Transformation of Poorly Water-Soluble Drugs into Lipophilic Ionic Liquids Enhances Oral Drug Exposure from Lipid Based Formulations

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NMR and MS Characterization Data

Cinnarizine lauryl(dodecyl)sulfate (Cin DDS). Method 2; Yield 95%. ^{1}H NMR ($CDCl_3$) δ 10.07 (br s, 1H), 7.44-7.16 (m, 15H), 6.80 (d, *J* = 15.8 Hz, 1H), 6.39 (dt, *J* = 16.0, 7.2 Hz, 1H), 4.36 (s, 1H), 4.10 (t, *J* = 6.8 Hz, 2H), 3.88 (d, *J* = 7.2 Hz, 2H), 3.48 (br s, 2H), 2.96 (br s, 4H), 2.62 (br s, 2H), 1.69 (quin, *J* = 6.8 Hz, 2H), 1.37-1.24 (br s, 18H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 141.1, 140.7, 134.9, 129.0, 128.8, 128.7, 127.5 (2C), 127.0, 116.2, 75.0, 68.2, 59.0, 51.6, 48.5, 31.8, 29.6, 29.5 (3C), 29.4, 29.3, 29.2, 25.8, 22.6, 14.1. HRMS (+ve) calcd 369.2331, found 369.2333. HRMS (–ve) calcd 265.1474, found 265.1482.

Cinnarizine octadecylsulfate (Cin OS). Method 2; Yield 92%. ^{1}H NMR (DMSO-d_6) δ 9.48 (br s, 1H), 7.51-7.19 (m, 15H), 6.80 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.6, 7.2 Hz, 1H), 4.46 (s, 1H), 3.88 (br s, 2H), 3.66 (t, *J* = 6.7 Hz, 2H), 3.33 (br s, 2H), 3.12 (br s, 2H), 2.87 (br s, 2H), 2.24 (br s, 2H), 1.47 (quin, *J* = 6.8 Hz, 2H), 1.29-1.18 (br s, 30H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 141.8, 138.5, 135.5, 128.7, 128.6, 128.5, 127.6, 127.2, 126.8, 118.4, 73.7, 65.7, 57.4, 50.9, 48.5, 31.4, 29.1 (11C), 28.9, 28.8, 25.6, 22.1, 14.0. HRMS (+ve) calcd 369.2331, found 369.2333. HRMS (–ve) calcd 349.2413, found 349.2422.

Cinnarizine 7-ethyl-2-methyl-4-undecylsulfate (niaproof, Cin NP). Method 2; Yield 90%, Method 3; Yield 91%. ^{1}H NMR ($CDCl_3$) δ 10.54 (br s, 1H), 7.43-7.16 (m, 15H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.40 (dt, *J* = 16.0, 7.2 Hz, 1H), 4.51 (m, 1H), 4.36 (s, 1H), 3.85 (d, *J* = 7.4 Hz, 2H), 3.50 (d, *J* = 10.9 Hz, 2H), 2.94(d, *J* = 10.1 Hz, 4H), 2.67 (br s, 2H), 1.86 (m, 1H), 1.79-1.62 (m, 3H), 1.41-1.21 (m, 12H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.85 (td, *J* = 6.7 Hz, 2.3, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). HRMS (+ve) calcd 369.2331, found 369.2332. HRMS (–ve) calcd 293.1787, found 293.1787.

Cinnarizine oleate (Cin OL). Method 3; Yield 94%. ^{1}H NMR ($CDCl_3$) δ 9.83 (br s, 1H), 7.42-7.15 (m, 15H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.29 (dt, *J* = 15.7, 7.1 Hz, 1H), 5.39-5.31 (m, 2H), 4.26 (s, 1H), 3.36 (d, *J* = 7.0 Hz, 2H), 2.76 (br s, 4H), 2.54 (br s, 4H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.02 (m, 4H), 1.61 (quin, *J* = 7.2 Hz, 2H), 1.32-1.27 (m, 20H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (DMSO-

d_6/$CDCl_3$) δ 175.3, 142.4, 136.2, 133.6, 129.5, 129.3, 128.2, 128.1, 127.4, 127.3, 126.6, 126.0, 124.5, 75.5, 59.8, 52.4, 50.7, 34.0, 31.4, 29.3, 29.2, 29.0, 28.8 (4C), 28.7, 26.7 (2C), 24.6, 22.2, 13.8. HRMS (+ve) calcd 369.2331, found 369.2333. HRMS (–ve) calcd 281.2481, found 281.2487.

Cinnarizine stearate (Cin ST). Method 2; Yield 88%. ^{1}H NMR ($CDCl_3$) δ 8.55 (br s, 1H), 7.41-7.17 (m, 15H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 16.0, 7.2 Hz, 1H), 4.27 (s, 1H), 3.41 (d, *J* = 7.0 Hz, 2H), 2.81 (br s, 4H), 2.58 (br s, 4H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.62 (quin, *J* = 7.6 Hz, 2H), 1.32-1.26 (br s, 28H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 178.3, 142.1, 136.6, 135.9, 128.6 (2C), 128.2, 127.7, 127.1, 126.6, 121.2, 75.7, 59.3, 51.9, 49.9, 35.5, 31.9, 29.7 (8C), 29.6, 29.4 (3C), 25.5, 22.7, 14.1. HRMS (+ve) calcd 369.2331, found 369.2333. HRMS (–ve) calcd 283.2637, found 283.2635.

Cinnarizine bis(trifluoromethane)sulfonimide (triflimide, Cin Trif). Method 3; Yield 97%. ^{1}H NMR ($CDCl_3$) δ 7.43-7.19 (m, 15H), 6.79 (d, *J* = 15.8 Hz, 1H), 6.22 (dt, *J* = 15.5, 7.5 Hz, 1H), 4.32 (s, 1H), 3.87 (d, *J* = 7.5 Hz, 2H), 3.51(br s, 2H), 3.01 (br s, 4H), 2.48 (br s, 2H), (NH not observed). ^{13}C NMR ($CDCl_3$) δ 141.8, 141.1, 134.7, 129.4, 129.0, 128.9, 127.7, 127.6, 127.1, 119.8 (q, *J* = 321.0 Hz), 114.9, 75.0, 59.5, 52.4, 48.5. HRMS (+ve) calcd 369.2331, found 369.2333. HRMS (–ve) calcd 279.9173, found 279.9184.

Halofantrine decylsulfate. Hf•HCl was either purchased directly or prepared from the corresponding free base using the procedure described for Cin•HCl . Method 1; Yield 94%, Method 2; Yield 90%. ^{1}H NMR ($CDCl_3$) δ 9.29 (br s, 1H), 8.55 (s, 1H), 8.26 (s, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 8.15 (d, *J* = 8.7 Hz, 1H), 7.76 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 5.67 (dd, *J* = 9.0, 2.0 Hz, 1H), 5.41 (br s, 1H), 3.99 (t, *J* = 6.9 Hz, 2H), 3.51-3.46 (m, 2H), 3.10 (br s, 4H), 2.35-2.31 (m, 1H), 2.17-2.07 (m, 1H), 1.73-1.65 (m, 4H), 1.59-1.52 (m, 2H), 1.40-1.31 (m, 4H), 1.29-1.16 (m, 14 H), 0.93 (t, *J* = 7.3 Hz, 6H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 138.7, 133.6, 132.4, 131.1, 130.9, 128.4 (q, *J* = 32.3 Hz), 128.3, 127.9, 126.9, 125.0, 124.1 (q, *J* = 270.7 Hz), 123.9 (d, *J* = 2.7 Hz), 120.8, 120.6, 120.4 (d, *J* = 3.9 Hz), 68.3, 67.9, 52.8, 51.8, 32.2, 31.9, 29.6

(2C), 29.4, 29.3 (2C), 25.8, 25.2, 22.7, 19.9, 14.1, 13.5. HRMS (+ve) calcd 500.1735, found 500.1741. HRMS (–ve) calcd 237.1161, found 237.1170.

Halofantrine lauryl(dodecyl)sulfate. Method 3; Yield 95%. ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.25 (s, 1H), 8.23 (d, *J* = 1.5 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.74 (dd, *J* = 8.7, 1.2 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H) 5.64 (dd, *J* = 8.9, 1.9 Hz, 1H), 3.97 (t, *J* = 6.9 Hz, 2H), 3.44 (t, *J* = 6.7 Hz, 2H), 3.05 (t, *J* = 8.2 Hz, 4H), 2.32-2.28 (m, 1H), 2.14-2.04 (m, 1H), 1.72-1.64 (m, 4H), 1.58-1.51 (m, 2H), 1.40-1.27 (m, 22H), 0.93 (t, *J* = 7.3 Hz, 6H), 0.87 (t, *J* = 6.9 Hz, 3H), (OH and NH not observed). ^{13}C NMR ($CDCl_3$) δ 138.8, 133.6, 132.4, 131.1, 130.9, 128.4 (q, *J* = 32.3 Hz), 128.3, 127.9, 126.9, 125.0, 124.1 (q, *J* = 270.8 Hz), 123.8 (d, *J* = 2.8 Hz), 120.8, 120.6, 120.4 (d, *J* = 3.9 Hz), 68.3, 68.2, 52.8, 51.9, 32.2, 31.9, 29.7 (2C), 29.6, 29.5 29.4 (2C), 29.3, 25.8, 25.4, 22.7, 20.0, 14.1, 13.6. HRMS (+ve) calcd 500.1735, found 500.1740. HRMS (–ve) calcd 265.1474, found 265.1481.

Halofantrine oleate. Method 3; Yield 97%. ^{1}H NMR ($CDCl_3$) δ 8.83 (s, 1H), 8.54 (s, 1H), 8.52 (d, *J* = 1.6 Hz, 1H), 8.23 (d, *J* = 8.7 Hz, 1H), 7.84 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.71 (d, *J* = 1.9 Hz, 1H), 5.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.38-5.29 (m, 2H), 3.02-2.88 (m, 2H), 2.78-2.70 (m, 2H), 2.64-2.56 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.21-2.14 (m, 1H), 2.07-1.98 (m, 5H), 1.64-1.56 (m, 6H), 1.43-1.26 (m, 24H), 0.97 (t, *J* = 7.3 Hz, 6H), 0.88 (t, *J* = 6.9 Hz, 3H), (OH and NH not observed). ^{13}C NMR ($CDCl_3$) δ 179.6, 139.8, 133.9, 132.4, 131.5, 131.4, 130.0, 129.9, 128.8, 128.4 (q, *J* = 32.3 Hz), 128.1, 127.6, 124.9, 124.3 (q, *J* = 270.7 Hz), 123.5 (d, *J* = 3.1 Hz), 121.1, 121.0, 120.9 (d, *J* = 4.0 Hz), 70.2, 52.6 (2C), 51.9, 36.1, 32.6, 32.0, 29.9 (2C), 29.6 (2C), 29.5, 29.4 (3C), 27.3, 26.9, 25.8, 22.8, 20.6, 14.2, 14.0. HRMS (+ve) calcd 500.1735, found 500.1741. HRMS (–ve) calcd 281.2481, found 281.2483.

Halofantrine bis(trifluoromethane)sulfonimide (triflimide). Method 3; Yield 93%. ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H), 8.10 (s, 1H), 8.08 (d, *J* = 1.3 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 5.63 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.50-3.43 (m, 1H), 3.34-3.28 (m, 1H), 3.14 (t, *J* = 8.1 Hz, 4H), 2.31-2.26 (m, 1H), 2.01 (m, 1H), 1.77-1.62 (m, 4H), 1.44-1.34 (m,

4H), 0.95 (t, *J* = 7.3 Hz, 6H), (OH and NH not observed). ^{13}C NMR ($CDCl_3$) δ 137.3, 133.7, 132.9, 131.3, 130.3, 128.8 (q, *J* = 32.3 Hz), 128.5, 128.1, 126.7, 124.2, 124.1 (q, *J* = 270.7 Hz), 124.0 (d, *J* = 2.7 Hz), 120.9, 120.7 (d, *J* = 3.9 Hz), 120.6, 119.8 (q, *J* = 319.1 Hz), 69.9, 53.7, 52.8, 30.9, 25.6, 19.7, 13.3. HRMS (+ve) calcd 500.1735, found 500.1741. HRMS (–ve) calcd 279.9173, found 279.9183.

Itraconazole lauryl(dodecyl)sulfate. Itz•HCl was prepared in chloroform (or dichloromethane) from the corresponding free base and HCl (2M in diethyl ether) in 1:1 stoichiometric ratio. ^{1}H NMR of protonated itraconazole is consistent with the literature data.[1] Modified Method 3 (ethyl acetate was used as a solvent instead of chloroform or dichloromethane) was used to make Itz dodecylsulfate. Yield 92%. ^{1}H NMR ($CDCl_3$) δ 8.42 (s, 1H), 7.99 (s, 1H), 7.66 (overlap d and s, 3H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.50 (overlap 2 x d, 3H), 7.29 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 4.83 (q, *J* = 14.8 Hz, 2H), 4.42-4.36 (m, 1H), 4.33-4.25 (m, 1H), 4.09 (t, *J* = 6.8 Hz, 2H), 3.93 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.86-3.77 (m, 6H), 3.69-3.61 (m, 5H), 1.92-1.81 (m, 1H), 1.77-1.71 (m, 1H), 1.69-1.63 (m, 2H), 1.39 (d, *J* = 6.7 Hz, 3H), 1.36-1.22 (m, 18H), 0.88 (overlap 2 x t, 6H), (NH not observed). ^{13}C NMR ($CDCl_3$) δ 158.4, 151.8, 149.3, 148.4, 144.6, 136.2, 135.5, 133.8, 133.6, 133.1, 131.4, 129.6, 127.4, 127.3, 123.5, 122.3, 117.6, 116.0, 107.4, 74.4, 68.3, 67.4, 66.7, 55.0, 53.7, 52.7, 47.1, 31.8, 29.6, 29.5 (3C), 29.3 (3C), 28.3, 25.7, 22.6, 19.2, 14.1, 10.7. HRMS (+ve) calcd 705.2471, found 705.2438. HRMS (–ve) calcd 265.1474, found 265.1480.

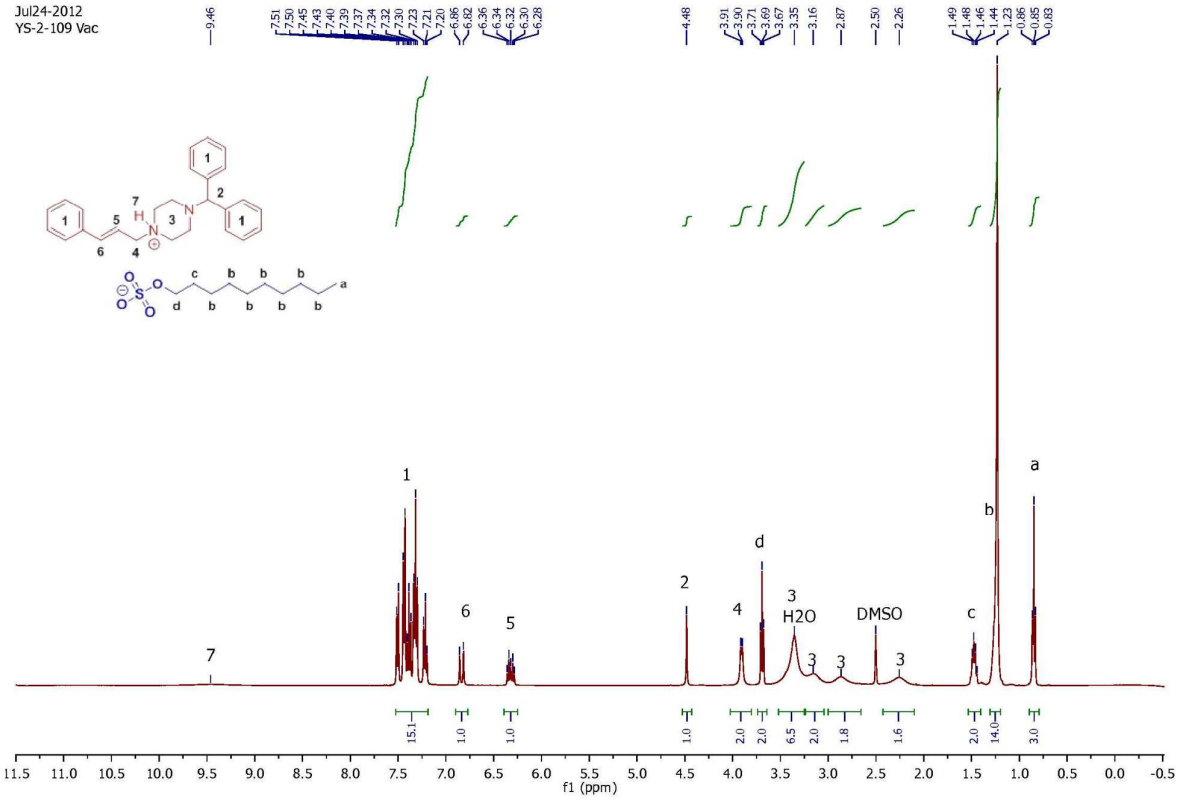
Itraconazole 7-ethyl-2-methyl-4-undecylsulfate (niaproof, Itz NP). Modified Method 3 (ethyl acetate was used as a solvent instead of chloroform or dichloromethane) was used to make Itz niaproof. Yield 94%. ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.92 (s, 1H), 7.64 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.55 (br s, 2H), 7.49 (overlap 2 x d, 3H), 7.28 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.92 (d, *J* = 9.1 Hz, 2H), 4.81 (q, *J* = 14.8 Hz, 2H), 4.55-4.49 (m, 1H), 4.41-4.35 (m, 1H), 4.34-4.25 (m, 1H), 3.93 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.84-3.74 (m, 6H), 3.60-3.53 (m, 5H), 1.91-1.78 (m, 2H), 1.76-1.61 (m, 4H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.37-1.19 (m, 12H), 0.93-0.83 (m, 12H), 0.79

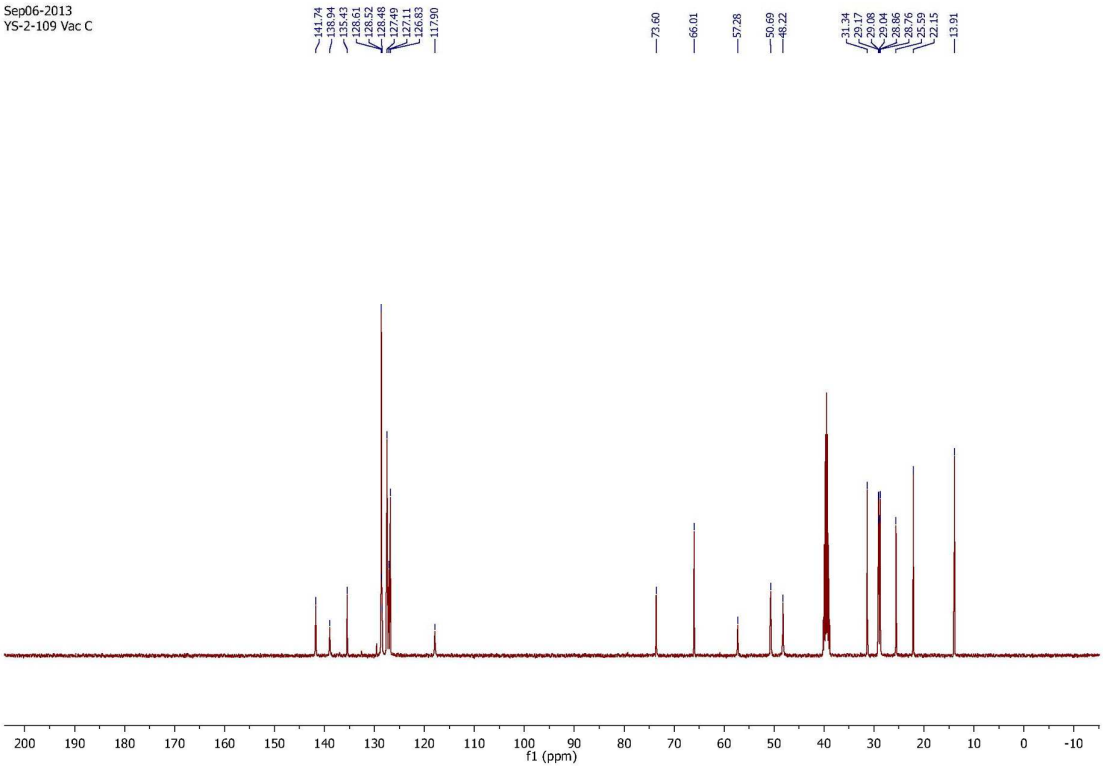
(t, *J* = 6.8 Hz, 3H), (NH not observed). HRMS (+ve) calcd 705.2471, found 705.2466. HRMS (–ve) calcd 293.1787, found 293.1792.

Dextromethorphan decylsulfate. Method 2. ^{1}H NMR (DMSO-d_6) (major diastereoisomer) δ 9.46 (s, 1H), 7.12-7.15 (m, 1H), 6.81-6.84 (m, 2H), 3.73 (s, 3H), 3.66 (t, J = 6.8 Hz, 2H), 3.60-3.62 (m, 1H), 3.11-3.22 (m, 2H), 2.93-3.01 (m, 2H), 2.83 (d, J = 4.8Hz, 3H), 2.36-2.47 (m, 2H), 1.91 (dt, J = 12.4, 2.4Hz, 1H), 1.74 (dt, J = 13.6, 4.4Hz, 1H), 1.58-1.65 (m, 1H), 1.41-1.53 (m, 5H), 1.20-1.40 (m, 16H), 1.11-1.19 (m, 1H), 0.92-1.01 (m, 1H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (d^{6}-DMSO, 100MHz) δ 158.5, 138.5, 129.3, 125.9, 112.1, 110.6, 65.5, 59.0, 55.0, 47.1, 41.9, 40.1, 38.8, 35.4, 34.9, 34.7, 31.3, 29.1 (mC), 29.0, 28.8, 28.7, 25.5, 25.4, 25.3, 22.5, 21.4, 14.0. ^{1}H NMR (DMSO-d_6) (minor diastereoisomer) δ 9.46 (s, 1H), 7.12-7.15 (m, 1H), 6.81-6.84 (m, 2H), 3.73 (s, 3H), 3.66 (t, J = 6.8 Hz, 2H), 3.53-3.57 (m, 1H), 3.11-3.22 (m, 2H), 2.93-3.01 (m, 2H), 2.95 (d, J = 4.8Hz, 3H), 2.36-2.47 (m, 2H), 2.17-2.22 (m, 1H), 2.04 (dt, J = 14.0, 4.4Hz, 1H), 1.58-1.65 (m, 1H), 1.41-1.53 (m, 5H), 1.20-1.40 (m, 16H), 1.11-1.19 (m, 1H), 0.92-1.01 (m, 1H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 158.6, 138.7, 129.0, 125.4, 112.2, 110.7, 65.5, 58.8, 55.0, 45.1, 41.9, 40.1, 38.8, 36.4, 34.9, 34.3, 33.2, 31.3, 29.1 (mC), 29.0, 28.8, 28.7, 25.5, 25.4, 24.9, 22.5, 22.1, 21.4, 14.0. HRMS $^{+}$ve mode: calcd. for $C_{18}H_{26}NO^{+}$ 272.2009 found 272.2010 (0.35ppm). HRMS $^{-}$ve mode: calcd. for $C_{10}H_{21}O_4S^{-}$ 237.1166 found 237.1172 (2.46 ppm).

NMR Spectra

Cinnarizine decylsulfate:





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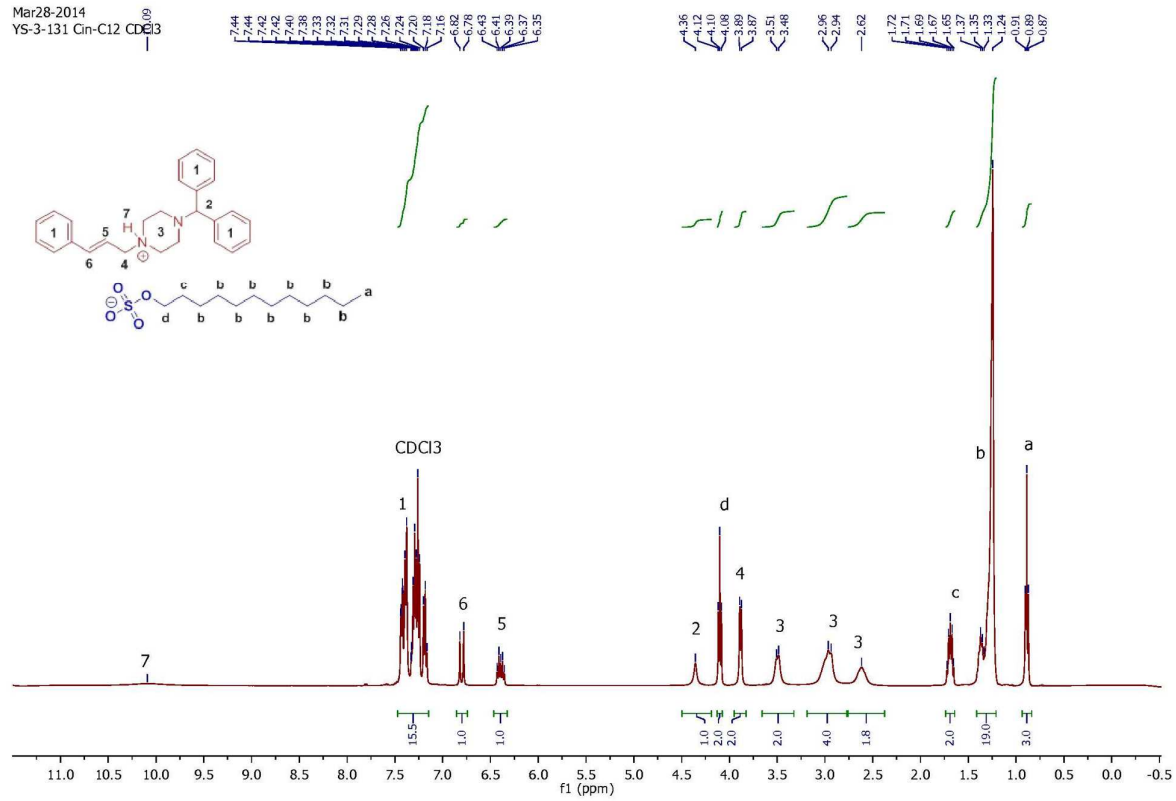

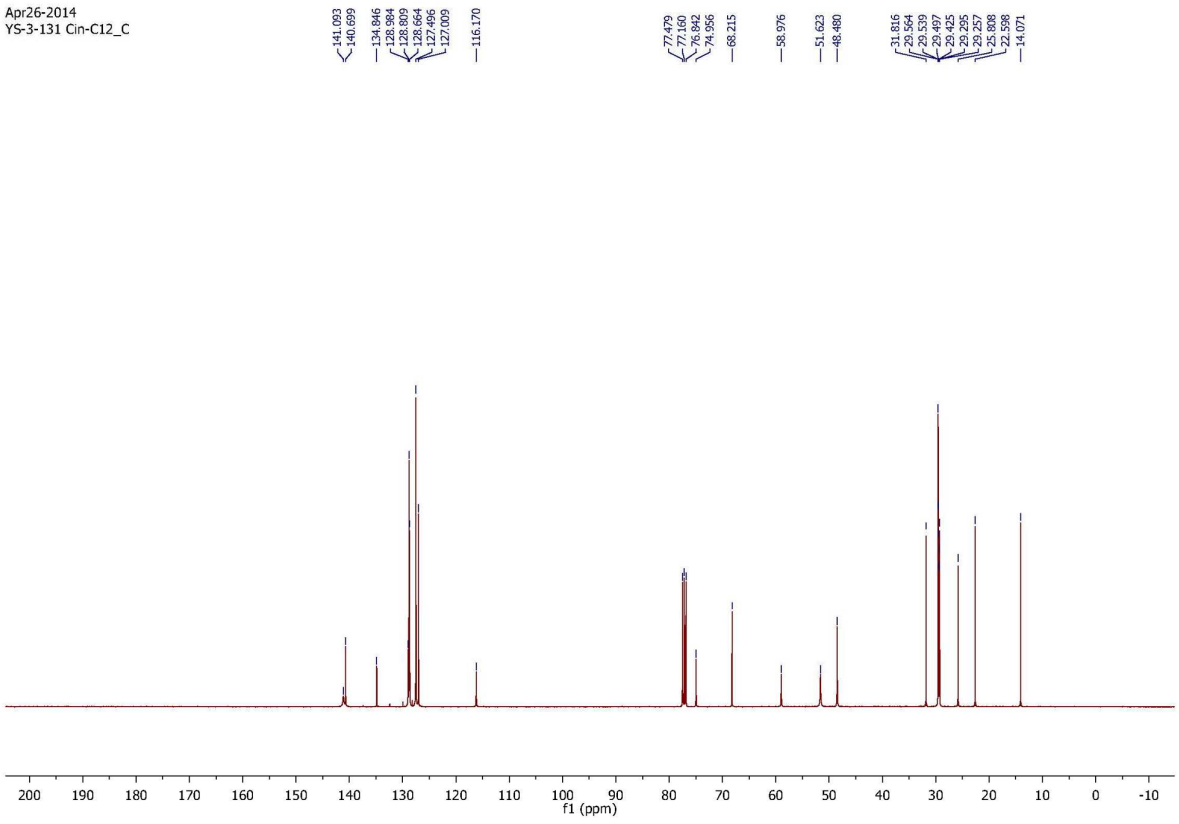

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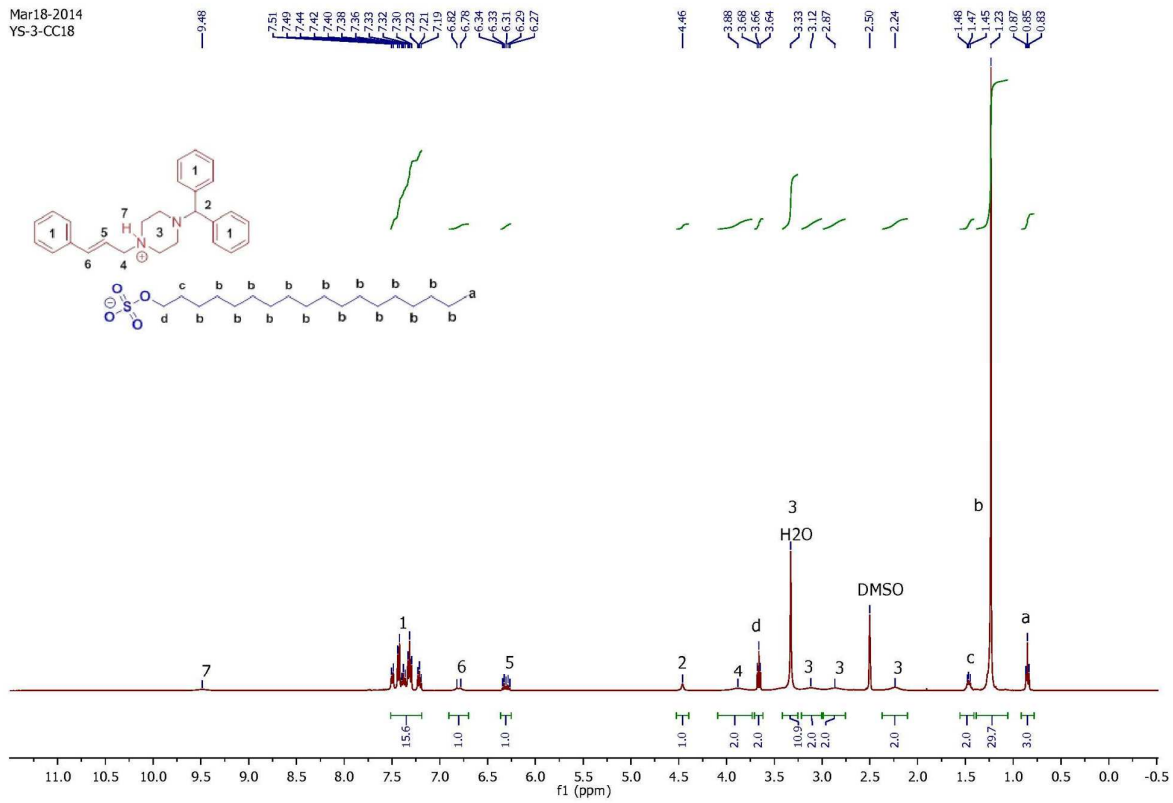

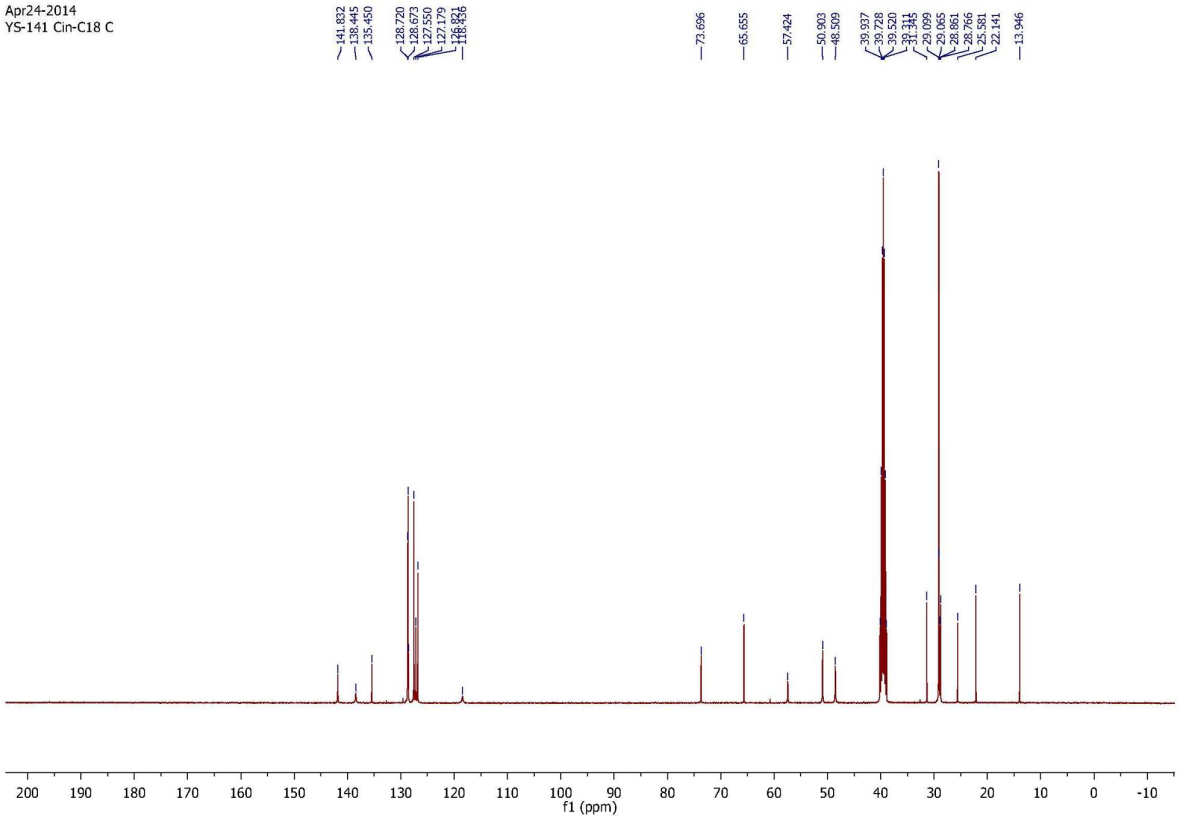

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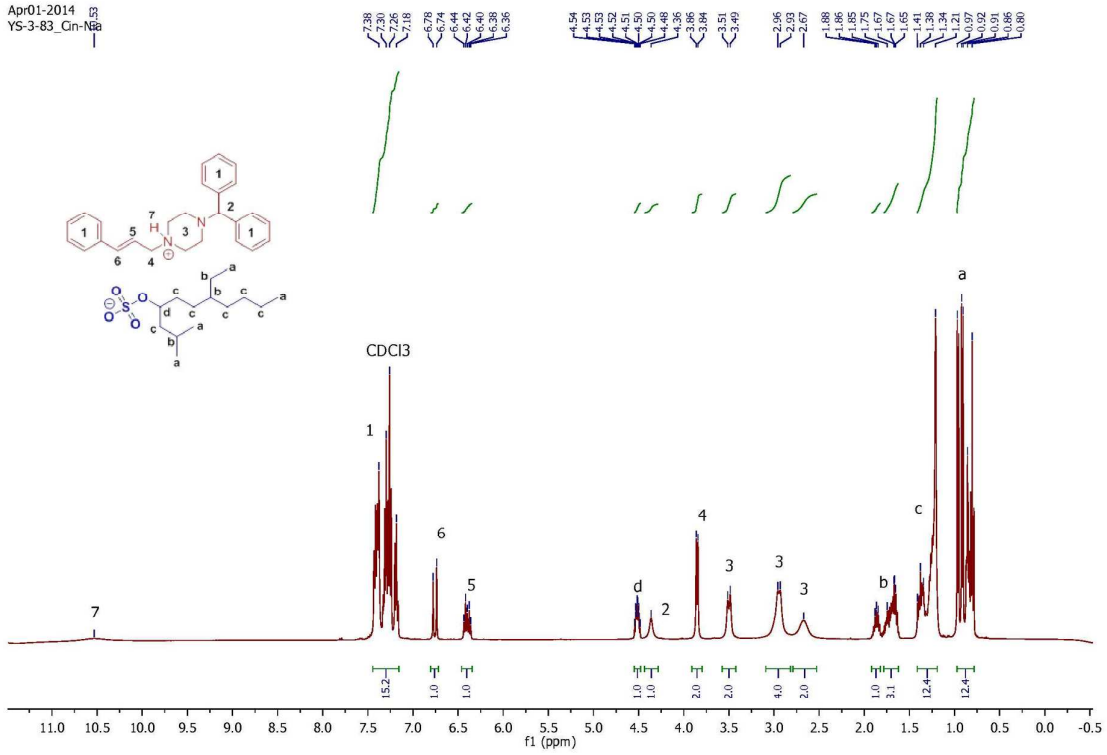

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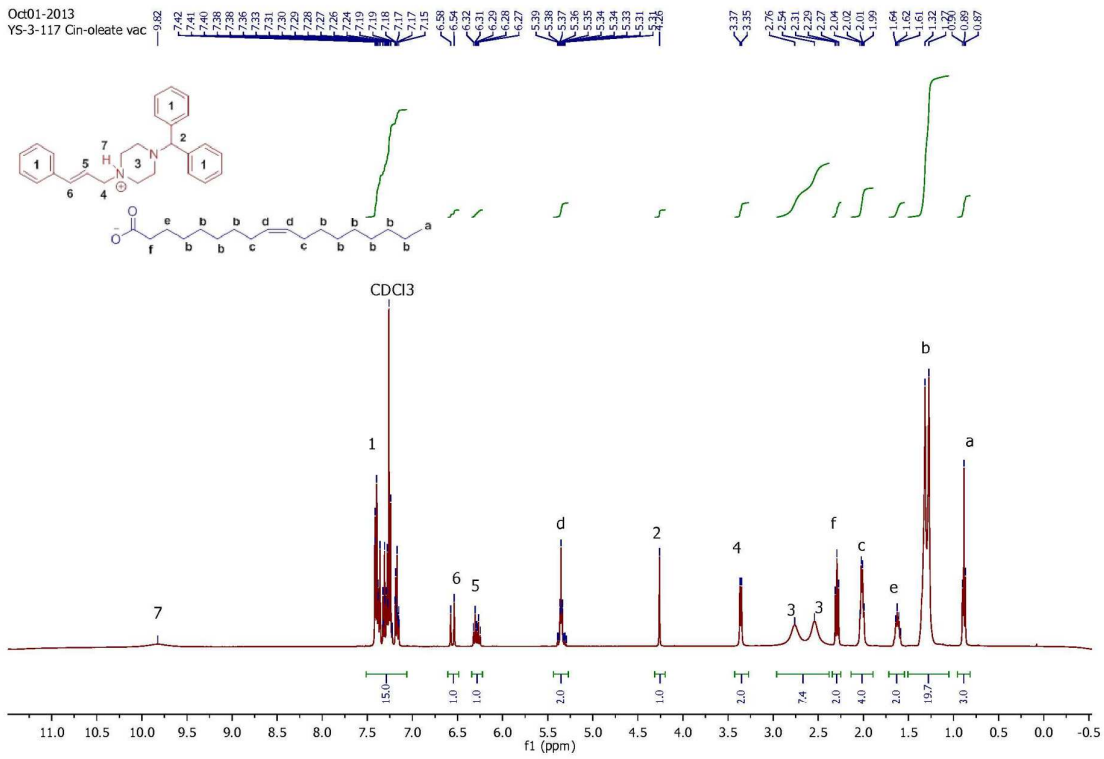

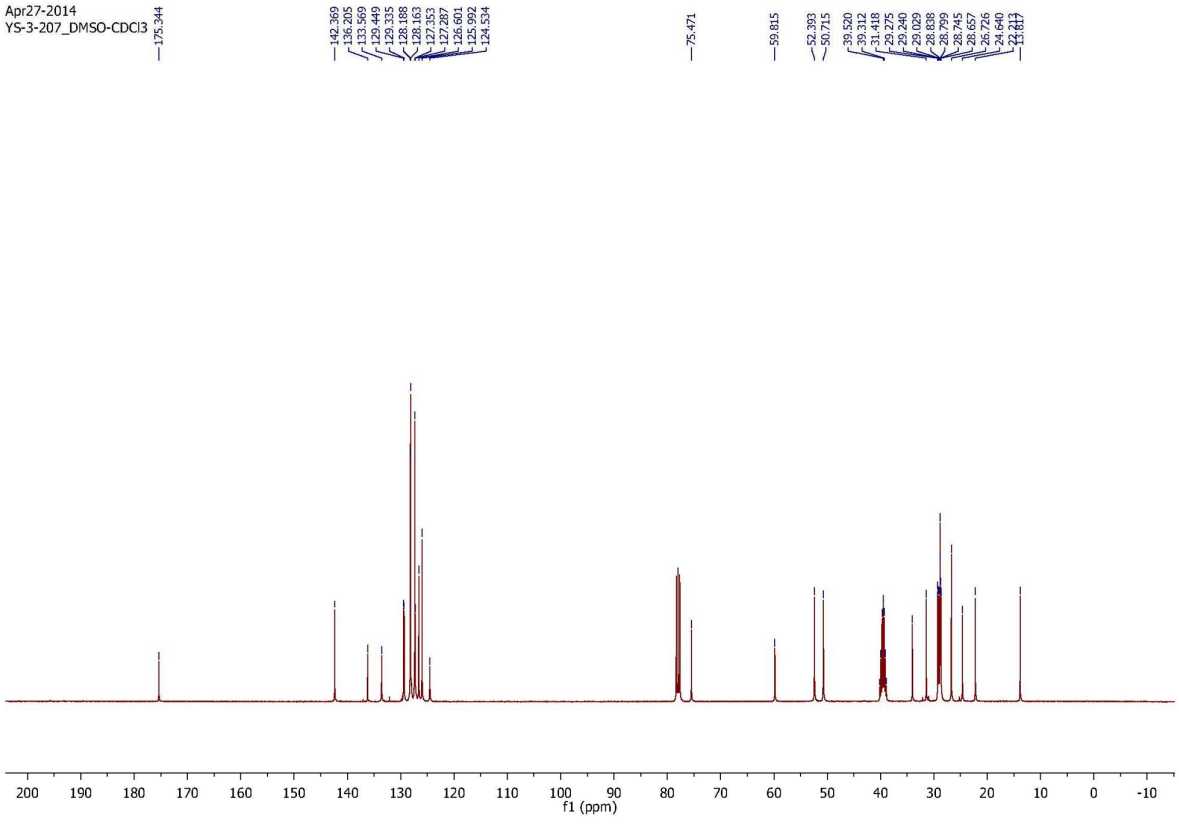

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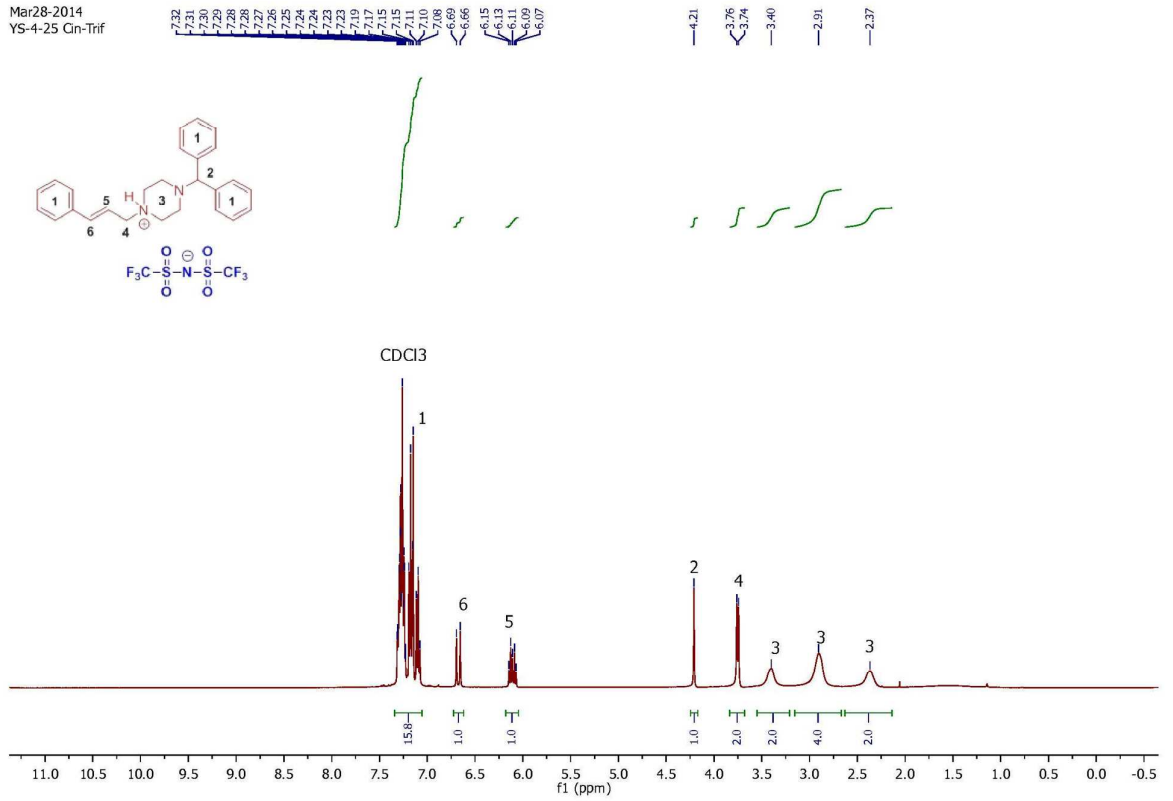
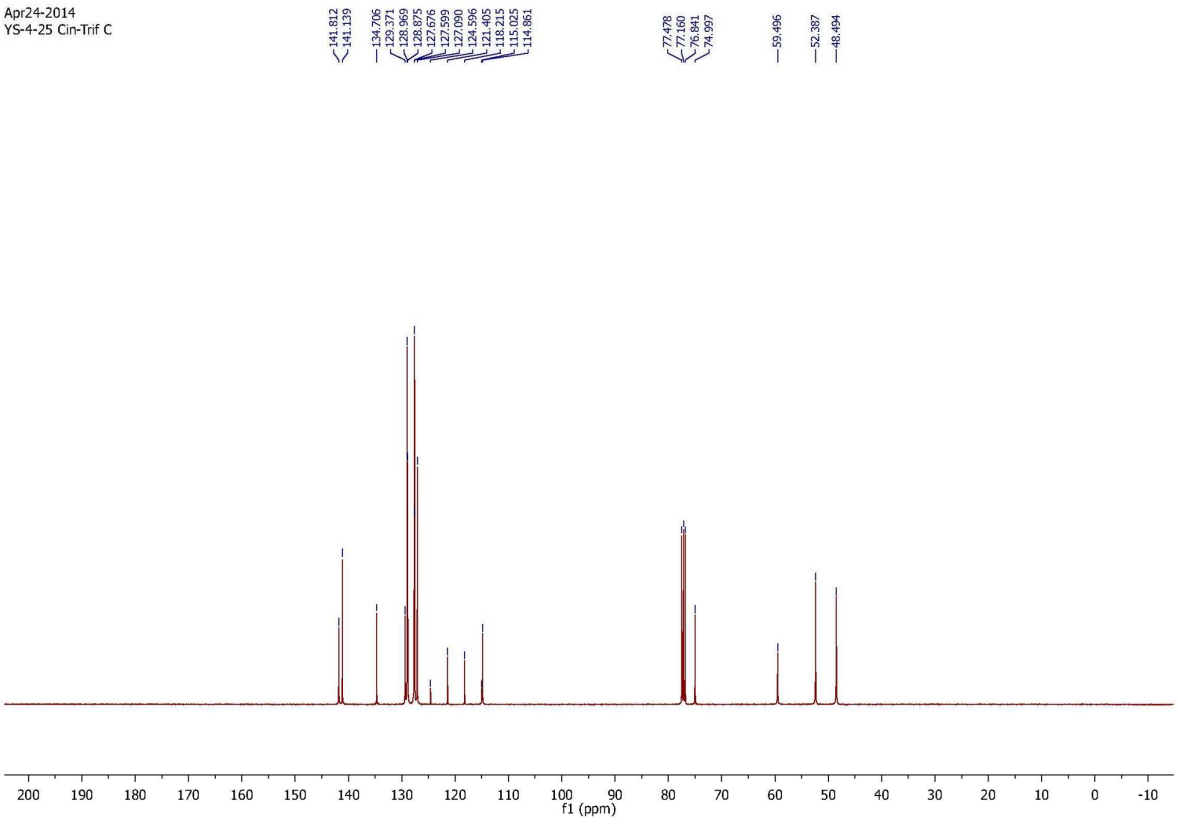
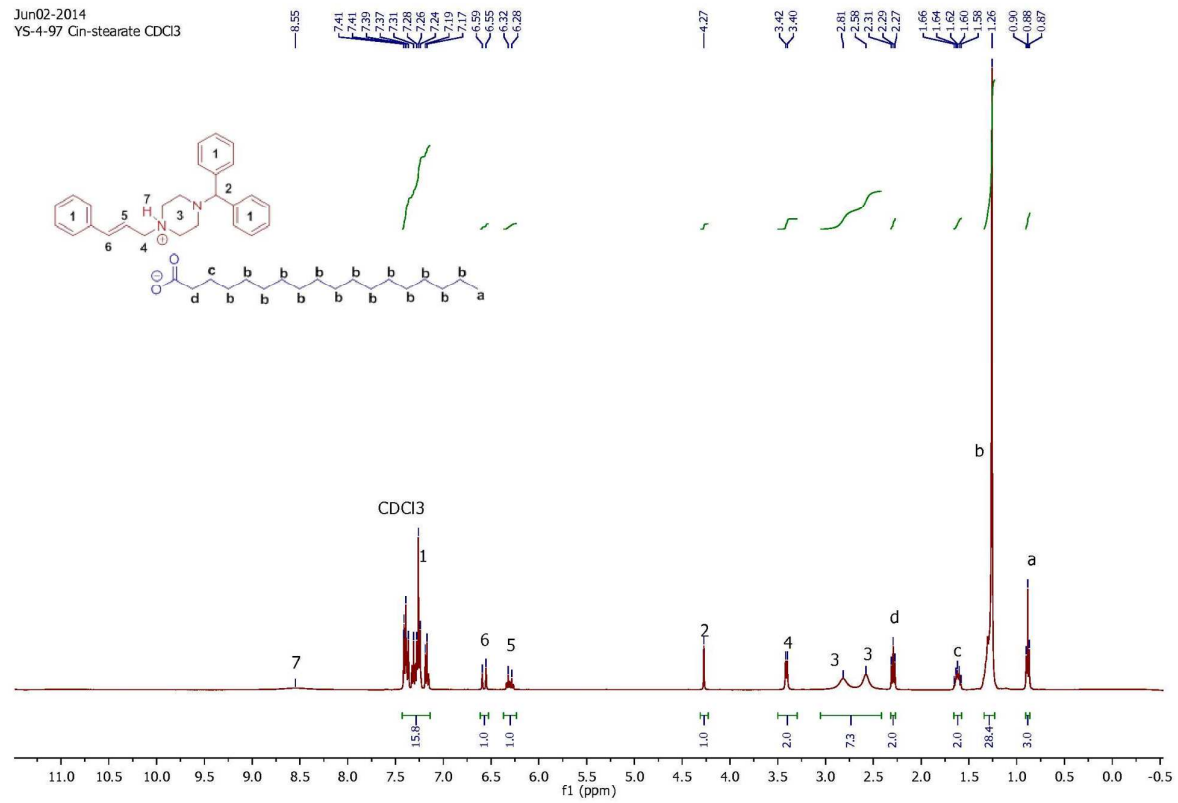
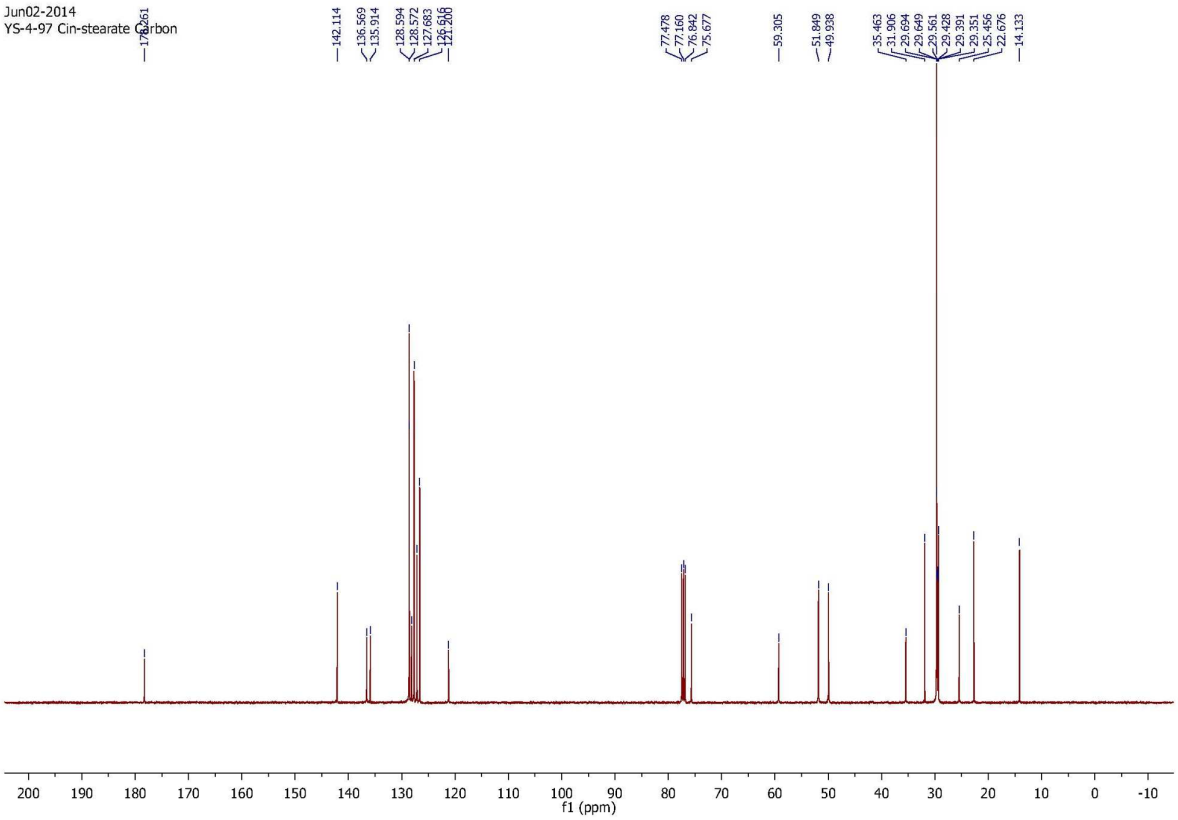


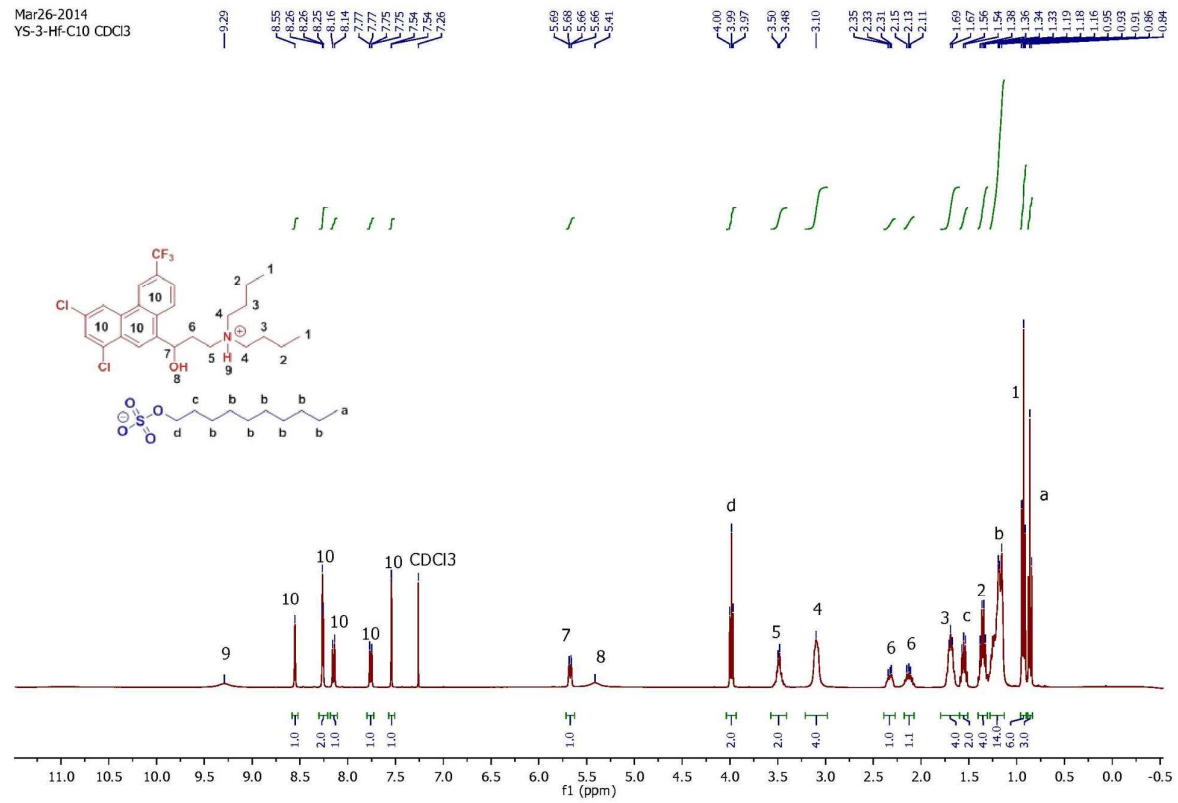


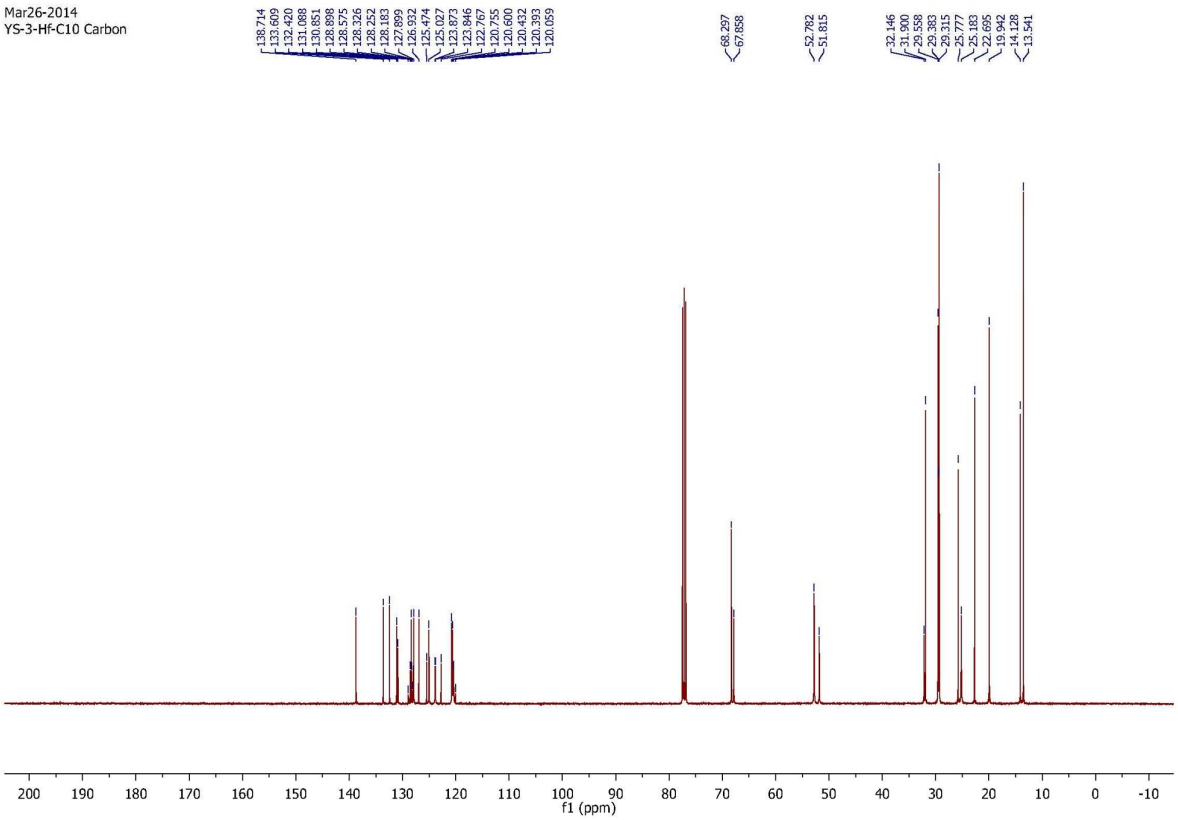
Cinnarizine stearate:



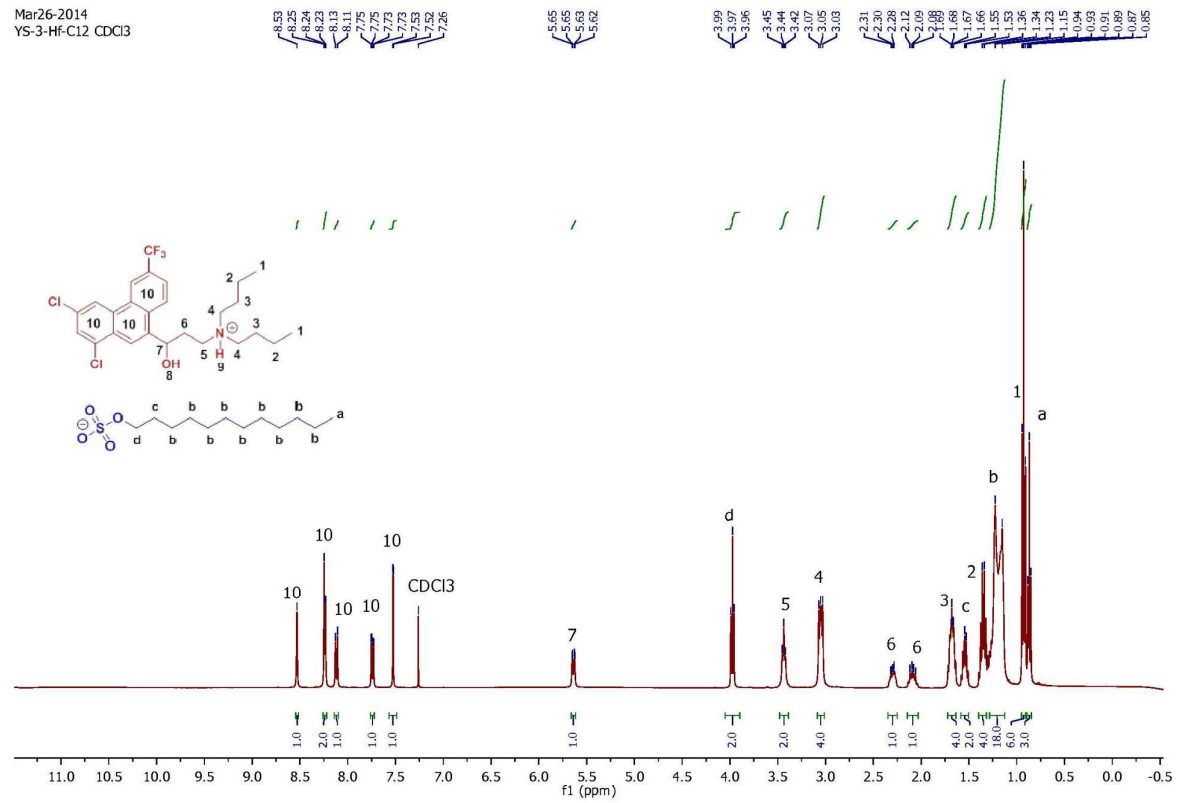


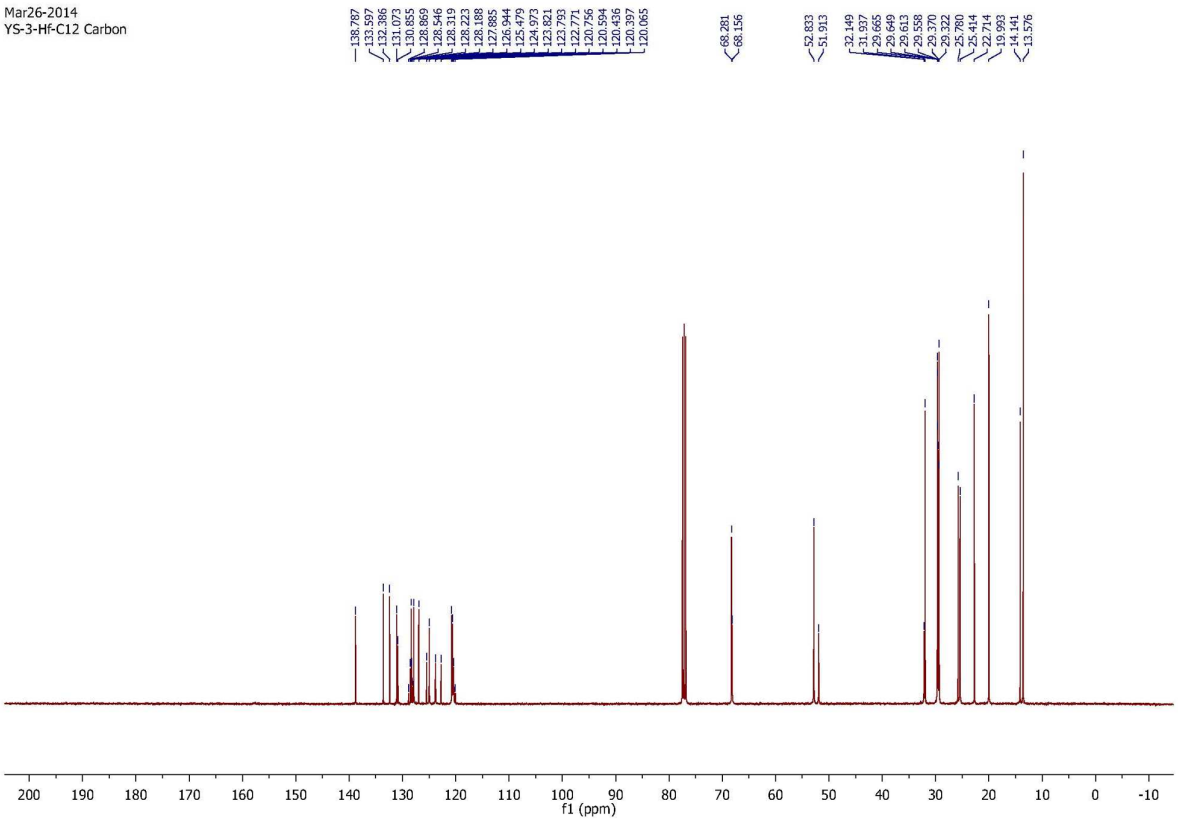
Halofantrine decylsulfate:



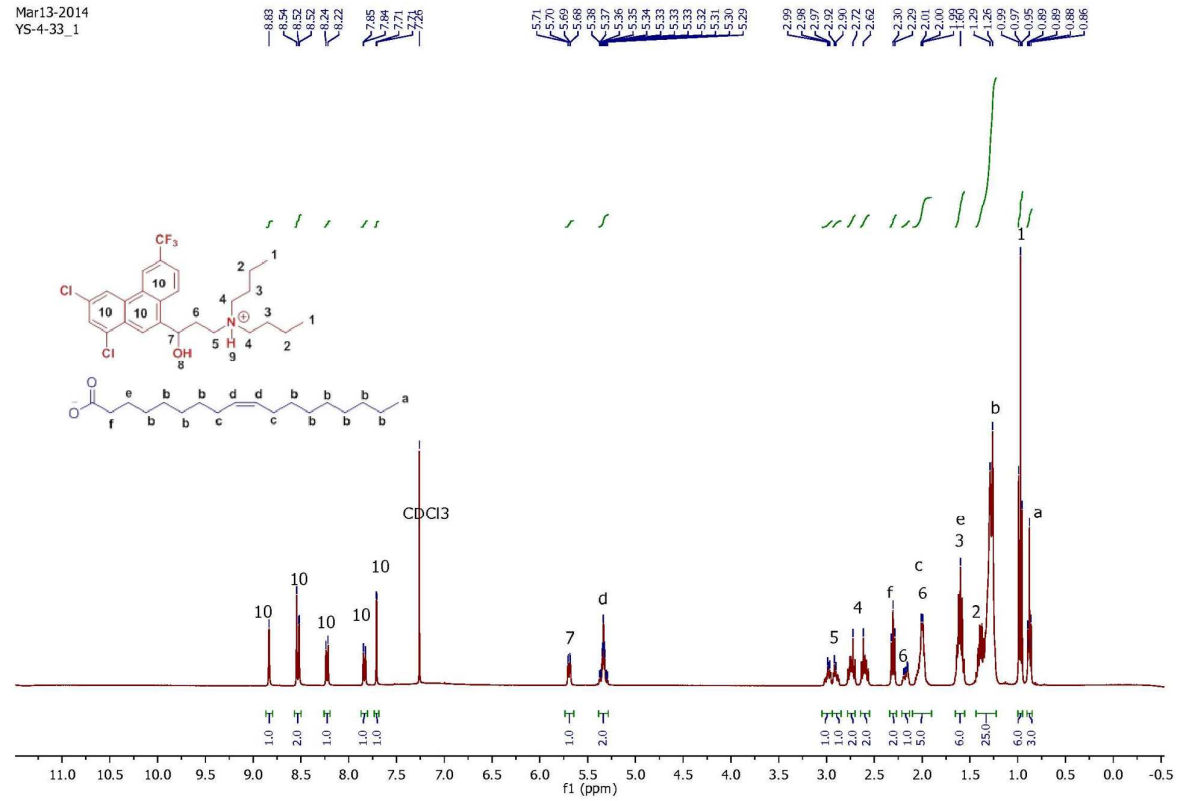


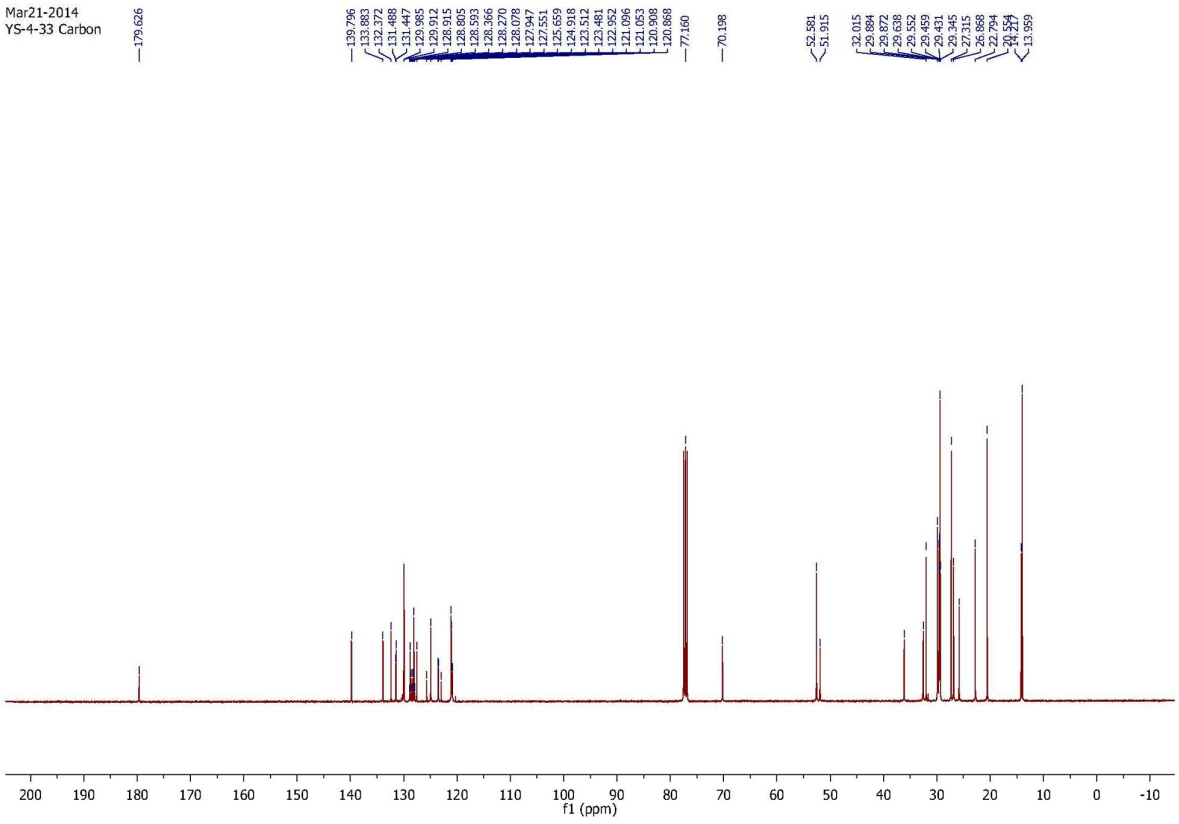
Halofantrine dodecylsulfate:



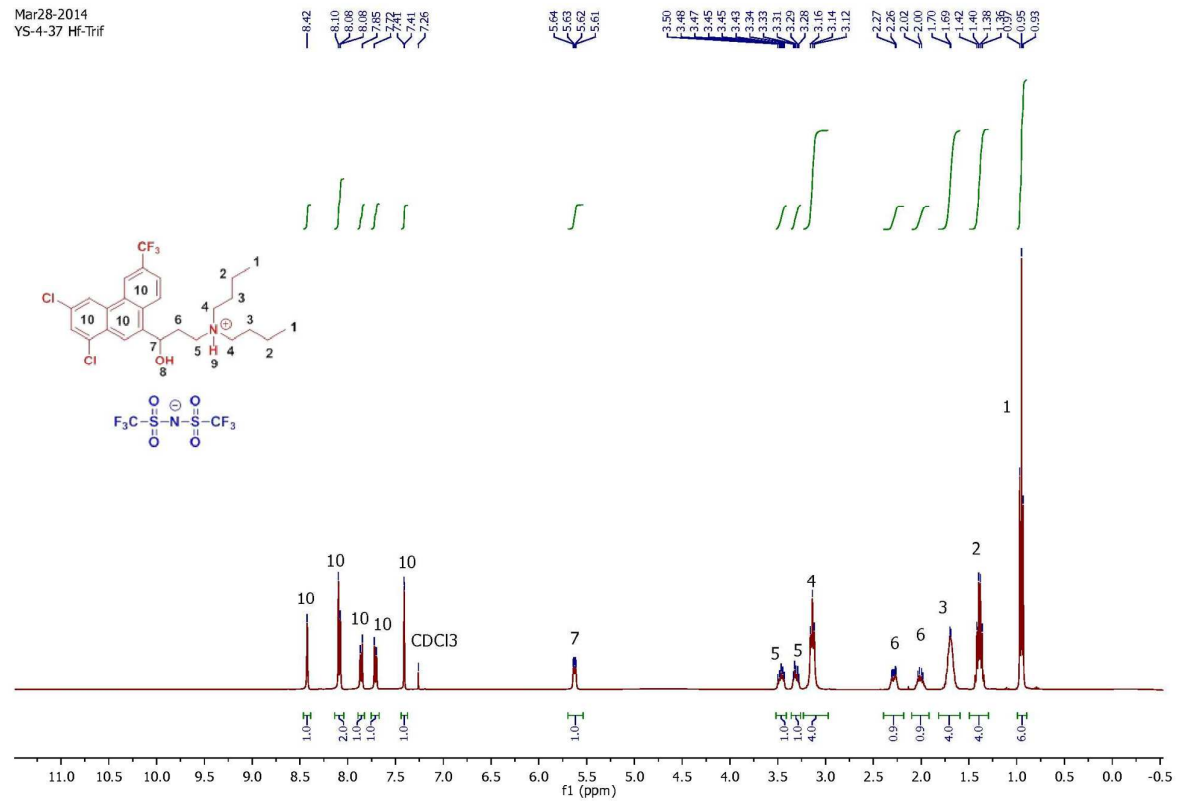


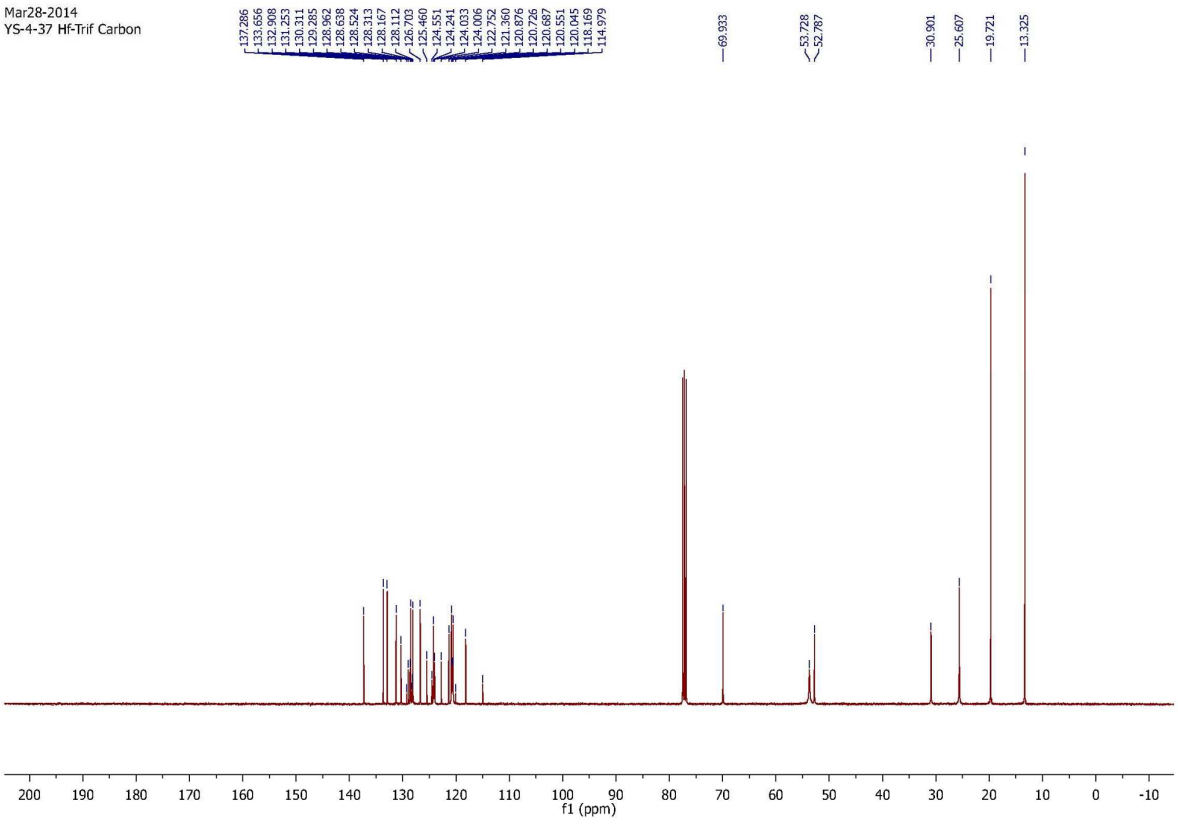
Halofantrine oleate:



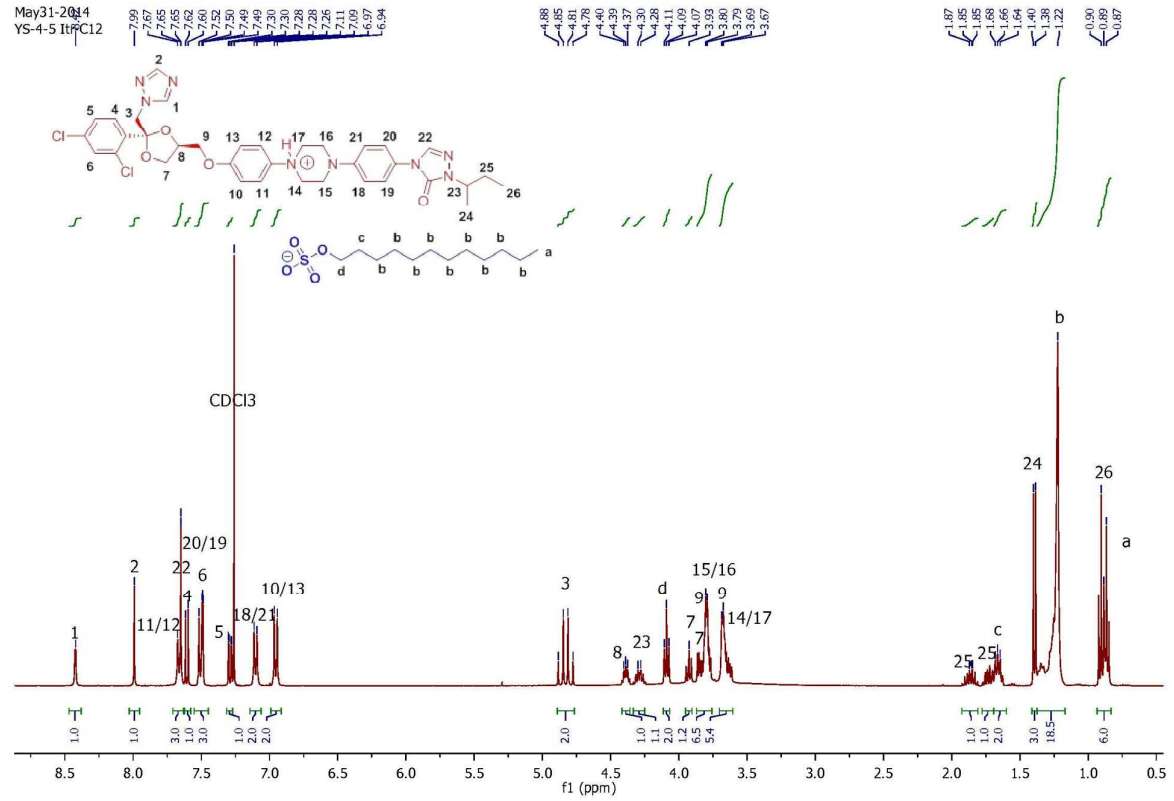


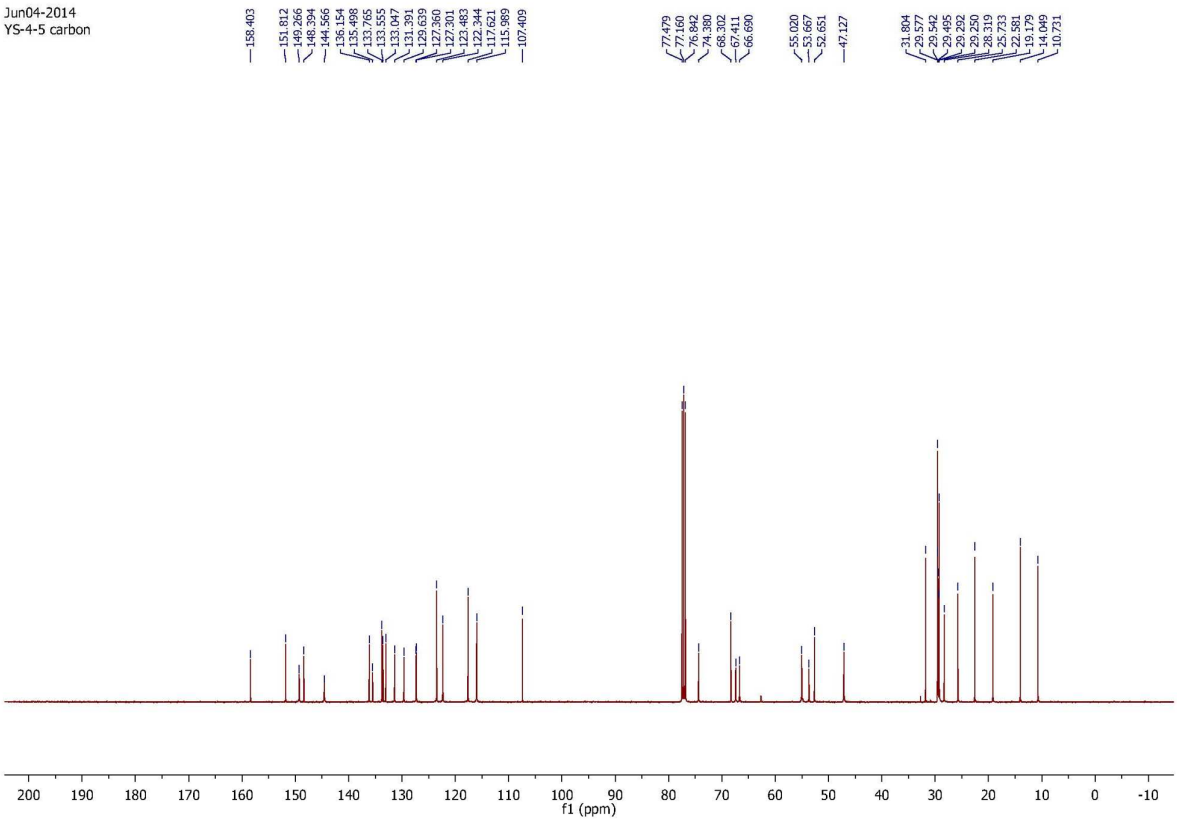
Halofantrine triflimide:



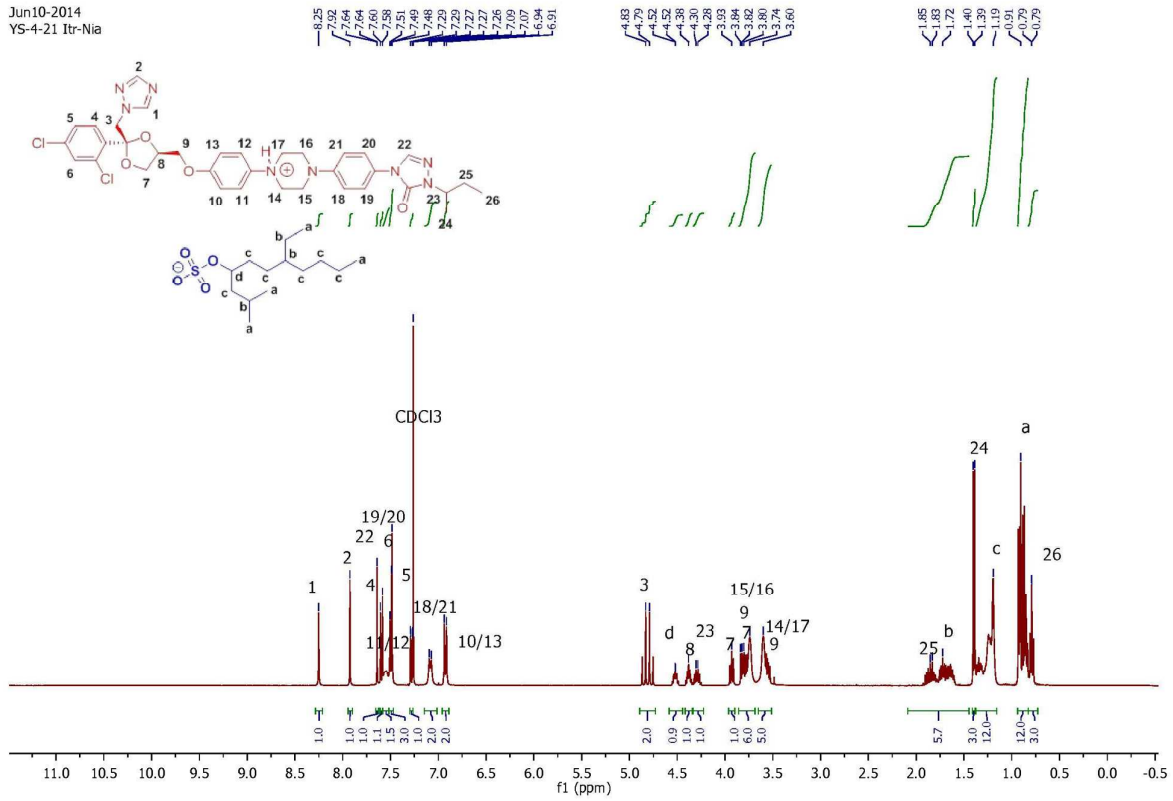


Itraconazole lauryl(dodecyl)sulfate:

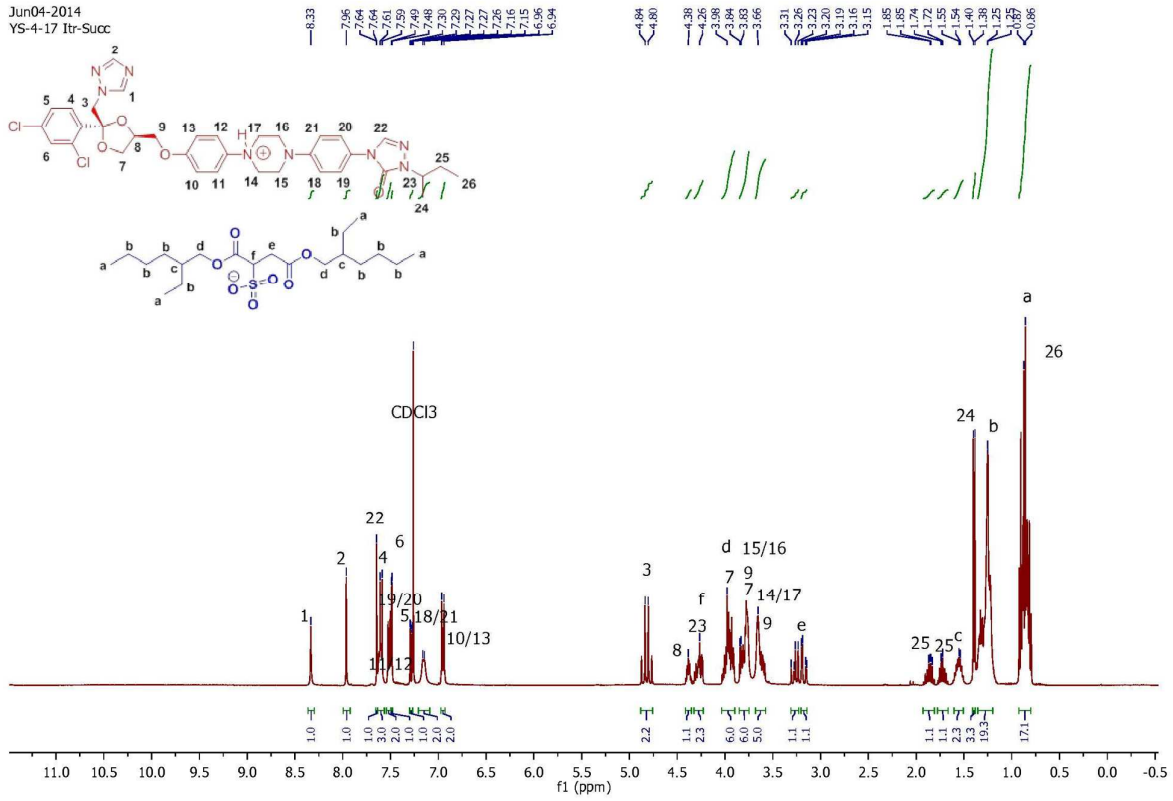




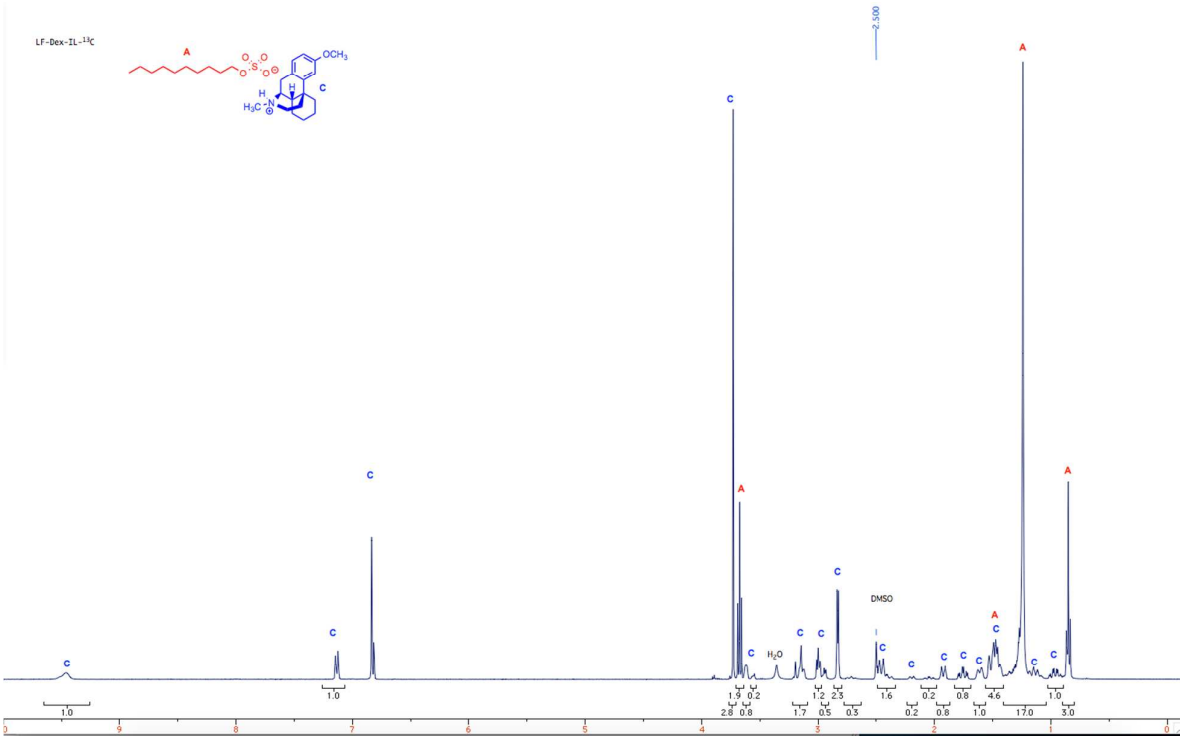
Itraconazole 7-ethyl-2-methyl-4-undecylsulfate:

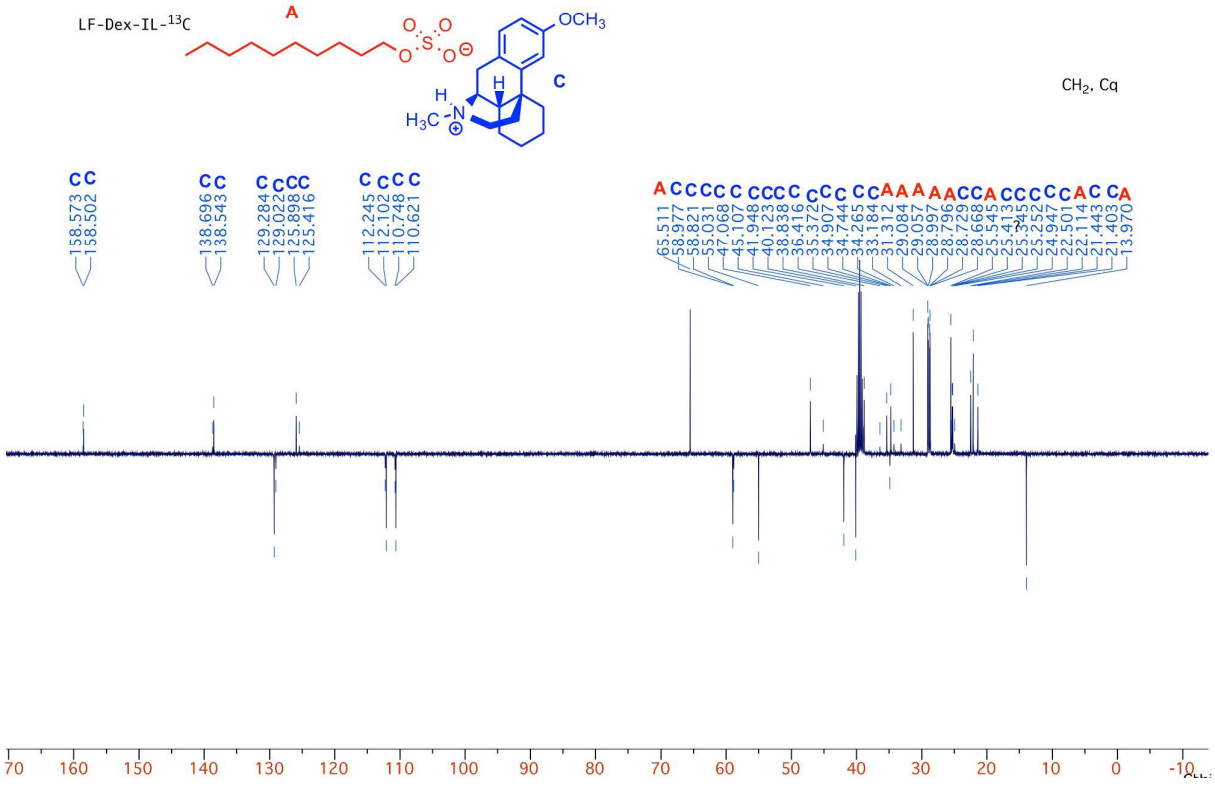


Itraconazole dioctyl sulfosuccinate (docusate):



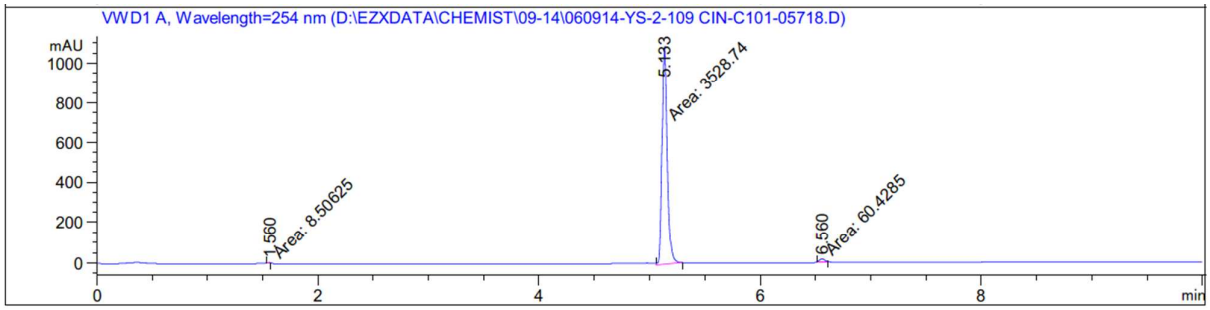
Dextromethorphan decylsulfate:





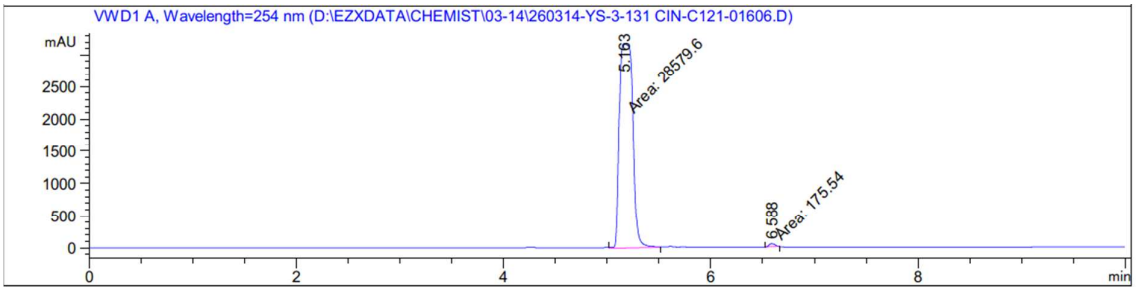
HPLC Data

Cinnarizine decylsulfate:



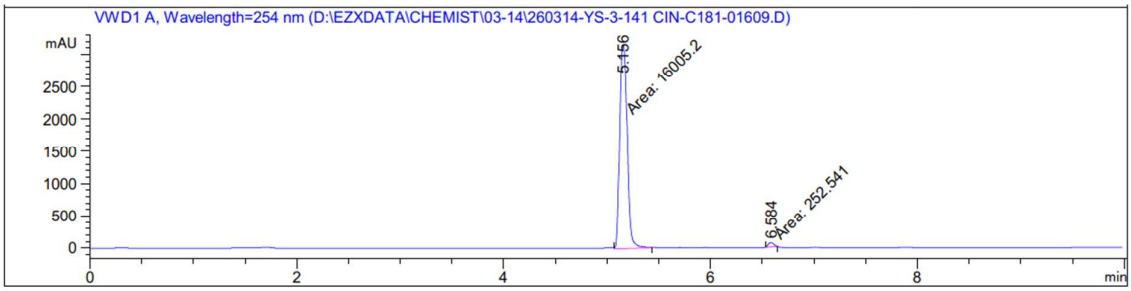
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.560	MM	0.0273	8.50625	5.18367	0.2364
2	5.133	MM	0.0539	3528.73950	1092.12317	98.0839
3	6.560	MM	0.0596	60.42853	16.90952	1.6797
Totals :				3597.67428	1114.21636	

Cinnarizine dodecyl(lauryl)sulfate:



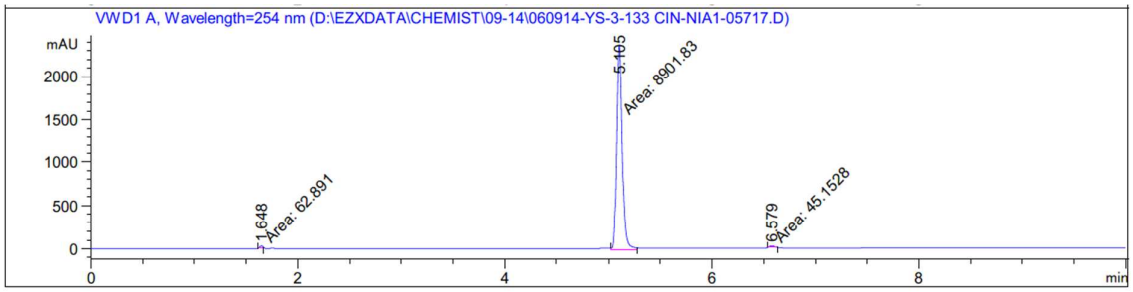
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.163	MM	0.1498	2.85796e4	3179.97534	99.3895
2	6.588	MM	0.0630	175.53996	46.41528	0.6105
Totals :				2.87552e4	3226.39062	

Cinnarizine octadecylsulfate:



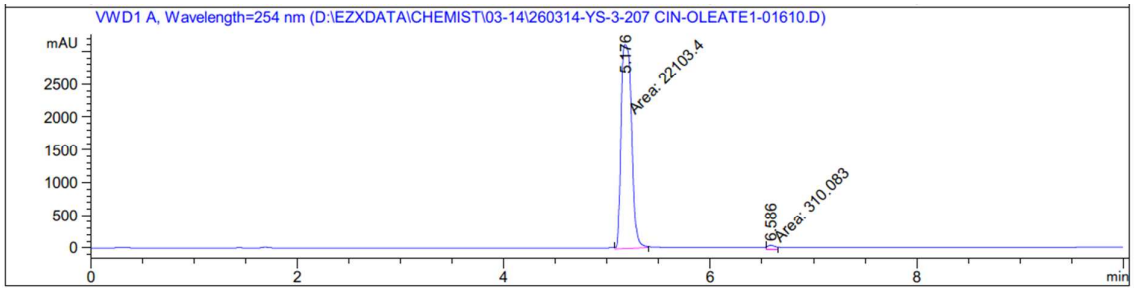
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.156	MM	0.0844	1.60052e4	3161.47949	98.4466
2	6.584	MM	0.0610	252.54074	68.95586	1.5534
Totals :				1.62577e4	3230.43536	

Cinnarizine 7-ethyl-2-methyl-4-undecylsulfate:



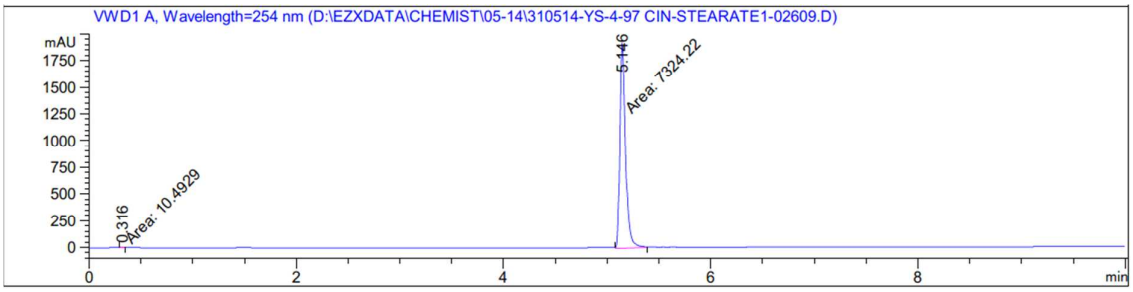
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.648	MM	0.0346	62.89105	30.32072	0.6980
2	5.105	MM	0.0623	8901.82520	2381.98926	98.8008
3	6.579	MM	0.0435	45.15281	17.29811	0.5011
Totals :				9009.86905	2429.60809	

Cinnarizine oleate:



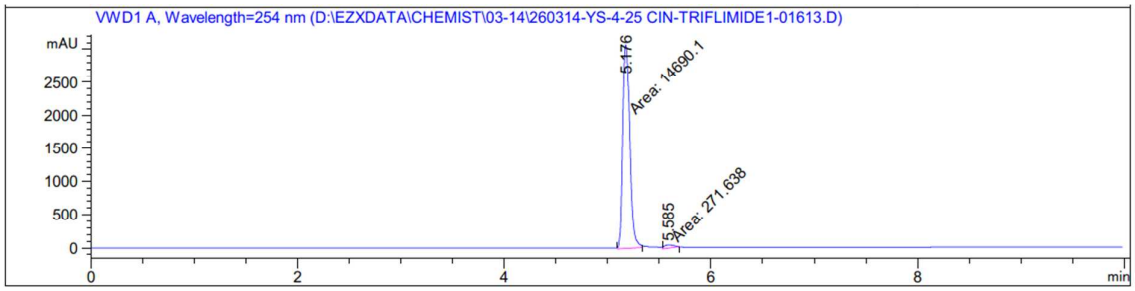
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.176	MM	0.1180	2.21034e4	3122.27222	98.6165
2	6.586	MM	0.0900	310.08304	57.42811	1.3835
Totals :				2.24135e4	3179.70033	

Cinnarizine stearate:



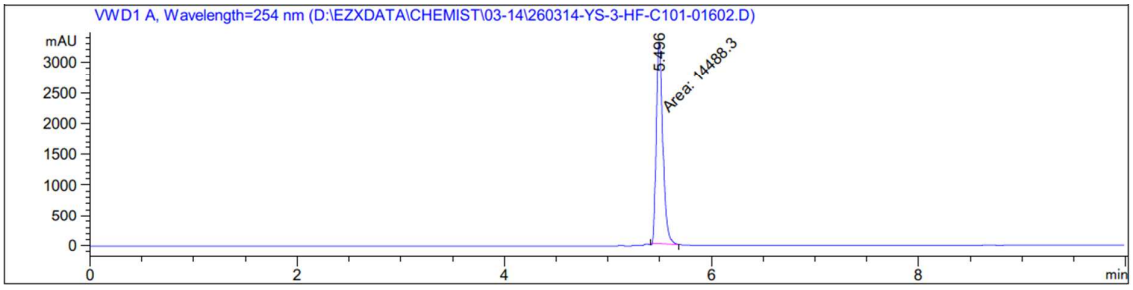
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.316	MM	0.0528	10.49295	3.31268	0.1431
2	5.146	MM	0.0635	7324.21777	1922.77136	99.8569
Totals :				7334.71072	1926.08405	

Cinnarizine triflimide:



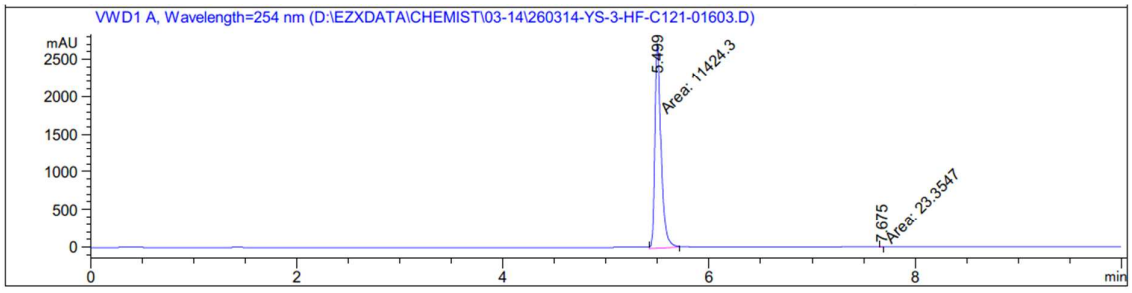
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.176	MM	0.0794	1.46901e4	3083.47437	98.1845
2	5.585	MM	0.1022	271.63788	44.30341	1.8155
Totals :				1.49618e4	3127.77777	

Halofantrine decylsulfate:



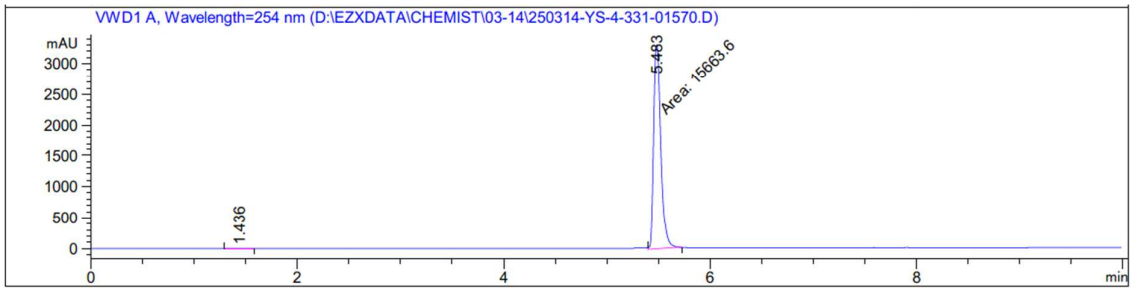
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.496	MM	0.0735	1.44883e4	3286.19971	100.0000
Totals :				1.44883e4	3286.19971	

Halofantrine dodecyl(lauryl)sulfate:



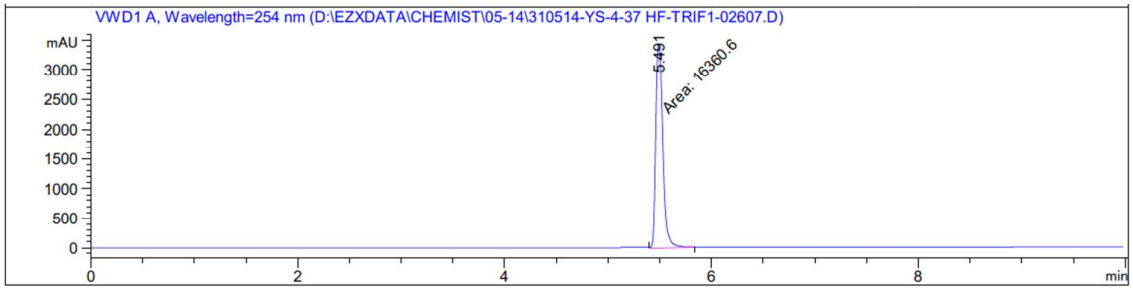
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.499	MM	0.0702	1.14243e4	2711.93164	99.7960
2	7.675	MM	0.0423	23.35470	9.20907	0.2040
Totals :				1.14477e4	2721.14071	

Halofantrine oleate:



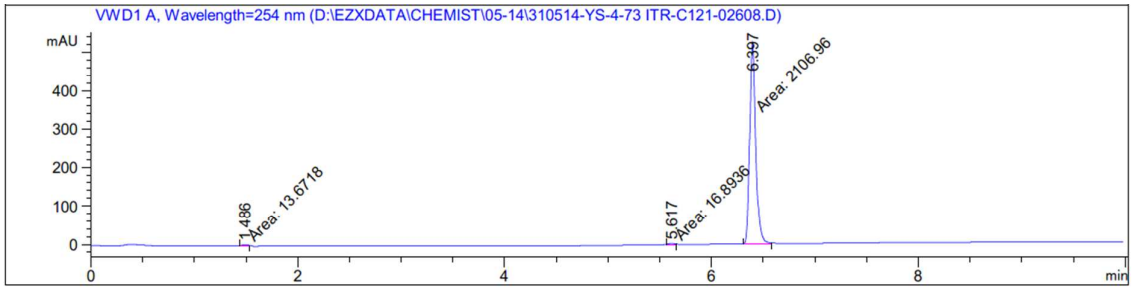
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.436	BV	0.1218	16.05455	1.95872	0.1024
2	5.483	MM	0.0788	1.56636e4	3313.78369	99.8976
Totals :				1.56796e4	3315.74242	

Halofantrine triflimide:



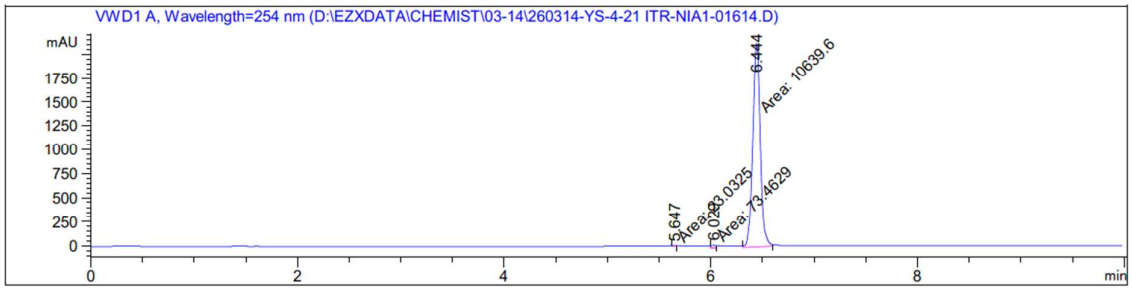
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.491	MM	0.0792	1.63606e4	3444.04907	100.0000
Totals :				1.63606e4	3444.04907	

Itraconazole dodecyl(lauryl)sulfate:



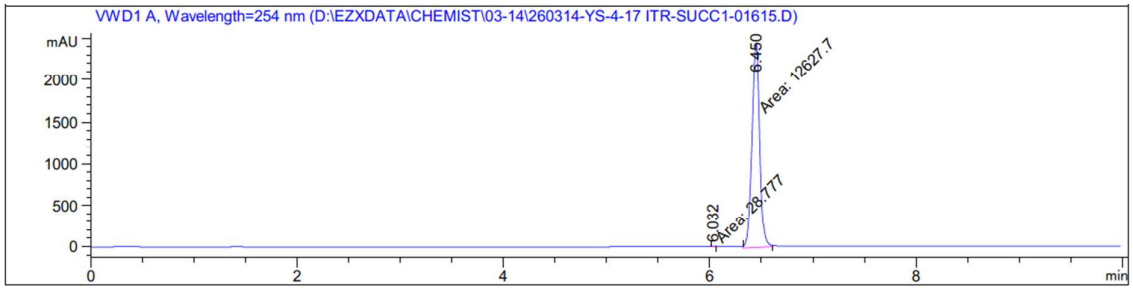
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.486	MM	0.0748	13.67178	3.04769	0.6396
2	5.617	MM	0.0717	16.89361	3.92568	0.7903
3	6.397	MM	0.0671	2106.96362	523.37634	98.5701
Totals :				2137.52901	530.34972	

Itraconazole 7-ethyl-2-methyl-4-undecylsulfate:



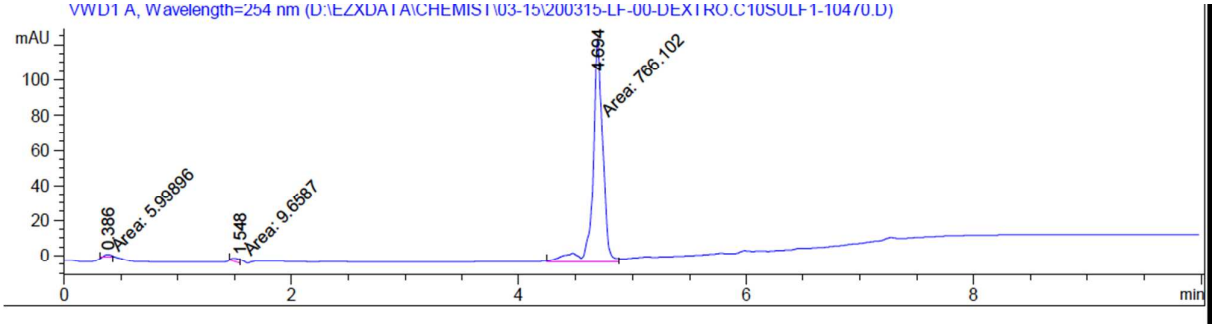
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.647	MM	0.0464	23.03249	8.27913	0.2145
2	6.029	MM	0.0525	73.46292	23.31160	0.6843
3	6.444	MM	0.0835	1.06396e4	2124.58911	99.1012
Totals :				1.07361e4	2156.17984	

Itraconazole dioctyl sulfosuccinate (docusate):



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.032	MM	0.0434	28.77697	11.05480	0.2274
2	6.450	MM	0.0858	1.26277e4	2452.97925	99.7726
Totals :				1.26565e4	2464.03405	

Dextromethorphan decylsulfate:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.386	MM	0.0679	5.99896	1.47308	0.7674
2	1.548	MM	0.0706	9.65870	2.28010	1.2355
3	4.694	MM	0.1010	766.10223	126.43117	97.9971

Dextromethorphan Decylsulfate Synthesis and Characterisation

Materials: Dextromethorphan hydrobromide monohydrate was from Sigma-Aldrich (St. Louis, MO, USA); acetonitrile, ethanol, petroleum spirit, chloroform, dichloromethane, methanol, ethyl acetate, diethyl ether were from Merck (Bayswater, Victoria, Australia) and used without any pre-treatment. All other chemicals and solvents were of analytical purity or high performance liquid chromatography (HPLC) grade. Decylsulfate ammonium salt was synthesized as described previously.[2]

Synthetic Method: Method 2 from main manuscript. Dextromethorphan hydrobromide monohydrate (1.02 g, 2.70 mmol) was dissolved in CH_2Cl_2 (25 mL) and decylsulfate ammonium salt (0.69 g, 2.70 mmol) was dissolved in distilled water (25 mL). The two solutions were mixed and the obtained biphasic solution was stirred vigorously for 3 h. The CH_2Cl_2 phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined CH_2Cl_2 phases were washed with cold distilled water (15 mL) until a negative $AgNO_3$ precipitate test was obtained. The organic phase was then dried (anhydrous Na_2SO_4), filtered and evaporated to afford the desired product, which was dried at 50 ^oC under high vacuum (0.1 mmHg). Yield 90%.

Melting Point of dextromethorphan and its salt forms:

Dextromethorphan (free base) (cLogP 3.89; $cLogD_{7.4}$ 2.17): 111 ^oC

Dextromethorphan. $HBr.H_2O$: 122 ^oC (decomp.)

Dextromethorphan decylsulfate: 62 – 68 ^oC

Dextromethorphan HPLC Assay:

Solubility samples were assayed for dextromethorphan via HPLC, using an Alliance 2695 separation module and 486 tunable UV absorbance detector (Waters Instruments, Milford, MA) and a Phenomenex Gemini C18 5µm, 150 x 4.6 mm column. The mobile phase comprised 0.1% v/v

orthophosphoric acid in 60:40 (v/v) water: acetonitrile and the flow rate was 1 mL/min. The injection volume was 30 µL and UV absorbance was monitored at 215 nm. The retention time was 1.4 min and the concentration range of the calibration standards was 0.5-100 µg/mL.

Dextromethorphan solubility:

The equilibrium solubility of the dextromethorphan was measured in the MC SEDDS formulation (30% (w/w) 1:1 Captex 355:Capmul MCM, 60% Kolliphor EL, 10% EtOH). Drug or drug-IL (0.5 g) was added to 0.5 g of formulation. The formulations were incubated at 37 °C for 3-7 days in order to reach equilibrium. Samples were collected at regular intervals and centrifuged (21,000 x g, 37 °C, 10 min). The resulting particle-free supernatant was accurately weighed (15-40 mg) and dissolved in chloroform:methanol (5 mL, 2:1, v/v). Following further dilution with acetonitrile and mobile phase, samples were analysed for drug content by HPLC. All solubility tests were performed in triplicate and equilibrium solubility defined as the value attained when at least three consecutive solubility samples varied by ≤5%.

Dextromethorphan solubility in MC SEDDS:

Dextromethorphan (free base) = 66.1 ± 3.2 mg/g

Dextromethorphan.HBr.H_2O = 23.5 ± 0.9 mg/g (Dextromethorphan free base equivalents)

Dextromethorphan decylsulfate = 93.3 ± 4.1 mg/g (Dextromethorphan free base equivalents)

Equilibrium Solubility of Cin DS and Itz DoS in Individual Excipients

Table S1. Equilibrium solubility (37 °C, n = 3, ± SD) of Itz DoS and Cin DS ILs in lipids and surfactants (mg/g free base equivalent). Methods as described in the main manuscript.

	Capmul MCM	**Captex 355**	**Kolliphor® EL**	**Tween80**	**Maisine™ 35-1**	**Soybean oil**
Cin DS	326.7± 9.5	324.1± 10.9	318.5 ± 0.9	331.5 ± 2.8	313.1 ± 6.4	37.2 ± 0.9
Itz DoS	228.8± 4.0	157.5 ± 8.0	120.8 ± 2.4	119.6 ± 3.4	165.1 ± 0.5	17.2 ± 1.0

Pharmacokinetic Parameter Estimates

The pharmacokinetic parameters for Cin and Itz after oral administration of the SEDDS formulations and control suspension formulations are given in Tables S2 and S3 below.

Table S2: Summary of the pharmacokinetic parameters for Cin FB after oral administration of either Cin FB or Cin IL to overnight fasted rats as either a solution in a SEDDS, as a suspension in the same SEDDS or as an aqueous suspension formulation. Values are expressed as means ($n \geq 4$) ± SEM. Due to lack of solubility of Cin FB in the SEDDS formulation it could not be administered as a solution at the high dose and instead was administered as a suspension. The Cin IL formulation allows administration as a solution in SEDDS at much higher dose than Cin FB and provides for significantly better exposure than the equivalent suspension formulation of Cin FB.

	Dose[a] ($mg.kg^{-1}$)	**AUC** $_{0\text{-}24h}$ ($ng.h.mL^{-1}$)	$\mathbf{C_{max}}$ ($ng.mL^{-1}$)	$\mathbf{T_{max}}$ (h)	**F%**[b]
Cin IL SEDDS solution	125	26063 ± 2370	2629 ± 248	4.9 ± 0.8	176
Cin FB SEDDS suspension	125	14770 ± 1860	1800 ± 283	2.8 ± 0.3	100
Cin FB aqueous suspension	125	5277 ± 2671	355.7 ± 80.0	2.0 ± 0.6	36
Cin FB SEDDS solution	35	5844 ± 487	1305 ± 64.2	2.0 ± 0.0	141
Cin IL SEDDS solution	35	5240 ± 494	916.2 ± 107	2.2 ± 0.2	127

[a] Cin dose expressed in free base equivalents.
[b] F% is relative bioavailability compared to Cin FB SEDDS suspension at 125 mg/kg dose.
In all cases, the SEDDS was LC[1] SEDDS (30% w/w lipid (soybean oil:Maisine™ 35-1, 1:1), 60% Kolliphor® EL, 10% ethanol). The aqueous suspension vehicle contained 0.5% w/v sodium carboxymethylcellulose, 0.4% w/v Tween 80 and 0.9% w/v NaCl in water.

Table S3: Pharmacokinetic parameters for Itz FB after oral administration of Itz FB or Itz docusate ionic liquid (Itz IL) to rats. Values are expressed as means ($n \geq 4$) ± SEM. The formation of the Itz IL permitted administration as a solution in the SEDDS formulation. Itz FB was not sufficiently soluble in the SEDDS formulation to allow administration as a solution in the SEDDS at any reasonable dose and was therefore dosed as a suspension in the SEDDS formulation and also as an aqueous suspension. The same dose was administered as the commercial Sporanox® formulation of Itz FB. Itz FB was also administered as a physical mixture (PM) with the docusate counterion in the same proportions as that in the Itz IL. The physcial mixture was dispersed/suspended in the SEDDS formulation. The physcial mixture was dosed at a slightly higher dose in an attempt to get plasma concentrations about the LOQ.

	Dose[a] ($mg.kg^{-1}$)	**$AUC_{0\text{-last}}$ ($ng.h.mL^{-1}$)**	**C_{max} ($ng.mL^{-1}$)**	**T_{max} (h)**	**F%[b]**
Itz FB aqueous suspension	20	<LOQ[c]	< 50[d]	-	NA
Itz FB SEDDS suspension	20	<LOQ[c]	< 50[d]	-	NA
Itz FB Sporanox	20	5855 ± 1158	460 ± 31	3.8 ±1.4	100
Itz IL SEDDS solution	20	14420 ± 687	1065 ± 87	2.8 ± 0.5	246
Itz FB + docusate sodium PM[e] SEDDS suspension	30	1010 ± 230	90 ± 6.3	2.2 ± 0.2	11.4

[a] Itz dose expressed in free base equivalents.
[b] F% is relative bioavailability compared to the current commercial formulation.
[c] At all time points Itz plasma concentrations were below the limit of quantification (LOQ) of the assay.
[d] Since plasma concentrations were below the LOQ, Cmax is quoted as less than the LOQ, which was 50 ng/mL.
[e] PM is a physical mixture of Itz FB and docusate sodium in the same SEDDS formulation
In all cases, the SEDDS is LC^2 SEDDS ((w/w): 60% lipid (soybean oil:Maisine™ 35-1, 1:1), 30% Kolliphor® EL, 10% ethanol). The aqueous suspension vehicle contained 0.5% w/v sodium carboxymethylcellulose, 0.4% w/v Tween 80 and 0.9% w/v NaCl in water.

Histology of Gastric and Intestinal Regions of the Rat:

Method: At the conclusion of the Cin pharmacokinetic study and after the collection of the last blood sample (24 h), each animal was euthanised with a lethal dose of penobarbitone (550 mg/kg) administered via the carotid artery cannula. Immediately after euthanasia the stomach and duodenum were removed, dissected and rinsed with saline prior to being placed in a 5% v/v formaldehyde solution. The stomachs from untreated (blank) rats were also taken and processed in the same manner for a control comparison. All samples were sent to Gribbles Veterinary Pathology (Clayton, Australia) where glandular and non-glandular stomach and duodenal sections underwent blinded histological examination, imaging and scoring.

Results: Figure S1 below is a representative light microscopy image (x100 magnification) of the rat non glandular stomach 24 hours after administraion of the LC[1] SEDDS formulation containing the IL, Cin DS. In all animals, histological assessment concluded that the non-glandular stomach consisted of normal keratinized epithelium (red arrow) and unremarkable lamina propria (Indicated by black arrow). Further examination of the glandular stomach and the small intestine also failed to reveal any evidence of damaged epithelia. The observations of no histological damage were consistent across all animals.

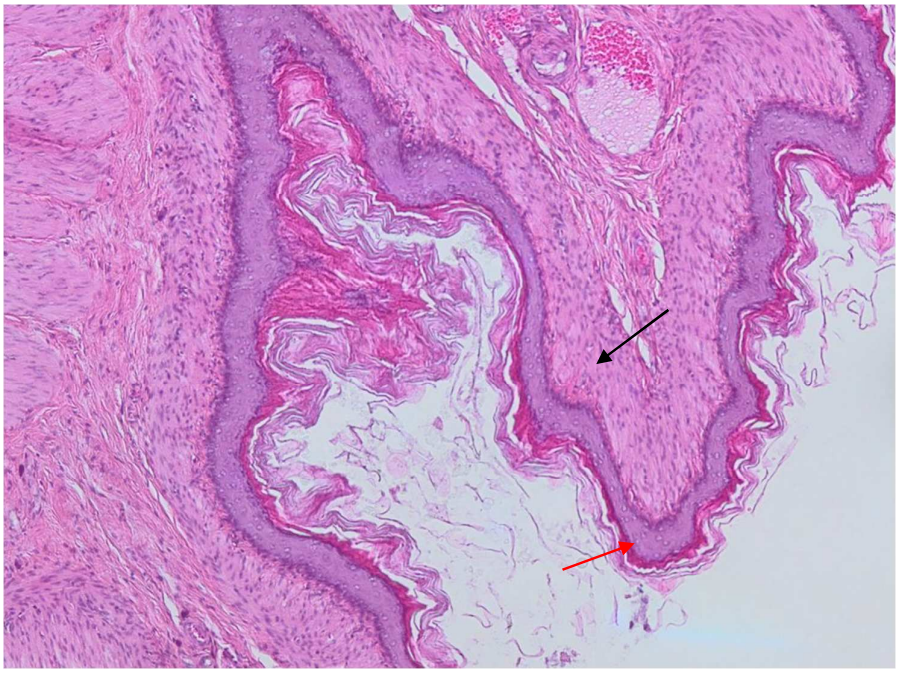


Figure S1: Light microscopy image of the non-glandular stomach of a rat following administration of LC[1] SEDDS containing the IL, Cin DS. The red arrow shows normal keratinized epithelium and the black arrow the lamina propria.

Figure S2 below is a representative light microscopy image (x100 magnification) of the rat non glandular stomach 24 hours after administraion LC[1] SEDDS containing Cin FB. The histological assessment was essentially the same as that for the formulation containing the ionic liquid and concluded that the non-glandular stomach consisted of normal keratinized epithelium (red arrow) and unremarkable lamina propria (Indicated by black arrow). Additional examination of the glandular stomach and the small intestine also failed to reveal evidence of damaged epithelia. The observations of no histological damage were consistent across all animals.

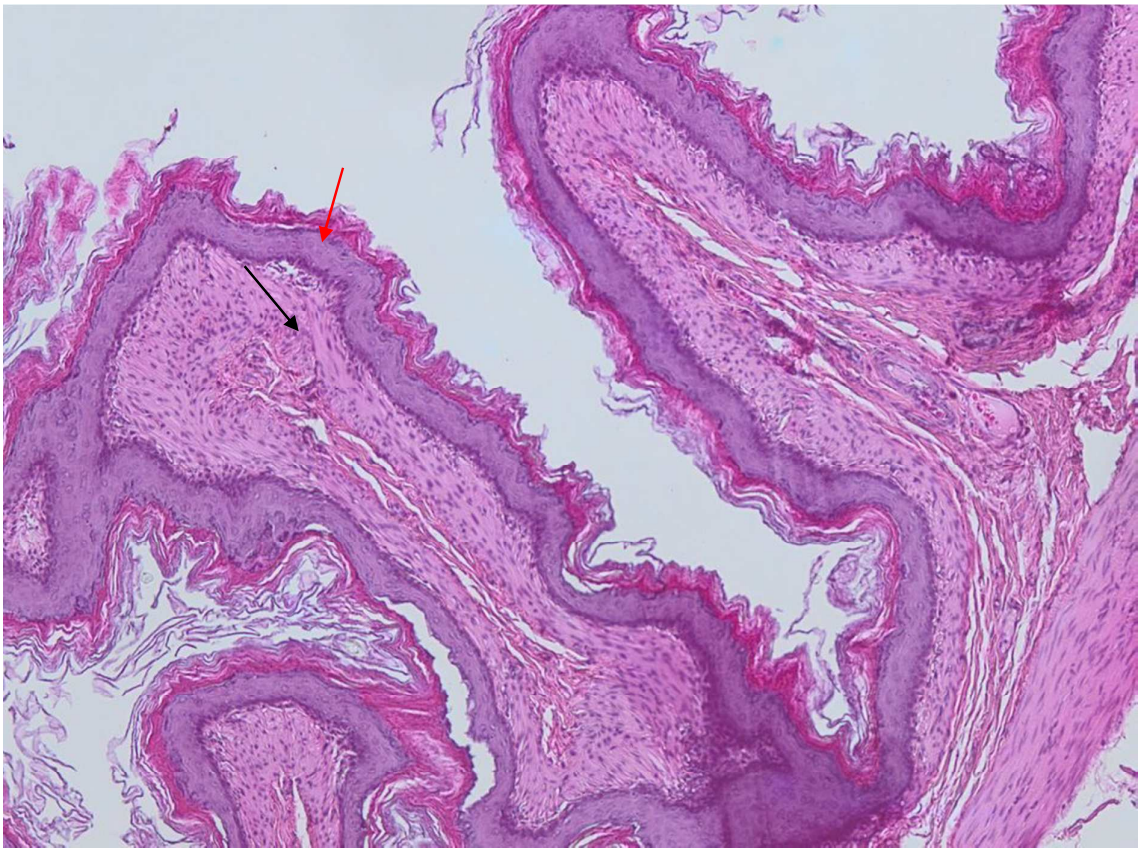


Figure S2: Light microscopy image of the non-glandular stomach of a rat following administration of LC[1] SEDDS contaning Cin FB. The red arrow shows normal keratinized epithelium and the black arrow the lamina propria.

References

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