Efficient Routes to a Diverse Array of Amino Alcohol-Derived Chiral Fragments

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General Experimental Procedures

All reactions were performed in round-bottom flasks or glass vials fitted with rubber septa under a positive pressure of nitrogen or argon. Air- and moisture-sensitive liquids were transferred by syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (ca. 10-20 mbar) at 40 °C. Analytical thin-layer chromatography was performed using glass plates pre-coated with silica gel (250 μm, 60 Å, SiliCycle) impregnated with fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (where applicable), then were stained by submersion in aqueous potassium permanganate or ceric ammonium molybdate solutions followed by brief heating or *via* submersion in a silica-supported iodine chamber. Flash chromatography was performed using a CombiFlash Rf 150 purification system (Teledyne Isco) and RediSep normal-phase silica flash columns (60 Å, 35-70 μm, Teledyne Isco). Unless otherwise indicated, reagents were used as purchased from a commercial supplier. Solvents were

dispensed under a nitrogen atmosphere from a double alumina column solvent purification system or purchased from a commercial supplier in air- and moisture-free packaging.

Instrumentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using Bruker UltraShield Avance 300 (300 MHz) or Bruker UltraShield Avance 400 (400 MHz) NMR spectrometers at ambient temperature. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26 ppm; $(CD)_3SO$, δ 2.50 ppm; CD_3OD, δ 3.31 ppm; D_2O, δ 4.79 ppm; C_5D_5N δ 8.74 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), integration, coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance spectra were recorded using Bruker UltraShield Avance 300 (75 MHz) or Bruker UltraShield Avance 400 (100 MHz) NMR spectrometers at ambient temperature. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CHCl_3$, δ 77.1 ppm; $(CD)_3SO$, δ 39.5 ppm; CD_3OD, δ 49.0 ppm; C_5D_5N δ 150.4 ppm). Infrared (IR) spectra were obtained using a Thermo Electron Nicolet Avatar 370 DTGS FT-IR with a Smart Orbit diamond attenuated total reflectance (ATR) accessory. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad). Optical rotation measurements were obtained using a Rudolph Research Autopol IV polarimeter with a 2 mL, 1.0 dm, TempTrol cell. Data are represented as follows: temperature, wavelength (D = 589 nm), specific rotation, and concentration (*c*) in 10 mg/mL. ESI-MS spectra were obtained on a Waters 2975 LC/MicroMass ZQ 2000 single quad mass spectrometer. High-resolution mass spectra (HRMS) were obtained at The Broad Institute of Harvard and MIT analytical chemistry facility. Thermodynamic (equilibrium) solubility measurements were performed at Bayer Pharma AG *via* a modified shake-flask method with LC-MS/MS quantification.

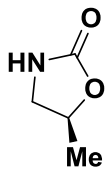
Preparation of Amino Alcohol Building Blocks

Amino alcohols **1**-**4** and **7** were purchased from commercial sources. Amino alcohols **5**, **6**, **8**, and **9** were prepared according to previously published procedures.[1-2]

Abbreviations

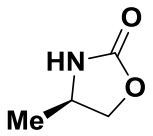
Boc	*tert*-butoxycarbonyl
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
ELSD	evaporative light scattering detector
ESI	electrospray ionization
EtOAc	ethyl acetate
FTIR	Fourier transform infrared spectroscopy
HRMS	high-resolution mass spectra
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LRMS	low-resolution mass spectra
MeCN	acetonitrile
MeOH	methanol
NMR	nuclear magnetic resonance
PBS	phosphate-buffered saline
RT	room temperature
SID	surface-induced dissociation
THF	tetrahydrofuran
UPLC	ultra performance liquid chromatography
UV	ultraviolet

General Procedure A (oxazolidinones). The amino alcohol (1.0 equiv.) and CDI (1.0 equiv.) were dissolved in THF (0.7 M), followed by dropwise addition of triethylamine (1.0 equiv.) at RT. After stirring for 16 h at 60 °C, the solution was concentrated *in vacuo* and the residue was purified *via* flash chromatography on silica gel (gradients indicated) to afford the oxazolidinone.

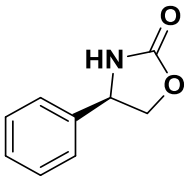


(*S*)-5-methyloxazolidin-2-one (10a). (*S*)-1-aminopropan-2-ol (1.03 mL, 13.3 mmol, 1.0 equiv.), diethyl carbonate (1.94 mL, 16.0 mmol, 1.2 equiv.), and sodium ethoxide (9.1 mg, 0.133 mmol,

0.01 equiv.) were charged to a three-necked flask equipped with a digital thermocouple, magnetic stir bar, and a Vigreux column fitted with a distillation head. The neat mixture was heated to T_{pot} = 150 °C; ethanol began to distill at T_{pot} = 95 °C. After bulk ethanol distillation (ca. 1 mL), the solution was cooled to RT and concentrated *in vacuo* to yield the title compound as a yellow oil (1.04 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.90 (brs, 1H), 4.83 – 4.71 (m, 1H), 3.72 – 3.67 (m, 1H), 3.22 – 3.17 (m, 1H), 1.44 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 160.1, 73.6, 47.6, 20.7; HRMS (ESI) *m/z* calcd for $[C_4H_7NO_2 + H]^+$ 102.0555 found 102.0555. Purity: >75% (^{1}H NMR).[3]

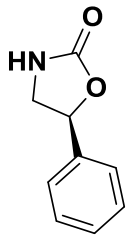


(*R*)-4-methyloxazolidin-2-one (10b). (*R*)-2-aminopropan-1-ol (1.04 mL, 13.3 mmol, 1.0 equiv.), diethyl carbonate (1.94 mL, 16.0 mmol, 1.2 equiv.), and sodium ethoxide (9.1 mg, 0.133 mmol, 0.01 equiv.) were charged to a three-necked flask equipped with a digital thermocouple, magnetic stir bar, and a Vigreux column fitted with a distillation head. The neat mixture was heated to 125 °C; ethanol began to distill at T_{pot} = 95 °C. After bulk ethanol distillation, the solution was cooled to 60 °C and poured into cold chloroform (2.6 mL). The solution was thoroughly chilled in an ice-water bath and the resulting suspension was filtered to afford the title compound as a white solid (1.13 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.04 (brs, 1H), 4.49 (t, 1H, J = 7.7 Hz), 4.06 – 3.92 (m, 2H), 1.29 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 160.0, 71.8, 48.4, 20.9; HRMS (ESI) *m/z* calcd for $[C_4H_7NO_2 + H]^+$ 102.0555 found 102.0556. Purity: >85% (^{1}H NMR).[4]

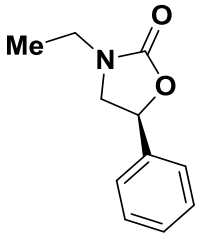


(*R*)-4-phenyloxazolidin-2-one (10c). Using general procedure **A** with (*R*)-2-amino-2-phenylethanol (183 mg, 1.33 mmol, 1.0 equiv.), CDI (216 mg, 1.33 mmol, 1.0 equiv.), and triethylamine (186 µL, 1.33 mmol, 1.0 equiv.) in THF (2 mL). After stirring for 16 h at 60 °C and purification *via* flash chromatography on silica gel (0 to 80% EtOAc/hexanes), the title

compound was afforded as a white solid (87 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.45 – 7.35 (m, 5H), 5.27 (brs, 1H), 4.96 (t, 1H, J = 7.1 Hz), 4.75 (t, 1H, J = 8.6 Hz), 4.21 (dd, 1H, J = 8.6, 7.1 Hz); HRMS (ESI) *m/z* calcd for $[C_9H_9NO_2 + H]^+$ 164.0712 found 164.0709. Purity: 79.1% (UPLC, UV_{214}).[5]

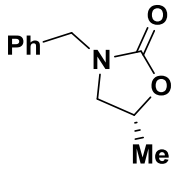


(*S*)-5-phenyloxazolidin-2-one (10d). Using general procedure **A** with (*S*)-2-amino-1-phenylethanol (183 mg, 1.33 mmol, 1.0 equiv.), CDI (216 mg, 1.33 mmol, 1.0 equiv.), and triethylamine (186 µL, 1.33 mmol, 1.0 equiv.) in THF (2 mL). After stirring for 16 h at 60 °C and purification *via* flash chromatography on silica gel (0 to 5% MeOH/DCM), the title compound was afforded as a white solid (184 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.45 – 7.35 (m, 5H), 5.63 (t, 1H, J = 8.6 Hz), 5.47 (brs, 1H), 3.99 (td, 1H, J = 8.5, 0.9 Hz), 3.55 (ddd, 1H, J = 8.6, 7.7, 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 159.5, 138.6, 129.1, 125.8, 78.0, 48.4; HRMS (ESI) *m/z* calcd for $[C_9H_9NO_2 + H]^+$ 164.0712 found 164.0711. Purity: 96.2% (UPLC, UV_{214}).[6]

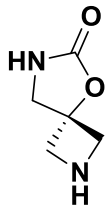


(*S*)-3-ethyl-5-phenyloxazolidin-2-one (10e). Using general procedure **A** with (*S*)-2-(ethylamino)-1-phenylethanol (220 mg, 1.33 mmol, 1.0 equiv.), CDI (216 mg, 1.33 mmol, 1.0 equiv.), and triethylamine (186 µL, 1.33 mmol, 1.0 equiv.) in THF (2 mL). After stirring for 16 h at 60 °C and purification *via* flash chromatography on silica gel (0 to 5% MeOH/DCM), the title compound was afforded as a colorless oil (101 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.44 – 7.33 (m, 5H), 5.49 (dd, 1H, J = 8.6, 7.7 Hz), 3.92 (t, 1H, J = 8.6 Hz). 3.47 – 3.27 (m, 3H), 1.18 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 157.8, 139.1, 129.0, 128.9, 125.7, 74.5, 51.8,

39.1, 12.7; HRMS (ESI) *m/z* calcd for $[C_{11}H_{13}NO_2 + H]^+$ 192.1025 found 192.1027. Purity: 97.6% (UPLC, UV_{214}).[7]



(*R*)-3-benzyl-5-methyloxazolidin-2-one (10f). Using general procedure **A** with (*R*)-1-(benzylamino)-propan-2-ol (220 mg, 1.33 mmol, 1.0 equiv.), CDI (216 mg, 1.33 mmol, 1.0 equiv.), and triethylamine (186 µL, 1.33 mmol, 1.0 equiv.) in THF (2 mL). After stirring for 16 h at 60 °C and purification *via* flash chromatography on silica gel (0 to 5% MeOH/DCM), the title compound was afforded as a colorless oil (151 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.39 – 7.25 (m, 5H), 4.67 – 4.56 (m, 1H), 4.47 – 4.35 (m, 2H), 3.49 (t, 1H, *J* = 8.4 Hz), 2.97 (dd, 1H, *J* = 8.4, 6.9 Hz), 1.38 (t, 3H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 158.2, 136.1, 129.0, 128.3, 128.0, 70.2, 51.0, 48.5, 20.1; HRMS (ESI) *m/z* calcd for $[C_{11}H_{13}NO_2 + H]^+$ 192.1025 found 192.1028. Purity: 98.2% (UPLC, UV_{214}).

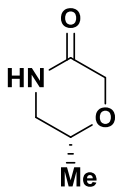


5-oxa-2,7-diazaspiro[3.4]octan-6-one (10g). Using general procedure **A** and *N*-Boc deprotection.

tert-butyl-3-(aminomethyl)-3-hydroxyazetidine-1-carboxylate (1.0 g, 4.94 mmol, 1.0 equiv.), CDI (1.0 g, 6.18 mmol, 1.25 equiv.), and triethylamine (861 µL, 6.18 mmol, 1.25 equiv.) were combined in THF (7.5 mL). After stirring for 16 at RT and purification *via* flash chromatography on silica gel (0 to 20% MeOH/DCM) and trituration (diethyl ether), *tert*-butyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate (**S1**) was isolated as crystals (87.4 mg, 8%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.4 (brs, 1H), 4.30 (dd, 2H, *J* = 10.0, 1.3 Hz), 4.02 (dd, 2H, *J* = 10.0, 1.3 Hz), 3.79 (s, 2H), 1.44 (s, 9H); LRMS (ESI) *m/z* calcd for $[C_{10}H_{16}N_2O_4 - H]^-$ 227.03 found 227.18.

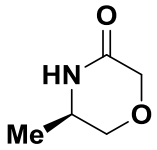
N-Boc deprotection. *tert*-butyl-6-oxo-5-oxa-2,7-diazaspiro[3.4]octane-2-carboxylate was suspended in water (7.5 mL) and heated to 110 °C for 3 h, after which the material had fully dissolved. After concentration *in vacuo*, 5-oxa-2,7-diazaspiro[3.4]octan-6-one was obtained as a white solid (48 mg, quant.). ^{1}H NMR (300 MHz, CD_3OD) δ_H 3.95 – 3.92 (m, 2H), 3.79 (s, 2H), 3.69 – 3.66 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ_C 160.6, 81.9, 59.5, 51.6. HRMS (ESI) *m/z* calcd for $[C_5H_8N_2O_2 + H]^+$ 129.0664 found 129.0666. Purity: 92.2% (UPLC, ELSD).

General Procedure B (morpholinones). The amino alcohol (1.0 equiv.) was added to a suspension of sodium hydride (60% in mineral oil; 2.25 equiv.) in THF (0.20 M based on amino alcohol) at 0 °C under a nitrogen atmosphere. After stirring at 0 °C for 10 min., the solution was warmed to RT. After 30 min., ethyl chloroacetate (1.25 equiv.) was added dropwise and the resulting solution was stirred at RT. After 16 h, saturated aqueous ammonium chloride solution was added. The layers were separated and the aqueous layer was extracted with EtOAc three times. Combined organic extracts were sequentially washed with saturated aqueous sodium chloride solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was adsorbed onto silica or celite and purified *via* flash chromatography on silica gel (gradients indicated) to afford the morpholinone.

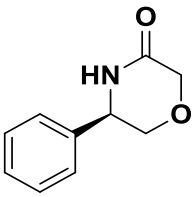


(*R*)-6-methylmorpholin-3-one (11a). Using general procedure **B** with minor modifications, (*R*)-1-aminopropan-2-ol (250 mg, 3.33 mmol, 1.0 equiv.), sodium hydride (60% in mineral oil; 333 mg, 2.5 mmol), and ethyl chloroacetate (0.445 mL, 4.16 mmol, 1.25 equiv.) in DMF (33 mL). After 16 h at 100 °C and removal of bulk solvent under reduced pressure, the residue was partitioned between water and a 3:1 mixture of chloroform-isopropanol. After extracting the aqueous layer with the chloroform-isopropanol mixture four times, the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified *via* flash chromatography on silica gel (0 to 5% MeOH/EtOAc) to yield the title compound as a white solid (20.2 mg, 5.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 (brs, 1H), 4.21 (d, 1H, J = 16.8 Hz),

4.13 (d, 1H, *J* = 16.8 Hz), 3.84 – 3.76 (m, 1H), 3.27 – 3.17 (m, 1H), 1.24 (d, 3H, *J* = 6.16 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.4, 69.3, 67.6, 47.8, 18.3; HRMS (ESI) *m/z* calcd for $[C_5H_9NO_2 + H]^+$ 116.0712 found 116.0714. Purity: >80% (UPLC, UV_{214}).[8]

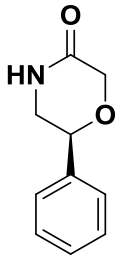


(*R*)-5-methylmorpholin-3-one (11b). Using general procedure **B** with (*R*)-2-aminopropan-1-ol (500 mg, 6.66 mmol, 1.0 equiv.), sodium hydride (60% in mineral oil; 599 mg, 15.0 mmol, 2.25 equiv.), and ethyl chloroacetate (0.891 mL, 8.32 mmol, 1.25 equiv.) in THF (33 mL). After stirring for 16 h and an aqueous work-up, the residue was purified *via* flash chromatography on silica gel(0 to 8% MeOH/DCM; 1% NH_3 modified) to yield a white solid (350 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.07 (brs, 1H), 4.07 (d, 1H, *J* = 16.7 Hz), 3.98 (d, 1H, *J* = 16.7 Hz), 3.79 (dd, 1H, *J* = 11.6, 3.9 Hz), 3.64 – 3.57 (m, 1H), 3.33 – 3.23 (m, 1H), 1.09 (d, 3H, *J* = 6.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.6, 69.2, 67.2, 47.1, 18.0; HRMS (ESI) *m/z* calcd for $[C_5H_9NO_2 + H]^+$ 116.0712 found 116.0713. Purity: 94.0% (UPLC, UV_{214}).[8]

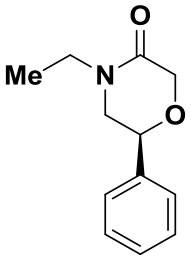


(*R*)-5-phenylmorpholin-3-one (11c). Using general procedure **B** with (*R*)-2-amino-2-phenylethanol (5.10 g, 36.4 mmol, 1.0 equiv.), sodium hydride (60% in mineral oil; 3.28 g, 82.0 mmol, 2.25 equiv.), and ethyl chloroacetate (4.88 mL, 45.6 mmol, 1.25 equiv.) in THF (200 mL). After stirring for 16 h and an aqueous work-up, the residue was purified *via* flash chromatography on silica gel (0 to 10% MeOH/DCM; 1% NH_3 modified) to afford the title compound as a white solid (2.38 g, 37%). $^{23}[\alpha]_D$ = -99.2 (*c* = 1.00; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.43 – 7.31 (m, 5H), 6.29 (brs, 1H), 4.75 (dd, 1H, *J* = 8.4, 4.1 Hz), 4.32 (d, 1H, *J* = 16.8 Hz), 4.23 (d, 1H, *J* = 16.8 Hz), 4.05 (dd, 1H, *J* = 11.8, 4.1 Hz), 3.56 (dd, 1H, *J* = 11.8, 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.9, 137.7, 129.2, 128.9, 126.8, 70.4, 68.0, 56.9; FTIR

(neat; cm^{-1}) 3179 (br), 3065 (w), 2861 (w), 1668 (s); HRMS (ESI) *m/z* calcd for $[C_{10}H_{11}NO_2 + H]^+$ 178.0868 found 178.0872. Purity: 99.1% (UPLC, UV_{214}).

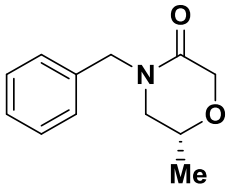


(*S*)-6-phenylmorpholin-3-one (11d). Using general procedure **B** with (*S*)-2-amino-1-phenylethanol (5.0 g, 36.4 mmol, 1.0 equiv.), sodium hydride (60% in mineral oil; 3.28 g, 82.0 mmol, 2.25 equiv.), and ethyl chloroacetate (4.88 mL, 45.6 mmol, 1.25 equiv.) in THF (200 mL). After stirring for 16 h and an aqueous work-up, the residue was purified *via* flash chromatography on silica gel (0 to 9% MeOH/DCM; 1% NH_3 modified) to yield a white solid (1.85 g, 29%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.98 (brs, 1H), 7.38 – 7.31 (m, 5H), 4.72 (dd, 1H, *J* = 8.7, 4.9 Hz), 4.41 (d, 1H, *J* = 16.9 Hz), 4.31 (d, 1H, *J* = 16.9 Hz), 3.54 – 3.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.2, 137.8, 128.8, 128.7, 126.1, 75.2, 68.2, 47.9; HRMS (ESI) *m/z* calcd for $[C_{10}H_{11}NO_2 + H]^+$ 178.0868 found 178.0873. Purity: 96.4% (UPLC, UV_{214}).

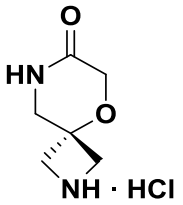


(*S*)-4-ethyl-6-phenylmorpholin-3-one (11e). Using general procedure **B** with minor modifications, (*S*)-2-(ethylamino)-1-phenylethanol (100 mg, 0.605 mmol 1.0 equiv.), sodium hydride (60% in mineral oil; 26.6 mg, 0.667 mmol, 1.1 equiv.), and ethyl chloroacetate (64.8 µL, 0.605 mmol, 1.00 equiv.) in THF (7.1 mL). After stirring for 3 h at 70 °C and an aqueous work-up, the residue was purified *via* flash chromatography on silica gel (0 to 60% EtOAc/hexanes) to yield a white, crystalline solid (60 mg, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.40 – 7.33 (m, 5H), 4.75 (dd, 1H, *J* = 11.4, 3.3 Hz), 4.38 (d, 1H, *J* = 16.5 Hz), 4.26 (d, 1H, *J* = 16.5 Hz), 3.63 – 3.31 (m, 3H), 3.31 (dd, 1H, *J* = 11.4, 3.3 Hz), 1.15 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz,

$CDCl_3$) δ_C 166.1, 137.9, 128.6, 128.5, 126.0, 75.5, 68.1, 52.0, 41.3, 12.1; HRMS (ESI) *m/z* calcd for $[C_{12}H_{15}NO_2 + H]^+$ 206.1181 found 206.1183. Purity: 98.8% (UPLC, UV_{214}).



(*R*)-4-benzyl-6-methylmorpholin-3-one (11f). Using general procedure **B**, (*R*)-1-(benzylamino)propan-2-ol (250 mg, 1.51 mmol 1.0 equiv.), sodium hydride (60% in mineral oil; 136 mg, 3.40 mmol, 2.25 equiv.), and ethyl chloroacetate (202 µL, 1.89 mmol, 1.25 equiv.) in THF (6.0 mL). After stirring for 16 h and an aqueous work-up, the residue was purified *via* flash chromatography on silica gel (0 to 5% MeOH/DCM) to yield a clear, pale yellow oil (255 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H. 7.35 – 7.23 (m, 5H), 4.69 (d, 1H, *J* = 14.7 Hz), 4.46 (d, 1H, *J* = 14.7 Hz), 4.30 (d, 1H, *J* = 16.6 Hz), 4.19 (d, 1H, *J* = 16.6 Hz), 3.86 – 3.76 (m, 1H), 3.14 – 3.00 (m, 2H), 1.18 (d, 3H, *J* = 1.18 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 166.9, 136.3, 128.9, 128.3, 127.8, 69.8, 67.9, 51.8, 49.6, 18.4; HRMS (ESI) *m/z* calcd for $[C_{12}H_{15}NO_2 + H]^+$ 206.1181 found 206.1183. Purity: 97.8% (UPLC, UV_{214}).



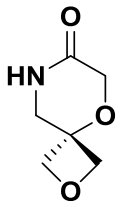
5-oxa-2,8-diazaspiro[3.5]nonan-7-one hydrochloride (11g). Prepared in three steps *via* an alternative procedure.

Step 1. *tert*-Butyl 3-(aminomethyl)-3-hydroxyazetidine-1-carboxylate (2.0 g, 9.89 mmol, 1 equiv.) was added to a solution of triethylamine (1.8 mL, 12.9 mmol, 1.3 equiv.) in DCM (50 mL) at 0 °C. A solution of chloroacetyl chloride (945 µL, 11.9 mmol, 1.2 equiv.) in DCM (50 mL) was added *via* dropping funnel to the cooled amino alcohol solution over 15 min. The solution was stirred at 0 °C for 30 min. After stirring at RT for 4 h, the solution was concentrated *in vacuo* and purified *via* flash chromatography on silica gel (0 to 7% MeOH/DCM) to yield *tert*-

butyl 3-((2-chloroacetamido)methyl)-3-hydroxyazetidine-1-carboxylate (**S2**) as a beige foam (2.42 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.18 (br t, 1H, J = 4.6 Hz), 4.45 (brs, 1H), 4.09 (s, 2H), 3.84 (s, 4H), 3.63 (d, 1H, J = 4.6 Hz), 1.42 (s, 9H); LRMS (ESI) *m/z* calcd for $[C_{11}H_{19}N_2O_4Cl - H]^-$ 277.10 found 277.00.

Step 2. *tert*-Butyl 3-((2-chloroacetamido)methyl)-3-hydroxyazetidine-1-carboxylate (2.42 g, 8.68 mmol, 1.0 equiv.) was added to a stirred suspension of sodium hydride (608 mg, 15.2 mmol, 1.75 equiv.) in dioxane (87 mL) at 0 °C. The solution was heated to 80 °C. After 16 h, an additional portion of sodium hydride (300 mg) was added. After an additional 6 h, the solution was cooled to RT and quenched *via* the careful addition of saturated aqueous ammonium chloride solution. Volatiles were removed under reduced pressure and the residue was partitioned between DCM and water. The aqueous layer was extracted with DCM three times. Combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified *via* flash chromatography on silica gel (0 to 9% MeOH/DCM) to yield *tert*-butyl 7-oxo-5-oxa-2,8-diazasipro[3.5]nonane-2-carboxylate (**S3**) as a white solid (450 mg, 21%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.30 – 7.35 (m, 1H), 4.18 (s, 2H), 3.96 (d, 2H, J = 9.5), 3.80 (d, 2H, J = 9.5 Hz), 3.52 (s, 2H), 1.42 (s, 9H); LRMS (ESI) *m/z* calcd for $[C_{11}H_{18}N_2O_4 + H]^+$ 243.13 found 242.92.

Step 3. *tert*-Butyl-7-oxo-5-oxa-2,8-diazasipro[3.5]nonane-2-carboxylate (250 mg, 1.03 mmol, 1.0 equiv.) was dissolved in dioxane (2.6 mL) and a 4.0 M solution of hydrochloric acid in dioxane (1290 µL, 5.16 mmol, 5.0 equiv.) was added in one portion at RT. After 6 h, a white solid had precipitated. The suspension was concentrated *in vacuo*, triturated with diethyl ether, and filtered over a fine frit to yield the title compound as a white solid (203 mg, quant.). ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ_H 9.93 (brs, 1H), 9.64 (brs, 1H), 8.18 (s, 1H), 4.12 (s, 2H), 4.03 – 3.97 (m, 2H), 3.91 – 3.87 (m, 2H), 3.56 (d, 2H, J = 2.55 Hz); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ_C 166.0, 70.3, 63.2, 53.1, 45.4; HRMS (ESI) *m/z* calcd for $[C_{12}H_{15}NO_2 + H]^+$ 143.0821 found 143.0818. Purity: >99.9% (UPLC, ELSD).

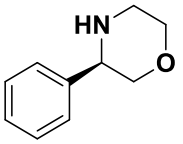


2,5-dioxa-8-azaspiro[3.5]nonan-7-one (11h). Prepared in two steps *via* an alternate procedure.

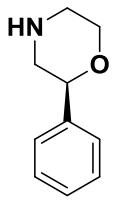
Step 1. 3-(aminomethyl)oxetan-3-ol (900 mg, 8.73 mmol, 1.0 equiv.) was dissolved in MeCN (58 mL) and water (27.3 mL). Potassium carbonate (2.41 g, 17.5 mmol, 2.0 equiv.) was added, followed by dropwise addition of chloroacetyl chloride (1.04 mL, 13.1 mmol, 1.5 equiv.) at 0 °C. After stirring for 1 h at 0 °C, the crude mixture was transferred to separatory funnel and extracted with a 3:1 mixture of chloroform-isopropanol four times. The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield 2-chloro-*N*-((3-hydroxyoxetan-3-yl)methyl)acetamide (**S4**) as a pale orange oil that was used without further purification. (1.39 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.13 (brs, 1H), 4.61 (d, 2H, J = 7.6 Hz), 4.45 (d, 2H, J = 7.6 Hz), 4.11 (s, 2H), 3.79 (d, 2H, J 5.9 Hz), 3.48 (s, 1H); LRMS (ESI) *m/z* calcd for $[C_6H_{10}ClNO_3 + H]^+$ 180.04 found 179.90.

Step 2. 2-chloro-*N*-((3-hydroxyoxetan-3-yl)methyl)acetamide (1.39 g, 7.74 mmol, 1.0 equiv.) was dissolved in THF (77 mL), cooled to 0 °C, and sodium hydride (244 mg, 9.67 mmol, 1.25 equiv.; 95% as solid) was added in one portion. Heated to reflux for 16 h, after which a second portion of sodium hydride (300 mg) was added. After refluxing for an additional 16 h, the suspension was cooled to 0 °C and quenched *via* the careful addition of sat. aqueous ammonium chloride solution. After removal of volatiles under reduced pressure, the residue was partitioned between water and a 3:1 mixture of chloroform-isopropanol and the aqueous layer was extracted with a 3:1 mixture of chloroform-isopropanol three times. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified *via* flash chromatography on silica gel (0 to 15% MeOH/DCM) to yield 2,5-dioxa-8-azaspiro[3.5]nonan-7-one as an opaque, crystalline solid (274 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 (brs, 1H), 4.72 (d, 2H, J = 7.3 Hz), 4.46 (d, 2H, J = 7.3 Hz), 4.21 (s, 2H), 3.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.4, 78.6, 73.0, 63.8, 46.9; HRMS (ESI) *m/z* calcd for $[C_6H_9NO_3 - H]^-$ 142.0504 found 142.0500. Purity: >90% (^{1}H NMR and LRMS).

General Procedure for the reduction of morpholinones to morpholines. The morpholinone (1.0 equiv.) was dissolved in THF (0.75 M) and cooled to 0 °C. A 1.0 M solution of $LiAlH_4$ in THF (2.0 equiv.) was added dropwise. After warming to RT over 30 min., the suspension was heated to 70 °C for 16 h. The suspension was cooled to 0 °C and quenched *via* the sequential addition of water, 15% aqueous NaOH solution, and a second portion of water (Fieser method). The crude mixture was extracted with EtOAc three times and the combined organic extracts were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified *via* flash chromatography on silica gel (gradients indicated) to afford the morpholine.

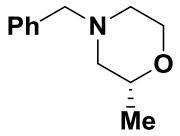


(*R*)-3-phenylmorpholine (11i). Using the procedure described above with (*R*)-5-phenylmorpholin-3-one (129 mg, 0.73 mmol, 1.0 equiv.) and a 1.0 M solution of $LiAlH_4$ in THF (1.5 mL, 1.46 mmol, 2.0 equiv.) in THF (970 µL). After an aqueous work-up and purification *via* flash chromatography on silica gel (0 to 20% MeOH/DCM), the title compound was afforded as a yellow oil (89 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.41 – 7.24 (m, 5H), 3.94 – 3.80 (m, 3H), 3.66 (td, 1H, J = 11.1, 2.8 Hz), 3.44 – 3.37 (m, 1H), 3.12 (td, 1H, J = 11.5, 3.3 Hz), 3.02 – 2.96 (m, 1H), 2.23 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 140.6, 128.6, 127.9, 127.3, 73.8, 67.3, 60.7, 46.7; FTIR (neat; cm^{-1}) 3239 (w), 2957 (w), 2847 (w), 1104 (s), 702 (s); HRMS (ESI) *m/z* calcd for $[C_{10}H_{13}NO + H]^+$ 164.1075 found 164.1075. Purity: 92.9% (UPLC, UV_{214}).[9]

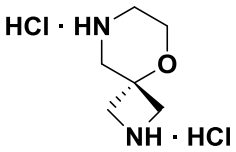


(*S*)-2-phenylmorpholine (11j). As per **11i** with (*S*)-6-phenylmorpholin-3-one (70 mg, 0.395 mmol, 1.0 equiv.) and a 2.0 M solution of $LiAlH_4$ in THF (395 µL, 0.395 mmol, 2.0 equiv.) in THF (2.0 mL). After an aqueous work-up and purification *via* flash chromatography on silica gel (0 to 10% MeOH/DCM), the title compound was afforded as a colorless oil (37 mg, 57%). ^{1}H

NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.25 (m, 5H), 4.48 (dd, 1H, *J* = 10.3, 2.5 Hz), 4.08 – 4.01 (m, 1H), 3.81 – 3.74 (m, 1H), 3.09 – 3.02 (m, 1H), 3.00 – 2.96 (m, 1H), 2.91 – 2.86 (m, 1H), 2.83 – 2.77 (m, 1H), 1.88 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 140.7, 128.5, 127.8, 126.2, 79.5, 68.6, 53.4, 45.9; HRMS (ESI) *m/z* calcd for $[C_{10}H_{13}NO + H]^+$ 164.1075 found 164.1076. Purity: 93.4% (UPLC, UV_{214}).



(*R*)-4-benzyl-2-methylmorpholine (11k). As per **11i** with (*S*)-6-phenylmorpholin-3-one (70 mg, 0.395 mmol, 1.0 equiv.) and a 2.0 M solution of $LiAlH_4$ in THF (395 µL, 0.395 mmol, 2.0 equiv.) in THF (2.0 mL). After an aqueous work-up and purification *via* flash chromatography on silica gel (0 to 40% EtOAc/hexanes), the title compound was afforded as a colorless oil (37 mg, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.33 – 7.23 (m, 5H), 3.83 (ddd, 1 H, *J* = 11.4, 3.4, 1.6 Hz), 3.71 – 3.60 (m, 2H), 3.49 (d, 2H, *J* = 3.0 Hz), 2.71 (dt, 1H, *J* = 11.4 Hz, 2.0 Hz), 2.66 (dq, 1H, *J* = 11.4, 2.0 Hz), 2.15 (td, 1H, *J* = 11.4, 3.4 Hz), 1.82 (m, 1H), 1.12 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.0, 129.3, 128.4, 127.3, 72.0, 67.0, 63.4, 60.2, 53.1, 19.3; HRMS (ESI) *m/z* calcd for $[C_{12}H_{17}NO + H]^+$ 192.1388 found 192.1389. Purity: 98.0% (UPLC, UV_{214}).



5-oxa-2,8-diazaspiro[3.5]nonane dihydrochloride (11l). As per **11i** with minor modifications and *N*-Boc deprotection.

tert-butyl-7-oxo-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (160 mg, 0.660 mmol, 1.0 equiv.) and $LiAlH_4$ (77 mg, 2.03 mmol, 3.0 equiv.) in THF (7.0 mL). After stirring for 2 h at RT, the reaction was cooled to 0 °C and quenched *via* careful addition of saturated aqueous Na_2SO_4 solution (77 µL). The crude mixture was filtered over a pad of celite, washed with diethyl ether, and concentrated *in vacuo*. The residue was loaded onto Si-Tosic Acid functionalized silica gel, washed with MeOH, and the product was eluted with 3 N NH_3 in MeOH. Upon concentration *in vacuo*, *tert*-butyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (**S5**) was isolated as a pale oil

(75 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.82 – 3.74 (m, 4H), 3.63 – 3.57 (m, 2H), 2.92 (s, 2H), 2.81 – 2.74 (m, 2H), 1.42 (s, 9H). LRMS (ESI) *m/z* calcd for $[C_{11}H_{20}N_2O_3 + H]^+$ 229.15 found 229.07.

N-Boc deprotection. *tert*-butyl-5-oxa-2,8-diazaspiro[3.5]nonane-2-carboxylate (75 mg, 0.329 mmol, 1.0 equiv.) was dissolved in dioxane (2.0 mL) and a 4.0 M solution of HCl in dioxane (986 µL, 3.94 mmol, 12.0 equiv.) was added in one portion. After stirring at RT for 1 h, concentration *in vacuo*, and trituration with diethyl ether, the title compound was isolated as a hygroscopic off-white solid (30.2 mg, 46%). ^{1}H NMR (300 MHz, CD_3OD) δ_H 4.32 (d, 2H, J = 12.1 Hz), 4.10 (d, 2H, J = 12.1 Hz), 4.02 (m, 2H), 3.55 (s, 2H), 3.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 73.1, 60.7, 55.9, 47.0, 43.1; HRMS (ESI) *m/z* calcd for $[C_6H_{12}N_2O + H]^+$ 129.1028 found 129.1028. Purity: >99.9% (UPLC, ELSD).

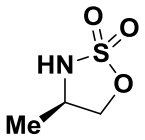
General Procedure C (sulfamidates).

Step 1. Imidazole (4.0 equiv.), thionyl chloride (1.2 equiv.), and triethylamine (2.5 equiv.) were combined in DCM (0.05 M based on amino alcohol; 45% total volume) and cooled to -40 °C. A solution of the secondary amino alcohol (1.0 equiv.) in DCM (remaining 55% volume) was added *via* dropping funnel over 90 min. After stirring at -40 °C for an additional 1-2 h, the solution was warmed to RT and quenched *via* the addition of water. The layers were separated and the aqueous layer was extracted with DCM three times. Combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified *via* flash chromatography on silica gel (gradients indicated) to afford the tertiary sulfimidate intermediate (mixture of diastereomers).

Step 2. The sulfimidate intermediate (1.0 equiv.) was dissolved in a 9:1 mixture of MeCN and water (0.050 M) and cooled to 0 °C. Sodium periodate (1.1 equiv.) and $RuCl_3 \cdot xH_2O$ (7 mol%) were added and the suspension was vigorously stirred at 0 °C for 30 min. The suspension was passed through a celite plug, washed copiously with MeCN, and volatiles were removed *in vacuo*. DCM and dilute aqueous $Na_2S_2O_3$ solution was added to the residue, the layers were separated, and the aqueous layer was extracted with DCM three times. Combined organic

extracts were dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified *via* flash chromatography on silica gel (gradients indicated) to afford the tertiary sulfamidate.

Step 3. The *N*-Boc protected sulfamidate (1.0 equiv.) was dissolved in DCM (0.1 M) and TFA (10 equiv.) was carefully added. After stirring at RT for 16 h, the solution was concentrated *in vacuo* and residual TFA was removed *via* azeotroping with toluene three times. The residue was purified *via* flash chromatography on silica gel (gradients indicated) to afford the secondary sulfamidate.



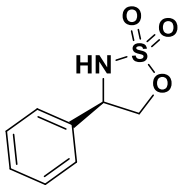
(*R*)-4-methyl-1,2,3-oxathiazolidine 2,2-dioxide (12a). Using general procedure **C**, steps 1-3.

Step 1. (*R*)-*tert*-butyl-(1-hydroxypropan-2-yl)carbamate (100 mg, 0.571 mmol, 1.0 equiv.), imidazole (155 mg, 2.28 mmol, 4.0 equiv.), thionyl chloride (50 µL, 0.685 mmol, 1.2 equiv.), and triethylamine (199 µL, 1.43 mmol, 2.5 equiv.) were combined in DCM (7.6 mL) as described. After an aqueous work up and concentration *in vacuo*, the mixture of sulfamidite diastereomers (107 mg, 85%; as crude) was obtained and used in the next reaction without further purification.

Step 2. *tert*-butyl-(4*R*)-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2-oxide (100 mg, 0.452 mmol, 1.0 equiv.; mixture of diastereomers), sodium periodiate (106 mg, 0.497 mmol, 1.1 equiv.) and $RuCl_3 \cdot xH_2O$ (6.6 µg, 3.16 µmol, 7 mol%) were combined in MeCN (3.4 mL) and water (2.8 mL) as described. After filtration and an aqueous work up (*R*)-*tert*-butyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate-2,2-dioxide (98 mg, 91%; as crude) was obtained and used in the next reaction without further purification.

Step 3. (*R*)-*tert*-butyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate-2,2-dioxide (98 mg, 0.413 mmol, 1.0 equiv.) and TFA (316 µL, 4.13 mmol, 10.0 equiv.) were combined in DCM (4.1 mL). After 16 h, concentration *in vacuo*, the residue was dissolved in 50% EtOAc/hexanes (20 mL)

and made basic with ca. 7 drops triethylamine. The basic solution (pH=8~9) was passed through a plug of silica, eluting with 50% EtOAc/hexanes. After concentration *in vacuo*, (*R*)-4-methyl-1,2,3-oxathiazolidine 2,2-dioxide was obtained as a clear, colorless oil (56 mg, 99%) ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.70 (brs, 1H), 4.66 – 4.60 (m, 1H), 4.14 – 4.05 (m, 2H), 1.40 (d, 3H, J = 6.1 Hz); HRMS (ESI) *m/z* calcd for $[C_3H_7NO_3S - H]^-$ 136.0068 found 136.0068. Purity: >85% (^{1}H NMR).[10]



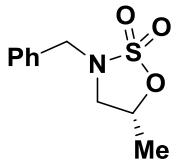
(*R*)-4-phenyl-1,2,3-oxathiazolidine 2,2-dioxide (12b). Using general procedure **C**, steps 1-3.

Step 1. (*R*)-*tert*-butyl-(2-hydroxy-1-phenylethyl)carbamate (2.50 g, 10.5 mmol, 1.0 equiv.), imidazole (2.87 g, 42.1 mmol, 4.0 equiv.), thionyl chloride (922 µL, 12.6 mmol, 1.2 equiv.), and triethylamine (3.67 mL, 26.3 mmol, 2.5 equiv.) were combined in DCM (180 mL) as described. After an aqueous work up and purification *via* flash chromatography on silica gel (0 to 18% EtOAc/hexanes), the sulfimidate intermediate was isolated as a mixture of diastereomers (**S6** and **S7**) (2.48 g, 83%). **S6** (less polar): white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.48 – 7.29 (m, 5H), 5.01 – 4.94 (m, 2H), 4.89 – 4.81 (m, 1H), 1.36 (brs, 9H). LRMS (ESI) *m/z* calcd for $[C_{13}H_{17}NO_4S + H_2O]^+$ 301.10 found 301.12. **S7** (more polar): clear, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 – 7.30 (m, 3H), 7.23 – 7.20 (m, 2H), 5.32 (dd, 1H, J = 9.0, 6.14 Hz), 5.17 (brs, 1H), 4.54 (d, 1H, J = 9.0 Hz), 1.42 (brs, 9H). LRMS (ESI) *m/z* calcd for $[C_{13}H_{17}NO_4S + H_2O]^+$ 301.10 found 301.12.

Step 2. (4*R*)-*tert*-butyl-4-phenyl-1,2,3-oxathiazolidine-3-carboxylate-2-oxide (1.98 g, 6.99 mmol, 1.0 equiv.; mixture of diastereomers), sodium periodiate (1.64 g, 7.69 mmol, 1.1 equiv.) and $RuCl_3 \cdot xH_2O$ (11 mg, 0.049 mmol, 7 mol%) were combined in MeCN (76 mL) and water (64 mL) as described. After filitration, an aqueous work up, and purification *via* flash chromatography on silica gel (0 to 25% EtOAc/hexanes), (*R*)-*tert*-butyl-4-phenyl-1,2,3-oxathiazolidine-3-carboxylate-2,2-dioxide (**S8**) was isolated as a pearlescent, white solid (1.38 g,

66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.38 (m, 5H), 5.29 (dd, 1H, J = 6.7, 4.2 Hz), 4.87 (dd, 1H, J = 9.2, 6.7 Hz), 4.40 (dd, 1H, J = 9.2, 4.2 Hz), 1.43 (brs, 9H). LRMS (ESI) *m/z* calcd for $[C_{13}H_{17}NO_5S + H_2O]^+$ 317.09 found 317.07.

Step 3. (*R*)-*tert*-butyl-4-phenyl-1,2,3-oxathiazolidine-3-carboxylate-2,2-dioxide (1.07 g, 3.57 mmol, 1.0 equiv.) and TFA (2.74 mL, 35.7 mmol, 10.0 equiv.) were combined in DCM (36 mL). After 16 h, concentration *in vacuo*, and purification *via* flash chromatography on silica gel (0 to 40% EtOAc/hexanes), (*R*)-4-phenyl-1,2,3-oxathiazolidine 2,2-dioxide was isolated as a white solid (665 mg, 93%). $^{23}[\alpha]_D$ = -39.5 (c = 1.00; $CHCl_3$) (lit. $^{24}[\alpha]_D$ = -38.9, c = 0.30, 96.2 %ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.38 (m, 5H), 5.10 – 5.05 (m, 1H), 4.96 (d, 1H, J = 6.7 Hz), 4.83 (dd, 1H, J = 8.6, 6.8 Hz), 4.44 (t, 1H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 135.5, 129.6, 129.5, 126.8, 75.2, 59.7; FTIR (neat; cm^{-1}) 3321 (br), 1337 (m), 1174 (s), 902 (s), 775 (s); HRMS (ESI) *m/z* calcd for $[C_8H_9NO_3S - H]^-$ 198.0225 found 198.0229. Purity: 92.6% (UPLC, UV_{214}).[11]

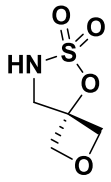


(*R*)-3-benzyl-5-methyl-1,2,3-oxathiazolidine-2,2-dioxide (12c). Using general procedure **C**, steps 1 and 2.

Step 1. (*R*)-1-(benzylamino)propan-2-ol (1.0 g, 6.05 mmol, 1.0 equiv.), imidazole (1.65 mg, 24.2 mmol, 4.0 equiv.), thionyl chloride (530 µL, 7.26 mmol, 1.2 equiv.), and triethylamine (2.11 mL, 15.1 mmol, 2.5 equiv.) were combined in DCM (80.6 mL) as described. After an aqueous work up and purification *via* flash chromatography on silica gel (0 to 40% EtOAc/hexanes), the sulfimidate intermediate was isolated as a mixture of diastereomers (**S9**) (670 mg, 52%). Diastereomer 1 (less polar): clear, colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.40 – 7.29 (m, 5H), 4.70 (dp, 1H, J = 10.2, 6.1 Hz), 4.34 (d, 1H, J = 13.4 Hz), 3.85 (d, 1H, J = 13.4 Hz), 3.34 (dd, 1H, J = 9.4, 6.1 Hz), 3.13 (dd, 1H, J = 10.2, 9.4 Hz), 1.58 (d, 3H, J = 6.1 Hz). LRMS (ESI) *m/z* calcd for $[C_{10}H_{13}NO_2S + H]^+$ 212.29 found 212.06. Diastereomer 2 (more polar): clear, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 – 7.28 (m, 5H), 5.22 (m, 1H), 4.35 (d, 1H, J =

13.8 Hz), 3.99 (d, 1H, *J* = 13.8 Hz), 3.47 (dd, 1H, *J* = 8.9, 6.6 Hz), 2.89 (dd, 1H, *J* = 8.9, 4.4, Hz), 1.38 (d, 3H, *J* = 6.6 Hz). LRMS (ESI) *m/z* calcd for $[C_{10}H_{13}NO_2S + H]^+$ 212.29 found 212.06.

Step 2. (5*R*)-3-benzyl-5-methyl-1,2,3-oxathiazolidine-2-oxide (670 mg, 3.17 mmol, 1.0 equiv.; mixture of diastereomers), sodium periodiate (746 mg, 3.49 mmol, 1.1 equiv.) and $RuCl_3 \cdot xH_2O$ (5.0 mg, 0.022 mmol, 7 mol%) were combined in MeCN (34.6 mL) and water (28.8 mL) as described. After filitration, an aqueous work up, and purification *via* flash chromatography on silica gel (0 to 30% EtOAc/hexanes), (*R*)-3-benzyl-5-methyl-1,2,3-oxathiazolidine-2,2-dioxide was isolated as a clear, colorless oil (554 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.33 (m, 5H), 4.88 (dp, 1H, *J* = 8.0, 6.2 Hz), 4.33 (d, 1H, *J* = 13.6 Hz), 4.10 (d, 1H, *J* = 13.6 Hz), 3.42 (dd, 1H, *J* = 9.5, 6.2 Hz), 3.04 (dd, 1H, *J* = 9.5, 8.0 Hz), 1.50 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 134.6, 129.0, 128.8, 128.6, 53.9, 51.4, 19.5; HRMS (ESI) *m/z* calcd for $[C_{10}H_{13}NO_3S + H]^+$ 228.0694 found 228.0700.



2,5-dioxa-6-thia-7-azaspiro[3.4]octane-6,6-dioxide (12d). Using general procedure **C**, steps 1-3.

Step 1. *tert*-butyl-((3-hydroxyoxetan-3-yl)methyl)carbamate (100 mg, 0.492 mmol, 1.0 equiv.), imidazole (134 mg, 1.97 mmol, 4.0 equiv.), thionyl chloride (43 µL, 0.590 mmol, 1.2 equiv.), and triethylamine (171 µL, 1.23 mmol, 2.5 equiv.) were combined in DCM (6.6 mL) as described. After an aqueous work up and concentration *in vacuo* the mixture of sulfamidite diastereomers (110 mg, 90%; as crude) was obtained and used in the next reaction without further purification.

Step 2. *tert*-butyl-2,5-dioxa-6-thia-7-azaspiro[3.4]octane-7-carboxylate-6-oxide (110 mg, 0.441 mmol, 1.0 equiv.; mixture of diastereomers), sodium periodiate (104 mg, 0.485 mmol, 1.1

equiv.) and $RuCl_3 \cdot xH_2O$ (641 µg, 3.09 µmol, 7 mol%) were combined in MeCN (3.4 mL) and water (2.8 mL) as described. After filtration and an aqueous work up *tert*-butyl-2,5-dioxa-6-thia-7-azaspiro[3.4]octane-7-carboxylate-6,6-dioxide (111 mg, 95%; as crude) was obtained and used in the next reaction without further purification.

Step 3. *tert*-butyl-2,5-dioxa-6-thia-7-azaspiro[3.4]octane-7-carboxylate-6,6-dioxide (110 mg, 0.418 mmol, 1.0 equiv.) and TFA (320 µL, 4.18 mmol, 10.0 equiv.) were combined in DCM (4.2 mL). After 16 h, concentration *in vacuo*, the residue was dissolved in 50% EtOAc/hexanes (20 mL) and made basic with ca. 7 drops triethylamine resulting in a white precipitate. The basic solution (pH=8~9) was filtered, the solid was recrystallized (hexanes), and 2,5-dioxa-6-thia-7-azaspiro[3.4]octane-6,6-dioxide was obtained as a white solid (57 mg, 82%). ^{1}H NMR (400 MHz, CD_3OD) δ_H 4.90 (d, 2H, J = 8.0 Hz), 4.75 (d, 2H, J = 8.0 Hz), 3.86 (s, 2H), 1.32 (t, 1H, J = 7.3 Hz); HRMS (ESI) *m/z* calcd for $[C_4H_7NO_4S + H]^+$ 166.0174 found 166.0178. Purity: >80% (^{1}H NMR).

General Procedure D (six-membered sultams):

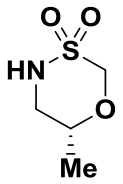
Step 1. The amino alcohol (1.0 equiv.) was dissolved in DCM (0.1 M based on amino alcohol; 85% total volume) and triethylamine (1.6 equiv.) was added in one portion at RT. After cooling to 0 °C, a solution of chloromethanesulfonyl chloride (1.7 equiv.) in DCM (remaining 15% volume) was added dropwise, after which the solution was warmed to RT. After six hours the starting material had been completely consumed and the solution was partially concentrated *in vacuo*, adsorbed onto silica or celite, and purified *via* flash chromatography on silica gel (gradients indicated) to afford the α-chlorosulfonamide intermediate.

Step 2 (for secondary α-chlorosulfonamides). The α-chlorosulfonamide (1.0 equiv.) was dissolved in DMF (0.1 M based on α-chlorosulfonamide; 50% total volume) and a solution of *p*-methoxybenzyl bromide (1.1 equiv.) and potassium carbonate (3.0 equiv.) in DMF (remaining 50% volume) was added dropwise to the sulfonamide solution at RT. After stirring for 45 min., the solution was diluted with EtOAc and quenched *via* the addition of aqueous 1 M HCl. The aqueous layer was extracted with EtOAc three times and the combined organic extracts were

sequentially washed with water, 5% aqueous LiCl solution, and brine. The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified *via* flash chromatography on silica gel (gradients indicated) to yield the *p*-methoxybenzyl protected α-chlorosulfonamide intermediate.

Step 3. The α-chlorosulfonamide intermediate (1.0 equiv.) was dissolved in DMF (0.2 M) and cesium carbonate (2.0 equiv.) was added in one portion. The suspension was heated to 80 °C and allowed to stir for 16 h. After concentrating under reduced pressure, the residue was partitioned between EtOAc and water, the layers were separated, and the aqueous layer was extracted with EtOAc three times. Combined organic extracts were sequentially washed with water, 5% aqueous LiCl solution, and brine. The organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification *via* flash chromatography on silica gel (gradients indicated) yielded the six-membered lactam.

Step 4 (for *p*-methoxybenzyl protected sultams). The protected six-membered lactam (1.0 equiv.) was dissolved in a 9:1 mixture of MeCN and water. Ceric ammonium nitrate (3.0 equiv.) was added in one portion and the solution was stirred for 1 to 16 h. After concentrating under reduced pressure, the orange residue was partitioned between a 3:1 mixture of chloroform-isopropanol and water and the layers were separated. The aqueous layer was extracted with the chloroform-isopropanol mixture three times and the combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified *via* recrystallization or trituration (hexanes/DCM) to yield the six-membered lactam.



(*R*)-6-methyl-1,3,4-oxathiazinane-3,3-dioxide (13a). Using general procedure **D**, steps 1-4.

Step 1. (*R*)-1-amino-propan-2-ol (524 µL, 6.67 mmol, 1.0 equiv.), triethylamine (1.49 mL, 10.7 mmol, 1.6 equiv.), and chloromethanesulfonyl chloride (1.16 mL, 11.5 mmol, 1.7 equiv.) were combined in DCM (67 mL). After stirring for 16 h and purification *via* flash chromatography on

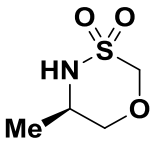
silica gel (0 to 100% EtOAc/hexanes), (*R*)-1-chloro-*N*-(2-hydroxypropyl)methanesulfonamide (**S10**) was isolated as a clear, colorless oil (1.05 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.74 (t, 1H, *J* = 6.1 Hz), 4.58 (s, 2H), 3.96 (dqd, 1H, *J* = 7.8, 6.3, 3.1 Hz), 3.30 (ddd, 1H, *J* = 13.5, 6.1, 3.1 Hz), 3.06 (ddd, 1H, *J* = 13.5, 7.8, 6.1 Hz), 2.81 (brs, 1H), 1.21 (d, 3H, *J* = 6.3 Hz); LRMS (ESI) *m/z* calcd for $[C_4H_{10}ClNO_3S - H]^-$ 186.00 found 186.09.

Step 2. (*R*)-1-chloro-*N*-(2-hydroxypropyl)methanesulfonamide (1.92 g, 10.2 mmol, 1.0 equiv.), *p*-methoxybenzyl bromide (1.59 mL, 10.5 mmol, 1.1 equiv.), and potassium carbonate (4.24 g, 30.7 mmol, 3.0 equiv.) were combined in DMF (102 mL). After stirring for 1 h, an additional 400 µL of *p*-methoxybenzyl bromide was added. After stirring for a further 2 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 55% EtOAc/hexanes), (*R*)-1-chloro-*N*-(2-hydroxypropyl)-*N*-(4-methoxybenzyl)methanesulfonamide (**S11**) was isolated as a colorless oil (2.16 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.28 (d, 2H, *J* = 8.6 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 4.69 (d, 1H, *J* = 12.0 Hz), 4.68 (d, 1H, *J* = 15.1 Hz), 4.57 (d, 1H, *J* = 12.0 Hz), 4.41 (d, 1H, *J* = 15.1 Hz), 3.94 (dqd, 1H, *J* = 9.1, 6.3, 2.6 Hz), 3.80 (s, 3H), 3.35 (dd, 1H, *J* = 15.2, 9.1 Hz), 3.12 (dd, 1H, *J* = 15.2, 2.6 Hz), 2.14 (brs, 1H), 1.09 (d, 3H, *J* = 6.3 Hz); LRMS (ESI) *m/z* calcd for $[C_{12}H_{18}ClNO_4S + Na]^+$ 330.05 found 330.24.

Step 3. (*R*)-1-chloro-*N*-(2-hydroxypropyl)-*N*-(4-methoxybenzyl)methanesulfonamide (2.16 g, 7.01 mmol, 1.0 equiv.) and cesium carbonate (4.57 g, 14.0 mmol, 2.0 equiv.) were combined in DMF (35 mL). After stirring at 80 °C for 16 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 50% EtOAc/hexanes), (*R*)-4-(4-methoxybenzyl)-6-methyl-1,3,4-oxathiazinane-3,3-dioxide (**S12**) was isolated as a colorless oil that solidified upon standing (1.51 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.23 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.6 Hz), 4.64 (s, 2H), 4.47 (d, 1H, *J* = 14.0 Hz), 3.96 (d, 1H, *J* = 14.0 Hz), 3.86 (dqd, 1H, *J* = 10.4, 6.3, 2.3 Hz), 3.79 (s, 3H), 3.33 (dd, 1H, *J* = 13.6, 10.4 Hz), 2.95 (dd, 1H, *J* = 13.6, 2.3 Hz), 1.15 (d, 3H, *J* = 6.3 Hz); LRMS (ESI) *m/z* calcd for $[C_{12}H_{17}NO_4S + Na]^+$ 294.08 found 294.08.

Step 4. (*R*)-4-(4-methoxybenzyl)-6-methyl-1,3,4-oxathiazinane-3,3-dioxide (1.51 g, 5.57 mmol, 1.0 equiv.) and ceric ammonium nitrate (9.15 g, 16.7 mmol, 3.0 equiv.) were dissolved in MeCN (50 mL) and water (5.6 mL). After stirring for 24 h, an aqueous work-up, and purification *via*

flash chromatography on silica gel (0 to 10% MeOH/DCM), followed by trituration (hexanes/DCM), and preperative thin-layer chromatography (5% MeOH/DCM; iodine visualization), the title compound was obtained as a white solid (42.5 mg, 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.87 (d, 1H, J = 4.7 Hz), 4.75 (d, 1H, J = 11.7 Hz), 4.66 (d, 1H, J = 11.7 Hz), 3.82 (dqd, 1H, J = 10.4, 6.3, 2.2 Hz), 3.59 (dd, 1H, J = 14.7, 10.4 Hz), 3.32 (ddd, 1H, J = 14.7, 4.7, 2.2 Hz), 1.22 (d, 3H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 82.8, 73.7, 52.0, 17.2; HRMS (ESI) *m/z* calcd for $[C_4H_9NO_3S - H]^-$ 150.0225 found 150.0230. Purity: 91.2% (UPLC, UV_{214}).



(*R*)-5-methyl-1,3,4-oxathiazinane-3,3-dioxide (13b). Using general procedure **D**, steps 1-4.

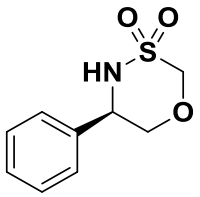
Step 1. (*R*)-2-amino-propan-1-ol (519 µL, 6.67 mmol, 1.0 equiv.), triethylamine (1.49 mL, 10.7 mmol, 1.6 equiv.), and chloromethanesulfonyl chloride (1.16 mL, 11.5 mmol, 1.7 equiv.) were combined in DCM (67 mL). After stirring for 16 h and purification *via* flash chromatography on silica gel (0 to 100% EtOAc/hexanes), (*R*)-1-chloro-*N*-(1-hydroxypropan-2-yl)methanesulfonamide (**S13**) was isolated as a pale yellow oil (830 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.62 (d, 1H, J = 8.2 Hz), 4.62 (d, 1H, J = 12.2 Hz), 4.55 (d, 1H, J = 12.2 Hz), 3.69 – 3.59 (m, 1H), 3.51 – 3.46 (m, 1H), 3.08 (brs, 1H), 1.23 (d, 3H, J = 6.6 Hz); LRMS (ESI) *m/z* calcd for $[C_4H_{10}ClNO_3S + H]^+$ 188.02 found 188.00.

Step 2. (*R*)-1-chloro-*N*-(1-hydroxypropan-2-yl)methanesulfonamide (825 mg, 4.40 mmol, 1.0 equiv.), *p*-methoxybenzyl bromide (715 µL, 4.84 mmol, 1.1 equiv.), and potassium carbonate (1.82 g, 13.2 mmol, 3.0 equiv.) were combined in DMF (44 mL). After stirring for 1 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 55% EtOAc/hexanes), (*R*)-1-chloro-*N*-(1-hydroxypropan-2-yl)-*N*-(4-methoxybenzyl)methanesulfonamide (**S14**) was isolated as a clear, colorless oil (230 mg, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.34 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.6 Hz), 4.44 (s, 2H), 4.42 (d, 1H, J = 12.1 Hz), 4.30 (d, 1H, J = 12.1 Hz), 4.09 – 4.00 (m, 1H), 3.78 (s, 3H), 3.54 –

3.41 (m, 2H), 2.14 (brs, 1H), 1.17 (d, 3H, J = 6.9 Hz) ; LRMS (ESI) *m/z* calcd for $[C_{12}H_{18}ClNO_4S + Na]^+$ 330.05 found 329.94.

Step 3. (*R*)-1-chloro-*N*-(1-hydroxypropan-2-yl)-*N*-(4-methoxybenzyl)methanesulfonamide (230 mg, 0.747 mmol, 1.0 equiv.) and cesium carbonate (487 mg, 1.50 mmol, 2.0 equiv.) were combined in DMF (3.7 mL). After stirring at 80 °C for 16 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 55% EtOAc/hexanes), (*R*)-4-(4-methoxybenzyl)-5-methyl-1,3,4-oxathiazinane-3,3-dioxide (**S15**) was isolated as a white solid (166 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.27 (d, 2H, J = 8.5 Hz), 6.88 (d, 2H, J = 8.5 Hz), 4.64 (d, 1H, J = 11.3 Hz), 4.60 (d, 1H, J = 11.3 Hz), 4.56 (d, 1H, J = 15.0 Hz), 4.11 (d, 1H, J = 15.0 Hz), 3.81 (s, 3H), 3.75 – 3.63 (m, 3H), 1.31 (d, 3H, J = 6.6 Hz); LRMS (ESI) *m/z* calcd for $[C_{12}H_{17}NO_4S + Na]^+$ 294.08 found 294.05.

Step 4. (*R*)-4-(4-methoxybenzyl)-5-methyl-1,3,4-oxathiazinane-3,3-dioxide (166 mg, 0.612 mmol, 1.0 equiv.) and ceric ammonium nitrate (1.0 g, 1.83 mmol, 3.0 equiv.) were dissolved in MeCN (5.5 mL) and water (612 µL). After stirring for 48 h, an aqueous work-up, and purification *via* trituration (hexanes/DCM), the title compound was obtained as a white solid (23.6 mg, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.74 (d, 1H, J = 11.6 Hz), 4.45 (d, 1H, J = 11.6 Hz), 4.27 (d, 1H, J = 7.8 Hz), 4.05 – 3.93 (m, 1H), 3.95 (dd, 1H, J = 12.0, 3.0 Hz), 3.25 (dd, 1H, J = 12.0, 10.4 Hz), 1.17 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 82.1, 72.8, 53.0, 16.3; HRMS (ESI) *m/z* calcd for $[C_4H_9NO_3S - H]^-$ 150.0225 found 150.0228. Purity: >95% (^{1}H NMR and LRMS).



(*R*)-5-phenyl-1,3,4-oxathiazinane-3,3-dioxide (13c). Using general procedure **D**, steps 1-4.

Step 1. (*R*)-2-amino-2-phenylethanol (400 mg, 2.92 mmol, 1.0 equiv.), triethylamine (650 µL, 4.67 mmol, 1.6 equiv.), and chloromethanesulfonyl chloride (509 µL, 5.04 mmol, 1.7 equiv.) were combined in DCM (39 mL). After stirring for 16 h and purification *via* flash

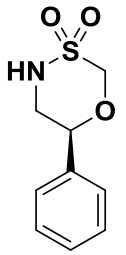
chromatography on silica gel (0 to 60% EtOAc/hexanes), (*R*)-1-chloro-*N*-(2-hydroxy-1-phenylethyl)methanesulfonamide (**S16**) was isolated as a white foam (396 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.39 – 7.29 (m, 5H), 6.47 (d, 1H, *J* = 8.0 Hz), 4.66 (td, 1H, *J* = 8.0 Hz, 4.2 Hz), 4.34 (d, 1H, *J* = 12.1 Hz), 4.08 (d, 1H, *J* = 12.1 Hz), 3.87 – 3.71 (2H, m), 3.35 (brs, 1H); LRMS (ESI) *m/z* calcd for $[C_9H_{12}ClNO_3S - H]^-$ 248.02 found 248.14.

Step 2. (*R*)-1-chloro-*N*-(2-hydroxy-1-phenylethyl)methanesulfonamide (396 mg, 1.59 mmol, 1.0 equiv.), *p*-methoxybenzyl bromide (272 µL, 1.74 mmol, 1.1 equiv.), and potassium carbonate (658 mg, 4.76 mmol, 3.0 equiv.) were combined in DMF (16 mL). After stirring for 1 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 40% EtOAc/hexanes), (*R*)-1-chloro-*N*-(2-hydroxy-1-phenylethyl)-*N*-(4-methoxybenzyl)methanesulfonamide (**S17**) was isolated as a hazy oil (173 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.44 – 7.36 (m, 5H), 7.14 (d, 2H, *J* = 8.7 Hz), 6.8 (d, 2H, *J* = 8.7 Hz), 5.1 (dd, 1H, *J* = 8.5, 6.1 Hz), 4.41 (d, 1H, *J* = 15.2 Hz), 4.27 (d, 1H, *J* = 15.2 Hz), 4.26 (d, 1H, *J* = 12.1 Hz), 4.07 (d, 1H, *J* = 12.1 Hz), 4.13 – 4.02 (m, 2H), 3.78 (s, 3H), 2.08 (brs, 1H); LRMS (ESI) *m/z* calcd for $[C_{17}H_{20}ClNO_4S + Na]^+$ 392.07 found 392.24.

Step 3. (*R*)-1-chloro-*N*-(2-hydroxy-1-phenylethyl)-*N*-(4-methoxybenzyl)methanesulfonamide (172 mg, 0.465 mmol, 1.0 equiv.) and cesium carbonate (303 mg, 0.930 mmol, 2.0 equiv.) were combined in DMF (2.3 mL). After stirring at 80 °C for 16 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 40% EtOAc/hexanes), (*R*)-4-(4-methoxybenzyl)-5-phenyl-1,3,4-oxathiazinane-3,3-dioxide (**S18**) was isolated as a colorless oil (104 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.32 – 7.23 (m, 3H), 7.17 – 7.14 (m, 2H), 6.85 (d, 2H, *J* = 8.6 Hz), 6.68 (d, 1H, *J* = 8.6), 4.79 – 4.72 (m, 3H), 4.19 (s, 2H), 3.99 – 3.88 (m, 2H), 3.76 (s, 3H); LRMS (ESI) *m/z* calcd for $[C_{17}H_{19}NO_4S + Na]^+$ 356.09 found 356.10.

Step 4. (*R*)-4-(4-methoxybenzyl)-5-phenyl-1,3,4-oxathiazinane-3,3-dioxide (103 mg, 0.309 mmol, 1.0 equiv.) and ceric ammonium nitrate (508 mg, 0.927 mmol, 3.0 equiv.) were dissolved in MeCN (2.8 mL) and water (309 µL). After stirring for 16 h, an aqueous work-up, and purification *via* trituration (hexanes/DCM), the title compound was obtained as an off-white solid (36.1 mg, 55%). $^{23}[\alpha]_D$ = -90.4 (*c* = 1.00; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.46 –

7.31 (m, 5H), 5.00 (dt, 1H, *J* = 10.6, 7.1, 3.1 Hz), 4.80 (d, 1H, *J* = 11.5 Hz), 4.62 (d, 1H, *J* = 11.5 Hz), 4.56 (d, 1H, *J* = 7.1 Hz), 4.16 (dd, 1H, *J* = 12.1, 3.1 Hz), 3.66 (dd, 1H, *J* = 12.1, 10.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 134.56, 129.52, 129.48, 126.71, 82.34, 72.46, 60.69; FTIR (neat; cm^{-1}) 3222 (br), 1323 (m), 1152 (s), 1074 (s); HRMS (ESI) *m/z* calcd for $[C_9H_{11}NO_3S + H]^+$ 214.0538 found 214.0537. Purity: 98.1% (UPLC, UV_{214}).



(*S*)-6-phenyl-1,3,4-oxathiazinane-3,3-dioxide (13d). Using general procedure **D**, steps 1-4.

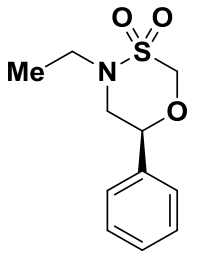
Step 1. (*S*)-2-amino-1-phenylethanol (100 mg, 0.729 mmol, 1.0 equiv.), triethylamine (163 µL, 1.17 mmol, 1.6 equiv.), and chloromethanesulfonyl chloride (127 µL, 1.26 mmol, 1.7 equiv.) were combined in DCM (11 mL). After stirring for 16 h and purification *via* flash chromatography on silica gel (0 to 75% EtOAc/hexanes), (*S*)-1-chloro-*N*-(2-hydroxy-2-phenylethyl)methanesulfonamide (**S19**) was isolated as a clear, colorless oil which solidified upon standing (127 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.40 – 7.29 (m, 5H), 5.50 (dd, 1H, *J* = 7.4, 4.9 Hz), 4.86 (dt, 1H, *J* = 8.0, 3.5 Hz), 4.47 (s, 2H), 3.47 (ddd, 1H, *J* = 13.7, 7.4, 3.5 Hz), 3.33 (ddd, 1H, *J* = 13.7, 8.0, 4.9 Hz), 2.91 (d, 1H, *J* = 3.5 Hz); LRMS (ESI) *m/z* calcd for $[C_9H_{12}ClNO_3S – H]^-$ 248.01 found 248.14.

Step 2. (*S*)-1-chloro-*N*-(2-hydroxy-2-phenylethyl)methanesulfonamide (100 mg, 0.400 mmol, 1.0 equiv.), *p*-methoxybenzyl bromide (69 µL, 0.441 mmol, 1.1 equiv.), and potassium carbonate (166 mg, 1.20 mmol, 3.0 equiv.) were combined in DMF (4 mL). After stirring for 30 min., an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 25% EtOAc/hexanes), (S)-1-chloro-*N*-(2-hydroxy-2-phenylethyl)-*N*-(4-methoxybenzyl)methanesulfonamide (**S20**) was isolated as a clear, colorless oil (115 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.38 – 7.25 (m, 7 H), 6.94 – 6.88 (m, 2H), 4.86 (dt, 1H, *J* = 9.2, 3.0 Hz), 4.73 (d, 1H, *J* = 11.9 Hz), 4.66 (d, 1H, *J* = 15.0 Hz), 4.54 (d, 1H, *J* = 11.9 Hz), 4.47 (d,

1H, *J* = 15.0 Hz), 3.81 (s, 3H), 3.61 (dd, 1H, *J* = 15.4, 9.2 Hz), 3.26 (dd, 1H, *J* = 15.4, 3.0 Hz), 3.11 (d, 1H, *J* = 2.5 Hz).; LRMS (ESI) *m/z* calcd for $[C_{17}H_{20}ClNO_4S + H - H_2O]^+$ 352.08 found 352.06.

Step 3. (S)-1-chloro-*N*-(2-hydroxy-2-phenylethyl)-*N*-(4-methoxybenzyl)methanesulfonamide (115 mg, 0.311 mol, 1.0 equiv.) and cesium carbonate (203 mg, 0.622 mmol, 2.0 equiv.) were combined in DMF (1.6 mL). After stirring at 80 °C for 16 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 25% EtOAc/hexanes), (*S*)-4-(4-methoxybenzyl)-6-phenyl-1,3,4-oxathiazinane-3,3-dioxide (**S21**) was isolated as white solid plates (91 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.36 – 7.26 (m, 7H), 6.93 – 6.89 (m, 2H), 4.80 (s, 2H), 4.71 (dd, 1H, *J* = 10.6, 2.4 Hz), 4.59 (d, 1H, *J* = 14.0 Hz), 4.06 (d, 1H, *J* = 14.0 Hz), 3.81 (s, 3H), 3.70 (dd, 1H, *J* = 14.0, 10.6 Hz), 3.15 (dd, 1H, *J* = 14.0, 2.4 Hz); LRMS (ESI) *m/z* calcd for $[C_{17}H_{19}NO_4S + Na]^+$ 356.09 found 356.20.

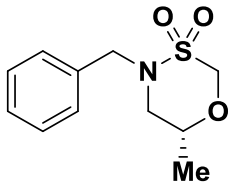
Step 4. (*S*)-4-(4-methoxybenzyl)-6-phenyl-1,3,4-oxathiazinane-3,3-dioxide (238 mg, 0.714 mmol, 1.0 equiv.) and ceric ammonium nitrate (1.17 g, 2.14 mmol, 3.0 equiv.) were dissolved in MeCN (6.4 mL) and water (714 µL). After stirring for 24 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 10% MeOH/DCM; 1% NH_3 modified) and trituration (hexanes/DCM), the title compound was obtained as a white solid (88.1 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.40 – 7.36 (m, 5H), 4.94 (d, 1H, *J* = 11.8 Hz), 4.83 (dd, 1H, *J* = 11.8, 1.8 Hz), 4.81 – 4.69 (m, 2H), 3.95 (dt, 1H, *J* = 14.9, 10.2 Hz), 3.50 (ddd, 1H, *J* = 14.9, 4.4, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 135.9, 129.2, 129.0, 126.3, 83.1, 79.5, 52.3; HRMS (ESI) *m/z* calcd for $[C_9H_{11}NO_3S + H]^+$ 214.0538 found 214.0532. Purity: 99.6% (UPLC, UV_{214}).



(*S*)-4-ethyl-6-phenyl-1,3,4-oxathiazinane-3,3-dioxide (13e). Using general procedure **D**, steps 1 and 3.

Step 1. (*S*)-2-(ethylamino)-1-phenylethanol (500 mg, 2.87 mmol, 1.0 equiv.), triethylamine (641 µL, 4.60 mmol, 1.6 equiv.), and chloromethanesulfonyl chloride (502 µL, 4.97 mmol, 1.7 equiv.) were combined in DCM (29 mL). After stirring for 16 h and purification *via* flash chromatography on silica gel (0 to 25% EtOAc/hexanes), (*S*)-1-chloro-*N*-ethyl-*N*-(2-hydroxy-2-phenylethyl)methanesulfonamide (**S22**) was isolated as a white solid (138 mg, 20%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.38 – 7.29 (m, 5H), 4.91 (dd, 1H, J = 9.1, 3.2 Hz), 4.62 (d, 1H, J = 12.1 Hz), 4.48 (d, 1H, J = 12.1 Hz), 3.65 – 3.52 (m, 1H), 3.50 – 3.35 (m, 1H), 2.65 (brs, 1H), 1.24 (t, 3H, J = 7.1 Hz); LRMS (ESI) *m/z* calcd for $[C_{11}H_{16}ClNO_3S + Na]^+$ 300.04 found 299.98.

Step 3. (*S*)-1-chloro-*N*-(2-hydroxy-2-phenylethyl)-*N*-(4-methoxybenzyl)methanesulfonamide (69 mg, 0.248 mol, 1.0 equiv.) and cesium carbonate (162 mg, 0.497 mmol, 2.0 equiv.) were combined in DMF (1.2 mL). After stirring at 80 °C for 16 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 20% EtOAc/hexanes), (*S*)-4-ethyl-6-phenyl-1,3,4-oxathiazinane-3,3-dioxide was isolated as a clear, colorless oil that solidified upon standing (51 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.46 – 7.36 (m, 5H), 4.86 (dd, 1H, J = 10.7, 2.4 Hz), 4.73 (s, 2H), 3.83 (dd, 1H, J = 13.9, 10.7 Hz), 3.42 – 3.27 (m, 3H), 1.23 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 136.4, 129.0, 128.8, 126.4, 81.3, 78.3, 55.8, 42.0, 13.5; HRMS (ESI) *m/z* calcd for $[C_{11}H_{15}NO_3S + H]^+$ 242.0851 found 242.0855. Purity: 98.9% (UPLC, UV_{214}).

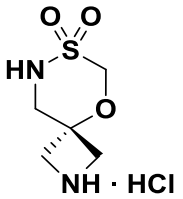


(*R*)-4-benzyl-6-methyl-1,3,4-oxathiazinane-3,3-dioxide (13f). Using general procedure **D**, steps 1 and 3.

Step 1. (*R*)-1-(benzylamino)propan-2-ol (129 mg, 0.781 mmol, 1.0 equiv.), triethylamine (174 µL, 1.25 mmol, 1.6 equiv.), and chloromethanesulfonyl chloride (136 µL, 1.35 mmol, 1.7 equiv.) were combined in DCM (11 mL). After stirring for 16 h and purification *via* flash chromatography on silica gel (0 to 40% EtOAc/hexanes), (*R*)-*N*-benzyl-1-chloro-*N*-(2-

hydroxypropyl)methanesulfonamide (**S23**) was isolated as a pale yellow oil (74 mg, 34%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.38 – 7.31 (m, 5H), 4.81 – 4.72 (m, 2H), 4.62 – 4.46 (m, 2H), 3.96 (dtt, 1H, *J* = 9.2, 6.3, 2.6 Hz), 3.39 (dd, 1H, *J* = 15.3, 9.2 Hz), 3.14 (dd, 1H, *J* = 15.3, 2.6 Hz), 1.92 (brs, 1H), 1.11 (d, 3H, *J* = 6.3 Hz); LRMS (ESI) *m/z* calcd for $[C_{11}H_{16}ClNO_3S + H]^+$ 278.06 found 278.50.

Step 3. (*R*)-*N*-benzyl-1-chloro-*N*-(2-hydroxypropyl)methanesulfonamide (74 mg, 0.268 mol, 1.0 equiv.) and cesium carbonate (175 mg, 0.536 mmol, 2.0 equiv.) were combined in DMF (2.7 mL). After stirring at 80 °C for 8 h, filtration, and purification *via* flash chromatography on silica gel (0 to 55% EtOAc/hexanes), (*R*)-4-benzyl-6-methyl-1,3,4-oxathiazinane-3,3-dioxide was isolated as a clear, colorless oil (36 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.40 – 7.30 (m, 5H), 4.68 (s, 2H), 4.57 (d, 1H, *J* = 14.2 Hz), 4.02 (d, 1H, *J* = 14.2 Hz), 3.90 (dqd, 1H, *J* = 10.4, 6.3, 2.3 Hz), 3.39 (dd, 1H, *J* = 13.6, 10.4 Hz), 2.97 (d, 1H, *J* = 13.6, 2.3 Hz), 1.17 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 135.1, 129.0, 128.9, 128.3, 81.3, 72.7, 55.0, 49.7, 17.5; HRMS (ESI) *m/z* calcd for $[C_{11}H_{15}NO_3S + H]^+$ 242.0851 found 242.0860. Purity: 98.0% (UPLC, UV_{214}).



5-oxa-7-thia-2,8-diazaspir[3.5]nonane-7,7-dioxide hydrochloride (13g). Using general procedure **D**, steps 1-4, plus *N*-Boc deprotection.

Step 1. *tert*-butyl-3-(aminomethyl)-3-hydroxyazetidine-1-carboxylate (2.00 g, 9.89 mmol, 1.0 equiv.), triethylamine (2.21 mL, 15.8 mmol, 1.6 equiv.), and chloromethanesulfonyl chloride (1.73 mL, 17.1 mmol, 1.7 equiv.) were combined in DCM (100 mL). After stirring for 16 h and purification *via* flash chromatography on silica gel (0 to 100% EtOAc/hexanes), *tert*-butyl-3-((chloromethylsulfonamido)methyl)-3-hydroxyazetidine-1-carboxylate (**S24**) was isolated as a white foam (1.20 g, 39%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.50 (brs, 1H), 4.58 (s, 2H), 3.92 (d, 2H, *J* = 9.7 Hz), 3.85 (d, 2H, *J* = 9.7 Hz), 3.52 (brs, 1H), 3.48 (s, 2H), 1.44 (s, 9H); LRMS (ESI) *m/z* calcd for $[C_{10}H_{19}ClN_2O_5S - H]^-$ 313.06 found 312.98.

Step 2. *tert*-butyl-3-((chloromethylsulfonamido)methyl)-3-hydroxyazetidine-1-carboxylate (1.20 g, 3.81 mmol, 1.0 equiv.), *p*-methoxybenzyl bromide (592 µL, 4.00 mmol, 1.1 equiv.), and potassium carbonate (1.58 g, 11.4 mmol, 3.0 equiv.) were combined in DMF (38 mL). After stirring for 1 h, an addition portion of *p*-methoxybenzyl bromide (700 µL) was added. After stirring for an additional 3 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 45% EtOAc/hexanes), *tert*-butyl-3-((1-chloro-*N*-(4-methoxybenzyl)methylsulfonamido)methyl)-3-hydroxyazetidine-1-carboxylate (**S25**) was isolated as a white foam (1.62 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.29 – 7.26 (m, 2H), 6.88 – 6.86 (m, 2H), 4.56 (s, 2H), 4.51 (s, 2H), 4.29 (s, 1H), 3.83 – 3.74 (m, 4H), 3.77 (s, 3H), 3.60 (s, 2H), 1.38 (s, 9H); LRMS (ESI) *m/z* calcd for $[C_{18}H_{27}ClN_2O_6S - H + HCO_2H]^-$ 479.13 found 479.16.

Step 3. *tert*-butyl-3-((1-chloro-*N*-(4-methoxybenzyl)methylsulfonamido)methyl)-3-hydroxyazetidine-1-carboxylate (1.62 g, 3.72 mol, 1.0 equiv.) and cesium carbonate (2.43 g, 7.45 mmol, 2.0 equiv.) were combined in DMF (19 mL). After stirring at 100 °C for 48 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 45% EtOAc/hexanes), *tert*-butyl-8-(4-methoxybenzyl)-5-oxa-7-thia-2,8-diazaspiro[3.5]nonane-2-carboxylate-7,7-dioxide (**S26**) was isolated as a white foam (1.20 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.28 – 7.22 (m, 2H), 6.92 – 6.90 (m, 2H), 4.61 (s, 2H), 2.07 (s, 2H), 3.90 (d, 2H, J = 9.6 Hz), 3.83 (s, 3H), 3.61 (d, 2H, J = 9.6 Hz), 3.34 (s, 2H), 1.39 (s, 9H); LRMS (ESI) *m/z* calcd for $[C_{18}H_{26}N_2O_6S - H + HCO_2H]^-$ 443.15 found 443.12.

Step 4. *tert*-butyl-8-(4-methoxybenzyl)-5-oxa-7-thia-2,8-diazaspiro[3.5]nonane-2-carboxylate-7,7-dioxide (1.20 g, 3.01 mmol, 1.0 equiv.) and ceric ammonium nitrate (4.95 g, 9.03 mmol, 3.0 equiv.) were dissolved in MeCN (27 mL) and water (3 µL). After stirring for 24 h, an aqueous work-up, and purification *via* flash chromatography on silica gel (0 to 10% MeOH/DCM) *tert*-butyl-5-oxa-7-thia-2,8-diazaspiro[3.5]nonane-2-carboxylate 7,7-dioxide (**S27**) was obtained as an off white foam (197 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.63 (s, 2H), 3.97 (d, 2H, J = 9.5 Hz), 3.90 (d, 2H, J = 9.5 Hz), 3.74 (d, 2H, J = 6.6 Hz), 1.91 (s, 1H), 1.44 (s, 9H); LRMS (ESI) *m/z* calcd for $[C_{10}H_{18}N_2O_5S - H]^-$ 277.09 found 277.04.

N-Boc deprotection. *tert*-butyl-8-(4-methoxybenzyl)-5-oxa-7-thia-2,8-diazaspiro[3.5]nonane-2-carboxylate-7,7-dioxide (119 mg, 0.428 mmol, 1.0 equiv.) was dissolved in dioxane (750 µL) and a 4.0 M solution of HCl in dioxane (1.0 mL, 4.00 mmol, 9.4 equiv.) was added in one portion at RT. After 16 h, a white solid had precipitated. The suspension was concentrated *in vacuo*, triturated with diethyl ether, and filtered over a fine frit to yield the title compound as a white solid (86 mg, 94%). ^{1}H NMR (400 MHz, 2:1 C_5D_5N-D_2O) δ_H 4.96 (s, 2H), 4.20 (s, 4H), 4.02 (s, 2H); ^{13}C NMR (100 MHz, 2:1 C_5D_5N-D_2O) δ_C 77.1, 72.5, 52.4, 50.0; HRMS (ESI) *m/z* calcd for $[C_5H_{10}N_2O_3S + H]^+$ 179.0490 found 179.0492. Purity: >99.9% (UPLC, ELSD).

General Procedure E (seven-membered lactams):

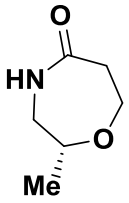
Step 1. To a solution of amino alcohol (1.0 equiv.) in DCM (0.1 M) under N_2 was added Boc_2O (1.05 equiv.), followed by triethylamine (2.0 equiv.). The mixture was left to stir overnight at RT, then diluted with DCM, and washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (gradients indicated).

Step 2. To a solution of *N*-Boc protected amino alcohol (1.0 equiv.) in *t*-BuOH (0.2 M) was added Cs_2CO_3 (1.0 equiv.) and *t*-Butyl acrylate (20.0 equiv.). The mixture was stirred at RT overnight, then diluted with EtOAc and washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (gradients indicated) to obtain vinyl sulfonamides.

Step 3. The *N*-Boc-oxa-conjugate intermediate (1.0 equiv.) was dissolved in 4.0 M HCl in dioxane (20.0 equiv) and left to stir overnight at RT. The reaction was cooled over ice and diluted with cold ether. The white precipitate was filtered to afford the amino acid hydrochloride salt which was used in the following step without any further purification.

Step 4. The intermediate amino acid salt was dissolved in dioxane (0.01 M), treated with T3P (2.5 equiv.), triethylamine (3.5 equiv.) and left to stir overnight at RT. The suspension was

concentrated in *vacuo* and the crude was purified was purified by flash chromatography on silica gel (gradients indicated) to obtain the title compounds.

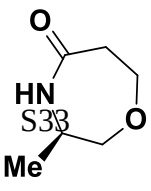


(*R*)-2-methyl-1,4-oxazepan-5-one (14a). Using general procedure **E**, steps 2-4.

Step 2. (*R*)-*tert*-butyl (2-hydroxypropyl)carbamate (1.61 g, 9.19 mmol, 1.0 equiv.), Cs_2CO_3 (2.99 g,z 9.19 mmol, 1.0 equiv.), and *tert*-butyl acrylate (26.7 ml, 184 mmol, 20.0 equiv.) in *t*-BuOH (51.0 mL) were reacted to obtain (*R*)-*tert*-butyl 3-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)propanoate (**S28**; 2.25 g, 7.42 mmol, 81%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.09 (s, 1H), 3.79 – 3.65 (m, 1H), 3.64 – 3.56 (m, 1H), 3.55 – 3.44 (m, 1H), 3.40 – 3.26 (m, 1H), 2.96 (ddd, 1H, *J* = 13.7, 7.4, 4.5 Hz), 2.49 – 2.40 (m, 2H), 1.46 (s, 9H), 1.42 (s, 9H), 1.11 (d, 3H, *J* = 6.2 Hz). LRMS (ES+) Calcd for $[C_{15}H_{29}NO_5 + Na]^+$ 326.19 found 326.21. Purity: 95.19% (UPLC, UV_{214}).

Step 3. (*R*)-*tert*-butyl 3-((1-((*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)propanoate (1.2 g, 3.96 mmol, 1.0 equiv.) was left to stir in a 4.0 M solution of HCl in dioxane (19.78 mL, 79 mmol, 20 equiv.) overnight at RT to obtain (*R*)-3-((1-aminopropan-2-yl)oxy)propanoic acid hydrogen chloride (**S29**; 0.7 g, 3.83 mmol, 97%) as an off-white solid after filtration. ^{1}H NMR (400 MHz, CD_3OD) δ_H 3.91 – 3.83 (m, 1H), 3.82 – 3.72 (m, 1H), 3.69-3.61 (m, 1H), 3.10 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.85 (dd, 1H, *J* = 13.0, 9.0 Hz), 2.61 (t, 2H, *J* = 5.9 Hz), 1.22 (d, 3H, *J* = 6.2 Hz).; LRMS (ESI+) m/z calcd for $[C_6H_{13}NO_3 + H]^+$ 148.10 found 148.08.

Step 4. (*R*)-3-((1-aminopropan-2-yl)oxy)propanoic acid hydrogen chloride (0.25 g, 1.69 mmol, 1.0 equiv.), T3P (2.53 mL, 4.25 mmol, 2.5 equiv.) and triethylamine (0.83 mL, 5.95 mmol, 3.5 equiv) in dioxane (340 mL) were reacted to obtain (*R*)-2-methyl-1,4-oxazepan-5-one (73 mg,



0.56 mmol, 33%) as a white solid after purification by flash chromatography on silica gel (0 to 10% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.98 (ddd, 1H, *J* = 12.7, 5.3, 2.6 Hz), 3.71 – 3.61 (m, 2H), 3.35 – 3.24 (m, 1H), 3.02 (ddd, 1H, *J* = 15.3, 7.6, 1.1 Hz), 2.87 (ddd, 1H, *J* = 15.5, 11.0, 2.6 Hz), 2.54 – 2.45 (m, 1H), 1.16 (d, 3H, *J* = 6.5 Hz); HRMS (ESI+) m/z calcd for $[C_6H_{11}NO_2 + H]^+$ 130.0868 found 130.0868.

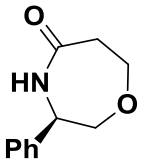
(*R*)-3-methyl-1,4-oxazepan-5-one (14b). Using general procedure **E**, steps 1-4.

Step 1. (*R*)-2-aminopropan-1-ol (1.00 g, 13.3 mmol, 1.0 equiv.), Boc_2O (3.05 g, 13.98 mmol, 1.05 eq.), and triethylamine (1.86 ml, 13.31 mmol, 1.2 eq.) were stirred overnight in DCM (133 mL) to obtain (*R*)-*tert*-butyl (1-hydroxypropan-2-yl)carbamate (**S30**; 1.94 g, 11.07 mmol, 83 %) as an oil upon iiwork-up and purification by flash chromatography on silica gel (0 to 50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.27 – 5.10 (m, 1H), 4.07 (s, 1H), 3.55 – 3.39 (m, 1H), 3.39 – 3.21 (m, 2H), 1.22 (s, 9H), 0.93 (d, 3H, *J* = 6.8 Hz); LRMS (ESI+) m/z calcd for $[C_8H_{17}NO_3 + Na]^+$ 198.11 found 198.11.

Step 2. (*R*)-*tert*-butyl (1-hydroxypropan-2-yl)carbamate (1.94 g, 11.07 mmol, 1.0 equiv.), Cs_2CO_3 (3.61 g, 11.07 mmol, 1.0 equiv.), and *tert*-butyl acrylate (32.1 ml, 221 mmol, 20.0 equiv.) in *t*-BuOH (55.4 mL) were reacted to obtain (*R*)-*tert*-butyl3-(2-((*tert*-butoxycarbonyl)amino)propoxy)propanoate (**S31**; 2.96 g, 9.79 mmol, 88%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.94 – 4.72 (m, 1H), 3.35 (brs, 1H), 3.27 (t, *J* = 6.3 Hz, 2H), 3.06 – 2.86 (m, 2H), 2.05 (t, 2H, *J* = 6.3 Hz), 1.04 (s, 9H), 1.01 (s, 9H), 0.73 (d, 3H, *J* = 7.1); LRMS (ESI+) m/z calcd for $[C_{15}H_{29}NO_5 + Na]^+$ 326.21 found 326.21.

Step 3. (*R*)-*tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)propoxy)propanoate (2.9 g, 9.56 mmol, 1.0 equiv.) was left to stir in a 4.0 M solution of HCl in dioxane (47.8 mL, 191 mmol, 20 equiv.) overnight at RT to obtain (*R*)-3-(2-aminopropoxy)propanoic acid hydrogen chloride (**S32**; 1.40 g, 7.62 mmol, 80%) as an off-white solid after filtration. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.83 – 3.70 (m, 2H), 3.70 – 3.61 (m, 1H), 3.52 – 3.45 (m, 2H), 2.61 (t, 2H, *J* = 6.0 Hz), 1.30 (d, 3H, *J* = 6.3 Hz,); LRMS (ESI+) m/z calcd for $[C_6H_{13}NO_3 + H]^+$ 148.10 found 148.51.

Step 4. (*R*)-3-(2-aminopropoxy)propanoic acid hydrogen chloride (0.4 g, 2.72 mmol, 1.0 equiv.), T3P (4.05 mL, 6.79 mmol, 2.5 equiv.) and triethylamine (1.33 mL, 9.51 mmol, 3.5 equiv) in dioxane (272 mL) were reacted to obtain (*R*)-3-methyl-1,4-oxazepan-5-one (120 mg, 0.93 mmol, 34%) as a white solid after purification by flash chromatography on silica gel (0 to 25% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.11 (brs, 1H), 3.87 (ddd, 1H, *J* = 12.5, 5.5, 2.6 Hz), 3.73 (d, 1H, *J* = 12.4 Hz), 3.69 – 3.61 (m, 1H), 3.61-3.52 (m, 1H), 3.27 (dd, 1H, *J* = 12.4, 8.3 Hz), 2.81 (ddd, 1H, *J* = 15.5, 10.7, 2.6 Hz), 2.43 (dd, 1H, *J* = 10.4, 5.1 Hz), 1.08 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_c 176.89, 77.22, 65.59, 50.34, 41.09, 17.17; HRMS (ESI+) m/z calcd for $[C_6H_{11}NO_2 + H]^+$ 180. 130.0868 found 130.0870. Purity: 97.04% (UPLC, UV_{214}).



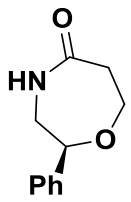
(R)-3-phenyl-1,4-oxazepan-5-one (14c). Using general procedure **E**, steps 1-4.

Step 1. (*R*)-2-amino-2-phenylethanol (0.7 g, 5.1 mmol, 1.0 equiv.), Boc_2O (1.17 g, 5.36 mmol, 1.05 equiv.), and triethylamine (1.42 ml, 10.21 mmol, 2.0 equiv.) in DCM (51 mL) were reacted to obtain (*R*)-*tert*-butyl (2-hydroxy-1-phenylethyl)carbamate (**S33**; 1.1 g, 4.64 mmol, 91 %) as a white solid after work-up and purification by flash chromatography on silica gel (0 to 50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37-7.33 (m, 2H), 7.32 – 7.27 (m, 3H), 5.30 – 5.18 (m, 1H), 4.75 (brs, 1H), 3.99 – 3.71 (m, 2H), 2.40 (brs, 1H), 1.43 (s, 9H); LRMS (ESI+) m/z calcd for $[C_{13}H_{19}NO_3 + Na]^+$ 260.13 found 260.13.

Step 2. (*R*)-*tert*-butyl(2-hydroxy-1-phenylethyl)carbamate (0.5 g, 2.1 mmol, 1.0 equiv.), Cs_2CO_3 (0.68 g, 2.11 mmol, 1.0 equiv.), and *tert*-butyl acrylate (6.1 ml, 42.1 mmol, 20.0 equiv.) in *t*-BuOH (10.5 mL) were reacted to obtain (*R*)-*tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)-2-phenylethoxy)propanoate (**S34**; 0.71 g, 1.94 mmol, 92%) as a clear oil after work-up and purification by flash chromatography on silica gel (0 to 50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.28 – 7.24 (m, 4H), 7.18 (ddt, 1H, *J* = 6.7 , 5.1, 2.8 Hz), 5.61 – 5.39 (m, 1H), 4.85 – 4.63 (m, 1H), 3.70 – 3.53 (m, 4H), 2.40 (t, 2H, *J* = 6.1 Hz), 1.41 (s, 9H), 1.37 (s, 9H); LRMS (ESI+) m/z calcd for $[C_{20}H_{31}NO_5 + Na]^+$ 388.21 found 388.21.

Step 3. (*R*)-*tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)-2-phenylethoxy)propanoate (0.3 g, 0.82 mmol, 1.0 equiv.) was left to stir in a 4.0 M solution of HCl in dioxane (4.1 mL, 16.42 mmol, 20 equiv.) overnight at RT to obtain (*R*)-3-(2-amino-2-phenylethoxy)propanoic acid hydrogen chloride (**S35**; 0.2 g, 0.82 mmol, 99%) as a white solid after filtration. ^{1}H NMR (400 MHz, CD_3OD) δ_H 7.49 – 7.38 (m, 5H), 4.53 (dd, 1H, *J* = 7.6, 5.3 Hz), 3.91 – 3.75 (m, 4H), 2.64 (t, 2H, *J* = 5.9 Hz); LRMS (ESI+) m/z calcd for $[C_{11}H_{15}NO_3 + H]^+$ 210.11 found 210.88.

Step 4. (*R*)-3-(2-amino-2-phenylethoxy)propanoic acid Hydrogen chloride (0.56 g, 2.69 mmol, 1.0 equiv.), T3P (2.0 mL, 6.71 mmol, 2.5 equiv) and triethylamine (1.31 mL, 9.40 mmol, 3.5 equiv.) in dioxane (269 mL) were reacted to obtain (*R*)-3-phenyl-1,4-oxazepan-5-one (425 mg, 2.22 mmol, 83%) as a white solid after purification by flash chromatography on silica gel (0 to 20% MeOH/DCM). $^{23}[\alpha]_D$ = -53.1 (*c* = 1.00; $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.41 – 7.35 (m, 3H), 7.30 (dd, 2H, *J* = 7.9, 1.7 Hz), 5.84 (s, 1H), 4.77 – 4.69 (m, 1H), 4.05 (ddd, 1H, *J* = 12.6, 5.3, 2.7 Hz), 3.97 – 3.92 (m, 1H), 3.84 – 3.69 (m, 3H), 3.02 (ddd, 1H, *J* = 15.9, 11.0, 2.7 Hz), 2.68 – 2.60 (m, 1H);ii ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.1, 137.9, 129.4, 128.8, 126.6, 77.1, 65.9, 59.9, 41.1; HRMS (ESI+) m/z calcd for $[C_{11}H_{13}NO_2 + H]^+$ 192.1025 found 192.1026; FTIR (neat; cm^{-1}) 3203 (br), 3065 (w), 2861 (w), 1660 (s); Purity: 99.05% (UPLC, UV_{214}).



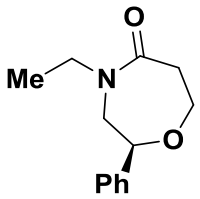
(S)-2-phenyl-1,4-oxazepan-5-one (14d). Using general procedure **E**, steps 1-4.

Step 1. (*S*)-2-amino-1-phenylethanol (0.7 g, 5.1 mmol, 1.0 equiv.), Boc_2O (1.17 g, 5.36 mmol, 1.05 eq.), and triethylamine (1.42 ml, 10.21 mmol, 2.0 eq.) were stirred overnight in DCM (51 mL) to obtain (*S*)-*tert*-butyl (2-hydroxy-2-phenylethyl)carbamate (**S36**; 1.2 g, 4.6 mmol, 90 %) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38 –7.27 (m, 5H), 5.01 (brs, 1H), 4.86 – 4.71 (m, 1H), 3.51 – 3.41 (s, 1H), 3.32 (brs, 1H), 3.28 – 3.21 (m, 1H), 1.44 (s, 9H); LRMS (ESI+) m/z calcd for $[C_{11}H_{19}NO_3 + Na]^+$ 260.13 found 260.16.

Step 2. (*S*)-*tert*-butyl(2-hydroxy-2-phenylethyl)carbamate (1.47 g, 6.19 mmol, 1.0 equiv.), Cs_2CO_3 (2.02 g, 6.19 mmol, 1.0 equiv.), and *tert*-butyl acrylate (17.98 ml, 124 mmol, 20.0 equiv.) in *t*-BuOH (31.0 mL) were reacted to obtain (*S*)-*tert*-butyl 3-(2-((tert-butoxycarbonyl)amino)-1-phenylethoxy)propanoate (**S37**; 1.98 g, 5.42 mmol, 87%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.34 – 7.27 (m, 5H), 5.22 – 4.99 (m, 1H), 4.35 (dd, 1H, *J* = 9.2, 3.6 Hz), 3.65 – 3.35 (m, 4H), 2.51 – 2.41 (m, 2H), 1.45 (s, 9H), 1.41 (s, 9H); LRMS (ES+) Calcd for $[C_{20}H_{31}NO_5 + Na]^+$ 388.21 found 388.24.

Step 3. (*S*)-*tert*-butyl 3-(2-((*tert*-butoxycarbonyl)amino)-1-phenylethoxy)propanoate (1.4 g, 3.83 mmol, 1.0 equiv.) was left to stir in a 4.0 M solution of HCl in dioxane (19.2 mL, 77 mmol, 20 equiv.) overnight at RT to obtain (*S*)-3-(2-amino-1-phenylethoxy)propanoic acid hydrogen chloride (**S38**; 0.91 g, 3.71 mmol, 97%) as an off-white solid after filtration. ^{1}H NMR (400 MHz, CD_3OD) δ_H 7.41 (d, *J* = 4.7 Hz, 4H), 7.38 – 7.34 (m, 1H), 4.66 (dd, 1H, *J* = 9.9, 3.6 Hz), 3.71 – 3.57 (m, 2H), 3.18 – 3.02 (m, 2H), 2.62 (t, 2H, *J* = 6.0 Hz); LRMS (ESI+) m/z calcd for $[C_{11}H_{15}NO_3 + H]^+$ 210.11 found 210.63. Purity: 98.23% (UPLC, UV_{214}).

Step 4. (*S*)-3-(2-amino-1-phenylethoxy)propanoic acid (0.25 g, 1.2 mmol, 1.0 equiv.), T3P (1.78 mL, 2.99 mmol, 2.5 equiv.) and triethylamine (0.58 mL, 4.18 mmol, 3.5 equiv) in dioxane (239 mL) were reacted to obtain (*S*)-2-phenyl-1,4-oxazepan-5-oneone (131 mg, 0.68 mmol, 57%) as a white solid after purification by flash chromatography on silica gel (0 to 10% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.24 (m, 5H), 6.73 (brs, 1H), 4.51 – 4.45 (m, 1H), 4.15 (ddt, *J* = 12.8, 4.6, 2.2 Hz, 1H), 3.83 (ddd, 1H, *J* = 12.6, 11.3, 0.9 Hz), 3.65 – 3.52 (m, 1H), 3.17 (ddd, 1H, *J* = 15.4, 7.7, 1.2 Hz), 3.02 (ddt, 1H, *J* = 15.7, 11.1, 2.2 Hz), 2.63 – 2.51 (m, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 177.5, 139.8, 128.7, 128.2, 126.0, 83.3, 65.4, 50.7, 40.9; HRMS (ESI+) m/z calcd for $[C_{11}H_{13}NO_2 + H]^+$ 192.1025 found 192.1031.



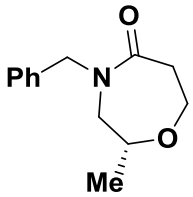
(*S*)-4-ethyl-2-phenyl-1,4-oxazepan-5-one (14e). Using general procedure **E**, steps 1-4.

Step 1. (*S*)-2-(ethylamino)-1-phenylethanol (0.23 g, 1.39 mmol, 1.0 equiv.), Boc_2O (0.32 g, 1.46 mmol, 1.05 eq.), and triethylamine (0.38 ml, 2.78 mmol, 2.0 eq.) were stirred overnight in DCM (14 mL) to obtain (*S*)-*tert*-butyl ethyl(2-hydroxy-2-phenylethyl)carbamate (**S39**; 0.37 g, 1.38 mmol, 99 %) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 25% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42 – 7.16 (m, 5H), 4.94 – 4.73 (m, 1H), 3.52 – 3.01 (m, 4H), 1.44 (brs, 9H), 1.07 – 0.90 (m, 3H); LRMS (ES+) Calcd for $[C_{15}H_{23}NO_3 + H]^+$ 288.16 found 288.14.

Step 2. (*S*)-*tert*-butyl ethyl(2-hydroxy-2-phenylethyl)carbamate (0.36 g, 1.36 mmol, 1.0 equiv.), Cs_2CO_3 (0.44 g, 1.36 mmol, 1.0 equiv.), and *tert*-butyl acrylate (3.94 ml, 27.1 mmol, 20.0 equiv.) in *t*-BuOH (13.6 mL) were reacted to obtain (*R*)-*tert*-butyl 3-((1-(benzyl(*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)propanoate (**S40**; 0.39 g, 1.01 mmol, 74.5%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.09 (m, 5H), 4.52 – 4.43 (m, 1H), 3.67 – 3.40 (m, 2H), 3.39 – 3.02 (m, 4H), 2.44 – 2.34 (m 2H), 1.39 (brs, 18H), 0.98 (brs, 3H); LRMS (ES+) Calcd for $[C_{22}H_{35}NO_5 + Na]^+$ 416.24 found 416.35.

Step 3. (*S*)-*tert*-butyl 3-(2-((*tert*-butoxycarbonyl)(ethyl)amino)-1-phenylethoxy)propanoate (0.77 g, 0.84 mmol, 1.0 equiv.) was left to stir in a 4.0 M solution of HCl in dioxane (4.19 mL, 16.77 mmol, 20 equiv.) overnight at RT to obtain (*S*)-3-(2-(ethylamino)-1-phenylethoxy)propanoic acid hydrogen chloride (**S41**; 0.19g, 0.72 mmol, 86%) as an oil after filtration. ^{1}H NMR (400 MHz, CD_3OD) δ_H 7.25 – 7.09 (m, 5H), 4.60 (p, J = 6.1 Hz, 1H), 3.48 – 3.38 (m, 2H), 3.03 – 2.88 (m, 4H), 2.47 – 2.35 (m, 2H), 1.21 – 1.11 (m, 3H); LRMS (ESI+) m/z calcd for $[C_{13}H_{19}NO_3 + H]^+$ 238.14 found 238.38.

Step 4. (*S*)-3-(2-(ethylamino)-1-phenylethoxy)propanoic acid hydrogen chloride (0.19 g, 0.83 mmol, 1.0 equiv.), T3P (1.24 mL, 2.07 mmol, 2.5 equiv.) and triethylamine (0.40 mL, 2.91 mmol, 3.5 equiv) in dioxane (166 mL) were reacted to obtain (*S*)-4-ethyl-2-phenyl-1,4-oxazepan-5-one (0.16 mg, 0.71 mmol, 86%) as a white solid after purification by flash chromatography on silica gel (0 to 20% MeOH/DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.31 – 7.17 (m, 5H), 4.38 – 4.28 (m, 1H), 4.05 (ddd, 1H, *J* = 12.6, 5.3, 2.5 Hz), 3.78 – 3.61 (m, 2H), 2.94 (ddd, 1H, *J* = 15.5, 11.3, 2.5 Hz), 2.54 (dd, 1H, *J* = 15.4, 5.2 Hz), 1.05 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 173.6, 140.2, 128.6, 128.1, 125.7, 82.5, 65.4, 57.3, 43.3, 41.0, 13.2; HRMS (ESI+) m/z calcd for $[C_{13}H_{17}NO_2 + H]^+$ 220.1338 found 220.1339. Purity: 98.78% (UPLC, UV_{214}).



(*R*)-4-benzyl-2-methyl-1,4-oxazepan-5-one (14f). Using general procedure **E**, steps 1-4.

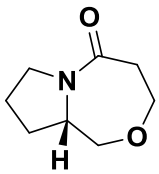
Step 1. (*R*)-1-(benzylamino)propan-2-ol (0.44 g, 2.66 mmol, 1.0 equiv.), Boc_2O (0.61 g, 2.8 mmol, 1.05 eq.), and triethylamine (0.74 ml, 5.33 mmol, 2.0 eq.) were stirred overnight in DCM (26 mL) to obtain (*R*)-*tert*-butyl benzyl(2-hydroxypropyl)carbamate (**S42**; 0.62 g, 2.35 mmol, 88 %) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 25% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.31 – 7.11 (m, 5H), 4.47 (brs, 2H), 3.95 (m, 1H), 3.30 – 2.93 (m, 2H), 1.42 (s, 9H) 1.11 – 1.06 (m, 3H); LRMS (ES+) Calcd for $[C_{15}H_{23}NO_3 + H]^+$ 288.16 found 288.11.

Step 2. (*R*)-*tert*-butyl benzyl(2-hydroxypropyl)carbamate (0.52 g, 1.96 mmol, 1.0 equiv.), Cs_2CO_3 (0.64 g, 1.96 mmol, 1.0 equiv.), and *tert*-butyl acrylate (5.69 ml, 39.2 mmol, 20.0 equiv.) in *t*-BuOH (20.0 mL) were reacted to obtain (*R*)-*tert*-butyl 3-((1-(benzyl(*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)propanoate (**S43**; 0.77 g, 1.96 mmol, 100%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.00 (m, 5H), 4.68 – 4.25 (m, 2H), 3.81 – 3.35 (m, 2H),

3.34 – 2.85 (m, 3H), 2.50 – 2.21 (m, 2H), 1.51 – 1.24 (m, 18H), 1.09 – 0.86 (m, 3H).LRMS (ES+) Calcd for $[C_{22}H_{35}NO_5 + Na]^+$ 416.24 found 416.30.

Step 3. (*R*)-*tert*-butyl 3-((1-(benzyl(*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)propanoate (0.77 g, 1.96 mmol, 1.0 equiv.) was left to stir in a 4.0 M solution of HCl in dioxane (9.78 mL, 39.1 mmol, 20 equiv.) overnight at RT to obtain (*R*)-*tert*-butyl 3-((1-(benzyl(*tert*-butoxycarbonyl)amino)propan-2-yl)oxy)propanoate hydrogen chloride (**S44**; 0.46g, 1.69 mmol, 87%) as an off-white solid after filtration. ^{1}H NMR (400 MHz, CD_3OD) δ_H 3.91 – 3.83 (m, 1H), 3.82 – 3.72 (m, 1H), 3.69-3.61 (m, 1H), 3.10 (dd, 1H, *J* = 13.2, 3.2 Hz), 2.85 (dd, 1H, *J* = 13.0, 9.0 Hz), 2.61 (t, 2H, *J* = 5.9 Hz), 1.22 (d, 3H, *J* = 6.2 Hz); LRMS (ESI+) m/z calcd for $[C_6H_{13}NO_3 + H]^+$ 238.14 found 238.51.

Step 4. (*R*)-3-((1-(benzylamino)propan-2-yl)oxy)propanoic acid hydrogen chloride (0.25 g, 1.05 mmol, 1.0 equiv.), T3P (1.57 mL, 2.63 mmol, 2.5 equiv.) and triethylamine (0.51 mL, 3.68 mmol, 3.5 equiv) in dioxane (211 mL) were reacted to obtain (*R*)-4-benzyl-2-methyl-1,4-oxazepan-5-one (0.12 mg, 0.56 mmol, 52.8%) as a white solid after purification by flash chromatography on silica gel (0 to 20% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.16 (m, 5H), 4.64 (d, 1H, *J* = 14.7 Hz), 4.46 (d, 1H, *J* = 14.7 Hz), 3.95 (ddd, 1H, *J* = 12.6, 5.5, 2.3 Hz), 3.75 – 3.53 (m, 1H), 3.51 – 3.27 (m, 2H), 2.99 (d, 1H, *J* = 15.3 Hz), 2.91 (ddd, 1H, *J* = 15.4, 10.9, 2.4 Hz), 2.63 (dd, 1H, *J* = 15.3, 5.5 Hz), 0.99 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 174.4, 137.1, 128.6, 128.1, 127.5, 75.2, 64.6, 55.8, 51.5, 40.8, 19.5; HRMS (ESI+) m/z calcd for $[C_{13}H_{17}NO_2 + H]^+$ 220.1338 found 220.1340. Purity: 97.98% (UPLC, UV_{214}).



(*S*)-hexahydro-1H,5H-pyrrolo[2,1-c][1,4]oxazepin-5-one (14i). Using general procedure **E**, steps 2-4.

Step 2. (*S*)-*tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (1.0 g, 4.97 mmol, 1.0 equiv.), Cs_2CO_3 (1.62 g, 4.97 mmol, 1.0 equiv.), and *tert*-butyl acrylate (14.42 ml, 99 mmol, 20.0 equiv.) in *t*-BuOH (28.8 mL) were reacted to obtain (*S*)-*tert*-butyl 2-((3-(*tert*-butoxy)-3-

oxopropoxy)methyl)pyrrolidine-1-carboxylate (**S45**; 1.46 g, 4.43 mmol, 89%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.84 (brs, 1H), 3.70 – 3.55 (m, 2H), 3.54 – 3.40 (m, 1H), 3.36 – 3.19 (m, 3H), 2.40 (t, 2H, *J* = 6.3 Hz), 1.90 – 1.76 (m, 3H), 1.75 – 1.67 (m, 1H), 1.41 (s, 9H), 1.39 (s, 9H). LRMS (ES+) Calcd for $[C_{17}H_{31}NO_5 + Na]^+$ 352.21 found 352.16.

Step 3. (*S*)-*tert*-butyl 2-((3-(*tert*-butoxy)-3-oxopropoxy)methyl)pyrrolidine-1-carboxylate (1.45 g, 4.40 mmol, 1.0 equiv.) was left to stir in a 4.0 M solution of HCl in dioxane (22.01 mL, 88 mmol, 20 equiv.) overnight at RT to obtain (*S*)-3-(pyrrolidin-2-ylmethoxy)propanoic acid hydrogen chloride (0.76 g, 3.62 mmol, 82%) as an oil after filtration which was used directly in step four. LRMS (ESI+) m/z calcd for $[C_8H_{15}NO_3 + H]^+$ 174.11 found 174.07.

Step 4. (*S*)-3-(pyrrolidin-2-ylmethoxy)propanoic acid hydrogen chloride (0.5 g, 2.89 mmol, 1.0 equiv.), T3P (4.29 mL, 7.22 mmol, 2.5 equiv.) and triethylamine (1.41 mL, 10.10 mmol, 3.5 equiv) in dioxane (144 mL) were reacted to obtain (*S*)-hexahydropyrrolo[2,1-c][1,4]oxazepin-5(1H)-one (0.32 g, 2.14 mmol, 74.1%) as a solid upon purification by flash chromatography on silica gel (0 to 20% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.92 – 3.79 (m, 3H), 3.72 – 3.62 (m, 1H), 3.55 – 3.42 (m, 1H), 3.24 (ddd, *J* = 11.8, 9.8, 6.6 Hz, 1H), 3.13 (dd, 1H, *J* = 12.7, 9.2 Hz), 2.78 (ddd, 1H, *J* = 15.3, 11.3, 2.5 Hz), 2.46 (dd, 1H, *J* = 15.5, 5.0 Hz), 2.05 (dddd, 1H, *J* = 13.9, 7.5, 3.1, 1.5 Hz), 1.79 (ddq, 1H, *J* = 15.3, 6.5, 3.3 Hz), 1.70 – 1.56 (m, 1H), 1.41 (dddd, 1H, *J* = 12.7, 10.9, 9.1, 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 172.3, 74.5, 65.7, 59.5, 47.0, 41.4, 29.6, 22.9; HRMS (ESI+) m/z calcd for $[C_8H_{13}NO_2 + H]^+$ 156.1025 found 156.1025. Purity: 100% (UPLC, UV_{214}).

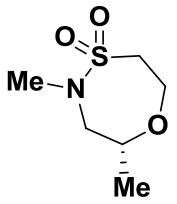
General Procedure F (seven-membered sultams):

Step 1. To a solution of amino alcohol (1.0 equiv.) in DCM (0.5 M) under N_2 at 0 °C was added TBSCl (1.0-2.0 equiv.), followed by triethylamine (1.0-3.0 equiv.). The mixture was warmed to RT, stirred overnight, diluted with DCM, and washed with brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (gradients indicated).

Step 2. To a solution of *O*-TBS protected amino alcohol (1.0 equiv.) in dry DCM (0.2 M) at 0 °C was added triethylamine (3.5 equiv.) and 2-chloroethanesulfonyl chloride (1.0 equiv.). The mixture was stirred 2 h at 0 °C and then diluted with DCM, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (gradients indicated) to obtain vinyl sulfonamides.

Step 3 (for secondary vinyl sulfonamides). To a mixture of vinyl sulfonamide (1.0 equiv.) and potassium carbonate (2.0-4.0 equiv.) in MeCN (0.5 M) was added MeI (1.0-2.0 equiv.) dropwise at RT. The mixture was stirred at 80 °C and reaction progress was monitored by LCMS. Upon completion, the mixture was cooled, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (gradients indicated) to obtain *N*-methyl vinyl sulfonamides.

Step 4. To a solution of *N*-alkyl vinyl sulfonamide (1.0 equiv.) in THF (0.04 M) at RT was added TBAF (1.0 equiv.) and the mixture was stirred for 2 h. The reaction was quenched with sat. aq. NH_4Cl, and extracted with DCM (3 x). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by flash chromatography on silica gel (gradients indicated) to obtain the title compounds.



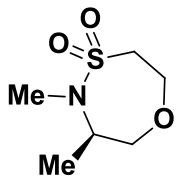
(*R*)-5,7-dimethyl-1,4,5-oxathiazepane 4,4-dioxide (15a). Using general procedure **F**, steps 1-4.

Step 1. (*R*)-1-aminopropan-2-ol (1.00 g, 13.3 mmol, 1.0 equiv.), TBSCl (2.41 g, 16.0 mmol, 1.1 equiv.), and triethylamine (2.04 ml, 14.6 mmol, 1.2 equiv.) in DCM (27 mL) were reacted to obtain (*R*)-2-((*tert*-butyldimethylsilyl)oxy)propan-1-amine (**S46**; 1.96 g, 10.35 mmol, 78 %) as an oil upon work-up and purification (SiO_2, 0 to 20% MeOH/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.84 – 3.72 (m, 1H), 2.74 – 2.51 (m, 2H), 1.11 (d, 3H, J = 6.1 Hz), 0.90 (s, 9H), 0.07 (s, 6H); LRMS (ES+) Calcd for $[C_9H_{23}NOSi + H]^+$ 190.16 found 190.04.

Step 2. (*R*)-2-((*tert*-butyldimethylsilyl)oxy)propan-1-amine (0.8 g, 4.22 mmol, 1.0 equiv.), triethylamine (2.06 ml, 14.8 mmol, 3.5 equiv.), and 2-chloroethanesulfonyl chloride (0.444 ml, 4.22 mmol, 1.0 equiv.) in DCM (21 mL) were reacted to obtain (*R*)-N-(2-((*tert*-butyldimethylsilyl)oxy)propyl)ethenesulfonamide (**S47**; 1.12 g, 4.01 mmol, 95%) as a crude oil upon work-up, which was taken on to the next step without purification.

Step 3. (*R*)-N-(2-((*tert*-butyldimethylsilyl)oxy)propyl)ethenesulfonamide (1.02 g, 3.65 mmol, 1.0 equiv.), potassium carbonate (2.0 g, 14.6 mmol, 4.0 equiv.), and MeI (0.5 mL, 8.02 mmol, 2.2 equiv.) in MeCN (7.3 mL) were reacted for 48 h at 80 °C to obtain (*R*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-*N*-methylethenesulfonamide (**S48**; 0.75 g, 2.56 mmol, 70%) as a clear oil upon purification by flash chromatography on silica gel (0 to 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.42 (dd, 1H, *J* = 16.6, 9.9 Hz), 6.20 (d, 1H, *J* = 16.6 Hz), 5.97 (d, 1H, *J* = 9.9 Hz), 4.03 (pd, 1H, *J* = 6.2, 4.6 Hz), 3.04 (dd, 1H, *J* = 14.0, 4.7 Hz), 2.93 (dd, 1H, *J* = 14.0, 6.7 Hz), 2.89 (s, 3H), 1.17 (d, 3H *J* = 6.1 Hz), 0.89 (s, 9H), 0.09 (d, 6H, *J* = 2.4 Hz); LRMS (ES+) Calcd for $[C_{12}H_{27}NO_3SSi + H]^+$ 294.16 found 294.57.

Step 4. (*R*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)propyl)-*N*-methylethenesulfonamide (83 mg, 0.283 mmol, 1.0 equiv.) and TBAF (1.0 M in THF, 0.28 mL, 0.283 mmol, 1.0 equiv.) in THF (13 mL) were reacted to obtain the title compound (38.4 mg, 0.214 mmol, 76%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 50% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.27 (dp, 1H, *J* = 9.2, 6.3 Hz), 4.06 (ddd, 1H, *J* = 13.8, 6.1, 3.7 Hz), 3.77 (ddd, 1H, *J* = 13.8, 6.7, 3.7 Hz), 3.41 – 3.21 (m, 4H), 3.00 (s, 3H), 1.19 (d, 3H, J = 6.4 Hz). Purity: >90% (^{1}H NMR).



(*R*)-5,6-dimethyl-1,4,5-oxathiazepane 4,4-dioxide (15b). Using general procedure **F**, steps 1-4.

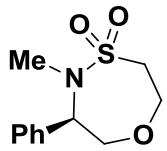
Step 1. (*R*)-2-aminopropan-1-ol (1.00 g, 13.3 mmol), TBSCl (2.41 g, 16.0 mmol, 1.1 eq.), and triethylamine (2.04 ml, 14.6 mmol, 1.2 eq.) were stirred overnight in DCM (27 mL) to obtain (*R*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-amine (**S49**; 2.05 g, 10.83 mmol, 81 %) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 20% MeOH/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.51 (dd, 1H, *J* = 9.7, 4.3 Hz), 3.28 (dd, 1H, *J* = 9.7, 7.5 Hz), 2.97 (dqd, 1H, *J* = 7.5, 6.5, 4.3 Hz), 1.01 (d, 3H, *J* = 6.5 Hz), 0.90 (s, 9H), 0.06 (s, 6H); LRMS (ES+) Calcd for $[C_9H_{23}NOSi+ H]^+$ 190.16 found 190.04.

Step 2. (*R*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-amine (1.04 g, 5.49 mmol, 1.0 equiv.), triethylamine (2.68 ml, 19.2 mmol, 3.5 equiv.), and 2-chloroethanesulfonyl chloride (0.606 ml, 5.77 mmol, 1.05 equiv.) in DCM (27 mL) were reacted to obtain (*R*)-*N*-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)ethenesulfonamide (**S50**; 1.29 g, 4.62 mmol, 84%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.54 (dd, 1H, *J* = 16.6, 9.9 Hz), 6.26 (d, 1H, *J* = 16.6 Hz), 5.90 (d, 1H, *J* = 9.9 Hz), 4.52 (d, 1H, *J* = 7.0 Hz), 3.64 (dd, 1H, *J* = 9.8, 4.1 Hz), 3.55 – 3.34 (m, 2H), 1.20 (d, 3H, *J* = 6.4 Hz), 0.90 (s, 9H), 0.06 (d, 6H, *J* = 0.6 Hz); LRMS (ES+) Calcd for $[C_{11}H_{25}NO_3SSi + H]^+$ 280.14 found 280.07.

Step 3. (*R*)-*N*-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)ethenesulfonamide (0.6 g, 2.147 mmol, 1.0 equiv.), potassium carbonate (0.89 g, 6.44 mmol, 3.0 equiv.), and MeI (0.27 mL, 4.29 mmol, 2.0 equiv.) in MeCN (4.3 mL) were reacted for 48 h at 80 °C to obtain (*R*)-*N*-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-*N*-methylethenesulfonamide (**S51**; 0.537 g, 1.83 mmol, 85%) as a clear oil upon purification by flash chromatography on silica gel (0 to 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.47 (dd, 1H, *J* = 16.6, 9.9 Hz), 6.17 (d, 1H, *J* = 16.6 Hz), 5.84 (d, 1H, *J* = 9.9 Hz), 4.01 (dtd, 1H, *J* = 13.1, 6.9, 6.2 Hz), 3.56 (d, 2H, *J* = 6.2 Hz), 2.73 (s, 3H), 1.13 (d, 3H, *J* = 6.9 Hz), 0.89 (s, 9H), 0.05 (d, 6H, *J* = 1.5 Hz); LRMS (ES+) Calcd for $[C_{12}H_{27}NO_3SSi + H]^+$ 294.16 found 294.06.

Step 4. (*R*)-*N*-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-*N*-methylethenesulfonamide (0.3 g, 1.02 mmol, 1.0 equiv.) and TBAF (1.0 M in THF, 1.1 mL, 1.07 mmol, 1.05 equiv.) in THF (26 mL) were reacted to obtain (*R*)-5,6-dimethyl-1,4,5-oxathiazepane 4,4-dioxide (0.142 g, 0.792

mmol, 78%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.05 – 3.84 (m, 4H), 3.78 (dd, 1H, *J* = 12.6, 11.4 Hz), 3.43 – 3.22 (m, 2H), 2.91 (s, 3H), 1.15 (d, 3H, *J* = 6.6 Hz); HRMS (ES+) Calcd for $[C_6H_{13}NO_3S + H]^+$ 180.0694 found 180.0694. Purity: >95% (^{1}H NMR).



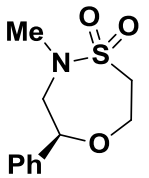
(*R*)-5-methyl-6-phenyl-1,4,5-oxathiazepane 4,4-dioxide (15c). Using general procedure **F**, steps 1-4.

Step 1. (*R*)-2-amino-2-phenylethanol (1.00 g, 7.29 mmol), TBSCl (1.32 g, 8.75 mmol, 1.1 eq.), and triethylamine (1.11 mL, 8.02 mmol, 1.2 eq) were stirred overnight in DCM (15 mL) to obtain (*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethanamine (**S52**; 1.53 g, 6.08 mmol, 83 %) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.23 (m, 5H), 4.05 (dd, 1H, *J* = 8.4, 3.9 Hz), 3.70 (dd, 1H, *J* = 9.8, 3.9 Hz), 3.49 (dd, 1H, *J* = 9.8, 8.4 Hz), 0.87 (s, 9H), 0.00 (d, 6H, *J* = 1.2 Hz); LRMS (ES+) Calcd for $[C_{14}H_{25}NOSi + H]^+$ 252.15 found 252.04

Step 2. (R)-2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethanamine (1.04 g, 4.14 mmol, 1.0 equiv.), triethylamine (2.0 mL, 14.5 mmol, 3.5 equiv.), and 2-chloroethanesulfonyl chloride (0.46 mL, 4.34 mmol, 1.05 equiv.) in DCM (21 mL) were reacted to obtain (*R*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)ethenesulfonamide (**S53**; 1.16 g, 3.40 mmol, 82 %) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.26 (m, 5H), 6.28 (dd, 1H, *J* = 16.5, 9.8 Hz), 6.07 (d, 1H, *J* = 16.6 Hz), 5.71 (d, 1H, *J* = 9.8 Hz, 1H), 5.13 (d, 1H, *J* = 5.8 Hz, 1H), 4.44 (td, 1H, *J* = 6.0, 4.3 Hz), 3.87 (dd, 1H, *J* = 10.2, 4.3 Hz), 3.68 (dd, 1H, *J* = 10.2, 6.2 Hz), 0.86 (s, 9H), -0.02 (d, 6H, *J* = 7.5 Hz); LRMS (ES+) Calcd for $[C_{16}H_{27}NO_3SSi + H]^+$ 342.16 found 342.09.

Step 3. (*R*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)ethenesulfonamide (0.606 g, 1.77 mmol 1.0 equiv.), potassium carbonate (0.736 g, 5.32 mmol, 3.0 equiv.), and MeI (0.22 mL, 3.55 mmol, 2.0 equiv.) in MeCN (3.5 mL) were reacted for 48 h at 80 °C to obtain (*R*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)-*N*-methylethenesulfonamide (**S54**; 0.536 g, 1.507 mmol, 85%) as a white solid upon purification by flash chromatography on silica gel (0 to 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43 – 7.28 (m, 5H), 6.50 (dd, 1H, *J* = 16.6, 9.9 Hz), 6.21 (d, 1H, *J* = 16.6 Hz), 5.85 (d, 1H, *J* = 9.9 Hz), 5.11 (t, *J* = 7.0 Hz, 1H), 4.05 (d, 2H, *J* = 7.0 Hz), 2.73 (s, 3H), 0.92 (s, 9H), 0.12 (d, 6H, *J* = 3.2 Hz); LRMS (ES+) Calcd for $[C_{17}H_{29}NO_3SSi + H]^+$ 356.17 found 356.14.

Step 4. (*R*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-1-phenylethyl)-*N*-methylethenesulfonamide (0.25 g, 0.703 mmol, 1.0 equiv.) and TBAF (1.0 M in THF, 0.7 mL, 0.70 mmol 1.0 equiv.) in THF (17 mL) were reacted to obtain (*R*)-5-methyl-6-phenyl-1,4,5-oxathiazepane 4,4-dioxide (64 mg, 0.265 mmol, 38%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 20% EtOAc/hexanes). $^{23}[\alpha]_D$ = + 36.4 (*c* = 0.617; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 – 7.28 (m, 5H), 4.53 (dd, 1H, *J* = 11.1, 5.7 Hz), 4.28 (dd, 1H, *J* = 13.2, 11.1 Hz), 4.22 – 4.07 (m, 2H), 3.99 (ddd,1H, *J* = 13.4, 7.3, 4.6 Hz), 3.44 – 3.35 (m, 2H), 2.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 136.1, 128.8, 128.2, 127.4, 77.4, 77.1, 76.8, 74.5, 65.3, 63.8, 55.2, 36.0; HRMS (ES+) Calcd for $[C_{11}H_{15}NO_3S + H]^+$ 242.0851 found 242.0853; FTIR (neat; cm^{-1}) 2356 (br), 2174 (w), 1335 (s), 1140 (s), 1111 (s), 741 (s), 701 (s). Purity: 99.33% (UPLC, UV_{214}).



(*S*)-5-methyl-7-phenyl-1,4,5-oxathiazepane 4,4-dioxide (15d). Using general procedure **F**, steps 1-4.

Step 1. (*S*)-2-amino-1-phenylethanol (1.00 g, 7.29 mmol), TBSCl (1.32 g, 8.75 mmol, 1.1 eq.), and triethylamine (1.12 ml, 8.02 mmol, 1.2 eq.) in DCM (15 mL) were reacted to obtain (*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-phenylethanamine (**S55**; 1.3 g, 5.17 mmol, 71 %) as an oil upon

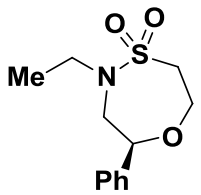
work-up and purification by flash chromatography on silica gel (0 to 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 – 7.18 (m, 5H), 4.65 (dd, 1H, *J* = 5.8, 4.8 Hz), 2.91 – 2.76 (m, 2H), 0.91 (s, 9H), 0.06 (s, 3H), -0.10 (s, 3H); LRMS (ES+) Calcd for $[C_{14}H_{25}NOSi + H]^+$ 252.18 found 252.05.

Step 2. (*S*)-2-((*tert*-butyldimethylsilyl)oxy)-2-phenylethanamine (0.89 g, 3.54 mmol, 1.0 equiv.), triethylamine (1.7 mL, 12.4 mmol, 3.5 equiv.), and 2-chloroethanesulfonyl (0.39 mL, 3.72 mmol, 1.05 equiv.) in DCM (18 mL) were reacted to obtain (*S*)-*N*-(2-((*ter*t-butyldimethylsilyl)oxy)-2-phenylethyl)ethenesulfonamide (**S56**; 0.909 g, 2.66 mmol, 75%) as white solid upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.27 (m, 5H), 4.84 (dd, 1H, *J* = 7.2, 4.2 Hz), 4.47 (t, 1H, *J* = 6.2 Hz), 3.22 (ddd, 1H, *J* = 13.0, 7.4, 4.2 Hz), 3.11 (ddd, 1H, *J* = 13.0, 7.3, 5.0 Hz), 0.90 (s, 9H), 0.07 (s, 3H), -0.11 (s, 3H); LRMS (ES+) Calcd for $[C_{16}H_{27}NO_3SSi + H]^+$ 342.16 found 342.12.

Step 3. (*S*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-2-phenylethyl)ethenesulfonamide (0.598 g, 1.75 mmol, 1.0 equiv.), potassium carbonate (0.726 g, 5.25 mmol, 3.0 equiv.), and MeI (0.22 mL, 3.50 mmol, 2.0 equiv.) in MeCM (3.5 mL) were reacted for 3 d at 80 °C to obtain (*S*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-2-phenylethyl)-*N*-methylethenesulfonamide (**S57**; 0.52 g, 1.46 mmol, 84%) as a white solid upon purification by flash chromatography on silica gel (0 to 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.27 (m, 5H), 6.28 (dd, 1H, *J* = 16.6, 9.7 Hz), 6.16 (d, 1H, *J* = 16.5 Hz), 5.89 (d, 1H, *J* = 9.7 Hz), 4.90 (dd, 1H, *J* = 7.8, 4.6 Hz), 3.21 (dd, 1H, *J* = 14.4, 4.6 Hz), 3.12 (dd, 1H, *J* = 14.3, 7.8 Hz), 2.79 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), -0.11 (s, 3H); LRMS (ES+) Calcd for $[C_{17}H_{29}NO_3SSi+ H]^+$ 356.17 found 356.15.

Step 4. (*S*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-2-phenylethyl)-*N*-methylethenesulfonamide (0.25 g, 0.703 mmol, 1.0 equiv.) and TBAF (1.0 M in THF, 0.7 mL, 0.70 mmol 1.0 equiv.) in THF (17 mL) were reacted to obtain (*S*)-5-methyl-7-phenyl-1,4,5-oxathiazepane 4,4-dioxide (90 mg, 0.373 mmol, 53%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47 – 7.27 (m, 5H), 5.16 (dd, 1H, *J* = 10.0, 5.3 Hz), 4.22 (ddd, 1H, *J* = 13.7, 5.4, 3.7 Hz), 3.95 (ddd, 1H, *J* = 13.8, 8.5, 3.0

Hz), 3.63 (dd, 1H, *J* = 15.0, 5.3 Hz), 3.58 – 3.36 (m, 3H), 3.07 (s, 3H); HRMS (ES+) Calcd for $[C_{11}H_{15}NO_3S + H]^+$ 242.0851 found 242.0856. Purity: 99.56% (UPLC, UV_{214}).



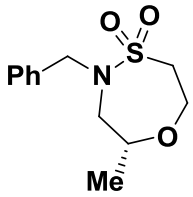
(*S*)-5-Ethyl-7-phenyl-1,4,5-oxathiazepane 4,4-dioxide (15e). Using general procedure **F**, steps 1-2 and 4.

Step 1. (*S*)-2-(Ethylamino)-1-phenylethanol (0.34 g, 2.06 mmol), TBSCl (0.620 g, 4.12 mmol, 2.0 eq.), and triethylamine (0.860 ml, 6.17 mmol, 3.0 eq.) in DCM (4.1 mL) were reacted to obtain (*S*)-2-((*tert*-butyldimethylsilyl)oxy)-N-ethyl-2-phenylethanamine (**S58**; 0.2 g, 0.716 mmol, 34 %) as an oil upon work-up and purification by flash chromatography on silica gel (50 to 100% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H δ 7.34 – 7.26 (m, 5H), 4.81 (dd, 1H, *J* = 8.5, 4.0 Hz), 2.80 (dd, 1H, *J* = 12.0, 8.5 Hz), 2.74 – 2.58 (m, 3H), 1.10 (t, 3H, *J* = 7.1 Hz), 0.89 (s, 9H), 0.04 (s, 3H), -0.15 (s, 3H); LRMS (ES+) Calcd for $[C_{16}H_{29}NOSi + H]^+$ 280.21 found 280.04.

Step 2. (*S*)-2-((*ter*t-butyldimethylsilyl)oxy)-*N*-ethyl-2-phenylethanamine (0.198 g, 0.708 mmol, 1.0 equiv.), triethylamine (0.35 mL, 2.48 mmol, 3.5 equiv.), and 2-chloroethanesulfonyl chloride (78 µL, 0.744 mmol 1.05 equiv.) in DCM (3.5 mL) were reacted to obtain (*S*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-2-phenylethyl)-*N*-ethylethenesulfonamide (**S59**; 0.208 g, 0.563 mmol, 79%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 – 7.26 (m, 5H), 6.26 (dd, 1H, *J* = 16.5, 9.4 Hz), 6.20 – 6.12 (m, 1H), 5.88 – 5.79 (m, 1H), 4.95 (dd, 1H, *J* = 7.3, 5.2 Hz), 3.36 – 3.08 (m, 4H), 1.04 (t, 3H, *J* = 7.1 Hz), 0.88 (s, 9H), 0.09 (s, 3H), -0.12 (s, 3H); LRMS (ES+) Calcd for $[C_{18}H_{31}NO_3SSi + H]^+$ 370.19 found 370.18.

Step 4. (*S*)-*N*-(2-((*tert*-butyldimethylsilyl)oxy)-2-phenylethyl)-*N*-ethylethenesulfonamide (0.2 g, 0.541 mmol, 1.0 equiv.) and TBAF (1.0 M in THF, 0.65 mL, 0.649 mmol 1.2 equiv.) in THF (13

mL) were reacted to obtain (*S*)-5-ethyl-7-phenyl-1,4,5-oxathiazepane 4,4-dioxide (76 mg, 0.298 mmol, 55%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 – 7.28 (m, 5H), 5.10 (dd, 1H, *J* = 10.4, 4.8 Hz), 4.25 (dt, 1H, *J* = 13.6, 4.2 Hz), 3.94 (ddd, 1H, *J* = 13.6, 9.5, 3.0 Hz), 3.59 (dd, 1H, *J* = 14.7, 4.8 Hz), 3.53 – 3.32 (m, 6H), 1.22 (t, 3H, *J* = 7.1 Hz); HRMS (ES+) Calcd for $[C_{12}H_{17}NO_3S + H]^+$ 256.1007 found 256.1014. Purity: 99.55% (UPLC, UV_{214}).

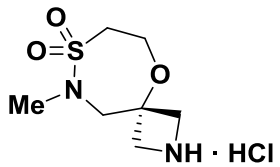


(*R*)-5-Benzyl-7-methyl-1,4,5-oxathiazepane 4,4-dioxide (15f). Using general procedure **F**, steps 1-2 and 4.

Step 1. (*R*)-1-(benzylamino)propan-2-ol (0.222 g, 1.34 mmol), TBSCl (0.405 g, 2.69 mmol, 2.0 eq.), and triethylamine (0.562 ml, 4.03 mmol, 3.0 eq.) in DCM (2.7 mL) were reacted to obtain (*R*)-*N*-benzyl-2-((*tert*-butyldimethylsilyl)oxy)propan-1-amine (**S60**; 0.219 g, 0.784 mmol, 58 %) as a clear oil upon work-up and purification by flash chromatography on silica gel (0 to 50% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36 – 7.20 (m, 5H), 3.99 (pd, 1H, *J* = 6.2, 4.9 Hz), 3.87 – 3.72 (m, 2H), 2.62 – 2.55 (m, 2H), 1.14 (d, 3H, *J* = 6.1 Hz), 0.88 (s, 9H), 0.07 (s, 6H); LRMS (ES+) Calcd for $[C_{16}H_{29}NOSi + H]^+$ 280.21 found 280.63.

Step 2. (*R*)-*N*-benzyl-2-((*ter*t-butyldimethylsilyl)oxy)propan-1-amine (0.218 g, 0.780 mmol, 1.0 equiv.), triethylamine (0.38 mL, 2.73 mmol, 3.5 equiv.), and 2-chloroethanesulfonyl chloride (86 µL, 0.819 mmol, 1.05 equiv.) in DCM (4 mL) were reacted to obtain (*R*)-*N*-benzyl-*N*-(2-((*tert*-butyldimethylsilyl)oxy)propyl)ethenesulfonamide (**S61**; 0.166 g, 0.449 mmol, 58%) as an oil upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7 7.40 – 7.27 (m, 5H), 6.30 (dd, 1H, *J* = 16.5, 9.6 Hz), 6.18 (d, 1H, *J* = 16.5 Hz), 5.84 (d, 1H, *J* = 9.6 Hz), 4.58 – 4.41 (m, 2H), 4.06 – 3.88 (m, 1H), 3.09 (ddd, 1H, *J* = 14.5, 5.4, 0.7 Hz), 2.99 (dd, 1H, *J* = 14.6, 6.9 Hz), 1.08 (d, 3H, *J* = 6.1 Hz), 0.88 (s, 9H), 0.05 (d, 6H, *J* = 5.0 Hz); LRMS (ES+) Calcd for $[C_{18}H_{31}NO_3SSi + H]^+$ 370.19 found 370.00.

Step 4. (*R*)-*N*-benzyl-*N*-(2-((*tert*-butyldimethylsilyl)oxy)propyl)ethenesulfonamide (0.166 g, 0.449 mmol, 1.0 equiv.) and TBAF (1.0 M in THF, 0.45 mL, 0.449 mmol, 1.0 equiv.) in THF (11 mL) were reacted to obtain (*R*)-5-benzyl-7-methyl-1,4,5-oxathiazepane 4,4-dioxide (47 mg, 0.184 mmol, 41%) as a clear oil upon work-up and purification by flash chromatography on silica gel (0 to 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7 7.43 – 7.28 (m, 5H), 4.57 (d, 1H, *J* = 14.6 Hz), 4.43 (d, 1H, *J* = 14.6 Hz), 4.23 (ddd, 1H, *J* = 10.8, 6.5, 4.8 Hz), 4.13 (ddd, 1H, *J* = 13.8, 5.9, 3.5 Hz), 3.83 (ddd, 1H, *J* = 13.8, 7.6, 3.4 Hz), 3.52 – 3.34 (m, 2H), 3.15 (dd, 1H, *J* = 15.2, 10.3 Hz), 3.03 (dd, 1H, *J* = 15.2, 4.8 Hz), 1.13 (d, 3H, *J* = 6.4 Hz); HRMS (ES+) Calcd for $[C_{12}H_{17}NO_3S + H]^+$ 256.1007 found 256.1013. Purity: 99.32% (UPLC, UV_{214}).



9-Methyl-5-oxa-8-thia-2,9-diazaspiro[3.6]decane 8,8-dioxide hydrochloride (15g). Using general procedure **F**, steps 1-4.

Step 1. *tert*-butyl 3-(aminomethyl)-3-hydroxyazetidine-1-carboxylate (0.388 g, 1.918 mmol), TBSCl (0.347 g, 2.30 mmol, 1.2 equiv.), and triethylamine (0.535 ml, 3.84 mmol, 2.0 equiv.) in DCM (3.8 mL) were reacted to obtain *tert*-butyl 3-(aminomethyl)-3-((*tert*-butyldimethylsilyl)oxy)azetidine-1-carboxylate (**S62**; 0.51 g, 1.61 mmol, 84%) as a clear oil upon purification by flash chromatography on silica gel (0 to 20 % MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (d, 4H, *J* = 2.0 Hz), 2.85 (s, 2H), 1.44 (s, 9H), 0.90 (s, 9H), 0.13 (s, 6H). LRMS (ES+) Calcd for $[C_{15}H_{32}N_2O_3Si + H]^+$ 317.23 found 317.20.

Step 2. *tert*-butyl 3-(aminomethyl)-3-((*tert*-butyldimethylsilyl)oxy)azetidine-1-carboxylate (0.56 g, 1.77 mmol, 1.0 equiv.), triethylamine (0.86 mL, 6.19 mmol, 3.5 equiv.), and 2-chloroethanesulfonyl chloride (0.19 mL, 1.86 mmol, 1.05 equiv.) in DCM (8.8 mL) were reacted to obtain *tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-3-(vinylsulfonamidomethyl)azetidine-1-carboxylate (**S63**; 0.616 g, 1.515 mmol, 86%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 50% EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H

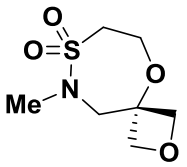
6.53 (dd, 1H, *J* = 16.5, 9.8 Hz), 6.29 (d, 1H, *J* = 16.5 Hz), 6.00 (d, 1H, *J* = 9.8 Hz), 4.40 (t, 1H, *J* = 6.2 Hz), 3.86 (s, 4H), 3.21 (d, 2H, *J* = 6.1 Hz), 1.44 (s, 9H), 0.89 (s, 9H), 0.16 (s, 6H); LRMS (ES+) Calcd for $[C_{17}H_{34}N_2O_5SSi - Boc + H]^+$ 307.15 found 307.09.

Step 3. *tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-3-(vinylsulfonamidomethyl)azetidine-1-carboxylate (0.6 g, 1.48 mmol 1.0 equiv.), potassium carbonate (0.612 g, 4.43 mmol, 3.0 equiv.), and MeI (0.18 mL, 2.95 mmol, 2.0 equiv.) in MeCN (3 mL) were reacted for 3 d at 80 °C to obtain *tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-3-((*N*-methylvinylsulfonamido)methyl)azetidine-1-carboxylate (**S64**; 0.56 g, 1.33 mmol, 90%) as an oil upon purification by flash chromatography on silica gel (0 to 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.42 (dd, 1H, *J* = 16.5, 9.9 Hz), 6.24 (d, 1H, *J* = 16.5 Hz), 6.03 (d, 1H, *J* = 9.9 Hz), 4.02 (s, 2H), 3.86 (d, 2H, *J* = 9.4 Hz), 3.23 (d, 2H, *J* = 26.3 Hz), 2.91 (s, 3H), 1.44 (s, 9H), 0.89 (s, 9H), 0.19 (s, 6H); LRMS (ES+) Calcd for $[C_{18}H_{36}N_2O_5SSi - Boc + H]^+$ 321.17 found 321.30

Step 4. *tert*-butyl3-((*tert*-butyldimethylsilyl)oxy)-3-((*N*-methylvinylsulfonamido)methyl)azetidine-1-carboxylate (0.13 g, 0.309 mmol, 1.0 equiv.) and TBAF (1.0 M in THF, 0.32 mL, 0.325 mmol, 1.05 equiv.) in THF (7.7 mL) were reacted to obtain *tert*-butyl 9-methyl-5-oxa-8-thia-2,9-diazaspiro[3.6]decane-2-carboxylate 8,8-dioxide (**S65**; 86 mg, 0.281 mmol, 91%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.95 (dd, 2H, *J* = 9.4, 1.0 Hz), 3.91 – 3.82 (m, 4H), 3.75 (s, 2H), 3.44 – 3.37 (m, 2H), 2.91 (s, 3H), 1.44 (s, 9H); LRMS (ES+) Calcd for $[C_{12}H_{22}N_2O_5S - CH_3 + H]^+$ 293.12 found 293.23.

N-Boc deprotection. To a solution of *tert*-butyl 9-methyl-5-oxa-8-thia-2,9-diazaspiro[3.6]decane-2-carboxylate 8,8-dioxide (42 mg, 0.137 mmol, 1.0 equiv.) in dioxane (0.24 mL) at RT was added a solution of 4.0 M HCl (240 µl, 0.960 mmol, 7.0 equiv.) in dioxane. The mixture was stirred overnight and concentrated, azeotroping with toluene, to give 9-methyl-5-oxa-8-thia-2,9-diazaspiro[3.6]decane 8,8-dioxide hydrochloride (28 mg, 0.136 mmol, 99%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ_H 4.30 – 4.21 (m, 2H), 4.12 – 3.99 (m, 4H), 3.86 (s, 2H), 3.68 (s,

3H), 3.54 – 3.46 (m, 2H), 2.88 (s, 2H); HRMS (ES+) Calcd for $[C_7H_{14}N_2O_3S + H]^+$ 207.0803 found 207.0804. Purity: 100% (UPLC, ELSD).



9-methyl-2,5-dioxa-8-thia-9-azaspiro[3.6]decane 8,8-dioxide (15h). Using general procedure **F**, steps 1-4.

Step 1. 3-(aminomethyl)oxetan-3-ol (1.16 g, 11.3 mmol, 1.0 equiv.), TBSCl (2.04 g, 13.5 mmol, 1.2 equiv.), and triethylamine (3.14 ml, 22.5 mmol, 2.0 equiv.) in DCM (22 mL) were reacted to obtain (3-((*tert*-butyldimethylsilyl)oxy)oxetan-3-yl)methanamine (**S66**; 1.05 g, 4.85 mmol, 43%) as a clear oil upon work-up and purification by flash chromatography on silica gel (0 to 20% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.70 – 4.57 (m, 2H), 4.45 – 4.36 (m, 2H), 3.02 (d, 2H, J = 0.7 Hz), 0.91 (s, 9H), 0.13 (s, 6H); LRMS (ES+) Calcd for $[C_{10}H_{23}NO_2Si + H]^+$ 218.16 found 218.09.

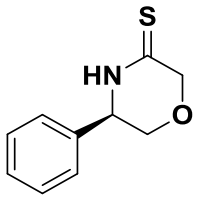
Step 2. (3-((*tert*-butyldimethylsilyl)oxy)oxetan-3-yl)methanamine (0.5 g, 2.30 mmol 1.0 equiv.), triethylamine (1.1 mL, 8.05 mmol, 3.5 equiv.), and 2-chloroethanesulfonyl chloride (0.25 mL, 2.41 mmol, 1.05 equiv.) in DCM (11 mL) were reacted to obtain *N*-((3-((*tert*-butyldimethylsilyl)oxy)oxetan-3-yl)methyl)ethenesulfonamide (**S67**; 0.65 g, 2.11 mmol, 92%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.54 (dd, 1H, J = 16.5, 9.8 Hz), 6.31 (d, 1H, J = 16.5 Hz), 6.00 (d, 1H, J = 9.8 Hz), 4.72 – 4.58 (m, 2H), 4.50 – 4.37 (m, 3H), 3.37 (d, 2H, J = 6.0 Hz), 0.90 (s, 9H), 0.16 (s, 6H); LRMS (ES+) Calcd for $[C_{12}H_{25}NO_4SSi + H]^+$ 308.14 found 308.12.

Step 3. *N*-((3-((*tert*-butyldimethylsilyl)oxy)oxetan-3-yl)methyl)ethenesulfonamide (0.3 g, 0.976 mmol, 1.0 equiv.), potassium carbonate (0.405 g, 2.93 mmol, 3.0 equiv.), and MeI (0.12 mL, 1.95 mmol, 2.0 equiv.) in MeCN (2 mL) were reacted for 24 h at 80 °C to obtain *N*-((3-((*tert*-butyldimethylsilyl)oxy)oxetan-3-yl)methyl)-*N*-methylethenesulfonamide (**S68**; 0.276 g, 0.858

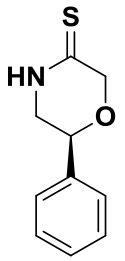
mmol, 88%) as a white solid upon purification by flash chromatography on silica gel (0 to 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.24 (dd, 1H, *J* = 16.6, 9.9 Hz), 6.06 (d, 1H, *J* = 16.6 Hz), 5.83 (d, 1H, *J* = 9.9 Hz), 4.50 – 4.34 (m, 4H), 3.20 (s, 2H), 2.71 (s, 3H), 0.70 (s, 9H), -0.00 (s, 6H); LRMS (ES+) Calcd for $[C_{13}H_{27}NO_4SSi + H]^+$ 322.15 found 322.11.

Step 4. *N*-((3-((*tert*-butyldimethylsilyl)oxy)oxetan-3-yl)methyl)-*N*-methylethenesulfonamide (0.15 g, 0.467 mmol, 1.0 equiv.) and TBAF (1 M in THF, 0.49 mL, 0.490 mmol 1.05 equiv.) in THF (12 mL) were reacted to obtain 9-methyl-2,5-dioxa-8-thia-9-azaspiro[3.6]decane 8,8-dioxide (70 mg, 0.338 mmol, 72%) as a white solid upon work-up and purification by flash chromatography on silica gel (0 to 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.68 (dd, 2H, *J* = 7.0, 0.8 Hz), 4.54 (dd, 2H, *J* = 7.0, 0.8 Hz), 3.93 – 3.84 (m, 4H), 3.44 – 3.34 (m, 2H), 2.87 (s, 3H); HRMS (ES+) Calcd for $[C_7H_{13}NO_4S + H]^+$ 208.0644 found 208.0650. Purity: >99 % (^{1}H NMR).

Preparation of thioamides 7 and 8.

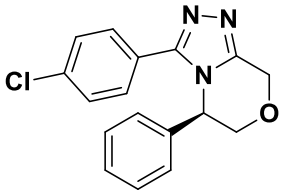


(*R*)-5-phenyl-morpholine-3-thione (16). (R)-5-phenylmorpholin-3-one (1.00 g, 5.64 mmol, 1.0 equiv.) and Lawesson's reagent (1.37 g, 3.39 mmol, 0.60 equiv.) were combined in THF (38 mL). After stirring at 70 °C for 3 h, the solution was cooled to RT concentrated *in vacuo*. The residue was purified *via* flash chromatography on silica gel (0 to 45% EtOAc/hexanes) and triturated with (hexanes-DCM) to yield a white solid (855 mg, 78%). $^{23}[\alpha]_D$ = -112.96 (*c* = 1.00; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.31 (brs, 1H), 7.45 – 7.37 (m, 3H), 7.34 – 7.27 (m, 2H), 4.72 (d, 1H, *J* = 17.9 Hz), 4.70 – 4.66 (m, 1H), 4.57 (d, 1H, *J* = 17.9 Hz), 4.13 (dd, 1H, *J* = 12.0, 4.4 Hz), 3.65 (dd, 1H, *J* = 12.0, 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 199.0, 137.3, 128.96, 128.95, 126.1, 74.1, 74.0, 49.4; FTIR (neat; cm^{-1}) 3334 (br), 2360 (m), 2341 (m), 1544 (s), 1286 (s), 1156 (s), 1045 (s), 698 (s); HRMS (ESI) *m/z* calcd for $[C_{10}H_{11}NOS + H]^+$ 194.0640 found 194.0640. Purity: 98.6% (UPLC, UV_{214}).



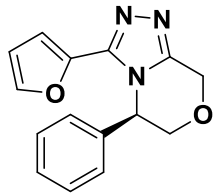
(*S*)-6-phenylmorpholine-3-thione (17). (*S*)-6-phenylmorpholin-3-one (400 mg, 2.26 mmol, 1.0 equiv.) and Lawesson's reagent (548 mg, 1.35 mmol, 0.60 equiv.) were combined in THF (15.0 mL). After stirring at 55 °C for 3 h, the solution was cooled to RT concentrated *in vacuo*. The residue was purified *via* flash chromatography on silica gel (0 to 40% EtOAc/hexanes) and triturated with (hexanes-DCM) to yield a white solid (210 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.68 (brs, 1H), 7.49 – 7.34 (m, 5H), 4.90 (d, 1H, J = 18.3 Hz), 4.76 (dd, 1H, J = 9.1, 4.6 Hz), 4.66 (d, 1H, J = 18.3 Hz), 3.57 – 3.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 199.0, 137.3, 128.96, 128.95, 126.1, 74.1, 74.0, 49.4; HRMS (ESI) *m/z* calcd for $[C_{10}H_{11}NOS + H]^+$ 194.0640 found 194.0642. Purity: 93.3% (UPLC, UV_{214}).

General Procedure G (triazoles). The thioamide (1.0 equiv.) and hydrazide (2.0 equiv.) were combined in *tert*-butanol (0.2 M). After stirring at 135 °C for 16 h, the solution was cooled to RT, concentrated *in vacuo*, and purified *via* flash chromatography on silica gel (gradients indicated), recrystallization (solvents indicated), or trituration (solvents indicated) to afford the triazole.

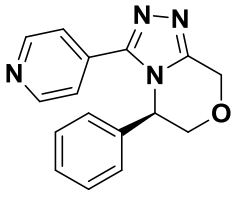


(*R*)-3-(4-chlorophenyl)-5-phenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-c][1,4]oxazine (18). Using general procedure **G** with (*R*)-5-phenylmorpholine-3-thione (100 mg, 0.517 mmol, 1.0 equiv.) and 4-chlorobenzohydrazide (177 mg, 1.04 mmol, 2.0 equiv.) in *tert*-butanol (2.6 mL). After stirring at 135 °C for 16 h, the solution was concentrated *in vacuo* and purified *via* trituration (hexanes/DCM/MeOH) followed by flash chromatography on silica gel (0 to 10% MeOH/DCM) to yield the title compound as a white solid (102 mg, 63%). $^{23}[\alpha]_D$ = -186.34 (c = 1.00; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.32 – 7.22 (m, 7H), 6.97 – 6.91 (m, 2H), 5.36 –

5.30 (m, 1H), 5.28 (d, 1H, J = 15.6 Hz), 5.09 (d. 1H, J = 15.6 Hz), 4.20 (dd, 1H, J = 12.1, 3.8 Hz), 4.03 (dd, 1H, J = 12.1, 3.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 152.7, 149.3, 137.3, 136.4, 129.8, 129.3, 129.02, 128.99, 126.4, 125.3, 70.8, 64.0, 58.2; FTIR (neat; cm^{-1}) 1473 (m), 1456 (m), 1104 (m), 771 (s), 669 (s), 650 (s); HRMS (ESI) *m/z* calcd for $[C_{17}H_{14}ClN_3O + H]^+$ 312.0904 found 312.0906. Purity: 98.7% (UPLC, UV_{214}).



(*R*)-3-(furan-2-yl)-5-phenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-c][1,4]oxazine (19). Using general procedure **G** with (*R*)-5-phenylmorpholine-3-thione (207 mg, 1.07 mmol, 1.0 equiv.) and furan-2-carbohydrazide (270 mg, 2.14 mmol, 2.0 equiv.) in *tert*-butanol (5.4 mL). After stirring at 135 °C for 4 h, the thioamide had been consumed and the solution was concentrated *in vacuo*. Purification *via* flash chromatography on silica gel (0 to 10% MeOH/DCM) followed by recrystallization (hexanes/DCM) yielded the title compound as pale orange needles (113 mg, 39%). $^{23}[\alpha]_D$ = -171.64 (c = 1.00; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.39 – 7.34 (m, 1H), 7.33 – 7.26 (m, 3H), 7.03 – 6.99 (m, 2H), 6.80 – 6.77 (m, 1H), 6.37 – 6.35 (m, 1H), 5.66 – 5.63 (m, 1H), 5.27 (d, 1H, J = 15.4 Hz), 5.02 (d, 1H, J = 15.4 Hz), 4.22 (dd, 1H, J = 12.1, 3.9 Hz), 4.09 (dd, 1H, J = 12.1, 2.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 148.6, 146.0, 143.8, 141.8, 137.9, 129.0, 128.6, 126.1, 111.8, 70.6, 63.9, 58.2; FTIR (neat; cm^{-1}) 1516 (m), 1451 (m), 1099 (s), 905 (m), 771 (s), 698 (m), 669 (m); HRMS (ESI) *m/z* calcd for $[C_{15}H_{13}N_3O_2 + H]^+$ 268.1086 found 268.1088. Purity: 99.3% (UPLC, UV_{214}).



(*R*)-5-phenyl-3-(pyridin-4-yl)-5,6-dihydro-8*H*-[1,2,4]triazolo[3,4-c][1,4]oxazine (20). Using general procedure **G** with (*R*)-5-phenylmorpholine-3-thione (183 mg, 0.947 mmol, 1.0 equiv.) and isonicotinohydrazide (260 mg, 1.89 mmol, 2.0 equiv.) in *tert*-butanol (4.7 mL). After stirring at 135 °C for 4 h, the solution was concentrated *in vacuo* and triturated with ice-cold ethanol (absolute). Upon filtration the title compound was obtained as a white solid (104 mg, 39%).

$^{23}[\alpha]_D$ = -152.62 (*c* = 1.00; $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.54 – 8.52 (m, 2H), 7.35 – 7.26 (m, 5H), 6.98 – 6.94 (m, 2H), 5.44 – 5.41 (m, 1H), 5.28 (d, 1H, *J* = 15.7 Hz), 5.11 (d, 1H, *J* = 15.7 Hz), 4.22 (dd, 1H, *J* = 12.1, 3.8 Hz), 4.03 (dd, 1H, *J* = 12.1, 3.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 151.3, 150.1, 150.0, 136.9, 134.7, 129.4, 129.2, 126.4, 122.2, 70.8, 64.0, 58.5; FTIR (neat; cm^{-1}) 1448 (m), 1096 (m), 768 (m), 669 (s), 650 (m), 403 (m); HRMS (ESI) *m/z* calcd for $[C_{16}H_{14}N_4O + H]^+$ 279.1246 found 279.1249. Purity: 99.6% (UPLC, UV_{214}).

Shake-Flask Thermodynamic Solubility Assay

For **10g**, **11c**, **11e**, **11l**, **12a-d**, **13f**, and **16-20**, 1-2 mg of accurately weighed solid compound were dissolved in 1.0 mL PBS (pH = 6.5) in a 4 mL glass vial equipped with a magnetic stir bar. The suspensions were stirred for 24 h (± 2 h) at room temperature, then phases were separated by centrifugation. Each sample was analyzed by HPLC with UV-detection in triplicate with two injection volumes (5 and 50 µL).

A calibration curve was generated by accurately weighing 0.5 to 1.2 mg of solid compound into a 25 mL volumetric flask to which a 50% aqueous MeCN solution was added (to 25 mL). The standard solutions were analyzed across three injection volumes from which the calculated solubility values (mg/L and mM) were obtained.

Modified Solution Solubility Assay (pH = 6.5)

For **10c-f**, **11d**, **11f**, **11g**, **11j**, **11k**, **13b-e**, **13g**, **14c-14f**, **14i**, and **15d-g**, 2 mg of solid compound were dissolved in 40 µL DMSO (*c* = 50 g/L). 10 µL of this stock solution were added to 990 µL PBS (pH = 6.5) to generate a 500 µg/mL solution. These solutions were added individually to a 96-well microtiter plate and shaken for 24 h at 25 °C to reach (or approach) equilibrium. The solutions (or suspensions) were transferred to centrifuge tubes and undissolved material was separated by ultracentrifugation at 114000 g for 30 min. The supernatant of each sample was diluted with a MeCN:H_2O (8:2) solution and quantified using LC-MS/MS for detection.

A calibration curve was generated by adding 10 µL DMSO stock (*c* = 50 g/L) to 823 µL DMSO (*c* = 600 µg/mL). The amount of compound was determined at five different concentrations. The

areas of sample and standard injections were determined, from which the calculated solubility values (mg/L and mM) were obtained.

Modified Solution Solubility Assay (pH = 7.4)

For **10a**, **10b**, **11a**, **11b**, **11h**, **11i**, **13a**, **14a**, **14b, 15a**, **15b**, **15c**, and **15h**, solubility was determined in PBS (pH = 7.4) with 1% DMSO. Each compound was prepared in triplicate at 500 μM in both 100% DMSO and PBS with 1% DMSO. Compounds were allowed to equilibrate at room temperature with a 750 rpm vortex shake for 18 h. After equilibration, samples were analyzed by UPLC-MS with compounds detected by SIR detection on a single quadrupole mass spectrometer. The DMSO samples were used to create a two-point calibration curve to which the response in PBS was fit.

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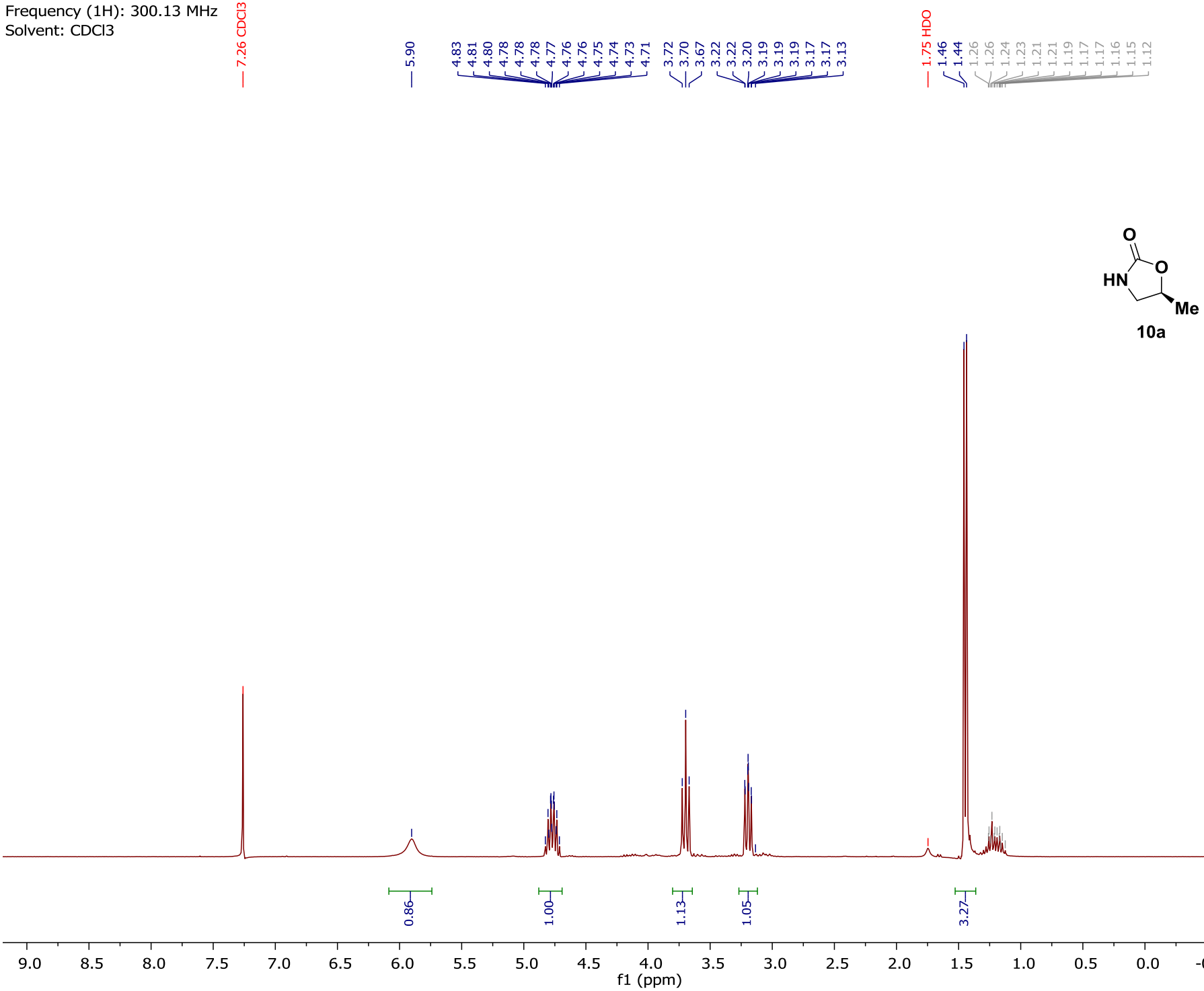
Solvent: CDCl3



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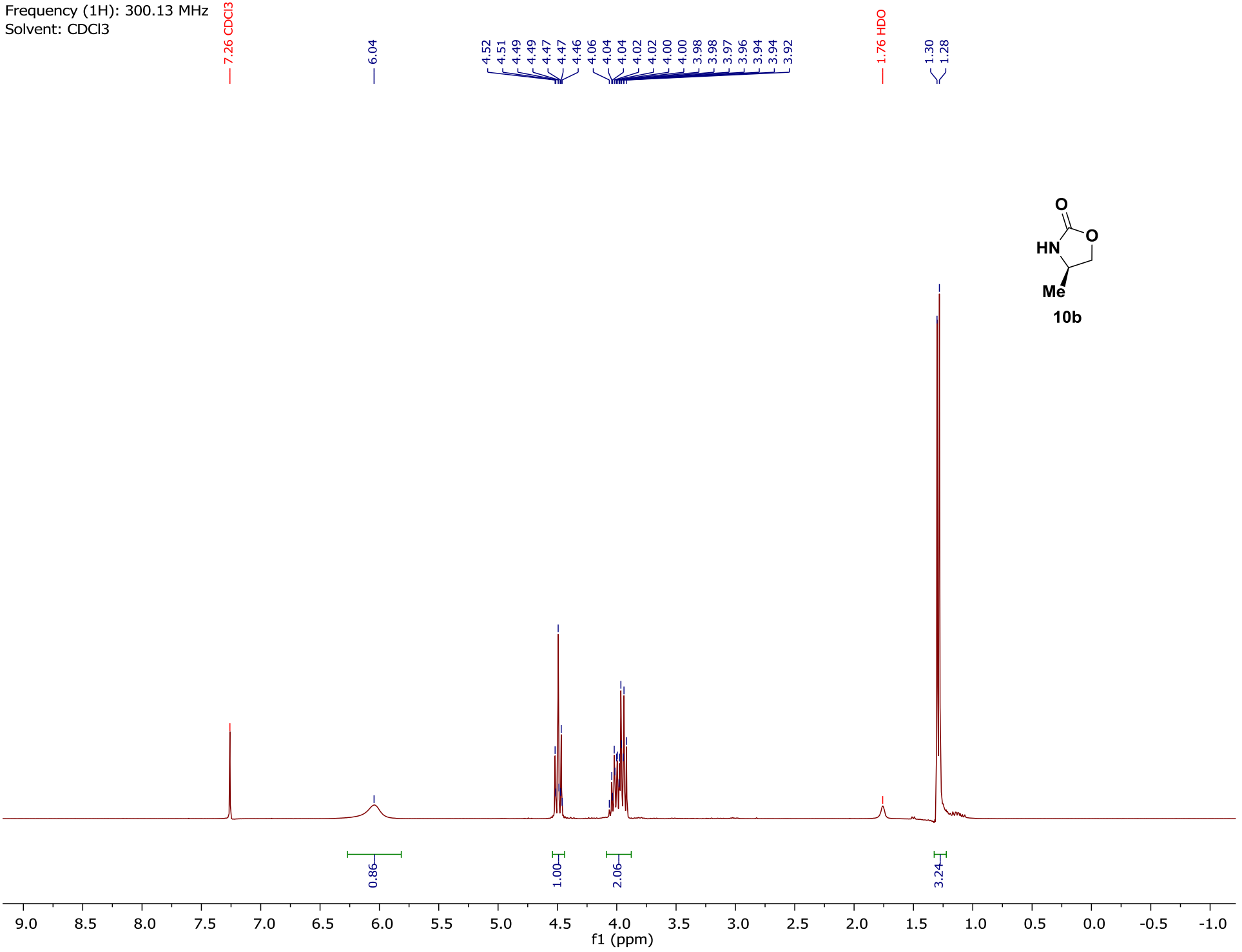
Solvent: CDCl3



Frequency (1H): 300.13 MHz
Solvent: CDCl3

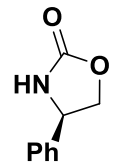
7.45 7.44 7.44 7.43 7.42 7.42 7.42 7.41 7.40 7.40 7.40 7.40 7.39 7.39 7.37 7.37 7.36 7.35 7.35 7.35 7.34 7.33 7.26 CDCl3

4.98 4.96 4.95 4.93 4.78 4.77 4.75 4.72 4.71 4.23 4.23 4.21 4.20 4.20 4.18

2.05

1.56 HDO

0.96 0.93 0.91



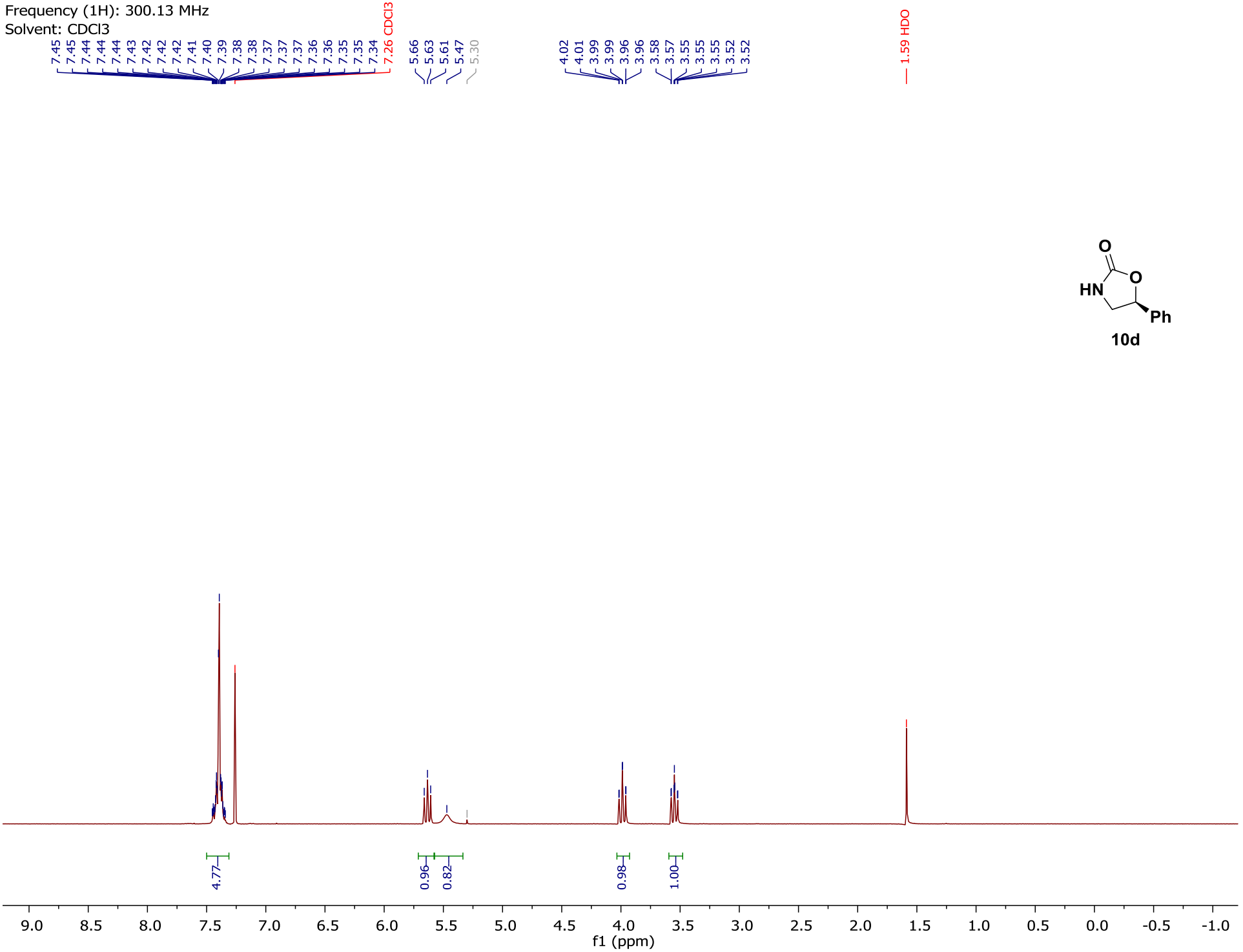
10c

5.27 0.67 0.91 1.08 1.00

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

f1 (ppm)

Frequency (1H): 300.13 MHz
Solvent: CDCl3



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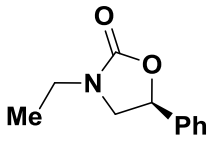
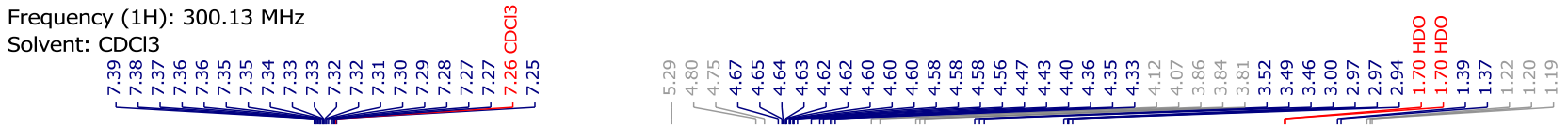
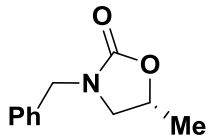
Solvent: CDCl3



10e

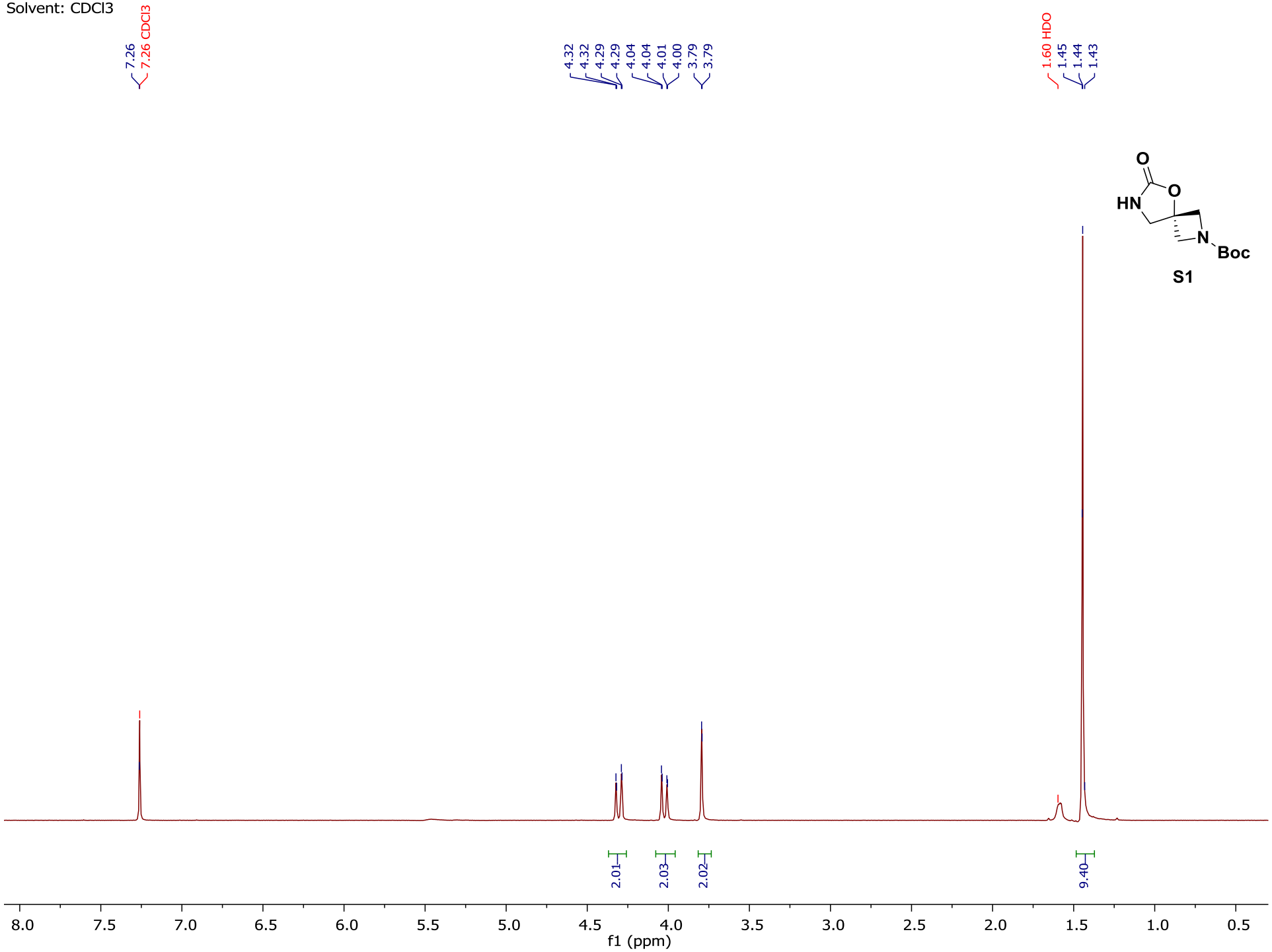
Frequency (1H): 300.13 MHz
Solvent: CDCl3





10f

Frequency (1H): 300.17 MHz
Solvent: CDCl3



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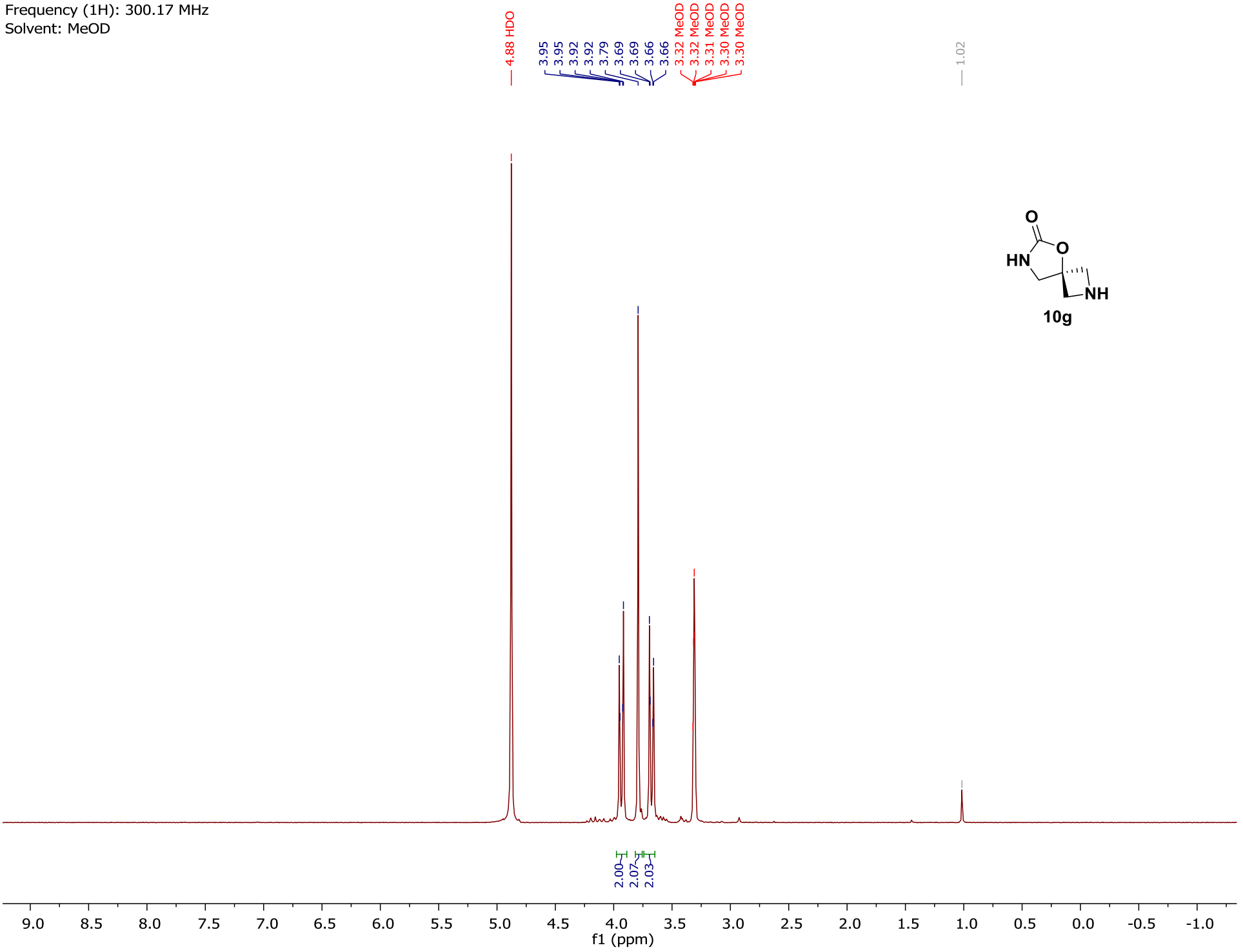

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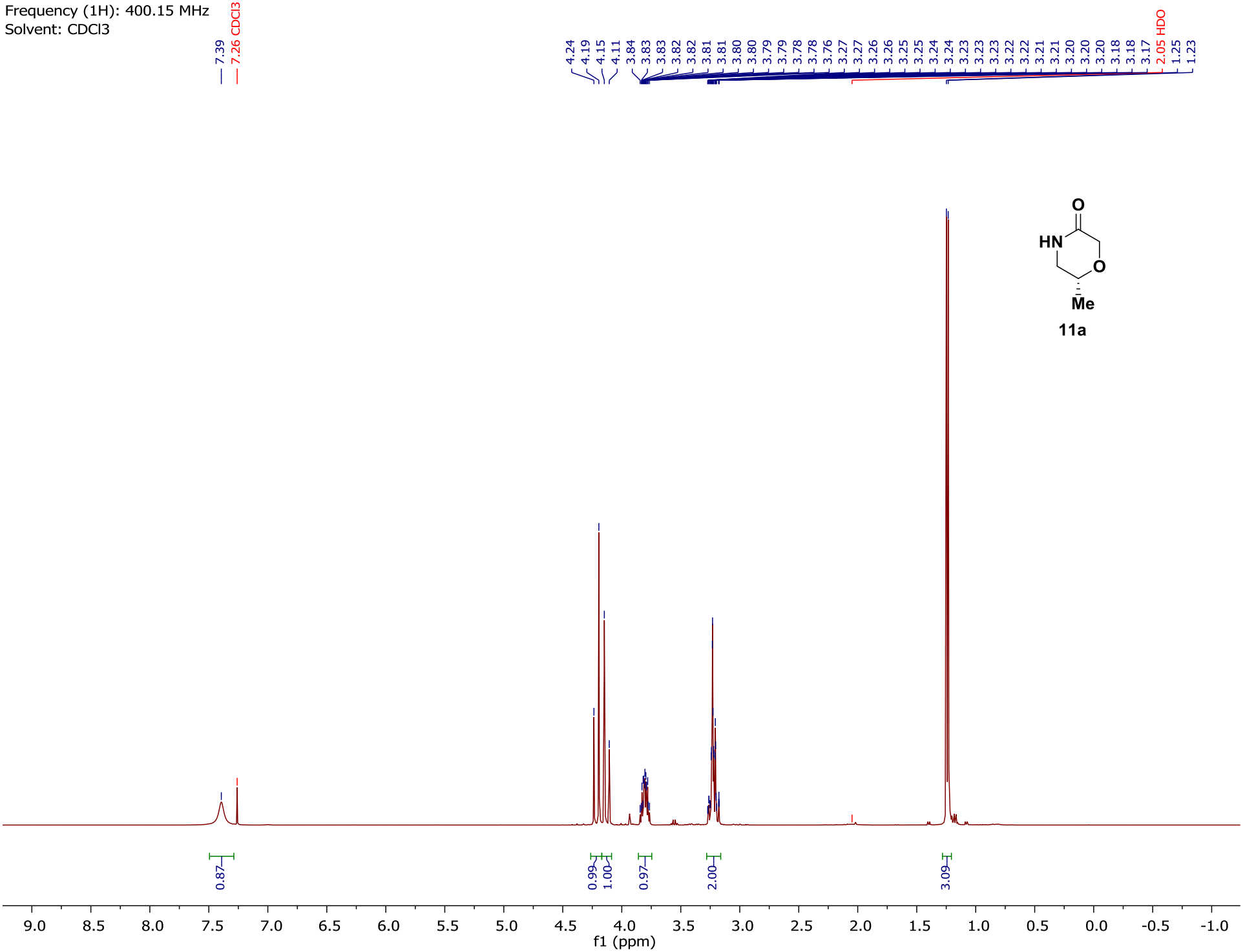
Solvent: CDCl3



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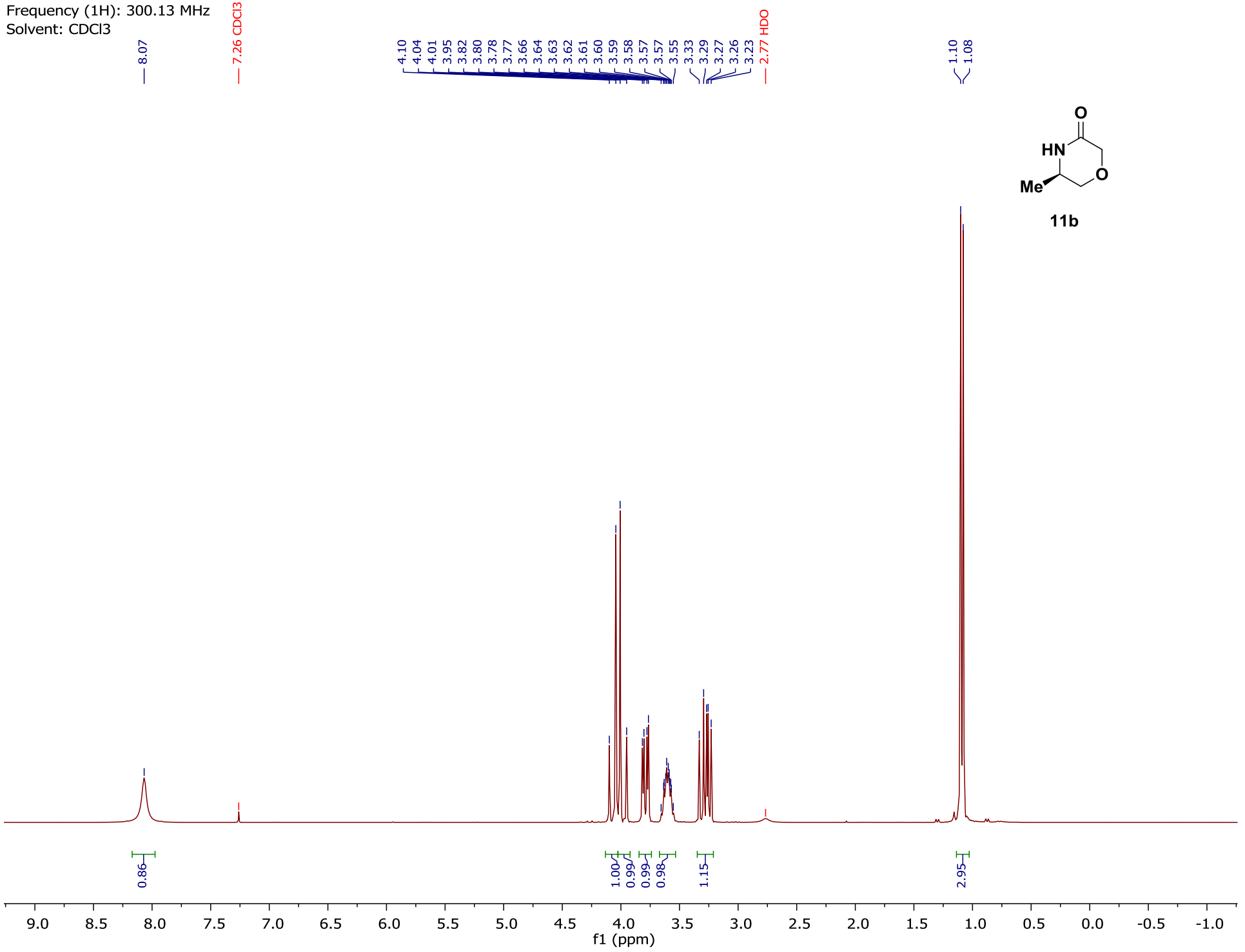
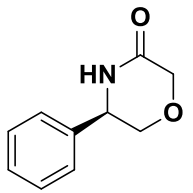


Frequency (1H): 400.15 MHz
Solvent: CDCl3

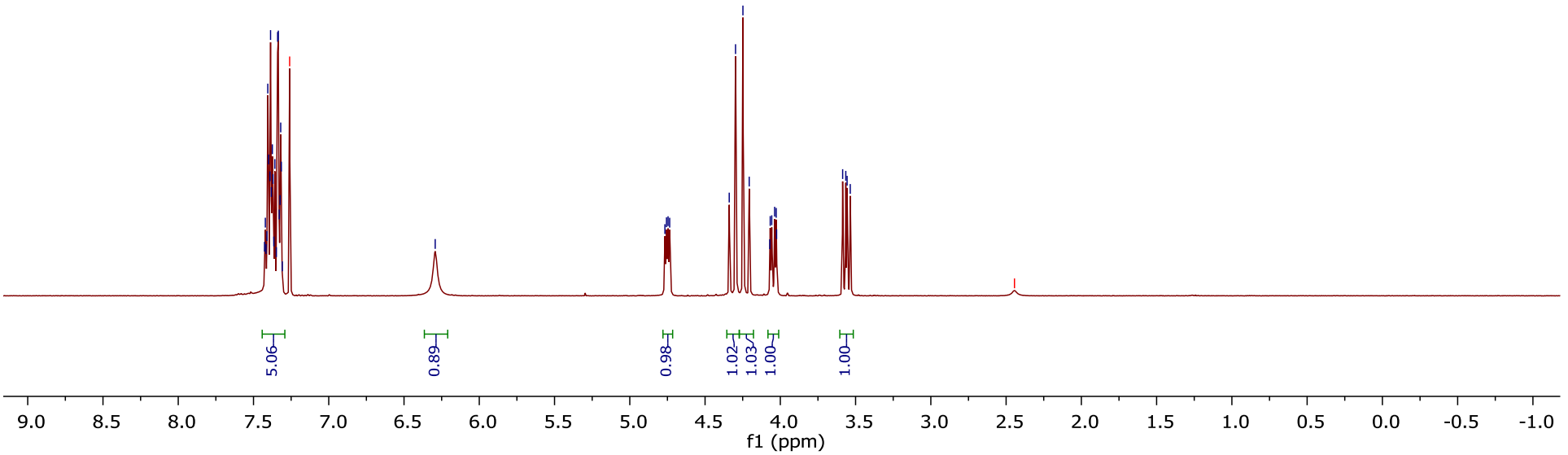
7.43 7.42 7.42 7.41 7.41 7.40 7.39 7.39 7.38 7.37 7.37 7.36 7.36 7.35 7.34 7.33 7.33 7.32 7.32 7.32 7.31 7.26 CDCl3 6.29

4.77 4.76 4.75 4.74 4.34 4.30 4.25 4.21 4.07 4.07 4.06 4.04 4.03 4.02 3.59 3.56 3.56 3.54

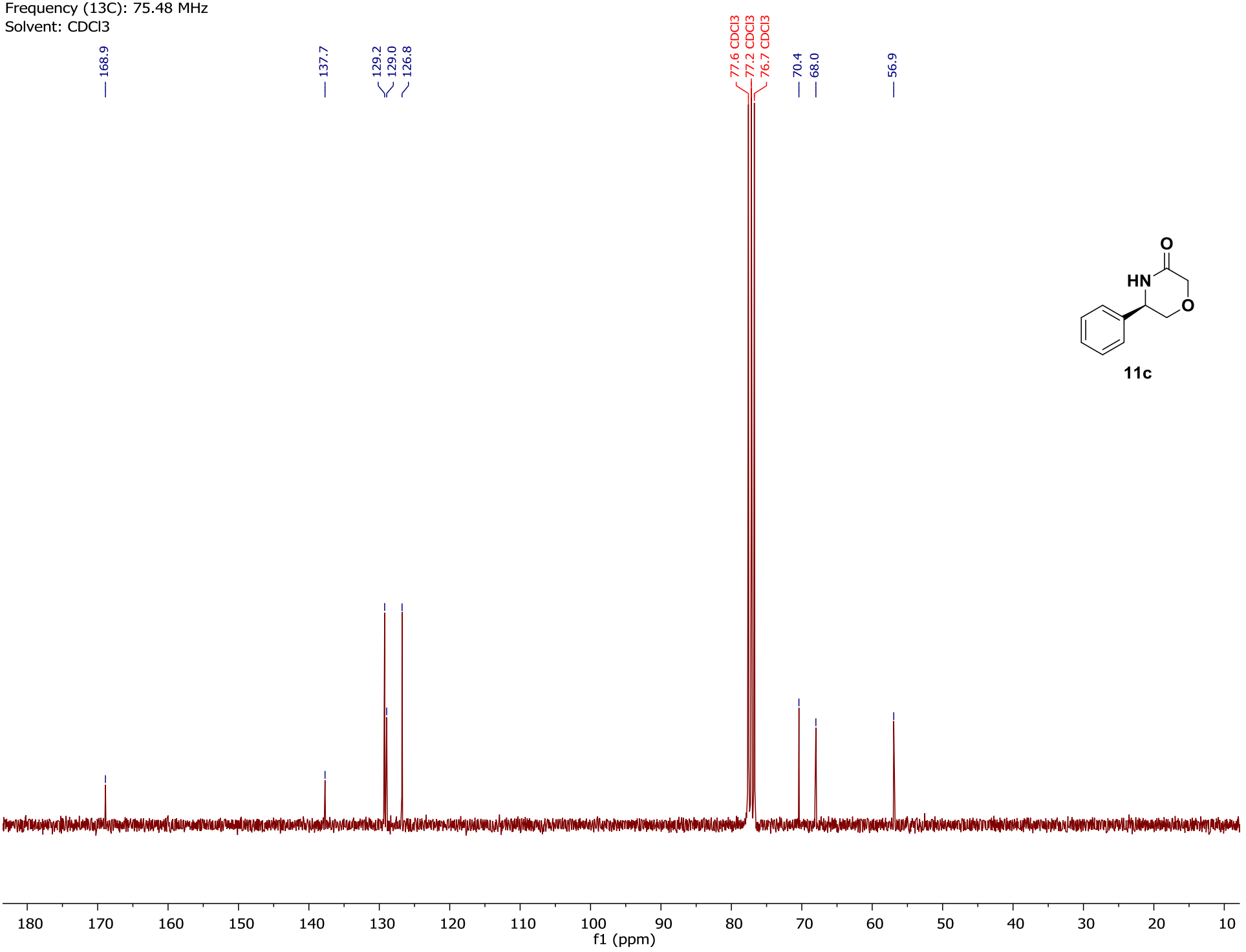
2.44 HDO



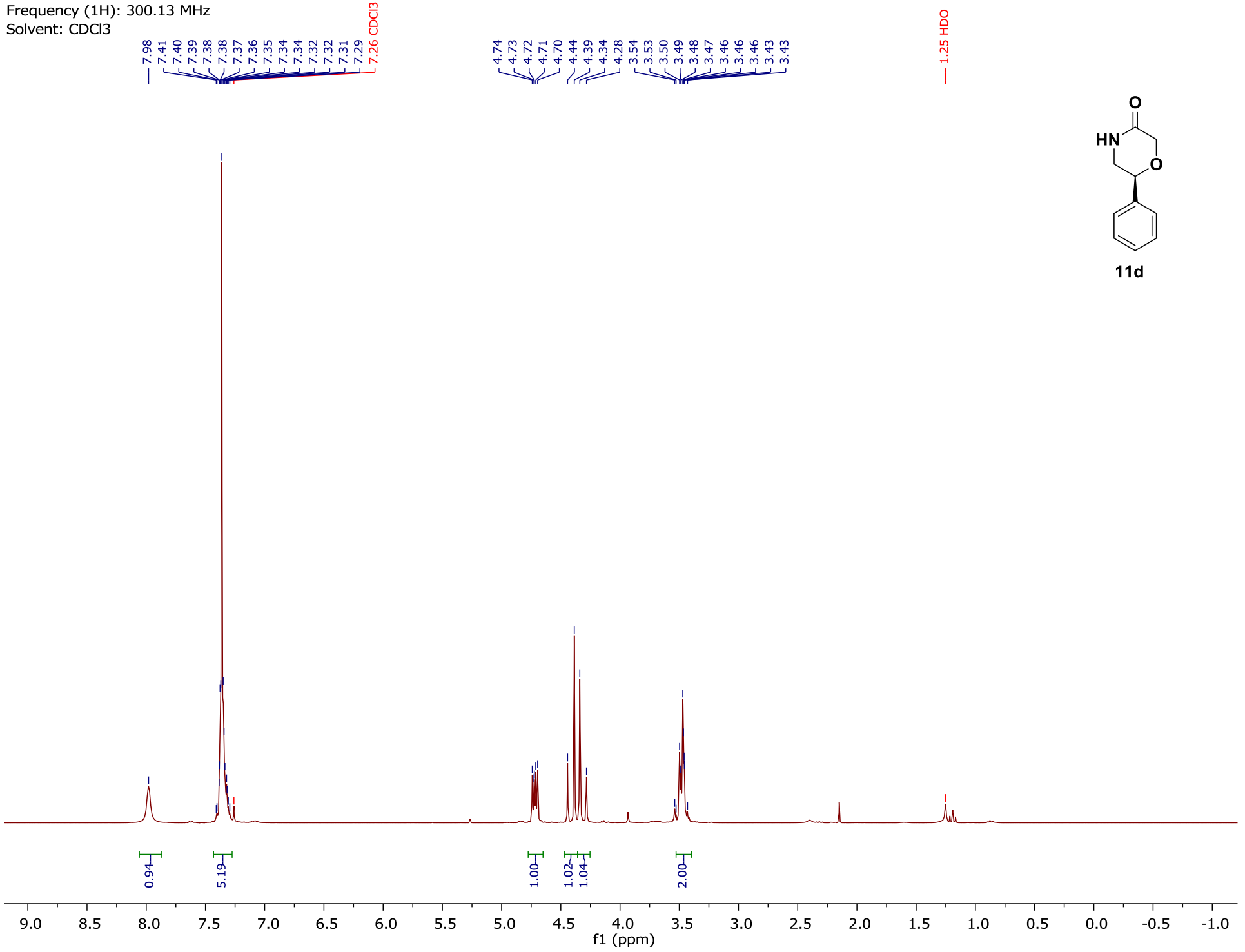
11c



Frequency (13C): 75.48 MHz
Solvent: CDCl3

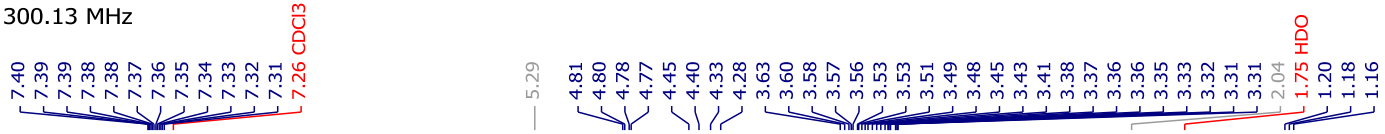


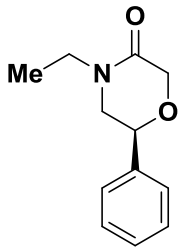
Frequency (1H): 300.13 MHz
Solvent: CDCl3



11d

Frequency (1H): 300.13 MHz
Solvent: CDCl3





11e

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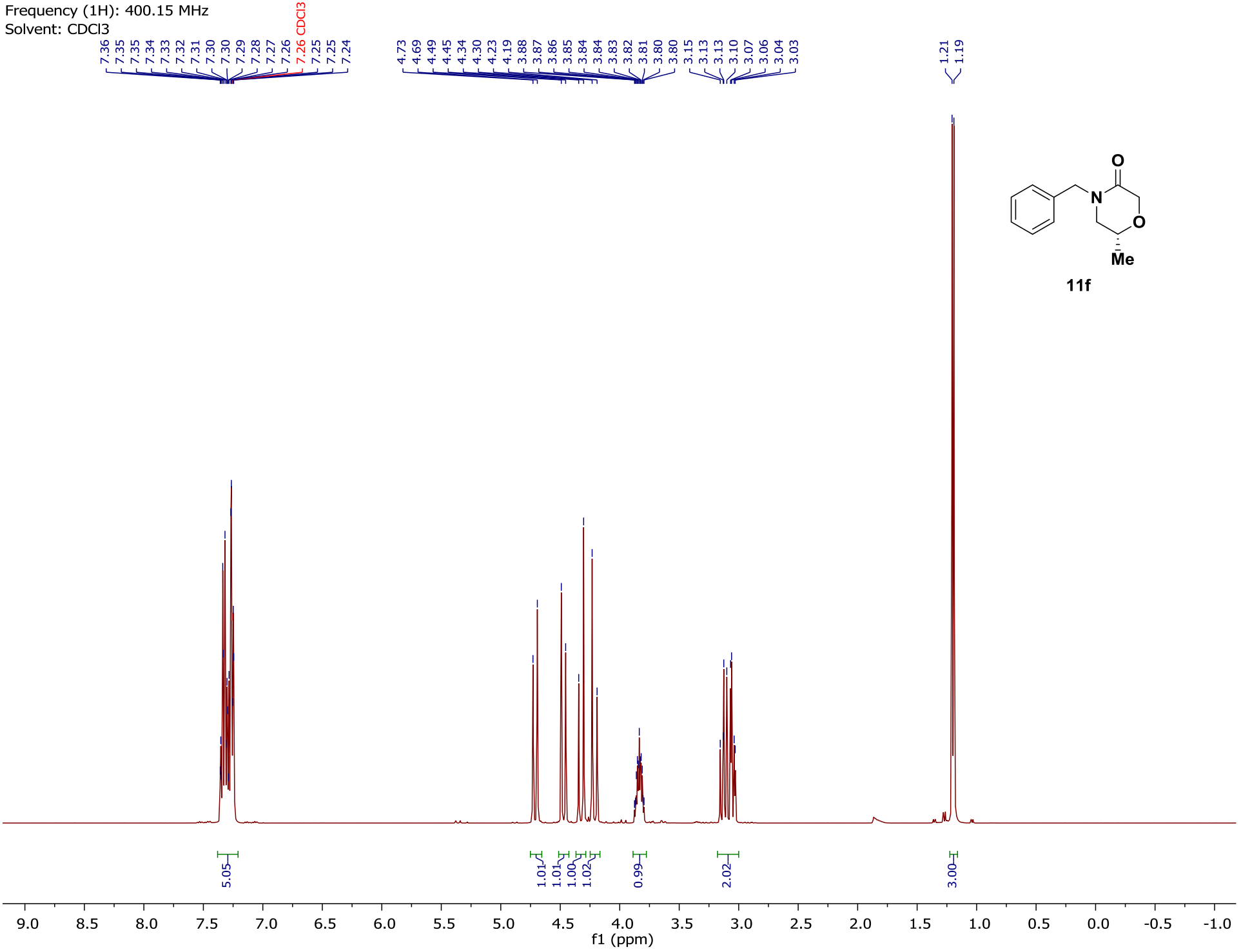

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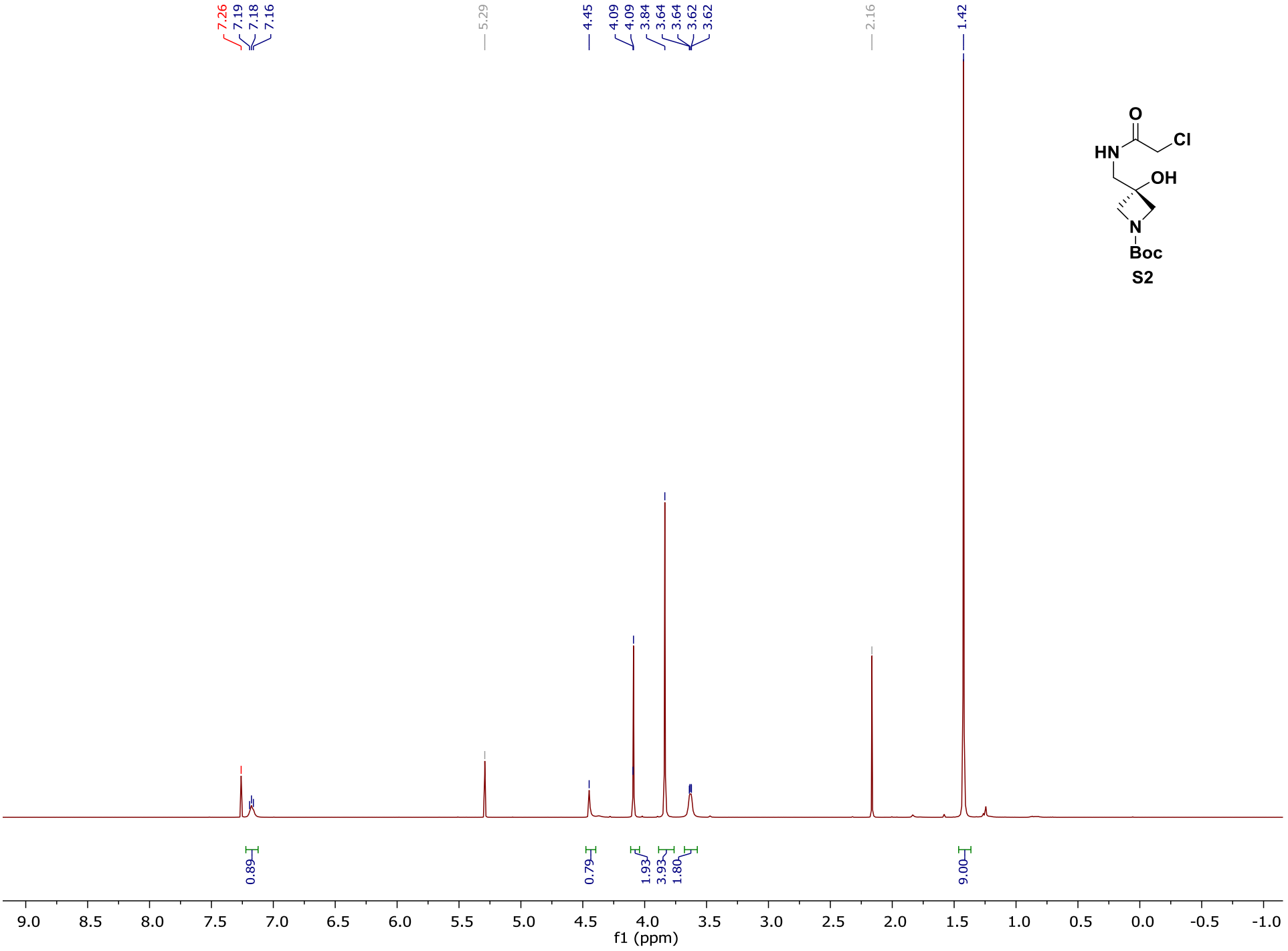
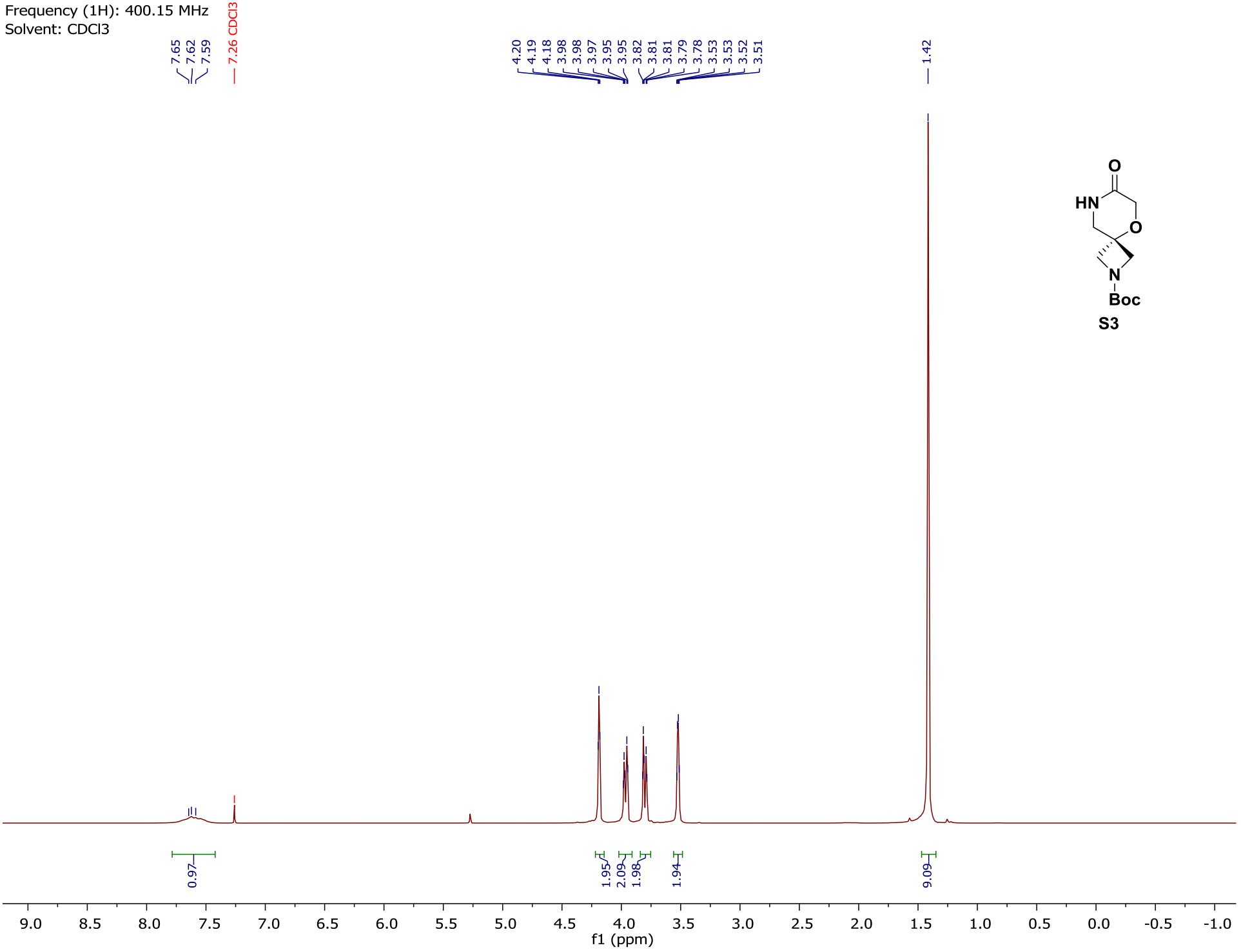
Solvent: CDCl3



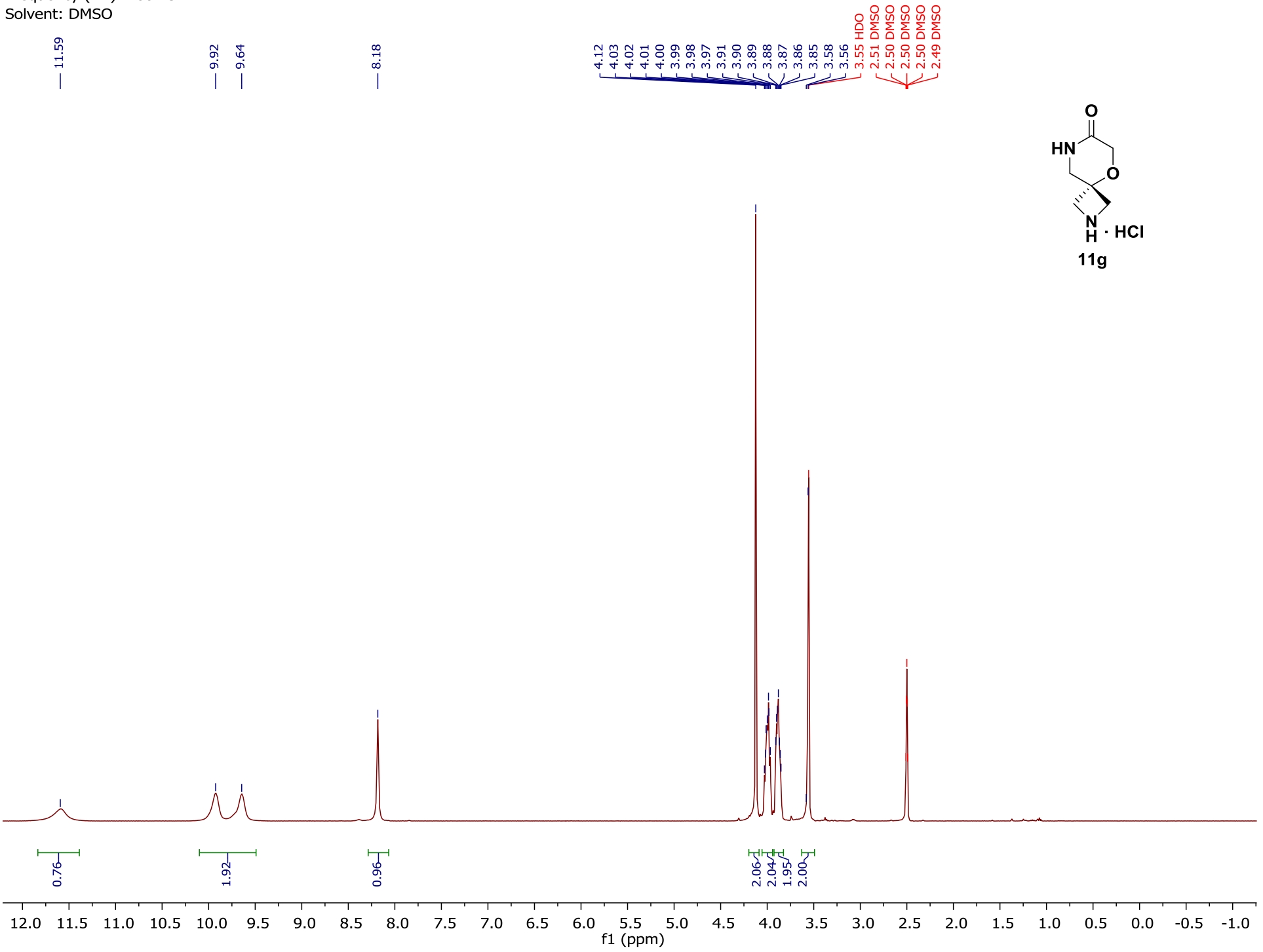
S2

Frequency (1H): 400.15 MHz
Solvent: CDCl3

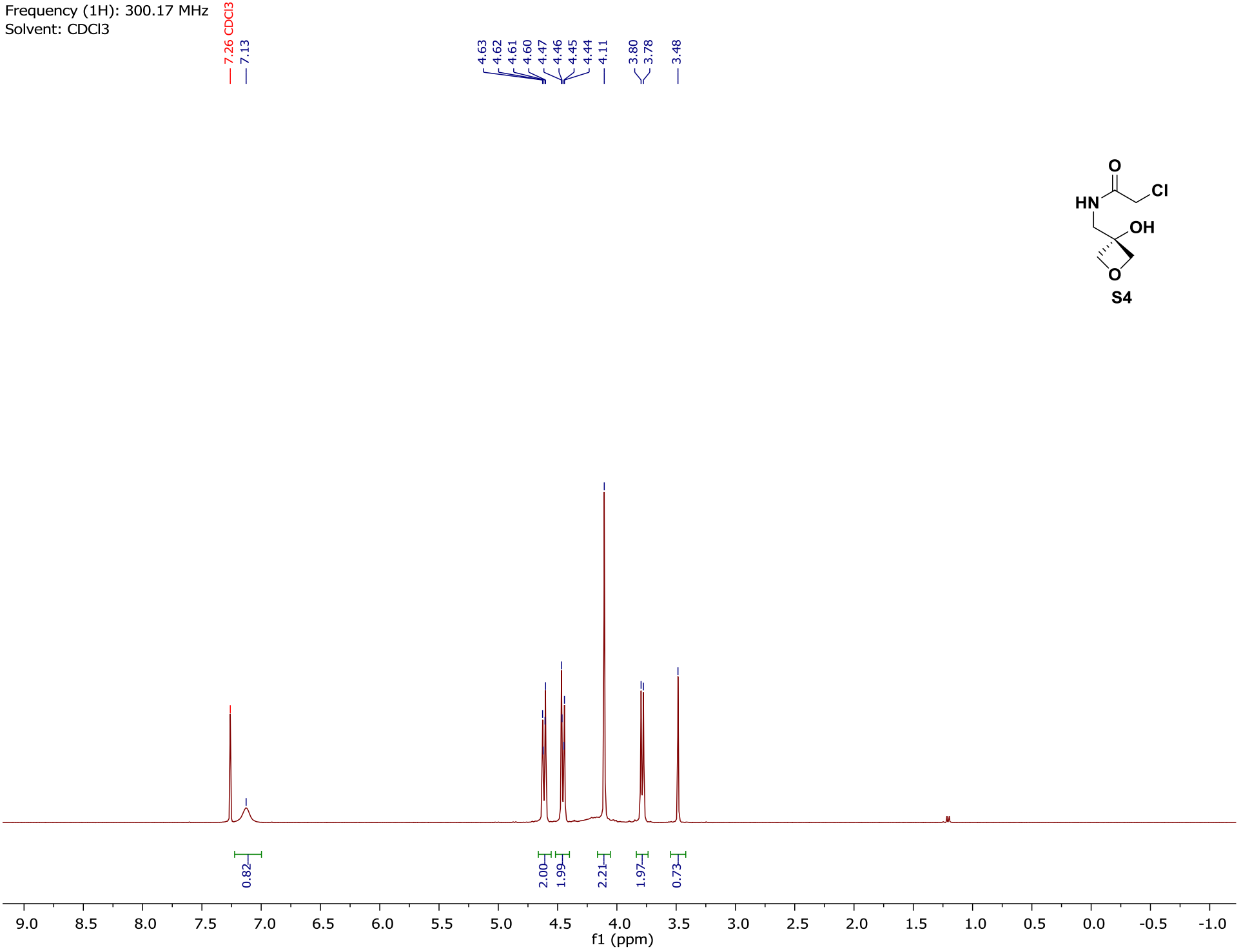


S3

Frequency (1H): 400.15 MHz
Solvent: DMSO

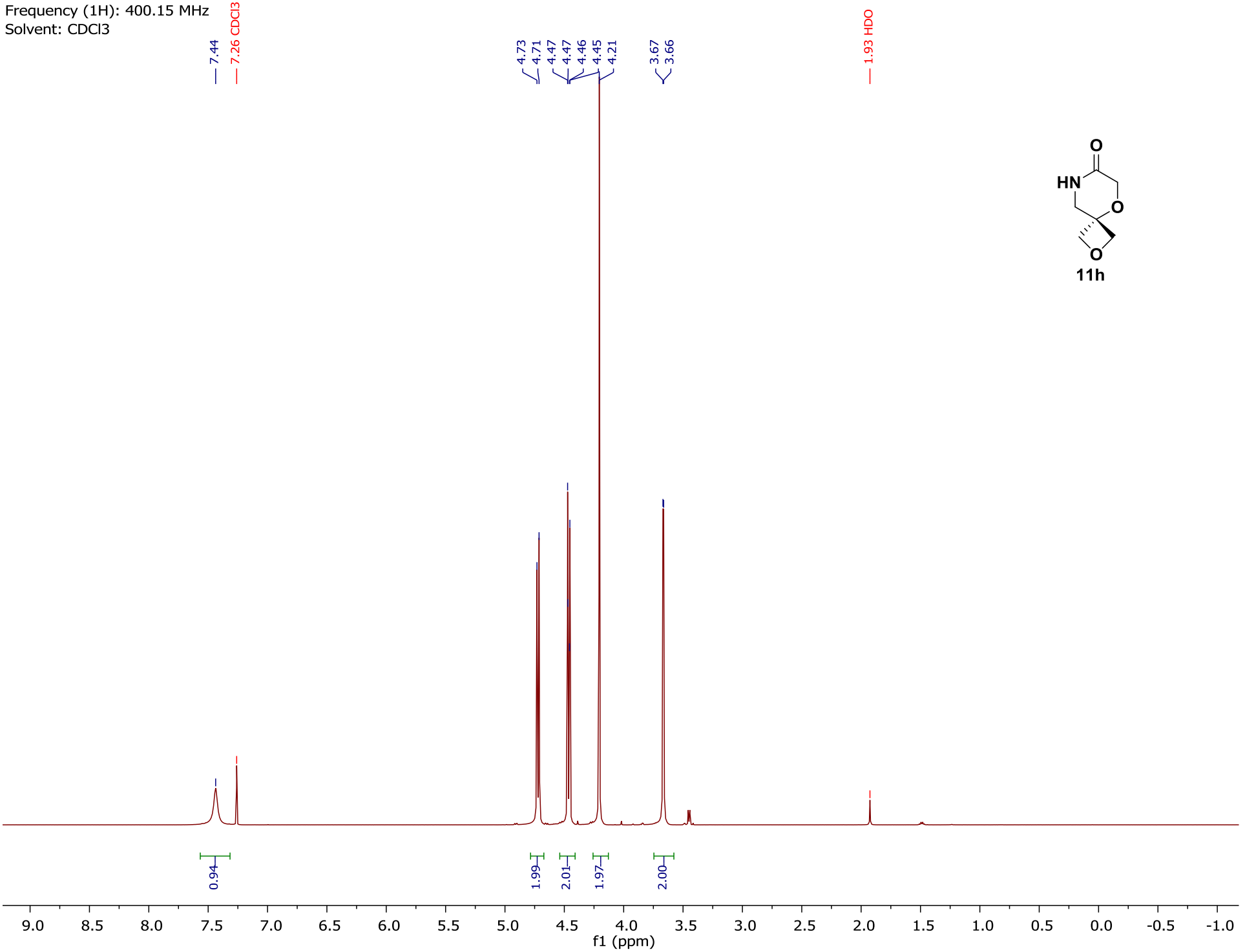


Frequency (1H): 300.17 MHz
Solvent: CDCl3



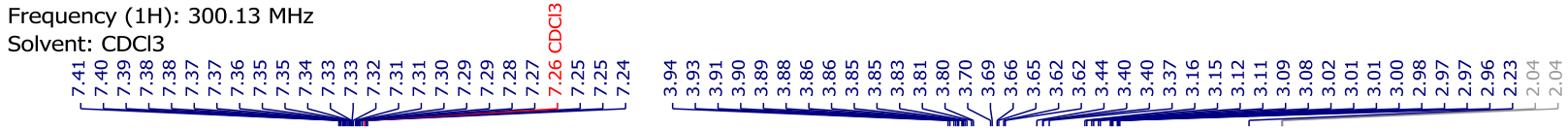
S4

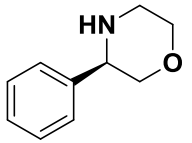
Frequency (1H): 400.15 MHz
Solvent: CDCl3



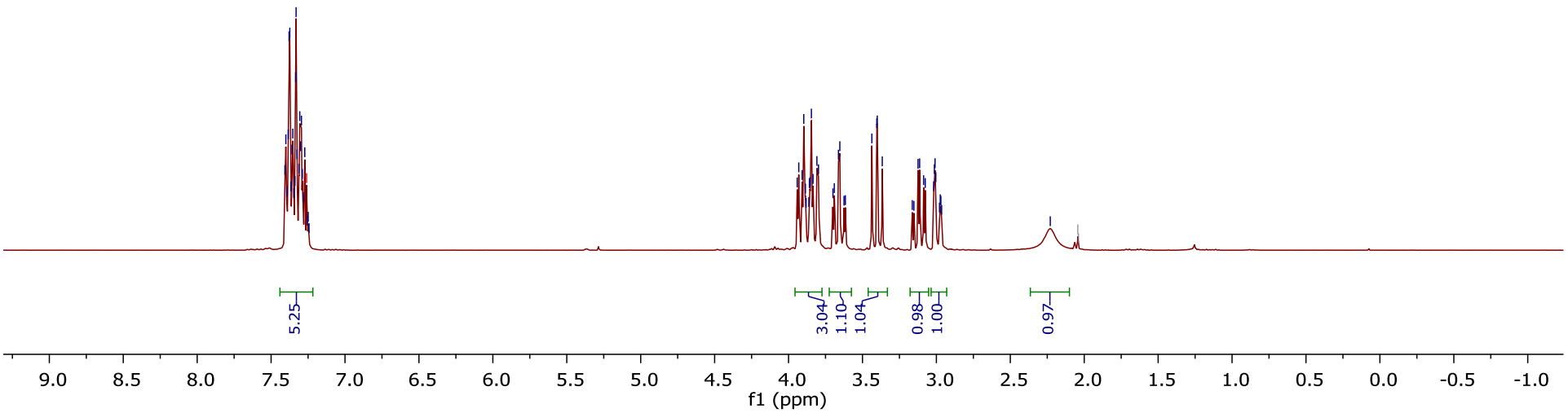
11h

Frequency (1H): 300.13 MHz
Solvent: CDCl3

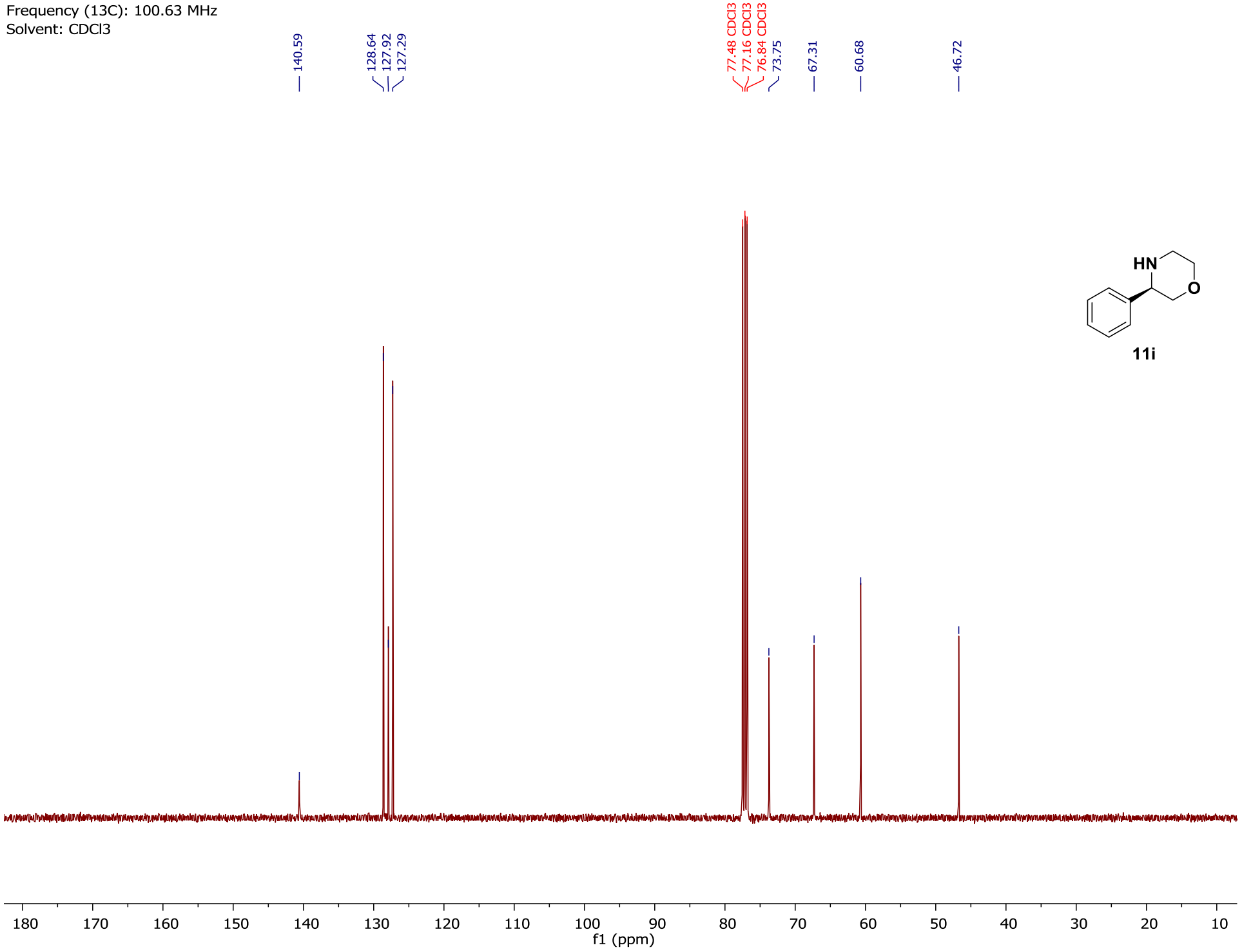




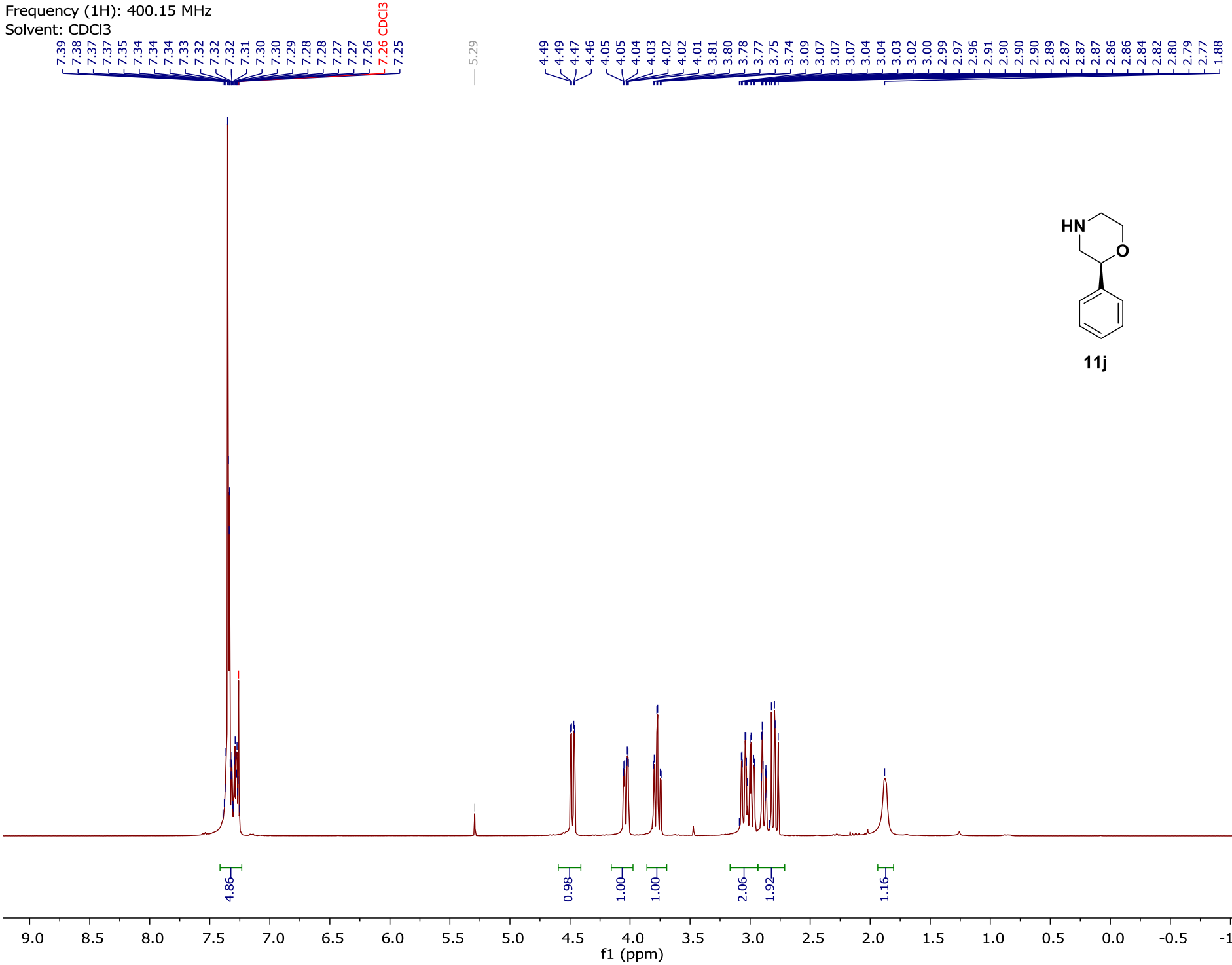
11i

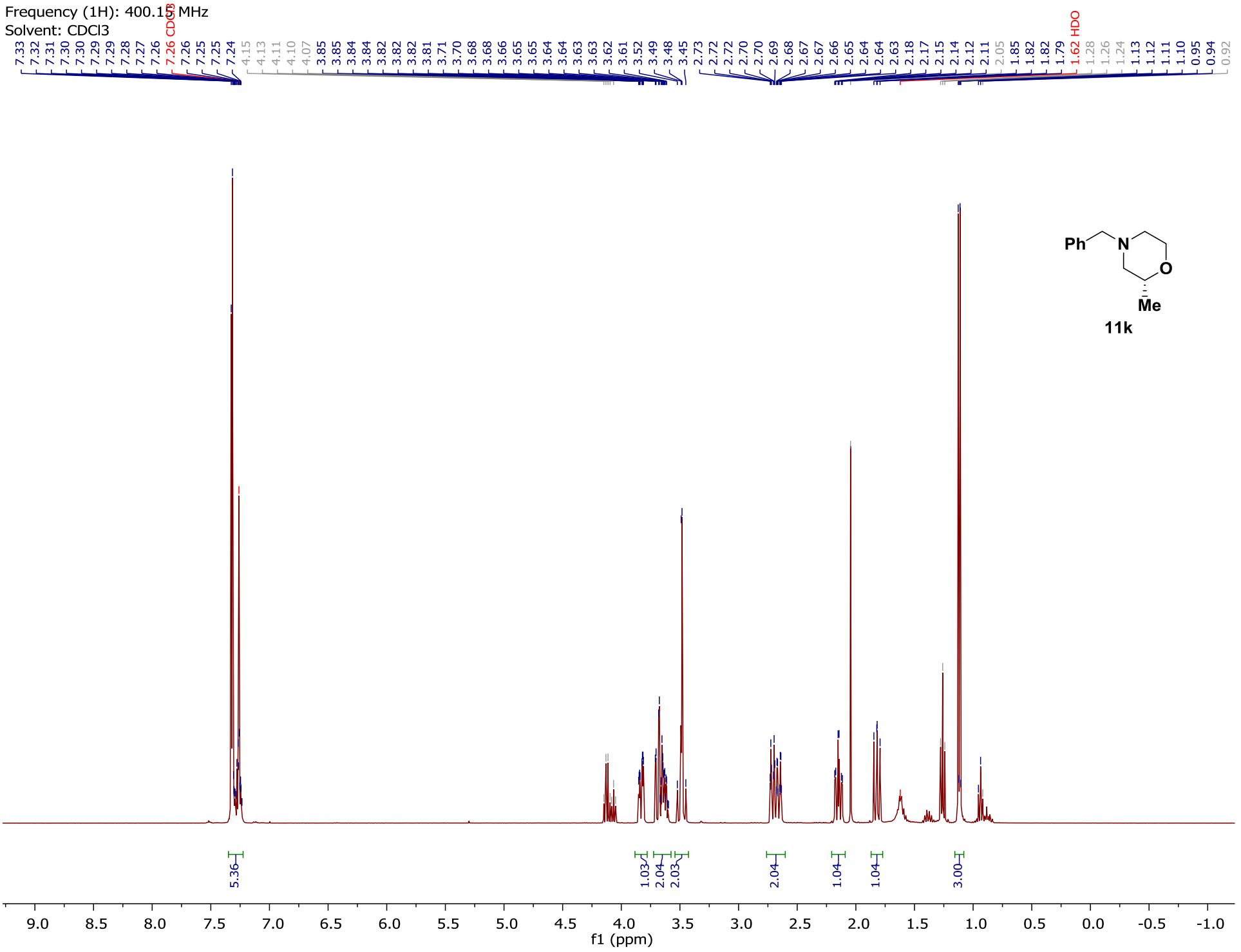


Frequency (13C): 100.63 MHz
Solvent: CDCl3

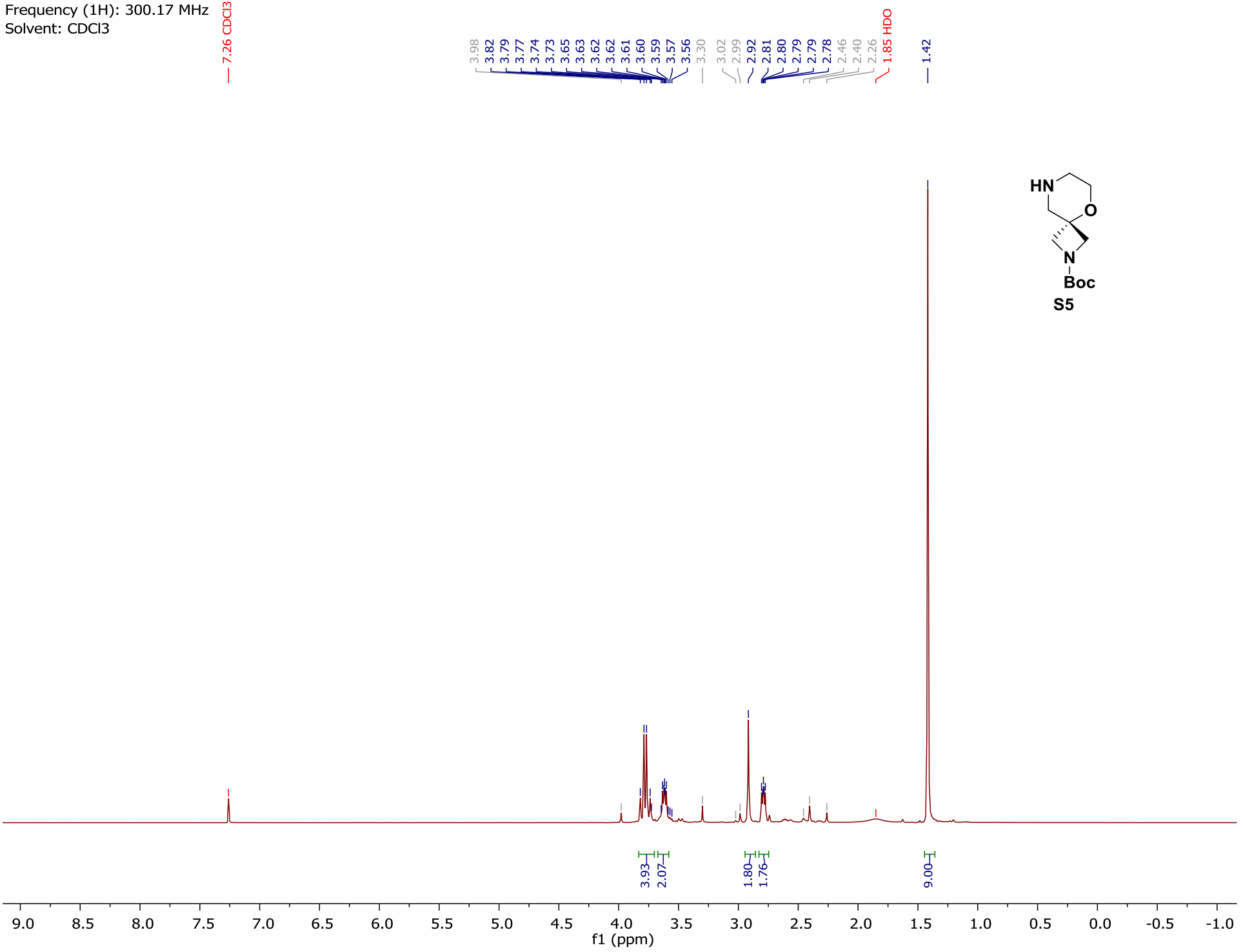


Frequency (1H): 400.15 MHz
Solvent: CDCl3

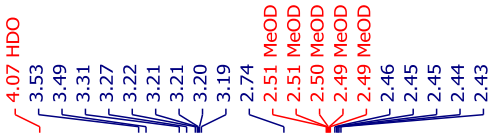


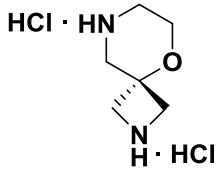

Frequency (1H): 400.13 MHz
Solvent: CDCl3
7.33 7.32 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.26 7.26 CDCl3 7.26 7.25 7.25 7.24 4.15 4.13 4.11 4.10 4.07 3.85 3.85 3.84 3.84 3.82 3.82 3.82 3.81 3.71 3.70 3.68 3.68 3.66 3.65 3.65 3.64 3.64 3.63 3.63 3.62 3.61 3.52 3.49 3.48 3.45 2.73 2.72 2.72 2.70 2.70 2.69 2.68 2.67 2.67 2.66 2.65 2.64 2.64 2.63 2.18 2.17 2.15 2.14 2.12 2.11 2.05 1.85 1.82 1.82 1.79 1.62 HDO 1.28 1.26 1.24 1.13 1.12 1.11 1.10 0.95 0.94 0.92
Ph
N
O
Me
11k
5.36
1.03
2.04
2.03
2.04
1.04
1.04
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

Frequency (1H): 300.17 MHz
Solvent: CDCl3

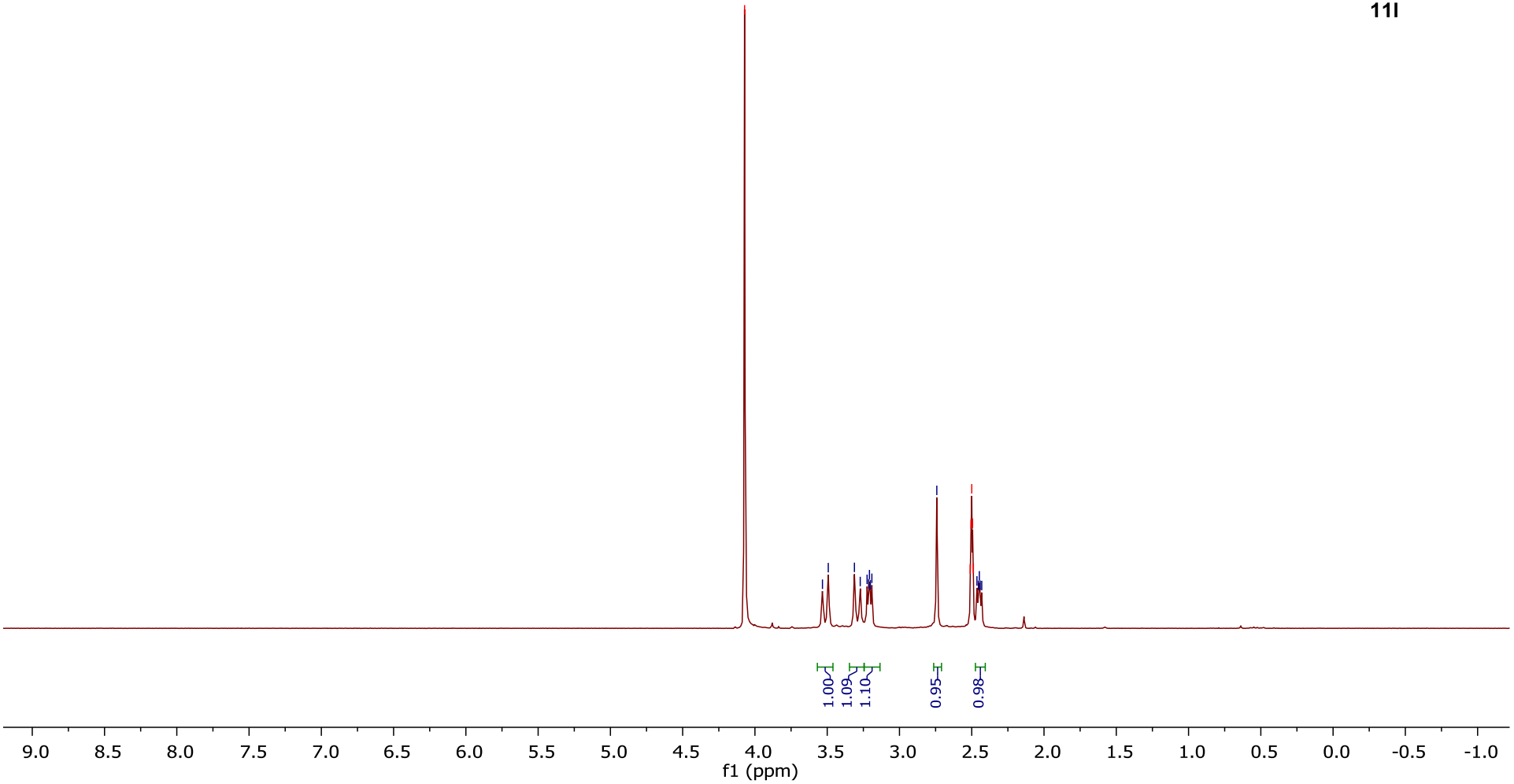


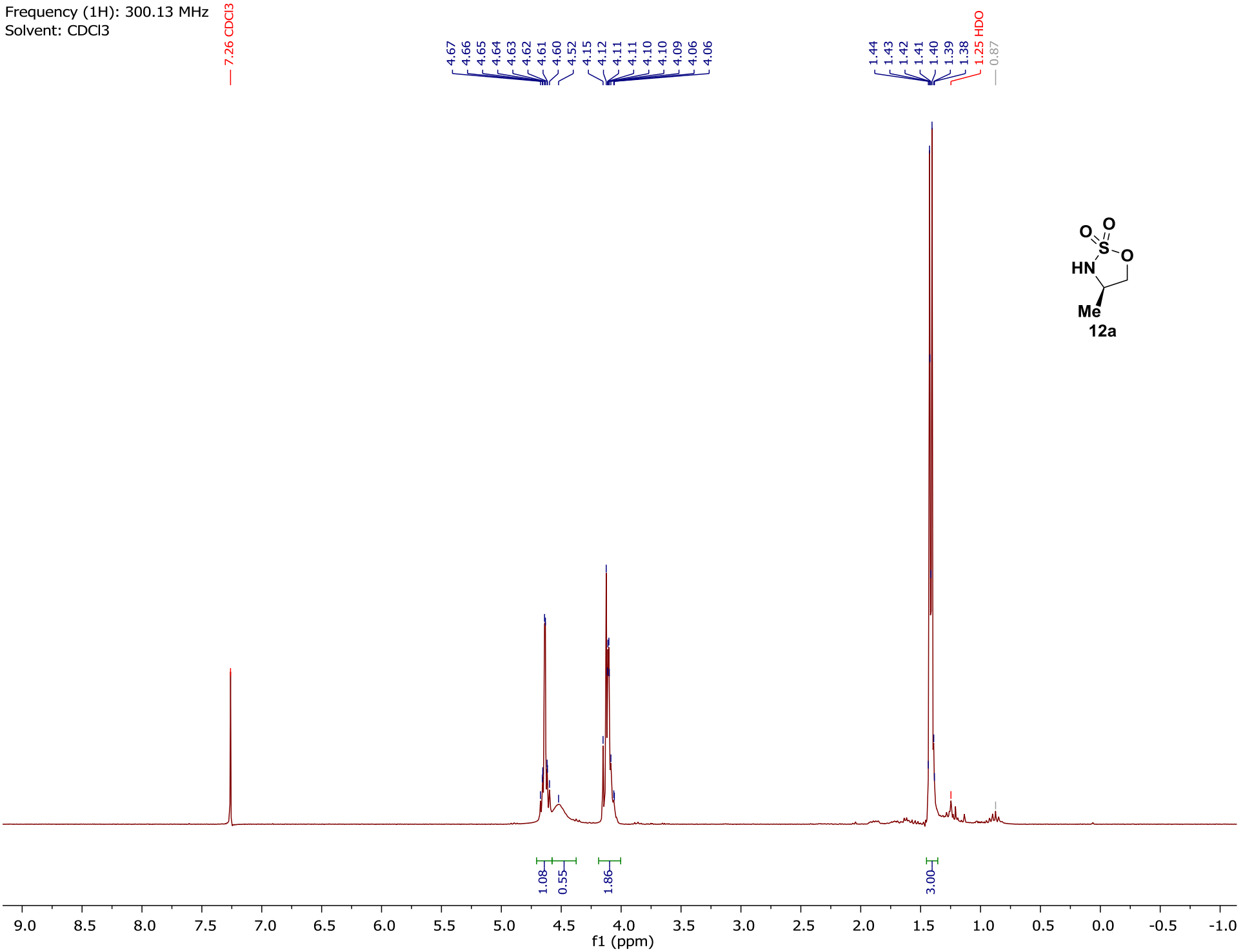
Frequency (1H): 300.17 MHz
Solvent: MeOD





11l




Frequency (1H): 300.13 MHz
Solvent: CDCl3
7.26 CDCl3
4.67
4.66
4.65
4.64
4.63
4.62
4.61
4.60
4.52
4.15
4.12
4.11
4.11
4.10
4.10
4.09
4.06
4.06
1.44
1.43
1.42
1.41
1.40
1.39
1.38
1.25 HDO
0.87
O
O
S
O
HN
Me
12a
1.08
0.55
1.86
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

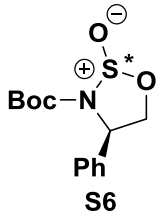
Frequency (1H): 400.15 MHz
Solvent: CDCl3

7.47 7.47 7.46 7.45 7.45 7.45 7.44 7.41 7.41 7.40 7.39 7.39 7.38 7.37 7.37 7.36 7.35 7.35 7.35 7.34 7.33 7.32 7.32 7.31 7.31 7.26 CDCl3 7.25

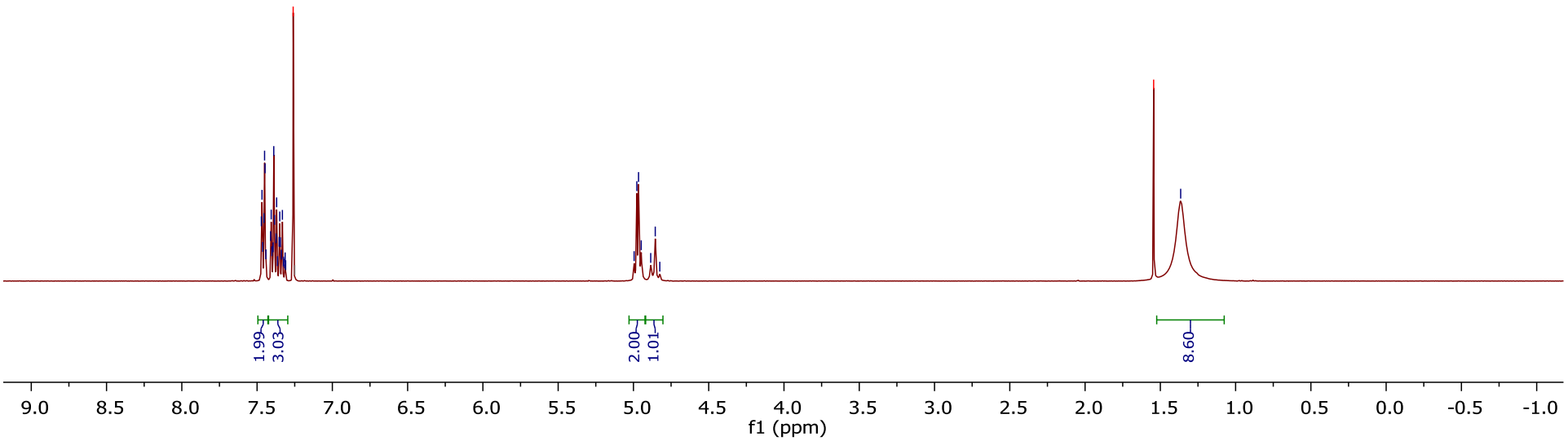
5.00 4.98 4.97 4.95 4.89 4.86 4.82

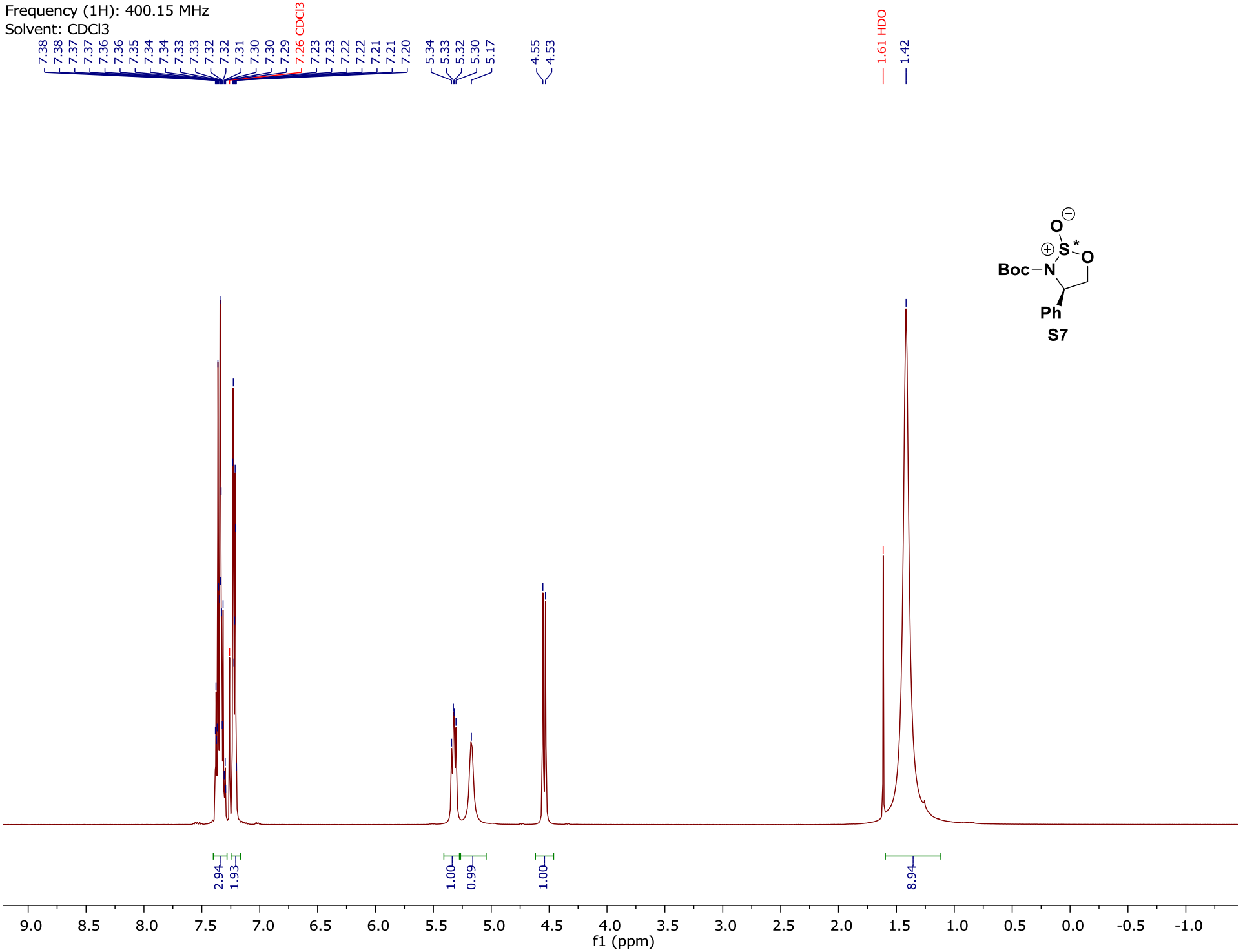
1.54 HDO

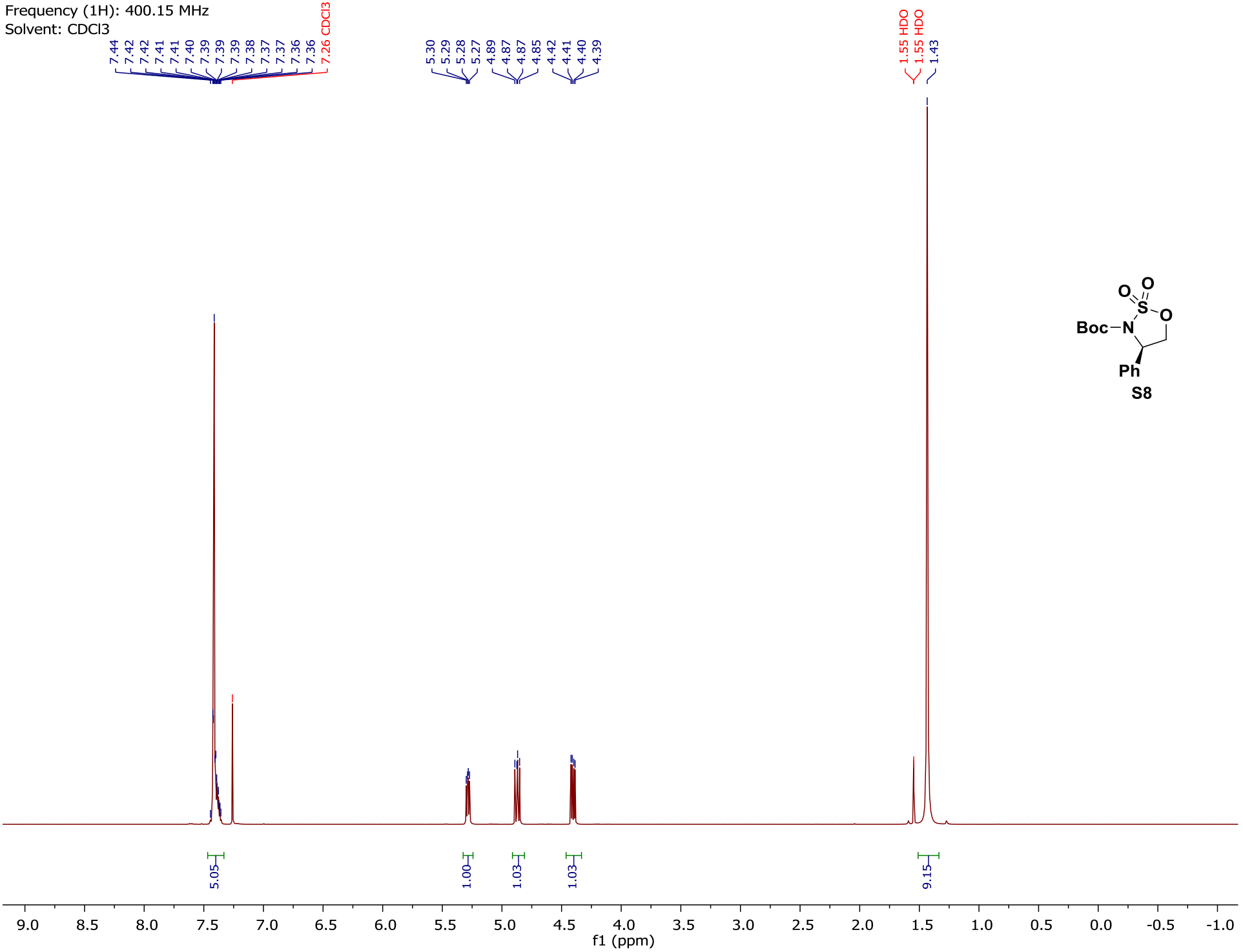
1.36

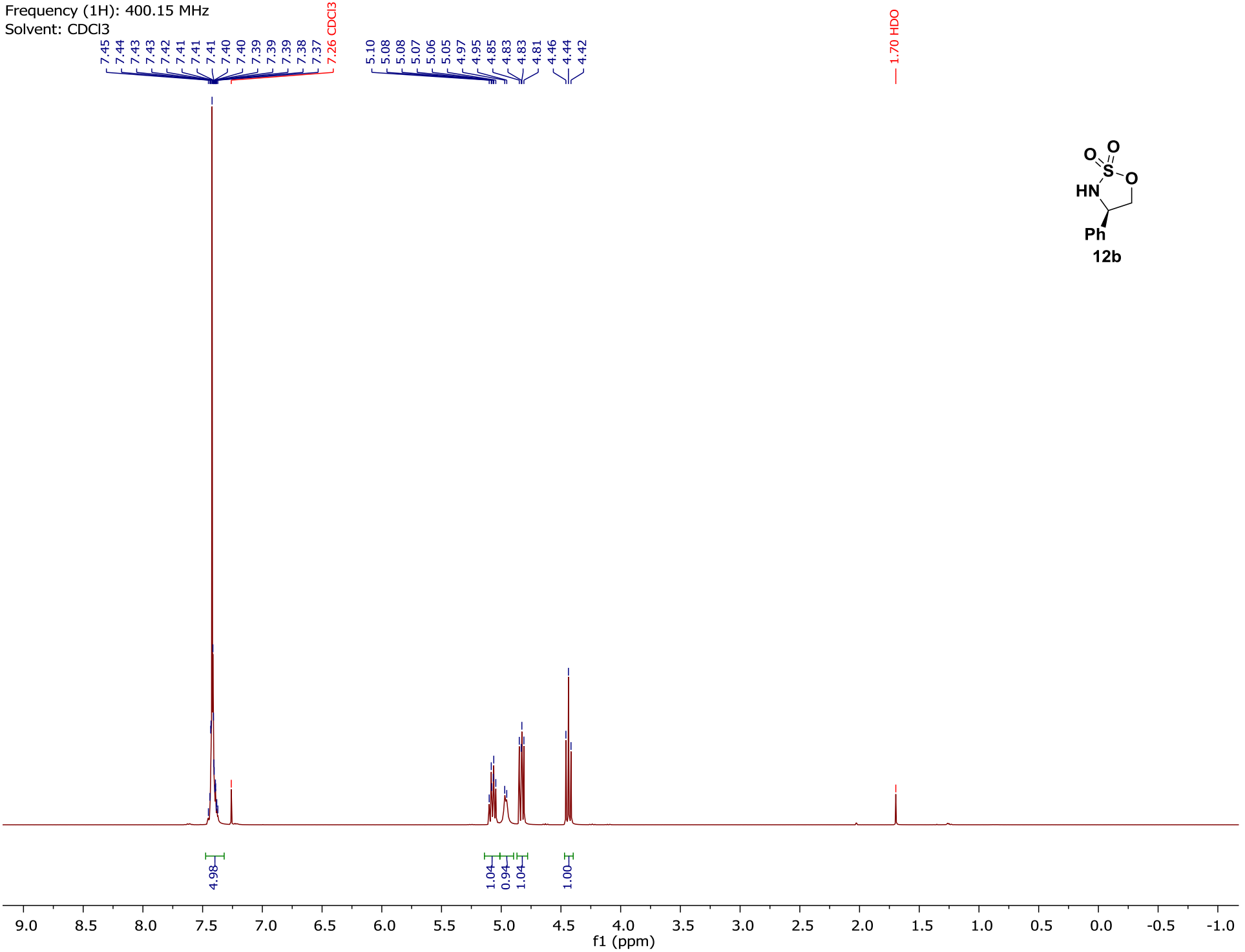


S6

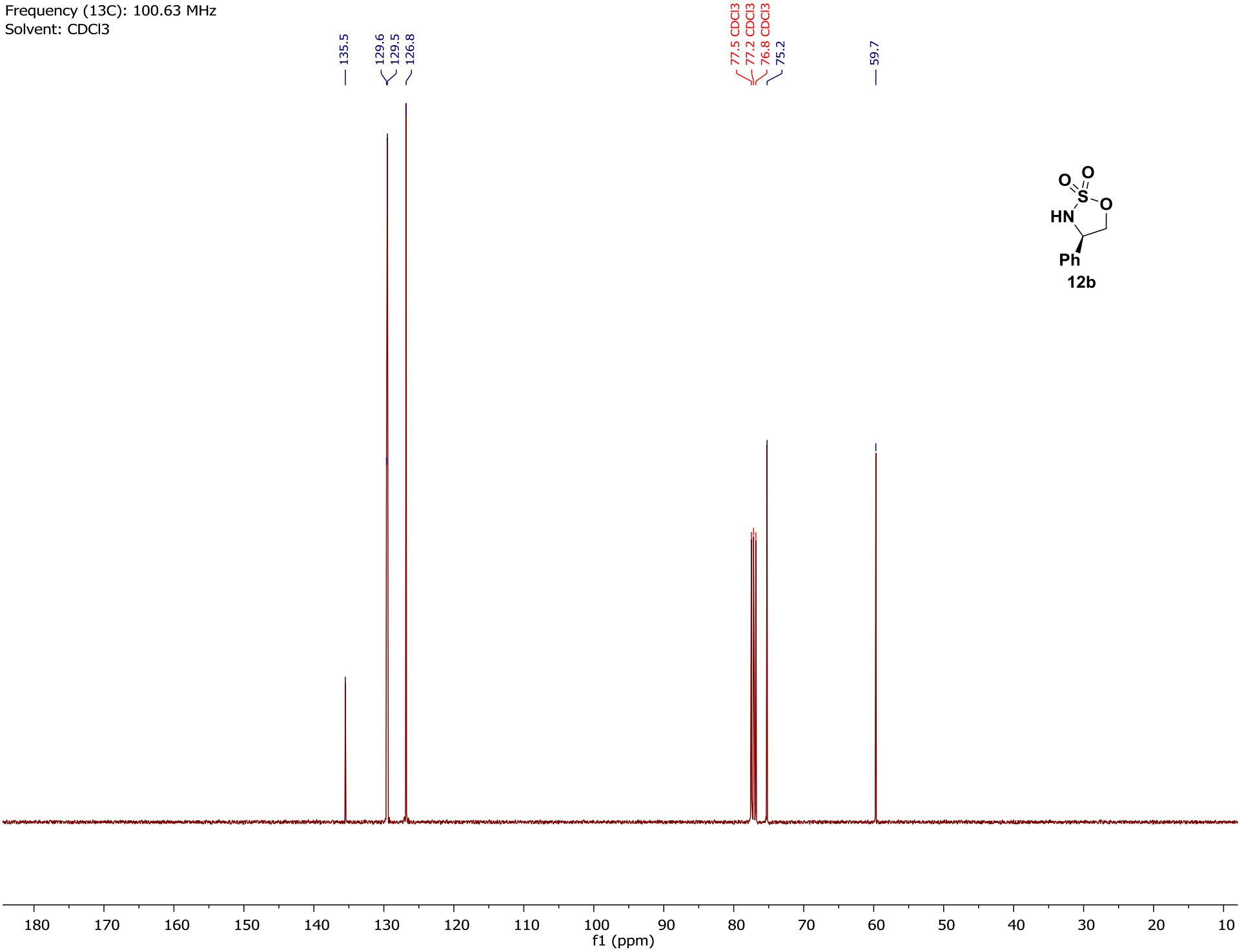



Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.38 7.38 7.37 7.37 7.36 7.36 7.35 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.30 7.30 7.29 7.26 CDCl3 7.23 7.23 7.22 7.22 7.21 7.21 7.20
5.34 5.33 5.32 5.30 5.17
4.55 4.53
1.61 HDO
1.42
Boc
N
S*
O
O
Ph
S7
2.94
1.93
1.00
0.99
1.00
8.94
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

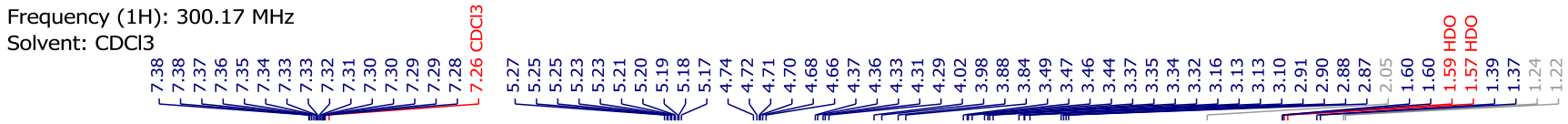

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.44
7.42
7.42
7.41
7.41
7.40
7.39
7.39
7.39
7.38
7.37
7.37
7.36
7.36
7.26 CDCl3
5.30
5.29
5.28
5.27
4.89
4.87
4.87
4.85
4.42
4.41
4.40
4.39
1.55 HDO
1.55 HDO
1.43
Boc
N
S
O
O
O
Ph
S8
5.05
1.00
1.03
1.03
9.15
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

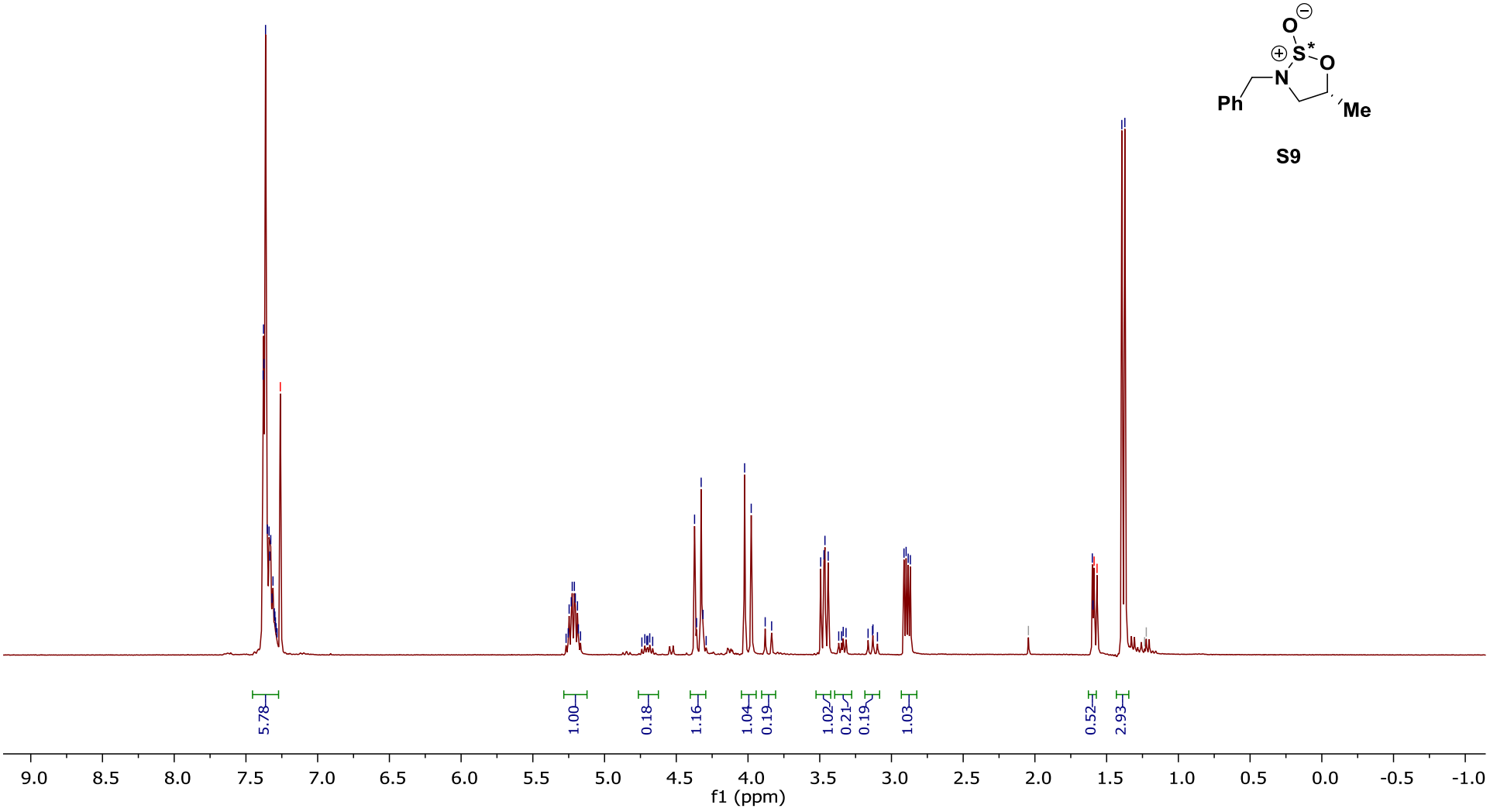

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.45
7.44
7.43
7.43
7.42
7.41
7.41
7.41
7.40
7.40
7.39
7.39
7.39
7.38
7.37
7.26 CDCl3
5.10
5.08
5.08
5.07
5.06
5.05
4.97
4.95
4.85
4.83
4.83
4.81
4.46
4.44
4.42
1.70 HDO
O
O
S
O
HN
Ph
12b
4.98
1.04
0.94
1.04
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

Frequency (13C): 100.63 MHz
Solvent: CDCl3

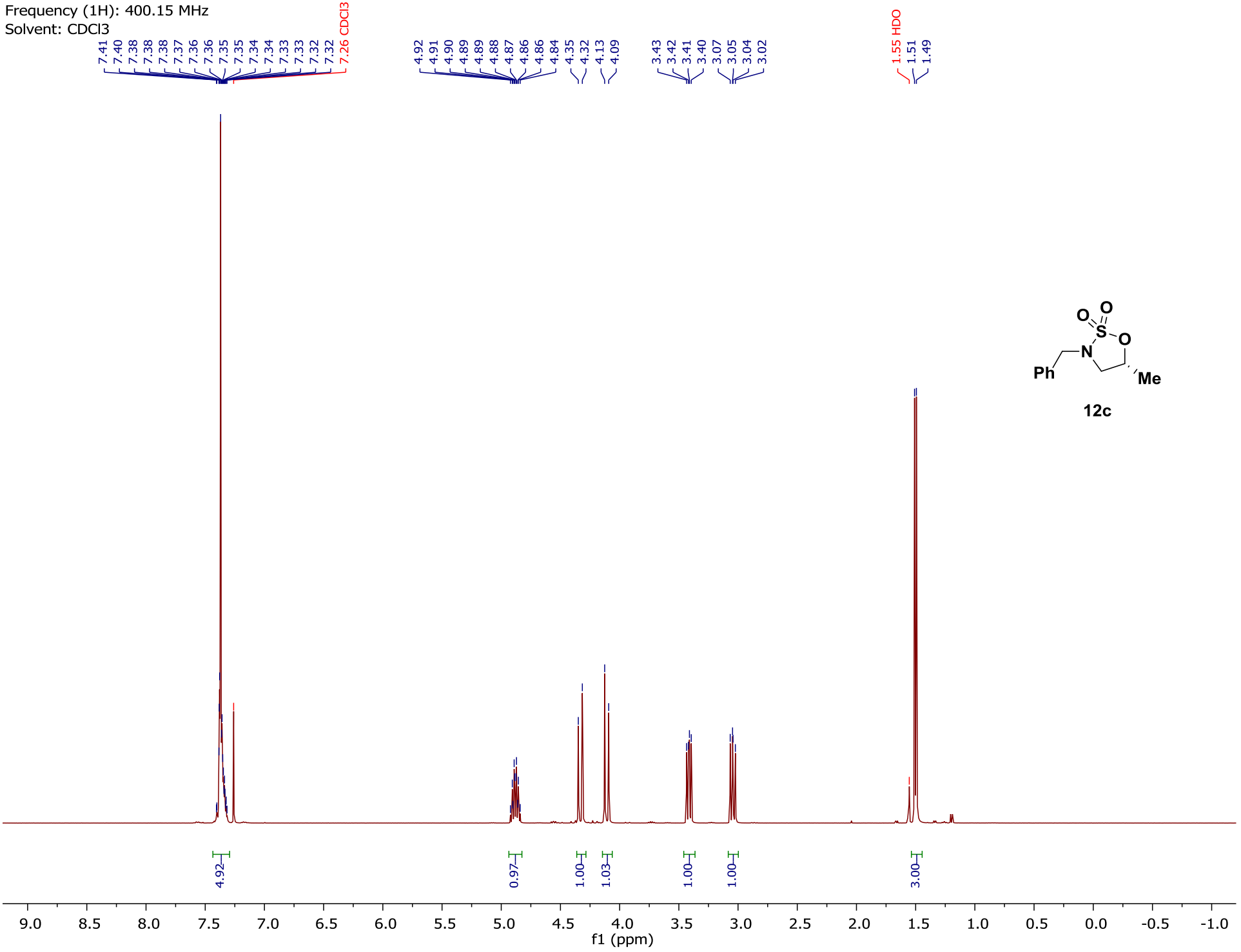


Frequency (1H): 300.17 MHz
Solvent: CDCl3

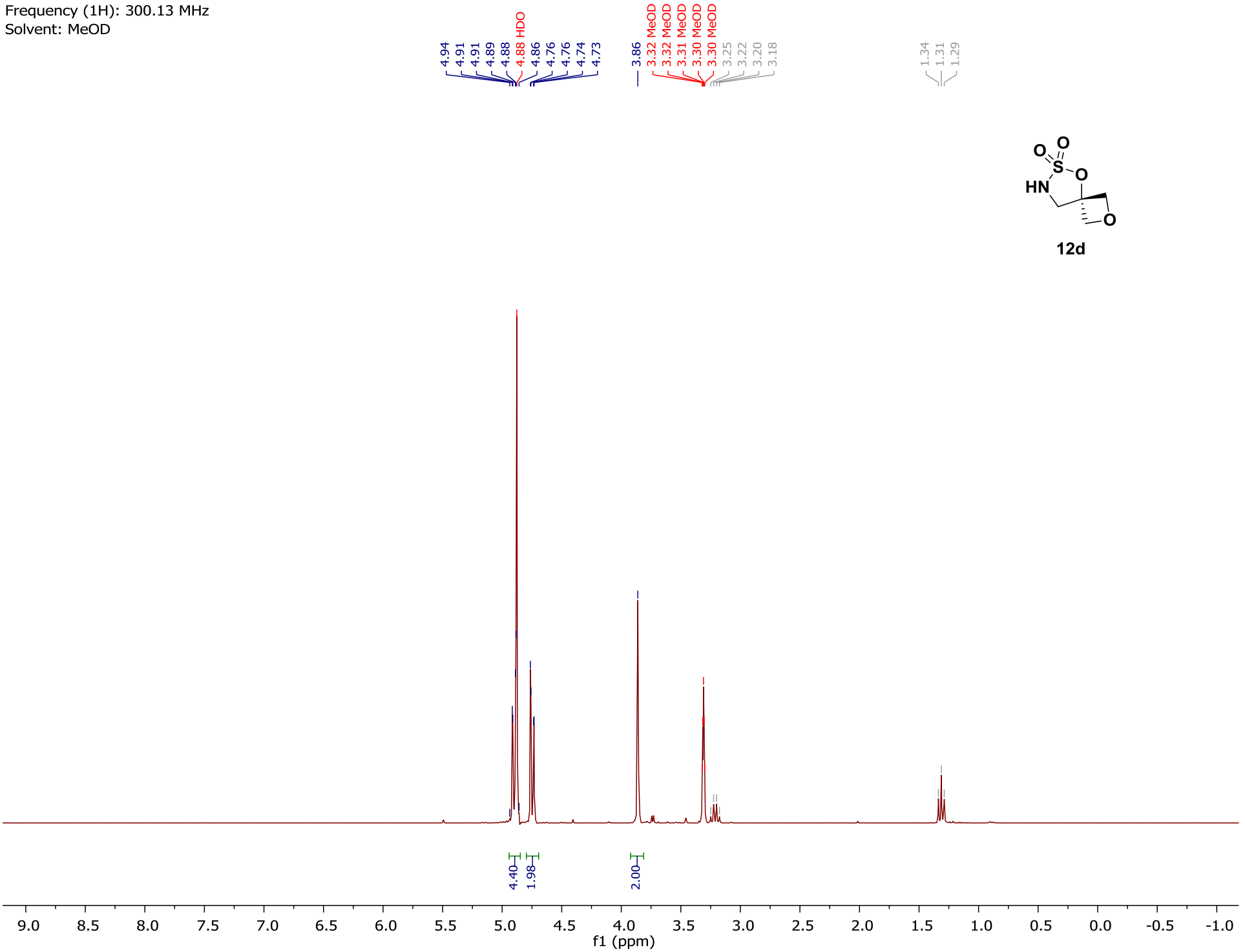




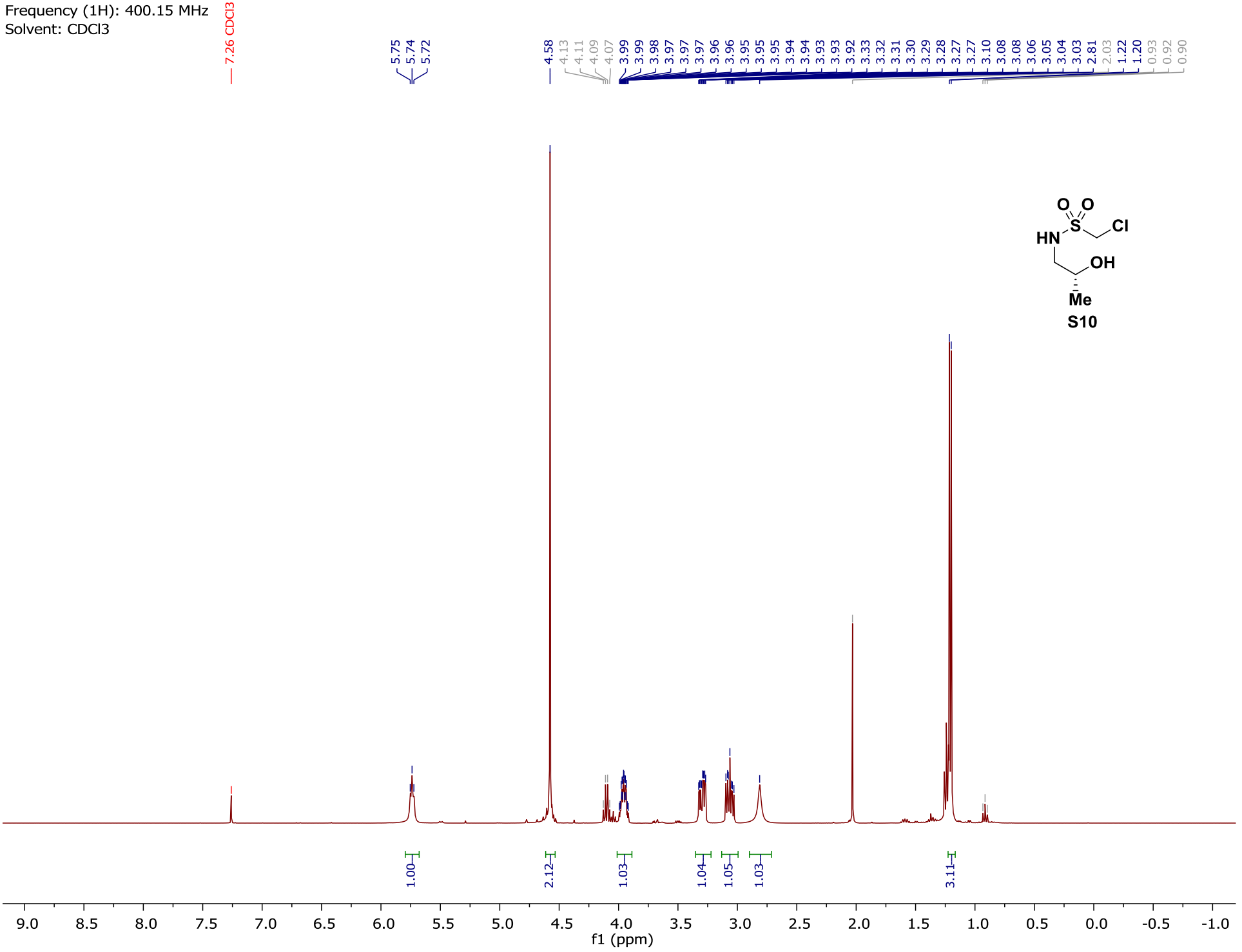
S9


Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.41 7.40 7.38 7.38 7.38 7.37 7.36 7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.32 7.26 CDCl3
4.92 4.91 4.90 4.89 4.89 4.88 4.87 4.86 4.86 4.84 4.35 4.32 4.13 4.09
3.43 3.42 3.41 3.40 3.07 3.05 3.04 3.02
1.55 HDO 1.51 1.49
O O S O N Ph Me
12c
4.92 0.97 1.00 1.03 1.00 1.00 3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

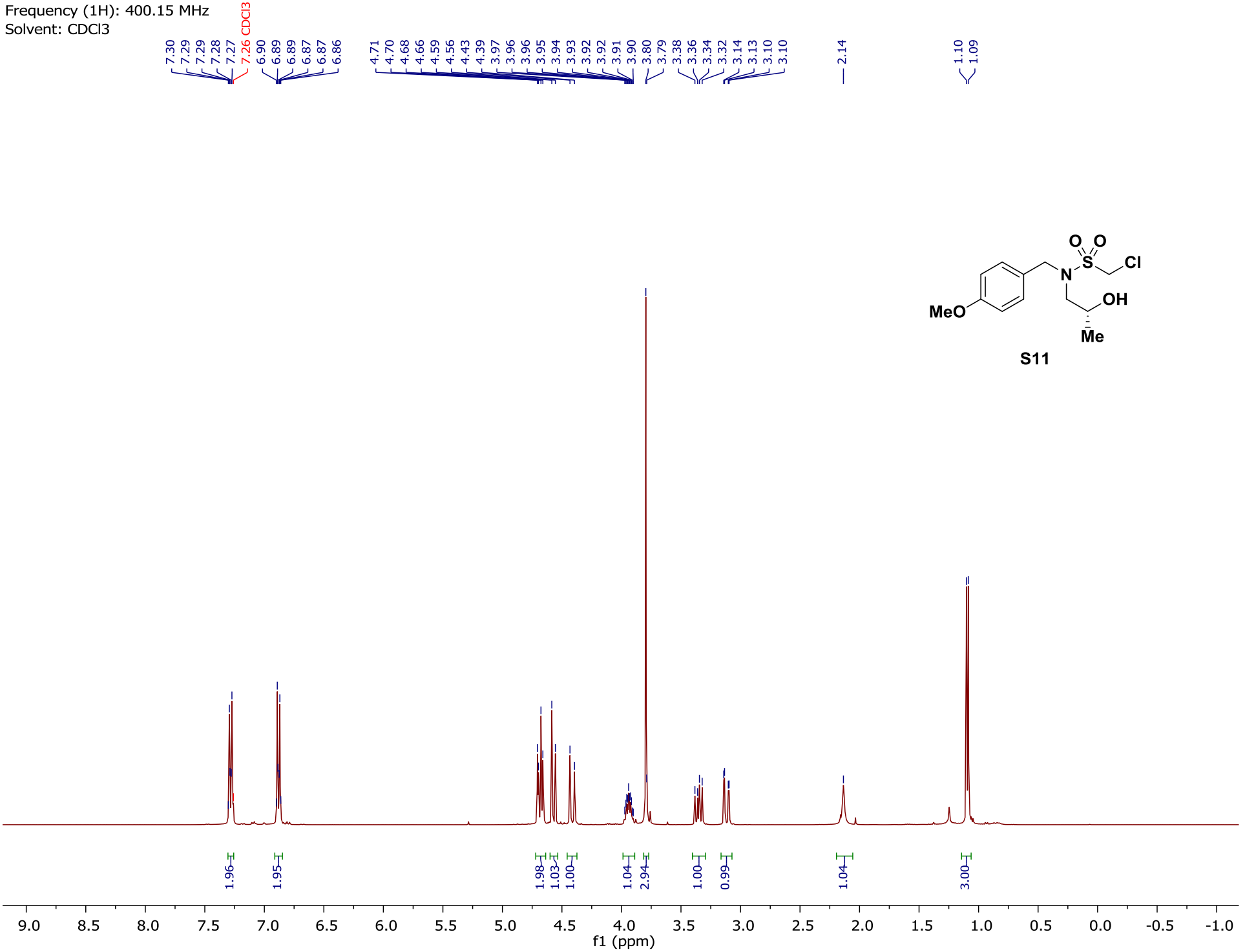
Frequency (1H): 300.13 MHz
Solvent: MeOD



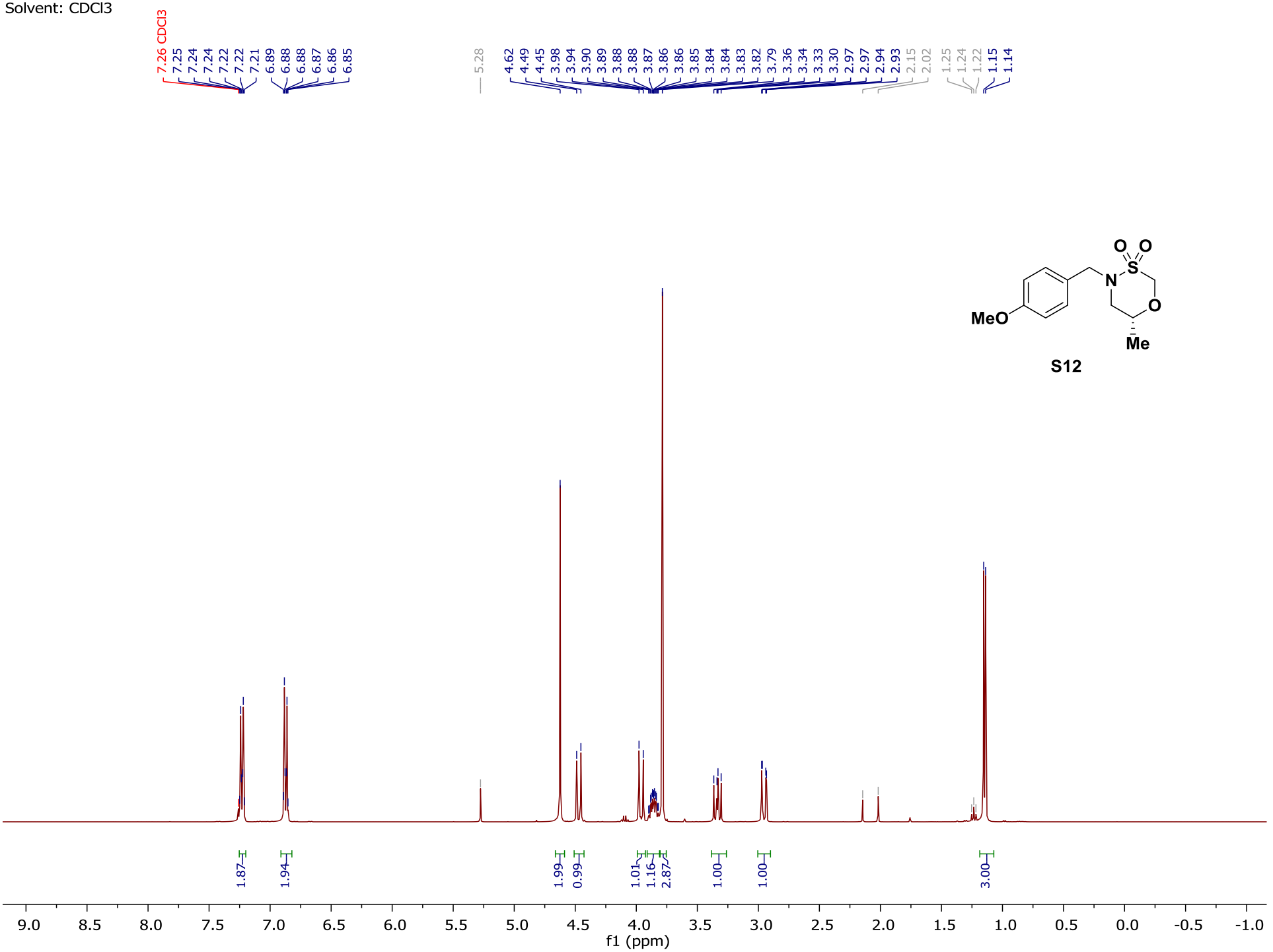
Frequency (1H): 400.15 MHz
Solvent: CDCl3



Frequency (1H): 400.15 MHz
Solvent: CDCl3

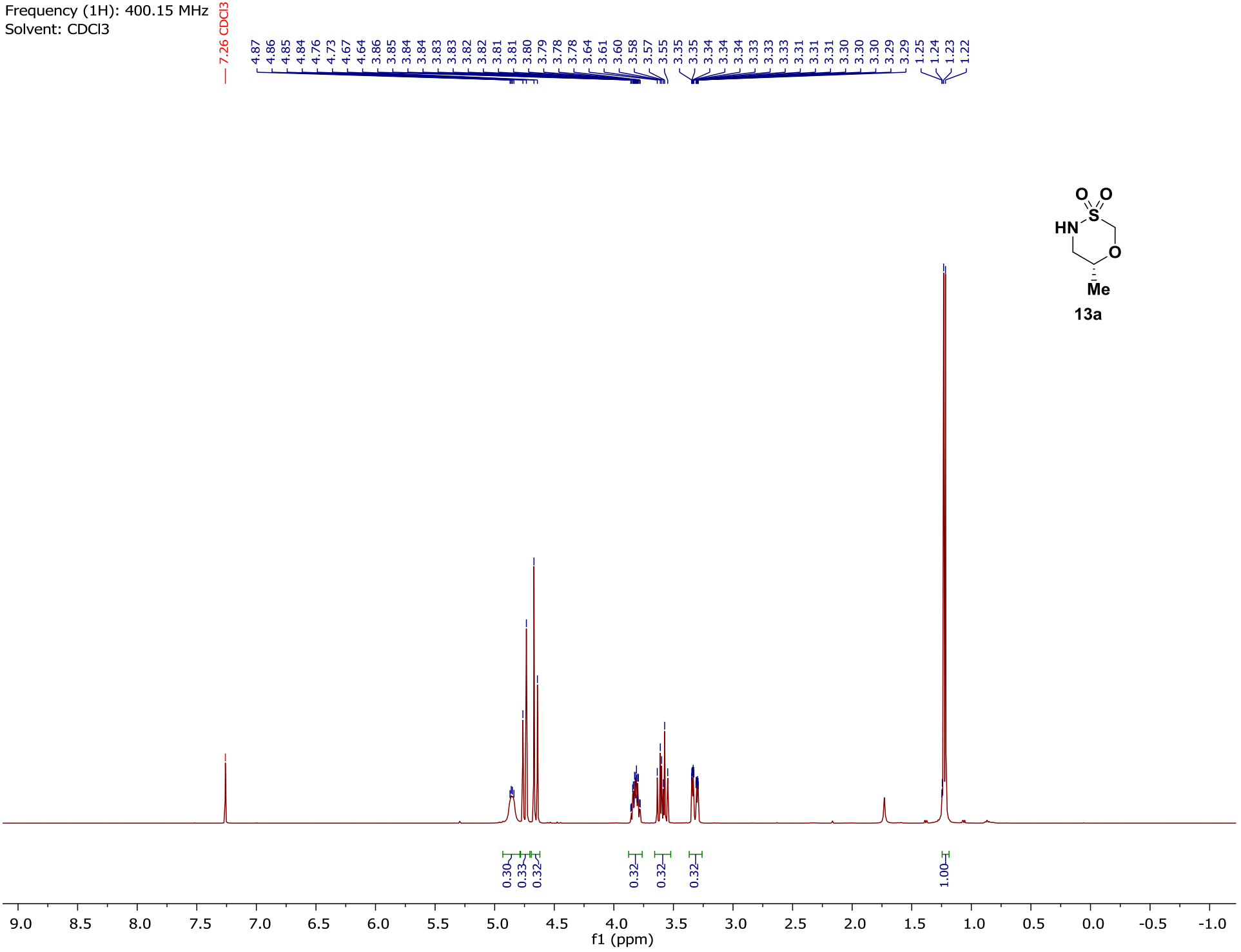


Frequency (1H): 400.15 MHz
Solvent: CDCl3

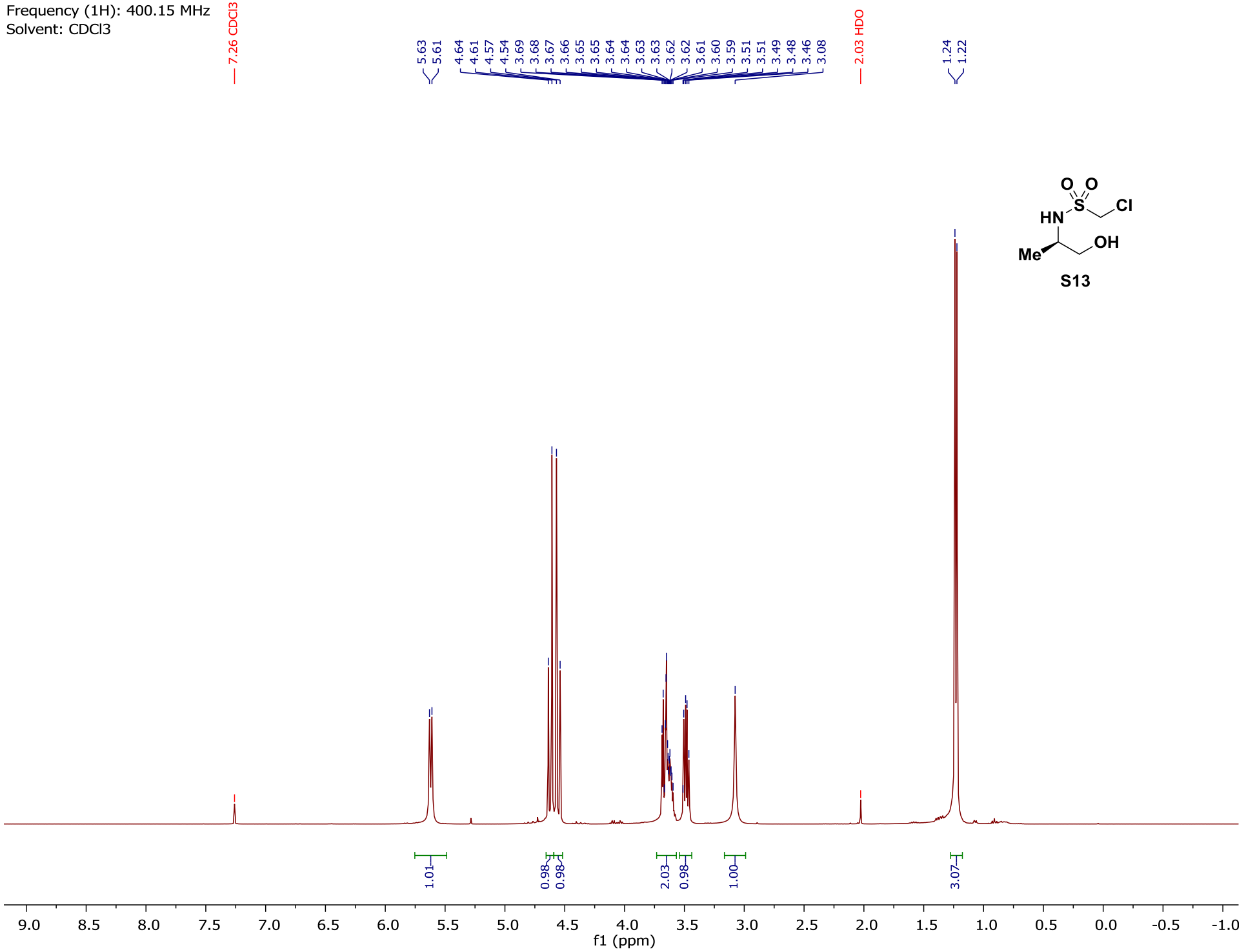


S12

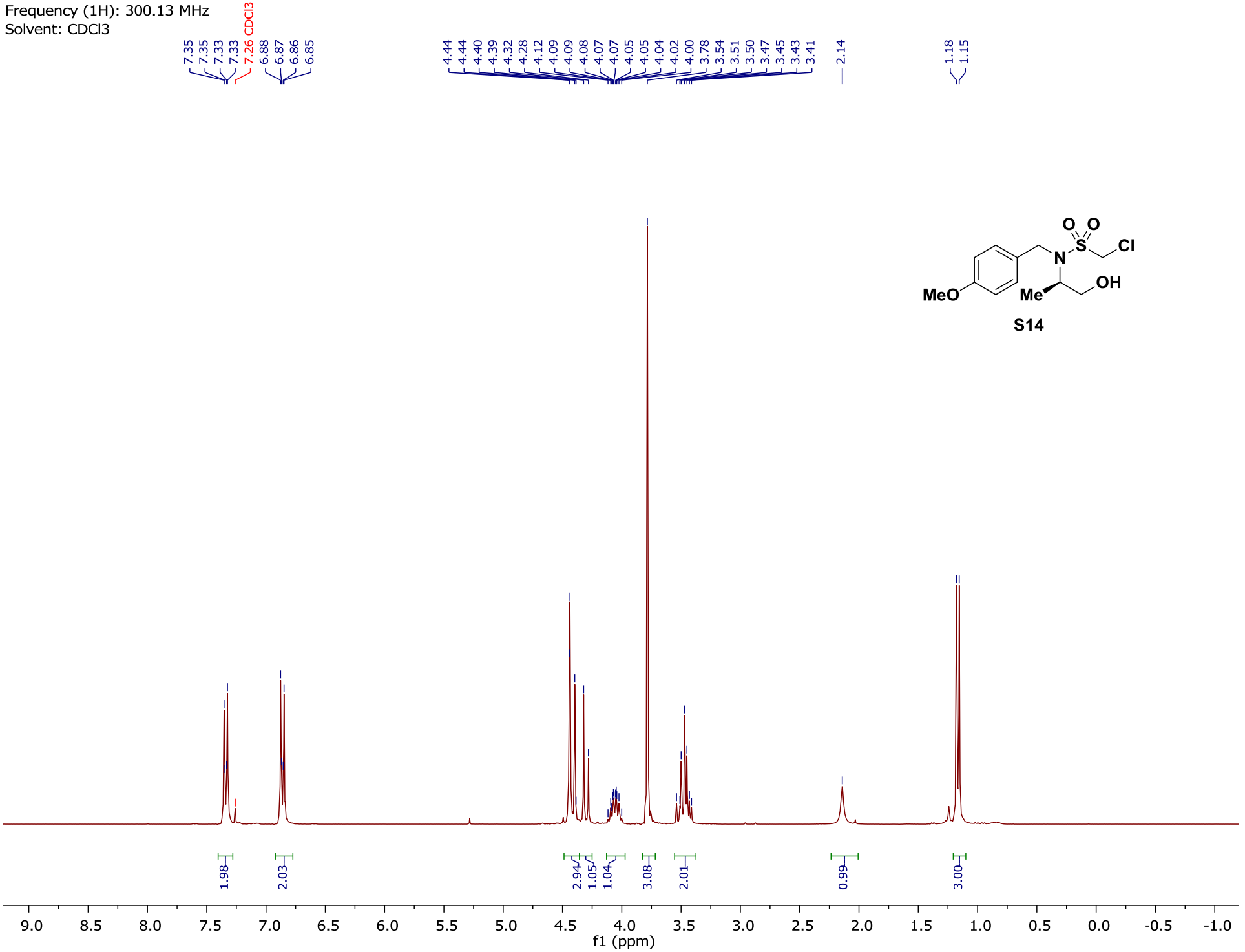
Frequency (1H): 400.15 MHz
Solvent: CDCl3



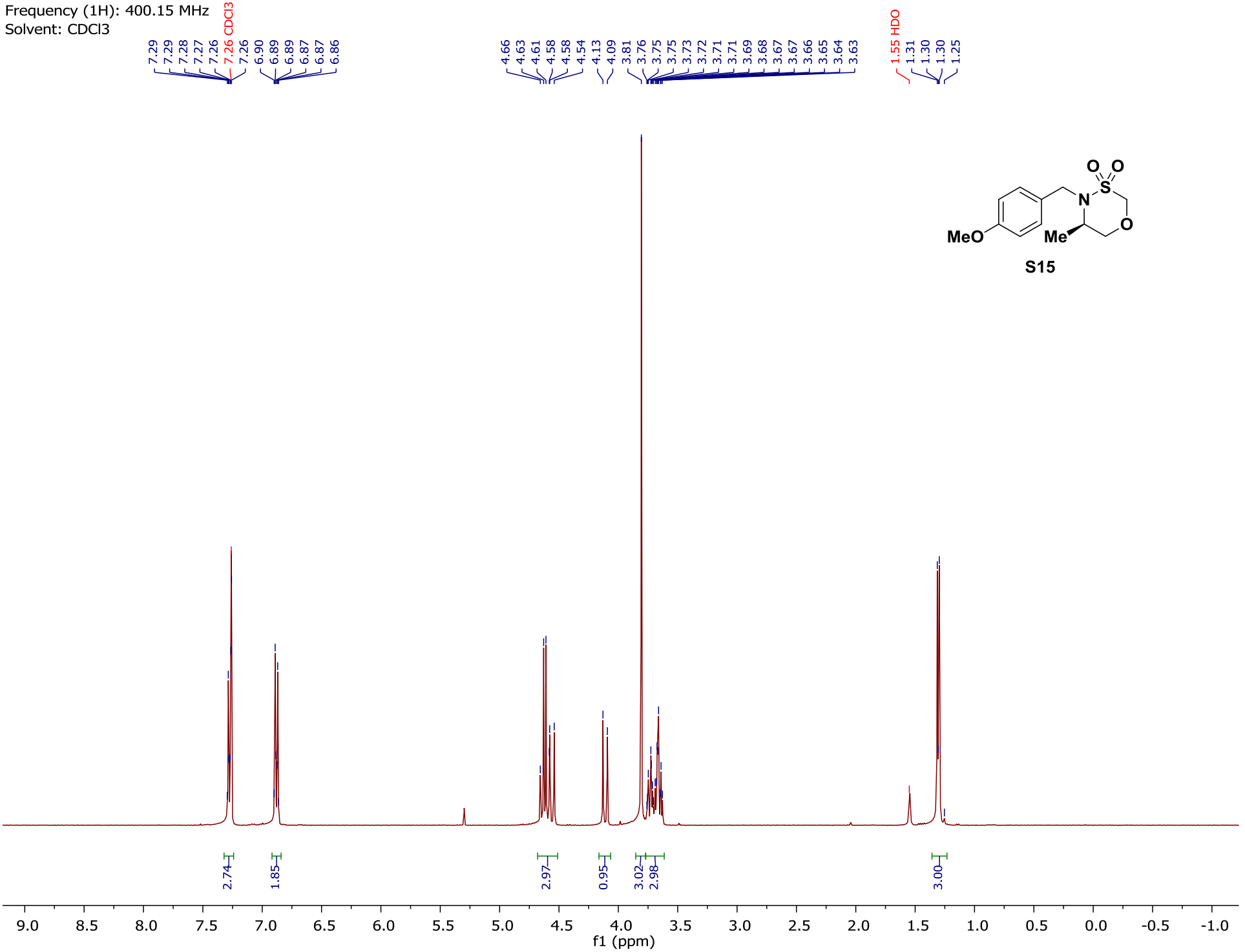
Frequency (1H): 400.15 MHz
Solvent: CDCl3



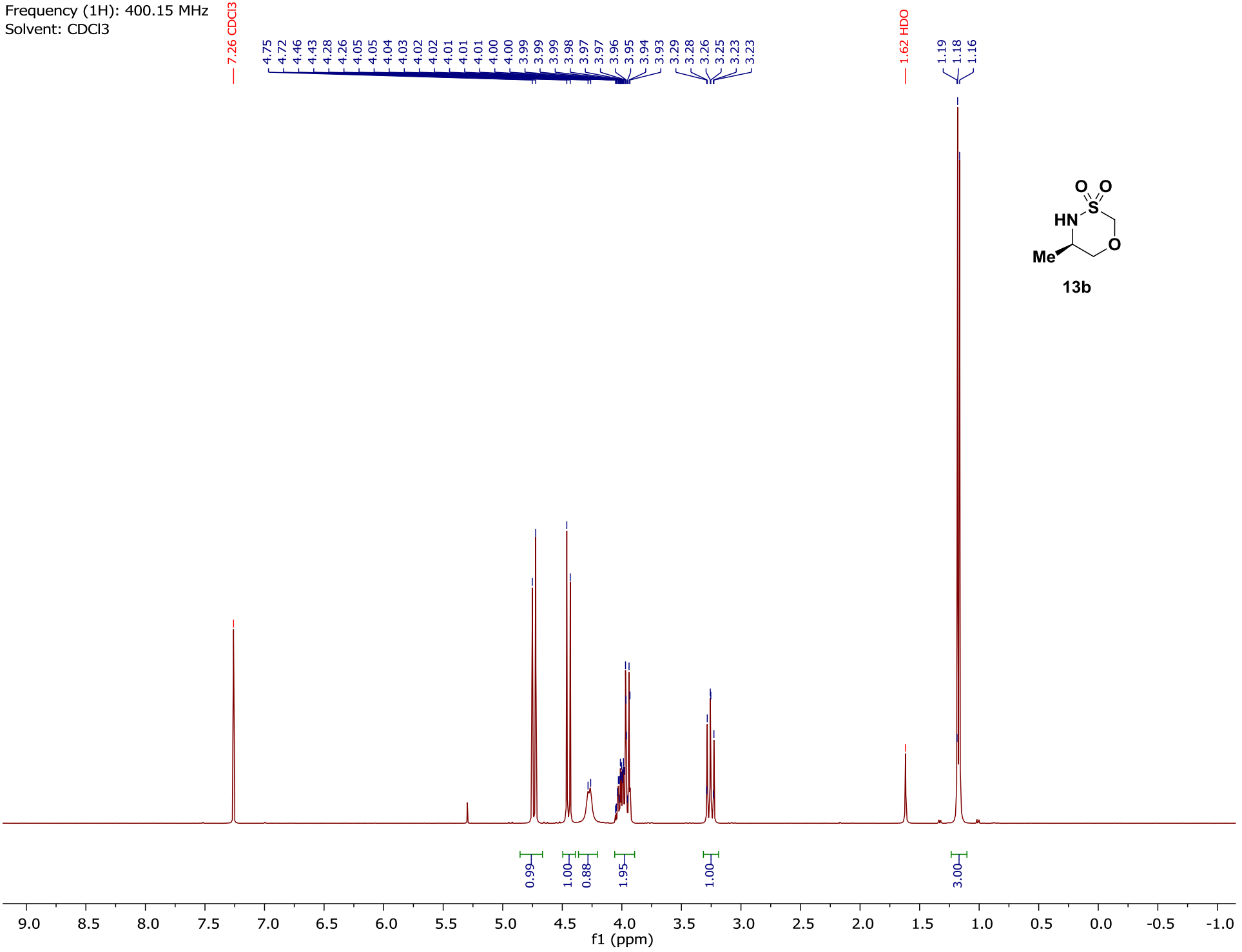
Frequency (1H): 300.13 MHz
Solvent: CDCl3



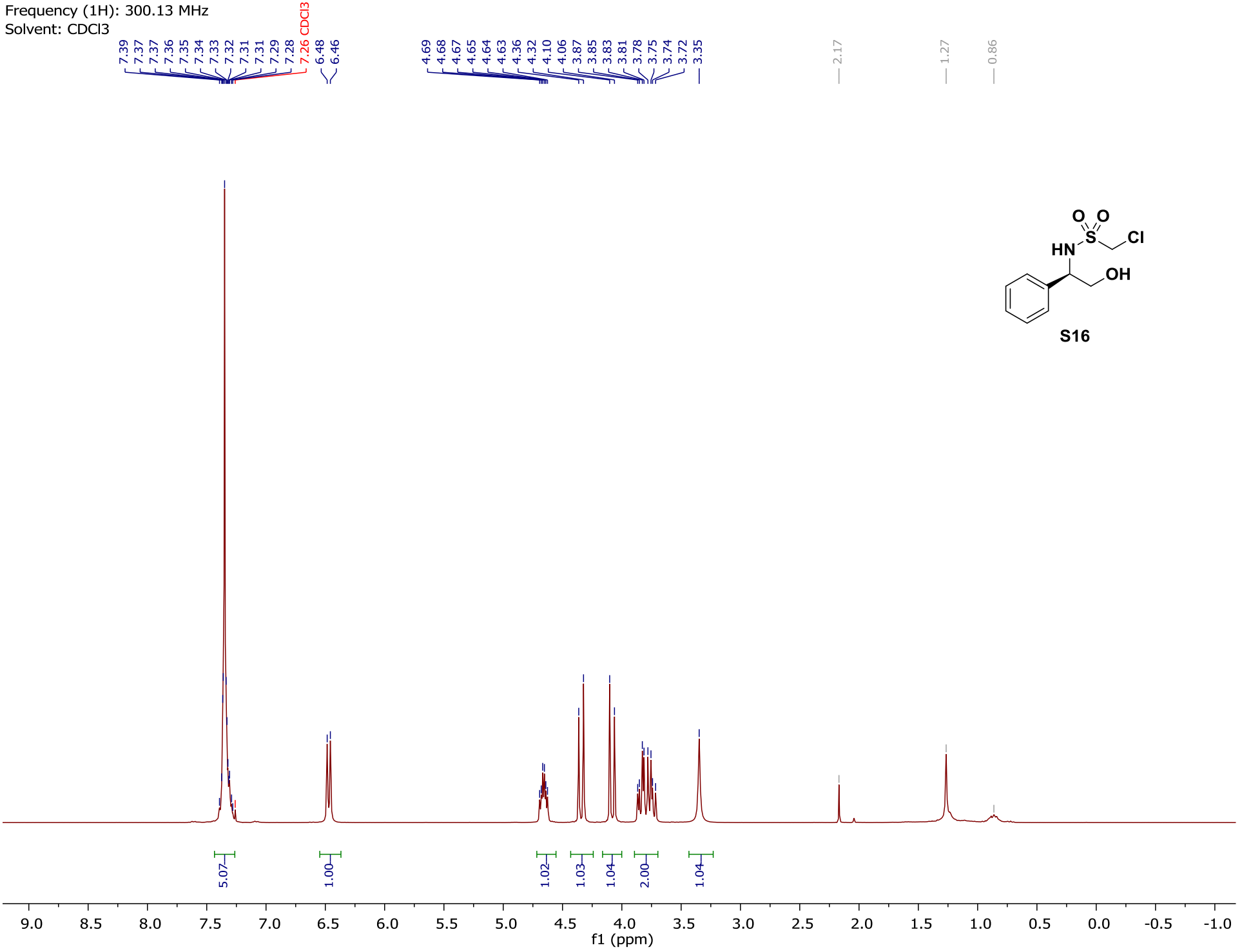
Frequency (1H): 400.15 MHz
Solvent: CDCl3



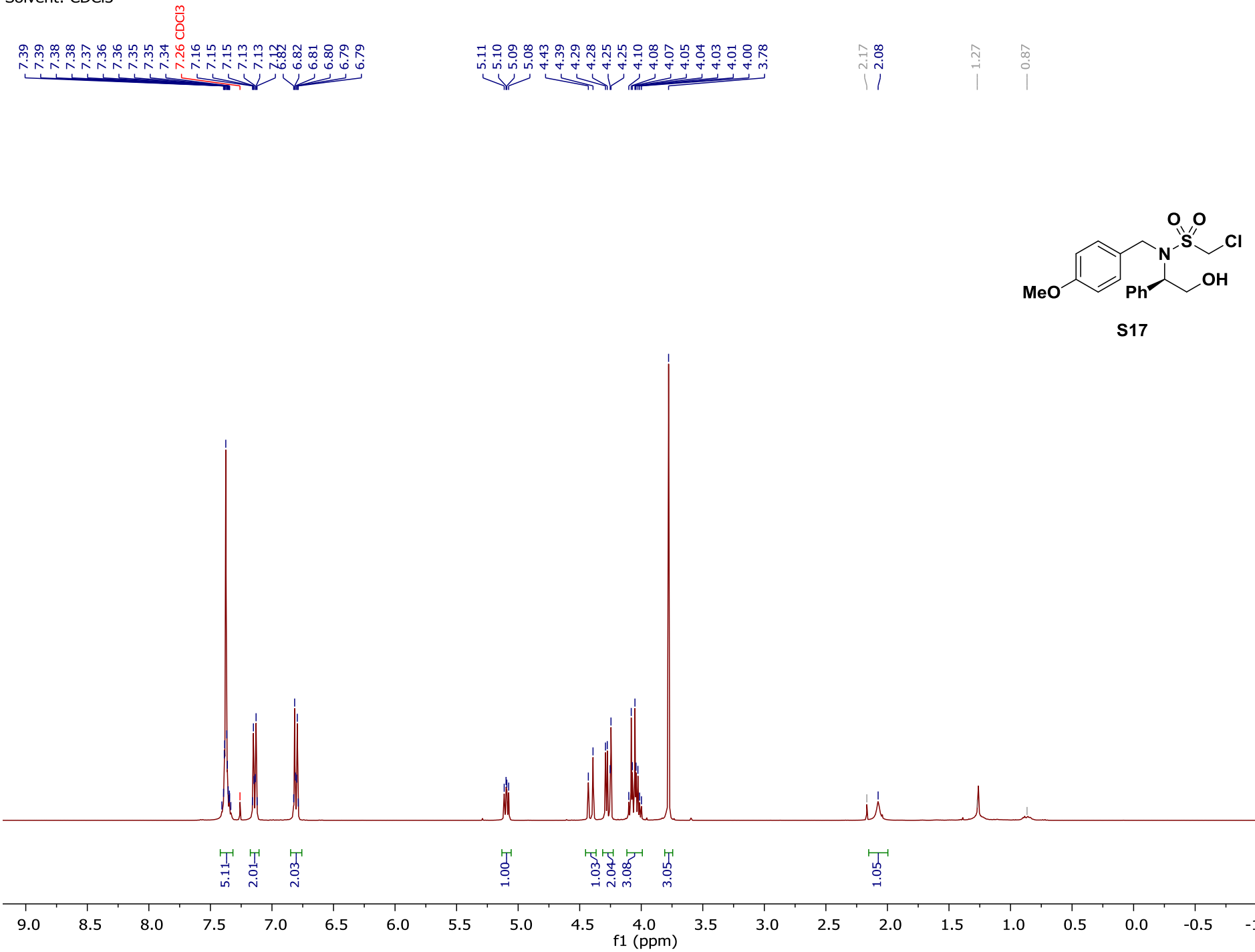
Frequency (1H): 400.15 MHz
Solvent: CDCl3



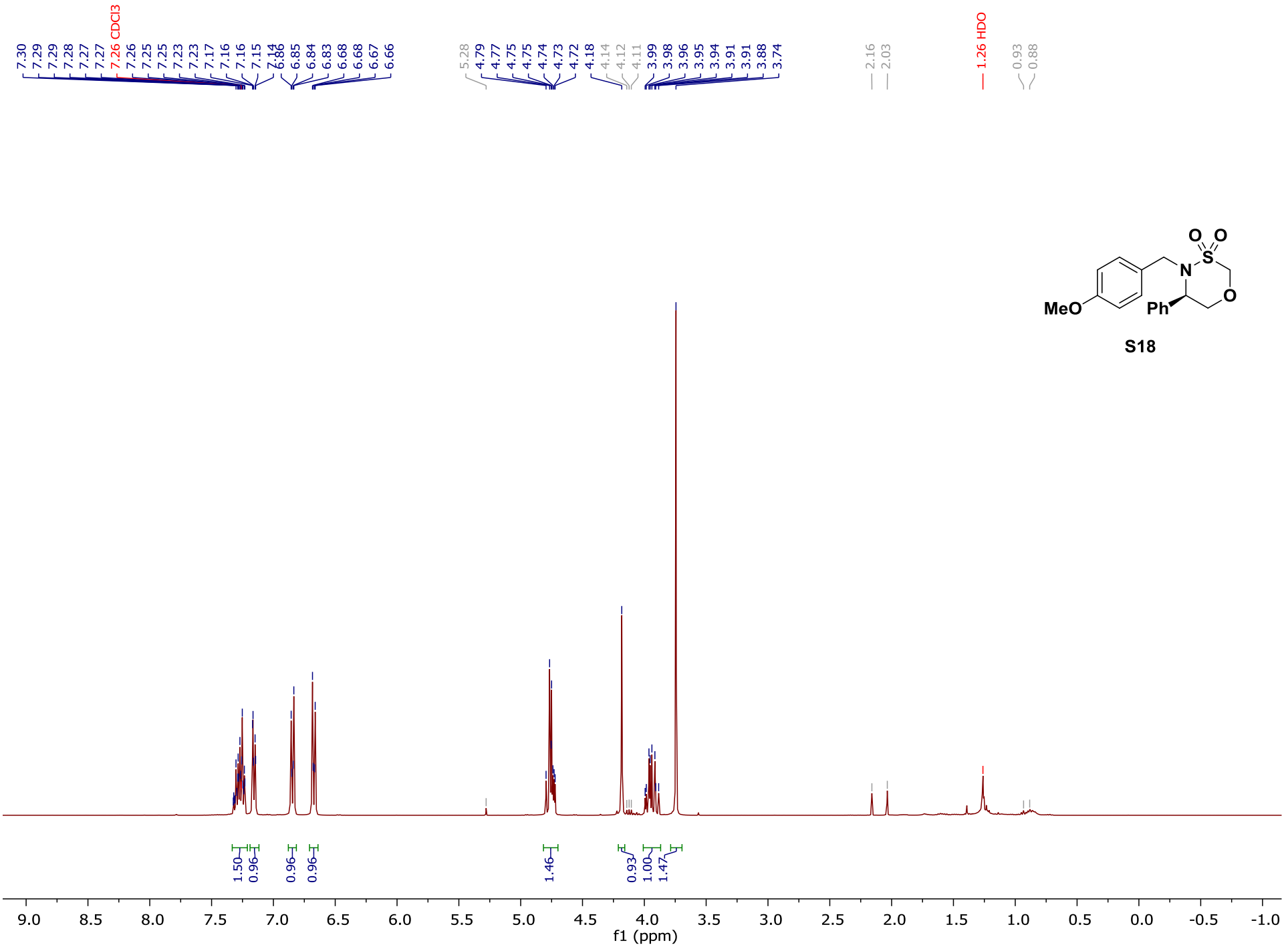
Frequency (1H): 300.13 MHz
Solvent: CDCl3



Frequency (1H): 400.15 MHz
Solvent: CDCl3



Frequency (1H): 400.15 MHz
Solvent: CDCl3

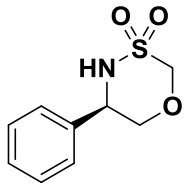


Frequency (1H): 300.13 MHz
Solvent: CDCl3

7.43 7.42 7.41 7.41 7.41 7.40 7.40 7.39 7.39 7.38 7.38 7.37 7.35 7.33 7.32 7.31 7.31 7.30 7.30 7.26 CDCl3 5.03 5.02 5.01 5.00 4.99 4.97 4.96 4.81 4.81 4.77 4.77 4.64 4.62 4.62 4.60 4.59 4.58 4.18 4.17 4.14 4.13 3.70 3.67 3.66 3.63 3.48

1.59 HDO

1.25



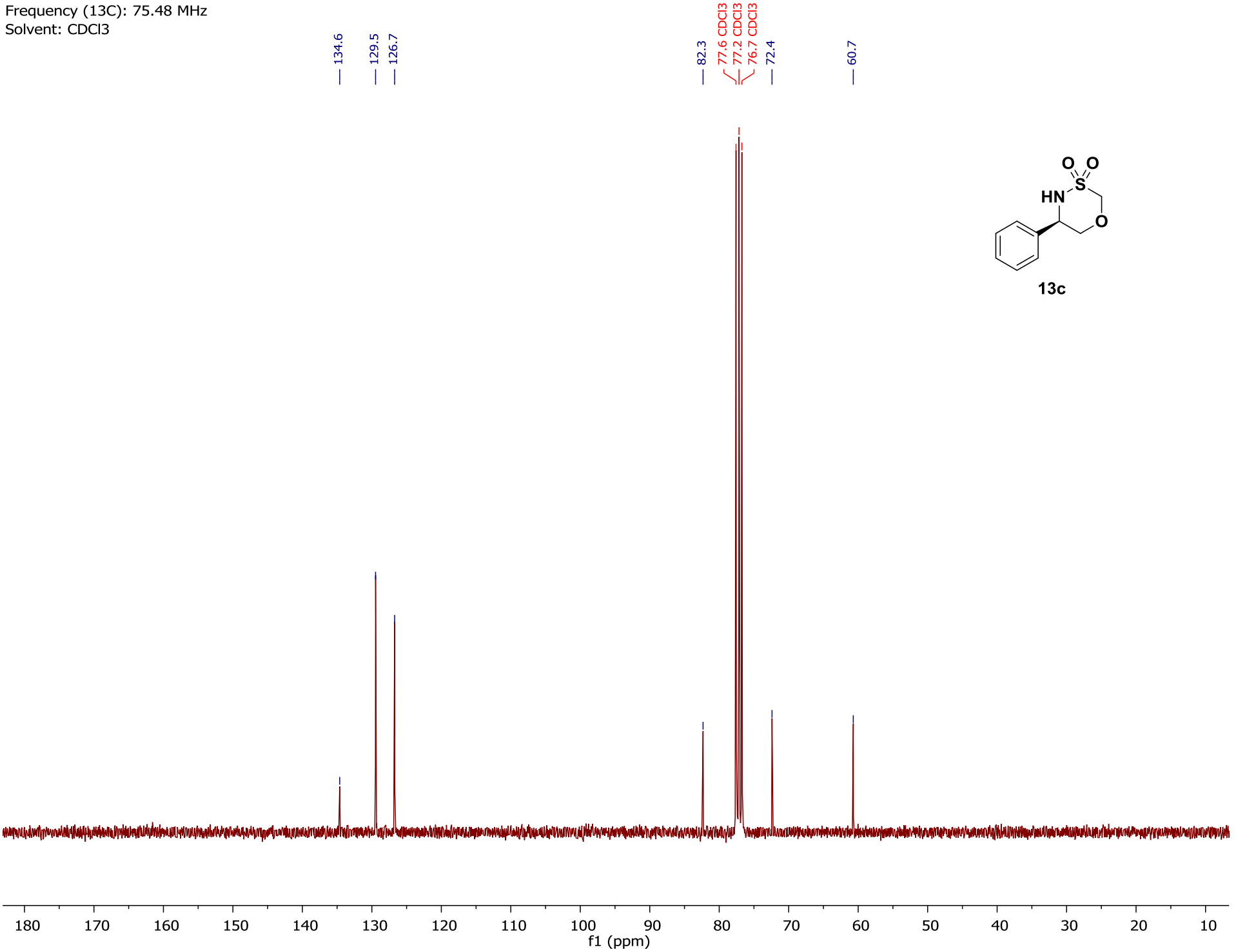
13c

5.00 1.00 1.02 1.92 1.00 1.01

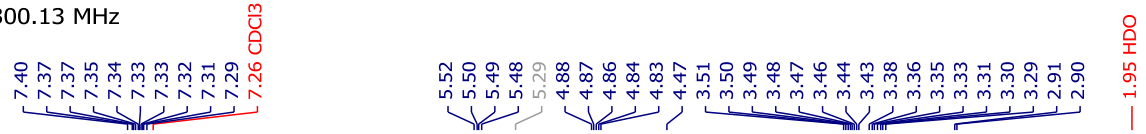
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

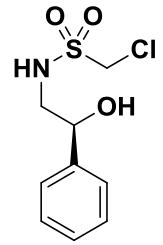
f1 (ppm)

Frequency (13C): 75.48 MHz
Solvent: CDCl3

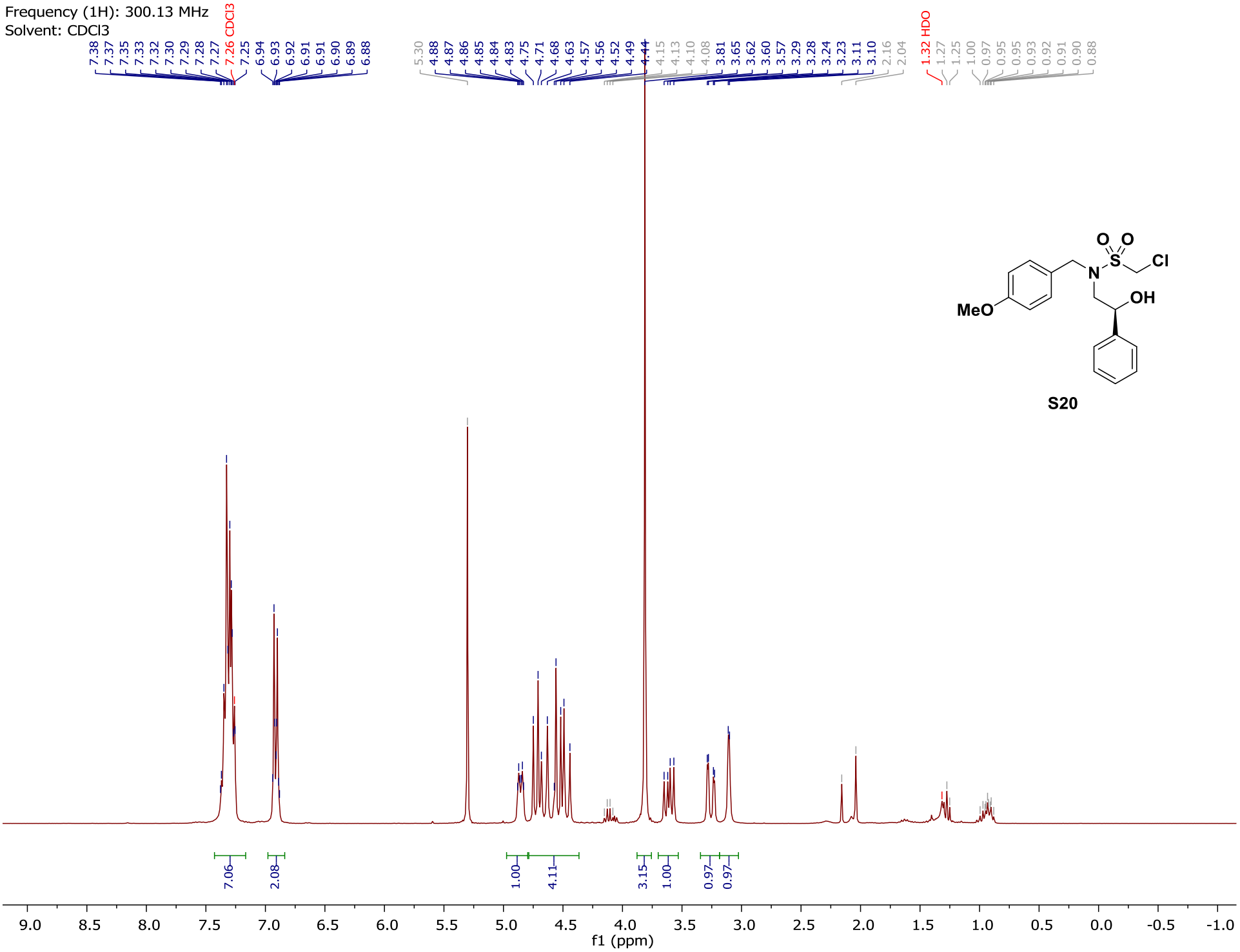


Frequency (1H): 300.13 MHz
Solvent: CDCl3

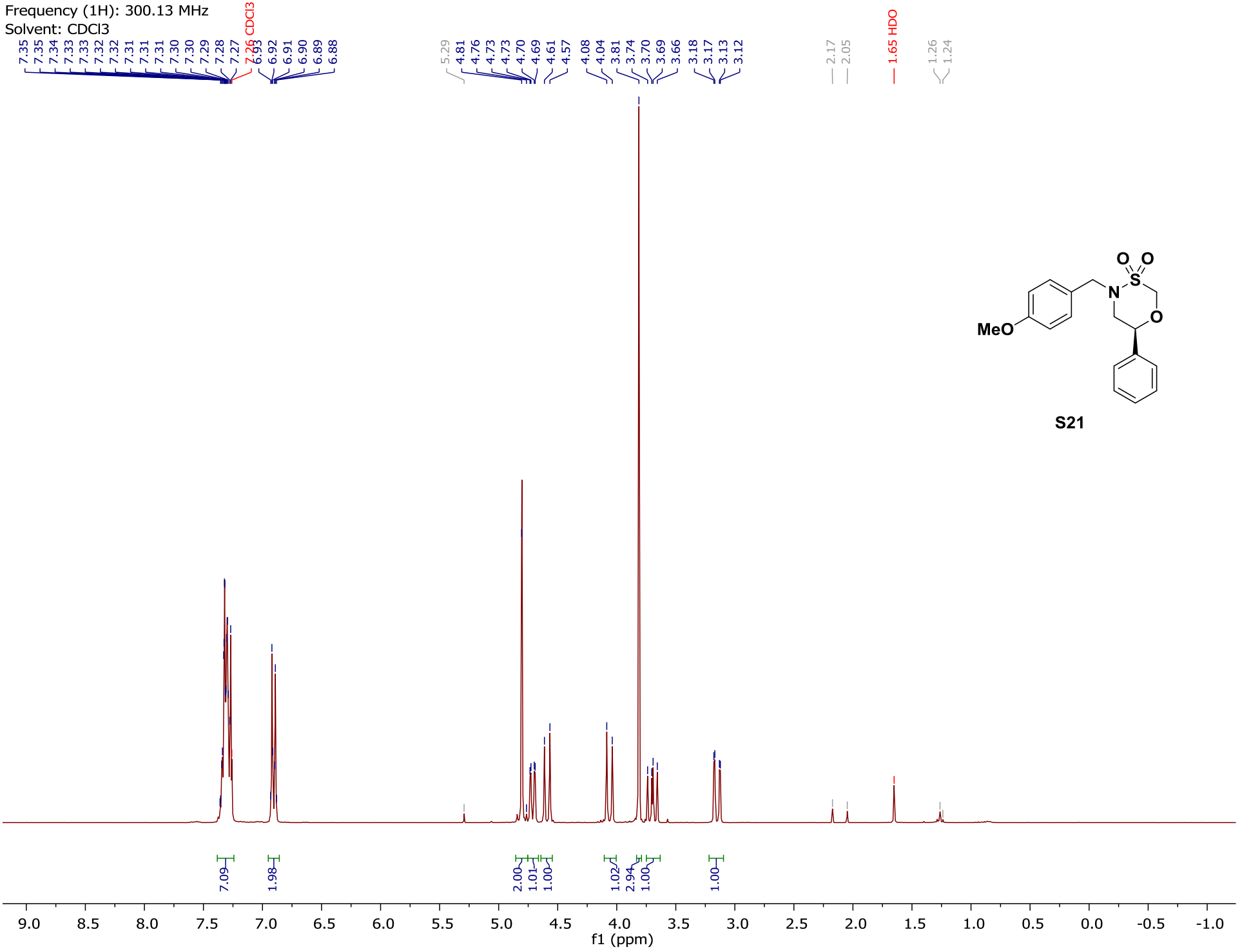




S19

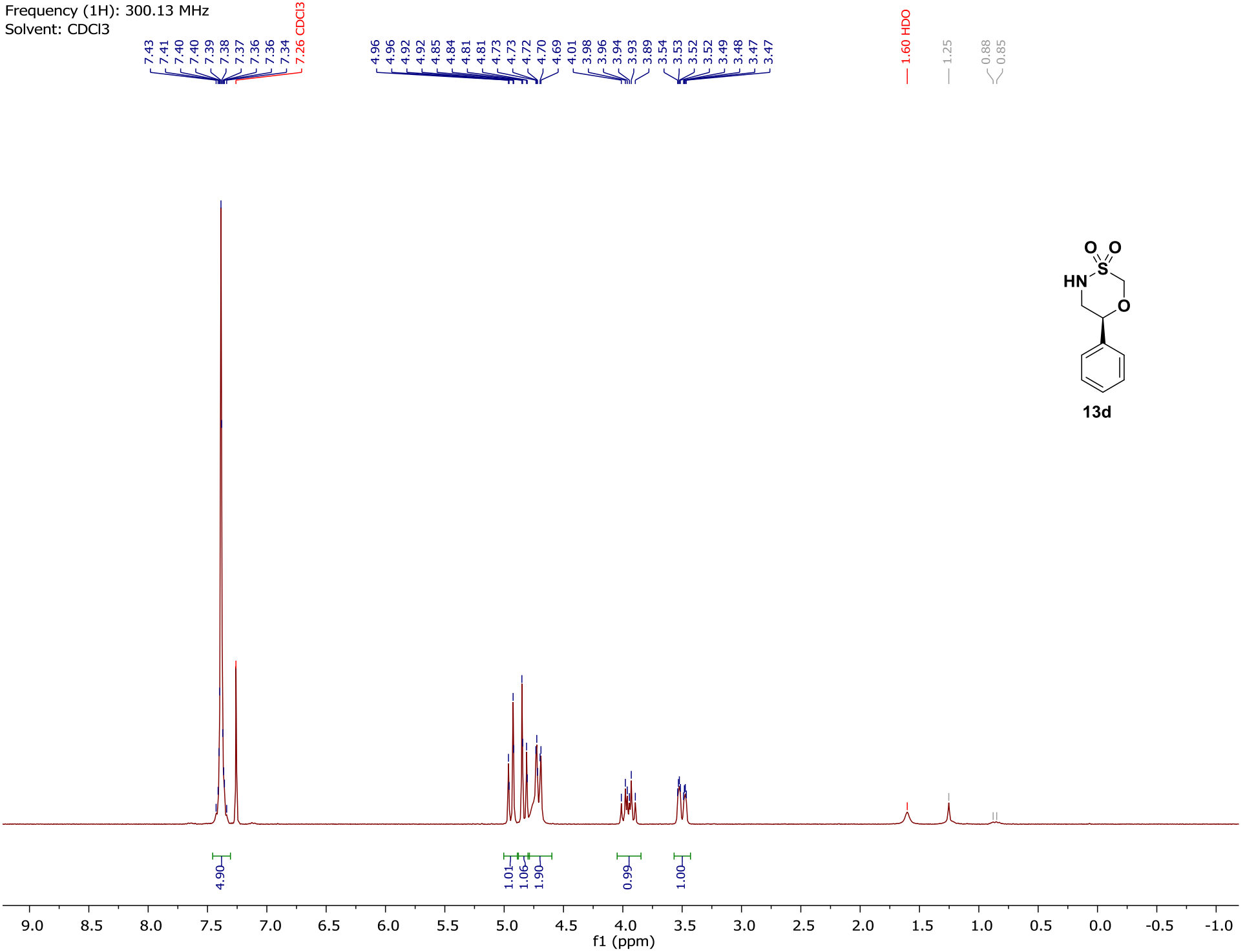

Frequency (1H): 300.13 MHz
Solvent: CDCl3
CDCl3
HDO
MeO
OH
Cl
S20
f1 (ppm)

Frequency (1H): 300.13 MHz
Solvent: CDCl3

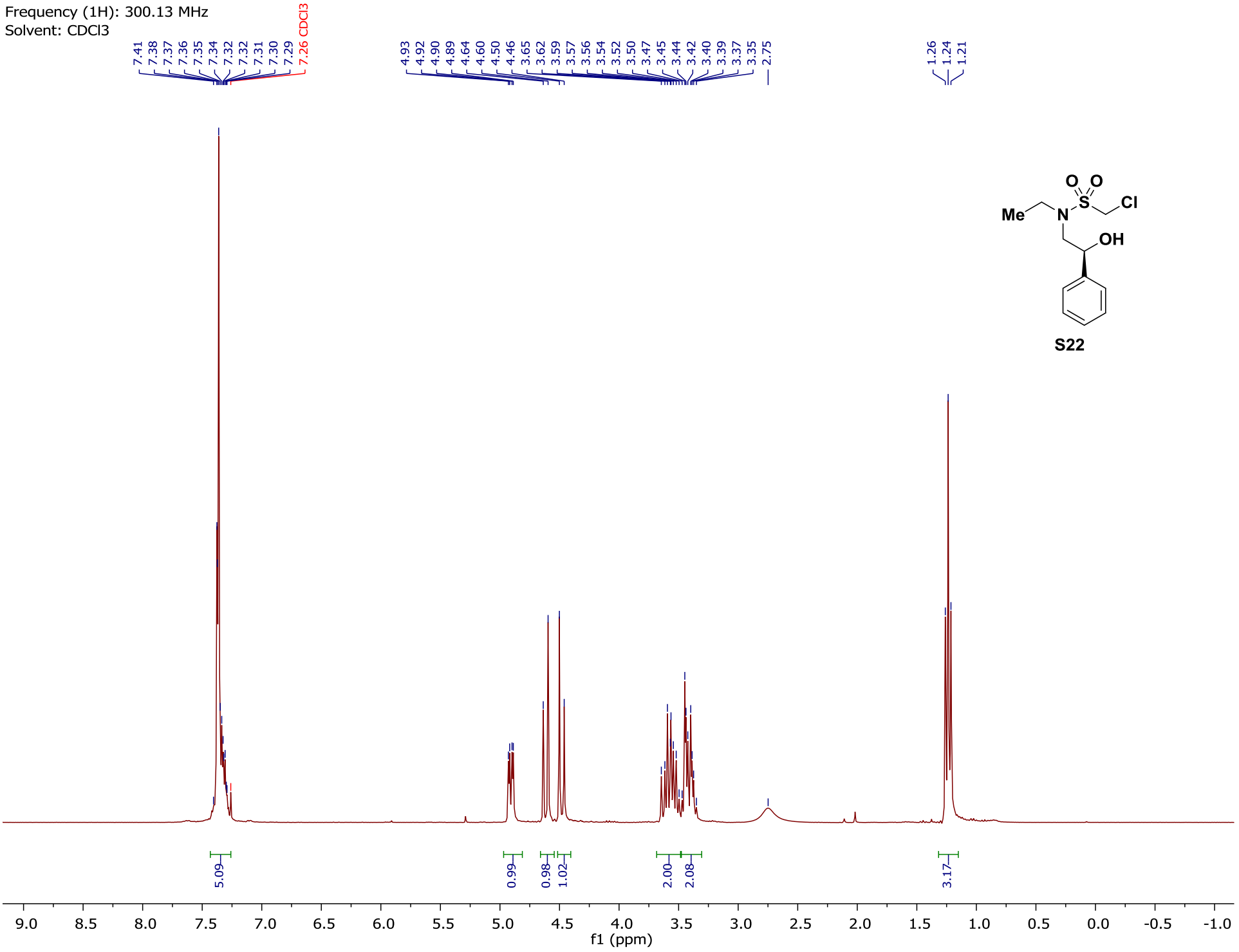


S21

Frequency (1H): 300.13 MHz
Solvent: CDCl3

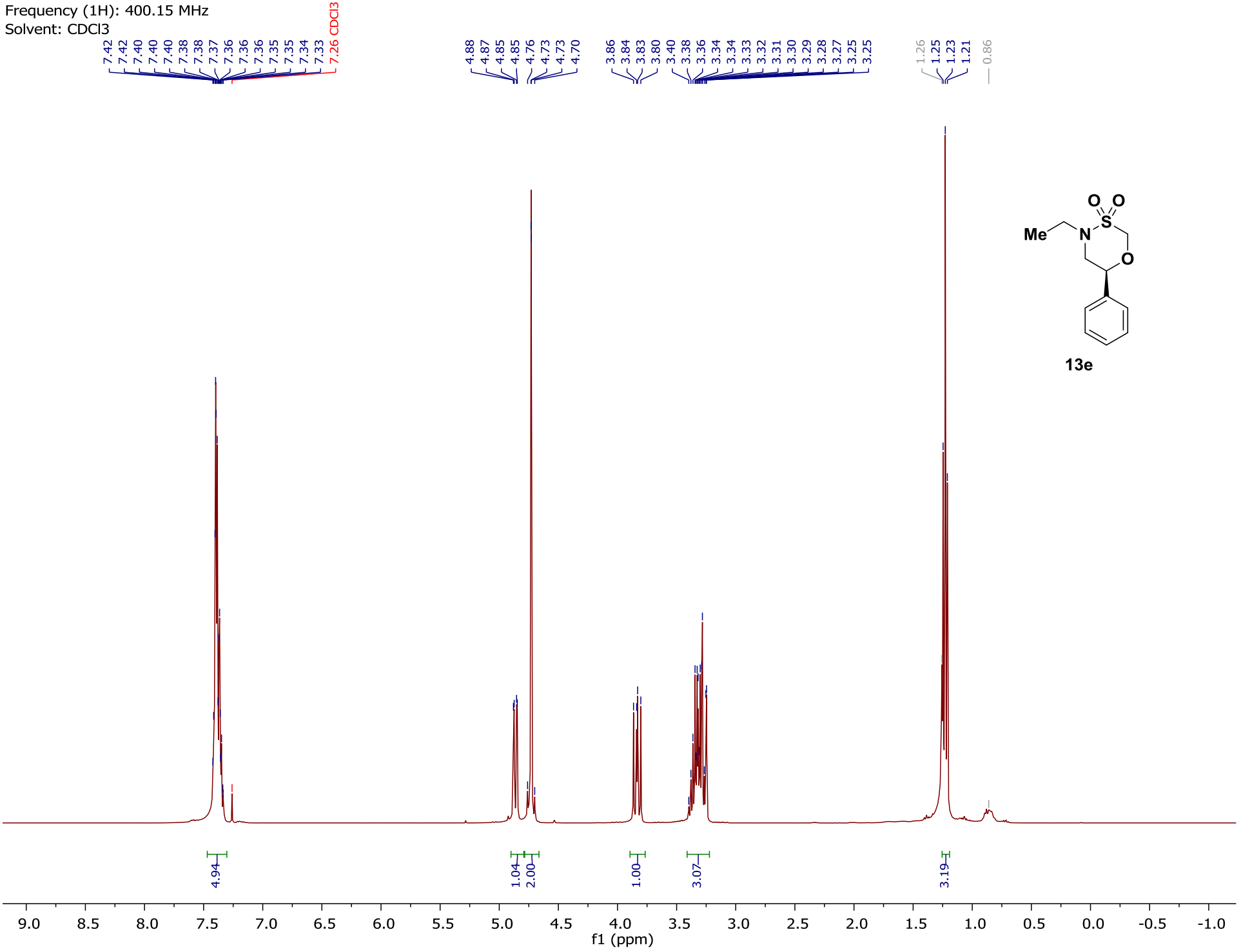


Frequency (1H): 300.13 MHz
Solvent: CDCl3

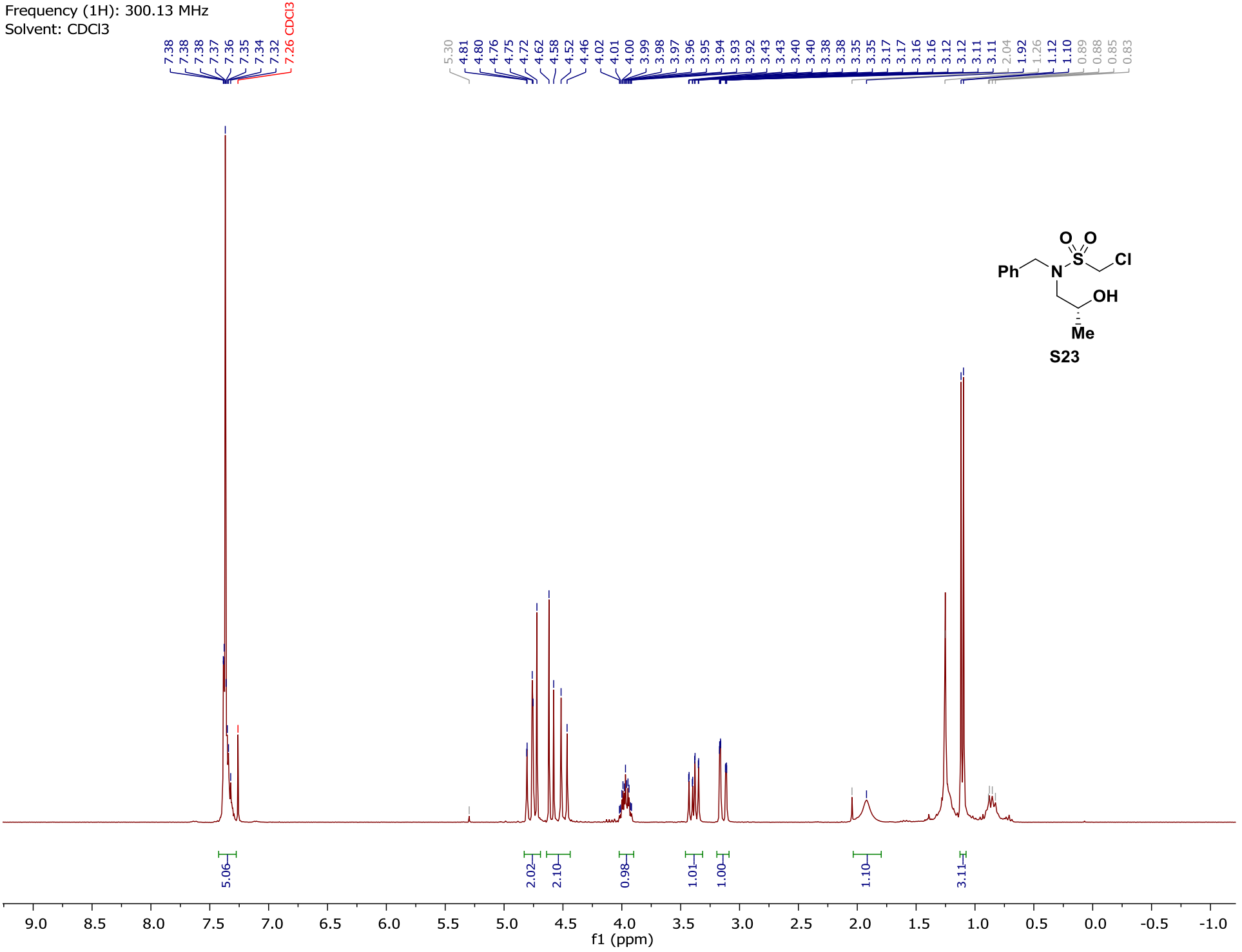


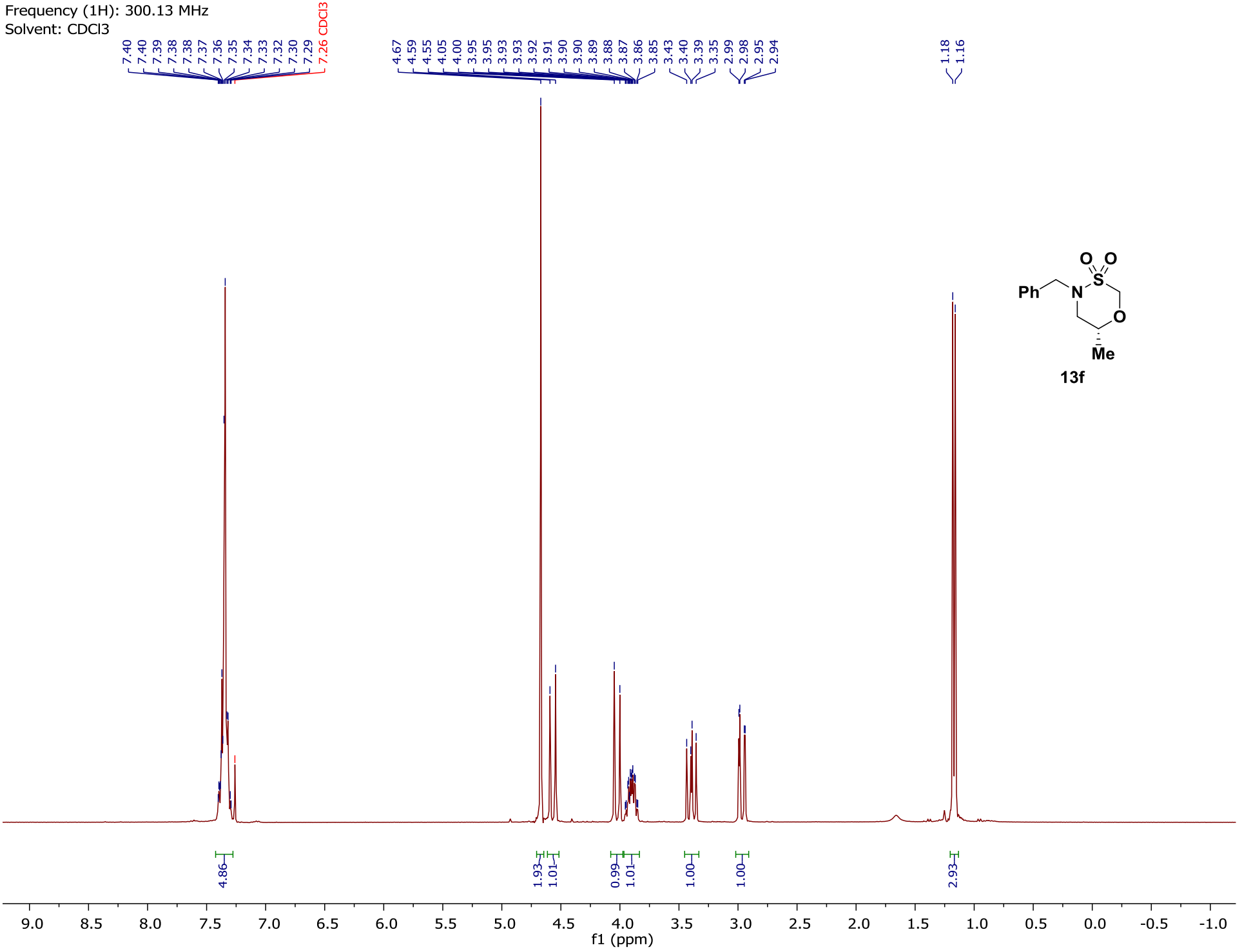
S22

Frequency (1H): 400.15 MHz
Solvent: CDCl3

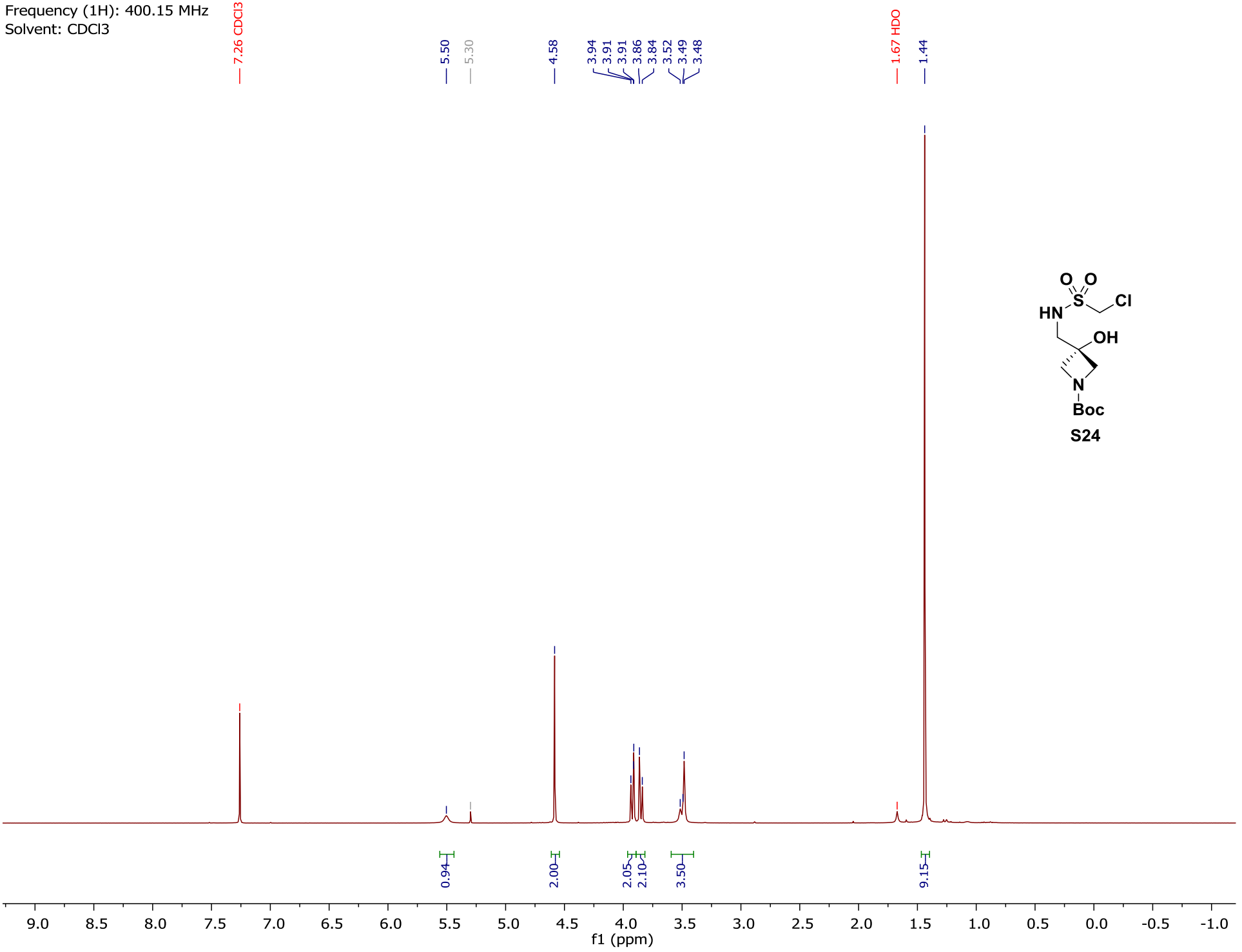


Frequency (1H): 300.13 MHz
Solvent: CDCl3



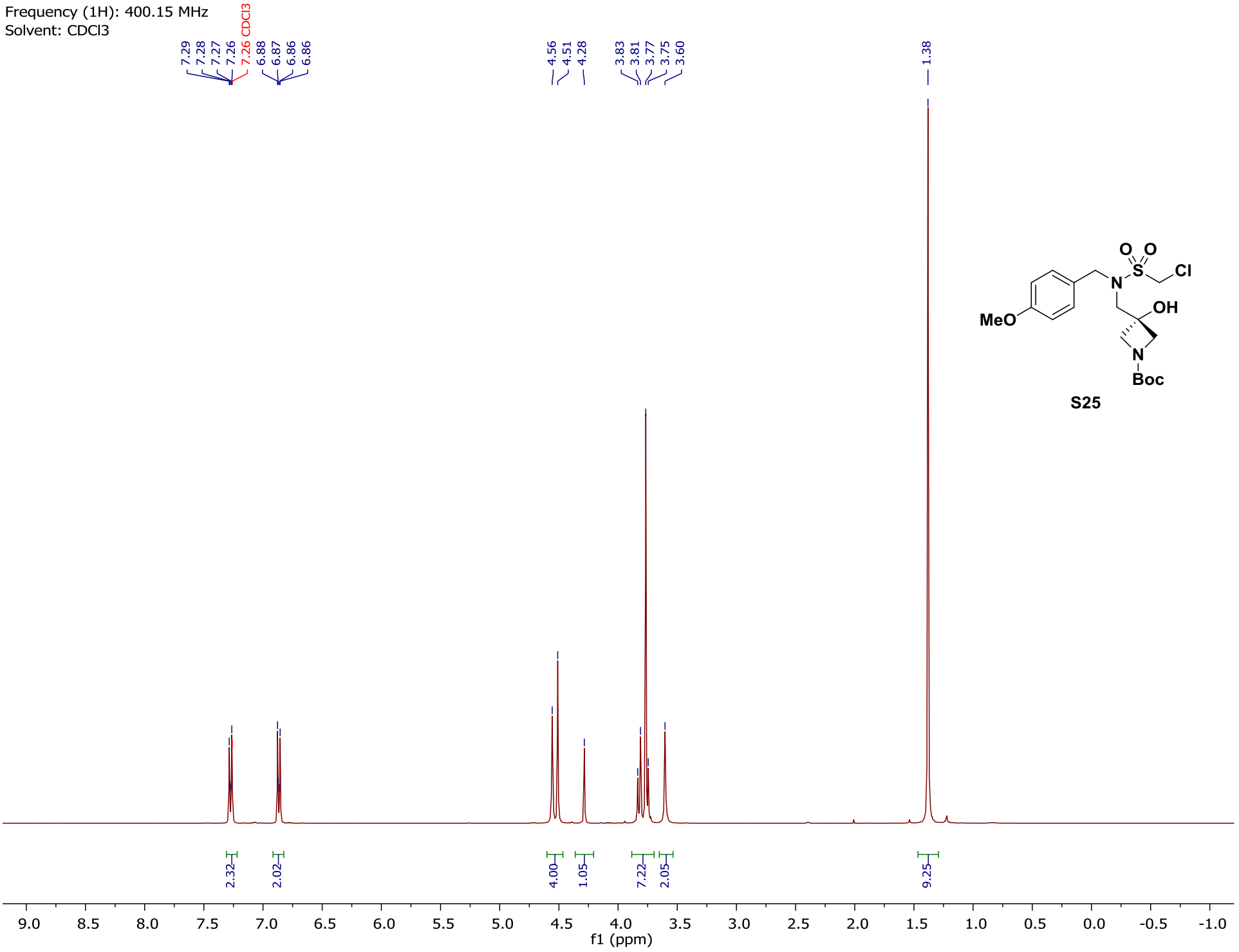

Frequency (1H): 300.13 MHz
Solvent: CDCl3
7.40
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.34
7.33
7.32
7.30
7.29
7.26 CDCl3
4.67
4.59
4.55
4.05
4.00
3.95
3.95
3.93
3.93
3.92
3.91
3.90
3.90
3.89
3.88
3.87
3.86
3.85
3.43
3.40
3.39
3.35
2.99
2.98
2.95
2.94
1.18
1.16
Ph
N
S
O
O
O
Me
13f
4.86
1.93
1.01
0.99
1.01
1.00
1.00
2.93
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
-1.0
f1 (ppm)

Frequency (1H): 400.15 MHz
Solvent: CDCl3



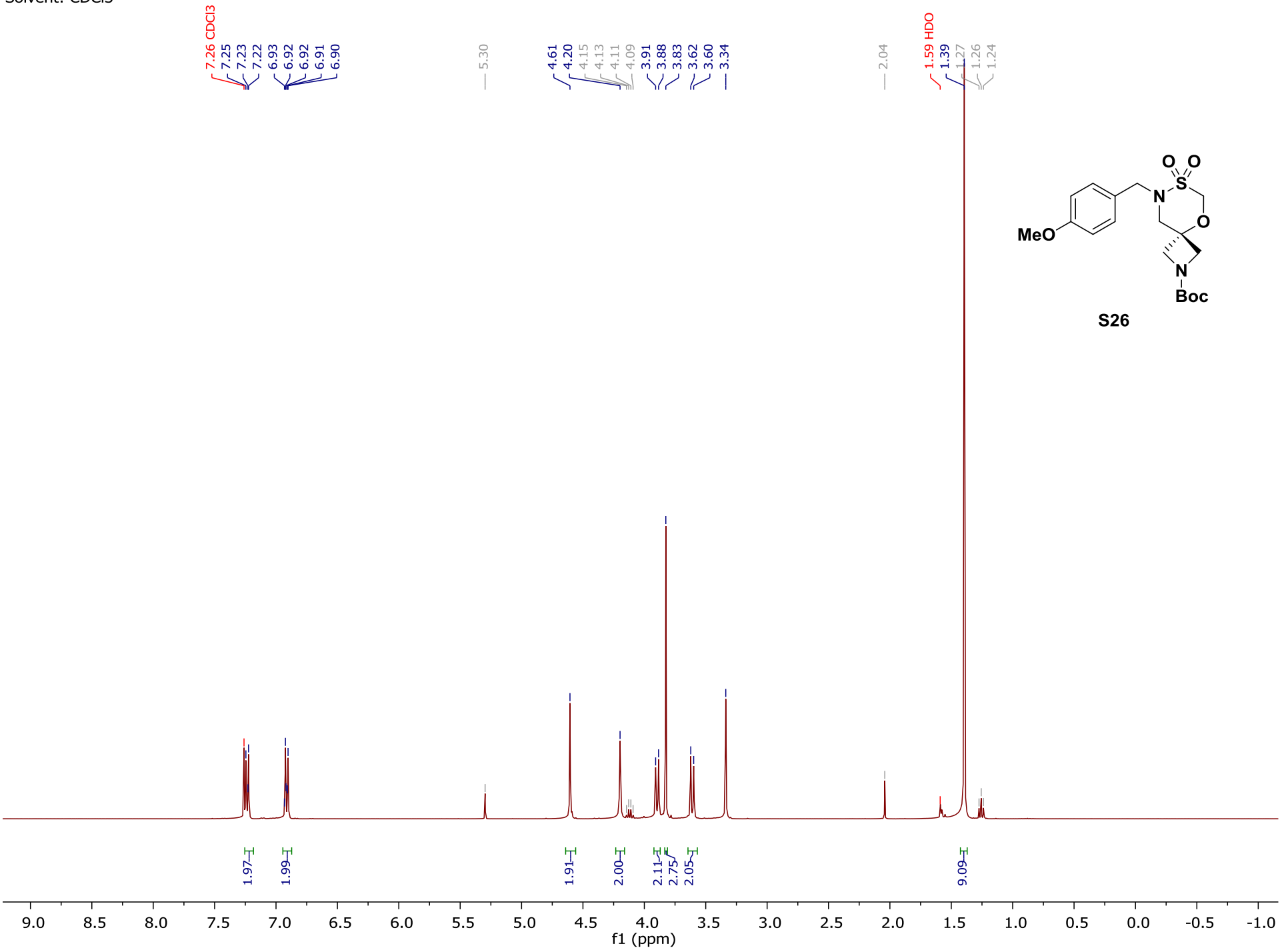
S24

Frequency (1H): 400.15 MHz
Solvent: CDCl3



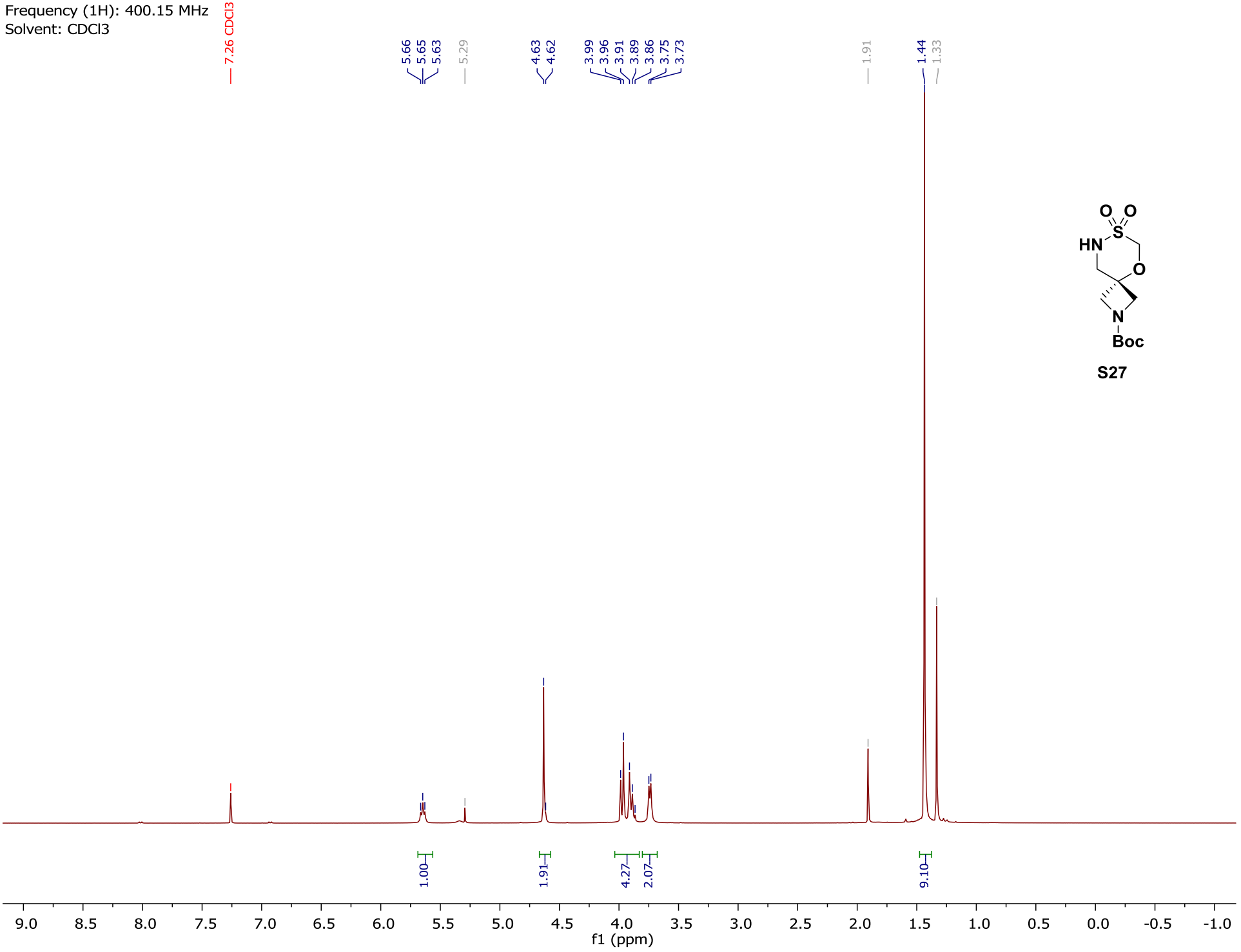
S25

Frequency (1H): 400.15 MHz
Solvent: CDCl3



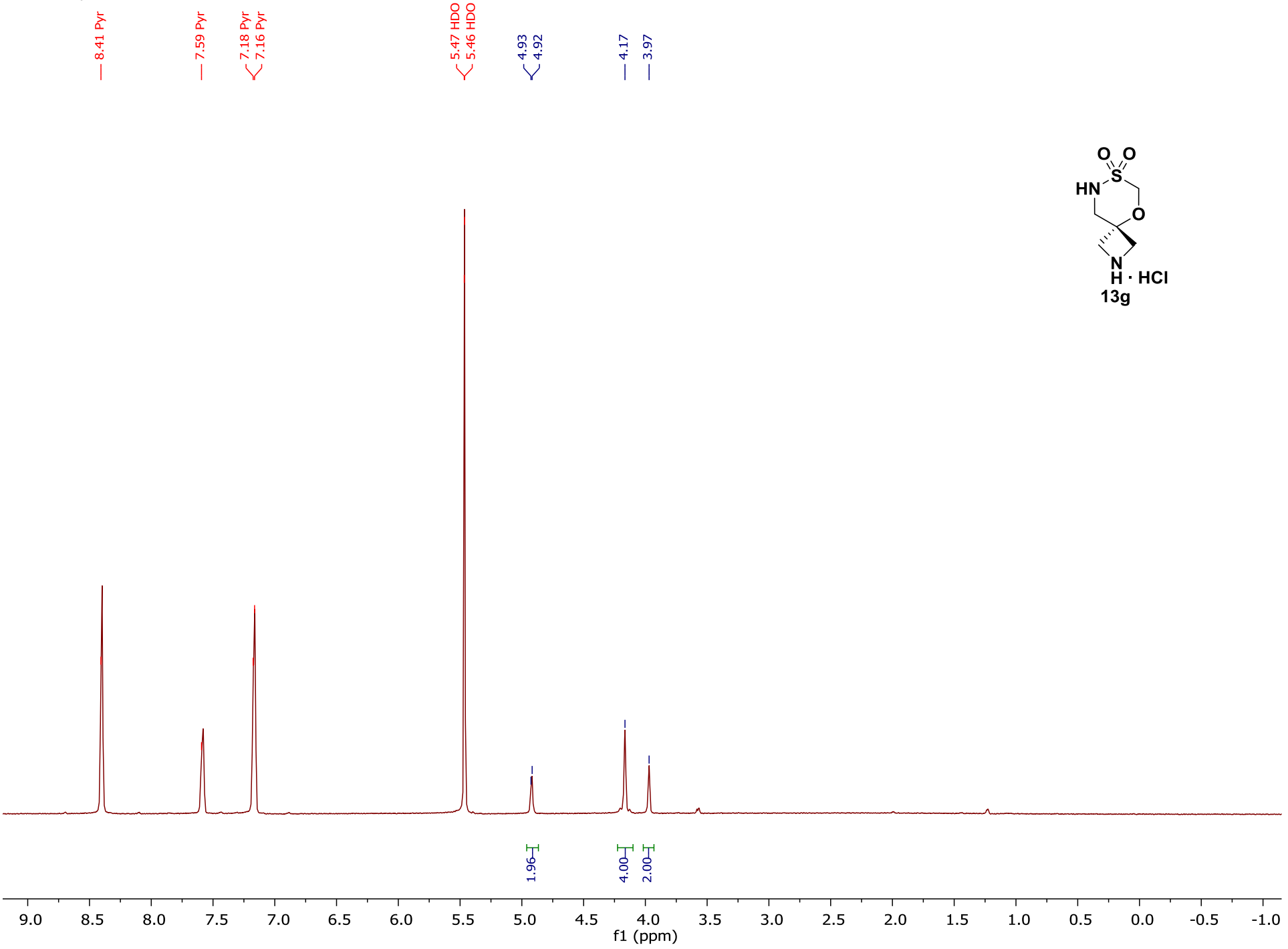
S26

Frequency (1H): 400.15 MHz
Solvent: CDCl3



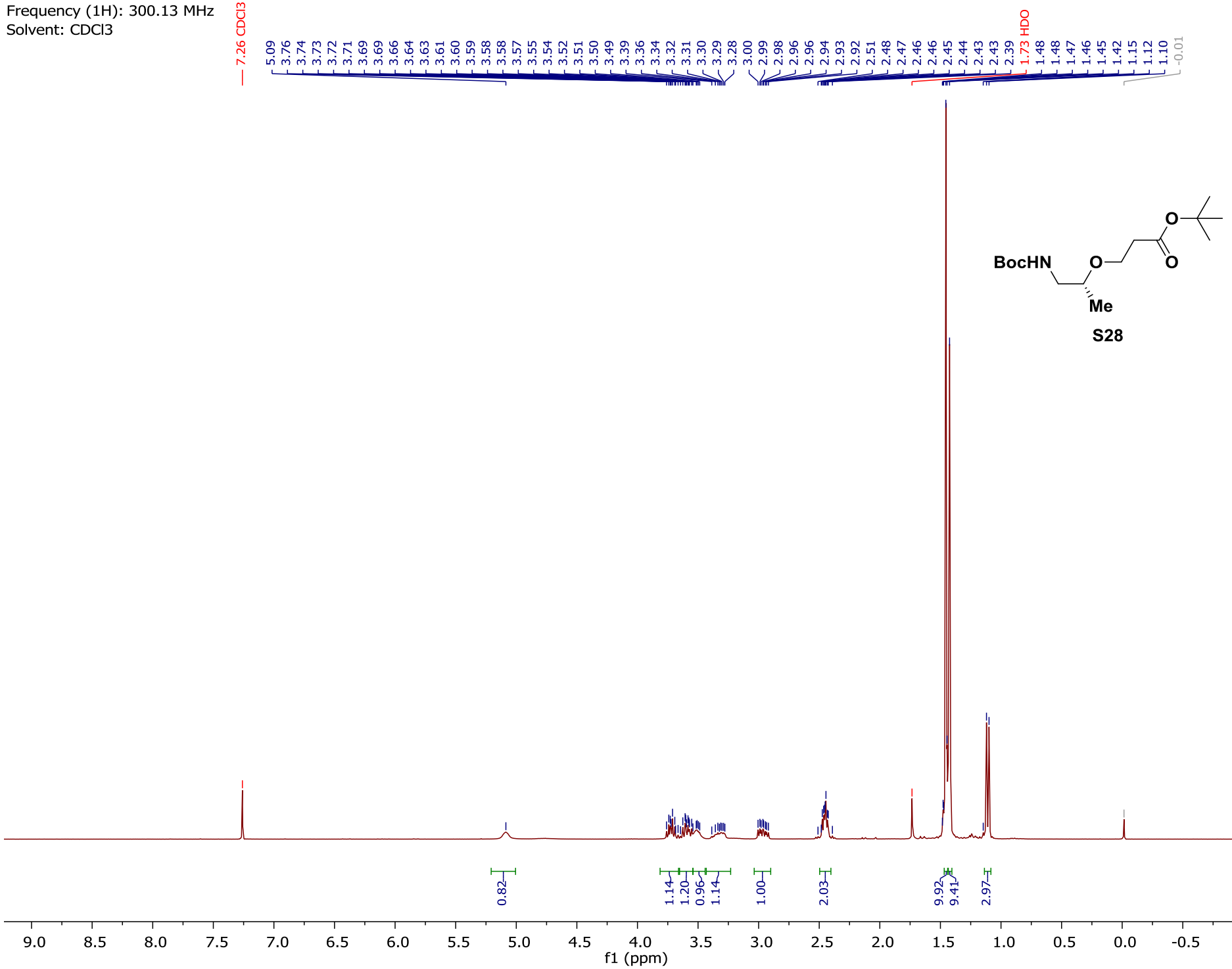
S27

Frequency (1H): 300.17 MHz
Solvent: Pyr-D2O

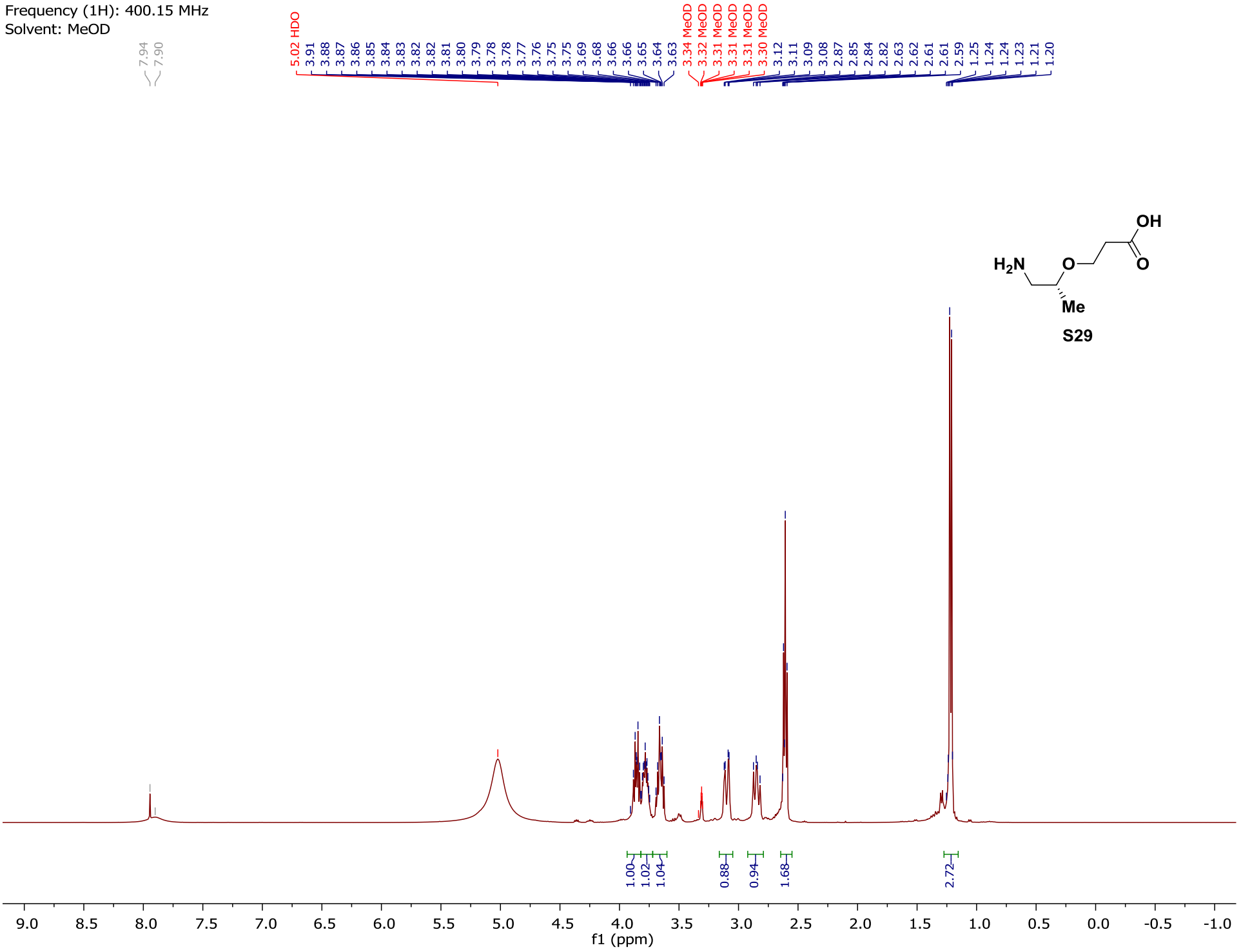


13g

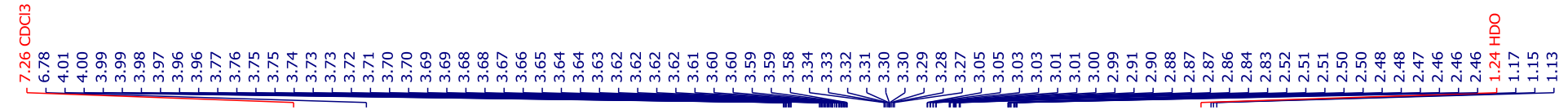
Frequency (1H): 300.13 MHz
Solvent: CDCl3

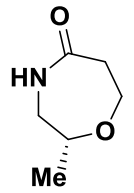


Frequency (1H): 400.15 MHz
Solvent: MeOD

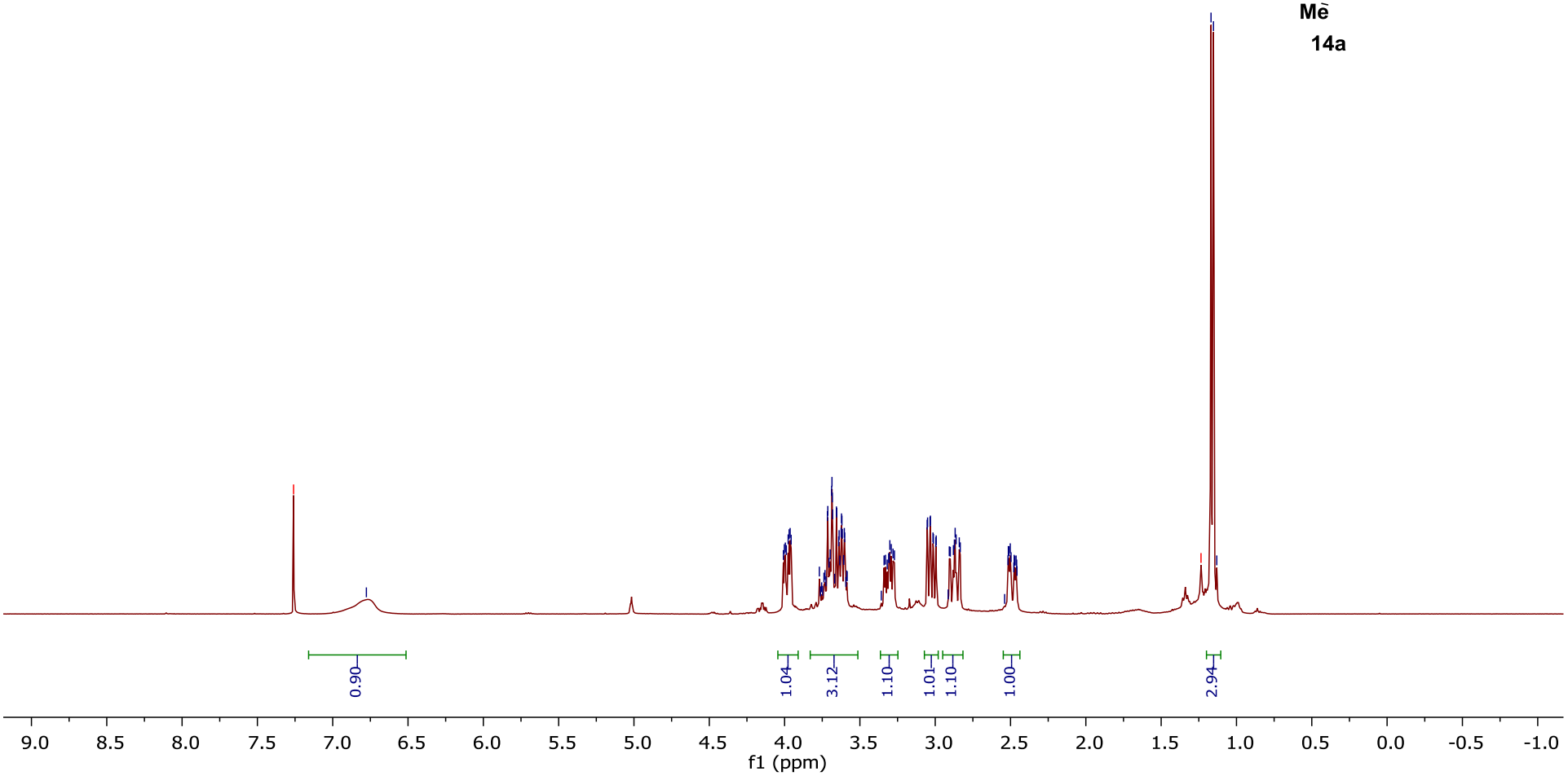


Frequency (1H): 400.15 MHz
Solvent: CDCl3

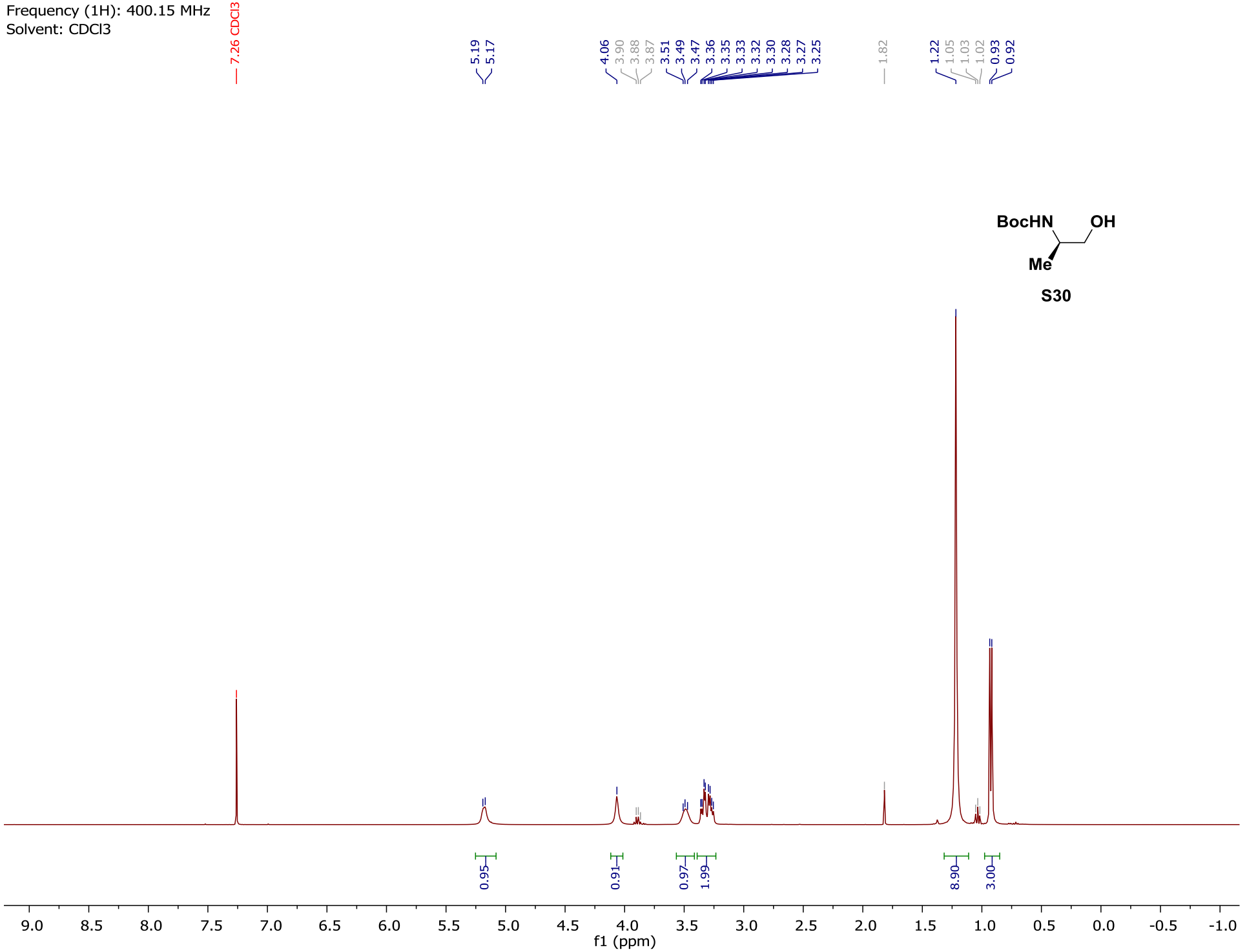




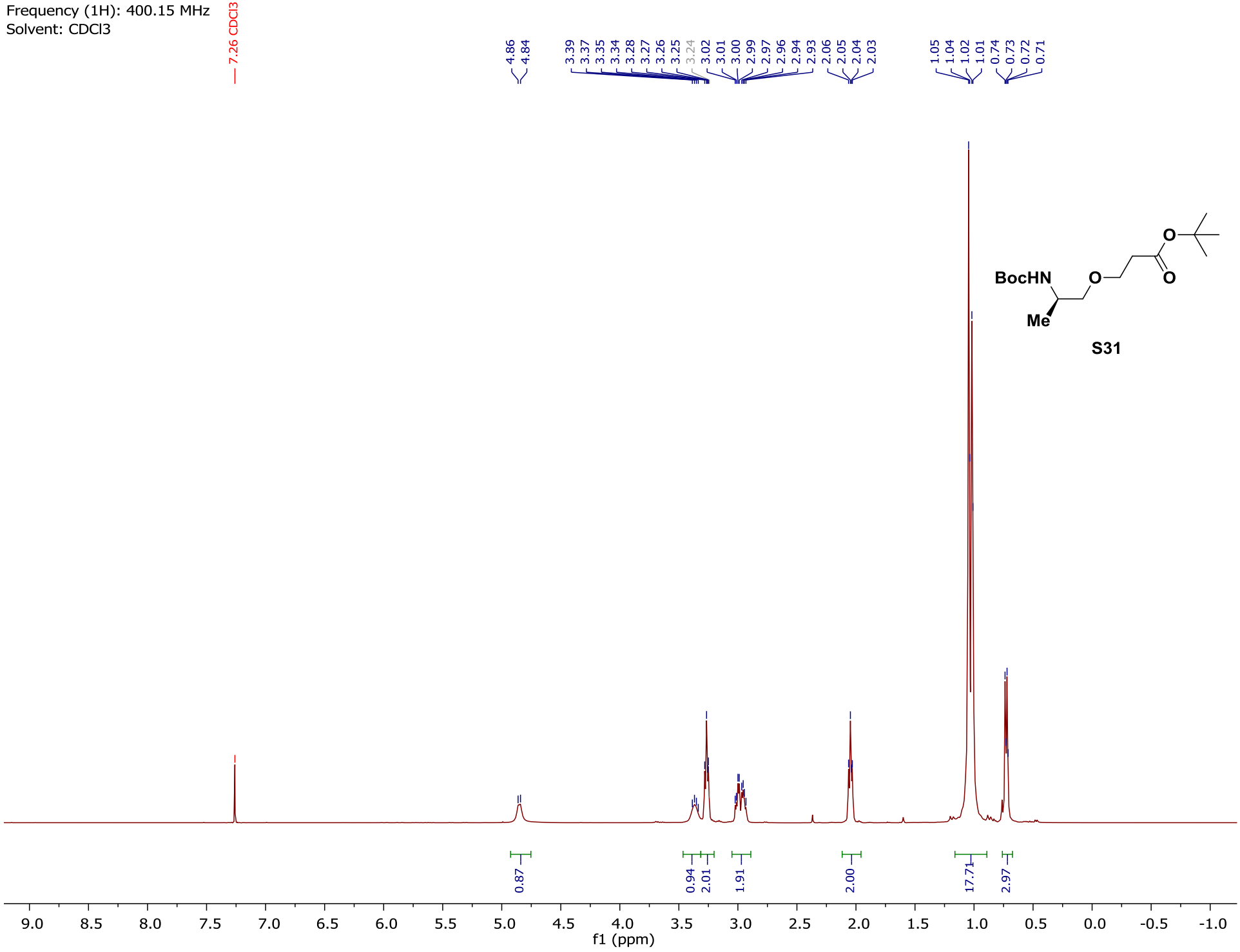
14a



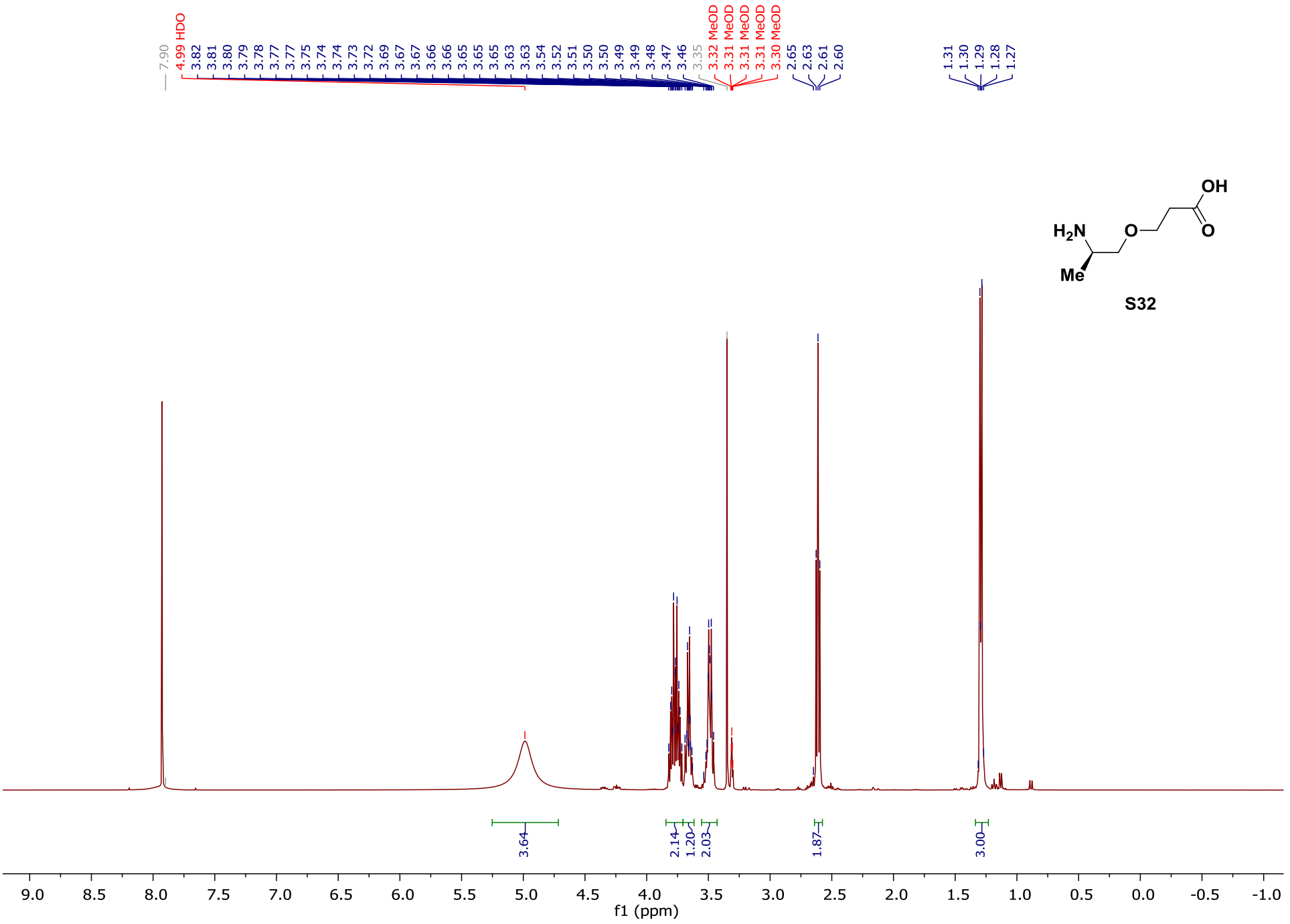
Frequency (1H): 400.15 MHz
Solvent: CDCl3



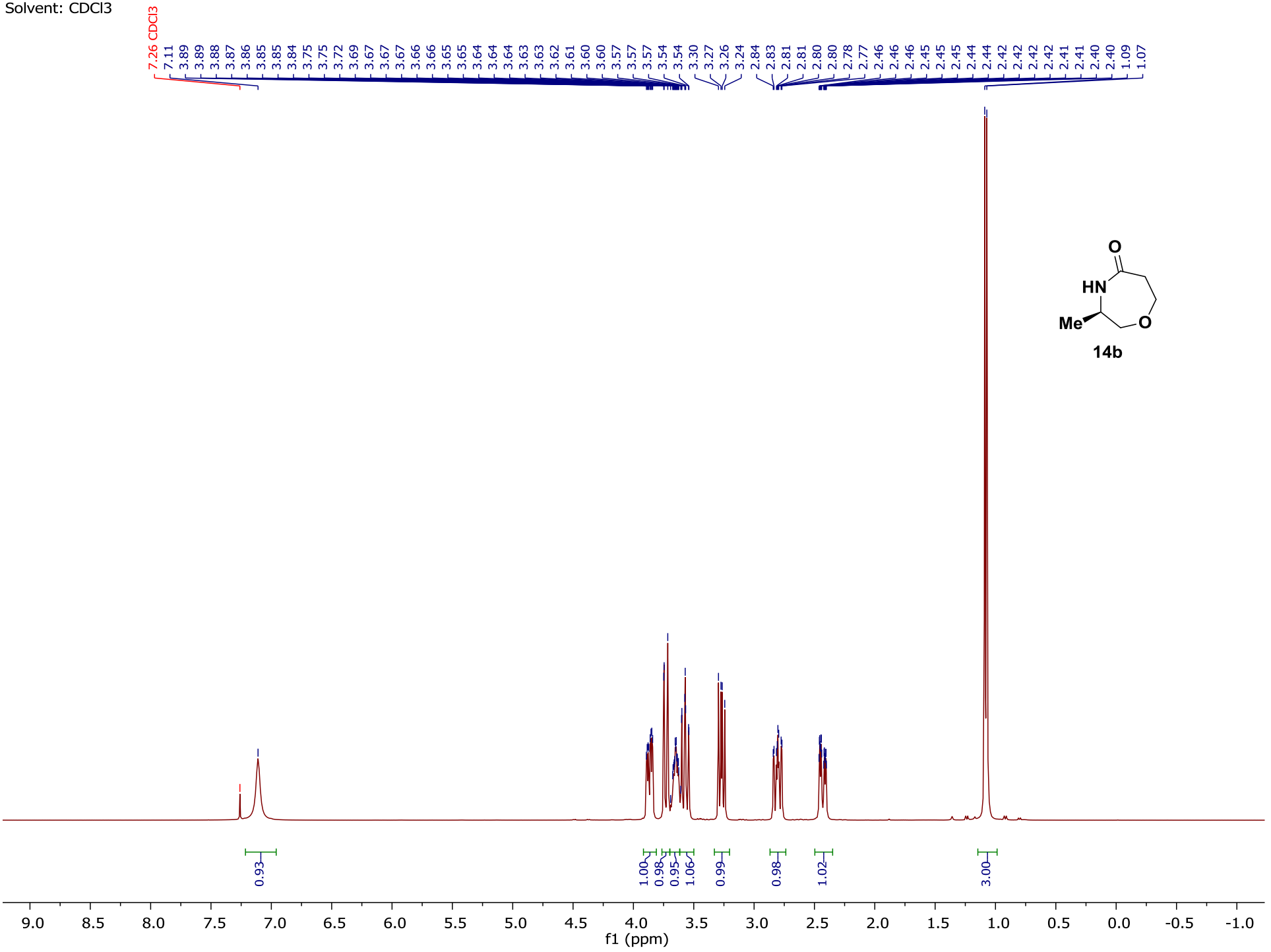
Frequency (1H): 400.15 MHz
Solvent: CDCl3

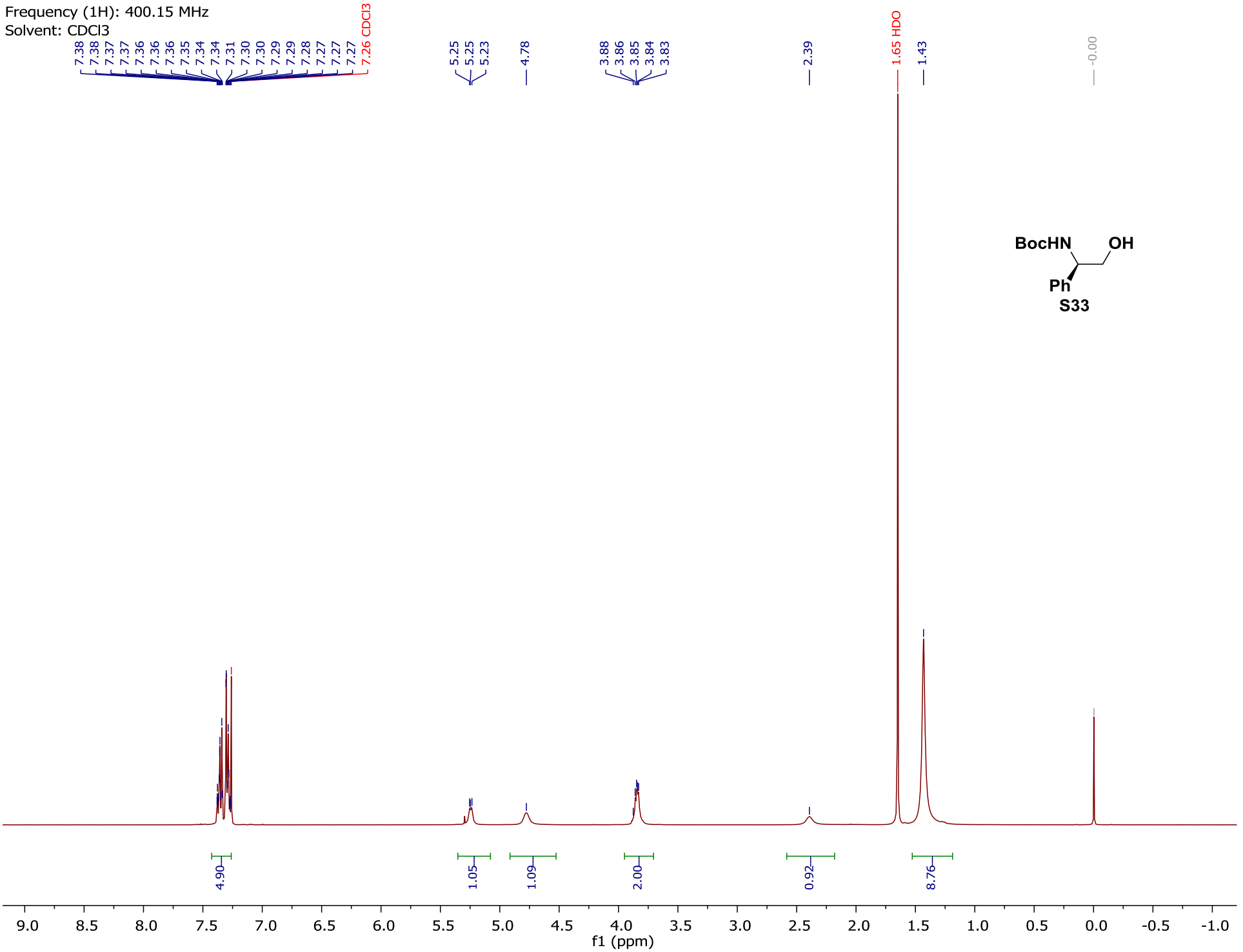


Frequency (1H): 400.15 MHz
Solvent: MeOD

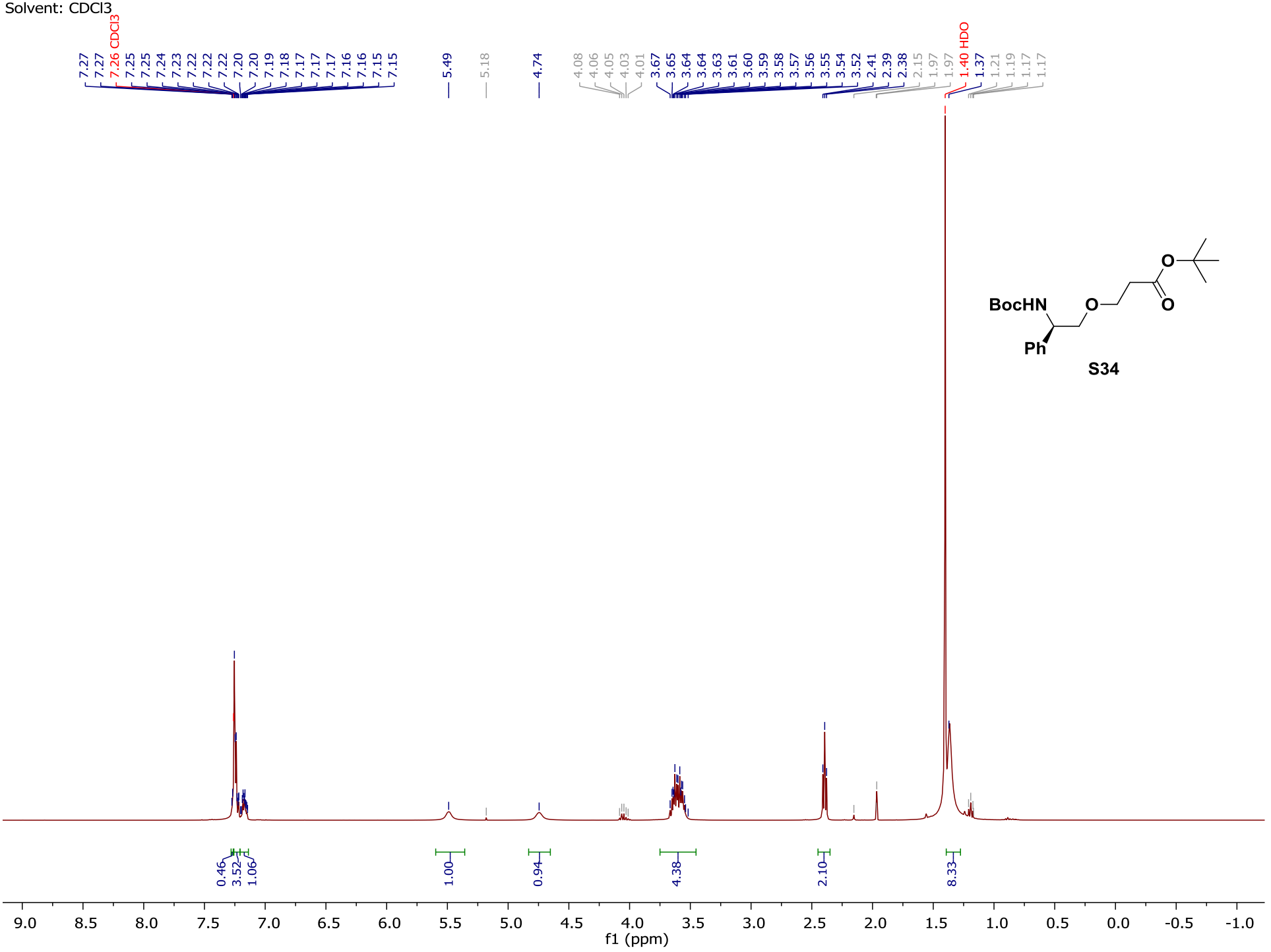


Frequency (1H): 400.15 MHz
Solvent: CDCl3

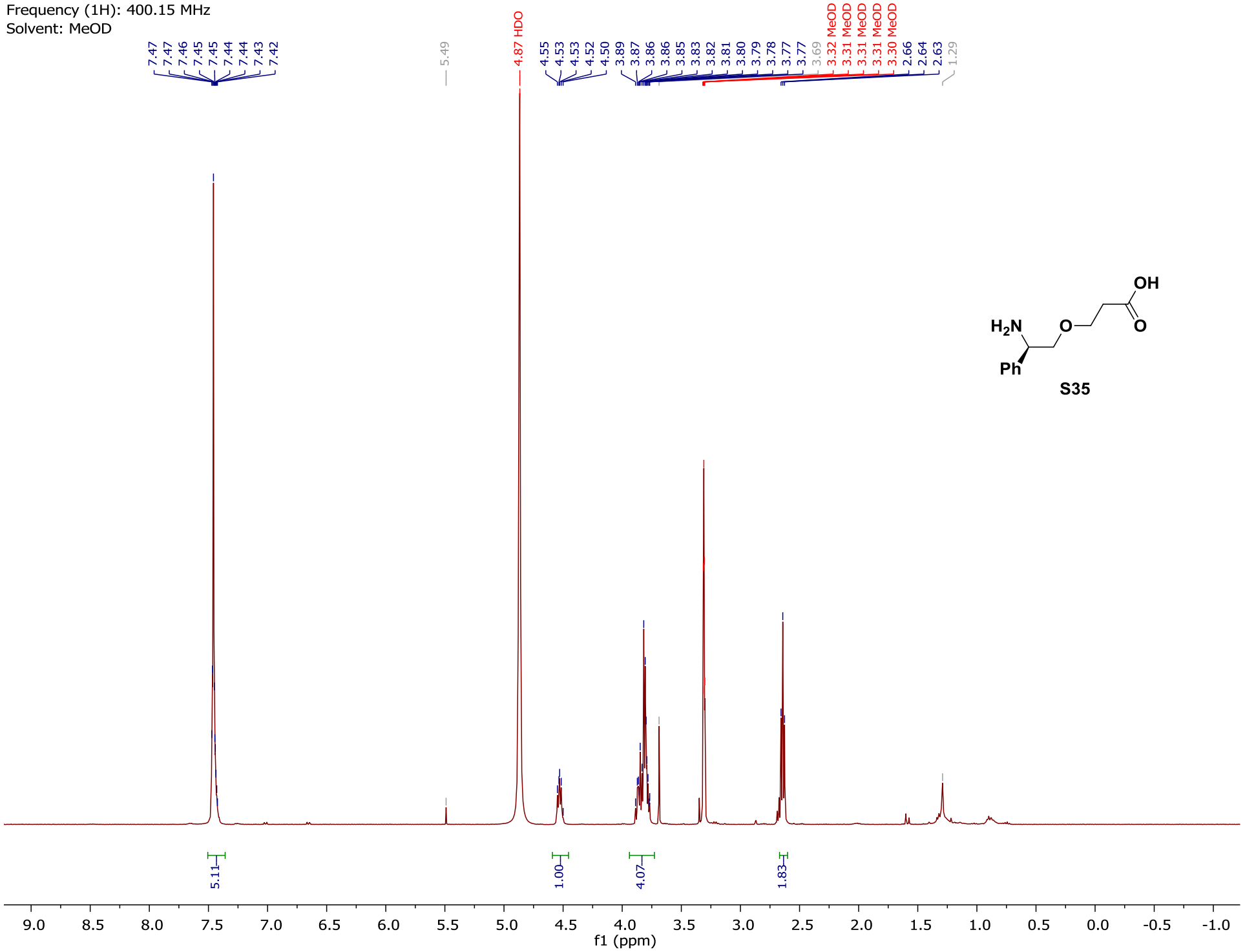



Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.38 7.38 7.37 7.37 7.36 7.36 7.36 7.35 7.34 7.34 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.27 7.27 7.26 CDCl3
5.25 5.25 5.23
4.78
3.88 3.86 3.85 3.84 3.83
2.39
1.65 HDO
1.43
-0.00
BocHN
OH
Ph
S33
4.90
1.05
1.09
2.00
0.92
8.76
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

Frequency (1H): 400.15 MHz
Solvent: CDCl3

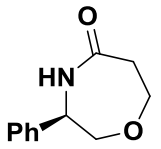


Frequency (1H): 400.15 MHz
Solvent: MeOD



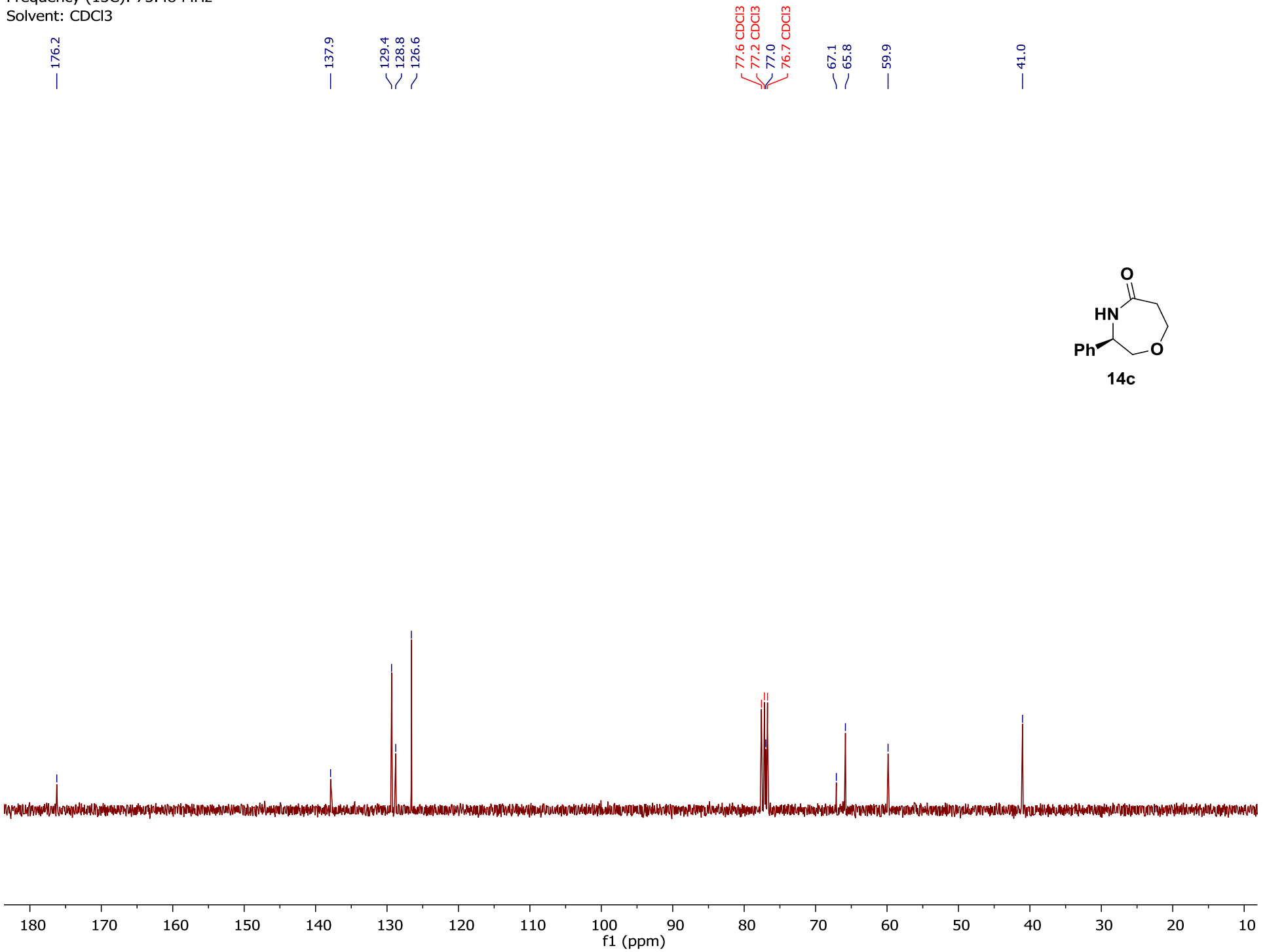
Frequency (1H): 400.15 MHz
Solvent: CDCl3

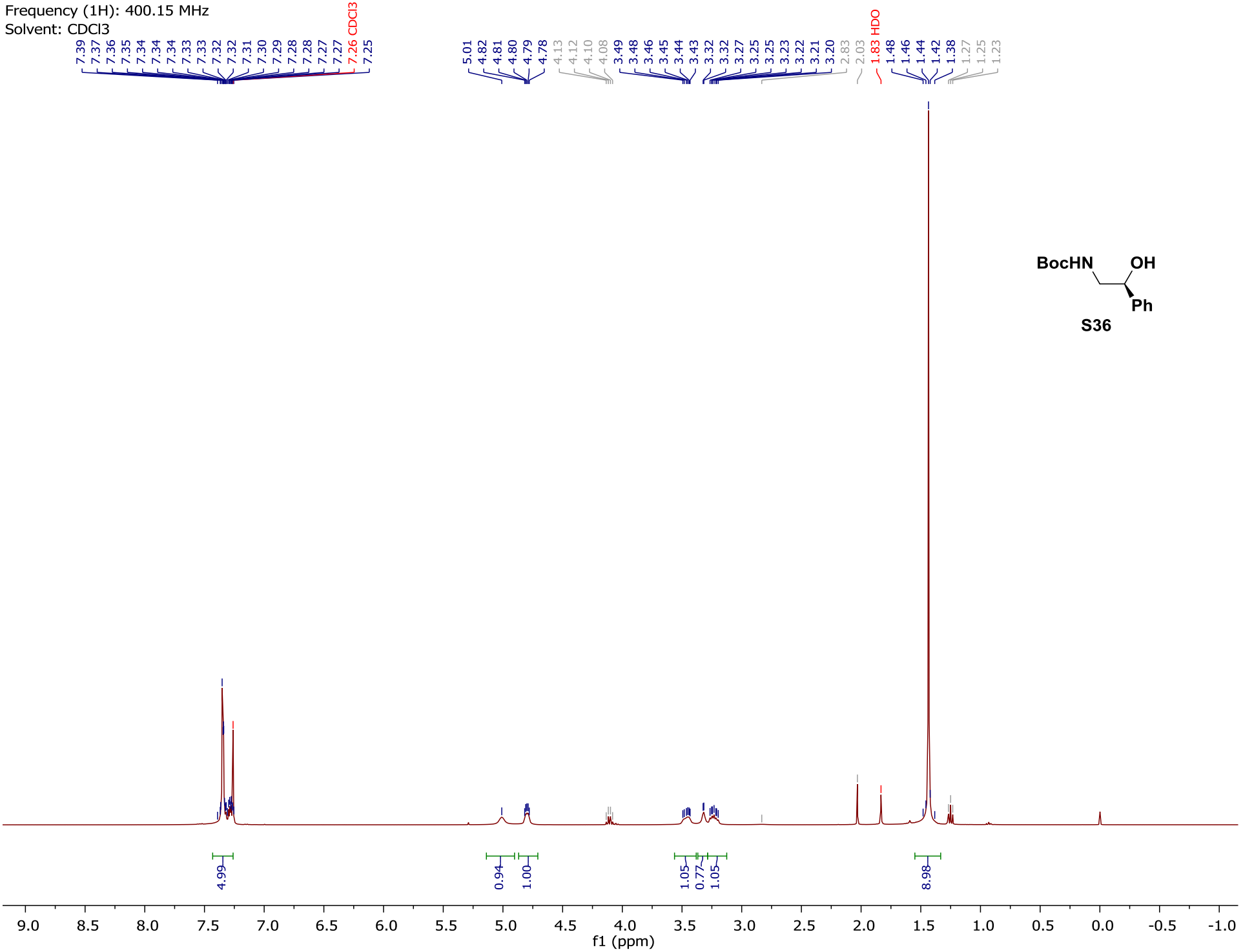
7.32 7.30 7.28 7.27 7.26 CDCl3 7.22 7.20 7.18 5.93 4.64 4.62 3.97 3.95 3.93 3.92 3.86 3.83 3.72 3.69 3.66 3.03 2.94 2.92 2.91 2.90 2.88 2.56 2.55 2.52 2.51 1.54 HDO 1.29 1.17 0.90 0.79



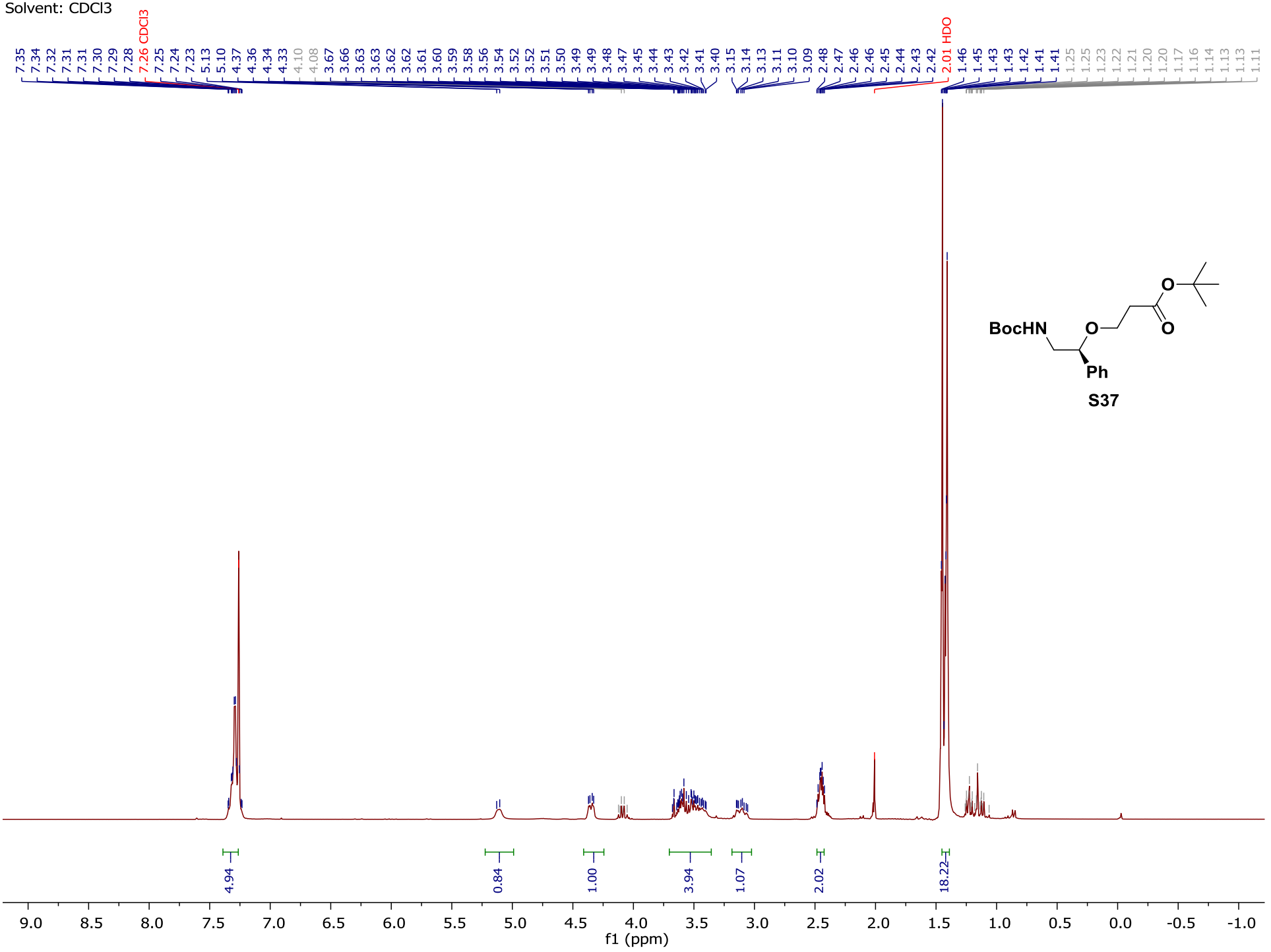
14c

Frequency (13C): 75.48 MHz
Solvent: CDCl3

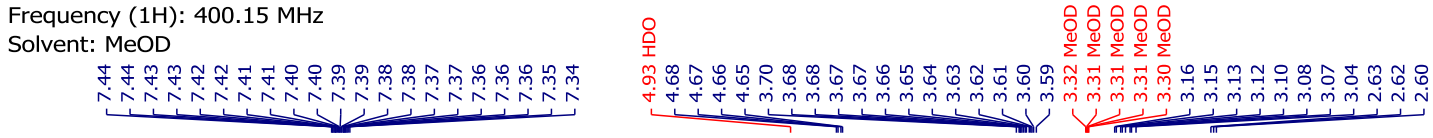


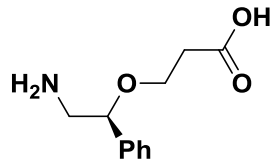

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.39 7.37 7.36 7.35 7.34 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.30 7.29 7.28 7.28 7.27 7.27 7.26 CDCl3 7.25
5.01 4.82 4.81 4.80 4.79 4.78 4.13 4.12 4.10 4.08 3.49 3.48 3.46 3.45 3.44 3.43 3.32 3.32 3.27 3.25 3.25 3.23 3.22 3.21 3.20 2.83 2.03 1.83 HDO 1.48 1.46 1.44 1.42 1.38 1.27 1.25 1.23
BocHN
OH
Ph
S36
4.99
0.94
1.00
1.05
0.77
1.05
8.98
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 -1.0
f1 (ppm)

Frequency (1H): 300.13 MHz
Solvent: CDCl3



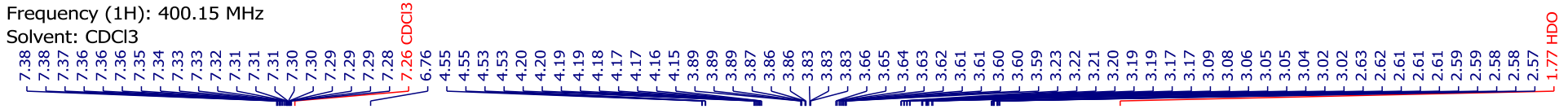
Frequency (1H): 400.15 MHz
Solvent: MeOD

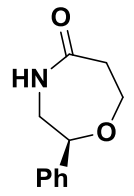




S38

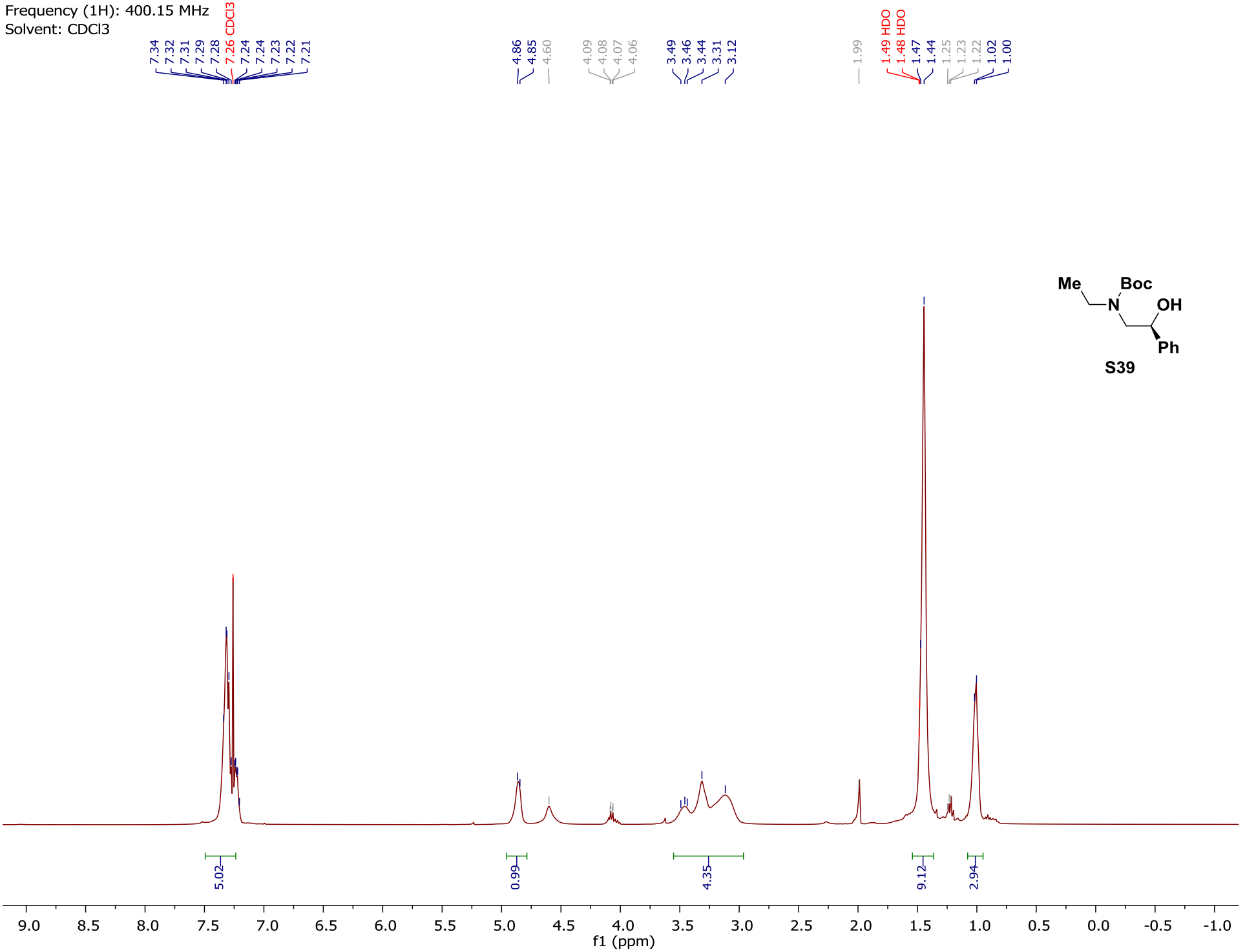
Frequency (1H): 400.15 MHz
Solvent: CDCl3



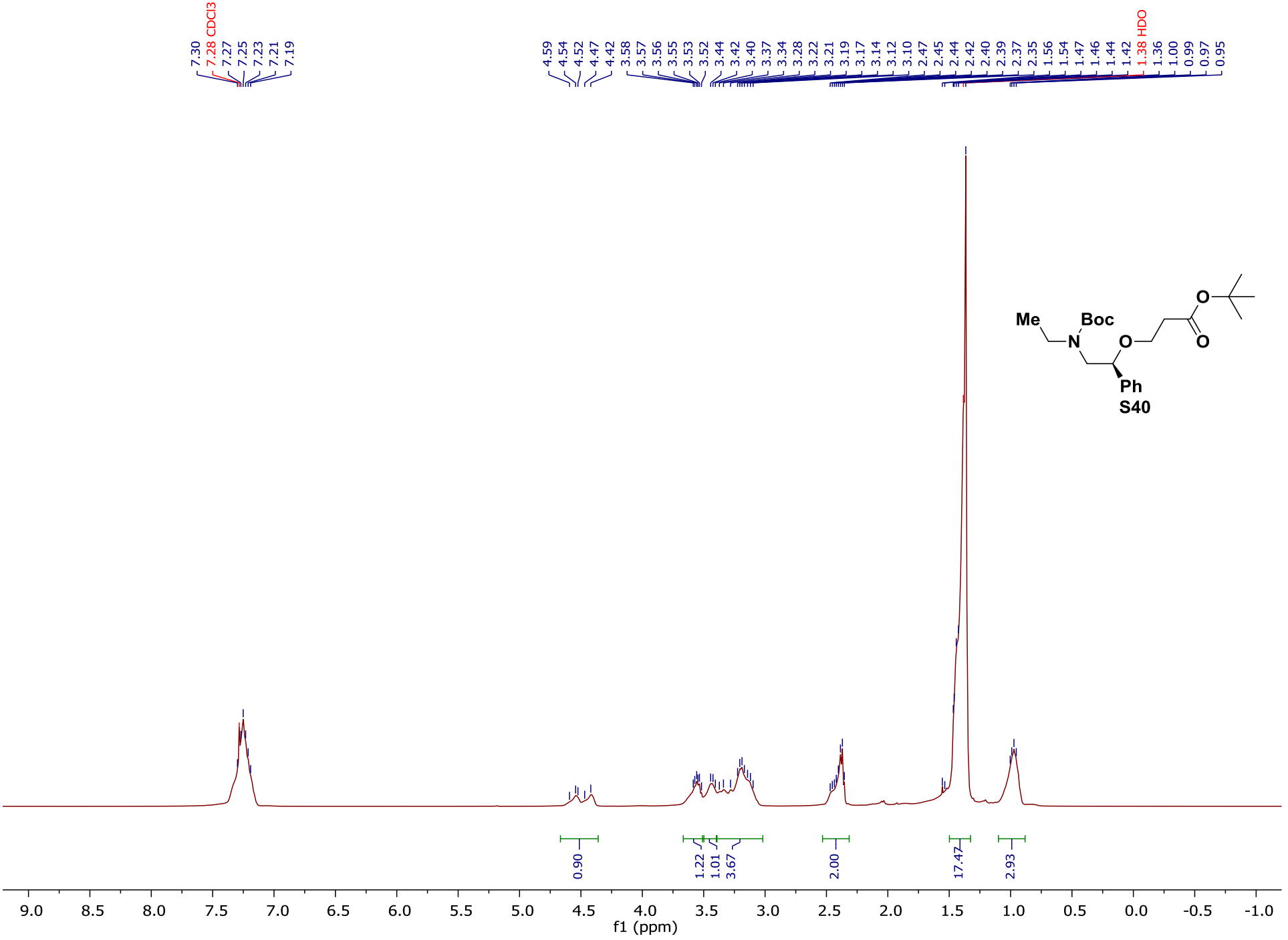


14d

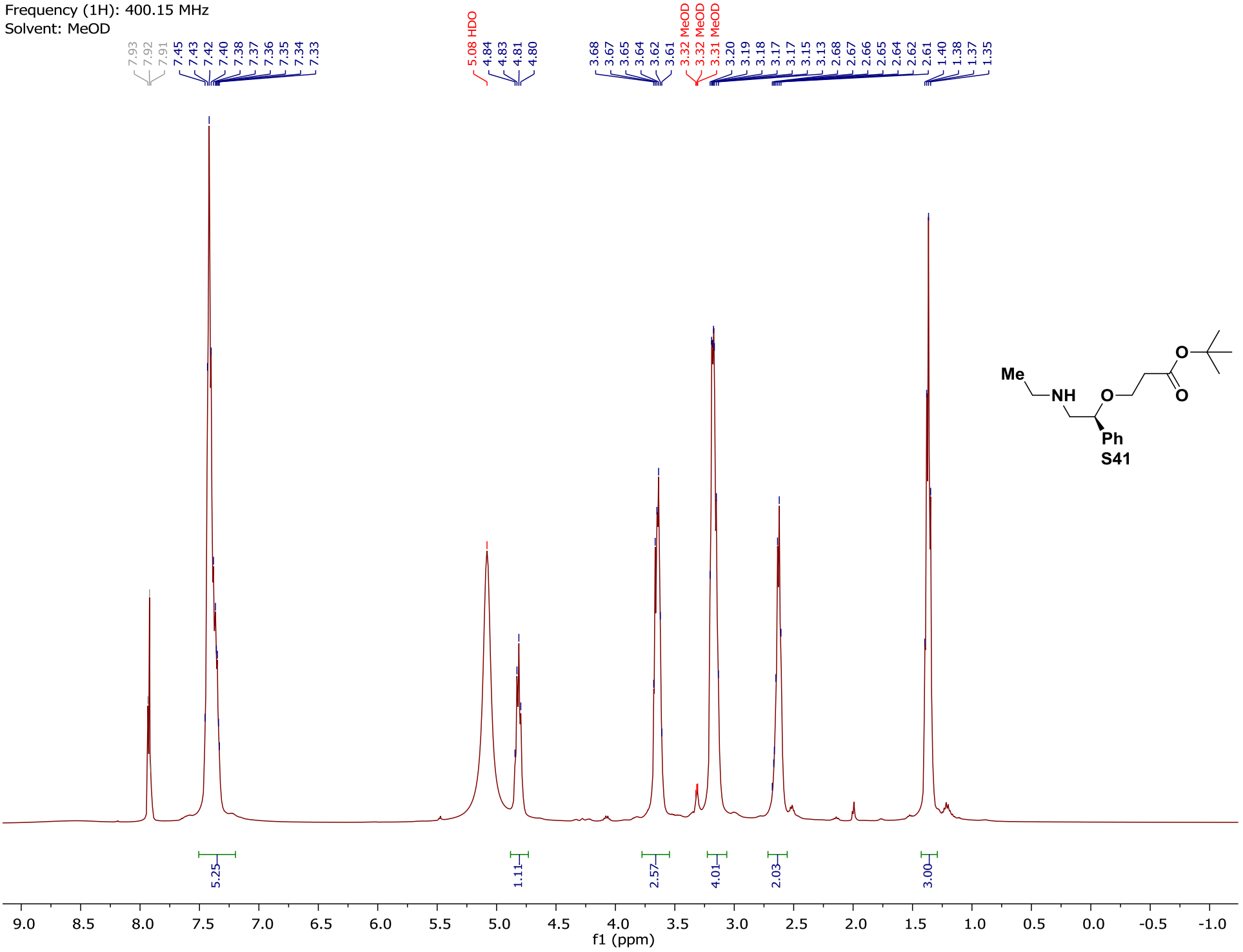
Frequency (1H): 400.15 MHz
Solvent: CDCl3



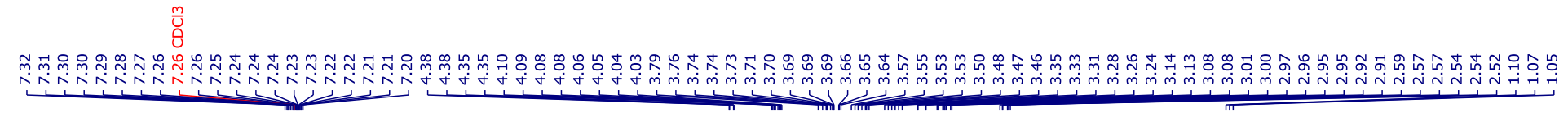
Frequency (1H): 400.15 MHz
Solvent: CDCl3

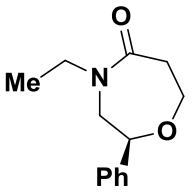


Frequency (1H): 400.15 MHz
Solvent: MeOD

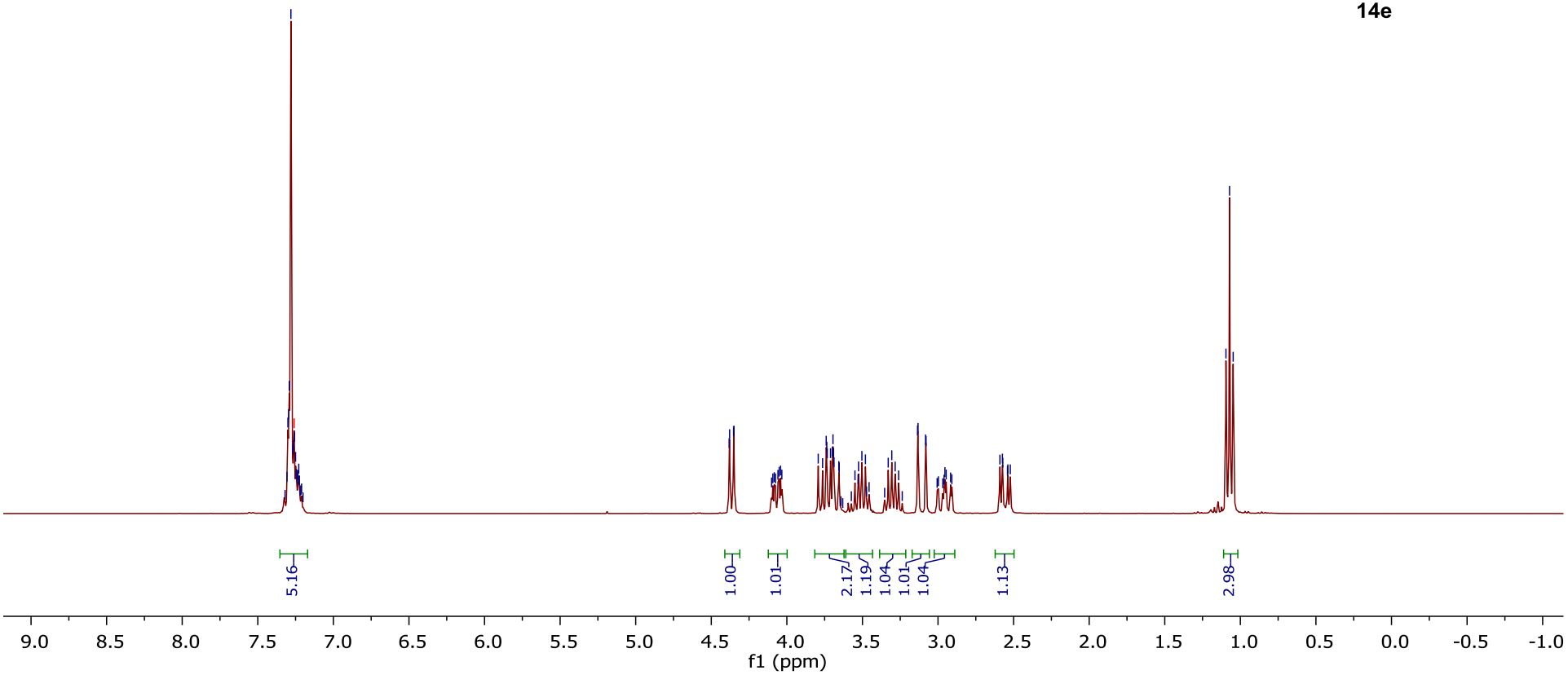


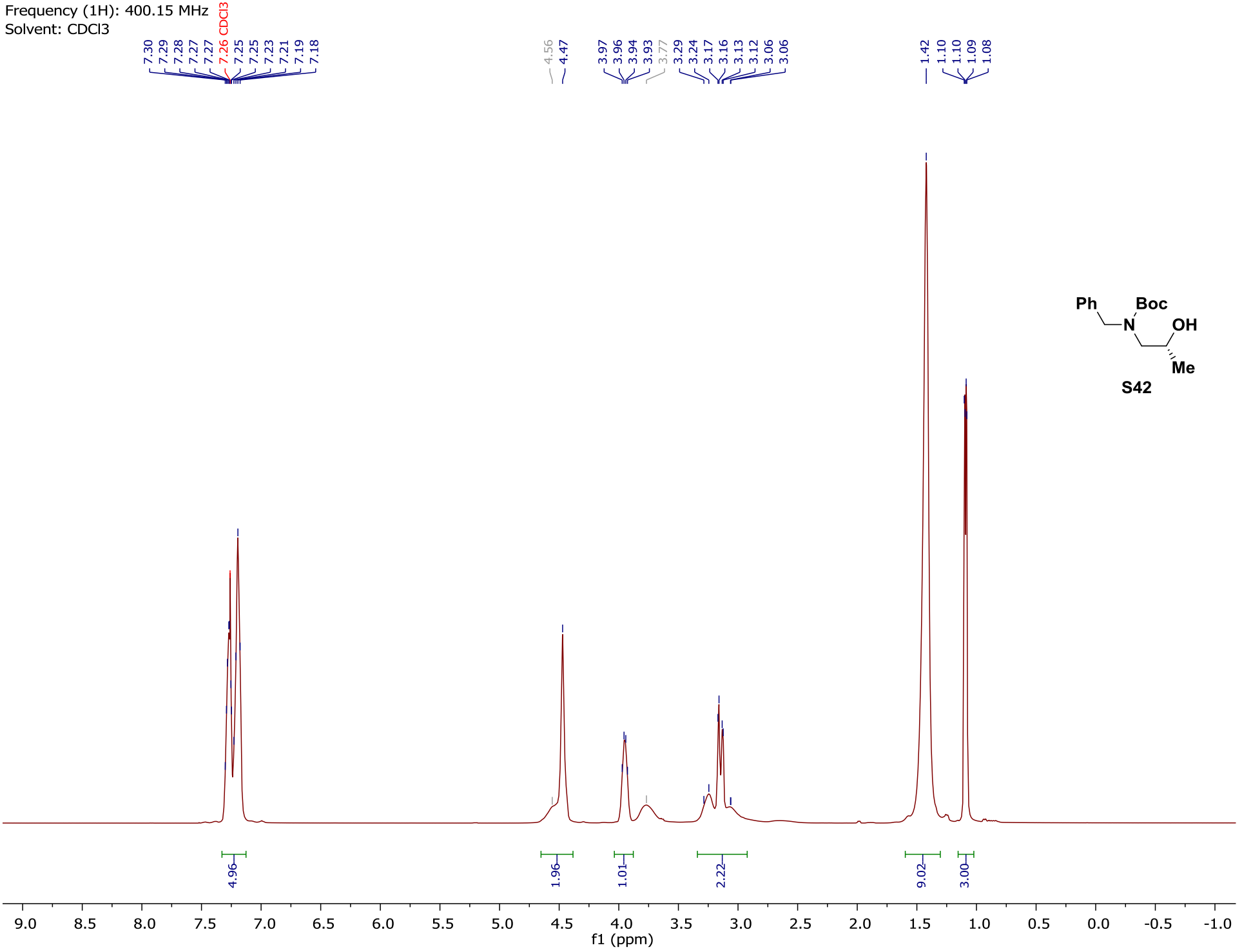
Frequency (1H): 300.13 MHz
Solvent: CDCl3



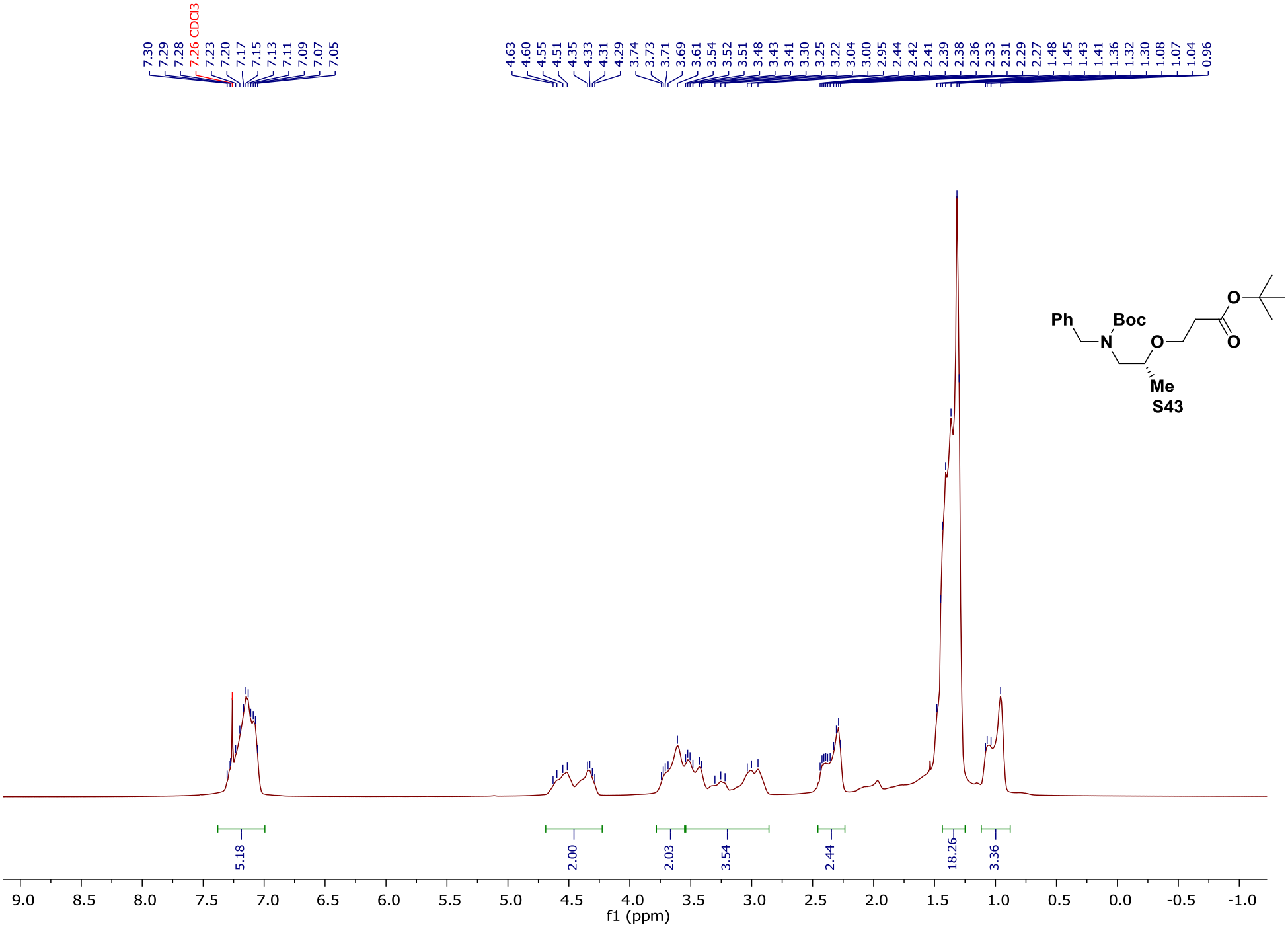


14e

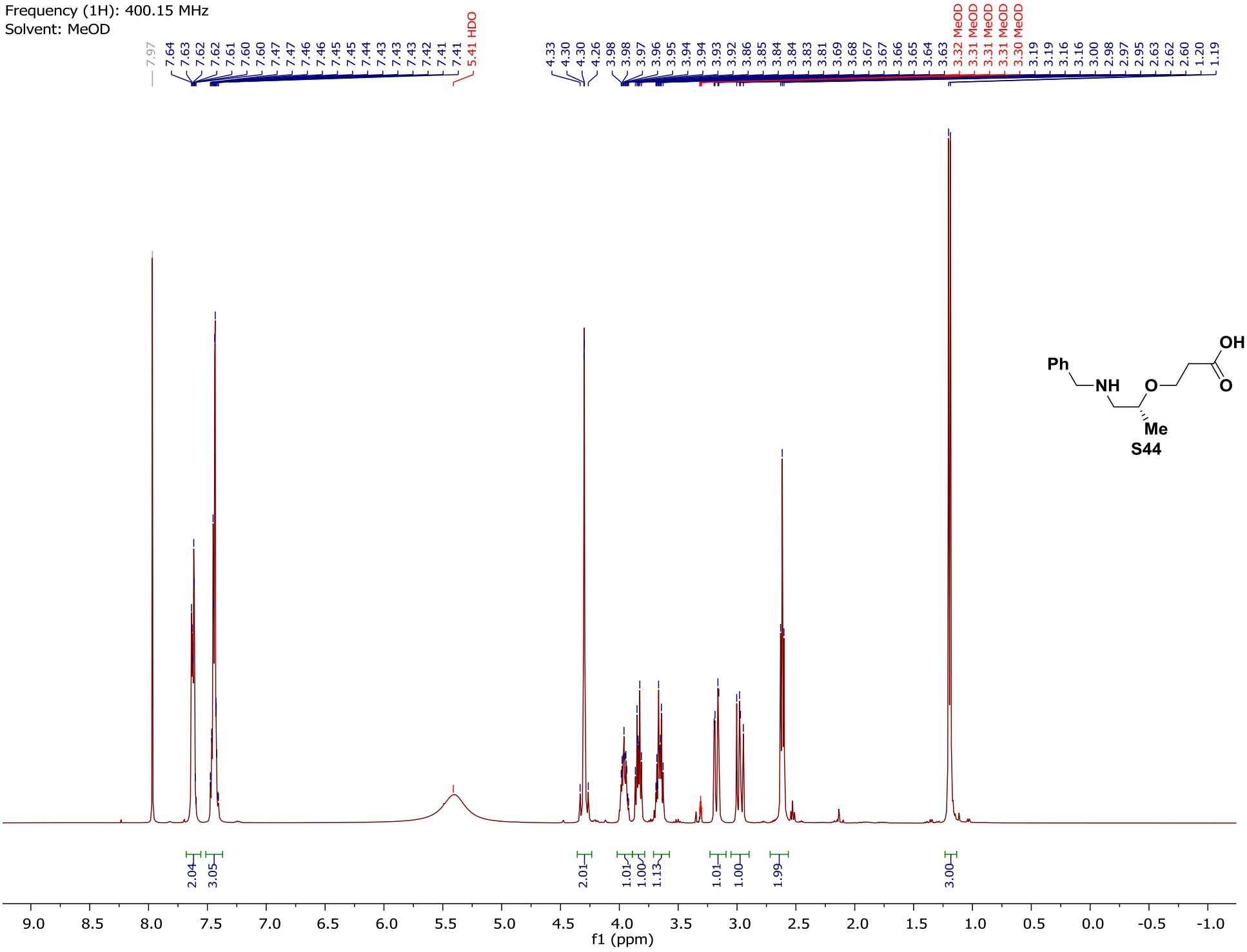



Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.30
7.29
7.28
7.27
7.27
7.26 CDCl3
7.25
7.25
7.23
7.21
7.19
7.18
4.56
4.47
3.97
3.96
3.94
3.93
3.77
3.29
3.24
3.17
3.16
3.13
3.12
3.06
3.06
1.42
1.10
1.10
1.09
1.08
Ph
Boc
N
OH
Me
S42
4.96
1.96
1.01
2.22
9.02
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

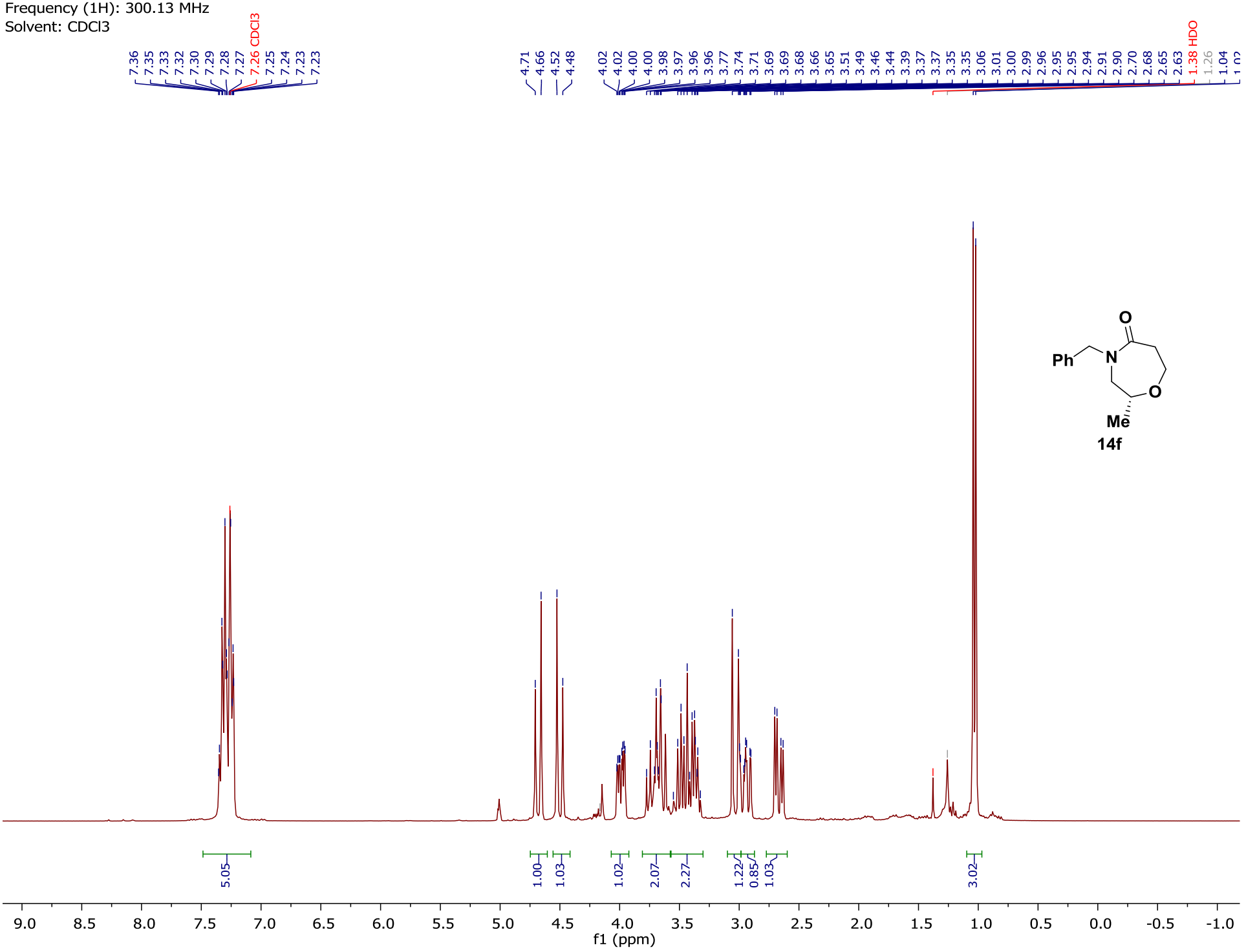
Frequency (1H): 400.15 MHz
Solvent: CDCl3



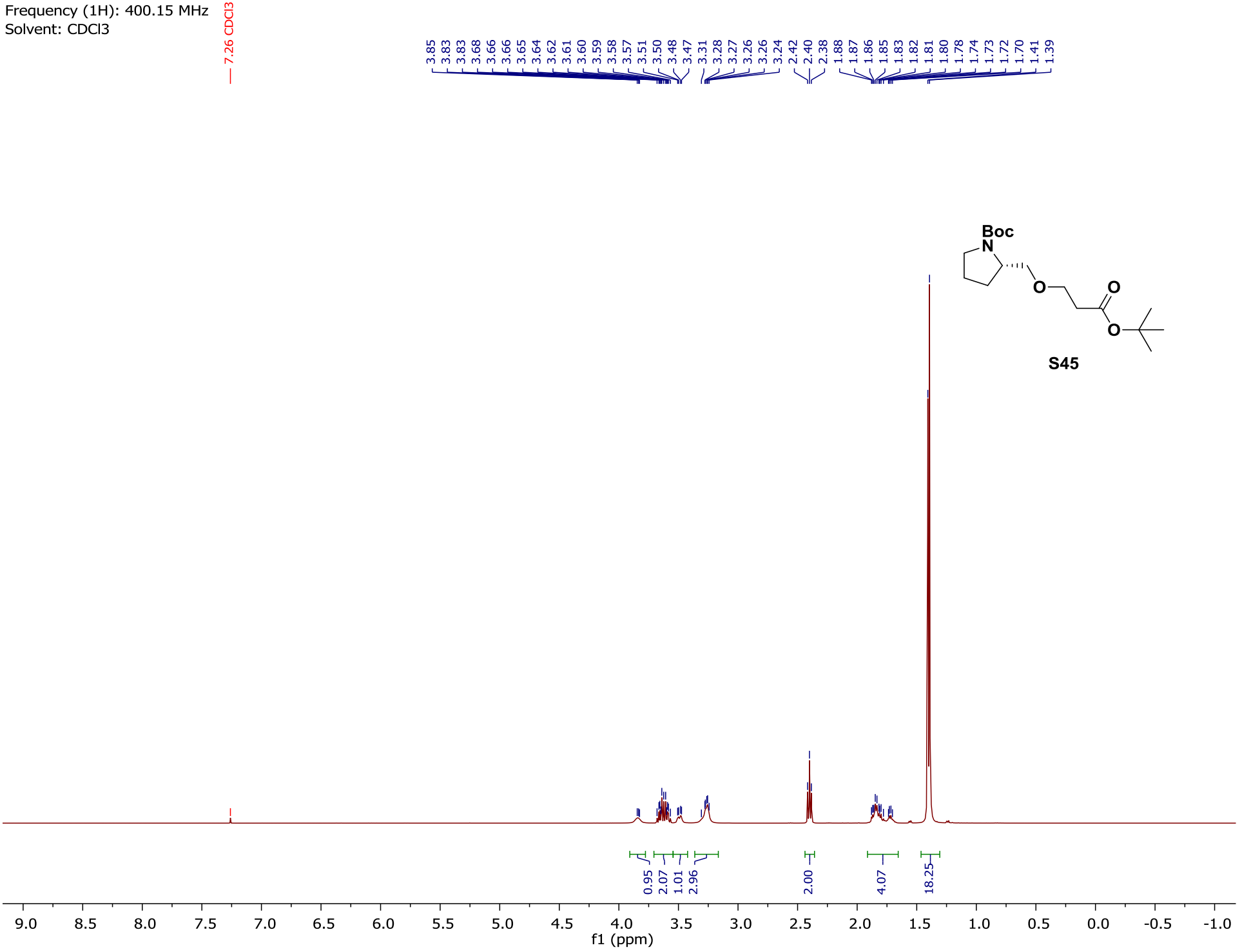
Frequency (1H): 400.15 MHz
Solvent: MeOD



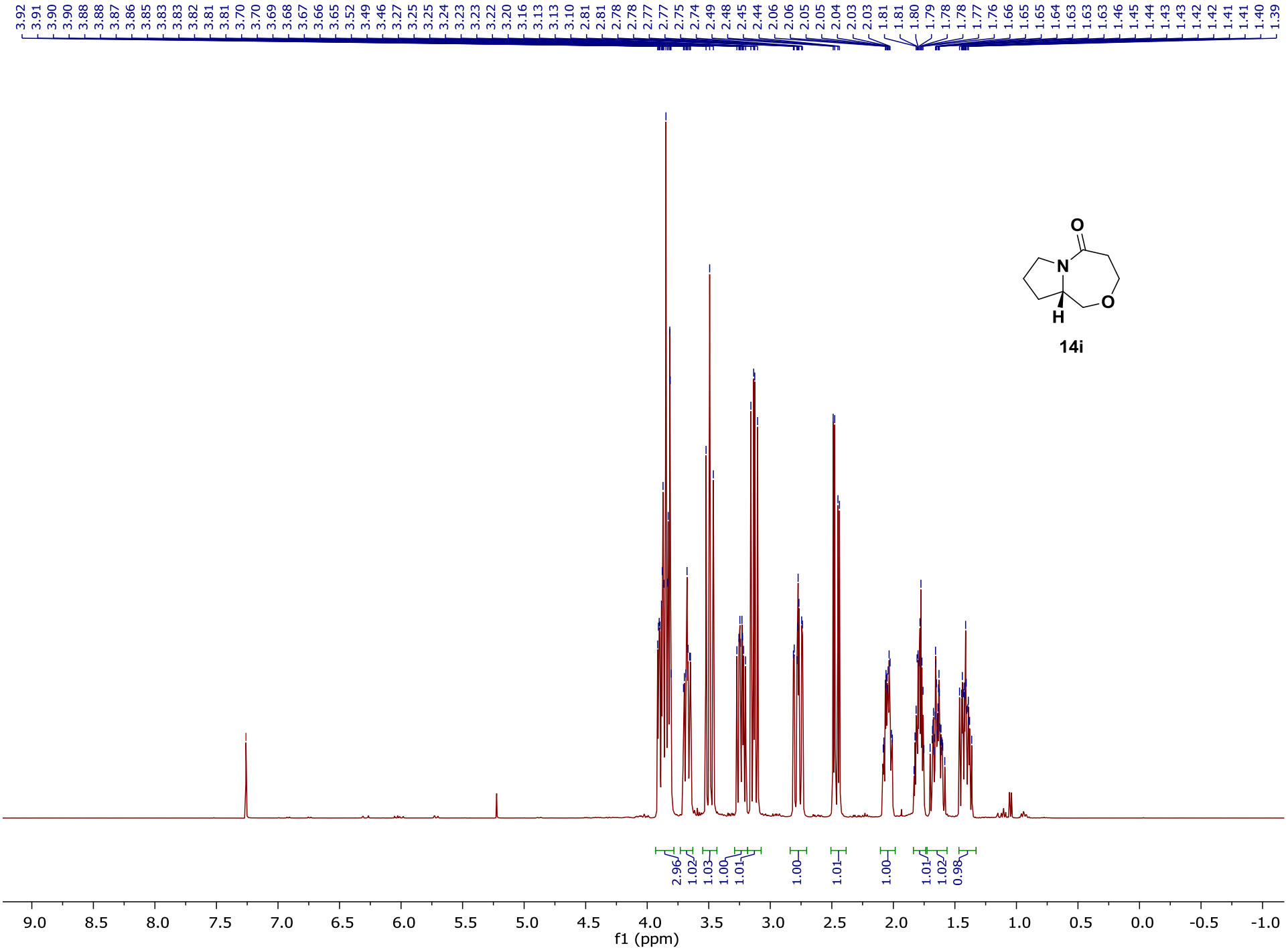
Frequency (1H): 300.13 MHz
Solvent: CDCl3

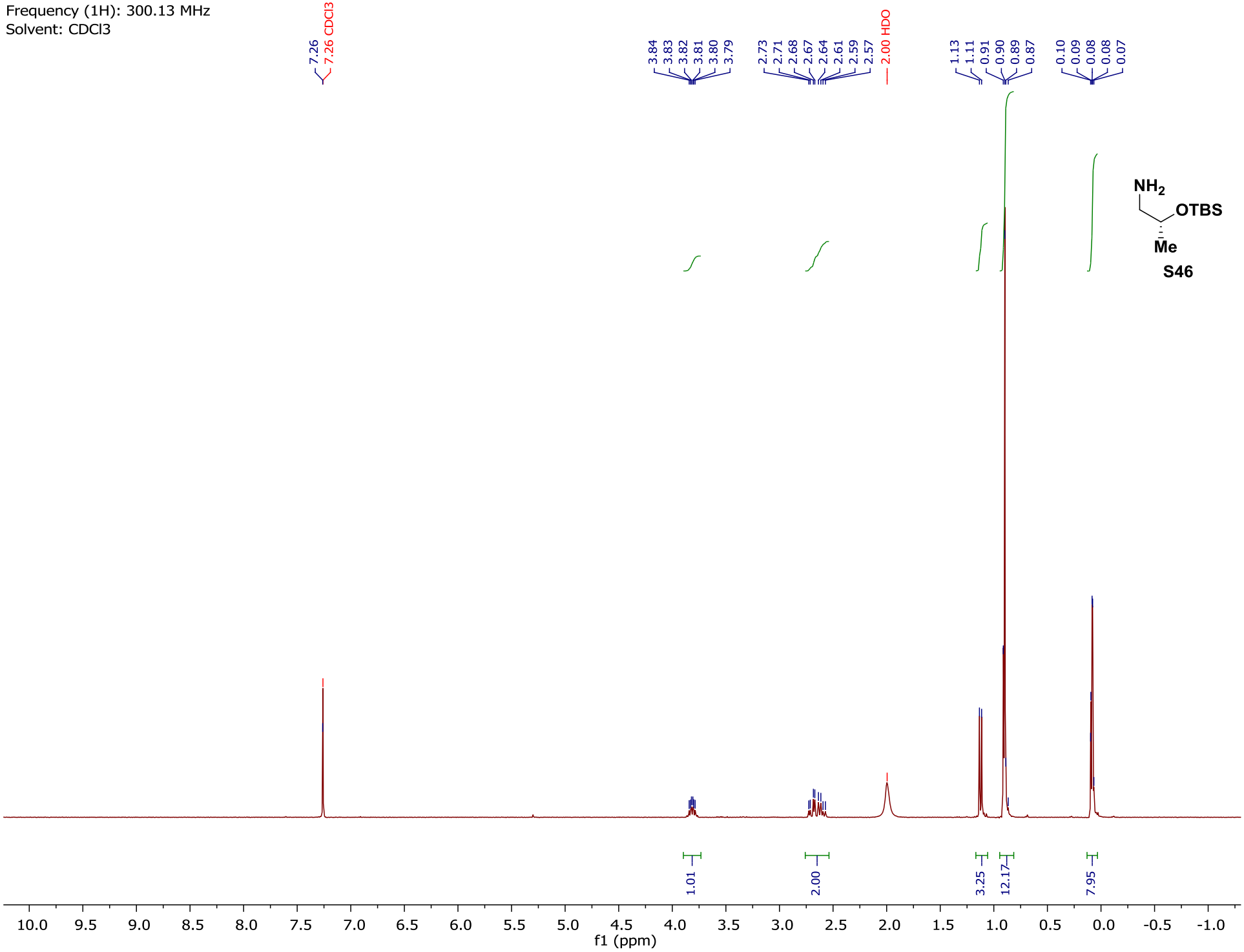


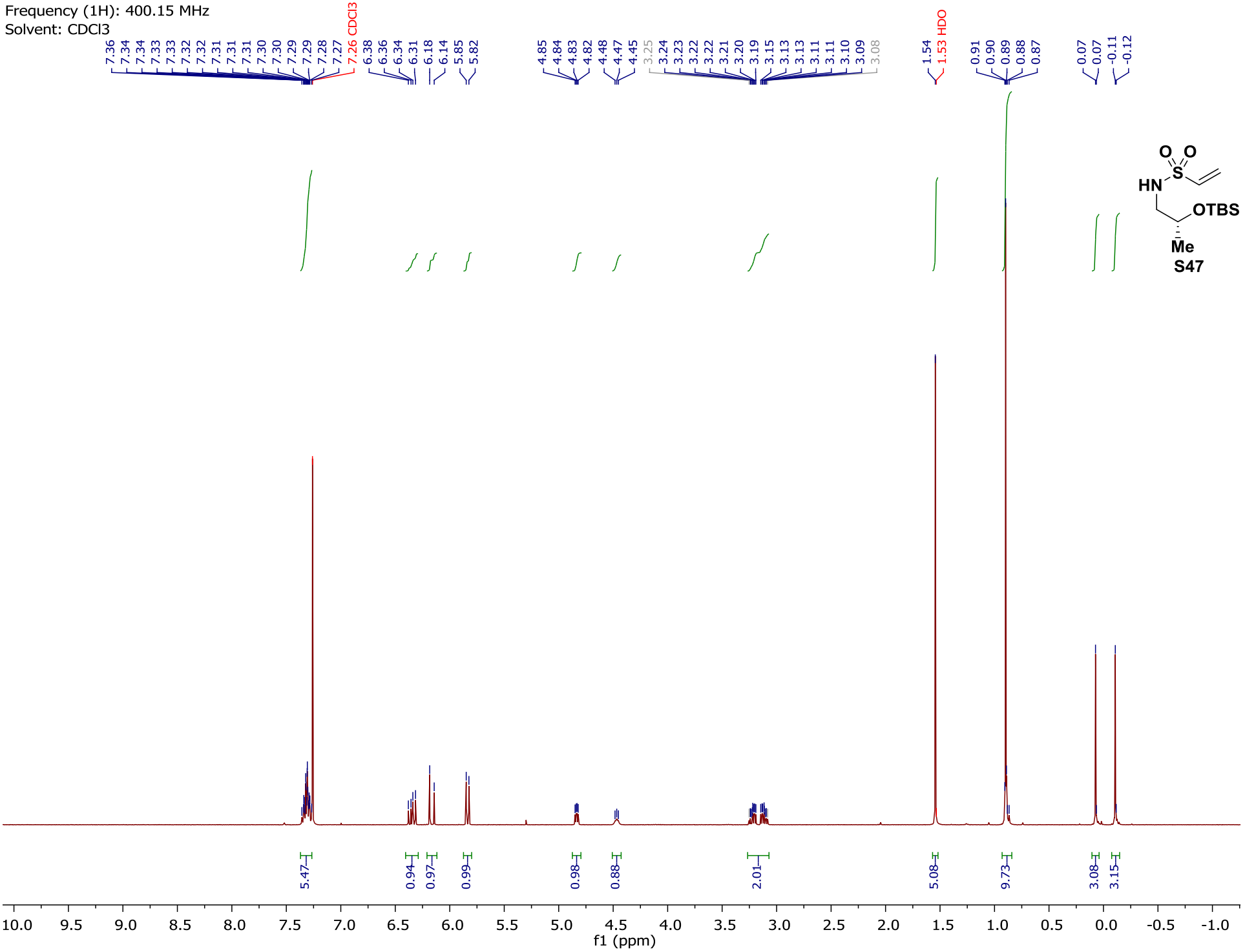
Frequency (1H): 400.15 MHz
Solvent: CDCl3



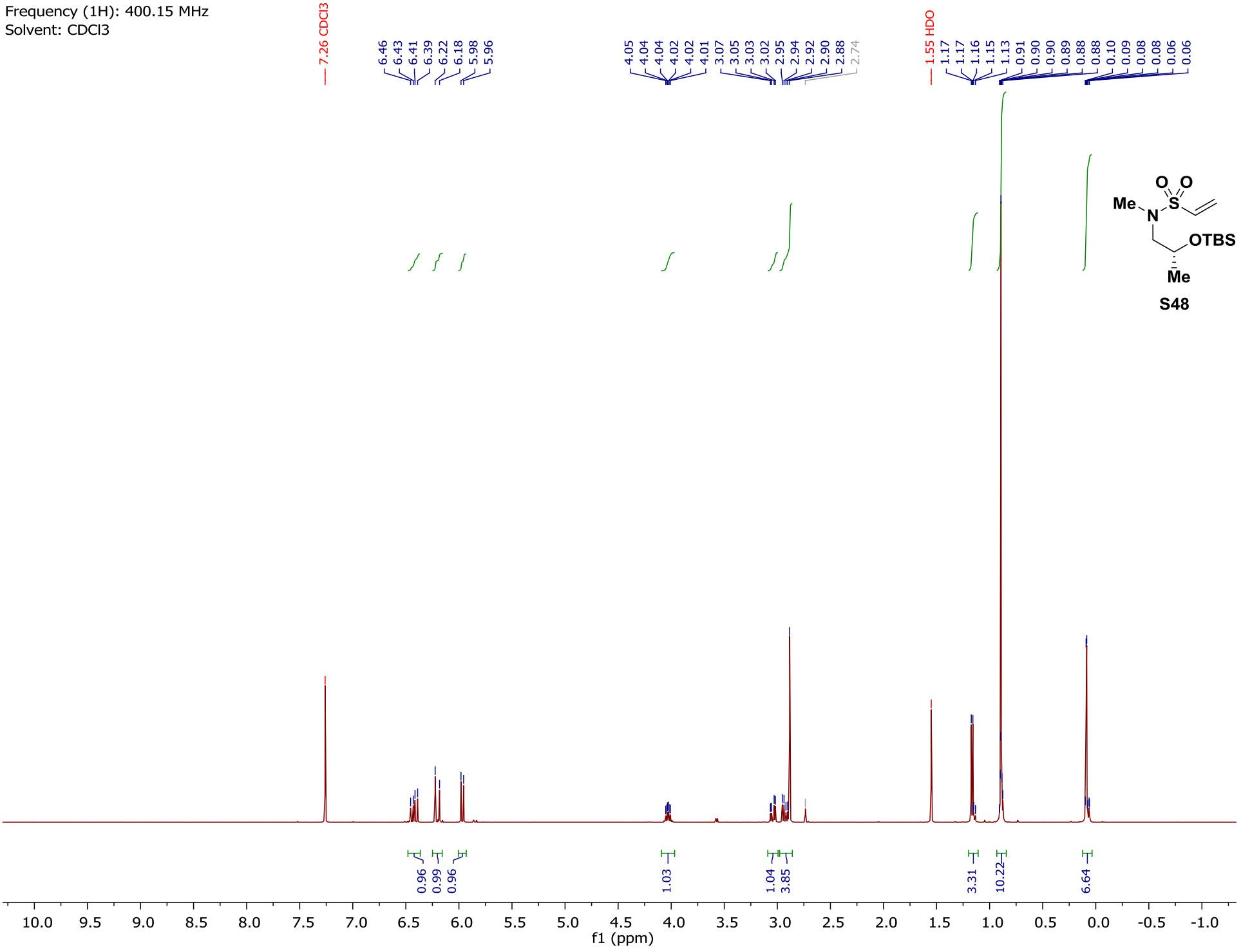
Frequency (1H): 400.15 MHz
Solvent: CDCl3




Frequency (1H): 300.13 MHz
Solvent: CDCl3
7.26
7.26 CDCl3
3.84
3.83
3.82
3.81
3.80
3.79
2.73
2.71
2.68
2.67
2.64
2.61
2.59
2.57
2.00 HDO
1.13
1.11
0.91
0.90
0.89
0.87
0.10
0.09
0.08
0.08
0.07
NH2
OTBS
Me
S46
1.01
2.00
3.25
12.17
7.95
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
-1.0
f1 (ppm)

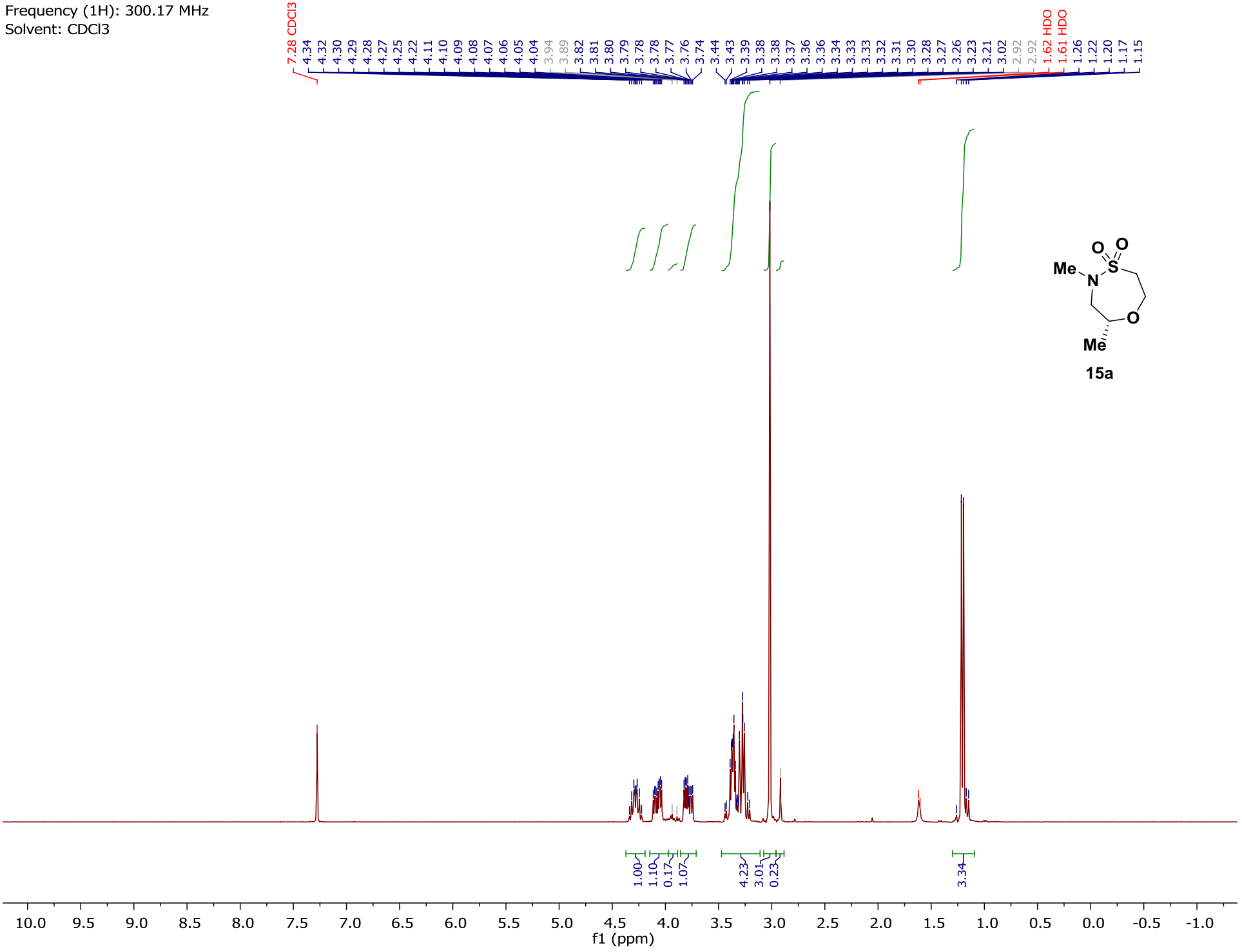

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.36 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.26 CDCl3 6.38 6.36 6.34 6.31 6.18 6.14 5.85 5.82
4.85 4.84 4.83 4.82 4.48 4.47 4.45 3.25 3.24 3.23 3.22 3.22 3.21 3.20 3.19 3.15 3.13 3.13 3.11 3.11 3.10 3.09 3.08
1.54 1.53 HDO 0.91 0.90 0.89 0.88 0.87 0.07 0.07 -0.11 -0.12
O O S HN OTBS Me
S47
5.47 0.94 0.97 0.99 0.98 0.88 2.01 5.08 9.73 3.08 3.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

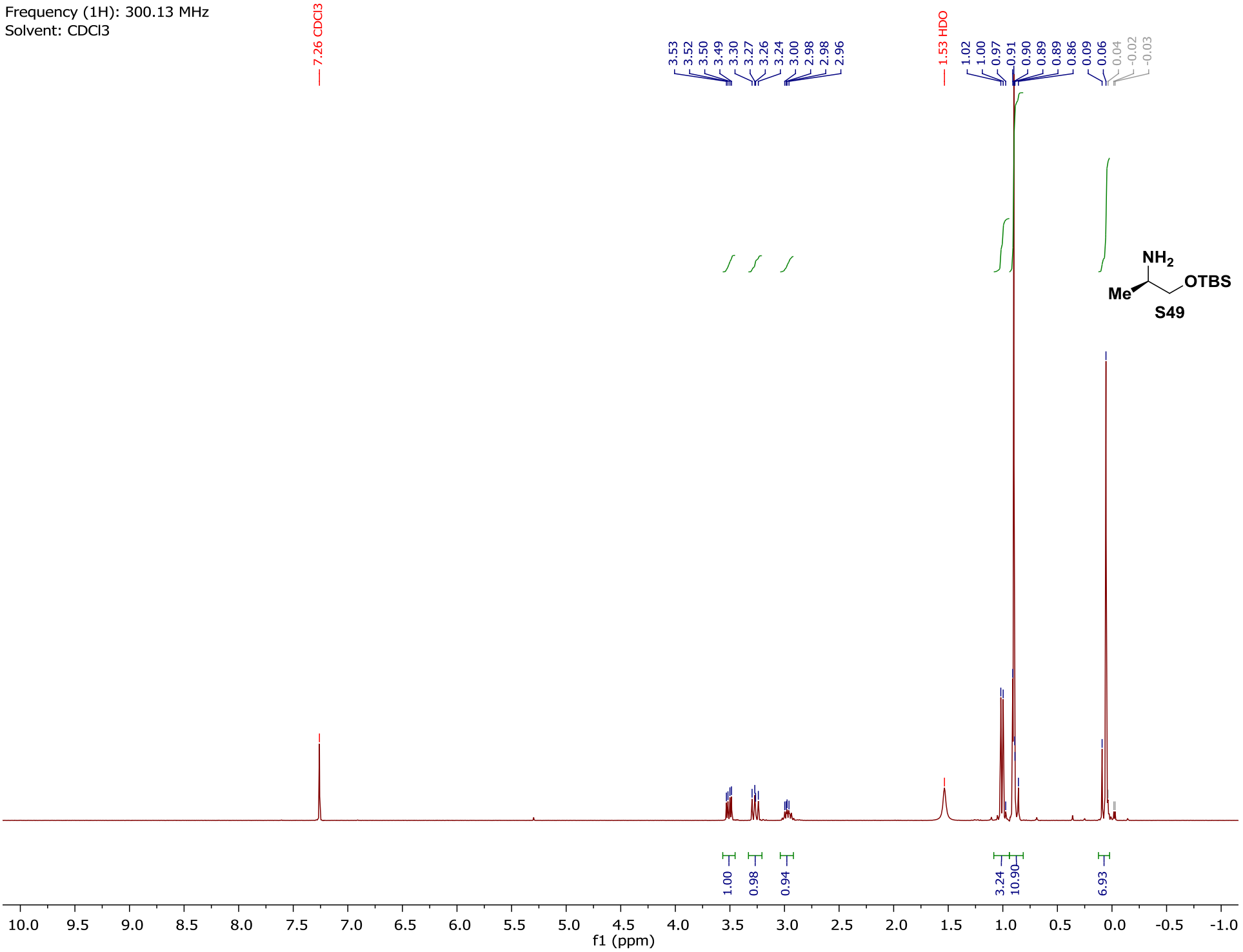
Frequency (1H): 400.15 MHz
Solvent: CDCl3



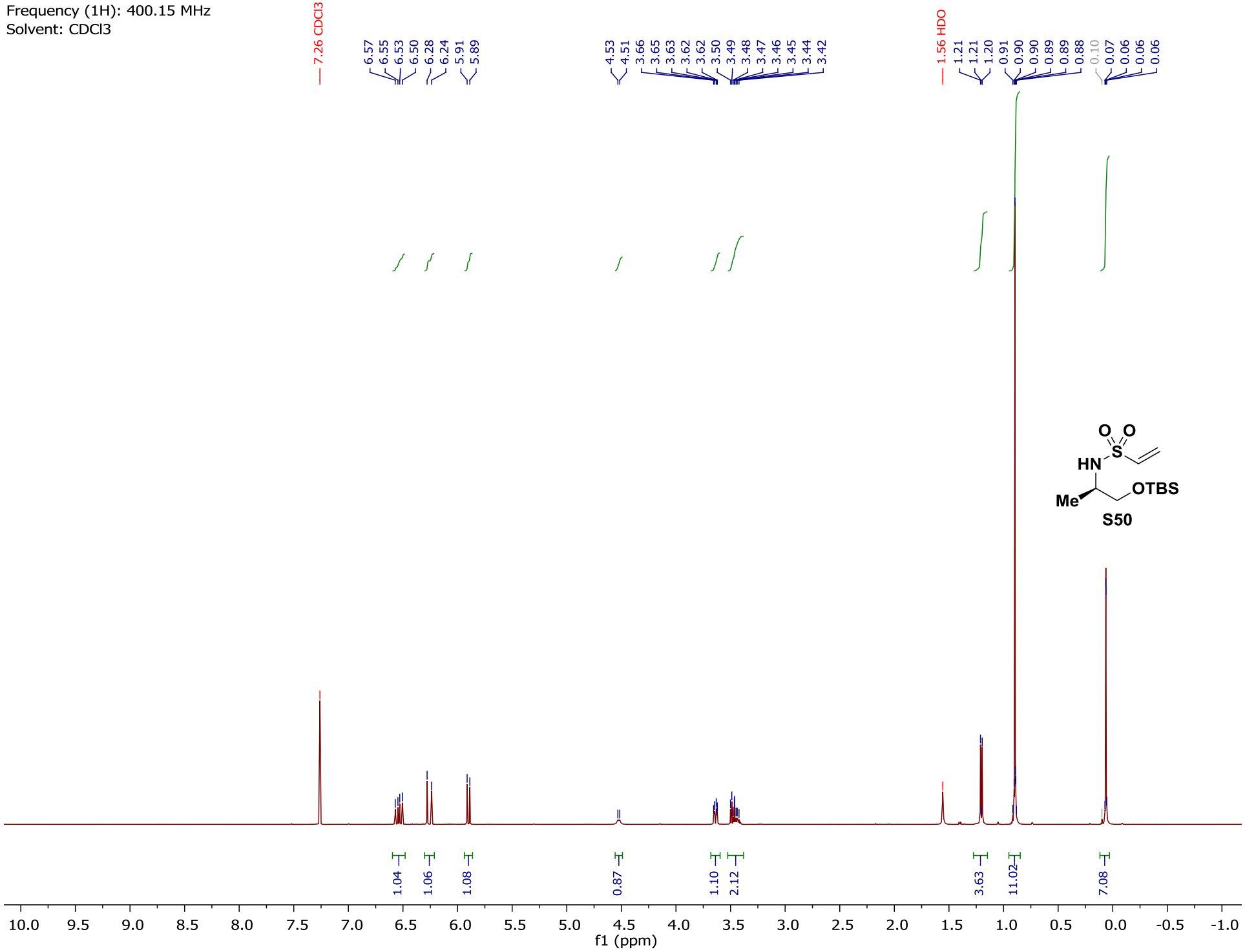
S48

Frequency (1H): 300.17 MHz
Solvent: CDCl3

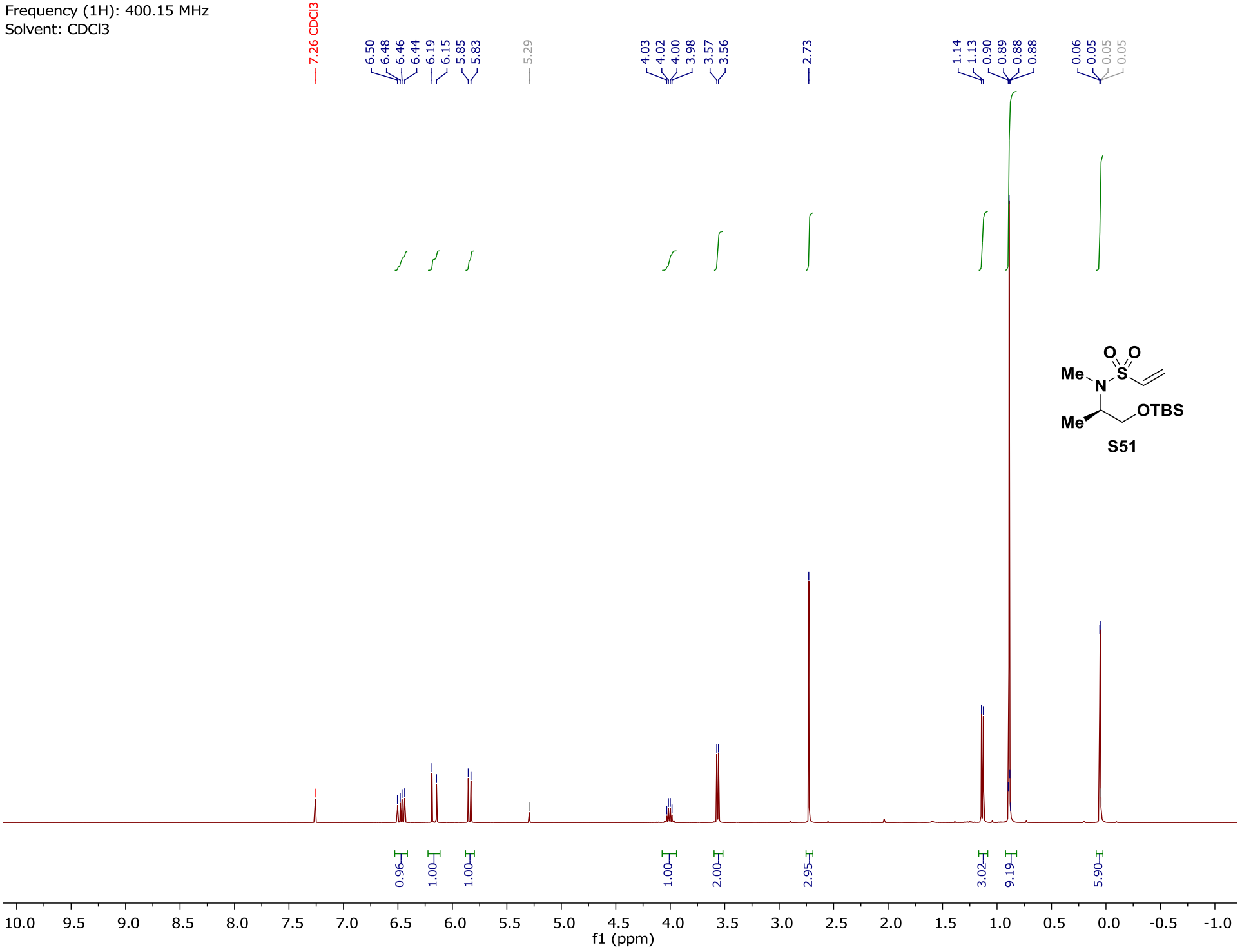



Frequency (1H): 300.13 MHz
Solvent: CDCl3
7.26 CDCl3
3.53
3.52
3.50
3.49
3.30
3.27
3.26
3.24
3.00
2.98
2.98
2.96
1.53 HDO
1.02
1.00
0.97
0.91
0.90
0.89
0.89
0.86
0.09
0.06
0.04
-0.02
-0.03
NH2
Me
OTBS
S49
1.00
0.98
0.94
3.24
10.90
6.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

Frequency (1H): 400.15 MHz
Solvent: CDCl3

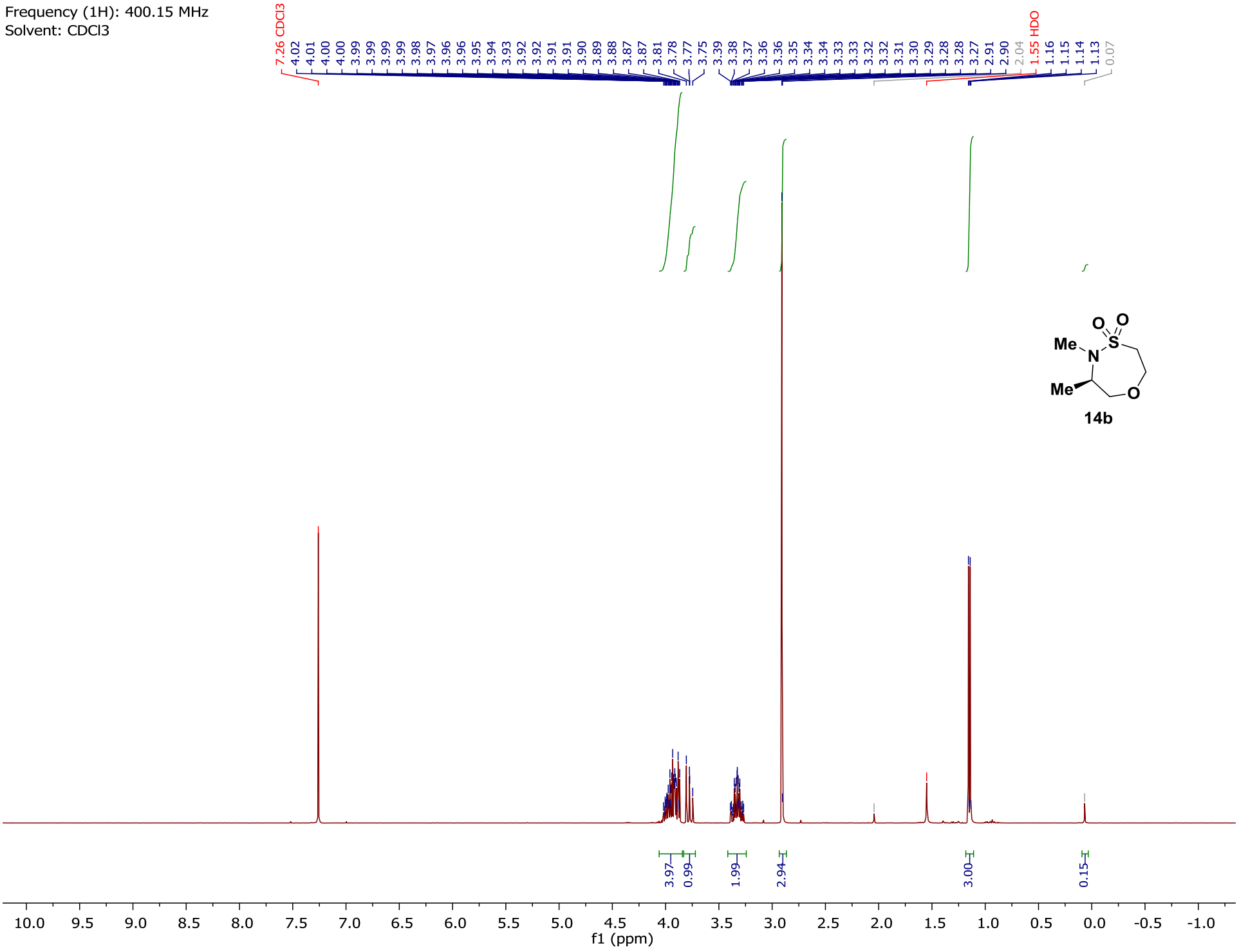


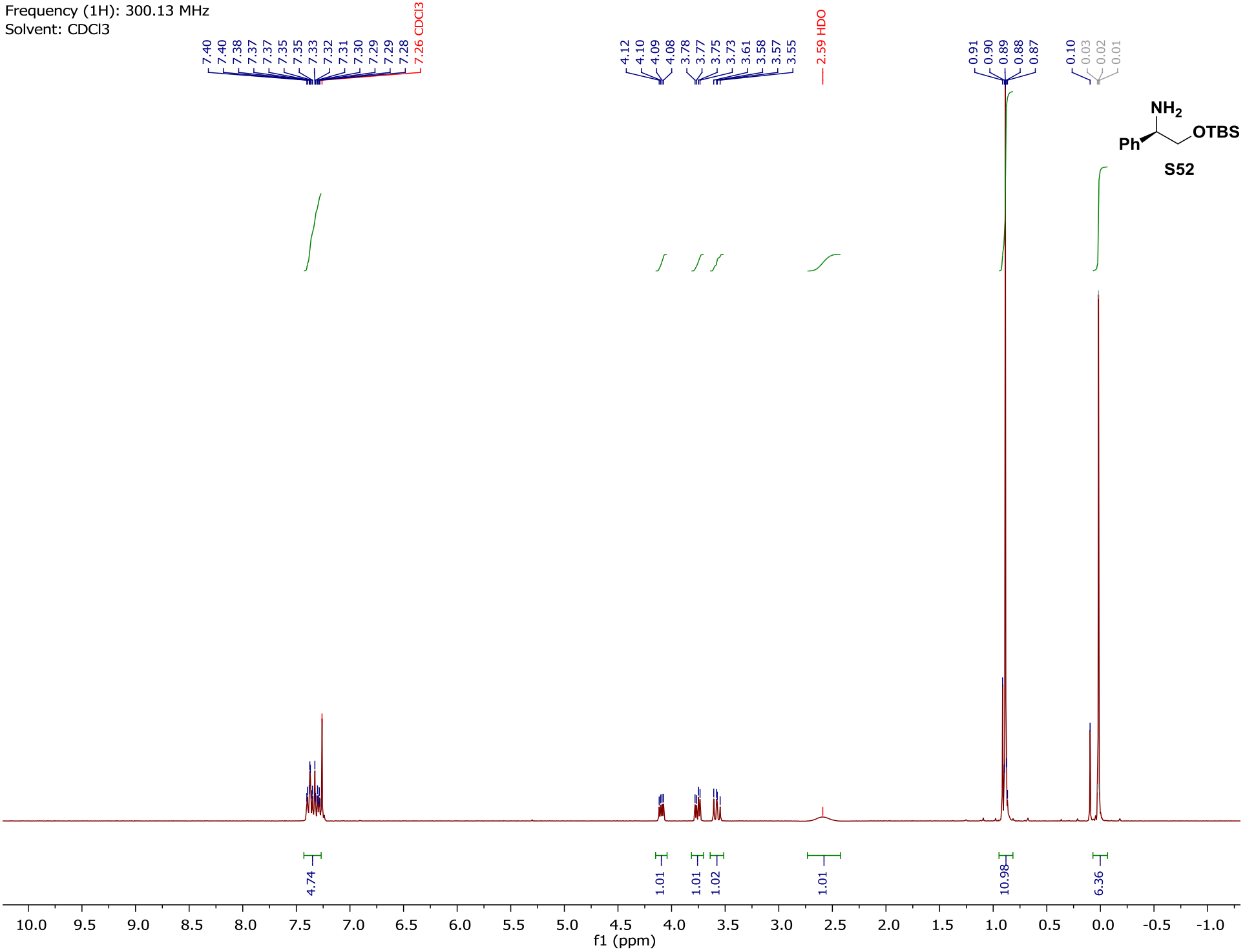
Frequency (1H): 400.15 MHz
Solvent: CDCl3



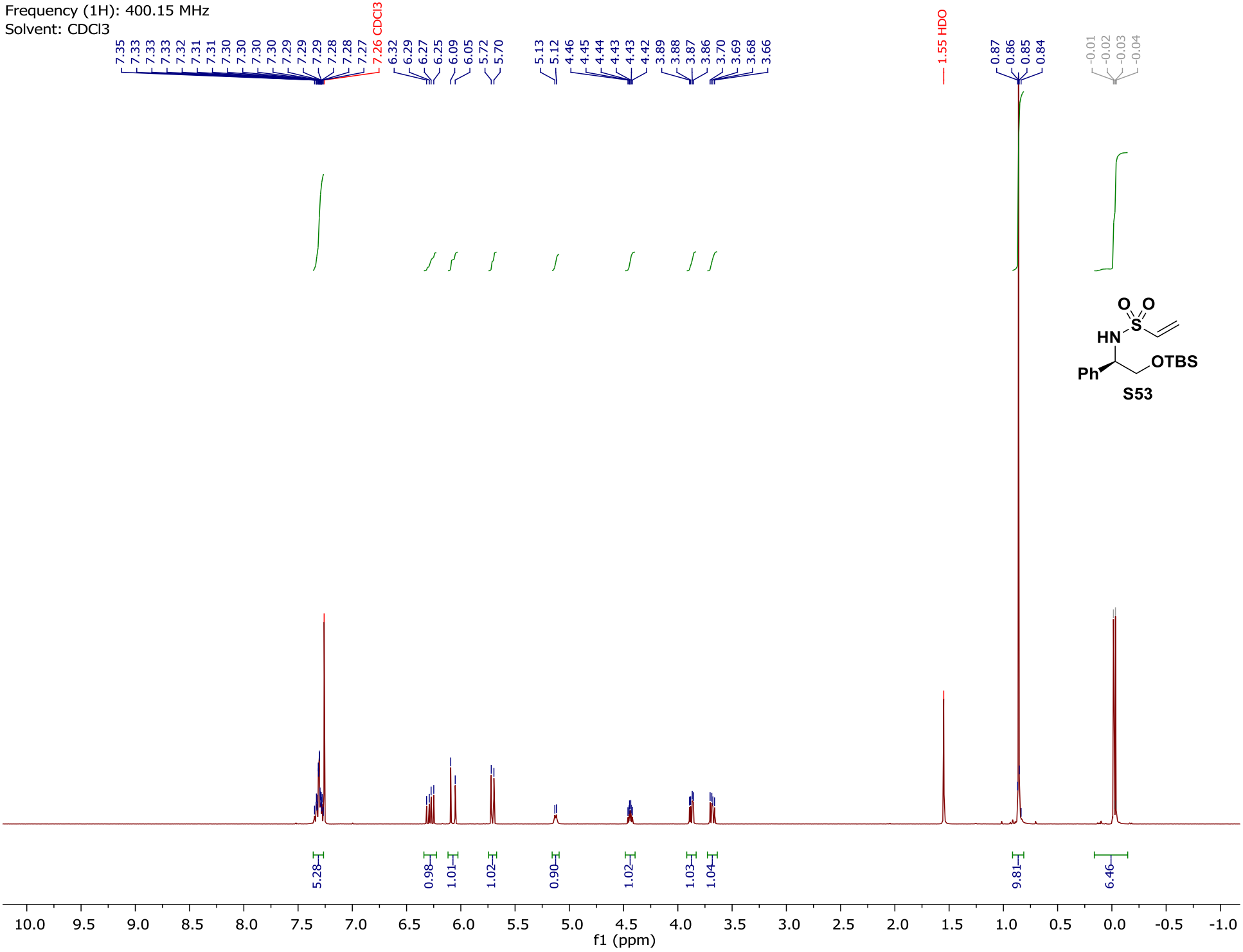
S51

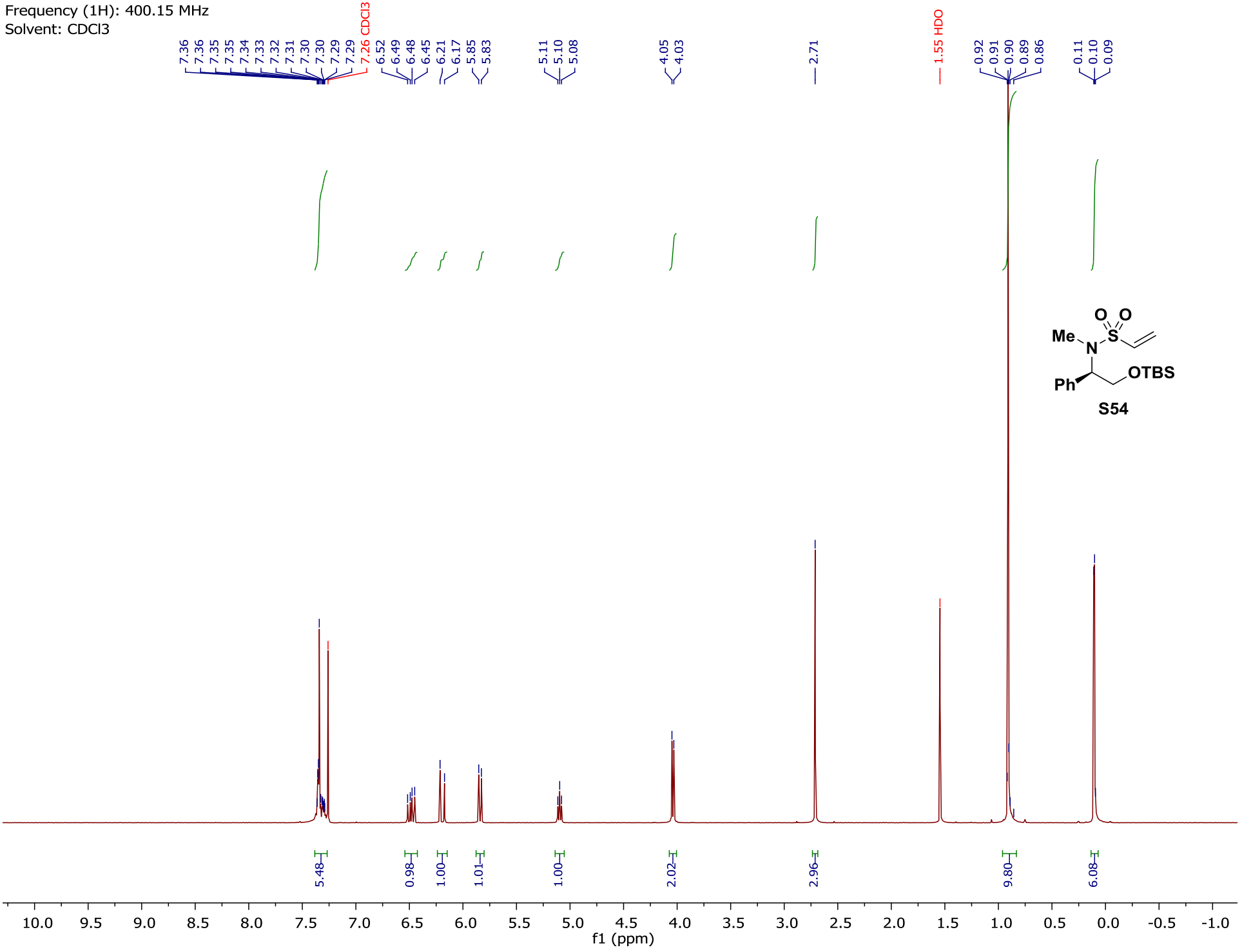
Frequency (1H): 400.15 MHz
Solvent: CDCl3



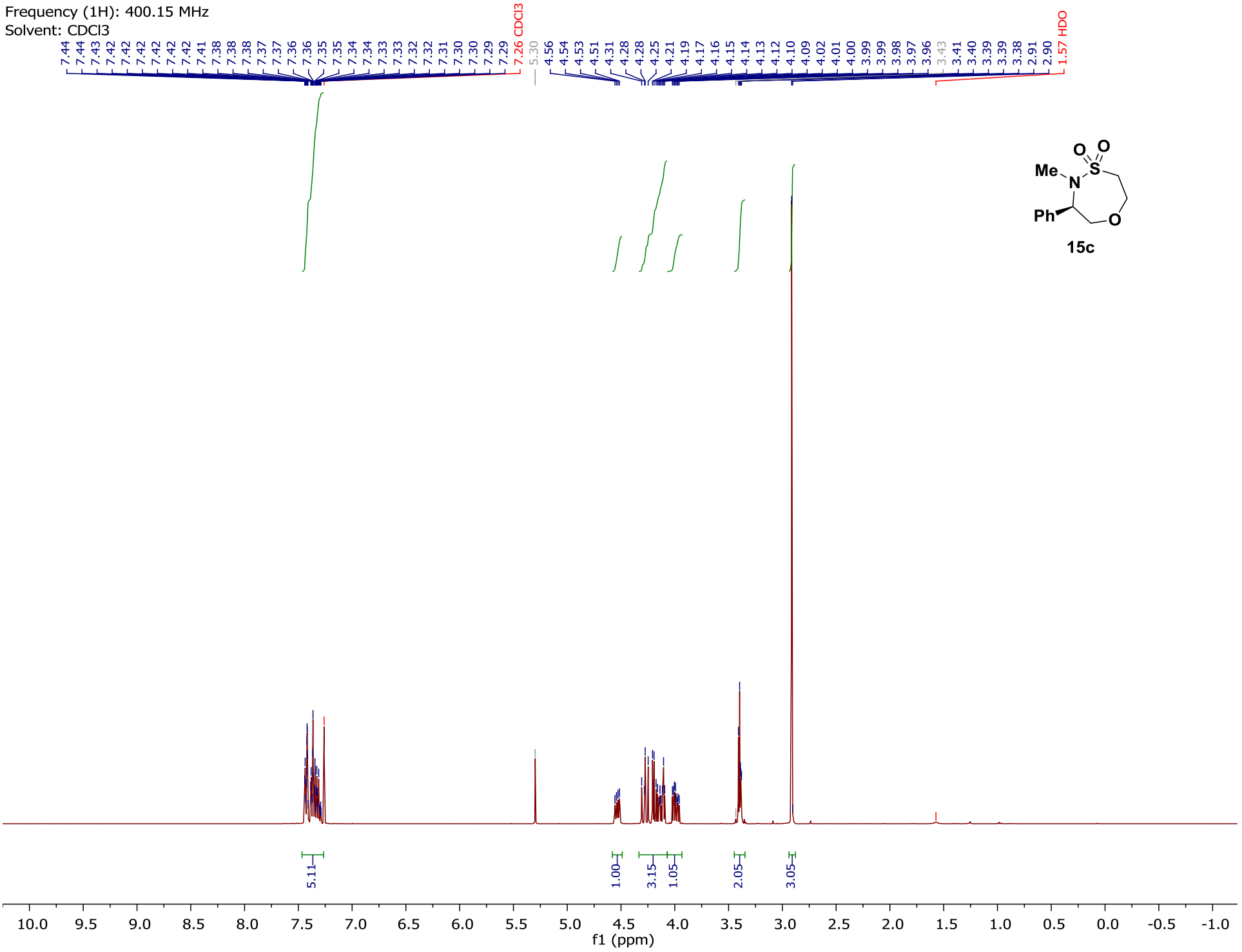

Frequency (1H): 300.13 MHz
Solvent: CDCl3
7.40
7.40
7.38
7.37
7.37
7.35
7.35
7.33
7.32
7.31
7.30
7.29
7.29
7.28
7.26 CDCl3
4.12
4.10
4.09
4.08
3.78
3.77
3.75
3.73
3.61
3.58
3.57
3.55
2.59 HDO
0.91
0.90
0.89
0.88
0.87
0.10
0.03
0.02
0.01
NH2
OTBS
Ph
S52
4.74
1.01
1.01
1.02
1.01
10.98
6.36
10.0
9.5
9.0
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
-1.0
f1 (ppm)

Frequency (1H): 400.15 MHz
Solvent: CDCl3



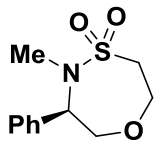

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.36
7.36
7.35
7.35
7.34
7.33
7.32
7.31
7.30
7.30
7.29
7.29
7.26 CDCl3
6.52
6.49
6.48
6.45
6.21
6.17
5.85
5.83
5.11
5.10
5.08
4.05
4.03
2.71
1.55 HDO
0.92
0.91
0.90
0.89
0.86
0.11
0.10
0.09
Me
N
O
O
S
Ph
OTBS
S54
5.48
0.98
1.00
1.01
1.00
2.02
2.96
9.80
6.08
10.0
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
-1.0
f1 (ppm)

Frequency (1H): 400.15 MHz
Solvent: CDCl3

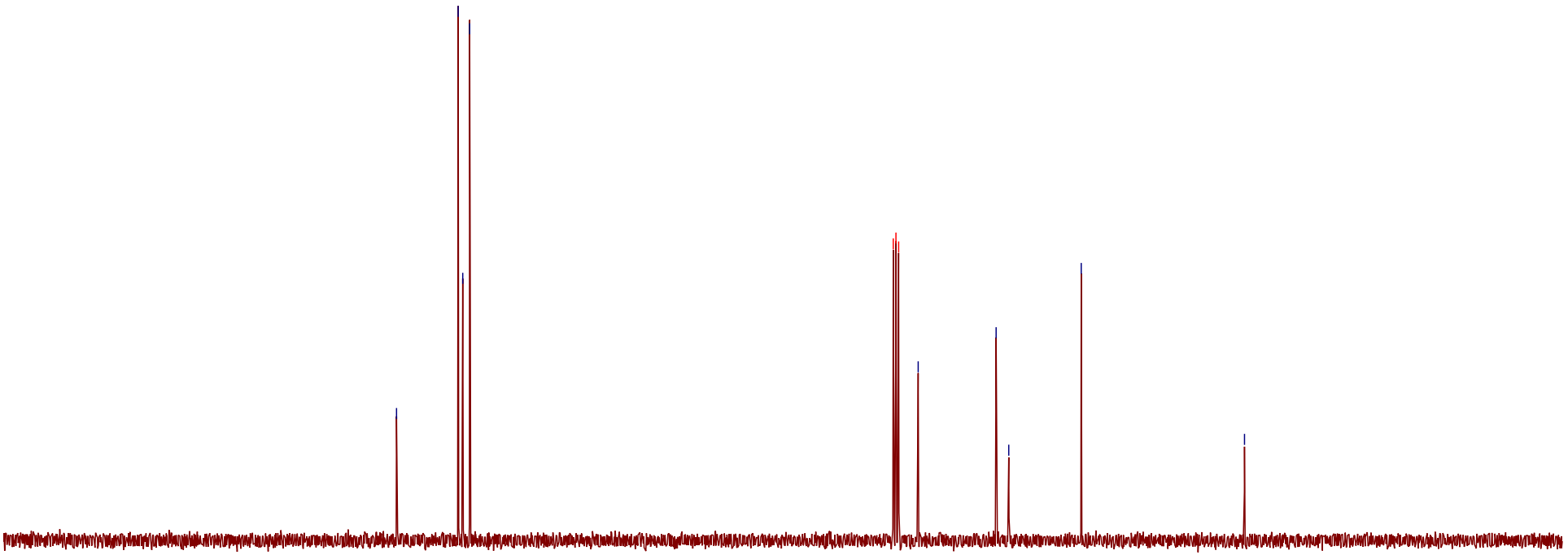


Frequency (13C): 100.63 MHz
Solvent: CDCl3

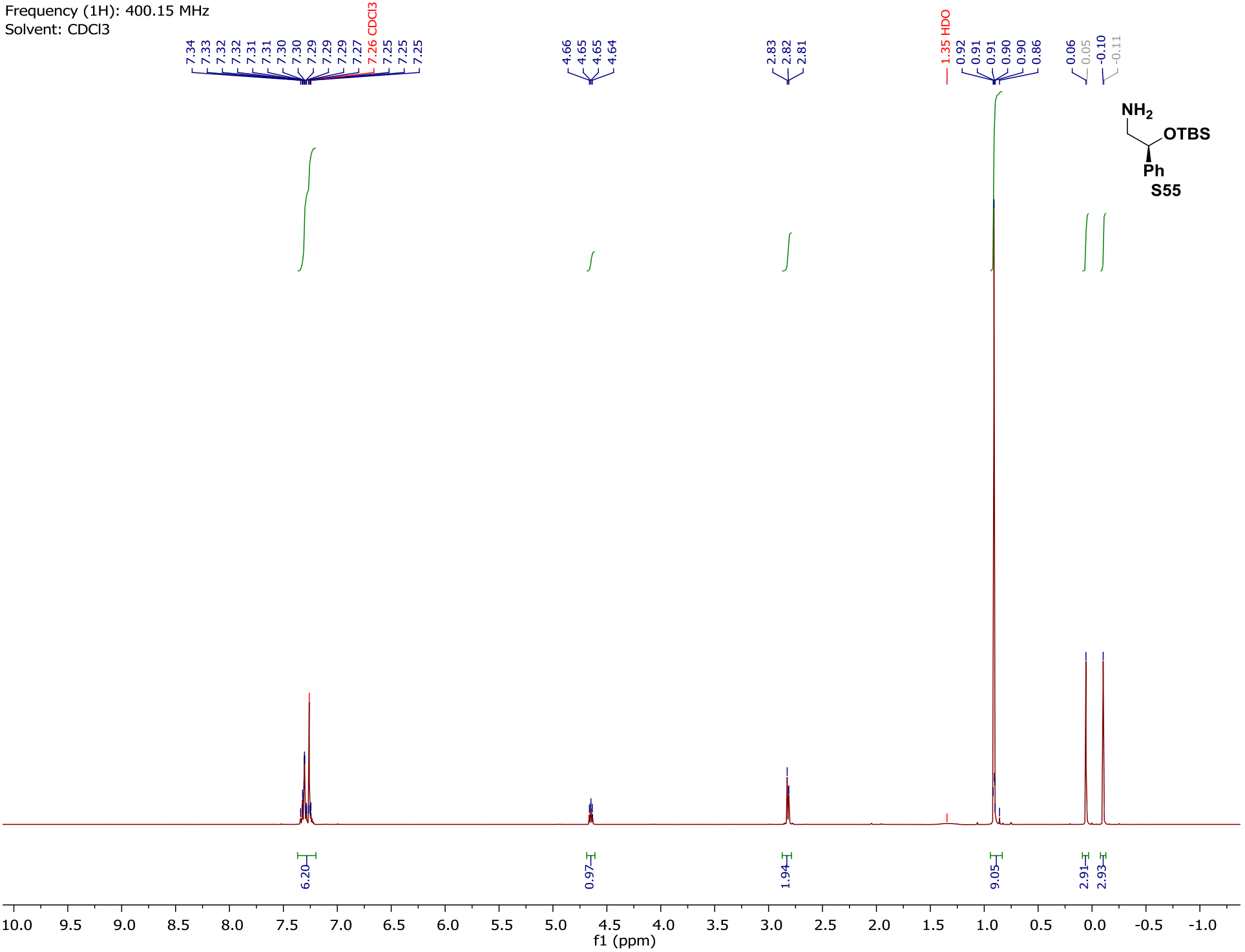
136.02
128.74
128.20
127.38
77.39 CDCl3
77.07 CDCl3
76.75 CDCl3
74.44
65.24
63.75
55.20
35.93

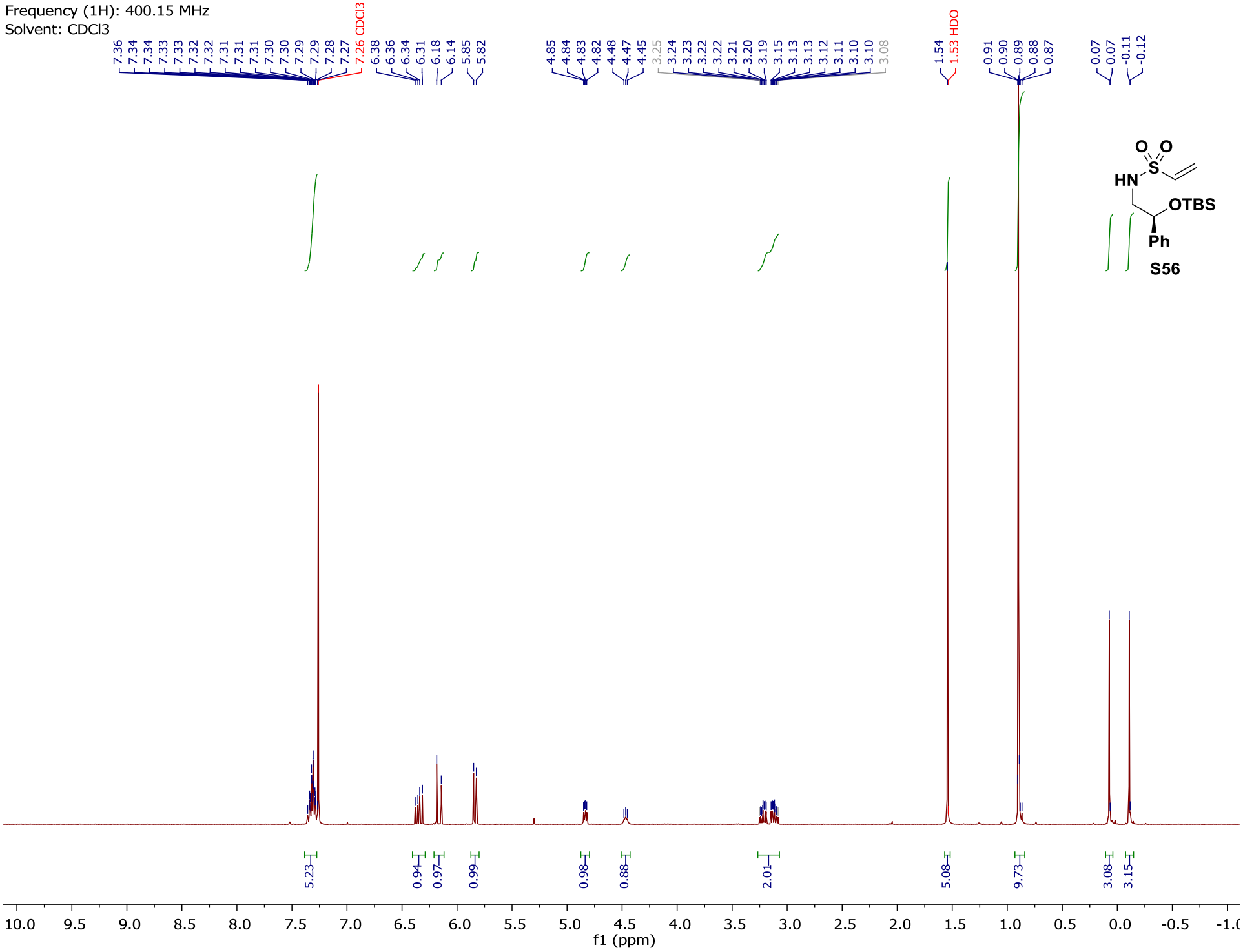


15c

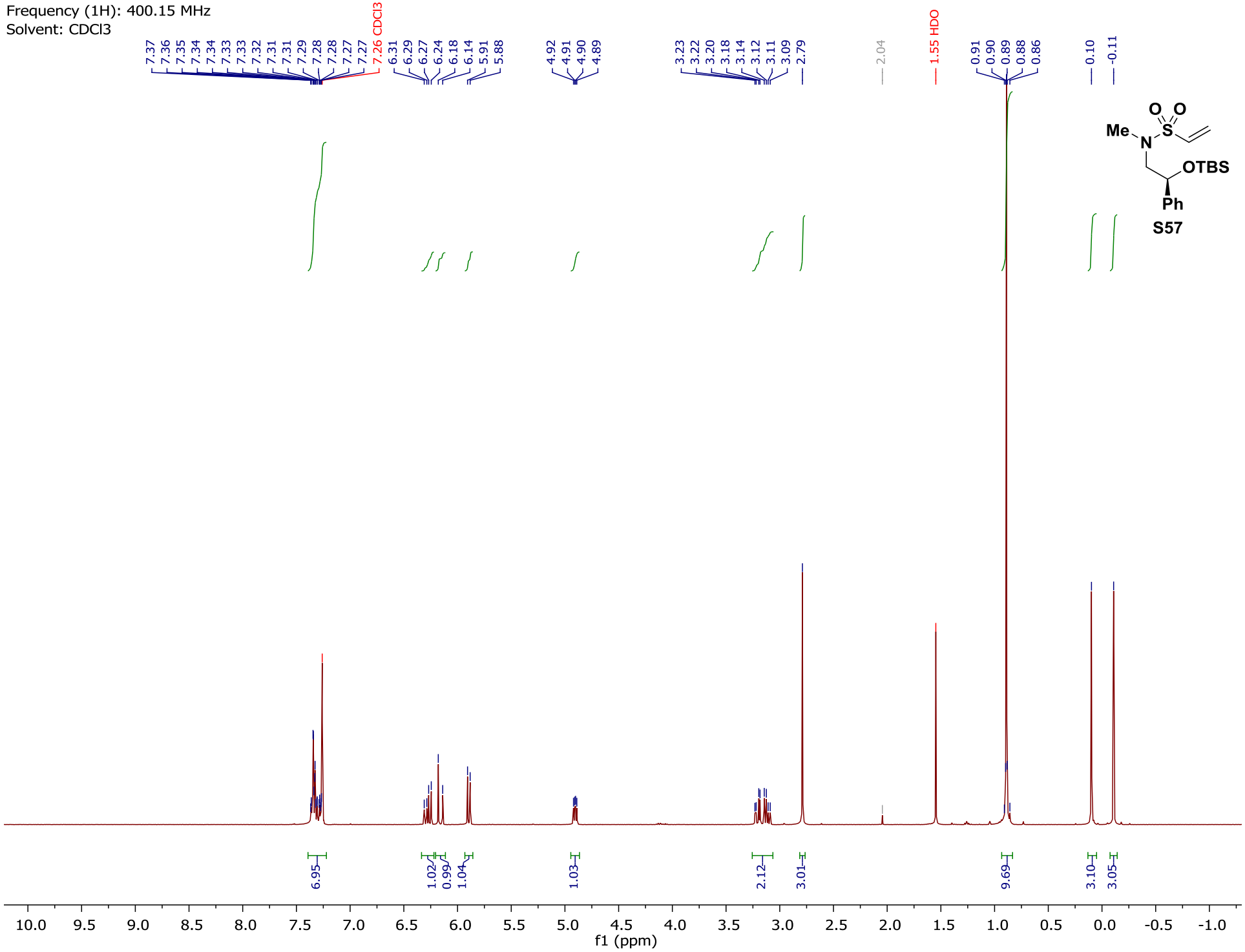


180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

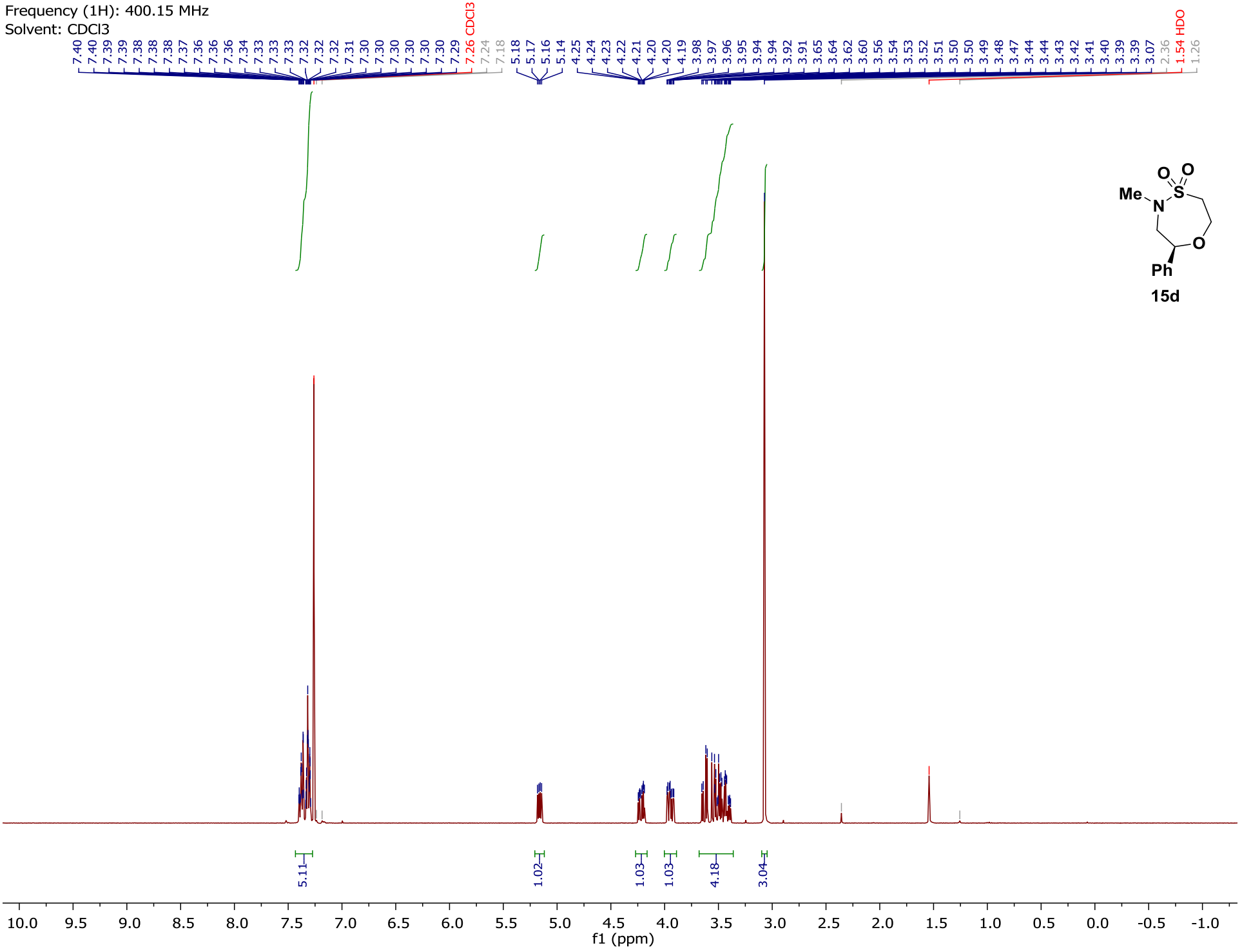

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.29
7.27
7.26 CDCl3
7.25
7.25
7.25
4.66
4.65
4.65
4.64
2.83
2.82
2.81
1.35 HDO
0.92
0.91
0.91
0.90
0.90
0.86
0.06
0.05
-0.10
-0.11
NH2
OTBS
Ph
S55
6.20
0.97
1.94
9.05
2.91
2.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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
-1.0
f1 (ppm)

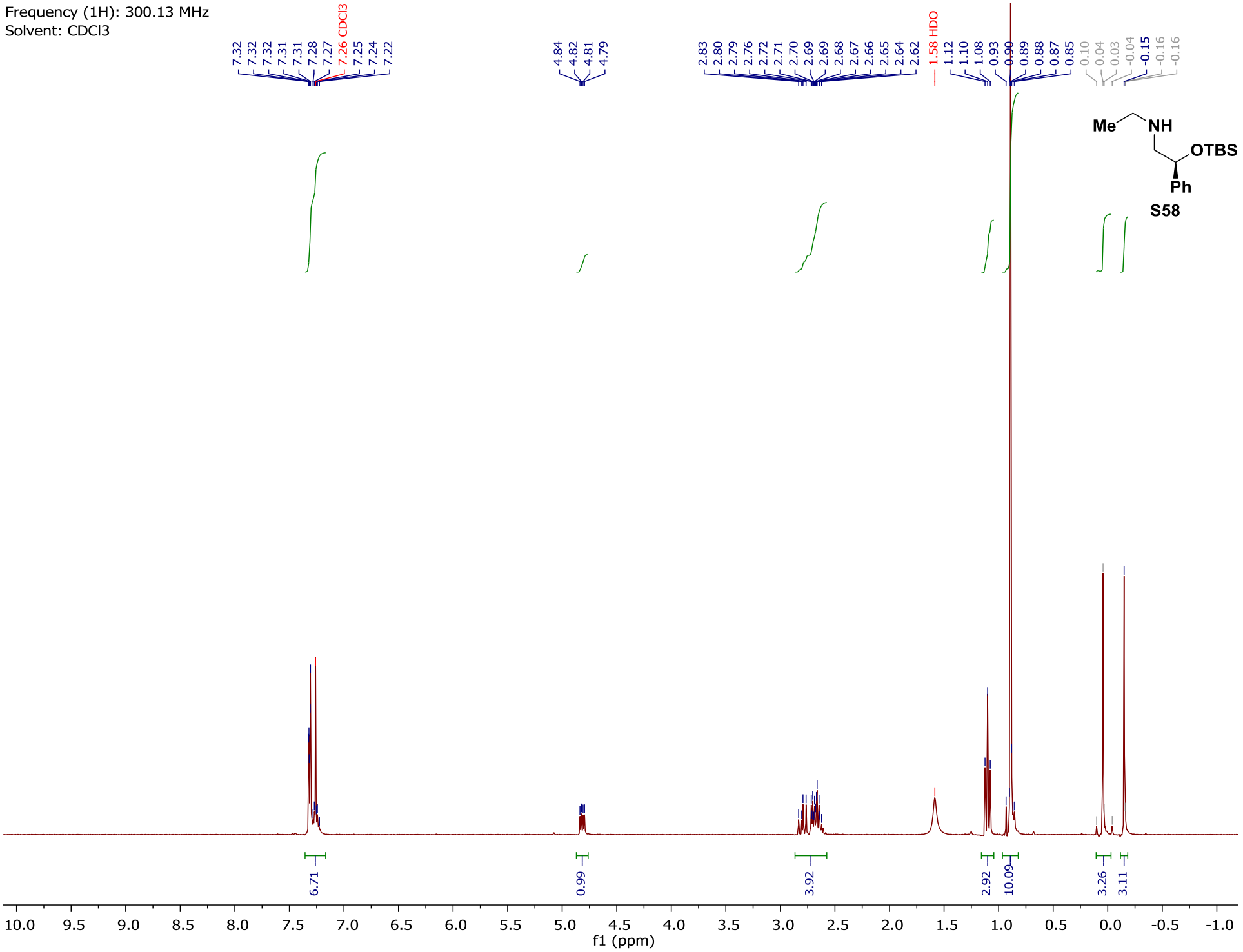

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.36 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.27 7.26 CDCl3
6.38 6.36 6.34 6.31 6.18 6.14 5.85 5.82
4.85 4.84 4.83 4.82 4.48 4.47 4.45 3.25 3.24 3.23 3.22 3.22 3.21 3.20 3.19 3.15 3.13 3.13 3.12 3.11 3.10 3.10 3.08
1.54 1.53 HDO
0.91 0.90 0.89 0.88 0.87
0.07 0.07 -0.11 -0.12
O O
S
HN
OTBS
Ph
S56
5.23 0.94 0.97 0.99 0.98 0.88 2.01 5.08 9.73 3.08 3.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

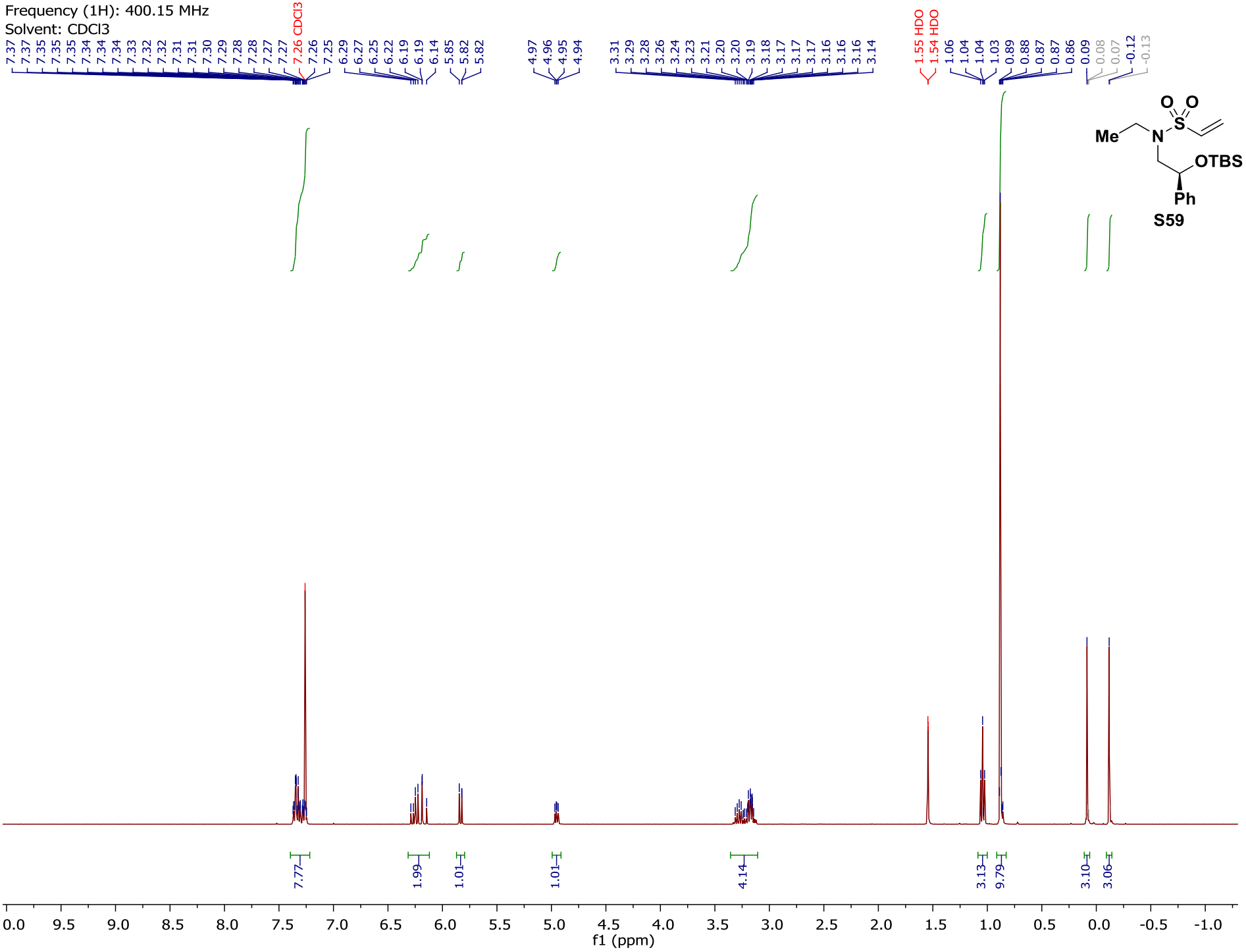
Frequency (1H): 400.15 MHz
Solvent: CDCl3

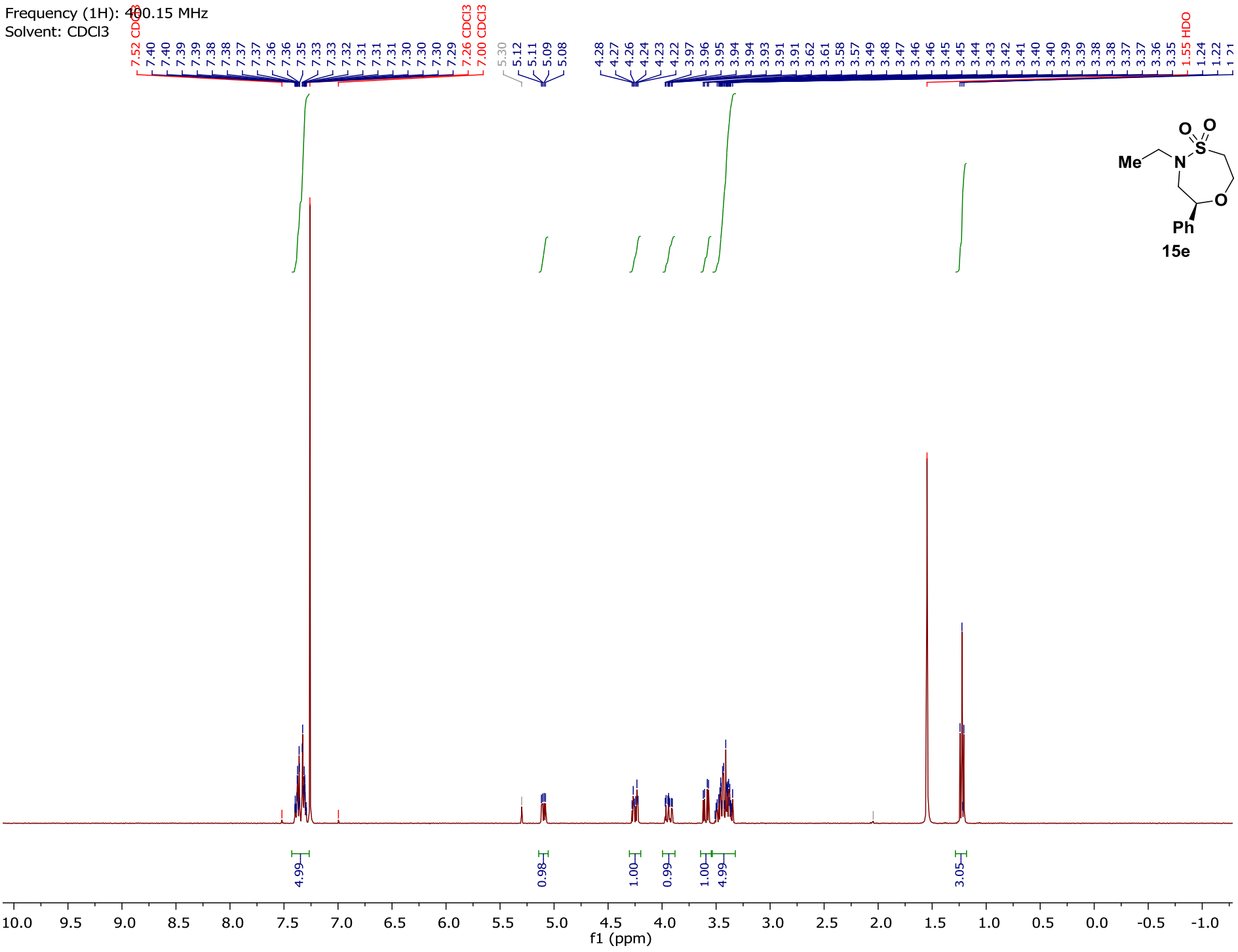


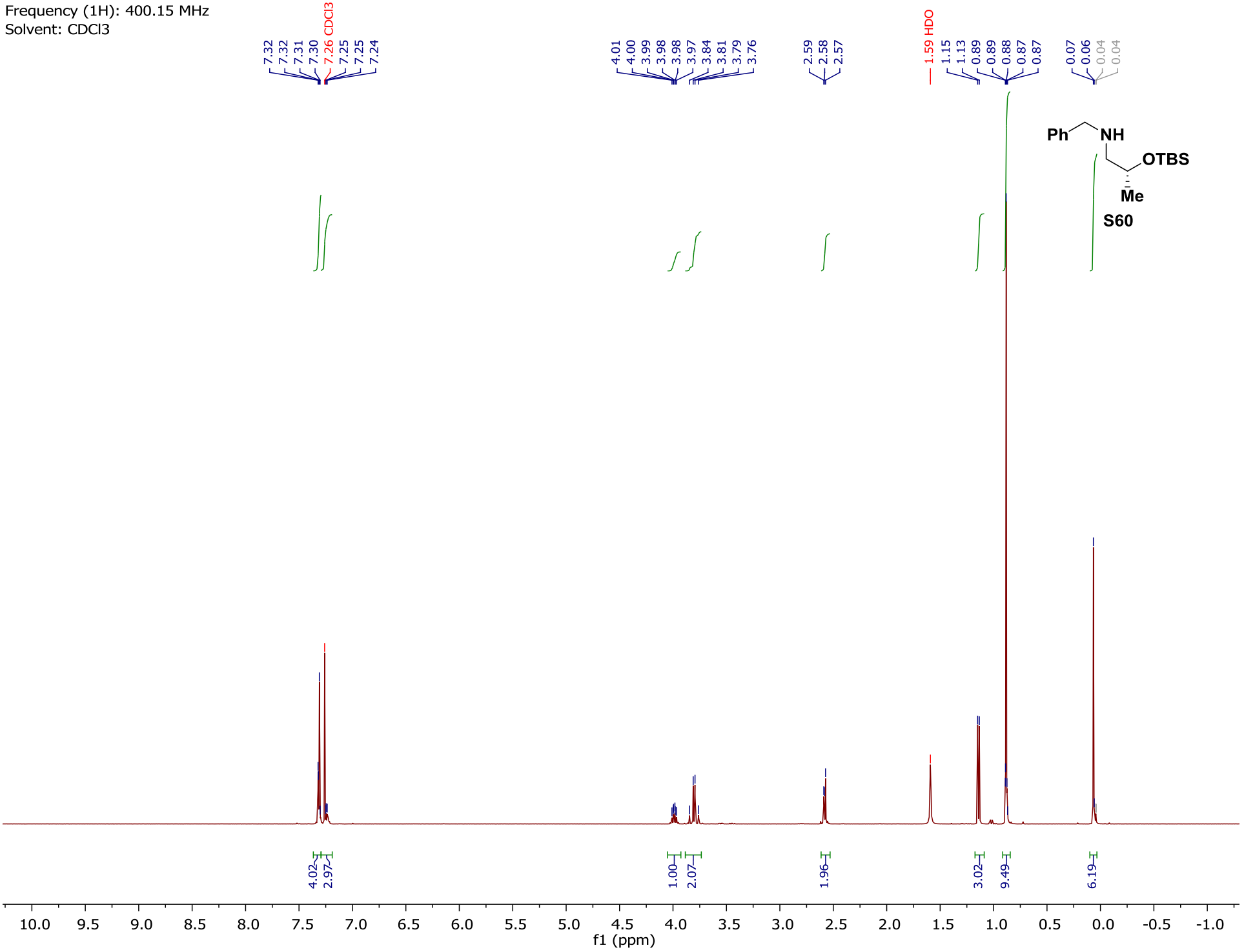
S57

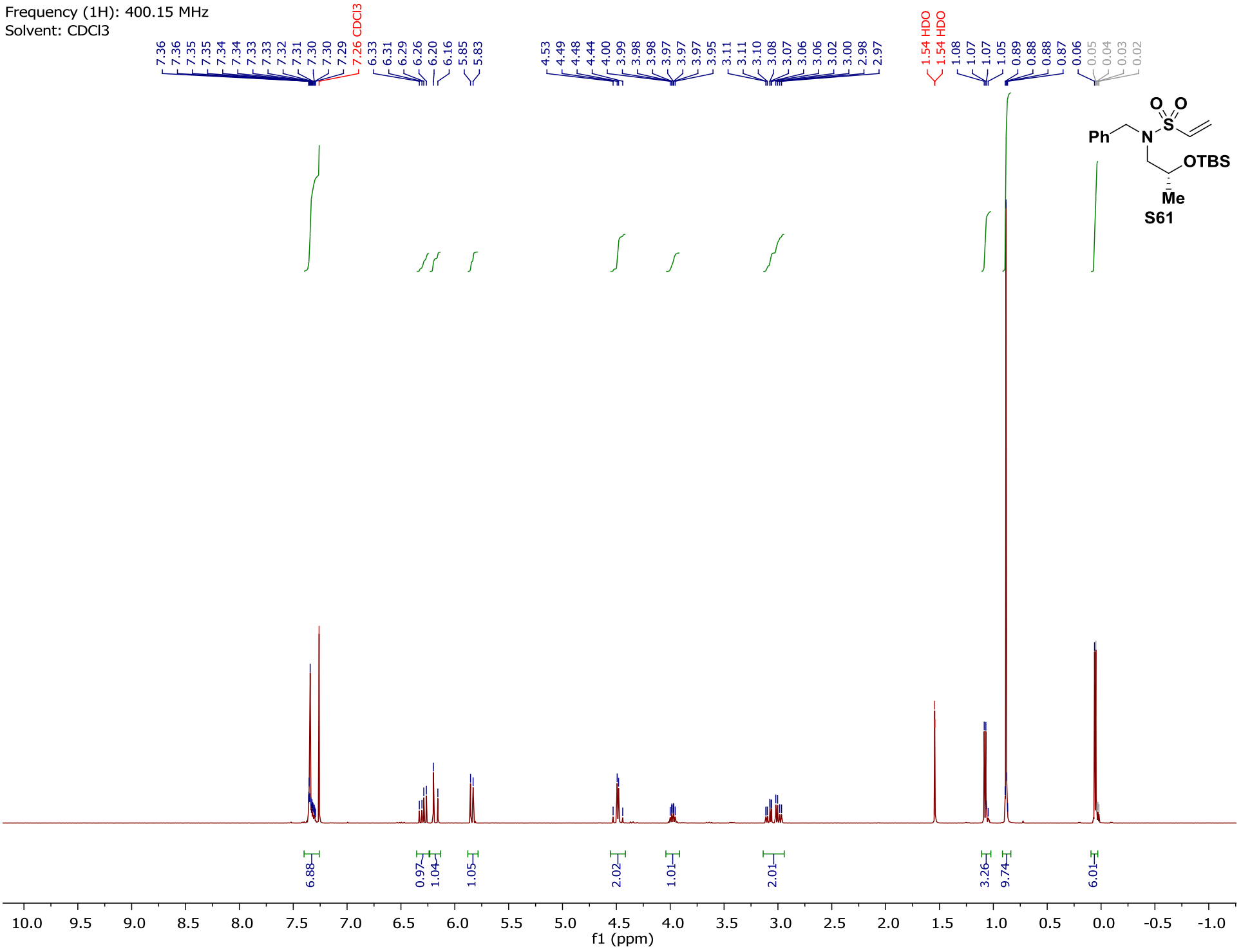

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.40 7.40 7.39 7.39 7.38 7.38 7.38 7.37 7.36 7.36 7.36 7.34 7.33 7.33 7.33 7.32 7.32 7.32 7.31 7.30 7.30 7.30 7.30 7.30 7.30 7.29 7.26 CDCl3 7.24 7.18
5.18 5.17 5.16 5.14
4.25 4.24 4.23 4.22 4.21 4.20 4.20 4.19 3.98 3.97 3.96 3.95 3.94 3.94 3.92 3.91 3.65 3.64 3.62 3.60 3.56 3.54 3.53 3.52 3.51 3.50 3.50 3.49 3.48 3.47 3.44 3.44 3.43 3.42 3.41 3.40 3.39 3.39 3.07 2.36 1.54 HDO 1.26
O O S Me N O Ph
15d
5.11 1.02 1.03 1.03 4.18 3.04
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 -1.0
f1 (ppm)


Frequency (1H): 300.13 MHz
Solvent: CDCl3
7.32 7.32 7.32 7.31 7.31 7.28 7.27 7.26 CDCl3 7.25 7.24 7.22
4.84 4.82 4.81 4.79
2.83 2.80 2.79 2.76 2.72 2.71 2.70 2.69 2.69 2.68 2.67 2.66 2.65 2.64 2.62
1.58 HDO
1.12 1.10 1.08 0.93 0.90 0.89 0.88 0.87 0.85
0.10 0.04 0.03 -0.04 -0.15 -0.16 -0.16
Me NH OTBS Ph
S58
6.71 0.99 3.92 2.92 10.09 3.26 3.11
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 -1.0
f1 (ppm)

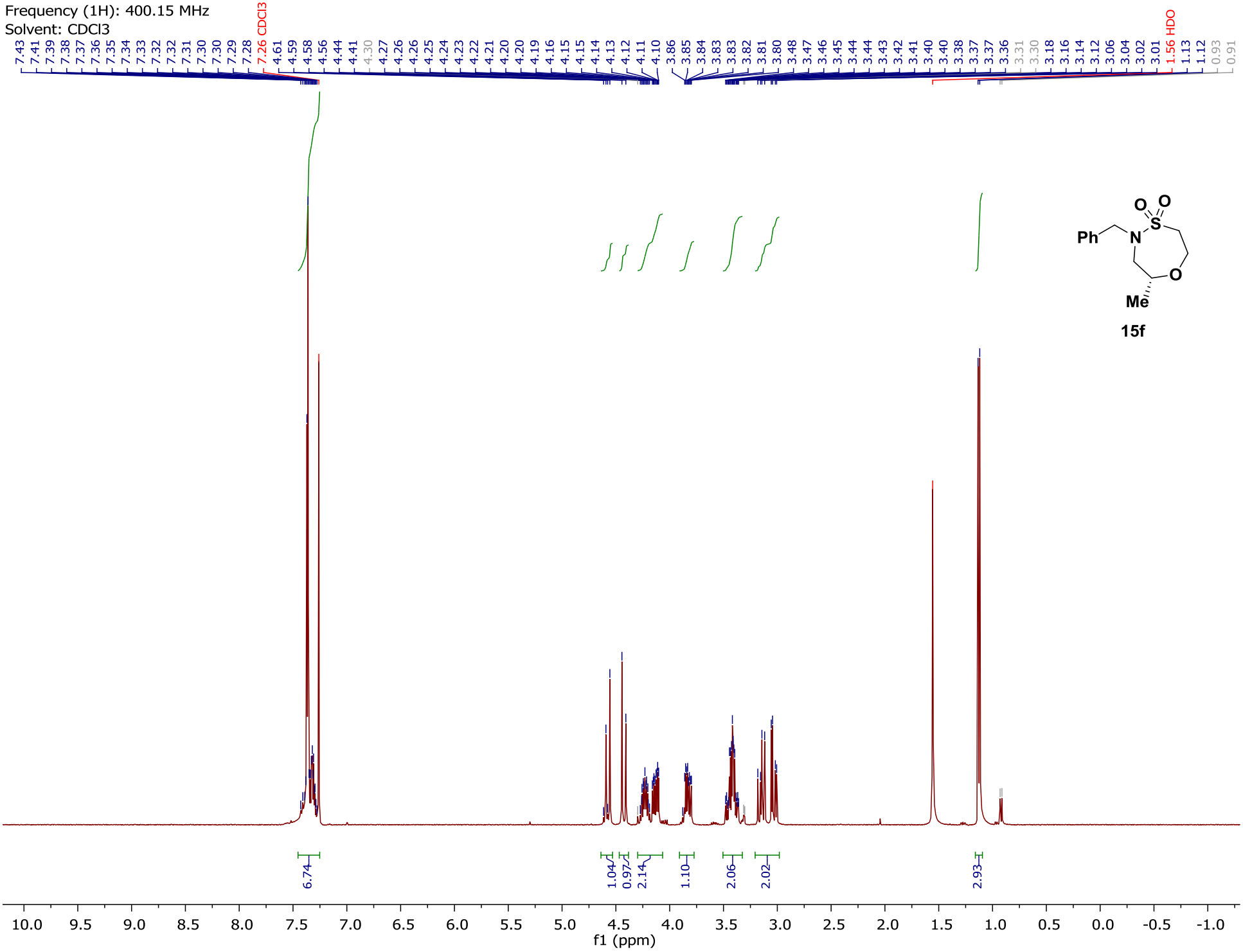

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.37 7.37 7.35 7.35 7.35 7.34 7.34 7.34 7.33 7.32 7.32 7.31 7.31 7.30 7.29 7.28 7.28 7.27 7.27 7.26 CDCl3 7.26 7.25 6.29 6.27 6.25 6.22 6.19 6.19 6.14 5.85 5.82 5.82
4.97 4.96 4.95 4.94
3.31 3.29 3.28 3.26 3.24 3.23 3.21 3.20 3.20 3.19 3.18 3.17 3.17 3.17 3.16 3.16 3.16 3.14
1.55 HDO 1.54 HDO 1.06 1.04 1.04 1.03 0.89 0.88 0.87 0.87 0.86 0.09 0.08 0.07 -0.12 -0.13
Me
N
O O
S
OTBS
Ph
S59
7.77
1.99
1.01
1.01
4.14
3.13
9.79
3.10
3.06
0.0 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 -1.0
f1 (ppm)


Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.52 CDCl3
7.26 CDCl3
7.00 CDCl3
5.30
1.55 H2O
Me
N
O
S
O
O
Ph
15e
4.99
0.98
1.00
0.99
1.00
4.99
3.05
f1 (ppm)

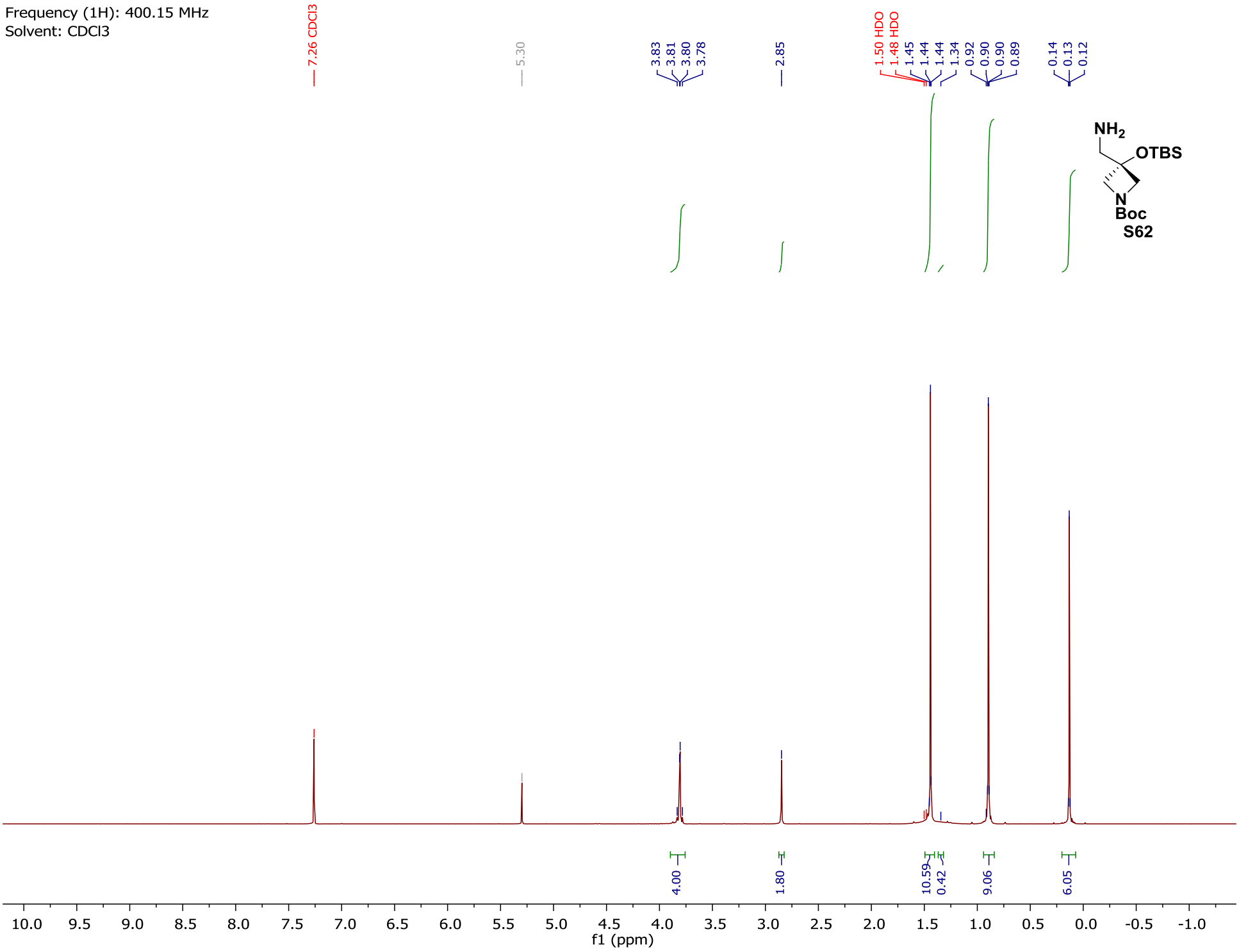

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.32
7.32
7.31
7.30
7.26 CDCl3
7.25
7.25
7.24
4.01
4.00
3.99
3.98
3.98
3.97
3.84
3.81
3.79
3.76
2.59
2.58
2.57
1.59 HDO
1.15
1.13
0.89
0.89
0.88
0.87
0.87
0.07
0.06
0.04
0.04
Ph
NH
OTBS
Me
S60
4.02
2.97
1.00
2.07
1.96
3.02
9.49
6.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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
-1.0
f1 (ppm)


Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.36 7.36 7.35 7.35 7.34 7.34 7.33 7.33 7.32 7.31 7.30 7.30 7.29 7.26 CDCl3
6.33 6.31 6.29 6.26 6.20 6.16 5.85 5.83
4.53 4.49 4.48 4.44 4.00 3.99 3.98 3.98 3.97 3.97 3.97 3.95 3.11 3.11 3.10 3.08 3.07 3.06 3.06 3.02 3.00 2.98 2.97
1.54 HDO 1.54 HDO
1.08 1.07 1.07 1.05 0.89 0.88 0.88 0.87 0.06 0.05 0.04 0.03 0.02
O O S Ph N OTBS Me
S61
6.88 0.97 1.04 1.05 2.02 1.01 2.01 3.26 9.74 6.01
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 -1.0
f1 (ppm)

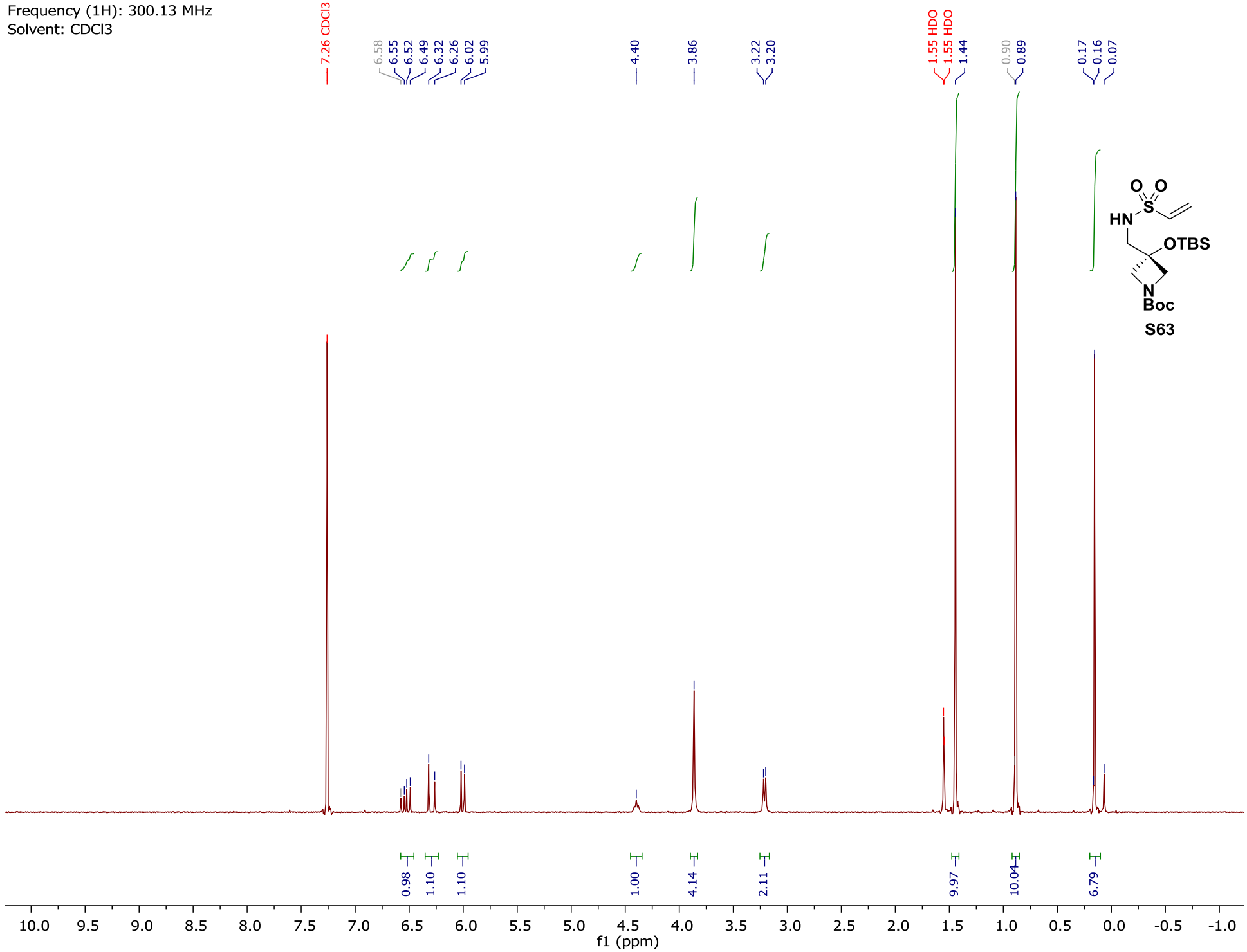
Frequency (1H): 400.15 MHz
Solvent: CDCl3



Frequency (1H): 400.15 MHz
Solvent: CDCl3

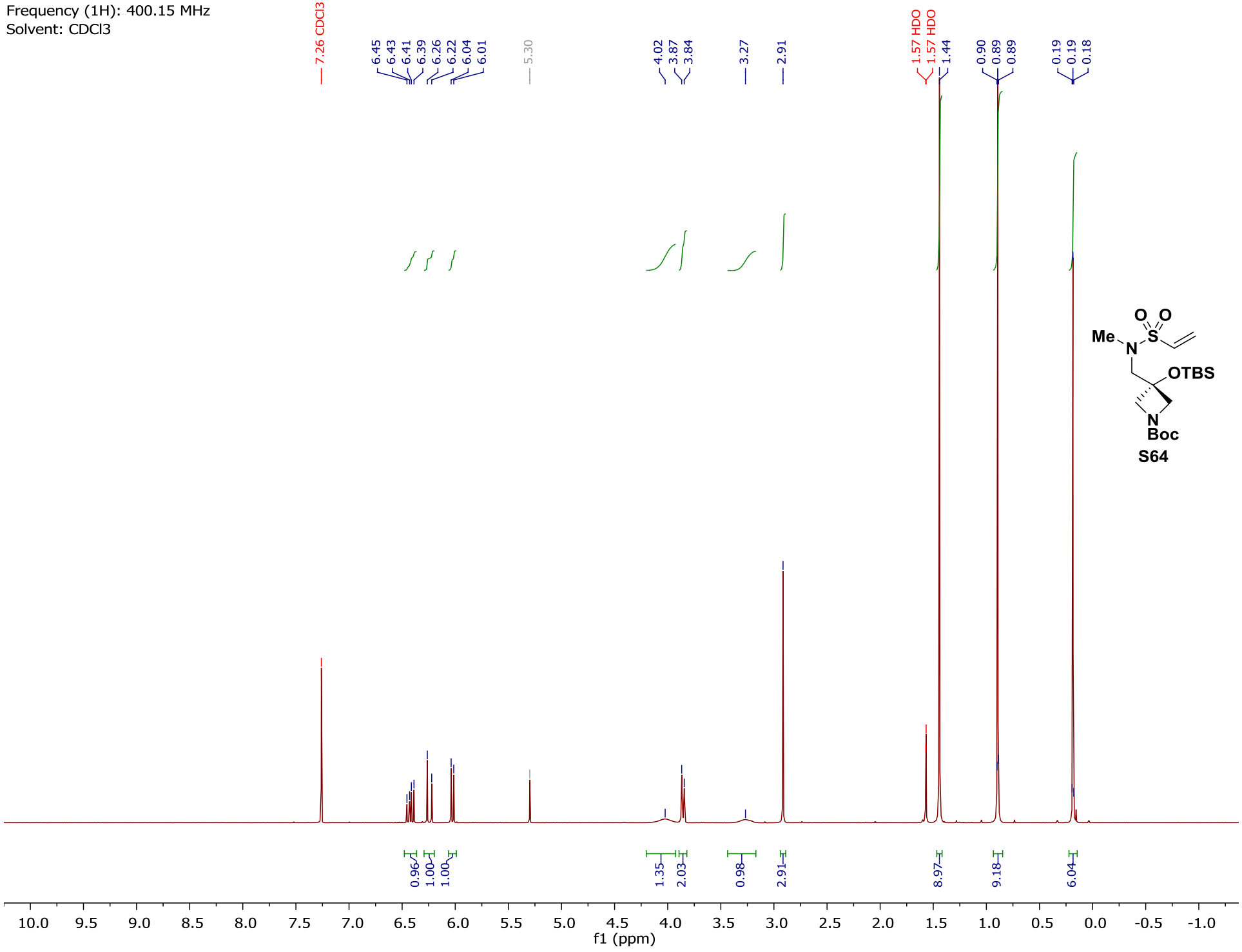


Frequency (1H): 300.13 MHz
Solvent: CDCl3



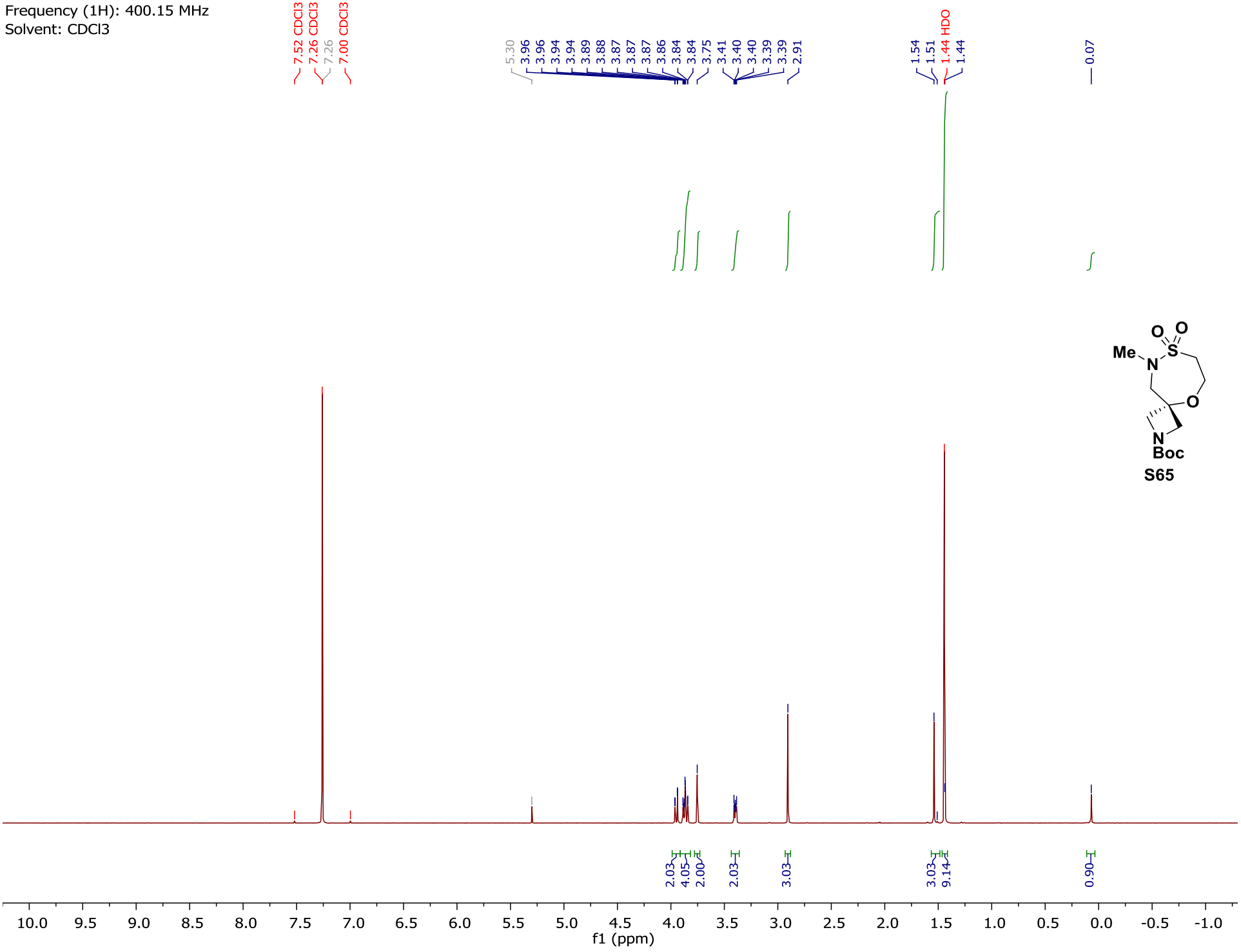
S63

Frequency (1H): 400.15 MHz
Solvent: CDCl3



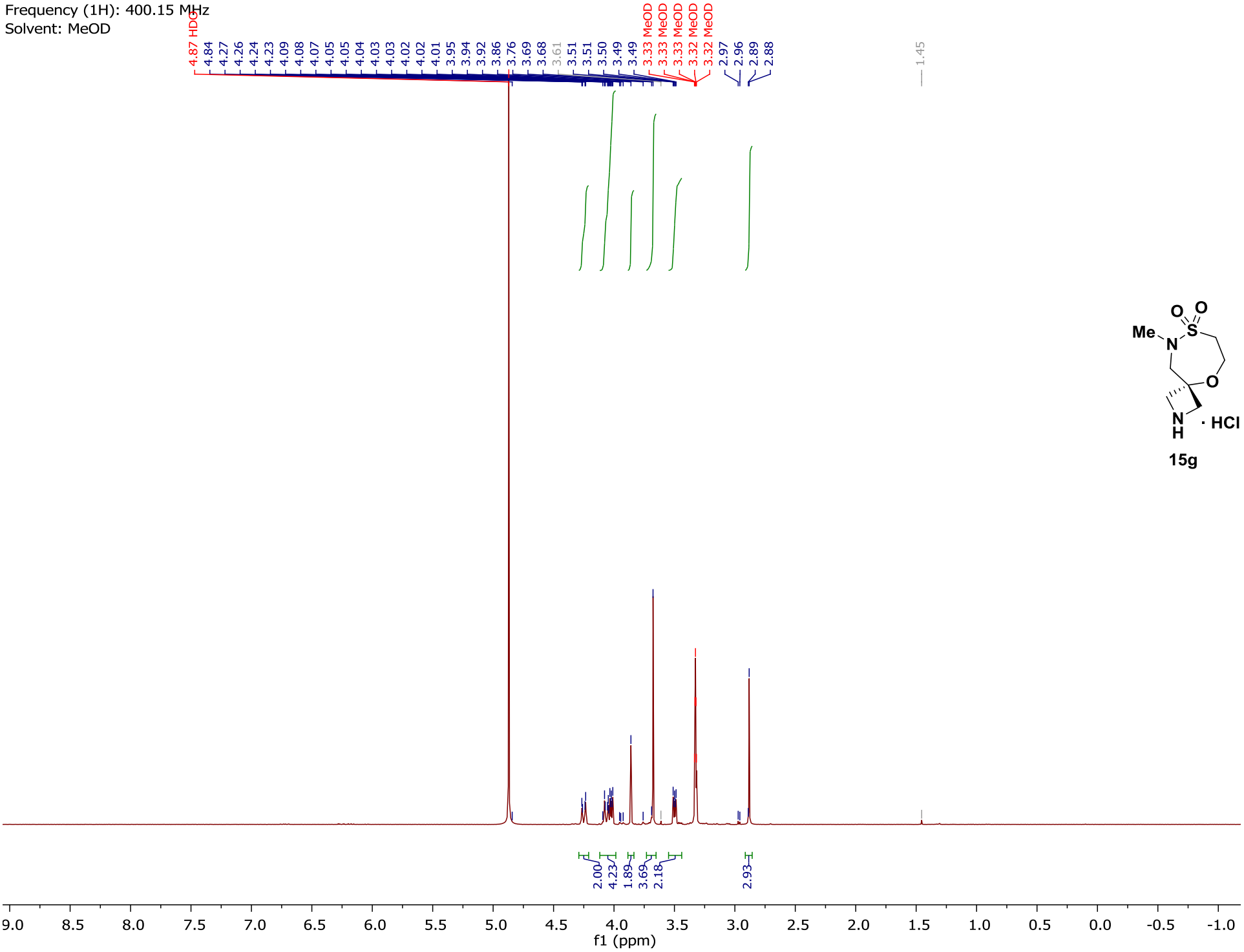
S64

Frequency (1H): 400.15 MHz
Solvent: CDCl3

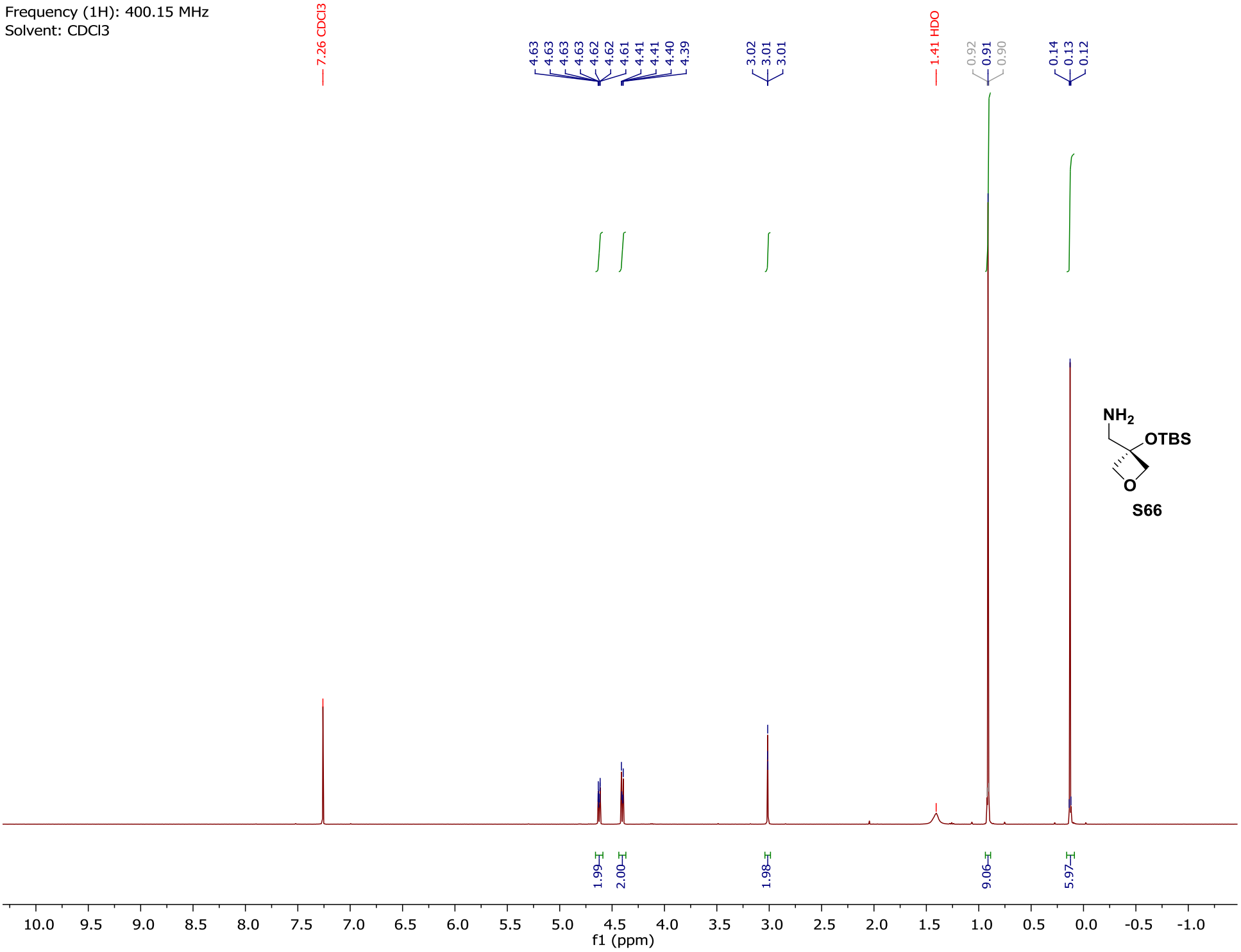


S65

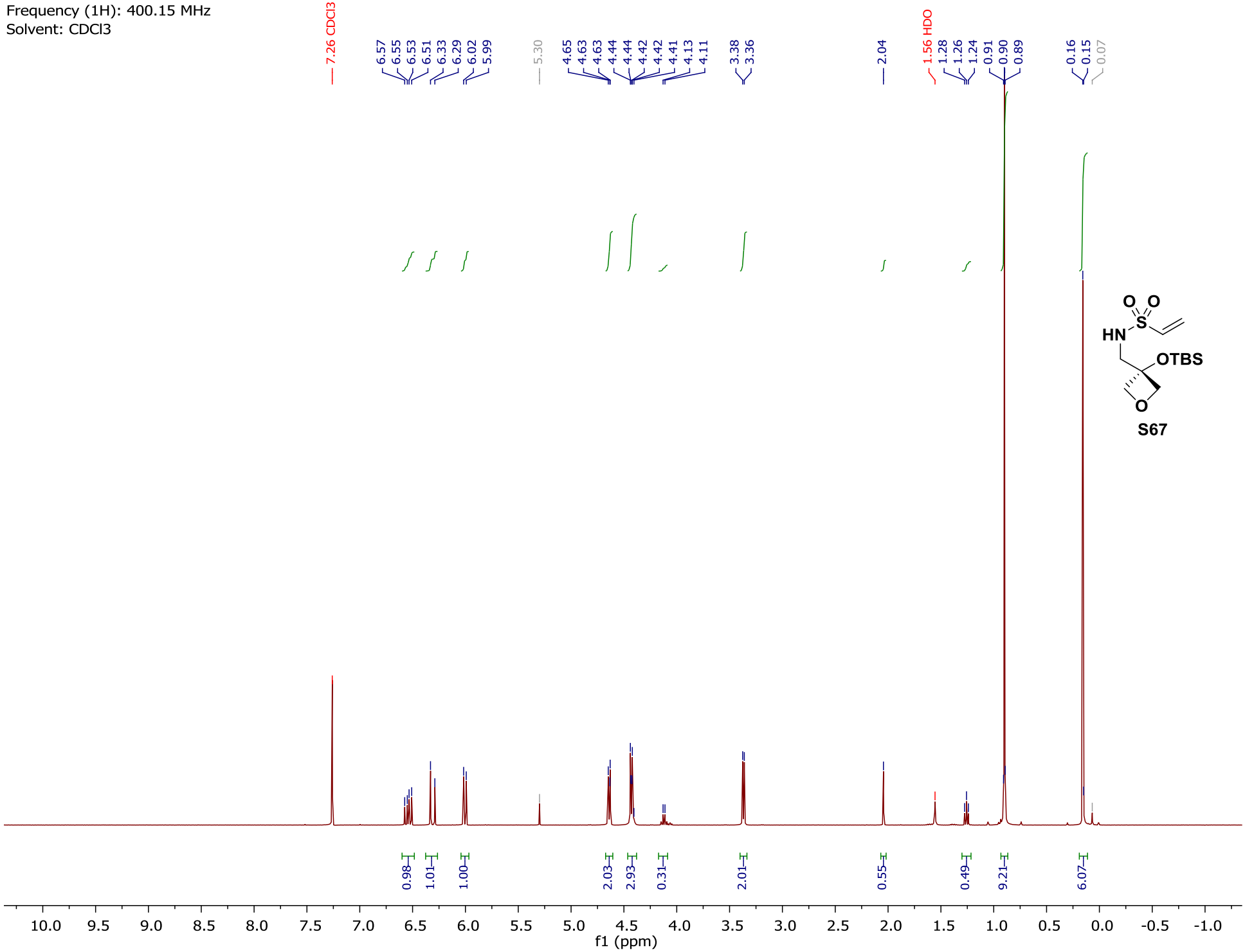
Frequency (1H): 400.15 MHz
Solvent: MeOD



15g

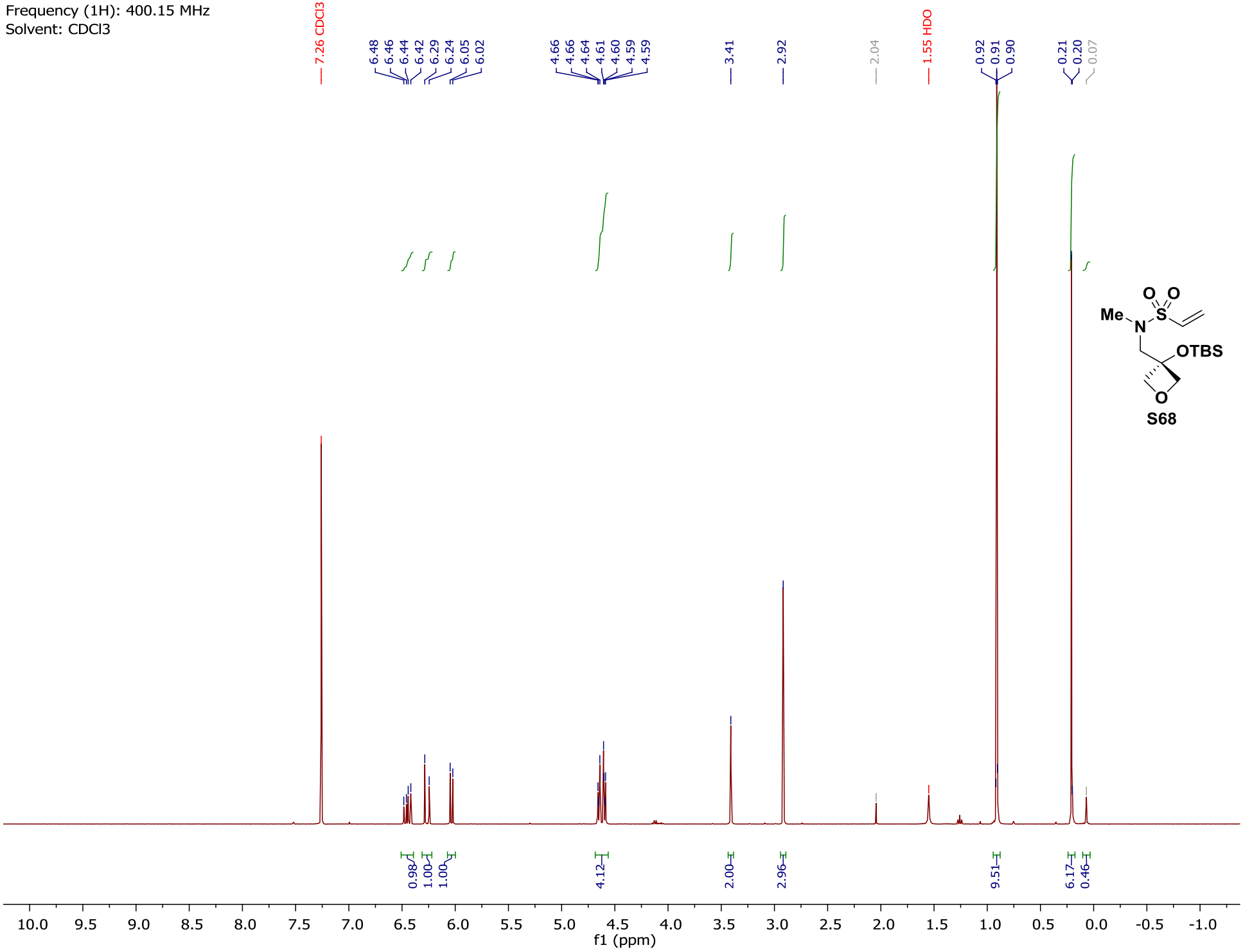

Frequency (1H): 400.15 MHz
Solvent: CDCl3
7.26 CDCl3
4.63
4.63
4.63
4.63
4.62
4.62
4.61
4.41
4.41
4.40
4.39
3.02
3.01
3.01
1.41 HDO
0.92
0.91
0.90
0.14
0.13
0.12
NH2
OTBS
O
S66
1.99
2.00
1.98
9.06
5.97
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

Frequency (1H): 400.15 MHz
Solvent: CDCl3



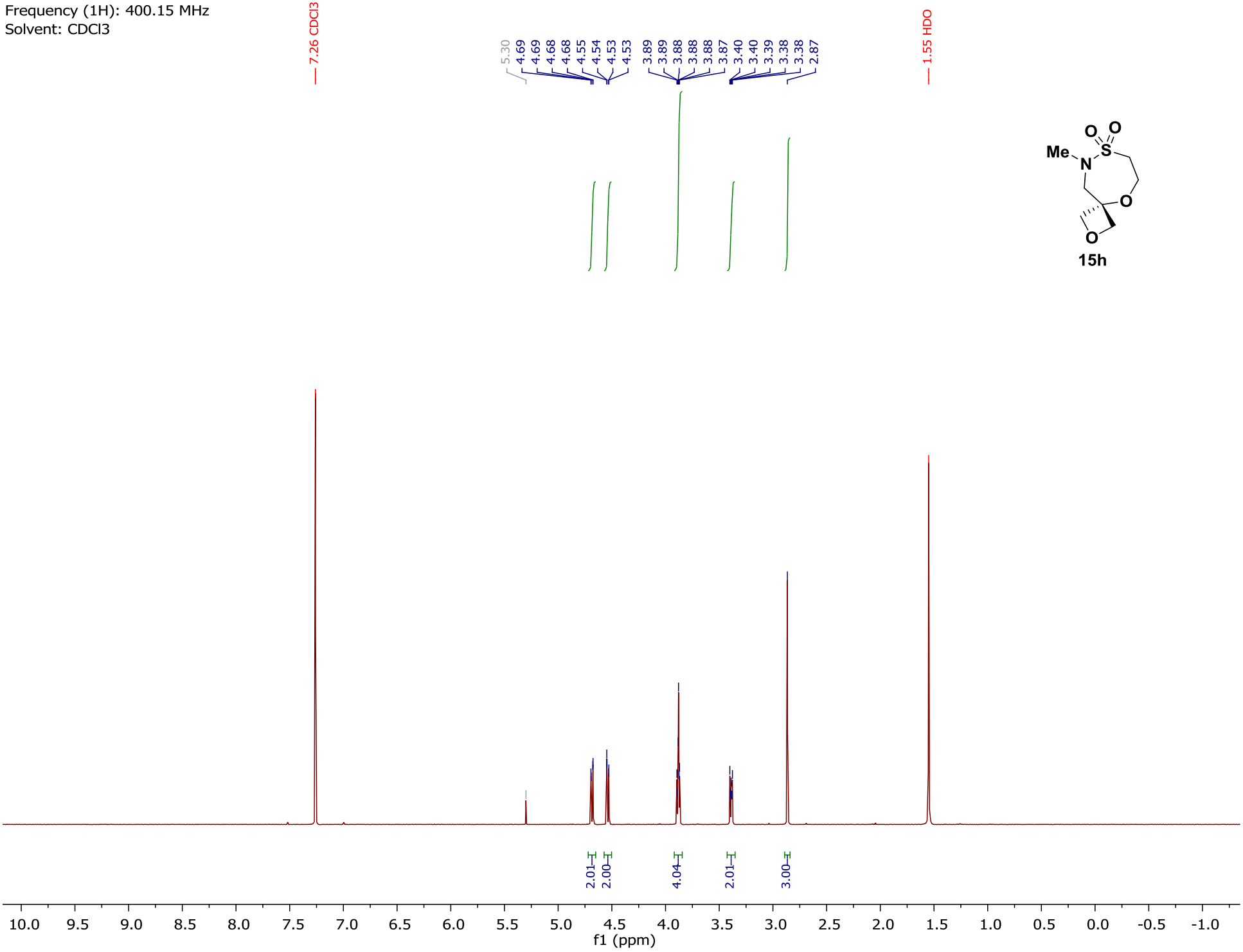
S67

Frequency (1H): 400.15 MHz
Solvent: CDCl3



S68

Frequency (1H): 400.15 MHz
Solvent: CDCl3



15h