Supporting Information:

Small Molecule Inhibitors of the TLR3/dsRNA Complex

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Supplemental Information

General Methods.

NMR spectra were acquired on Bruker 300 spectrometer, running at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ or $(CD_3)_2CO$ using residual $CHCl_3$ (7.28 ppm) and $(CH_3)_2CO$ (2.05 ppm) as the internal standard. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ or $(CD_3)_2CO$ using residual $CHCl_3$ (77.16 ppm) and $(CH_3)_2CO$ (29.84 and 206.26 ppm) as internal reference. Thin layer chromatography was performed on Merck Kieselgel 60 Å F254 or Silicycle 60Å F254 plates eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid. Compounds were purified using flash chromatography (FC) (Silica gel 60, 200-400 mesh, Sorbent Tech.) or recrystalization. Optical rotations (Na D line) were obtained using a microcell with 1 dm path length on a Jasco P-1030 polarimeter. Specific rotations ([α], Unit: $°cm^2/g$) are based on the equation $\alpha = (100 \cdot \alpha)/(l \cdot c)$ and are reported as unit-less numbers where the concentration c is in g/l00 mL and the path length l is in decimeters. Mass spectrometry was performed at the mass spectrometry facility of the Department of Chemistry at University of Colorado at Boulder on a double focusing high resolution mass spectrometer. Compounds were named using ChemDraw 11.0. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.

Virtual Screening.

The *Enamine* drug database (1.2 million small molecules) was docked into the dsRNA-binding domain of TLR3 (PDB: 3CIY[1]) using Glide 5.6. The molecules are created, as appropriate, with multiple protonation and tautomeric states. The TLR3 conformations were prepared using standard Glide protocols. This includes addition of hydrogens, restrained energy-minimizations of the protein structure with the Optimized Potentials for Liquid Simulations-All Atom (OPLS-AA) force field, and finally setting up the Glide grids using the Protein and Ligand Preparation Module. All 1.2 million compounds were first docked and ranked using High Throughput Virtual Screening (HTVS) Glide, continued with standard precision (SP) Glide for the top 10000 compounds. The resultant top 5000 compounds were then docked using the more accurate and computationally intensive extra-precision (XP) mode. Initial top-ranked 100 compounds were selected and ranked by predicted binding energy.

The selection of the candidate molecules was based on the following criteria: (1) Predicted binding energy and spatial complementarity. (2) Reasonable chemical structures found in the dsRNA-binding site of TLR3. (3) Existence of at least one hydrogen bond between the ligand and one of the dsRNA-recognizing residues on the TLR3 surface (e.g. His 539, Asn 541, and Ser 571, etc). (4) Protonation state and the tautomeric form of the ligand have to be acceptable. As a result,

the initial 100 candidate compounds were filtered and yielded 9 potential TLR3 hits for cellular assays.

TLR3 Inhibition Assay.

RAW 264.7 (Mouse leukaemic monocyte macrophage cell line) cells were grown in RPMI 1640 medium, supplemented with 10% FBS, penicillin (100 U/mL) and streptomycin (100 mg/mL). RAW cells were then planted in 96-well plates at 100,000 cells per well and grown for 24 h in the media descried previously at 37°C in a 5% CO_2 humidified incubator. After 24 h, non-adherent cells and media were removed and replaced with fresh RPMI 1640 medium (only RPMI). The adherent macrophages were treated with high molecular weight polyinosine-polycytidylic acid (poly (I:C)) (10 μg/mL) (Invivogen, CA), an agonist of TLR3, and then added different concentrates of potential inhibitor. Two rows were only treated with Poly (I:C) as blank controls. Plates were then incubated for an additional 24 h. Following incubation, 100 μL of media was removed and added to flat black 96-well microfluor plates (Thermo Scientific, MA, USA). To each well, 10 μL of 2, 3-diaminonaphthalene (0.05 mg/mL in 0.62 M aqueous HCl solution) was added and incubated for 15 min in the dark. The reaction was quenched by addition of 5 μL of a 3 M aqueous NaOH solution and the plate was read on Beckman Coulter DTX880 reader (Beckman Coulter, CA, USA) with excitation at 365 nm and emission at 450 nm. The nitrite (a stable metabolite of nitric oxide) concentration was determined from a nitrite standard curve.[2] The inhibition rate (%) of NO release was determined using the following formula: Inhibition (%) = [Poly (I:C) (OD_{450}) – Compounds (OD_{450})]/[Poly (I:C) (OD_{450})-Control (OD_{450})]×100. The IC_{50} values for both inhibition and cytotoxicity were determined using software Origin v7.5.

Cytokine-Specific ELISA.

RAW 264.7 cells were planted in 6-well plates in duplicate at 1,000,000 cells per well with 3 mL of medium (RPMI 1640 medium, supplemented with 10% FBS, penicillin (100 U/mL) and streptomycin (100 mg/mL)) and grown for 24 h at 37°C in a 5% CO_2 humidified incubator. After 24 h, non-adherent cells and media were removed and replaced with fresh RPMI 1640 medium (3 mL/well). Two wells of adherent macrophages were treated with Poly (I:C) (Invivogen, 15 μg/mL). One of the two wells was treated with 27 μM compound **4a**. One additional well was treated with only **4a** (27 μM) only. Plates were then incubated for an additional 24 h. After removal of the medium, cells were washed with PBS (3 x 1 mL), the 6 well plate was put on ice, then 500 μL of lysis buffer was added in each well (Lysis Buffer: 120 μL 0.5M EDTA; 12 mL Mammalian Protein Extraction Reagent, 100 μL cocktail, 0.36 mL NaCl (5 M, aqueous)). After 5 min, the mixture was transferred into corresponding 1.5 mL tube, spun for 20 min at 13.2 K rpm in a cold room. Approximately

400 μL of supernatant were collected into new tubes, frozen at -80 °C until ready for cytokine measurement. The production of the cytokine interleukin-1β (IL-1β) and TNF-α was quantified with an enzyme-linked immunosorbent assay (ELISA) using cytokine-specific capture antibodies, biotinylated monoclonal detection antibodies, and recombinant human cytokine standards according to commercially available ELISA kits (R&D Systems, MN).

Nitric Oxide TLR Selectivity Assay.

This assay was run using the same protocols with the "TLR3 Inhibition Assay" previously described. LPS (lipopolysaccharide), FSL-1 ((S,R)-(2,3-bispalmitoyloxypropyl)-Cys-Gly-Asp-Pro-Lys-His-Pro-Lys-Ser-Phe), R848 (4-amino-2-(ethoxymethyl)-α, α-dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol) and Pam_3CSK_4 (N-palmitoyl-S-[2,3-bis(palmitoyloxy)-(2RS)-propyl]-[R]-cysteinyl-[S]-seryl-[S]-lysyl-[S]-lysyl-[S]-lysyl-[S]-lysine.3HCl) were used to selectively activate TLR4, TLR2/6, TLR7 and TLR2/1 in place of Poly (I:C), respectively.

Fluorescence Anisotropy Assay.

Fluorescence polarization experiments were performed at 25 °C using a Horiba Fluorolog-3 fluorometer. For direct binding measurements, serial dilutions of TLR3 (R&D, MN) were made in Tris buffer (pH= 7.2), and an aliquot (5 μL) of 1 μg/mL rhodamine labeled Poly (I:C) (Invivogen, CA), was added to a total volume of 500 μL. The competition binding solution was incubated for 30 minutes at 25 °C. Serial dilutions of **4a** or **1a** were incubated with 20 μM TLR3 and rhodamine-labeled Poly (I:C) for 30 min at room temperature.

Regression analysis was carried out using Origin 8.5 (OriginLab) ligand binding macro module. Experimental data were fitted into equation (1) to determine the IC_{50} values, which in turn can be related to the known affinity of the Poly (I:C) (K_d= 19.0 ± 0.9 nM, Fukuda K. et al. *J. Biol. Chem*. **2008**, *283*, 22787) to acquire the inhibitory constant K_i using equation (2).

Equation (1): $y= min+ (max-min)/(1+10^{x-logIC50})$

(y= total binding, x= log concentration of and rhodamine-labeled Poly (I:C), min= nonspecific binding, max= maximum binding in absence of ligand)

Equation (2): $K_i= IC_{50}/(1+[L]/K_d)$

([L]= concentration of rhodamine-labeled Poly (I:C))

Cytochrome P450 Toxicity Assay.

Test agent was incubated (two wells per condition) with microsomes at 37 °C. Control incubations containing vehicle or reference inhibitors were run along side the test agents. The final assay will contain test agent, probe substrates at the indicated concentration, 2 mM NADPH, 3 mM $MgCl_2$ in 50 mM potassium phosphate buffer, pH 7.4. The final microsomal concentration was 0.5 mg/mL. The maximum solvent concentration in the final assay was ≤ 0.5% to minimize the inhibition of Cyps by solvent. NADPH was added last to start the assay. At the end of ten minutes incubation, the assay was stopped by the addition of acetonitrile containing internal standard, the samples were centrifuged, and the amount of probe metabolite in the supernatant was determined by LC/MS/MS. (Testing was done by Apredica, Watertown, MA using subcellular fractions).

WST-1 Cytotoxicity Assay. In a 96-well plate 5,000 cells in 100 μL media (RPMI 1640 medium, supplemented with 10% FBS, penicillin (100 U/mL) and streptomycin (100 mg/mL)) per well. Eight wells were left empty for blank controls. The plates were incubated (37 ^{o}C, 5% CO_2) overnight to allow the cells to attach to the wells. WST-1 proliferation reagent (Roche) was added to the cells (10 μL per well) and continued to incubate for 1-2 h at 37 °C. Plates were checked visually by comparing the colour of wells with media without cells (colour remained pink) with wells contained untreated cells (colour is orange). When a clear difference could be seen by naked eye, results were read by spectrophotometer at 490nm. Cytotoxicity (%) was determined using the following formula: Cytotoxicity (%) = (1 – [Compounds (OD_{490}) – Background (OD_{490})]/[Control (OD_{490})–Background (OD_{490})])×100.

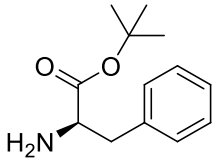
Kinase Profiling Assay

Compounds **4a** was profiled against a panel of 12 representative kinases (AKT1, CAMK1, DDR2, GSK-3α, MAPK1, MET, PAK1, PDGFRB, PIM1, PKC-γ, PLK4 and SRC) using the KinaseSeeker™ assay (Luceome Biotechnologies, Tucson, AZ)[3]. After it was determined that compounds **4a** did not inhibit the luciferase control, profiling was done in duplicate against each kinase. The values of %Inhibition and %Activity Remaining were calculated using the following equations:

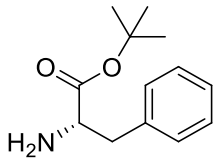
$$\% \text{ Inhibition} = (ALU_{control} - ALU_{sample}) / ALU_{control} \times 100$$

$$\% \text{ Activity Remaining} = 100 - \% \text{ Inhibition}$$

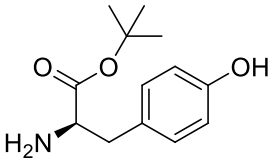
Profiling data for all kinases was plotted as % activity remaining vs. kinases profiled. Reference data for staurosporine (a nonspecific kinase inhibitor) was served as the positive control.



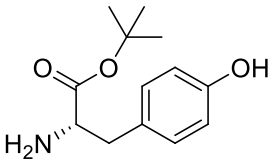
(*R*)-phenylalanine *tert*-butyl ester (**A1**). To a solution of D-phenylalanine (1.651 g, 10.0 mmol) in *tert*-butyl acetate (20 mL) at 0 ^{o}C, was slowly added $HClO_4$ (0.85 mL, 15 mmol).[4] The reaction mixture was stirred at room temperature for 12 h then washed with H_2O (25 mL) and 1.0 M HCl solution (15 mL). The resultant aqueous solution was adjusted to pH 9 by addition of 10 % K_2CO_3 solution, and then extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated to give an oil. This was purified by flash chromatography on silica gel, using a grading of ethyl acetate/hexane ((1:5) to (2:5)), to give **A1** as a colorless oil; (2.020 g, 89.3%). Spectral data were in accordance with those published. $[\alpha]_D^{25}$: -39.5 (c = 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.29 (m, 2H), 7.27-7.22 (m, 3H), 3.63 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.09-3.02 (m, 1H), 2.89-2.82 (m, 2H), 1.47 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.34, 137.57, 129.39, 128.41, 126.65, 81.12, 56.33, 41.29, 28.00; LRMS (ESI): calcd for: $C_{13}H_{19}NO_2$ $[M + H]^+$ = 222.1, obsd $[M + H]^+$ = 222.1, $[M + Na]^+$ = 244.1, obsd $[M + Na]^+$ = 244.1.



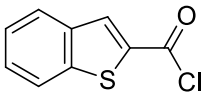
***(S)*-phenylalanine *tert*-butyl ester** (**B1**). Following the **A1** synthetic method, using L-phenylalanine (1.651 g, 10.0 mmol) instead of D-phenylalanine to give **B1** as a colorless oil; (2.01g, 88.9%). $[\alpha]_D^{25}$: +49.8 (c = 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.28 (m, 2H), 7.27-7.22 (m, 3H), 3.63 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.09-3.02 (m, 1H), 2.89-2.82 (m, 2H), 1.44 (m, 11 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.34, 137.58, 129.38, 128.41, 126.64, 81.11, 56.33, 41.30, 28.00; LRMS (ESI): calcd for: $C_{13}H_{19}NO_2$ $[M + H]^+$ = 222.1, obsd $[M + H]^+$ = 222.1, $[M + Na]^+$ = 244.1.



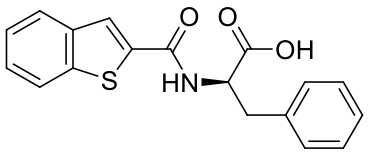
(*R*)-tyrosine *tert*-butyl ester (**A2**). Following the **A1** synthetic method, using D-tyrosine (1.812 g, 10.0 mmol) instead of D-phenylalanine to give **A2** as colorless oil; (1.41 g, 60.2%). $[\alpha]_D^{25}$: +41.3 (c = 0.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.06 (s, 1H), 7.04 (s, 1H), 6.70 (s, 1H), 6.67 (s, 1H), 3.61 (m, 1H), 3.05-2.98 (m, 1H), 3.82-2.75 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.08, 155.44, 130.39, 127.92, 115.69, 81.65, 55.99, 39.81, 28.04; LRMS (ESI): calcd for: $C_{13}H_{19}NO_3$ $[M + H]^+$ = 238.1, obsd $[M + H]^+$ = 238.1, $[M + Na]^+$ = 260.1, obsd $[M + Na]^+$ = 260.1.



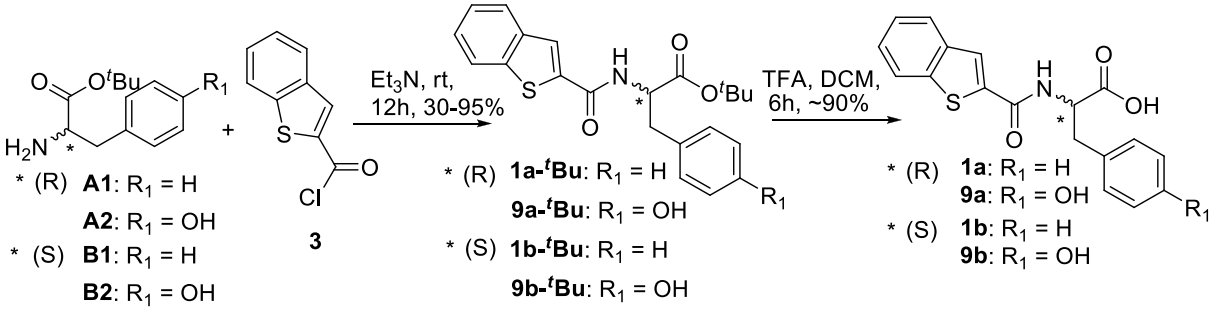
***(S)*-tyrosine *tert*-butyl ester** (**B2**). Following the **A1** synthetic method, using L-tyrosine (1.812 g, 10.0 mmol) instead of D-phenylalanine to give **B2** as colorless oil; (1.42 g, 60.8%). $[\alpha]_D^{25}$: -55.5 (c = 0.23, $CHCl_3$); ^1H-NMR (300 MHz, $CDCl_3$): δ 7.08 (s, 1H), 7.04 (s, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 3.61 (m, 1H), 3.04-2.98 (m, 1H), 3.82-2.75 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.02, 155.55, 130.40, 127.76, 115.73, 81.68, 55.95, 39.77, 28.03; LRMS (ESI): calcd for: $C_{13}H_{19}NO_3$ $[M + H]^+$ = 238.1, obsd $[M + H]^+$ = 238.1, $[M + Na]^+$ = 260.1, obsd $[M + Na]^+$ = 260.1.



Benzo[b]thiophene-2-carbonyl chloride (**3**)**.** Thianaphthene-2-carboxylic acid (356.42 mg, 2 mmol) was suspended in dry toluene (6 mL), thionyl chloride (4.4 mL, 60 mmol) and DMF (0.05 mL) were added at room temperature, and then the mixture was refluxed 8 h.[5] The volatiles were removed at reduced pressure to give benzo[b]thiophene-2-carbonyl chloride as a yellow power. Purified by flash chromatography on silica gel, using ethyl acetate/hexane (1:9) as eluent, give **3** as a white power (393.64 mg, 94.9%). Spectral data were in accordance with those published.^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.04-7.89 (m, 2H), 7.60-7.46 (m, 2H. ^{13}C NMR (300 MHz, $CDCl_3$): δ 161.14, 144.07, 138.05, 136.59, 135.89, 128.75, 126.68, 125.66, 122.91.



(*R*)-2-(benzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (1a)



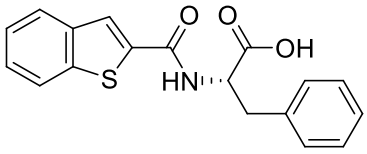
Method A.

To a solution of D-phenylalanine *tert*-butyl ester (110.65 mg, 0.5 mmol) in dry dichloromethane (3 mL) at 0 ^{o}C was added triethylamine (0.086 mL, 0.55 mmol) and benzo[b]thiophene-2-carbonyl chloride (98.33 mg, 0.5 mmol).[6] The reaction mixture was stirred at room temperature overnight and then washed with H_2O (3 x 15 mL) and the organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. Purified by flash chromatography on silica gel, using ethyl acetate/hexane (1:9) as eluent, give **1a-^{t}Bu** as colorless oil (176.43 mg, 92.5%). $[\alpha]_D^{25}$: -38.8 (c = 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.82 (m, 2H), 7.75 (d, *J* = 0.9 Hz, 1H), 7.47-7.38 (m, 2H), 7.35-7.27 (m, 3H), 7.25-7.21 (m, 2H), 6.77 (d, *J* = 7.5 Hz, 1H), 5.03-4.96 (m, 1H), 3.27 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.51, 161.58, 140.99, 139.05, 138.07, 136.01, 129.65, 128.45, 127.09, 126.39, 125.38, 125.11, 124.90, 122.70, 82.81, 54.02, 38.05, 28.02; HRMS (ESI): calcd for: $C_{22}H_{23}NO_3S$ $[M + Na]^+$ = 404.1304, obsd $[M + Na]^+$ = 404.1291.

Then **1a-^{t}Bu** (95.37 mg, 0.25 mmol) was dissolved in 2 mL of CH_2Cl_2 and 2 mL TFA was add under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using HOAc/ethyl acetate (1:100) as the eluent, to give **1a** (73.29 mg, 90.1%); $[\alpha]_D^{25}$: -25.9 (c = 0.21, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.55 (bs, 1H), 7.83-7.72 (m, 3H), 7.45-7.34 (m, 2H), 7.32-7.21 (m, 5H), 6.83 (d, *J* = 7.5 Hz, 1H), 5.12 (m, 1H), 3.41-3.25 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.13, 162.59, 141.05, 138.91, 136.97, 135.51, 129.44, 128.75, 127.34, 126.29, 125.27, 124.99, 124.94, 122.66, 53.82, 37.35; HRMS (ESI): calcd for: $C_{18}H_{15}NO_3S$ $[M + H]^+$ = 326.0830, obsd $[M + H]^+$ = 326.0845.

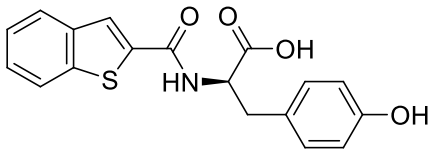
Method B. To a solution of **A1** (110.65 mg, 0.5 mmol) in dry dichloromethane (3 mL) was added HATU (171.09 mg,

0.45 mmol), DIPEA (0.174 mL, 1 mmol) and benzo[b]thiophene-2-carboxylic acid (93.56 mg, 0.525 mmol). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure, using ethyl acetate/hexane (1:9) as eluent, give **1a-^{t}Bu** as a colorless oil (181.01 mg, 94.9 %). Then **1a-^{t}Bu** (95.37 mg, 0.25 mmol) was dissolved in 2 mL of CH_2Cl_2 and 2 mL TFA was add under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using HOAc/ethyl acetate (1:100) as the eluent, to give **1a** (73.29 mg, 90.1%).



***(S)*-2-(benzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (1b)**. Following the general method B, using **B1** (110.65mg, 0.5 mmol) instead of **A1** to give **1b-^{t}Bu** as a colorless oil; (182.55 mg, 95.6%). $[\alpha]_D^{25}$: +41.6 (c = 0.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (bs, 1H), 7.78-7.69 (m, 3H), 7.47-7.38 (m, 2H), 7.42-7.29 (m, 3H), 7.27-7.20 (m, 4H), 6.89 (d, *J* = 8.2 Hz, 1H), 5.07 (m, 1H), 3.38-3.21 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.24, 162.64, 141.02, 138.90, 137.01, 135.64, 129.39, 128.73, 127.28, 126.58, 126.24, 125.25, 124.94, 122.62, 53.98, 37.31; HRMS (ESI): calcd for: $C_{18}H_{15}NO_3S$ $[M + Na]^+$ = 348.0651, obsd $[M + Na]^+$ = 348.0665.

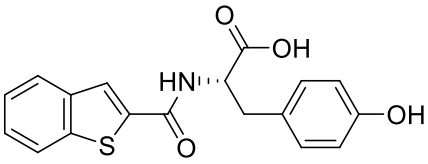
Then **1b-^{t}Bu** (95.37 mg, 0.25 mmol) was dissolved in 2 mL of CH_2Cl_2 and 2 mL TFA was add under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using HOAc/ethyl acetate (1:100) as the eluent, to give **1a**; (74.11 mg, 91.1%). $[\alpha]_D^{25}$: +26.1 (c = 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.47 (bs, 1H), 7.78-7.69 (m, 3H), 7.47-7.38 (m, 2H), 7.42-7.29 (m, 3H), 7.27-7.20 (m, 4H), 6.89 (d, *J* = 8.2 Hz, 1H), 5.07 (m, 1H), 3.38-3.21 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.24, 162.64, 141.02, 138.90, 137.01, 135.64, 129.39, 128.73, 127.28, 126.58, 126.24, 125.25, 124.94, 122.62, 53.98, 37.31; HRMS (ESI): calcd for: $C_{18}H_{15}NO_3S$ $[M + Na]^+$ = 348.0651, obsd $[M + Na]^+$ = 348.0665



***(R)*-2-(benzo[b]thiophene-2-carboxamido)-3-(4-hydroxyphenyl)propanoic acid (9a)**. Following general method B, to a solution of **A2** (237.29 mg, 1.0 mmol) in dry dichloromethane (5 mL) at 0 ^{o}C was added triethylamine (0.172 mL, 1.1

mmol) and **3** (196.65 mg, 1.0 mmol). The reaction mixture was stirred at room temperature overnight and then washed with H_2O (3 x 15 mL) and the organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. Purified by flash chromatography on silica gel, using ethyl acetate/hexane (2:5) as eluent, give **9a-^{t}Bu** as colorless oil (120.44 mg, 30.3%). $[\alpha]_D^{25}$: +41.1 (c = 0.41, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.82 (m, 2H), 7.77 (s, 1H), 7.47-7.38 (m, 2H), 7.08-7.05 (m, 2H), 6.79-6.71(m, 3H), 4.98-4.92 (m, 1H), 3.25-3.12 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.71, 161.73, 155.01, 141.99, 139.03, 137.84, 130.74, 127.59, 126.45, 125.58, 125.15, 124.93, 122.70, 115.38, 82.97, 54.13, 37.25, 28.04. HRMS (ESI): calcd for: $C_{22}H_{23}NO_4S$ $[M + Na]^+$ = 420.1240, obsd $[M + Na]^+$ = 420.1257.

Then **9a-^{t}Bu** (99.37 mg, 0.25 mmol) was dissolved in 2 mL of CH_2Cl_2 and 2 mL TFA was add under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using HOAc/ethyl acetate (1:100) as the eluent, to give **9a**; (75.78 mg, 88.8%). $[\alpha]_D^{25}$: +22.7 (c = 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 8.04 (s, 1H), 7.99-7.90 (m, 2H), 7.49-7.40 (m, 2H), 7.20-7.17 (m, 2H), 6.78-6.75 (m, 2H), 4.91-4.84 (m, 1H), 3.30-3.06 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 161.56, 156.11, 140.93, 139.46, 130.25, 128.01, 126.24, 125.12, 124.88, 124.81, 122.57, 115.09, 36.22; HRMS (ESI): calcd for: $C_{18}H_{15}NO_4S$ $[M + Na]^+$ = 364.0614, obsd $[M + Na]^+$ = 364.0626.

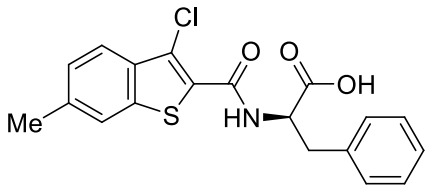


***(S)-tert*-butyl 2-(benzo[b]thiophene-2-carboxamido)-3-(4-hydroxyphenyl)propanoate (9b)**

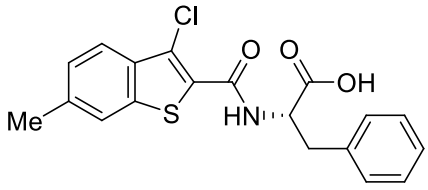
Following the **9a** synthetic method, using **B2** (237.29 mg, 1.0 mmol) instead of **A2** to give **9b-^{t}Bu** as colorless oil; (124.03 mg, 31.2%). $[\alpha]_D^{25}$: -44.6 (c = 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86-7.77 (m, 3H), 7.46-7.36 (m, 2H), 7.28 (s, 1H), 7.06-7.03 (m, 2H), 7.78-7.75 (m, 2H), 6.29 (s, 1H), 4.99-4.92 (m, 1H), 3.23-3.10 (m, 2H), 1.48 (s, 9H); ^{13}C NMR(300 MHz, $CDCl_3$): δ 178.83, 161.85, 155.21, 141.00, 139.02, 137.73, 130.68, 127.34, 125.67, 125.17, 124.93, 122.69, 115.43, 83.04, 54.17, 37.27, 28.03; HRMS (ESI): calcd for: $C_{22}H_{23}NO_4S$ $[M + Na]^+$ = 420.1244, obsd $[M + Na]^+$ = 420.1240.

Then **9b-^{t}Bu** (99.37 mg, 0.25 mmol) was dissolved in 2 mL of CH_2Cl_2 and 2 mL TFA was add under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using HOAc/ethyl acetate (1:100) as the

eluent, to give **9b**; (76.04 mg, 89.1%). $[\alpha]_D^{25}$: -21.6 (c = 0.27, $CHCl_3$); ^1H NMR (300 MHz, acetone-d_6): δ 8.03-7.89 (m, 3H), 7.49-7.39 (m, 2H), 7.19-7.16 (m, 2H), 6.76-6.73 (m, 2H), 4.85-4.80 (m, 1H), 3.29-3.06 (m, 2H); ^{13}C NMR(300 MHz, acetone-d_6): δ 172.79, 161.58, 156.13, 140.92, 139.47, 130.29, 128.11, 126.22, 125.14, 124.90, 124.79, 122.55, 115.13, 78.31, 54.65, 36.29; HRMS (ESI): calcd for: $C_{18}H_{15}NO_4S$ $[M + Na]^+$ = 364.0618, obsd $[M + Na]^+$ = 364.0614.



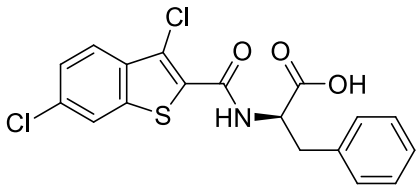
***(R)*-2-(3-chloro-6-methylbenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**2a**). Following general method B, to a solution of **A1** (110.65 mg, 0.5 mmol) in dry dichloromethane (3 mL) was added HATU (171.09 mg, 0.45 mmol), DIPEA (0.174 mL, 1 mmol) and 3-chloro-6-methylbenzo[b]thiophene-2-carboxylic acid (113.34 mg, 0.50 mmol). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure to give an yellow oil. Then the oil was dissolved in 2 mL of CH_2Cl_2 and 2 mL TFA was add under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using HOAc/ethyl acetate (1:100) as the eluent, to give **2a**; (178.51 mg, 95.5%). $[\alpha]_D^{25}$: -31.7 (c = 0.36, $CHCl_3$); ^1H NMR (300 MHz, acetone-d_6): δ 7.80-7.75 (m, 3H), 7.41-7.24 (m, 6H), 5.03-4.97 (m, 1H), 3.44-3.26 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.57, 159.83, 138.30, 138.05, 136.67, 134.65, 131.57, 129.50, 128.39, 127.54, 126.87, 122.57, 122.51, 118.78, 54.03, 36.85, 20.73; HRMS (ESI): calcd for: $C_{19}H_{16}ClNO_3S$ $[M - H]^-$ = 372.0467, obsd $[M - H]^-$ = 472.0484.



***(S)*-2-(3-chloro-6-methylbenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**2b**)

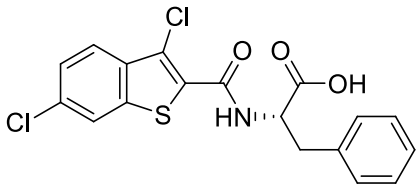
Following the **2a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to give **2b** white powder; (179.63 mg, 96.1%). $[\alpha]_D^{25}$: +23.9 (c = 0.29, $CHCl_3$); ^1H NMR (300 MHz, acetone-d_6): δ 7.76-7.72 (m, 3H), 7.39-7.22 (m, 6H), 5.04-4.98 (m, 1H), 3.44-3.26 (m, 2H), 2.48 (s, 3H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.81, 159.86, 138.26, 138.03, 136.71, 134.63, 131.56, 129.53, 128.38, 127.49, 126.86, 122.53, 122.49, 118.80, 54.13, 36.88, 20.75; HRMS (ESI): calcd

for: $C_{19}H_{16}ClNO_3S$ [M - H]$^-$ = 372.0467, obsd [M - H]$^-$ = 472.0475.



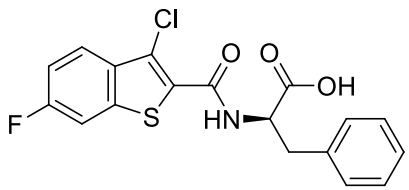
***(R)*-2-(3,6-dichlorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (3a)**

Following the **2a** synthetic method, using 3,6-dichlorobenzo[b]thiophene-2-carboxylic acid (123.55 mg, 0.5 mmol) instead of 3-chloro-6-methylbenzo[b]thiophene-2-carboxylic acid to give **3a** as a white powder; (182.94 mg, 92.8%). $[\alpha]_D^{25}$: -23.2 (c = 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.79 (s, 1H), 7.78 (d, *J* = 1.5 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 6.9 Hz, 1H), 7.42 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.37-7.25 (m, 5H), 5.16-5.14 (m, 1H), 3.41-3.28 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.51, 160.41, 138.97, 135.33, 135.18, 134.21, 132.38, 129.47, 128.82, 127.52, 126.51, 124.16, 122.38, 119.64, 54.12, 37.28; HRMS (ESI): calcd for: $C_{18}H_{13}Cl_2NO_3S$ [M - H]$^-$ = 391.9920, obsd [M -H]$^-$ = 391.9921.



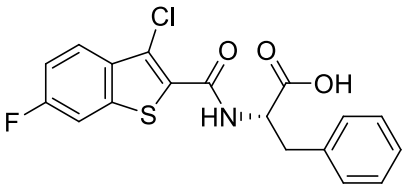
***(S)*-2-(3,6-dichlorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (3b)**

Following the **2a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to get **3b** as a white powder (183.93 mg, 93.3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.23 (s, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.42 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.37-7.25 (m, 5H), 5.16-5.14 (m, 1H), 3.39-3.33 (m, 2H). $[\alpha]_D^{25}$: +17.5 (c = 0.16, $CHCl_3$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.54, 160.40, 138.96, 135.32, 135.19, 134.20, 132.40, 129.47, 128.82, 127.51, 126.55, 124.15, 122.37, 119.62, 54.07, 37.28. HRMS (ESI): calcd for: $C_{18}H_{13}Cl_2NO_3S$ [M-H]$^-$ = 391.9920, obsd [M-H]$^-$ = 391.9916.



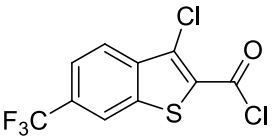
***(R)*-2-(3-chloro-6-fluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (4a).**

Following the **2a** synthetic method, using 3-chloro-6-fluorobenzo[b]thiophene-2-carboxylic acid (115.32 mg, 0.5 mmol) instead of 3-chloro-6-methylbenzo[b]thiophene-2-carboxylic acid to give **4a** as a white powder; (177.01 mg, 93.7%). $[\alpha]_D^{25}$: -21.9 (c = 0.37, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 7.95-7.76 (m, 3H), 7.44-7.22 (m, 6H), 5.04-4.97 (m, 1H), 3.45-3.26 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.48, 163.90, 160.62, 159.50, 139.15, 136.67, 133.50, 129.50, 128.40, 126.89, 124.94, 118.57, 115.15, 114.82, 109.30, 108.95, 53.95, 36.78; HRMS (ESI): calcd for: $C_{18}H_{13}ClFNO_3S$ $[M + H]^+$ = 378.0361, obsd $[M + H]^+$ = 378.0347.

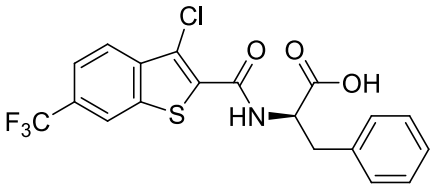


***(S)*-2-(3-chloro-6-fluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (4b).**

Following the **4a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to give **4b** as a white powder; (175.31 mg, 92.8%). $[\alpha]_D^{25}$: +15.5 (c = 0.38, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 8.03-7.77 (m, 3H), 7.44-7.25 (m, 6H), 5.03-4.97 (m, 1H), 3.45-3.26 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 163.90, 160.62, 159.50, 139.01, 136.65, 133.57, 129.50, 128.40, 126.88, 124.94, 115.15, 114.82, 109.31, 108.96, 54.06, 36.79; HRMS (ESI): calcd for: $C_{18}H_{13}ClFNO_3S$ $[M + H]^+$ = 378.0361, obsd $[M + H]^+$ = 378.0352.

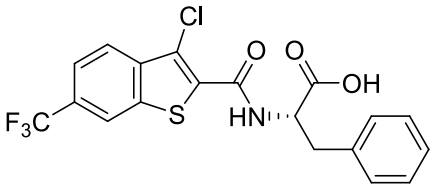


3-chloro-6-(trifluoromethyl)benzo[b]thiophene-2-carbonyl chloride (5) . To a mixture of p-trifluoromethylcinnamic acid (864.64 mg, 4.0 mmol) and pyridine (0.045 mL, 0.56 mmol) was added approximately 1/3 of thionyl chloride (0.667 mL).[7] The mixture was heated to 140 ^{o}C, and the rest of the thionyl chloride was added at a rate such as not to drop the temperature below 135 ^{o}C (40 min). The mixture was then heated at, 140-145 ^{o}C for an additional 12 h and concentrated unger reduce pressure. The mixture solid was dissolved in hot hexanes (20 mL) and decanted to separate pyridine hydrochloride. For recrystallizations from the solution afforded **5** as a yellow crystals; (277.56 mg, 23.2%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18-8.14 (m, 2H), 7.80 (dd, *J* = 1.2, 8.4 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.99, 139.70, 139.24, 132.54, 131.84, 131.41, 130.07, 125.59, 122.95, 120.61.



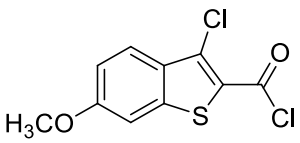
***(R)*-2-(3-chloro-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (5a)**.

Following general method B, to a solution of **A1** (55.33 mg, 0.25 mmol) in dry dichloromethane (2 mL) at 0 ^{o}C was added triethylamine (0.043 mL, 0.28 mmol) and **5** (74.78 mg, 0.25 mmol). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. Then dissolved the oil mixture in 2 mL CH_2Cl_2 and 2 mL TFA was add under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using HOAc/ethyl acetate (1:100) as the eluent, to give **5a**; (100.64 mg, 94.1%). $[\alpha]_D^{25}$: -21.1 (c = 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.71-7.61 (m, 2H), 7.37-7.26 (m, 5H), 6.83 (s, 1H), 5.17-5.15 (m, 1H), 3.45-3.30 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.31, 160.07, 139.09, 137.76, 135.24, 135.13, 129.90, 129.46, 128.84, 127.56, 125.63, 123.89, 122.16, 120.45, 120.40, 119.49, 54.09, 39.26, 29.70; HRMS (ESI): calcd for: $C_{19}H_{13}ClF_3NO_3S$ $[M-H]^-$ = 426.0184, obsd $[M-H]^-$ = 426.0170.

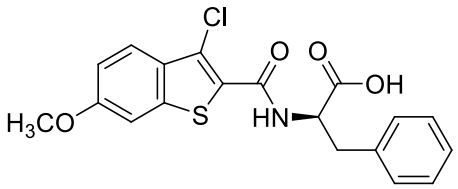


***(S)*-2-(3-chloro-6-(trifluoromethyl)benzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (5b)**

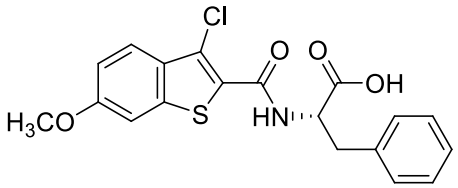
Following the **5a** synthetic method, using **B1** (55.33 mg, 0.25 mmol) instead of **A1** to give **5b** as a yellow powder (99.57 mg, 93.1%). $[\alpha]_D^{25}$: +24.7 (c = 0.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.69-7.61 (m, 2H), 7.36-7.25 (m, 5H), 7.04 (s, 1H), 5.15-5.13 (m, 1H), 3.44-3.29 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.32, 160.09, 139.05, 137.72, 135.22, 135.18, 129.87, 129.45, 128.83, 127.53, 125.62, 123.85, 122.14, 120.43, 120.37, 119.48, 54.20, 37.26, 29.70; HRMS (ESI): calcd for: $C_{19}H_{13}ClF_3NO_3S$ $[M-H]^-$ = 426.0184, obsd $[M-H]^-$ = 426.0180.



3-chloro-6-methoxybenzo[b]thiophene-2-carbonyl chloride (**5-1**). Following the **5** synthetic method, using p-methoxylcinnamic acid (712.72 mg, 4.0 mmol) instead of p-trifluoromethylcinnamic acid to give **5-1** as a yellow crystals; (265.29 mg, 25.4%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 2.1 Hz, 1H), 7.16 (dd, *J* = 2.1, 9.0 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 161.68, 157.82, 142.98, 131.26, 130.96, 126.57, 125.82, 117.76, 103.76, 55.87.

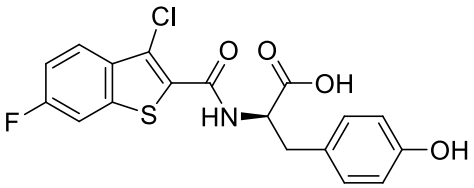


***(R)*-2-(3-chloro-6-methoxybenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**6a**). Following the **5a** synthetic method, using **5-1** instead of **5** to give **6a** as a white powder; (92.78 mg, 95.2%). $[\alpha]_D^{25}$: -18.9 (c = 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 6.9 Hz, 1H), 7.34-7.24 (m, 6H), 7.08 (dd, *J* = 2.4, 9.0 Hz, 1H), 5.16-5.13 (m, 1H), 3.90 (s, 3H), 3.43-3.28 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.46, 160.92, 159.95, 140.09, 135.34, 132.52, 130.84, 129.50, 128.99, 128.76, 124.43, 124.14, 119.85, 116.46, 114.00, 104.32, 55.71, 54.04, 37.35; HRMS (ESI): calcd for: $C_{19}H_{16}ClNO_4S$ $[M-H]^-$ = 388.0416, obsd $[M-H]^-$ = 388.0407.



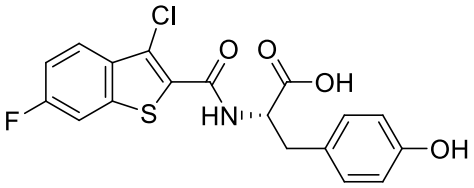
***(S)*-2-(3-chloro-6-methoxybenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**6b**).

Following the **6a** synthetic method, using **B1** (55.33 mg, 0.25 mmol) instead of **A1** to get **6b** as a white powder; (88.78 mg, 91.1%). $[\alpha]_D^{25}$: +16.5 (c = 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.79 (s, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.34-7.23 (m, 6H), 7.07 (dd, *J* = 2.4, 9.0 Hz, 1H), 5.18-5.12 (m, 1H), 3.89 (s, 3H), 3.43-3.28 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.50, 160.91, 159.94, 140.08, 135.36, 132.54, 130.83, 129.51, 128.97, 128.76, 127.41, 124.12, 119.87, 116.45, 113.99, 104.31, 55.71, 54.06, 37.36; HRMS (ESI): calcd for: $C_{19}H_{16}ClNO_4S$ $[M-H]^-$ = 388.0416, obsd $[M-H]^-$ = 388.0402.



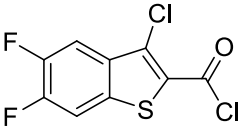
***(R)*-2-(3-chloro-6-fluorobenzo[b]thiophene-2-carboxamido)-3-(4-hydroxyphenyl)propanoic acid** (**7a**).

Following the **9a** synthetic method, using 3-chloro-6-fluorobenzo[b]thiophene-2-carbonyl chloride (249.09 mg, 1.0 mmol) instead of **3** to give **7a** as a colorless oil; (145.32 mg, 36.9%). $[\alpha]_D^{25}$: +18.3 (c = 0.37, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 7.97-7.87 (m, 2H), 7.73 (d, *J* = 6.6 Hz, 1H), 7.45-7.38 (m, 1H), 7.18-7.15 (m, 2H), 6.80-6.77 (m, 2H), 4.96-4.90 (m, 1H), 3.34-3.16 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.56, 163.89, 160.62, 159.45, 156.42, 139.16, 133.55, 130.54, 127.03, 124.94, 118.51, 115.22, 114.80, 109.29, 108.95, 54.14, 35.98; HRMS (ESI): calcd for: $C_{18}H_{13}ClFNO_4S$ $[M - H]^-$ = 392.0165, obsd $[M - H]^-$ = 392.0174.

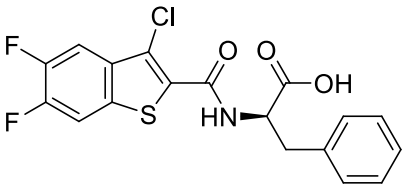


***(S)*-2-(3-chloro-6-fluorobenzo[b]thiophene-2-carboxamido)-3-(4-hydroxyphenyl)propanoic acid** (**7b**).

Following the **9a** synthetic method, using **B2** instead of **A2** to give **7b** as a colorless oil; (147.68 mg, 37.5%). $[\alpha]_D^{25}$: -20.3 (c = 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 7.96-7.87 (m, 2H), 7.75 (d, *J* = 6.0 Hz, 1H), 7.44-7.38 (m, 1H), 7.18-7.15 (m, 2H), 6.79-6.77 (m, 2H), 4.93-4.91 (m, 1H), 3.34-3.17 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.90, 163.86, 160.58, 159.44, 156.40, 139.13, 133.52, 132.97, 130.55, 127.12, 124.90, 118.49, 115.21, 114.76, 109.26, 108.91, 54.42, 36.03; HRMS (ESI): calcd for: $C_{18}H_{13}ClFNO_4S$ $[M - H]^-$ = 392.0165, obsd $[M - H]^-$ = 392.0170.

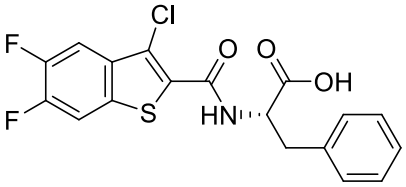


3-chloro-5,6-difluorobenzo[b]thiophene-2-carbonyl chloride (**5-2**). Following **5** synthetic method, using 3.4-difluorocinnamic acid (736.56 mg, 4.0 mmol) instead of p-trifluoromethylcinnamic acid to give **5-2** as a yellow crystals; (272.42 mg, 25.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83-7.77 (m, 1H), 7.70-7.65 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 157.62, 154.54, 152.40, 151.11, 149.05, 135.99, 133.59, 112.22, 110.97.



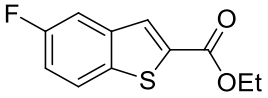
***(R)*-2-(3-chloro-5,6-difluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (8a)**

Following the **5a** synthetic method, using **5-2** (66.77 mg, 0.25 mmol) instead of **5** to give **8a** as a white powder; (91.63 mg, 92.6%). $[\alpha]_D^{25}$: -15.9 (c = 0.19, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 7.91 (s, 1H), 7.63-7.52 (m, 3H), 7.37-7.25 (m, 5H), 5.16-5.09 (m, 1H), 3.43-3.28 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 175.39, 160.02, 152.99, 151.92, 149.63, 148.61, 135.17, 133.75, 133.25, 129.45, 128.82, 127.53, 118.84, 110.98, 110.77, 110.50, 54.05, 37.28; HRMS (ESI): calcd for: $C_{18}H_{12}ClF_2NO_3S$ $[M - H]^-$ = 394.0122, obsd $[M -H]^-$ = 394.0137.



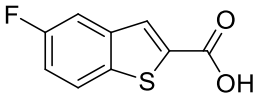
***(S)*-2-(3-chloro-5,6-difluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid (8b)**.

Following the **8a** synthetic method, using **B1** (55.33 mg, 0.25 mmol) instead of **A1** to get **8b** as a white powder; (93.51 mg, 94.5%). $[\alpha]_D^{25}$: +22.3 (c = 0.43, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 7.80 (s, 1H), 7.64-7.51 (m, 3H), 7.34-7.24 (m, 5H), 5.16-5.10 (m, 1H), 3.43-3.28 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 175.44, 160.03, 153.01, 151.93, 149.64, 148.62, 135.14, 133.75, 133.28, 129.45, 128.83, 127.55, 188.89, 110.98, 110.79, 110.53, 54.04, 37.28; HRMS (ESI): calcd for: $C_{18}H_{12}ClF_2NO_3S$ $[M - H]^-$ = 394.0122, obsd $[M -H]^-$ = 394.0127.

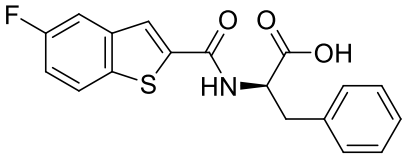


Ethyl 5-fluorobenzo[b]thiophene-2-carboxylate (8). To a mixture of 2,5-difluorobenzaldehyde (217.28 μL, 2 mmol) and potassium carbonate (595.53 mg, 2.5 mmol) in DMF (3 mL) was added ethyl thioglycolate (219.30 μL, 2 mmol) dropwise with ice cooling.[8] The mixture was stirred at room temperature for 30 min and at 60 ^{o}C for 12 h, poured into water, and extracted with EtOAc. The extract was washed with water, dried, and concentrated, and the residue was suspended in EtOH and collected by filtration to give **8** as crystals; (271.34 mg, 60.5%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.83-7.78 (m, 1H), 7.55-7.51 (m, 1H), 7.26-7.19 (m, 1H), 4.46-4.39 (q, 2H), 1.46-1.41 (t, 3H). ^{13}C NMR

(300 MHz, $CDCl_3$): δ 162.47, 159.25, 139.63, 137.60, 136.29, 129.75, 124.11, 116.24, 110.65, 61.74, 14.29.

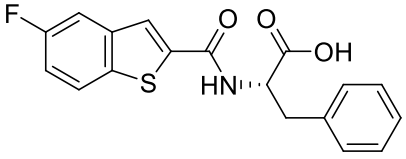


5-fluorobenzo[b]thiophene-2-carboxylic acid (**8-acid**). To a mixture of **8** (246.68 mg, 1.1 mmol) and LiOH (75.9 mg, 3.3 mmol) in THF (9 mL) was added MeOH (1 mL) and H_2O (3 mL), stirred at room temperature for 6 h. Then HCl (1 M) was added to the reaction mixture to pH = 4, and extracted with EtOAc (3 x 15 mL), wash with H_2O (3 x 20 mL). The organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure. Purified by flash chromatography on silica gel, using ethyl acetate/hexane (4:1) as eluent, give **8-acid** as white powder; (212.79 mg, 98.6%). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.14 (s, 1H), 8.10-8.05 (m, 1H), 7.80-7.76 (m, 1H), 7.41-7.34 (m, 1H). ^{13}C NMR (300 MHz, acetone-d_6): δ 162.52, 159.31, 140.12, 137.78, 130.11, 124.65, 116.10, 110.66.



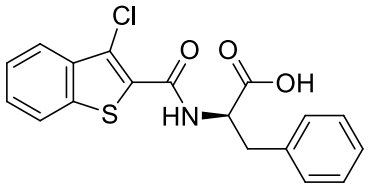
***(R)*-2-(5-fluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**10a**).

Following the **2a** synthetic method, using **8-1** (88.10 mg, 0.5 mmol) instead of 3-chloro-6-methylbenzo[b]thiophene-2-carboxylic acid to give **10a** as a colorless oil; (158.29 mg, 92.2%). $[\alpha]_D^{25}$: -16.6 (c = 0.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.72-7.67 (m, 1H), 7.60 (s, 1H), 7.38-7.15 (m, 7H), 6.84 (d, *J* = 7.2 Hz, 1H), 5.08-5.06 (m, 1H), 3.38-3.21 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 172.07, 162.46, 161.42, 159.27, 141.99, 140.50, 137.50, 136.64, 129.21, 128.33, 126.61, 124.55, 115.22, 114.89, 110.23, 109.92, 54.13, 36.98; HRMS (ESI): calcd for: $C_{18}H_{14}FNO_3S$ [M - H]$^-$ = 342.0606, obsd [M -H]$^-$ = 342.0592.

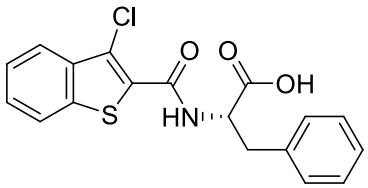


***(S)*-2-(5-fluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**10b**). Following the **10a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to get **10b** as a white powder; (163.96 mg, 95.5%). $[\alpha]_D^{25}$: +21.8 (c = 0.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.74-7.69 (m, 1H), 7.60 (s, 1H), 7.39-7.16 (m, 7H), 6.86 (d, *J* = 7.5 Hz, 1H), 5.09-5.07 (m, 1H), 3.39-3.22 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.03, 162.49, 162.17,

159.27, 139.84, 139.51, 136.42, 135.52, 129.37, 128.76, 127.36, 125.57, 124.05, 115.93, 110.45, 53.87, 37.31; HRMS (ESI): calcd for: $C_{18}H_{14}FNO_3S$ [M - H]$^-$ = 342.0606, obsd [M -H]$^-$ = 342.0596.

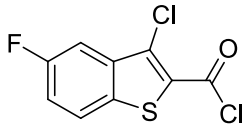


***(R)*-2-(3-chlorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**11a**). Following the **2a** synthetic method, using 3-chlorobenzo[b]thiophene-2-carboxylic acid (106.33 mg, 0.5 mmol) instead of 3-chloro-6-methylbenzo[b]thiophene-2-carboxylic acid to get **11a** as a colorless oil; (167.14 mg, 92.9%). $[\alpha]_D^{25}$: -19.9 (c = 0.34, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 8.05-7.99 (m, 1H), 7.90-7.87 (m, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.61-7.54 (m, 2H), 7.37-7.22 (m, 5H), 5.05-4.98 (m, 1H), 3.45-3.27 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.54, 159.75, 137.75, 136.74, 136.67, 132.78, 129.51, 128.40, 127.67, 126.88, 125.74, 123.03, 122.82, 118.87, 54.10, 36.83; HRMS (ESI): calcd for: $C_{18}H_{14}ClNO_3S$ [M - H]$^-$ = 358.0310, obsd [M - H]$^-$ = 358.0318.



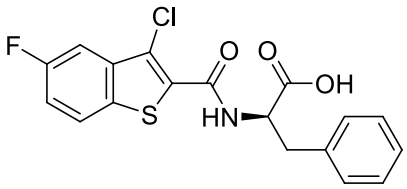
***(S)*-2-(3-chlorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**11b**).

Following the **11a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to get **11b** as a colorless oil; (164.98 mg, 91.7%). $[\alpha]_D^{25}$: +23.3 (c = 0.42, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 8.06-8.00 (m, 1H), 7.91-7.87 (m, 1H), 7.80 (d, *J* = 6.9 Hz, 1H), 7.62-7.55 (m, 2H), 7.37-7.22 (m, 5H), 5.05-4.98 (m, 1H), 3.45-3.26 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.56, 159.74, 137.75, 136.74, 136.67, 132.78, 129.51, 128.40, 127.67, 126.88, 125.74, 123.03, 122.83, 118.86, 54.09, 36.83; HRMS (ESI): calcd for: $C_{18}H_{14}ClNO_3S$ [M - H]$^-$ = 358.0310, obsd [M -H]$^-$ = 358.0312.



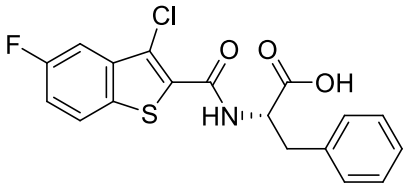
3-chloro-5-fluorobenzo[b]thiophene-2-carbonyl chloride (**5-3**). Following **5** synthetic method, using 3-fluorocinnamic acid (664.60 mg, 4.0 mmol) instead of p-trifluoromethylcinnamic acid to give 3-chloro-5-fluorobenzo[b]thiophene-2-

carbonyl chloride as a yellow crystals; (279.97 mg, 28.1%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.82 (m, 1H), 7.71-7.67 (m, 1H), 7.45-7.38 (m, 1H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 163.12, 159.84, 158.09, 135.88, 131.76, 124.71, 119.67, 119.33, 110.13.



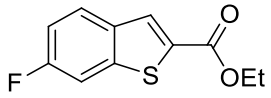
***(R)*-2-(3-chloro-5-fluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**12a**).

Following the **5a** synthetic method, using 3-chloro-5-fluorobenzo[b]thiophene-2-carbonyl chloride (62.27 mg, 0.25 mmol) instead of **5** to give **12a** as a white powder; (82.6 mg, 91.7%). $[\alpha]_D^{25}$: -16.8 (c = 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 8.10-8.06 (m, 1H), 7.81 (d, *J* = 6.9, 1H), 7.61-7.57 (m, 1H), 7.46-7.28 (m, 6H), 5.03-4.97 (m, 1H), 3.45-3.26 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.51, 163.02, 159.79, 138.08, 136.67, 135.36, 133.43, 129.49, 128.39, 126.88, 125.28, 118.22, 116.80, 116.46, 108.25, 107.92, 54.15, 36.79; HRMS (ESI): calcd for: $C_{18}H_{13}ClFNO_3S$ $[M - H]^-$ = 376.0216, obsd $[M -H]^-$ = 376.0200.



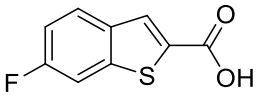
***(S)*-2-(3-chloro-5-fluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**12b**).

Following the **12a** synthetic method, using **B1** (55.33 mg, 0.25 mmol) instead of **A1** to give **12b** as a white powder; (87.65 mg, 92.8%). $[\alpha]_D^{25}$: +22.3 (c = 0.29, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 8.11-8.06 (m, 1H), 7.81 (d, *J* = 7.2, 1H), 7.61-7.57 (m, 1H), 7.46-7.22 (m, 6H), 5.03-4.97 (m, 1H), 3.40-3.26 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.50, 163.02, 159.80, 138.09, 136.66, 135.36, 133.46, 129.49, 128.39, 126.88, 125.29, 118.28, 116.80, 116.46, 108.25, 107.93, 54.14, 36.79; HRMS (ESI): calcd for: $C_{18}H_{13}ClFNO_3S$ $[M - H]^-$ = 376.0216, obsd $[M -H]^-$ = 376.0221.

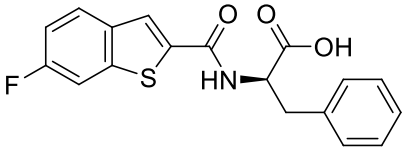


Ethyl 6-fluorobenzo[b]thiophene-2-carboxylate (**8-1**).

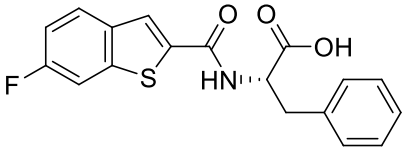
Following **8** synthetic method, using 2,4-difluorobenzaldehyde (218.8 μL, 2 mmol) instead of 2,5-difluorobenzaldehyde to give 8-1 as a white crystals; (278.97 mg, 62.2%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.86-7.81 (m, 1H), 7.56-7.52 (m, 1H), 7.21-7.14 (m, 1H), 4.45-4.38 (q, 2H), 1.45-1.40 (t, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 163.60, 160.31, 143.37, 135.28, 133.75, 129.82, 126.89, 114.57, 108.83, 61.65, 14.31.



6-fluorobenzo[b]thiophene-2-carboxylic acid (8-1-acid). Following the 5-fluorobenzo[b]thiophene-2-carboxylic acid synthetic method, give **8-1-acid** as a white powder; (211.72 mg, 98.1%). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.14 (s, 1H), 8.08-8.04 (m, 1H), 7.86-7.82 (m, 1H), 7.34-7.27 (m, 1H). ^{13}C NMR (300 MHz, acetone-d_6): δ 163.56, 160.31, 143.43, 135.86, 130.06, 127.34, 114.39, 108.81.

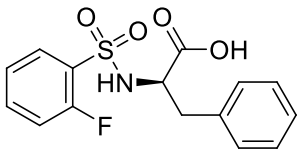


***(R)*-2-(6-fluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**13a**). Following the **2a** synthetic method, using **8-1-acid** (98.10 mg, 0.5 mmol) instead of 3-chloro-6-methylbenzo[b]thiophene-2-carboxylic acid to give **13a** as a colorless oil (159.84 mg, 93.1%). $[\alpha]_D^{25}$: -21.1 (c = 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.98 (s, 1H), 7.90-7.86 (m, 1H), 7.75-7.71 (m, 1H), 7.34-7.13 (m, 6H), 4.95-4.87 (m, 1H), 3.36-3.10 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 172.09, 163.11, 161.49, 159.87, 142.28, 139.46, 137.49, 136.19, 129.22, 128.33, 126.89, 126.63, 126.61, 124.44, 114.09, 108.67, 54.08, 37.01; HRMS (ESI): calcd for: $C_{18}H_{14}FNO_3S$ $[M-H]^-$ = 342.0606, obsd $[M-H]^-$ = 342.0594.

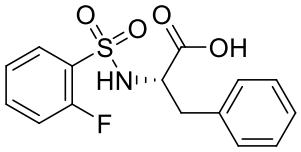


***(S)*-2-(6-fluorobenzo[b]thiophene-2-carboxamido)-3-phenylpropanoic acid** (**13b**). Following the **13a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to give **13b** as colorless oil; (154.68 mg, 90.1%). $[\alpha]_D^{25}$: +15.7 (c = 0.26, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 8.08 (d, *J* = 8.1 Hz, 1H), 8.03 (s, 1H), 7.96-7.91 (m, 1H), 7.80-7.76 (m, 1H), 7.39-7.18 (m, 6H), 4.98-4.92 (m, 1H), 3.36-3.15 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 172.17, 163.11,

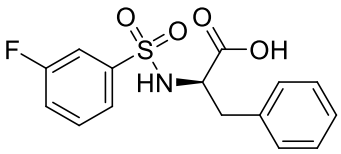
161.48, 159.86, 142.28, 139.43, 137.51, 136.19, 129.23, 128.32, 126.89, 126.76, 126.60, 124.43, 114.09, 108.67, 54.12, 37.02; HRMS (ESI): calcd for: $C_{18}H_{14}FNO_3S$ $[M-H]^-$ = 342.0606, obsd $[M-H]^-$ = 342.0593.



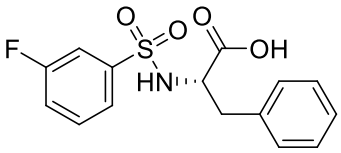
***(R)*-2-(2-fluorophenylsulfonamido)-3-phenylpropanoic acid** (**14a**). To a solution of **A1** (110.65 mg, 0.5 mmol) in dry dichloromethane (3 mL) at 0 ^oC was added triethylamine (0.086 mL, 0.55 mmol) and 2-fluorobenzenesulfonyl chloride (66.88 µL, 0.50 mmol). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. Then dissolved the oil mixture in 2 mL CH_2Cl_2 and 2 mL TFA was add under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using ethyl acetate/hexane (2:5) as the eluent, to give **14a**; (105.42 mg, 65.2%). $[\alpha]_D^{25}$: -11.7 (c = 0.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.60-7.52 (m, 1H), 7.27-7.21 (m, 4H), 7.16-7.09 (m, 3H), 5.27 (d, *J* = 9 Hz, 1H), 4.41 (m, 1H), 3.20-3.06 (m, 2H); ^{13}C NMR(300 MHz, acetone-d_6): δ 171.41, 160.51, 157.15, 136.54, 134.91, 134.80, 129.48, 129.31, 128.18, 126.68, 124.15, 117.04, 116.76, 57.31, 38.36; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_4S$ $[M + H]^+$ = 324.0690, obsd $[M + H]^+$ = 324.0700.



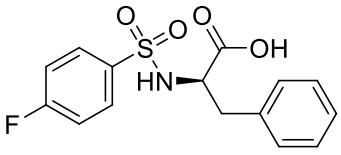
***(S)*-2-(2-fluorophenylsulfonamido)-3-phenylpropanoic acid** (**14b**). Following the **14a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to give **14b** as a colorless oil; (102.01 mg, 63.1%). $[\alpha]_D^{25}$: +16.3 (c = 0.39, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (dd, *J*=1.8, 7.8 Hz, 1H), 7.59-7.52 (m, 1H), 7.26-7.21 (m, 4H), 7.15-7.08 (m, 3H), 5.27 (d, *J* = 9 Hz, 1H), 4.43 (m, 1H), 3.20-3.05 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.53, 160.51, 157.15, 136.55, 134.91, 134.79, 129.48, 129.31, 128.18, 126.68, 124.15, 117.04, 116.75, 57.32, 38.37; HRMS (ESI): calcd for $C_{15}H_{14}FNO_4S$: $[M + Na]^+$ = 346.0508, obsd $[M + Na]^+$ = 324.0520.



***(R)*-2-(3-fluorophenylsulfonamido)-3-phenylpropanoic acid (15a)**. Following the **14a** synthetic method, using 3-fluorobenzenesulfonyl chloride (66.19 μL, 0.5 mmol) instead of 2-fluorobenzenesulfonyl chloride to give **15a** as a colorless oil; (103.95 mg, 64.3%). $[\alpha]_D^{25}$: -16.5 (c = 0.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.32 (m, 3H), 7.25-7.20 (m, 4H), 7.10-7.08 (m, 2H), 5.45 (d, *J* = 7.8 Hz, 1H), 4.25 (m, 1H), 3.19-2.91 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 163.89, 160.56, 141.51, 134.71, 130.88, 129.34, 128.68, 127.47, 122.75, 120.24, 119.96, 114.49, 114.17, 56.86 38.74; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_4S$ $[M - H]^-$ = 322.0555, obsd $[M - H]^-$ = 322.0549.

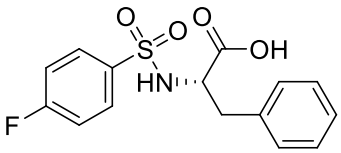


***(S)*-2-(3-fluorophenylsulfonamido)-3-phenylpropanoic acid (15b)**. Following the **15a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to give **14b** as a colorless oil; (106.54 mg, 65.9%). $[\alpha]_D^{25}$: +15.1 (c = 0.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.50 (m, 1H), 7.40-7.36 (m, 2H), 7.27-7.22 (m, 4H), 7.12-7.08 (m, 2H), 5.11 (d, *J* = 9 Hz, 1H), 4.26 (m, 1H), 3.20-2.98 (m, 2H); ^{13}C NMR(300 MHz, $CDCl_3$): δ 163.89, 160.56, 141.49, 134.67, 130.88, 129.33, 128.70, 127.49, 122.75, 120.26, 119.98, 114.49, 114.17, 56.85, 38.72; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_4S$ $[M - H]^-$ = 322.0555, obsd $[M - H]^-$ = 322.0543.

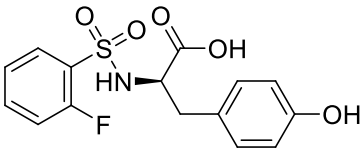


***(R)*-2-(4-fluorophenylsulfonamido)-3-phenylpropanoic acid (16a)**.

Following the **14a** synthetic method, using 4-fluorobenzenesulfonyl chloride (97.31 mg, 0.5 mmol) instead of 2-fluorobenzenesulfonyl chloride to give **16a** as a colorless oil; (108.48 mg, 67.1%). $[\alpha]_D^{25}$: -19.1 (c = 0.41, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.73 (m, 2H), 7.24-7.21 (m, 7H), 6.92 (d, *J* = 9 Hz, 1H), 4.21-4.14 (m, 1H), 3.15-2.90 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.55, 166.28, 162.95, 137.53, 136.53, 129.74, 129.62, 129.39, 128.24, 126.68, 115.93, 115.63, 57.29, 38.49; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_4S$ $[M + Na]^+$ = 346.0520, obsd $[M + Na]^+$ = 346.0513.



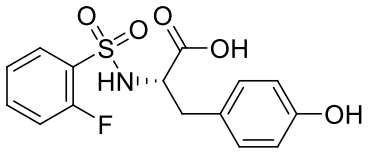
***(S)*-2-(4-fluorophenylsulfonamido)-3-phenylpropanoic acid (16b)**. Following the **16a** synthetic method, using **B1** (110.65 mg, 0.5 mmol) instead of **A1** to get **16b** as a colorless oil (102.34 mg, 63.3%). $[\alpha]_D^{25}$: +14.4 (c = 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.78-7.71 (m, 2H), 7.26-7.17 (m, 7H), 6.92 (d, *J* = 9 Hz, 1H), 4.25-4.13 (m, 1H), 3.15-2.90 (m, 2H); ^{13}C NMR(300 MHz, acetone-d_6): δ 171.56, 166.28, 162.95, 137.52, 136.53, 129.74, 129.62, 129.39, 128.24, 126.68, 115.94, 115.63, 57.31, 38.48; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_4S$ $[M + Na]^+$ = 346.0520, obsd $[M + Na]^+$ = 346.0523.



***(R)*-2-(2-fluorophenylsulfonamido)-3-(4-hydroxyphenyl)propanoic acid (17a)**. Following general method B, to a solution of **A2** (118.65 mg, 0.5 mmol) in dry dichloromethane (3 mL) at 0 ^oC was added triethylamine (0.086 mL, 0.55 mmol) and 2-fluorobenzenesulfonyl chloride (147.14 µL, 1.1 mmol). The reaction mixture was stirred at room temperature overnight and then washed with H_2O (3x15 mL) and the organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purified by flash chromatography on silica gel, using ethyl acetate/hexane (2:5) as the eluent, give **10** as a colorless oil (238.87 mg, 86.3%). $[\alpha]_D^{25}$: +31.8 (c = 0.29, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.86-7.75 (m, 2H), 7.73-7.65 (m, 1H), 7.60-7.53 (m, 1H), 7.34-7.22 (m, 3H), 7.19-7.11 (m, 1H), 7.04-6.99 (m, 1H), 5.35 (d, *J* = 8.7 Hz, 1H), 4.19-4.12 (m, 1H), 3.03-3.01 (d, 2H), 1.20 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.17, 161.10, 157.65, 148.42, 136.86, 135.22, 134.74, 131.43, 130.99, 129.95, 127.74, 124.59, 124.34, 123.55, 122.00, 117.57, 117.29, 117.13, 116.84, 83.12, 57.03, 39.06, 27.62.

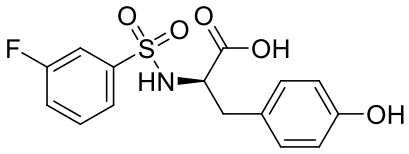
Intermediate **10** (138.40 mg, 0.25 mmol) was dissolved in a solution of 2 N NaOH/EtOH/water (0.96 g/10 mL/2 mL) and heated at 80 °C. After 24 h, the solvent was evaporated and the byproduct was recrystallized from ethanol.[9] The side product (benzenesulfonic acid) was filtered off, and the filtrate was evaporated to dryness. Then dissolved the oil mixture in 2 mL CH_2Cl_2 and 2 mL TFA was added under argon. The reaction mixture was stirred at room temperature for 12 h (TLC monitor). The solvent was removed under reduce pressure and the crude compound was purified by flash chromatography on silica gel, using ethyl acetate/hexane (1:5) as the eluent, to give **17a** as a colorless oil; (55.16mg,

60.3%). $[\alpha]_D^{25}$: +17.7 (c = 0.32, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 7.75-7.59 (m, 2H), 7.30-7.16 (m, 2H), 7.06-7.03 (m, 2H), 6.92 (s, 1H), 6.69-6.66 (m, 2H), 4.19-4.15 (m, 1H), 3.09-2.87 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.58, 160.50, 157.14, 156.14, 134.81, 130.31, 129.48, 129.08, 127.02, 124.17, 117.03, 116.75, 114.98, 57.59, 37.61; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_5S$ $[M + Na]^+$ = 362.0468, obsd $[M + Na]^+$ = 362.0480.



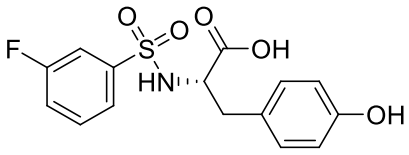
***(S)*-2-(2-fluorophenylsulfonamido)-3-(4-hydroxyphenyl)propanoic acid (17b)**.

Following **10** synthesis method, using **B2** (118.65 mg, 0.5 mmol) instead of **A2** to give **17b** as colorless oil; (82.42 mg, 48.6%). $[\alpha]_D^{25}$: -15.9 (c = 0.39, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 7.76-7.70 (m, 1H), 7.64-7.59 (m, 1H), 7.30-7.16 (m, 2H), 7.06-7.05 (m, 2H), 6.69-6.66 (m, 2H), 4.18-4.14 (m, 1H), 3.09-2.87 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.71, 160.51, 157.14, 156.12, 134.81, 130.35, 129.50, 129.06, 127.08, 124.17, 117.03, 116.75, 114.97, 57.65, 37.63; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_5S$ $[M + Na]^+$ = 362.0468, obsd $[M + Na]^+$ = 362.0468.



***(R)*-2-(3-fluorophenylsulfonamido)-3-(4-hydroxyphenyl)propanoic acid (18a)**.

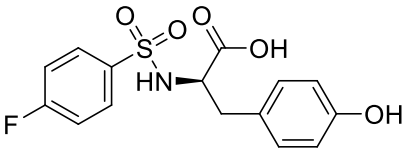
Following **17a** synthetic method, using 2-fluorobenzenesulfonyl chloride (145.62 μL, 1.1 mmol) instead of 2-fluorobenzenesulfonyl chloride to give the final compound **18a** as a colorless oil; (77.34 mg, 45.6%). $[\alpha]_D^{25}$: +21.3 (c = 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6): δ 7.95-7.76 (m, 3H), 7.41-7.25 (m, 6H), 5.04-4.97 (m, 1H), 3.45-2.26 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.50, 163.90, 160.62, 139.15, 136.64, 133.50, 129.49, 128.40, 126.89, 124.94, 118.56, 115.15, 109.30, 54.04, 36.79; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_5S$ $[M + Na]^+$ = 362.0469, obsd $[M + Na]^+$ = 362.0475.



***(S)*-2-(3-fluorophenylsulfonamido)-3-(4-hydroxyphenyl)propanoic acid (18b)**.

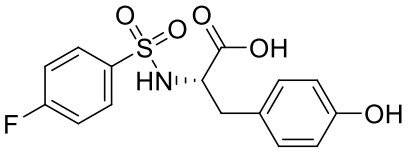
Following **18a** synthetic method, using **B2** (118.65 mg, 0.5 mmol) instead of **A2** to give **18b** as a colorless oil; (56.33 mg,

49.8%). $[\alpha]_D^{25}$: -14.4 (c = 0.27, $CHCl_3$); ^1H NMR (300 MHz, acetone-d_6): δ 8.20 (s, 1H), 7.56-7.48 (m, 2H), 7.44-7.35 (m, 2H), 7.03-6.95 (m, 3H), 6.70-6.65 (m, 2H), 4.18-4.11 (m, 1H), 3.06-2.81 (m, 2H); ^{13}C NMR(300 MHz, acetone-d_6): δ 171.53, 163.77, 160.48, 156.28, 143.54, 131.00, 130.36, 126.92, 122.75, 119.25, 115.07, 113.89, 113.57, 57.63, 37.74; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_5S$ $[M + Na]^+$ = 362.0469, obsd $[M + Na]^+$ = 362.0485.



***(R)*-2-(4-fluorophenylsulfonamido)-3-(4-hydroxyphenyl)propanoic acid (19a)**.

Following **17a** synthetic method, using 4-fluorobenzenesulfonyl chloride (214.08 mg, 1.1 mmol) instead of 2-fluorobenzenesulfonyl chloride to give the final compound **19a**； as a colorless oil; (93.99 mg, 55.4%). $[\alpha]_D^{25}$: +12.8 (c = 0.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.77-7.73 (m, 2H), 7.24-7.21 (m, 7H), 6.92 (d, *J* = 9 Hz, 1H), 4.21-4.14 (m, 1H), 3.15-2.90 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.55, 166.28, 162.95, 137.53, 136.53, 129.74, 129.62, 129.39, 128.24, 126.68, 115.93, 115.63, 57.29, 38.49; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_4S$ $[M + Na]^+$ = 346.0520, obsd $[M + Na]^+$ = 346.0513.



***(S)*-2-(4-fluorophenylsulfonamido)-3-(4-hydroxyphenyl)propanoic acid (19b)**.

Following **19a** synthetic method, using **B2** (118.65 mg, 0.5 mmol) instead of **A2** to give **19b** as a colorless oil; (96.03 mg, 56.6%). $[\alpha]_D^{25}$: -13.7 (c = 0.23, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.78-7.71 (m, 2H), 7.26-7.17 (m, 7H), 6.92 (d, *J* = 9 Hz, 1H), 4.25-4.13 (m, 1H), 3.15-2.90 (m, 2H); ^{13}C NMR (300 MHz, acetone-d_6): δ 171.56, 166.28, 162.95, 137.52, 136.53, 129.74, 129.62, 129.39, 128.24, 126.68, 115.94, 115.63, 57.31, 38.48; HRMS (ESI): calcd for: $C_{15}H_{14}FNO_4S$ $[M + Na]^+$ = 346.0520, obsd $[M + Na]^+$ = 346.0523.

Complete Reference 6

Zhang, S.Y., Jouanguy, E., Ugolini, S., Smahi, A., Elain, G., Romero, P., Segal, D., Sancho-Shimizu, V., Lorenzo, L., Puel, A., Picard, C., Chapgier, A., Plancoulaine, S., Titeux, M., Cognet, C., von Bernuth, H., Ku, C. L., Casrouge, A., Zhang, X. X., Barreiro, L., Leonard, J., Hamilton, C., Lebon, P., Héron, B., Vallée, L., Quintana-Murci, L., Hovnanian, A., Rozenberg, F., Vivier, E., Geissmann, F., Tardieu, M., Abel, L., Casanova, J. L. *Science*, 2007, *317*, 1522.

Supplementary References:

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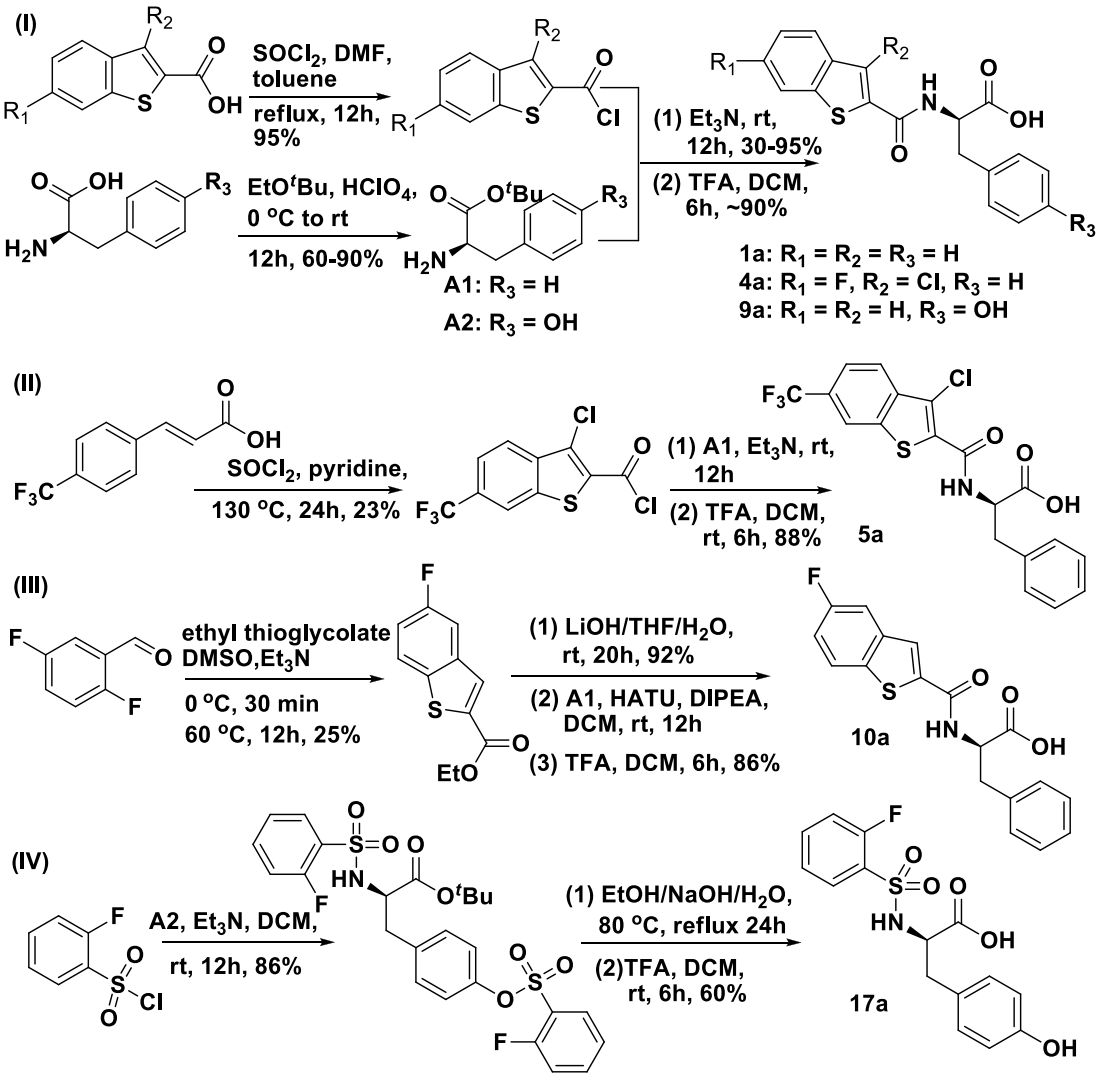
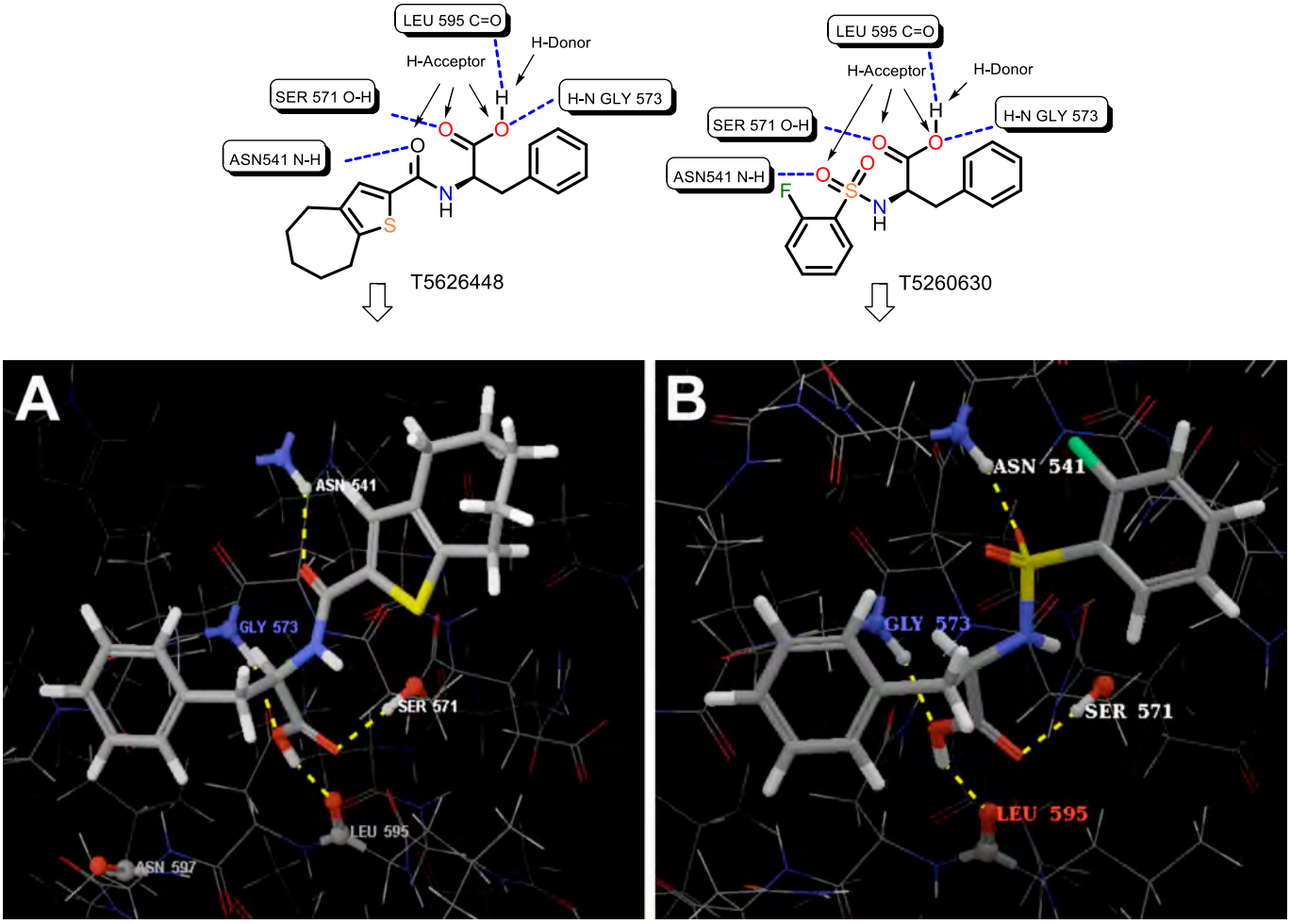
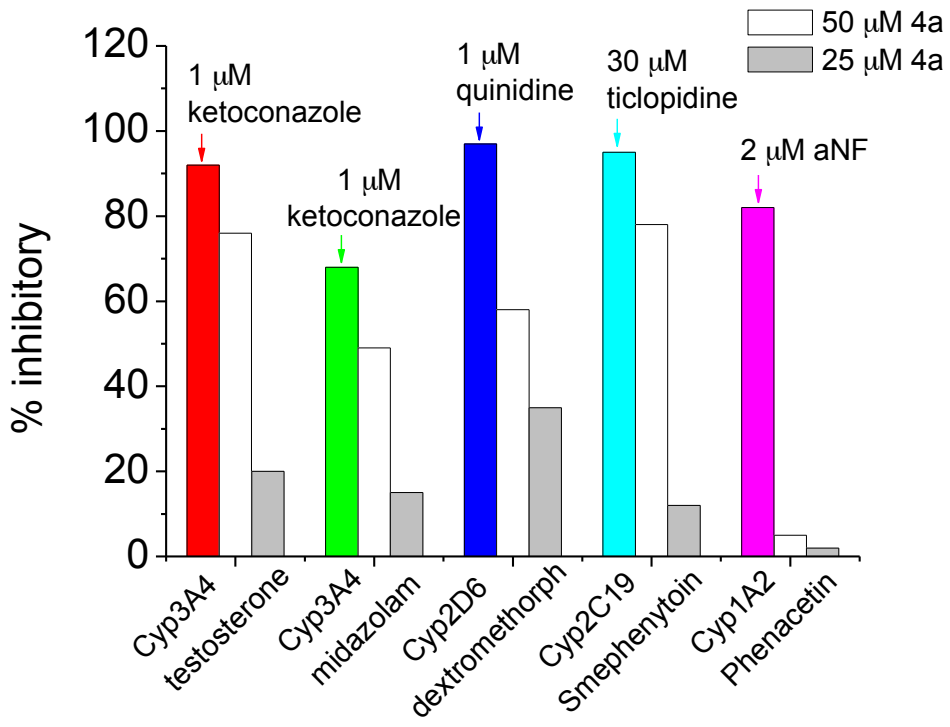
Supplementary Scheme S1. Representative syntheses of the TLR3 inhibitors

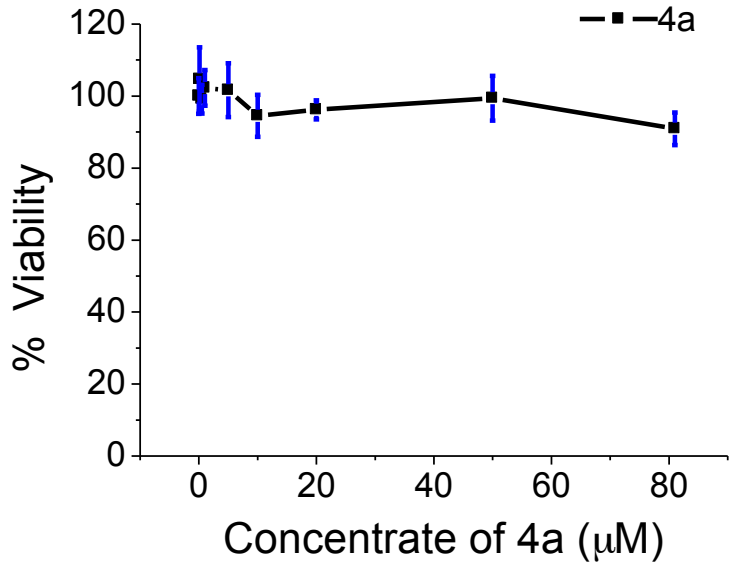




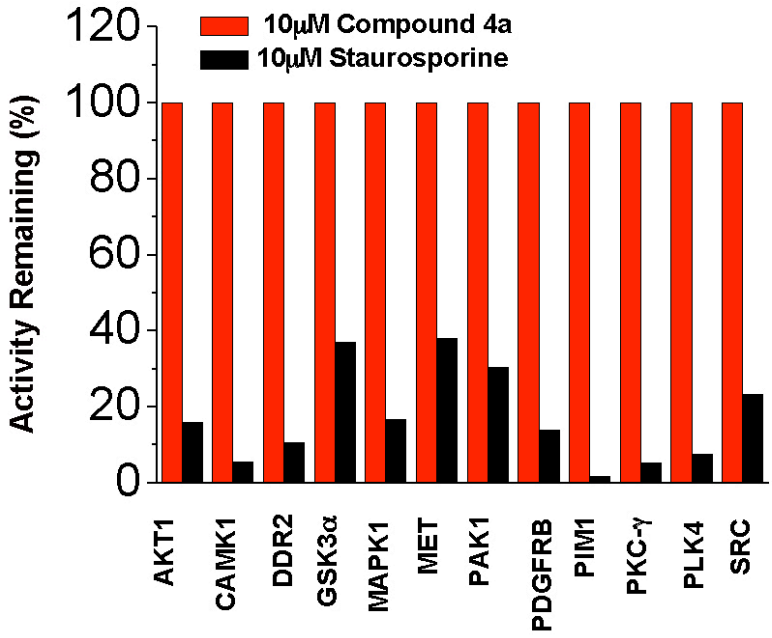
Supplementary Figure S1 Molecular docking results of the two hits selected in the cellular assay: (A) **T5626448** and (B) **T5260630**. Visual inspection suggested that varying the substituents on the benzene or thiophene rings could enhance the molecular recognition to TLR3 with better spatial complementarity and additional intermolecular contacts.



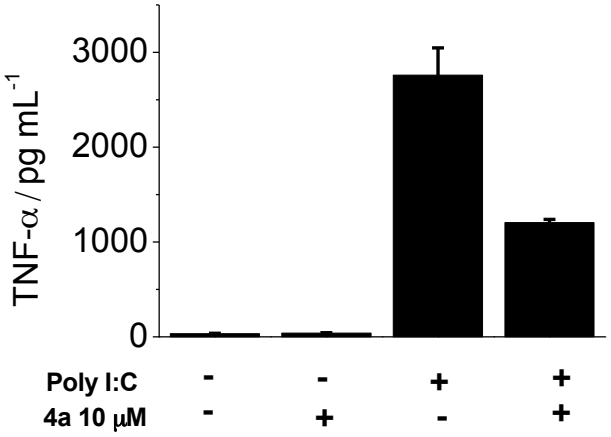
Supplementary Figure S2 The toxicity (test by Apredica Inc. MA.) of **4a** to different Cytochrome P450 (CYP450) enzymes at 25 μM and 50 μM. Ketoconazole, quinidine, ticlopidine and aNF specifically inhibit Cyp3A4, Cyp2D6, Cyp2C19 and Cyp1A2 respectively. At a concentration of 25 μM, **4a** shows low unspecific, P450 inhibitory activity.



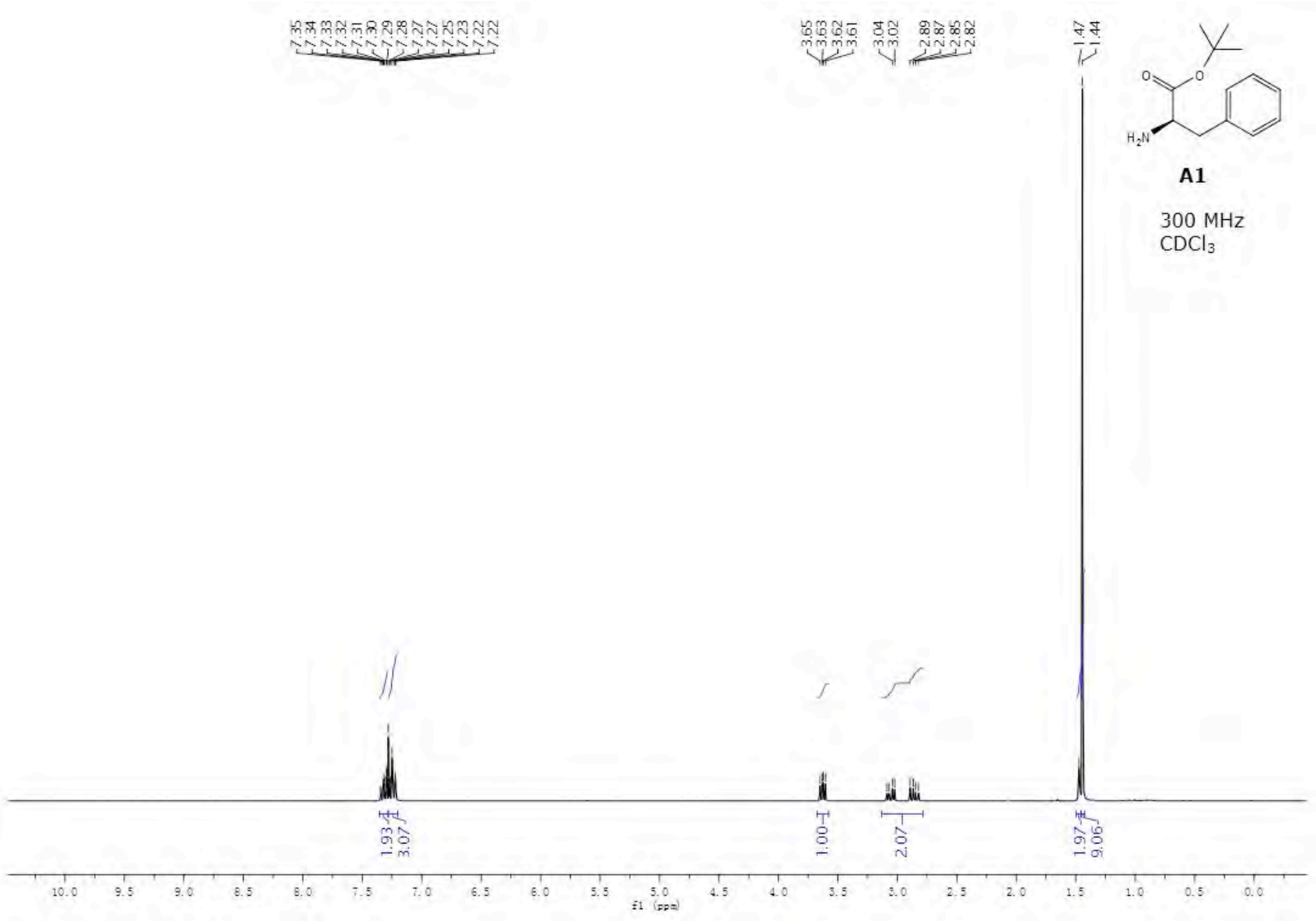
Supplementary Figure S3 Cellular viability of RAW 264.7 cells with **4a** at various concentration, showing low cytotoxicity.



Supplementary Figure S4 Kinases profiling results showed that compound **4a** (10 μM) did not affect activities of representative kinases (Luceome Biotechnologies, Tucson, AZ).



Supplementary Figure S5 Inhibitory effects on TNF-α in the RAW 264.7 cells by compound **4a** at 10 μM. Consistent with the NO synthase assay results, approximately 60% of inhibition was observed.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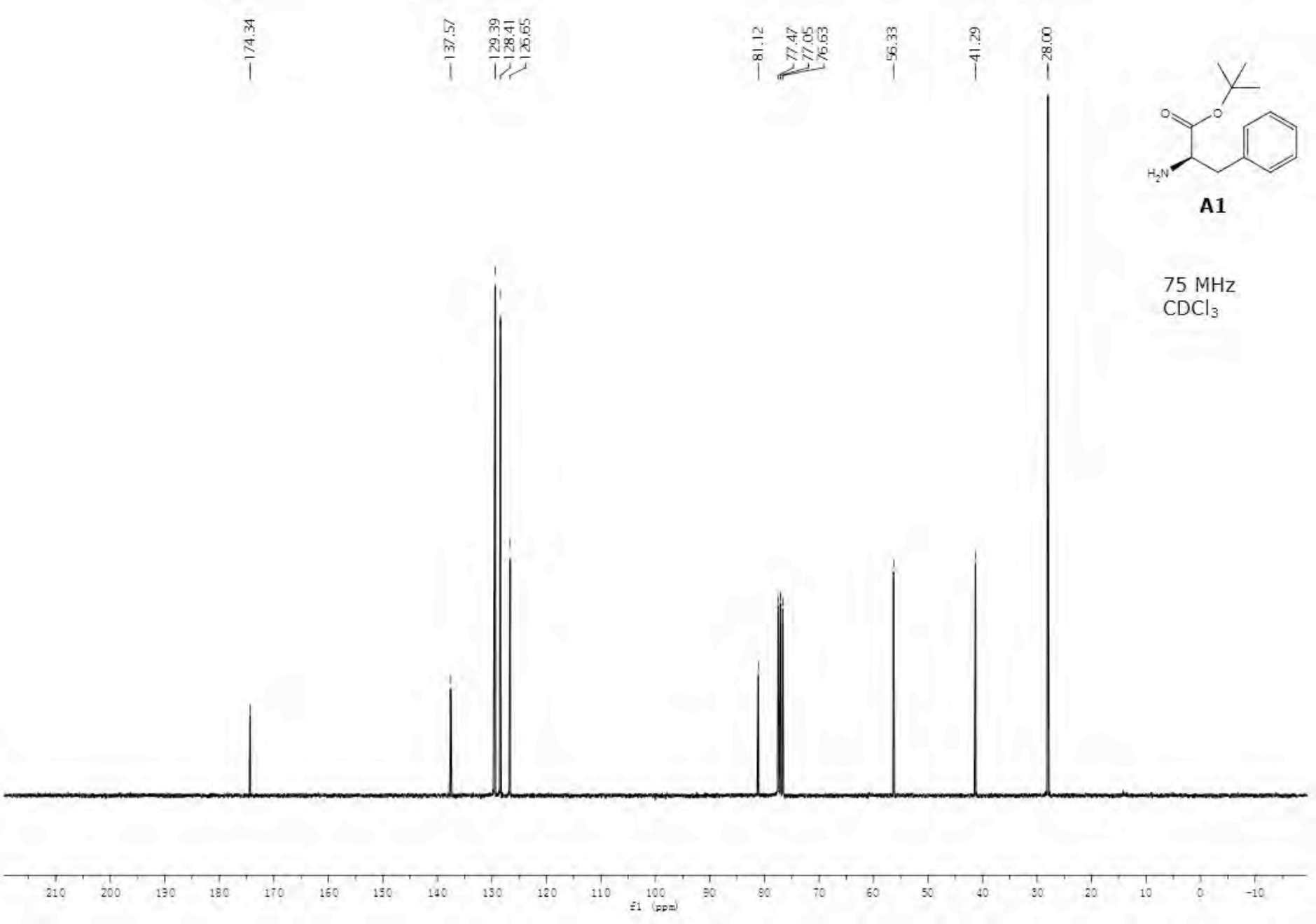
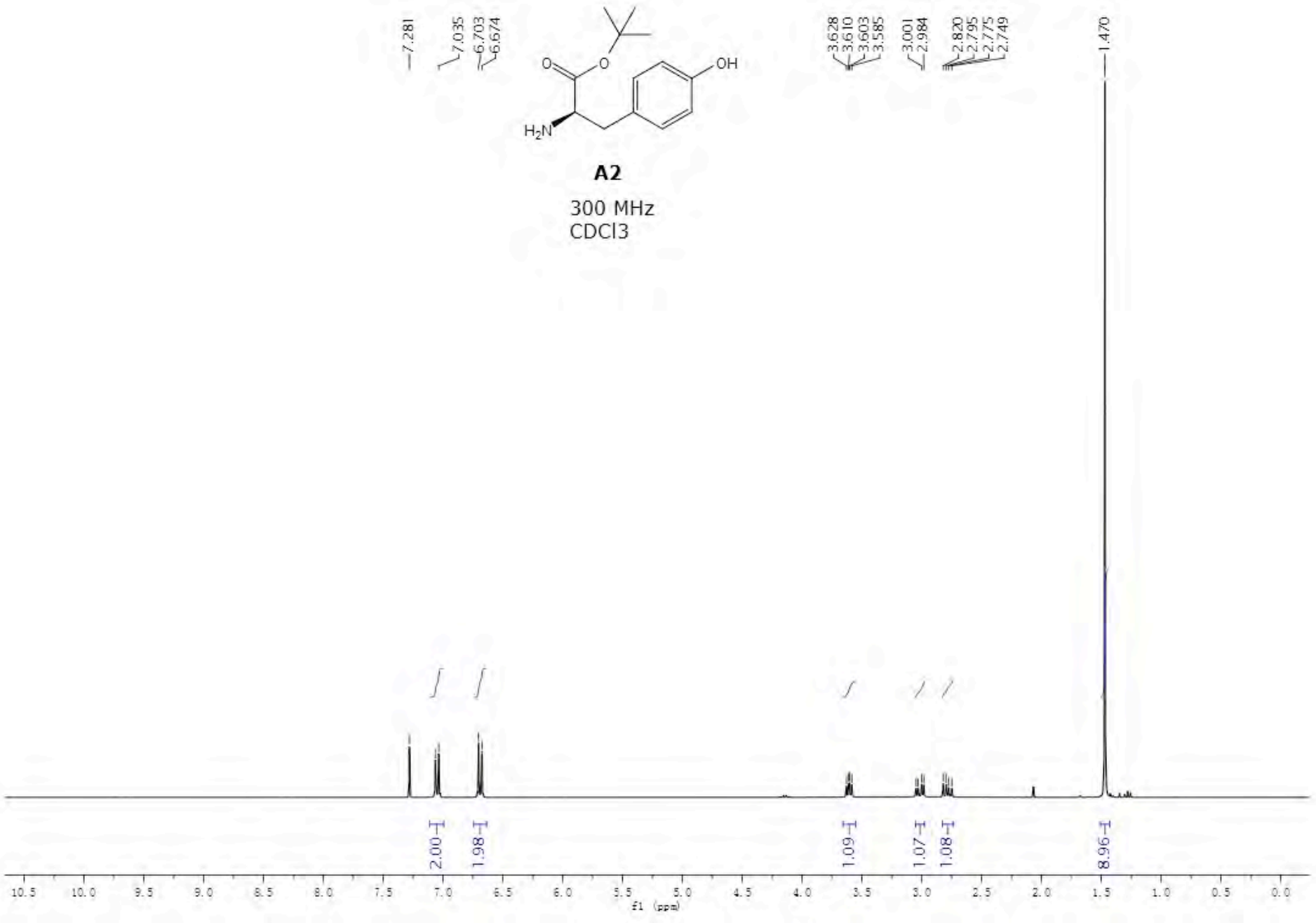
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.27
7.27
7.25
7.23
7.22
7.22
3.65
3.63
3.62
3.61
3.04
3.02
2.89
2.87
2.85
2.82
1.47
1.44
A1
300 MHz
CDCl3
1.93
3.07
1.00
2.07
1.97
9.06
f1 (ppm)


174.34
137.57
129.39
128.41
126.65
81.12
77.47
77.05
76.63
56.33
41.29
28.00
A1
75 MHz
CDCl3
f1 (ppm)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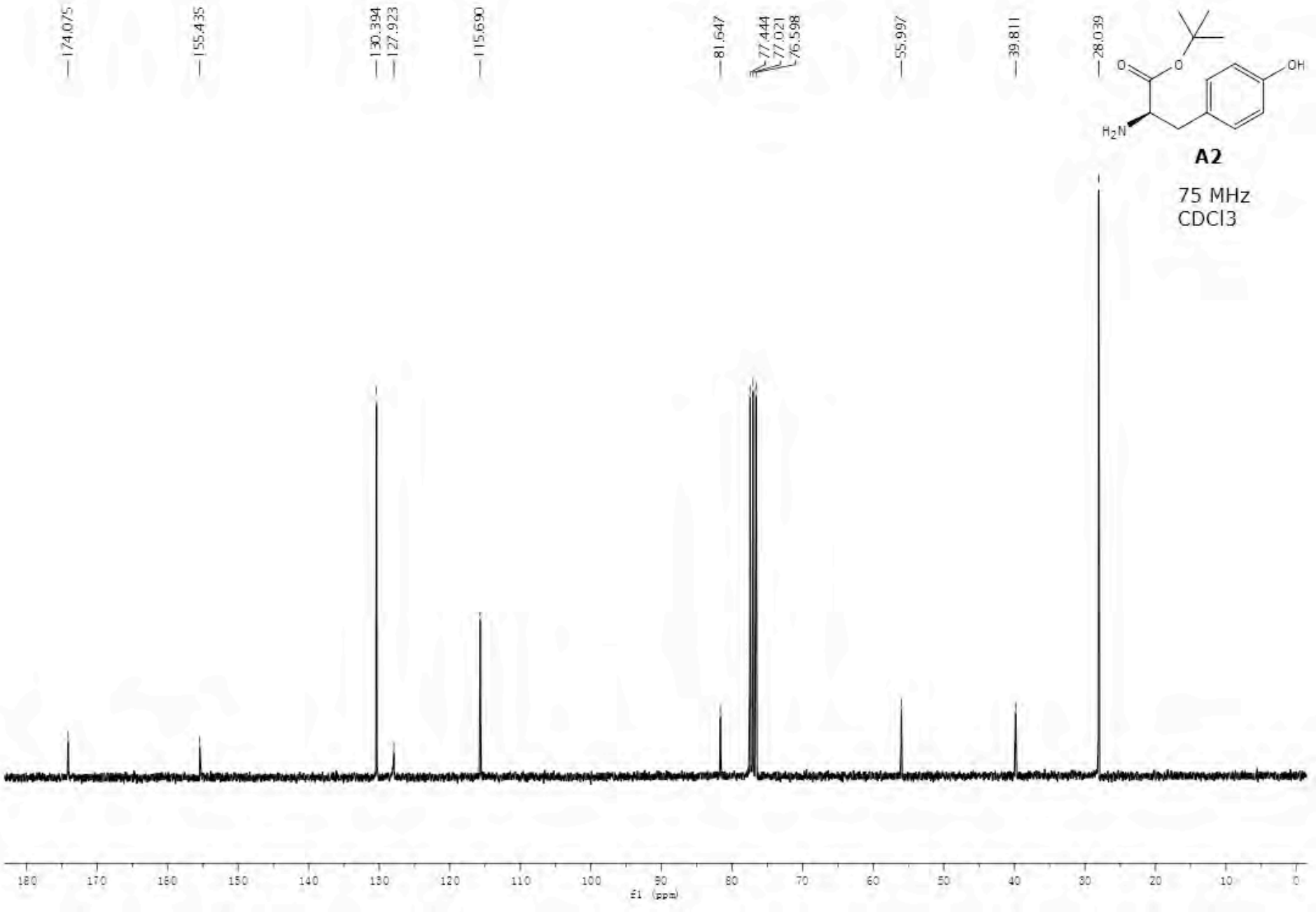
7.035
6.703
6.674
3.628
3.610
3.603
3.585
3.001
2.984
2.820
2.795
2.775
2.749
1.470
O
O
OH
H2N
A2
300 MHz
CDCl3
2.00
1.98
1.09
1.07
1.08
8.96
f1 (ppm)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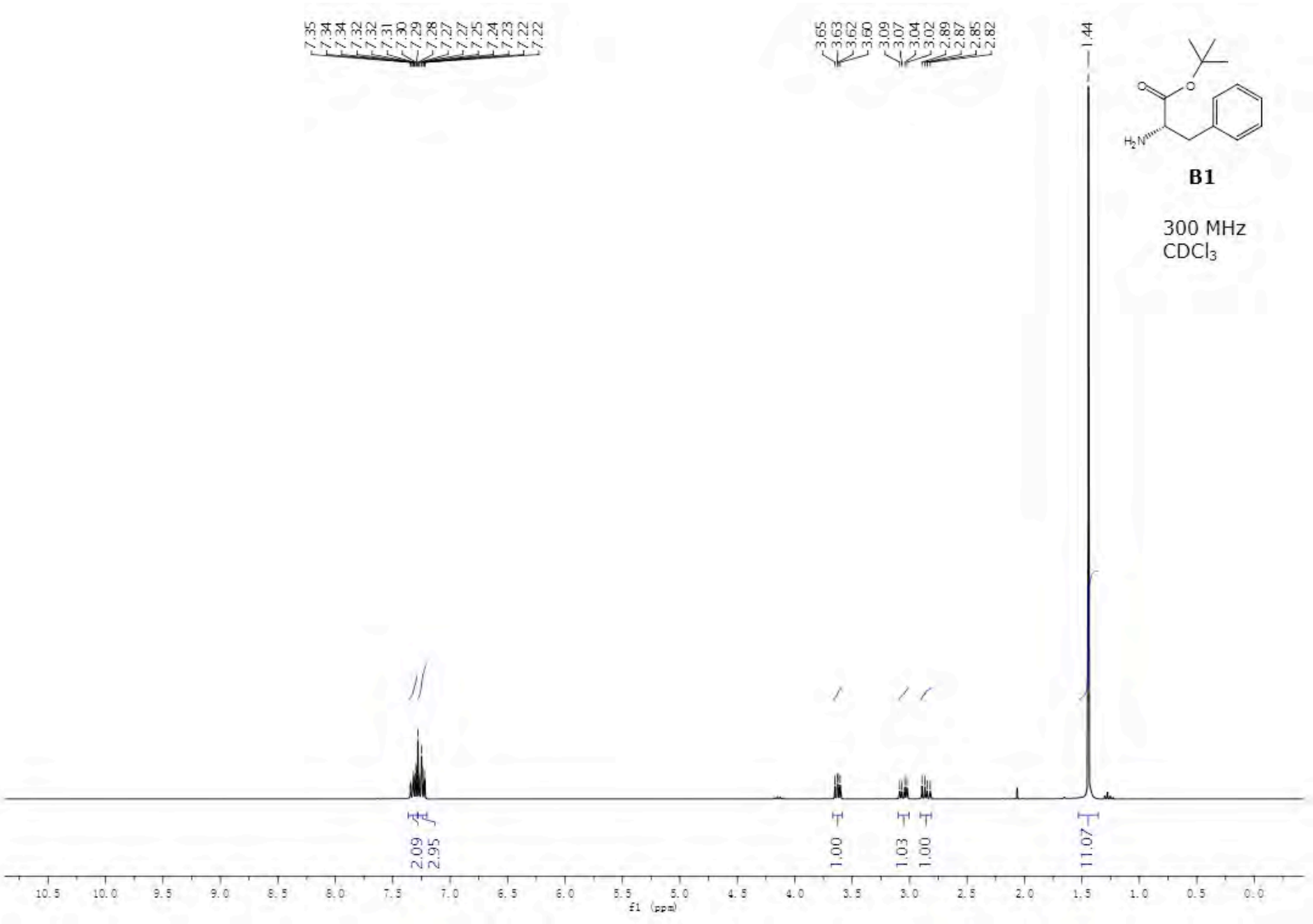
81.647
77.444
77.021
76.598
55.997
39.811
28.039
O
O
OH
H2N
A2
75 MHz
CDCl3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.31
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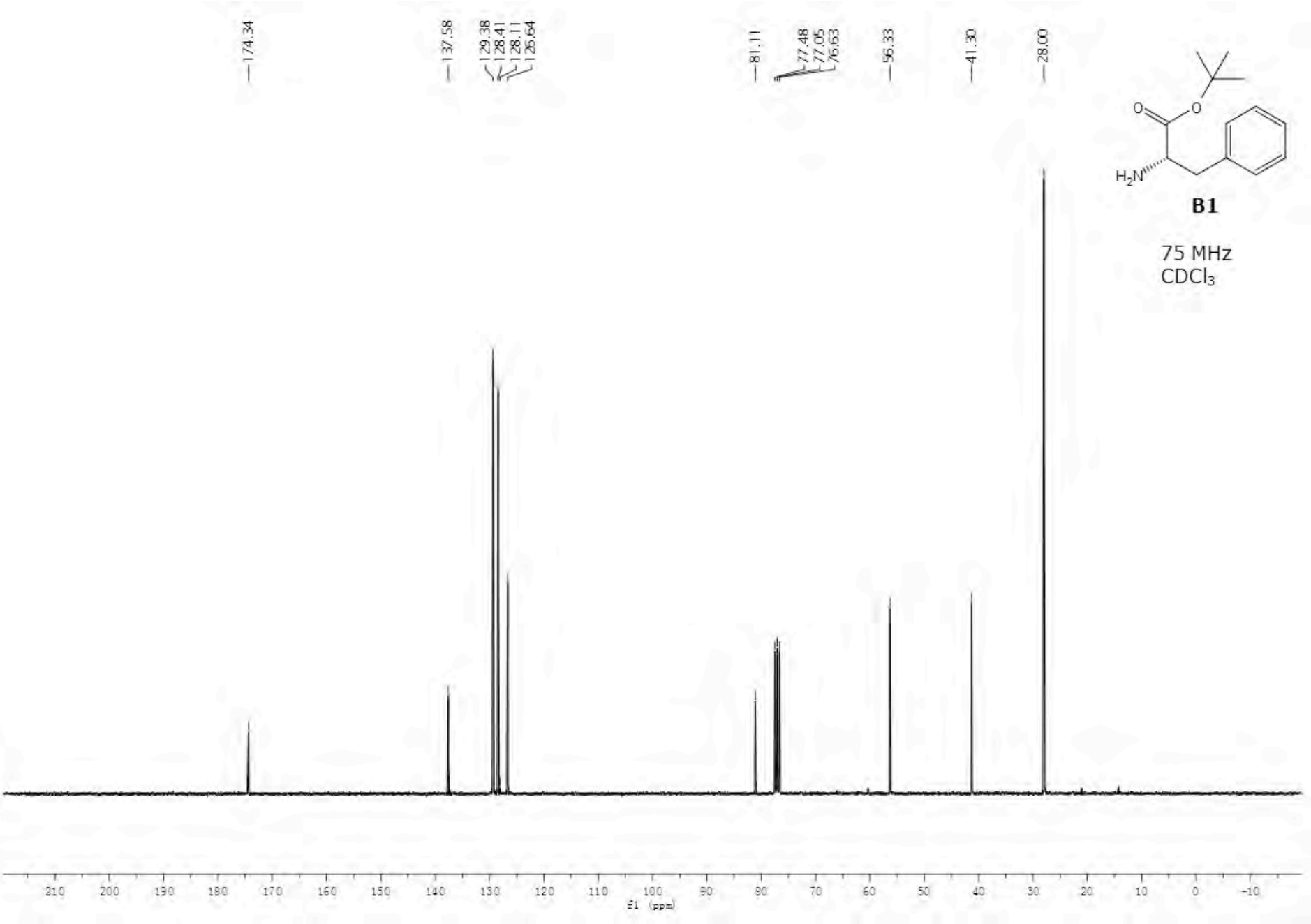
7.29
7.28
7.27
7.27
7.25
7.24
7.23
7.22
7.22
3.65
3.63
3.62
3.60
3.09
3.07
3.04
3.02
2.89
2.87
2.85
2.82
1.44
B1
300 MHz
CDCl3
2.09
2.95
1.00
1.03
1.00
11.07
f1 (ppm)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128.11
126.64
81.11
77.48
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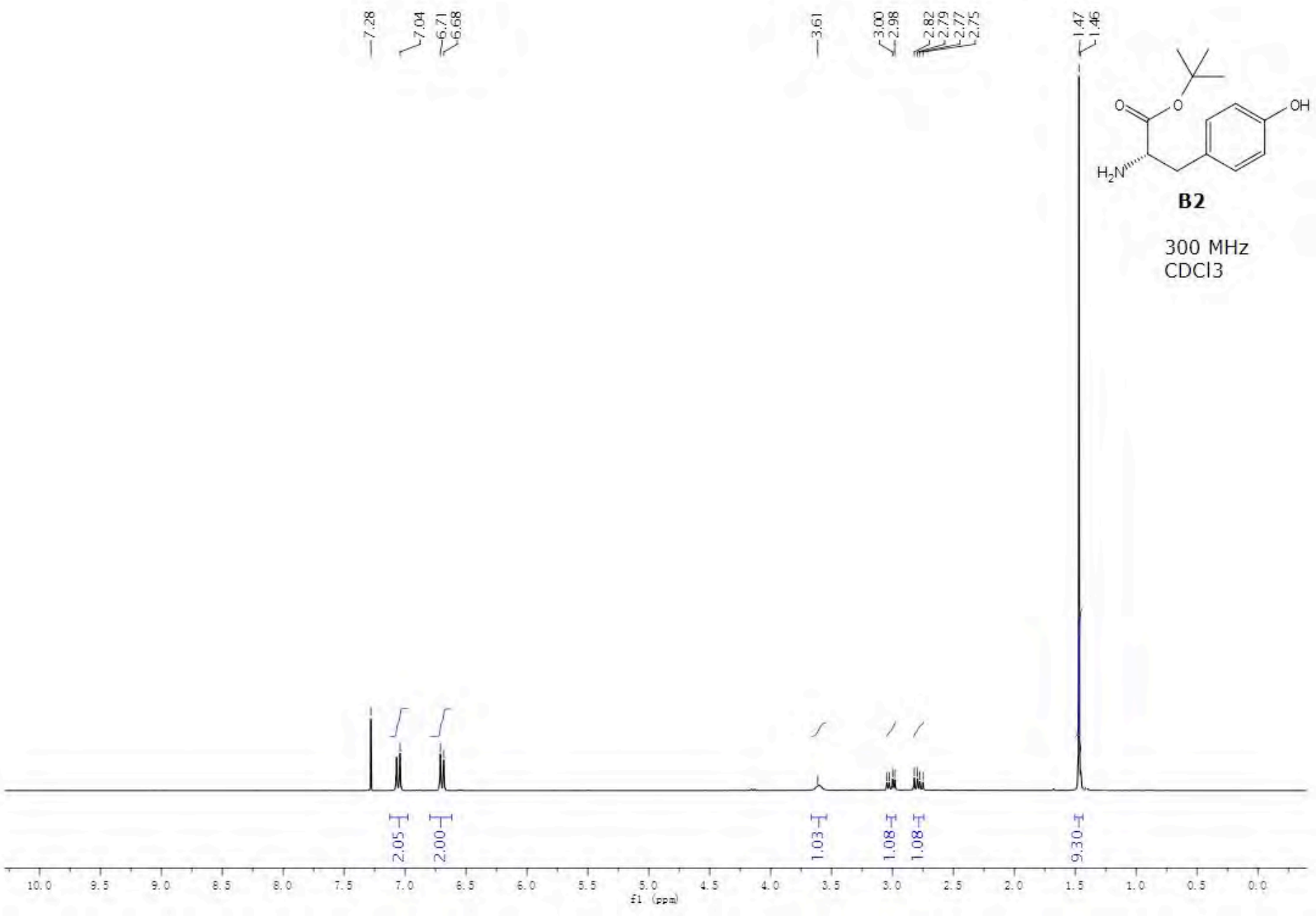
76.63
56.33
41.30
28.00
O
O
H2N
B1
75 MHz
CDCl3
f1 (ppm)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7.04
6.71
6.68
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3.00
2.98
2.82
2.79
2.77
2.75
1.47
1.46
O
O
OH
H2N
B2
300 MHz
CDCl3
2.05
2.00
1.03
1.08
1.08
9.30
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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3.5
3.0
2.5
2.0
1.5
1.0
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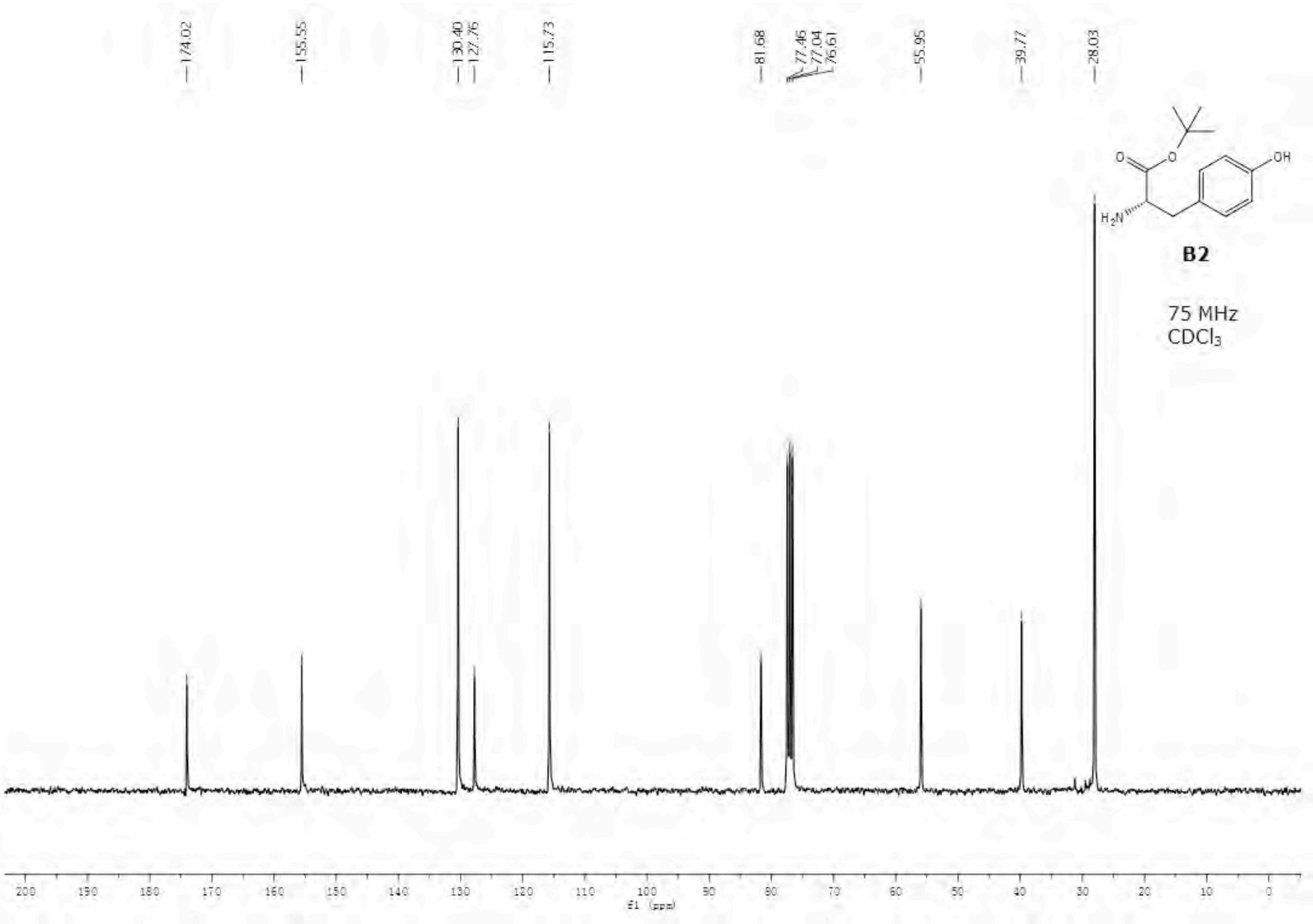
0.0
f1 (ppm)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155.55
130.40
127.76
115.73
81.68
77.46
77.04
76.61
55.95
39.77
28.03
O
O
OH
H2N
B2
75 MHz
CDCl3
200
190
180
170
160
150
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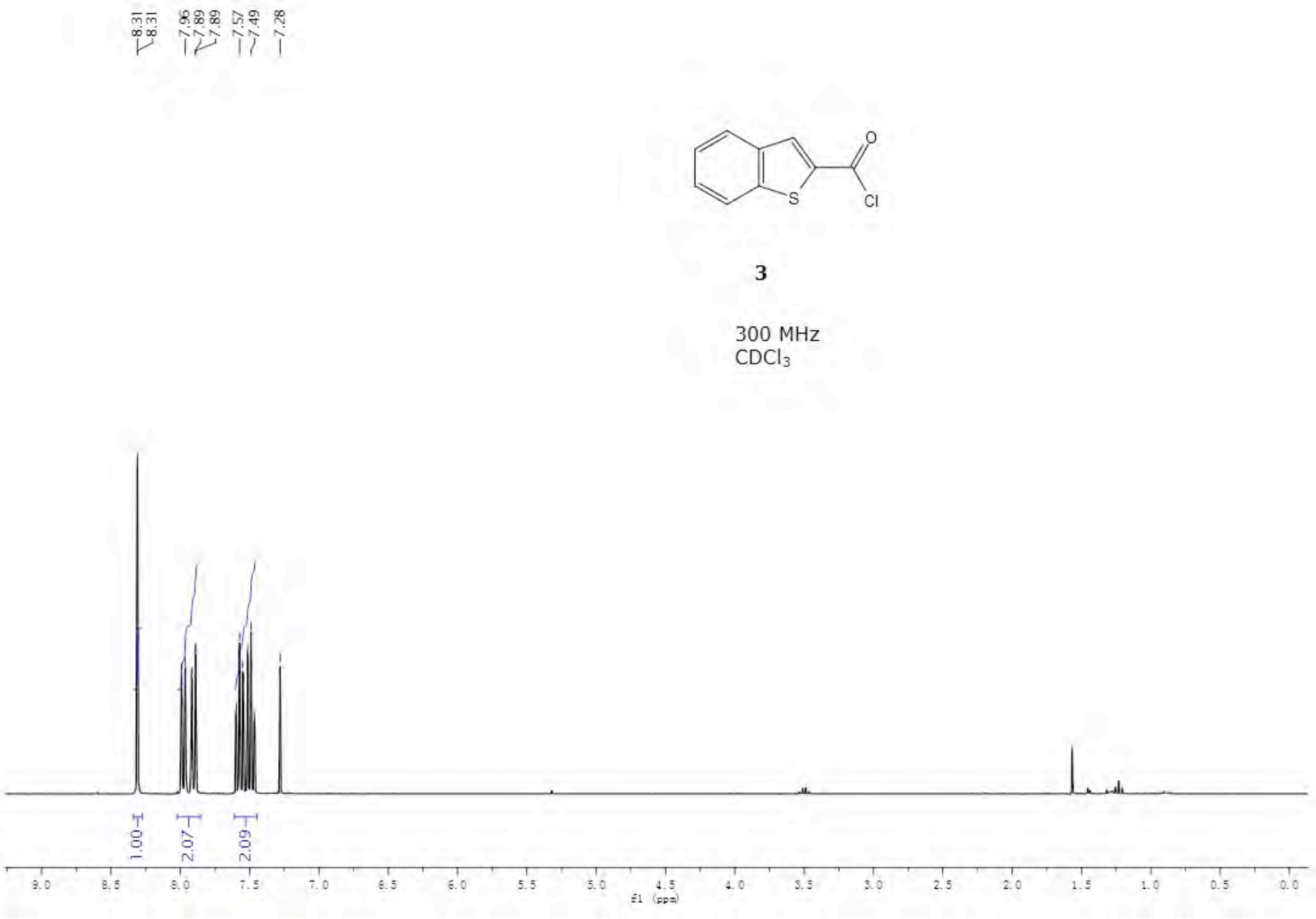
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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8.31
7.96
7.89
7.89
7.57
7.49
7.28
O
S
Cl
3
300 MHz
CDCl3
1.00
2.07
2.09
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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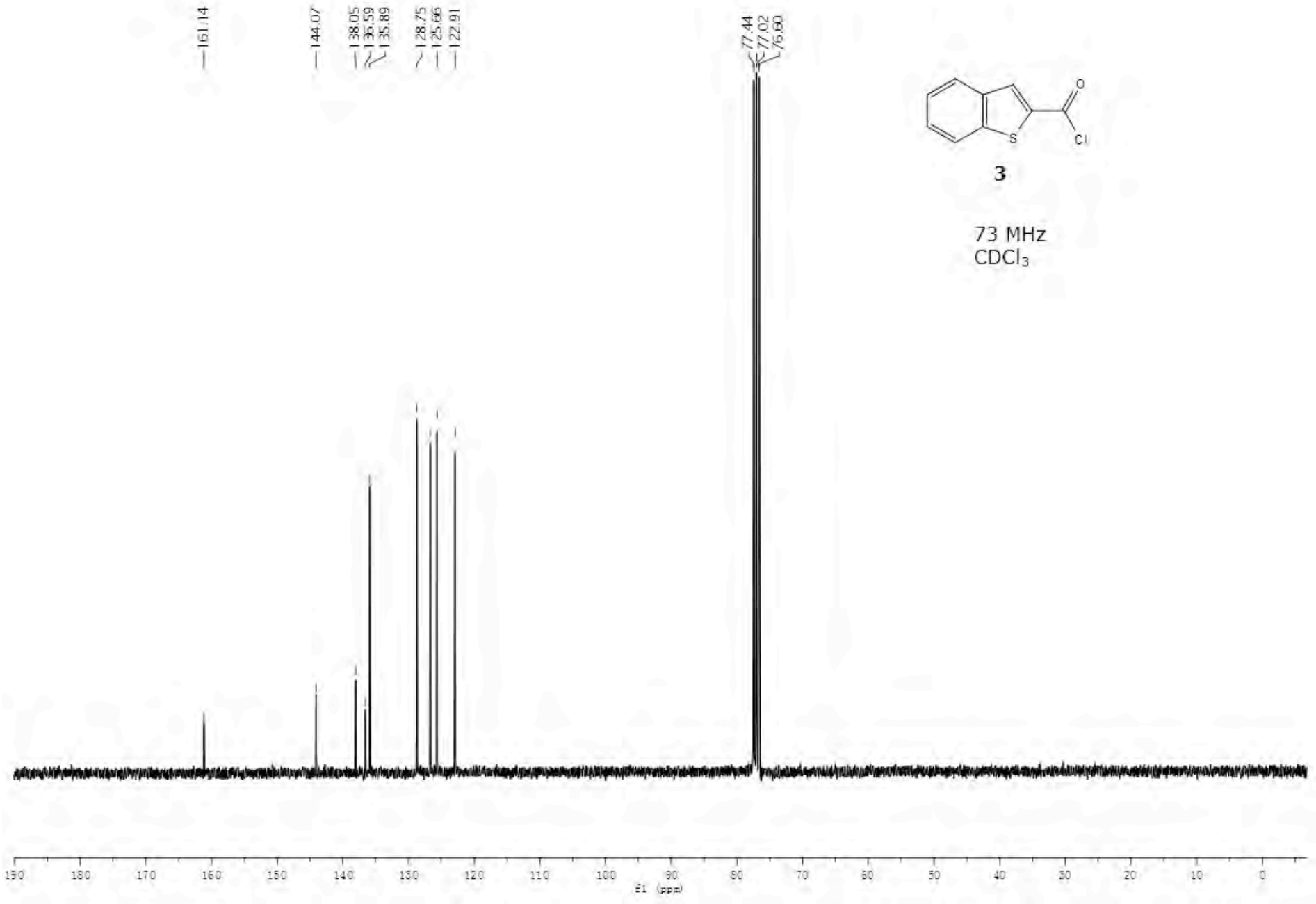
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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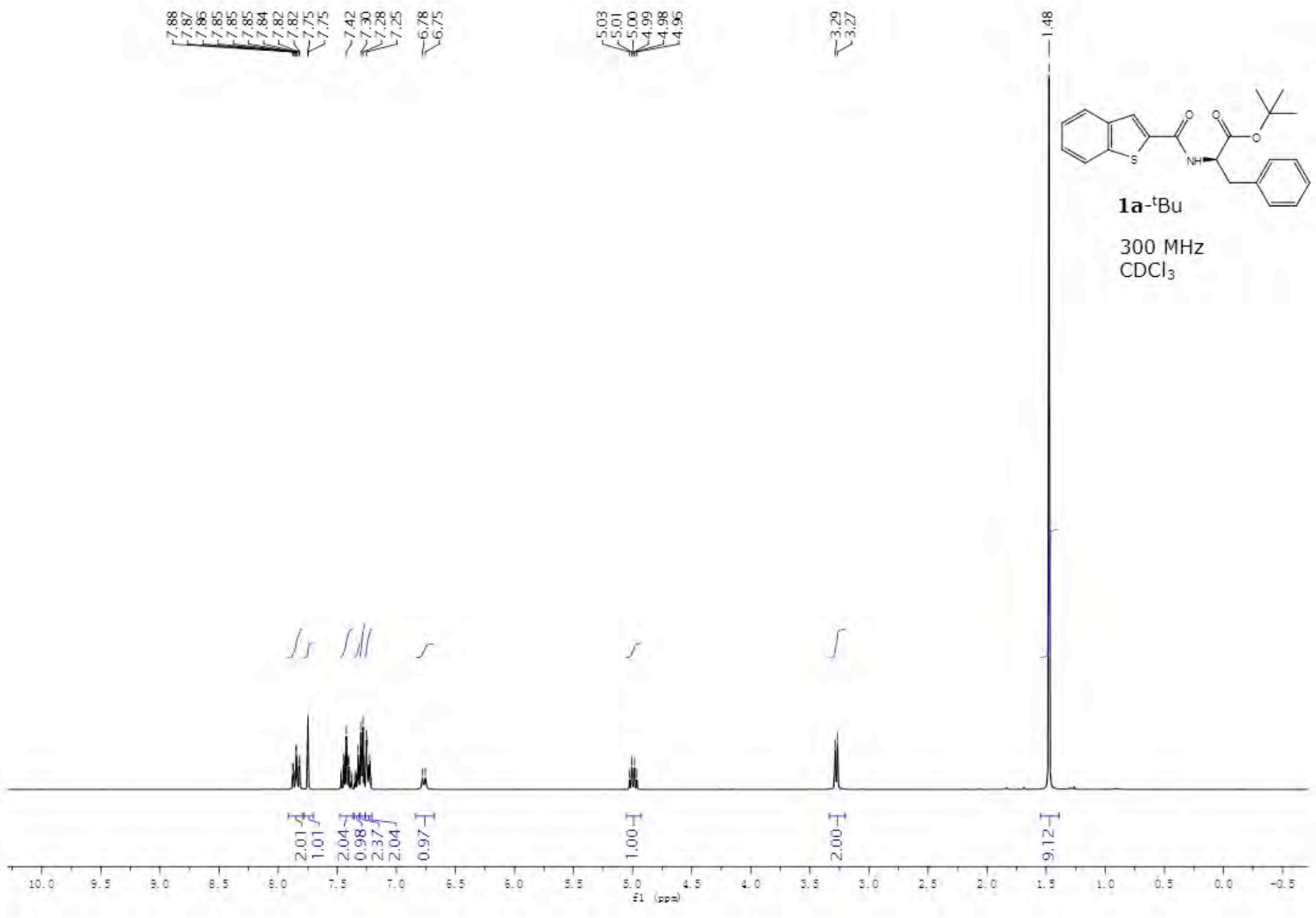
S
Cl
3
73 MHz
CDCl3
f1 (ppm)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7.86
7.85
7.85
7.85
7.84
7.82
7.82
7.75
7.75
7.42
7.30
7.28
7.25
6.78
6.75
5.03
5.01
5.00
4.99
4.98
4.96
3.29
3.27
1.48
1a-tBu
300 MHz
CDCl3
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2.04
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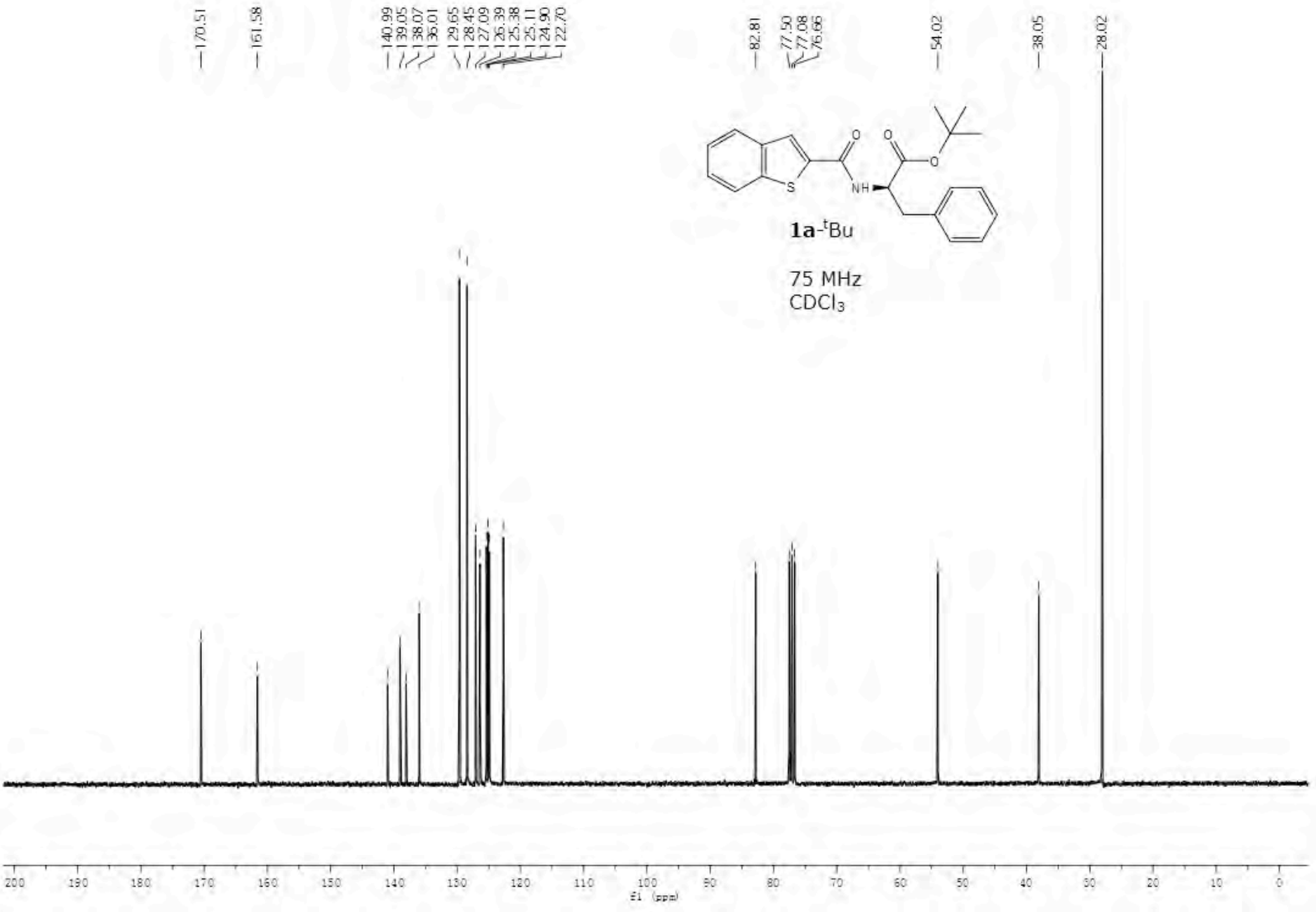
2.04
0.97
1.00
2.00
9.12
f1 (ppm)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139.05
138.07
135.01
129.65
128.45
127.09
126.39
125.38
125.11
124.90
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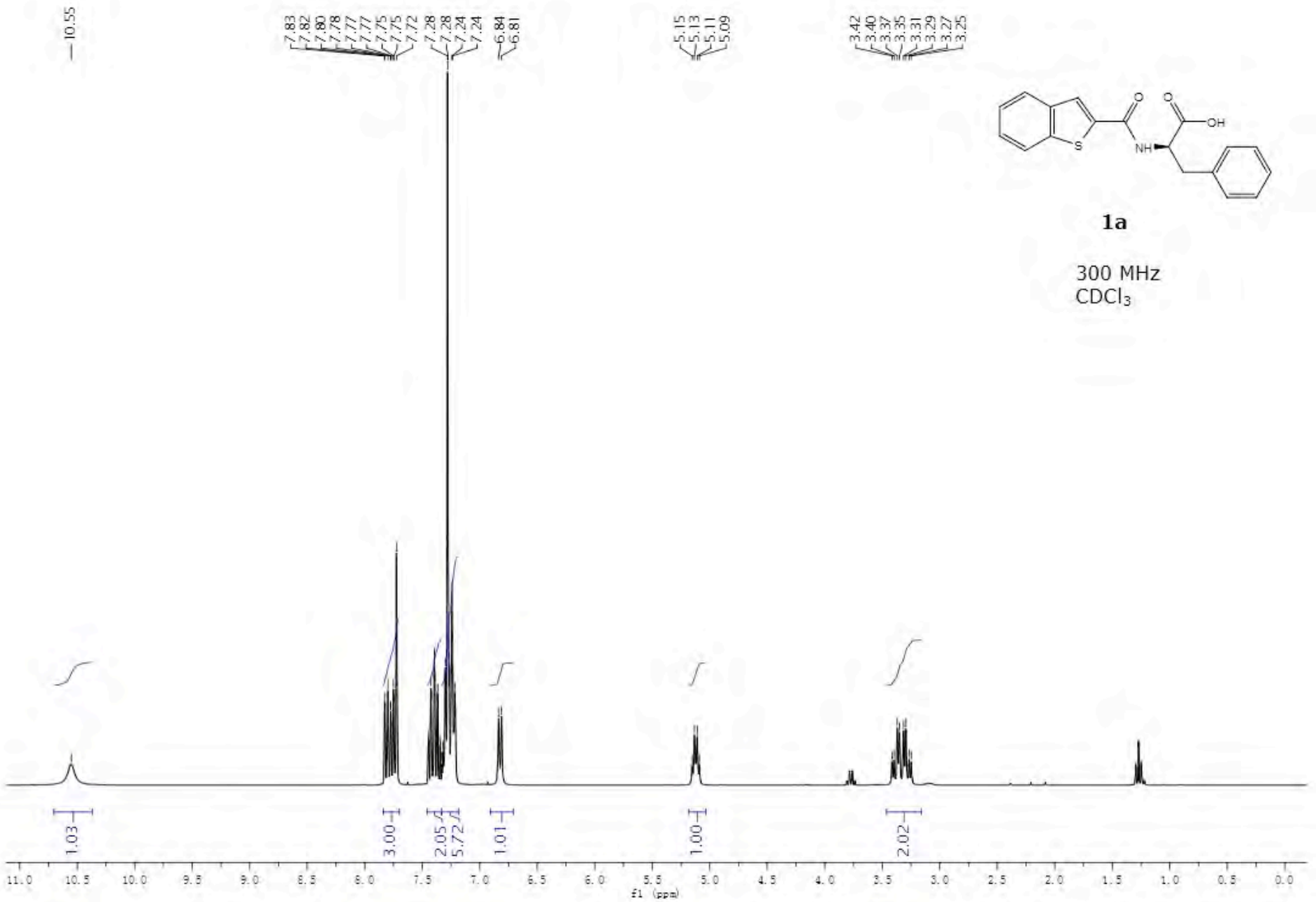
77.90
77.08
76.66
54.02
38.05
28.02
1a-tBu
75 MHz
CDCl3
f1 (ppm)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7.82
7.80
7.78
7.77
7.77
7.75
7.75
7.72
7.28
7.28
7.24
7.24
6.84
6.81
5.15
5.13
5.11
5.09
3.42
3.40
3.37
3.35
3.31
3.29
3.27
3.25
O
O
OH
NH
S
1a
300 MHz
CDCl3
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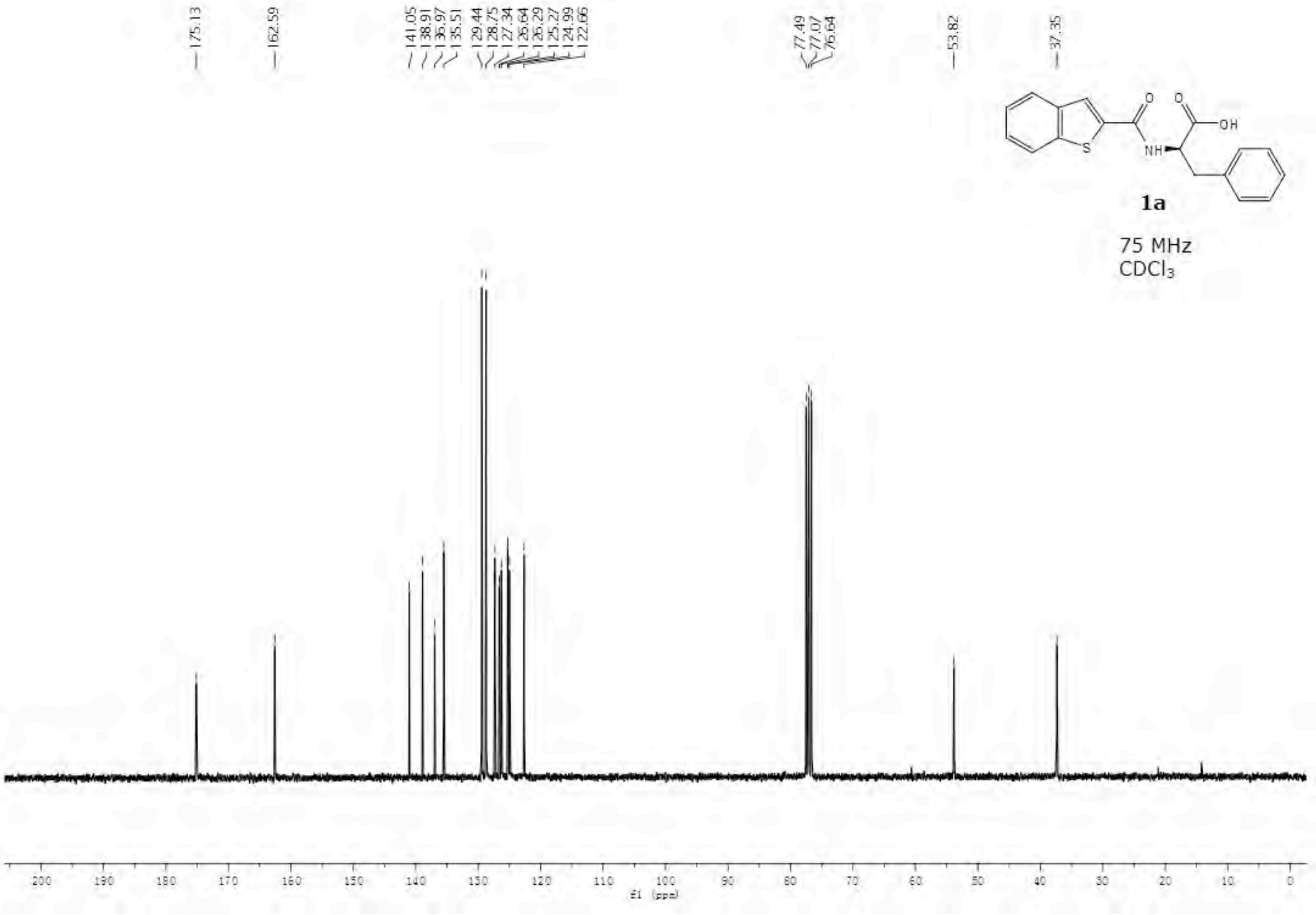
3.00
2.05
5.72
1.01
1.00
2.02
f1 (ppm)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141.05
138.91
136.97
135.51
129.44
128.75
127.34
126.64
126.29
125.27
124.99
122.66
77.49
77.07
76.64
53.82
37.35
O
O
OH
NH
S
1a
75 MHz
CDCl3
200
190
180
170
160
150
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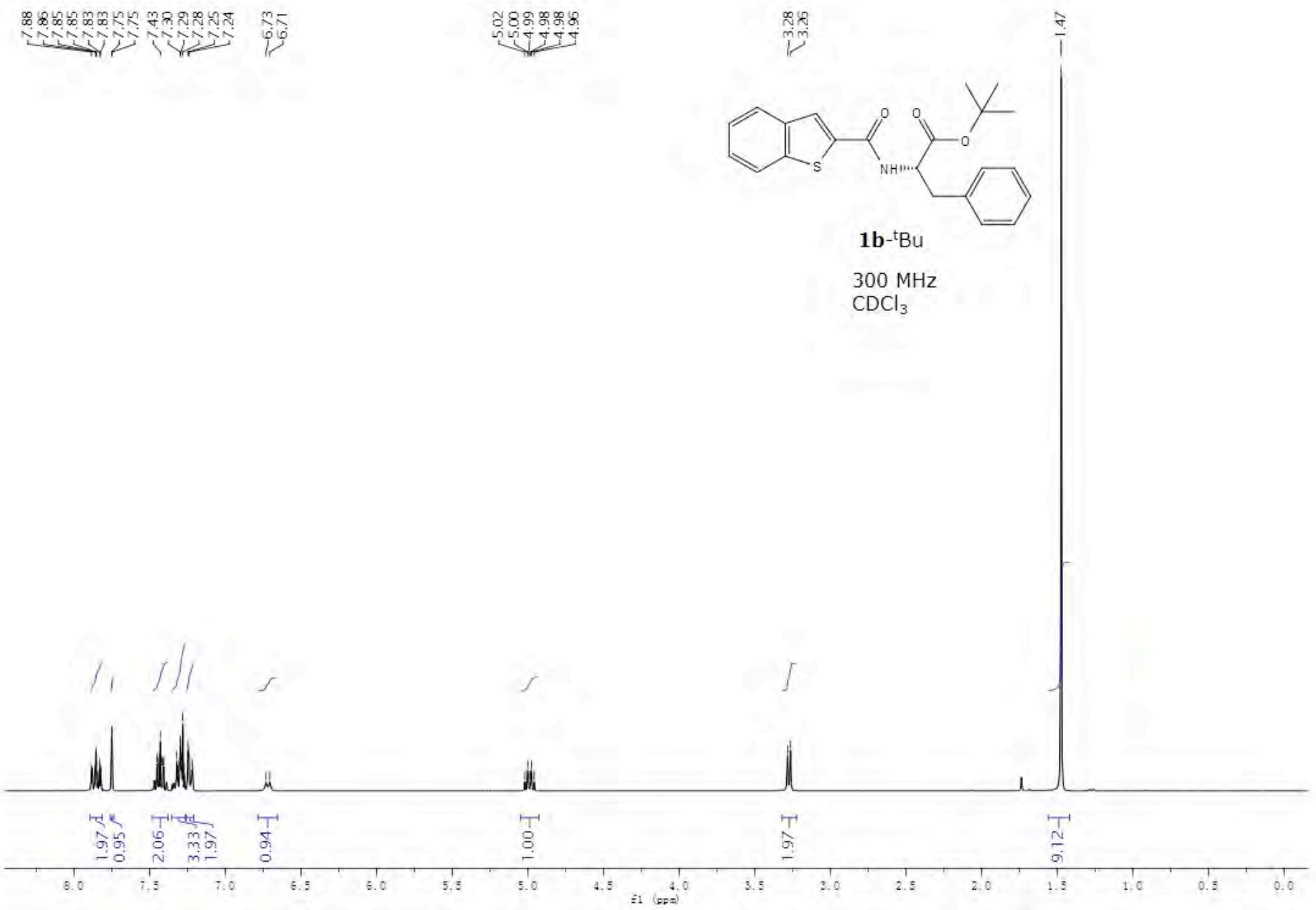
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.85
7.83
7.83
7.75
7.75
7.43
7.30
7.29
7.28
7.25
7.24
6.73
6.71
5.02
5.00
4.99
4.98
4.98
4.96
3.28
3.26
1.47
O
O
O
S
NH
1b-tBu
300 MHz
CDCl3
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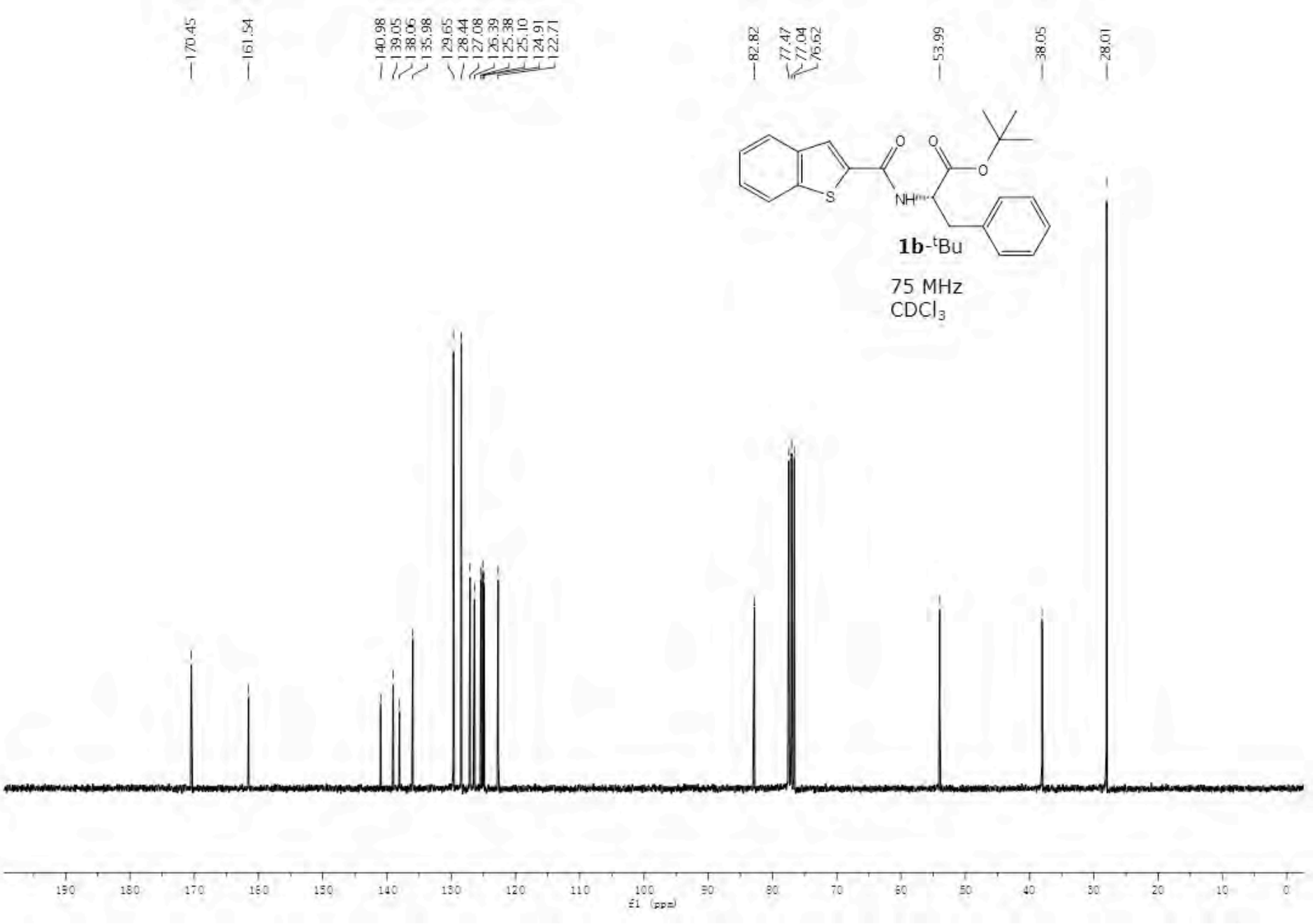
3.33
1.97
0.94
1.00
1.97
9.12
f1 (ppm)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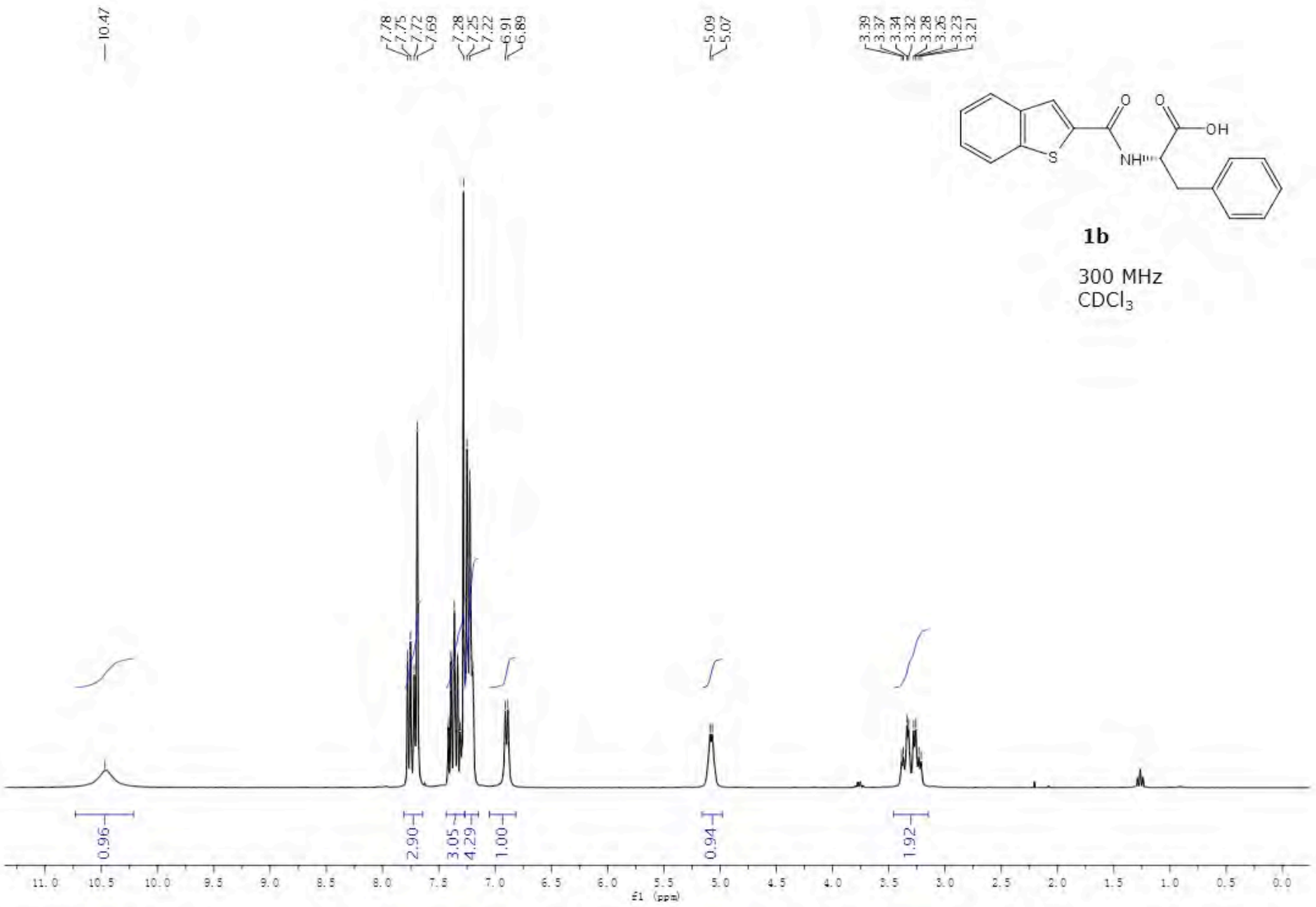
129.65
128.44
127.08
126.39
125.38
125.10
124.91
122.71
82.82
77.47
77.04
76.62
53.99
38.05
28.01
1b-tBu
75 MHz
CDCl3
f1 (ppm)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7.72
7.69
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7.22
6.91
6.89
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5.07
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3.34
3.32
3.28
3.25
3.23
3.21
O
O
OH
NH
S
1b
300 MHz
CDCl3
0.96
2.90
3.05
4.29
1.00
0.94
1.92
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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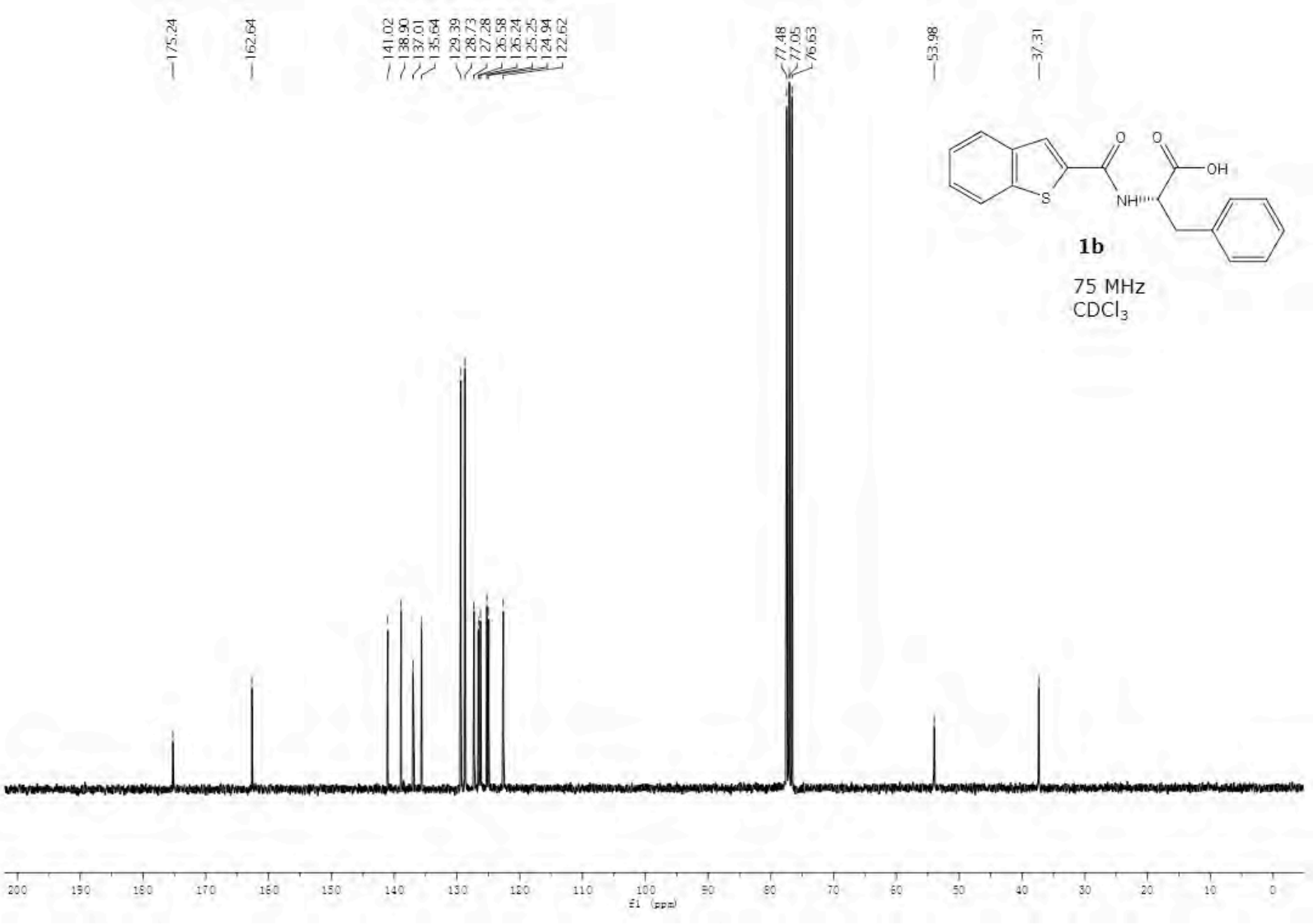
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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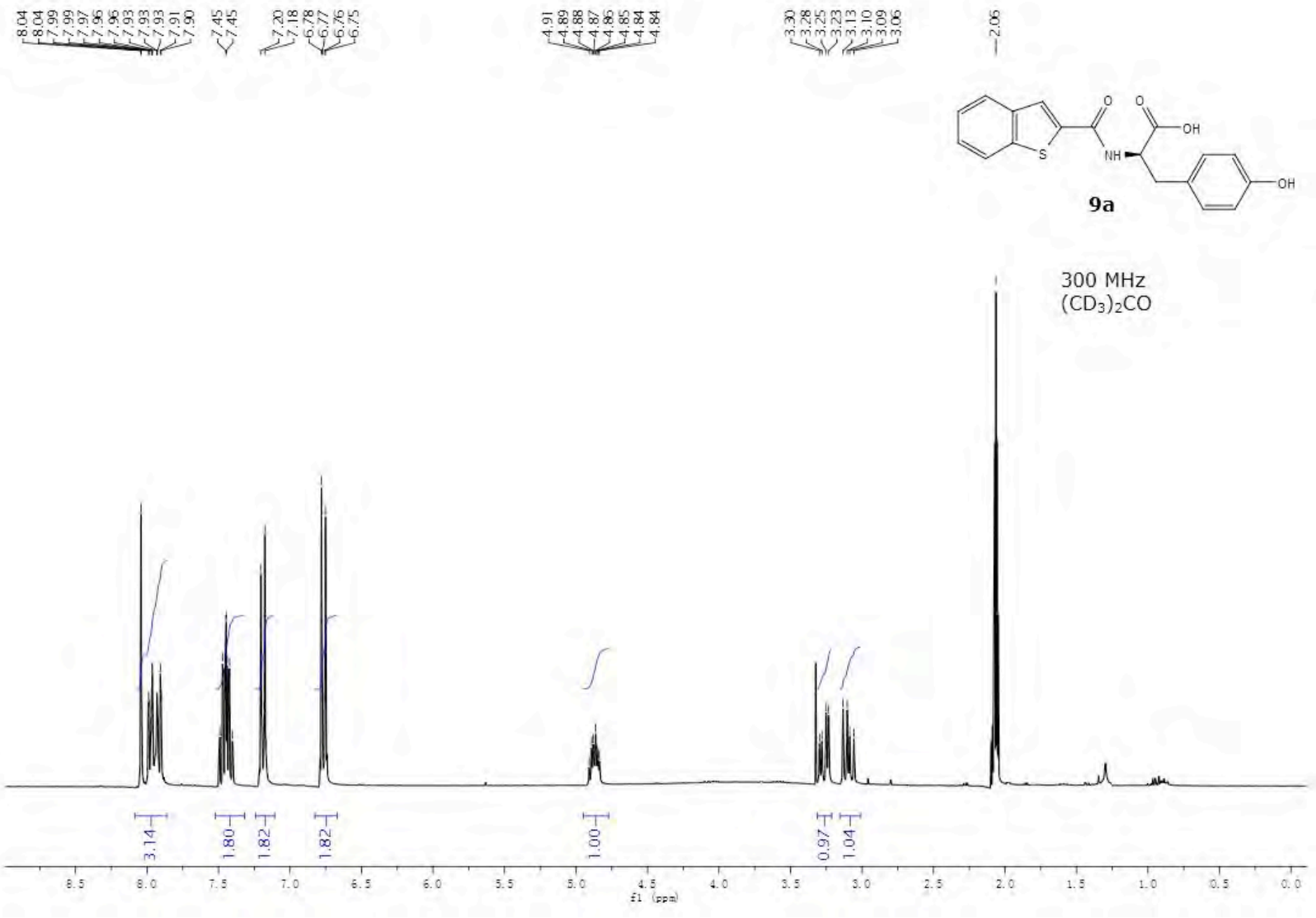
137.01
135.64
129.39
128.73
127.28
126.58
126.24
125.25
124.94
122.62
77.48
77.05
76.63
53.98
37.31
O
O
OH
NH
S
1b
75 MHz
CDCl3
f1 (ppm)


8.04
8.04
7.99
7.99
7.97
7.96
7.96
7.93
7.93
7.91
7.90
7.45
7.45
7.20
7.18
6.78
6.77
6.76
6.75
4.91
4.89
4.88
4.87
4.86
4.85
4.84
4.84
3.30
3.28
3.25
3.23
3.13
3.10
3.09
3.06
2.06
O
O
OH
NH
S
OH
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(CD3)2CO
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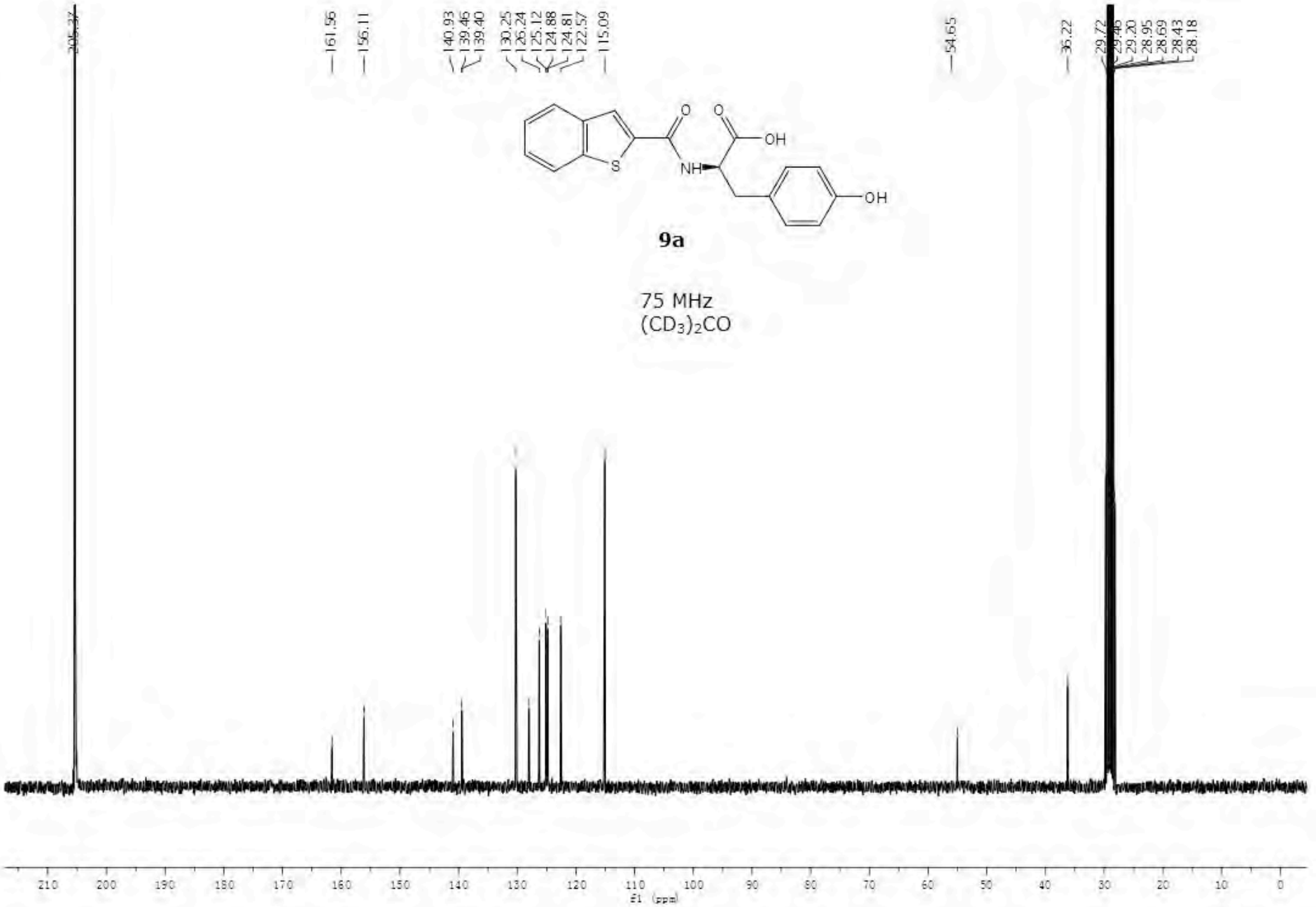
1.82
1.00
0.97
1.04
f1 (ppm)


205.37
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139.46
139.40
130.25
126.24
125.12
124.88
124.81
122.57
115.09
54.65
36.22
29.72
29.46
29.20
28.95
28.69
28.43
28.18
O
O
OH
NH
S
OH
9a
75 MHz
(CD3)2CO
210
200
190
180
170
160
150
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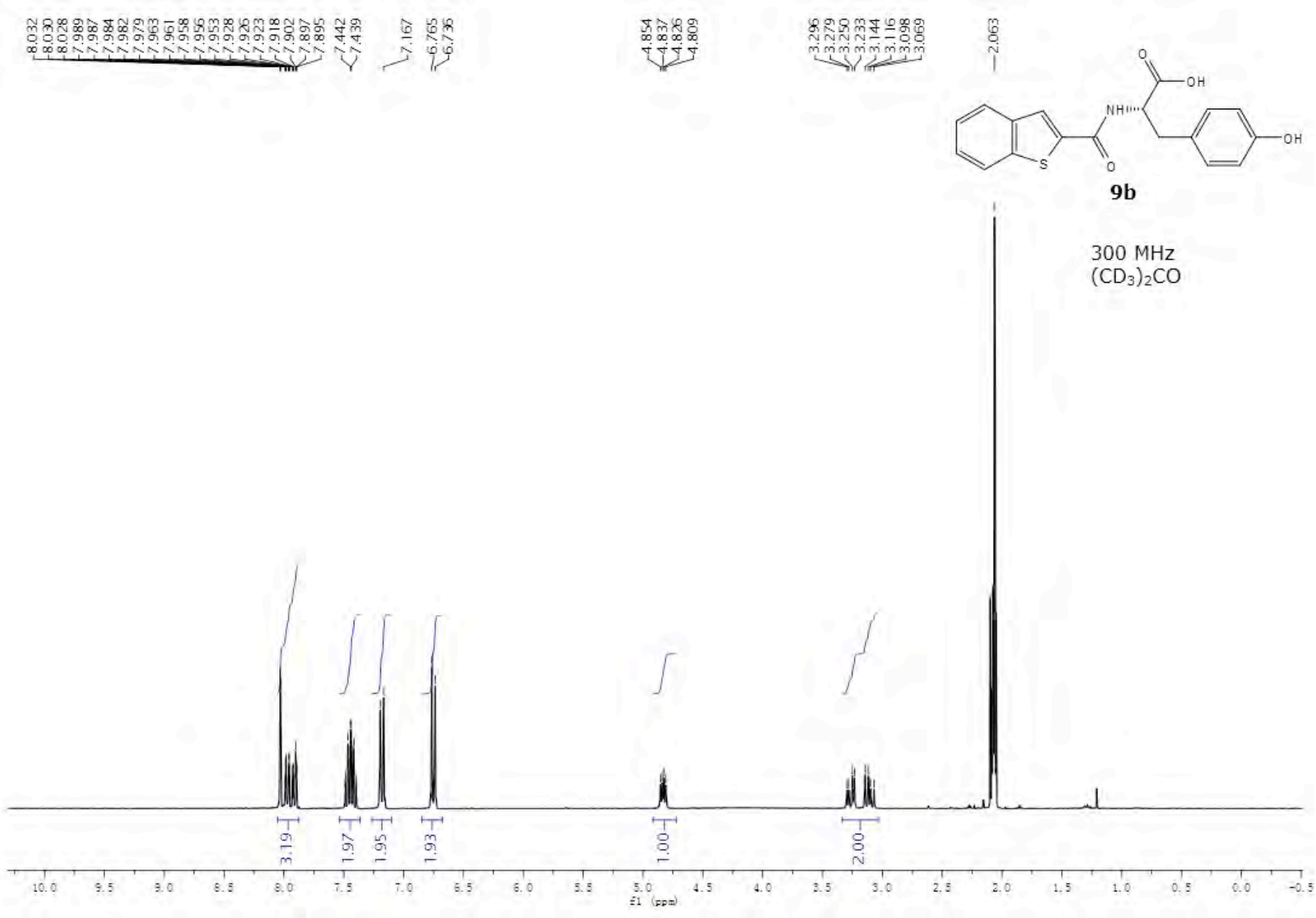
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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7.956
7.953
7.928
7.926
7.923
7.918
7.902
7.897
7.895
7.442
7.439
7.167
6.765
6.736
4.854
4.837
4.826
4.809
3.296
3.279
3.250
3.233
3.144
3.116
3.098
3.069
2.063
OH
NH
O
OH
S
O
9b
300 MHz
(CD3)2CO
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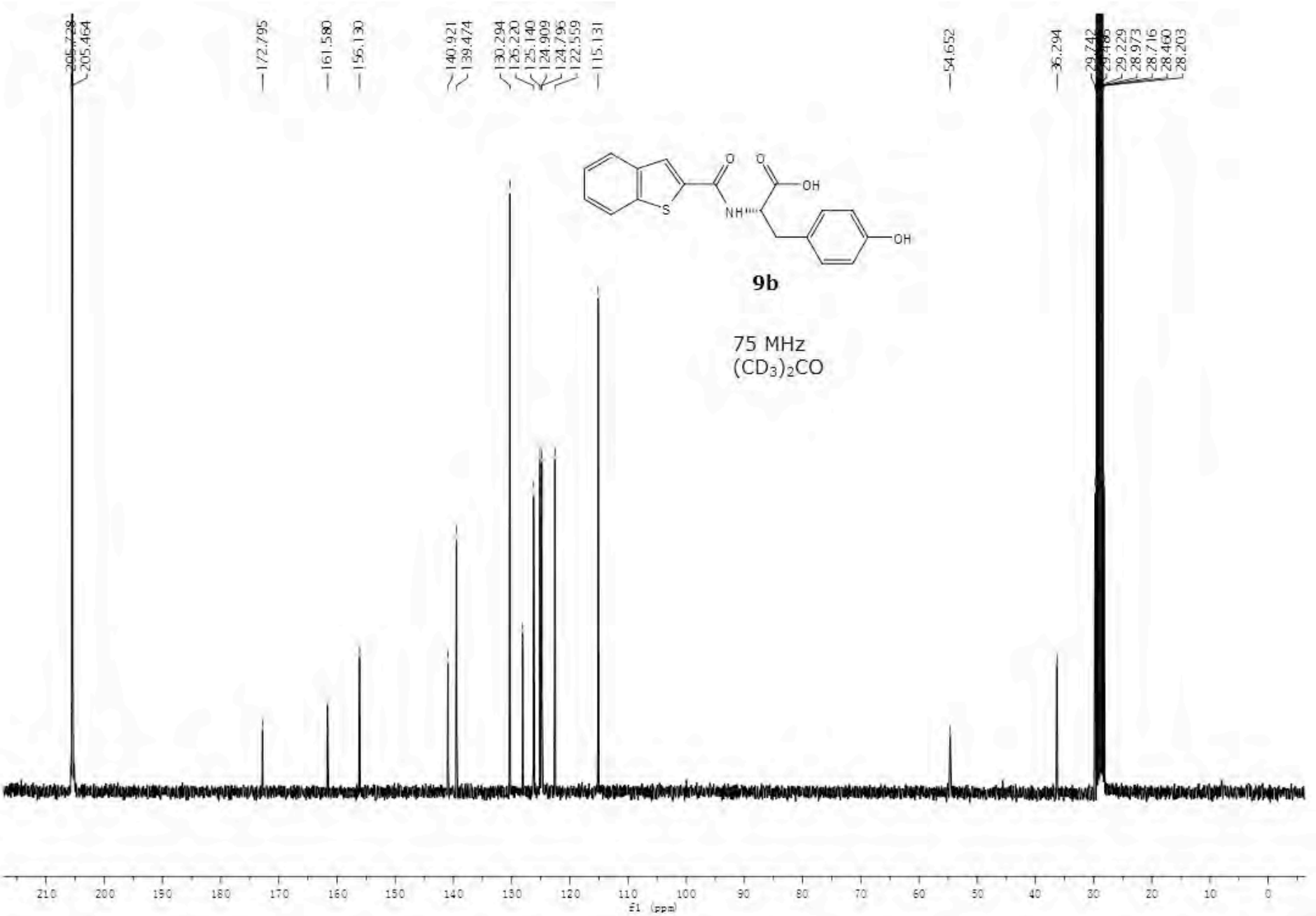
1.95
1.93
1.00
2.00
f1 (ppm)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122.559
115.131
54.652
36.294
29.742
29.486
29.229
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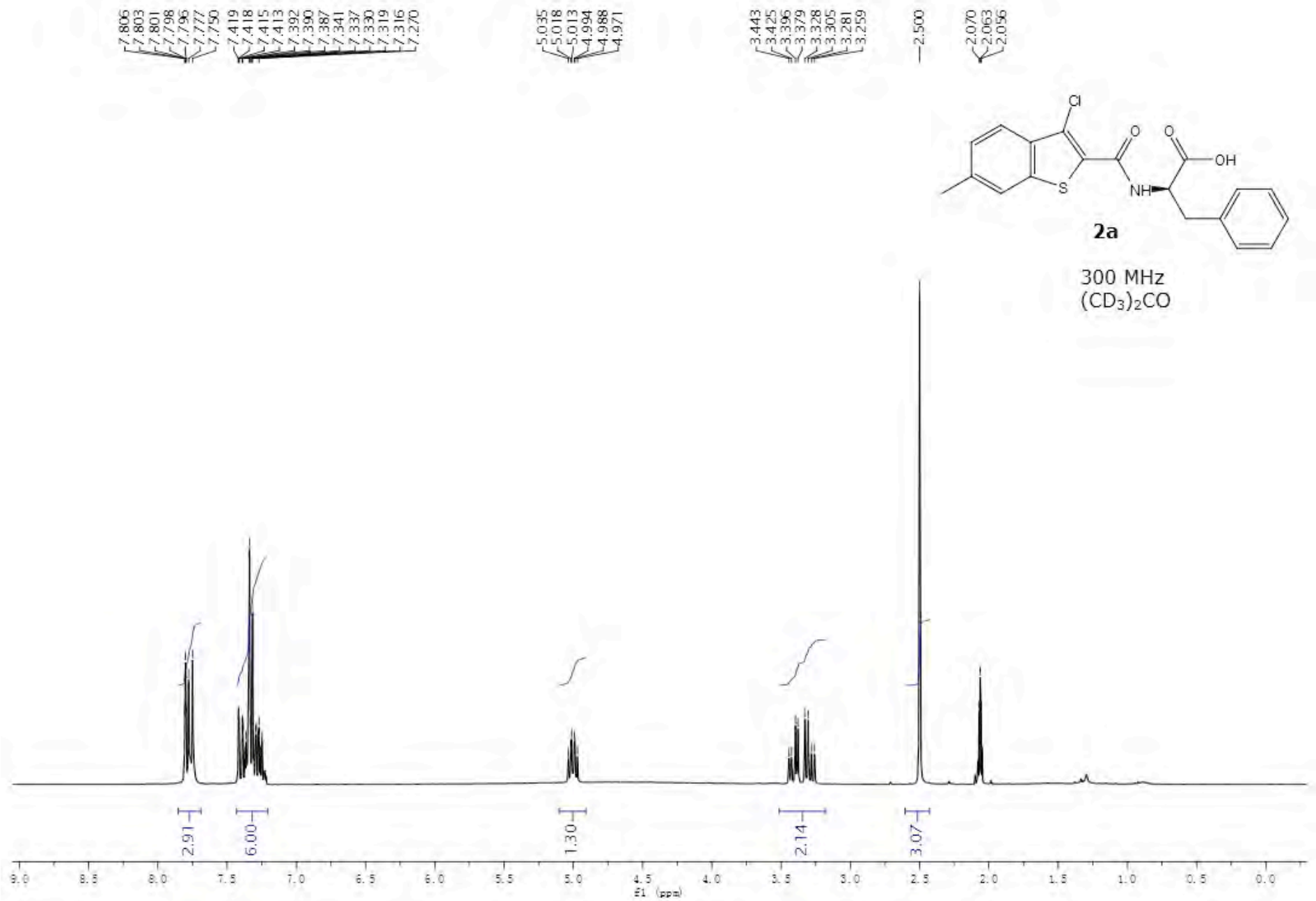
O
O
OH
NH
S
OH
9b
75 MHz
(CD3)2CO
f1 (ppm)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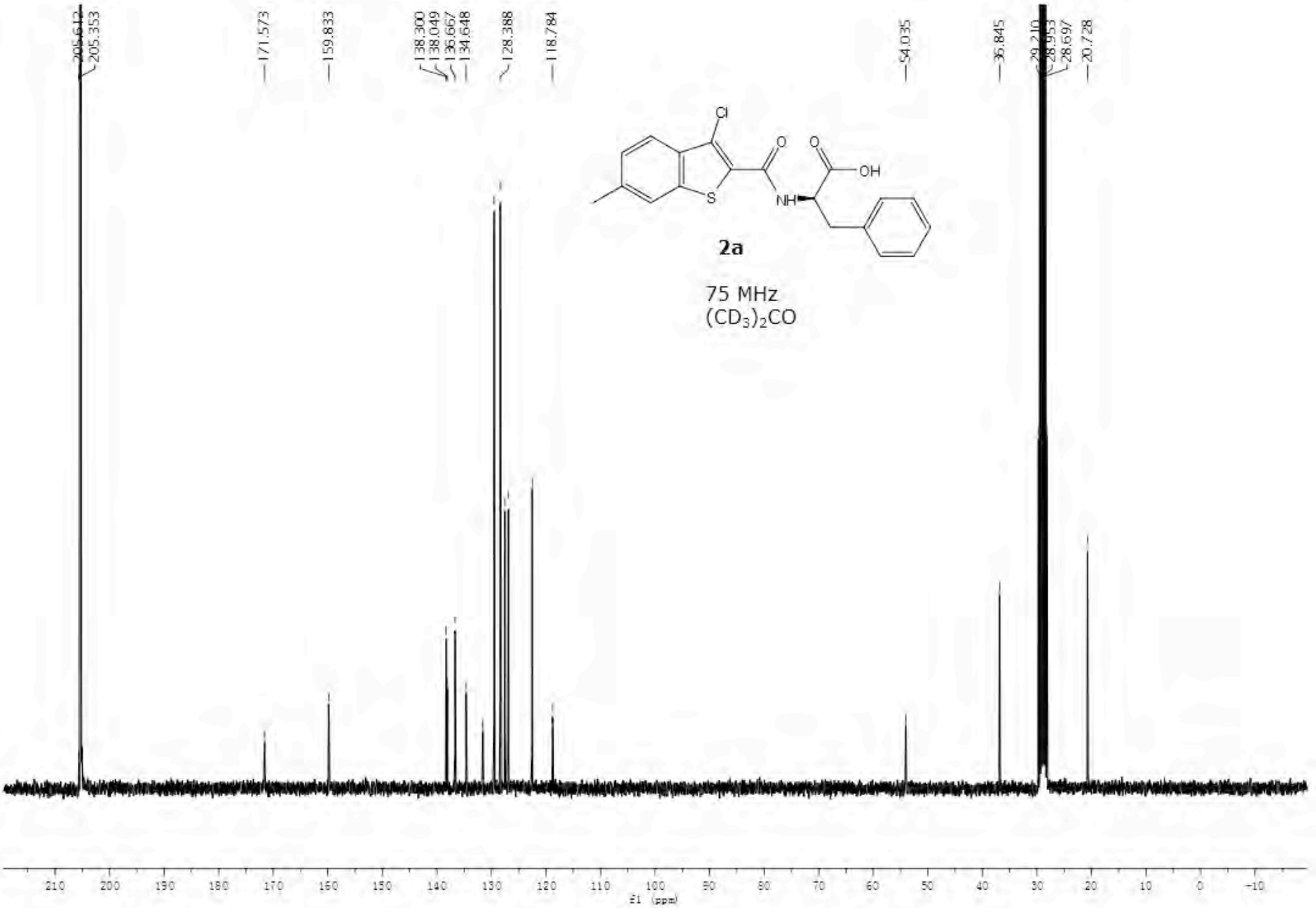
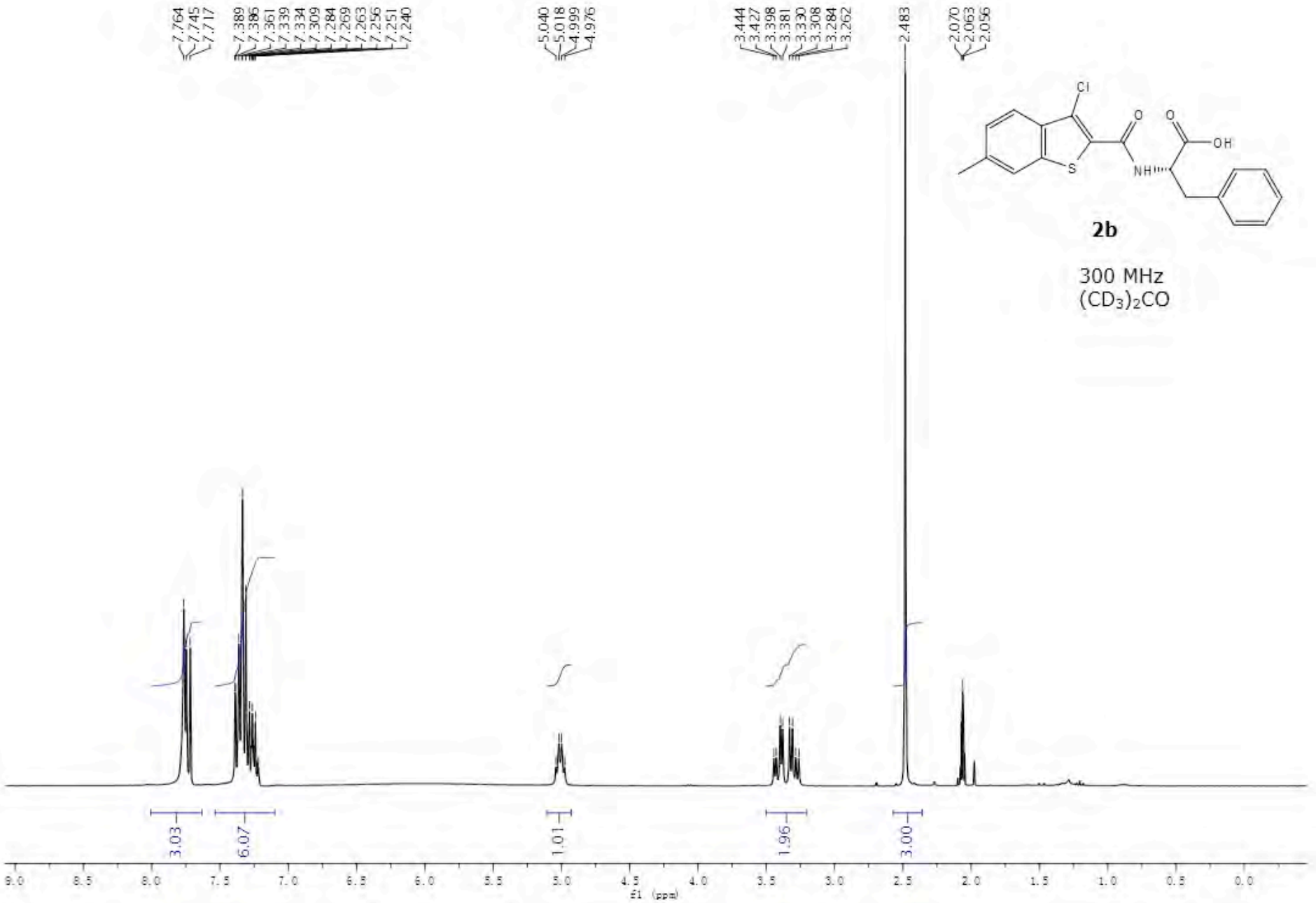
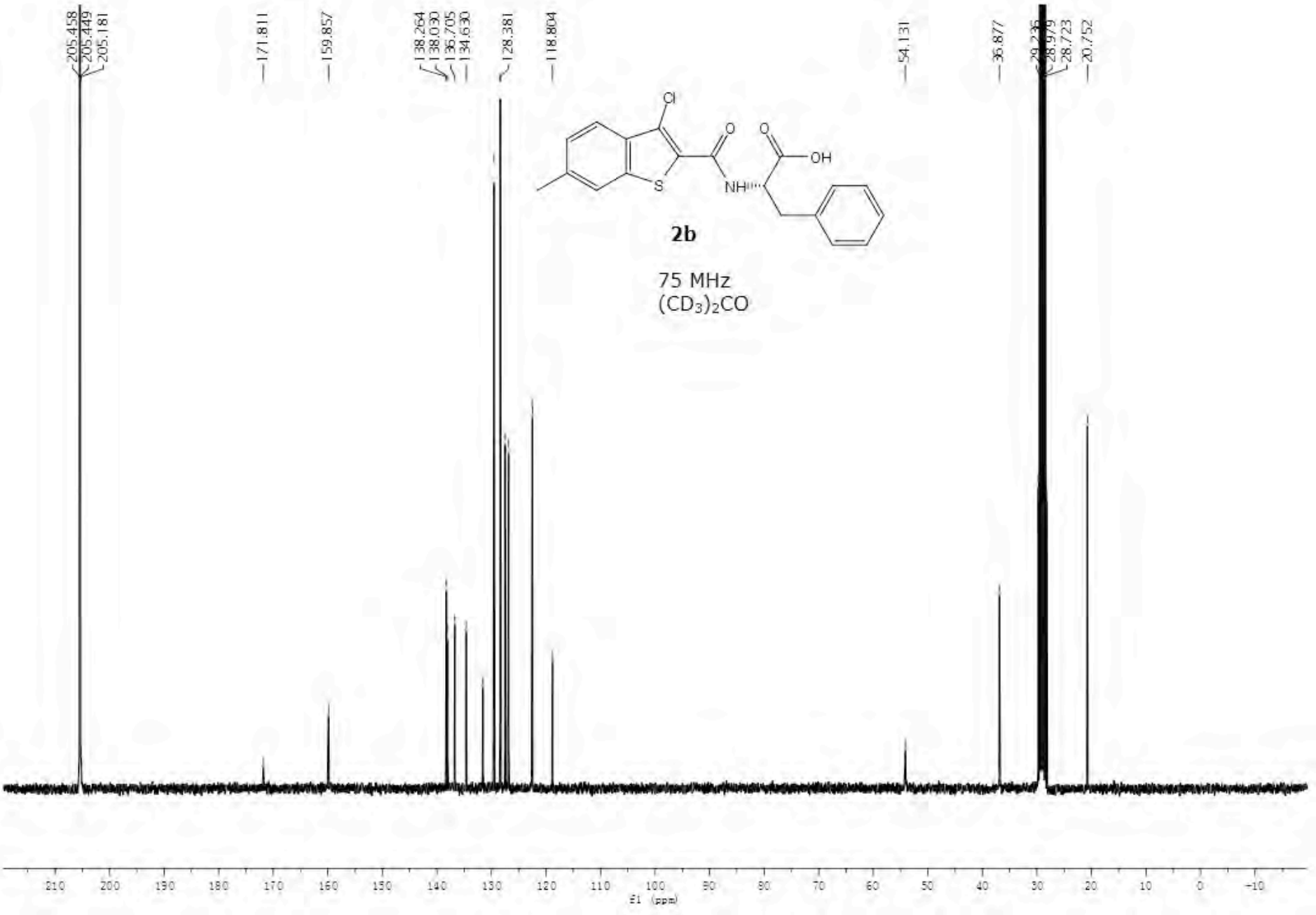
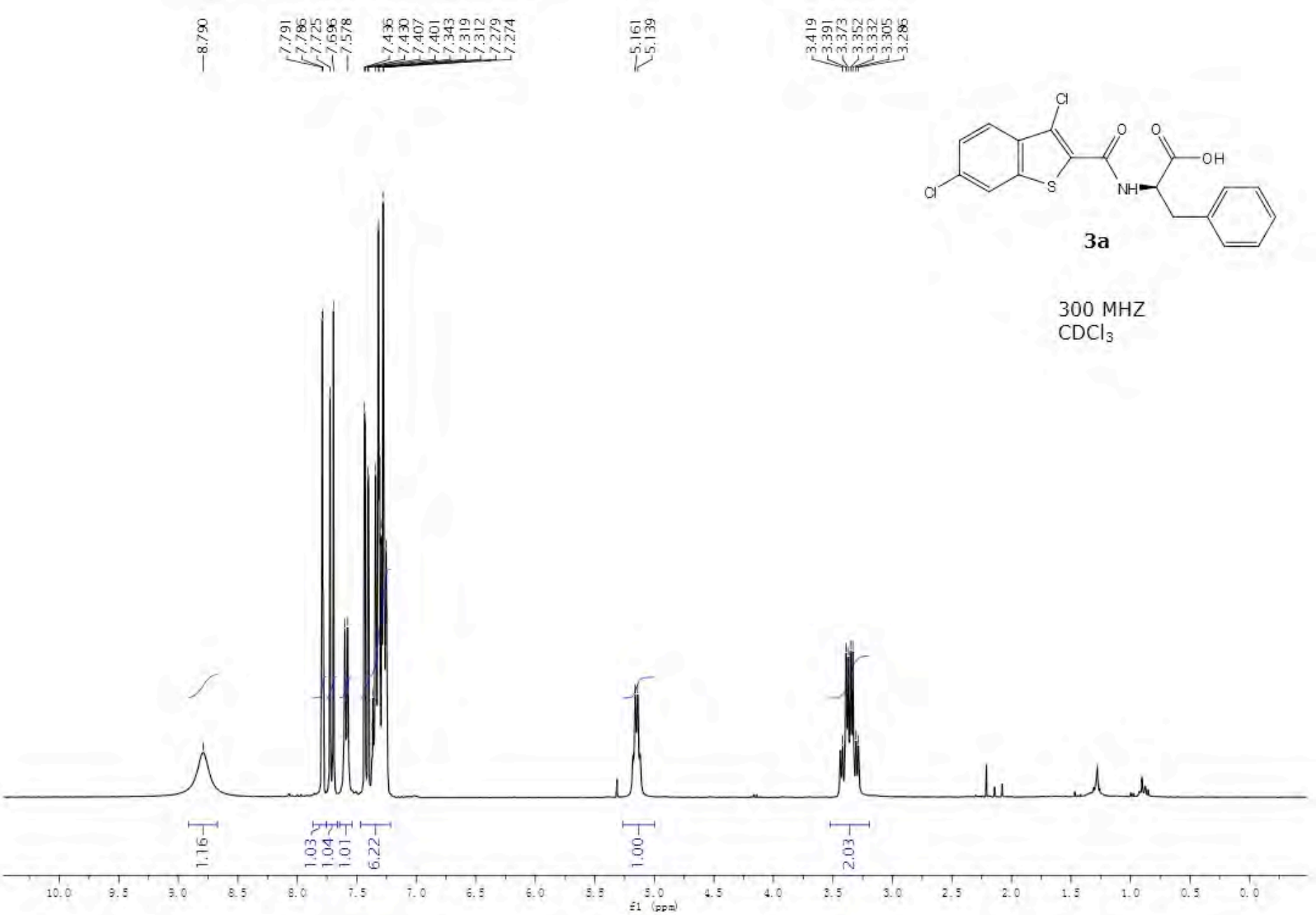
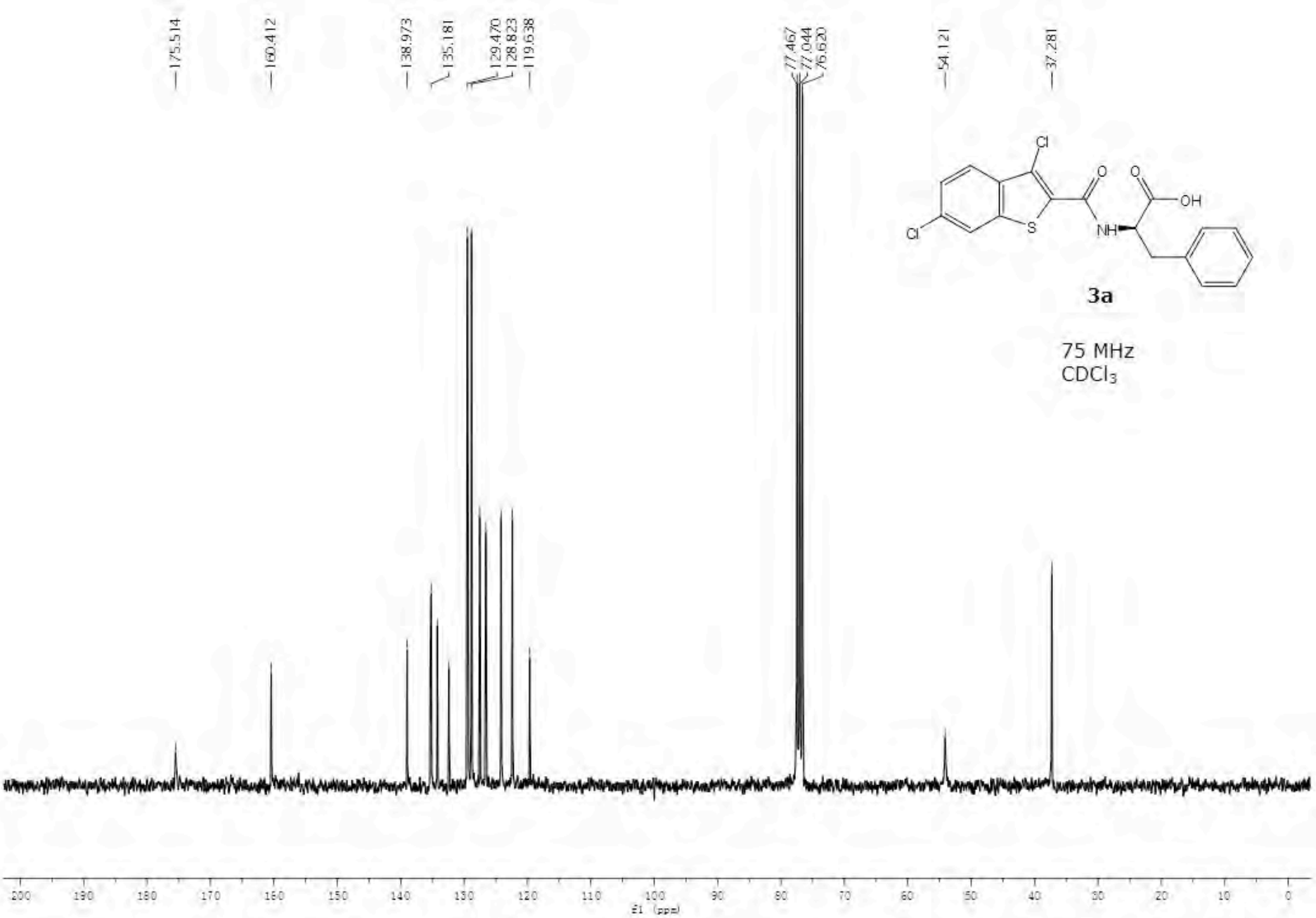
7.392
7.390
7.387
7.341
7.337
7.330
7.319
7.316
7.270
5.035
5.018
5.013
4.994
4.988
4.971
3.443
3.425
3.396
3.379
3.328
3.305
3.281
3.259
2.500
2.070
2.063
2.056
Cl
O
O
OH
NH
S
2a
300 MHz
(CD3)2CO
2.91
6.00
1.30
2.14
3.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

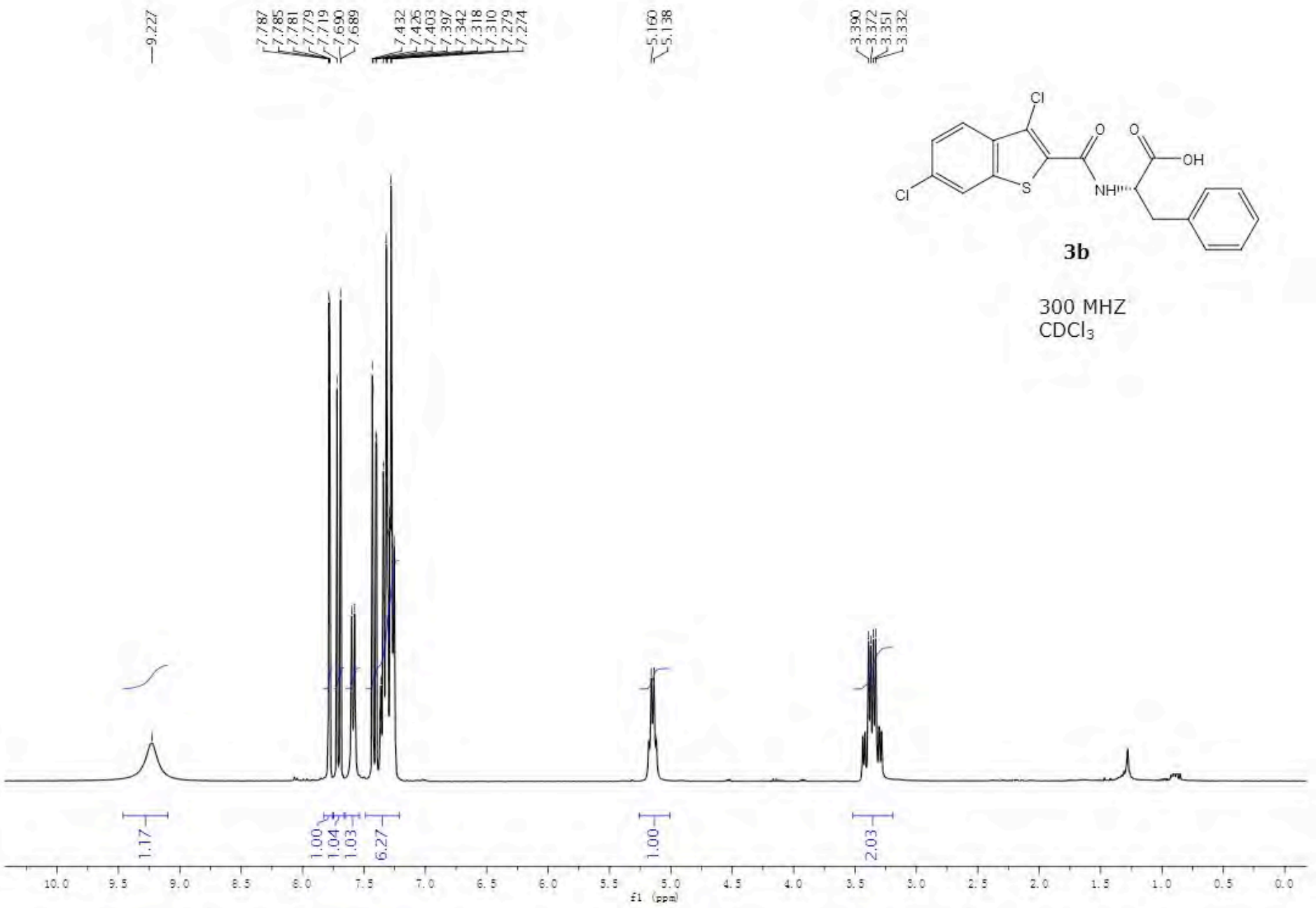

205.612
205.353
171.573
159.833
138.300
138.049
135.667
134.648
128.388
118.784
54.035
36.845
29.210
28.953
28.697
20.728
Cl
O
O
OH
S
NH
2a
75 MHz
(CD3)2CO
f1 (ppm)

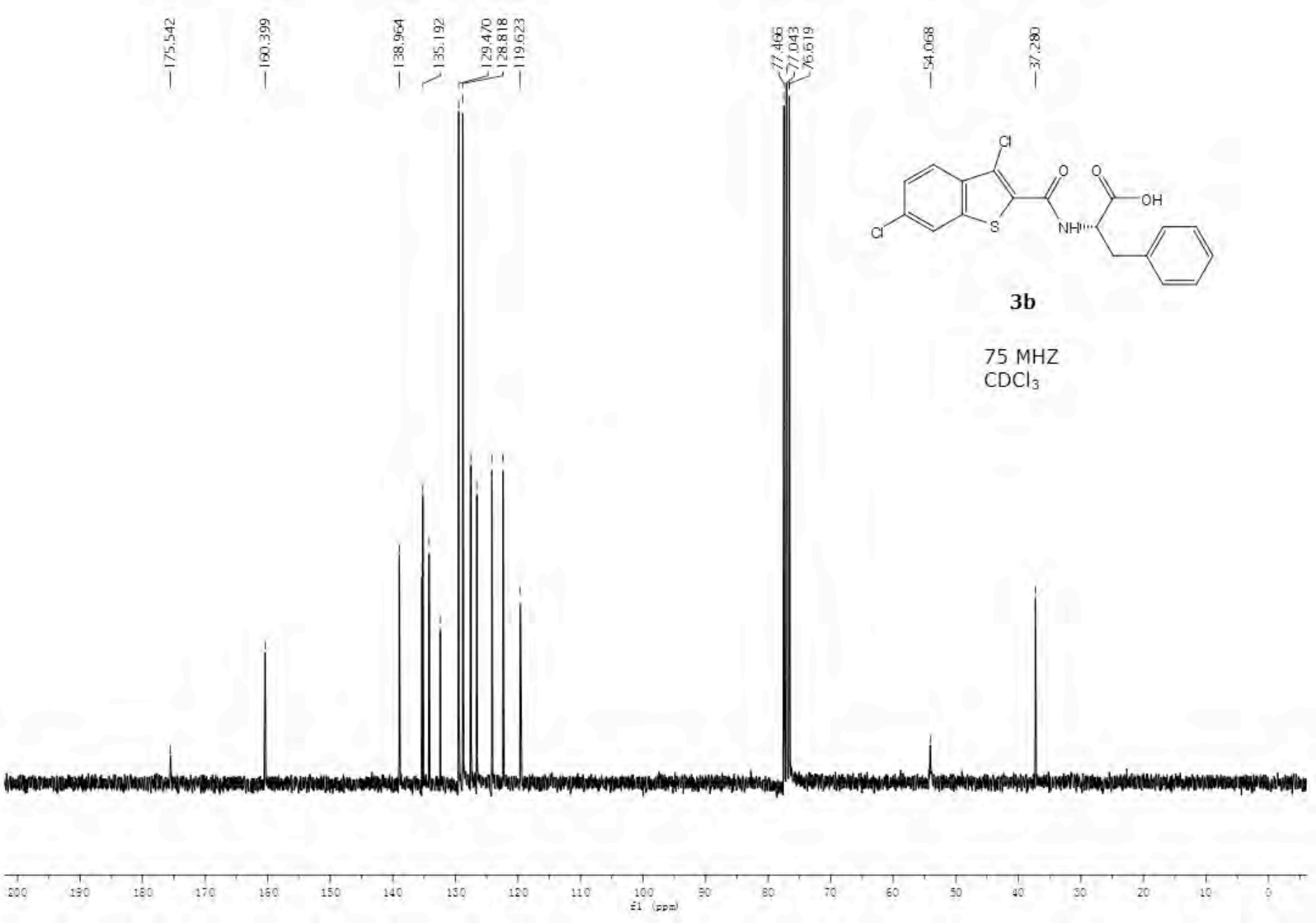

7.764
7.745
7.717
7.389
7.386
7.361
7.339
7.334
7.309
7.284
7.269
7.263
7.256
7.251
7.240
5.040
5.018
4.999
4.976
3.444
3.427
3.398
3.381
3.330
3.308
3.284
3.262
2.483
2.070
2.063
2.056
Cl
O
O
OH
S
NH
2b
300 MHz
(CD3)2CO
3.03
6.07
1.01
1.96
3.00
f1 (ppm)

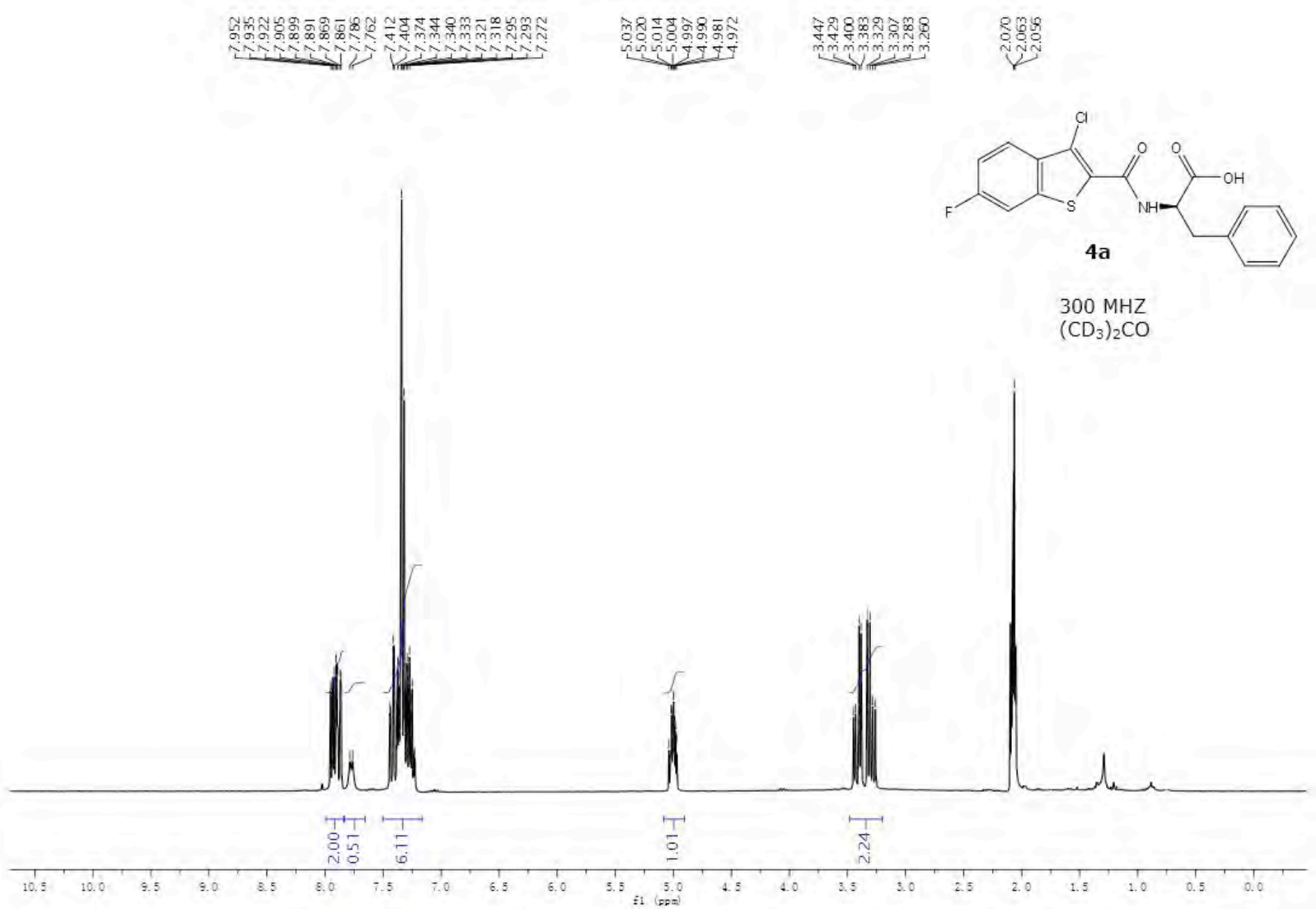

205.458
205.449
205.181
171.811
159.857
138.264
138.030
136.705
134.630
128.381
118.804
54.131
36.877
29.236
28.979
28.723
20.752
Cl
O
O
OH
S
NH
2b
75 MHz
(CD3)2CO
f1 (ppm)

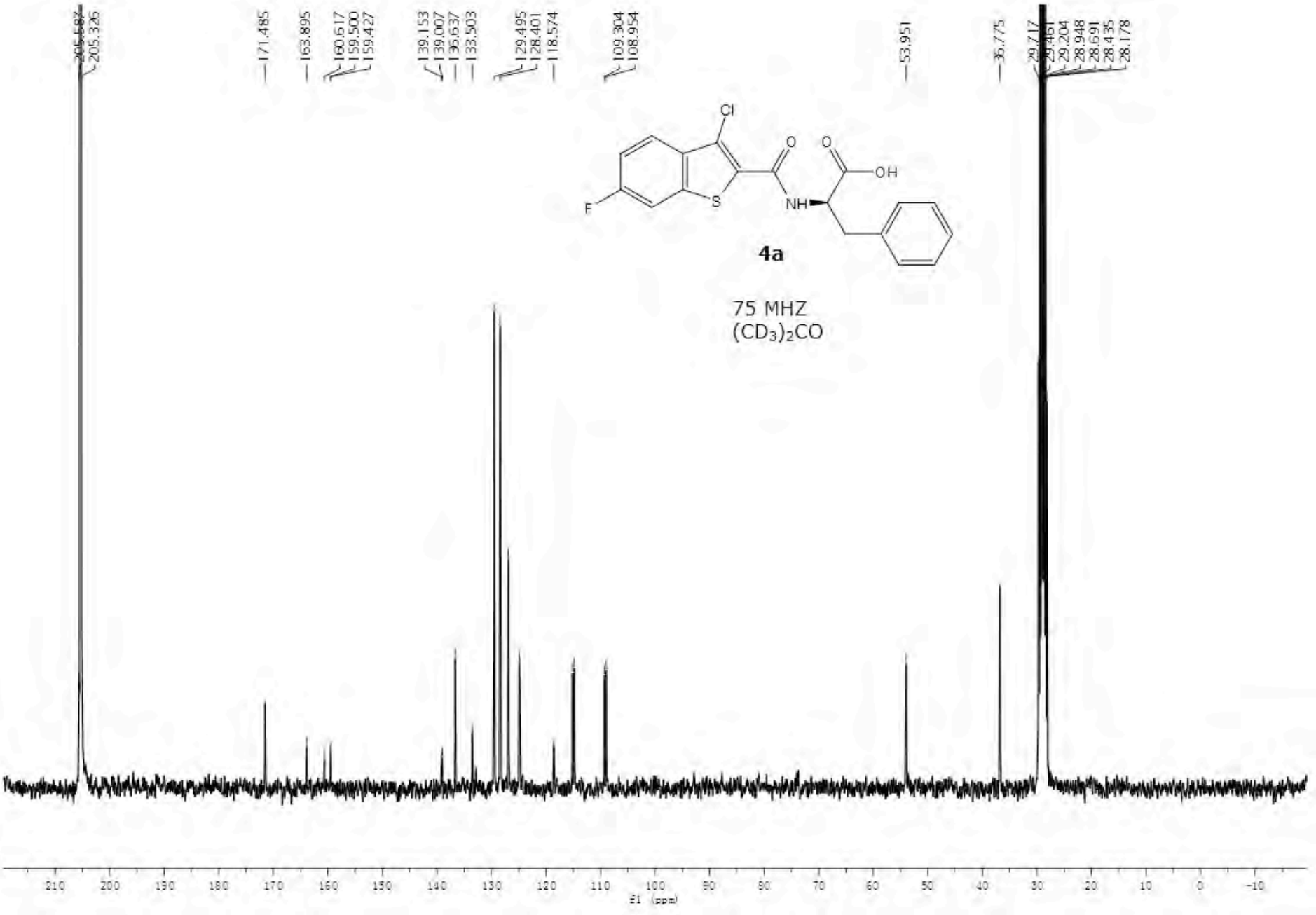

8.790
7.791
7.786
7.725
7.696
7.578
7.436
7.430
7.407
7.401
7.343
7.319
7.312
7.279
7.274
5.161
5.139
3.419
3.391
3.373
3.352
3.332
3.305
3.285
Cl
O
O
OH
S
NH
Cl
3a
300 MHZ
CDCl3
1.16
1.03
1.04
1.01
6.22
1.00
2.03
f1 (ppm)

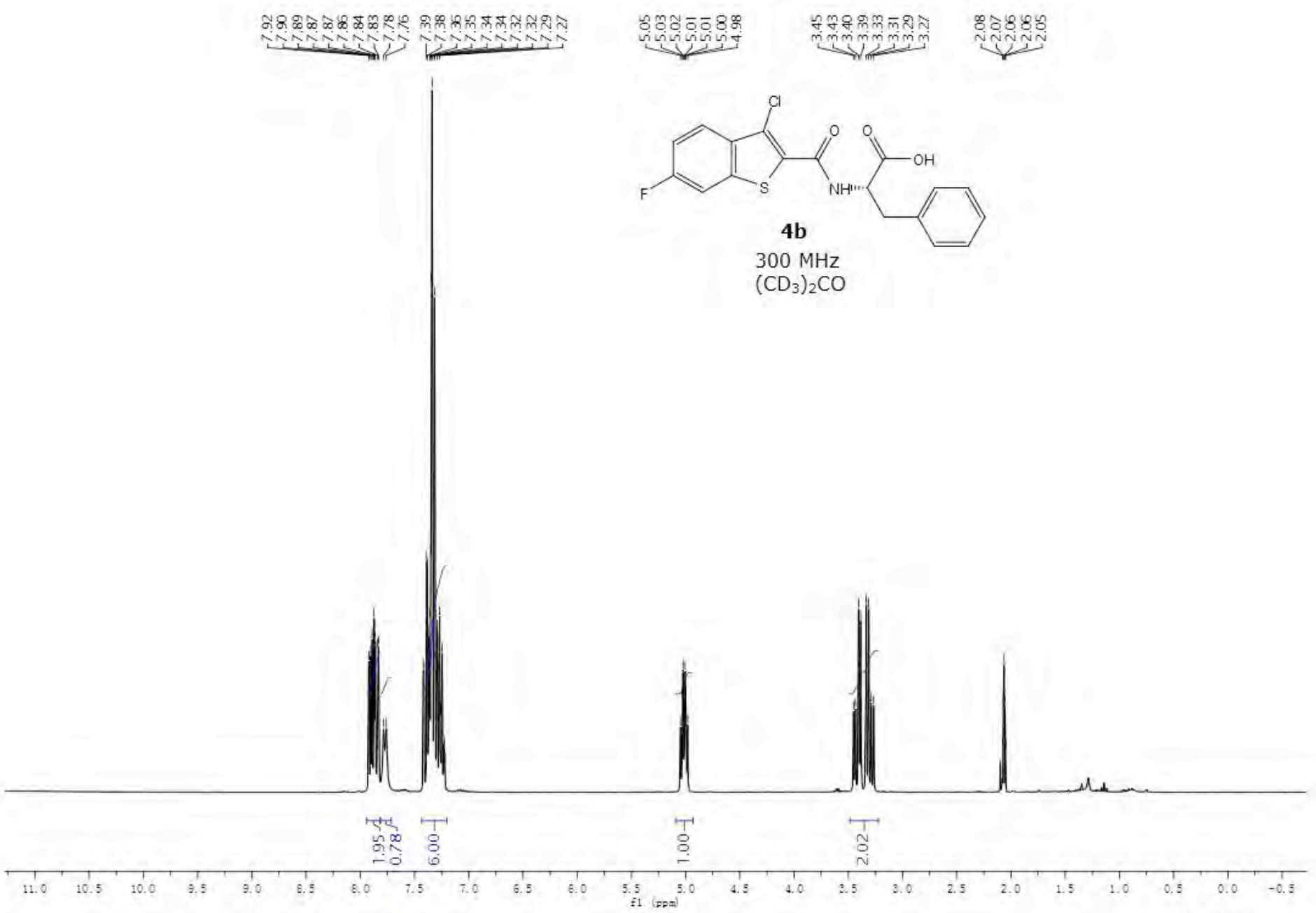

175.514
160.412
138.973
135.181
129.470
128.823
119.638
77.467
77.044
76.620
54.121
37.281
Cl
Cl
S
O
O
OH
NH
3a
75 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

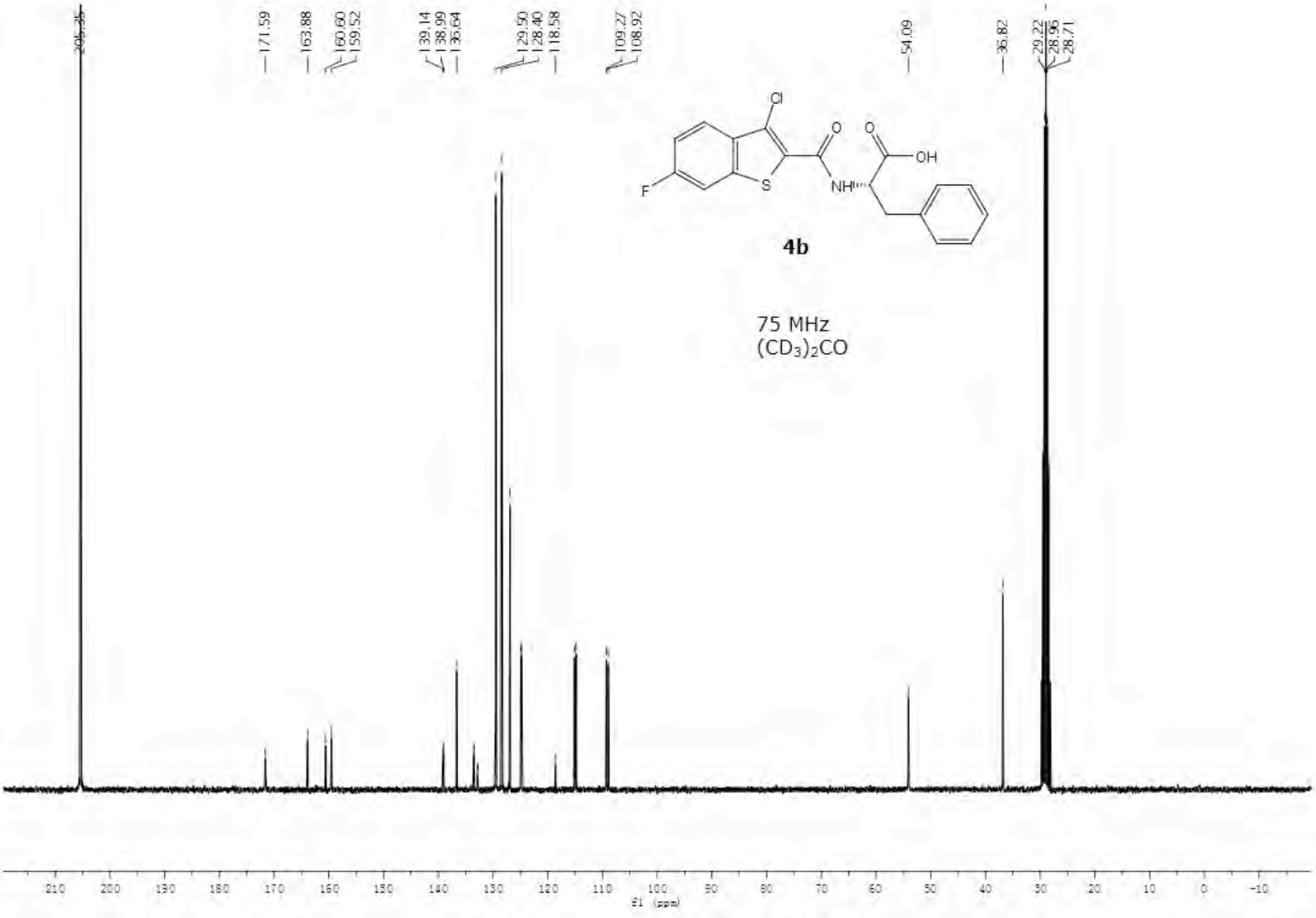

9.227
7.787
7.785
7.781
7.779
7.719
7.690
7.689
7.432
7.426
7.403
7.397
7.342
7.318
7.310
7.279
7.274
5.160
5.138
3.390
3.372
3.351
3.332
Cl
O
O
OH
S
NH
Cl
3b
300 MHZ
CDCl3
1.17
1.00
1.04
1.03
6.27
1.00
2.03
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

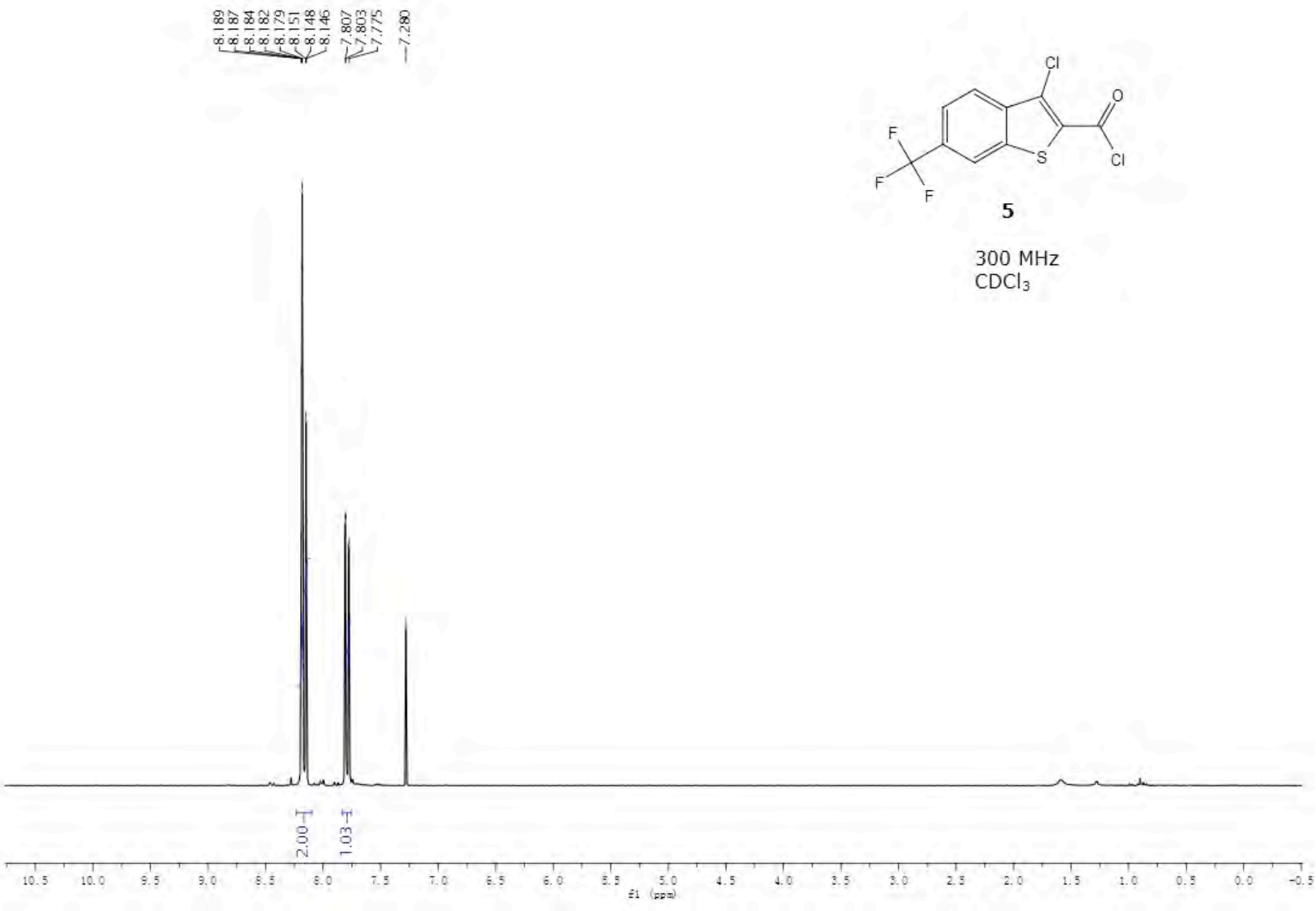

175.542
160.399
138.964
135.192
129.470
128.818
119.623
77.466
77.043
76.619
54.068
37.280
Cl
O
O
OH
Cl
S
NH
3b
75 MHZ
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

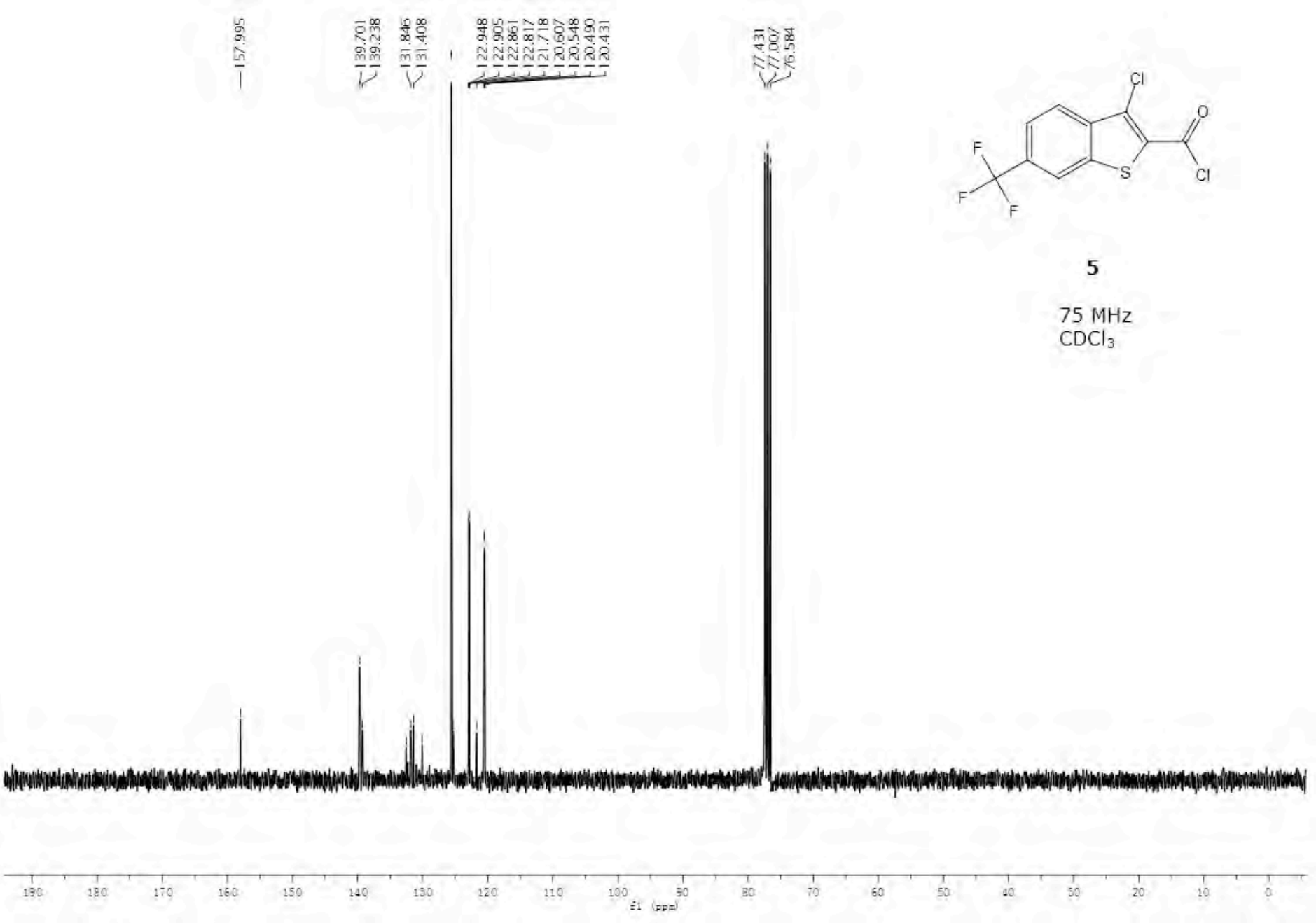

7.952
7.935
7.922
7.905
7.899
7.891
7.869
7.861
7.786
7.762
7.412
7.404
7.374
7.344
7.340
7.333
7.321
7.318
7.295
7.293
7.272
5.037
5.020
5.014
5.004
4.997
4.990
4.981
4.972
3.447
3.429
3.400
3.383
3.329
3.307
3.283
3.260
2.070
2.063
2.056
Cl
O
O
OH
S
NH
F
4a
300 MHZ
(CD3)2CO
2.00
0.51
6.11
1.01
2.24
f1 (ppm)

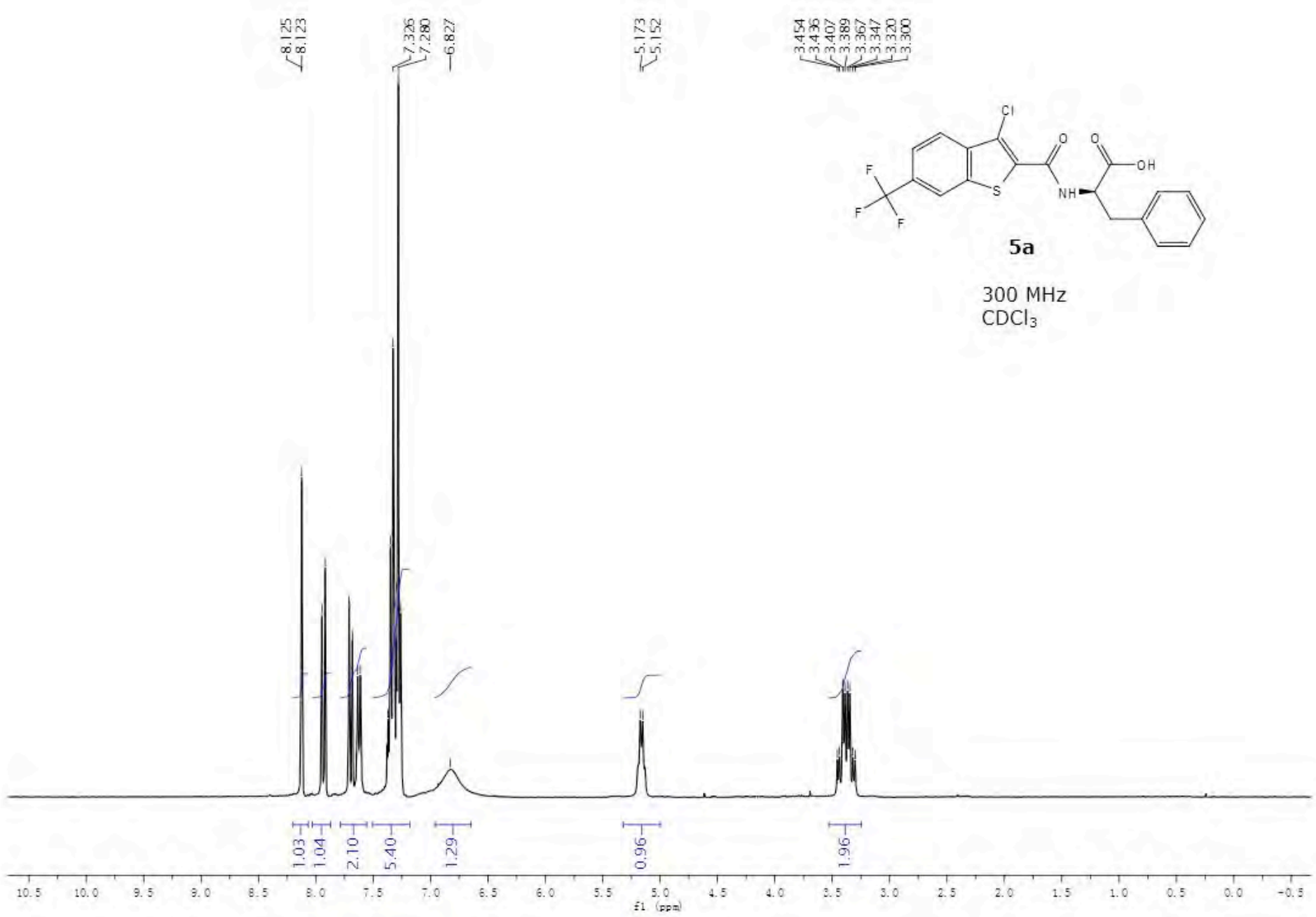

205.687
205.326
171.485
163.895
160.617
159.500
159.427
139.153
139.007
136.637
133.503
129.495
128.401
118.574
109.304
108.954
53.951
36.775
29.717
29.461
29.204
28.948
28.691
28.435
28.178
Cl
O
O
OH
S
NH
F
4a
75 MHZ
(CD3)2CO
f1 (ppm)

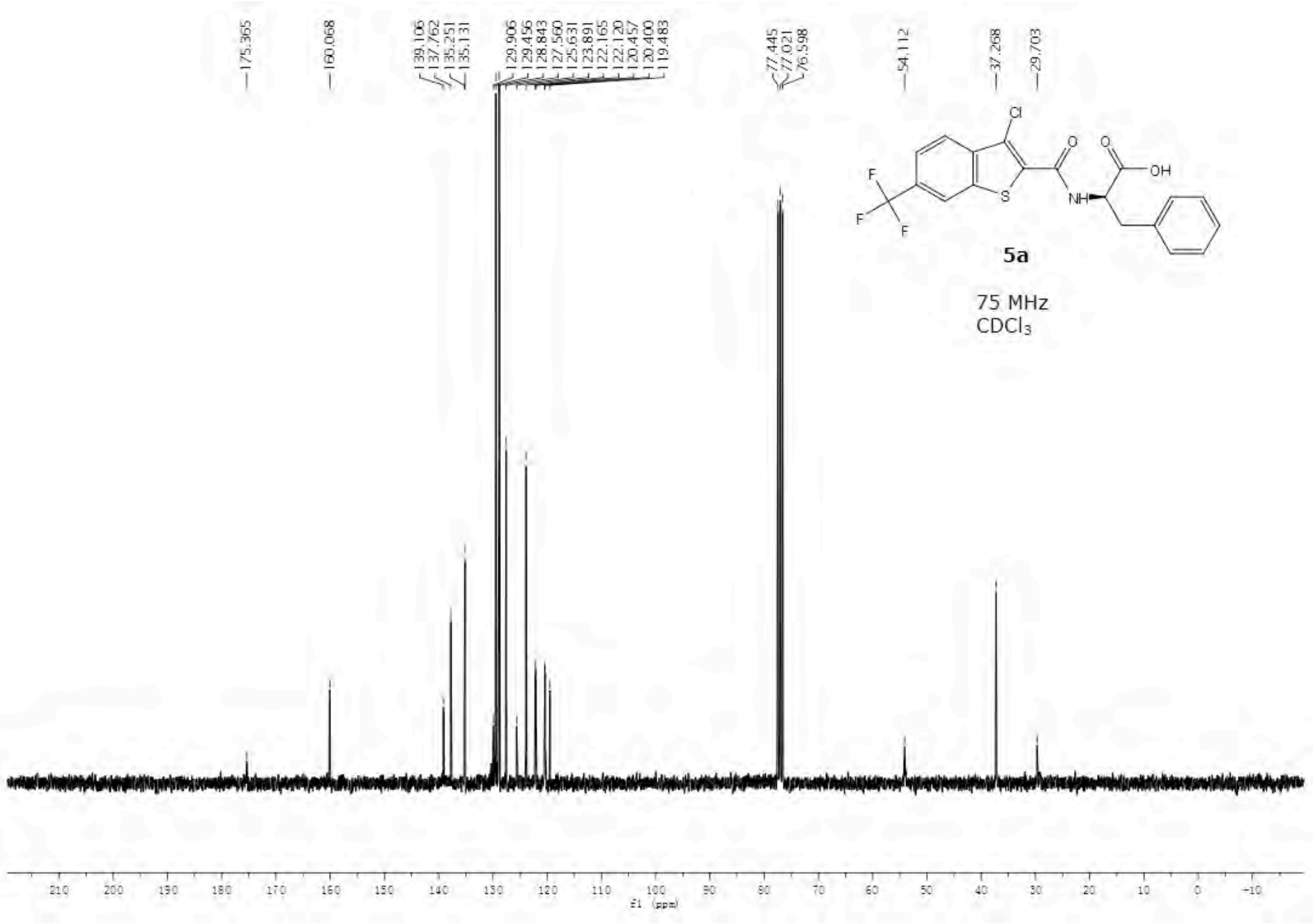

7.92
7.90
7.89
7.87
7.87
7.85
7.84
7.83
7.78
7.76
7.39
7.38
7.35
7.35
7.34
7.34
7.32
7.29
7.27
5.05
5.03
5.02
5.01
5.01
5.00
4.98
3.45
3.43
3.40
3.39
3.33
3.31
3.29
3.27
2.08
2.07
2.06
2.06
2.05
Cl
O
O
OH
F
S
NH
4b
300 MHz
(CD3)2CO
1.95
0.78
6.00
1.00
2.02
f1 (ppm)

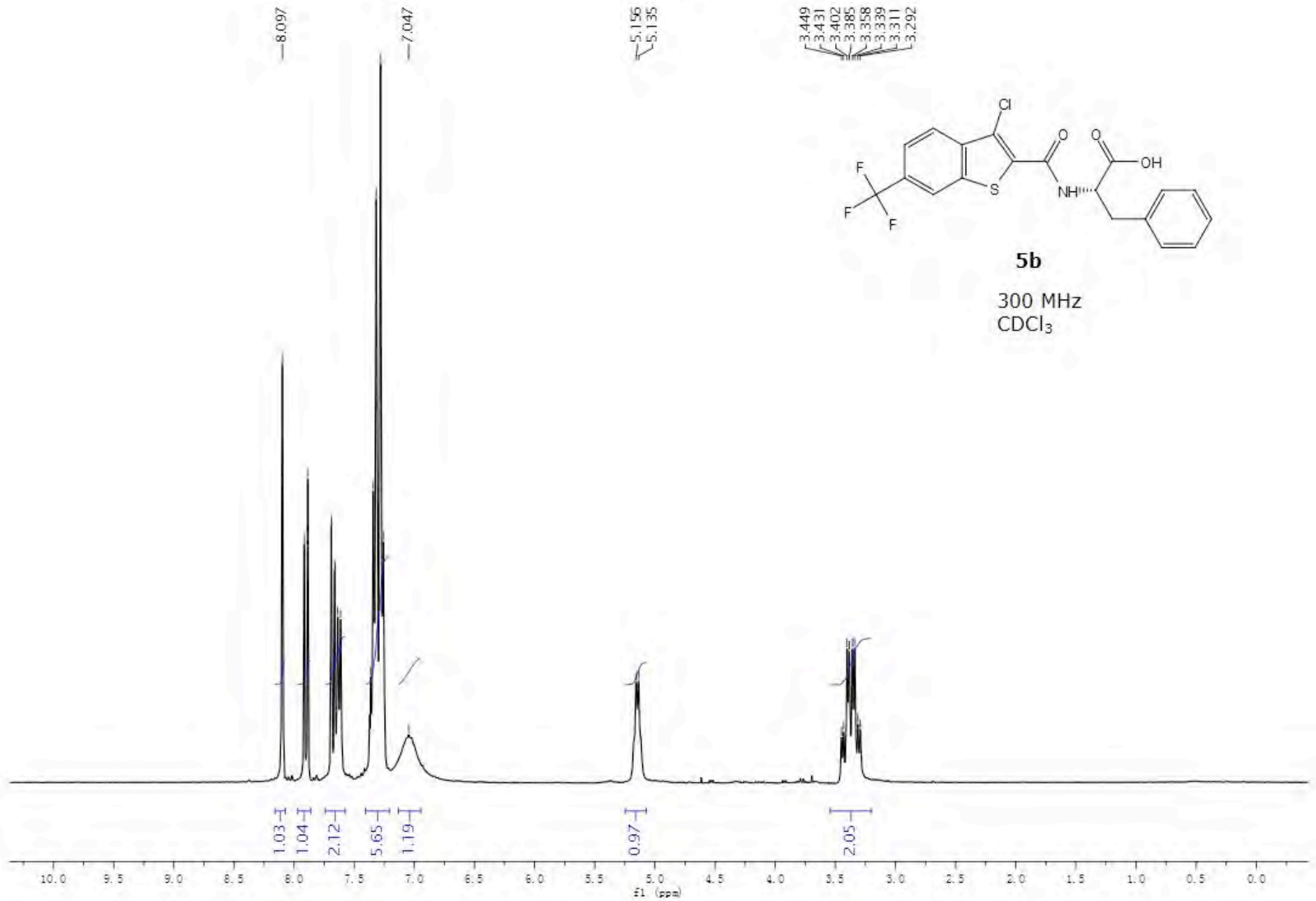

205.35
171.59
163.88
160.60
159.52
139.14
138.99
135.64
129.50
128.40
118.58
109.27
108.92
54.09
36.82
29.22
28.96
28.71
Cl
O
O
OH
S
NH
F
4b
75 MHz
(CD3)2CO
f1 (ppm)

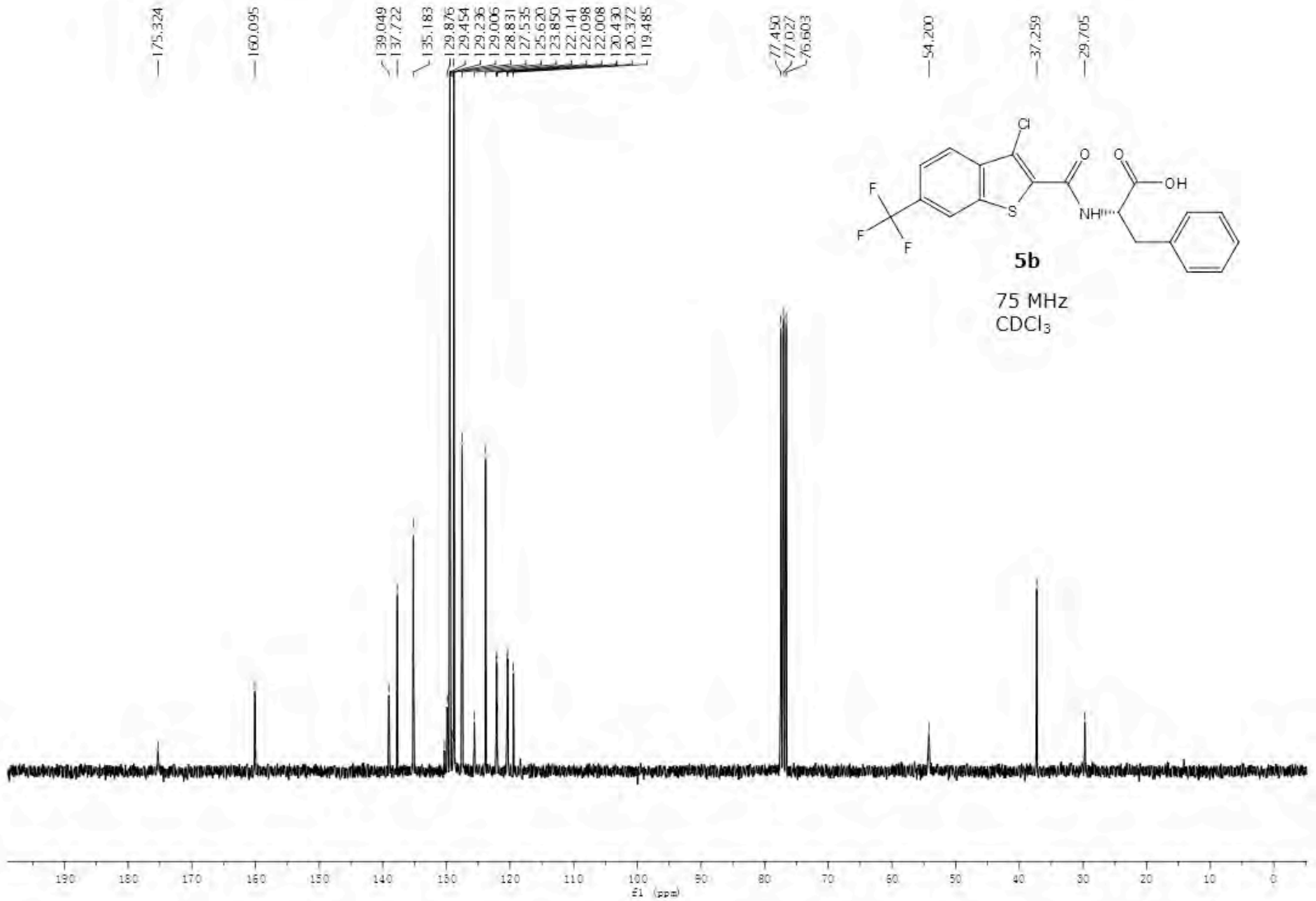

8.189
8.187
8.184
8.182
8.179
8.151
8.148
8.146
7.807
7.803
7.775
7.280
Cl
O
S
Cl
F
F
F
5
300 MHz
CDCl3
2.00
1.03
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


157.995
139.701
139.238
131.846
131.408
122.948
122.905
122.861
122.817
121.718
120.607
120.548
120.490
120.431
77.431
77.007
76.584
Cl
O
F
S
Cl
F
F
5
75 MHz
CDCl3
f1 (ppm)

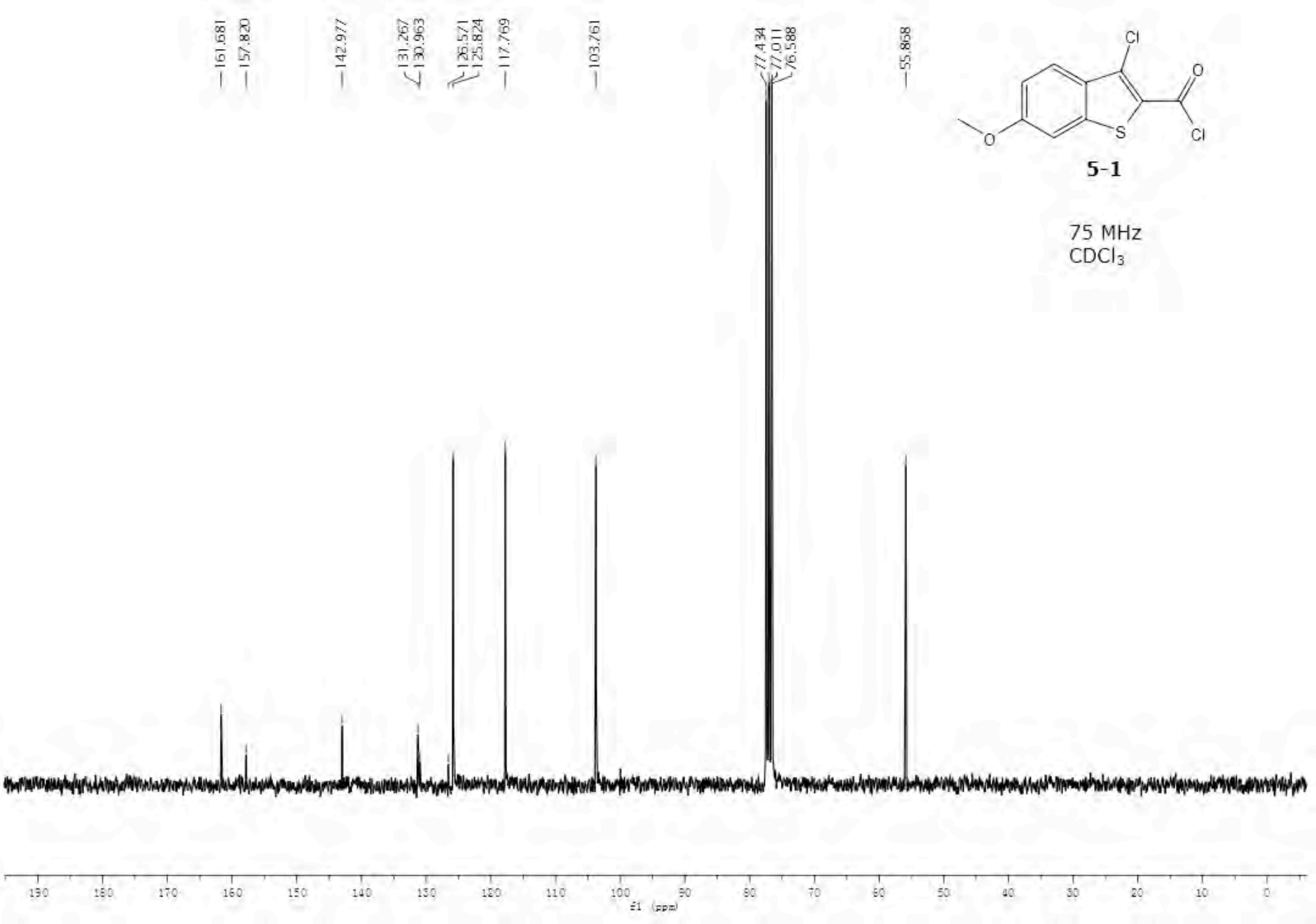

8.125
8.123
7.326
7.280
6.827
5.173
5.152
3.454
3.436
3.407
3.389
3.367
3.347
3.320
3.300
Cl
O
O
OH
NH
S
F
F
F
5a
300 MHz
CDCl3
1.03
1.04
2.10
5.40
1.29
0.96
1.96
f1 (ppm)

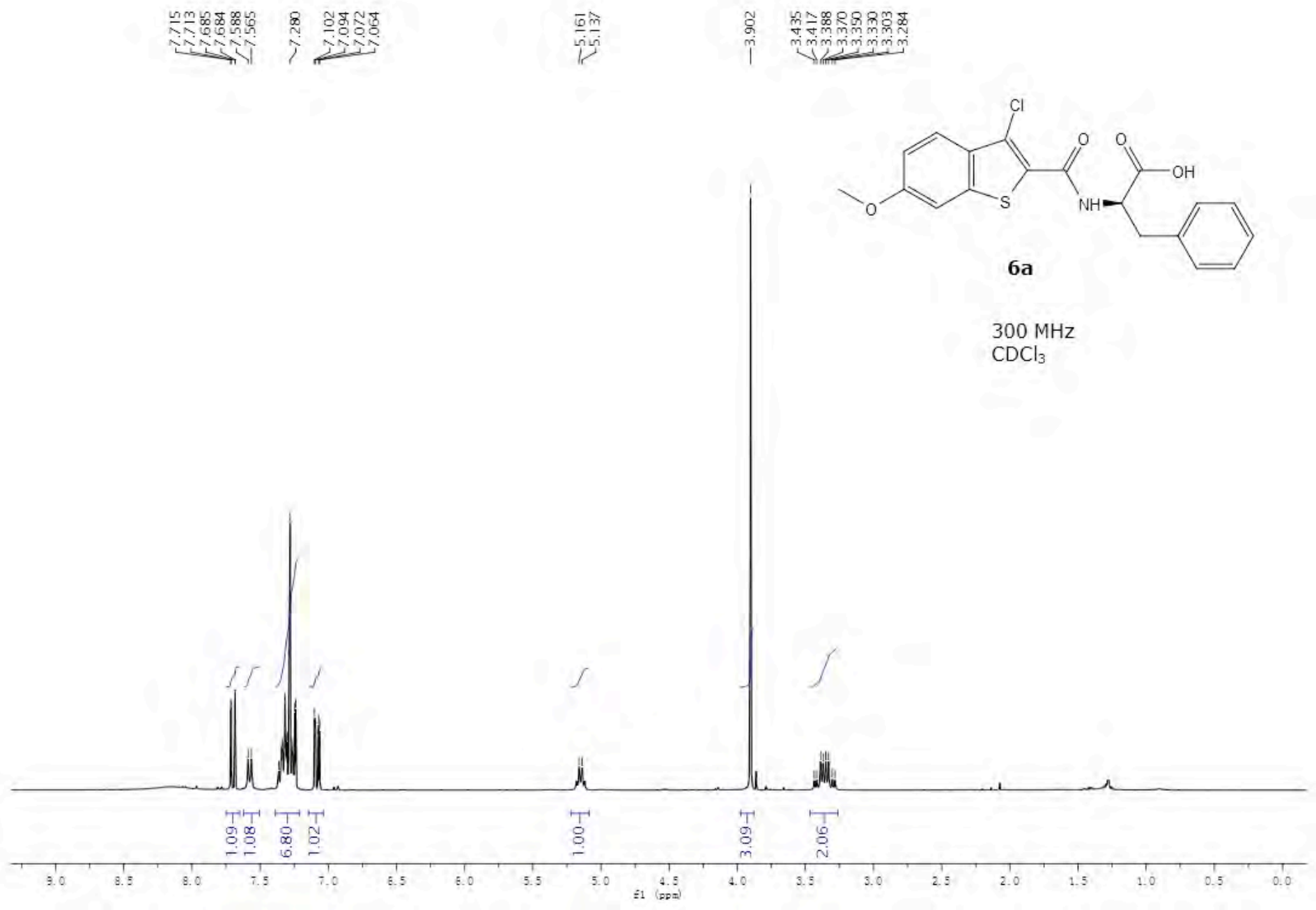

175.365
160.068
139.106
137.762
135.251
135.131
129.906
129.456
128.843
127.560
125.631
123.891
122.165
122.120
120.457
120.400
119.483
77.445
77.021
76.598
54.112
37.268
29.703
Cl
O
O
OH
NH
S
F
F
F
5a
75 MHz
CDCl3
f1 (ppm)

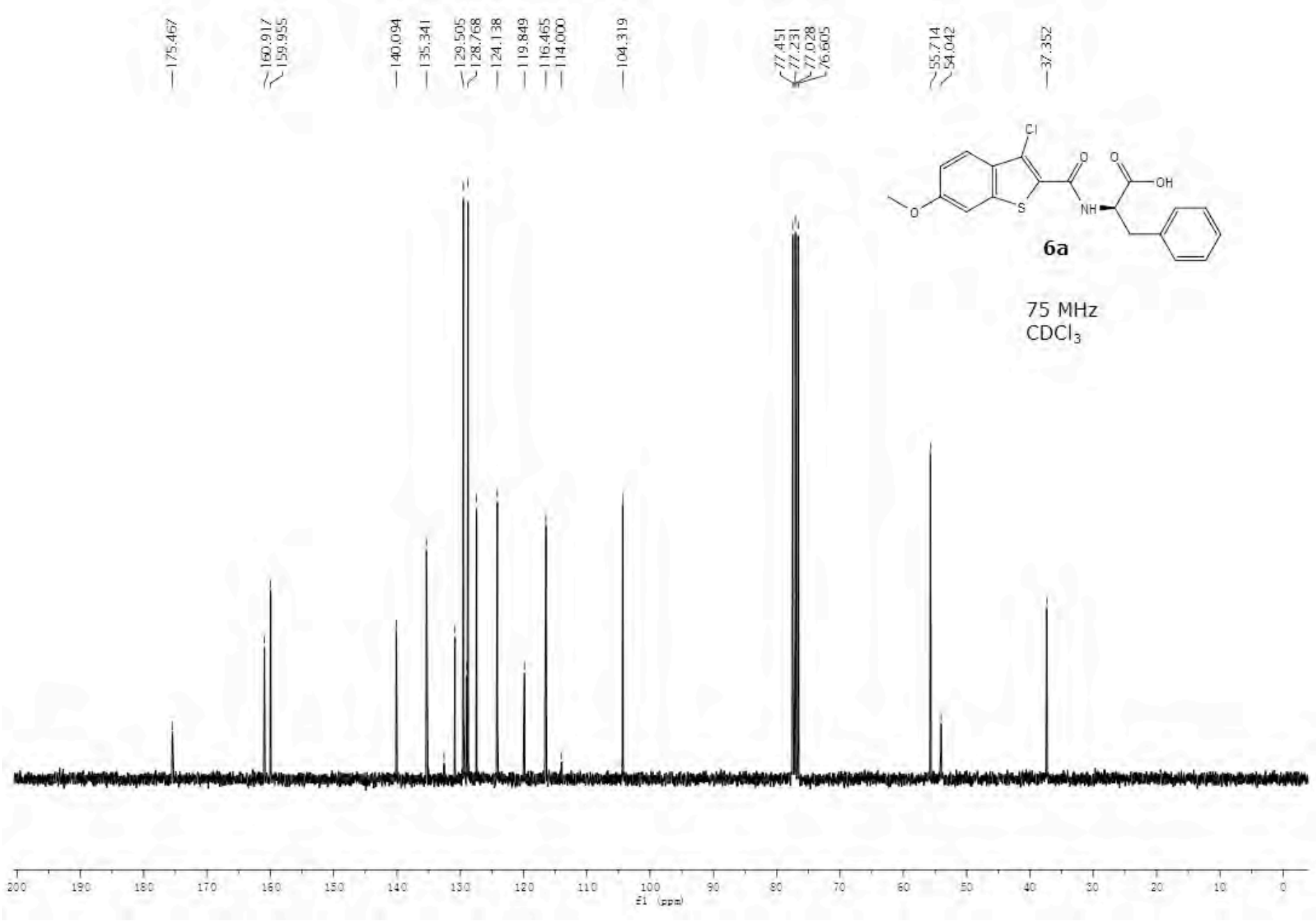

8.097
7.047
5.156
5.135
3.449
3.431
3.402
3.385
3.358
3.339
3.311
3.292
Cl
O
O
OH
F
F
F
S
NH
5b
300 MHz
CDCl3
1.03
1.04
2.12
5.65
1.19
0.97
2.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

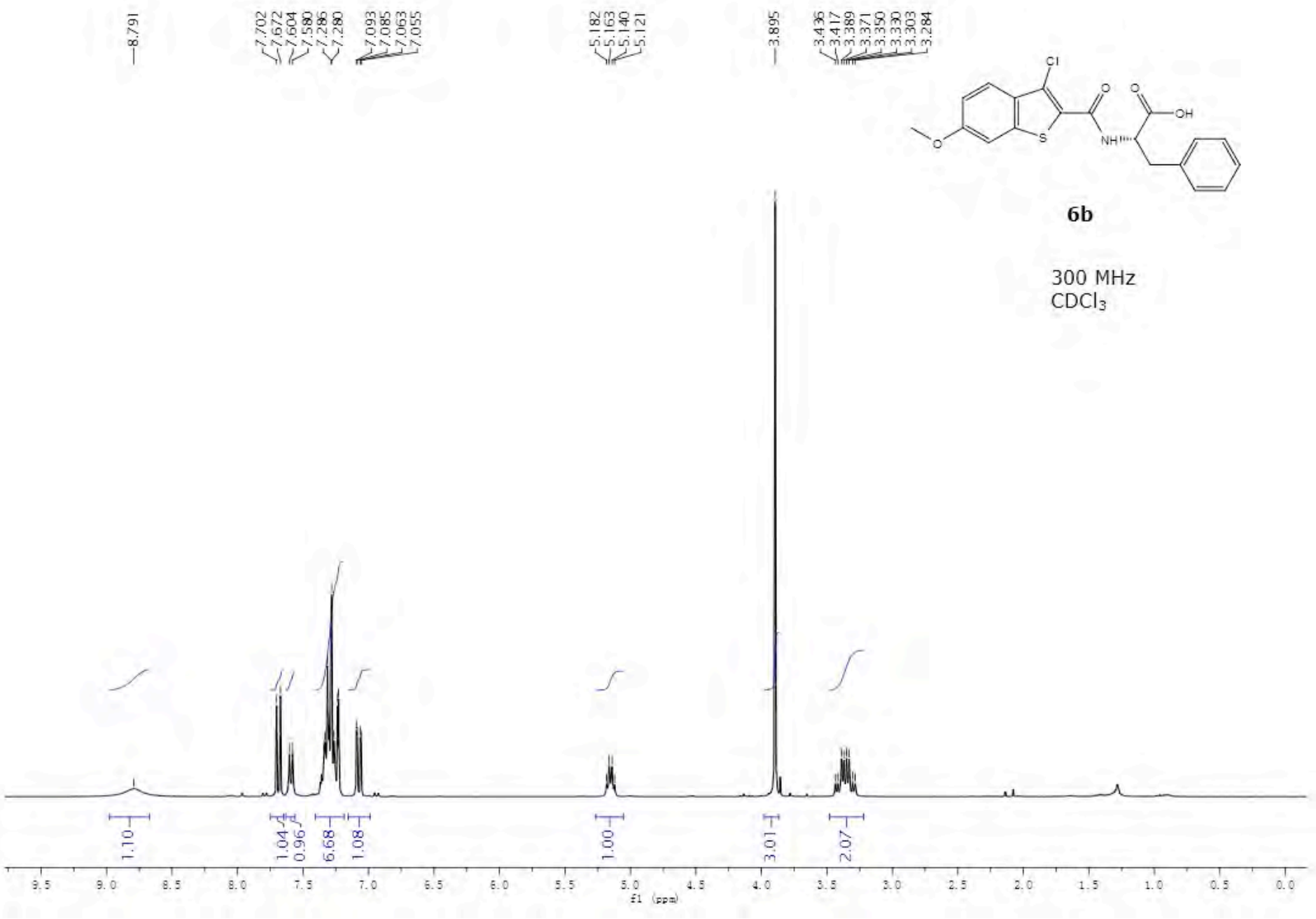

175.324
160.095
139.049
137.722
135.183
129.876
129.454
129.236
129.006
128.831
127.535
125.620
123.850
122.141
122.098
122.008
120.430
120.372
119.485
77.450
77.027
76.603
54.200
37.259
29.705
Cl
O
O
OH
NH
S
F
F
F
5b
75 MHz
CDCl3
f1 (ppm)

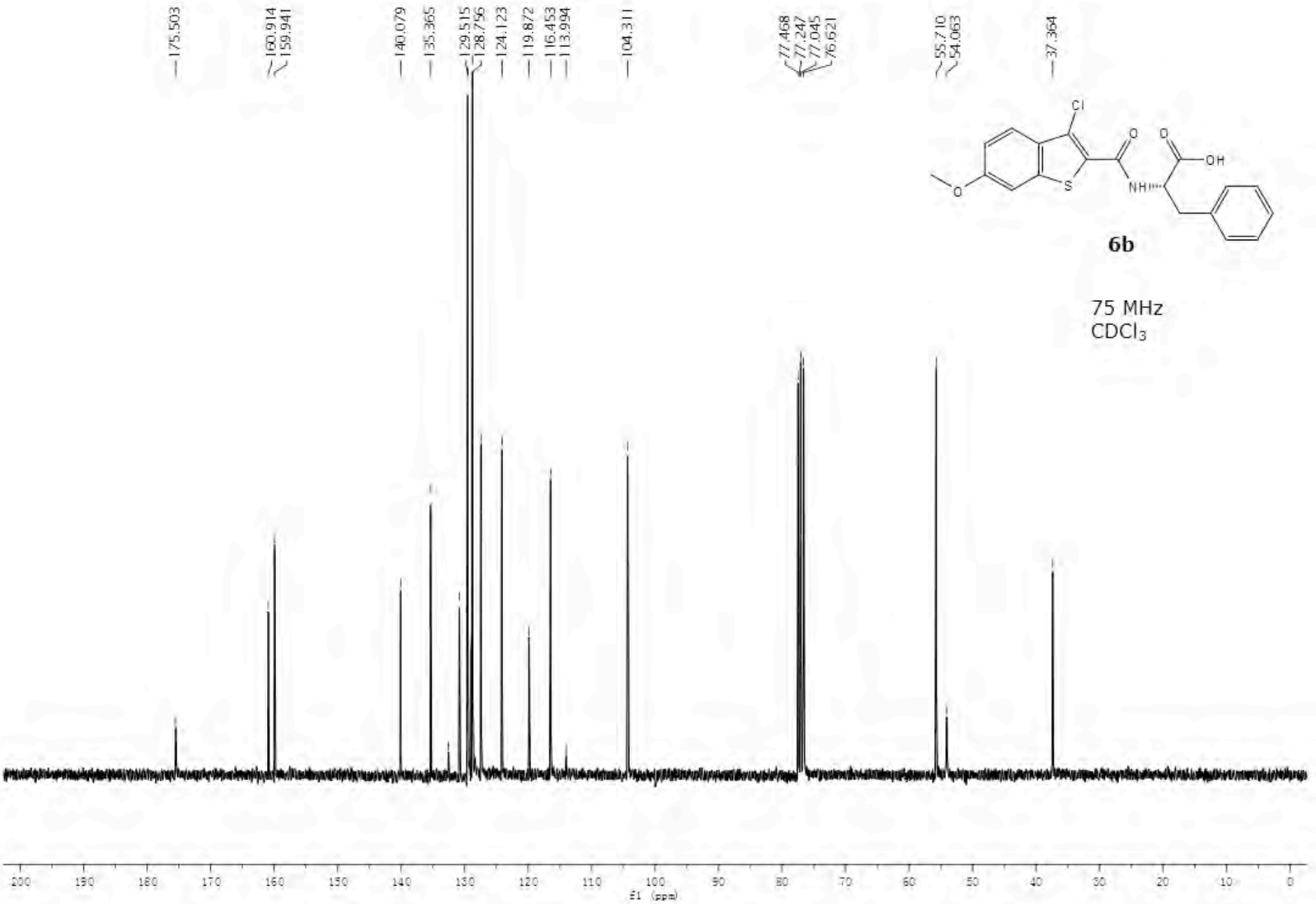

7.904
7.902
7.874
7.872
7.280
7.237
7.230
7.174
7.167
7.144
7.137
3.950
Cl
O
O
S
Cl
5-1
300 MHz
CDCl3
1.02
1.00
1.01
3.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

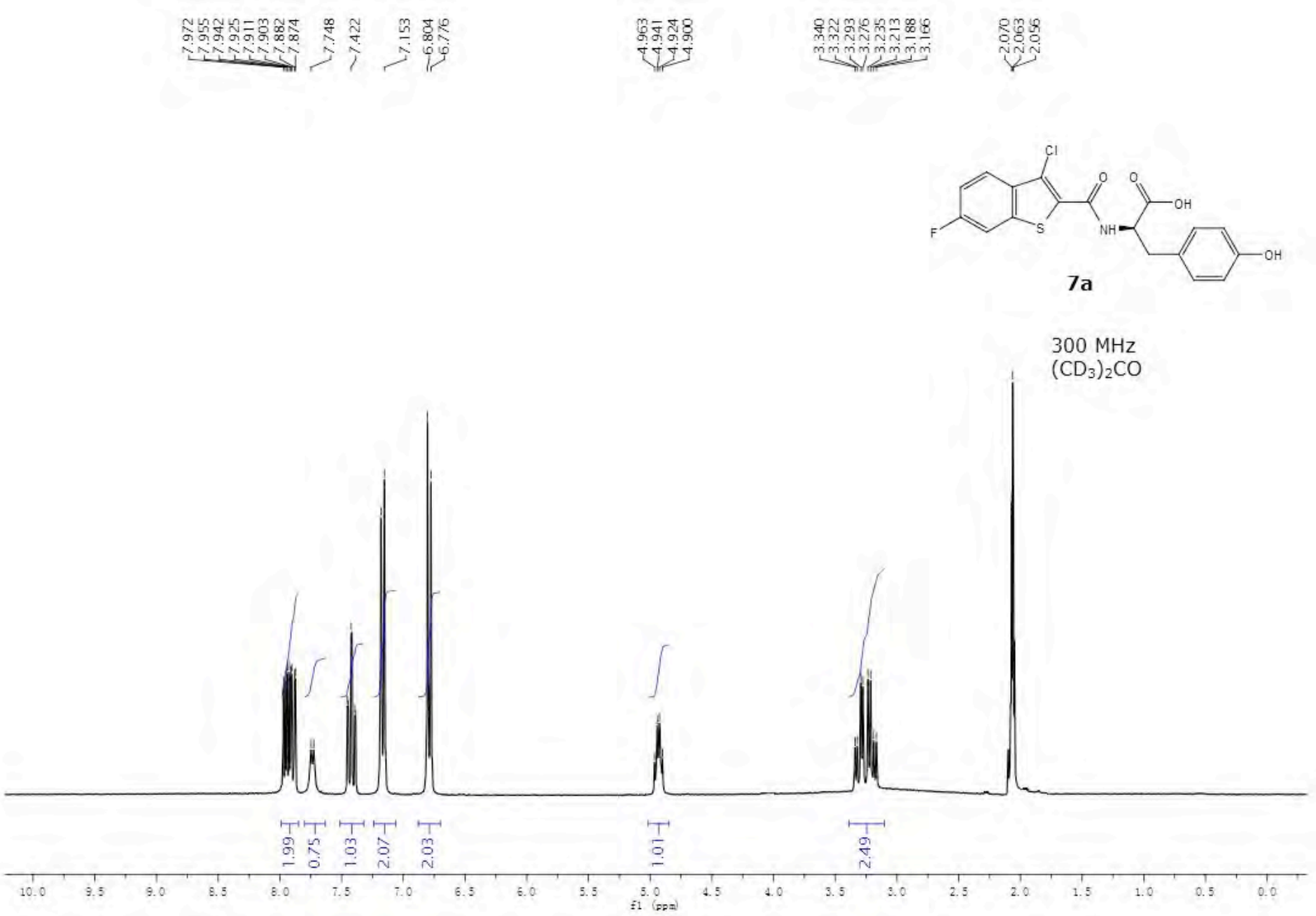

161.681
157.820
142.977
131.257
130.963
126.571
125.824
117.769
103.761
77.434
77.011
76.588
55.868
Cl
O
S
Cl
O
5-1
75 MHz
CDCl3
f1 (ppm)

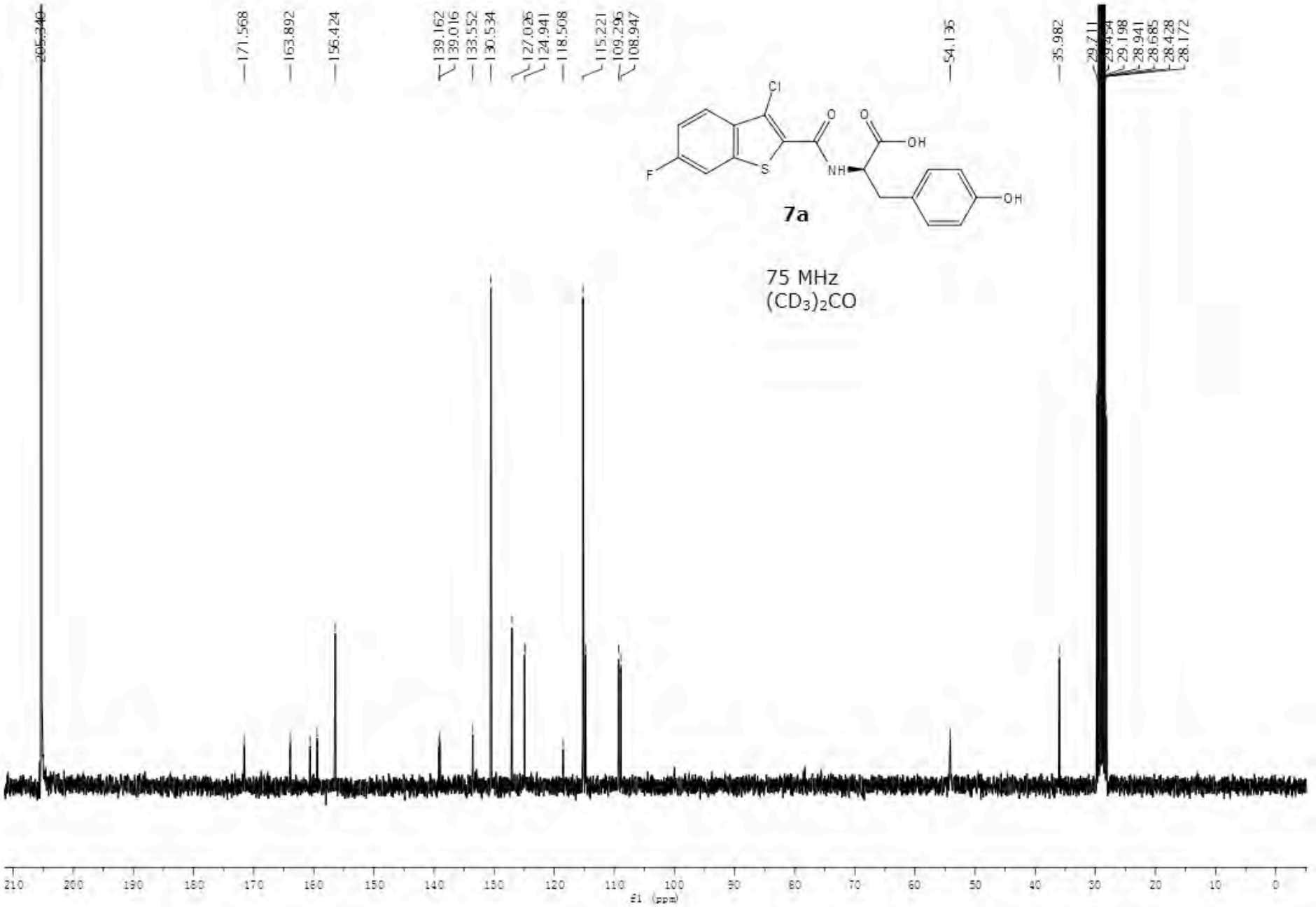

7.715
7.713
7.685
7.684
7.588
7.565
7.280
7.102
7.094
7.072
7.064
5.161
5.137
3.902
3.435
3.417
3.388
3.370
3.350
3.330
3.303
3.284
Cl
O
O
OH
NH
S
O
6a
300 MHz
CDCl3
1.09
1.08
6.80
1.02
1.00
3.09
2.06
f1 (ppm)

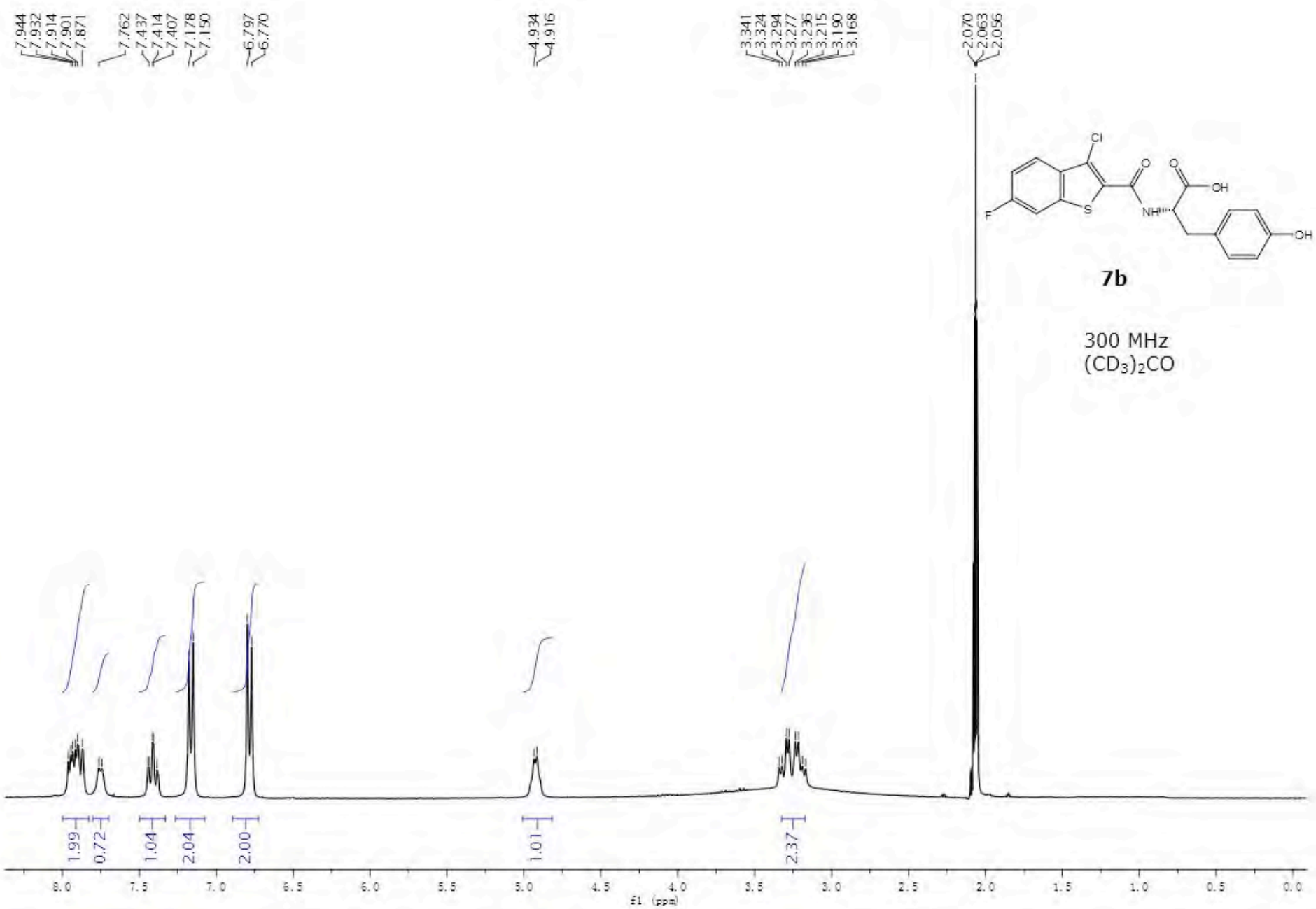

175.467
160.917
159.955
140.094
135.341
129.505
128.768
124.138
119.849
116.465
114.000
104.319
77.451
77.231
77.028
76.605
55.714
54.042
37.352
Cl
O
O
OH
NH
S
O
6a
75 MHz
CDCl3
f1 (ppm)

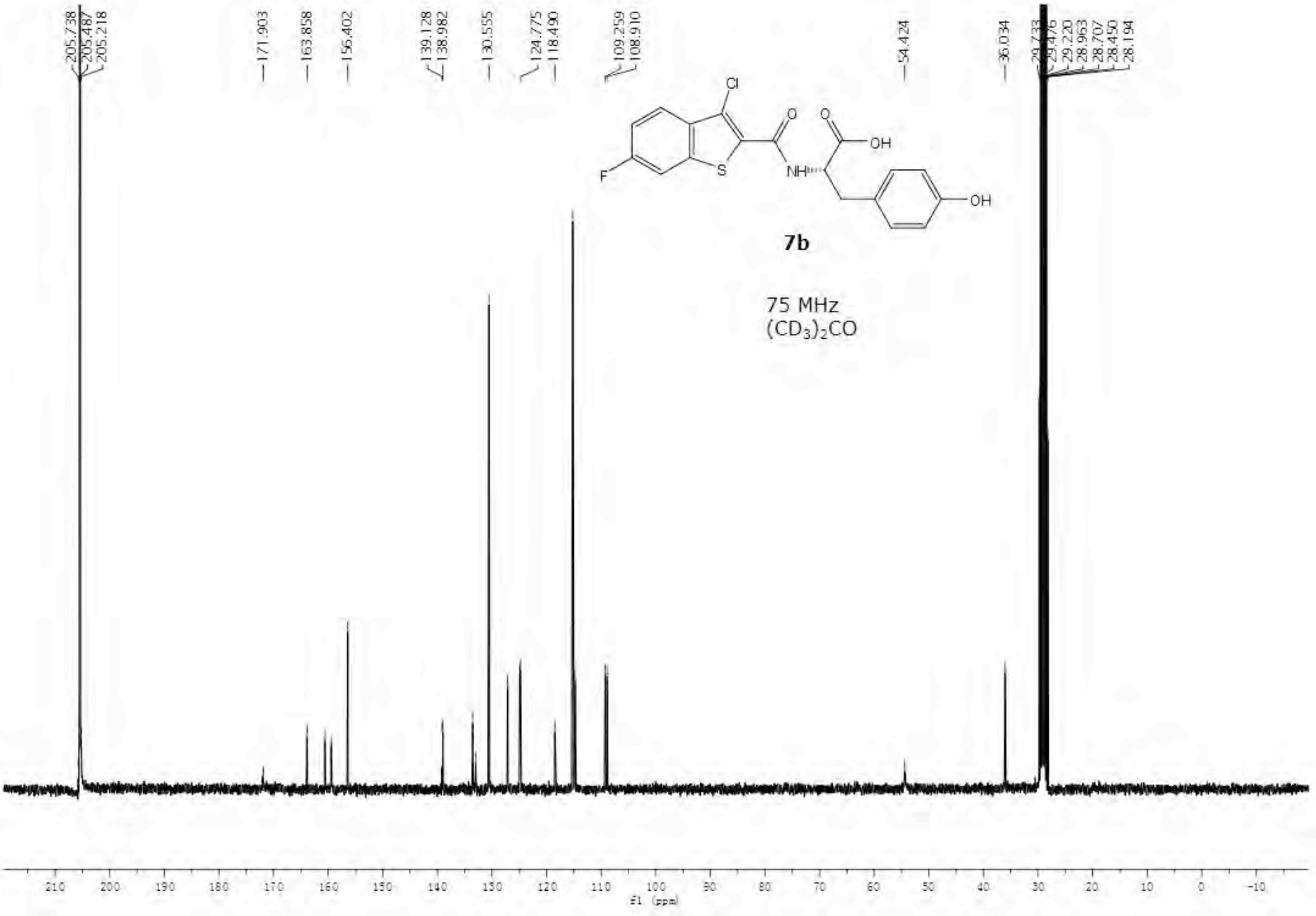

8.791
7.702
7.672
7.604
7.580
7.286
7.280
7.093
7.085
7.063
7.055
5.182
5.163
5.140
5.121
3.895
3.436
3.417
3.389
3.371
3.350
3.330
3.303
3.284
Cl
O
O
OH
NH
S
O
6b
300 MHz
CDCl3
1.10
1.04
0.96
6.68
1.08
1.00
3.01
2.07
f1 (ppm)

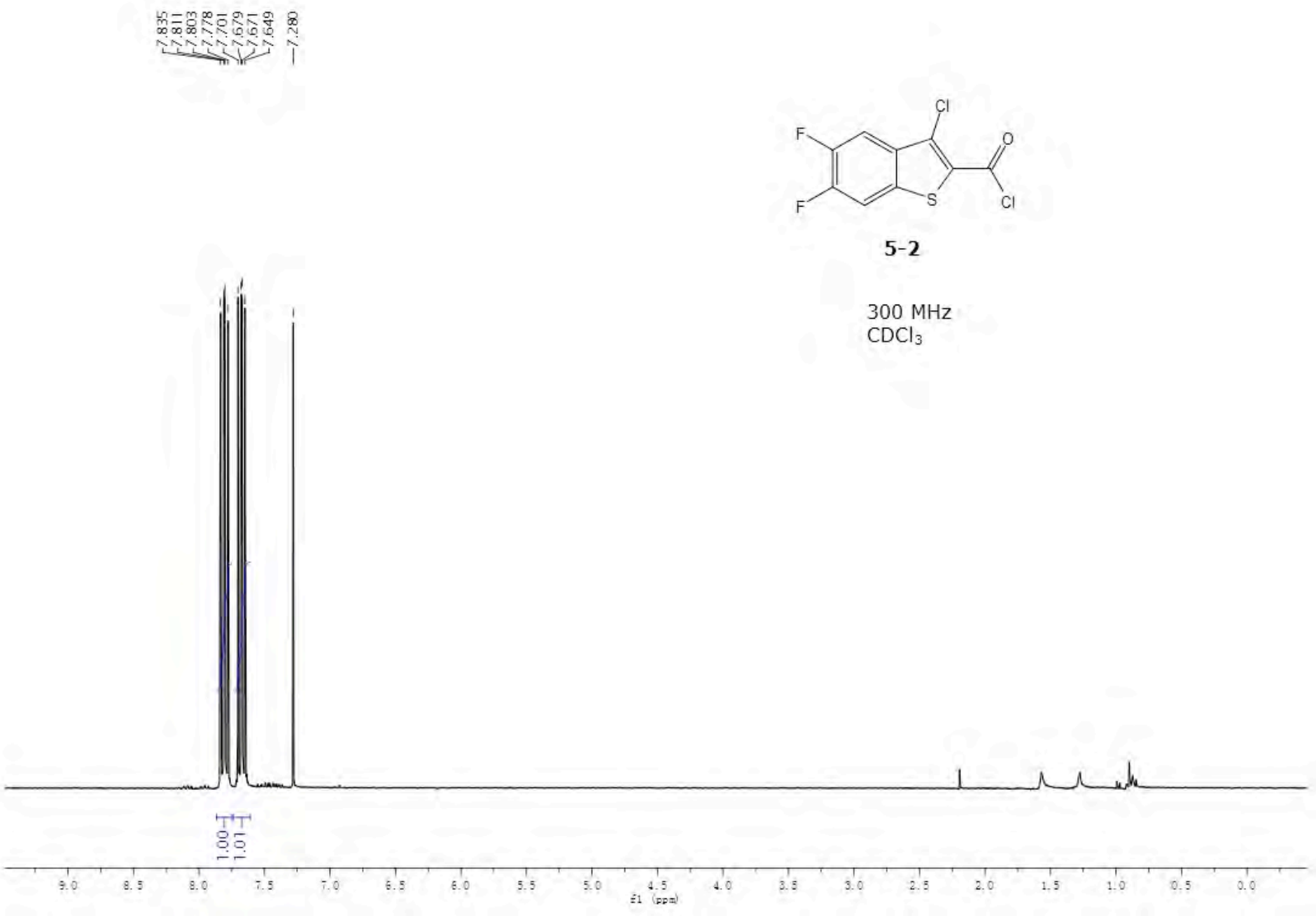

175.503
160.914
159.941
140.079
135.365
129.515
128.796
124.123
119.872
116.453
113.994
104.311
77.468
77.247
77.045
76.621
55.710
54.063
37.364
Cl
O
O
OH
NH
S
O
6b
75 MHz
CDCl3
f1 (ppm)

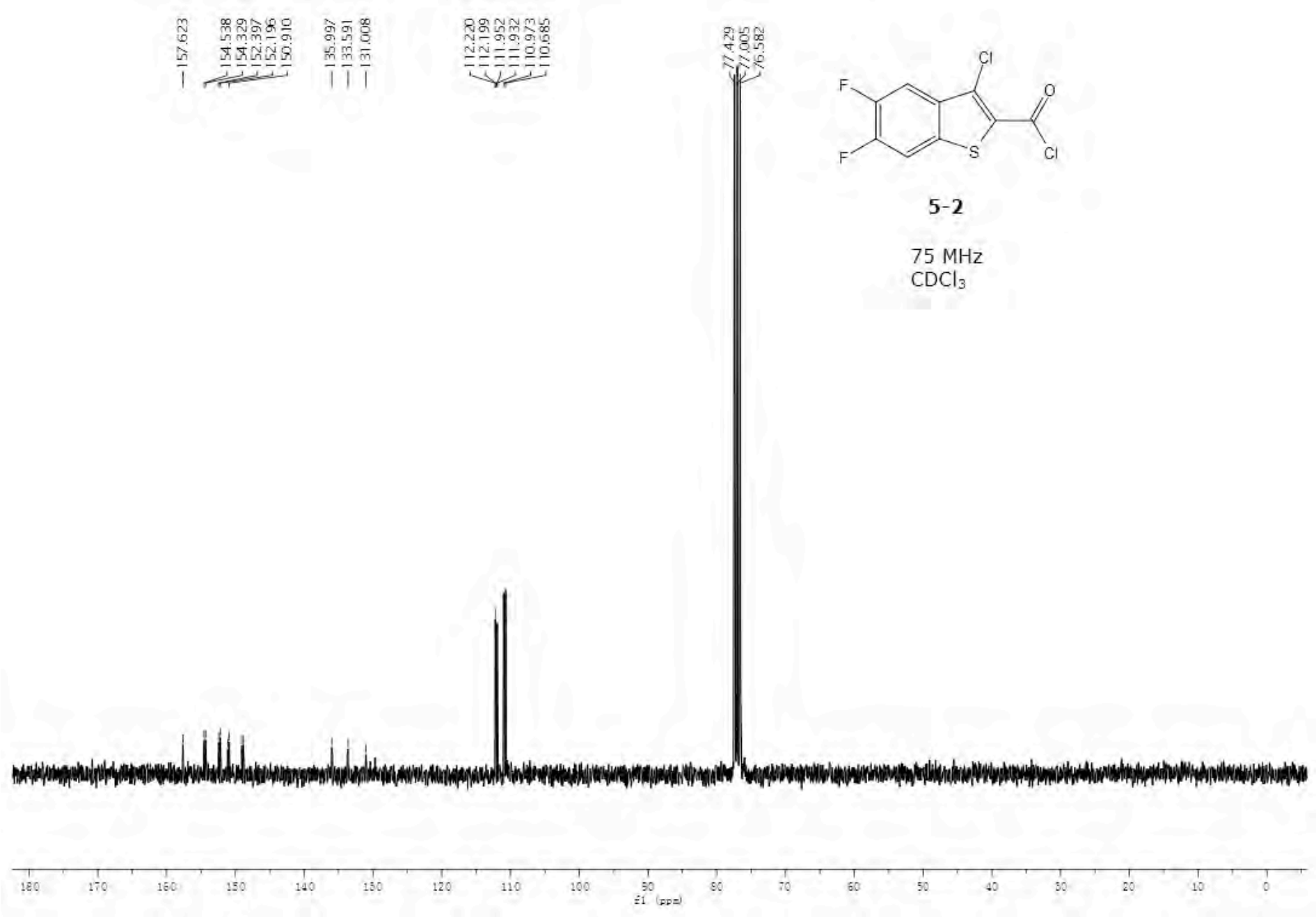

7.972
7.955
7.942
7.925
7.911
7.903
7.882
7.874
7.748
7.422
7.153
6.804
6.776
4.963
4.941
4.924
4.900
3.340
3.322
3.293
3.276
3.235
3.213
3.188
3.166
2.070
2.063
2.056
Cl
O
O
OH
F
S
NH
OH
7a
300 MHz
(CD3)2CO
1.99
0.75
1.03
2.07
2.03
1.01
2.49
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

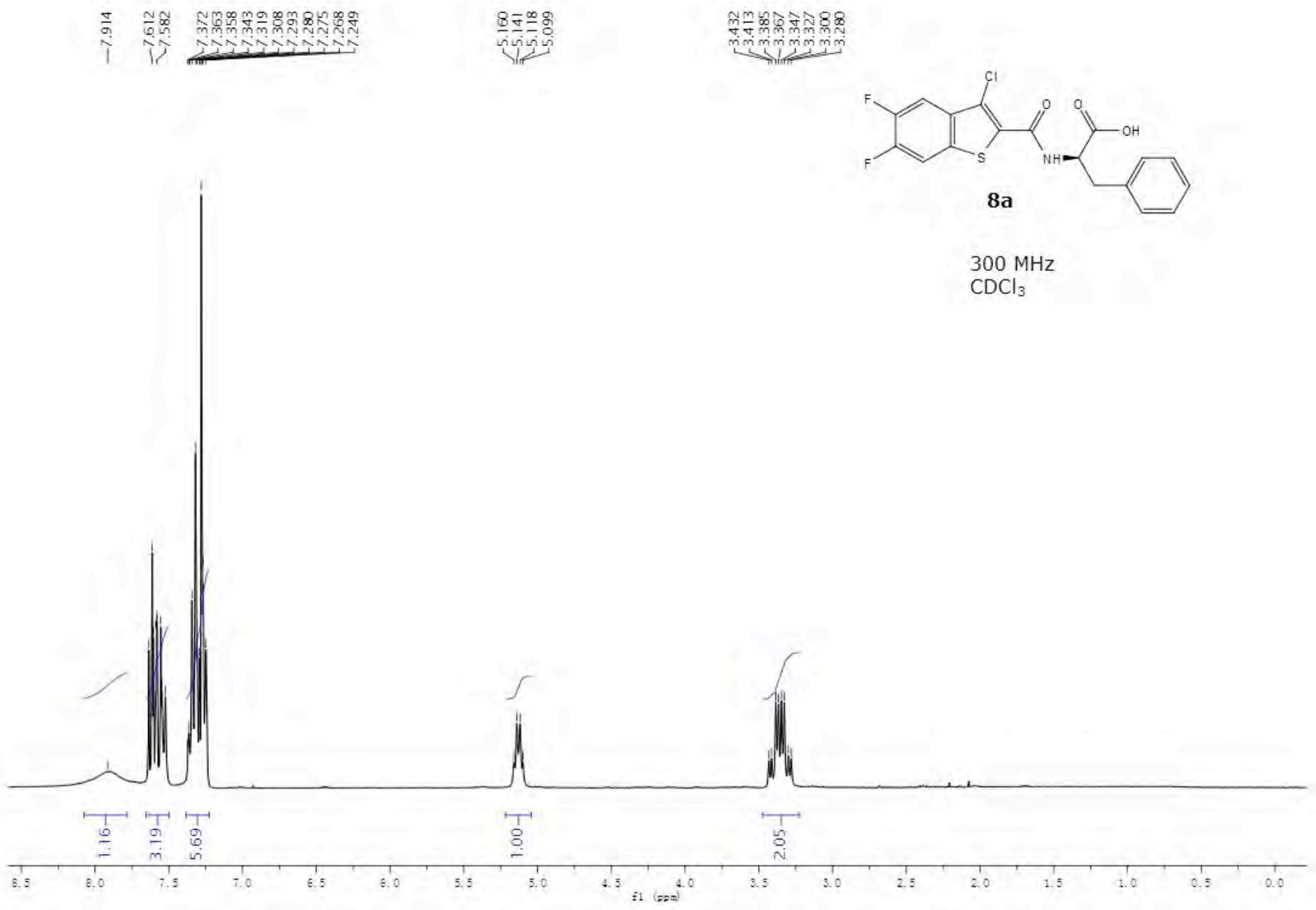

205.340
171.568
163.892
156.424
139.162
139.016
133.552
130.534
127.026
124.941
118.508
115.221
109.296
108.947
54.136
35.982
29.711
29.454
29.198
28.941
28.685
28.428
28.172
Cl
O
O
OH
F
S
NH
OH
7a
75 MHz
(CD3)2CO
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

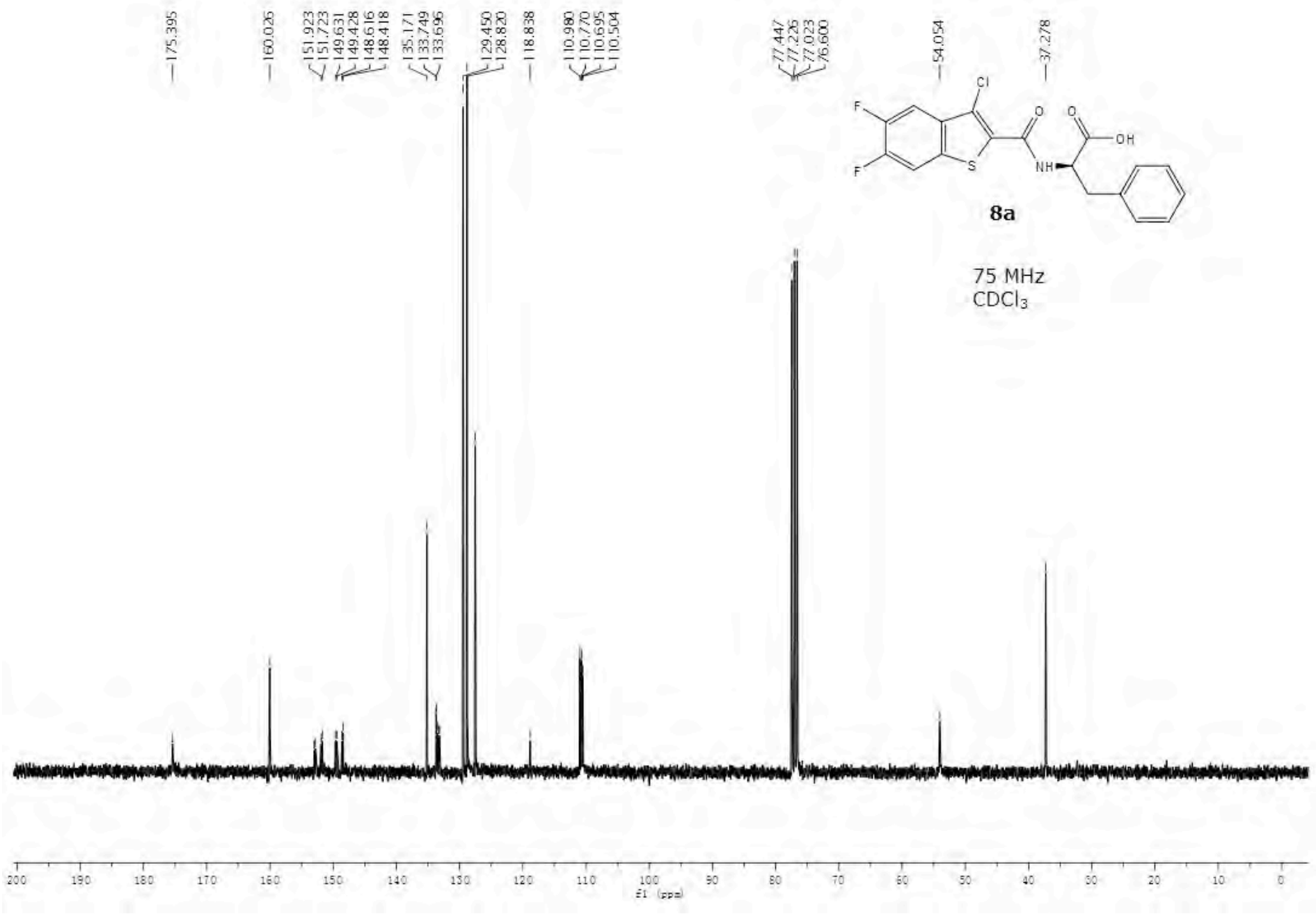

7.944
7.932
7.914
7.901
7.871
7.762
7.437
7.414
7.407
7.178
7.150
6.797
6.770
4.934
4.916
3.341
3.324
3.294
3.277
3.236
3.215
3.190
3.168
2.070
2.063
2.056
Cl
O
O
OH
F
S
NH
OH
7b
300 MHz
(CD3)2CO
1.99
0.72
1.04
2.04
2.00
1.01
2.37
f1 (ppm)

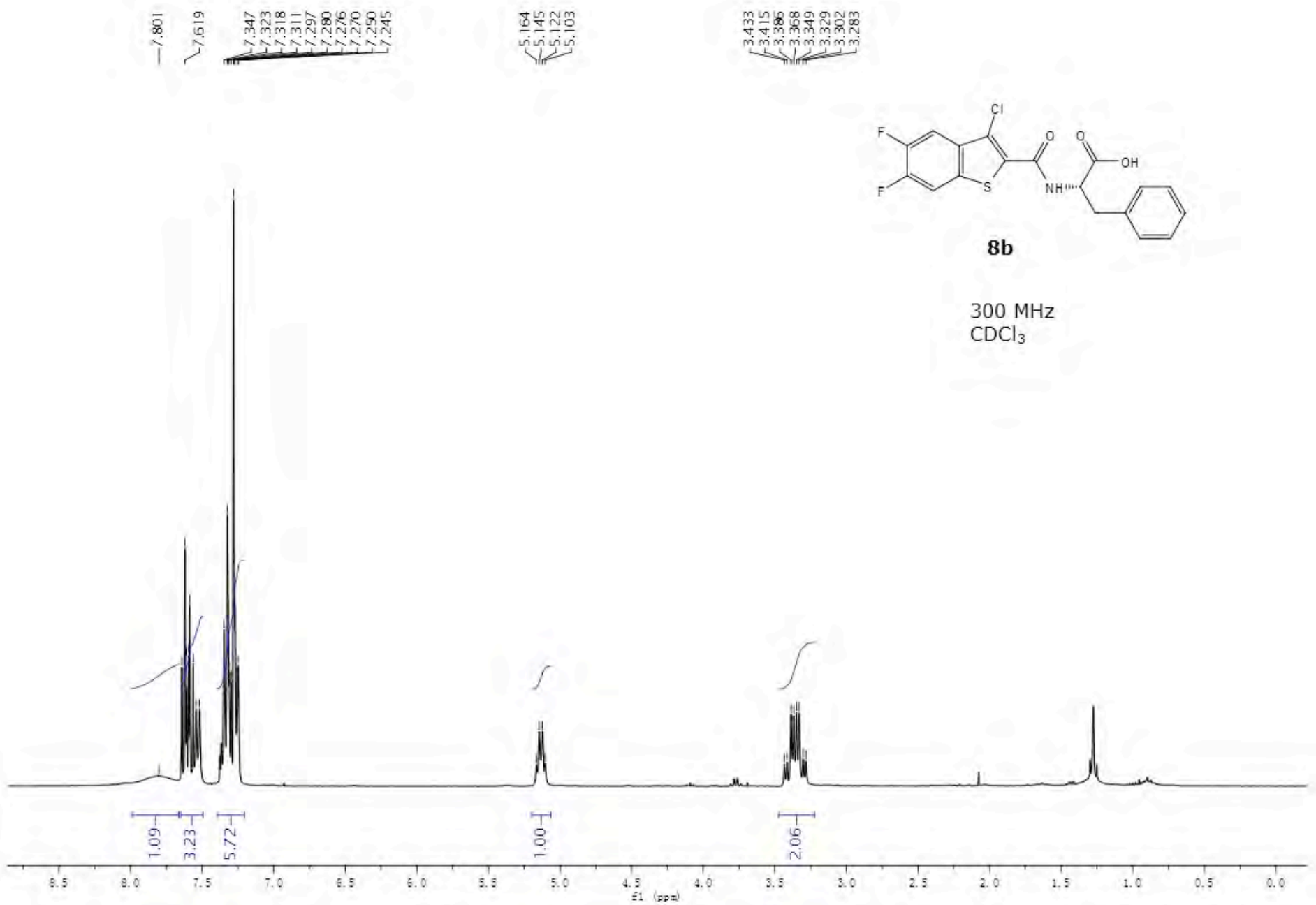

205.738
205.487
205.218
171.903
163.858
156.402
139.128
138.982
130.555
124.775
118.490
109.259
108.910
54.424
36.034
29.733
29.476
29.220
28.963
28.707
28.450
28.194
Cl
O
O
OH
F
S
NH
OH
7b
75 MHz
(CD3)2CO
f1 (ppm)

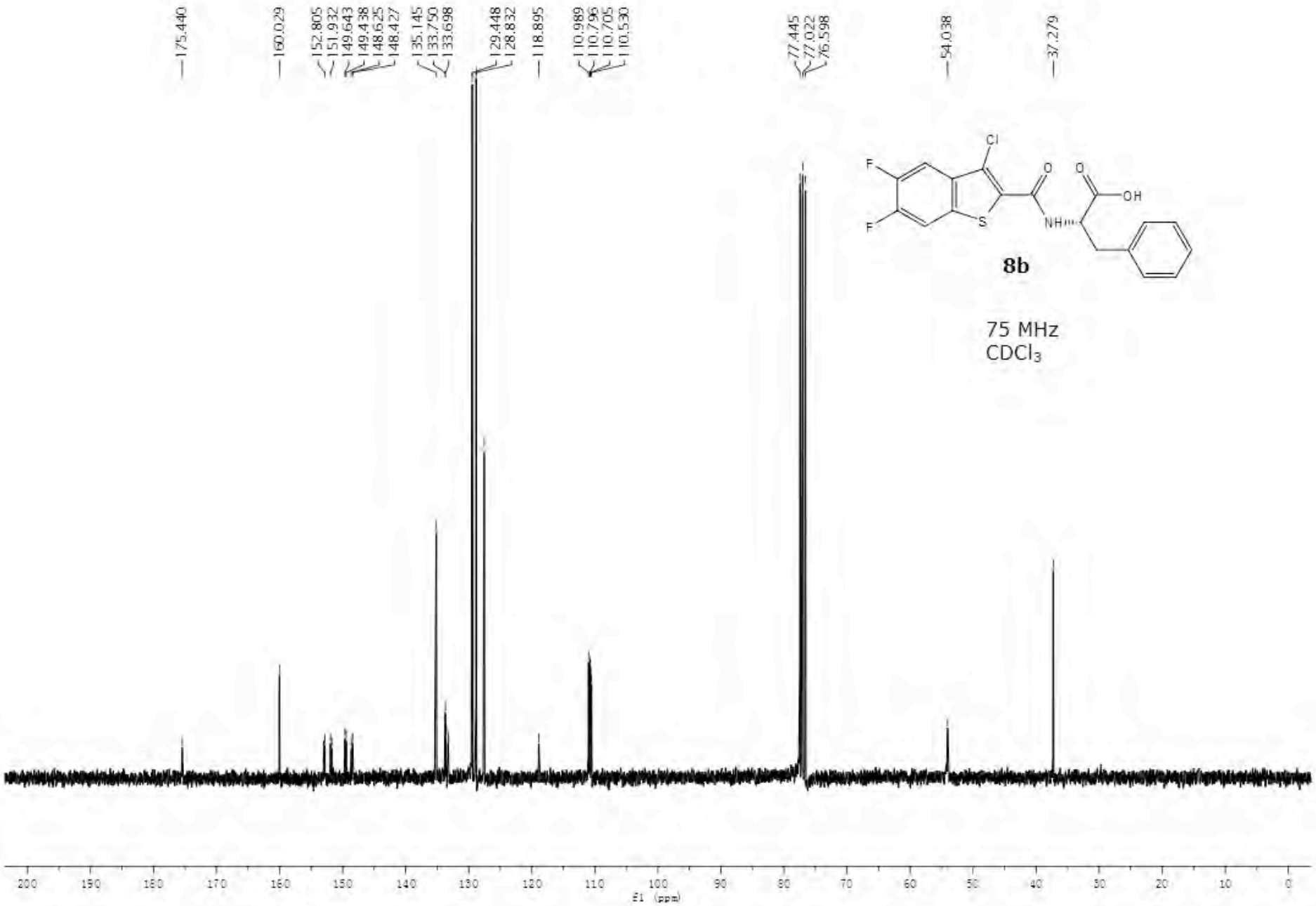

7.835
7.811
7.803
7.778
7.701
7.679
7.671
7.649
7.280
Cl
F
O
F
S
Cl
5-2
300 MHz
CDCl3
1.00
1.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

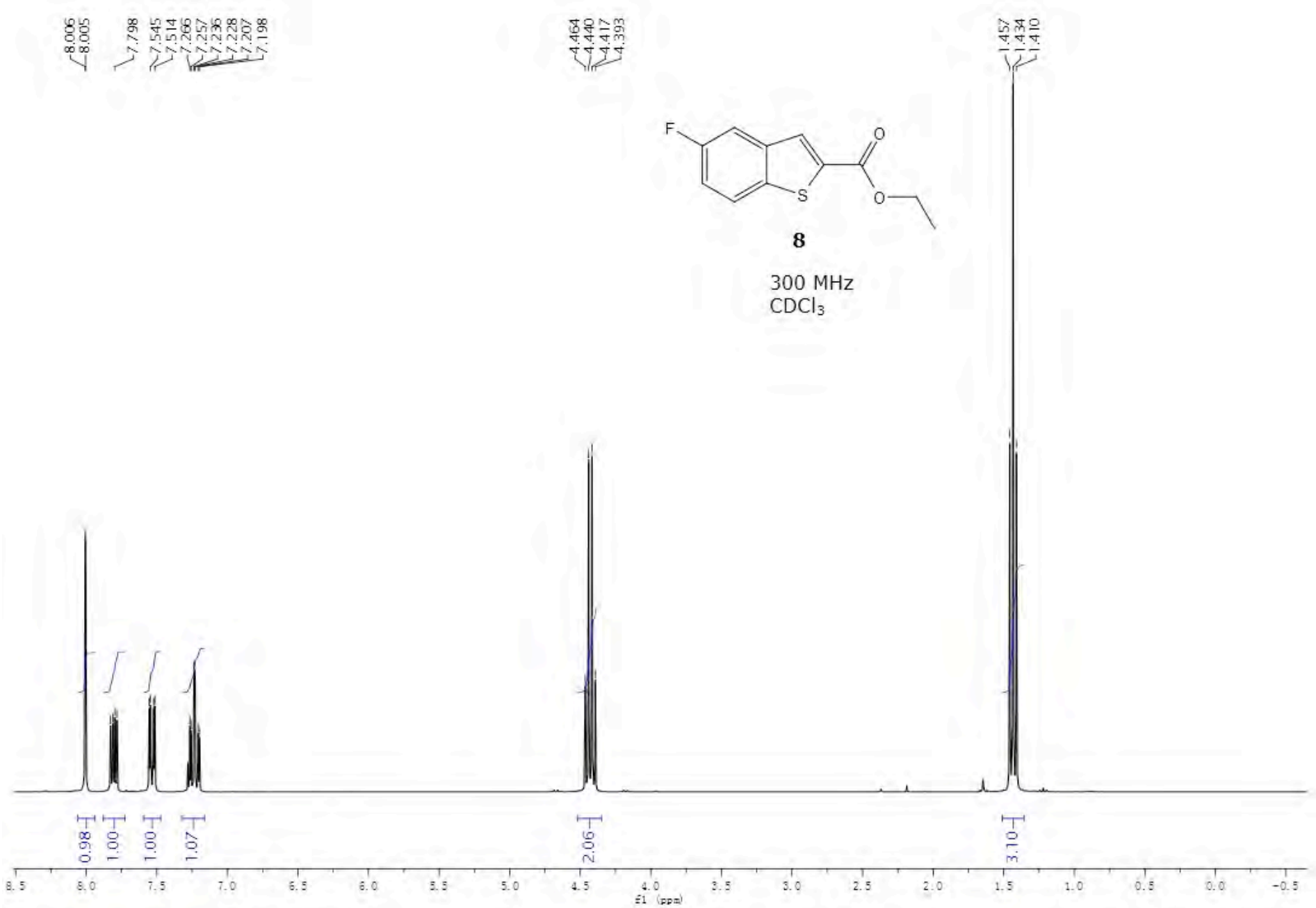

157.623
154.538
154.329
152.397
152.196
150.910
135.997
133.591
131.008
112.220
112.199
111.952
111.932
110.973
110.685
77.429
77.005
76.582
Cl
F
F
O
S
Cl
5-2
75 MHz
CDCl3
f1 (ppm)

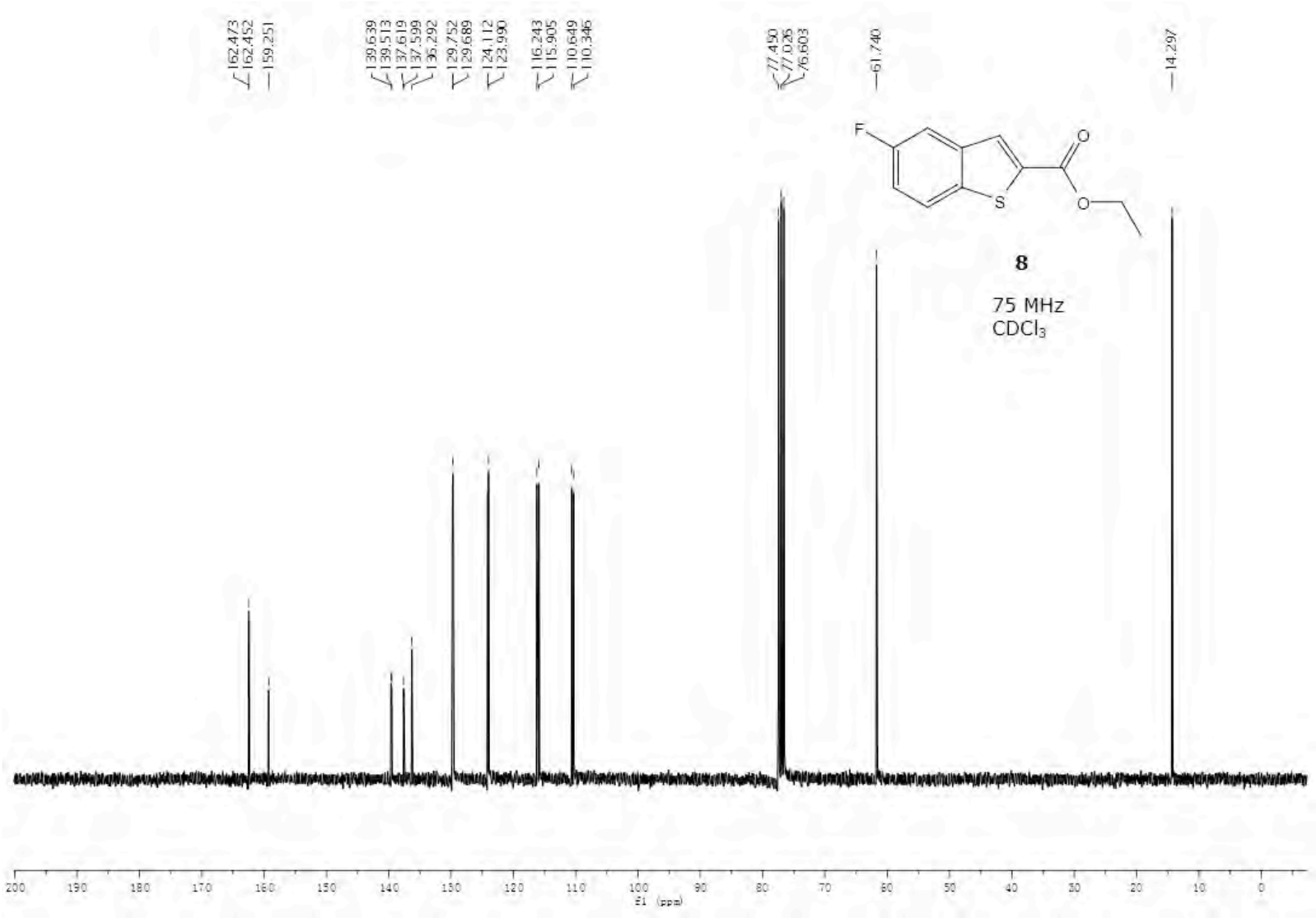

7.914
7.612
7.582
7.372
7.363
7.358
7.343
7.319
7.308
7.293
7.280
7.275
7.268
7.249
5.160
5.141
5.118
5.099
3.432
3.413
3.385
3.367
3.347
3.327
3.300
3.280
Cl
F
F
S
O
O
OH
NH
8a
300 MHz
CDCl3
1.16
3.19
5.69
1.00
2.05
f1 (ppm)

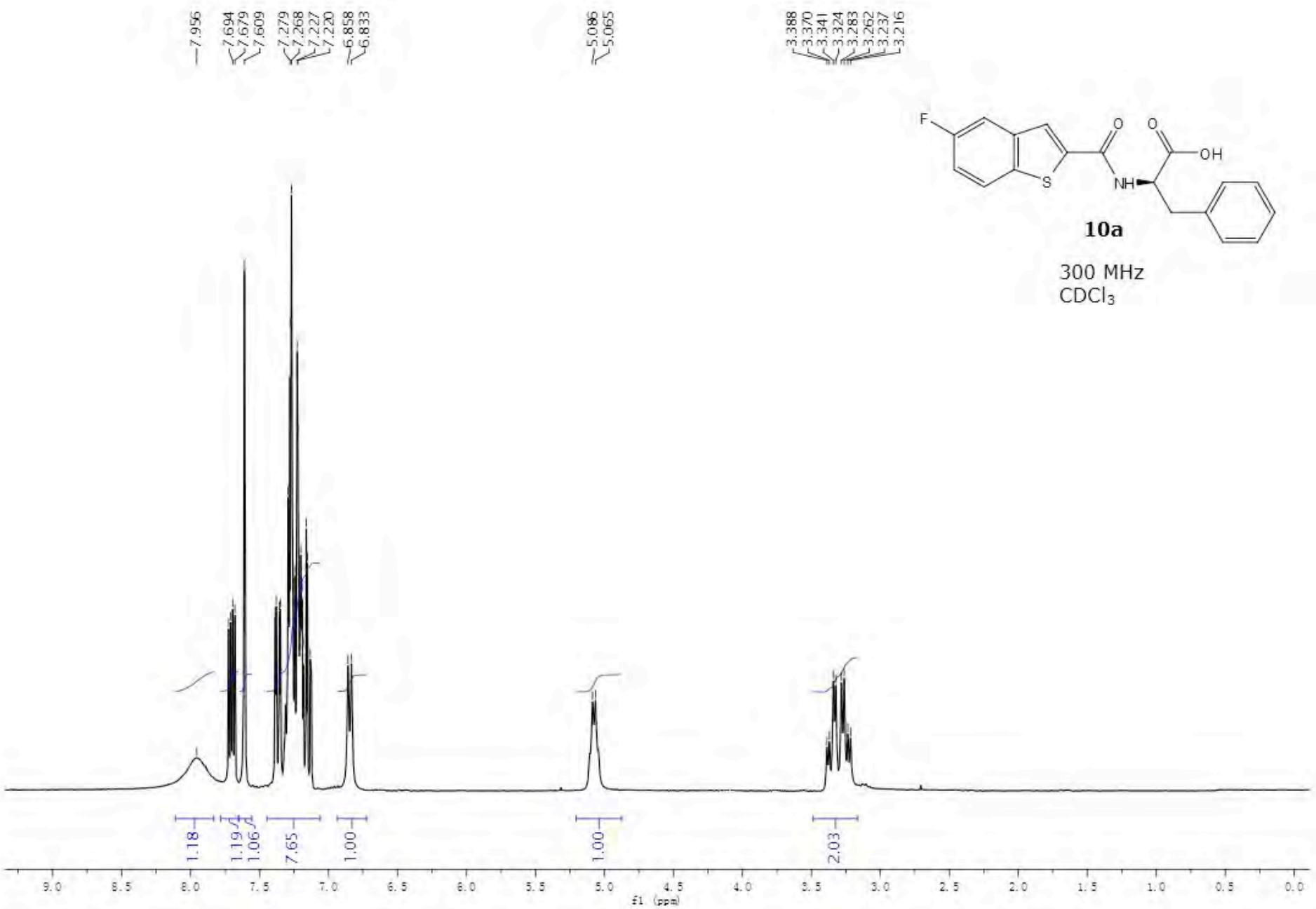

175.395
160.026
151.923
151.723
149.631
149.428
148.616
148.418
135.171
133.749
133.696
129.450
128.820
118.838
110.980
110.770
110.695
110.504
77.447
77.225
77.023
76.600
54.054
37.278
Cl
F
F
O
O
OH
S
NH
8a
75 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

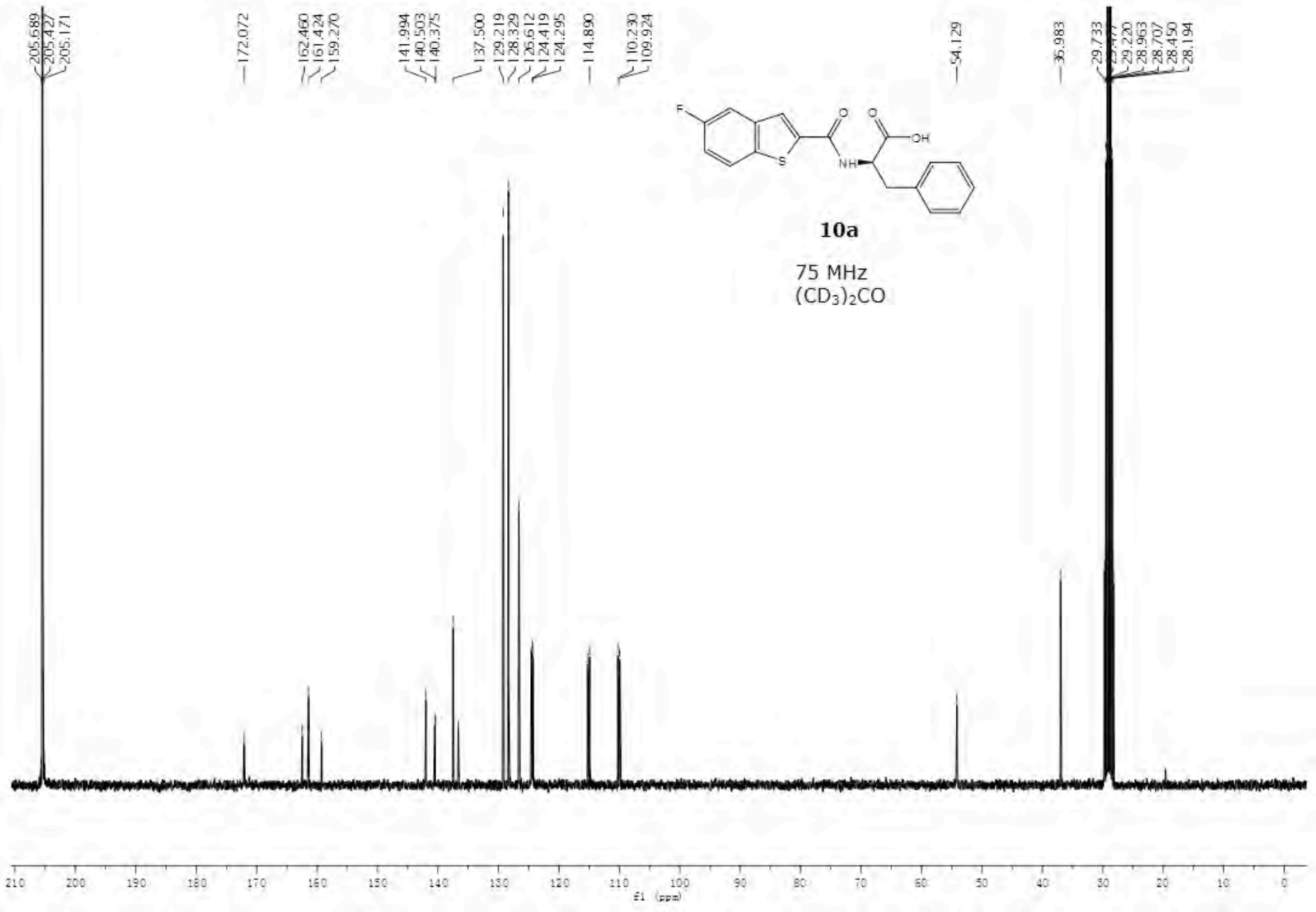

7.801
7.619
7.347
7.323
7.318
7.311
7.297
7.280
7.276
7.270
7.250
7.245
5.164
5.145
5.122
5.103
3.433
3.415
3.386
3.368
3.349
3.329
3.302
3.283
Cl
F
F
S
O
O
OH
NH
8b
300 MHz
CDCl3
1.09
3.23
5.72
1.00
2.06
f1 (ppm)

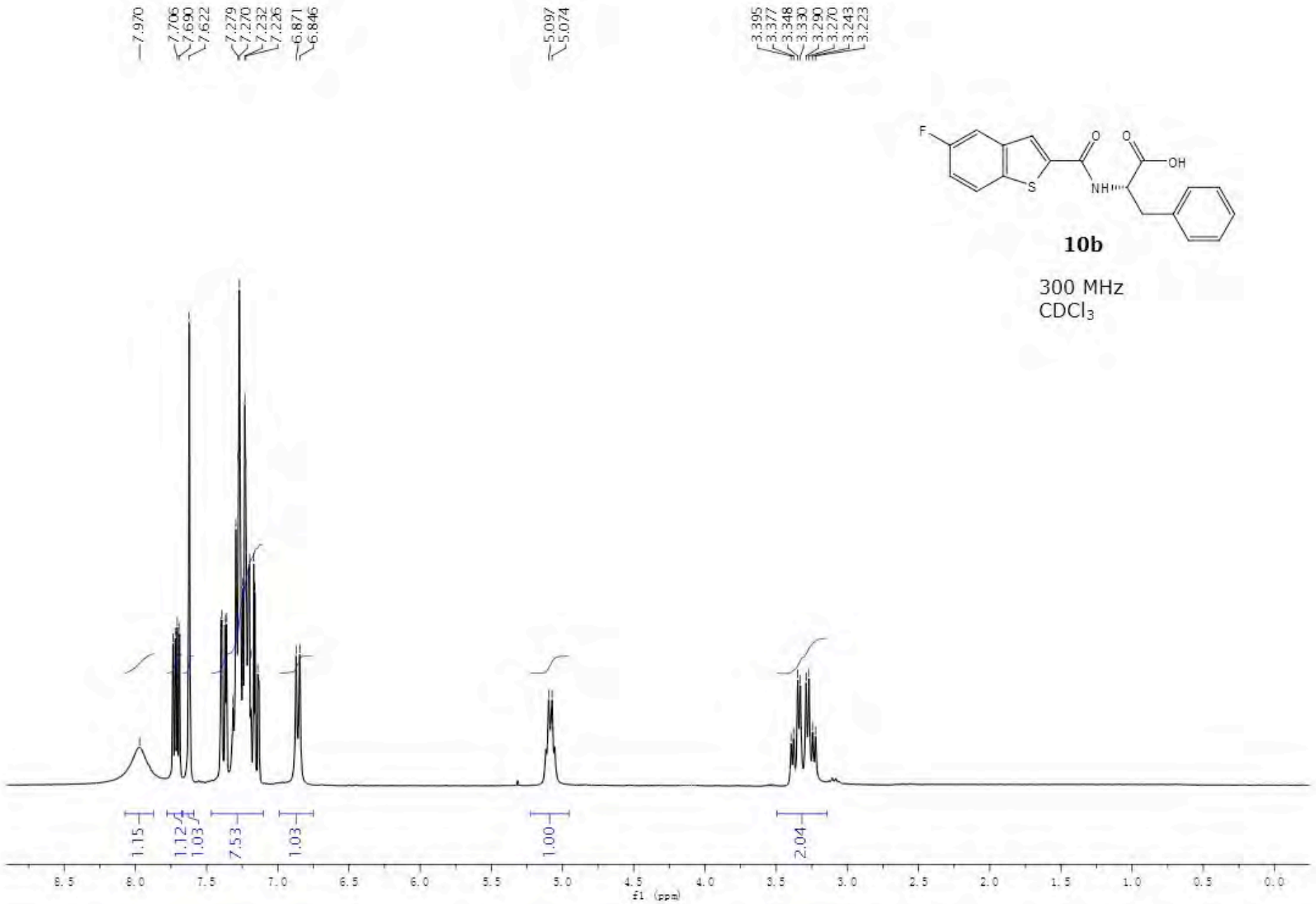

175.440
160.029
152.805
151.932
149.643
149.438
148.625
148.427
135.145
133.790
133.698
129.448
128.832
118.895
110.989
110.796
110.705
110.530
77.445
77.022
76.598
54.038
37.279
Cl
F
F
O
O
OH
NH
S
8b
75 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

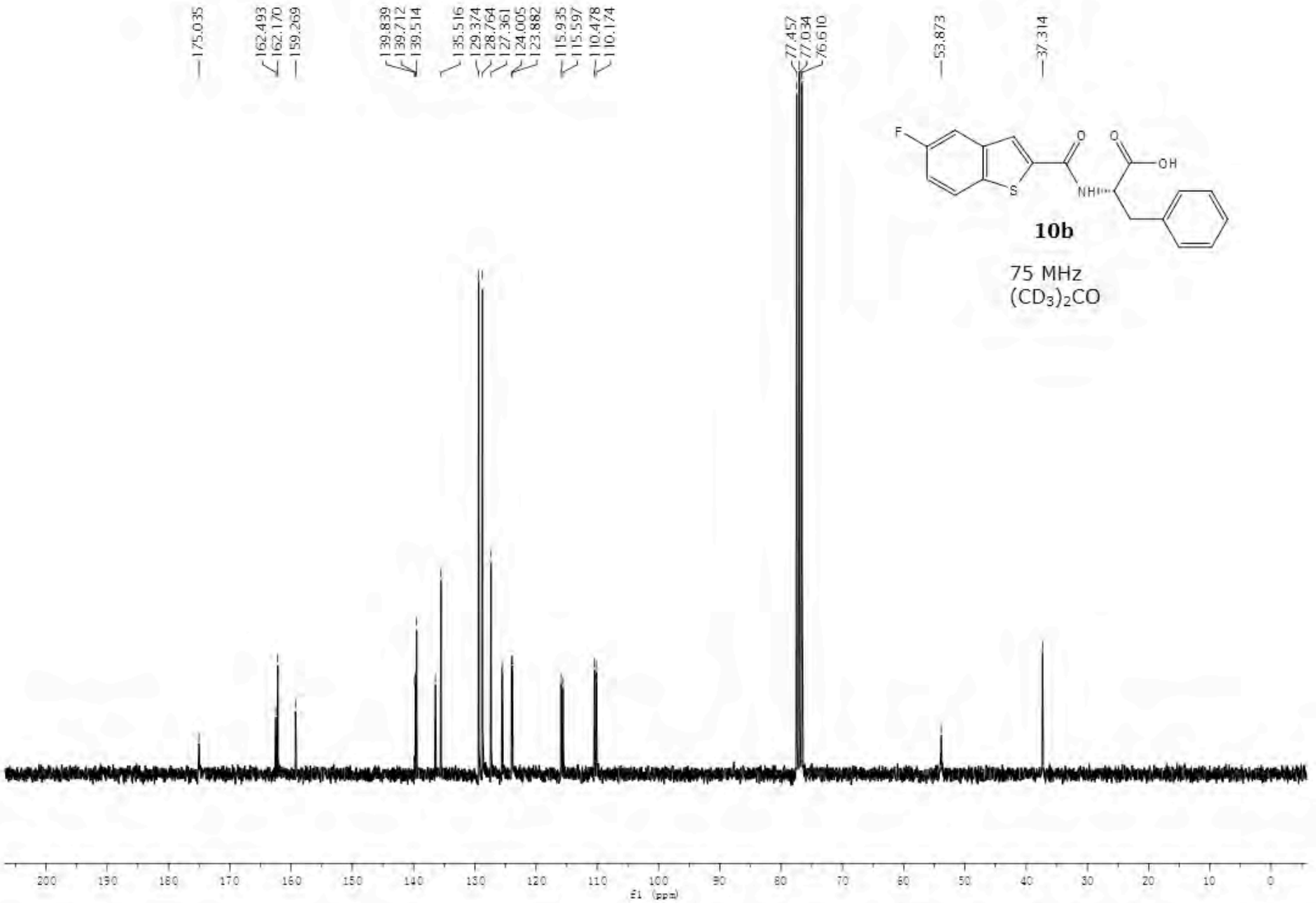

8.006
8.005
7.798
7.545
7.514
7.266
7.257
7.236
7.228
7.207
7.198
4.464
4.440
4.417
4.393
1.457
1.434
1.410
F
O
S
O
8
300 MHz
CDCl3
0.98
1.00
1.00
1.07
2.06
3.10
f1 (ppm)

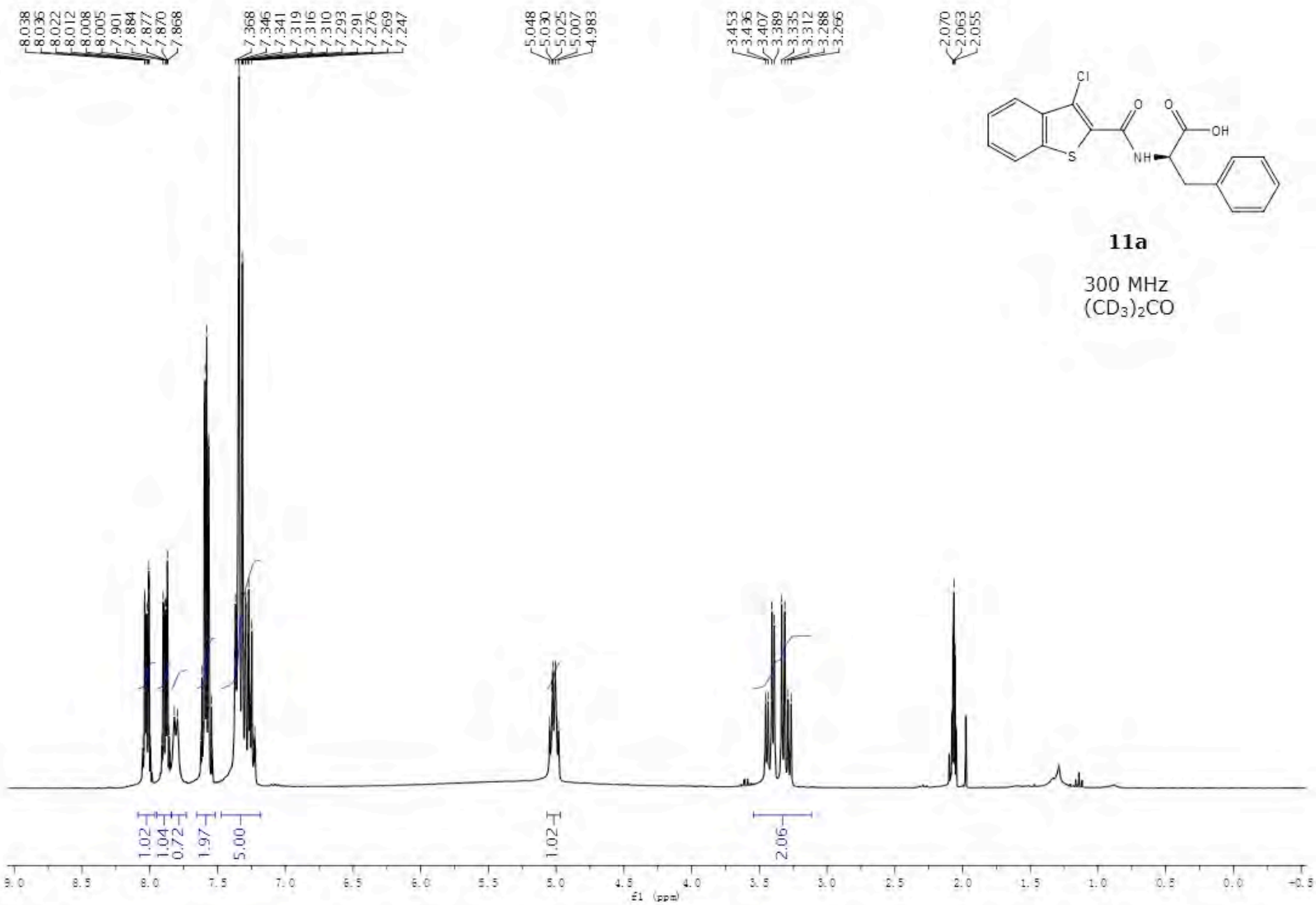

162.473
162.452
159.251
139.639
139.513
137.619
137.599
136.292
129.752
129.689
124.112
123.990
116.243
115.905
110.649
110.346
77.450
77.025
76.603
61.740
14.297
F
S
O
O
8
75 MHz
CDCl3
f1 (ppm)

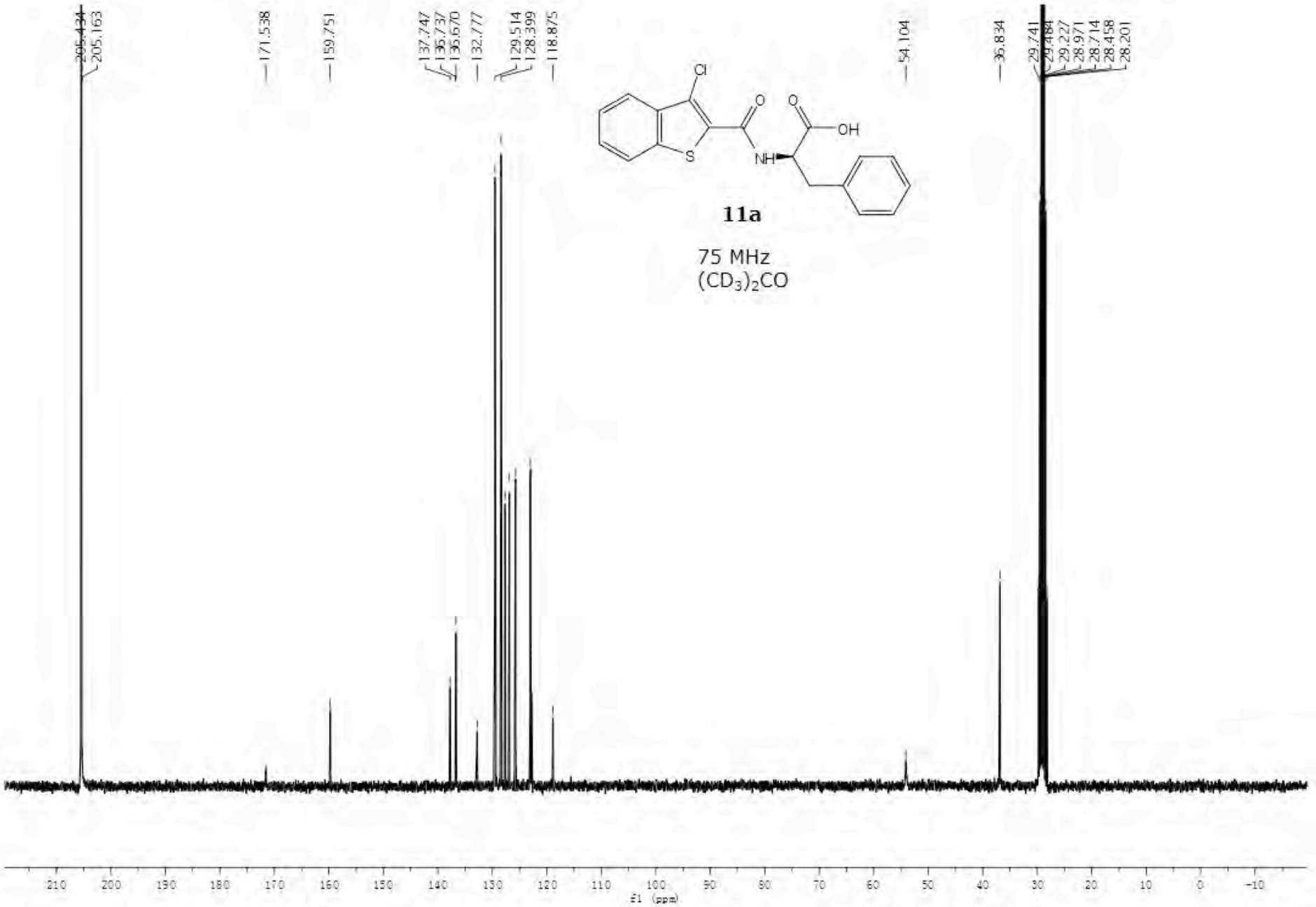

7.956
7.694
7.679
7.609
7.279
7.268
7.227
7.220
6.858
6.833
5.085
5.065
3.388
3.370
3.341
3.324
3.283
3.262
3.237
3.216
F
S
NH
O
O
OH
10a
300 MHz
CDCl3
1.18
1.19
1.06
7.65
1.00
1.00
2.03
f1 (ppm)

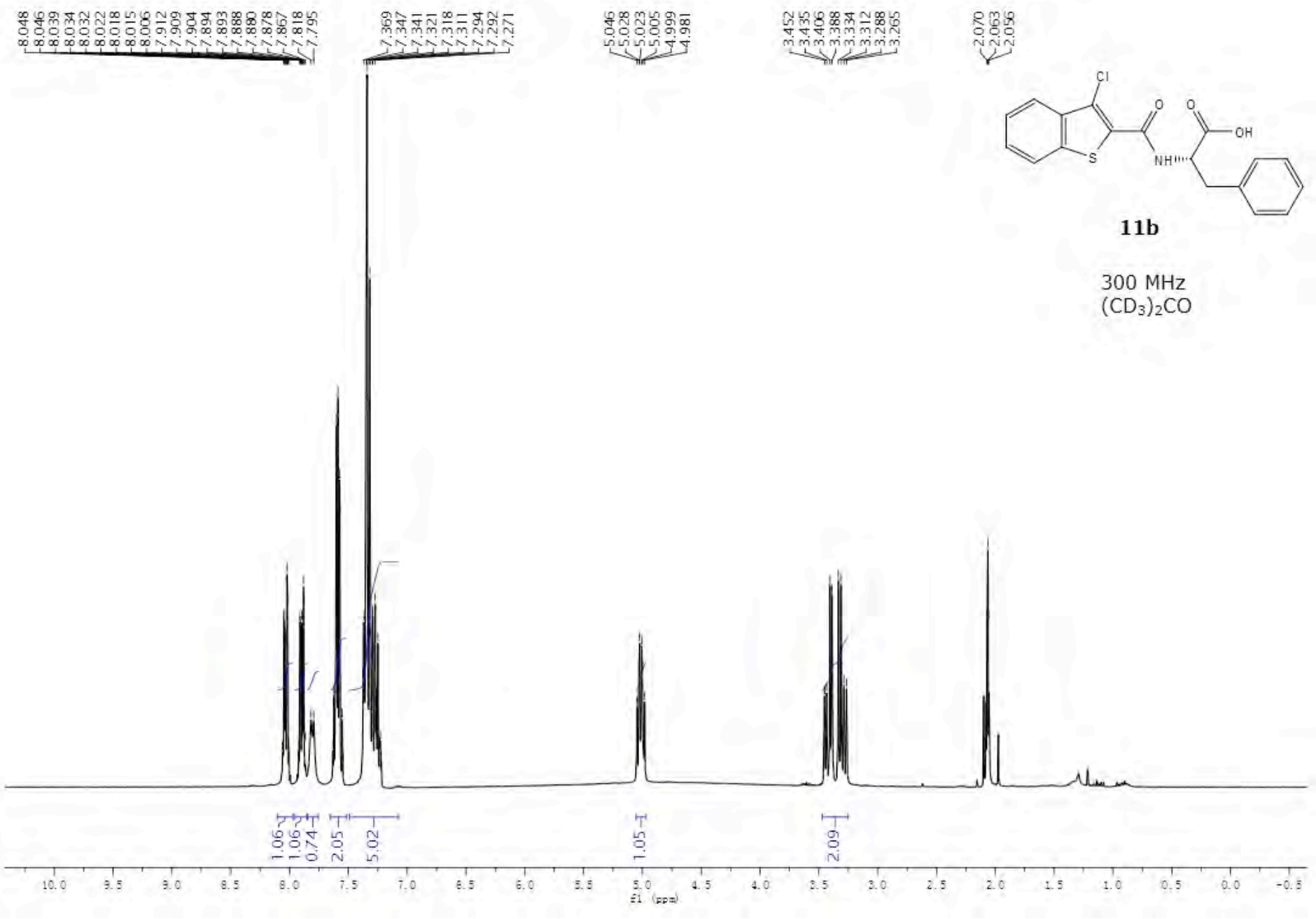

205.689
205.427
205.171
172.072
162.460
161.424
159.270
141.994
140.503
140.375
137.500
129.219
128.329
125.612
124.419
124.295
114.890
110.230
109.924
54.129
36.983
29.733
29.220
28.963
28.707
28.450
28.194
F
S
NH
O
O
OH
10a
75 MHz
(CD3)2CO
f1 (ppm)

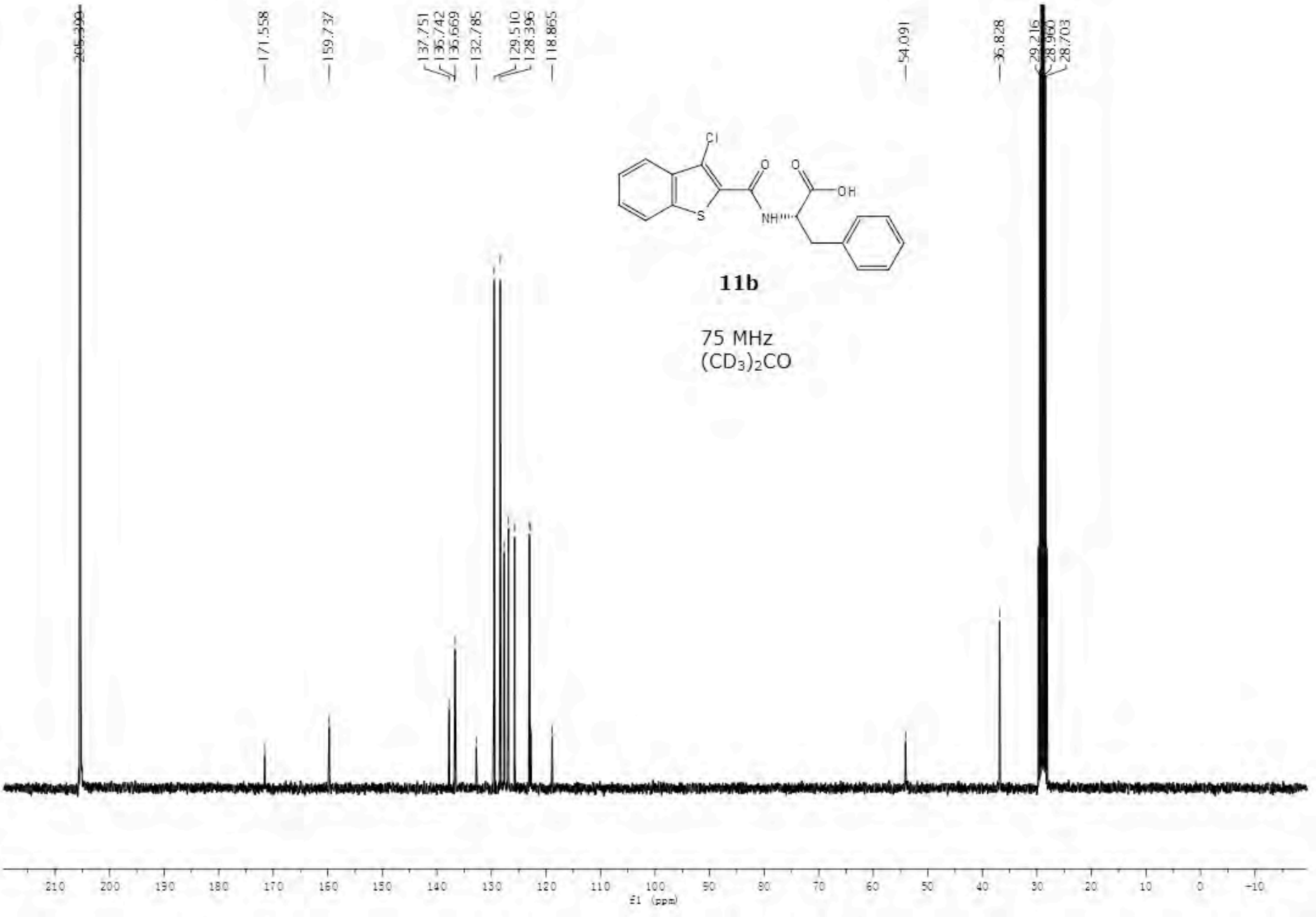

7.970
7.706
7.690
7.622
7.279
7.270
7.232
7.226
6.871
6.846
5.097
5.074
3.395
3.377
3.348
3.330
3.290
3.270
3.243
3.223
F
S
O
NH
O
OH
10b
300 MHz
CDCl3
1.15
1.12
1.03
7.53
1.03
1.00
2.04
f1 (ppm)

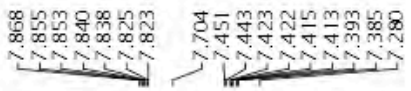

175.035
162.493
162.170
159.269
139.839
139.712
139.514
135.516
129.374
128.764
127.361
124.005
123.882
115.935
115.597
110.478
110.174
77.457
77.034
76.610
53.873
37.314
F
S
O
O
OH
NH
10b
75 MHz
(CD3)2CO
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

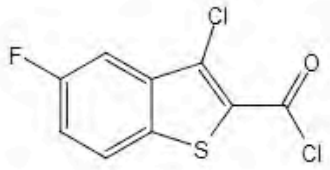

8.038
8.035
8.022
8.012
8.008
8.005
7.901
7.884
7.877
7.870
7.868
7.368
7.346
7.341
7.319
7.316
7.310
7.293
7.291
7.276
7.269
7.247
5.048
5.030
5.025
5.007
4.983
3.453
3.436
3.407
3.389
3.335
3.312
3.288
3.266
2.070
2.063
2.055
Cl
O
O
OH
NH
S
11a
300 MHz
(CD3)2CO
1.02
1.04
0.72
1.97
5.00
1.02
2.06
f1 (ppm)


205.434
205.163
171.538
159.751
137.747
135.737
135.670
132.777
129.514
128.399
118.875
54.104
36.834
29.741
29.484
29.227
28.971
28.714
28.458
28.201
Cl
O
O
OH
S
NH
11a
75 MHz
(CD3)2CO
f1 (ppm)


8.048
8.046
8.039
8.034
8.032
8.022
8.018
8.015
8.006
7.912
7.909
7.904
7.894
7.893
7.888
7.880
7.878
7.867
7.818
7.795
7.369
7.347
7.341
7.321
7.318
7.311
7.294
7.292
7.271
5.046
5.028
5.023
5.005
4.999
4.981
3.452
3.435
3.406
3.388
3.334
3.312
3.288
3.265
2.070
2.063
2.056
Cl
O
O
OH
S
NH
11b
300 MHz
(CD3)2CO
1.06
1.06
0.74
2.05
5.02
1.05
2.09
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)

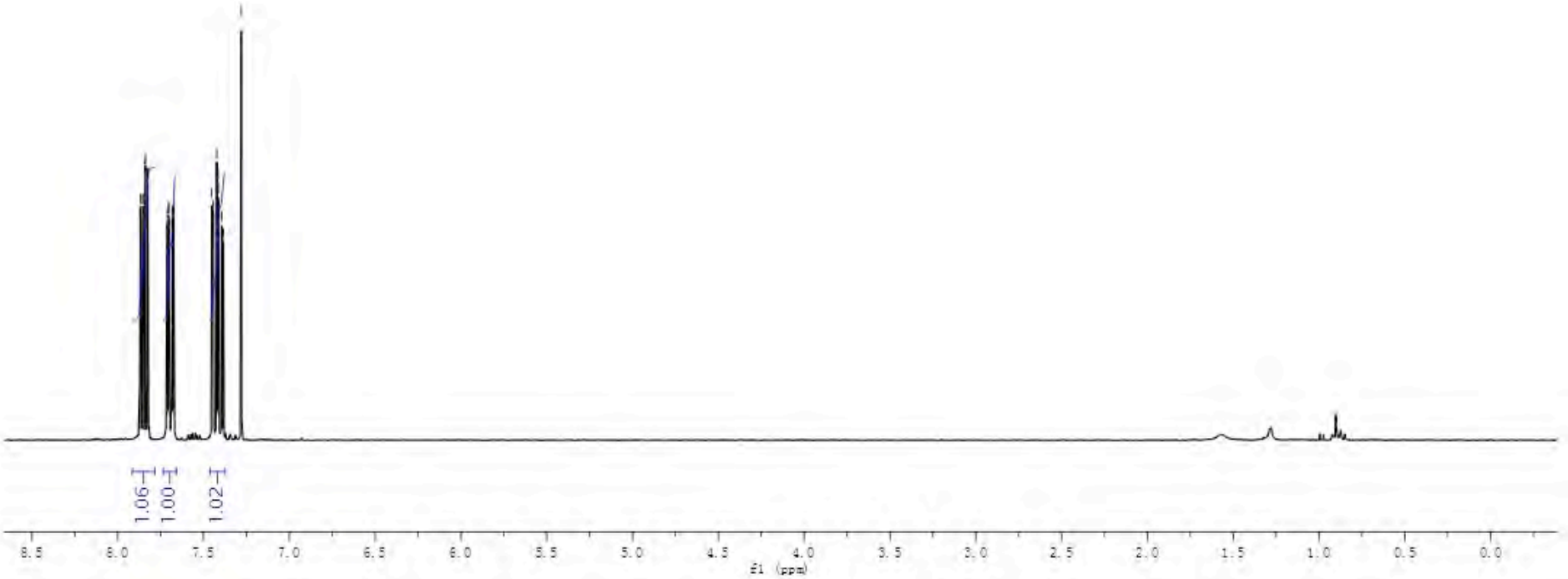

205.399
171.558
159.737
137.751
135.742
135.669
132.785
129.510
128.396
118.865
54.091
36.828
29.216
28.960
28.703
Cl
O
O
OH
S
NH
11b
75 MHz
(CD3)2CO
f1 (ppm)

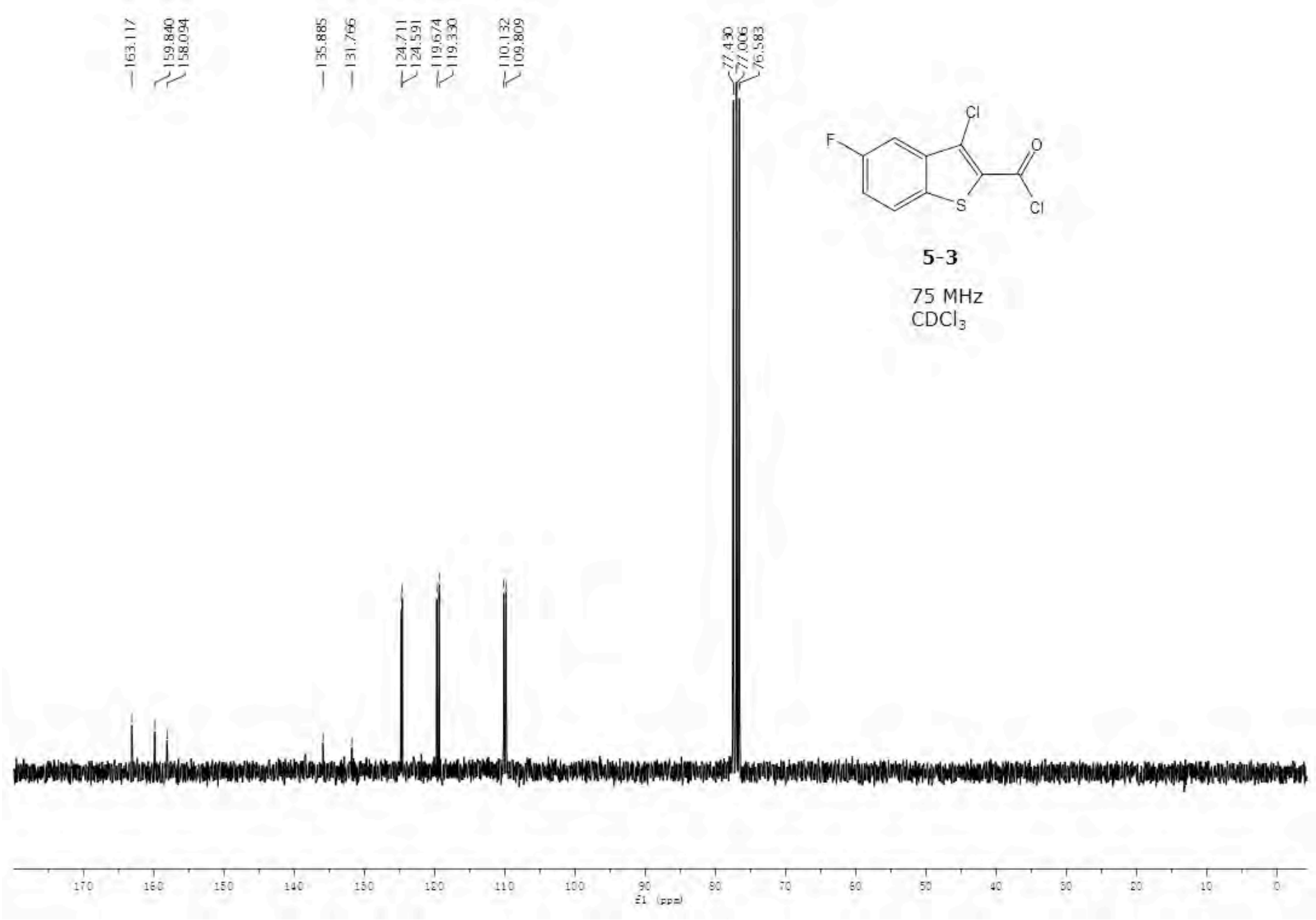


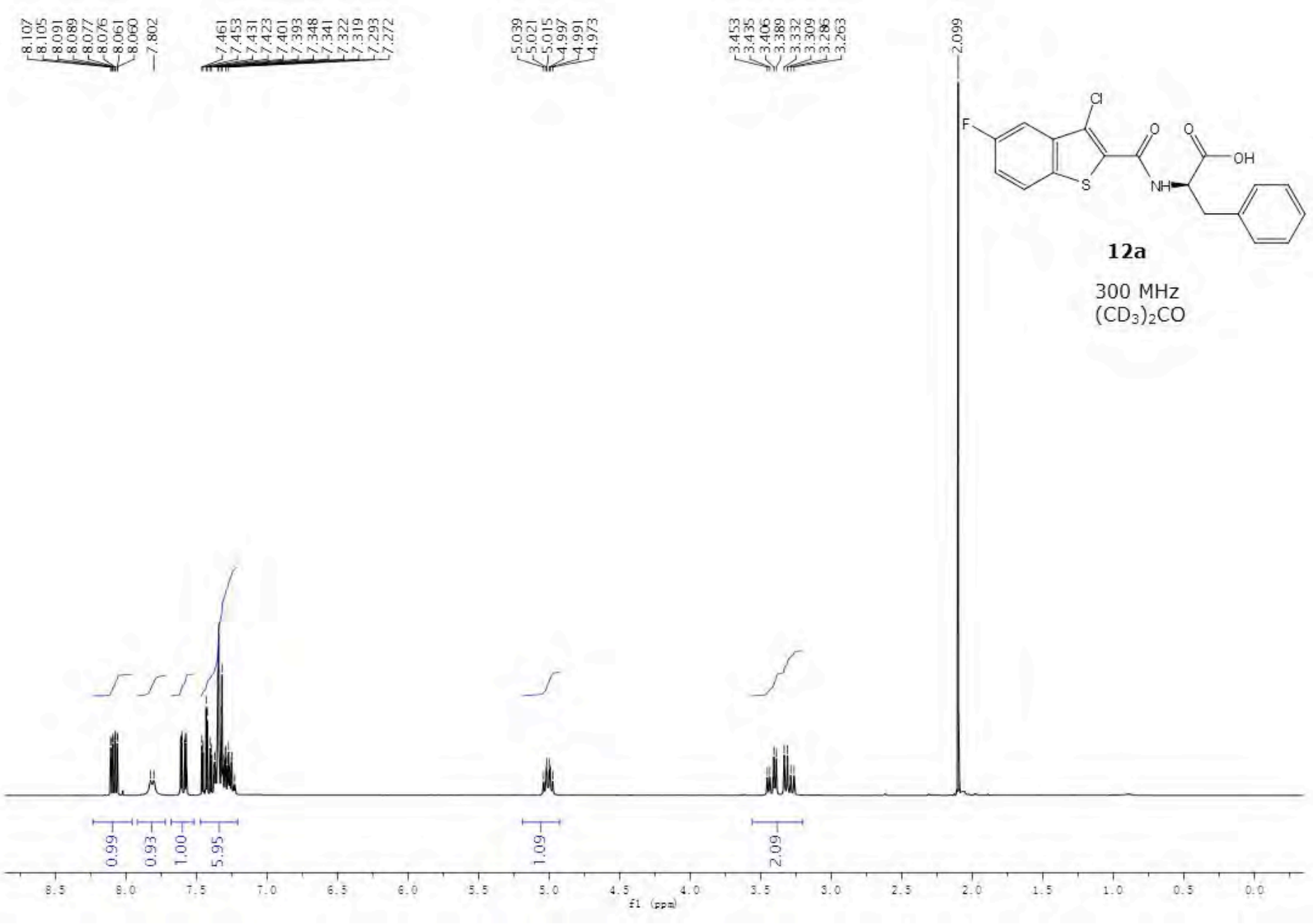


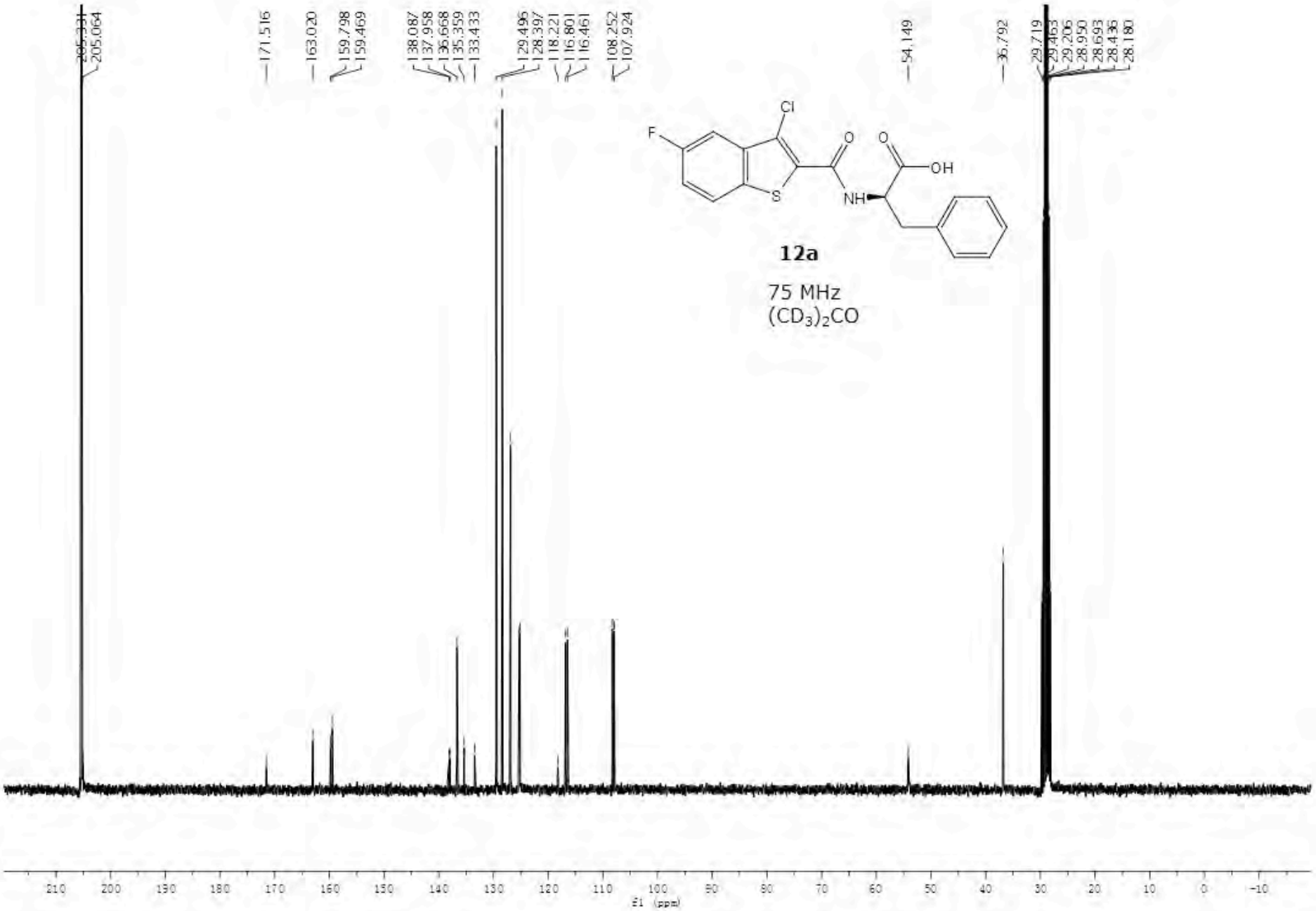
5-3

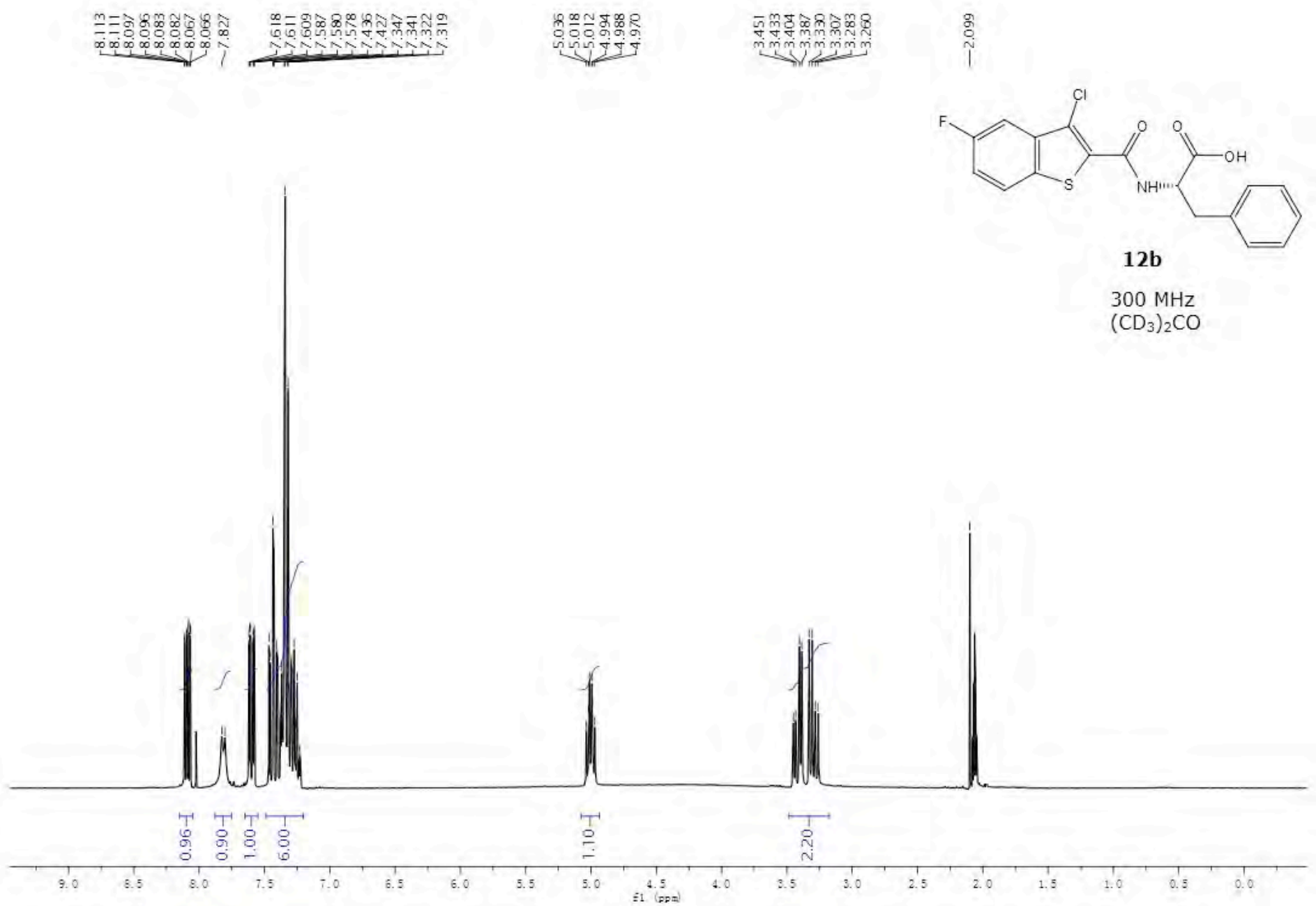
300 MHz
$CDCl_3$

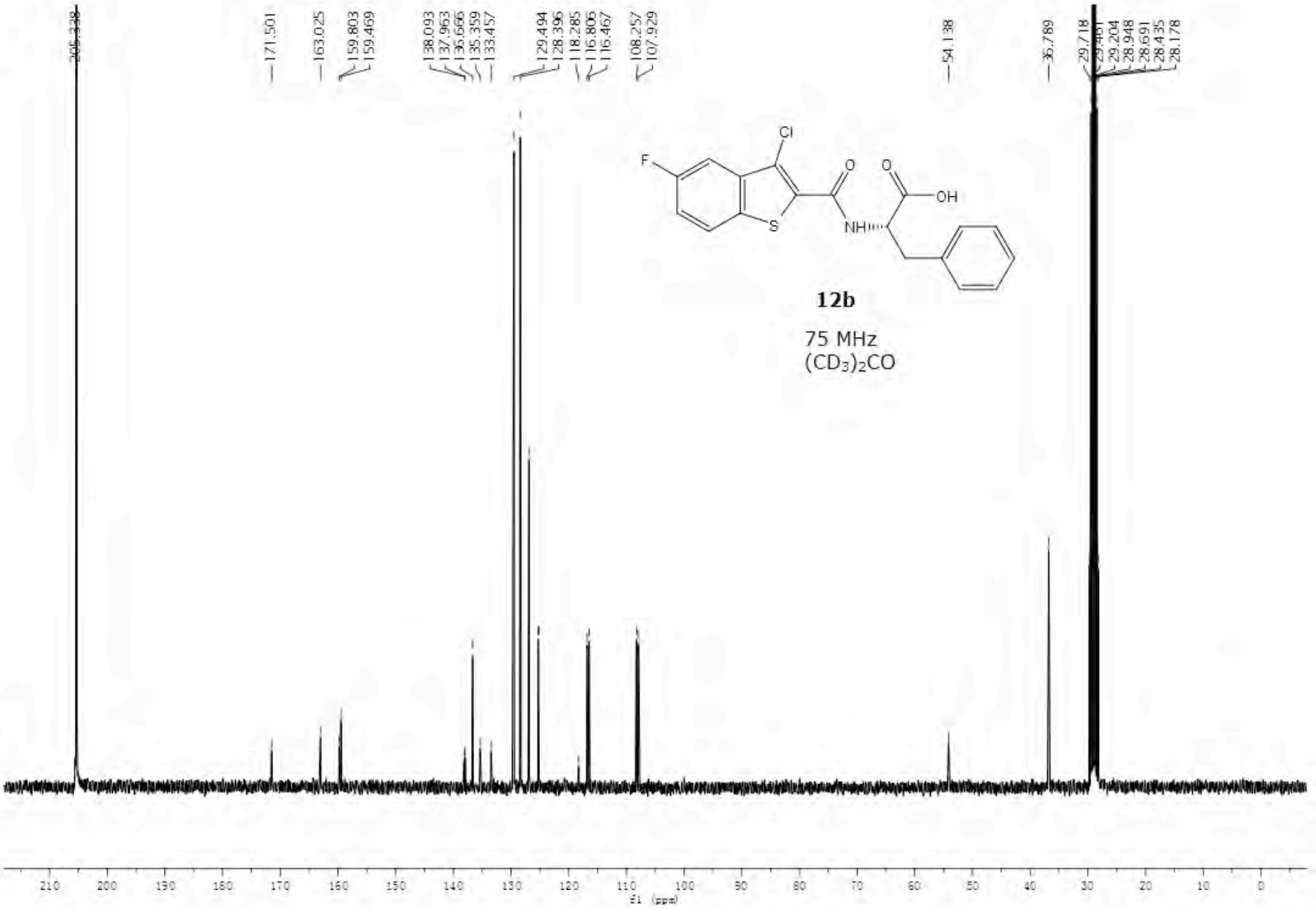


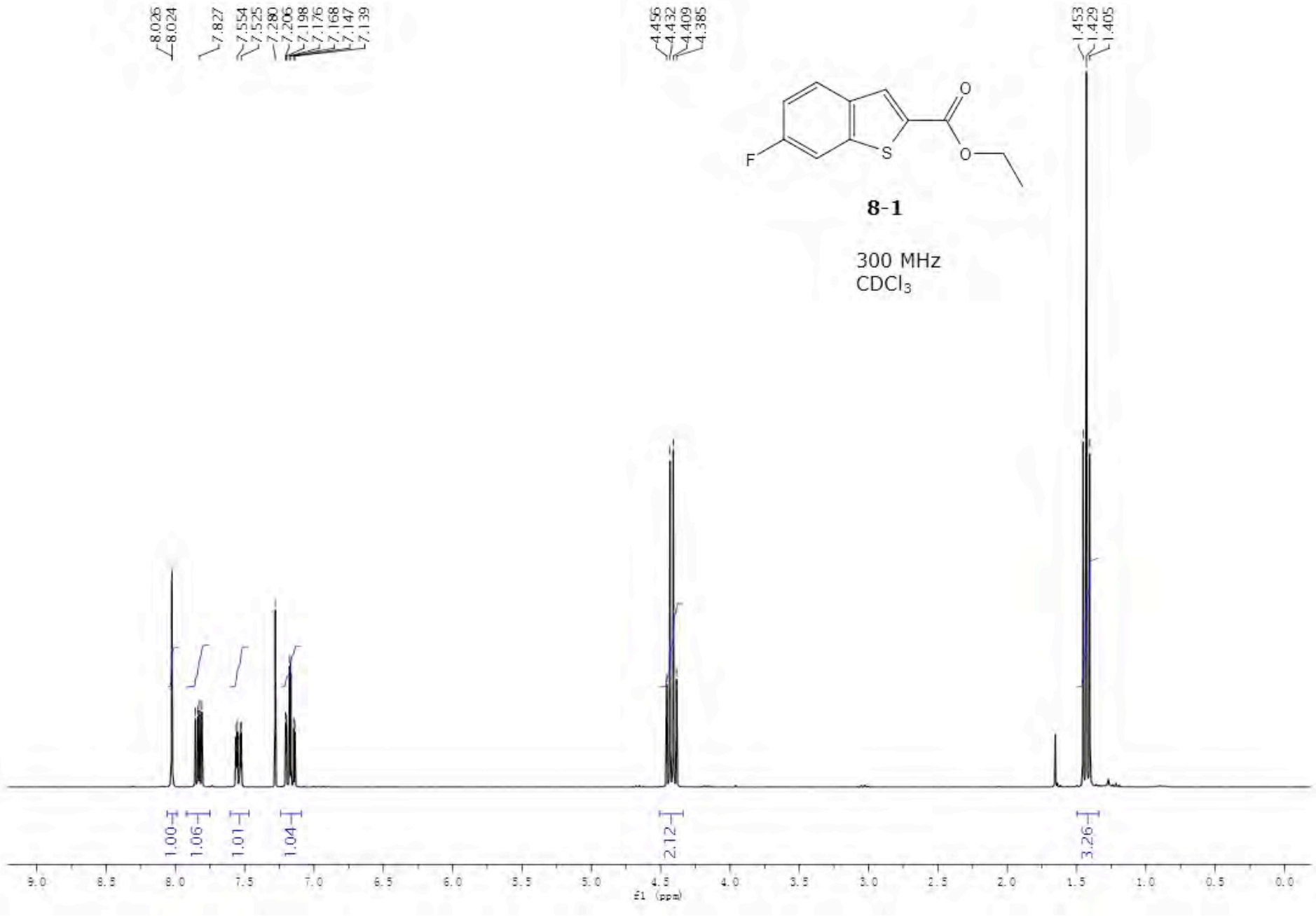

163.117
159.840
158.094
135.885
131.766
124.711
124.591
119.674
119.330
110.132
109.809
77.430
77.006
76.583
Cl
F
O
S
Cl
5-3
75 MHz
CDCl3
f1 (ppm)

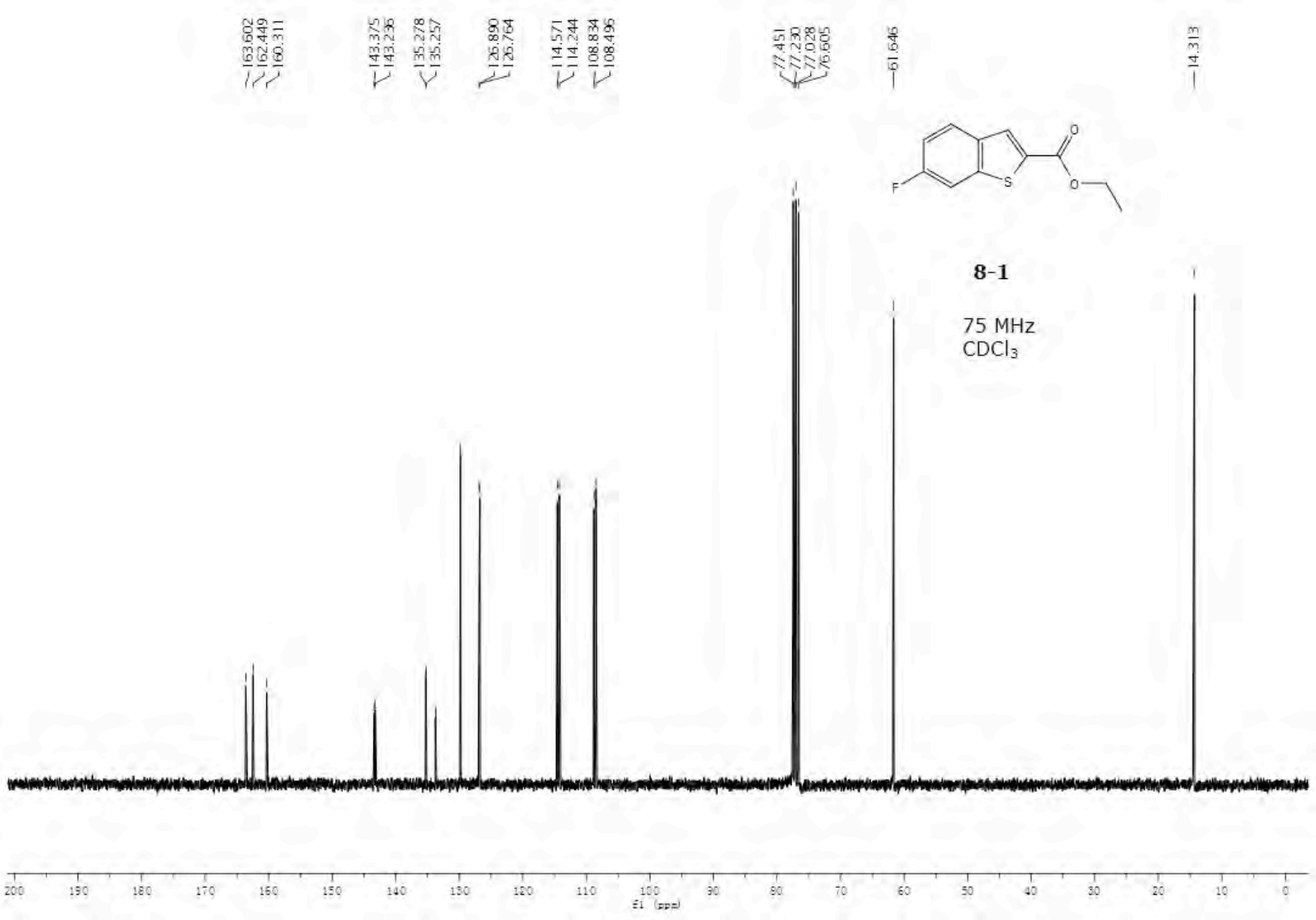

8.107
8.105
8.091
8.089
8.077
8.076
8.061
8.060
7.802
7.461
7.453
7.431
7.423
7.401
7.393
7.348
7.341
7.322
7.319
7.293
7.272
5.039
5.021
5.015
4.997
4.991
4.973
3.453
3.435
3.406
3.389
3.332
3.309
3.286
3.263
2.099
Cl
F
O
O
OH
S
NH
12a
300 MHz
(CD3)2CO
0.99
0.93
1.00
5.95
1.09
2.09
8.5
8.0
7.5
7.0
6.5
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)

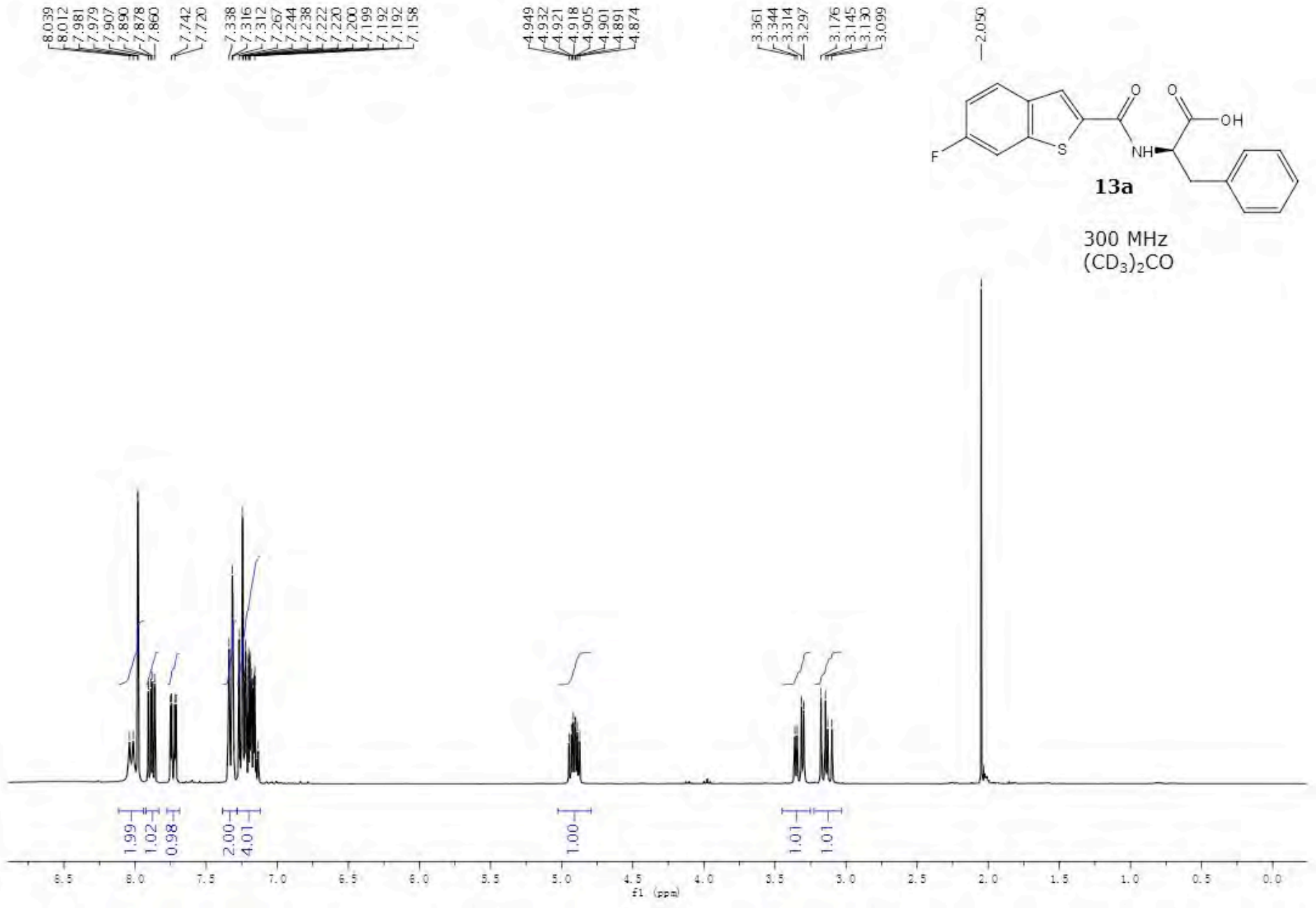

205.331
205.064
171.516
163.020
159.798
159.469
138.087
137.958
135.668
135.359
133.433
129.495
128.397
118.221
116.801
116.461
108.252
107.924
54.149
36.792
29.719
29.463
29.206
28.990
28.693
28.436
28.180
Cl
F
O
O
OH
S
NH
12a
75 MHz
(CD3)2CO
f1 (ppm)

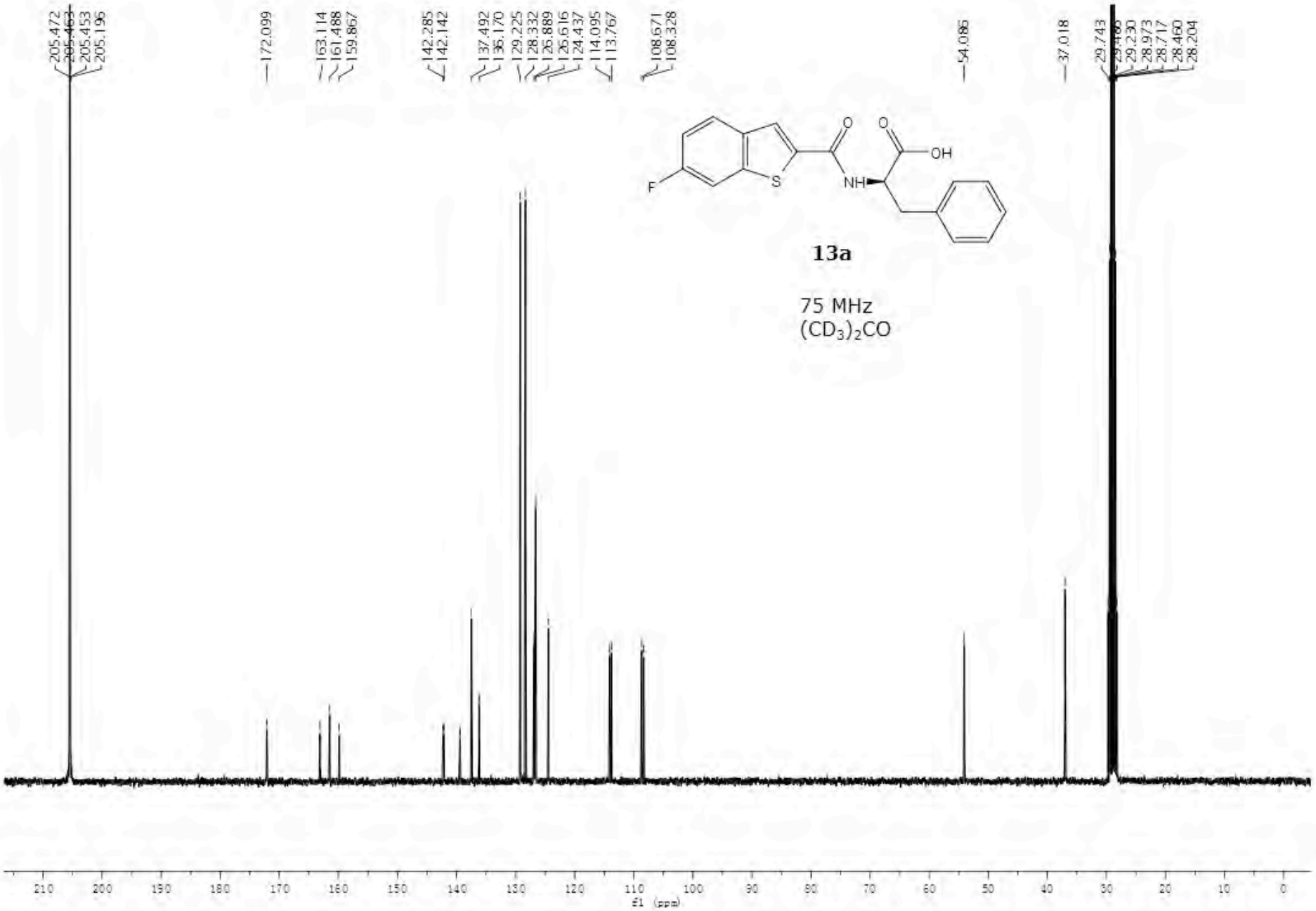

8.113
8.111
8.097
8.096
8.083
8.082
8.067
8.066
7.827
7.618
7.611
7.609
7.587
7.580
7.578
7.436
7.427
7.347
7.341
7.322
7.319
5.035
5.018
5.012
4.994
4.988
4.970
3.451
3.433
3.404
3.387
3.330
3.307
3.283
3.260
2.099
Cl
F
O
O
OH
S
NH
12b
300 MHz
(CD3)2CO
0.96
0.90
1.00
6.00
1.10
2.20
f1 (ppm)

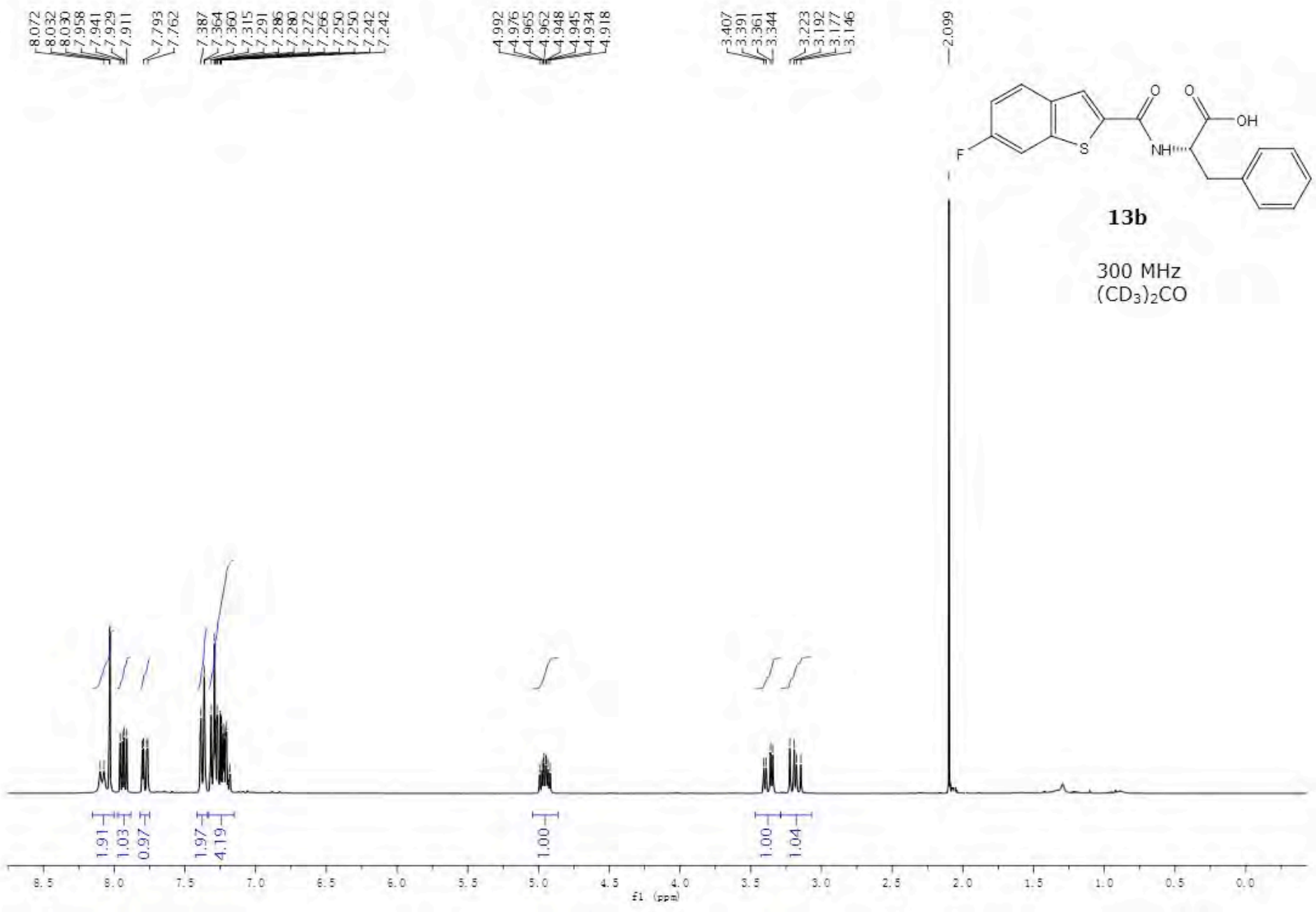

205.338
171.501
163.025
159.803
159.469
138.093
137.963
136.666
135.359
133.457
129.494
128.396
118.285
116.805
116.467
108.257
107.929
54.138
36.789
29.718
29.461
29.204
28.948
28.691
28.435
28.178
Cl
F
O
O
OH
NH
S
12b
75 MHz
(CD3)2CO
f1 (ppm)

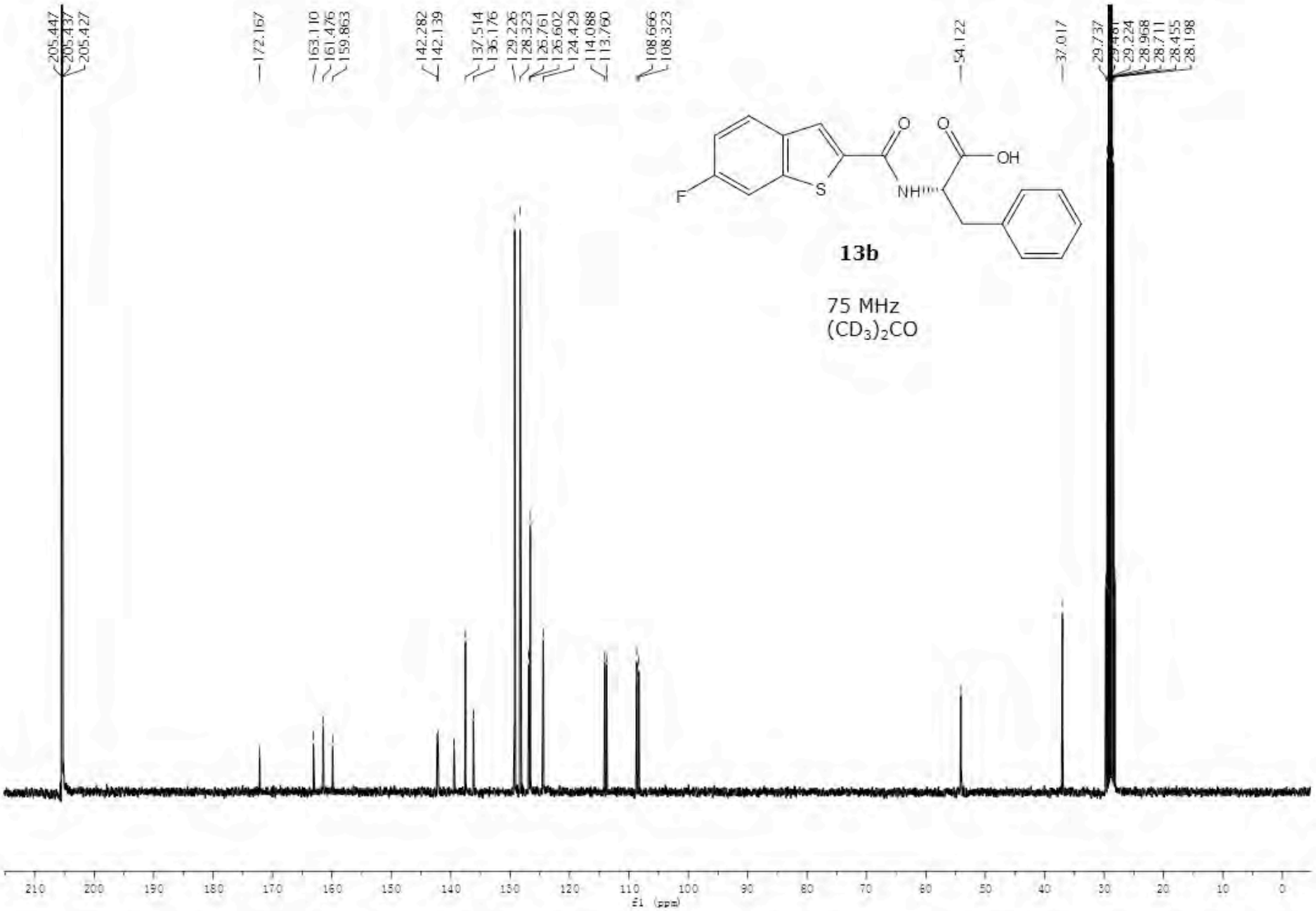

8.026
8.024
7.827
7.554
7.525
7.280
7.206
7.198
7.176
7.168
7.147
7.139
4.456
4.432
4.409
4.385
1.453
1.429
1.405
F
S
O
O
8-1
300 MHz
CDCl3
1.00
1.06
1.01
1.04
2.12
3.26
f1 (ppm)

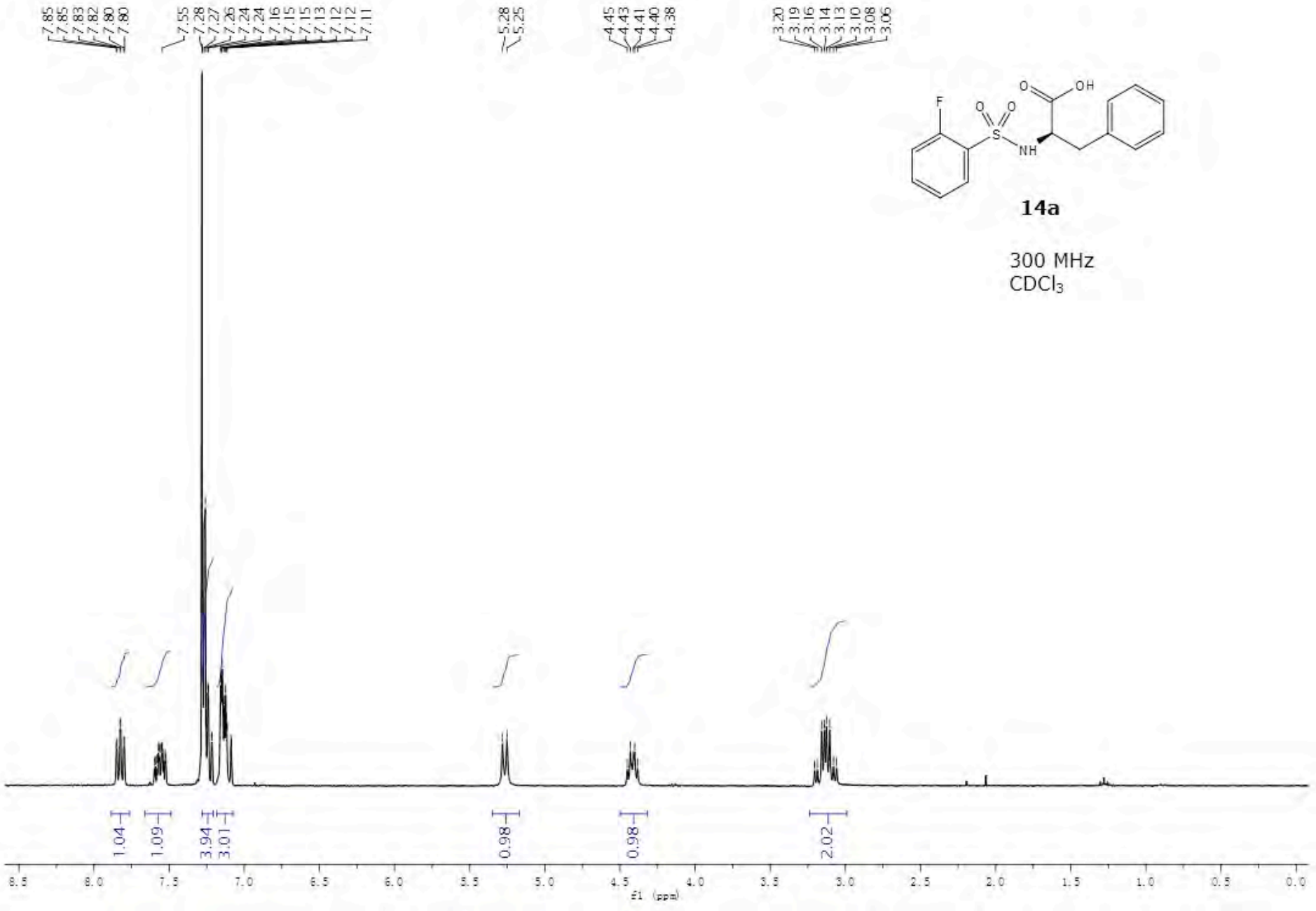

163.602
162.449
160.311
143.375
143.236
135.278
135.257
125.890
125.764
114.571
114.244
108.834
108.496
77.451
77.230
77.028
76.605
61.646
14.313
F
S
O
O
8-1
75 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

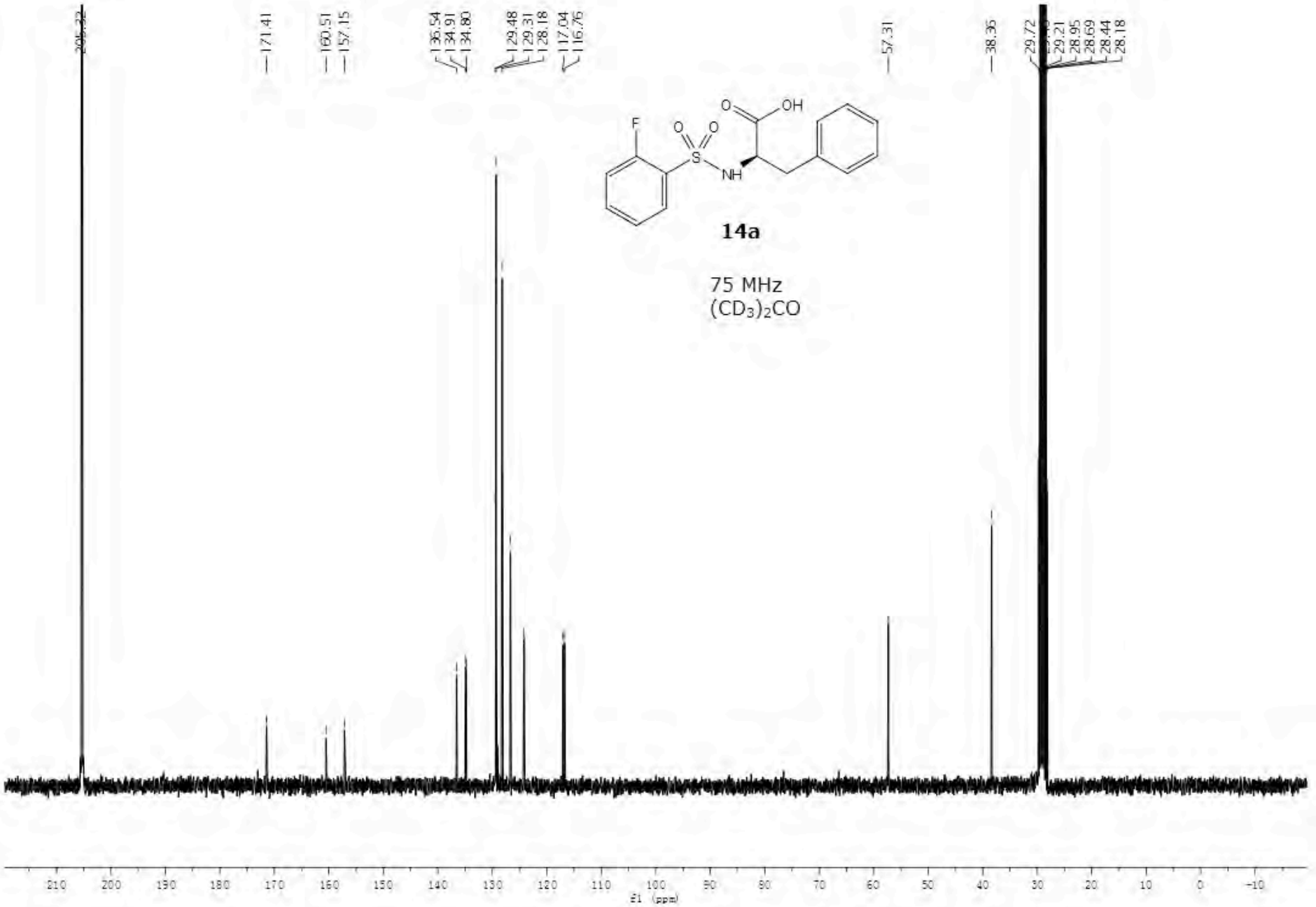

8.039
8.012
7.981
7.979
7.907
7.890
7.878
7.860
7.742
7.720
7.338
7.316
7.312
7.267
7.244
7.238
7.222
7.220
7.200
7.199
7.192
7.192
7.158
4.949
4.932
4.921
4.918
4.905
4.901
4.891
4.874
3.361
3.344
3.314
3.297
3.176
3.145
3.130
3.099
2.050
F
S
NH
O
O
OH
13a
300 MHz
(CD3)2CO
1.99
1.02
0.98
2.00
4.01
1.00
1.01
1.01
f1 (ppm)

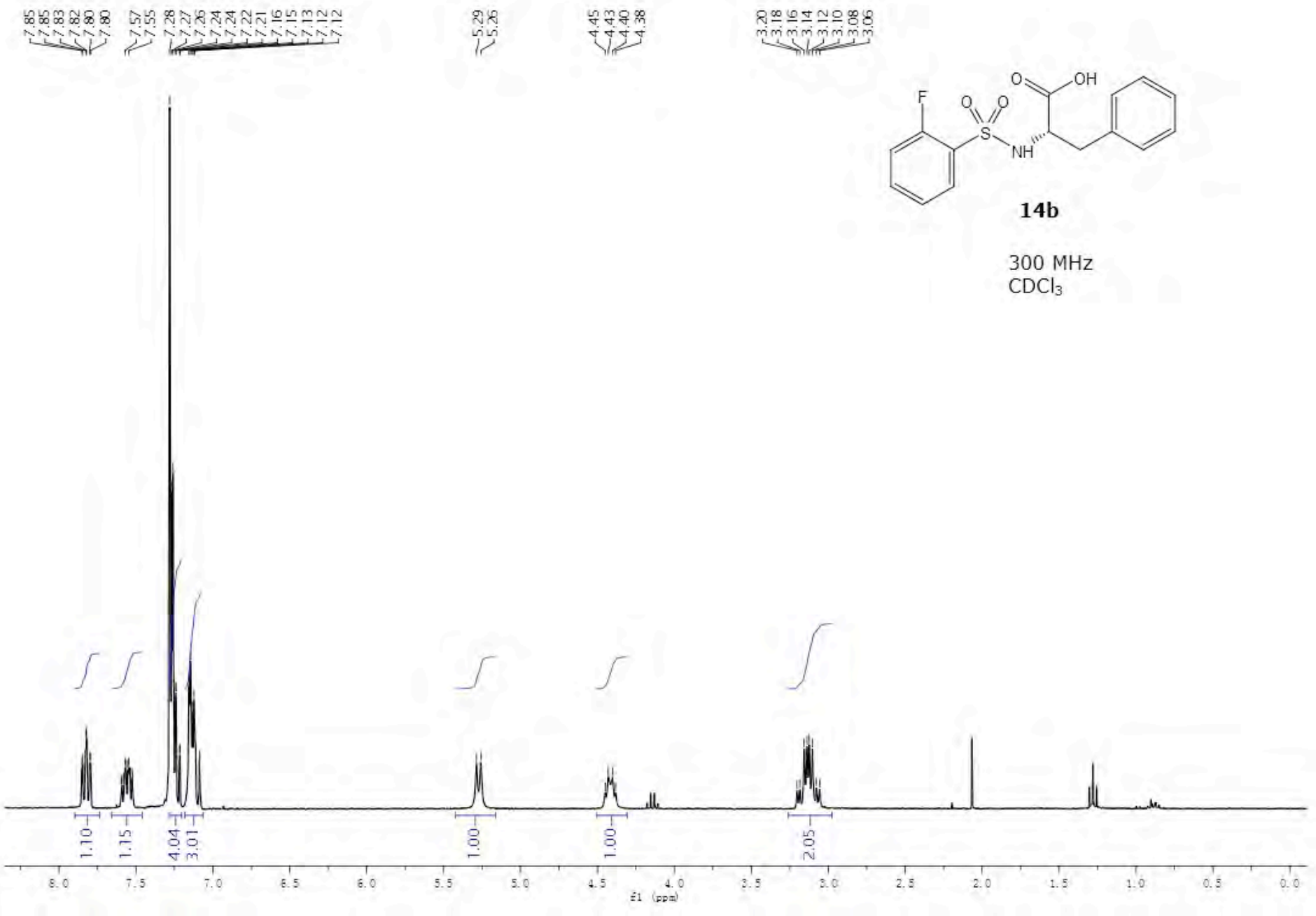

205.472
205.463
205.453
205.196
172.099
163.114
161.488
159.867
142.285
142.142
137.492
136.170
129.225
128.332
125.889
125.616
124.437
114.095
113.767
108.671
108.328
54.085
37.018
29.743
29.460
29.230
28.973
28.717
28.460
28.204
F
S
NH
OH
O
O
13a
75 MHz
(CD3)2CO
f1 (ppm)

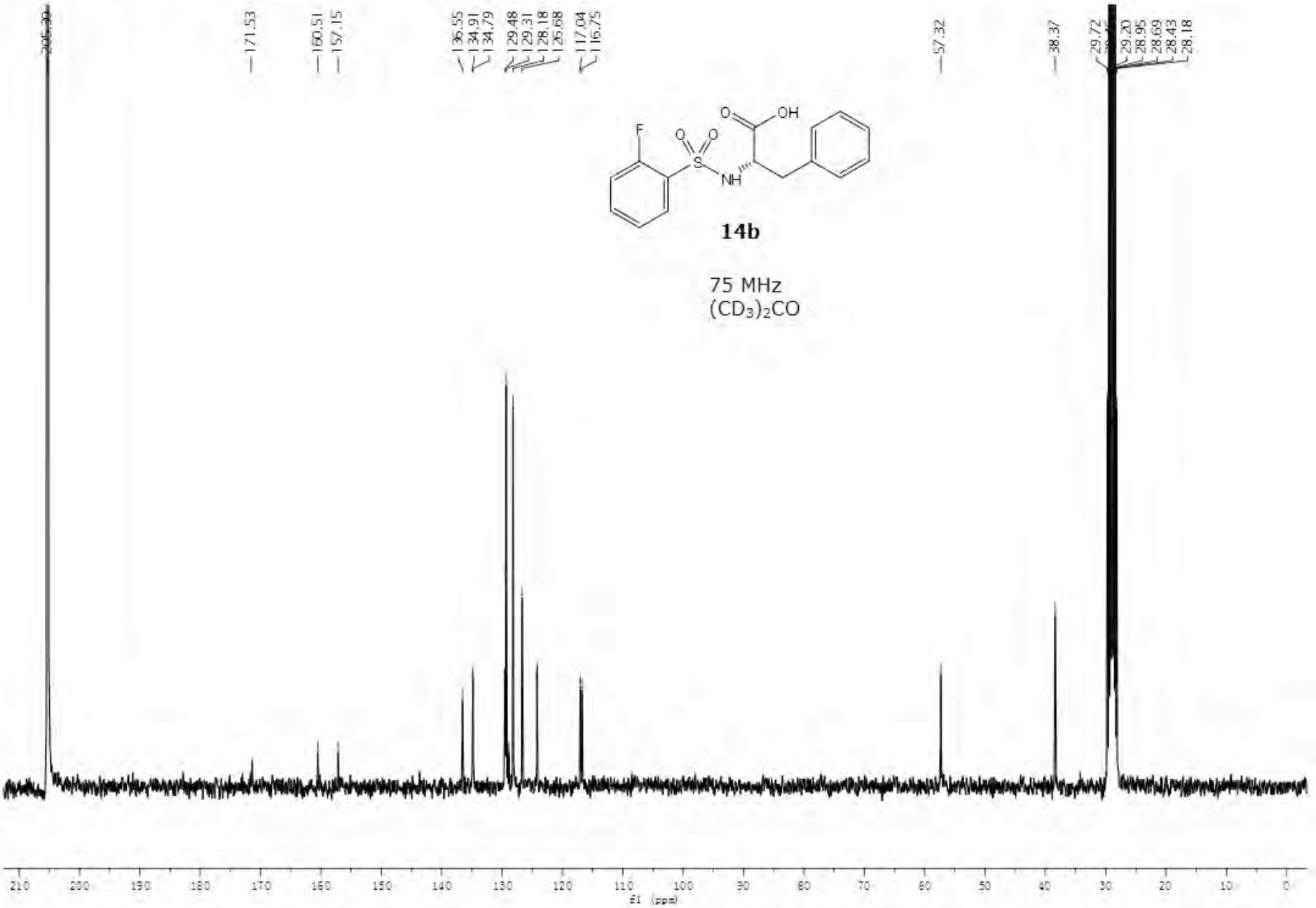

8.072
8.032
8.030
7.958
7.941
7.929
7.911
7.793
7.762
7.387
7.364
7.360
7.315
7.291
7.286
7.280
7.272
7.266
7.250
7.250
7.242
7.242
4.992
4.976
4.965
4.962
4.948
4.945
4.934
4.918
3.407
3.391
3.361
3.344
3.223
3.192
3.177
3.146
2.099
O
O
OH
NH
S
F
13b
300 MHz
(CD3)2CO
1.91
1.03
0.97
1.97
4.19
1.00
1.00
1.04
f1 (ppm)

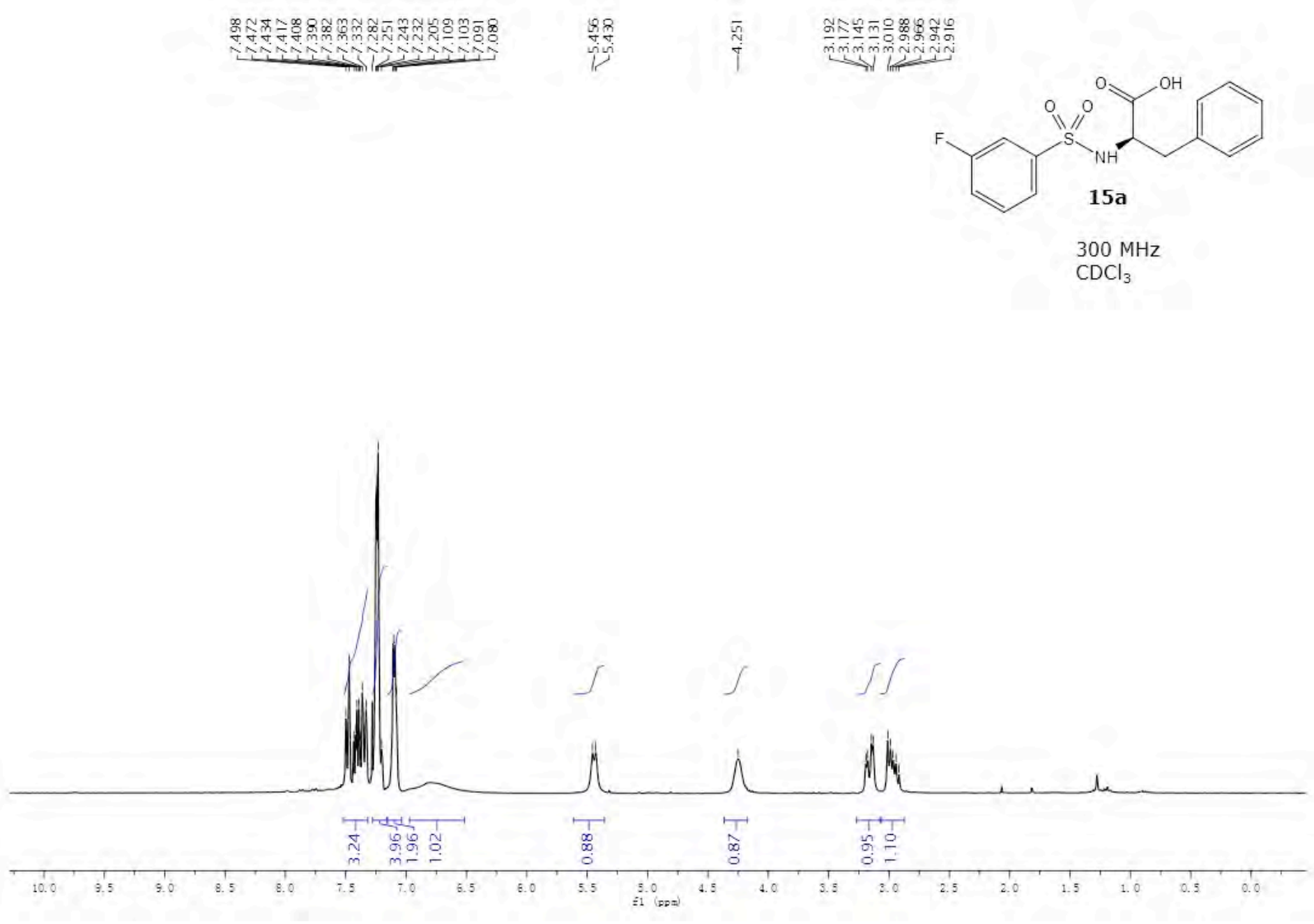

205.447
205.437
205.427
172.167
163.110
161.476
159.863
142.282
142.139
137.514
135.176
129.225
128.323
125.761
125.602
124.429
114.088
113.760
108.666
108.323
54.122
37.017
29.737
29.461
29.224
28.968
28.711
28.455
28.198
O
O
OH
NH
S
F
13b
75 MHz
(CD3)2CO
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

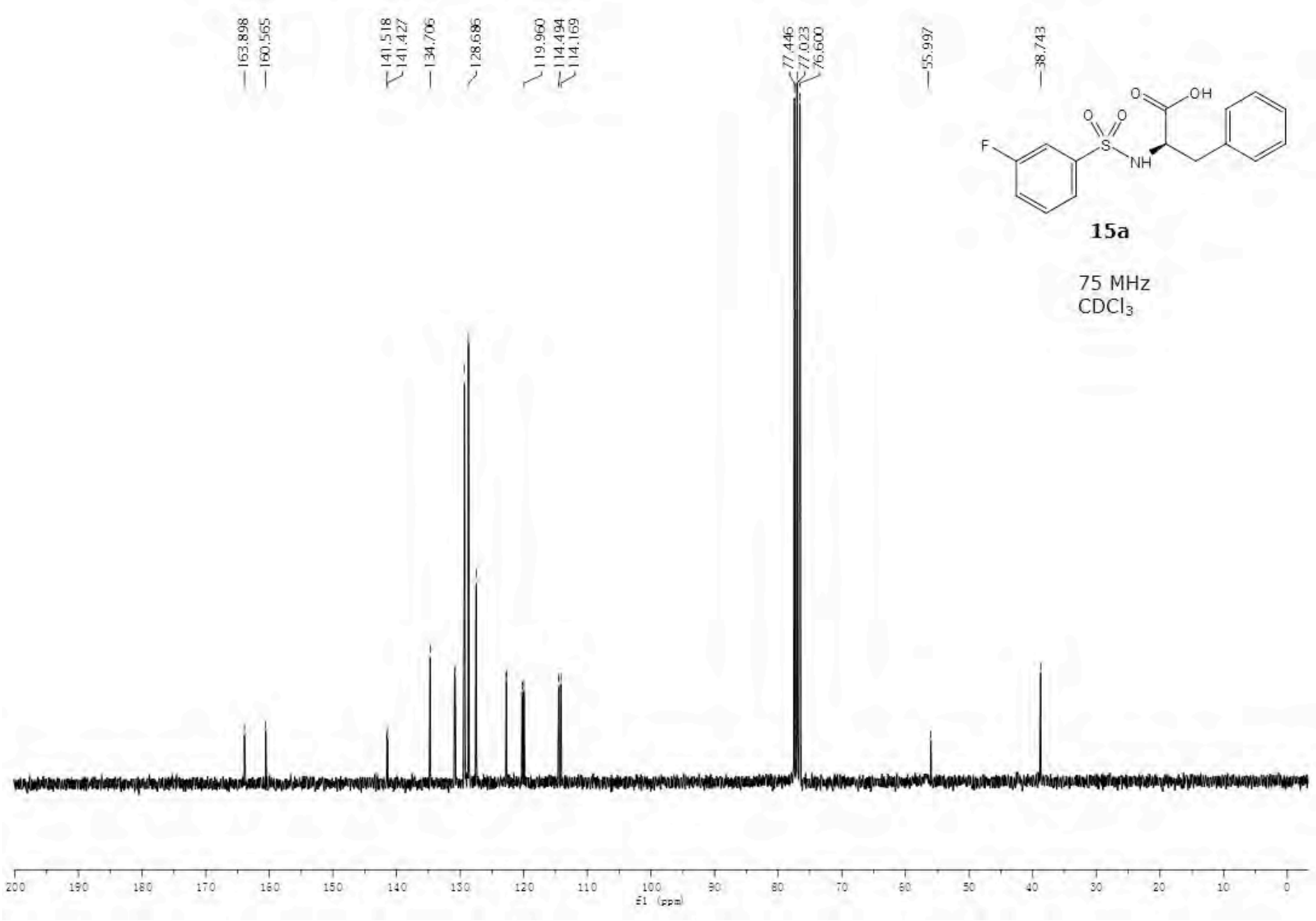

7.85
7.85
7.83
7.82
7.80
7.80
7.55
7.28
7.27
7.26
7.24
7.24
7.16
7.15
7.15
7.13
7.12
7.12
7.11
5.28
5.25
4.45
4.43
4.41
4.40
4.38
3.20
3.19
3.16
3.14
3.13
3.10
3.08
3.06
F
O
O
S
NH
O
OH
14a
300 MHz
CDCl3
1.04
1.09
3.94
3.01
0.98
0.98
2.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

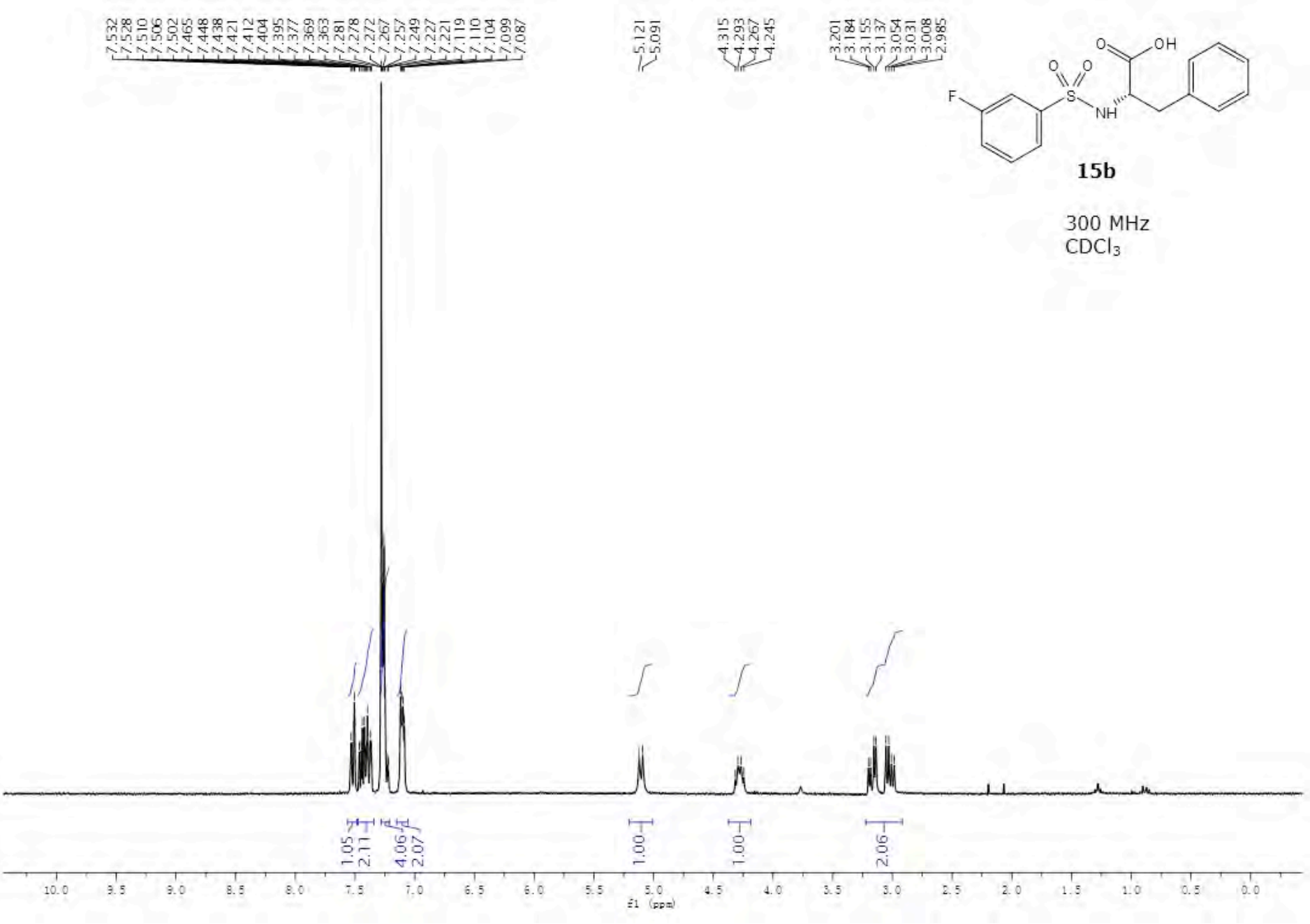

205.32
171.41
160.51
157.15
136.54
134.91
134.80
129.48
129.31
128.18
117.04
116.76
57.31
38.35
29.72
29.21
28.95
28.69
28.44
28.18
F
O
O
S
NH
O
OH
14a
75 MHz
(CD3)2CO
f1 (ppm)

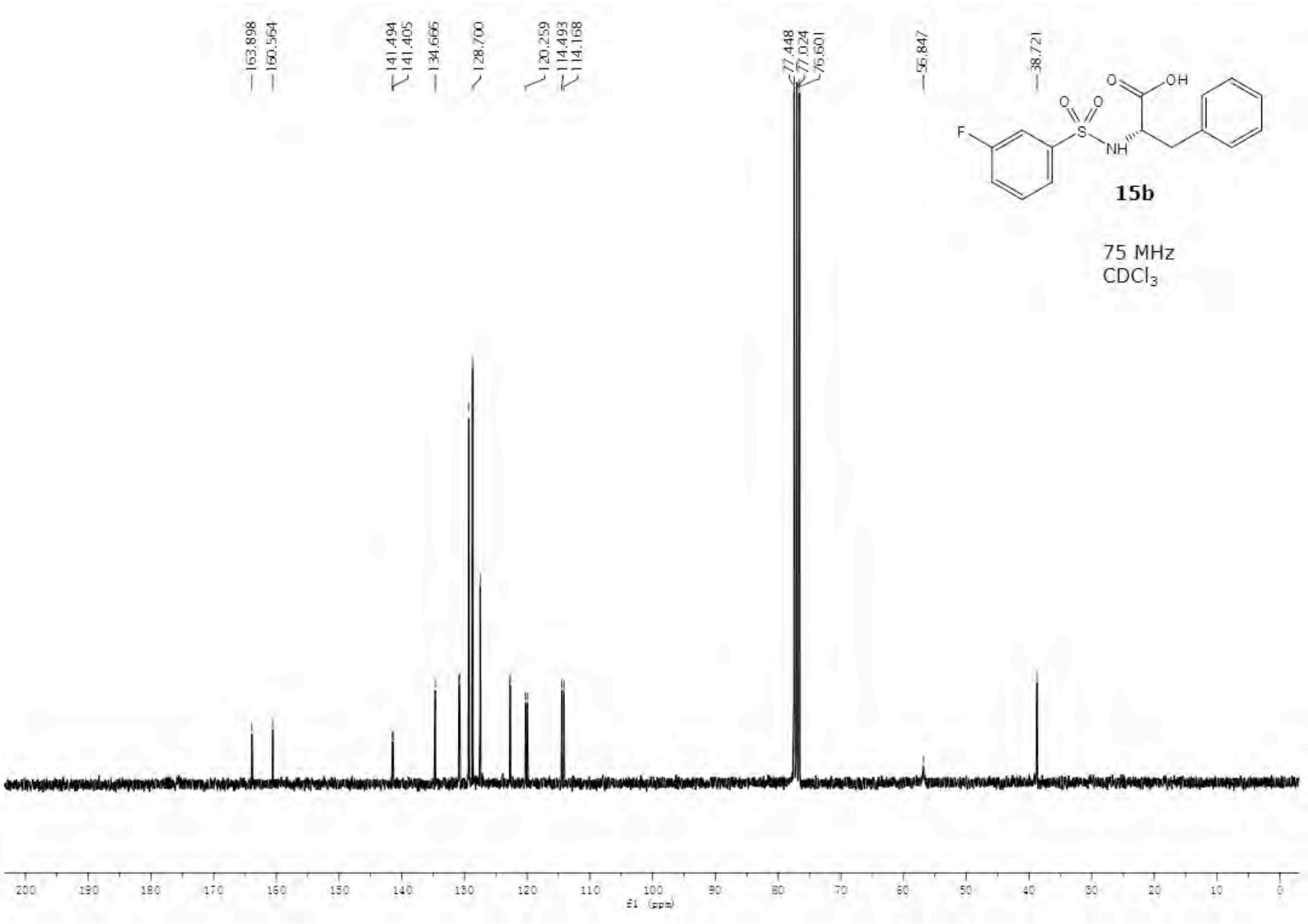

7.85
7.85
7.83
7.82
7.80
7.80
7.57
7.55
7.28
7.27
7.26
7.24
7.24
7.22
7.21
7.16
7.15
7.13
7.12
7.12
5.29
5.26
4.45
4.43
4.40
4.38
3.20
3.18
3.16
3.14
3.12
3.10
3.08
3.06
F
O
O
S
NH
O
OH
14b
300 MHz
CDCl3
1.10
1.15
4.04
3.01
1.00
1.00
2.05
f1 (ppm)


205.30
171.53
160.51
157.15
136.55
134.91
134.79
129.48
129.31
128.18
125.68
117.04
116.75
57.32
38.37
29.72
29.20
28.95
28.69
28.43
28.18
F
O
OH
S
NH
14b
75 MHz
(CD3)2CO
f1 (ppm)


7.498
7.472
7.434
7.417
7.408
7.390
7.382
7.363
7.332
7.282
7.251
7.243
7.232
7.205
7.109
7.103
7.091
7.080
5.456
5.430
4.251
3.192
3.177
3.145
3.131
3.010
2.988
2.966
2.942
2.916
O
OH
O
O
S
NH
F
15a
300 MHz
CDCl3
3.24
3.96
1.96
1.02
0.88
0.87
0.95
1.10
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)


163.898
160.565
141.518
141.427
134.706
128.685
119.960
114.494
114.169
77.446
77.023
76.600
55.997
38.743
O
OH
O
O
S
NH
F
15a
75 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.532
7.528
7.510
7.506
7.502
7.465
7.448
7.438
7.421
7.412
7.404
7.395
7.377
7.369
7.363
7.281
7.278
7.272
7.267
7.257
7.249
7.227
7.221
7.119
7.110
7.104
7.099
7.087
5.121
5.091
4.315
4.293
4.267
4.245
3.201
3.184
3.155
3.137
3.054
3.031
3.008
2.985
F
S
NH
O
O
O
OH
15b
300 MHz
CDCl3
1.05
2.11
4.06
2.07
1.00
1.00
2.06
f1 (ppm)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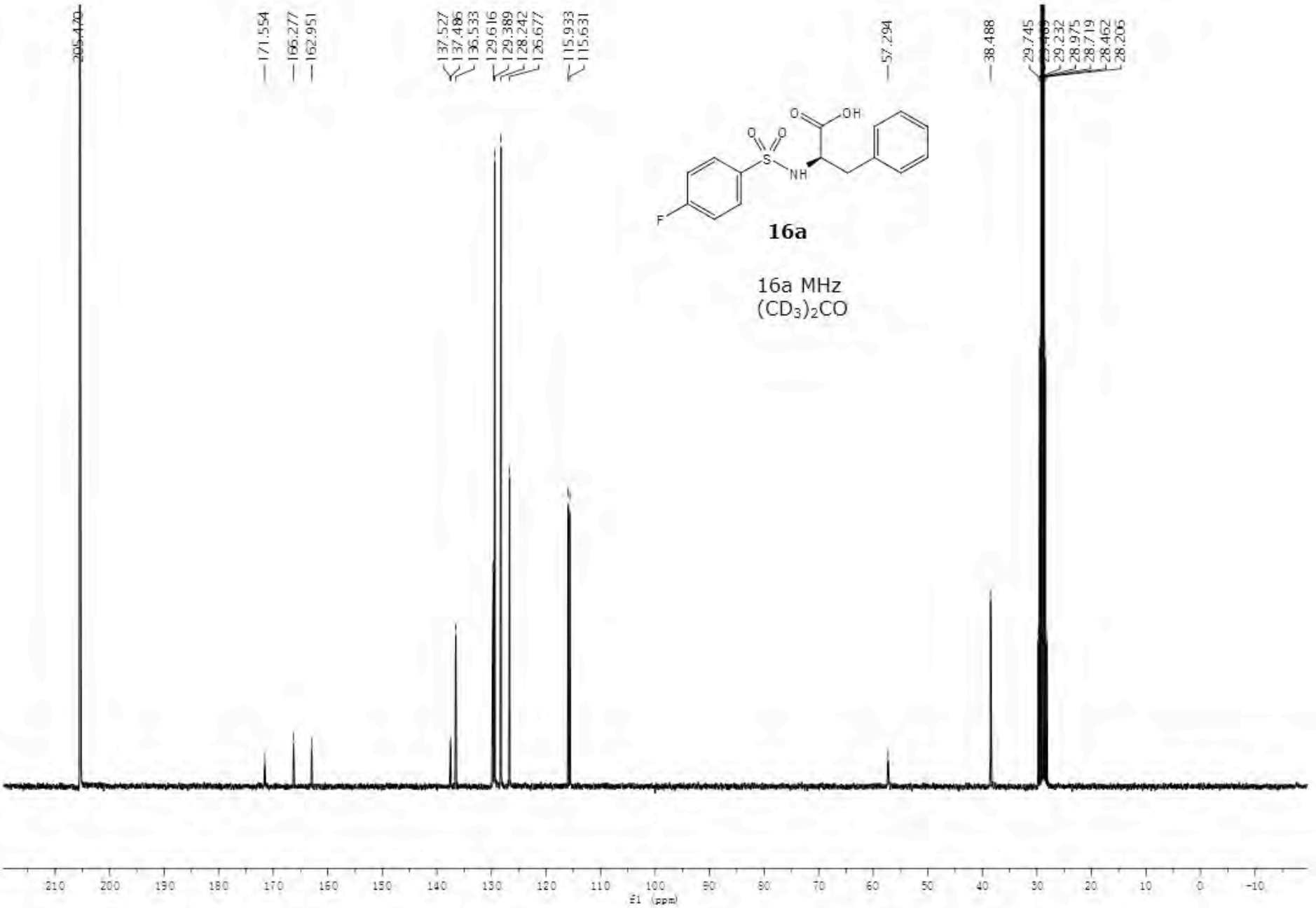
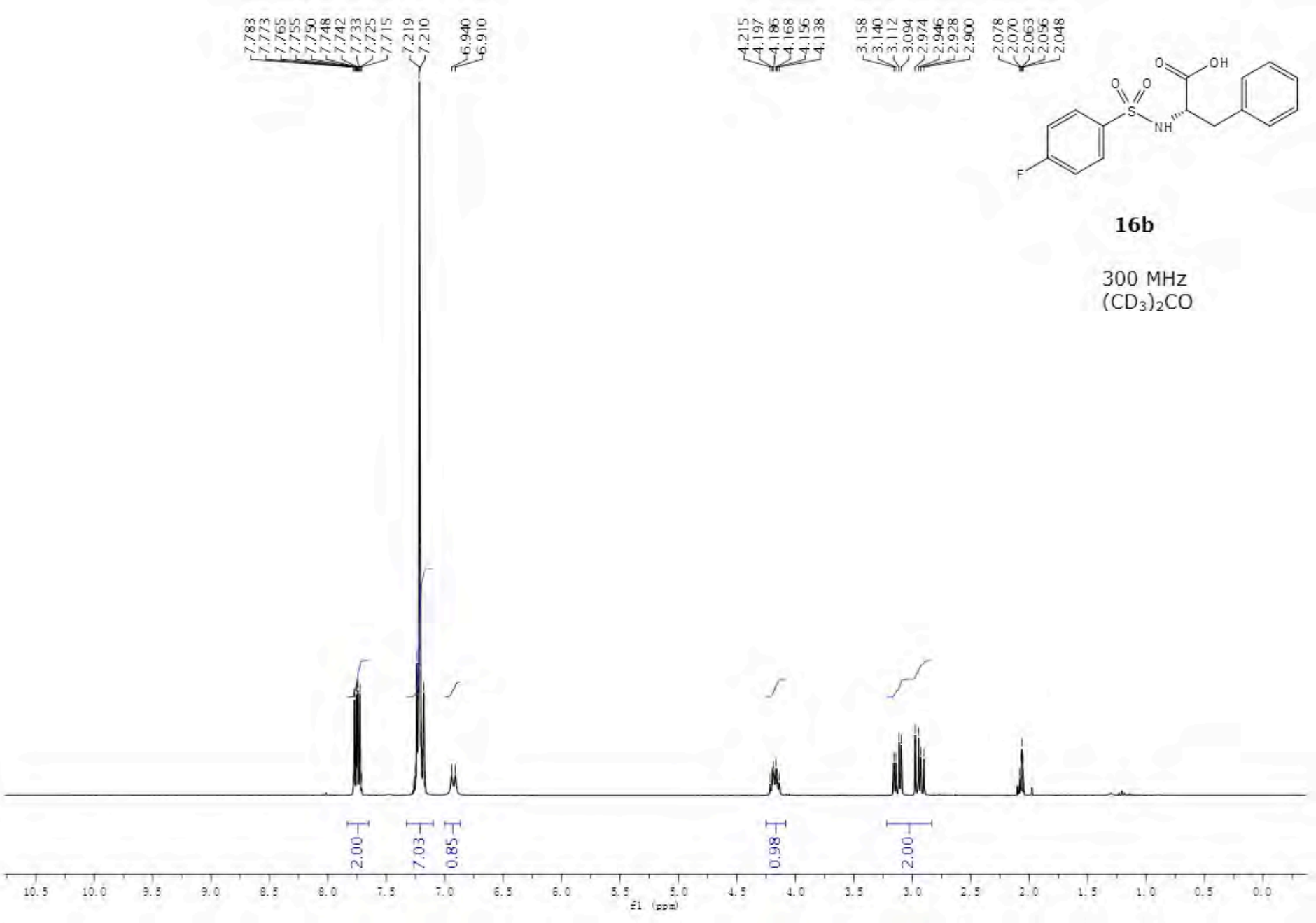
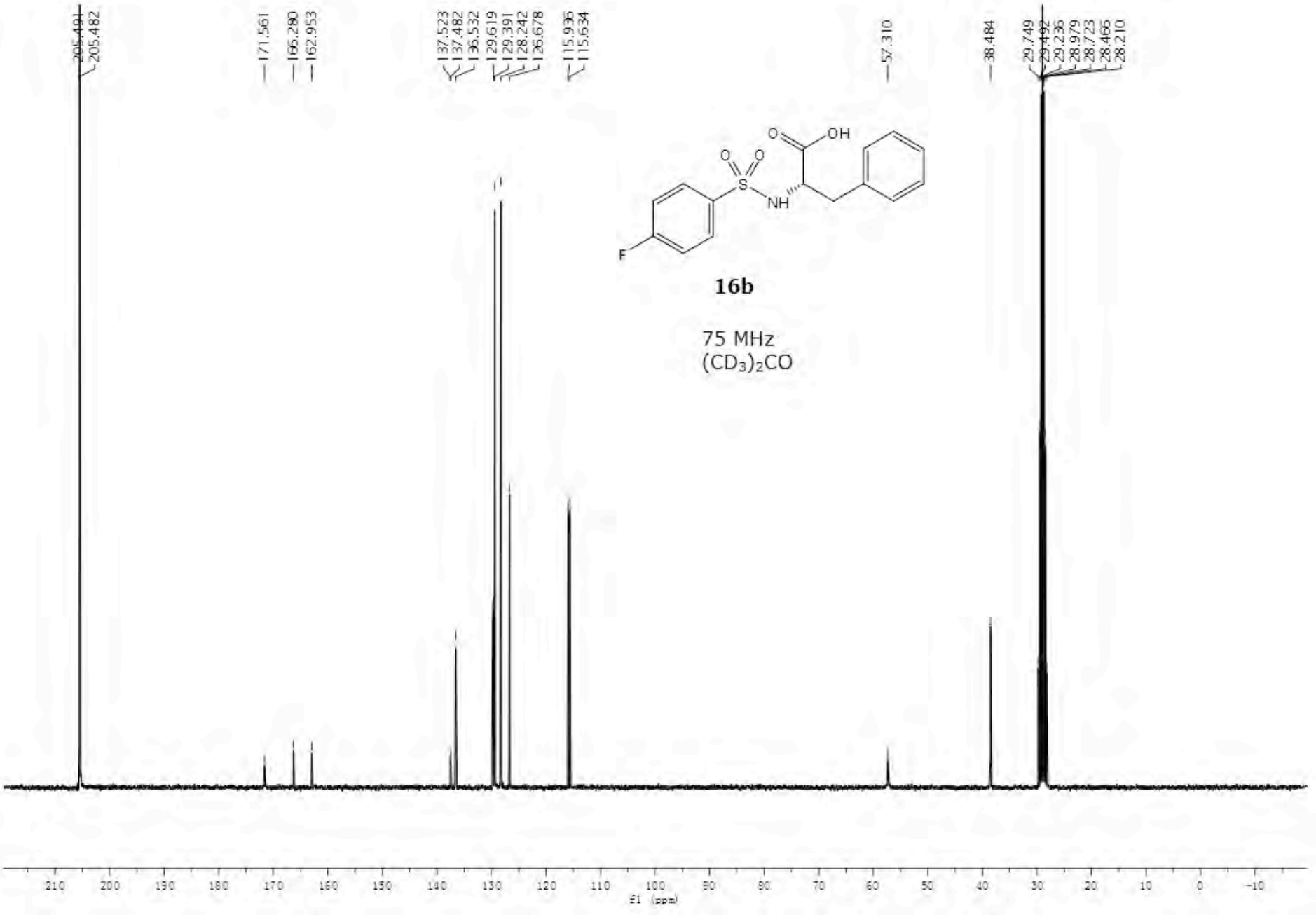
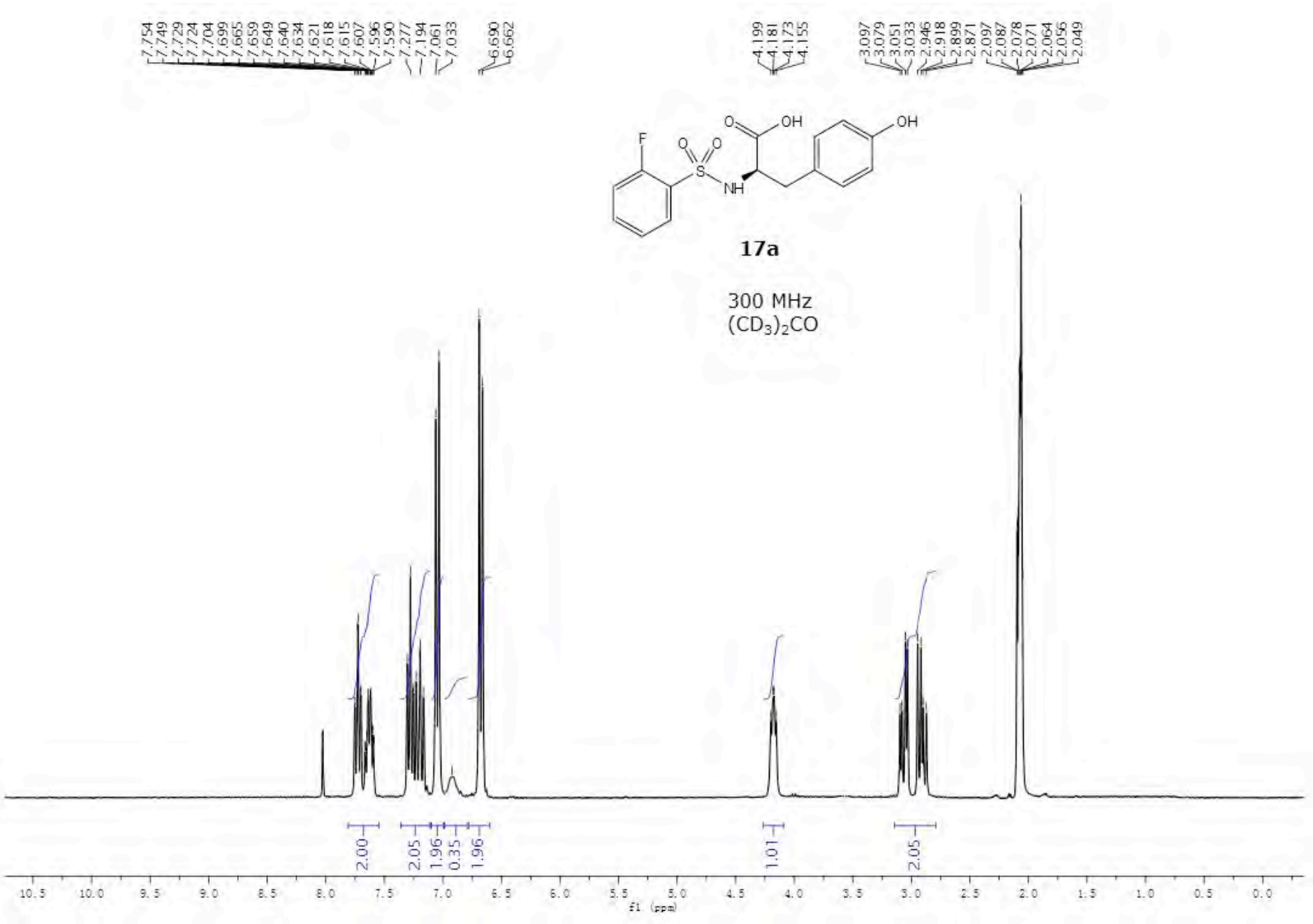
160.564
141.494
141.405
134.666
128.700
120.259
114.493
114.168
77.448
77.024
76.601
56.847
38.721
O
OH
O
O
S
NH
F
15b
75 MHz
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

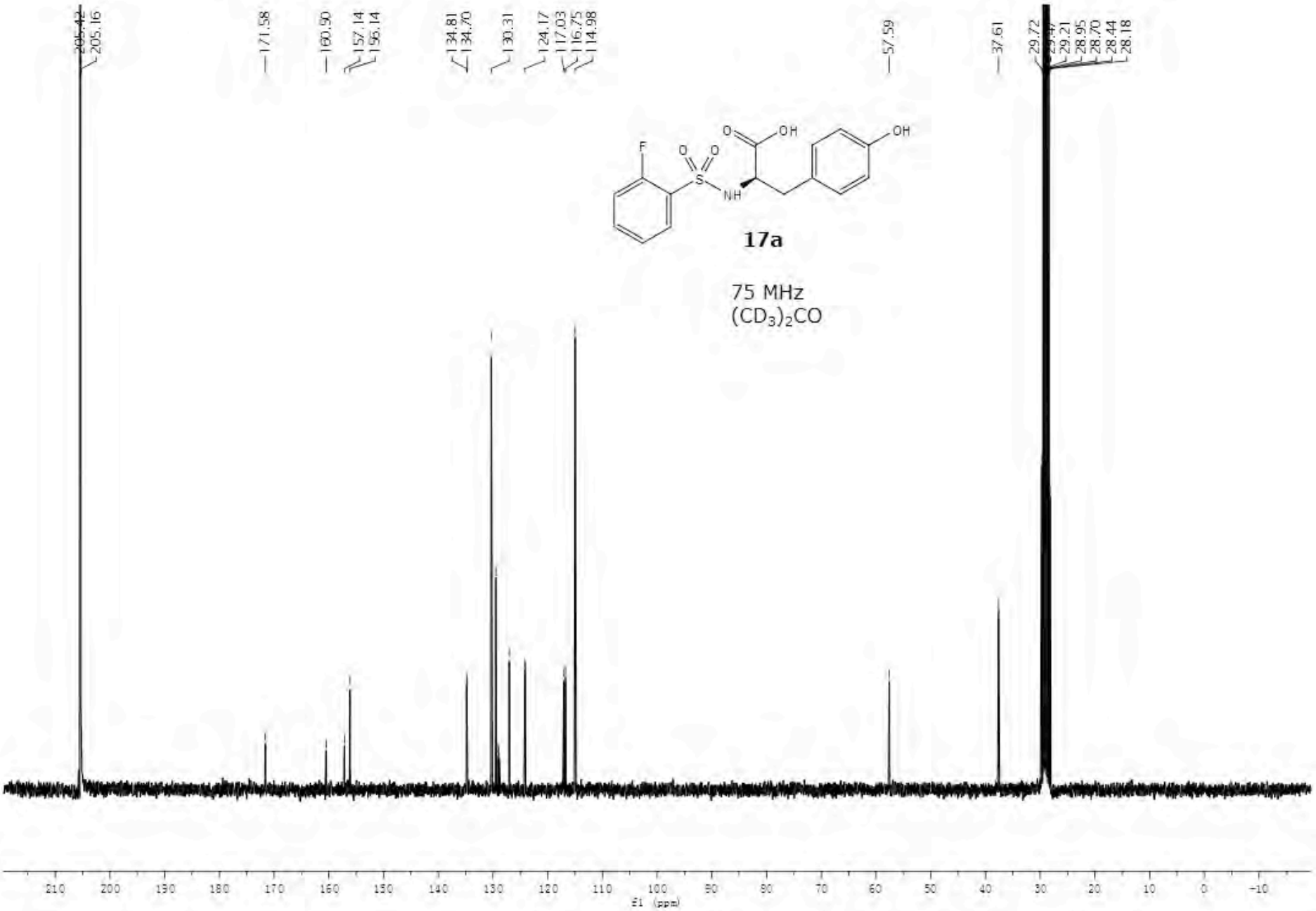

7.772
7.765
7.755
7.749
7.748
7.742
7.732
7.725
7.219
7.211
6.940
6.910
4.214
4.196
4.185
4.167
4.155
4.137
3.158
3.140
3.112
3.094
2.974
2.946
2.928
2.900
2.070
2.063
2.056
O
OH
O
O
S
NH
F
16a
300 MHz
(CD3)2CO
2.03
7.03
0.85
0.99
2.02
f1 (ppm)

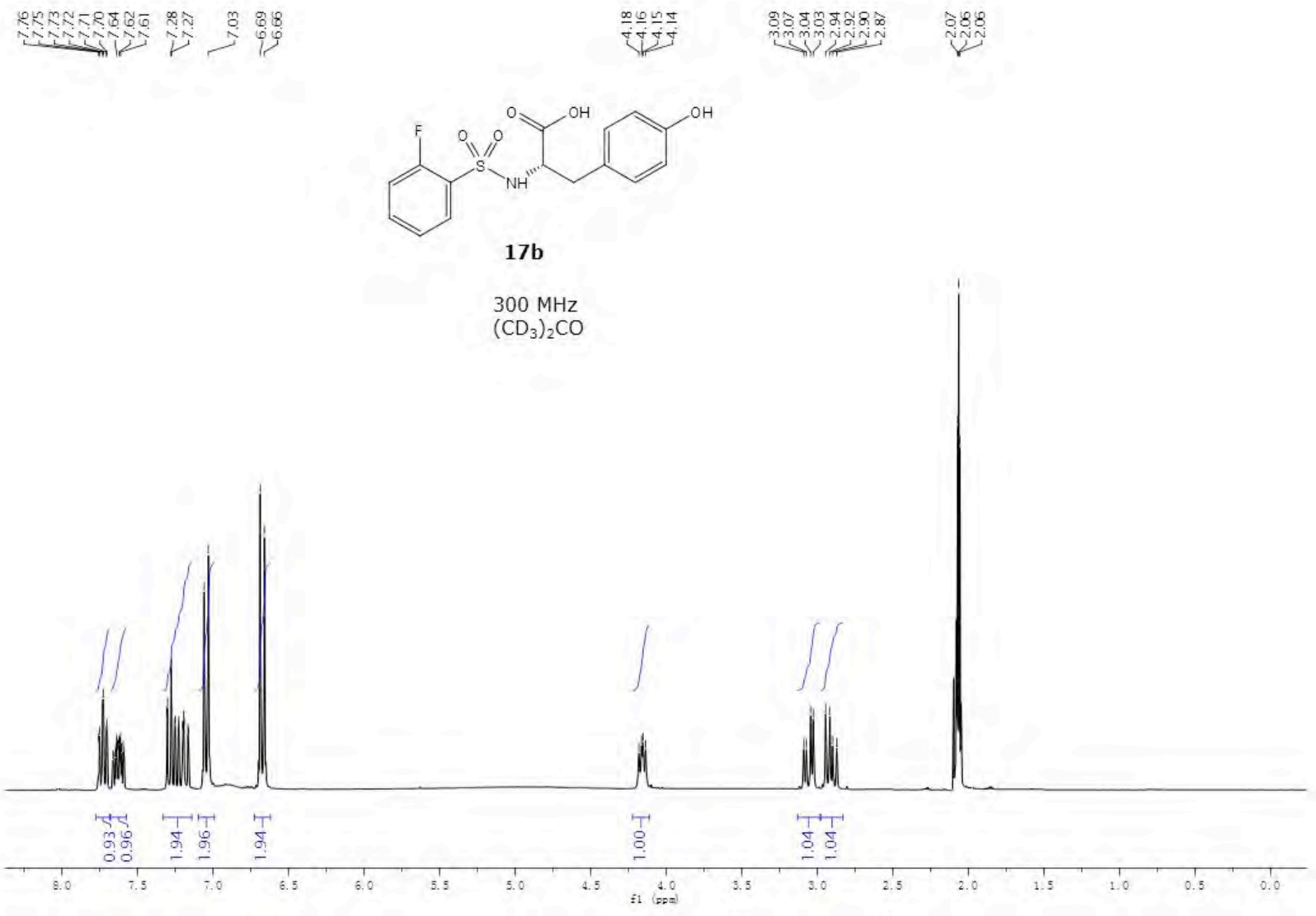

205.470
171.554
166.277
162.951
137.527
137.486
136.533
129.616
129.389
128.242
126.677
115.933
115.631
57.294
38.488
29.745
29.232
28.975
28.719
28.462
28.206
O
OH
S
NH
F
16a
16a MHz
(CD3)2CO
f1 (ppm)

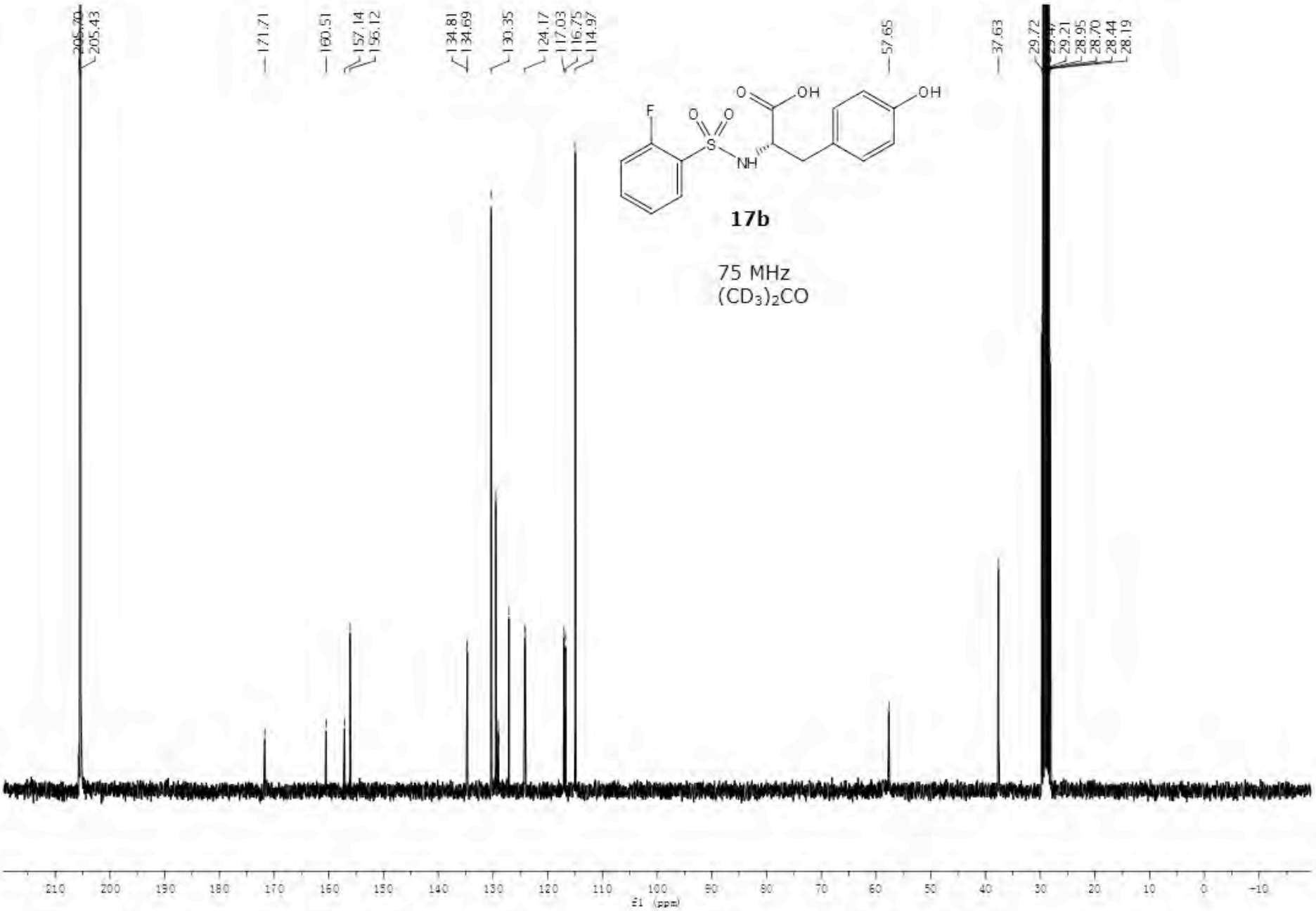

7.783
7.773
7.765
7.755
7.750
7.748
7.742
7.733
7.725
7.715
7.219
7.210
6.940
6.910
4.215
4.197
4.185
4.168
4.156
4.138
3.158
3.140
3.112
3.094
2.974
2.946
2.928
2.900
2.078
2.070
2.063
2.056
2.048
O
OH
O
S
NH
F
16b
300 MHz
(CD3)2CO
2.00
7.03
0.85
0.98
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

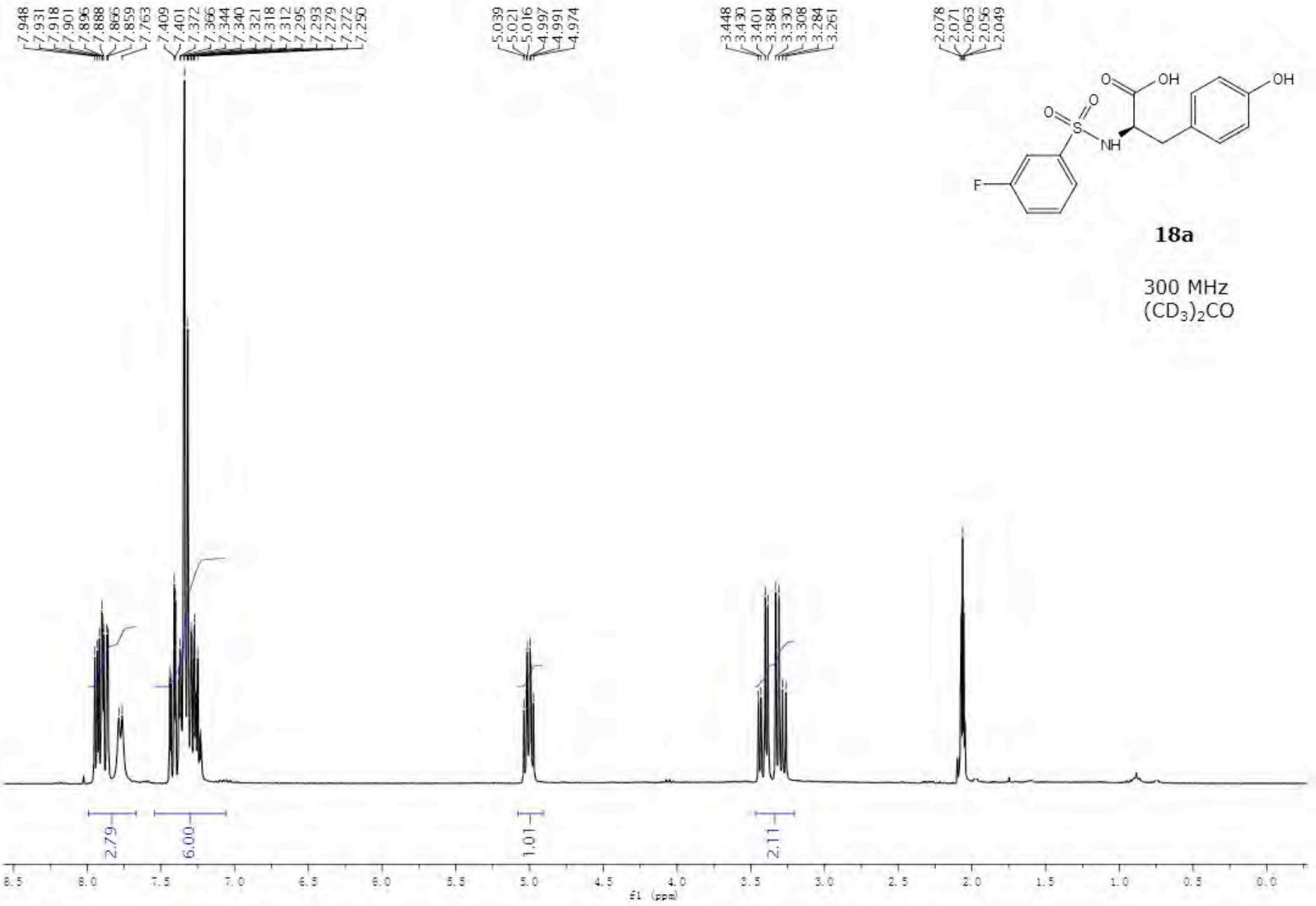

205.491
205.482
171.561
166.280
162.953
137.523
137.482
136.532
129.619
129.391
128.242
125.678
115.936
115.634
57.310
38.484
29.749
29.492
29.236
28.979
28.723
28.466
28.210
OH
O
O
S
NH
F
16b
75 MHz
(CD3)2CO
f1 (ppm)

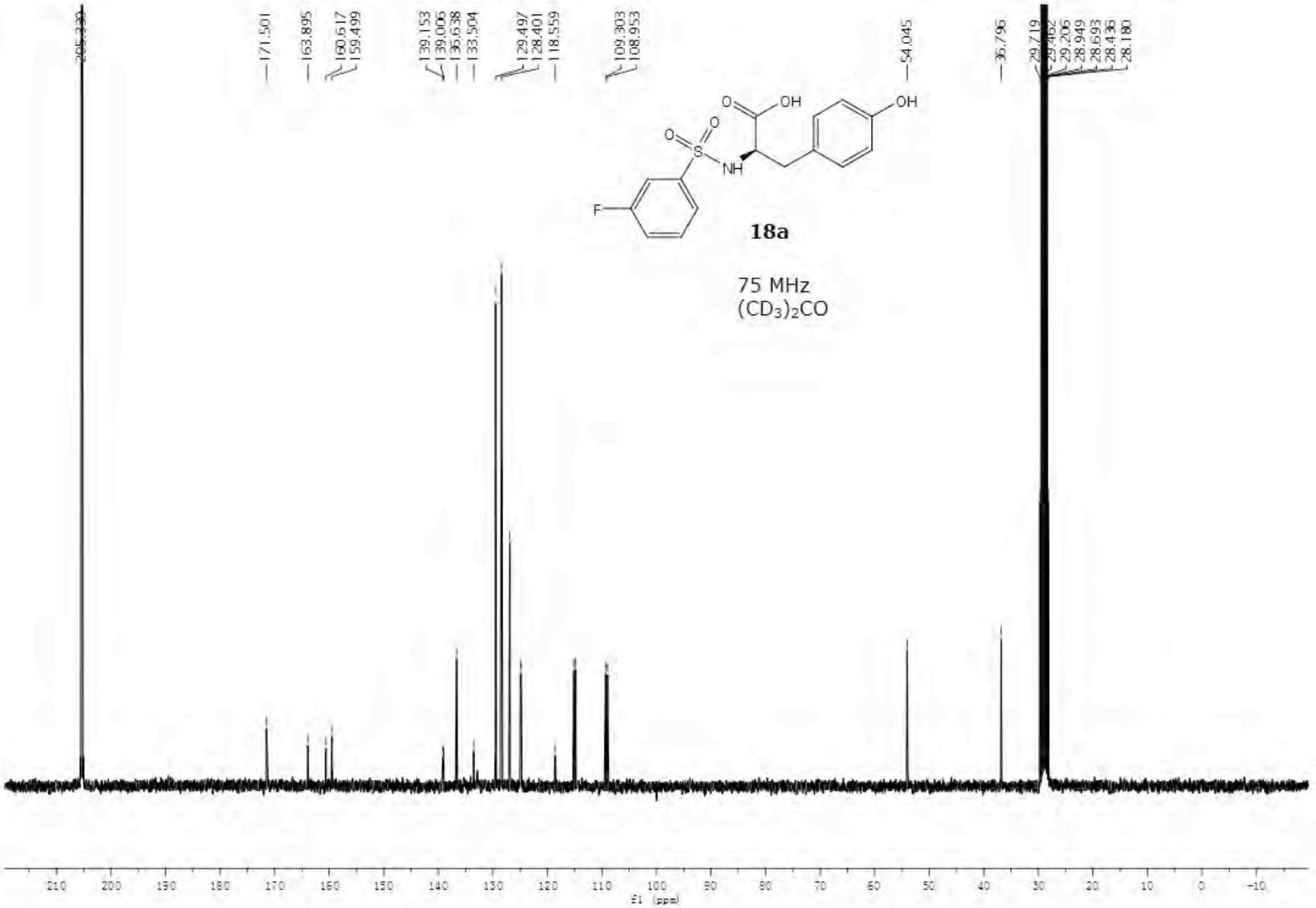

7.754
7.749
7.729
7.724
7.704
7.699
7.665
7.659
7.649
7.640
7.634
7.621
7.618
7.615
7.607
7.596
7.590
7.277
7.194
7.061
7.033
6.690
6.662
4.199
4.181
4.173
4.155
3.097
3.079
3.051
3.033
2.946
2.918
2.899
2.871
2.097
2.087
2.078
2.071
2.064
2.056
2.049
F
O
O
S
NH
O
OH
OH
17a
300 MHz
(CD3)2CO
2.00
2.05
1.96
0.35
1.96
1.01
2.05
f1 (ppm)

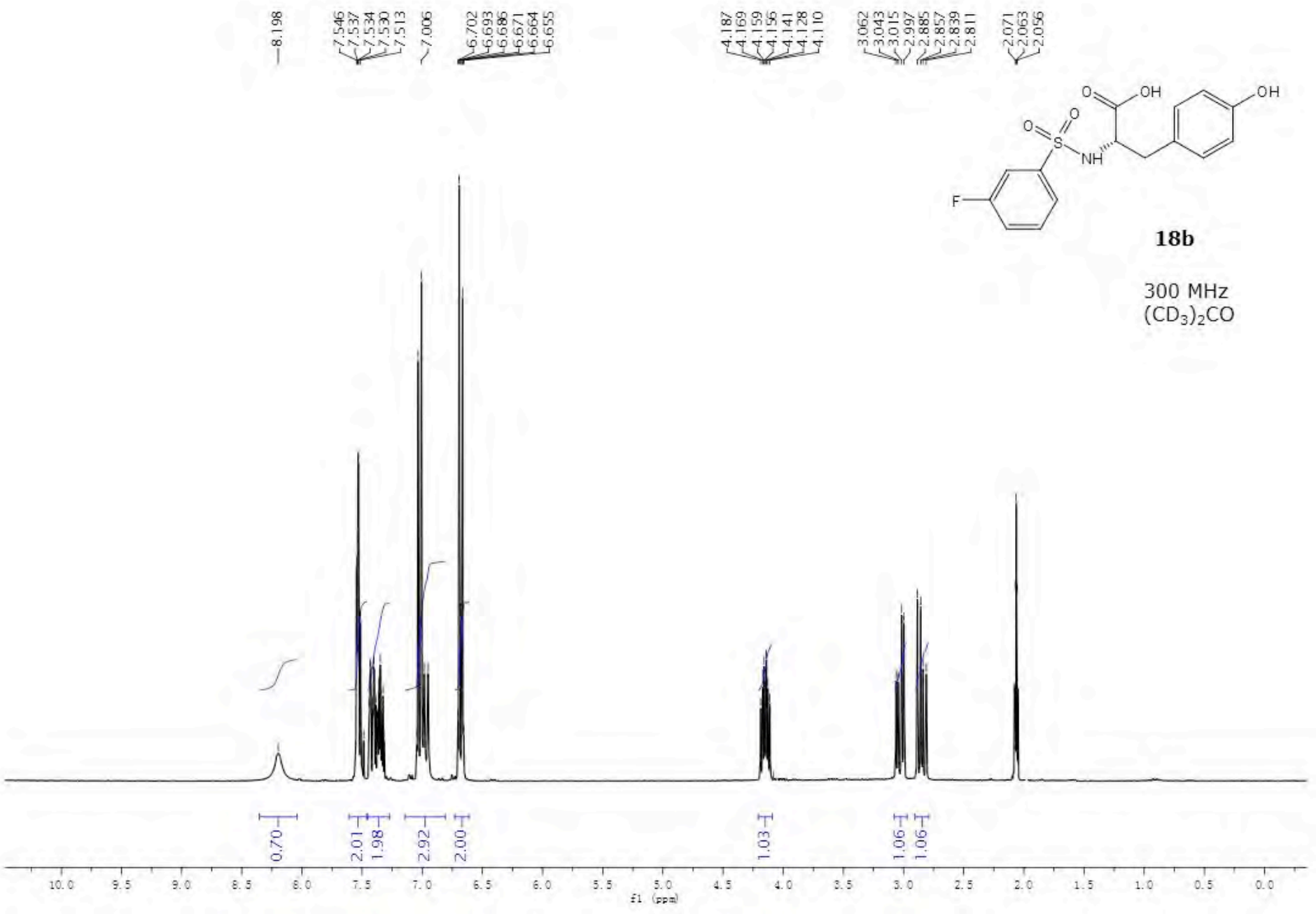

205.42
205.16
171.58
160.90
157.14
156.14
134.81
134.70
130.31
124.17
117.03
116.75
114.98
57.59
37.61
29.72
29.21
28.95
28.70
28.44
28.18
F
O
O
S
NH
O
OH
OH
17a
75 MHz
(CD3)2CO
f1 (ppm)

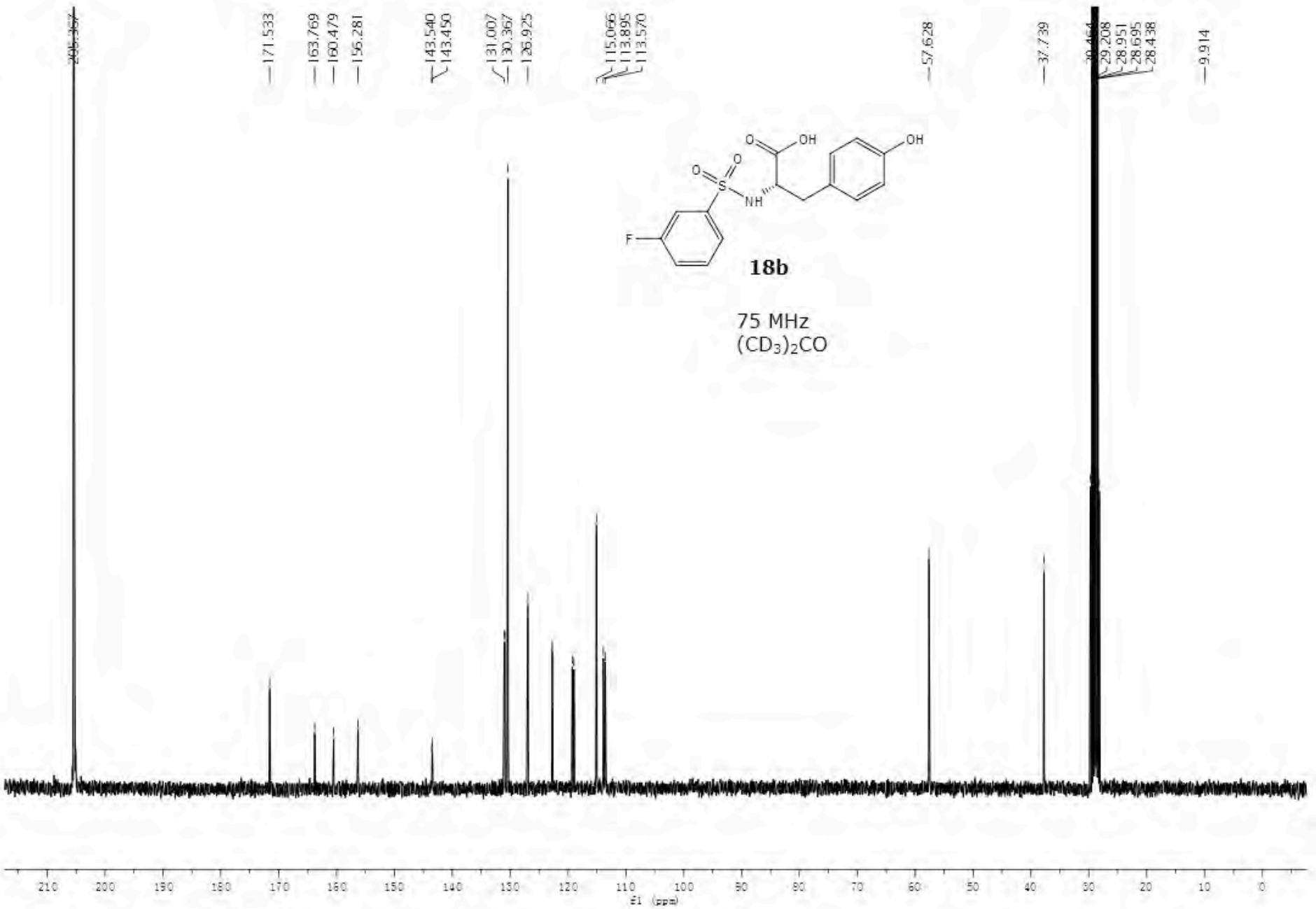

7.76
7.75
7.73
7.72
7.71
7.70
7.64
7.62
7.61
7.28
7.27
7.03
6.69
6.66
4.18
4.16
4.15
4.14
3.09
3.07
3.04
3.03
2.94
2.92
2.90
2.87
2.07
2.06
2.06
F
O
O
S
NH
O
OH
OH
17b
300 MHz
(CD3)2CO
0.93
0.96
1.94
1.96
1.94
1.00
1.04
1.04
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

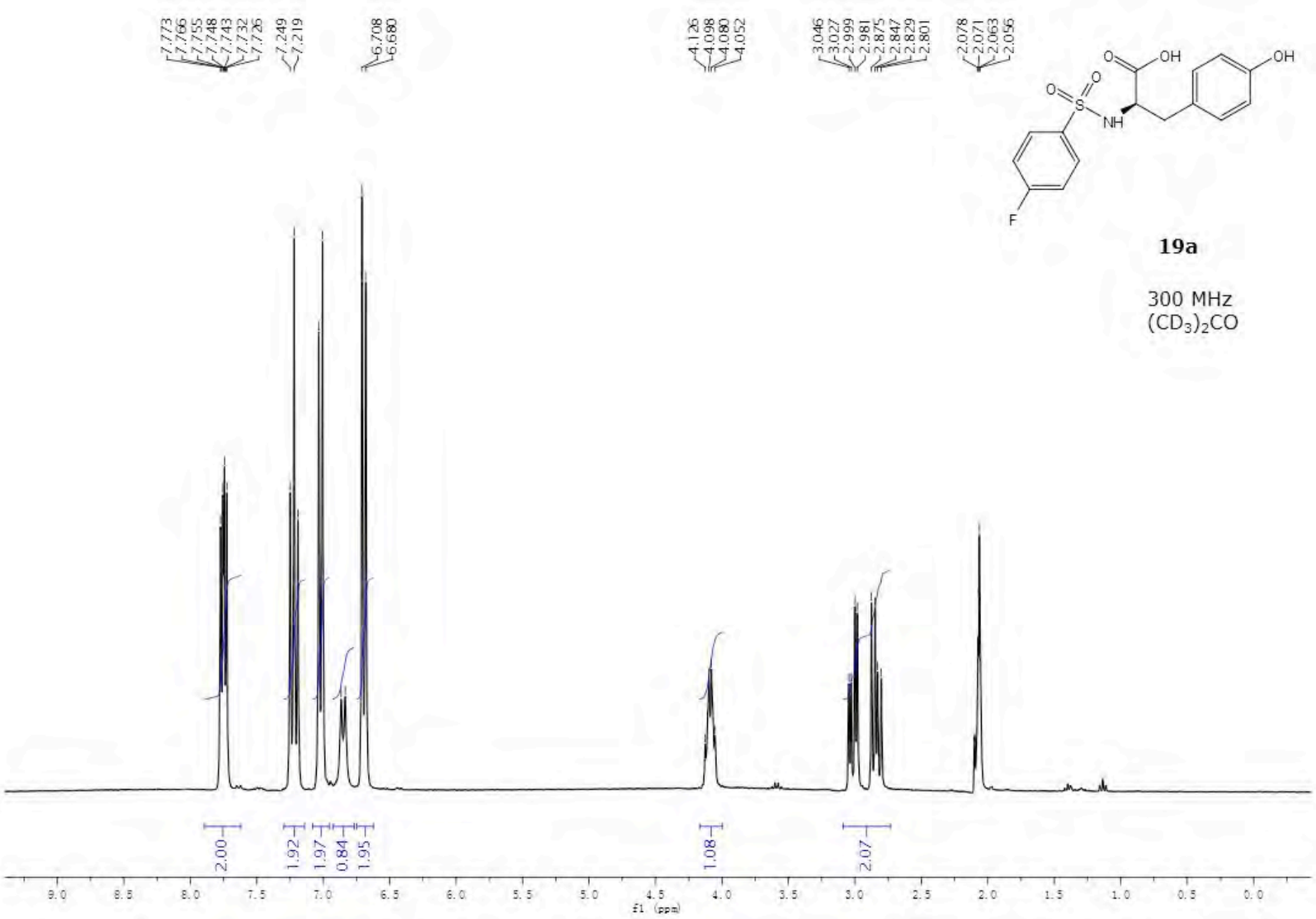

205.70
205.43
171.71
160.51
157.14
155.12
134.81
134.69
130.35
124.17
117.03
116.75
114.97
57.65
37.63
29.72
29.21
28.95
28.70
28.44
28.19
F
O
O
S
NH
O
OH
OH
17b
75 MHz
(CD3)2CO
f1 (ppm)

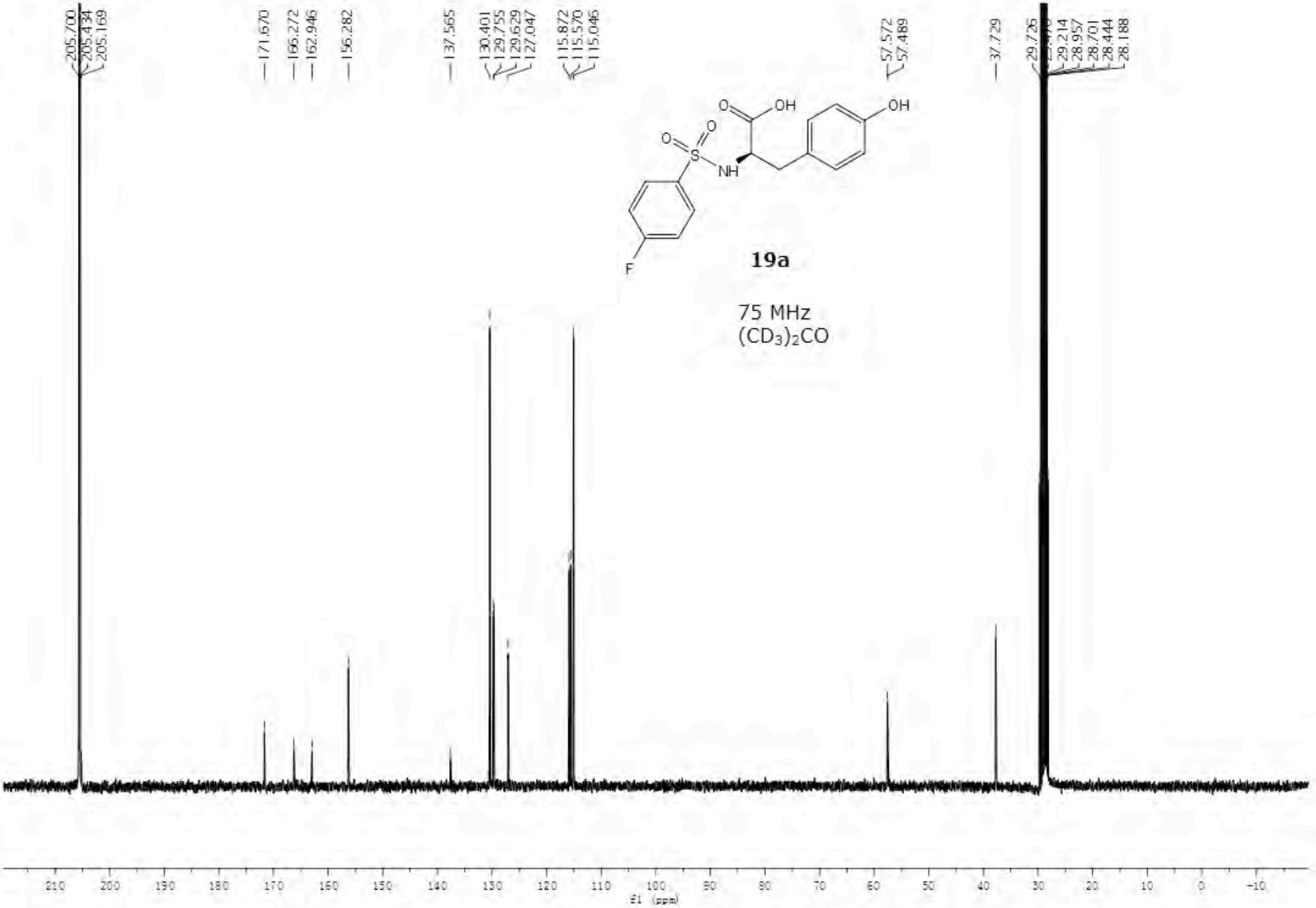

7.948
7.931
7.918
7.901
7.896
7.888
7.865
7.859
7.763
7.409
7.401
7.372
7.366
7.344
7.340
7.321
7.318
7.312
7.295
7.293
7.279
7.272
7.250
5.039
5.021
5.016
4.997
4.991
4.974
3.448
3.430
3.401
3.384
3.330
3.308
3.284
3.261
2.078
2.071
2.063
2.056
2.049
OH
OH
O
O
S
NH
F
18a
300 MHz
(CD3)2CO
2.79
6.00
1.01
2.11
f1 (ppm)

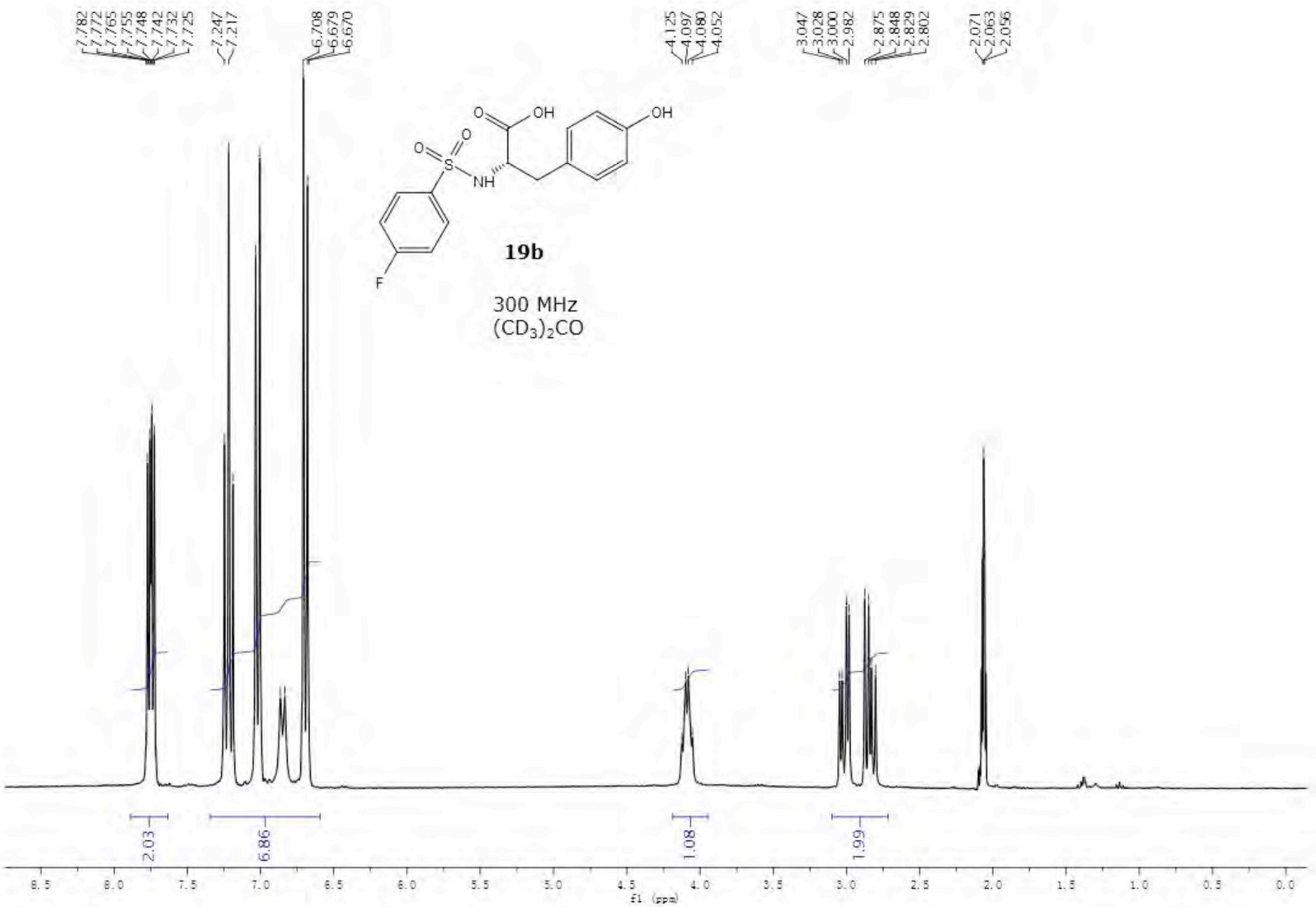

205.330
171.501
163.895
160.617
159.499
139.153
139.006
136.638
133.504
129.497
128.401
118.559
109.303
108.953
54.045
36.796
29.719
29.462
29.206
28.949
28.693
28.436
28.180
OH
OH
O
O
S
NH
F
18a
75 MHz
(CD3)2CO
f1 (ppm)

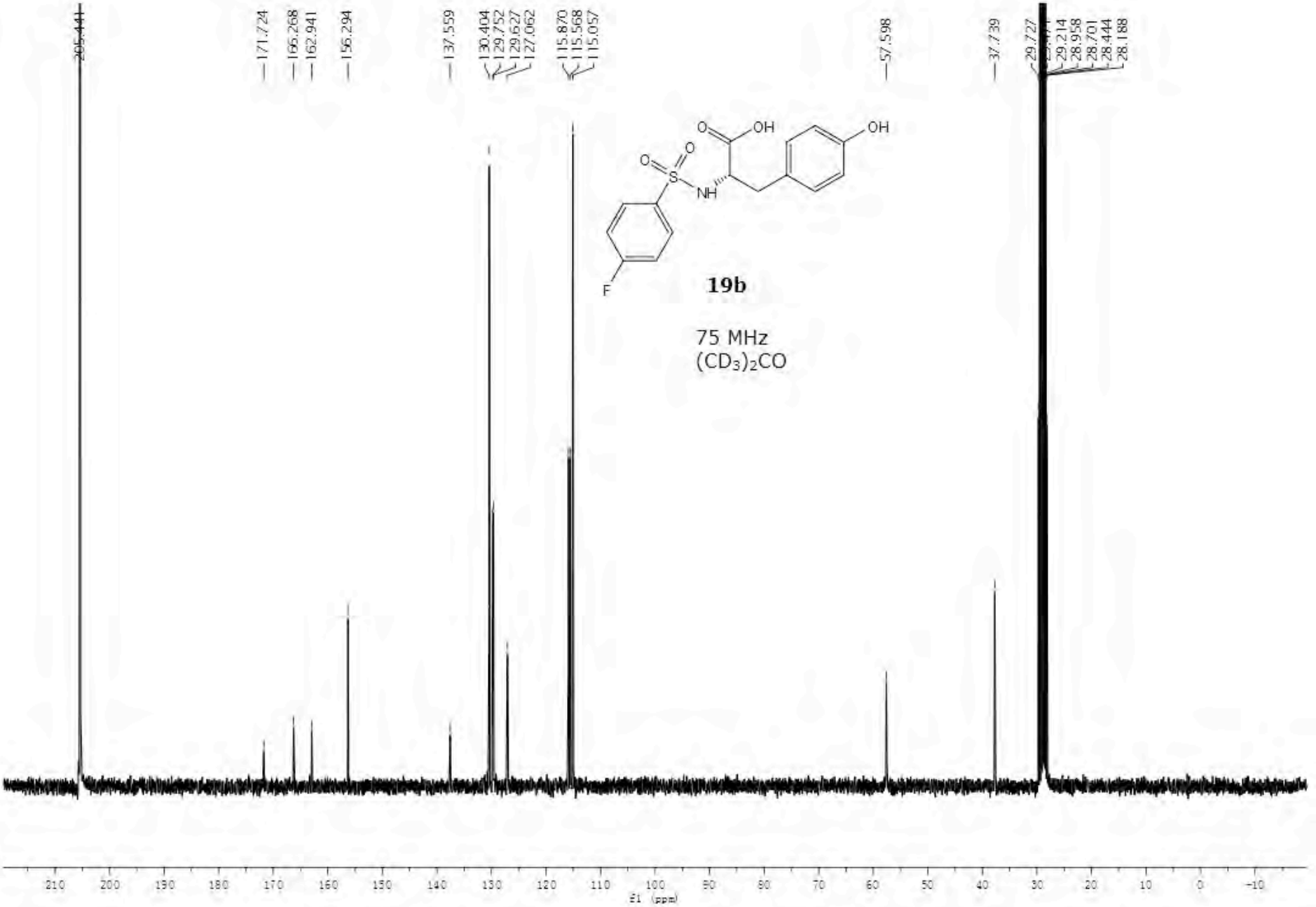

8.198
7.546
7.537
7.534
7.530
7.513
7.006
6.702
6.693
6.686
6.671
6.664
6.655
4.187
4.169
4.159
4.155
4.141
4.128
4.110
3.062
3.043
3.015
2.997
2.885
2.857
2.839
2.811
2.071
2.063
2.056
OH
OH
O
O
S
NH
F
18b
300 MHz
(CD3)2CO
0.70
2.01
1.98
2.92
2.00
1.03
1.06
1.06
f1 (ppm)


205.367
171.533
163.769
160.479
156.281
143.540
143.450
131.007
130.367
126.925
115.066
113.895
113.570
57.628
37.739
29.464
29.208
28.951
28.695
28.438
9.914
OH
OH
O
O
S
NH
F
18b
75 MHz
(CD3)2CO
f1 (ppm)


7.773
7.766
7.755
7.748
7.743
7.732
7.726
7.249
7.219
6.708
6.680
4.126
4.098
4.080
4.052
3.046
3.027
2.999
2.981
2.875
2.847
2.829
2.801
2.078
2.071
2.063
2.056
OH
OH
O
O
S
NH
F
19a
300 MHz
(CD3)2CO
2.00
1.92
1.97
0.84
1.95
1.08
2.07
f1 (ppm)


205.700
205.434
205.169
171.670
166.272
162.946
156.282
137.565
130.401
129.755
129.629
127.047
115.872
115.570
115.046
57.572
57.489
37.729
29.726
29.214
28.957
28.701
28.444
28.188
OH
OH
O
O
S
NH
F
19a
75 MHz
(CD3)2CO
f1 (ppm)


7.782
7.772
7.765
7.755
7.748
7.742
7.732
7.725
7.247
7.217
6.708
6.679
6.670
4.125
4.097
4.080
4.052
3.047
3.028
3.000
2.982
2.875
2.848
2.829
2.802
2.071
2.063
2.056
OH
OH
O
O
S
NH
F
19b
300 MHz
(CD3)2CO
2.03
6.86
1.08
1.99
f1 (ppm)


205.441
171.724
166.268
162.941
156.294
137.559
130.404
129.752
129.627
127.062
115.870
115.568
115.057
57.598
37.739
29.727
29.214
28.958
28.701
28.444
28.188
OH
OH
O
O
S
NH
F
19b
75 MHz
(CD3)2CO
f1 (ppm)