Supporting Information

Divergent Synthesis of Monosubstituted and Unsymmetrial 3,6-Disubstituted Tetrazines from Carboxylic Ester Precursors

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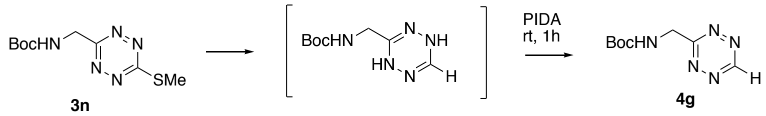
General Considerations Experimental Procedures

All reactions were conducted in flame dried round-bottom flasks. All reactions using microwave heating was conducted in 5 mL microwave reaction tubes. All optimization reactions were conducted in 4 mL sealed vials. Silica gel chromatography was performed on Silicycle Siliaflash irregular P60 silica gel (40-63 μm, 60 Å) or on Yamazen reverse phase prepacked Universal Column C18-silica gel (40-60 μm, 120 Å). Automated column chromatography was performed on a Teledyne Isco Combiflash Rf. Commercially available chemicals were purchased from Sigma-Aldrich, Combi-Blocks, Acros Organics, Alfa Aesar and TCI Chemicals. Solvents were purchased from Thermo Fisher Chemical, Acros Organics and Millipore Sigma. Anhydrous dichloromethane was freshly prepared by an alumina column solvent purification system. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone. Deuterated solvents were purchased from Cambridge Isotope. A Bruker AV400 was used to record NMR spectra (^{1}H: 400 MHz, ^{13}C: 101 MHz). Chemical shifts are reported in ppm. Multiplicities are reported as follow: singlet (s), doublet (d), triplet (t), quartet (q), pentet (pent), sextet (sext), heptet (hept), multiplet (m), 'broad' (br), and 'apparent' (app). ^{13}C NMR resonances are proton decoupled and an APT pulse sequence was used to determine type of carbon as follows: quaternary and methylene (C or CH_2) carbons appear 'up' and methine and methyl (CH or CH_3) carbons appear 'down'. High resolution mass spectra were obtained using a Waters GCT Premier. Infrared spectra were taken on a Nicolet Magna IR 560 spectrometer. Stopped-flow kinetics were obtained using an Applied Photophysics Ltd. SX 18MV-R stopped-flow spectrophotometer.

Optimization

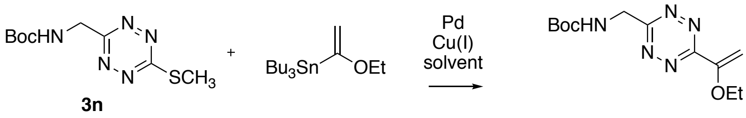
Table S1. Optimization of synthesizing 3-monosubstituted tetrazines.



All reactions were conducted with 0.04 mmol scale of **3n** at concentration of 0.1 M THF (entry 9 is in 0.1 M toluene). Oxidation of dihydrotetrazine was accomplished by adding PIDA (1 equiv.) and stirring at room temperature for 1 h. Yield was calculated by NMR with benzyl benzoate as internal standard.

Entry	Catalyst	Reductant	Temperature	Time	Conversion (%)	NMR Yield (%)
1	5%wt Pd/C (10 mol%)	$HSiEt_3$ (4 equiv.)	r.t.	24 h	3	Trace
2	5%wt Pd/C (10 mol%)	hydrogen	r.t.	24 h	3	Trace
3	5%wt Pd/C (10 mol%)	$HSiEt_3$ (4 equiv.)	70 °C	3 h	94	52
4	$PdCl_2$ (10 mol%)	$HSiEt_3$ (4 equiv.)	70 °C	3 h	97	69
5	$Pd(OAc)_2$ (10 mol%)	$HSiEt_3$ (4 equiv.)	70 °C	3 h	96	59
6	$PdCl_2(ACN)_2$ (10 mol%)	$HSiEt_3$ (4 equiv.)	70 °C	3 h	95	61
7	$[PdCl(allyl)]_2$ (10 mol%)	$HSiEt_3$ (4 equiv.)	70 °C	3 h	90	58
8	$Pd(acac)_2$ (10 mol%)	$HSiEt_3$ (4 equiv.)	70 °C	3 h	86	49
9	$Ni(cod)_2$ (10 mol%)	$HSiEt_3$ (4 equiv.)	70 °C	2 h	2	0
10	$NiCl_2$ (10 mol%)	$HSiEt_3$ (4 equiv.)	70 °C	2 h	1	0
11	$PdCl_2$ (10 mol%)	$HSiEt_3$ (6 equiv.)	70 °C	3 h	100	51
12	$PdCl_2$ (10 mol%)	$HSiEt_3$ (3 equiv.)	70 °C	3 h	88	80
13	$PdCl_2$ (10 mol%)	$HSiEt_3$ (3 equiv.)	45 °C	20 h	90	83
14	$PdCl_2$ (10 mol%)	$HSiEt_3$ (3 equiv.)	45 °C	30 h	73	66
15	$PdCl_2$ (10 mol%)	$HSiEt_3$ (3 equiv.)	r.t.	30 h	61	57

Table S1. Optimization of synthesizing 3-monosubstituted tetrazines.



All reactions were conducted with 0.04 mmol scale of **3n** and 2 equiv. of α-tributylstannyl ethylvinylether. Yields were calculated by NMR with benzyl benzoate as an internal standard. PIDA (1 equiv.) was added after reactions with CuBr•SMe_2 due to tetrazine reduction under these conditions.

Entry	Catalyst	Cu	Solvent (conc. of **3n**)	Temperature	Time	NMR yield (%)
1	$Pd_2(dba)_3$ (10 mol%) PPh_3 (40 mol%)	CuTc (2 equiv.)	THF (0.1 M)	70 °C	30 min	10
2	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	THF (0.1 M)	70 °C	30 min	16
3	$Pd(PPh_3)_4Cl_2$ (20 mol%)	CuTc (2 equiv.)	THF (0.1 M)	70 °C	30 min	14
4	$Pd(dppf)Cl_2$ (20 mol%)	CuTc (2 equiv.)	THF (0.1 M)	70 °C	30 min	11
5	$Pd(OAc)_2$ (20 mol%) PPh_3 (40 mol%)	CuTc (2 equiv.)	THF (0.1 M)	70 °C	30 min	0
6	$Pd(PPh_3)_4$ (20 mol%)	CuBr·SMe_2 (2.2 equiv.)	dioxane (0.1 M)	50 °C	14 h	25
7	$Pd(PPh_3)_4Cl_2$ (20 mol%)	CuBr·SMe_2 (2.2 equiv.)	dioxane (0.1 M)	50 °C	14 h	24
8	$Pd(PPh_3)_4$ (20 mol%)	CuBr·SMe_2 (3 equiv.)	THF (0.1 M)	50 °C	14 h	24
9	$Pd(PPh_3)_4$ (20 mol%)	CuBr·SMe_2 (2.2 equiv.)	THF (0.1 M)	50 °C	14 h	24
10	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	THF (0.1 M)	70 °C	3 min	30
11	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	THF (0.1 M)	r.t.	1 h	17
12	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	dioxane (0.1 M)	70 °C	6 min	35
13	$Pd(PPh_3)_4$ (20 mol%)	CuTc (1.5 equiv.)	dioxane (0.1 M)	70 °C	10 min	27
14	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	dioxane/hexane 1/1 (0.1 M)	70 °C	30 min	15
15	$Pd(PPh_3)_4$ (20 mol%)	CuMeSal (2 equiv.)	dioxane (25 mM)	70 °C	5 min	34
16	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	dioxane (25 mM)	70 °C	3 min	48
17	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	dioxane (10 mM)	70 °C	8 min	50
18	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	dioxane (5 mM)	70 °C	15 min	55
19	$Pd(PPh_3)_4$ (20 mol%)	CuTc (2 equiv.)	dioxane (2 mM)	70 °C	30 min	35
20	$Pd(PPh_3)_4$ (15 mol%)	CuTc (2 equiv.)	dioxane (5 mM)	70 °C	15 min	58
21	$Pd(PPh_3)_4$ (15 mol%)	CuTc (2 equiv.)	dioxane (5 mM)	100 °C	16 min	61
22	$Pd(PPh_3)_4$ (15 mol%)	CuTc (2 equiv.)	dioxane (5 mM)	100 °C	18 min	58
23	$Pd(PPh_3)_4$ (15 mol%)	CuTc (2 equiv.)	dioxane (5 mM)	100 °C	20 min	57

Tetrazine stability in PBS buffer in ambient light at 25°C

Solutions (3 mL) of tetrazine **5b**, **5l** and **6c** (400 μM) were prepared in PBS buffer (pH 7.4) in vials and stored in ambient light at 25 °C. Tetrazine concentrations were determined by recording the absorbance at 518 nm (**6c**) and 520 nm (**5b** and **5l**) in cuvettes in day 0, 1, 3 and 5. A solution of **6a** (50 μM) was prepared in PBS buffer (pH 7.4) in vials and stored in ambient light at room temperature. Tetrazine concentration was determined by recording the absorbance at 520 nm in cuvettes at day 0, 1, 3 and 5. Results show **5b**, **5l**, **6c** and **6a** have 1.8%, 1.7%, 3.9% and 0.8% decomposition per day respectively.

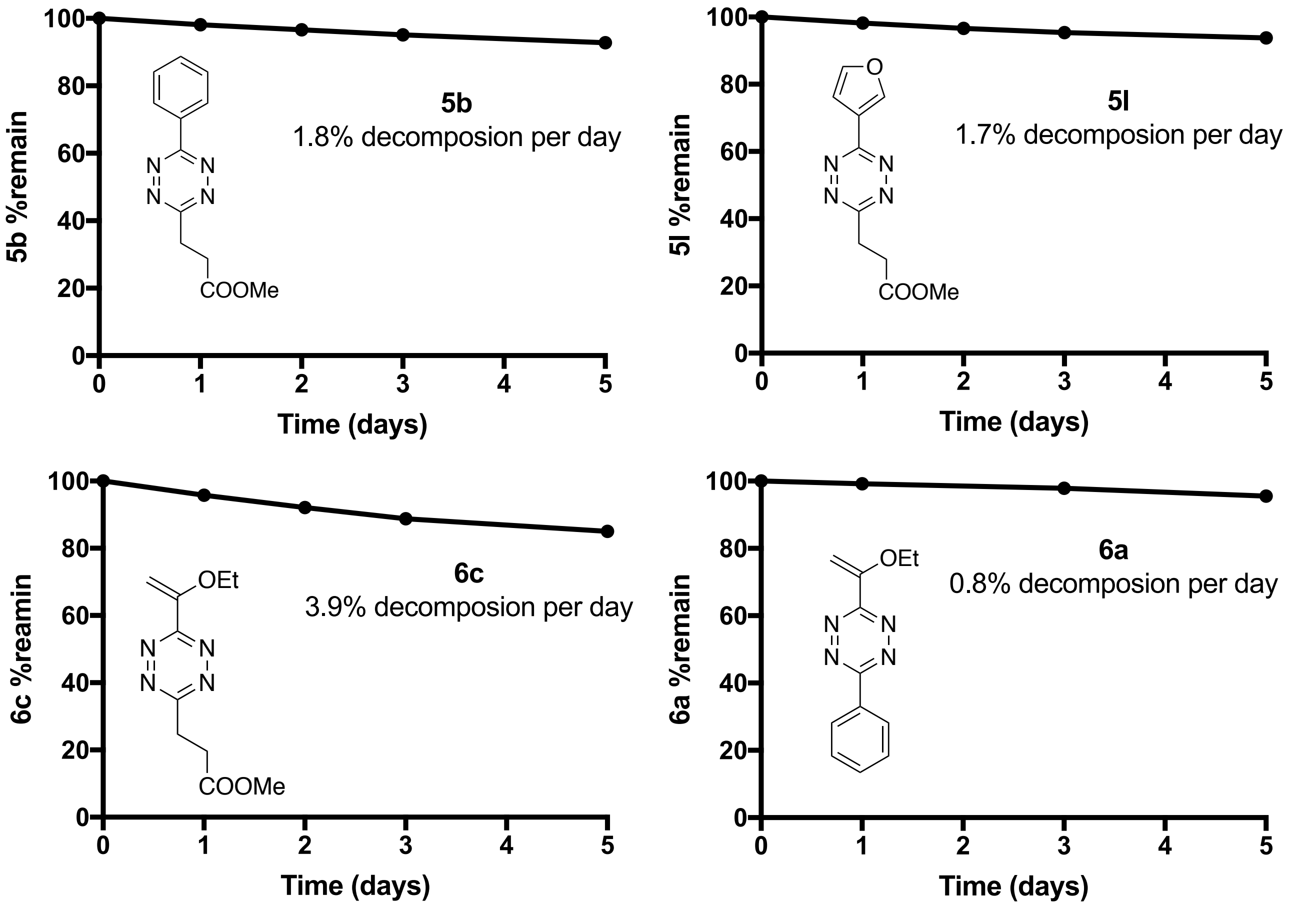
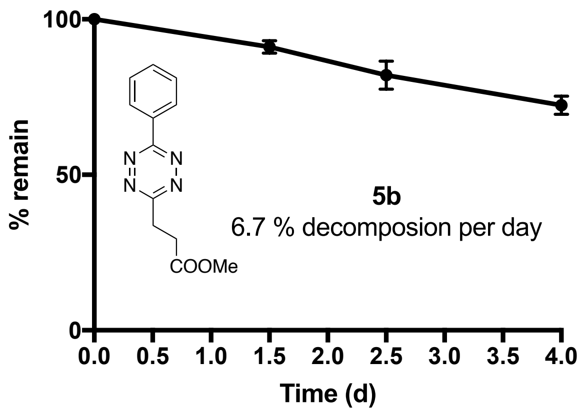


Figure S1A. Stability of tetrazine **5b**, **5l**, **6c** and **6a** in PBS buffer in ambient light at 25 °C

Tetrazine stability in Opti-MEM media in ambient light at 25°C

Solutions (10 mL) of tetrazine **5b** and **6c** (400 μM) were prepared in Opti-MEM media in vials and stored in ambient light at 25 °C. 2 mL of solution was extracted by 2 mL of Et_2O in different time point. Tetrazine concentrations were determined by recording the absorbance of Et_2O at 545 nm. Results show **5b** and **6c** have 6.7% and 10.8% decomposition per day respectively.



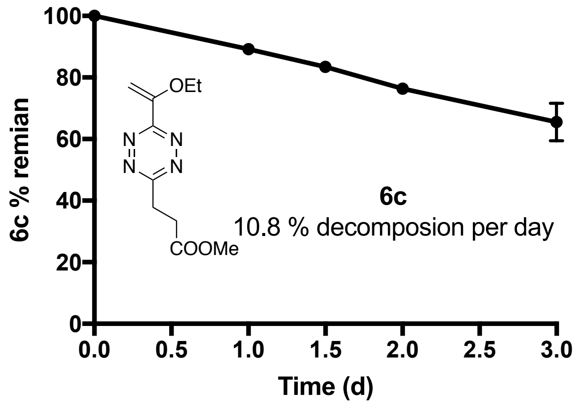
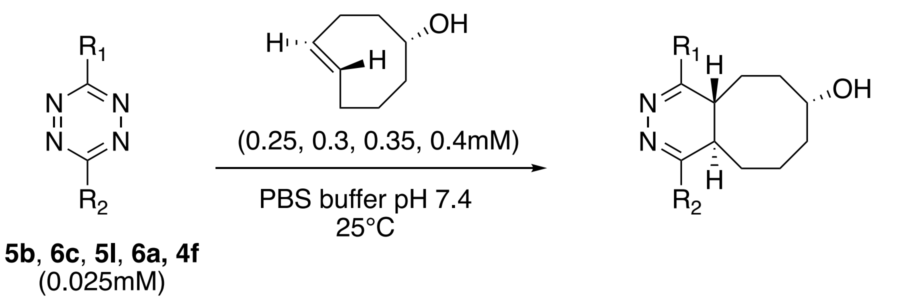


Figure S1B. Stability of tetrazine **5b** and **6c** in Opti-MEM media in ambient light at 25 °C

Stopped-flow kinetic analysis of terazines 5b, 6b, 6h, 6e and 4f with *eq*-5-hydroxy-*trans*-cyclooctene in PBS buffer at 25°C



Solutions (5 mL) of tetrazines **5b**, **6c**, **5l**, **6a** and **4f** (0.050 mM) was prepared in PBS buffer (pH 7.4). Solutions (10 mL) of *eq*-5-hydroxy-*trans*-cyclooctene (0.50, 0.60, 0.70, 0.80 mM) were prepared in PBS buffer (pH 7.4). The reactions between tetrazines and *trans*-cyclooctene were measured under pseudo-first order conditions using SX 18MV-R stopped-flow spectrophotometer (Applied Photophysics Ltd.). Each solution of tetrazine and *trans*-cyclooctene were injected in equal volumes via 3 mL syringes into the stopped-flow instrument at 25 °C, resulting in final concentration of 0.025 mM of tetrazines and 0.25, 0.30, 0.35, 0.40 mM *trans*-cyclooctene. The reaction was monitored by the decay of absorbance associated with the tetrazines (**5b** at 263 nm, **6c** at 268 nm, **5l** at 274 nm, **6a** at 296 nm, **4f** at 266 nm). Reaction were repeated in triplicate. With Prism software, an observed rate constant, k_{obs}, was obtained by nonlinear regression. Second order rate constants, k_2, were calculated by linear regression between k_{obs} and final concentration of *trans*-cyclooctene.

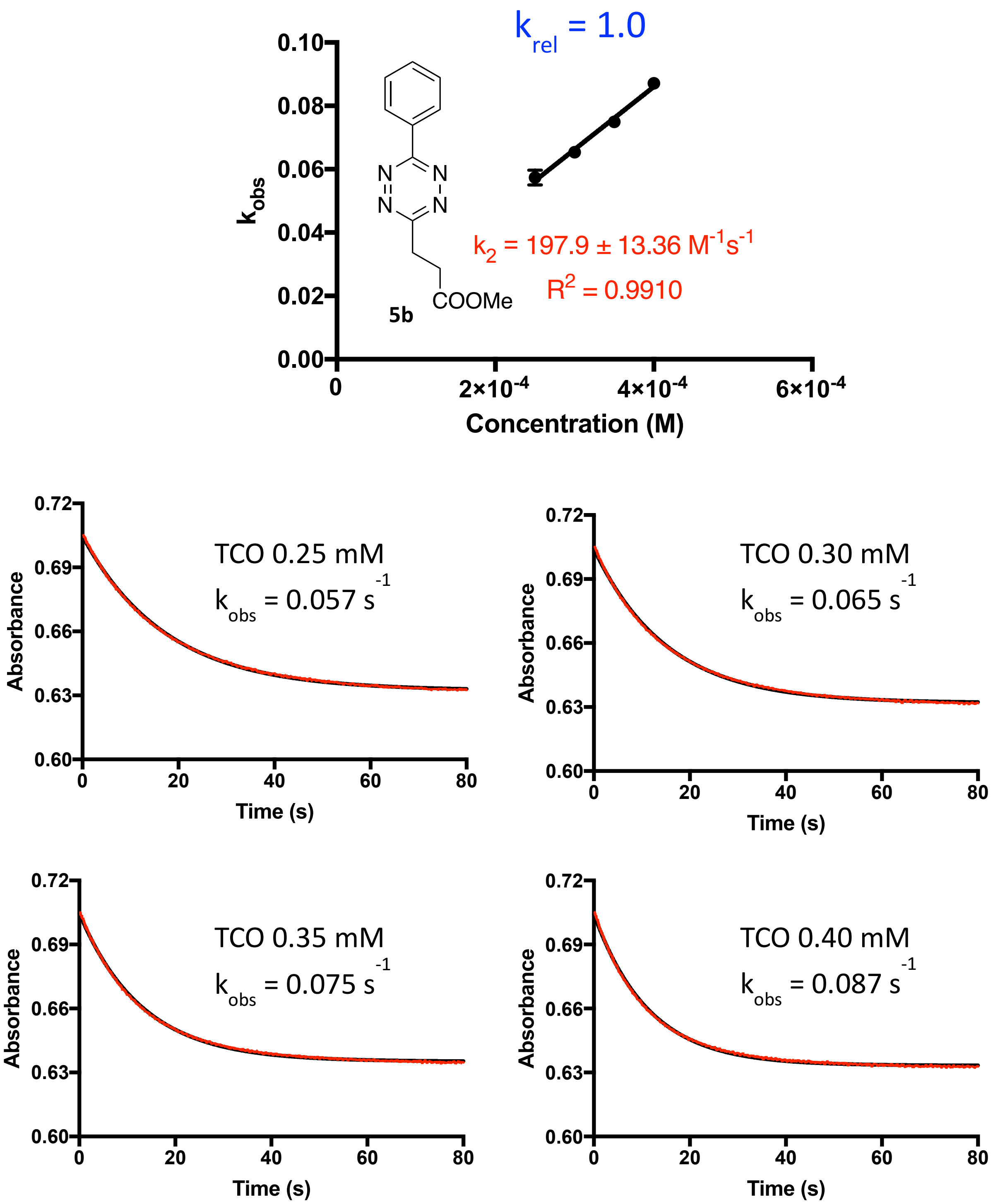


Figure S2A Pseudo-first order stopped-flow kinetics of tetrazine **5b** and eq. 5-hydoxy-*trans*-cyclooctene. The plot shows the decay of absorbance at 263 nm measured by a stopped-flow instrument (red curve). The nonlinear regression calculation by prism software is fitted as black curve. Triplicate k_{obs} results are show on plot of k_{obs} across four different concentrations of trans-cyclooctene. Second-order rate constant k_2 was calculated by prism software, indicating relative rate, k_{rel}, of **5b** as 1.0.

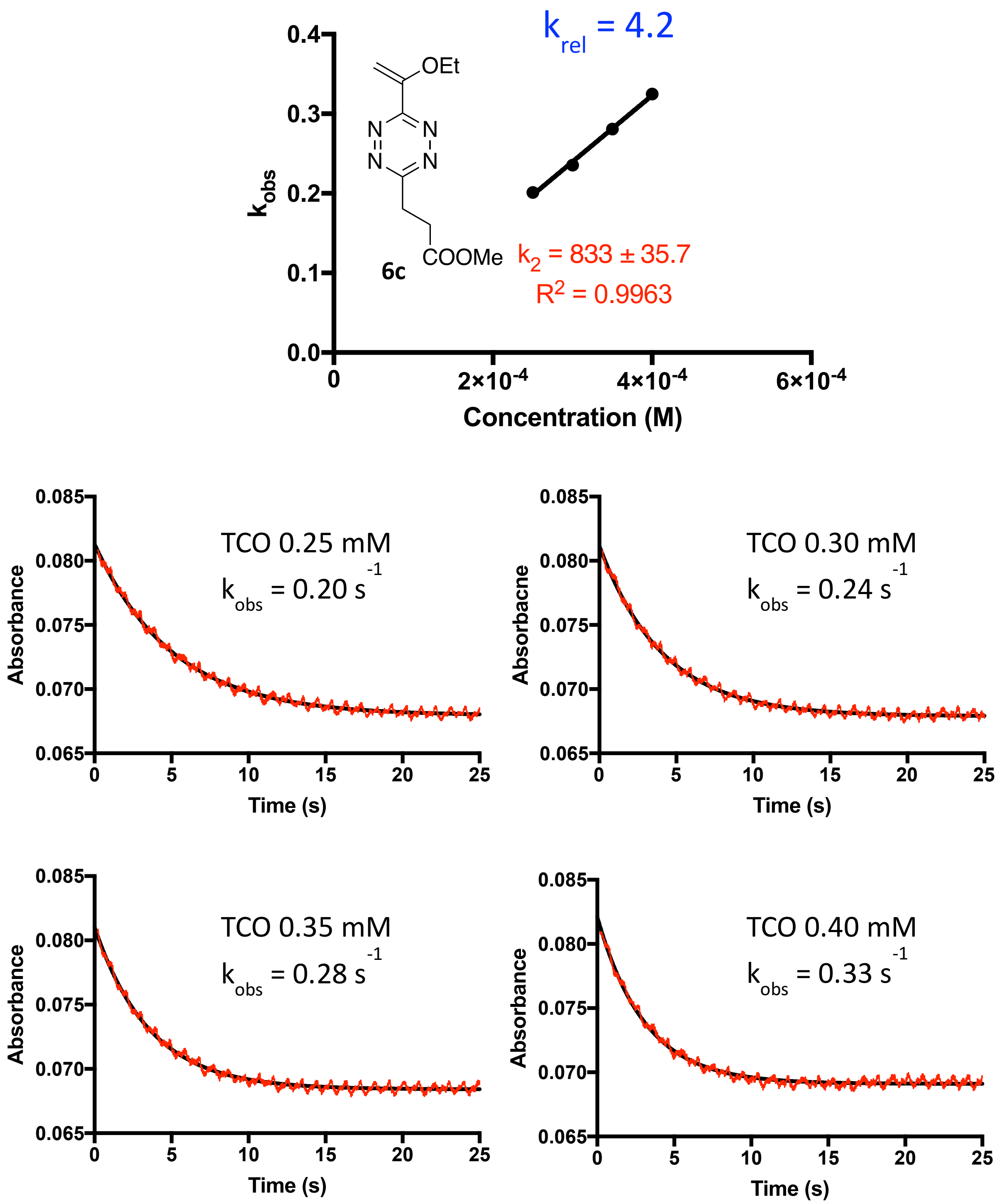


Figure S2B Pseudo-first order stopped-flow kinetics of tetrazine **6c** and eq. 5-hydoxy-*trans*-cyclooctene. The plot shows the decay of absorbance at 268 nm measured by a stopped-flow instrument (red curve). The nonlinear regression calculation by prism software is fitted as black curve. Triplicate k_{obs} results are show on plot of k_{obs} across four different concentrations of *trans*-cyclooctene. Second-order rate constant k_2 was calculated by prism software, indicating relative rate, k_{rel}, of **6c** as 4.2.

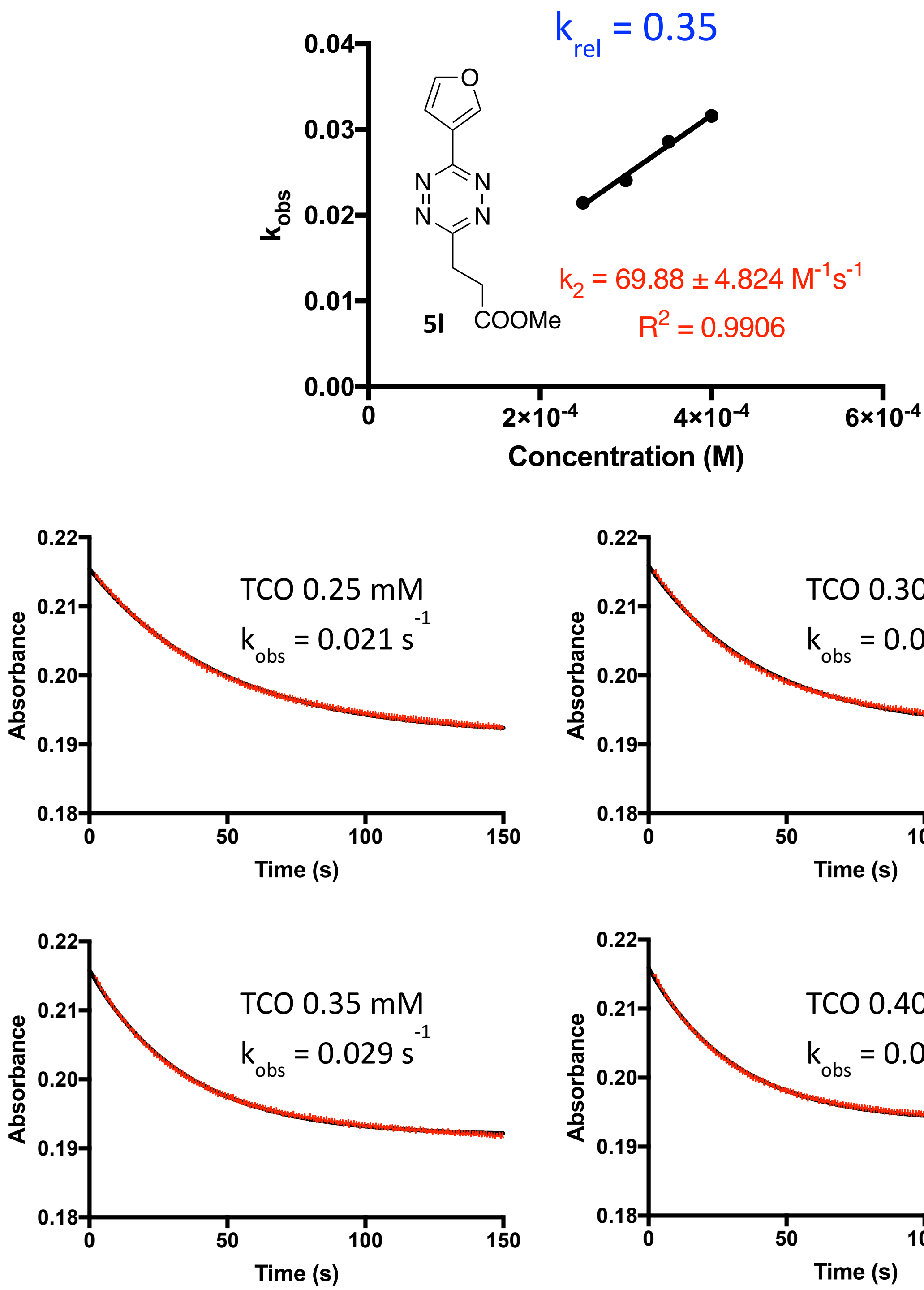


Figure S2C Pseudo-first order stopped-flow kinetics of tetrazine **5l** and eq. 5-hydoxy-*trans*-cyclooctene. The plot shows the decay of absorbance at 274 nm measured by a stopped-flow instrument (red curve). The nonlinear regression calculation by prism software is fitted as black curve. Triplicate k_{obs} results are show on plot of k_{obs} across four different concentrations of *trans*-cyclooctene. Second-order rate constant k_2 was calculated by prism software, indicating relative rate, k_{rel}, of **5l** as 0.35.

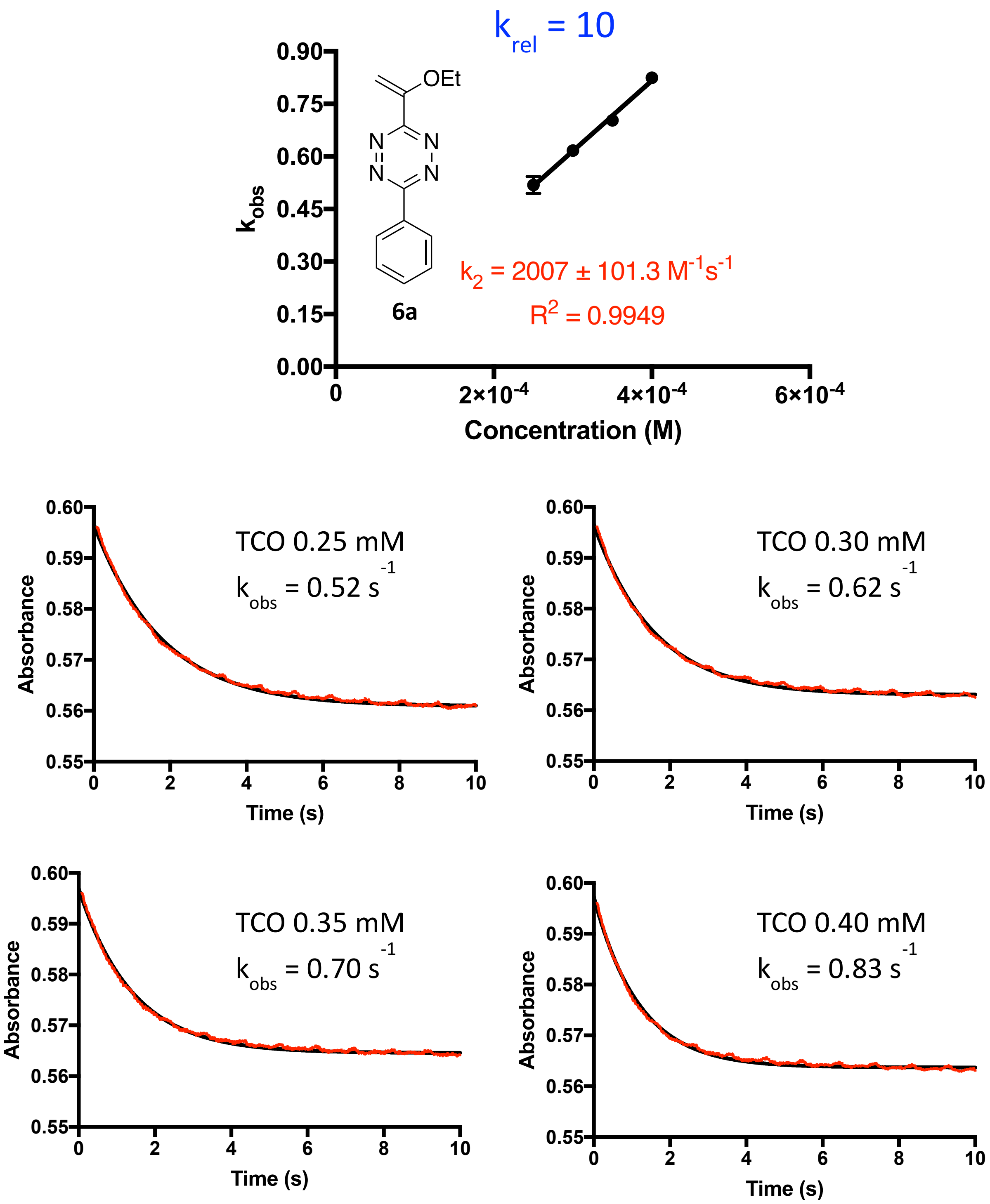


Figure S2D Pseudo-first order stopped-flow kinetics of tetrazine **6a** and eq. 5-hydoxy-*trans*-cyclooctene. The plot shows the decay of absorbance at 296 nm measured by a stopped-flow instrument (red curve). The nonlinear regression calculation by prism software is fitted as black curve. Triplicate k_{obs} results are show on plot of k_{obs} across four different concentrations of *trans*-cyclooctene. Second-order rate constant k_2 was calculated by prism software, indicating relative rate, k_{rel}, of **6a** as 10.

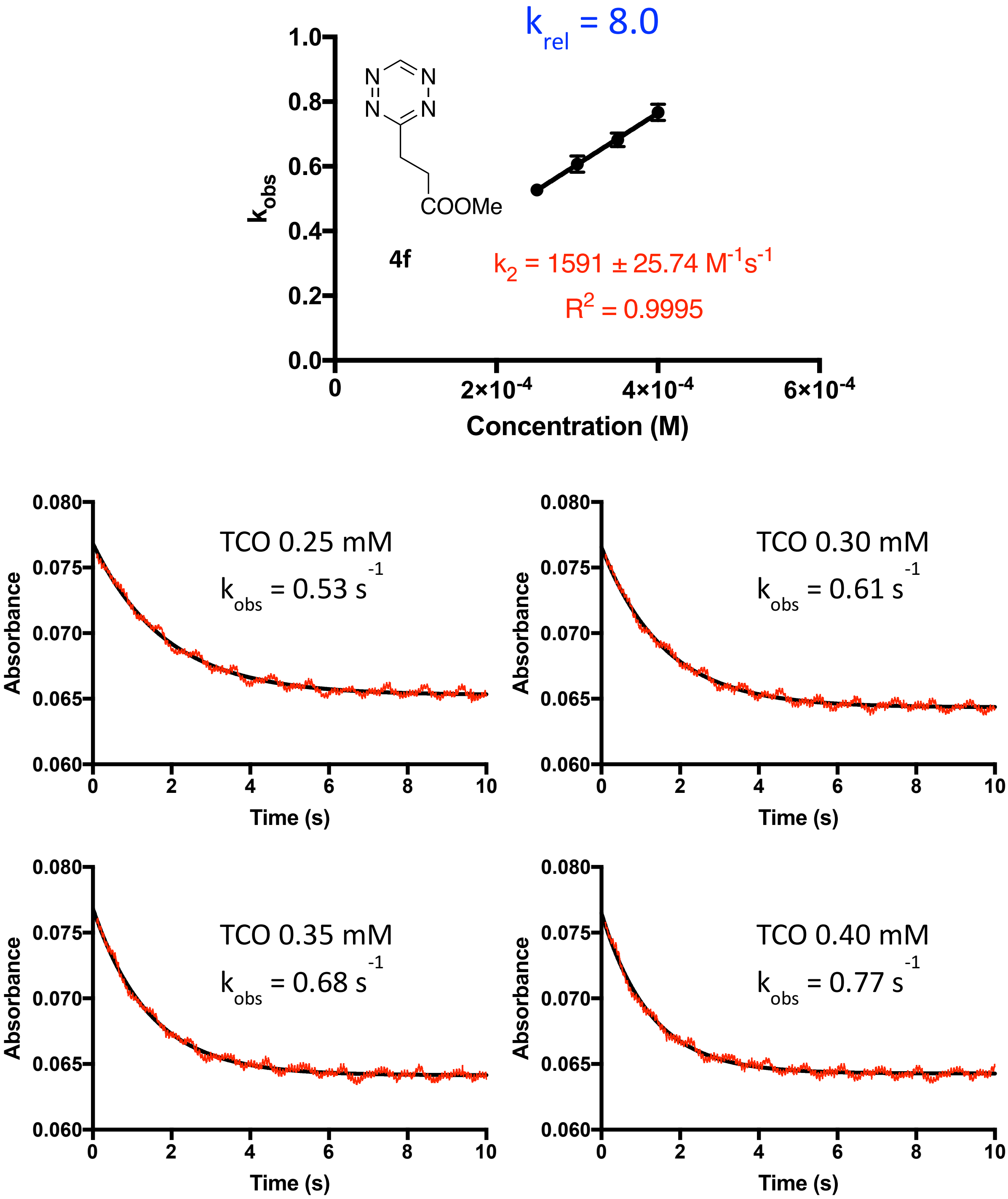


Figure S2E Pseudo-first order stopped-flow kinetics of tetrazine **4f** and eq. 5-hydoxy-*trans*-cyclooctene. The plot shows the decay of absorbance at 266 nm measured by a stopped-flow instrument (red curve). The nonlinear regression calculation by prism software is fitted as black curve. Triplicate k_{obs} results are show on plot of k_{obs} across four different concentrations of *trans*-cyclooctene. Second-order rate constant k_2 was calculated by prism software, indicating relative rate, k_{rel}, of **4f** as 8.0.

Differential Scanning Calorimetry (DSC)

DSC data of *S*-methylisothiocarbonohydrazidium iodide (**2**) was obtained on a Mettler-Toledo Differential Scanning Calorimeter 3+. Samples were loaded into a goldplated high-pressure pan, held at 30°C for 10 minutes, then a gradient of 30°C to 400 °C at 5 °C/min. Appropriate precautions should be followed when handling compound **2**, as this compound is flagged as potentially shock and explosive positive by the Pfizer-modified Yoshida correlation. Quoting Sperry et al.,[1] "The Yoshida correlations are mathematical equations used to predict a material's potential to exhibit impact sensitivity and explosivity as a function of its DSC… Yoshida correlations are meant to be very conservative to ensure that all compounds that have the potential to be either shock-sensitive and/or explosive are flagged. Pfizer (as well as many other pharmaceutical companies) has taken the Yoshida correlations and applied an additional degree of conservatism to further reduce the likelihood of any false negatives so that all materials that could exhibit impact sensitivity or explosivity are thoroughly studied before their use in large-scale manufacture of active pharmaceutical ingredients (APIs) begins."

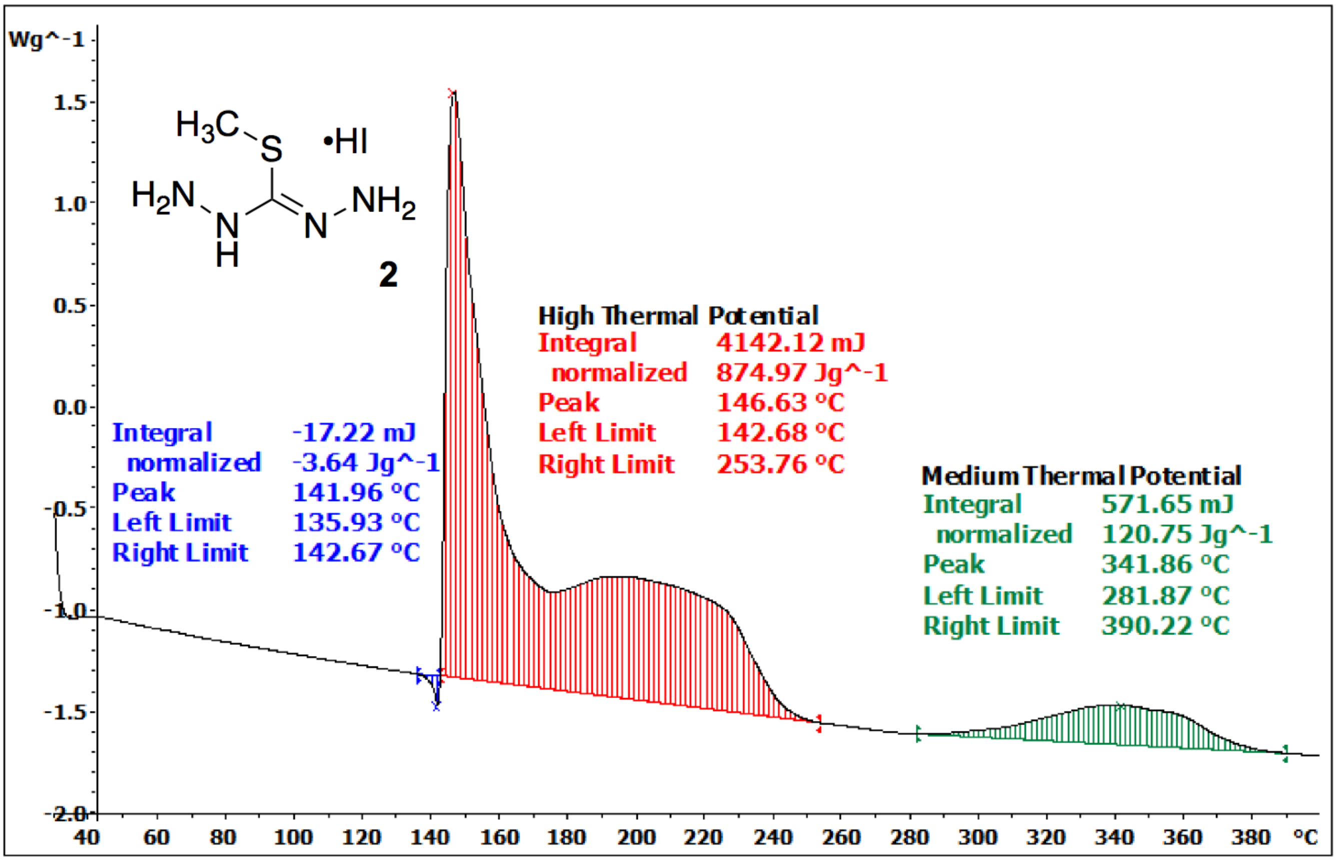
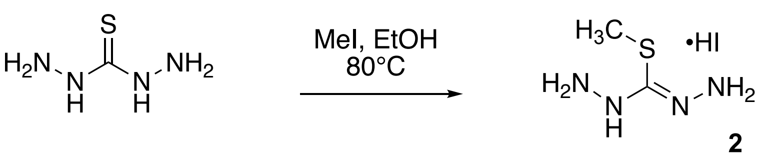


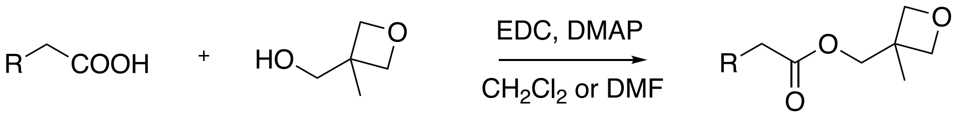
Figure S3 DSC result of methyl thiocarbohydrazide iodide salt **(2)**

Synthesis of methyl thiocarbohydrazide iodide salt (2)



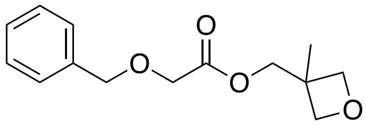
Compound **2** was prepared according to literature protocol.[2] A dry round bottom flask was charged with thiocarbohydrazide (500 mg, 4.71 mmol, 1 equiv.), methyl iodide (323 µL, 5.18 mmol, 1.1 equiv.) and ethanol (15 mL, 0.3 M). After refluxing at 80 °C for 3 h, reaction mixture was cooled down and hexane was added. After cooling down in freezer (-20 °C) overnight, the reaction mixture was filtered, solid was washed with cold ethanol:hexane 1:1 and drying under vacuum, a white solid (700 mg, 2.82 mmol, 60%) was collected and used directly without further purification.

General protocol for the synthesis of oxetane esters



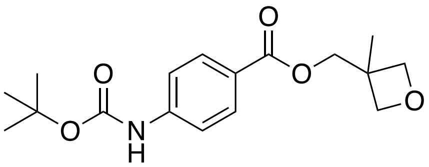
A dry round-bottom flask was charged with 3-methyl-3-oxetanemethanol (1.1 equiv.), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl, 1.2 equiv.) and DMAP (0.10 equiv.). The flask was outfitted with a septum-fitted gas inlet adapter and then evacuated and filled with nitrogen. Anhydrous CH_2Cl_2 or DMF was added to the flask via syringe. The flask was cooled by an ice bath (0 °C), and the carboxylic acid (1 equiv.) was added. After stirring under nitrogen at 0 °C for 15 min and at r.t overnight, the reaction mixture was diluted with CH_2Cl_2. The solution was washed with saturated sodium bicarbonate solution, water and brine, and the organics were dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel.

(3-methyloxetan-3-yl)methyl 2-(benzyloxy)acetate (1a)



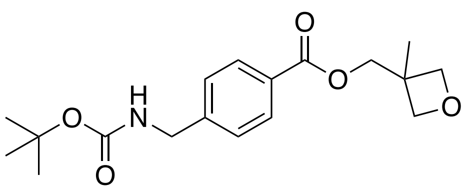
The general protocol was followed with benzyloxyacetic acid (1196 mg, 11.83 mmol), 3-methyl-3-oxetanemethanol (1329 mg, 13.02 mmol), EDC (2721 mg, 14.20 mmol), DMAP (144.5 mg, 1.183 mmol) in CH_2Cl_2 (24 mL, 0.25 M). A colorless oil (2783 mg, 11.12 mmol, 94%) was obtained after column chromatography (Hexane:EA 100:0 to 75:25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.67 (m, 5H), 4.64 (s, 2H), 4.50 (d, *J* = 6.0 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.26 (s, 2H), 4.15 (s, 2H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.56 (C), 137.01 (C), 128.60 (CH), 128.15 (CH), 128.12 (CH), 79.50 (CH_2), 73.45 (CH_2), 68.99 (CH_2), 67.01 (CH_2), 39.12 (C), 21.18 (CH_3). IR (KBr), υ/cm^{-1} 3064, 3031, 2962, 2872, 1750, 1455, 1257, 1197, 1127, 981, 740, 699. HRMS $[M+H]^+$ m/z calcd. for $[C_{14}H_{19}O_4]^+$ 251.1283, found 251.1278.

(3-methyloxetan-3-yl)methyl 4-((*tert*-butoxycarbonyl)amino)benzoate (1b)



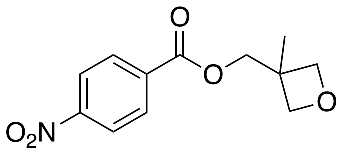
The general protocol was followed with 4-(Boc-amino)benzoic acid (1899 mg, 8.01 mmol), 3-methyl-3-oxetanemethanol (900 mg, 8.81 mmol), EDC (1843 mg, 9.62 mmol), DMAP (97.8 mg, 0.801 mmol) in CH_2Cl_2 (16 mL, 0.5 M). A white solid (2468 mg, 7.68 mmol, 96%) was obtained after column chromatography (Hexane:EA 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (app d, *J* = 8.8 Hz, 2H), 7.43 (app d, *J* = 8.8 Hz, 2H), 6.74 (s, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 4.45 (d, *J* = 6.0 Hz, 2H), 4.37 (s, 2H), 1.53 (s, 9H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.29 (C), 152.26 (C), 143.09 (C), 131.09 (CH), 124.12 (C), 117.52 (CH), 81.42 (C), 79.80 (CH_2), 68.95 (CH_2), 39.45 (C), 28.41 (CH_3), 21.46 (CH_3). IR (KBr), υ/cm^{-1} 3375, 3100, 3060, 2971, 2886, 1724, 1678, 1600, 1543, 1411, 1324, 1240, 1159, 1115, 863, 767. HRMS $[M+H]^+$ m/z calcd. for $[C_{17}H_{24}O_5N]^+$ 322.1654, found 322.1646.

(3-methyloxetan-3-yl)methyl 4-(((*tert*-butoxycarbonyl)amino)methyl)benzoate (1c)



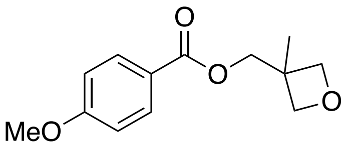
The general protocol was followed with Boc-(4-aminophenyl)acetic acid (2010 mg, 8.01 mmol), 3-methyl-3-oxetanemethanol (900 mg, 8.82 mmol), EDC (1834 mg, 9.62 mmol), DMAP (97.8 mg, 0.801 mmol) in CH_2Cl_2 (16 mL, 0.25 M). A white solid (2520 mg, 7.52 mmol, 94%) was obtained after column chromatography (Hexane:EA 100:0 to 75:25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (app d, *J* = 8.2 Hz, 2H), 7.36 (app d, *J* = 8.2 Hz, 2H), 4.95 (s, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.38 (s, 2H), 4.37 (s, 2H), 1.46 (s, 9H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.46 (C), 156.02 (C), 144.75 (C), 130.11 (CH), 128.97 (C), 127.36 (CH), 79.97 (C), 79.75 (CH_2), 69.12 (CH_2), 44.44 (CH_2), 39.42 (C), 28.52 (CH_3), 21.44 (CH_3). IR (KBr), υ/cm^{-1} 3386, 3008, 2981, 2946, 2880, 1717, 1689, 1517, 1289, 1275, 1246, 1170, 1110, 983, 756. HRMS $[M+H]^+$ m/z calcd. for $[C_{18}H_{26}O_5N]^+$ 336.1811, found 336.1804.

(3-methyloxetan-3-yl)methyl 4-nitrobenzoate (1d)



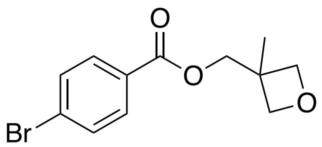
The general protocol was followed with 4-nitro-benzoic acid (1191 mg, 7.12 mmol), 3-methyl-3-oxetanemethanol (800 mg, 7.84 mmol), EDC (1638 mg, 8.55 mmol), DMAP (86.9 mg, 0.712 mmol) in CH_2Cl_2 (35 mL, 0.2 M). A white solid (1520 mg, 6.05 mmol, 85%) was obtained after column chromatography (Hexane:Acetone 10:0 to 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (app d, *J* = 9.0 Hz, 2H), 8.21 (app d, *J* = 9.0 Hz, 2H), 4.61 (d, *J* = 6.1 Hz, 2H), 4.47 (d, *J* = 6.1 Hz, 2H), 4.44 (s, 2H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.70 (C), 150.68 (C), 135.26 (C), 130.82 (CH), 123.71 (CH), 79.49 (CH_2), 69.92 (CH_2), 39.32 (C), 21.24 (CH_3). IR (KBr), υ/cm^{-1} 3010, 3000, 2961, 2874, 1715, 1708, 1607, 1525, 1344, 1280, 1263, 979, 847, 719. HRMS $[M+H]^+$ m/z calcd. for $[C_{12}H_{14}O_5N]^+$ 252.0872, found 252.0863.

(3-methyloxetan-3-yl)methyl 4-methoxybenzoate (1e)



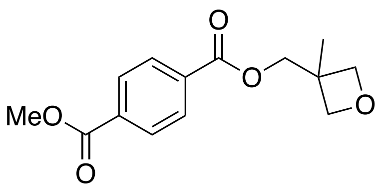
The general protocol was followed with 4-nitro-benzoic acid (608 mg, 3.56 mmol), 3-methyl-3-oxetanemethanol (400 mg, 3.92 mmol), EDC (819 mg, 4.27 mmol), DMAP (43.5 mg, 0.356 mmol) in CH_2Cl_2 (16 mL, 0.25 M). A colorless oil (576 mg, 2.40 mmol, 61%) was obtained after column chromatography (Hexane:Acetone 10:0 to 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (app d, *J* = 8.9 Hz, 2H), 6.93 (app d, *J* = 8.9 Hz, 2H), 4.64 (d, *J* = 5.9 Hz, 2H), 4.45 (d, *J* = 5.9 Hz, 2H), 4.36 (s, 2H), 3.86 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.41 (C), 163.63 (C), 131.79 (CH), 122.38 (C), 113.82 (CH), 79.78 (CH_2), 68.82 (CH_2), 55.59 (CH_3), 39.43 (C), 21.45 (CH_3). IR (KBr), υ/cm^{-1} 3078, 2962, 2871, 1717, 1607, 1512, 1256, 1168, 1103, 982, 770. HRMS $[M+H]^+$ m/z calcd. for $[C_{13}H_{17}O_4]^+$ 237.1127, found 237.1120.

(3-methyloxetan-3-yl)methyl 4-bromobenzoate (1f)



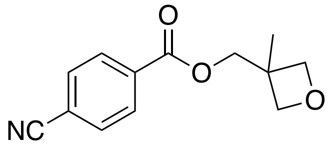
The general protocol was followed with 4-bromobenzoic acid (604 mg, 3.03 mmol), 3-methyl-3-oxetanemethanol (340 mg, 3.33 mmol), EDC (690 mg, 3.64 mmol), DMAP (37.0 mg, 0.303 mmol) in CH_2Cl_2 (15 mL, 0.20 M). A white solid (812 mg, 2.85 mmol, 95%) was obtained after column chromatography (Hexane:EA 10:0 to 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (app d, *J* = 8.6 Hz, 2H), 7.62 (app d, *J* = 8.6 Hz, 2H), 4.65 (d, *J* = 6.0 Hz, 2H), 4.49 (d, *J* = 6.0 Hz, 2H), 4.42 (s, 2H), 1.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.96 (C), 131.97 (CH), 131.28 (CH), 128.87 (C), 128.50 (C), 79.69 (CH_2), 69.37 (CH_2), 39.40 (C), 21.40 (CH_3). IR (KBr), υ/cm^{-1} 3065, 2963, 2873, 1721, 1590, 1484, 1398, 1263, 1174, 1104, 1012, 982, 848, 756. HRMS $[M+H]^+$ m/z calcd. for $[C_{12}H_{14}O_3Br]^+$ 285.0126, found 285.0120.

methyl ((3-methyloxetan-3-yl)methyl) terephthalate (1g)



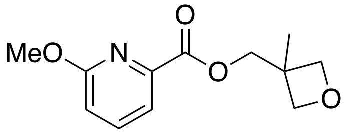
The general protocol was followed with monomethyl terephthalate (1440 mg, 8.01 mmol), 3-methyl-3-oxetanemethanol (900 mg, 8.82 mmol), EDC (1840 mg, 9.62 mmol), DMAP (97.9 mg, 0.801 mmol) in CH_2Cl_2 (32 mL, 0.25 M). A white solid (1956mg, 7.40 mmol, 93%) was obtained after column chromatography (Hexane:EA 10:0 to 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (app s, 4H), 4.65 (d, *J* = 6.0 Hz, 2H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.43 (s, 2H), 3.96 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.36 (C), 165.90 (C), 134.27 (C), 133.74 (C), 129.79 (CH), 129.75 (CH), 79.71 (CH_2), 69.58 (CH_2), 52.67 (CH_3), 39.43 (C), 21.42 (CH_3). IR (KBr), υ/cm^{-1} 3012, 2964, 2936, 2871, 1732, 1716, 1506, 1436, 1395, 1279, 1249, 1125, 1105, 1016, 979, 726. HRMS $[M+H]^+$ m/z calcd. for $[C_{14}H_{17}O_5]^+$ 265.1076, found 265.1067.

(3-methyloxetan-3-yl)methyl 4-cyanobenzoate (1h)



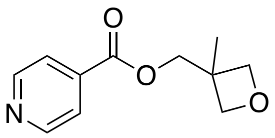
The general protocol was followed with 4-cyanobenzoic acid (608 mg, 3.56 mmol), 3-methyl-3-oxetanemethanol (400 mg, 3.92 mmol), EDC (920 mg, 4.27 mmol), DMAP (43.5 mg, 0.356 mmol) in CH_2Cl_2 (16 mL, 0.25 M). A white solid (795 mg, 3.44 mmol, 86%) was obtained after column chromatography (Hexane:EA 10:0 to 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (app d, *J* = 8.5 Hz, 2H), 7.77 (app d, *J* = 8.5 Hz, 2H), 4.62 (d, *J* = 6.0 Hz, 2H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.44 (s, 2H), 1.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.04 (C), 133.78 (C), 132.48 (CH), 130.28 (CH), 118.05 (C), 116.78 (C), 79.60 (CH_2), 69.86 (CH_2), 39.40 (C), 21.34 (CH_3). IR (KBr), υ/cm^{-1} 3051, 2960, 2927, 2873, 2231, 1725, 1610, 1461, 1406, 1377, 1280, 1264, 1118, 1107, 981, 766. HRMS $[M+H]^+$ m/z calcd. for $[C_{13}H_{14}O_3N]^+$ 232.0974, found 232.0964

(3-methyloxetan-3-yl)methyl 6-methoxypicolinate (1i)



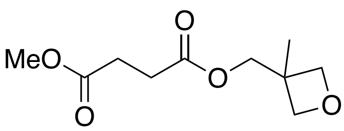
The general protocol was followed with 6-methoxypyridine-2-carboxylic acid (640 mg, 4.18 mmol), 3-methyl-3-oxetanemethanol (472 mg, 4.62 mmol), EDC (962 mg, 5.02 mmol), DMAP (50.9 mg, 0.418 mmol) in CH_2Cl_2 (20 mL, 0.2 M). A colorless oil (833 mg, 3.50 mmol, 84%) was obtained after column chromatography (Hexane:EA 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 - 7.63 (m, 2H), 6.93 (dd, *J* = 7.2, 2.0 Hz, 1H), 4.64 (d, *J* = 6.0 Hz, 2H), 4.44 (d, *J* = 6.0 Hz, 2H), 4.42 (s, 2H), 4.00 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.17 (C), 164.01 (C), 145.21 (C), 139.10 (CH), 118.69 (CH), 115.59 (CH), 79.70 (CH_2), 69.51 (CH_2), 53.69 (CH_3), 39.44 (C), 21.35 (CH_3). IR (KBr), υ/cm^{-1} 3078, 2957, 2872, 1740, 1721, 1595, 1574, 1470, 1415, 1329, 1274, 1140, 1028, 985, 825, 770. HRMS $[M+H]^+$ m/z calcd. for $[C_{12}H_{16}O_4N]^+$ 238.1079, found 238.1073.

(3-methyloxetan-3-yl)methyl isonicotinate (1j)



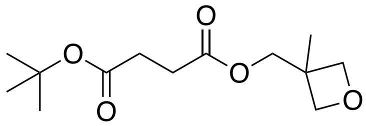
The general protocol was followed with 4-picolinic acid (985 mg, 8.01 mmol), 3-methyl-3-oxetanemethanol (900 mg, 8.82 mmol), EDC (1840 mg, 9.62 mmol), DMAP (97.9 mg, 0.801 mmol) in CH_2Cl_2 (16 mL, 0.5 M). A yellow oil (1410 mg, 6.80 mmol, 85%) was obtained after column chromatography (Hexane:EA 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (app d, *J* = 6.0 Hz, 2H), 7.85 (app d, *J* = 6.0 Hz, 2H), 4.61 (d, *J* = 6.0 Hz, 2H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.43 (s, 2H), 1.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.50 (C), 151.16 (CH), 137.39 (C), 123.23 (CH), 79.86 (CH_2), 70.16 (CH_2), 39.66 (C), 21.59 (CH_3). IR (KBr), υ/cm^{-1} 3034, 2935, 2873, 1730, 1678, 1562, 1408, 1387, 1287, 1124, 1092, 981, 759. HRMS $[M+H]^+$ m/z calcd. for $[C_{11}H_{14}O_3N]^+$ 208.0974, found 208.0969.

methyl ((3-methyloxetan-3-yl)methyl) succinate (1k)



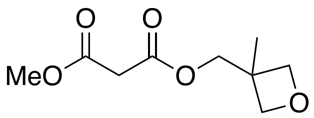
The general protocol was followed with monomethyl succinate (1159 mg, 9.821 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (1103 mg, 10.80 mmol), EDC (2254 mg, 11.79 mmol), DMAP (120.0 mg, 0.9821 mmol) in CH_2Cl_2 (20 mL, 0.5 M). A colorless oil (1992 mg, 9.167 mmol, 94%) was obtained after column chromatography (Hexane:EA 100:0 to 75:25). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.50 (d, *J* = 6.0 Hz, 2H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.18 (s, 2H), 3.69 (s, 3H), 2.70 – 2.66 (m, 2H), 2.65 – 2.62 (m, 2H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.79 (C), 172.44 (C), 79.62 (C), 69.01 (CH_2), 52.04 (CH_3), 39.16 (CH_2), 29.12 (CH_2), 28.94 (CH_2), 21.25 (CH_3). IR (KBr), υ/cm^{-1} 2958, 2874, 1739, 1438, 1356, 1216, 1159, 981. HRMS $[M+H]^+$ m/z calcd. for $[C_{10}H_{17}O_5]^+$ 217.1076, found 217.1068.

***tert*-butyl ((3-methyloxetan-3-yl)methyl) succinate (1l)**



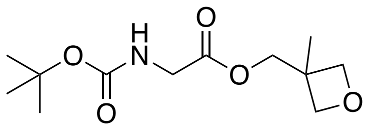
The general protocol was followed with mono-tert-butyl succinate (1861 mg, 10.68 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (1200 mg, 11.75 mmol), EDC (2457 mg, 12.82 mmol), DMAP (130.5 mg, 1.068 mmol) in CH_2Cl_2 (21 mL, 0.5 M). A colorless oil (2538 mg, 9.788 mmol, 92%) was obtained after column chromatography (Hexane:EA 100:0 to 75:25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (d, *J* = 6.0 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.19 (s, 2H), 2.64 - 2.61 (m, 2H), 2.58 - 2.54 (m, 2H), 1.44 (s, 9H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.71 (C), 171.56 (C), 80.97 (C), 79.72 (CH_2), 68.97 (CH_2), 39.20 (C), 30.37 (CH_2), 28.20 (CH_3), 21.31 (CH_3). IR (KBr), υ/cm^{-1} 2973, 2935, 2873, 1732, 1459, 1393, 1367, 1248, 1149, 983, 848. HRMS $[M+H]^+$ m/z calcd. for $[C_{13}H_{23}O_5]^+$ 259.1545, found 259.1539.

methyl ((3-methyloxetan-3-yl)methyl) malonate (1m)



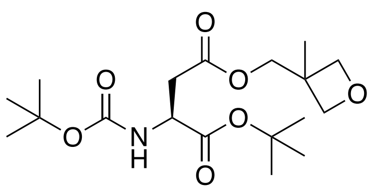
The general protocol was followed with monomethyl malonate (942 μL, 8.99 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (1010 mg, 9.89 mmol), EDC (2070mg, 10.8 mmol), DMAP (110 mg, 0.899 mmol) in CH_2Cl_2 (18 mL, 0.5 M). A colorless oil (1237 mg, 6.11 mmol, 68%) was obtained after column chromatography (Hexane:EA 10:0 to 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, *J* = 6.0 Hz, 2H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.23 (s, 2H), 3.74 (s, 3H), 3.43 (s, 2H), 1.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.93 (C), 166.65 (C), 79.47 (CH_2), 69.65 (CH_2), 52.70 (CH_3), 41.33 (CH_2), 39.16 (C), 21.15 (CH_3). IR (KBr), υ/cm^{-1} 2959, 2875, 1737, 1438, 1338, 1277, 1202, 1151, 1024, 979. HRMS $[M+H]^+$ m/z calcd. for $[C_9H_{15}O_5]^+$ 203.0919, found 203.0913.

(3-methyloxetan-3-yl)methyl 2-((*tert*-butoxycarbonyl)amino)acetate (1n)



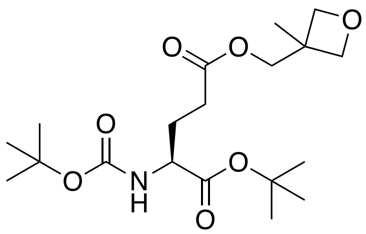
The general protocol was followed with Boc-glycine (1964 mg, 11.21 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (1259 mg, 12.33 mmol), EDC (2579 mg, 13.45 mmol), DMAP (137.0 mg, 1.121 mmol) in CH_2Cl_2 (22 mL, 0.5 M). A colorless oil (2613 mg, 10.07 mmol, 90%) was obtained after column chromatography (Hexane:EA 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (s, 1H), 4.49 (d, *J* = 6.1 Hz, 2H), 4.37 (d, *J* = 6.1 Hz, 2H), 4.24 (s, 2H), 3.93 (d, *J* = 5.7 Hz, 2H), 1.44 (s, 9H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.67 (C), 155.82 (C), 80.21 (C), 79.55 (CH_2), 69.59 (CH_2), 42.43 (CH_2), 39.16 (C), 28.41 (CH_3), 21.17 (CH_3). IR (KBr), υ/cm^{-1} 3355, 2972, 2935, 2875, 1755, 1717, 1523, 1457, 1366, 1284, 1252, 1166, 1055, 985. HRMS $[M+H]^+$ m/z calcd. for $[C_{12}H_{22}O_5N]^+$ 260.1498, found 260.1492.

(*S*)-1-*tert*-butyl 4-((3-methyloxetan-3-yl)methyl) 2-((*tert*-butoxycarbonyl)amino)succinate (1o)



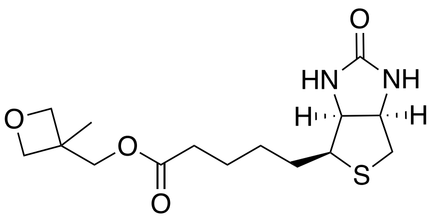
The general protocol was followed with N-Boc-L-aspartic acid 1-tert-butyl ester (1502 mg, 5.19 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (583 mg, 5.71 mmol), EDC (1194 mg, 6.23 mmol), DMAP (63.4 mg, 0.519 mmol) in CH_2Cl_2 CH2CL2(10 mL, 0.5 M). A colorless oil (1608 mg, 4.21 mmol, 81%) was obtained after column chromatography (Hexane:EA 100:0 to 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (d, *J* = 8.4 Hz, 1H), 4.54 – 4.42 (m, 3H), 4.40 (d, *J* = 6.1 Hz, 2H), 4.24 (d, *J* = 11.1 Hz, 1H), 4.14 (d, *J* = 11.1 Hz, 1H), 2.98 (dd, *J* = 16.8, 4.7 Hz, 1H), 2.85 (dd, *J* = 16.8, 4.8 Hz, 1H), 1.45 (s, 9H), 1.43 (s, 9H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.20 (C), 170.05 (C), 155.57 (C), 82.55 (C), 80.02 (C), 79.63 (C), 79.58 (CH_2), 69.17 (CH_2), 50.64 (CH), 39.19 (C), 37.11 (CH_2), 28.45 (CH_3), 28.04 (CH_3), 21.19 (CH_3). IR (KBr), υ/cm^{-1} 3357, 2976, 2935, 2875, 1738, 1501, 1458, 1392, 1367, 1251, 1154, 984, 848. HRMS $[M+H]^+$ m/z calcd. for $[C_{18}H_{32}O_7N]^+$ 374.2179, found 374.2173.

(*S*)-1-*tert*-butyl 5-((3-methyloxetan-3-yl)methyl) 2-((*tert*-butoxycarbonyl)amino)pentanedioate (1p)



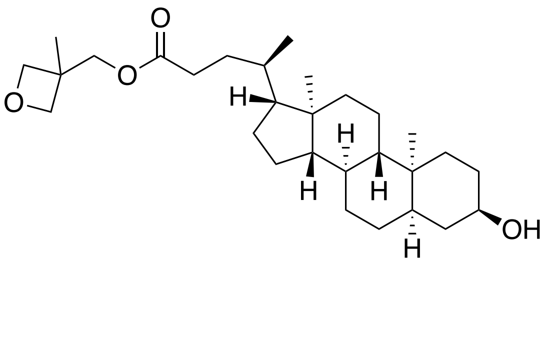
The general protocol was followed with N-Boc-L-glutamic acid 1-tert-butyl ester (3023 mg, 9.972 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (1120 mg, 10.96 mmol), EDC (2291 mg, 11.97 mmol), DMAP (121.8 mg, 0.9972 mmol) in CH_2Cl_2 (18 mL, 0.25 M). A colorless oil (3287 mg, 8.476 mmol, 85%) was obtained after column chromatography (Hexane:EA 100:0 to 75:25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (d, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 6.0 Hz, 2H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.22 - 4.13 (m, 3H), 2.51 - 2.35 (m, 2H), 2.21 - 2.12 (m, 1H), 1.94 - 1.84 (m, 1H), 1.45 (s, 9H), 1.42 (s, 9H), 1.32 (s, 3H), peak at 4.85, 4.04 ppm due to minor rotamer. ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.03 (C), 171.42 (C), 155.53 (C), 82.36 (C), 79.92 (C), 79.66 (CH_2), 68.98 (CH_2), 53.40 (CH), 39.13 (C), 30.27 (CH_2), 28.41 (CH_3), 28.19 (CH_2), 28.09 (CH_3), 21.28 (CH_3). IR (KBr), υ/cm^{-1} 3361, 2976, 2935, 2874, 1739, 1716, 1517, 1455, 1392, 1367, 1251, 1156, 1050, 982. HRMS $[M+H]^+$ m/z calcd. for $[C_{19}H_{34}O_7N]^+$ 388.2335, found 388.2328.

(3-methyloxetan-3-yl)methyl 5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanoate (1q)



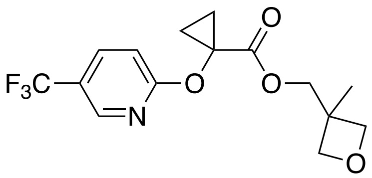
The general protocol was followed with biotin (219 mg, 0.896 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (100 mg, 0.986 mmol), EDC (220 mg, 1.08 mmol), DMAP (10.9 mg, 0.0896mmol) in CH_2Cl_2 (9 mL, 0.1 M). A white solid (242 mg, 0.736 mmol, 82%) was obtained after column chromatography (CH_2Cl_2:Acetone 100:0 to 50:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.54 (s, 1H), 4.61 – 4.42 (m, 3H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.29 (app dd, *J* = 7.8, 4.6 Hz, 1H), 4.13 (s, 2H), 3.20 - 3.09 (m, 1H), 2.90 (dd, *J* = 12.8, 5.0 Hz, 1H), 2.72 (d, *J* = 12.8 Hz, 1H), 2.39 (t, *J* = 7.5 Hz, 2H), 1.85 – 1.61 (m, 4H), 1.54 – 1.38 (m, 2H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.91 (C), 163.68 (C), 79.65 (CH_2), 68.53 (CH_2), 62.04 (CH), 60.20 (CH), 55.58 (CH), 40.70 (CH_2), 39.16 (C), 33.97 (CH_2), 28.52 (CH_2), 28.37 (CH_2), 24.97 (CH_2), 21.35 (CH_3). IR (KBr), υ/cm^{-1} 3214, 2931, 2871, 1735, 1702, 1461, 1269, 1170, 981, 634. HRMS $[M+H]^+$ m/z calcd. for $[C_{15}H_{25}O_4N_2S]^+$ 329.1535, found 329.1528.

(*R*)-(3-methyloxetan-3-yl)methyl 4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (1r)



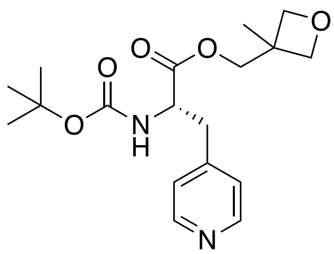
The general protocol was followed with lithocholic acid (203 mg, 0.537 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (220 mg, 2.15 mmol), EDC (124 mg, 0.65 mmol), DMAP (6.56 mg, 0.0537 mmol) in CH_2Cl_2 (4.3 mL, 0.12 M). A white solid (243 mg, 0.526 mmol, 98%) was obtained after column chromatography (Hexane:Et_2O 100:0 to 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (d, J = 5.9 Hz, 2H), 4.38 (d, J = 5.9 Hz, 2H), 4.15 (s, 2H), 3.69 - 3.56 (m, 1H), 2.40 (ddd, J = 15.4, 10.0, 5.1 Hz, 1H), 2.27 (ddd, J = 15.4, 9.4, 6.6 Hz, 1H), 2.00 - 1.92 (m, 1H), 1.90 – 0.95 (m, 29H), 0.98 – 0.88 (m, 6H), 0.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.55 (C), 79.76 (CH_2), 71.99 (CH), 68.64 (CH_2), 56.60 (CH), 56.03 (CH), 42.86 (CH_2), 42.19 (CH), 40.52 (CH), 40.28 (C), 39.19(C), 36.55 (C), 35.95 (CH), 35.48 (CH), 35.45 (CH_2), 34.69 (CH_2), 31.28 (CH_2), 31.12 (CH_2), 30.66 (CH_2), 28.34, (CH_2) 27.31 (CH_2), 26.54 (CH_2), 24.33 (CH_2), 23.51 (CH_3), 21.38 (CH_3), 20.94 (CH_2), 18.37 (CH_3), 12.18 (CH_3). IR (KBr), υ/cm^{-1} 3412, 2934, 2866, 1738, 1450, 1377, 1247, 1163, 1034, 982, 736. HRMS $[M+H]^+$ m/z calcd. for $[C_{29}H_{49}O_4]^+$ 461.1631, found 461.3625.

(3-methyloxetan-3-yl)methyl 6-(1-((5-(trifluoromethyl)pyridin-2-yl)oxy)cyclopropanoate (1s)



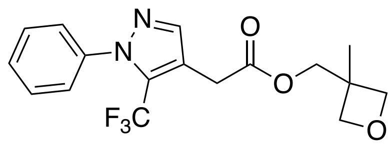
The general protocol was followed with 6-(1-((5-(trifluoromethyl)pyridin-2-yl)oxy)cyclopropanoic acid (241 mg, 1.02 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (114 mg, 1.12 mmol), EDC (233 mg, 1.22 mmol), DMAP (12.4 mg, 0.102 mmol) in CH_2Cl_2 (5 mL, 0.2 M). A white solid (288 mg, 0.869 mmol, 89%) was obtained after column chromatography (CH_2Cl_2:MeOH 100:0 to 90:10). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 - 8.41 (m, 1H), 7.81 (dd, J = 8.7, 2.4 Hz, 1H), 6.88 (app d, J = 8.7 Hz, 1H), 4.31 (d, J = 6.0 Hz, 2H), 4.22 (d, J = 6.0 Hz, 2H), 4.18 (s, 2H), 1.71 – 1.64 (m, 2H), 1.36 – 1.29 (m, 2H), 1.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.58 (C), 165.22 (C), 144.93 (q, J_{C-F} = 43.7 Hz, CH), 136.17 (q, J_{C-F} = 31.3 Hz, CH), 123.89 (q, J_{C-F} = 269.7 Hz, C), 121.24 (q, J_{C-F} = 33.0 Hz, C), 111.22 (CH), 79.33 (CH_2), 69.39 (CH_2), 57.97 (CH_2), 39.21 (C), 20.93(CH_3), 16.77 (CH_2). IR (KBr), υ/cm^{-1} 3021, 2965, 2875, 1738, 1613, 1580, 1493, 1396, 1330, 1289, 1159, 1127, 1079, 984, 837. HRMS $[M+H]^+$ m/z calcd. for $[C_{15}H_{17}O_4NF_3]^+$ 332.1110, found 332.1102.

(*S*)-(3-methyloxetan-3-yl)methyl 2-((*tert*-butoxycarbonyl)amino)-3-(pyridin-4-yl)propanoate (1r)



The general protocol was followed with (S)-2-((tert-butoxycarbonyl)amino)-3-(pyridin-4-yl)propanoic acid (236 mg, 0.899 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (101 mg, 0.989 mmol), EDC (207 mg, 1.08 mmol), DMAP (11.0 mg, 0.0899 mmol) in CH_2Cl_2 (6.5 mL, 0.2 M). A white solid (267 mg, 0.761 mmol, 86%) was obtained after column chromatography (CH_2Cl_2:MeOH 100:0 to 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (app d, J = 6.1 Hz, 2H), 7.12 (app d, J = 6.1 Hz, 2H), 5.11 (d, J = 8.2 Hz, 1H), 4.74 - 4.50 (m, 1H), 4.42 (dd, J = 6.1, 2.5 Hz, 2H), 4.38 (dd, J = 6.1, 3.6 Hz, 2H), 4.26 (d, J = 11.1 Hz, 1H), 4.18 (d, J = 11.1 Hz, 1H), 3.16 (dd, J = 13.9, 6.2 Hz, 1H), 3.06 (dd, J = 13.9, 6.8 Hz, 1H), 1.43 (s, 9H), 1.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.70 (C), 155.06 (C), 150.04 (CH), 145.32 (C), 124.61 (CH), 80.49 (C), 79.44 (CH_2), 69.99 (CH_2), 53.84 (CH), 39.07 (CH_2), 38.02 (C), 28.36 (CH_3), 21.07 (CH_3). IR (KBr), υ/cm^{-1} 3194, 2972, 2874, 1745, 1710, 1604, 1539, 1366, 1274, 1250, 1216, 1168, 980. HRMS $[M+H]^+$ m/z calcd. for $[C_{18}H_{27}O_5N_2]^+$ 351.1920, found 351.1912.

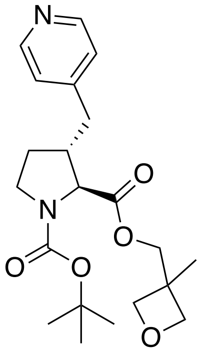
(3-methyloxetan-3-yl)methyl 2-(1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)acetate (1u)



The general protocol was followed with (1-phenyl-5-trifluoromethyl-1H-pyrazol-4-yl)-acetic acid (250 mg, 0.927 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (104 mg, 1.02 mmol), EDC (213 mg, 1.11 mmol), DMAP (11.3 mg, 0.0927 mmol) in CH_2Cl_2 (4.6 mL, 0.2 M). A colorless oil (285 mg, 0.805 mmol, 87%) was obtained after column chromatography (CH_2Cl_2:MeOH 100:0 to

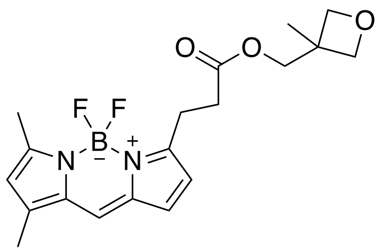
90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.54 – 7.36 (m, 5H), 4.50 (d, *J* = 6.0 Hz, 2H), 4.39 (d, *J* = 6.0 Hz, 2H), 4.25 (s, 2H), 3.76 (s, 2H), 1.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.39 (C), 141.19 (CH), 139.48 (C), 129.95 (q, $J_{C\text{-}F}$ = 37.6 Hz, C), 129.37 (CH), 129.15 (CH), 126.08 (CH), 120.31 (q, $J_{C\text{-}F}$ = 268.2 Hz, C), 116.33 (C), 79.56 (CH_2), 69.58 (CH_2), 39.18 (C), 29.98 (CH_2), 21.18 (CH_3). IR (KBr), υ/cm^{-1} 3066, 2965, 2876, 1743, 1598, 1504, 1473, 1399, 1311, 1247, 1183, 1092, 1058, 975, 769, 695. HRMS $[M+H]^+$ m/z calcd. for $[C_{17}H_{18}O_3N_2F_3]^+$ 355.1270, found 355.1265.

(2*S*,3*S*)-1-*tert*-butyl 2-((3-methyloxetan-3-yl)methyl) 3-(pyridin-4-ylmethyl)pyrrolidine-1,2-dicarboxylate (1v)



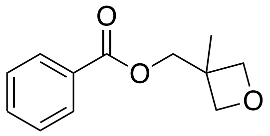
The general protocol was followed with (2S,3S)-1-[(2-methylpropan-2-yl)oxycarbonyl]-3-(pyridin-4-ylmethyl)pyrrolidine-2-carboxylic acid (248 mg, 0.81 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (91 mg, 0.89 mmol), EDC (186 mg, 0.97 mmol), DMAP (10 mg, 0.081 mmol) in CH_2Cl_2 (4 mL, 0.2 M). A colorless oil (276 mg, 0.70 mmol, 87%) was obtained after column chromatography (CH_2Cl_2:MeOH 100:0 to 95:5). Two rotmers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (app dd, *J* = 6.0, 1.5 Hz, 4H), 8.52 (app dd, *J* = 6.0, 1.5 Hz, 4H), 7.13 (app dd, *J* = 6.0, 1.5 Hz, 2H), 7.11 (app dd, *J* = 6.0, 1.5 Hz, 2H), 4.54 – 4.44 (m, 4H), 4.40 (d, *J* = 6.0 Hz, 2H), 4.37 (d, *J* = 6.0 Hz, 2H), 4.26 (d, *J* = 11.2 Hz, 1H), 4.21 (s, 1H), 4.21 (s, 1H), 4.15 (d, *J* = 11.1 Hz, 1H), 4.08 (d, *J* = 5.0 Hz, 1H), 3.98 (d, *J* = 5.1 Hz, 1H), 3.68 – 3.41 (m, 4H), 2.98 - 2.92 (m, 2H), 2.69 - 2.55 (m, 4H), 2.02 - 1.93 (m, 2H), 1.68 - 1.58 (m, 2H), 1.45 (s, 9H), 1.41 (s, 9H), 1.32 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.69 (C), 172.47 (C), 154.41 (C), 153.79 (C), 150.14 (CH), 150.08 (CH), 148.08 (C), 148.01 (C), 124.42 (CH), 124.33 (CH), 80.49 (C), 80.30 (C), 79.53 (CH_2), 79.51 (CH_2), 79.43 (CH_2), 79.40 (CH_2), 69.22 (CH_2), 69.05 (CH_2), 64.15 (CH), 63.82 (CH), 45.66 (CH_2), 45.40 (CH_2), 45.19 (CH), 44.11 (CH), 39.34 (C), 39.31 (C), 38.60 (CH_2), 38.57 (CH_2), 29.91 (CH_2), 29.22 (CH_2), 28.54 (CH_3), 28.47 (CH_3), 21.27 (CH_3), 21.25 (CH_3). IR (KBr), υ/cm^{-1} 3069, 2971, 2935, 2873, 1793, 1750, 1699, 1602, 1456, 1385, 1255, 1166, 1126, 982. HRMS $[M+H]^+$ m/z calcd. for $[C_{21}H_{31}O_5N_2]^+$ 391.2233, found 391.2224.

5,5-difluoro-7,9-dimethyl-3-(3-((3-methyloxetan-3-yl)methoxy)-3-oxopropyl)-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (1w)



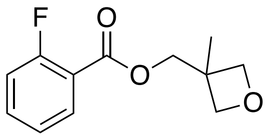
The general protocol was followed with BODIPY-FL propionic acid (69 mg, 0.24 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (29 mg, 0.28 mmol), EDC (55 mg, 0.28 mmol), DMAP (3.0 mg, 0.024 mmol) in CH_2Cl_2 (4.8 mL, 0.05 M). An orange solid (90 mg, 0.24 mmol, 100%) was obtained after column chromatography (CH_2Cl_2:MeOH 100:0 to 99:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.88 (d, *J* = 4.0 Hz, 1H), 6.27 (d, *J* = 4.0 Hz, 1H), 6.12 (s, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.35 (d, *J* = 6.0 Hz, 2H), 4.20 (s, 2H), 3.31 (app t, *J* = 7.5 Hz, 2H), 2.82 (app t, *J* = 7.5 Hz, 2H), 2.56 (s, 3H), 2.25 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.69 (C), 160.70 (C), 156.78 (C), 144.11 (C), 135.36 (C), 133.33 (C), 128.06 (CH), 123.96 (CH), 120.61 (CH), 116.55 (CH), 79.72 (CH_2), 69.05 (CH_2), 39.12 (C), 33.34 (CH_2), 23.99 (CH_2), 21.24 (CH_3), 15.08 (CH_3), 11.43 (CH_3). IR (KBr), υ/cm^{-1} 3107, 3063, 2962, 2934, 2873, 1734, 1607, 1529, 1489, 1251, 1173, 1135, 1085, 974, 668. HRMS $[M+H]^+$ m/z calcd. for $[C_{19}H_{24}O_3N_2F_2B]^+$ 377.1848, found 377.1831.

(3-methyloxetan-3-yl)methyl benzoate (1x)



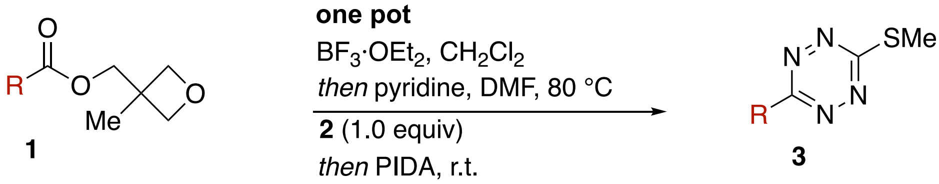
The general protocol was followed with benzoic acid (1730 mg, 14.17 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (1560 μL, 15.59 mmol), EDC (3281 mg, 17.11 mmol), DMAP (171.1 mg, 1.417 mmol) in CH_2Cl_2 (28 mL, 0.5 M). A colorless oil (2804 mg, 13.57 mmol, 96%) was obtained after column chromatography (Hexane:EA 10:0 to 8:2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 – 7.98 (m, 2H), 7.81 – 7.52 (m, 1H), 7.53 – 7.26 (m, 2H), 4.65 (d, *J* = 6.0 Hz, 2H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.39 (s, 2H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.59 (C), 133.25 (CH), 129.93 (C), 129.69 (CH), 128.54 (CH), 79.68 (CH_2), 69.06 (CH_2), 39.35 (C), 21.36 (CH_3). IR (KBr), υ/cm^{-1} 3064, 3035, 2963, 2872, 1718, 1602, 1452, 1315, 1282, 1113, 983, 712. HRMS $[M+H]^+$ m/z calcd. for $[C_{11}H_{14}O_3N]^+$ 207.1021, found 207.1014.

(3-methyloxetan-3-yl)methyl 2-fluoro benzoate (1y)



The general protocol was followed with 2-fluorobenzoic acid (1242 mg, 8.87 mmol) was added into mixture of 3-Methyl-3-oxetanemethanol (823 mg, 8.06 mmol), EDC (1854 mg, 9.67 mmol), DMAP (105 mg, 0.806 mmol) in CH_2Cl_2 (17 mL, 0.5 M). A colorless oil (1889 mg, 8.43 mmol, 95%) was obtained after column chromatography (Hexane:EA 10:0 to 9:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (td, *J* = 7.5, 1.9 Hz, 1H), 7.52 (m, 1H), 7.21 (td, *J* = 7.6, 1.1 Hz, 1H), 7.13 (m, 1H), 4.61 (d, *J* = 6.0 Hz, 2H), 4.44 (d, *J* = 6.0 Hz, 2H), 4.41 (s, 2H), 1.42 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.60 (d, $J_{C\text{-}F}$ = 3.9 Hz, C), 162.10 (d, $J_{C\text{-}F}$ = 258.7 Hz, C), 134.82 (d, $J_{C\text{-}F}$ = 9.0 Hz, CH), 132.24 (CH), 124.14 (d, $J_{C\text{-}F}$ = 3.9 Hz, CH), 118.50 (d, $J_{C\text{-}F}$ = 10.2 Hz, C), 117.16 (d, $J_{C\text{-}F}$ = 22.2 Hz, CH), 79.67 (CH_2), 69.58 (CH_2), 39.30 (C), 21.32 (CH_3). HRMS $[M+H]^+$ m/z calcd. for $[C_{12}H_{14}O_3F]^+$ 225.0927, found 225.0918.

General protocol A for the one-pot synthesis of tetrazine thioethers (R=alkyl)



A dry round-bottom flask was charged with the oxetane ester **1** (1.0 equiv.) and a magnetic stirbar. The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and refilled with nitrogen. Anhydrous CH_2Cl_2 (to 1.0 M in oxetane ester) was added via syringe and the resulting solution was cooled by an ice/brine bath (–12 °C) and boron trifluoride etherate (0.50–1.5 equiv.) was added via syringe. The resulting mixture was allowed to stir under nitrogen with continued cooling by the cold bath (maintained between –12 °C to –4 °C) for 3–6 h. The reactions were monitored by TLC of aliquots that were quenched with trimethylamine before spotting the TLC plate. When the oxetane was completely consumed, the reaction mixture was quenched with pyridine (2.0–3.0 equiv.), and then **2** (0.70–0.80 equiv.) and DMF (to 1.0 M in **2**) were added. The mixture was stirred vigorously and vacuum was carefully applied to remove CH_2Cl_2. The resulting mixture was then heated by an oil bath at 80 °C and the mixture was allowed to stir under nitrogen at 80 °C for 20-30 min. After cooling to r.t., PIDA (0.70–0.80 equiv.) was added to the flask and the mixture allowed to stir at r.t. for 30 min. The mixture was diluted with CH_2Cl_2 and sequentially washed with saturated sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel.

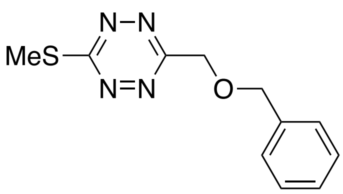
General protocol B for the one-pot synthesis of tetrazine thioethers (R = aryl)

A dry round-bottom flask was charged with the oxetane ester (1.0 equiv.) and a magnetic stirbar. The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and refilled with nitrogen. Anhydrous CH_2Cl_2 (to 1.0 M in oxetane ester) was added via syringe and the resulting solution was cooled by an ice/brine bath (–5 °C) and boron trifluoride etherate (0.50–1.5 equiv.) was added via syringe. The resulting mixture was allowed to stir under nitrogen with continued cooling by the cold bath (maintained between –5 °C to –0 °C) for 3–6 h. The reactions were monitored by TLC of aliquots that were quenched with trimethylamine before spotting the TLC plate. When the oxetane was completely consumed, the reaction mixture was quenched with pyridine (2.0–3.0 equiv.), and then **2** (0.70 equiv.) and DMF (to 1.0 M in **2**) were added. The mixture was stirred vigorously and vacuum was carefully applied to remove CH_2Cl_2. The resulting mixture was then heated by an oil bath at 80 °C and the mixture was allowed to stir under nitrogen at 80 °C for 1–2 h. After cooling to r.t., PIDA (0.70 equiv.) was added to the flask and the mixture allowed to stir at r.t. for 1 h. The mixture was diluted with CH_2Cl_2 and sequentially washed with saturated sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel.

General protocol C for the one-pot synthesis of tetrazine thioethers (R = 4-pyridyl or 3-methoxypyrid-2-yl)

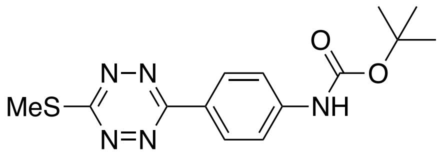
A dry round-bottom flask was charged with the oxetane ester (1.0 equiv.) and a magnetic stirbar. The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and refilled with nitrogen. Anhydrous CH_2Cl_2 (to 1.0 M in oxetane ester) was added via syringe and the resulting solution was cooled by an ice/brine bath (–0 °C) and boron trifluoride etherate (1.2 equiv.) was added via syringe. The resulting mixture was allowed to stir under nitrogen with continued cooling by the cold bath for 2 h, followed by stirring for 12 h at r.t. The reactions were monitored by TLC of aliquots that were quenched with trimethylamine before spotting the TLC plate. When the oxetane was completely consumed, the reaction mixture was quenched with pyridine (3.0 equiv.), and then **2** (0.70 equiv.) and DMF (to 1.0 M in **2**) were added. The mixture was stirred vigorously and vacuum was carefully applied to remove CH_2Cl_2. The resulting mixture was then heated by an oil bath at 80 °C and the mixture was allowed to stir for 2 h. After cooling to r.t., PIDA (0.70 equiv.) was added to the flask and the mixture allowed to stir at r.t. for 2 h. The mixture was diluted with CH_2Cl_2 and sequentially washed with saturated sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel.

3-((benzyloxy)methyl)-6-(methylthio)-1,2,4,5-tetrazine (3a)



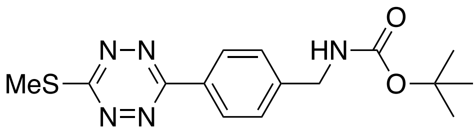
General protocol A was followed using BF_3•OEt_2 (222 μL, 1.81 mmol), **1a** (905 mg, 3.62 mmol), CH_2Cl_2 (3.6 mL) for 4 h at –12 °C to –4 °C; Pyridine (580 μL, 7.24 mmol), **2** (714 mg, 2.90 mmol) and DMF (2.9 mL) for 20 min at 80 °C; and PIDA (930 mg, 2.91 mmol) at r.t. for 30 min. A red oil (336 mg, 1.35 mmol, 70%) was obtained after chromatography (hexane:acetone 100:0 to 98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.27 (m, 5H), 5.05 (s, 2H), 4.77 (s, 2H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.87 (C), 164.33 (C), 137.15 (C), 128.69 (CH), 128.23 (CH), 128.21 (CH), 73.78 (CH_2), 69.63 (CH_2), 13.54 (CH_3). IR (KBr), υ/cm^{-1} 3063, 3030, 2930, 2863, 1454, 1327, 1305, 1163, 1098, 893, 740, 699. HRMS $[M+H]^+$ m/z calcd. for $[C_{11}H_{13}ON_4S]^+$ 249.0810, found 249.0802

tert-butyl (4-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)phenyl)carbamate (3b)



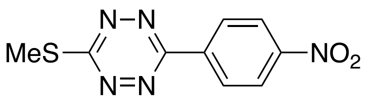
General protocol B was followed using BF_3•OEt_2 (85.2 μL, 0.692 mmol), **1b** (442 mg, 1.38 mmol), CH_2Cl_2 (1.38 mL) for 4 h at –2 °C to –0 °C; Pyridine (222 μL, 2.77 mmol), **2** (240 mg, 0.969 mmol) and DMF (0.82 mL) for 2 h at 80 °C; and PIDA (267 mg, 0.969 mmol) at r.t. for 1 h. A red solid (245 mg, 0.767 mmol, 56%) was obtained after purified by chromatography (Hexane:Et_2O 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (app d, J = 8.8 Hz, 2H), 7.58 (app d, J = 8.6 Hz, 2H), 6.71 (s, 1H), 2.78 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.73 (C), 162.02 (C), 152.34 (C), 142.41 (C), 128.74 (CH), 125.92 (C), 118.51 (CH), 81.45 (C), 28.43 (CH_3), 13.59 (CH_3). IR (KBr), υ/cm^{-1} 3368, 3100, 3007, 2980, 2964, 2928, 1708, 1592, 1526, 1510, 1361, 1312, 1244, 1171, 1053, 853. HRMS $[M+H]^+$ m/z calcd. for $[C_{14}H_{18}O_2N_5S]^+$ 320.1181, found 320.1167.

tert-butyl 4-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)benzylcarbamate (3c)



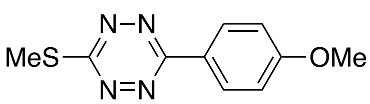
General protocol B was followed using BF_3•OEt_2 (165 μL, 1.33 mmol), **1c** (892 mg, 2.66 mmol), CH_2Cl_2 (2.7 mL) for 4 h at –5 °C to –0 °C; Pyridine (430 μL, 5.32 mmol), **2** (462 mg, 1.86 mmol) and DMF (2.2 mL) for 1.5 h at 80 °C; and PIDA (599 mg, 1.86 mmol) at r.t. for 1 h. A red solid (403 mg, 1.21 mmol, 65%) was obtained after purified by chromatography (CH_2Cl_2:acetone 100:0 to 97:3). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (app d, J = 8.4 Hz, 2H), 7.49 (app d, J = 8.4 Hz, 2H), 4.95 (s, 1H), 4.43 (d, J = 6.1 Hz, 2H), 2.79 (s, 3H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.36 (C), 162.23 (C), 156.05 (C), 143.78 (C), 130.72 (C), 128.22 (CH), 127.89 (CH), 79.97 (C), 44.52 (CH_2), 28.54 (CH_3), 13.59 (CH_3). IR (KBr), υ/cm^{-1} 3352, 3021, 2974, 2930, 1684, 1512, 1355, 1249, 1195, 1166, 1051, 894. HRMS $[M+H]^+$ m/z calcd. for $[C_{15}H_{20}O_2N_5S]^+$ 334.1338, found 334.1323.

3-(methylthio)-6-(4-nitrophenyl)-1,2,4,5-tetrazine (3d)



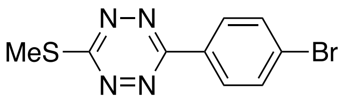
General protocol B was followed using BF_3•OEt_2 (54 μL, 0.54 mmol), **1d** (271 mg, 1.1 mmol), CH_2Cl_2 (1.1 mL) for 6 h at 0 °C; Pyridine (174 μL, 1.1 mmol), **2** (187 mg, 0.76 mmol) and DMF (0.76 mL) for 2 h at 80 °C; and PIDA (254 mg, 0.76 mmol) at r.t. for 1 h. A red solid (126 mg, 0.51 mmol, 67%) was obtained after purified by chromatography (Hexane:CH_2Cl_2 7:3 to 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (app d, J = 9.0 Hz, 2H), 8.43 (app d, J = 9.0 Hz, 2H), 2.83 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.67 (C), 160.99 (C), 150.26 (C), 137.52 (C), 128.44 (CH), 124.54 (CH), 13.71 (CH_3). IR (KBr), υ/cm^{-1} 3079, 2926, 1604, 1516, 1342, 1193, 871. HRMS $[M+H]^+$ m/z calcd. for $[C_9H_8O_2N_5S]^+$ 250.0399, found 250.0389.

3-(4-methoxyphenyl)-6-(methylthio)-1,2,4,5-tetrazine (3e)



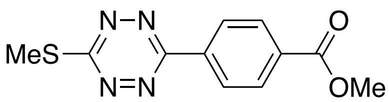
General protocol B was followed using BF_3•OEt_2 (79 μL, 0.64 mmol), **1e** (302 mg, 1.3 mmol), CH_2Cl_2 (1.3 mL) for 4 h at –5 °C to –0 °C; Pyridine (207 μL, 2.6 mmol), **2** (222 mg, 0.89 mmol) and DMF (0.9 mL) for 2 h at 80 °C; and PIDA (289 mg, 0.89 mmol) at r.t. for 1 h. A red solid (143 mg, 0.62 mmol, 69%) was obtained after purified by chromatography (Hexane:EA 10:0 to 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (app d, J = 9.0 Hz, 2H), 7.07 (app d, J = 9.0 Hz, 2H), 3.91 (s, 3H), 2.78 (s,3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.50 (C), 163.20 (C), 162.19 (C), 129.42 (CH), 124.08 (C), 114.83 (CH), 55.65 (CH_3), 13.57 (CH_3). IR (KBr), υ/cm^{-1} 3003, 2936, 2838, 1603, 1513, 1424, 1353, 1252, 1192, 1037, 846. HRMS $[M+H]^+$ m/z calcd. for $[C_{10}H_{11}ON_4S]^+$ 235.0654, found 230.0645.

3-(4-bromophenyl)-6-(methylthio)-1,2,4,5-tetrazine (3f)



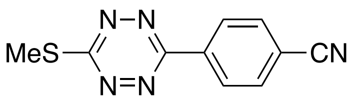
General protocol B was followed using BF_3•OEt_2 (67 μL, 0.54 mmol), **1f** (305 mg, 1.1 mmol), CH_2Cl_2 (1.1 mL) for 4 h at –2 °C to –0 °C; Pyridine (173 μL, 1.1 mmol), **2** (186 mg, 0.75 mmol) and DMF (0.75 mL) for 2 h at 80 °C; and PIDA (242 mg, 0.75 mmol) at r.t. for 1 h. A red solid (115 mg, 0.41 mmol, 54%) was obtained after purified by chromatography (Hexane:EA 100:0 to 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (app d, J = 8.6 Hz, 2H), 7.72 (app d, J = 8.6 Hz, 2H), 2.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.72 (C), 161.87 (C), 132.73 (CH), 130.67 (C), 129.01 (CH), 127.51 (C), 13.63 (CH_3). IR (KBr), υ/cm^{-1}3093, 2924, 1585, 1355, 1194, 1004, 800. HRMS $[M+H]^+$ m/z calcd. for $[C_9H_8N_4SBr]^+$ 282.9653, found 282.9643.

methyl 4-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)benzoate (3g)



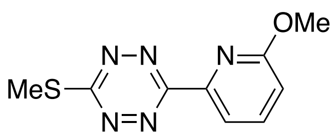
General protocol B was followed using BF_3•OEt_2 (116 μL, 0.938 mmol), **1g** (248 mg, 0.938 mmol), CH_2Cl_2 (0.94 mL) for 4 h at 0 °C; Pyridine (190 μL, 2.36 mmol), **2** (165 mg, 0.657 mmol) and DMF (0.66 mL) for 2 h at 80 °C; and PIDA (213 mg, 0.657 mmol) at r.t. for 1 h. A red solid (135 mg, 0.514 mmol, 79%) was obtained after purified by chromatography (Hexane: $CH_2Cl_2$1:1 to 3:7). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (app d, J = 8.5 Hz, 2H), 8.24 (app d, J = 8.5 Hz, 2H), 3.98 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.04 (C), 166.52 (C), 161.82 (C), 135.72 (C), 133.43 (C), 130.51 (CH), 127.50 (CH), 52.63 (CH_3), 13.65 (CH_3). IR (KBr), υ/cm^{-1} 3060, 2994, 2945, 1713, 1355, 1276, 1190, 1111, 768. HRMS $[M+H]^+$ m/z calcd. for $[C_{11}H_{11}O_2N_4S]^+$ 263.0603, found 263.0593

4-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)benzonitrile (3h)



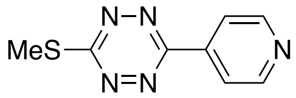
General protocol B was followed using BF_3•OEt_2 (162 μL, 1.31 mmol), **1h** (300 mg, 1.31 mmol), CH_2Cl_2 (1.3 mL) for 6 h at 0 °C; Pyridine (212 μL, 2.63 mmol), **2** (227 mg, 0.917 mmol) and DMF (0.9 mL) for 2 h at 80 °C; and PIDA (296 mg, 0.917 mmol) at r.t. for 1 h. A red solid (140 mg, 0.611 mmol, 67%) was obtained after purified by chromatography (Hexane:EA 9:1 to 8:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (app d, J = 8.5 Hz, 2H), 8.24 (app d, J = 8.5 Hz, 2H), 3.98 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.53 (C), 161.17 (C), 135.87 (C), 133.12 (CH), 127.94 (CH), 118.32 (C), 115.78 (C), 13.69 (CH_3). IR (KBr), υ/cm^{-1} 3096, 2923, 2852, 2227, 1653, 1394, 853. HRMS $[M+H]^+$ m/z calcd. for $[C_{10}H_8N_5S]^+$ 230.0500, found 230.0493

3-(6-methoxypyridin-2-yl)-6-(methylthio)-1,2,4,5-tetrazine (3i)



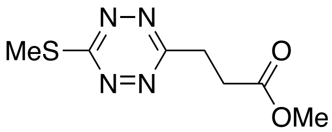
General protocol B was followed using BF_3•OEt_2 (190 μL, 1.54 mmol), **1i** (305 mg, 1.29 mmol), CH_2Cl_2 (1.3 mL) for 2 h at 0 °C followed by 12 h at r.t.; Pyridine (310 μL, 3.84 mmol), **2** (223 mg, 0.903 mmol) and DMF (0.9 mL) for 2 h at 80 °C; and PIDA (290 mg, 0.903 mmol) at r.t. for 2 h. A red solid (128mg, 61%) was obtained after purified by chromatography (Hexane:CH_2Cl_2 1:1 to 3:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J = 7.4, 0.8 Hz, 1H), 7.80 (dd, J = 8.3, 7.4 Hz, 1H), 6.98 (dd, J = 8.3, 0.8 Hz, 1H), 4.10 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.05 (C), 164.74 (C), 162.04 (C), 147.69 (C), 139.58 (CH), 117.10 (CH), 114.52 (CH), 53.94 (CH_3), 13.63 (CH_3). IR (KBr), υ/cm^{-1} 3016, 2922, 2852, 1632, 1473, 1352, 1295, 1212, 1189. HRMS $[M+H]^+$ m/z calcd. for $[C_9H_{10}ON_5S]^+$ 236.0606, found 236.0597

3-(methylthio)-6-(pyridin-4-yl)-1,2,4,5-tetrazine (3j)



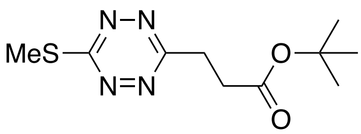
General protocol B was followed using BF_3•OEt_2 (100 μL, 0.810 mmol), **1j** (140 mg, 0.675 mmol), CH_2Cl_2 (0.68 mL) for 2 h at 0 °C followed by 12 h at r.t.; Pyridine (164 μL, 2.03 mmol), **2** (118 mg, 0.473 mmol) and DMF (0.47 mL) for 2 h at 80 °C; and PIDA (152 mg, 0.473 mmol) at r.t. for 2 h. A red solid (50.5 mg, 0.246 mmol, 51%) was obtained after purified by chromatography (Hexane:Acetone 100:0 to 9:1). ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (app d, J = 6.2 Hz, 2H), 8.37 (app d, J = 6.2 Hz, 2H), 2.82 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.10 (C), 161.09 (C), 151.13 (CH), 139.26 (C), 120.92 (CH), 13.69 (CH_3). IR (KBr), υ/cm^{-1} 3085, 2923, 1594, 1560, 1355, 1194, 905. HRMS $[M+H]^+$ m/z calcd. for $[C_8H_8N_5S]^+$ 206.0500, found 206.0492

methyl 3-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)propanoate (3k)



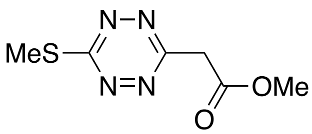
General protocol A was followed using BF_3•OEt_2 (147 μL, 1.19 mmol), **1k** (515 mg, 2.38 mmol), CH_2Cl_2 (1.4 mL) for 4 h at –12 °C to –4 °C; Pyridine (384 μL, 4.76 mmol), **2** (473 mg, 1.90 mmol) and DMF (1.9 mL) for 20 min at 80 °C; and PIDA (611 mg, 1.90 mmol) at r.t. for 30 min. A red solid (277 mg, 1.29 mmol, 68%) was obtained after purified by chromatography (Hexane:EA 100:0 to 85:15). ^1H NMR (600 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.59 (app t, J = 7.1 Hz, 2H), 3.03 (app t, J = 7.1 Hz, 2H), 2.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.85 (C), 172.58 (C), 166.37 (C), 52.15 (CH_3), 30.77 (CH_2), 29.39, (CH_2) 13.51 (CH_3). IR (KBr), υ/cm^{-1} 2953, 2932, 2849, 1737, 1437, 1338, 1292, 1199, 1163. HRMS $[M+H]^+$ m/z calcd. for $[C_7H_{11}O_2N_4S]^+$ 215.0603, found 215.0596

***tert*-butyl 3-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)propanoate (3l)**



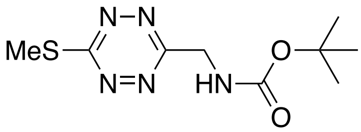
General protocol A was followed using BF_3•OEt_2 (466 μL, 3.78 mmol), **1l** (1950 mg, 7.55 mmol), CH_2Cl_2 (7.6 mL) for 6 h at –12 °C to –4 °C; Pyridine (1.22 mL, 15.1 mmol), **2** (1.50 g, 6.04 mmol) and DMF (6.0 mL) for 20 min at 80 °C; and PIDA (1.95 mg, 6.04 mmol) at r.t. for 30 min. A red solid (896 mg, 3.50 mmol, 60%) was obtained after purified by chromatography (Hexane:EA 10:0 to 9:1). ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (app t, J = 7.1 Hz, 2H), 2.93 (app t, J = 7.1 Hz, 2H), 2.73 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.69 (C), 171.31 (C), 166.76 (C), 81.22 (C), 32.39 (CH_2), 29.68 (CH_2), 28.17 (CH_3), 13.51 (CH_3). IR (KBr), υ/cm^{-1} 2953, 2931, 1734, 1636, 1436, 1198, 1160. HRMS $[M+H]^+$ m/z calcd. for $[C_{10}H_{17}O_2N_4S]^+$ 257.1072, found 257.1061

methyl 2-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)acetate (3m)



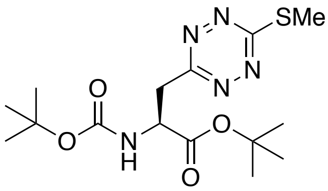
General protocol A was followed using BF_3•OEt_2 (670 μL, 5.44 mmol), **1m** (2200 mg, 10.9 mmol), CH_2Cl_2 (10 mL) for 4 h at –12 °C to –4 °C; Pyridine (1760 μL, 21.8 mmol), **2** (2159 mg, 8.71 mmol) and DMF (8.7 mL) for 20 min at 80 °C; and PIDA (2800 mg, 8.71 mmol) at r.t. for 30 min. A red oil (1041 mg, 5.20 mmol, 60%) was obtained after purified by chromatography (Hexane:CH_2Cl_2 8:2 to 6:4). ^1H NMR (400 MHz, $CDCl_3$) δ 4.32 (s, 2H), 3.77 (s, 3H), 2.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.43 (C), 168.68 (C), 162.36 (C), 52.95 (CH_3), 40.38 (CH_2), 13.55 (CH_3). IR (KBr), υ/cm^{-1} 2954, 2847, 1743, 1436, 1358, 1257, 1206, 1069. HRMS $[M+H]^+$ m/z calcd. for $[C_6H_9O_2N_4S]^+$ 201.0446, found 201.0440

***tert*-butyl ((6-(methylthio)-1,2,4,5-tetrazin-3-yl)methyl)carbamate (3n)**



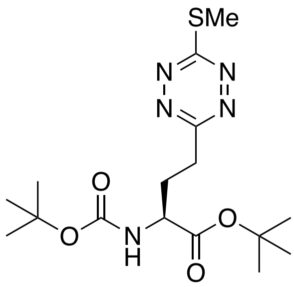
General protocol A was followed using BF_3•OEt_2 (264 μL, 2.14 mmol), **1n** (1100 mg, 4.28 mmol), CH_2Cl_2 (4.3 mL) for 4 h at –12 °C to –4 °C; Pyridine (690 μL, 8.56 mmol), **2** (850 mg, 3.42 mmol) and DMF (3.4 mL) for 20 min at 80 °C; and PIDA (1101 mg, 3.42 mmol) at r.t. for 30 min. A red solid (602 mg, 2.34 mmol, 69%) was obtained after purified by chromatography (Hexane:EA 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (s, 1H), 4.88 (d, *J* = 6.0 Hz, 2H), 2.72 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.67 (C), 164.44 (C), 155.86 (C), 80.43 (C), 43.18 (CH_2), 28.40 (CH_3), 13.50 (CH_3). IR (KBr), υ/cm^{-1} 3356, 2978, 2833, 1704, 1517, 1367, 1280, 1170.HRMS [M+H]$^+$ m/z calcd. for $[C_9H_{15}O_2N_5S]^+$ 258.1025, found 258.1013

(*S*)-*tert*-butyl 2-((*tert*-butoxycarbonyl)amino)-3-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)propanoate (3o)



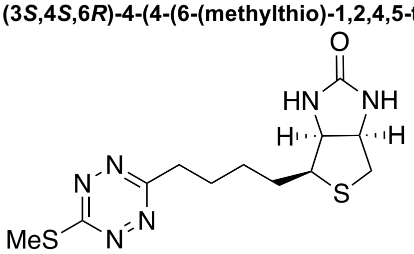
General protocol A was followed using BF_3•OEt_2 (86 μL, 0.68 mmol), **1o** (510 mg, 1.4 mmol), CH_2Cl_2 (1.4 mL) for 4 h at –12 °C to –4 °C; Pyridine (220 μL, 2.74 mmol), **2** (238 mg, 0.96 mmol) and DMF (0.9 mL) for 20 min at 80 °C; and PIDA (307 mg, 0.96 mmol) at r.t. for 30 min. A red oil (475 mg, 1.3 mmol, 64%) was obtained after purified by chromatography (Hexane:Et_2O 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (d, *J* = 7.9 Hz, 1H), 4.72- 4.67 (m, 1H), 3.74 (dd, *J* = 14.6, 5.2 Hz, 1H), 3.62 (dd, *J* = 14.6, 7.0 Hz, 1H), 2.71 (s, 3H), 1.41 (s, 9H), 1.37 (s, 9H), peak at 5.09, 4.60ppm due to minor rotamer. ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.92 (C), 169.79 (C), 164.70 (C), 155.17 (C), 83.06 (C), 80.16 (C), 52.85 (CH), 37.75 (CH_2), 28.34 (CH_3), 28.00 (CH_3), 13.45 (CH_3). IR (KBr), υ/cm^{-1} 3344, 2979, 2933, 1737, 1713, 1502, 1367, 1154. HRMS [M+H]$^+$ m/z calcd. for $[C_{15}H_{26}O_4N_5S]^+$ 372.1706, found 372.1691

(*S*)-*tert*-butyl 2-((*tert*-butoxycarbonyl)amino)-4-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)butanoate (3p)



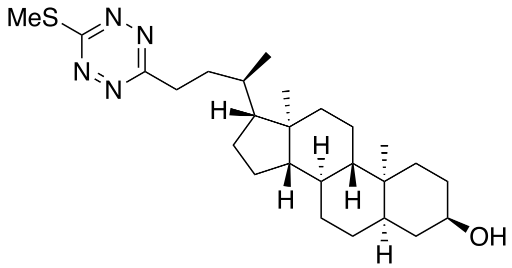
General protocol A was followed using BF_3•OEt_2 (118 μL, 0.955 mmol), **1p** (524 mg, 1.91 mmol), CH_2Cl_2 (1.9 mL) for 4 h at –12 °C to –4 °C; Pyridine (309 μL, 3.83 mmol), **2** (322 mg, 1.34 mmol) and DMF (1.3 mL) for 20 min at 80 °C; and PIDA (431 mg, 1.34 mmol) at r.t. for 30 min. A red solid (720 mg, 1.87 mmol, 70%) was obtained after purified by chromatography (Hexane:Et_2O 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, *J* = 8.2 Hz, 1H), 4.35 (app dt, *J* = 8.2, 4.8 Hz, 1H), 3.39 - 3.24 (m, 2H), 2.72 (s, 3H), 2.51 - 2.43 (m, 1H), 2.24 - 2.15 (m, 1H), 1.47 (s, 9H), 1.43 (s, 9H), peak at 4.90, 4.18ppm due to minor rotamer. ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.67 (C), 171.30 (C), 167.23 (C), 155.42 (C), 82.61 (C), 80.05 (C), 53.52 (CH), 31.25 (CH_2), 30.66 (CH_2), 28.42 (CH_3), 28.12 (CH_3), 13.49 (CH_3). IR (KBr), υ/cm^{-1} 3369, 2977, 2917, 2849, 1722, 1636, 1367, 1164, 738. HRMS [M+H]$^+$ m/z calcd. for $[C_{16}H_{28}O_4N_5S]^+$ 386.1862, found 386.1847

(3*S*,4*S*,6*R*)-4-(4-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)butyl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (3q)



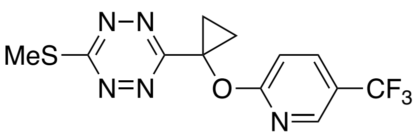
General protocol A was followed using BF_3•OEt_2 (121 μL, 0.982 mmol), **1q** (215 mg, 0.654 mmol), CH_2Cl_2 (0.65 mL) for 4 h at –12 °C to –4 °C; Pyridine (159 μL, 1.96 mmol), **2** (112 mg, 0.452 mmol) and DMF (0.45 mL) for 20 min at 80 °C; and PIDA (140 mg, 0.452 mmol) at r.t. for 30 min. A red solid (95.9 mg, 0.294 mmol, 66%) was obtained after purified by chromatography (CH_2Cl_2:MeOH 100:0 to 95:5). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.17 (s, 1H), 5.35 (s, 1H), 4.51 (app dd, *J* = 7.6, 5.0 Hz, 1H), 4.32 (app dd, *J* = 7.6, 5.0 Hz, 1H), 3.27 (t, *J* = 7.7 Hz, 2H), 3.18 - 3.14 (m, 1H), 2.90 (dd, *J* = 12.8, 5.0 Hz, 1H), 2.76 - 2.69 (m, 4H), 2.03 -1.90 (m, 2H), 1.86 – 1.70 (m, 2H), 1.62-1.50 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.54 (C), 167.90 (C), 163.84 (C), 62.00 (CH), 60.23 (CH), 55.63 (CH), 40.69 (CH_2), 34.01 (CH_2), 28.40 (CH_2), 28.37 (CH_2), 28.36 (CH_2), 13.51 (CH_3). IR (KBr), υ/cm^{-1} 3422, 2931, 2859, 1702, 1460, 1265, 1159, 739.HRMS [M+H]$^+$ m/z calcd. for $[C_{12}H_{19}ON_6S_2]^+$ 327.1062, found 327.1049

(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-4-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)butan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (3r)



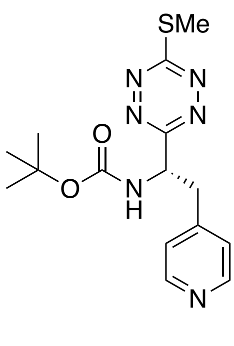
General protocol A was followed using BF_3•OEt_2 (227 μL, 1.79 mmol), **1r** (550 mg, 1.19 mmol), CH_2Cl_2 (1.20 mL) for 4 h at –12 °C to –4 °C; Pyridine (290 μL, 3.58 mmol), **2** (206 mg, 0.831 mmol) and DMF (0.83 mL) for 20 min at 80 °C; and PIDA (267 mg, 0.831 mmol) at r.t. for 30 min. A red solid (365 mg, 0.798 mmol, 67%) was obtained after purified by chromatography (CH_2Cl_2:Et_2O 100:0 to 85:15). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.65 – 3.58 (m, 1H), 3.28 (ddd, *J* = 14.0, 10.7, 4.9 Hz, 1H), 3.12 (ddd, *J* = 14., 10.7, 6.2 Hz, 1H), 2.72 (s, 3H), 2.09 – 1.94 (m, 2H), 1.92 – 1.71 (m, 4H), 1.69 – 1.45 (m, 7H), 1.45 – 0.84 (m, 20H), 0.65 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.36, 168.79, 67.24, 56.66, 56.13, 42.97, 42.27, 40.62, 40.36, 36.65, 36.03, 35.77, 35.52, 34.94, 34.74, 31.48, 30.74, 28.39, 27.35, 26.57, 24.35, 23.52, 21.00, 18.64, 13.45, 12.24. IR (KBr), υ/cm^{-1} 3362, 2932, 2863, 1449, 1360, 1313, 1162, 1068, 737. HRMS [M+H]$^+$ m/z calcd. for $[C_{26}H_{43}ON_4S]^+$ 459.3158, found 459.3142

3-(methylthio)-6-(1-((5-(trifluoromethyl)pyridin-2-yl)oxy)cyclopropyl)-1,2,4,5-tetrazine (3s)



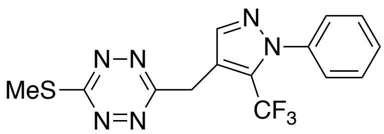
General protocol A was followed using BF_3•OEt_2 (53.1 μL, 0.432 mmol), **1s** (95.4 mg, 0.288 mmol), CH_2Cl_2 (0.29 mL) for 4 h at –12 °C to –4 °C; Pyridine (69.7 μL, 0.864 mmol), **2** (50.1 mg, 0.202 mmol) and DMF (0.20 mL) for 20 min at 80 °C; and PIDA (65.0 mg, 0.202 mmol) at r.t. for 30 min. A red oil (43.2 mg, 0.131 mmol, 65%) was obtained after purified by chromatography (Hexane: Et_2O 10:0 to 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.83 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 2.70 (s, 3H), 2.10 – 1.89 (m, 2H), 1.82 – 1.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.22 (C), 167.13 (C), 164.93 (C), 144.83 (CH, q, J_{C-F} = 4.1 Hz), 136.31 (CH, q, J_{C-F} = 1.5 Hz), 123.89 (C, q, J_{C-F} = 269.7 Hz), 121.27 (C, q, J_{C-F} = 32.9 Hz), 111.69 (CH), 59.04 (C), 19.45 (CH_2), 13.49 (CH_3). IR (KBr), υ/cm^{-1} 3016, 2931, 2853, 1614, 1582, 1492, 1289, 1208, 1125. HRMS [M+H]$^+$ m/z calcd. for $[C_{12}H_{11}ON_5SF_3]^+$ 330.0636, found 330.0624

(*S*)-*tert*-butyl (1-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)-2-(pyridin-4-yl)ethyl)carbamate (3t)



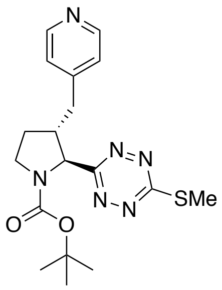
General protocol A was followed using BF_3•OEt_2 (51 μL, 0.42 mmol), **1t** (97 mg, 0.28 mmol), CH_2Cl_2 (0.28mL) for 4 h at –12 °C to –4 °C; Pyridine (67 μL, 0.83 mmol), **2** (50 mg, 0.20 mmol) and DMF (0.2 mL) for 20 min at 80 °C; and PIDA (60 mg, 0.20 mmol) at r.t. for 30 min. A red oil (39 mg, 0.11 mmol, 55%) was obtained after purified by chromatography (CH_2Cl_2:MeOH 100:0 to 97:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (m, 2H), 7.08 - 7.07 (m, 2H), 5.65 – 5.62 (m, 1H), 5.53 - 5.51 (m, 1H), 3.44 - 3.39 (m, 1H), 3.30 - 3.24 (m, 1H), 2.74 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.94 (C), 166.05 (C), 155.00 (C), 149.96 (CH), 145.18 (C), 124.99 (CH), 80.73 (C), 53.78 (CH_2), 40.82 (CH_2), 28.35 (CH_3), 13.57 (CH_3). IR (KBr), υ/cm^{-1} 3006, 2925, 2852, 1710, 1604, 1519, 1366, 1249, 1165. HRMS $[M+H]^+$ m/z calcd. for $[C_{15}H_{21}O_2N_6S]^+$ 349.1447, found 349.1443

3-(methylthio)-6-((1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)methyl)-1,2,4,5-tetrazine (3u)



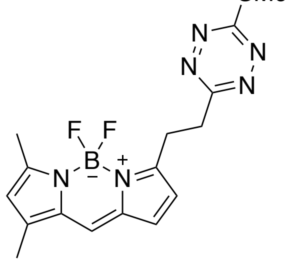
General protocol A was followed using BF_3•OEt_2 (88 μL, 0.72 mmol), **1u** (102 mg, 0.29 mmol), CH_2Cl_2 (0.29 mL) for 4 h at –12 °C to –4 °C; Pyridine (117 μL, 1.4 mmol), **2** (50 mg, 0.20 mmol) and DMF (0.20 mL) for 20 min at 80 °C; and PIDA (65 mg, 0.20 mmol) at r.t. for 30 min. A red solid (48 mg, 0.14 mmol, 68%) was obtained after purified by chromatography (Hexane:$CH_2Cl_2$3:7 to 0:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.56 – 7.40 (m, 5H), 4.66 (d, *J* = 1.4 Hz, 2H), 2.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.19 (C), 165.89 (C), 141.21 (CH), 139.51 (C), 129.98 (q, $J_{C\text{-}F}$ = 37.6 Hz, C), 129.62 (CH), 129.19 (CH), 126.12 (CH), 120.45 (q, $J_{C\text{-}F}$ = 268.5 Hz, C), 118.02 (C), 29.65 (CH_2), 13.56 (CH_3). IR (KBr), υ/cm^{-1} 3056, 2974 2933, 2825, 1653, 1528, 1266, 740, 702. HRMS $[M+H]^+$ m/z calcd. for $[C_{14}H_{12}N_6F_3S]^+$ 353.0796, found 353.0784

(2*S*,3*S*)-*tert*-butyl 2-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)-3-(pyridin-4-ylmethyl)pyrrolidine-1-carboxylate (3v)



General protocol A was followed using BF_3•OEt_2 (42 μL, 0.34 mmol), **1v** (90 mg, 0.23 mmol), CH_2Cl_2 (0.23 mL) for 4 h at –12 °C to –4 °C; Pyridine (56 μL, 0.68 mmol), **2** (40 mg, 0.16 mmol) and DMF (0.16 mL) for 20 min at 80 °C; and PIDA (51 mg, 0.16 mmol) at r.t. for 30 min. A red solid (41 mg, 0.11 mmol, 64%) was obtained after purified by chromatography (CH_2Cl_2:Acetone 10:0 to 85:15). Two rotamers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 - 8.46 (m, 4H), 7.09 (d, *J* = 5.0 Hz, 2H), 7.04 (d, *J* = 5.0 Hz, 2H), 5.00 (d, *J* = 5.6 Hz, 1H), 4.86 (d, *J* = 6.2 Hz, 1H), 3.83 (ddd, *J* = 11.3, 7.9, 3.7 Hz, 1H), 3.76 – 3.57 (m, 3H), 3.07 – 2.64 (m, 12H), 2.33 – 2.04 (m, 2H), 1.83 – 1.68 (m, 2H), 1.40 (s, 9H), 1.13 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.25 (C), 176.15 (C), 168.47 (C), 168.08 (C), 154.40 (C), 153.35 (C), 150.09 (CH, both rotamers), 147.78 (C), 147.67 (C), 124.41 (CH), 124.29 (CH), 80.48 (C, both rotamers), 65.12 (CH), 64.88 (CH), 48.33 (CH), 47.20 (CH), 46.38 (CH_2), 46.26 (CH_2), 37.79 (CH_2, both rotamers), 29.77 (CH_2), 29.71 (CH_2), 28.48 (CH_3), 28.25 (CH_3), 13.53 (CH_3, both rotamers). IR (KBr), υ/cm^{-1} 3057, 2962, 2917, 2850, 1726, 1640, 1529, 1266, 741. HRMS $[M+H]^+$ m/z calcd. for $[C_{18}H_{25}O_2N_6S]^+$ 389.1760, found 389.1745

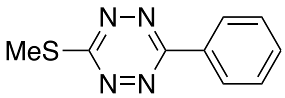
5,5-difluoro-7,9-dimethyl-3-(2-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)ethyl)-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (3w)



General protocol A was followed using BF_3•OEt_2 (20 μL, 0.16 mmol), **1w** (40 mg, 0.11 mmol), CH_2Cl_2 (0.16 mL) for 4 h at –12 °C to –4 °C; Pyridine (27 μL, 0.33 mmol), **2** (19 mg, 0.077 mmol) and DMF (77 μL) for 20 min at 80 °C; and PIDA (24 mg, 0.077 mmol) at r.t. for 30 min. An orange solid (16 mg, 0.043 mmol, 57%) was obtained after purified by chromatography (Hexane: $CH_2Cl_2$1:1 to 1:9). ^{1}H

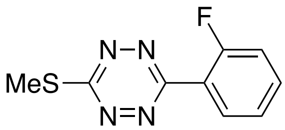
NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.86 (d, *J* = 4.0 Hz, 1H), 6.25 (d, *J* = 4.0 Hz, 1H), 6.12 (s, 1H), 3.71 (app t, *J* = 7.5, 1.3 Hz, 2H), 3.60 (app t, *J* = 7.5 Hz, 2H), 2.73 (s, 3H), 2.56 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.69 (C), 166.95 (C), 161.16 (C), 155.99 (C), 144.33 (C), 135.58 (C), 133.37 (C), 127.97 (CH), 124.04 (CH), 120.80 (CH), 116.72 (CH), 33.60 (CH_2), 26.84 (CH_2), 15.16 (CH_3), 13.51 (CH_3), 11.49 (CH_3). IR (KBr), υ/cm^{-1} 3062, 3030, 2930, 2864, 1454, 1327, 1306, 1163, 1098, 893, 741, 699. HRMS $[M+H]^+$ m/z calcd. for $[C_{16}H_{18}N_6F_2BS]^+$ 375.1375, found 375.1369

3-(methylthio)-6-phenyl-1,2,4,5-tetrazine (3x)



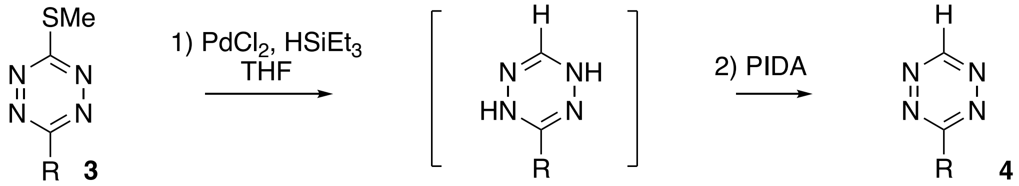
General protocol B was followed using BF_3•OEt_2 (362 μL, 2.94 mmol), **1x** (1200 mg, 5.87 mmol), CH_2Cl_2 (0.59 mL) for 4 h at –5 °C to –0 °C; Pyridine (948 μL, 11.7 mmol), **2** (1019 mg, 4.11 mmol) and DMF (4.1 mL) for 1 h at 80 °C; and PIDA (1323 mg, 4.11 mmol) at r.t. for 30 min. A red solid (587 mg, 2.87 mmol, 72%) was obtained after purified by chromatography (CH_2Cl_2: ether 100:0 to 95:5). ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 – 8.20 (m, 2H), 8.09 – 7.46 (m, 3H), 2.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.43 (C), 162.44 (C), 132.45 (CH), 131.71 (C), 129.38 (CH), 127.62 (CH), 13.60 (CH_3). IR (KBr), υ/cm^{-1} 3074, 3014, 2936, 1356, 1196, 897, 760. HRMS $[M+H]^+$ m/z calcd. for $[C_9H_9N_4S]^+$ 205.0548, found 205.0540

3-(methylthio)-2-fluoro-6-phenyl-1,2,4,5-tetrazine (3y)



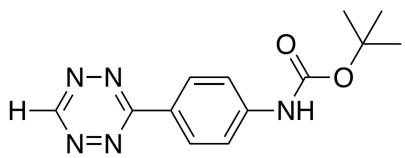
General protocol B was followed using BF_3•OEt_2 (98.5 μL, 0.798 mmol), **1y** (358 mg, 1.60 mmol), CH_2Cl_2 (1.6 mL) for 6 h at –2 °C to –0 °C; Pyridine (258 μL, 3.19 mmol), **2** (277 mg, 1.12 mmol) and DMF (1.1 mL) for 1 h at 80 °C; and PIDA (361 mg, 1.12 mmol) at r.t. for 1 h. A red solid (177 mg, 0.797 mmol, 50%) was obtained after purified by chromatography (Hexane: EA 100:0 to 95:5). ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (td, *J* = 7.6, 1.8 Hz, 1H), 7.59 (m, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (m, 1H), 2.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.21 (C), 162.06 (d, $J_{C\text{-}F}$ = 5.5 Hz, C), 161.33 (d, $J_{C\text{-}F}$ = 257.0 Hz, C), 133.76 (d, $J_{C\text{-}F}$ = 8.5 Hz, CH), 131.07 (d, $J_{C\text{-}F}$ = 1.4 Hz, CH), 124.88 (d, $J_{C\text{-}F}$ = 3.9 Hz, CH), 120.57 (d, $J_{C\text{-}F}$ = 9.9 Hz, C), 117.43 (d, $J_{C\text{-}F}$ = 21.5 Hz, CH), 13.58 (CH_3). HRMS $[M+H]^+$ m/z calcd. for $[C_9H_8N_4FS]^+$ 223.0454, found 223.0447

General procedure for the synthesis of 3-monosubstituted tetrazines



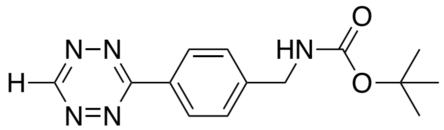
To a dry round-bottom flask was added tetrazine thioether **3** (1 equiv.) and $PdCl_2$ (10 mol%). The flask was outfitted with a septum-fitted gas inlet adapter, and was twice evacuated and backfilled with nitrogen. Triethylsilane (3 equiv.) and anhydrous THF (to 0.1 M in **3**) were added via syringe, and the flask was heated by an oil bath at 45 °C. The mixture was allowed to stir at 45 °C for 24 h. PIDA (1.2 equiv) was added as a solid at r.t. After stirring at room temperature for 1 h, the reaction mixture was diluted with CH_2Cl_2, transferred to a separatory funnel and was sequentially washed with saturated sodium bicarbonate, water, brine, dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel.

tert-butyl (4-(1,2,4,5-tetrazin-3-yl)phenyl)carbamate (4a)



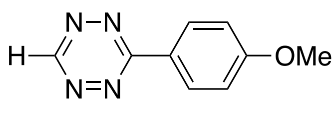
The general protocol for thioether reduction was followed using **3b** (67 mg, 0.21 mmol), $PdCl_2$ (3.7 mg, 0.021 mmol), $HSiEt_3$ (0.10 mL, 0.63 mmol), THF (2.1 mL) and PIDA (80 mg, 0.25 mmol). A pink solid (47 mg, 0.17 mmol, 82%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 97:3). ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.57 (app d, *J* = 8.9 Hz, 2H), 7.61 (d, *J* = 8.9 Hz, 2H), 6.75 (s, 1H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.12, 157.58, 152.28, 143.24, 129.65, 125.82, 118.51, 81.60, 28.43. IR (KBr), υ/cm^{-1} 3055, 2932, 2862, 1653, 1528, 1266, 741. HRMS $[M+H]^+$ m/z calcd. for $[C_{13}H_{16}O_2N_5]^+$ 274.1304, found 274.1293

tert-butyl 4-(1,2,4,5-tetrazin-3-yl)benzylcarbamate (4b)



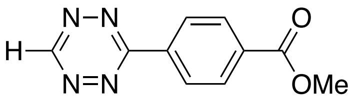
The general protocol for thioether reduction was followed using **3c** (150 mg, 0.45 mmol), $PdCl_2$ (8.0 mg, 0.045 mmol), $HSiEt_3$ (0.22 mL, 1.4 mmol), THF (4.5 mL) and PIDA (174 mg, 0.54 mmol). A pink solid (106 mg, 0.37 mmol, 82%) was obtained after column chromatography (Hexane:Et_2O 100:0 to 85:15). ^1H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.59 (app d, *J* = 8.1 Hz, 2H), 7.52 (app d, *J* = 8.1 Hz, 2H), 4.98 (s, 1H), 4.45 (d, *J* = 6.2 Hz, 2H), 1.48(s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.35, 157.87, 156.06, 144.79, 130.60, 128.65, 128.21, 79.96, 44.43, 28.51. IR (KBr), υ/cm^{-1} 3352, 3087, 2980, 2930, 2884, 1702, 1684, 1610, 1510, 1435, 1349, 1247, 1168. HRMS $[M+H]^+$ m/z calcd. for $[C_{14}H_{18}O_2N_5]^+$ 288.1460, found 288.1449

3-(4-methoxyphenyl)-1,2,4,5-tetrazine (4c)



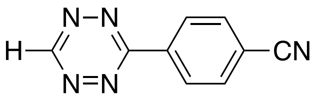
The general protocol for thioether reduction was followed using **3e** (50 mg, 0.21 mmol), $PdCl_2$ (3.8 mg, 0.021 mmol), $HSiEt_3$ (0.10 mL, 0.64 mmol), THF (2.1 mL) and PIDA (82 mg, 0.26 mmol). A pink solid (34 mg, 0.18 mmol, 85%) was obtained after column chromatography (Hexane:Et_2O 100:0 to 94:6). ^1H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.58 (app d, *J* = 8.9 Hz, 2H), 7.09 (app d, *J* = 8.9 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.21, 163.86, 157.44, 130.28, 124.00, 114.92, 55.67. IR (KBr), υ/cm^{-1} 3058, 2963, 2932, 2871, 1640, 1529, 1267, 740. HRMS $[M+H]^+$ m/z calcd. for $[C_9H_9ON_4]^+$ 189.0776, found 189.0769

methyl 4-(1,2,4,5-tetrazin-3-yl)benzoate (4d)



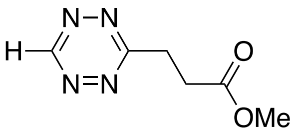
The general protocol for thioether reduction was followed using **3g** (50 mg, 0.19 mmol), $PdCl_2$ (3.3 mg, 0.019 mmol), $HSiEt_3$ (0.091 mL, 0.57 mmol), THF (1.9 mL) and PIDA (73 mg, 0.23 mmol). A pink solid (30 mg, 0.14 mmol, 73%) was obtained after column chromatography (Hexane:EA 100:0 to 92:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.72 (app d, *J* = 8.7 Hz, 2H), 8.27 (app d, *J* = 8.7 Hz, 2H), 3.99 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.37, 166.12, 158.11, 135.61, 134.28, 130.58, 128.39, 52.67. IR (KBr), υ/cm^{-1} 3060, 2994, 2946, 1714, 1432, 1355, 1275, 1190, 1111, 767. HRMS $[M+H]^+$ m/z calcd. for $[C_{10}H_9O_2N_4]^+$ 217.0726, found 217.0720

4-(1,2,4,5-tetrazin-3-yl)benzonitrile (4e)



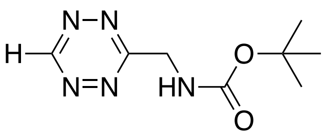
The general protocol for thioether reduction was followed using **3h** (50 mg, 0.22 mmol), $PdCl_2$ (3.9 mg, 0.022 mmol), $HSiEt_3$ (0.10 mL, 0.65 mmol), THF (2.2 mL) and PIDA (84 mg, 0.26 mmol). A pink solid (27 mg, 0.15 mmol, 68%) was obtained after column chromatography (Hexane:Et_2O 100:0 to 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.78 (app d, *J* = 8.5 Hz, 2H), 7.93 (app d, *J* = 8.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.49, 158.28, 135.68, 133.20, 128.83, 118.10, 116.74. IR (KBr), υ/cm^{-1} 3095, 3053, 2931, 2225, 1445, 1354, 1200, 903, 855.

methyl 3-(1,2,4,5-tetrazin-3-yl)propanoate (4f)



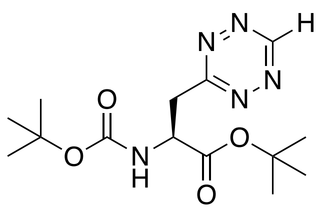
The general protocol for thioether reduction was followed using **3k** (225 mg, 1.05 mmol), $PdCl_2$ (18.6 mg, 0.105 mmol), $HSiEt_3$ (0.510 mL, 3.15 mmol), THF (10.5 mL) and PIDA (405 mg, 1.26 mmol). A pink solid (133 mg, 0.790 mmol, 75%) was obtained after column chromatography (Hexane:EA 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 3.86 – 3.50 (m, 5H), 3.09 (app t, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.48, 171.59, 158.22, 52.19, 30.53, 30.29. IR (KBr), υ/cm^{-1} 2962, 2918, 2838, 1726, 1653, 1529, 1266, 740. HRMS $[M+H]^+$ m/z calcd. for $[C_6H_9O_2N_4]^+$ 169.0726, found 169.0720

***tert*-butyl ((1,2,4,5-tetrazin-3-yl)methyl)carbamate (4g)**



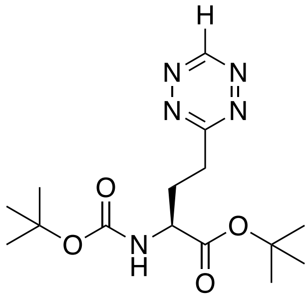
The general protocol for thioether reduction was followed using **3n** (200 mg, 0.777 mmol), $PdCl_2$ (13.7 mg, 0.0777 mmol), $HSiEt_3$ (371 μL, 2.33 mmol), THF (7.8 mL) and PIDA (300 mg, 0.932 mmol). A pink solid (129 mg, 0.611 mmol, 79%) was obtained after column chromatography (Hexane:EA 100:0 to 82:18). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 5.60 (s, 1H), 5.01 (d, *J* = 6.0 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.53, 158.82, 155.90, 80.66, 43.89, 28.41. IR (KBr), υ/cm^1 3350, 2979, 2934, 1709, 1517, 1251, 1168. HRMS $[M+H]^+$ m/z calcd. for $[C_8H_{14}O_2N_5]^+$ 212.1147, found 212.1140

(*S*)-*tert*-butyl 2-((*tert*-butoxycarbonyl)amino)-3-(1,2,4,5-tetrazin-3-yl)propanoate (4h)



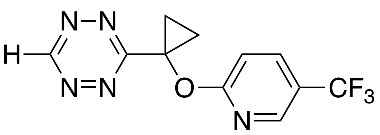
The general protocol for thioether reduction was followed using **3o** (165 mg, 0.444 mmol), $PdCl_2$ (7.86 mg, 0.0444 mmol), $HSiEt_3$ (213 µL, 1.33 mmol), THF (4.4 mL) and PIDA (170 mg, 0.533 mmol). A pink solid (95.2 mg, 0.293 mmol, 66%) was obtained after column chromatography (Hexane:Et_2O 100:0 to 75:25). ^1H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 5.47 (d, *J* = 7.8 Hz, 1H), 4.80 - 4.76 (m, 1H), 3.87 (dd, *J* = 14.7, 5.2 Hz, 1H), 3.75 (dd, *J* = 14.7, 7.3 Hz, 1H), 1.41 (s, 9H), 1.37 (s, 9H), peak at 5.13, 4.71 ppm due to minor rotamer. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.01, 169.64, 158.19, 155.18, 83.21, 80.29, 52.83, 38.75, 28.35, 27.98. IR (KBr), υ/cm^{-1} 3371, 2979, 2833, 1715, 1502, 1368, 1251, 155, 1058, 892, 845. HRMS $[M+H]^+$ m/z calcd. for $[C_{14}H_{24}O_4N_5]^+$ 326.1828, found 326.1817

(*S*)-*tert*-butyl 2-((*tert*-butoxycarbonyl)amino)-4-(1,2,4,5-tetrazin-3-yl)butanoate (4i)



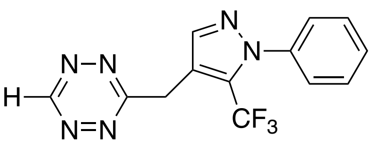
The general protocol for thioether reduction was followed using **3p** (291 mg, 0.755 mmol), $PdCl_2$ (13.4 mg, 0.0755 mmol), $HSiEt_3$ (360 µL, 2.26 mmol), THF (7.6 mL) and PIDA (293 mg, 0.906 mmol). A pink solid (200 mg, 0.589 mmol, 78%) was obtained after column chromatography (Hexane:EA 100:0 to 85:15). ^1H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 5.17 (d, *J* = 8.2 Hz, 1H), 4.36 (app td, *J* = 8.2, 4.8 Hz, 1H), 3.50 – 3.35 (m, 2H), 2.58 – 2.49 (m, 1H), 2.29 – 2.20 (m, 1H), 1.47 (s, 9H), 1.42 (s, 9H), peak at 4.93, 4.19ppm due to minor rotamer. ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.43, 171.22, 158.12, 155.44, 82.67, 80.09, 53.50, 31.60, 31.05, 28.43, 28.14. IR (KBr), υ/cm^{-1} 3372, 2980, 2936, 1730, 1700, 1505, 1366, 1153, 1050, 893. HRMS $[M+H]^+$ m/z calcd. for $[C_{15}H_{26}O_4N_5]^+$ 340.1985, found 340.1973

3-(1-((5-(trifluoromethyl)pyridin-2-yl)oxy)cyclopropyl)-1,2,4,5-tetrazine (4j)



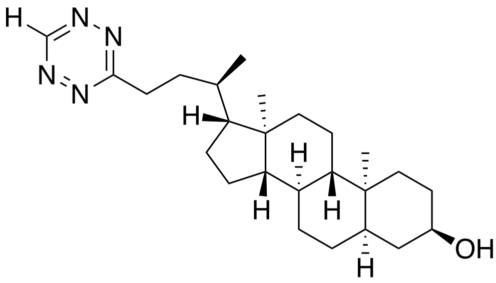
The general protocol for thioether reduction was followed using **3s** (40 mg, 0.12 mmol), $PdCl_2$ (2.1 mg, 0.012 mmol), $HSiEt_3$ (58 µL, 0.36 mmol), THF (1.2 mL) and PIDA (46 mg, 0.14 mmol). A pink solid (24 mg, 0.097 mmol, 71%) was obtained after column chromatography (Hexane: $CH_2Cl_2$8:2 to 6:4). ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.23 – 8.22 (m, 1H), 7.85 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 2.07 (app dd, *J* = 8.8, 5.9 Hz, 2H), 1.78 (app dd, *J* = 8.7, 5.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.18 (C), 164.80 (C), 157.72 (CH), 144.74 (CH, q, J_{C-F} = 4.4 Hz), 136.41 (CH, q, J_{C-F} = 3.3 Hz), 123.86 (C, q, J_{C-F} = 269.7 Hz), 121.42 (C, q, J_{C-F} = 33.0 Hz) 111.78 (CH), 59.35 (C), 20.50 (CH_2). IR (KBr), υ/cm^{-1} 3088, 2923, 2851, 1615, 1581, 1492, 1453, 1329, 1288, 1189, 1127, 1078. HRMS $[M+H]^+$ m/z calcd. for $[C_{11}H_{19}ON_5F_3]^+$ 284.0759, found 284.0749

3-((1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)methyl)-1,2,4,5-tetrazine (4k)



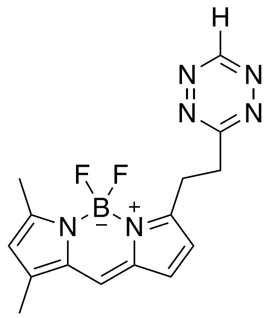
The general protocol for thioether reduction was followed using **3u** (53 mg, 0.15 mmol), $PdCl_2$ (2.7 mg, 0.015 mmol), $HSiEt_3$ (72 µL, 0.45 mmol), THF (1.5 mL) and PIDA (57 mg, 0.18 mmol). A pink solid (35 mg, 0.11 mmol, 75%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 95:5). ^1H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.74 (s, 1H), 7.50 – 7.44 (m, 5H), 4.78 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.99, 158.30, 141.26, 139.43, 130.11 (q, J_{C-F} = 37.7 Hz), 129.67, 129.20, 126.11 (q, J_{C-F} = 1.0 Hz), 120.38 (q, J_{C-F} = 268.4 Hz) 117.47 (q, J_{C-F} = 1.8 Hz), 30.62. IR (KBr), υ/cm^{-1} 3077, 1924, 2853, 1598, 1503, 1472, 1309, 1183, 1132, 1091, 975. HRMS $[M+H]^+$ m/z calcd. for $[C_{13}H_{10}N_6F_3]^+$ 307.0919, found 307.0908

(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-17-((*R*)-4-(1,2,4,5-tetrazin-3-yl)butan-2-yl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (4l)



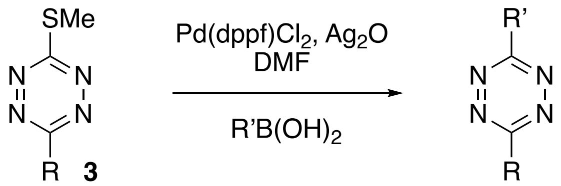
The general protocol for thioether reduction was followed using **3r** (180 mg, 0.39 mmol), $PdCl_2$ (7.0 mg, 0.039 mmol), $HSiEt_3$ (0.19 mL, 1.2 mmol), THF (3.9 mL) and PIDA (170 mg, 0.533 mmol). After aqueous work up and rotary evaporation, THF (1.0 ml), TFA (0.2 mL) and water (0.2 mL) was added into crude and stirred for 2 h at r.t. The resulting residue was concentrated. A pink solid (112 mg, 0.27 mmol, 70%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 3.63 (tt, J = 10.8, 5.3 Hz, 1H), 3.40 (ddd, J = 14.0, 10.8, 5.0 Hz, 1H), 3.24 (ddd, J = 14.0, 10.5, 6.1 Hz, 1H), 2.15 – 2.03 (m, 1H), 2.02 – 0.77 (m, 32H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.02, 158.05, 72.01, 56.61, 55.99, 42.94, 42.20, 40.54, 40.30, 36.58, 35.97, 35.83, 35.47, 35.00, 34.71, 32.46, 30.68, 29.86, 28.40, 27.31, 26.54, 24.33, 23.52, 20.96, 18.63, 12.21.. IR (KBr), υ/cm^{-1} 3366, 2959, 2934, 2830, 1653, 1527, 1267, 741. HRMS [M+H]$^+$ m/z calcd. for $[C_{25}H_{41}ON_4]^+$ 413.3280, found 413.3254

3-(2-(1,2,4,5-tetrazin-3-yl)ethyl)-5,5-difluoro-7,9-dimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (4m)

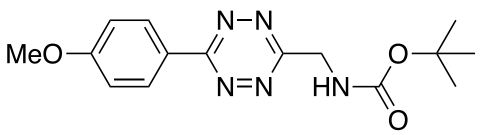


The general protocol for thioether reduction was followed using **3w** (16 mg, 0.043 mmol), $PdCl_2$ (0.76 mg, 0.0043 mmol), $HSiEt_3$ (21 μL, 0.13 mmol), THF (0.43 mL) and PIDA (17 mg, 0.051 mmol). An orange solid (8.5 mg, 0.026 mmol, 61%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.09 (s, 1H), 6.86 (d, J = 4.0 Hz, 1H), 6.24 (d, J = 4.0 Hz, 1H), 6.12 (s, 1H), 3.82 (app t, J = 7.6 Hz, 2H), 3.65 (app t, J = 7.6 Hz, 2H), 2.55 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.11, 161.38, 158.19, 155.49, 144.50, 135.67, 133.33, 127.89, 124.09, 120.89, 116.70, 34.68, 26.74, 15.17, 11.49. HRMS [M+H]$^+$ m/z calcd. for $[C_{15}H_{16}N_6BF_2]^+$ 329.1498, found 329.1483

Synthesis of unsymmetrical tetrazines via Ag-mediated Liebeskind coupling with boronic acids

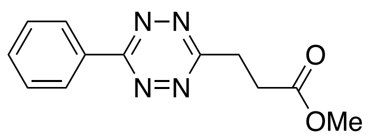


***tert*-butyl ((6-(4-methoxyphenyl)-1,2,4,5-tetrazin-3-yl)methyl)carbamate (5a)**



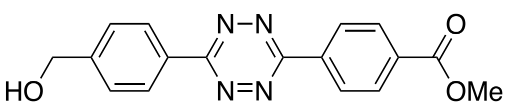
To a dry round bottomed flask was sequentially charged with **3n** (54 mg, 0.21 mmol), Pd(dppf)Cl_2 (23 mg, 0.031 mmol, 15 mol%), 4-methoxyphenylboronic acid (61 mg, 0.40 mmol) and Ag_2O (122 mg, 0.52 mmol). The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and filled with nitrogen. DMF (2.1 mL) was added to the flask via syringe. After heating under nitrogen at 60 °C for 20 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (hexane:EA 10:0 to 8:2) to give the title compound as a pink solid (50 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (app d, *J* = 9.0 Hz, 2H), 7.09 (app d, *J* = 9.0 Hz, 2H), 5.57 (s, 1H), 4.99 (d, *J* = 5.7 Hz, 2H), 3.92 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.83 (C), 164.82 (C), 163.68 (C), 155.91 (C), 130.15 (CH), 123.96 (C), 114.91 (CH), 80.47 (C), 55.69 (CH_3), 43.53 (CH_2), 28.47 (CH_3). IR (KBr), υ/cm^{-1} 3360, 3056, 2973, 2928, 1712, 1678, 1605, 1525, 1396, 1260, 1158. HRMS $[M+H]^+$ m/z calcd. for $[C_{15}H_{20}O_3N_5]^+$ 318.1566, found 318.1553

methyl 3-(6-phenyl-1,2,4,5-tetrazin-3-yl)propanoate (5b)



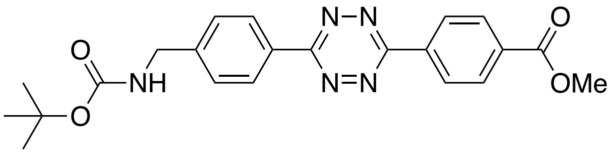
To a microwave reaction tube was sequentially charged with **3k** (54 mg, 0.25 mmol), Pd(dppf)Cl_2 (28 mg, 0.038 mmol, 15 mol%), phenylboronic acid (92 mg, 0.76 mmol), Ag_2O (146 mg, 0.63 mmol) and DMF (2.5 mL) in glove box. After heating under nitrogen at 100 °C for 3 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (hexane:EA 100:0 to 85:15) to give the title compound as pink solid (52 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 – 8.38 (m, 2H), 7.78 – 7.43 (m, 3H), 4.17 – 3.34 (m, 5H), 3.12 (app t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.63 (C), 168.57 (C), 164.51 (C), 132.82 (CH), 131.80 (C), 129.40 (CH), 128.14 (CH), 52.19 (CH_3), 30.77 (CH_2), 29.83 (CH_2). IR (KBr), υ/cm^{-1} 3063, 3001, 2950, 2926, 1736, 1375, 1301, 1234, 1175, 758, 696. HRMS $[M+H]^+$ m/z calcd. for $[C_{12}H_{13}O_2N_4]^+$ 245.1039, found 245.1031

methyl 4-(6-(4-(hydroxymethyl)phenyl)-1,2,4,5-tetrazin-3-yl)benzoate (5c)



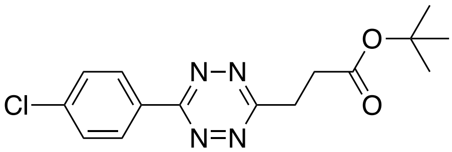
To a dry round bottomed flask was sequentially charged with **3g** (48 mg, 0.18 mmol), Pd(dppf)Cl_2 (20 mg, 0.028 mmol, 15 mol%), *p*-hydroxymethylphenylboronic acid (54 mg, 0.35 mmol) and Ag_2O (107 mg, 0.46 mmol). The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and filled with nitrogen. DMF (1.8 mL) was added to the flask via syringe. After heating under nitrogen at 60 °C for 20 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (CH_2Cl_2:Et_2O 100:0 to 93:7) to give the title compound as pink solid (35 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (app d, *J* = 8.5 Hz, 2H), 8.53 (app d, *J* = 8.3 Hz, 2H), 8.26 (app d, *J* = 8.5 Hz, 2H), 7.64 (app d, *J* = 8.3 Hz, 2H), 5.47 (t, *J* = 5.5 Hz, 1H), 4.66 (d, *J* = 5.5 Hz, 2H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.73 (C), 163.37 (C), 162.79 (C), 147.98 (C), 136.19 (C), 132.75 (C), 130.19 (CH), 130.04 (C), 127.85 (CH), 127.67 (CH), 127.22 (CH), 62.49 (CH_2), 52.60 (CH_3). IR (KBr), υ/cm^{-1} 3345, 3058, 3012, 2957, 2919, 1720, 1607, 1509, 1394, 1280, 1112, 1010, 697. HRMS $[M+H]^+$ m/z calcd. for $[C_{17}H_{15}O_3N_4]^+$ 323.1144, found 323.1132

methyl 4-(6-(4-(((*tert*-butoxycarbonyl)amino)methyl)phenyl)-1,2,4,5-tetrazin-3-yl)benzoate (5d)



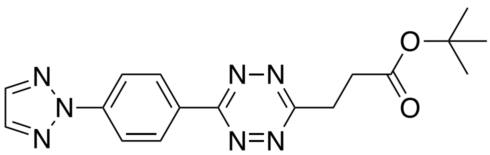
To a dry round bottomed flask was sequentially charged with **3g** (47 mg, 0.18 mmol), Pd(dppf)Cl_2 (20 mg, 0.027 mmol, 15 mol%), 4-(*tert*-Butoxycarbonylaminomethyl)phenylboronic acid (85 mg, 0.34 mmol) and Ag_2O (103 mg, 0.45 mmol). The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and filled with nitrogen. DMF (1.8 mL) was added to the flask via syringe. After heating under nitrogen at 60 °C for 20 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (CH_2Cl_2:Et_2O 100:0 to 97:3) to give the title compound as a pink solid (61 mg, 81%). ^{1}H NMR (400 MHz, DMSO-*d*) δ 8.67 (app d, *J* = 8.4 Hz, 2H), 8.52 (app d, *J* = 8.1 Hz, 2H), 8.26 (app d, *J* = 8.4 Hz, 2H), 7.56 (m, 3H), 4.28 (d, *J* = 6.0 Hz, 2H), 3.93 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 165.72 (C), 163.32 (C), 162.80 (C), 145.51 (C), 136.17 (C), 132.76 (C), 130.18 (CH), 130.15 (C), 127.93 (CH), 127.85 (CH), 127.76 (C), 78.06 (C), 52.59 (CH_3), 43.30 (CH_2), 28.28 (CH_3). IR (KBr), υ/cm^{-1} 3348, 3081, 3008, 2984, 2947, 1722, 1683, 1606, 1512, 1394, 1277, 1250, 1168, 1111. HRMS [M+H]$^+$ m/z calcd. for $[C_{22}H_{24}O_4N_5]^+$ 422.1828, found 422.1815

***tert*-butyl 3-(6-(4-chlorophenyl)-1,2,4,5-tetrazin-3-yl)propanoate (5e)**



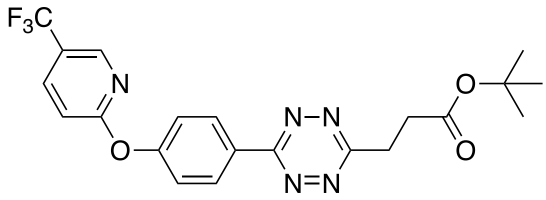
To a dry round bottomed flask was sequentially charged with **3l** (70 mg, 0.27 mmol), Pd(dppf)Cl_2 (30 mg, 0.040 mmol, 15 mol%), 4-chlorophenylboronic acid (80 mg, 0.51 mmol) and Ag_2O (156 mg, 0.67 mmol). The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and filled with nitrogen. DMF (2.7 mL) was added to the flask via syringe. After heating under nitrogen at 60 °C for 20 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (hexane:EA 10:0 to 9:1) to give the title compound as pink solid (67 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (m, 2H), 7.57 (m, 2H), 3.65 (app t, *J* = 7.1Hz, 2H), 3.01 (app t, *J* = 7.1Hz, 2H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.31 (C), 169.09 (C), 163.77 (C), 139.30 (C), 130.38 (C), 129.76 (CH), 129.37 (CH), 81.30 (C), 32.33(CH_2), 30.15 (CH_2), 28.18 (CH_3). IR (KBr), υ/cm^{-1} 3055, 2980, 2932, 1730, 1598, 1398, 1366, 1265, 1153, 1095, 848, 738. HRMS (ESI+) [M+H]$^+$ Calculated for $[C_{15}H_{18}O_2N_4Cl]^+$ 321.1118; found 321.1114

***tert*-butyl 3-(6-(4-(2*H*-1,2,3-triazol-2-yl)phenyl)-1,2,4,5-tetrazin-3-yl)propanoate (5f)**



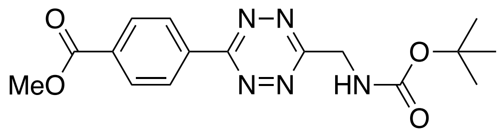
To a dry round bottomed flask was sequentially charged with **3l** (80 mg, 0.31 mmol), Pd(dppf)Cl_2 (34 mg, 0.047 mmol, 15 mol%), 4-(triazol-2-yl)phenylboronic acid (112 mg, 0.59 mmol) and Ag_2O (181 mg, 0.67 mmol). The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and filled with nitrogen. DMF (3.1 mL) was added to the flask via syringe. After heating under nitrogen at 60 °C for 20 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (Hexane:EA 10:0 to 90:1) to give the title compound as pink solid (66 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (m, 2H), 8.33 (m, 2H), 7.89 (s, 2H), 3.66 (app t, *J* = 7.1Hz, 2H), 3.03 (app t, *J* = 7.1Hz, 2H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.33 (C), 169.02 (C), 163.76 (C), 142.82 (C), 136.48 (CH), 130.82 (C), 129.37 (CH), 119.56 (CH), 81.30 (C), 32.38 (CH_2), 30.17 (CH_2), 28.20 (CH_3). IR (KBr), υ/cm^{-1} 3089, 3005, 2977, 2915, 2848, 1720, 1605, 1403, 1365, 1263, 945. HRMS (ESI+) [M+H]$^+$ Calculated for $[C_{17}H_{20}O_2N_7]^+$ 354.1678; found 354.1674.

***tert*-butyl 3-(6-(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1,2,4,5-tetrazin-3-yl)propanoate (5g)**



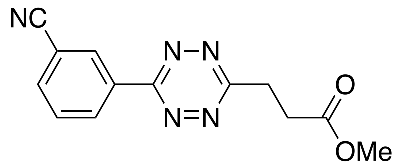
To a dry round bottomed flask was sequentially charged with **3l** (60 mg, 0.23 mmol), Pd(dppf)Cl_2 (26 mg, 0.035 mmol, 15 mol%), 3-([5-(trifluoromethyl)pyridin-2-yl]oxy)phenylboronic acid (198 mg, 0.70 mmol) and Ag_2O (135 mg, 0.59 mmol). The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and filled with nitrogen. DMF (2.3 mL) was added to the flask via syringe. After heating under nitrogen at 60 °C for 20 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (Hexane:EA 10:0 to 90:1) to give the title compound as pink solid (68 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.50 (m, 1H), 8.46 – 8.43 (m, 1H), 8.42 – 8.39 (m, 1H), 7.99 – 7.93 (m, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.16 – 7.08 (m, 1H), 3.65 (app, t, *J* = 7.1 Hz, 2H), 3.01 (app, t, *J* = 7.1 Hz, 2H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.28 (C), 169.17 (C), 165.47 (C, q, J_{C-F} = 1.1Hz), 163.75 (C), 154.03 (C), 145.50 (q, J_{C-F} = 4.4Hz, CH), 137.06 (q, J_{C-F} = 3.1Hz, CH), 133.68 (C), 130.81 (CH), 125.88 (CH), 125.02 (CH), 123.71 (q, J_{C-F} = 272.5 Hz, C), 122.01 (q, J_{C-F} = 33.5Hz, C), 121.1 (CH), 111.9 (CH), 81.26 (C), 32.36 (CH_2), 30.10 (CH_2), 28.12 (CH_3). IR (KBr), υ/cm^{-1} 3005, 2932, 1724, 1614, 1589, 1489, 1394, 1328, 1262, 1130, 1078, 757, 689. HRMS (ESI+) $[M+H]^+$ Calculated for $[C_{21}H_{21}O_3N_5F_3]^+$ 448.1596 found 448.1599.

methyl 4-(6-(((*tert*-butoxycarbonyl)amino)methyl)-1,2,4,5-tetrazin-3-yl)benzoate (5h)



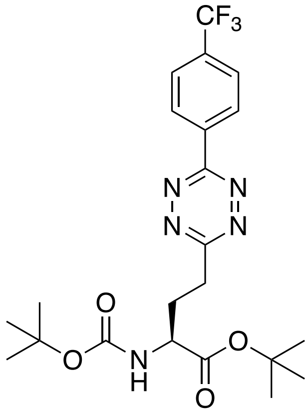
To a microwave reaction tube was sequentially charged with **3n** (57 mg, 0.22 mmol), Pd(dppf)Cl_2 (24 mg, 0.033 mmol, 15 mol%), 4-methoxycarbonylphenylboronic acid (120 mg, 0.66 mmol), Ag_2O (128 mg, 0.55 mmol) and DMF (2.2 mL) in glove box. After heating under nitrogen at 100 °C for 3 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (CH_2Cl_2:Et_2O 100:0 to 95:5) to give the title compound as pink solid (53 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (app d, *J* = 8.3 Hz, 2H), 8.24 (app d, *J* = 8.3 Hz, 2H), 5.62 (s, 1H), 5.05 (d, *J* = 5.8 Hz, 2H), 3.98 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.95 (C), 166.42 (C), 164.59 (C), 155.95 (C), 135.52 (C), 133.95 (C), 130.52 (CH), 128.20 (CH), 80.63 (C), 52.67 (CH_2), 43.67 (CH_3), 28.45 (CH_3). IR (KBr), υ/cm^{-1} 3070, 2979, 2930, 1723, 1697, 1515, 1367, 1281, 1251, 1171, 1110. HRMS $[M+H]^+$ m/z calcd. for $[C_{16}H_{20}O_4N_5]^+$ 346.1515, found 346.1503

methyl 3-(6-(3-cyanophenyl)-1,2,4,5-tetrazin-3-yl)propanoate (5i)



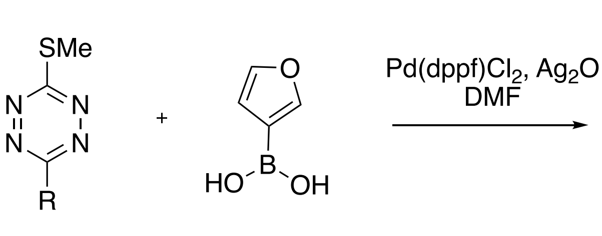
To a microwave reaction tube was sequentially charged with **3k** (55 mg, 0.26 mmol), Pd(dppf)Cl_2 (28 mg, 0.038 mmol, 15 mol%), 3-cyanophenylboronic acid (112 mg, 0.76 mmol), Ag_2O (147 mg, 0.64 mmol) and DMF (2.5 mL) in glove box. After heating under nitrogen at 100 °C for 3 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (Hexane:EA 100:0 to 75:25) to give the title compound as pink solid (42 mg, 61%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.92 (app t, *J* = 1.7 Hz, 1H), 8.84 (ddd, *J* = 7.9, 1.7, 1.2 Hz, 1H), 7.91 (app dt, *J* = 7.9, 1.2 Hz, 1H), 7.74 (td, *J* = 7.9, 0.6 Hz, 1H), 3.74 (app t, *J* = 7.0 Hz, 2H), 3.71 (s, 3H), 3.13 (app t, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.51 (C), 169.41 (C), 162.96 (C), 135.74 (CH), 133.20 (C), 131.91 (CH), 131.54 (CH), 130.34 (CH), 118.05 (C), 113.90 (C), 52.20 (CH_3), 30.58 (CH_2), 29.89 (CH_2). IR (KBr), υ/cm^{-1} 3079, 2954, 2924, 2232, 1737, 1603, 1437, 1396, 1369, 1198, 1176, 905, 687. HRMS $[M+H]^+$ m/z calcd. for $[C_{13}H_{12}O_2N_5]^+$ 270.0991, found 270.0981

(*S*)-*tert*-butyl 2-((*tert*-butoxycarbonyl)amino)-4-(6-(4-(trifluoromethyl)phenyl)-1,2,4,5-tetrazin-3-yl)butanoate (5j)



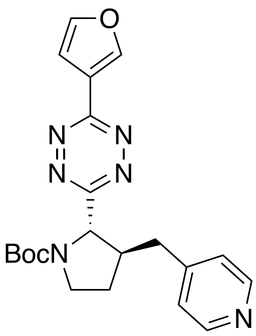
To a microwave reaction tube was sequentially charged with **3p** (72 mg, 0.19 mmol), Pd(dppf)Cl_2 (21 mg, 0.028 mmol, 15 mol%), 4-trifluoromethylboronic acid (107 mg, 0.56 mmol), Ag_2O (108 mg, 0.47 mmol) and DMF (1.9 mL) in glove box. After heating under nitrogen at 100 °C for 3 h, the DMF was removed by rotary evaporation under high vacuum. The residue was purified by column chromatography (CH_2Cl_2:Et_2O 100:0 to 97:3) to give the title compound as pink solid (37 mg, 56%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.73 (app d, *J* = 8.2 Hz, 2H), 7.86 (app d, *J* = 8.2 Hz, 2H), 5.17 (d, *J* = 8.0 Hz, 1H), 4.40 (app dt, *J* = 8.0, 4.9 Hz, 1H), 3.72 - 3.32 (m, 2H), 2.65 - 2.49 (m, 1H), 2.38 - 2.20 (m, 1H), 1.49 (s, 9H), 1.41 (s, 9H), peak at 4.92, 4.24 ppm due to minor rotamer. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.26 (C), 170.03 (C), 163.46 (C), 155.45 (C), 135.17 (C), 134.26 (q, J_{C-F} = 32.7 Hz, C), 128.39 (CH), 126.30 (q, J_{C-F} = 1.9 Hz, CH), 123.83 (q, J_{C-F} = 271.0 Hz, C), 82.72 (C), 80.11 (C), 53.50 (CH), 31.18 (CH_2), 28.40 (CH_3), 28.14 (CH_3). IR (KBr), υ/cm^{-1} 3378, 3063, 2980, 2932, 1713, 1502, 1395, 1368, 1325, 1168, 1138, 1069, 859, 606. HRMS $[M+H]^+$ m/z calcd. for $[C_{22}H_{29}O_4N_5F_3]^+$ 484.2172, found 484.2160

Synthesis of furyl-substituted tetrazines via Ag-mediated Liebeskind coupling with 3-furanboronic acid



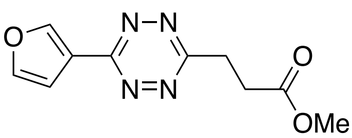
To a microwave reaction tube was sequentially charged with tetrazine thioether **3** (1 equiv.) Pd(dppf)Cl_2 (30 mol%), 3-furanboronic acid (6 equiv.), Ag_2O (5 equiv.) and DMF (0.05 M) in glove box. After heating under nitrogen at 100 °C for 3 h, the DMF was removed by rotary evaporation under high vacuum. Mixture of product and unreacted starting material was collect by flash column chromatography on silica gel and concentrated by rotary evaporation. **Purification method A: oxidizing unreacted starting material.** To a dry round bottom flask was charged with the mixture and CH_2Cl_2 (0.1 M). *m*CPBA (0.3 equiv.) was added at 0°C. After stirring at 0 °C for 2 h, 5% sodium bisulfite aqueous solution was added to quench excessive *m*CPBA. Aqueous and organic layers were separated. Aqueous layer was extracted by CH_2Cl_2 twice. All organic layers were combined, sequentially washed with saturate sodium bicarbonate solution, water, brine, dried over sodium sulfate and concentrated by rotary evaporation. The residue was purified by flash column chromatography on silica gel. **Purification method B: reverse phase chromatography.** Two 14 g YAMAZEN C18 columns were stacked. Tetrazine mixture was dissolved in minimum amount of methanol, diluted by water and loaded on column. H_2O:MeOH 10:0 to 0:10 was used as the eluent, flow rate 15 mL/min.

(2*S*,3*S*)-*tert*-butyl 2-(6-(furan-3-yl)-1,2,4,5-tetrazin-3-yl)-3-(pyridin-4-ylmethyl)pyrrolidine-1-carboxylate (5k)



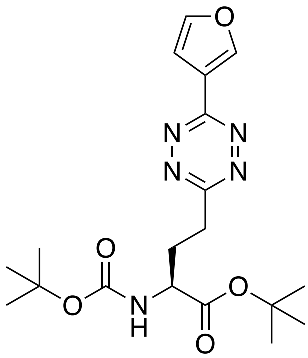
The general protocol was followed with **3v** (21 mg, 0.054 mmol), Pd(dppf)Cl_2 (12 mg, 0.016 mmol), 3-furanboronic acid (36 mg, 0.32 mmol), Ag_2O (63 mg, 0.27 mmol) and DMF (1.1 ml). A pink solid (13 mg, 0.033 mmol, 60%) was obtained following purification method B. Two rotamers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.43 (m, 6H), 7.63 (s, 1H), 7.61 (s, 1H), 7.23 (s, 1H), 7.21 (s, 1H), 7.10 (app d, *J* = 4.5 Hz, 2H), 7.06 (app d, *J* = 4.5 Hz, 2H), 5.08 (d, *J* = 4.8 Hz, 1H), 4.94 (d, *J* = 5.9 Hz, 1H), 3.92 – 3.66 (m, 4H), 3.09 – 2.72 (m, 6H), 2.08 – 2.03 (m, 2H), 1.87 – 1.69 (m, 2H), 1.40 (s, 9H), 1.11 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.35 (C), 169.89 (C), 162.37 (C), 162.28 (C), 154.45 (C), 153.37 (C), 150.08 (CH, both rotamers), 147.80 (C), 147.70 (C), 146.24 (CH), 146.12 (CH), 145.18 (CH), 145.01 (CH), 124.45 (CH), 124.33 (CH), 121.13 (C), 120.88 (C), 108.78 (CH, both rotamers), 80.50 (C, both rotamers), 65.42 (CH), 65.16 (CH), 48.41 (CH), 47.23 (CH), 46.40 (CH_2), 46.30 (CH_2), 37.83 (CH_2, both rotamers), 29.79 (CH_2), 29.70 (CH_2), 28.49 (CH_3), 28.24 (CH_3). IR (KBr), υ/cm^{-1} 3128, 3027, 2976, 2930, 1696, 1600, 1515, 1389, 1367, 1161, 1126, 1081, 935, 878, 736. HRMS [M+H]$^+$ m/z calcd. for $[C_{21}H_{25}O_3N_6]^+$ 409.1988, found 409.1976

methyl 3-(6-(furan-3-yl)-1,2,4,5-tetrazin-3-yl)propanoate (5l)



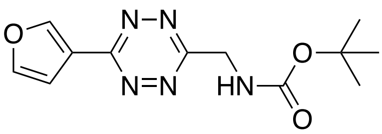
The general protocol was followed with **3k** (42 mg, 0.20 mmol), Pd(dppf)Cl_2 (43 mg, 0.059 mmol), 3-furanboronic acid (132 mg, 1.2 mmol), Ag_2O (227 mg, 0.98 mmol) and DMF (3.9 ml). A pink solid (28 mg, 0.12 mmol, 61%) was obtained following purification method A after column chromatography (Hexane:EA 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 - 8.50 (m, 1H), 7.61 (app t, *J* = 1.7 Hz, 1H), 7.22 (dd, *J* = 1.8, 0.8 Hz, 1H), 3.70 (s, 3H), 3.66 (app t, *J* = 7.1 Hz, 2H), 3.08 (app t, *J* = 7.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.62 (C), 168.22 (C), 162.07 (C), 145.99 (CH), 145.03 (CH), 121.10 (C), 108.76 (CH), 52.18 (CH_3), 30.76 (CH_2), 29.89 (CH_2). IR (KBr), υ/cm^{-1} 3145, 2931, 1730, 1591, 1258, 1194, 1168, 1084. HRMS [M+H]$^+$ m/z calcd. for $[C_{10}H_{11}O_3N_4]^+$ 235.0831, found 235.0823

(*S*)-*tert*-butyl 2-((*tert*-butoxycarbonyl)amino)-4-(6-(furan-3-yl)-1,2,4,5-tetrazin-3-yl)butanoate (5m)



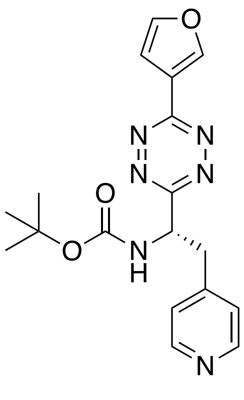
The general protocol was followed with **3p** (75 mg, 0.19 mmol), Pd(dppf)Cl_2 (43 mg, 0.058 mmol), 3-furanboronic acid (131 mg, 1.2 mmol), Ag_2O (225 mg, 0.97 mmol) and DMF (3.9 ml). A pink solid (43 mg, 0.11 mmol, 56%) was obtained following purification method A after column chromatography (Hexane:EA 100:0 to 85:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.64 (app t, *J* = 1.7 Hz, 1H), 7.25 (dd, *J* = 1.8, 0.8 Hz, 1H), 5.18 (d, *J* = 8.2 Hz, 1H), 4.41 (app td, *J* = 7.9, 4.8 Hz, 1H), 3.51 - 3.35 (m, 2H), 2.71 – 2.46 (m, 1H), 2.32 - 2.23 (m, 1H), 1.51 (s, 9H), 1.45 (s, 9H), peak at 4.94, 4.24ppm due to minor rotamer. ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.33 (C), 169.12 (C), 161.95 (C), 155.44 (C), 145.93 (CH), 145.02 (CH), 121.13 (C), 108.76 (CH), 82.65 (C), 80.08 (C), 53.57 (CH), 31.26 (CH_2), 31.19 (CH_2), 28.43 (CH_3), 28.15 (CH_3). IR (KBr), υ/cm^{-1} 3366, 3131, 2979, 2933, 1715, 1589, 1515, 1368, 1250, 1159, 873. HRMS [M+H]$^+$ m/z calcd. for $[C_{19}H_{28}O_5N_5]^+$ 406.2090, found 406.2079

***tert*-butyl ((6-(furan-3-yl)-1,2,4,5-tetrazin-3-yl)methyl)carbamate (5n)**



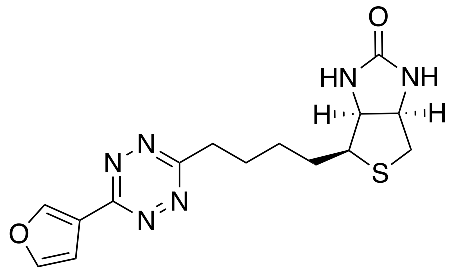
The general protocol was followed with **3n** (50 mg, 0.19 mmol), Pd(dppf)Cl_2 (43 mg, 0.058 mmol), 3-furanboronic acid (130 mg, 1.2 mmol), Ag_2O (225 mg, 0.97 mmol) and DMF (3.9 ml). A pink solid (34 mg, 0.12 mmol, 62%) was obtained following purification method A after column chromatography (Hexane:EA 10:0 to 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 - 8.52 (m, 1H), 7.61 (app t, *J* = 1.8 Hz, 1H), 7.21 (app d, *J* = 1.8 Hz, 1H), 5.60 (s, 1H), 4.96 (d, *J* = 6.0 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.20 (C), 162.65 (C), 155.92 (C), 146.23 (CH), 145.07 (CH), 120.94 (C), 108.72 (CH), 80.45 (C), 43.61 (CH_2), 28.42 (CH_3). IR (KBr), υ/cm^{-1} 3360, 3138, 2979, 2931, 1711, 1588, 1368, 1250, 1161. HRMS [M+H]$^+$ m/z calcd. for $[C_{12}H_{16}O_3N_5]^+$ 278.1253, found 278.1242

(*S*)-*tert*-butyl (1-(6-(furan-3-yl)-1,2,4,5-tetrazin-3-yl)-2-(pyridin-4-yl)ethyl)carbamate (5o)



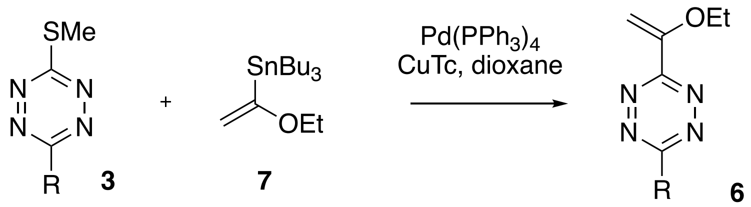
The general protocol was followed with **3t** (18 mg, 0.052 mmol), Pd(dppf)Cl_2 (11 mg, 0.016 mmol), 3-furanboronic acid (35 mg, 0.31 mmol), Ag_2O (60 mg, 0.26 mmol) and DMF (1.0 ml). A pink solid (9.0 mg, 0.024 mmol, 47%) was obtained following purification method B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 - 8.49 (m, 3H), 8.50 (app d, *J* = 5.0 Hz, 2H), 7.63 (app t, *J* = 1.8 Hz, 1H), 7.22 (app d, *J* = 1.8 Hz, 1H), 7.08 (app d, *J* = 5.0 Hz, 2H), 5.73 - 5.51 (m, 1H), 5.58 (d, *J* = 8.8 Hz, 1H), 3.46 (dd, *J* = 14.0, 5.9 Hz, 1H), 3.30 (dd, *J* = 14.0, 7.6 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.81 (C), 162.69 (C), 155.05 (C), 150.14 (CH), 146.56 (CH), 145.24 (CH), 144.96 (C), 124.79 (CH), 120.85 (C), 108.76 (CH), 80.74 (C), 54.13 (CH), 40.85 (CH_2), 28.36 (CH_3). IR (KBr), υ/cm^{-1} 3337, 3153, 3028, 2978, 2930, 1708, 1609, 1589, 1515, 1367, 1250, 1161. HRMS [M+H]$^+$ m/z calcd. for $[C_{18}H_{21}O_3N_6]^+$ 369.1675, found 369.1662

(3a*S*,4*S*,6a*R*)-4-(4-(6-(furan-3-yl)-1,2,4,5-tetrazin-3-yl)butyl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (5p)



The general protocol was followed with **3q** (40 mg, 0.12 mmol), $Pd(dppf)Cl_2$ (27 mg, 0.037 mmol), 3-furanboronic acid (81 mg, 0.72 mmol), Ag_2O (141 mg, 0.61 mmol) and DMF (2.4 ml). A pink solid (20 mg, 0.058 mmol, 48%) was obtained following purification method B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 - 8.48 (m, 1H), 7.61 (app t, *J* = 1.6 Hz, 1H), 7.21 (app d, *J* = 1.6 Hz, 1H), 6.12 (s, 1H), 5.32 (s, 1H), 4.53 (app dd, *J* = 7.4, 4.9 Hz, 1H), 4.33 (app dd, *J* = 7.4, 5.0 Hz, 1H), 3.34 (app t, *J* = 7.7 Hz, 2H), 3.20 3.15 (m, 1H), 2.91 (dd, *J* = 12.8, 5.0 Hz, 1H), 2.74 (d, *J* = 12.8 Hz, 1H), 2.09 - 1.93 (m, 2H), 1.91 – 1.69 (m, 2H), 1.70 – 1.48 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.71 (C), 163.60 (C), 161.95 (C), 145.86 (CH), 145.00 (CH), 121.13 (C), 108.75 (CH), 62.01 (CH), 60.23 (CH), 55.56 (CH), 40.70 (CH_2), 34.49 (CH_2), 28.40 (CH_2), 28.36 (CH_2), 28.33 (CH_2). IR (KBr), υ/cm^{-1} 3223, 3134, 2932, 2858, 1703, 1589, 1515, 1462, 1267, 1159, 872. HRMS $[M+H]^+$ m/z calcd. for $[C_{15}H_{19}O_2N_6S]^+$ 347.1290, found 347.1279

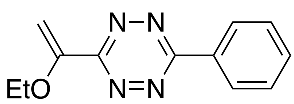
Synthesis of vinylether-substituted tetrazine via Cu-mediated Liebeskind coupling with tributyl(1-ethoxyvinyl)tin



To a dry round-bottom flask was added tetrazine thioether **3** (1 equiv.), $Pd(PPh_3)_4$ (15 mol%) and CuTc (2 equiv.) The flask was outfitted with a septum-fitted gas inlet adapter, and was twice evacuated and backfilled with nitrogen. Tributyl(1-ethoxyvinyl)tin **7** (2 equiv.) and anhydrous dioxane (5 mM in **3**) were added via syringe, and the flask was heated by an oil bath at 100 °C for 16-30 min. After cooling down, the reaction mixture was diluted with hexane and filtered through short pad of 10% K_2CO_3 modified silica gel. Et_2O was used to washed off all red fractions. The residue was concentrated by rotary evaporation and purified by flash column chromatography on 10% K_2CO_3 modified silica gel.

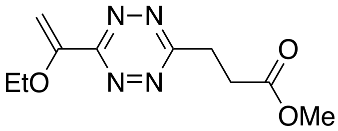
Vinylether tetrazines with alkyl substituents 6h-k was stored as 1-5 mM solution in CH_2Cl_2 in -20 °C to prevent self-condensation.

3-(1-ethoxyvinyl)-6-phenyl-1,2,4,5-tetrazine (6a)



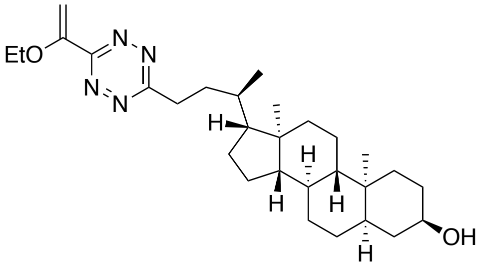
The general protocol was followed with **3x** (50 mg, 0.24 mmol), $Pd(PPh_3)_4$ (43 mg, 0.037 mmol), CuTc (94 mg, 0.49 mmol), tributyl(1-ethoxyvinyl)tin (0.17 mL, 0.49 mmol) and 1,4-dioxane (49 mL) at 100 °C for 30 min. A pink soild (41 mg, 0.18 mmol, 74%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 96:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.72 – 7.46 (m, 3H), 6.02 (d, *J* = 2.9 Hz, 1H), 4.93 (d, *J* = 2.9 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 1.55 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.15 (C), 161.78 (C), 153.73 (C), 133.00 (CH), 131.74 (C), 129.44 (CH), 128.30 (CH), 93.16 (CH_2), 64.67 (CH_2), 14.51 (CH_3). IR (KBr), υ/cm^{-1} 3072, 2978, 2929, 1614, 1599, 1421, 1314, 1182, 1056. HRMS $[M+H]^+$ m/z calcd. for $[C_{12}H_{13}ON_4]^+$ 229.1089, found 229.1082

methyl 3-(6-(1-ethoxyvinyl)-1,2,4,5-tetrazin-3-yl)propanoate (6c)



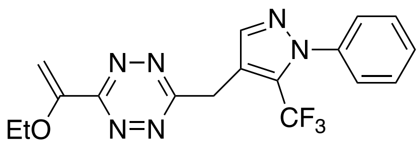
The general protocol was followed with **3k** (50 mg, 0.23 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol), CuTc (90 mg, 0.47 mmol), tributyl(1-ethoxyvinyl)tin (0.16 mL, 0.47 mmol) and 1,4-dioxane (47 mL) at 100 °C for 30 min. A pink oil (29 mg, 0.12 mmol, 52%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 97:3). ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, *J* = 2.9 Hz, 1H), 4.90 (d, *J* = 2.9 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.82 – 3.59 (m, 5H), 3.07 (app t, *J* = 7.1 Hz, 2H), 1.52 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) 172.52 (C), 168.84 (C), 162.13 (C), 153.57 (C), 93.19 (C), 64.65 (CH_2), 52.15 (CH_3), 30.66 (CH_2), 29.84 (CH_2), 14.45 (CH_3). IR (KBr), υ/cm^{-1} 2923, 2851, 1737, 1620, 1437, 1378, 1271, 1160, 1056, 847. HRMS $[M+H]^+$ m/z calcd. for $[C_{10}H_{15}O_3N_4]^+$ 239.1144, found 239.1123

(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-17-((*R*)-4-(6-(1-ethoxyvinyl)-1,2,4,5-tetrazin-3-yl)butan-2-yl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol (6b)



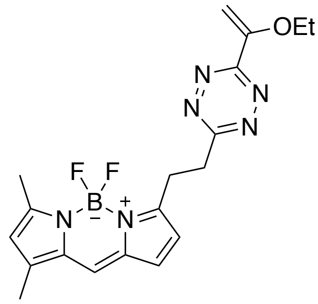
The general protocol was followed with **3r** (62 mg, 0.14 mmol), $Pd(PPh_3)_4$ (23 mg, 0.020 mmol), CuTc (52 mg, 0.27 mmol), tributyl(1-ethoxyvinyl)tin (0.092 mL, 0.27 mmol) and 1,4-dioxane (27 mL) at 100 °C for 16 min. A pink oil (41 mg, 0.082 mmol, 61%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 85:15). ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (d, *J* = 2.9 Hz, 1H), 4.88 (d, *J* = 2.9 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.67 - 3.57 (m, 1H), 3.38 (ddd, *J* = 14.1, 10.5, 5.0 Hz, 1H), 3.23 (ddd, *J* = 14.1, 10.1, 6.4 Hz, 1H), 2.06 (dddd, *J* = 13.2, 10.1, 6.4, 2.7 Hz, 1H), 2.11 – 1.95 (m, 2H), 1.91 – 0.93 (m, 30H), 0.92 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.26, 161.93, 153.72, 92.82, 72.01, 64.62, 56.59, 56.07, 42.93, 42.20, 40.54, 40.30, 36.57, 35.96, 35.76, 35.47, 34.86, 34.70, 31.93, 30.68, 28.37, 27.31, 26.53, 24.33, 23.51, 20.95, 18.58, 14.46, 12.22. IR (KBr), υ/cm^{-1} 3390, 2934, 2836, 1670, 1618, 1447, 1379, 1269, 1160, 1057, 736. HRMS $[M+H]^+$ m/z calcd. for $[C_{29}H_{47}O_2N_4]^+$ 483.3699, found 483.3685

3-(1-ethoxyvinyl)-6-((1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-4-yl)methyl)-1,2,4,5-tetrazine (6d)



The general protocol was followed with **3u** (27 mg, 0.075 mmol), $Pd(PPh_3)_4$ (13 mg, 0.011 mmol), CuTc (29 mg, 0.15 mmol), tributyl(1-ethoxyvinyl)tin (0.051 mL, 0.15 mmol) and 1,4-dioxane (15 mL) at 100 °C for 16 min. A pink oil (16 mg, 0.042 mmol, 57%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 97:3). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.60 – 7.38 (m, 5H), 6.01 (d, *J* = 2.9 Hz, 1H), 4.93 (d, *J* = 2.9 Hz, 1H), 4.76 (s, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 1.52 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.28 (C), 162.13 (C), 153.44 (C), 141,24 (CH), 139.49 (C), 130.63 (q, J_{C-F} = 37.8 Hz, C), 129.61 (CH), 129.17 (CH), 126.13 (q, J_{C-F} = 0.8 Hz, CH), 120.30 (q, J_{C-F} = 268.7 Hz, C), 117.74 (q, J_{C-F} = 1.5 Hz, C), 93.64 (C), 64.71 (CH_2), 30.12 (CH_2), 30.10 (CH_2), 14.45 (CH_3). IR (KBr), υ/cm^{-1} 3064, 2983, 2930, 1618, 1598, 1502, 1398, 1310, 1184, 1159, 1132, 1091, 1053, 975, 768, 695. HRMS $[M+H]^+$ m/z calcd. for $[C_{17}H_{16}ON_6F_3]^+$ 377.1338, found 377.1317

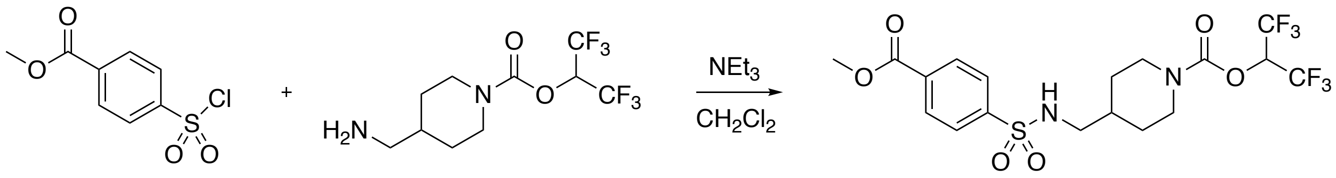
3-(2-(6-(1-ethoxyvinyl)-1,2,4,5-tetrazin-3-yl)ethyl)-5,5-difluoro-7,9-dimethyl-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (6e)



The general protocol was followed with **3w** (20 mg, 0.053 mmol), $Pd(PPh_3)_4$ (9.3 mg, 0.0080 mmol), CuTc (21 mg, 0.11 mmol), tributyl(1-ethoxyvinyl)tin (0.038 mL, 0.11 mmol) and 1,4-dioxane (11 mL) at 100 °C for 16 min. An orange solid (10 mg, 0.026 mmol, 47%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 99:1). ^1H NMR (600 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.85 (d, *J* = 4.0 Hz, 1H), 6.24 (d, *J* = 4.0 Hz, 1H), 6.11 (s, 1H), 5.95 (d, *J* = 2.9 Hz, 1H), 4.89 (d, *J* = 2.9 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.81 (app t, *J* = 7.6 Hz, 2H), 3.66 (app t, *J* = 7.6 Hz, 2H), 2.56 (s, 3H), 2.25 (s, 3H), 1.52 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.44 (C), 162.05 (C), 161.14 (C), 155.94 (C), 153.69 (C) 144.31 (C), 133.59 (C), 127.95 (CH), 124.05 (CH), 120.78 (CH), 116.79 (CH), 93.13 (C), 64.63 (CH_2), 34.03 (CH_2), 26.67 (CH_2), 15.15 (CH_3), 14.47 (CH_3), 11.49 (CH_3). HRMS $[M+H]^+$ m/z calcd. for $[C_{19}H_{22}ON_6F_2B]^+$ 399.1916, found 399.1898

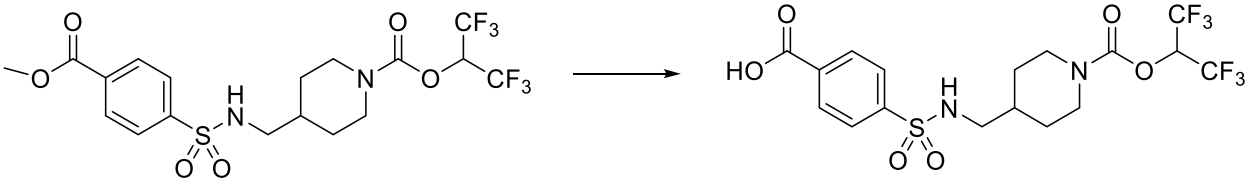
Synthesis of new MAGL probes

1,1,1,3,3,3-hexafluoropropan-2-yl 4-(((4-(methoxycarbonyl)phenyl)sulfonamido)methyl)piperidine-1-carboxylate



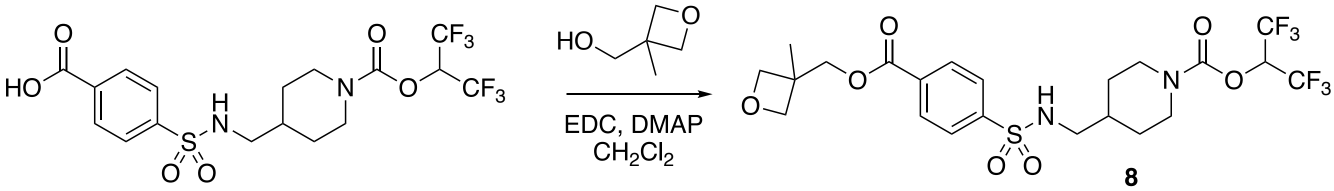
A round bottom flask was charged with 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(aminomethyl)piperidine-1-carboxylate hydrochloride(1.30 g, 3.8 mmol) and methyl 4-(chlorosulfonyl)benzoate(1.77 g, 7.54 mmol). The flask was outfitted with a septum-fitted gas inlet adapter and then evacuated and filled with nitrogen. Anhydrous CH_2Cl_2 (50 mL) was added to the flask via syringe. The flask was cooled by an ice bath (0 °C), and triethylamine (763 mg, 7.54 mmol) was added. After stirring under nitrogen at 20 °C for 1 h, the reaction was diluted with CH_2Cl_2 (50 mL), then the organic phase was washed with water (50 mL x2) and brine (50 mL), dried over sodium sulfate, filtered and concentrated by rotary evaporation. An off-white solid (1.20 g, 2.37 mmol, 63%) was obtained after column chromatography (petroleum ether:EA 100:0 to 55:45). ^{1}H NMR (400 MHz, $CDCl_3$) 8.19 (app d, J = 8.6 Hz, 2H), 7.92 (app d, J = 8.5 Hz, 2H), 5.73 (hept, J = 6.2 Hz, 1H), 4.55 (t, J = 6.6 Hz, 1H), 4.31 – 4.04 (m, 2H), 3.97 (s, 3H), 2.99 – 2.72 (m, 4H), 1.83 – 1.67 (m, 3H), 1.20 – 1.03 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 165.65, 151.02, 145.18, 133.25, 130.48, 127.30, 121.34 (q, $J_{C\text{-}F}$ = 282.0 Hz), 67.68 (hept, $J_{C\text{-}F}$ = 33.0 Hz), 52.97, 47.91, 44.19, 43.70, 35.76, 29.47, 29.10. HRMS $[M+H]^+$ m/z calcd. for $[C_{18}H_{20}O_6N_2F_6SNa]^+$ 529.0844, found 529.0844

4-(N-((1-(((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)carbonyl)piperidin-4-yl)methyl)sulfamoyl)benzoic acid



A round bottom flask was charged with 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(((4-(methoxycarbonyl)phenyl)sulfonamido)methyl) piperidine-1-carboxylate (880 mg, 1.74 mmol), LiOH.H_2O (182 mg, 4.34 mmol) in THF (20 mL) and H_2O (20 mL). After strring at 20°C for 2 h, the mixture was acidized by 2 N HCl to pH 3~4 and extracted by EA (50 mL x 2). The organic phase was washed with water (30 mL) and brine (30 mL x2), dried over Na2SO4, filtered and concentrated by rotary evaporation. An off-white solid (735 mg, 1.53 mmol, 86%) was obtained after triturating from CH_2Cl_2/Hexane (3 mL/15 mL). ^{1}H NMR (400 MHz, DMSO) δ 13.40 (s, 1H), 8.12 (app d, J = 8.5 Hz, 2H), 8.05 – 7.60 (m, 3H), 6.52 (hept, J = 6.4 Hz, 1H), 3.91 (t, J = 14.2 Hz, 2H), 3.05 – 2.74 (m, 2H), 2.67 (t, J = 6.3 Hz, 2H), 1.80 – 1.37 (m, 3H), 1.37 – 0.68 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 166.24, 150.56, 144.30, 134.07, 130.14, 126.71, 120.90 (q, $J_{C\text{-}F}$ = 281.0 Hz), 67.20 (hept, $J_{C\text{-}F}$ = 33.2 Hz), 47.45, 44.21, 43.76, 35.31, 29.03, 28.65. LCMS $[M+H]^-$ m/z calcd. for $[C_{17}H_{16}O_6N_2F_6SNa]^+$ 515.0687, found 515.0685

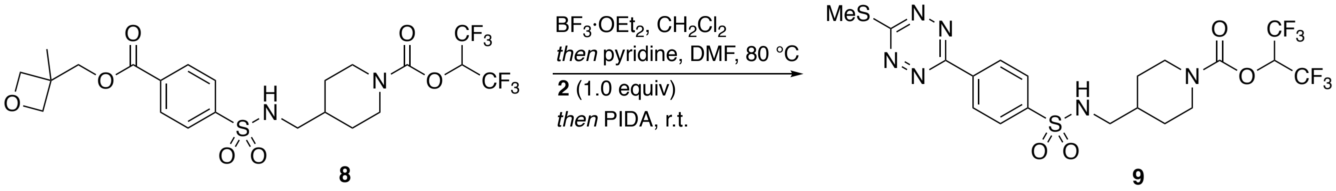
1,1,1,3,3,3-hexafluoropropan-2-yl 4-((4-(((3-methyloxetan-3 yl)methoxy)carbonyl) phenylsulfonamido) methyl)piperidine-1-carboxylate (8)



8

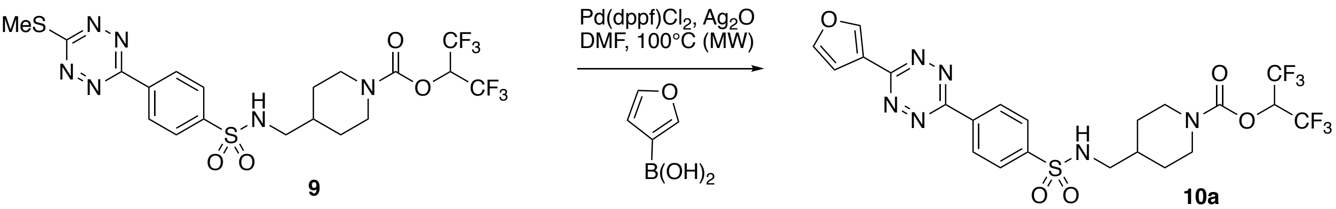
A dry round-bottom flask was charged with 3-methyl-3-oxetanemethanol (57.0 mg, 0.559 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (117 mg, 0.609 mmol) and DMAP (6.20 mg, 0.0508 mmol). The flask was outfitted with a septum-fitted gas inlet adapter and then evacuated and filled with nitrogen. Anhydrous CH_2Cl_2 (5 mL, 0.1 M) was added to the flask via syringe. The flask was cooled by an ice bath (0 °C), and 4-(N-((1-(((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)carbonyl)piperidin-4-yl)methyl)sulfamoyl)benzoic acid (250 mg, 0.508 mmol) was added. After stirring under nitrogen at 0 °C for 15 min and at r.t overnight, the reaction mixture was diluted with CH_2Cl_2. The solution was washed with saturated sodium bicarbonate solution, water and brine, and the organics were dried over sodium sulfate and concentrated by rotary evaporation. A white solid (280 mg, 0.486 mmol, 96%) was obtained after column chromatography (CH_2Cl_2:EA 100:0 to 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (app d, J = 8.4 Hz, 2H), 7.94 (app d, J = 8.4 Hz, 2H), 5.73 (hept, J = 6.3 Hz, 1H), 4.64 - 4.61 (m, 3H), 4.49 (d, J = 6.0 Hz, 2H), 4.44 (s, 2H), 4.27 - 4.06 (m, 2H), 2.99 - 2.76 (m, 4H), 1.89 – 1.65 (m, 3H), 1.44 (s, 3H), 1.23 – 1.05 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.52 (C), 161.22 (C), 151.45 (C), 143.20 (C), 135.91 (C), 128.27 (CH), 127.91 (CH), 120.80 (q, $J_{C\text{-}F}$ = 281.6 Hz, C), 68.16 (hept, $J_{C\text{-}F}$ = 34.2 Hz, CH), 48.51 (CH_2), 44.79 (CH_2), 44.19 (CH_2), 36.47 (CH), 29.56 (CH_2), 29.20 (CH_2), 13.68 (CH_3). HRMS $[M+H]^+$ m/z calcd. for $[C_{22}H_{27}O_7N_2F_6S]^+$ 577.1443, found 577.1421

1,1,1,3,3,3-hexafluoropropan-2-yl 4-((4-(6-(methylthio)-1,2,4,5-tetrazin-3-yl)phenylsulfonamido)methyl)piperidine-1-carboxylate (9)



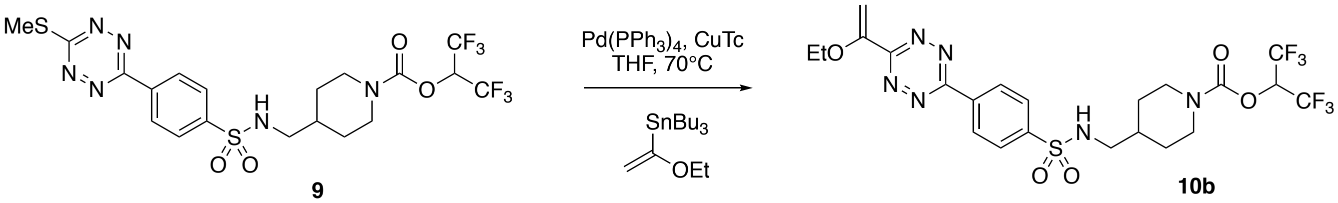
A dry round-bottom flask was charged with **8** (93 mg, 0.16 mmol) and a magnetic stirbar. The flask was outfitted with a septum-fitted gas inlet adapter, evacuated and refilled with nitrogen. Anhydrous CH_2Cl_2 (0.16 mL) was added via syringe and the resulting solution was cooled by an ice/brine bath (–5 °C) and BF_3•OEt_2 (10 μL, 0.081 mmol) was added via syringe. The resulting mixture was allowed to stir under nitrogen with continued cooling by the cold bath (maintained between –5 °C to –0 °C) for 4 h. Reaction mixture was quenched with pyridine (39 μL, 0.48 mmol), and then **2** (28 mg, 0.11 mmol) and DMF (0.11 mL) were added. The mixture was stirred vigorously and vacuum was carefully applied to remove CH_2Cl_2. The resulting mixture was then heated by an oil bath at 80 °C and the mixture was allowed to stir under nitrogen at 80 °C for 2 h. After cooling to r.t., PIDA (36 mg, 0.11 mmol) was added to the flask and the mixture allowed to stir at r.t. for 1 h. The mixture was diluted with CH_2Cl_2 and sequentially washed with saturated sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated by rotary evaporation. A red solid (47 mg, 0.082 mmol, 72%) was obtained after purified by chromatography (CH_2Cl_2:Et_2O 100:0 to 95:5). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.69 (app d, J = 8.5 Hz, 2H), 8.05 (app d, J = 8.5 Hz, 2H), 5.72 (hept, J = 6.3 Hz, 1H), 4.80 (t, J = 6.6 Hz, 1H), 4.19 - 4.13 (m, 2H), 2.93 (t, J = 6.5 Hz, 2H), 2.92 - 2.82 (m, 2H), 2.82 (s, 3H), 1.81 - 1.71 (m, 3H), 1.22 - 1.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.52 (C), 161.22 (C), 151.45 (C), 143.20 (C), 135.91 (C), 128.27 (CH), 127.91 (CH), 120.80 (q, $J_{C\text{-}F}$ = 281.6 Hz, C), 68.16 (hept, $J_{C\text{-}F}$ = 34.2 Hz, CH), 48.51 (CH_2), 44.79 (CH_2), 44.19 (CH_2), 36.47 (CH), 29.56 (CH_2), 29.20 (CH_2), 13.68 (CH_3). IR (KBr), υ/cm^{-1} 3060, 2932, 2834, 1734, 1653, 1527, 1267, 1183, 740. HRMS $[M+H]^+$ m/z calcd. for $[C_{19}H_{21}O_4N_6F_6S_2]^+$ 575.0970, found 575.0956

1,1,1,3,3,3-hexafluoropropan-2-yl 4-((4-(6-(furan-3-yl)-1,2,4,5-tetrazin-3-yl)phenylsulfonamido) methyl)piperidine-1-carboxylate (10a)



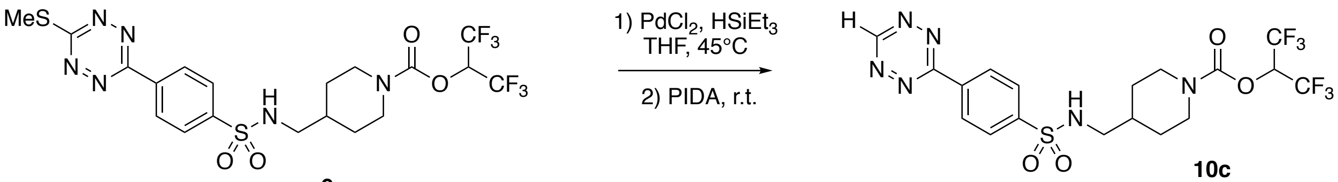
To a microwave reaction tube was sequentially charged with **9** (28 mg, 0.049 mmol), Pd(dppf)Cl_2 (11 mg, 0.015 mmol), 3-furanboronic acid (33 mg, 0.29 mmol), Ag_2O (57 mg, 0.24 mmol) and DMF (1.0 ml) in glove box. After heating under nitrogen at 100 °C for 3 h, the DMF was removed by rotary evaporation under high vacuum. A pink solid (21 mg, 0.036 mmol, 74%) was obtained after reverse phase chromatography with two stacked 14 g YAMAZEN C18 columns (H_2O:MeOH 10:0 to 0:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 8.4 Hz, 2H), 8.60 (s, 1H), 8.08 (d, J = 8.3 Hz, 2H), 7.67 (t, J = 1.7 Hz, 1H), 7.29 (d, J = 1.7 Hz, 1H), 5.73 (hept, J = 6.1 Hz, 1H), 4.61 (t, J = 6.6 Hz, 1H), 4.18 (t, J = 14.3 Hz, 1H), 2.95 (t, J = 6.6 Hz, 1H), 2.91 – 2.73 (m, 1H), 1.92 – 1.68 (m, 2H), 1.16 (t, J = 13.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.70 (C), 162.10 (C), 151.46 (C), 146.70 (CH), 145.36 (CH), 143.45 (C), 136.07 (C), 128.60 (CH), 127.95 (CH), 122.81 (q, $J_{C\text{-}F}$ = 279.9 Hz, C), 121.02 (C), 108.77 (CH), 68.16 (hept, $J_{C\text{-}F}$ = 34.2 Hz, CH), 48.54 (CH_2), 44.80 (CH_2), 44.20 (CH_2), 36.50 (CH), 29.57 (CH_2), 29.21 (CH_2). HRMS $[M+H]^+$ m/z calcd. for $[C_{22}H_{21}O_5N_6F_6S]^+$ 595.1198, found 595.1180

1,1,1,3,3,3-hexafluoropropan-2-yl 4-((4-(6-(1-ethoxyvinyl)-1,2,4,5-tetrazin-3-yl)phenylsulfonamido) methyl)piperidine-1-carboxylate (10b)



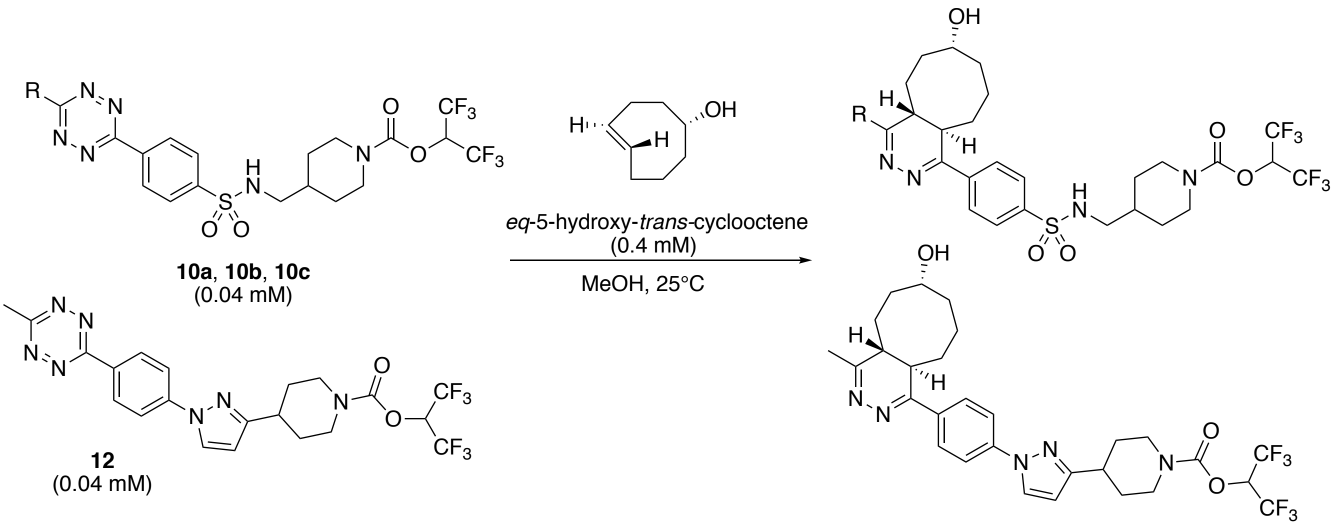
To a dry round-bottom flask was added **9** (15 mg, 0.026 mmol), $Pd(PPh_3)_4$ (4.5 mg, 0.039 mmol), CuTc (10 mg, 0.052 mmol). The flask was outfitted with a septum-fitted gas inlet adapter, and was twice evacuated and backfilled with nitrogen. Tributyl(1-ethoxyvinyl)tin (0.017 mL, 0.052 mmol) and anhydrous dioxane (5.2 mL) were added via syringe, and the flask was heated by an oil bath at 100 °C for 30 min. After cooling down, the reaction mixture was diluted with hexane and filtered through short pad of 10% K_2CO_3 modified silica gel. Et_2O was used to washed off all red fractions. A pink oil (11 mg, 0.018 mmol, 67%) was obtained after column chromatography with 10% K_2CO_3 modified silica gel (CH_2Cl_2:Et_2O 100:0 to 85:15). ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (app d, J = 8.5 Hz, 2H), 8.07 (app d, J = 8.5 Hz, 2H), 6.09 (d, J = 3.0 Hz, 1H), 5.72 (hept, J = 6.3 Hz, 1H), 5.01 (d, J = 3.0 Hz, 1H), 4.65 (t, J = 6.6 Hz, 1H), 4.21 - 4,14 (m, 4H), 2.94 (app t, J = 6.5 Hz, 2H), 2.90 - 2.80 (m, 2H), 1.90 - 1.70 (m, 3H), 1.56 (t, J = 7.0 Hz, 3H), 1.20 - 1.13 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.05 (C), 162.04 (C), 153.42 (C), 151.46 (C), 143.72 (C), 135.77 (C), 128.95 (CH), 127.94 (CH) , 120.81 (q, J_{C-F} = 281.0 Hz, C), 94.37 (C), 68.16 (hept, J_{C-F} = 34.2 Hz, C), 64.84 (CH_2), 48.55 (C), 44.79 (CH_2), 44.19 (CH_2), 36.50 (CH), 29.56 (CH_2), 29.21 (CH_2), 14.49 (CH_3). HRMS $[M+H]^+$ m/z calcd. for $[C_{22}H_{25}O_5N_6F_6S]^+$ 599.1511, found 599.1496

1,1,1,3,3,3-hexafluoropropan-2-yl 4-((4-(1,2,4,5-tetrazin-3-yl)phenylsulfonamido)methyl)piperidine-1-carboxylate (10c)



To a dry round-bottom flask was added **9** (20 mg, 0.035 mmol), $PdCl_2$ (0.62 mg, 0.0035 mmol). The flask was outfitted with a septum-fitted gas inlet adapter, and was twice evacuated and backfilled with nitrogen. Triethylsilane (17 μL, 0.10 mmol) and anhydrous THF (0.35 mL) were added via syringe, and the flask was heated by an oil bath at 45 °C. The mixture was allowed to stir at 45 °C for 24 h. PIDA (12 mg, 0.042 mmol) was added as a solid at r.t. After stirring at room temperature for 1 h, the reaction mixture was diluted with CH_2Cl_2, transferred to a separatory funnel and was sequentially washed with saturated sodium bicarbonate, water, brine, dried over sodium sulfate and concentrated by rotary evaporation. A pink solid (10 mg, 0.019 mmol, 54%) was obtained after column chromatography (CH_2Cl_2:Et_2O 100:0 to 95:5). ^1H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.81 (app d, J = 8.6 Hz, 2H), 8.10 (app d, J = 8.6 Hz, 2H), 5.73 (hept, J = 5.9 Hz, 1H), 4.65 (t, J = 6.6 Hz, 1H), 4.19 (app d, J = 13.6 Hz, 1H), 4.15 (app d, J = 13.6 Hz, 1H), 2.95 (app t, J = 6.6 Hz, 2H), 2.90 (app td, J = 13.0, 2.1 Hz, 1H), 2.84 (app td, J = 13.0, 2.1 Hz, 1H), 1.18 - 1.69 (m, 3H), 1.20 - 1.12 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.53, 158.32, 151.45, 144.14, 135.72, 129.20, 127.99, 120.80 (q, J_{C-F} = 281.0 Hz), 69.16 (hept, J_{C-F} = 34.2 Hz), 48.54, 44.78, 44.19, 36.50, 29.55, 29.20. HRMS $[M+H]^+$ m/z calcd. for $[C_{18}H_{19}O_4N_6F_6S]^+$ 529.1093, found 529.0932

Stopped-flow kinetic analysis of MAGL terazines 10a, 10b, 10c and 12[3] with *eq*-5-hydroxy-*trans*-cyclooctene in MeOH at 25°C



Solutions (3 mL) of tetrazines **10a**, **10b**, **10c** and **12** (0.080 mM) was prepared in MeOH. Solutions (3 mL) of *eq*-5-hydroxy-*trans*-cyclooctene (0.80 mM) were prepared in MeOH. The reactions between tetrazines and *trans*-cyclooctene were measured under pseudo-first order conditions using SX 18MV-R stopped-flow spectrophotometer (Applied Photophysics Ltd.). Each solution of tetrazine and *trans*-cyclooctene were injected in equal volumes via 3 mL syringes into the stopped-flow instrument at 25 °C, resulting in final concentration of 0.04 mM of tetrazines and 0.40 mM *trans*-cyclooctene. The reaction was monitored by the decay of absorbance associated with the tetrazines (10a and 10b at 300 nm, 10c at 280 nm). Reaction were repeated in triplicate. With Prism software, an observed rate constant, k_{obs}, was obtained by nonlinear regression.

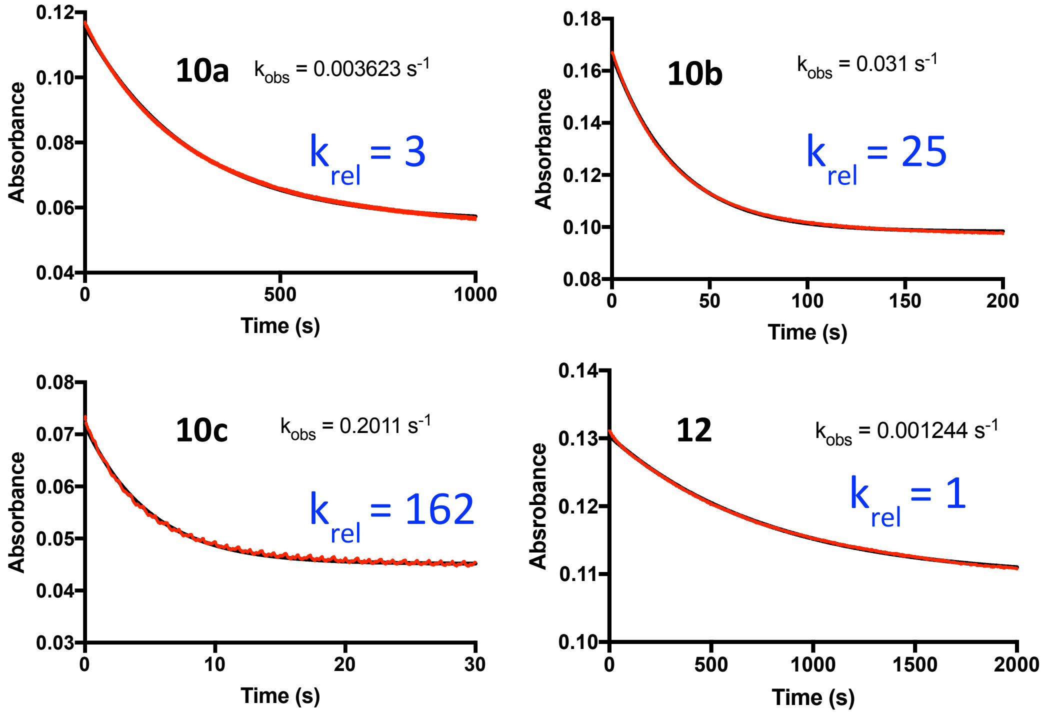


Figure S4 Pseudo-first order stopped-flow kinetics of tetrazine **10a, 10b, 10c** and eq. 5-hydoxy-*trans*-cyclooctene. The plot shows the decay of absorbance at 300 nm, 300 nm, 280 nm respectively measured by a stopped-flow instrument (red curve). The nonlinear regression calculation by prism software is fitted as black curve.

MAGL Probe Experiment

Materials. Tetrazine amine was purchased from Click Chemistry Tools. TCO-TAMRA were synthesized according to literature protocol.[4] Human brain vascular pericytes and pericyte growth supplement were purchased from ScienCell Research Laboratories. Phosphate-based saline (PBS) was purchased from Mediatech, Inc.. Media and other supplements for cell culture were purchased from Thermo Fisher Scientific unless otherwise noted. For cell experiments, all reagents were prepared as 1000x stock solutions in DMSO and stored at -80°C.

MAGL in vitro activity assay. The MAGL in vitro activity assay was performed based on a reported protocol.[5] Briefly, human MAGL enzyme was pre-treated with compounds at room temperature for 30 min, and subsequently incubated with 7-hydroxycoumarinyl arachidonate (7-HCA) as a substrate at room temperature for 1 h. The fluorescence signals were measured on an Envision plate reader (excitation 355 nm, emission 460 nm).

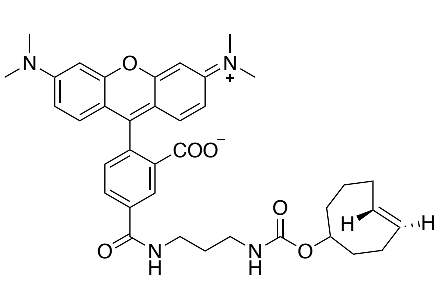
Cell culture and probe treatment. Human brain vascular pericytes were cultured in Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 (DMEM/F-12) GlutaMAX media supplemented with 5% heat-inactivated fetal bovine serum (HI FBS), 1x pericyte growth supplement (PGS), and 1x penicillin-streptomycin at 37 °C with 5% CO_2 in a humidified environment. Cells were plated in 6-well plates and cultured overnight in growth media.

To assess cellular potency of probe **10c**, live cells were treated with **10c** (0.32 nM – 10 μM) at 37 °C for 1 h, after which the cells were washed with fresh media. The media were then placed with fresh media containing 2 μM of TCO-TAMRA, and the cells were incubated at 37 °C for 30 min. The reaction was quenched by replacing the media with PBS containing 100 μM tetrazine amine, and the cells were washed with cold PBS and harvested with a scrapper.

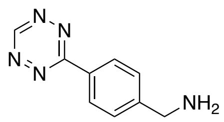
To measure the cellular labeling kinetics of TCO-TAMRA with **10c** and **12**, live cells were treated with **10c** (1 μM) or **12** (32 nM) at 37 °C for 1 h. At these concentrations, both probes achieved full labeling of MAGL. Subsequently, the cells were washed with fresh growth media, which were placed with fresh media containing 50 nM, 200 nM, or 2 μM of TCO-TAMRA, and the cells were incubated at 37 °C for 2, 5, 10, 15, 20, 30, and 60 min. To quench the reaction, the media were replaced with PBS containing 100 μM tetrazine amine, and the cells were washed with cold PBS and harvested with a scrapper.

The suspensions were centrifuged at 10,000xg for 1 min at 37 °C, and the cell pellets were lysed in PBS containing 0.25% sodium dodecyl sulfate (SDS) with sonication. The protein concentration was measured with a bicinchoninic acid (BCA) assay kit (Thermo Scientific) and normalized.

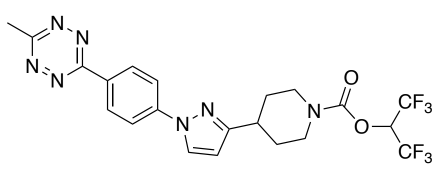
In-gel fluorescence and data analysis. The proteomes were analyzed with 1.0 mm thick 4-12% bis-tris protein gels in 2-(*N*-morpholino)ethanesulfonic acid (MES) buffer. The gels were scanned with a Typhoon FLA 9500 Biomolecular Imager (GE Healthcare) with the TAMRA channel with 532 nm excitation and a 575 nm long pass emission filter. To measure the total protein loading, the gels were treated with ClearPage Instant Blue (CBS Scientific) overnight, and after brief destaining with water, scanned with an Odyssey Imager (Li-COR) at the 700 nm channel. The in-gel fluorescence images were processed with ImageJ software (v1.47, NIH), and the intensities were quantified with Image Studio (v5.2, Li-COR) with background subtraction. The coomassie images were processed and quantified with the Image Studio software. For data fitting, the fluorescence intensities of the two MAGL bands were averaged and fitted with a dose-response (for cellular potency) or exponential (for kinetics) equation with Prism v7.02 (GraphPad).



TCO-TAMRA
(equatorial)



Tetrazine-amine



MAGL probe with 6-methyltetrazen-3-yl substituent
12

Figure S5 Stucture of reagents in live cell experiments

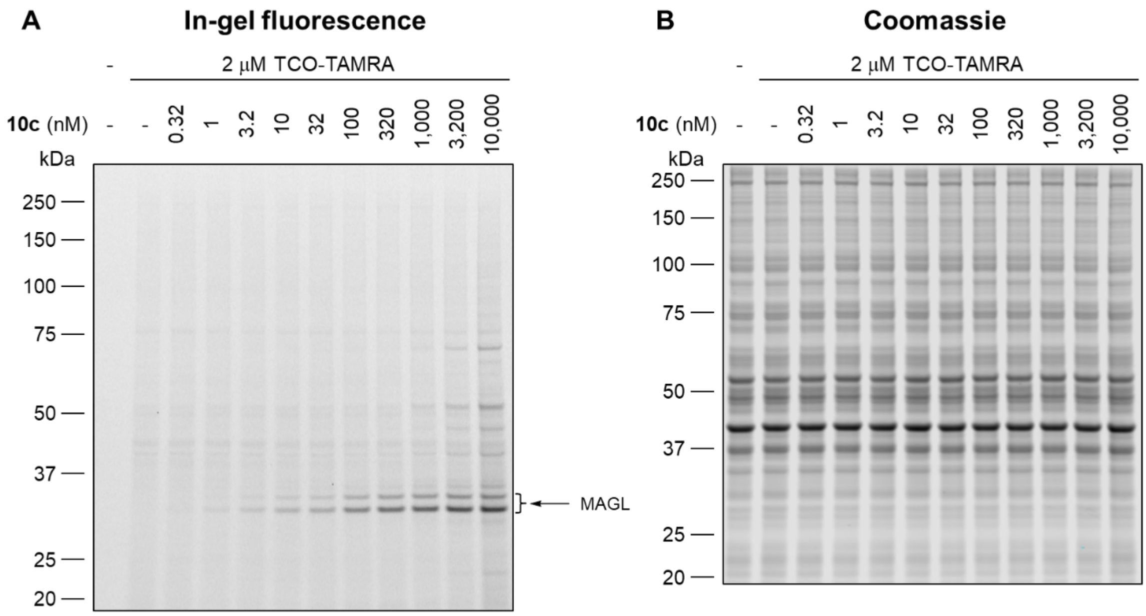


Figure S6 Representative cellular potency data of **10c** in live human brain vascular pericytes. (A) Full gel of in-gel fluorescence data in Figure 3C. (B) Coomassie staining of total proteins.

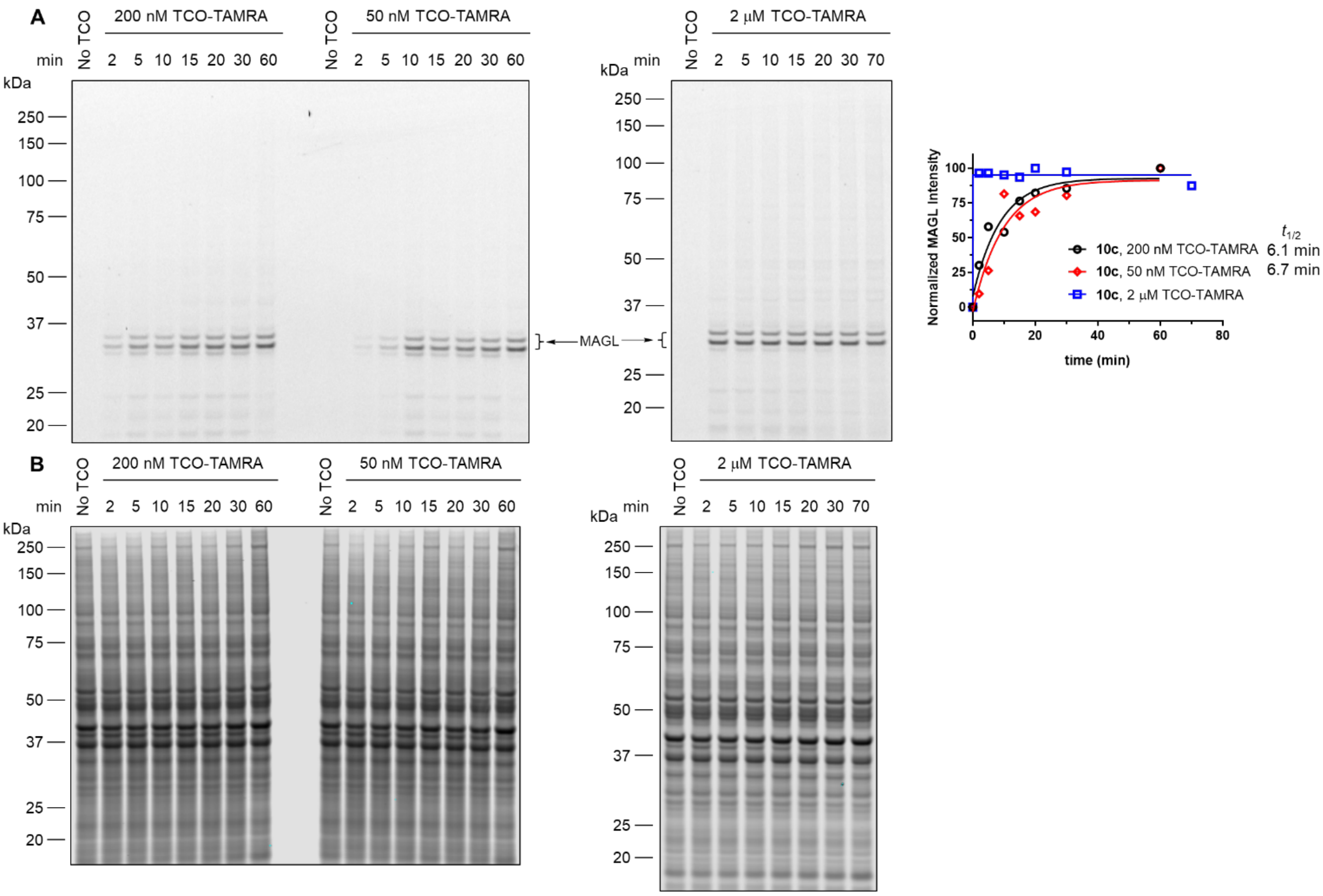


Figure S7 Cellular labeling kinetics of TCO-TAMRA with **10c** (1 µM, 1 h) in live human brain vascular pericytes. (A) Full gel of in-gel fluorescence data (200 nM TCO-TAMRA in Figure 3D). (B) Coomassie staining of total proteins.

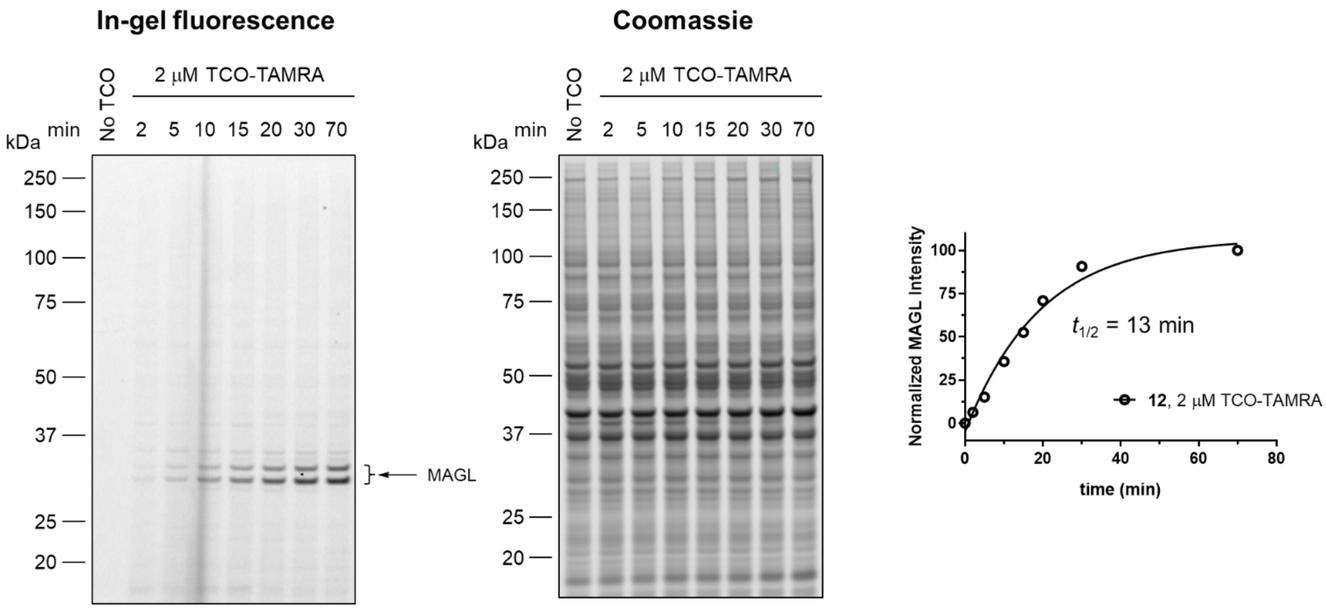


Figure S8 Cellular labeling kinetics of TCO-TAMRA with **12** (32 nM, 1 h) in live human brain vascular pericytes.

References

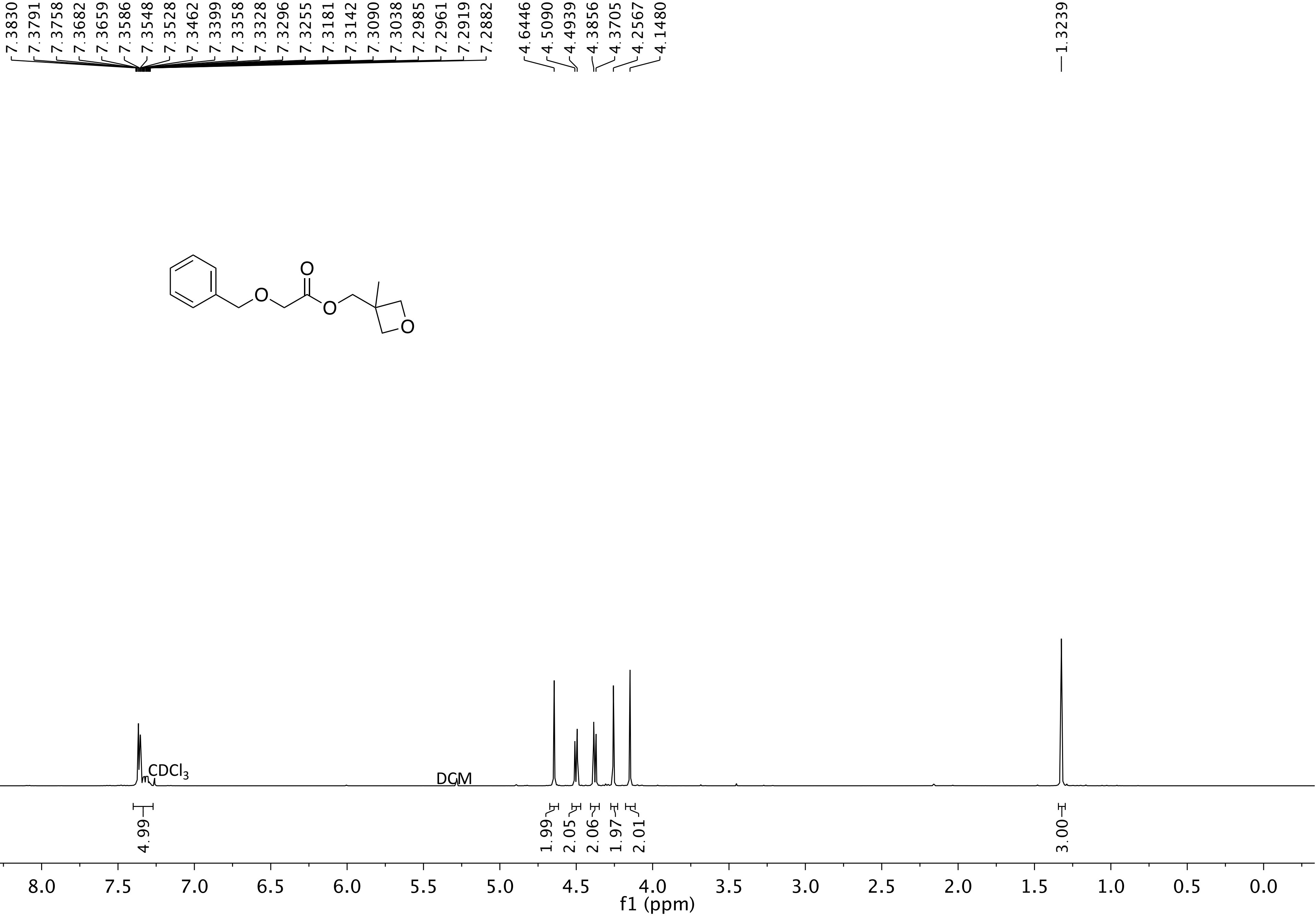
[1] *Org. Process Res. Dev.* **2018**, *22*, 1262−1275,

[2] E. S. Scott, L. F. Audrieth, *J. Org. Chem.* **1954**, *19*, 1231-1237.

[3] W. D. Lambert, Y. Fang, S. Mahapatra, Z. Huang, C. W. am Ende, J. M. Fox, *J. Am. Chem. Soc.* **2019**, *141*, 17068-17074.

[4] H. E. Murrey, J. C. Judkins, C. W. am Ende, T. E. Ballard, Y. Fang, K. Riccardi, L. Di, E. R. Guilmette, J. W. Schwartz, J. M. Fox, D. S. Johnson, *J. Am. Chem. Soc.* **2015**, *137*, 11461-11475.

[5] C. R. Butler, E. M. Beck, A. Harris, Z. Huang, L. A. McAllister, C. W. am Ende, K. Fennell, T. L. Foley, K. Fonseca, S. J. Hawrylik, D. S. Johnson, J. D. Knafels, S. Mente, G. S. Noell, J. Pandit, T. B. Phillips, J. R. Piro, B. N. Rogers, T. A. Samad, J. Wang, S. Wan, M. A. Brodney, *J. Med. Chem.* **2017**, *60*, 9860-9873.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2.06
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2.01
3.00
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6.0
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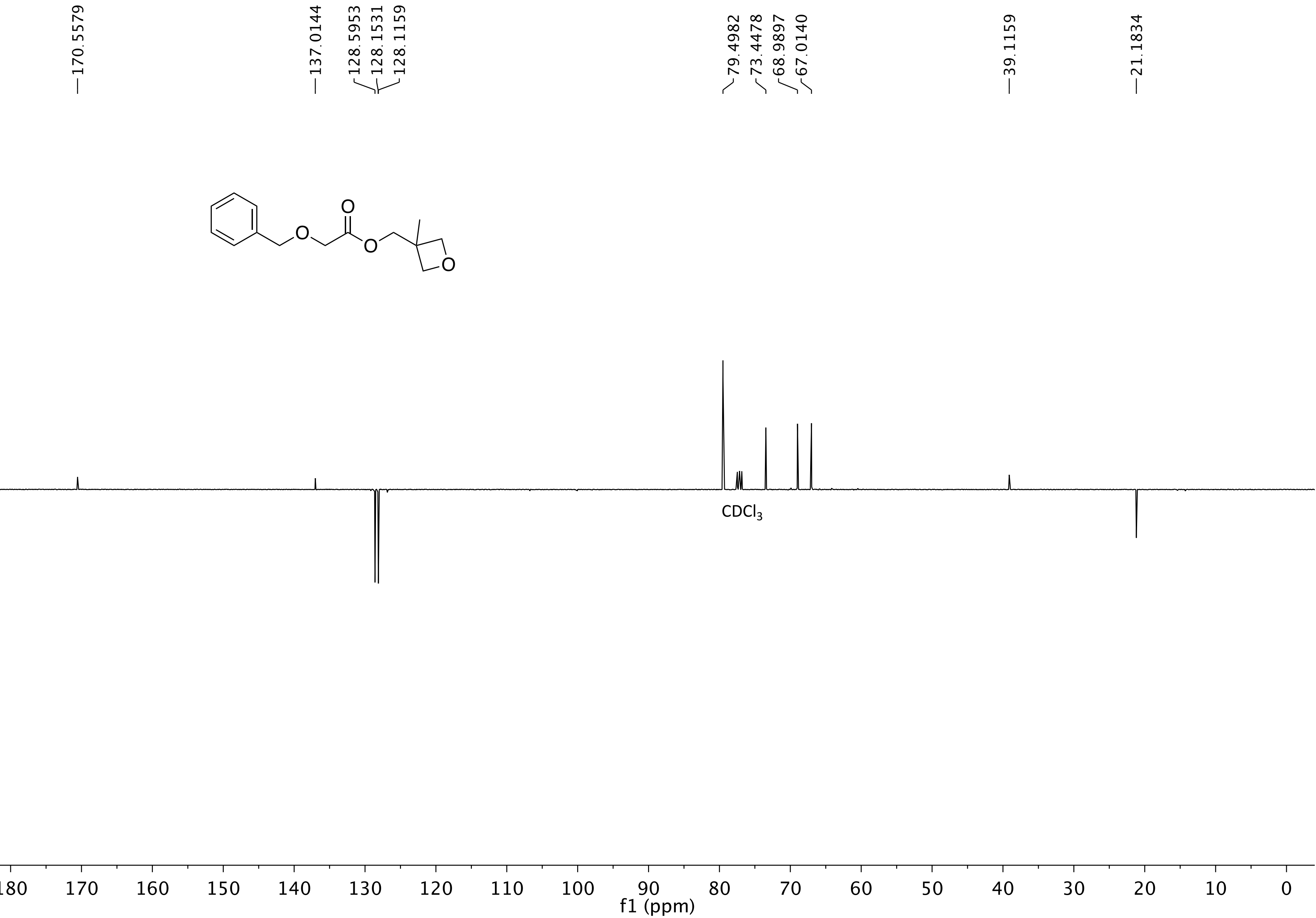
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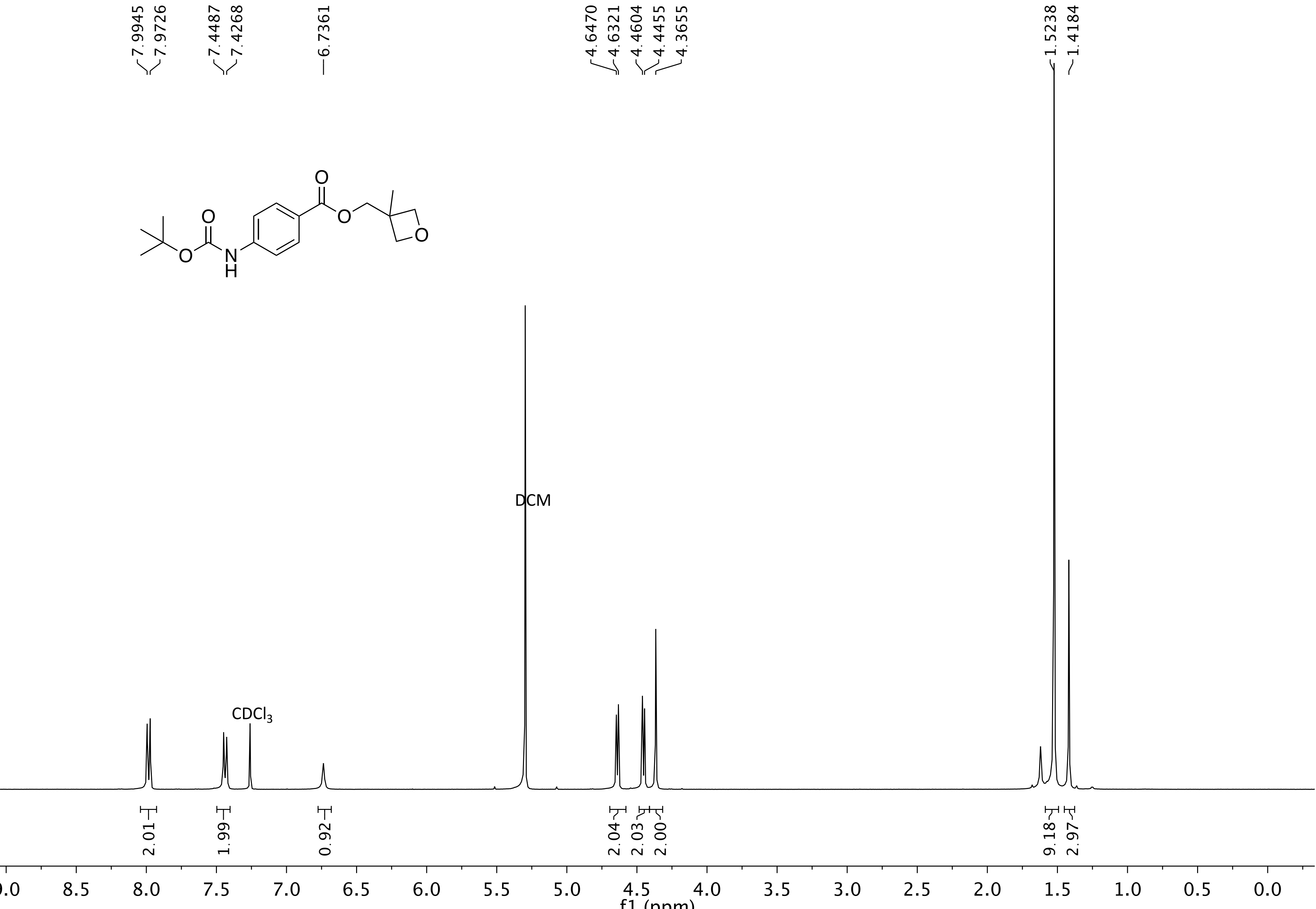
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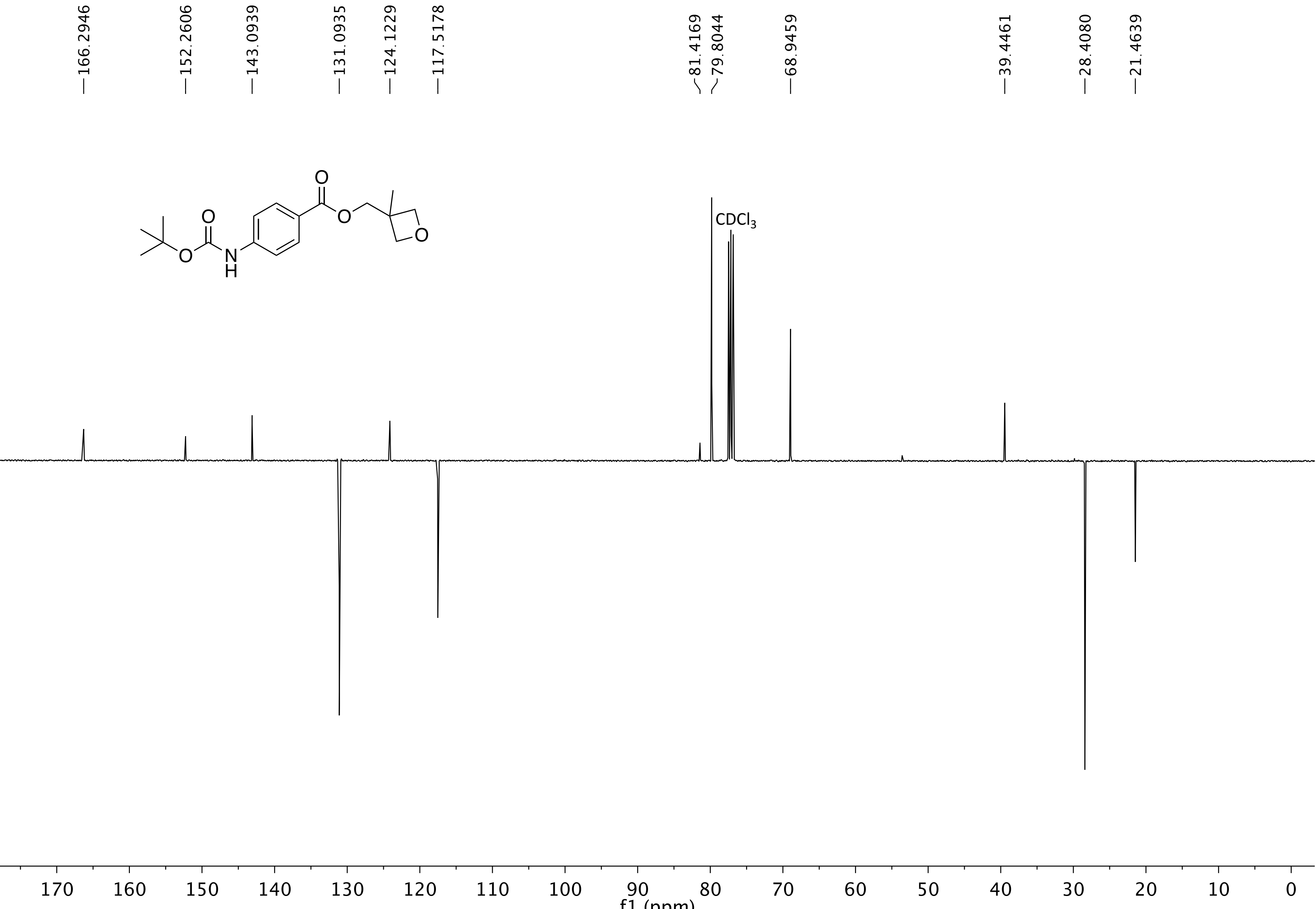

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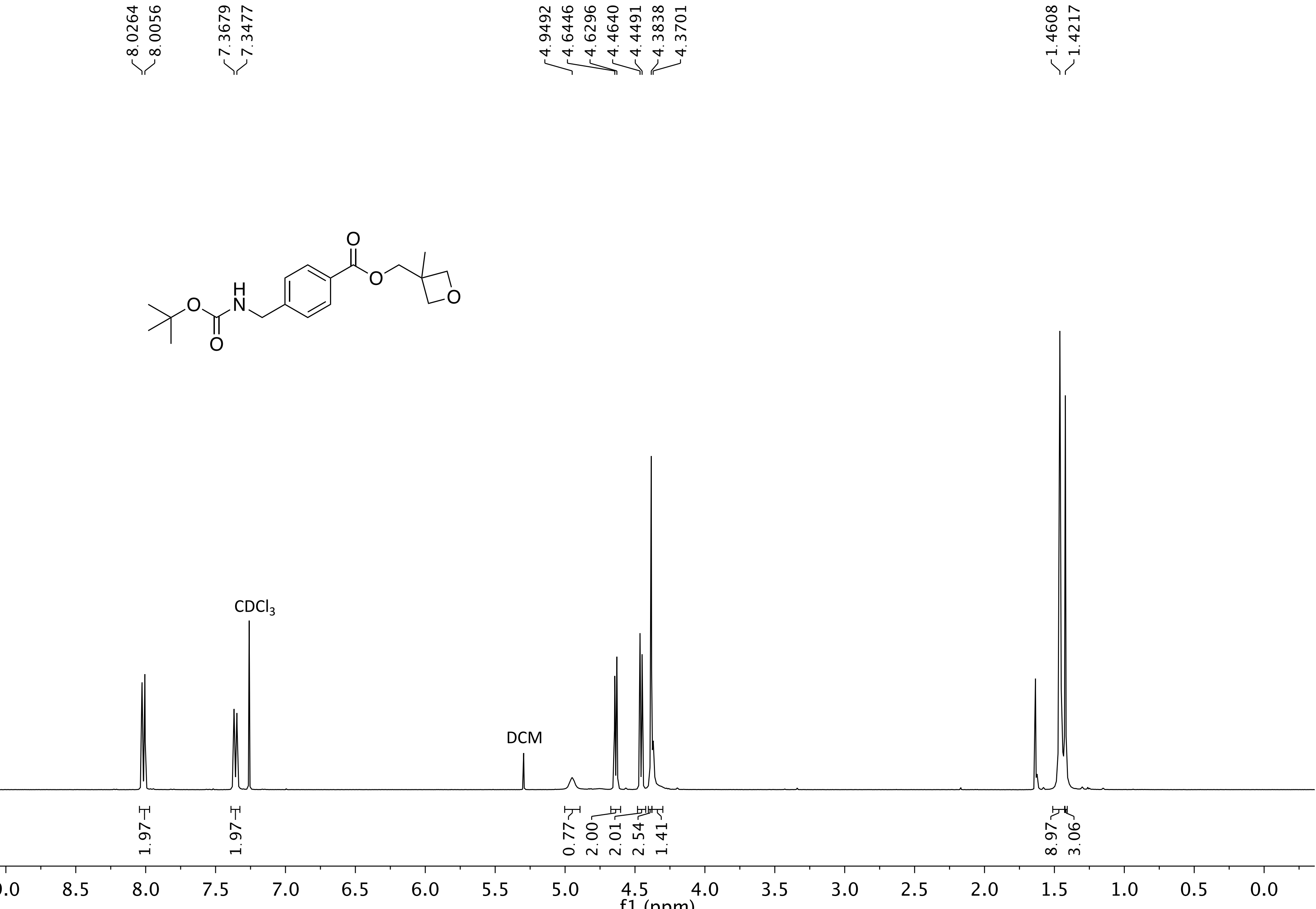
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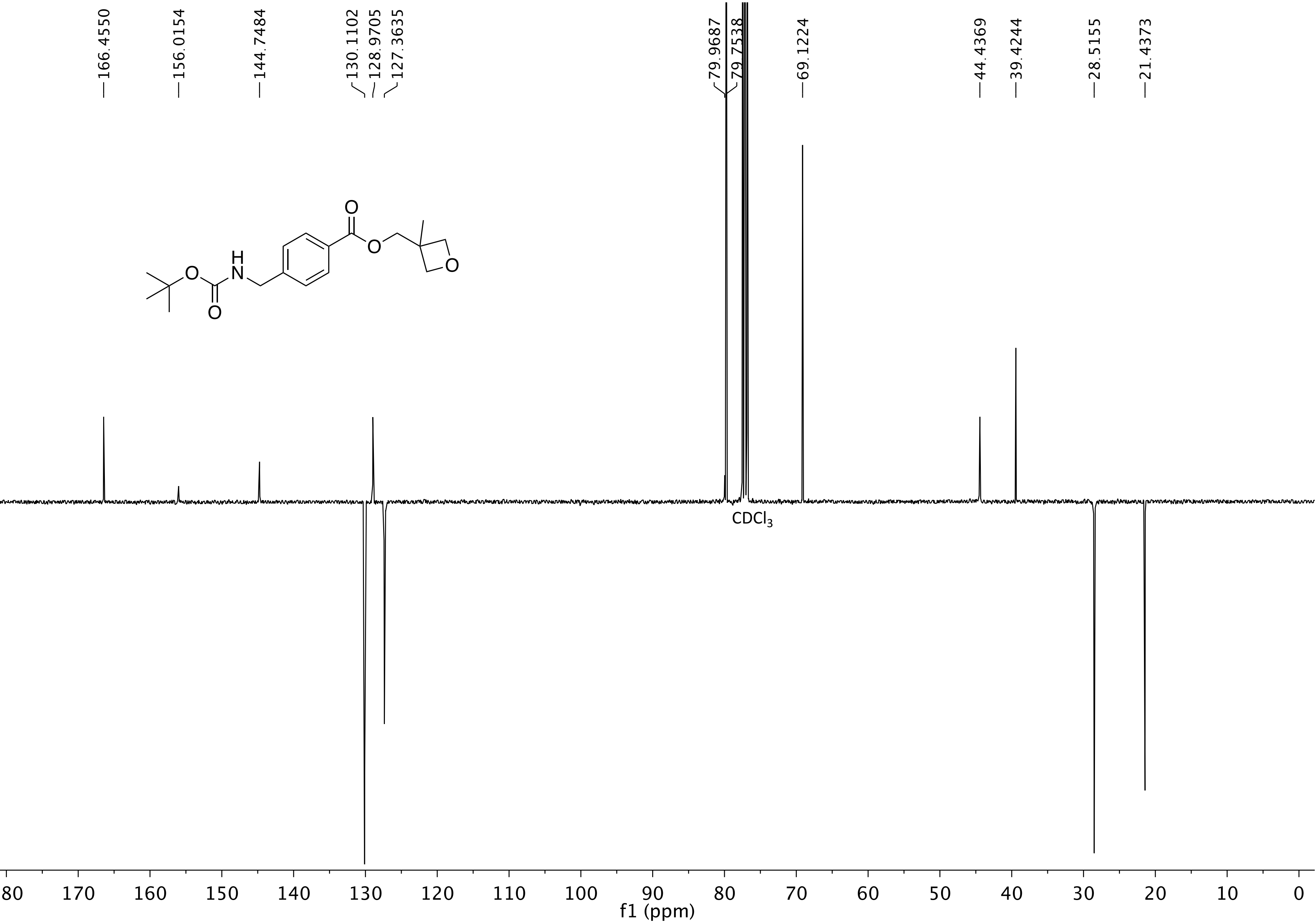

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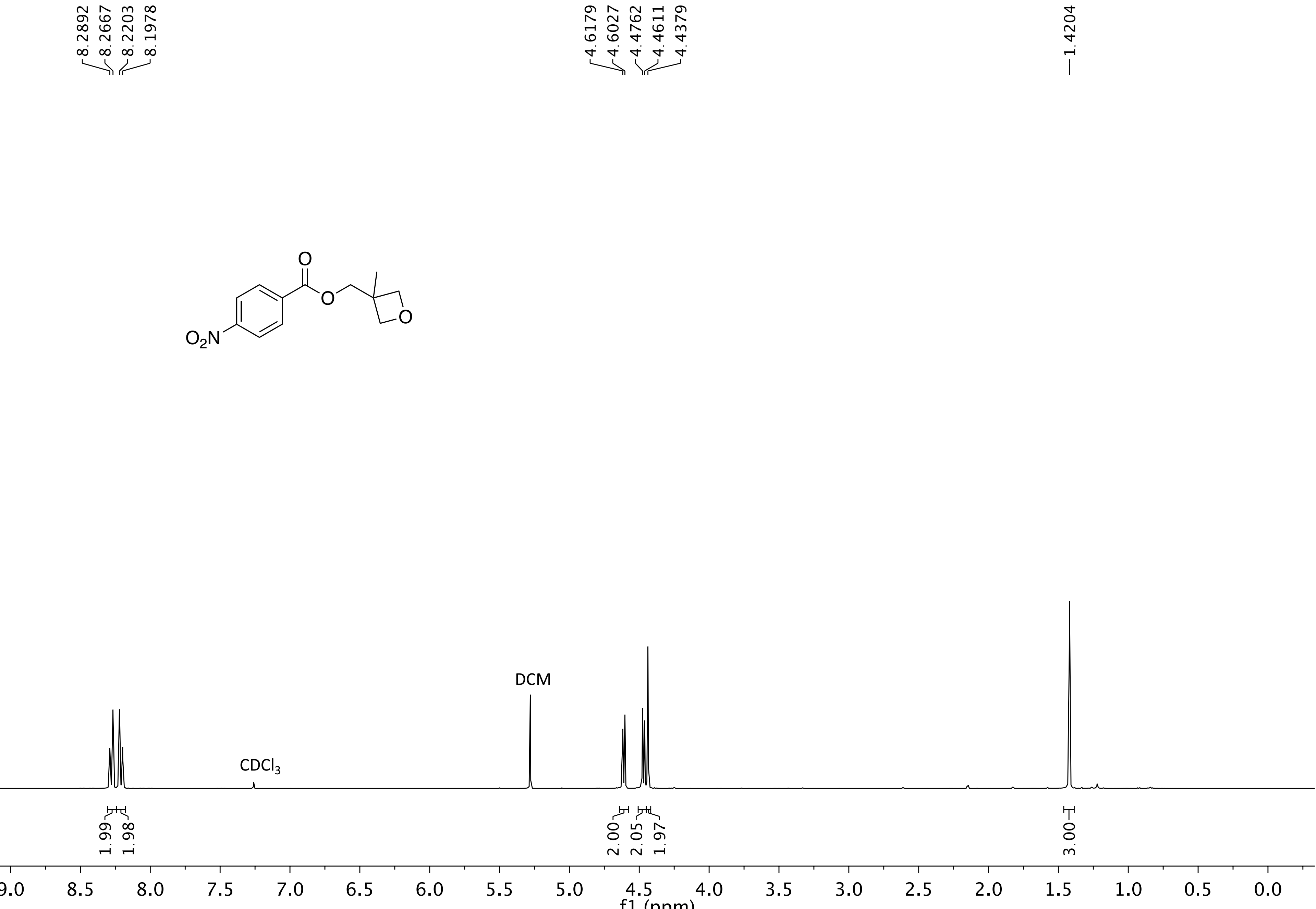
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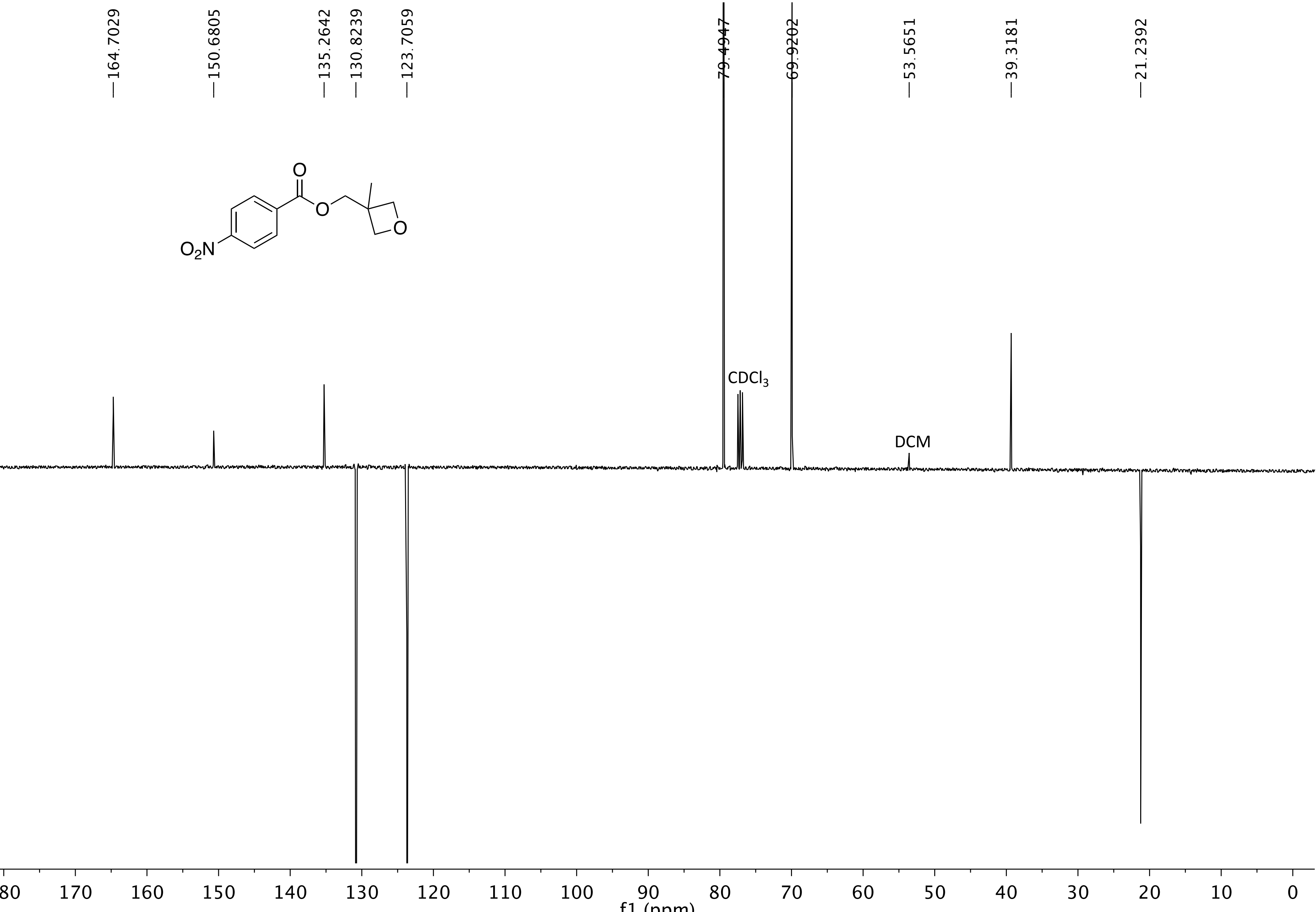

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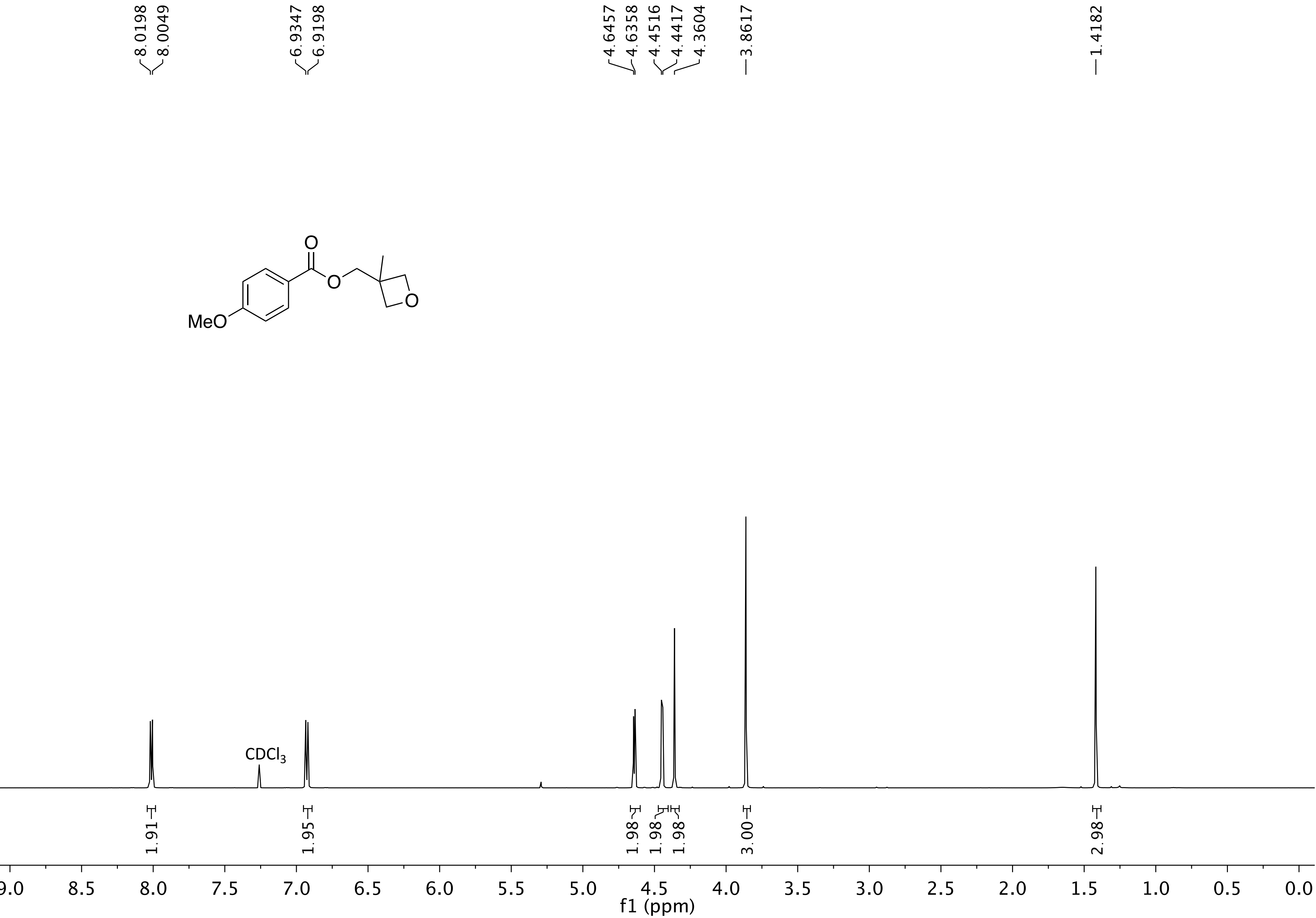
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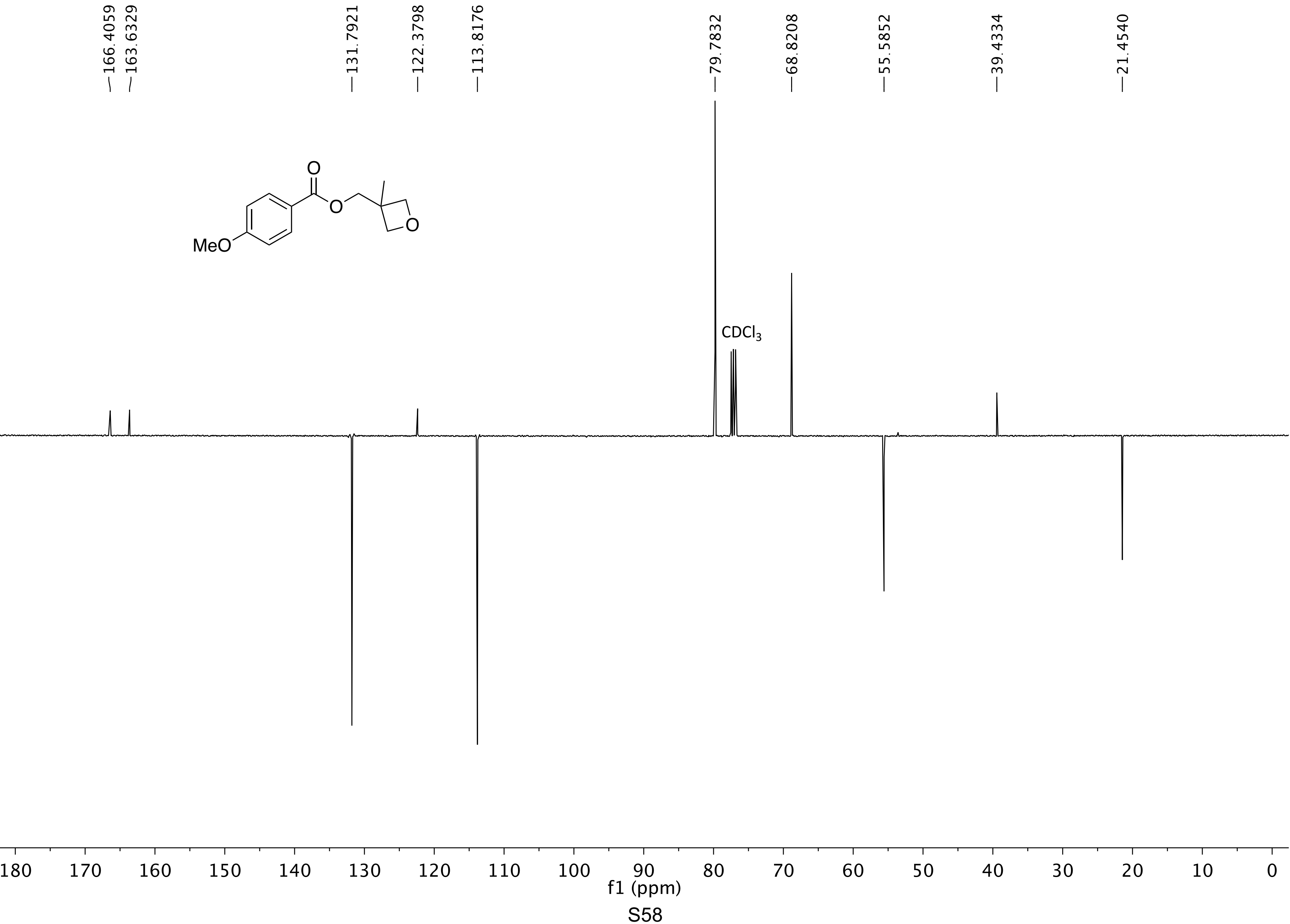

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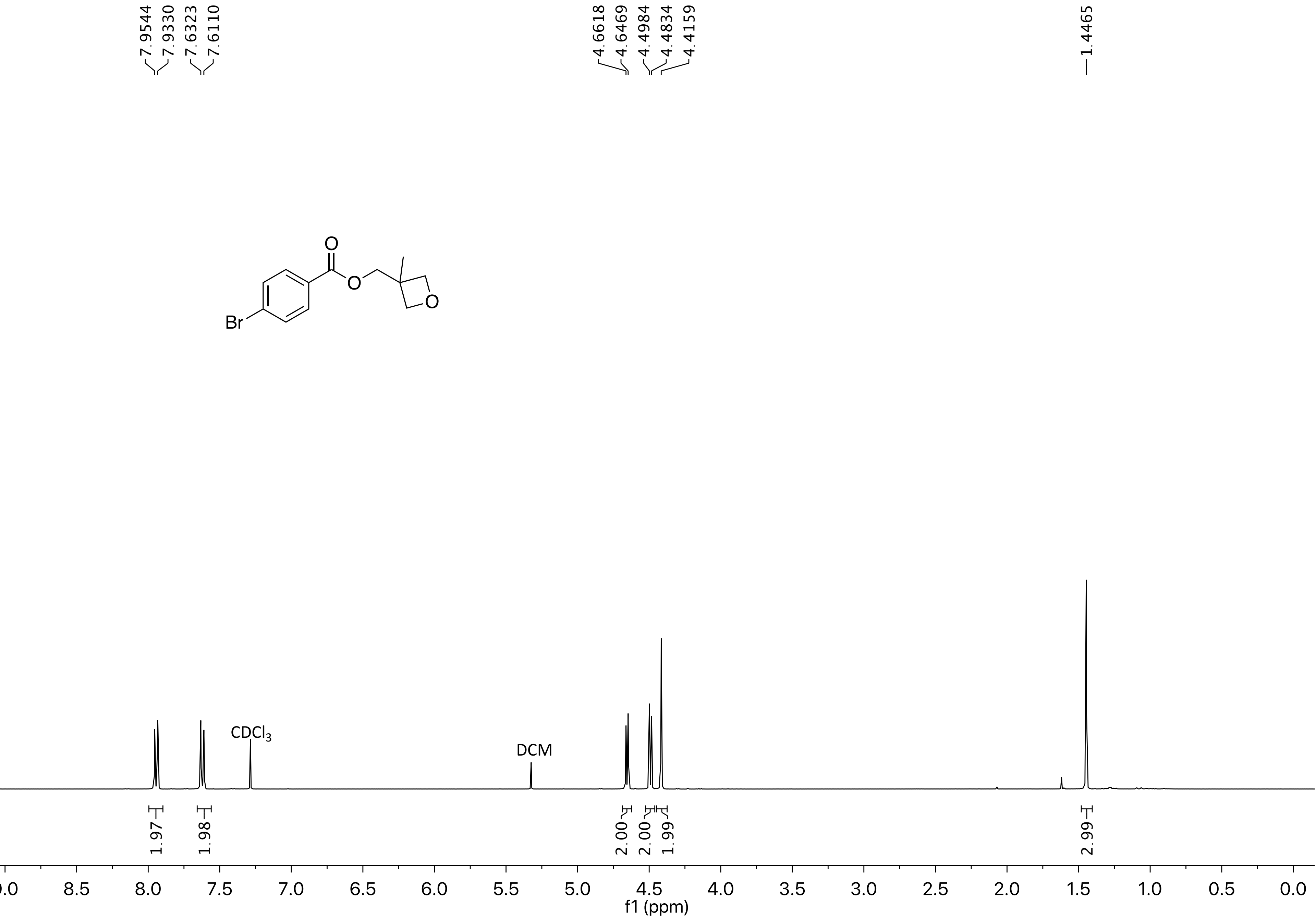
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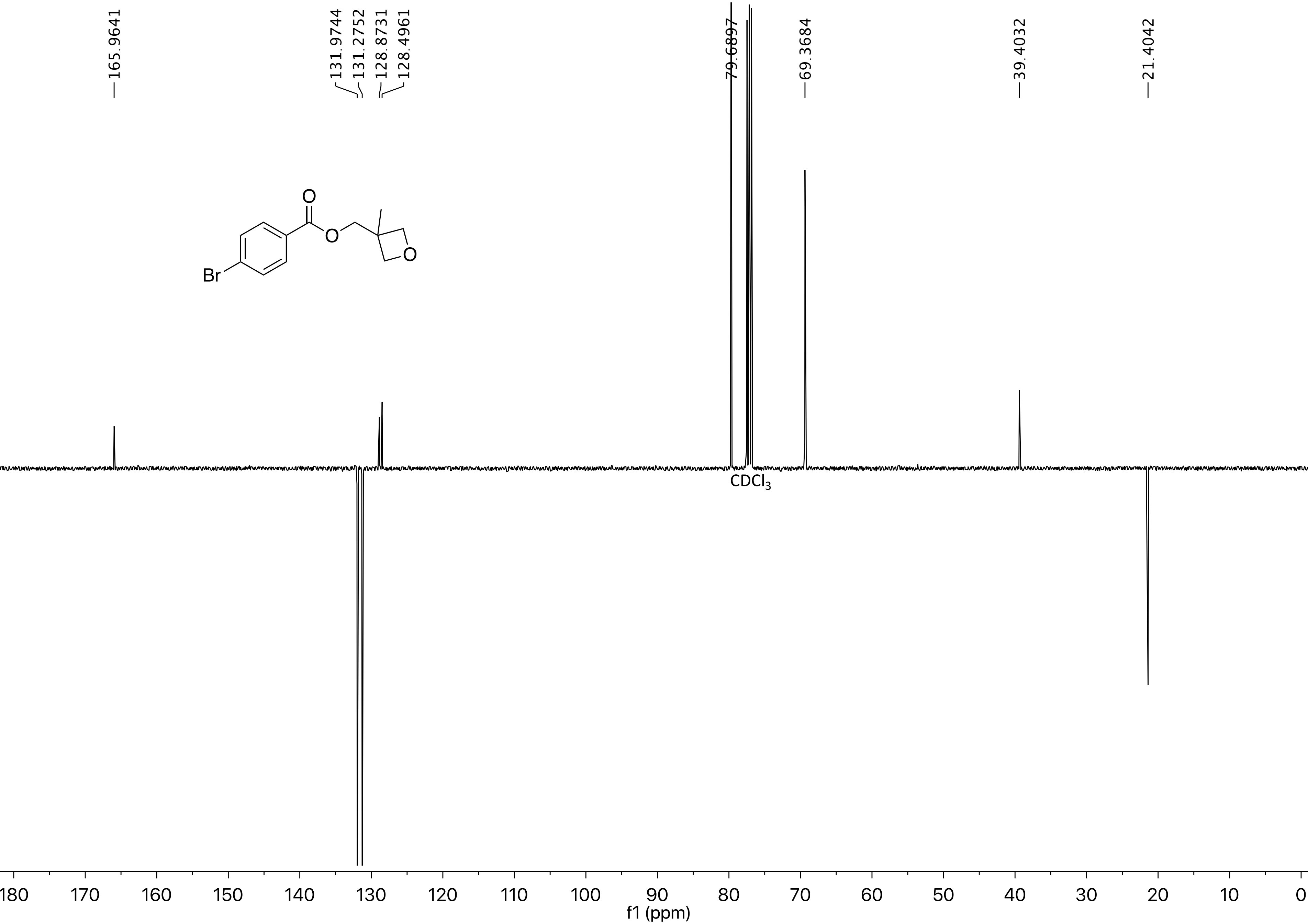

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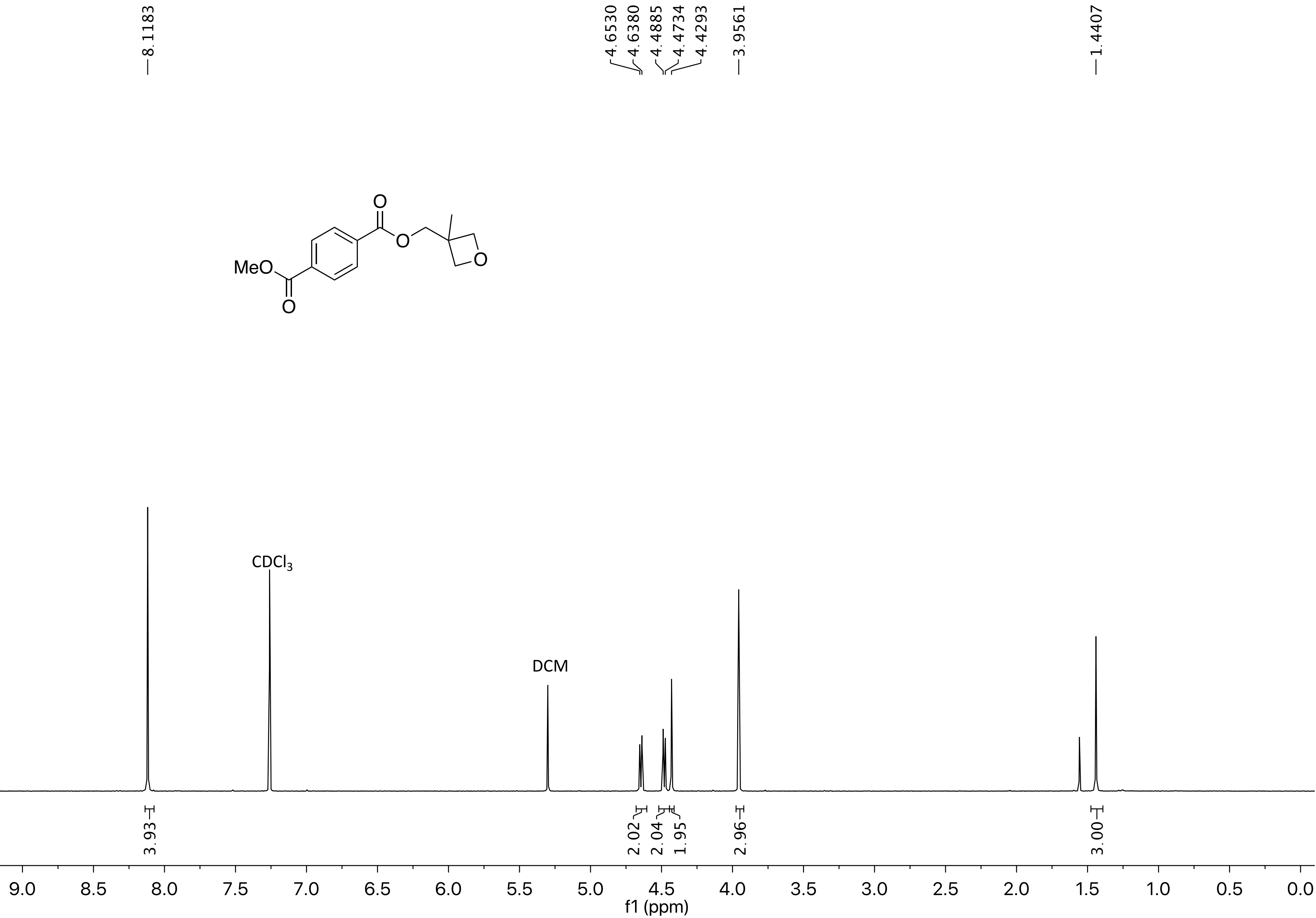

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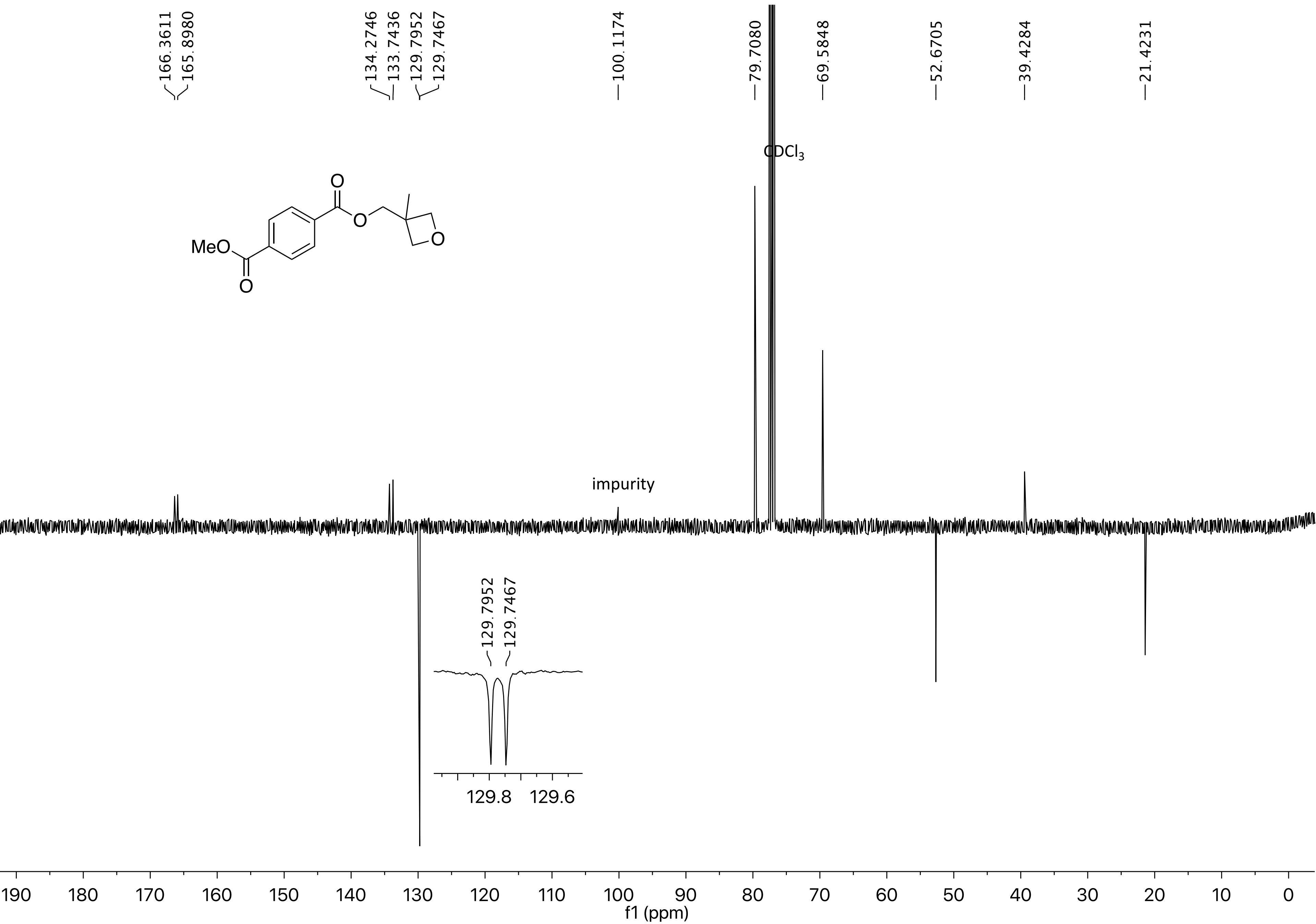

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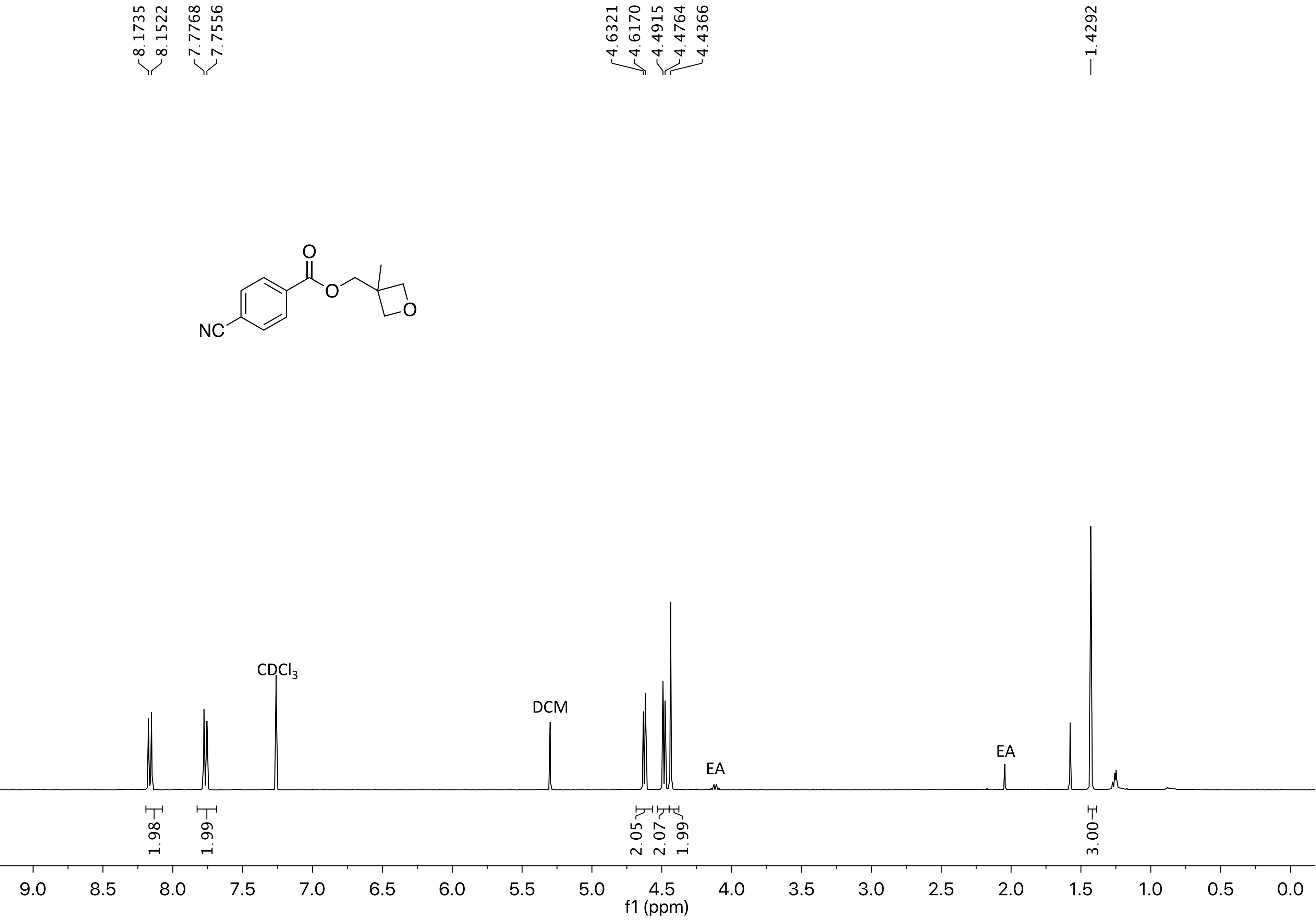
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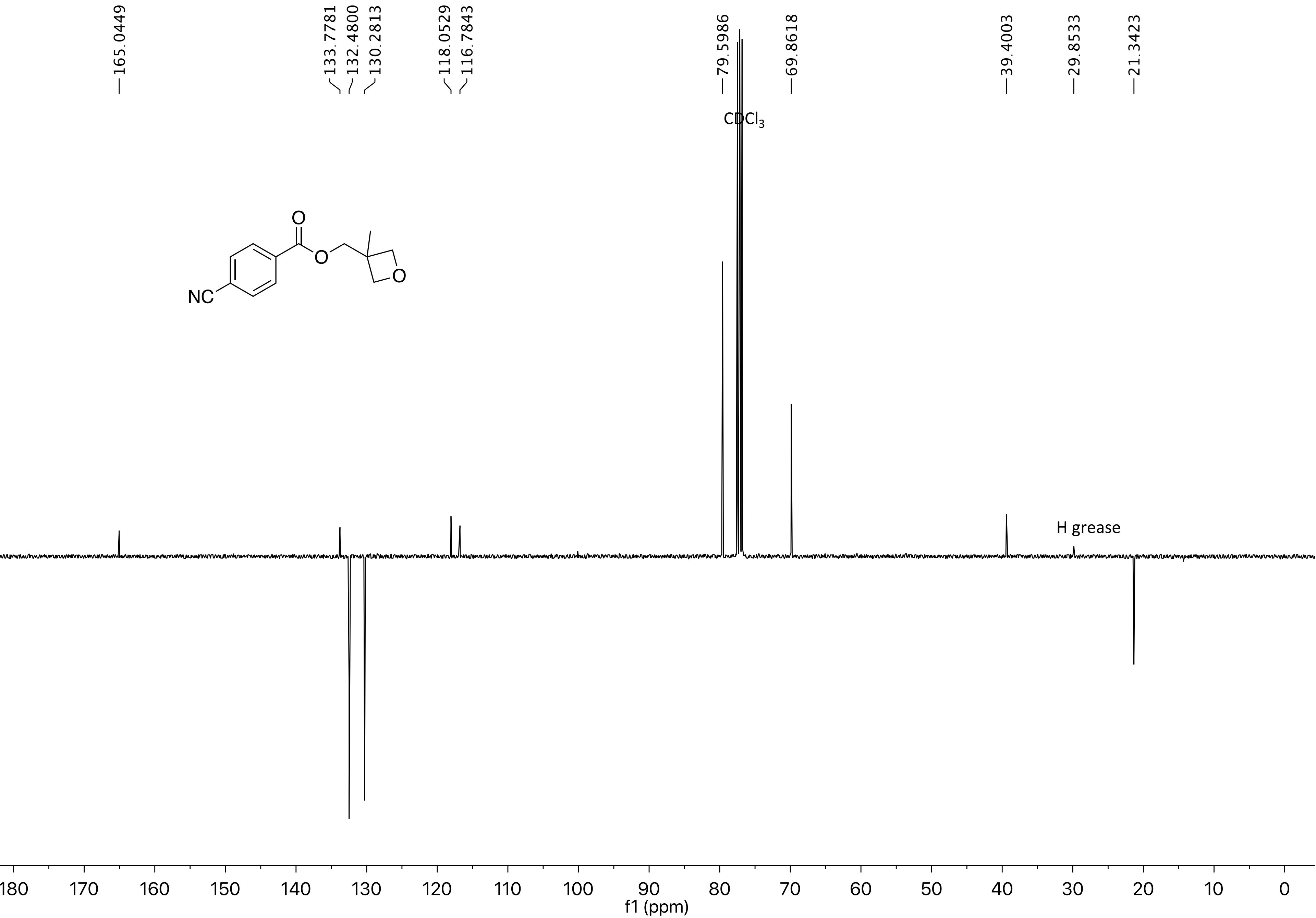
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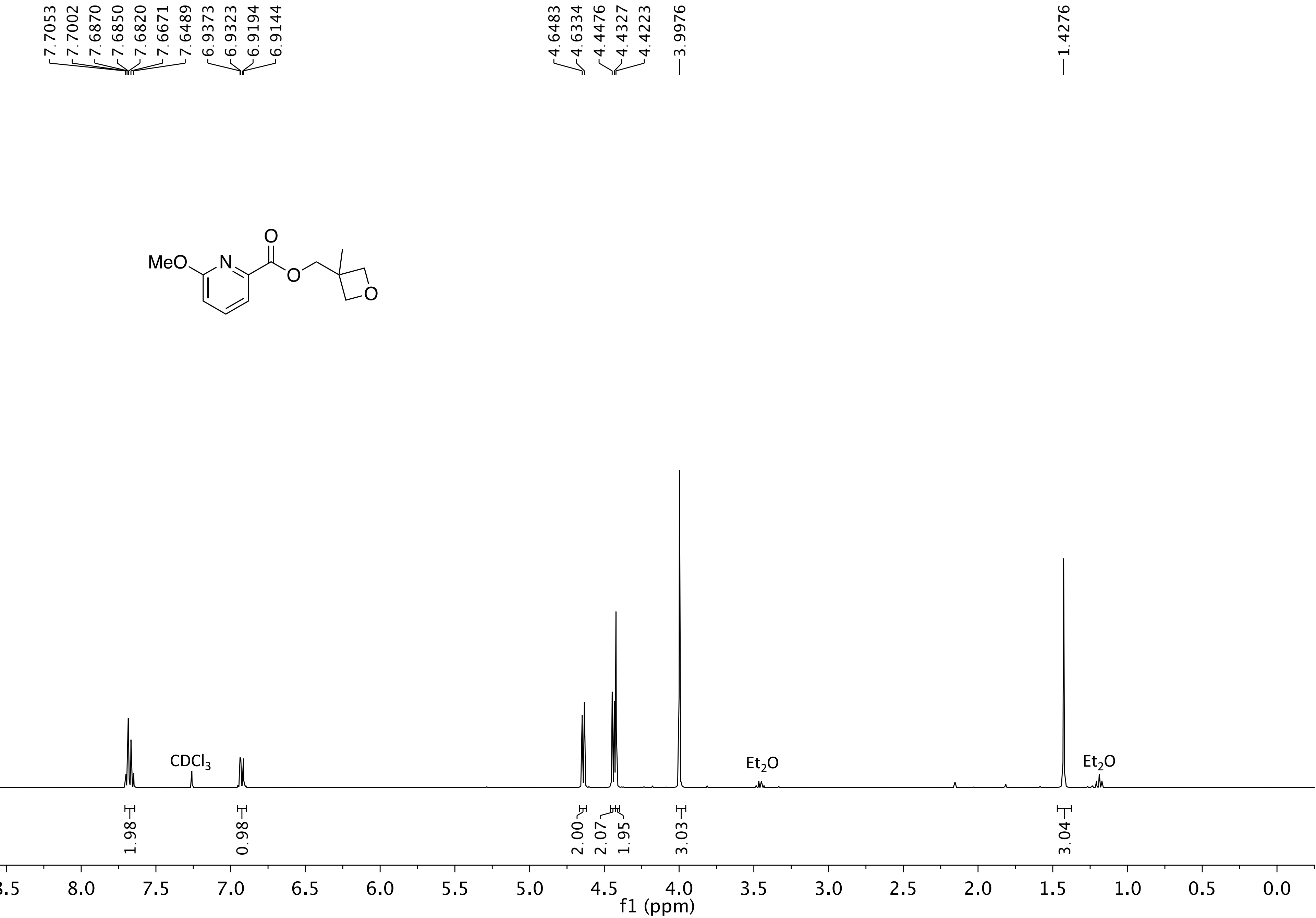
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4.6483
4.6334
4.4476
4.4327
4.4223
3.9976
1.4276
MeO
N
O
O
O
CDCl3
Et2O
Et2O
1.98
0.98
2.00
2.07
1.95
3.03
3.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
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1.5
1.0
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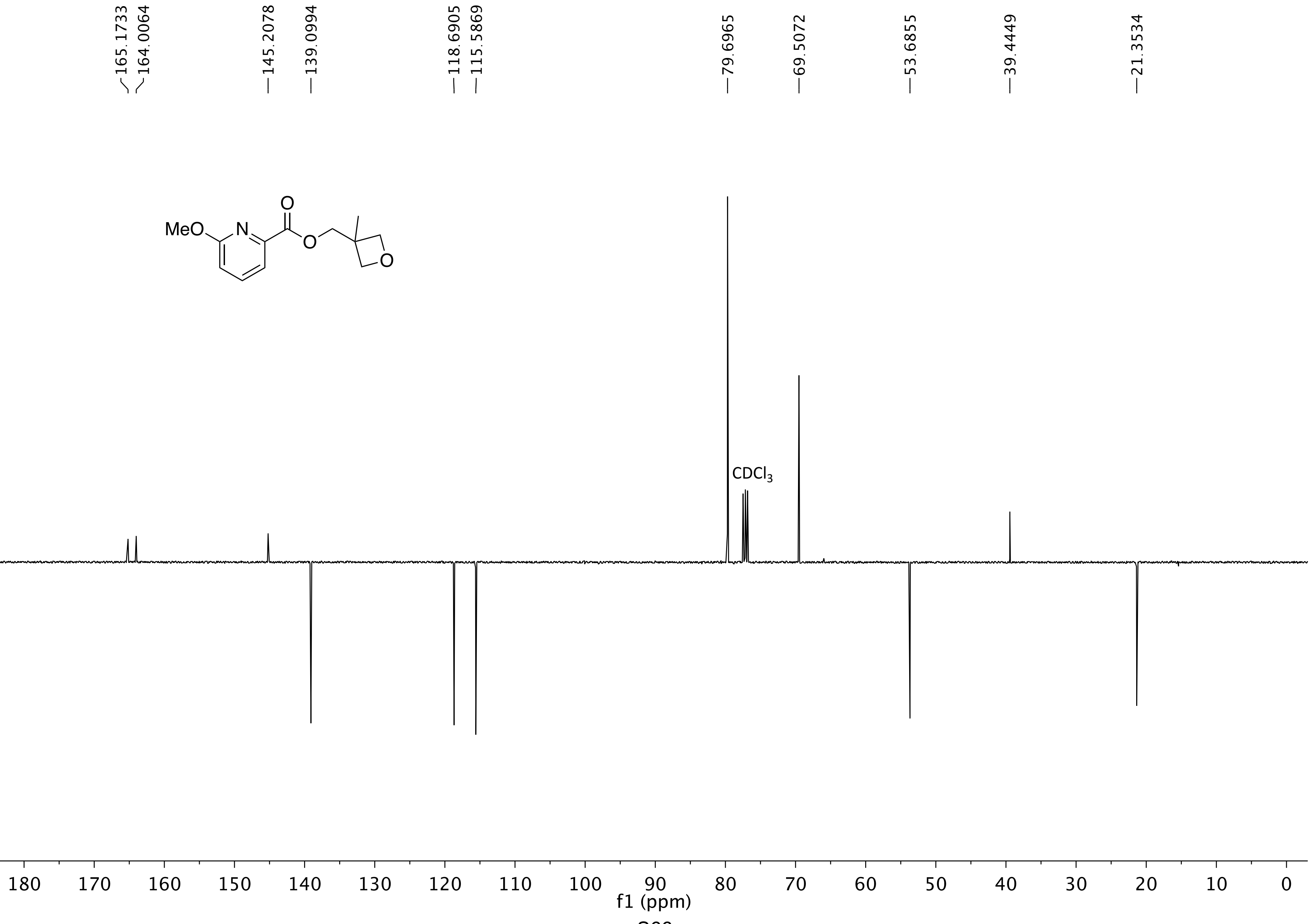
0.0
f1 (ppm)



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145.2078
139.0994
118.6905
115.5869
79.6965
69.5072
53.6855
39.4449
21.3534
MeO
N
O
O
O
CDCl3
180
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130
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110
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70
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50
40
30
20
10
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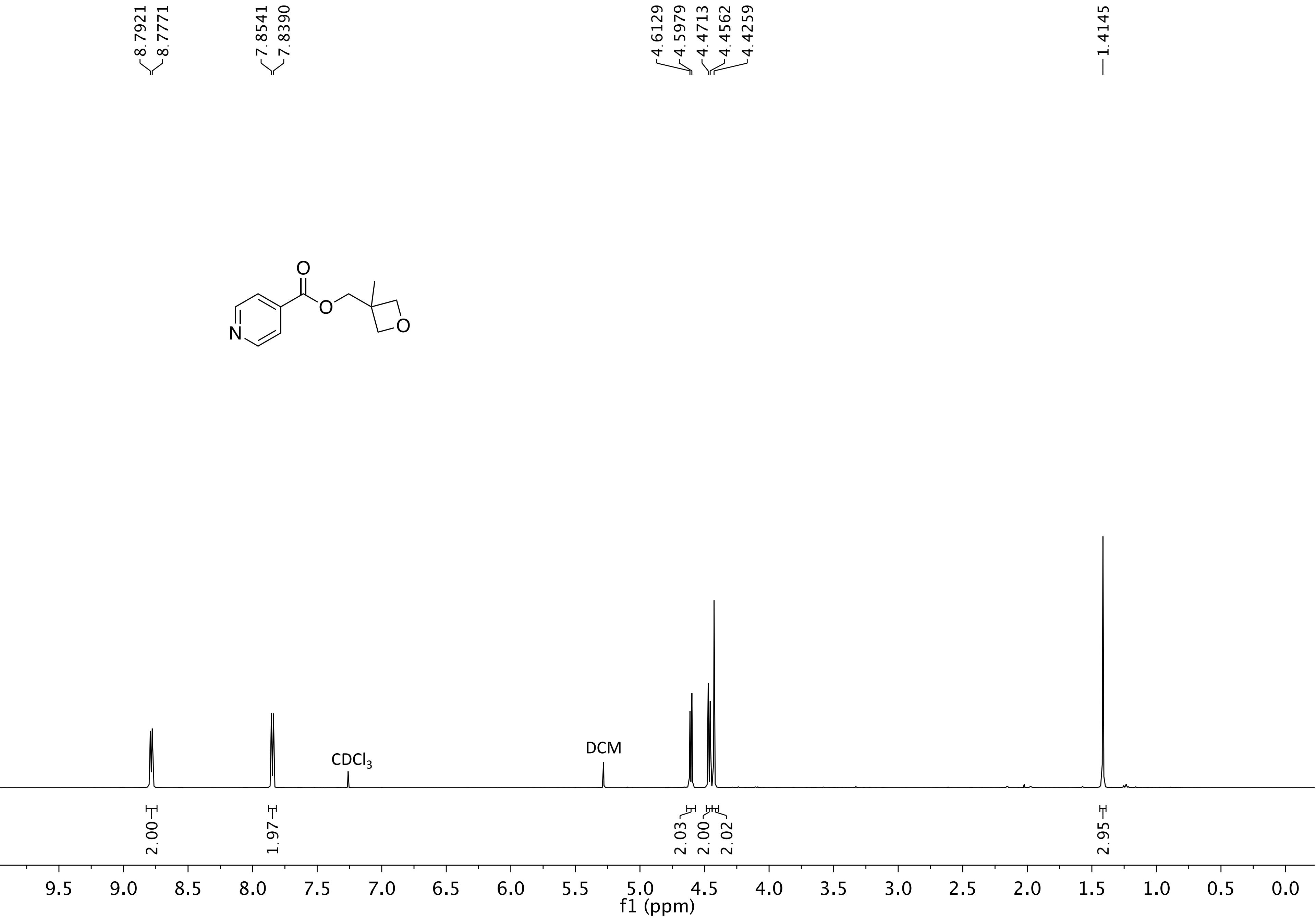
f1 (ppm)



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4.5979
4.4713
4.4562
4.4259
1.4145
O
O
N
O
CDCl3
DCM
2.00
1.97
2.03
2.00
2.02
2.95
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
2.0
1.5
1.0
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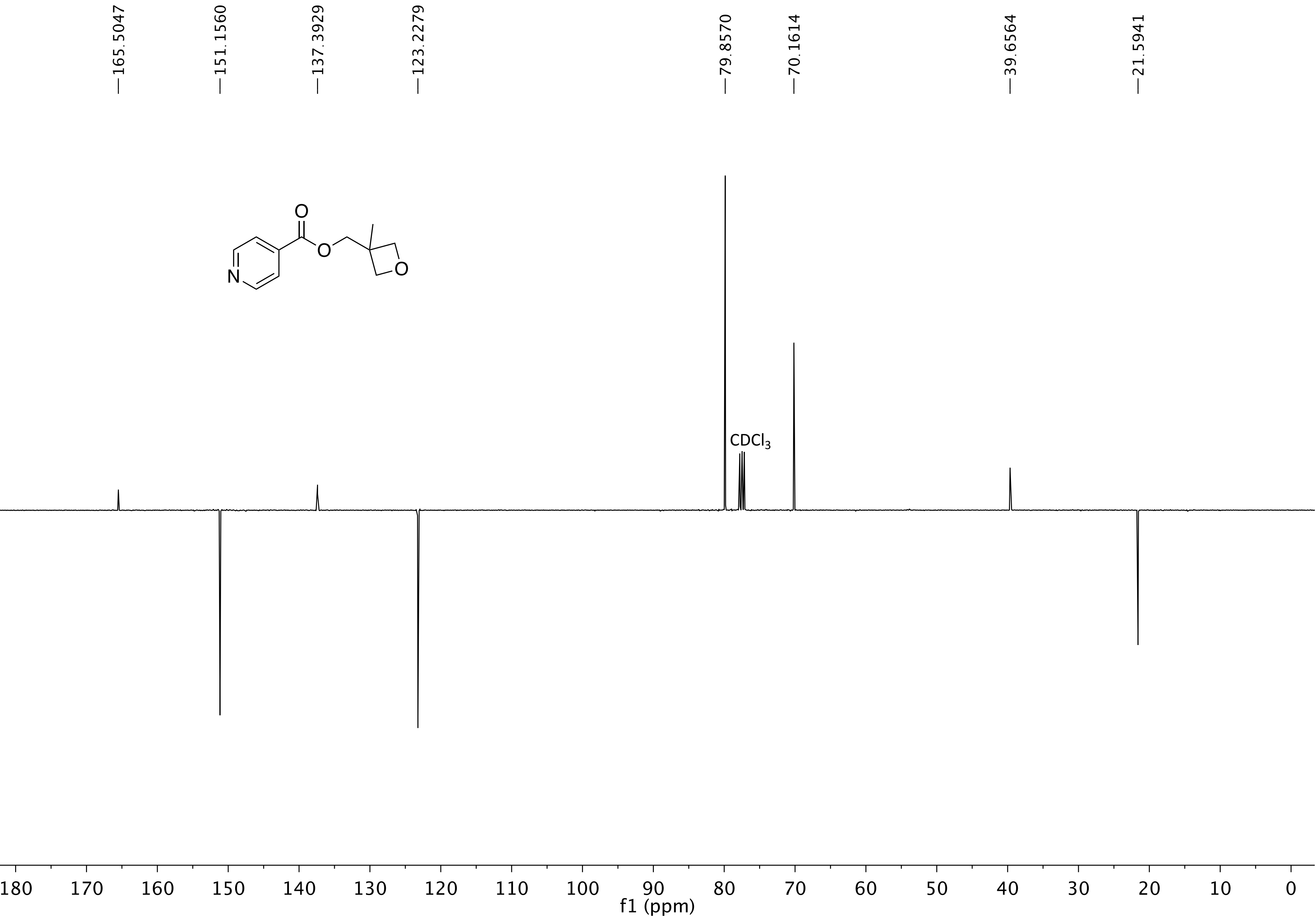
0.0
f1 (ppm)



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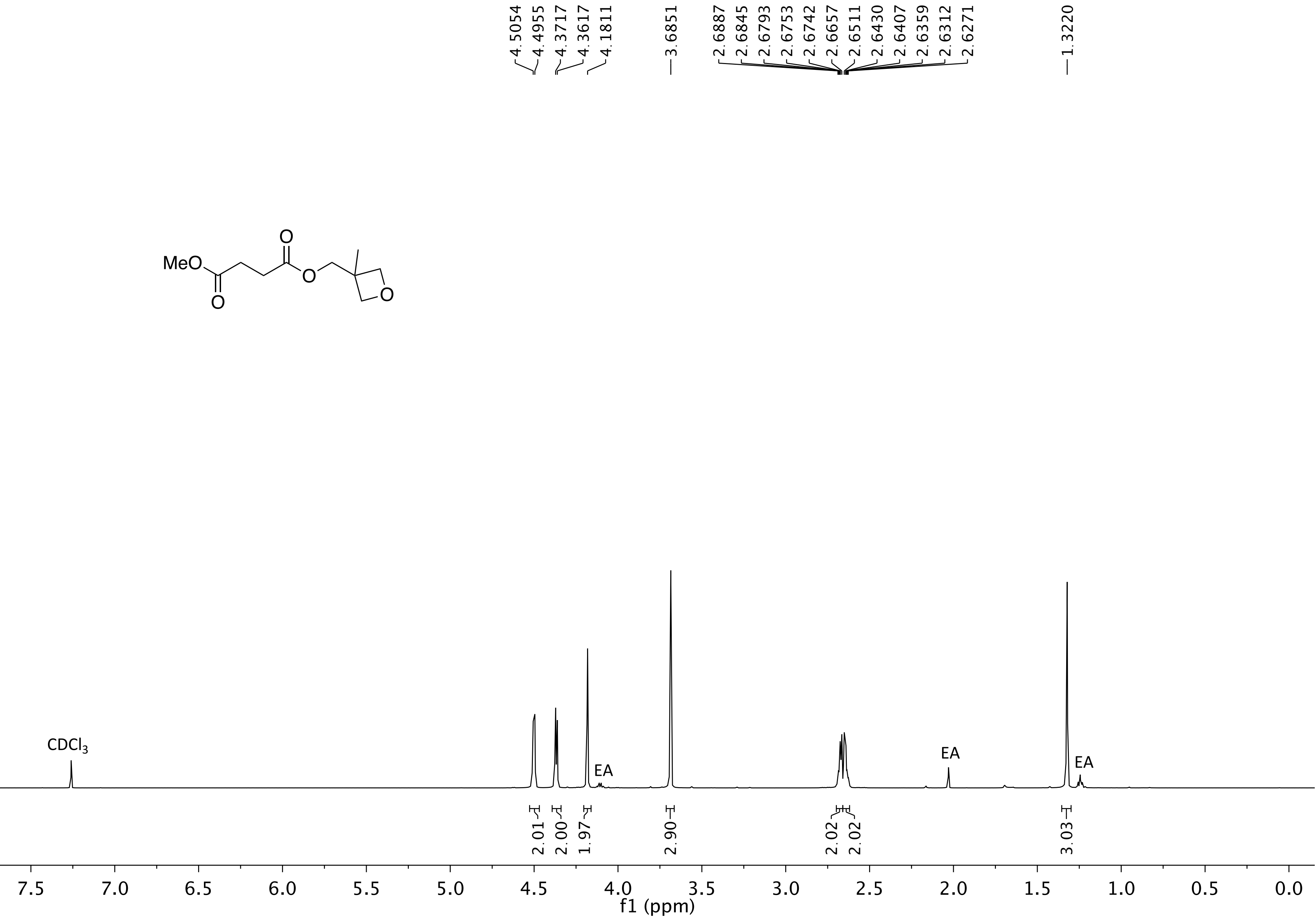
137.3929
123.2279
79.8570
70.1614
39.6564
21.5941
CDCl3
O
O
N
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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4.1811
3.6851
2.6887
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2.6742
2.6657
2.6511
2.6430
2.6407
2.6359
2.6312
2.6271
1.3220
CDCl3
EA
EA
EA
2.01
2.00
1.97
2.90
2.02
2.02
3.03
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
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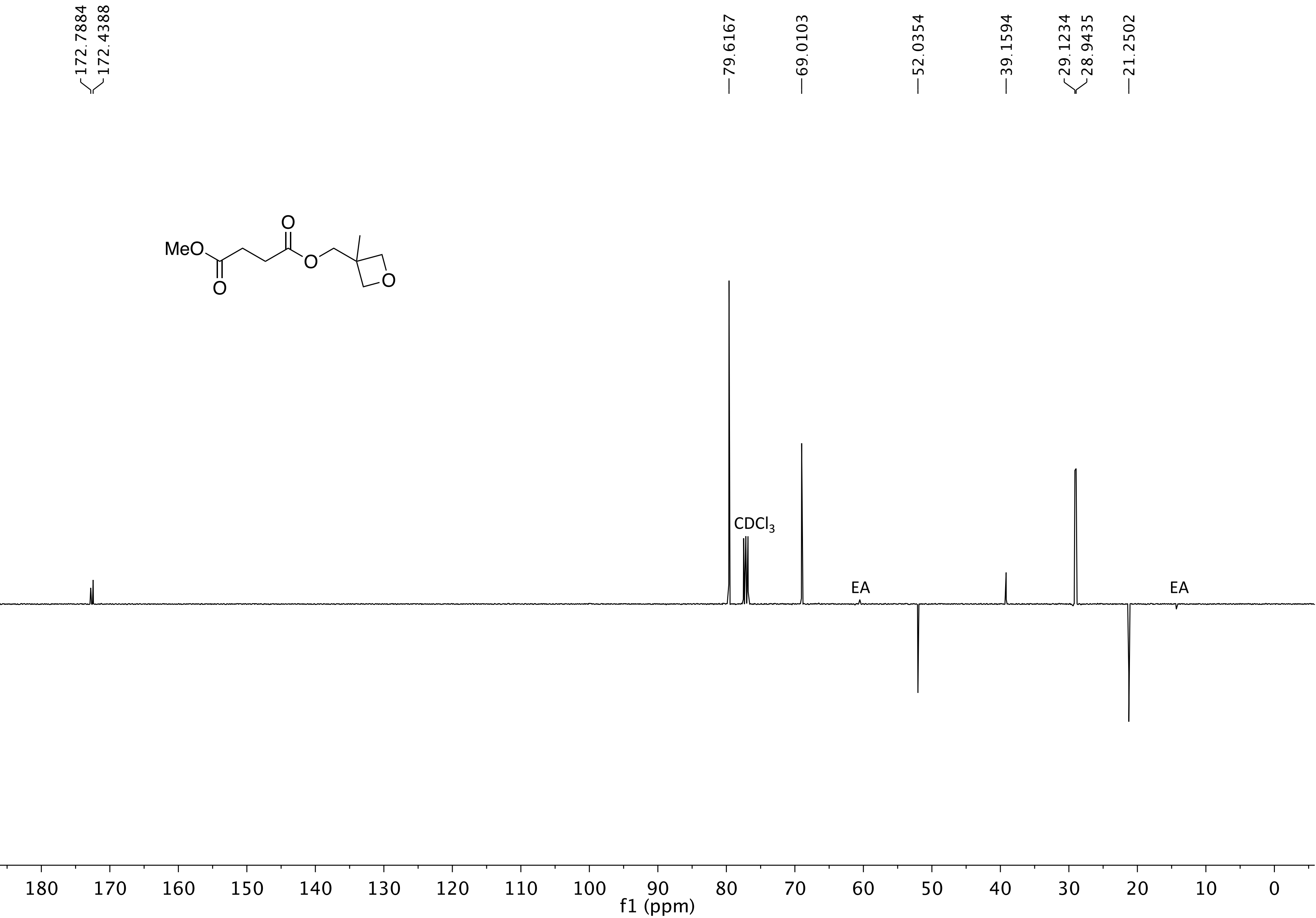
f1 (ppm)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172.4388
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69.0103
52.0354
39.1594
29.1234
28.9435
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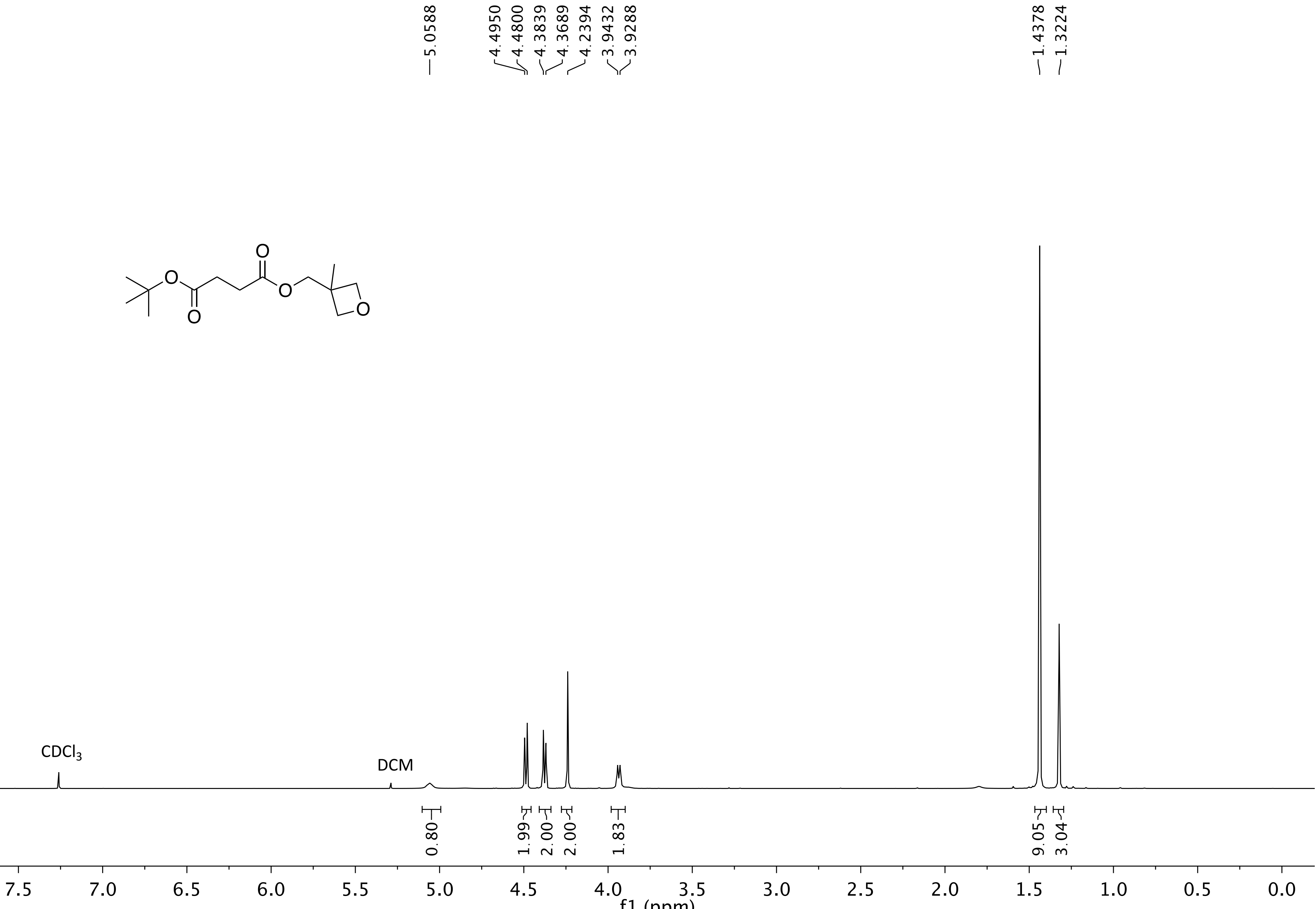
MeO
O
O
O
O
CDCl3
EA
EA
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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4.4800
4.3839
4.3689
4.2394
3.9432
3.9288
1.4378
1.3224
CDCl3
DCM
0.80
1.99
2.00
2.00
1.83
9.05
3.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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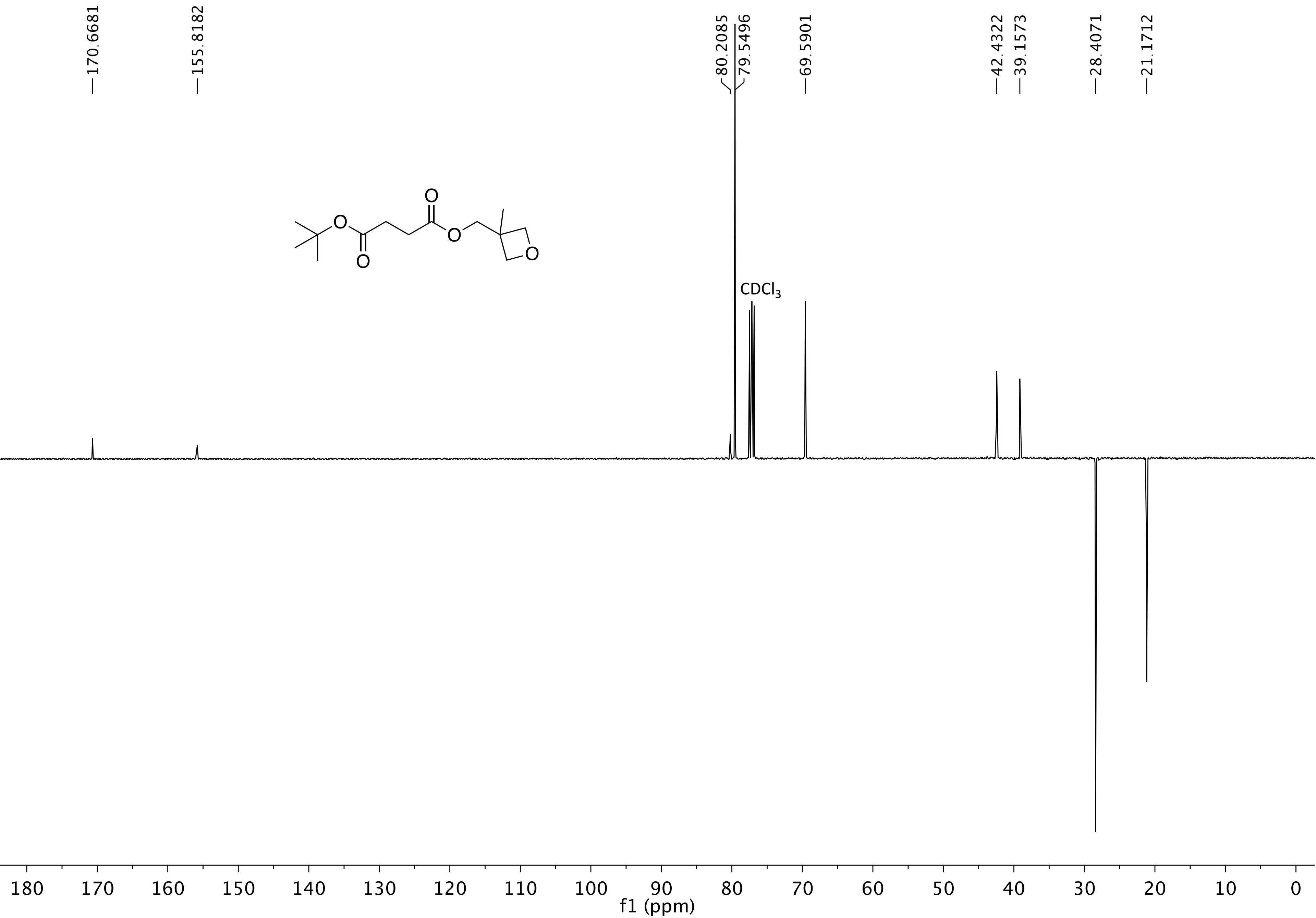
0.0
f1 (ppm)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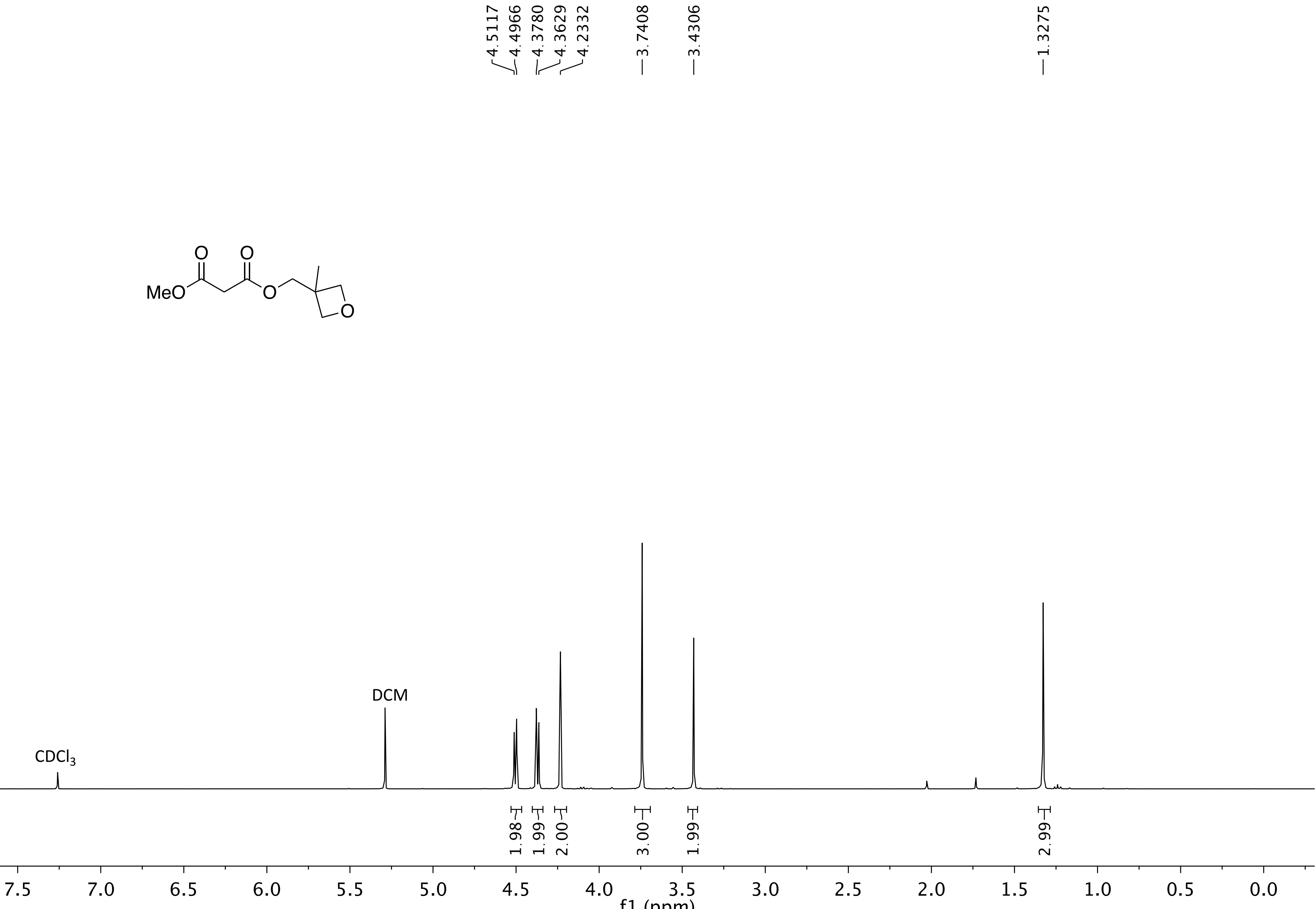
155.8182
80.2085
79.5496
69.5901
42.4322
39.1573
28.4071
21.1712
CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


MeO
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O
O
O
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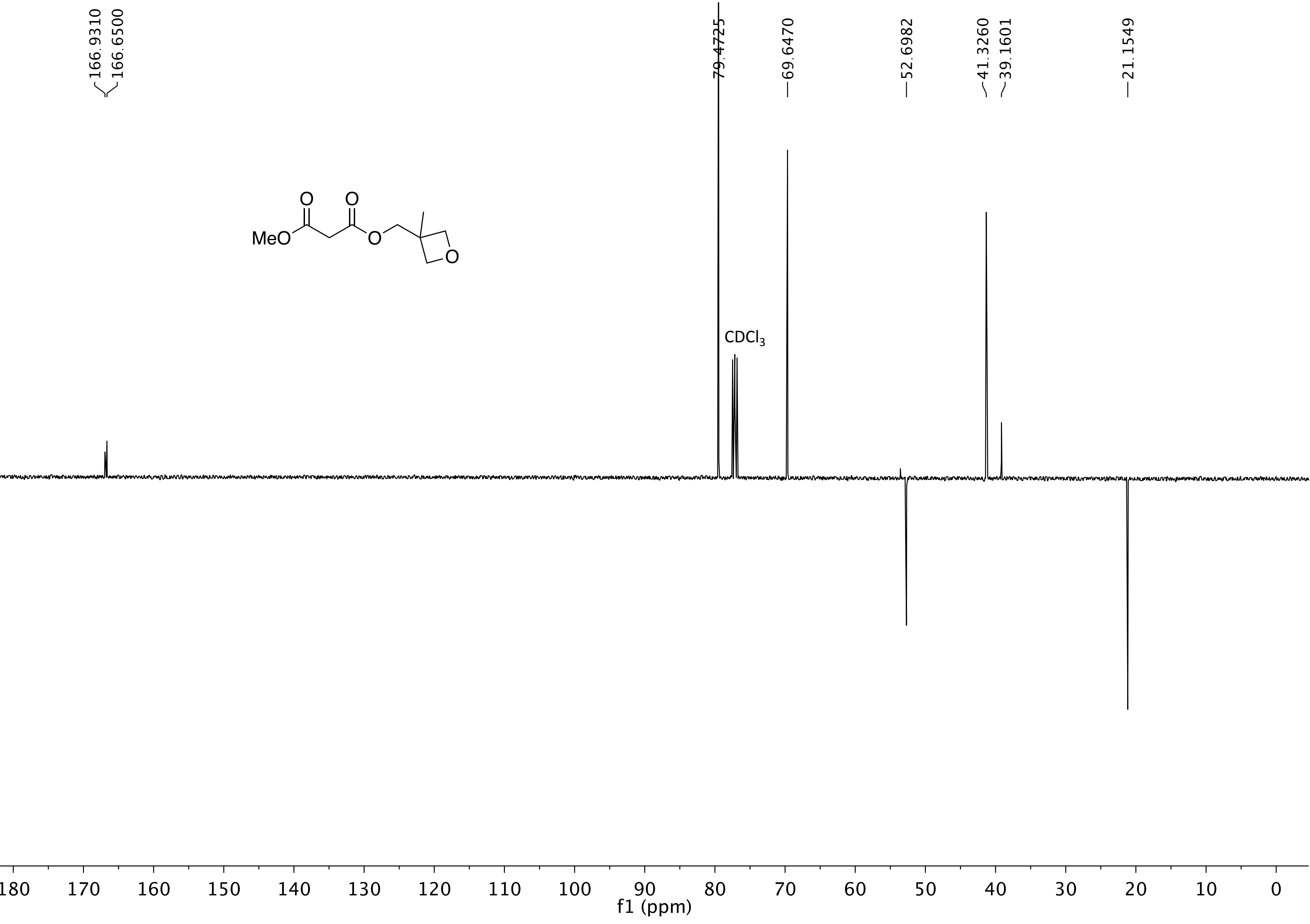
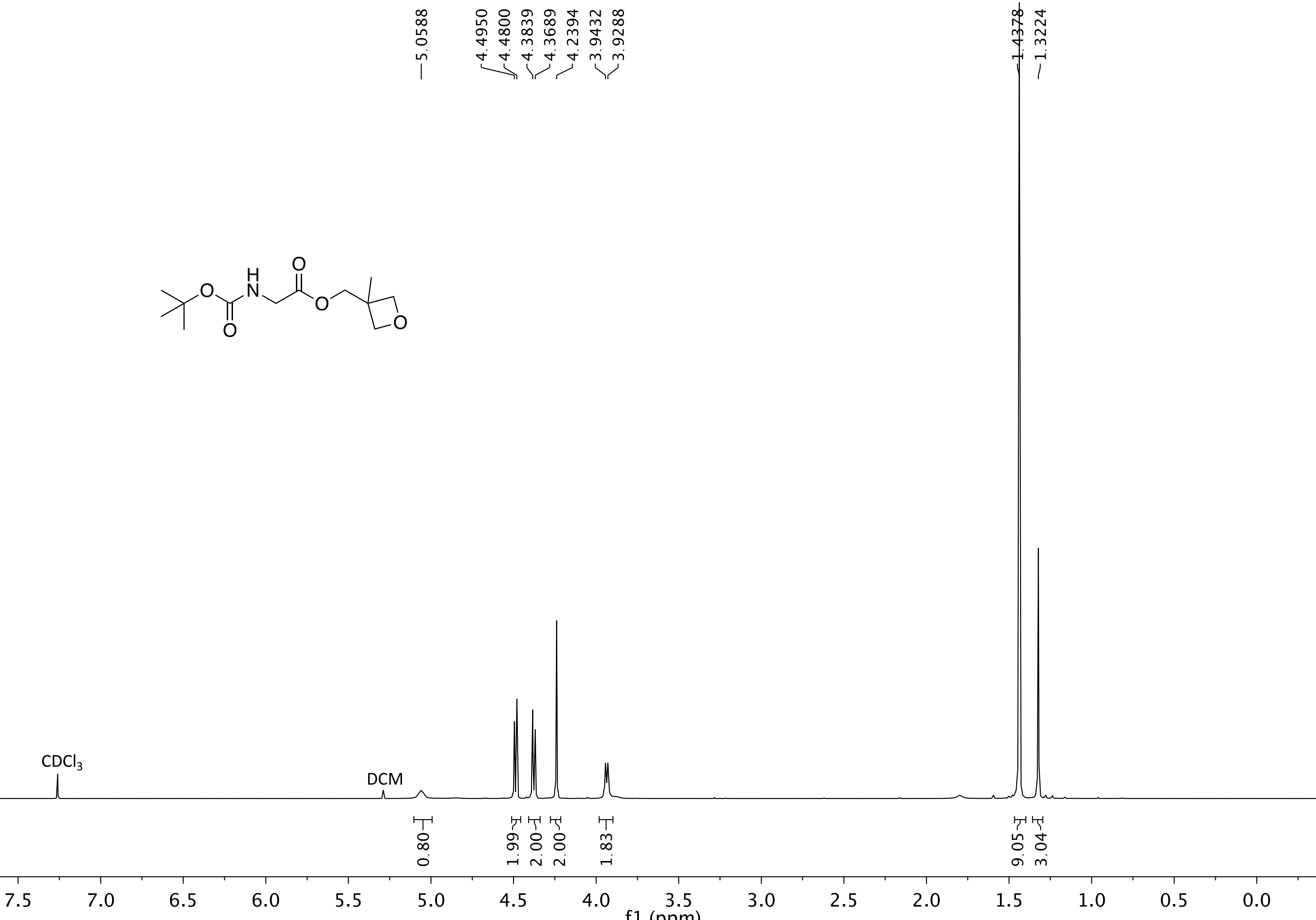
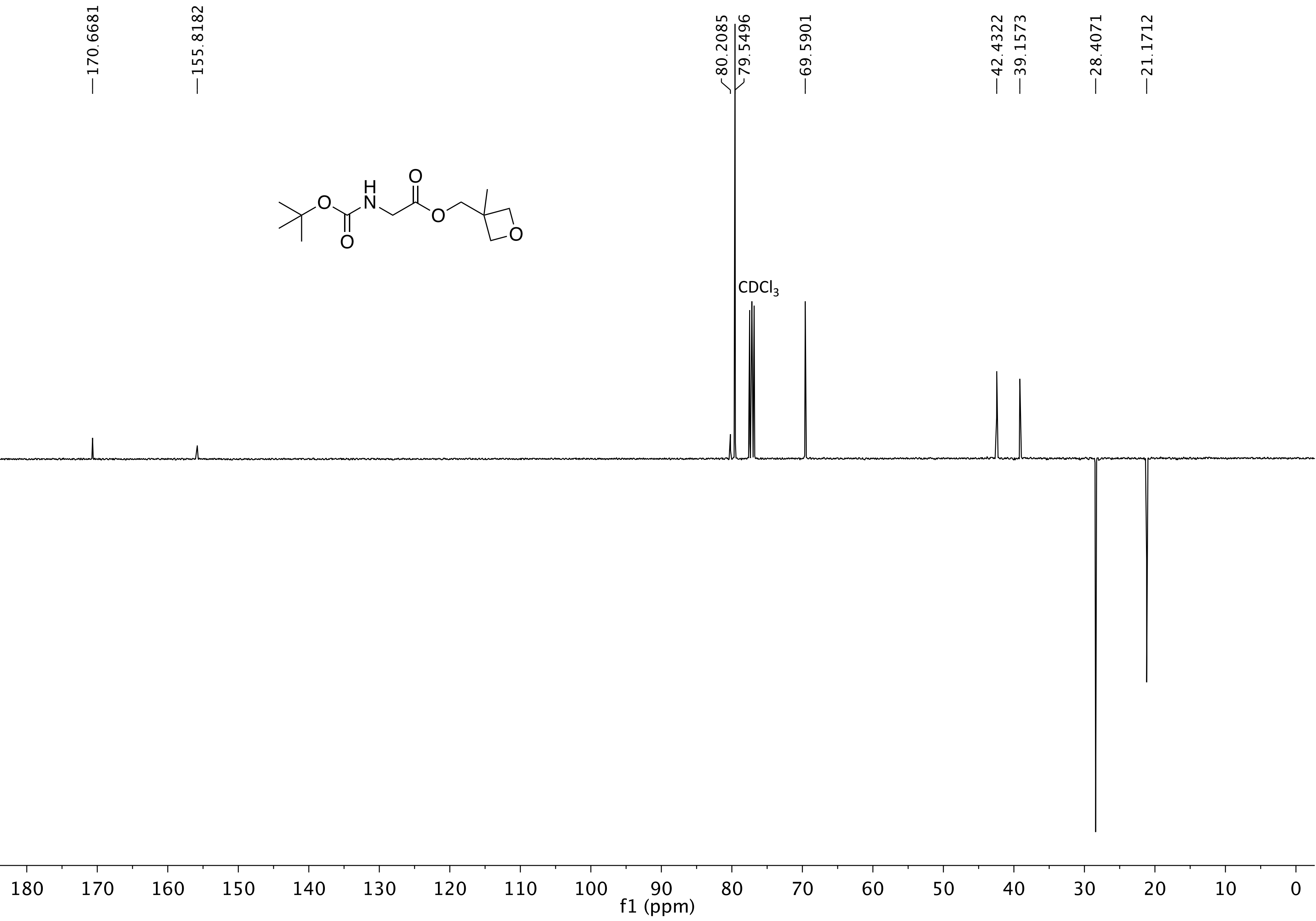
4.3780
4.3629
4.2332
3.7408
3.4306
1.3275
CDCl$_3$
DCM
1.98
1.99
2.00
3.00
1.99
2.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



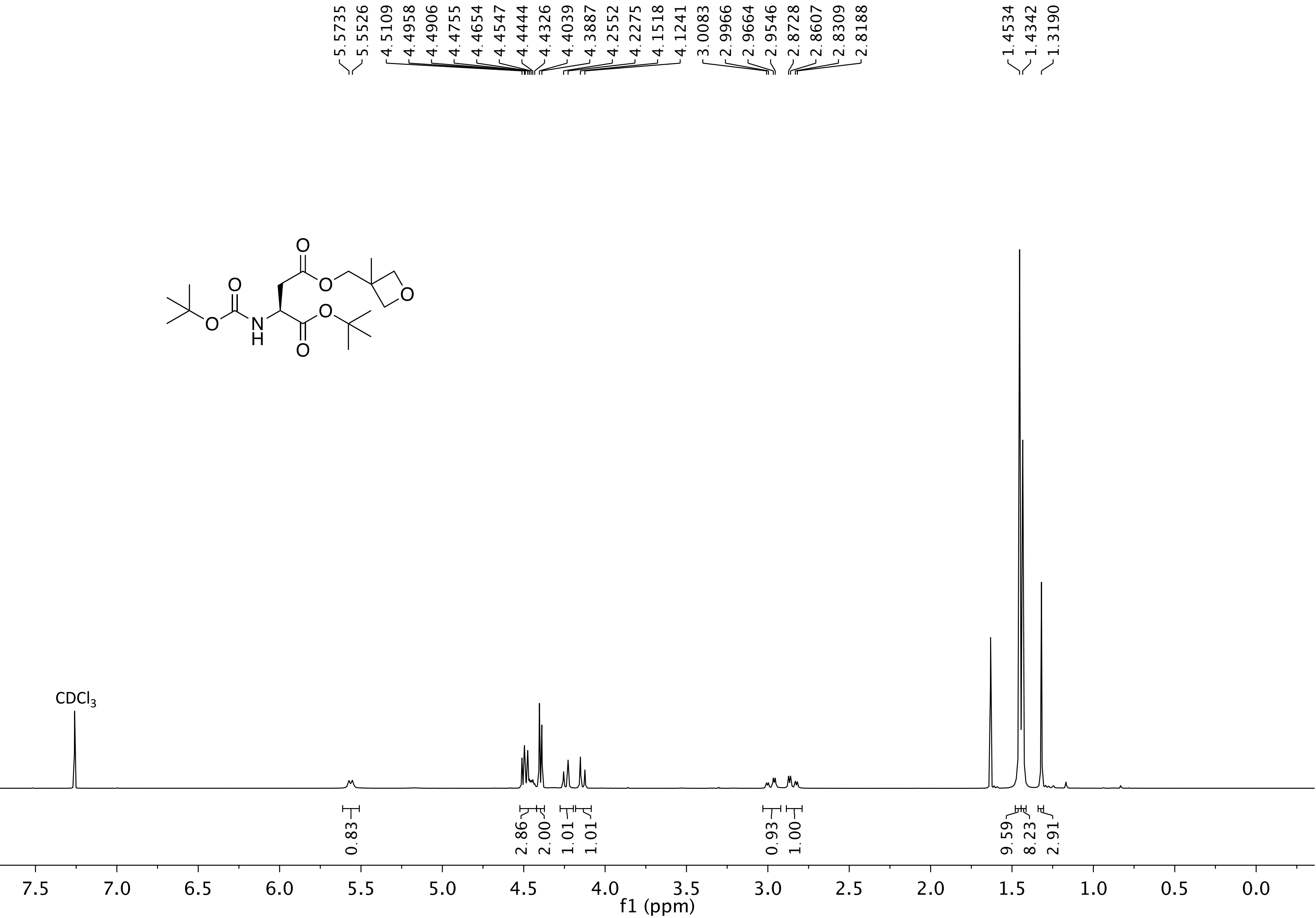
166.9310
166.6500
79.4725
69.6470
52.6982
41.3260
39.1601
21.1549
MeO
O
O
O
O
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



5.0588
4.4950
4.4800
4.3839
4.3689
4.2394
3.9432
3.9288
1.4378
1.3224
CDCl3
DCM
0.80
1.99
2.00
2.00
1.83
9.05
3.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



170.6681
155.8182
80.2085
79.5496
69.5901
42.4322
39.1573
28.4071
21.1712
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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4.4654
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4.4444
4.4326
4.4039
4.3887
4.2552
4.2275
4.1518
4.1241
3.0083
2.9966
2.9664
2.9546
2.8728
2.8607
2.8309
2.8188
1.4534
1.4342
1.3190
O
O
O
O
N
H
O
O
O
O
CDCl3
0.83
2.86
2.00
1.01
1.01
0.93
1.00
9.59
8.23
2.91
7.5
7.0
6.5
6.0
5.5
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4.5
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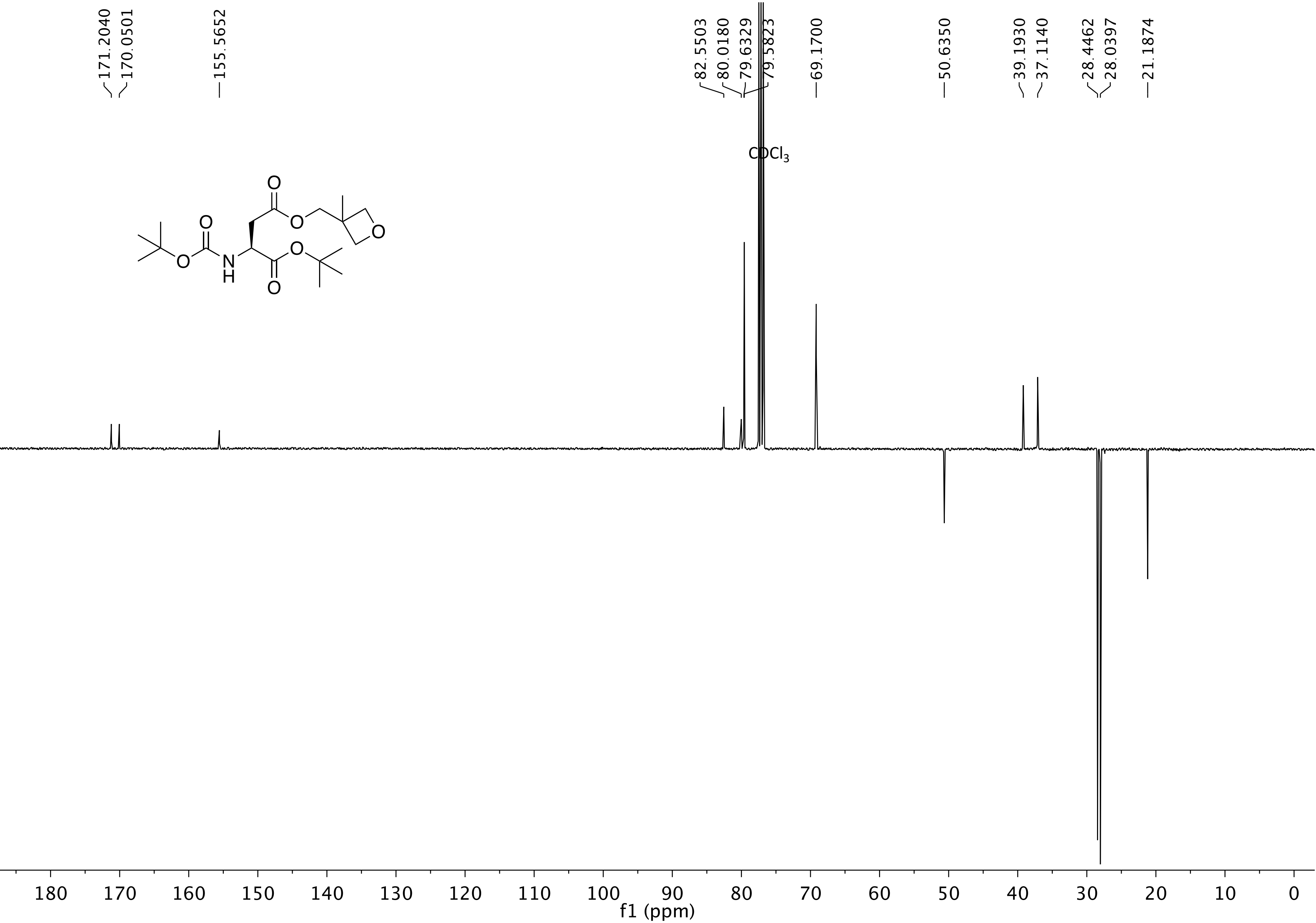
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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80.0180
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79.5823
69.1700
50.6350
39.1930
37.1140
28.4462
28.0397
21.1874
CDCl3
O
O
O
O
N
H
O
O
O
180
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160
150
140
130
120
110
100
90
80
70
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50
40
30
20
10
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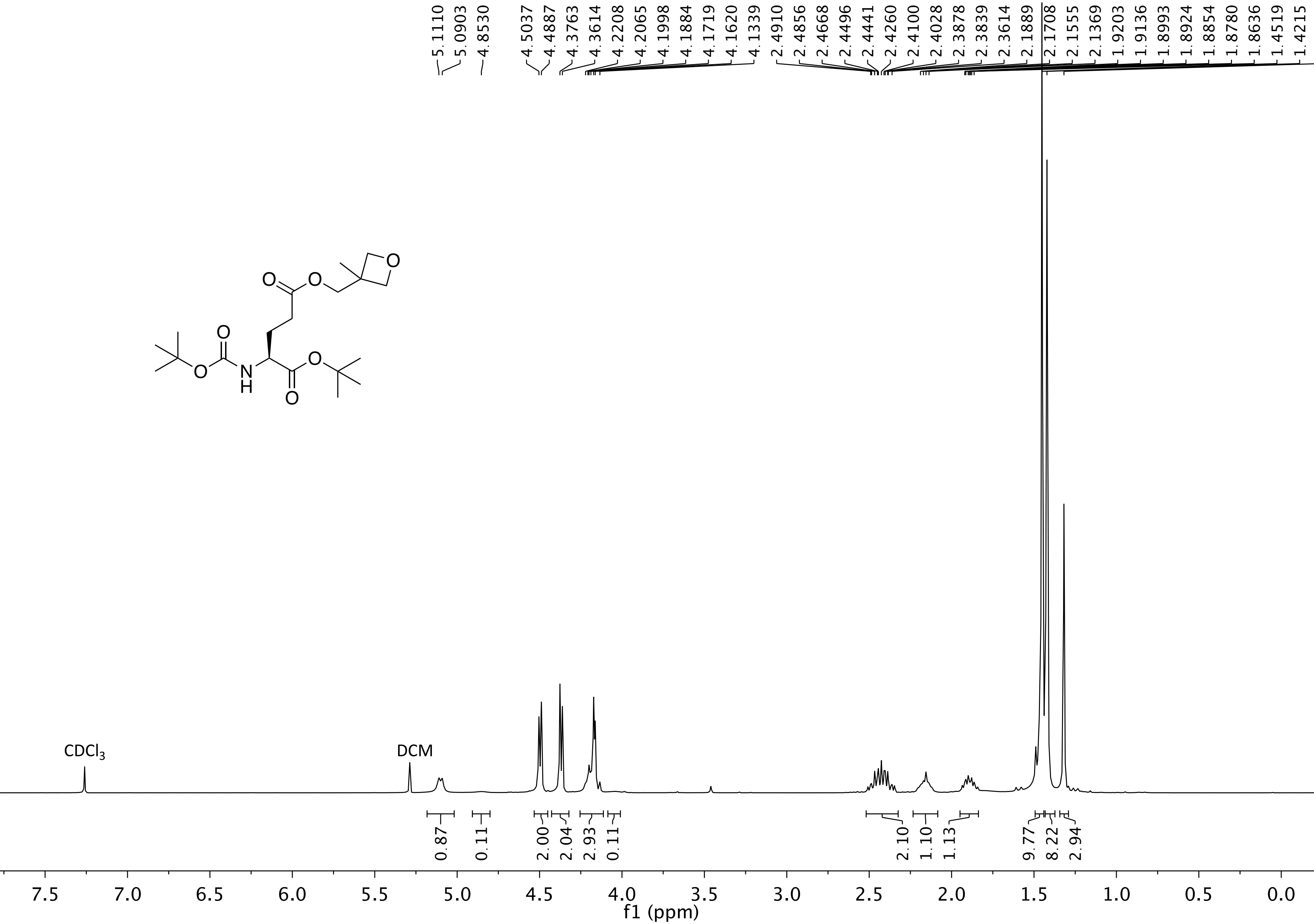
f1 (ppm)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4.8530
4.5037
4.4887
4.3763
4.3614
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4.1884
4.1719
4.1620
4.1339
2.4910
2.4856
2.4668
2.4496
2.4441
2.4260
2.4100
2.4028
2.3878
2.3839
2.3614
2.1889
2.1708
2.1555
2.1369
1.9203
1.9136
1.8993
1.8924
1.8854
1.8780
1.8636
1.4519
1.4215
CDCl3
DCM
0.87
0.11
2.00
2.04
2.93
0.11
2.10
1.10
1.13
9.77
8.22
2.94
7.5
7.0
6.5
6.0
5.5
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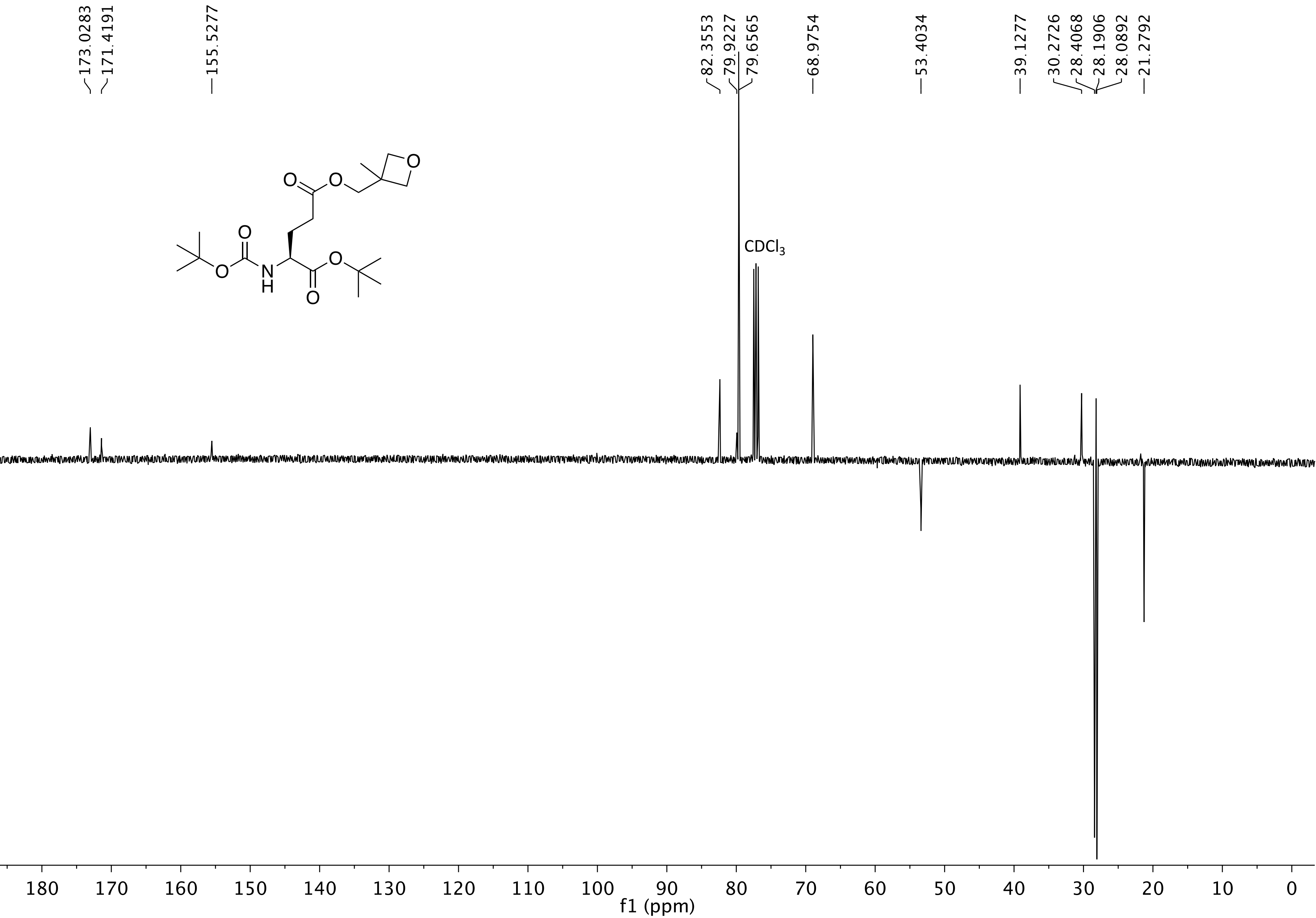
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



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155.5277
82.3553
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68.9754
53.4034
39.1277
30.2726
28.4068
28.1906
28.0892
21.2792
CDCl3
180
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160
150
140
130
120
110
100
90
80
70
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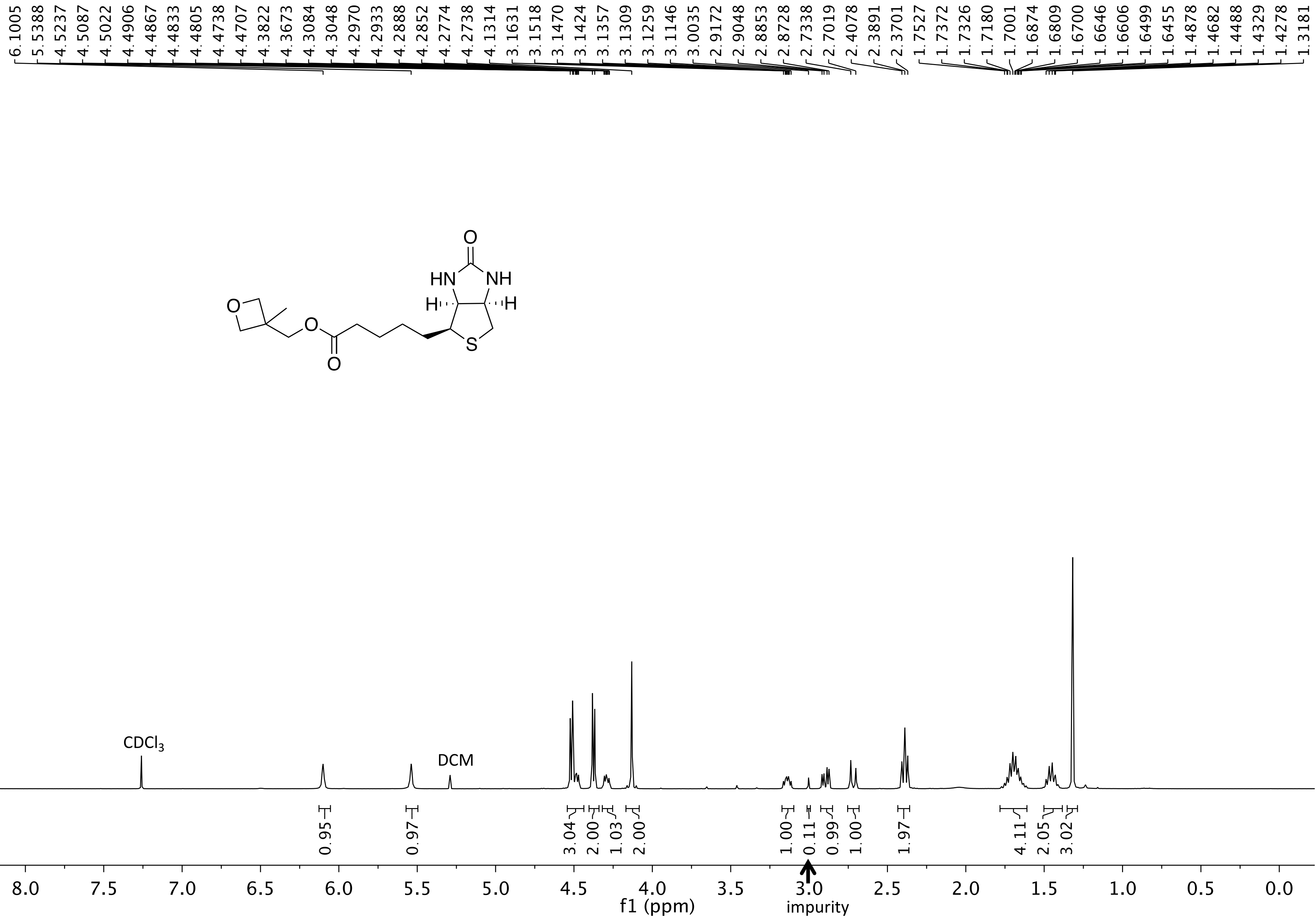
50
40
30
20
10
0
f1 (ppm)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4.3822
4.3673
4.3084
4.3048
4.2970
4.2933
4.2888
4.2852
4.2774
4.2738
4.1314
3.1631
3.1518
3.1470
3.1424
3.1357
3.1309
3.1259
3.1146
3.0035
2.9172
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2.8853
2.8728
2.7338
2.7019
2.4078
2.3891
2.3701
1.7527
1.7372
1.7326
1.7180
1.7001
1.6874
1.6809
1.6700
1.6646
1.6606
1.6499
1.6455
1.4878
1.4682
1.4488
1.4329
1.4278
1.3181
O
HN
NH
H
H
O
O
S
O
CDCl3
DCM
0.95
0.97
3.04
2.00
1.03
2.00
1.00
0.11
0.99
1.00
1.97
4.11
2.05
3.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.0
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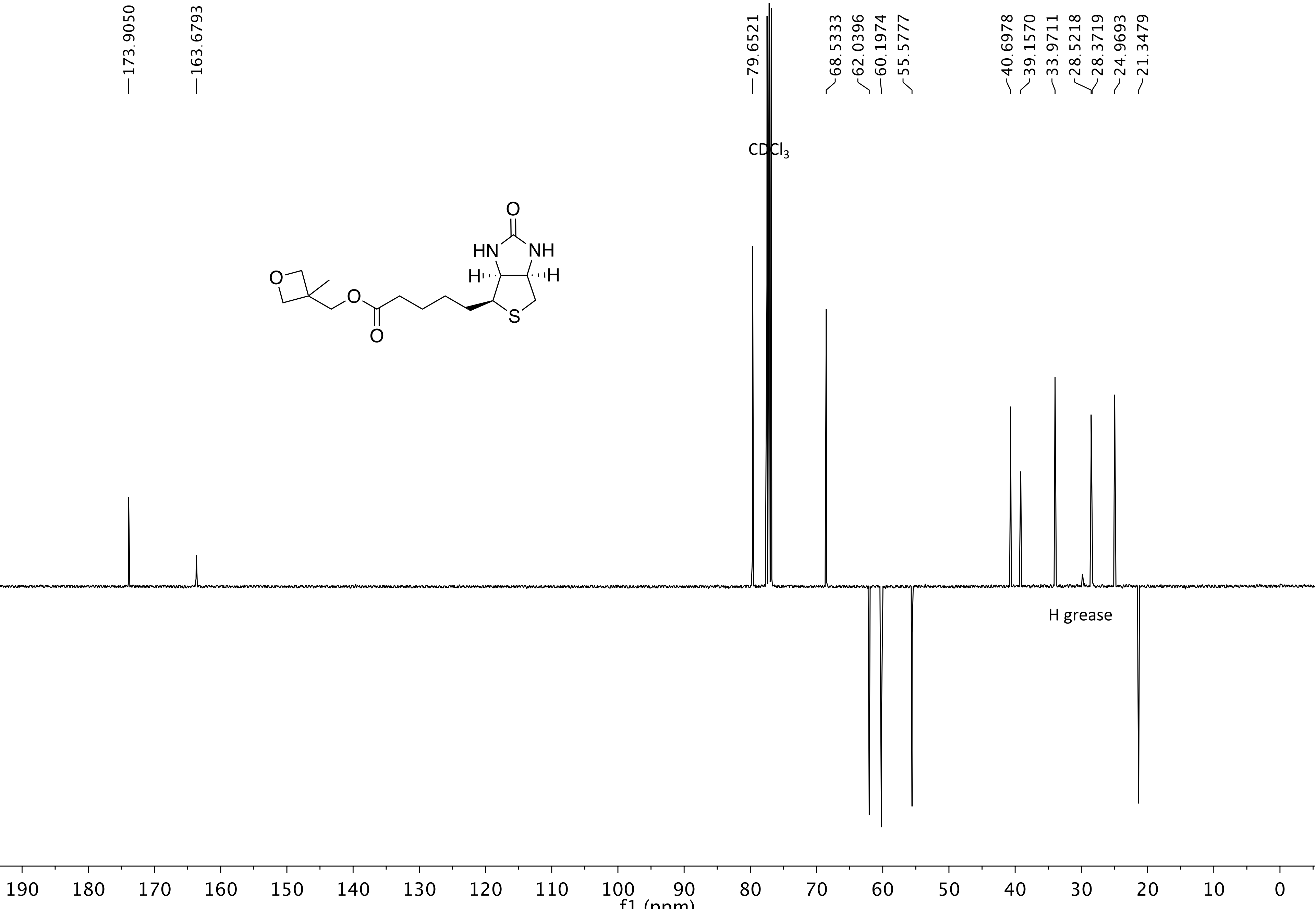
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
impurity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55.5777
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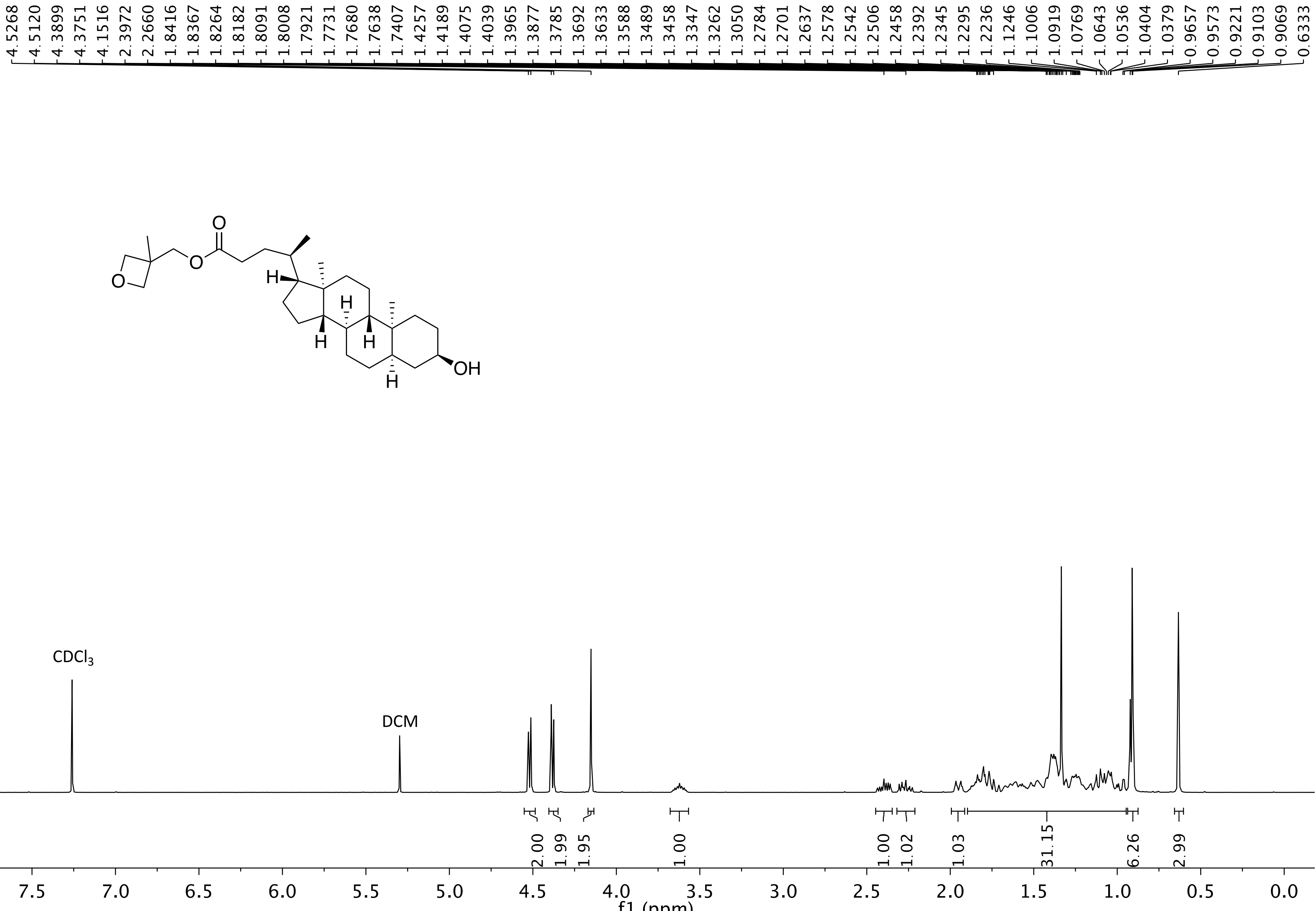
39.1570
33.9711
28.5218
28.3719
24.9693
21.3479
CDCl3
H grease
O
HN
NH
H
H
O
O
O
S
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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1.8182
1.8091
1.8008
1.7921
1.7731
1.7680
1.7638
1.7407
1.4257
1.4189
1.4075
1.4039
1.3965
1.3877
1.3785
1.3692
1.3633
1.3588
1.3489
1.3458
1.3347
1.3262
1.3050
1.2784
1.2701
1.2637
1.2578
1.2542
1.2506
1.2458
1.2392
1.2345
1.2295
1.2236
1.1246
1.1006
1.0919
1.0769
1.0643
1.0536
1.0404
1.0379
0.9657
0.9573
0.9221
0.9103
0.9069
0.6333
O
O
O
H
H
H
H
H
OH
CDCl3
DCM
2.00
1.99
1.95
1.00
1.00
1.02
1.03
31.15
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2.99
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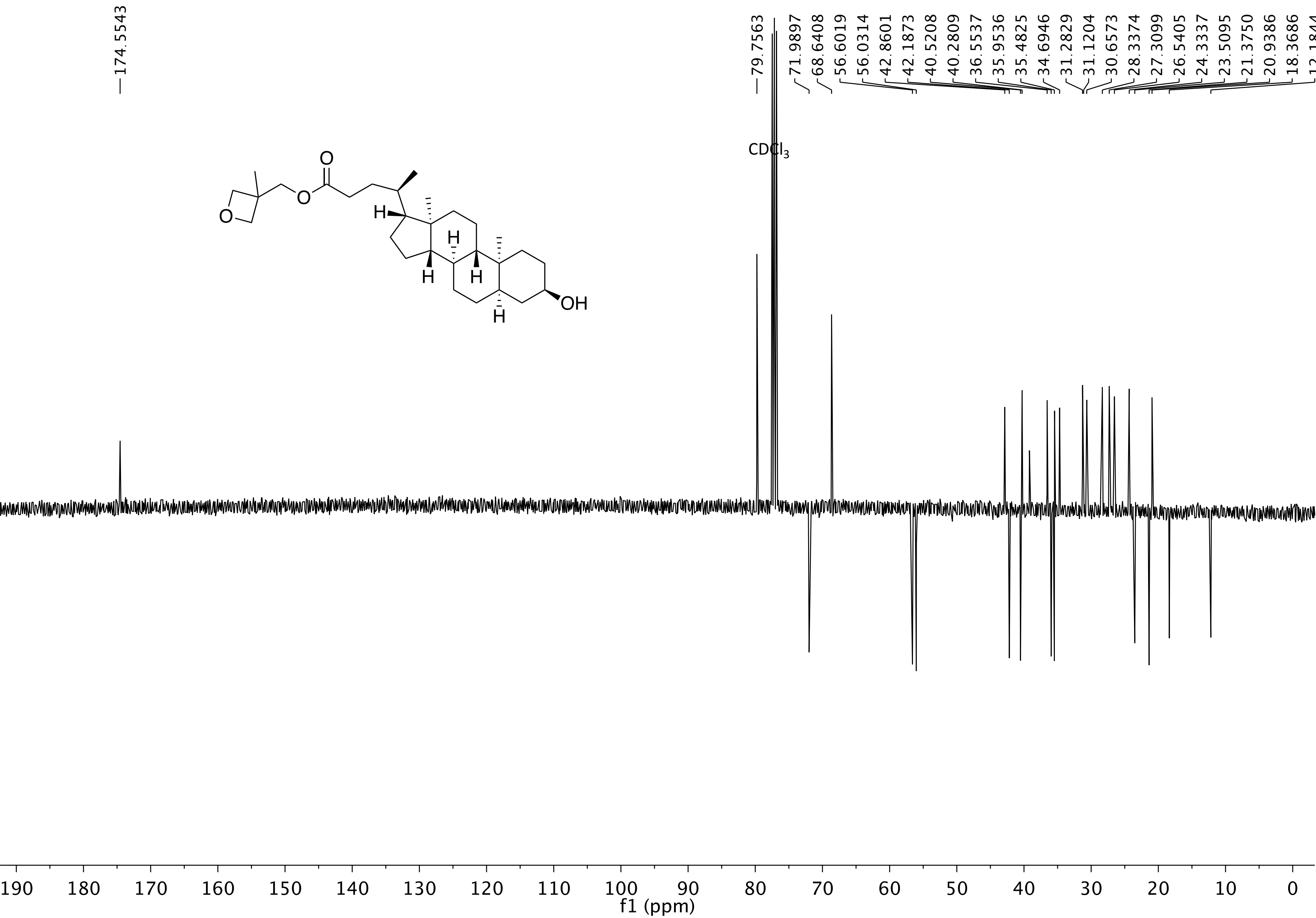
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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36.5537
35.9536
35.4825
34.6946
31.2829
31.1204
30.6573
28.3374
27.3099
26.5405
24.3337
23.5095
21.3750
20.9386
18.3686
12.184
CDCl3
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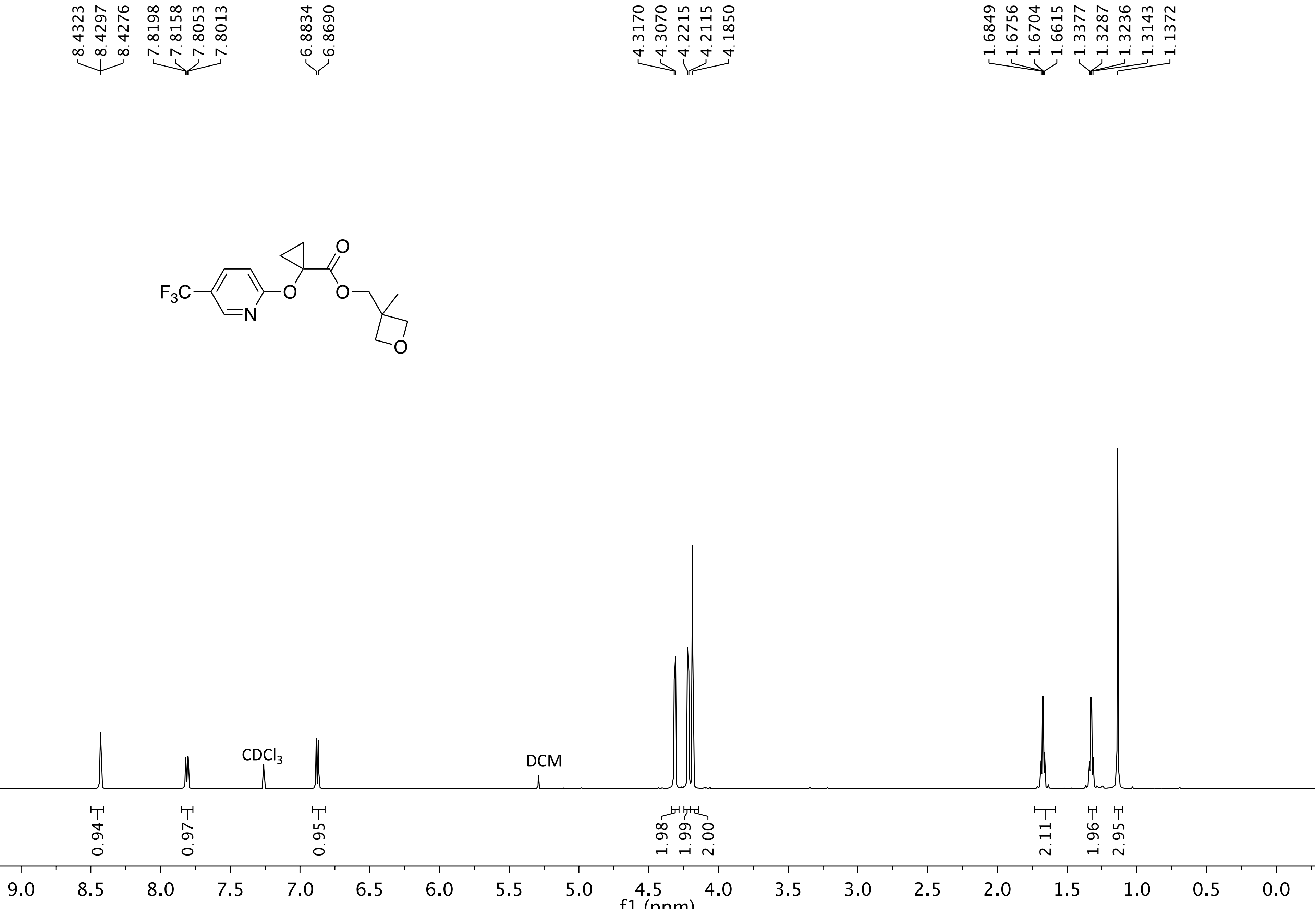
O
O
H
H
H
H
H
OH
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.8013
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6.8690
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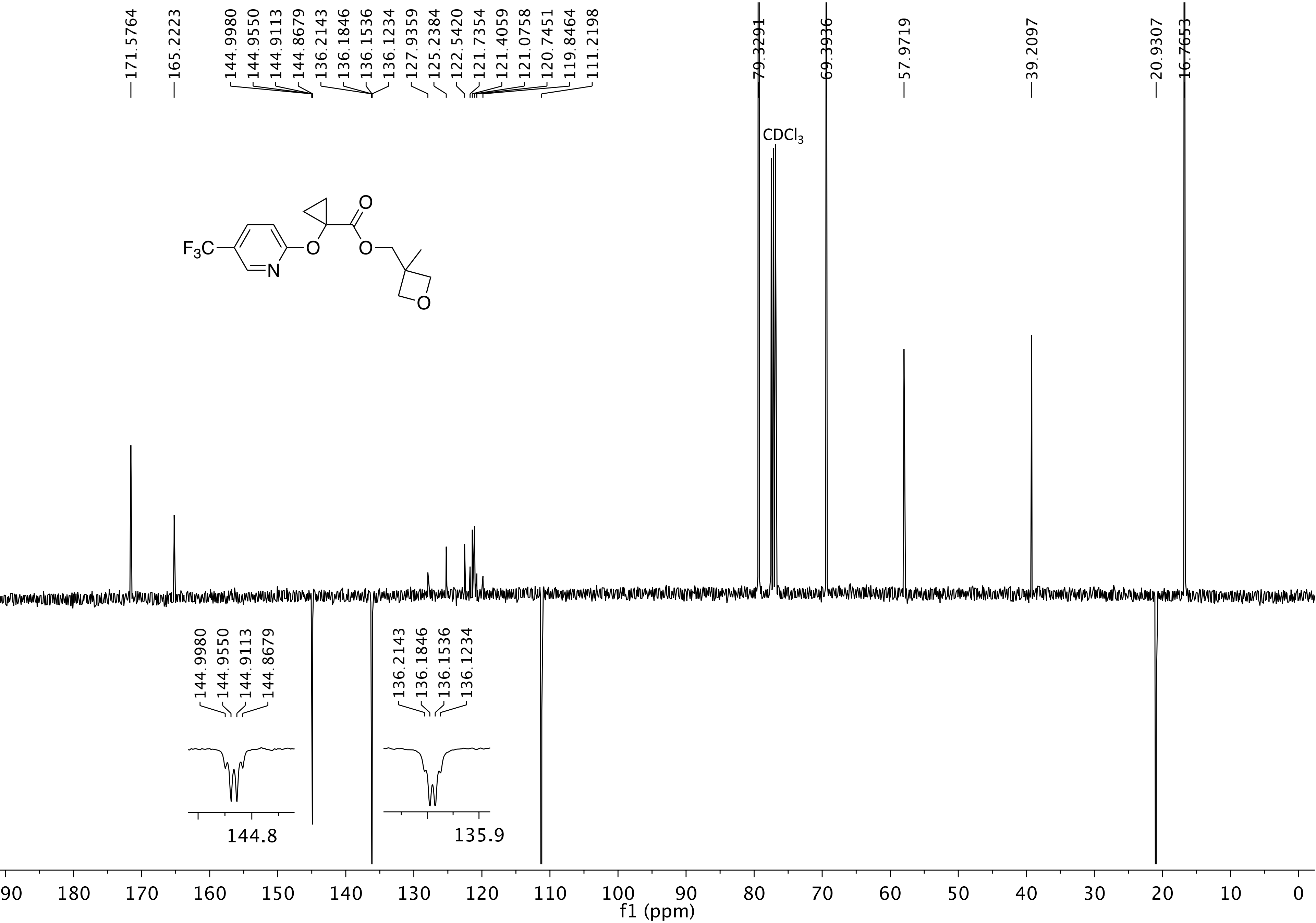
4.3070
4.2215
4.2115
4.1850
1.6849
1.6756
1.6704
1.6615
1.3377
1.3287
1.3236
1.3143
1.1372
F_3C
N
O
O
O
O
CDCl3
DCM
0.94
0.97
0.95
1.98
1.99
2.00
2.11
1.96
2.95
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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127.9359
125.2384
122.5420
121.7354
121.4059
121.0758
120.7451
119.8464
111.2198
79.3291
69.3936
57.9719
39.2097
20.9307
16.7653
CDCl3
F3C
O
N
O
O
O
144.8
135.9
190
180
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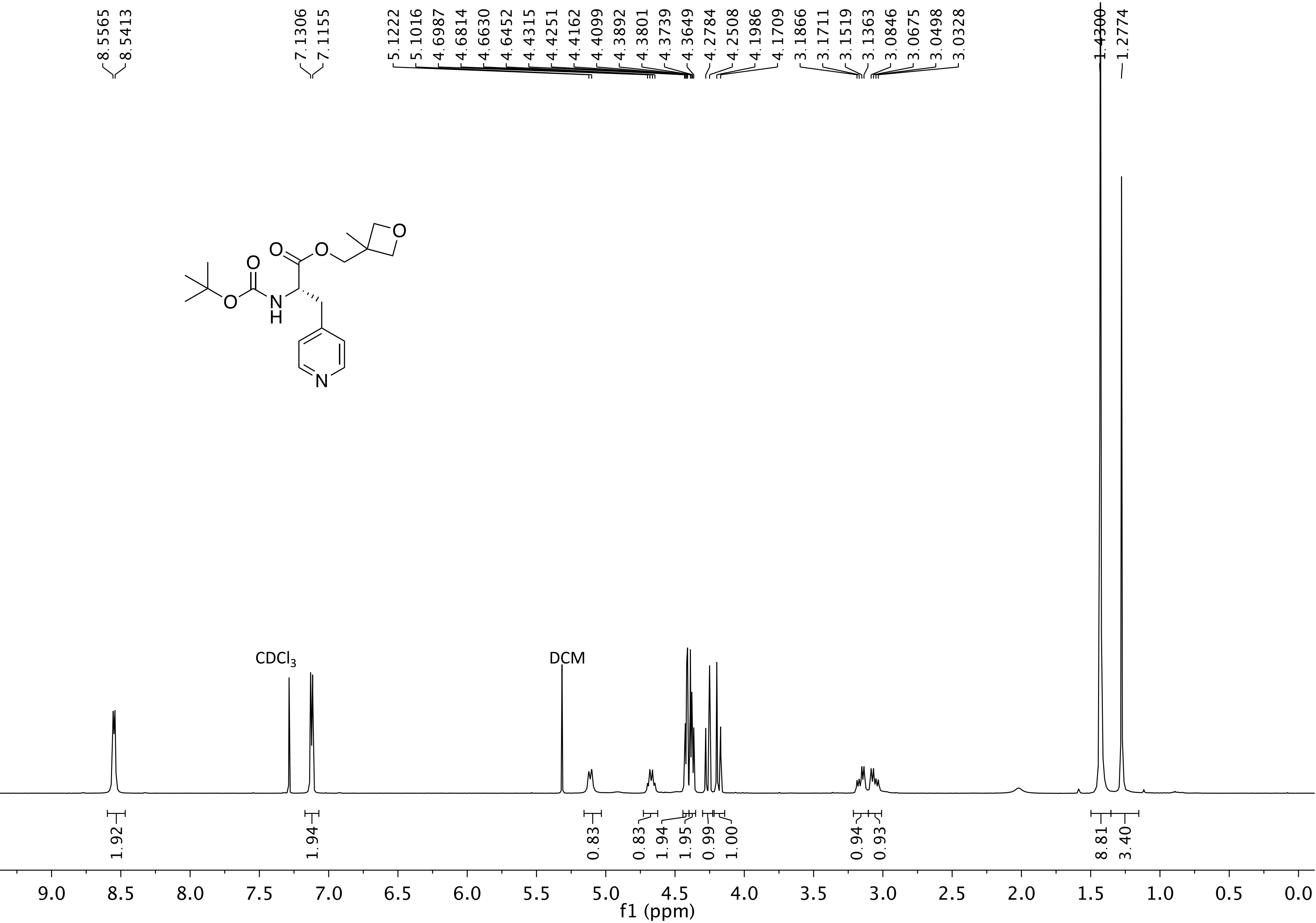
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



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7.1155
5.1222
5.1016
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4.6630
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4.4315
4.4251
4.4162
4.4099
4.3892
4.3801
4.3739
4.3649
4.2784
4.2508
4.1986
4.1709
3.1866
3.1711
3.1519
3.1363
3.0846
3.0675
3.0498
3.0328
1.4300
1.2774
O
O
O
O
O
N
H
N
CDCl$_3$
DCM
1.92
1.94
0.83
0.83
1.94
1.95
0.99
1.00
0.94
0.93
8.81
3.40
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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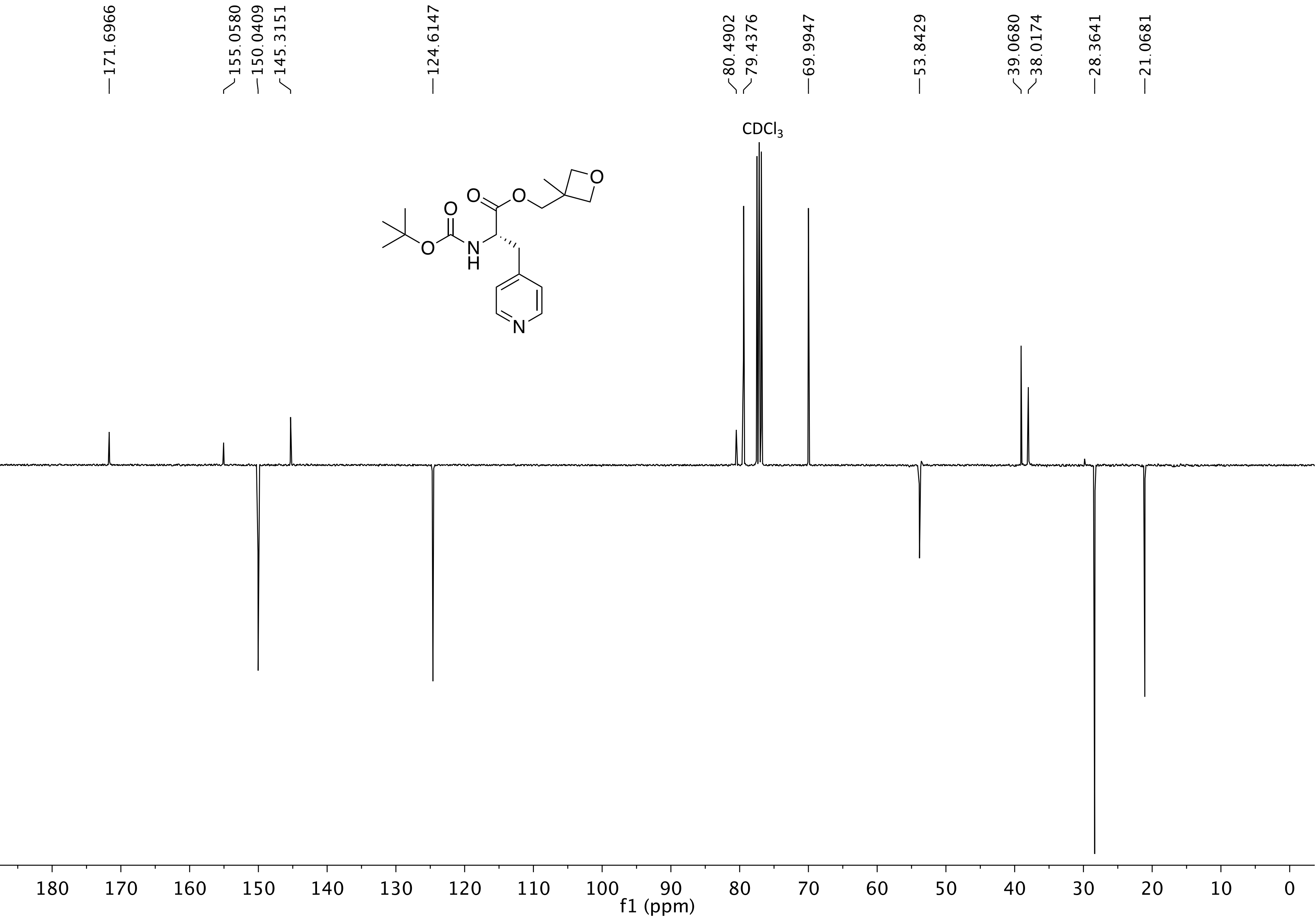
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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79.4376
69.9947
53.8429
39.0680
38.0174
28.3641
21.0681
CDCl$_3$
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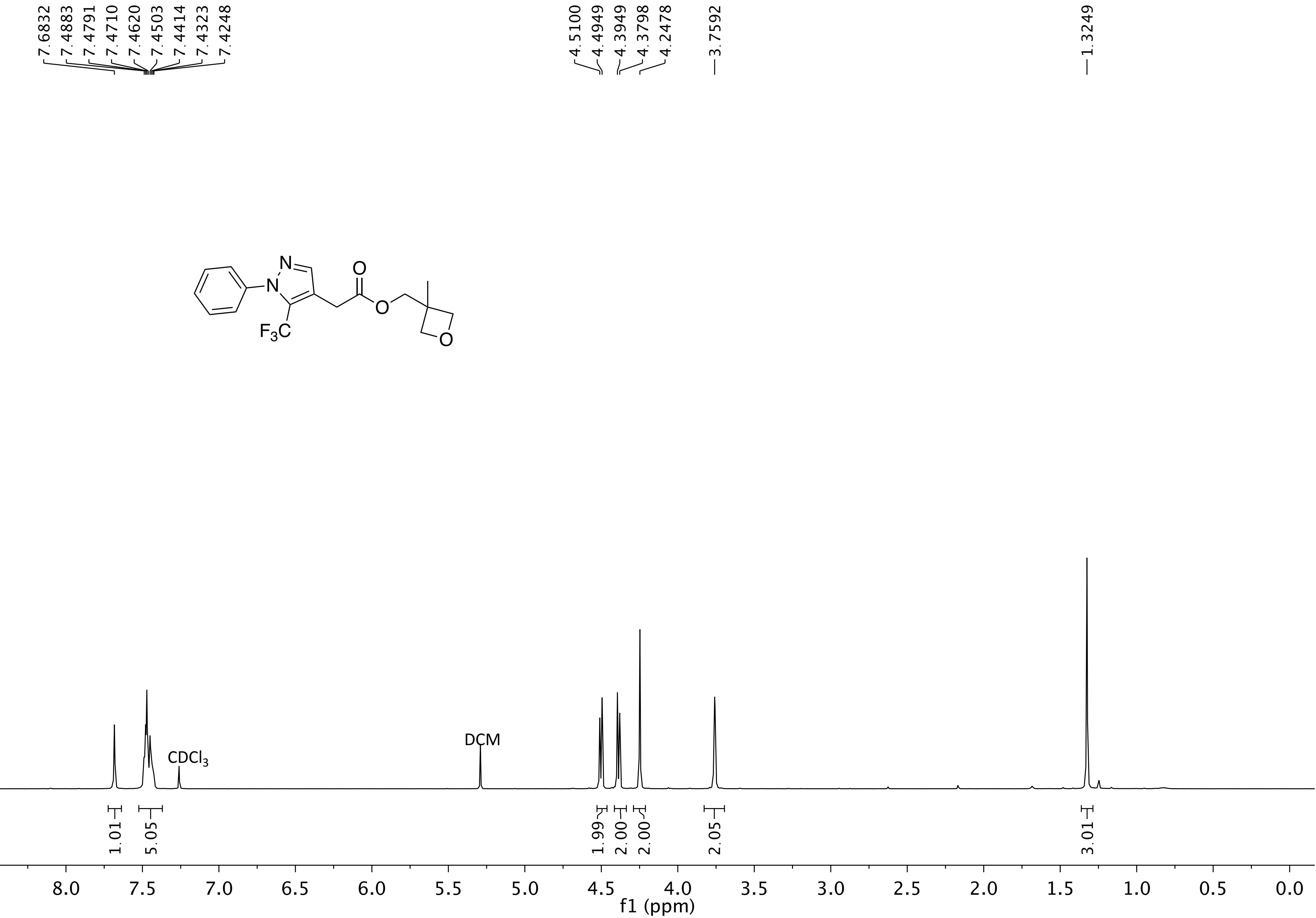
O
O
O
O
N
H
N
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



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7.4791
7.4710
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7.4503
7.4414
7.4323
7.4248
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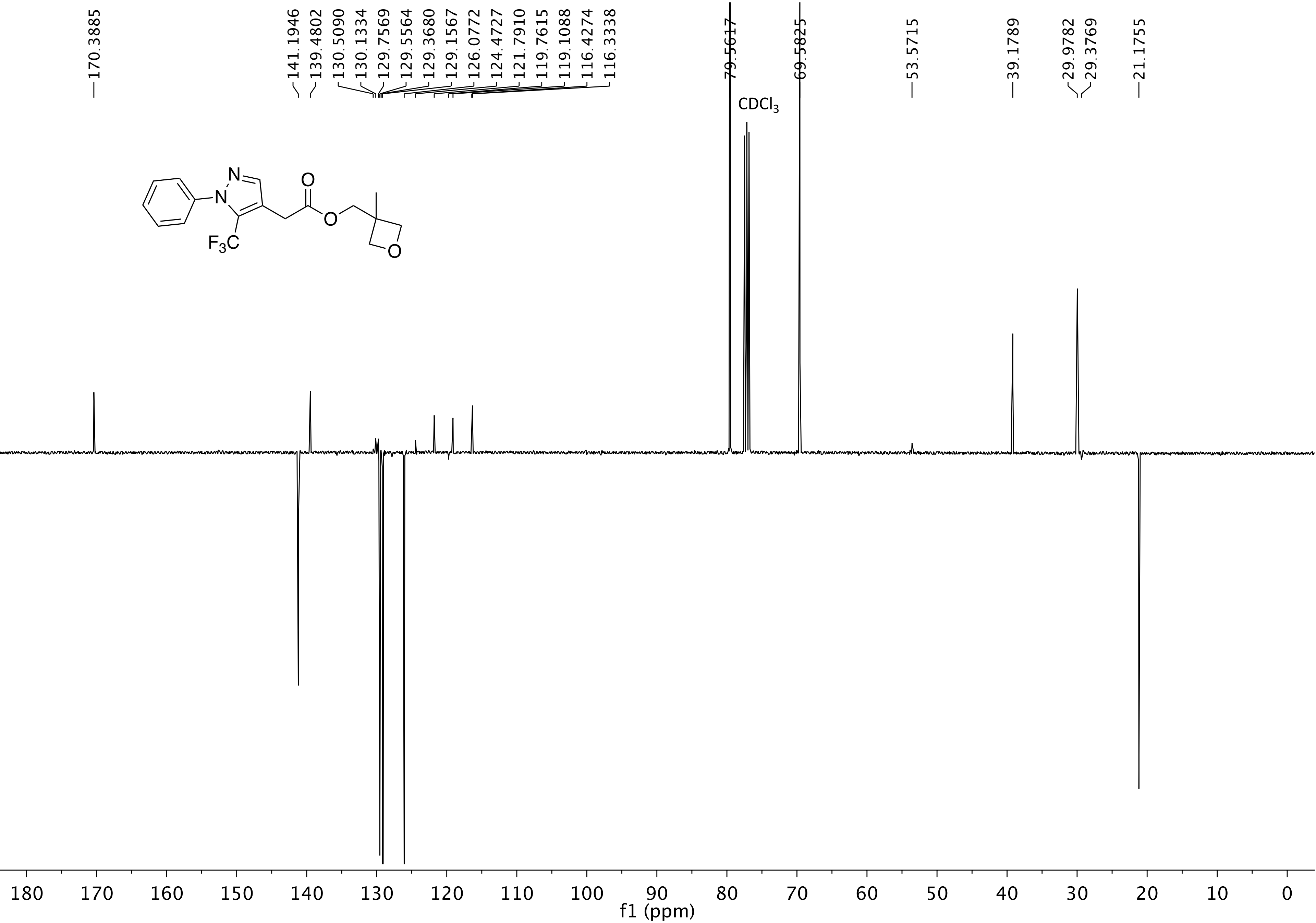
4.4949
4.3949
4.3798
4.2478
3.7592
1.3249
CDCl3
DCM
1.01
5.05
1.99
2.00
2.00
2.05
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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139.4802
130.5090
130.1334
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129.5564
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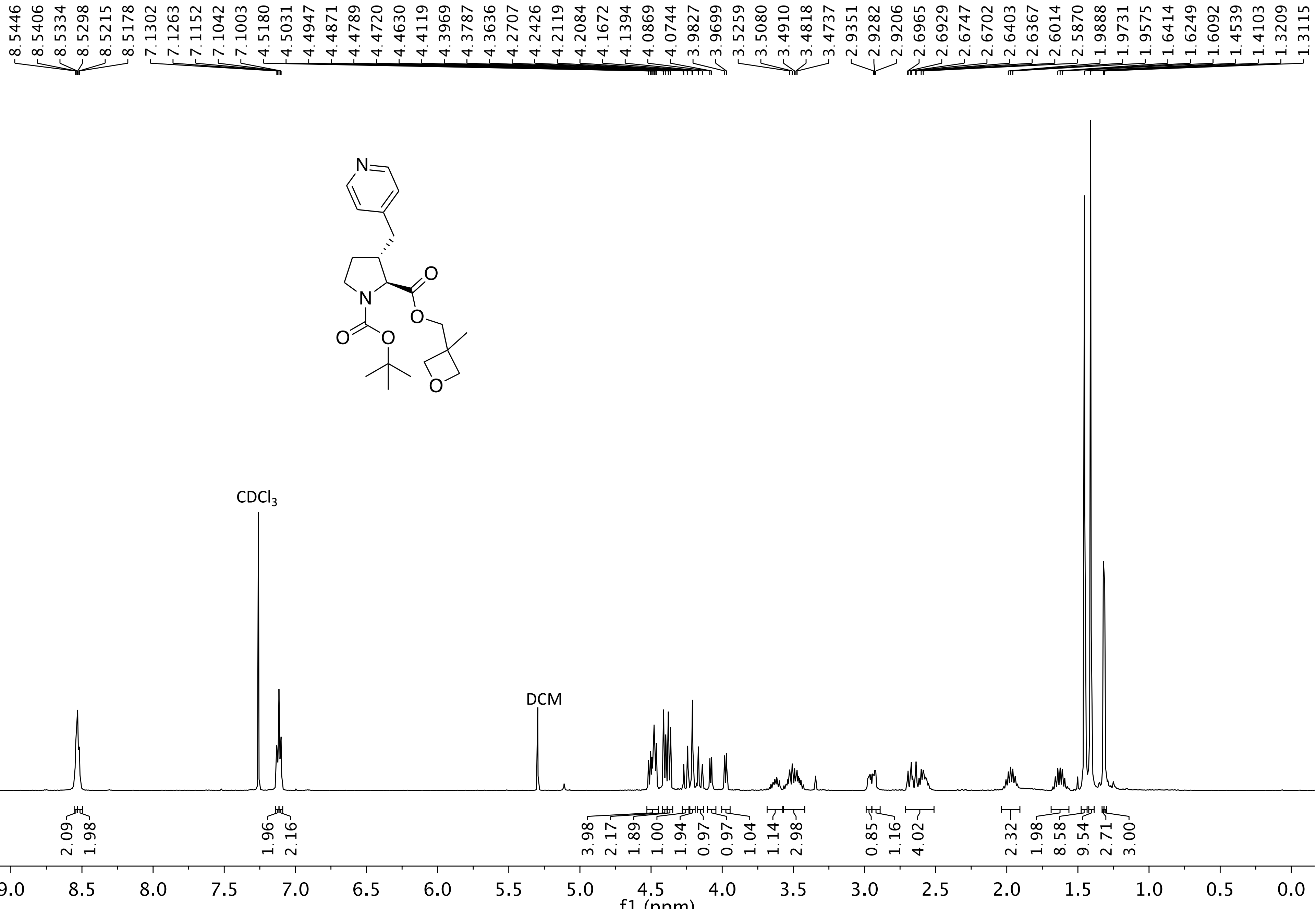
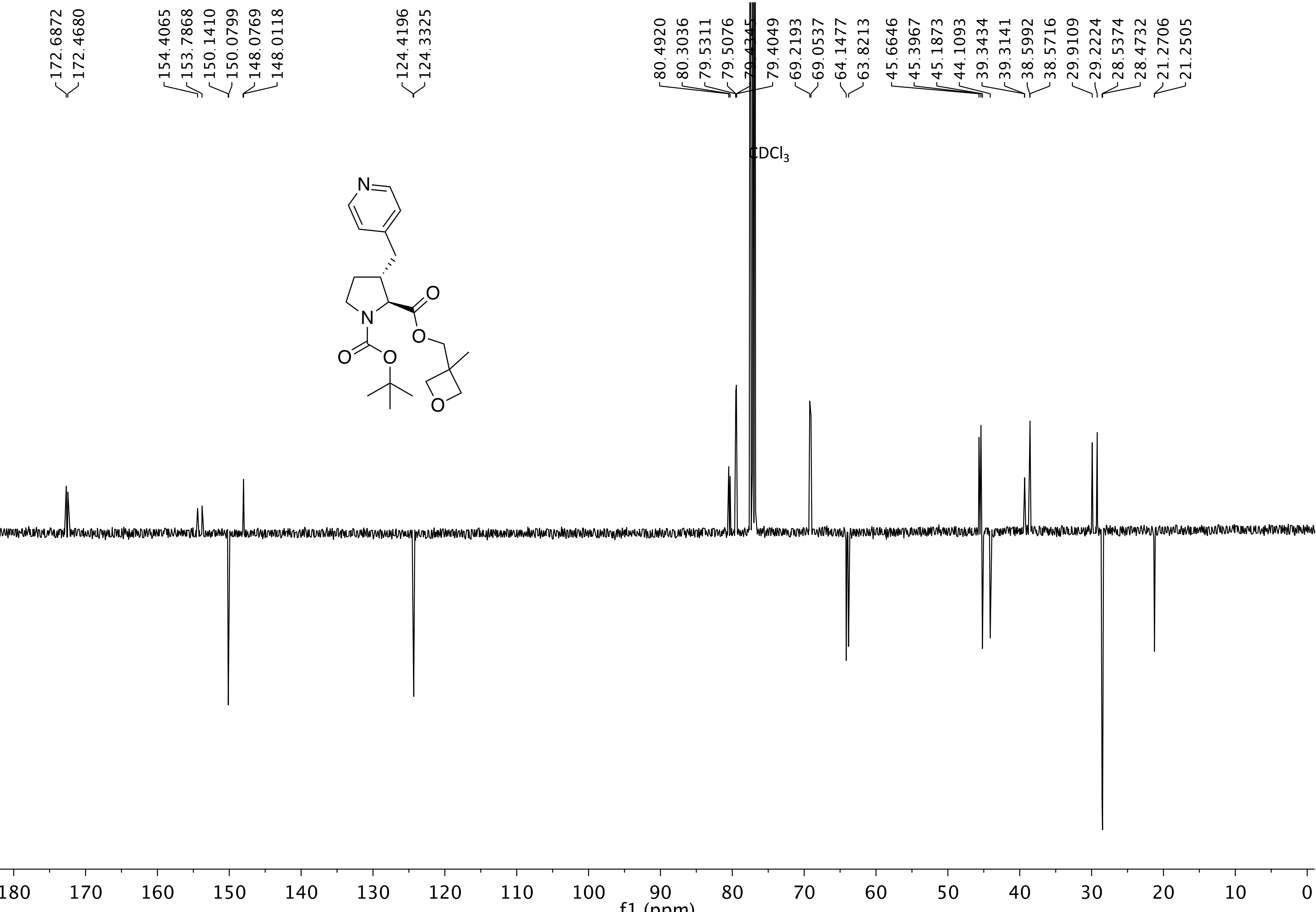
129.1567
126.0772
124.4727
121.7910
119.7615
119.1088
116.4274
116.3338
79.5617
CDCl3
69.5825
53.5715
39.1789
29.9782
29.3769
21.1755
N
N
O
O
O
F3C
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.5446 8.5406 8.5334 8.5298 8.5215 8.5178 7.1302 7.1263 7.1152 7.1042 7.1003 4.5180 4.5031 4.4947 4.4871 4.4789 4.4720 4.4630 4.4119 4.3969 4.3787 4.3636 4.2707 4.2426 4.2119 4.2084 4.1672 4.1394 4.0869 4.0744 3.9827 3.9699 3.5259 3.5080 3.4910 3.4818 3.4737 2.9351 2.9282 2.9206 2.6965 2.6929 2.6747 2.6702 2.6403 2.6367 2.6014 2.5870 1.9888 1.9731 1.9575 1.6414 1.6249 1.6092 1.4539 1.4103 1.3209 1.3115
CDCl3
DCM
2.09 1.98 1.96 2.16 3.98 2.17 1.89 1.00 1.94 0.97 0.97 1.04 1.14 2.98 0.85 1.16 4.02 2.32 1.98 8.58 9.54 2.71 3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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150.0799
148.0769
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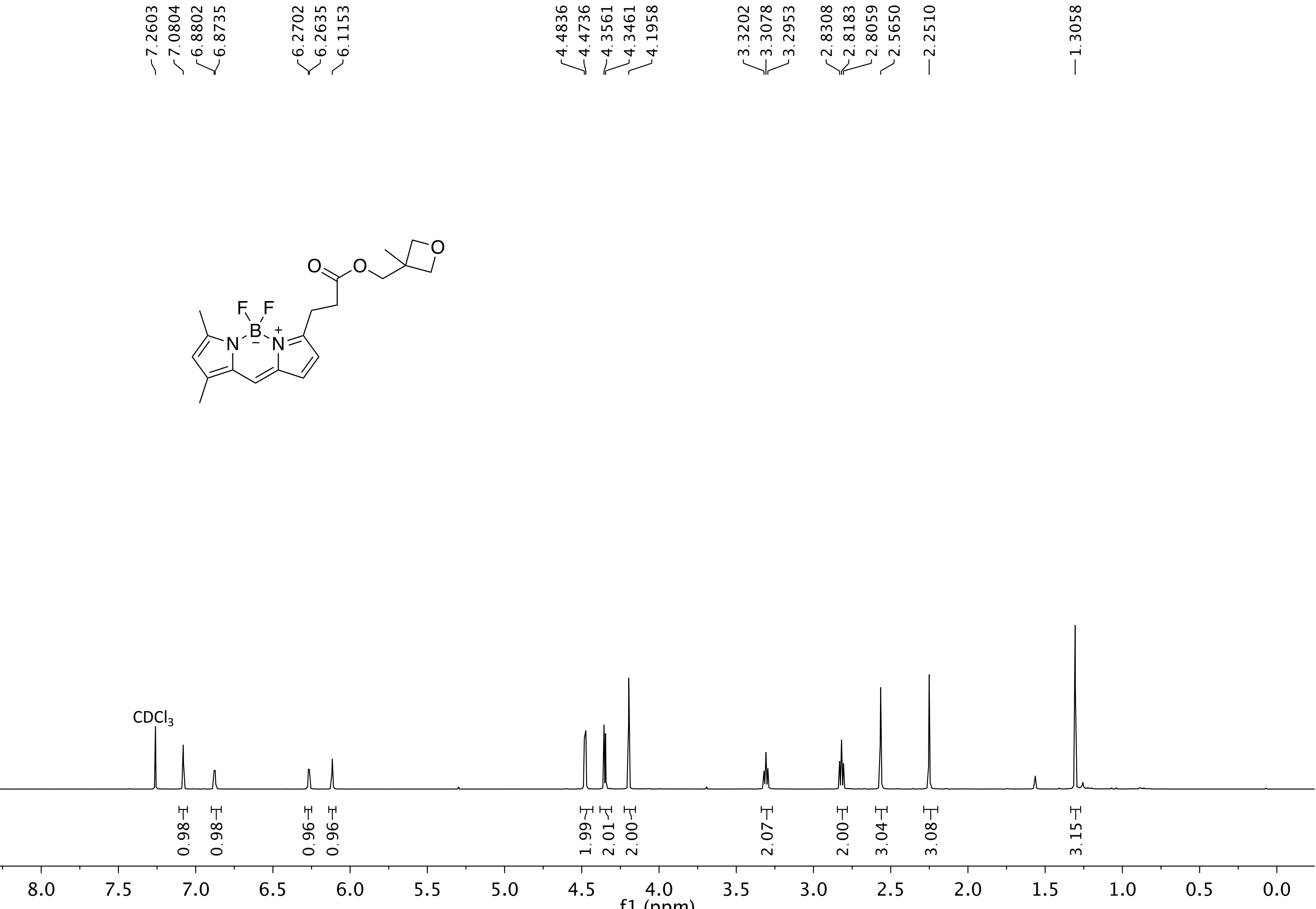
124.3325
80.4920
80.3036
79.5311
79.5076
79.4345
79.4049
69.2193
69.0537
64.1477
63.8213
45.6646
45.3967
45.1873
44.1093
39.3434
39.3141
38.5992
38.5716
29.9109
29.2224
28.5374
28.4732
21.2706
21.2505
CDCl$_3$
N
O
O
O
N
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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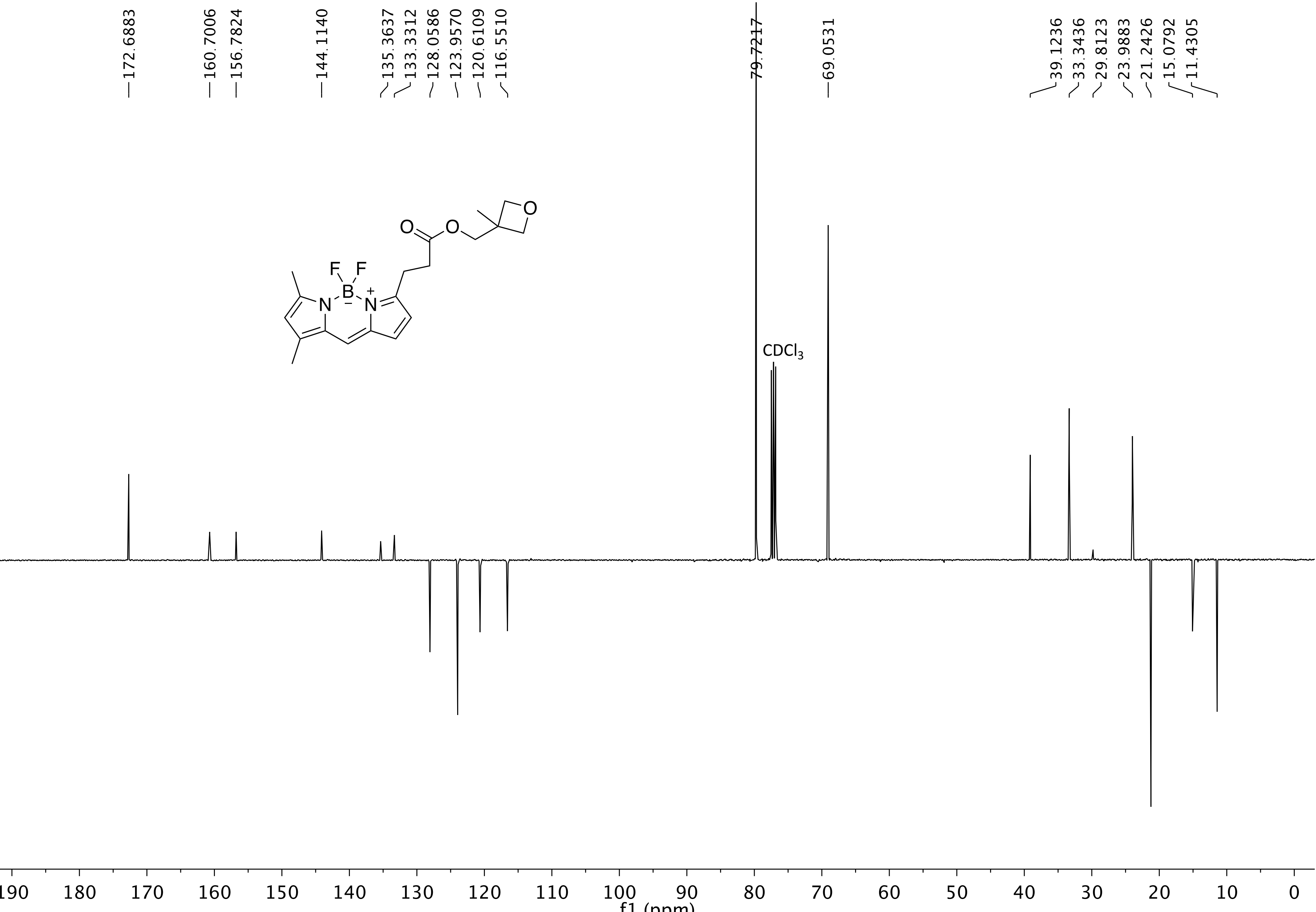
7.0804
6.8802
6.8735
6.2702
6.2635
6.1153
4.4836
4.4736
4.3561
4.3461
4.1958
3.3202
3.3078
3.2953
2.8308
2.8183
2.8059
2.5650
2.2510
1.3058
O
O
O
F
F
N
B
N
+
−
CDCl3
0.98
0.98
0.96
0.96
1.99
2.01
2.00
2.07
2.00
3.04
3.08
3.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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156.7824
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135.3637
133.3312
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123.9570
120.6109
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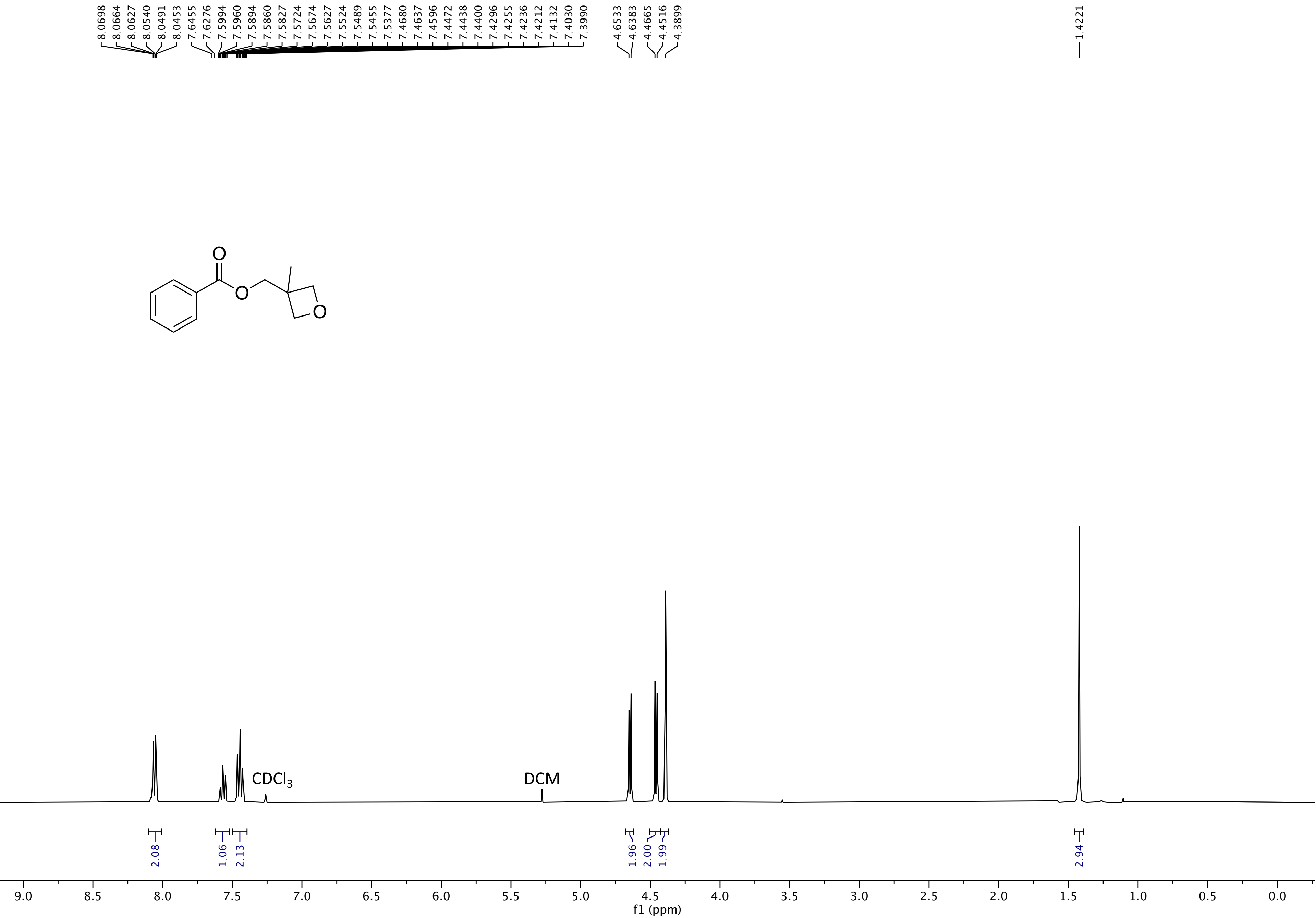
79.7217
69.0531
39.1236
33.3436
29.8123
23.9883
21.2426
15.0792
11.4305
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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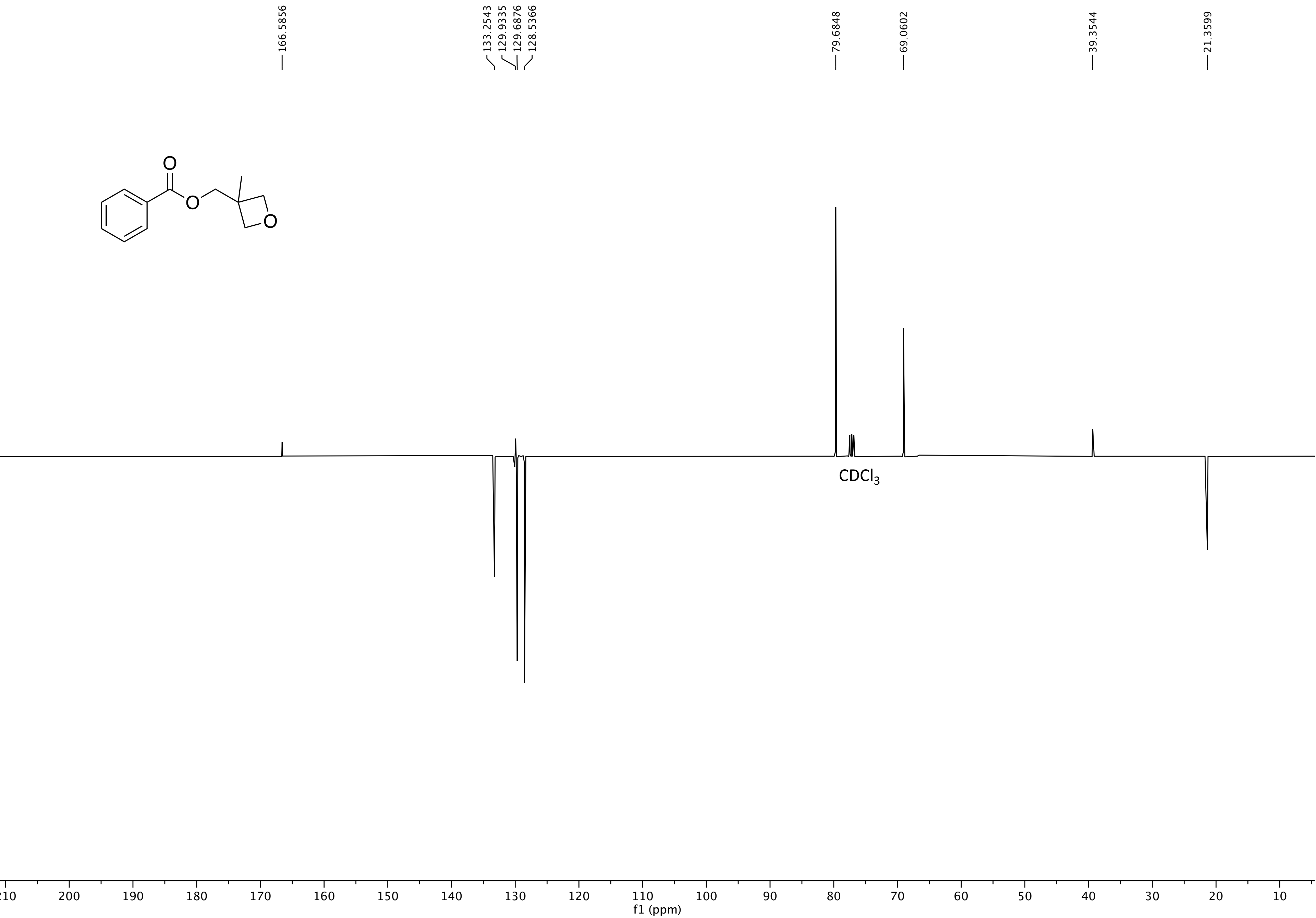
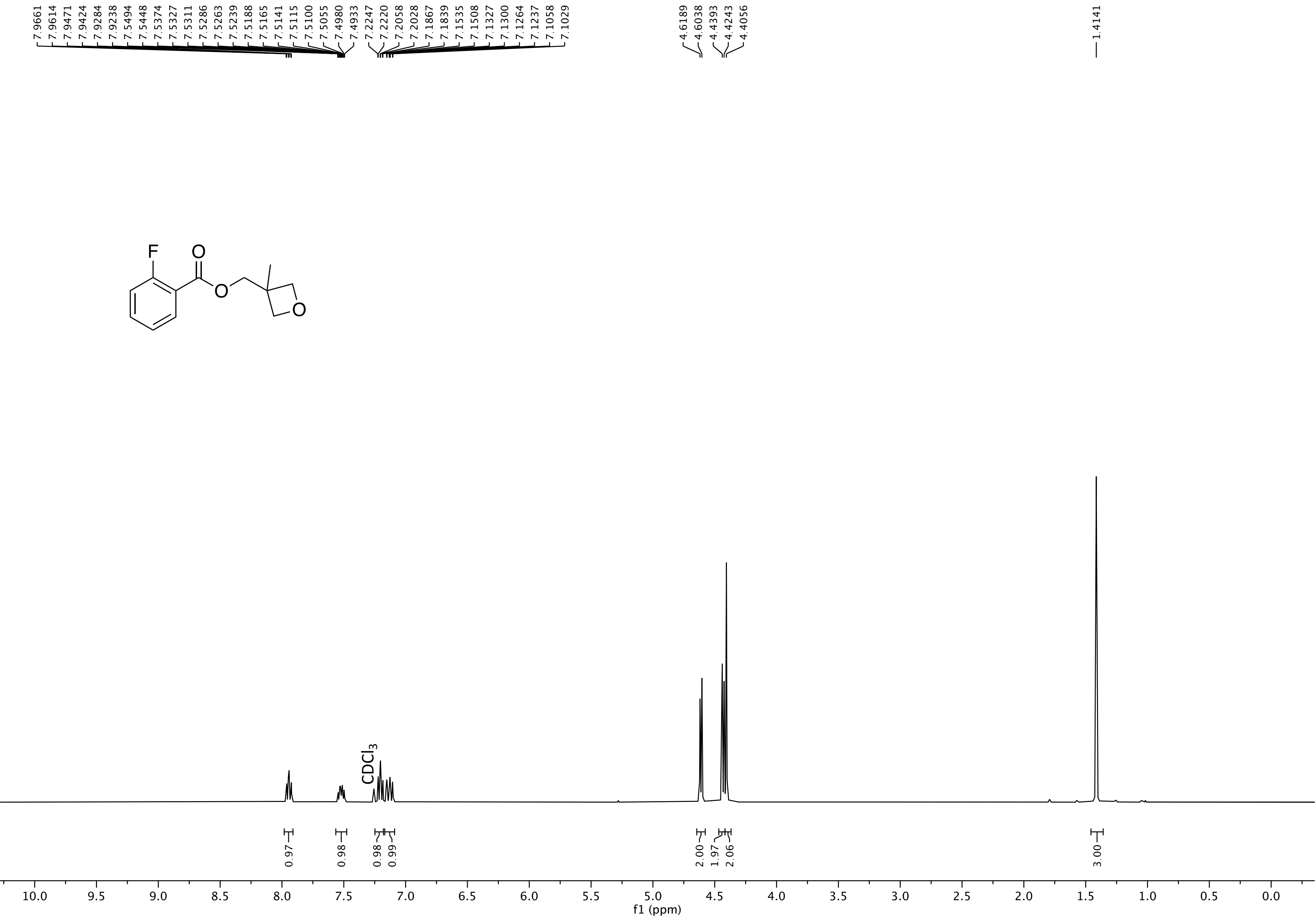
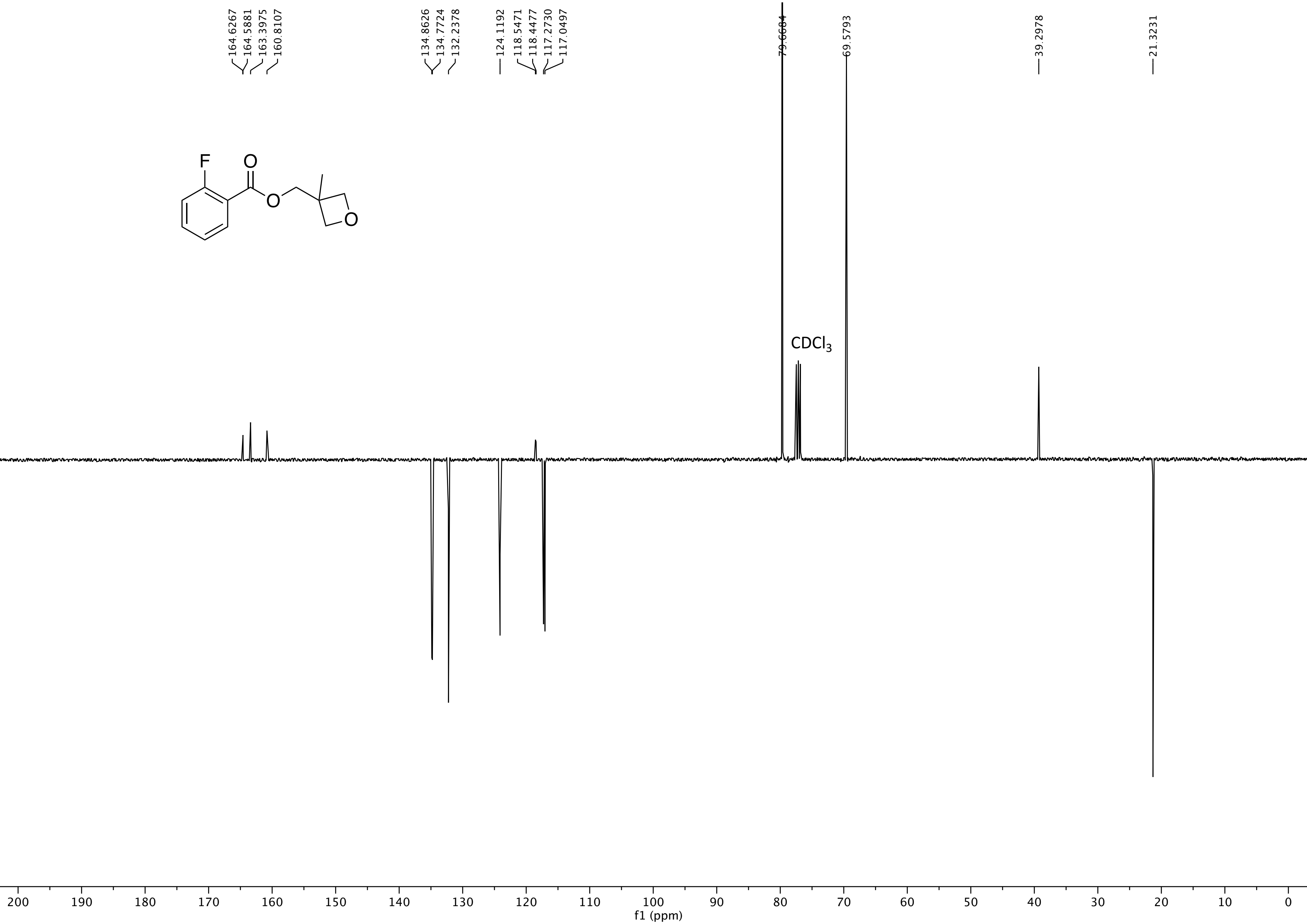
8.0664
8.0627
8.0540
8.0491
8.0453
7.6455
7.6276
7.5994
7.5960
7.5894
7.5860
7.5827
7.5724
7.5674
7.5627
7.5524
7.5489
7.5455
7.5377
7.4680
7.4637
7.4596
7.4472
7.4438
7.4400
7.4296
7.4255
7.4236
7.4212
7.4132
7.4030
7.3990
4.6533
4.6383
4.4665
4.4516
4.3899
1.4221
O
O
O
CDCl3
DCM
2.08
1.06
2.13
1.96
2.00
1.99
2.94
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



166.5856
133.2543
129.9335
129.6876
128.5366
79.6848
69.0602
39.3544
21.3599
CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.9661
7.9614
7.9471
7.9424
7.9284
7.9238
7.5494
7.5448
7.5374
7.5327
7.5311
7.5286
7.5263
7.5239
7.5188
7.5165
7.5141
7.5115
7.5100
7.5055
7.4980
7.4933
7.2247
7.2220
7.2058
7.2028
7.1867
7.1839
7.1535
7.1508
7.1327
7.1300
7.1264
7.1237
7.1058
7.1029
4.6189
4.6038
4.4393
4.4243
4.4056
1.4141
F
O
O
O
CDCl3
0.97
0.98
0.98
0.99
2.00
1.97
2.06
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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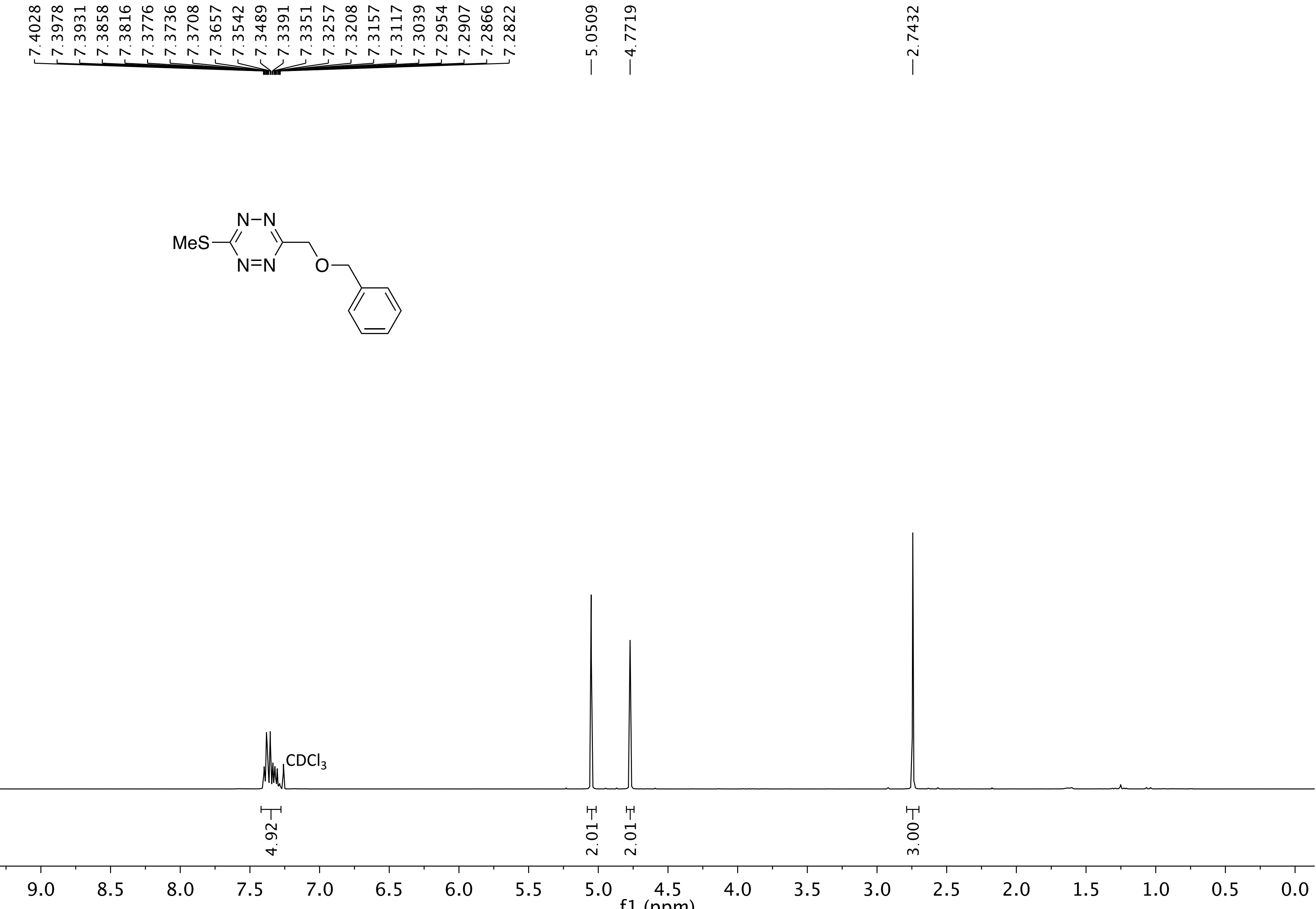
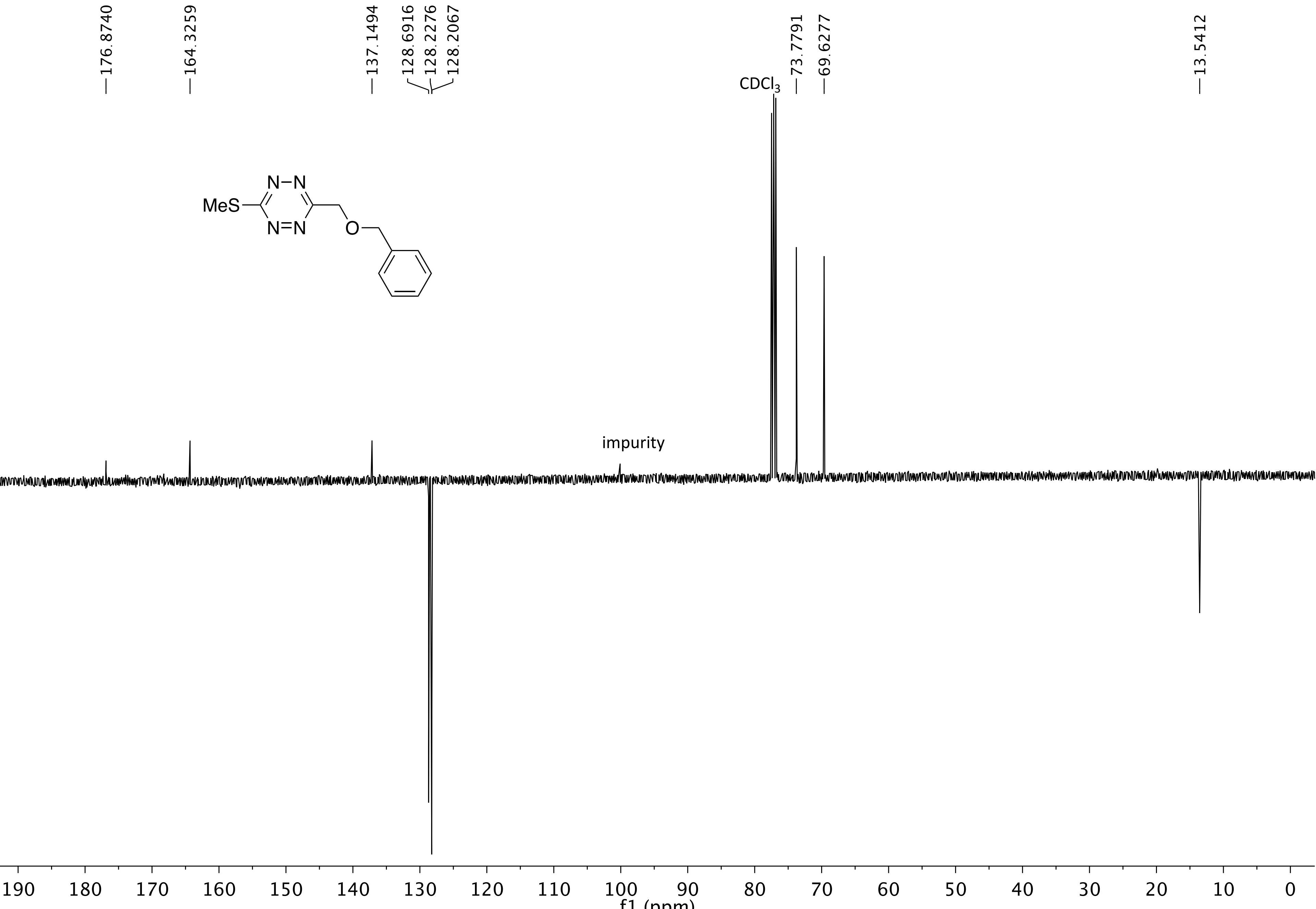
164.5881
163.3975
160.8107
134.8626
134.7724
132.2378
124.1192
118.5471
118.4477
117.2730
117.0497
79.6684
69.5793
39.2978
21.3231
F
O
O
O
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



7.4028
7.3978
7.3931
7.3858
7.3816
7.3776
7.3736
7.3708
7.3657
7.3542
7.3489
7.3391
7.3351
7.3257
7.3208
7.3157
7.3117
7.3039
7.2954
7.2907
7.2866
7.2822
5.0509
4.7719
2.7432
MeS
N−N
N=N
O
CDCl3
4.92
2.01
2.01
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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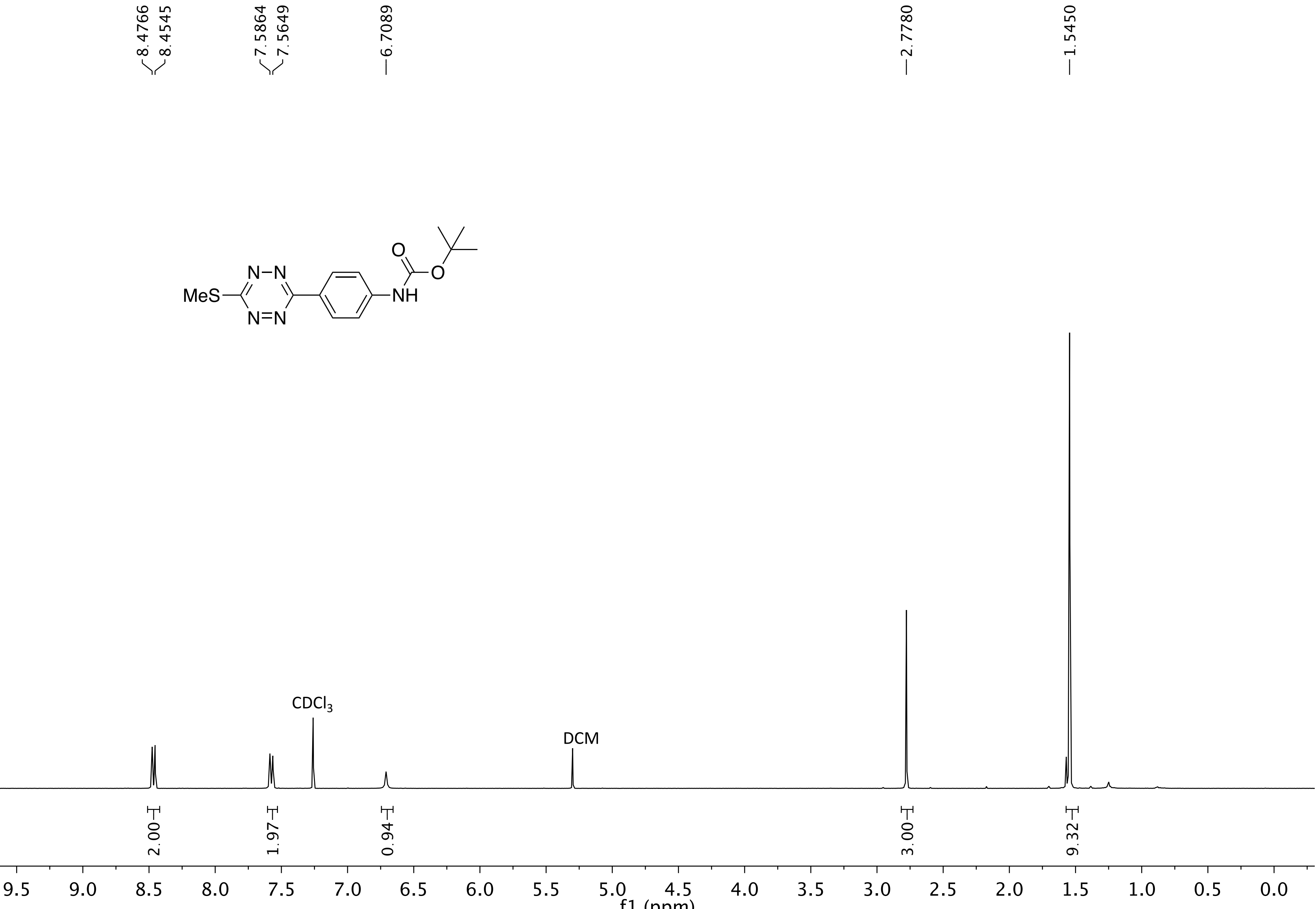
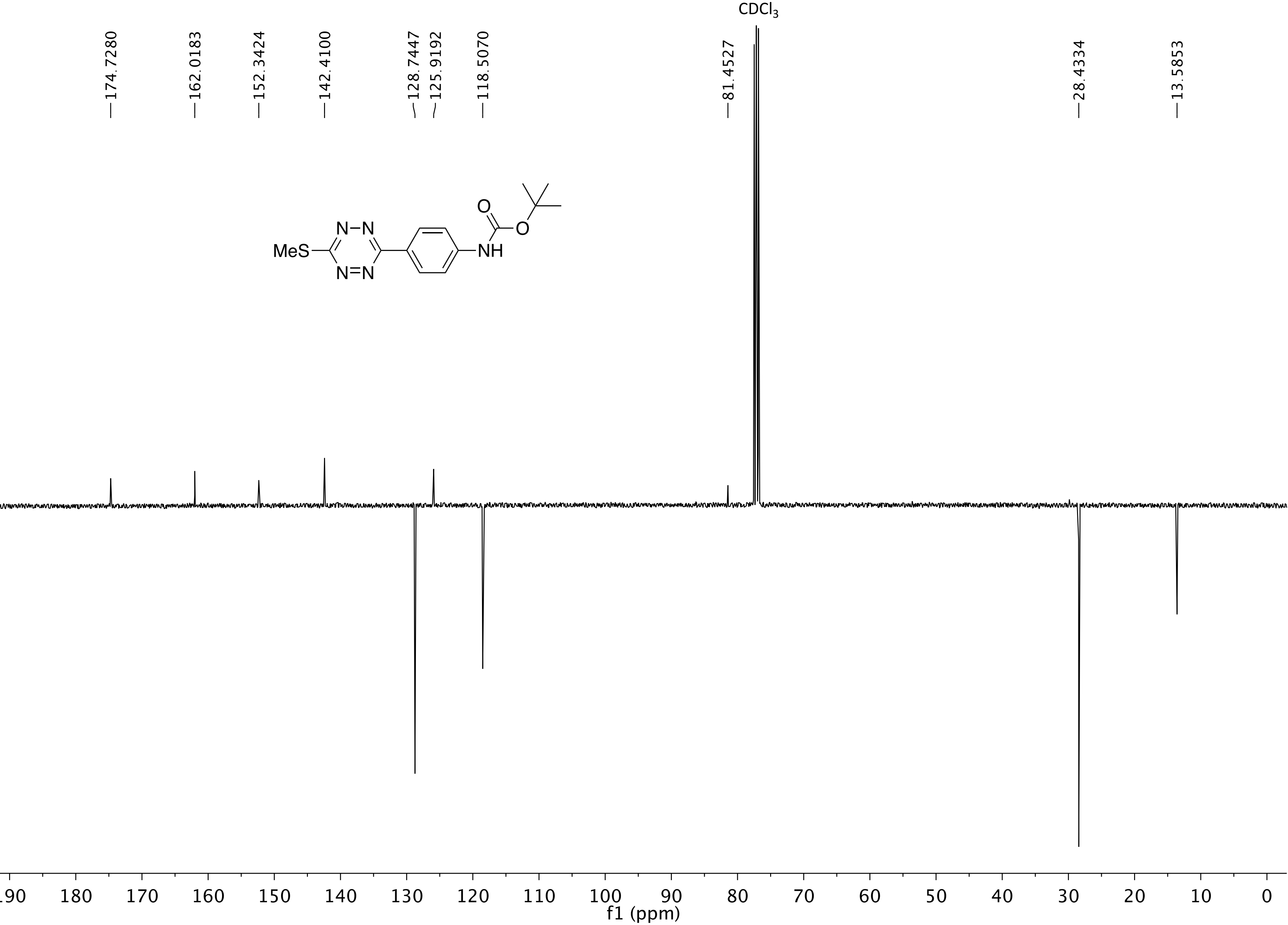
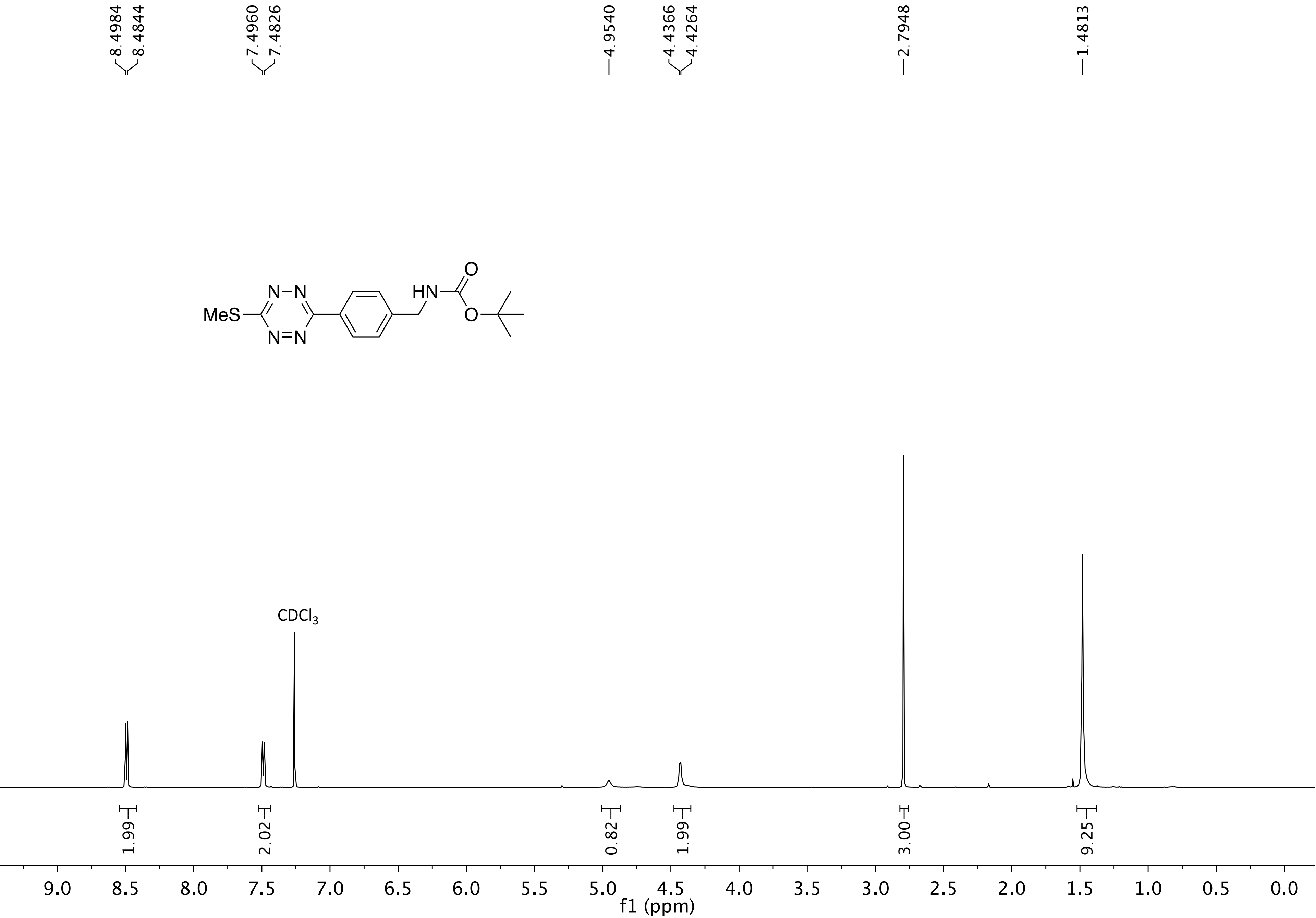
164.3259
137.1494
128.6916
128.2276
128.2067
CDCl3
73.7791
69.6277
13.5412
MeS
N–N
N=N
O
impurity
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

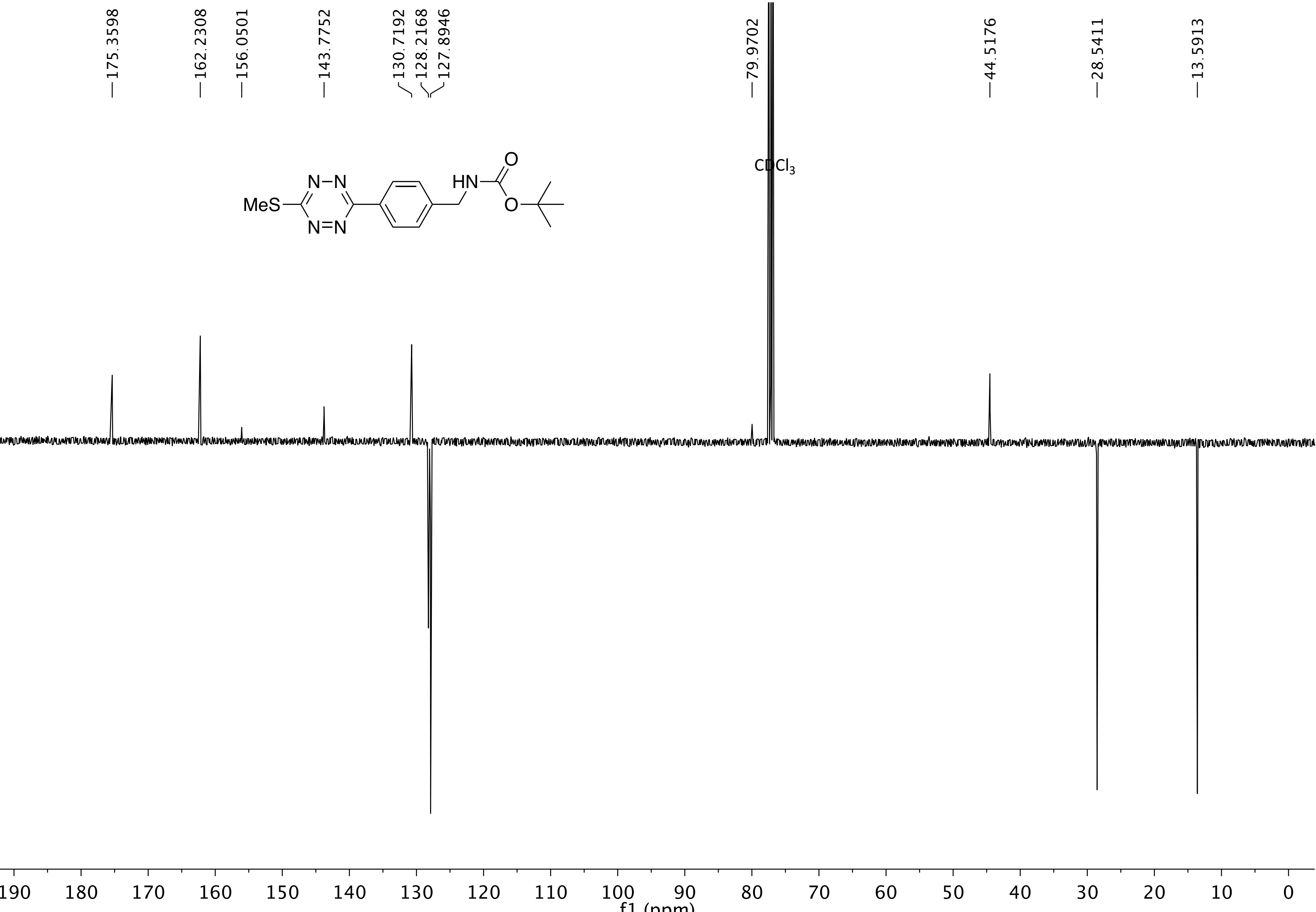


8.4766
8.4545
7.5864
7.5649
6.7089
2.7780
1.5450
MeS
N−N
N=N
O
O
NH
CDCl3
DCM
2.00
1.97
0.94
3.00
9.32
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

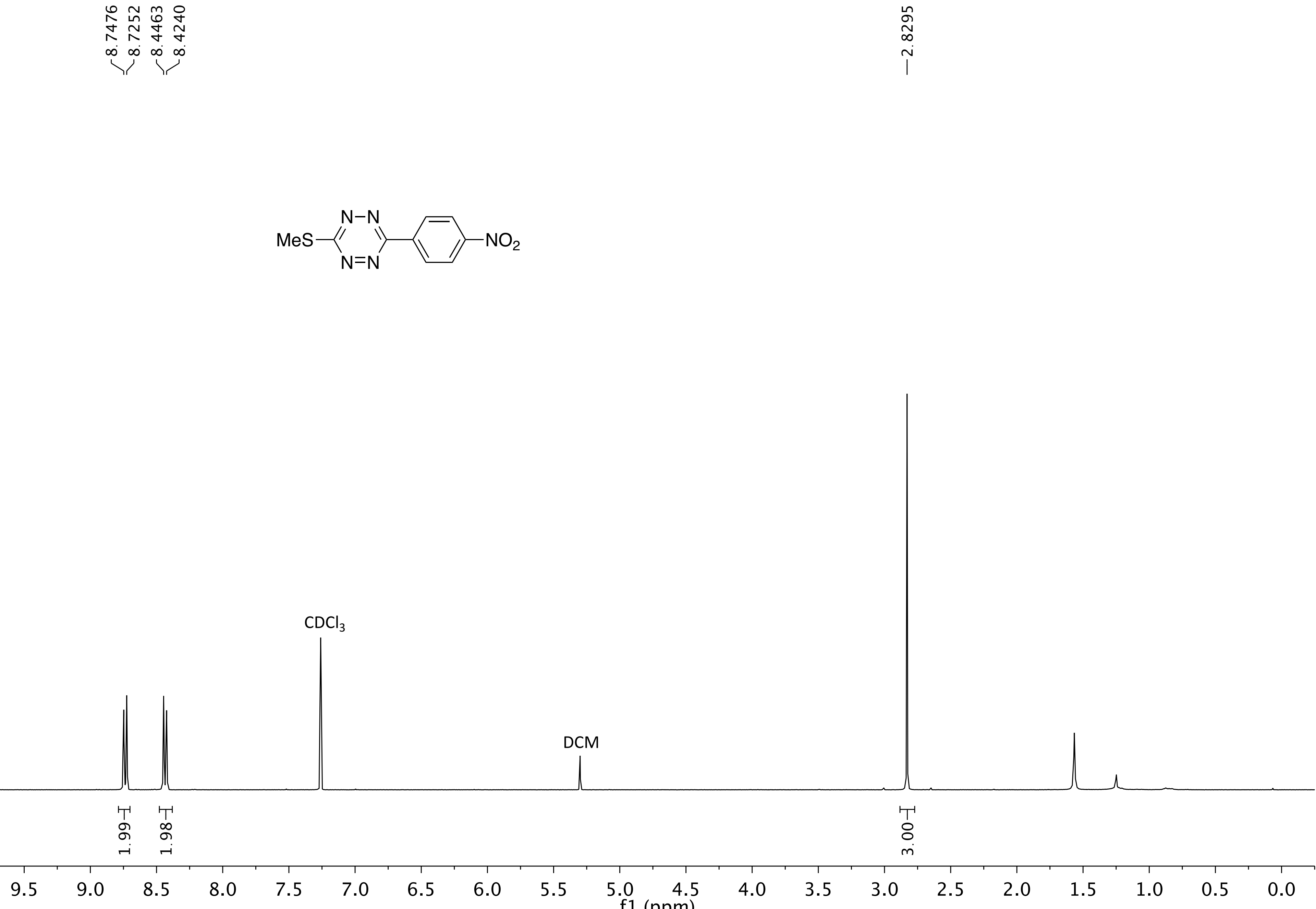


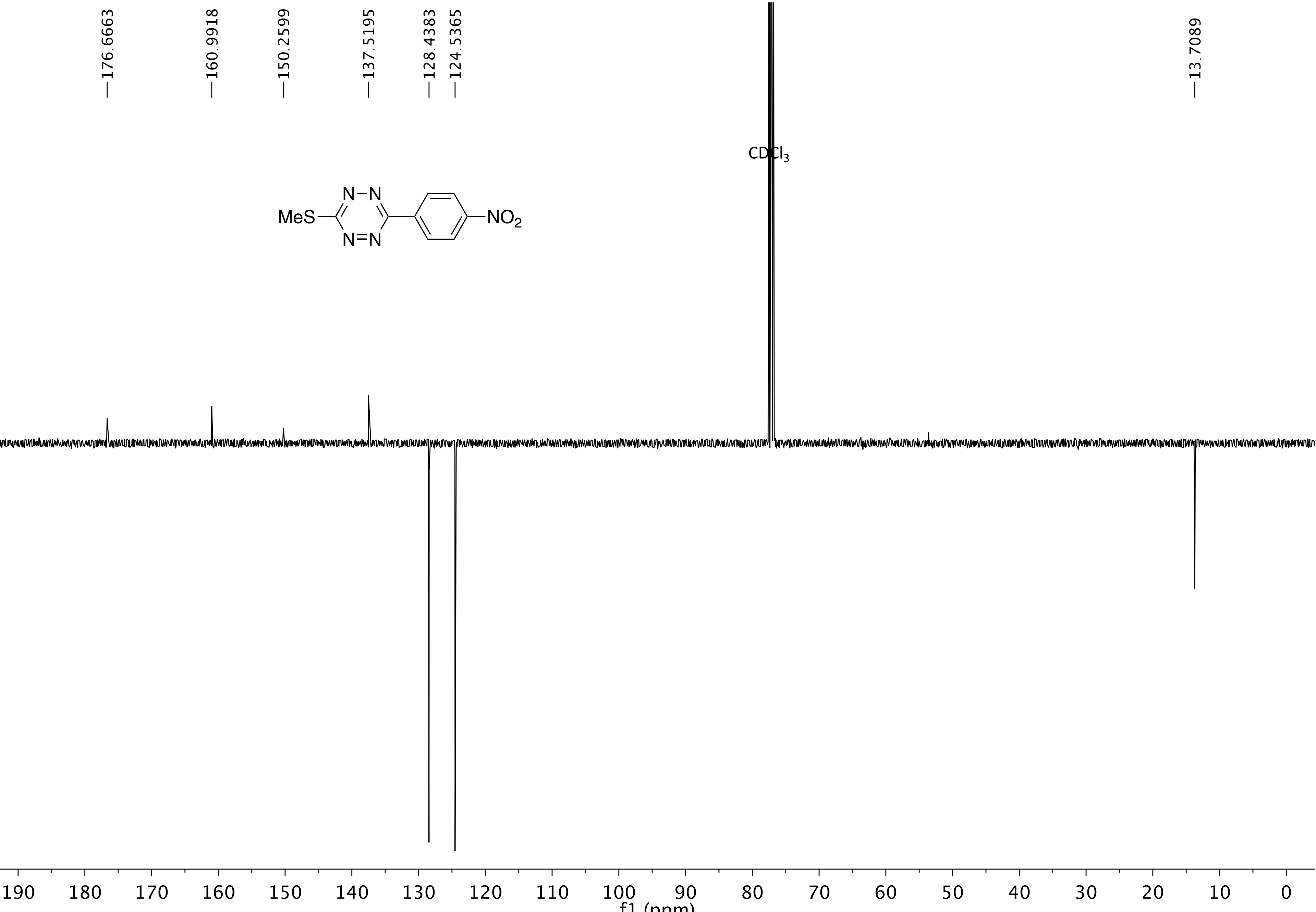
CDCl3
174.7280
162.0183
152.3424
142.4100
128.7447
125.9192
118.5070
81.4527
28.4334
13.5853
MeS
N
NH
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

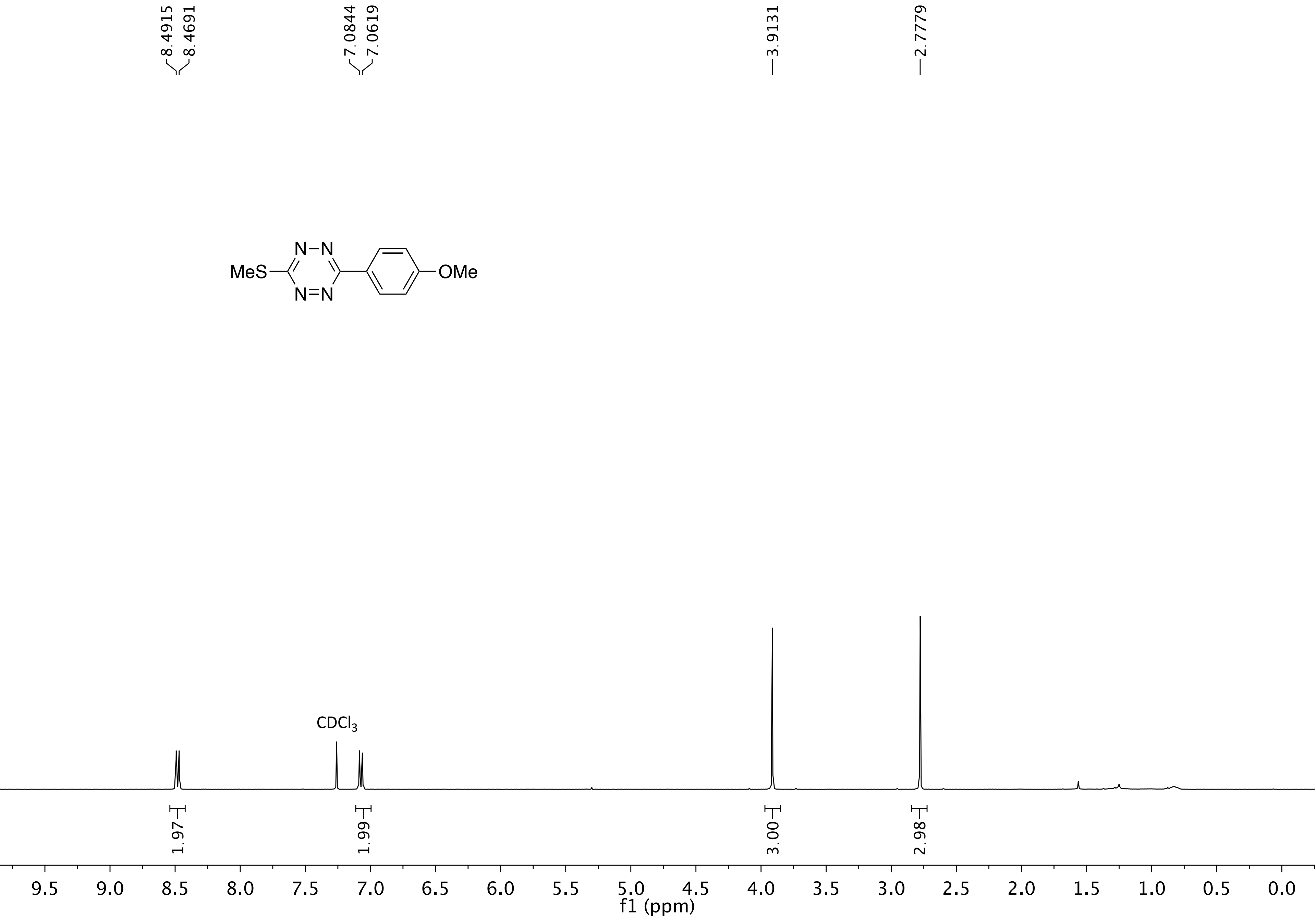

8.4984
8.4844
7.4960
7.4826
4.9540
4.4366
4.4264
2.7948
1.4813
MeS
N–N
N=N
HN
O
O
CDCl3
1.99
2.02
0.82
1.99
3.00
9.25
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

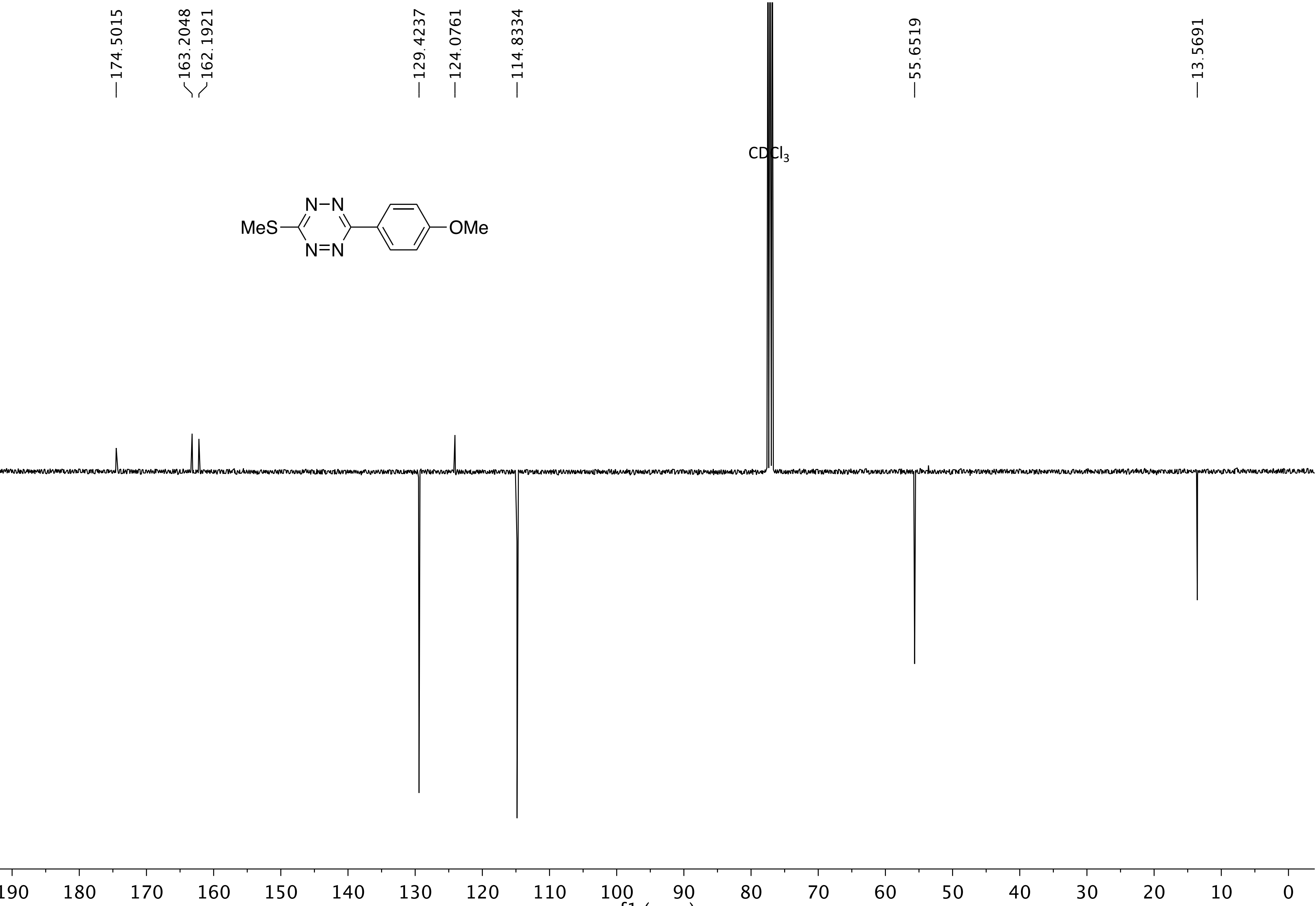


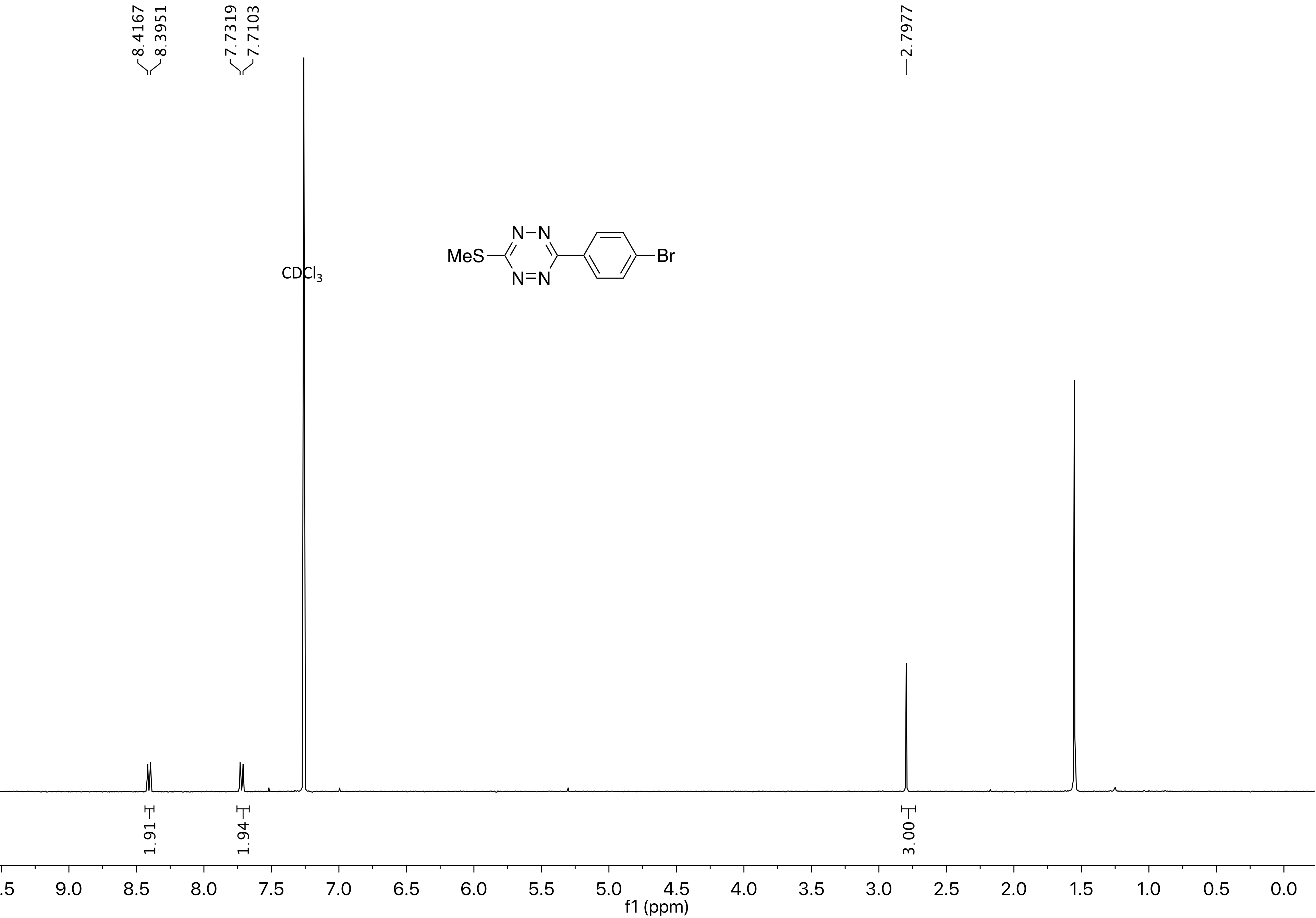
175.3598
162.2308
156.0501
143.7752
130.7192
128.2168
127.8946
79.9702
44.5176
28.5411
13.5913
CDCl3
MeS
HN
f1 (ppm)


8.7476
8.7252
8.4463
8.4240
2.8295
MeS
N−N
N=N
NO2
CDCl3
DCM
1.99
1.98
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


176.6663
160.9918
150.2599
137.5195
128.4383
124.5365
13.7089
CDCl3
MeS
N
NO2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.4915
8.4691
7.0844
7.0619
3.9131
2.7779
MeS
N−N
N=N
OMe
CDCl3
1.97
1.99
3.00
2.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


174.5015
163.2048
162.1921
129.4237
124.0761
114.8334
55.6519
13.5691
CDCl3
MeS
N
N
N
N
OMe
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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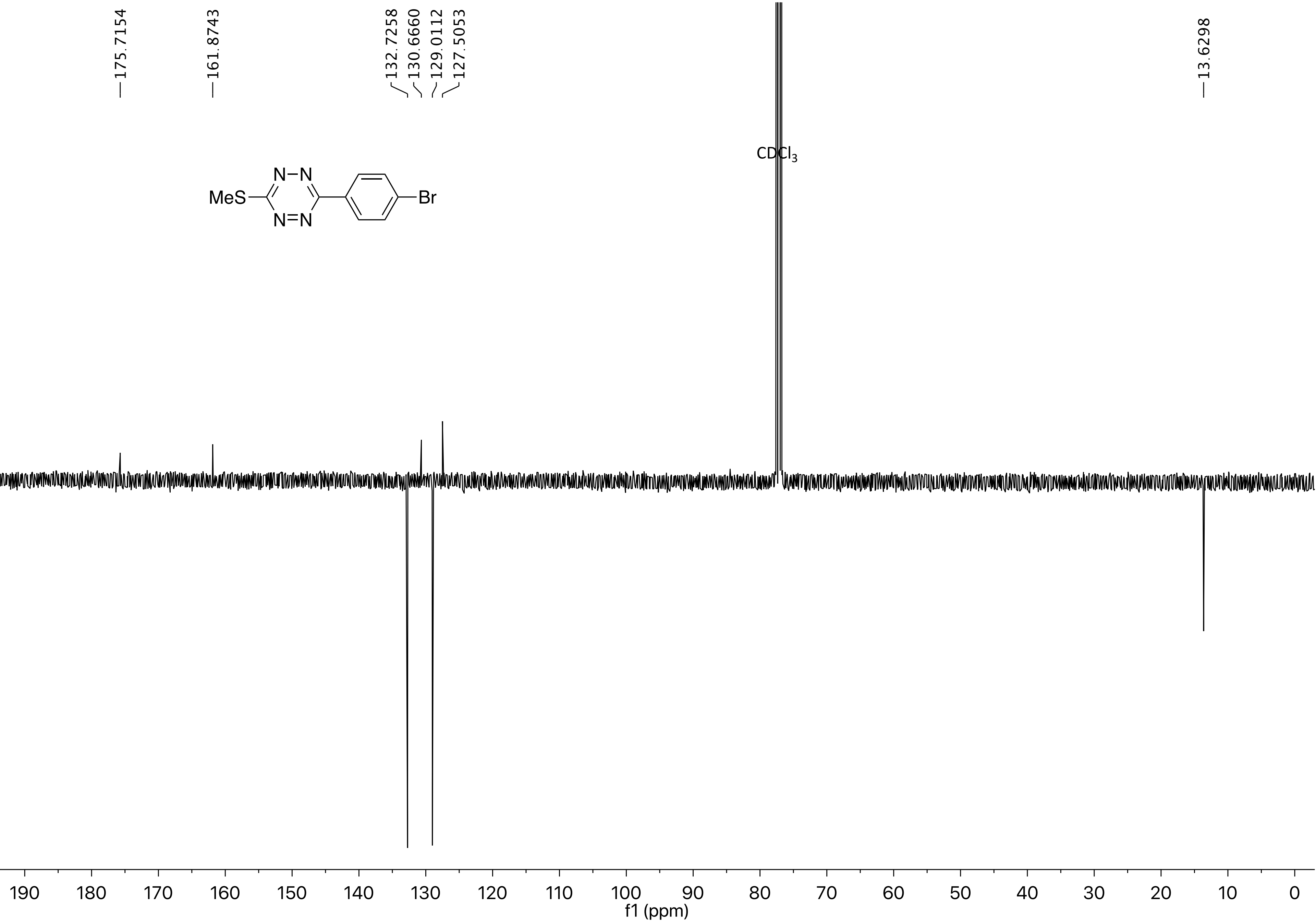
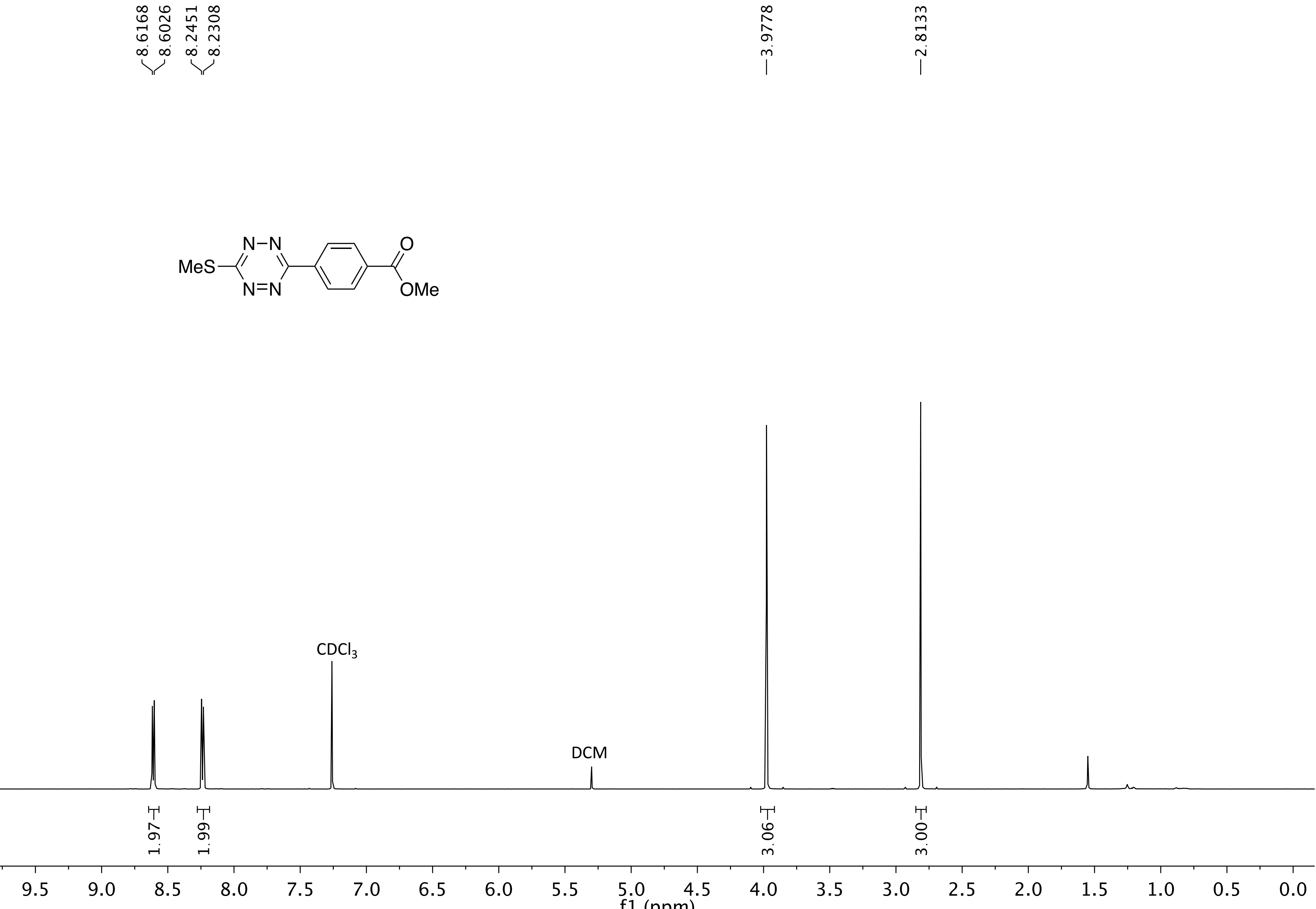
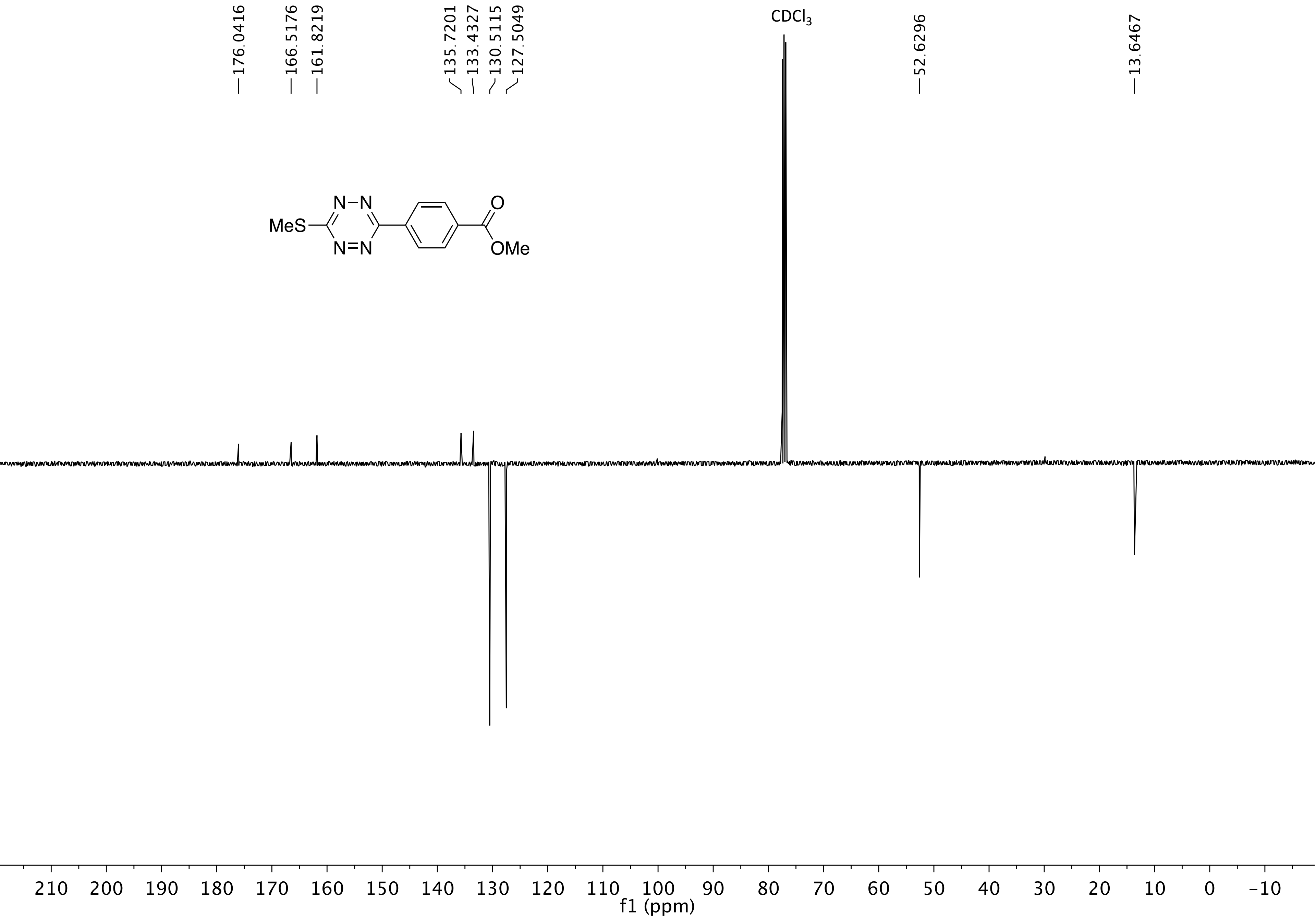
7.7319
7.7103
2.7977
CDCl3
MeS
N–N
N=N
Br
1.91
1.94
3.00
.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



175.7154
161.8743
132.7258
130.6660
129.0112
127.5053
13.6298
CDCl3
MeS
N
N
N
N
Br
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeS
N−N
N=N
O
OMe
8.6168
8.6026
8.2451
8.2308
3.9778
2.8133
CDCl3
DCM
1.97
1.99
3.06
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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166.5176
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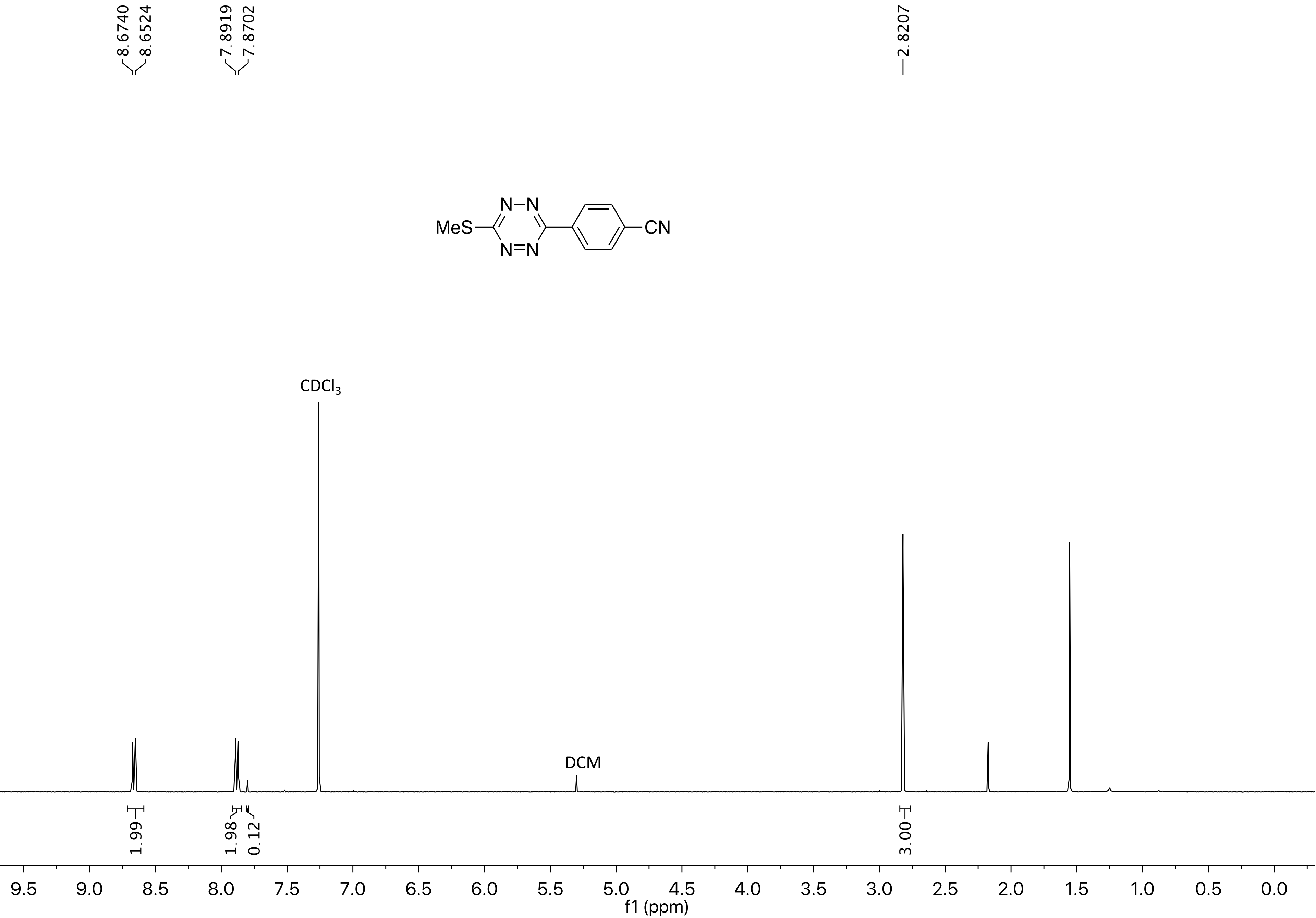
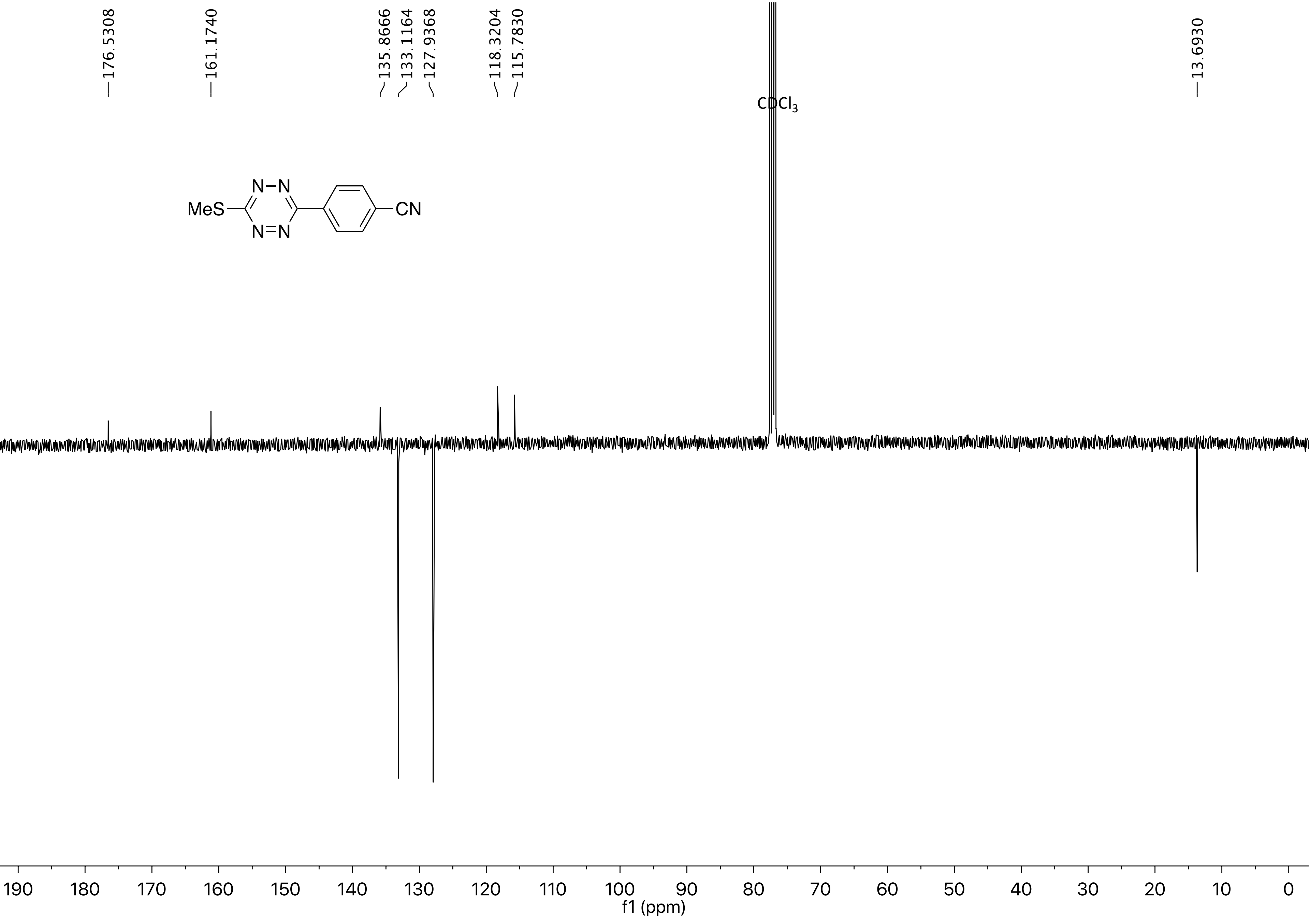
135.7201
133.4327
130.5115
127.5049
CDCl3
52.6296
13.6467
MeS
N−N
N=N
O
OMe
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


8.6740
8.6524
7.8919
7.8702
2.8207
MeS
N−N
N=N
CN
CDCl3
DCM
1.99
1.98
0.12
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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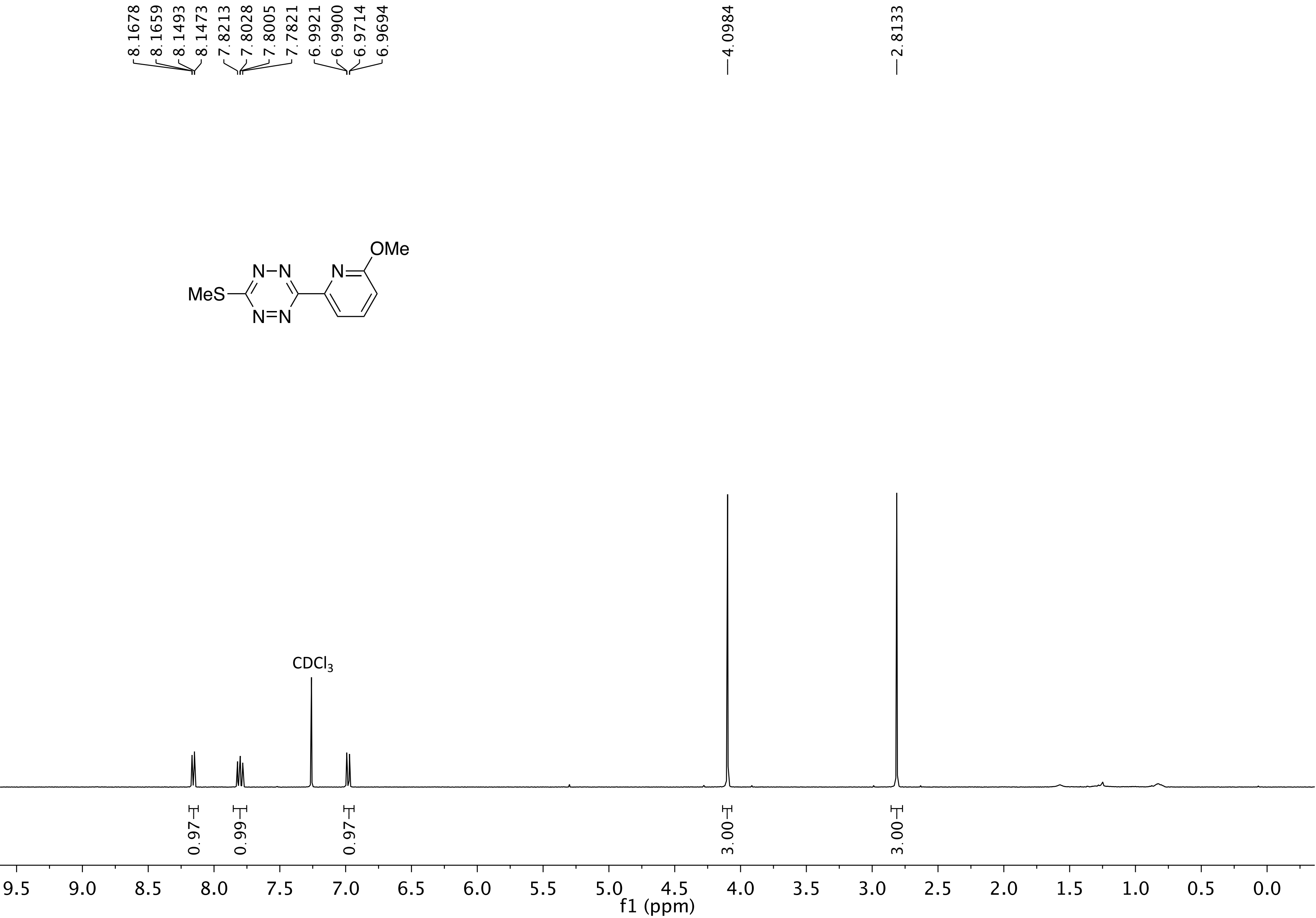
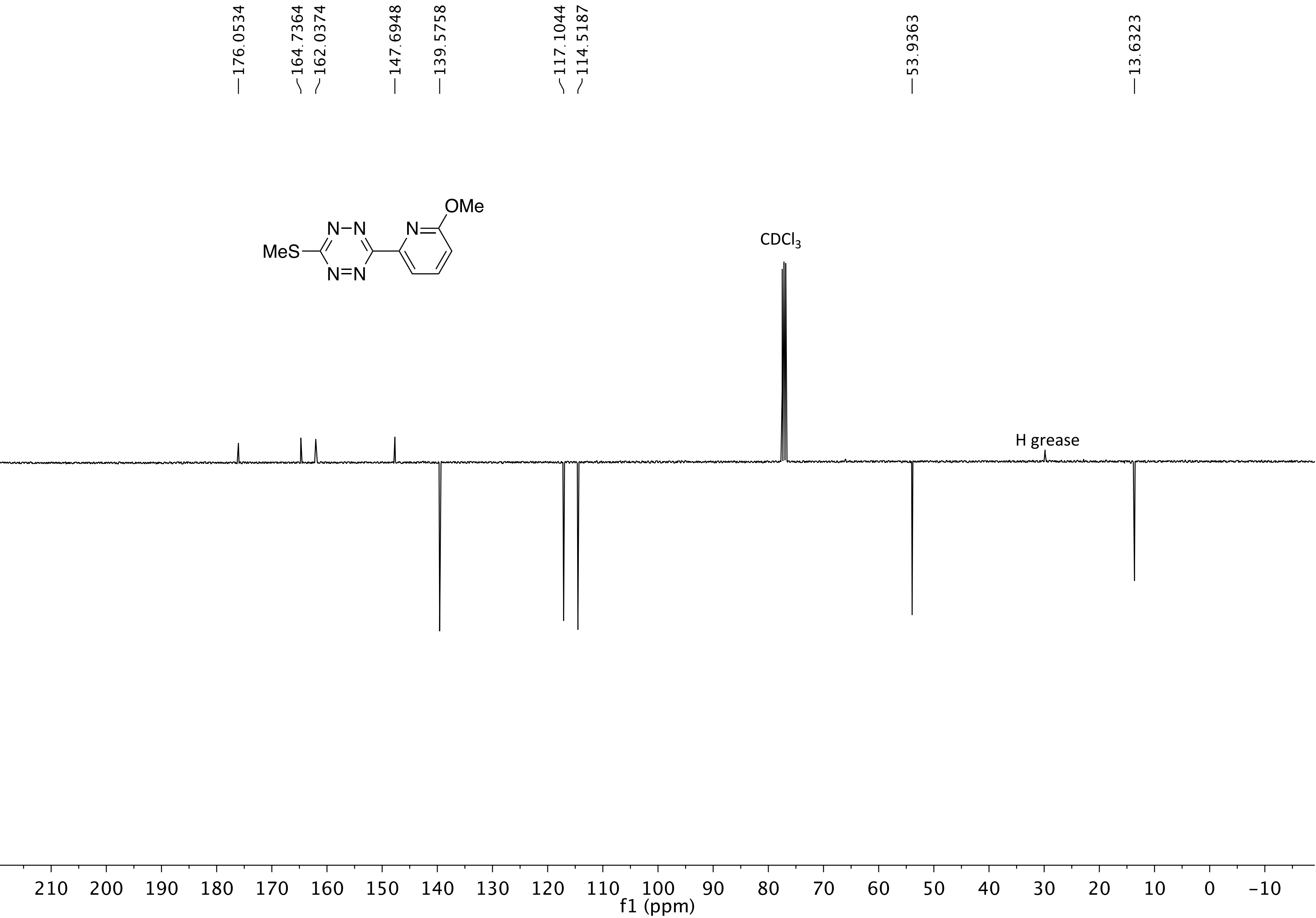
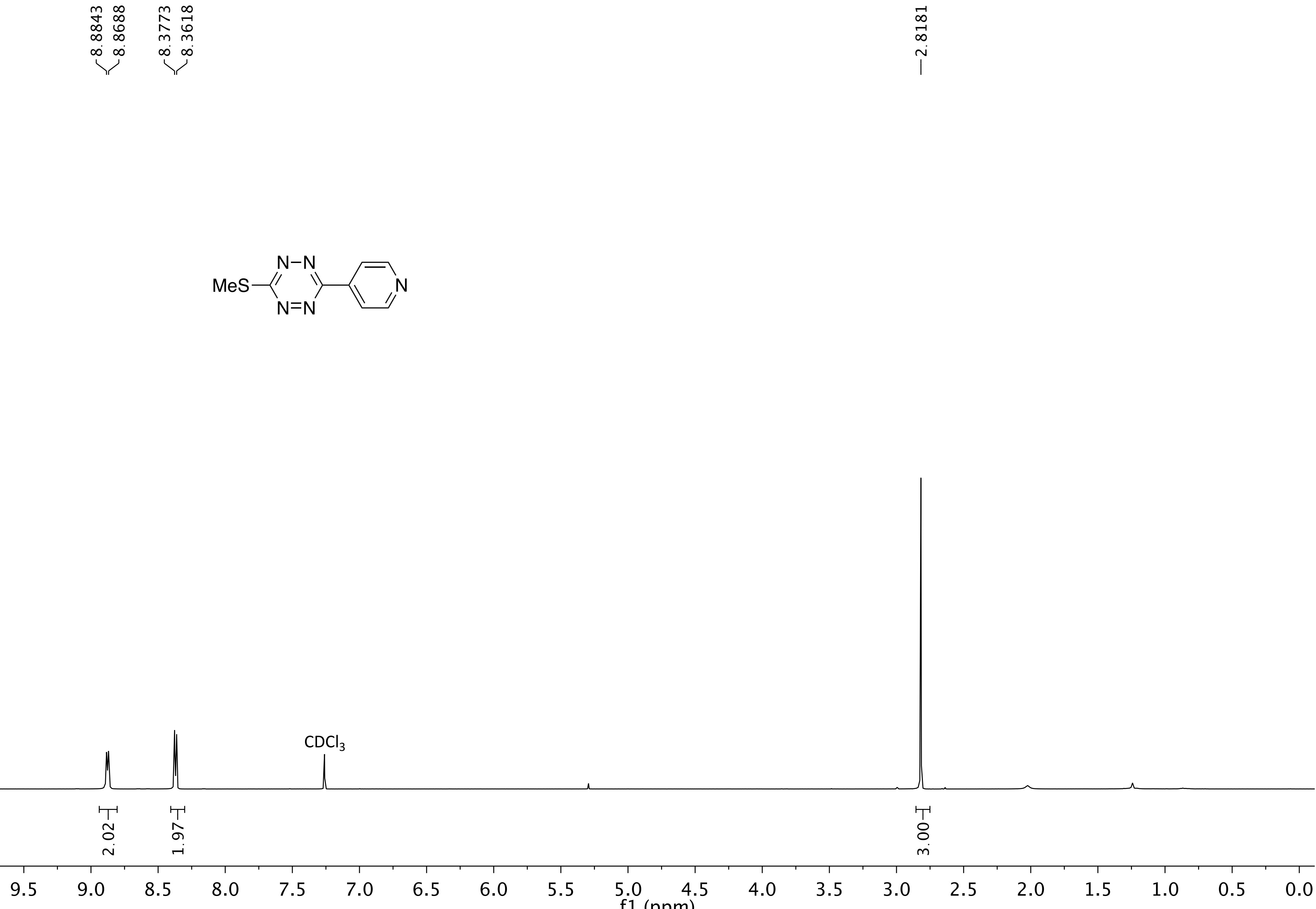
161.1740
135.8666
133.1164
127.9368
118.3204
115.7830
13.6930
CDCl3
MeS
N−N
N=N
CN
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

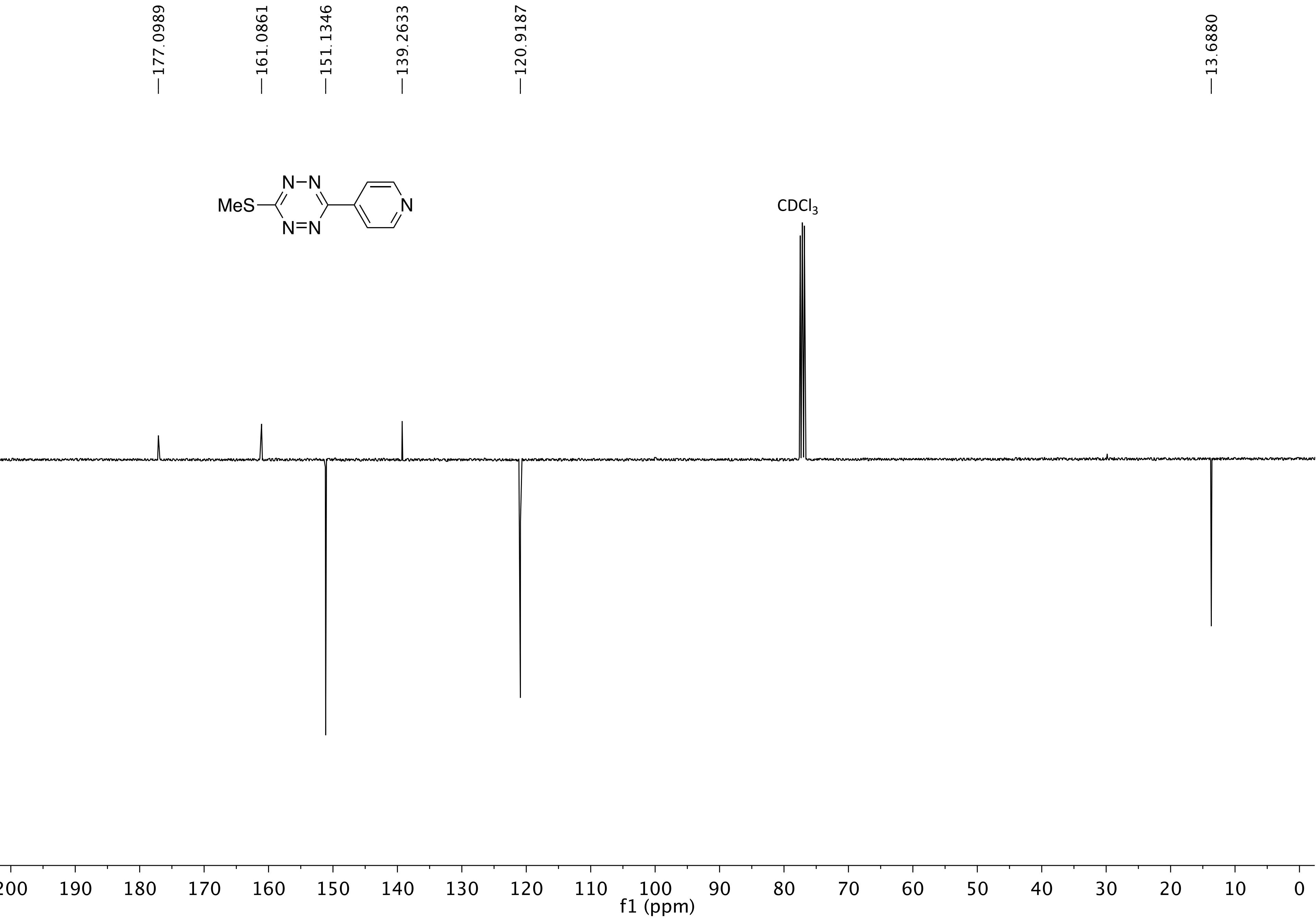


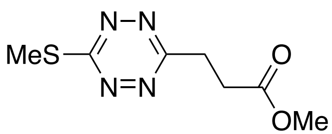
8.1678
8.1659
8.1493
8.1473
7.8213
7.8028
7.8005
7.7821
6.9921
6.9900
6.9714
6.9694
4.0984
2.8133
OMe
N–N
N
MeS
N=N
CDCl3
0.97
0.99
0.97
3.00
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

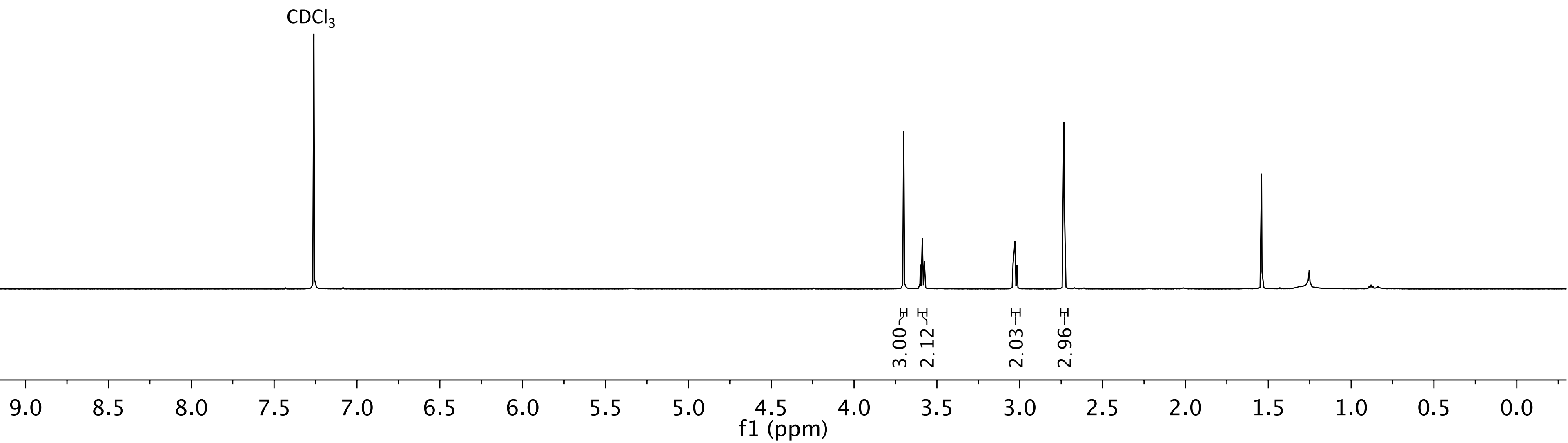

176.0534
164.7364
162.0374
147.6948
139.5758
117.1044
114.5187
53.9363
13.6323
MeS
N
OMe
CDCl3
H grease
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 –10
f1 (ppm)

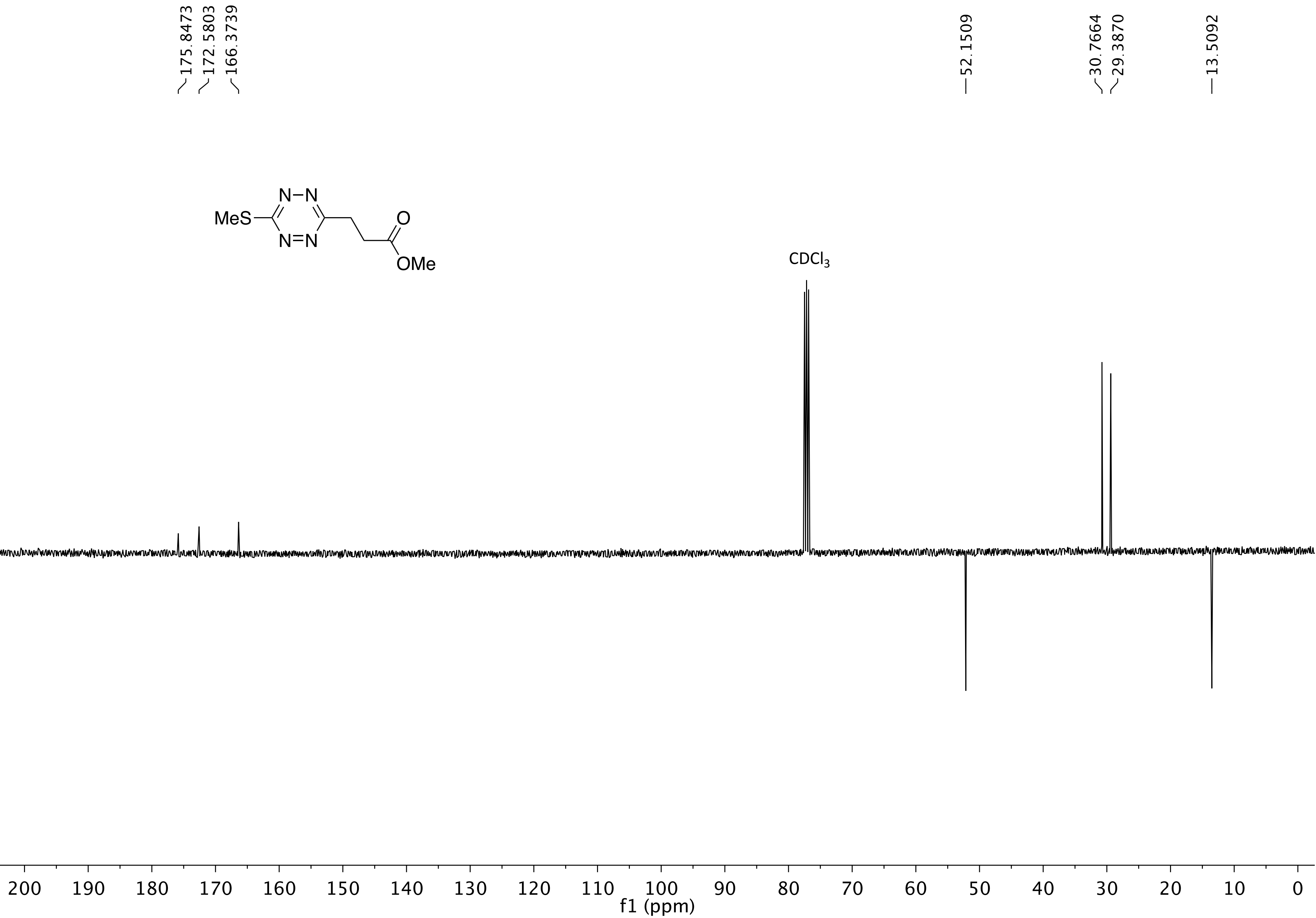


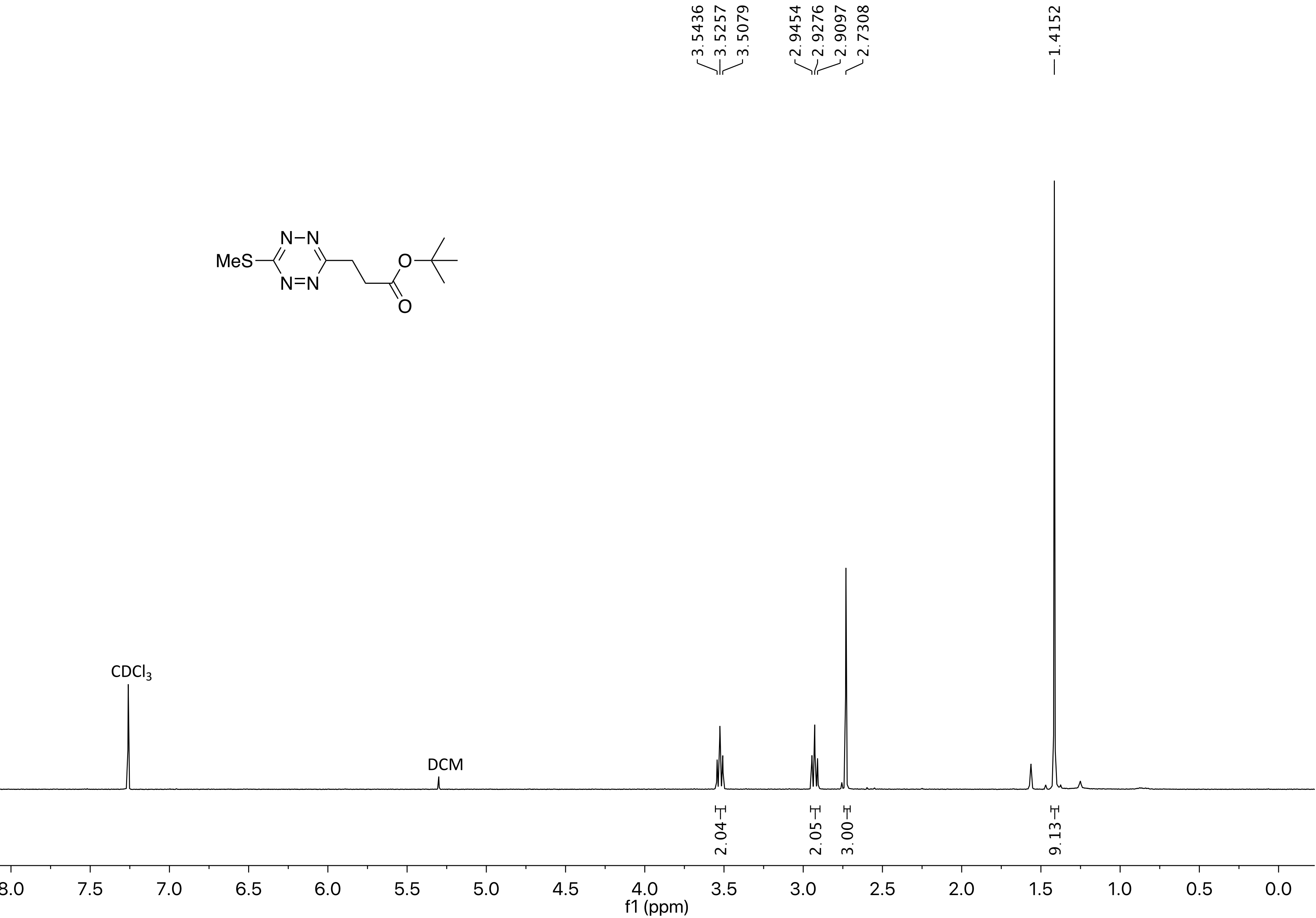
8.8843
8.8688
8.3773
8.3618
2.8181
MeS
N
CDCl3
2.02
1.97
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


177.0989
161.0861
151.1346
139.2633
120.9187
13.6880
MeS
N
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

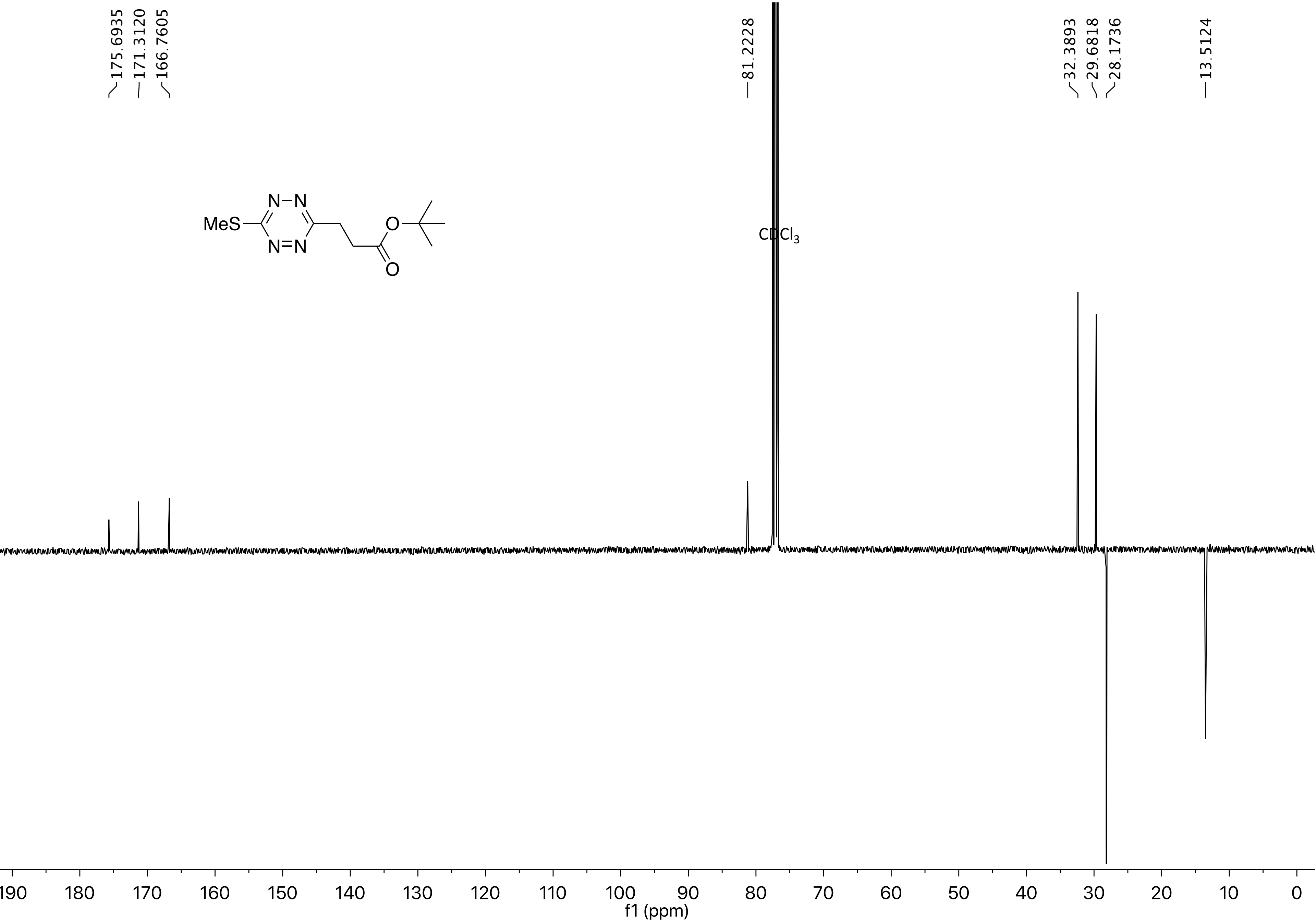

MeS
N
N
N
N
O
OMe

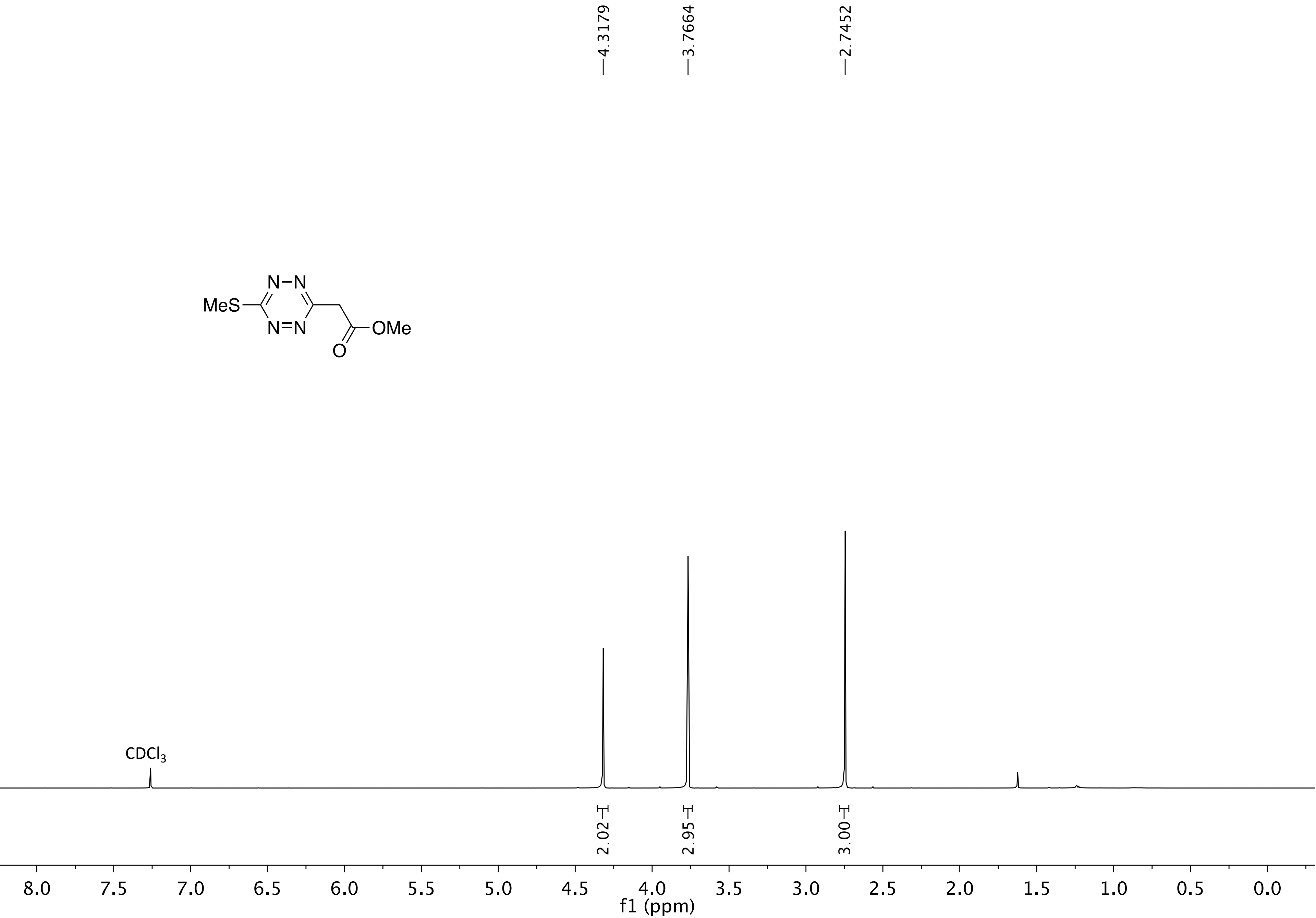

3.7006
3.5998
3.5879
3.5761
3.0406
3.0287
3.0168
2.7336
CDCl3
3.00
2.12
2.03
2.96
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


175.8473
172.5803
166.3739
52.1509
30.7664
29.3870
13.5092
MeS
N–N
N=N
O
OMe
CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

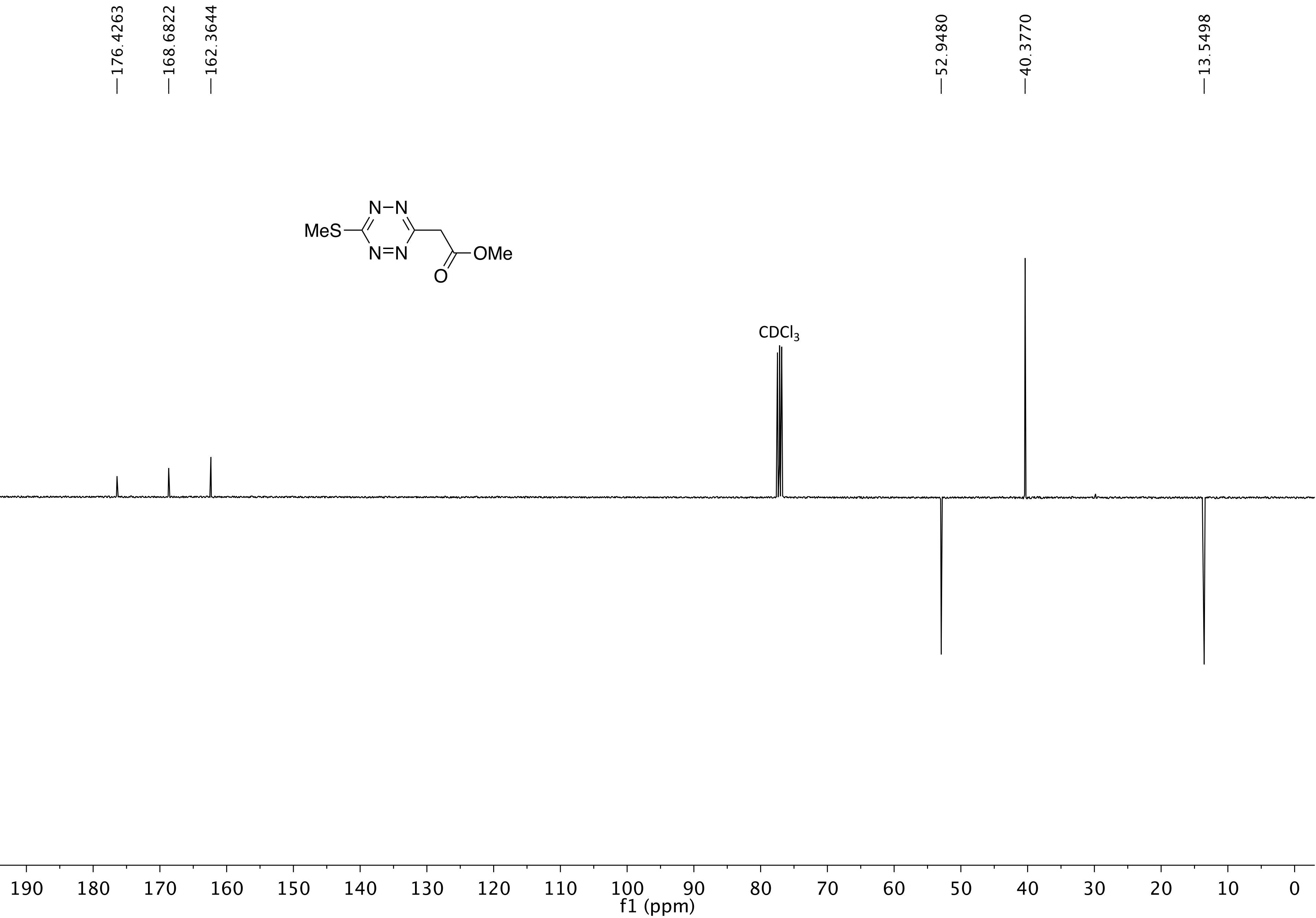


MeS
N−N
N=N
O
O
3.5436
3.5257
3.5079
2.9454
2.9276
2.9097
2.7308
1.4152
CDCl3
DCM
2.04
2.05
3.00
9.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

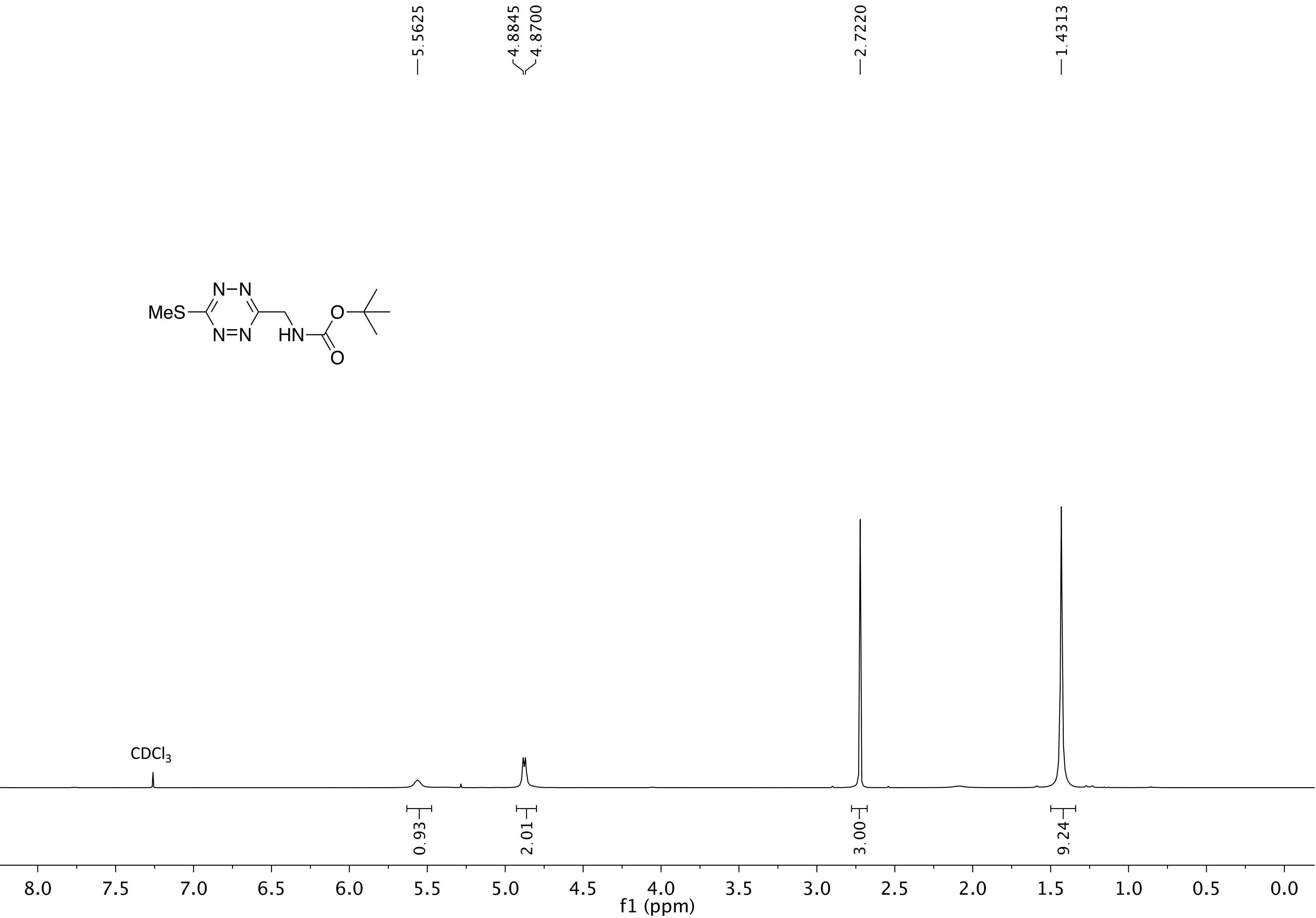

175.6935
171.3120
166.7605
81.2228
32.3893
29.6818
28.1736
13.5124
MeS
N
N
N
N
O
O
CDCl$_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

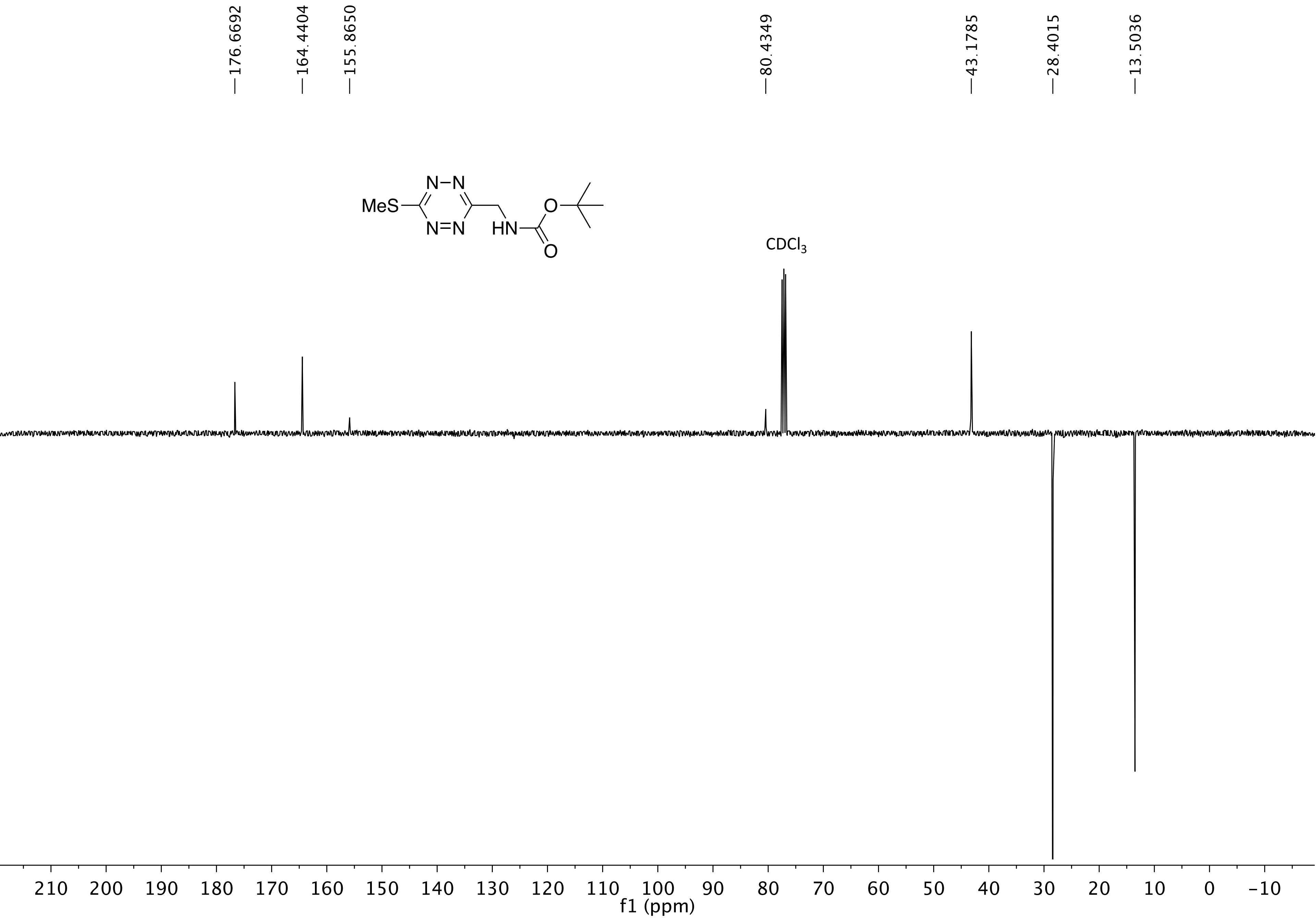


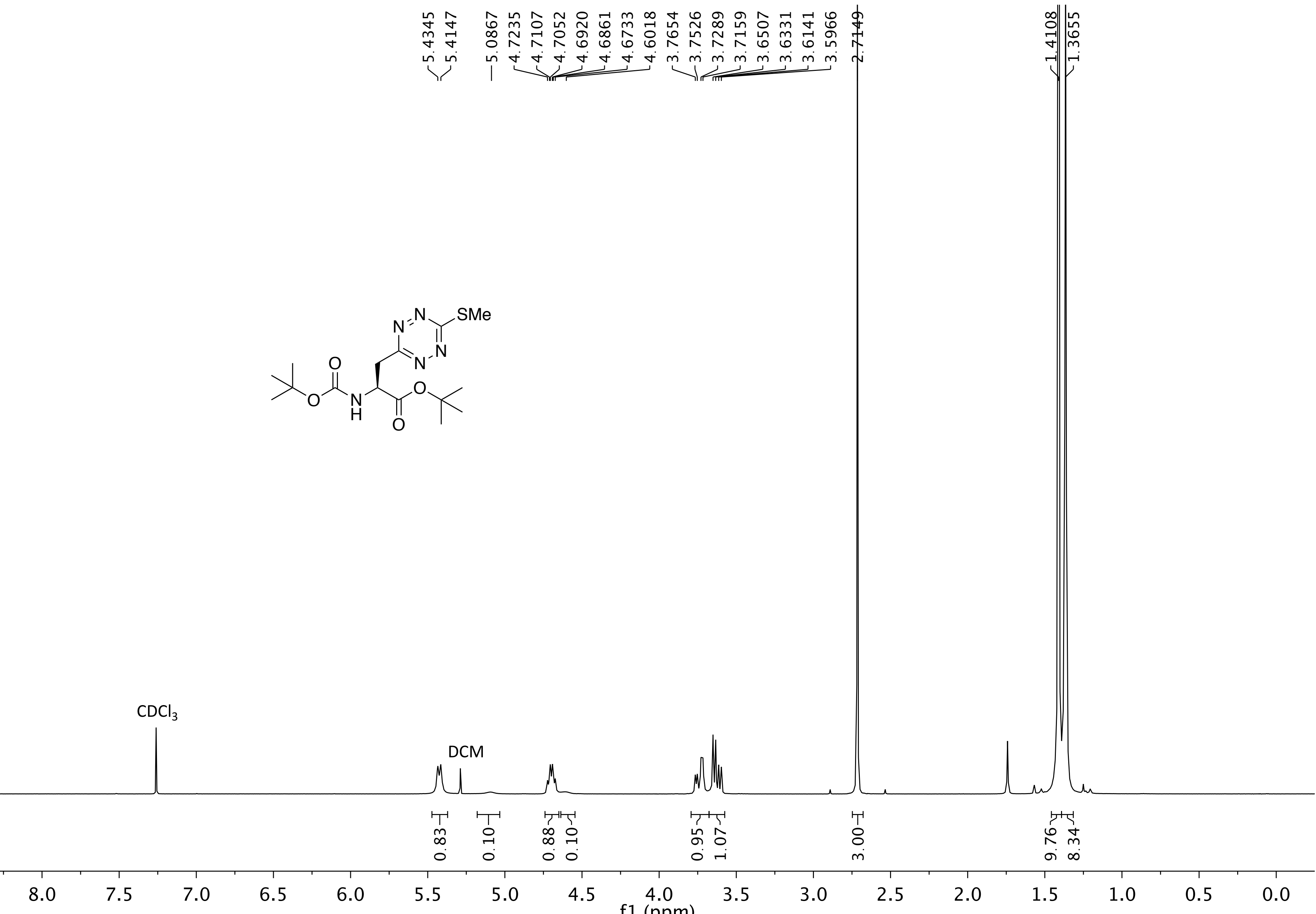
4.3179
3.7664
2.7452
MeS
N
OMe
O
CDCl3
2.02
2.95
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



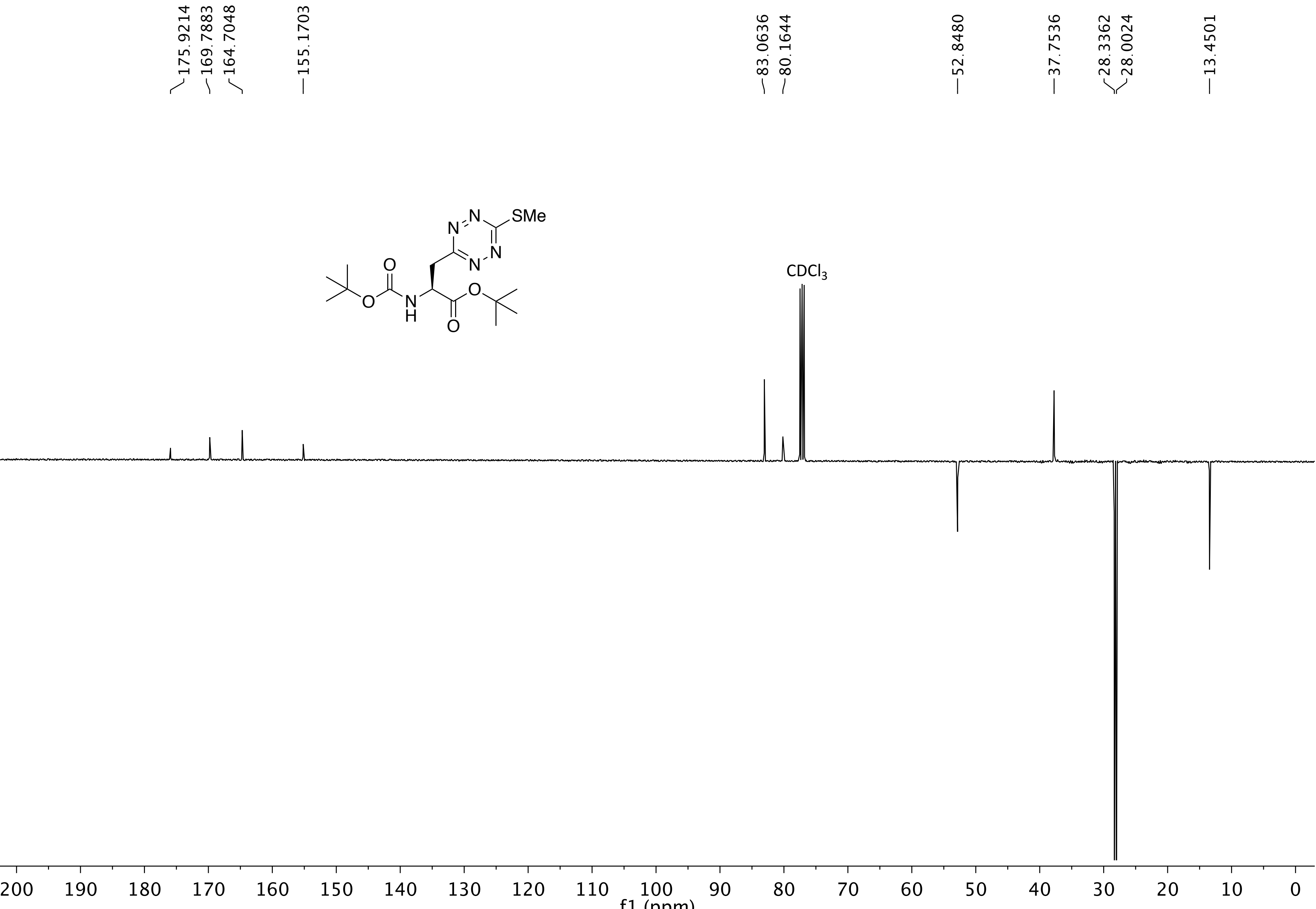
176.4263
168.6822
162.3644
52.9480
40.3770
13.5498
MeS
N
N
N
N
OMe
O
CDCl3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


5.5625
4.8845
4.8700
2.7220
1.4313
MeS
N−N
N=N
HN
O
O
CDCl$_3$
0.93
2.01
3.00
9.24
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

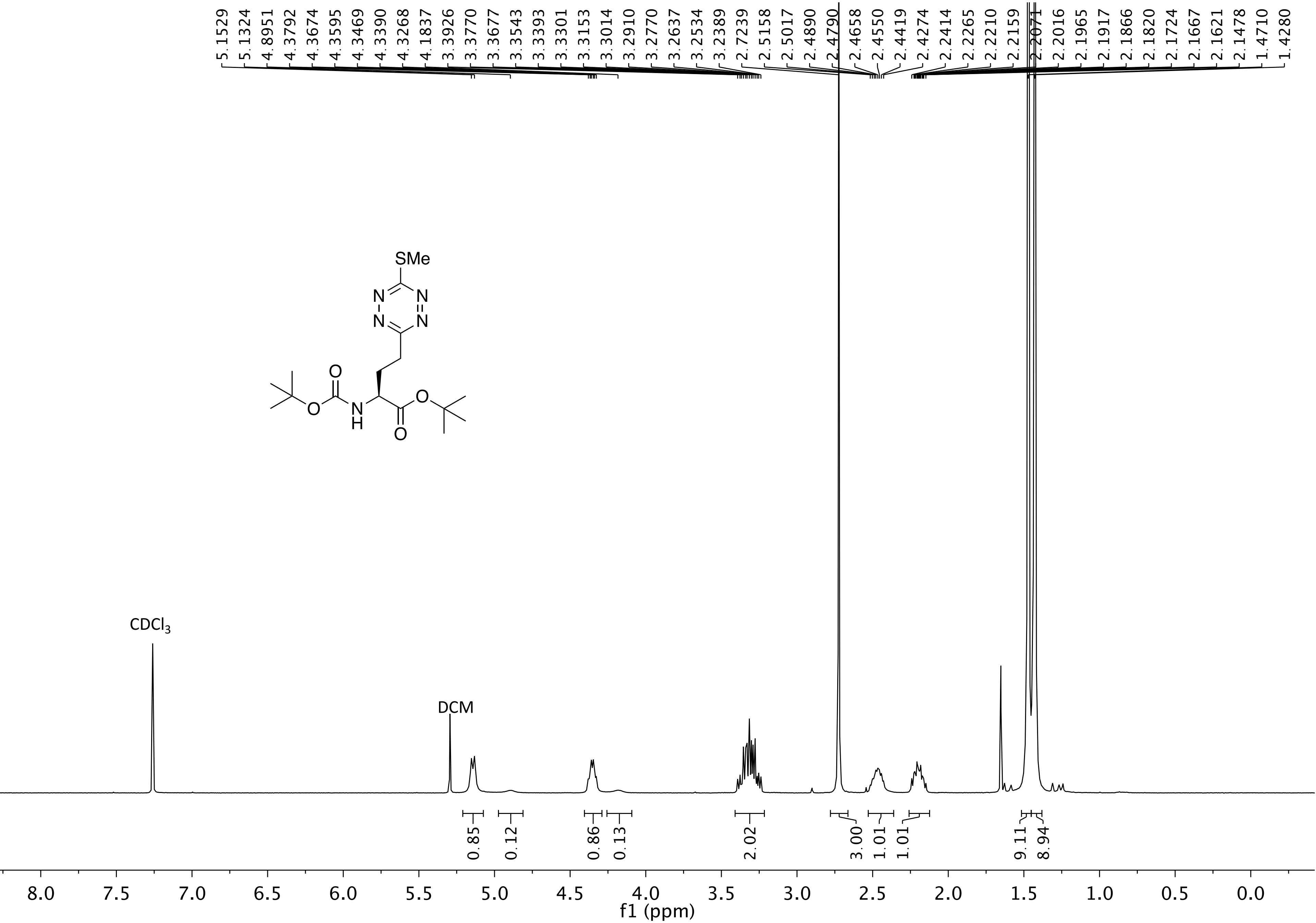

176.6692
164.4404
155.8650
80.4349
43.1785
28.4015
13.5036
MeS
N−N
N=N
HN
O
O
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

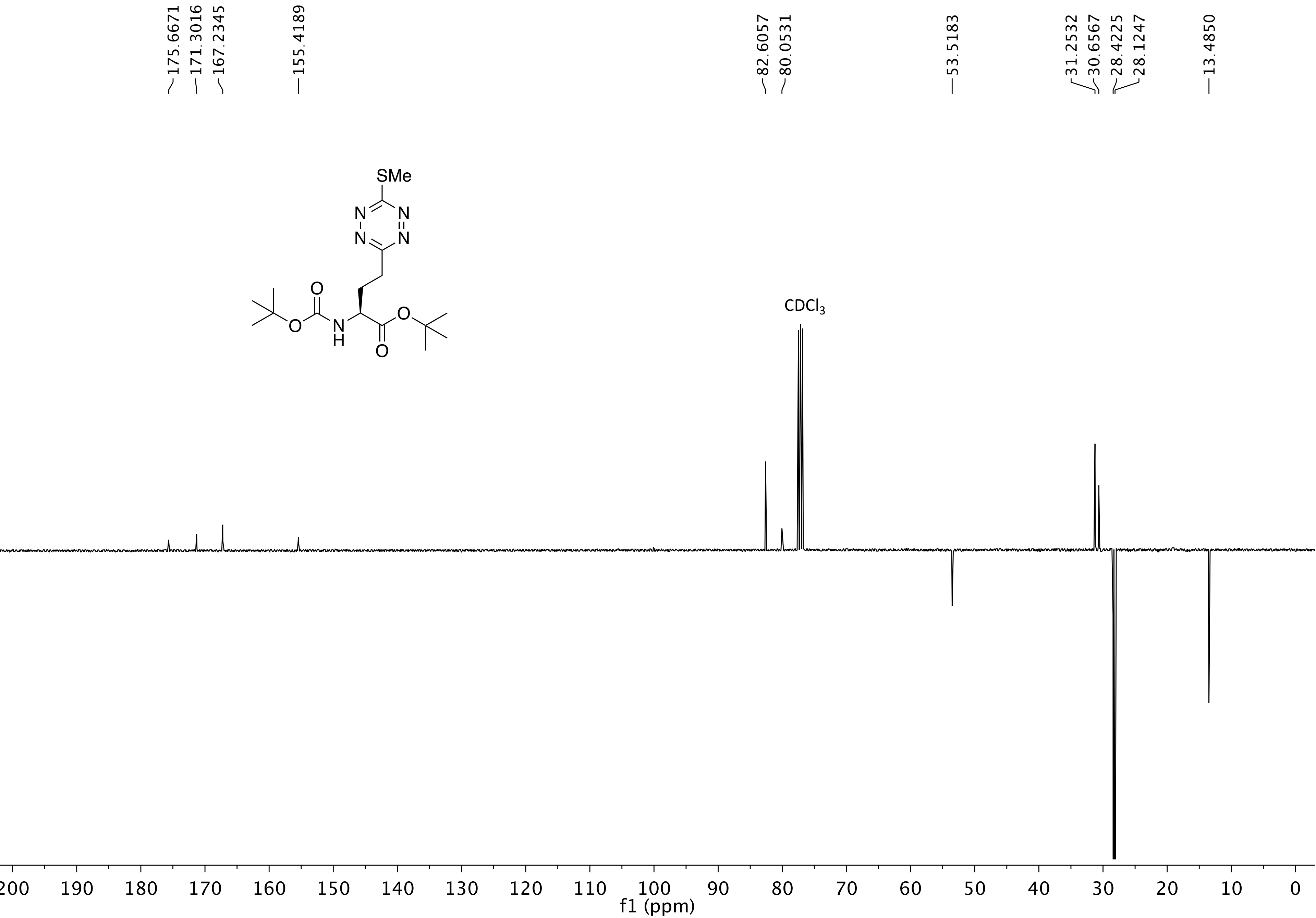


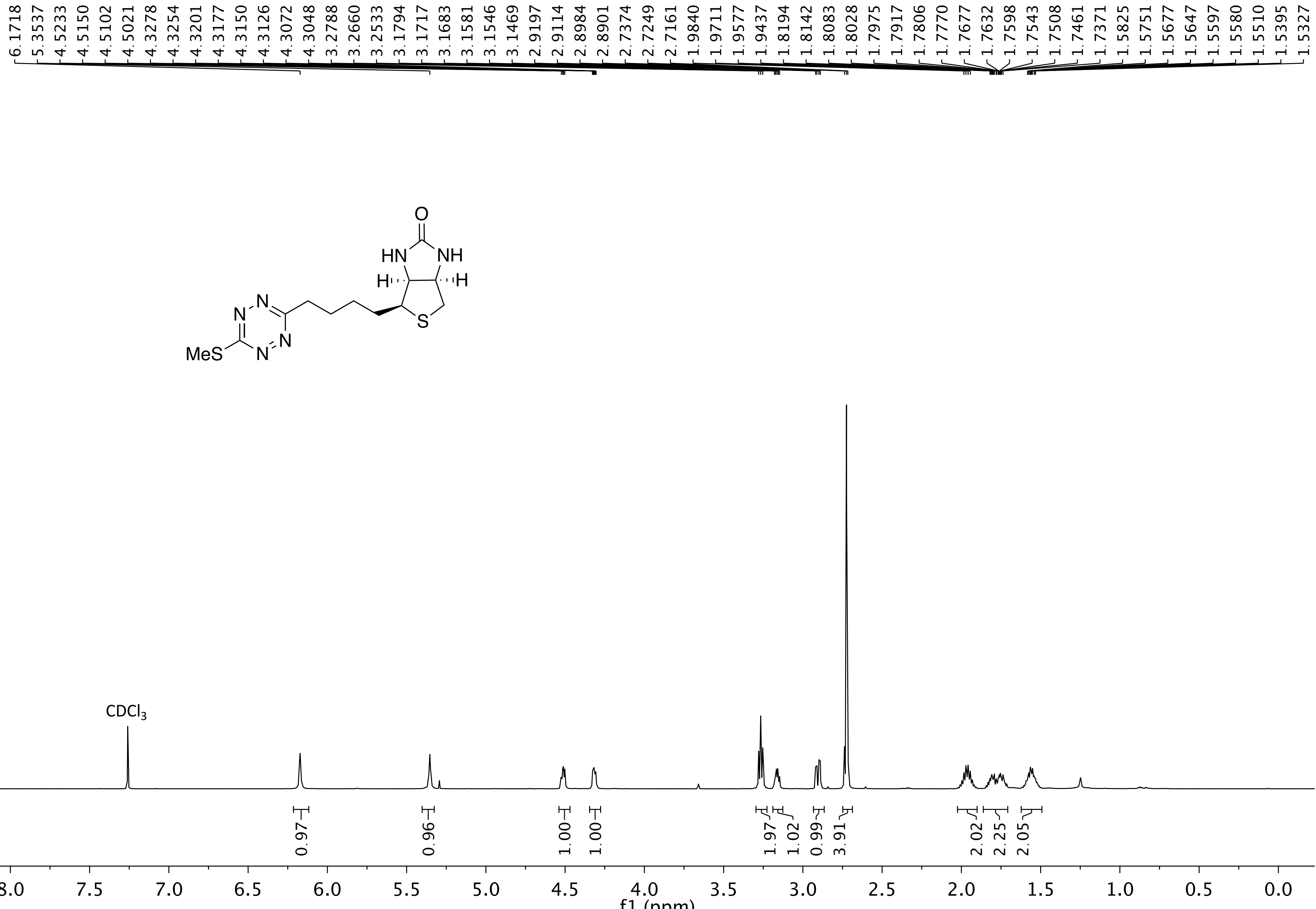
5.4345
5.4147
5.0867
4.7235
4.7107
4.7052
4.6920
4.6861
4.6733
4.6018
3.7654
3.7526
3.7289
3.7159
3.6507
3.6331
3.6141
3.5966
2.7149
1.4108
1.3655
SMe
CDCl3
DCM
0.83
0.10
0.88
0.10
0.95
1.07
3.00
9.76
8.34
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



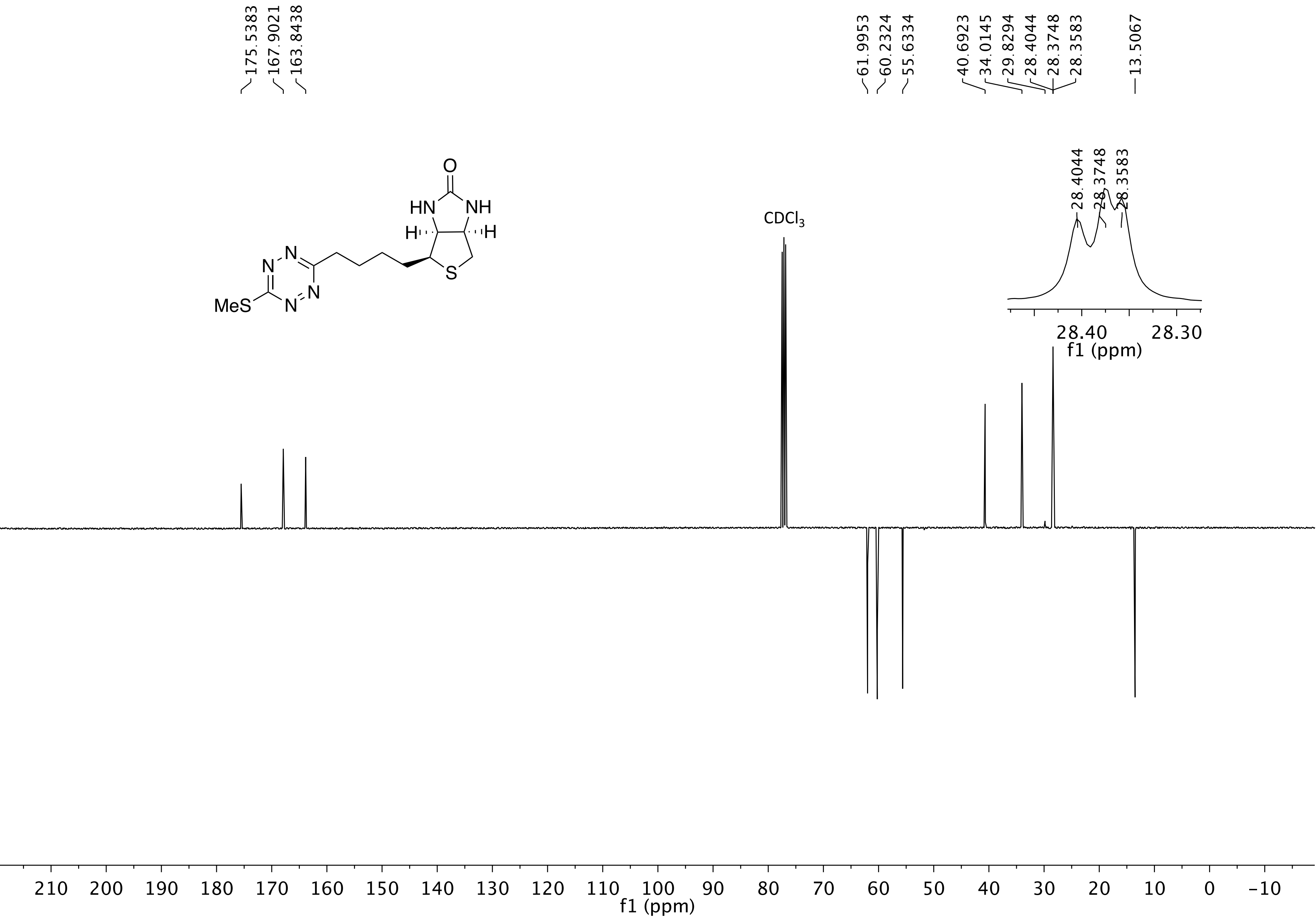
175.9214
169.7883
164.7048
155.1703
83.0636
80.1644
52.8480
37.7536
28.3362
28.0024
13.4501
SMe
N
O
N
H
O
O
O
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


5.1529
5.1324
4.8951
4.3792
4.3674
4.3595
4.3469
4.3390
4.3268
4.1837
3.3926
3.3770
3.3677
3.3543
3.3393
3.3301
3.3153
3.3014
3.2910
3.2770
3.2637
3.2534
3.2389
2.7239
2.5158
2.5017
2.4890
2.4790
2.4658
2.4550
2.4419
2.4274
2.2414
2.2265
2.2210
2.2159
2.2071
2.2016
2.1965
2.1917
2.1866
2.1820
2.1724
2.1667
2.1621
2.1478
1.4710
1.4280
SMe
N
N
N
N
O
O
N
H
O
O
CDCl3
DCM
0.85
0.12
0.86
0.13
2.02
3.00
1.01
1.01
9.11
8.94
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


175.6671
171.3016
167.2345
155.4189
82.6057
80.0531
53.5183
31.2532
30.6567
28.4225
28.1247
13.4850
SMe
N
N
N
N
O
O
N
H
O
O
CDCl$_3$
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



6.1718 5.3537 4.5233 4.5150 4.5102 4.5021 4.3278 4.3254 4.3201 4.3177 4.3150 4.3126 4.3072 4.3048 3.2788 3.2660 3.2533 3.1794 3.1717 3.1683 3.1581 3.1546 3.1469 2.9197 2.9114 2.8984 2.8901 2.7374 2.7249 2.7161 1.9840 1.9711 1.9577 1.9437 1.8194 1.8142 1.8083 1.8028 1.7975 1.7917 1.7806 1.7770 1.7677 1.7632 1.7598 1.7543 1.7508 1.7461 1.7371 1.5825 1.5751 1.5677 1.5647 1.5597 1.5580 1.5510 1.5395 1.5327
O
HN
NH
H
H
S
N
N
N
N
MeS
CDCl3
0.97
0.96
1.00
1.00
1.97
1.02
0.99
3.91
2.02
2.25
2.05
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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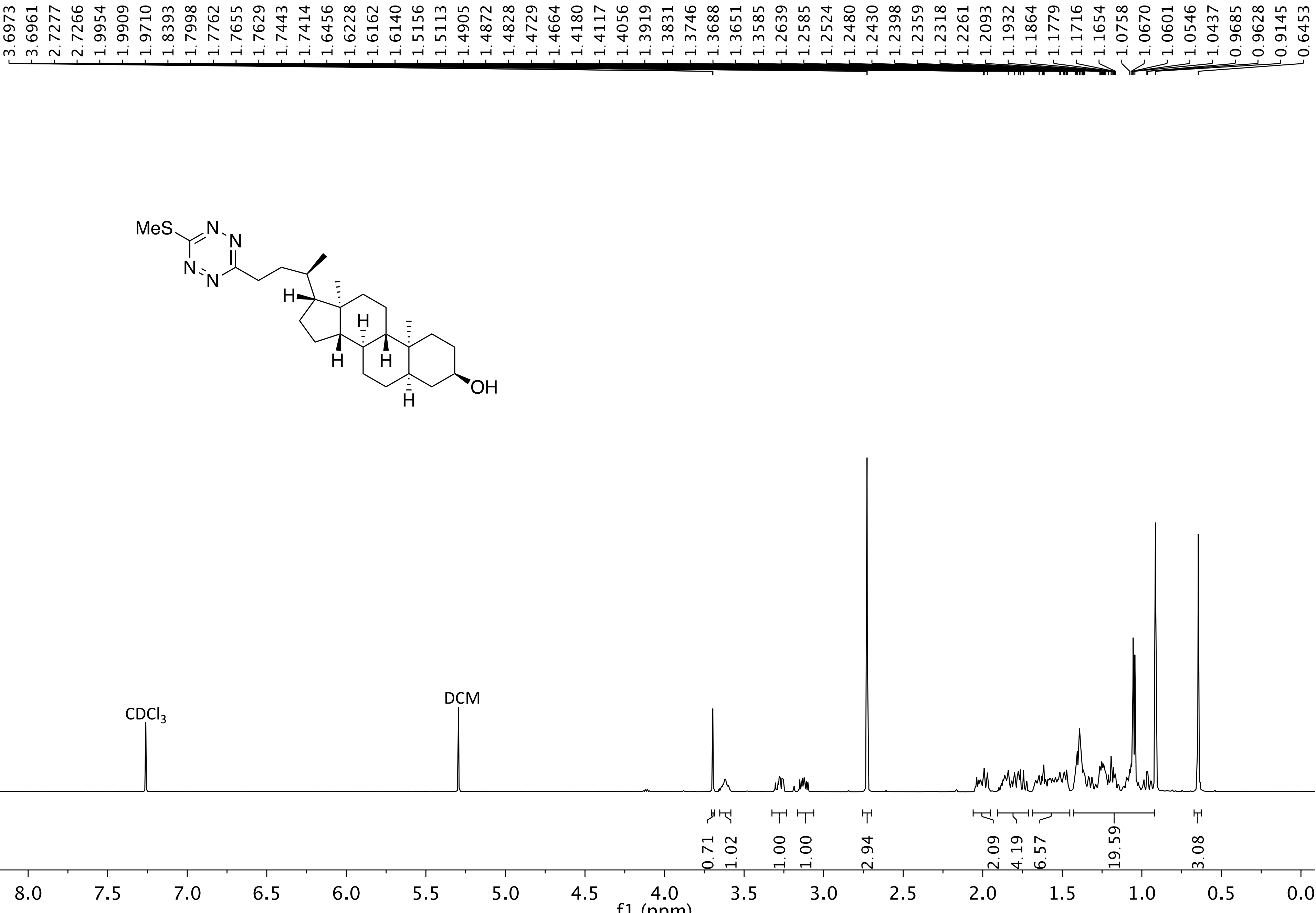
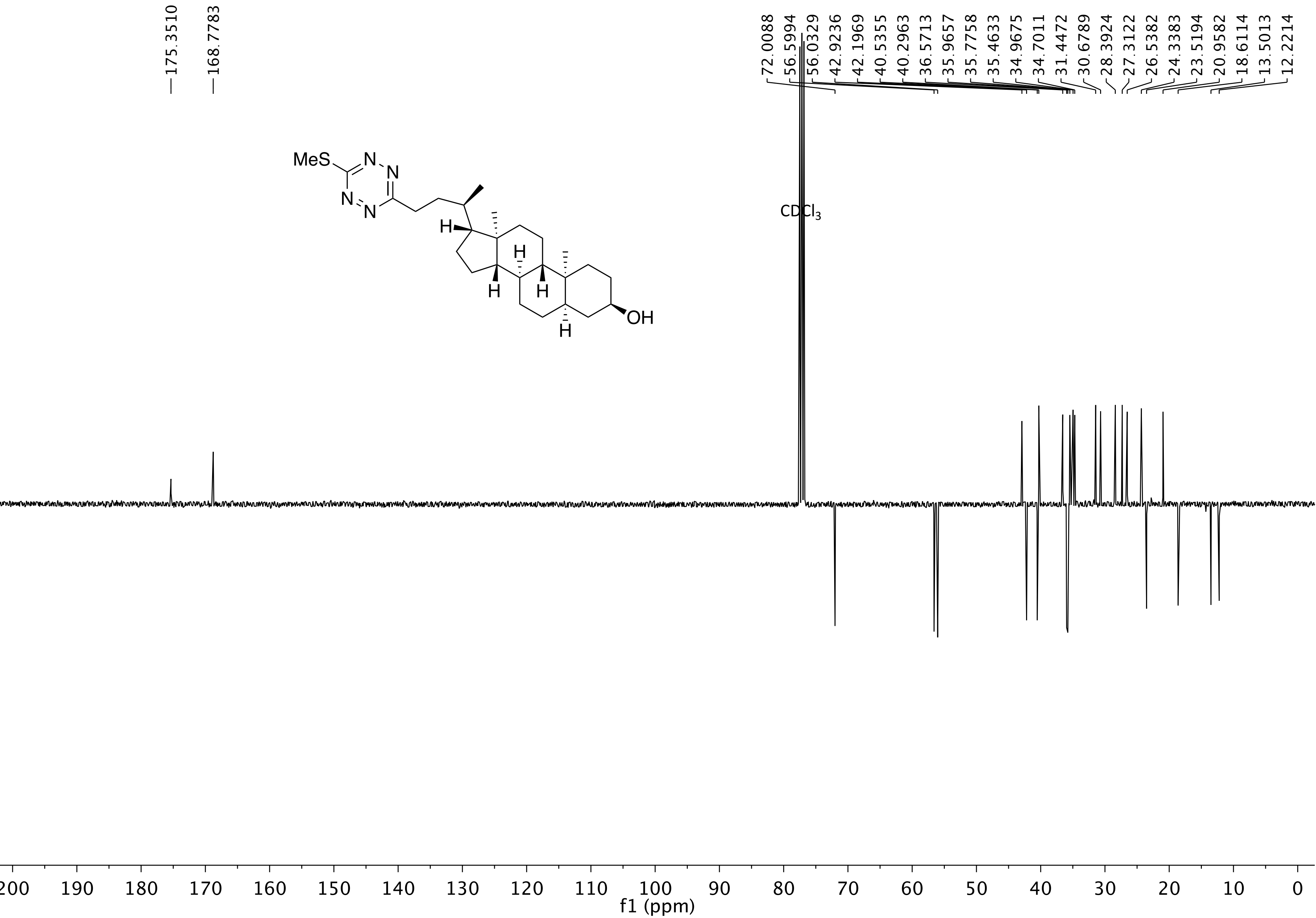
163.8438
61.9953
60.2324
55.6334
40.6923
34.0145
29.8294
28.4044
28.3748
28.3583
13.5067
CDCl3
MeS
28.40
28.30
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


3.6973
3.6961
2.7277
2.7266
1.9954
1.9909
1.9710
1.8393
1.7998
1.7762
1.7655
1.7629
1.7443
1.7414
1.6456
1.6228
1.6162
1.6140
1.5156
1.5113
1.4905
1.4872
1.4828
1.4729
1.4664
1.4180
1.4117
1.4056
1.3919
1.3831
1.3746
1.3688
1.3651
1.3585
1.2639
1.2585
1.2524
1.2480
1.2430
1.2398
1.2359
1.2318
1.2261
1.2093
1.1932
1.1864
1.1779
1.1716
1.1654
1.0758
1.0670
1.0601
1.0546
1.0437
0.9685
0.9628
0.9145
0.6453
MeS
N
N
N
N
H
H
H
H
H
OH
CDCl3
DCM
0.71
1.02
1.00
1.00
2.94
2.09
4.19
6.57
19.59
3.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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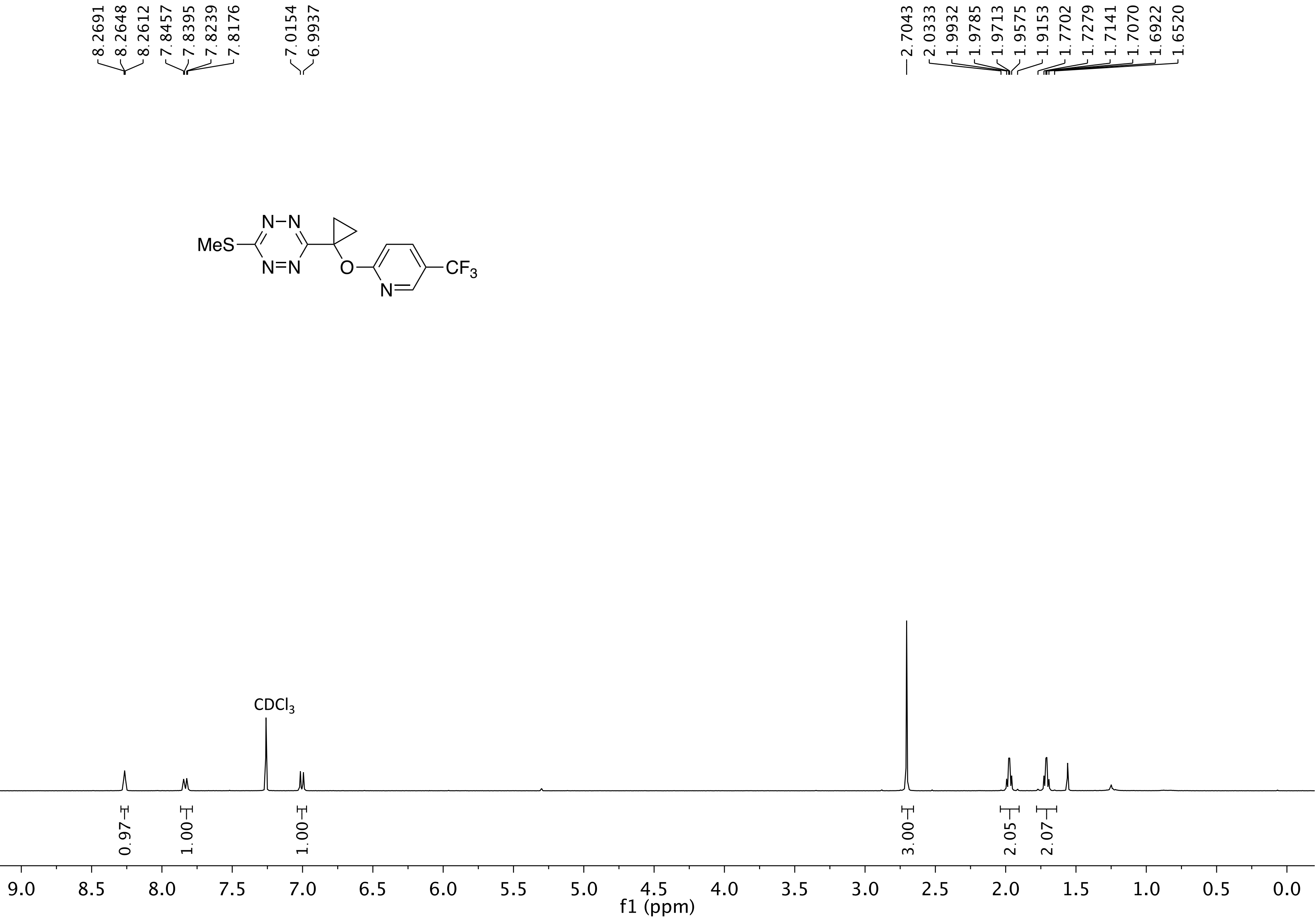
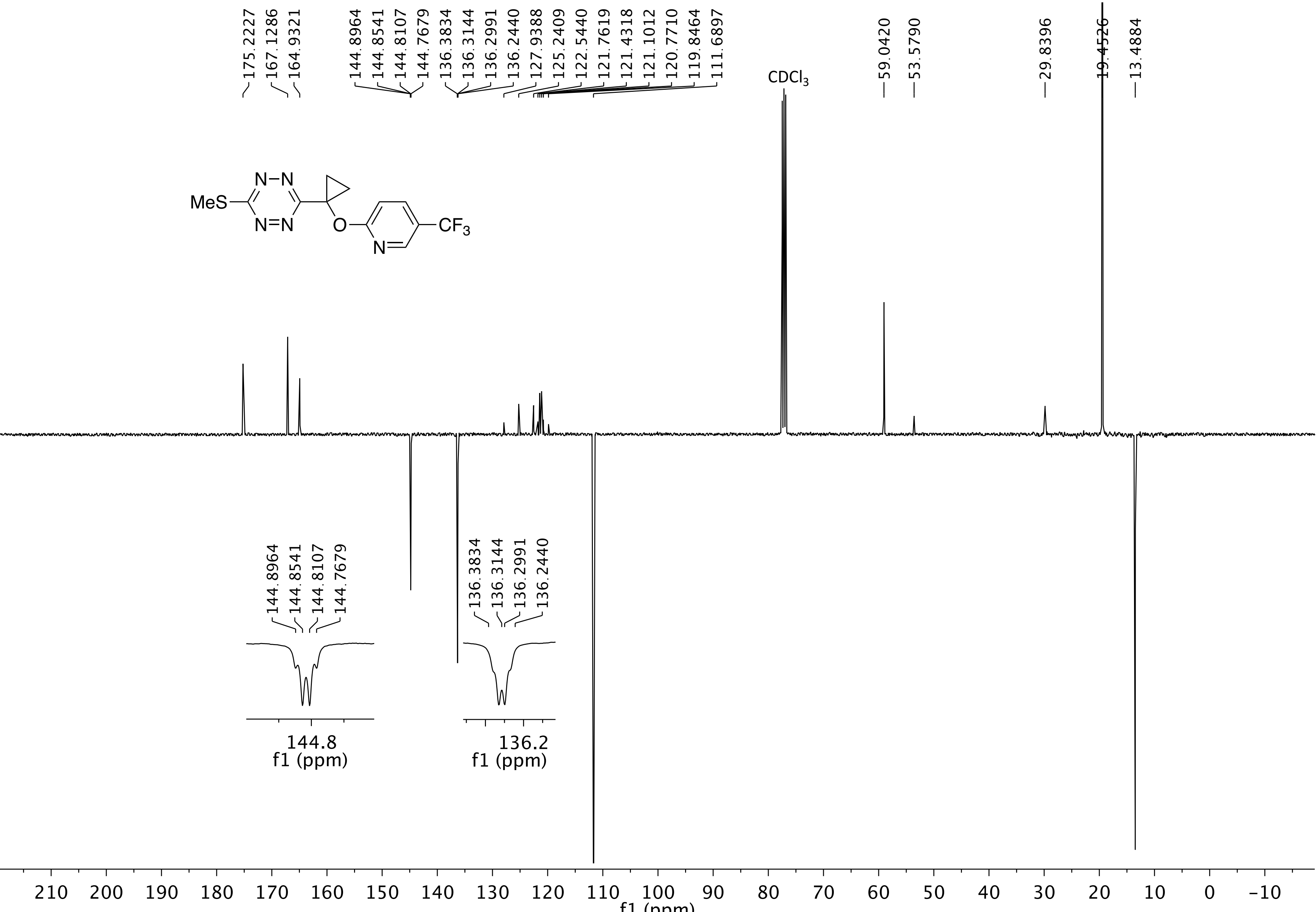
72.0088
56.5994
56.0329
42.9236
42.1969
40.5355
40.2963
36.5713
35.9657
35.7758
35.4633
34.9675
34.7011
31.4472
30.6789
28.3924
27.3122
26.5382
24.3383
23.5194
20.9582
18.6114
13.5013
12.2214
MeS
N
N
N
N
H
H
H
H
H
OH
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



8.2691
8.2648
8.2612
7.8457
7.8395
7.8239
7.8176
7.0154
6.9937
2.7043
2.0333
1.9932
1.9785
1.9713
1.9575
1.9153
1.7702
1.7279
1.7141
1.7070
1.6922
1.6520
MeS
N
O
CF3
CDCl3
0.97
1.00
1.00
3.00
2.05
2.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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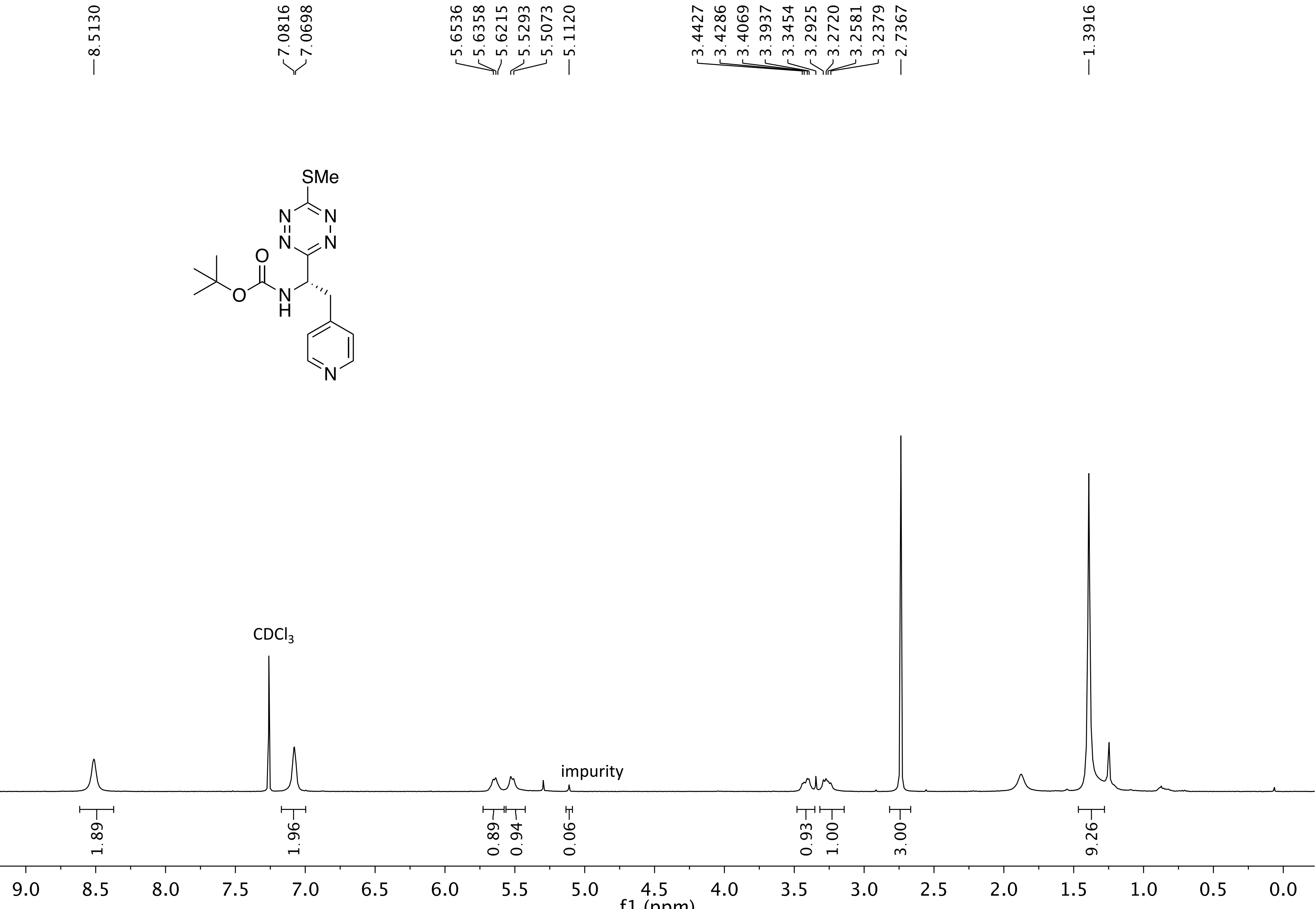
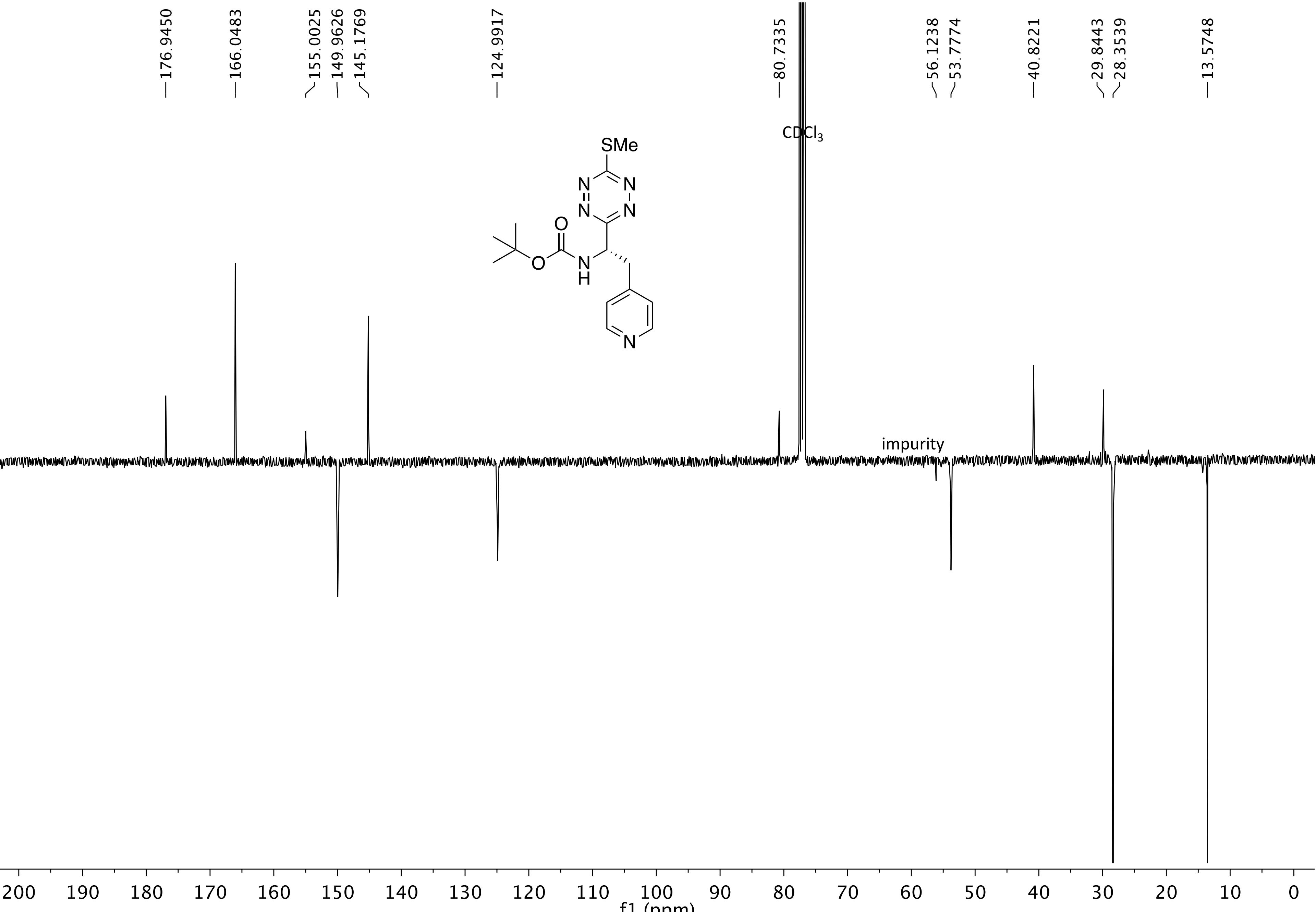
164.9321
144.8964
144.8541
144.8107
144.7679
136.3834
136.3144
136.2991
136.2440
127.9388
125.2409
122.5440
121.7619
121.4318
121.1012
120.7710
119.8464
111.6897
CDCl$_3$
59.0420
53.5790
29.8396
19.4526
13.4884
MeS
N
O
CF$_3$
144.8
f1 (ppm)
136.2
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 –10
f1 (ppm)



8.5130
7.0816
7.0698
5.6536
5.6358
5.6215
5.5293
5.5073
5.1120
3.4427
3.4286
3.4069
3.3937
3.3454
3.2925
3.2720
3.2581
3.2379
2.7367
1.3916
SMe
O
N
H
CDCl3
impurity
1.89
1.96
0.89
0.94
0.06
0.93
1.00
3.00
9.26
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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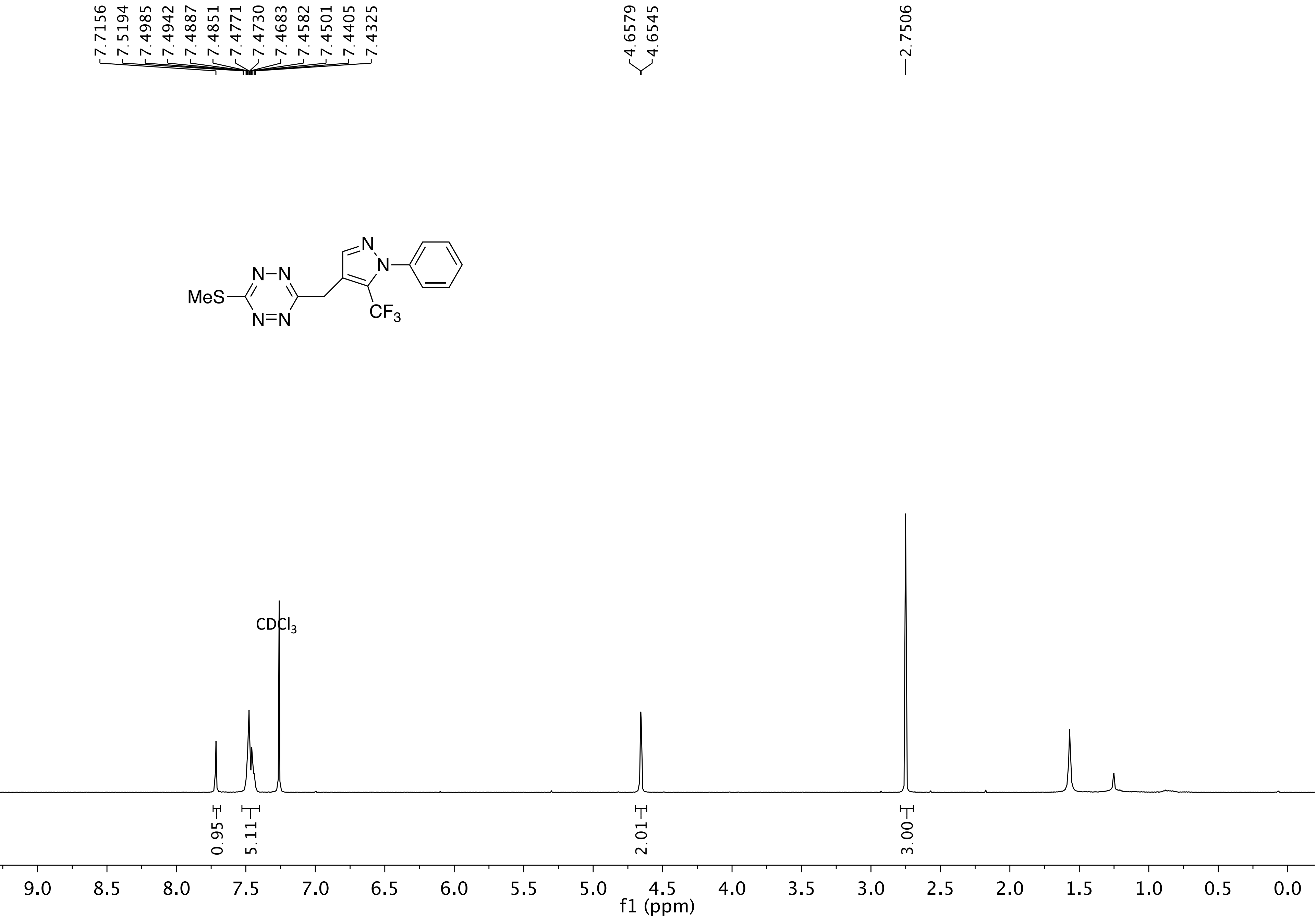
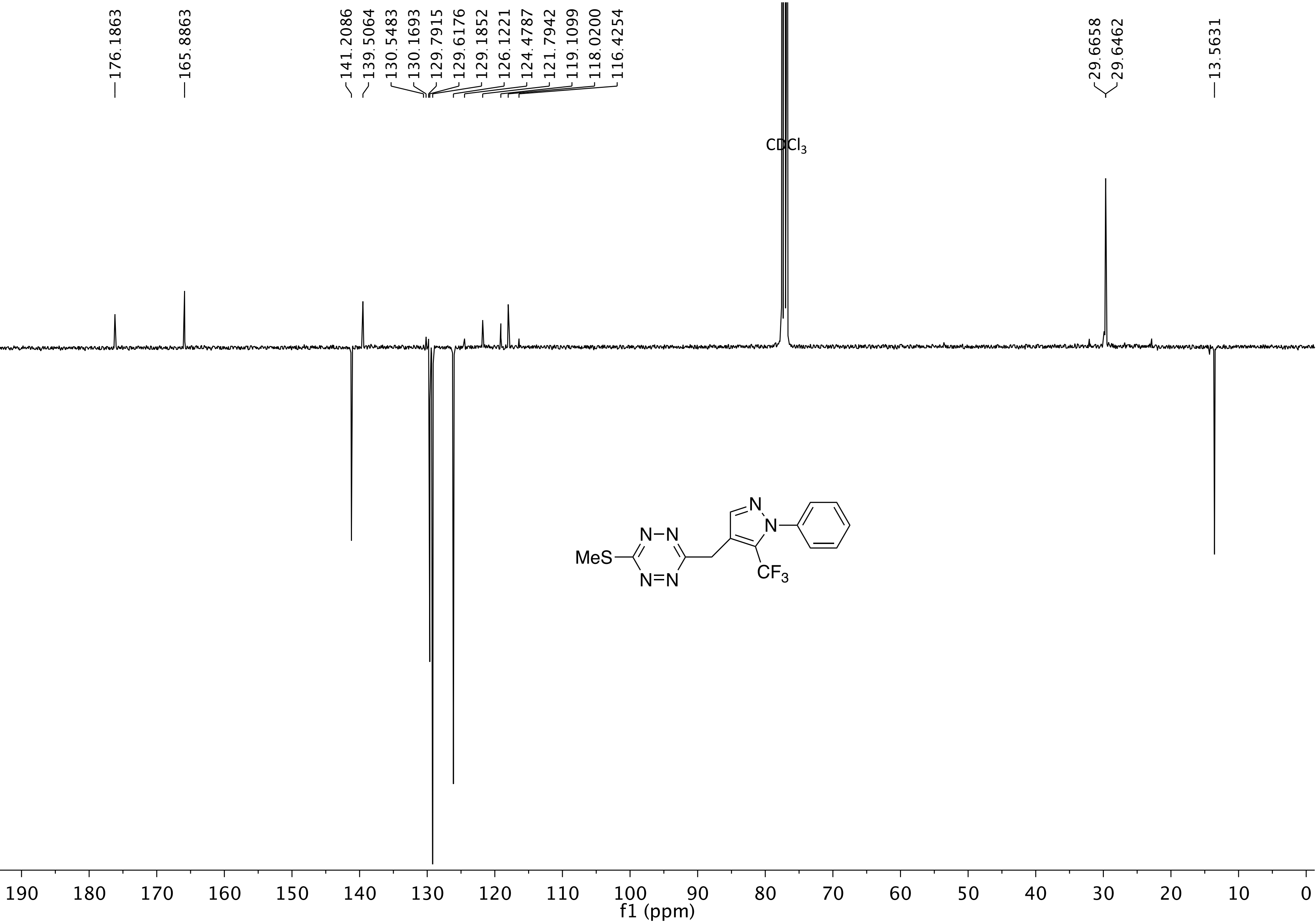
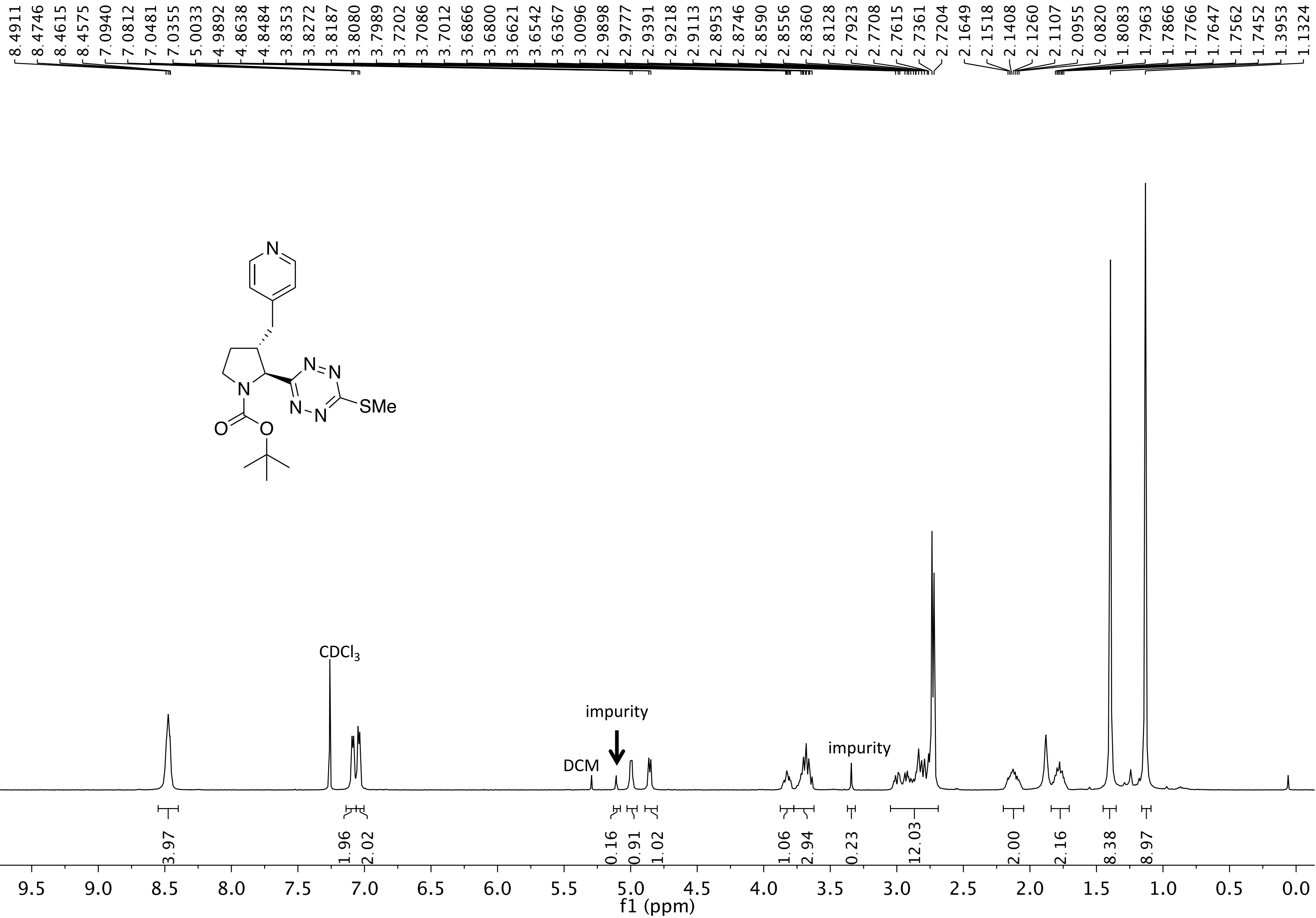
166.0483
155.0025
149.9626
145.1769
124.9917
80.7335
56.1238
53.7774
40.8221
29.8443
28.3539
13.5748
CDCl3
SMe
N
N
N
N
O
O
N
H
N
impurity
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

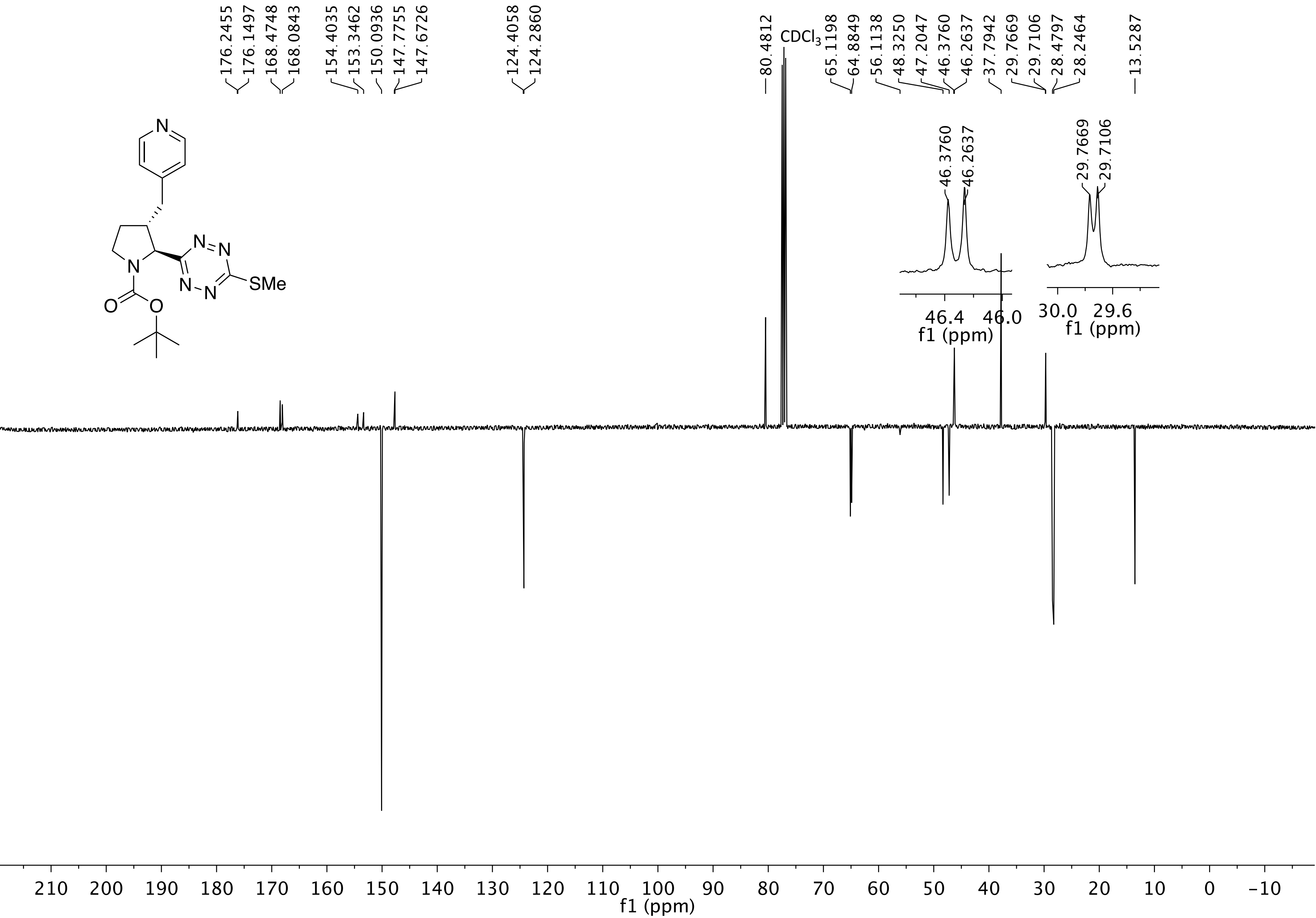

MeS
N
CF3
7.7156
7.5194
7.4985
7.4942
7.4887
7.4851
7.4771
7.4730
7.4683
7.4582
7.4501
7.4405
7.4325
4.6579
4.6545
2.7506
CDCl3
0.95
5.11
2.01
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

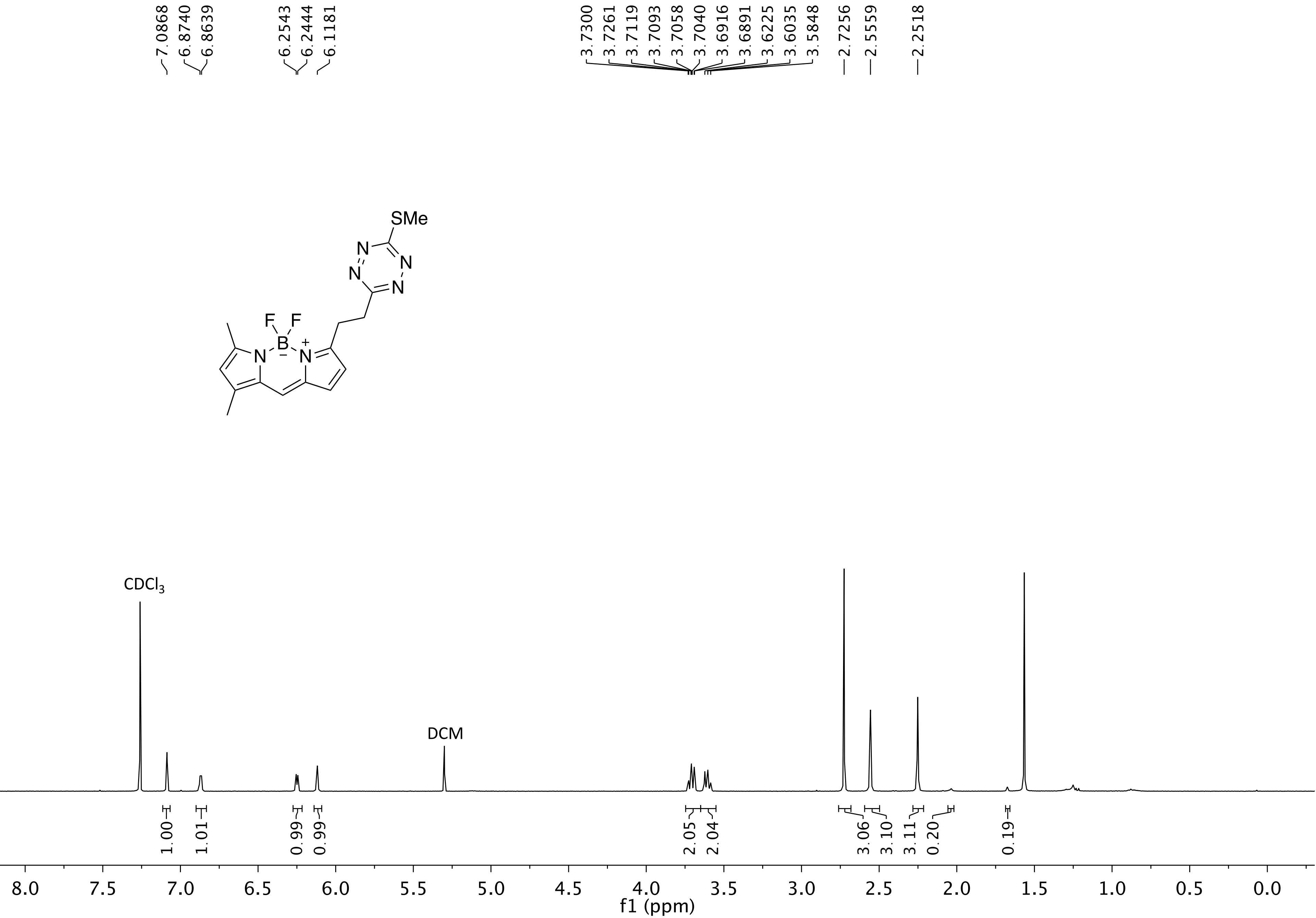


176.1863
165.8863
141.2086
139.5064
130.5483
130.1693
129.7915
129.6176
129.1852
126.1221
124.4787
121.7942
119.1099
118.0200
116.4254
29.6658
29.6462
13.5631
CDCl$_3$
MeS
N
N
N
N
N
N
CF$_3$
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



8.4911
8.4746
8.4615
8.4575
7.0940
7.0812
7.0481
7.0355
5.0033
4.9892
4.8638
4.8484
3.8353
3.8272
3.8187
3.8080
3.7989
3.7202
3.7086
3.7012
3.6866
3.6800
3.6621
3.6542
3.6367
3.0096
2.9898
2.9777
2.9391
2.9218
2.9113
2.8953
2.8746
2.8590
2.8556
2.8360
2.8128
2.7923
2.7708
2.7615
2.7361
2.7204
2.1649
2.1518
2.1408
2.1260
2.1107
2.0955
2.0820
1.8083
1.7963
1.7866
1.7766
1.7647
1.7562
1.7452
1.3953
1.1324
N
N
N
N
N
N
SMe
O
O
CDCl3
impurity
DCM
impurity
3.97
1.96
2.02
0.16
0.91
1.02
1.06
2.94
0.23
12.03
2.00
2.16
8.38
8.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


176.2455
176.1497
168.4748
168.0843
154.4035
153.3462
150.0936
147.7755
147.6726
124.4058
124.2860
80.4812
CDCl$_3$
65.1198
64.8849
56.1138
48.3250
47.2047
46.3760
46.2637
37.7942
29.7669
29.7106
28.4797
28.2464
13.5287
46.3760
46.2637
46.4
46.0
f1 (ppm)
29.7669
29.7106
30.0
29.6
f1 (ppm)
N
N
N
N
N
N
SMe
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)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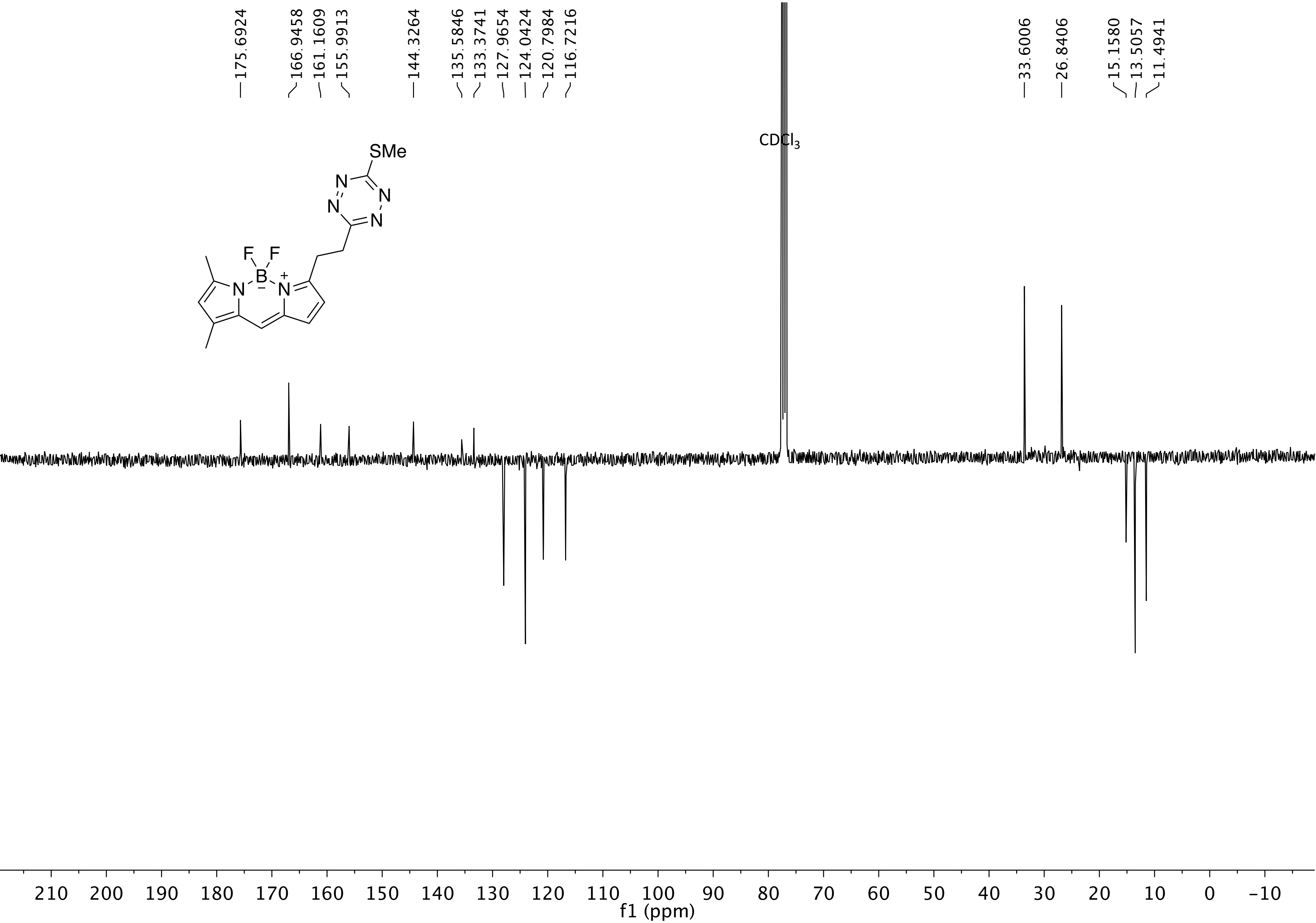
6.8740
6.8639
6.2543
6.2444
6.1181
3.7300
3.7261
3.7119
3.7093
3.7058
3.7040
3.6916
3.6891
3.6225
3.6035
3.5848
2.7256
2.5559
2.2518
SMe
N
N
N
N
F
F
B
N
N
+
−
CDCl3
DCM
1.00
1.01
0.99
0.99
2.05
2.04
3.06
3.10
3.11
0.20
0.19
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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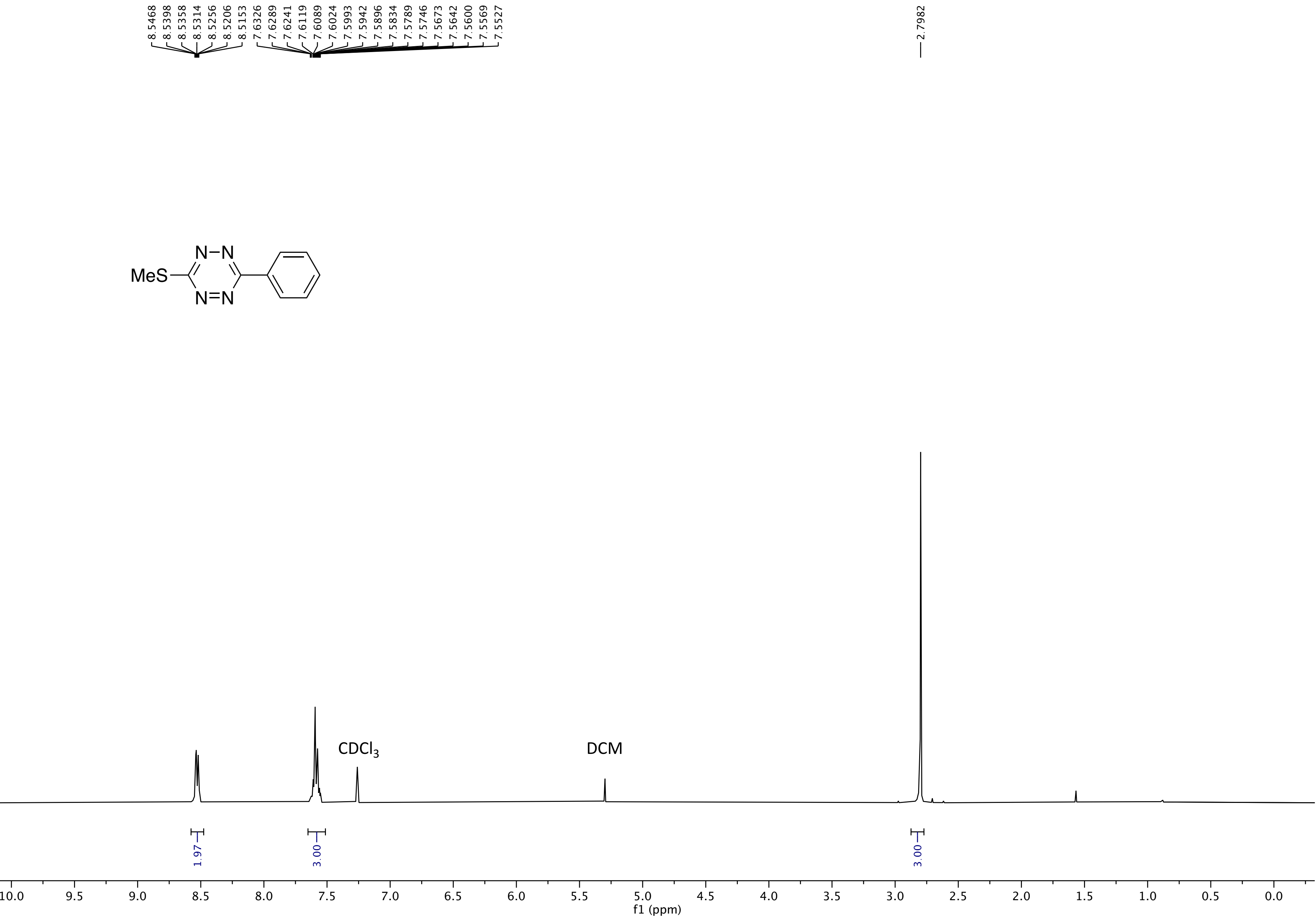
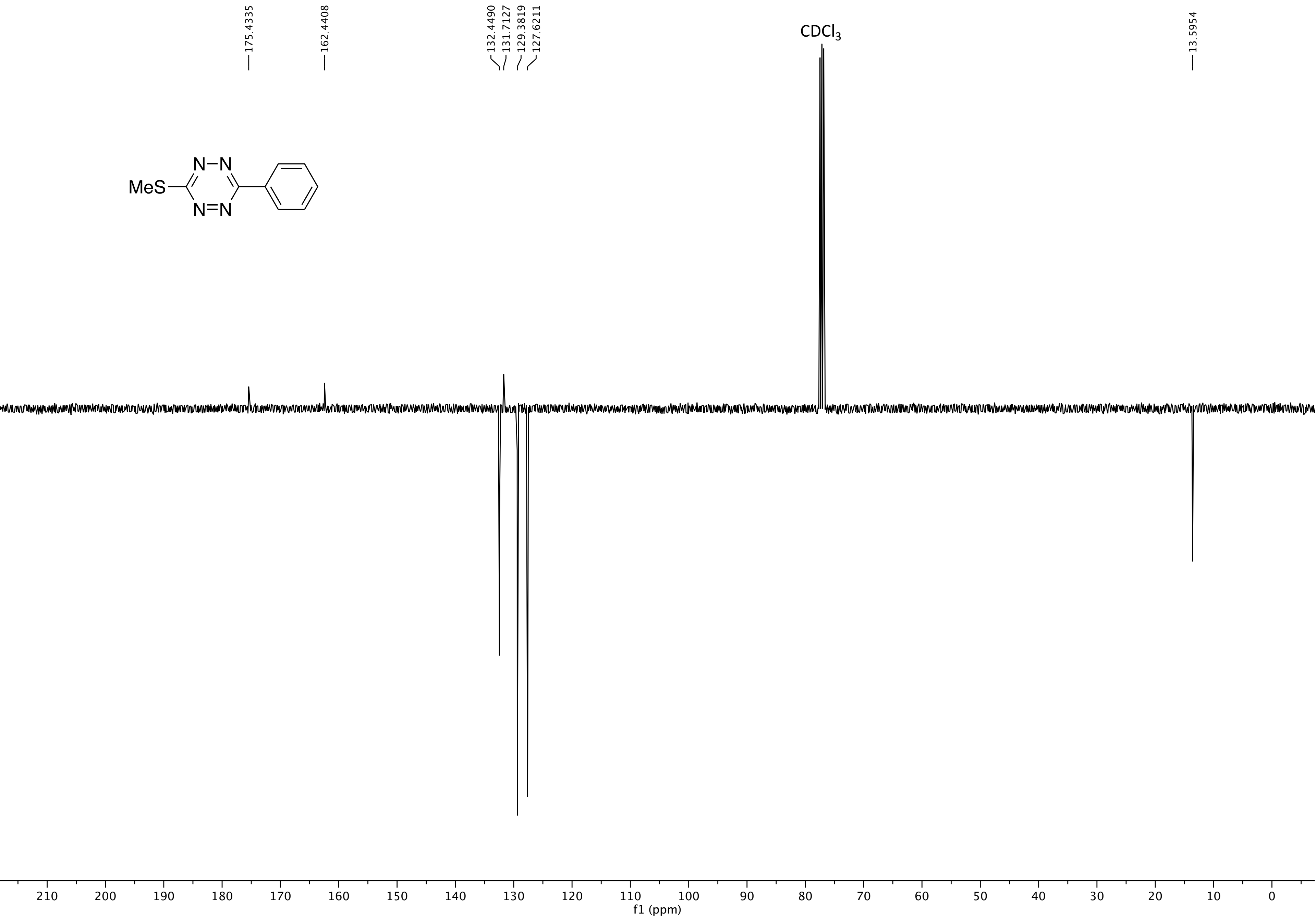
166.9458
161.1609
155.9913
144.3264
135.5846
133.3741
127.9654
124.0424
120.7984
116.7216
33.6006
26.8406
15.1580
13.5057
11.4941
CDCl$_3$
SMe
N
N
N
N
F
F
B
N
N
+
−
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


8.5468
8.5398
8.5358
8.5314
8.5256
8.5206
8.5153
7.6326
7.6289
7.6241
7.6119
7.6089
7.6024
7.5993
7.5942
7.5896
7.5834
7.5789
7.5746
7.5673
7.5642
7.5600
7.5569
7.5527
2.7982
MeS
N
CDCl3
DCM
1.97
3.00
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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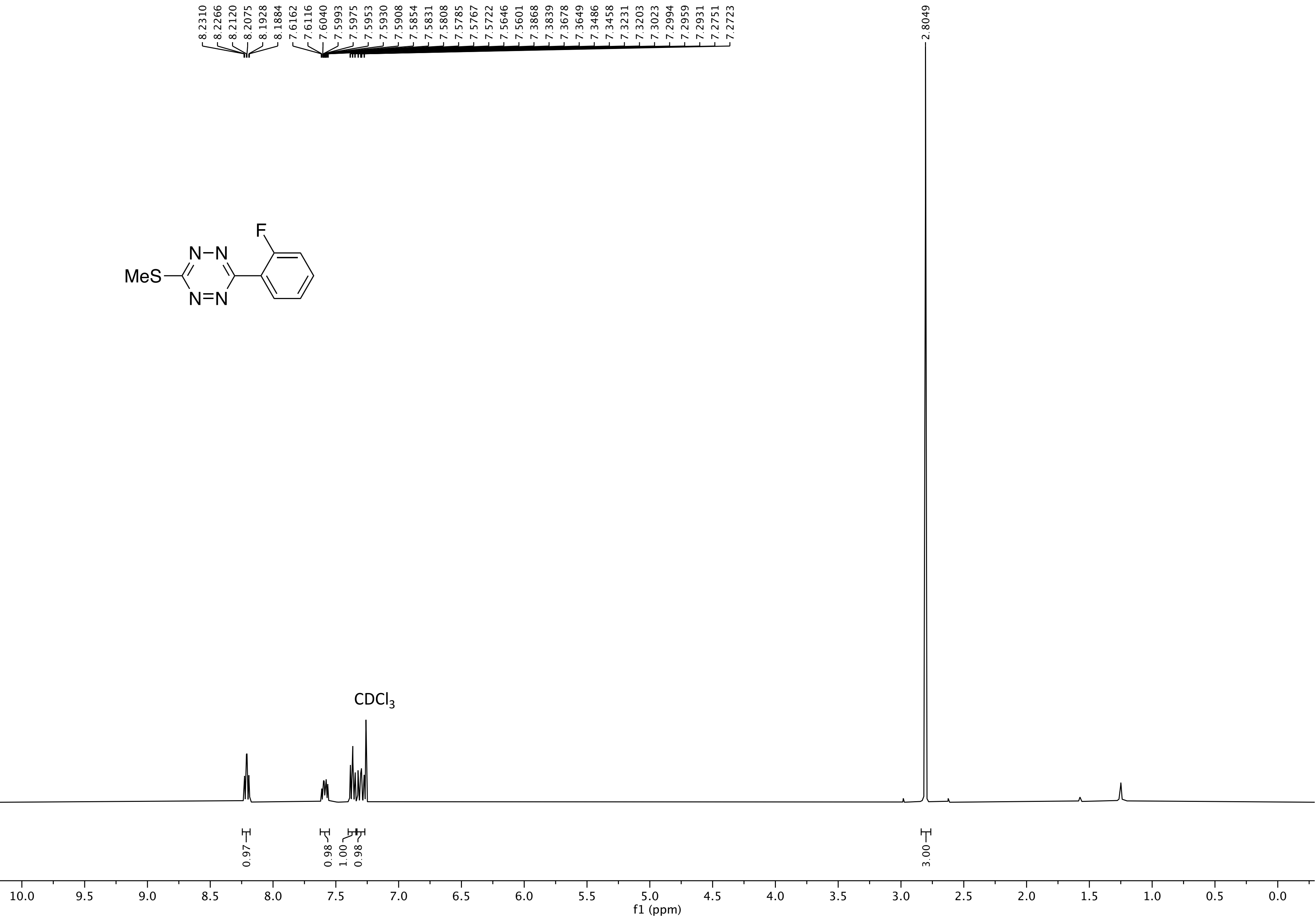
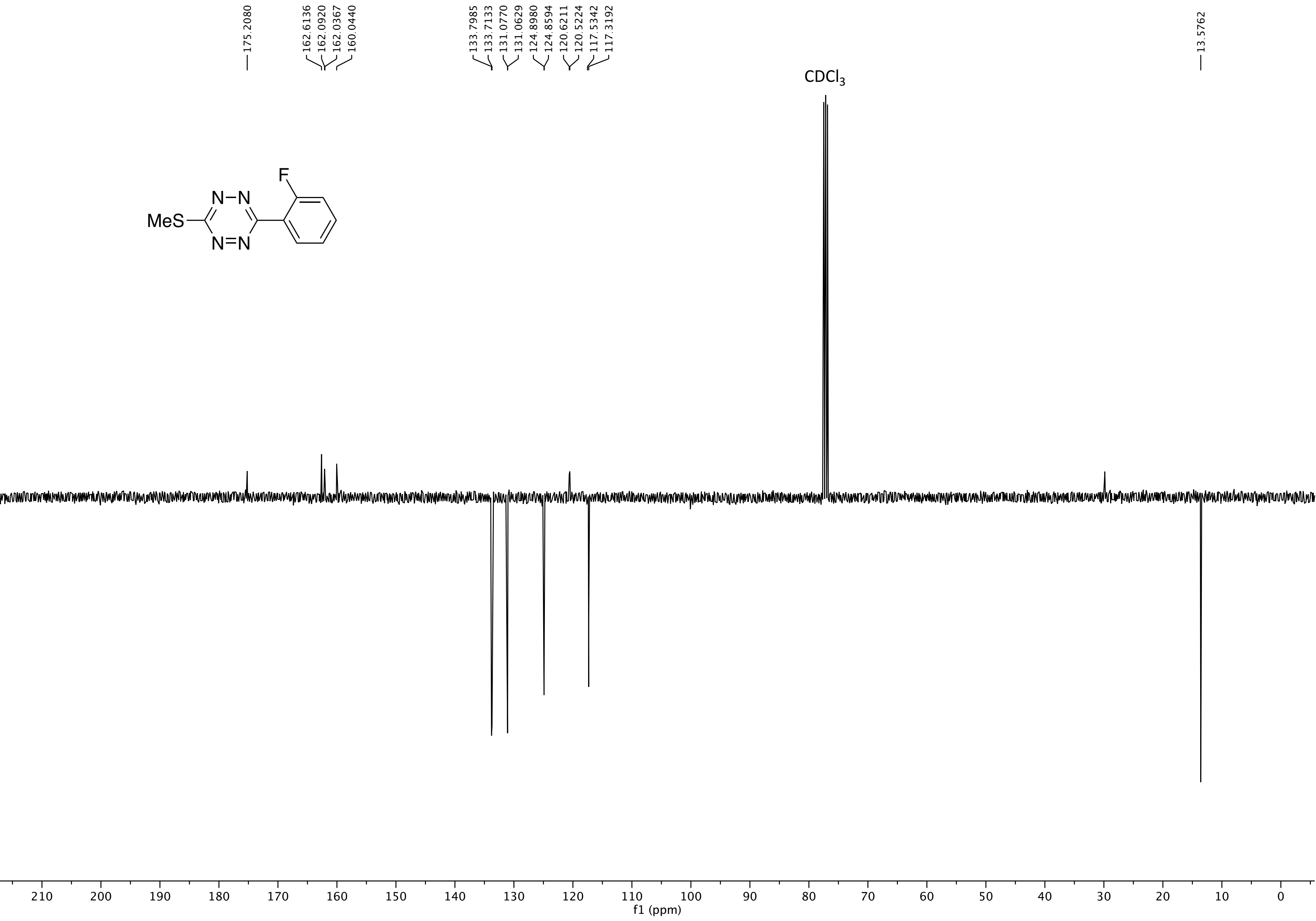
162.4408
132.4490
131.7127
129.3819
127.6211
CDCl$_3$
13.5954
MeS
N
N
N
N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.2310
8.2266
8.2120
8.2075
8.1928
8.1884
7.6162
7.6116
7.6040
7.5993
7.5975
7.5953
7.5930
7.5908
7.5854
7.5831
7.5808
7.5785
7.5767
7.5722
7.5646
7.5601
7.3868
7.3839
7.3678
7.3649
7.3486
7.3458
7.3231
7.3203
7.3023
7.2994
7.2959
7.2931
7.2751
7.2723
2.8049
F
N−N
MeS
N=N
CDCl$_3$
0.97
0.98
1.00
0.98
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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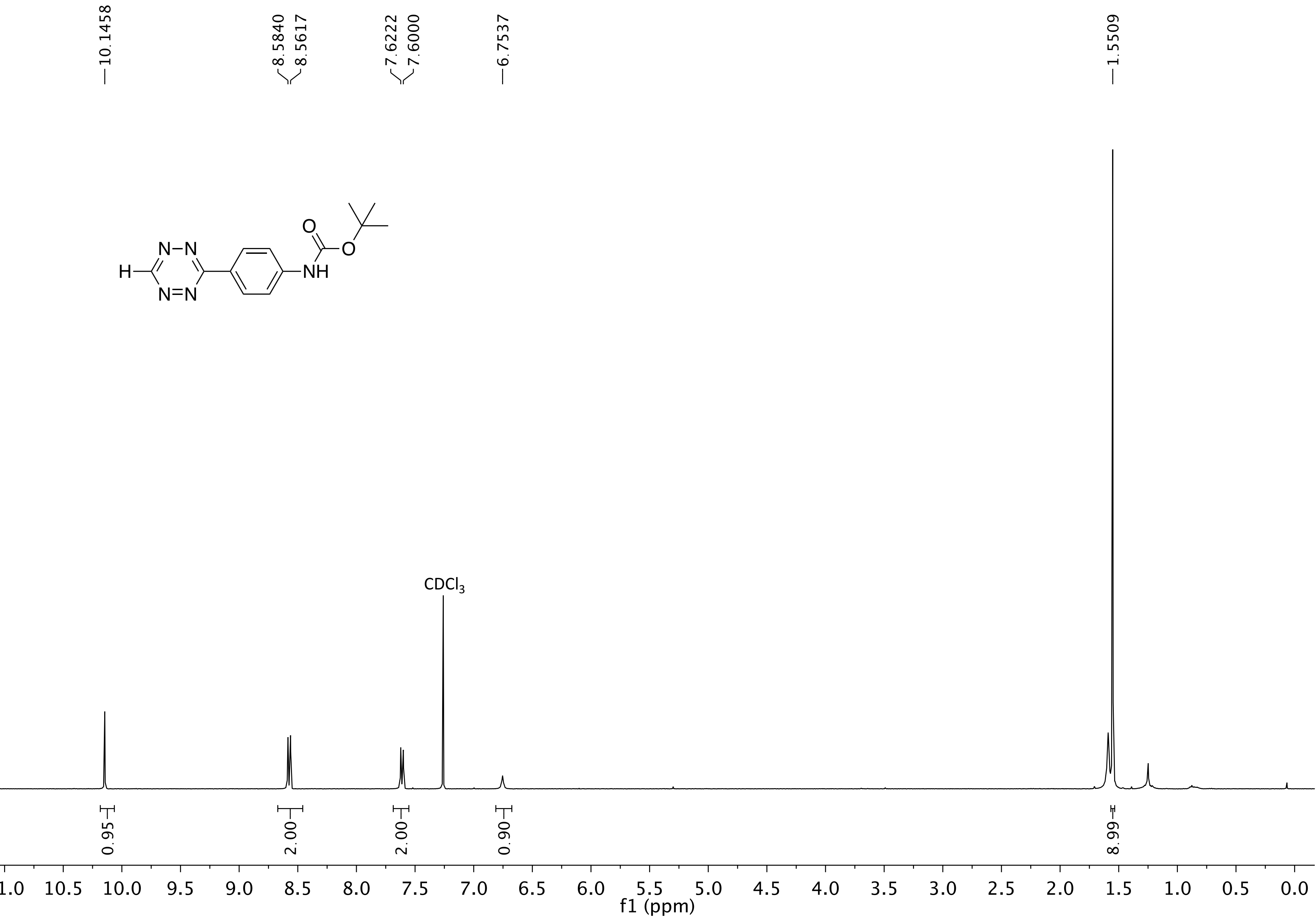
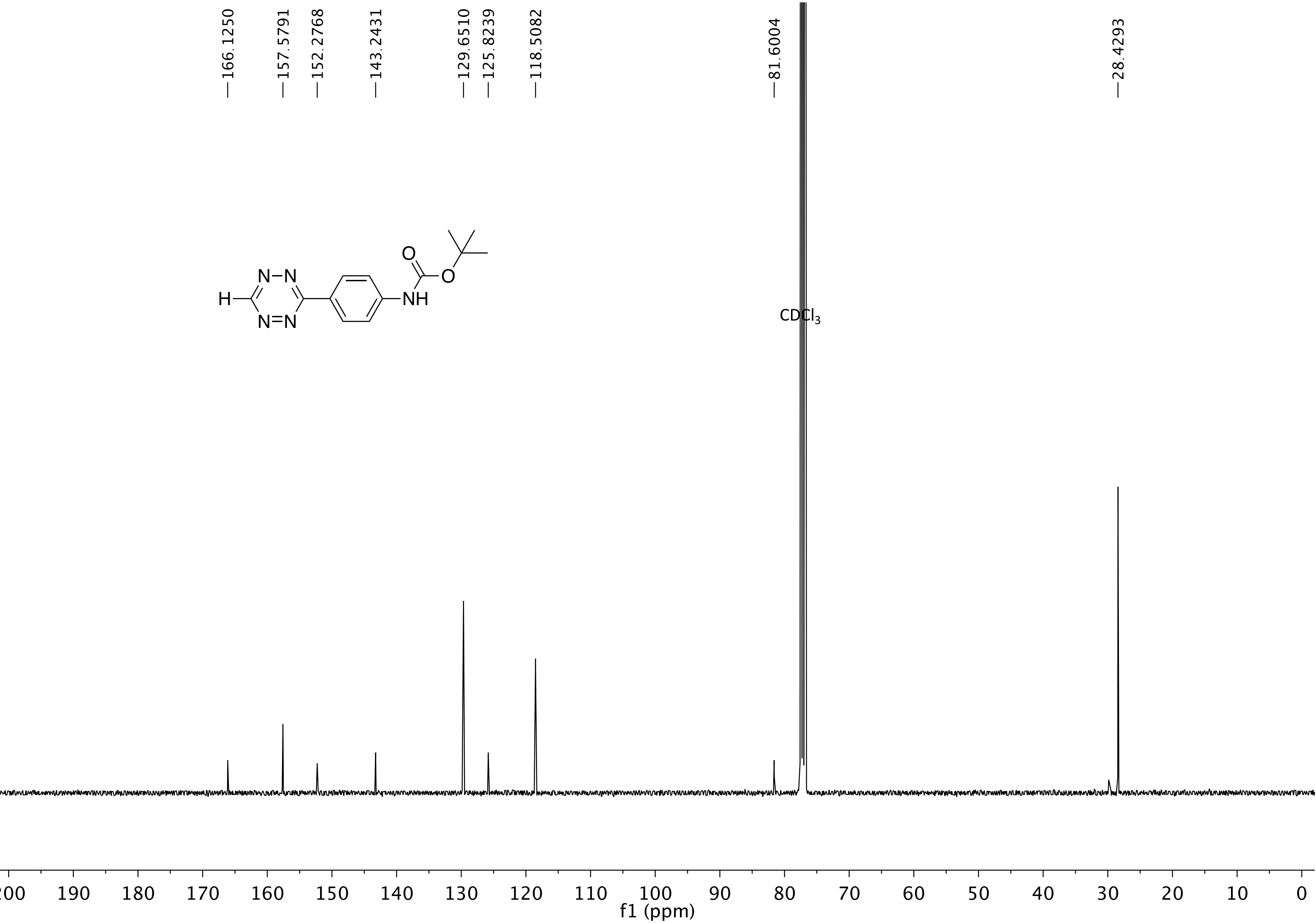
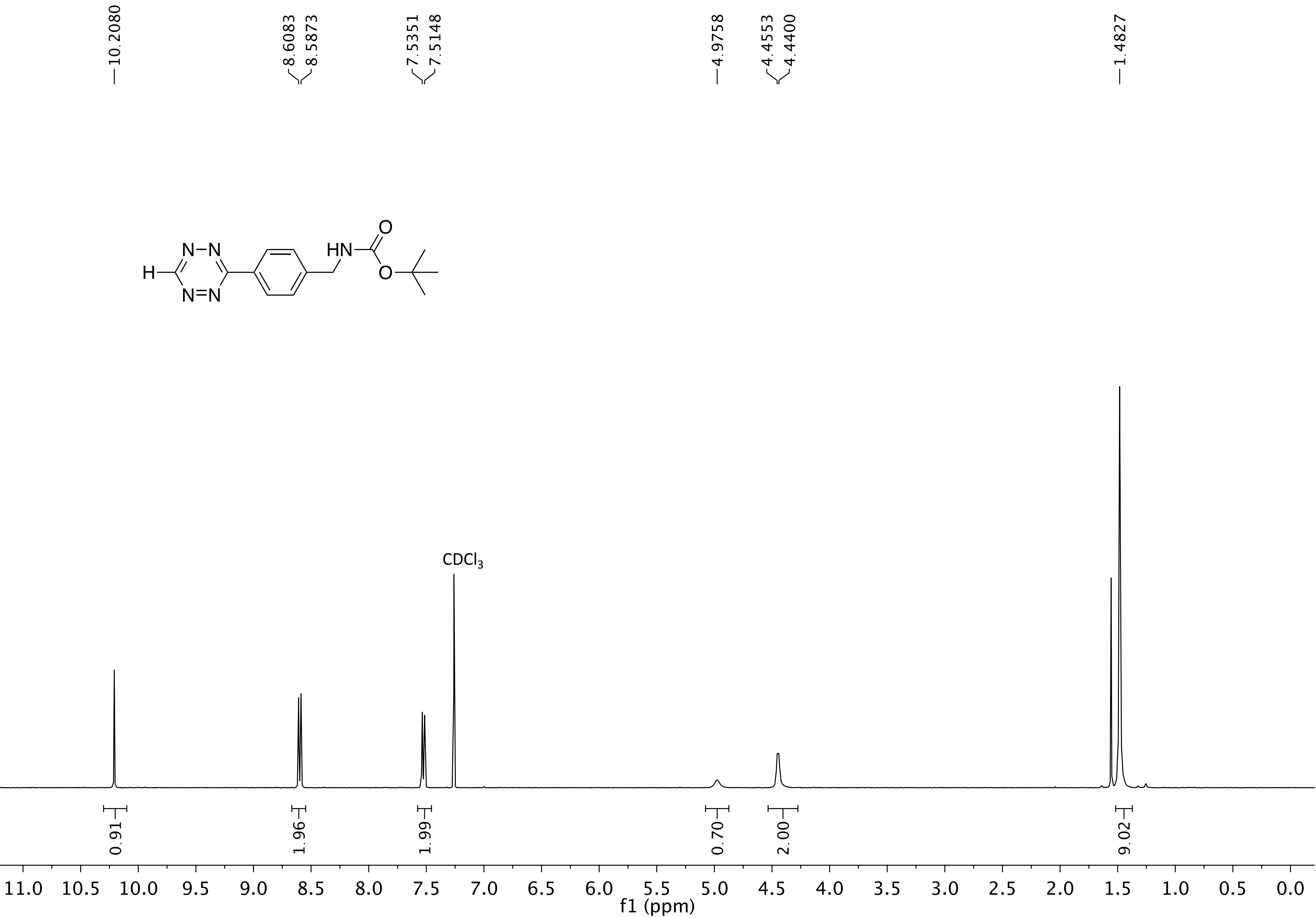
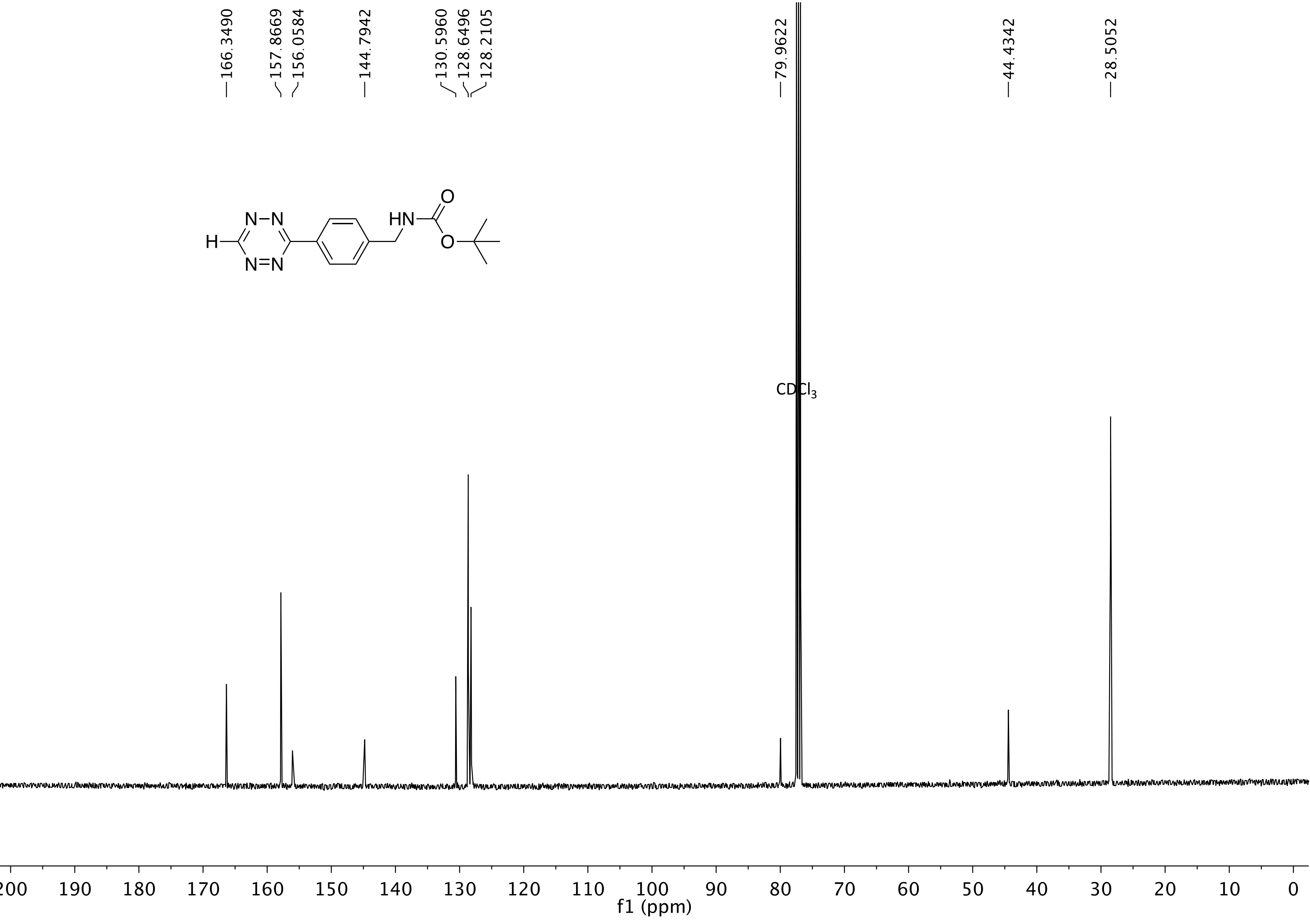
162.0920
162.0367
160.0440
133.7985
133.7133
131.0770
131.0629
124.8980
124.8594
120.6211
120.5224
117.5342
117.3192
13.5762
CDCl3
F
N
N
MeS
N
N
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

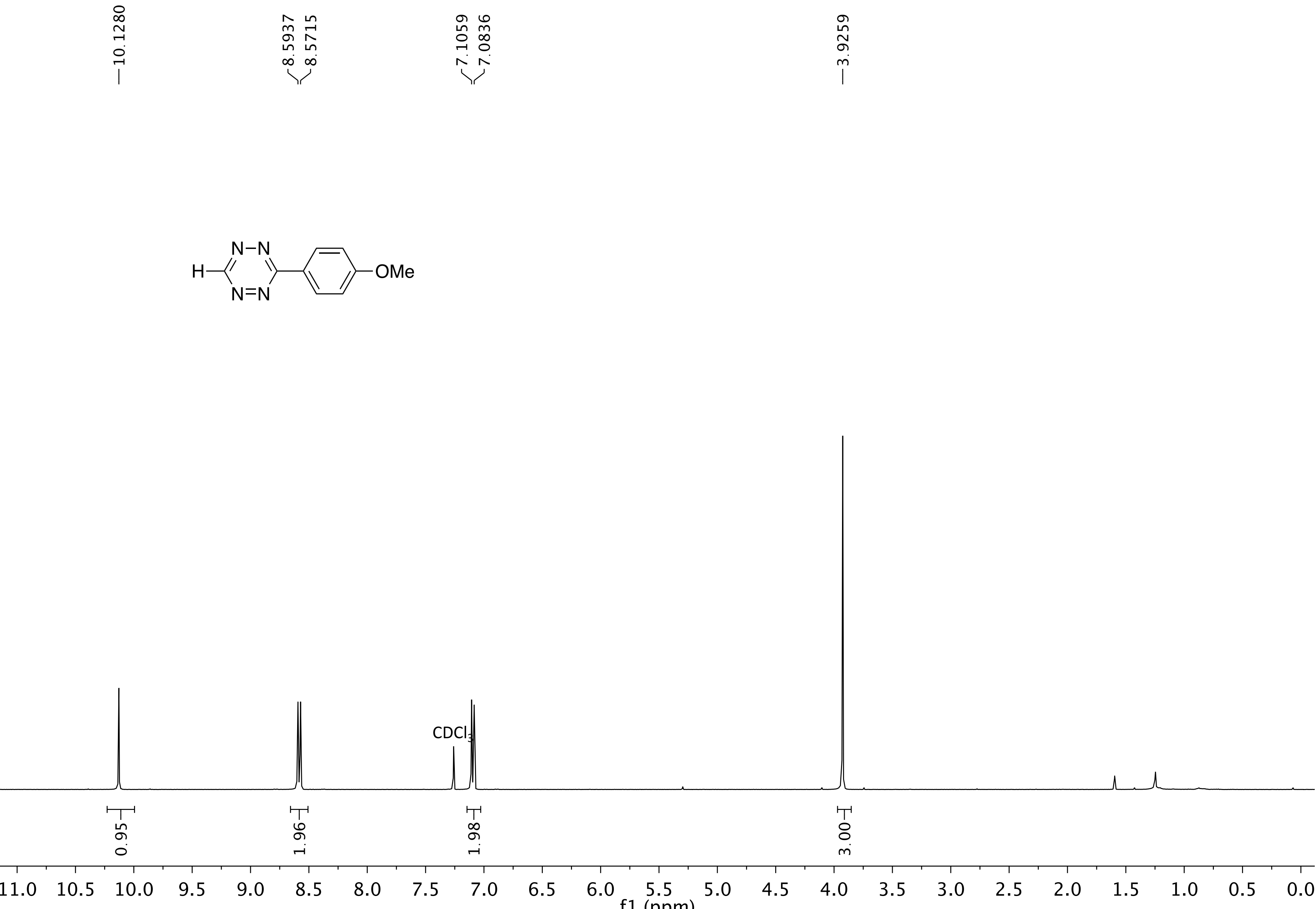


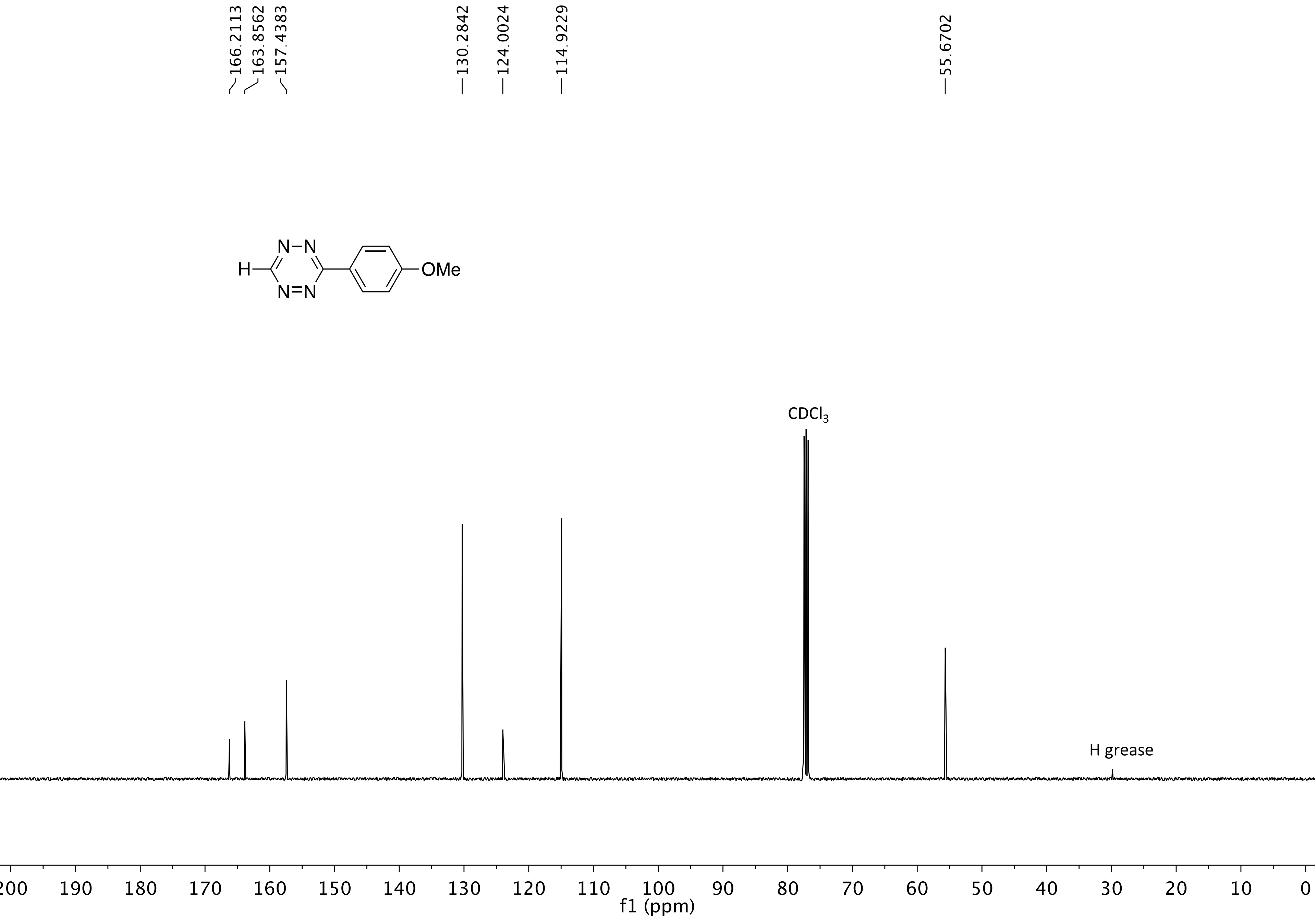
10.1458
8.5840
8.5617
7.6222
7.6000
6.7537
1.5509
CDCl3
0.95
2.00
2.00
0.90
8.99
f1 (ppm)

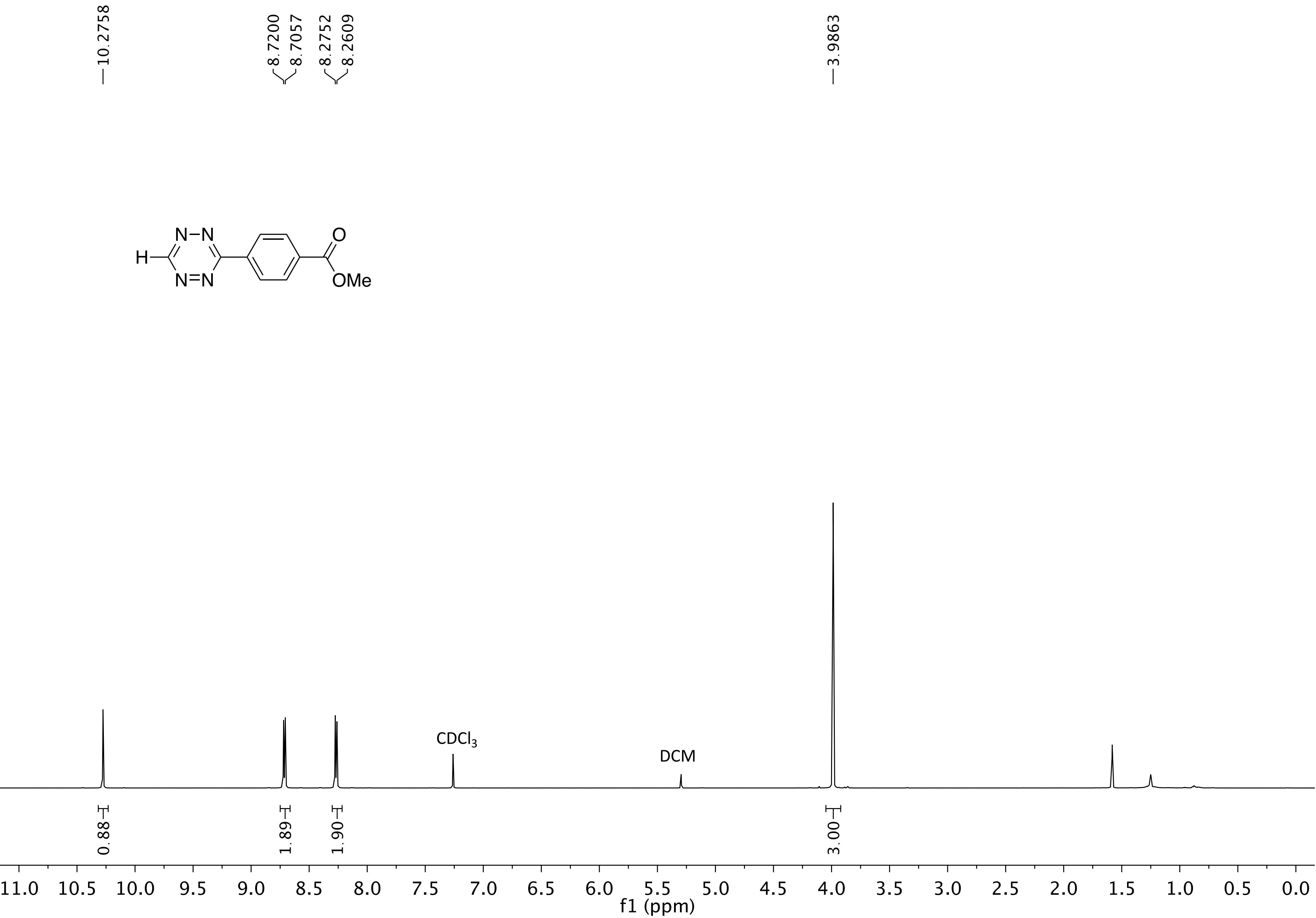

166.1250
157.5791
152.2768
143.2431
129.6510
125.8239
118.5082
81.6004
28.4293
CDCl3
H
N
N
N
N
O
O
NH
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

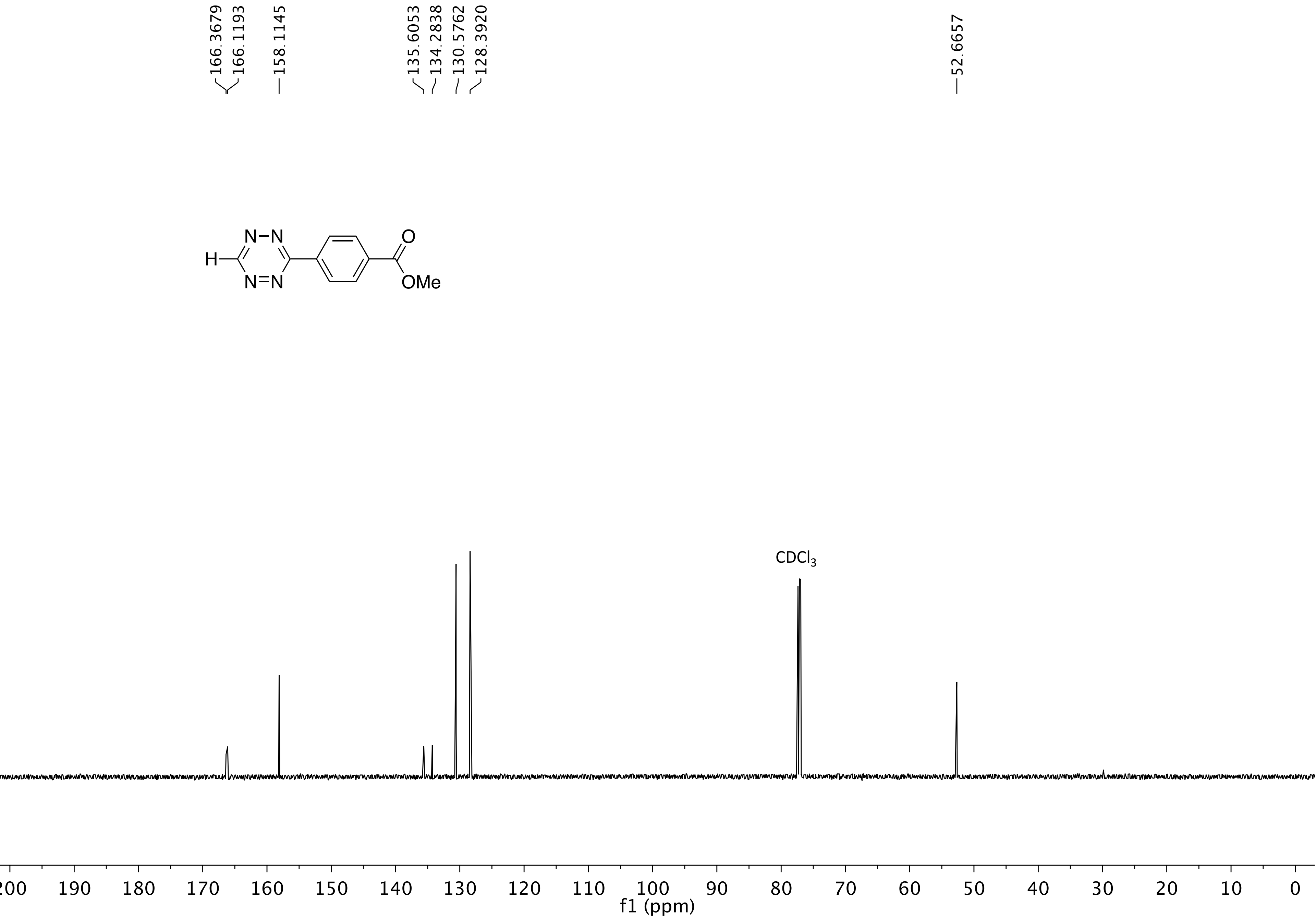

10.2080
8.6083
8.5873
7.5351
7.5148
4.9758
4.4553
4.4400
1.4827
H
N–N
N=N
HN
O
O
CDCl3
0.91
1.96
1.99
0.70
2.00
9.02
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

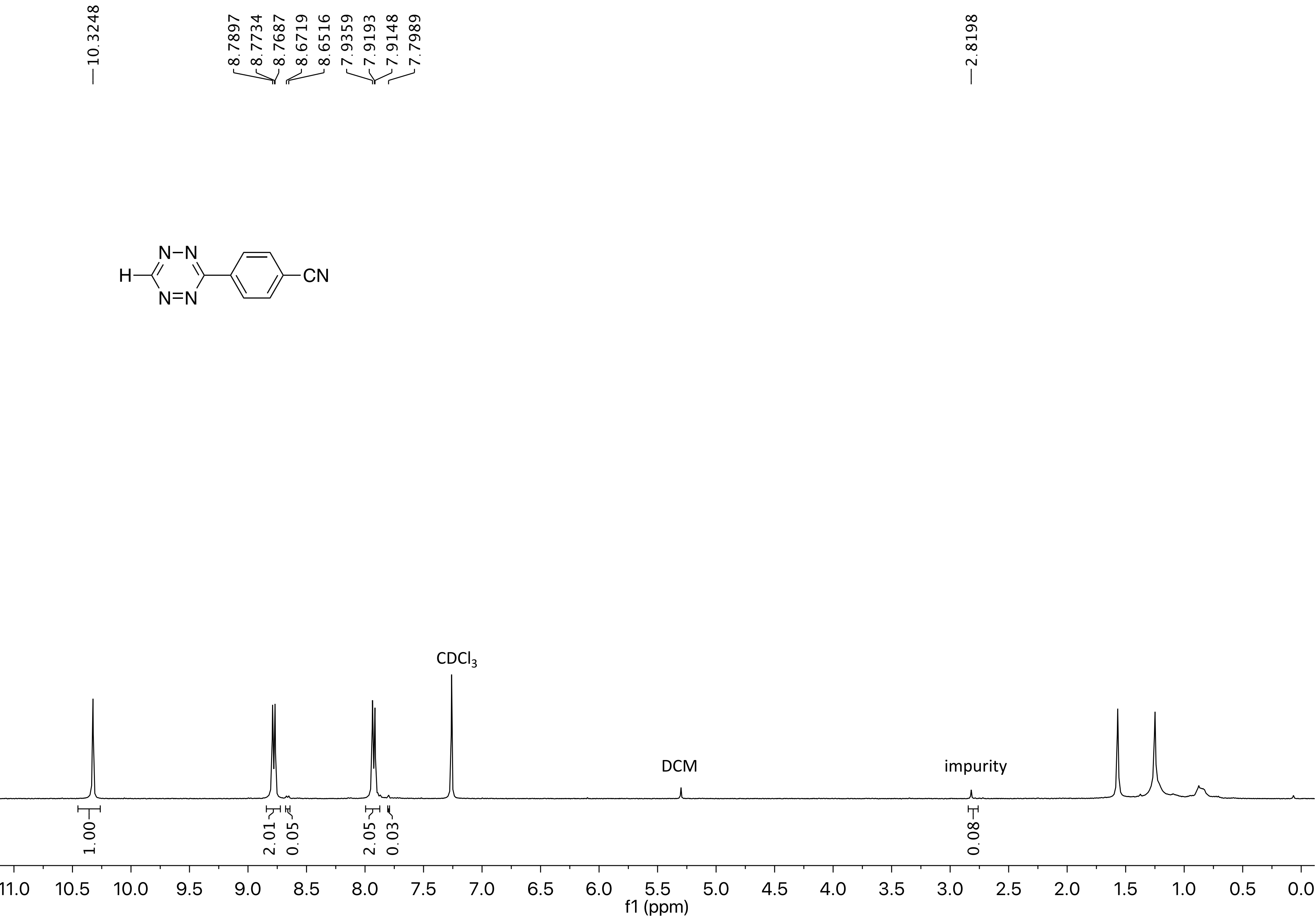

166.3490
157.8669
156.0584
144.7942
130.5960
128.6496
128.2105
79.9622
44.4342
28.5052
HN
O
O
H
N−N
N=N
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


10.1280
8.5937
8.5715
7.1059
7.0836
3.9259
H
N–N
N=N
OMe
CDCl3
0.95
1.96
1.98
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

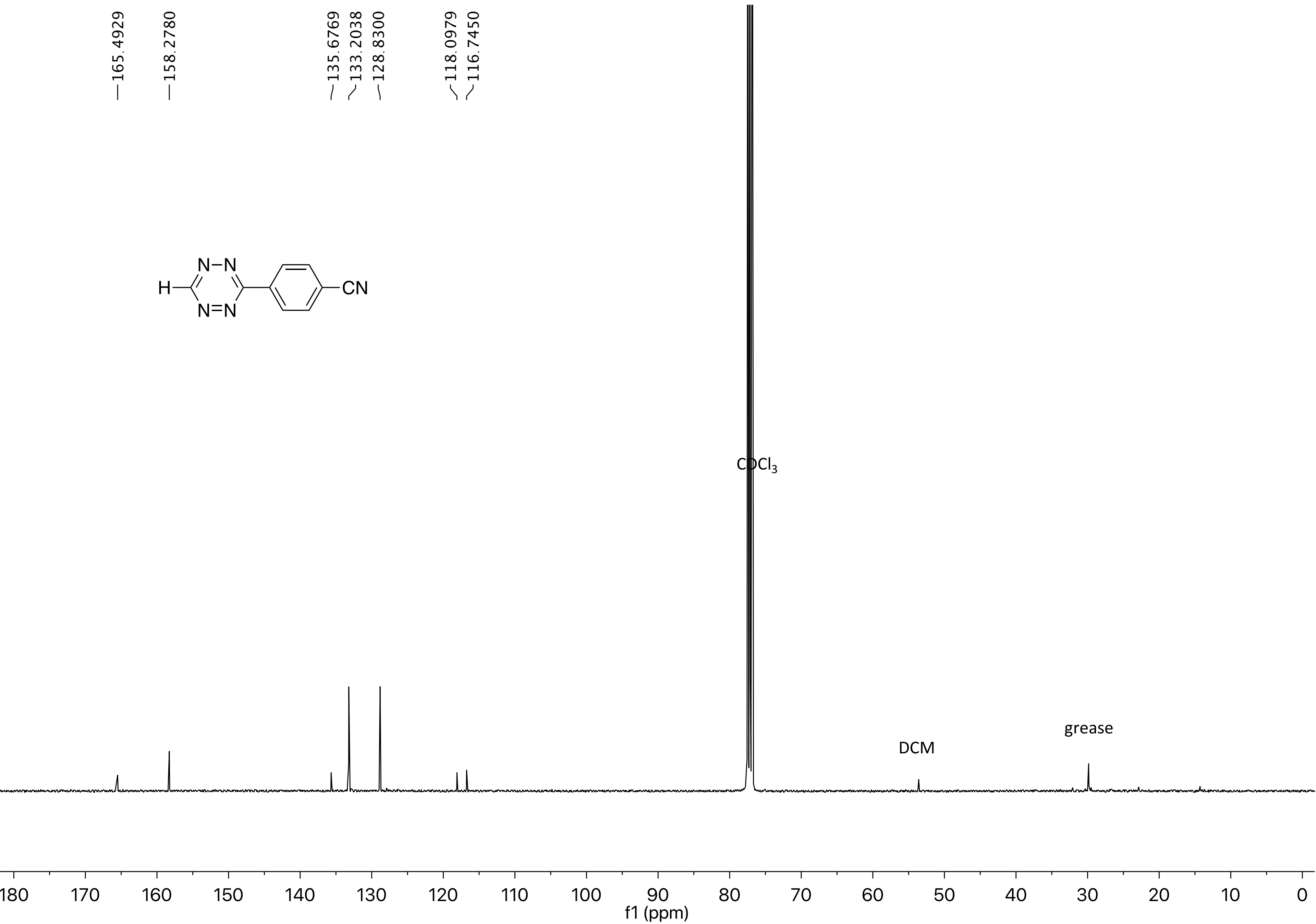

166.2113
163.8562
157.4383
130.2842
124.0024
114.9229
55.6702
H
N
N
N
N
OMe
CDCl3
H grease
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

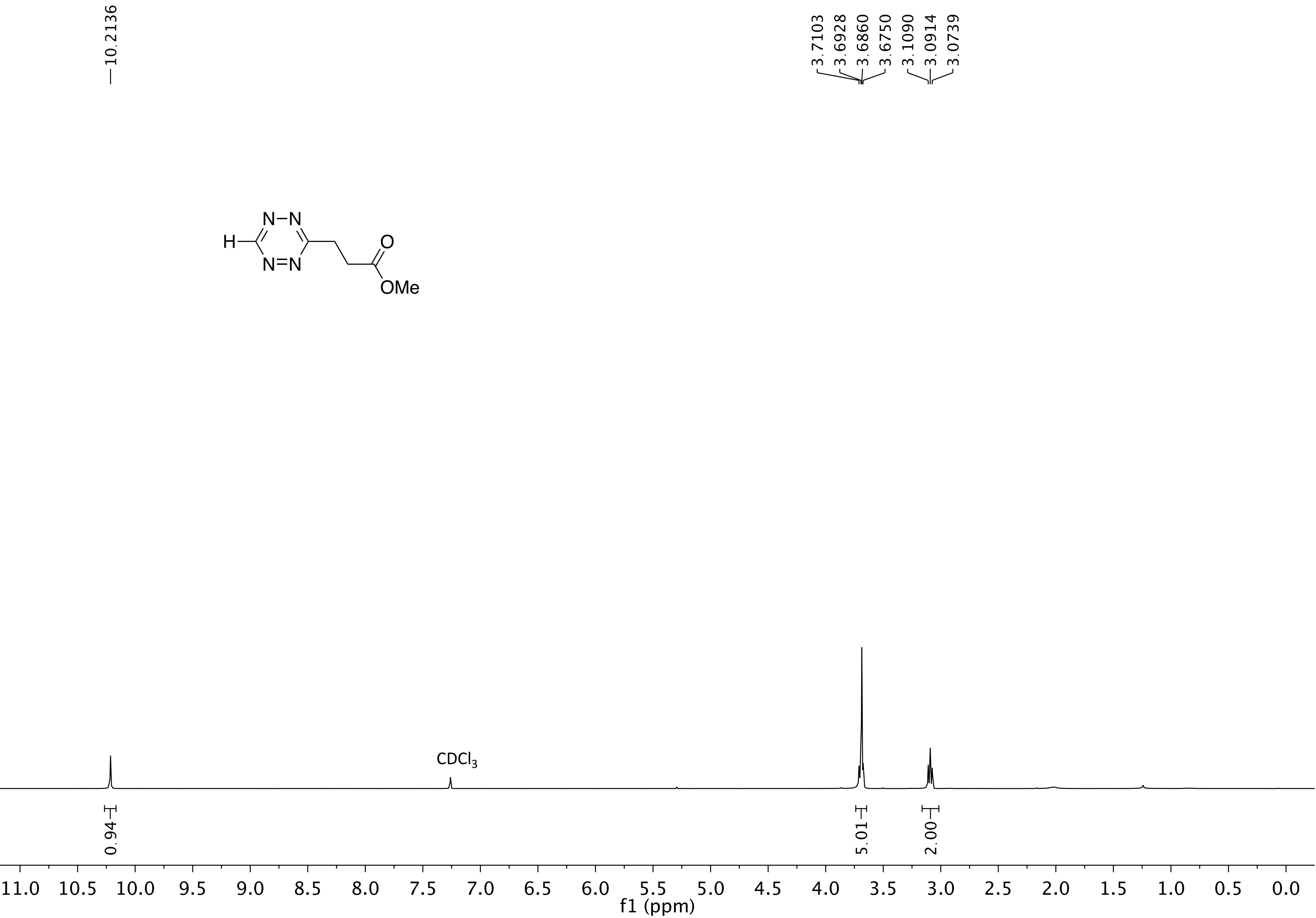

10.2758
8.7200
8.7057
8.2752
8.2609
3.9863
H
N−N
N=N
O
OMe
CDCl3
DCM
0.88
1.89
1.90
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


166.3679
166.1193
158.1145
135.6053
134.2838
130.5762
128.3920
52.6657
N
N
N
N
H
O
OMe
CDCl$_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

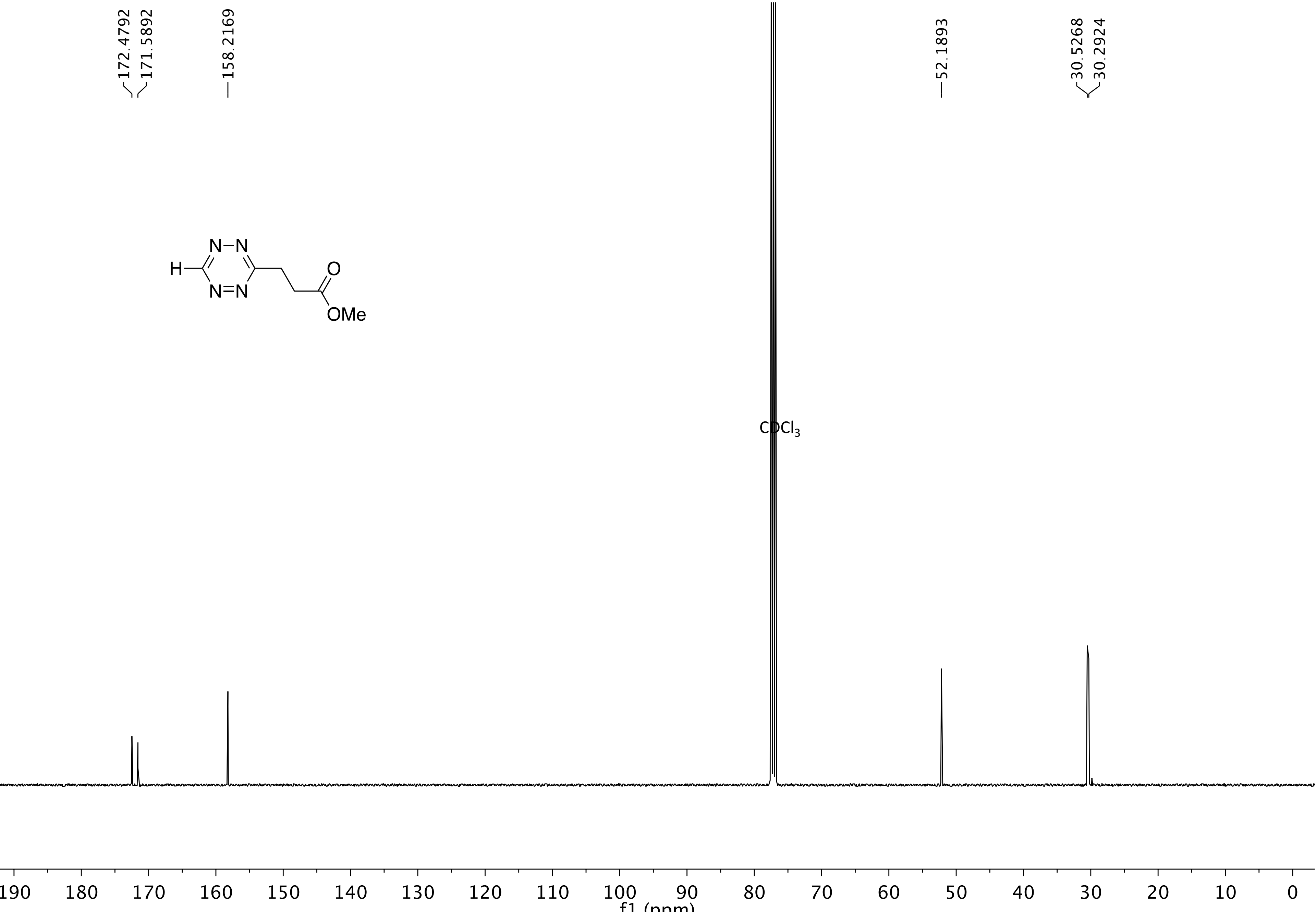


10.3248
8.7897
8.7734
8.7687
8.6719
8.6516
7.9359
7.9193
7.9148
7.7989
2.8198
H
N
CN
CDCl3
DCM
impurity
1.00
2.01
0.05
2.05
0.03
0.08
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

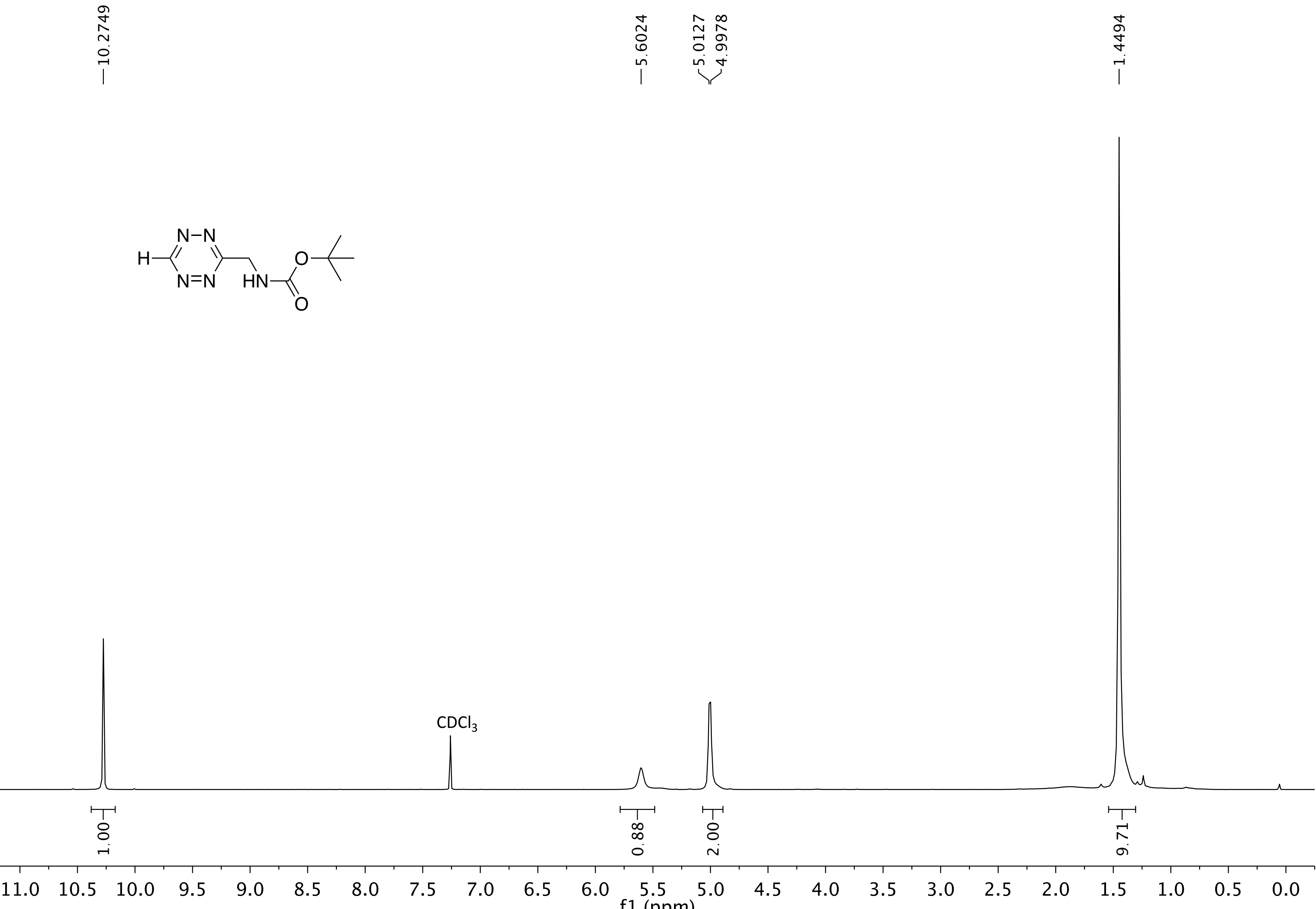

165.4929
158.2780
135.6769
133.2038
128.8300
118.0979
116.7450
H
N–N
N=N
CN
CDCl3
DCM
grease
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



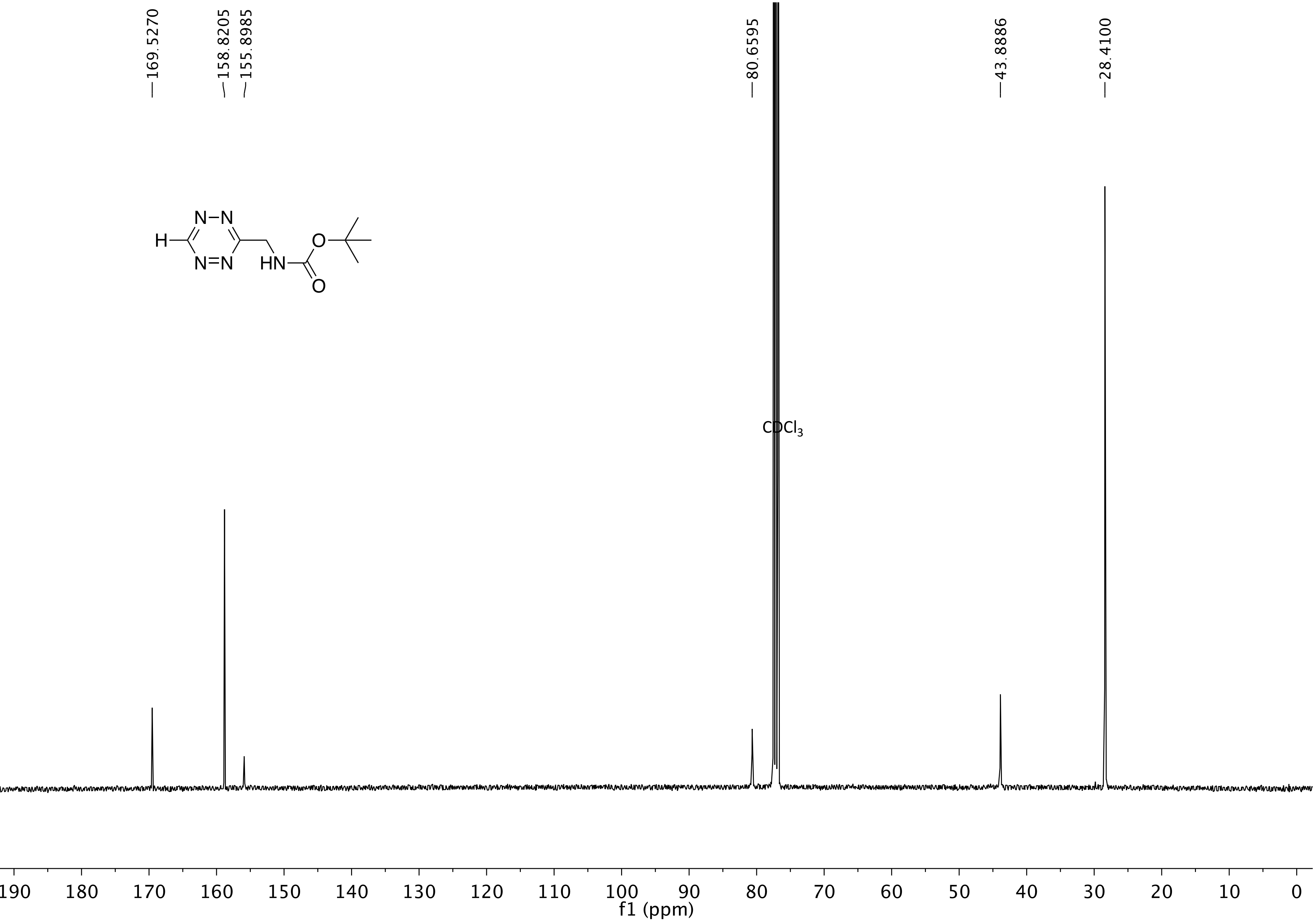
10.2136
3.7103
3.6928
3.6860
3.6750
3.1090
3.0914
3.0739
H
N–N
N=N
O
OMe
CDCl3
0.94
5.01
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



172.4792
171.5892
158.2169
52.1893
30.5268
30.2924
H
N
N
N
N
O
OMe
CDCl3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



10.2749
5.6024
5.0127
4.9978
1.4494
H
N
HN
O
CDCl3
1.00
0.88
2.00
9.71
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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158.8205
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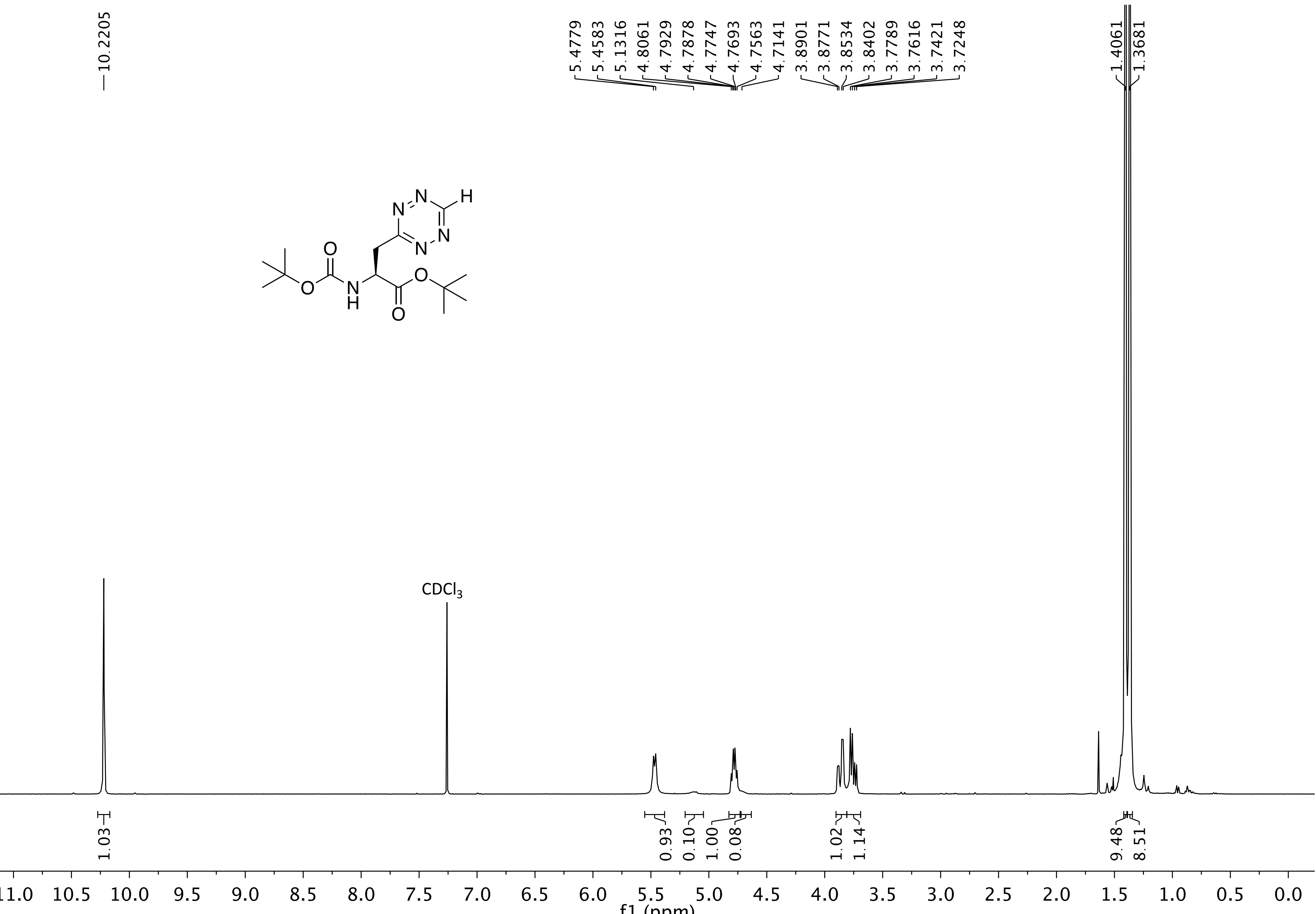
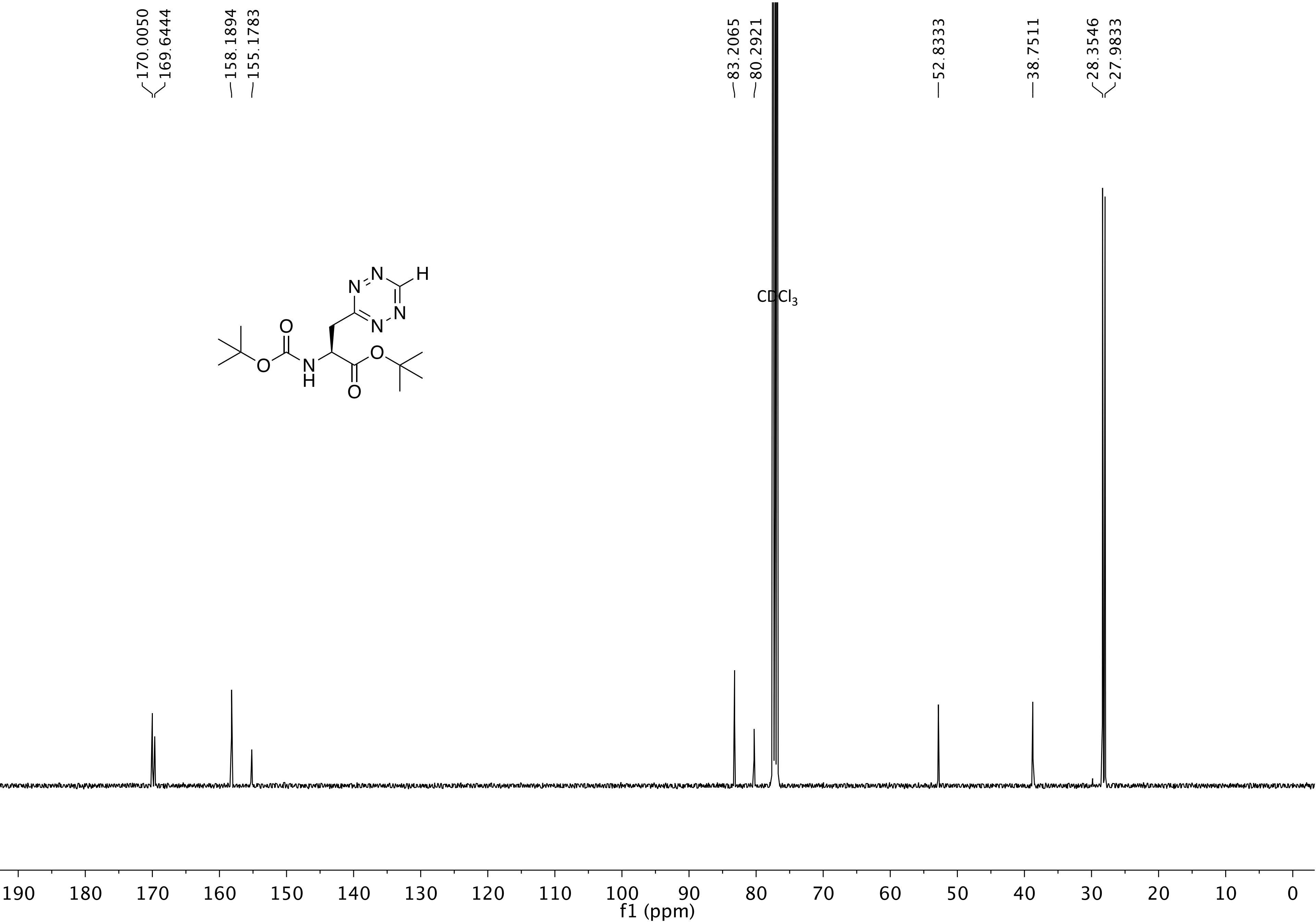
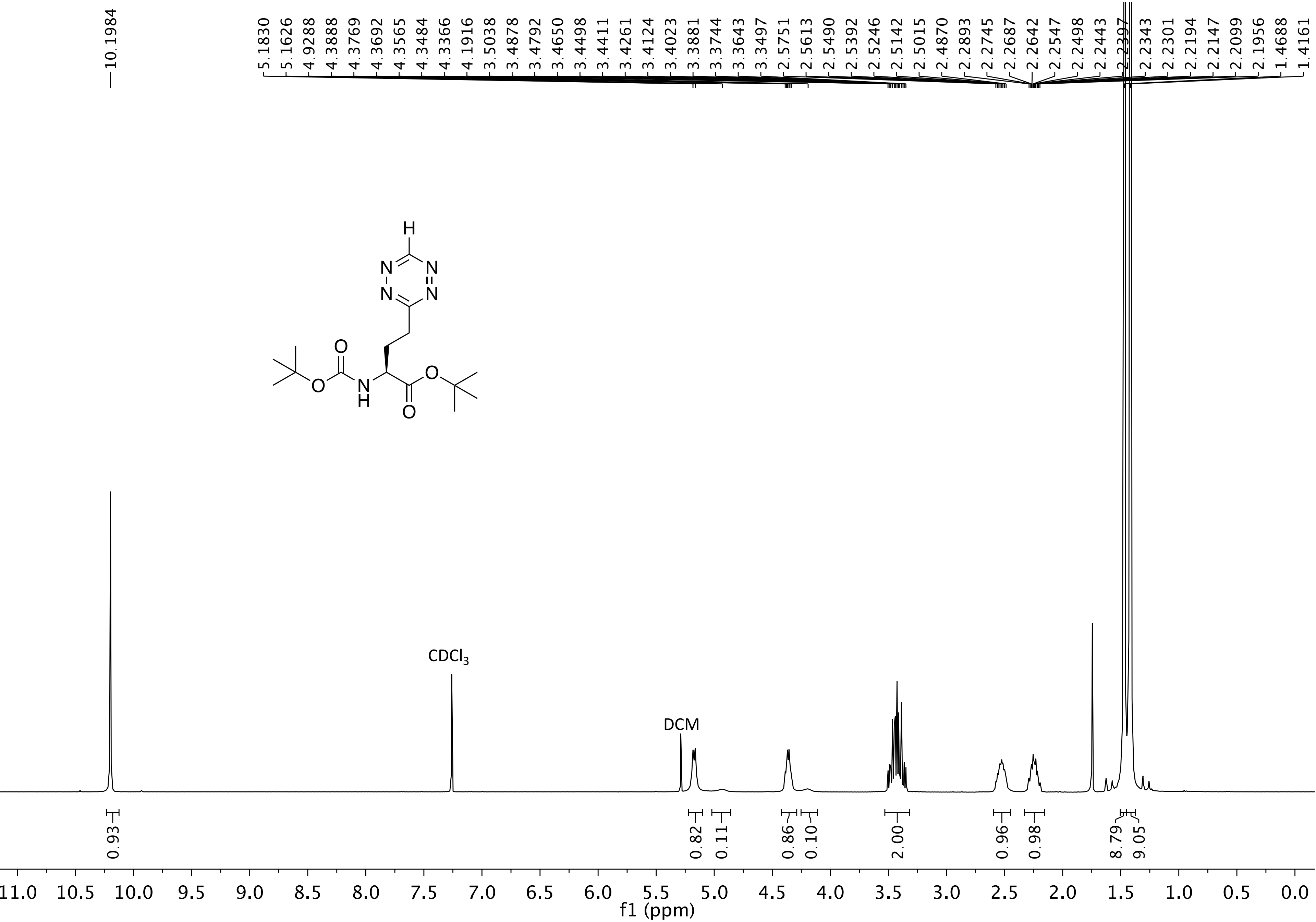
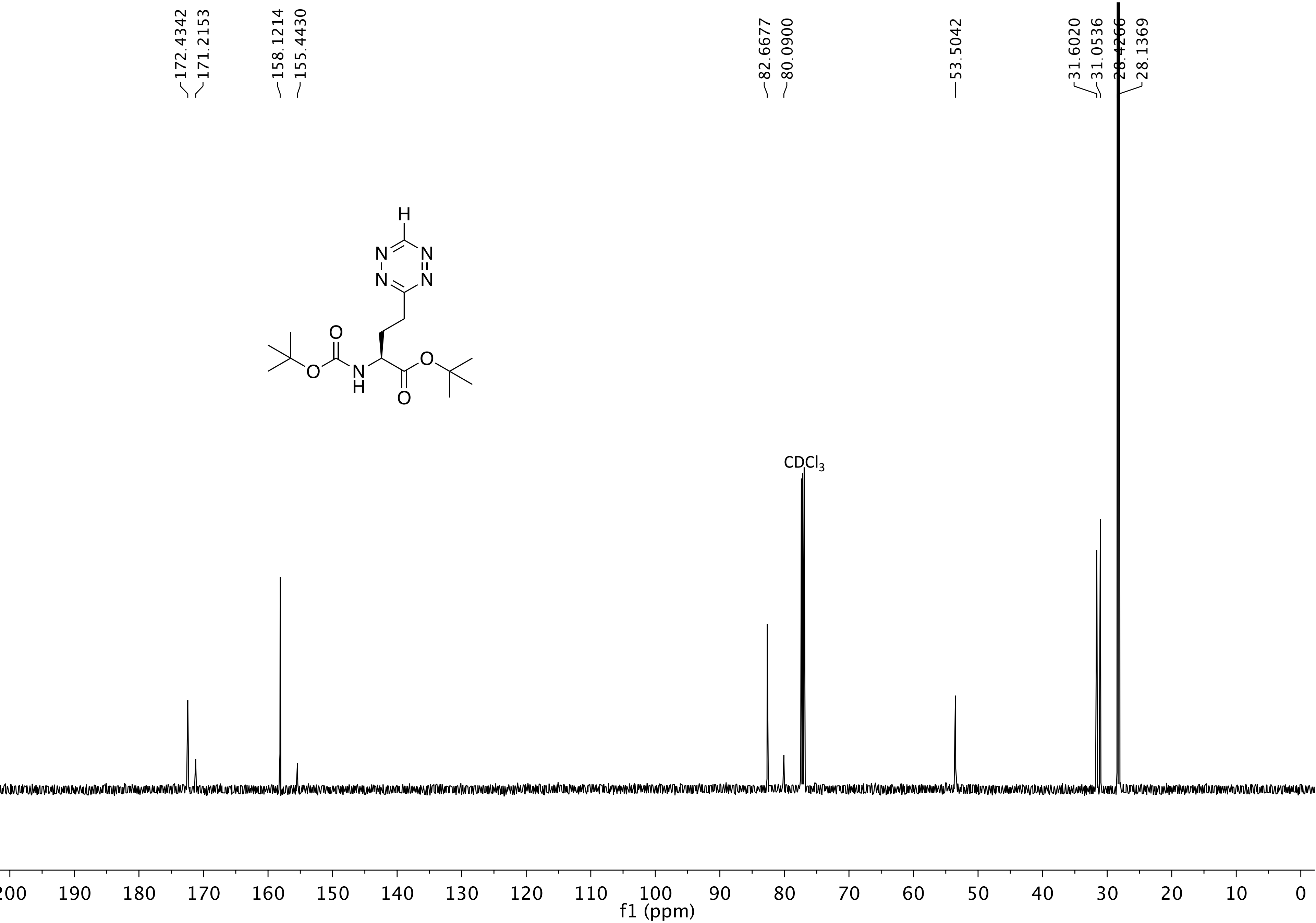
80.6595
43.8886
28.4100
CDCl$_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


10.2205
5.4779
5.4583
5.1316
4.8061
4.7929
4.7878
4.7747
4.7693
4.7563
4.7141
3.8901
3.8771
3.8534
3.8402
3.7789
3.7616
3.7421
3.7248
1.4061
1.3681
CDCl3
1.03
0.93
0.10
1.00
0.08
1.02
1.14
9.48
8.51
f1 (ppm)


170.0050
169.6444
158.1894
155.1783
83.2065
80.2921
52.8333
38.7511
28.3546
27.9833
CDCl3
N
N
H
N
N
O
O
N
H
O
O
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


10.1984
5.1830
5.1626
4.9288
4.3888
4.3769
4.3692
4.3565
4.3484
4.3366
4.1916
3.5038
3.4878
3.4792
3.4650
3.4498
3.4411
3.4261
3.4124
3.4023
3.3881
3.3744
3.3643
3.3497
2.5751
2.5613
2.5490
2.5392
2.5246
2.5142
2.5015
2.4870
2.2893
2.2745
2.2687
2.2642
2.2547
2.2498
2.2443
2.2397
2.2343
2.2301
2.2194
2.2147
2.2099
2.1956
1.4688
1.4161
H
N
N
N
N
O
O
N
H
O
O
CDCl3
DCM
0.93
0.82
0.11
0.86
0.10
2.00
0.96
0.98
8.79
9.05
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



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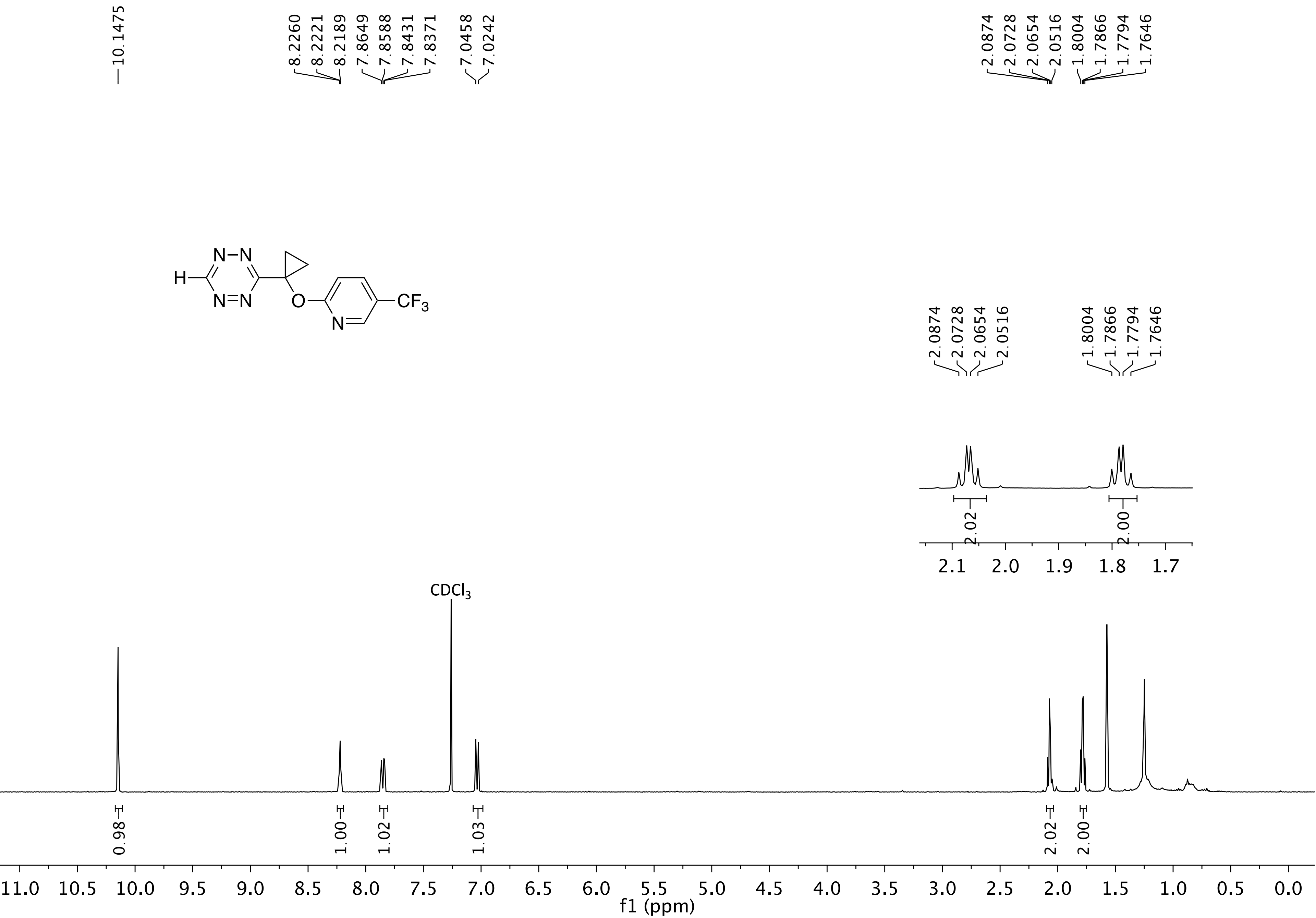
171.2153
158.1214
155.4430
82.6677
80.0900
53.5042
31.6020
31.0536
28.4266
28.1369
CDCl3
H
N
N
N
N
O
O
N
H
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



10.1475
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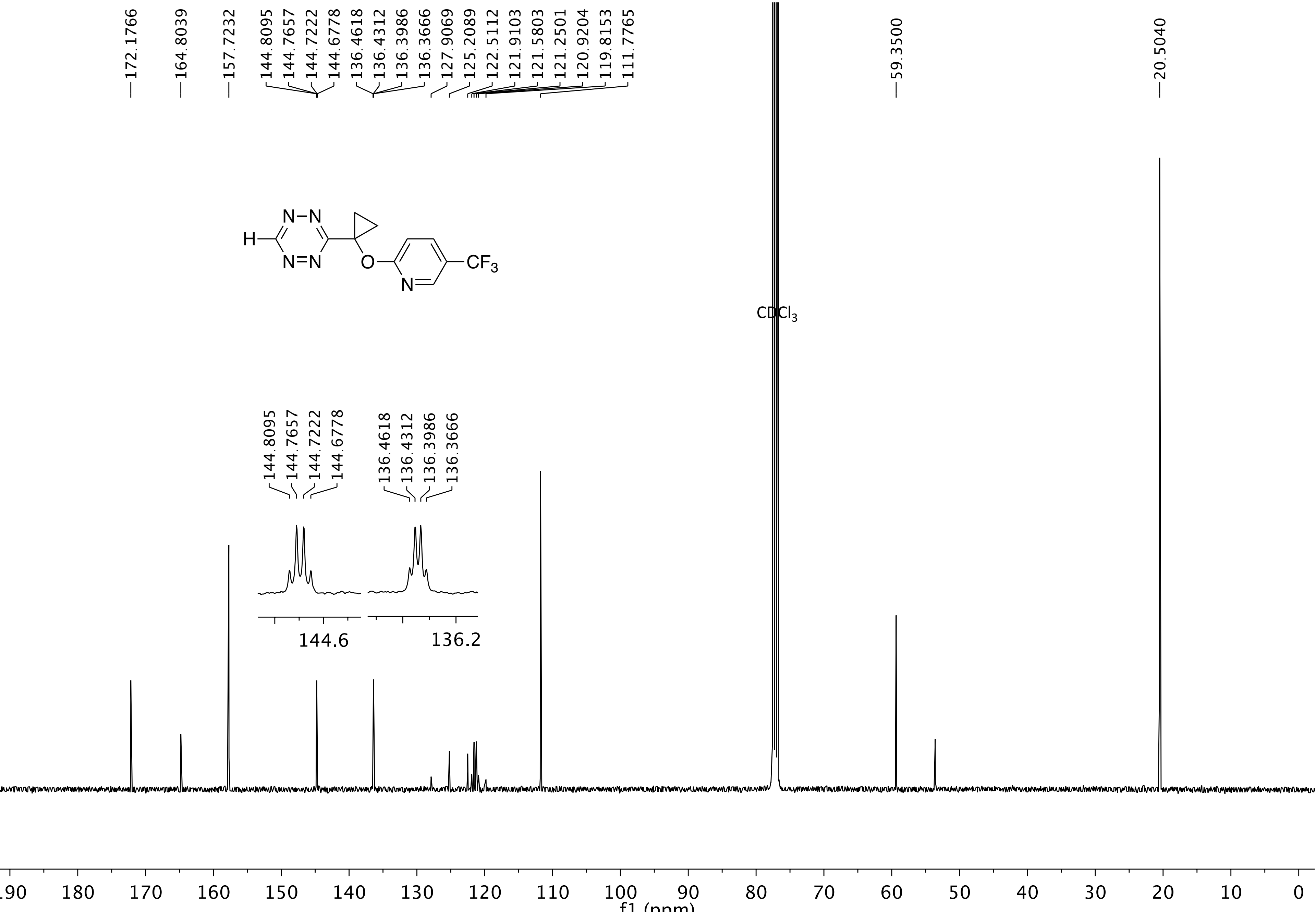
8.2221
8.2189
7.8649
7.8588
7.8431
7.8371
7.0458
7.0242
2.0874
2.0728
2.0654
2.0516
1.8004
1.7866
1.7794
1.7646
H
N–N
N=N
O
N
CF3
CDCl3
0.98
1.00
1.02
1.03
2.02
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
2.1 2.0 1.9 1.8 1.7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157.7232
144.8095
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144.6778
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136.4312
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136.3666
127.9069
125.2089
122.5112
121.9103
121.5803
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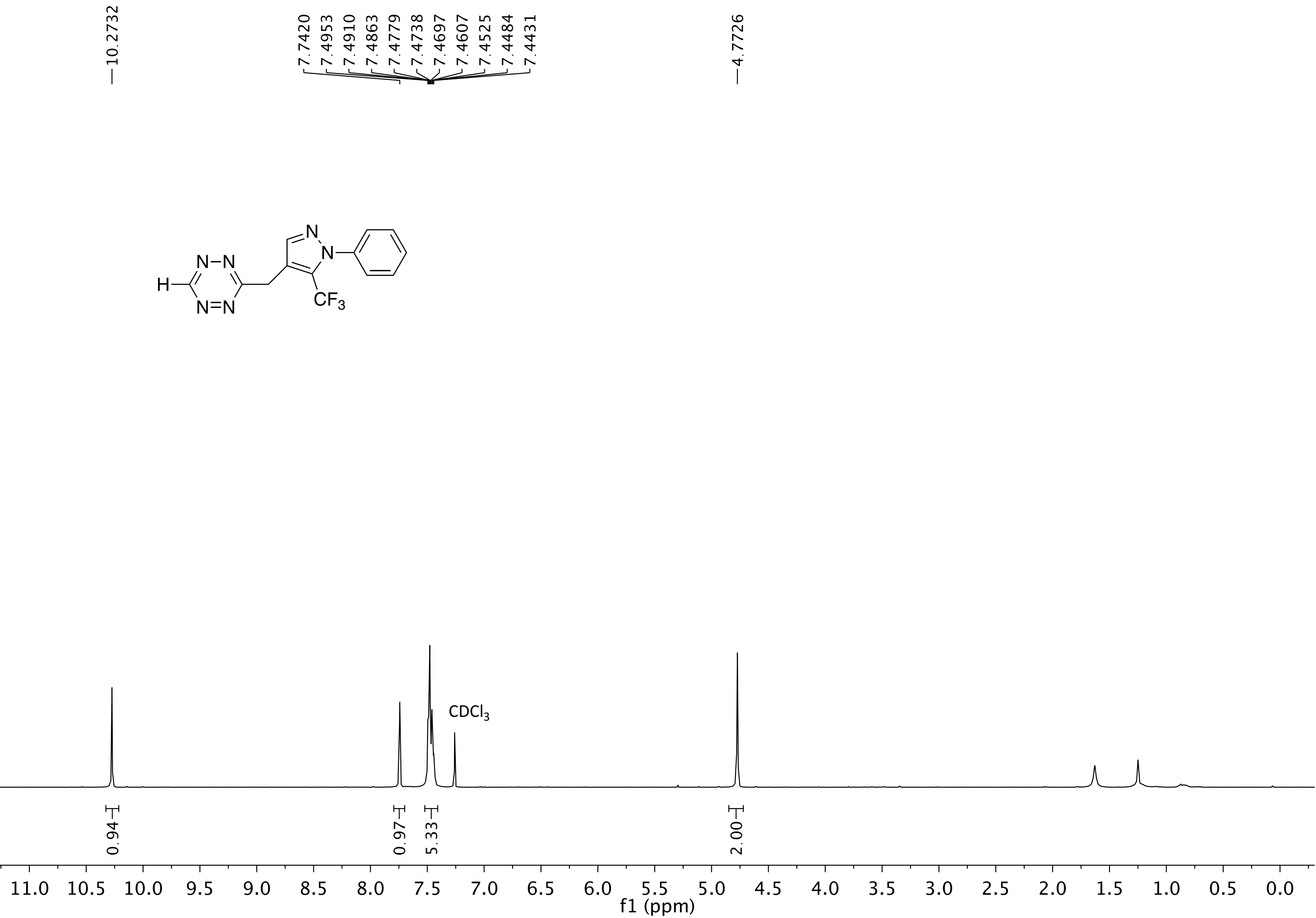
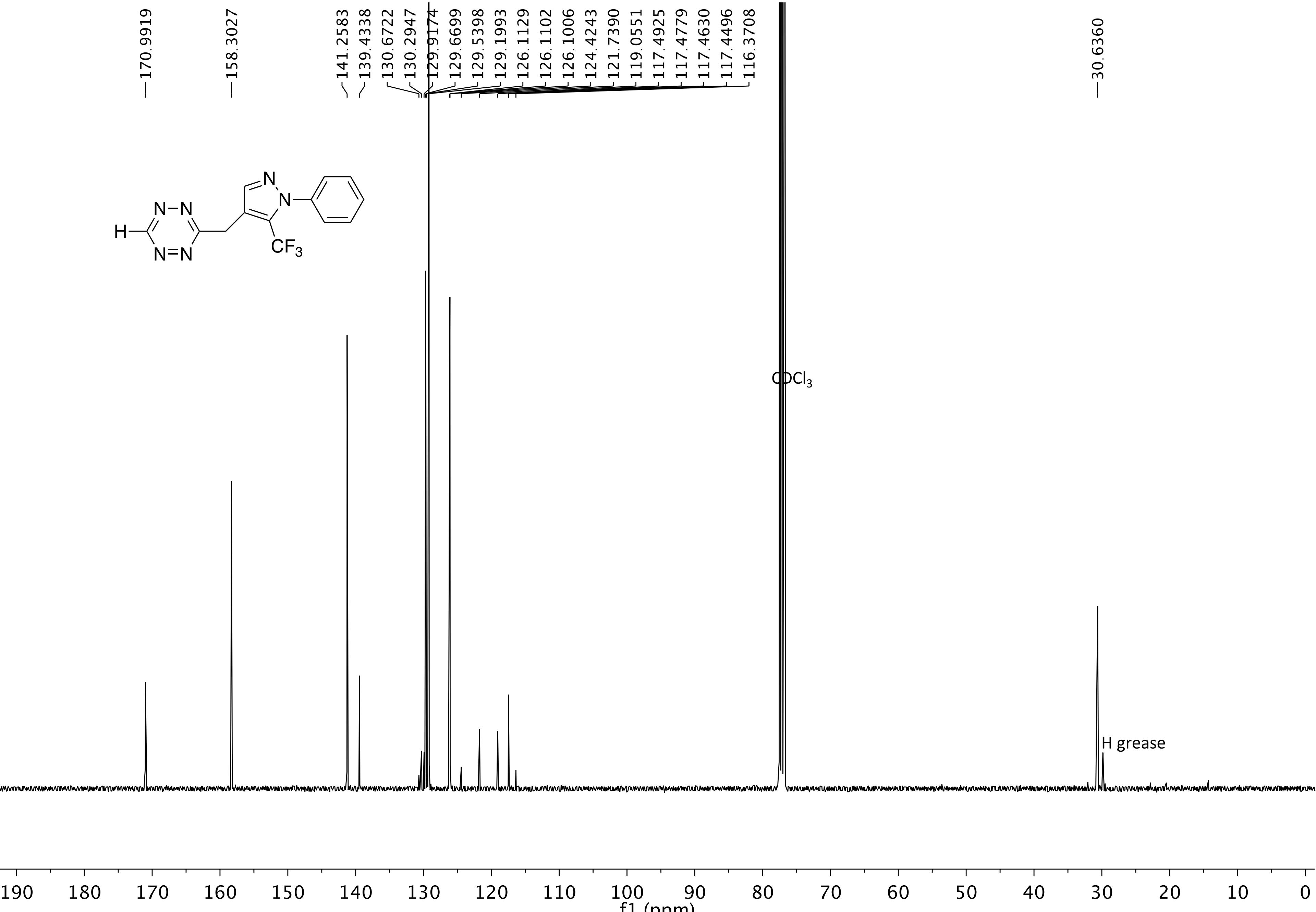
120.9204
119.8153
111.7765
59.3500
20.5040
CDCl3
144.6
136.2
f1 (ppm)


10.2732
7.7420
7.4953
7.4910
7.4863
7.4779
7.4738
7.4697
7.4607
7.4525
7.4484
7.4431
4.7726
H
N–N
N=N
N
N
CF3
CDCl3
0.94
0.97
5.33
2.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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126.1006
124.4243
121.7390
119.0551
117.4925
117.4779
117.4630
117.4496
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CF_3
$CDCl_3$
H grease
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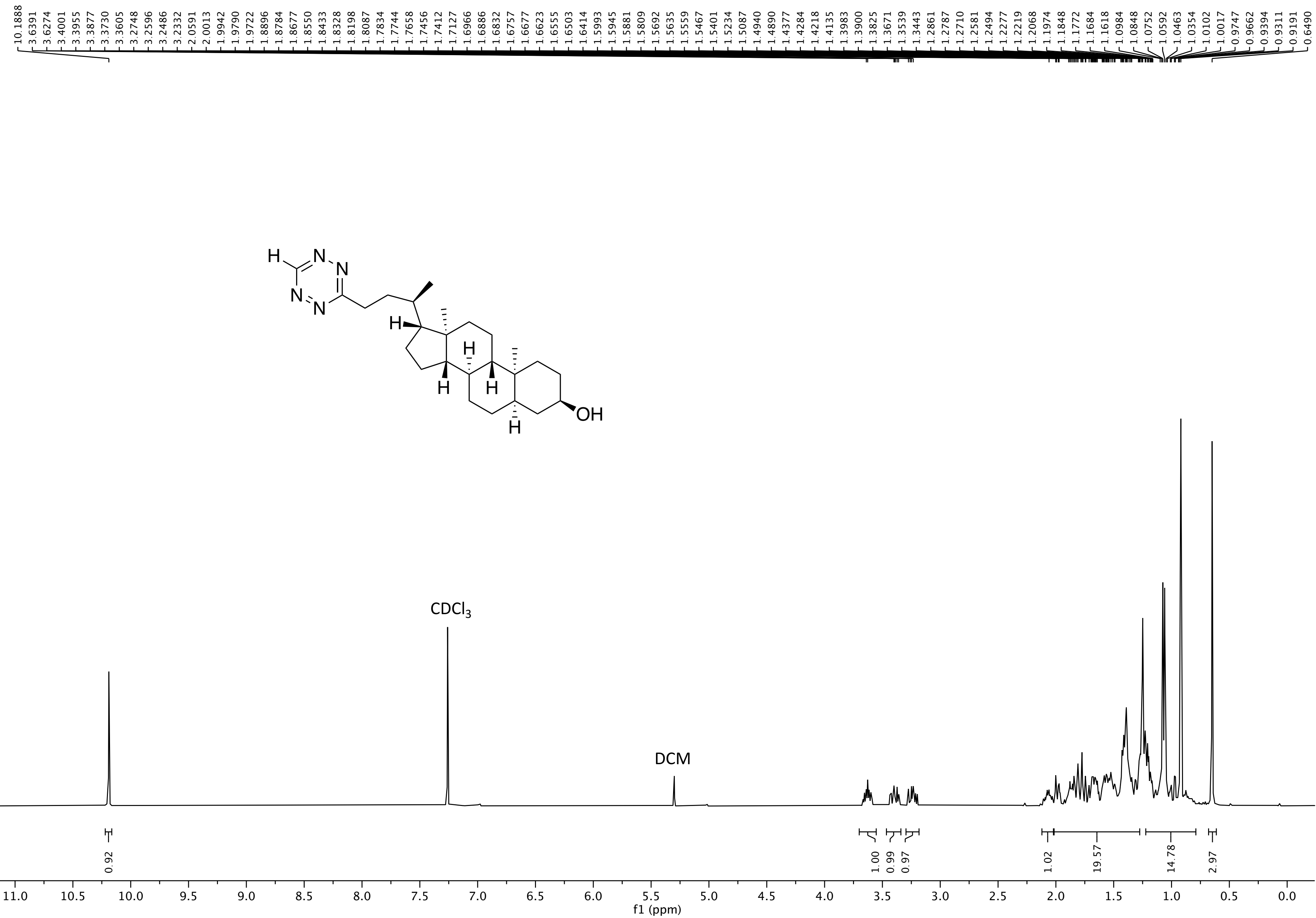
f1 (ppm)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3.3730
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3.2748
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3.2486
3.2332
2.0591
2.0013
1.9942
1.9790
1.9722
1.8896
1.8784
1.8677
1.8550
1.8433
1.8328
1.8198
1.8087
1.7834
1.7744
1.7658
1.7456
1.7412
1.7127
1.6966
1.6886
1.6832
1.6757
1.6677
1.6623
1.6555
1.6503
1.6414
1.5993
1.5945
1.5881
1.5809
1.5692
1.5635
1.5559
1.5467
1.5401
1.5234
1.5087
1.4940
1.4890
1.4377
1.4284
1.4218
1.4135
1.3983
1.3900
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1.3671
1.3539
1.3443
1.2861
1.2787
1.2710
1.2581
1.2494
1.2277
1.2219
1.2068
1.1974
1.1848
1.1772
1.1684
1.1618
1.0984
1.0848
1.0752
1.0592
1.0463
1.0354
1.0102
1.0017
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0.9662
0.9394
0.9311
0.9191
0.6490
H
N
N
N
N
H
H
H
H
H
OH
CDCl3
DCM
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0.99
0.97
1.02
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14.78
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10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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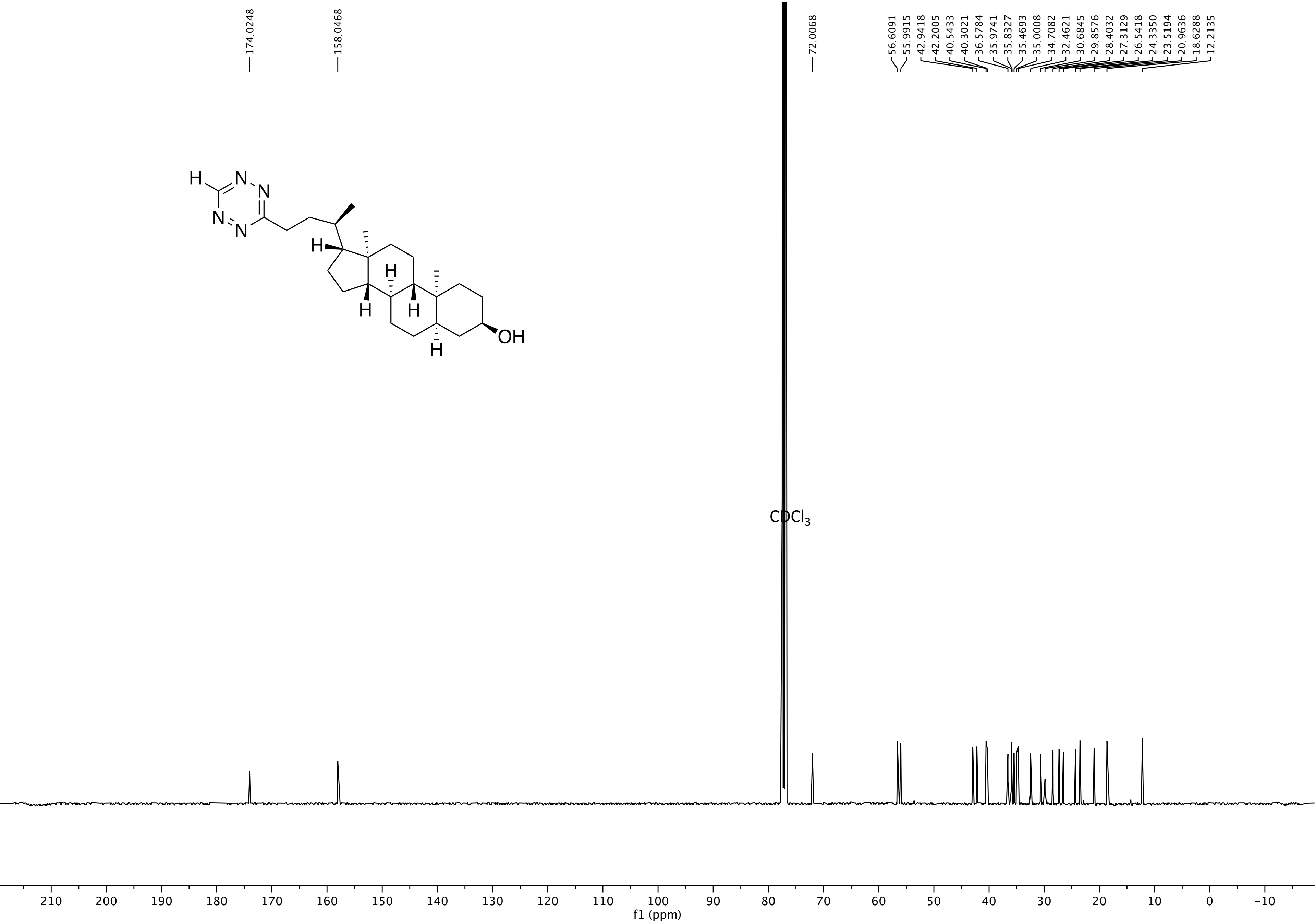
f1 (ppm)



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35.9741
35.8327
35.4693
35.0008
34.7082
32.4621
30.6845
29.8576
28.4032
27.3129
26.5418
24.3350
23.5194
20.9636
18.6288
12.2135
CDCl3
H
N
N
N
N
H
H
H
H
H
OH
210
200
190
180
170
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120
110
100
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80
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60
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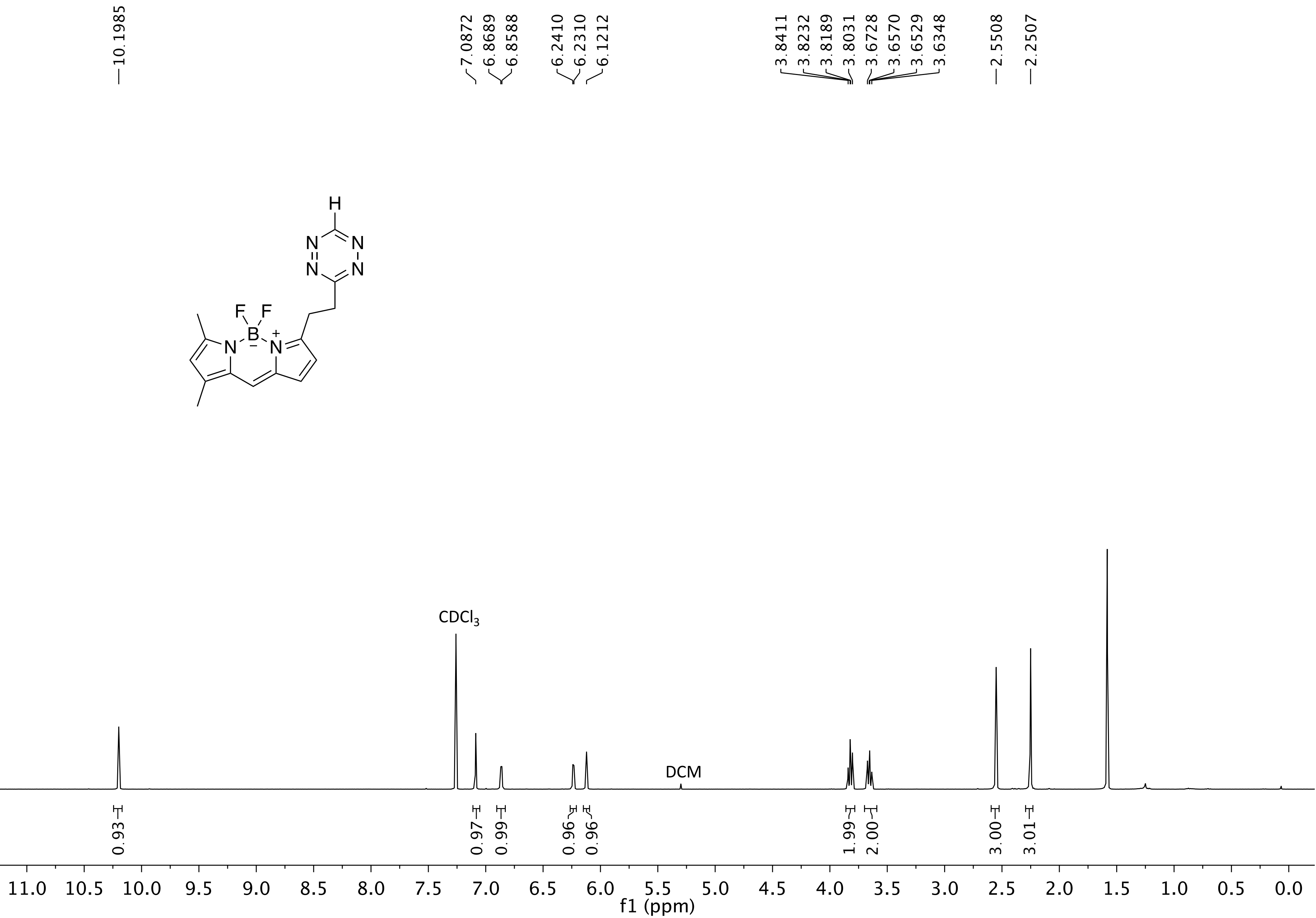
40
30
20
10
0
–10
f1 (ppm)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6.1212
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3.8189
3.8031
3.6728
3.6570
3.6529
3.6348
2.5508
2.2507
H
N
N
N
N
F
F
B
N
N
CDCl3
DCM
0.93
0.97
0.99
0.96
0.96
1.99
2.00
3.00
3.01
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
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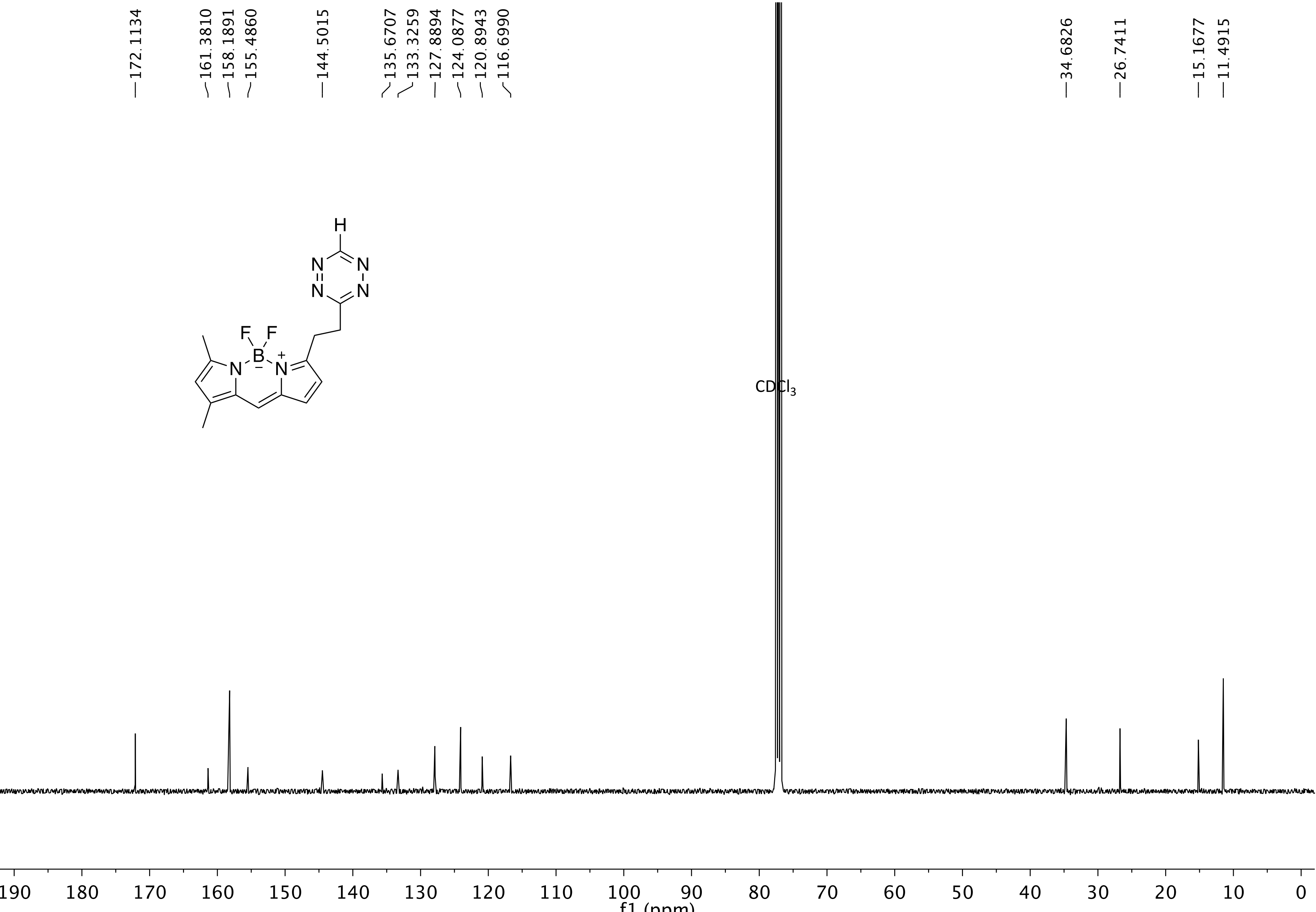
0.0
f1 (ppm)



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158.1891
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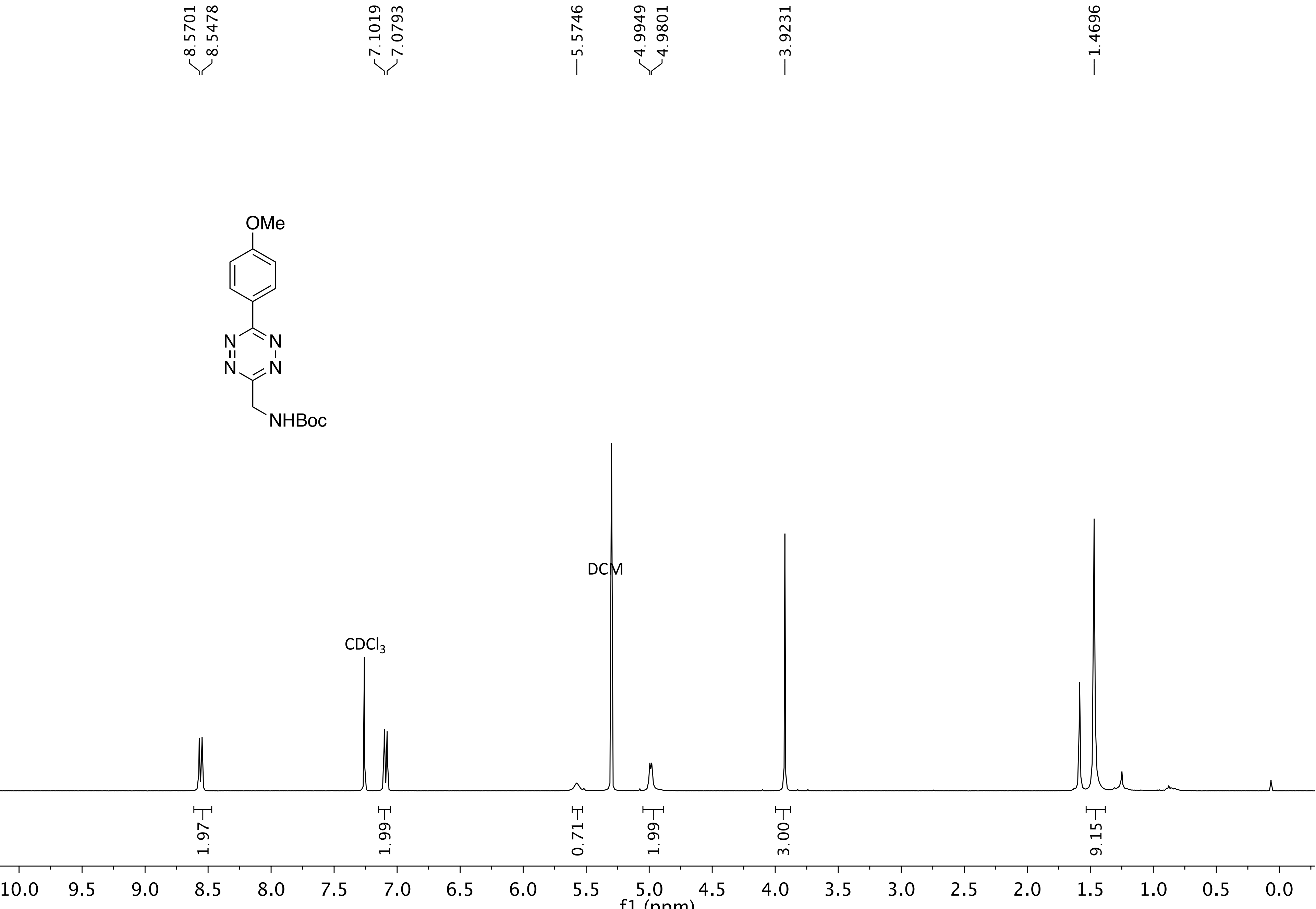
133.3259
127.8894
124.0877
120.8943
116.6990
34.6826
26.7411
15.1677
11.4915
CDCl3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



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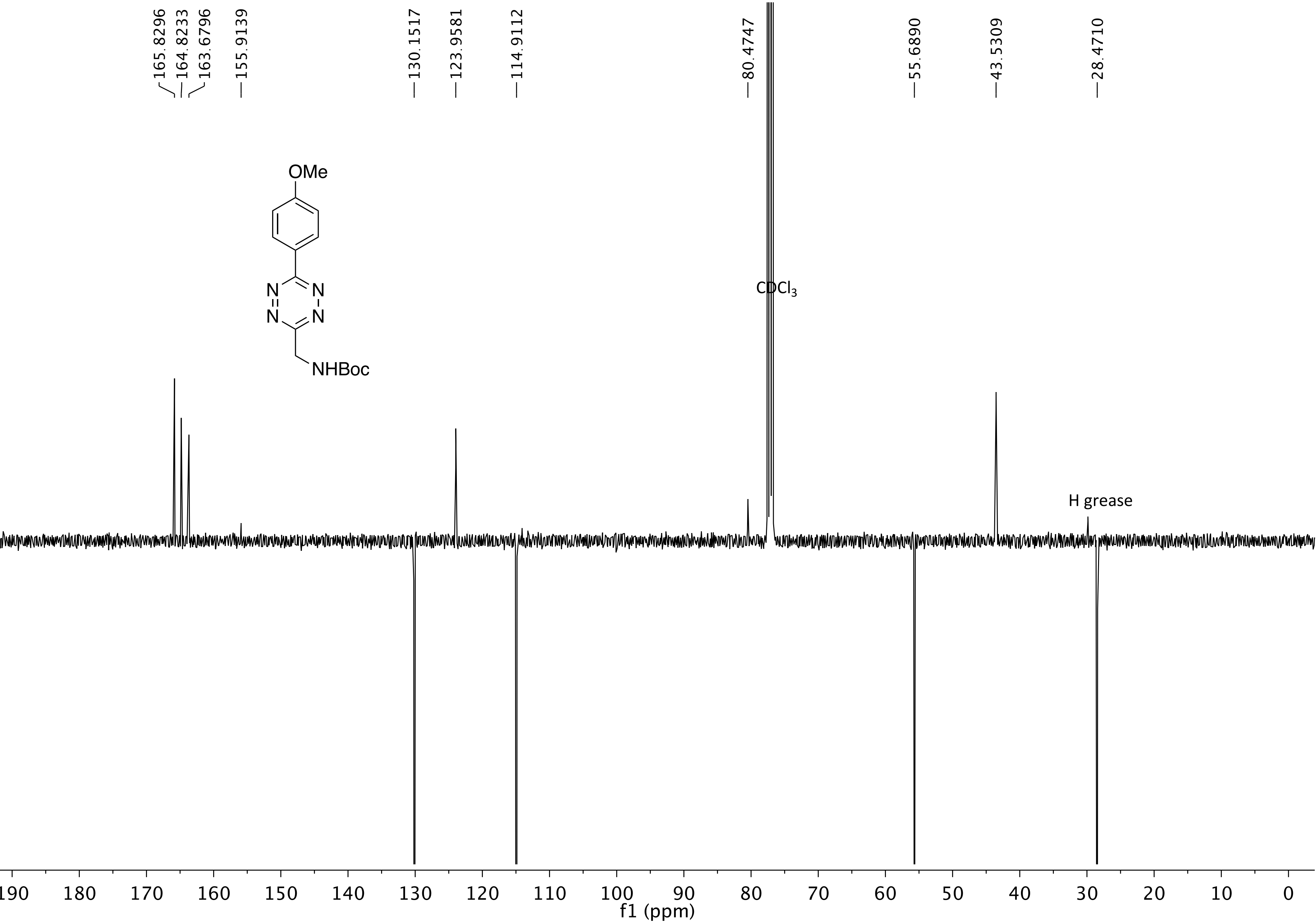
5.5746
4.9949
4.9801
3.9231
1.4696
OMe
N
N
N
N
NHBoc
DCM
CDCl3
1.97
1.99
0.71
1.99
3.00
9.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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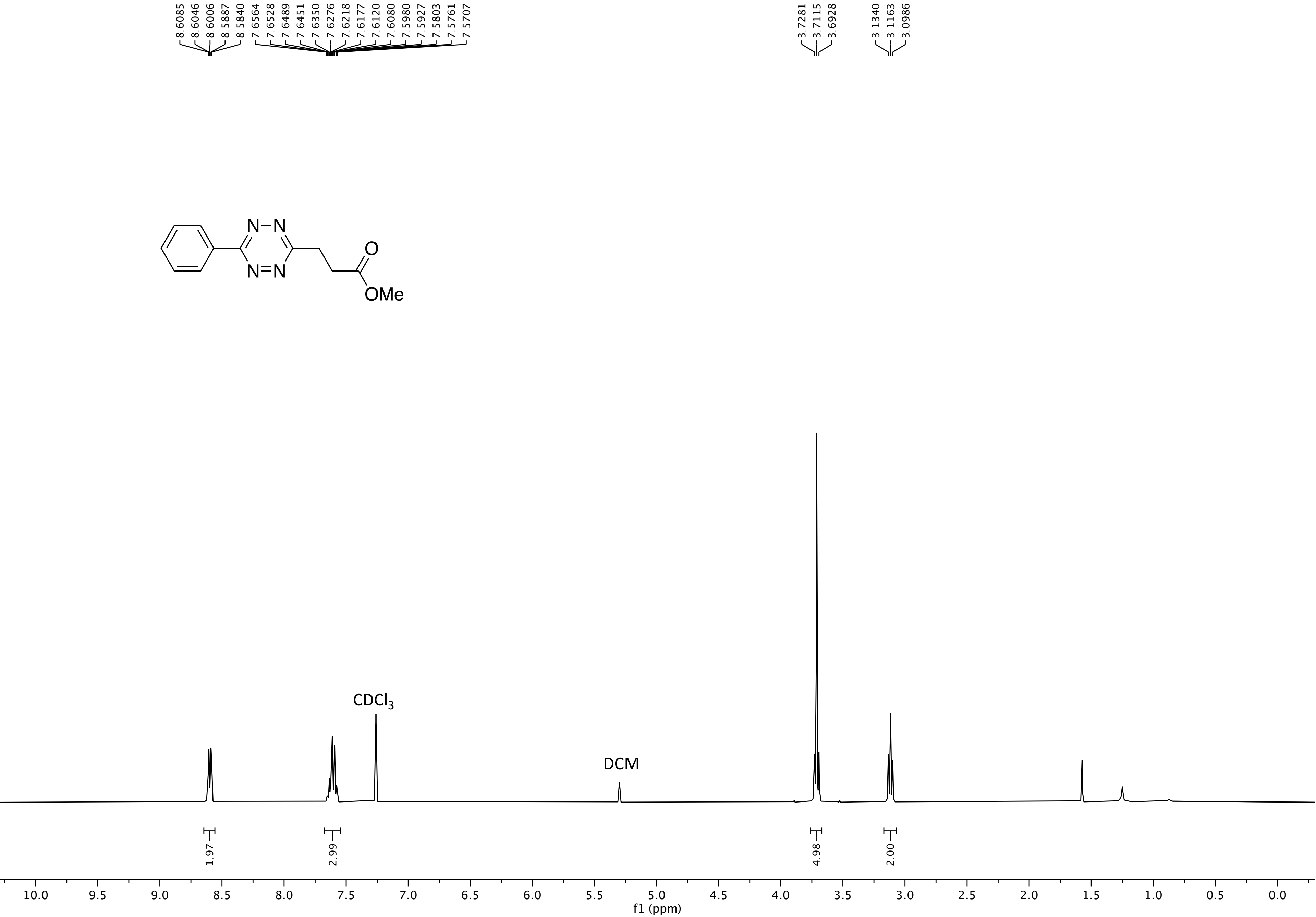
130.1517
123.9581
114.9112
80.4747
55.6890
43.5309
28.4710
OMe
N
N
N
N
NHBoc
CDCl3
H grease
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.5887
8.5840
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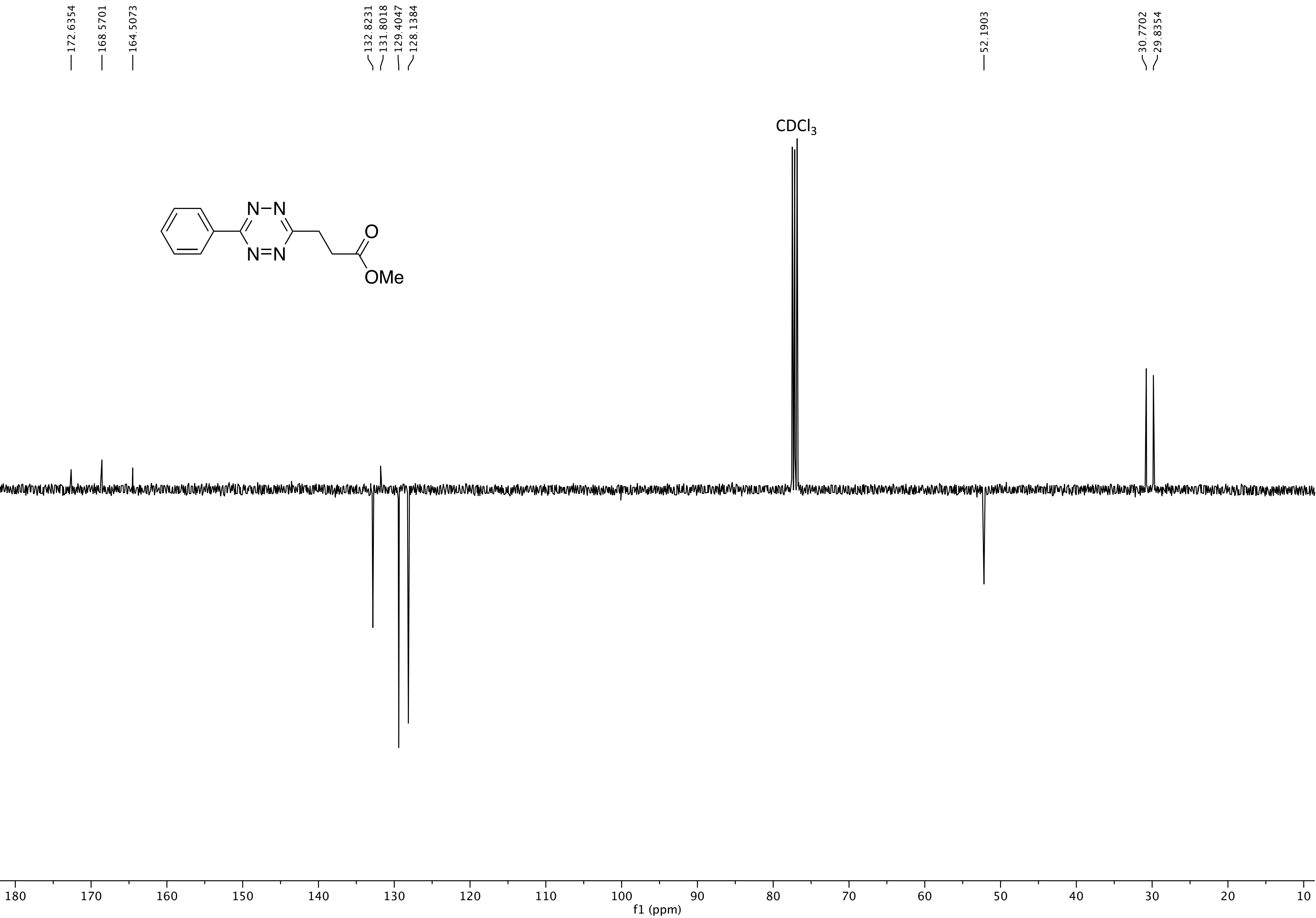
7.6528
7.6489
7.6451
7.6350
7.6276
7.6218
7.6177
7.6120
7.6080
7.5980
7.5927
7.5803
7.5761
7.5707
3.7281
3.7115
3.6928
3.1340
3.1163
3.0986
N–N
N=N
O
OMe
CDCl3
DCM
1.97
2.99
4.98
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



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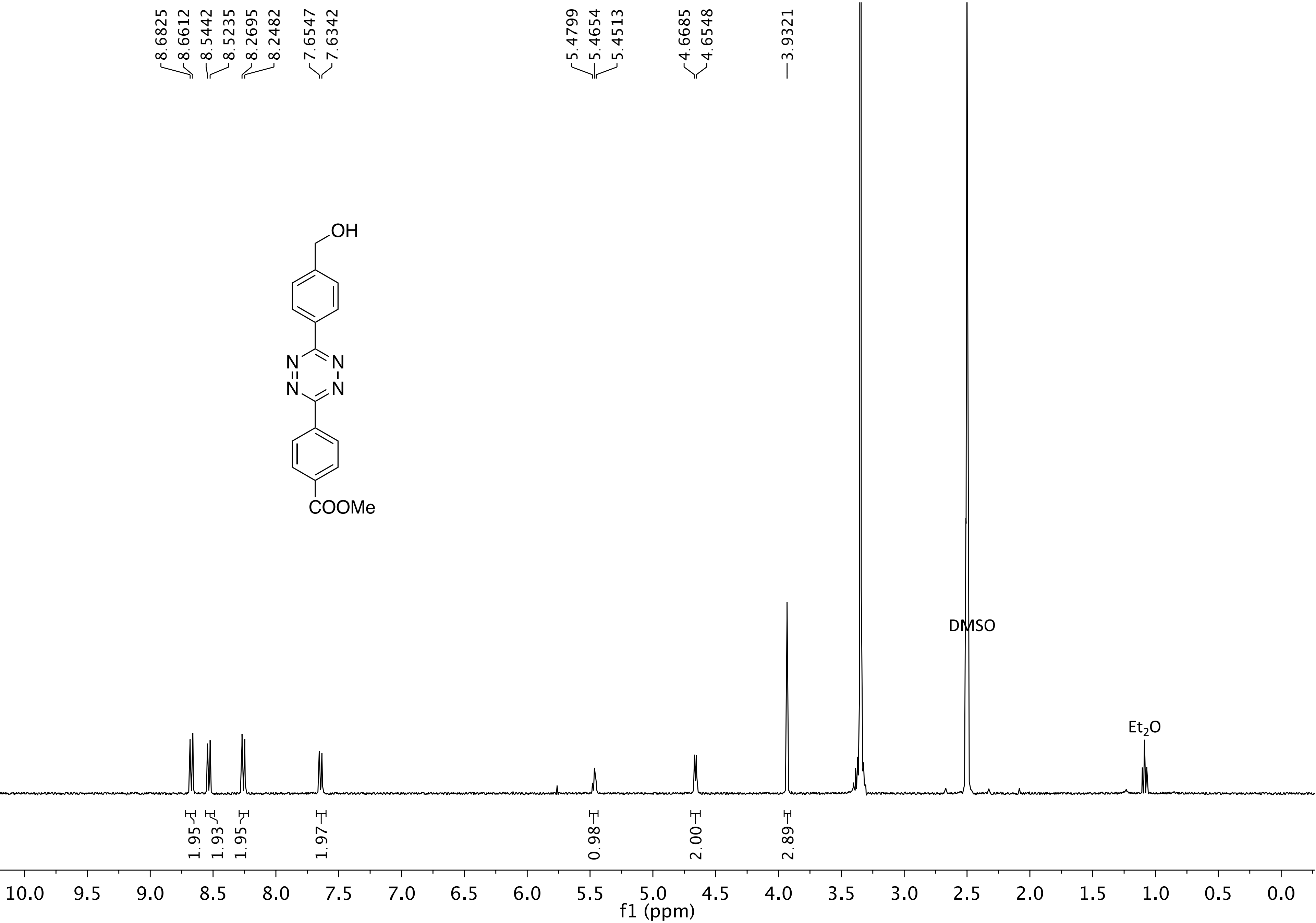
164.5073
132.8231
131.8018
129.4047
128.1384
52.1903
30.7702
29.8354
CDCl3
N−N
N=N
O
OMe
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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7.6547
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4.6685
4.6548
3.9321
OH
N
N
N
N
COOMe
DMSO
Et2O
1.95
1.93
1.95
1.97
0.98
2.00
2.89
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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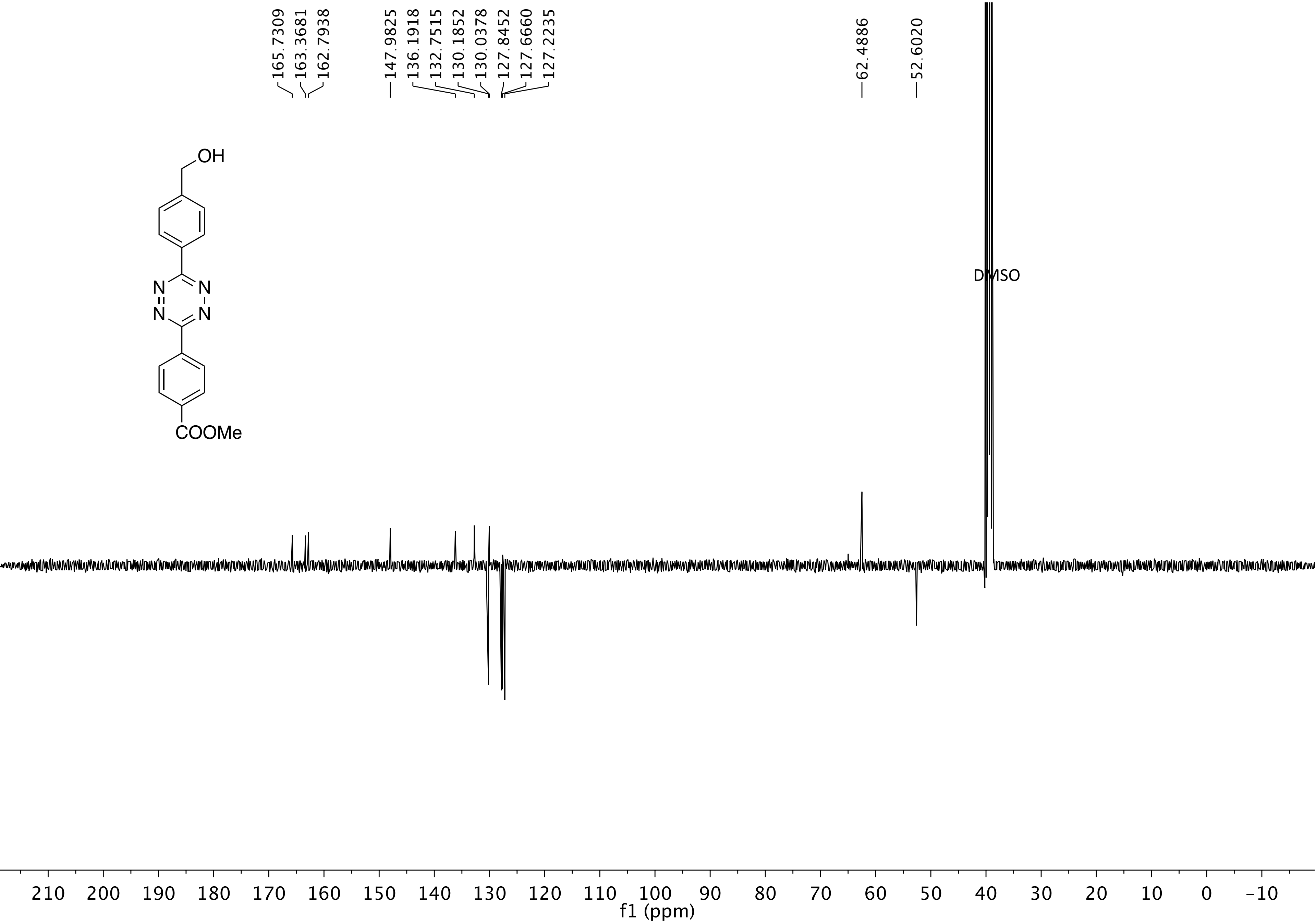
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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127.2235
62.4886
52.6020
OH
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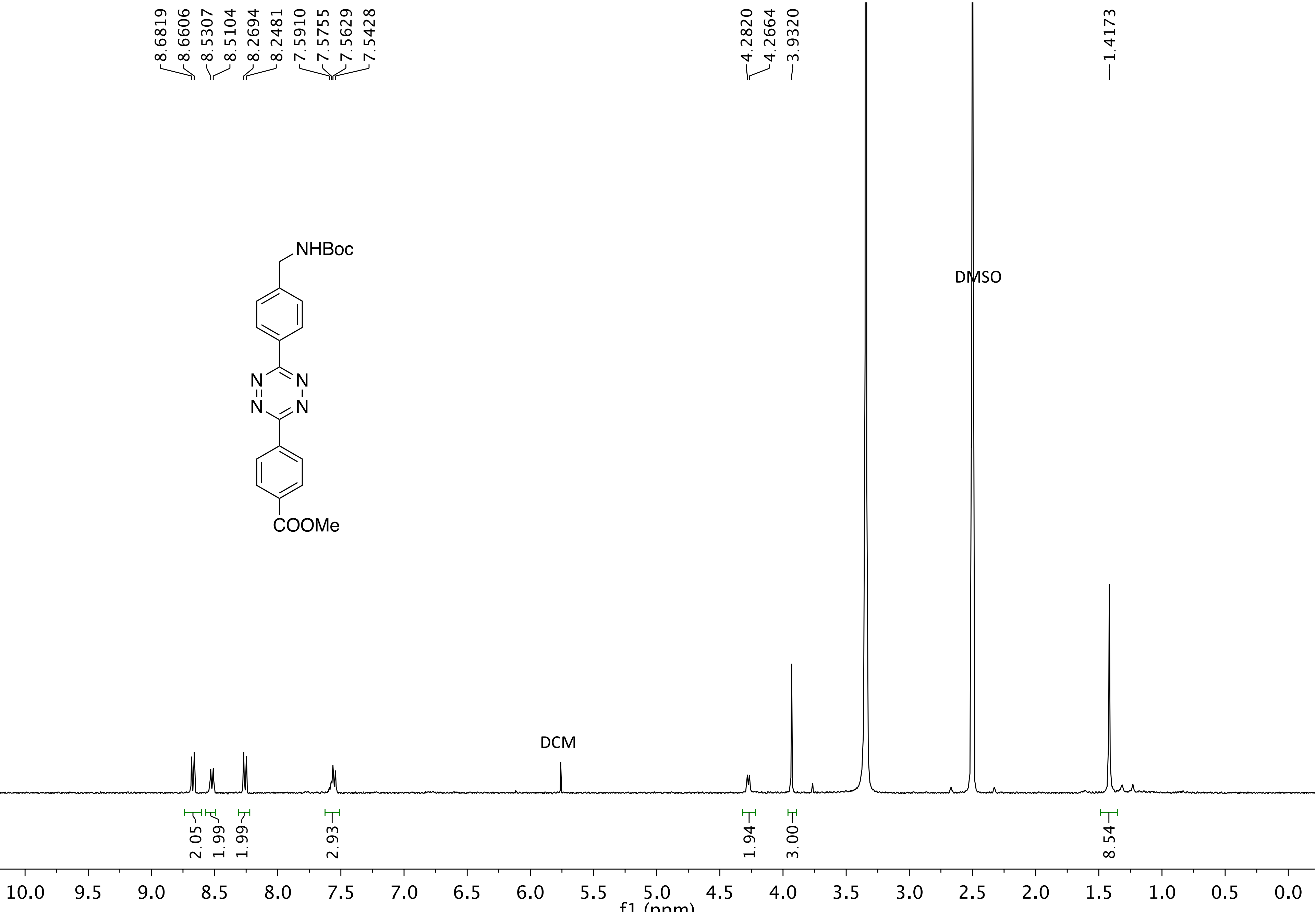
N
N
N
COOMe
DMSO
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 –10
f1 (ppm)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8.5104
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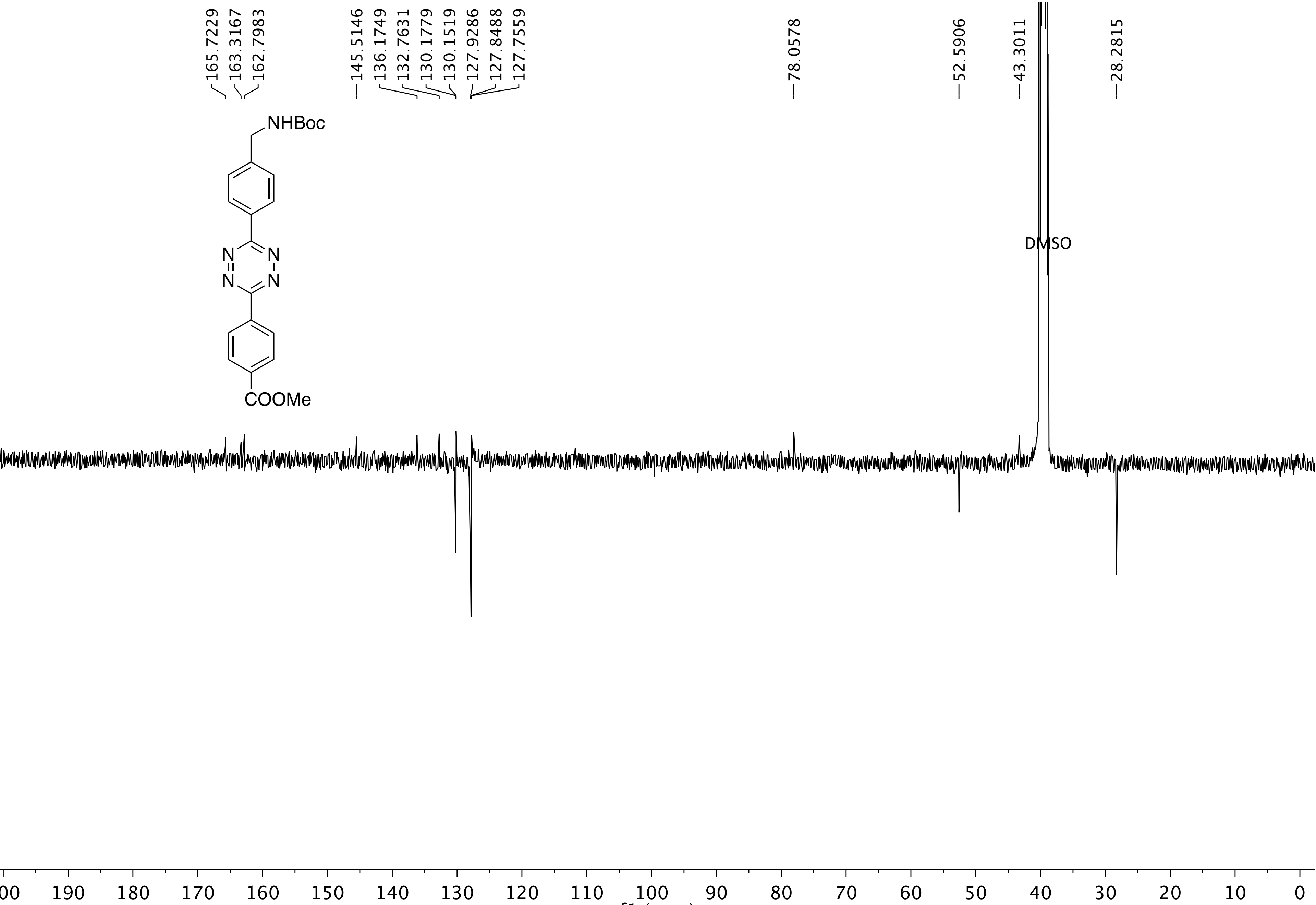
8.2481
7.5910
7.5755
7.5629
7.5428
4.2820
4.2664
3.9320
1.4173
NHBoc
N
N
N
N
COOMe
DMSO
DCM
2.05
1.99
1.99
2.93
1.94
3.00
8.54
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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162.7983
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130.1779
130.1519
127.9286
127.8488
127.7559
78.0578
52.5906
43.3011
28.2815
NHBoc
N
N
N
N
COOMe
DMSO
200
190
180
170
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150
140
130
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110
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90
80
70
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50
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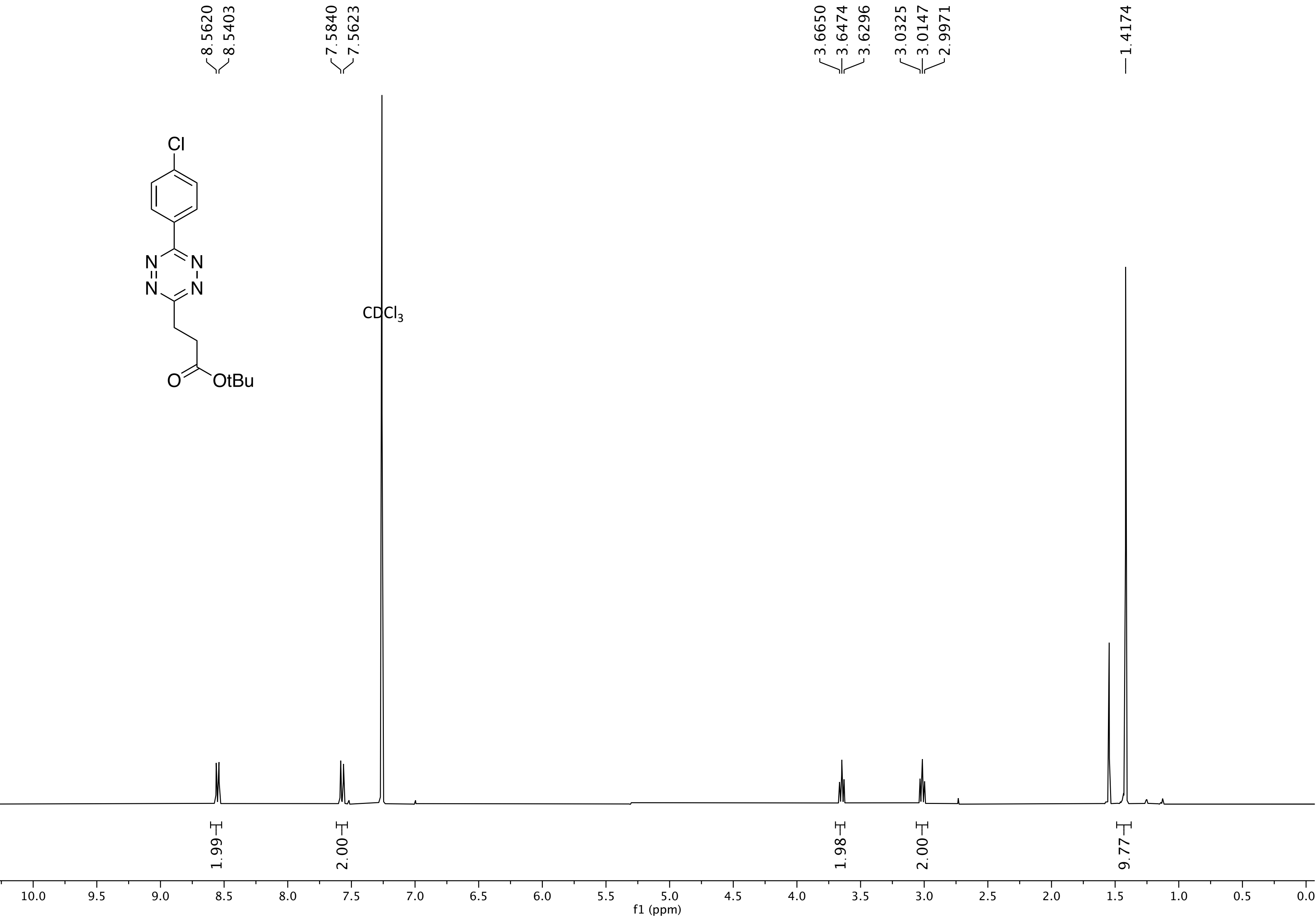
0
f1 (ppm)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Cl
N
N
N
N
O
OtBu
CDCl3
1.99
2.00
1.98
2.00
9.77
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
2.0
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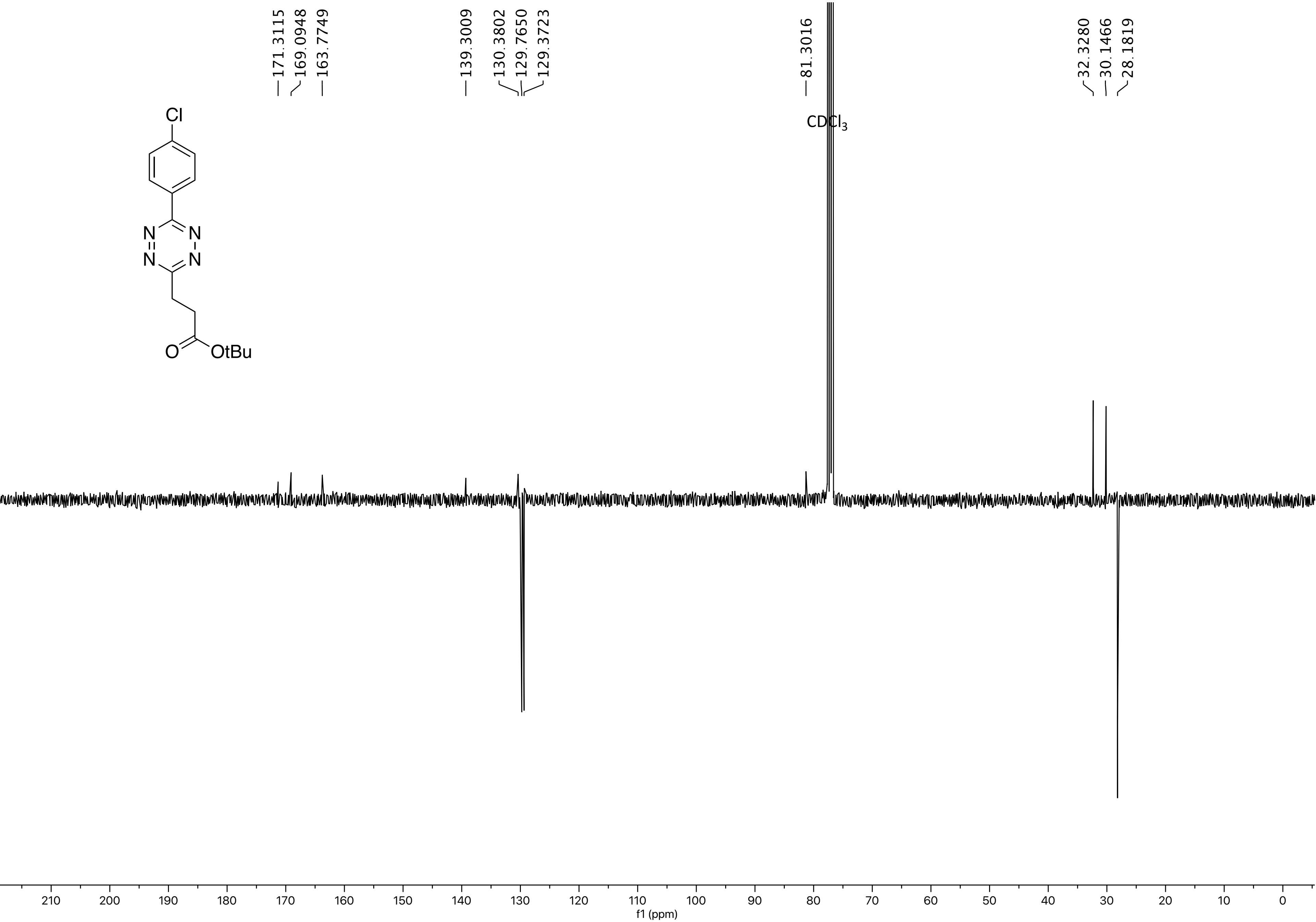
1.0
0.5
0.0
f1 (ppm)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129.3723
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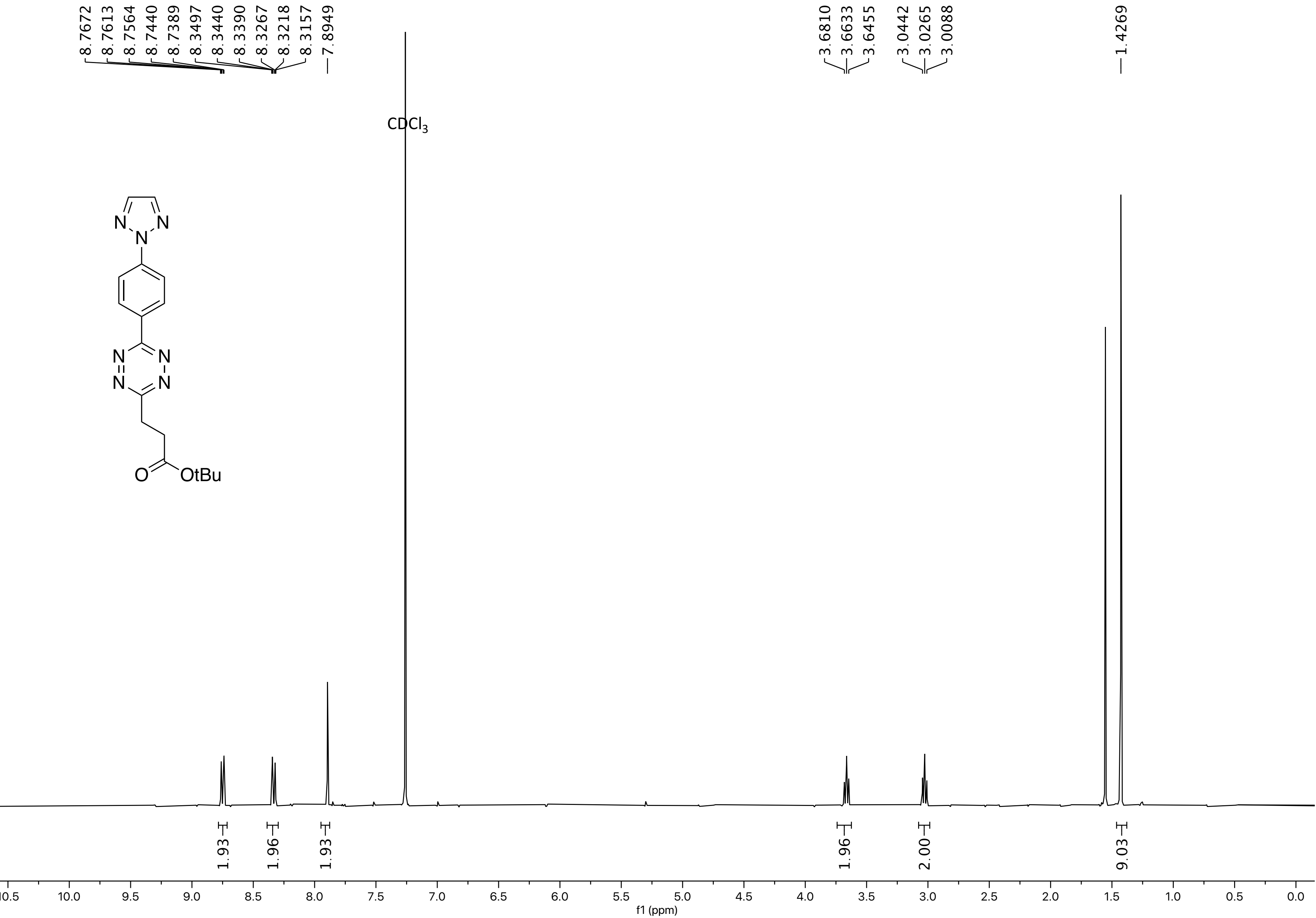
30.1466
28.1819
CDCl3
Cl
N
N
N
N
O
OtBu
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.3218
8.3157
7.8949
3.6810
3.6633
3.6455
3.0442
3.0265
3.0088
1.4269
CDCl3
N
N
N
N
N
N
N
O
OtBu
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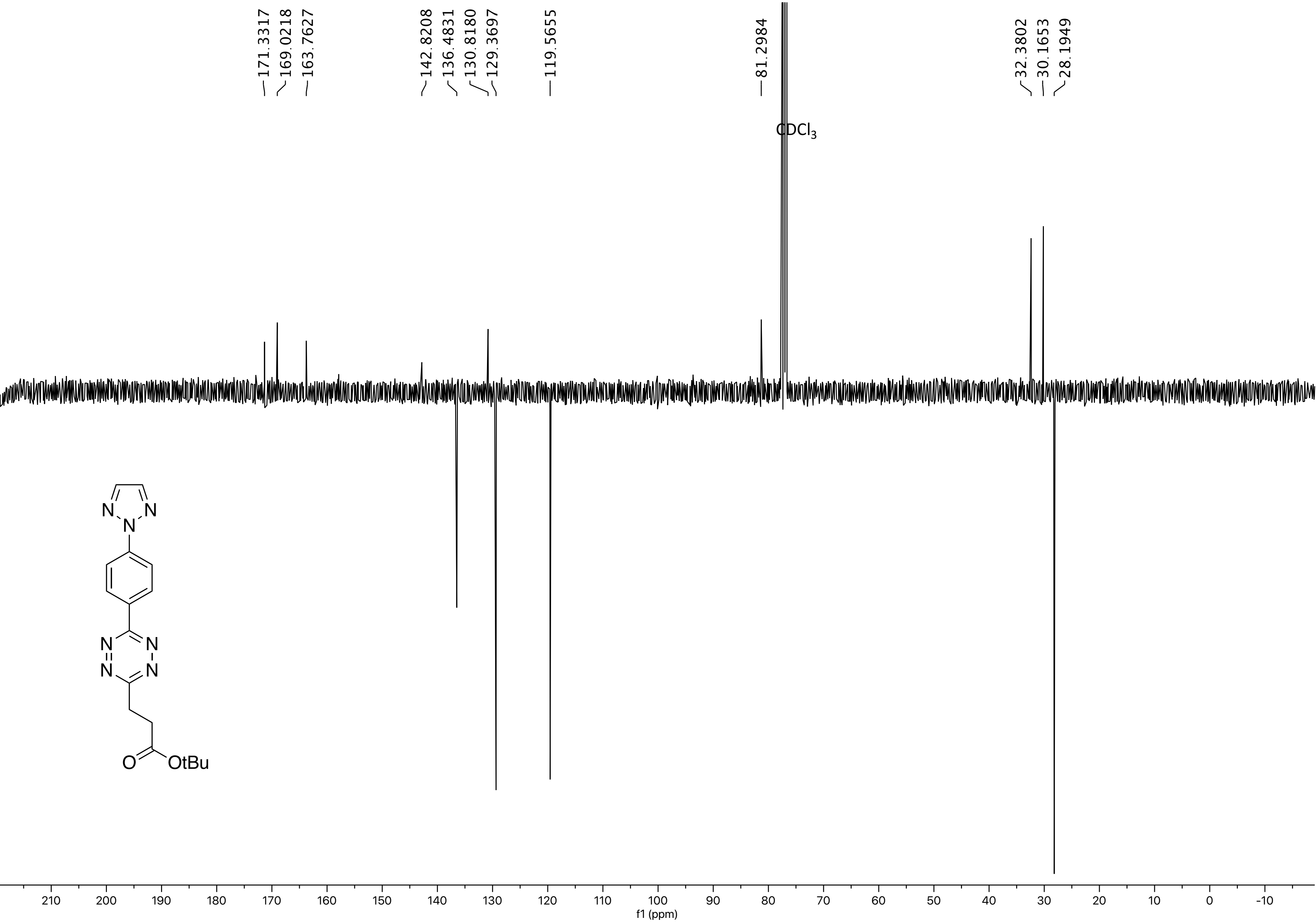
1.96
1.93
1.96
2.00
9.03
f1 (ppm)



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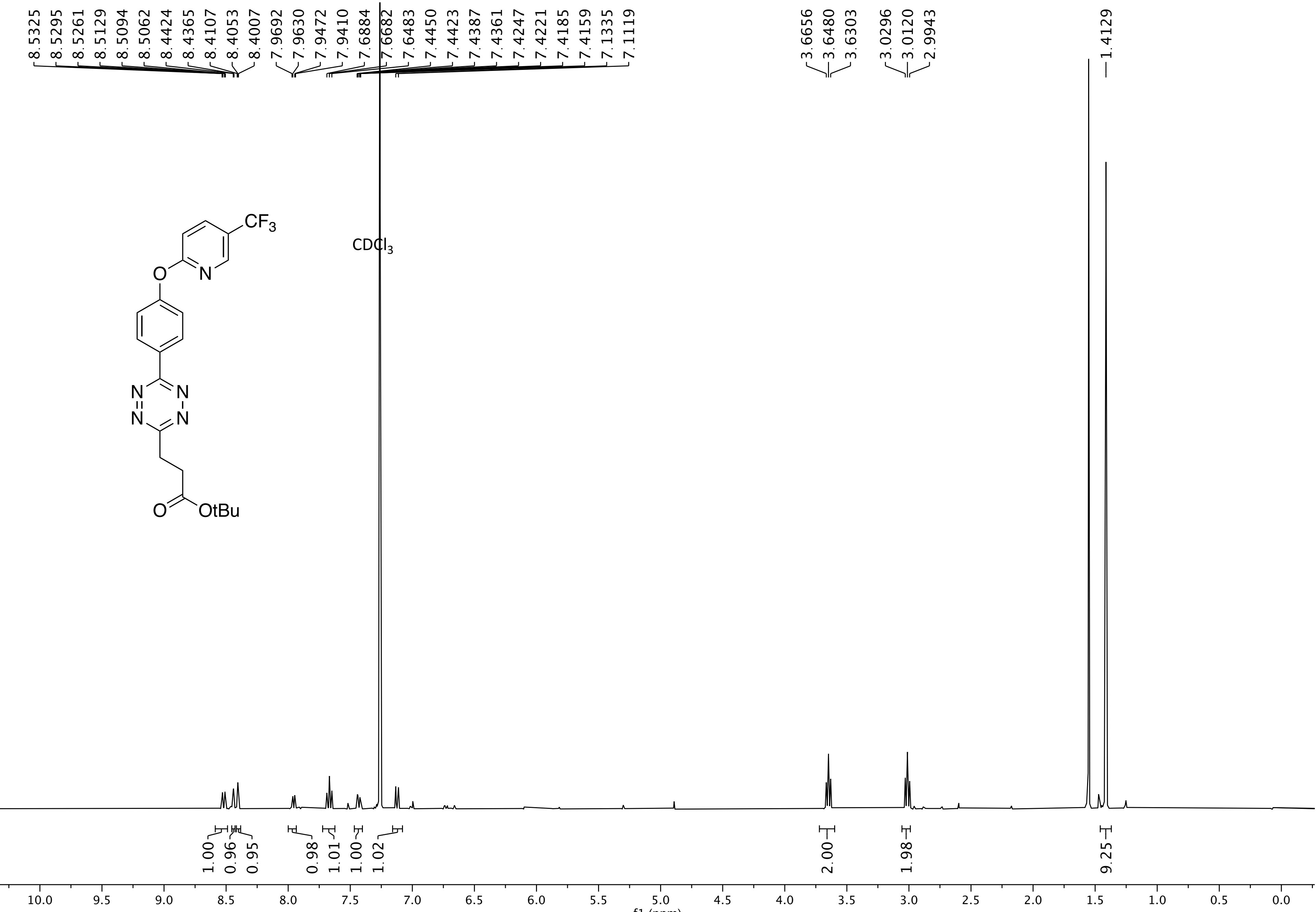
81.2984
32.3802
30.1653
28.1949
CDCl3
N
N
N
N
N
N
N
N
N
O
OtBu
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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7.9692
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7.9472
7.9410
7.6884
7.6682
7.6483
7.4450
7.4423
7.4387
7.4361
7.4247
7.4221
7.4185
7.4159
7.1335
7.1119
3.6656
3.6480
3.6303
3.0296
3.0120
2.9943
1.4129
CF3
O
N
N
N
N
N
O
OtBu
CDCl3
1.00
0.96
0.95
0.98
1.01
1.00
1.02
2.00
1.98
9.25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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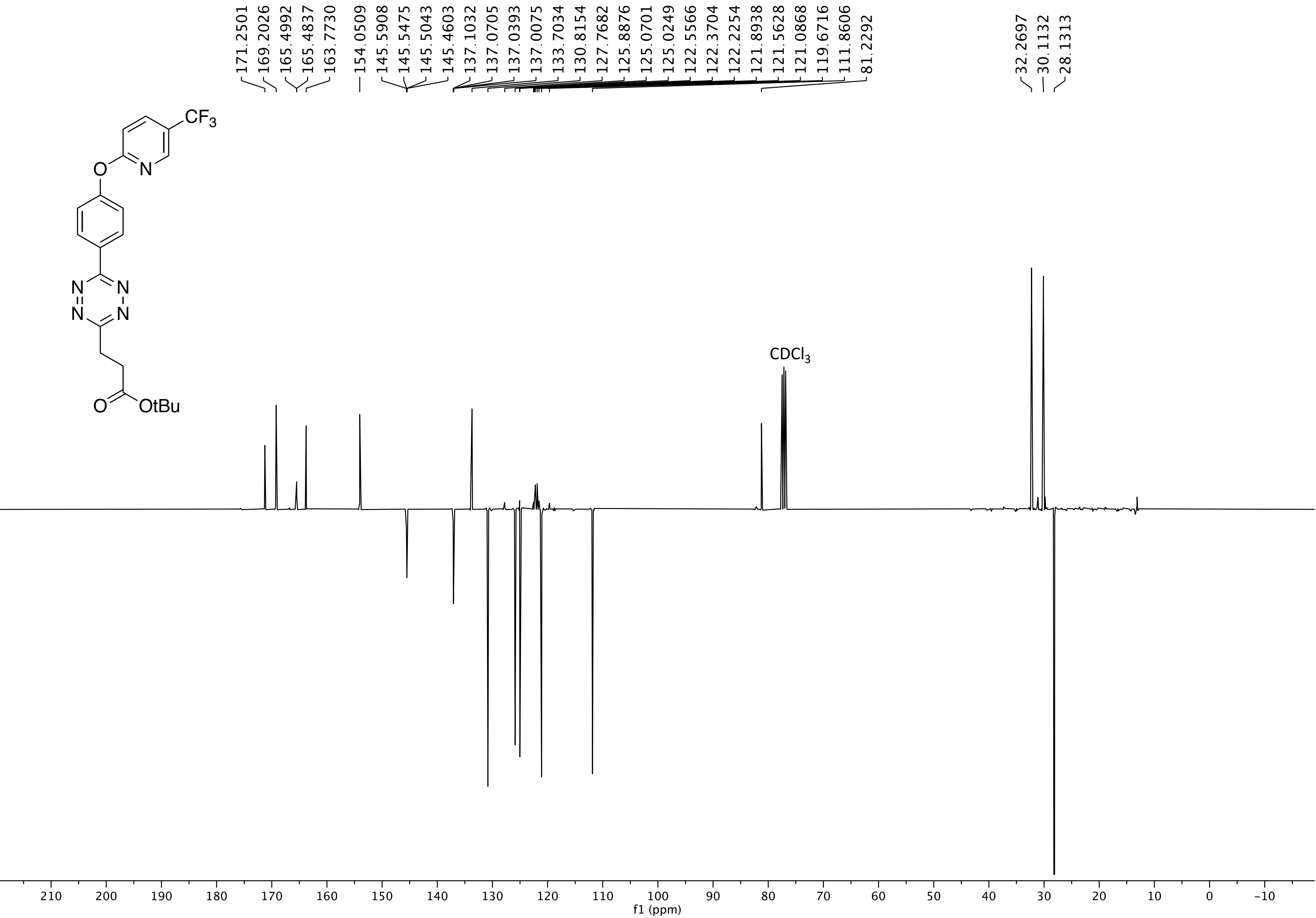
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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145.4603
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137.0705
137.0393
137.0075
133.7034
130.8154
127.7682
125.8876
125.0701
125.0249
122.5566
122.3704
122.2254
121.8938
121.5628
121.0868
119.6716
111.8606
81.2292
32.2697
30.1132
28.1313
CF3
O
N
N
N
N
N
O
OtBu
CDCl3
210
200
190
180
170
160
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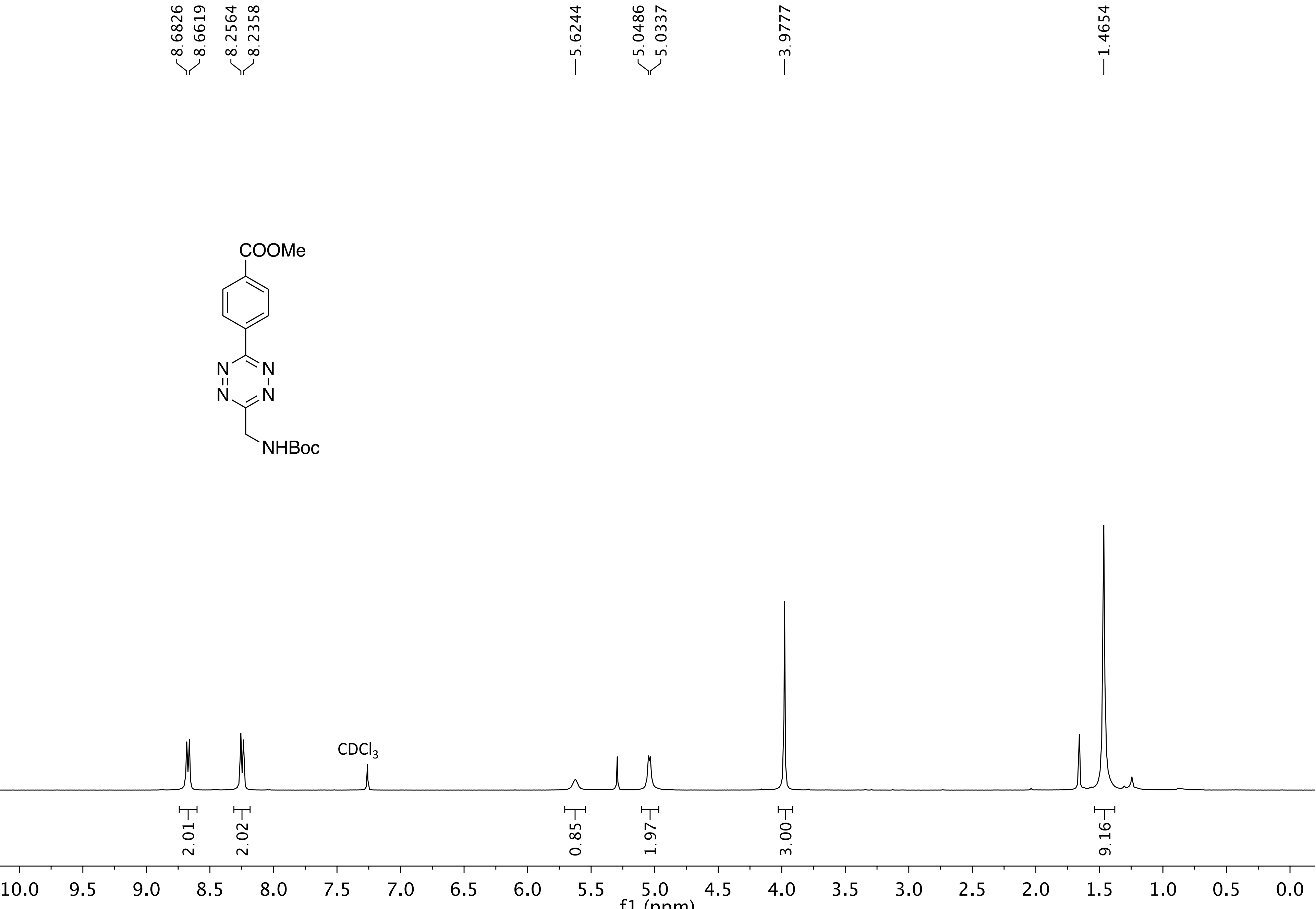
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)



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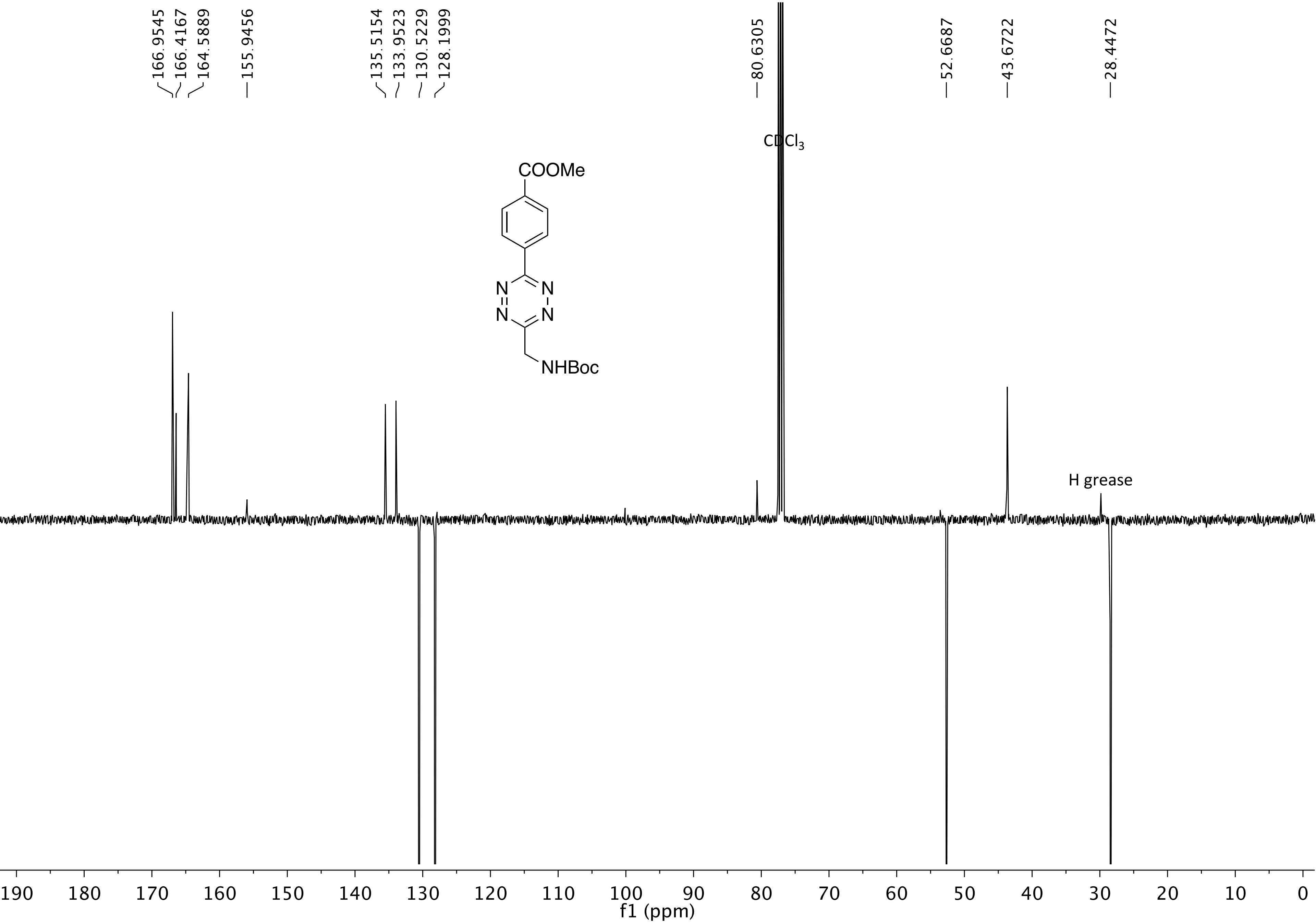
5.0486
5.0337
3.9777
1.4654
COOMe
N
N
N
N
NHBoc
CDCl3
2.01
2.02
0.85
1.97
3.00
9.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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52.6687
43.6722
28.4472
CDCl3
COOMe
N
N
N
N
NHBoc
H grease
190
180
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150
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120
110
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90
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70
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50
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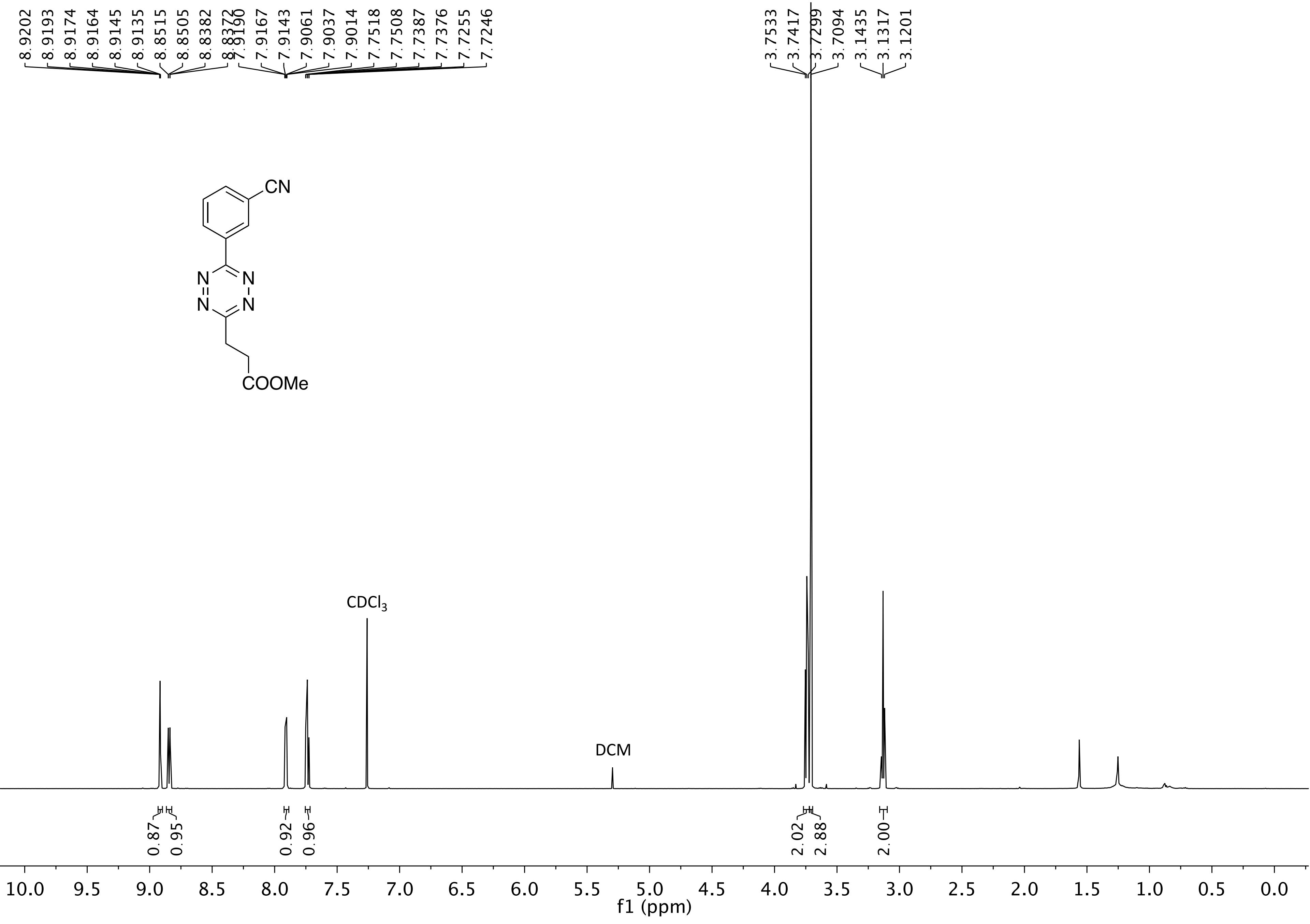
30
20
10
0
f1 (ppm)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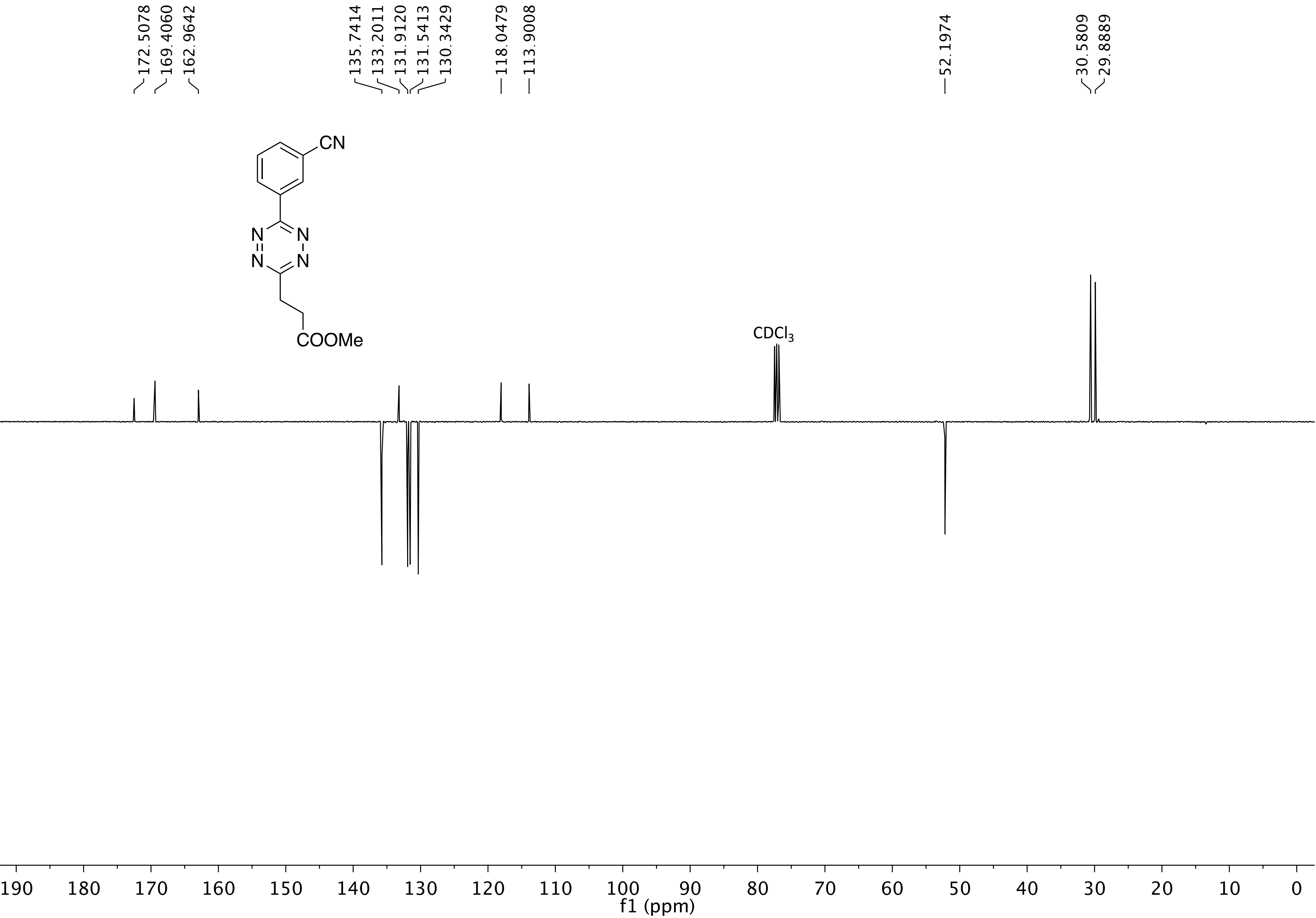
7.9167
7.9143
7.9061
7.9037
7.9014
7.7518
7.7508
7.7387
7.7376
7.7255
7.7246
3.7533
3.7417
3.7299
3.7094
3.1435
3.1317
3.1201
CN
N
N
N
N
COOMe
CDCl3
DCM
0.87
0.95
0.92
0.96
2.02
2.88
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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162.9642
135.7414
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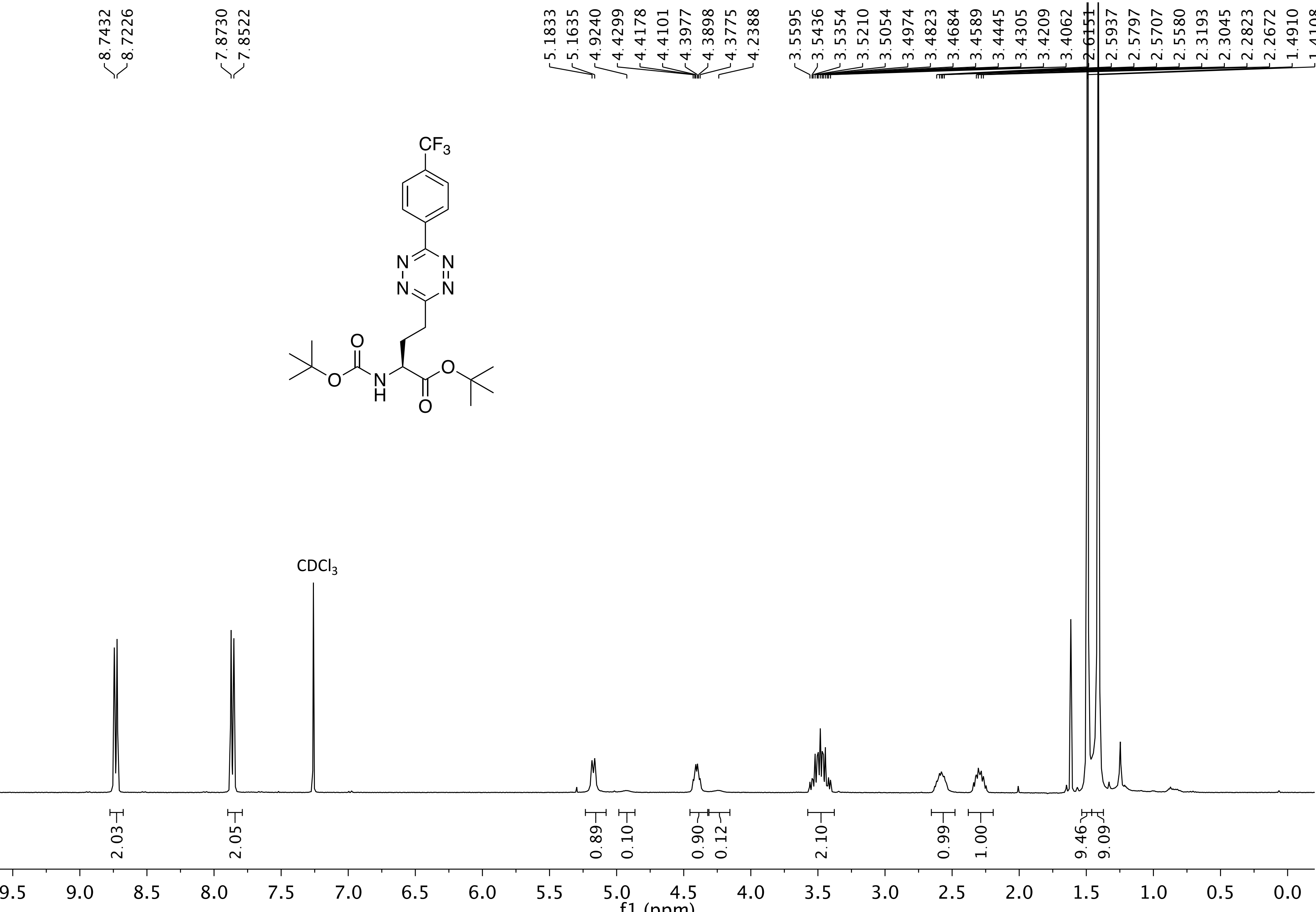
131.5413
130.3429
118.0479
113.9008
52.1974
30.5809
29.8889
CN
N
N
N
N
COOMe
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



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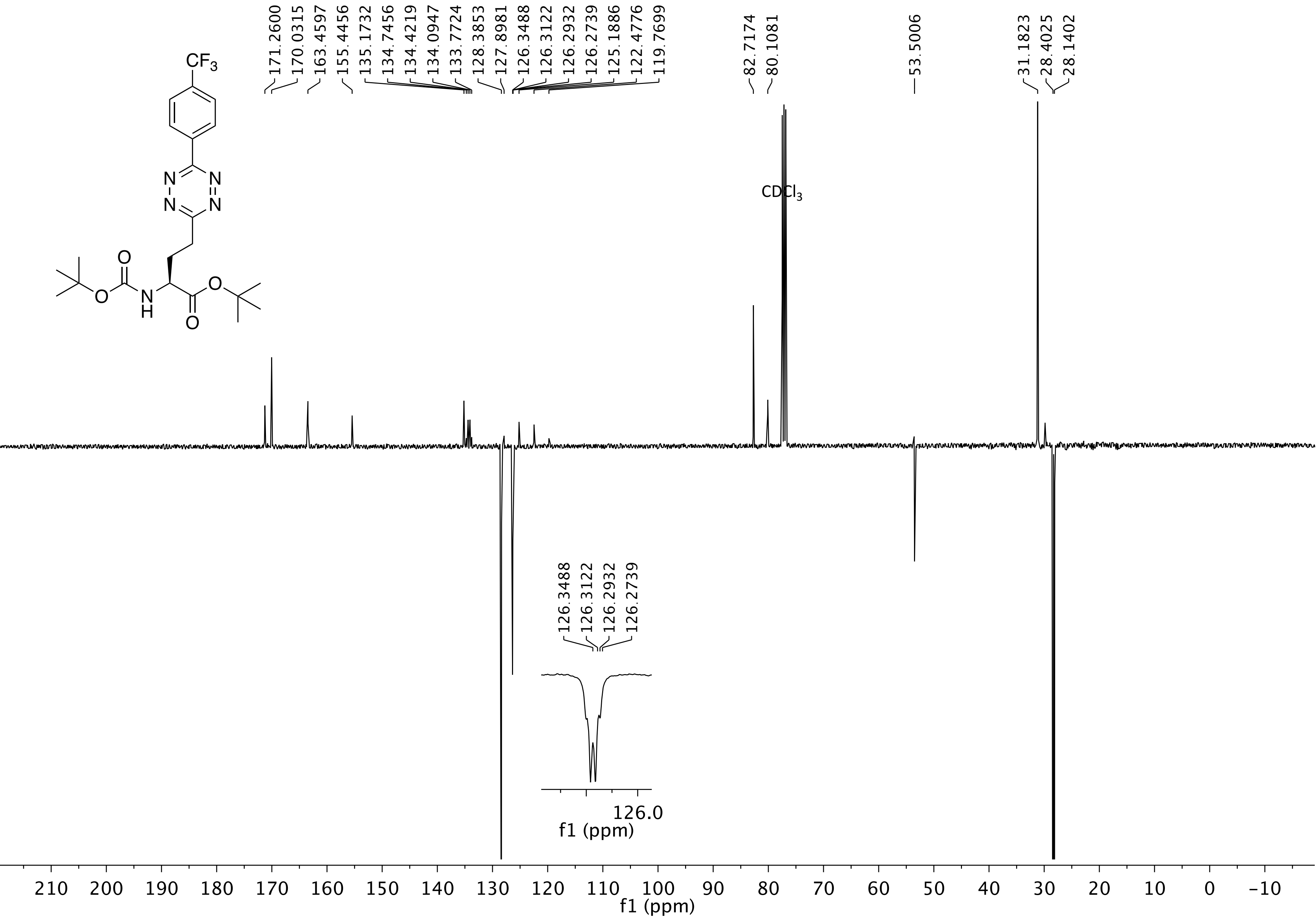
8.7226
7.8730
7.8522
5.1833
5.1635
4.9240
4.4299
4.4178
4.4101
4.3977
4.3898
4.3775
4.2388
3.5595
3.5436
3.5354
3.5210
3.5054
3.4974
3.4823
3.4684
3.4589
3.4445
3.4305
3.4209
3.4062
2.6151
2.5937
2.5797
2.5707
2.5580
2.3193
2.3045
2.2823
2.2672
1.4910
CF3
N
N
N
N
O
O
N
H
O
O
CDCl3
2.03
2.05
0.89
0.10
0.90
0.12
2.10
0.99
1.00
9.46
9.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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N
N
N
O
O
N
H
O
O
171.2600
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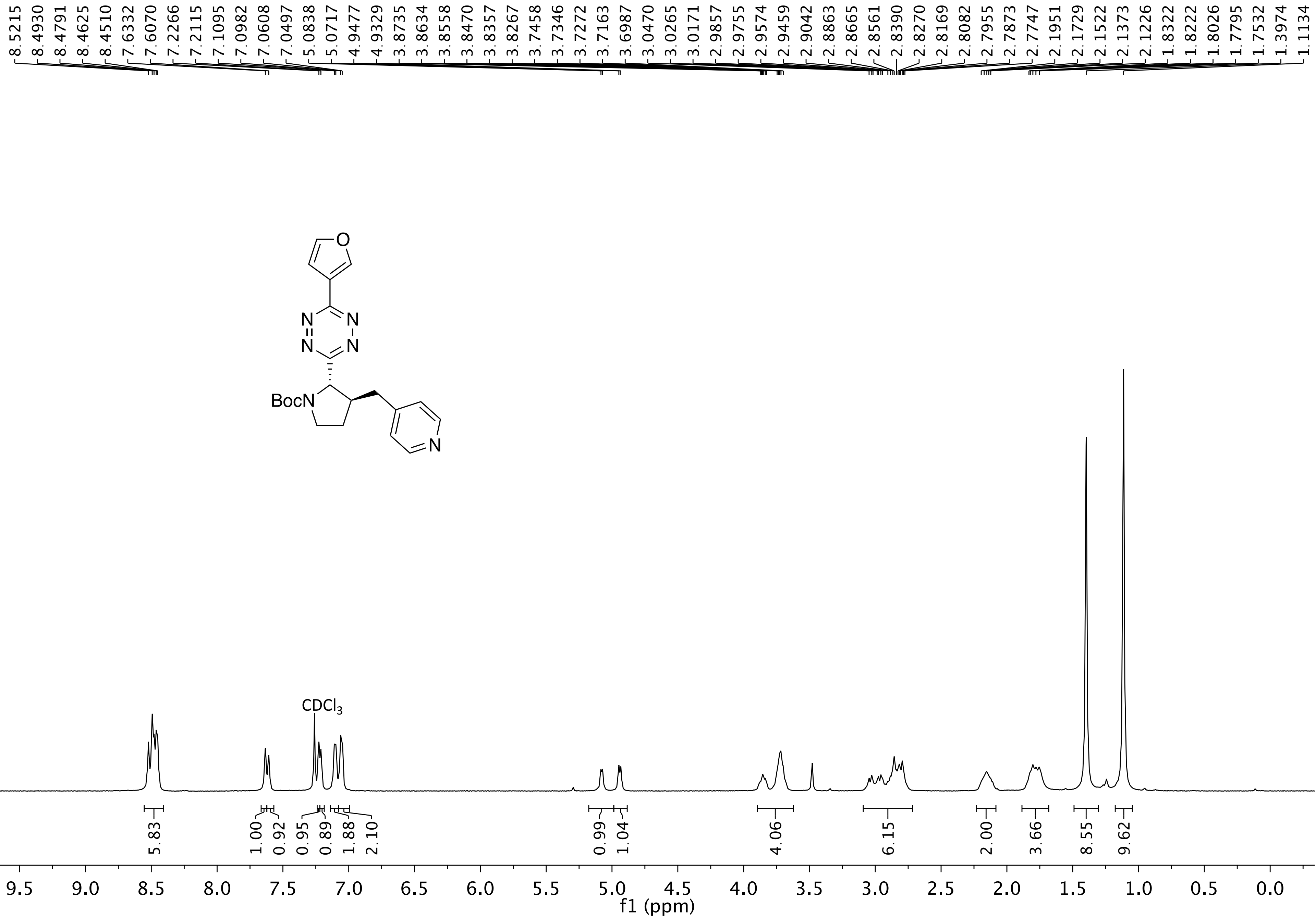
163.4597
155.4456
135.1732
134.7456
134.4219
134.0947
133.7724
128.3853
127.8981
126.3488
126.3122
126.2932
126.2739
125.1886
122.4776
119.7699
82.7174
80.1081
53.5006
31.1823
28.4025
28.1402
CDCl3
126.3488
126.3122
126.2932
126.2739
126.0
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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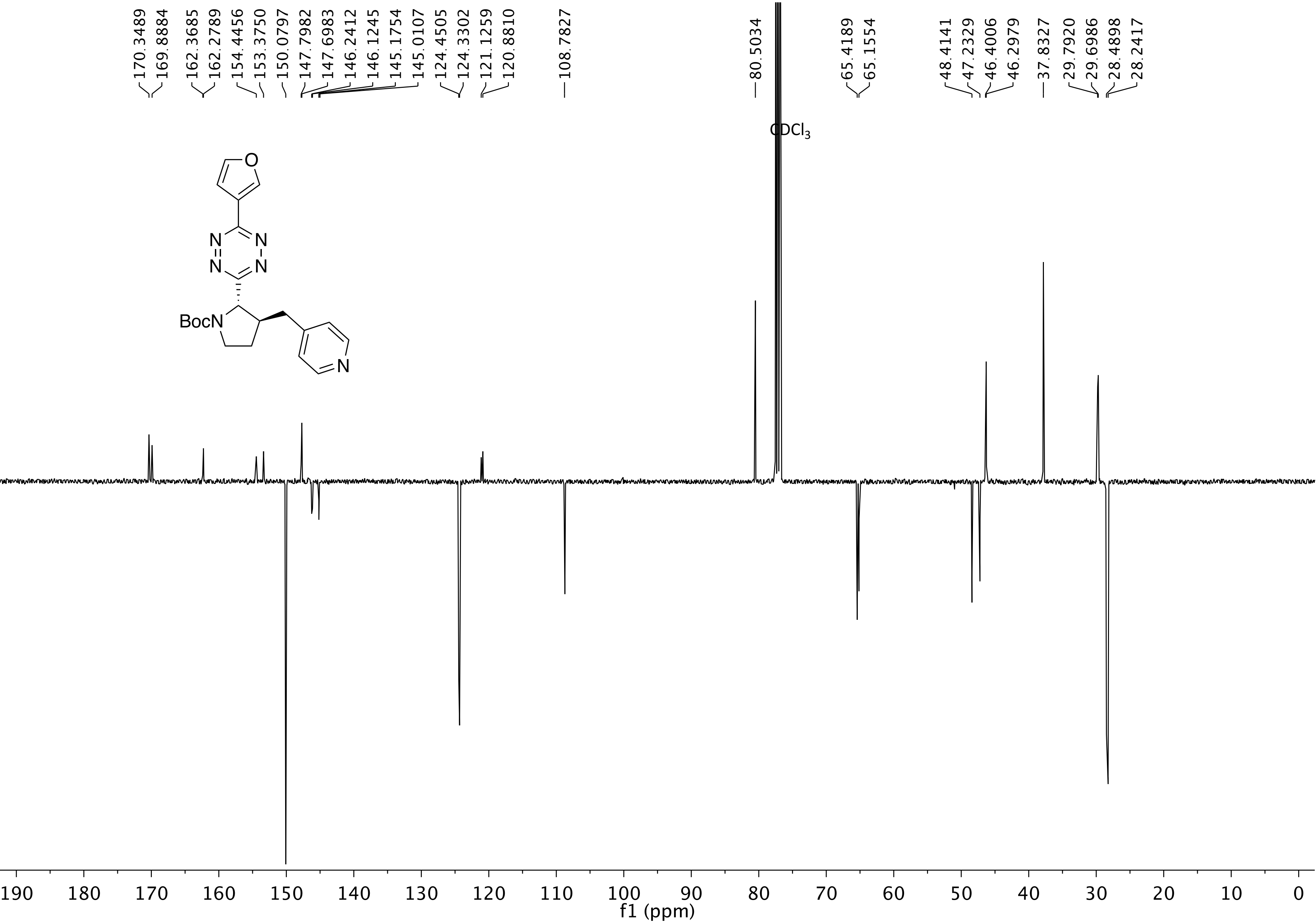
7.1095
7.0982
7.0608
7.0497
5.0838
5.0717
4.9477
4.9329
3.8735
3.8634
3.8558
3.8470
3.8357
3.8267
3.7458
3.7346
3.7272
3.7163
3.6987
3.0470
3.0265
3.0171
2.9857
2.9755
2.9574
2.9459
2.9042
2.8863
2.8665
2.8561
2.8390
2.8270
2.8169
2.8082
2.7955
2.7873
2.7747
2.1951
2.1729
2.1522
2.1373
2.1226
1.8322
1.8222
1.8026
1.7795
1.7532
1.3974
1.1134
O
N
N
N
N
BocN
N
CDCl$_3$
5.83
1.00
0.92
0.95
0.89
1.88
2.10
0.99
1.04
4.06
6.15
2.00
3.66
8.55
9.62
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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162.3685
162.2789
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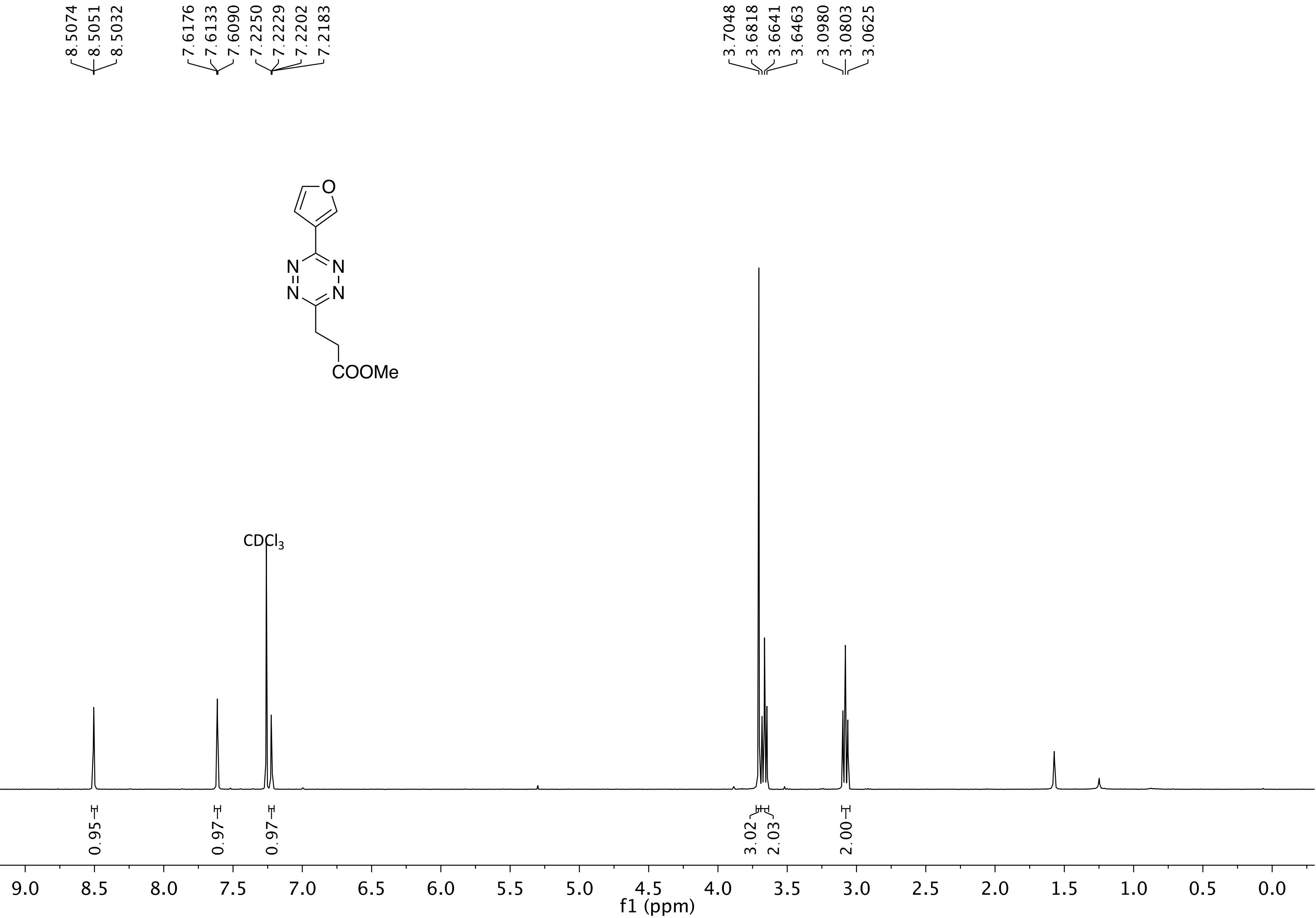
153.3750
150.0797
147.7982
147.6983
146.2412
146.1245
145.1754
145.0107
124.4505
124.3302
121.1259
120.8810
108.7827
80.5034
65.4189
65.1554
48.4141
47.2329
46.4006
46.2979
37.8327
29.7920
29.6986
28.4898
28.2417
CDCl3
O
N
N
N
N
BocN
N
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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8.5032
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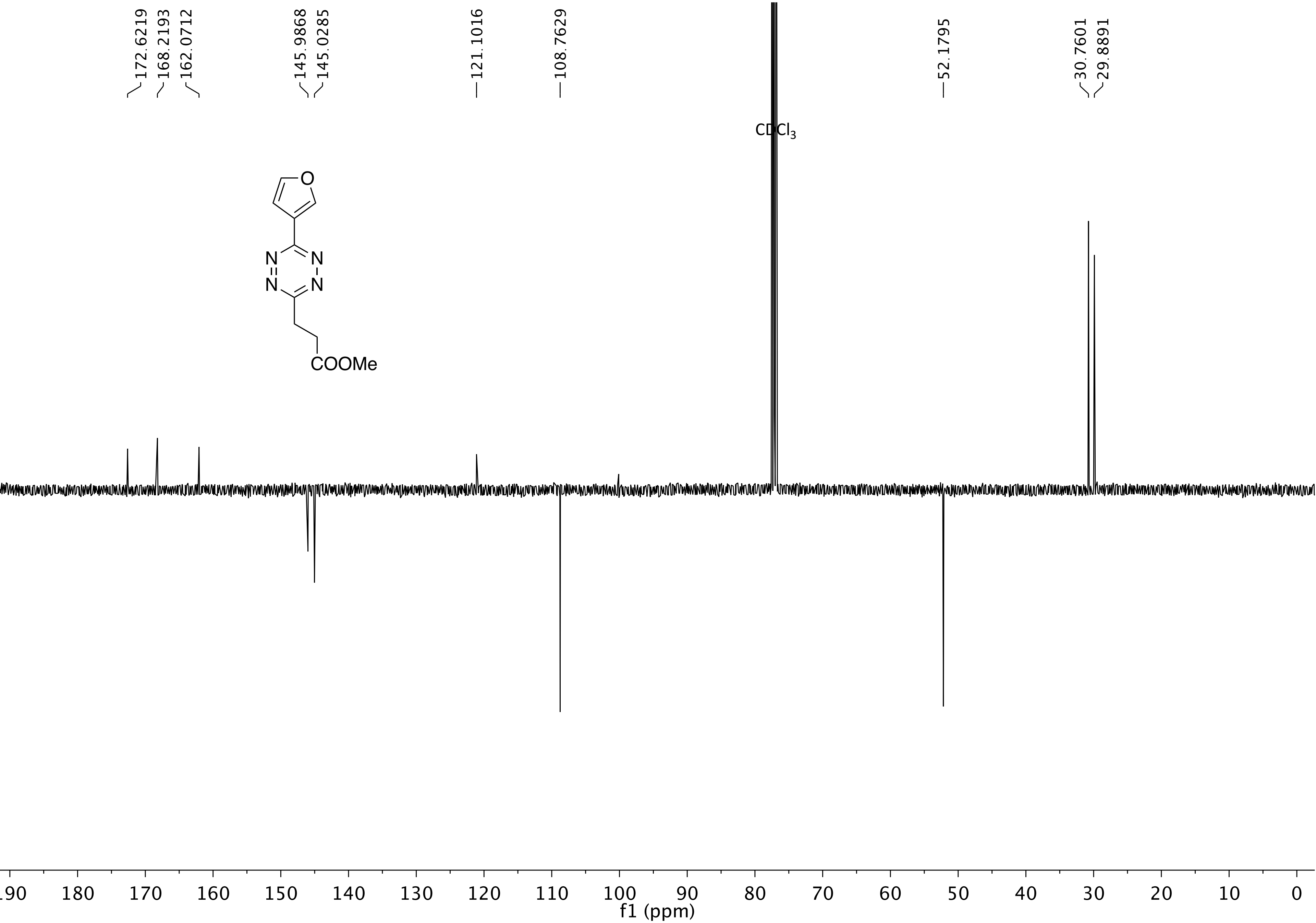
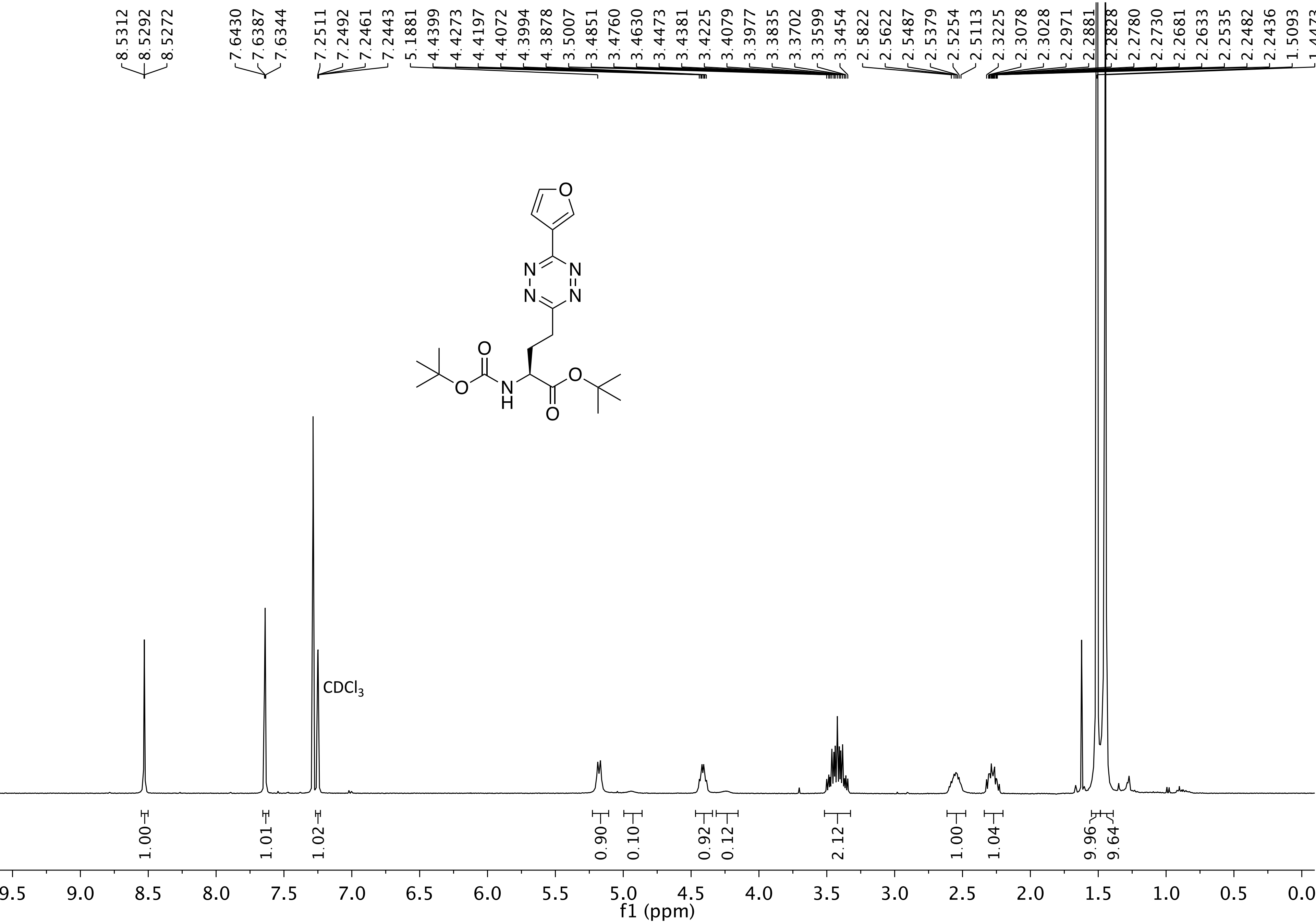
7.6133
7.6090
7.2250
7.2229
7.2202
7.2183
3.7048
3.6818
3.6641
3.6463
3.0980
3.0803
3.0625
O
N
N
N
N
COOMe
CDCl3
0.95
0.97
0.97
3.02
2.03
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



172.6219
168.2193
162.0712
145.9868
145.0285
121.1016
108.7629
52.1795
30.7601
29.8891
CDCl3
O
N
N
N
N
COOMe
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



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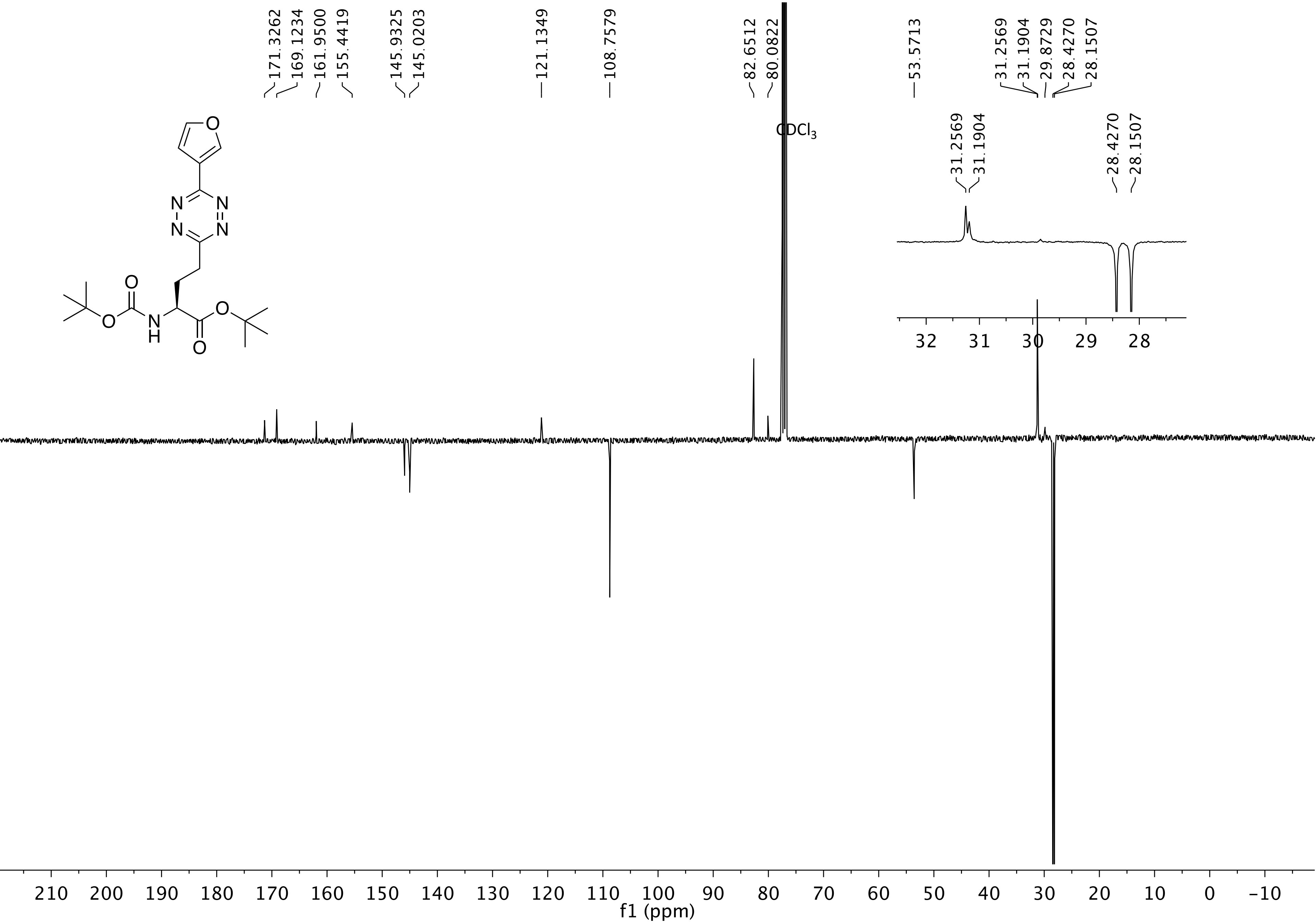
7.6387
7.6344
7.2511
7.2492
7.2461
7.2443
5.1881
4.4399
4.4273
4.4197
4.4072
4.3994
4.3878
3.5007
3.4851
3.4760
3.4630
3.4473
3.4381
3.4225
3.4079
3.3977
3.3835
3.3702
3.3599
3.3454
2.5822
2.5622
2.5487
2.5379
2.5254
2.5113
2.3225
2.3078
2.3028
2.2971
2.2881
2.2828
2.2780
2.2730
2.2681
2.2633
2.2535
2.2482
2.2436
1.5093
$CDCl_3$
1.00
1.01
1.02
0.90
0.10
0.92
0.12
2.12
1.00
1.04
9.96
9.64
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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161.9500
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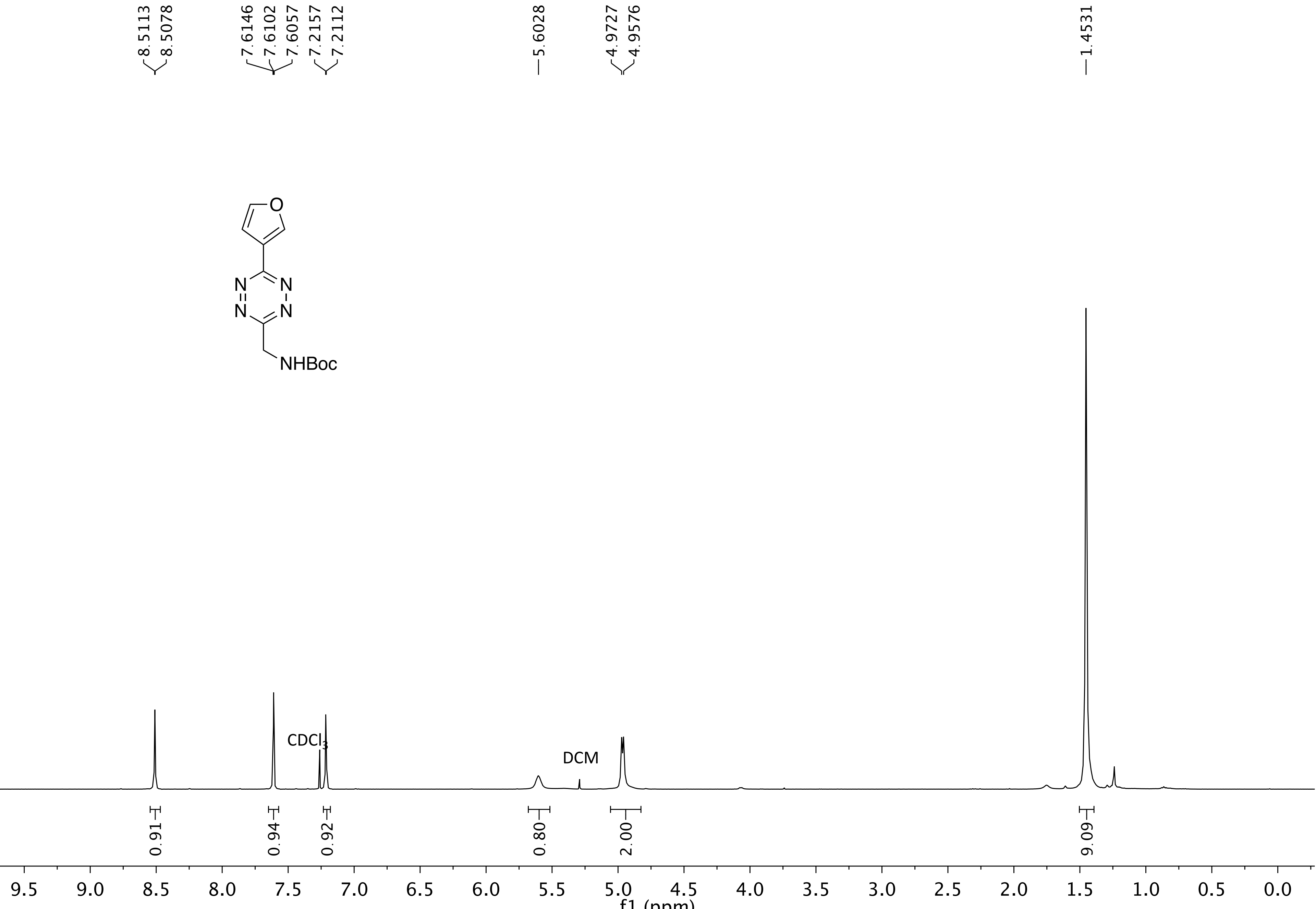
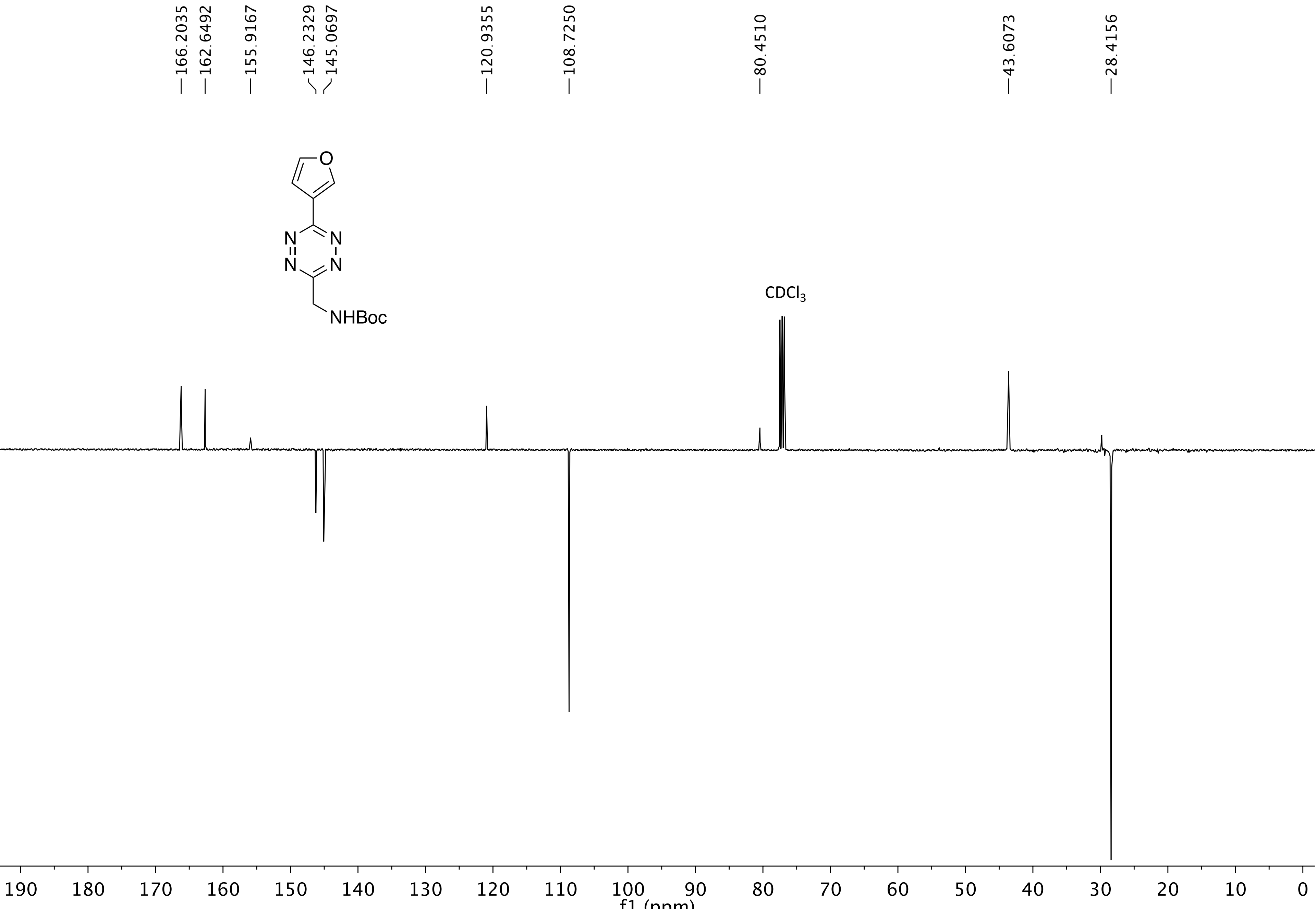
145.9325
145.0203
121.1349
108.7579
82.6512
80.0822
53.5713
31.2569
31.1904
29.8729
28.4270
28.1507
CDCl3
31.2569
31.1904
28.4270
28.1507
32 31 30 29 28
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 –10
f1 (ppm)


8.5113
8.5078
7.6146
7.6102
7.6057
7.2157
7.2112
5.6028
4.9727
4.9576
1.4531
O
N
N
N
N
NHBoc
CDCl3
DCM
0.91
0.94
0.92
0.80
2.00
9.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



166.2035
162.6492
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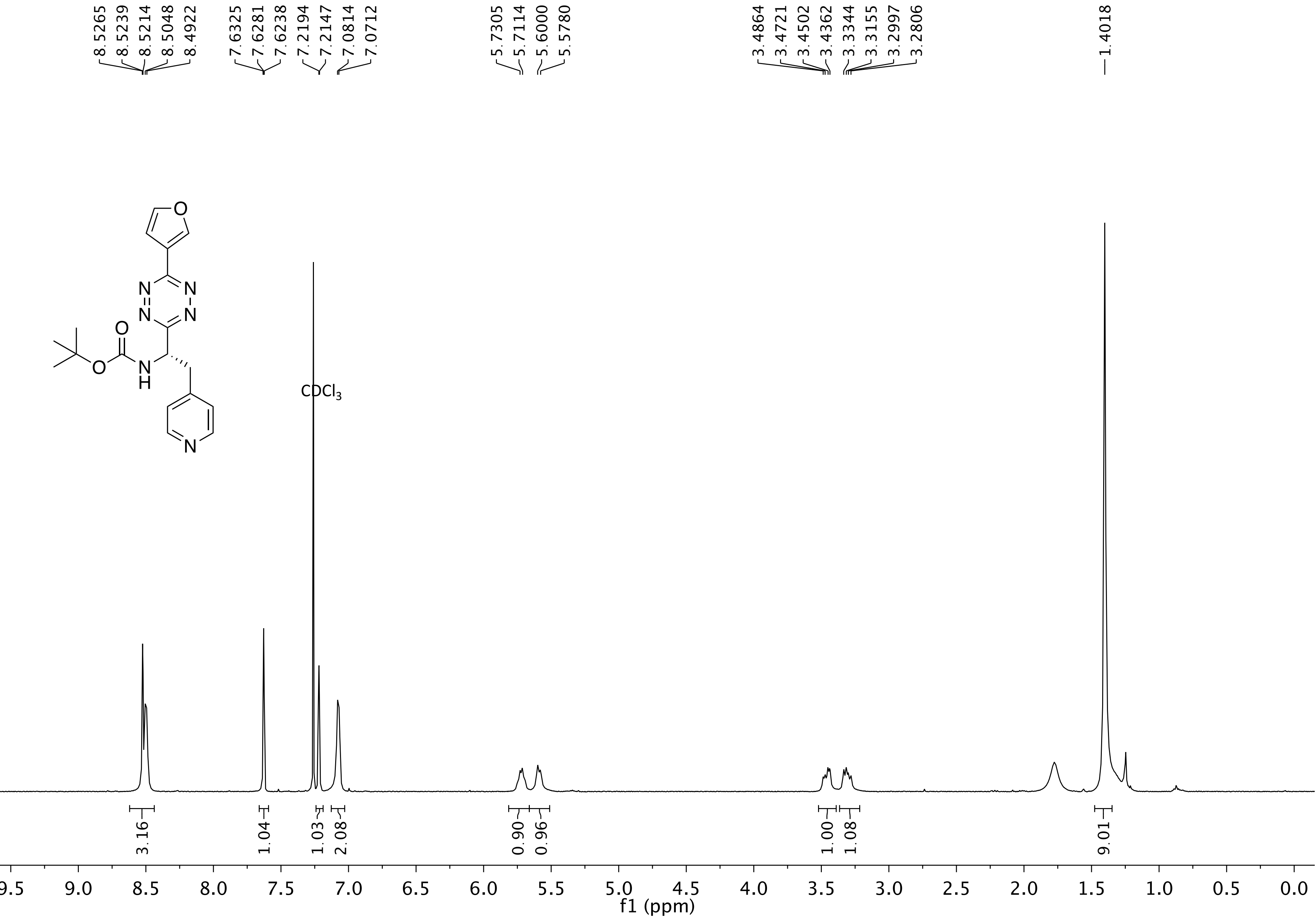
146.2329
145.0697
120.9355
108.7250
80.4510
43.6073
28.4156
NHBoc
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



8.5265
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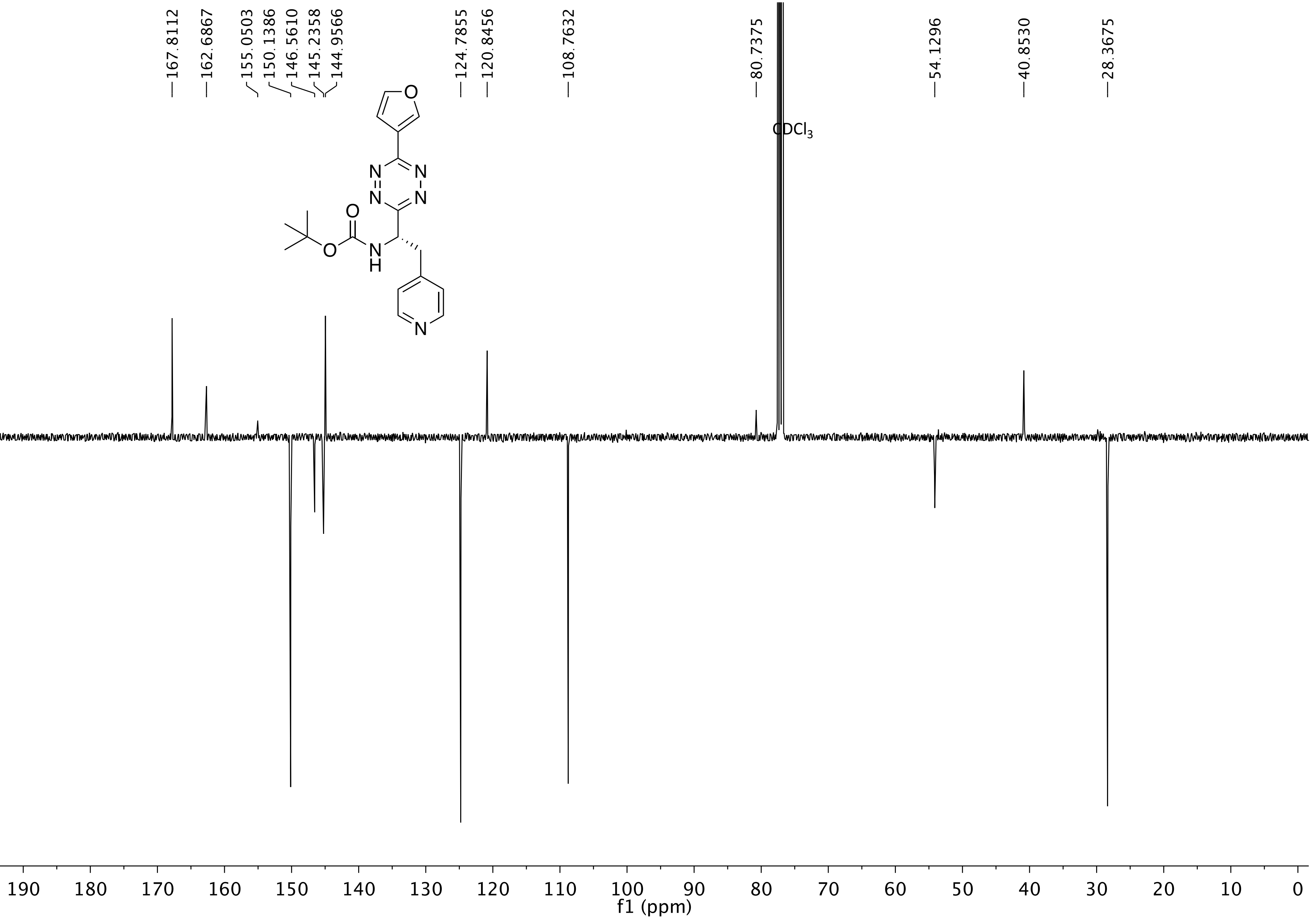
8.5214
8.5048
8.4922
7.6325
7.6281
7.6238
7.2194
7.2147
7.0814
7.0712
5.7305
5.7114
5.6000
5.5780
3.4864
3.4721
3.4502
3.4362
3.3344
3.3155
3.2997
3.2806
1.4018
CDCl3
3.16
1.04
1.03
2.08
0.90
0.96
1.00
1.08
9.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



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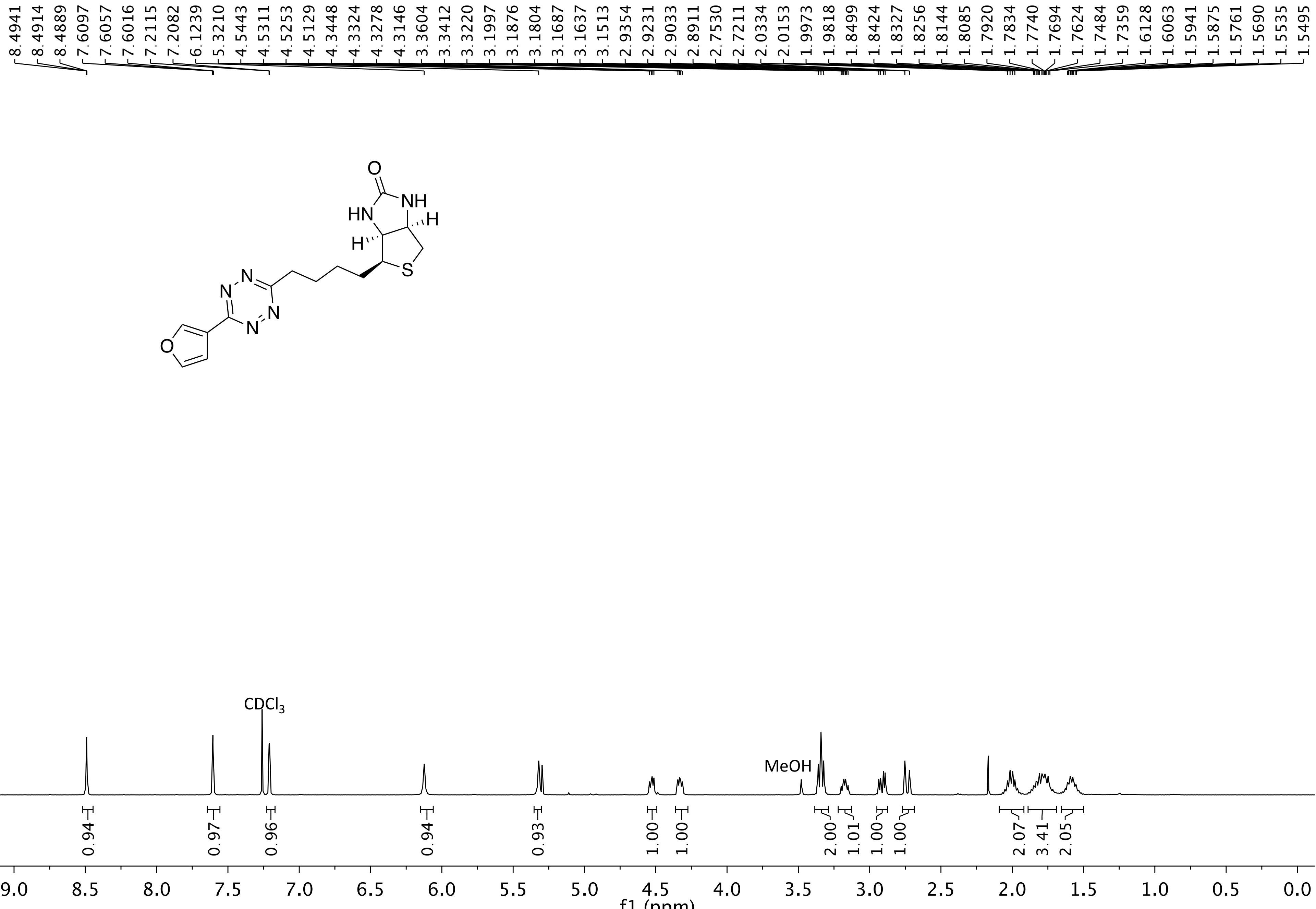
162.6867
155.0503
150.1386
146.5610
145.2358
144.9566
124.7855
120.8456
108.7632
80.7375
54.1296
40.8530
28.3675
CDCl$_3$
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.6057
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7.2115
7.2082
6.1239
5.3210
4.5443
4.5311
4.5253
4.5129
4.3448
4.3324
4.3278
4.3146
3.3604
3.3412
3.3220
3.1997
3.1876
3.1804
3.1687
3.1637
3.1513
2.9354
2.9231
2.9033
2.8911
2.7530
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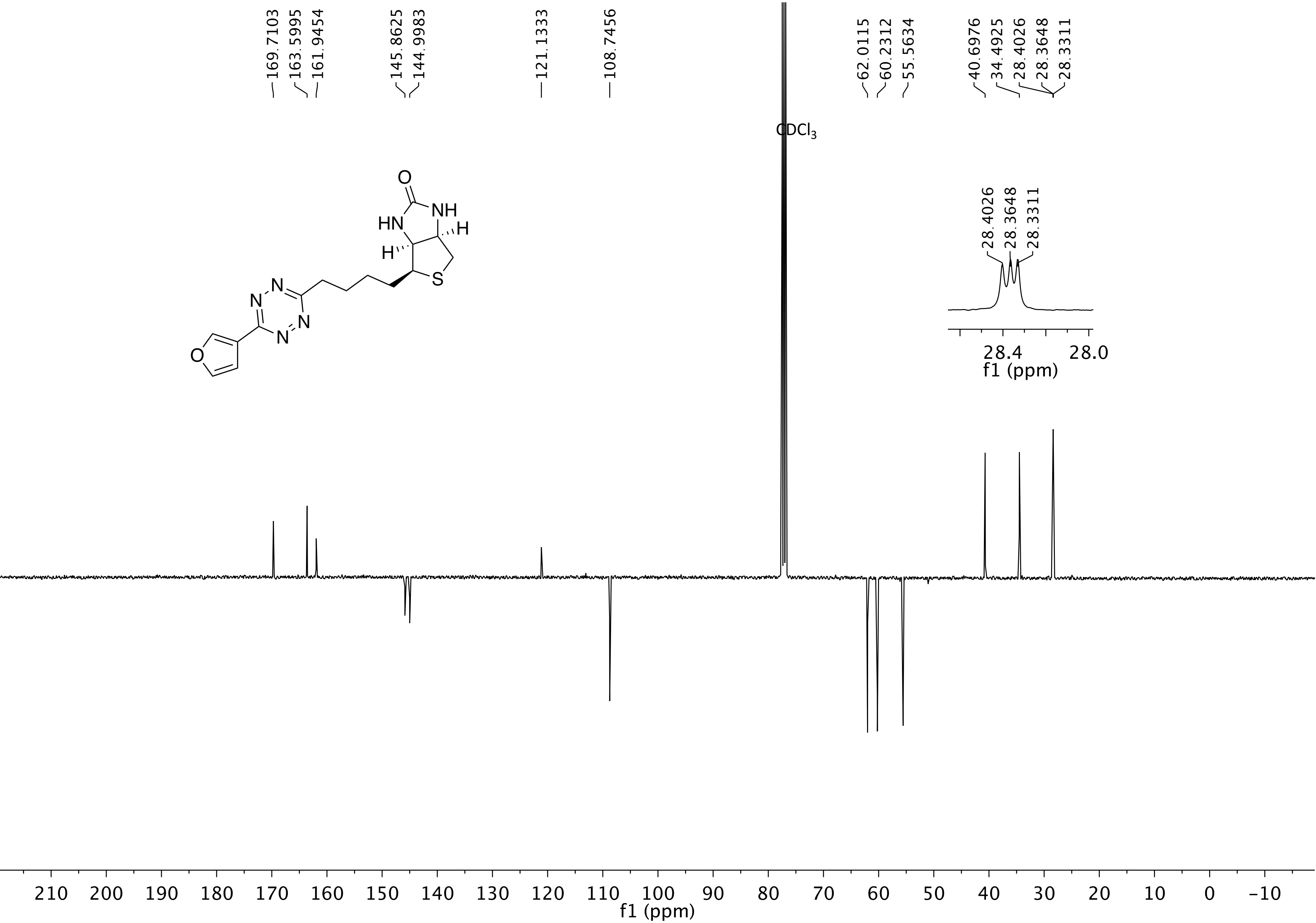
2.0153
1.9973
1.9818
1.8499
1.8424
1.8327
1.8256
1.8144
1.8085
1.7920
1.7834
1.7740
1.7694
1.7624
1.7484
1.7359
1.6128
1.6063
1.5941
1.5875
1.5761
1.5690
1.5535
1.5495
O
NH
HN
H
H
S
N
N
N
N
O
$CDCl_3$
MeOH
0.94
0.97
0.96
0.94
0.93
1.00
1.00
2.00
1.01
1.00
1.00
2.07
3.41
2.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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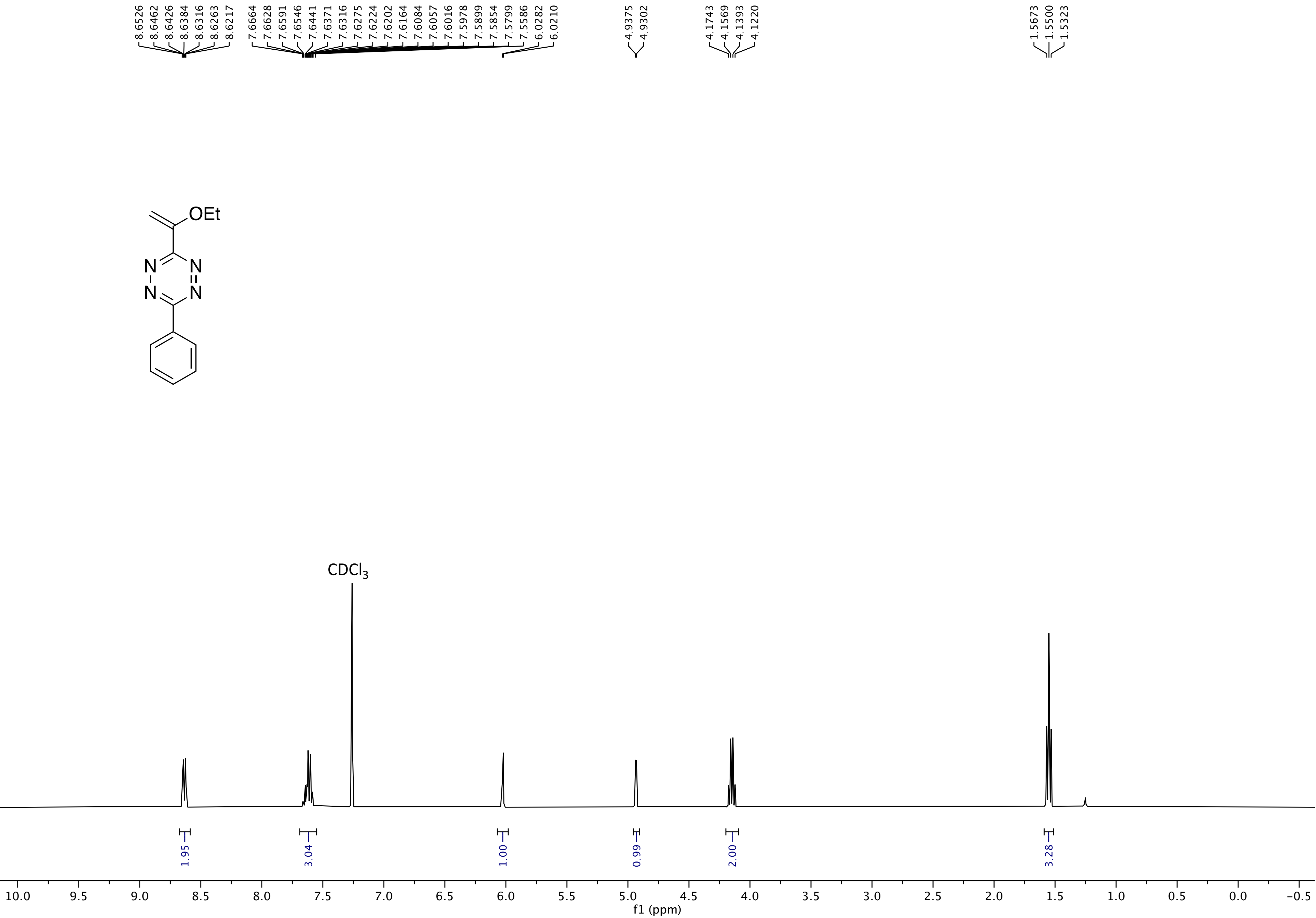
108.7456
62.0115
60.2312
55.5634
40.6976
34.4925
28.4026
28.3648
28.3311
CDCl3
O
NH
HN
H
H
S
N
N
N
N
O
28.4026
28.3648
28.3311
28.4
28.0
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)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8.6426
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8.6217
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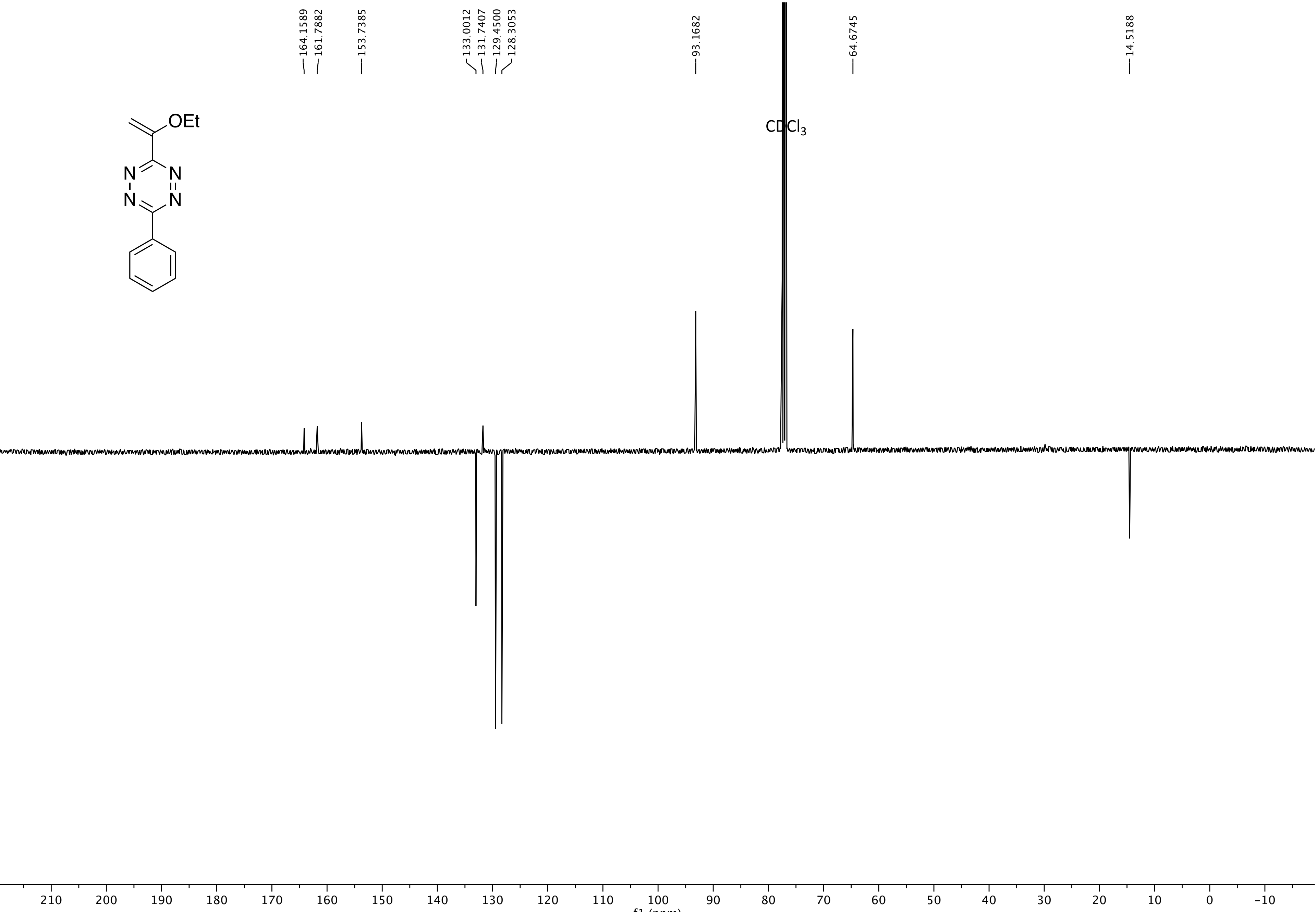
7.6628
7.6591
7.6546
7.6441
7.6371
7.6316
7.6275
7.6224
7.6202
7.6164
7.6084
7.6057
7.6016
7.5978
7.5899
7.5854
7.5799
7.5586
6.0282
6.0210
4.9375
4.9302
4.1743
4.1569
4.1393
4.1220
1.5673
1.5500
1.5323
OEt
N
N
N
N
CDCl3
1.95
3.04
1.00
0.99
2.00
3.28
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
f1 (ppm)



OEt
N
N
N
N
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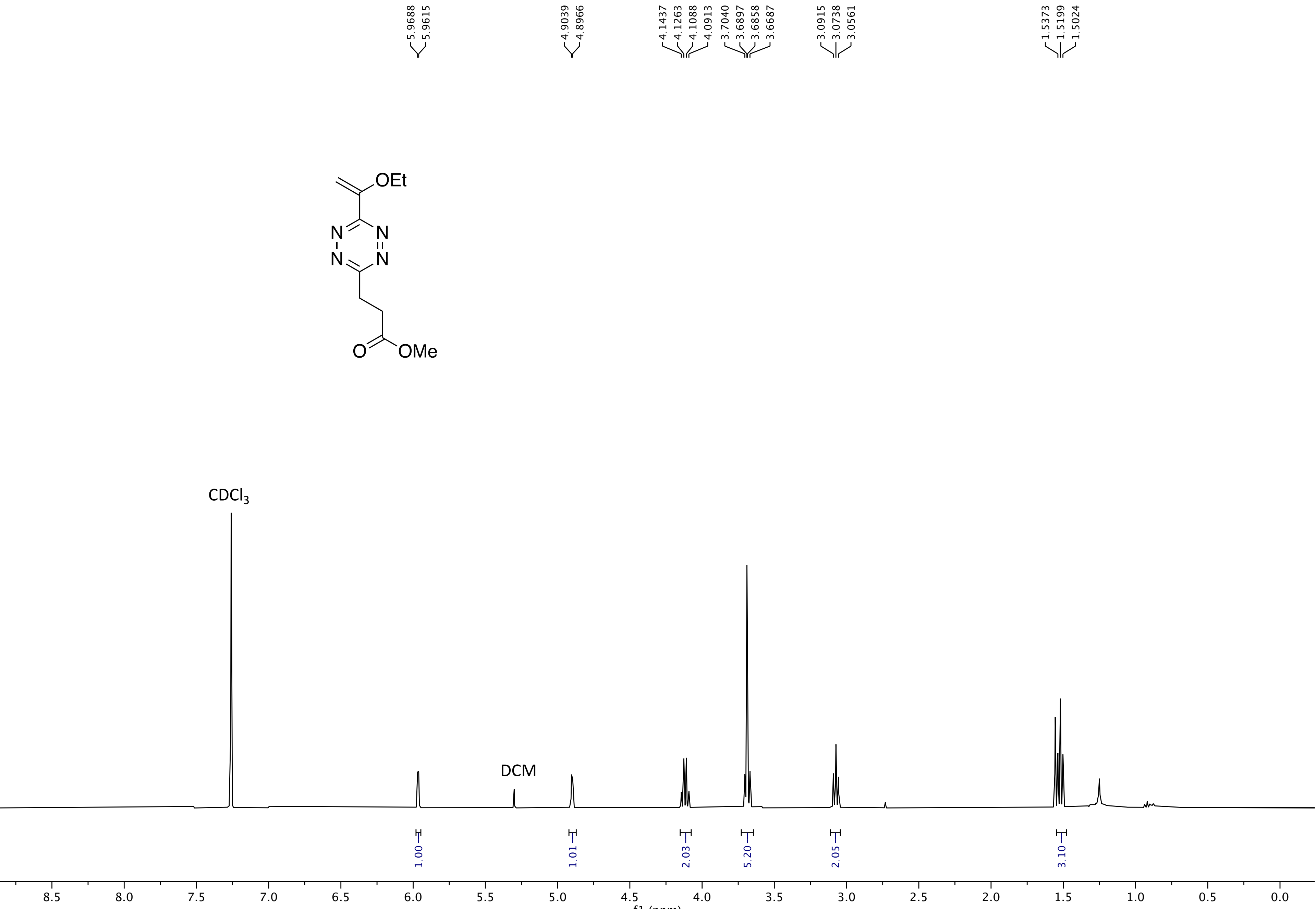
153.7385
133.0012
131.7407
129.4500
128.3053
93.1682
64.6745
14.5188
CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)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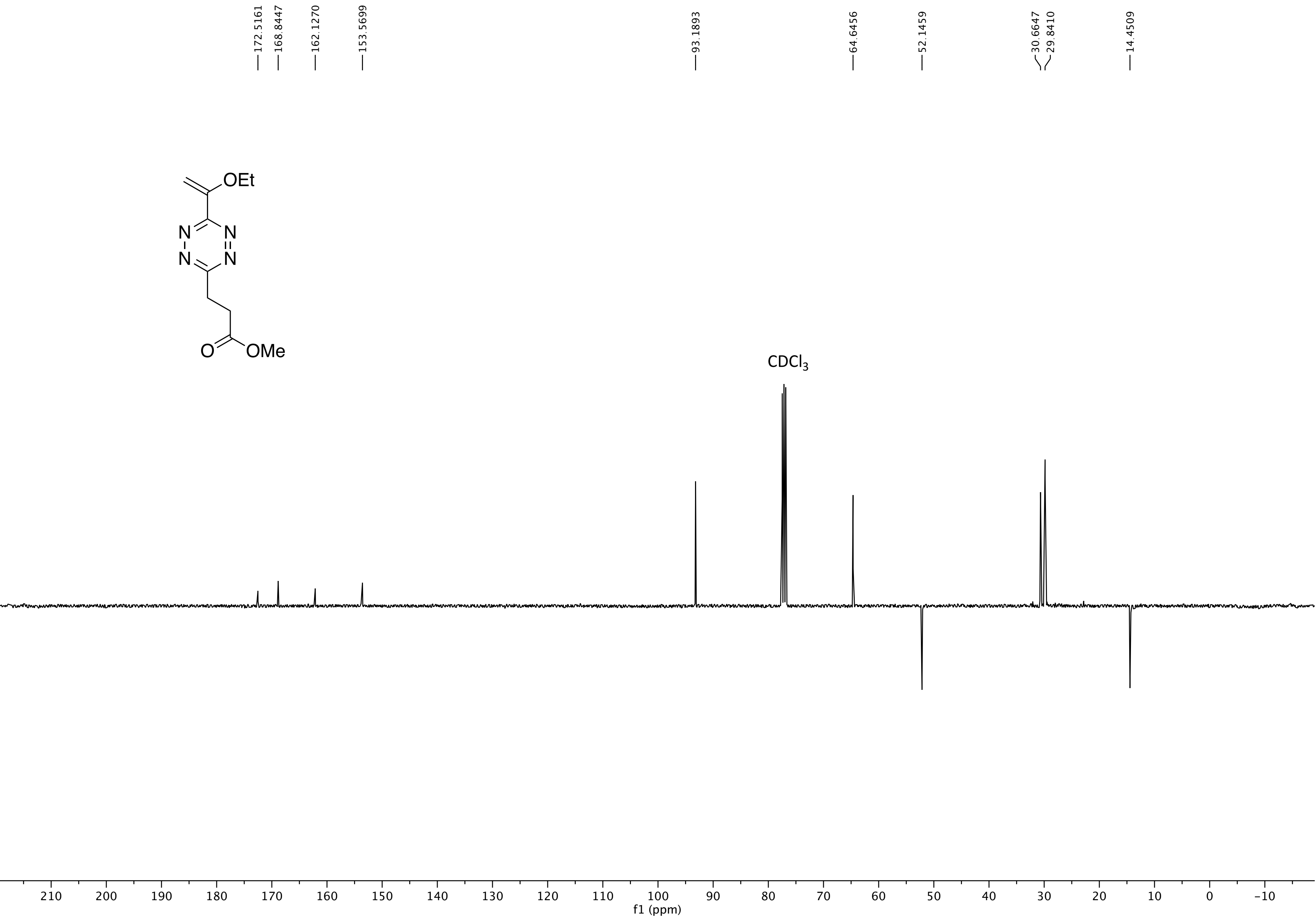
4.1088
4.0913
3.7040
3.6897
3.6858
3.6687
3.0915
3.0738
3.0561
1.5373
1.5199
1.5024
OEt
N
N
N
N
O
OMe
CDCl3
DCM
1.00
1.01
2.03
5.20
2.05
3.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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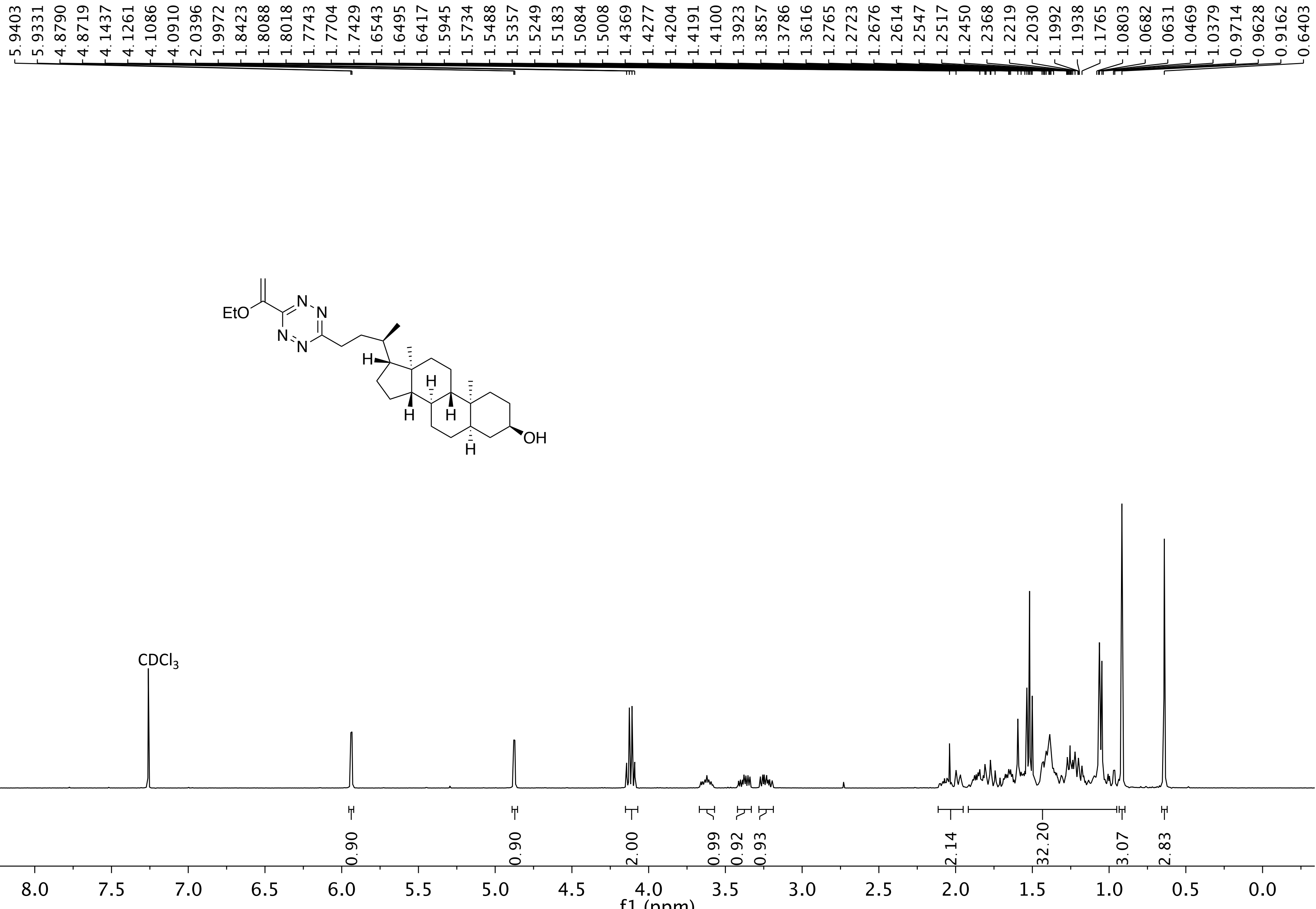
52.1459
30.6647
29.8410
14.4509
OEt
N
N
N
N
O
OMe
CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
f1 (ppm)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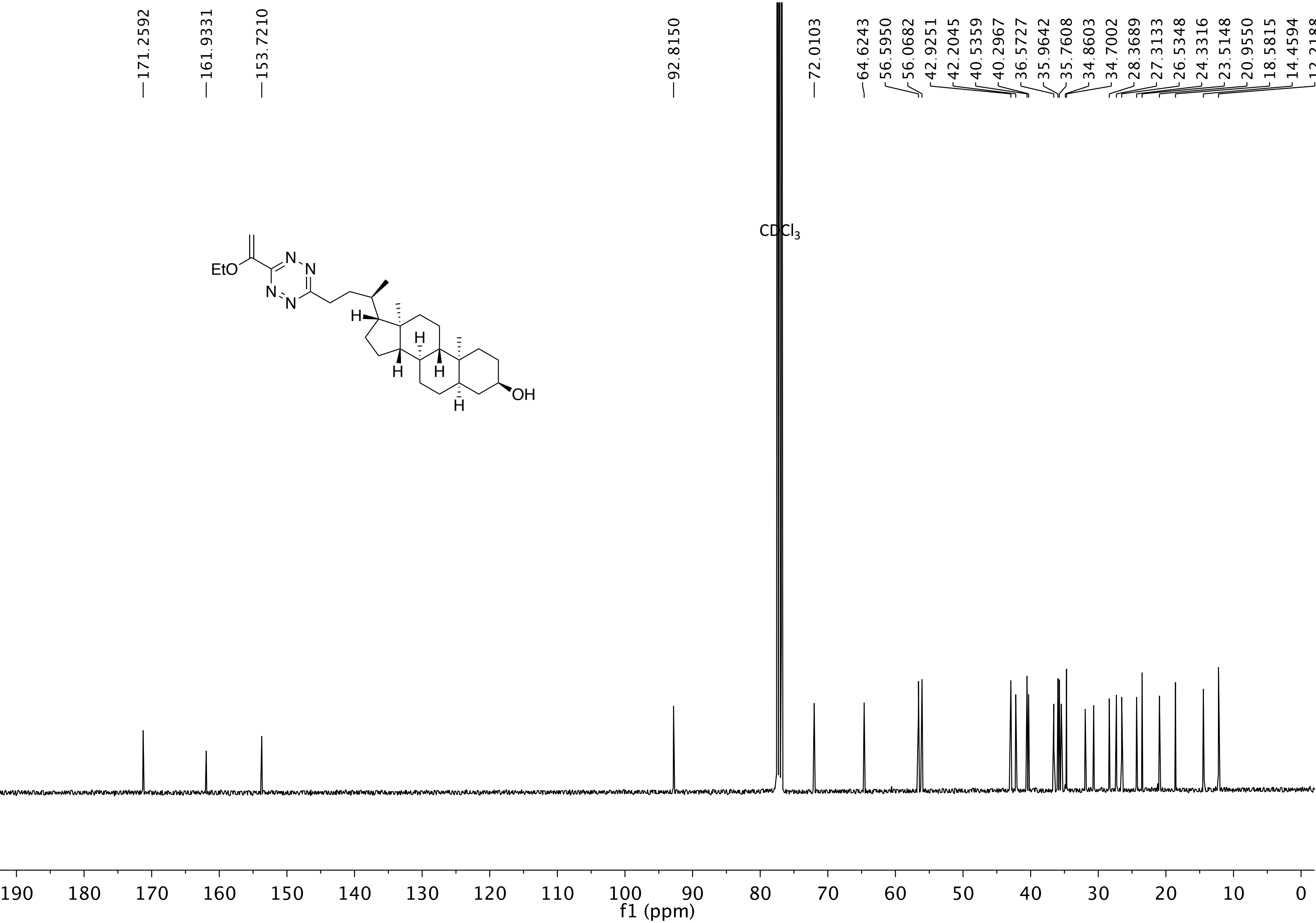
5.9331
4.8790
4.8719
4.1437
4.1261
4.1086
4.0910
2.0396
1.9972
1.8423
1.8088
1.8018
1.7743
1.7704
1.7429
1.6543
1.6495
1.6417
1.5945
1.5734
1.5488
1.5357
1.5249
1.5183
1.5084
1.5008
1.4369
1.4277
1.4204
1.4191
1.4100
1.3923
1.3857
1.3786
1.3616
1.2765
1.2723
1.2676
1.2614
1.2547
1.2517
1.2450
1.2368
1.2219
1.2030
1.1992
1.1938
1.1765
1.0803
1.0682
1.0631
1.0469
1.0379
0.9714
0.9628
0.9162
0.6403
EtO
N
N
N
N
H
H
H
H
H
OH
CDCl$_3$
0.90
0.90
2.00
0.99
0.92
0.93
2.14
32.20
3.07
2.83
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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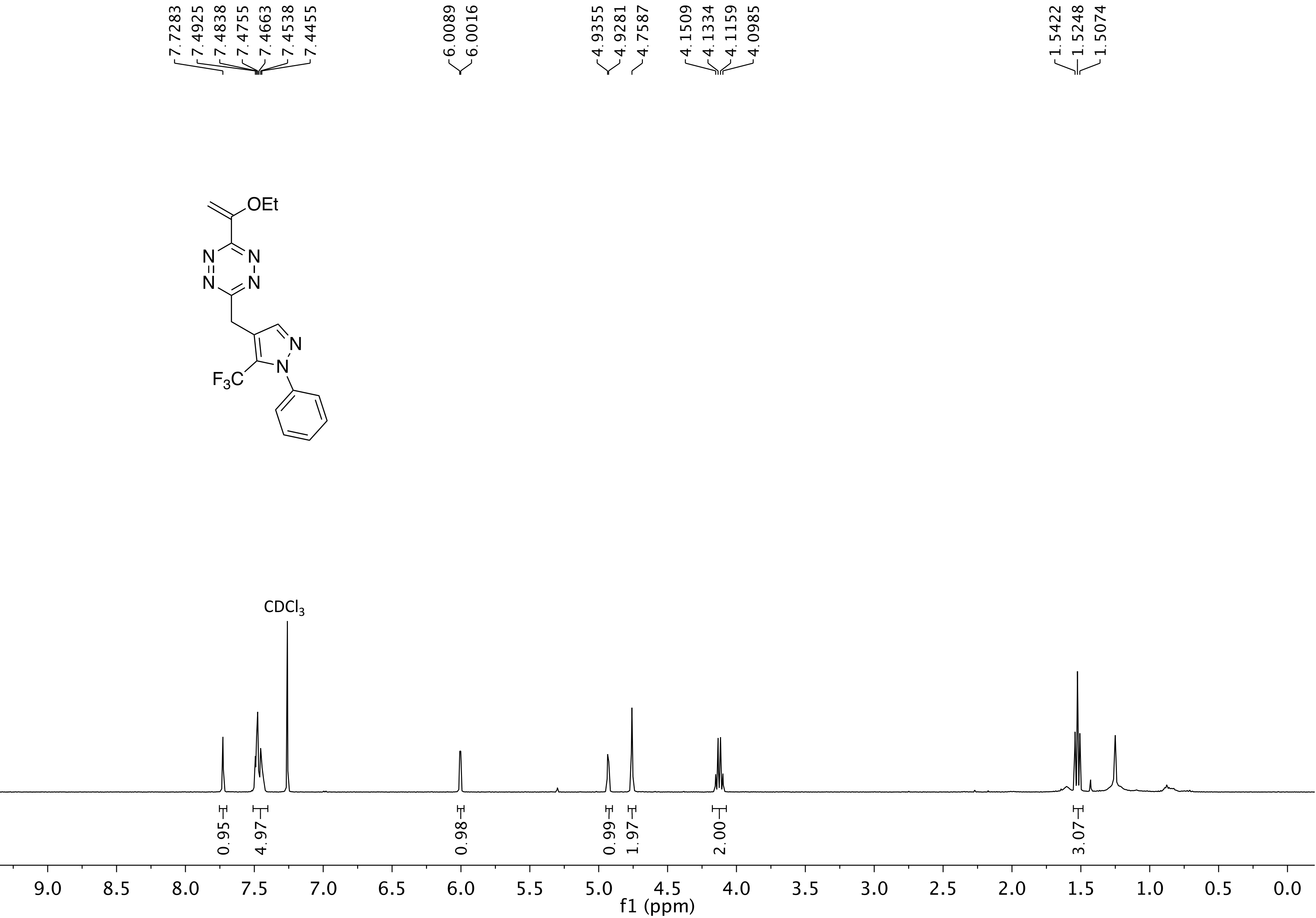
153.7210
92.8150
72.0103
64.6243
56.5950
56.0682
42.9251
42.2045
40.5359
40.2967
36.5727
35.9642
35.7608
34.8603
34.7002
28.3689
27.3133
26.5348
24.3316
23.5148
20.9550
18.5815
14.4594
$CDCl_3$
EtO
N
OH
H
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.4455
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6.0016
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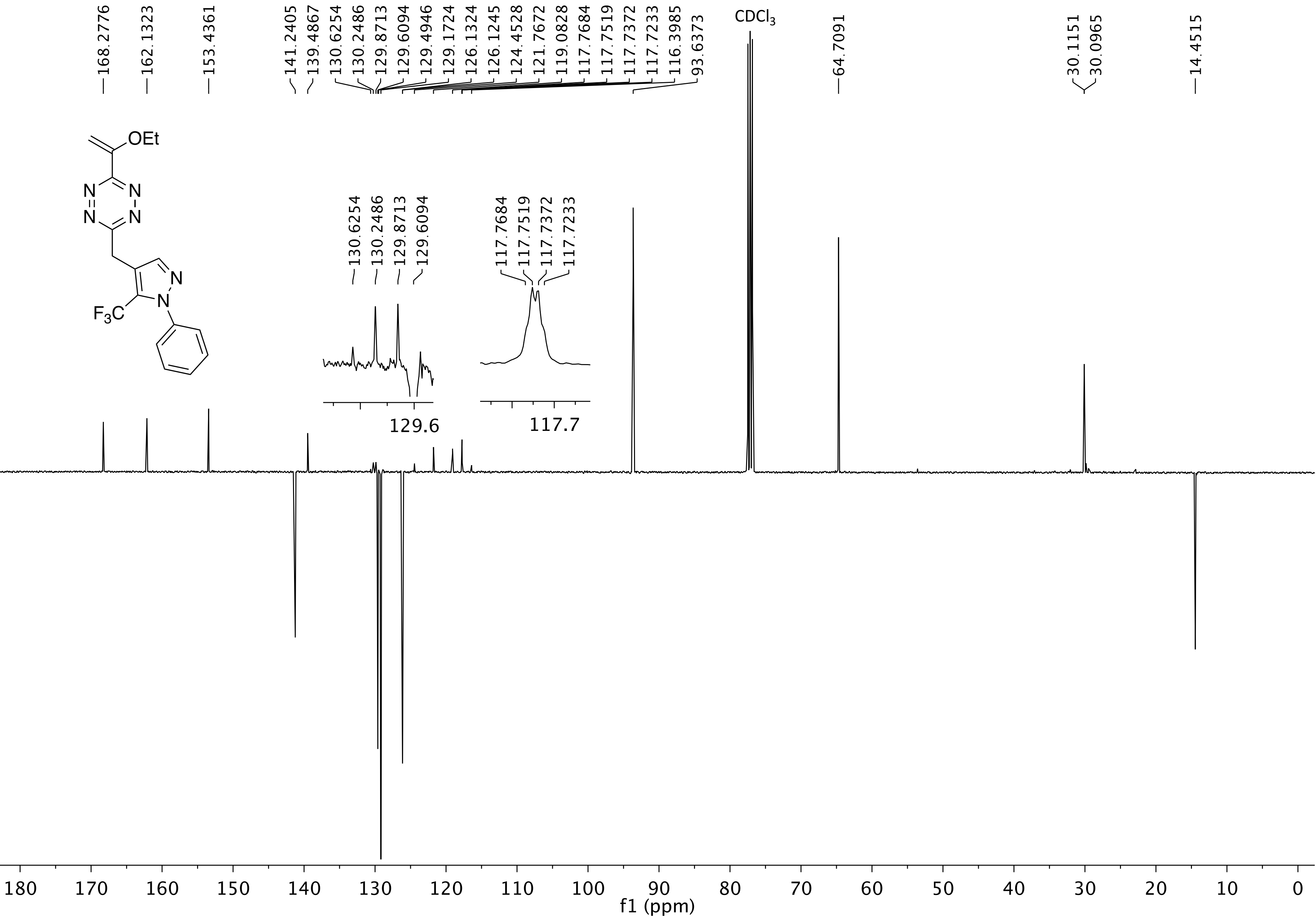
4.9281
4.7587
4.1509
4.1334
4.1159
4.0985
1.5422
1.5248
1.5074
OEt
N
N
N
N
N
N
F3C
CDCl3
0.95
4.97
0.98
0.99
1.97
2.00
3.07
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



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153.4361
141.2405
139.4867
130.6254
130.2486
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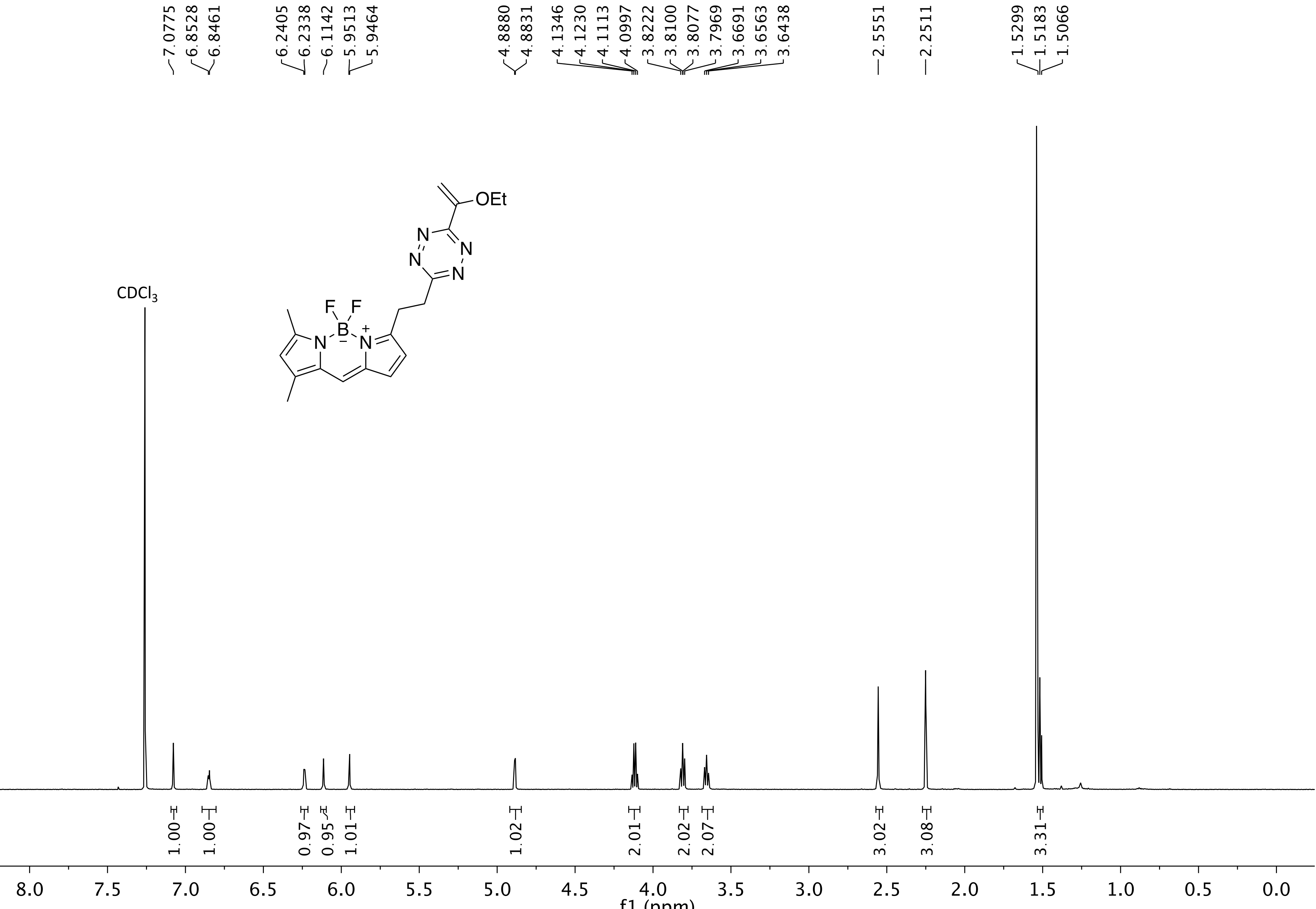
129.6094
129.4946
129.1724
126.1324
126.1245
124.4528
121.7672
119.0828
117.7684
117.7519
117.7372
117.7233
116.3985
93.6373
CDCl3
64.7091
30.1151
30.0965
14.4515
OEt
N
N
N
N
N
N
F3C
129.6
117.7
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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6.2338
6.1142
5.9513
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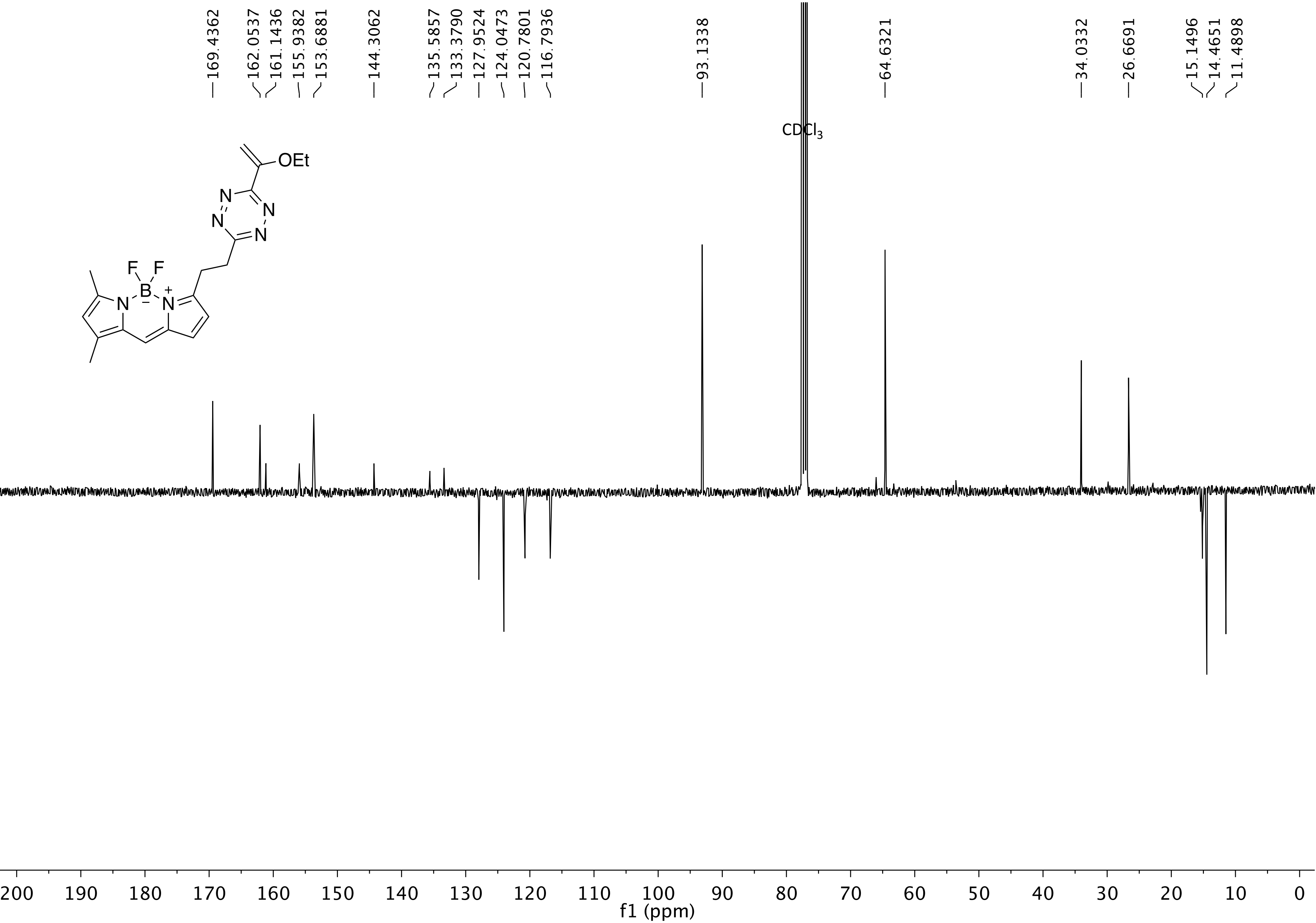
4.8831
4.1346
4.1230
4.1113
4.0997
3.8222
3.8100
3.8077
3.7969
3.6691
3.6563
3.6438
2.5551
2.2511
1.5299
1.5183
1.5066
CDCl3
OEt
1.00
1.00
0.97
0.95
1.01
1.02
2.01
2.02
2.07
3.02
3.08
3.31
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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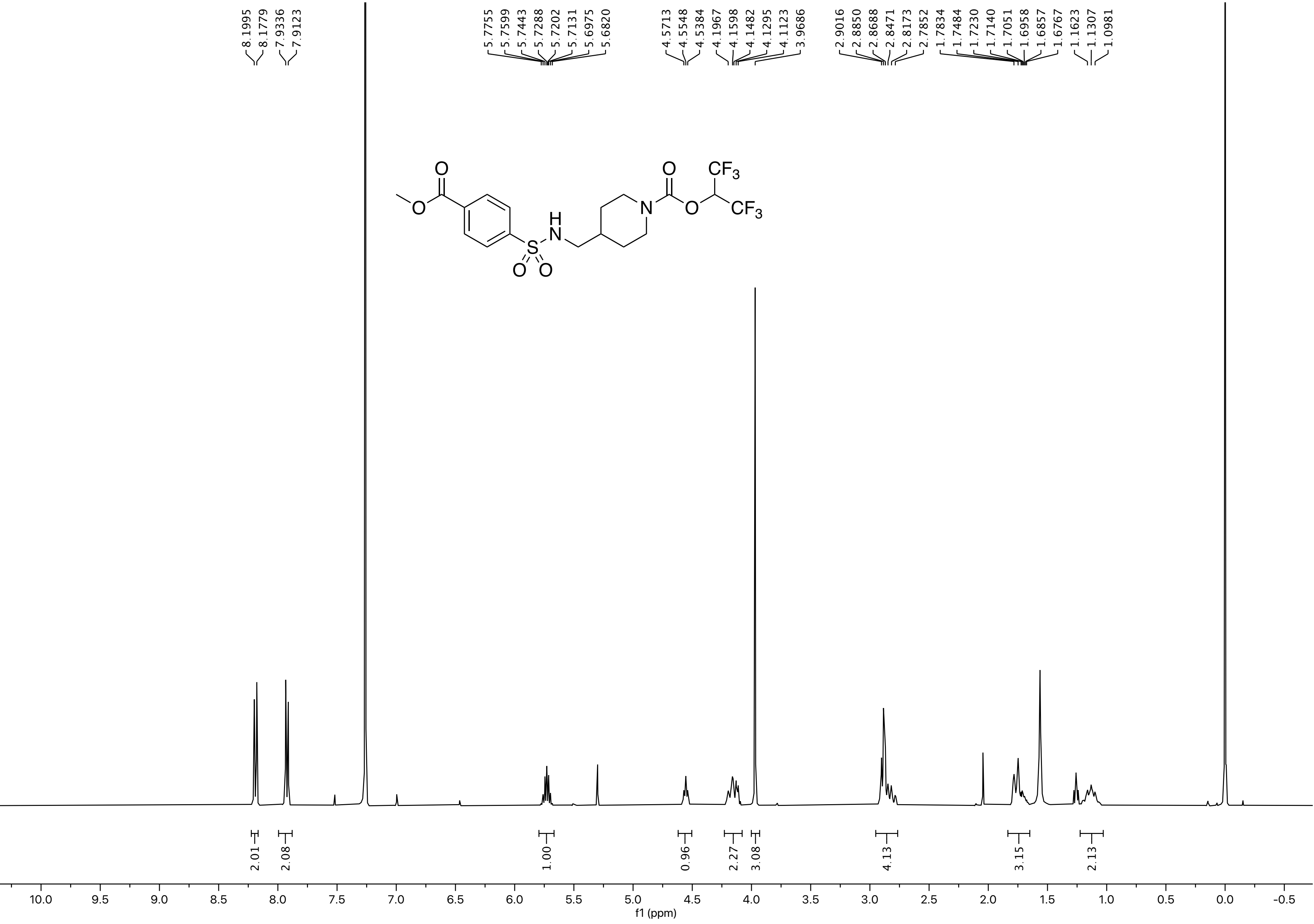
127.9524
124.0473
120.7801
116.7936
93.1338
64.6321
34.0332
26.6691
15.1496
14.4651
11.4898
CDCl$_3$
OEt
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



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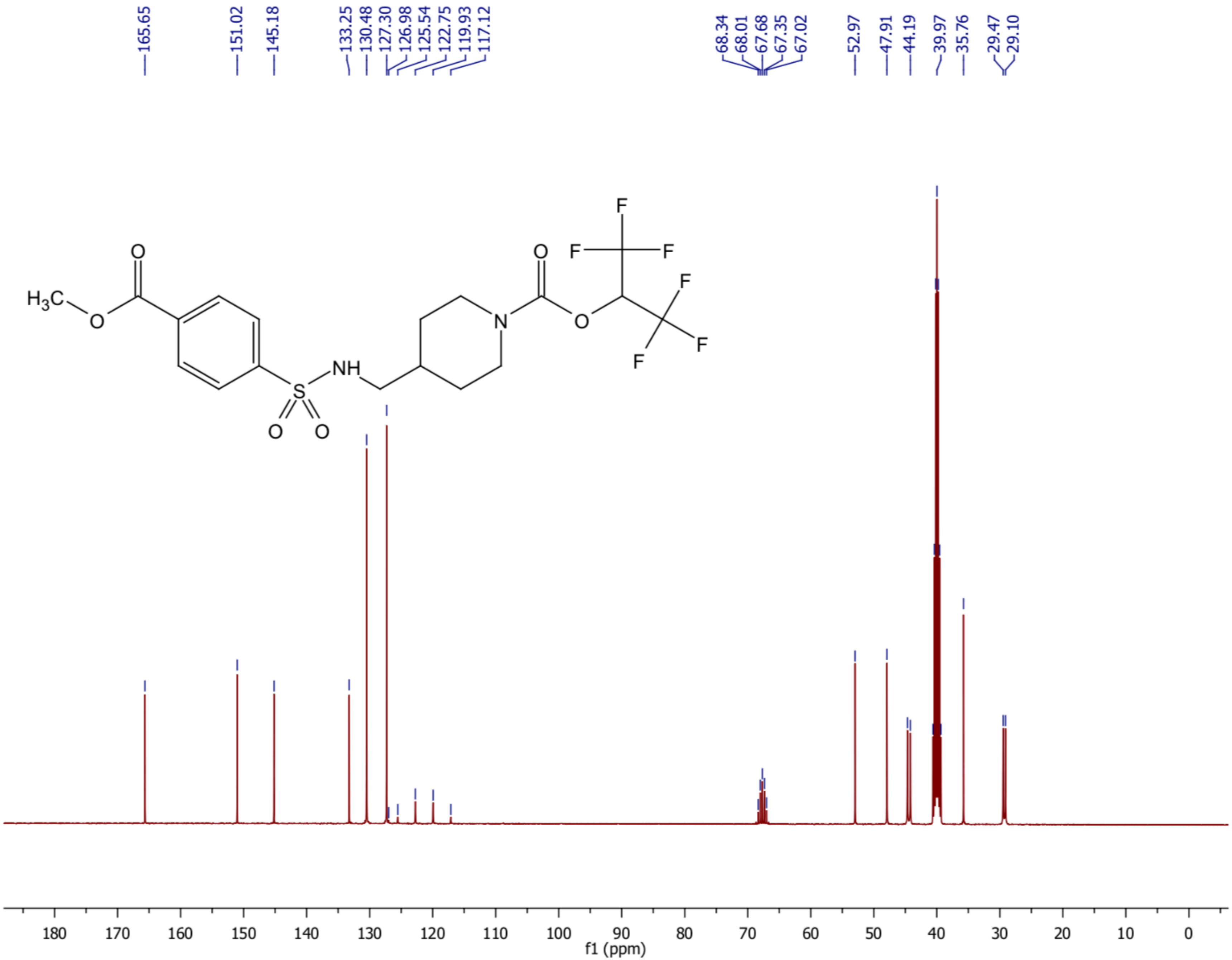
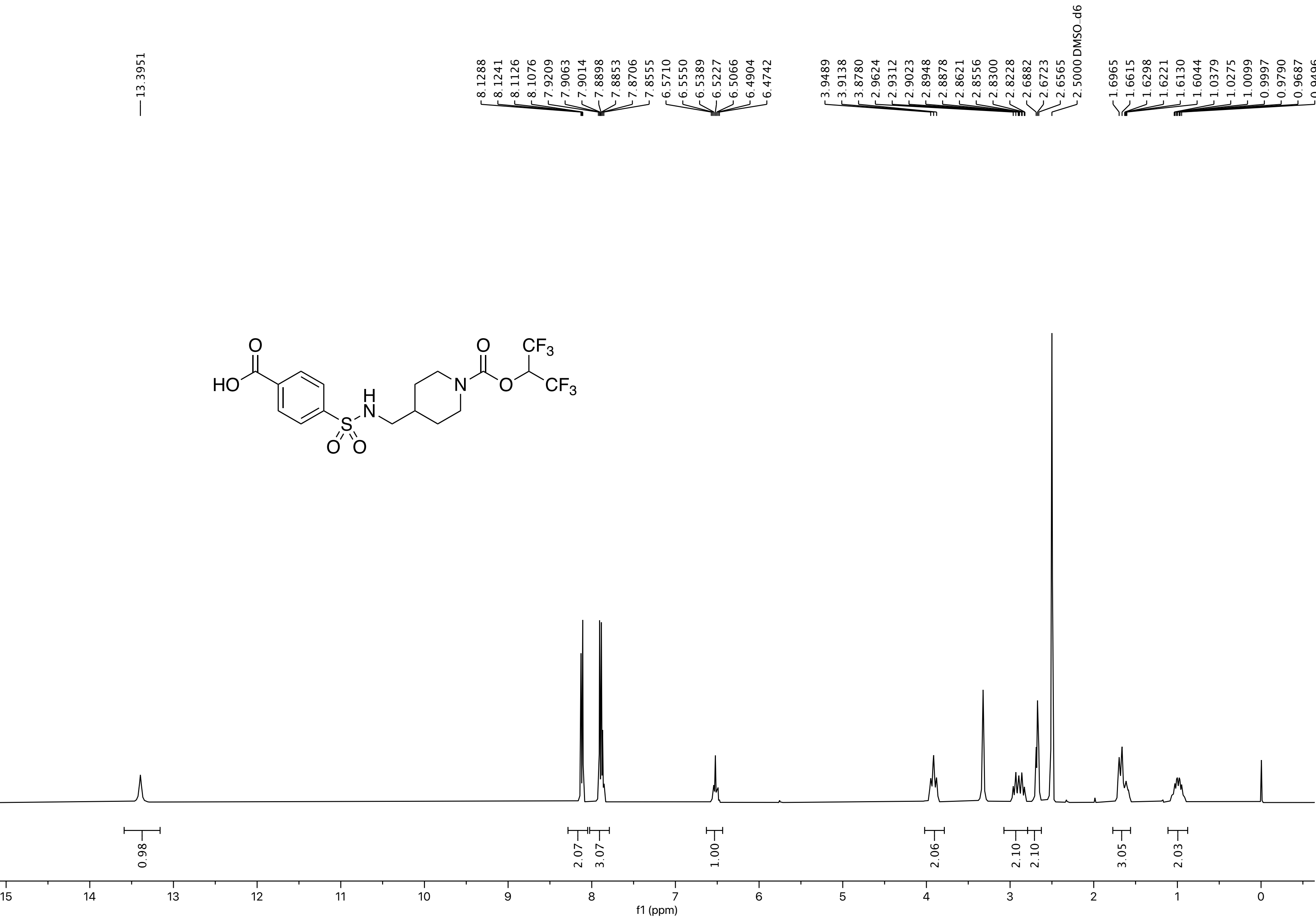
8.1779
7.9336
7.9123
5.7755
5.7599
5.7443
5.7288
5.7202
5.7131
5.6975
5.6820
4.5713
4.5548
4.5384
4.1967
4.1598
4.1482
4.1295
4.1123
3.9686
2.9016
2.8850
2.8688
2.8471
2.8173
2.7852
1.7834
1.7484
1.7230
1.7140
1.7051
1.6958
1.6857
1.6767
1.1623
1.1307
1.0981
2.01
2.08
1.00
0.96
2.27
3.08
4.13
3.15
2.13
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


165.65
151.02
145.18
133.25
130.48
127.30
126.98
125.54
122.75
119.93
117.12
68.34
68.01
67.68
67.35
67.02
52.97
47.91
44.19
39.97
35.76
29.47
29.10
F
F
F
F
F
F
O
O
H3C
O
N
O
NH
S
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.1241
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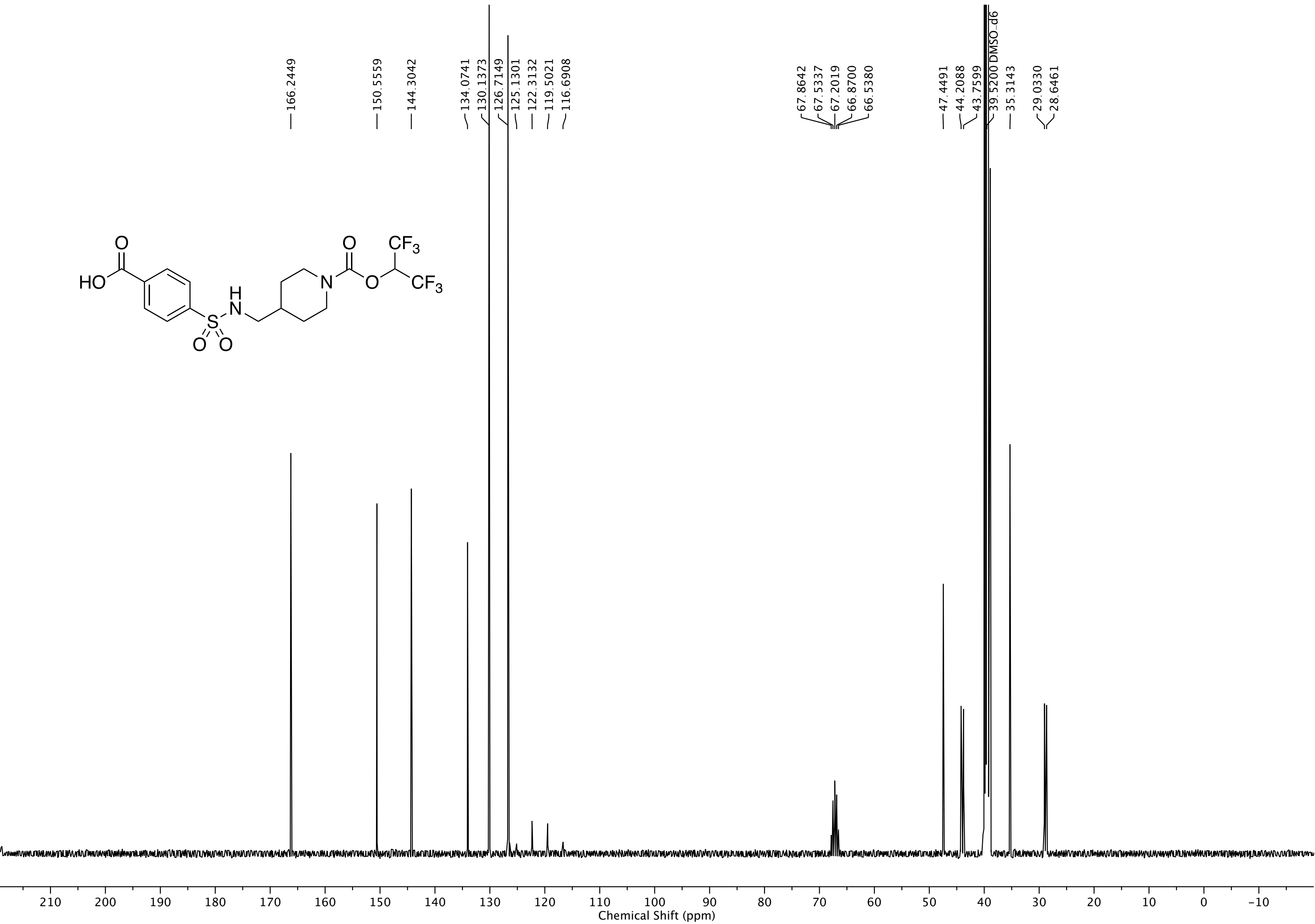
7.9209
7.9063
7.9014
7.8898
7.8853
7.8706
7.8555
6.5710
6.5550
6.5389
6.5227
6.5066
6.4904
6.4742
3.9489
3.9138
3.8780
2.9624
2.9312
2.9023
2.8948
2.8878
2.8621
2.8556
2.8300
2.8228
2.6882
2.6723
2.6565
2.5000 DMSO_d6
1.6965
1.6615
1.6298
1.6221
1.6130
1.6044
1.0379
1.0275
1.0099
0.9997
0.9790
0.9687
HO
O
H
N
S
O
O
N
O
O
CF3
CF3
0.98
2.07
3.07
1.00
2.06
2.10
2.10
3.05
2.03
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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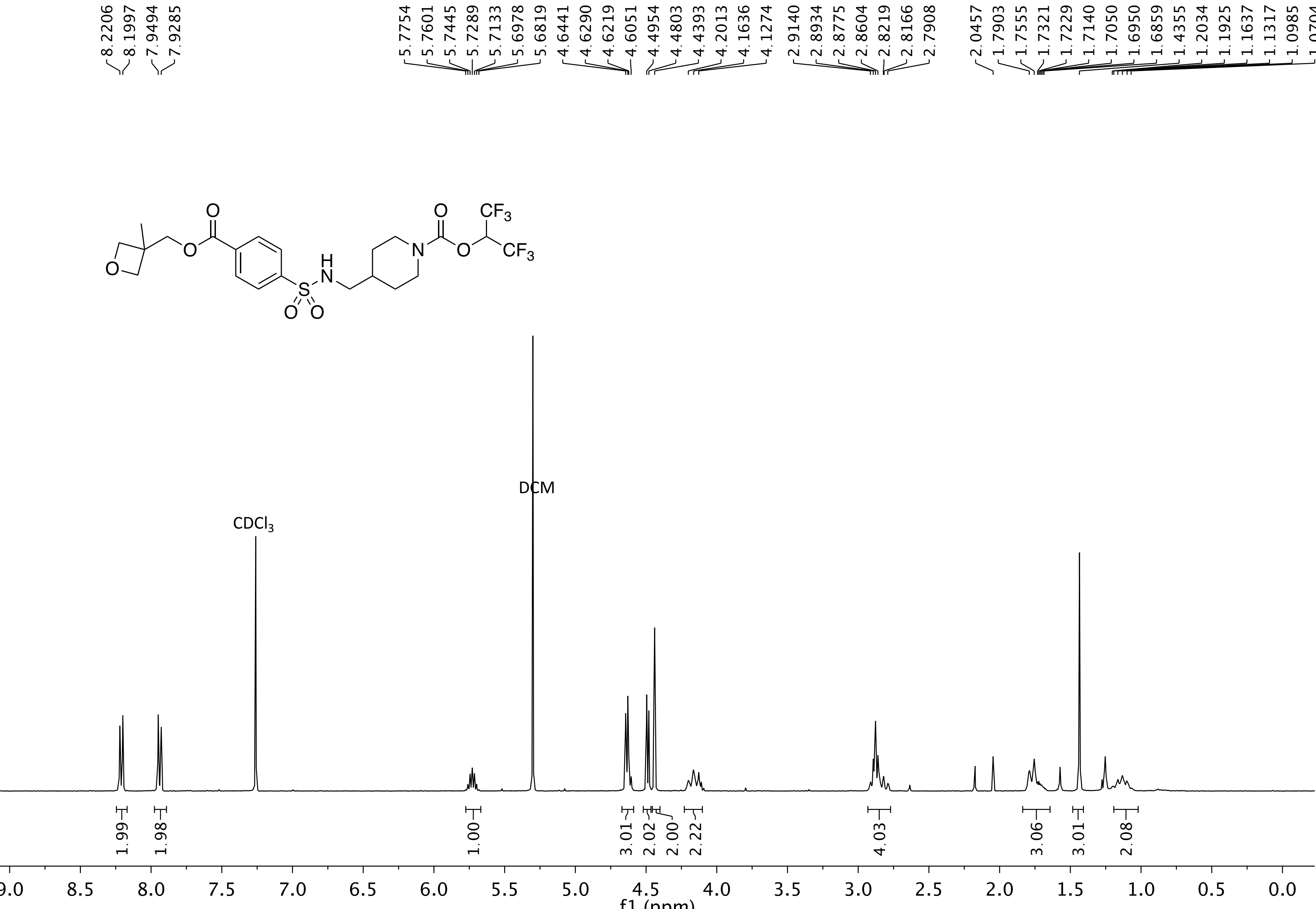
150.5559
144.3042
134.0741
130.1373
126.7149
125.1301
122.3132
119.5021
116.6908
67.8642
67.5337
67.2019
66.8700
66.5380
47.4491
44.2088
43.7599
39.5200 DMSO_d6
35.3143
29.0330
28.6461
O
HO
H
N
S
O
O
N
O
O
CF3
CF3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
–10
Chemical Shift (ppm)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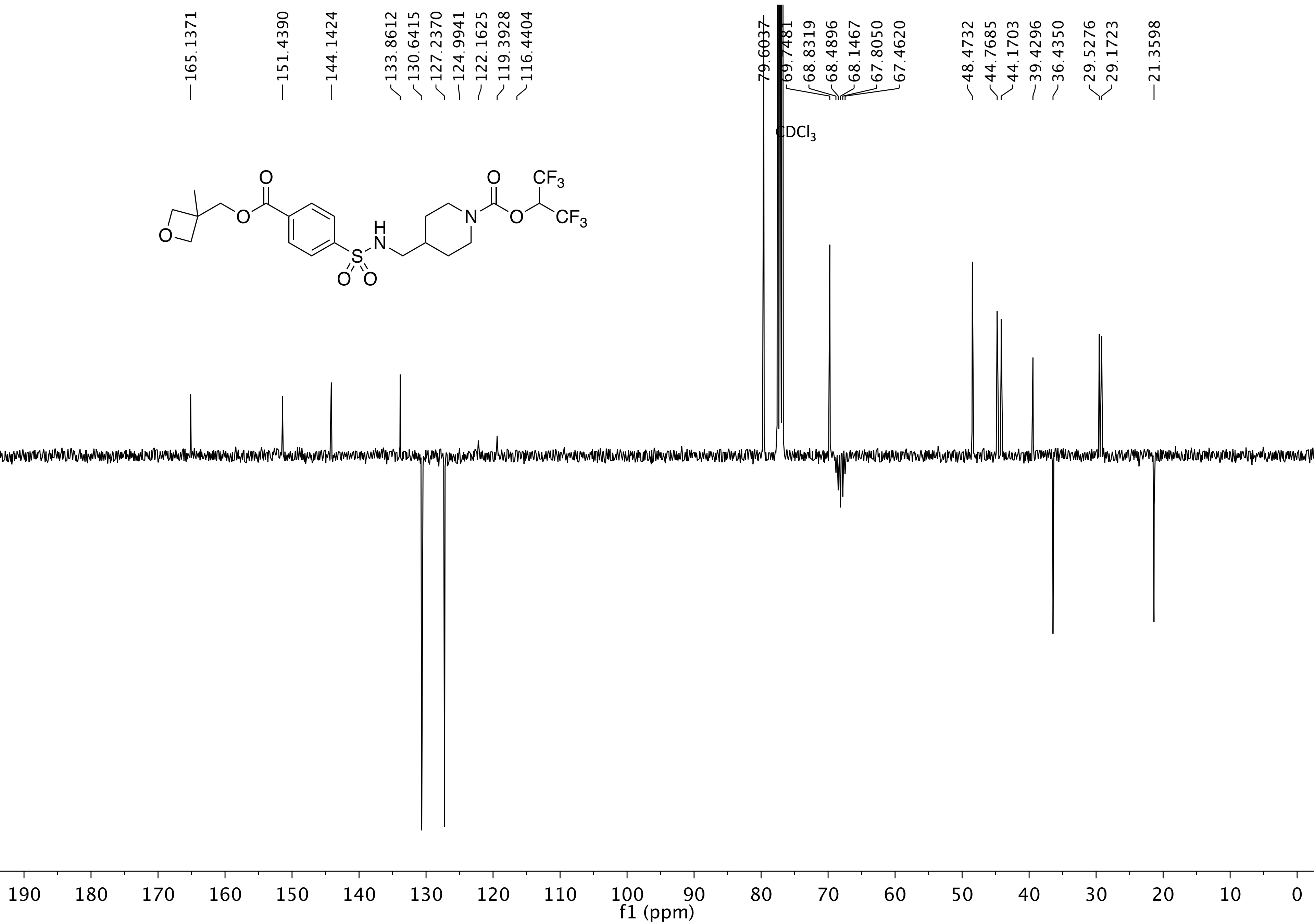
7.9494
7.9285
5.7754
5.7601
5.7445
5.7289
5.7133
5.6978
5.6819
4.6441
4.6290
4.6219
4.6051
4.4954
4.4803
4.4393
4.2013
4.1636
4.1274
2.9140
2.8934
2.8775
2.8604
2.8219
2.8166
2.7908
2.0457
1.7903
1.7555
1.7321
1.7229
1.7140
1.7050
1.6950
1.6859
1.4355
1.2034
1.1925
1.1637
1.1317
1.0985
CDCl3
DCM
1.99
1.98
1.00
3.01
2.02
2.00
2.22
4.03
3.06
3.01
2.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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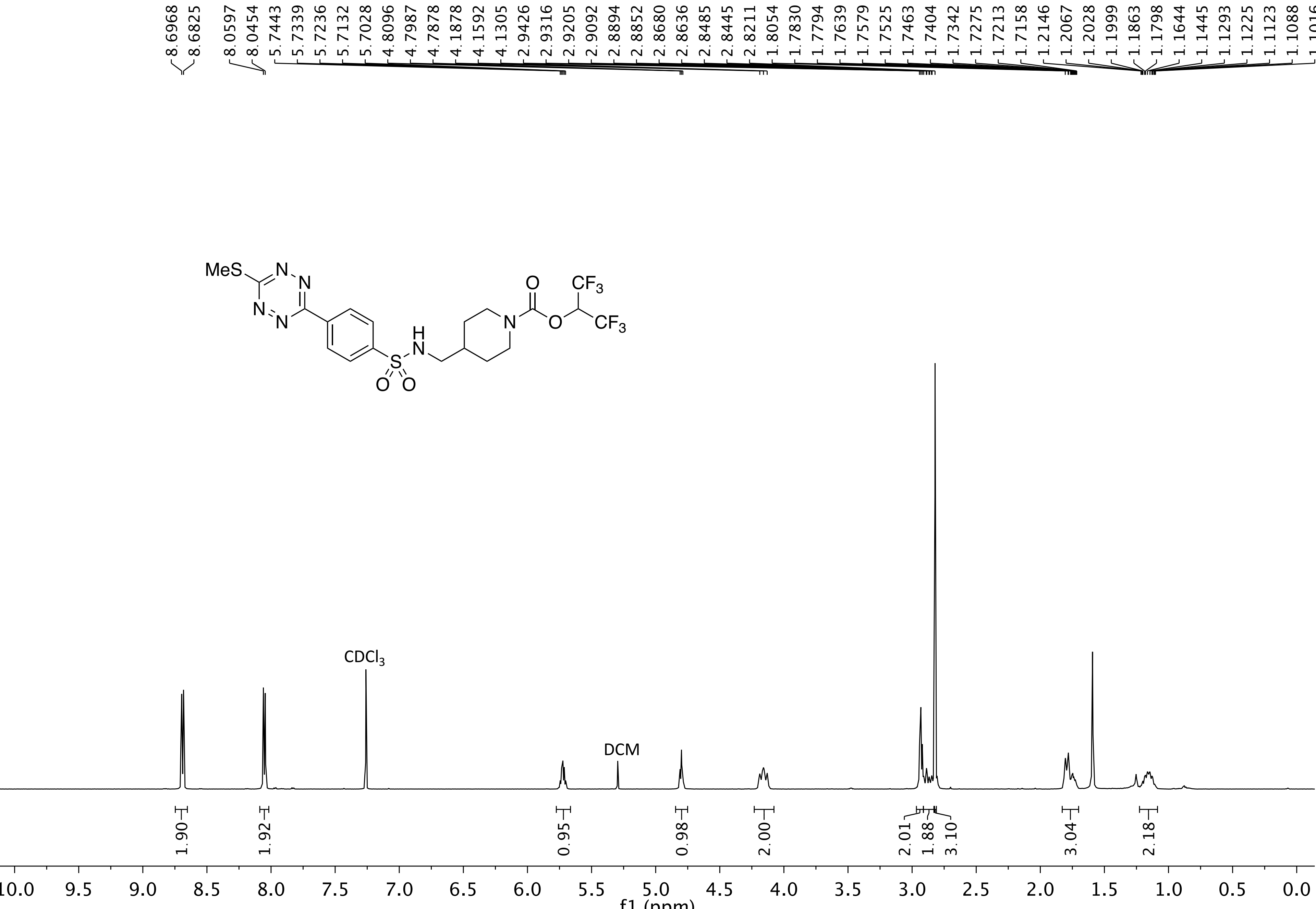
144.1424
133.8612
130.6415
127.2370
124.9941
122.1625
119.3928
116.4404
79.6037
69.7481
68.8319
68.4896
68.1467
67.8050
67.4620
48.4732
44.7685
44.1703
39.4296
36.4350
29.5276
29.1723
21.3598
CDCl3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



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8.0597
8.0454
5.7443
5.7339
5.7236
5.7132
5.7028
4.8096
4.7987
4.7878
4.1878
4.1592
4.1305
2.9426
2.9316
2.9205
2.9092
2.8894
2.8852
2.8680
2.8636
2.8485
2.8445
2.8211
1.8054
1.7830
1.7794
1.7639
1.7579
1.7525
1.7463
1.7404
1.7342
1.7275
1.7213
1.7158
1.2146
1.2067
1.2028
1.1999
1.1863
1.1798
1.1644
1.1445
1.1293
1.1225
1.1123
1.1088
MeS
N
N
N
N
H
N
S
O
O
N
O
O
CF3
CF3
CDCl3
DCM
1.90
1.92
0.95
0.98
2.00
2.01
1.88
3.10
3.04
2.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
2.0
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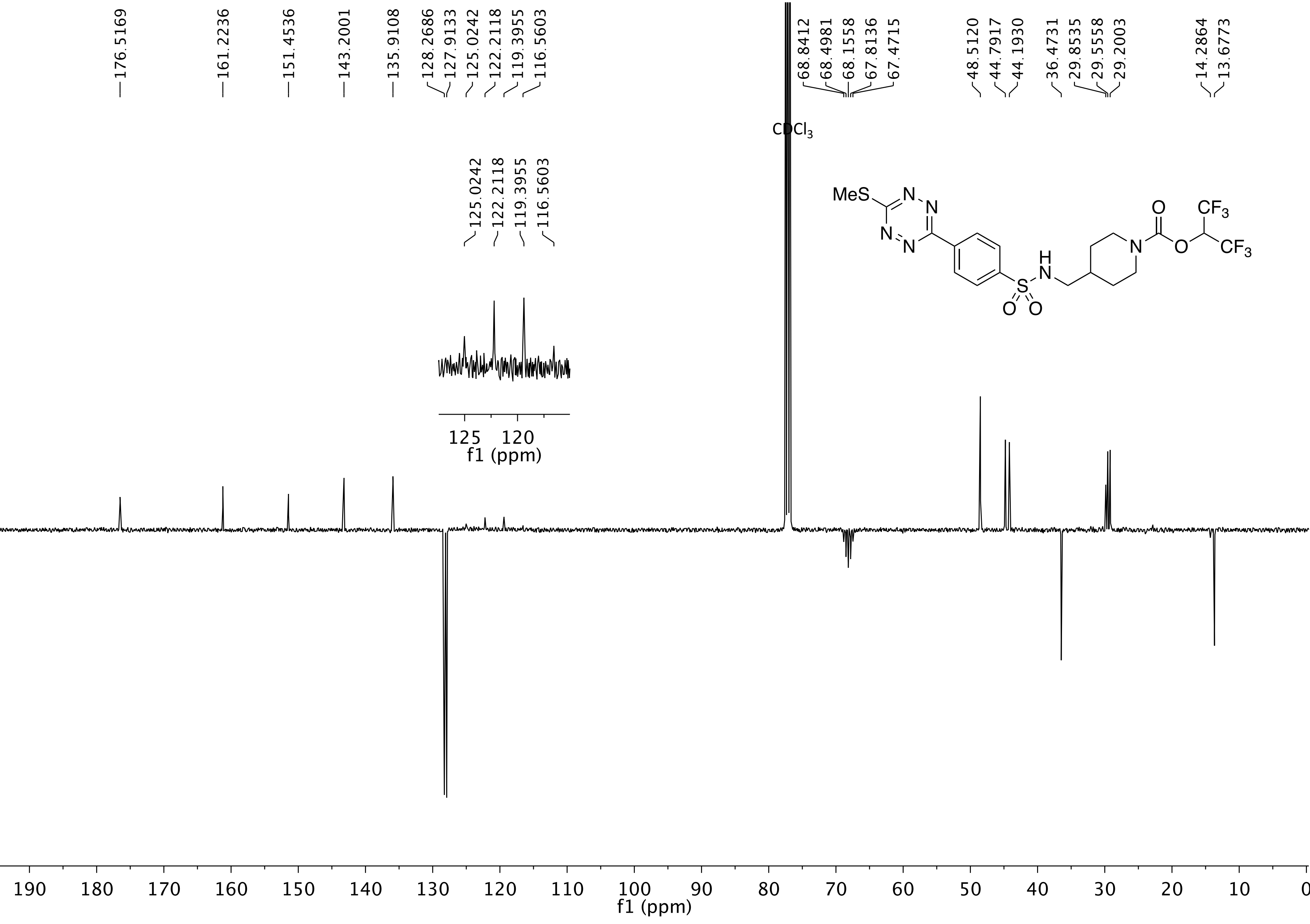
1.0
0.5
0.0
f1 (ppm)



176.5169
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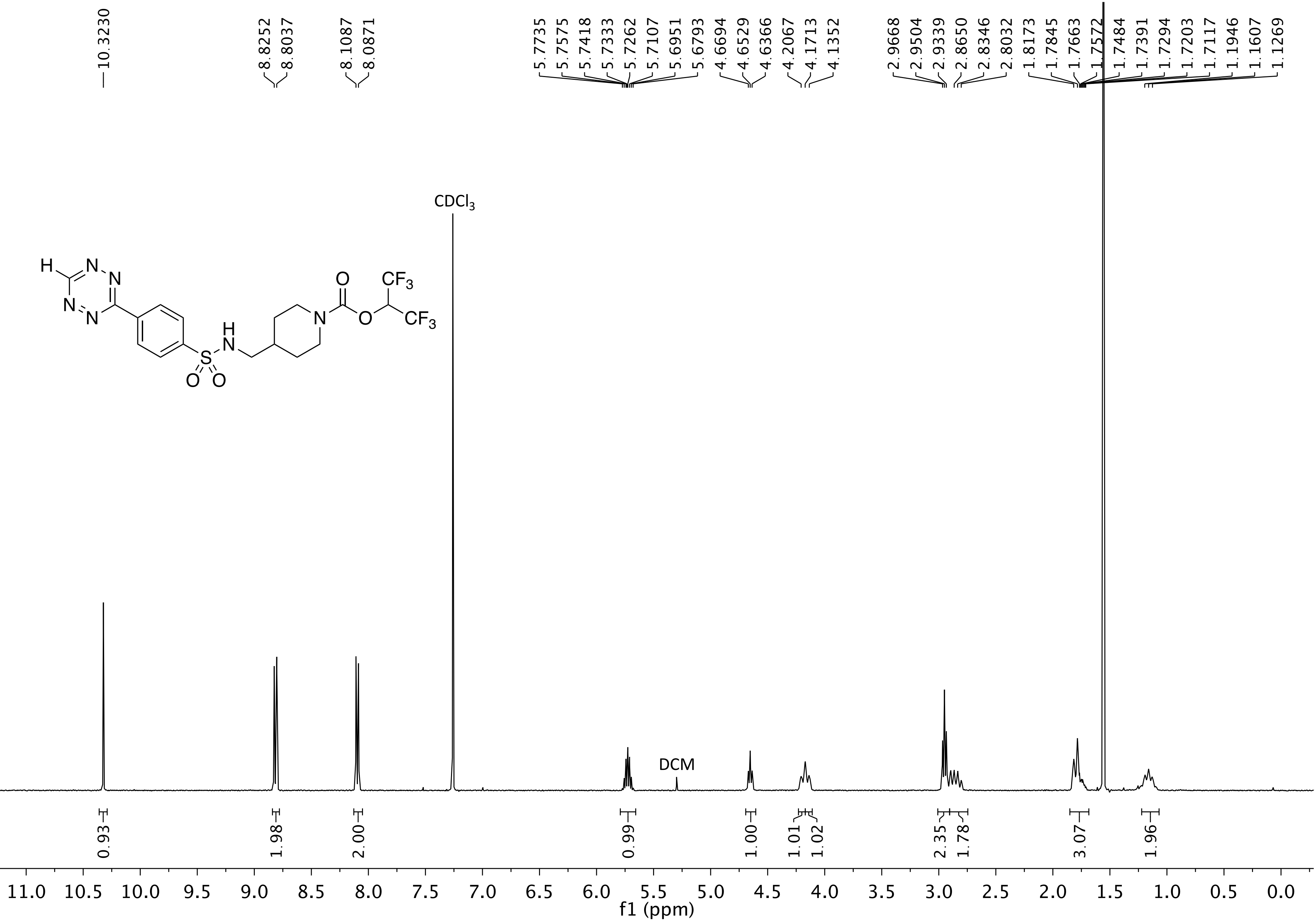
127.9133
125.0242
122.2118
119.3955
116.5603
68.8412
68.4981
68.1558
67.8136
67.4715
48.5120
44.7917
44.1930
36.4731
29.8535
29.5558
29.2003
14.2864
13.6773
CDCl3
MeS
N
O
CF3
H
S
125
120
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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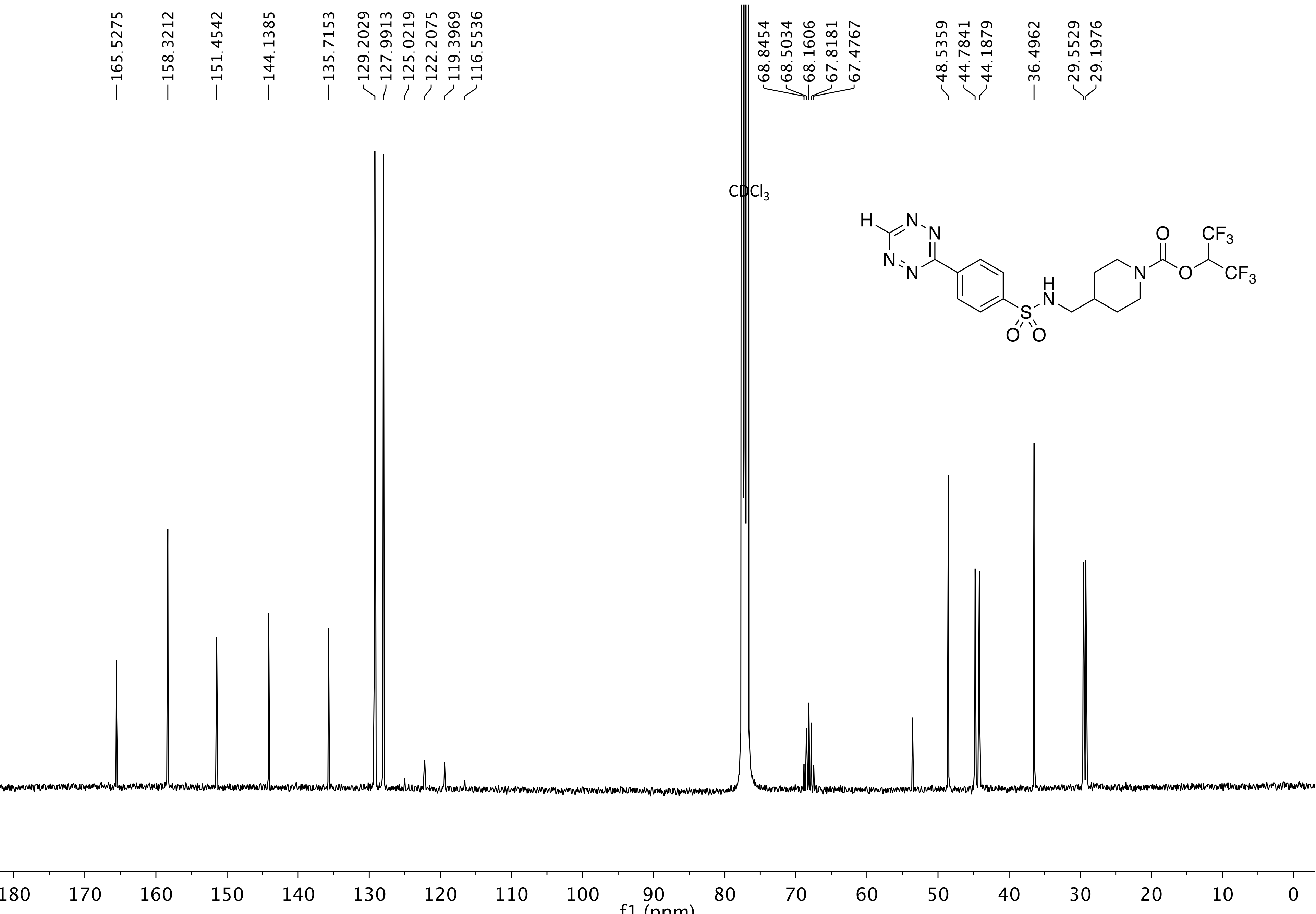
5.7107
5.6951
5.6793
4.6694
4.6529
4.6366
4.2067
4.1713
4.1352
2.9668
2.9504
2.9339
2.8650
2.8346
2.8032
1.8173
1.7845
1.7663
1.7572
1.7484
1.7391
1.7294
1.7203
1.7117
1.1946
1.1607
1.1269
CDCl3
DCM
0.93
1.98
2.00
0.99
1.00
1.01
1.02
2.35
1.78
3.07
1.96
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



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127.9913
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68.8454
68.5034
68.1606
67.8181
67.4767
48.5359
44.7841
44.1879
36.4962
29.5529
29.1976
CDCl3
H
N
N
N
N
O
CF3
N
O
CF3
H
N
S
O
O
180
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150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
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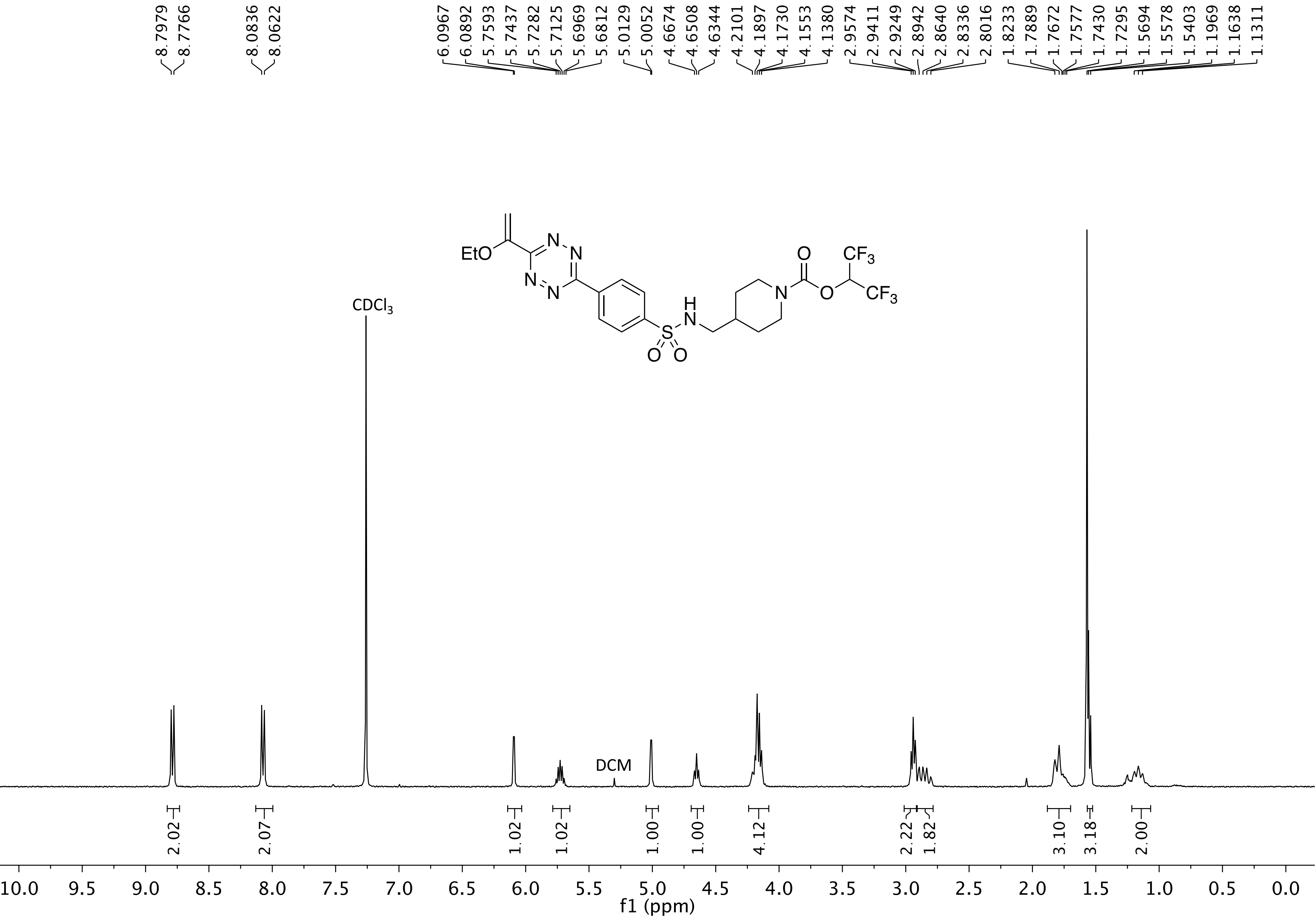
f1 (ppm)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5.6812
5.0129
5.0052
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4.6508
4.6344
4.2101
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4.1730
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4.1380
2.9574
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2.9249
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2.8336
2.8016
1.8233
1.7889
1.7672
1.7577
1.7430
1.7295
1.5694
1.5578
1.5403
1.1969
1.1638
1.1311
EtO
N
CF3
O
H
$CDCl_3$
DCM
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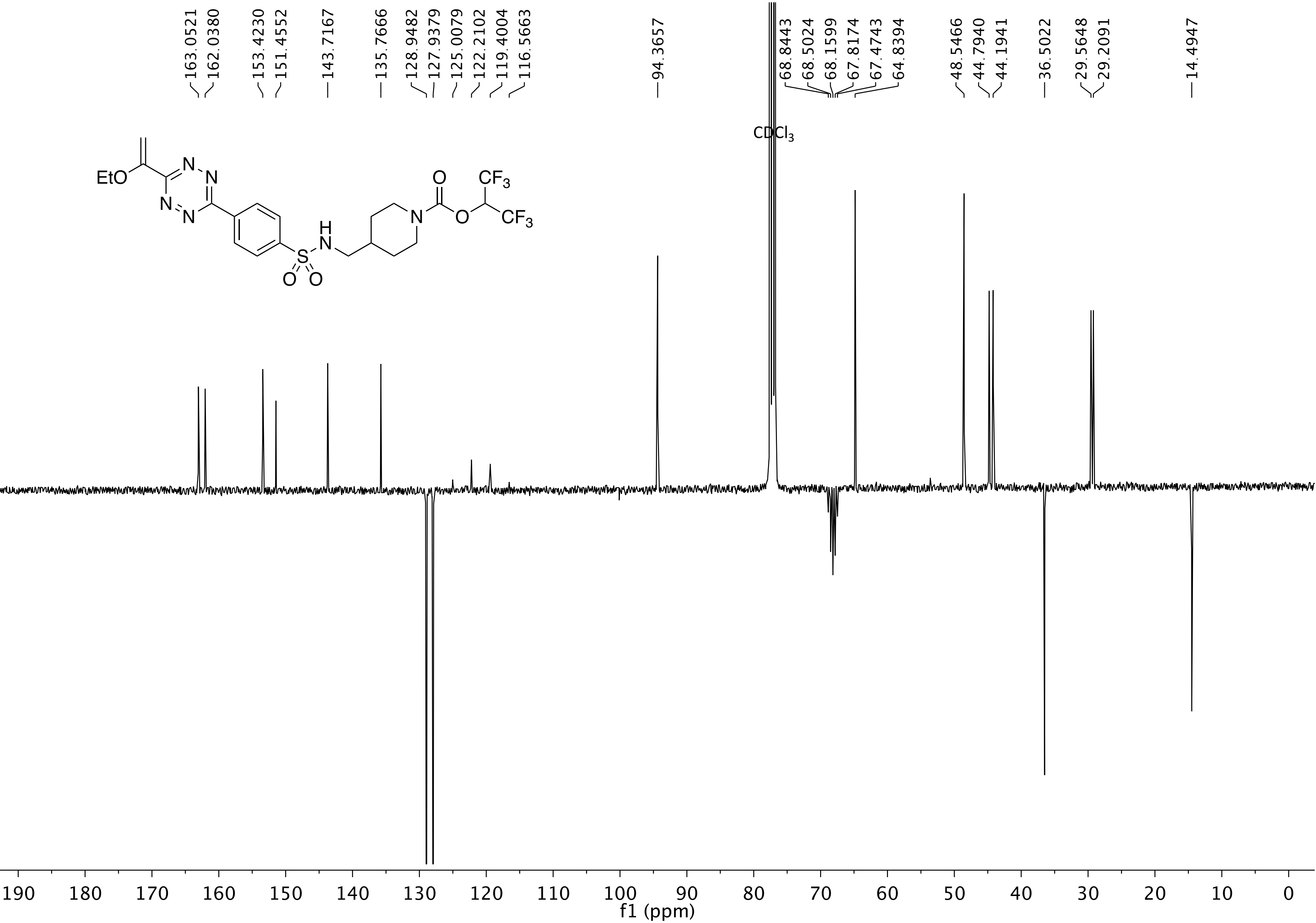
2.07
1.02
1.02
1.00
1.00
4.12
2.22
1.82
3.10
3.18
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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67.8174
67.4743
64.8394
48.5466
44.7940
44.1941
36.5022
29.5648
29.2091
14.4947
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N
O
CF3
H
S
CF3
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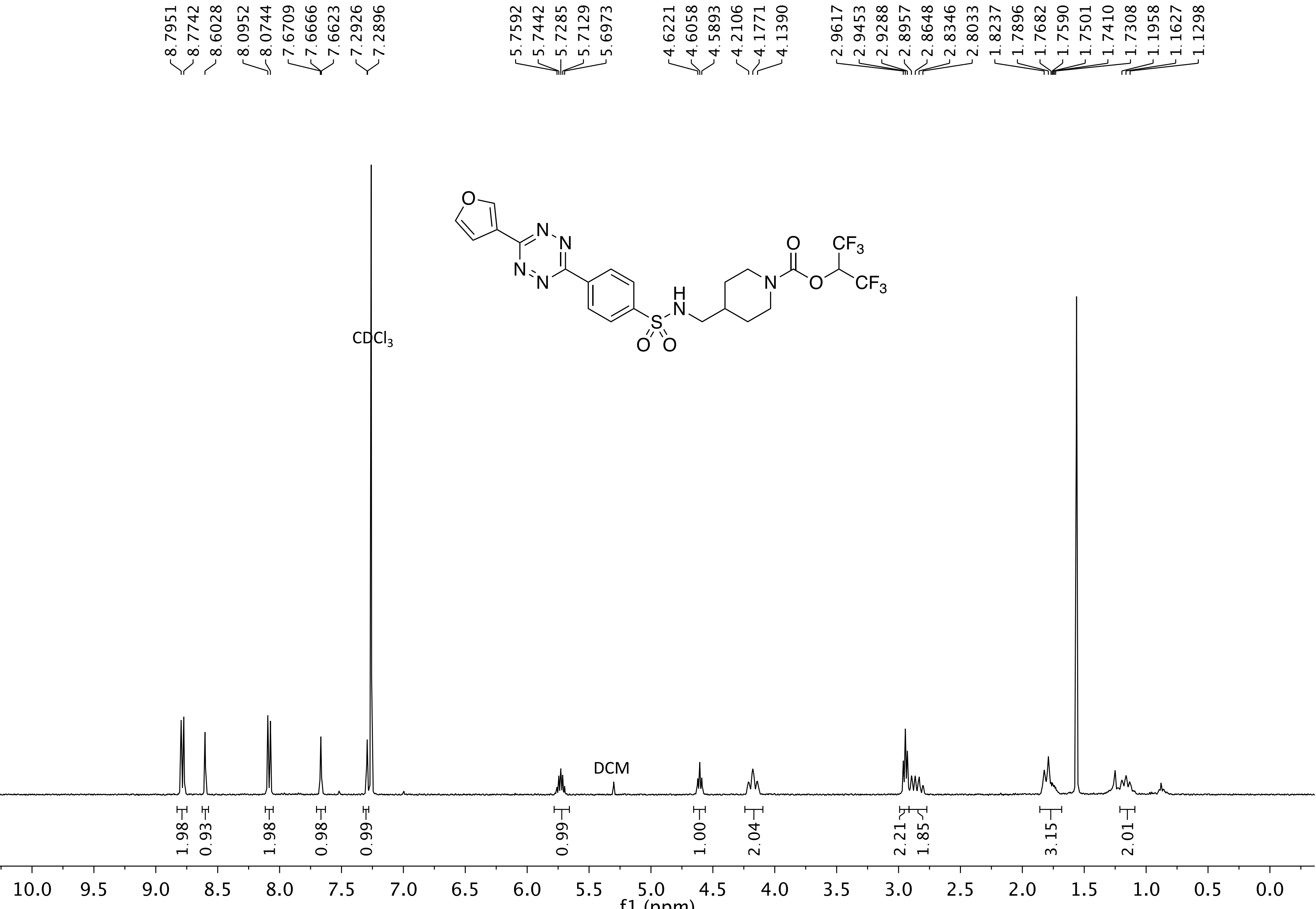
f1 (ppm)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5.7442
5.7285
5.7129
5.6973
4.6221
4.6058
4.5893
4.2106
4.1771
4.1390
2.9617
2.9453
2.9288
2.8957
2.8648
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2.8033
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1.7682
1.7590
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1.7410
1.7308
1.1958
1.1627
1.1298
CDCl3
DCM
1.98
0.93
1.98
0.98
0.99
0.99
1.00
2.04
2.21
1.85
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2.01
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9.5
9.0
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8.0
7.5
7.0
6.5
6.0
5.5
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3.5
3.0
2.5
2.0
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1.0
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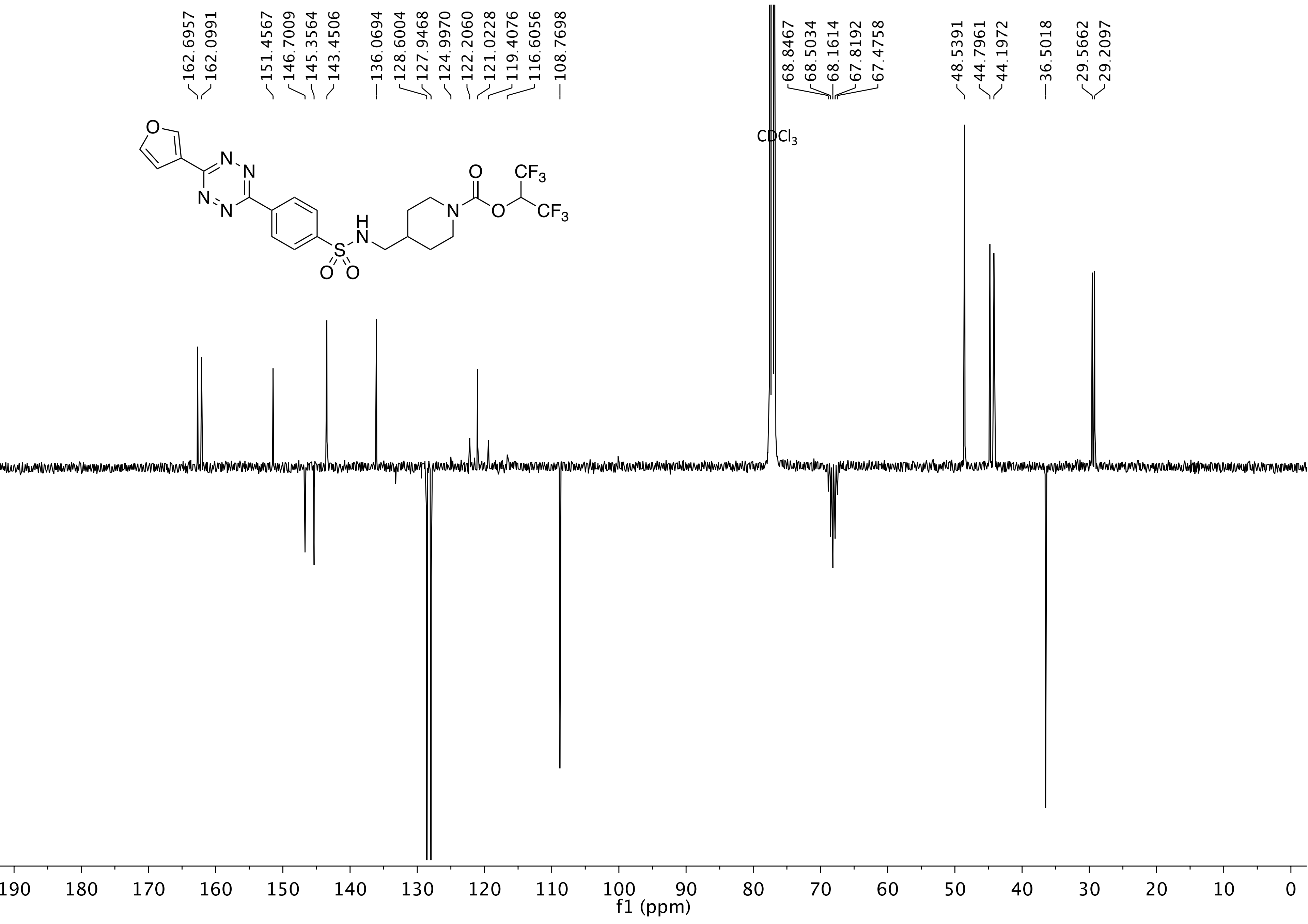
0.0
f1 (ppm)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121.0228
119.4076
116.6056
108.7698
68.8467
68.5034
68.1614
67.8192
67.4758
48.5391
44.7961
44.1972
36.5018
29.5662
29.2097
CDCl3
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180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)