Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Probing the effect of counterion structure on API IL physical form and lipid solubility

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Experimental

Materials

Cinnarizine and lumefantrine were purchased from AK Scientific (CA, USA). 1-hexanol, 1-decanol, 1-tetradecanol, 1-hexadecanol, 1-octadecanol, 2-ethyl-1-hexanol, 2-butyl-1-octanol, 2-hexyl-1-decanol, 2-octyl-1-dodecanol, sulfamic acid, pyridine (anhydrous) and 1-octyl sulfate were purchased from Sigma Aldrich (MO, USA). 2-Decanol was purchased from Acros (NJ, USA), 3-decanol and 4-decanol were purchased from Alfa Aesar (Heysham, England). 5-Decanol was purchased from TCI America (OR, USA). Glyceryl tricaprylate/caprate (Captex® 355 EP/NF) and Glycerol monocaprylocaprate (Capmul® MCM EP) were supplied by Anzchem (NSW, Australia). Polyoxyl castor oil (Kolliphor® RH 40) was obtained from BASF (VIC, Australia). Glycerol/glyceryl monolinoleate (Maisine™ 35-1) was supplied by Trapeze Associates Pty. Ltd. (NSW, Australia). Soybean oil and butylated hydroxytoluene were purchased from Sigma Aldrich (MO, USA). Ethanol, methanol and dichloromethane were purchased from Merck (VIC, Australia). Sodium taurodeoxycholate >95% (NaTDC), 4-bromophenylboronic acid, and porcine pancreatin (8 X USP specification activity) were purchased from Sigma Aldrich (MO, USA). Phosphatidylcholine (PC) (Lipoid E PC S, ~99.2% pure, from egg yolk) was obtained from Lipoid (Ludwigshafen, Germany). The 0.6 M and 0.2 M sodium hydroxide solutions were diluted from a stock solution of 1.0 M sodium hydroxide that was purchased from Science Supply (VIC, Australia). Formic acid was purchased from Sigma Aldrich (NSW, Australia). All solvents used were of analytical purity or high-performance liquid chromatography (HPLC) grade.

Characterisation of Ionic liquids

Successful lipophilic salt synthesis was confirmed using Nuclear Magnetic Resonance (NMR) spectroscopy, Liquid Chromatography-Mass Spectrometry (LC-MS) and High Resolution Mass Spectrometry (HR-MS) techniques. All final compounds had a purity of >95%. Samples prepared for NMR spectroscopy were dissolved in $CDCl_3$, MeOH-d_3 or DMSO-d_6, while samples prepared for LC-MS and HR-MS were dissolved in MeCN. The melting point / glass transition ranges of all compounds were assessed using an Axiolab Laboratory Microscope (manufactured 1997, S/N 982650) supplied by Carl Zeiss. The microscope was fitted with cross polarising filters and coupled to a Linkam HFS91 hot stage connected to a Linkam TP93 system controller. Images were captured with a Canon LA-DC52C PowerShot A70 camera using Canon Utilities RemoteCapture version 2.7.2.16 software.

^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were obtained at 400.13 Hz and 100.62 Hz respectively, on a Bruker Advance III Nanobay 400 MHz spectrometer coupled to the BACS 60 automatic sample changer. All spectra were processed using MestReNova 6.0 software. The chemical shifts of all 1H signals were measured relative to the expected solvent peaks of the NMR solvent; 2.50 ppm (dimethyl sulfoxide). The data for all spectra are reported in the following format: chemical shift (integration, coupling constant J (Hz), multiplicity). Multiplicity is defined as; s = singlet, d= doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, and m = multiplet. Subsequent abbreviations also include J (Hz) = coupling constant in Hertz.

Compounds were also identified through use of low resolution mass spectrometry, which was performed on an Agilent 6100 Series Single Quad LC/MS coupled with an Agilent 1200 Series HPLC, 1200 Series G1311A quaternary pump, 1200 series G1329A thermostatted autosampler, and 1200 series G1314B variable wavelength detector. The conditions for liquid chromatography were: reverse phase HPLC analysis using a Phenomenex Luna C8(2) 5 µm (50 x 4.6 mm) 100 Å column at a temperature of 30°C. Each sample (5 µL) was injected and then and run with a gradient of 5-100% (v/v) solvent A over 10 min. Solvent A was 99.9% acetonitrile, 0.1% formic acid and solvent B was 99.9% water with 0.1% formic acid. Detection was at a UV wavelength of 254 nm. The conditions for mass spectrometry were: quadrupole ion source with multimode-ES, drying gas temperature 300°C, and vaporizer temperature 200°C. The capillary voltage was 2000 V in positive mode, or 4000V in negative mode and the scan range was 100-1000 m/z with a step size of 0.1 sec over 10 min.

All high resolution mass spectrometry analyses were performed on an Agilent 6224 TOF LC/MS Mass Spectrometer coupled to an Agilent 1290 Infinity HPLC (Agilent, Palo Alto, CA). All data were acquired and reference mass corrected via a dual-spray electrospray ionisation (ESI) source. Each scan or data point on the Total Ion Chromatogram (TIC) is an average of 13,700 transients, producing a spectrum every second. Mass spectra were created by averaging the scans across each peak and background subtracting against the first 10 seconds of the TIC. Acquisition was performed using the Agilent Mass Hunter Data Acquisition software version B.05.00 Build 5.0.5042.2 and analysis was performed using Mass Hunter Qualitative Analysis version B.05.00 Build 5.0.519.13. The MS conditions were: electrospray ionisation, a drying gas flow of 11 L/min at a temperature of 325°C, a nebuliser at 45 psi, a capillary voltage of 4000 V, the fragmentor at 160 V, the skimmer

at 65 V, and the OCT RFV of 750 V. The scan range acquired was 100-1500 m/z. The internal reference ions in positive ion mode had a m/z of 121.050873 and 922.009798.

Chromatographic separation was performed using an Agilent Zorbax SB-C18 Rapid Resolution HT 2.1 x 50 mm, 1.8 µm column (Agilent Technologies, Palo Alto, CA) using an acetonitrile gradient (5% to 100%) over 3.5 minutes at 0.5 mL/min.

Equilibrium Solubility Experiments

The equilibrium solubility of all cinnarizine and lumefantrine compounds was assessed in model medium-chain and long-chain formulations (compositions listed in Table 4.1). The process involved the addition of 20 mg of compound into 200 mg of each LBF in a microcentrifuge tube. Each equilibrium solubility experiment was completed in triplicate, except for the third series of cinnarizine ILs, which were completed as a single sample trial. Equilibrium solubility was defined when the solubility measured across two consecutive days varied less than 5%. The samples were allowed to equilibrate at 37 °C and vortex-mixed twice a day to ensure the compounds were well dispersed in the LBF. The samples were left to equilibrate for at least 3 days. If all the compound was observed to be fully dissolved, the sample was centrifuged for 15 min at 14,800 rpm (21,000 x g) at 37 °C (Thermo Scientific, Heraeus Pico 21 Centrifuge) to confirm complete dissolution. Where no pellet was observed, another 20 mg of compound was added, and the process was repeated until complete dissolution was no longer observed and excess IL was evident. At each time point, samples were then centrifuged at 37 °C (14,800 rpm (21,000 x g), Thermo Scientific, Heraeus Pico 21 Centrifuge) and 20 mg aliquots of the supernatant taken and dissolved in 1 mL of chloroform:methanol (2:1). The chloroform:methanol mixture was then diluted 20-fold with acetonitrile, with a further dilution of 10- or 20-fold (depending on the mass of cinnarizine or lumefantrine IL in the LBF) with water : acetonitrile (1:1). The samples were then assayed by HPLC to determine the concentration of drug in the formulation.

HPLC Analysis

All HPLC analyses were conducted with a Waters Alliance 2695 Separation Module (Waters Alliance Instruments, Milford, USA). For the cinnarizine ILs, the column was a reverse phase Agilent Eclipse XDB 3.5 µm, 50 x 4.6 mm column. The injection volume was 50 µL and the UV detection was at 254 nm. The mobile phase was run isocratically and consisted of 20 mM ammonium dihydrogen phosphate at a pH of 4.2 (mobile phase A) and acetonitrile (mobile phase B). The mobile phase composition was 50:50 v/v and the flow rate was 1 mL/min. The retention time was approximately 2.4 minutes. Calibration standards were prepared and used at nominal concentrations from 20-20000 ng/mL.

For the lumefantrine salts, the column was a reverse phase C-18 Phenomenex 3 µm, 100 x 4.6 mm column. The injection volume was 50 µL and UV detection was at 254 nm. The mobile phase was run isocratically and consisted of water with 0.1% w/v formic acid (mobile phase A) and acetonitrile with 0.1% w/v formic acid (mobile phase B). The mobile phase composition was 45:55 v/v (A/B). The flow rate was 1 mL/min and the retention time was approximately 2.5 minutes. The calibration standards were prepared and used at nominal concentrations from 50-20000 ng/mL.

Both cinnarizine and lumefantrine assays were validated over two days. Intra-assay accuracy was determined by replicated analysis (n = 5) of three standards at the low, middle, and highest concentrations. Inter-assay accuracy was determined on two separate days. The data were expressed as a percentage of the measured concentration over the theoretical concentration. The mean accuracy of the lowest concentration (20 and 50 ng/mL for cinnarizine and lumefantrine, respectively) were within ± 15% of the theoretical concentration, while the mean accuracy of the middle and highest concentrations (5000 and 20000 ng/mL for both cinnarizine and lumefantrine) were within ± 10% of the theoretical concentration. Intra-assay precision and inter-assay precision were calculated in both runs for each of the three concentrations and expressed as the coefficient of variation. Precision was within ± 10% for all three concentrations. Linearity was performed on the standard curves for each analysis and linearity was accepted when the correlation coefficient (r^2) of the regression line was > 0.99.

Supporting Figures

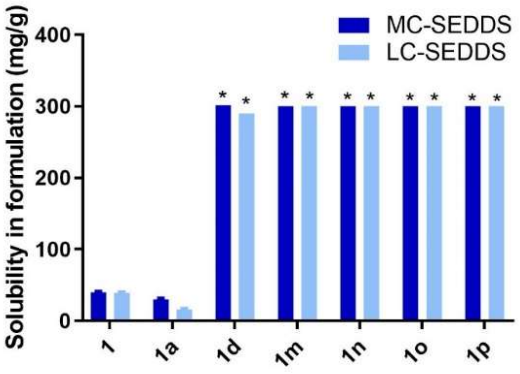


Figure SI 1 – Equilibrium solubility in MCF and LCF for cinnarizine (1), cinnarizine HCl (1a) and cinnarizine ILs (1-decyl sulfate 1d, 2-decyl sulfate 1m, 3-decyl sulfate 1n, 4-decyl sulfate 1o and 5-deycl sulfate 1p). Data are n = 1. * IL was miscible in formulation.

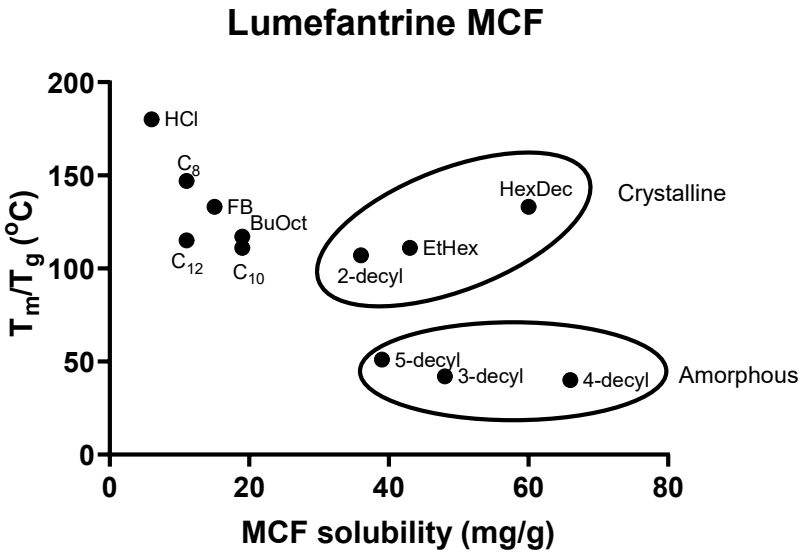


Figure SI 2 – Melting temperature - T_g/T_m (°C) vs MCF solubility (mg/g) for lumefantrine ILs.

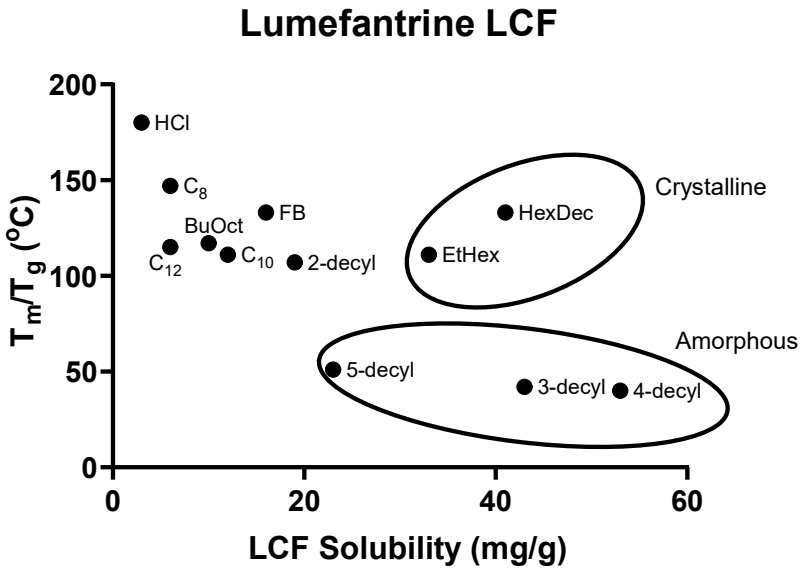
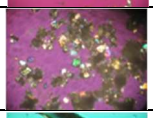
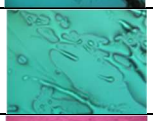
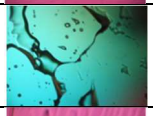
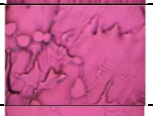
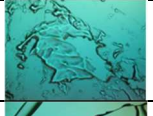
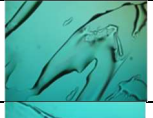
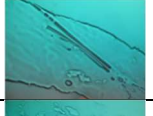
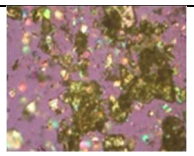
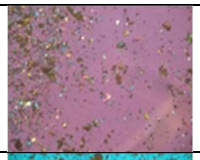
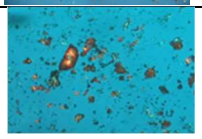
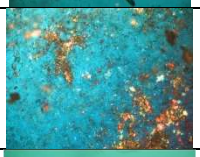
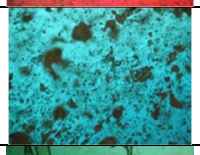


Figure SI 3 – Melting temperature - T_g/T_m (°C) vs LCF solubility (mg/g) for lumefantrine ILs.

Cinnarizine form	Cross-Polarised Microscope Image	Average Equilibrium Solubility in FB eqs. ± SD (mg/g)	
		MCF	LCF
free base **1**		39.7 ± 0.8	38.7 ± 0.8
hydrochloride **1a**		29.7 ± 1.0	15.8 ± 0.7
1-hexyl sulfate (C_6) **1b**		miscible (>325.5)	forms 3 layers
1-octyl sulfate (C_8) **1c**		miscible (>312.2)	172.8 ± 19.3
1-decyl sulfate (C_{10}) **1d**		miscible (n=1) (>301.6)	miscible (n=1) (>289.7)
1-dodecyl sulfate (C_{12}) **1e**		211.1 ± 9.2	161.8 ± 8.8
1-tetradecyl sulfate (C_{14}) **1f**		137.3 ± 10.1	19.2 ± 5.1
1-hexadecyl sulfate (C_{16}) **1g**		99.3 ± 4.3	16.5 ± 4.0
1-octadecyl sulfate (C_{18}) **1h**		65.3 ± 4.3	15.1 ± 4.0
2-ethyl-1-hexyl sulfate **1i**		miscible 308.9 ± 18.0	272.7 ± 20.1
2-butyl-1-octyl sulfate **1j**		miscible >262.1 ± 5.5	226.4 ± 15.3
2-hexyl-1-decyl sulfate **1k**		miscible (>260.9 ± 10.1)	miscible (>249.1 ± 16.3)
2-octyl-1-dodecyl sulfate **1l**		136.4 ± 6.7	112.1 ± 9.4
2-decyl sulfate **1m**		miscible (n=1)	miscible (n=1)
3-decyl sulfate **1n**		miscible (n=1)	miscible (n=1)
4-decyl sulfate **1o**		miscible (n=1)	miscible (n=1)
5-decyl sulfate **1p**		miscible (n=1)	miscible (n=1)

Lumefantrine form	Cross-Polarised Microscope Image	Average Equilibrium Solubility in FB eqs. ± SD (mg/g)	
		MCF	LCF
free base **2**		15.4 ± 0.3	16.2 ± 0.8
hydrochloride **2a**		5.8 ± 0.2	3.4 ± 0.4
1-octyl sulfate (C_8) **2b**		10.7 ± 1.0	6.4 ± 1.4
1-decyl sulfate (C_{10}) **2c**		19.2 ± 1.8	11.7 ± 1.5
1-dodecyl sulfate (C_{12}) **2d**		11.4 ± 1.6	6.2 ± 1.7
2-ethyl-1-hexyl sulfate **2e**		43.3 ± 1.7	33.1 ± 6.9
2-butyl-1-octyl sulfate **2f**		19.2 ± 1.2	10.2 ± 0.2
2-hexyl-1-decyl sulfate **2g**		59.7 ± 2.4	41.4 ± 2.2
docusate **2h**		miscible 288.5 ± 6.1	miscible 259.5 ± 5.9
2-decyl sulfate **2i**		36.3 ± 3.0	19.2 ± 1.9
3-decyl sulfate **2j**		48.2 ± 3.3	43.3 ± 1.1
4-decyl sulfate **2k**		66.4 ± 3.1	53.4 ± 3.9
5-decyl sulfate **2l**		37.8 ± 5.7	23.0 ± 1.6

Compound characterization details

*Cinnarizine.HCl (**1a**)*

^{1}H NMR (DMSO-d_6) δ 10.75 (s, 1H), 7.52 – 7.42 (m, 5H), 7.38 (t, J = 7.2 Hz, 3H), 7.32 (t, J = 7.2 Hz, 5H), 7.27 – 7.16 (m, 2H), 6.82 (d, J = 15.9 Hz, 1H), 6.45 – 6.32 (m, 1H), 4.47 (s, 1H), 3.88 (s, 2H), 3.11 (s, 2H), 2.84 (s, 2H), 2.37 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 142.0, 138.5, 135.4, 128.7, 128.6, 127.5, 127.2, 126.8, 118.0, 73.8, 64.9, 56.9, 50.3, 48.0. m/z $^{+}$ve mode – 369.4. Melting point: 207-210°C.

*Lumefantrine.HCl (**2a**)*

^{1}H NMR (DMSO-d_6) δ 10.17 (s, 1H), 8.20 (dd, J = 14.0, 3.9 Hz, 3H), 7.67 – 7.57 (m, 5H), 7.48 (dd, J = 8.4, 2.0 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 6.63 (d, J = 4.3 Hz, 1H), 5.95 – 5.85 (m, 1H), 3.44 – 3.37 (m, 1H), 3.29 – 3.27 (m, 1H), 3.27 – 3.10 (m, 3H), 1.77 – 1.58 (m, 4H), 1.41 – 1.26 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.4, 139.1, 138.2, 135.0, 134.9, 134.4, 133.6, 133.5, 132.5, 131.6, 130.9, 130.5, 129.0, 128.4, 126.9, 125.8, 122.6, 121.1, 64.8, 56.9, 53.3, 52.7, 24.7, 24.5, 19.5, 19.4, 13.6, 13.5. m/z $^{+}$ve mode – 528.2. Melting point: 180-200°C.

Sodium 2-hexyl-1-decyl sulfate

^{1}H NMR (DMSO-d_6) δ 3.57 (d, J = 5.7 Hz, 2H), 1.54 – 1.41 (m, 1H), 1.35 – 1.09 (m, 24H), 0.96 - 0.78 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 68.2, 37.3, 31.3, 30.7, 29.5, 29.1, 29.0, 28.7, 26.2, 26.1 (2C), 14.0. m/z $^{-}$ve mode – 321.1

*Cinnarizine 1-hexyl sulfate (**1b**)*

93% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.60 – 7.18 (m, 15H), 6.85 (d, J = 15.8 Hz, 1H), 6.47 – 6.26 (m, 1H), 4.50 (s, 1H), 3.94 (s, 2H), 3.68 (t, J = 6.8 Hz, 2H), 3.46 (d, J = 11.8 Hz, 2H), 3.15 (dd, J = 21.4, 10.5 Hz, 2H), 2.90 (d, J = 12.6 Hz, 2H), 2.24 (t, J = 11.8 Hz, 2H), 1.53 – 1.44 (m, 2H), 1.27 (d, J = 10.7 Hz, 6H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 139.1, 135.3, 128.7, 128.7, 127.5, 127.2, 126.9, 117.6, 73.5, 65.7, 57.1, 50.7, 48.2, 31.0, 29.0, 25.2, 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2336 HRMS –ve mode *calcd for* $C_6H_{13}O_4S^-$ 181.0535 *found* 181.0537.

*Cinnarizine 1-octyl sulfate (**1c**)*

88% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.59 – 7.12 (m, 15H), 6.84 (d, J = 15.8 Hz, 1H), 6.38 – 6.23 (m, 1H), 4.49 (s, 1H), 3.93 (s, 2H), 3.67 (t, J = 6.8 Hz, 2H), 3.43 (s, 2H), 3.13 (s, 2H), 2.89 (d, J = 11.6 Hz, 2H), 2.23 (t, J = 12.0 Hz, 2H), 1.53 – 1.42 (m, 2H), 1.24 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 139.1, 135.3, 128.7, 128.6, 127.5, 127.2, 126.8, 117.6, 73.5, 65.8, 57.1, 50.7, 48.1, 31.2, 29.1, 28.7 (2C), 25.5, 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2334 HRMS –ve mode *calcd for* $C_8H_{17}O_4S^-$ 205.0848 *found* 205.0853.

*Cinnarizine 1-decyl sulfate (**1d**)*

96% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.57 – 7.15 (m, 15H), 6.84 (d, J = 15.8 Hz, 1H), 6.43 – 6.23 (m, 1H), 4.49 (s, 1H), 3.93 (s, 2H), 3.67 (t, J = 6.8 Hz, 2H), 3.44 (s, 2H), 3.14 (s, 2H), 2.90 (d, J = 12.1 Hz, 2H), 2.24 (t, J = 11.6 Hz, 2H), 1.53 – 1.43 (m, 2H), 1.33 – 1.19 (m, 14H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 139.0, 135.3, 128.7 (2C), 127.5, 127.2, 126.8, 117.7, 73.5, 65.5, 57.1, 50.8, 48.2, 31.3, 29.1, 29.0, 29.0, 28.8, 28.7, 25.5, 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2334 HRMS –ve mode *calcd for* $C_{10}H_{21}O_4S^-$ 237.1161 *found* 237.1168.

*Cinnarizine 1-dodecyl sulfate (**1e**)*

92% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.57 – 7.13 (m, 16H), 6.83 (d, J = 15.8 Hz, 1H), 6.39 – 6.22 (m, 1H), 4.48 (s, 1H), 3.92 (s, 2H), 3.66 (t, J = 6.7 Hz, 2H), 3.43 (s, 2H), 3.13 (s, 2H), 2.89 (d, J = 11.7 Hz, 2H), 2.25 (d, J = 11.5 Hz, 2H), 1.55 – 1.40 (m, 2H), 1.26 (m, 18H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 139.1, 135.3, 128.8, 128.7, 127.5, 127.2, 126.9, 117.6, 73.5, 65.5, 57.1, 50.7, 48.2, 31.3, 29.1 (2C), 29.0, 28.8, 28.7, 25.5, 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2326 HRMS –ve mode *calcd for* $C_{12}H_{25}O_4S^-$ 265.1474 *found* 265.1484.

*Cinnarizine 1-tetradecyl sulfate (**1f**)*

93% yield. ^{1}H NMR (DMSO-d_6) δ 9.45 (s, 1H), 7.62 – 7.13 (m, 15H), 6.83 (d, J = 15.8 Hz, 1H), 6.48 – 6.13 (m, 1H), 4.48 (s, 1H), 3.91 (s, 2H), 3.67 (t, J = 6.8 Hz, 2H), 3.43 (s, 2H), 3.13 (s, 2H), 2.87 (s, 2H), 2.23 (s, 2H), 1.46 (m, 2H), 1.25 (m, 22H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 138.9, 135.3, 128.7 (2C), 127.5, 127.2, 126.8, 117.8, 73.5, 65.5, 57.2, 50.8, 48.3, 31.3, 29.1, 29.0 (2C), 28.8, 28.7, 25.5, 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2329 HRMS –ve mode *calcd for* $C_{14}H_{29}O_4S^-$ 293.1787 *found* 293.1795.

*Cinnarizine 1-hexadecyl sulfate (**1g**)*

93% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.55 – 7.15 (m, 15H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.37 – 6.25 (m, 1H), 4.48 (s, 1H), 3.92 (s, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 3.43 (s, 2H), 3.13 (s, 2H), 2.87 (s, 2H), 2.23 (s, 2H), 1.52 – 1.41 (m, 2H), 1.25 (m, 26H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 138.9, 135.3, 128.7, 128.7, 127.5, 127.2, 126.8, 117.8, 73.5, 65.5, 57.2, 50.8, 48.3, 31.3, 29.1, 29.0, 29.0, 28.8, 28.7, 25.5, 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2335 HRMS –ve mode *calcd for* $C_{16}H_{33}O_4S^-$ 321.2100 *found* 321.2104.

*Cinnarizine 1-octadecyl sulfate (**1h**)*

92% yield. ^{1}H NMR (DMSO-d_6) δ 9.47 (s, 1H), 7.74 – 7.08 (m, 15H), 6.82 (d, J = 15.8 Hz, 1H), 6.52 – 6.12 (m, 1H), 4.48 (s, 1H), 3.88 (s, 2H), 3.67 (t, J = 6.8 Hz, 2H), 3.43 (m, 1H), 3.13 (m, 2H), 2.87 (s, 2H), 2.28 (m, 2H), 1.59 – 1.38 (m, 2H), 1.23 (s, 30H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 138.9, 135.3, 128.7, 128.7, 127.5, 127.2, 126.8, 117.8, 73.5, 65.5, 57.2, 50.8, 48.3, 31.3, 29.1, 29.0 (2C) 28.8, 28.7, 25.5, 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2332 HRMS –ve mode *calcd for* $C_{18}H_{37}O_4S^-$ 349.2413 *found* 349.2419.

*Cinnarizine 2-ethyl-1-hexyl sulfate (**1i**)*

89% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.45 – 7.36 (m, 6H), 7.32 (t, *J* = 7.6 Hz, 5H), 7.22 (t, *J* = 7.3 Hz, 2H), 6.82 (d, *J* = 15.5 Hz, 1H), 6.36 – 6.26 (m, 1H), 4.47 (s, 1H), 3.89 (s, 2H), 3.64 – 3.53 (m, 2H), 3.42 (s, 2H), 3.25-2.75 (m, 4H), 2.28 (s, 2H), 1.41 (dt, *J* = 11.9, 5.9 Hz, 1H), 1.34 – 1.14 (m, 8H), 0.85 (dt, *J* = 14.9, 4.9 Hz, 6H). ^{13}C NMR (DMSO-d_6) δ 141.8, 138.6, 135.4, 128.7, 128.6, (2C), 127.5, 127.1, 126.8, 118.3, 73.6, 67.8, 57.3, 50.8, 38.8, 29.9, 28.4, 23.2, 22.5, 13.9, 10.8. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2334 HRMS –ve mode *calcd for* $C_8H_{17}O_4S^-$ 205.0848 *found* 205.0855.

*Cinnarizine 2-butyl-1-octyl sulfate (**1j**)*

96% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.37 (m, 6H), 7.32 (dd, *J* = 9.4, 5.6 Hz, 5H), 7.22 (t, *J* = 7.3 Hz, 2H), 6.83 (d, *J* = 15.9 Hz, 1H), 6.38 – 6.24 (m, 1H), 4.48 (s, 1H), 3.91 (s, 2H), 3 .58 (d, *J* = 5.7 Hz, 2H), 3.43 (s, 2H), 3.13 (s, 2H), 2.87 (s, 2H), 2.23 (s, 2H), 1.51-1.41 (m, 1H), 1.33 – 1.10 (m, 16H), 0.85 (dd, *J* = 6.8, 5.5 Hz, 6H). ^{13}C NMR (DMSO-d_6) δ 141.7, 138.9, 135.3, 128.7 (2C), 127.5, 127.2, 126.8, 117.7, 73.5, 68.2, 57.2, 50.7, 48.2, 37.3, 31.3, 30.7, 30.4, 29.1, 28.4, 26.1, 22.5, 22.1, 13.9 (2C). HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2313 HRMS –ve mode *calcd for* $C_{12}H_{25}O_4S^-$ 265.1474 *found* 265.1483.

*Cinnarizine 2-hexyl-1-decyl sulfate (**1k**)*

91% yield. ^{1}H NMR (DMSO-d_6) δ 9.47 (s, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.47 – 7.38 (m, 6H), 7.33 (t, *J* = 7.6 Hz, 5H), 7.22 (t, *J* = 7.3 Hz, 2H), 6.83 (d, *J* = 16.6 Hz, 1H), 6.41 – 6.23 (m, 1H), 4.49 (s, 1H), 3.92 (s, 2H), 3.58 (d, *J* = 5.7 Hz, 2H), 3.44 (s, 2H), 3.13 (s, 2H), 2.88 (s, 2H), 2.24 (s, 2H), 1.53-1.42 (s, 1H), 1.33 – 1.08 (m, 24H), 0.86 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6) δ 141.7, 138.8, 135.3, 128.7, 128.7, 127.5, 127.2, 126.8, 117.8, 73.6, 68.1, 57.2, 50.8, 48.3, 37.3, 31.3, 30.7, 29.4, 29.1, 29.0, 28.7, 26.1 (2C), 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2333 *found* 369.2335 HRMS –ve mode *calcd for* $C_{16}H_{33}O_4S^-$ 321.2100 *found* 321.2109.

*Cinnarizine 2-octyl-1-dodecyl sulfate (**1l**)*

93% yield. ^{1}H NMR (DMSO-d_6) δ 9.47 (s, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.37 (m, 6H), 7.33 (dd, *J* = 9.4, 5.6 Hz, 5H), 7.23 (t, *J* = 7.3 Hz, 2H), 6.84 (d, *J* = 15.1 Hz, 1H), 6.38 – 6.25 (m, 1H), 4.49 (s, 1H), 3.93 (s, 2H), 3.57 (d, *J* = 5.6 Hz, 2H), 3.44 (s, 2H), 3.14 (s, 2H), 2.88 (s, 2H), 2.24 (s, 2H), 1.53-1.42 (m, 1H), 1.33 – 1.11 (m, 34H), 0.86 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 141.7, 138.8, 135.4, 128.7, 128.6, 127.5, 127.2, 126.8, 117.9, 73.6, 68.2, 63.5, 57.2, 50.8, 48.3, 37.3, 31.3, 30.6, 29.4, 29.4, 29.0, 28.7, 26.1, 22.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2333 *found* 369.2334 HRMS –ve mode *calcd for* $C_{20}H_{41}O_4S^-$ 377.2726 *found* 377.2736.

*Cinnarizine 2-decyl sulfate (**1m**)*

96% yield. ^{1}H NMR (DMSO-d_6) δ 9.47 (s, 1H), 7.54 – 7.20 (m, 15H), 6.85 (d, *J* = 15.8 Hz, 1H), 6.38 – 6.26 (m, 1H), 4.50 (s, 1H), 4.11 (dt, *J* = 12.4, 6.4 Hz, 1H), 3.93 (d, *J* = 6.4 Hz, 2H), 3.46 (d, *J* = 11.8 Hz, 2H), 3.15 (q, *J* = 10.2 Hz, 2H), 2.90 (d, *J* = 13.1 Hz, 2H), 2.24 (t, *J* = 12.4 Hz, 2H), 1.52 – 1.41 (m, 1H), 1.38 – 1.19 (m, 14H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 139.1, 135.3, 128.7 (2C), 127.5, 127.2, 126.9, 117.5, 73.5, 72.3, 57.1, 50.7, 48.2, 36.7, 31.3, 29.1, 29.0, 28.7, 24.9, 22.1, 20.8, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2334 HRMS –ve mode *calcd for* $C_{10}H_{21}O_4S^-$ 237.1161 *found* 237.1170.

*Cinnarizine 3-decyl sulfate (**1n**)*

96% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.53 – 7.48 (m, 2H), 7.46 – 7.37 (m, 6H), 7.36 – 7.29 (m, 5H), 7.25 – 7.19 (m, 2H), 6.84 (d, *J* = 15.8 Hz, 1H), 6.36 – 6.25 (m, 1H), 4.49 (s, 1H), 4.00 – 3.86 (m, 3H), 3.45 (d, *J* = 11.7 Hz, 2H), 3.21 – 3.08 (m, 2H), 2.89 (d, *J* = 12.6 Hz, 2H), 2.23 (t, *J* = 11.8 Hz, 2H), 1.54 – 1.37 (m, 4H), 1.33 – 1.17 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.7, 139.1, 135.3, 128.7 (2C), 127.5, 127.2, 126.9, 117.5, 77.0, 73.5, 57.1, 50.7, 48.2, 33.3, 31.3, 29.2, 28.7, 26.5, 24.6, 22.1, 13.9, 9.2. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2335 HRMS –ve mode *calcd for* $C_{10}H_{21}O_4S^-$ 237.1161 *found* 237.1169.

*Cinnarizine 4-decyl sulfate (**1o**)*

94% yield. ^{1}H NMR (DMSO-d_6) δ 9.46 (s, 1H), 7.53 – 7.48 (m, 2H), 7.46 – 7.37 (m, 6H), 7.35 – 7.30 (m, 5H), 7.25 – 7.19 (m, 3H), 6.83 (d, *J* = 15.8 Hz, 1H), 6.36 – 6.26 (m, 1H), 4.48 (s, 1H), 4.01 (p, *J* = 5.9 Hz, 1H), 3.96 – 3.85 (m, 2H), 3.50 – 3.39 (m, 2H), 3.13 (br, s, 2H), 2.88 (d, *J* = 11.7 Hz, 2H), 2.23 (t, *J* = 11.4 Hz, 2H), 1.51 – 1.36 (m, 4H), 1.33 – 1.19 (m, 10H), 0.87 – 0.81 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 141.7, 135.3, 128.7 (2C), 127.5, 127.2, 126.8, 117.7, 75.7, 73.5, 57.1, 50.7, 48.2, 36.1, 34.0, 31.3, 28.9, 24.5, 22.1, 17.8, 14.1, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2335 HRMS –ve mode *calcd for* $C_{10}H_{21}O_4S^-$ 237.1161 *found* 237.1172.

*Cinnarizine 5-decyl sulfate (**1p**)*

93% yield. ^{1}H NMR (DMSO-d_6) δ 9.52 (s, 1H), 7.57 (d, *J* = 7.1 Hz, 2H), 7.53 – 7.43 (m, 6H), 7.43 – 7.35 (m, 5H), 7.28 (t, *J* = 7.3 Hz, 2H), 6.90 (d, *J* = 15.8 Hz, 1H), 6.43 – 6.31 (m, 1H), 4.55 (s, 1H), 4.06 (p, *J* = 6.0 Hz, 1H), 3.99 (s, 2H), 3.49 (s, 2H), 3.19 (s, 2H), 2.95 (d, *J* = 11.9 Hz, 2H), 2.30 (t, *J* = 11.2Hz, 2H), 1.59 – 1.43 (m, 4H), 1.40 – 1.22 (m, 10H), 0.91 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR (DMSO-d_6) δ 141.7, 139.0, 135.3, 128.7 (2C), 127.5, 127.2, 126.8, 117.7, 75.9, 73.5, 57.2, 50.7, 48.2, 33.9, 33.6, 31.5, 26.8, 24.2, 22.3, 22.1, 14.0, 13.9. HRMS +ve mode *calcd for* $C_{26}H_{29}N_2^+$ 369.2331 *found* 369.2335 HRMS –ve mode *calcd for* $C_{10}H_{21}O_4S^-$ 237.1161 *found* 237.1169.

*Lumefantrine 1-octyl sulfate (**2b**)*

99% yield. ^{1}H NMR (DMSO-d_6) δ 9.25 (s, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.57 (m, 5H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 6.61 (s, 1H), 5.72 (s, 1H), 3.66 (t, *J* = 6.7 Hz, 2H), 3.47 – 3.35 (m, 2H), 3.29 – 3.10 (m, 4H), 1.75 – 1.57 (m, 4H), 1.52 – 1.42 (m, 2H), 1.42 – 1.17 (m, 14H), 1.00 – 0.80 (m, 9H). ^{13}C NMR (DMSO-d_6) δ 141.4, 138.7, 138.3, 135.1, 134.4, 133.6, 132.6, 131.7, 130.9, 130.6, 129.0, 128.4, 127.1, 125.3, 122.7, 121.2, 65.6, 64.8, 56.6, 31.3, 29.1, 28.7, (m), 25.5, 25.0, 22.1, 19.4, 13.9, 13.5. HRMS +ve mode calcd for $C_{30}H_{33}Cl_3NO^+$ 528.1628 found 528.1638. HRMS –ve mode calcd for $C_8H_{17}O_4S^-$ 205.0848 found 205.0854.

*Lumefantrine 1-decyl sulfate (**2c**)*

98% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.24 (d, *J* = 1.9 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.68 – 7.58 (m, 5H), 7.53 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.38 (d, *J* = 1.7 Hz, 1H), 6.61 (s, 1H), 5.72 (s, 1H), 3.66 (t, *J* = 6.7 Hz, 2H), 3.47 – 3.35 (m, 2H), 3.30 – 3.09 (m, 4H), 1.75 – 1.56 (m, 4H), 1.52 – 1.43 (m, 2H), 1.38 (s, 2H), 1.35 – 1.19 (m, 16H), 0.99 – 0.82 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 141.4, 138.5, 137.1, 135.5, 134.9, 134.6 (2C), 134.0, 133.5, 133.4, 130.6, 129.2, 129.0, 128.2, 126.8, 124.1, 123.9, 120.8, 68.7, 65.5, 59.0, 54.9, 32.0, 29.7, 29.6, 29.5, 29.4 (2C), 25.9, 25.5, 22.8, 20.0, 14.2, 13.7. HRMS +ve mode calcd for $C_{30}H_{33}Cl_3NO^+$ 528.1628 found 528.1636. HRMS –ve mode calcd for $C_{10}H_{21}O_4S^-$ 237.1161 found 237.1172.

*Lumefantrine 1-dodecyl sulfate (**2d**)*

99% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.68 – 7.57 (m, 5H), 7.52 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 6.61 (s, 1H), 5.72 (s, 1H), 3.66 (t, *J* = 6.7 Hz, 2H), 3.48 – 3.35 (m, 2H), 3.30 – 3.11 (m, 4H), 1.77 – 1.56 (m, 4H), 1.51 – 1.18 (m, 24H), 1.00 – 0.79 (m, 9H). ^{13}C NMR (DMSO-d_6) δ 141.4, 138.7, 138.3, 135.1, 134.4, 133.6, (m), 132.6, 131.7, 130.9, 130.6, 129.0, 128.4, 127.1, 125.3, 122.7, 121.2, 65.6, 64.7, 56.6, 31.3, 29.1, (m), 29.0, 28.8, 28.7, 25.5, 24.9, 22.1, 19.4, 13.9, 13.5. HRMS +ve mode calcd for $C_{30}H_{33}Cl_3NO^+$ 528.1628 found 528.1637. HRMS –ve mode calcd for $C_{12}H_{25}O_4S^-$ 265.1474 found 265.1482.

*Lumefantrine 2-ethyl-1-hexyl sulfate (**2e**)*

97% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.67 – 7.58 (m, 5H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H), 6.61 (d, *J* = 3.9 Hz, 1H), 5.79 – 5.67 (m, 1H), 3.62 – 3.54 (m, 2H), 3.46 – 3.34 (m, 2H), 3.30 – 3.12 (m, 4H), 1.74 – 1.58 (m, 4H), 1.45 – 1.15 (m, 14H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 141.5, 138.6, 137.0, 135.5, 135.0, 134.7, 134.6, 134.0, 133.6, 133.5, 130.6, 129.3, 129.1, 128.3, 126.8, 124.1, 124.0, 120.9, 70.9, 65.5, 59.4, 39.3, 30.2, 29.0, 25.5, 23.5, 23.1, 20.1, 14.2, 13.7, 11.0. HRMS +ve mode *calcd for* $C_{30}H_{33}Cl_3NO^+$ 528.1628 *found* 528.1635. HRMS –ve mode *calcd for* $C_8H_{17}O_4S^-$ 205.0848 *found* 205.0850.

*Lumefantrine 2-butyl-1-octyl sulfate (**2f**)*

99% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.68 – 7.58 (m, 5H), 7.52 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 6.61 (s, 1H), 5.72 (s, 1H), 3.56 (d, *J* = 5.7 Hz, 2H), 3.45 – 3.36 (m, 2H), 3.29 – 3.12 (m, 4H), 1.78 – 1.55 (m, 4H), 1.48 – 1.13 (m, 21H), 0.98 – 0.81 (m, 12H). ^{13}C NMR ($CDCl_3$) δ 141.4, 138.5, 137.1, 135.4, 134.9, 134.6, 134.5, 134.0, 133.5, 133.4, 130.6, 129.2, 129.0, 128.2, 126.8, 124.1, 123.9, 120.8, 71.2, 65.4, 59.1, 54.9, 37.9, 31.9, 31.0, 30.6, 29.7, 25.5, 23.1, 22.8, 20.0, 14.2 (2C), 13.7. HRMS +ve mode *calcd for* $C_{30}H_{33}Cl_3NO^+$ 528.1628 *found* 528.1636. HRMS –ve mode *calcd for* $C_{12}H_{25}O_4S^-$ 265.1474 *found* 265.1480.

*Lumefantrine 2-hexyl-1-decyl sulfate (**2g**)*

96% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.67 – 7.57 (m, 5H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H), 6.61 (d, *J* = 4.2 Hz, 1H), 5.78 – 5.65 (m, 1H), 3.56 (d, *J* = 5.7 Hz, 2H), 3.45 – 3.35 (m, *J* = 13.3 Hz, 2H), 3.29 – 3.13 (m, 4H), 1.75 – 1.58 (m, 4H), 1.49 – 1.12 (m, 30H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 141.6, 138.6, 136.9, 135.6, 135.1, 134.7, 134.5, 134.1, 133.7, 133.6, 130.7, 129.5, 129.3, 129.2, 128.5, 126.8, 124.1, 124.0, 121.1, 71.4, 65.6, 59.8, 56.1, 54.6, 38.0, 32.1, 32.0, 31.1, 30.1, 29.8 (2C), 29.5, 26.9, 26.8, 25.5, 22.8, 20.1, 14.3, 14.2, 13.7. HRMS +ve mode *calcd for* $C_{30}H_{33}Cl_3NO^+$ 528.1628 *found* 528.1636. HRMS –ve mode *calcd for* $C_{16}H_{33}O_4S^-$ 321.2100 *found* 321.2111.

*Lumefantrine docusate (**2h**)*

98% yield. ^{1}H NMR (DMSO-d_6) δ 9.28 (s, 1H), 8.35-8.11 (m,3H), 8.01 (d, J = 8.5 Hz, 1H), 7.71-7.55 (m, 5H), 7.52 (dd, J = 8.4, 1.8 Hz, 1H), 7.38 (d, J = 1.7Hz, 1H), 6.61 (d, J = 3.7 Hz, 1H), 5.73 (s, 1H), 3.99-3.77 (m, 4H), 3.61 (dd, J = 11.5, 3.6 Hz, 1H),3.30-3.10 (m, 4H), 2.99-2.71 (m, 2H), 1.65 (d, J = 6.8 Hz, 4H), 1.49 (s, 2H), 1.42-1.15 (m, 20H),1.03-0.73 (m, 18H). ^{13}C NMR (DMSO-d_6) δ 171.0, 168.3, 141.4, 138.3, 135.1, 134.4,133.6, 133.5, 132.6, 131.6, 130.8, 130.7, 129.0, 128.3, 127.1, 125.3, 122.8, 121.2, 66.1(2C), 66.0, 61.4, 56.5, 53.6, 51.9, 38.1, 34.1, 29.7, 29.6, 28.3, 23.2, 23.0, 22.4 (2C), 19.4, 13.9 (3C),13.5, 10.8(3C), 10.7. HRMS +ve mode calcd for $C_{30}H_{33}Cl_3NO^+$ 528.1628 *found* 528.1632. HRMS –ve mode *calcd for* $C_{20}H_{37}O_7S^-$ 421.2260 *found* 421.2246.

*Lumefantrine 2-decyl sulfate (**2i**)*

98% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.23 (d, *J* = 2.0 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.68 – 7.57 (m, 5H), 7.52 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H), 6.61 (d, *J* = 4.1 Hz, 1H), 5.77 – 5.69 (m, 1H), 4.10 (sex, *J* = 6.0 Hz, 1H), 3.46 – 3.34 (m, 2H), 3.30 – 3.11 (m, 4H), 1.75 – 1.57 (m, 4H), 1.49 – 1.19 (m, 18H), 1.10 (d, *J* = 6.3 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 141.6, 138.5, 138.0, 135.9, 135.0, 134.8, 134.7, 134.1, 133.4 (2C), 130.7, 129.3, 128.9, 128.2, 126.7, 124.1, 123.7, 120.9, 77.0, 65.5, 59.9, 54.7, 37.2, 32.0, 29.8, 29.7, 29.5, 26.7, 25.5, 22.8, 20.9, 20.3, 14.3, 13.9. HRMS +ve mode calcd for $C_{30}H_{33}Cl_3NO^+$ 528.1628 found 528.1635. HRMS –ve mode calcd for $C_{10}H_{21}O_4S^-$ 237.1161 found 237.1165.

*Lumefantrine 3-decyl sulfate (**2j**)*

98% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.23 (d, *J* = 1.9 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.68 – 7.58 (m, 5H), 7.52 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 6.61 (s, 1H), 5.73 (s, 1H), 3.95 (p, *J* = 5.9 Hz, 1H), 3.48 – 3.34 (m, 2H), 3.29 – 3.11 (m, 4H), 1.75 – 1.57 (m, 4H), 1.54 – 1.14 (m, 18H), 0.99 – 0.75 (m, 12H). ^{13}C NMR ($CDCl_3$) δ 141.3, 138.4, 137.0, 135.4, 134.8, 134.5 (2C), 133.9, 133.4, 133.3, 130.6, 129.1, 128.9, 128.1, 126.7, 124.0, 123.80 120.8, 81.3, 65.3, 58.9, 54.9, 33.7, 31.9, 29.8, 29.3, 26.9, 25.5, 25.1, 22.7, 20.0, 14.1, 13.6, 9.3. HRMS +ve mode *calcd for* $C_{30}H_{33}Cl_3NO^+$ 528.1628 *found* 528.1638. HRMS –ve mode *calcd for* $C_{10}H_{21}O_4S^-$ 237.1161 *found* 237.1168.

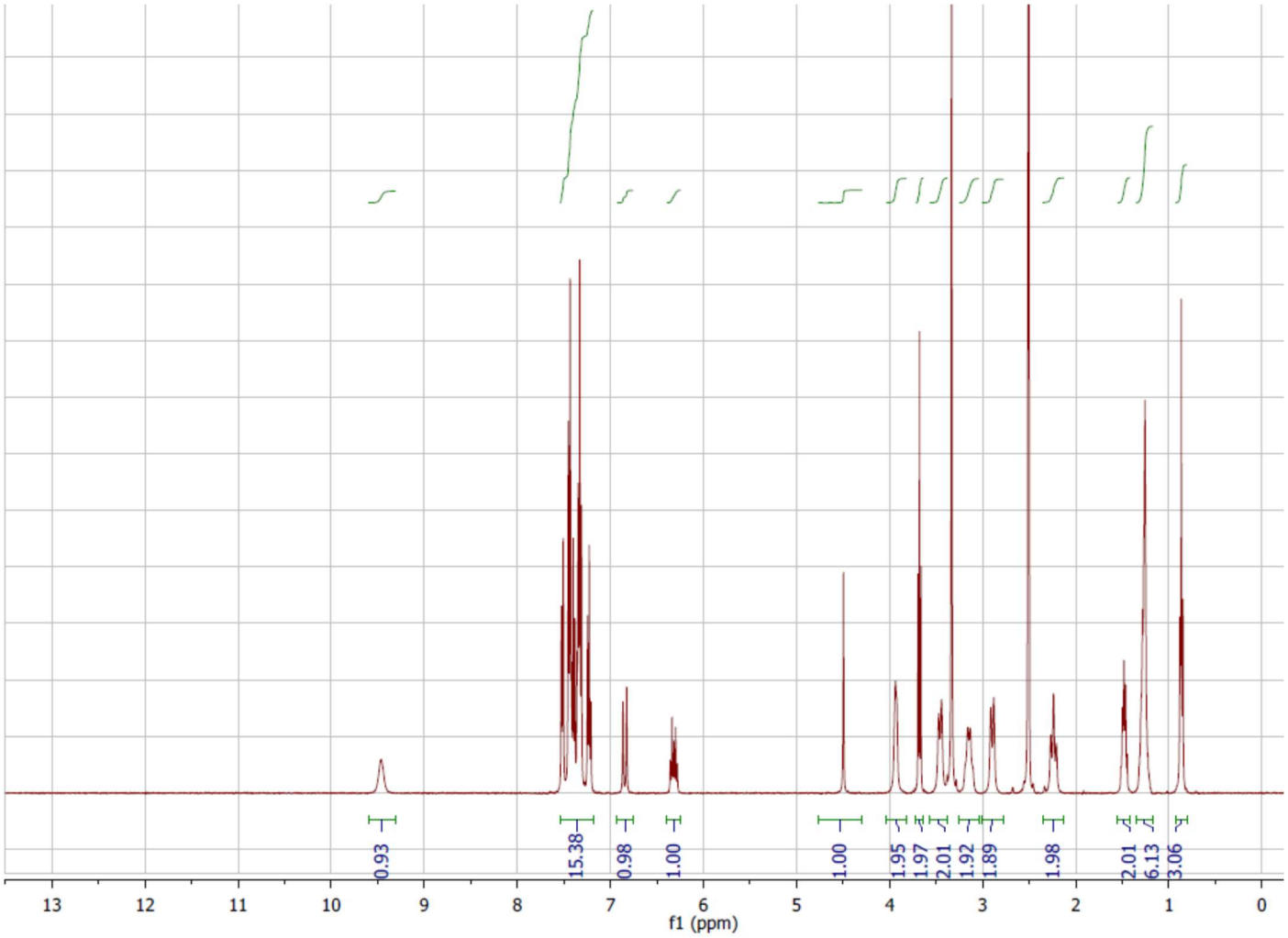
*Lumefantrine 4-decyl sulfate (**2k**)*

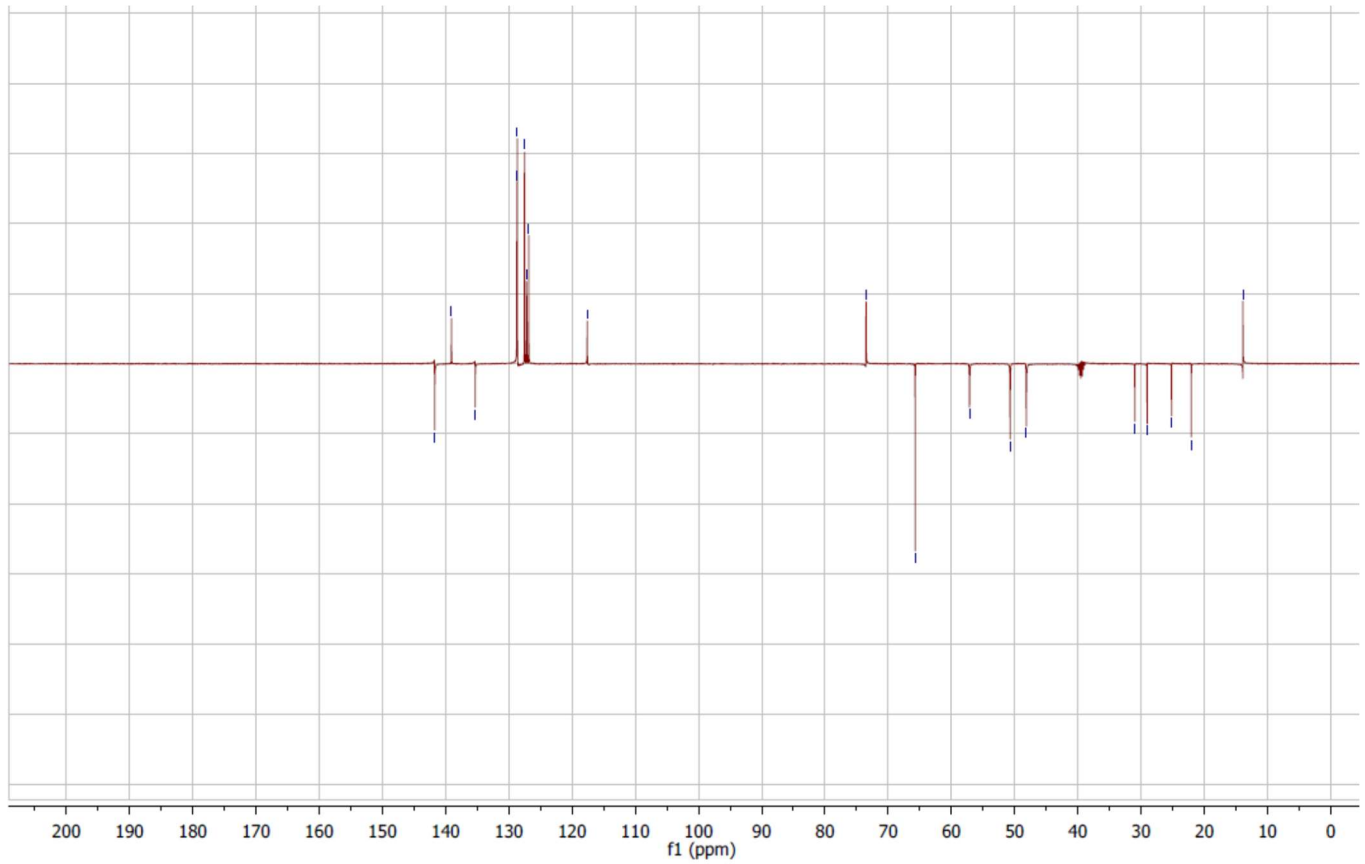
99% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.23 (d, *J* = 1.8 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.56 (m, 5H), 7.52 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 6.61 (s, 1H), 5.72 (s, 1H), 4.00 (p, *J* = 6.0 Hz, 1H), 3.45 – 3.34 (m, 2H), 3.28 – 3.11 (m, 4H), 1.75 – 1.56 (m, 4H), 1.49 – 1.36 (m, 6H), 1.33 – 1.16 (m, 14H), 0.97 – 0.76 (m, 14H). ^{13}C NMR ($CDCl_3$) δ 141.6, 138.5, 138.1, 135.9, 134.9, 134.8, 134.7, 134.1, 133.4 (2C), 130.7, 129.2, 128.9, 128.1, 126.7, 124.1, 123.7, 120.9, 80.5, 65.5, 59.7, 54.6, 36.5, 34.5, 31.9, 29.6, 26.8, 25.1, 22.8, 20.3, 18.5, 14.2 (2C), 13.9. HRMS +ve mode *calcd for* $C_{30}H_{33}Cl_3NO^+$ 528.1628 *found* 528.1636. HRMS –ve mode *calcd for* $C_{10}H_{21}O_4S^-$ 237.1161 *found* 237.1168.

*Lumefantrine 5-decyl sulfate (**2l**)*

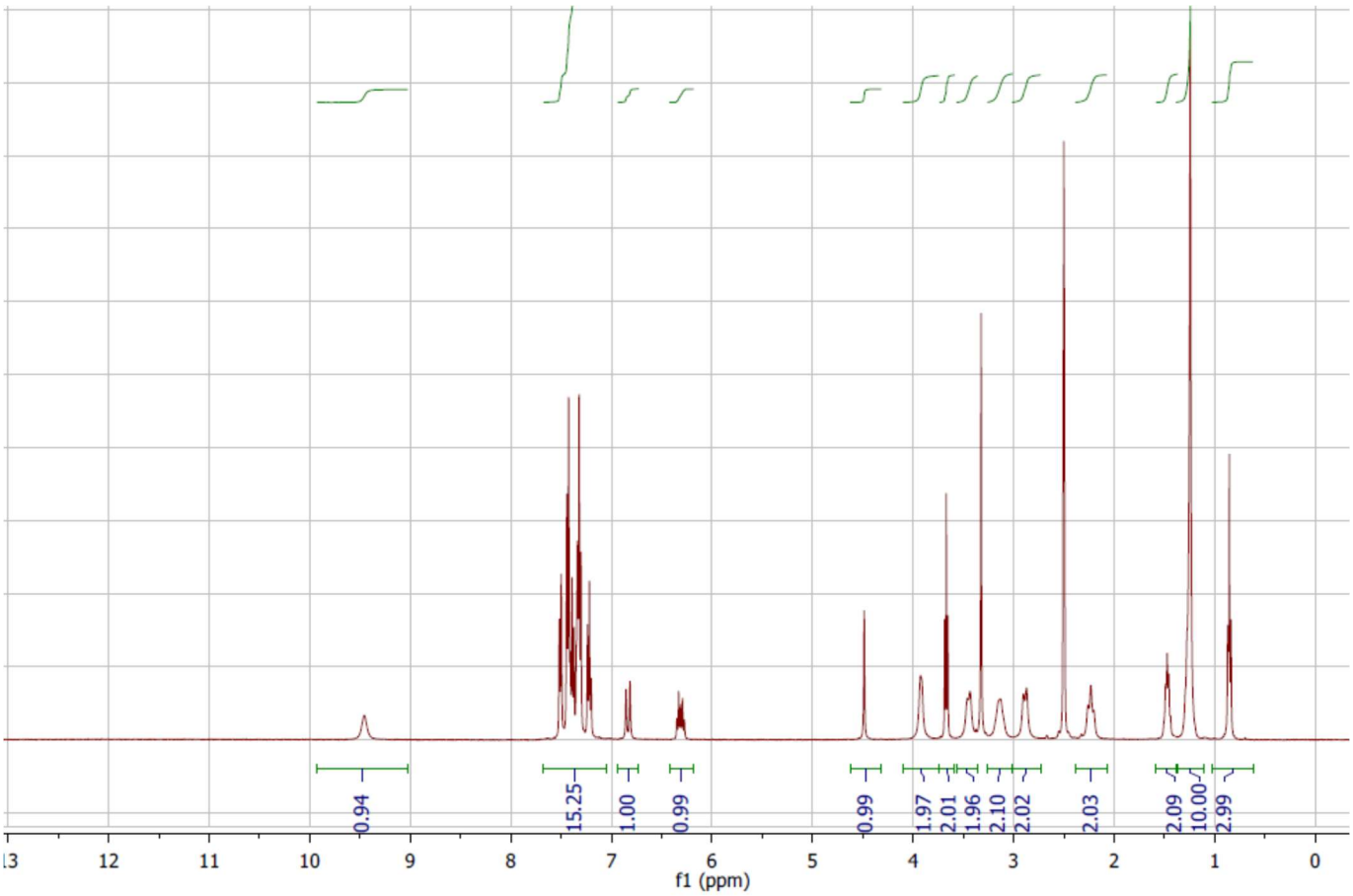
98% yield. ^{1}H NMR (DMSO-d_6) δ 9.26 (s, 1H), 8.22 (d, *J* = 1.8 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.67 – 7.57 (m, 5H), 7.52 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.38 (d, *J* = 1.5 Hz, 1H), 6.61 (s, 1H), 5.71 (s, 1H), 3.99 (p, *J* = 5.9 Hz, 1H), 3.47 – 3.36 (m, 1H), 3.28 – 3.07 (m, 3H), 1.74 – 1.56 (m, 4H), 1.51 – 1.14 (m, 18H), 0.99 – 0.77 (m, 12H). ^{13}C NMR ($CDCl_3$) δ 141.5, 138.5, 137.2, 135.6, 135.0, 134.7, 134.6, 134.1, 133.6, 133.5, 130.6, 129.3, 129.1, 128.3, 126.8, 124.1, 123.9, 121.0, 80.7, 65.5, 59.6, 55.1, 34.3, 34.0, 32.1, 27.3, 25.7, 24.8, 22.9, 22.7, 20.1, 14.2, 14.1, 13.7. HRMS +ve mode *calcd for* $C_{30}H_{33}Cl_3NO^+$ 528.1628 *found* 528.1637. HRMS –ve mode *calcd for* $C_{10}H_{21}O_4S^-$ 237.1161 *found* 237.1169.

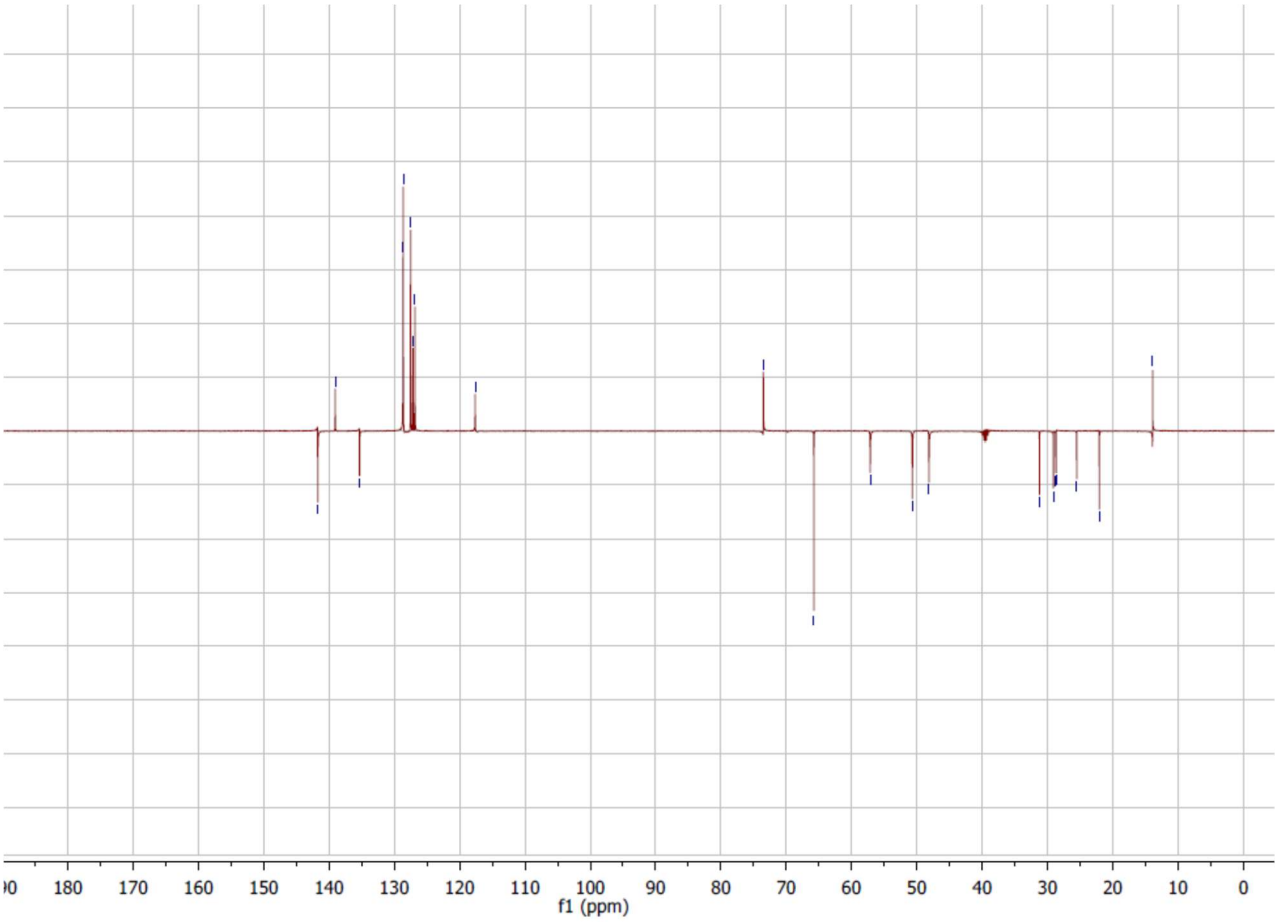
Cinnarizine 1-hexyl sulfate (1b)



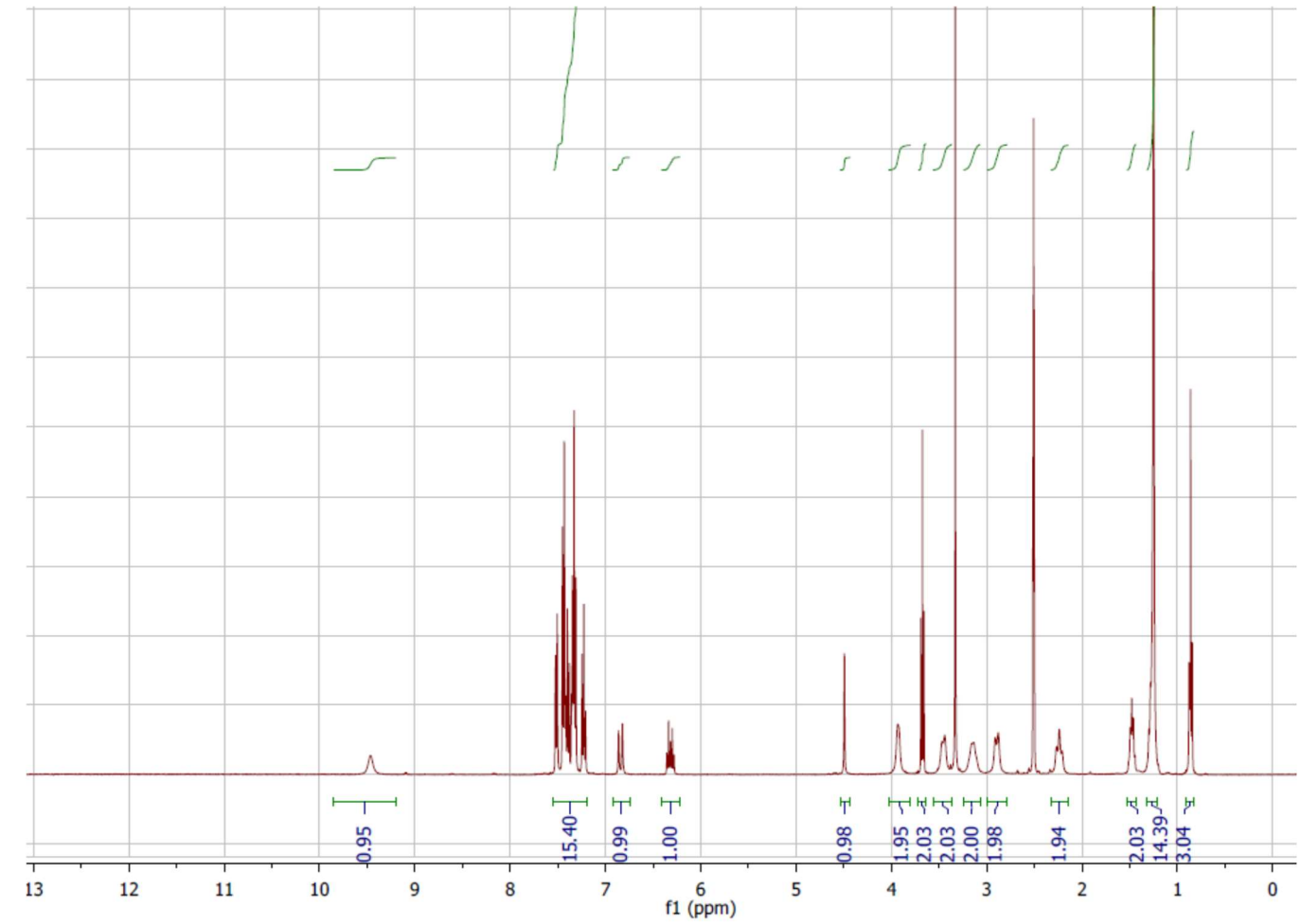


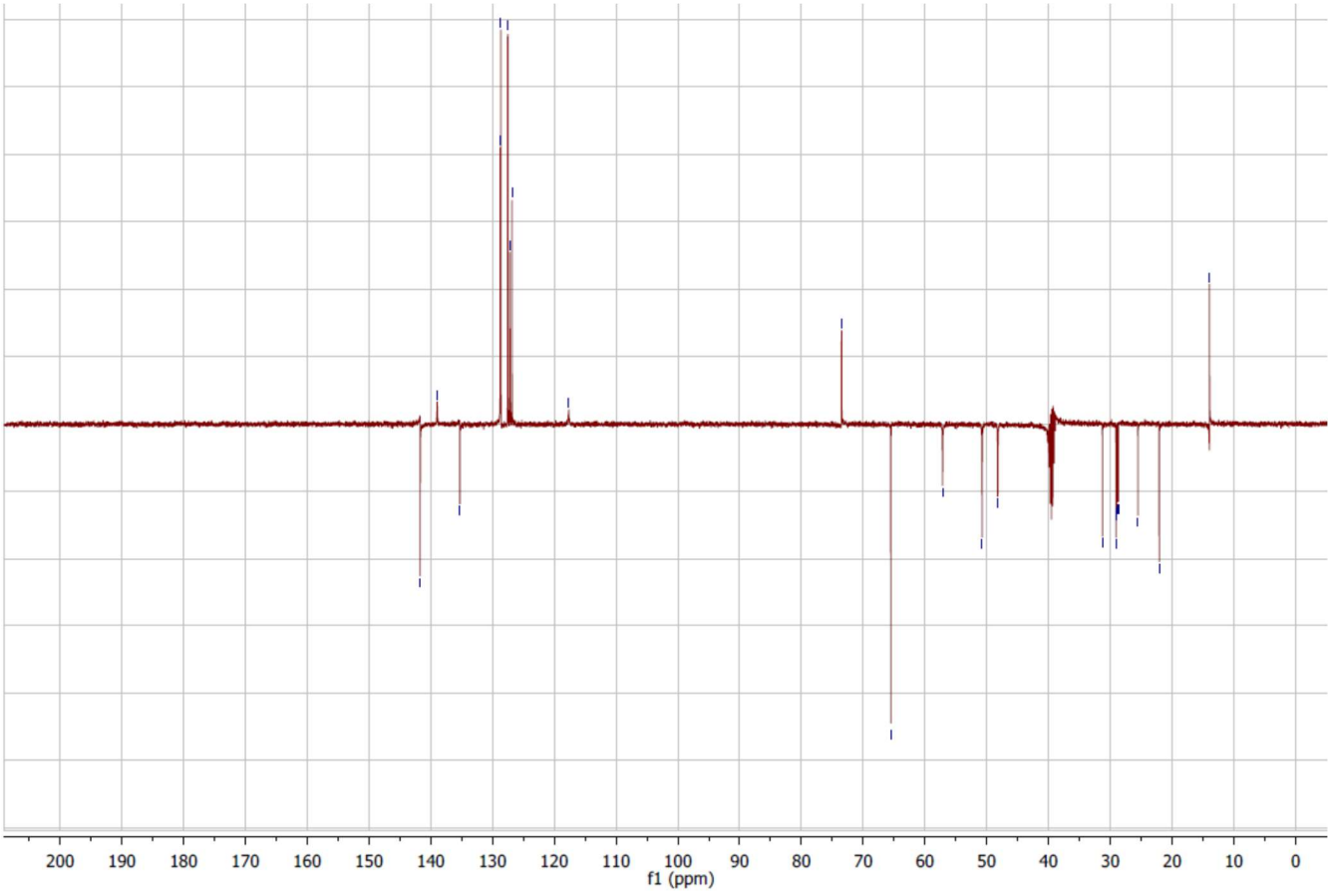
Cinnarizine 1-octyl sulfate (1c)



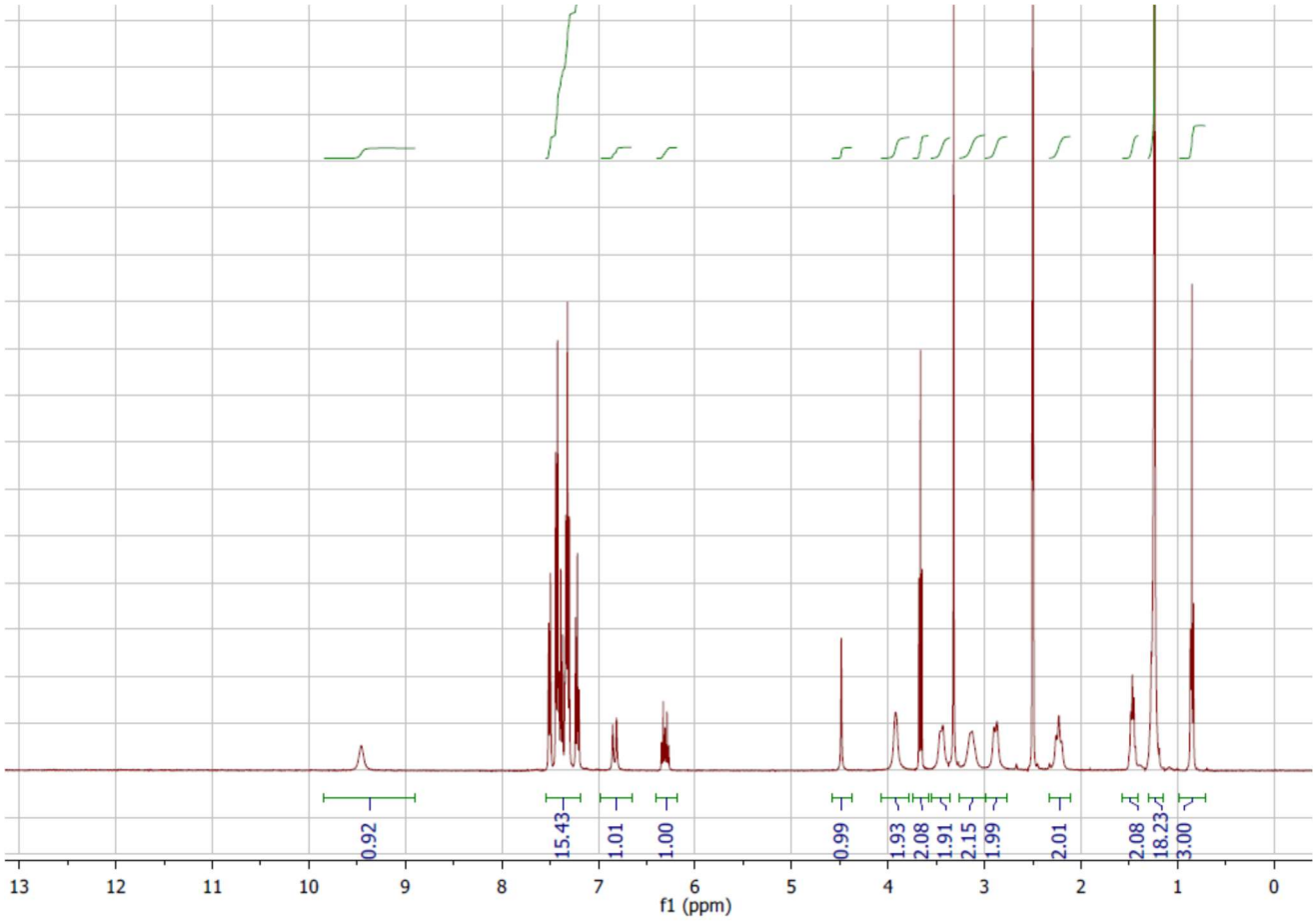


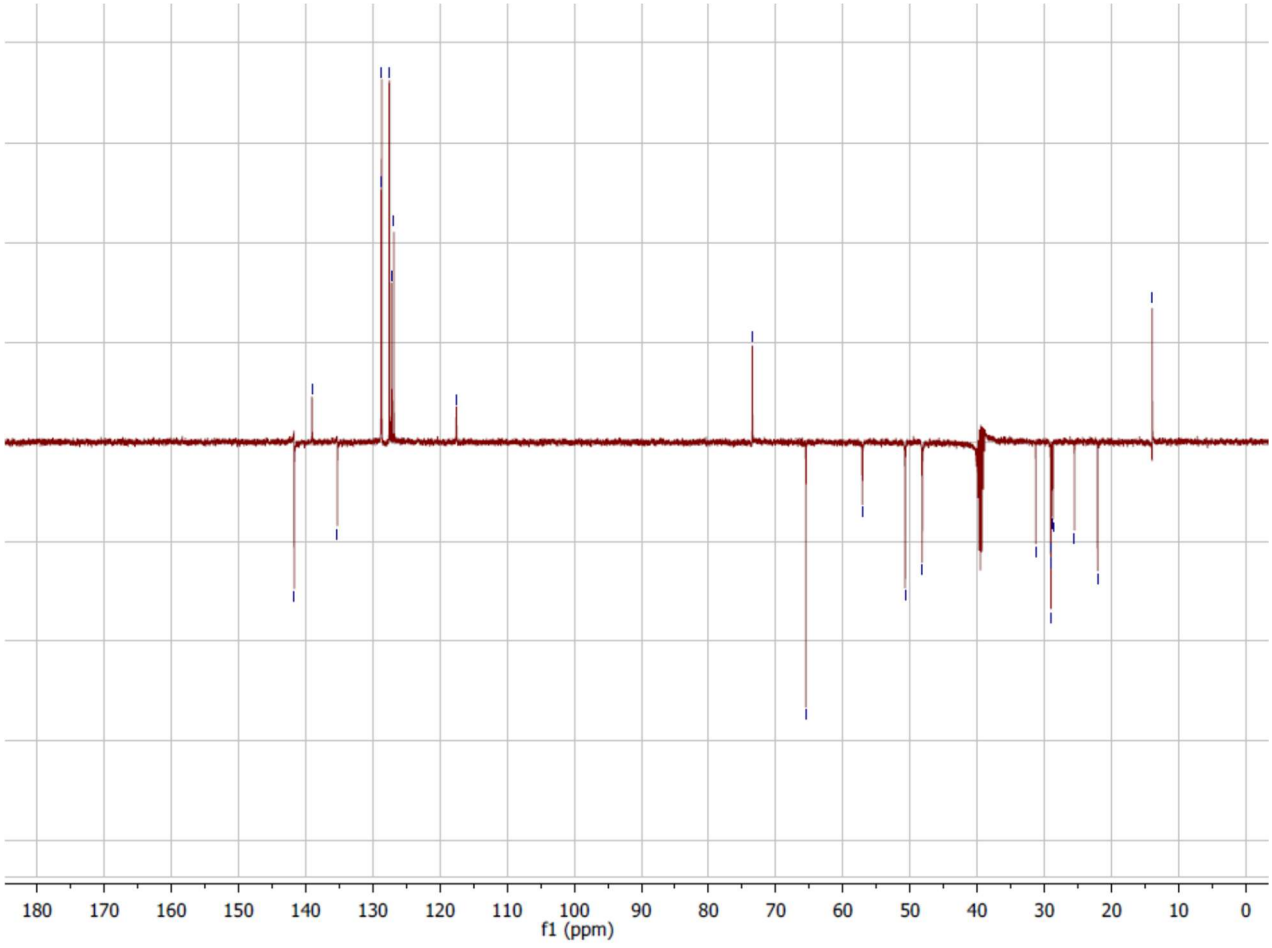
Cinnarizine 1-decyl sulfate (1d)



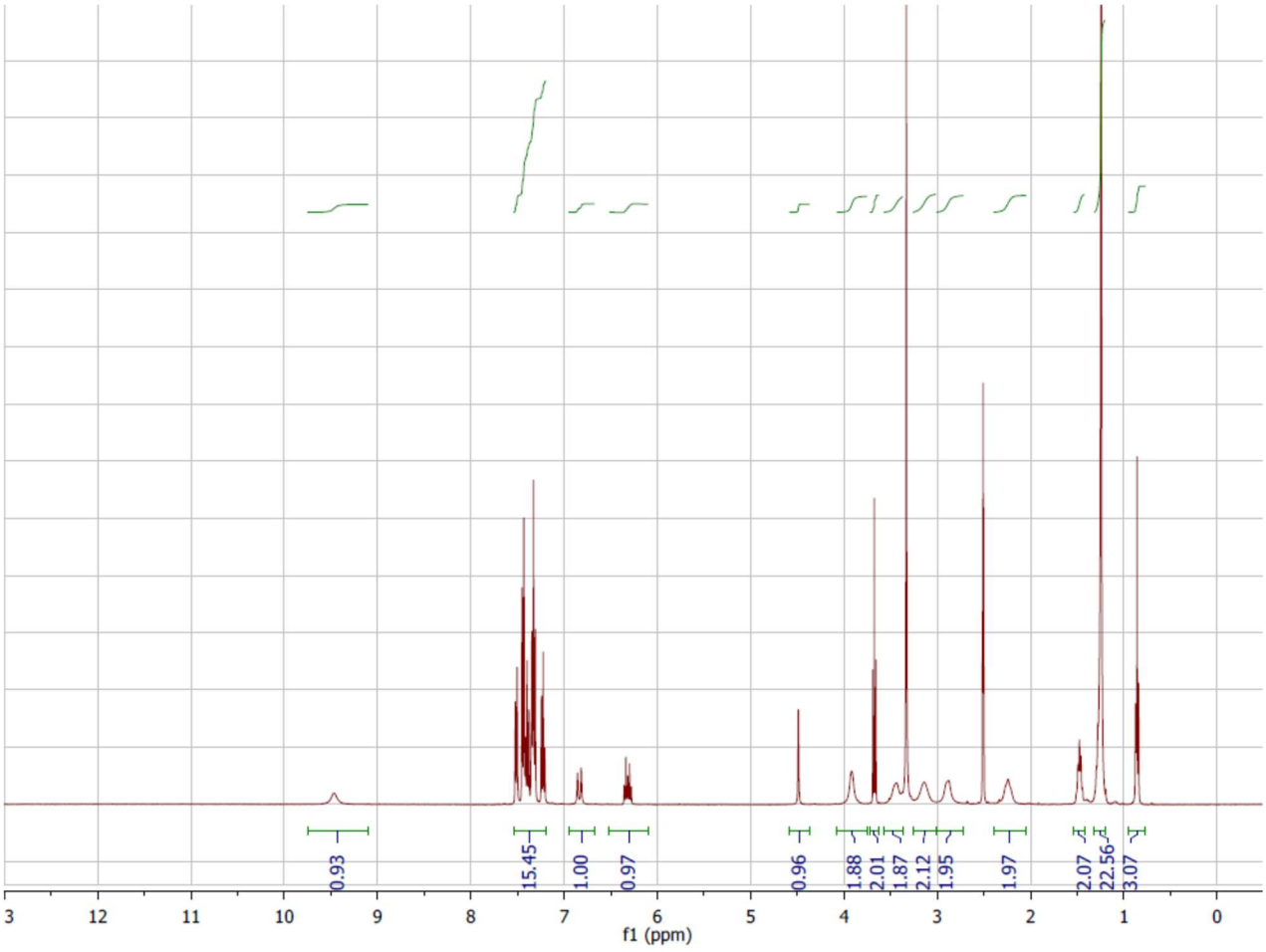


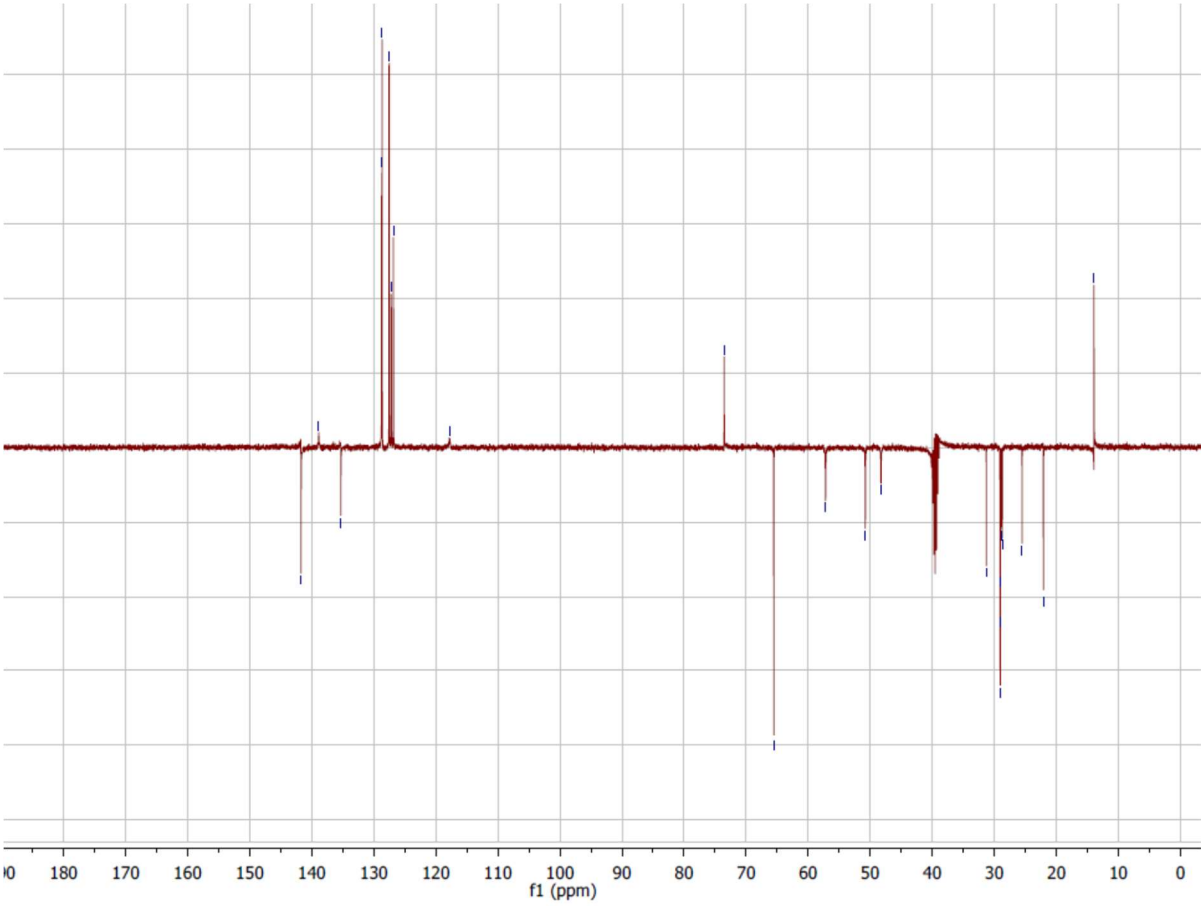
Cinnarizine 1-dodecyl sulfate (1e)



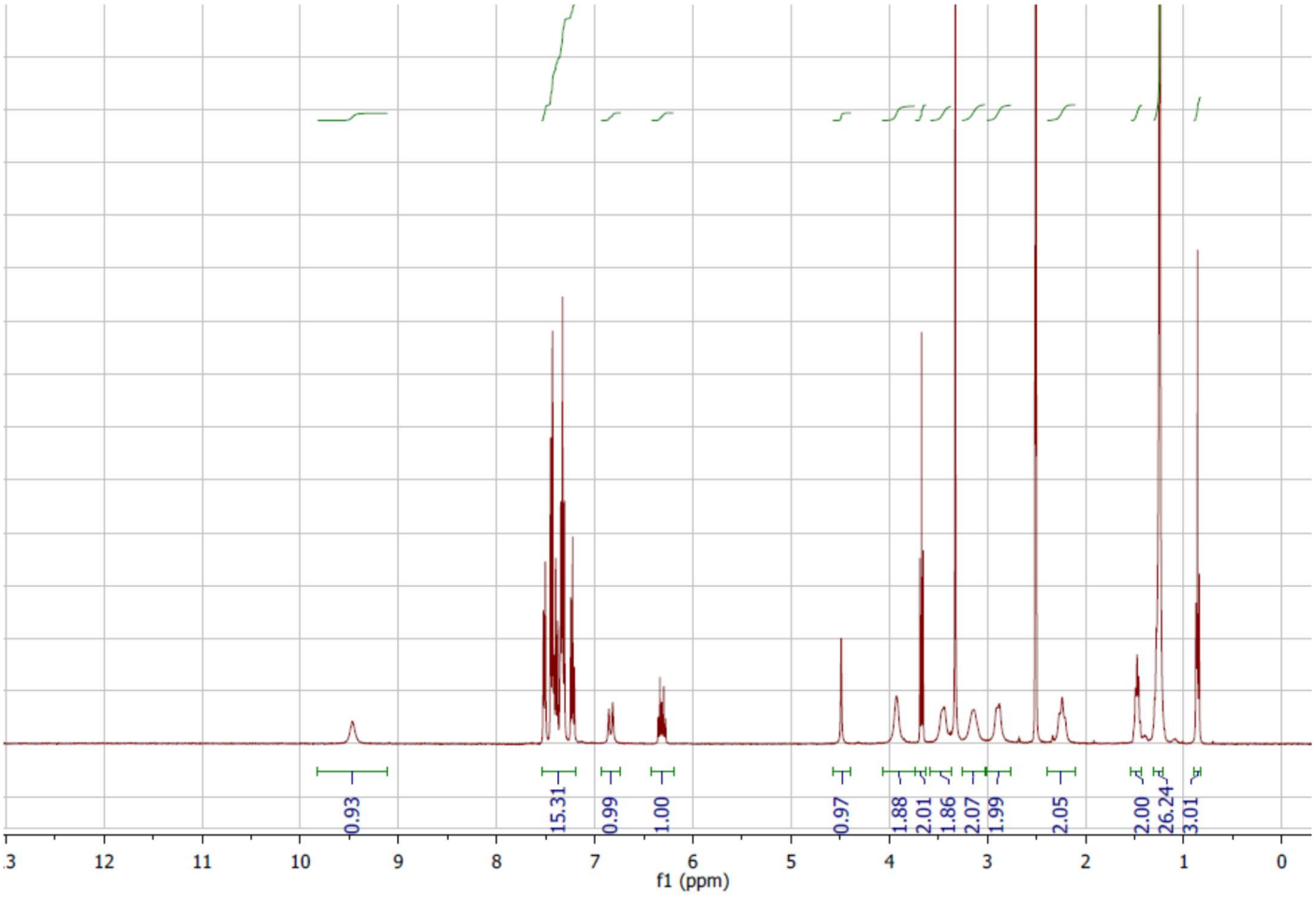


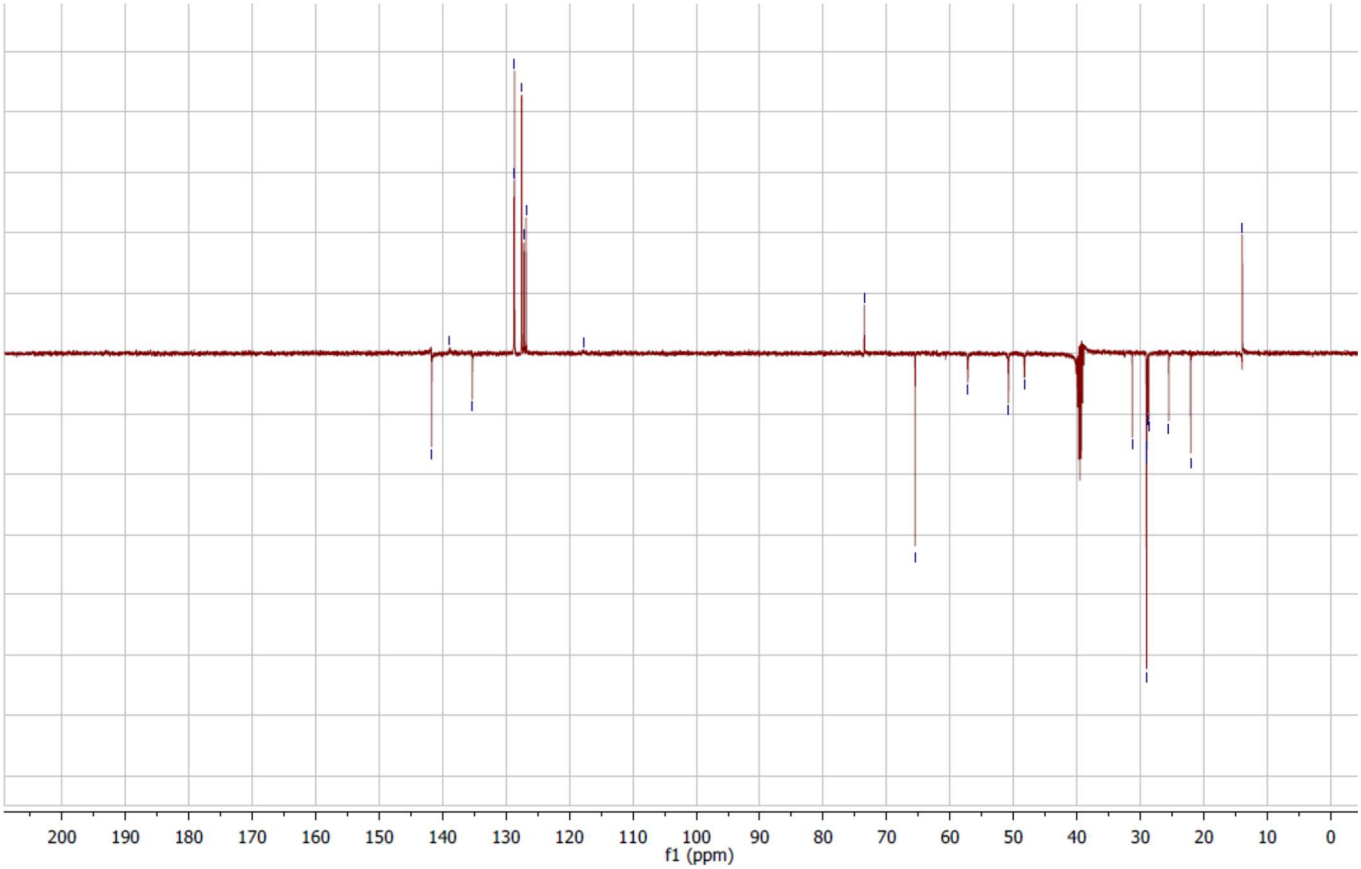
Cinnarizine 1-tetradecyl sulfate (1f)



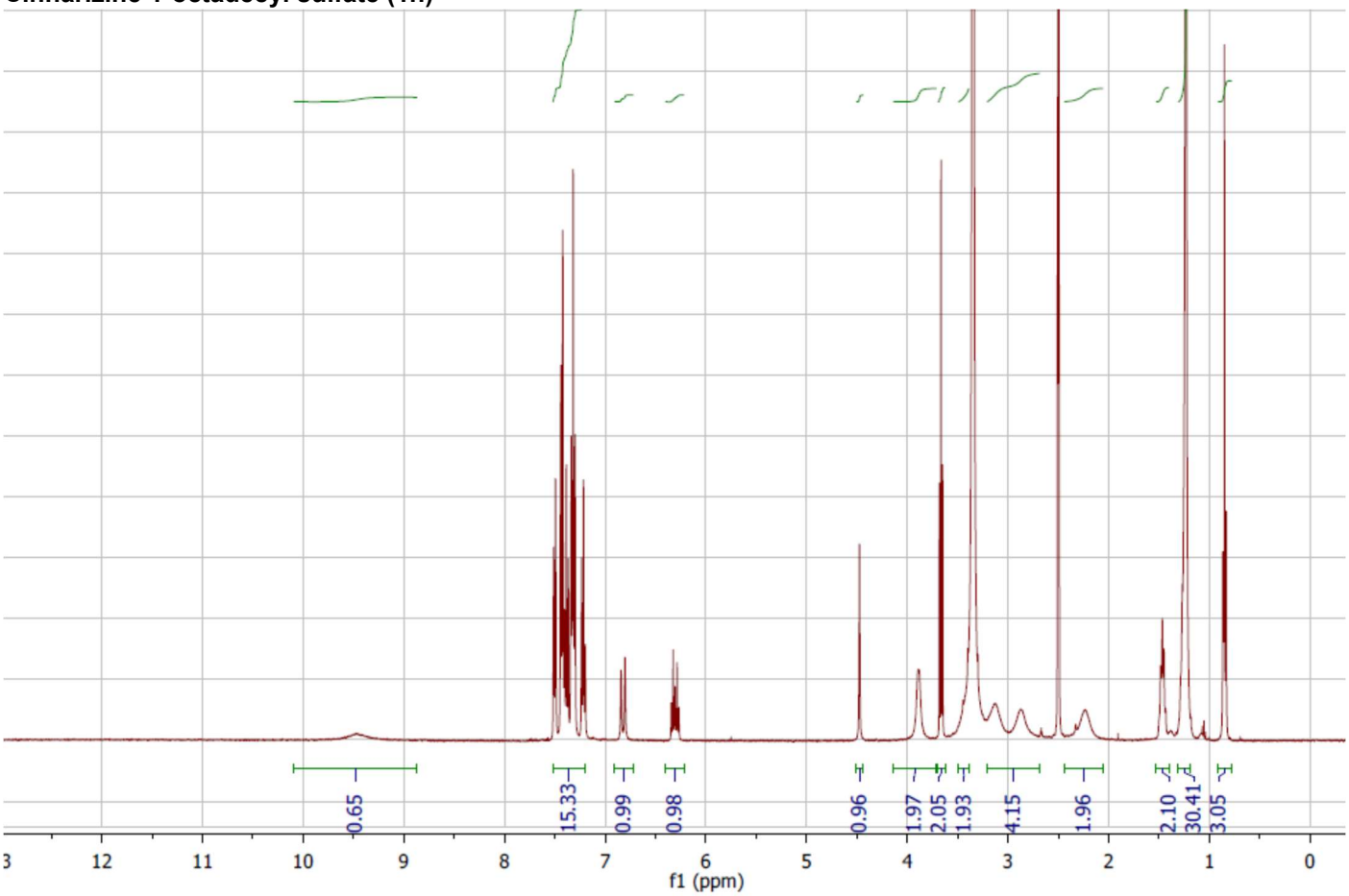


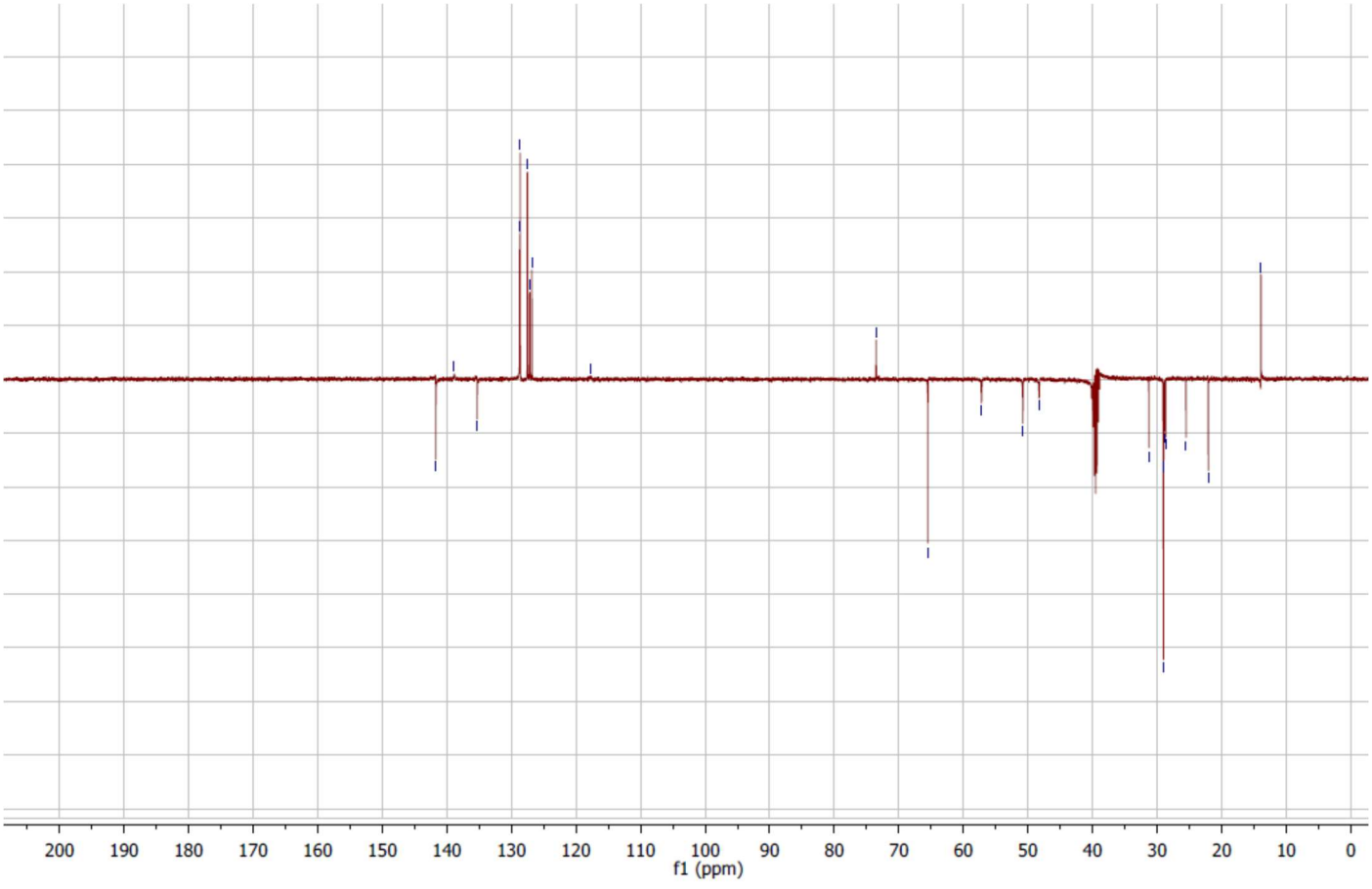
Cinnarizine 1-hexadecyl sulfate (1g)



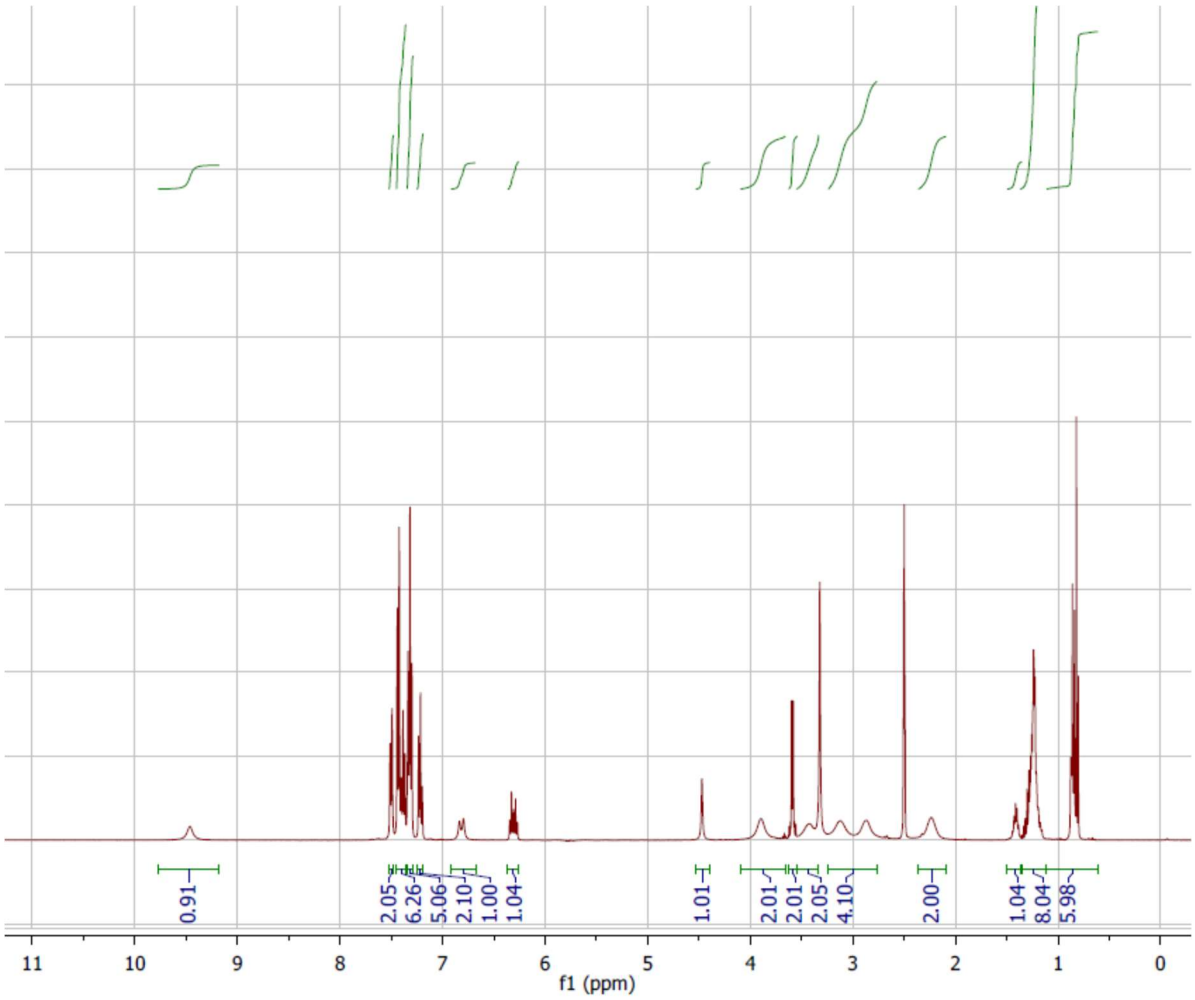


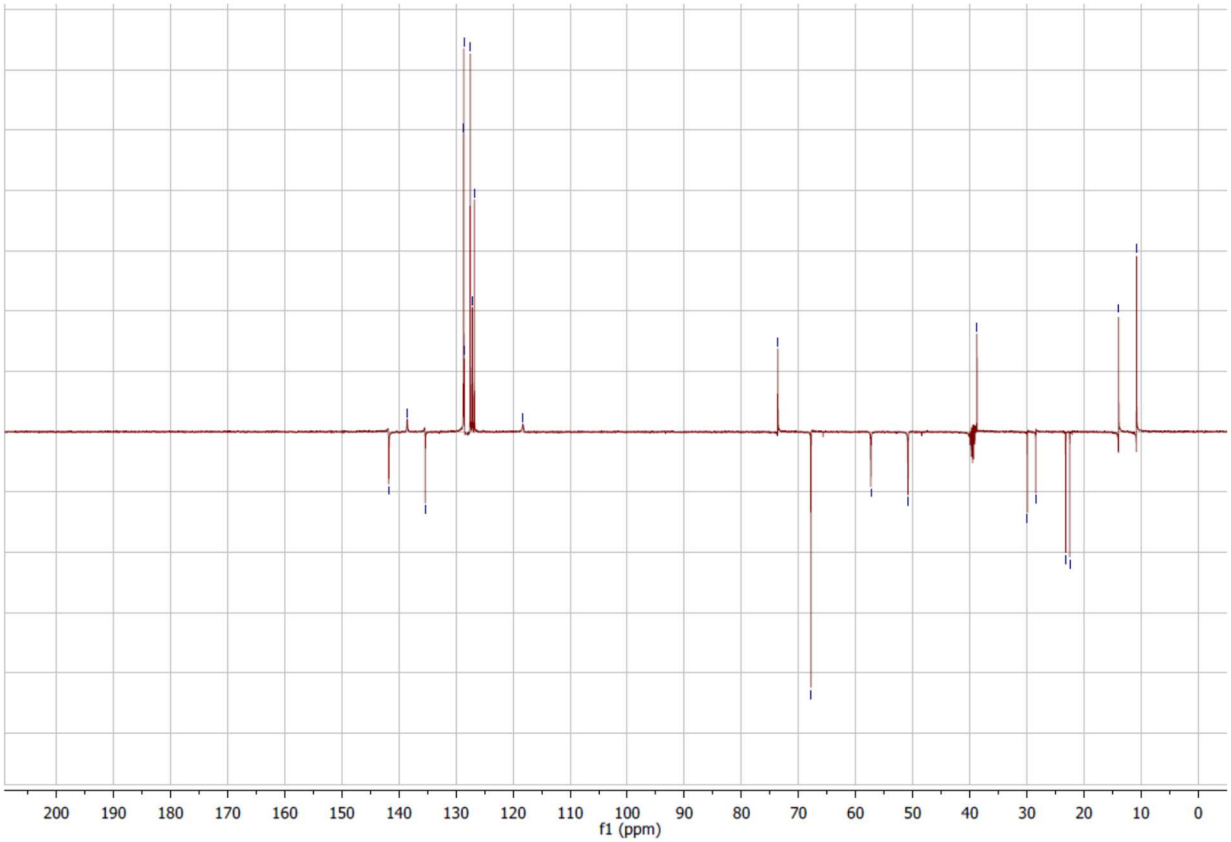
Cinnarizine 1-octadecyl sulfate (1h)



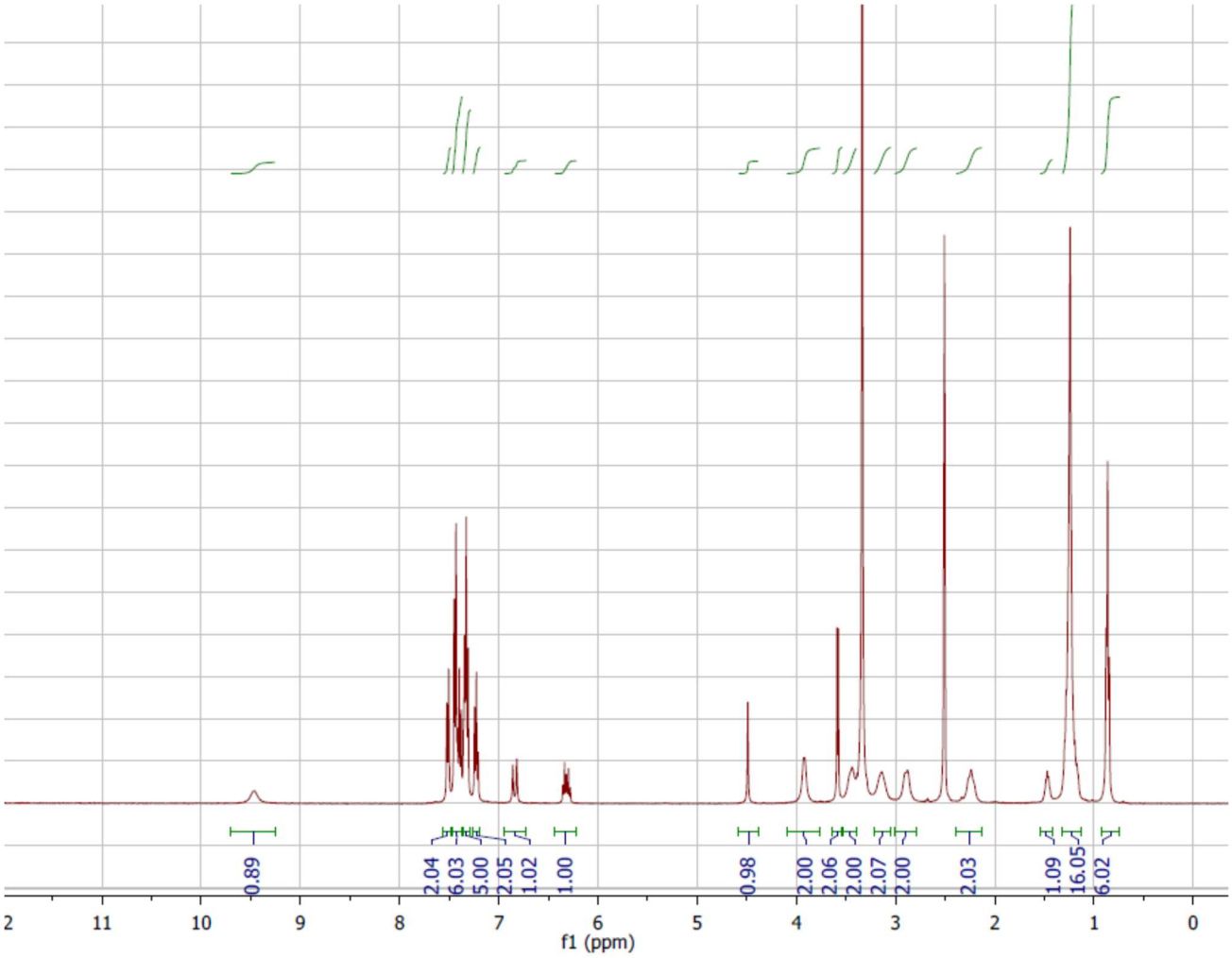


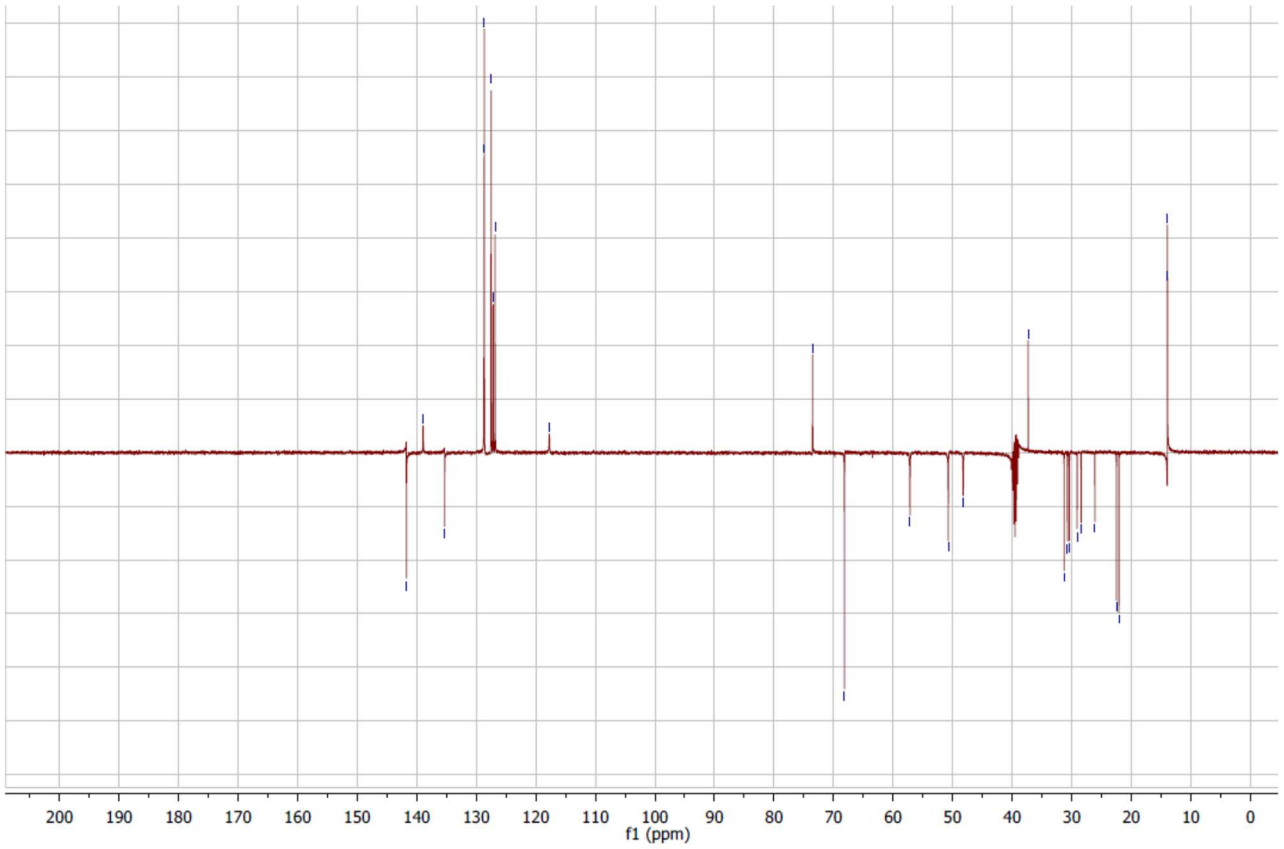
Cinnarizine 2-ethyl-1-hexyl sulfate (1i)



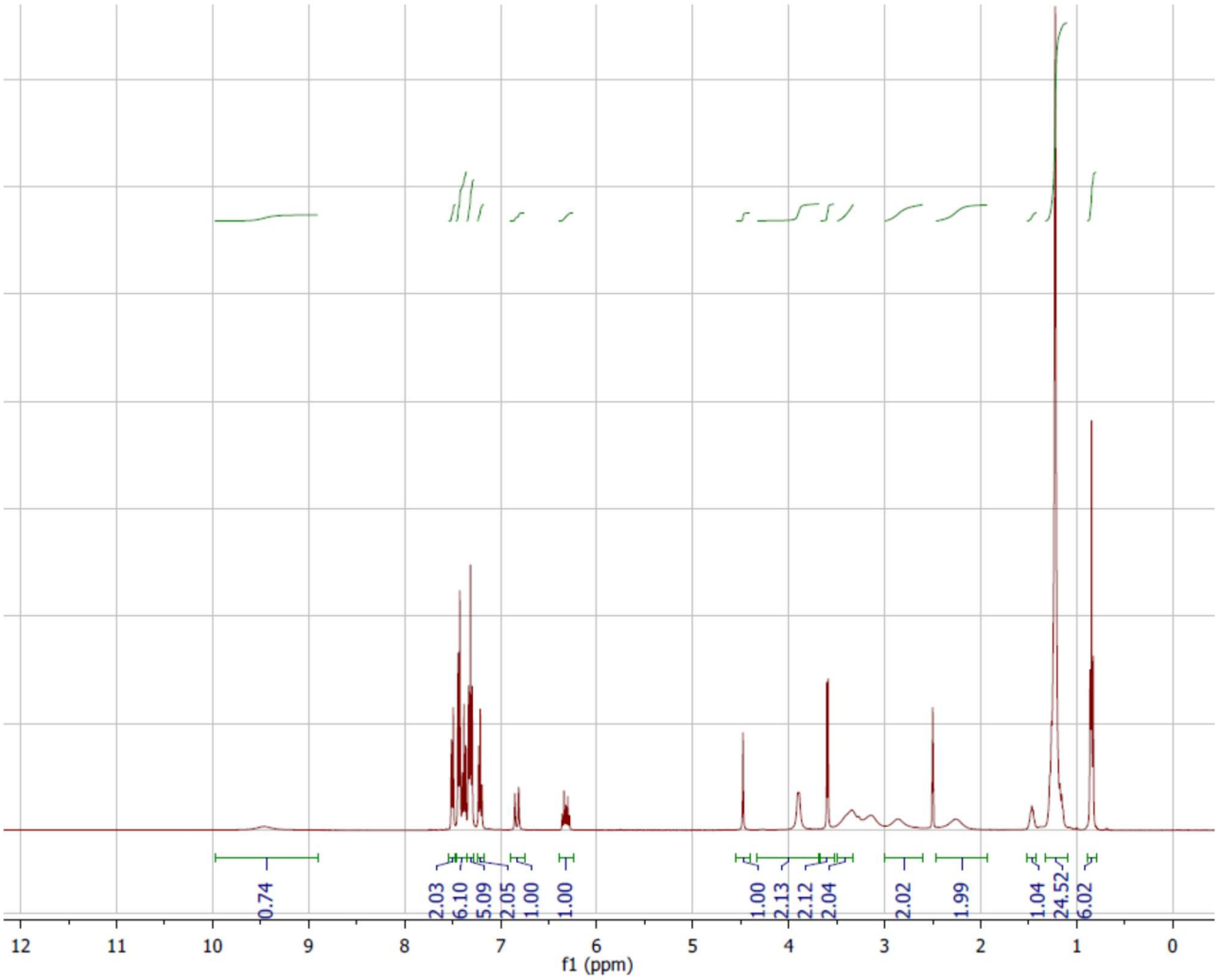


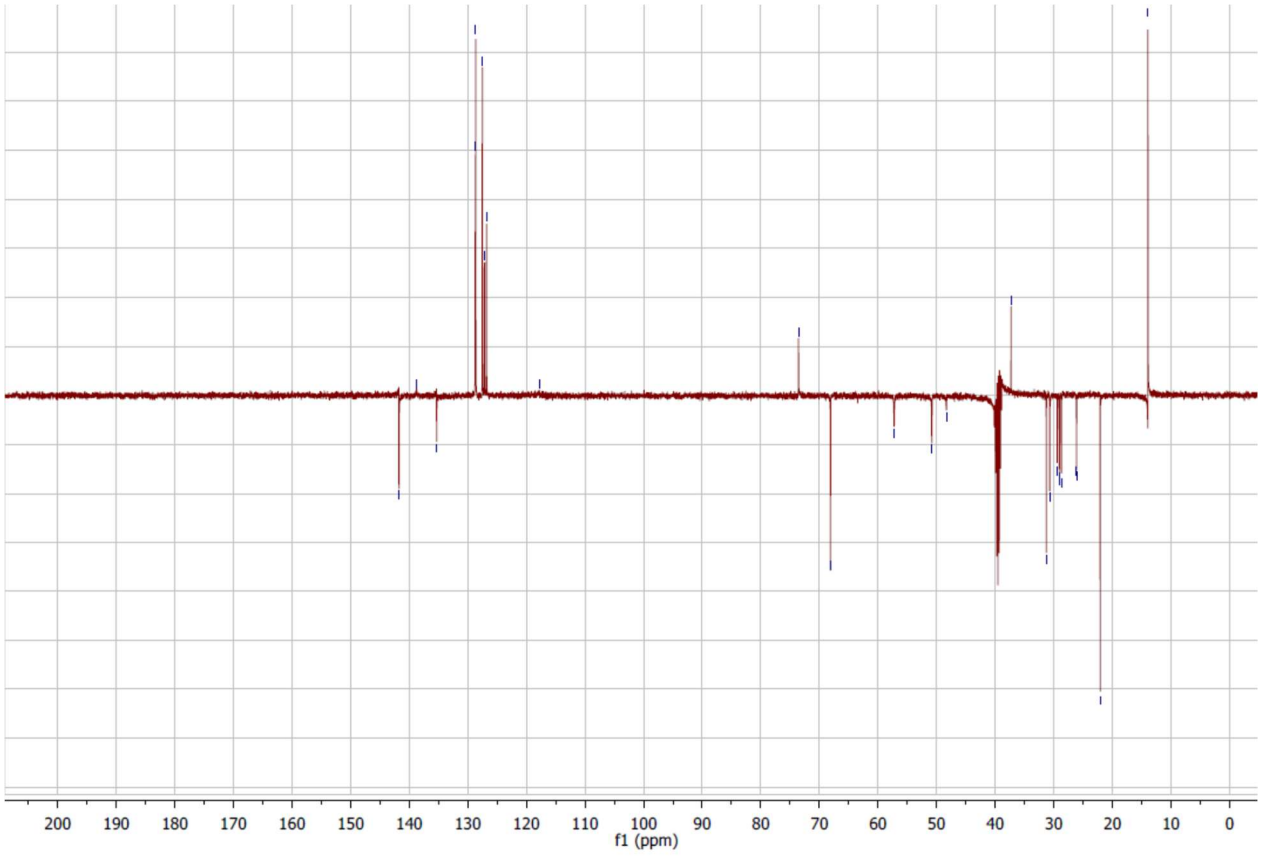
Cinnarizine 2-butyl-1-octyl sulfate (1j)



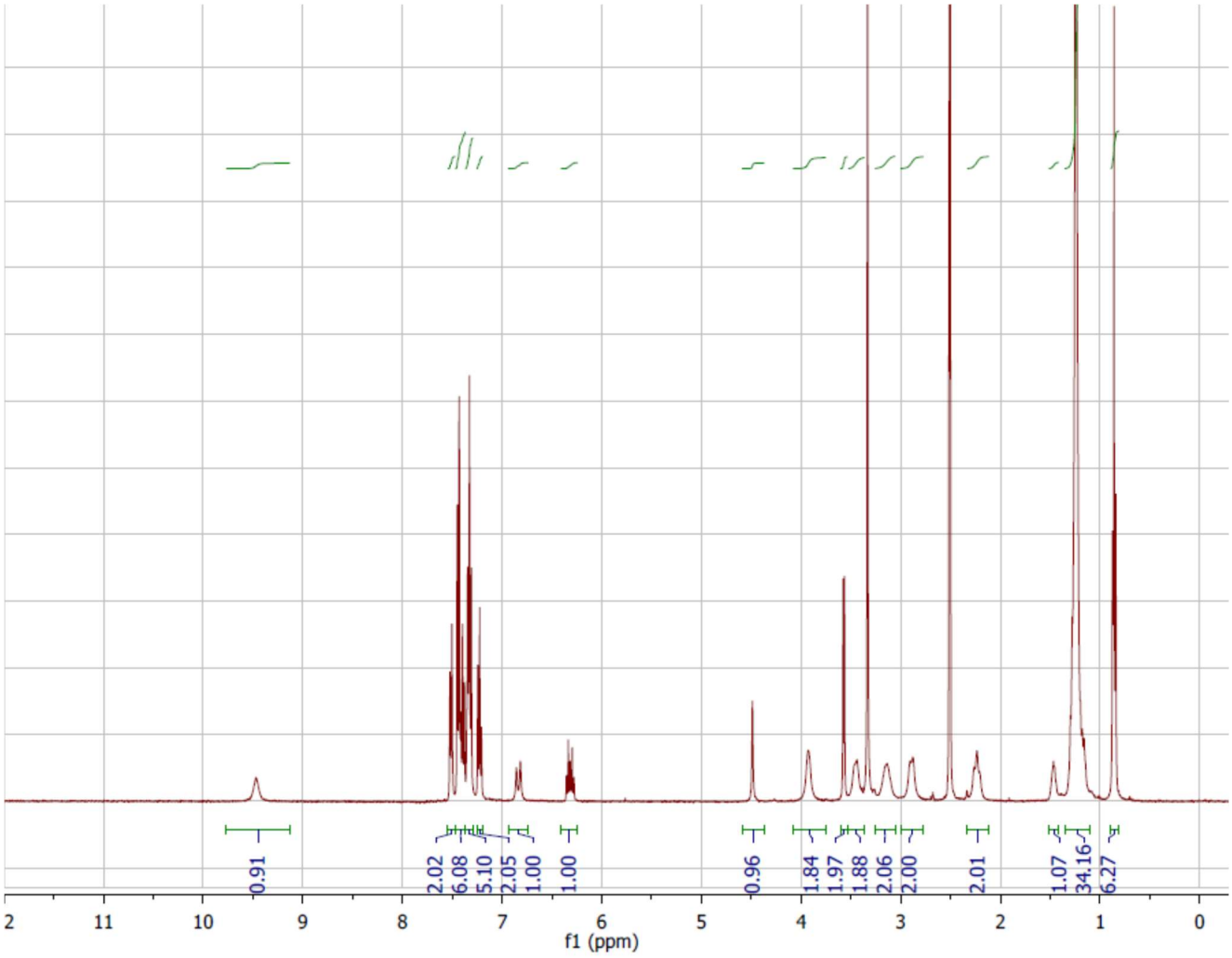


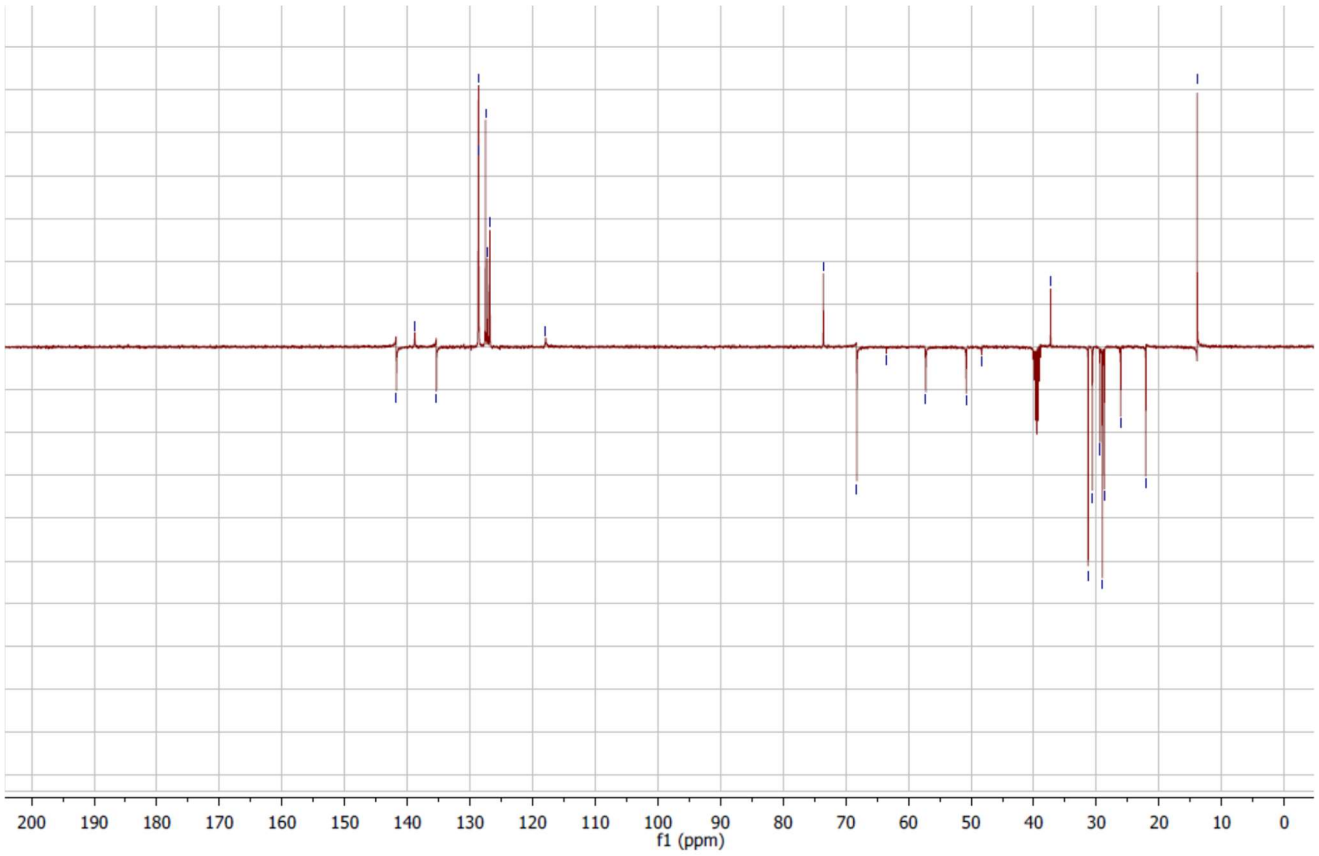
Cinnarizine 2-hexyl-1-decyl sulfate (1k)



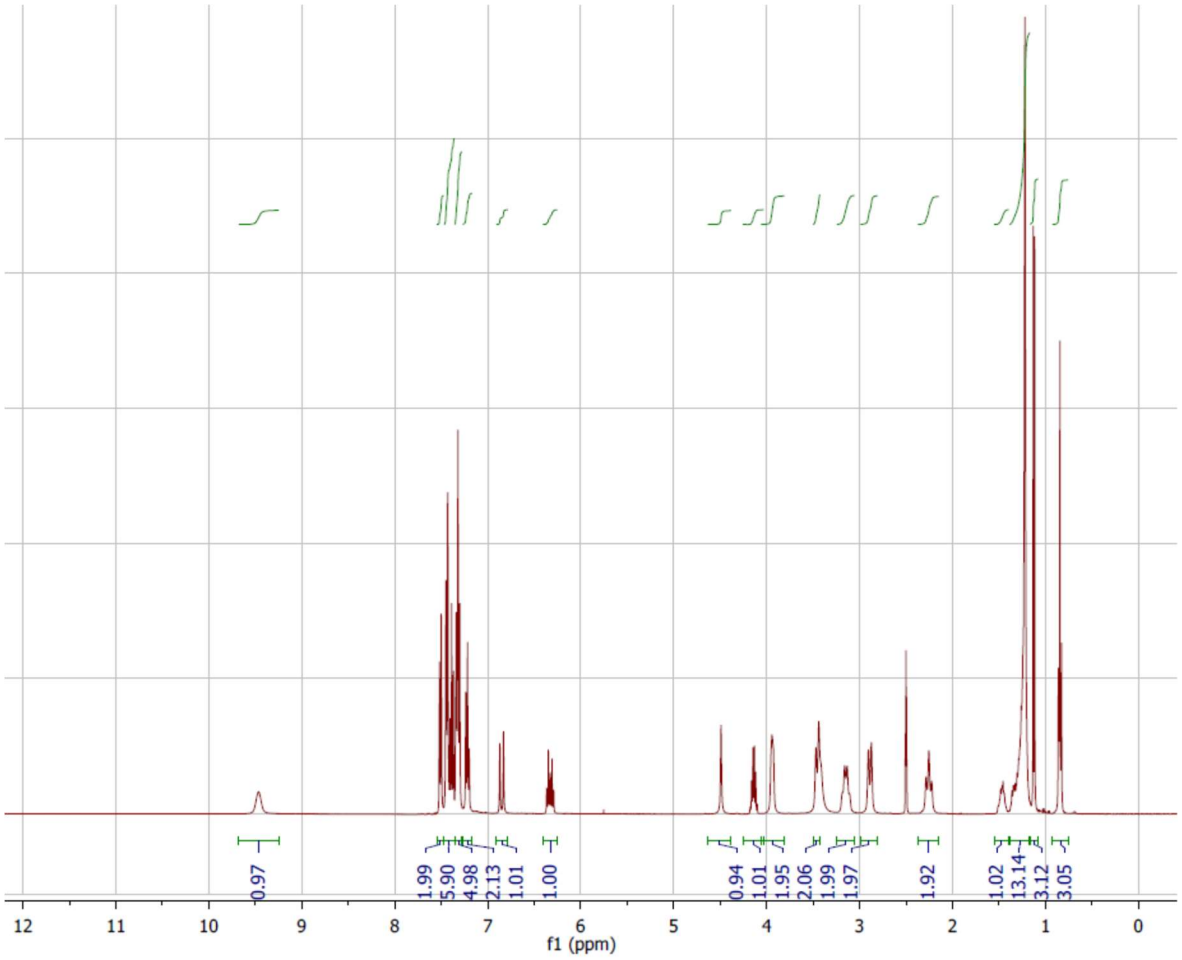


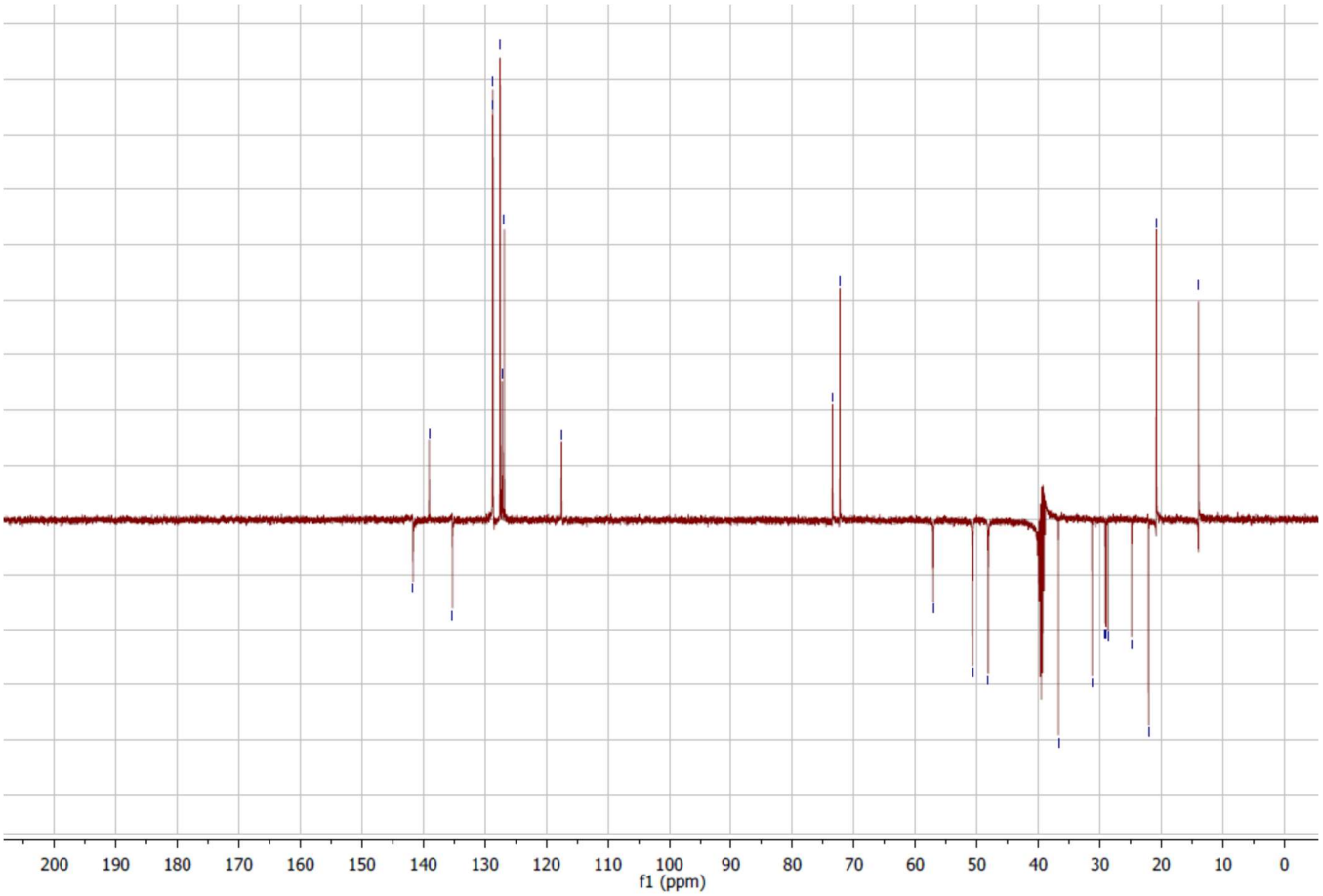
Cinnarizine 2-octyl-1-dodecyl sulfate (1l)



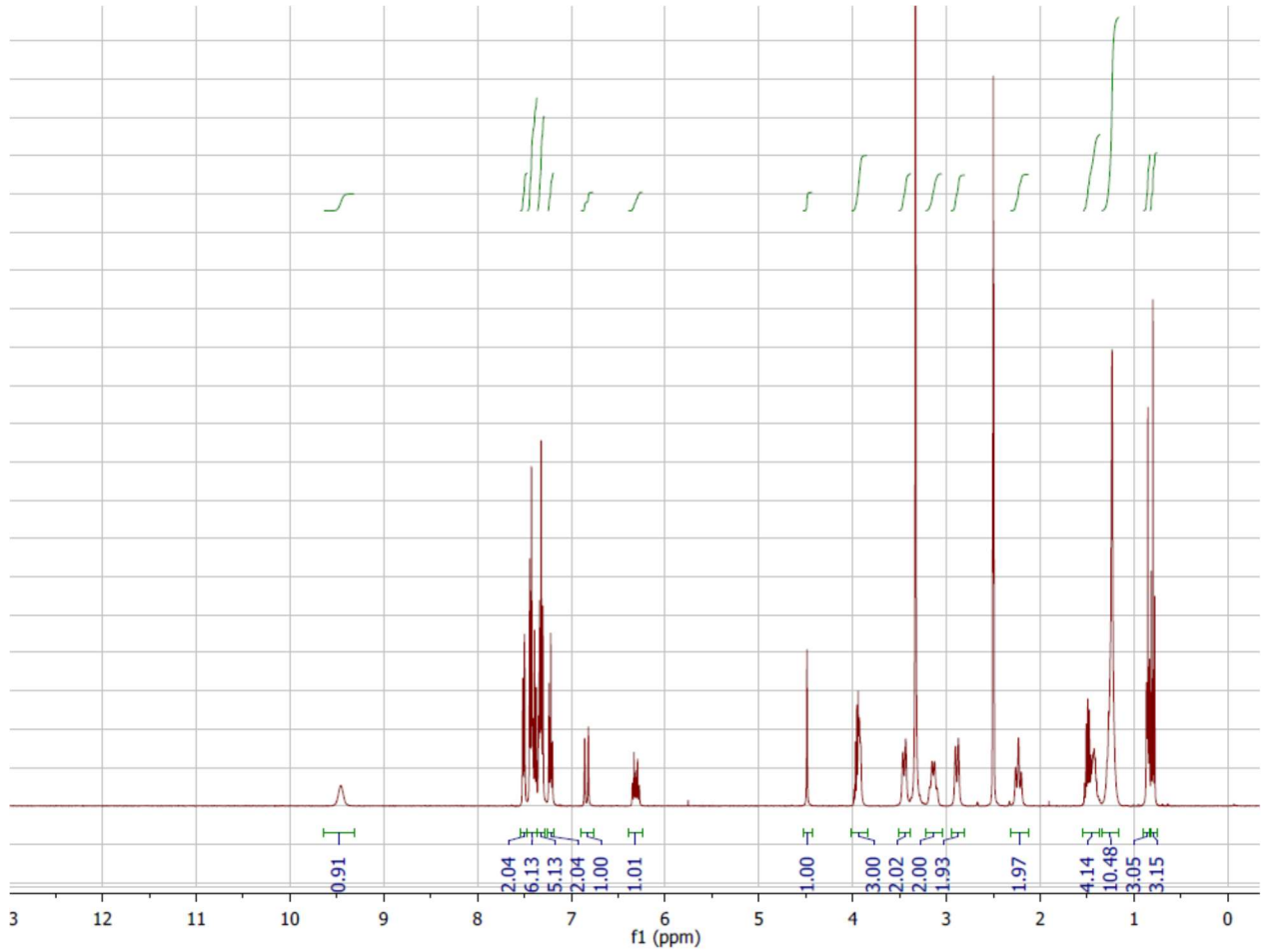


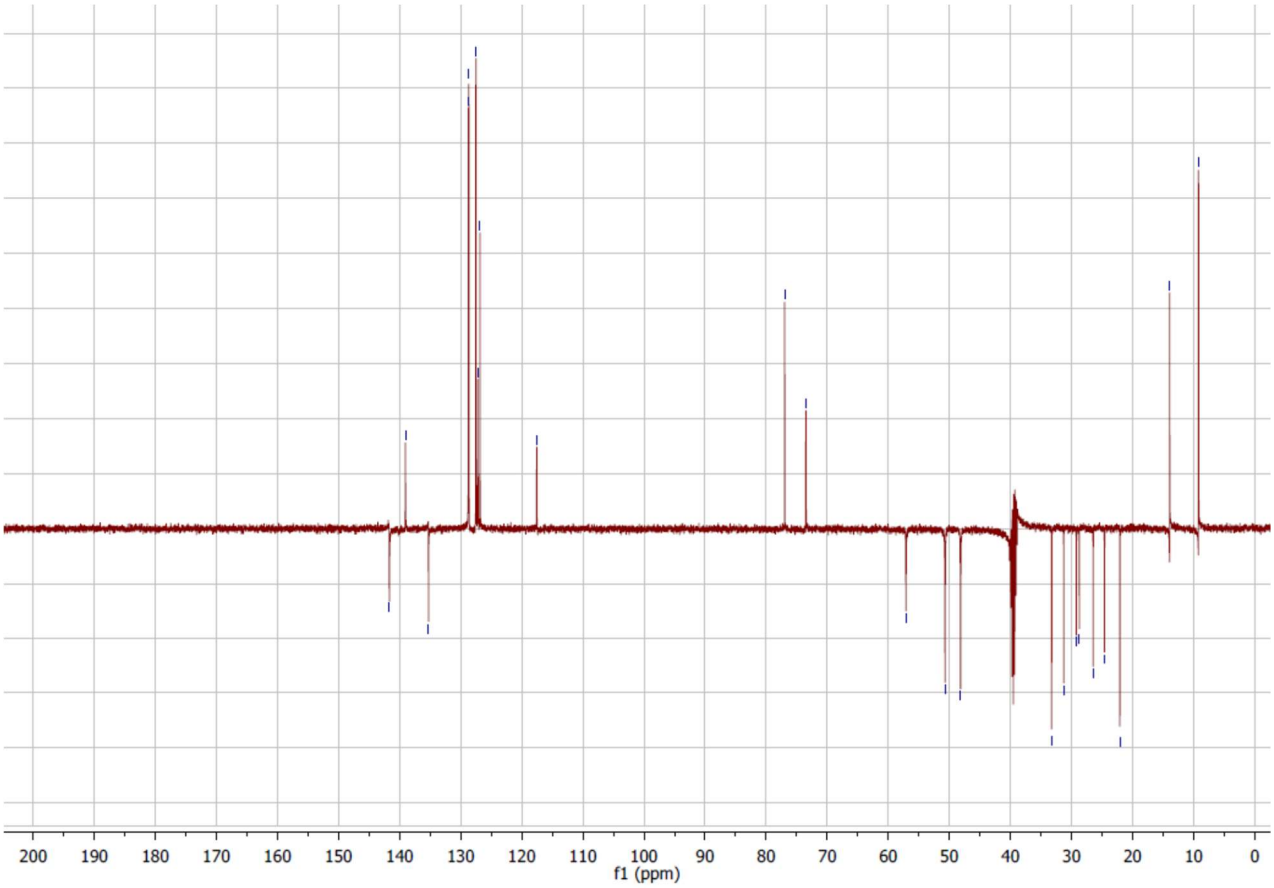
Cinnarizine 2-decyl sulfate (1m)



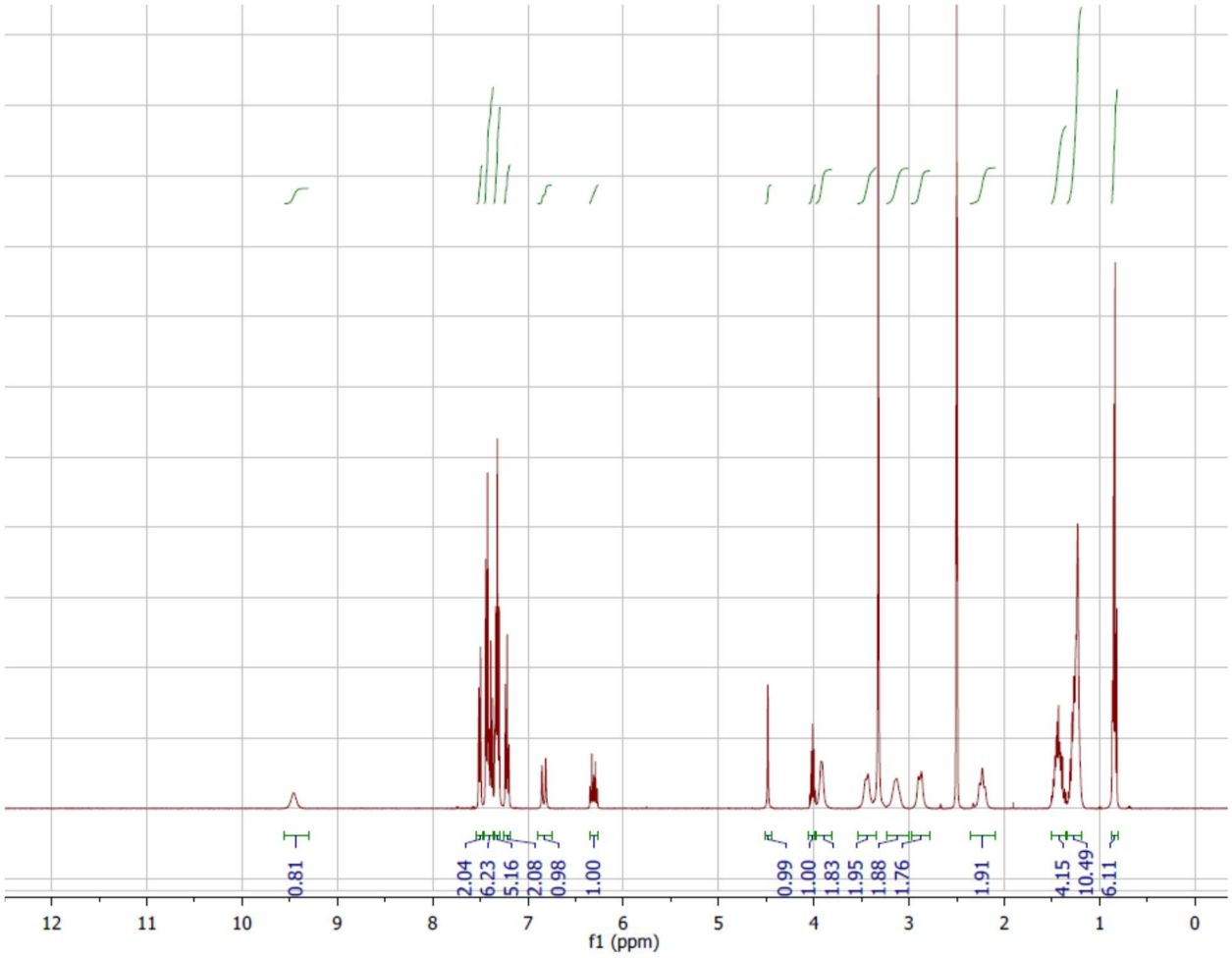


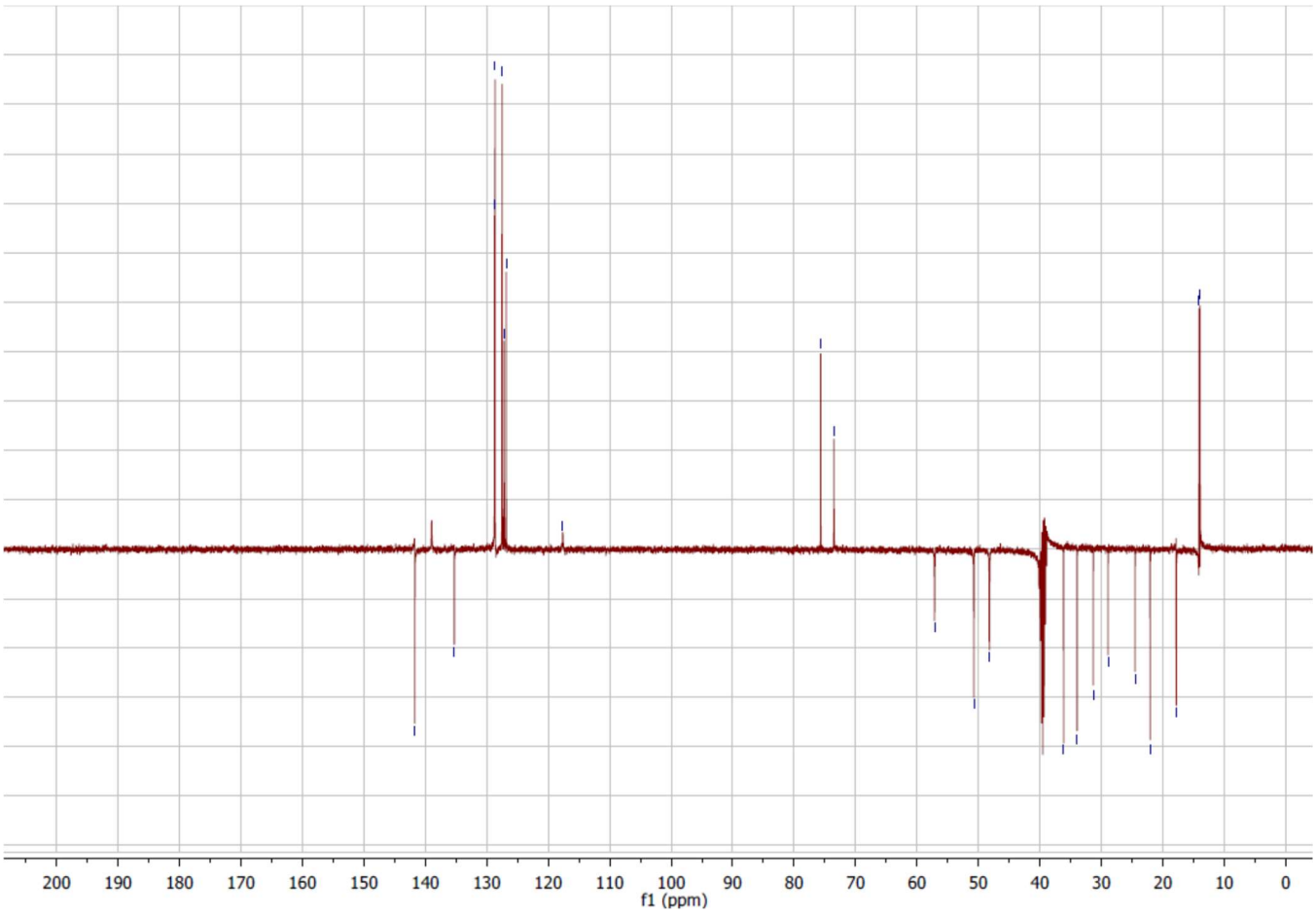
Cinnarizine 3-decyl sulfate (1n)



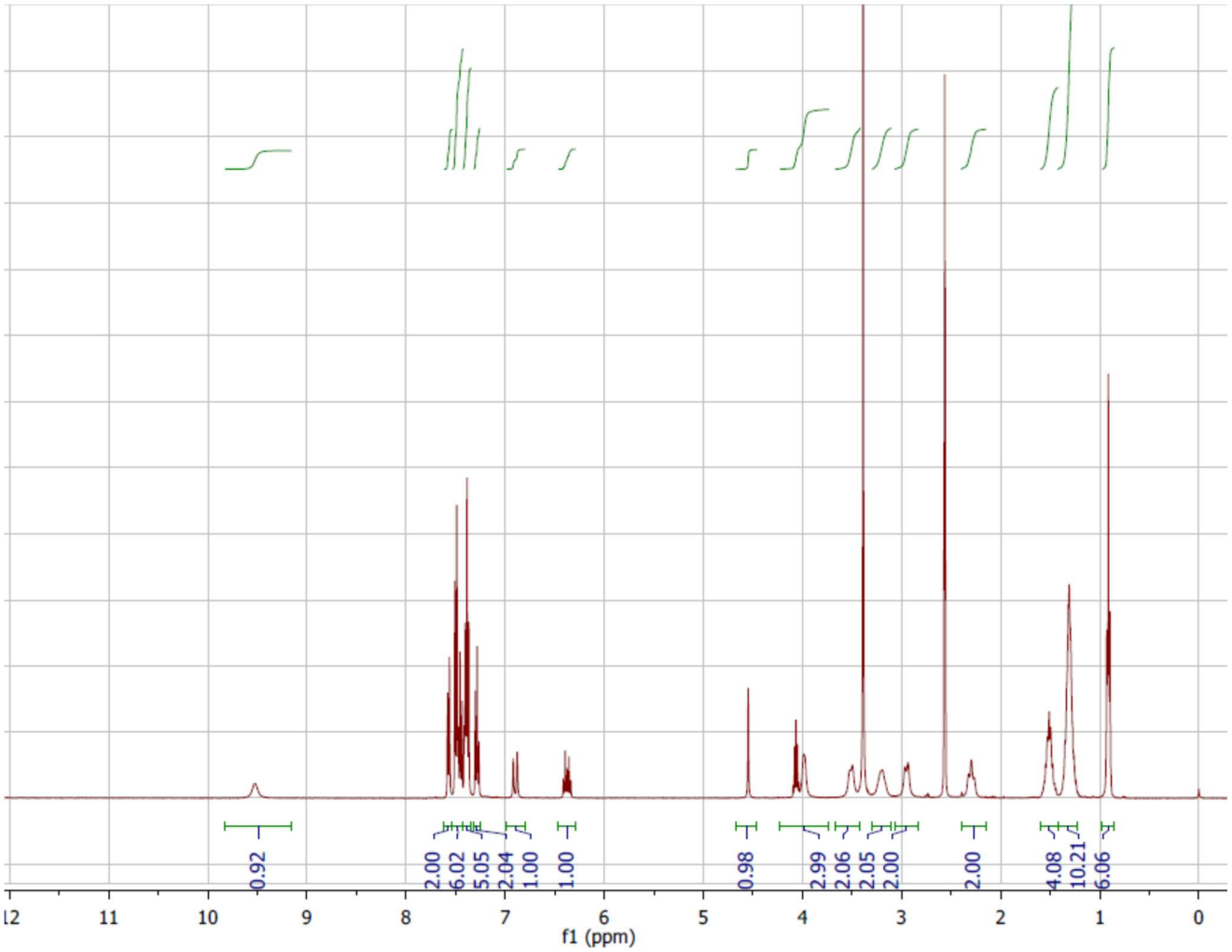


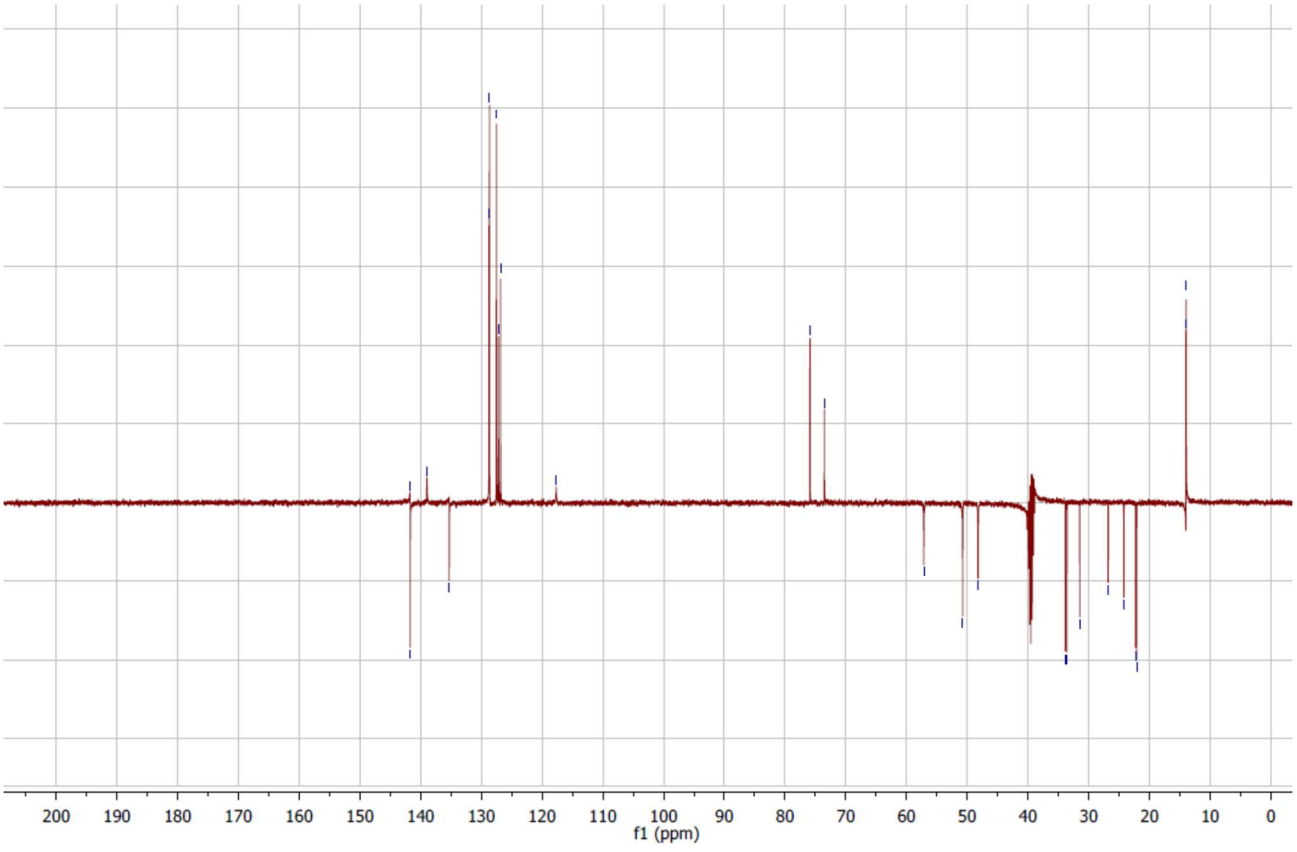
Cinnarizine 4-decyl sulfate (1o)



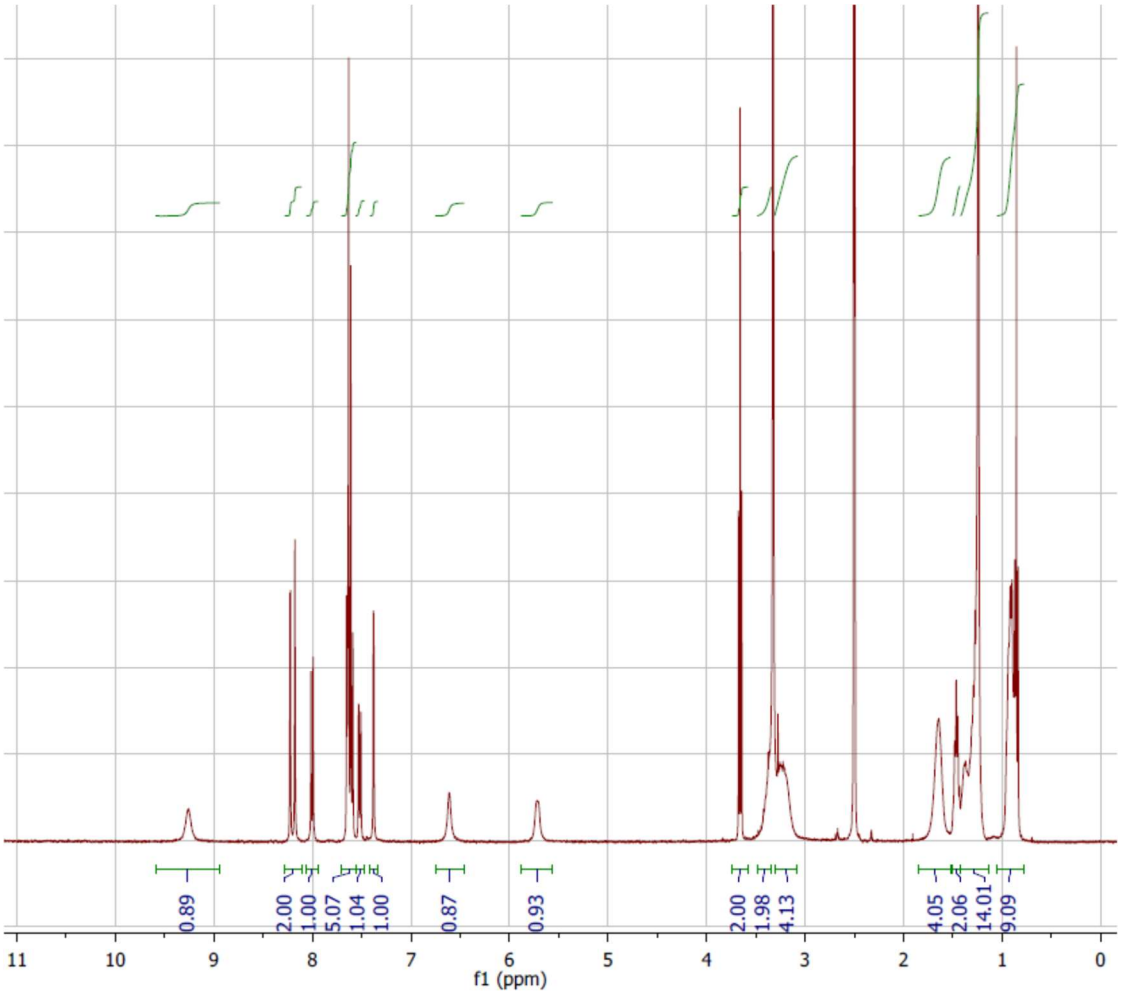


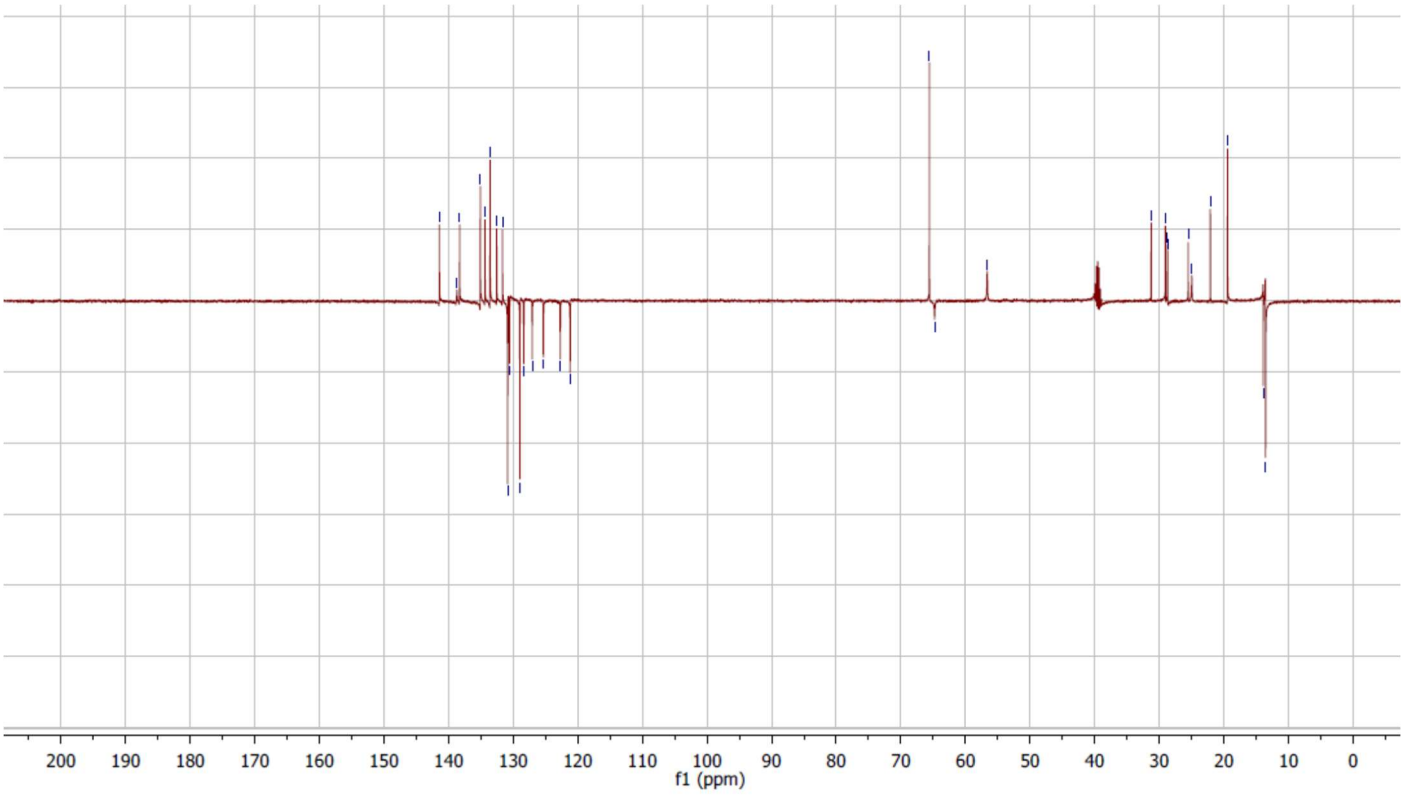
Cinnarizine 5-decyl sulfate (1p)



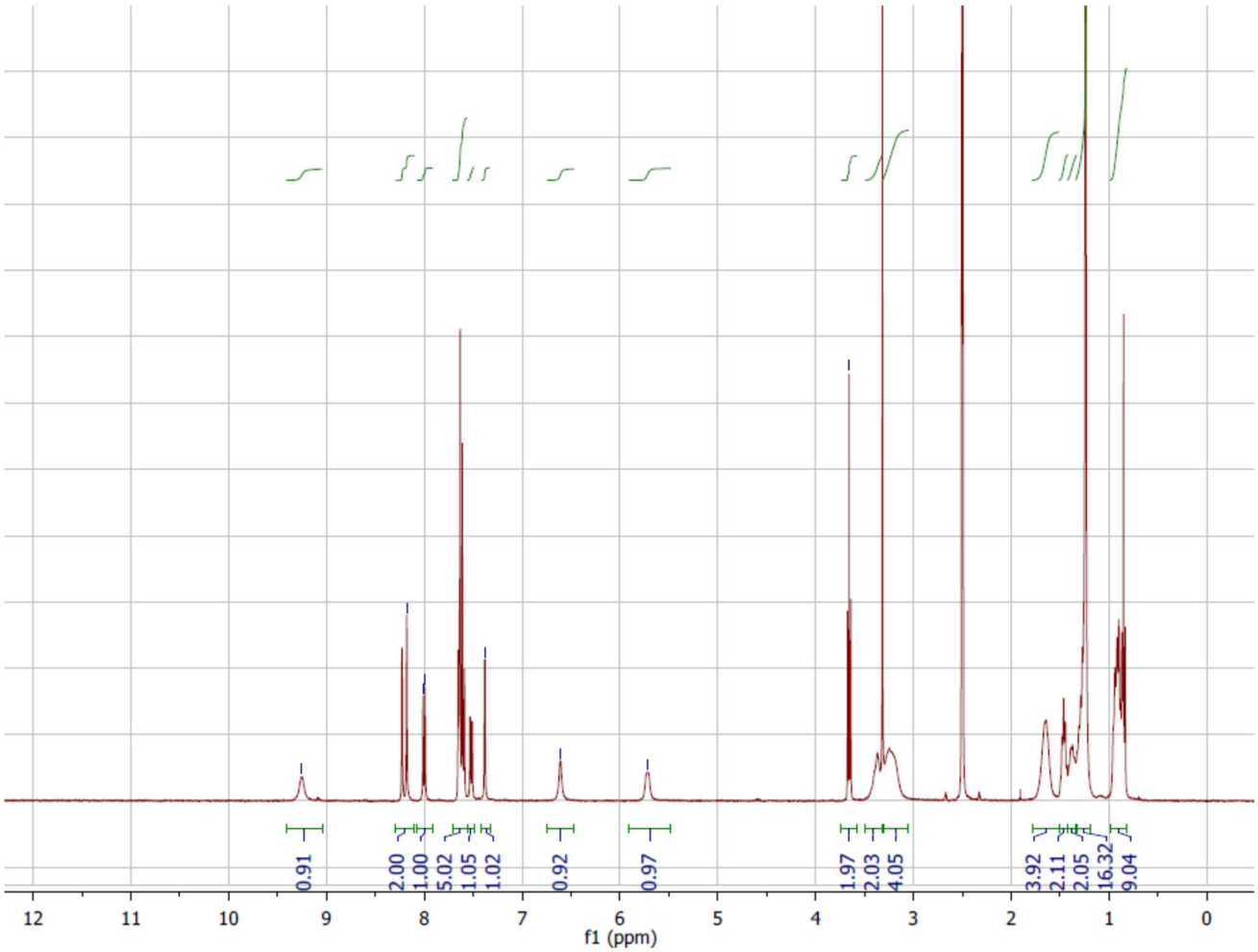


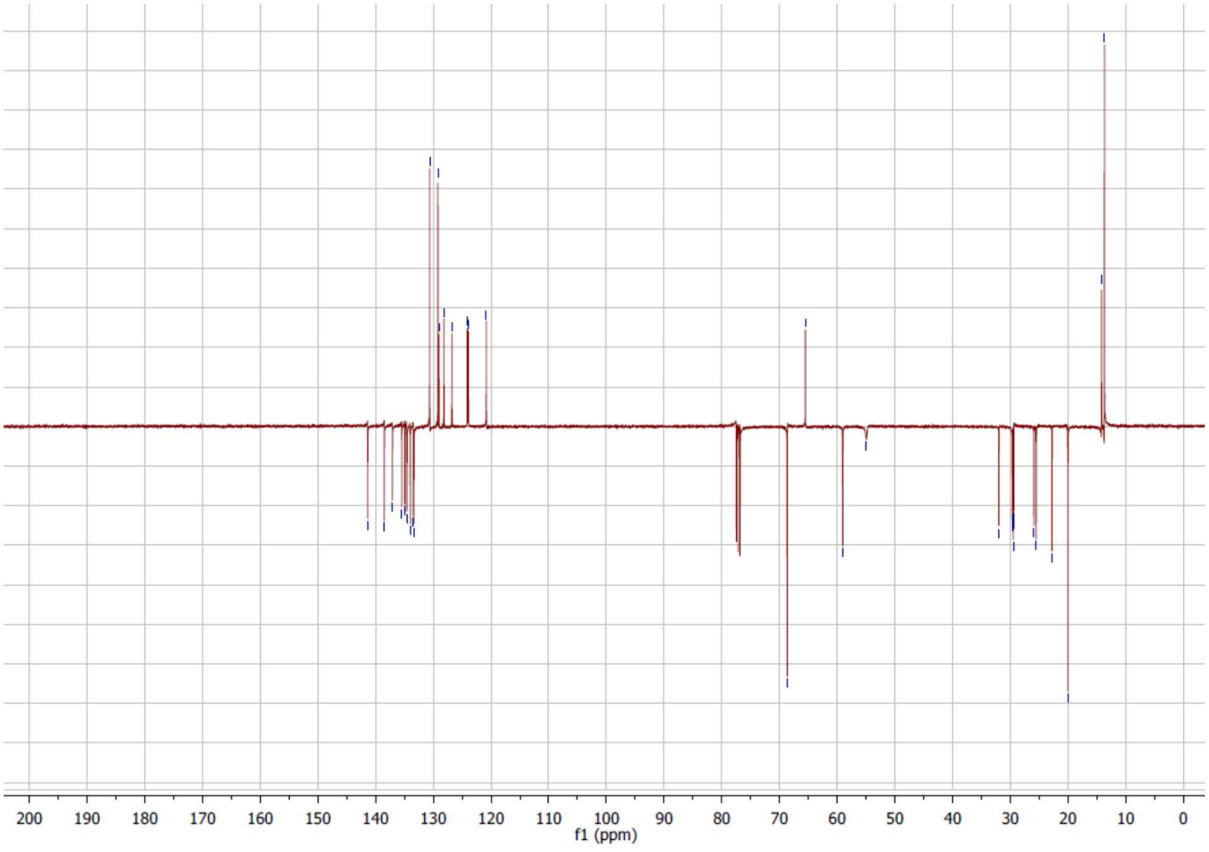
Lumefantrine 1-octyl sulfate (2b)



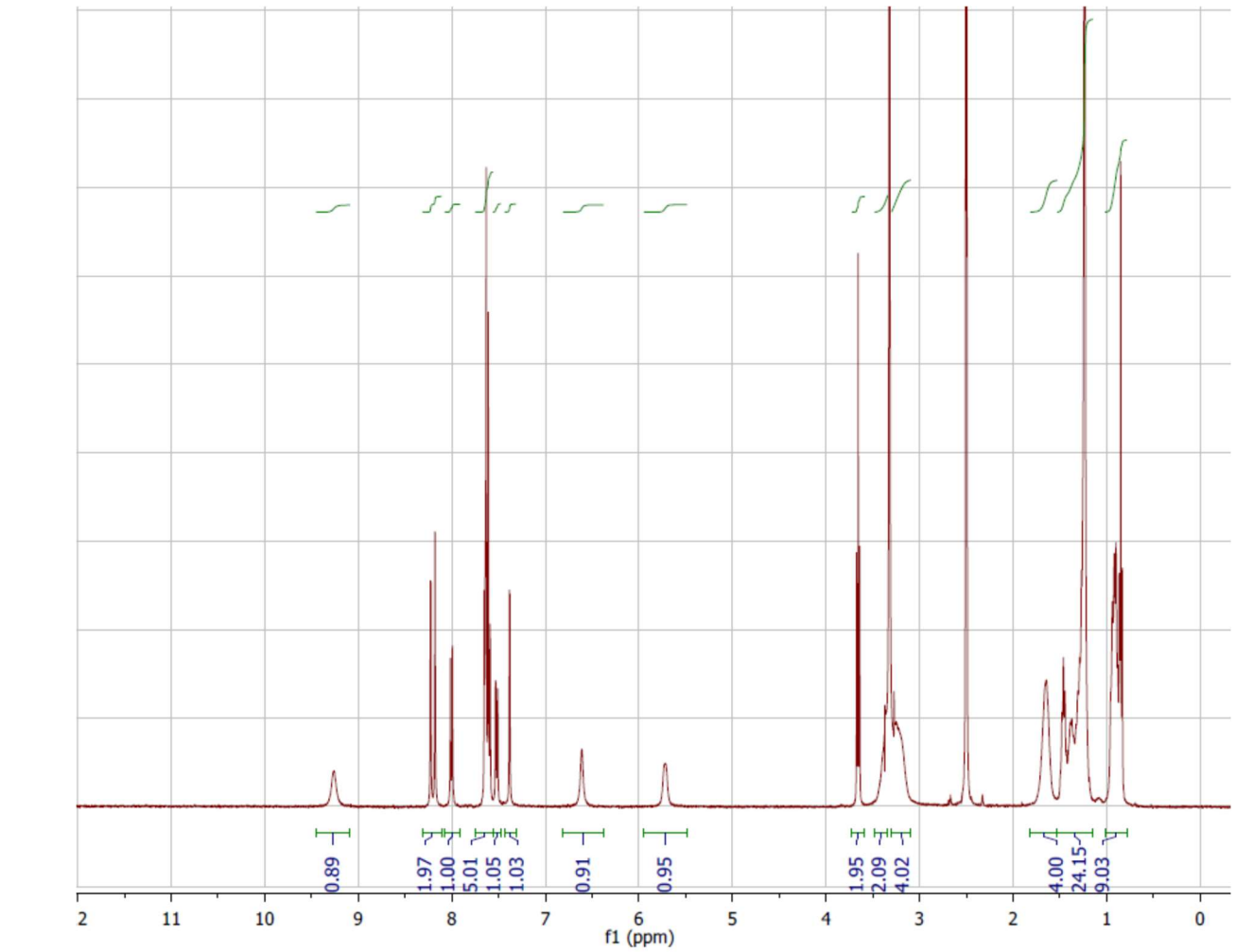


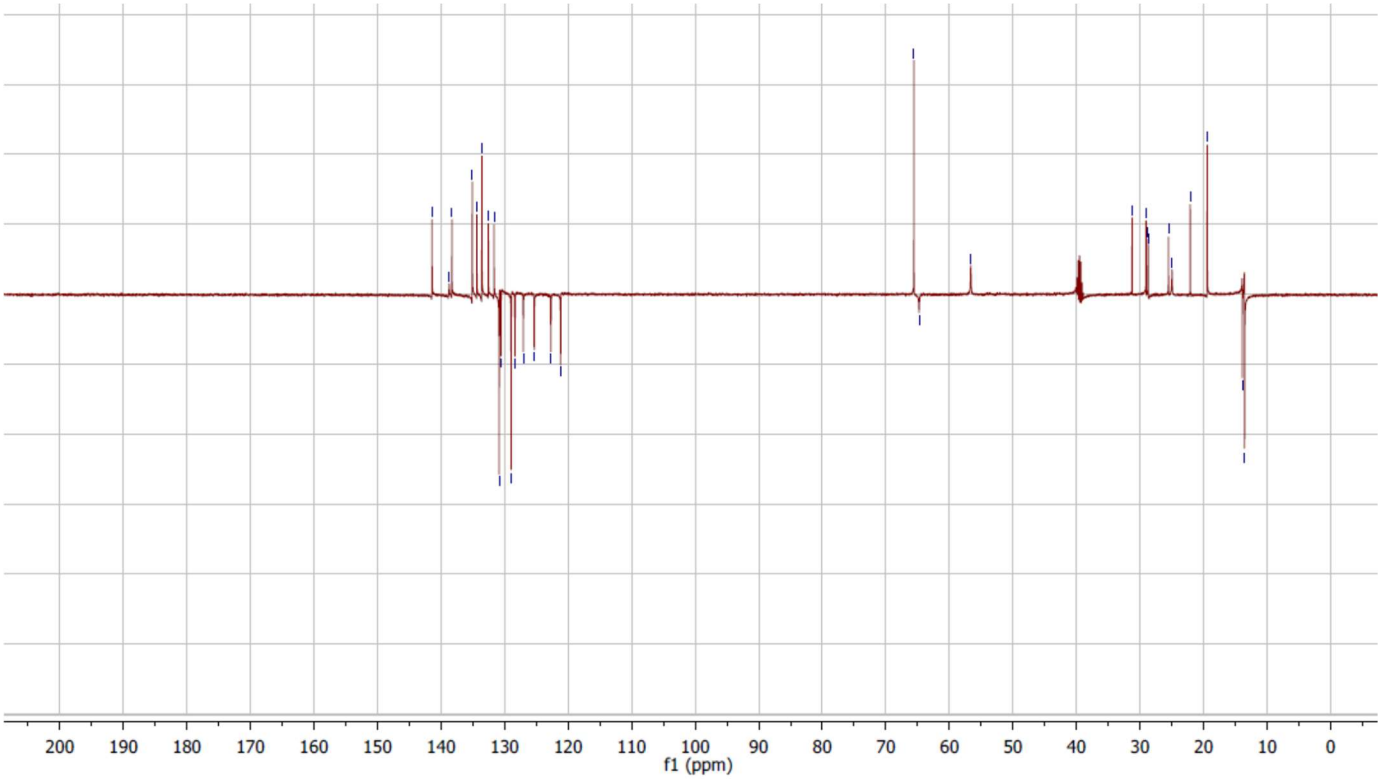
Lumefantrine 1-decyl sulfate (2c)



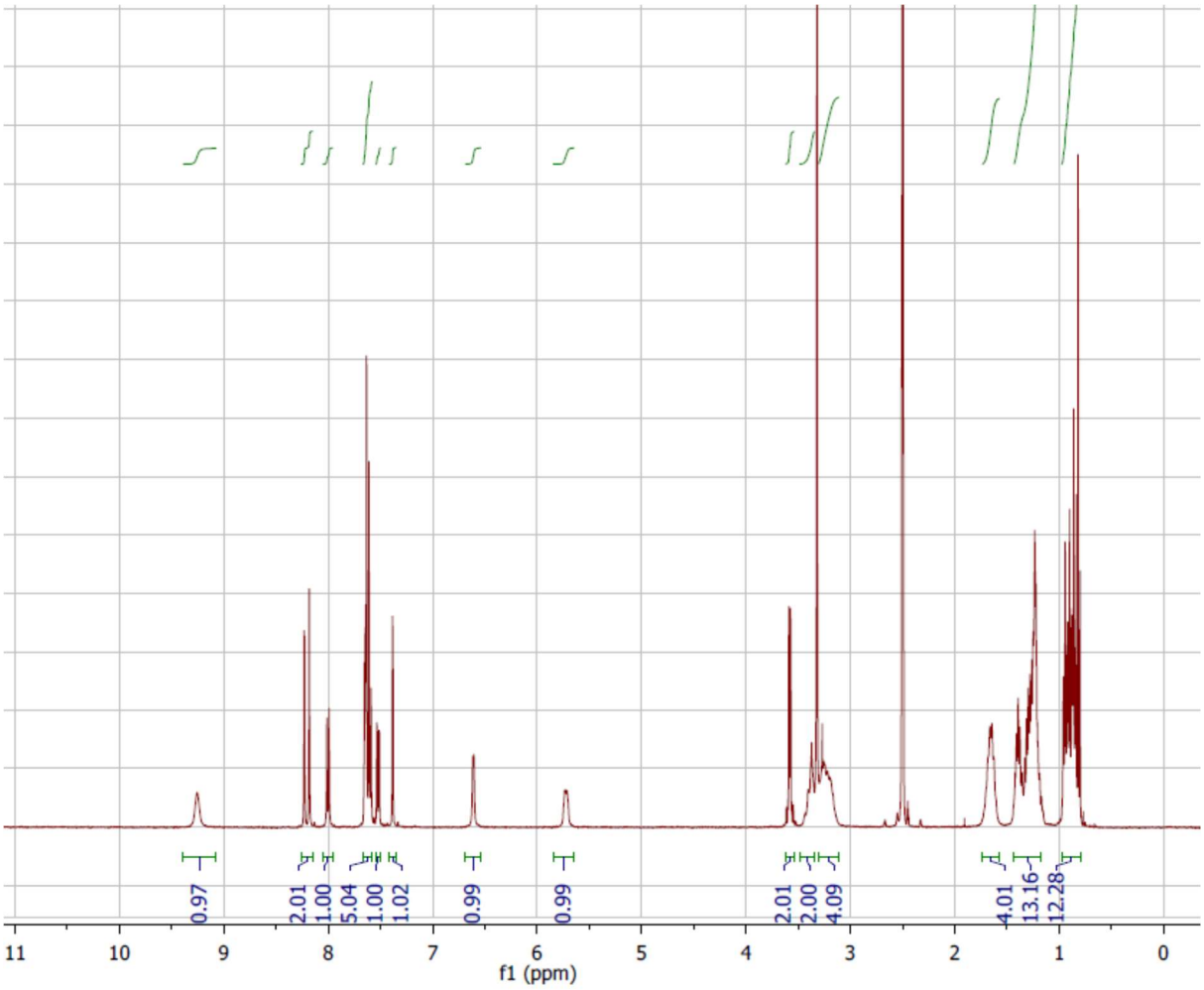


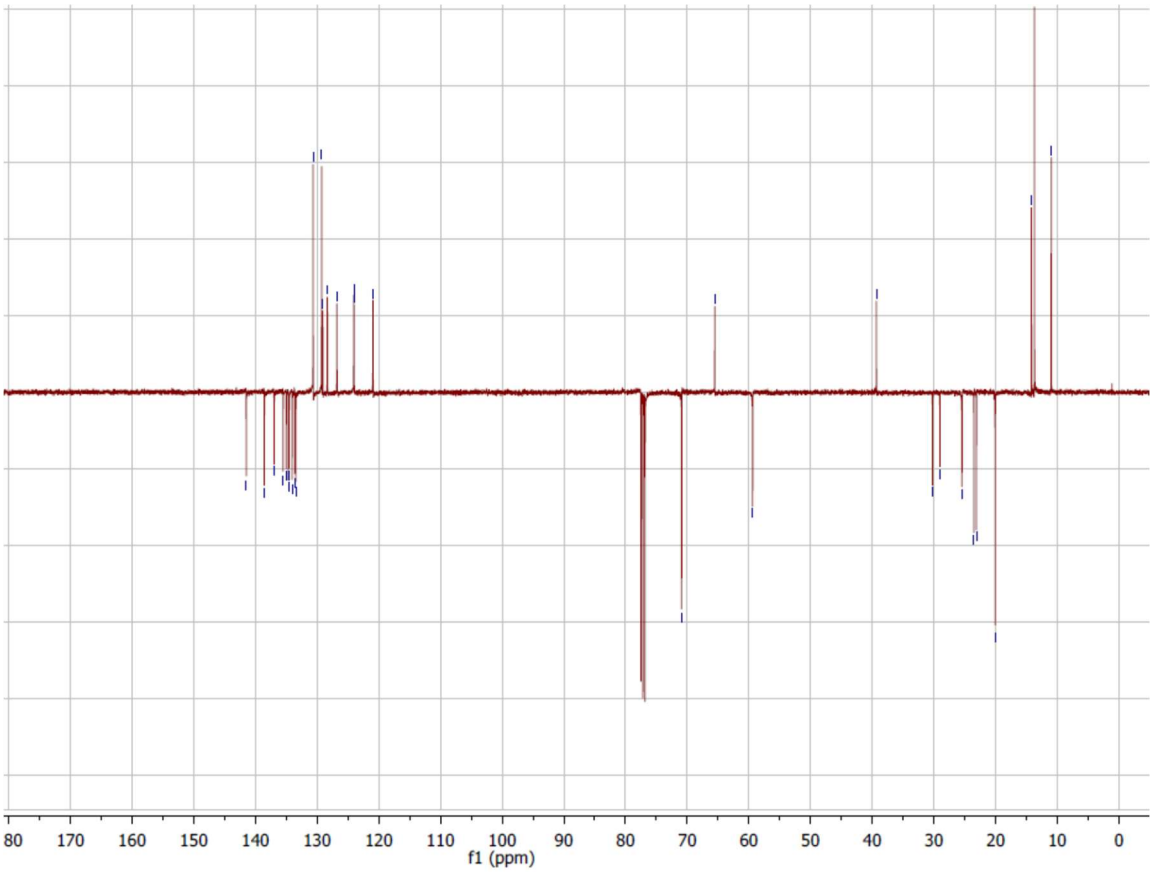
Lumefantrine 1-dodecyl sulfate (2d)



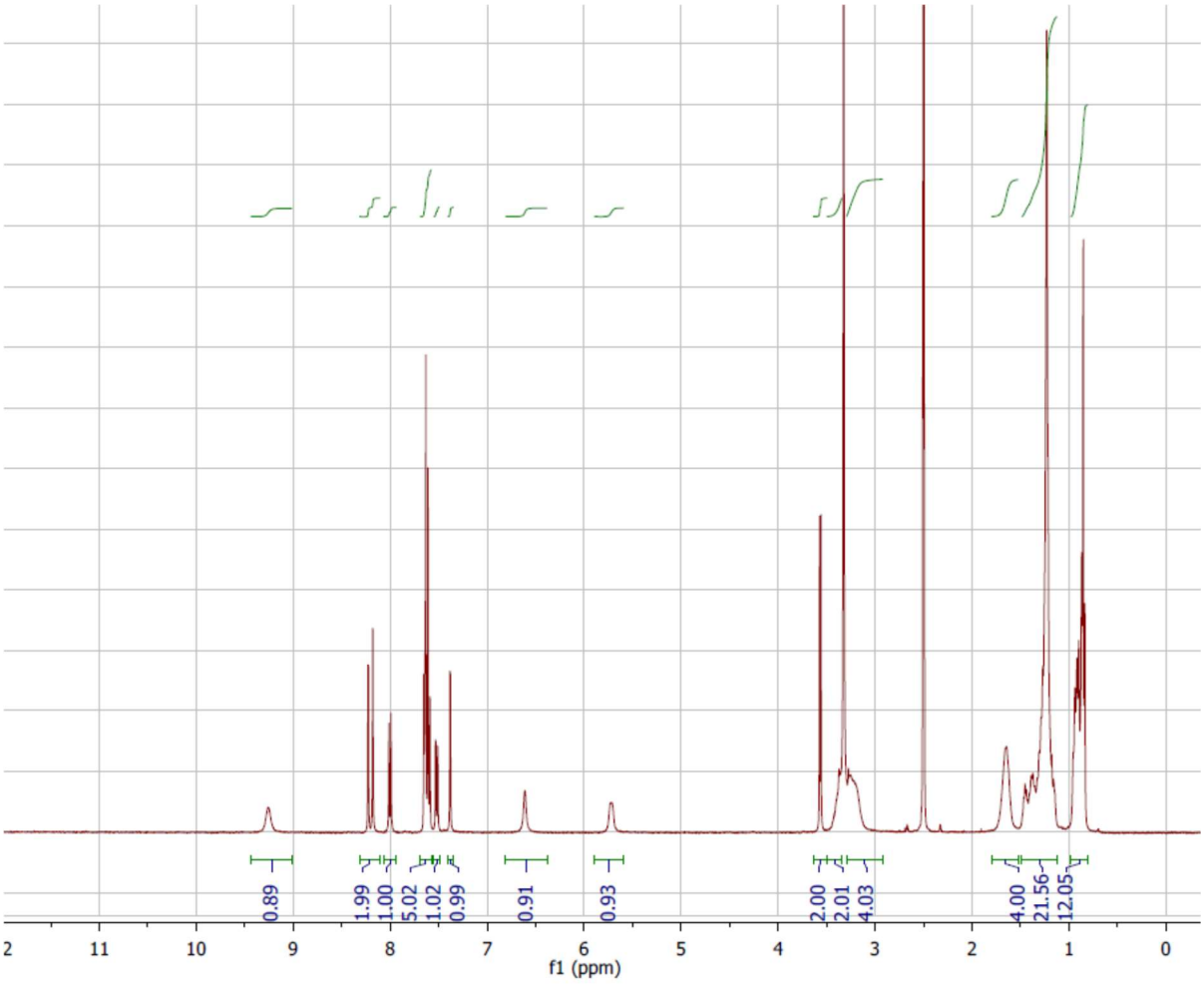


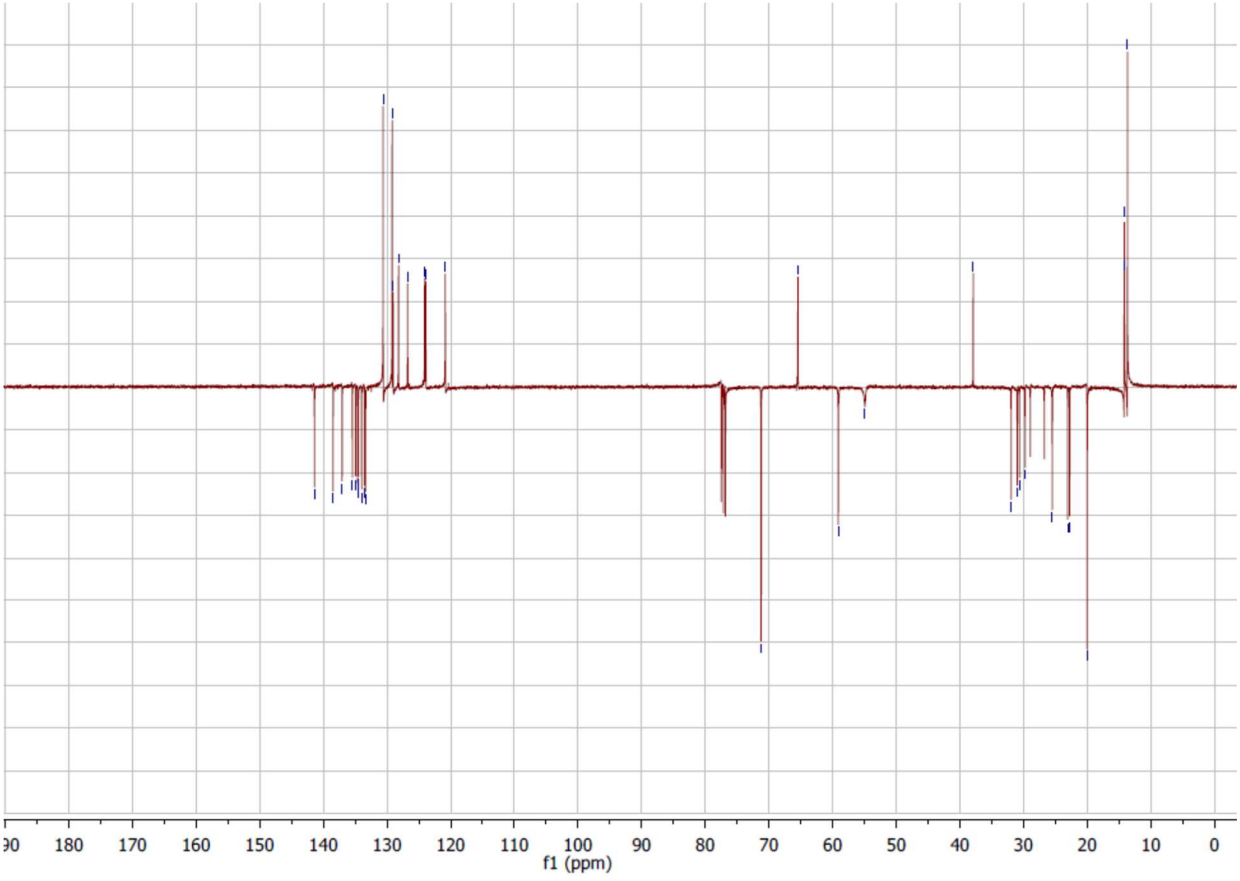
Lumefantrine 2-ethyl-1-hexyl sulfate (2e)



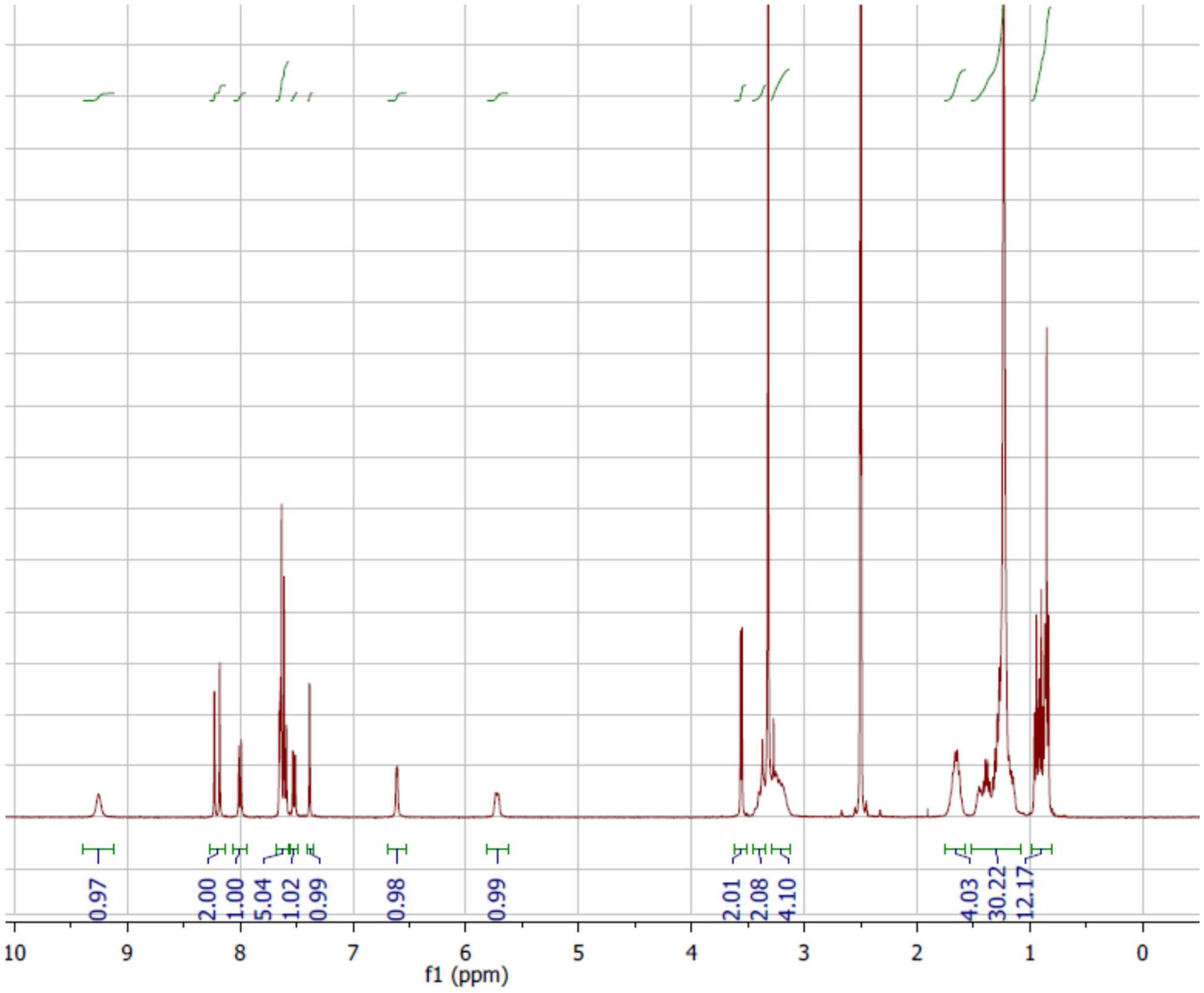


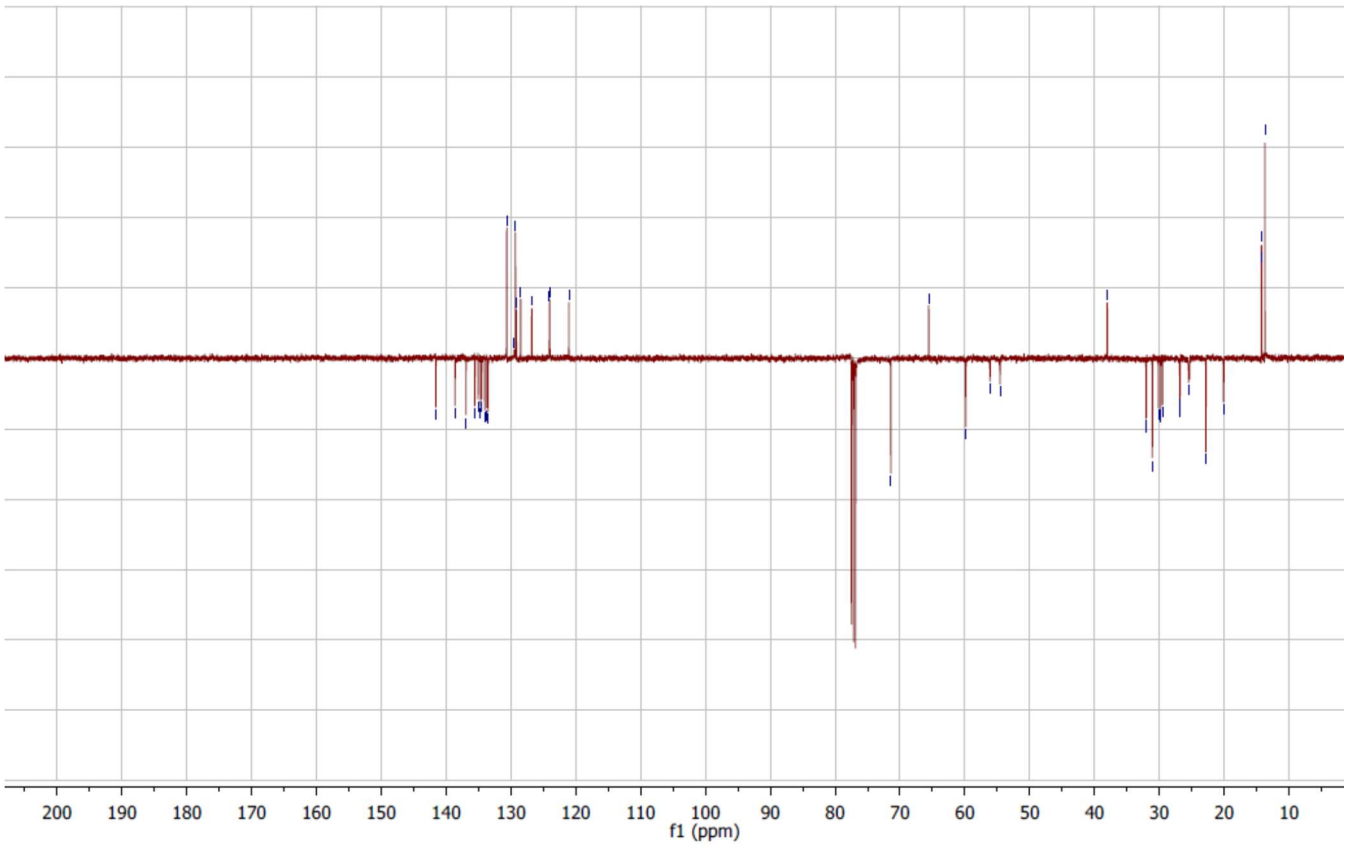
Lumefantrine 2-butyl-1-octyl sulfate (2f)



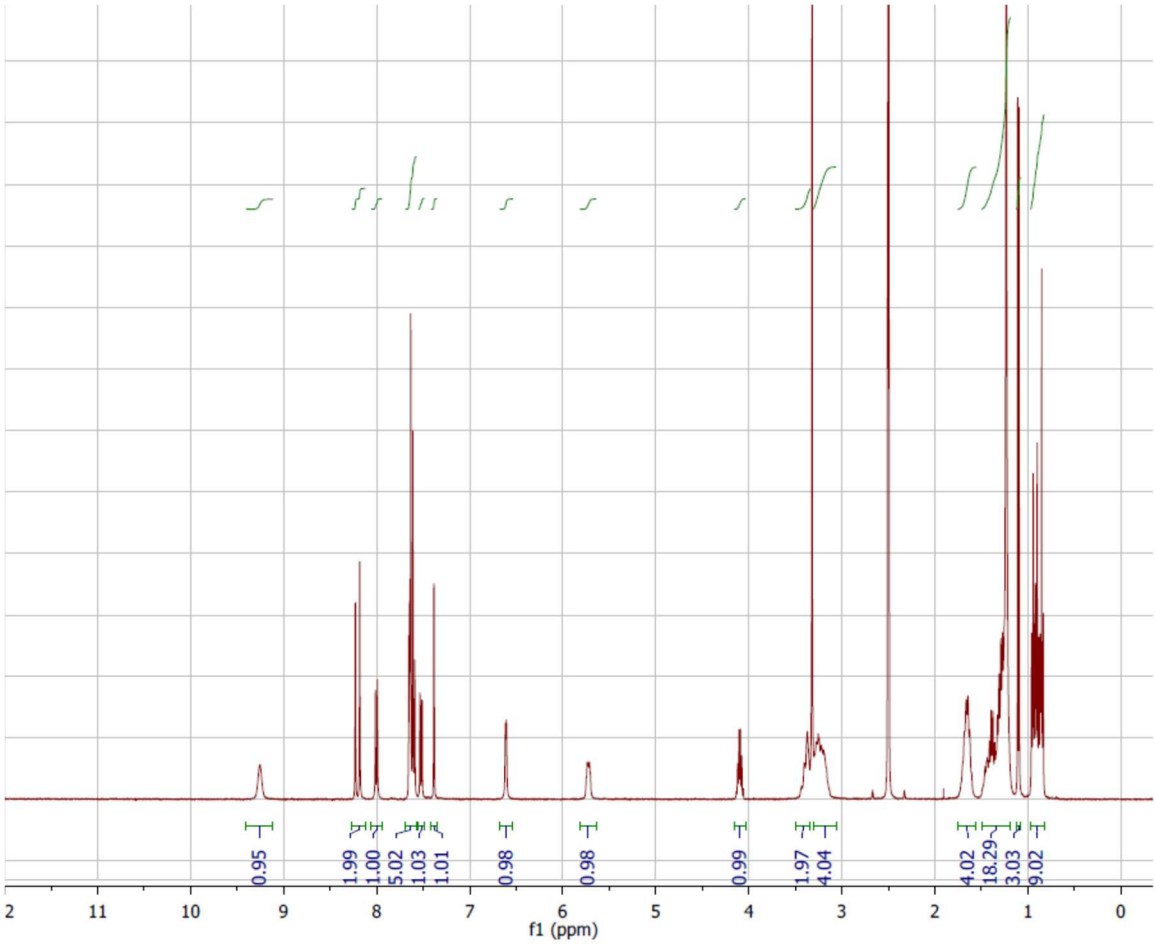


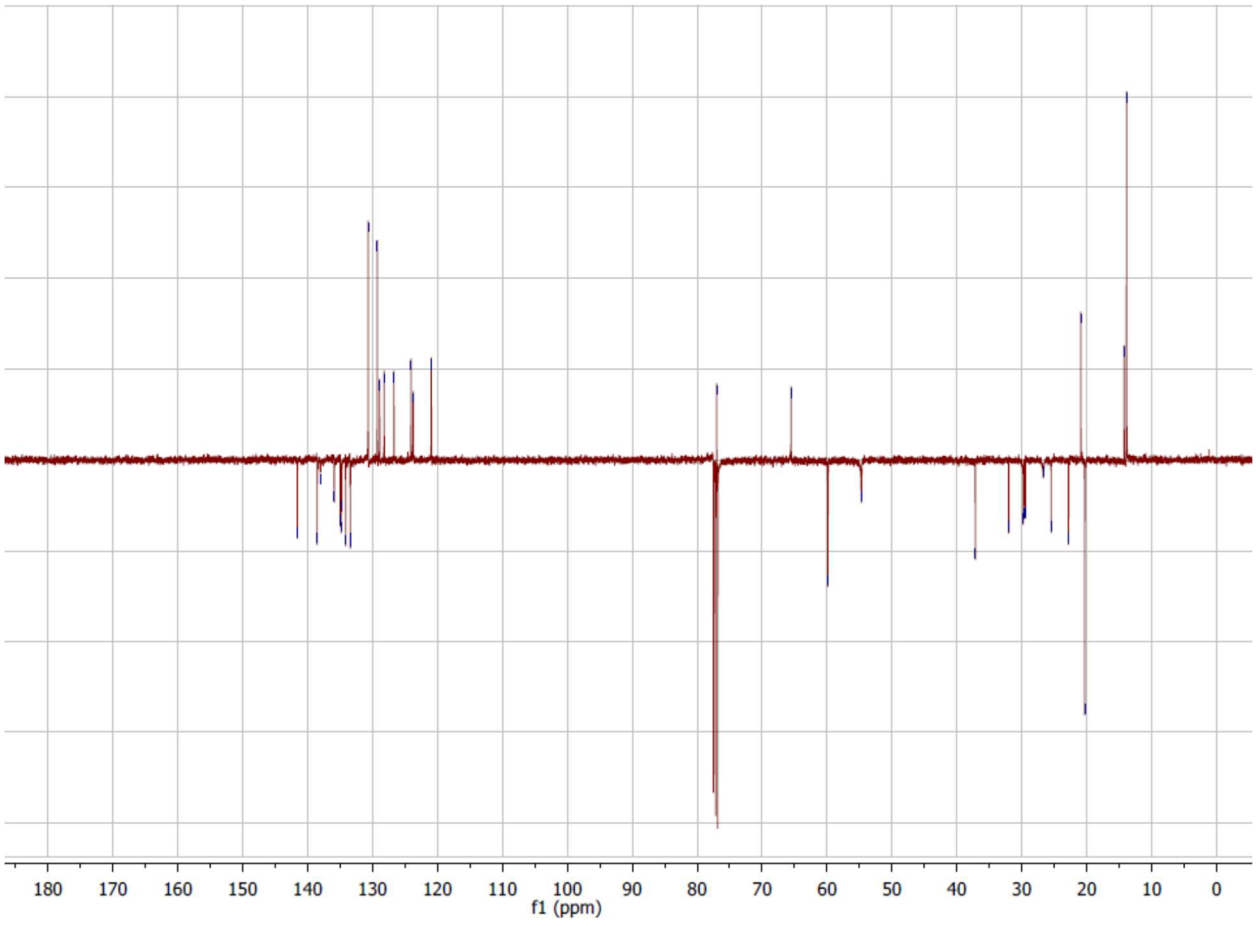
Lumefantrine 2-hexyl-1-decyl sulfate (2g)



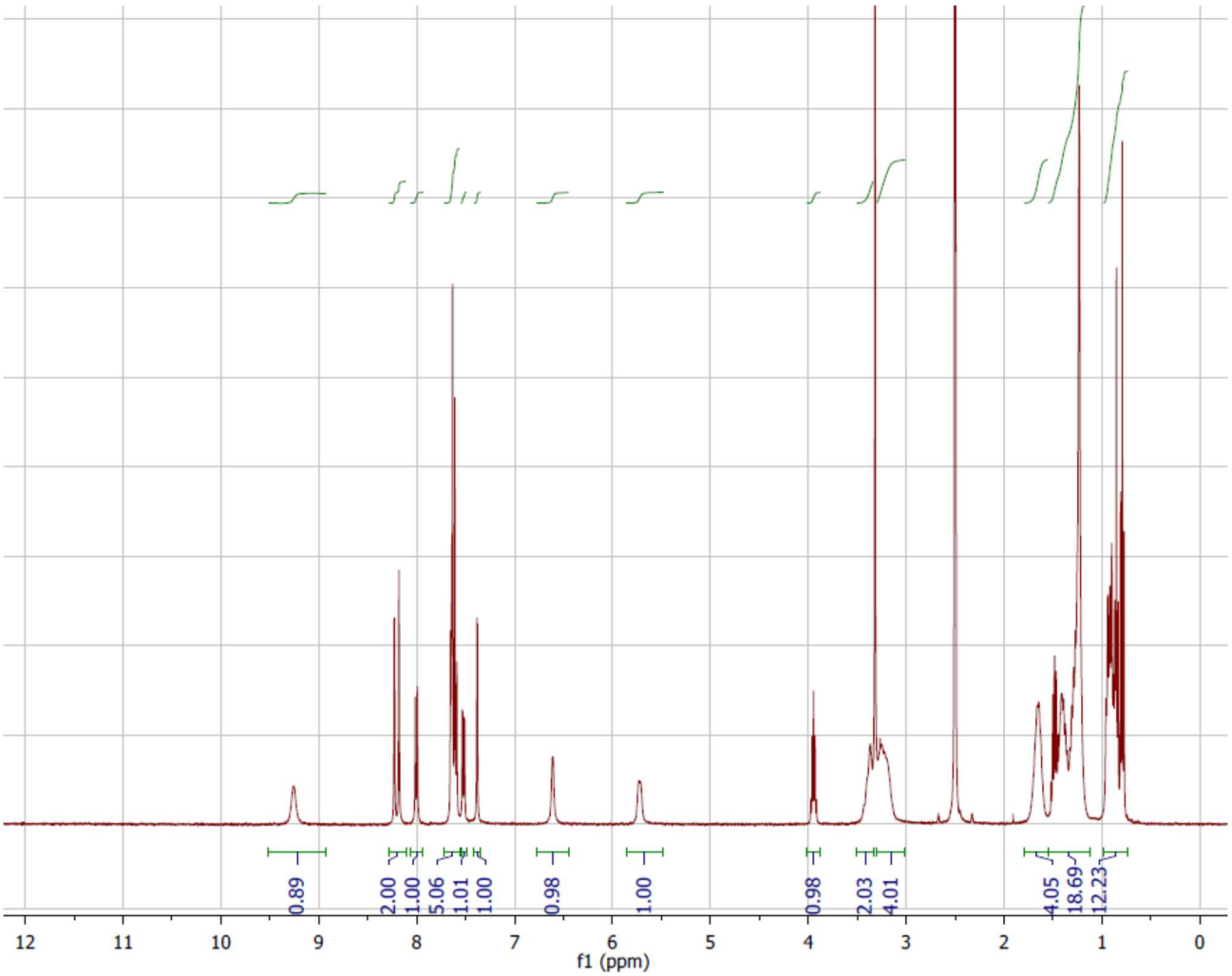


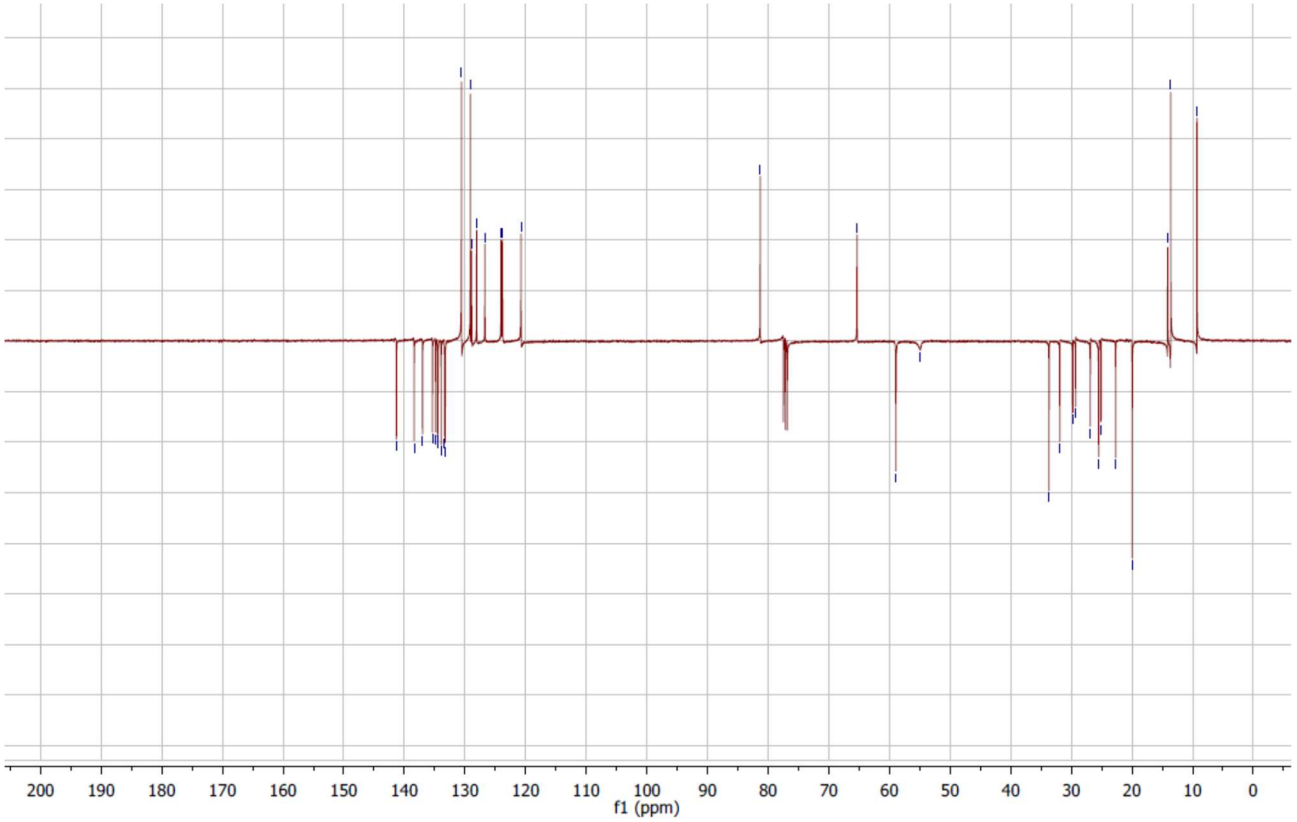
Lumefantrine 2-decyl sulfate (2i)



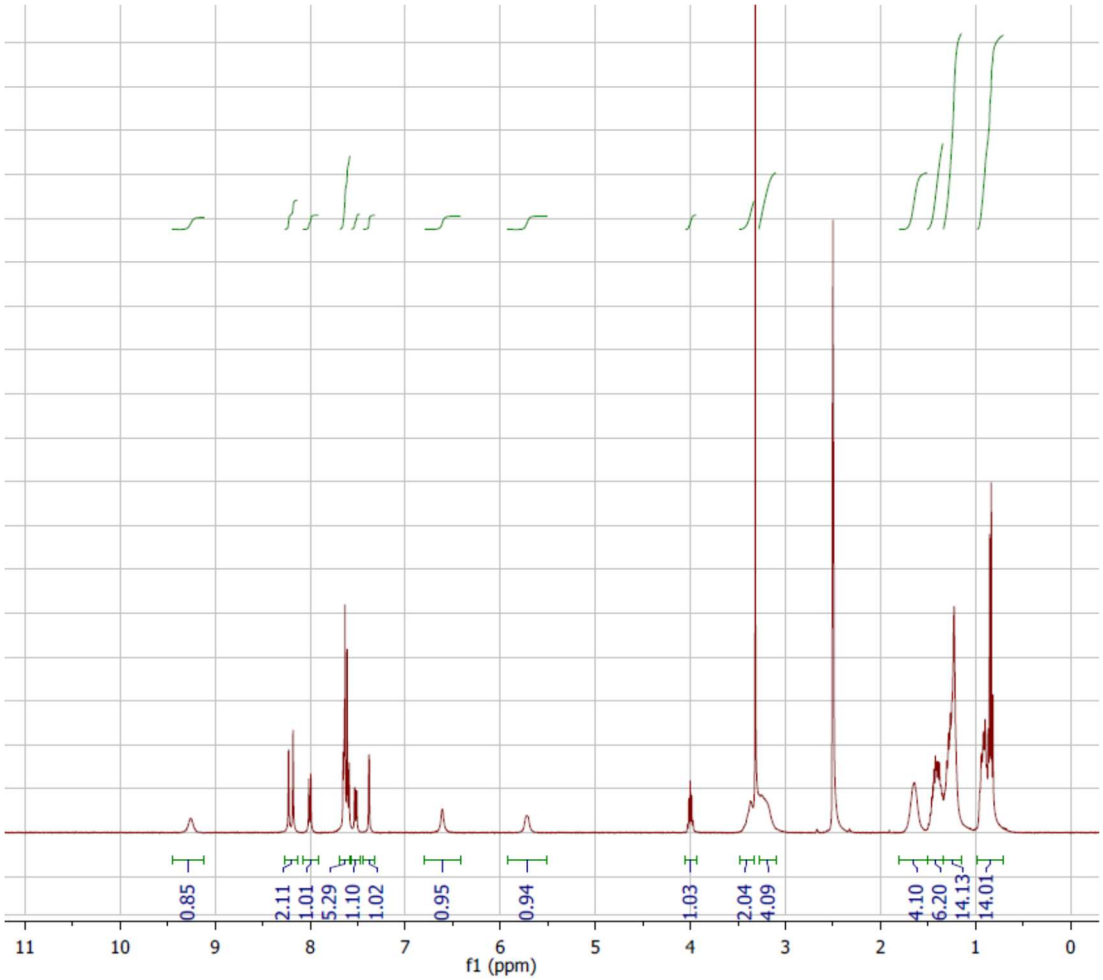


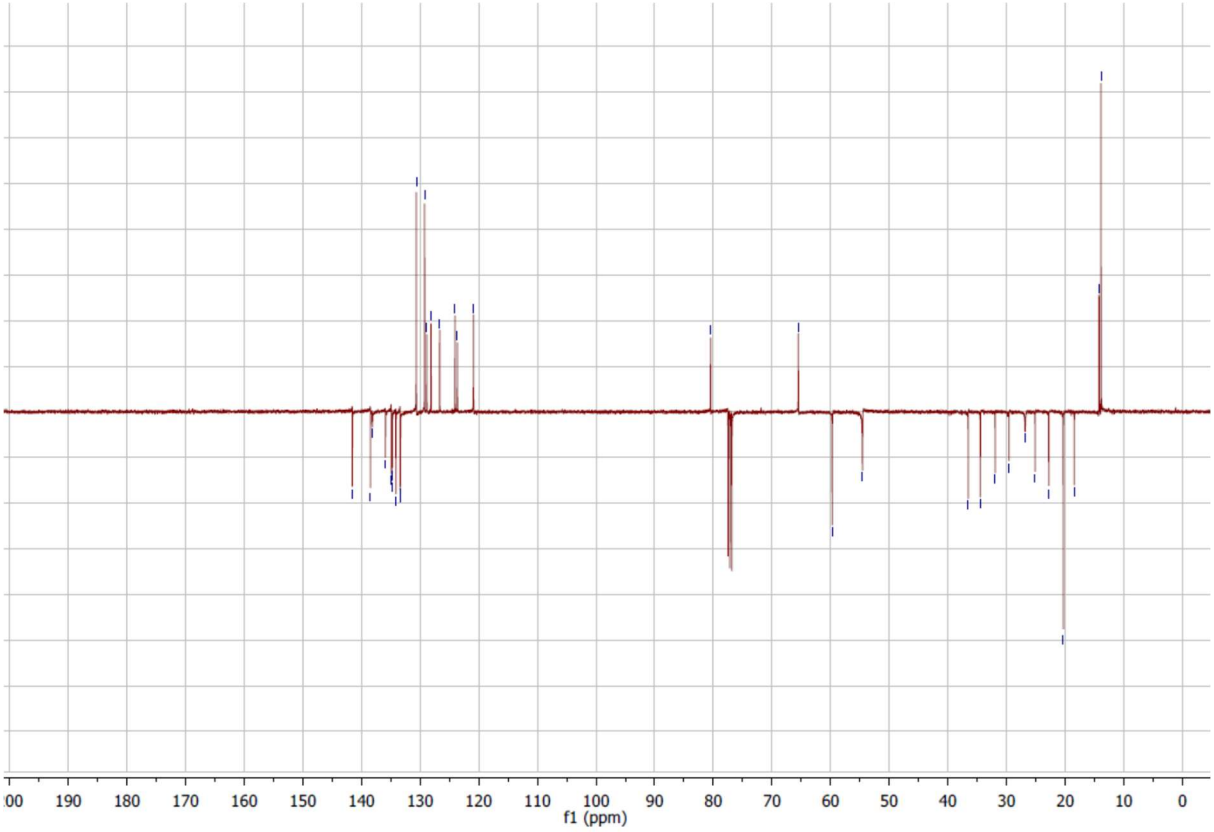
Lumefantrine 3-decyl sulfate (2j)



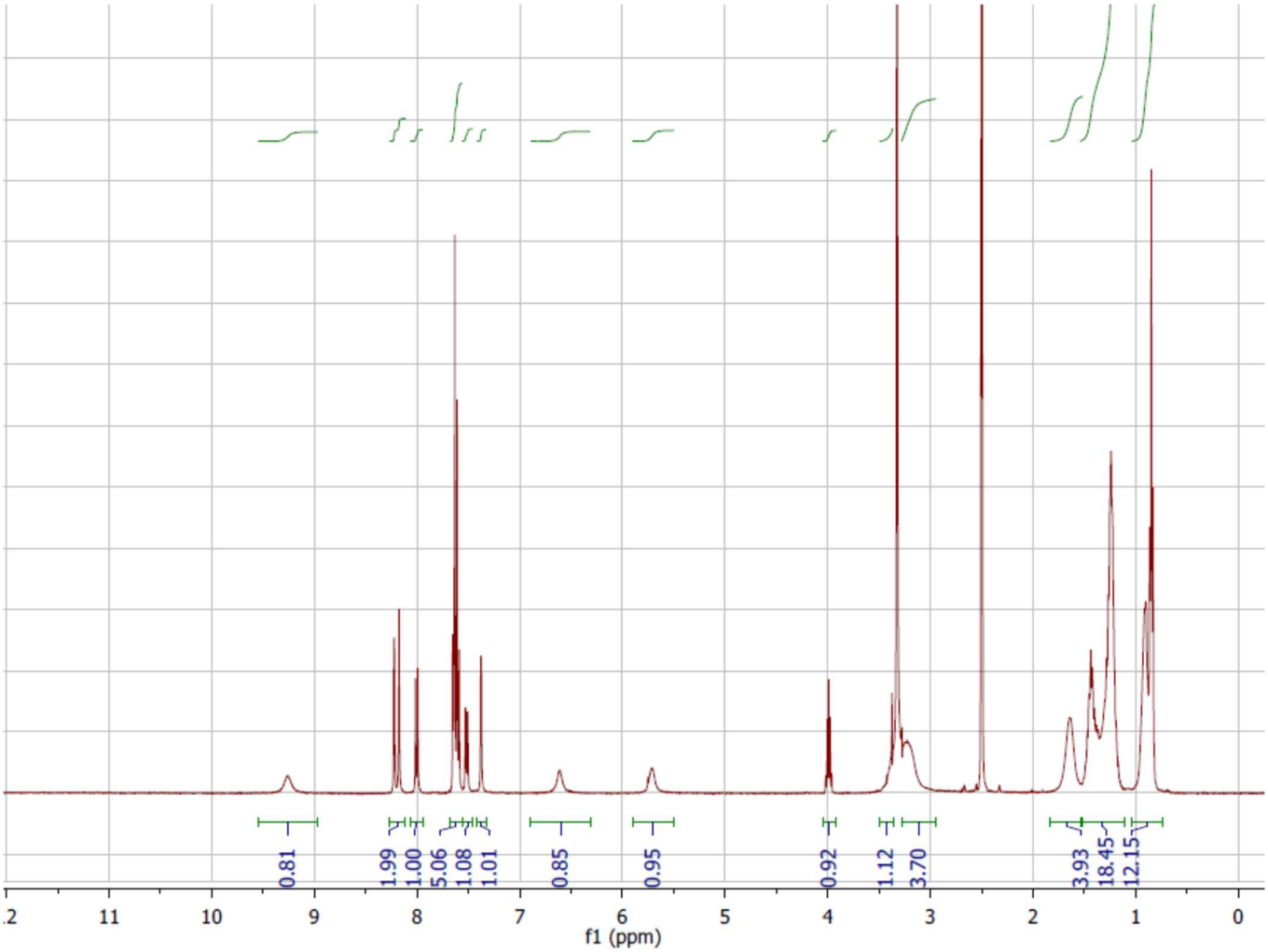


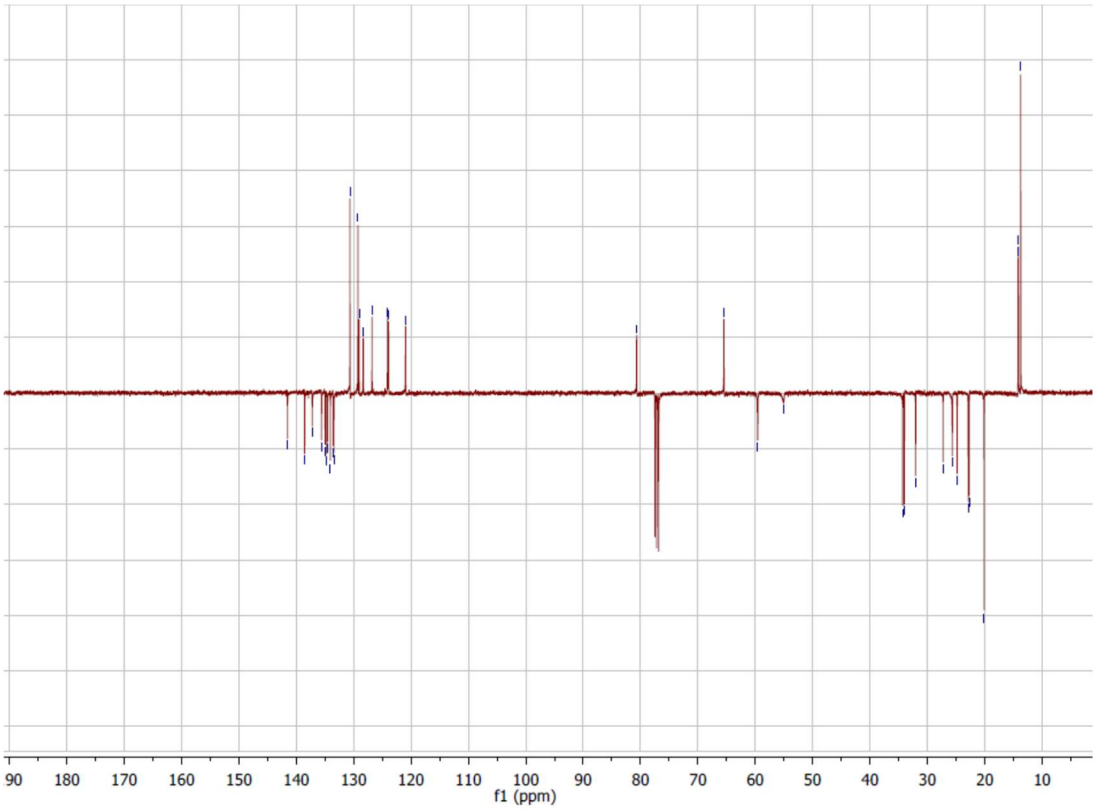
Lumefantrine 4-decyl sulfate (2k)



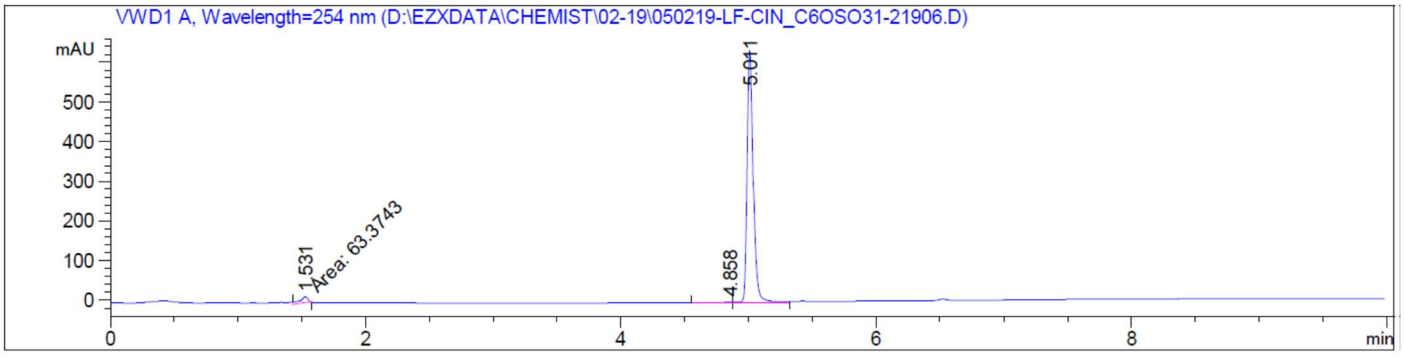


Lumefantrine 5-decyl sulfate (2l)



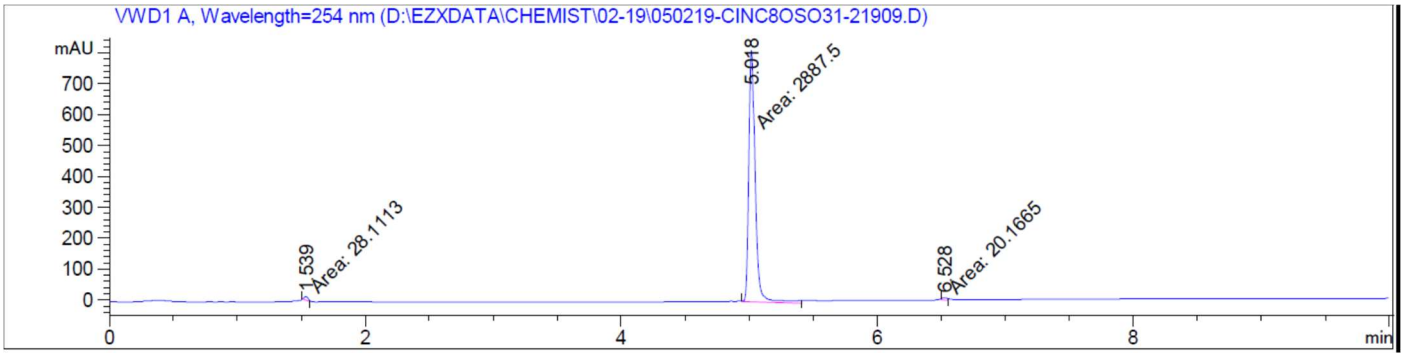


Cinnarizine 1-hexyl sulfate (1b)



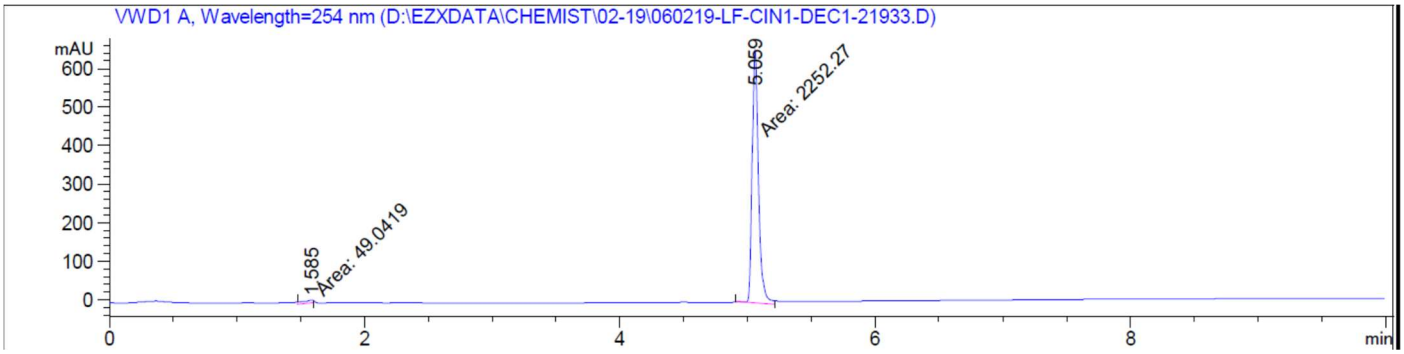
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.531	MM	0.0736	63.37429	14.34839	2.7558
2	4.858	VV	0.1823	33.75565	2.30706	1.4679
3	5.011	VB	0.0519	2202.51318	638.58942	95.7763

Cinnarizine 1-octyl sulfate (1c)



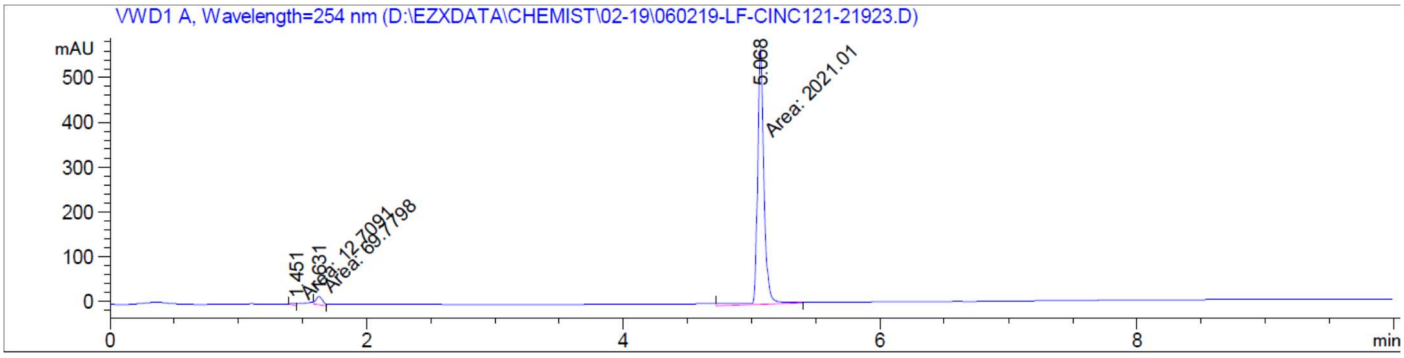
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.539	MM	0.0392	28.11135	11.94305	0.9575
2	5.018	MM	0.0589	2887.49927	817.47681	98.3555
3	6.528	MM	0.0501	20.16652	6.70210	0.6869

Cinnarizine 1-decyl sulfate (1d)



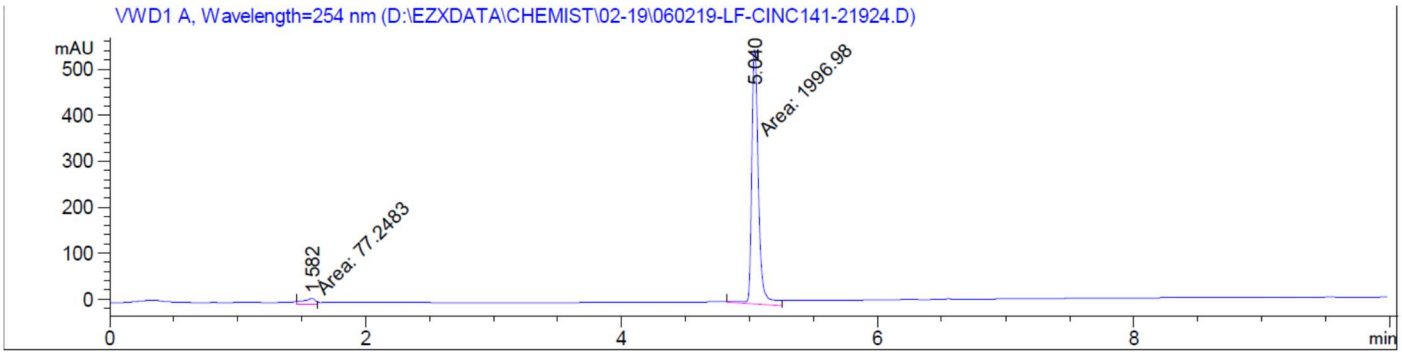
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.585	MM	0.1087	49.04191	7.52283	2.1310
2	5.059	MM	0.0571	2252.27002	657.60931	97.8690

Cinnarizine 1-dodecyl sulfate (1e)



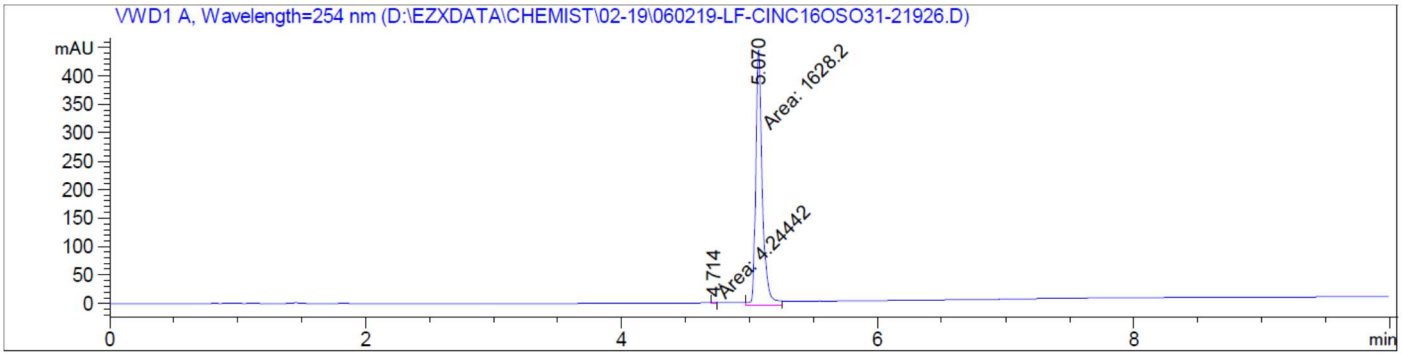
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.451	MM	0.0417	12.70907	5.07779	0.6042
2	1.631	MM	0.0586	69.77977	19.84502	3.3173
3	5.068	MM	0.0592	2021.00549	569.35156	96.0785

Cinnarizine 1-tetradecyl sulfate (1f)



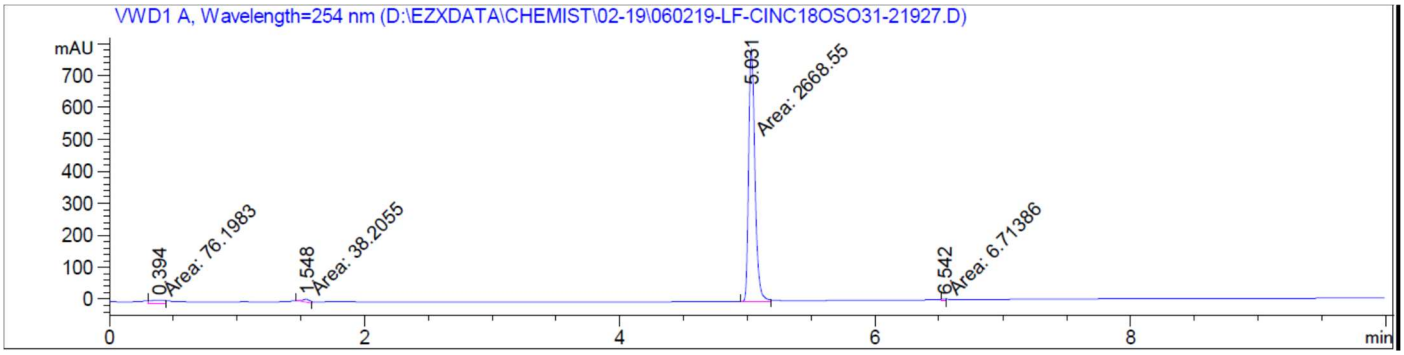
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.582	MM	0.1043	77.24832	12.34844	3.7242
2	5.040	MM	0.0599	1996.97595	555.87097	96.2758

Cinnarizine 1-hexadecyl sulfate (1g)



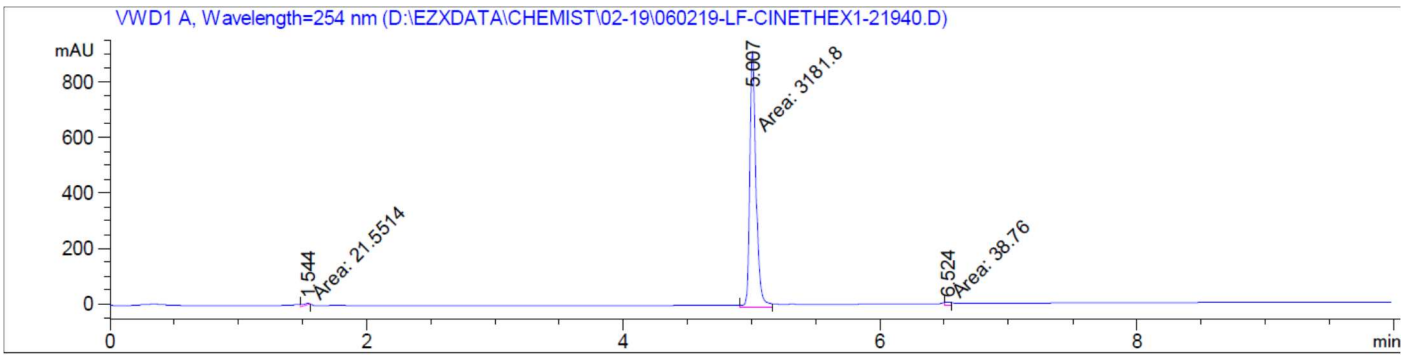
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.714	MM	0.0487	4.24442	1.45299	0.2600
2	5.070	MM	0.0602	1628.20068	450.96036	99.7400

Cinnarizine 1-octadecyl sulfate (1h)



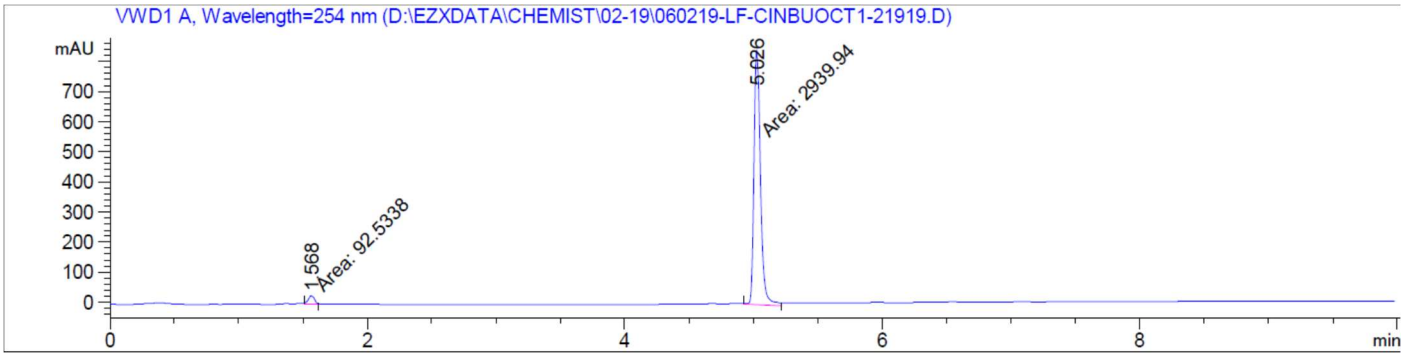
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.394	MM	0.1332	76.19827	9.53499	2.7314
2	1.548	MM	0.0675	38.20546	9.42859	1.3695
3	5.031	MM	0.0562	2668.55029	791.44305	95.6584
4	6.542	MM	0.0351	6.71386	3.18954	0.2407

Cinnarizine 2-ethyl-1-hexyl sulfate (1i)



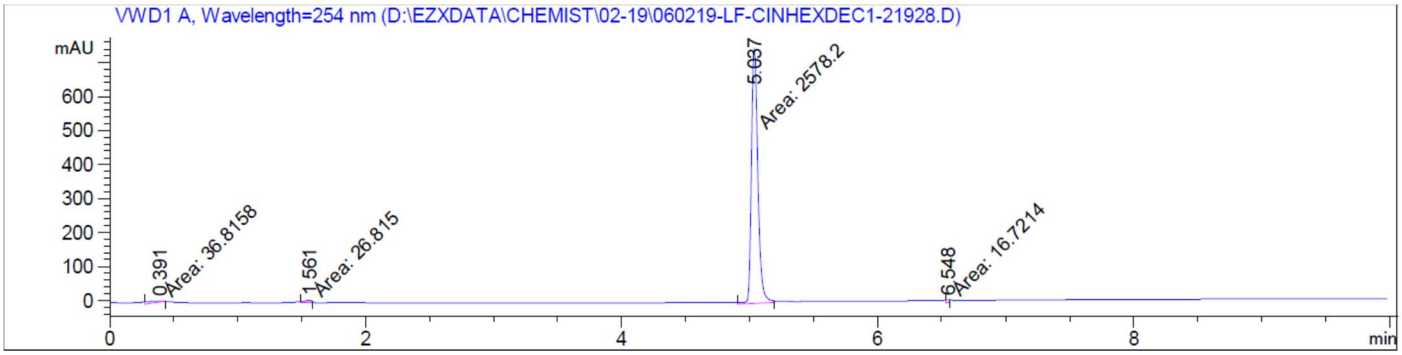
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.544	MM	0.0813	21.55141	4.41810	0.6647
2	5.007	MM	0.0574	3181.80493	924.52893	98.1398
3	6.524	MM	0.0513	38.76001	12.59955	1.1955

Cinnarizine 2-butyl-1-octyl sulfate (1j)



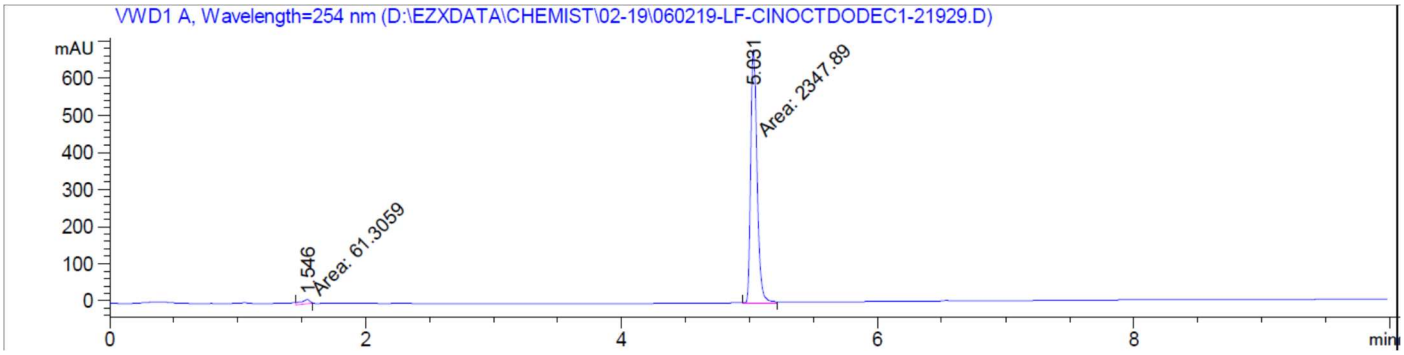
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.568	MM	0.0549	92.53381	28.11509	3.0514
2	5.026	MM	0.0576	2939.94141	850.56879	96.9486

Cinnarizine 2-hexyl-1-decyl sulfate (1k)



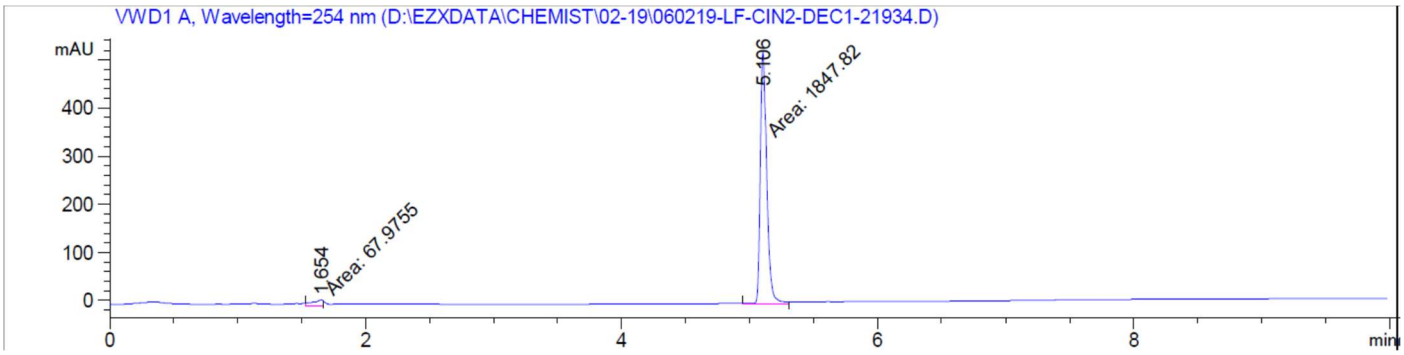
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.391	MM	0.2259	36.81583	2.71600	1.3848
2	1.561	MM	0.0660	26.81503	6.76927	1.0086
3	5.037	MM	0.0574	2578.19604	748.86572	96.9776
4	6.548	MM	0.0365	16.72144	7.63877	0.6290

Cinnarizine 2-octyl-1-dodecyl sulfate (1l)



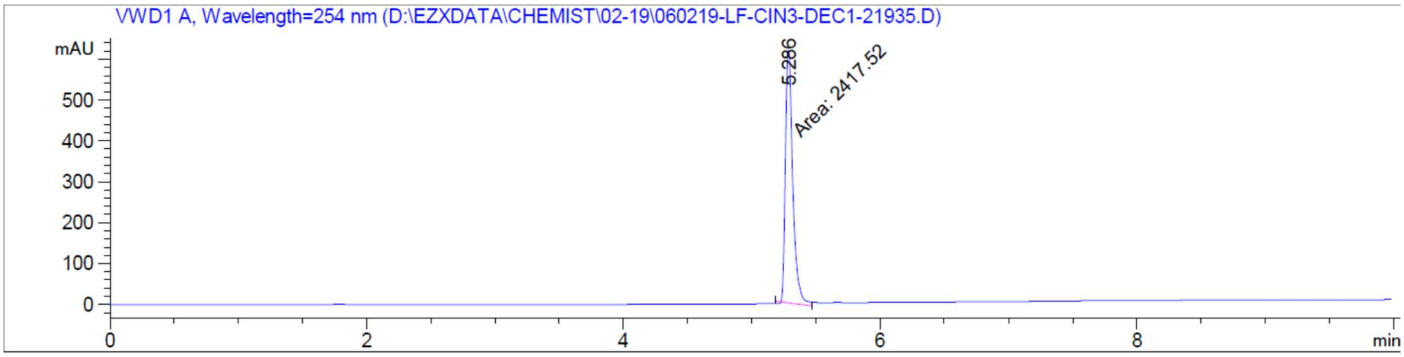
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.546	MM	0.0870	61.30591	11.74299	2.5447
2	5.031	MM	0.0569	2347.89282	687.38550	97.4553

Cinnarizine 2-decyl sulfate (1m)



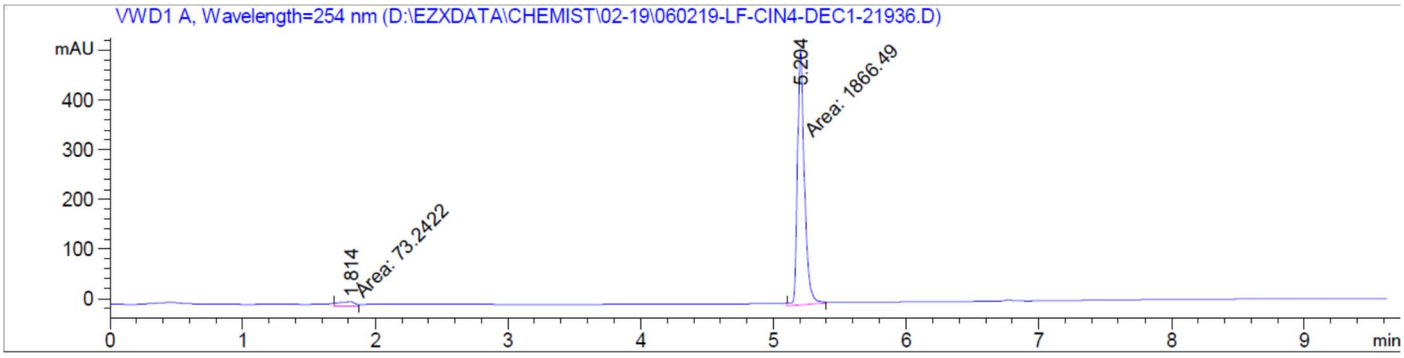
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.654	MM	0.0947	67.97550	11.96296	3.5482
2	5.106	MM	0.0584	1847.82227	527.02228	96.4518

Cinnarizine 3-decyl sulfate (1n)



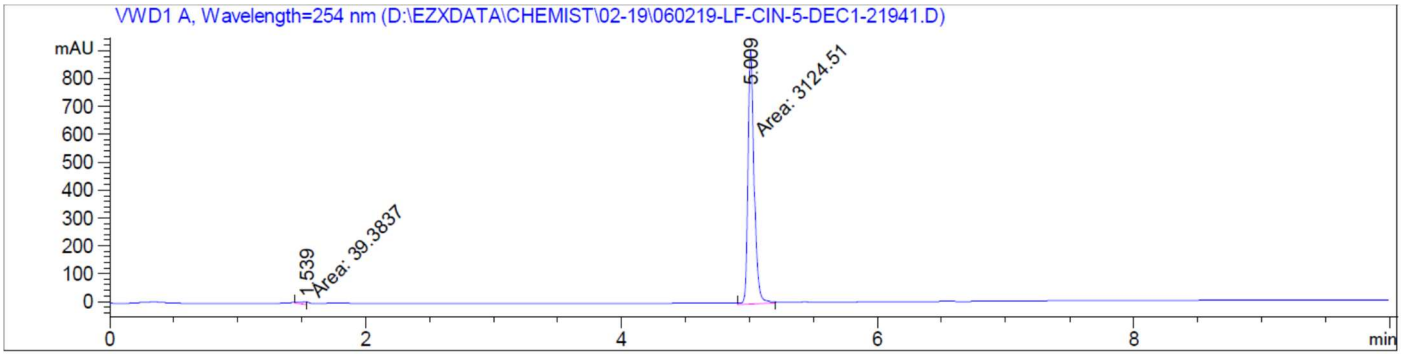
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.286	MM	0.0651	2417.52271	618.58954	100.0000

Cinnarizine 4-decyl sulfate (1o)



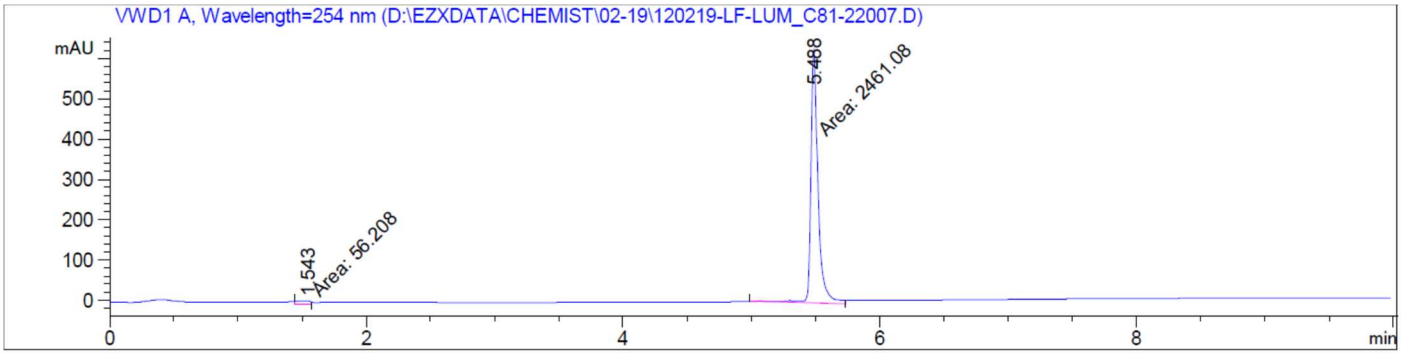
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.814	MM	0.1359	73.24225	8.98045	3.7759
2	5.204	MM	0.0604	1866.48999	514.80524	96.2241

Cinnarizine 5-decyl sulfate (1p)



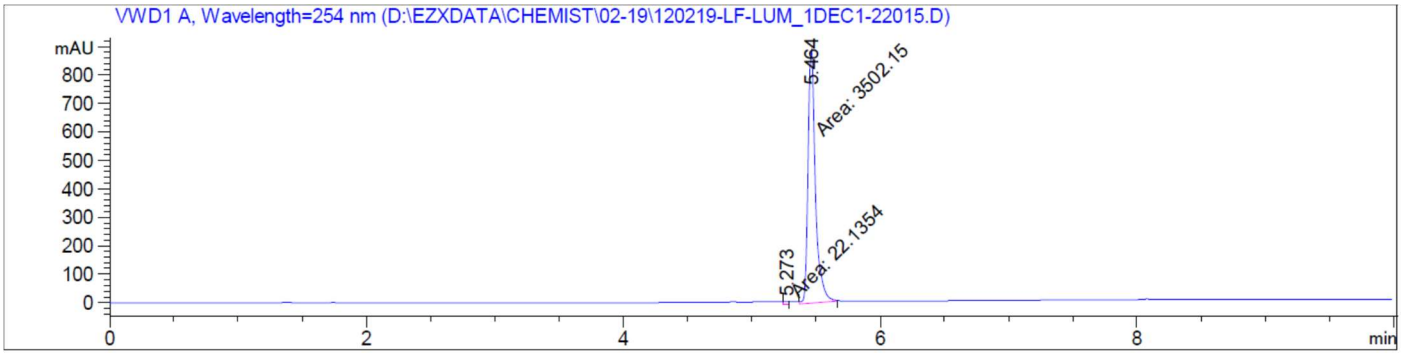
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.539	MM	0.0620	39.38372	10.58279	1.2448
2	5.009	MM	0.0570	3124.50659	913.85779	98.7552

Lumefantrine 1-octyl sulfate (2b)



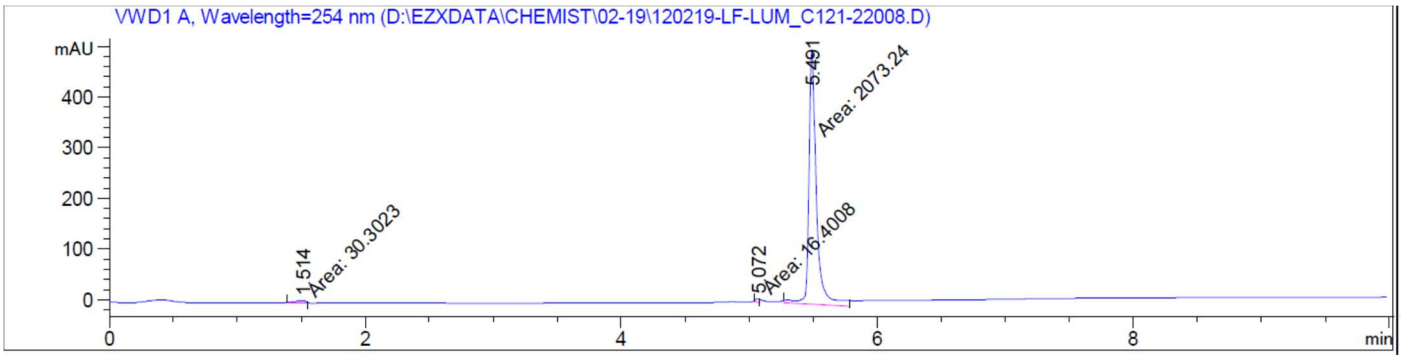
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.543	MM	0.1161	56.20802	8.06902	2.2329
2	5.488	MM	0.0650	2461.08154	630.96167	97.7671

Lumefantrine 1-decyl sulfate (2c)



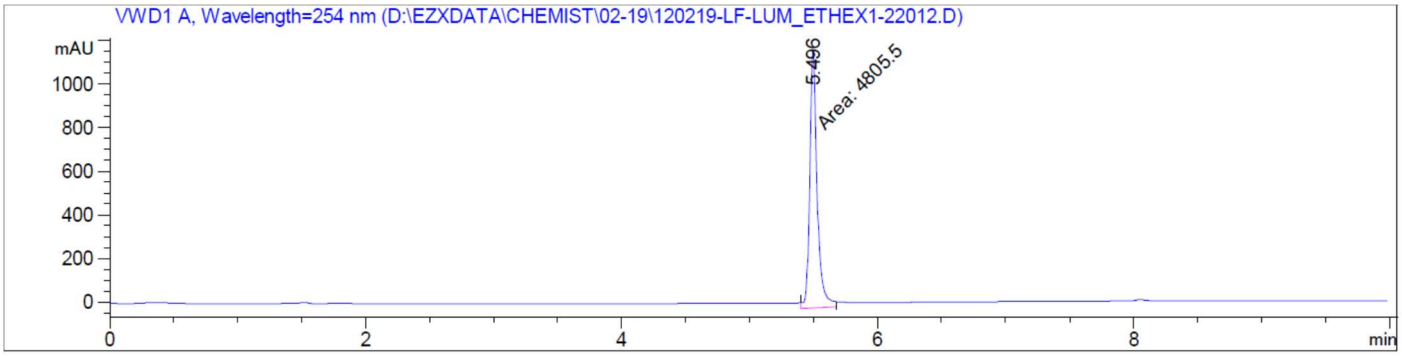
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.273	MM	0.0427	22.13540	8.63808	0.6281
2	5.464	MM	0.0655	3502.14502	891.38892	99.3719

Lumefantrine 1-dodecyl sulfate (2d)



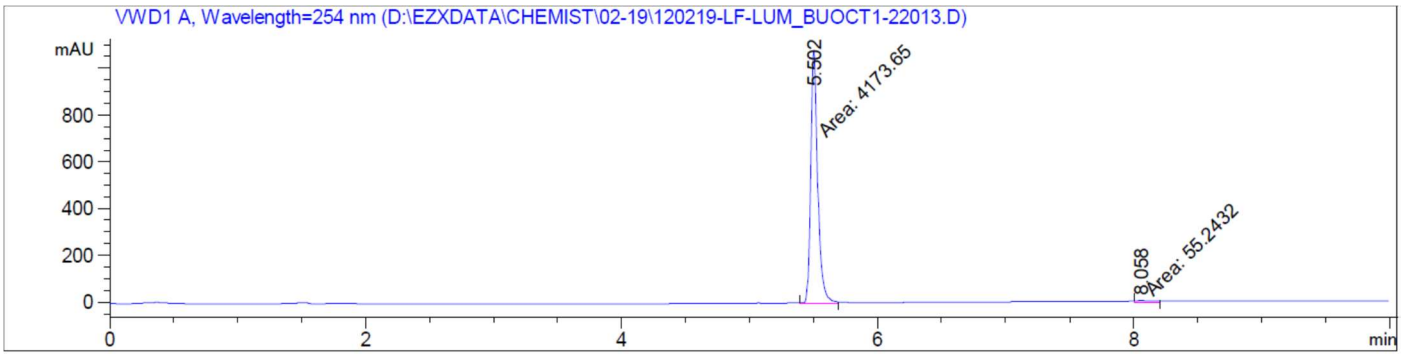
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.514	MM	0.1116	30.30226	4.52344	1.4294
2	5.072	MM	0.0344	16.40082	7.93905	0.7736
3	5.491	MM	0.0688	2073.23975	502.56836	97.7970

Lumefantrine 2-ethyl-1-hexyl sulfate (2e)



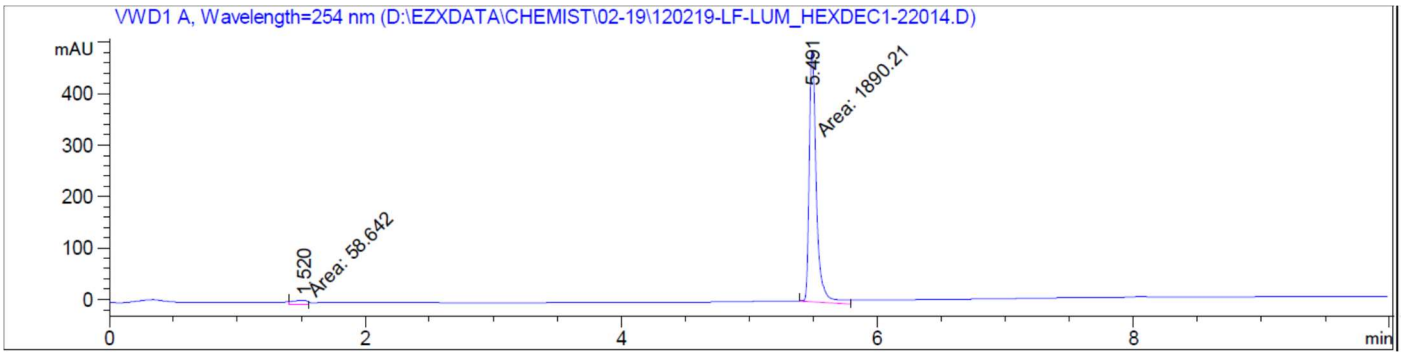
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.496	MM	0.0676	4805.49609	1184.70679	100.0000

Lumefantrine 2-butyl-1-octyl sulfate (2f)



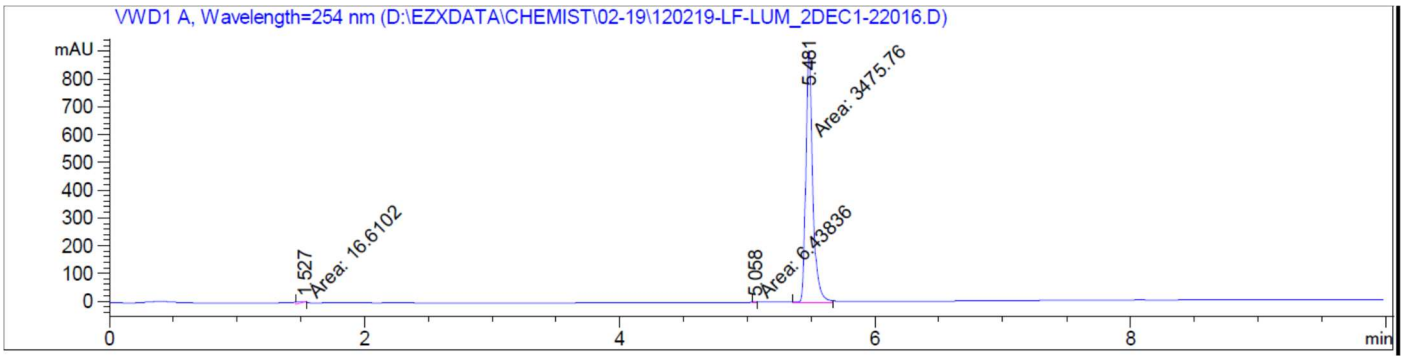
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.502	MM	0.0643	4173.65137	1081.32788	98.6937
2	8.058	MM	0.1489	55.24316	6.18348	1.3063

Lumefantrine 2-hexyl-1-decyl sulfate (2g)



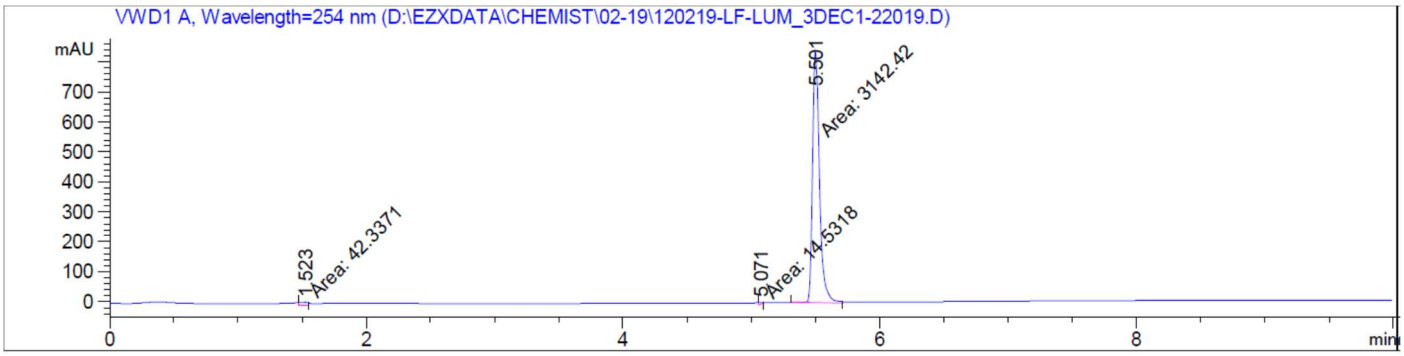
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.520	MM	0.1316	58.64204	7.42790	3.0091
2	5.491	MM	0.0642	1890.20642	490.96625	96.9909

Lumefantrine 2-decyl sulfate (2i)



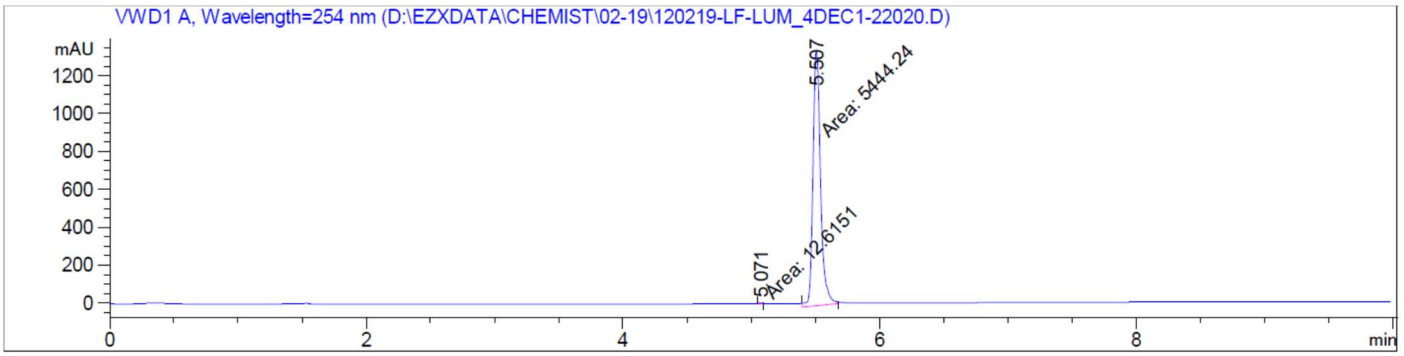
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.527	MM	0.3796	16.61019	7.29315e-1	0.4747
2	5.058	MM	0.0350	6.43836	3.06479	0.1840
3	5.481	MM	0.0636	3475.76392	910.59021	99.3412

Lumefantrine 3-decyl sulfate (2j)



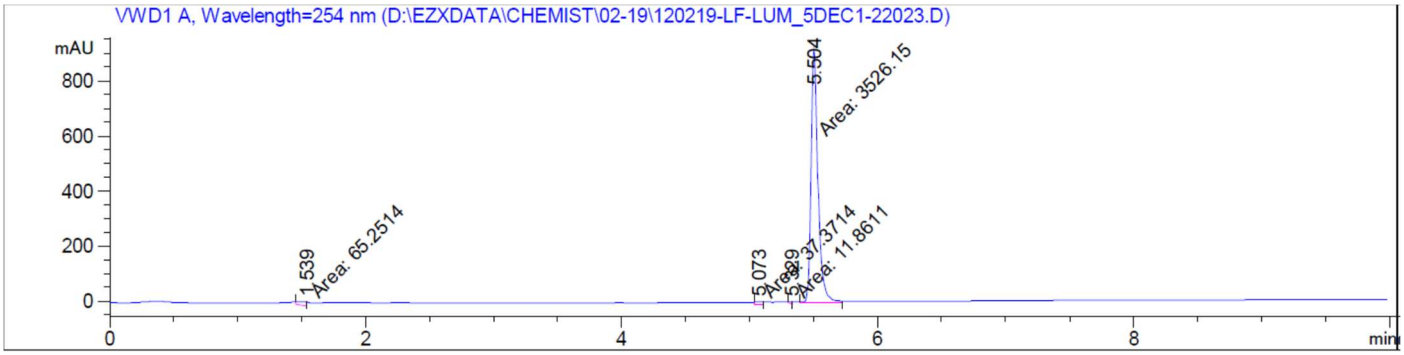
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.523	MM	0.0761	42.33713	9.27483	1.3233
2	5.071	MM	0.0345	14.53183	6.84277	0.4542
3	5.501	MM	0.0621	3142.41528	843.70856	98.2224

Lumefantrine 4-decyl sulfate (2k)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.071	MM	0.0419	12.61506	5.01455	0.2312
2	5.507	MM	0.0673	5444.24072	1349.08691	99.7688

Lumefantrine 5-decyl sulfate (2l)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.539	MM	0.0729	65.25144	14.92543	1.7923
2	5.073	MM	0.0632	37.37138	9.86303	1.0265
3	5.329	MM	0.0240	11.86115	8.25213	0.3258
4	5.504	MM	0.0639	3526.14893	919.78229	96.8554