Supporting Information for

Synthesis and biological evaluation of dual action *cyclo*-RGD/SMAC mimetic conjugates targeting $\alpha_v\beta_3/\alpha_v\beta_5$ integrins and IAP proteins

M. Mingozzi,[a] L. Manzoni,[b] D. Arosio,[b] A. Dal Corso,[a] M. Manzotti,[a] F. Innamorati,[a] L. Pignataro,[a] D. Lecis,[c] D. Delia,[c] P. Seneci,[*,a] and C. Gennari[*,a]

[a] *Università degli Studi di Milano, Dipartimento di Chimica, Via Golgi 19, I-20133, Milan, Italy. Email: PS, pierfausto.seneci@unimi.it; CG, cesare.gennari@unimi.it; fax: +39-02-50314072; tel: PS, +39-02-50314060; CG, +39-02-50314091.*
[b] *Istituto di Scienze e Tecnologie Molecolari, Consiglio Nazionale delle Ricerche, Via Golgi 19, I-20133 Milano, Italy.*
[c] *Fondazione IRCCS Istituto Nazionale dei Tumori, Dipartimento di Oncologia Sperimentale e Medicina Molecolare, Via Amadeo 42, I-20133 Milan, Italy.*

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Materials and Methods

Reactions requiring anhydrous conditions were carried out in flame-dried glassware, with magnetic stirring and under a nitrogen atmosphere. Commercially available reagents were used as received. Anhydrous solvents were purchased from commercial sources and withdrawn from the container by syringe, under a slight positive pressure of nitrogen. SMAC amine **16**[1] and *cyclo*[DKP-RGD]benzylamine **20**[2] were prepared according to literature procedures. Their analytical data were in agreement with those already published. Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution or ninhydrin. Flash column chromatography was performed according to the method of Still and co-workers using Chromagel 60 ACC (40-63 μm) silica gel.[3] Proton NMR spectra were recorded on a spectrometer operating at 400.16 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet of doublet. Carbon NMR spectra were recorded on a spectrometer operating at 100.63 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard. HPLC purifications were performed on a Dionex Ultimate 3000 instrument equipped with a Dionex RS Variable Wavelenght Detector (column: Atlantis® Prep T3 OBD™ 5 μm 19 x 100 mm). High resolution mass spectra (HRMS) were performed on a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics) – 4.7 T Magnet (Magnex) equipped with ESI source, available at CIGA (Centro Interdipartimentale Grandi Apparecchiature) c/o Università degli Studi di Milano. Low resolution mass spectra (MS) were recorded on a Waters Acquity™ UPLC-MS instrument (ESI source).

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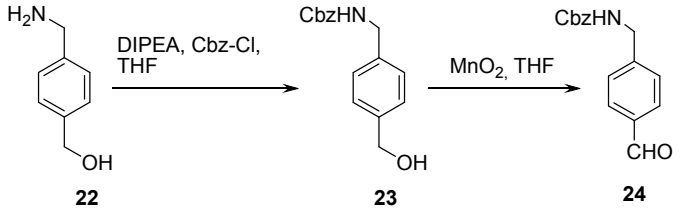
[1] P. Seneci, A. Bianchi, C. Battaglia, L. Belvisi, M. Bolognesi, A. Caprini, F. Cossu, E. De Franco, M. De Matteo, D. Delia, C. Drago, A. Khaled, D. Lecis, L. Manzoni, M. Marizzoni, E. Mastrangelo, M. Milani, I. Motto, D. Potenza, V. Rizzo, F. Servida, E. Turlizzi, M. Varrone, F. Vasile and C. Scolastico, *Bioorg. Med. Chem*., 2009, **17,** 5834.

[2] R. Colombo, M. Mingozzi, L. Belvisi, D. Arosio, U. Piarulli, N. Carenini, P. Perego, N. Zaffaroni, M. De Cesare, V. Castiglioni, E. Scanziani and C. Gennari, *J. Med. Chem*., 2012, **55**, 10460.

[3] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

Synthesis of cyclic RGD ligand-SMAC mimetic conjugate 12



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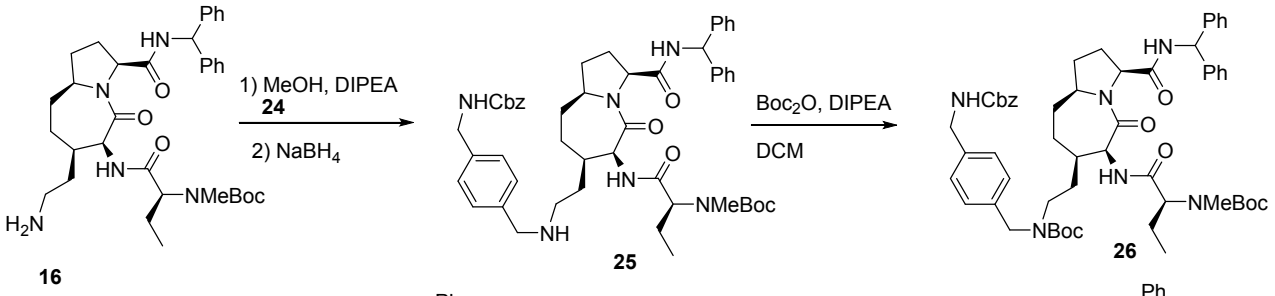

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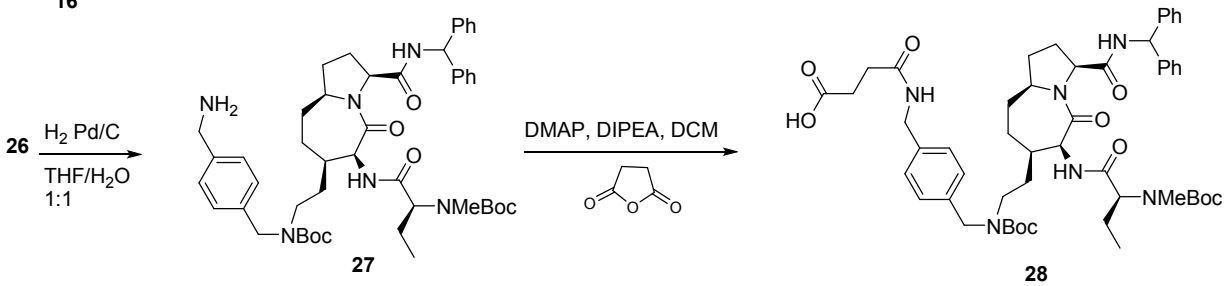

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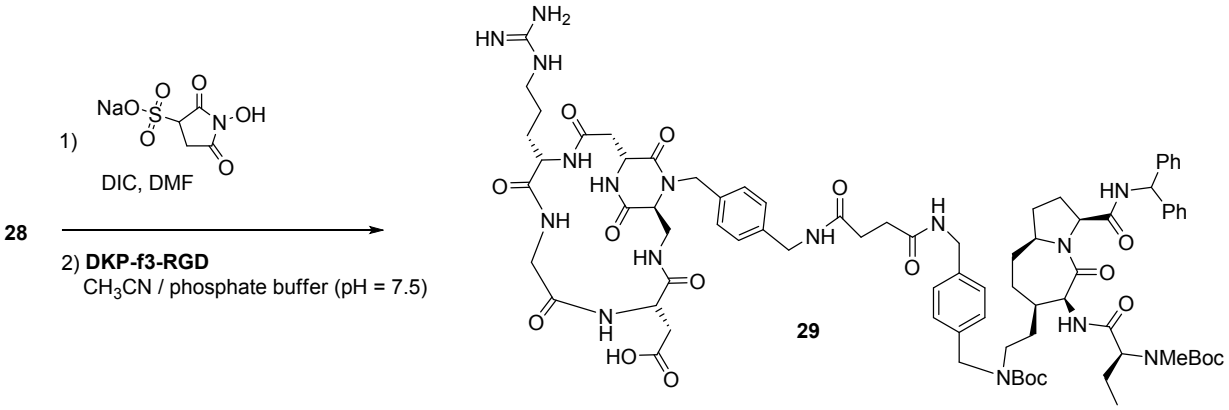

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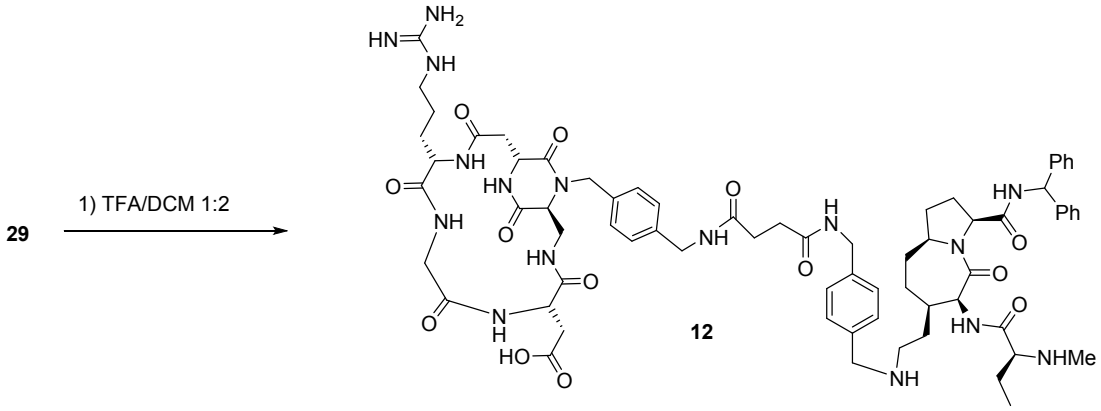
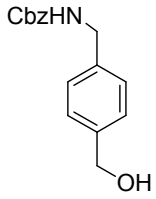


12

Scheme S1. General procedure for the synthesis of compound **12**.

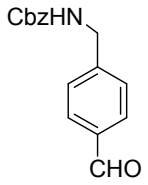
(4-(Benzyloxycarbonylamino)phenyl)methanol **23**.



(4-(aminomethyl)phenyl)methanol (800 mg, 5.83 mmol, 1 eq.) was dissolved in 60 mL of dry THF, under N_2 atmosphere. The mixture was cooled to 0°C and DIPEA (2 mL, 11.66 mmol, 2 eq.) was added dropwise. The resulting mixture was left stirring for 5 minutes at 0°C, then benzyl chloroformate (1.66 mL, 11.66 mmol, 2 eq.) was added dropwise. The reaction was left stirring at 0°C for 45 minutes, then it was allowed to reach room temperature. The mixture was left stirring at room temperature overnight. DIPEA.HCl was then removed by filtration over celite, and the filtrate was washed with AcOEt. The organic phase was concentrated at reduced pressure, the residue was redissolved in AcOEt and washed with a 1M solution of $KHSO_4$. The resulting organic phase was dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product was recrystallized from cold CH_2Cl_2 and the solid was washed with cold CH_2Cl_2, affording pure **23** as a white solid that was used without further purification (1.13 g, 4.14 mmol, 71%).

R_f = 0.5 (Hex/AcOEt, 3:7); ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 – 7.18 (m, 9H), 5.11 (s, 2H), 4.59 (s, 2H), 4.30 (s, 2H).

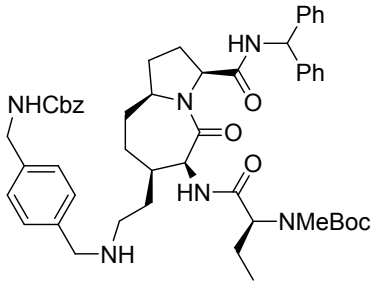
4-(Benzyloxycarbonylamino)benzaldehyde **24**.



Compound **23** (500 mg, 1.84 mmol, 1 eq.) was dissolved in 45 mL of dry THF, under N_2 atmosphere. MnO_2 (1.76 g, 20.27 mmol, 11 eq.) was added at room temperature and the reaction was left stirring overnight. MnO_2 was then filtered over celite, washing the filter with THF. The solvent was then evaporated affording pure **24** as a white solid that was used without further purification (480 mg, 1.78 mmol, 97%).

R_f = 0.55 (Hex/AcOEt, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.83 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.36 (m, 5H), 5.30 (br, 1H), 5.14 (s, 2H), 4.46 (d, J = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 192.2, 157.0, 146.3, 137.1, 136.0, 130.2, 128.9, 128.5, 128.3, 128.0, 67.2, 45.0.

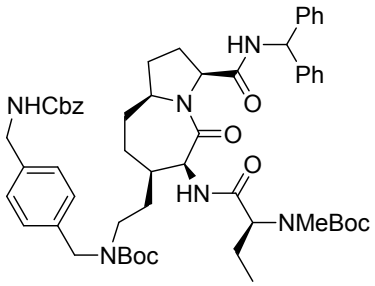
tert-butyl ((S)-1-(((3S,6S,7R,9aS)-3-(benzhydrylcarbamoyl)-7-(2-((4-((((benzyloxy)carbonyl)amino)methyl)benzyl)amino)ethyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)amino)-1-oxobutan-2-yl)(methyl)carbamate **25**.



A solution of compound **16** (20.6 mg, 0.030 mmol, 1.05 eq.) and dry DIPEA (7.42 µL, 0.043 mmol, 1.5 eq.) in dry MeOH (0.2 mL) was stirred into a flask containing compound **24** (7.8 mg, 0.029 mmol, 1 eq.) under nitrogen atmosphere. The mixture was left stirring at room temperature for 5 hours. $NaBH_4$ (2.2 mg, 0.058 mmol, 2 eq.) was then added stepwise (5 additions within 3 minutes), and the resulting mixture was reacted at room temperature for 30 minutes. The mixture was then concentrated at reduced pressure and 5 mL of a saturated solution of $NaHCO_3$ were added. The mixture was then extracted with AcOEt (7 ml, three times). The organic phase was dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 9:1 as eluant) to afford pure **25** as a white foam (21 mg, 0.024 mmol, 83% yield).

R_f = 0.53 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.99 (br s, 1H), 7.45 – 7.10 (m, 19H), 7.10 – 6.93 (m, 1H), 6.14 (d, J = 8.4 Hz, 1H), 5.41 (s, 1H), 5.10 (s, 2H), 4.68 (d, J = 6.8 Hz, 1H), 4.52 (t, J = 8.2 Hz, 1H), 4.43 (dd, J = 9.6, 5.8 Hz, 1H), 4.32 (d, J = 6.0 Hz, 2H), 3.86 (m, 1H), 3.78 (s, 2H), 2.78 (br s, 3H), 2.67 (br s, 1H), 2.48 (s, 1H), 2.35 (s, 1H), 2.28 – 2.14 (m, 1H), 1.99 – 1.57 (m, 7H), 1.56 – 1.30 (m, 12H), 1.14 (s, 1H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 172.9, 171.4, 171.0, 170.2, 156.7, 142.7, 142.0, 138.3, 137.9, 137.3, 129.0, 128.9, 128.8, 128.3, 128.3, 127.8, 127.7, 127.6, 127.5, 127.4, 80.5, 66.9, 61.5, 61.1, 60.6, 59.0, 57.2, 55.2, 53.6, 47.3, 45.0, 38.4, 35.0, 34.0, 33.8, 31.9, 30.9, 28.5, 26.1, 21.7, 10.7; MS (ESI) *m/z* calcd for $[C_{51}H_{65}N_6O_7]^+$: 873.49 $[M+H]^+$; found: 873.39.

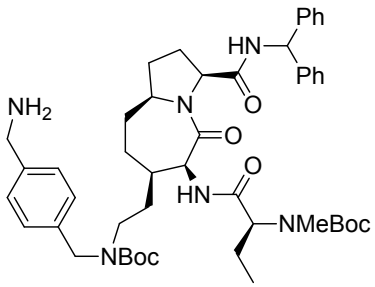
tert-butyl ((S)-1-(((3S,6S,7R,9aS)-3-(benzhydrylcarbamoyl)-7-(2-((4-((((benzyloxy)carbonyl)amino)methyl)benzyl)(tert-butoxycarbonyl)amino)ethyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)amino)-1-oxobutan-2-yl)(methyl)carbamate **26**.



A solution of compound **25** (21 mg, 0.024 mmol, 1 eq.) and dry DIPEA (8.2 µL, 0.048 mmol, 2 eq.) in dry CH_2Cl_2 (0.15 mL) was stirred in an ice bath under nitrogen atmosphere. A solution of Boc_2O (7.9 mg, 0.036 mmol, 1.5 eq.) in dry CH_2Cl_2 (0.1 mL) was then added. The resulting mixture was left stirring at 0°C for 1 hour under nitrogen atmosphere, then overnight at room temperature. As the reaction was not completed, additional Boc_2O (2.1 mg, 0.01 mmol, 0.4 eq.) was dissolved in dry CH_2Cl_2 (80 µl) and added to the mixture, which was reacted at room temperature for 4 hours. Then the solvent was removed at reduced pressure. The crude product filtered through a silica plug (CH_2Cl_2/MeOH 95:5 as eluant) to afford the desired product **26** as a white foam (23.2 mg, 0.024 mmol, 100% yield).

R_f = 0.62 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.18 (d, J = 8.4 Hz, 1H), 7.41 – 7.05 (m, 20H), 6.83 (t, J = 5.6 Hz, 1H), 6.19 (d, J = 8.7 Hz, 1H), 5.08 (s, 2H), 4.69 (d, J = 7.4 Hz, 1H), 4.63 – 4.24 (m, 6H), 4.05 – 3.92 (m, 1H), 3.33 – 3.18 (m, 1H), 3.17 – 2.88 (m, 1H), 2.78 (s, 3H), 2.33 – 2.10 (m, 2H), 2.02 – 1.57 (m, 7H), 1.56 – 1.21 (m, 22H), 0.87 (t, J = 7.4 Hz, 3H); MS (ESI) *m/z* calcd for $[C_{56}H_{73}N_6O_9]^+$: 973.54 $[M+H]^+$; found: 973.33.

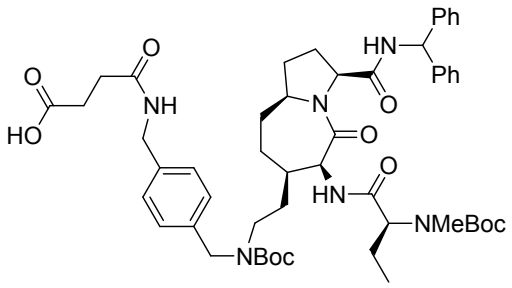
tert-butyl ((S)-1-(((3S,6S,7R,9aS)-7-(2-((4-(aminomethyl)benzyl)(tert-butoxycarbonyl)amino)ethyl)-3-(benzhydrylcarbamoyl)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-6-yl)amino)-1-oxobutan-2-yl)(methyl)carbamate **27**.



Compound **26** (18.4 mg, 0.019 mmol, 1 eq.) was dissolved in a mixture of THF/H_2O 1:1 (6.4 mL), and 10%Pd/C (2.01 mg, 0.002 mmol, 0.1 eq.) was added. The reaction mixture was subjected to three vacuum/hydrogen cycles to strip away oxygen, and then left stirring overnight at room temperature under 1 bar of hydrogen atmosphere. Hydrogen was then removed, the mixture was filtered through Celite, and the obtained cake was washed thoroughly with THF/H_2O 1:1. The filtrate was concentrated and dried to give the crude product **27** as white foam (17 mg, 0.019 mmol, 100% yield) that was used without further purification.

R_f = 0.23 (CH_2Cl_2/MeOH, 9:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.20 (d, J = 8.4 Hz, 1H), 7.41 – 7.04 (m, 14H), 6.19 (d, J = 8.7 Hz, 1H), 4.69 (d, J = 7.0 Hz, 1H), 4.64 – 4.25 (m, 5H), 4.06 – 3.93 (m, 1H), 3.78 (s, 1H), 3.29 – 3.19 (m, 1H), 3.19 – 2.91 (m, 2H), 2.79 (s, 3H), 2.28 – 2.20 (m, 1H), 2.21 – 2.11 (m, 1H), 2.02 – 1.31 (m, 29H), 0.88 (t, J = 7.4 Hz, 3H); MS (ESI) *m/z* calcd for $[C_{48}H_{67}N_6O_7]^+$: 839.51 $[M+H]^+$; found: 839.12.

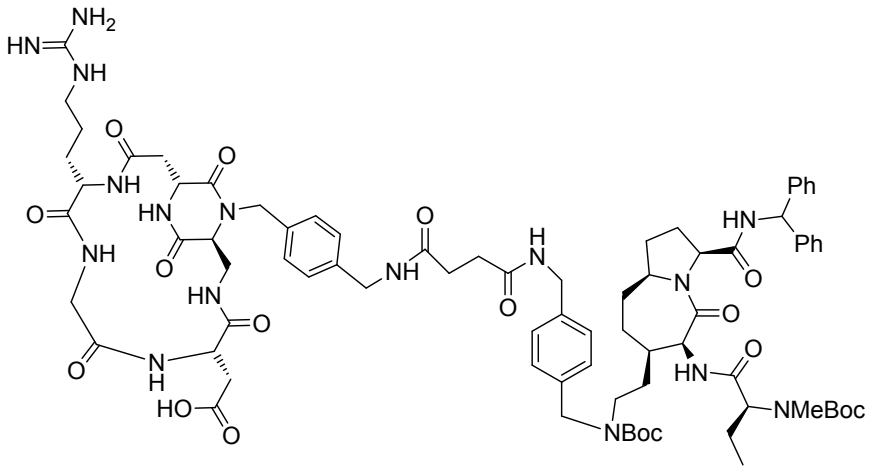
4-((4-(((2-((3S,6S,7R,9aS)-3-(benzhydrylcarbamoyl)-6-((S)-2-((tert-butoxycarbonyl)(methyl)amino)butanamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-7-yl)ethyl)(tert-butoxycarbonyl)amino)methyl)benzyl)amino)-4-oxobutanoic acid **28**.



Compound **27** (17 mg, 0.020 mmol, 1 eq.) was dissolved in dry CH_2Cl_2 (0.15 mL). Then, dry DIPEA (3.4 µL, 0.020 mmol, 1 eq.) was added and the mixture was stirred in an ice bath. DMAP (1.22 mg, 0.010 mmol, 0.5 eq.) and succinic anhydride (3.04 mg, 0.030 mmol, 1.5 eq.) were added. The reaction was then stirred at room temperature under nitrogen atmosphere for 2 hours. CH_2Cl_2 (15 mlL was then added, and the solution was washed with a $KHSO_4$ 1M solution (2 x 7 mL). The aqueous phase was extracted with CH_2Cl_2 (7 mL), then the combined organic phases were dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product was purified by reverse phase HPLC (gradient: from 70% H_2O + 0.2% HCOOH/30% acetonitrile + 0.2% HCOOH to 100% acetonitrile + 0.2% HCOOH in 10 minutes) to give the desired compound **28** as a white foam (17.6 mg, 0.0198 mmol, 99% yield).

t_R = 8.7 min; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.22 (d, J = 7.6 Hz, 1H), 7.65 (s, 1H), 7.39 – 7.01 (m, 15H), 6.19 (d, J = 8.6 Hz, 1H), 4.69 (d, J = 7.1 Hz, 1H), 4.64 – 4.23 (m, 6H), 4.07 – 3.90 (m, 1H), 3.32 – 2.89 (m, 2H), 2.80 (s, 3H), 2.60 (dd, J = 10.3, 4.1 Hz, 2H), 2.51 (dd, J = 10.2, 3.9 Hz, 2H), 2.31 – 2.19 (m, 1H), 2.19 – 2.09 (m, 1H), 2.07 – 1.55 (m, 9H), 1.56 – 1.36 (m, 20H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 174.2, 172.2, 170.9, 170.8, 156.3, 155.7, 143.5, 143.3, 139.2, 138.6, 129.4, 129.3, 128.6, 128.1, 128.0, 128.0, 79.7, 62.1, 60.6, 59.3, 57.3, 55.8, 50.7, 49.7, 43.4, 38.5, 34.6, 33.9, 33.6, 33.5, 31.1, 28.6, 27.4, 22.2, 11.0; MS (ESI) *m/z* calcd for $[C_{52}H_{71}N_6O_{10}]^+$: 939.52 $[M+H]^+$; found: 939.45.

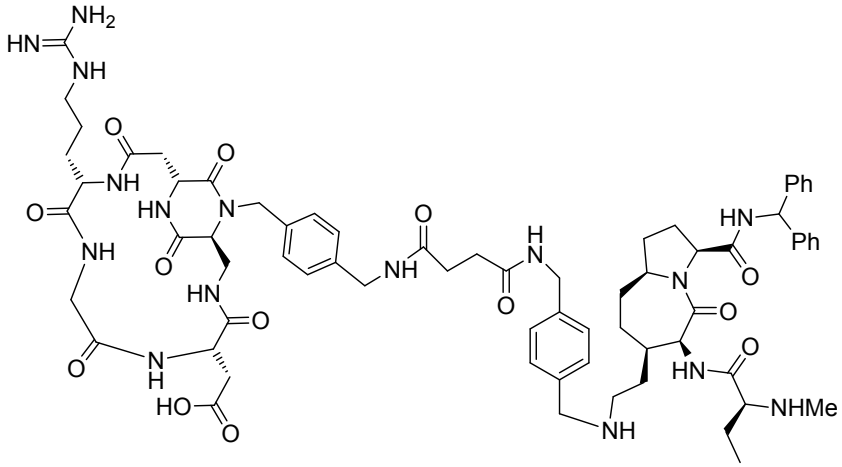
2-((1S,5S,11S,15R)-18-(4-((4-((4-(((2-((3S,6S,7R,9aS)-3-(benzhydrylcarbamoyl)-6-((S)-2-((tert-butoxycarbonyl)(methyl)amino)butanamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-7-yl)ethyl)(tert-butoxycarbonyl)amino)methyl)benzyl)amino)-4-oxobutanamido)methyl)benzyl)-11-(3-guanidinopropyl)-4,7,10,13,17,19-hexaoxo-3,6,9,12,16,18-hexaazabicyclo[13.2.2]nonadecan-5-yl)acetic acid **29**.



Compound **28** (20 mg, 0.021 mmol, 1 eq.) was dissolved under nitrogen atmosphere in a flame dried Schlenk tube in dry DMF (2 mL). Then *N*-hydroxysulfosuccinimide (5.7 mg, 0.026 mmol, 1.24 eq.) and *N*,*N*'-diisopropylcarbodiimide (4.94 µL, 0.032 mmol, 1.52 eq.) were added in a single portion at room temperature. The solution was stirred overnight, then DMF was removed under vacuum in the Schlenk tube. The resulting residue was then dissolved, in the same Schlenk tube, in CH_3CN (2 mL). A solution of compound **20** (11.0 mg, 0.0128 mmol, 0.67 eq.) dissolved in phosphate buffer solution (1 mL) was added, and the pH was adjusted to 7.5 with 0.2M NaOH. The resulting mixture was stirred at 0 °C overnight. The reaction mixture was then concentrated at reduced pressure and the crude residue was purified by HPLC (gradient: from 90% H_2O + 0.2% HCOOH / 10% acetonitrile + 0.2% HCOOH to 30% H_2O + 0.2% HCOOH / 70% acetonitrile + 0.2% HCOOH in 15 minutes). The desired compound was then freeze dried to give pure compound **29** as a white foam (9.7 mg, 0.010 mmol, 49% yield).

t_R = 12.1 min; ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1H), 7.38 – 7.12 (m, 18H), 6.13 (s, 1H), 5.15 (d, J = 14.9 Hz, 1H), 5.05 (dd, J = 10.2, 2.1 Hz, 1H), 4.69 – 4.59 (m, 2H), 4.58 – 4.23 (m, 10H), 4.11 – 4.01 (m, 2H), 3.97 (dd, J = 14.6, 7.3 Hz, 1H), 3.85 (d, J = 5.7 Hz, 1H), 3.52 (d, J = 17.1 Hz, 1H), 3.42 (dd, J = 14.3, 5.7 Hz, 1H), 3.28 – 2.92 (m, 4H), 2.88 – 2.72 (m, 5H), 2.60 – 2.51 (m, 4H), 2.45 (dd, J = 16.7, 5.5 Hz, 1H), 2.29 – 2.17 (m, 1H), 2.11 – 1.52 (m, 14H), 1.52 – 1.24 (m, 19H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 178.0, 174.5, 174.4, 173.8, 173.6, 173.5, 173.0, 172.6, 172.2, 171.5, 171.2, 170.6, 158.7, 143.1, 140.2, 140.0, 139.1, 138.7, 135.9, 129.7, 129.5, 129.3, 128.9, 128.7, 128.6, 128.5, 128.3, 81.7, 81.4, 62.8, 62.0, 60.8, 59.7, 58.3, 56.8, 53.4, 53.2, 51.4, 50.8, 48.1, 46.0, 43.9, 43.8, 42.2, 40.9, 40.1, 37.8, 37.2, 34.1, 33.7, 33.4, 32.3, 31.1, 30.9, 28.8, 27.8, 26.2, 23.0, 11.1; MS (ESI) *m/z* calcd for $[C_{79}H_{107}N_{16}O_{17}]^+$: 1551.80 $[M+H]^+$; found: 1552.30.

2-((1S,5S,11S,15R)-18-(4-((4-((4-(((2-((3S,6S,7R,9aS)-3-(benzhydrylcarbamoyl)-6-((S)-2-(methylamino)butanamido)-5-oxooctahydro-1H-pyrrolo[1,2-a]azepin-7-yl)ethyl)amino)methyl)benzyl)amino)-4-oxobutanamido)methyl)benzyl)-11-(3-guanidinopropyl)-4,7,10,13,17,19-hexaoxo-3,6,9,12,16,18-hexaazabicyclo[13.2.2]nonadecan-5-yl)acetic acid **12**.



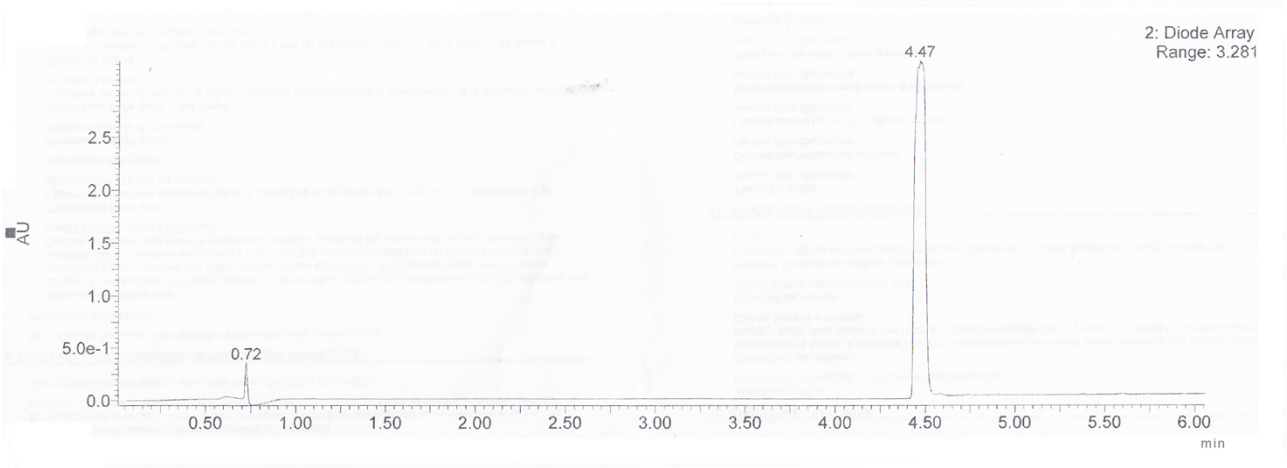
Compound **29** (9 mg, 0.0058 mmol, 1 eq.) was dissolved in CH_2Cl_2 (100 µl) and TFA (66 µl, 0.87 mmol, 150 eq.) was added at room temperature. The reaction was stirred at room temperature for 50 minutes, then the volatiles were removed at reduced pressure and the crude product was purified by HPLC (gradient: from 90% H_2O + 0.1% CF_3COOH / 10% acetonitrile + 0.1% CF_3COOH to 30% H_2O + 0.1% CF_3COOH / 70% acetonitrile + 0.1% CF_3COOH in 14 minutes). The desired compound was then freeze dried to give pure compound **12** (as tris-trifluoroacetate salt) as a white foam (9.8 mg, 0.0058 mmol, 100% yield).

t_R = 8.3 min;^{1}H NMR (400 MHz, CD_3CN) δ 7.95 (d, J = 8.1 Hz, 1H), 7.85 (dd, J = 8.2, 3.3 Hz, 1H), 7.40 – 7.14 (m, 18H), 6.05 (d, J = 8.1 Hz, 1H), 4.96 (d, J = 15.2 Hz, 1H), 4.73 (t, J = 6.7 Hz, 1H), 4.58 – 4.42 (m, 3H), 4.36 – 4.20 (m, 5H), 4.14 – 3.80 (m, 7H), 3.45 (d, J = 16.9 Hz, 1H), 3.33 (dd, J = 14.8, 6.3 Hz, 1H), 3.19 – 3.06 (m, 2H), 3.06 – 2.94 (m, 1H), 2.95 – 2.80 (m, 1H, overlapping with solvent signal), 2.80 – 2.64 (m, 2H), 2.63 – 2.43 (m, 9H), 2.25 – 2.13 (m, 1H), 2.10 – 1.40 (m, 15H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, CD_3CN) δ 174.0, 173.9, 173.2, 173.1, 172.2, 171.2, 170.8, 170.6, 170.0, 168.6, 158.0, 143.1, 142.9, 141.5, 140.0, 135.5, 131.2, 130.7, 129.7, 129.7, 129.1, 128.8, 128.8, 128.4, 128.3, 128.1, 63.2, 62.5, 60.5, 59.2, 58.0, 56.5, 54.9, 52.9, 51.8, 50.1, 48.3, 46.3, 43.4, 43.3, 41.8, 39.9, 39.0, 37.3, 35.7, 33.7, 32.9, 32.5, 32.3, 32.0, 29.1, 28.6, 27.0, 26.0, 23.9, 9.2; MS (ESI) *m/z* calcd for $[C_{69}H_{91}N_{16}O_{13}]^+$: 1351.69 $[M+H]^+$; found: 1352.40; HRMS (ESI) *m/z* calcd for $[C_{69}H_{90}N_{16}O_{13}Na]^+$: 1373.67655 $[M+Na]^+$; found: 1373.67702.

HPLC traces of the final products (11, 12, 13)

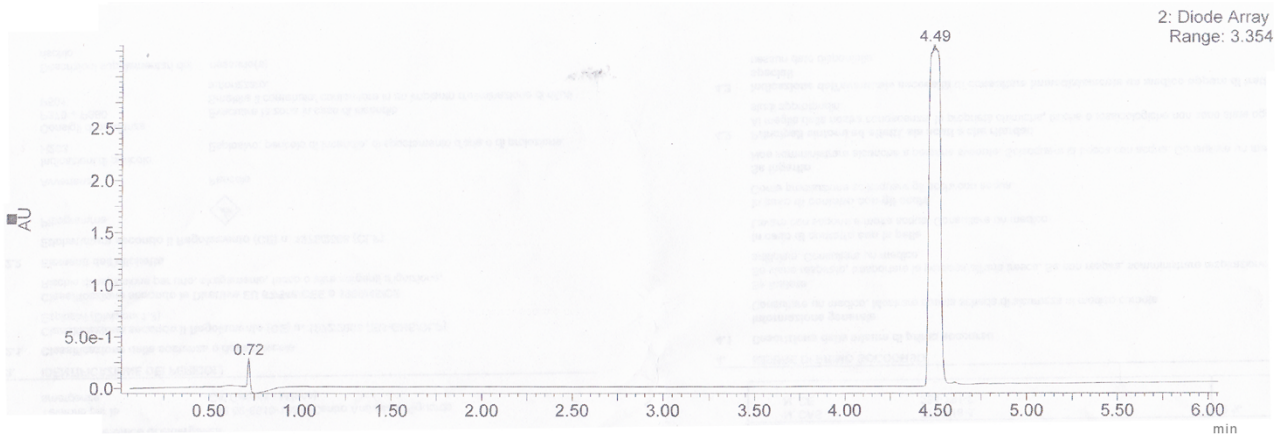
11

Gradient: 95% H_2O / 5% CH_3CN to 60% H_2O / 40% CH_3CN (column: Waters Acquity™ UPLC HSS T3 2.1 x 50mm; C_{18} 1.8µm)



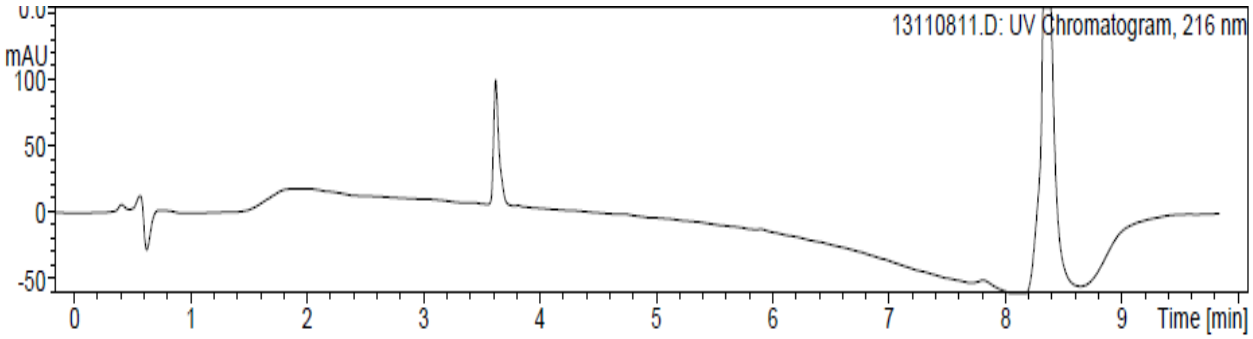
12

Gradient: 95% H_2O / 5% CH_3CN to 60% H_2O / 40% CH_3CN (column: Waters Acquity™ UPLC HSS T3 2.1 x 50mm; C_{18} 1.8µm)



13

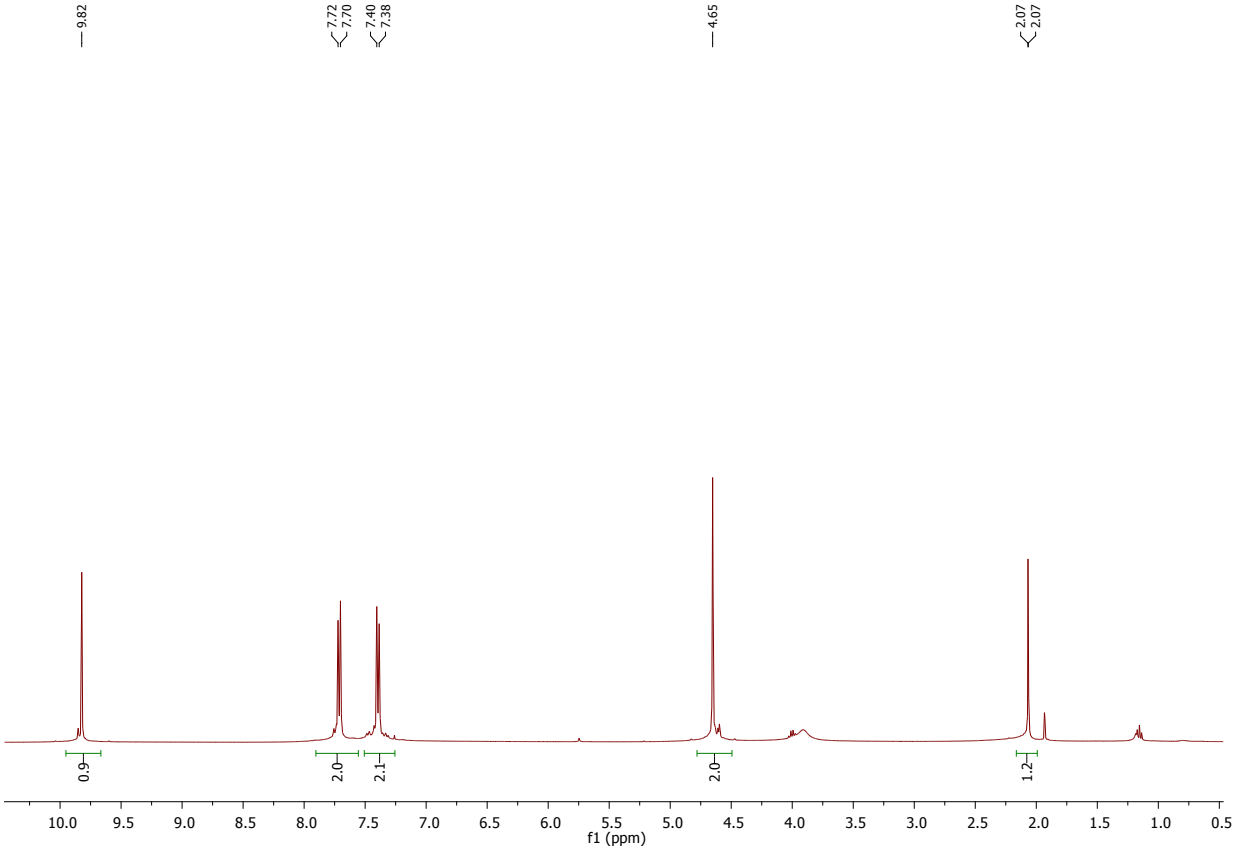
Gradient: from 90% H_2O + 0,05% TFA / 10% CH_3CN + 0,05% TFA to 10% H_2O + 0,05%TFA / 90% CH_3CN + 0,05% TFA in 6 minutes (column: Waters Atlantis 50 x 4.6mm; C_{18} 3µm).



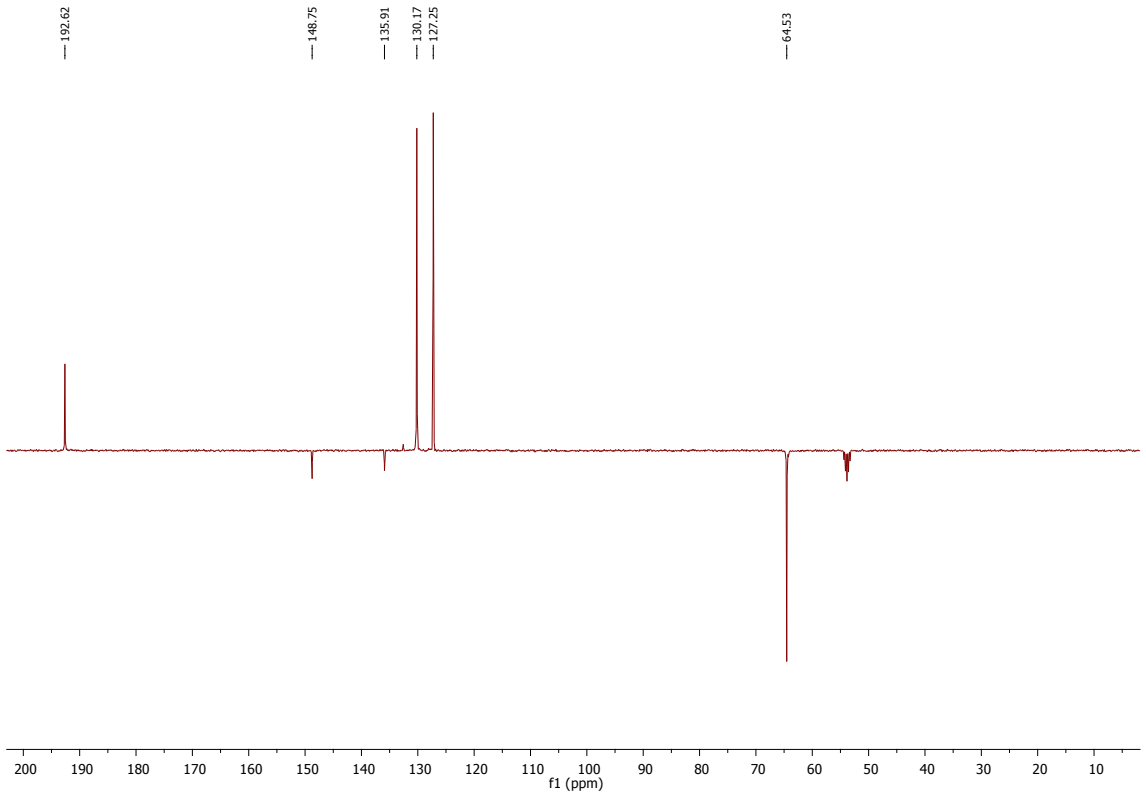
NMR traces of intermediates and final products (15, 17, 18, 19, 21, 11, 24, 25, 26, 27, 28, 29, 12, 32, 33, 34, 35, 37, 30, 41, 42, 43, 44, 46, 13)

15

^{1}H NMR (400 MHz, $CDCl_3$)

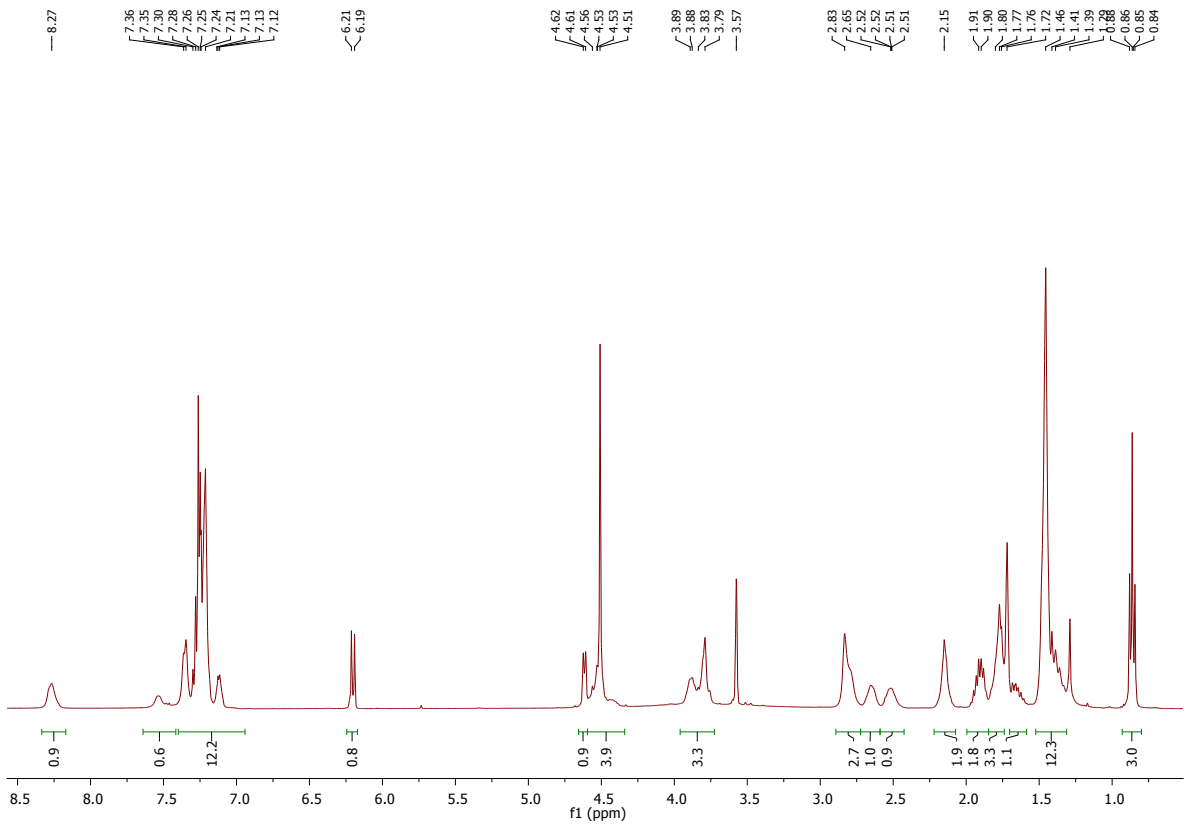


^{13}C NMR (101 MHz, CD_2Cl_2)

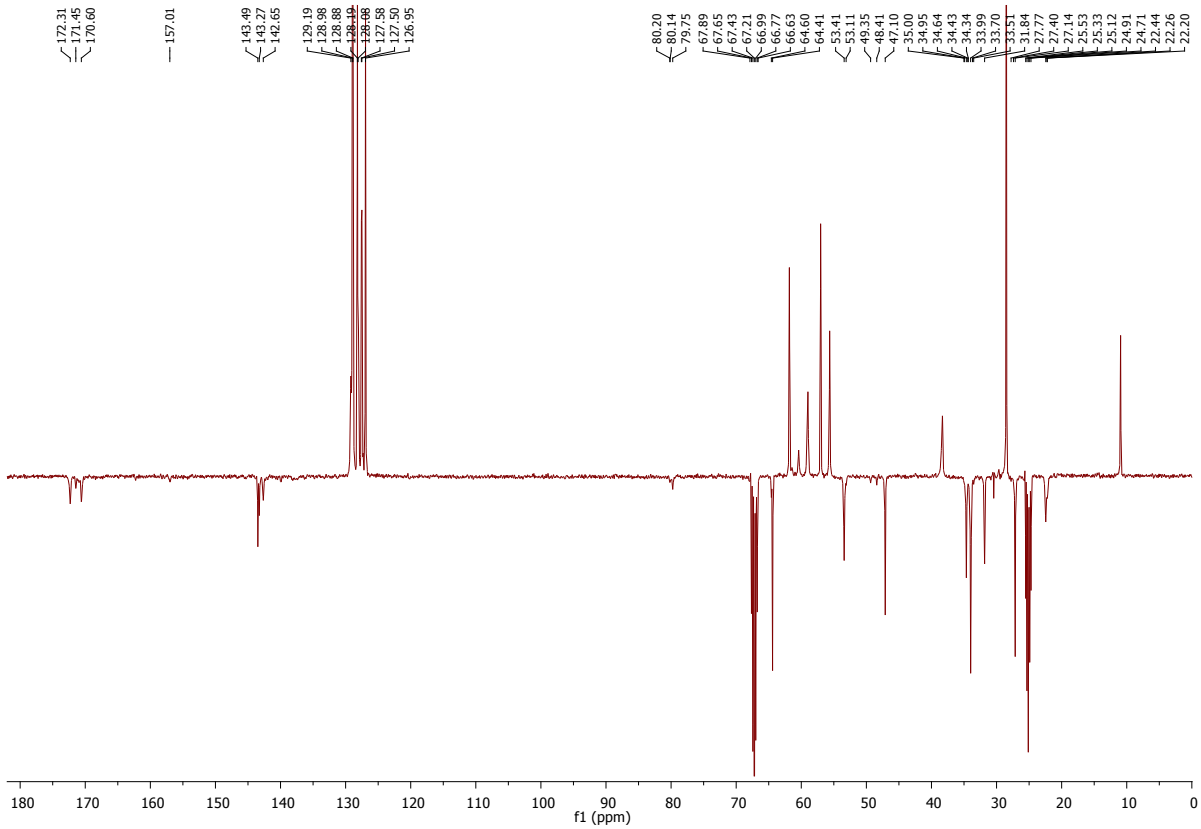


17

^{1}H NMR (400 MHz, THF-d_8)

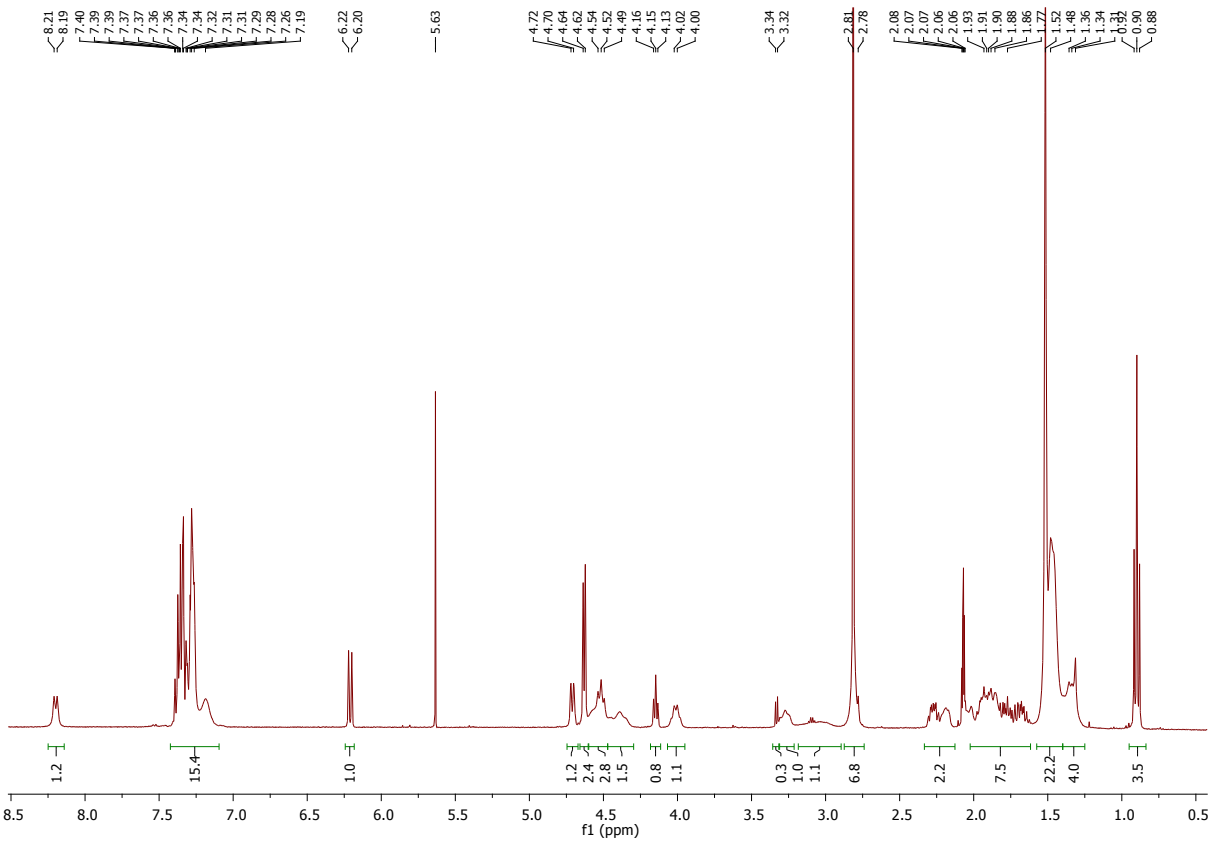


^{13}C NMR (101 MHz, THF-d_8)



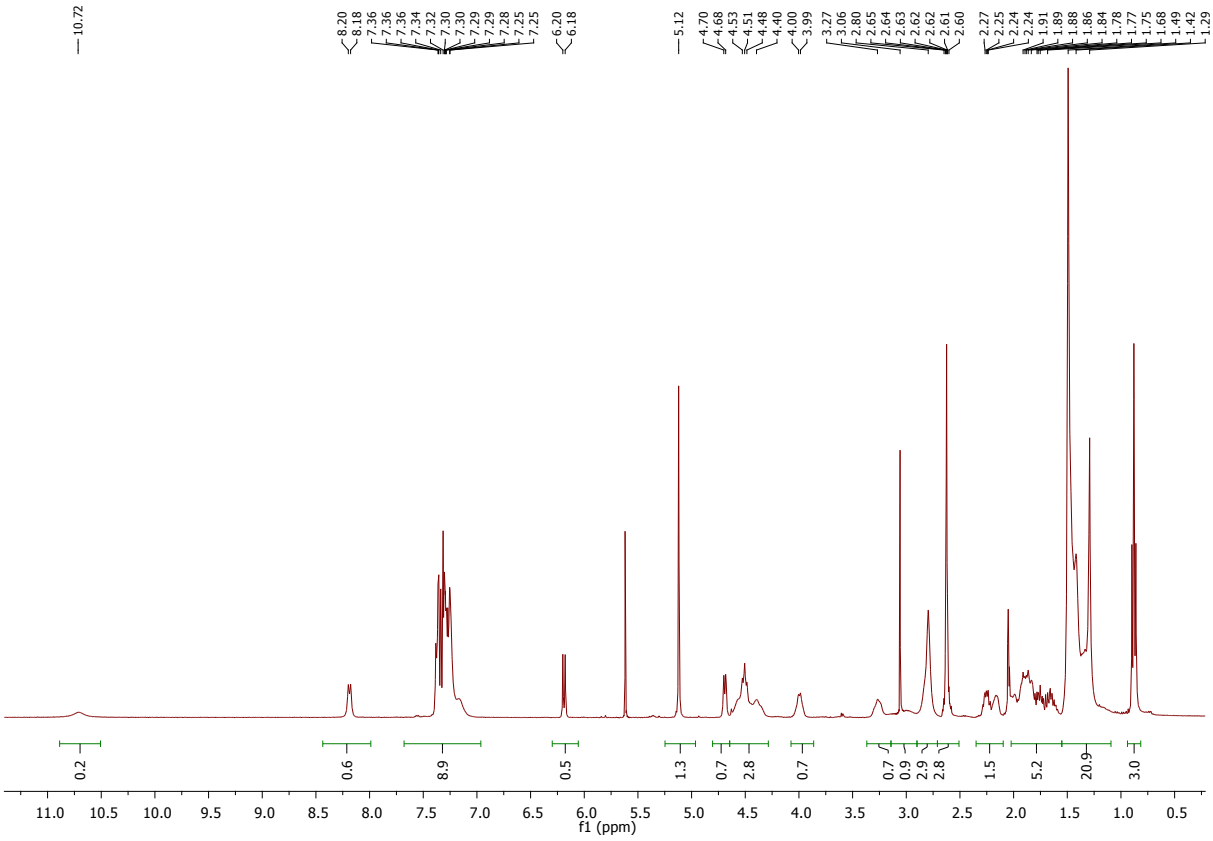
18

^{1}H NMR (400 MHz, acetone-d_6)

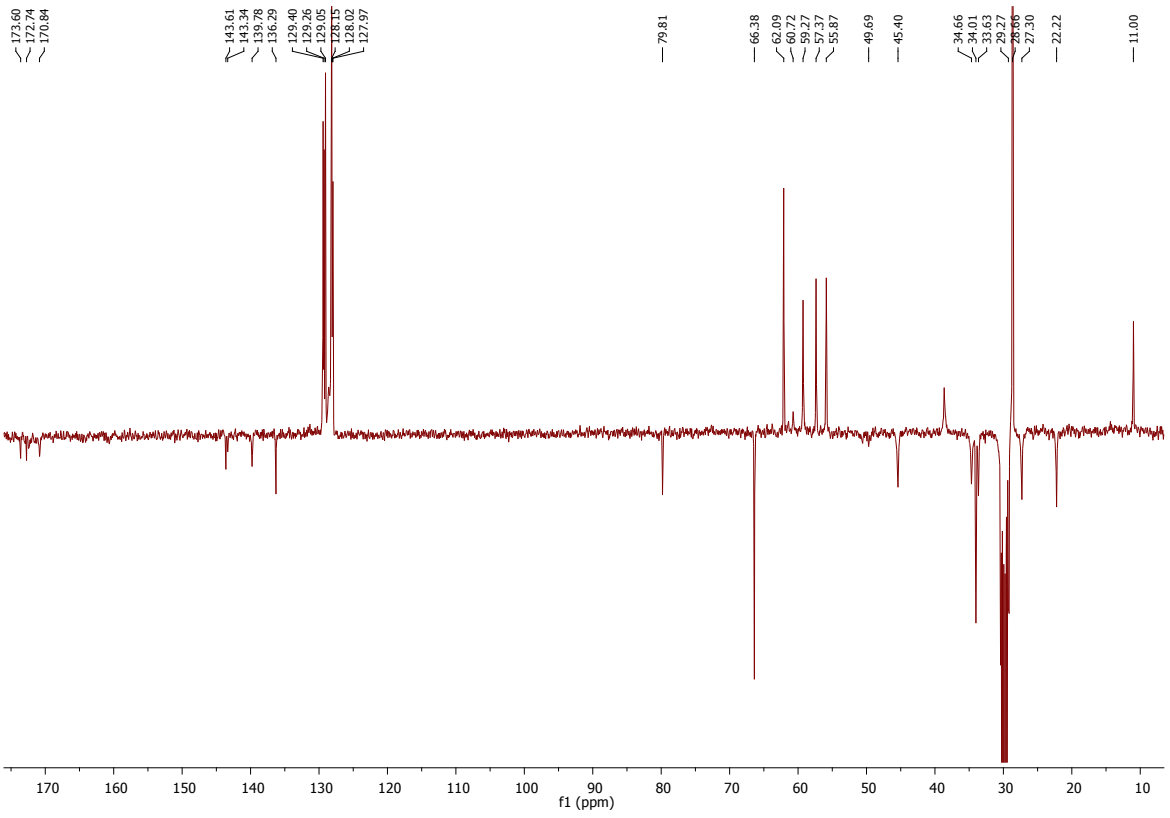


19

^{1}H NMR (400 MHz, acetone-d_6)

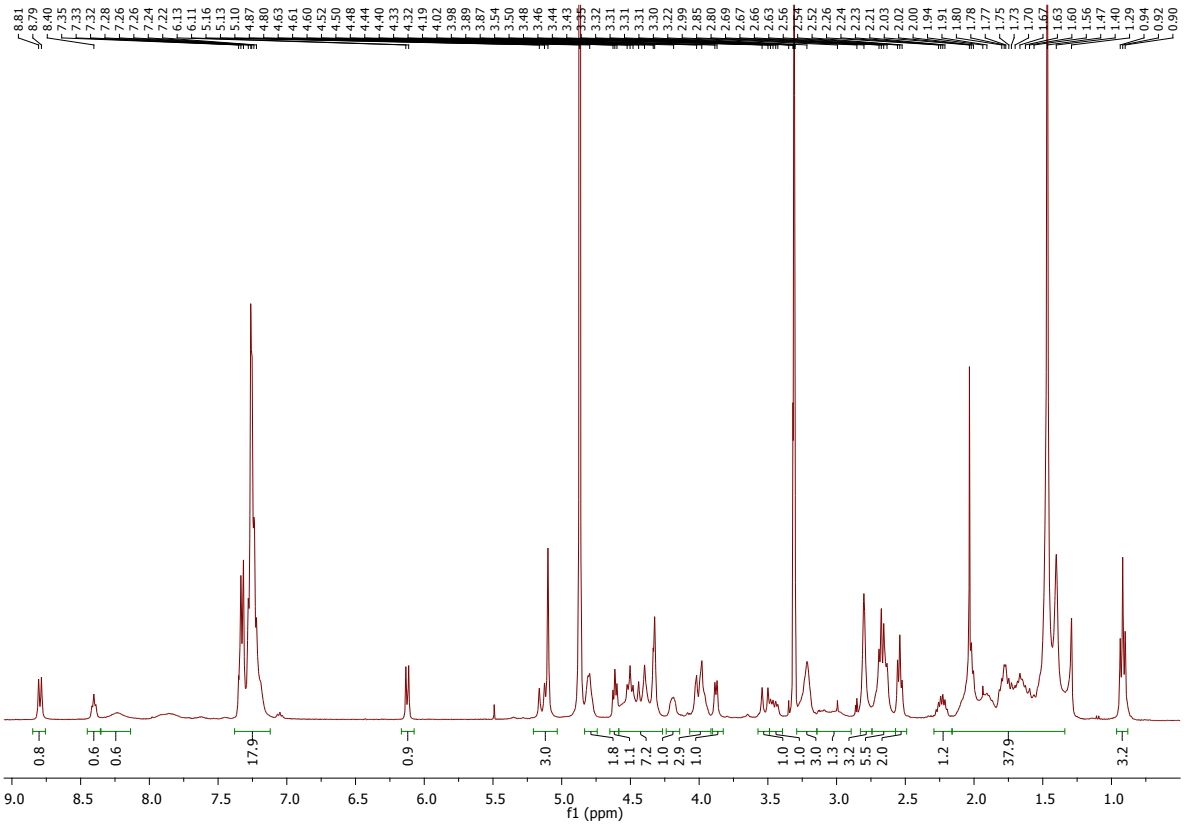


^{13}C NMR (101 MHz, acetone-d_6)

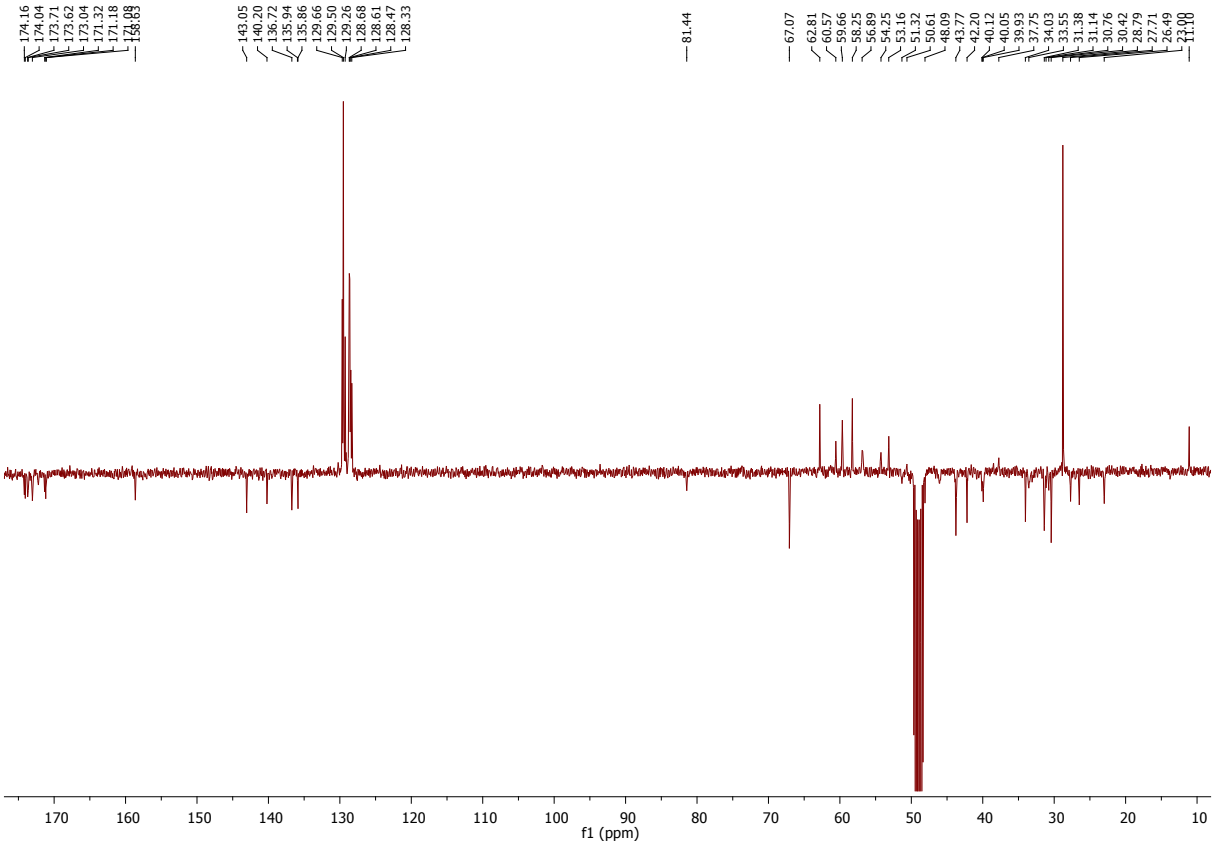


21

^{1}H NMR (400 MHz, CD_3OD)

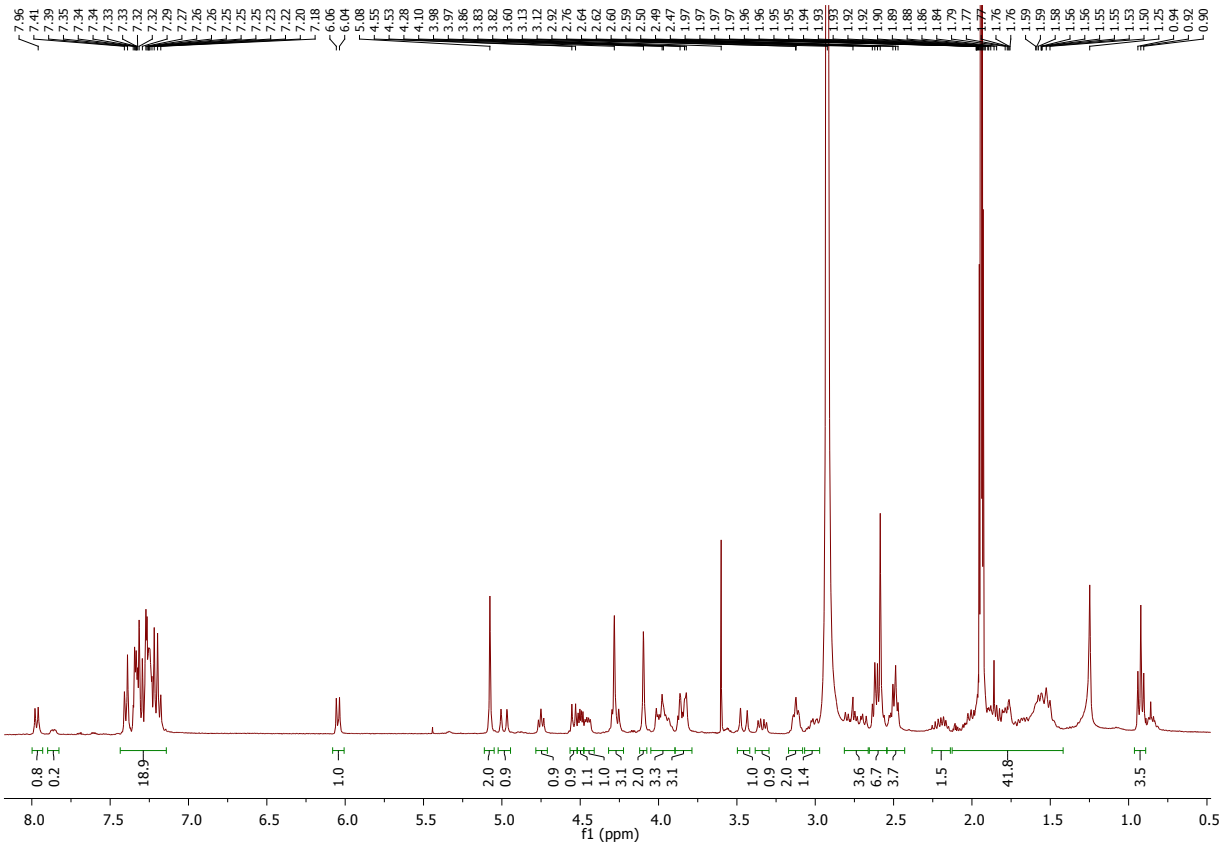


^{13}C NMR (101 MHz, CD_3OD)

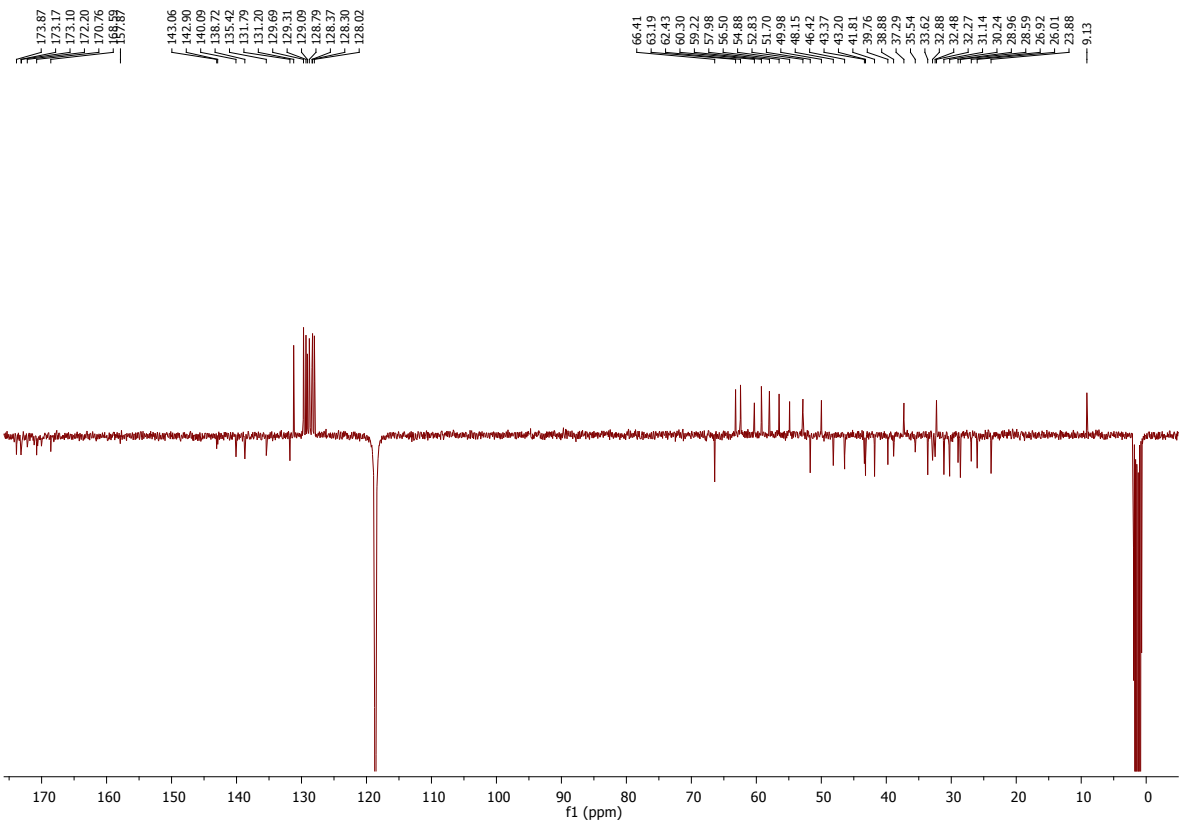


11

^{1}H NMR (400 MHz, CD_3CN)

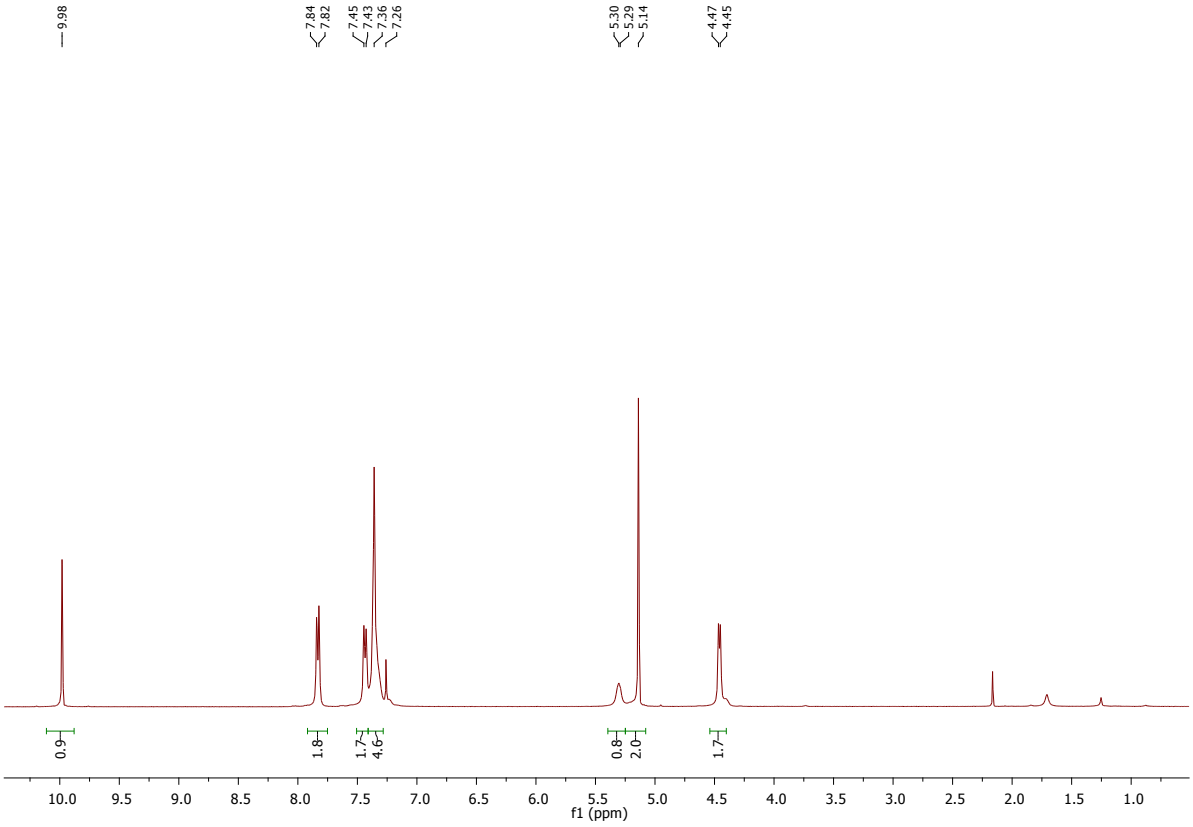


^{13}C NMR (101 MHz, CD_3CN)

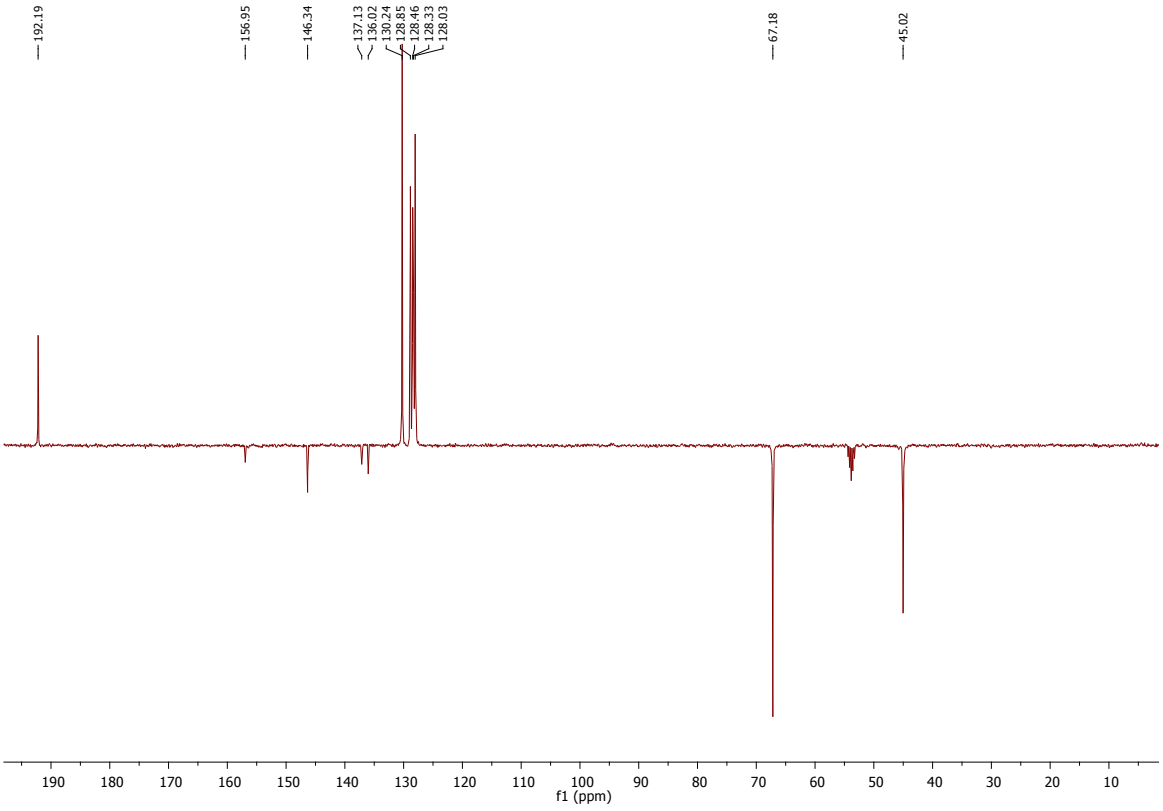


24

^{1}H NMR (400 MHz, $CDCl_3$)

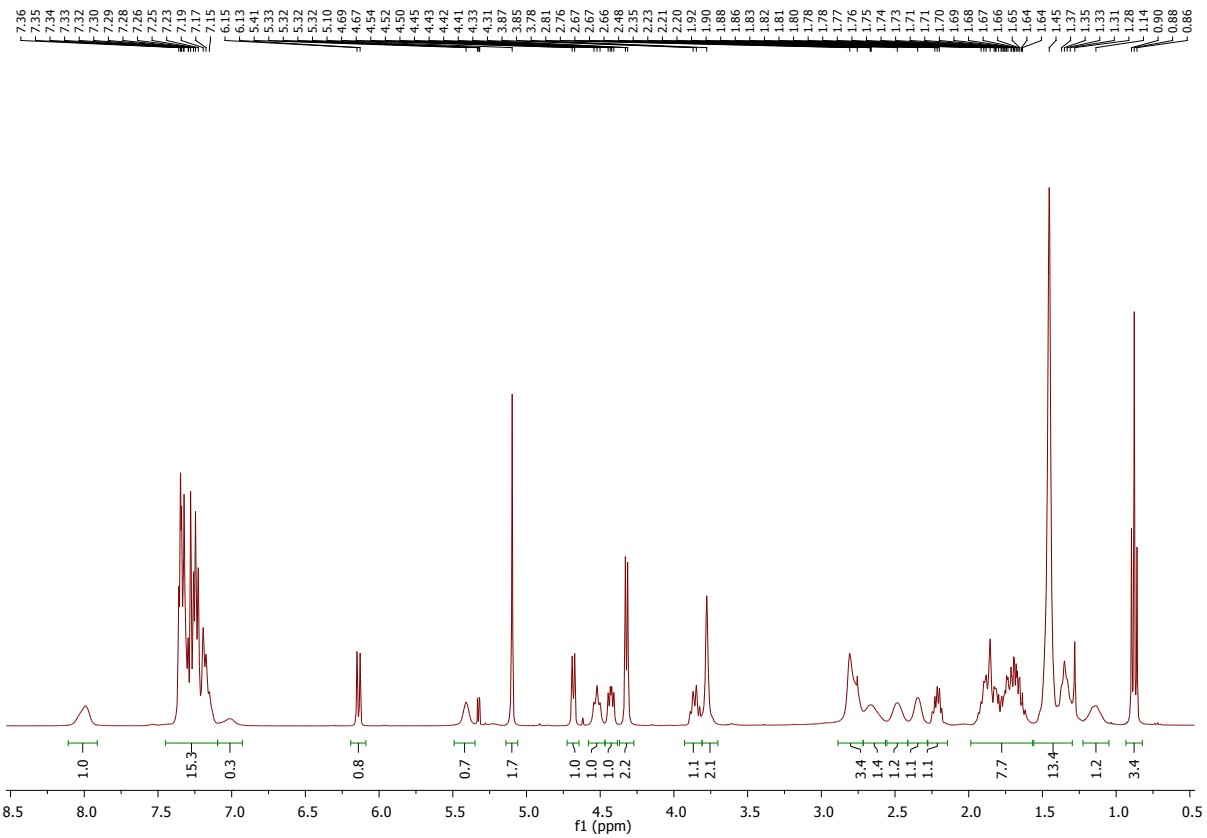


^{13}C NMR (101 MHz, CD_2Cl_2)

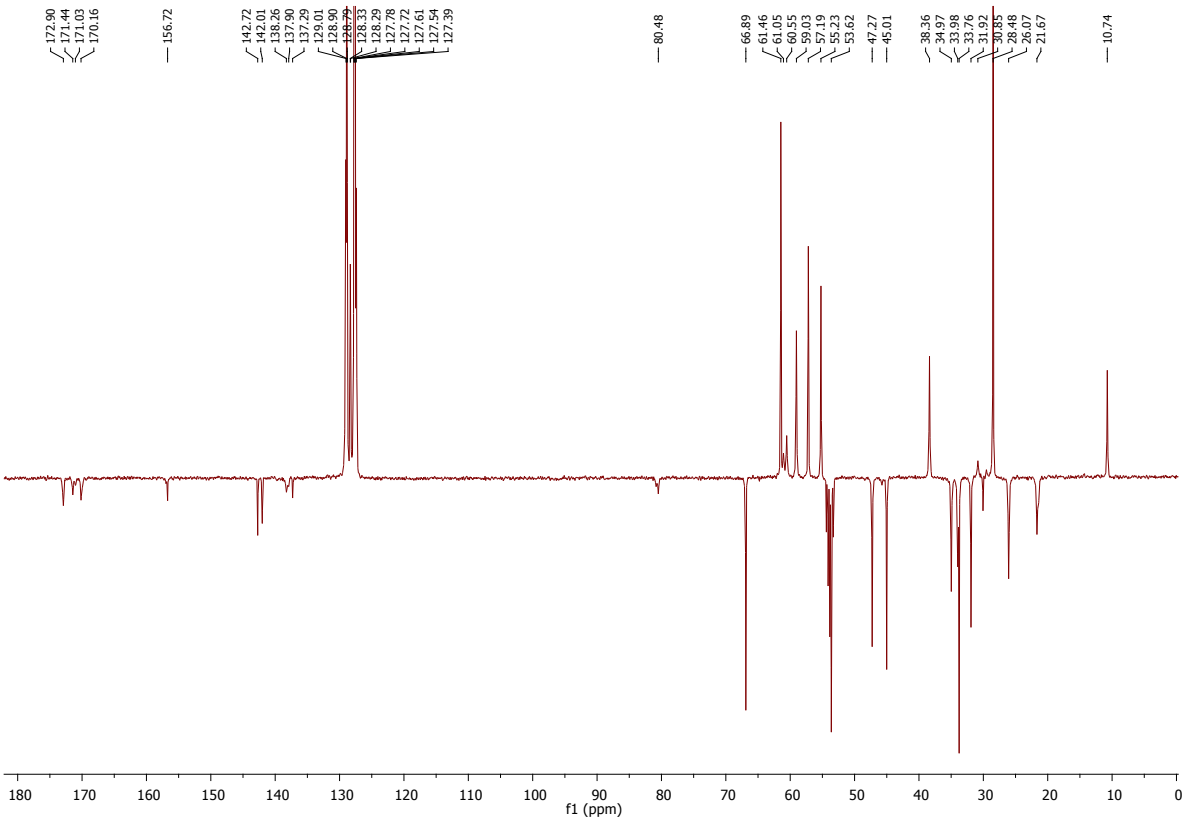


25

^{1}H NMR (400 MHz, CD_2Cl_2)

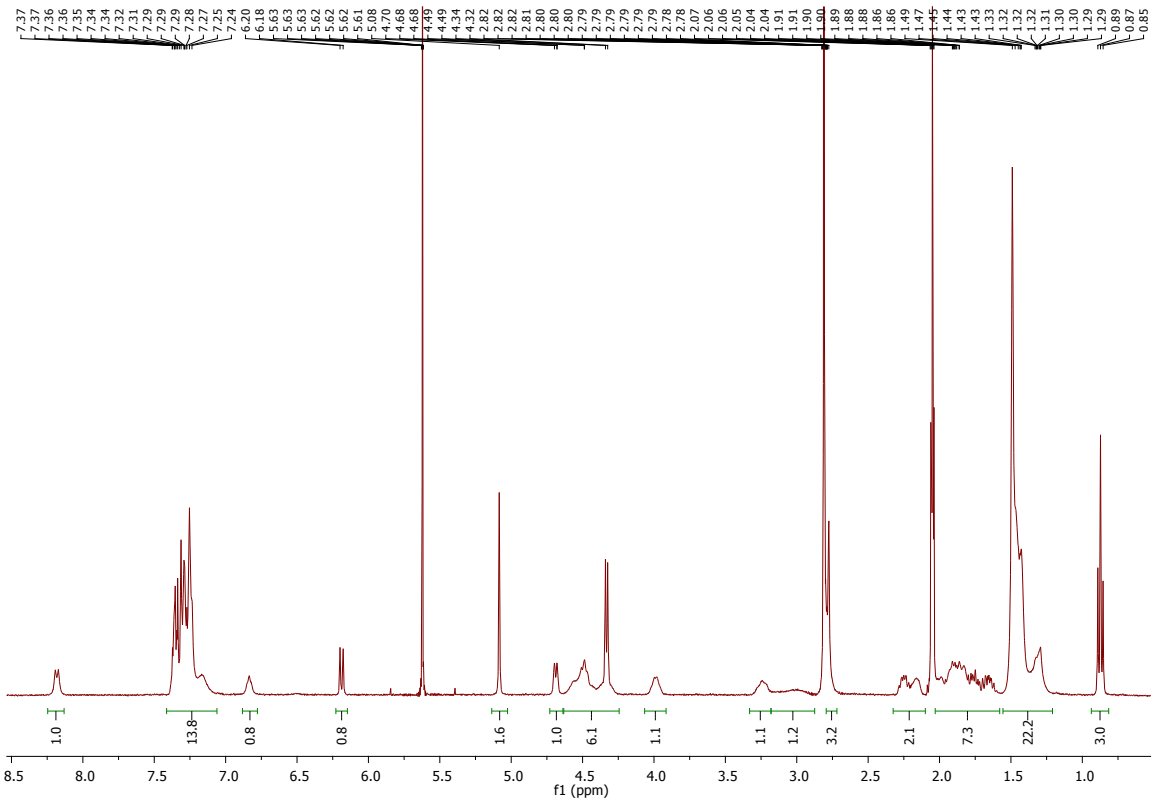


^{13}C NMR (101 MHz, CD_2Cl_2)



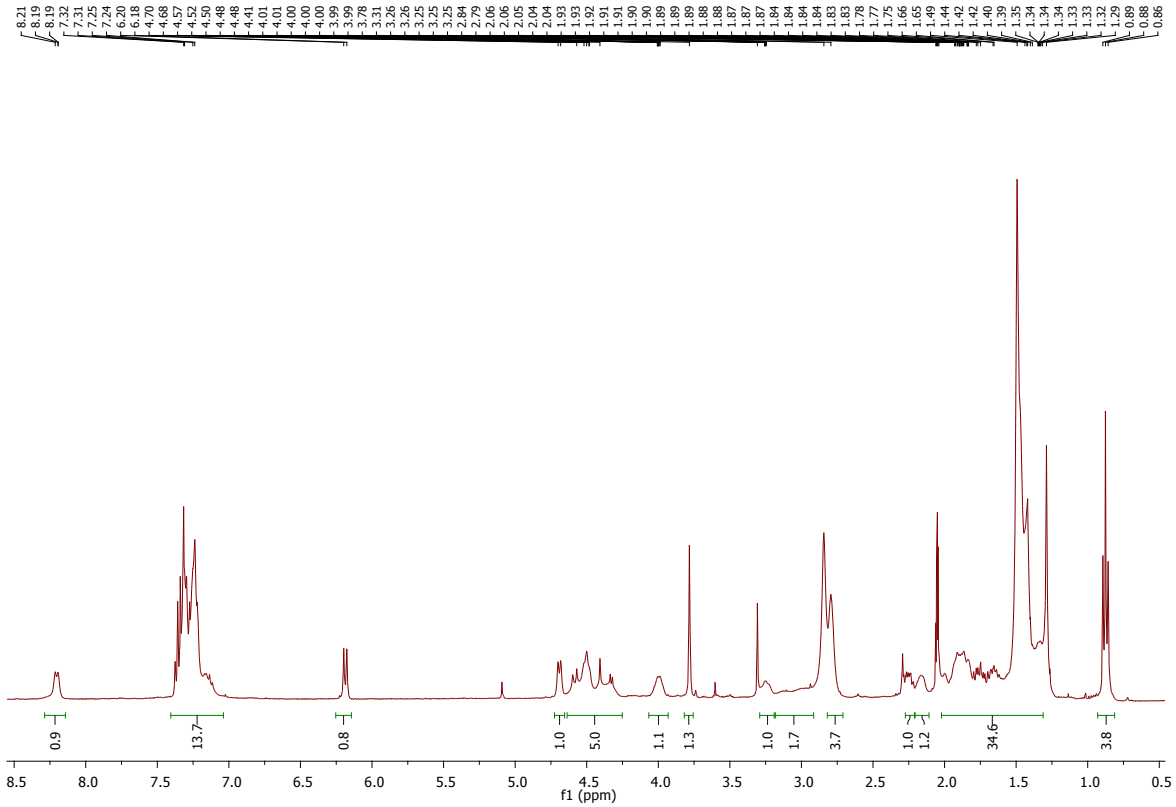
26

^{1}H NMR (400 MHz, acetone-d_6)



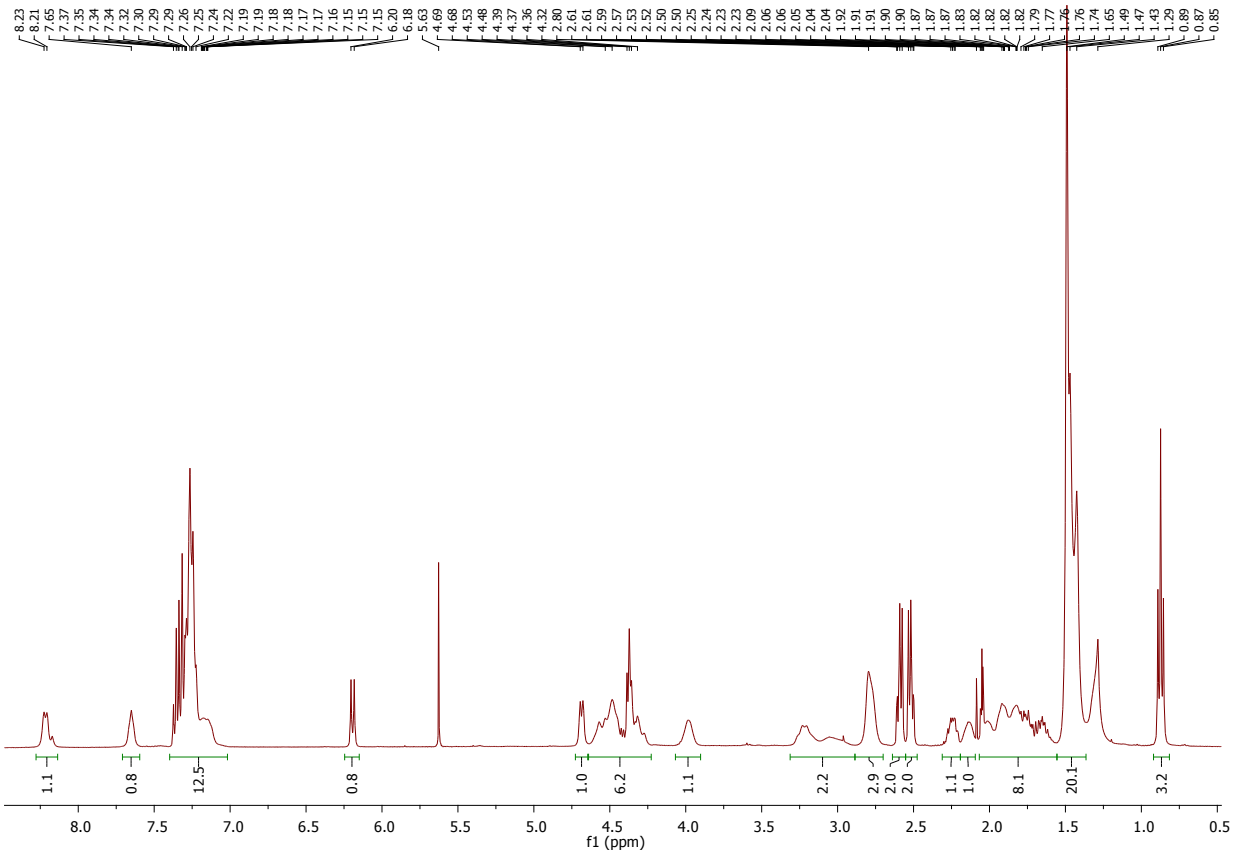
27

^{1}H NMR (400 MHz, acetone-d_6)

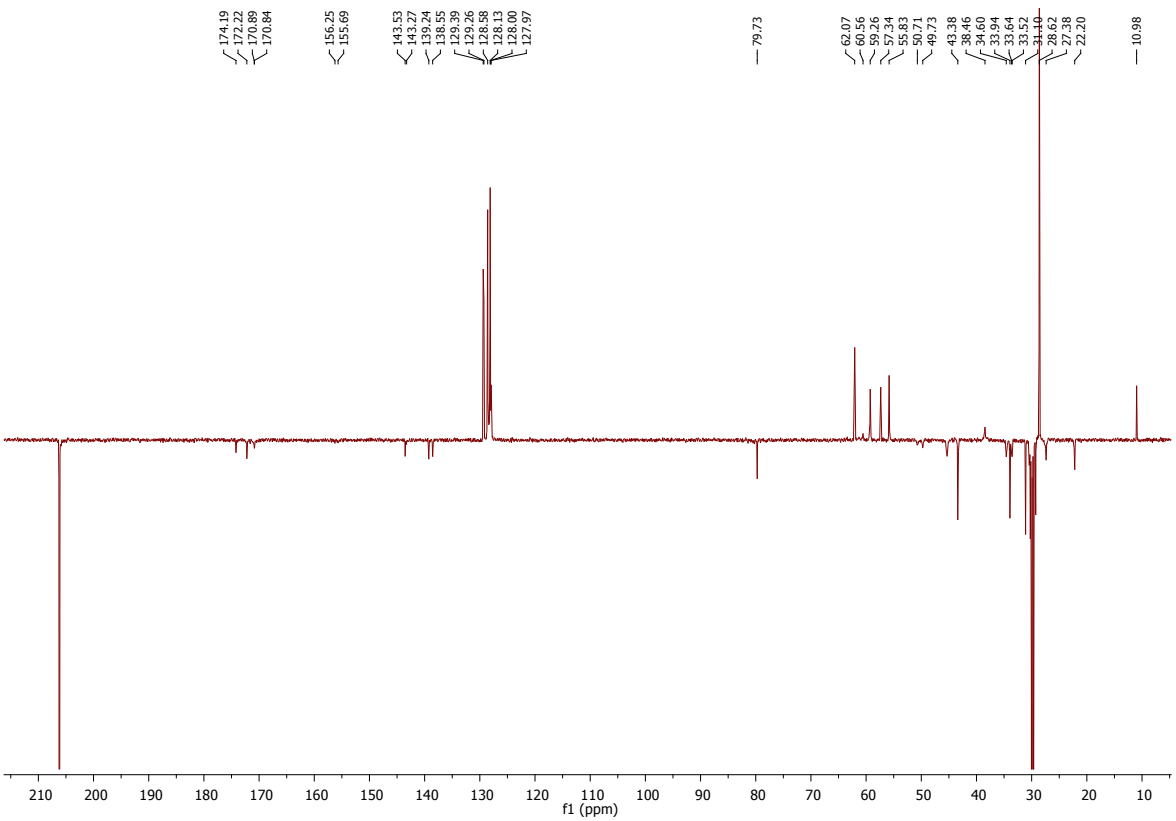


28

^{1}H NMR (400 MHz, acetone-d_6)

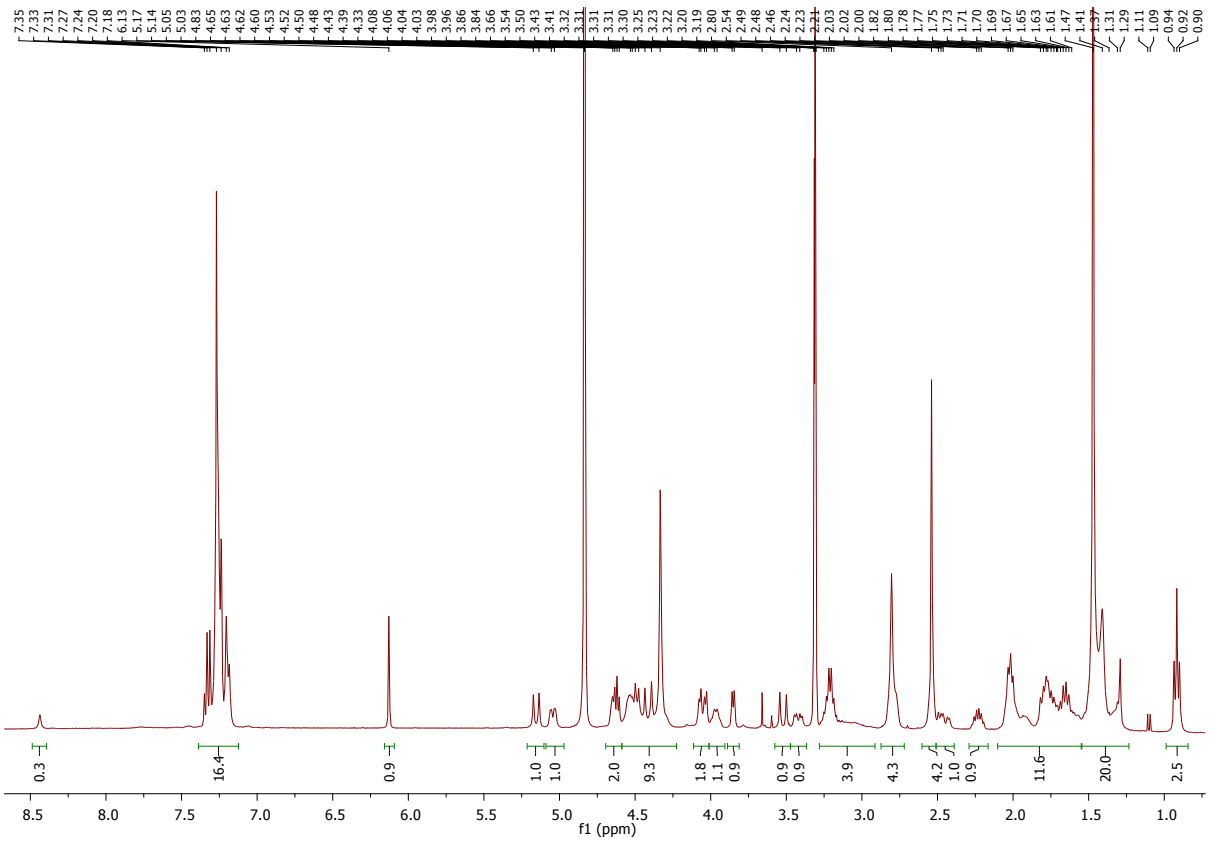


^{13}C NMR (101 MHz, acetone-d_6)

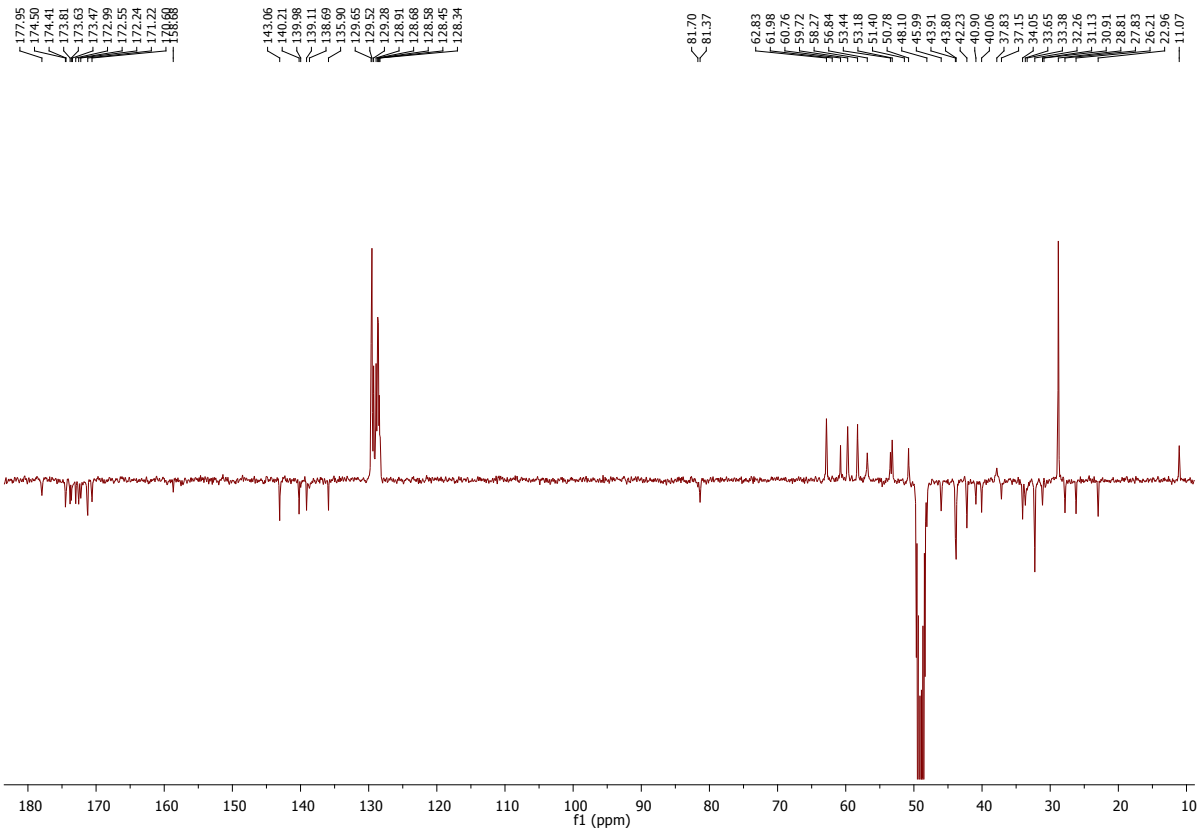


29

^{1}H NMR (400 MHz, CD_3OD)

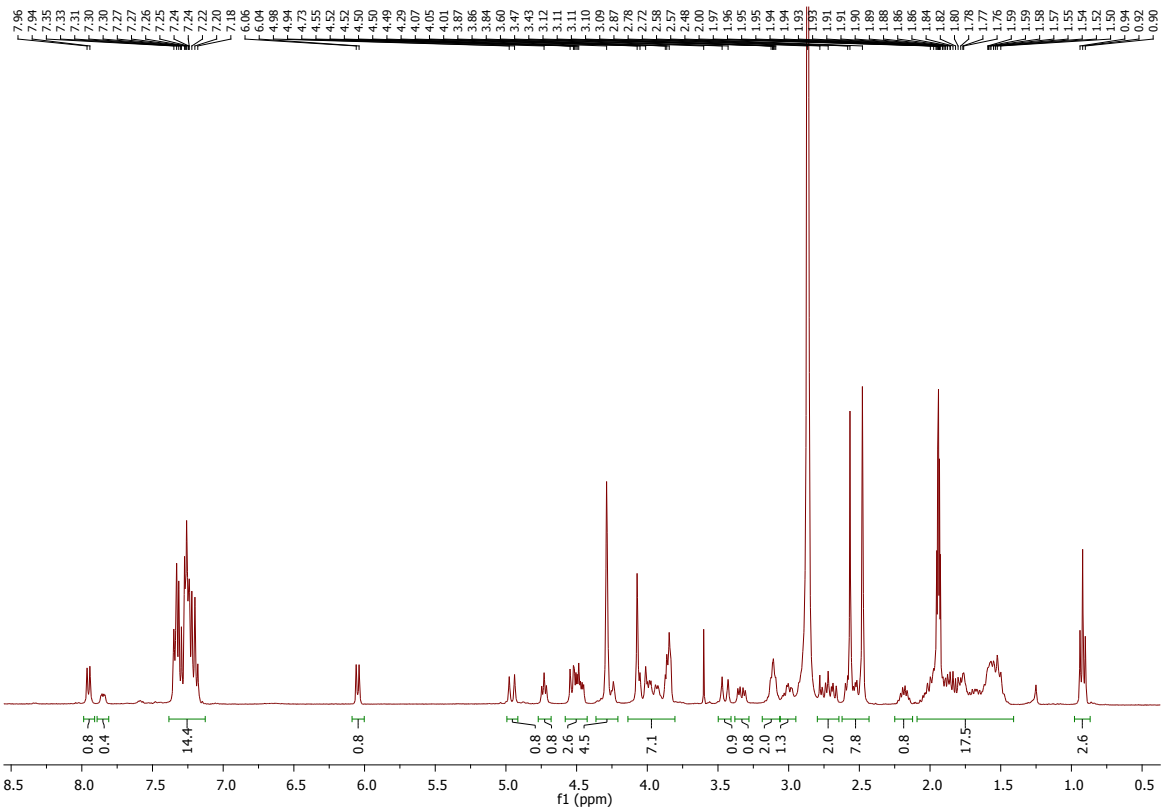


^{13}C NMR (101 MHz, CD_3OD)

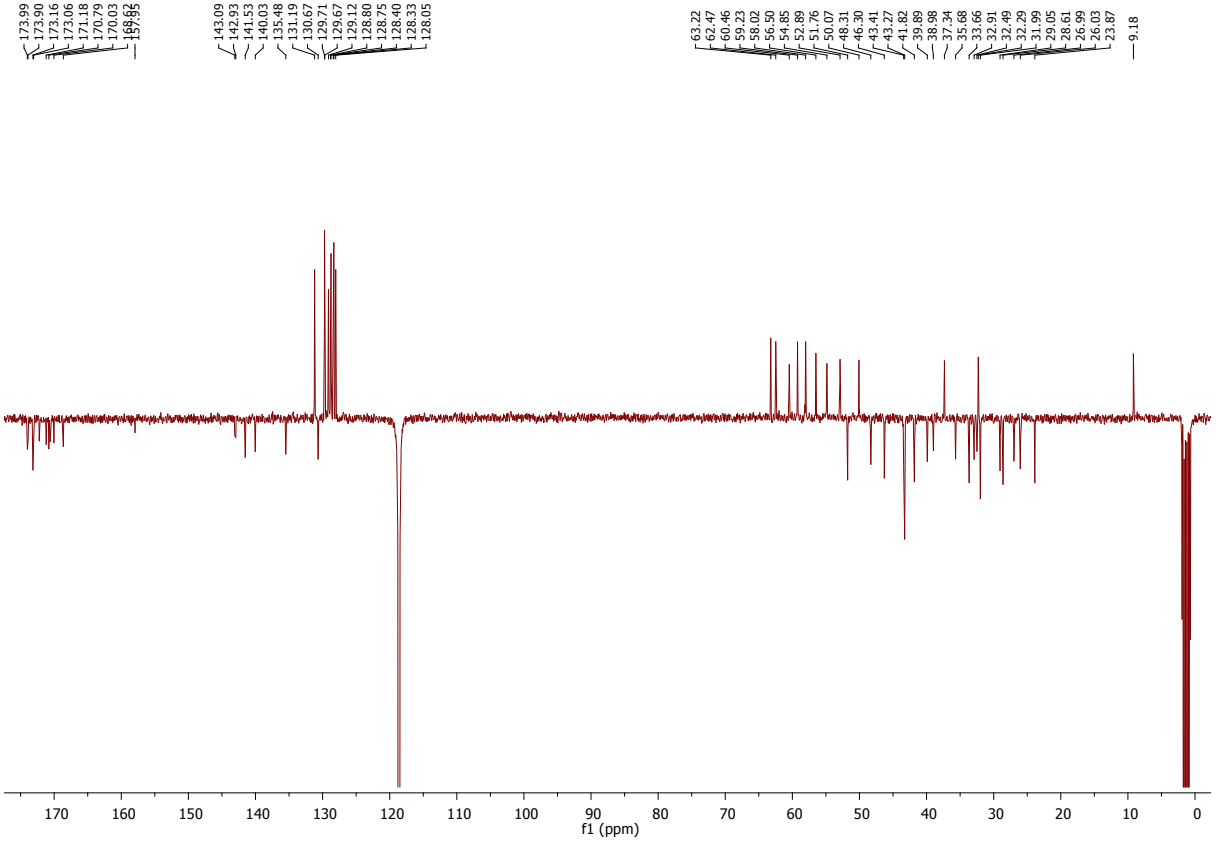


12

^{1}H NMR (400 MHz, CD_3CN)

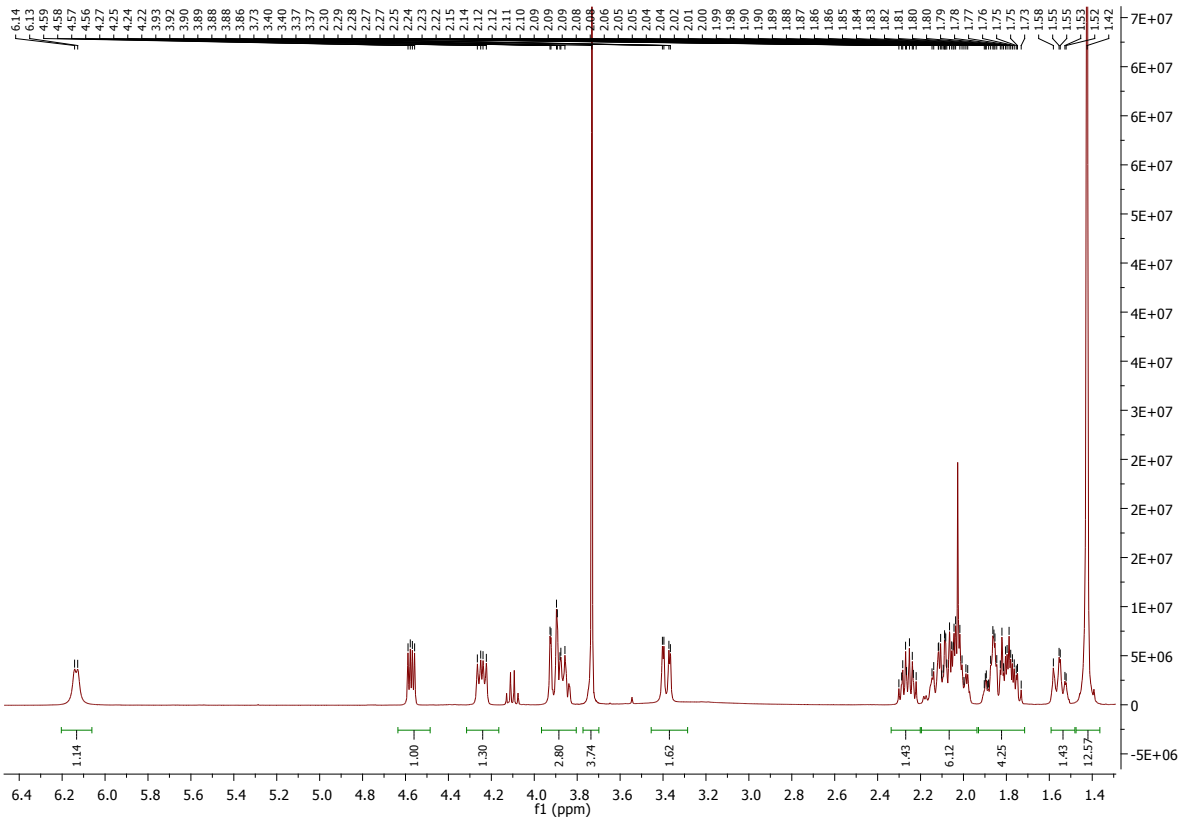


^{13}C NMR (101 MHz, CD_3CN)

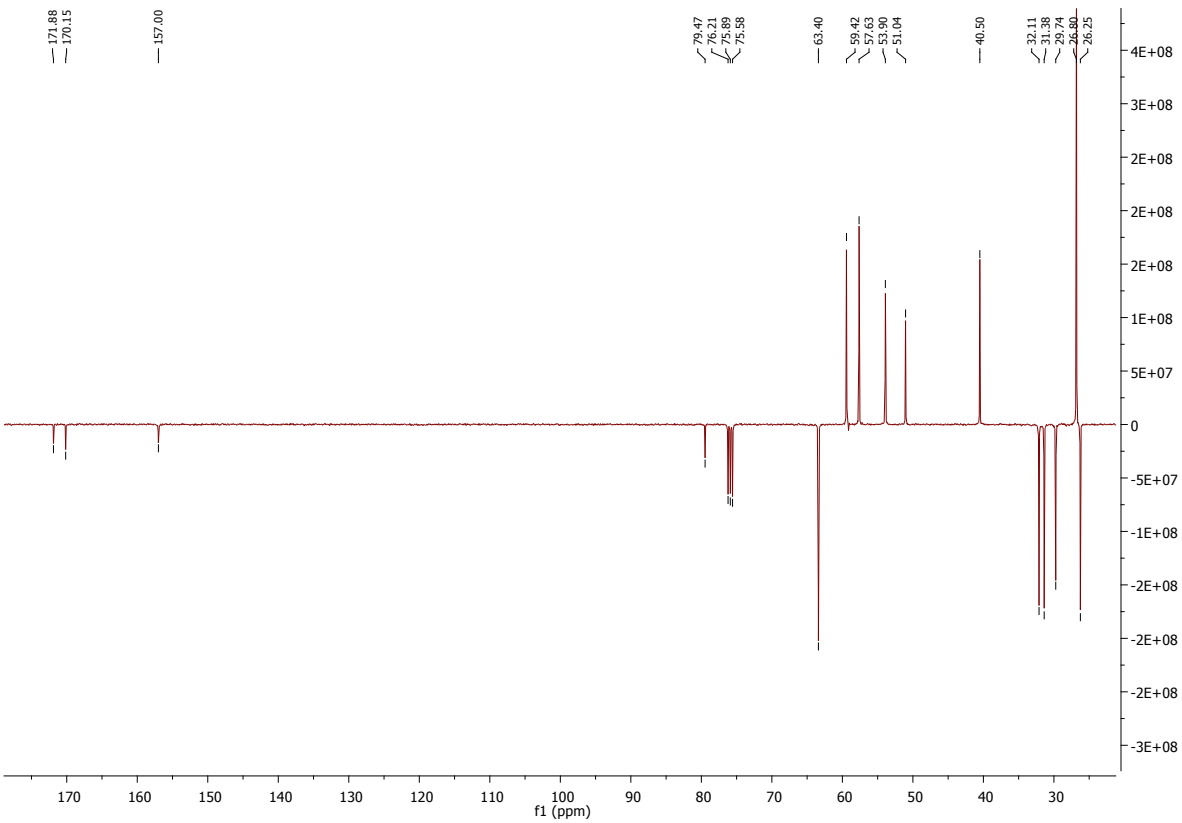


32

^{1}H NMR (400 MHz, $CDCl_3$)

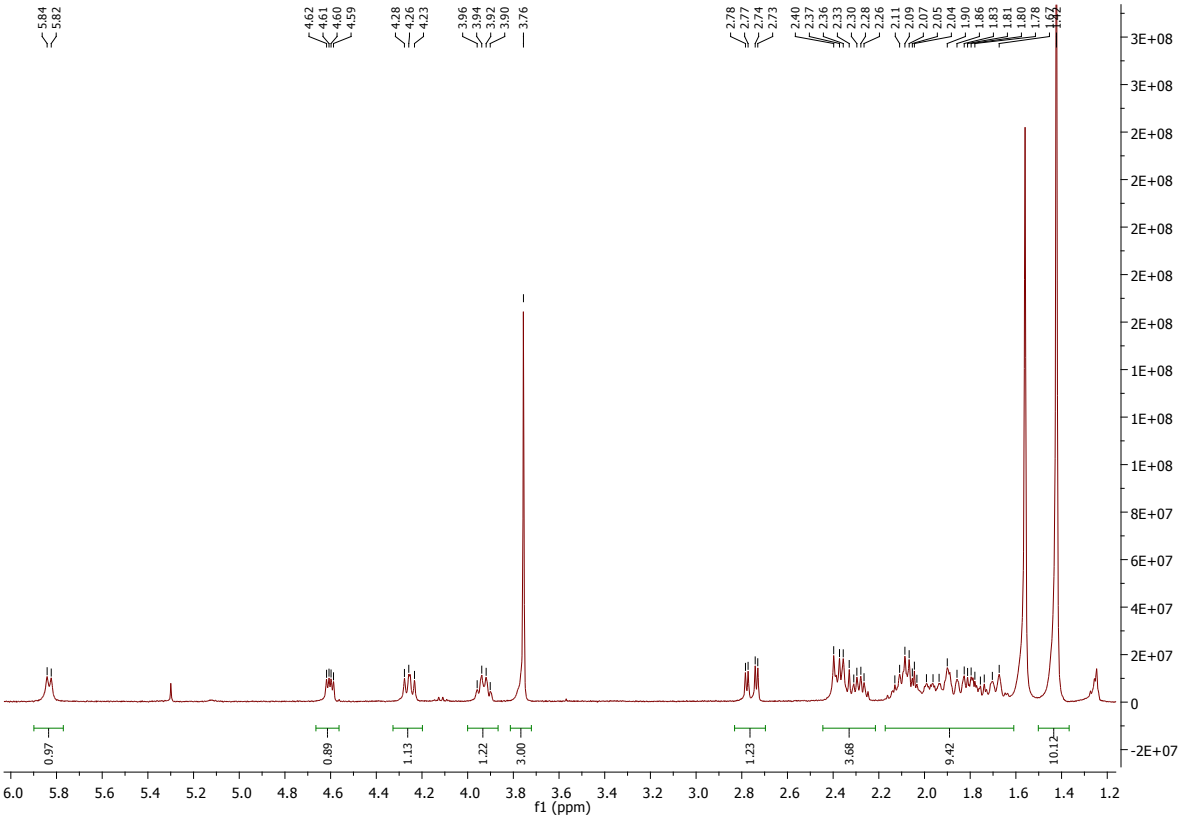


^{13}C NMR (101 MHz, $CDCl_3$)

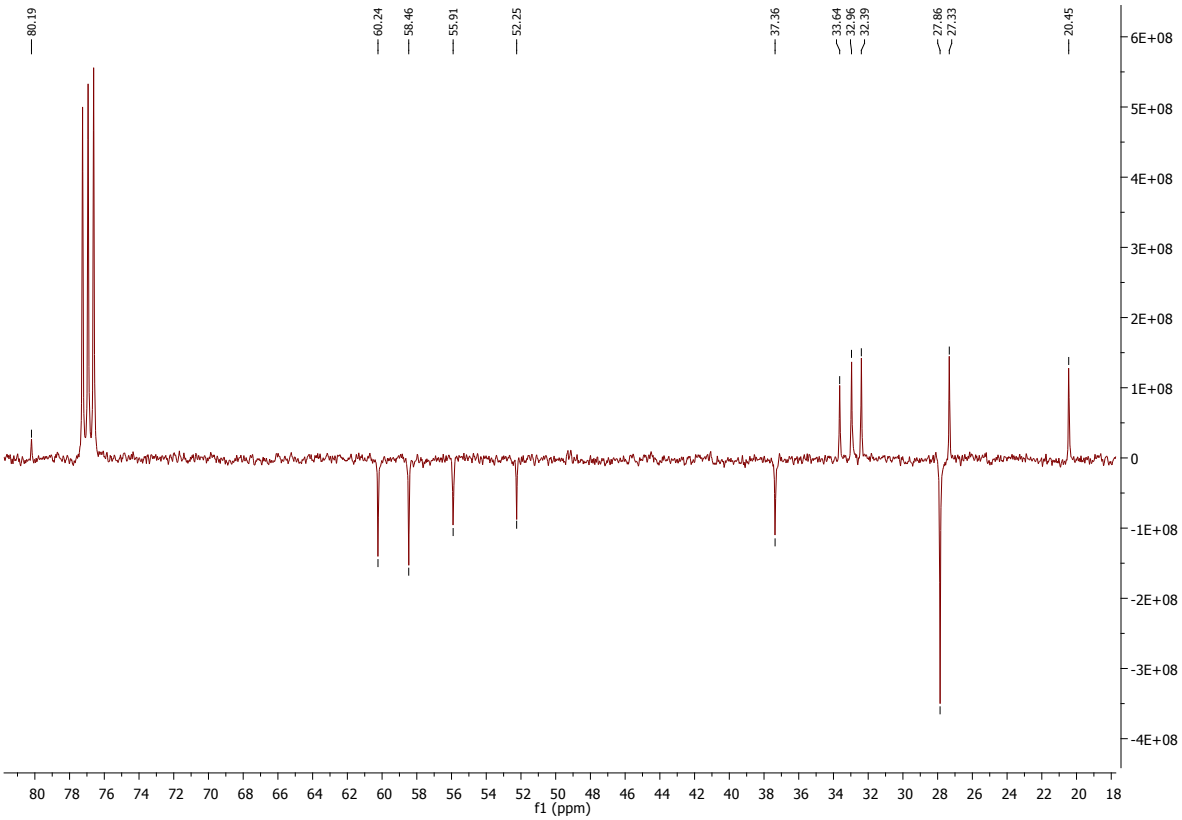


33

^{1}H NMR (400 MHz, $CDCl_3$)

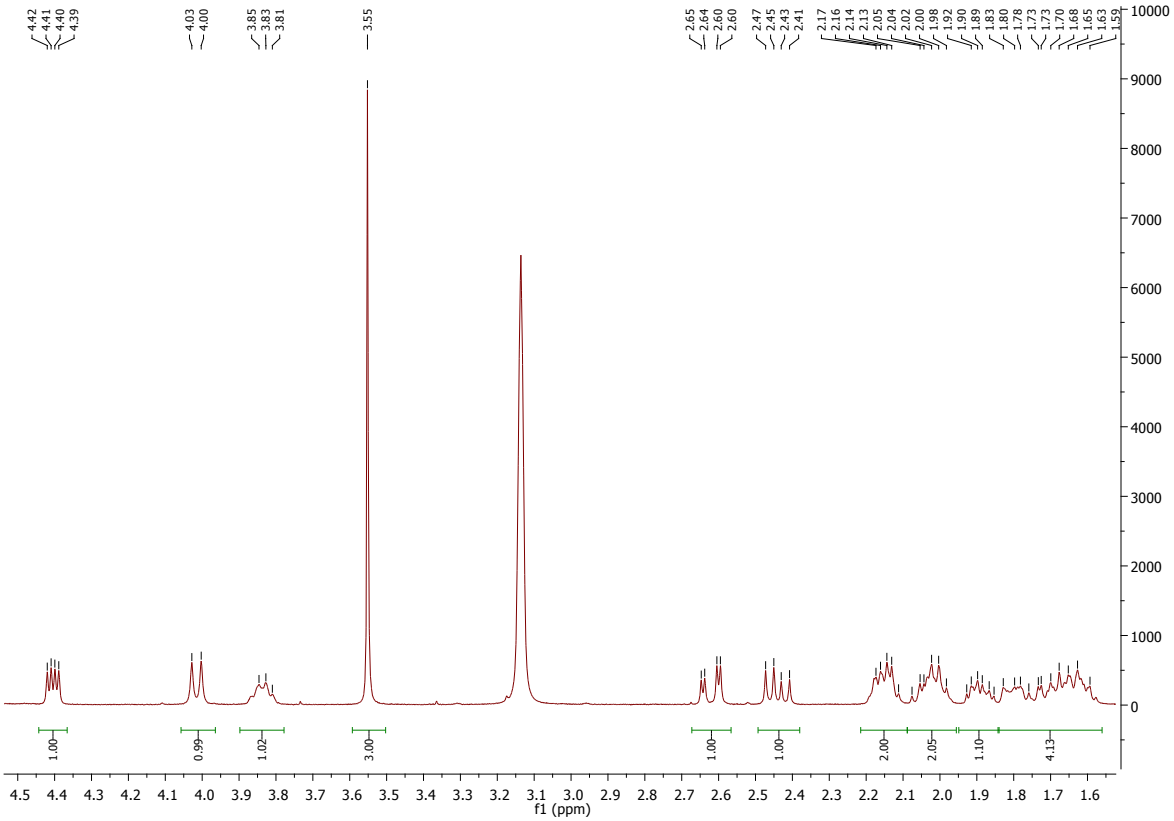


^{13}C NMR (101 MHz, $CDCl_3$)

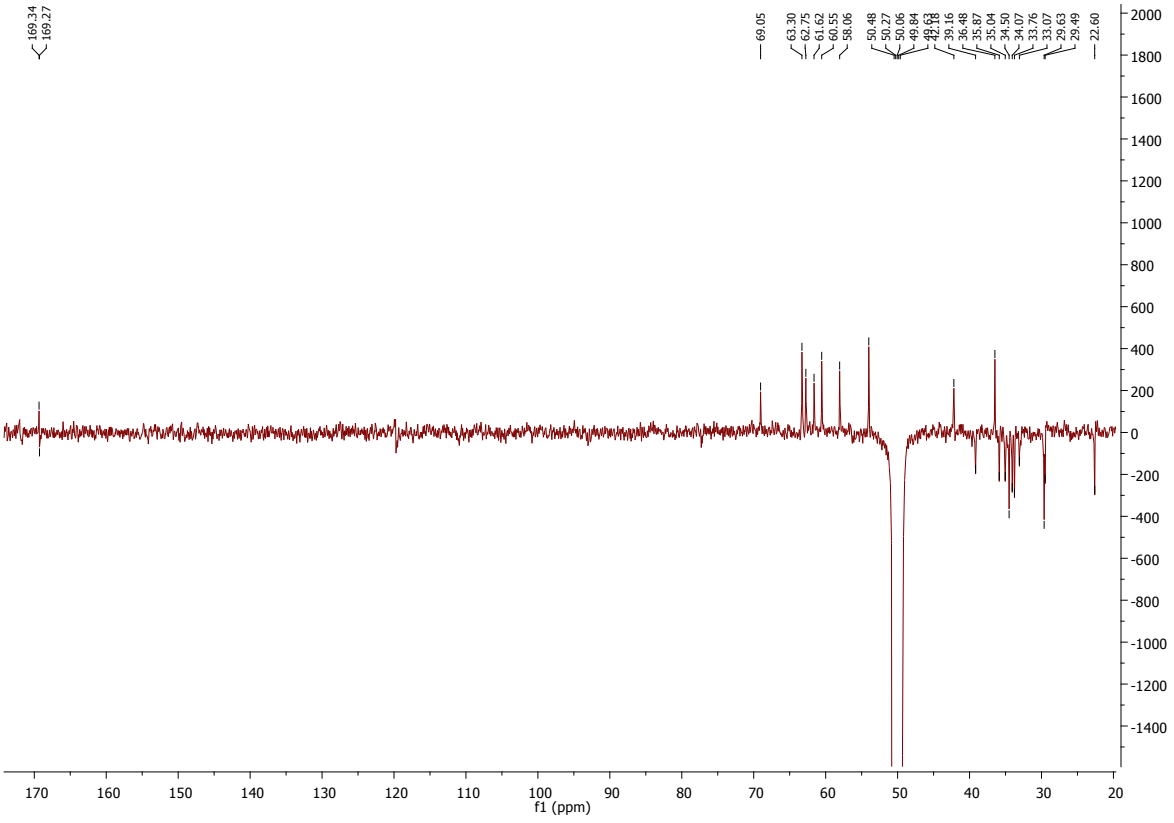


34

^{1}H NMR (400 MHz, CD_3OD)

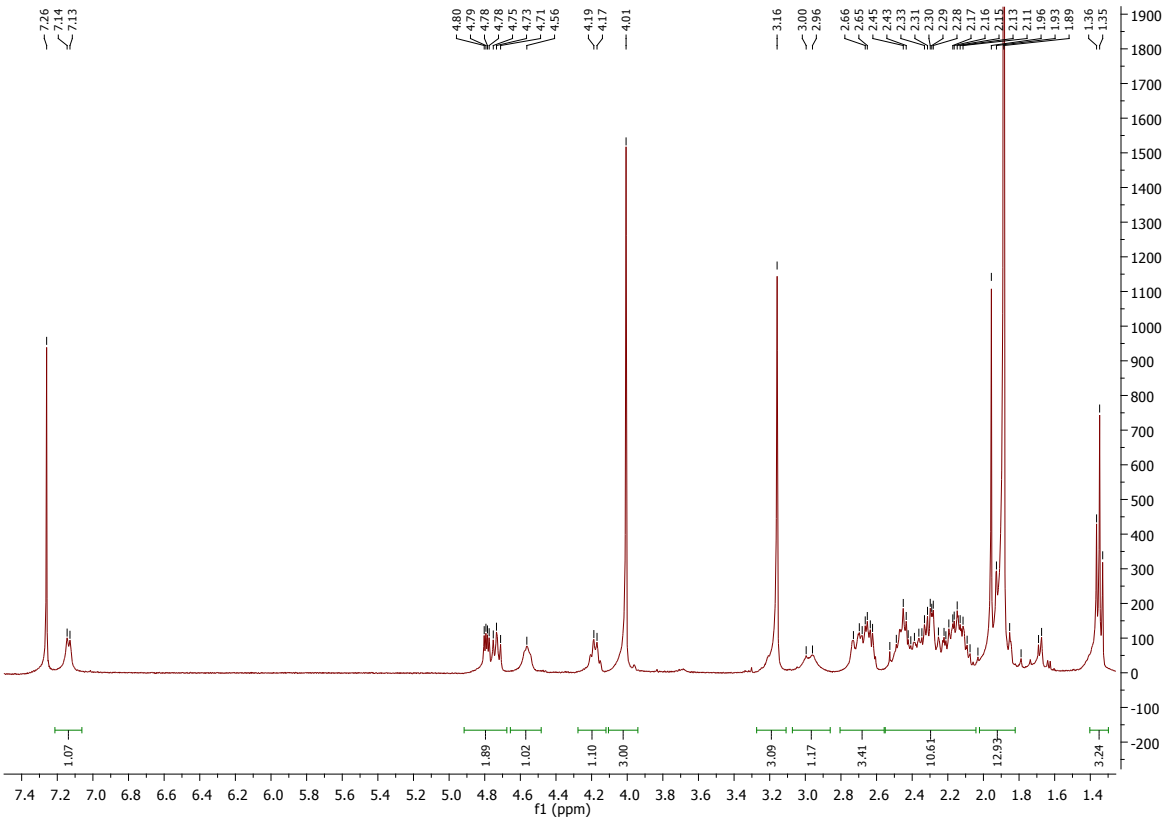


^{13}C NMR (101 MHz, CD_3OD)

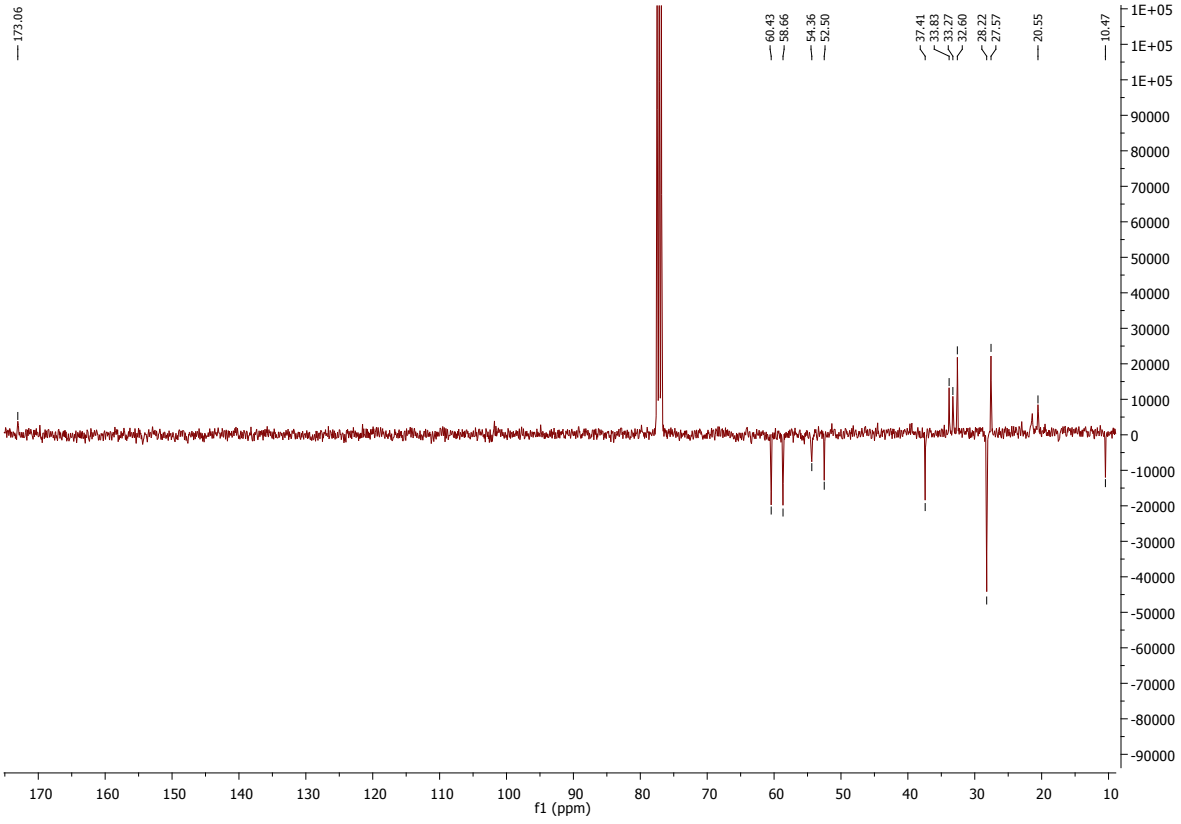


35

^{1}H NMR (400 MHz, $CDCl_3$)

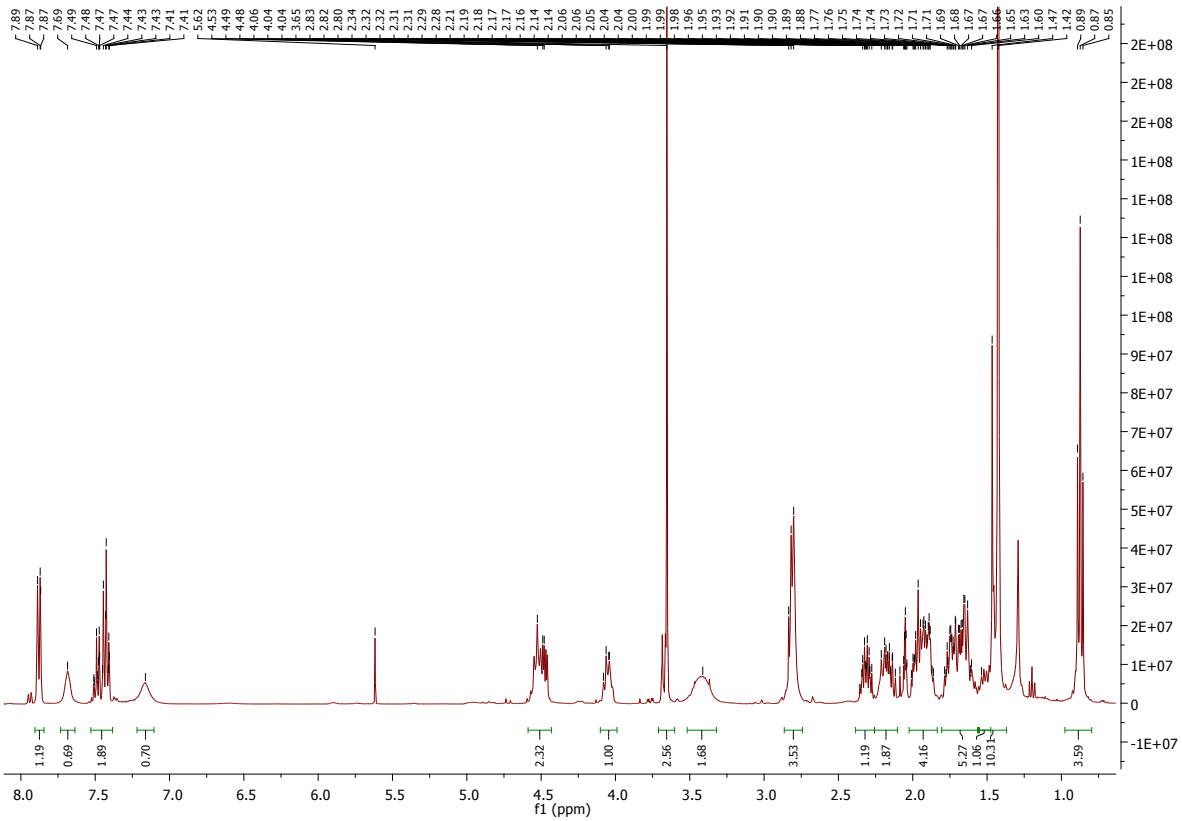


^{13}C NMR (101 MHz, $CDCl_3$)

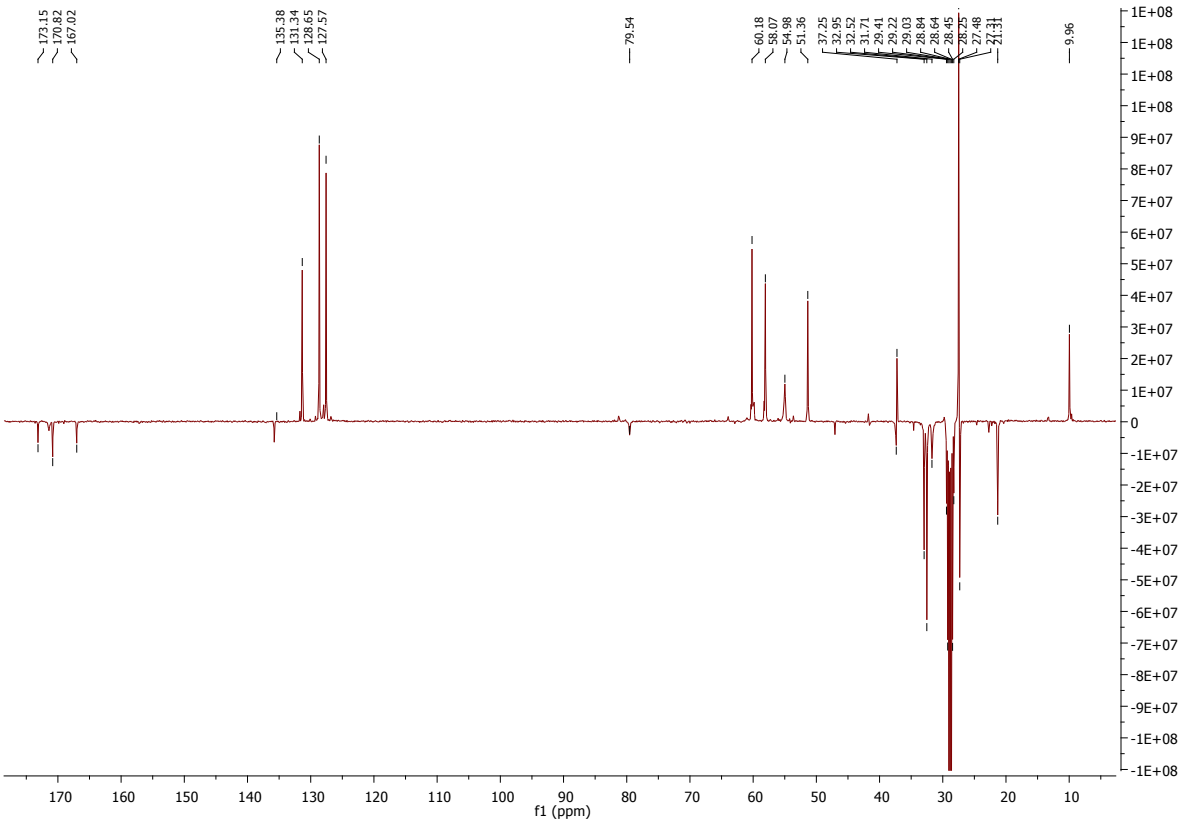


37

^{1}H NMR (400 MHz, Acetone-*d6*)

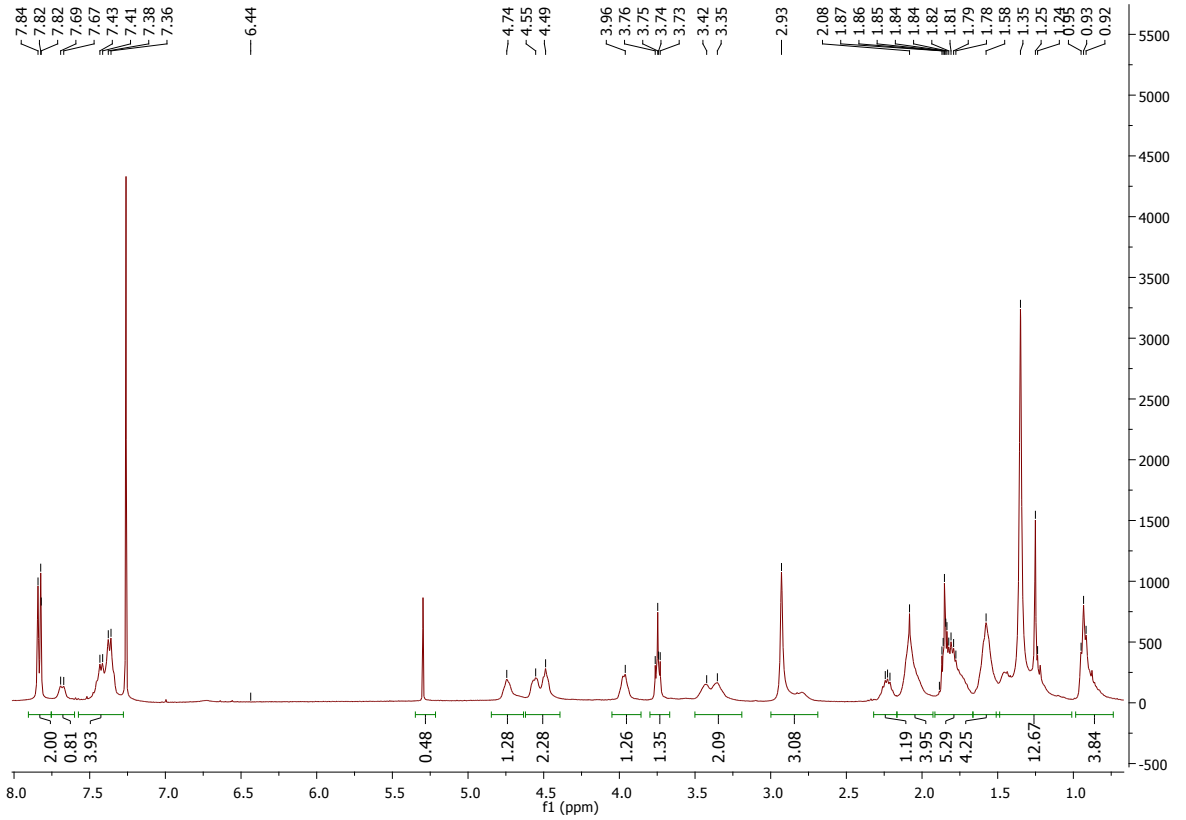


^{13}C NMR (101 MHz, Acetone-*d6*)

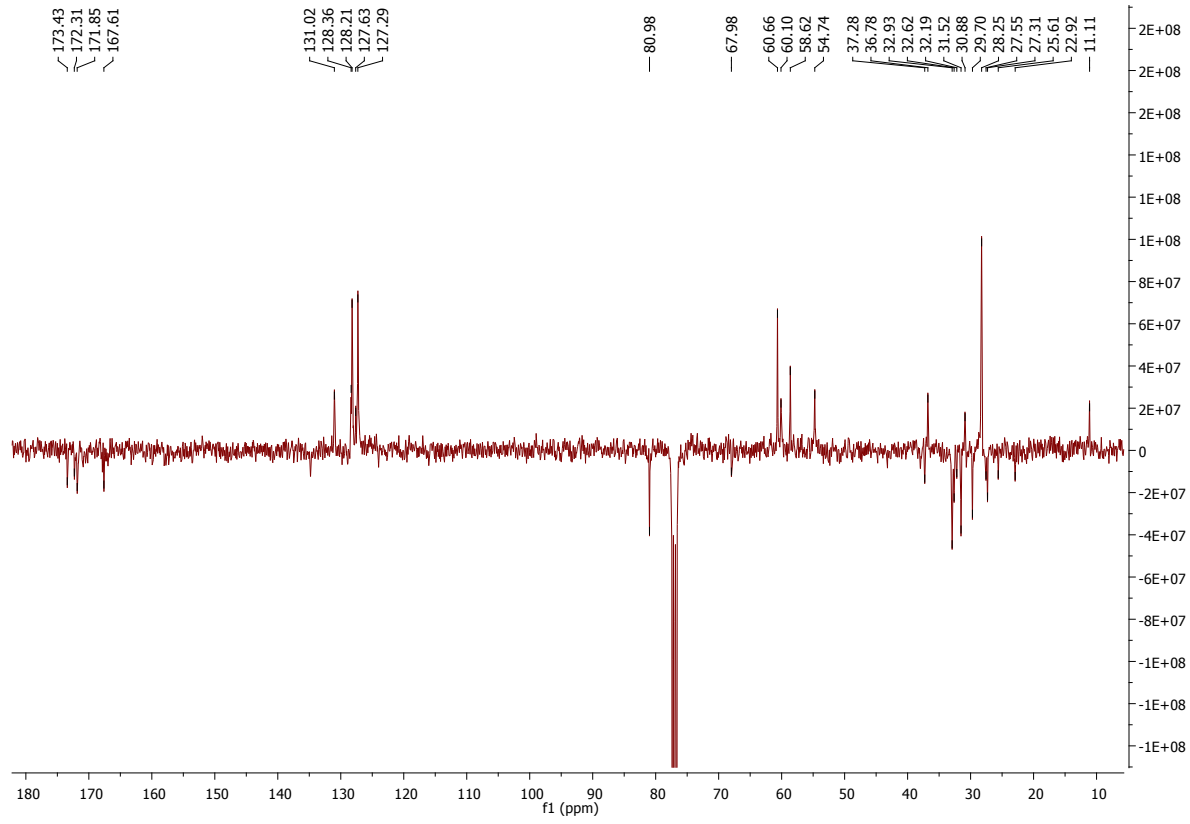


30

^{1}H NMR (400 MHz, $CDCl_3$)

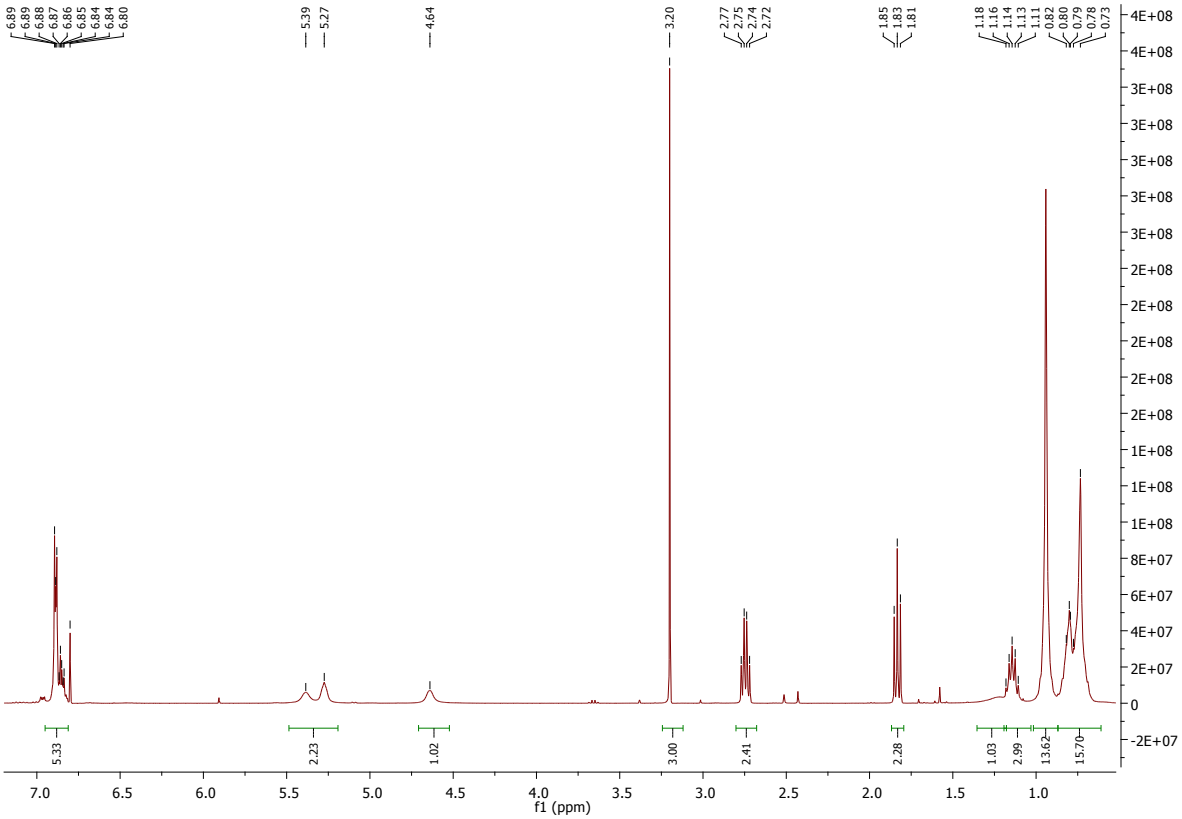


^{13}C NMR (101 MHz, $CDCl_3$)

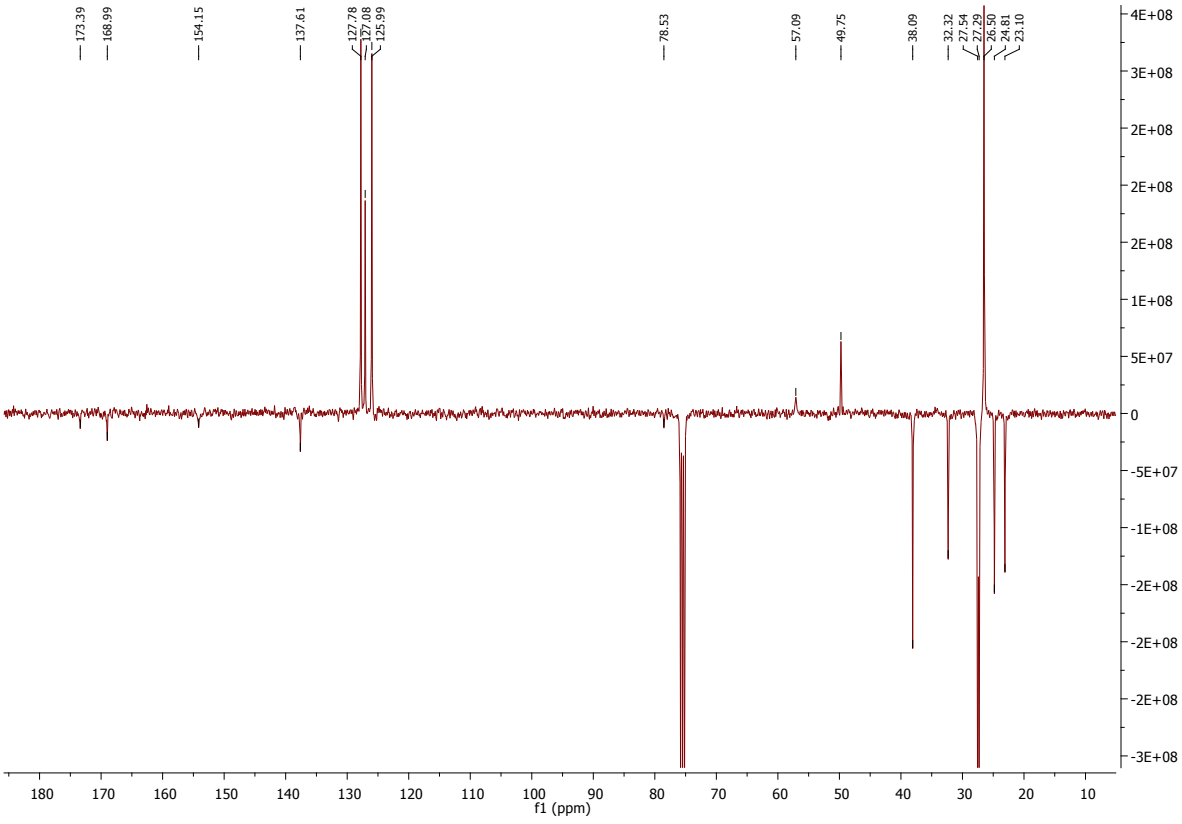


41

^{1}H NMR (400 MHz, $CDCl_3$)

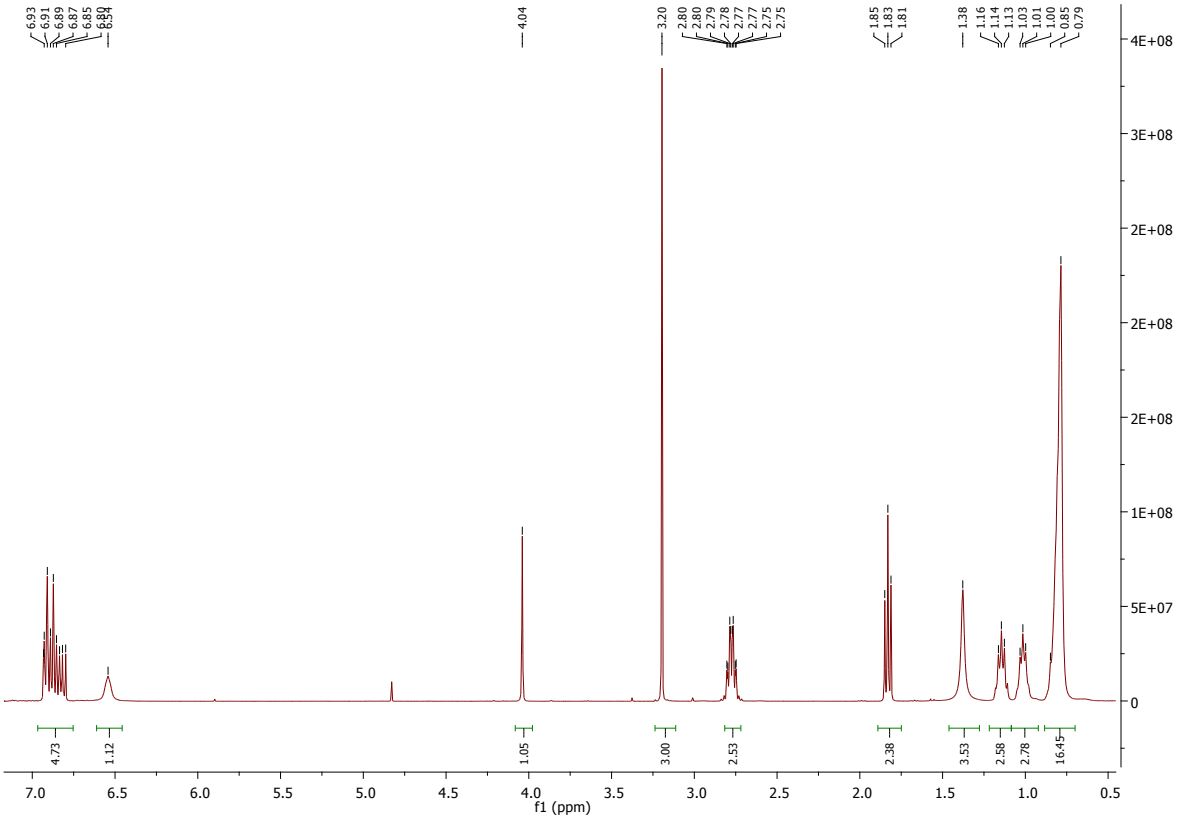


^{13}C NMR (101 MHz, $CDCl_3$)

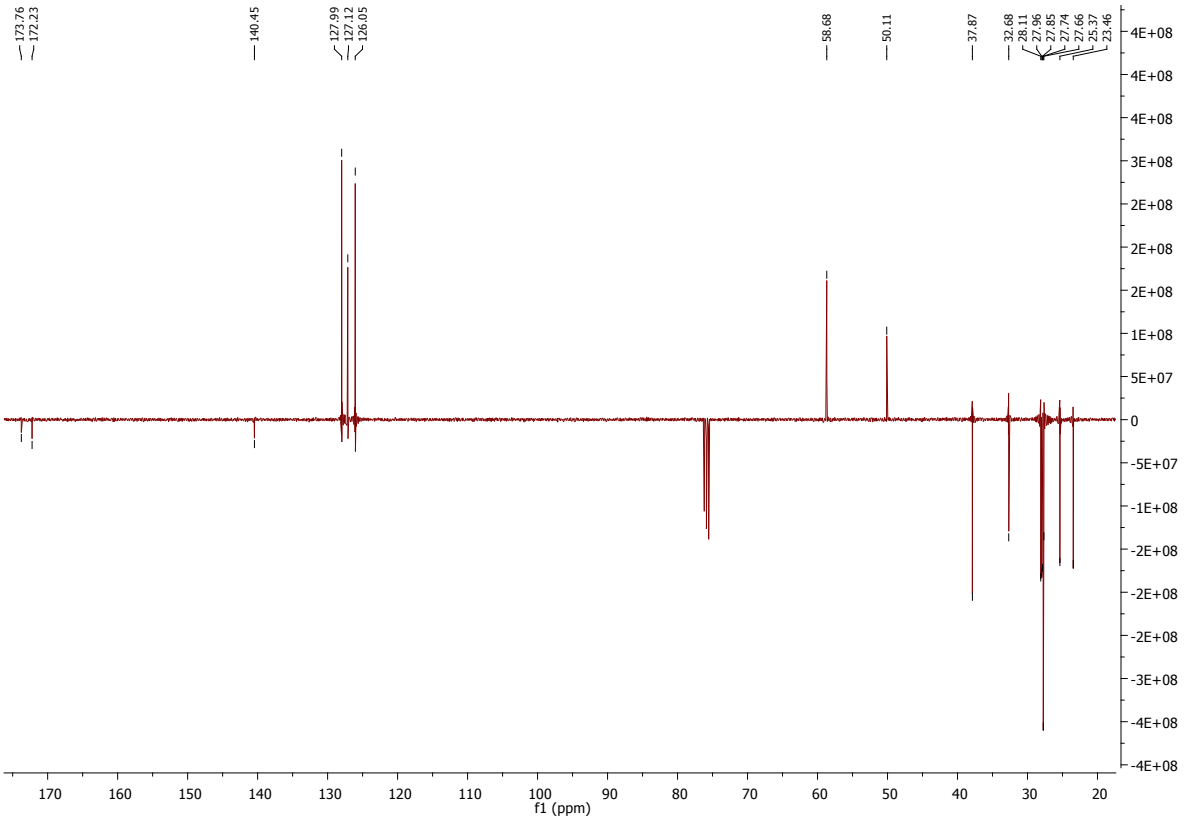


42

^{1}H NMR (400 MHz, $CDCl_3$)

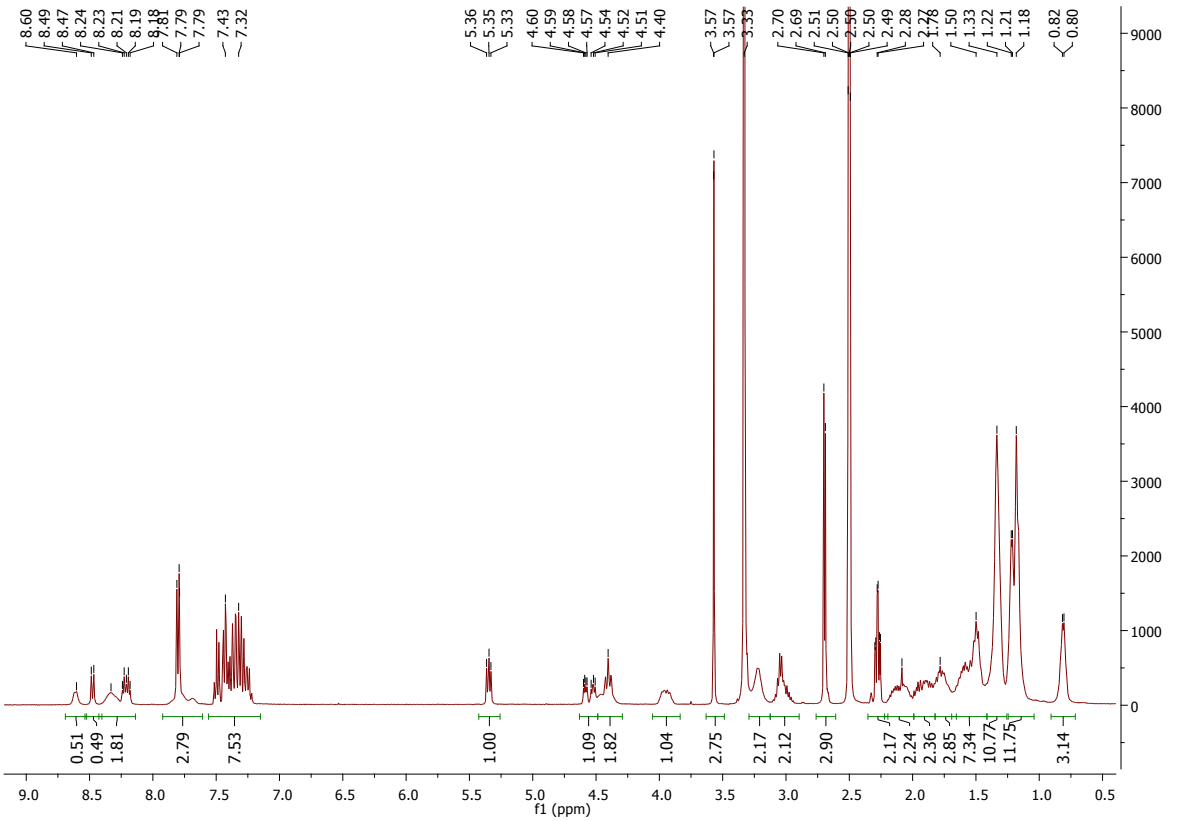


^{13}C NMR (101 MHz, $CDCl_3$)

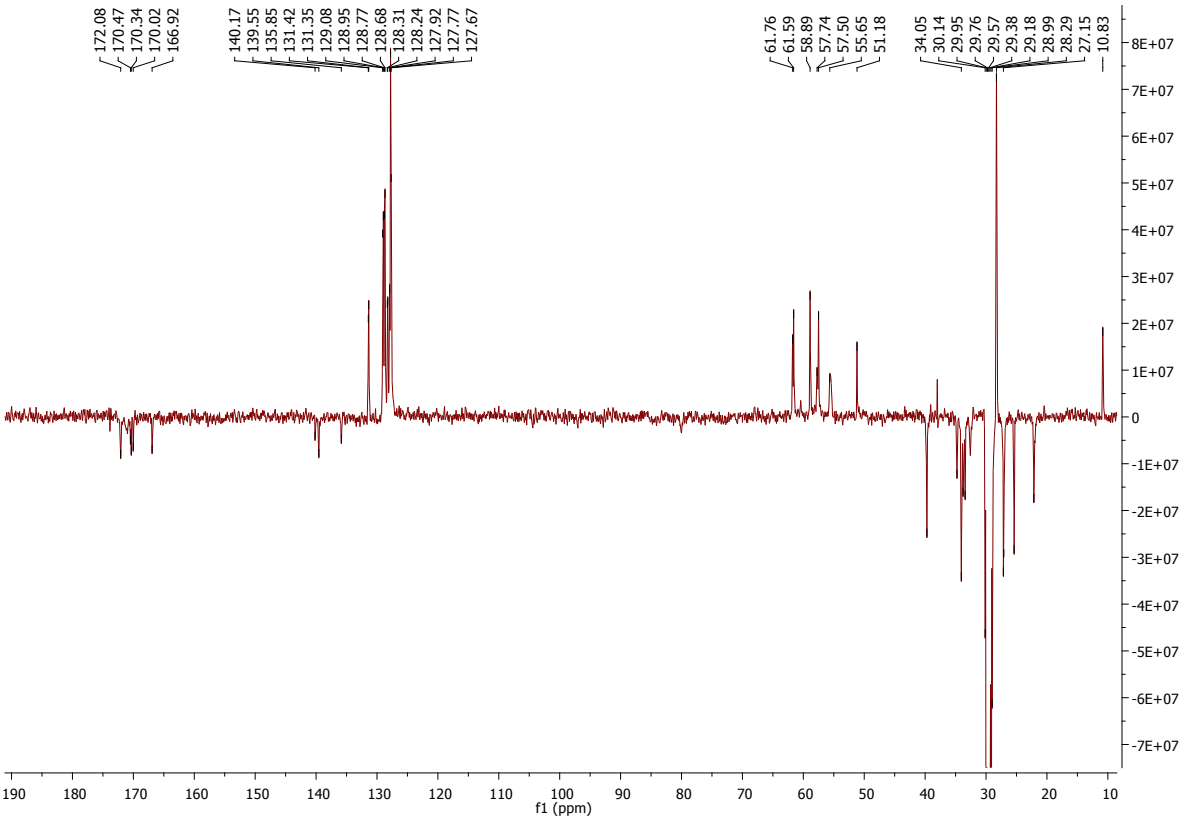


43

^{1}H NMR (400 MHz, DMSO-d_6)

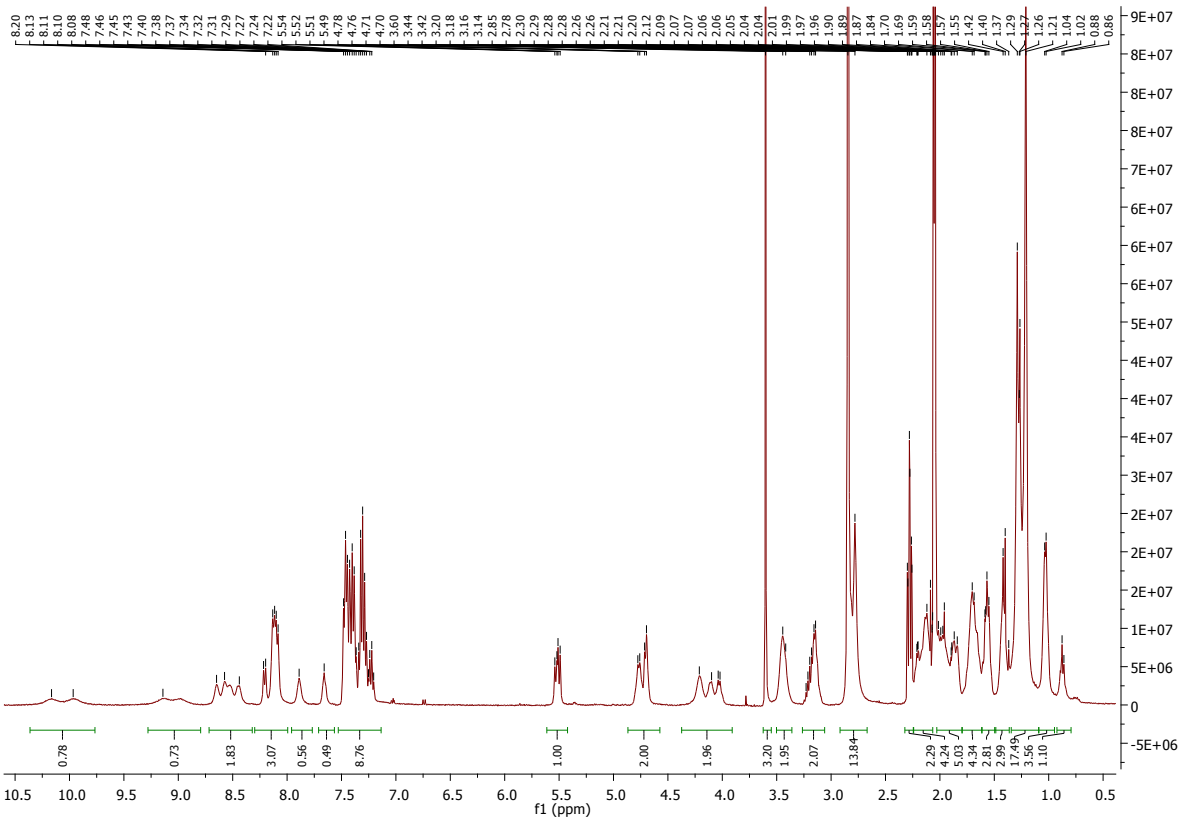


^{13}C NMR (101 MHz, Acetone-d_6)

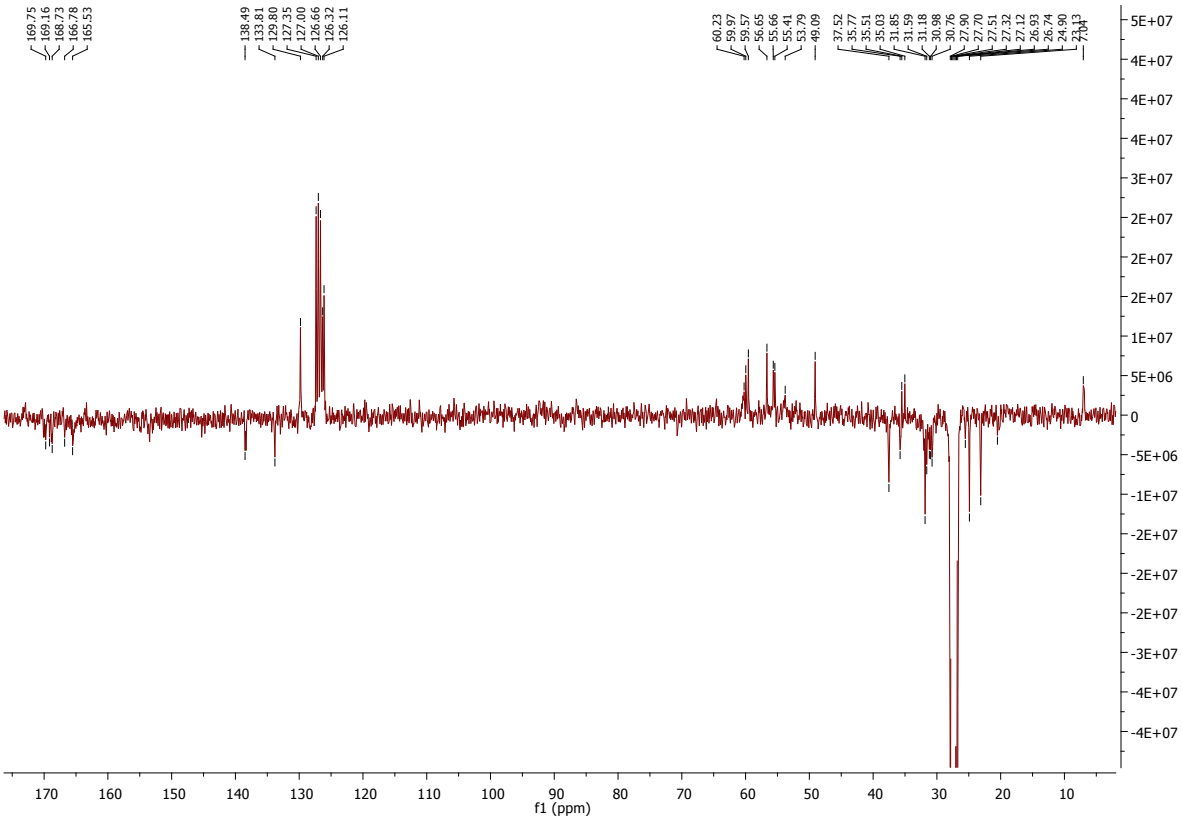


44

^{1}H NMR (400 MHz, Acetone-d_6)

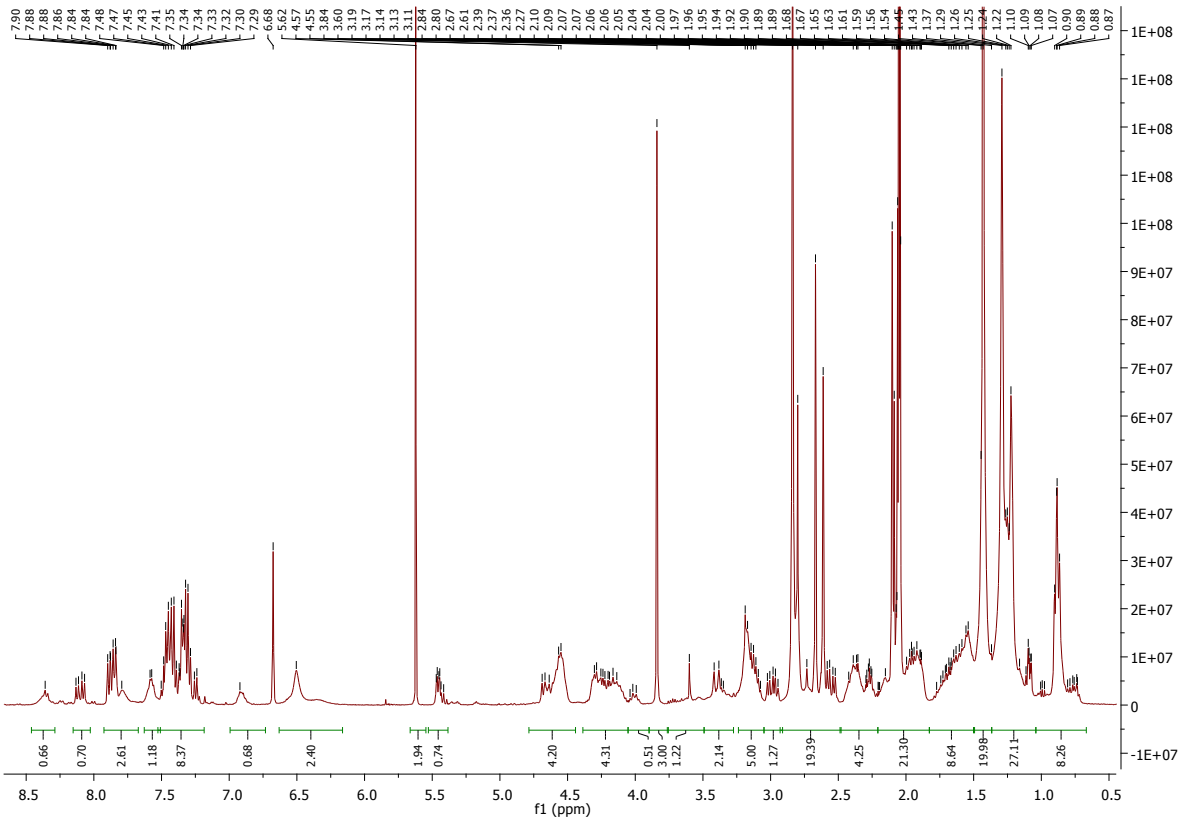


^{13}C NMR (101 MHz, Acetone-d_6)

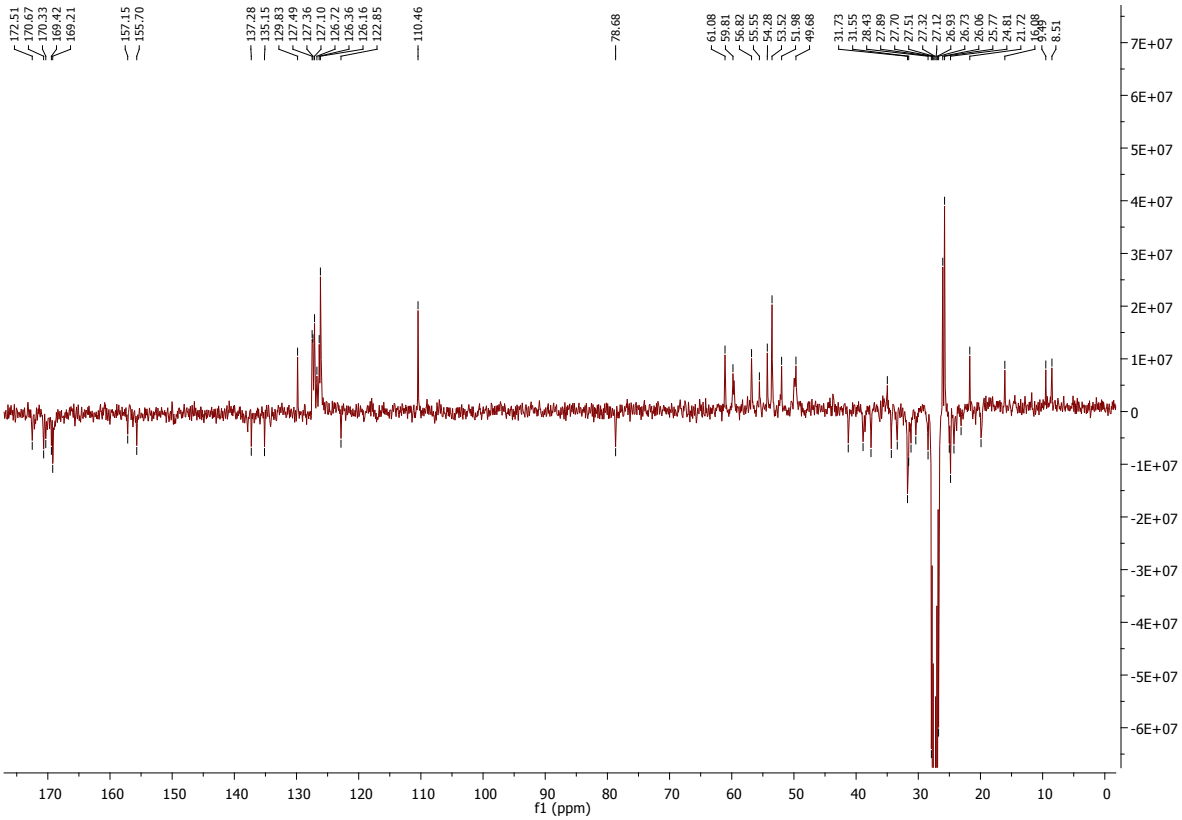


46

^{1}H NMR (400 MHz, Acetone-d_6)

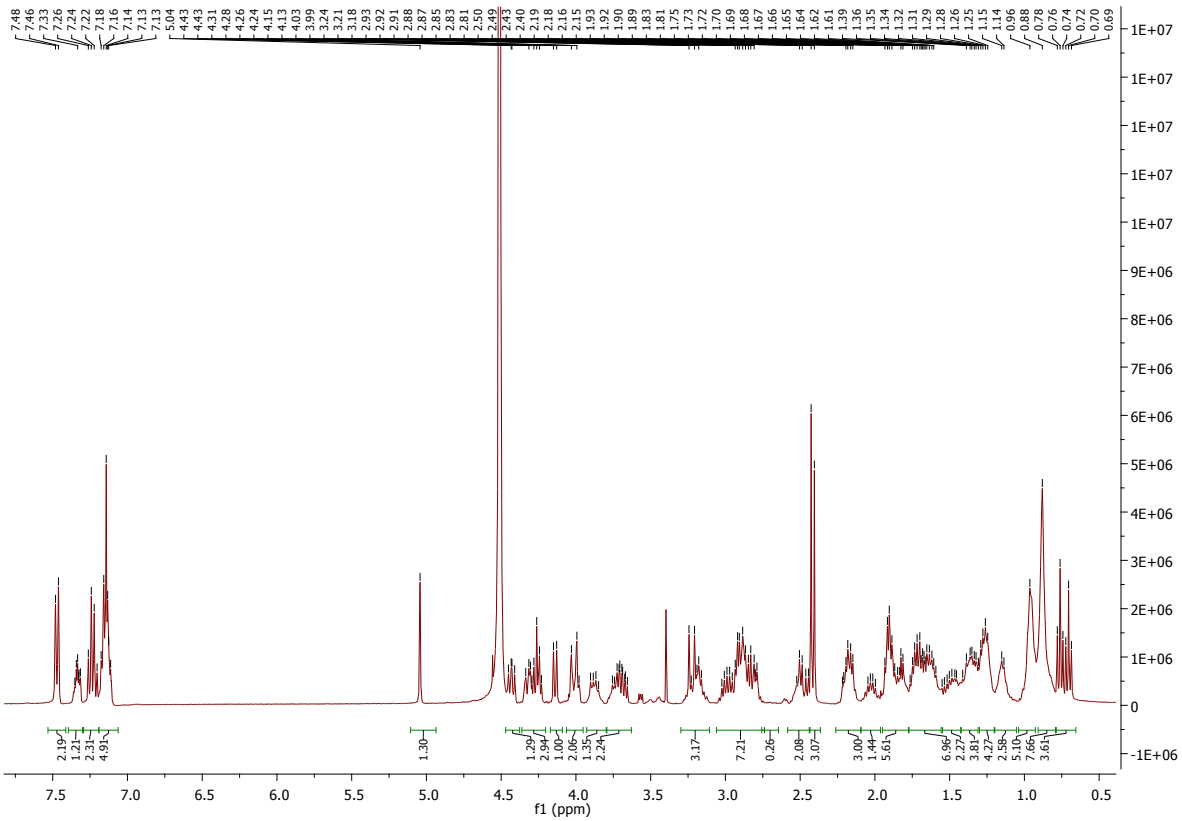


^{13}C NMR (101 MHz, Acetone-d_6)



13

^{1}H NMR (400 MHz, D_2O)



^{13}C NMR (75.6 MHz, D_2O)