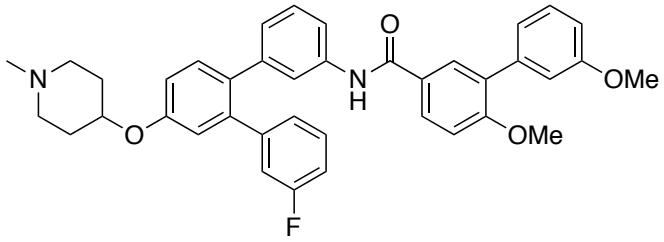
Aniline **18** (0.3 – 0.7 mmol) was dissolved into a solution of anhydrous CH_2Cl_2 (0.1 M) and Et_3N (3 eq). Acid chloride **7** (1.5 eq) was added to the reaction mixture, which was stirred at rt. After 16 h, the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by column chromatography (SiO_2, 1-4% MeOH in DCM) to afford **4**.

3',6-dimethoxy-*N*-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)-[1,1'-biphenyl]-3-carboxamide (4a):



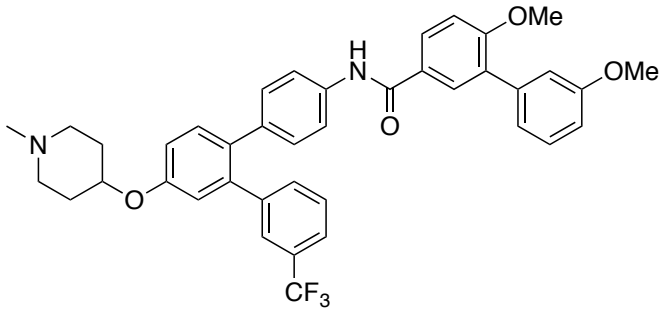
Colorless amorphous solid (26 mg, 15%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.14–2.21 (m, 2H), 2.43–2.54 (m, 2H), 2.71 (s, 3H), 3.06–3.21 (m, 4H), 3.84 (s, 3H), 3.88 (s, 3H), 4.69 (br, 1H), 6.67 (ddd, *J*=7.6, 1.7, 1.0 Hz, 1H), 6.92 (ddd, *J*=8.3, 2.6, 1.0 Hz, 1H), 6.94–6.98 (m, 2H), 7.04 (d, *J*=8.7 Hz, 1H), 7.07–7.14 (m, 3H), 7.26–7.32 (m, 2H), 7.35 (t, *J*=7.9 Hz, 1H), 7.41 (d, *J*=8.8 Hz, 1H), 7.43–7.48 (m, 3H), 7.60 (t, *J*=1.9 Hz, 1H), 7.79 (d, *J*=2.4 Hz, 1H), 7.84 (s, 1H), 7.88 ppm (dd, *J*=8.6, 2.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=27.75 (2C), 44.31, 50.30 (2C), 55.46, 55.98, 67.65, 111.18, 113.04, 115.03, 115.46, 118.22, 118.36, 121.42, 122.07, 123.76 (q, *J*=3.9 Hz), 124.13 (q, *J*=272.4 Hz), 126.42 (q, *J*=3.8 Hz), 126.22, 127.15, 128.51, 128.55, 128.65, 129.29, 129.67, 130.54 (q, *J*=32.2 Hz), 130.78, 132.41, 133.27, 134.05, 138.29, 138.90, 140.66, 141.27, 141.76, 155.99, 159.45, 159.47, 165.19 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{40}H_{37}F_3N_2O_4$: 667.2784, found 667.2755.

***N*-(3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-3-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (4b):**



Colorless amorphous solid (15 mg, 25%): ^{1}H NMR: (400 MHz, $CDCl_3$): δ=1.87–1.99 (m, 2H), 2.04–2.15 (m, 2H), 2.37 (s, 3H), 2.42 (br, 2H), 2.71–2.81 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.44 (br, 1H), 6.76 (d, *J*=7.6 Hz, 1H), 6.86 – 6.99 (m, 6H), 7.02–7.21 (m, 5H), 7.36 (t, *J*=7.9 Hz, 2H), 7.44–7.46 (m, 1H), 7.52 (d, *J*=8.2 Hz, 1H), 7.68 (d, *J*=3.9 Hz, 1H), 7.78 (d, *J*=2.2 Hz, 1H), 7.87 ppm (dd, *J*=8.5, 1.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.62 (2C), 46.14, 52.42 (2C), 55.47, 55.99, 71.59, 111.19, 113.10, 113.72 (d, *J*=21.0 Hz), 115.34, 115.42, 116.72 (d, *J*=21.8 Hz), 118.05, 118.18, 121.27, 122.09, 125.77 (d, *J*=2.7 Hz), 126.35, 127.30, 128.48, 128.63, 129.30, 129.51 (d, *J*=8.4 Hz), 129.65, 130.80, 132.10, 132.97, 138.06, 138.93, 140.62 (d, *J*=1.9 Hz), 141.89, 143.67 (d, *J*=7.7 Hz), 156.87, 159.44, 159.46, 162.53 (d, *J*=245.5 Hz), 165.17 ppm; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{39}H_{37}FN_2O_4$: 639.2635, found 639.2640.

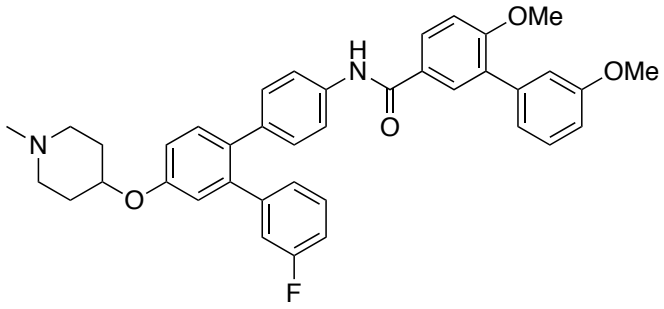
3',6-dimethoxy-*N*-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)-[1,1'-biphenyl]-3-carboxamide (4c):



Colorless amorphous solid (70 mg, 41%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.17–2.25 (m, 2H), 2.49–2.62 (m, 2H), 2.75 (s, 3H), 3.09–3.35 (m, 4H), 3.84 (s, 3H), 3.88 (s, 3H), 4.72 (br, 1H), 6.91 (ddd, *J*=8.3, 2.6, 1.0 Hz, 1H), 6.95 (d, *J*=2.5 Hz, 1H), 6.97 (dd, *J*=8.4, 2.7 Hz, 1H), 7.02–7.06 (m, 3H), 7.08 (dd, *J*=2.6, 1.5 Hz, 1H), 7.11 (ddd, *J*=7.6, 1.7, 1.0 Hz, 1H), 7.22–7.25 (m, 1H), 7.30 (t, *J*=8.5 Hz, 1H), 7.35 (t, *J*=7.9 Hz, 1H), 7.38 (d, *J*=8.4 Hz, 1H), 7.46–7.49 (m, 2H), 7.50–7.55 (m, 2H), 7.80 (d, *J*=2.4 Hz, 1H), 7.88 (s, 1H), 7.90 ppm (dd, *J*=2.4, 8.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=27.36 (2C), 44.09, 50.14 (2C), 55.47, 55.98, 66.82, 111.17, 113.06, 115.00, 115.45, 118.37, 119.84 (2C), 122.09, 123.79 (q, *J*=3.8 Hz), 124.12 (q, *J*=272.9 Hz), 126.37 (q, *J*=3.8 Hz), 127.15, 128.54,

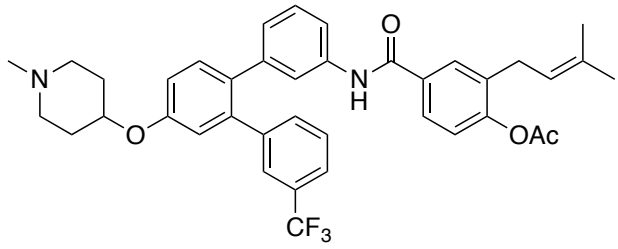
128.57, 129.28, 129.69, 130.53 (2C), 130.68 (q, *J*=32.4 Hz), 130.79, 132.31, 133.31, 134.02, 136.16, 136.99, 138.91, 140.71, 141.86, 155.74, 159.44, 159.47, 165.22 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{40}H_{37}F_3N_2O_4$: 667.2784, found 667.2697.

***N*-(3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-4-yl)-3',6-dimethoxy-[1,1'-biphenyl]-3-carboxamide (4d):**



Colorless amorphous solid (16 mg, 25%): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.89–2.00 (m, 2H), 2.08–2.17 (m, 2H), 2.39 (s, 3H), 2.47 (br, 2H), 2.74–2.82 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.45 (br, 1H), 6.86–7.00 (m, 6H), 7.02–7.13 (m, 5H), 7.13–7.21 (m, 1H), 7.32–7.38 (t, 2H), 7.49 (d, *J*=8.5 Hz, 2H), 7.74 (s, 1H), 7.79 (d, *J*=2.2 Hz, 1H), 7.88 ppm (dd, *J*=8.6, 2.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.80 (2C), 46.26, 52.63 (2C), 55.47, 55.98, 71.84, 111.19, 113.11, 113.69 (d, *J*=21.0 Hz), 115.40, 115.42, 116.76 (d, *J*=21.8 Hz), 118.09, 119.69 (2C), 122.09, 125.78 (d, *J*=2.7 Hz), 127.29, 128.46, 129.29, 129.54 (d, *J*=8.4 Hz), 129.62, 130.54 (2C), 130.82, 131.94, 132.79, 136.58, 136.94, 138.93, 140.59 (d, *J*=1.8 Hz), 143.83 (d, *J*=7.7 Hz), 156.80, 159.43, 159.45, 162.55 (d, *J*=245.6 Hz), 165.18 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{39}H_{37}FN_2O_4$: 617.2815, found 617.2799.

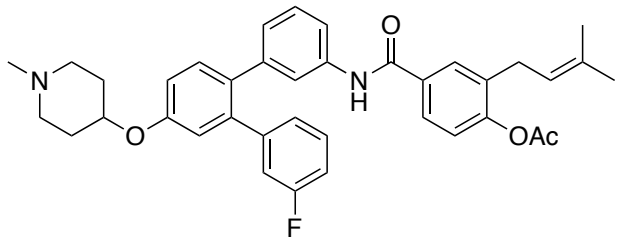
2-(3-methylbut-2-en-1-yl)-4-((4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)carbamoyl)phenyl acetate (4e):



Colorless amorphous solid (280 mg, 90%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.70 (d, *J*=1.4 Hz, 3H), 1.74 (d, *J*=1.4 Hz, 3H), 2.14–2.22 (m, 2H), 2.33 (s, 3H), 2.42–2.52 (m, 2H), 2.71 (s, 3H), 2.99–3.23 (m, 4H), 3.29 (d, *J*=7.2 Hz, 2H), 4.69 (s, 1H), 5.21 (th, *J*=7.2, 1.4 Hz, 1H), 6.71 (ddd, *J*=7.7, 1.7, 1.0 Hz, 1H), 6.94–7.00 (m, 2H), 7.10–7.16 (m, 2H), 7.26–7.34 (m, 2H), 7.40–7.45 (m, 2H), 7.45–7.49 (m, 2H), 7.55–7.57 (m, 1H), 7.65 (dd, *J*=8.3, 2.3 Hz, 1H), 7.73 (d, *J*=2.3 Hz, 1H), 7.78 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=18.05,

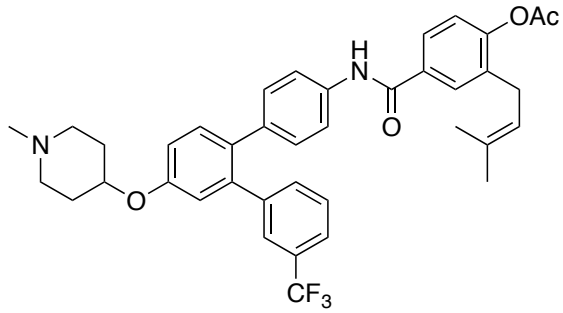
21.02, 25.89, 27.79 (2C), 28.97, 44.37, 50.41 (2C), 67.55, 115.07, 118.23, 118.38, 120.85, 121.46, 122.83, 123.78 (q, *J*=3.7 Hz), 124.14 (q, *J*=272.8 Hz), 125.71, 126.43, 126.44 (q, *J*=3.5 Hz), 128.57, 128.72, 129.51, 130.57 (q, *J*=32.2 Hz), 132.40, 132.99, 133.27, 133.95, 134.20, 134.66, 138.06, 140.68, 141.34, 141.76, 151.72, 156.07, 165.30, 169.20 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{39}H_{39}F_3N_2O_4$: 657.2940, found 657.2945.

4-((3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-3-yl)carbamoyl)-2-(3-methylbut-2-en-1-yl)phenyl acetate (4f):



Colorless amorphous solid (35 mg, 30%): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.71 (s, 3H), 1.75 (s, 3H), 1.87–2.00 (m, 2H), 2.04–2.15 (m, 2H), 2.34 (s, 3H), 2.38 (s, 3H), 2.45 (br, 2H), 2.70–2.83 (m, 2H), 3.29 (d, *J*=7.1 Hz, 2H), 4.45 (s, 1H), 5.22 (t, *J*=6.9 Hz, 1H), 6.79 (d, *J*=7.7 Hz, 1H), 6.86–6.99 (m, 5H), 7.09–7.21 (m, 3H), 7.36 (d, *J*=8.3 Hz, 1H), 7.40-7.44 (m, 1H), 7.51 (d, *J*=8.2 Hz, 1H), 7.62– 7.67 (m, 2H), 7.71–7.74 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=18.06, 21.03, 25.91, 28.95, 30.56 (2C), 46.05, 52.41 (2C), 71.45, 113.76 (d, *J*=21.0 Hz), 115.34, 116.72 (d, *J*=21.8 Hz), 118.06, 118.22, 120.85, 121.32, 122.83, 125.69, 125.75 (d, *J*=2.7 Hz), 126.52, 128.68, 129.44, 129.54 (d, *J*=8.4 Hz), 132.10, 132.90, 133.13, 134.22, 134.63, 137.85, 140.64 (d, *J*=1.8 Hz), 141.92, 143.64 (d, *J*=7.7 Hz), 151.67, 156.89, 162.54 (d, *J*=245.6 Hz), 165.31, 169.20 ppm; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{38}H_{39}FN_2O_4$: 629.2782, found 629.2792.

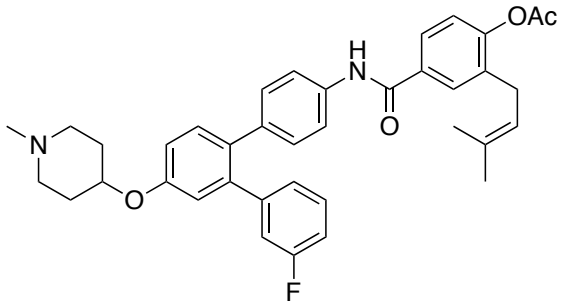
2-(3-methylbut-2-en-1-yl)-4-((4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)carbamoyl)phenyl acetate (4g):



Colorless amorphous solid (250 mg, 52%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.70 (d, *J*=1.4 Hz, 3H), 1.74 (d, *J*=1.4 Hz, 3H), 2.09–2.16 (m, 2H), 2.33 (s, 3H), 2.36–2.46 (m, 2H), 2.63

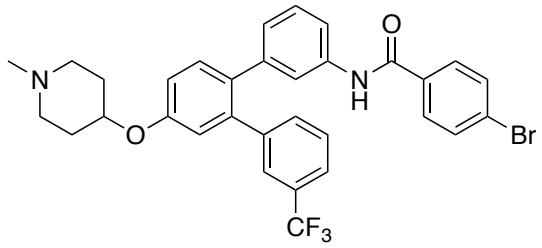
(s, 3H), 2.85–3.12 (m, 4H), 3.29 (d, *J*=7.2 Hz, 2H), 4.64 (s, 1H), 5.21 (th, *J*=7.2, 1.4 Hz, 1H), 6.96 (d, *J*=2.6 Hz, 1H), 6.99 (dd, *J*=8.5, 2.6 Hz, 1H), 7.03–7.07 (m, 2H), 7.12 (d, *J*=8.3 Hz, 1H), 7.23–7.26 (m, 1H), 7.31 (t, *J*=7.6 Hz, 1H), 7.38 (d, *J*=8.4 Hz, 1H), 7.46–7.52 (m, 4H), 7.67 (dd, *J*=8.4, 2.4 Hz, 1H), 7.74 (d, *J*=2.2 Hz, 1H), 7.81 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=18.06, 21.03, 25.89, 28.37 (2C), 28.97, 44.74, 50.81 (2C), 68.29, 115.14, 118.35, 119.85 (2C), 120.87, 122.84, 123.75 (q, *J*=3.2 Hz), 124.14 (q, *J*=272.3 Hz), 125.76, 126.41 (q, *J*=3.7 Hz), 128.55, 129.47, 130.58 (2C), 130.68 (q, *J*=32.2 Hz), 132.24, 132.99, 133.35, 133.62, 134.20, 134.64, 136.59, 136.69, 140.61, 141.97, 151.72, 156.15, 165.32, 169.18 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{39}H_{39}F_3N_2O_4$: 657.2940, found 657.2913.

4-((3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-4-yl)carbamoyl)-2-(3-methylbut-2-en-1-yl)phenyl acetate (4h):



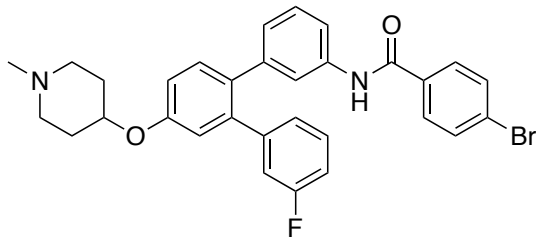
Colorless amorphous solid (24 mg, 21%): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.70 (s, 3H), 1.74 (s, 3H), 1.90–2.00 (m, 2H), 2.06–2.11 (m, 2H), 2.33 (s, 3H), 2.38 (s, 3H), 2.47 (br, 2H), 2.72–2.82 (m, 2H), 3.29 (d, *J*=7.1 Hz, 2H), 4.45 (br, 1H), 5.22 (t, *J*=7.1 Hz, 1H), 6.86–7.00 (m, 5H), 7.06–7.14 (m, 3H), 7.18 (q, *J*=7.6 Hz, 1H), 7.34 (d, *J*=8.4 Hz, 1H), 7.48 (d, *J*=8.4 Hz, 2H), 7.66 (d, *J*=8.2 Hz, 1H), 7.73 ppm (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ=18.06, 21.03, 25.90, 28.95, 30.47 (2C), 46.02, 52.33 (2C), 71.47, 113.74 (d, *J*=21.0 Hz), 115.39, 116.76 (d, *J*=21.7 Hz), 118.10, 119.76 (2C), 120.86, 122.84, 125.72, 125.76 (d, *J*=2.7 Hz), 129.39, 129.58 (d, *J*=8.3 Hz), 130.54 (2C), 131.98, 132.82, 133.10, 134.22, 134.62, 136.41, 137.14, 140.63 (d, *J*=1.7 Hz), 143.77 (d, *J*=7.7 Hz), 151.67, 156.72, 162.56 (d, *J*=245.6 Hz), 165.33, 169.20 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{38}H_{39}FN_2O_4$: 607.2972, found 607.3021.

4-bromo-*N*-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)benzamide (4i):



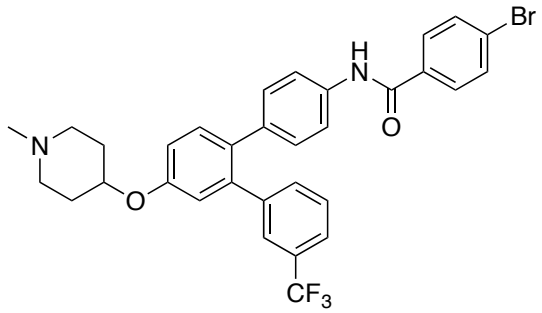
Colorless amorphous solid (47 mg, 27%): ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.98–2.10 (m, 2H), 2.20–2.29 (m, 2H), 2.50 (s, 3H), 2.71 (br, 2H), 2.90 (td, *J*=10.6, 9.7, 2 Hz, 2H), 4.54 (br, 1H), 6.73 (ddd, *J*=7.7, 1.8, 1.0 Hz, 1H), 6.94–7.00 (m, 2H), 7.14 (t, *J*=7.9 Hz, 1H), 7.28–7.34 (m, 2H), 7.39 (d, *J*=8.2 Hz, 1H), 7.42–7.49 (m, 3H), 7.51–7.54 (m, 1H), 7.57–7.63 (m, 2H), 7.68–7.74 (m, 2H), 7.84 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=29.46 (2C), 45.38, 51.60 (2C), 70.10, 115.21, 118.21, 118.41, 121.56, 123.67 (q, *J*=3.9 Hz), 124.15 (q, *J*=272.4 Hz), 126.51 (q, *J*=3.8 Hz), 126.69, 126.73, 128.53, 128.72, 128.79 (2C), 130.49 (q, *J*=32.2 Hz), 132.13 (2C), 132.20, 133.28, 133.33, 133.83, 137.80, 140.49, 141.59, 141.92, 156.64, 164.81 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{32}H_{28}BrF_3N_2O_2$: 609.1364, found 609.1392.

4-bromo-*N*-(3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-3-yl)benzamide (4j):



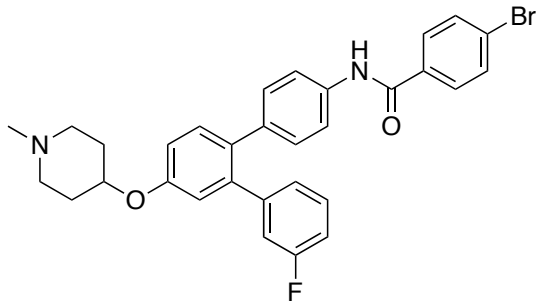
Colorless amorphous solid (10 mg, 14%): ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.90–2.01 (m, 2H), 2.07–2.19 (m, 2H), 2.40 (s, 3H), 2.49 (br, 2H), 2.74–2.84 (m, 2H), 4.46 (br, 1H), 6.80 (d, *J*=7.7 Hz, 1H), 6.85–7.01 (m, 5H), 7.13–7.21 (m, 2H), 7.36 (d, *J*=8.4 Hz, 1H), 7.42–7.45 (m, 1H), 7.47–7.54 (m, 1H), 7.59–7.64 (m, 2H), 7.65–7.73 ppm (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=29.71 (2C), 45.44, 51.68 (2C), 70.53, 113.81 (d, *J*=21.0 Hz), 115.26, 116.73 (d, *J*=21.8 Hz), 118.06, 118.34, 121.40, 125.72 (d, *J*=2.8 Hz), 126.73, 126.75, 128.74 (2C), 128.74, 129.58 (d, *J*=8.3 Hz), 132.14, 132.19 (2C), 133.03, 133.90, 137.65, 140.73 (d, *J*=2.0 Hz), 141.95, 143.53 (d, *J*=7.8 Hz), 156.72, 162.54 (d, *J*=245.7 Hz), 164.79 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{31}H_{28}BrFN_2O_2$: 559.1396, found 559.1375.

4-bromo-*N*-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)benzamide (4k):



Colorless amorphous solid (120 mg, 80%): ^{1}H NMR (500 MHz, $CDCl_3$/MeOD): δ=2.12–2.20 (m, 2H), 2.31–2.46 (m, 2H), 2.74 (s, 3H), 3.15 (br, 2H), 3.25–3.30 (m, 2H), 4.70 (br, 1H), 6.88 (d, *J*=2.6 Hz, 1H), 6.92 (dd, *J*=2.7, 8.5 Hz, 1H), 6.93–6.97 (m, 2H), 7.16-7.20 (m, 1H), 7.23 (t, *J*=7.6 Hz, 1H), 7.30 (d, *J*=8.4 Hz, 1H), 7.35–7.40 (m, 2H), 7.43–7.48 (m, 2H), 7.48–7.55 (m, 2H), 7.66–7.70 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$/MeOD) δ= 26.91 (2C), 43.58, 49.62 (2C), 65.97, 114.98, 118.07, 120.17 (2C), 123.53 (q, *J*=3.8 Hz), 123.96 (q, *J*=272.2 Hz), 126.22 (q, *J*=3.8 Hz), 126.36, 128.44, 129.00 (2C), 130.24 (2C), 130.41 (q, *J*=32.2 Hz), 131.70 (2C), 132.15, 133.14, 133.72, 133.91, 136.35, 136.79, 140.53, 141.74, 155.52, 165.76 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{32}H_{28}BrF_3N_2O_2$: 609.1364, found 609.1336.

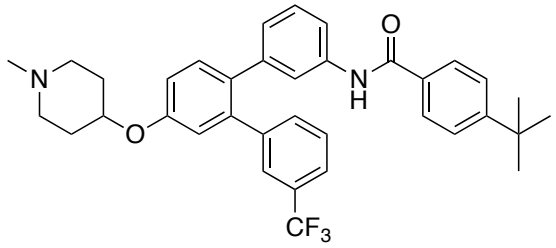
4-bromo-*N*-(3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-4-yl)benzamide (4l):



Colorless amorphous solid (22 mg, 23%): ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.96–2.06 (m, 2H), 2.13–2.24 (m, 2H), 2.48 (s, 3H), 2.70 (br, 2H), 2.83–2.92 (m, 2H), 4.51 (br, 1H), 6.83–6.99 (m, 5H), 7.08 (d, *J*=7.6 Hz, 2H), 7.17 (q, *J*=7.4 Hz, 1H), 7.34 (d, *J*=8.3 Hz, 1H), 7.47–7.51 (m, 2H), 7.57–7.62 (m, 2H), 7.72 (d, *J*=8.2 Hz, 2H), 7.86–7.96 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=29.51 (2C), 45.29, 51.44 (2C), 70.24, 113.79 (d, *J*=21.0 Hz), 115.29, 116.74 (d, *J*=21.8 Hz), 118.09, 119.88 (2C), 125.71 (d, *J*=2.7 Hz), 126.69, 128.78 (2C), 129.61 (d, *J*=8.4 Hz), 130.55 (2C), 132.01, 132.12 (2C), 132.96, 133.88, 136.30, 137.21, 140.71 (d, *J*=1.8 Hz), 143.64 (d, *J*=7. Hz 7), 156.49, 162.52 (d, *J*=245.7

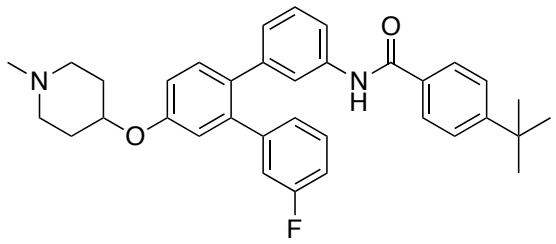
Hz), 164.88 ppm; HRMS-ESI *m/z* $[M+Na]^+$ calcd for $C_{31}H_{28}BrFN_2O_2$ 581.1216, found 581.1221.

4-(*tert*-butyl)-*N*-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)benzamide (4m):



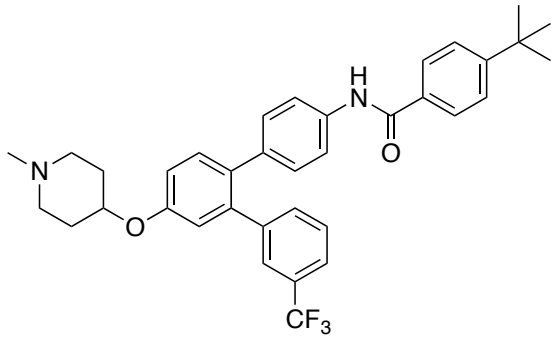
Colorless amorphous solid (36 mg, 36%): ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.34 (s, 9H), 1.93–2.02 (m, 2H), 2.08–2.15 (m, 2H), 2.42 (s, 3H), 2.53 (br, 2H), 2.77–2.86 (m, 2H), 4.48 (br, 1H), 6.71 (ddd, *J*=7.7, 1.7, 1.0 Hz, 1H), 6.95–7.00 (m, 2H), 7.13 (t, *J*=7.8 Hz, 1H), 7.27–7.33 (m, 2H), 7.39 (d, *J*=8.3 Hz, 1H), 7.43–7.52 (m, 6H), 7.74–7.81 ppm (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.19 (2C), 31.28 (3C), 35.12, 45.88, 52.16 (2C), 71.06, 115.28, 118.20, 118.22, 121.41, 125.86 (2C), 126.36, 123.59 (q, *J*=3.9 Hz), 124.17 (q, *J*=272.3 Hz), 126.49 (q, *J*=3.9 Hz), 126.96 (2C), 128.46, 128.66, 130.46 (q, *J*=32.2 Hz), 132.17, 132.14, 133.23, 133.33, 138.12, 140.38, 141.57, 142.04, 155.58, 156.84, 165.69 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{36}H_{37}F_3N_2O_2$: 587.2885, found 587.2872.

4-(*tert*-butyl)-*N*-(3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-3-yl)benzamide (4n):



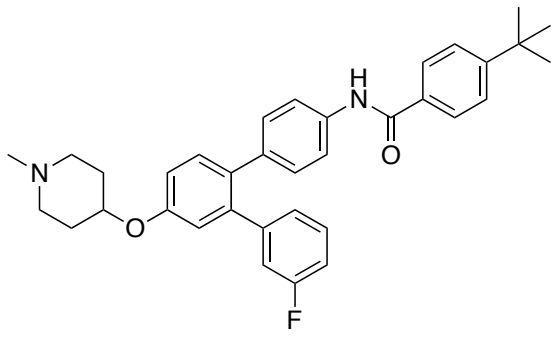
Colorless amorphous solid (12 mg, 20%): ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.35 (s, 9H), 1.88– 1.99 (m, 2H), 2.03–2.14 (s, 2H), 2.36 (s, 3H), 2.43 (br, 2H), 2.69–2.79 (m, 2H), 4.44 (br, 1H), 6.78 (d, *J*=7.7 Hz, 1H), 6.87–6.99 (m, 5H), 7.16 (t, *J*=7.8 Hz, 2H), 7.37 (d, *J*=8.3 Hz, 1H), 7.40–7.44 (m, 1H), 7.50 (d, *J*=8.3 Hz, 2H), 7.53 (d, *J*=8.3 Hz, 1H), 7.69 (br, 1H), 7.77 ppm (d, *J*=8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ= 30.61 (2C), 31.30 (3C), 35.15, 46.09, 52.43 (2C), 71.75, 113.72 (d, *J*=21.0 Hz), 115.35, 116.72 (d, *J*=21.7 Hz), 118.05, 118.17, 121.27, 125.77 (d, *J*=2.7 Hz), 125.89 (2C), 126.37, 126.96 (2C), 128.66, 129.51 (d, *J*=8.4 Hz), 132.10, 132.22, 132.91, 138.00, 140.62 (d, *J*=1.8 Hz), 141.90, 143.68 (d, *J*=7.7 Hz), 155.58, 156.92, 162.54 (d, *J*=245.5 Hz), 165.69 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{35}H_{37}FN_2O_2$: 537.2917, found 537.2903.

4-(*tert*-butyl)-*N*-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)benzamide (4o):



Colorless amorphous solid (48 mg, 32%): ^{1}H NMR (500 MHz, $CDCl_3$/MeOD): δ=1.30 (s, 9H), 2.15–2.24 (m, 2H), 2.43 (dt, *J*=15.7, 8.5 Hz, 2H), 2.75 (s, 3H), 3.16 (dt, *J*=13.6, 6.7 Hz, 2H), 3.25 (br, 2H), 4.71 (br, 1H), 6.92 (dd, *J*=2.6, 1.3 Hz, 1H), 6.95 (ddd, *J*=8.5, 2.7, 1.3 Hz, 1H), 6.99–7.02 (m, 2H), 7.20–7.23 (m, 1H), 7.26–7.30 (m, 1H), 7.35 (dd, *J*=8.4, 1.3 Hz, 1H), 7.40–7.52 (m, 6H), 7.73–7.79 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$/MeOD): δ=27.22 (2C), 31.16 (3C), 35.03, 43.79, 49.99 (2C), 66.69, 115.03, 118.19, 119.92 (2C), 123.66 (q, *J*=3.7 Hz), 124.05 (q, *J*=272.3 Hz), 126.29 (q, *J*=3.8 Hz), 125.70 (2C), 127.03 (2C), 128.51, 130.39 (2C), 130.53 (q, *J*=32.1 Hz), 131.90, 132.23, 133.25, 133.94, 136.22, 136.85, 140.60, 141.81, 155.56, 155.64, 166.22 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{36}H_{37}F_3N_2O_2$: 587.2885, found 587.2872.

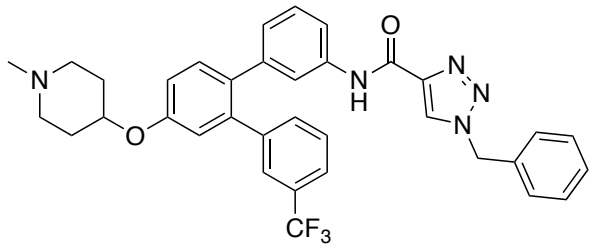
4-(*tert*-butyl)-*N*-(3''-fluoro-4'-((1-methylpiperidin-4-yl)oxy)-[1,1':2',1''-terphenyl]-4-yl)benzamide (4p):



Colorless amorphous solid (26 mg, 18%): ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.35 (s, 9H), 1.86–1.98 (m, 2H), 2.02–2.13 (m, 2H), 2.29–2.13 (m, 5H), 2.69–2.78 (m, 2H), 4.41 (br, 1H), 6.87–7.00 (m, 5H), 7.09 (d, *J*=8.4 Hz, 2H), 7.18 (q, *J*=8.0, 7.6 Hz, 1H), 7.34 (d, *J*=8.4 Hz, 1H), 7.49 (d, *J*=8.4 Hz, 4H), 7.72 (br, 1H), 7.78 ppm (d, *J*=8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.89 (2C), 31.30 (3C), 35.15, 46.31, 52.70 (2C), 72.06, 113.70 (d, *J*=21.0 Hz), 115.44, 116.77 (d, *J*=21.7 Hz), 118.10, 119.67 (2C), 125.79 (d, *J*=2.8 Hz), 125.90 (2C), 126.93 (2C), 129.55 (d, *J*=8.4 Hz), 130.55 (2C), 131.95, 132.22,

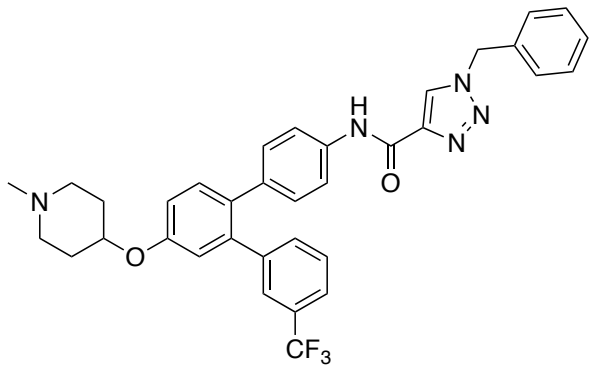
132.75, 136.54, 137.02, 140.59 (d, *J*=1.8 Hz), 143.84 (d, *J*=7.7 Hz), 155.58, 156.84, 162.57 (d, *J*=245.6 Hz), 165.68 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{35}H_{37}FN_2O_2$: 537.2917, found 537.2919.

1-benzyl-*N*-(4''-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)-1*H*-1,2,3-triazole-4-carboxamide (4q):



Colorless amorphous solid (25 mg, 17%): ^{1}H NMR (500 MHz, $CDCl_3$): δ= 2.19–2.26 (m, 2H), 2.48–2.62 (s, 2H), 2.77 (s, 3H), 3.08–3.35 (m, 4H), 4.74 (br, 1H), 5.58 (s, 2H), 6.71 (dt, *J*=1.4, 7.7 Hz, 1H), 6.95–7.00 (m, 2H), 7.12–7.17 (m, 1H), 7.27–7.33 (m, 4H), 7.36–7.43 (m, 4H), 7.43–7.47 (m, 2H), 7.49–7.53 (m, 2H), 8.03 (s, 1H), 8.85 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=27.49 (2C), 44.21, 50.17 (2C), 54.82, 67.22, 114.95, 118.17, 118.24, 121.04, 123.81 (q, *J*=3.9 Hz), 124.08 (q, *J*=272.3 Hz), 126.42 (d, *J*=3.7 Hz), 125.82, 126.38, 128.42 (2C), 128.56, 128.79, 129.35, 129.48 (2C), 130.58 (q, *J*=32.2 Hz), 132.38, 133.17, 133.70, 134.06, 137.52, 140.73, 141.32, 141.62, 143.79, 155.94, 157.78. ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{35}H_{32}F_3N_5O_2$: 612.2586, found 612.2592.

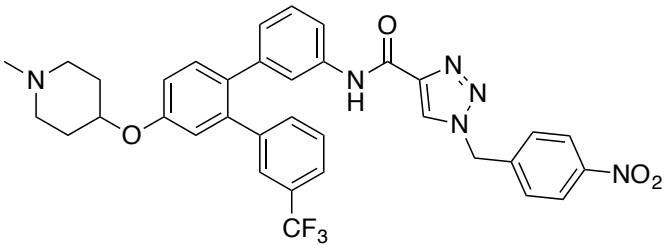
1-benzyl-*N*-(4''-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)-1*H*-1,2,3-triazole-4-carboxamide (4r):



Colorless amorphous solid (45 mg, 28%): ^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.87–2.02 (m, 2H), 2.04–2.15 (m, 2H), 2.32–2.47 (m, 5H), 2.75 (br, 2H), 4.44 (s, 1H), 5.58 (s, 2H), 6.96 (d, *J*=2.6 Hz, 1H), 6.99 (dd, *J*=2.6, 8.5 Hz, 1H), 7.03–7.06 (m, 2H), 7.26–7.32 (m, 4H), 7.35 (d, *J*=8.4 Hz, 1H), 7.38–7.43 (m, 3H), 7.44–7.48 (m, 2H), 7.50–7.54 (m, 2H), 8.03 (s, 1H), 8.88 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.71 (2C), 46.20, 52.57 (2C),

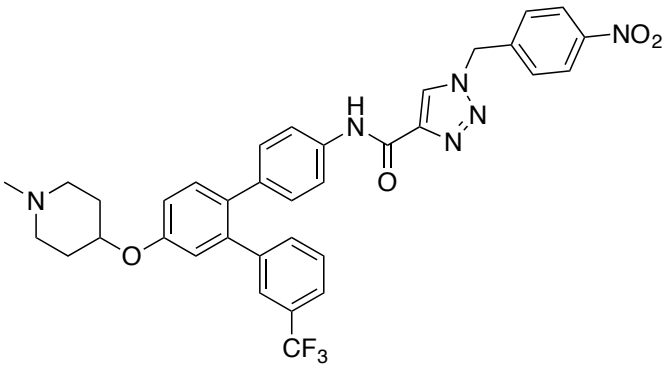
54.83, 71.93, 115.37, 118.24, 119.47 (2C), 123.58 (q, *J*=3.8 Hz), 124.15 (q, *J*=272.4 Hz), 126.53 (q, *J*=3.8 Hz), 125.77, 128.44 (2C), 128.44, 129.36, 129.49 (2C), 130.58 (q, *J*=32.2 Hz), 130.65 (2C), 131.99, 132.91, 133.34, 133.71, 136.00, 136.86, 140.35, 142.18, 143.86, 156.91, 157.77 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{35}H_{32}F_3N_5O_2$: 612.2586, found 612.2601.

_N_-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)-1-(4-nitrobenzyl)-1_H_-1,2,3-triazole-4-carboxamide (4s):



Colorless amorphous solid (38 mg, 34%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.24 (d, *J*=14.2 Hz, 2H), 2.57–2.70 (m, 2H), 2.82 (s, 3H), 3.19 (s, 2H), 3.39 (s, 2H), 4.79 (s, 1H), 5.72 (s, 2H), 6.73 (ddd, *J*=1.0, 1.7, 7.7 Hz, 1H), 6.95–6.99 (m, 2H), 7.16 (t, *J*=7.9 Hz, 1H), 7.27–7.33 (m, 2H), 7.40 (d, *J*=8.3 Hz, 1H), 7.42–7.44 (m, 1H), 7.44–7.48 (m, 3H), 7.50 (ddd, *J*=1.0, 2.2, 8.1 Hz, 1H), 7.54 (t, *J*=2.0 Hz, 1H), 8.18–8.28 (m, 3H), 8.85 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=27.02 (2C), 43.98, 49.66 (2C), 53.69, 66.35, 114.85, 118.22, 118.27, 121.08, 123.84 (q, *J*=3.6 Hz), 124.07 (q, *J*=272.4 Hz), 126.44 (q, *J*=3.8 Hz), 124.45, 124.60 (2C), 126.22, 126.52, 128.59, 128.86, 128.96 (2C), 130.58 (q, *J*=32.3 Hz), 132.39, 133.14, 134.11, 137.36, 140.77, 141.35, 141.55, 144.21, 148.38, 155.84, 157.46 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{35}H_{31}F_3N_6O_4$: 657.2437, found 657.2434.

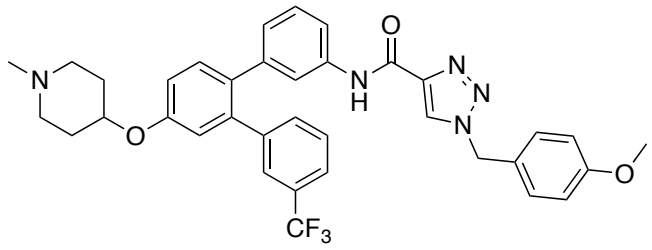
_N_-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)-1-(4-nitrobenzyl)-1_H_-1,2,3-triazole-4-carboxamide (4t):



Colorless amorphous solid (100 mg, 61%): ^{1}H NMR (500 MHz, $CDCl_3$/MeOD): δ=1.97 (s, 2H), 2.11 (s, 2H), 2.40 (s, 3H), 2.54 (s, 2H), 2.79 (s, 2H), 4.48 (s, 1H), 5.69 (s, 2H), 6.94 (d, *J*=2.4 Hz, 1H), 6.97 (dd, *J*=2.6, 8.5 Hz, 1H), 7.02–7.05 (m, 2H), 7.27–7.31 (m,

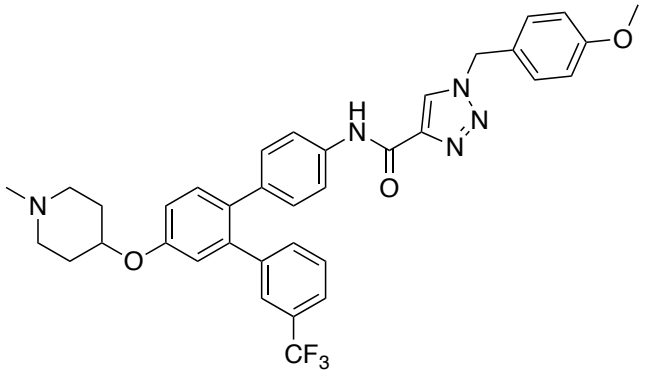
2H), 7.34 (d, *J*=8.5 Hz, 1H), 7.41–7.46 (m, 4H), 7.50–7.54 (m, 2H), 8.21–8.26 ppm (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$/MeOD): δ=29.78 (2C), 45.71, 51.94 (2C), 53.62, 70.83, 115.32, 118.21, 119.52 (2C), 123.56 (q, *J*=3.6 Hz), 124.08 (q, *J*=272.3 Hz), 124.55 (2C), 126.44, 126.50 (d, *J*=3.7 Hz), 128.47, 128.93 (2C), 130.61 (2C), 131.98, 132.99, 133.25, 135.73, 137.02, 140.37, 140.80, 142.04, 144.13, 148.33, 156.66, 157.61 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{35}H_{31}F_3N_6O_4$: 657.2437, found 657.2437.

1-(4-methoxybenzyl)-*N*-(4''-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)-1*H*-1,2,3-triazole-4-carboxamide (4u):



Colorless amorphous solid (15 mg, 10%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.01–2.13 (m, 2H), 2.22–2.31 (m, 2H), 2.56 (s, 3H), 2.83 (s, 2H), 2.92 – 3.00 (m, 2H), 3.81 (s, 3H), 4.58 (s, 1H), 5.50 (s, 2H), 6.71 (ddd, *J*=1.0, 1.7, 7.7 Hz, 1H), 6.89–6.93 (m, 2H), 6.95–6.99 (m, 2H), 7.14 (t, *J*=7.8 Hz, 1H), 7.23–7.25 (m, 1H), 7.26–7.32 (m, 3H), 7.38 (d, *J*=8.3 Hz, 1H), 7.43–7.46 (m, 2H), 7.49–7.54 (m, 2H), 7.99 (s, 1H), 8.84 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=29.09 (2C), 45.21, 51.29 (2C), 54.36, 55.52, 69.69, 114.81 (2C), 115.12, 118.07, 118.20, 121.05, 123.69 (q, *J*=3.8 Hz), 124.11 (q, *J*=272.4 Hz), 126.47 (q, *J*=4.0 Hz), 125.59, 125.63, 126.42, 128.50, 128.74, 130.05 (2C), 130.51 (q, *J*=32.5 Hz), 132.23, 133.21, 133.54, 137.49, 140.53, 141.50, 141.81, 143.70, 156.50, 157.83, 160.34 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{36}H_{34}F_3N_5O_3$: 642.2692, found 642.2693.

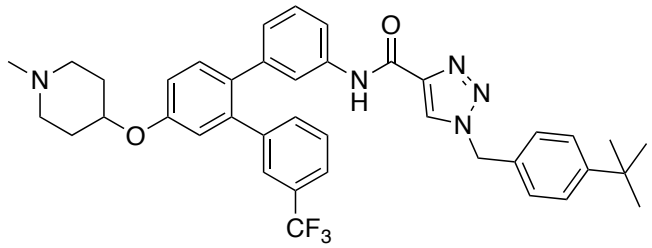
1-(4-methoxybenzyl)-*N*-(4''-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)-1*H*-1,2,3-triazole-4-carboxamide (4v):



Colorless amorphous solid (50 mg, 35%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.85–2.00 (m, 2H), 2.10 (ddt, *J*=3.5, 7.4, 11.6 Hz, 2H), 2.33–2.48 (m, 5H), 2.76 (s, 2H), 3.81 (s, 3H),

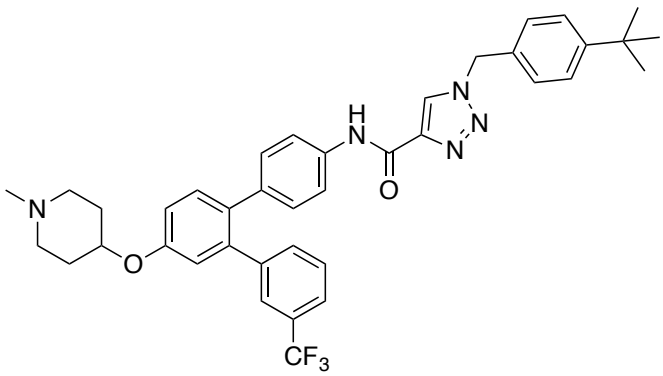
4.45 (s, 1H), 5.51 (s, 2H), 6.90–6.93 (m, 2H), 6.96 (d, *J*=2.6 Hz, 1H), 6.99 (dd, *J*=2.7, 8.5 Hz, 1H), 7.02–7.06 (m, 2H), 7.23–7.26 (m, 3H), 7.29 (t, *J*=7.6 Hz, 1H), 7.35 (d, *J*=8.4 Hz, 1H), 7.44–7.48 (m, 2H), 7.50–7.53 (m, 2H), 7.99 (s, 1H), 8.87 (s, 1H). ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.64 (2C), 46.16, 52.49 (2C), 54.38, 55.53, 71.97, 114.83 (2C), 115.36, 118.24, 119.46 2C), 123.58 (q, *J*=3.8 Hz), 124.15 (q, *J*=272.4 Hz), 126.52 (q, *J*=3.8 Hz), 125.55, 125.62, 128.45, 130.07 (2C), 130.58 (q, *J*=32.2 Hz), 130.64 (2C), 131.99, 132.93, 133.34, 136.02, 136.82, 140.35, 142.17, 143.74, 156.88, 157.83, 160.36. ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{36}H_{34}F_3N_5O_3$: 642.2692, found 642.2703.

1-(4-(*tert*-butyl)benzyl)-*N*-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-3-yl)-1*H*-1,2,3-triazole-4-carboxamide (4w):

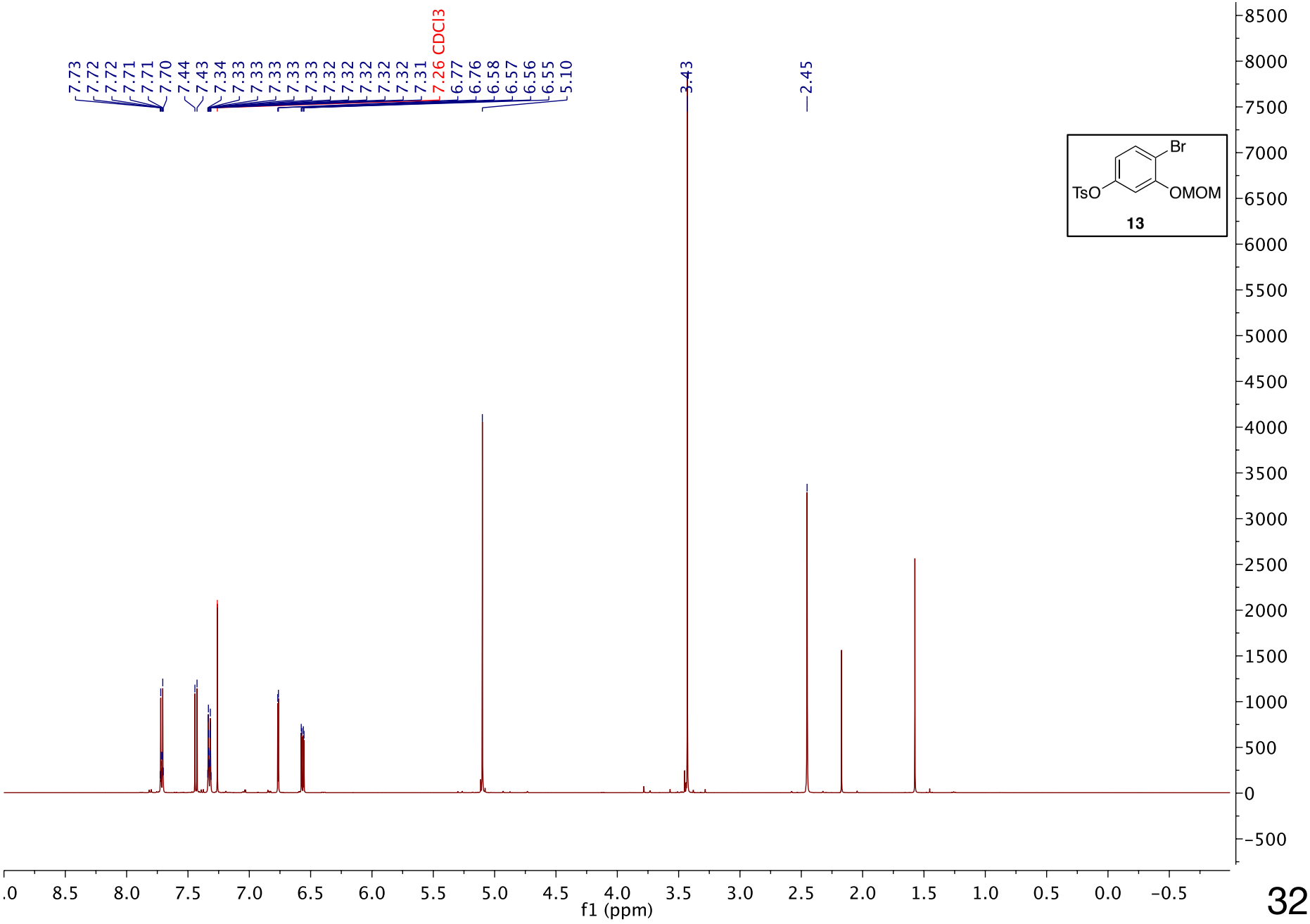


Colorless amorphous solid (45 mg, 40%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.31 (s, 9H), 1.90–2.01 (m, 2H), 2.10 (ddt, *J*=11.7, 7.4, 3.6 Hz, 2H), 2.37 (s, 5H), 2.77 (t, *J*=9.1 Hz, 2H), 4.46 (s, 1H), 5.53 (s, 2H), 6.72 (dt, *J*=7.7, 1.1 Hz, 1H), 6.96–7.00 (m, 2H), 7.13 (t, *J*=7.9 Hz, 1H), 7.22–7.26 (m, 2H), 7.28–7.31 (m, 2H), 7.37 (d, *J*=8.3 Hz, 1H), 7.40–7.47 (m, 4H), 7.49 (t, *J*=1.9 Hz, 1H), 7.54 (ddd, *J*=8.2, 2.2, 1.0 Hz, 1H), 8.02 (s, 1H), 8.85 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.53 (2C), 31.34 (3C), 34.81, 46.09, 52.39 (2C), 54.49, 71.70, 115.25, 117.98, 118.17, 121.06, 123.57 (q, *J*=3.8 Hz), 124.12 (q, *J*=272.4 Hz), 126.51 (q, *J*=4.0 Hz), 125.77, 126.39 (2C), 126.47, 128.30 (2C), 128.43, 128.68, 130.44 (q, *J*=32.1 Hz), 130.62, 132.07, 133.05, 133.23, 137.45, 140.34, 141.66, 141.97, 143.71, 152.53, 156.97, 157.82 ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{39}H_{40}F_3N_5O_2$: 668.3212, found 668.3183.

1-(4-(*tert*-butyl)benzyl)-*N*-(4'-((1-methylpiperidin-4-yl)oxy)-3''-(trifluoromethyl)-[1,1':2',1''-terphenyl]-4-yl)-1*H*-1,2,3-triazole-4-carboxamide (4x):



Colorless amorphous solid (84 mg, 66%): ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.32 (s, 9H), 1.95 (t, *J*=10.4 Hz, 2H), 2.03–2.14 (m, 2H), 2.36 (s, 5H), 2.76 (s, 2H), 4.44 (s, 1H), 5.54 (s, 2H), 6.96 (d, *J*=2.6 Hz, 1H), 6.99 (dd, *J*=8.5, 2.7 Hz, 1H), 7.03–7.06 (m, 2H), 7.23–7.26 (m, 3H), 7.27–7.31 (m, 1H), 7.35 (d, *J*=8.5 Hz, 1H), 7.40–7.43 (m, 2H), 7.44–7.48 (m, 2H), 7.50–7.54 (m, 2H), 8.01 (s, 1H), 8.88 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=30.70 (2C), 31.37 (3C), 34.85, 46.20, 52.51 (2C), 54.54, 71.84, 115.37, 118.24, 119.46 (2C), 123.58 (q, *J*=3.8 Hz), 124.15 (q, *J*=272.4 Hz), 126.52 (q, *J*=3.9 Hz), 125.73, 126.44 (2C), 128.34 (2C), 128.45, 130.58 (q, *J*=32.2 Hz), 130.61, 130.64 (2C), 131.99, 132.93, 133.35, 136.02, 136.83, 140.35, 142.17, 143.74, 152.59, 156.90, 157.84. ppm; HRMS-ESI *m/z* $[M+H]^+$ calcd for $C_{39}H_{40}F_3N_5O_2$ 668.3212, found 668.3226.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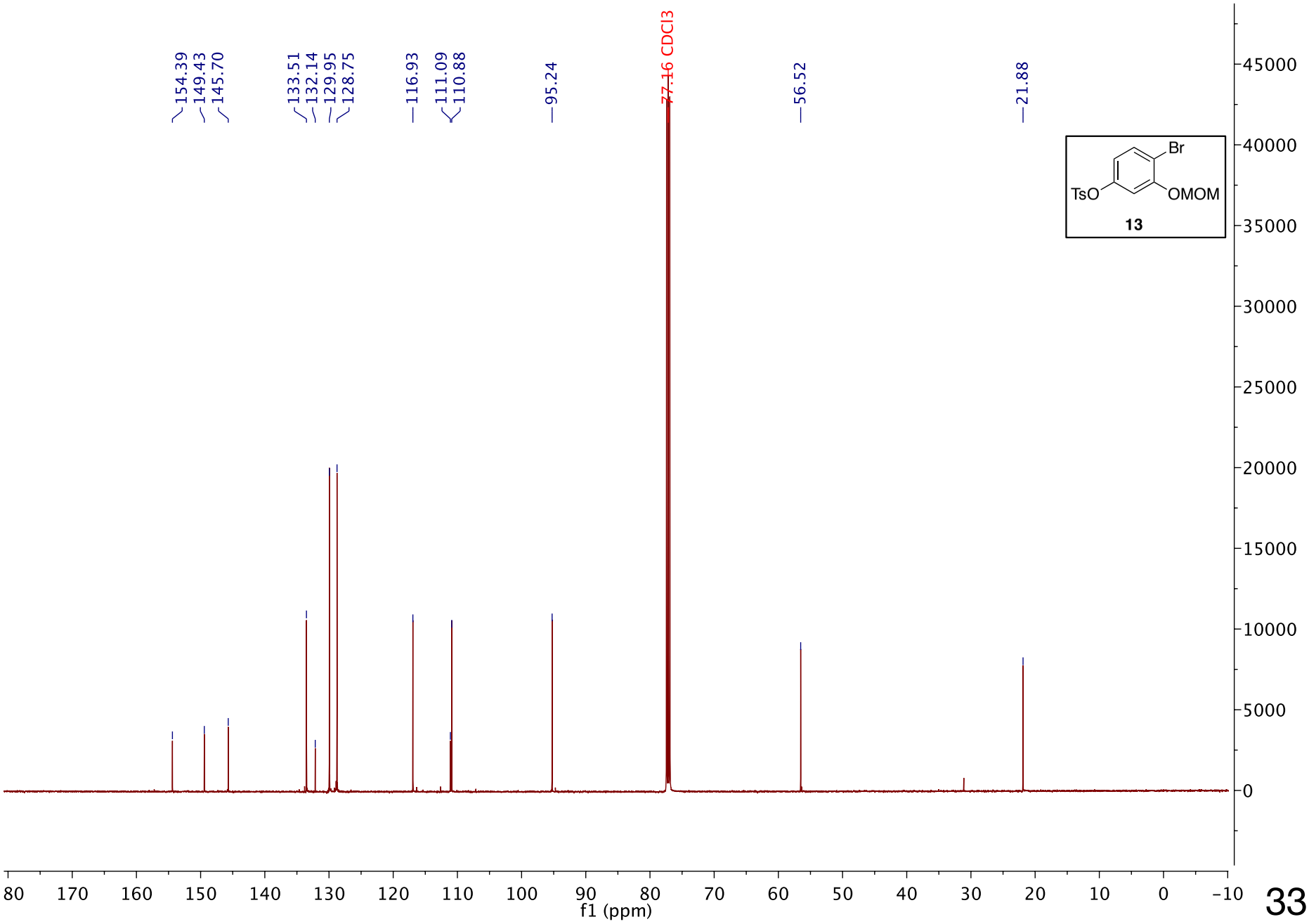
7.72
7.72
7.71
7.71
7.70
7.44
7.43
7.34
7.33
7.33
7.33
7.33
7.33
7.32
7.32
7.32
7.32
7.31
7.26 CDCl3
6.77
6.76
6.58
6.57
6.56
6.55
5.10
3.43
2.45
Br
TsO
OMOM
13
f1 (ppm)


154.39
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133.51
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128.75
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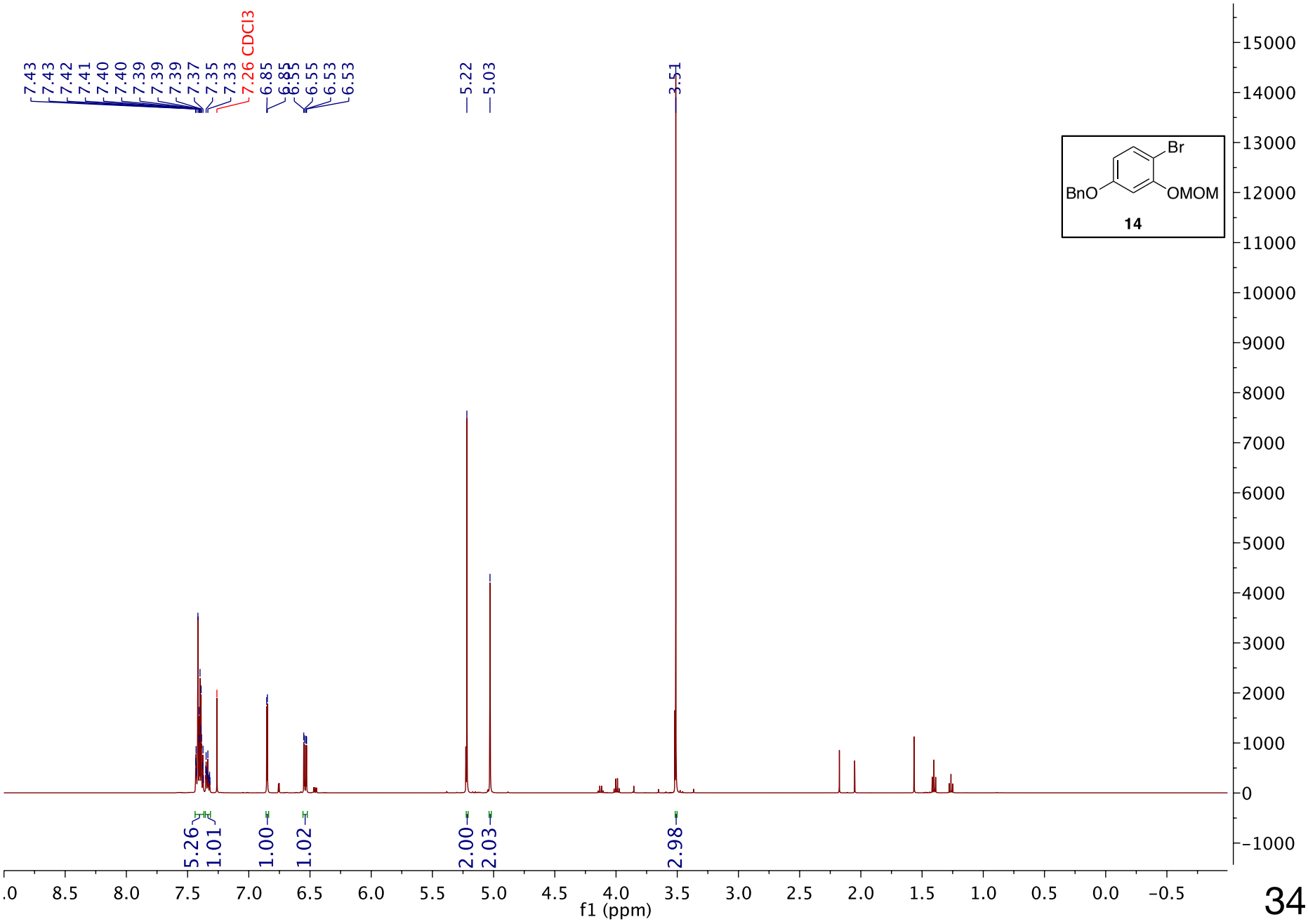
21.88
Br
TsO
OMOM
13
f1 (ppm)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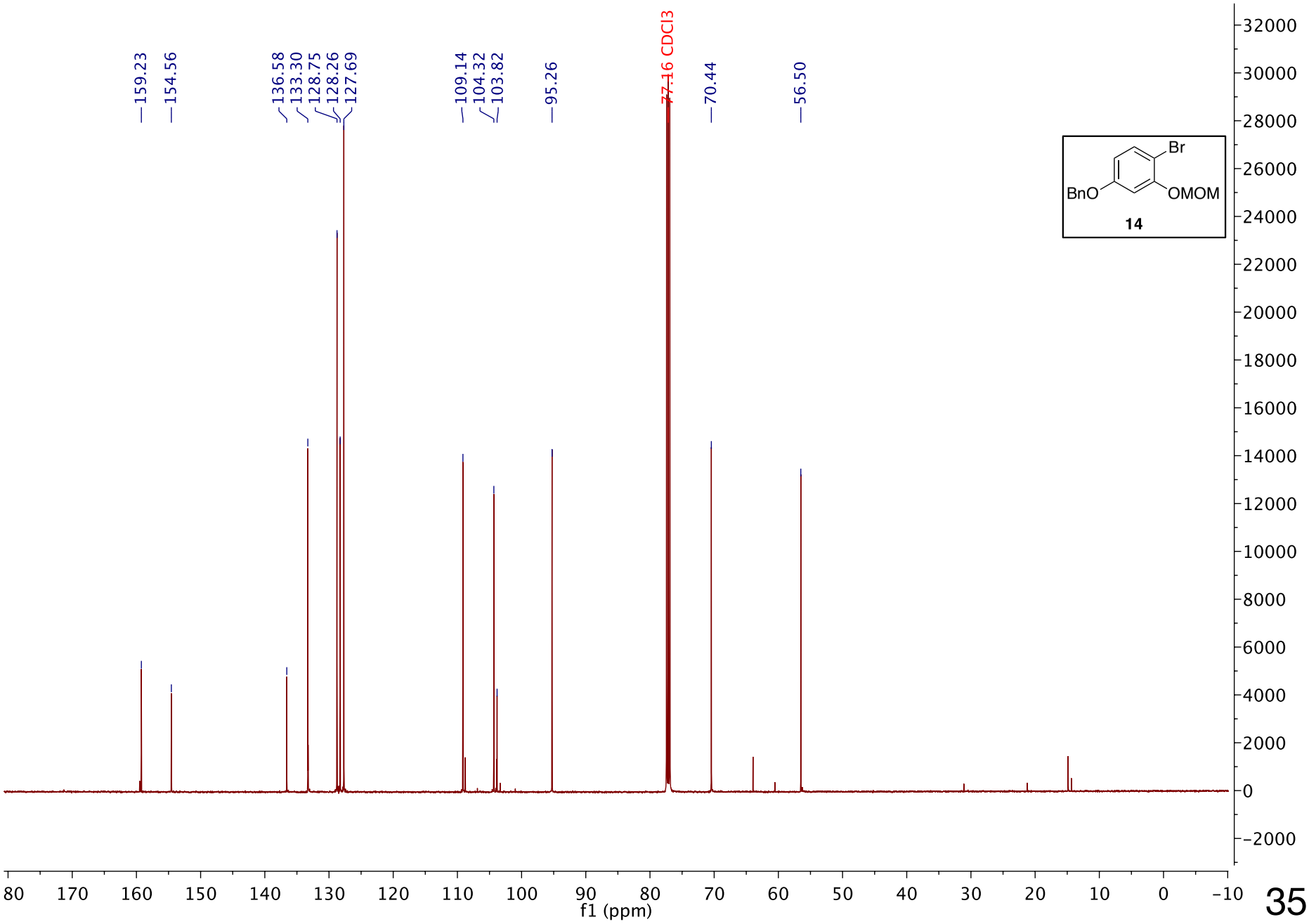
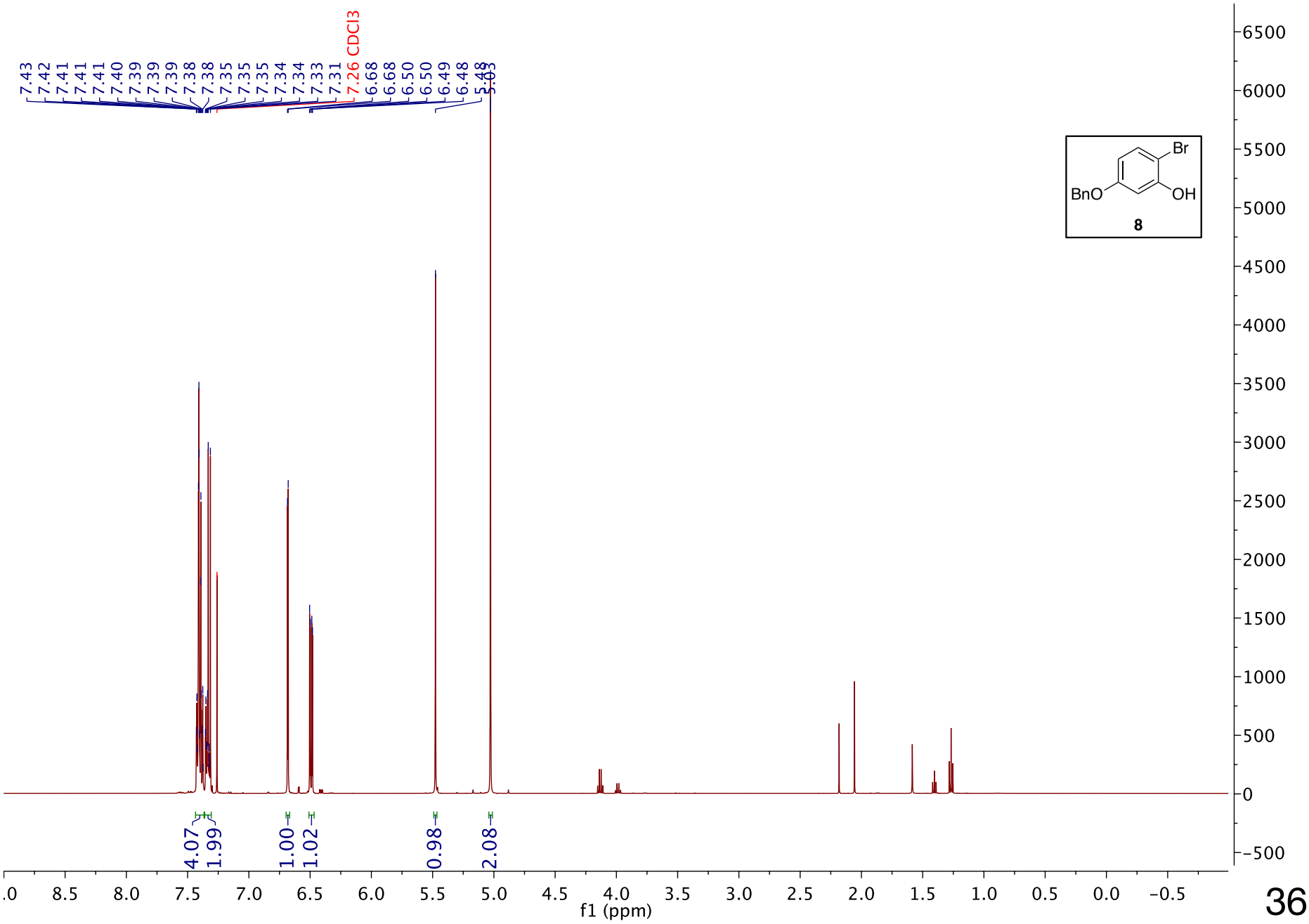
7.40
7.39
7.39
7.39
7.37
7.35
7.33
7.26 CDCl3
6.85
6.85
6.55
6.53
6.53
5.22
5.03
3.51
Br
BnO
OMOM
14
5.26
1.01
1.00
1.02
2.00
2.03
2.98
f1 (ppm)


159.23
154.56
136.58
133.30
128.75
128.26
127.69
109.14
104.32
103.82
95.26
77.16 CDCl3
70.44
56.50
Br
BnO
OMOM
14
f1 (ppm)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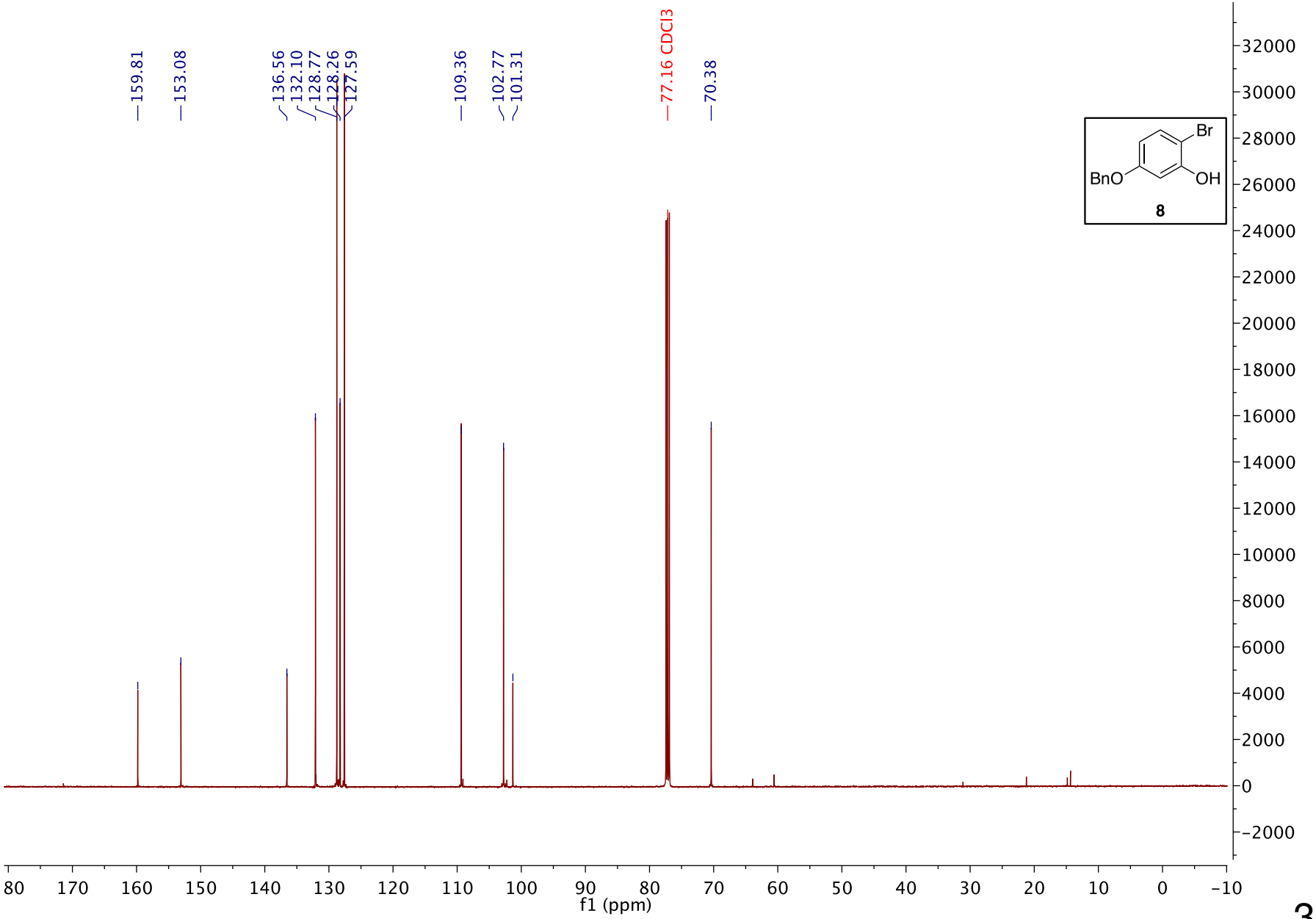
7.34
7.33
7.31
7.26 CDCl3
6.68
6.68
6.50
6.50
6.49
6.48
5.48
5.03
Br
BnO
OH
8
4.07
1.99
1.00
1.02
0.98
2.08
f1 (ppm)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109.36
102.77
101.31
77.16 CDCl3
70.38
Br
BnO
OH
8
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
80
170
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100
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40
30
20
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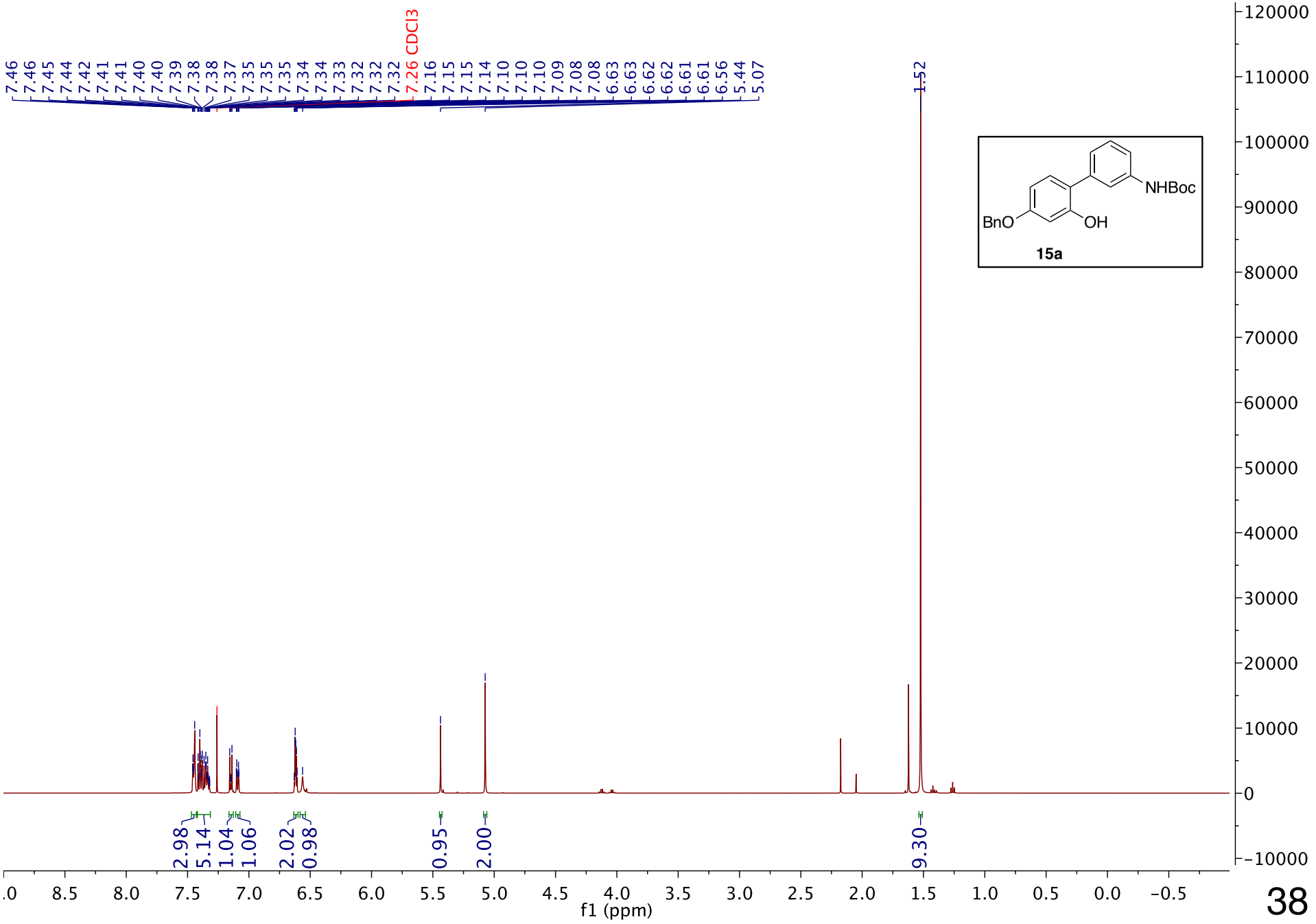
-10
f1 (ppm)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7.34
7.33
7.32
7.32
7.32
7.26 CDCl3
7.16
7.15
7.15
7.14
7.10
7.10
7.10
7.09
7.08
7.08
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6.63
6.62
6.62
6.61
6.61
6.56
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5.07
1.52
NHBoc
BnO
OH
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1.06
2.02
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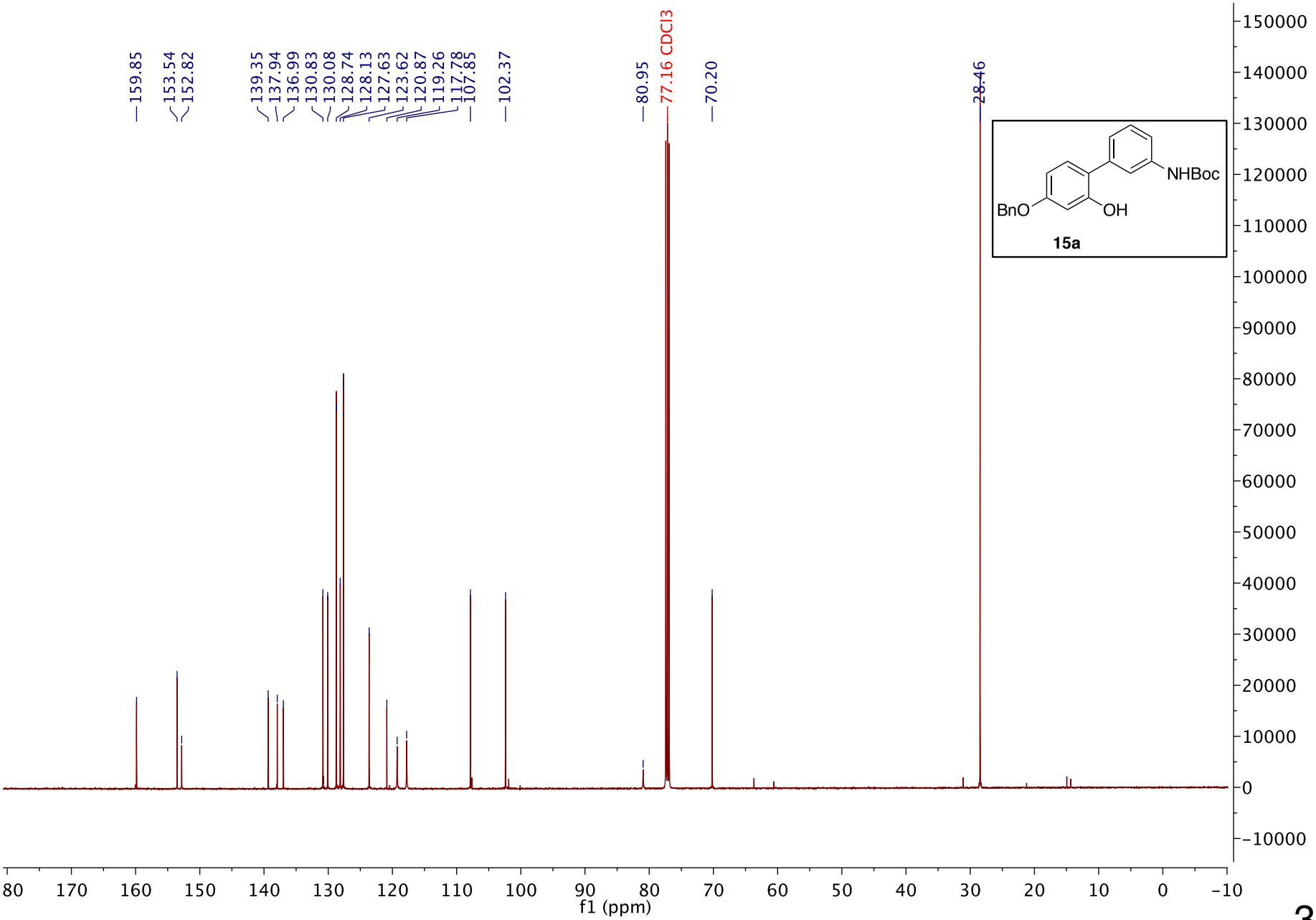
f1 (ppm)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120.87
119.26
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70.20
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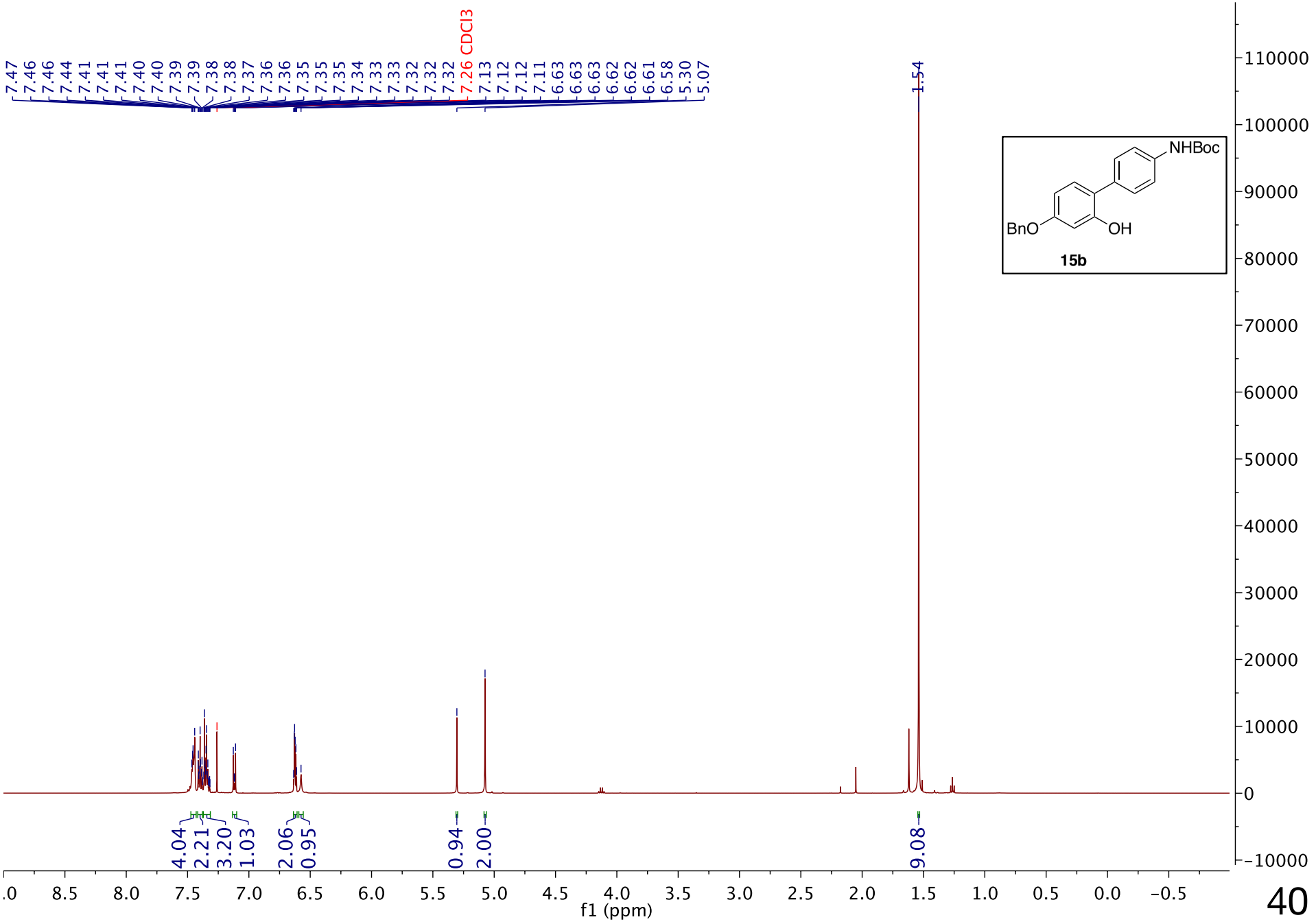
NHBoc
BnO
OH
15a
f1 (ppm)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7.32
7.32
7.32
7.26 CDCl3
7.13
7.12
7.12
7.11
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6.63
6.63
6.62
6.62
6.61
6.58
5.30
5.07
1.54
NHBoc
BnO
OH
15b
4.04
2.21
3.20
1.03
2.06
0.95
0.94
2.00
9.08
f1 (ppm)

159.66
153.55
152.89
137.86
137.00
131.57
130.83
129.83
128.73
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127.62
120.77
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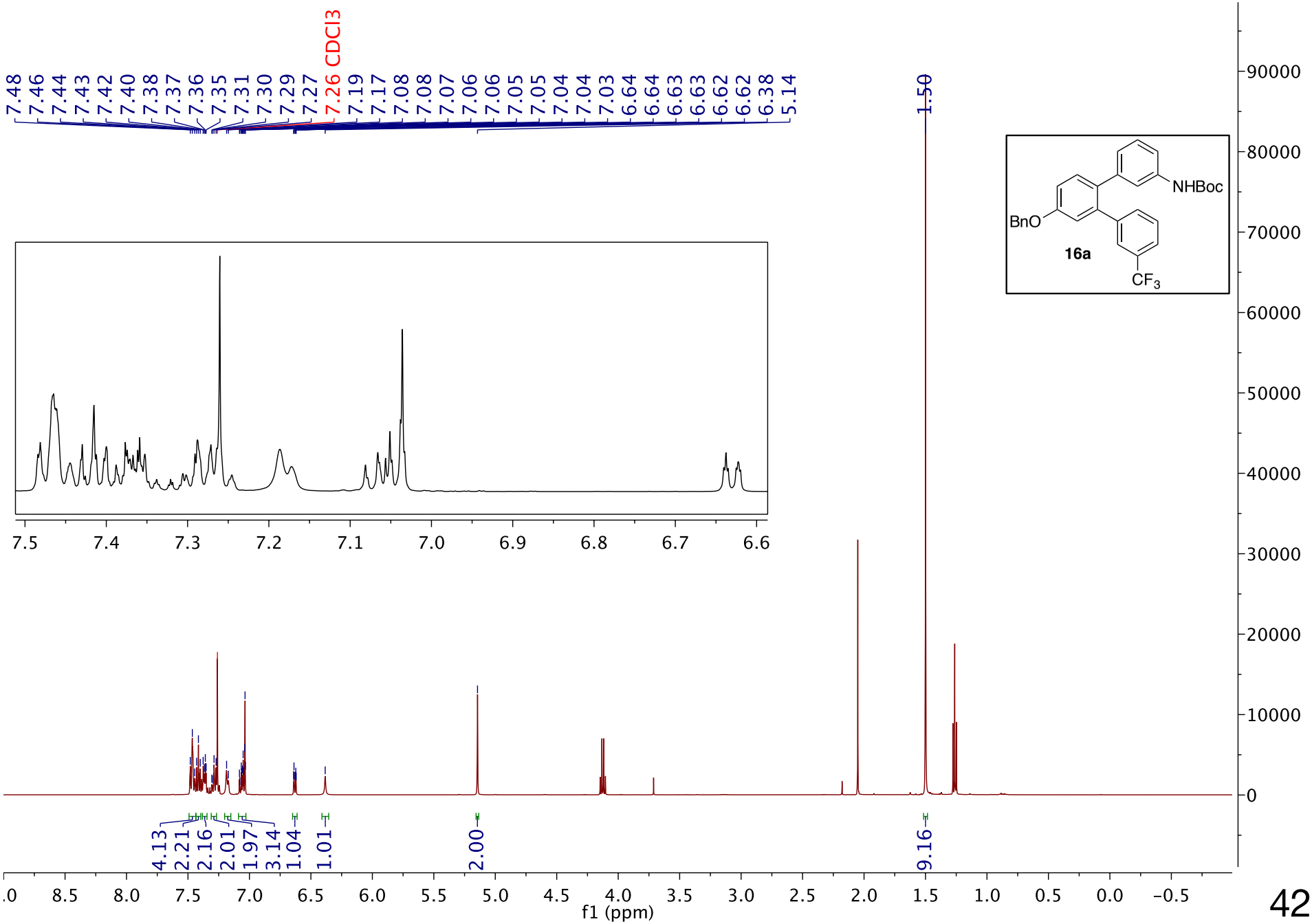
80.96
77.16 CDCl3
70.21
28.47
f1 (ppm)
15b
BnO
OH
NHBoc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7.29
7.27
7.26 CDCl3
7.19
7.17
7.08
7.08
7.07
7.06
7.06
7.05
7.05
7.04
7.04
7.03
6.64
6.64
6.63
6.63
6.62
6.62
6.38
5.14
1.50
NHBoc
BnO
16a
CF3
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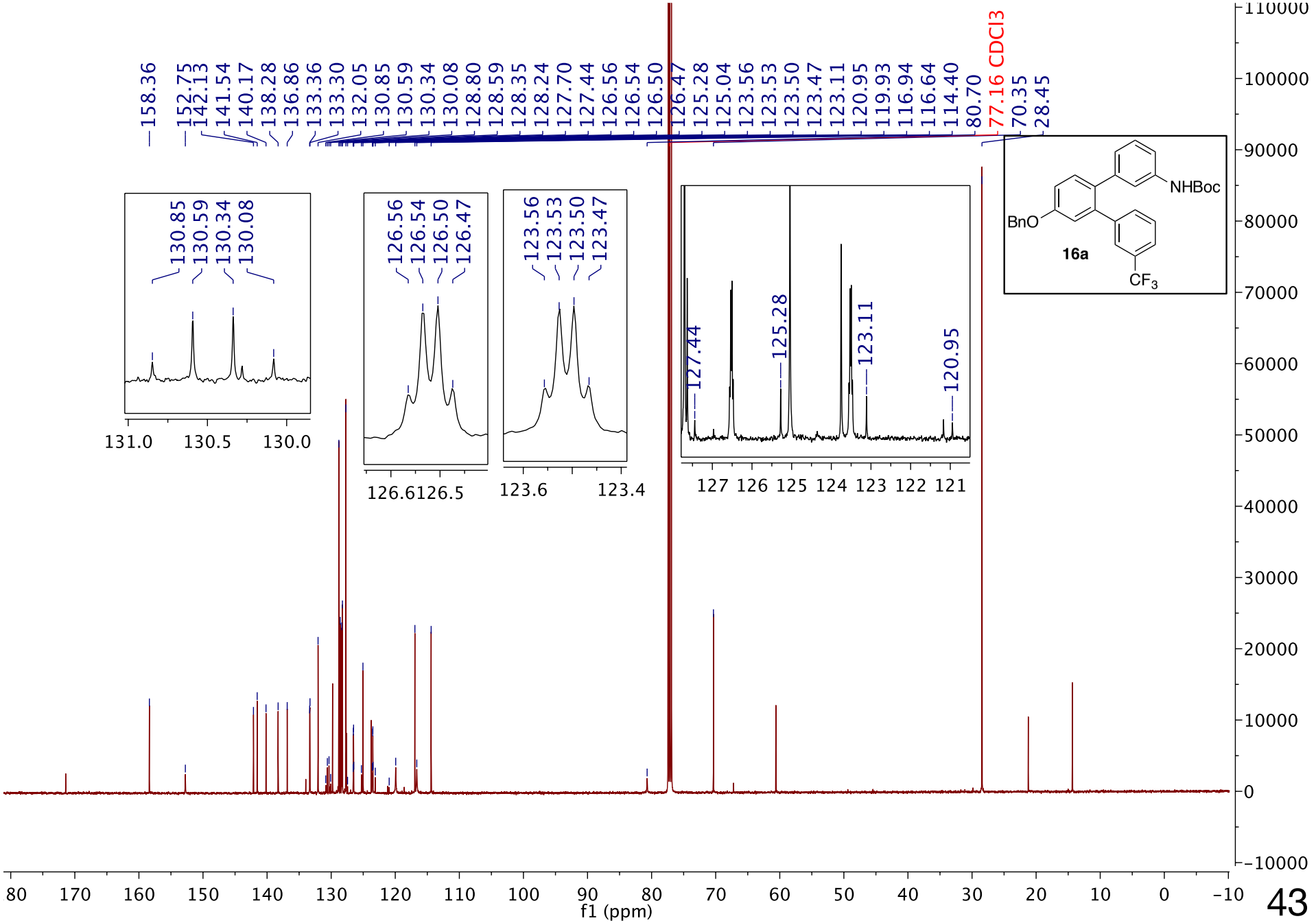
2.16
2.01
1.97
3.14
1.04
1.01
2.00
9.16
f1 (ppm)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130.85
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130.08
128.80
128.59
128.35
128.24
127.70
127.44
126.56
126.54
126.50
126.47
125.28
125.04
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123.50
123.47
123.11
120.95
119.93
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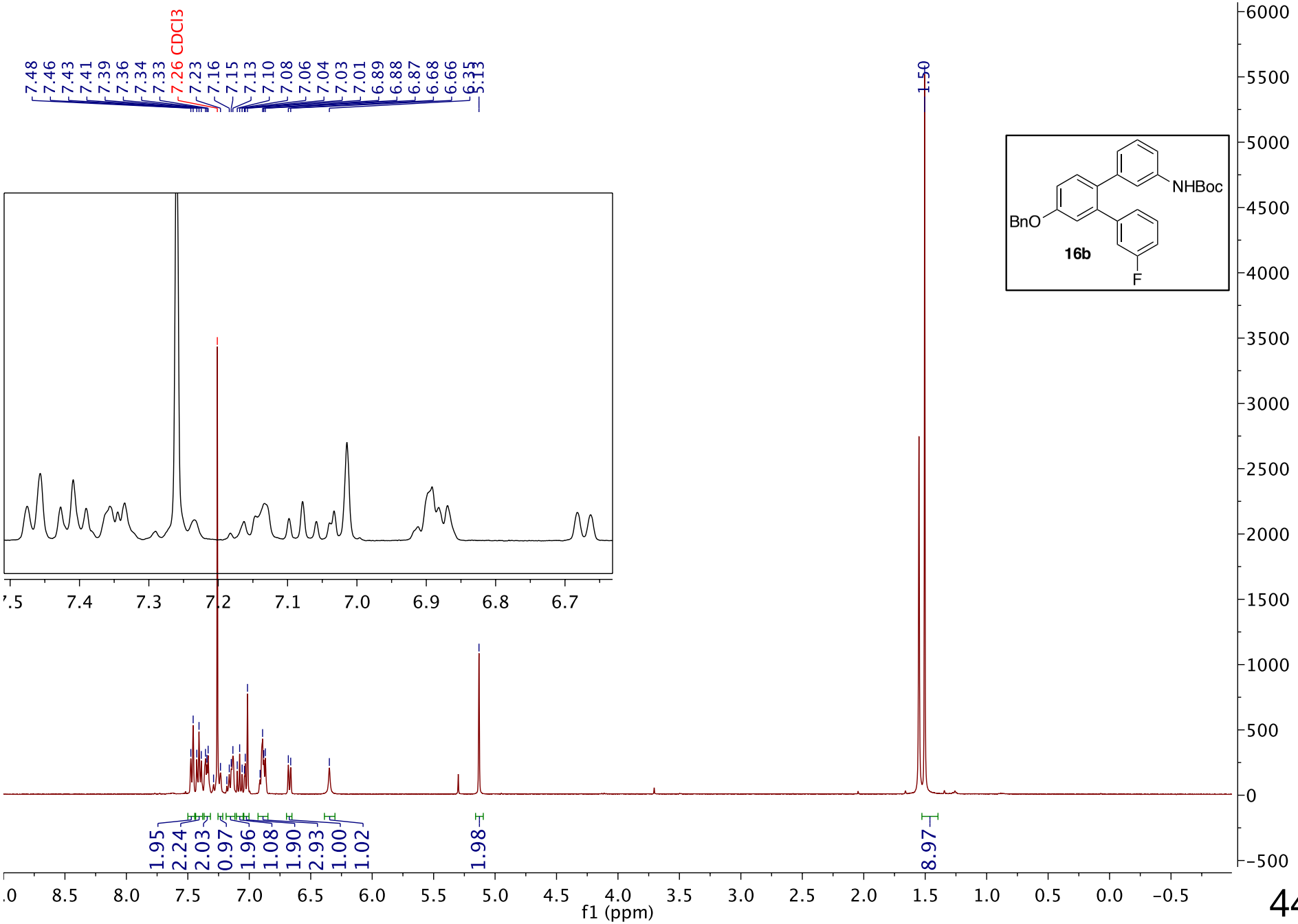
77.16 CDCl3
70.35
28.45
NHBoc
BnO
16a
CF3
f1 (ppm)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7.34
7.33
7.26 CDCl3
7.23
7.16
7.15
7.13
7.10
7.08
7.06
7.04
7.03
7.01
6.89
6.88
6.87
6.68
6.66
6.35
5.13
1.50
NHBoc
BnO
16b
F
1.95
2.24
2.03
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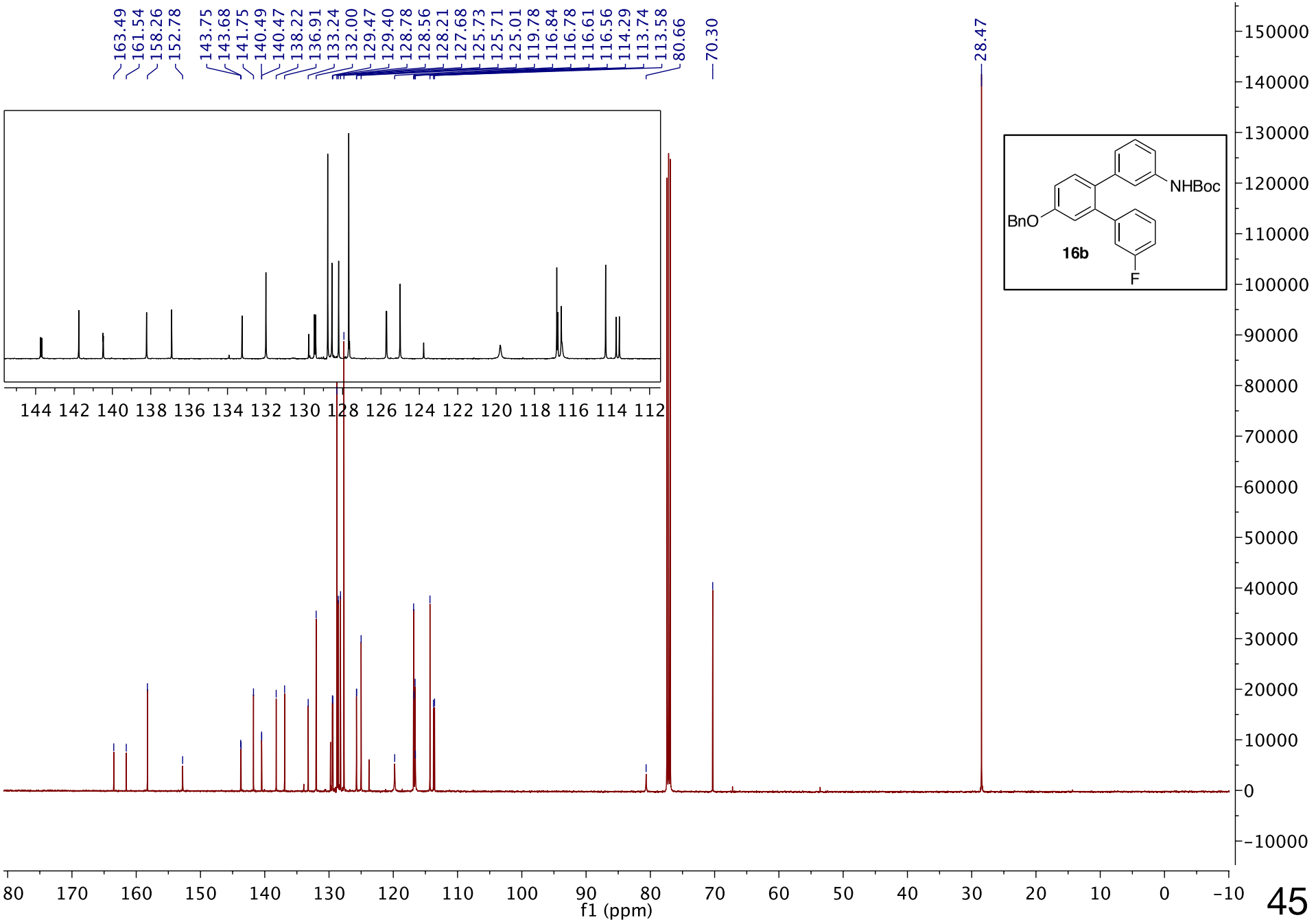
1.96
1.08
1.90
2.93
1.00
1.02
1.98
8.97
f1 (ppm)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129.40
128.78
128.56
128.21
127.68
125.73
125.71
125.01
119.78
116.84
116.78
116.61
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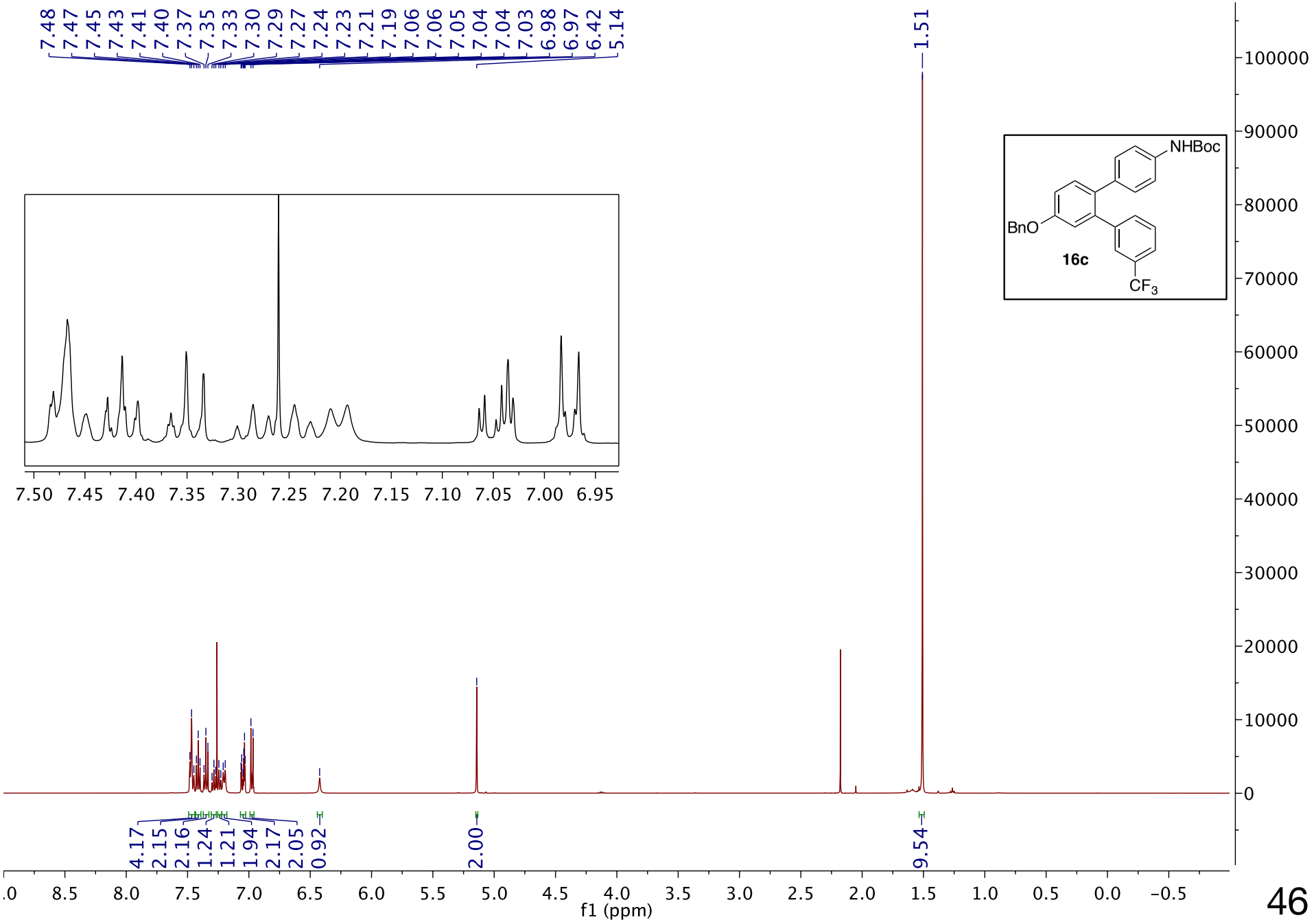
28.47
NHBoc
BnO
16b
F
f1 (ppm)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7.43
7.41
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7.24
7.23
7.21
7.19
7.06
7.06
7.05
7.04
7.04
7.03
6.98
6.97
6.42
5.14
1.51
NHBoc
BnO
16c
CF3
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100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
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1.24
1.21
1.94
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0.92
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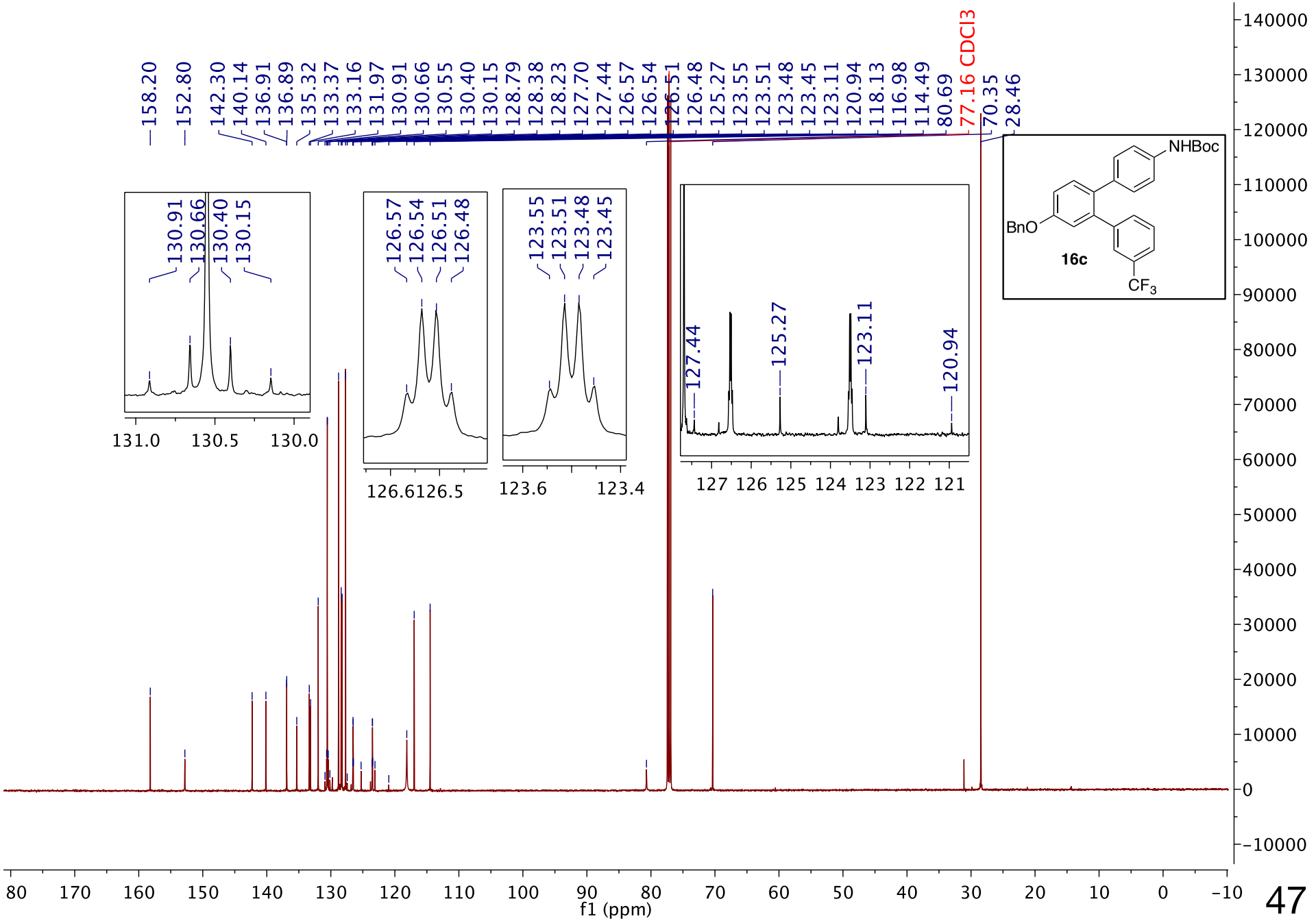
9.54
f1 (ppm)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123.51
123.48
123.45
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120.94
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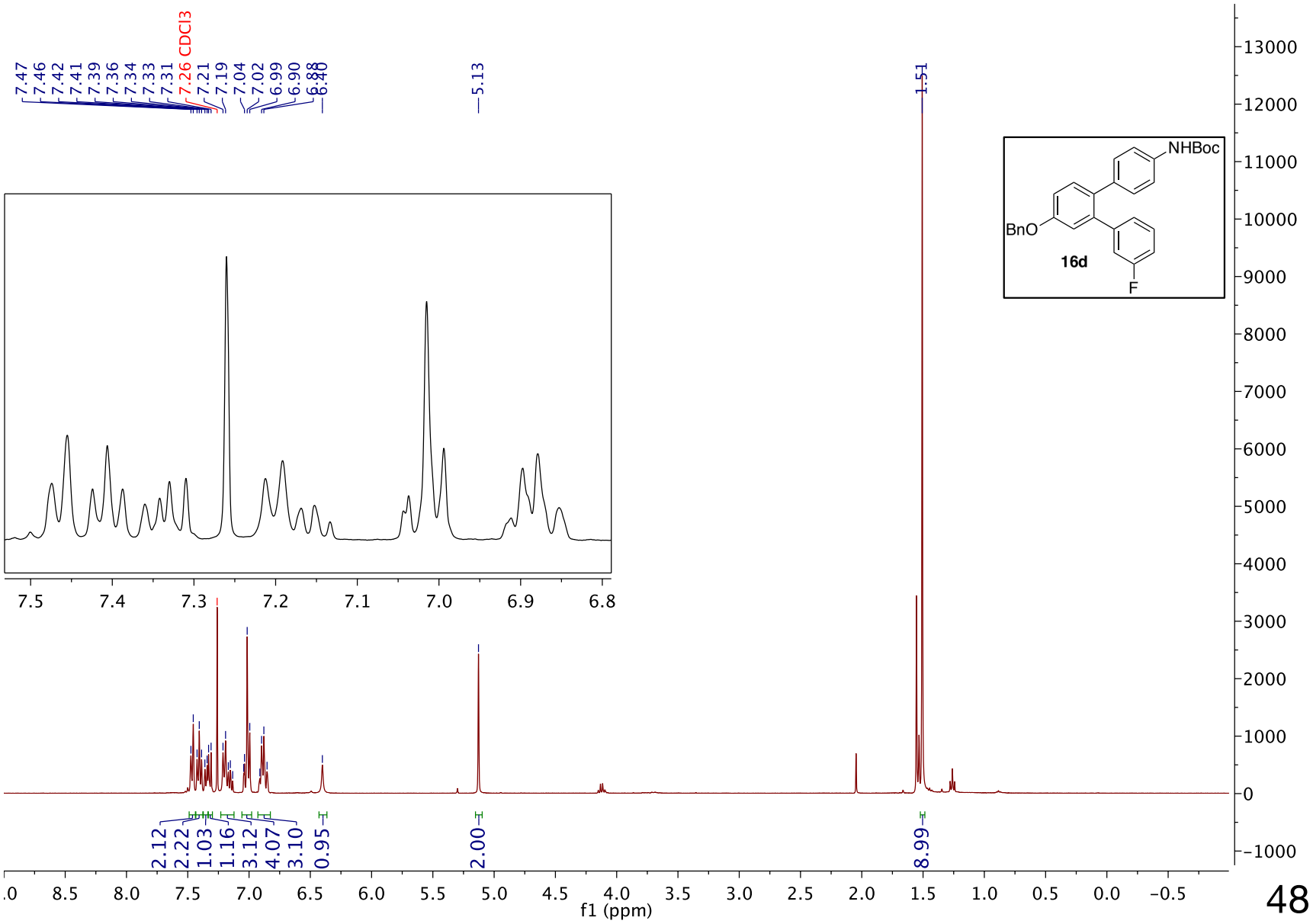
NHBoc
BnO
16c
CF3
f1 (ppm)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7.41
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7.33
7.31
7.26 CDCl3
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7.19
7.04
7.02
6.99
6.90
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6.88
6.40
5.13
1.51
NHBoc
BnO
16d
F
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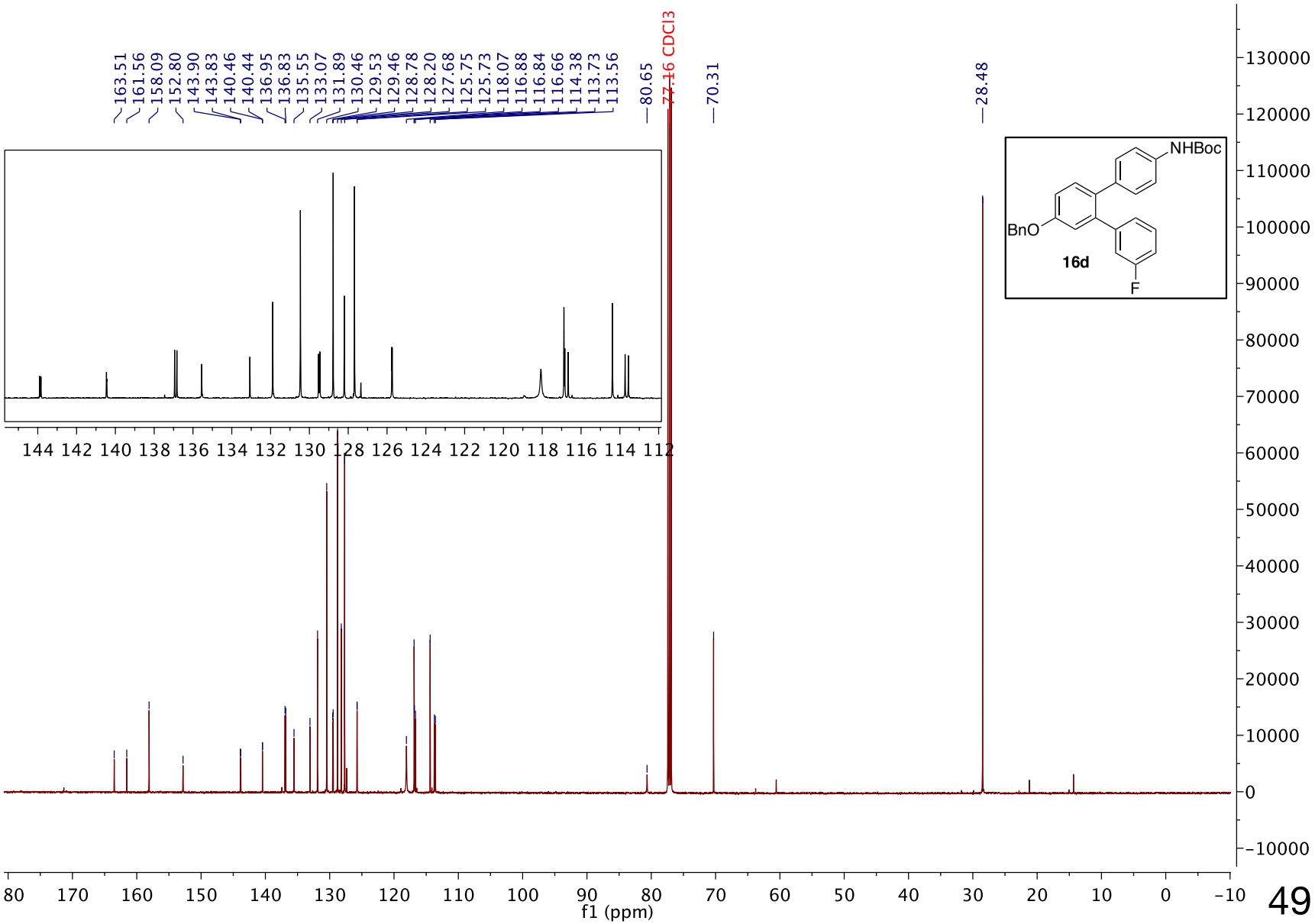
2.22
1.03
1.16
3.12
4.07
3.10
0.95
2.00
8.99
f1 (ppm)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140.44
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131.89
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129.53
129.46
128.78
128.20
127.68
125.75
125.73
118.07
116.88
116.84
116.66
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80.65
77.16 CDCl3
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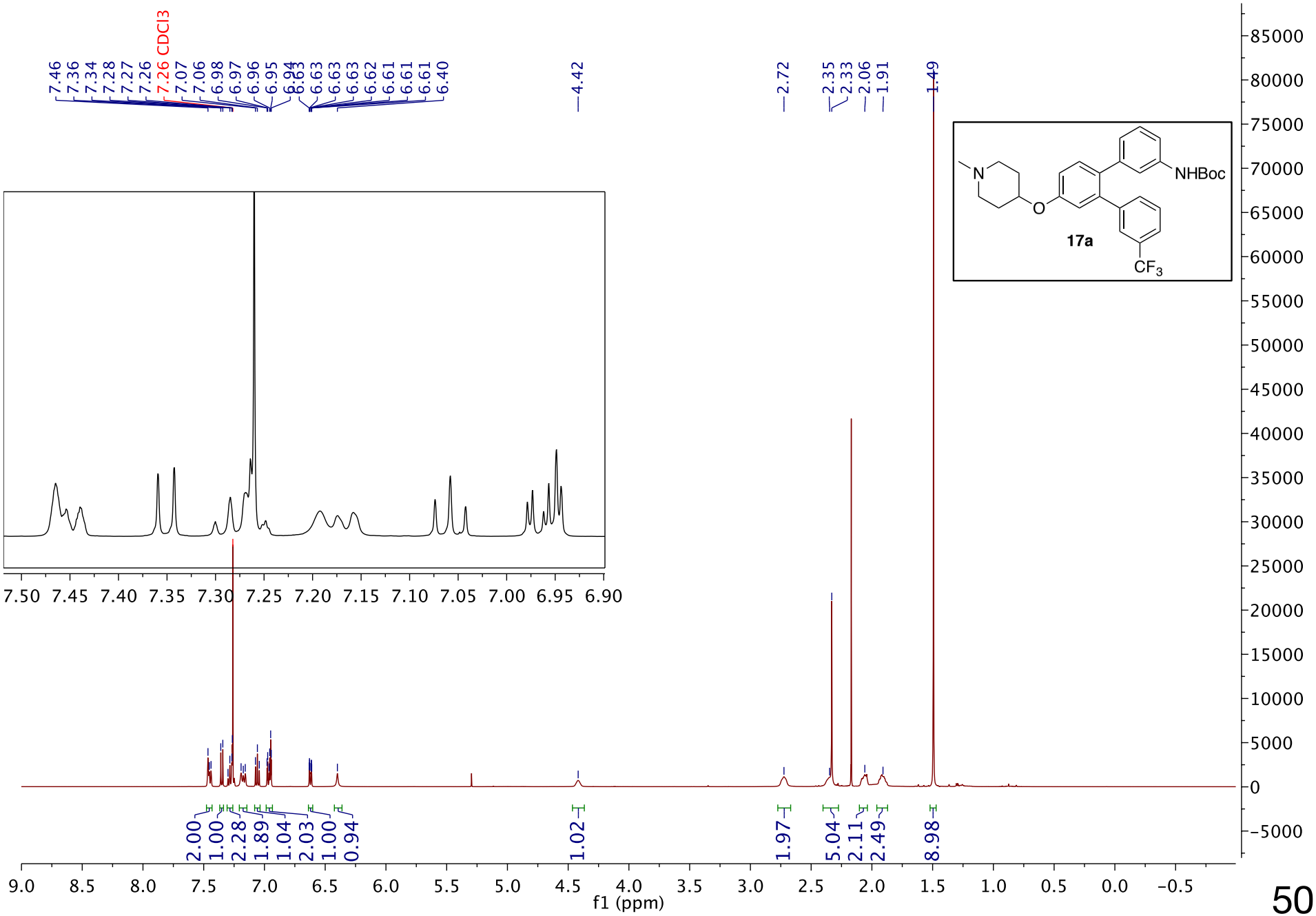
28.48
NHBoc
BnO
16d
F
f1 (ppm)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6.95
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6.63
6.63
6.62
6.61
6.61
6.61
6.40
4.42
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2.35
2.33
2.06
1.91
1.49
NHBoc
N
O
17a
CF3
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2.00
1.00
2.28
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1.00
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1.02
1.97
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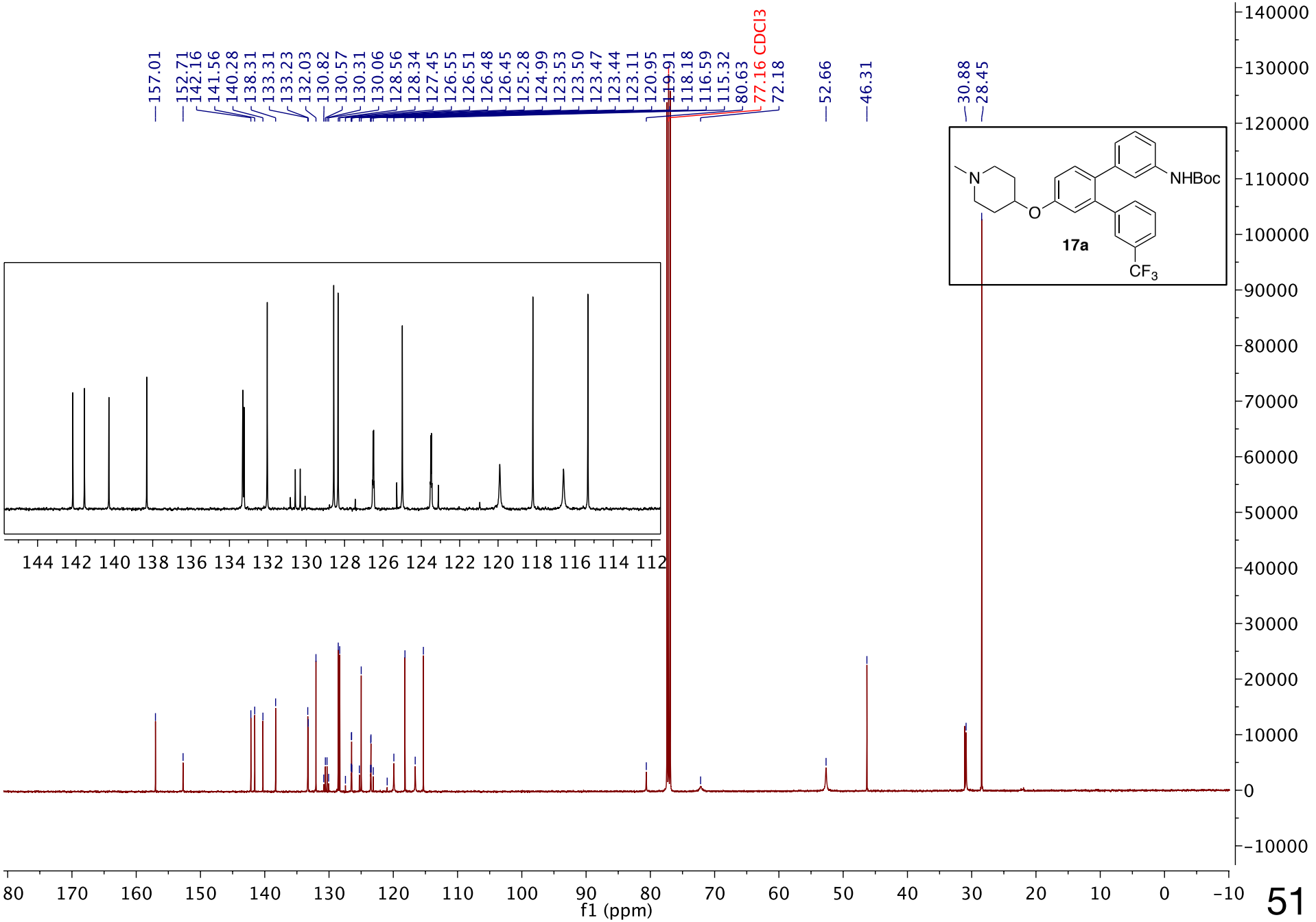
8.98
f1 (ppm)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127.45
126.55
126.51
126.48
126.45
125.28
124.99
123.53
123.50
123.47
123.44
123.11
120.95
119.91
118.18
116.59
115.32
80.63
77.16 CDCl3
72.18
52.66
46.31
30.88
28.45
NHBoc
N
O
17a
CF3
144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112
140000
130000
120000
110000
100000
90000
80000
70000
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30000
20000
10000
0
-10000
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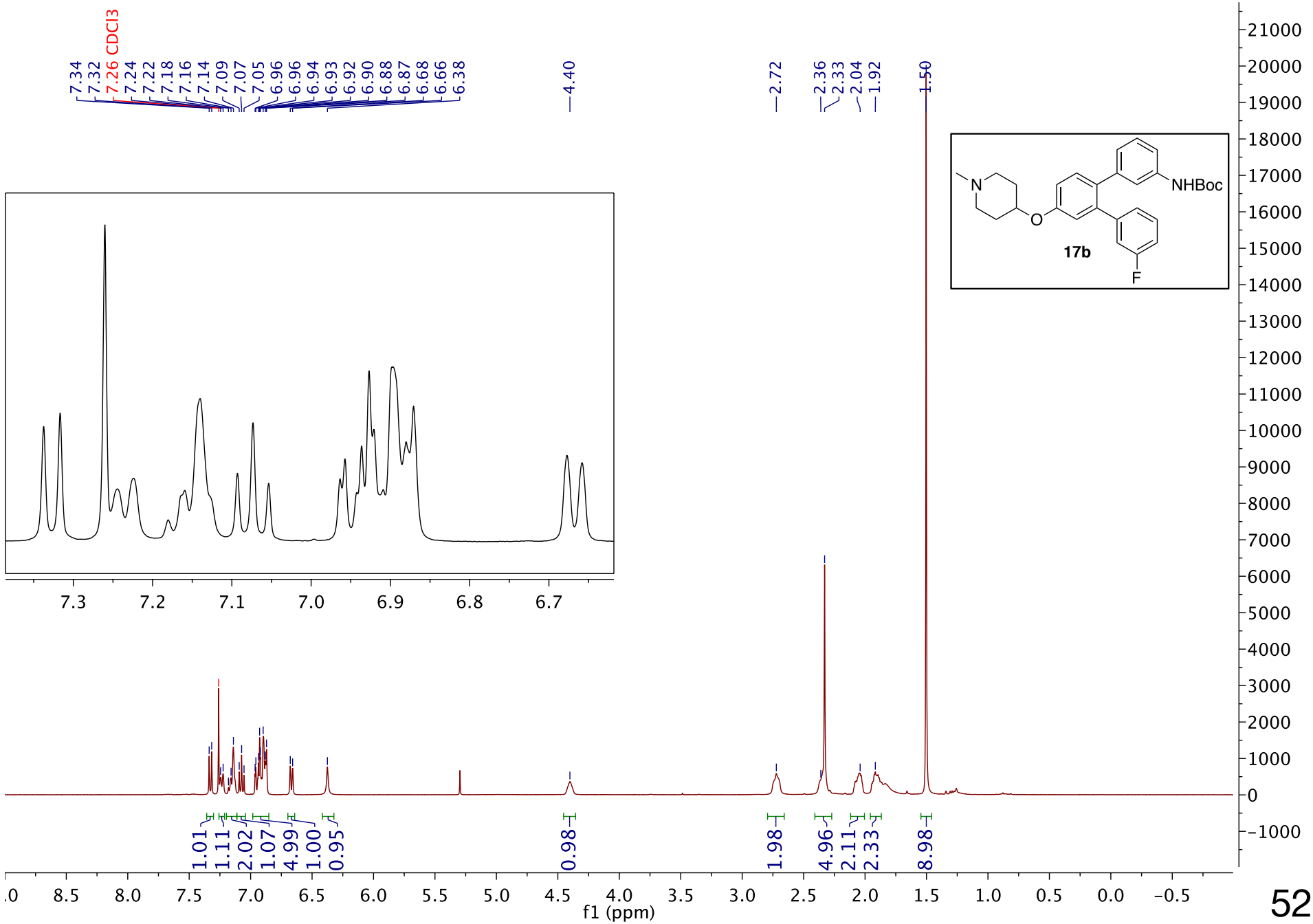
f1 (ppm)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6.94
6.93
6.92
6.90
6.88
6.87
6.68
6.66
6.38
4.40
2.72
2.36
2.33
2.04
1.92
1.50
NHBoc
N
O
F
17b
1.01
1.11
2.02
1.07
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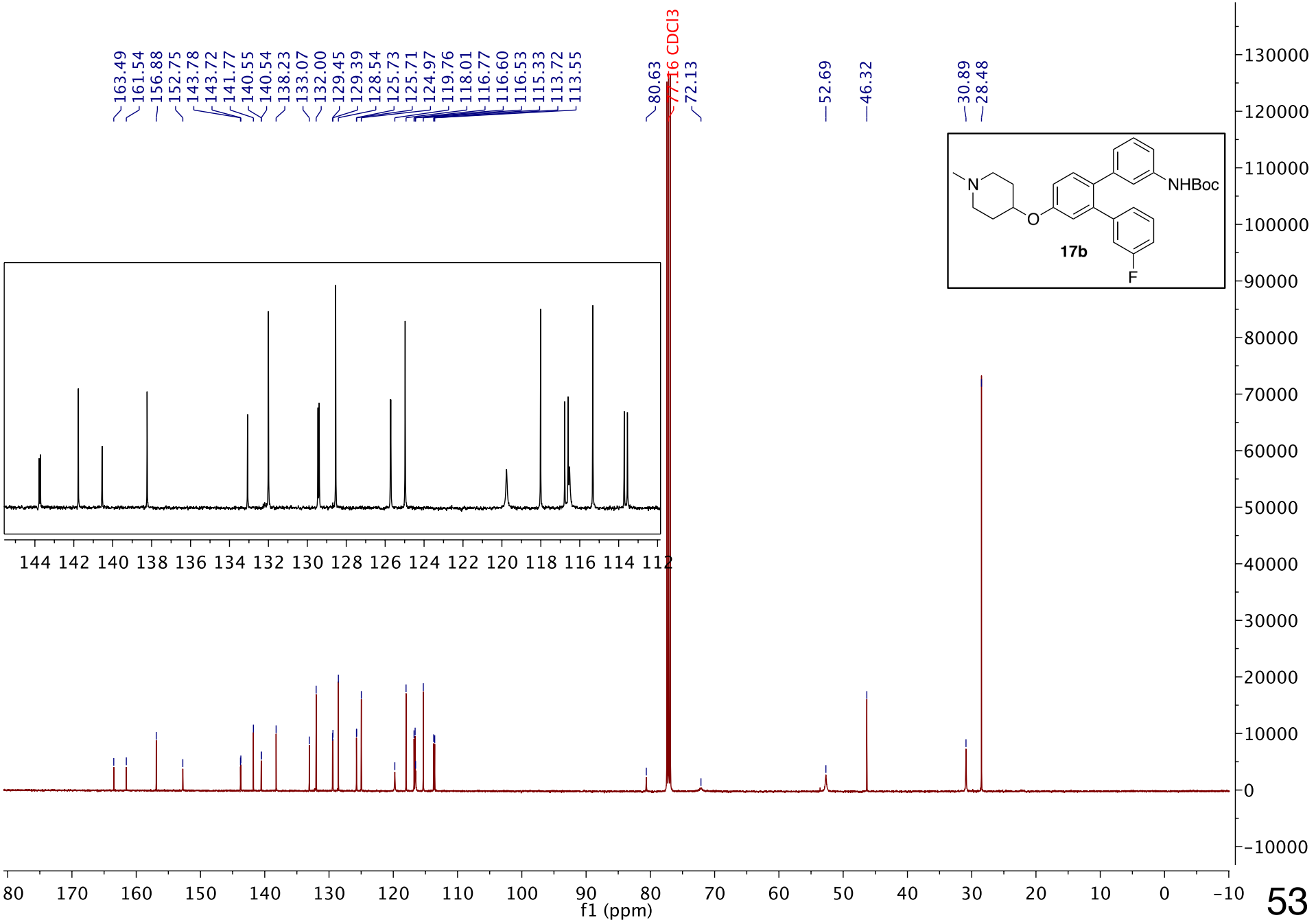
1.00
0.95
0.98
1.98
4.96
2.11
2.33
8.98
f1 (ppm)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77.16 CDCl3
72.13
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46.32
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28.48
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N
O
F
17b
144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112
130000
120000
110000
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80000
70000
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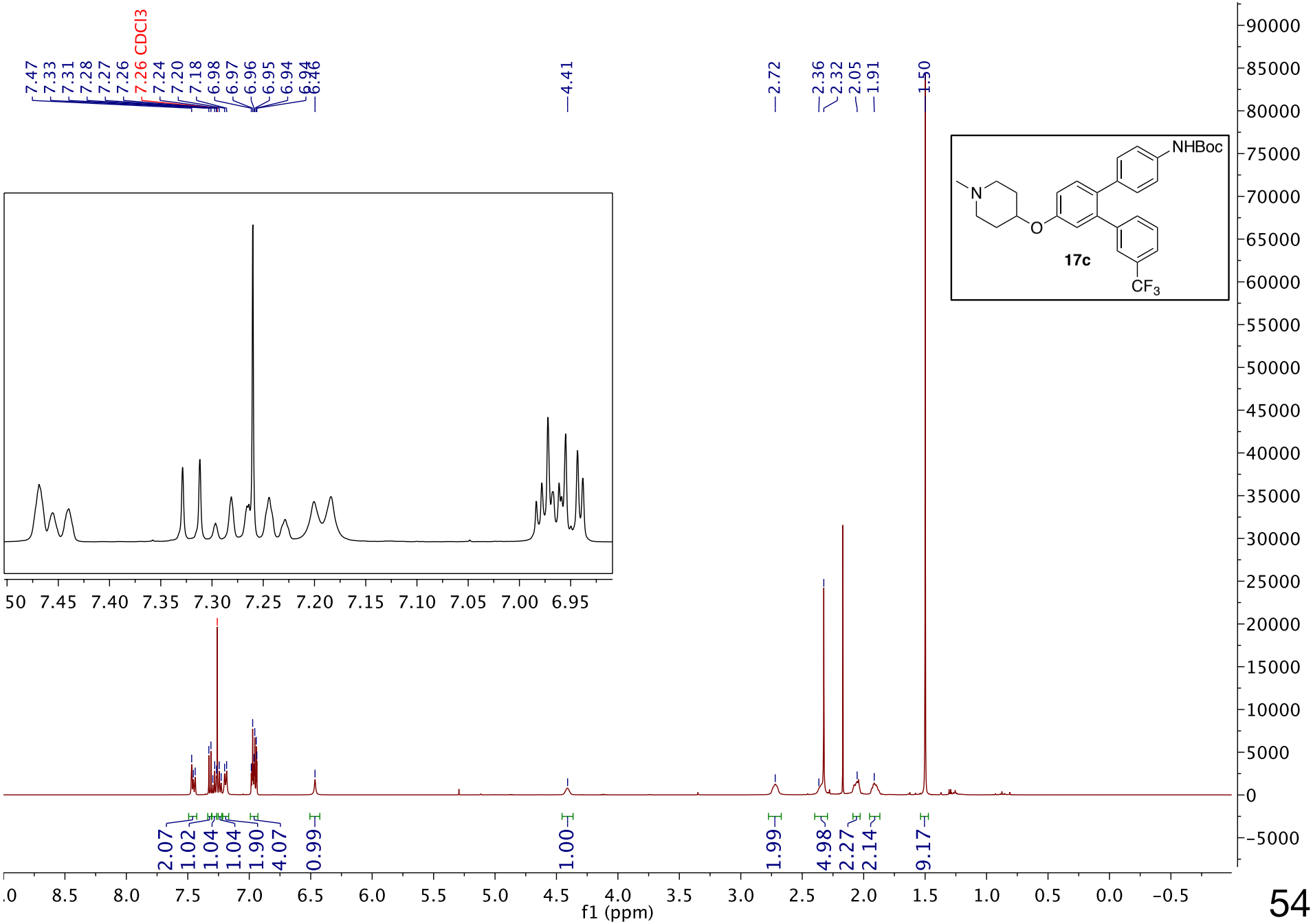
f1 (ppm)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7.26 CDCl3
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6.96
6.95
6.94
6.46
4.41
2.72
2.36
2.32
2.05
1.91
1.50
NHBoc
N
O
17c
CF3
f1 (ppm)
2.07
1.02
1.04
1.04
1.90
4.07
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1.00
1.99
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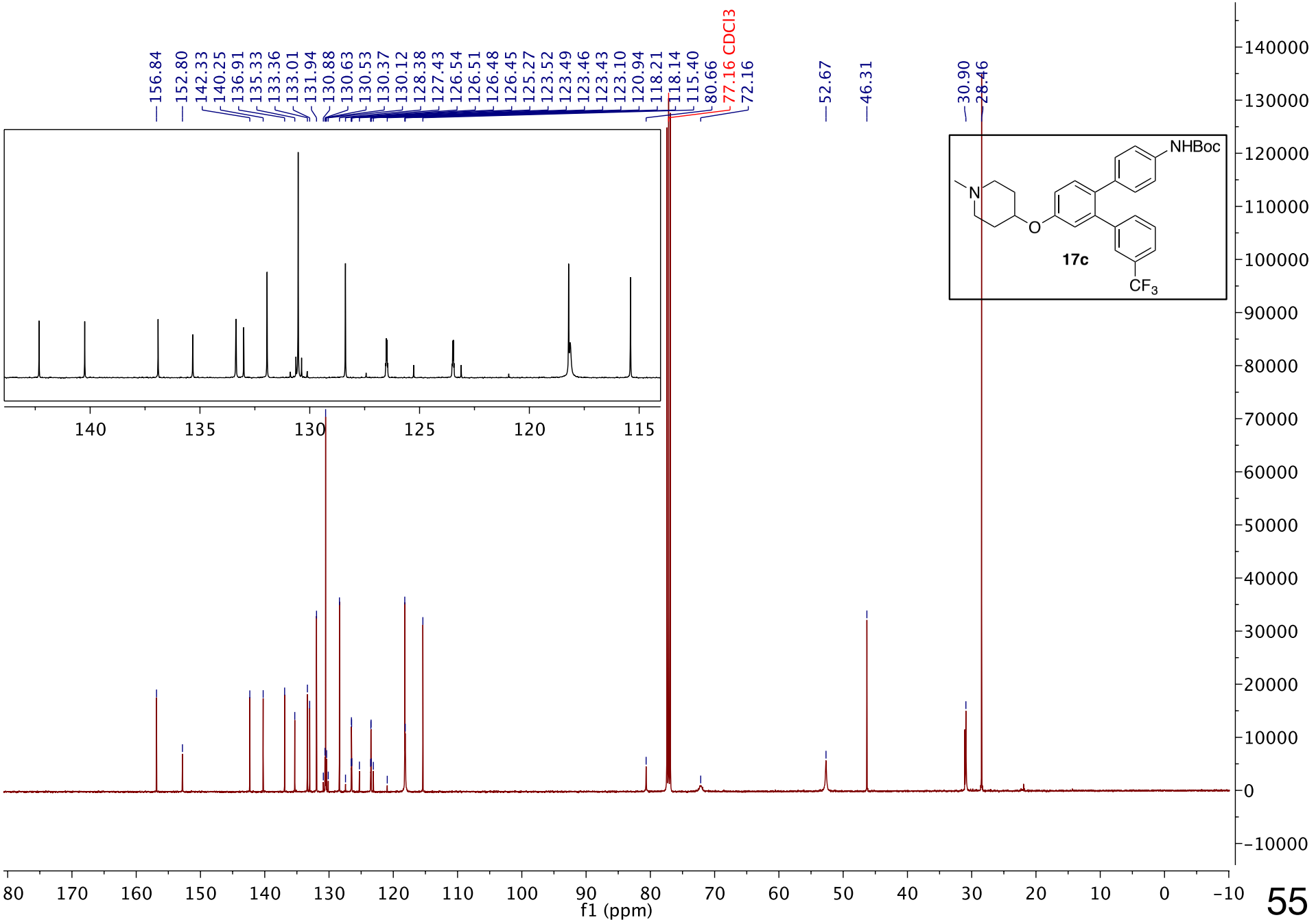
9.17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123.52
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123.10
120.94
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118.14
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80.66
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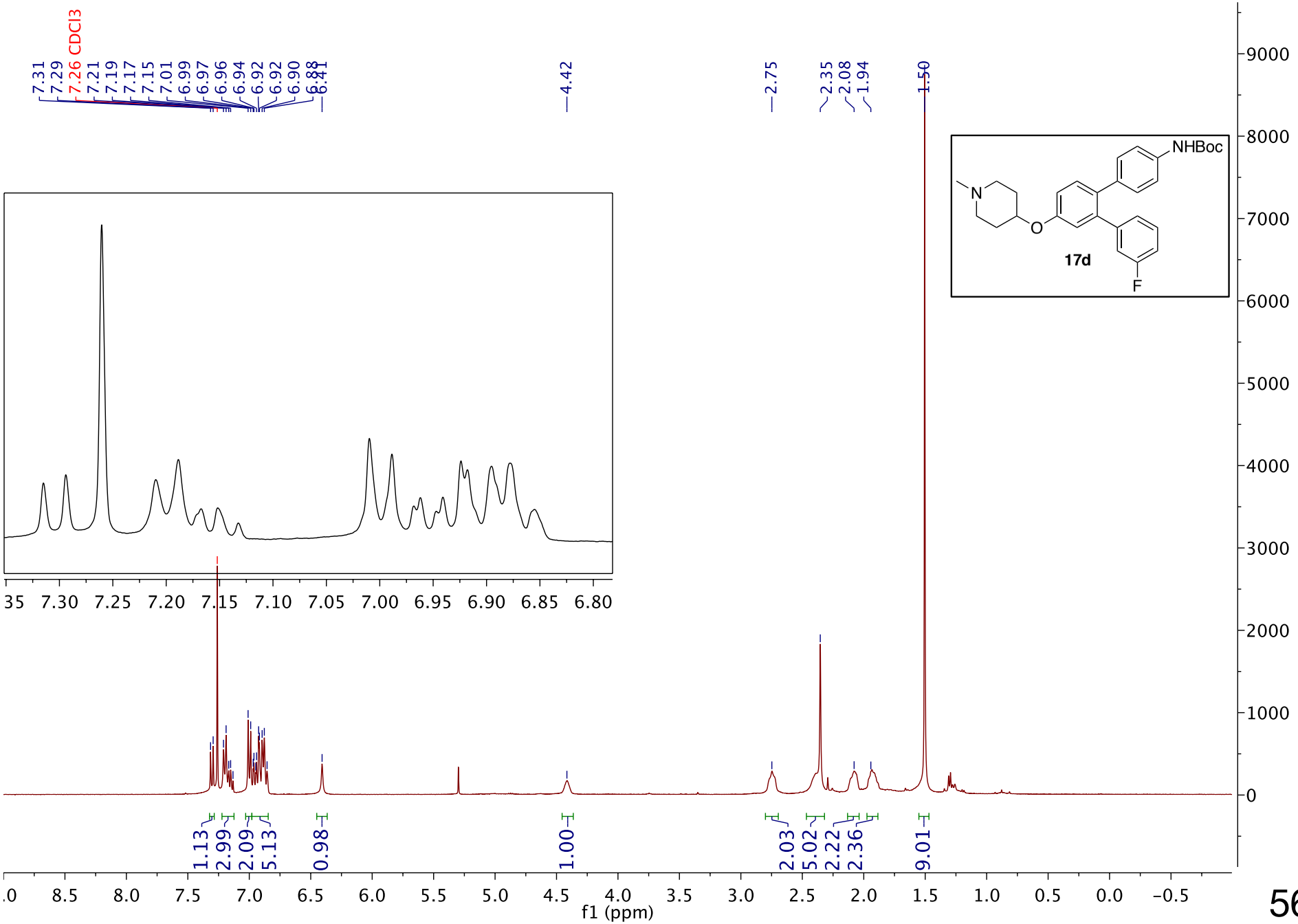
O
17c
CF3
f1 (ppm)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6.90
6.88
6.41
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2.08
1.94
1.50
NHBoc
N
O
F
17d
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5.13
0.98
1.00
2.03
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2.22
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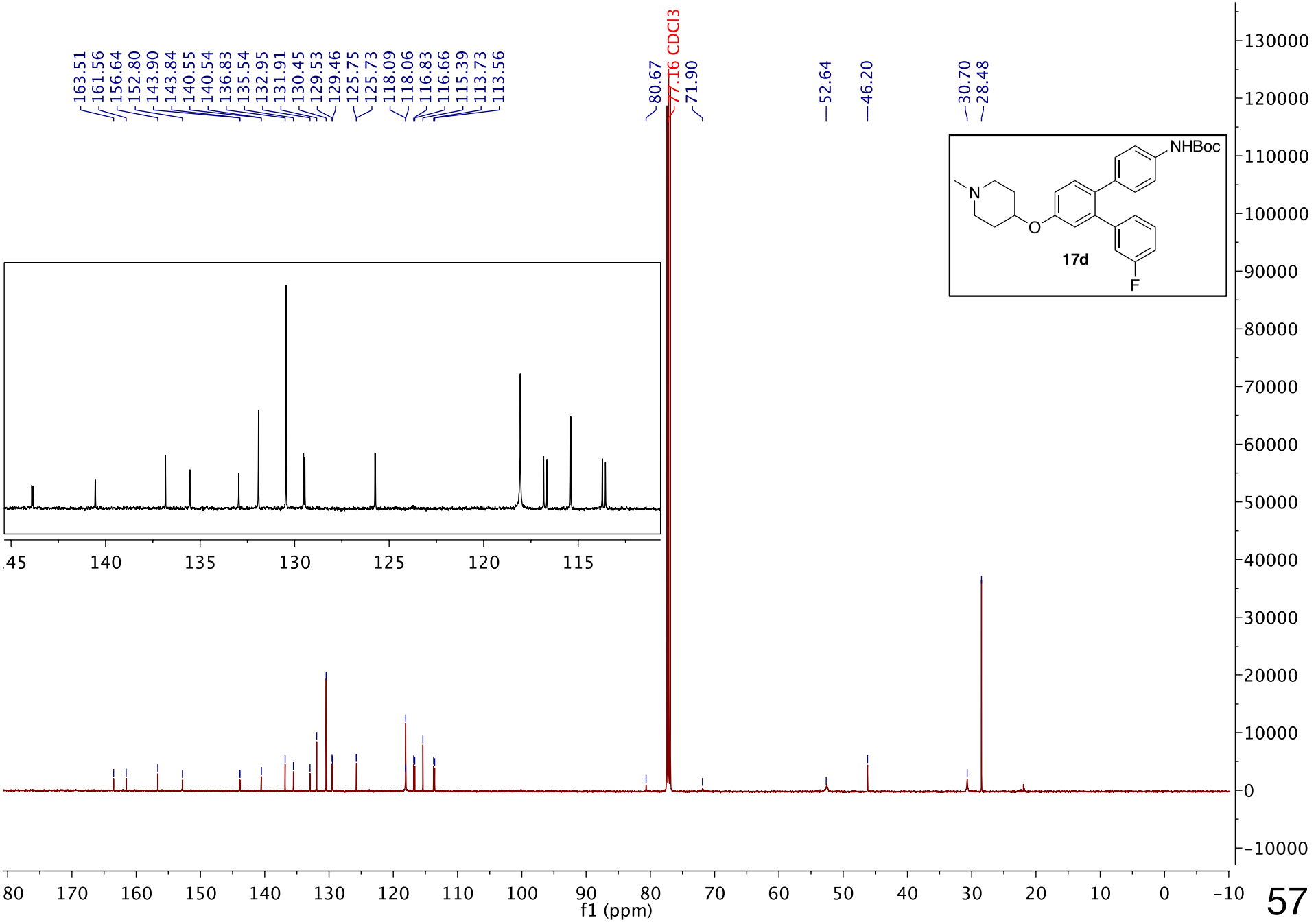
9.01
f1 (ppm)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118.06
116.83
116.66
115.39
113.73
113.56
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52.64
46.20
30.70
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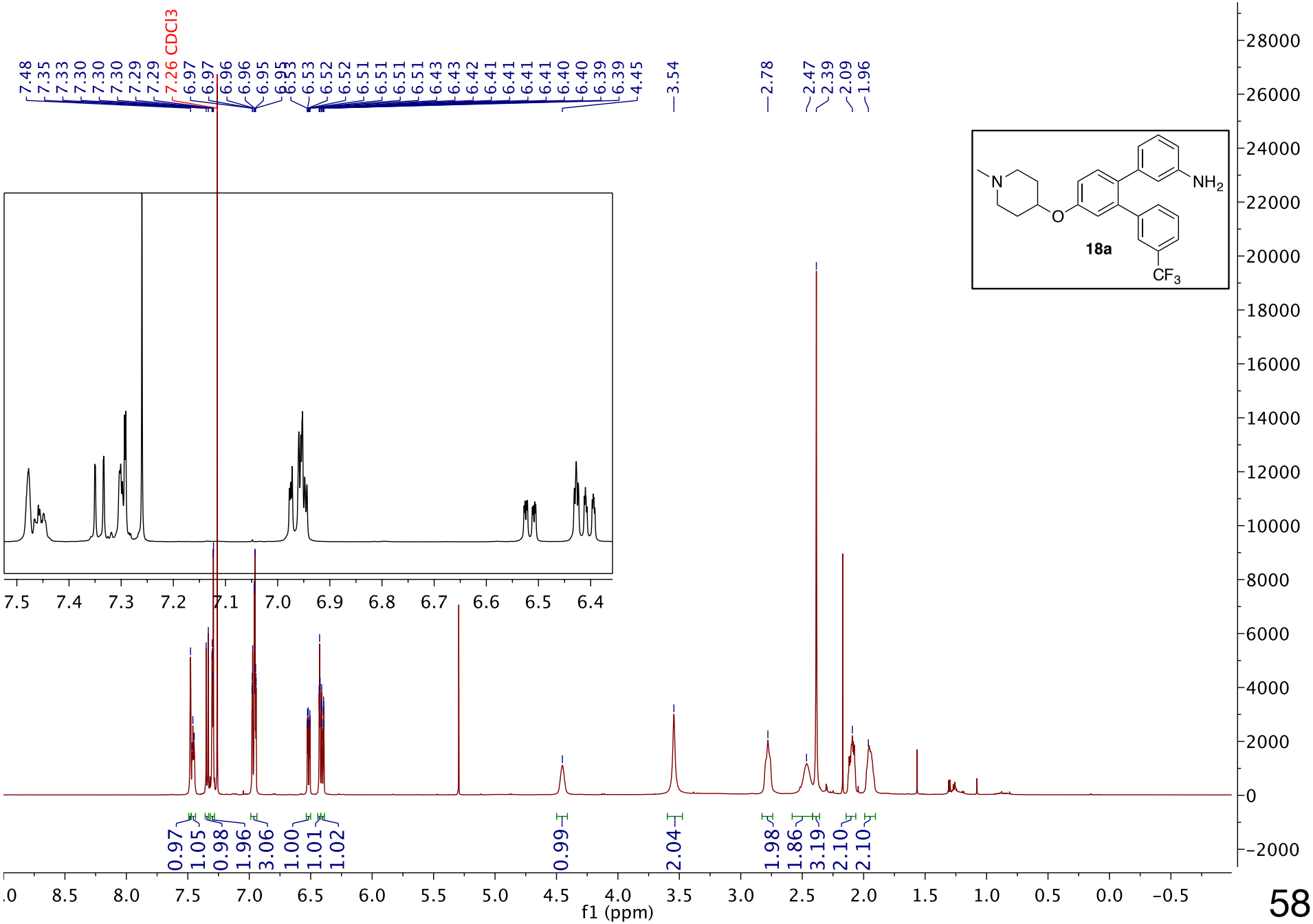
NHBoc
N
O
F
17d
f1 (ppm)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7.26 CDCl3
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18a
NH2
CF3
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O
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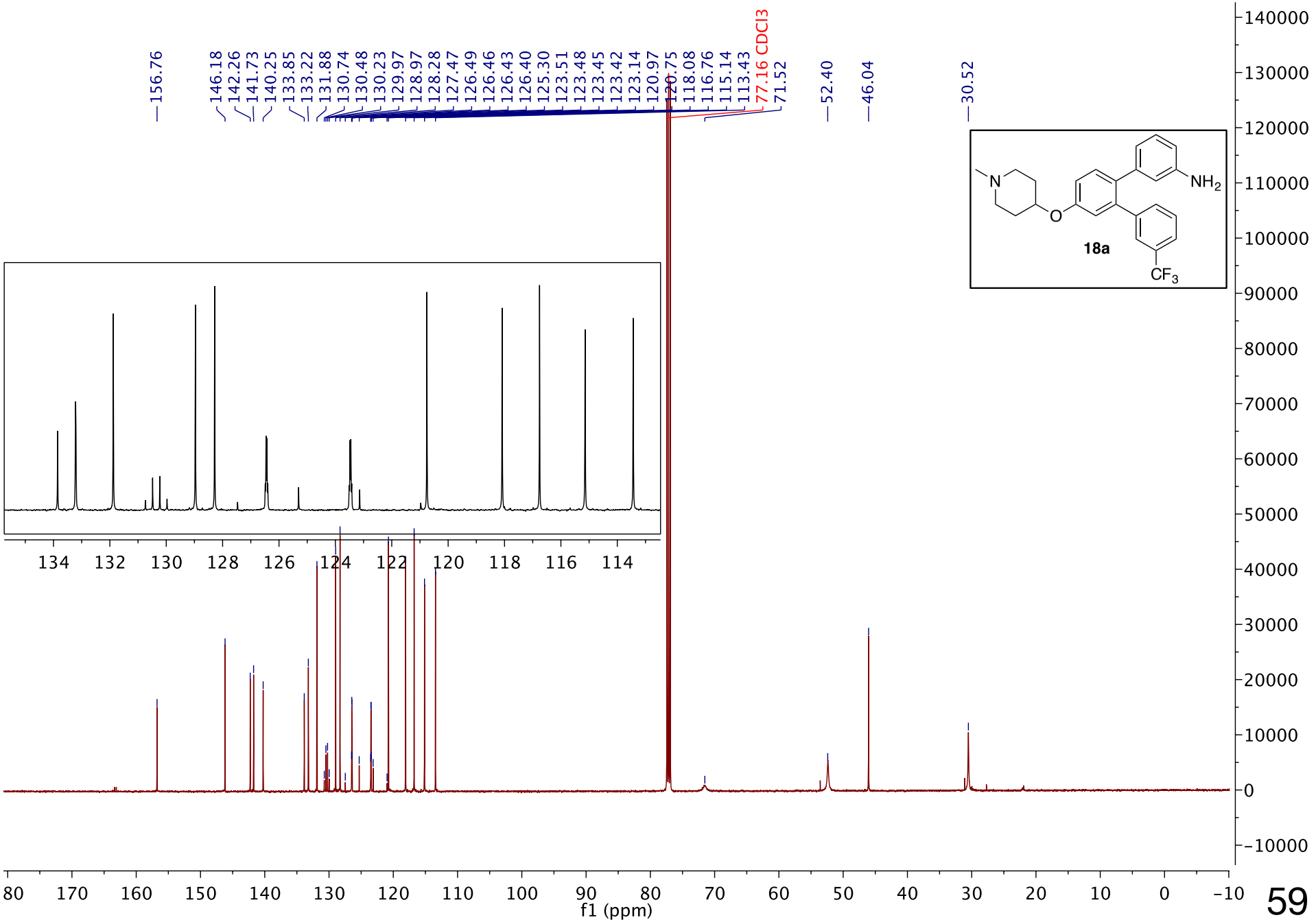
0.98
1.96
3.06
1.00
1.01
1.02
0.99
2.04
1.98
1.86
3.19
2.10
2.10
f1 (ppm)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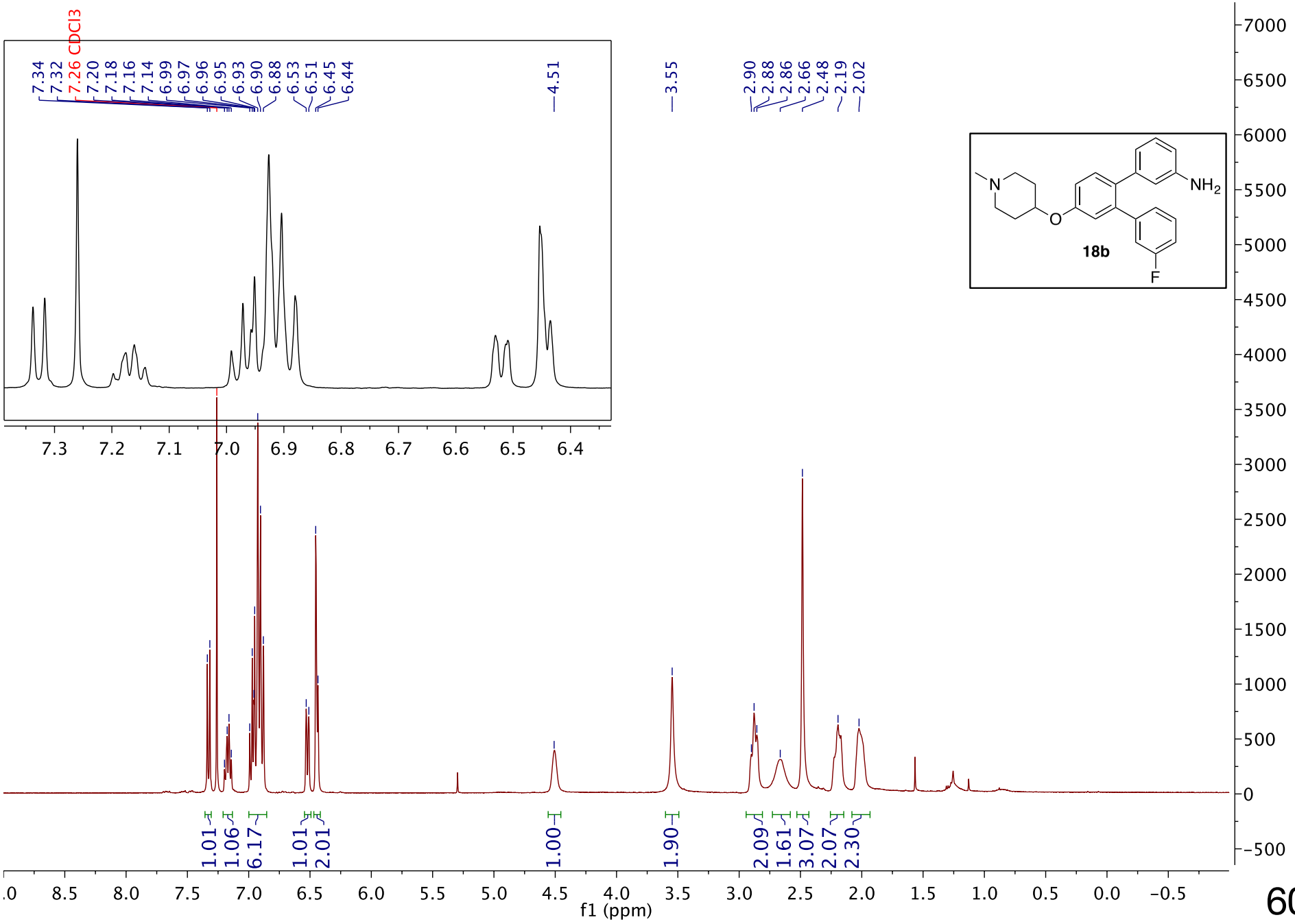
130.48
130.23
129.97
128.97
128.28
127.47
126.49
126.46
126.43
126.40
125.30
123.51
123.48
123.45
123.42
123.14
120.97
120.75
118.08
116.76
115.14
113.43
77.16 CDCl3
71.52
52.40
46.04
30.52
18a
NH2
CF3
f1 (ppm)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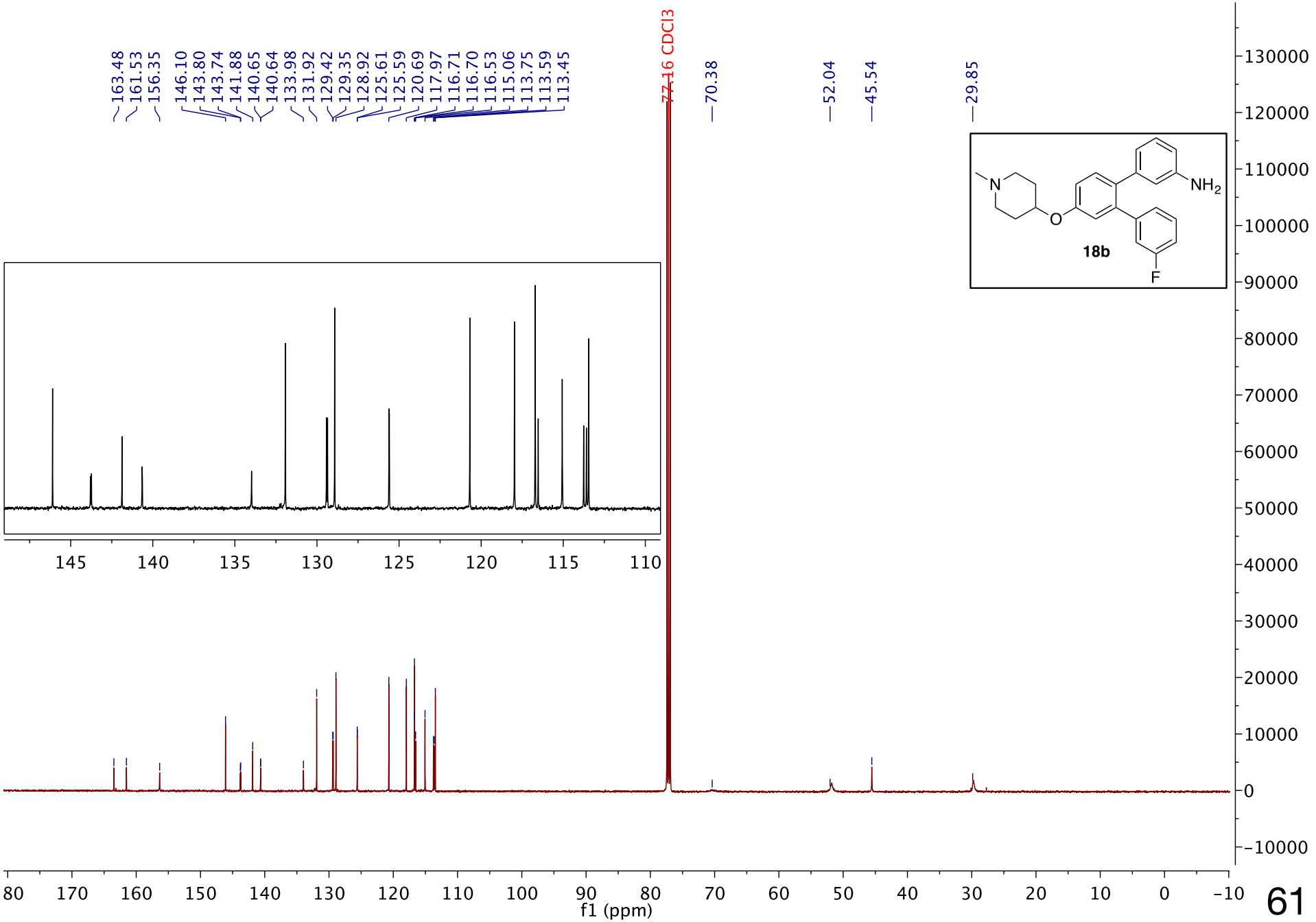
7.20
7.18
7.16
7.14
6.99
6.97
6.96
6.95
6.93
6.90
6.88
6.53
6.51
6.45
6.44
4.51
3.55
2.90
2.88
2.86
2.66
2.48
2.19
2.02
18b
NH2
N
O
F
f1 (ppm)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140.65
140.64
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131.92
129.42
129.35
128.92
125.61
125.59
120.69
117.97
116.71
116.70
116.53
115.06
113.75
113.59
113.45
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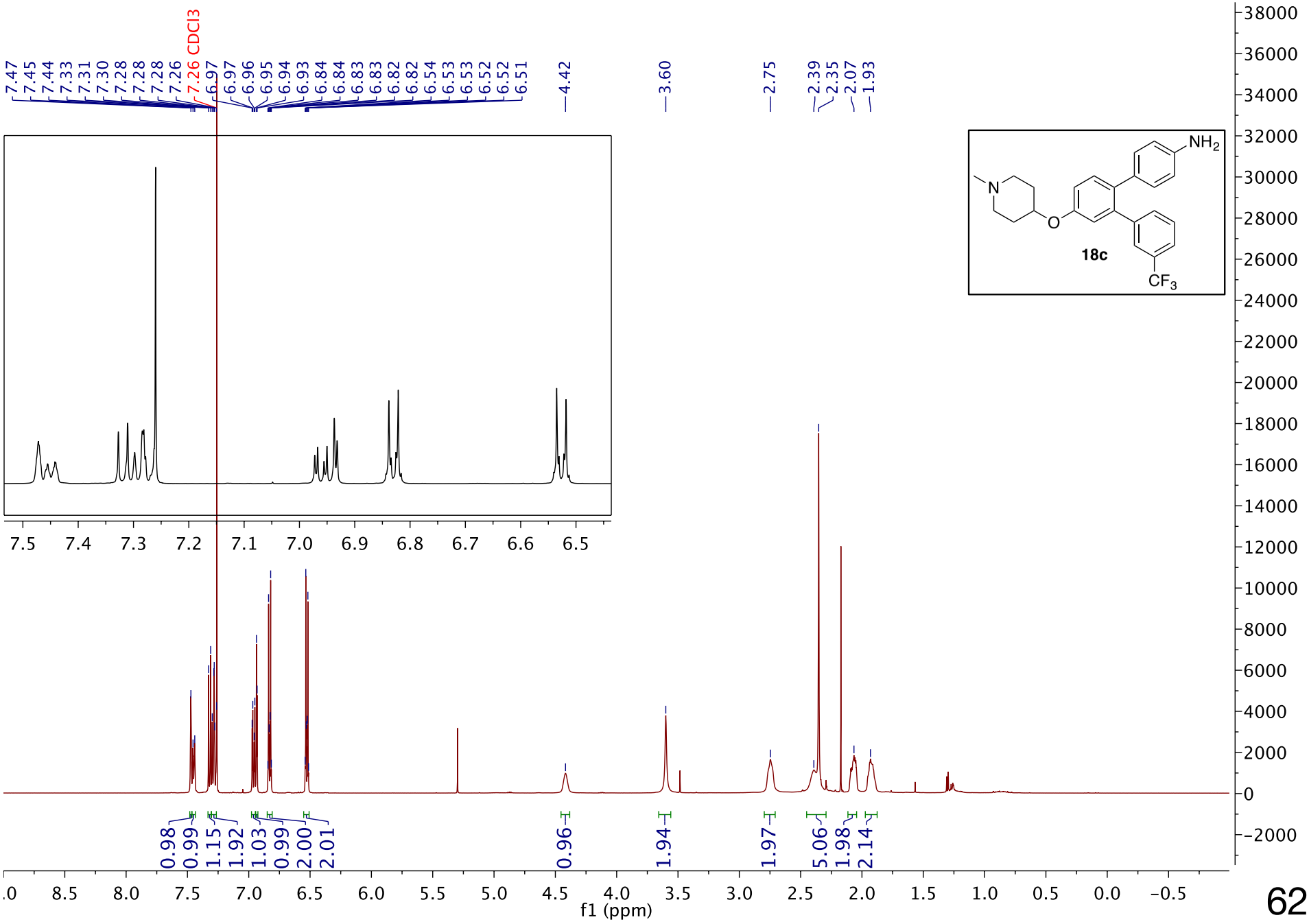
70.38
52.04
45.54
29.85
18b
NH2
N
O
F
f1 (ppm)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7.26
7.26 CDCl3
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6.97
6.96
6.95
6.94
6.93
6.84
6.84
6.83
6.83
6.82
6.82
6.54
6.53
6.53
6.52
6.52
6.51
4.42
3.60
2.75
2.39
2.35
2.07
1.93
18c
NH2
N
O
CF3
f1 (ppm)
0.98
0.99
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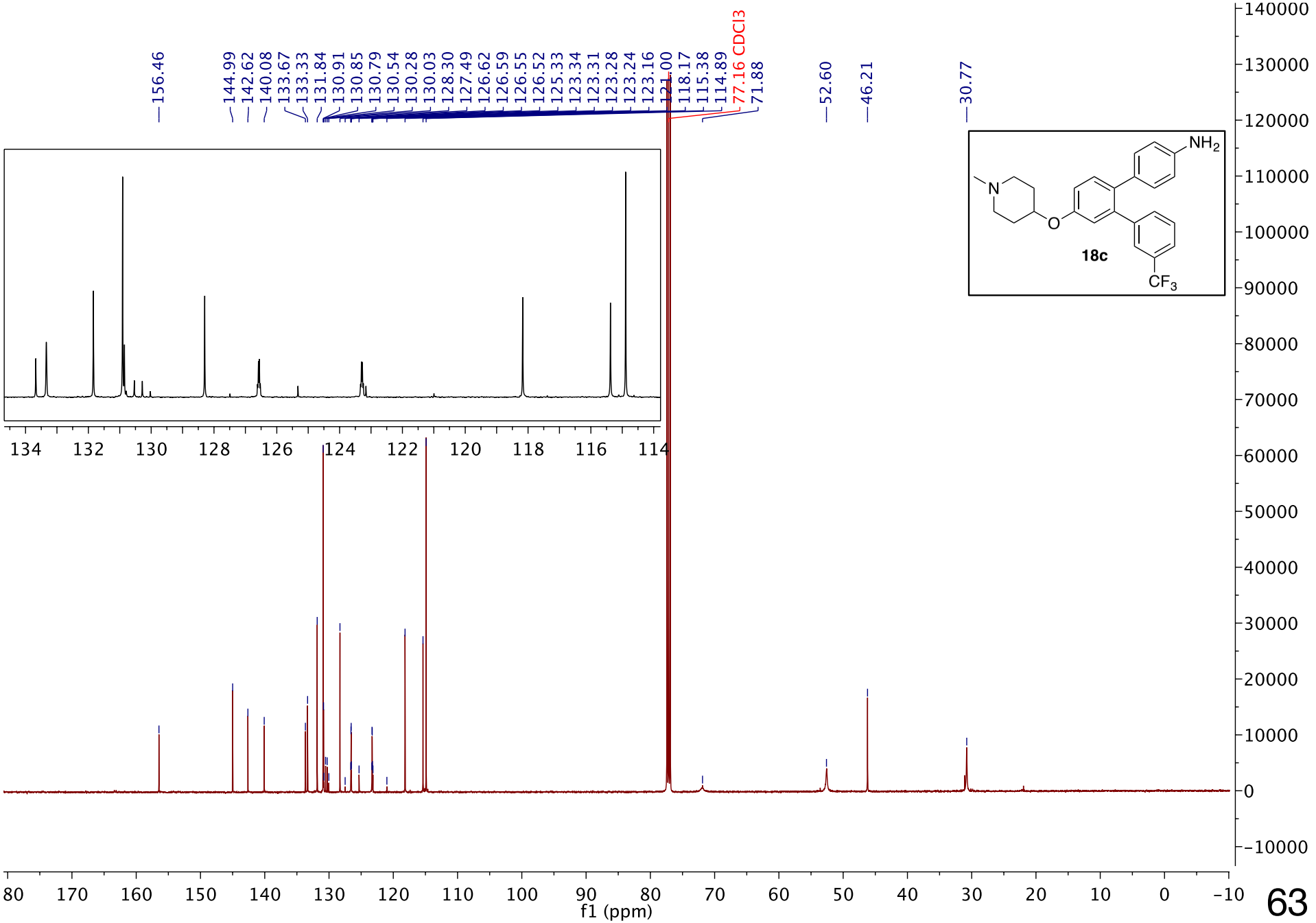
1.03
0.99
2.00
2.01
0.96
1.94
1.97
5.06
1.98
2.14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126.55
126.52
125.33
123.34
123.31
123.28
123.24
123.16
121.00
118.17
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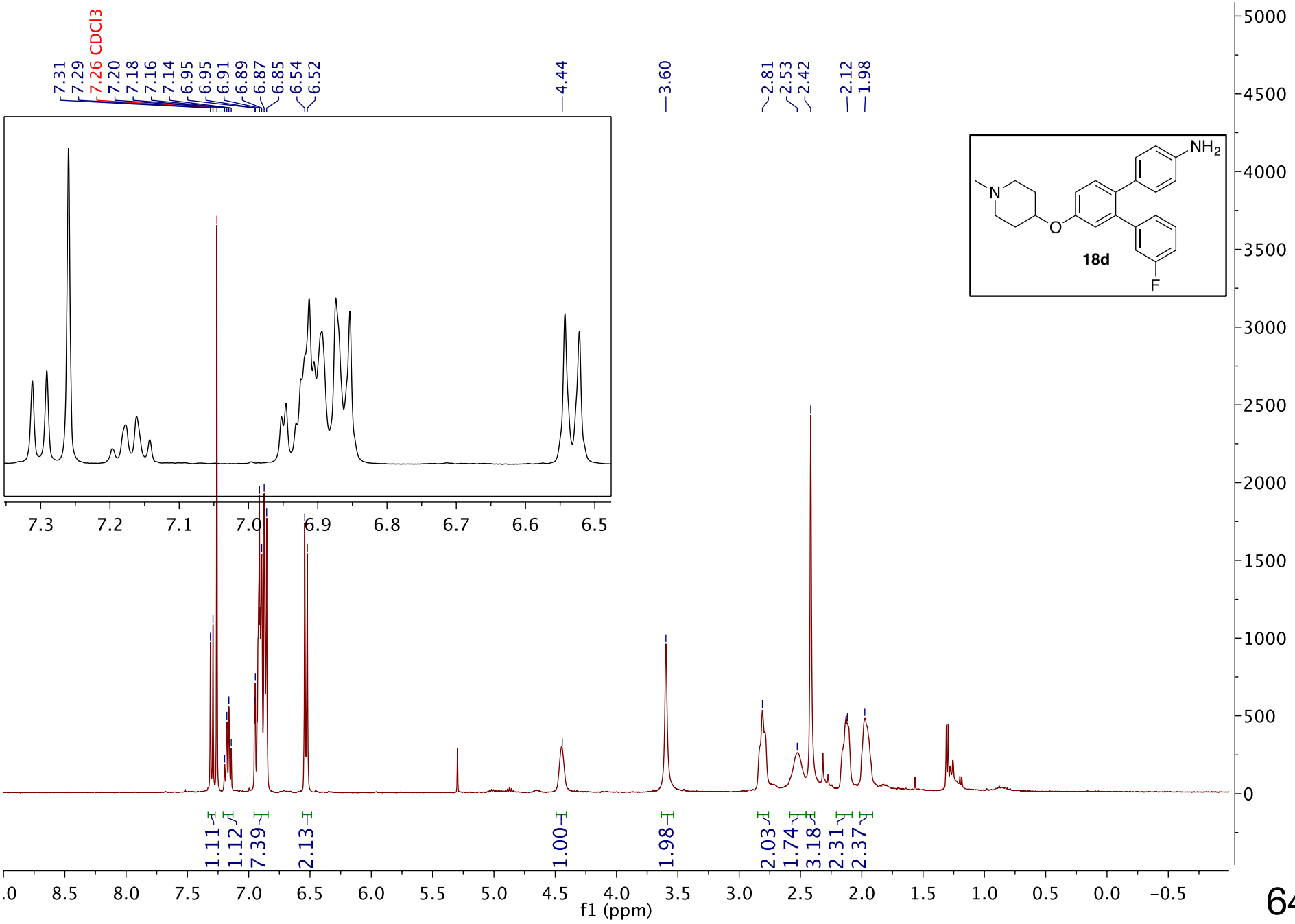
O
18c
CF3
f1 (ppm)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6.95
6.91
6.89
6.87
6.85
6.54
6.52
4.44
3.60
2.81
2.53
2.42
2.12
1.98
NH2
N
O
18d
F
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1.12
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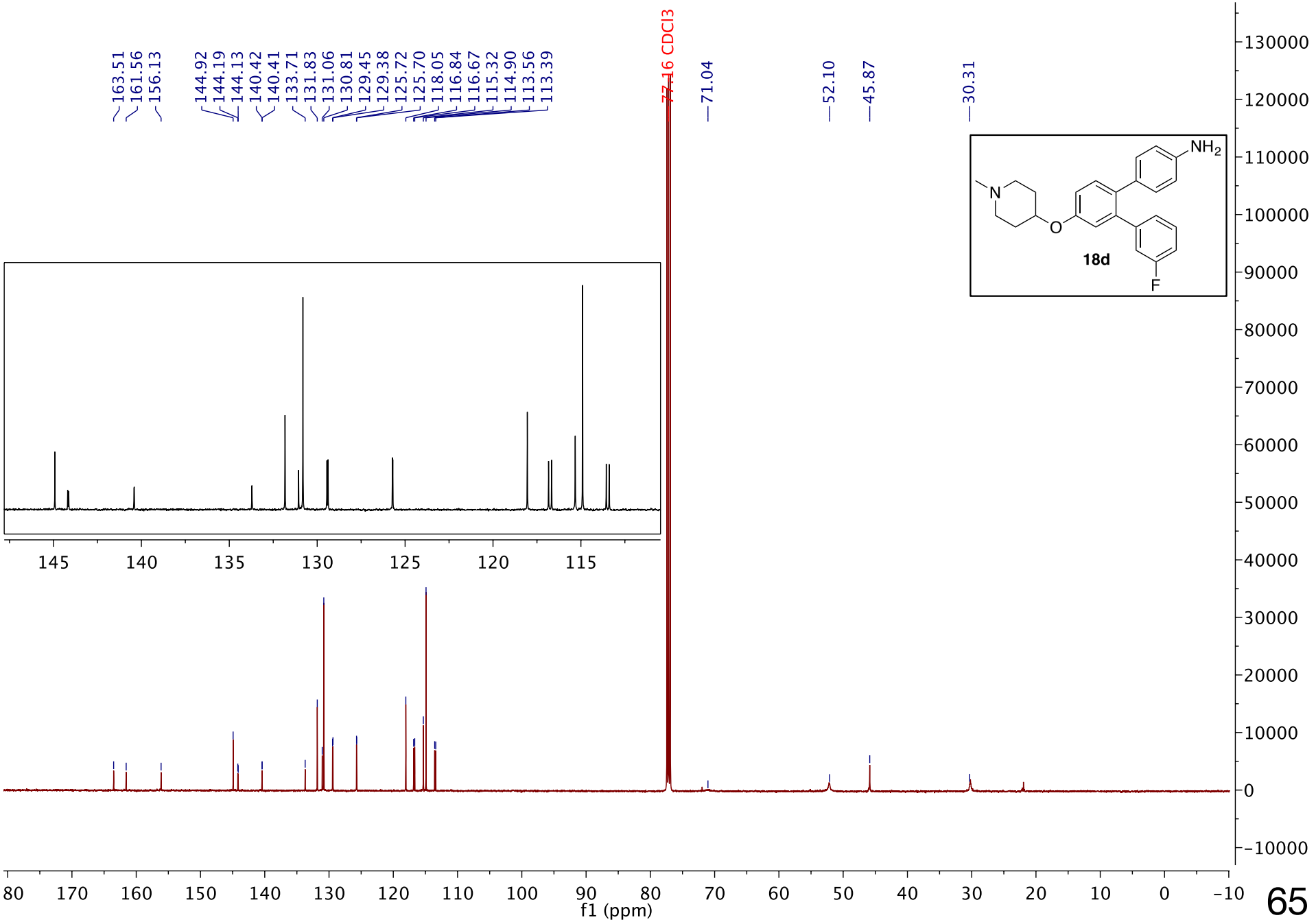
1.98
2.03
1.74
3.18
2.31
2.37
f1 (ppm)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140.41
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131.06
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129.45
129.38
125.72
125.70
118.05
116.84
116.67
115.32
114.90
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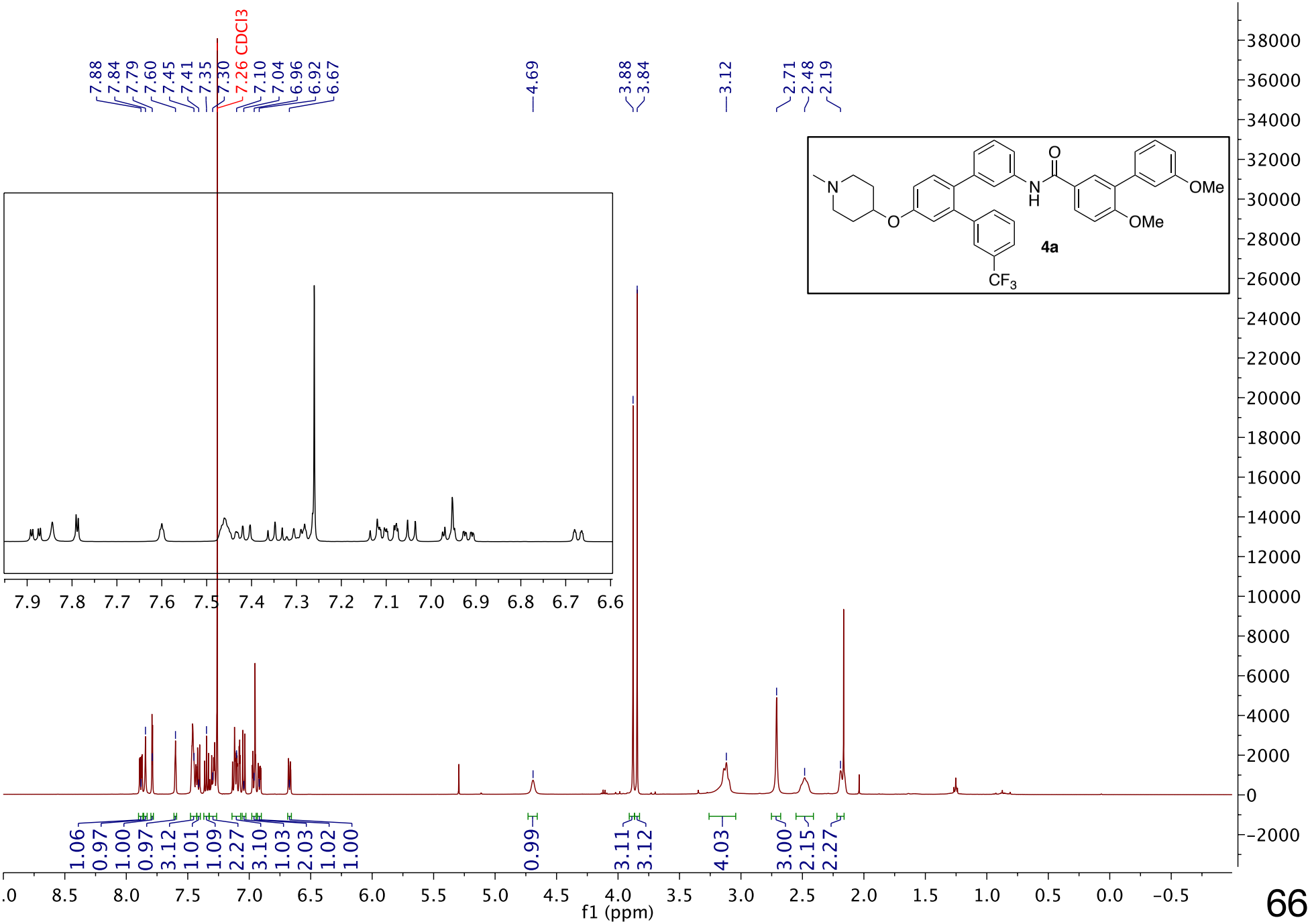
113.39
77.16 CDCl3
71.04
52.10
45.87
30.31
NH2
N
O
F
18d
f1 (ppm)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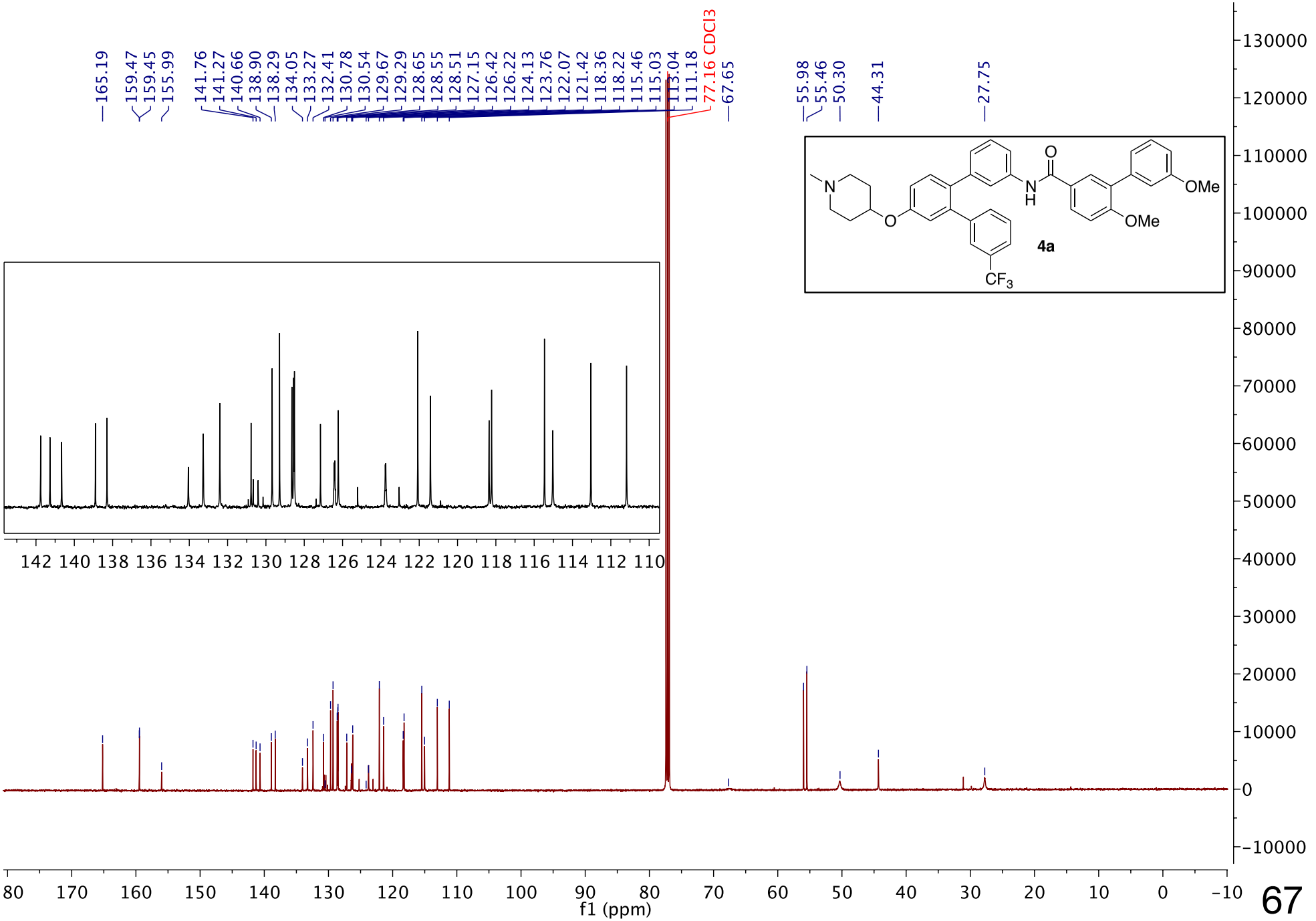
7.84
7.79
7.60
7.45
7.41
7.35
7.30
7.26 CDCl3
7.10
7.04
6.96
6.92
6.67
4.69
3.88
3.84
3.12
2.71
2.48
2.19
1.06
0.97
1.00
0.97
3.12
1.01
1.09
2.27
3.10
1.03
2.03
1.02
1.00
0.99
3.11
3.12
4.03
3.00
2.15
2.27
f1 (ppm)
4a
N
O
N
H
O
OMe
OMe
CF3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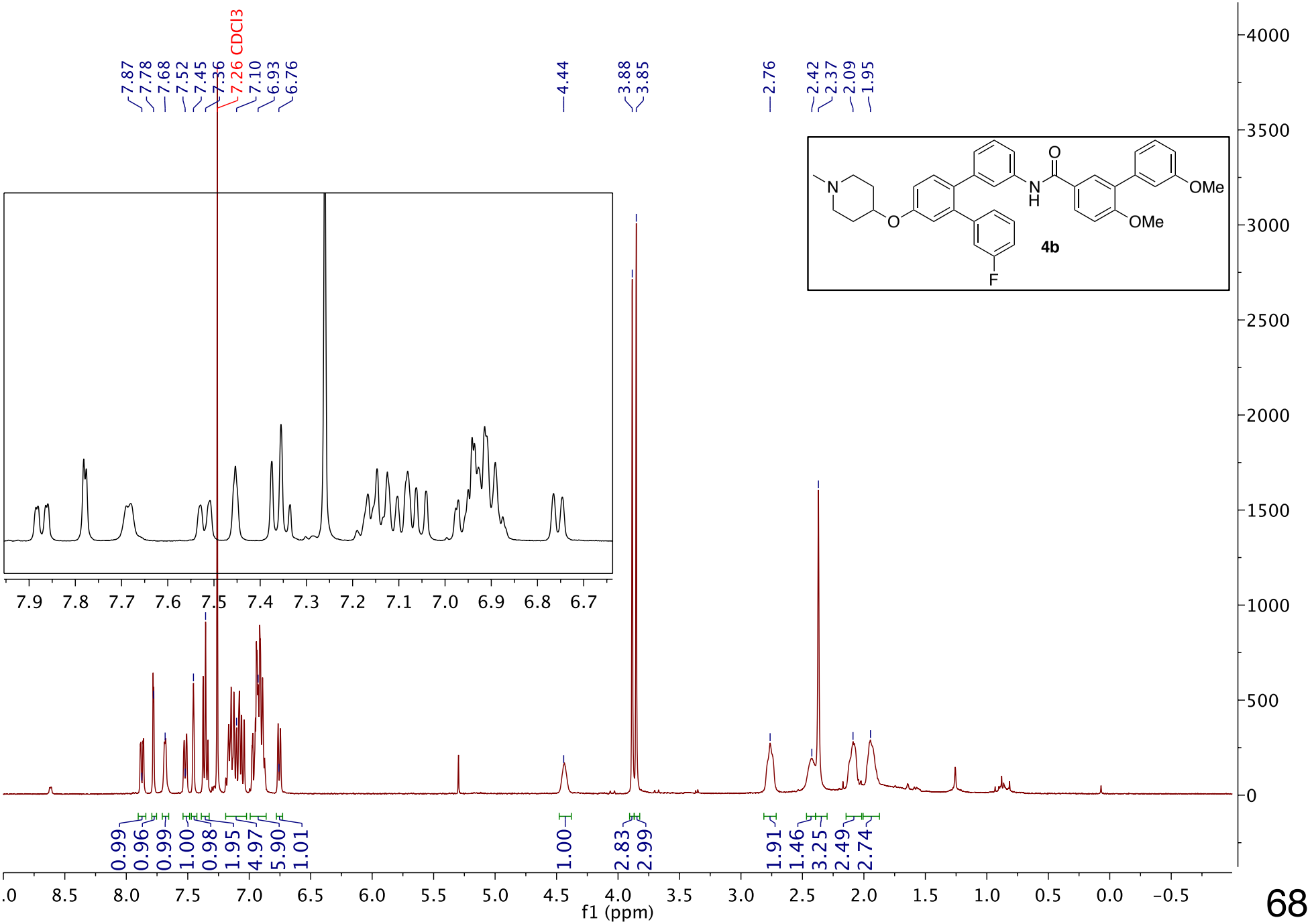
138.29
134.05
133.27
132.41
130.78
130.54
129.67
129.29
128.65
128.55
128.51
127.15
126.42
126.22
124.13
123.76
122.07
121.42
118.36
118.22
115.46
115.03
113.04
111.18
77.16 CDCl3
67.65
55.98
55.46
50.30
44.31
27.75
4a
OMe
OMe
CF3
f1 (ppm)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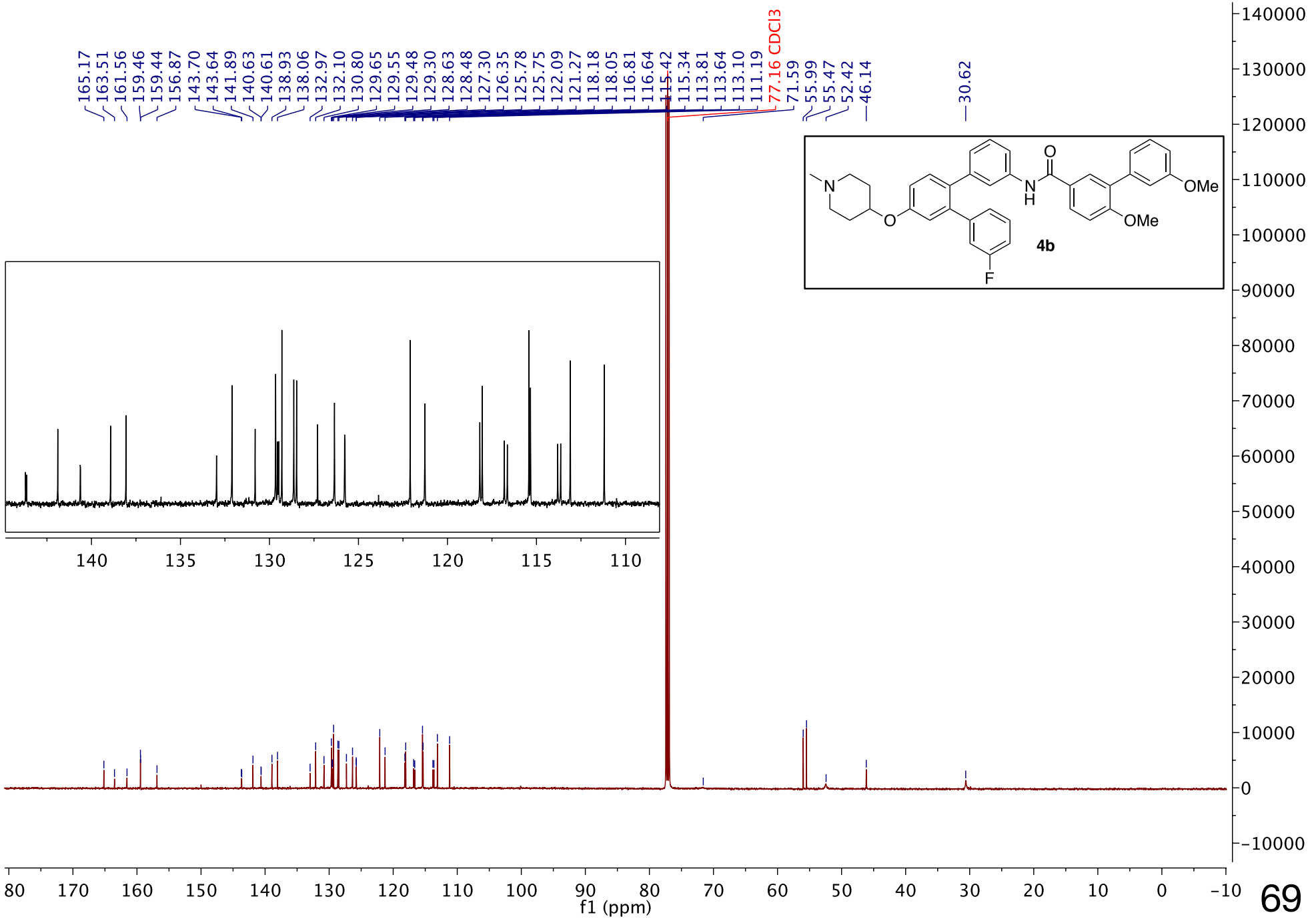
7.78
7.68
7.52
7.45
7.36
7.26 CDCl3
7.10
6.93
6.76
4.44
3.88
3.85
2.76
2.42
2.37
2.09
1.95
4b
F
O
N
H
OMe
OMe
0.99
0.96
0.99
1.00
0.98
1.95
4.97
5.90
1.01
1.00
2.83
2.99
1.91
1.46
3.25
2.49
2.74
f1 (ppm)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140.61
138.93
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132.97
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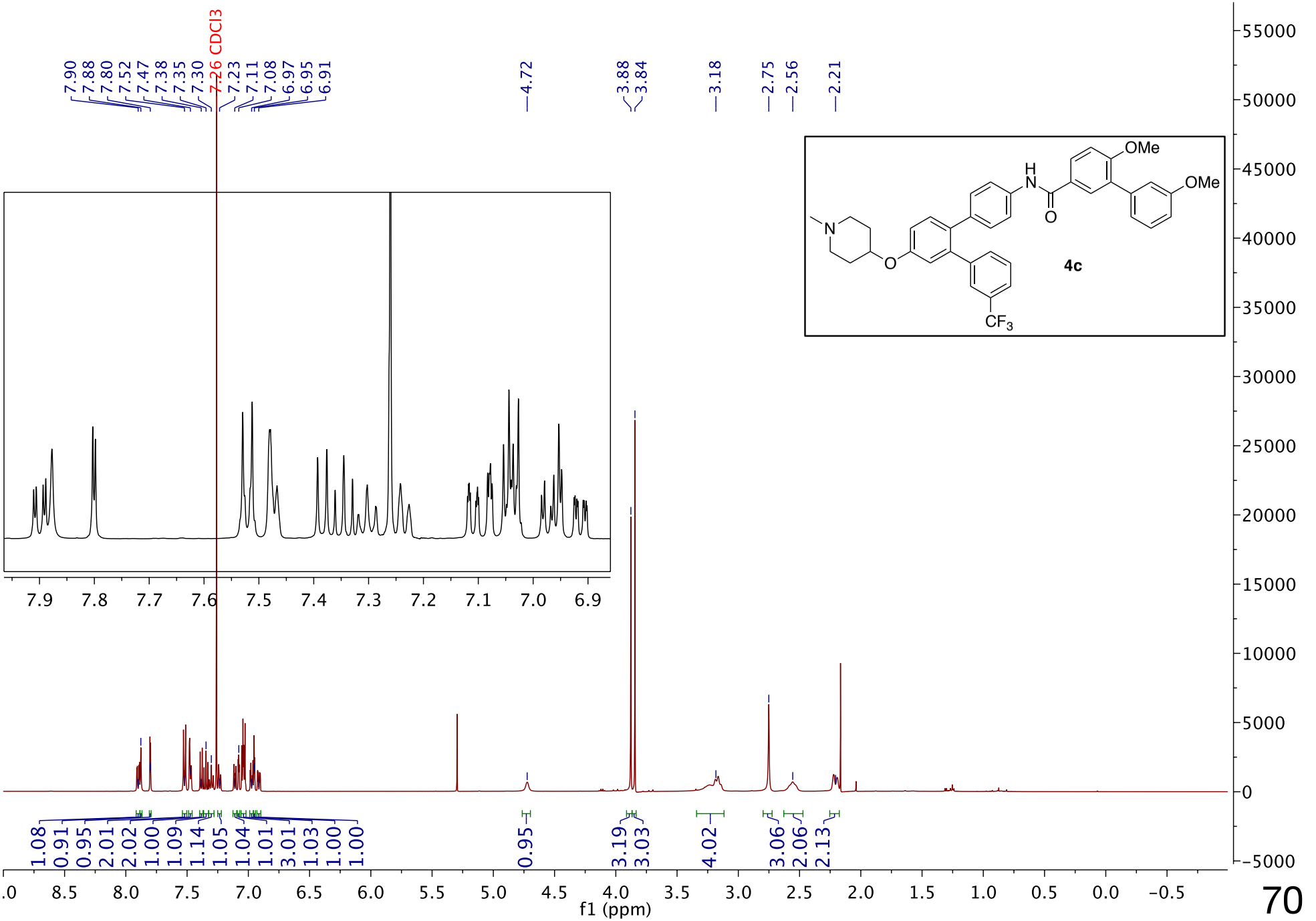
130.80
129.65
129.55
129.48
129.30
128.63
128.48
127.30
126.35
125.78
125.75
122.09
121.27
118.18
118.05
116.81
116.64
115.42
115.34
113.81
113.64
113.10
111.19
77.16 CDCl3
71.59
55.99
55.47
52.42
46.14
30.62
N
O
N
H
O
OMe
OMe
F
4b
f1 (ppm)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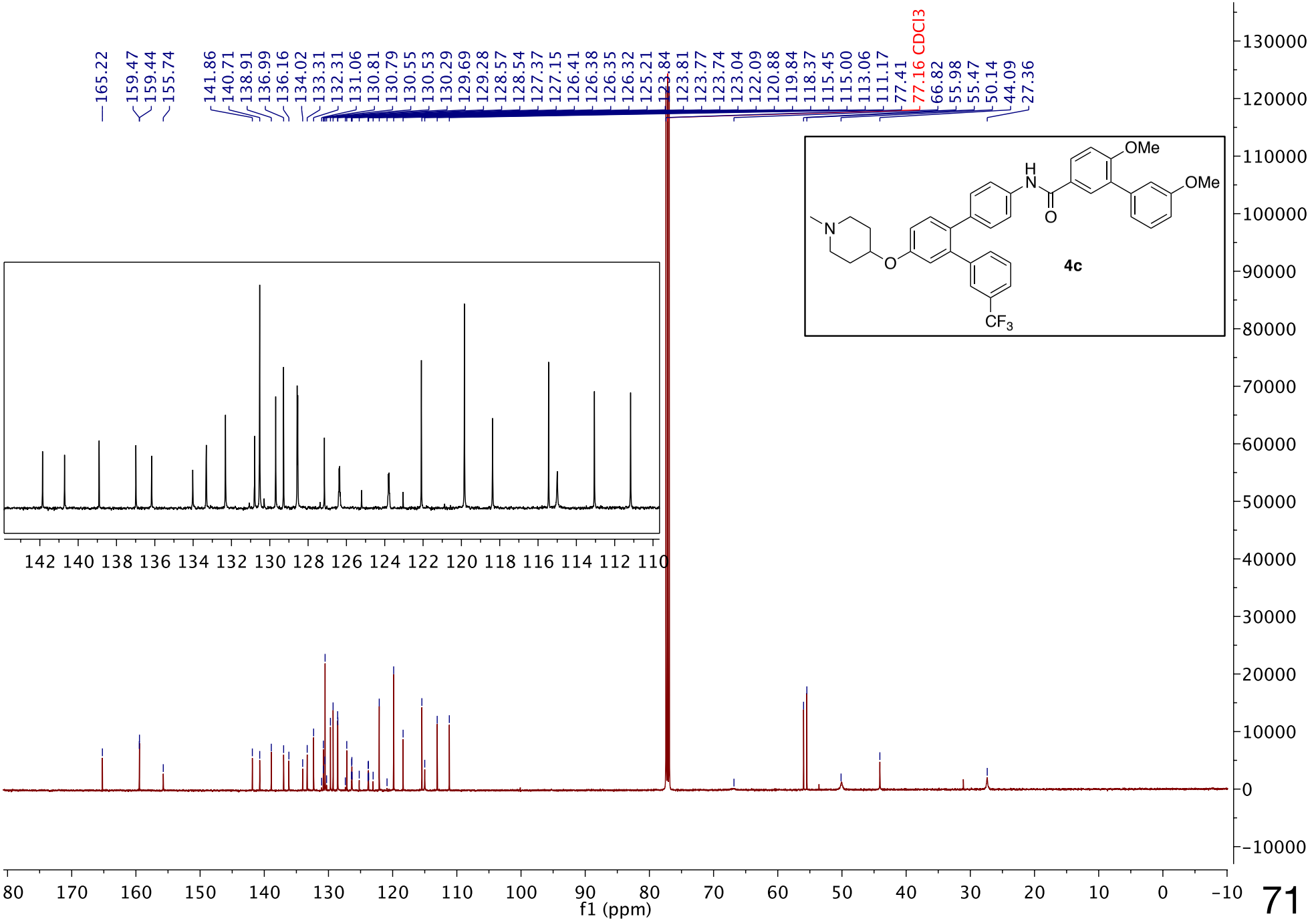
7.88
7.80
7.52
7.47
7.38
7.35
7.30
7.26 CDCl3
7.23
7.11
7.08
6.97
6.95
6.91
4.72
3.88
3.84
3.18
2.75
2.56
2.21
OMe
OMe
H
N
O
N
O
4c
CF3
1.08
0.91
0.95
2.01
2.02
1.00
1.09
1.14
1.05
1.04
1.01
3.01
1.03
1.00
1.00
0.95
3.19
3.03
4.02
3.06
2.06
2.13
f1 (ppm)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132.31
131.06
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130.79
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130.53
130.29
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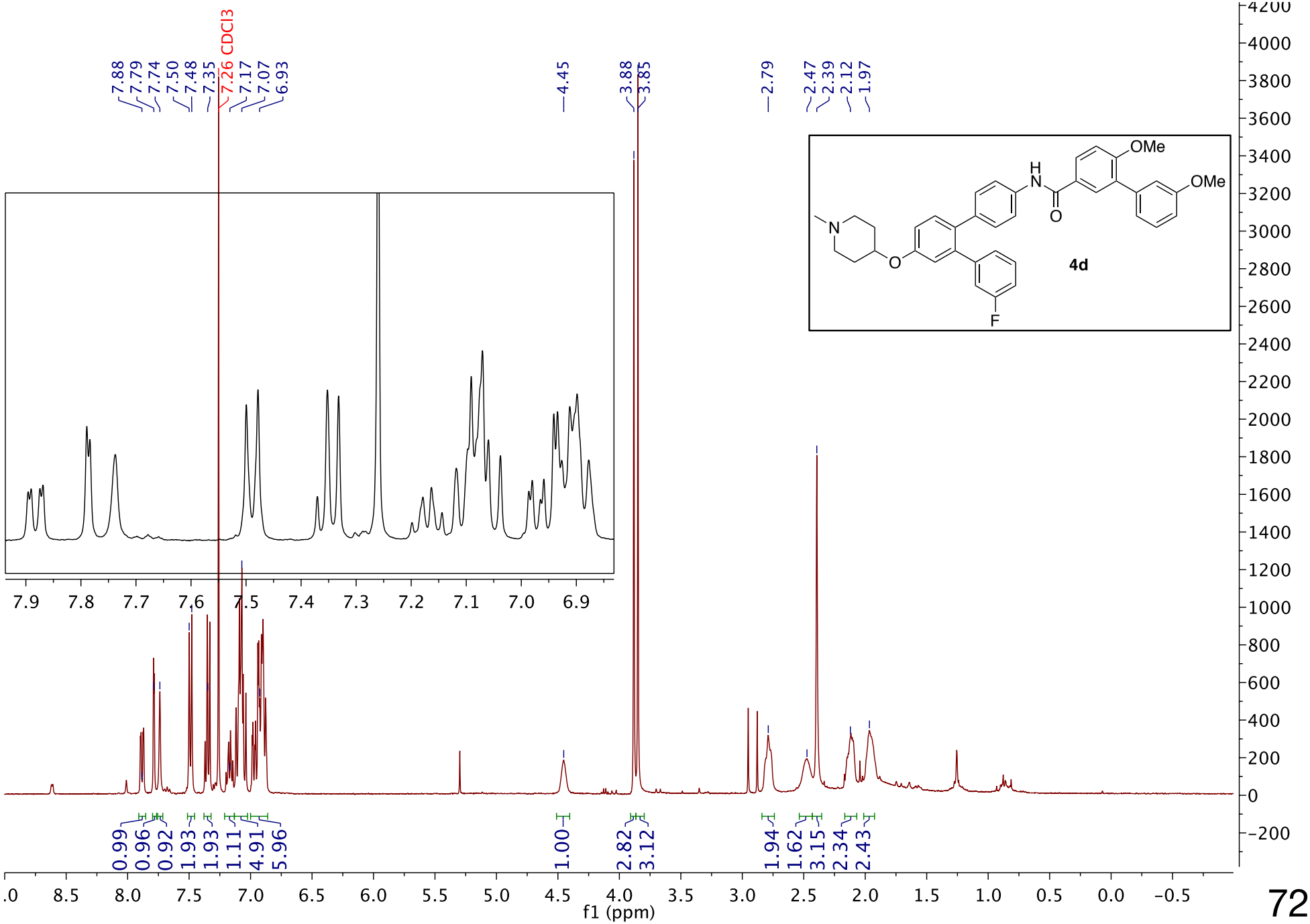
129.28
128.57
128.54
127.37
127.15
126.41
126.38
126.35
126.32
125.21
123.84
123.81
123.77
123.74
123.04
122.09
120.88
119.84
118.37
115.45
115.00
113.06
111.17
77.41
77.16 CDCl3
66.82
55.98
55.47
50.14
44.09
27.36
OMe
OMe
H
N
O
N
O
4c
CF3
142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112 110
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.35
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7.17
7.07
6.93
4.45
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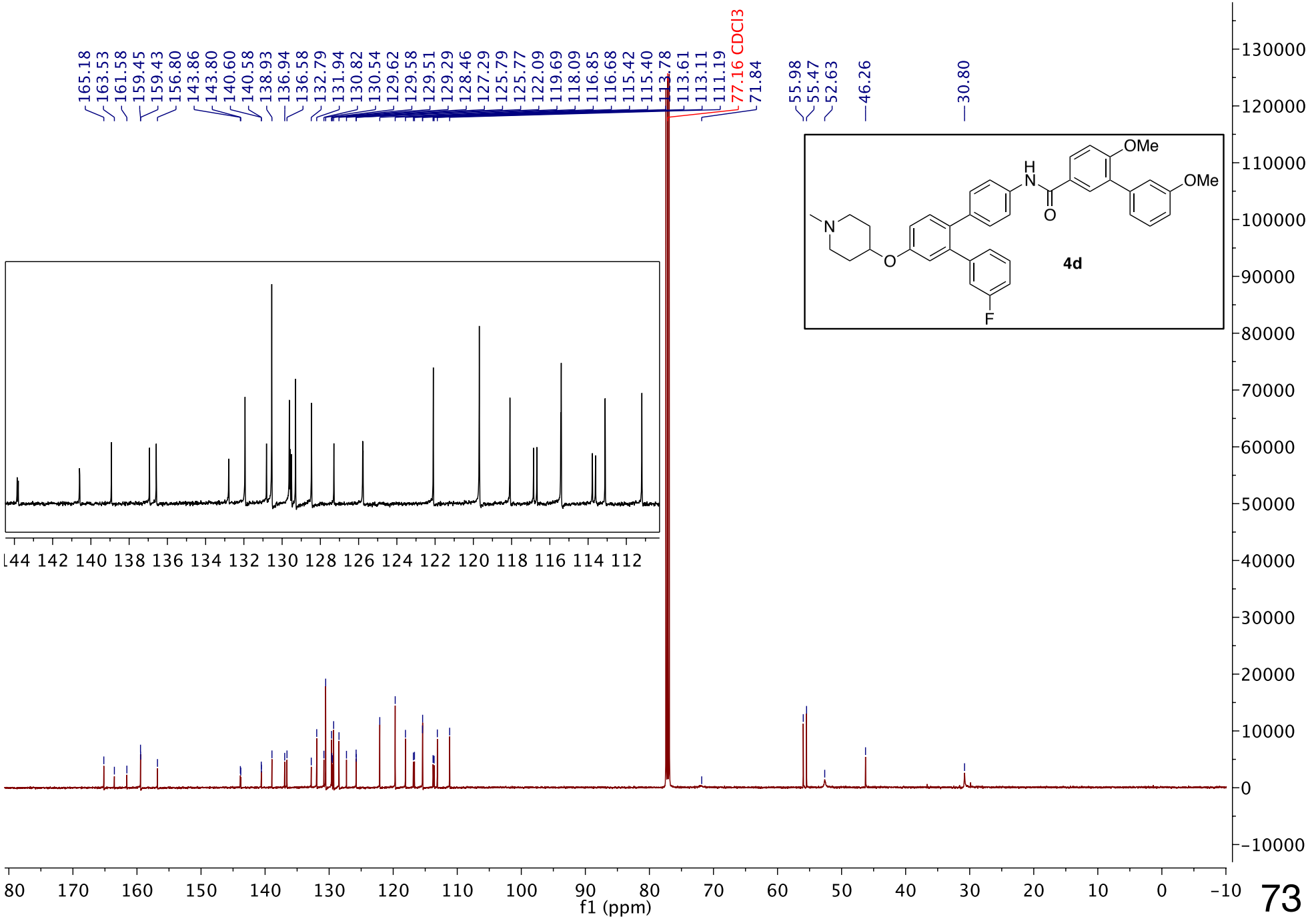
3.85
2.79
2.47
2.39
2.12
1.97
OMe
OMe
H
N
O
N
O
F
4d
0.99
0.96
0.92
1.93
1.93
1.11
4.91
5.96
1.00
2.82
3.12
1.94
1.62
3.15
2.34
2.43
f1 (ppm)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138.93
136.94
136.58
132.79
131.94
130.82
130.54
129.62
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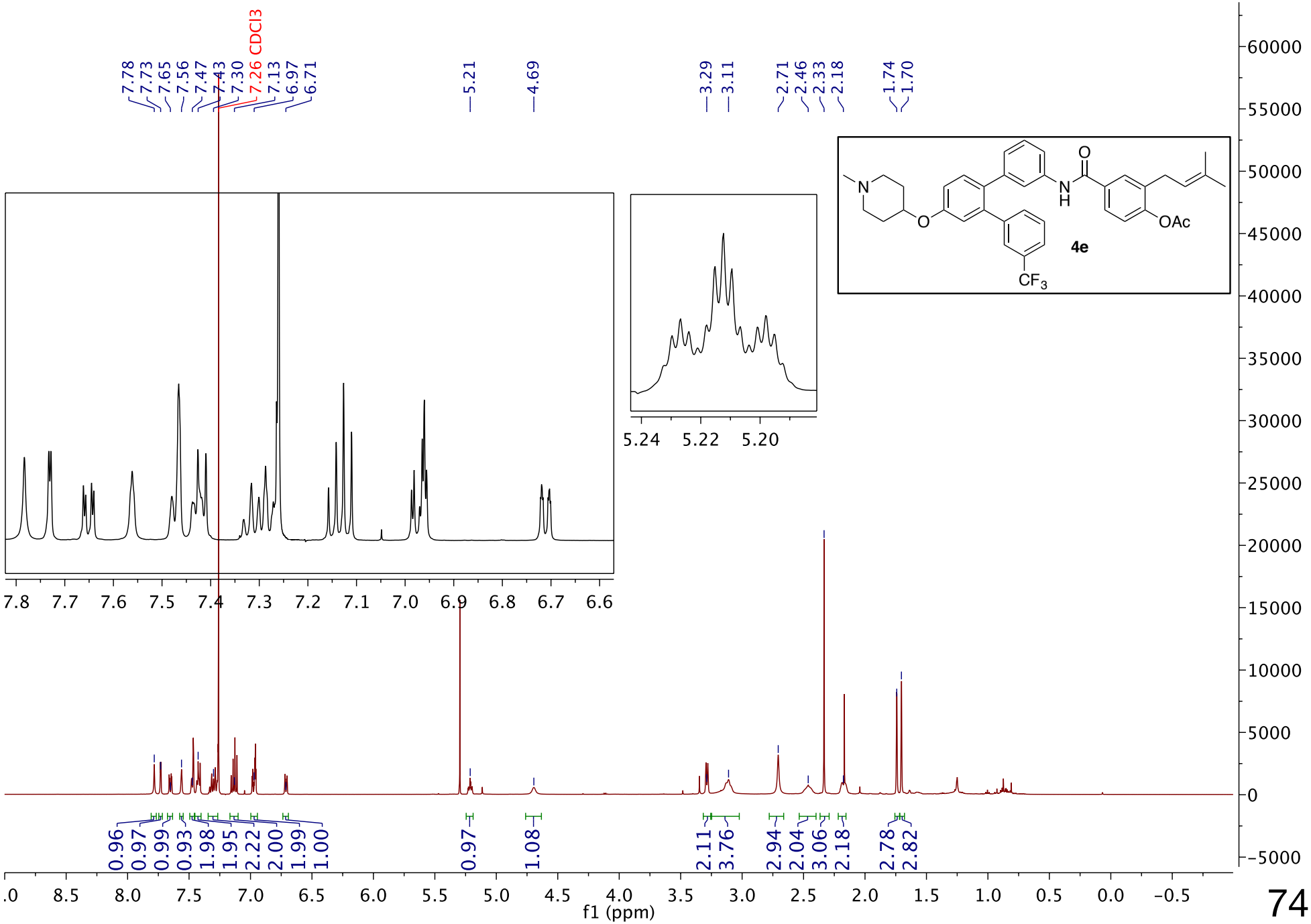
125.79
125.77
122.09
119.69
118.09
116.85
116.68
115.42
115.40
113.78
113.61
113.11
111.19
77.16 CDCl3
71.84
55.98
55.47
52.63
46.26
30.80
OMe
OMe
H
N
O
N
O
F
4d
144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000
80 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)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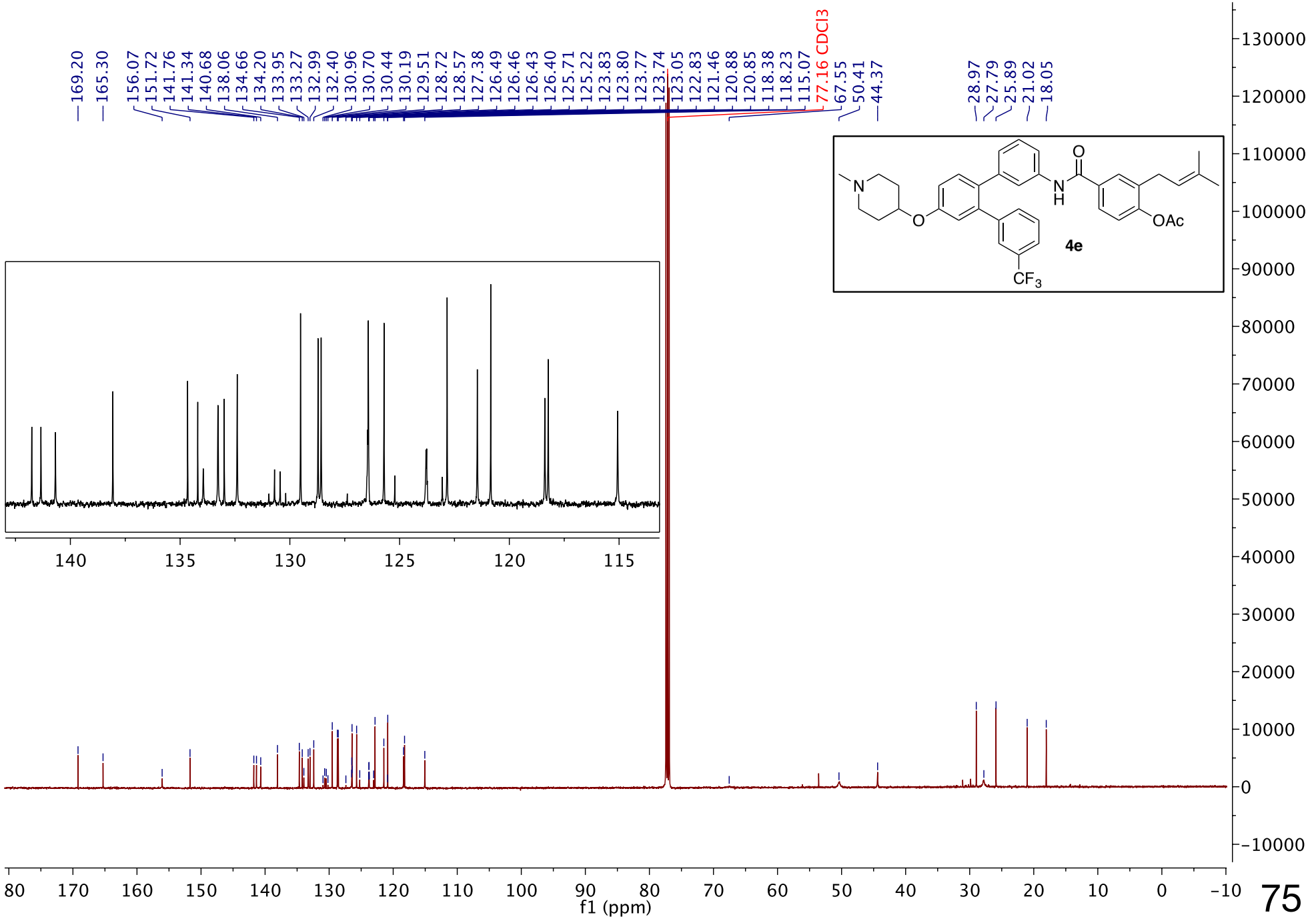
7.43
7.30
7.26 CDCl3
7.13
6.97
6.71
5.21
4.69
3.29
3.11
2.71
2.46
2.33
2.18
1.74
1.70
4e
O
N
H
N
O
OAc
CF3
5.24 5.22 5.20
7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6
0.96 0.97 0.99 0.93 1.98 1.95 2.22 2.00 1.99 1.00
0.97 1.08
2.11 3.76 2.94 2.04 3.06 2.18 2.78 2.82
f1 (ppm)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133.27
132.99
132.40
130.96
130.70
130.44
130.19
129.51
128.72
128.57
127.38
126.49
126.46
126.43
126.40
125.71
125.22
123.83
123.80
123.77
123.74
123.05
122.83
121.46
120.88
120.85
118.38
118.23
115.07
77.16 CDCl3
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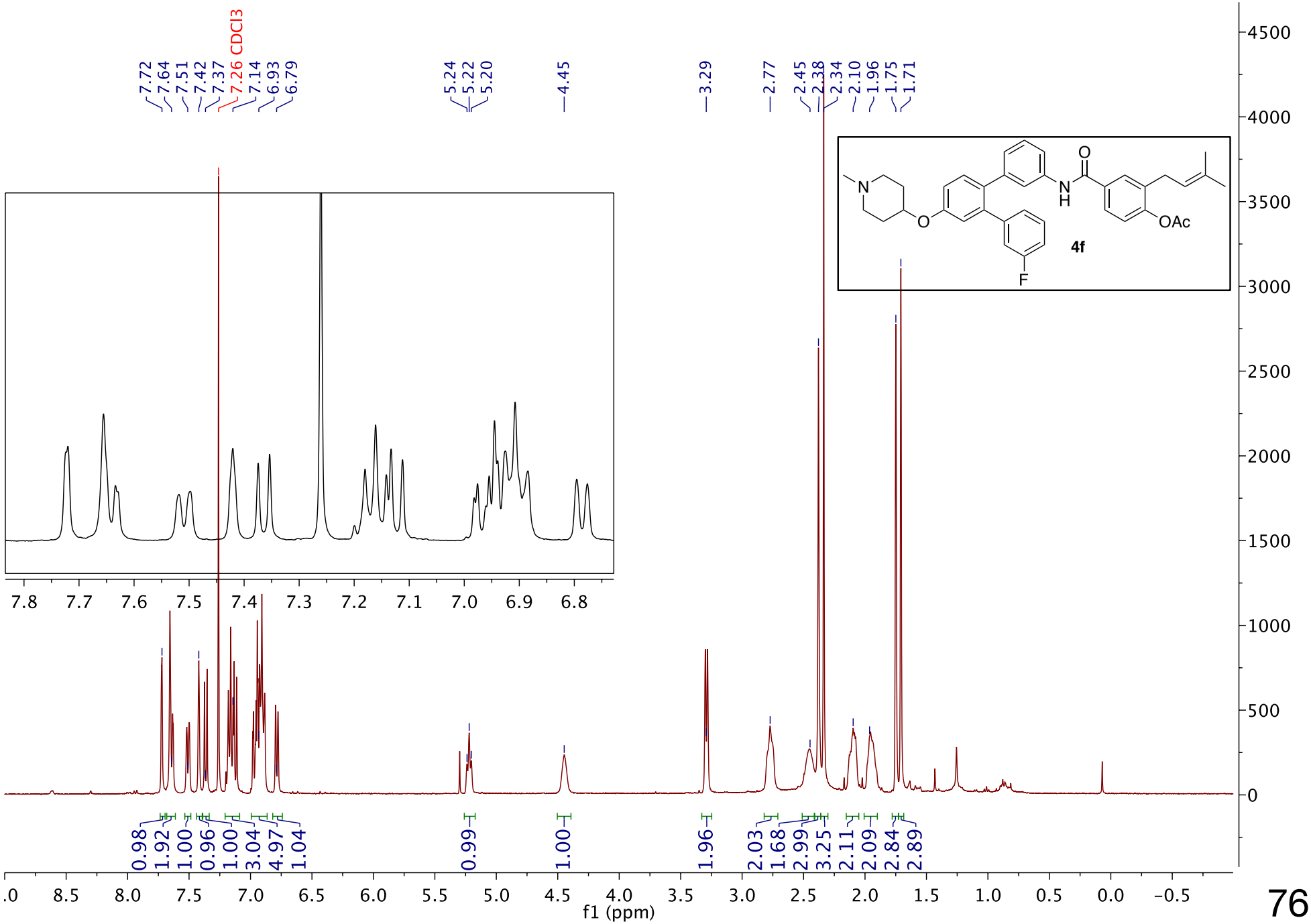
50.41
44.37
28.97
27.79
25.89
21.02
18.05
4e
f1 (ppm)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6.79
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5.20
4.45
3.29
2.77
2.45
2.38
2.34
2.10
1.96
1.75
1.71
4f
F
O
N
H
OAc
0.98
1.92
1.00
0.96
1.00
3.04
4.97
1.04
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1.00
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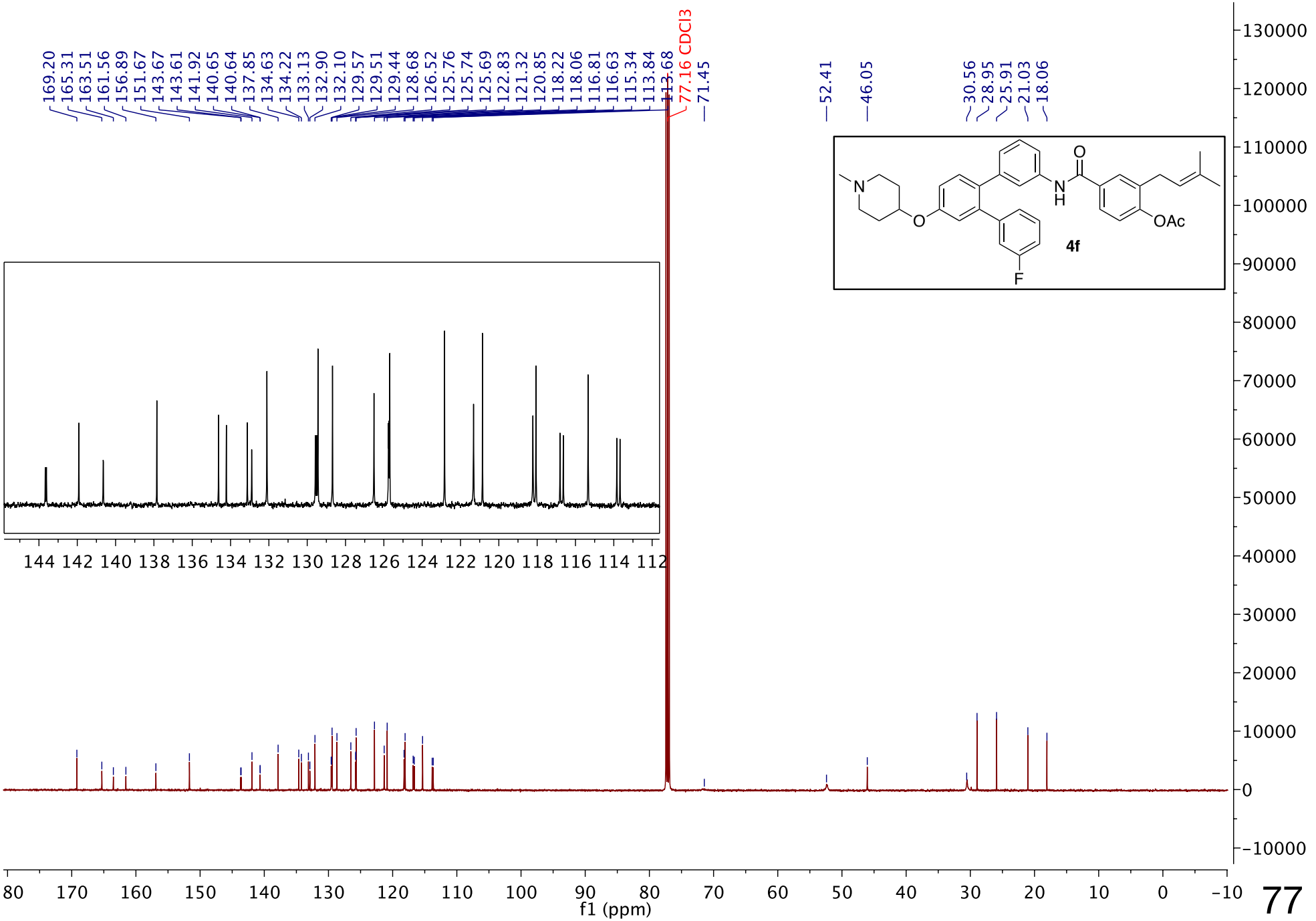
2.03
1.68
2.99
3.25
2.11
2.09
2.84
2.89
f1 (ppm)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137.85
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133.13
132.90
132.10
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129.51
129.44
128.68
126.52
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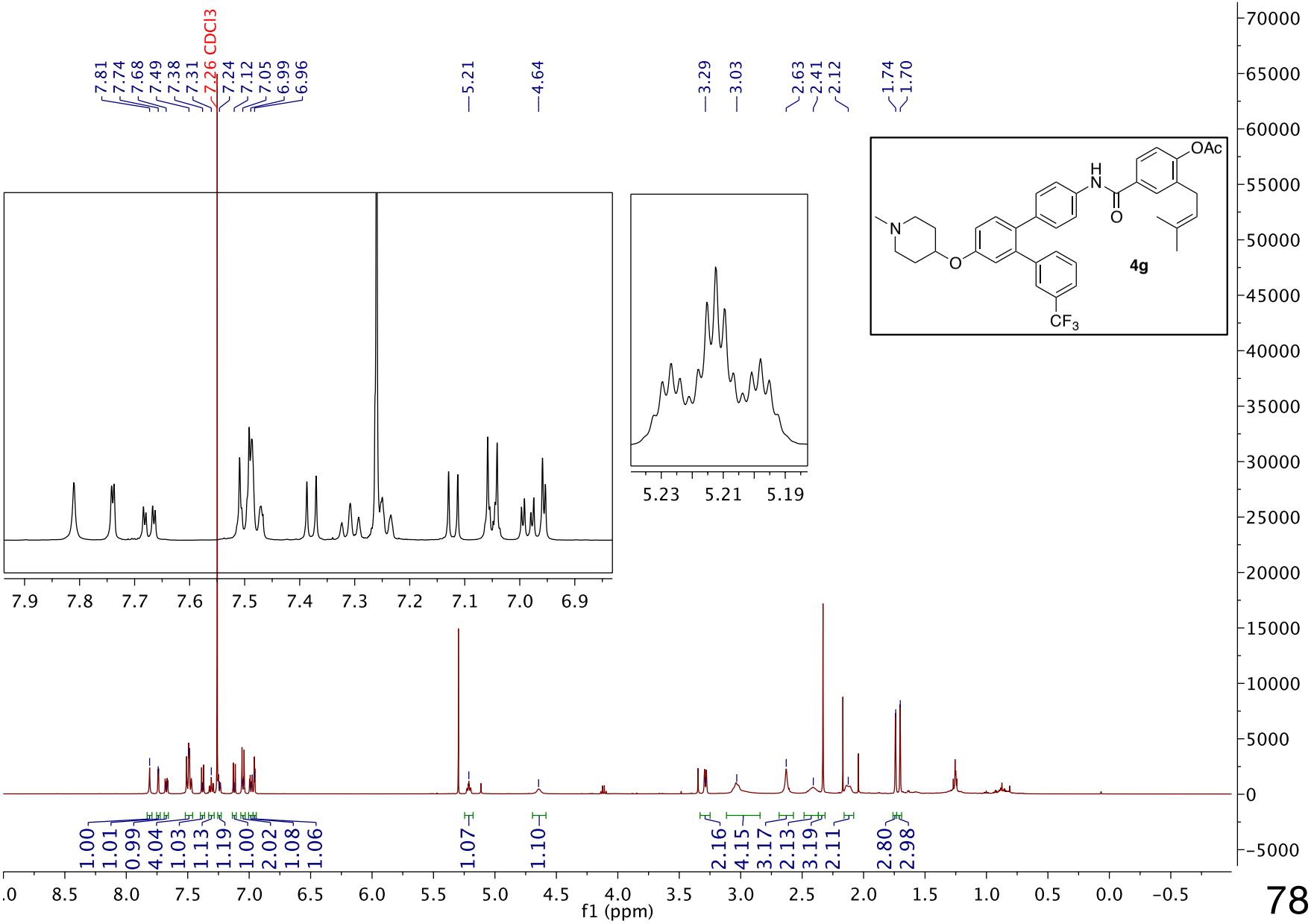
125.74
125.69
122.83
121.32
120.85
118.22
118.06
116.81
116.63
115.34
113.84
113.68
77.16 CDCl3
71.45
52.41
46.05
30.56
28.95
25.91
21.03
18.06
4f
144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112
f1 (ppm)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7.31
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7.24
7.12
7.05
6.99
6.96
5.21
4.64
3.29
3.03
2.63
2.41
2.12
1.74
1.70
OAc
N
H
O
N
O
CF3
4g
5.23
5.21
5.19
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
1.00
1.01
0.99
4.04
1.03
1.13
1.19
1.00
2.02
1.08
1.06
1.07
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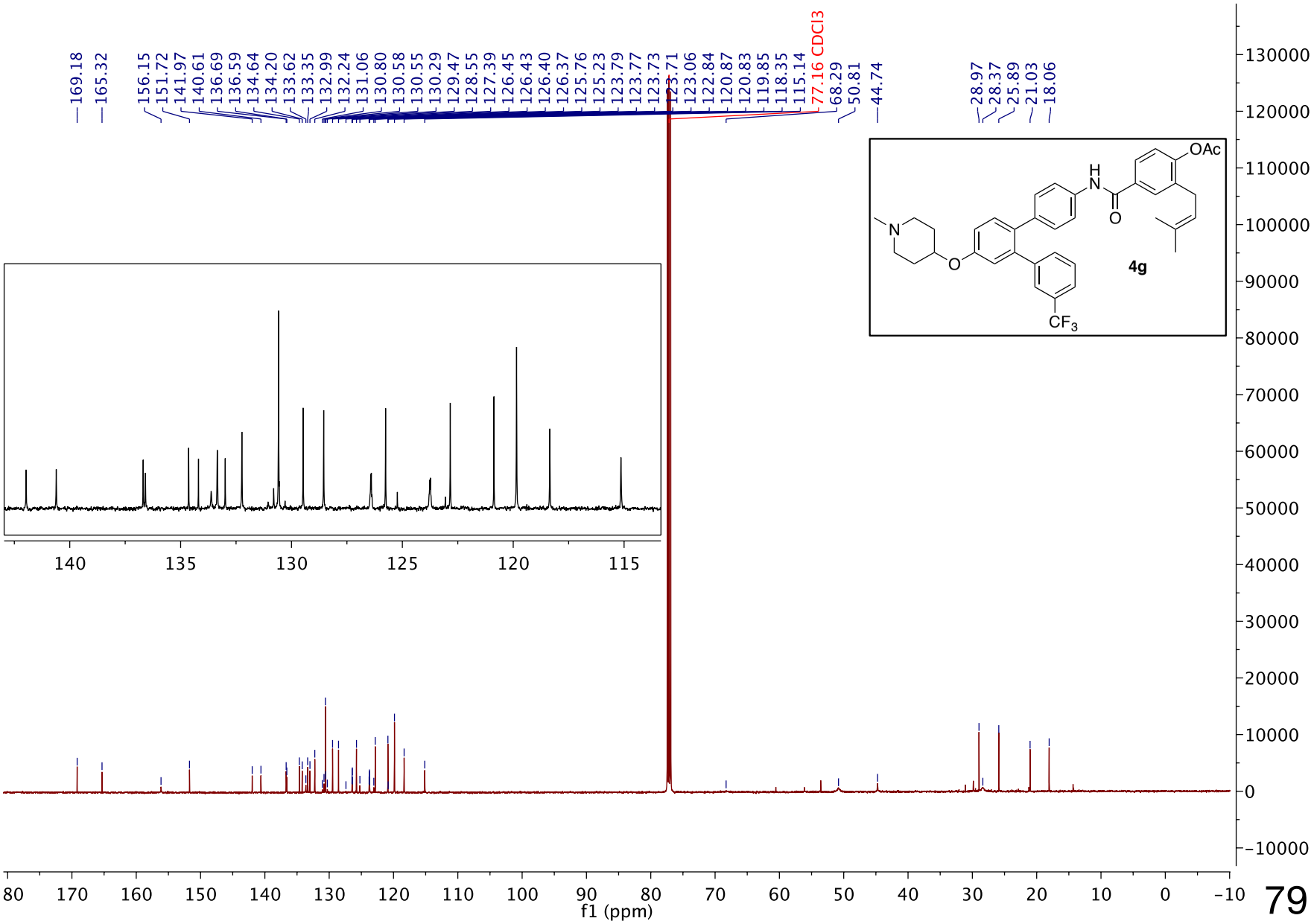
2.16
4.15
3.17
2.13
3.19
2.11
2.80
2.98
f1 (ppm)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165.32
156.15
151.72
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140.61
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136.59
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134.20
133.62
133.35
132.99
132.24
131.06
130.80
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130.55
130.29
129.47
128.55
127.39
126.45
126.43
126.40
126.37
125.76
125.23
123.79
123.77
123.73
123.71
123.06
122.84
120.87
120.83
119.85
118.35
115.14
77.16 CDCl3
68.29
50.81
44.74
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25.89
21.03
18.06
OAc
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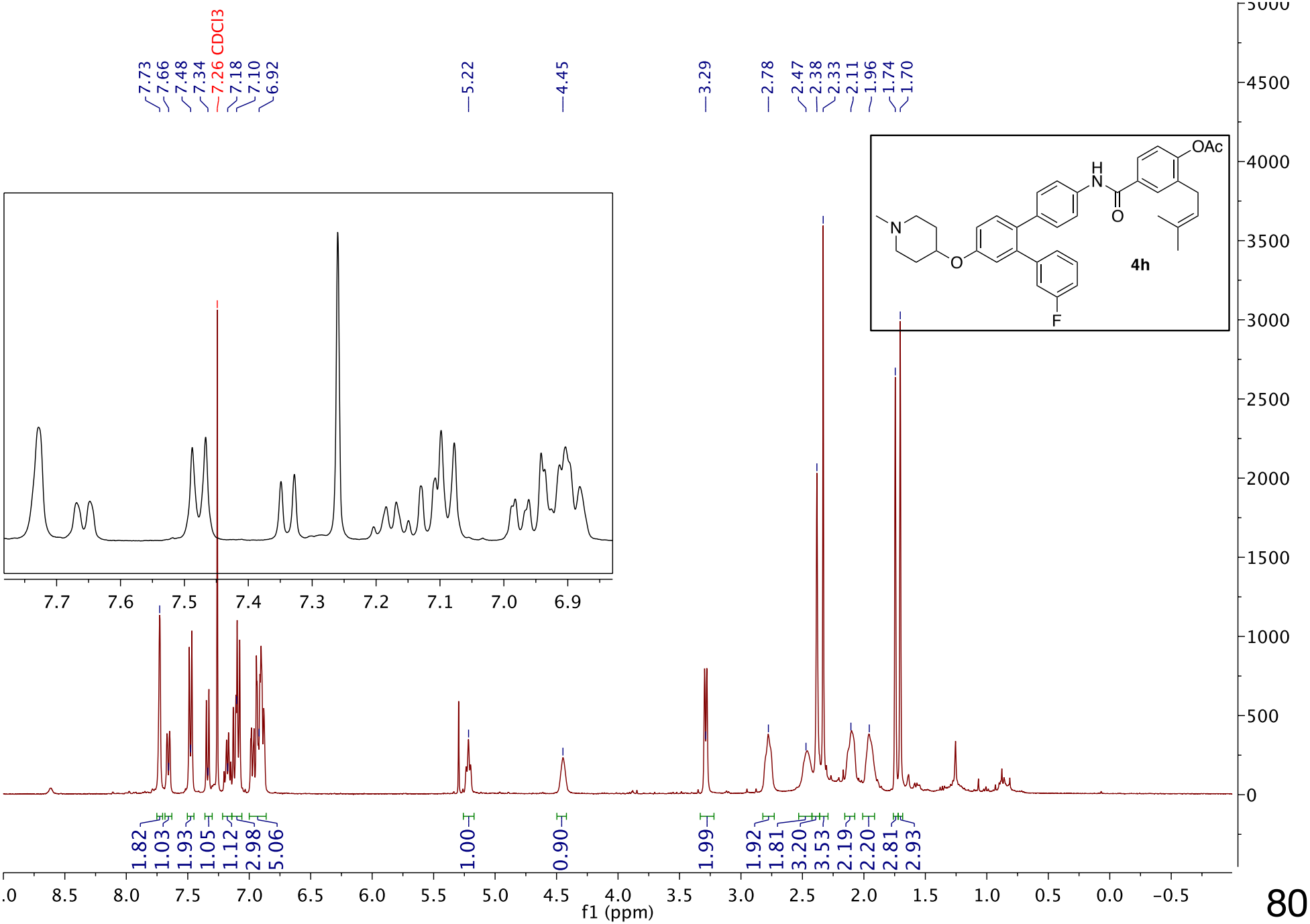
O
4g
CF3
f1 (ppm)


7.73
7.66
7.48
7.34
7.26 CDCl3
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7.10
6.92
5.22
4.45
3.29
2.78
2.47
2.38
2.33
2.11
1.96
1.74
1.70
OAc
H
N
O
N
O
F
4h
1.82
1.03
1.93
1.05
1.12
2.98
5.06
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1.92
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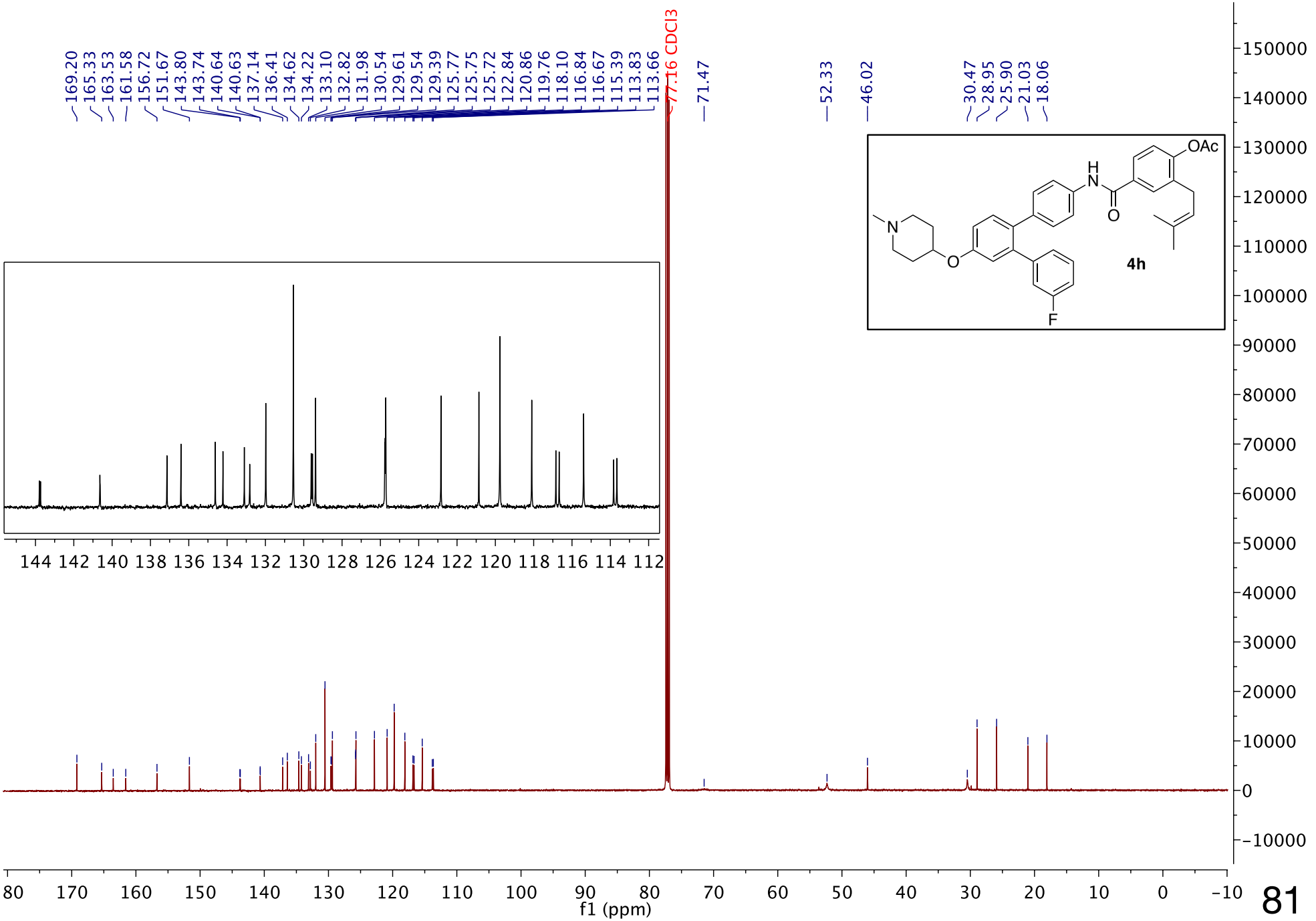
2.20
2.81
2.93
f1 (ppm)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134.62
134.22
133.10
132.82
131.98
130.54
129.61
129.54
129.39
125.77
125.75
125.72
122.84
120.86
119.76
118.10
116.84
116.67
115.39
113.83
113.66
77.16 CDCl3
71.47
52.33
46.02
30.47
28.95
25.90
21.03
18.06
OAc
H
N
O
N
O
F
4h
144 142 140 138 136 134 132 130 128 126 124 122 120 118 116 114 112
150000
140000
130000
120000
110000
100000
90000
80000
70000
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30000
20000
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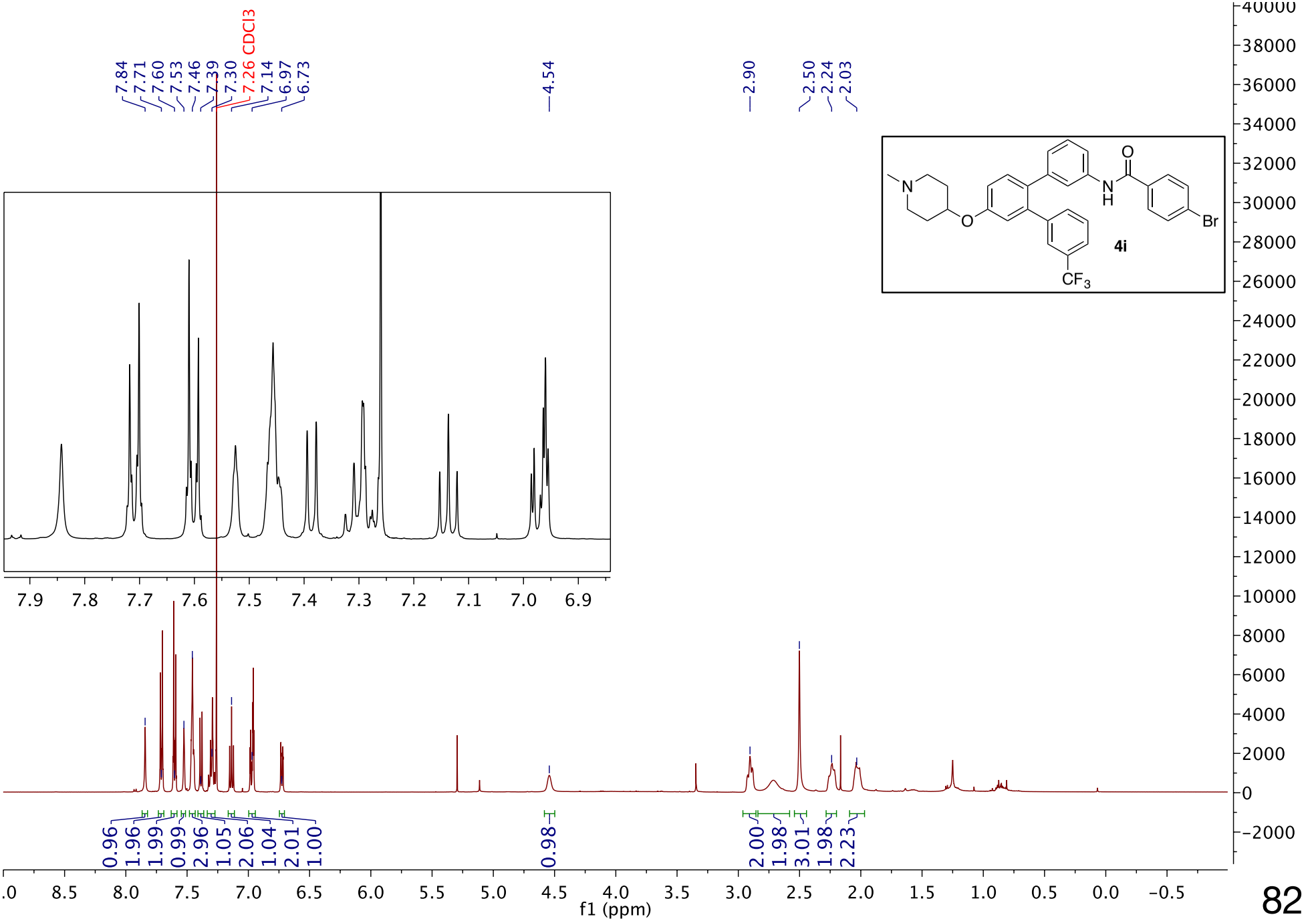
f1 (ppm)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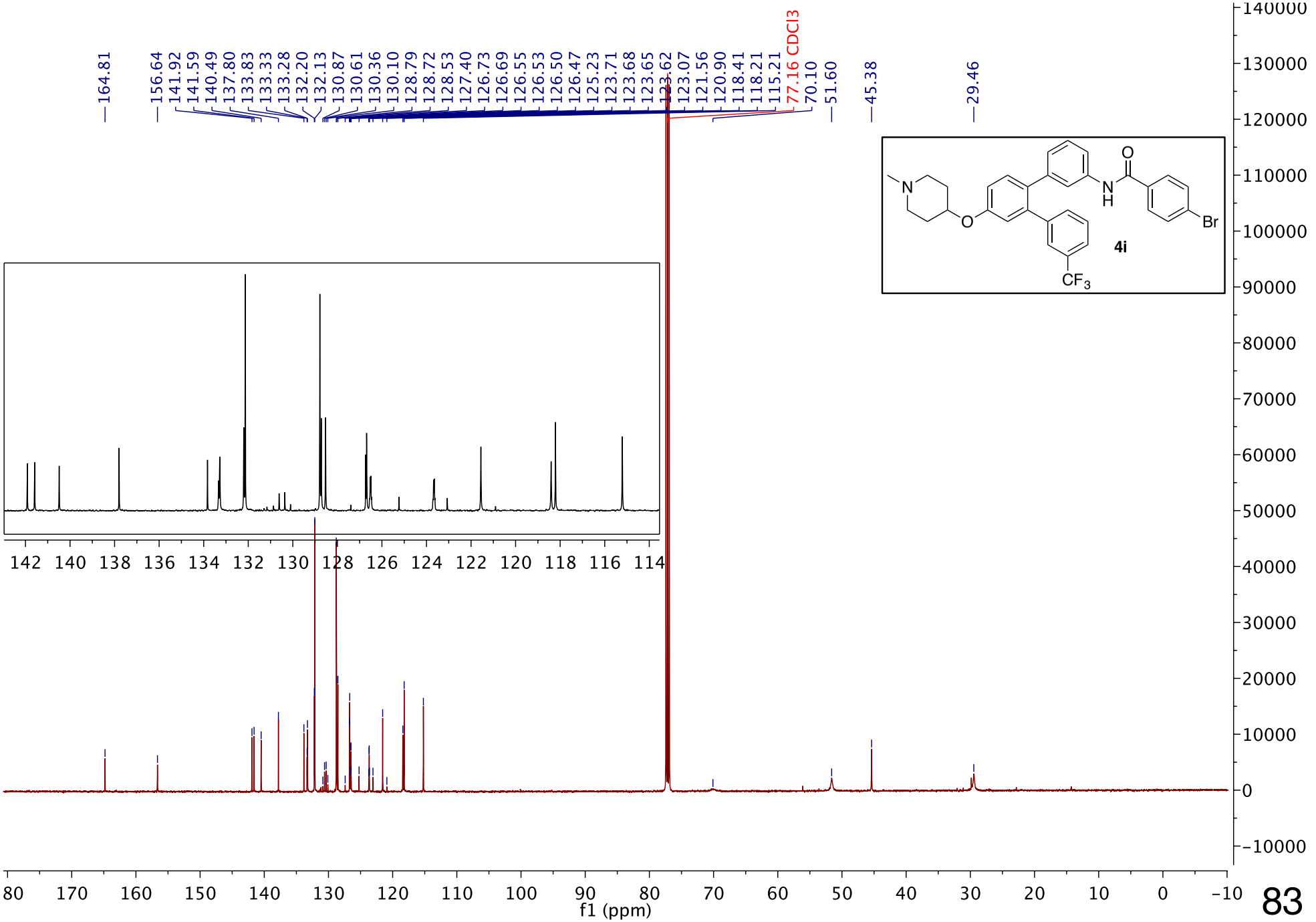
2.90
2.50
2.24
2.03
4i
Br
CF3
f1 (ppm)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130.10
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128.72
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126.73
126.69
126.55
126.53
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126.47
125.23
123.71
123.68
123.65
123.62
123.07
121.56
120.90
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115.21
77.16 CDCl3
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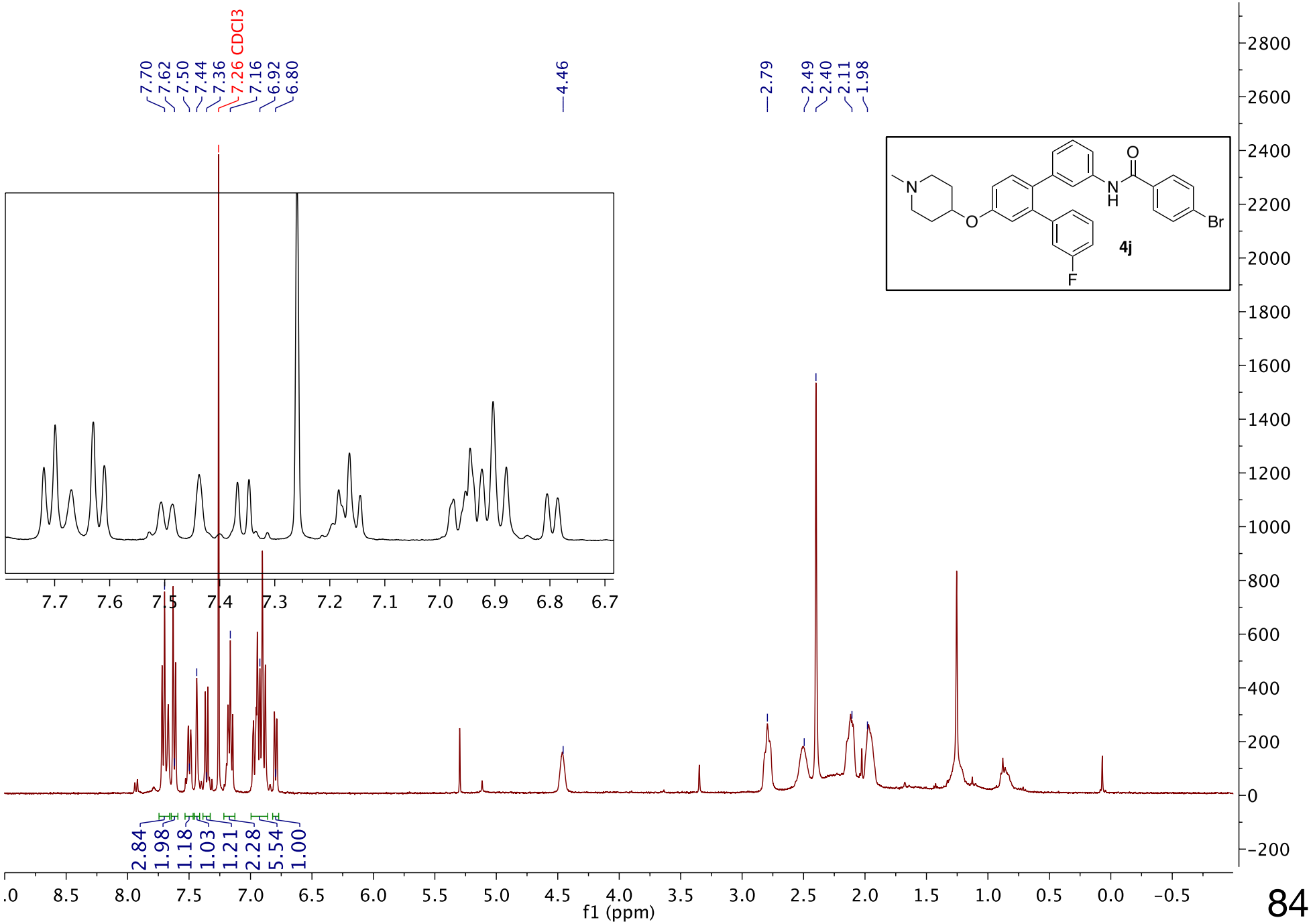
4i
Br
CF3
f1 (ppm)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6.80
4.46
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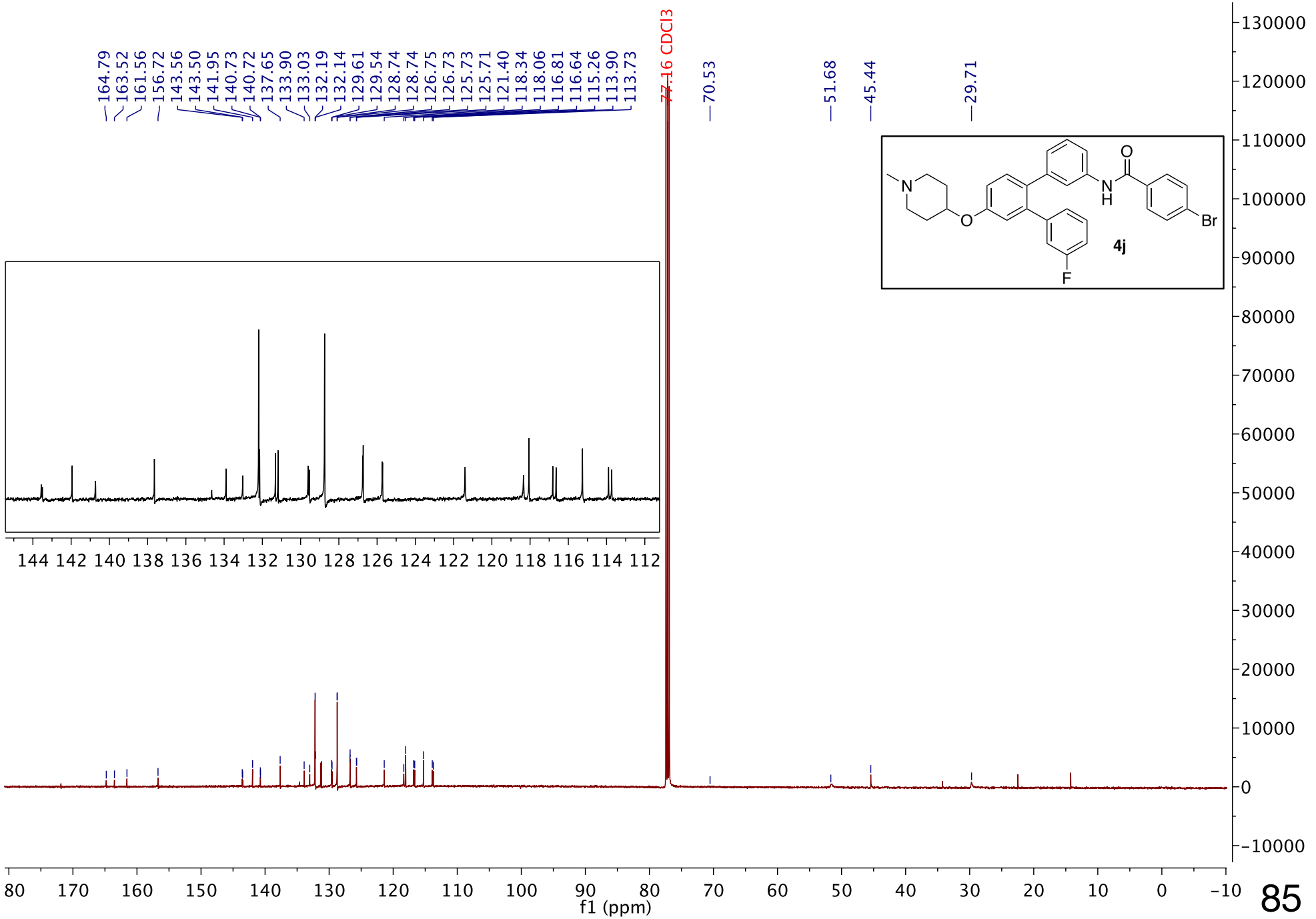
2.49
2.40
2.11
1.98
2.84
1.98
1.18
1.03
1.21
2.28
5.54
1.00
f1 (ppm)
4j
N
O
N
H
O
Br
F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129.61
129.54
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126.73
125.73
125.71
121.40
118.34
118.06
116.81
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113.73
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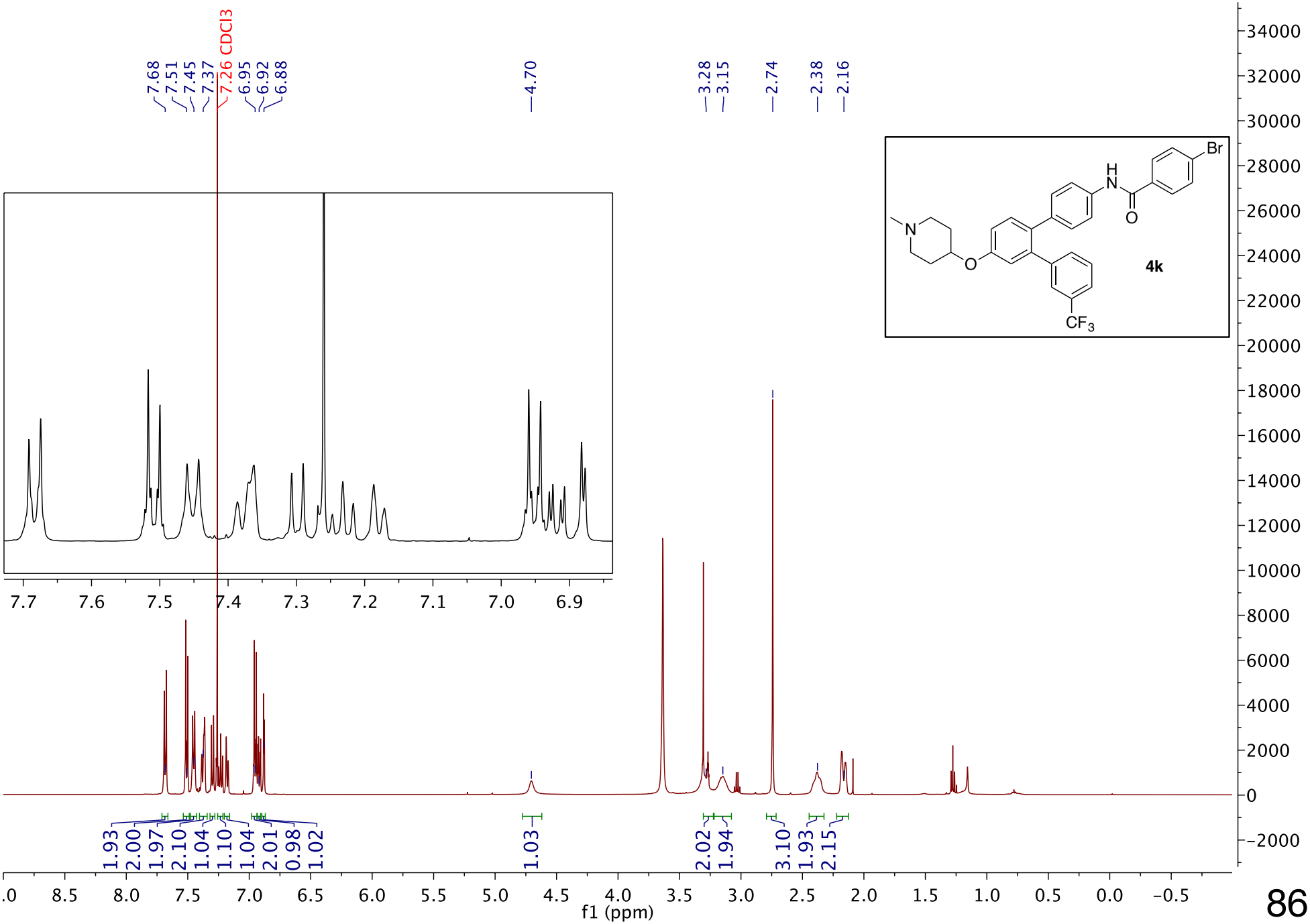
51.68
45.44
29.71
4j
f1 (ppm)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6.88
4.70
3.28
3.15
2.74
2.38
2.16
Br
H
N
O
N
O
CF3
4k
1.93
2.00
1.97
2.10
1.04
1.10
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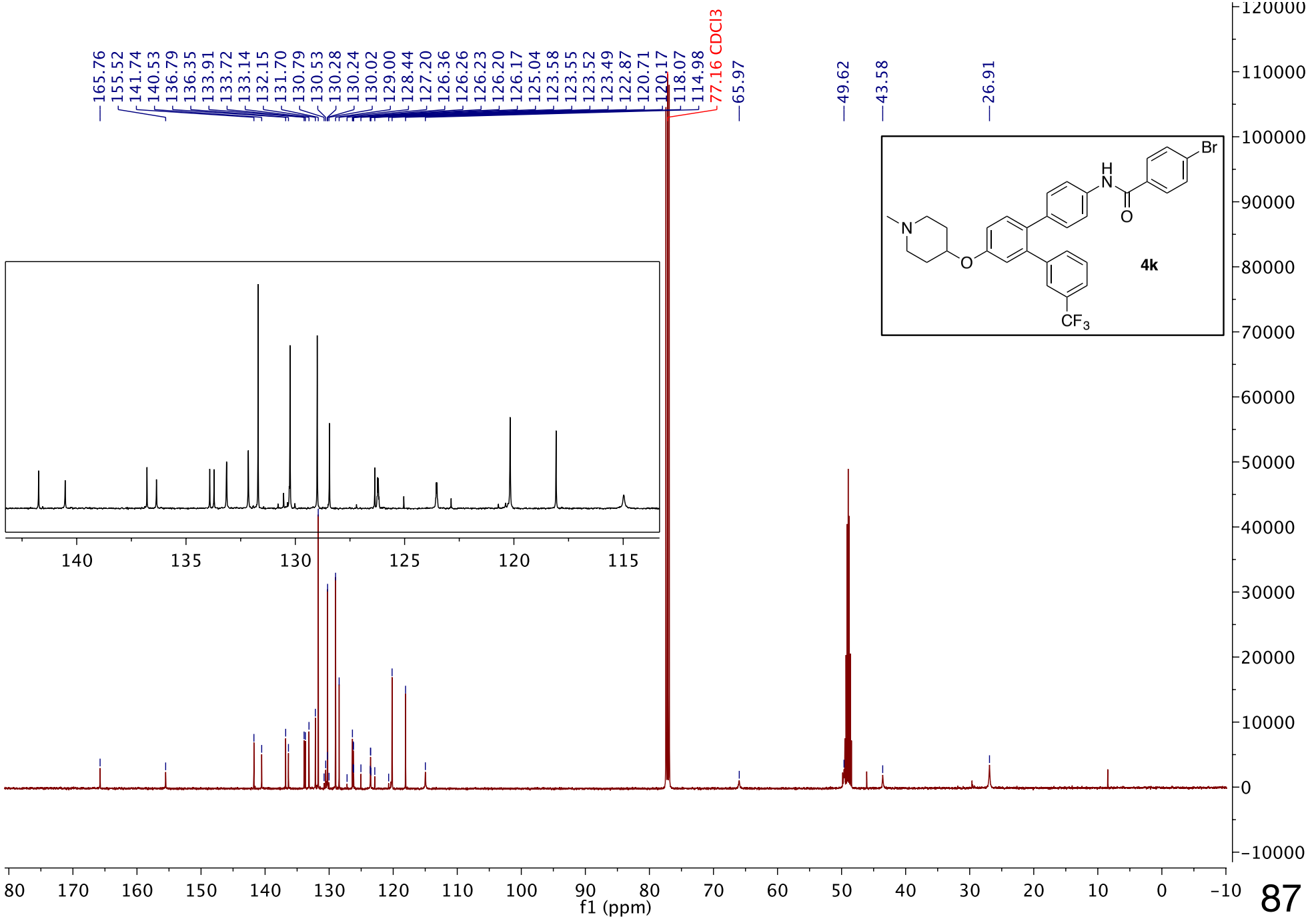
2.15
f1 (ppm)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130.28
130.24
130.02
129.00
128.44
127.20
126.36
126.26
126.23
126.20
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125.04
123.58
123.55
123.52
123.49
122.87
120.71
120.17
118.07
114.98
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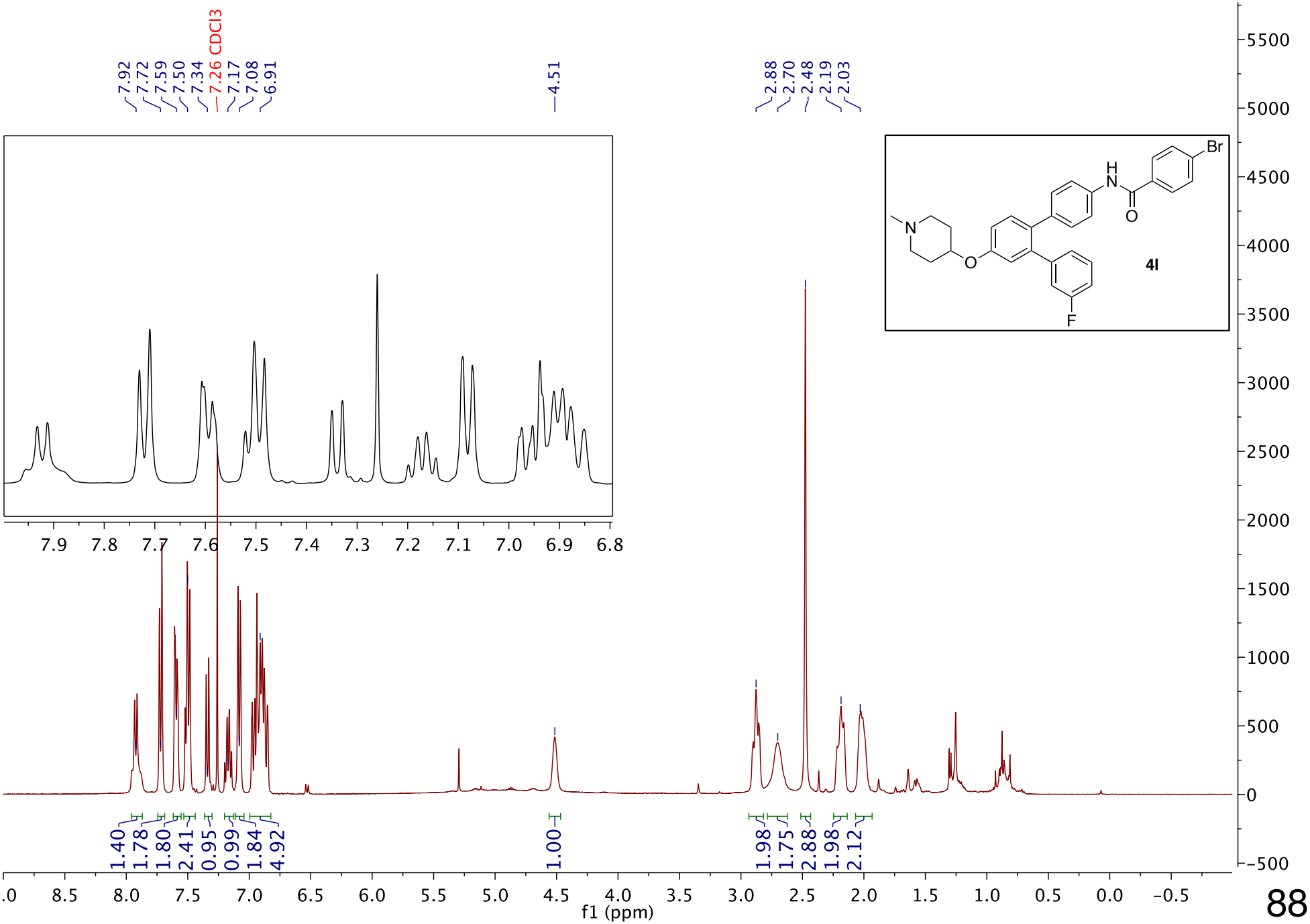
49.62
43.58
26.91
Br
H
N
O
N
O
CF3
4k
f1 (ppm)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7.17
7.08
6.91
4.51
2.88
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2.48
2.19
2.03
Br
H
N
O
N
O
F
4l
1.40
1.78
1.80
2.41
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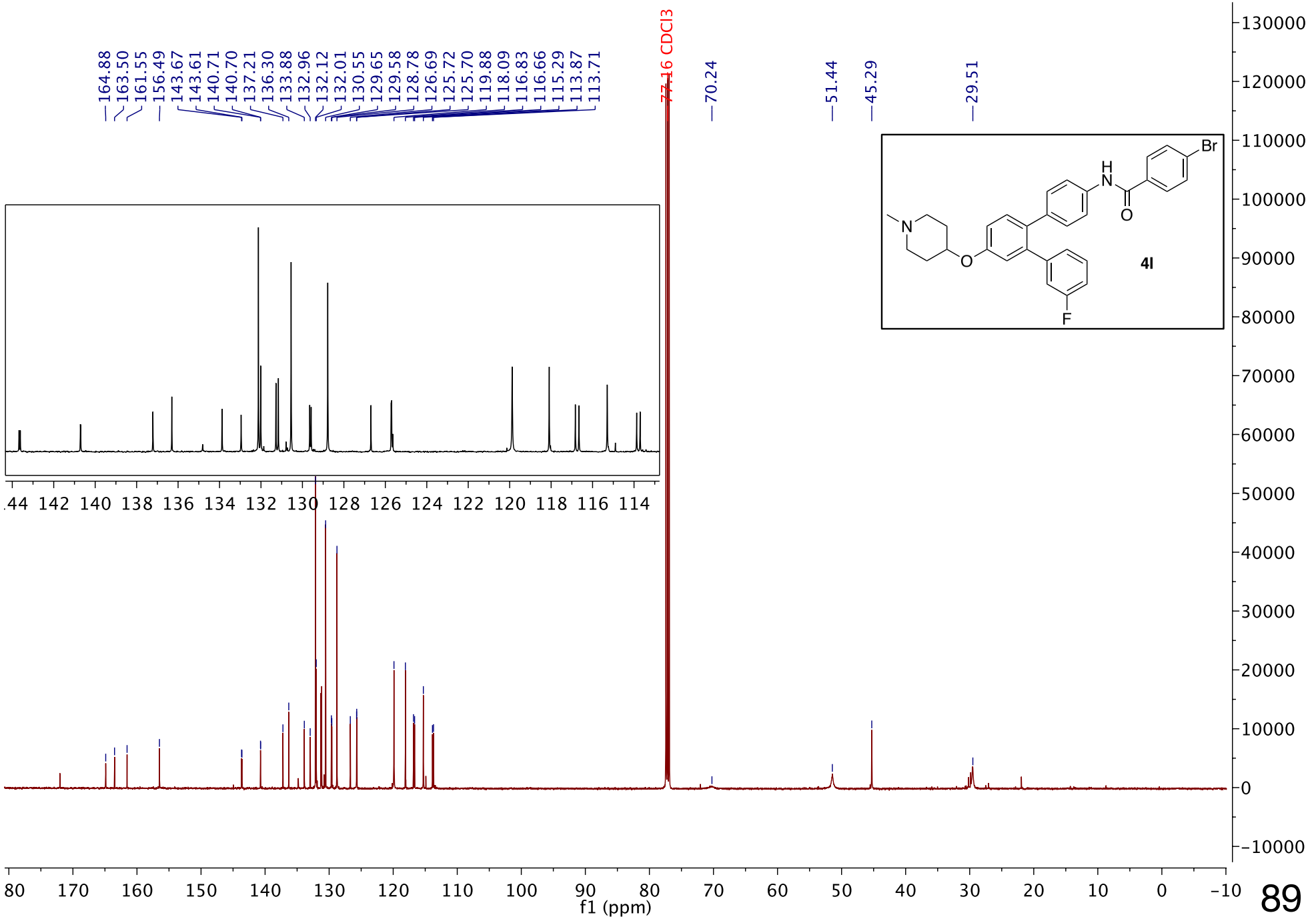
1.84
4.92
1.00
1.98
1.75
2.88
1.98
2.12
f1 (ppm)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125.70
119.88
118.09
116.83
116.66
115.29
113.87
113.71
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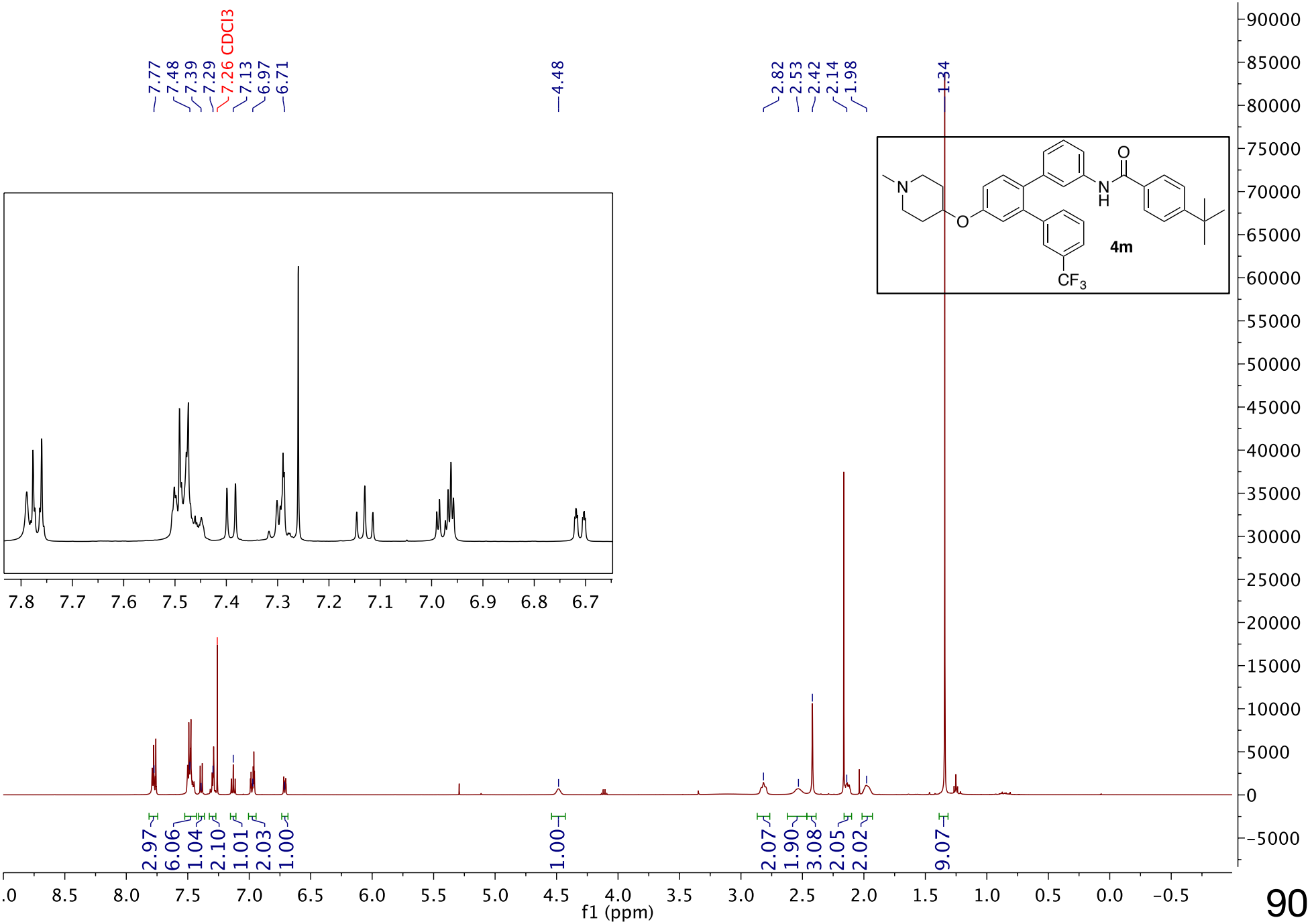
51.44
45.29
29.51
Br
H
N
O
N
O
F
4l
f1 (ppm)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7.13
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6.71
4.48
2.82
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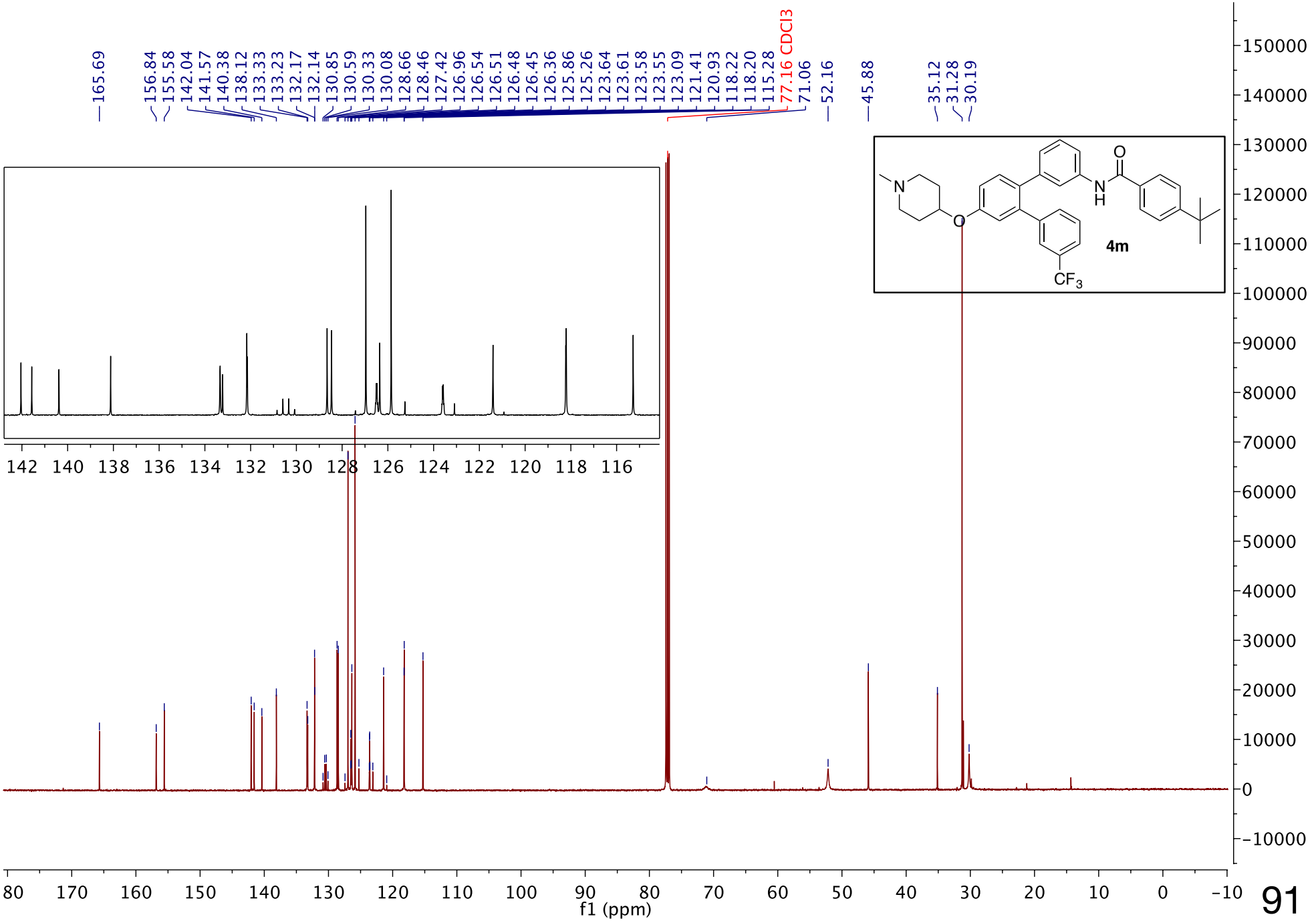
2.42
2.14
1.98
1.34
4m
CF3
f1 (ppm)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126.96
126.54
126.51
126.48
126.45
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125.26
123.64
123.61
123.58
123.55
123.09
121.41
120.93
118.22
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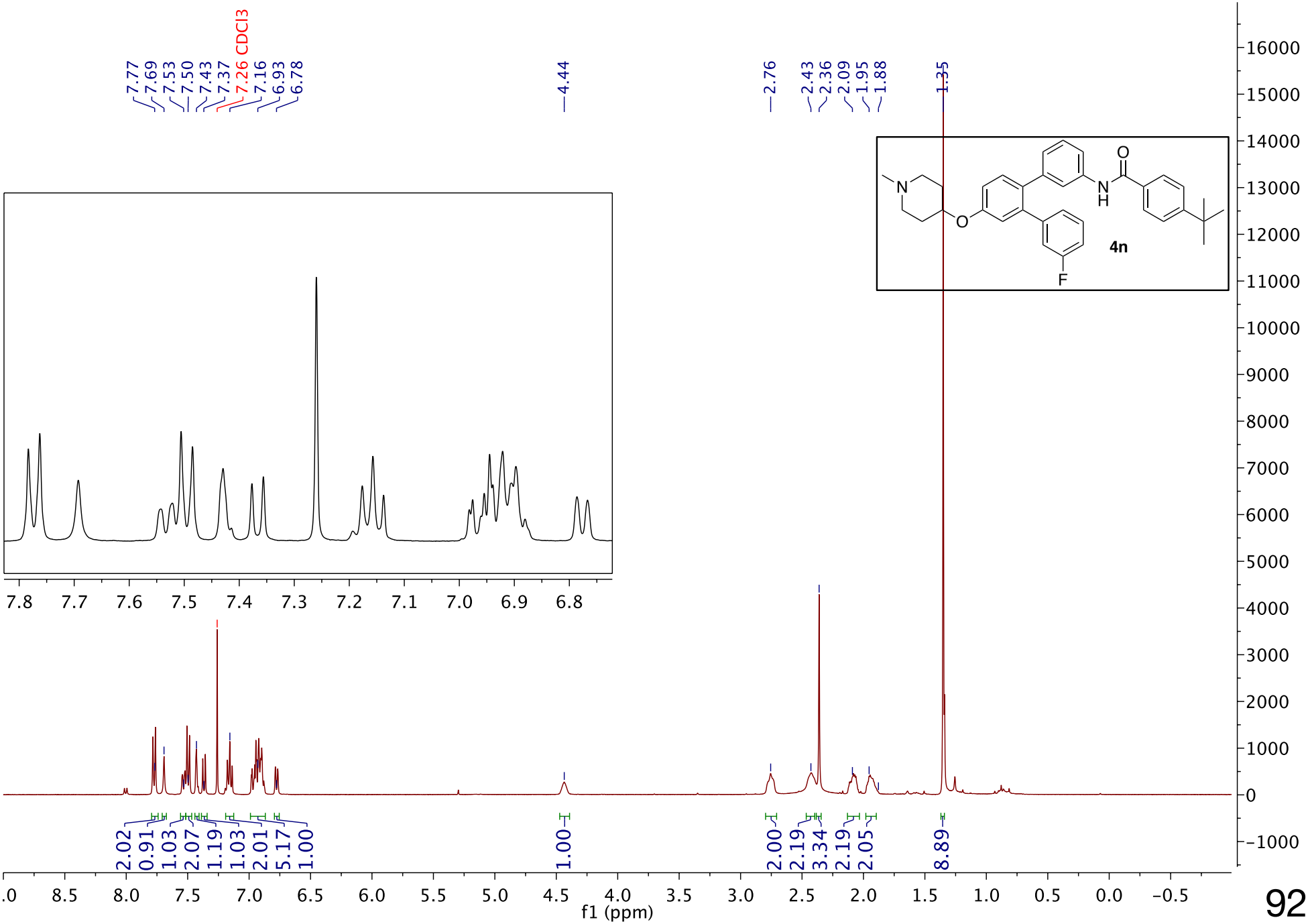
31.28
30.19
4m
CF3
f1 (ppm)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6.93
6.78
4.44
2.76
2.43
2.36
2.09
1.95
1.88
1.35
4n
F
f1 (ppm)
2.02
0.91
1.03
2.07
1.19
1.03
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5.17
1.00
1.00
2.00
2.19
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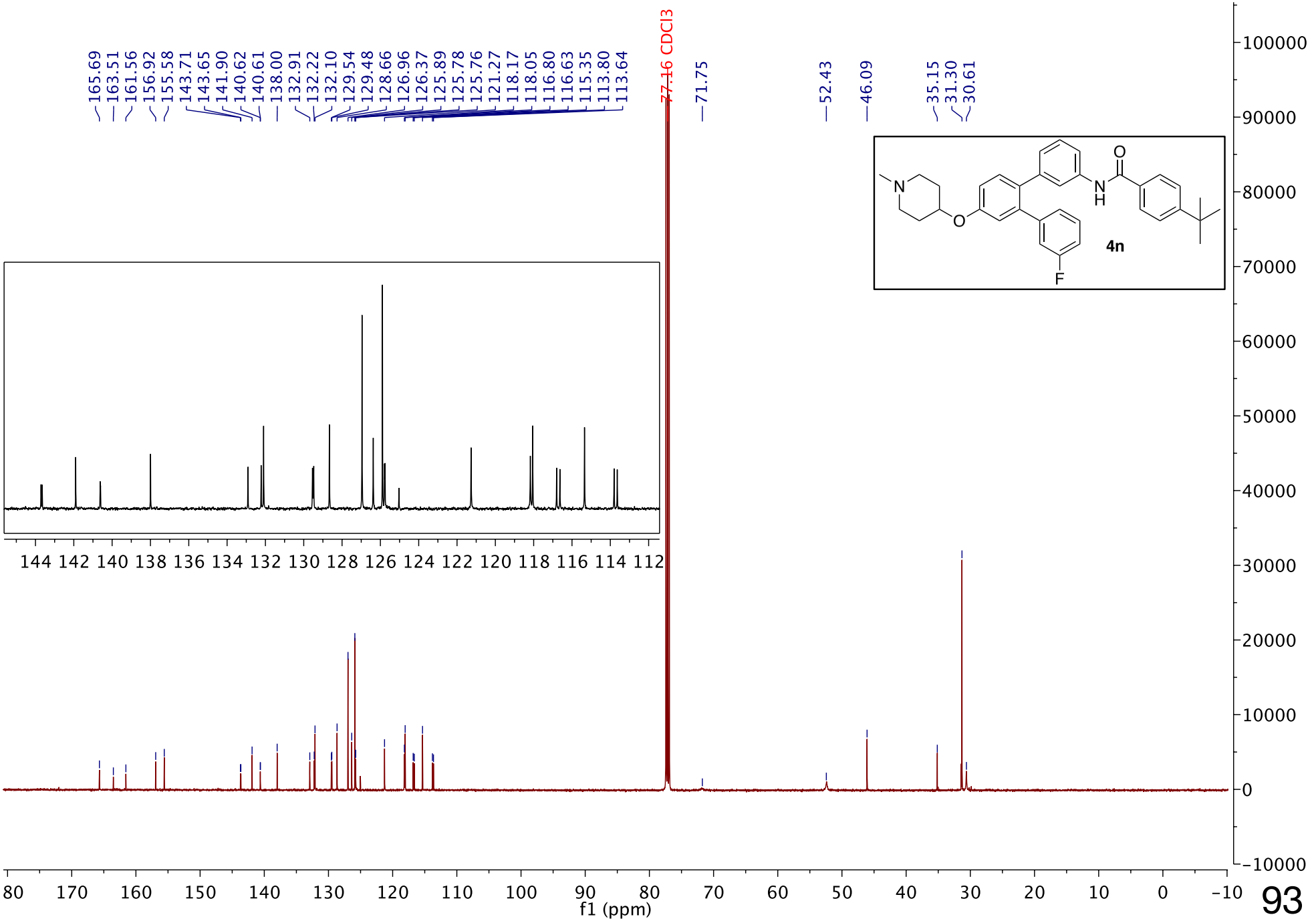
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125.89
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121.27
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118.05
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116.63
115.35
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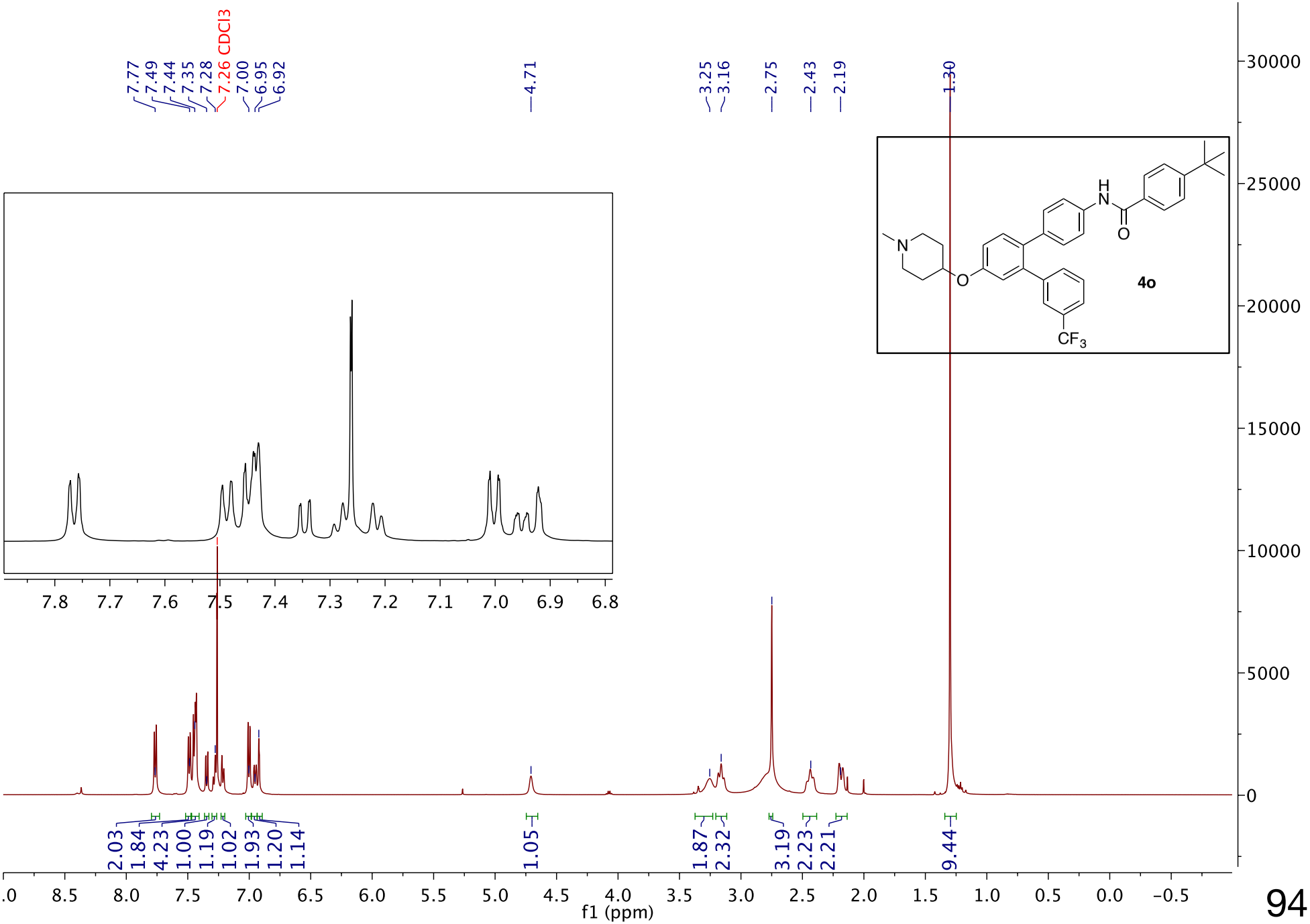
46.09
35.15
31.30
30.61
4n
f1 (ppm)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6.92
4.71
3.25
3.16
2.75
2.43
2.19
1.30
4o
2.03
1.84
4.23
1.00
1.19
1.02
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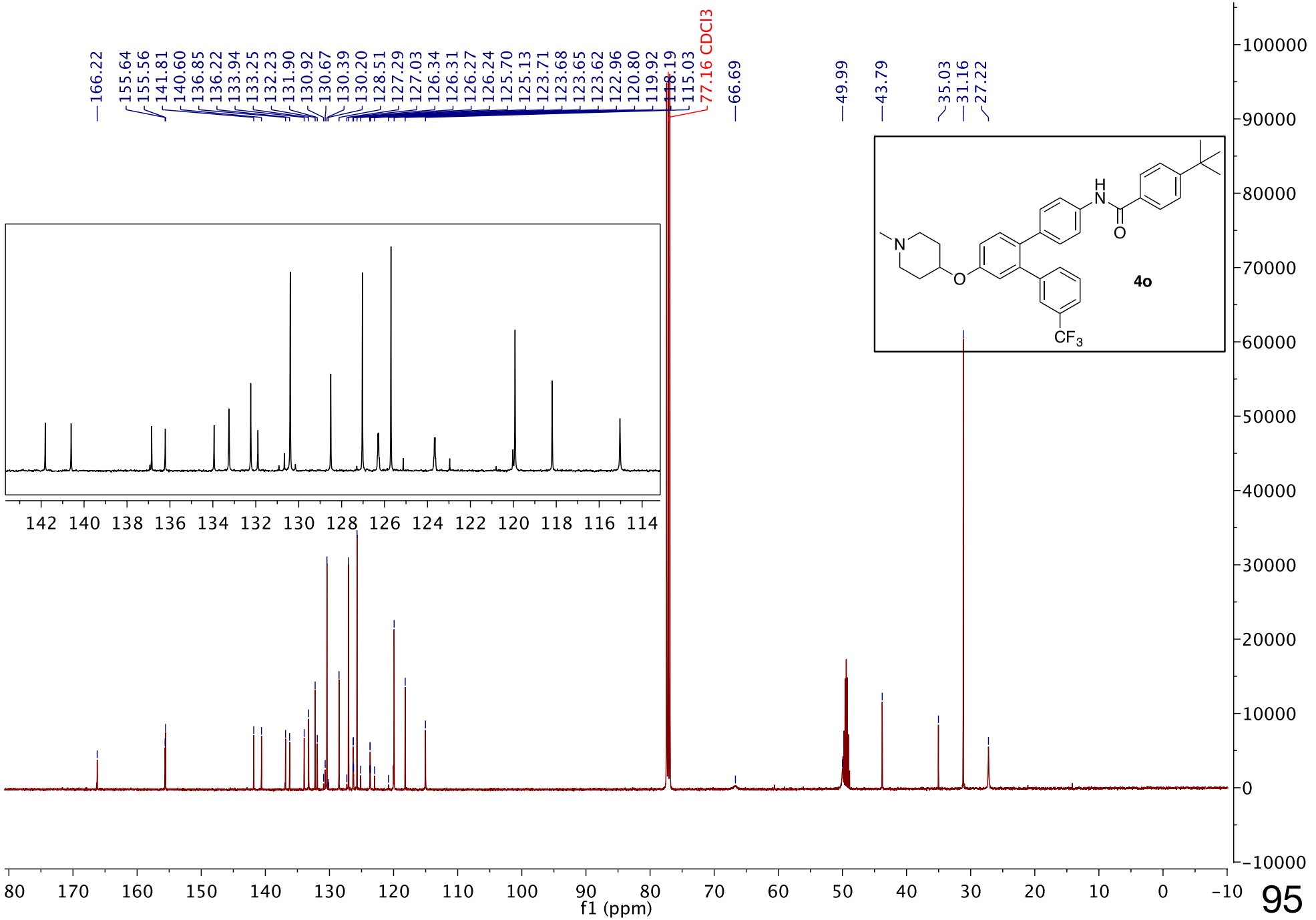
1.14
1.05
1.87
2.32
3.19
2.23
2.21
9.44
f1 (ppm)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130.67
130.39
130.20
128.51
127.29
127.03
126.34
126.31
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126.24
125.70
125.13
123.71
123.68
123.65
123.62
122.96
120.80
119.92
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77.16 CDCl3
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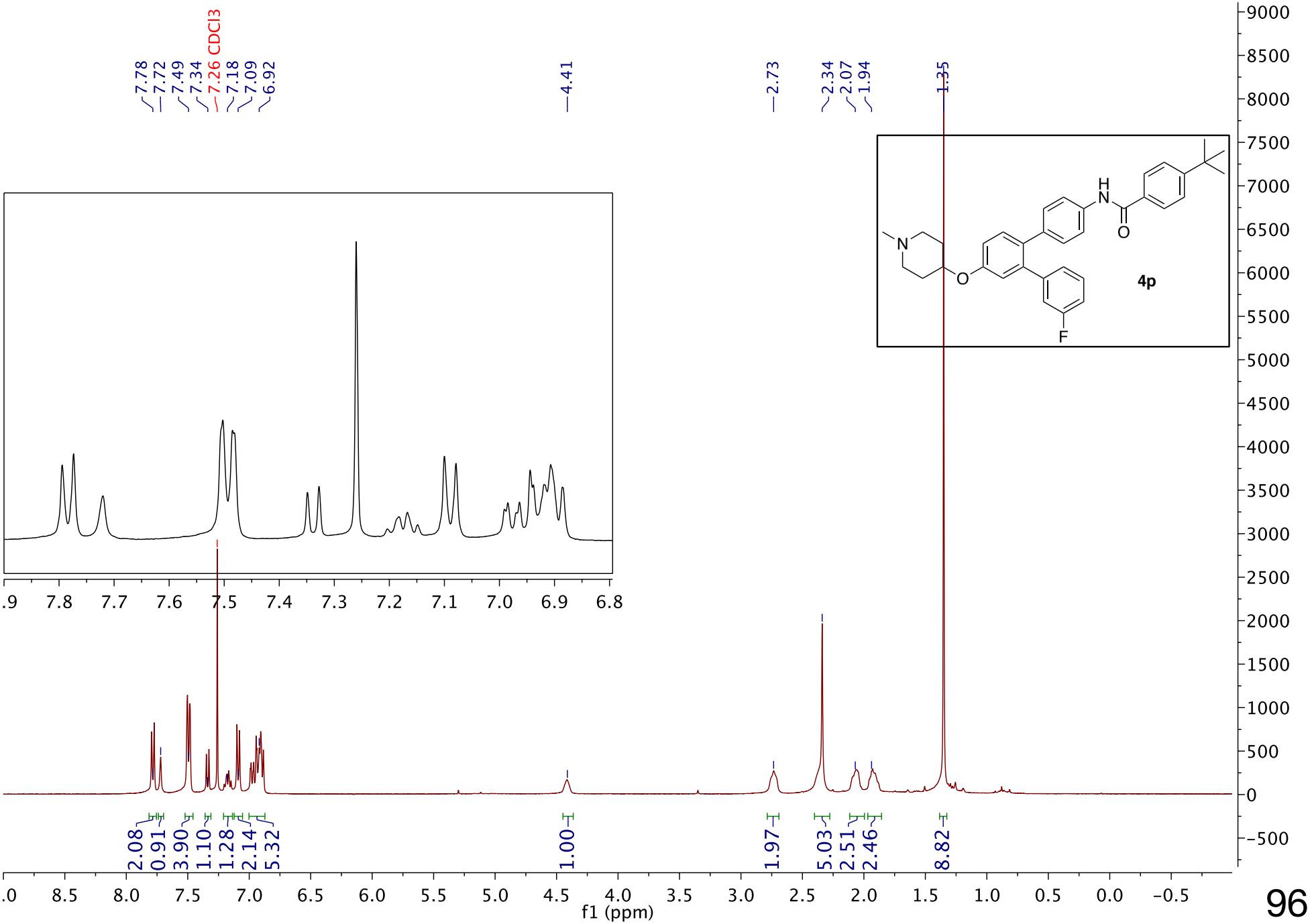
49.99
43.79
35.03
31.16
27.22
4o
f1 (ppm)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4.41
2.73
2.34
2.07
1.94
1.35
4p
F
2.08
0.91
3.90
1.10
1.28
2.14
5.32
1.00
1.97
5.03
2.51
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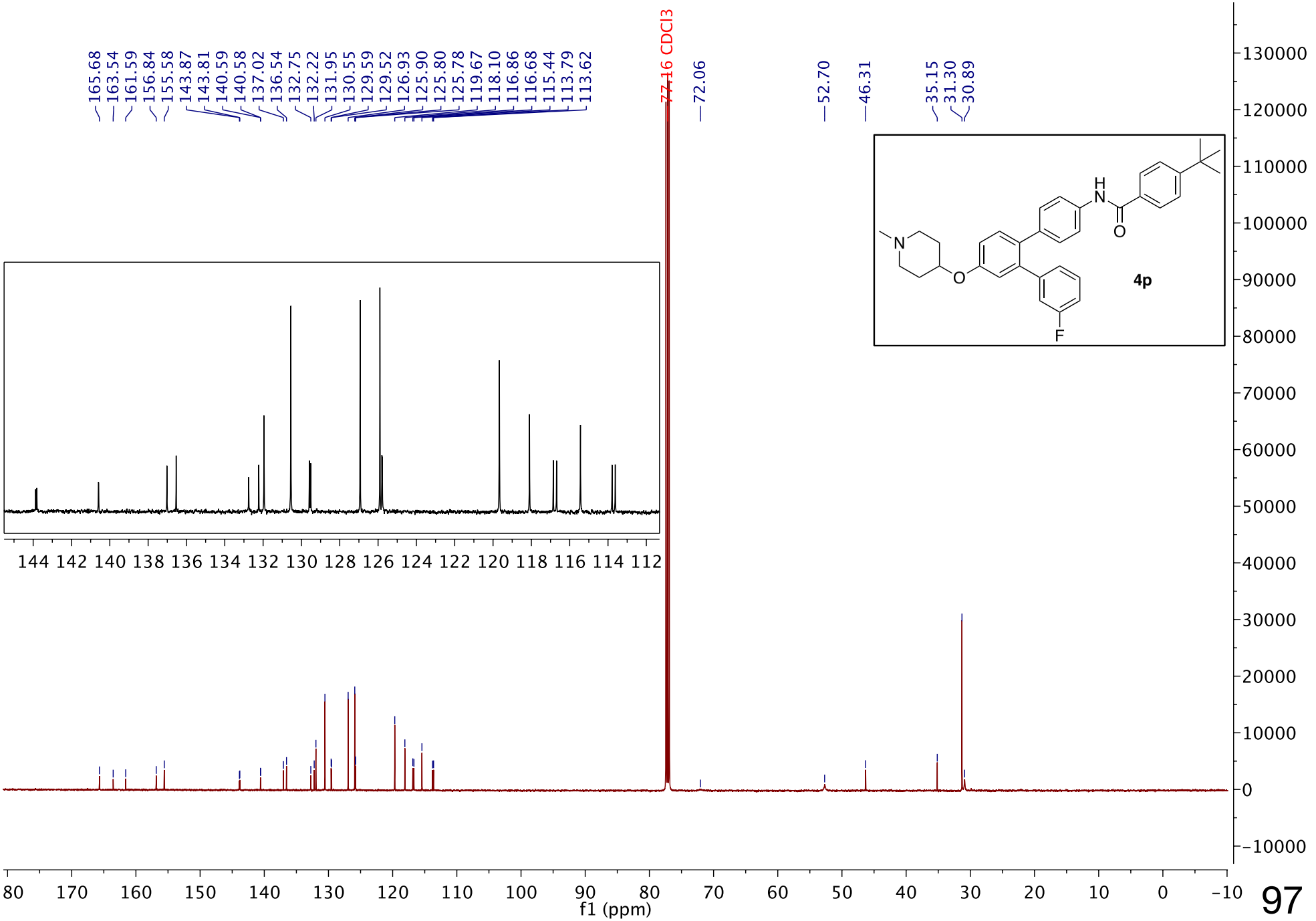
8.82
f1 (ppm)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125.78
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118.10
116.86
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115.44
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113.62
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31.30
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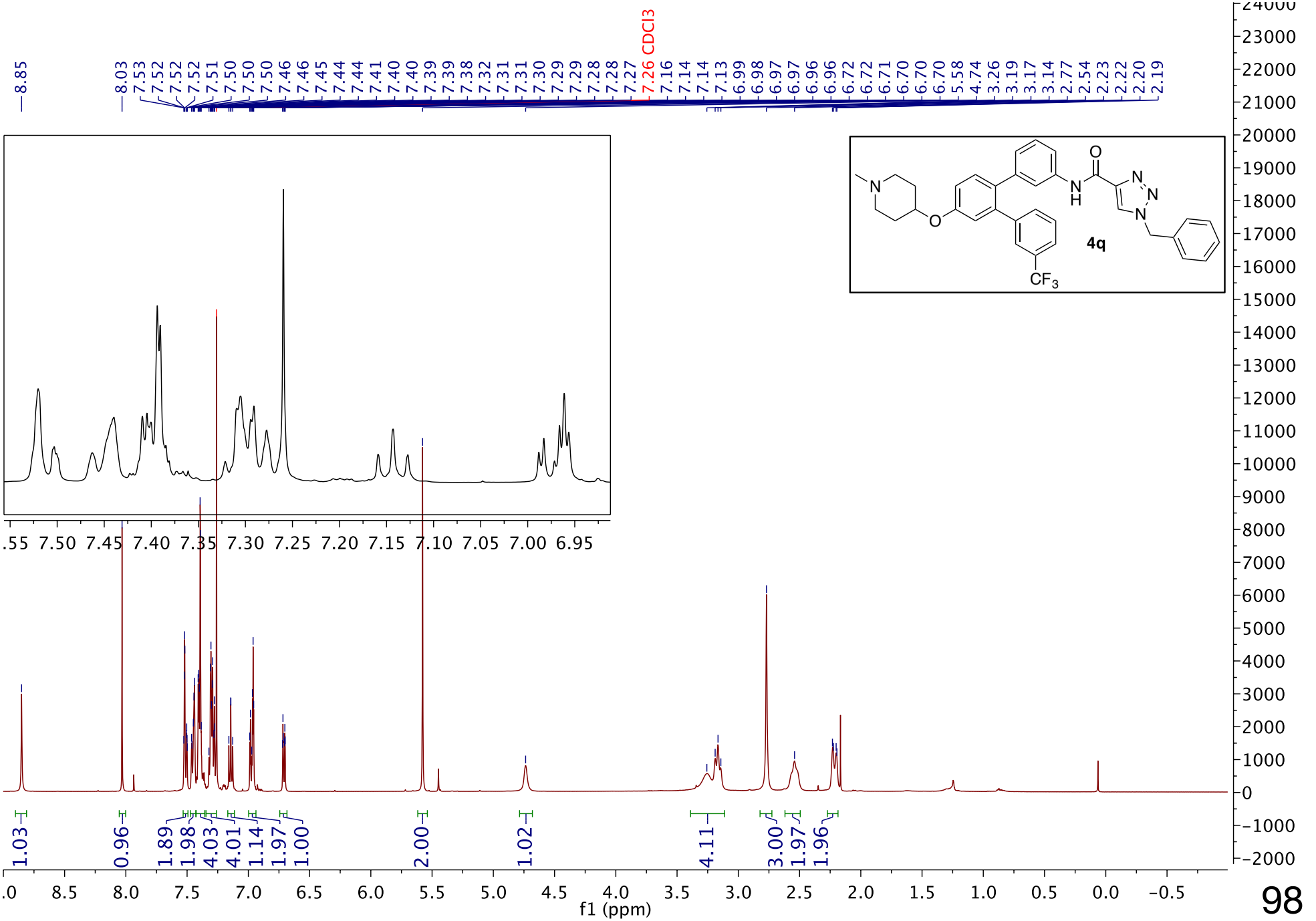
4p
F
f1 (ppm)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7.30
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7.29
7.28
7.28
7.27
7.26 CDCl3
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7.14
7.13
6.99
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6.96
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6.72
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4.74
3.26
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2.20
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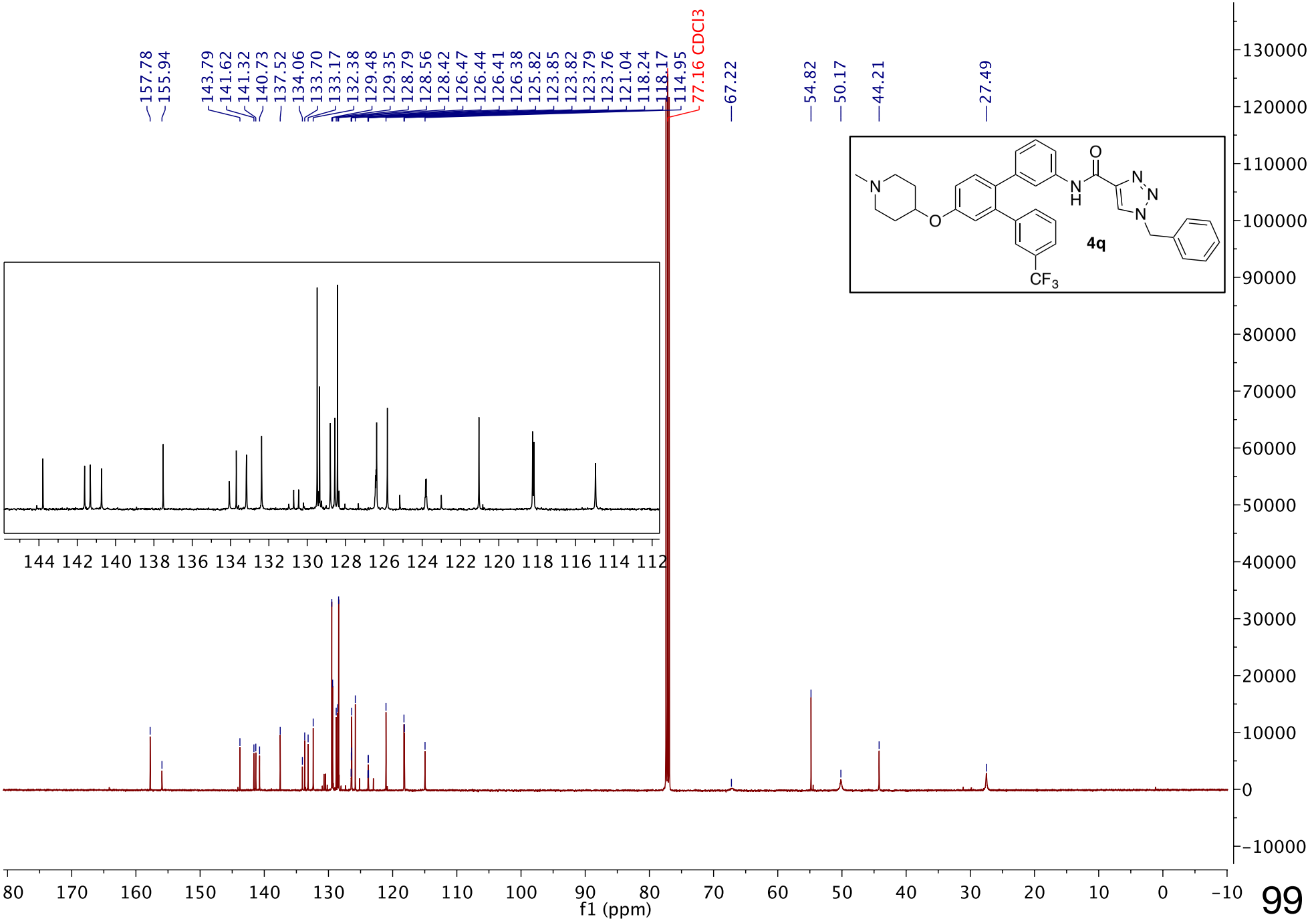
4q
CF3
f1 (ppm)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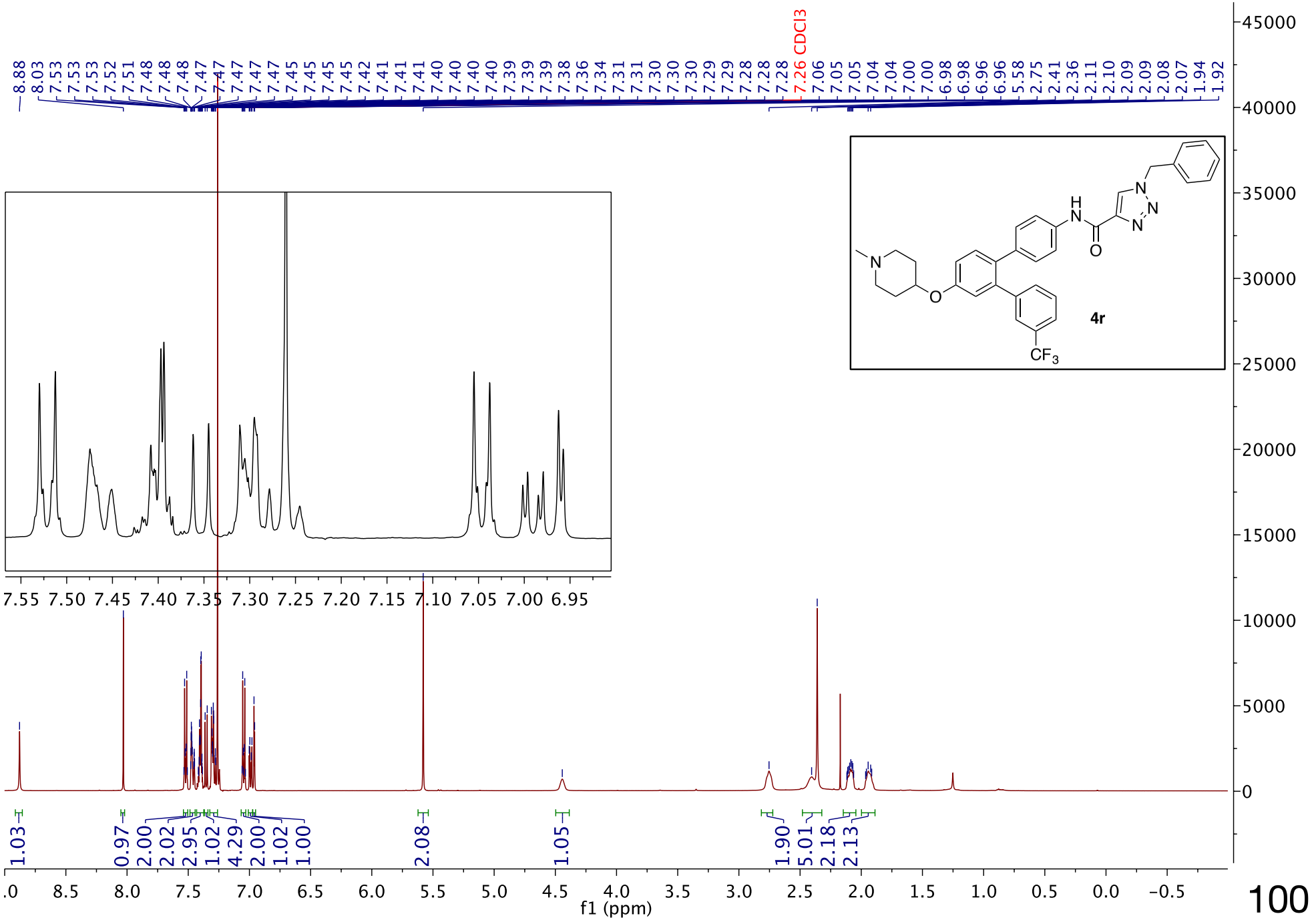
4q
CF3
f1 (ppm)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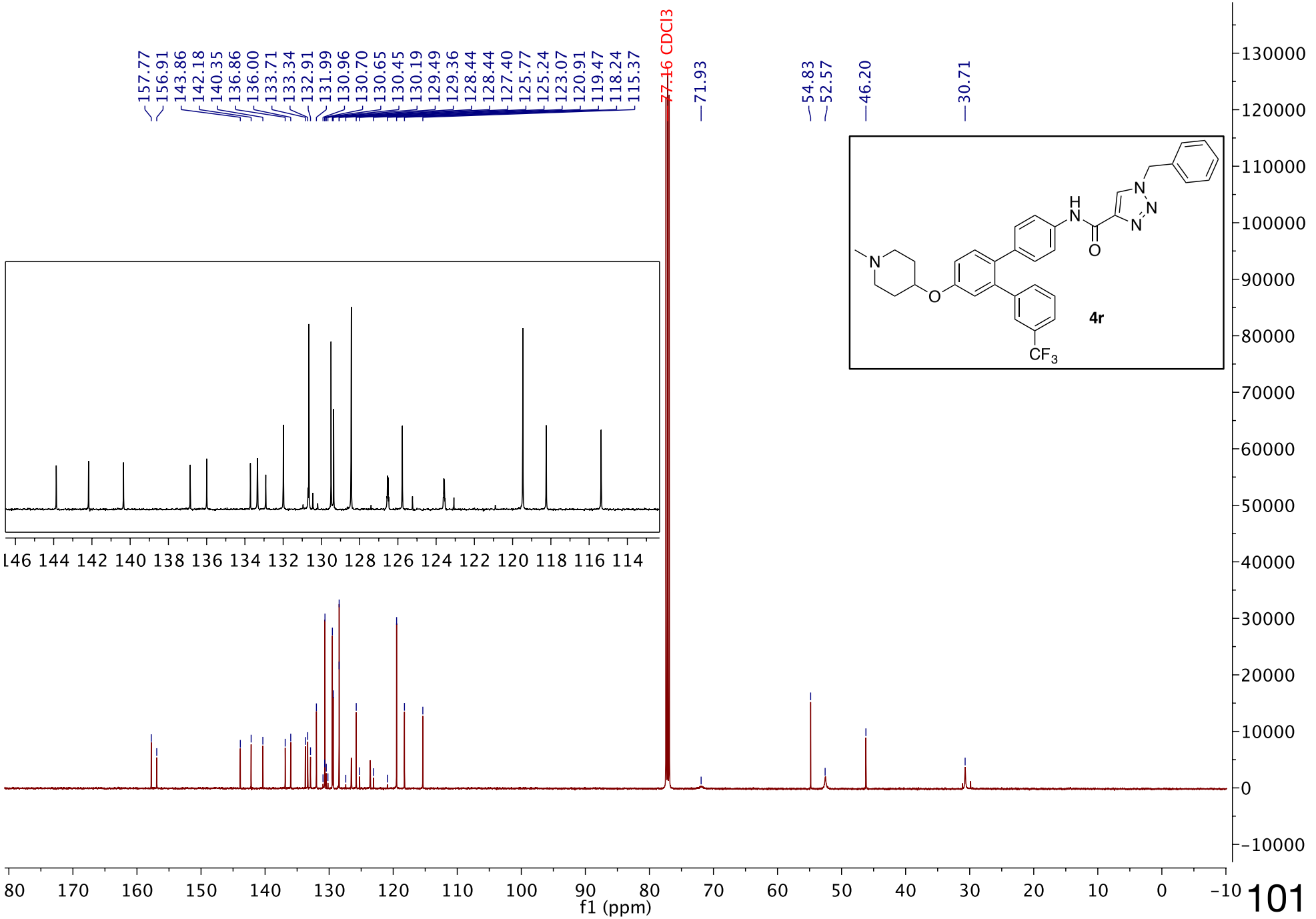
4r
CF3
7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95
1.03 0.97 2.00 2.02 2.95 1.02 4.29 2.00 1.02 1.00 2.08 1.05 1.90 5.01 2.18 2.13
f1 (ppm)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129.36
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128.44
127.40
125.77
125.24
123.07
120.91
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77.16 CDCl3
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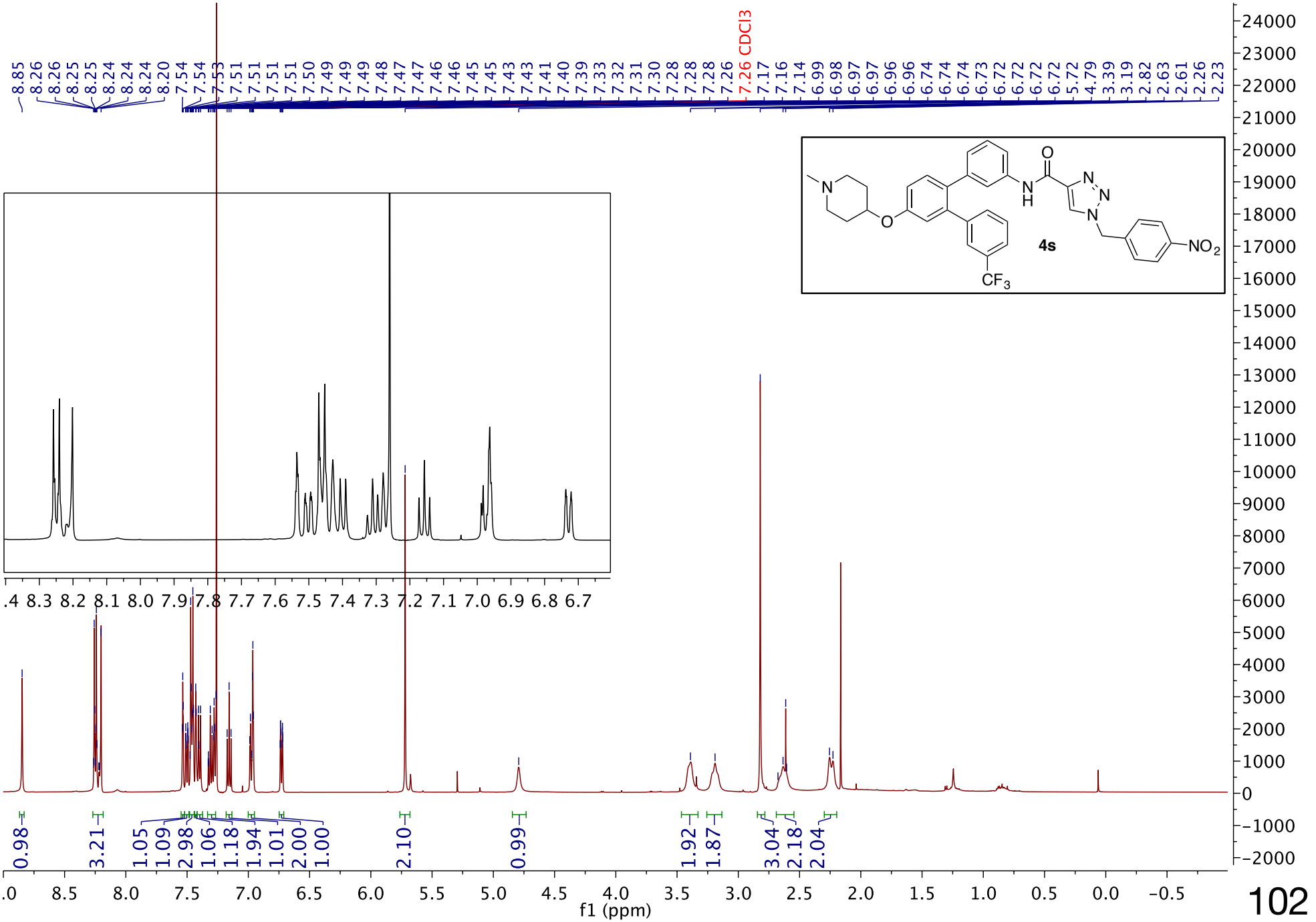
54.83
52.57
46.20
30.71
4r
CF3
f1 (ppm)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4s
NO2
CF3
f1 (ppm)
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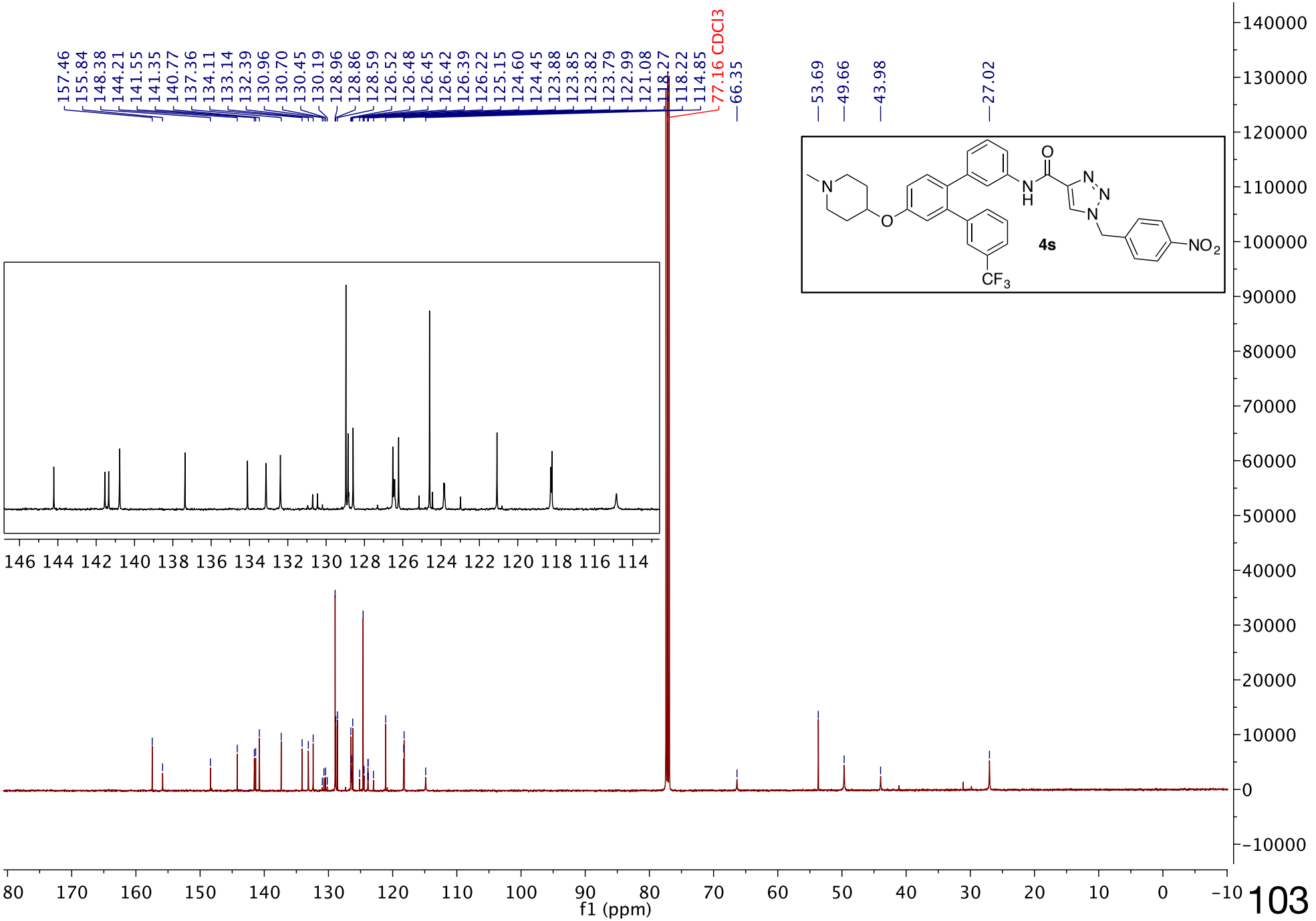
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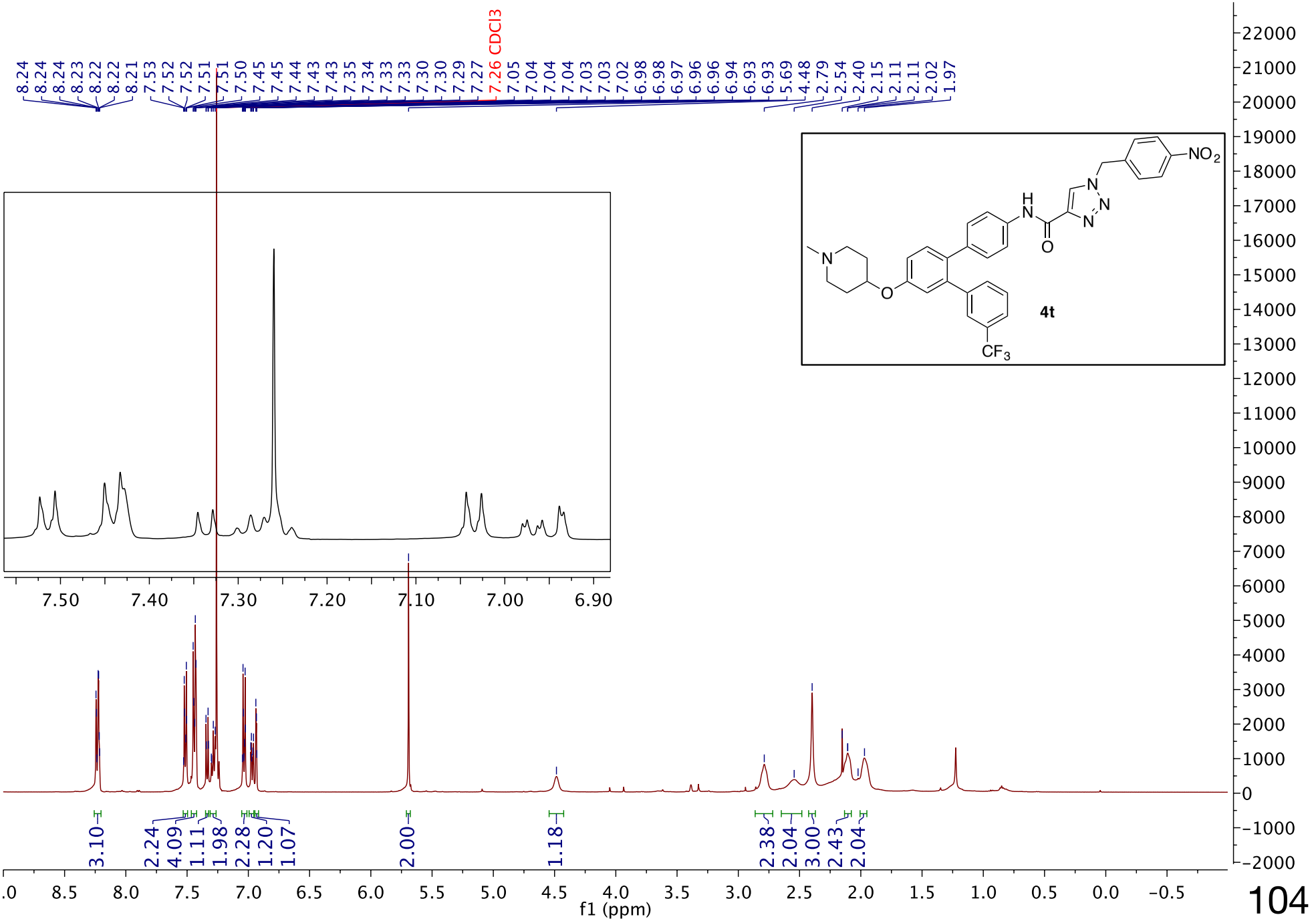
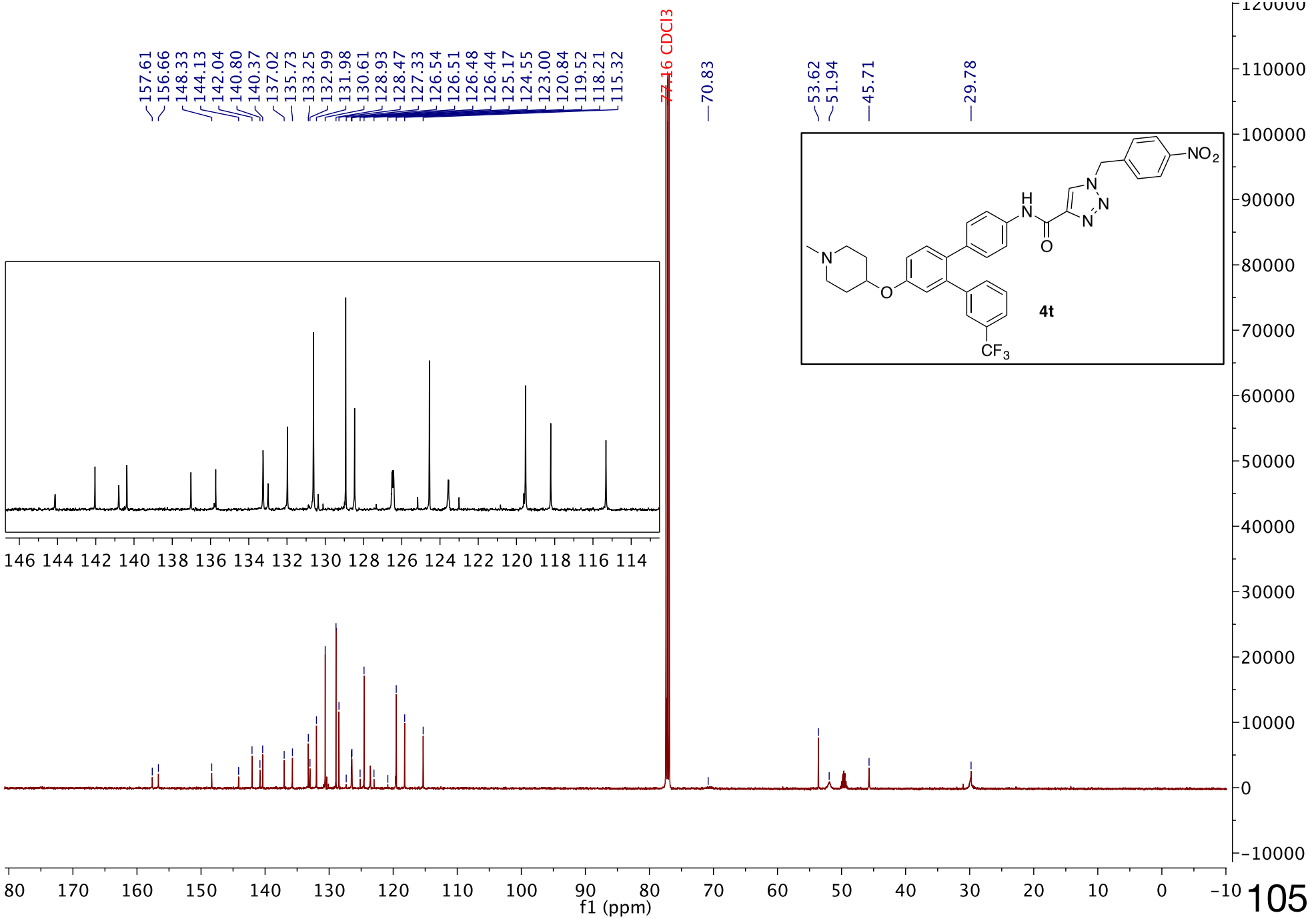
123.79
122.99
121.08
118.27
118.22
114.85
77.16 CDCl3
66.35
53.69
49.66
43.98
27.02
4s
NO2
CF3
f1 (ppm)


8.24 8.24 8.24 8.23 8.22 8.22 8.21 7.53 7.52 7.52 7.51 7.51 7.50 7.45 7.45 7.44 7.43 7.43 7.35 7.34 7.33 7.33 7.30 7.30 7.29 7.27 7.26 CDCl3 7.05 7.04 7.04 7.04 7.03 7.03 7.02 6.98 6.98 6.97 6.96 6.96 6.94 6.93 6.93 5.69 4.48 2.79 2.54 2.40 2.15 2.11 2.11 2.02 1.97
NO2
N
H
N
N
N
O
N
O
CF3
4t
7.50 7.40 7.30 7.20 7.10 7.00 6.90
22000 21000 20000 19000 18000 17000 16000 15000 14000 13000 12000 11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000 -2000
3.10 2.24 4.09 1.11 1.98 2.28 1.20 1.07 2.00 1.18 2.38 2.04 3.00 2.43 2.04
.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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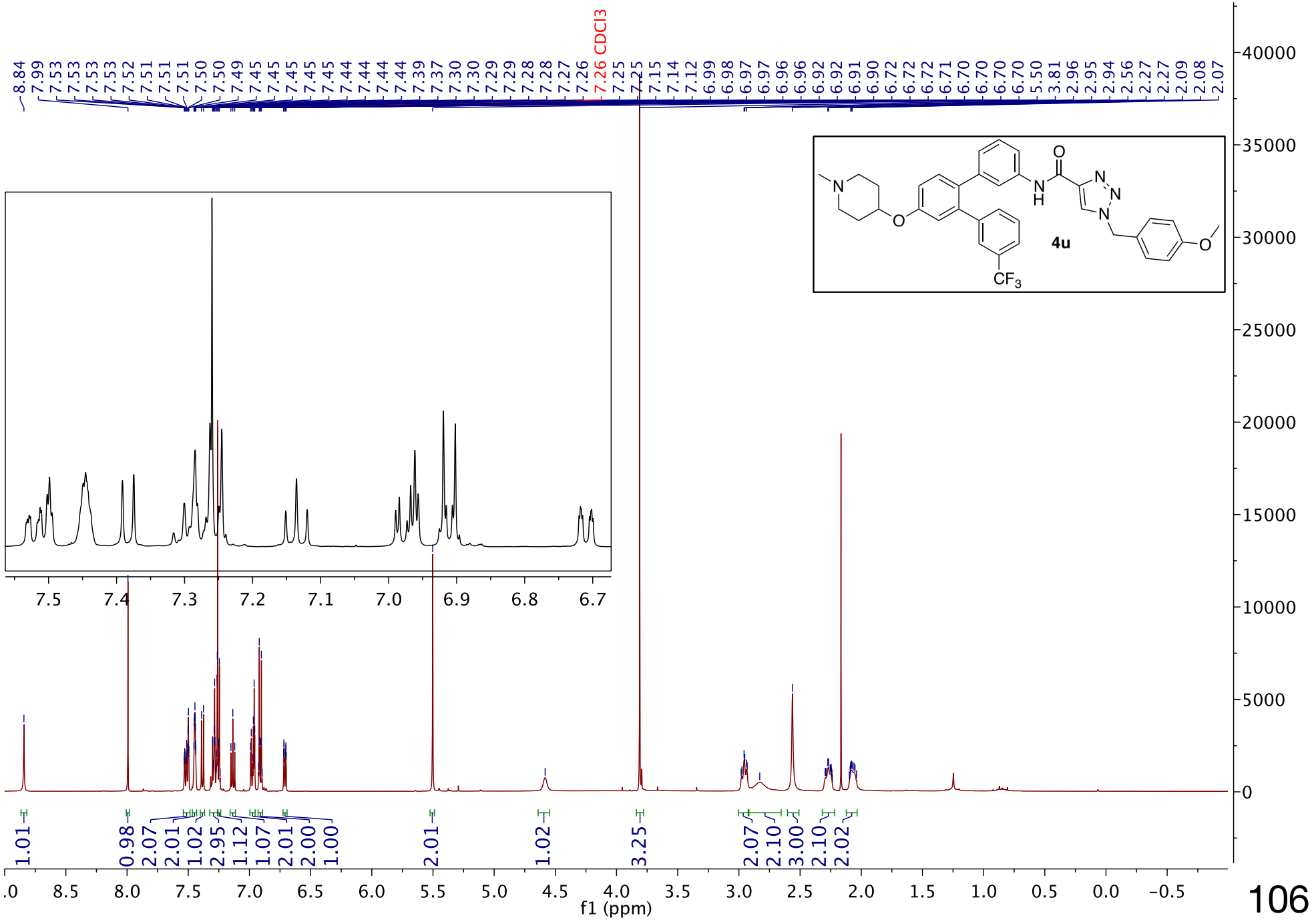
156.66
148.33
144.13
142.04
140.80
140.37
137.02
135.73
133.25
132.99
131.98
130.61
128.93
128.47
127.33
126.54
126.51
126.48
126.44
125.17
124.55
123.00
120.84
119.52
118.21
115.32
77.16 CDCl3
70.83
53.62
51.94
45.71
29.78
4t
NO2
CF3
f1 (ppm)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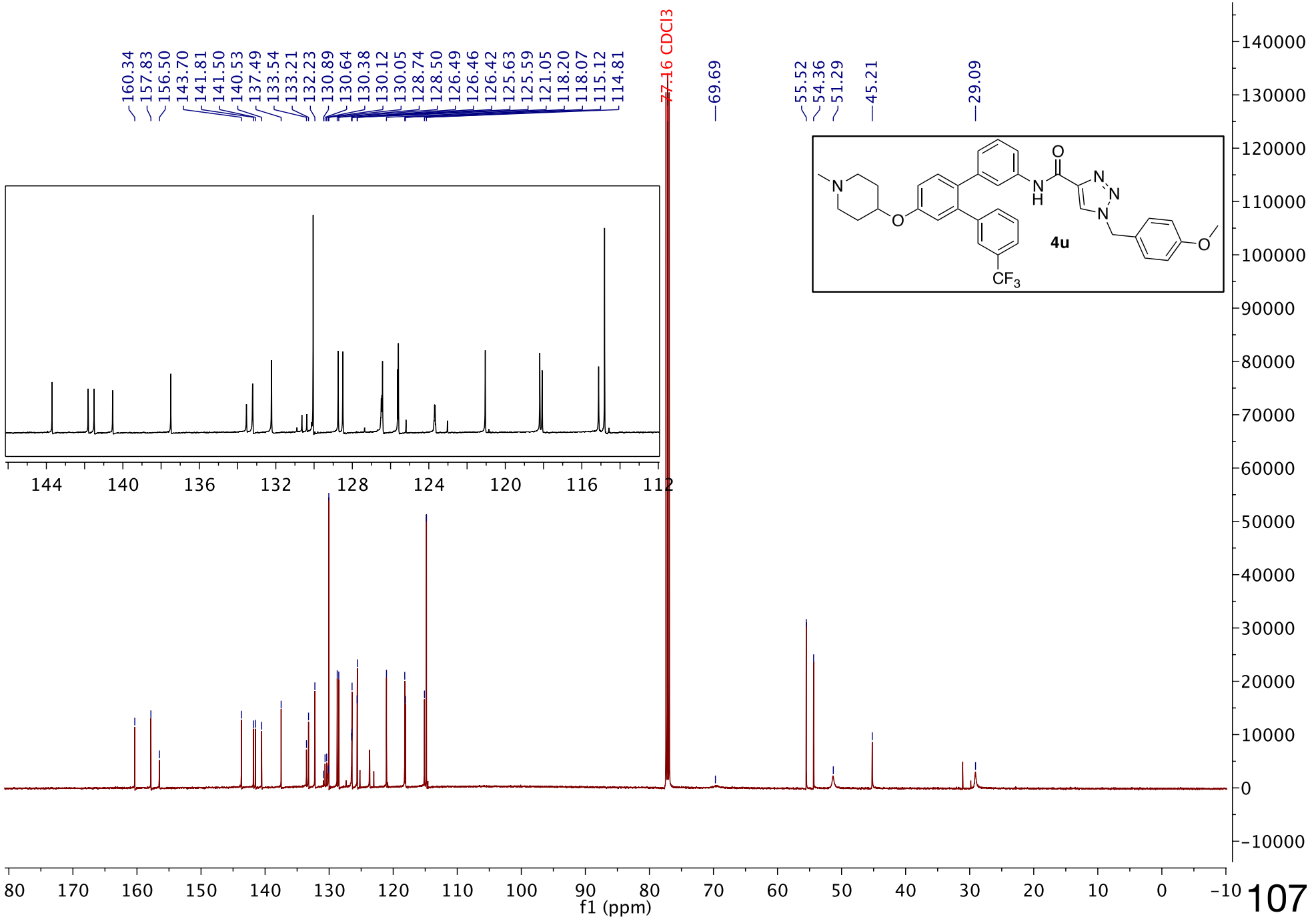
4u
CF3
1.01 0.98 2.07 2.01 1.02 2.95 1.12 1.07 2.01 2.00 1.00 2.01 1.02 3.25 2.07 2.10 3.00 2.10 2.02
f1 (ppm)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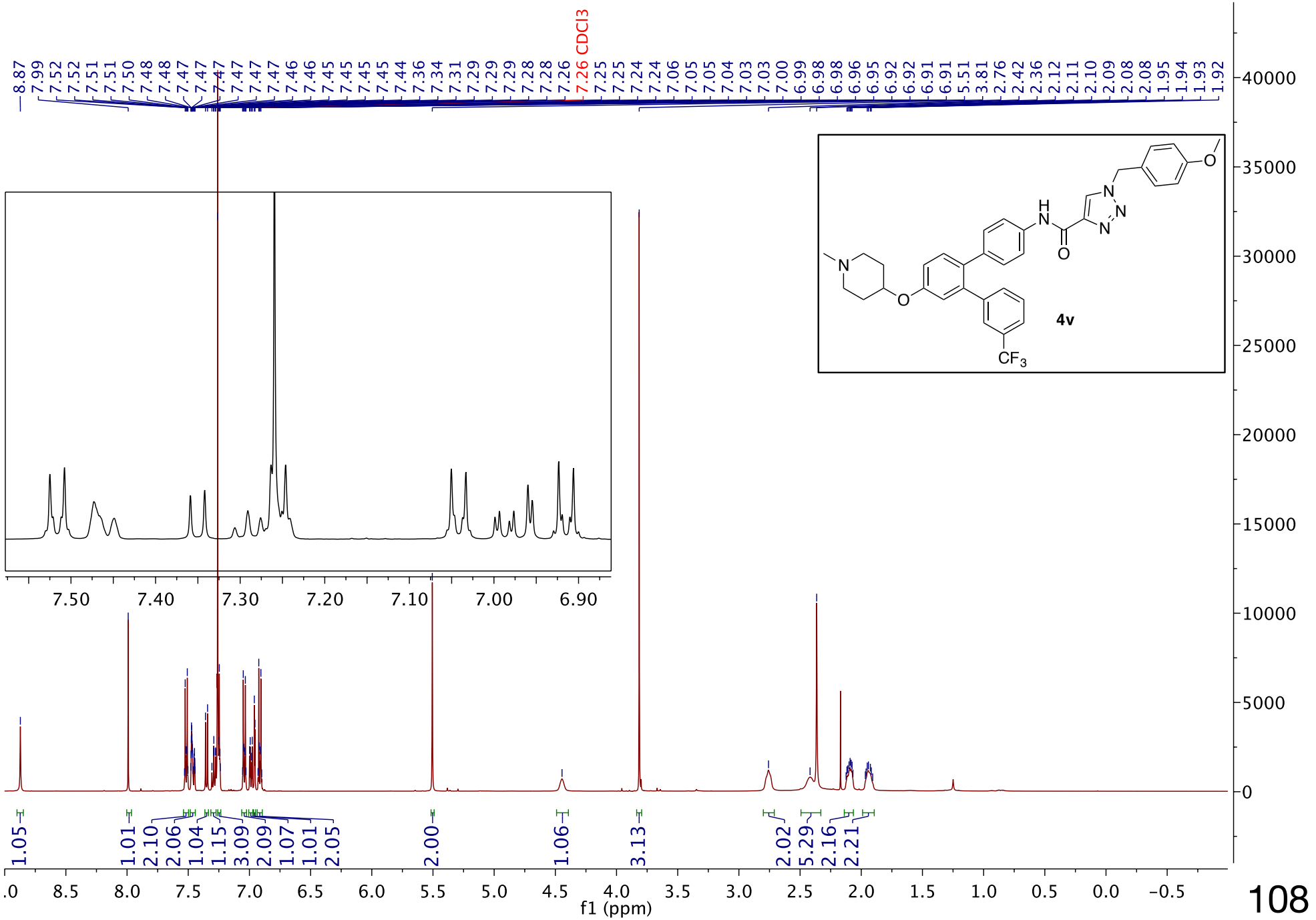
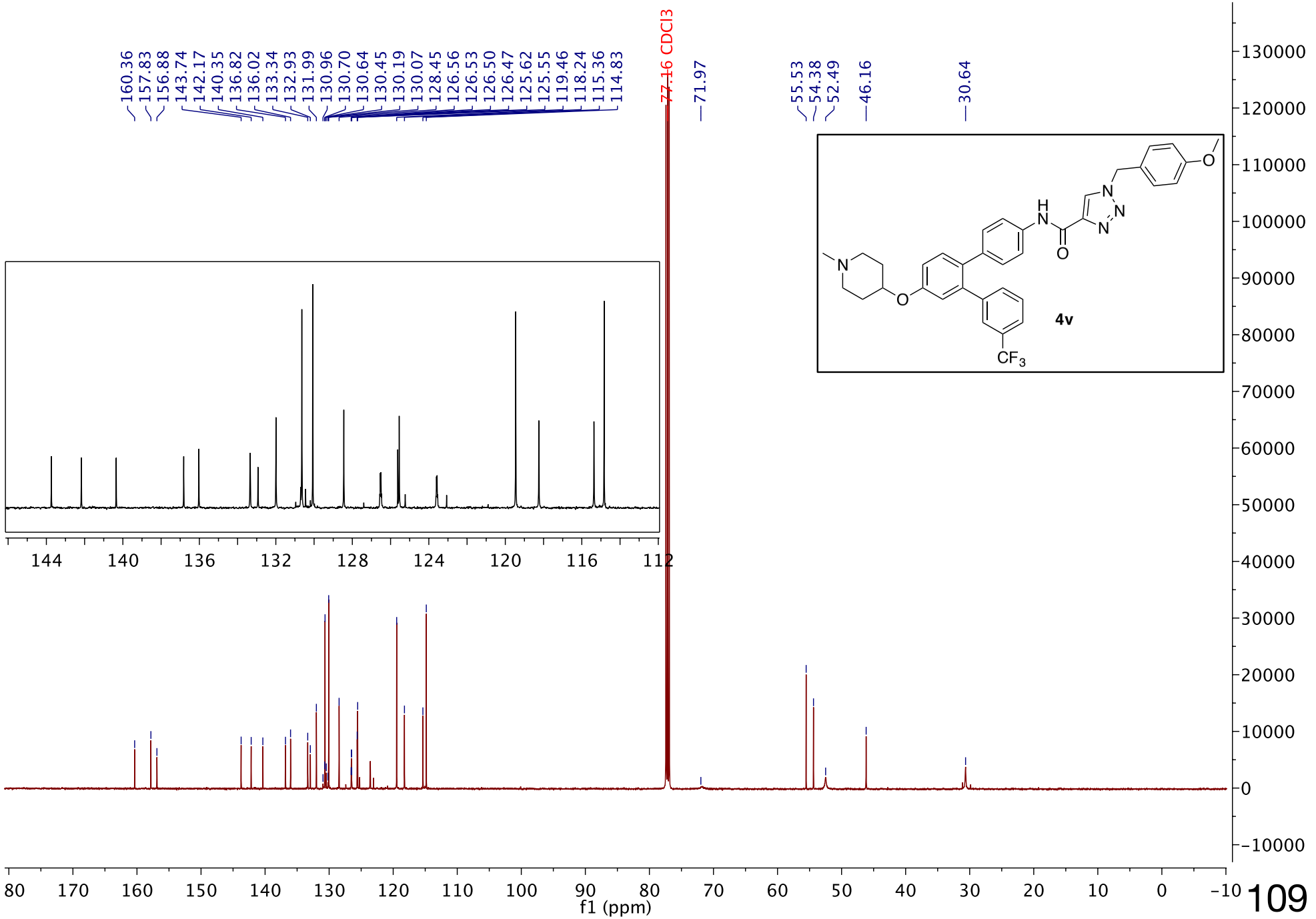
156.50
143.70
141.81
141.50
140.53
137.49
133.54
133.21
132.23
130.89
130.64
130.38
130.12
130.05
128.74
128.50
126.49
126.46
126.42
125.63
125.59
121.05
118.20
118.07
115.12
114.81
77.16 CDCl3
69.69
55.52
54.36
51.29
45.21
29.09
4u
f1 (ppm)


CDCl3
4v
f1 (ppm)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143.74
142.17
140.35
136.82
136.02
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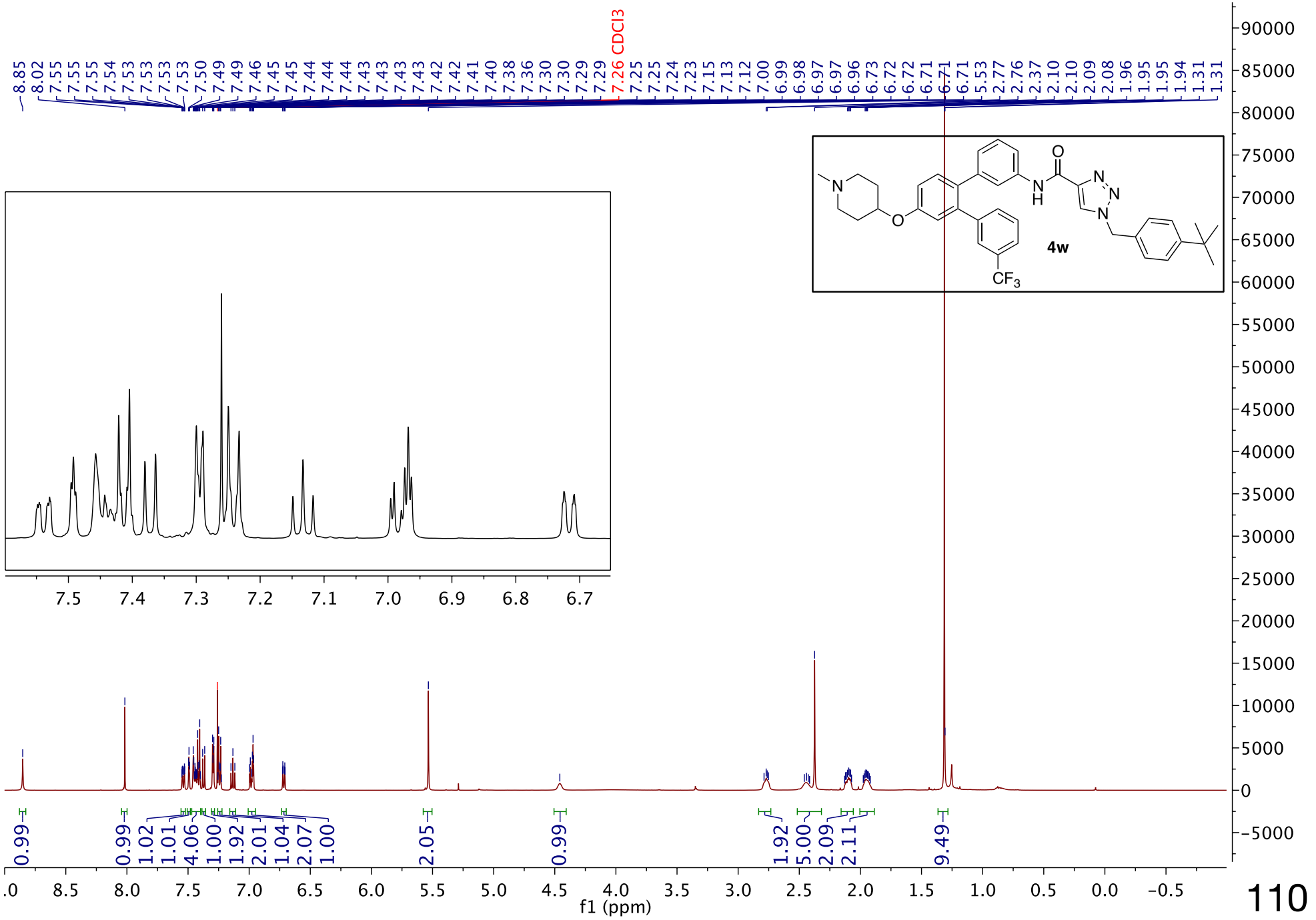
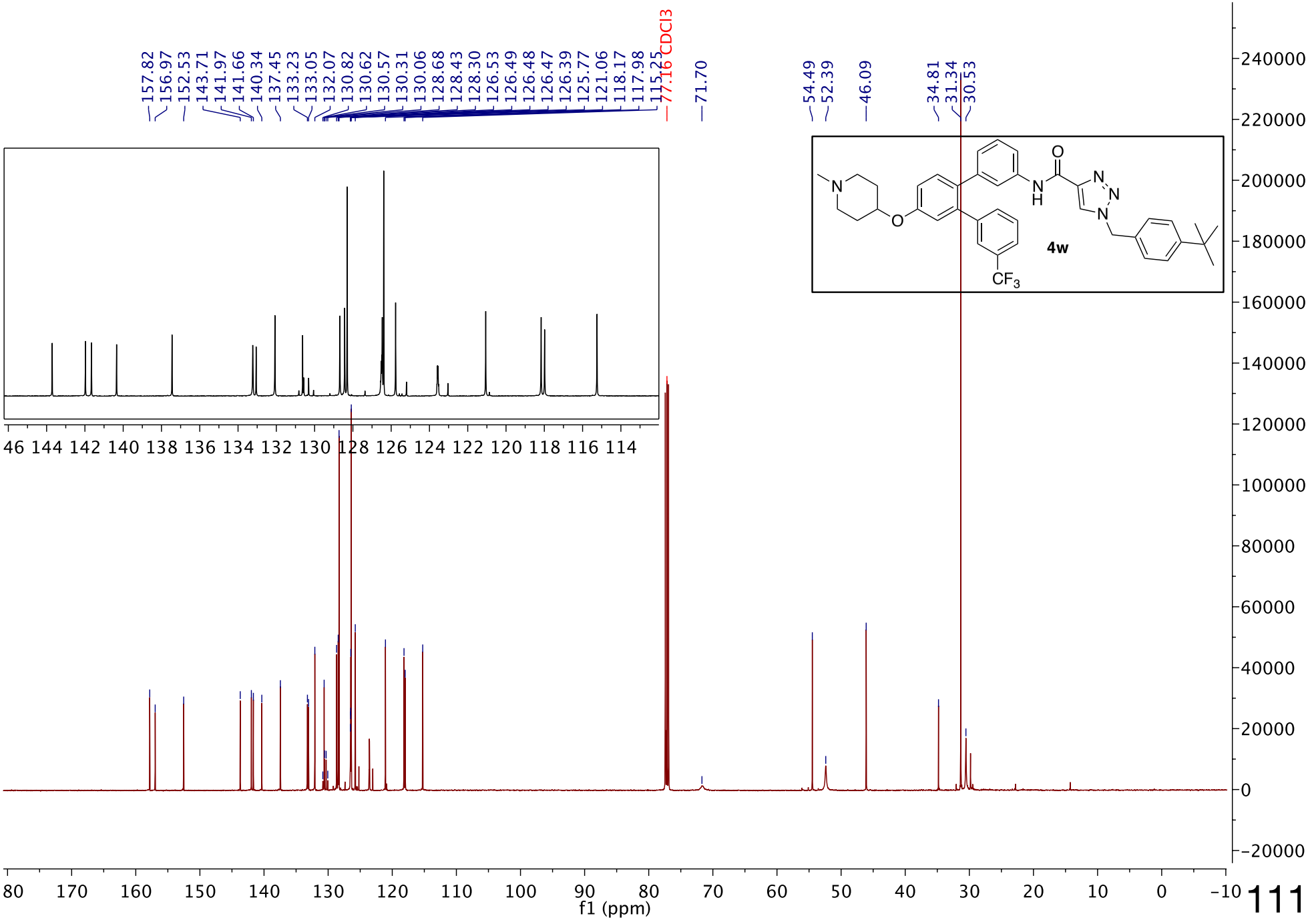
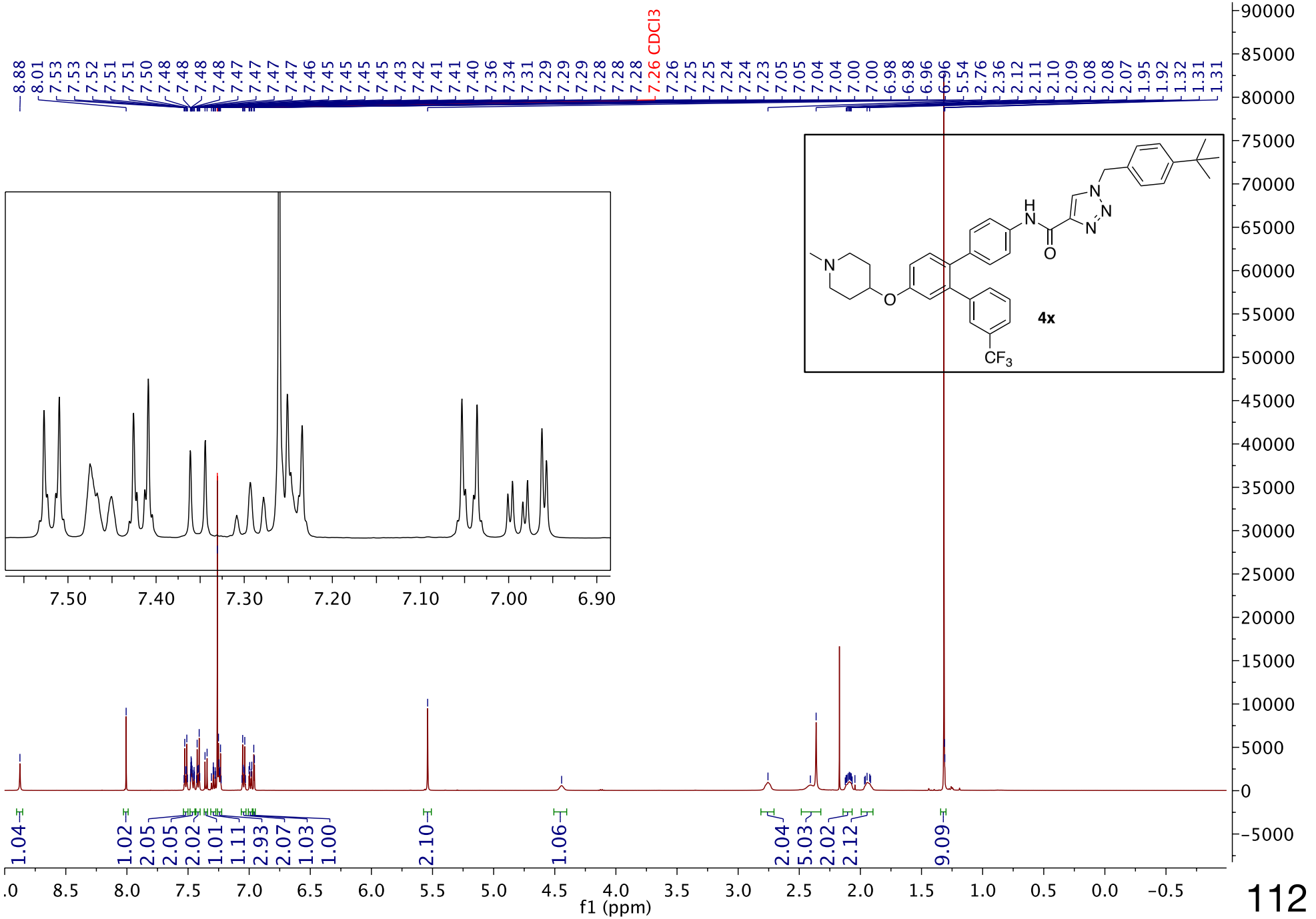
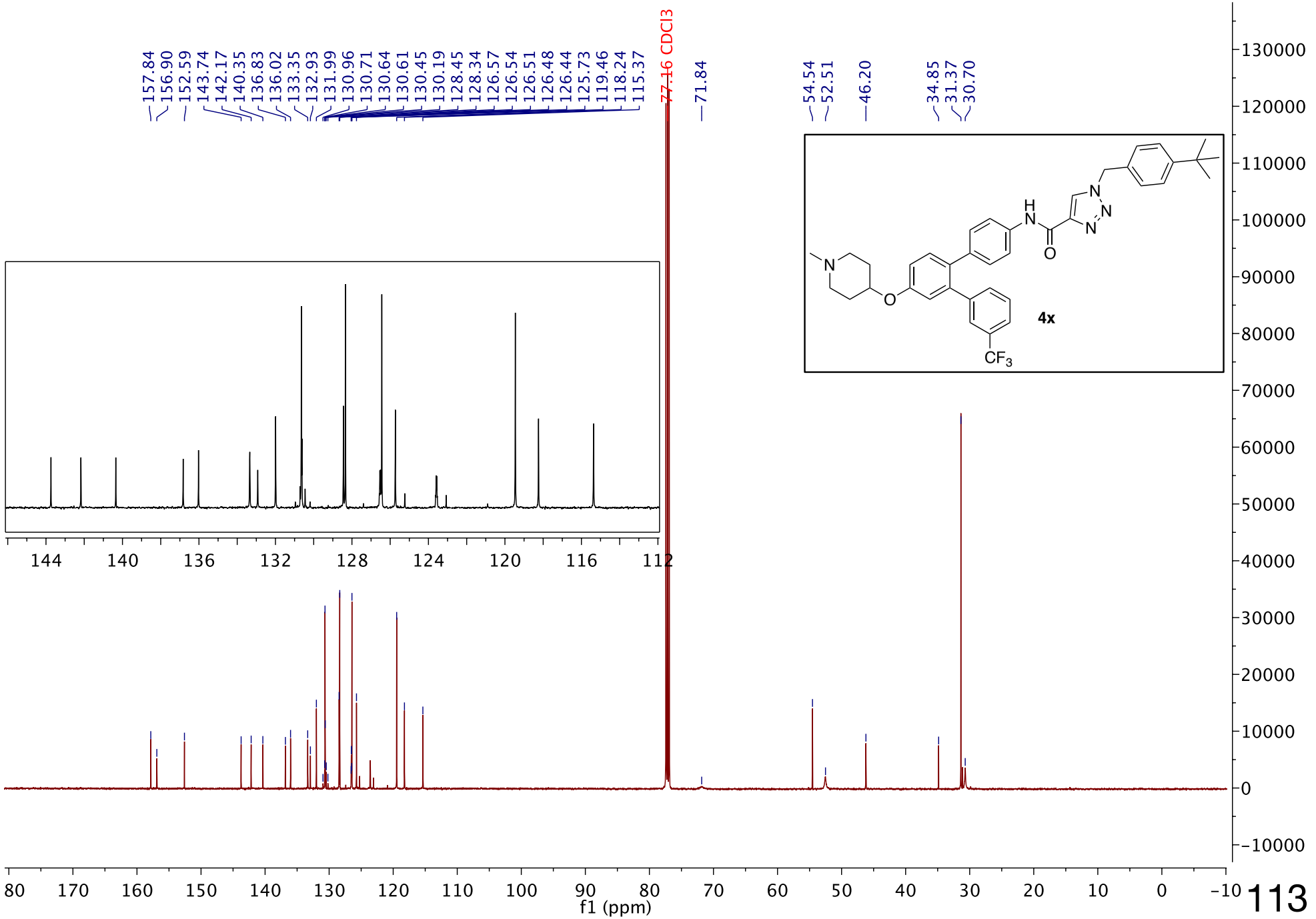
132.93
131.99
130.96
130.70
130.64
130.45
130.19
130.07
128.45
126.56
126.53
126.50
126.47
125.62
125.55
119.46
118.24
115.36
114.83
77.16 CDCl3
71.97
55.53
54.38
52.49
46.16
30.64
4v
f1 (ppm)


8.85 8.02 7.55 7.55 7.55 7.54 7.53 7.53 7.53 7.53 7.50 7.49 7.49 7.46 7.45 7.45 7.44 7.44 7.44 7.43 7.43 7.43 7.43 7.42 7.42 7.41 7.40 7.38 7.36 7.30 7.30 7.29 7.29 7.26 CDCl3 7.25 7.25 7.24 7.23 7.15 7.13 7.12 7.00 6.99 6.98 6.97 6.96 6.73 6.72 6.72 6.71 6.71 6.71 5.53 2.77 2.76 2.37 2.10 2.10 2.09 2.08 1.96 1.95 1.95 1.94 1.31 1.31
4w
CF3
0.99 0.99 1.02 1.01 4.06 1.00 1.92 2.01 1.04 2.07 1.00 2.05 0.99 1.92 5.00 2.09 2.11 9.49
f1 (ppm)


157.82
156.97
152.53
143.71
141.97
141.66
140.34
137.45
133.23
133.05
132.07
130.82
130.62
130.57
130.31
130.06
128.68
128.43
128.30
126.53
126.49
126.48
126.47
126.39
125.77
121.06
118.17
117.98
115.25
77.16 CDCl3
71.70
54.49
52.39
46.09
34.81
31.34
30.53
4w
CF3
f1 (ppm)


CDCl3
4x
f1 (ppm)


157.84
156.90
152.59
143.74
142.17
140.35
136.83
136.02
133.35
132.93
131.99
130.96
130.71
130.64
130.61
130.45
130.19
128.45
128.34
126.57
126.54
126.51
126.48
126.44
125.73
119.46
118.24
115.37
77.16 CDCl3
71.84
54.54
52.51
46.20
34.85
31.37
30.70
4x
f1 (ppm)