Traceless Release of Alcohols Using Thiol-Sensitive Oxanorbornadiene Linkers

Allison G. Aioub, Cody J. Higginson, M.G. Finn*

School of Chemistry & Biochemistry, Georgia Institute of Technology, 901 Atlantic Dr., Atlanta, GA 30332, USA E-mail: mgfinn@gatech.edu

Supporting Information

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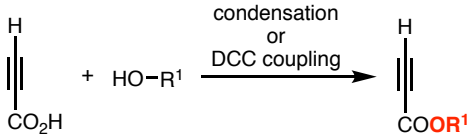
1. General Reagent Information

Unless otherwise noted, all reactions were carried out in oven-dried glassware under an atmosphere of dry argon. Dichloromethane, acetonitrile, and toluene were purified and dried by passing it under nitrogen pressure through two packed columns of neutral alumina (MBraun solvent purification system). Unless otherwise noted, all reagents were purchased from Alfa Aesar, Sigma Aldrich, Ark Pharma, Chem-Impex, or Strem Chemicals, and were used as received. Furan substrates **3** were prepared according to literature procedures.[1-3] Cholester-ester was synthesized according to a literature procedure[4]. All deuterated solvents were purchased from Cambridge Isotope Laboratories.

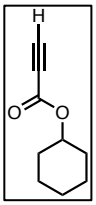
2. Instrumentation

Analytical Information: Compounds were characterized by ^{1}H NMR and ^{13}C NMR. NMR spectra were obtained on Brüker AMX-400, DRX-500, and AMX-700 instruments. Chemical shifts are reported in parts per million (ppm) relative to the central line of residual solvent. ^{13}C NMR were obtained with ^{1}H decoupling. High-resolution mass spectrometry was performed on an Agilent 6230 ESI-TOF LC/MS instrument (G6230B) operating at 4 GHz with internal reference. Analytical thin layer chromatography (TLC) was performed using MilliporeSigma glass plates coated with 0.25 mm silica gel containing PF 254 indicator and the compounds were visualized with UV light and potassium permanganate stain. Flash chromatography was carried out with Silicycle SilicaFlash. F60 (particle size 40-63 μm) silica gel. Preparatory TLC was performed on 20 cm x 20 cm glass plates with a 1000 μM layer of silica gel, purchased from AnalTech.

3. General Methods, Synthesis and characterization of new compounds

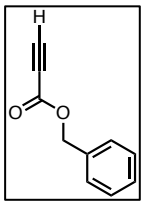


3.1 Procedures for propiolate synthesis:

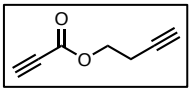


Cyclohexyl propiolate[5]: Propiolic acid (2.33 mL, 37.7 mmol, 1 equiv.) was dissolved in dry toluene (50 mL). Cyclohexanol (4.15 mL, 39.9 mmol, 1.05 equiv.) was added and the reaction flask was fitted with a Dean-Stark trap. Sulfuric acid (0.1 mL) was added and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the reaction mixture

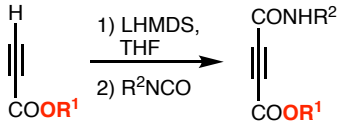
was washed with aqueous sodium bicarbonate and brine. The organic layer was separated, dried over $MgSO_4$, filtered, and concentrated via rotary evaporation. The crude product was purified via column chromatography on silica gel, eluting with 20% ethyl acetate in hexanes, to provide the title compound as a colorless oil. Yield: 4.30 g, 75% ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 (tt, *J* = 9.1, 4.0 Hz, 1H), 2.85 (s, 1H), 1.93 – 1.86 (m, 2H), 1.76 (dq, *J* = 13.7, 4.4 Hz, 2H), 1.59 – 1.44 (m, 3H), 1.42 – 1.23 (m, 4H).



Benzyl propiolate: Propiolic acid (455 mg, 6.5 mmol, 1 equiv.) and benzyl alcohol (756 mg, 7 mmol, 1.1 equiv.) were dissolved in dry CH_2Cl_2 (7.5 mL) and cooled to 0 °C under argon in an ice bath. A solution of pyridinium p-toluenesulfonate (163 mg, 0.65 mmol, 0.1 equiv.) and DCC (1.34 g, 6.5 mmol, 1 equiv.) in CH_2Cl_2 (7.5 mL) was then added over 30 min. The suspension was stirred for 5 h at room temperature, monitoring the reaction progress by TLC. Upon completion, the mixture was filtered through a plug of Celite® and the filtrate was concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with 30% ethyl acetate in hexanes to provide the title compound as a clear oil. Yield: 634 mg, 61% ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 5H), 5.23 (s, 2H), 2.90 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.64, 134.63, 128.84, 128.80, 128.69, 75.20, 74.65, 68.03. HRMS (ESI-TOF) calcd for $C_{10}H_8O_2$ [M + H^+] 161.0603 found: 160.9902.



But-3-yn-1-yl propiolate[6]: Propiolic acid (497 mg, 7.1 mmol, 1 equiv) and but-3-yn-1-ol (750 mg, 10.7 mmol, 1.5 equiv.) were dissolved in CH_2Cl_2 (10 mL) and cooled to -20 °C. A solution of DMAP (85 mg, 0.7 mmol, 0.1 equiv.) and DCC (1.898 g, 9.2 mmol, 1.3 equiv.) in CH_2Cl_2 (10 mL) was then added over 30 min. The suspension was stirred for 5 h at room temperature, monitoring the reaction progress by TLC. Upon completion, the mixture was filtered through a plug of Celite® and the filtrate was concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with 2% ethyl acetate in hexanes to provide the title compound as a yellow oil. Yield: 607 mg, 70% ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.27 (t, *J* = 7.0 Hz, 2H), 2.92 (s, 1H), 2.56 (td, *J* = 6.9, 2.6 Hz, 2H), 2.02 (t, *J* = 3.2 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 152.30, 79.20, 75.34, 74.32, 70.44, 63.68, 18.71.



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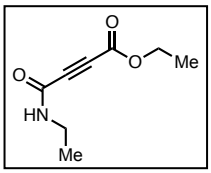
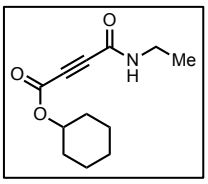
3.2 Ester-amide alkyne synthesis

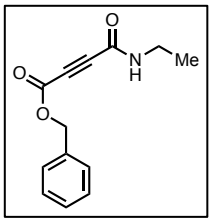


Ethyl 4-(ethylamino)-4-oxobut-2-ynoate: Ethyl propiolic acid (507 µL, 5.00 mmol, 1 equiv.) was dissolved in dry THF (18 mL) and cooled to -78 °C in a dry ice/acetone bath under argon. LHMDS (5.25 mL, 1 M in THF, 5.25 mL, 5.25 mmol, 1.05 equiv.) was added dropwise. The resulting solution was stirred for an additional 30 min at -78 °C. Then, ethyl isocyante (395 µL, 5.00 mmol, 1 equiv.) was added dropwise to the reaction mixture and the resulting solution was stirred for an additional 30 min. The reaction was then quenched by the addition of saturated NH_4Cl (20 mL) at -78 °C. The mixture was allowed to warm to room temperature. H_2O (10 mL) was added, the layers separated, and the aqueous layer extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with a gradient of ethyl acetate in hexanes to isolate the product as a yellow oil. Yield: 363 mg, 43% ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (s, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.37 (qd, *J* = 7.3, 5.8 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 152.30, 150.59, 76.84, 73.72, 62.88, 35.09, 14.39, 13.94, 13.92. HRMS (ESI-TOF) calcd for $C_8H_{11}NO_3$ [M + H^+] 170.0804, found 170.0812.

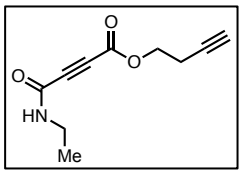


Cyclohexyl 4-(ethylamino)-4-oxobut-2-ynoate: Cyclohexyl propiolate (200 mg, 1.3 mmol, 1 equiv.) was dissolved in dry THF (5 mL) and cooled to -78 °C in a dry ice/acetone bath under argon. LHMDS (1 M in THF, 1.4 mL, 1.4 mmol, 1.05 equiv.) was added dropwise. The resulting solution was stirred for an additional 30 min at -78 °C. Then, ethyl isocyante (94 µL, 1.3 mmol, 1 equiv.) was added dropwise to the reaction mixture and the resulting solution was stirred for an additional 30 min. The reaction was then quenched by the addition of saturated NH_4Cl (20 mL) at -78 °C. The mixture was allowed to warm to room temperature. H_2O (10 mL) was added, the layers separated, and the aqueous layer extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with a gradient of ethyl acetate in hexanes, to give a clear oil. Yield: 223 mg, 77% ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (tq, *J* = 9.0, 4.2 Hz, 1H), 3.37 (qd, *J* = 7.3, 5.8 Hz, 2H), 1.88 (d, *J* = 7.3, 2H), 1.75 (dd, *J* = 9.4, 4.1 Hz, 2H),

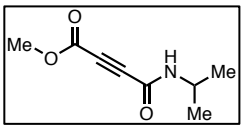
1.53 – 1.32 (m, 6H), 1.26 (t, J = 7.3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.08, 150.98, 77.51, 77.26, 77.01, 76.20, 74.41, 35.30, 31.50, 25.35, 23.77, 14.64. HRMS (ESI-TOF) calcd for $C_{12}H_{17}NO_3$ (M + H^+) 224.1281, found 224.1271.



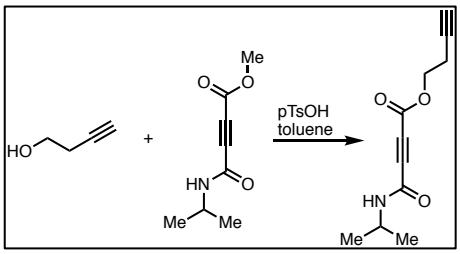
Benzyl 4-(ethylamino)-4-oxobut-2-ynoate: Benzyl propiolate (506.7 µL, 5.00 mmol, 1 equiv.) was dissolved in dry THF (18 mL) and cooled to -78 °C in a dry ice/acetone bath under argon. LHMDS (1 M in THF, 5.25 mL, 5.25 mmol, 1.05 equiv.) was added dropwise. The resulting solution was stirred for an additional 30 min at -78 °C. Then, ethyl isocyante (1.24 mL, 5.00 mmol, 1 equiv.) was added dropwise to the reaction mixture and the resulting solution was stirred for an additional 30 min. The reaction was then quenched by the addition of saturated NH_4Cl (20 mL) at -78 °C. The mixture was allowed to warm to room temperature. H_2O (10 mL) was added, the layers separated, and the aqueous layer extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with a gradient of ethyl acetate in hexanes to give a yellow viscous oil. Yield: 147 mg, 43% ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H), 6.59 (s, 1H), 4.50 (d, J = 5.9 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.07, 150.50, 136.32, 128.70, 127.82, 127.76, 76.78, 74.08, 62.74, 43.86, 13.72. HRMS (ESI-TOF) calcd for $C_{13}H_{13}NO_3$ (M + H^+) 232.1623, found 232.16808.



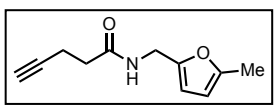
But-3-yn-1-yl 4-(ethylamino)-4-oxobut-2-ynoate: But-3-yn-1-yl propiolate (180 mg, 1.4 mmol, 1 equiv.) was dissolved in dry THF (5 mL) and cooled to -78 °C in a dry ice/acetone bath under argon. LHMDS (1 M in THF, 1.5 mL, 1.5 mmol, 1.05 equiv.) was added dropwise. The resulting solution was stirred for an additional 30 min at -78 °C. Then, ethyl isocyante (110 µL, 1.4 mmol, 1 equiv.) was added dropwise to the reaction mixture and the resulting solution was stirred for an additional 30 min. The reaction was then quenched by the addition of saturated NH_4Cl (20 mL) at -78 °C. The mixture was allowed to warm to room temperature. H_2O (10 mL) was added, the layers separated, and the aqueous layer extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with a gradient of ethyl acetate in hexanes to give a yellow oil. Yield: 199 mg, 76% ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (t, J = 6.8 Hz, 2H), 3.37 (qd, J = 7.3, 5.8 Hz, 2H), 2.58 (td, J = 6.7, 2.7 Hz, 2H), 2.03 (t, J = 2.7 Hz, 1H), 1.19 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.78, 150.28, 78.82, 77.09, 76.84, 76.59, 73.05, 70.38, 64.00, 63.95, 34.93, 18.55, 14.18. HRMS (ESI-TOF) calcd for $C_{10}H_{11}NO_3$ [M + Na^+] 216.0637, found 216.0639.



Methyl 4-(isopropylamino)-4-oxobut-2-ynoate[7]: Methyl propiolate (0.45 µL, 5.00 mmol, 1 equiv.) was dissolved in dry THF (18 mL) and cooled to -78 °C in a dry ice/acetone bath under argon. LHMDS (1 M in THF, 5.25 mL, 5.25 mmol, 1.05 equiv.) was added dropwise. The resulting solution was stirred for an additional 30 min at -78 °C. Then, isopropyl isocyante (490 µL, 5.00 mmol, 1 equiv.) was added dropwise to the reaction mixture and the resulting solution was stirred for an additional 30 min. The reaction was then quenched by the addition of saturated NH_4Cl (20 mL) at -78 °C. The mixture was allowed to warm to room temperature. H_2O (10 mL) was added, the layers separated, and the aqueous layer extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with a gradient of ethyl acetate in hexanes to isolate the product as a pale, yellow oil. Yield: 189 mg, 93% ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (dt, J = 8.1, 6.6 Hz, 1H), 3.83 (s, 3H), 1.20 (d, J = 6.6 Hz, 6H).

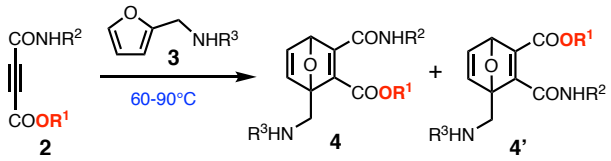


But-3-yn-1-yl 4-(isopropylamino)-4-oxobut-2-ynoate: Methyl 4-(isopropylamino)-4-oxobut-2-ynoate (101 mg, 0.6 mmol, 1 equiv.), but-3-yn-1-ol (84 mg, 1.2 mmol, 2 equiv.), and *p*-toluene sulfonic acid monohydrate (11 mg, 0.06 mmol, 0.1 equiv.) were dissolved in toluene (4 mL). The reaction flask was fitted with a jacketed condenser and the reaction mixture was heated to reflux overnight. The reaction was then cooled to room temperature, H_2O (5 mL) was added, the layers separated, and the aqueous layer extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with sodium bicarbonate, brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The crude product was purified via column chromatography, eluting with 30% ethyl acetate in hexanes to provide the title compound as a yellow oil. Yield: 75 mg, 60% ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 4.32 (t, J = 6.7 Hz, 2H), 4.13 (q, J = 6.8 Hz, 1H), 2.58 (td, J = 6.9, 2.5 Hz, 2H), 2.03 (d, J = 2.5 Hz, 1H), 1.20 (d, J = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.93, 149.67, 78.96, 77.96, 77.22, 76.97, 76.71, 72.93, 70.50, 64.06, 42.53, 22.25, 18.68 HRMS (ESI-TOF) calcd. for $C_{11}H_{13}NO_3$ [M + H^+] 208.0974, found 208.9722.

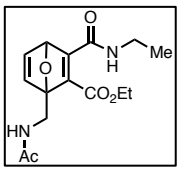


N-((5-methylfuran-2-yl)methyl)pent-4-ynamide: Pentynoic acid (166 µL, 1.5 mmol. 1.0 equiv.) was dissolved in dry CH_2Cl_2 (15 mL) and chilled to 4 °C. EDC•HCl (400 mg, 2.04 mmol, 2.04 equiv) was added in one portion while stirring at 4 °C and stirred for 15 minutes. Then, (5-methylfuran-2-yl)methanamine (166 µL, 1.5 mmol, 1 equiv.), Et_3N (224 µL, 1.7 mmol, 1.1 equiv.), and 10 mol% DMAP (17.8 mg) in dry CH_2Cl_2 (1 mL) was added dropwise. The reaction was stirred for two hours and was allowed to warm to room temperature.

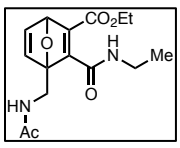
The crude reaction mixture was quenched by the addition of 1 N HCl (20 mL). The organic layer was then diluted to 25 mL with CH_2Cl_2 and washed with additional 1 N HCl (20 mL) and the layers were separated. The combined organic layers were washed with sodium bicarbonate and brine, dried over Na_2SO_4 and concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with 40% ethyl acetate in hexanes to provide the title compound as a white solid. Yield: 157 mg, 59%. ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.11 (d, J = 3.0 Hz, 1H), 5.89 (dd, J = 3.0, 1.2 Hz, 1H), 5.83 (s, 1H), 4.39 (d, J = 5.4 Hz, 2H), 2.55 (td, J = 7.2, 2.6 Hz, 2H), 2.42 (t, J = 7.3 Hz, 2H), 2.26 (d, J = 1.0 Hz, 3H), 1.99 (t, J = 2.6 Hz, 1H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.73, 152.23, 149.39, 108.63, 106.53, 83.15, 69.57, 36.97, 35.53, 15.04, 13.79. HRMS (ESI-TOF) calcd for $C_{11}H_{13}NO_2$ [M + K^+] 230.1929, found 230.2468.



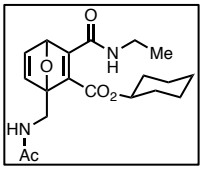
3.3 OND Synthesis



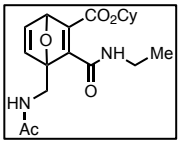
4a: Ethyl 4-(ethylamino)-4-oxobut-2-ynoate, (251.06 mg, 1.0 mmol, 1 equiv.) and N-(furan-2-ylmethyl)acetamide, 3, (220 mg, 1.3 mmol, 1.3 equiv.) were dissolved in 0.2 mL of toluene and heated to 60 °C overnight. The crude mixture was purified by flash chromatography, eluting with ethyl acetate and the product was isolated as a yellow solid. Conversion: 70%, isolated yield: 68 mg, 22%, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.26 (dd, under chloroform, 1H) 6.92 (d, J = 5.2 Hz, 1H), 5.80 (s, 1H), 5.72 (d, J = 2.0 Hz, 1H), 4.35 – 4.20 (m, 3H), 4.07 (dd, J = 14.5, 5.0 Hz, 1H), 3.41 – 3.27 (m, 2H), 1.99 – 1.96 (m, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.07, 164.35, 162.15, 160.47, 149.06, 144.08, 143.19, 97.30, 83.58, 62.13, 38.79, 34.59, 23.40, 14.40, 14.11. HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_2O_5$ (M + Na^+) 331.1270, found 331.12534.



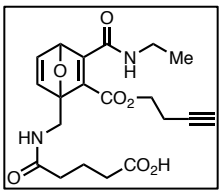
4a': Product isolated as a yellow solid. isolated yield: 52 mg, 17% ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.14 (dd, J = 5.3, 2.0 Hz, 1H), 7.03 (d, J = 5.2 Hz, 1H), 6.57 (s, 1H), 5.63 (d, J = 1.9 Hz, 1H), 4.38 – 4.21 (m, 3H), 4.13 – 4.11 (m, 2H), 3.36 (qd, J = 7.3, 5.5 Hz, 2H), 2.01 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.02, 164.28, 162.09, 160.39, 148.99, 144.02, 143.13, 97.23, 83.51, 62.06, 38.73, 34.52, 23.33, 14.34, 14.04.



4b: Cyclohexyl 4-(ethylamino)-4-oxobut-2-ynoate (222.8 mg, 0.98 mmol, 1 equiv.) and N-(furan-2-ylmethyl)acetamide (177.6 mg, 1.28 mmol, 1.3 equiv.) were dissolved in 0.2 mL of trifluorotoluene and heated to 60 °C overnight. The crude mixture was purified by flash chromatography, eluting with 1% methanol in ethyl acetate and the product was isolated as an amorphous yellow solid. Yield: 74.5 mg, 21% (both diasteromers present) ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.53 (s, 1H), 6.93 (d, *J* = 5.2 Hz, 1H), 5.73 (d, *J* = 2.0 Hz, 1H), 4.93 – 4.83 (m, 1H), 4.27 (dd, *J* = 14.5, 5.6 Hz, 1H), 4.12 (t, *J* = 6.8 Hz, 1H), 4.04 (dd, *J* = 14.5, 5.4 Hz, 1H), 3.44 – 3.23 (m, 3H), 1.92 (d, *J* = 5.5 Hz, 1H), 1.88 – 1.70 (m, 5H), 1.65 – 1.30 (m, 12H), 1.20 (dt, *J* = 10.0, 7.3 Hz, 4H). (mixed) ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.07, 169.74, 164.00, 162.12, 161.43, 151.00, 145.97, 145.26, 142.05, 142.02, 139.11, 110.29, 107.31, 96.06, 84.28, 78.56, 77.11, 76.85, 76.60, 75.42, 38.75, 36.40, 34.35, 34.01, 31.18, 31.09, 24.90, 23.59, 23.48, 22.96, 22.91, 14.34, 14.28.

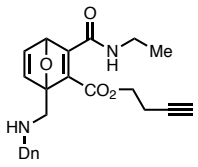


4b': The product was isolated as an amorphous yellow solid. Isolated yield: 10.7 mg, 3% ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.16 (dd, *J* = 5.2, 1.9 Hz, 1H), 7.05 (d, *J* = 5.3 Hz, 1H), 6.62 (s, 1H), 5.64 (d, *J* = 1.9 Hz, 1H), 4.92 (tt, *J* = 8.7, 3.8 Hz, 1H), 4.15 (d, *J* = 6.1 Hz, 2H), 3.42 – 3.34 (m, 2H), 1.94 (d, *J* = 11.7 Hz, 1H), 1.85 (d, *J* = 9.7 Hz, 2H), 1.77 (q, *J* = 3.8 Hz, 3H), 1.51 – 1.41 (m, 4H), 1.40 – 1.33 (m, 2H), 1.23 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.05, 163.76, 162.17, 159.94, 149.58, 143.98, 143.17, 97.25, 83.61, 77.21, 76.96, 76.71, 74.73, 38.79, 34.53, 31.37, 31.28, 25.12, 23.36, 14.37. HRMS (ESI-TOF) calcd for $C_{19}H_{26}N_2O_5$ ($M + H^+$) 363.1914, found 363.1888.

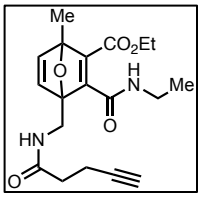


4c: But-3-yn-1-yl 4-(ethylamino)-4-oxobut-2-ynoate (73.6 mg, 0.36 mmol, 1.4 equiv.) and 5-((furan-2-ylmethyl)amino)-5-oxopentanoic acid (53 mg, 0.25 mmol, 1.0 equiv.) were dissolved in 0.2 mL of toluene and heated to 60 °C overnight. The reaction progress was monitored by TLC. The crude mixture was purified by flash chromatography, eluting with 50% hexanes, 49.5% ethyl acetate, and 0.5% acetic acid and the product was isolated as a white solid. Combined yield: 55.1 mg, 39%, single regioisomer: 12.3 mg, 8% ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.33 (t, NH, 1H), 7.27 (dd, *J* = 2.0, 5.2 Hz, 1H), 6.93 (d, *J* = 5.2 Hz, 1H), 5.95 (t, NH, *J* = 5.5 Hz, 1H), 5.73 (d, *J* = 2.0 Hz, 1H), 4.40 (dt, *J* = 10.6, 6.4 Hz, 1H), 4.32 – 4.26 (m, 2H), 4.14 (dd, *J* = 14.6, 5.3 Hz, 1H), 3.43 – 3.29 (m, 2H), 2.74 – 2.60 (m, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.29 (t, *J* = 7.3 Hz, 2H), 2.08 (t, *J* = 2.6 Hz, 1H), 1.95 (p, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 176.00, 172.55, 164.54, 163.40, 161.56, 145.69, 145.38, 142.22, 96.74, 84.71, 79.61, 77.34, 77.16, 76.98, 70.85, 63.79, 38.84, 38.73, 35.23, 34.75, 34.62, 32.78, 29.86,

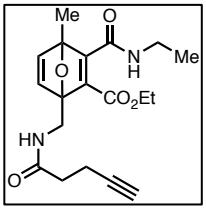
25.51, 20.77, 18.91, 14.60, 14.58. HRMS (ESI-TOF) calcd for $C_{20}H_{24}N_2O_7$ (M + H^+) 405.1660, found 405.16310.



4d: But-3-yn-1-yl 4-(ethylamino)-4-oxobut-2-ynoate, 2, (100 mg, 0.50 mmol, 1 equiv.) and 5-((furan-2-ylmethyl)amino)-5-oxopentanoic acid, 3, (257.4 mg, 0.78 mmol, 1.5 equiv.) were dissolved in 0.2 mL of trifluorotoluene and heated to 60 °C for 24 hours in the dark. The crude mixture was purified by flash chromatography, eluting with 20% acetone in hexanes and the product was isolated as a white solid. combined yield: 151.7 mg, 58%, single regioisomer: 55 mg, 21% ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.5 Hz, 1H), 8.31 – 8.18 (m, 3H), 7.54 (dt, *J* = 15.8, 8.0 Hz, 2H), 7.20 – 7.15 (m, 2H), 6.73 (d, *J* = 5.3 Hz, 1H), 5.62 (d, *J* = 2.1 Hz, 1H), 5.08 (ddd, *J* = 13.4, 8.1, 4.7 Hz, 1H), 4.19 (tq, *J* = 9.0, 5.2, 4.1 Hz, 2H), 3.95 (dd, *J* = 13.4, 7.9 Hz, 1H), 3.56 (dd, *J* = 13.4, 4.6 Hz, 1H), 3.39 – 3.26 (m, 3H), 2.88 (s, 6H), 2.65 – 2.51 (m, 3H), 2.01 (d, *J* = 2.7 Hz, 1H), 1.20 (d, *J* = 6.0 Hz, 1H), 1.17 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 163.97, 162.97, 161.31, 152.06, 145.52, 144.76, 141.44, 134.15, 130.77, 129.89, 129.80, 129.62, 128.69, 123.09, 118.50, 115.36, 95.80, 84.59, 79.62, 77.22, 77.03, 76.85, 70.64, 63.55, 45.43, 42.83, 34.56, 25.37, 18.60, 14.47. HRMS (ESI-TOF) calcd. for (M + H^+) 524.6113, found 524.18517.

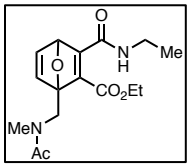


4e: The reaction was run in toluene according to General Procedure B. Ethyl 4-(ethylamino)-4-oxobut-2-ynoate, 2, (64.2 mg, 0.38 mmol, 1 equiv.) and N-((5-methylfuran-2-yl)methyl)pent-4-ynamide, 3, (76.1 mg, 0.40 mmol, 1.05 equiv.) were dissolved in 0.2 mL of toluene and heated to 60 °C for 24 hours. The reaction progress was monitored by TLC. The crude mixture was purified by preparative TLC, eluting with a mixture of 75% ethyl acetate in hexanes and the product was isolated as a yellow, oily solid. Conversion: 50%, Yield: 28 mg, 21% ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.68 (t, *J* = 5.6 Hz, 1H), 7.04 (d, *J* = 5.0 Hz, 1H), 6.86 (d, *J* = 5.0 Hz, 1H), 5.90 (d, *J* = 5.8 Hz, 1H), 4.25 (dddd, *J* = 29.6, 15.0, 7.1, 3.6 Hz, 3H), 4.01 (dd, *J* = 14.5, 4.6 Hz, 1H), 3.35 (qd, *J* = 7.3, 5.9 Hz, 2H), 2.51 (td, *J* = 7.4, 2.6 Hz, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.83 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.14, 170.79, 164.57, 162.41, 148.05, 146.56, 142.58, 94.09, 93.36, 82.72, 77.17, 76.99, 76.81, 69.35, 62.09, 38.50, 35.25, 34.30, 15.40, 14.83, 14.54, 13.97. HRMS (ESI-TOF) calcd for $C_{19}H_{24}N_2O_5$ (M + Na^+) 383.1583, found 383.1557.

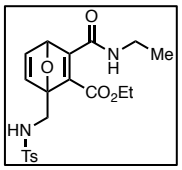


4e': The product was isolated as a yellow, oily solid. Yield: 7 mg, 9% ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.91 (d, *J* = 5.8 Hz, 1H), 7.03 (d, *J* = 5.1 Hz, 1H), 6.88 (d, *J* = 5.1 Hz, 1H), 6.68 (d, *J* = 6.0 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.22 (dt, *J* = 10.7, 7.1 Hz, 1H), 4.15 (dd, *J* = 14.3, 7.0 Hz, 1H), 3.94 (dd, *J* = 14.3, 4.6 Hz, 1H), 3.34 (tdd, *J*

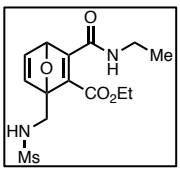
= 13.2, 8.8, 5.7 Hz, 2H), 2.53 (ddt, *J* = 10.2, 7.8, 4.9 Hz, 2H), 2.44 (t, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.77, 164.99, 162.71, 159.81, 150.58, 146.37, 143.94, 94.95, 92.27, 83.10, 77.21, 77.03, 76.85, 69.17, 61.86, 38.44, 35.50, 34.51, 16.11, 14.93, 14.51, 14.08.



4f: Ethyl 4-(ethylamino)-4-oxobut-2-ynoate, (84.5 mg, 1.1 equiv.) and N-(furan-2-ylmethyl)-N-methylacetamide, 3, (63.2 mg, 0.45 mmol, 1.0 equiv.) were dissolved in 0.4 mL of trifluorotoluene and heated to 60 °C overnight and then the heat was increased to 80 °C for an additional 6 hours. The crude mixture was purified by flash chromatography, eluting with a mixture of 50% ethyl acetate in hexanes and the product was isolated as a yellow oil. Yield: 6 mg, 10% ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.23 (d, *J* = 5.1 Hz, 1H), 7.05 (dd, *J* = 5.2, 1.9 Hz, 1H), 5.72 (s, 1H), 4.65 (dd, *J* = 14.7, 1.9 Hz, 1H), 4.37 (qd, *J* = 7.8, 7.4, 4.0 Hz, 1H), 4.32 – 4.28 (m, 1H), 3.99 (d, *J* = 14.8 Hz, 1H), 3.36 (ddq, *J* = 27.4, 13.7, 7.0 Hz, 2H), 3.07 (s, 3H), 2.12 (s, 3H), 1.40 (td, *J* = 7.2, 1.9 Hz, 3H), 1.20 (td, *J* = 7.2, 1.8 Hz, 4H). ^{13}C NMR (176 MHz, $CDCl_3$) (minor product is present in small quantities) δ 171.29, 165.18, 161.80, 161.49, 147.08, 144.71, 143.36, 97.56, 84.36, 62.15, 46.01, 38.00, 34.48, 21.77, 14.48, 13.99. HRMS (ESI-TOF) calcd for $C_{16}H_{22}N_2O_5$] (M + Na^+) 345.14267, found 345.13960.

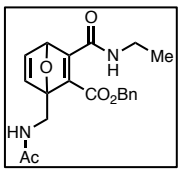


4g: Ethyl 4-(ethylamino)-4-oxobut-2-ynoate, (72 mg, 0.42 mmol, 1.3 equiv.) and N-(furan-2-ylmethyl)-4-methylbenzenesulfonamide, 3, (80.3 mg, 0.32 mmol, 1.0 equiv.) were dissolved in 0.2 mL of toluene and heated to 60 °C for 8 hours, the heat was turned up 120 °C overnight. The reaction progress was monitored using TLC. The crude mixture was purified by flash chromatography, eluting with a mixture of 50% ethyl acetate and the product was isolated as a yellow oily solid. Yield: 99 mg, 57% (both diasteromers present) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (t, *J* = 5.6 Hz, 1H), 7.76 – 7.71 (m, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.24 (dd, *J* = 5.3, 2.1 Hz, 1H), 6.83 (d, *J* = 5.2 Hz, 1H), 5.67 (d, *J* = 2.0 Hz, 1H), 4.75 (dd, *J* = 8.3, 4.3 Hz, 1H), 4.36 – 4.24 (m, 3H), 3.99 (dd, *J* = 12.8, 8.2 Hz, 1H), 3.54 (dd, *J* = 12.9, 4.3 Hz, 1H), 3.41 – 3.27 (m, 3H), 2.43 (s, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.35, 162.15, 161.39, 145.63, 145.22, 143.73, 141.30, 136.16, 129.79, 127.07, 95.53, 84.48, 62.41, 42.76, 34.48, 21.49, 14.39, 13.84. HRMS (ESI-TOF) calcd for $C_{20}H_{44}N_2O_6S$ (M + Na^+) 443.1253, found 443.1229.

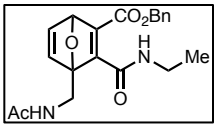


4h: Ethyl 4-(ethylamino)-4-oxobut-2-ynoate (70 mg, 0.41 mmol, 1.3 equiv.) and N-(furan-2-ylmethyl)methanesulfonamide, 3, (55.7 mg, 0.32 mmol, 1.0 equiv.) were dissolved in 0.2 mL of toluene and heated to 80 °C overnight. The reaction progress was monitored using TLC. The crude mixture was purified by flash chromatography, eluting

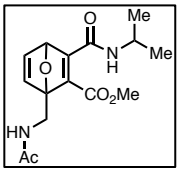
with a mixture of 70% ethyl acetate and the product was isolated as a yellow oily solid. Yield: 25 mg, 18% ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.30 (dd, *J* = 5.3, 2.0 Hz, 1H), 6.93 (d, *J* = 5.2 Hz, 1H), 5.73 (d, *J* = 2.0 Hz, 1H), 4.70 (s, 1H), 4.40 – 4.21 (m, 3H), 4.18 – 4.05 (m, 4H), 3.91 (dd, *J* = 13.5, 4.9 Hz, 1H), 3.44 – 3.24 (m, 3H), 1.78 – 1.60 (m, 3H), 1.37 (dt, *J* = 10.4, 7.1 Hz, 5H), 1.31 – 1.16 (m, 14H), 0.91 – 0.77 (m, 7H). ^{13}C NMR (176 MHz, $CDCl_3$) (both diasteromers) δ 164.40, 164.22, 162.46, 161.89, 161.47, 159.52, 149.18, 145.85, 145.19, 144.54, 142.82, 141.43, 97.24, 96.07, 84.62, 83.56, 77.21, 77.03, 76.85, 64.44, 62.50, 62.27, 42.68, 40.65, 40.41, 34.63, 34.58, 25.30, 14.42, 14.31, 14.08, 13.91. HRMS (ESI-TOF) calcd for $C_{14}H_{20}N_2O_6S$ (M + H^+) 345.1115, found 345.1092; (M + Na^+) 367.0937, found 367.09145.



4i: Benzyl 4-(ethylamino)-4-oxobut-2-ynoate (80.0 mg, 0.35 mmol, 1.0 equiv.) and N-(furan-2-ylmethyl)acetamide, 3, (48.1 mg, 0.35 mmol, 1.0 equiv.) were dissolved in 0.2 mL of trifluorotoluene and heated to 60 °C for 8 hours. The reaction progress was monitored by TLC. The crude mixture was purified by flash chromatography, eluting with a mixture of 1% methanol and ethyl acetate the product was isolated as a white solid. Conversion: 40%, Yield: 6 mg, 5% ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.50 – 7.35 (m, 5H), 7.27 (dd, *J* = 5.1, 1.9 Hz, 1H), 6.92 (d, *J* = 5.2 Hz, 1H), 5.74 (d, *J* = 2.0 Hz, 1H), 5.31 – 5.26 (m, 2H), 4.46 (d, *J* = 5.5 Hz, 1H), 4.23 (dd, *J* = 14.6, 6.2 Hz, 1H), 4.09 (dd, *J* = 14.6, 5.2 Hz, 1H), 3.42 – 3.25 (m, 2H), 1.16 (t, *J* = 7.3 Hz, 3H).

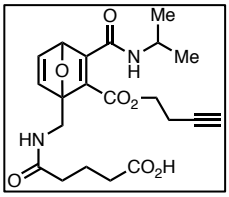


4i': The product was isolated as a white solid. Yield: 10 mg, 8% ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.48 – 7.33 (m, 5H), 7.15 (d, *J* = 4.9 Hz, 1H), 7.05 (dd, *J* = 5.4, 1.8 Hz, 1H), 6.54 (s, 1H), 5.67 (d, *J* = 2.0 Hz, 1H), 5.33 (dd, *J* = 12.3, 1.9 Hz, 1H), 5.21 (dd, *J* = 12.3, 1.9 Hz, 1H), 4.14 (dd, *J* = 6.2, 1.8 Hz, 2H), 3.42 – 3.29 (m, 2H), 1.18 (td, *J* = 7.3, 1.8 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.07, 164.06, 162.08, 160.87, 148.57, 144.10, 143.14, 134.54, 128.91, 128.88, 128.85, 128.45, 128.38, 97.38, 83.57, 77.20, 77.02, 76.84, 67.71, 38.74, 34.60, 29.71, 23.39, 14.35. HRMS (ESI-TOF) calcd for $C_{20}H_{22}N_2O_5$ (M + Na^+) 393.1427, found 393.14089.

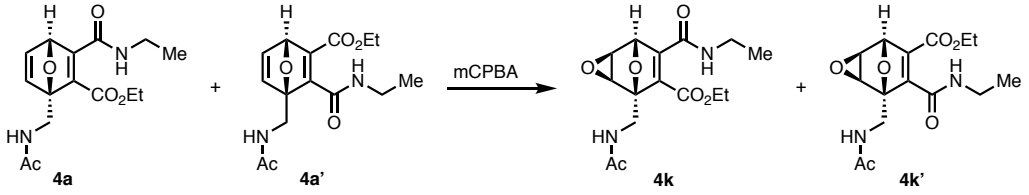


4j: Methyl 4-(isopropylamino)-4-oxobut-2-ynoate, 2, (55 mg, 0.32 mmol, 1.3 equiv.) and N-(furan-2-ylmethyl)acetamide, 3, (34.8 mg, 0.25 mmol, 1.0 equiv.) were placed in a glass vial and heated neat overnight at 60 °C. The reaction progress was monitored using TLC. The crude mixture was purified by flash chromatography, eluting with a mixture of 5% methanol and ethyl acetate. The product was isolated as a yellow, oily solid. Yield: 21 mg, 22% ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.6 Hz, 1H), 7.25 (dd, *J* = 5.2, 1.9 Hz, 1H), 6.91 (d, *J* = 5.2 Hz, 1H), 5.81 (s, 1H), 5.70 (t, *J* = 1.6 Hz, 1H), 4.23 (dd, *J* = 14.6, 6.3 Hz, 1H), 4.16 – 4.00 (m, 2 H),

3.83 (d, *J* = 4.3 Hz, 3H), 2.05 – 1.92 (m, 3H), 1.30 – 1.12 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.96, 169.85, 164.96, 164.45, 162.95, 161.12, 160.75, 160.47, 148.16, 145.36, 145.11, 143.89, 142.95, 141.93, 97.06, 96.28, 84.34, 83.33, 77.11, 77.06, 76.85, 76.60, 60.20, 52.60, 52.58, 41.64, 41.56, 38.53, 23.17, 22.95, 22.35, 22.23, 22.19, 20.87, 14.01, 13.93. HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_2O_5$ (M + Na^+) 331.1270, found 331.1241.



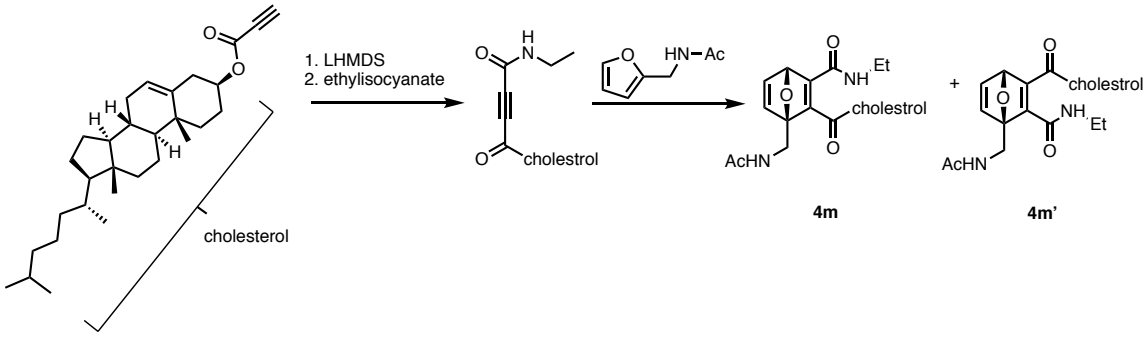
4l: But-3-yn-1-yl 4-(isopropylamino)-4-oxobut-2-ynoate, 2, (50 mg, 0.11 mmol, 1 equiv.) and 5-((furan-2-ylmethyl)amino)-5-oxopentanoic acid, 3, (36 mg, 0.17 mmol, 1.5 equiv.) were dissolved in 0.2 mL of toluene and heated to 60 °C overnight and then the heat was increased to 80 °C for 8 additional hours. The crude mixture was purified by flash chromatography, eluting with a mixture of 50% ethyl acetate and the product was isolated as a white oily solid. Yield: 24 mg, 52% (both diasteromers present) ^{1}H NMR (500 MHz $CDCl_3$) δ 8.30 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 5.0 Hz, 1H), 6.96 (d, *J* = 5.2 Hz, 1H), 5.73 (s, 1H), 4.40 (dt, *J* = 10.5, 6.4 Hz, 2H), 4.35 – 4.13 (m, 4H), 4.08 (tt, *J* = 12.5, 6.3 Hz, 2H), 3.51 (s, 1H), 2.67 (ddtd, *J* = 24.6, 13.5, 8.2, 6.6, 2.5 Hz, 3H), 2.40 (s, 1H), 2.35 (s, 1H), 2.27 (t, *J* = 7.3 Hz, 3H), 2.15 – 2.05 (m, 2H), 1.95 – 1.88 (m, 2H), 1.38 – 1.28 (m, 1H), 1.27 (s, 1H), 1.25 – 1.13 (m, 9H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 164.40, 163.83, 163.41, 160.73, 148.37, 145.39, 145.20, 144.24, 143.08, 142.28, 142.06, 97.32, 96.69, 84.51, 83.48, 79.55, 79.20, 77.20, 77.02, 76.84, 70.80, 70.64, 64.49, 63.60, 63.34, 50.87, 41.96, 41.82, 38.67, 35.38, 35.27, 29.71, 29.67, 25.35, 22.70, 22.54, 22.43, 22.39, 22.36, 18.90, 18.75. HRMS (ESI-TOF) calcd for $C_{21}H_{26}N_2O_7$ (M + H^+) 418.1818, found 419.1823, (M + Na^+) 441.1638, 441.1643.



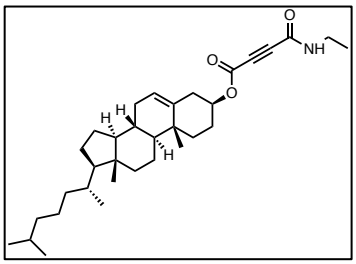
4k (yield: 8.9 mg, 43%) and 4k' (yield: 7.4 mg, 36%) were synthesized according to a literature procedure.[8]

4k: ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.39 (t, *J* = 5.5 Hz, 1H), 7.26 (s, 1H), 5.81 (t, *J* = 5.6 Hz, 1H), 5.23 (s, 1H), 4.38 – 4.30 (m, 2H), 4.19 (dd, *J* = 14.7, 6.5 Hz, 1H), 3.96 (dd, *J* = 14.7, 4.9 Hz, 1H), 3.88 (d, *J* = 3.5 Hz, 1H), 3.66 (d, *J* = 3.5 Hz, 1H), 3.41 – 3.29 (m, 3H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.32, 164.53, 160.91, 157.26, 141.30, 90.82, 79.43, 77.20, 77.02, 76.84, 62.93, 57.87, 56.64, 37.96, 34.62, 23.07, 14.39, 13.97.

4k': ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.31 (s, 1H), 6.19 (s, 1H), 5.05 (s, 1H), 4.36 – 4.26 (m, 3H), 4.24 – 4.18 (m, 1H), 4.02 (dd, *J* = 14.5, 5.8 Hz, 1H), 3.76 (s, 2H), 3.37 (dq, *J* = 11.7, 5.8, 4.8 Hz, 3H), 2.01 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.24, 163.90, 161.27, 156.00, 142.89, 91.42, 78.34, 77.20, 77.02, 76.84, 62.54, 57.48, 56.46, 37.92, 34.65, 23.23, 14.55, 14.38, 14.12. HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_2O_6$ ($M + H^+$) 325.1400, found 325.1408.

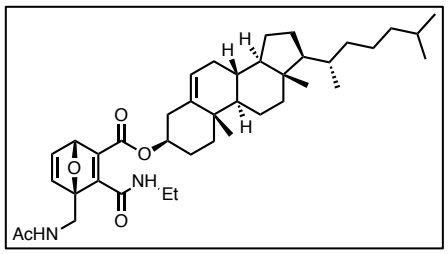


Cholesterol-ester-amide synthesis

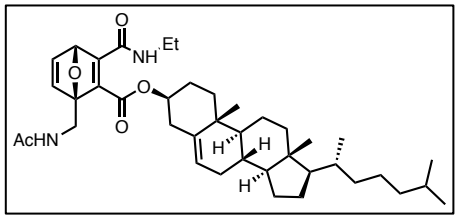


Cholesterol propiolic acid (438.3 mg, 1.00 mmol, 1 equiv.) was dissolved in dry THF (5 mL) and cooled to -78 °C in a dry ice/acetone bath under argon. LHMDS (1 M in THF, 1.05 mL, 1.05 mmol, 1.05 equiv.) was added dropwise. The resulting solution was stirred for an additional 30 min at -78 °C. Then, ethyl isocyante (78.8 µL, 1.0 mmol, 1 equiv.) was added dropwise to the reaction mixture and the resulting solution was stirred for an additional 30 min. The reaction was then quenched by the addition of saturated NH_4Cl (20 mL) at -78 °C. The mixture was allowed to warm to room temperature. H_2O (10 mL) was added, the layers separated, and the aqueous layer extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated via rotary evaporation. The crude product was purified via flash chromatography, eluting with a gradient of ethyl acetate in hexanes to provide the title compound as a white, oily solid. Yield: 72 mg, 63% ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (t, *J* = 5.9 Hz, 1H), 5.42 (d, *J* = 4.9 Hz, 1H), 4.76 (tt, *J* = 11.0, 5.1 Hz, 1H), 3.39 (p, *J* = 7.0 Hz, 2H), 2.40 (dd, *J* = 11.4, 3.7 Hz, 2H), 2.10 – 1.76 (m, 4H), 1.74 – 0.79 (m, 33H), 0.70 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 151.67, 150.62, 138.82, 123.36, 77.22, 77.03, 76.96, 76.71, 73.98, 56.60, 56.07, 49.91, 42.25, 39.63, 39.46, 37.66, 36.78, 36.48, 36.12, 35.73, 35.01, 31.83, 31.75, 28.16, 27.96, 27.43, 24.22, 23.77, 22.77, 22.51, 20.96, 19.19, 18.66, 14.34, 11.80.

Procedure for **4m** and **4m'**: Cholester-ester-amide (20 mg, 0.04 mmol, 1 equiv.) and furfurylamine (8 mg, 0.06 mmol, 1.5 equiv). were added to a 4 mL screw-cap vial with a magnetic stir bar followed by trifluoroethanol (200 μL). The reaction mixture was stirred at 60 °C overnight and then at 80 °C for an additional 24 h. The crude mixture was then concentrated and purified by preparative TLC, eluting with 1% methanol in ethyl acetate, to provide the title compound as a pale, yellow solid.



4m: yield: 10 mg, 25% ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.52 (q, *J* = 6.0 Hz, 1H), 7.27 – 7.23 (m, 1H), 6.93 (dd, *J* = 5.2, 1.2 Hz, 1H), 5.73 (d, *J* = 2.2 Hz, 1H), 5.45 – 5.35 (m, 1H), 4.76 – 4.67 (m, 1H), 4.20 (ddd, *J* = 17.7, 14.5, 5.4 Hz, 1H), 4.10 (dq, *J* = 14.4, 8.9, 8.0 Hz, 2H), 3.43 – 3.27 (m, 2H), 2.47 (d, *J* = 8.0 Hz, 1H), 2.42 – 2.28 (m, 1H), 2.06 – 1.94 (m, 5H), 1.94 – 1.42 (m, 9H), 1.40 – 1.29 (m, 2H), 1.29 – 1.22 (m, 3H), 1.18 (td, *J* = 7.3, 3.0 Hz, 2H), 1.17 – 1.03 (m, 6H), 1.02 – 0.88 (m, 4H), 0.86 (dd, *J* = 6.6, 3.1 Hz, 4H), 0.67 (s, 2H). ^{13}C NMR (complexity in splitting due to rotamers) (176 MHz, $CDCl_3$) δ 171.18, 170.11, 164.17, 164.15, 162.54, 162.49, 161.57, 145.94, 145.92, 145.47, 145.42, 142.26, 142.21, 139.04, 138.93, 123.44, 123.29, 96.23, 96.21, 84.51, 84.50, 77.20, 77.02, 76.84, 72.86, 60.41, 56.71, 56.69, 56.14, 50.06, 50.04, 42.32, 39.71, 39.52, 38.95, 37.96, 37.75, 36.94, 36.91, 36.61, 36.18, 35.78, 34.84, 34.54, 31.92, 31.81, 28.23, 28.03, 27.64, 27.53, 24.28, 23.82, 23.17, 23.16, 22.83, 22.57, 21.07, 21.04, 19.35, 18.73, 14.50, 14.48, 14.43, 14.21, 11.87.



4m': yield: 4 mg, 10% ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.70 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.13 (dt, *J* = 4.1, 1.9 Hz, 1H), 7.02 (d, *J* = 5.3 Hz, 1H), 6.58 (q, *J* = 5.7 Hz, 1H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 5.61 (t, *J* = 2.0 Hz, 1H), 5.45 – 5.37 (m, 2H), 4.72 (ddt, *J* = 16.5, 11.4, 5.2 Hz, 2H), 4.43 (d, *J* = 5.5 Hz, 1H), 4.12 (d, *J* = 6.0 Hz, 2H), 3.40 – 3.31 (m, 3H), 2.41 (d, *J* = 7.2 Hz, 1H), 2.38 – 2.27 (m, 2H), 2.12 – 2.06 (m, 1H), 2.05 – 2.01 (m, 2H), 2.01 (s, 3H), 1.99 – 1.88 (m, 3H), 1.83 (ddt, *J* = 19.5, 14.9, 6.8 Hz, 2H), 1.72 – 1.62 (m, 2H), 1.58 (s, 5H), 1.55 – 1.42 (m, 6H), 1.40 – 1.34 (m, 2H), 1.32 (td, *J* = 8.4, 3.7 Hz, 2H), 1.26 (tt, *J* = 9.3, 4.7 Hz, 2H), 1.20 (td, *J* = 7.3, 1.8 Hz, 3H), 1.09 (dd, *J* = 9.7, 3.4 Hz, 2H), 1.04 (s, 2H), 1.03 – 0.95 (m, 3H), 0.92 – 0.90 (m, 3H), 0.86 (dd, *J* = 6.6, 3.2 Hz, 5H), 0.06 (s, 1H). ^{13}C NMR (complexity in splitting due to rotamers) (176 MHz, $CDCl_3$) δ 170.12, 163.80, 162.22, 160.14, 160.11, 149.42, 144.09, 143.17, 142.24, 138.90, 138.86, 123.53, 123.42, 110.48, 107.51, 97.34, 97.32, 83.63, 77.20, 77.02, 76.83, 76.16, 56.67, 56.13, 50.02, 42.32, 39.69, 39.52, 38.85, 38.03, 37.94, 36.89, 36.59, 36.18, 35.78, 34.59, 31.92, 31.90, 31.82, 28.22, 28.03, 27.79, 27.68, 24.28, 23.83, 23.40,

23.22, 22.83, 22.57, 21.04, 19.34, 18.73, 14.43, 11.87. HRMS (ESI-TOF) calcd for $C_{40}H_{60}N_2O_5$ (M + H^+) 649.4580, found 649.4511, (M + Na^+) 671.4400, found 671.4400.

4. Thiol addition plots of 4d and 4d'

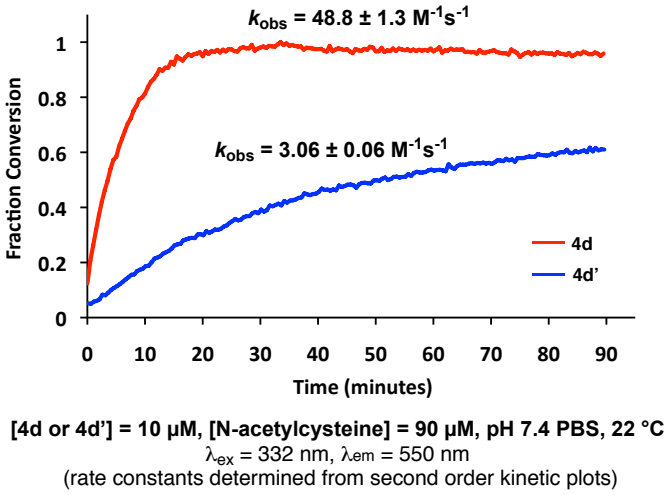


Figure S1. Rate of N-acetyl cysteine Michael addition with fluorogenic dansyl derivatives **4d** and **4d'**.

5.1 Epoxide thiol adduct and succinimide formation

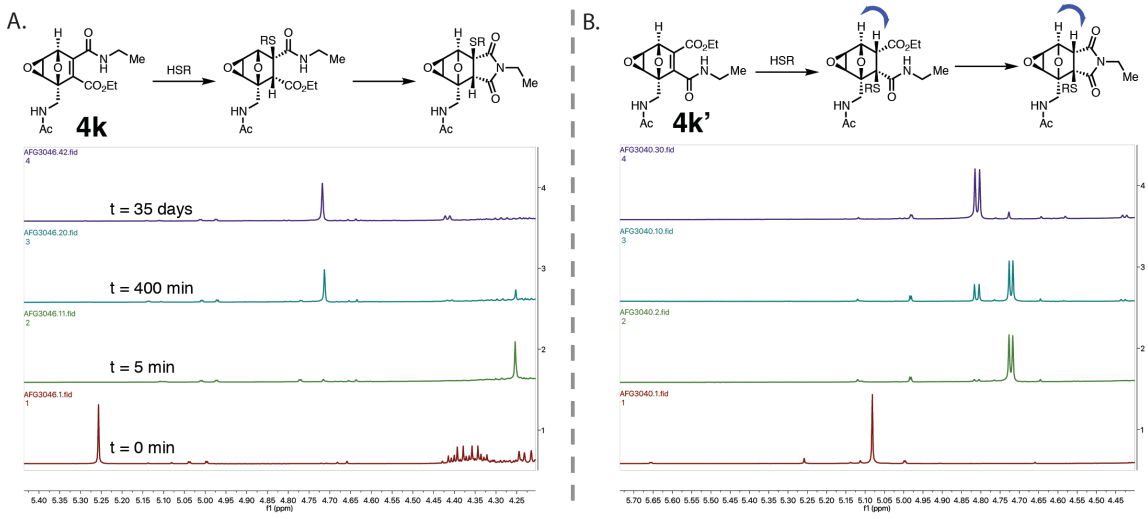
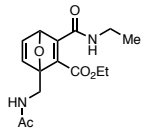
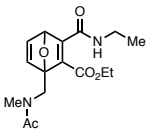
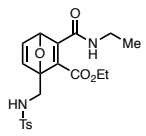
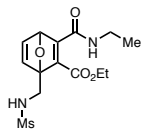
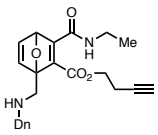
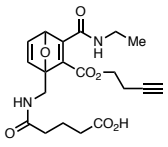
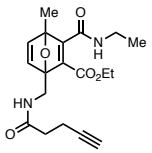
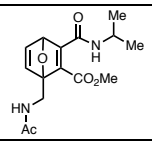
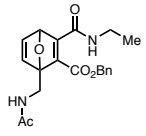


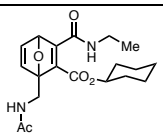
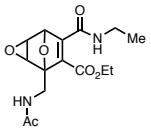
Figure S2. Regiospecific addition of thiol to epoxides **4k** (A) and **4k'** (B). The newly added C-H moiety in the **4k** adduct is a singlet (adjacent to the quaternary bridgehead position), whereas the corresponding resonance in **4k'** adduct is a doublet (split by the adjacent bridgehead-H). *Note: We are unable to unambiguously assign the stereochemistry of thiol addition, but we presume it to add to the exo face of the double bond.*

5.2 Kinetic Data Summary

Each half-life was calculated for the initial rates of both succinimide formation and rDA degradation. Below is a table for the rate for each of these transformations (succinimide or rDA degradation), the percentage of the conversion for the initial transformation that the rate is calculated from, and the R^2 value for the measurements in the rate calculation. These rates were all measured in $CDCl_3$.

Table S1. Summary of kinetic information.

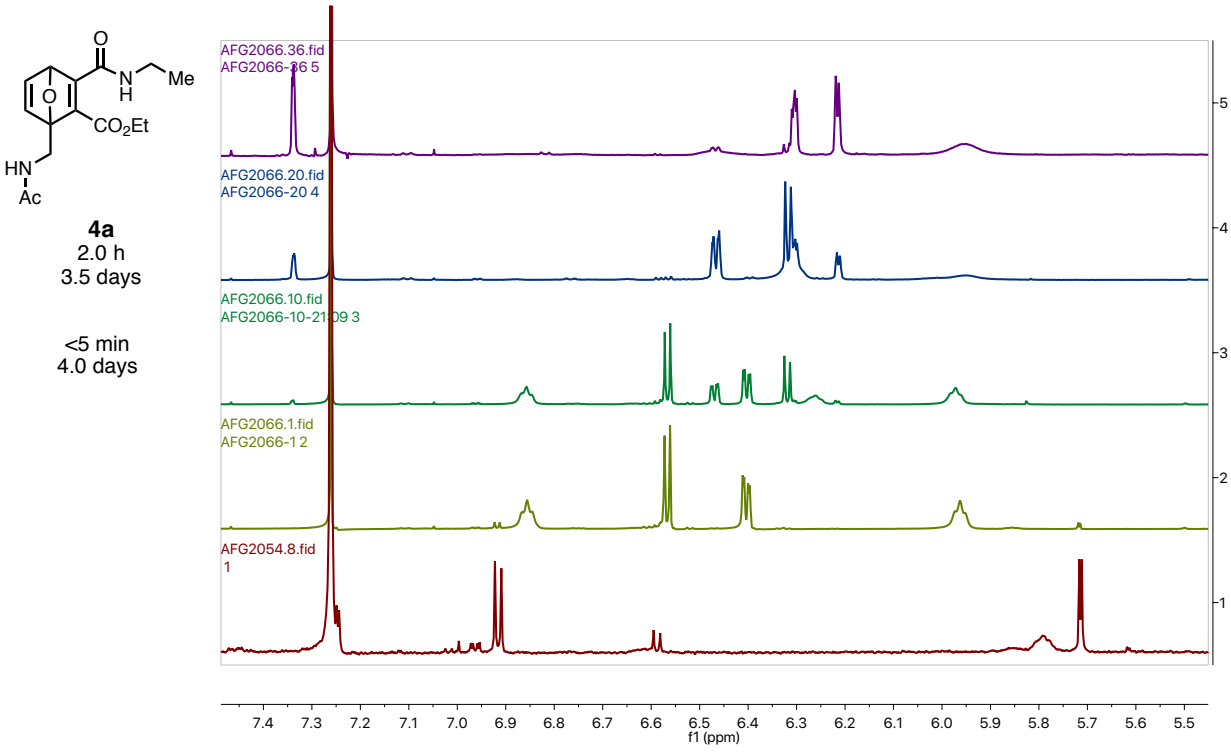
	Substrate	Half-life: succinimide	% of decay	Linear correlation	Half life: rDA	% of decay	Linear correlation
4a		2.0 h	4-22%	$R^2 = 0.97$	3.5 days	22 – 55%	$R^2 = 0.99$
4f		2.8 h	9 - 33%	$R^2 = 0.98$	5.8 days	43 – 93%	$R^2 = 0.99$
4g		2.7 h	10 – 27%	$R^2 = 0.99$	7.9 days	37 – 71%	$R^2 = 0.99$
4h		1.3 h	11 - 47%	$R^2 = 0.94$	4.0 days	20 – 46%	$R^2 = 0.99$
4d		1.1 ± 0.2 h	8-32%	$R^2 = 0.95$	6.3 ± 0.1 days	23 – 62%	$R^2 = 0.95$
4c		5.9 ± 0.5 h	17 – 24%	$R^2 = 0.95$	3.4 days	17 – 58%	$R^2 = 0.98$
4e		8.7 ± 1.1 min	6 – 47%	$R^2 = 0.99$	8.5 ± 0.4 h	55-73%	$R^2 = 0.99$
			45 – 85%	$R^2 = 0.94$		51 – 64%	$R^2 = 0.98$
4j		5.8 h	11 – 22%	$R^2 = 0.98$	9.7 days	35 – 96%	$R^2 = 0.99$
4i		1.1 hr	19 – 42%	$R^2 = 0.99$	3.0 days	24 – 51%	$R^2 = 0.99$

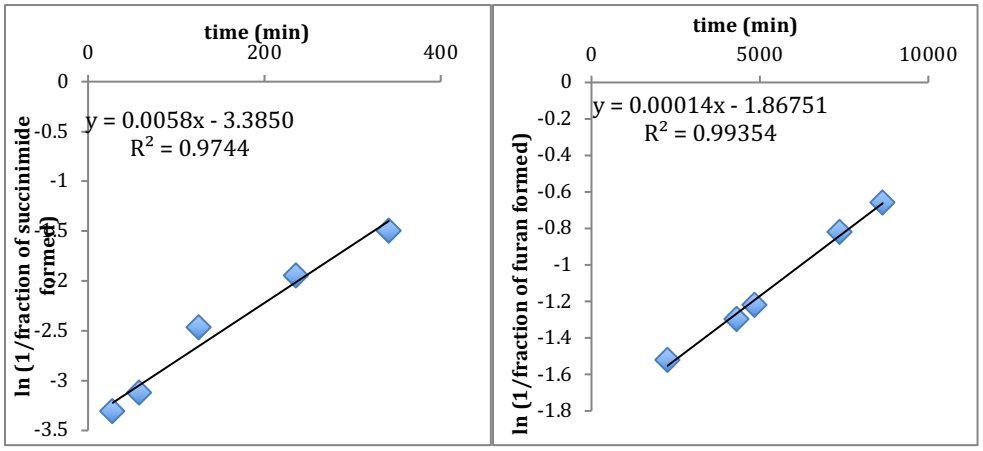
4b		7.6 ± 0.9 h	24 – 48%	$R^2 = 0.97$	4.5 ± 0.8 days	45 – 54%	$R^2 = 0.78$
			7 – 18%	$R^2 = 0.99$		44 – 73%	$R^2 = 0.98$
4k		42.3 min	15 – 30 %	$R^2 = 0.92$	no rDA	--	--

5.3 ^{1}H NMR and half-life traces for EA-ONDs

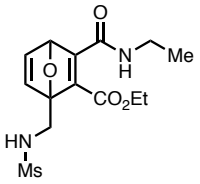
NMR traces and 1st order kinetic profiles for each of the compounds reported in the main text. The bottom (maroon) trace, labeled 1, is the starting material. Second from the bottom, trace 2, is the first time point after thiol and base addition. The next trace (if 4 traces shown) or two (if five traces are shown) demonstrate succinimide formation and rDA. The top trace, labeled 4 or 5, show the rDA product furan. These NMR traces are taken at different time points based on degradation time.

NMR solvent: $CDCl_3$

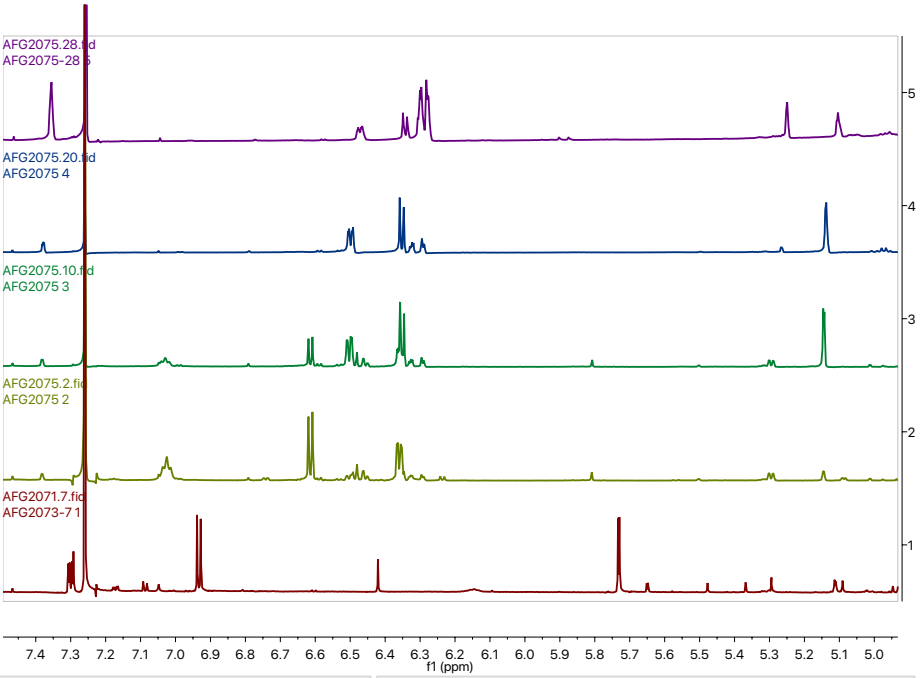


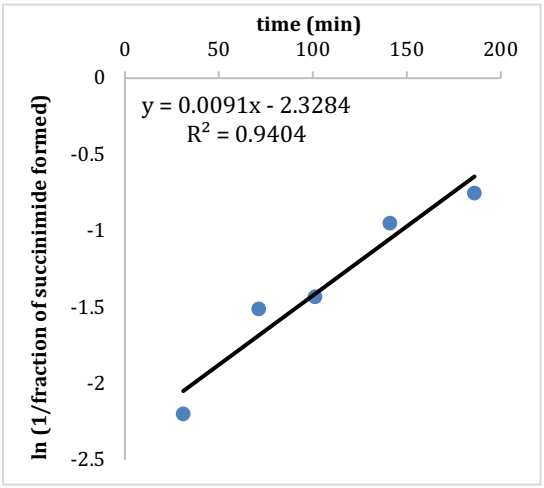


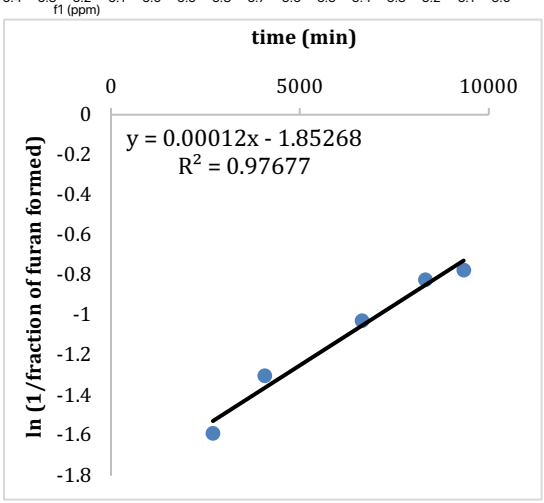
NMR solvent: $CDCl_3$



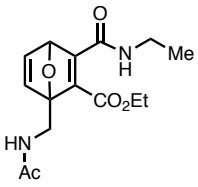
4h
1.3 h
4.0 days







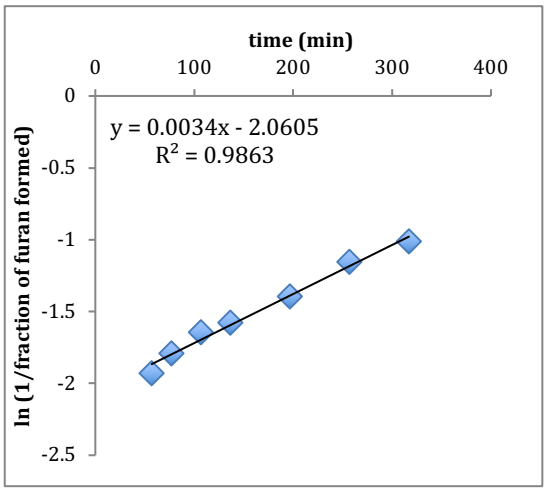
NMR solvent: CD_3OD



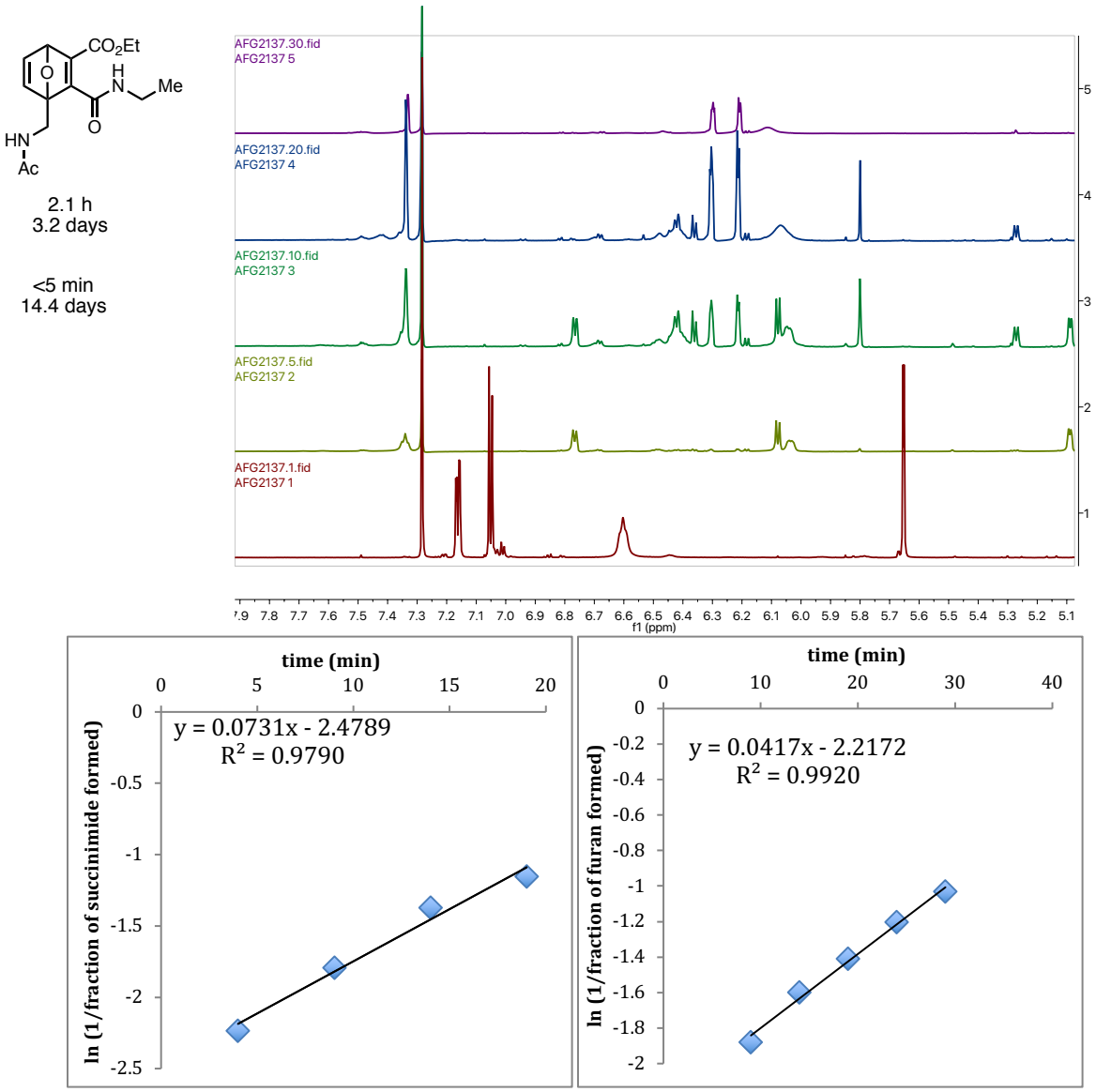
4a
2.0 h
3.5 days

<5 min
4.0 days

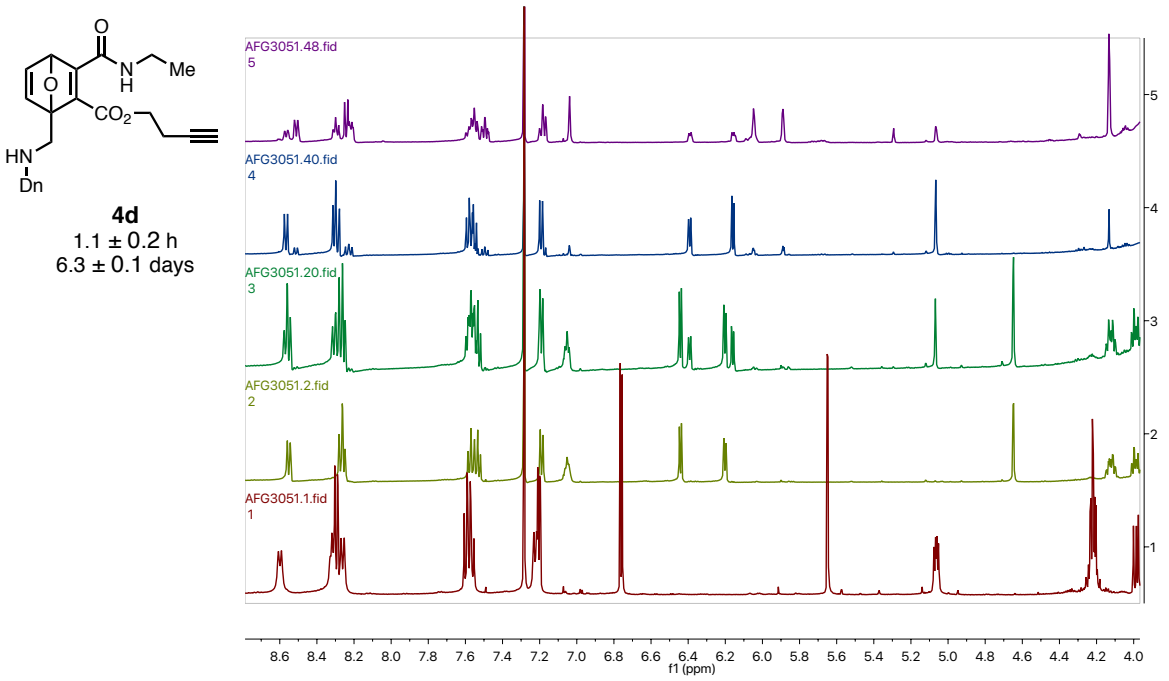
Succinimide forms in less than five minutes

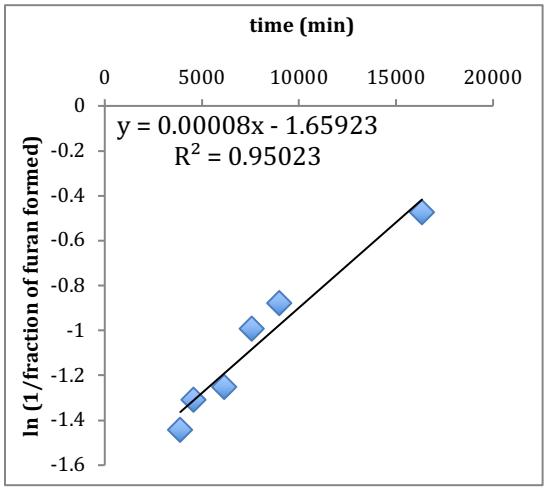


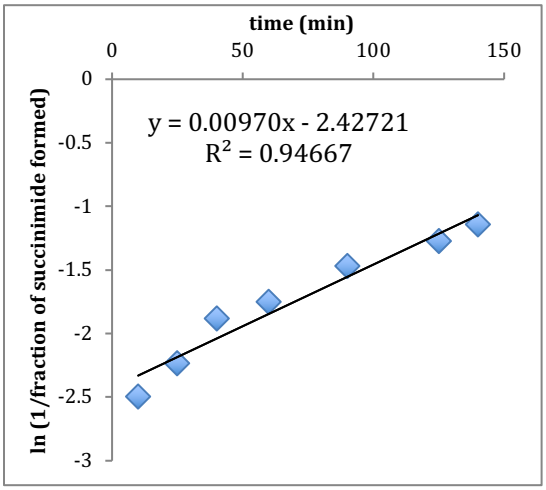
NMR solvent: $CDCl_3$



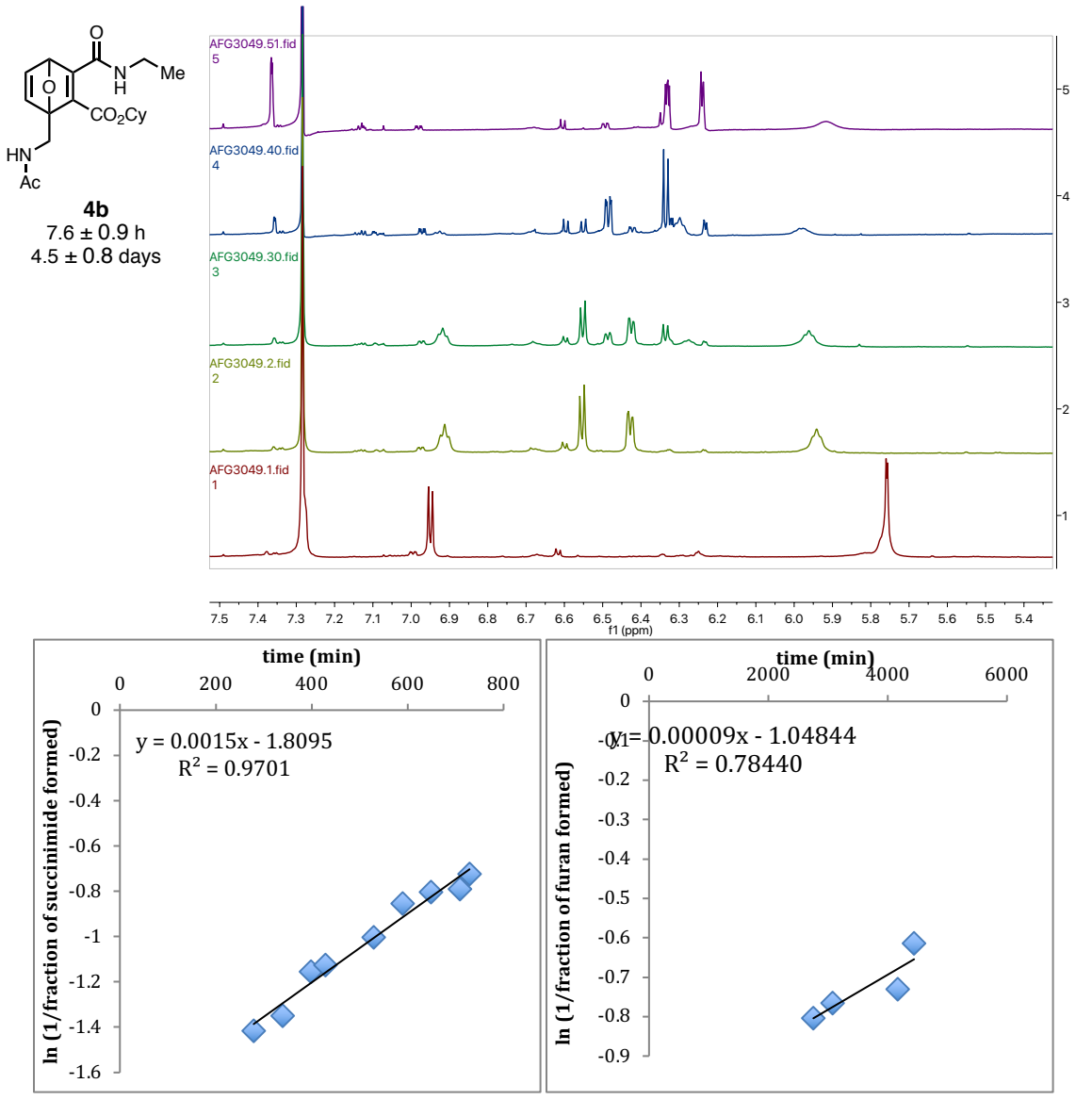
NMR solvent: $CDCl_3$



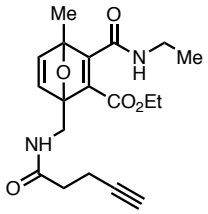




NMR solvent: $CDCl_3$

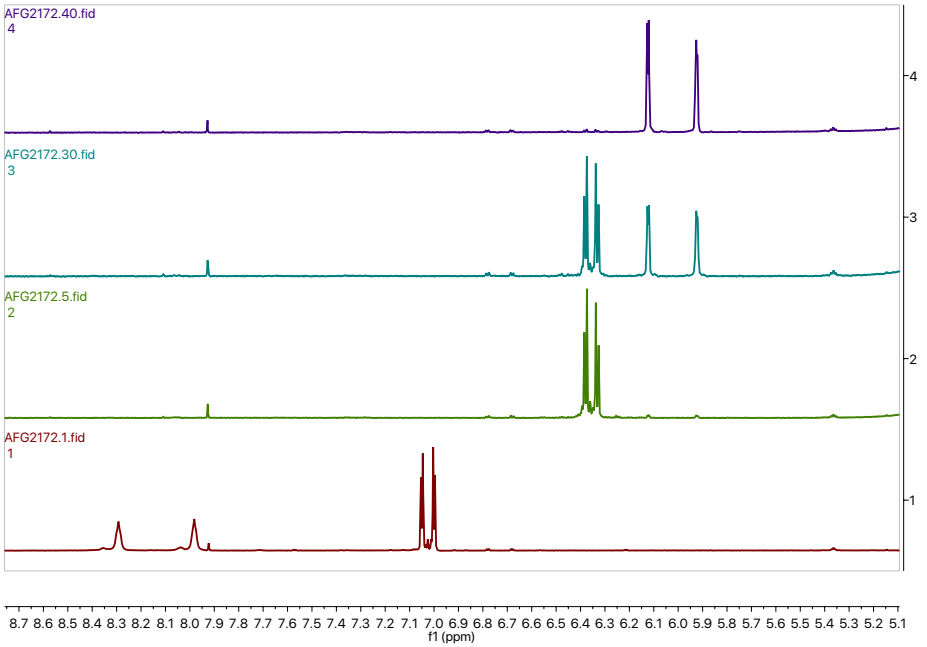


NMR solvent: CD_3OD

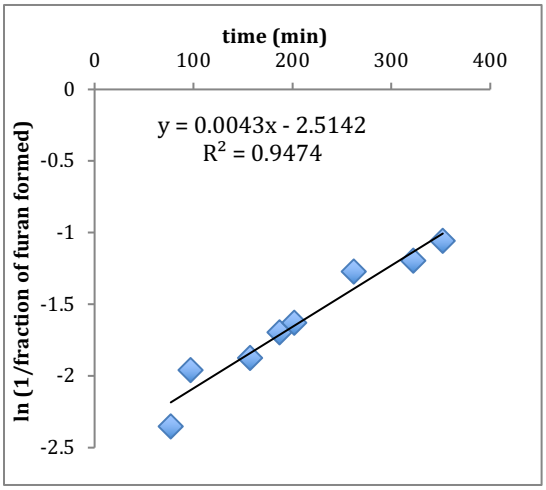


4e
8.7 ± 1.1 min
8.5 ± 0.4 hrs

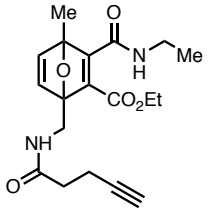
<5 min
2.7 hr



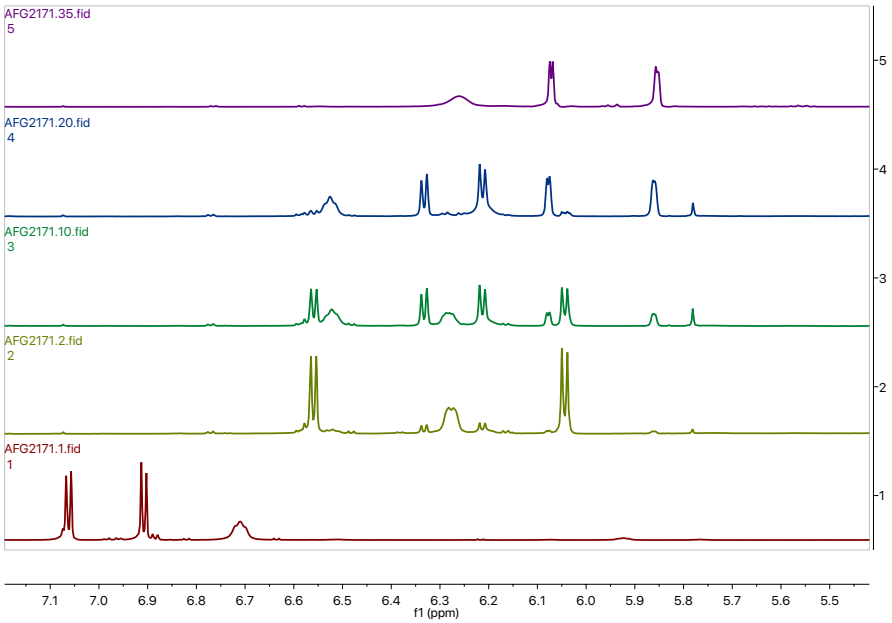
Succinimide formation is less than 5 minutes

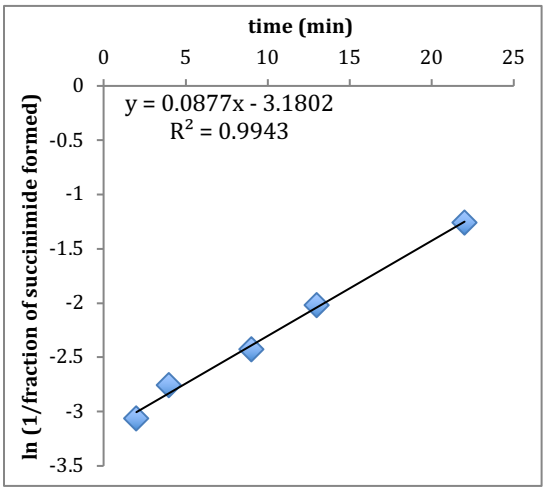


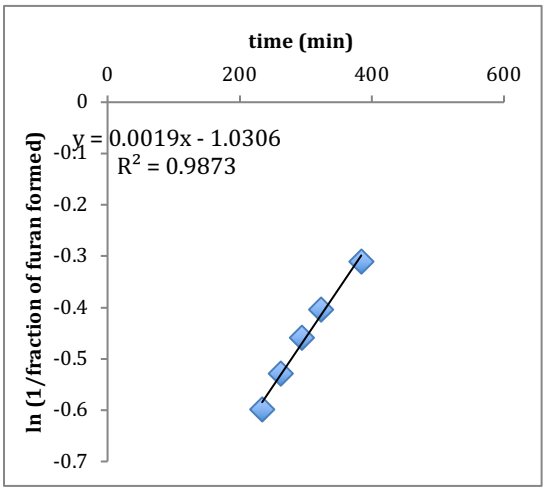
NMR solvent: $CDCl_3$



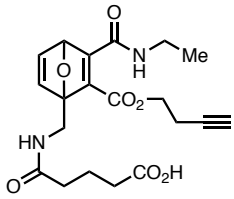
4e
8.7 ± 1.1 min
8.5 ± 0.4 hrs





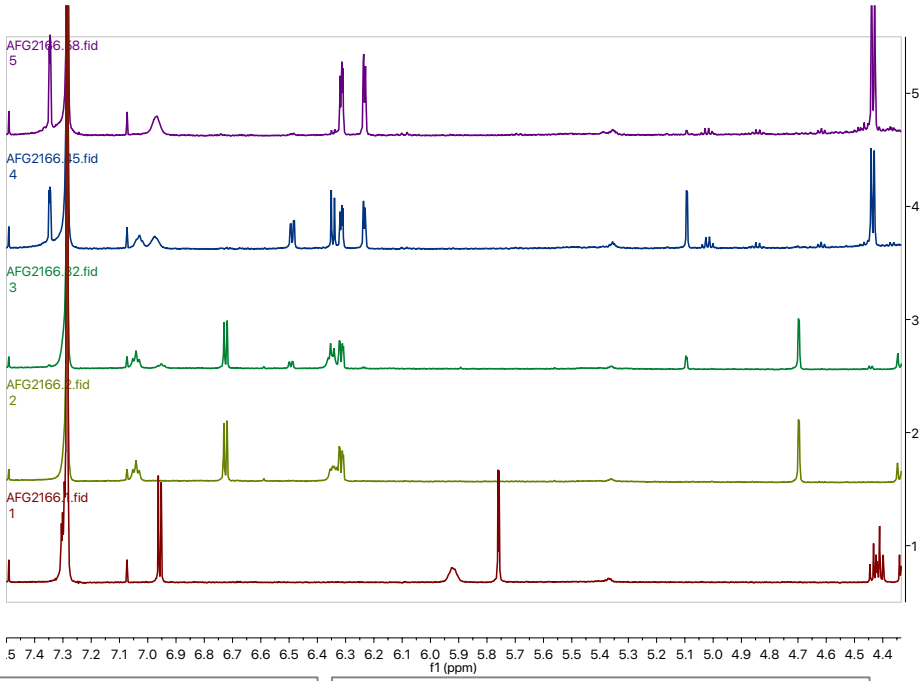


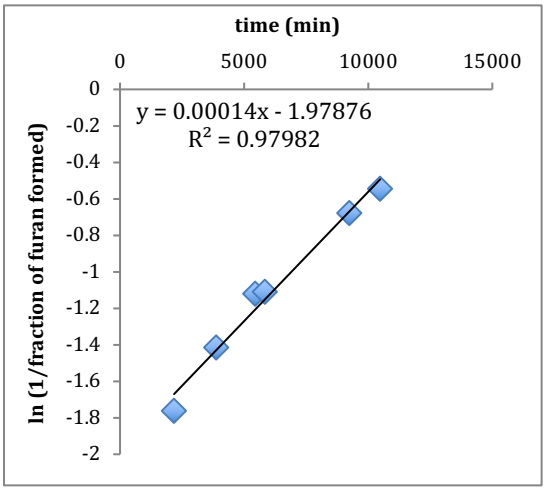
NMR solvent: $CDCl_3$

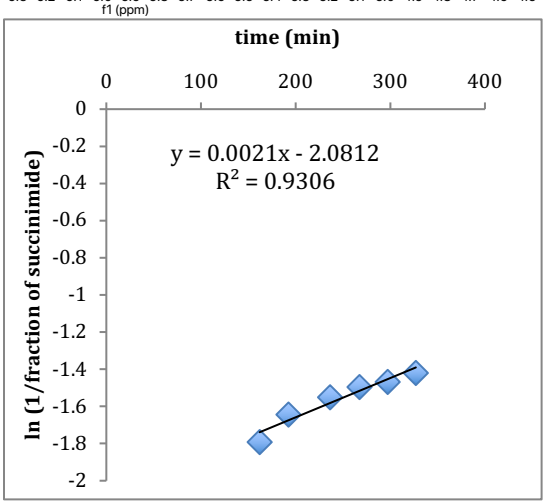


4c
5.9 ± 0.5 h
3.4 days

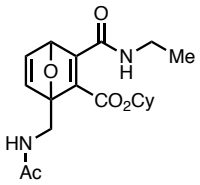
12.4 min
5.3 days





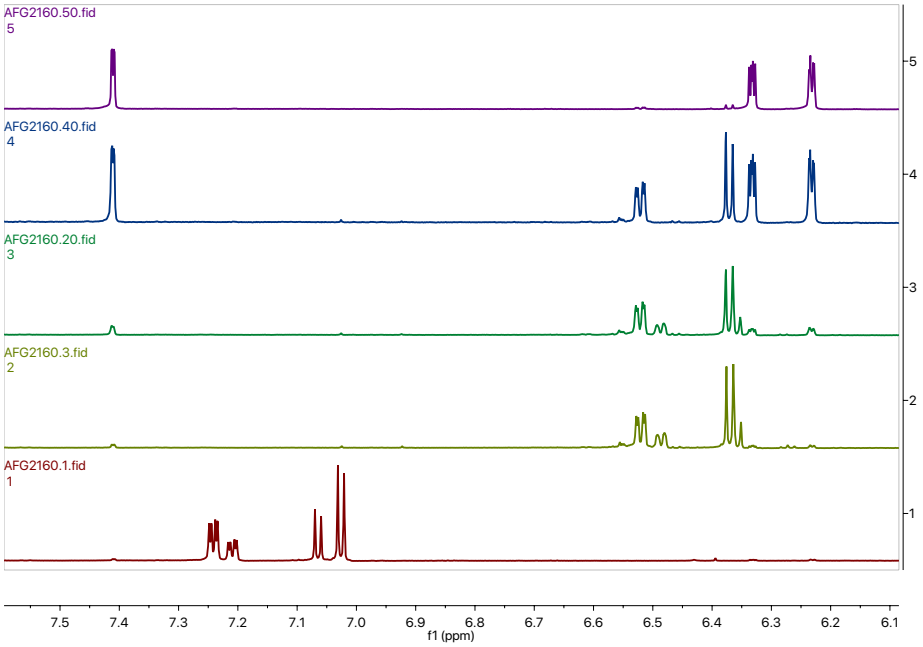


NMR solvent: CD_3OD

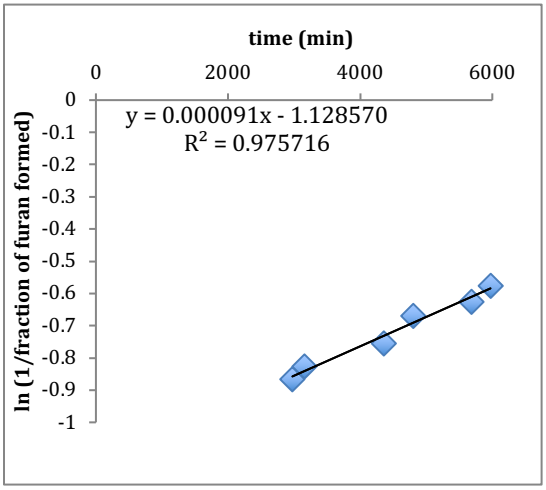


4b
7.6 ± 0.9 h
4.5 ± 0.8 days

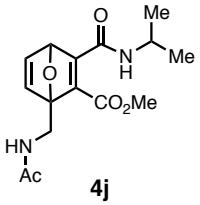
<5 min
5.3 days



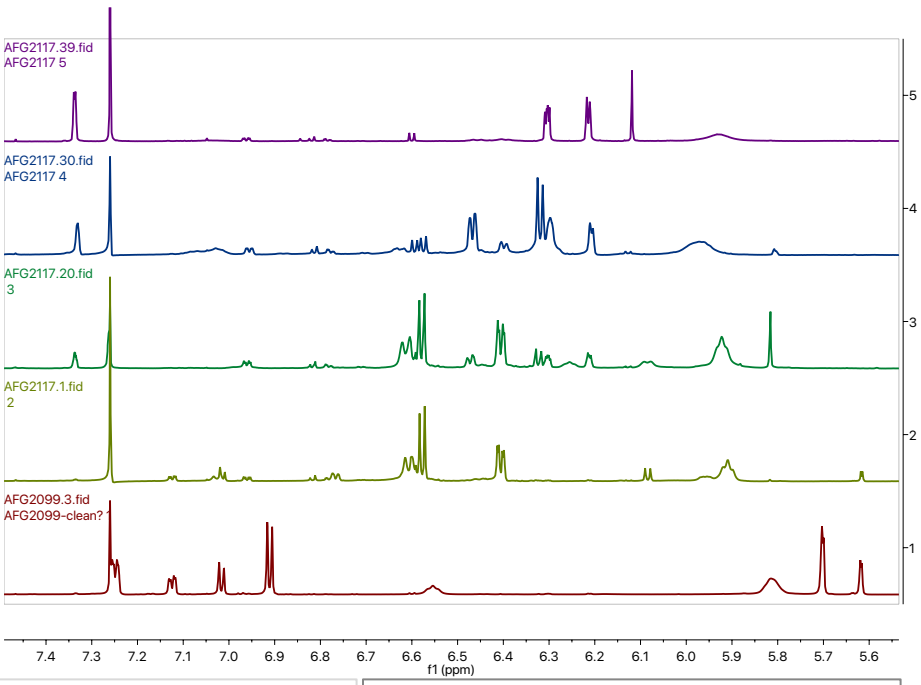
Succinimide forms in less than 5 minutes

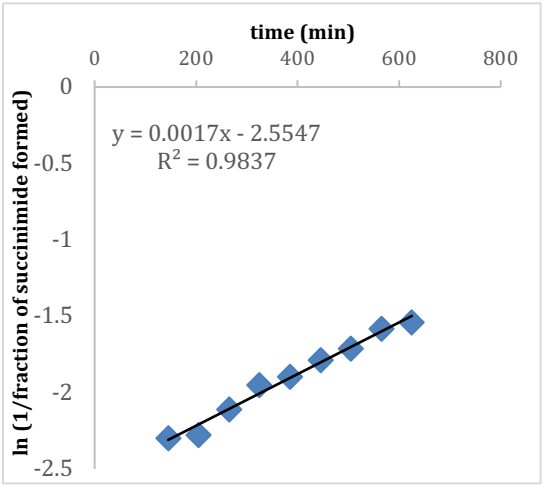


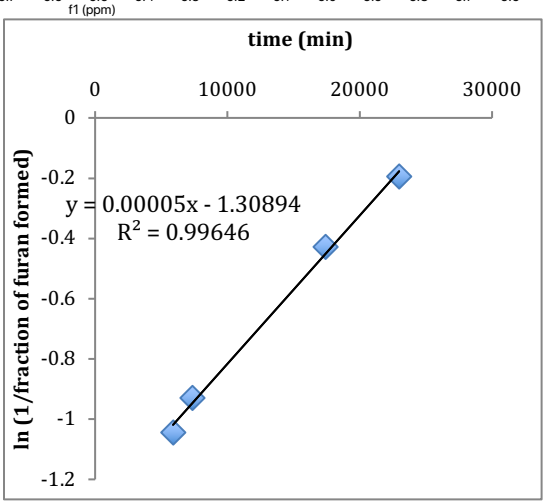
NMR solvent: $CDCl_3$



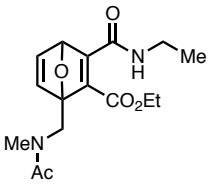
4j
6.8 h
9.7 days



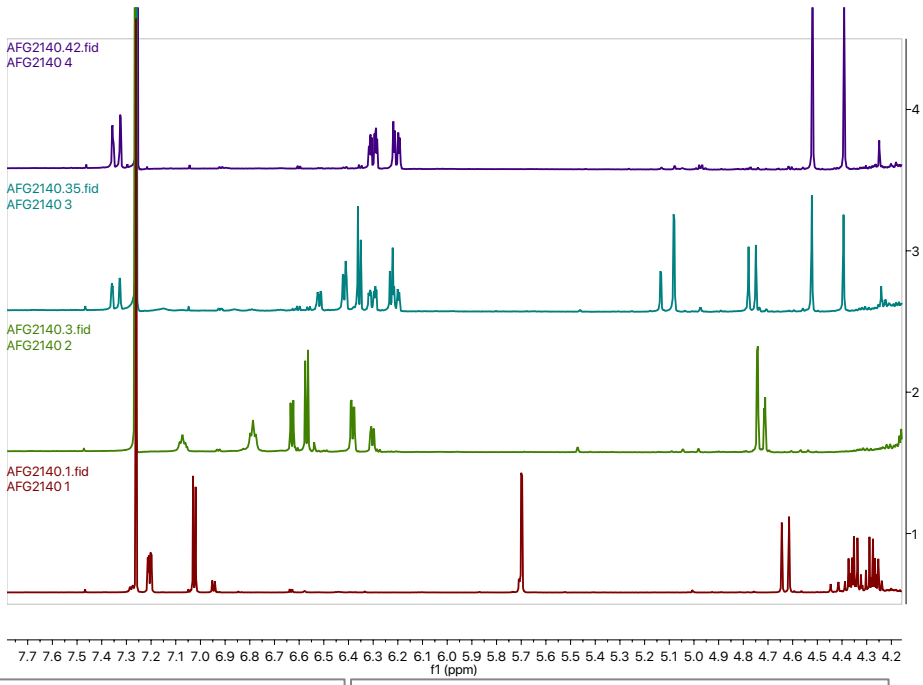


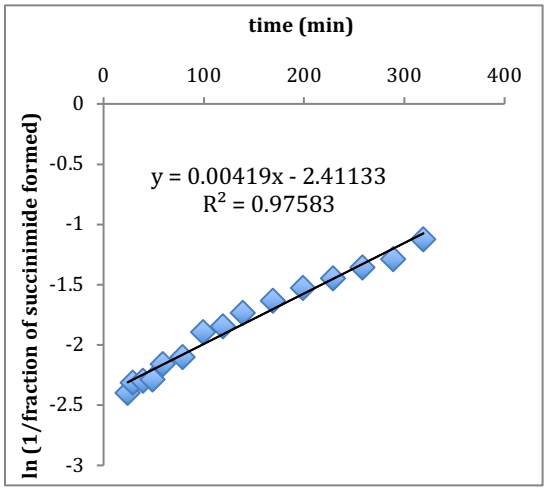


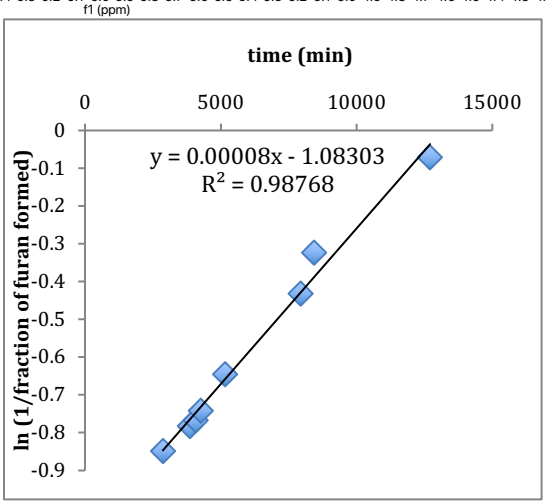
NMR solvent: $CDCl_3$



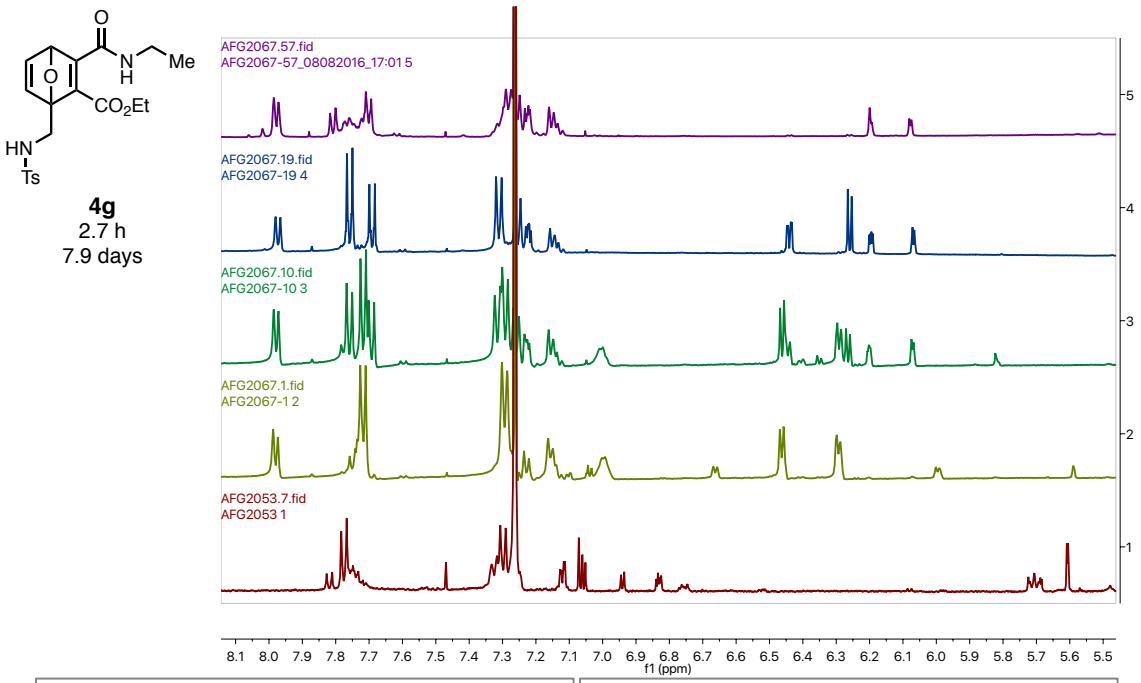
4f
2.8 h
5.8 days

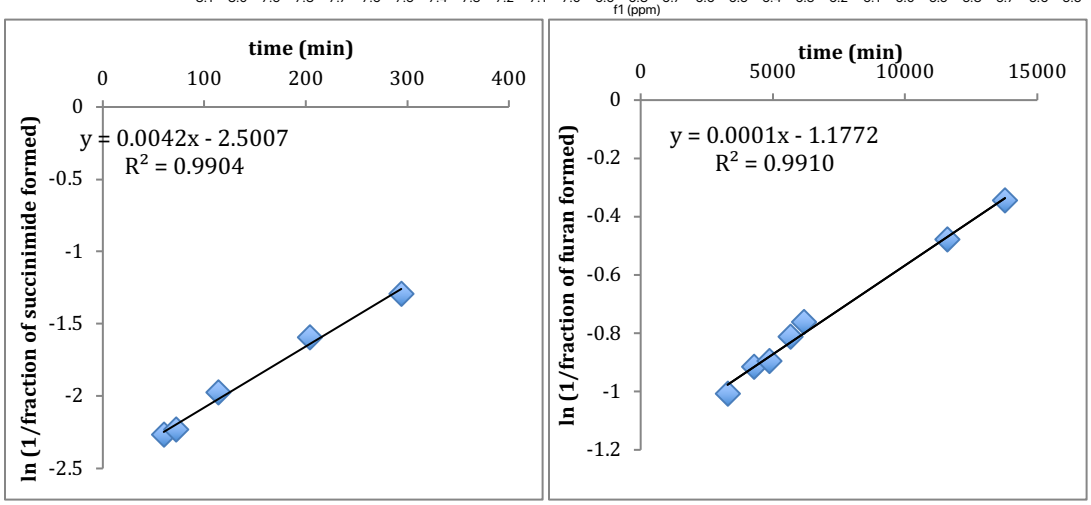




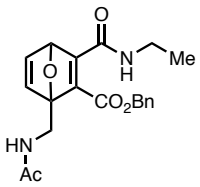


NMR solvent: $CDCl_3$

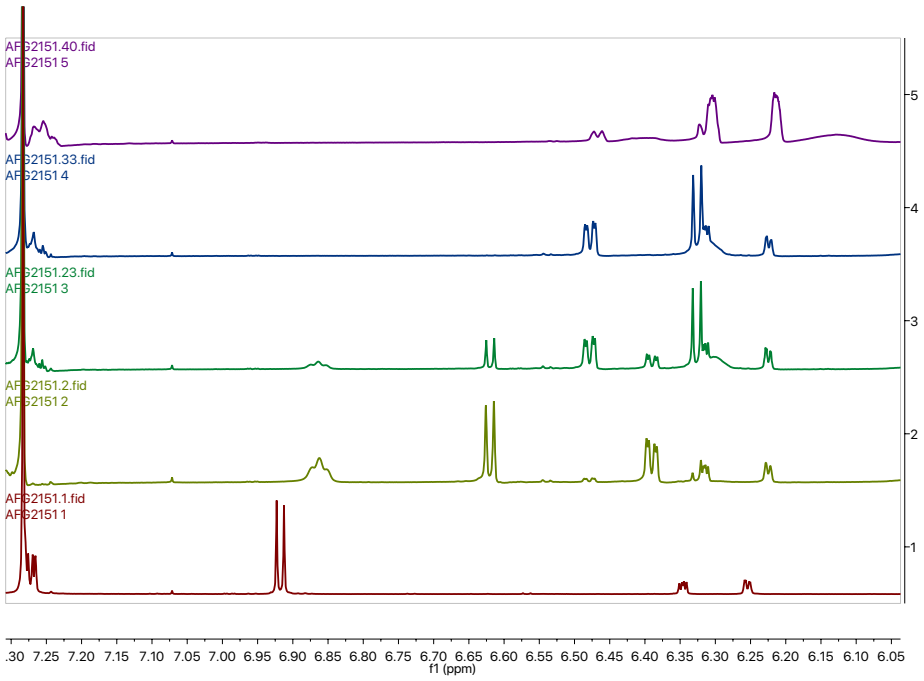


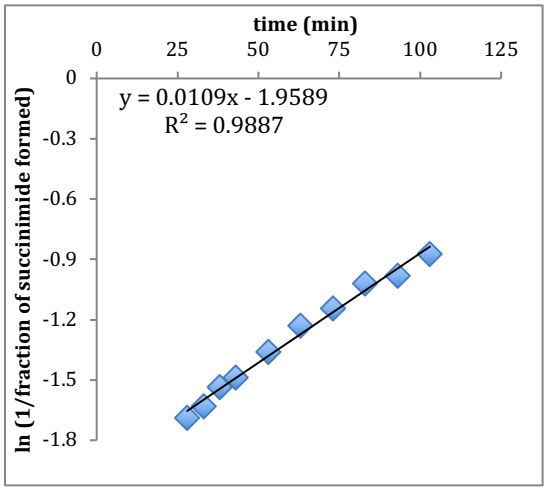


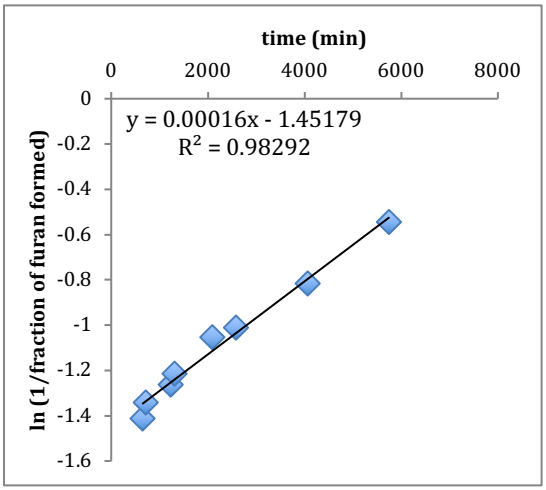
NMR solvent: $CDCl_3$



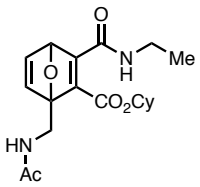
4i
1.1 h
3.0 days





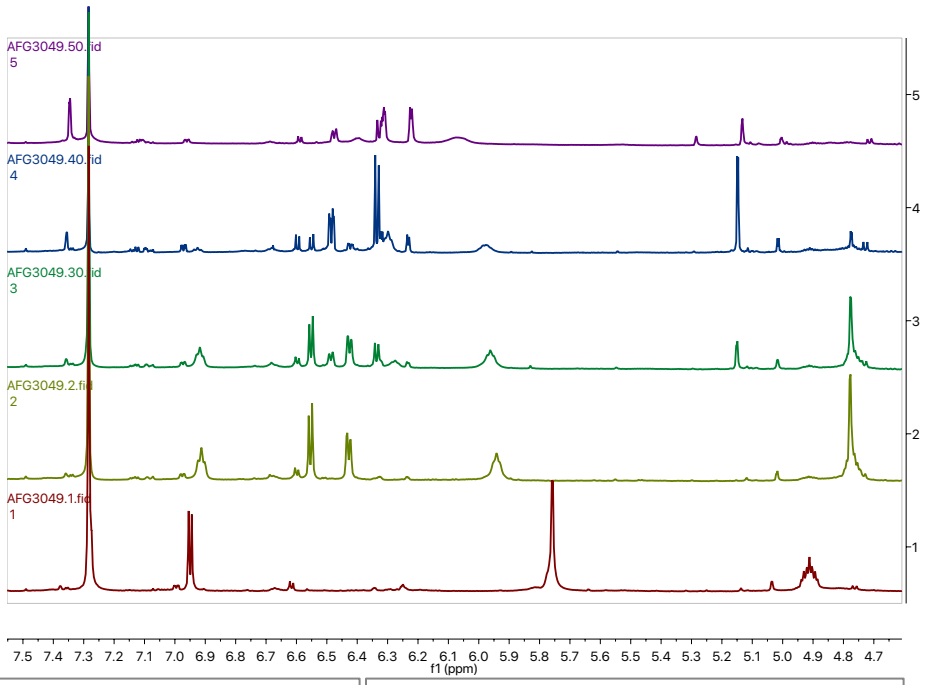


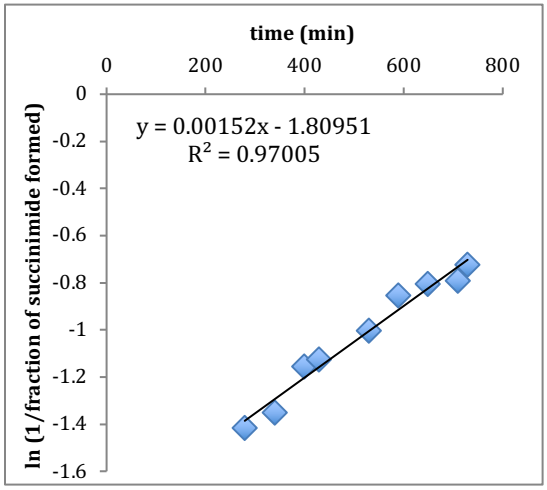
NMR solvent: $CDCl_3$

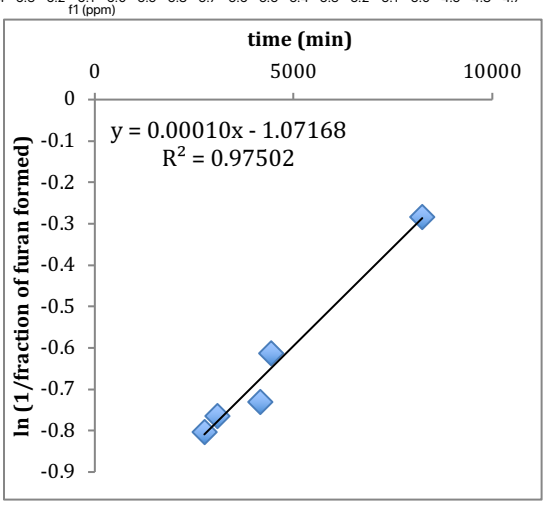


4b
7.6 ± 0.9 h
4.5 ± 0.8 days

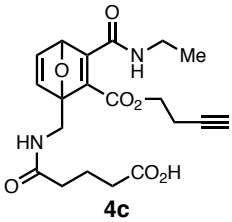
<5 min
5.3 days





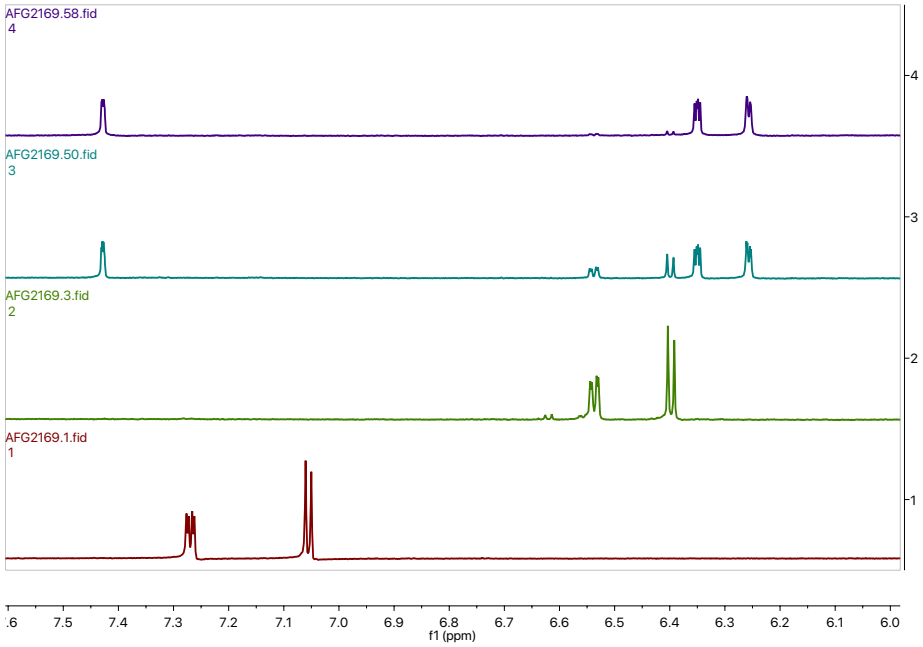


NMR solvent: CD_3OD

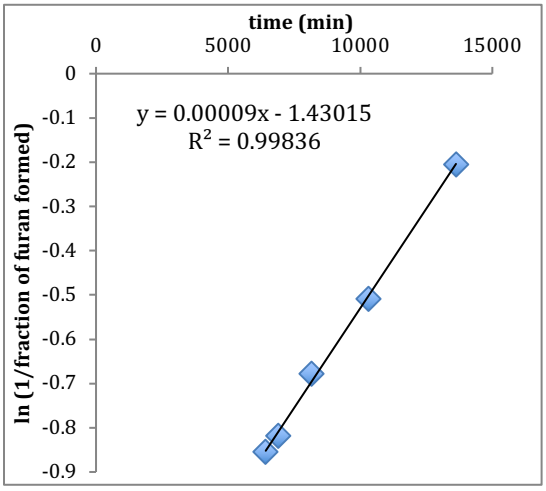


4c
5.9 ± 0.5 h
3.4 days

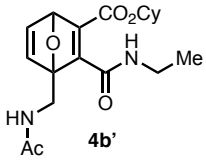
6.1 ± 1.5 min
6.0 ± 1.0 days



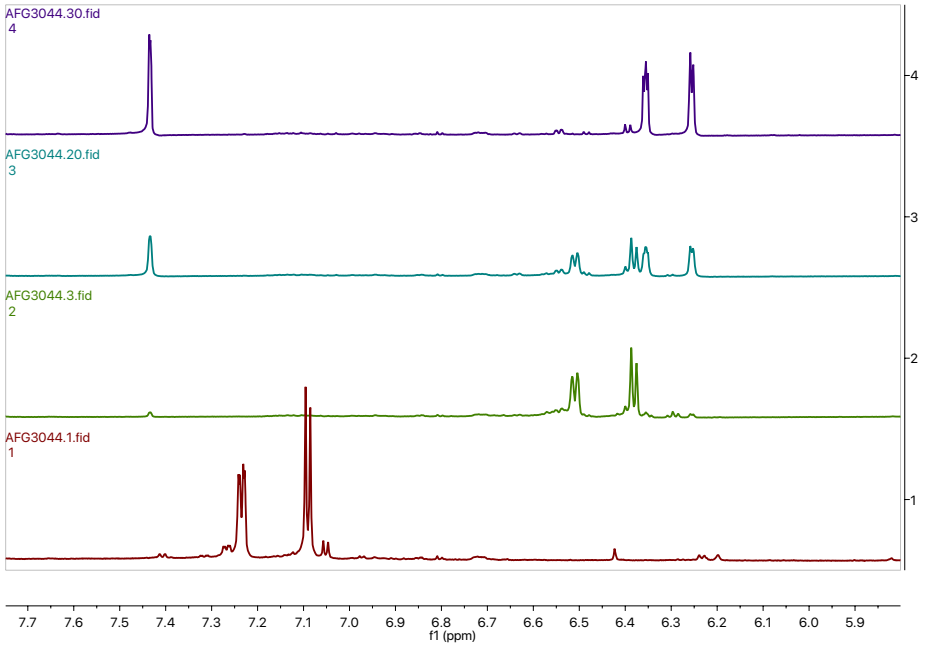
Succinimide forms in less than 5 minutes



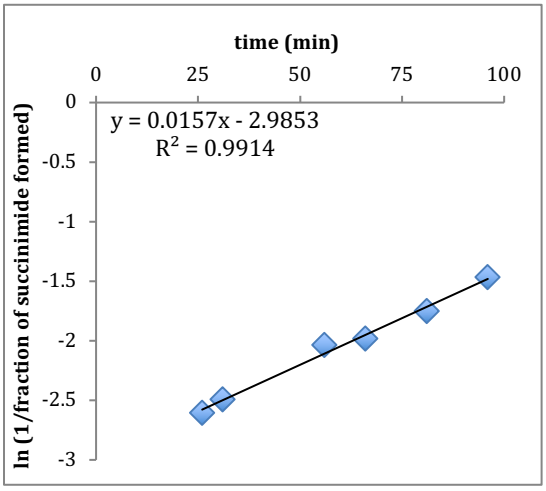
NMR solvent: CD_3OD



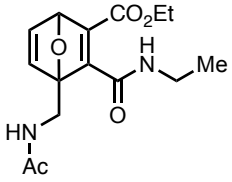
4b'



Succinimide forms in less than 5 minutes

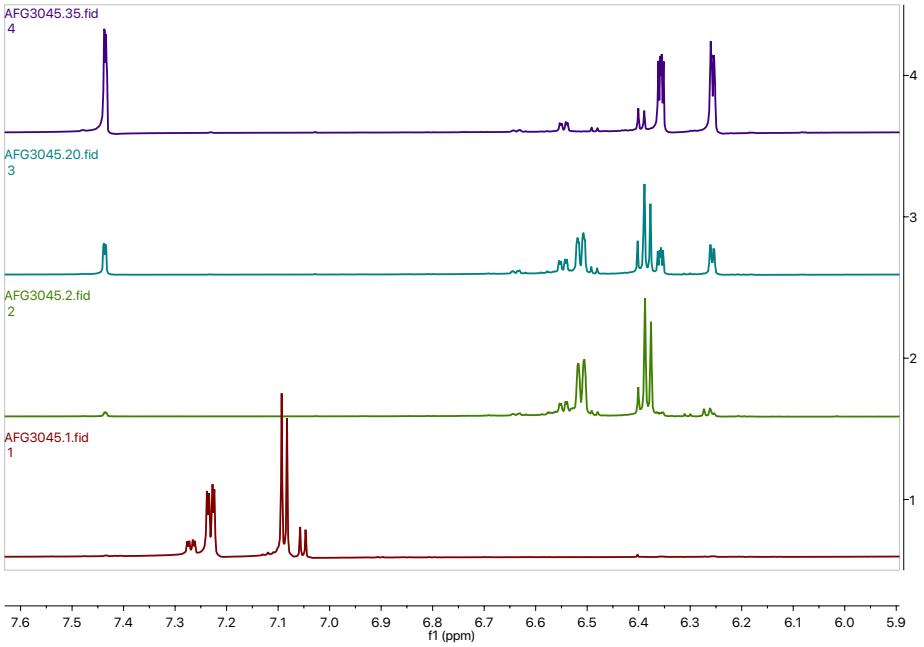


NMR solvent: CD_3OD

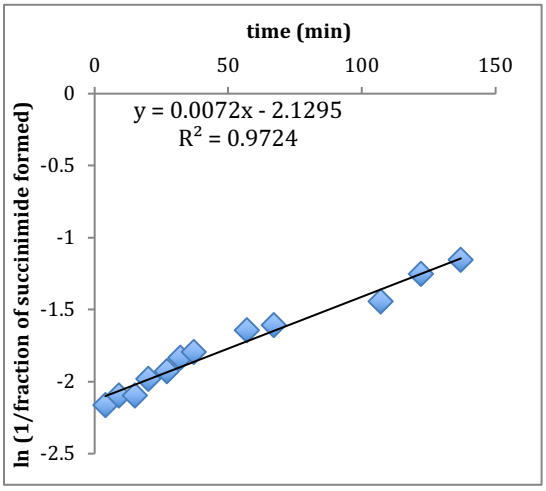


9.4 min
16.6 min

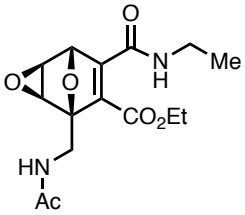
<5 min
1.6 h



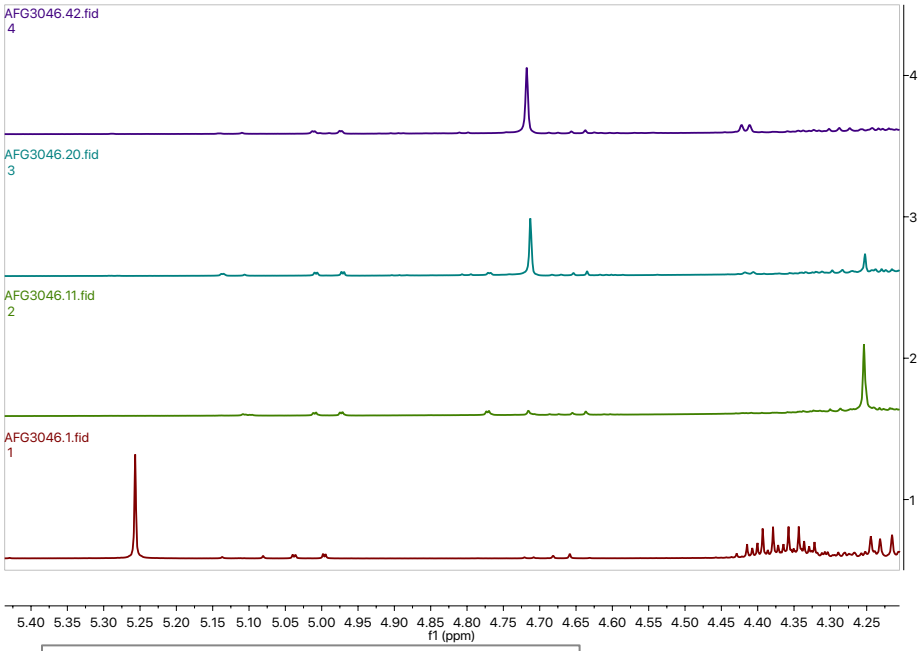
Succinimide forms in less than 5 minutes

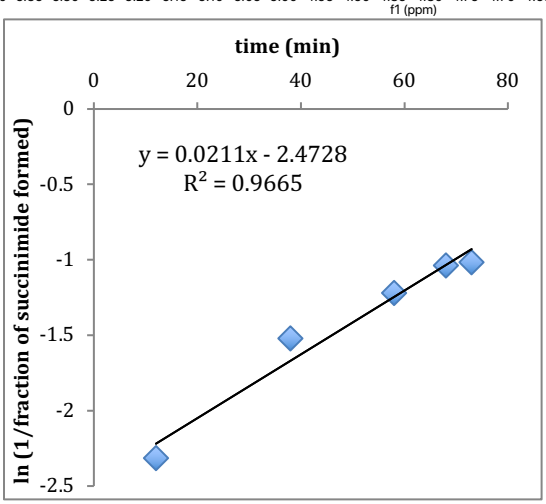


NMR solvent: $CDCl_3$

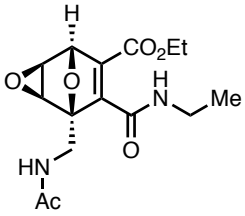


4k
42.3 min
no rDA

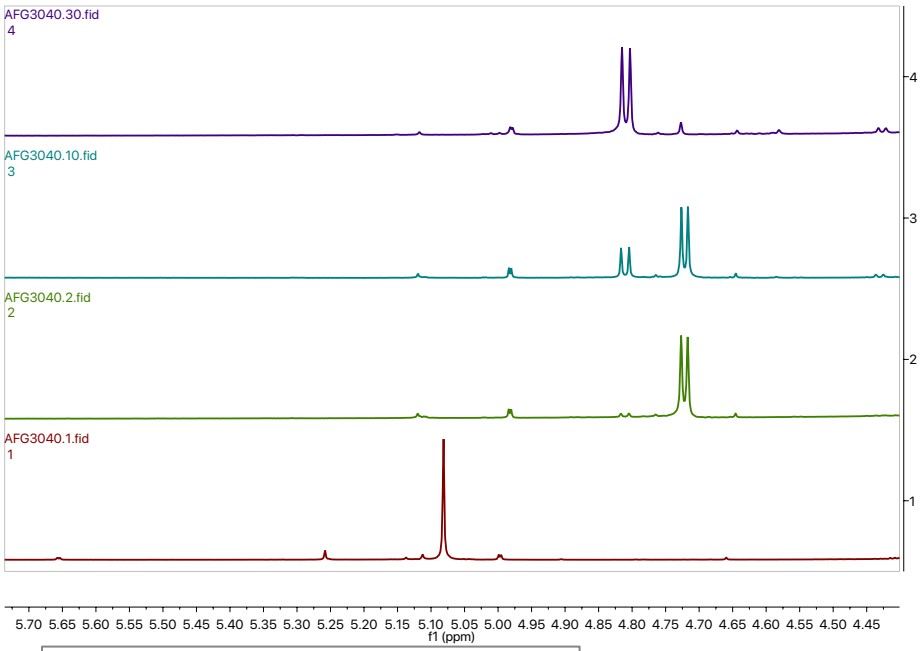


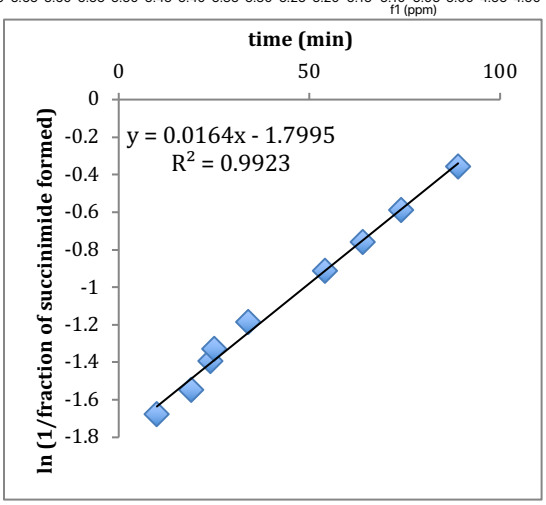


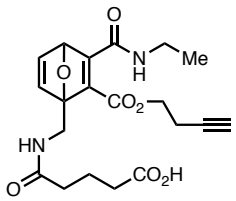
NMR solvent: $CDCl_3$



4k'
32.8 min
no rDA



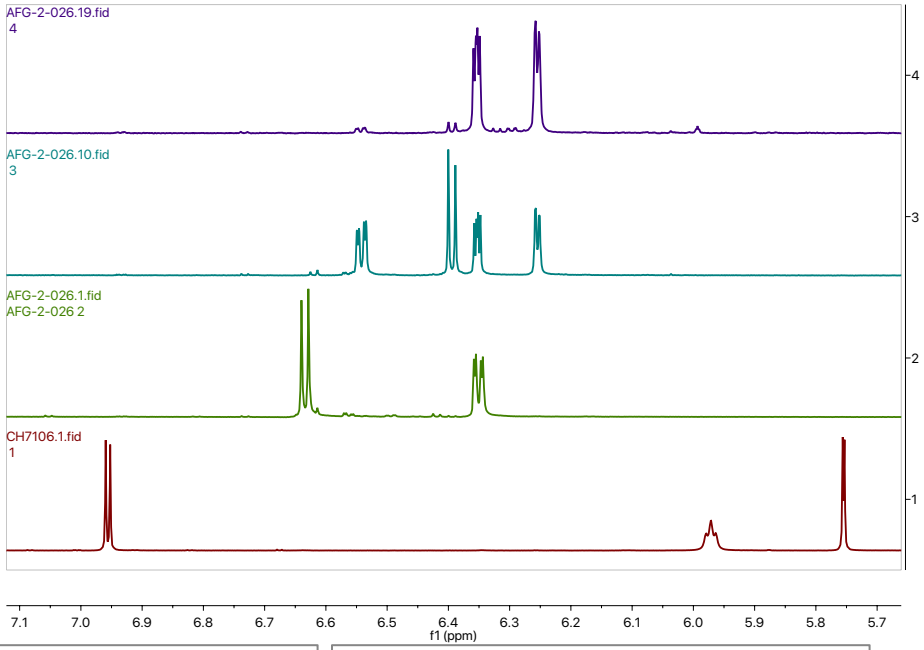


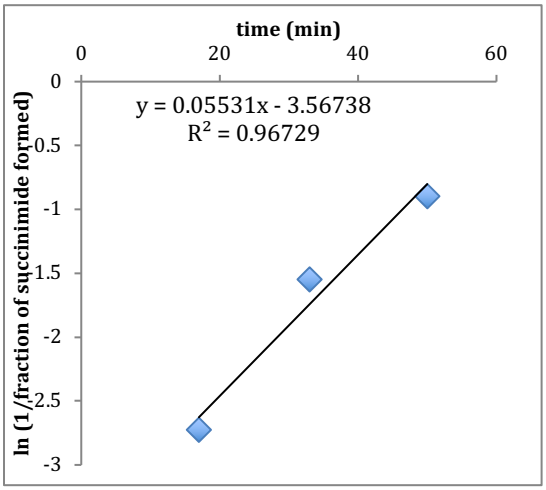


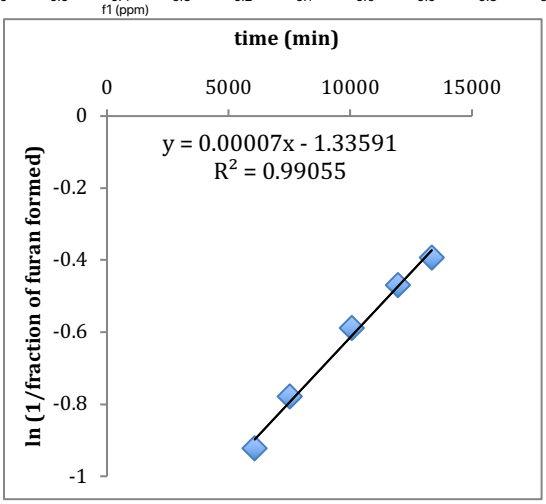
4c
5.9 ± 0.5 h
3.4 days

6.1 ± 1.5 min
6.0 ± 1.0 days

Starting material NMR is shown in $CDCl_3$ but kinetic measurements were done in CD_3OD.







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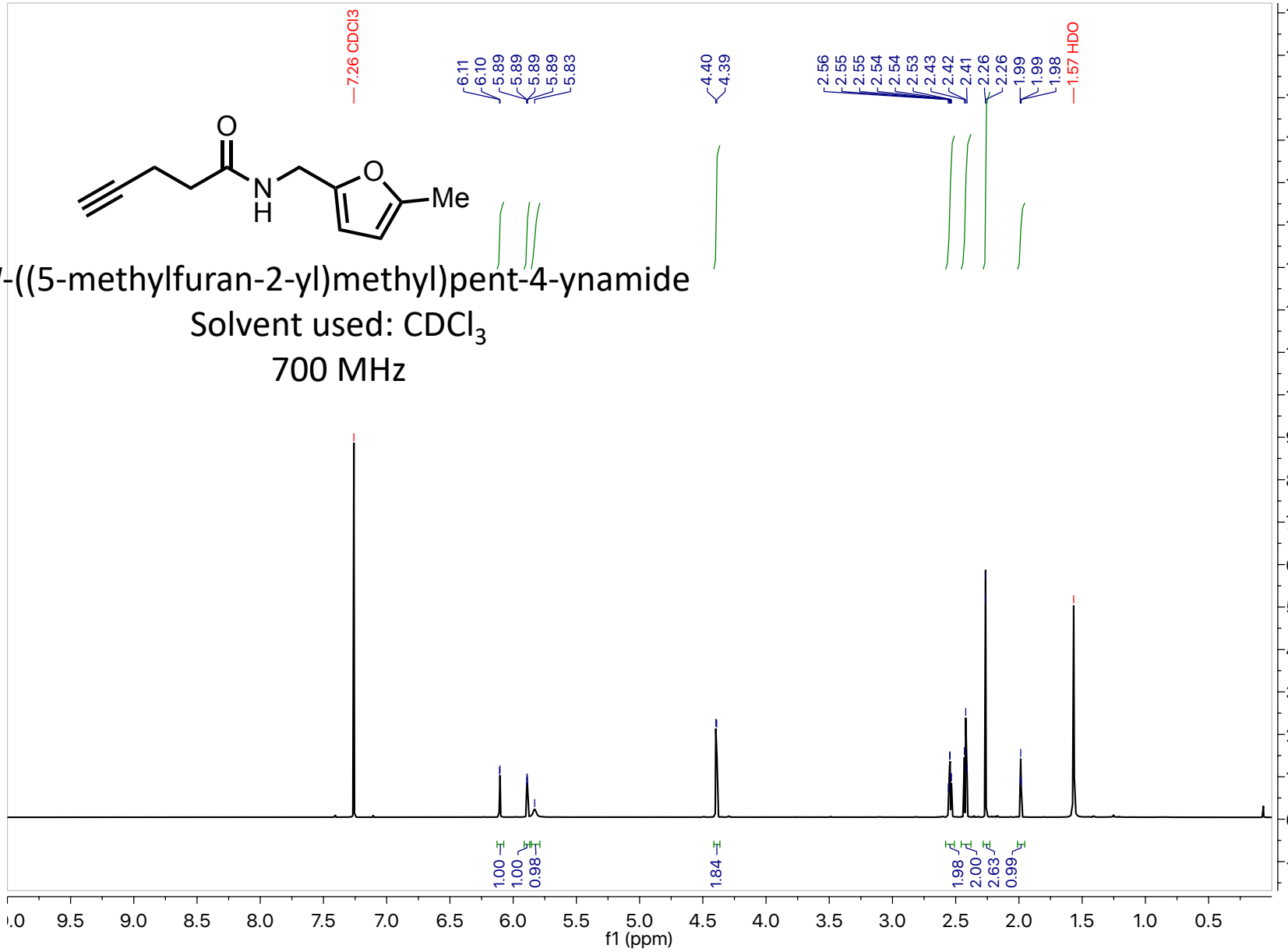
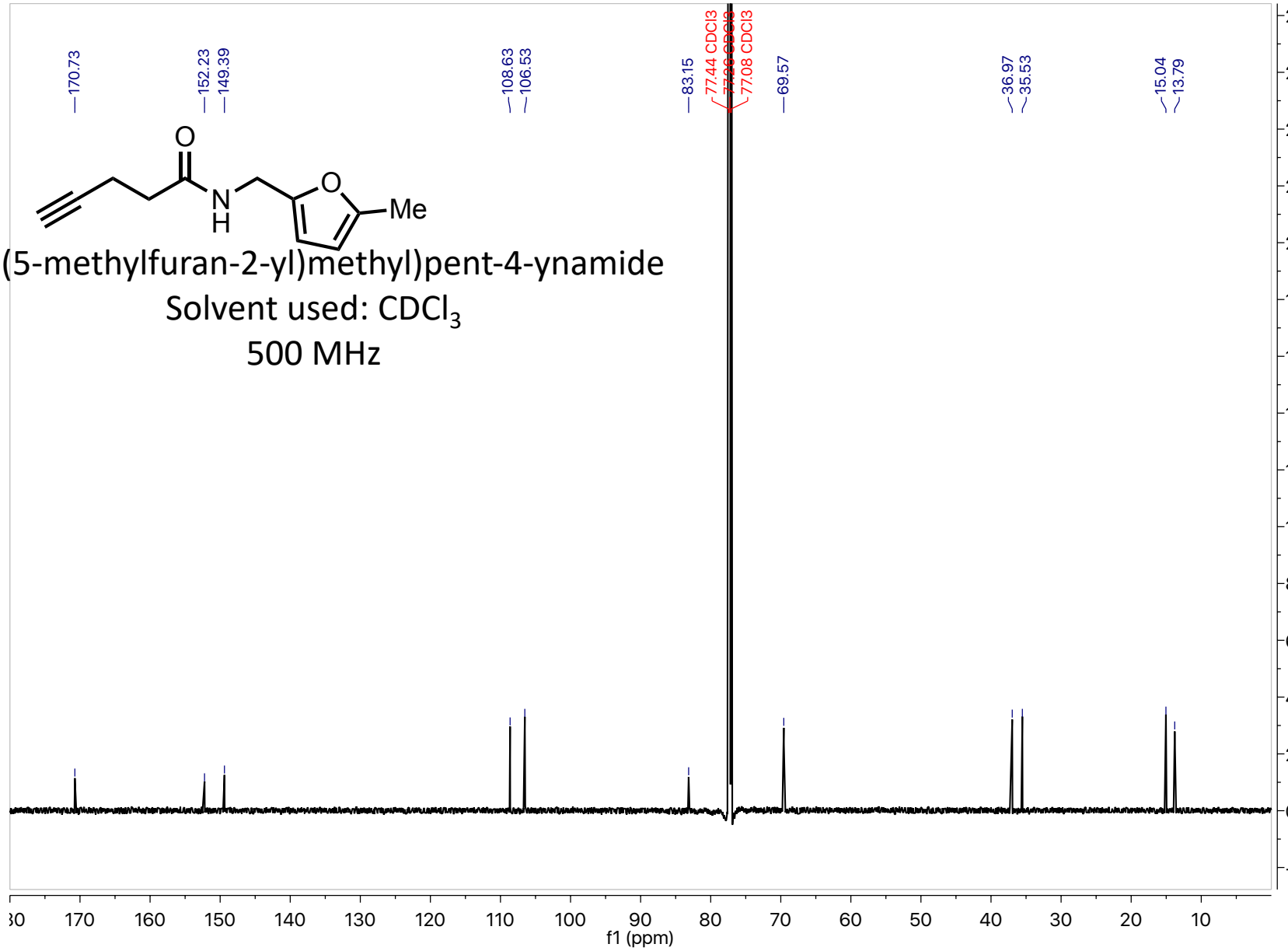
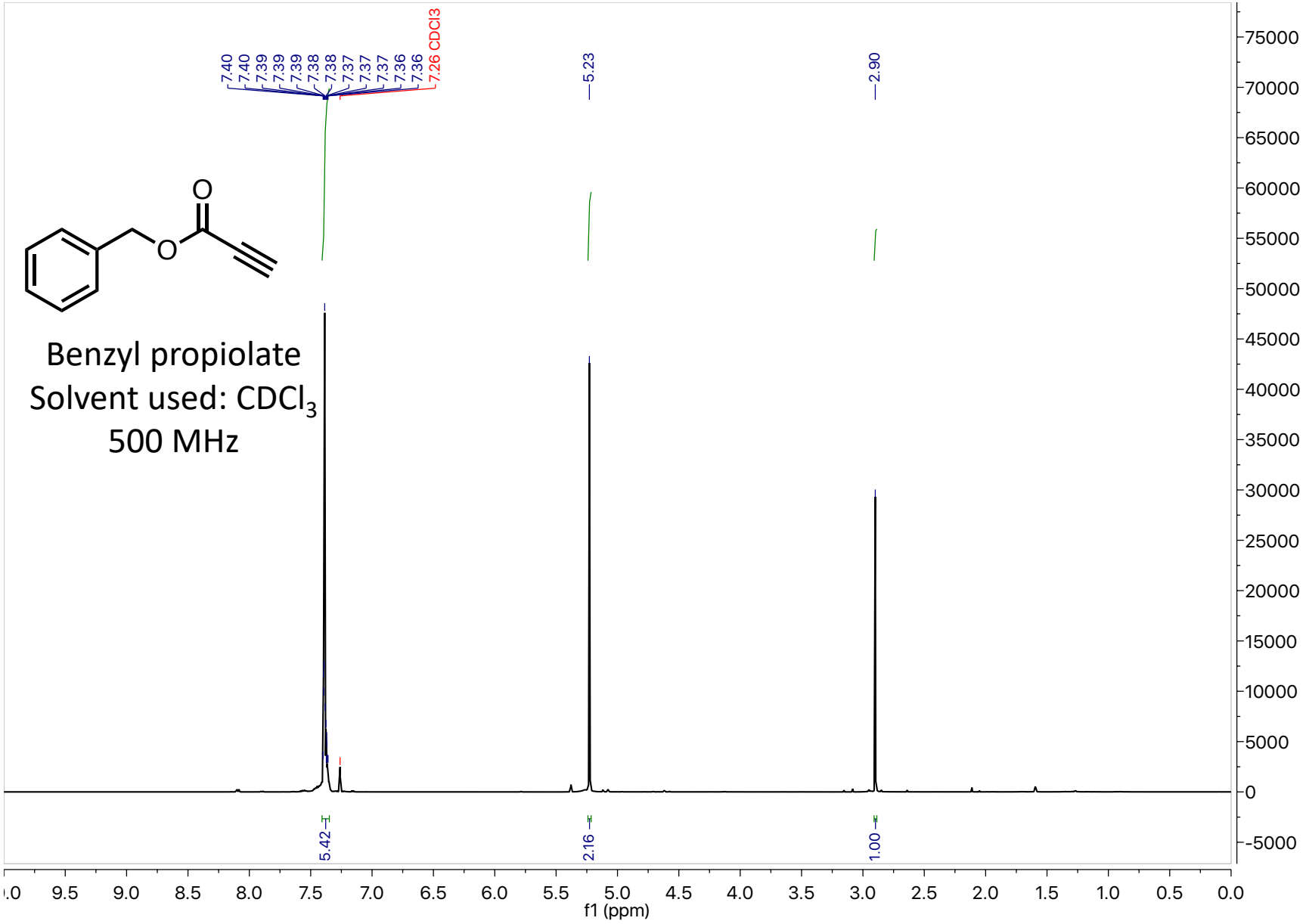


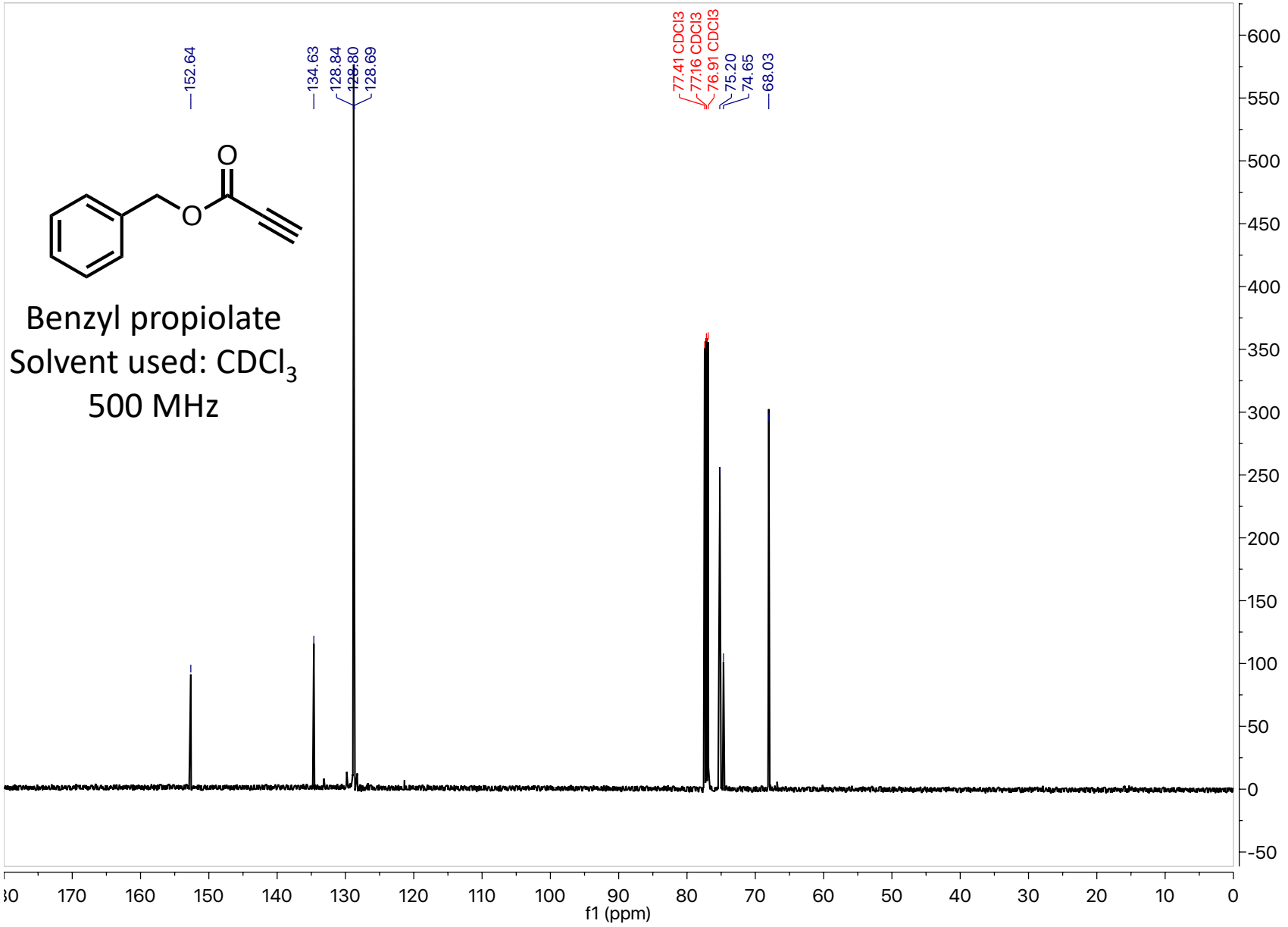
N-((5-methylfuran-2-yl)methyl)pent-4-ynamide

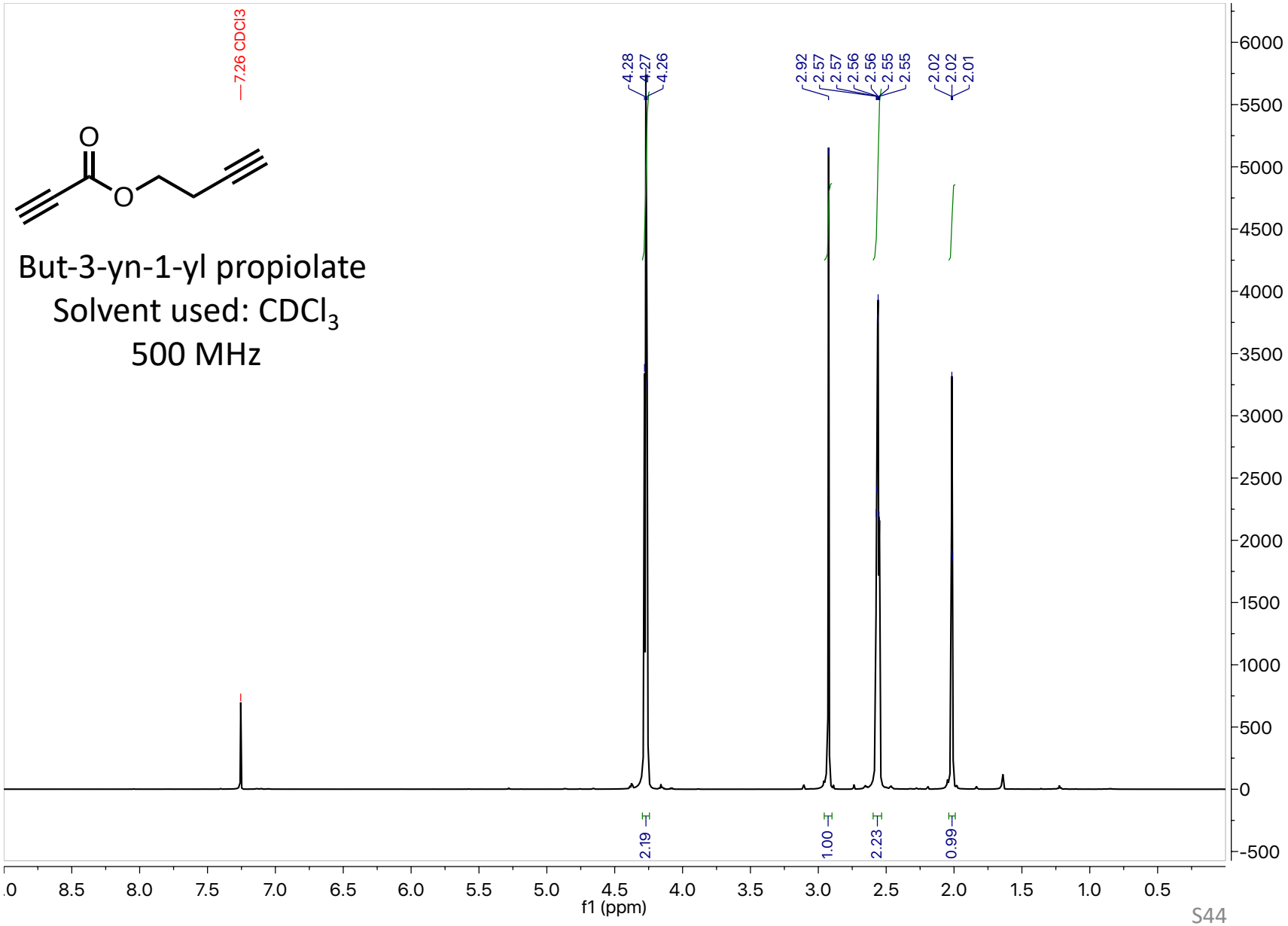
Solvent used: $CDCl_3$

700 MHz


170.73
152.23
149.39
108.63
106.53
83.15
77.44 CDCl3
77.08 CDCl3
69.57
36.97
35.53
15.04
13.79
O
N
H
O
Me
N-((5-methylfuran-2-yl)methyl)pent-4-ynamide
Solvent used: CDCl3
500 MHz
f1 (ppm)


7.40
7.40
7.39
7.39
7.39
7.38
7.38
7.37
7.37
7.37
7.36
7.36
7.26 CDCl3
5.23
2.90
O
O
Benzyl propiolate
Solvent used: CDCl3
500 MHz
5.42
2.16
1.00
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

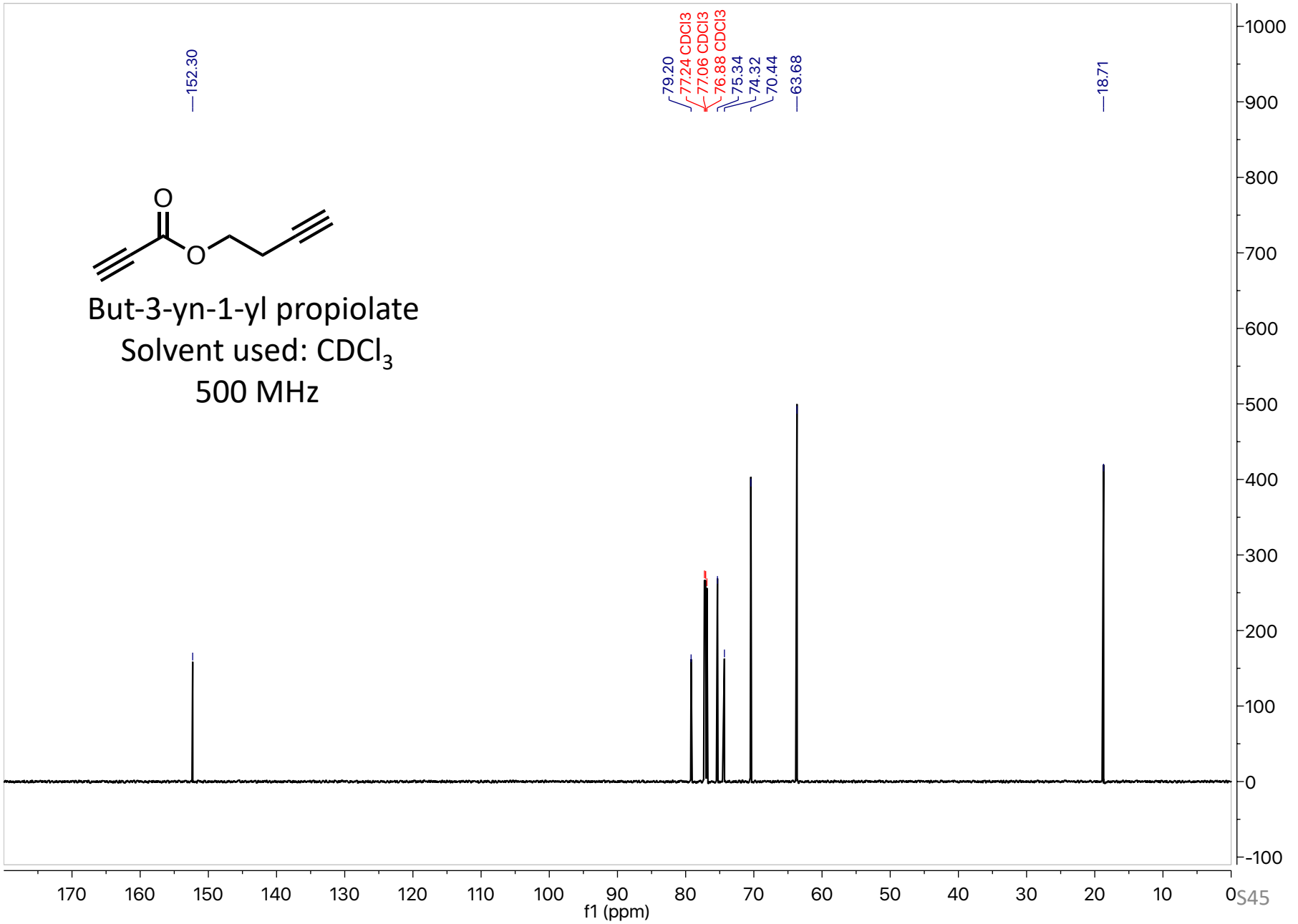

152.64
134.63
128.84
129.80
128.69
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
75.20
74.65
68.03
O
O
Benzyl propiolate
Solvent used: CDCl3
500 MHz
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

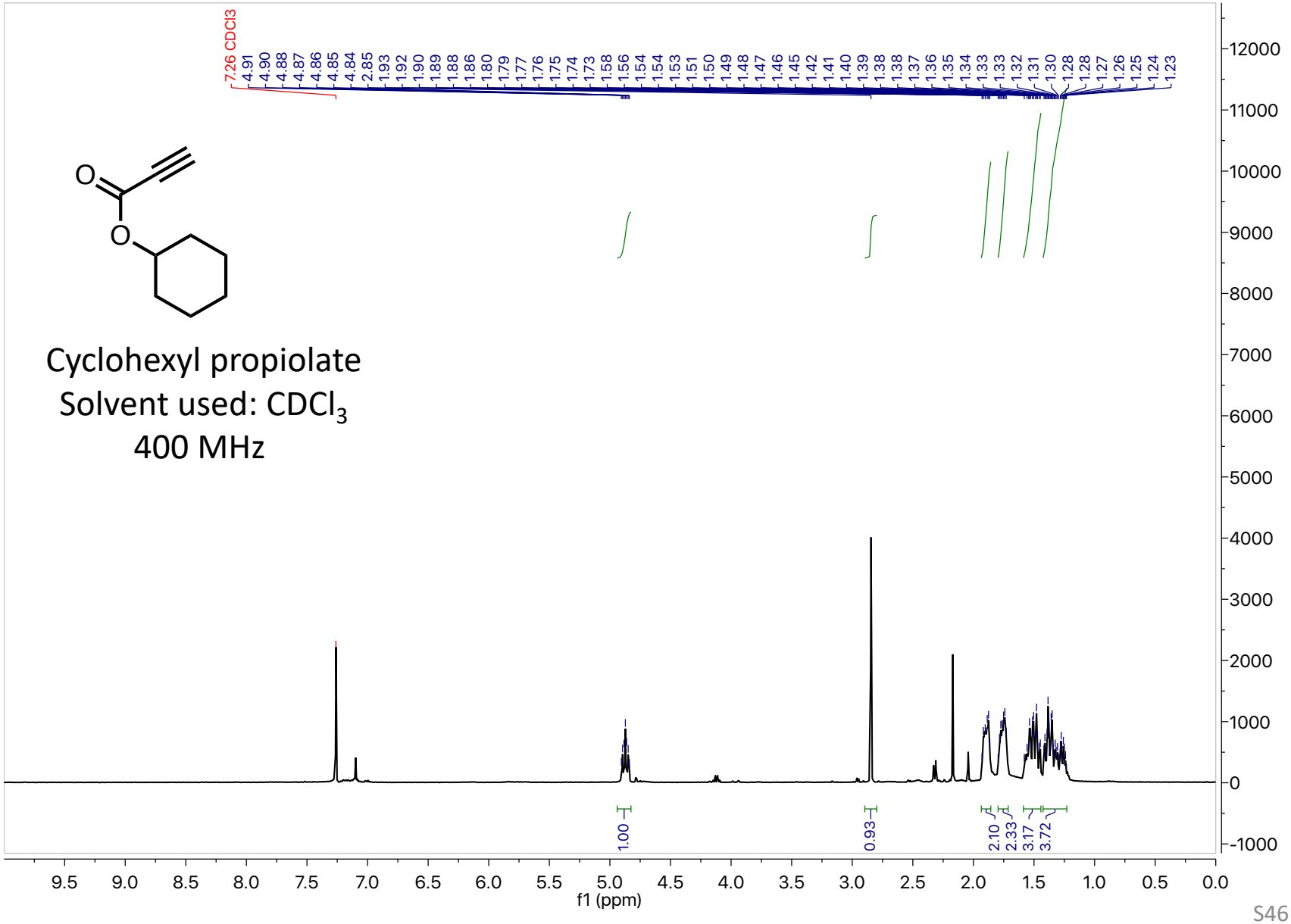


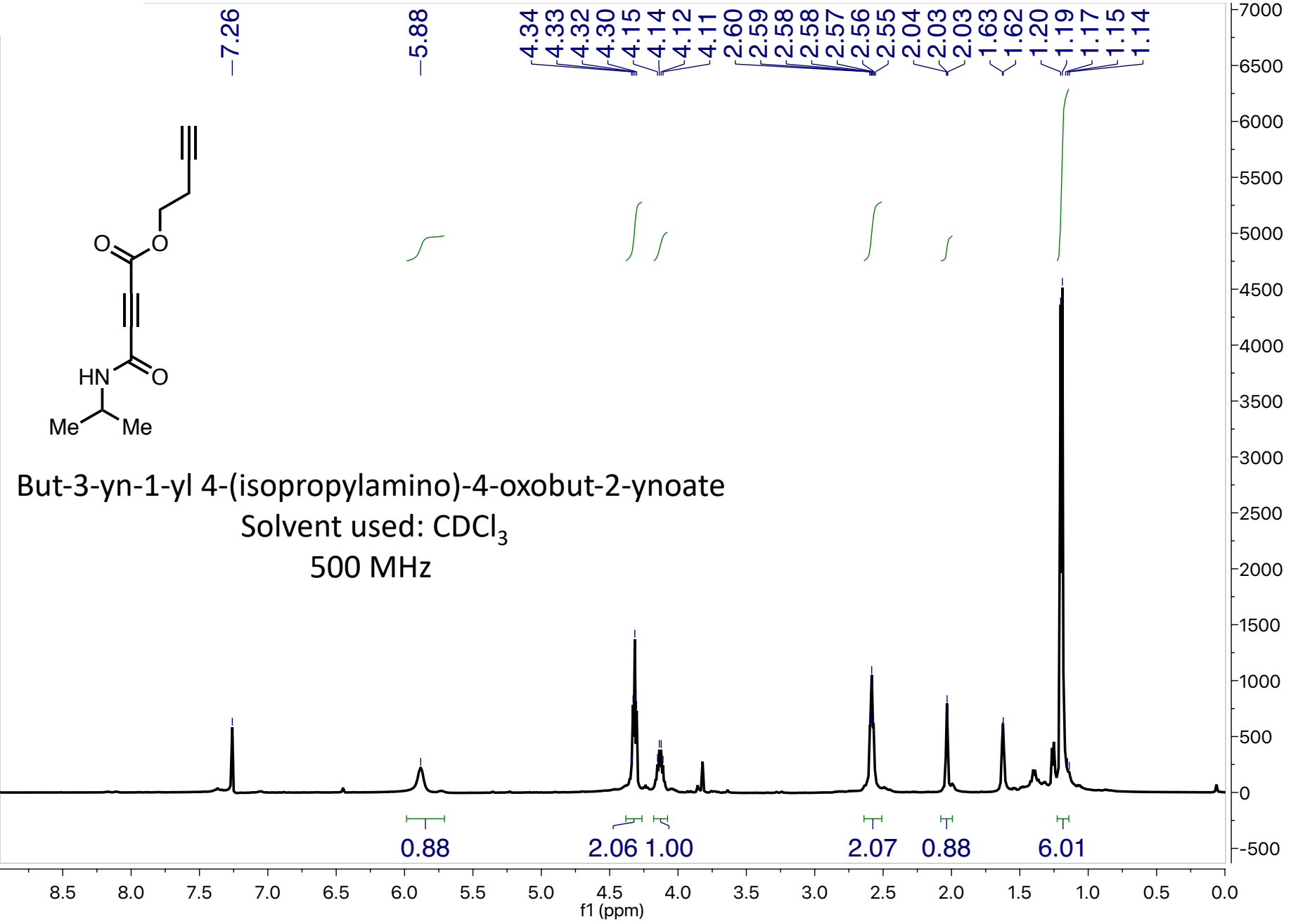
But-3-yn-1-yl propiolate

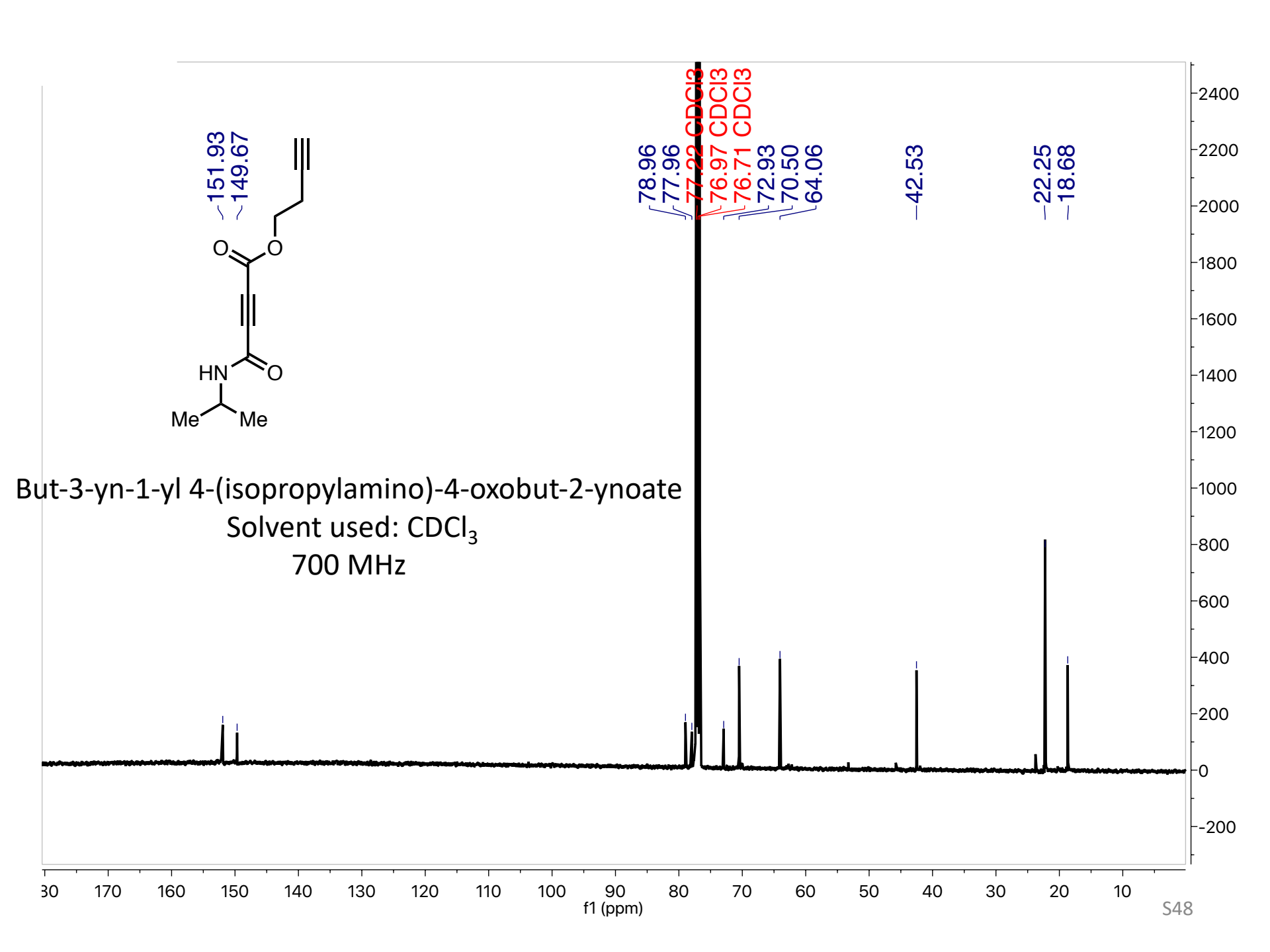
Solvent used: $CDCl_3$

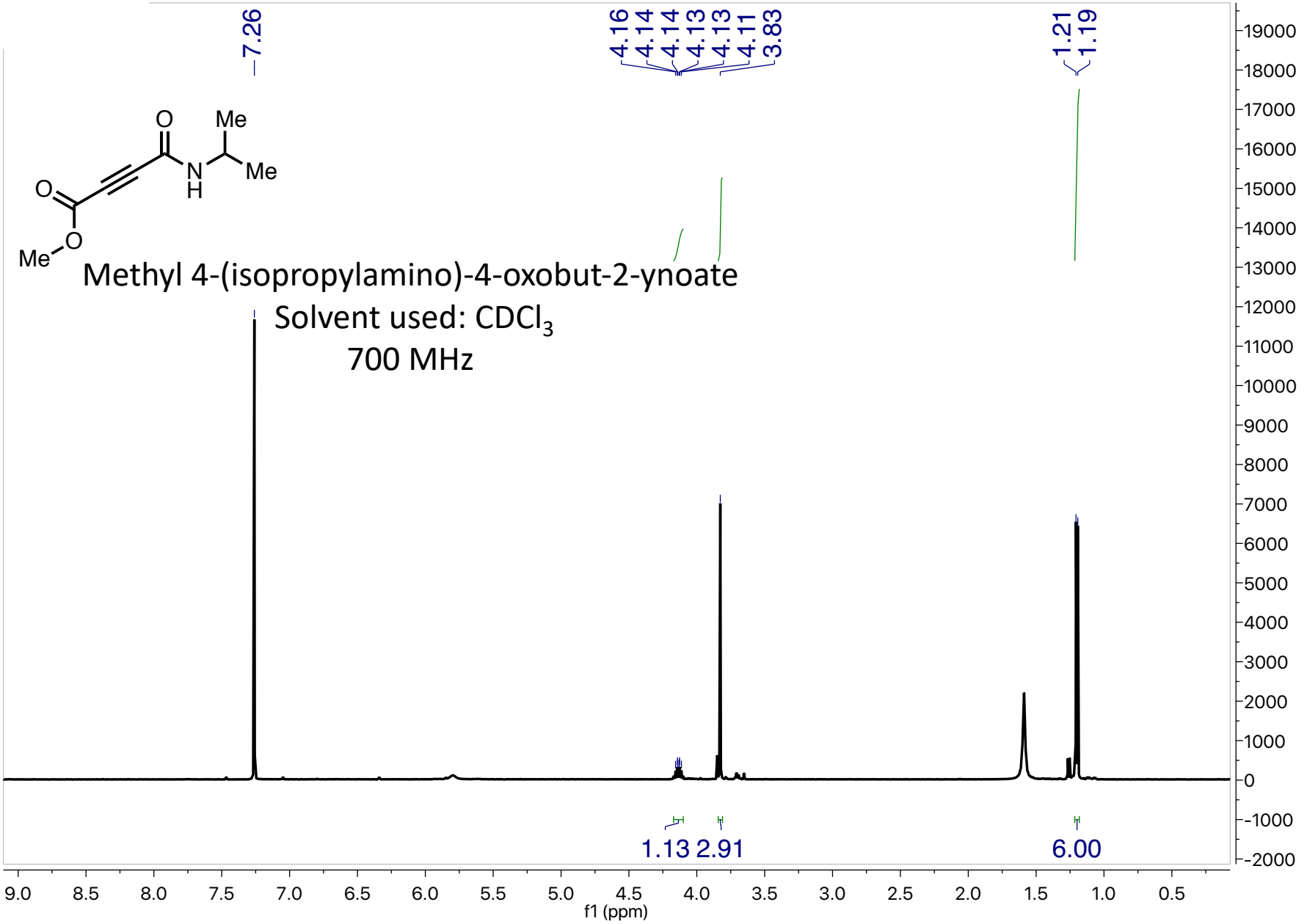
500 MHz

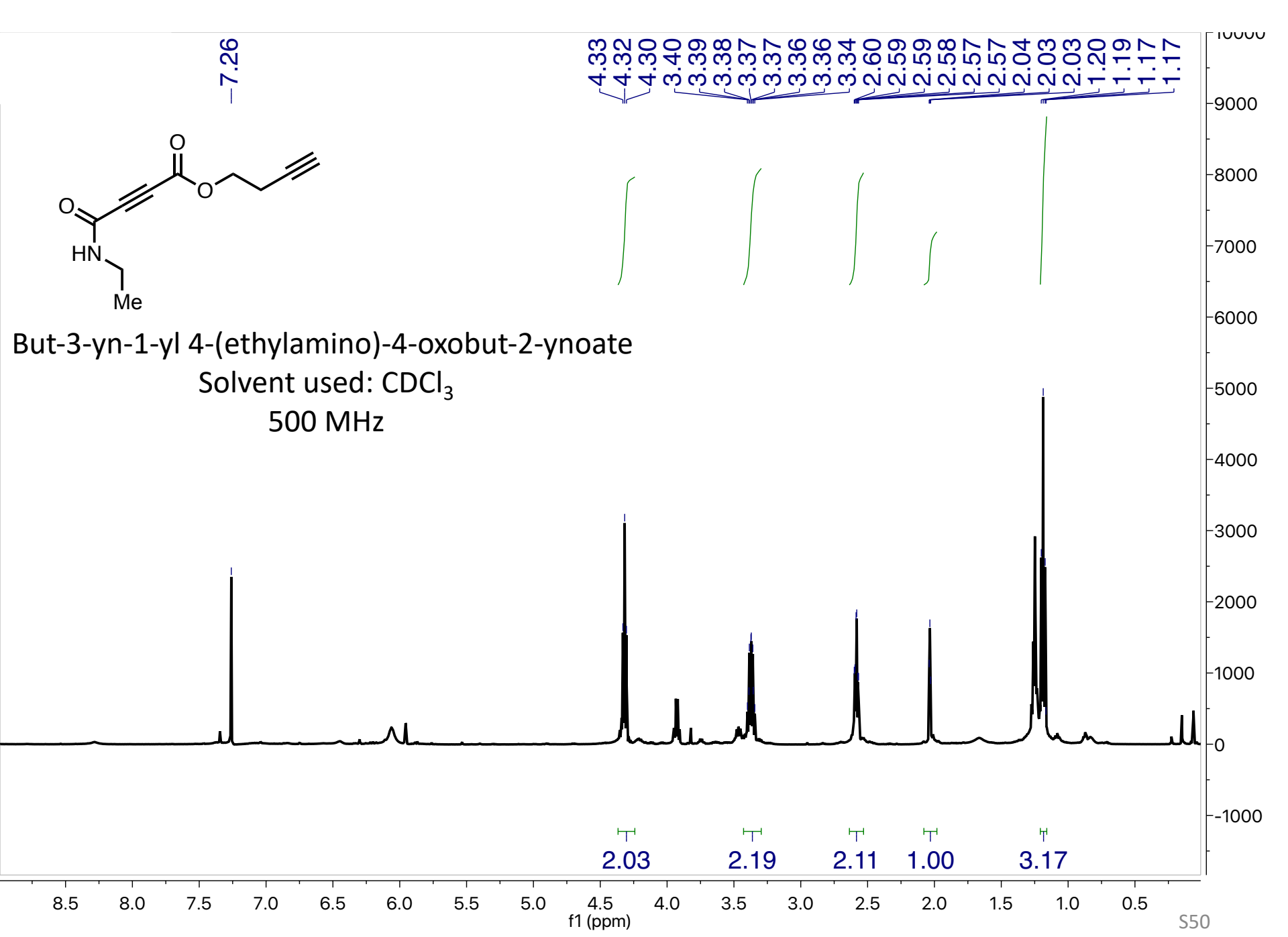

152.30
79.20
77.24 CDCl3
77.06 CDCl3
76.88 CDCl3
75.34
74.32
70.44
63.68
18.71
O
O
But-3-yn-1-yl propiolate
Solvent used: CDCl3
500 MHz
1000
900
800
700
600
500
400
300
200
100
0
-100
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

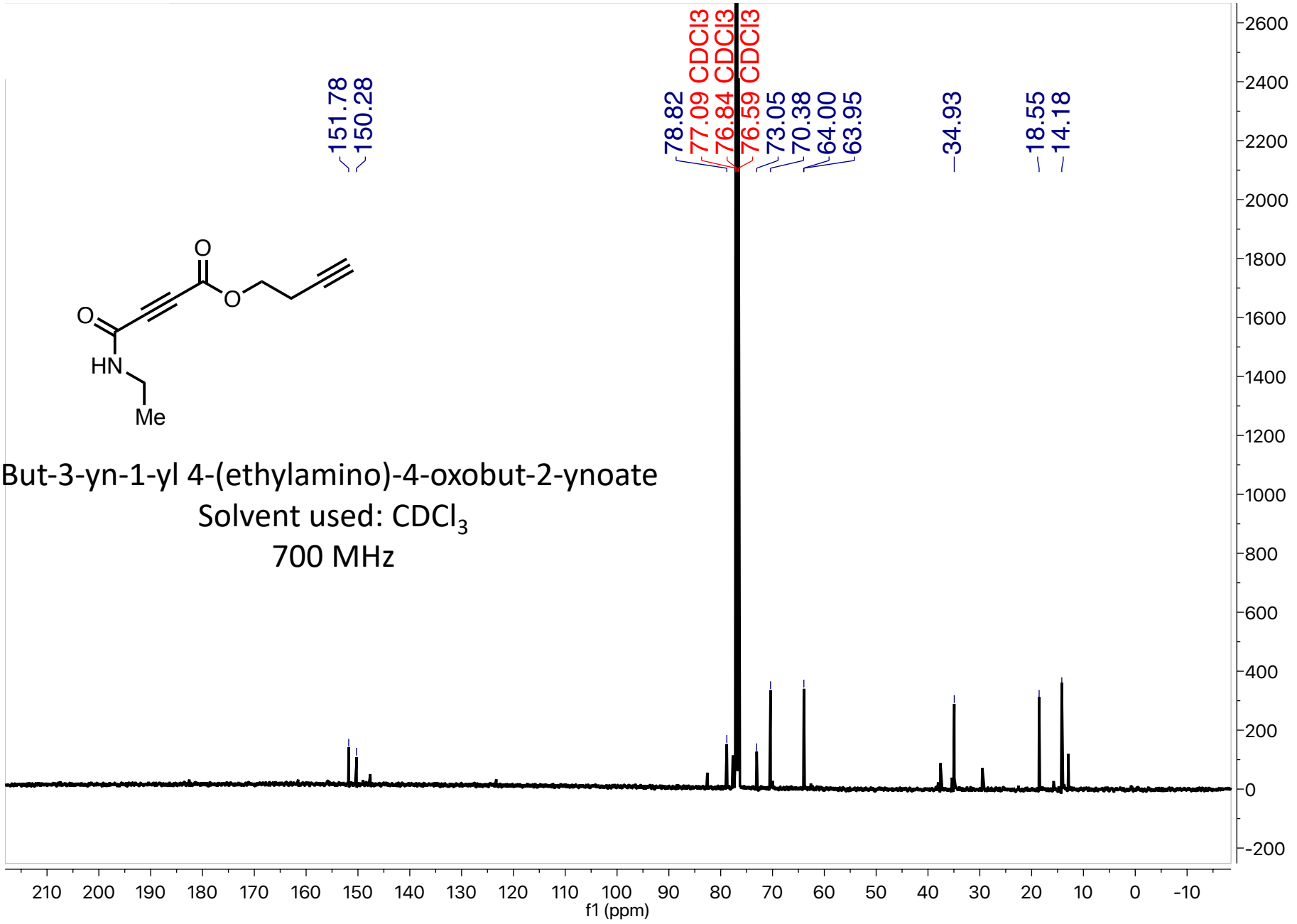

7.26 CDCl3
4.91 4.90 4.88 4.87 4.86 4.85 4.84 2.85 1.93 1.92 1.90 1.89 1.88 1.86 1.80 1.79 1.77 1.76 1.75 1.74 1.73 1.58 1.56 1.54 1.54 1.53 1.51 1.50 1.49 1.48 1.47 1.46 1.45 1.42 1.41 1.40 1.39 1.38 1.38 1.37 1.36 1.35 1.34 1.33 1.33 1.32 1.31 1.30 1.28 1.28 1.27 1.26 1.25 1.24 1.23
O
O
Cyclohexyl propiolate
Solvent used: CDCl3
400 MHz
1.00
0.93
2.10
2.33
3.17
3.72
f1 (ppm)


7.26
5.88
4.34
4.33
4.32
4.30
4.15
4.14
4.12
4.11
2.60
2.59
2.58
2.58
2.57
2.56
2.55
2.04
2.03
2.03
1.63
1.62
1.20
1.19
1.17
1.15
1.14
O
O
HN
O
Me
Me
But-3-yn-1-yl 4-(isopropylamino)-4-oxobut-2-ynoate
Solvent used: CDCl3
500 MHz
0.88
2.06
1.00
2.07
0.88
6.01
f1 (ppm)


151.93
149.67
78.96
77.96
77.22 CDCl3
76.97 CDCl3
76.71 CDCl3
72.93
70.50
64.06
42.53
22.25
18.68
O
O
HN
O
Me
Me
But-3-yn-1-yl 4-(isopropylamino)-4-oxobut-2-ynoate
Solvent used: CDCl3
700 MHz
f1 (ppm)


7.26
4.16
4.14
4.14
4.13
4.13
4.11
3.83
1.21
1.19
O
Me
N
H
Me
O
O
Me
Methyl 4-(isopropylamino)-4-oxobut-2-ynoate
Solvent used: CDCl3
700 MHz
1.13
2.91
6.00
f1 (ppm)

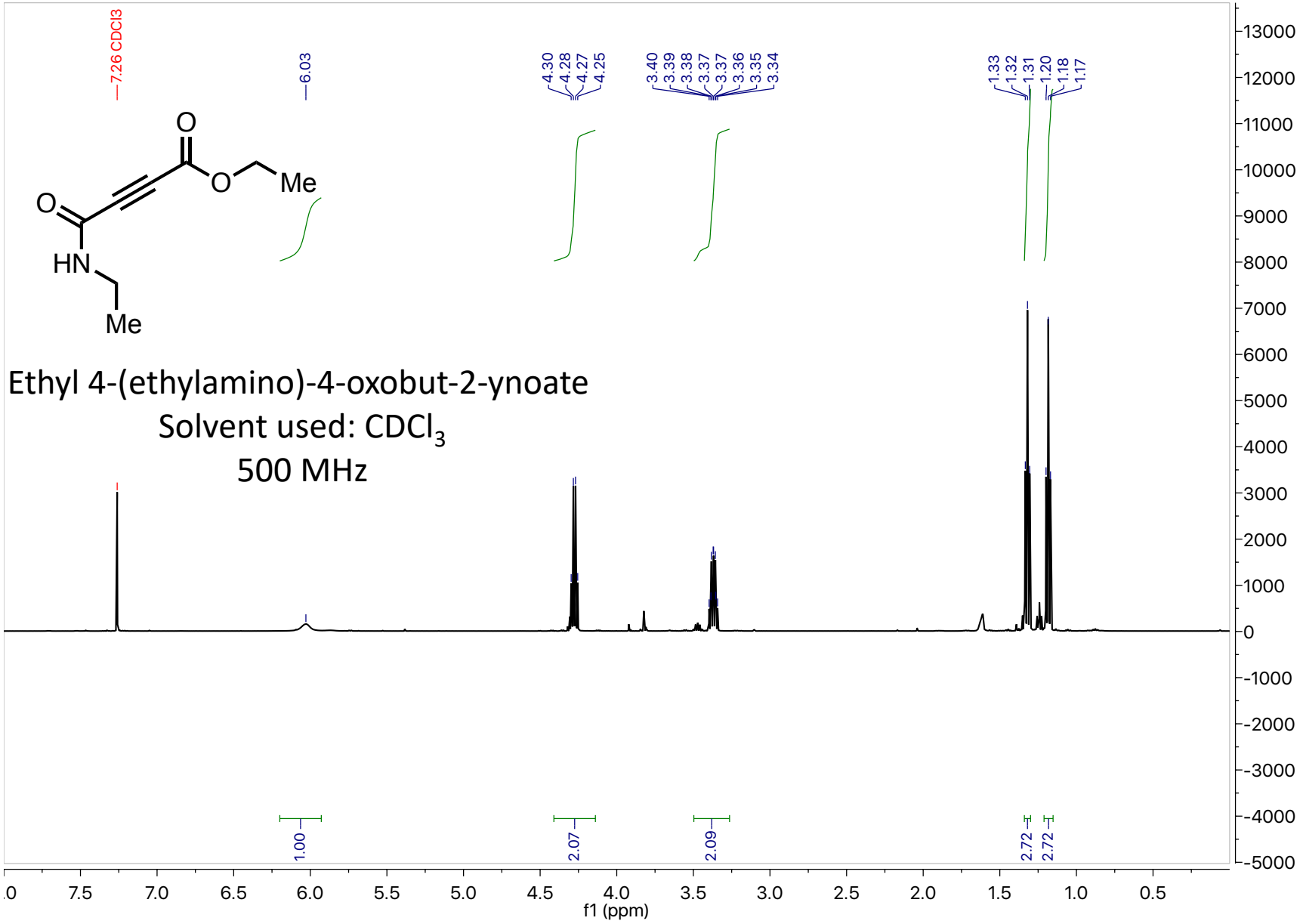

7.26
4.33
4.32
4.30
3.40
3.39
3.38
3.37
3.37
3.36
3.36
3.34
2.60
2.59
2.59
2.58
2.57
2.57
2.04
2.03
2.03
1.20
1.19
1.17
1.17
O
O
O
HN
Me
But-3-yn-1-yl 4-(ethylamino)-4-oxobut-2-ynoate
Solvent used: CDCl3
500 MHz
2.03
2.19
2.11
1.00
3.17
f1 (ppm)

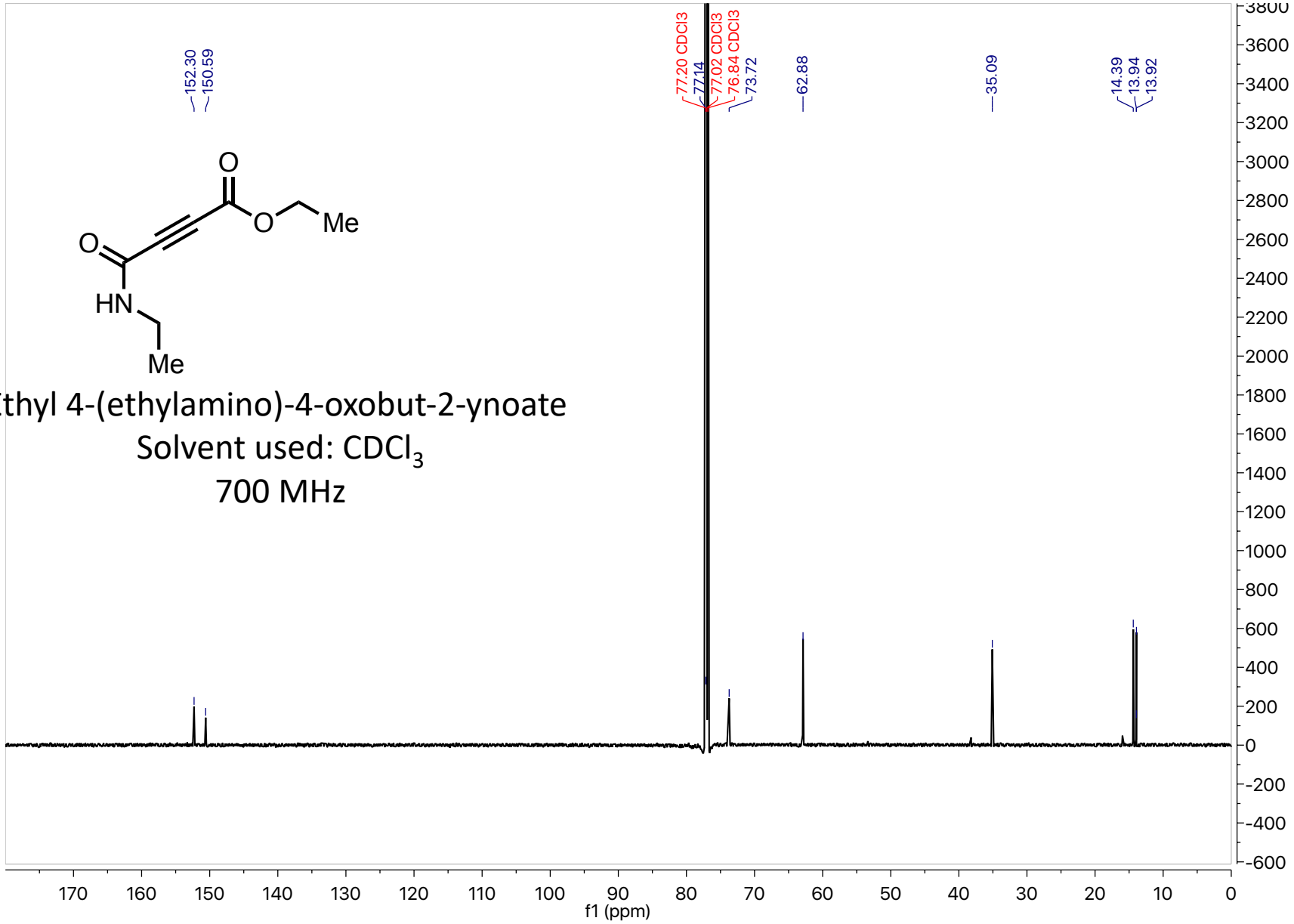


But-3-yn-1-yl 4-(ethylamino)-4-oxobut-2-ynoate

Solvent used: $CDCl_3$

700 MHz

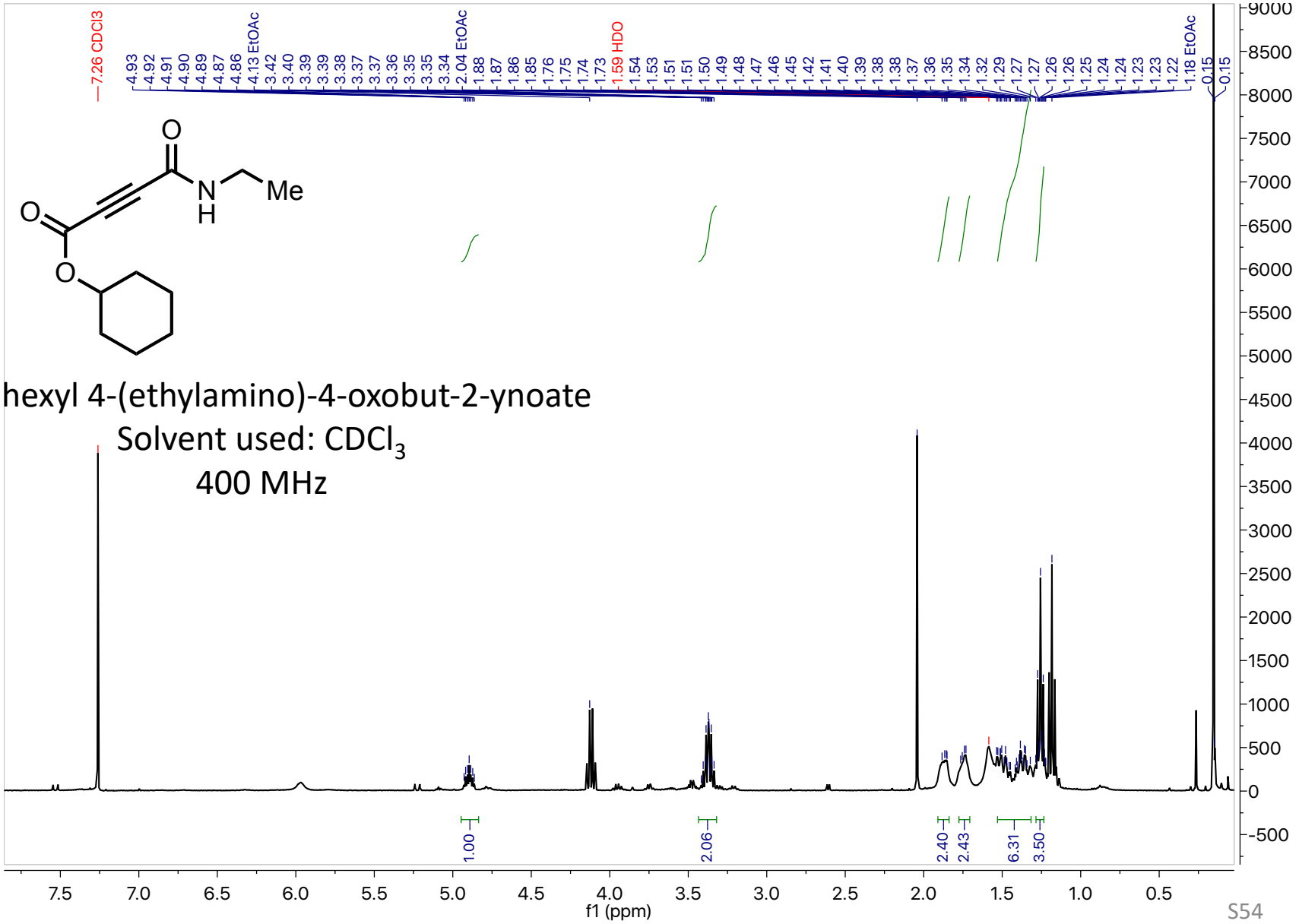

7.26 CDCl3
6.03
4.30
4.28
4.27
4.25
3.40
3.39
3.38
3.37
3.37
3.36
3.35
3.34
1.33
1.32
1.31
1.20
1.18
1.17
O
O
Me
O
HN
Me
Ethyl 4-(ethylamino)-4-oxobut-2-ynoate
Solvent used: CDCl3
500 MHz
1.00
2.07
2.09
2.72
2.72
f1 (ppm)



Ethyl 4-(ethylamino)-4-oxobut-2-ynoate

Solvent used: $CDCl_3$

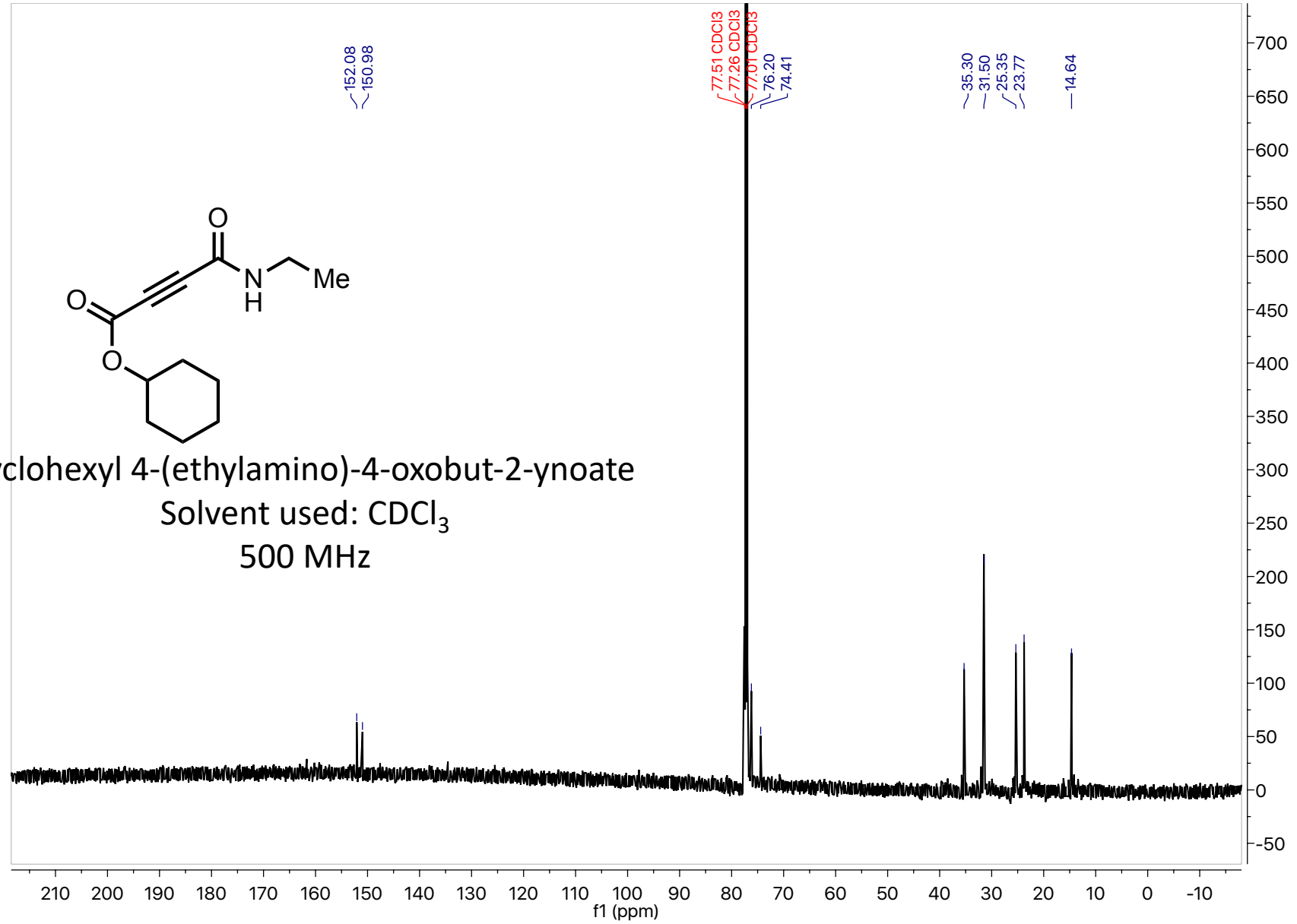
700 MHz



Cyclohexyl 4-(ethylamino)-4-oxobut-2-ynoate

Solvent used: $CDCl_3$

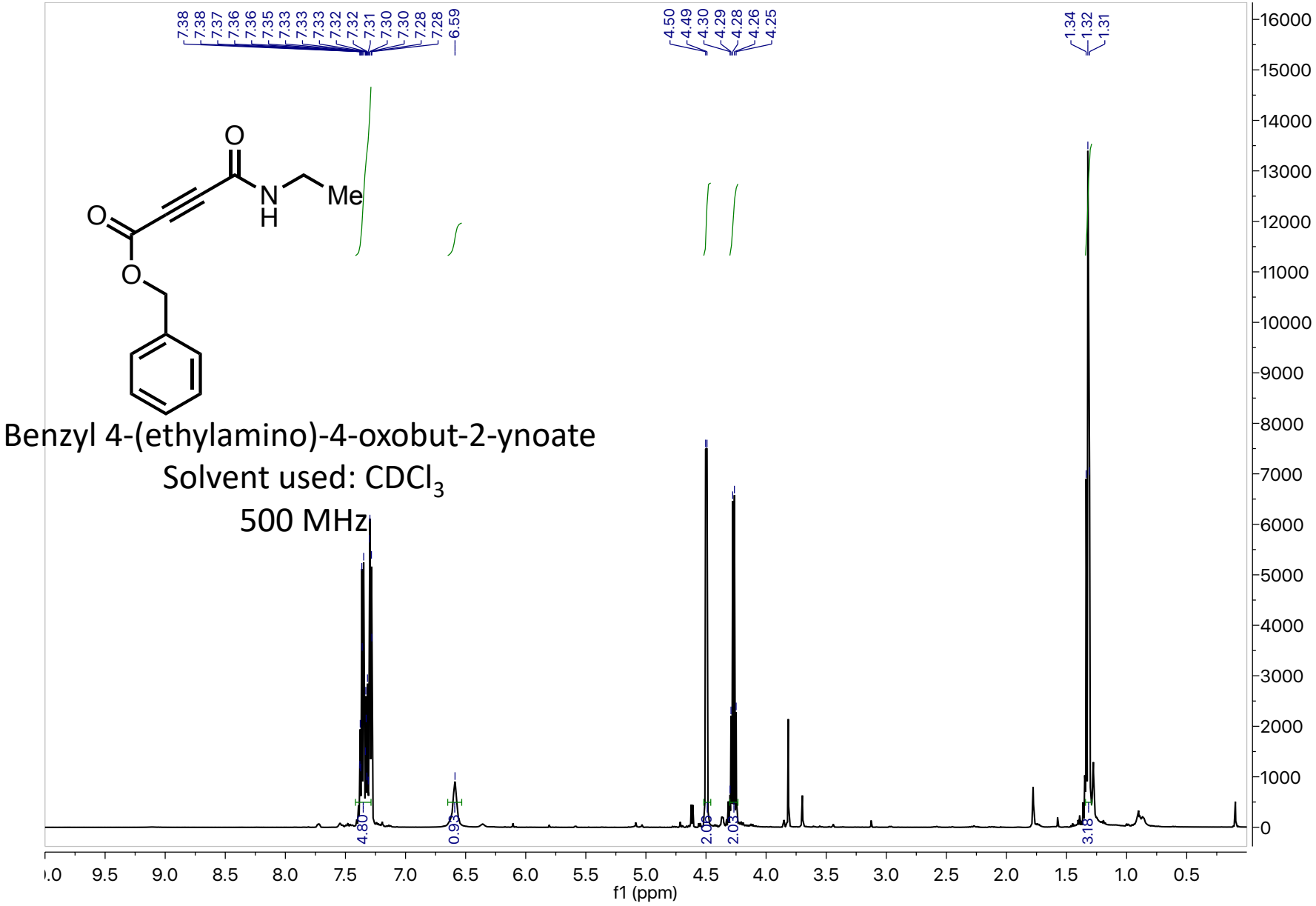
400 MHz

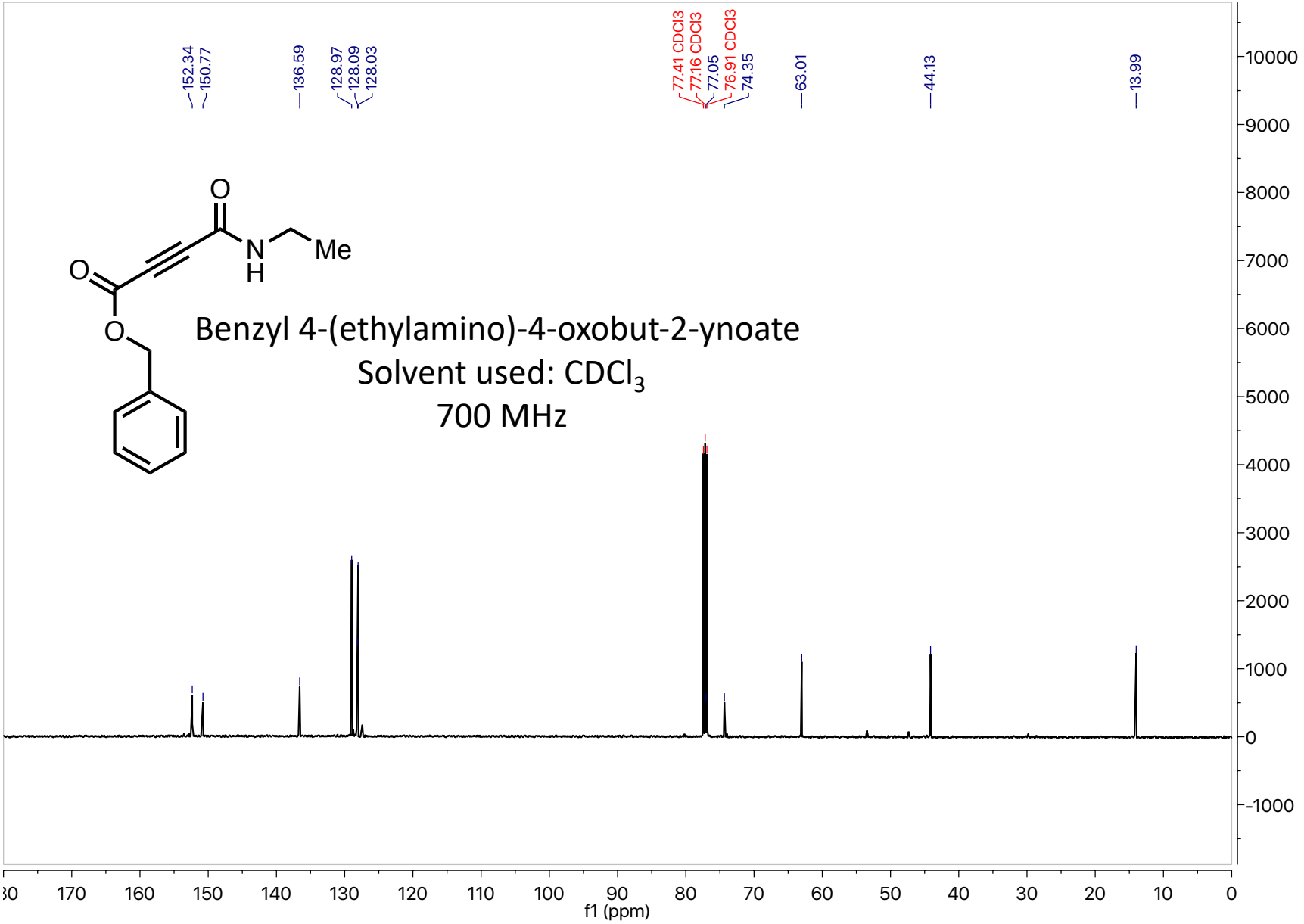


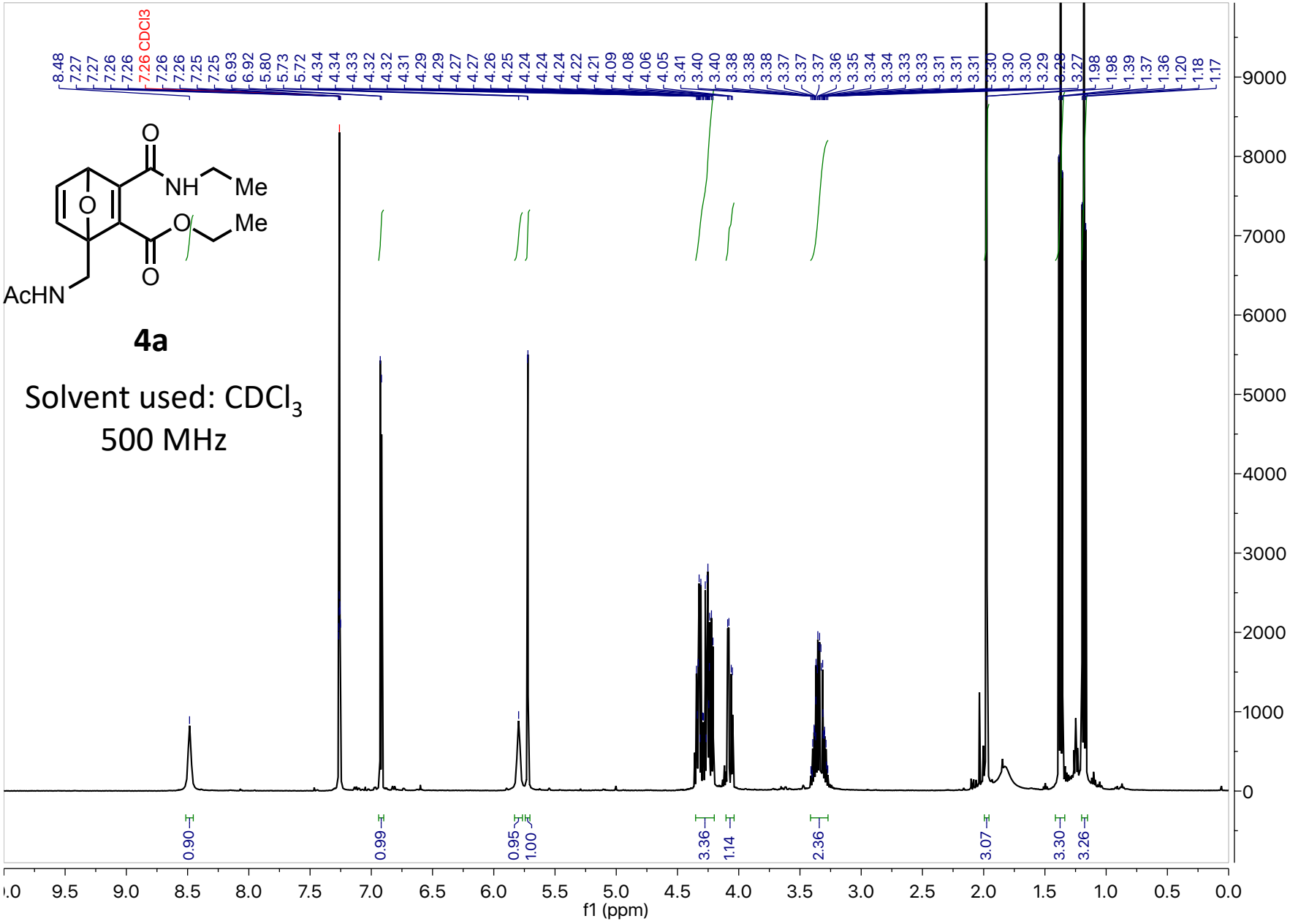
Cyclohexyl 4-(ethylamino)-4-oxobut-2-ynoate

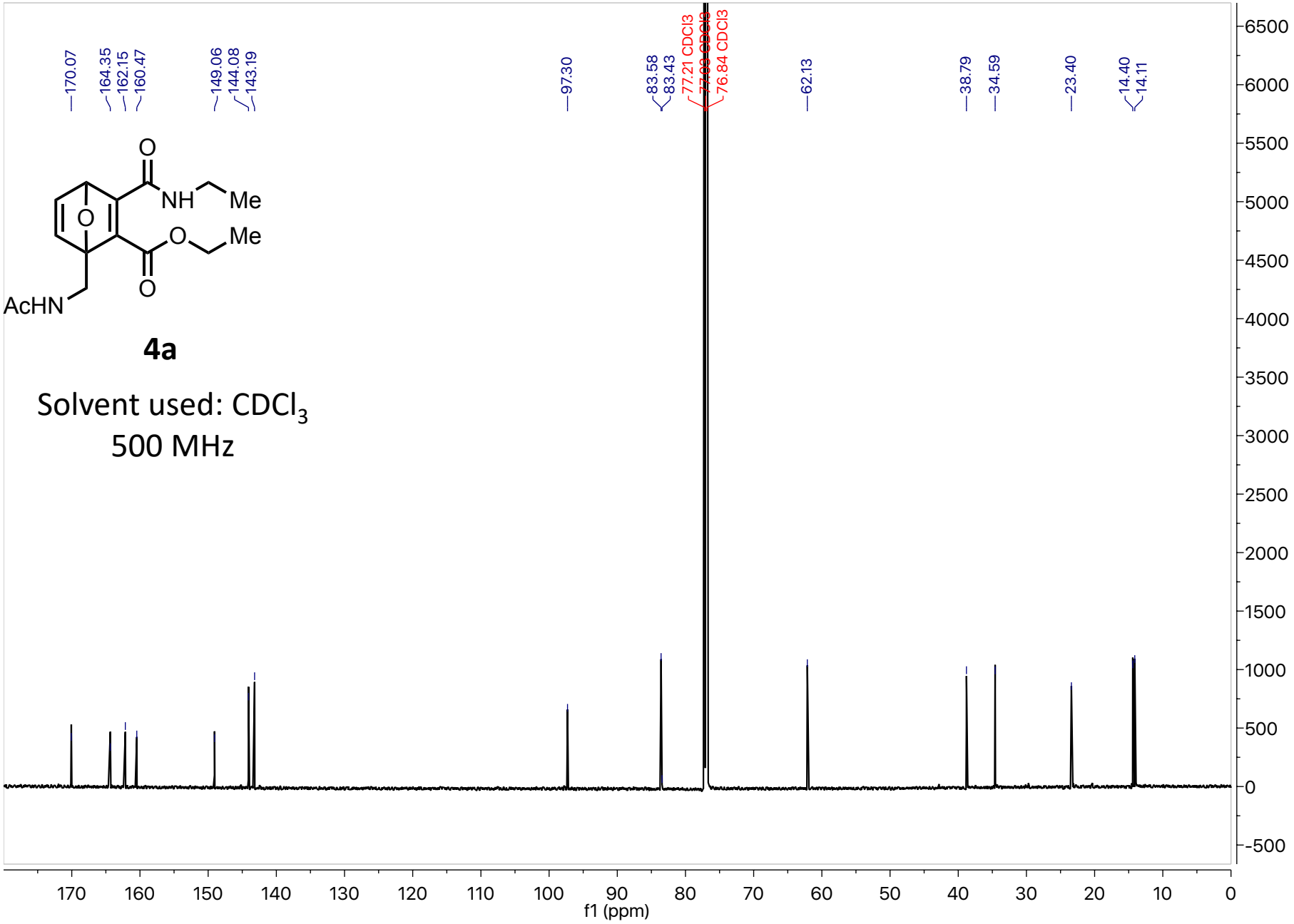
Solvent used: $CDCl_3$

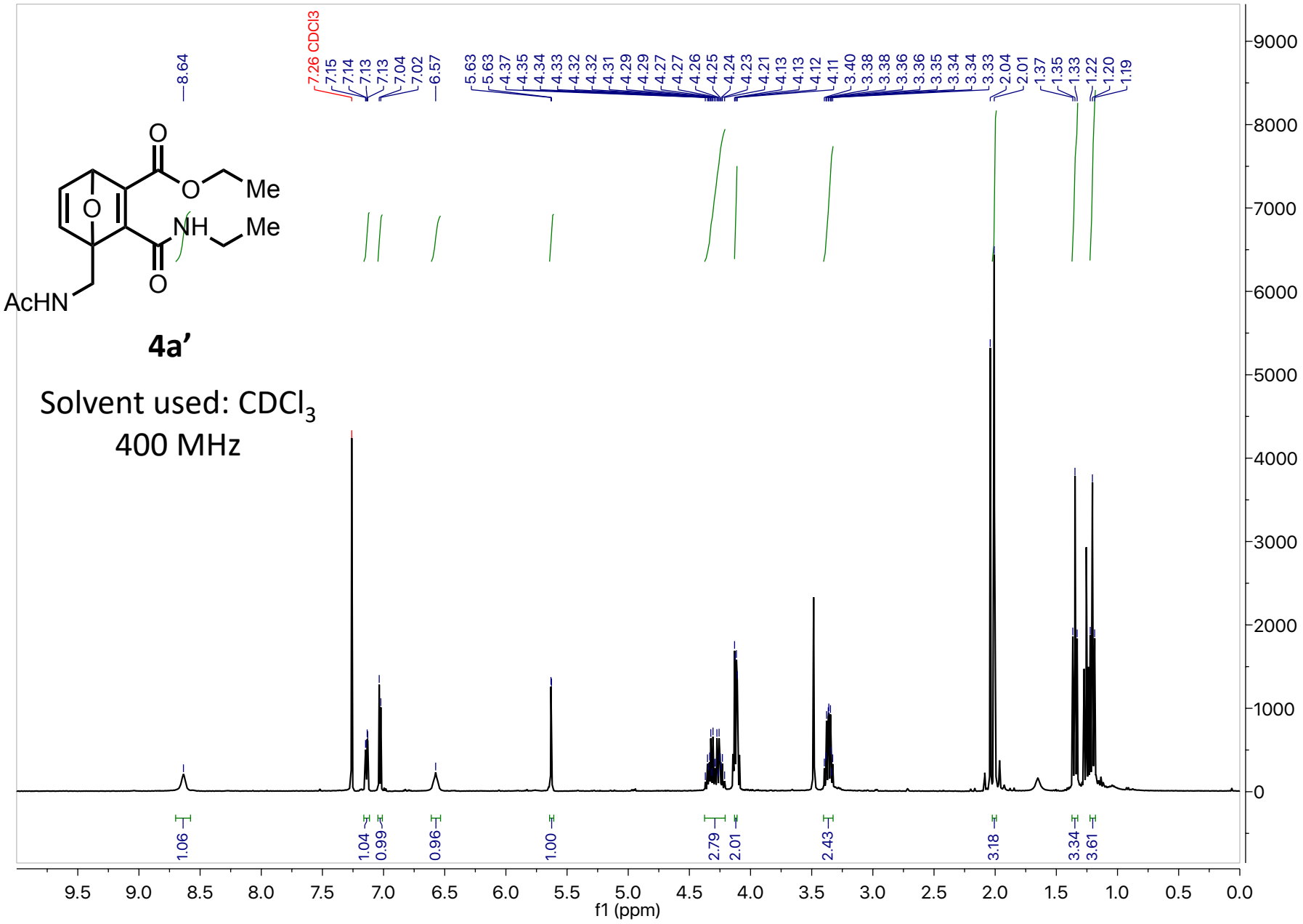
500 MHz

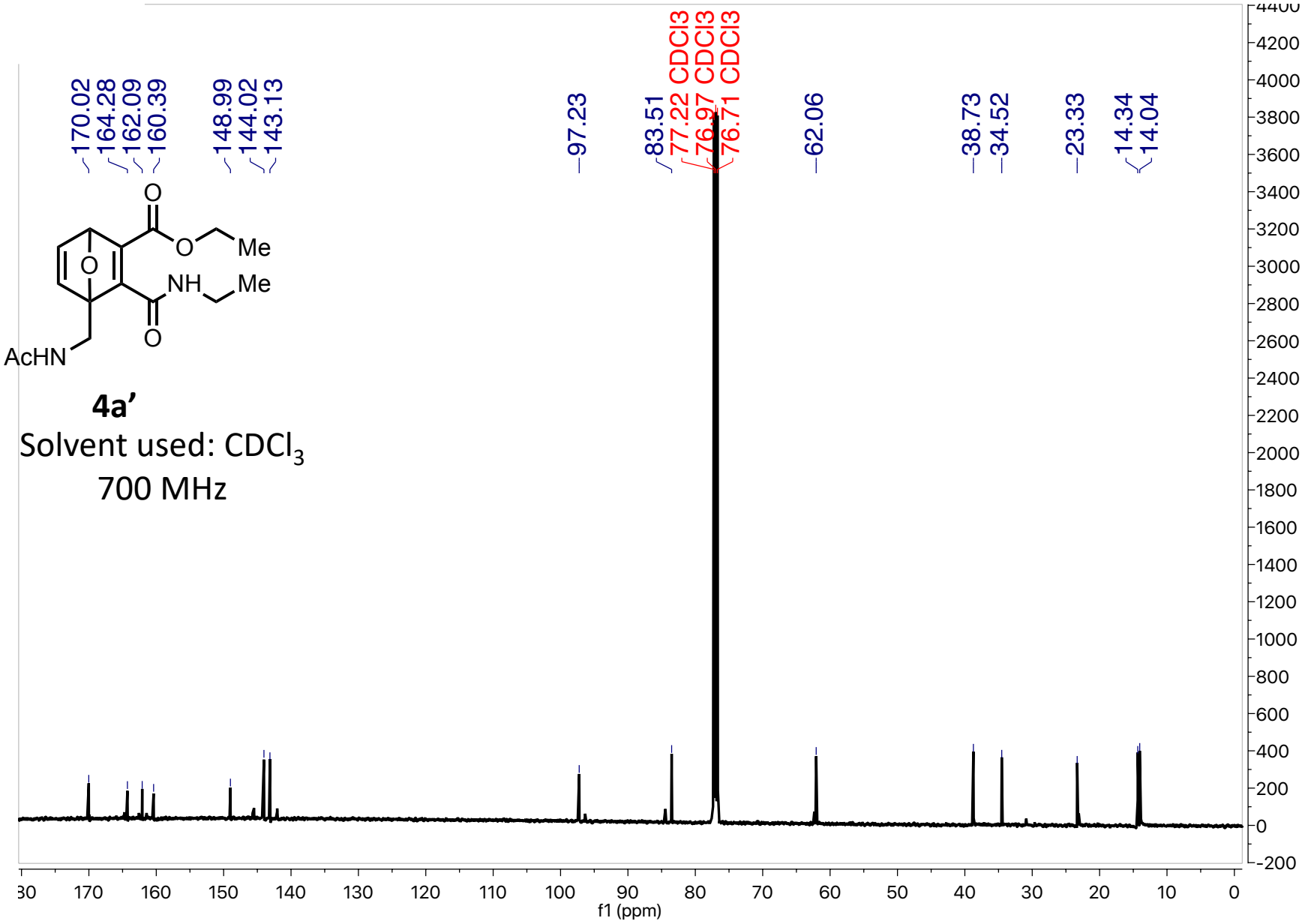

7.38
7.38
7.37
7.36
7.36
7.35
7.33
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.28
7.28
6.59
4.50
4.49
4.30
4.29
4.28
4.26
4.25
1.34
1.32
1.31
O
O
N
H
Me
O
Benzyl 4-(ethylamino)-4-oxobut-2-ynoate
Solvent used: CDCl3
500 MHz
4.80
0.93
2.08
2.03
3.18
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
f1 (ppm)


152.34
150.77
136.59
128.97
128.09
128.03
77.41 CDCl3
77.16 CDCl3
77.05
76.91 CDCl3
74.35
63.01
44.13
13.99
O
N
H
Me
O
O
Benzyl 4-(ethylamino)-4-oxobut-2-ynoate
Solvent used: CDCl3
700 MHz
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.48
7.27
7.27
7.26
7.26
7.26 CDCl3
7.26
7.26
7.25
7.25
6.93
6.92
5.80
5.73
5.72
4.34
4.34
4.33
4.32
4.32
4.31
4.29
4.29
4.27
4.27
4.26
4.25
4.24
4.24
4.24
4.22
4.21
4.09
4.08
4.06
4.05
3.41
3.40
3.40
3.38
3.38
3.38
3.37
3.37
3.37
3.36
3.35
3.34
3.34
3.33
3.33
3.31
3.31
3.31
3.30
3.30
3.30
3.29
3.28
3.27
1.98
1.98
1.39
1.37
1.36
1.20
1.18
1.17
O
NH
Me
O
O
Me
O
O
AcHN
4a
Solvent used: CDCl3
500 MHz
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0.90
0.99
0.95
1.00
3.36
1.14
2.36
3.07
3.30
3.26
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


170.07
164.35
162.15
160.47
149.06
144.08
143.19
97.30
83.58
83.43
77.21 CDCl3
76.84 CDCl3
62.13
38.79
34.59
23.40
14.40
14.11
O
NH
Me
O
O
Me
O
AcHN
4a
Solvent used: CDCl3
500 MHz
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

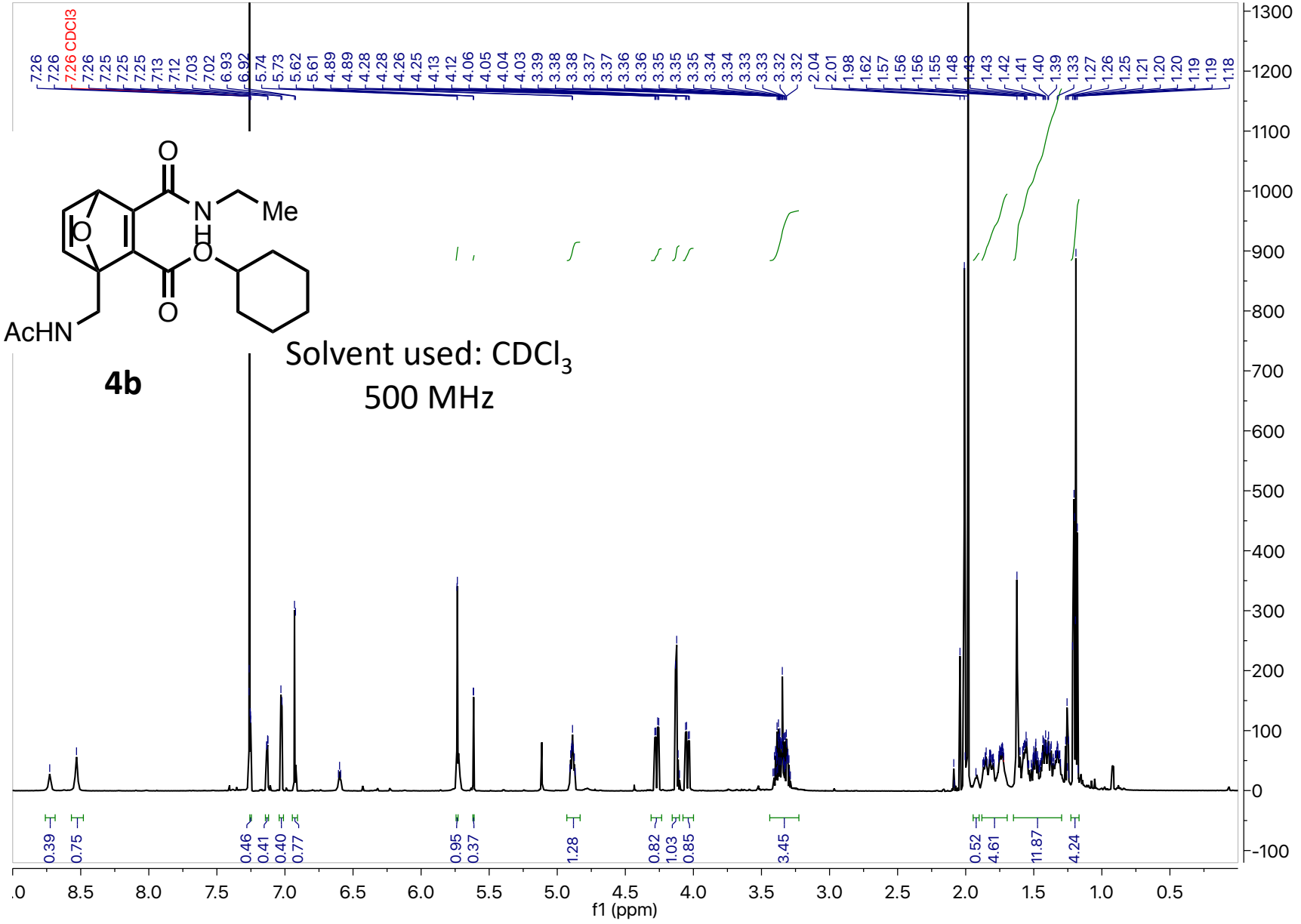

8.64
7.26 CDCl3
7.15
7.14
7.13
7.13
7.04
7.02
6.57
5.63
5.63
4.37
4.35
4.34
4.33
4.32
4.32
4.31
4.29
4.29
4.27
4.27
4.26
4.25
4.24
4.23
4.21
4.13
4.13
4.12
4.11
3.40
3.38
3.38
3.36
3.36
3.35
3.34
3.34
3.33
2.04
2.01
1.37
1.35
1.33
1.22
1.20
1.19
O
O
Me
O
NH
Me
O
AcHN
4a’
Solvent used: CDCl3
400 MHz
1.06
1.04
0.99
0.96
1.00
2.79
2.01
2.43
3.18
3.34
3.61
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

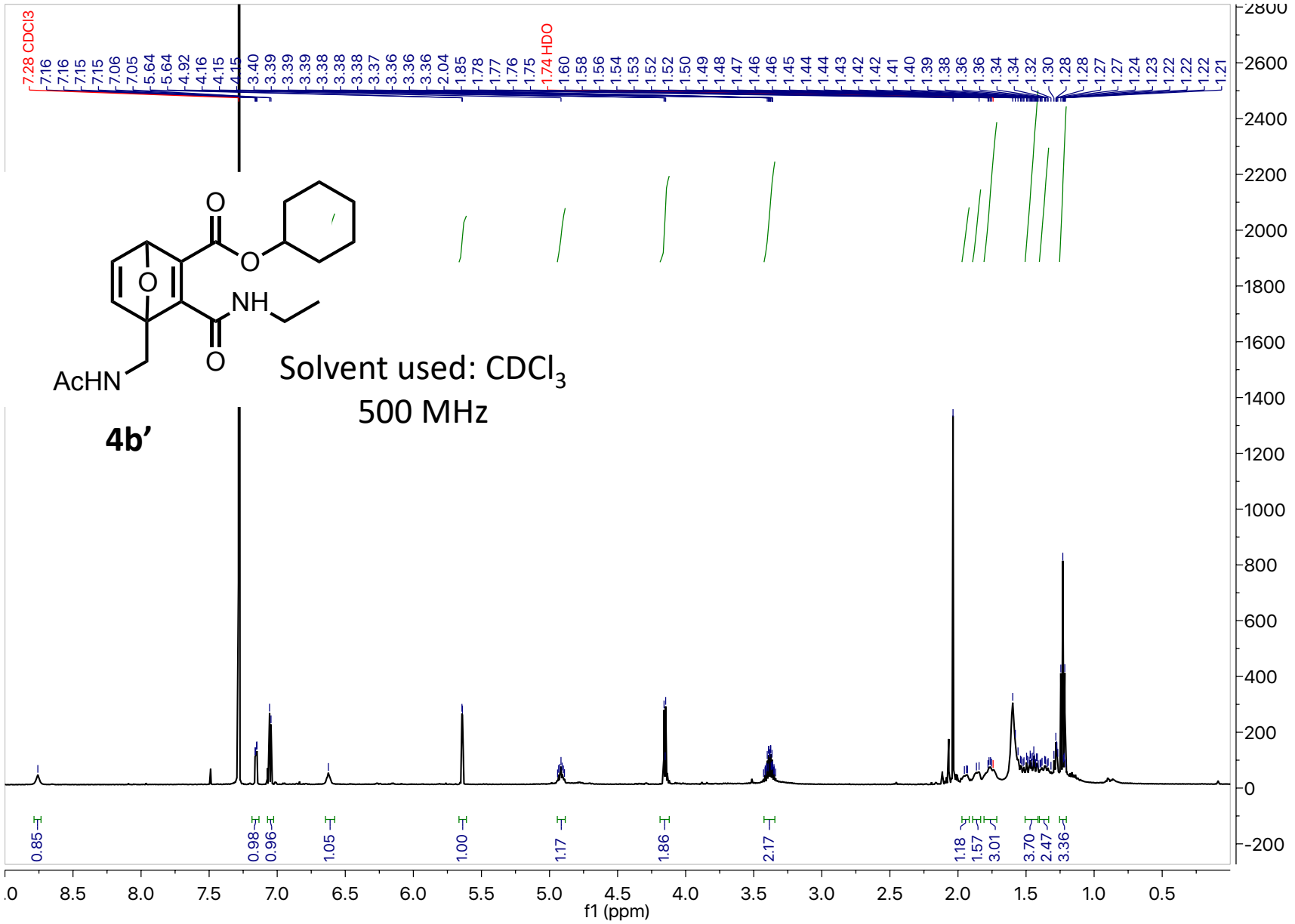


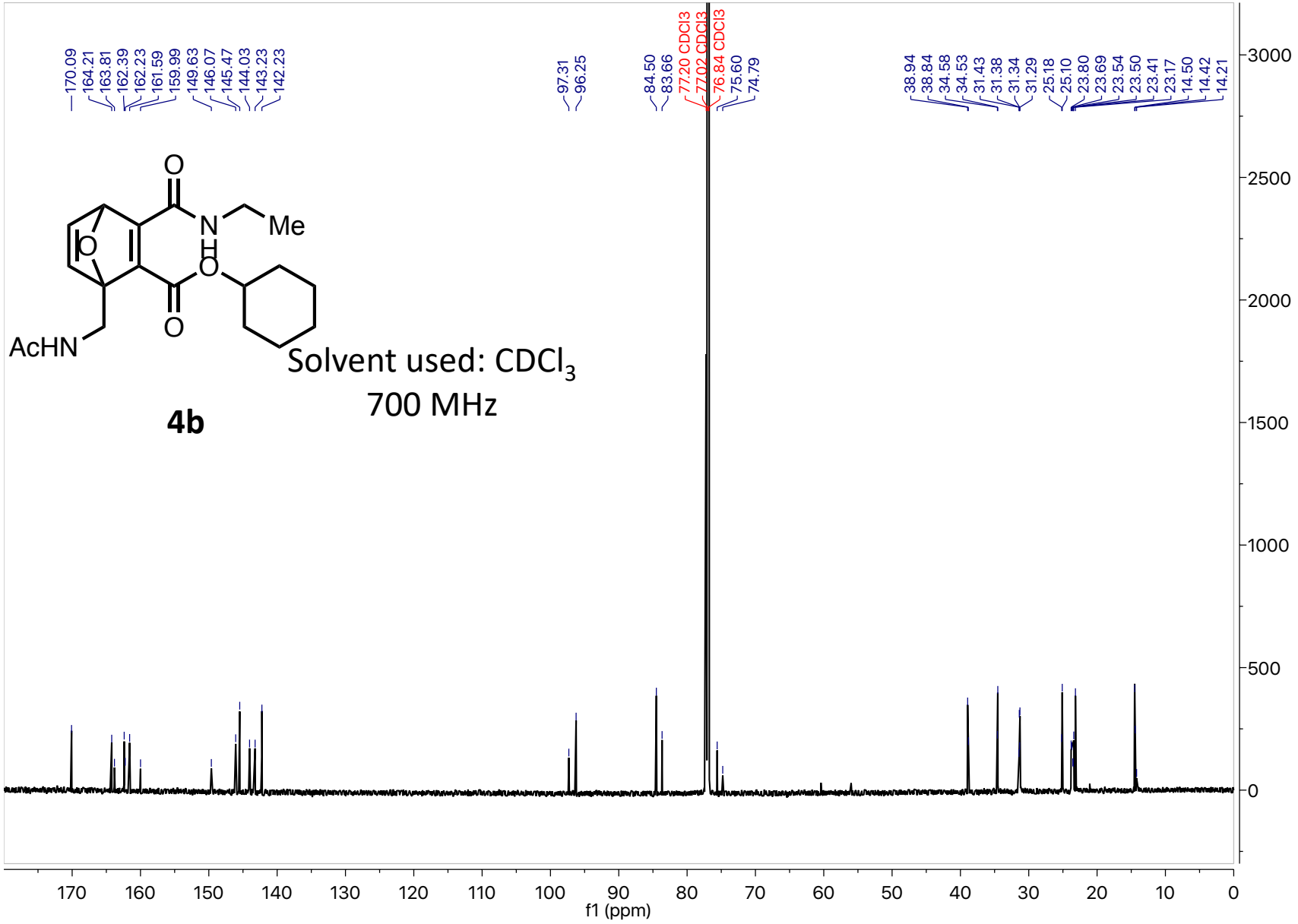
4a'

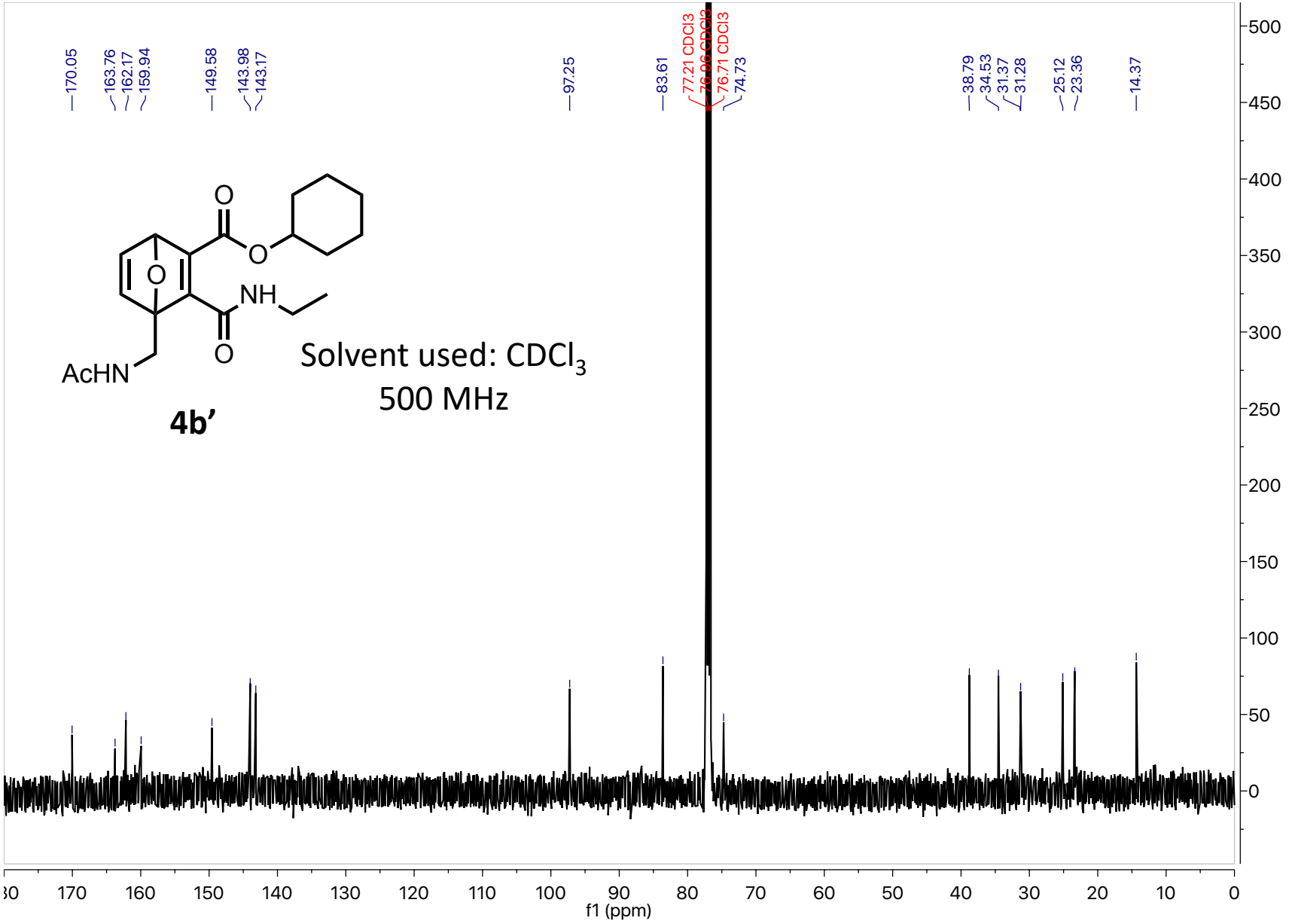
Solvent used: $CDCl_3$

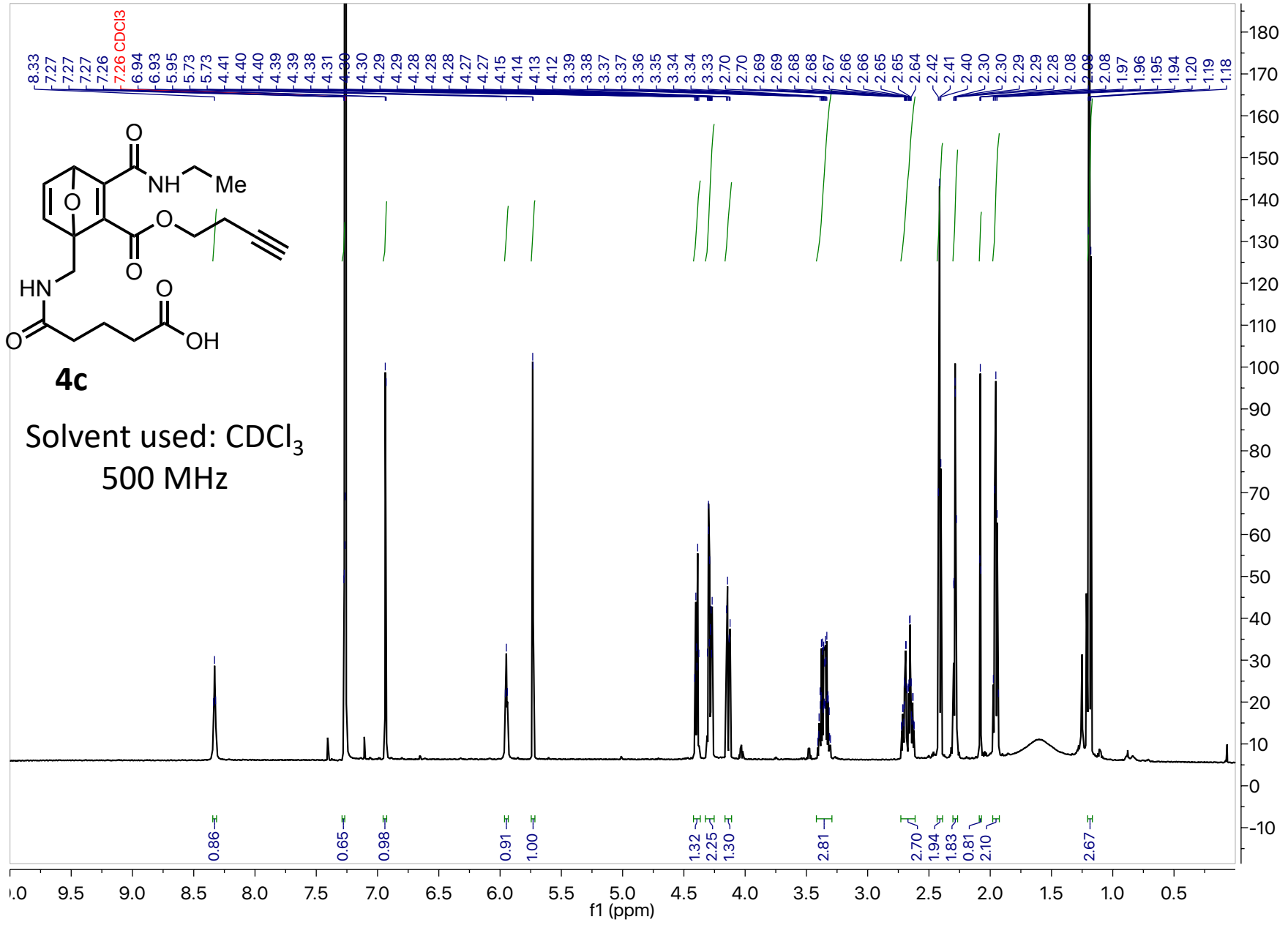
700 MHz

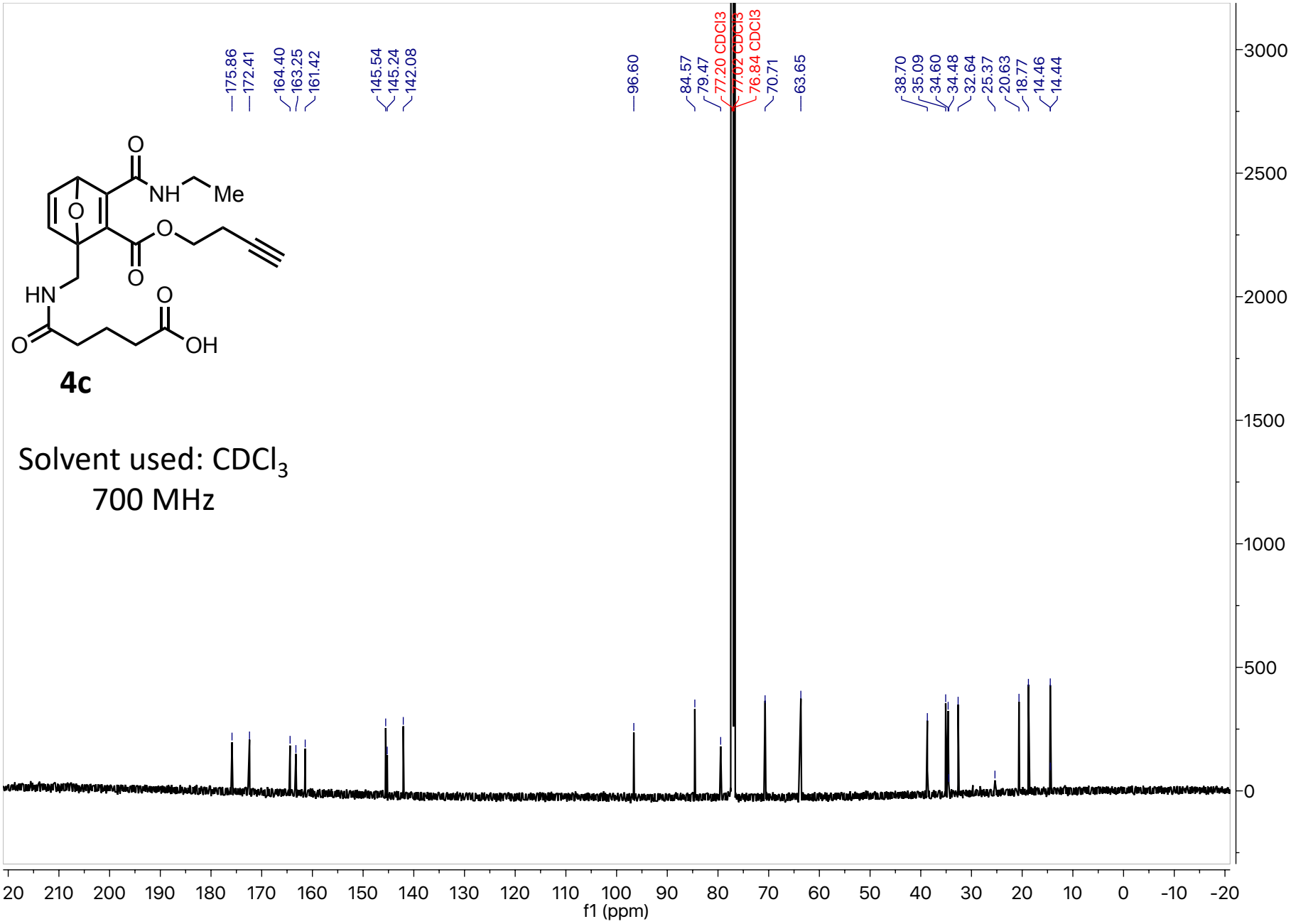

7.26 CDCl3
Me
AcHN
4b
Solvent used: CDCl3
500 MHz
f1 (ppm)

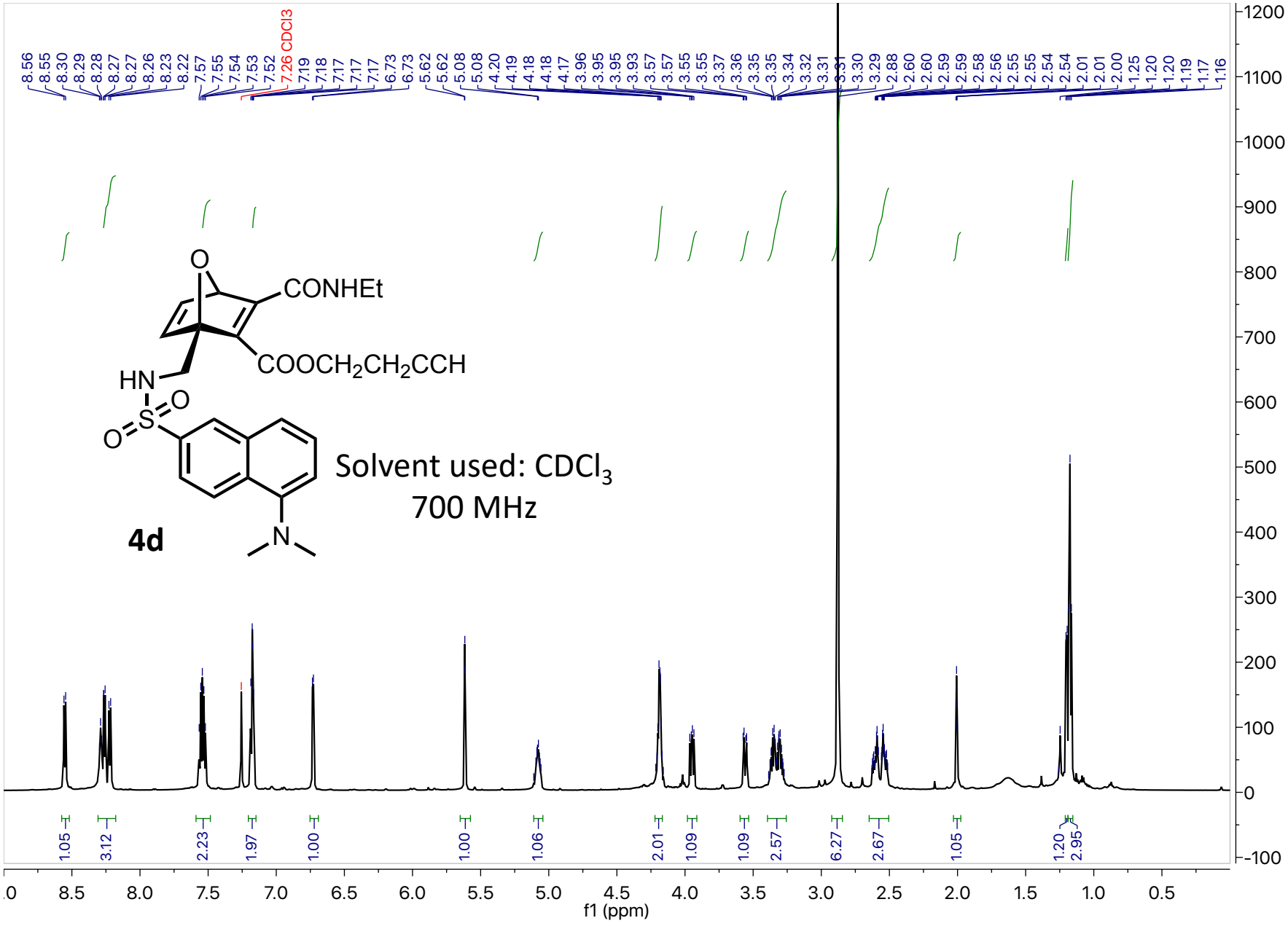

7.28 CDCl3
7.16
7.16
7.15
7.15
7.06
7.05
5.64
5.64
4.92
4.16
4.15
4.15
3.40
3.39
3.39
3.39
3.38
3.38
3.38
3.37
3.36
3.36
3.36
2.04
1.85
1.78
1.77
1.76
1.75
1.74 HDO
1.60
1.58
1.56
1.54
1.53
1.52
1.52
1.50
1.49
1.48
1.47
1.46
1.46
1.45
1.44
1.44
1.43
1.42
1.42
1.41
1.40
1.39
1.38
1.36
1.36
1.34
1.34
1.32
1.30
1.28
1.28
1.27
1.27
1.24
1.23
1.22
1.22
1.22
1.21
O
O
O
NH
O
AcHN
Solvent used: CDCl3
500 MHz
4b’
0.85
0.98
0.96
1.05
1.00
1.17
1.86
2.17
1.18
1.57
3.01
3.70
2.47
3.36
f1 (ppm)

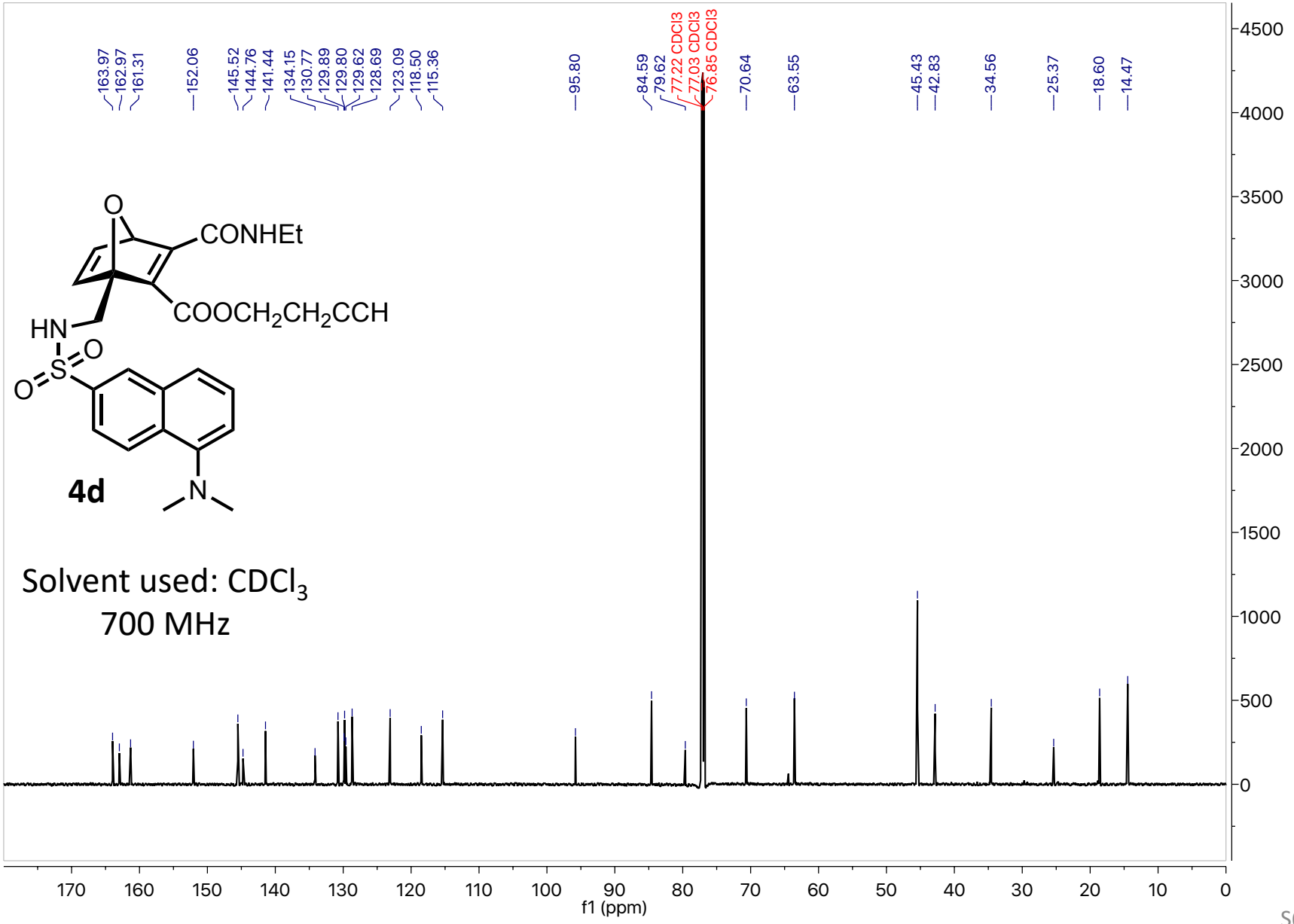

170.09
164.21
163.81
162.39
162.23
161.59
159.99
149.63
146.07
145.47
144.03
143.23
142.23
97.31
96.25
84.50
83.66
77.20 CDCl3
77.02 CDCl3
76.84 CDCl3
75.60
74.79
38.94
38.84
34.58
34.53
31.43
31.38
31.34
31.29
25.18
25.10
23.80
23.69
23.54
23.50
23.41
23.17
14.50
14.42
14.21
O
N
H
Me
O
O
O
AcHN
Solvent used: CDCl3
700 MHz
4b
3000
2500
2000
1500
1000
500
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

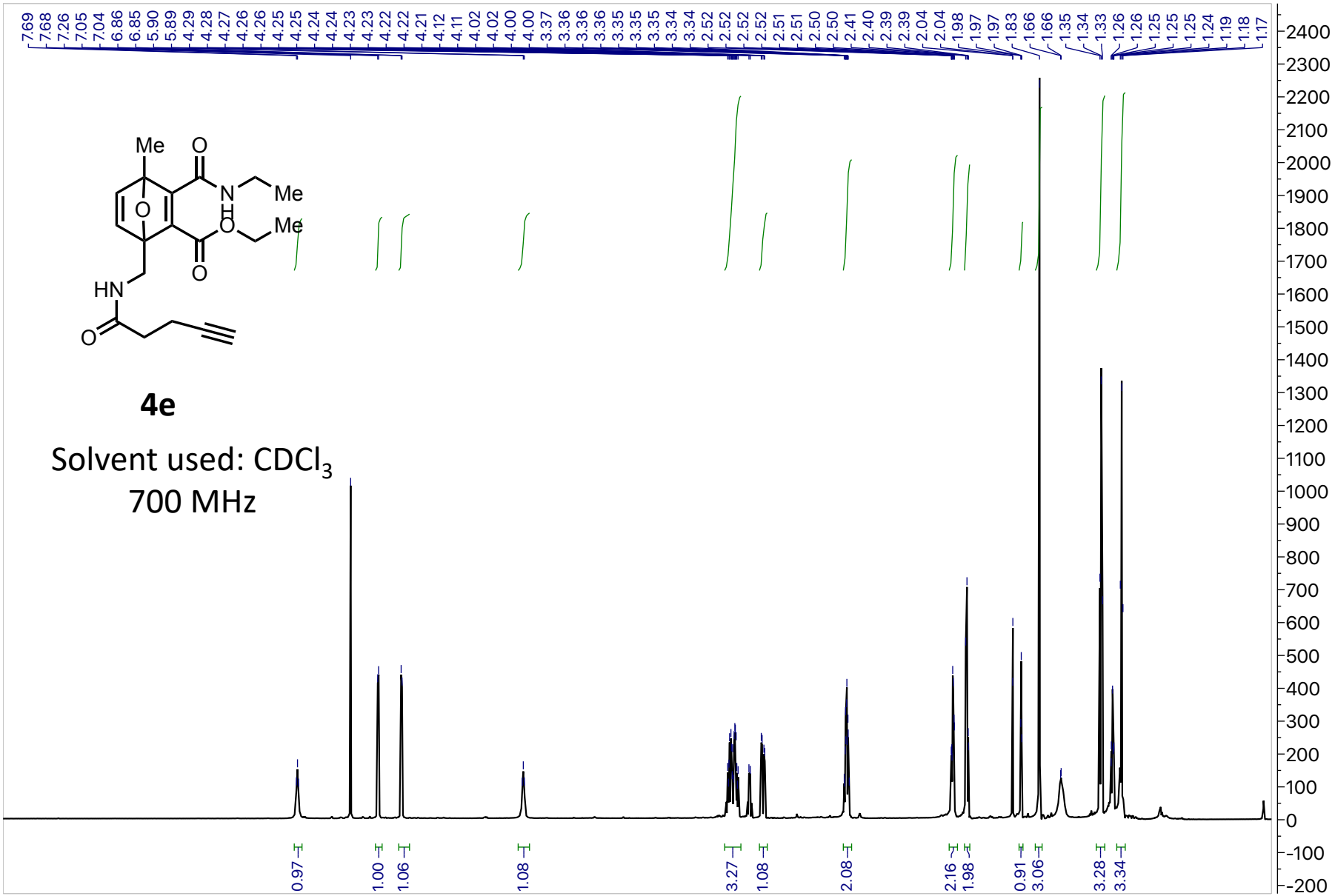

170.05
163.76
162.17
159.94
149.58
143.98
143.17
97.25
83.61
77.21 CDCl3
76.96 CDCl3
76.71 CDCl3
74.73
38.79
34.53
31.37
31.28
25.12
23.36
14.37
O
O
O
NH
O
AcHN
Solvent used: CDCl3
500 MHz
4b'
f1 (ppm)

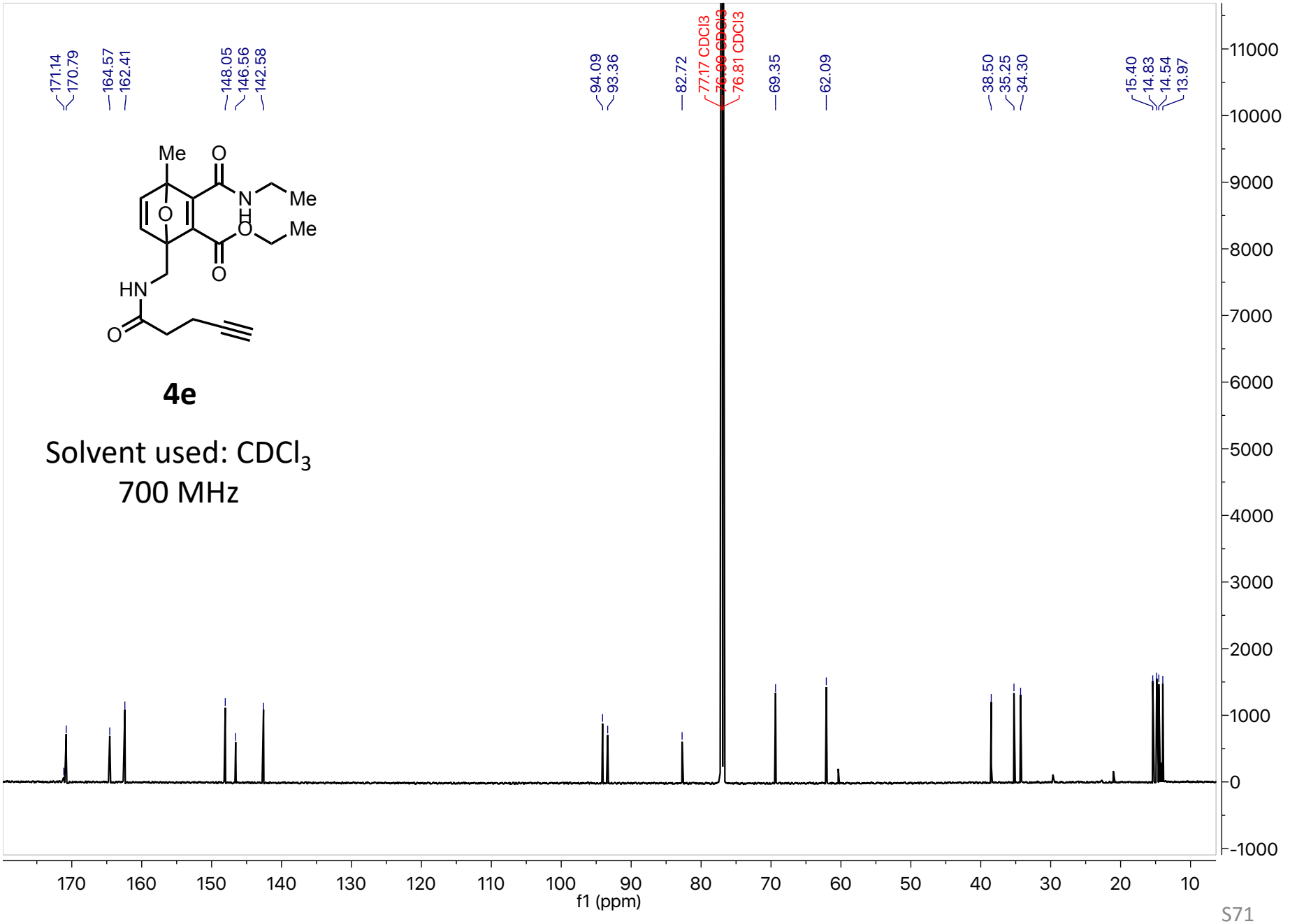

4c
Solvent used: $CDCl_3$
500 MHz
f1 (ppm)

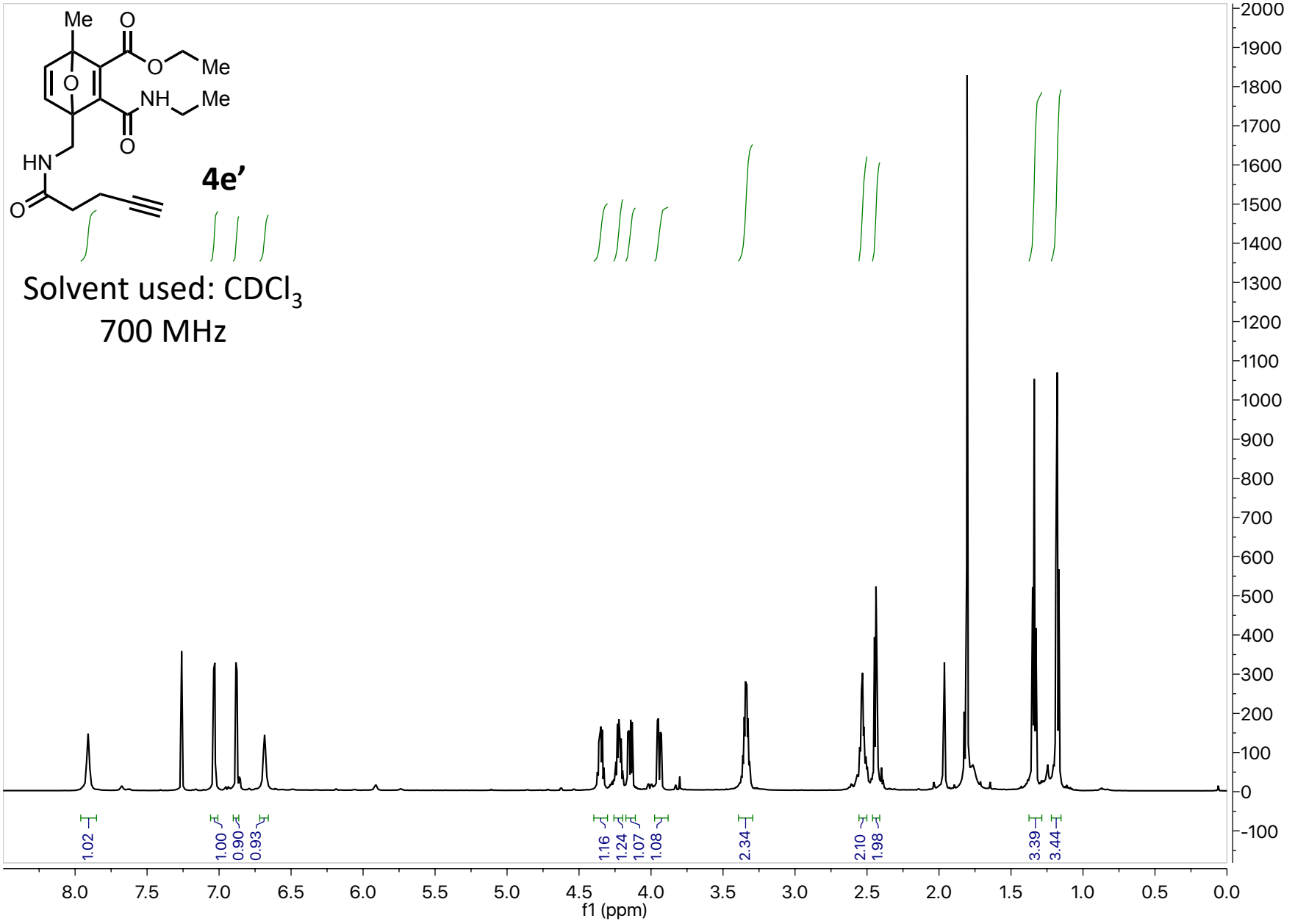

175.86
172.41
164.40
163.25
161.42
145.54
145.24
142.08
96.60
84.57
79.47
77.20 CDCl3
77.02 CDCl3
76.84 CDCl3
70.71
63.65
38.70
35.09
34.60
34.48
32.64
25.37
20.63
18.77
14.46
14.44
NH
Me
O
HN
OH
4c
Solvent used: CDCl3
700 MHz
f1 (ppm)

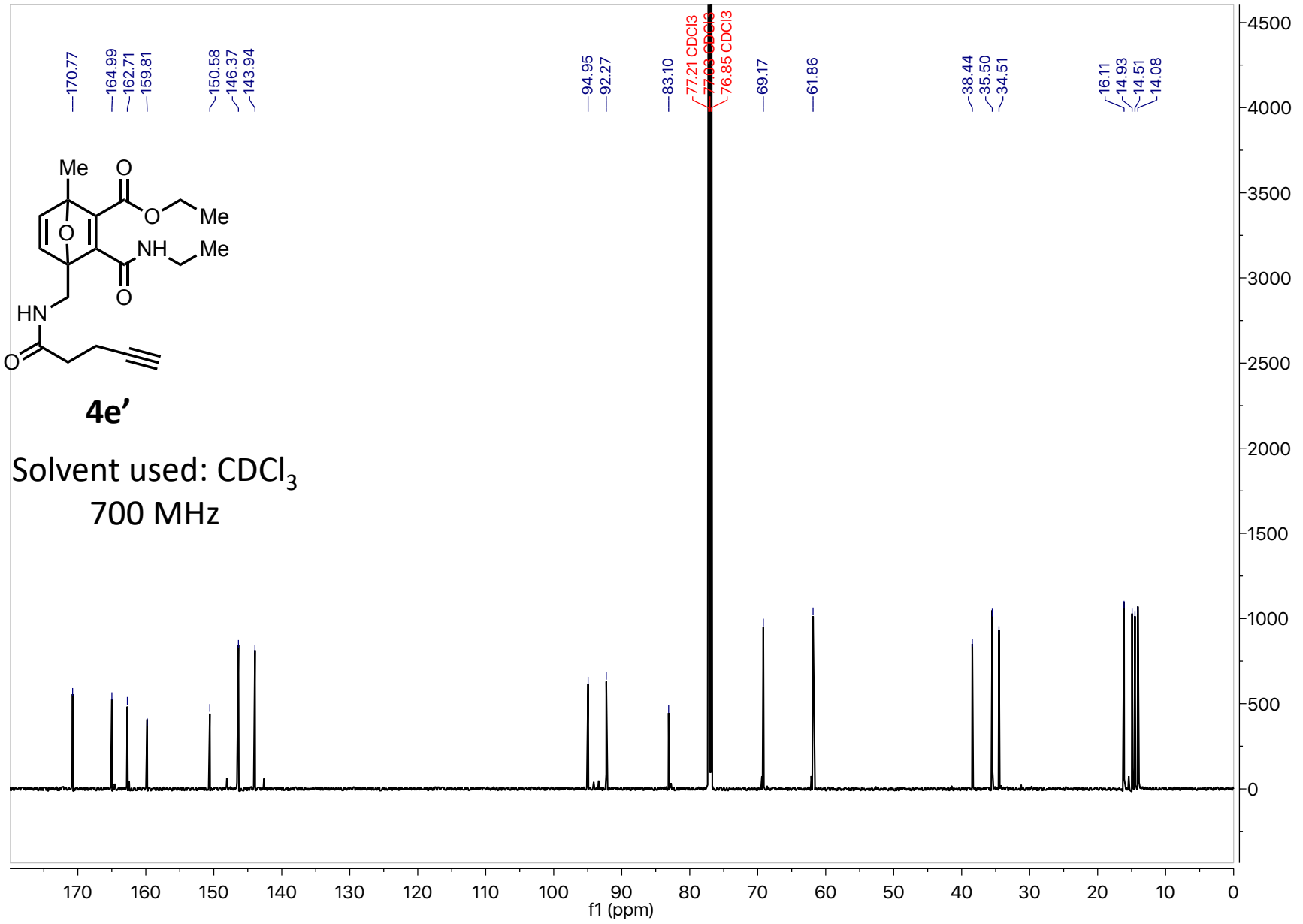

8.56 8.55 8.30 8.29 8.28 8.27 8.27 8.26 8.23 8.22 7.57 7.55 7.54 7.53 7.52 7.26 CDCl3 7.19 7.18 7.17 7.17 7.17 6.73 6.73 5.62 5.62 5.08 5.08 4.20 4.19 4.18 4.18 4.17 3.96 3.95 3.95 3.93 3.57 3.57 3.55 3.55 3.37 3.36 3.35 3.35 3.34 3.32 3.31 3.31 3.30 3.29 2.88 2.60 2.60 2.59 2.59 2.58 2.56 2.55 2.55 2.54 2.54 2.01 2.01 2.00 1.25 1.20 1.20 1.19 1.17 1.16
O
CONHEt
COOCH2CH2CCH
HN
S
O
O
N
4d
Solvent used: CDCl3
700 MHz
1.05 3.12 2.23 1.97 1.00 1.00 1.06 2.01 1.09 1.09 2.57 6.27 2.67 1.05 1.20 2.95
1200 1100 1000 900 800 700 600 500 400 300 200 100 0 -100
.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
f1 (ppm)


163.97
162.97
161.31
152.06
145.52
144.76
141.44
134.15
130.77
129.89
129.80
129.62
128.69
123.09
118.50
115.36
95.80
84.59
79.62
77.22 CDCl3
77.03 CDCl3
76.85 CDCl3
70.64
63.55
45.43
42.83
34.56
25.37
18.60
14.47
O
CONHEt
COOCH2CH2CCH
HN
O
S
O
O
4d
N
Solvent used: CDCl3
700 MHz
4500
4000
3500
3000
2500
2000
1500
1000
500
0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
O
N
H
Me
O
Me
O
HN
O
4e
Solvent used: CDCl3
700 MHz
f1 (ppm)


171.14
170.79
164.57
162.41
148.05
146.56
142.58
94.09
93.36
82.72
77.17 CDCl3
77.00 CDCl3
76.81 CDCl3
69.35
62.09
38.50
35.25
34.30
15.40
14.83
14.54
13.97
Me
O
N
H
Me
O
Me
O
O
HN
O
4e
Solvent used: CDCl3
700 MHz
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

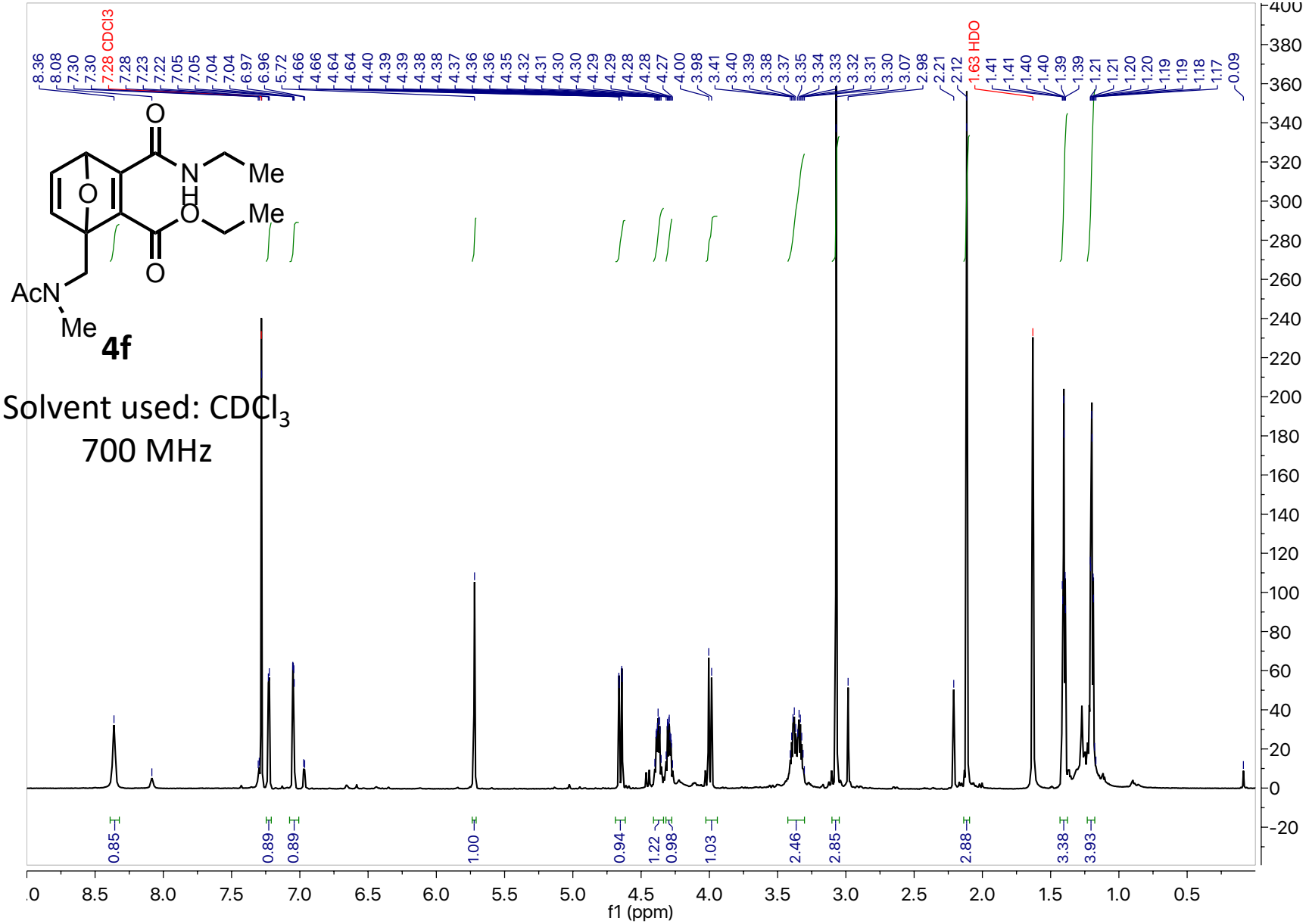

Me
O
O
Me
O
NH
Me
O
HN
O
4e’
Solvent used: CDCl3
700 MHz
1.02
1.00
0.90
0.93
1.16
1.24
1.07
1.08
2.34
2.10
1.98
3.39
3.44
f1 (ppm)

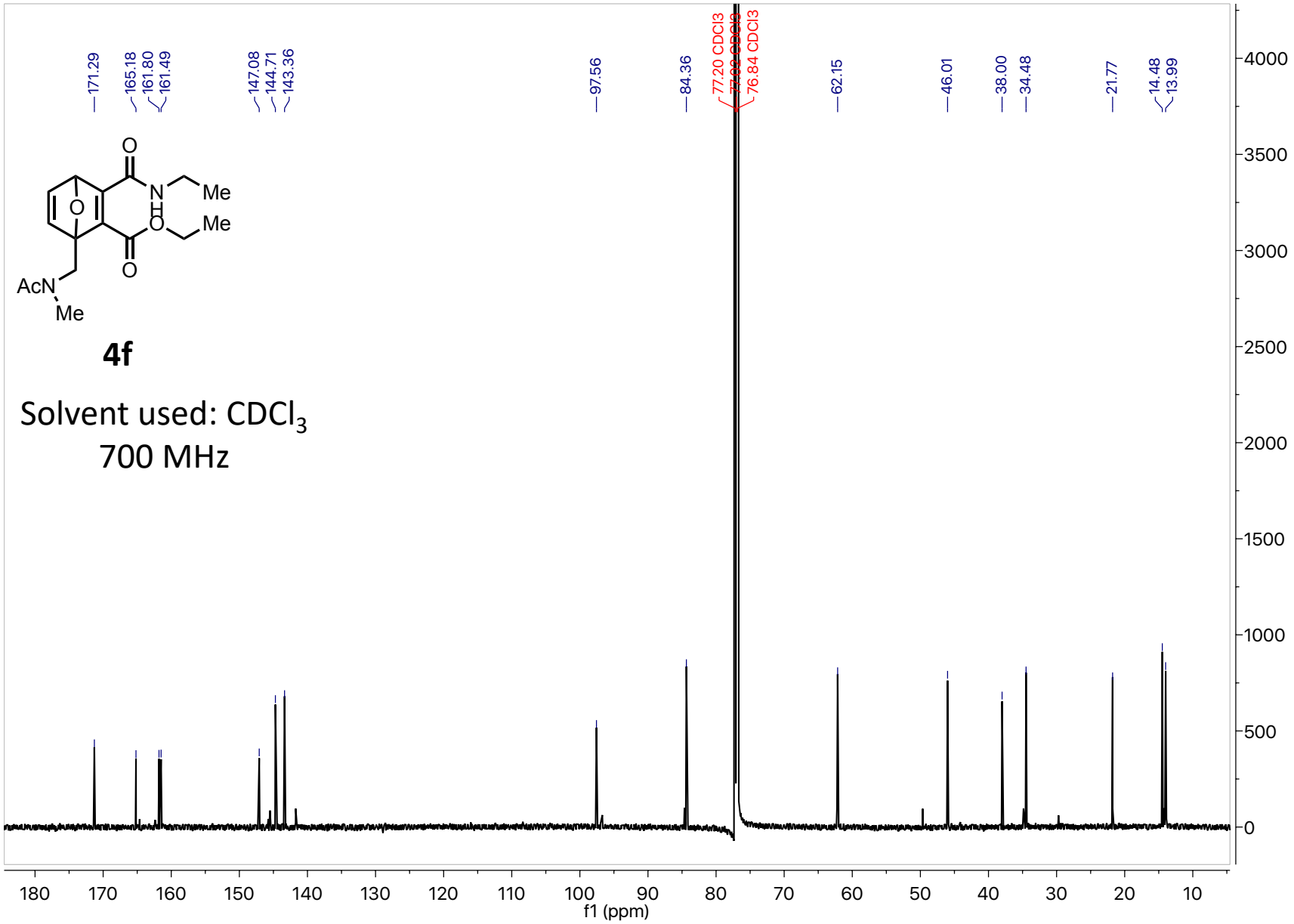


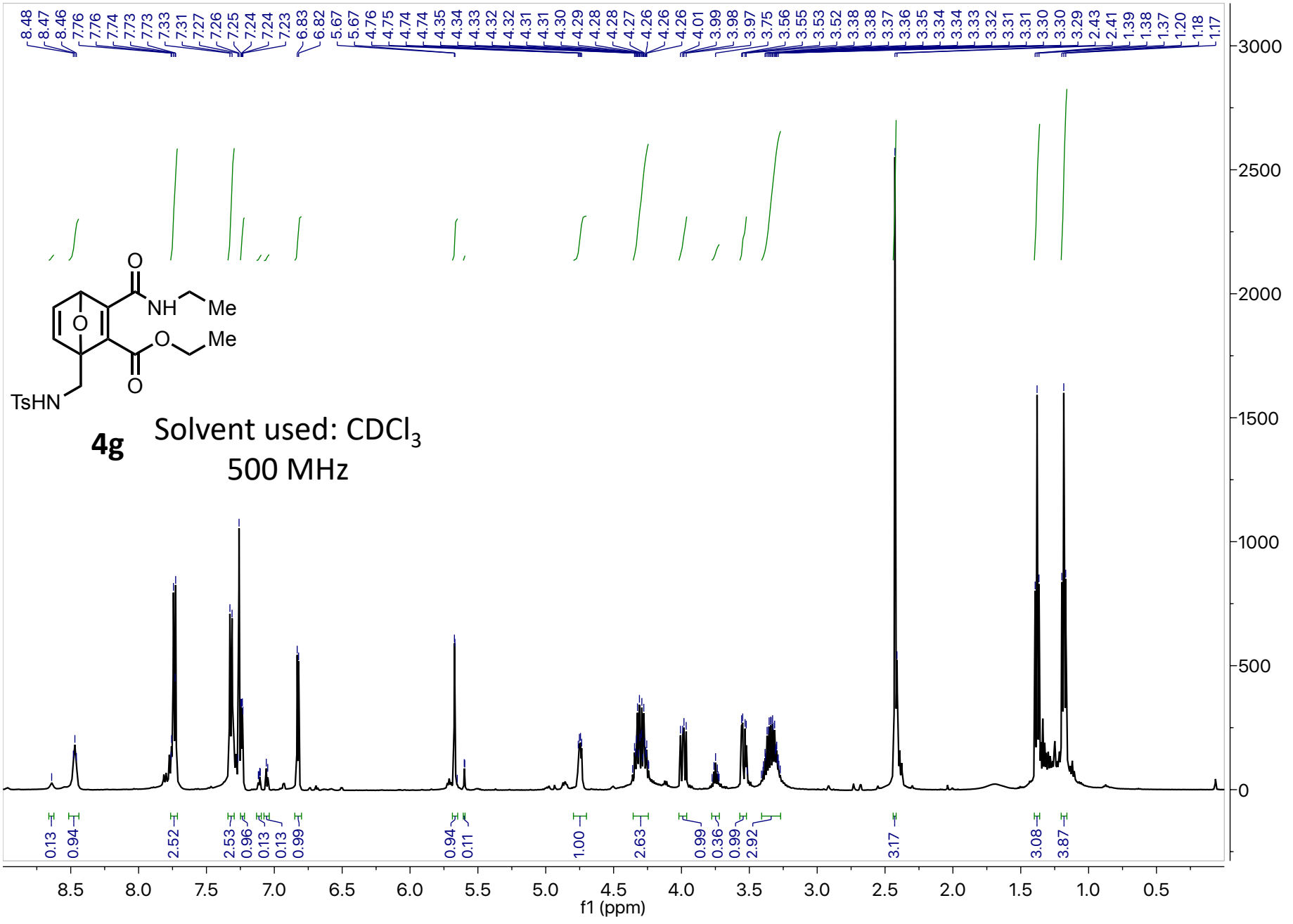
4e’

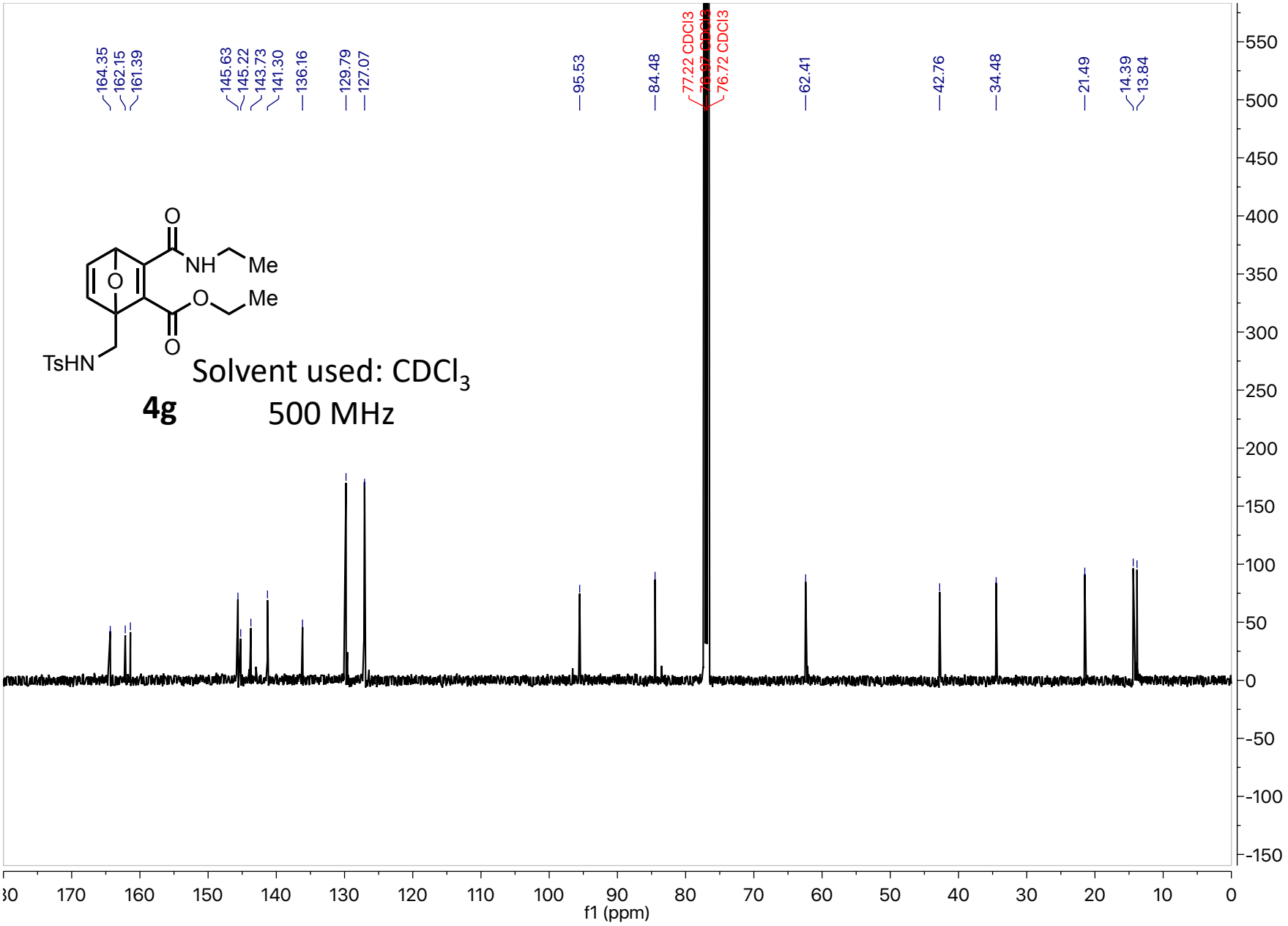
Solvent used: $CDCl_3$

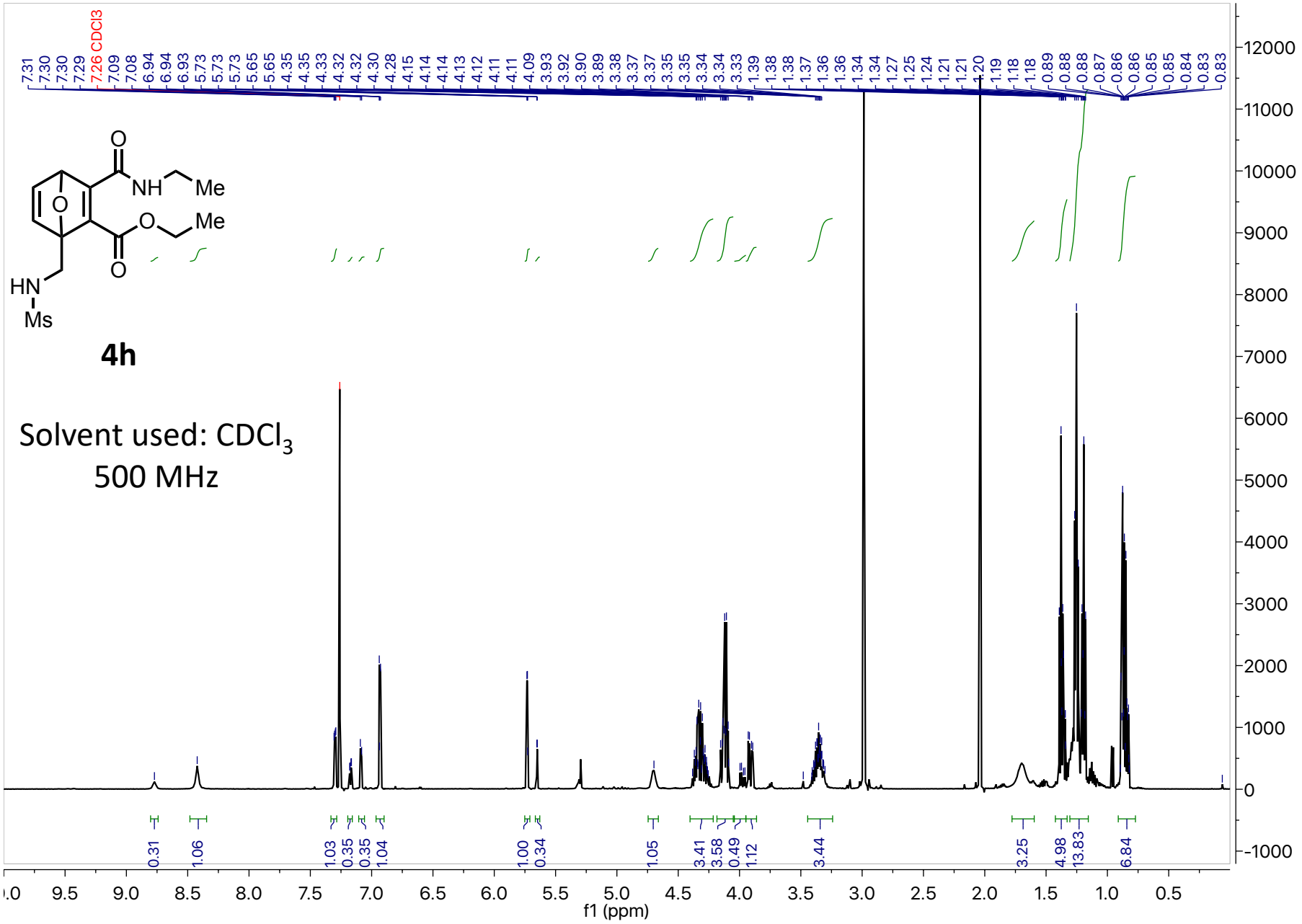
700 MHz

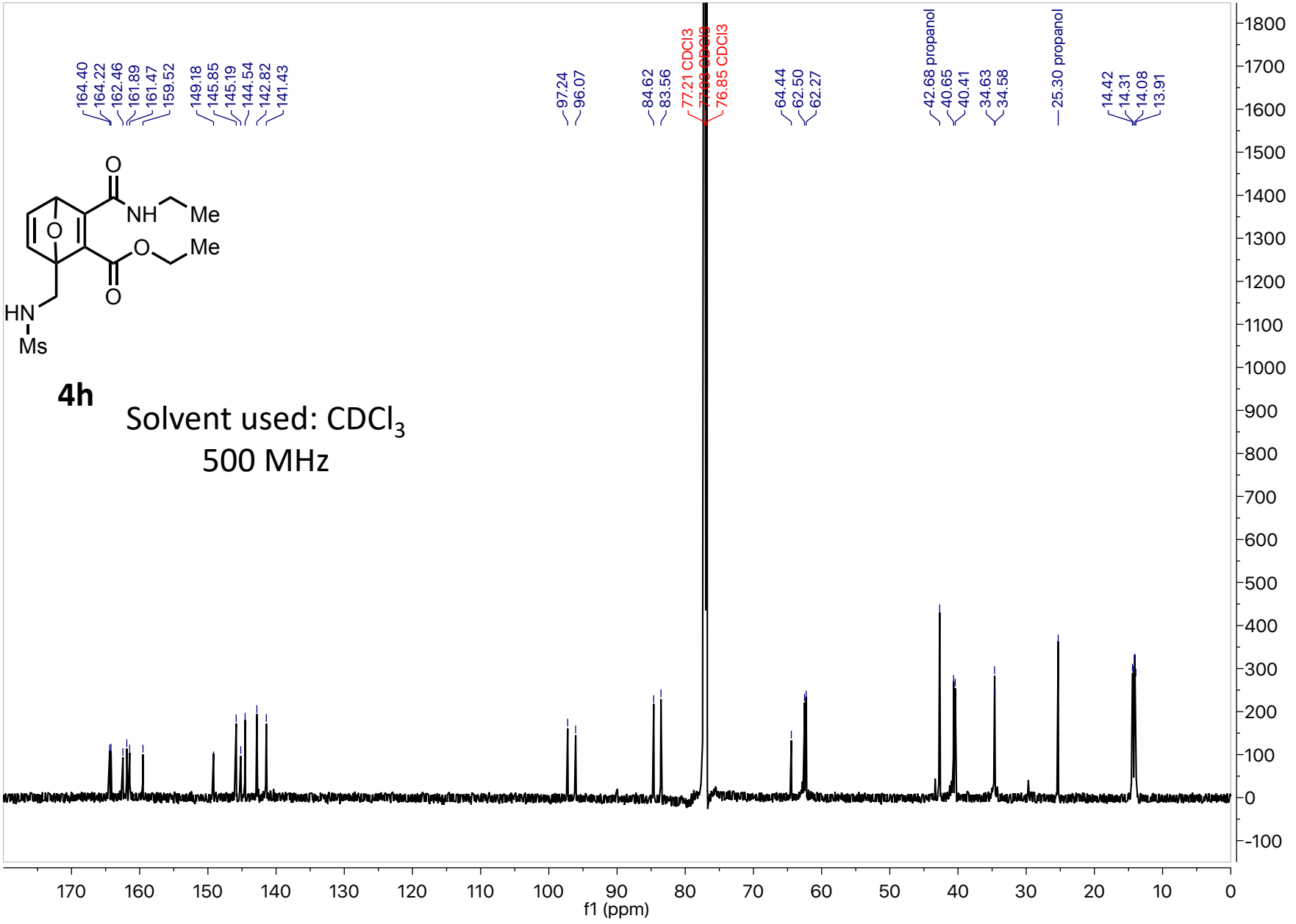

8.36 8.08 7.30 7.30 7.28 CDCl3 7.28 7.23 7.22 7.05 7.05 7.04 7.04 6.97 6.96 5.72 4.66 4.66 4.64 4.64 4.40 4.39 4.39 4.38 4.38 4.37 4.36 4.36 4.35 4.32 4.31 4.30 4.30 4.29 4.29 4.28 4.28 4.27 4.00 3.98 3.41 3.40 3.39 3.38 3.37 3.35 3.34 3.33 3.32 3.31 3.30 3.07 2.98 2.21 2.12 1.63 HDO 1.41 1.41 1.40 1.40 1.39 1.39 1.21 1.21 1.20 1.20 1.19 1.19 1.18 1.17 0.09
O
N
H
Me
O
Me
O
O
AcN
Me
4f
Solvent used: CDCl3
700 MHz
0.85 0.89 0.89 1.00 0.94 1.22 0.98 1.03 2.46 2.85 2.88 3.38 3.93
f1 (ppm)

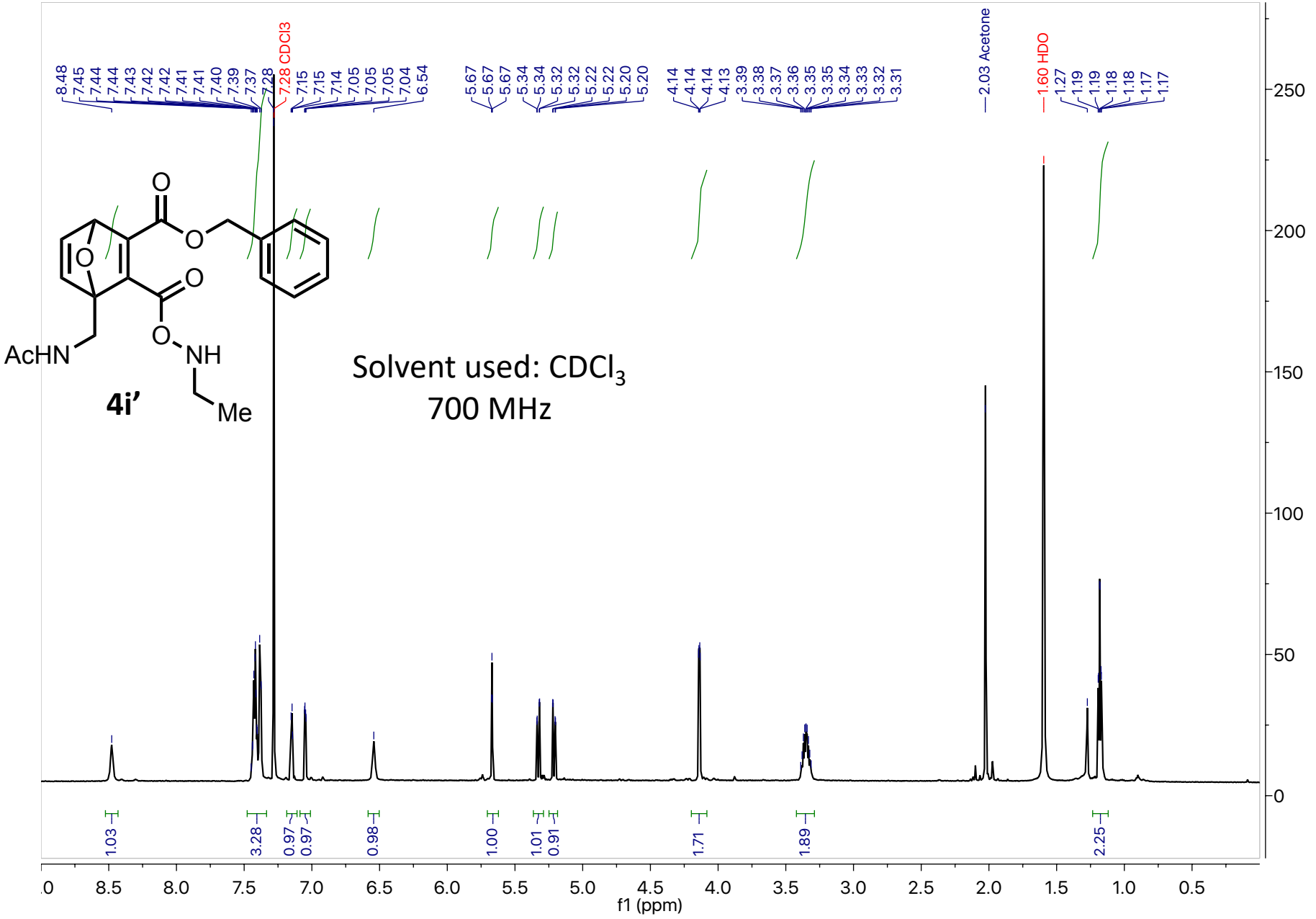

171.29
165.18
161.80
161.49
147.08
144.71
143.36
97.56
84.36
77.20 CDCl3
76.84 CDCl3
62.15
46.01
38.00
34.48
21.77
14.48
13.99
O
O
N
H
Me
O
Me
O
AcN
Me
4f
Solvent used: CDCl3
700 MHz
4000
3500
3000
2500
2000
1500
1000
500
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

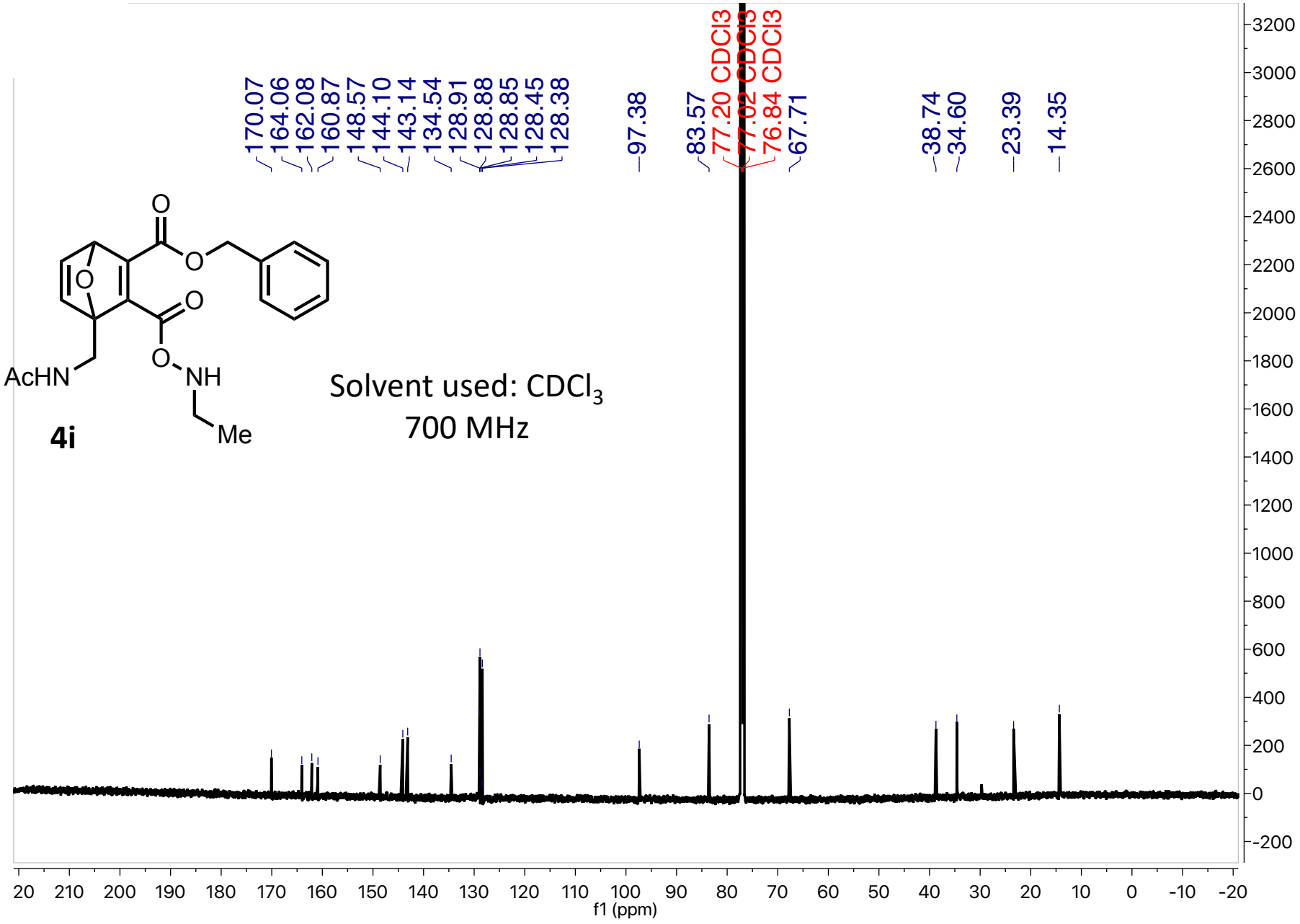

8.48 8.47 8.46 7.76 7.76 7.74 7.73 7.73 7.33 7.31 7.27 7.26 7.25 7.24 7.24 7.23 6.83 6.82 5.67 5.67 4.76 4.75 4.74 4.74 4.35 4.34 4.33 4.32 4.32 4.31 4.31 4.30 4.29 4.28 4.28 4.27 4.26 4.26 4.26 4.01 3.99 3.98 3.97 3.75 3.56 3.55 3.53 3.52 3.38 3.38 3.37 3.36 3.35 3.34 3.34 3.33 3.32 3.31 3.31 3.30 3.30 3.29 2.43 2.41 1.39 1.38 1.37 1.20 1.18 1.17
O
NH
Me
O
O
Me
O
TsHN
4g
Solvent used: CDCl3
500 MHz
0.13 0.94 2.52 2.53 0.96 0.13 0.13 0.99 0.94 0.11 1.00 2.63 0.99 0.36 0.99 2.92 3.17 3.08 3.87
3000
2500
2000
1500
1000
500
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
f1 (ppm)

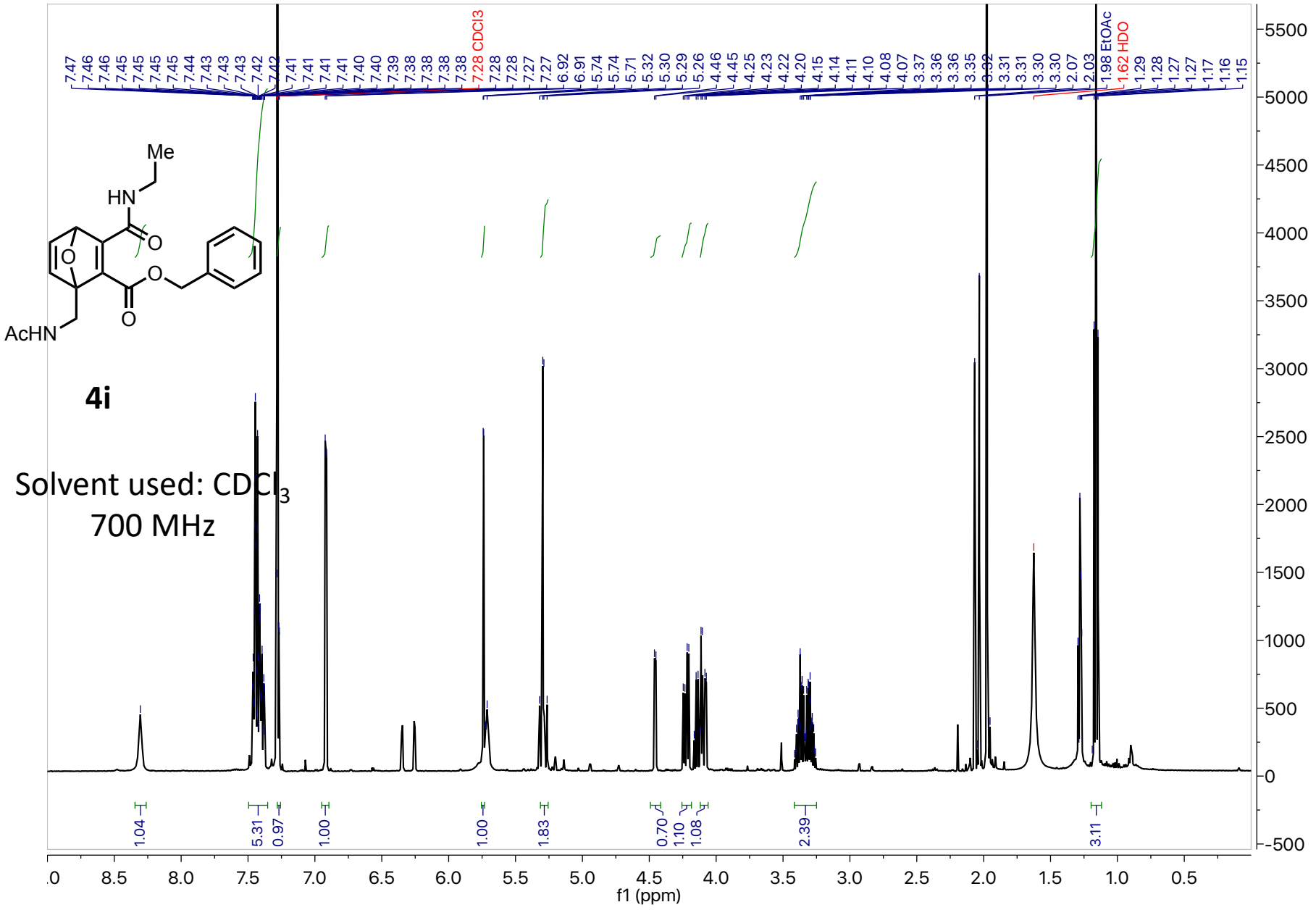

164.35
162.15
161.39
145.63
145.22
143.73
141.30
136.16
129.79
127.07
95.53
84.48
77.22 CDCl3
76.72 CDCl3
62.41
42.76
34.48
21.49
14.39
13.84
O
NH
Me
O
Me
O
O
TsHN
Solvent used: CDCl3
500 MHz
4g
f1 (ppm)

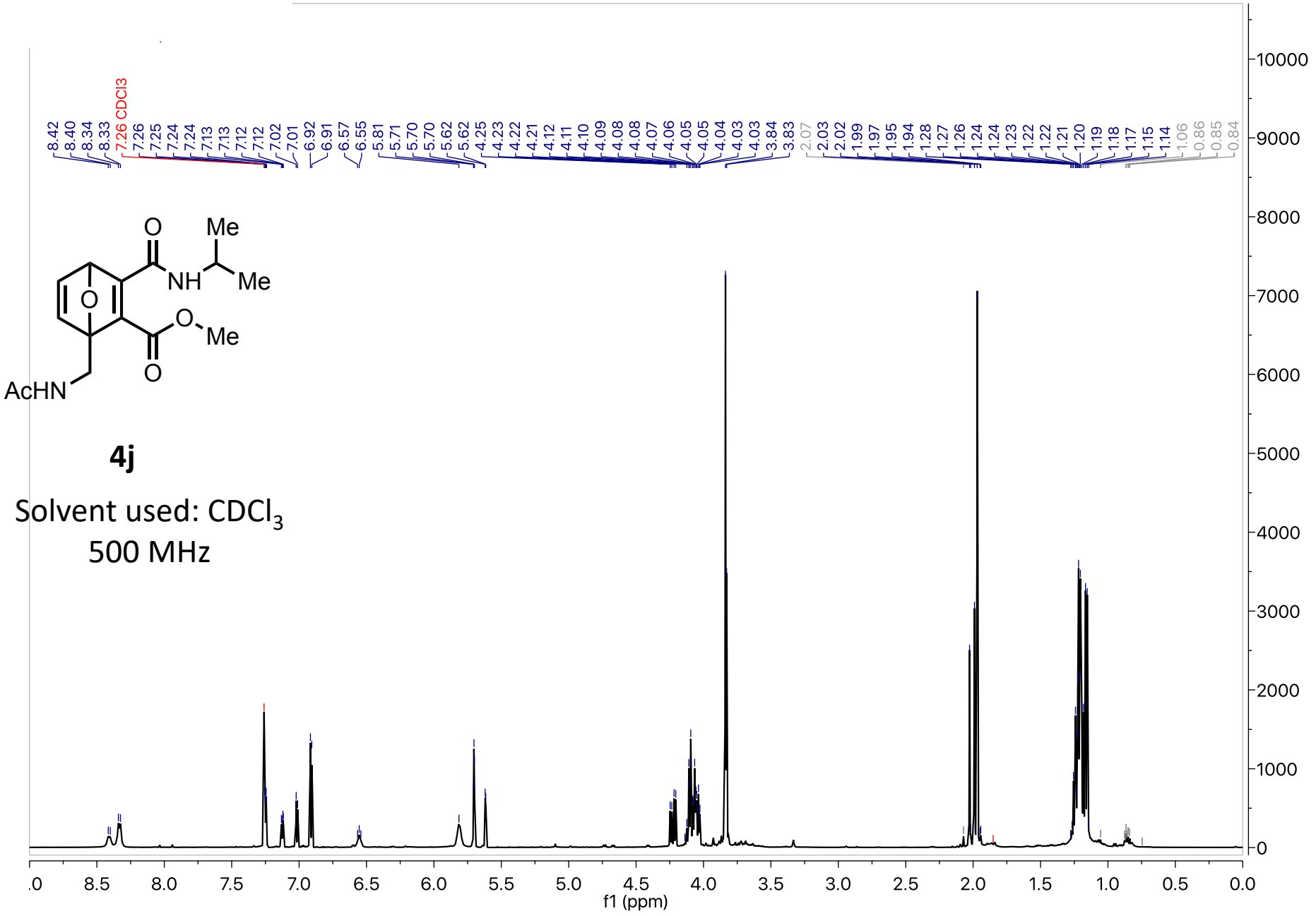

7.31 7.30 7.30 7.29 7.26 CDCl3 7.09 7.08 6.94 6.94 6.93 5.73 5.73 5.73 5.65 5.65 4.35 4.35 4.33 4.32 4.32 4.30 4.28 4.15 4.14 4.14 4.13 4.12 4.11 4.11 4.09 3.93 3.92 3.90 3.89 3.38 3.37 3.35 3.35 3.34 3.34 3.33 1.39 1.38 1.38 1.37 1.36 1.36 1.34 1.34 1.27 1.25 1.24 1.21 1.21 1.20 1.19 1.18 1.18 0.89 0.88 0.88 0.87 0.86 0.86 0.85 0.85 0.84 0.83 0.83
O
NH
Me
O
O
Me
O
HN
Ms
4h
Solvent used: CDCl3
500 MHz
0.31 1.06 1.03 0.35 0.35 1.04 1.00 0.34 1.05 3.41 3.58 0.49 1.12 3.44 3.25 4.98 13.83 6.84
12000 11000 10000 9000 8000 7000 6000 5000 4000 3000 2000 1000 0 -1000
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
f1 (ppm)


164.40
164.22
162.46
161.89
161.47
159.52
149.18
145.85
145.19
144.54
142.82
141.43
97.24
96.07
84.62
83.56
77.21 CDCl3
77.03 CDCl3
76.85 CDCl3
64.44
62.50
62.27
42.68 propanol
40.65
40.41
34.63
34.58
25.30 propanol
14.42
14.31
14.08
13.91
O
NH
Me
O
Me
O
O
HN
Ms
4h
Solvent used: CDCl3
500 MHz
f1 (ppm)


8.48
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.39
7.37
7.28
7.28 CDCl3
7.15
7.15
7.14
7.05
7.05
7.04
6.54
5.67
5.67
5.67
5.34
5.34
5.32
5.32
5.22
5.22
5.20
5.20
4.14
4.14
4.14
4.13
3.39
3.38
3.37
3.36
3.35
3.35
3.34
3.33
3.32
3.31
2.03 Acetone
1.60 HDO
1.27
1.19
1.19
1.18
1.18
1.17
1.17
AcHN
NH
Me
4i'
Solvent used: CDCl3
700 MHz
1.03
3.28
0.97
0.97
0.98
1.00
1.01
0.91
1.71
1.89
2.25
f1 (ppm)


170.07
164.06
162.08
160.87
148.57
144.10
143.14
134.54
128.91
128.88
128.85
128.45
128.38
97.38
83.57
77.20 CDCl3
77.02 CDCl3
76.84 CDCl3
67.71
38.74
34.60
23.39
14.35
AcHN
NH
Me
4i
Solvent used: CDCl3
700 MHz
f1 (ppm)

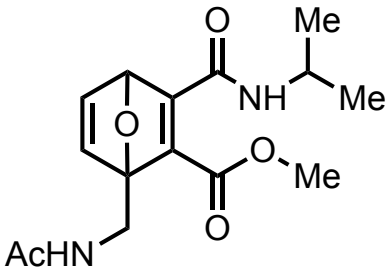

Me
HN
O
O
O
O
AcHN
4i
Solvent used: CDCl3
700 MHz
7.28 CDCl3
1.98 EtOAc
1.62 HDO
1.04
5.31
0.97
1.00
1.00
1.83
0.70
1.10
1.08
2.39
3.11
f1 (ppm)



4j

Solvent used: $CDCl_3$

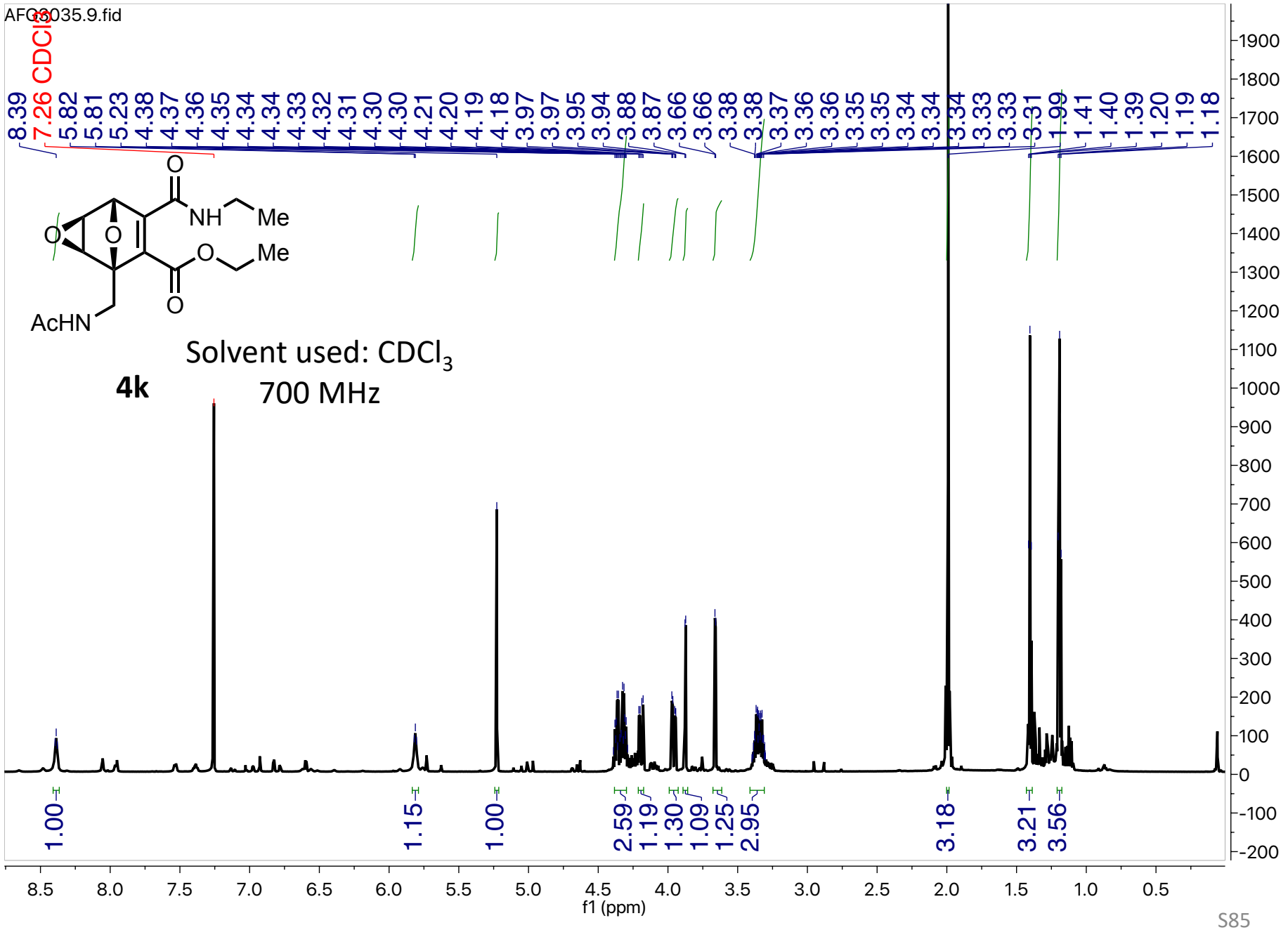
500 MHz

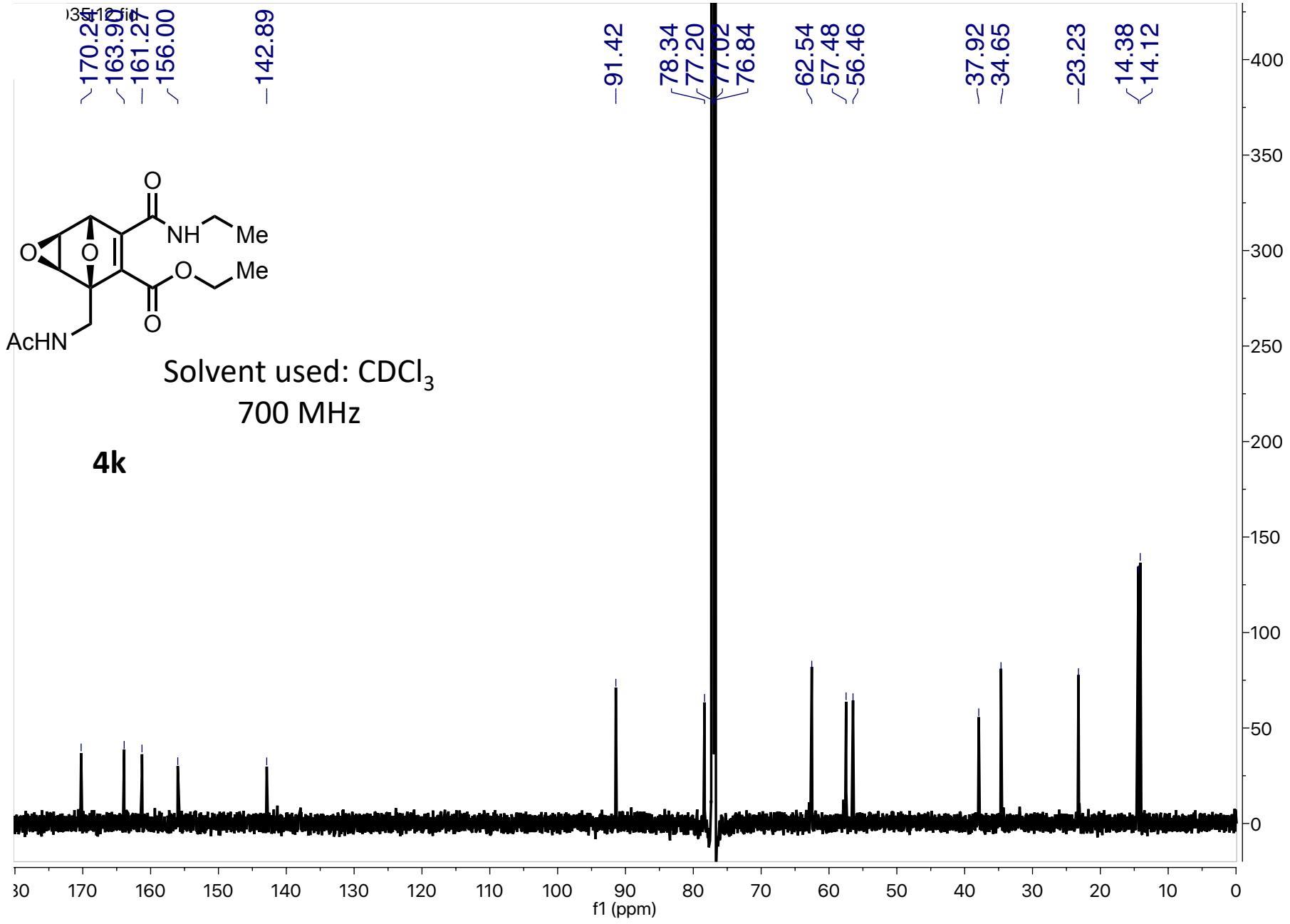


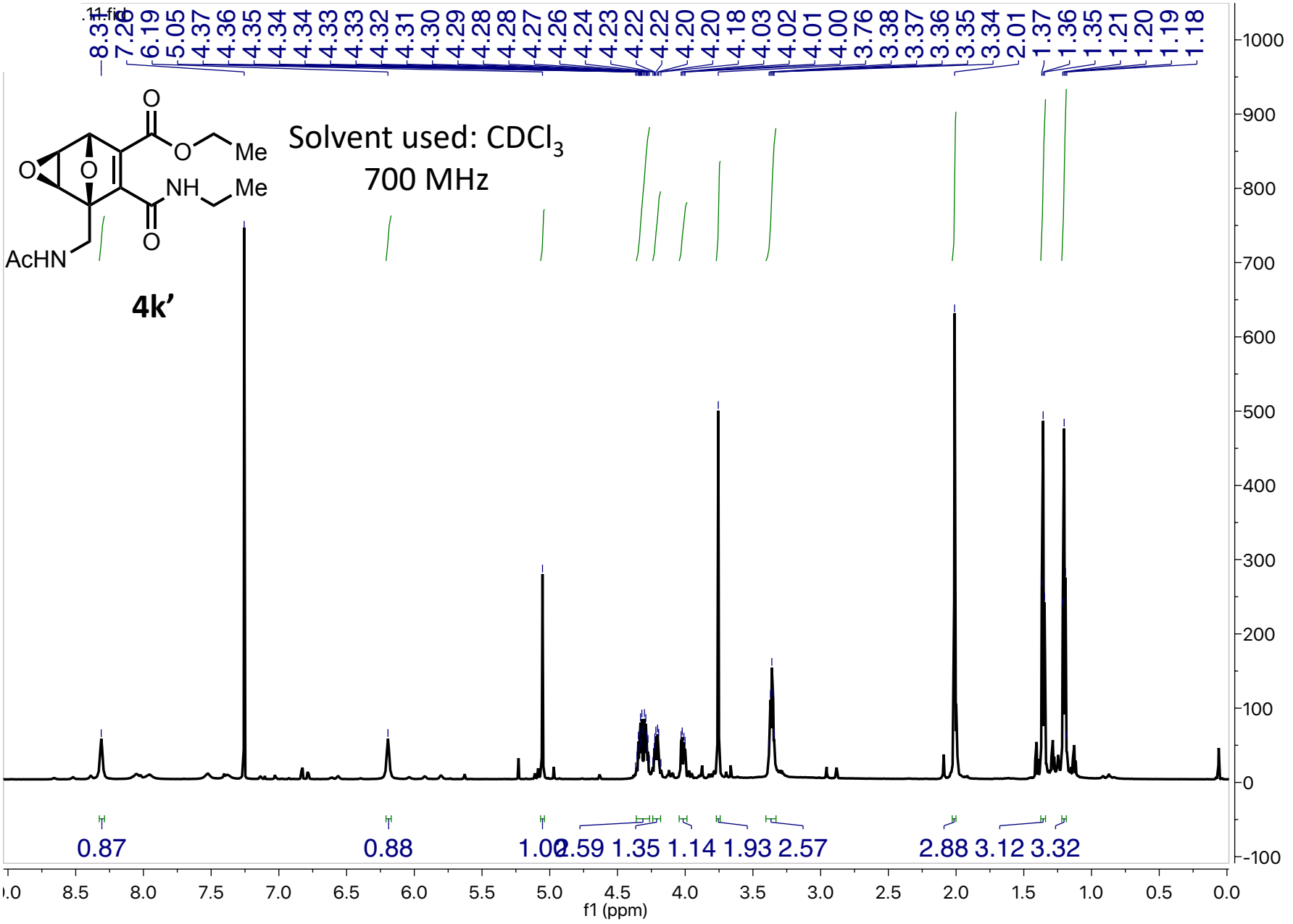
4j

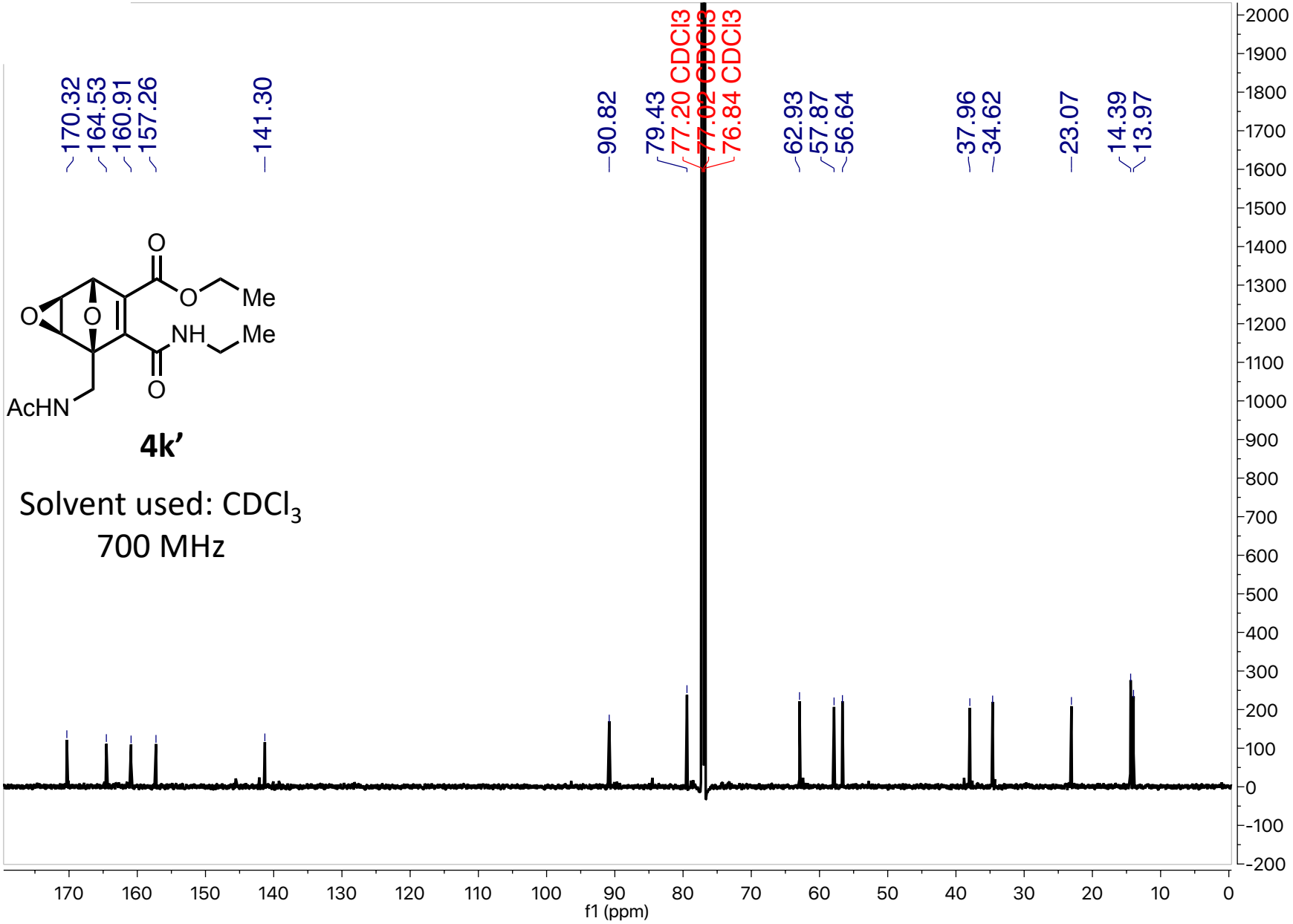
Solvent used: $CDCl_3$

500 MHz


AFG3035.9.fid
7.26 CDCl3
8.39
5.82
5.81
5.23
4.38
4.37
4.36
4.35
4.34
4.34
4.33
4.32
4.31
4.30
4.30
4.21
4.20
4.19
4.18
3.97
3.97
3.95
3.94
3.88
3.87
3.66
3.66
3.38
3.38
3.37
3.36
3.36
3.35
3.35
3.34
3.34
3.34
3.33
3.33
3.31
1.99
1.41
1.40
1.39
1.20
1.19
1.18
O
NH
Me
O
O
O
Me
O
AcHN
Solvent used: CDCl3
700 MHz
4k
1.00
1.15
1.00
2.59
1.19
1.30
1.09
1.25
2.95
3.18
3.21
3.56
f1 (ppm)


35-12.fid
170.24
163.90
161.27
156.00
142.89
91.42
78.34
77.20
77.02
76.84
62.54
57.48
56.46
37.92
34.65
23.23
14.38
14.12
O
NH
Me
O
O
Me
O
O
AcHN
Solvent used: CDCl3
700 MHz
4k
400
350
300
250
200
150
100
50
0
f1 (ppm)

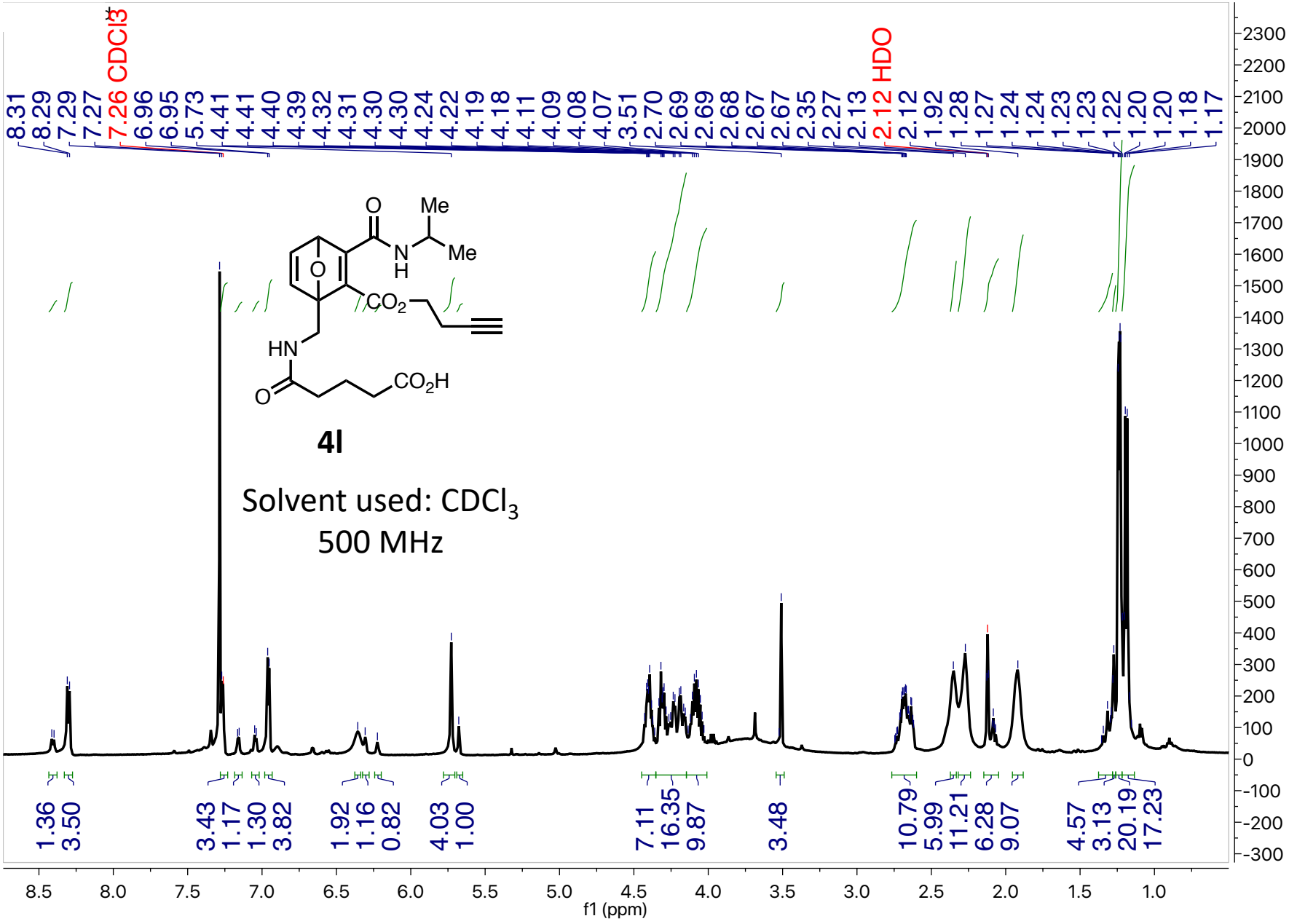

11.fid
8.31 7.26 6.19 5.05 4.37 4.36 4.35 4.34 4.34 4.33 4.33 4.32 4.31 4.30 4.29 4.28 4.28 4.27 4.26 4.24 4.23 4.22 4.22 4.20 4.20 4.18 4.03 4.02 4.01 4.00 3.76 3.38 3.37 3.36 3.35 3.34 2.01 1.37 1.36 1.35 1.21 1.20 1.19 1.18
Solvent used: CDCl3
700 MHz
4k'
0.87 0.88 1.00 2.59 1.35 1.14 1.93 2.57 2.88 3.12 3.32
f1 (ppm)

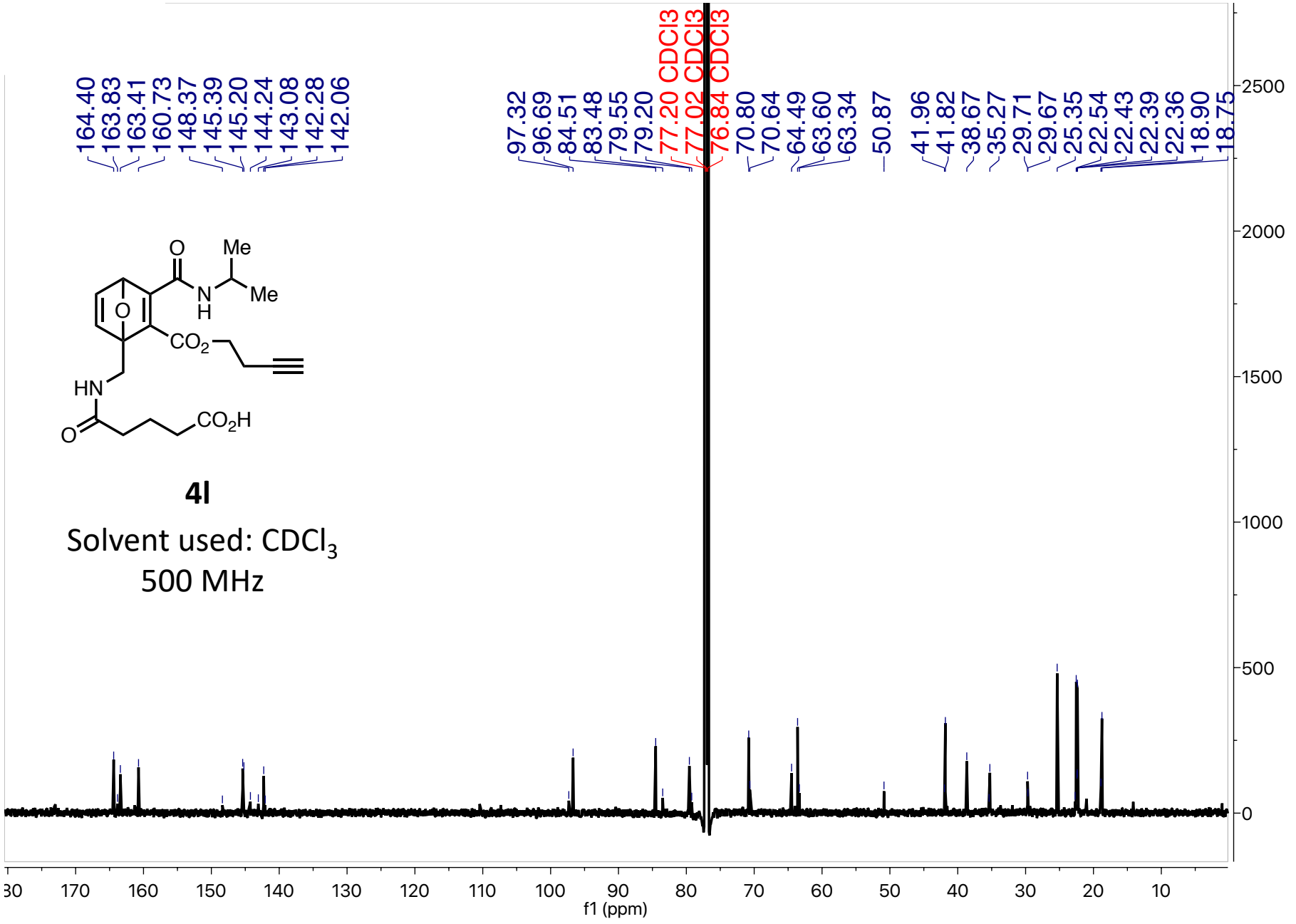


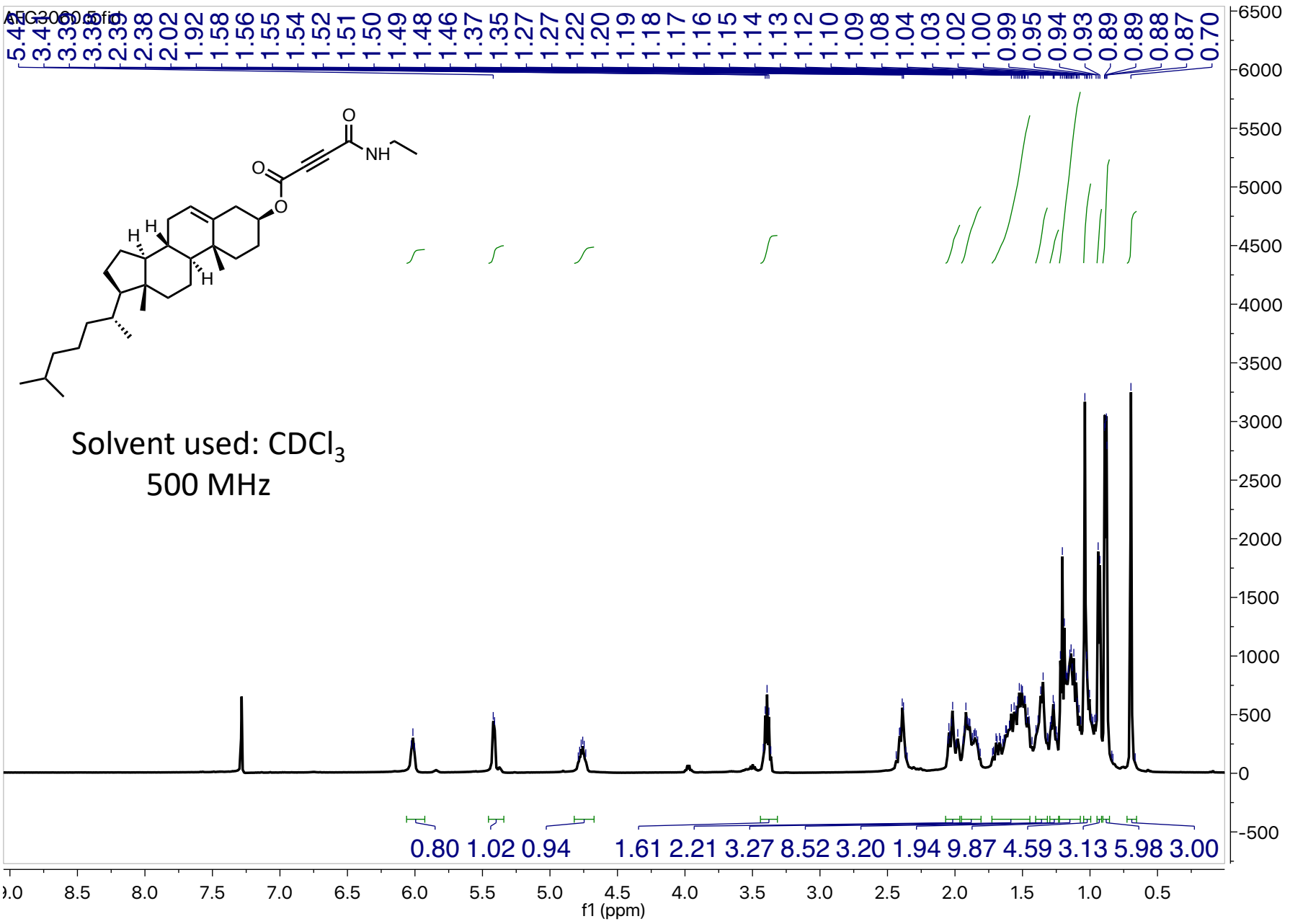
4k’

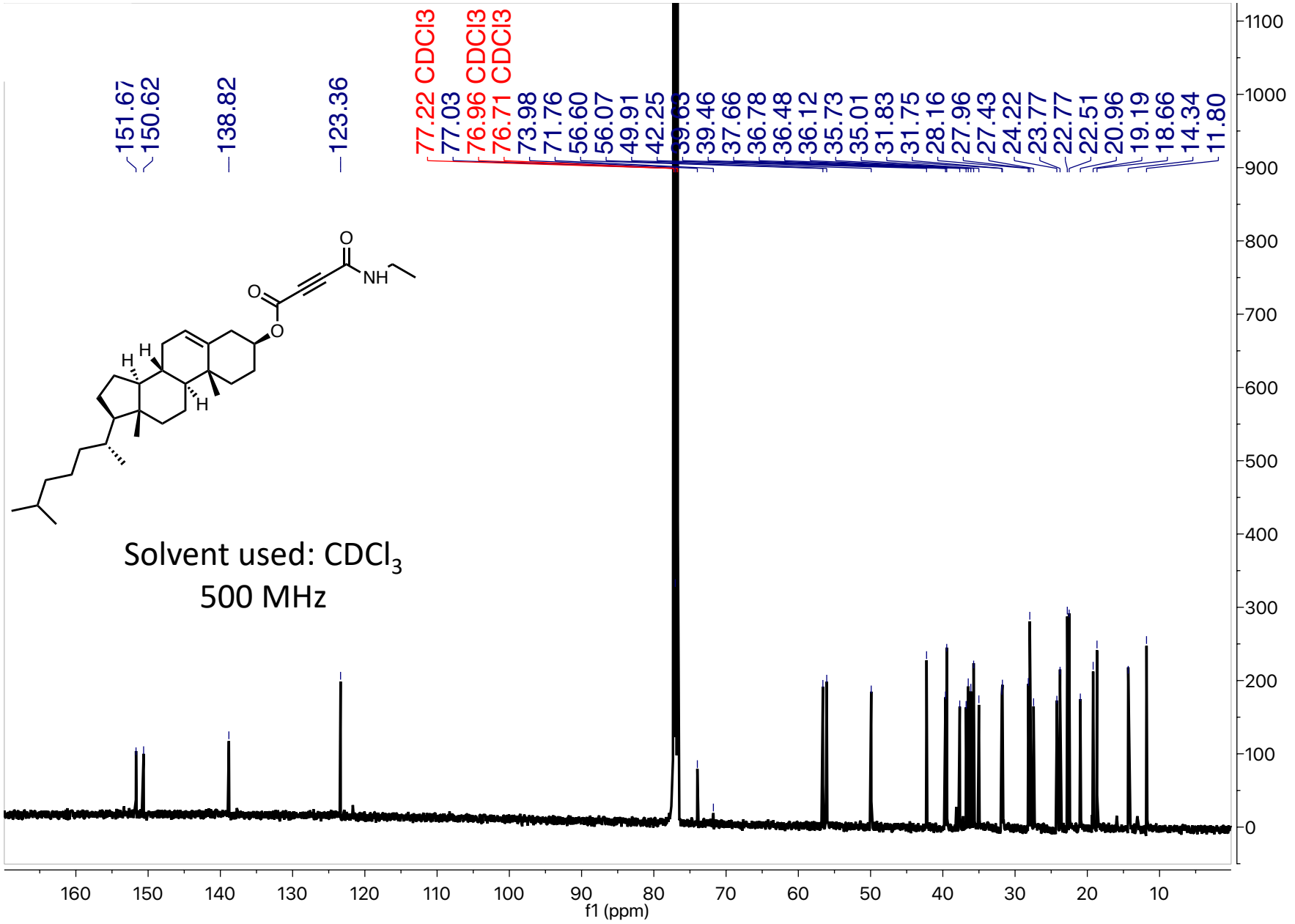
Solvent used: $CDCl_3$

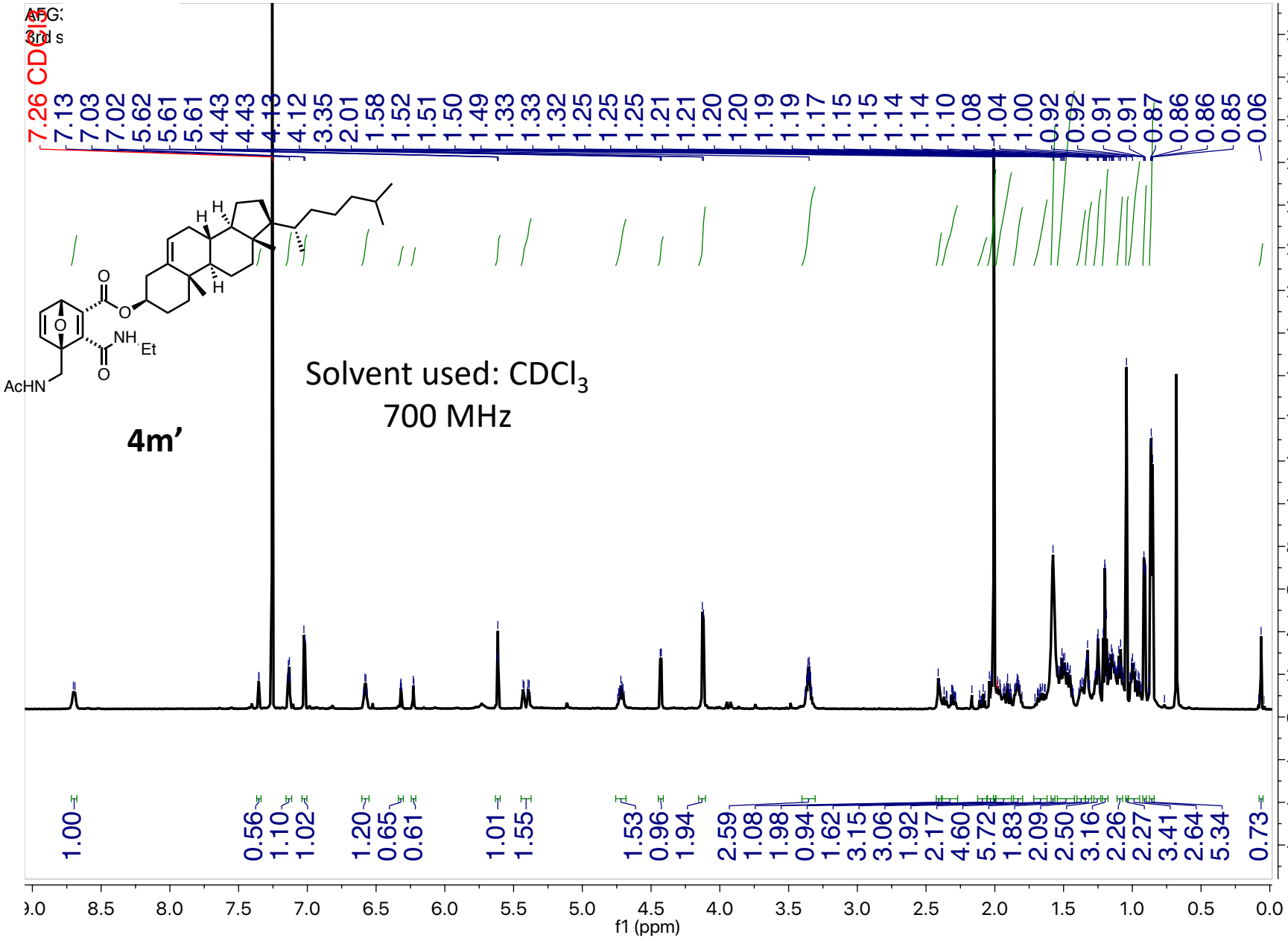
700 MHz

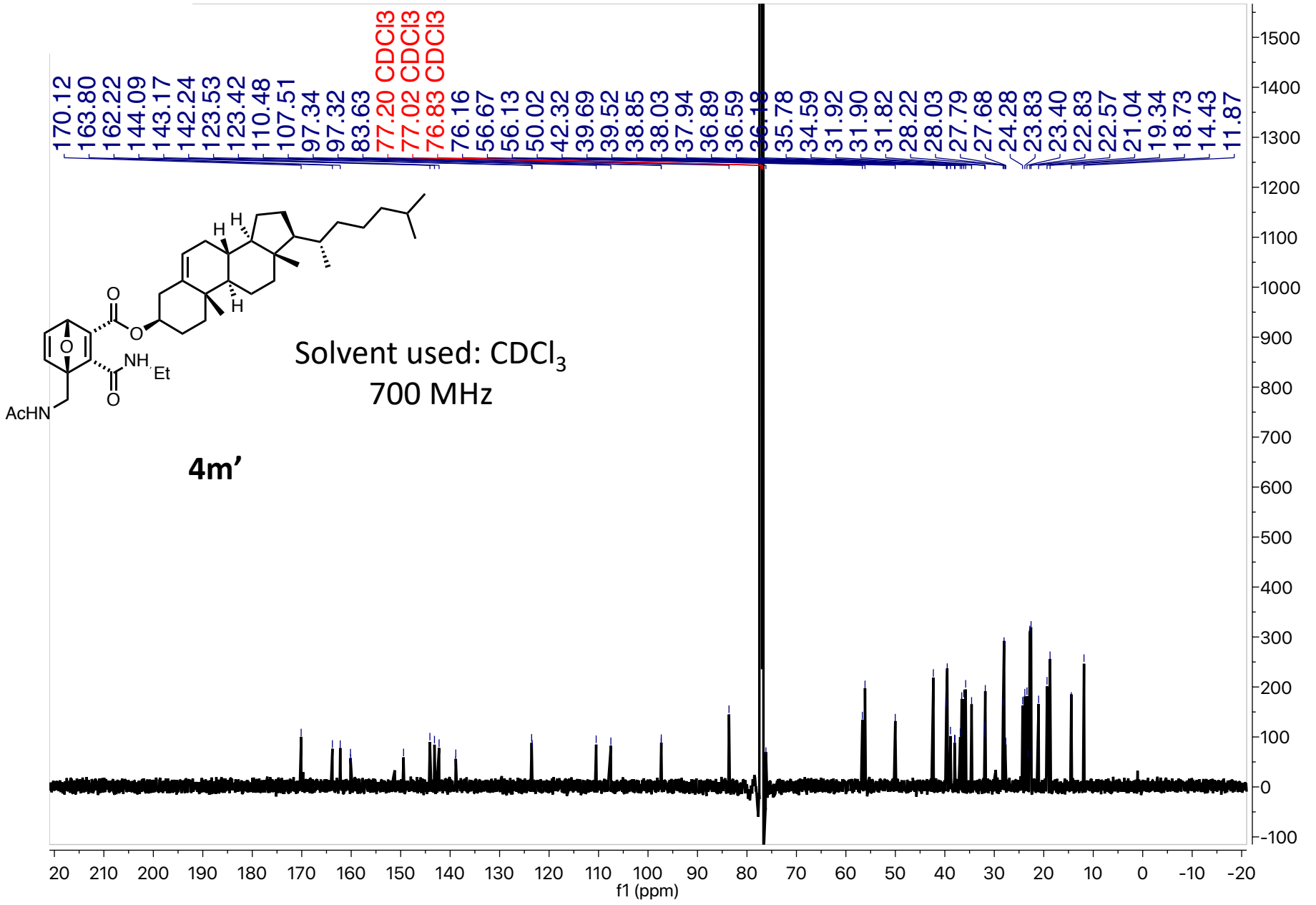

8.31 8.29 7.29 7.27 7.26 CDCl3 6.96 6.95 5.73 4.41 4.41 4.40 4.39 4.32 4.31 4.30 4.30 4.24 4.22 4.19 4.18 4.11 4.09 4.08 4.07 3.51 2.70 2.69 2.69 2.68 2.67 2.67 2.35 2.27 2.13 2.12 HDO 2.12 1.92 1.28 1.27 1.24 1.24 1.23 1.23 1.22 1.20 1.20 1.18 1.17
O
Me
N
H
Me
O
CO2
HN
O
CO2H
4l
Solvent used: CDCl3
500 MHz
1.36 3.50 3.43 1.17 1.30 3.82 1.92 1.16 0.82 4.03 1.00 7.11 16.35 9.87 3.48 10.79 5.99 11.21 6.28 9.07 4.57 3.13 20.19 17.23
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
f1 (ppm)

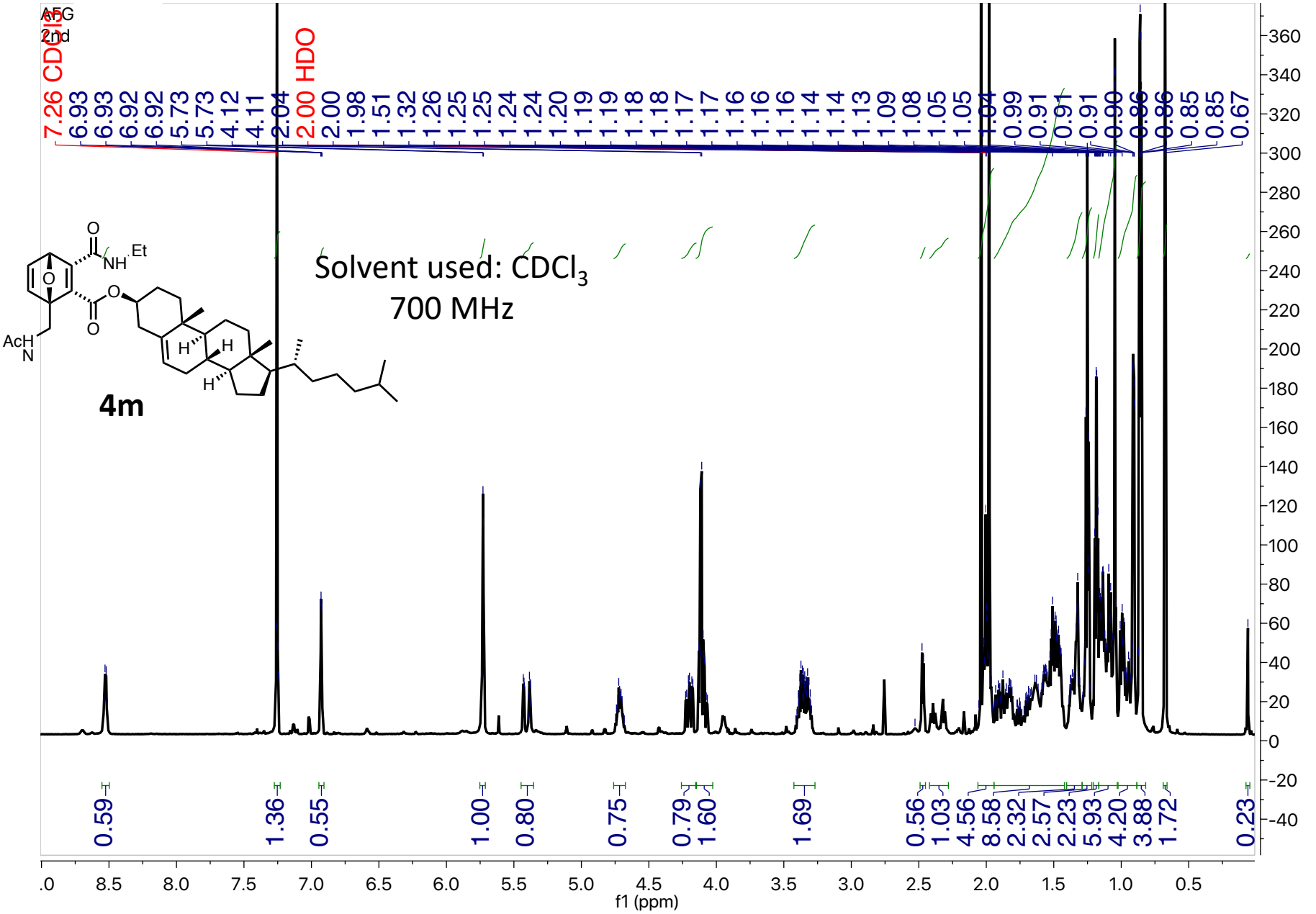

164.40
163.83
163.41
160.73
148.37
145.39
145.20
144.24
143.08
142.28
142.06
97.32
96.69
84.51
83.48
79.55
79.20
77.20 CDCl3
77.02 CDCl3
76.84 CDCl3
70.80
70.64
64.49
63.60
63.34
50.87
41.96
41.82
38.67
35.27
29.71
29.67
25.35
22.54
22.43
22.39
22.36
18.90
18.75
O
Me
N
H
Me
O
CO2
HN
O
CO2H
4l
Solvent used: CDCl3
500 MHz
2500
2000
1500
1000
500
0
f1 (ppm)

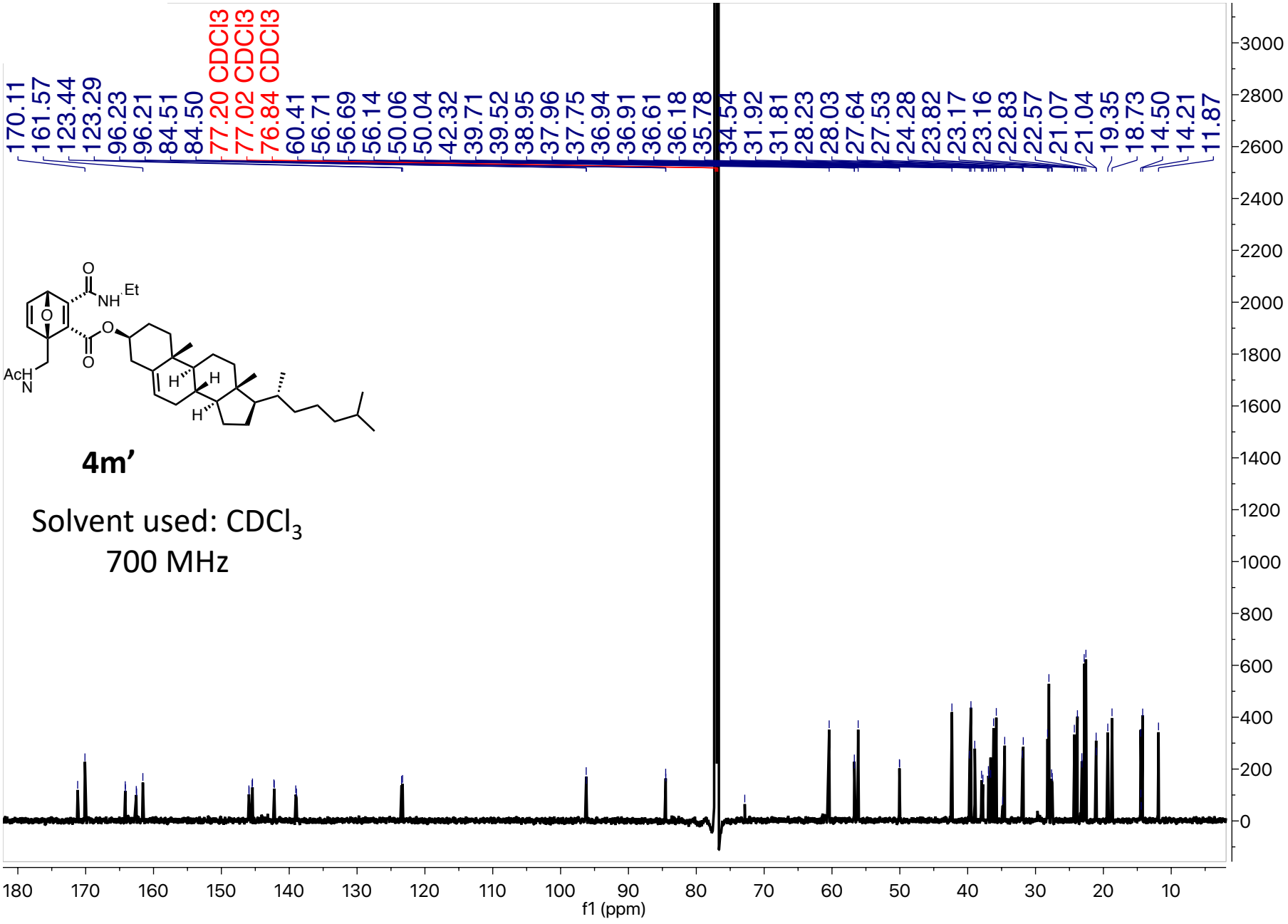

ANG3060.5fid
5.40 3.40 3.39 3.39 2.39 2.38 2.02 1.92 1.58 1.56 1.55 1.54 1.52 1.51 1.50 1.49 1.48 1.46 1.37 1.35 1.27 1.27 1.22 1.20 1.19 1.18 1.17 1.16 1.15 1.14 1.13 1.12 1.10 1.09 1.08 1.04 1.03 1.02 1.00 0.99 0.95 0.94 0.93 0.89 0.89 0.88 0.87 0.70
O
NH
O
O
H
H
H
Solvent used: CDCl3
500 MHz
0.80 1.02 0.94 1.61 2.21 3.27 8.52 3.20 1.94 9.87 4.59 3.13 5.98 3.00
f1 (ppm)


151.67
150.62
138.82
123.36
77.22 CDCl3
77.03
76.96 CDCl3
76.71 CDCl3
73.98
71.76
56.60
56.07
49.91
42.25
39.63
39.46
37.66
36.78
36.48
36.12
35.73
35.01
31.83
31.75
28.16
27.96
27.43
24.22
23.77
22.77
22.51
20.96
19.19
18.66
14.34
11.80
O
NH
O
O
H
H
H
Solvent used: CDCl3
500 MHz
1100
1000
900
800
700
600
500
400
300
200
100
0
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.26 CDCl3
7.13 7.03 7.02 5.62 5.61 5.61 4.43 4.43 4.13 4.12 3.35 2.01 1.58 1.52 1.51 1.50 1.49 1.33 1.33 1.32 1.25 1.25 1.25 1.21 1.21 1.20 1.20 1.19 1.19 1.17 1.15 1.15 1.14 1.14 1.10 1.08 1.04 1.00 0.92 0.92 0.91 0.91 0.87 0.86 0.86 0.85 0.06
1.00 0.56 1.10 1.02 1.20 0.65 0.61 1.01 1.55 1.53 0.96 1.94 2.59 1.08 1.98 0.94 1.62 3.15 3.06 1.92 2.17 4.60 5.72 1.83 2.09 2.50 3.16 2.26 2.27 3.41 2.64 5.34 0.73
f1 (ppm)
Solvent used: CDCl3
700 MHz
4m’
AcHN
NH
Et


170.12
163.80
162.22
144.09
143.17
142.24
123.53
123.42
110.48
107.51
97.34
97.32
83.63
77.20 CDCl3
77.02 CDCl3
76.83 CDCl3
76.16
56.67
56.13
50.02
42.32
39.69
39.52
38.85
38.03
37.94
36.89
36.59
36.18
35.78
34.59
31.92
31.90
31.82
28.22
28.03
27.79
27.68
24.28
23.83
23.40
22.83
22.57
21.04
19.34
18.73
14.43
11.87
Solvent used: CDCl3
700 MHz
4m'
AcHN
NH
Et
f1 (ppm)


AFG
2nd
7.26 CDCl3
2.00 HDO
6.93 6.93 6.92 6.92 5.73 5.73 4.12 4.11 2.04 2.00 1.98 1.51 1.32 1.26 1.25 1.25 1.24 1.24 1.20 1.19 1.19 1.18 1.18 1.17 1.17 1.16 1.16 1.16 1.14 1.14 1.13 1.09 1.08 1.05 1.05 1.04 0.99 0.91 0.91 0.91 0.90 0.86 0.86 0.85 0.85 0.67
Solvent used: CDCl3
700 MHz
4m
0.59 1.36 0.55 1.00 0.80 0.75 0.79 1.60 1.69 0.56 1.03 4.56 8.58 2.32 2.57 2.23 5.93 4.20 3.88 1.72 0.23
f1 (ppm)


170.11
161.57
123.44
123.29
96.23
96.21
84.51
84.50
77.20 CDCl3
77.02 CDCl3
76.84 CDCl3
60.41
56.71
56.69
56.14
50.06
50.04
42.32
39.71
39.52
38.95
37.96
37.75
36.94
36.91
36.61
36.18
35.78
34.54
31.92
31.81
28.23
28.03
27.64
27.53
24.28
23.82
23.17
23.16
22.83
22.57
21.07
21.04
19.35
18.73
14.50
14.21
11.87
O
NH
Et
O
O
O
AcH
N
H
H
H
4m’
Solvent used: CDCl3
700 MHz
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)