Supplementary Information

Expeditious and sustainable two-step synthesis of sinapoyl malate and analogues: towards non-endocrine disruptive bio-based and water-soluble bioactive compounds

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1. General Information

Syringaldehyde, *p*-coumaraldehyde, vanillin, 3,4-hydroxybenzaldehyde, aniline, pyridine, L-malic acid, L-lactic acid, L-tartaric acid, sodium carbonate, Meldrum's acid and DPPH were purchased from Sigma Aldrich. HCl_{conc} and solvents were purchased from Fisher scientific and used as received. All chemicals were used directly without purification.

Chromatographic purifications of products were performed on a flash-prep LC system puriFlash® 4100 from Interchim with prepacked silica column (30 µm, Interchim PF-Si30-HP), dual wavelength collection (λ = 254 and 320 nm) and a mixture of cyclohexane/ethyl acetate as eluant. ^{1}H NMR spectra were recorded on a Brucker Fourier 300 (300 MHz) and were calibrated with residual Acetone-d_6 or DMSO-d_6 protons signals at δ 2.05 or 2.50 ppm, respectively. Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, q = quartet, dd = doublet of doublets and m = multiplet), integration, coupling constant (Hz) and assignment. ^{13}C NMR spectra were recorded on a Brucker Fourier 300 (75 MHz) and were calibrated with Acetone-d_6 or DMSO-d_6 signals at δ 29.84 or 39.52 ppm respectively. Data are reported as follows: chemical shift (δ ppm) and attribution. All NMR assignments were made using COSY, HMBC and HSQC spectrum. UV/Vis spectra were recorded in ethanol (C = 10^{-5} mol/L) on an Agilent Cary 60 UV-Vis with 1 cm cuvette made of quartz and are reported in wavelength (nm). Melting points were recorded on a Mettler Toledo MP50 Melting Point System ($T_{initial}$: 40 °C; Heating: 3 °C/min) with ME-18552 sample tubes. High resolution mass spectrometries were performed on an Agilent 1290 system, equipped with a PDA UV detector, and a 6545 Q-TOF mass spectrometer (Wilmington, DE, USA). The source was equipped with a JetStream ESI probe operating at atmospheric pressure. Optical activities were determined in methanol on a Bellingham + Stanley ADP410 single wavelength polarimeter.

DPPH assays were adapted from Brand-Williams *et al.*[1]. In summary, DPPH$^{\bullet}$ solution was prepared by dissolving DPPH (m = 8.33 mg) in ethanol (V = 10 mL) to obtain solution 1 (C = 2 mM). Solution 1 was then diluted 10-times to afford solution 2 (C = 200 µM). In a 96 wells microplate, a mixture containing 10 µL of antiradical solution (final quantity in microwell were 80 to 2.5 nmol) and 190 µL of DPPH solution 2. Absorbance was recorded at 520 nm every 5 min for 7 h until stabilization of the signal. To determine the exact value of inhibition, a reference (190 µL of DPPH solution 2 with 10 µL of ethanol) and a blank (200 µL of ethanol) were performed at the same time as each experiment. All experiments were carried out in duplicate on a Thermo Scientific Multiskan FC using a 96-wells microplate.

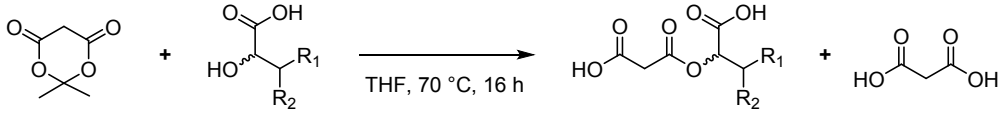
Antibacterial assays were carried out using *Escherichia coli* K12 strain overnight cultures diluted to an OD_{600} = 0.1 in a sterile 96-wells microplate with fresh LB medium, with or without addition of molecule of interest at different concentrations (from 5 to 0.02 %w) and the optical density was measured at 600 nm every 15 min for 20 h. Each microplate was controlled with blank.

The agonistic and antagonistic potentials of sinapic acid derivatives were analyzed following a literature method in which ERα, PXR, and AR transcriptional activities were monitored by using corresponding reporter cells HELN ERα, HELN AR, and HG5LN PXR cells, respectively[2]. Activities were measured in relative light units (RLUs) and 100% of activities were assigned to the RLU value obtained with 10 nM agonist control (estradiol (E2), R 1881, SR 12813). The sample (DMSO) was tested as a control without any compound.

2. Synthesis

2.1. Synthesis of intermediates

2.1.1. General Procedure 1 (GP1): Intermediates bearing 1 ester group



R_1 = H or OH
R_2 = H or COOH

Meldrum's acid (1.01 g, 7.03 mmol) and the corresponding acid (7.03 mmol, 1 eq.) were dissolved in THF (7 mL). The mixture was heated at 70 °C for 16 h under magnetic stirring. After cooling at r.t, the solvent was evaporated under reduced pressure to afford a crude mixture containing the intermediate and malonic acid, which was used in the next step without further purification.

- Intermediate from L-lactic acid

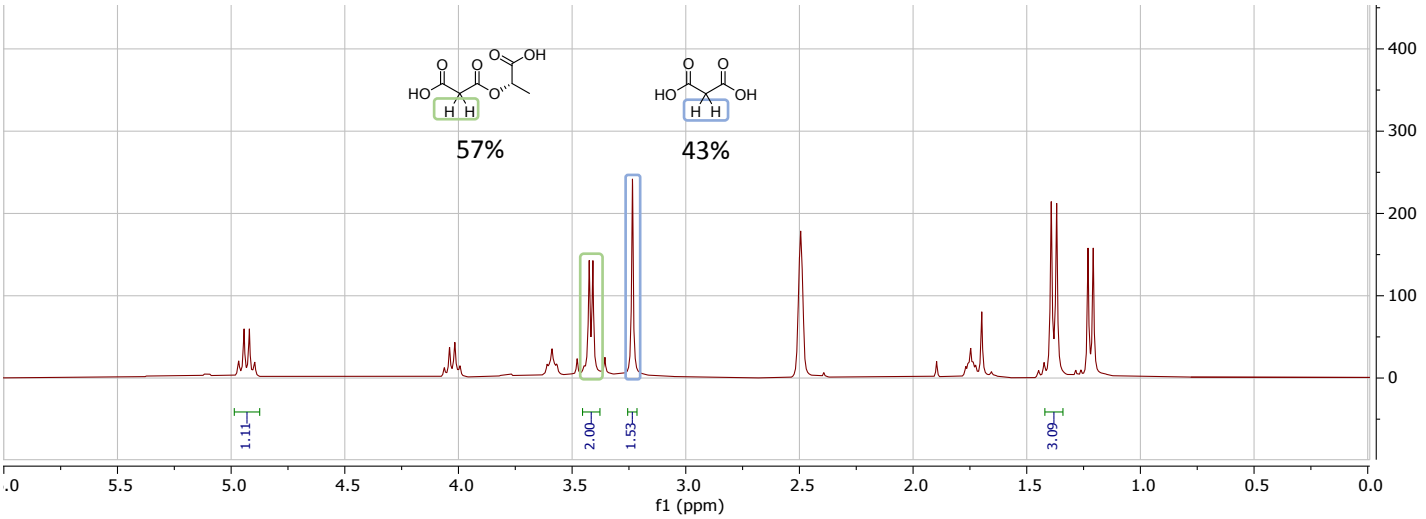


Figure S1: ^{1}H NMR spectrum of crude intermediate from lactic acid

- Intermediate from L-malic acid

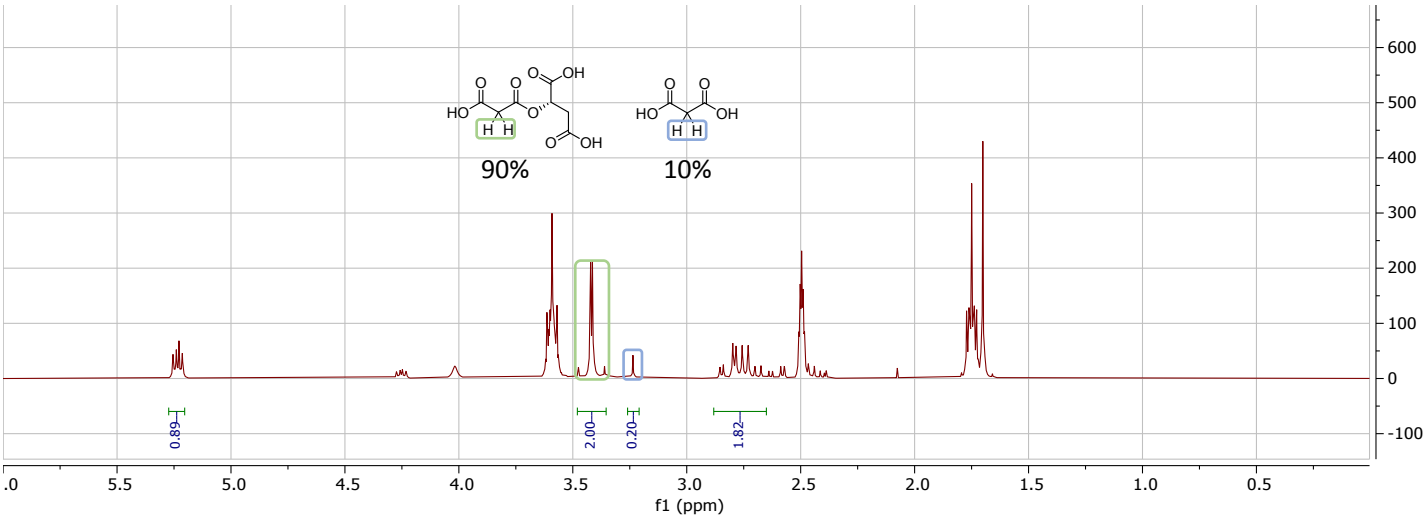


Figure S2: ^{1}H NMR spectrum of crude intermediate from malonic acid

- Intermediate from L-tartaric acid

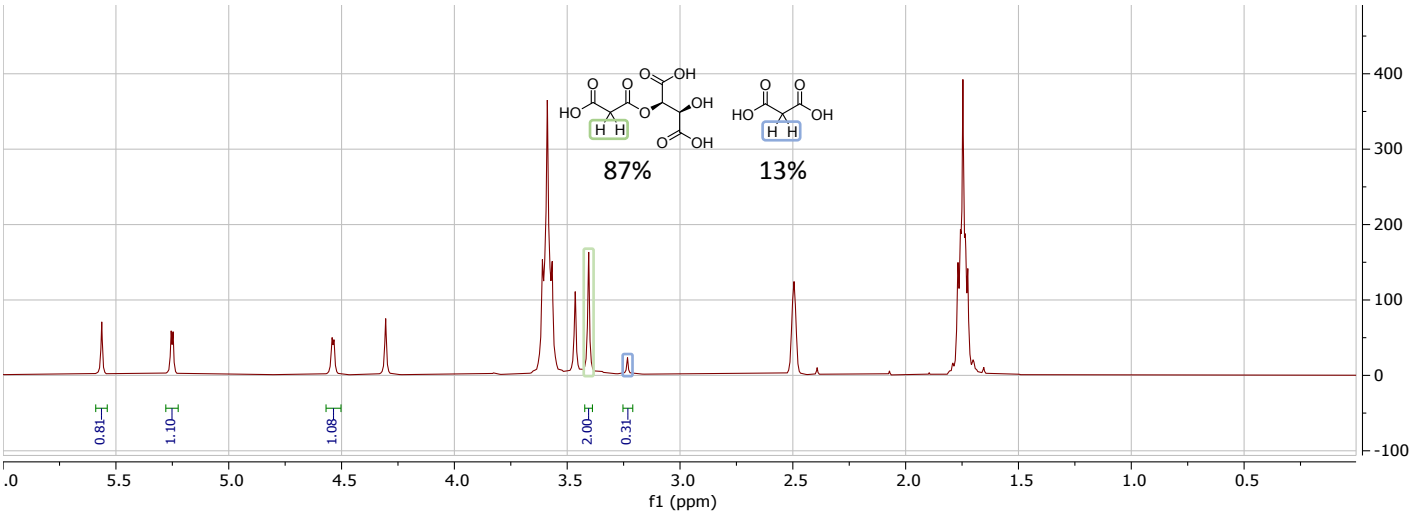
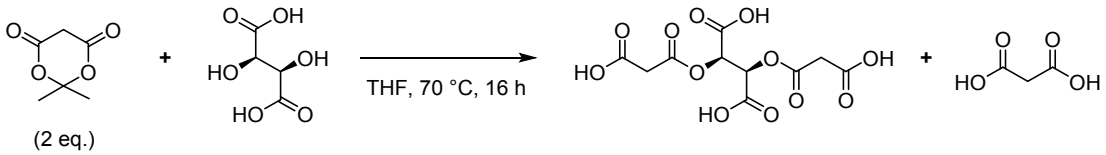


Figure S3: ^{1}H NMR spectrum of crude intermediate from tartaric acid

2.1.2. General Procedure 2 (GP2): Intermediate bearing 2 ester groups



L-Tartaric acid (1.00 g, 6.66 mmol) and Meldrum's acid (1.92 g, 13.3 mmol, 2 eq.) were dissolved in THF (7 mL). The mixture was heated at 70 °C for 16 h under magnetic stirring. After cooling at r.t, the solvent was evaporated under reduced pressure to afford a crude mixture containing the intermediate and malonic acid, which was used in the next step without further purification.

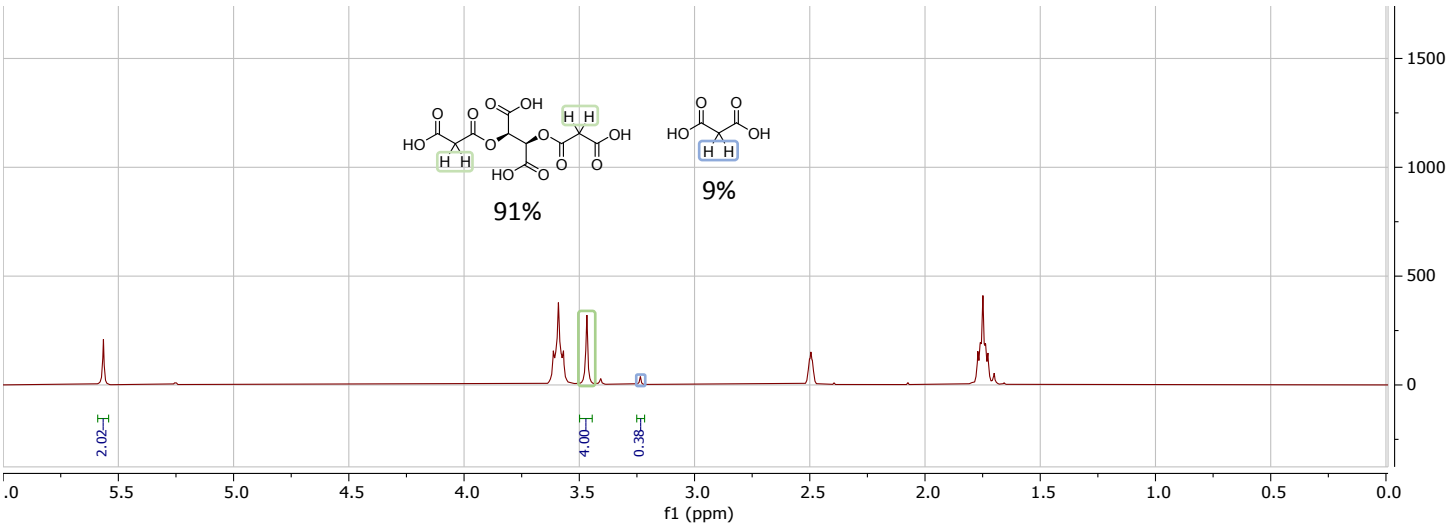
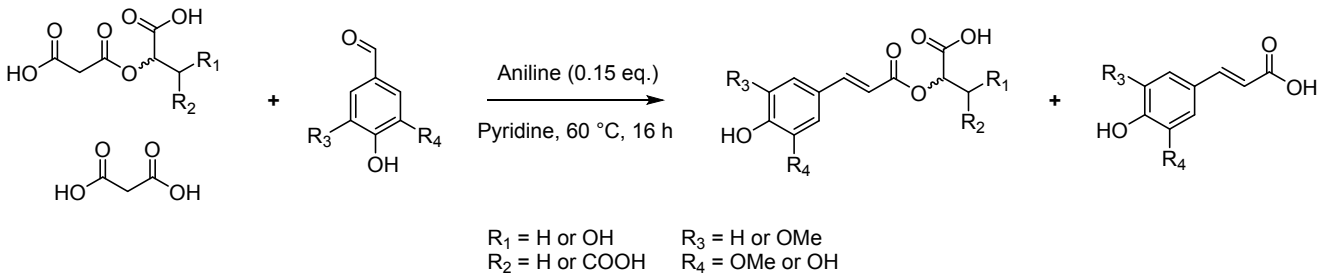


Figure S4: ^{1}H NMR spectrum of crude intermediate with 2 ester moieties from tartaric acid

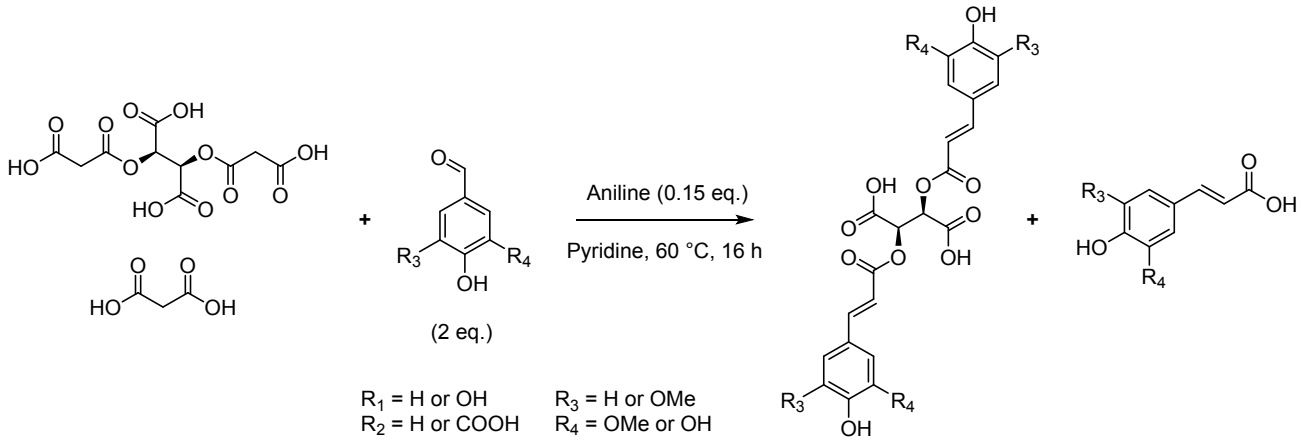
2.2. Synthesis of sinapoyl malate and analogues

2.2.1. General Procedure 3 (GP3): Molecules bearing 1 phenol group



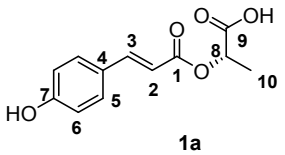
To crude malonic monoester/malonic acid mixture, *p*-hydroxybenzaldehyde (7.03 mmol, 1 eq. compared to Meldrum's acid from GP1) and aniline (100 µL, 1.10 mmol, 0.15 eq. compared to Meldrum's acid from GP1) were added in pyridine (5 mL). The reaction was stirred at 60 °C for 16 h. After cooling at r.t., the mixture was diluted in ethyl acetate and washed with saturated aqueous $NaHCO_3$. The aqueous layer was acidified with concentrated HCl until pH 1 and extracted with ethyl acetate. The resulting organic layer was dried with anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified using flash chromatography with cyclohexane/ethyl acetate as eluant.

2.2.2. General Procedure 4 (GP4): Molecules bearing 2 phenol groups



To crude malonic diester/malonic acid mixture, the corresponding phenolic aldehyde (13.3 mmol, 2 eq. compared to tartaric acid from GP2) and aniline (100 mL, 1.10 mmol, 0.15 eq. compared to tartaric acid from GP2) were added in pyridine (5 mL). The reaction was stirred at 60 °C for 16 h. After cooling at r.t., the mixture was diluted in ethyl acetate and washed with saturated aqueous $NaHCO_3$. The aqueous phase was acidified with concentrated HCl until pH 1 and extracted with ethyl acetate. The resulting organic layer was dried with anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified using flash chromatography with cyclohexane/ethyl acetate as eluant.

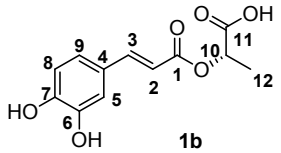
2.3. Characterization data



1a

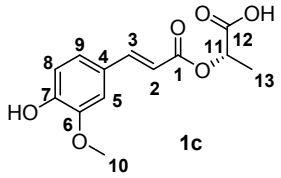
Coumaroyl-L-lactate (1a) was synthesized from 4-hyroxybenzaldehyde using GP3. White powder (0.46 g, 28%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 1.44 (d, 3H, J = 7.1 Hz, H10), 4.99 (q, 1H, J = 7.0 Hz, H8), 6.45 (d, 1H, J = 15.9 Hz, H2), 6.79 (d, 2H, J = 8.3 Hz, H6), 7.58 (m, 3H, H3+H5), 10.08 (s, 1H, H_{phenol}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm)

16.9 (C10), 68.3 (C8), 113.4 (C2), 115.8 (C6), 125.0 (C4), 130.5 (C5), 145.5 (C3), 160.0 (C7), 166.1 (C1), 172.1 (C9). $[\propto]_D^{25}$: +63 (c 0.02, MeOH). **Mp** (°C): 148-150. λ_{max} (nm): 315. ε (L.mol^{-1}.cm^{-1}): 27783. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{12}H_{13}O_5$: 237.0763; found: 237.0763.



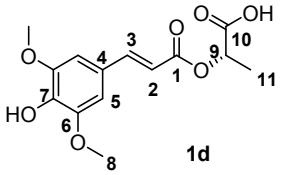
1b

Caffeoyl-L-lactate (1b) was synthesized from 3,4-dihydroxybenzaldehyde using GP3. Pale-yellow gum (0.65 g, 34%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 1.44 (d, 3H, *J* = 6.7 Hz, H12), 4.98 (q, 1H, *J* = 6.7 Hz, H10), 6.31 (d, 1H, *J* = 15.9 Hz, H2), 6.77 (d, 1H, *J* = 8.0 Hz, H8), 7.04 (m, 2H, H5+H9), 7.50 (d, 1H, *J* = 15.9 Hz, H3), 9.19 (s, 1H, H_{phenol}), 9.65 (s, 1H, H_{phenol}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 16.9 (C12), 68.3 (C10), 113.3 (C2), 115.0 (C5), 115.8 (C8), 121.6 (C9), 125.4 (C4), 145.6 (C6), 146.0 (C3), 148.7 (C7), 166.0 (C1), 172.2 (C11). $[\propto]_D^{25}$: +59 (c 0.02, MeOH). **Mp** (°C): 136-139. λ_{max} (nm): 332. ε (L.mol^{-1}.cm^{-1}): 18352. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{12}H_{13}O_6$: 253.0712; found: 253.0710.



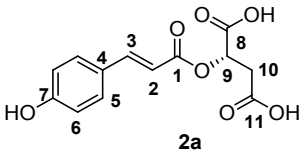
1c

Feruloyl-L-lactate (1c) was synthesized from vanillin using GP3. Pale-yellow oil (0.69 g, 36%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 1.45 (d, 3H, *J* = 7.1 Hz, H13), 3.82 (s, 3H, H10), 5.00 (q, 1H, *J* = 7.0 Hz, H11), 6.54 (d, 1H, *J* = 15.9 Hz, H2), 6.80 (d, 1H, *J* = 8.1 Hz, H8), 7.14 (dd, 1H, *J* = 8.2, 1.9 Hz, H9), 7.36 (d, 1H, *J* = 1.9 Hz, H5), 7.58 (d, 1H, *J* = 15.9 Hz, H3), 9.64 (s, 1H, H_{phenol}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 16.9 (C13), 56.7 (C10), 68.3 (C11), 111.2 (C5), 113.9 (C2), 115.6 (C8), 123.5 (C9), 125.6 (C4), 145.9 (C3), 148.0 (C6), 149.6 (C7), 166.1 (C1), 172.2 (C12). $[\propto]_D^{25}$: +53 (c 0.02, MeOH). λ_{max} (nm): 329. ε (L.mol^{-1}.cm^{-1}): 22950. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{13}H_{15}O_6$: 267.0869; found: 267.0867.



1d

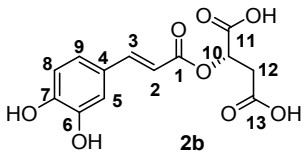
Sinapoyl-L-lactate (1d) was synthesized from syringaldehyde using GP3. Yellow powder (0.82 g, 40%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 1.45 (d, 3H, *J* = 7.0 Hz, H11), 3.80 (s, 6H, H8), 5.01 (q, 1H, *J* = 7.0 Hz, H9), 6.60 (d, 1H, *J* = 15.8 Hz, H2), 7.06 (s, 2H, H5), 7.59 (d, 1H, *J* = 15.9 Hz, H3), 9.02 (s, 1H, H_{phenol}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 16.9 (C11), 56.2 (C8), 68.3 (C9), 106.4 (C5), 114.4 (C2), 124.4 (C4), 138.5 (C7), 146.2 (C3), 148.1 (C6), 166.1 (C1), 172.2 (C10). $[\propto]_D^{25}$: +47 (c 0.02, MeOH). **Mp** (°C): 90-92. λ_{max} (nm): 330. ε (L.mol^{-1}.cm^{-1}): 22227. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{14}H_{17}O_7$: 297.0974; found: 297.0971.



2a

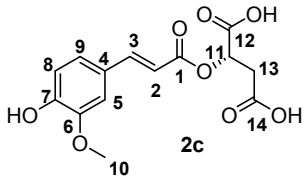
Coumaroyl-L-malate (2a) was synthesized from 3,4-dihydroxybenzaldehyde using GP3. Light-brown solid (1.21 g, 62%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 2.83 (m, 2H, H10), 5.31 (dd, 1H, *J* = 8.6, 4.0 Hz, H8), 6.44 (d, 1H, *J* = 16.0 Hz, H2), 6.79 (d, 2H, *J* = 8.6 Hz, H6), 7.59 (dd, 3H, *J* = 16.0, 8.6 Hz, H5+H2), 10.08 (s, 1H, H_{phenol}), 12.71 (m, 2H, H_{acide}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 35.9 (C10), 68.4 (C8), 113.2 (C3), 115.8 (C6), 124.9 (C4), 130.6 (C5), 145.9 (C2), 160.1

(C7), 165.8 (C1), 170.4 (C11), 170.8 (C9). $[\propto]_D^{25}$: +8.0 (c 0.02, MeOH). **Mp** (°C): 133-135. λ_{max} (nm): 315. **ε** (L.mol^{-1}.cm^{-1}): 21796. **HRMS** (*m/z*) [M+H]$^+$ calcd for $C_{13}H_{13}O_7$: 281.0661; found: 281.0657.



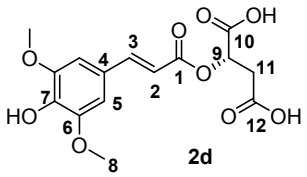
2b

Caffeoyl-L-malate (2b) was synthesized from 3,4-dihydroxybenzaldehyde using GP3. Light-brown solid (1.01 g, 49%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 2.82 (m, 2H, H12), 5.31 (dd, 1H, *J* = 8.5, 4.1 Hz, H10), 6.31 (d, 1H, *J* = 15.9 Hz, H2), 6.77 (d, 1H, *J* = 8.0 Hz, H8), 7.05 (m, 2H, H5+H9), 7.51 (d, 1H, *J* = 15.8 Hz, H3), 9.17 (s, 1H, H_{phenol}), 9.67 (s, 1H, H_{phenol}), 12.87 (s, 2H, H_{acide}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 36.0 (C12), 68.5 (C10), 113.1 (C2), 115.2 (C5), 115.9 (C8), 121.7 (C9), 125.4 (C4), 145.7 (C6), 146.4 (C3), 148.8 (C7), 165.9 (C1), 170.5 (C13), 170.9 (C11). $[\propto]_D^{25}$: +8.0 (c 0.02, MeOH). **Mp** (°C): 170-173. λ_{max} (nm): 333. **ε** (L.mol^{-1}.cm^{-1}): 19706. **HRMS** (*m/z*) [M+H]$^+$ calcd for $C_{13}H_{13}O_8$: 297.0604; found: 297.0606.



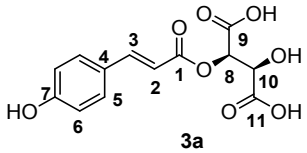
2c

Feruloyl-L-malate (2c) was synthesized from vanillin using GP3. Yellow solid (0.99 g, 46%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 2.85 (m, 2H, H13), 5.34 (dd, 1H, *J* = 8.6, 3.9 Hz, H11), 6.54 (d, 1H, *J* = 15.9 Hz, H2), 6.80 (d, 1H, *J* = 8.0 Hz, H8), 7.14 (dd, 1H, *J* = 8.2, 1.9 Hz, H9), 7.37 (d, 1H, *J* = 1.9 Hz, H5), 7.59 (d, 1H, *J* = 15.9 Hz, H3), 9.67 (s, 1H, H_{phenol}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 36.0 (C13), 55.8 (C10), 68.6 (C11), 111.2 (C5), 113.7 (C2), 115.6 (C8), 123.8 (C9), 125.6 (C4), 146.4 (C3), 148.1 (C6), 149.7 (C7), 166.0 (C1), 170.6 (C14), 170.9 (C12). $[\propto]_D^{25}$: +8.0 (c 0.02, MeOH). **Mp** (°C): 153-155. λ_{max} (nm): 329. **ε** (L.mol^{-1}.cm^{-1}): 20332. **HRMS** (*m/z*) [M+H]$^+$ calcd for $C_{14}H_{15}O_8$: 311.0767; found: 311.0767.



2d

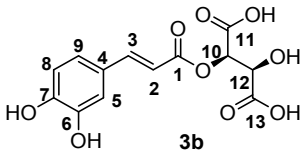
Sinapoyl-L-malate (2d) was synthesized from syringaldehyde using GP3. Light-yellow solid (1.13 g, 48%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 2.83 (m, 2H; H11), 3.80 (s, 6H, H8), 5.31 (dd, 1H, *J* = 8.7, 3.9 Hz, H9), 6.59 (d, 1H, *J* = 15.9 Hz, H2), 7.06 (s, 2H, H5), 7.58 (d, 1H, *J* = 15.9 Hz, H3), 9.03 (s, 1H, H_{phenol}), 12.69 (s, 2H, H_{acide}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 36.0 (C11), 56.1 (C8), 68.4 (C9), 106.4 (C5), 114.0 (C2), 124.3 (C4), 138.5 (C7), 146.6 (C3), 148.0 (C6), 165.9 (C1), 170.4 (C12), 170.8 (C10). $[\propto]_D^{25}$: +7.5 (c 0.02, MeOH). **Mp** (°C): 140-143. λ_{max} (nm): 333. **ε** (L.mol^{-1}.cm^{-1}): 20634. **HRMS** (*m/z*) [M+H]$^+$ calcd for $C_{15}H_{17}O_9$: 341.0873; found: 341.0871.



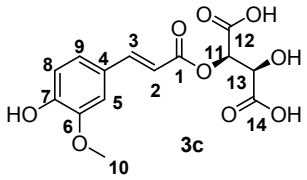
3a

Monocoumaroyl-L-tartrate (3a) was synthesized from 4-hydroxybenzaldehyde using GP3. Off-white solid (0.62 g, 30%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 4.62 (s, 1H, H10), 5.37 (s, 1H, H8), 6.39 (d, 1H, *J* = 15.9 Hz, H2), 6.82 (d, 2H, *J* = 8.1 Hz, H6), 7.57 (d, 2H, *J* = 8.2 Hz, H5), 7.66 (d, 1H, *J* = 15.9 Hz, H3), 10.09 (s, 1H, H_{phenol}), 13.17 (s, 2H, H_{acide}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 70.6 (C10), 73.7 (C8), 113.6 (C2), 116.3 (C6), 125.4 (C4), 131.0 (C5), 146.6

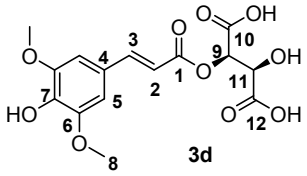
(C3), 160.6 (C7), 166.2 (C1), 169.1 (C9), 172.5 (C11). $[\alpha]_D^{25}$: -22 (c 0.02, MeOH). **Mp** (°C): 190-193. **λ_{max}** (nm): 316. **ε** (L.mol^{-1}.cm^{-1}): 24181. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{13}H_{13}O_8$: 297.0610; found: 297.0611.



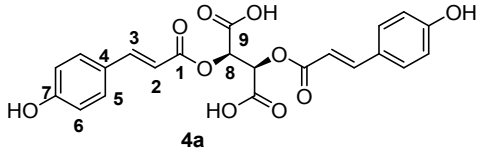
Monocaffeoyl-L-tartrate (3b) was synthesized from 3,4-dihydroxybenzaldehyde using GP3. Pale-yellow solid (0.63 g, 29%) after purification. **^{1}H NMR** (300 MHz, DMSO-*d_6*): δ (ppm) 4.59 (d, 1H, *J* = 2.6 Hz, H12), 5.34 (d, 1H, *J* = 2.5 Hz, H10), 6.25 (d, 1H, *J* = 15.9 Hz, H2), 6.78 (d, 1H, *J* = 8.1 Hz, H8), 7.02 (dd, 1H, *J* = 8.1, 2.0 Hz, H9), 7.06 (d, 1H, *J* = 1.9 Hz, H5), 7.58 (d, 1H, *J* = 15.9 Hz, H3), 9.25 (s, 1H, H_{phenol}), 9.66 (s, 1H, H_{phenol}). **^{13}C NMR** (75 MHz, DMSO-*d_6*): δ (ppm) 70.3 (C12), 73.4 (C10), 113.0 (C2), 115.0 (C5), 116.0 (C8), 121.7 (C9), 125.5 (C4), 145.7 (C6), 146.6 (C3), 148.8 (C7), 165.8 (C1), 168.8 (C11), 172.2 (C13). $[\alpha]_D^{25}$: -18 (c 0.02, MeOH). **Mp** (°C): 181-184. **λ_{max}** (nm): 332. **ε** (L.mol^{-1}.cm^{-1}): 16825. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{13}H_{13}O_9$: 313.0560; found: 313.0558.



Monoferuloyl-L-tartrate (3c) was synthesized from vanillin using GP3. Yellow solid (0.77 g, 34%) after purification. **^{1}H NMR** (300 MHz, DMSO-*d_6*): δ (ppm) 3.82 (s, 3H, H10), 4.60 (d, 1H, *J* = 2.6 Hz, H13), 5.36 (d, 1H, *J* = 2.5 Hz, H11), 6.48 (d, 1H, *J* = 15.9 Hz, H2), 6.80 (d, 1H, *J* = 8.1 Hz, H8), 7.12 (dd, 1H, *J* = 8.2, 1.9 Hz, H9), 7.33 (d, 1H, *J* = 2.0 Hz, H5), 7.64 (d, 1H, *J* = 15.9 Hz, H3), 9.70 (s, 1H, H_{phenol}). **^{13}C NMR** (75 MHz, DMSO-*d_6*): δ (ppm) 55.7 (C10), 70.1 (C13), 73.2 (C11), 111.0 (C5), 113.5 (C2), 115.6 (C8), 123.6 (C9), 125.5 (C4), 146.4 (C3), 148.0 (C6), 149.7 (C7), 165.9 (C1), 168.7 (C12), 172.1 (C14). $[\alpha]_D^{25}$: -23 (c 0.02, MeOH). **Mp** (°C): 80-83. **λ_{max}** (nm): 328. **ε** (L.mol^{-1}.cm^{-1}): 14930. **HRMS** (m/z) $[M+H]^+$ calcd for $C_{14}H_{15}O_9$: 327.0716; found: 327.0714.

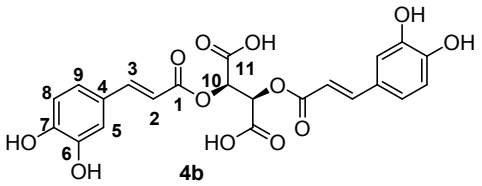


Monosinapoyl-L-tartrate (3d) was synthesized from syringaldehyde using GP3. Yellow solid (0.74 g, 30%) after purification. **^{1}H NMR** (300 MHz, DMSO-*d_6*): δ (ppm) 3.81 (s, 6H, H8), 4.62 (d, 1H, *J* = 2.6 Hz, H11), 5.38 (d, 1H, *J* = 2.6 Hz, H9), 6.55 (d, 1H, *J* = 15.9 Hz, H2), 7.03 (s, 2H, H5), 7.65 (d, 1H, *J* = 15.8 Hz, H3), 9.04 (s, 1H, H_{phenol}). **^{13}C NMR** (75 MHz, DMSO-*d_6*): δ (ppm) 56.1 (C8), 70.2 (C11), 73.3 (C12), 106.3 (C5), 114.0 (C2), 124.3 (C4), 138.6 (C7), 146.8 (C3), 148.1 (C6), 165.9 (C1), 168.7 (C10), 172.2 (C12). $[\alpha]_D^{25}$: -23 (c 0.02, MeOH). **Mp** (°C): 193-196. **λ_{max}** (nm): 332. **ε** (L.mol^{-1}.cm^{-1}): 18108. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{15}H_{17}O_{10}$: 357.0822; found: 357.0819.

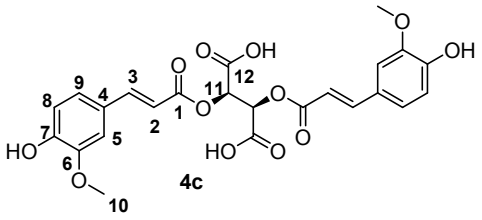


Dicoumaroyl-L-tartrate (4a) was synthesized from 4-hydroxybenzaldehyde using GP4. Pale-yellow solid (0.65 g, 22%) after purification. **^{1}H NMR** (300 MHz, DMSO-*d_6*): δ (ppm) 5.70 (s, 2H, H8), 6.50 (d, 2H, *J* = 16.0 Hz, H2), 6.81 (d, 4H, *J* = 8.5 Hz, H6), 7.65 (m, 6H, H5+H3), 10.12 (s, 2H, H_{phenol}), 13.64 (s, 2H, H_{acid}). **^{13}C NMR** (75 MHz, DMSO-*d_6*): δ (ppm) 70.7 (C8), 112.6

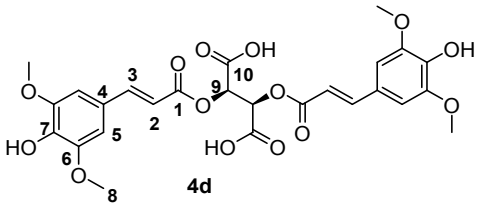
(C2), 115.9 (C6), 124.9 (C4), 130.8 (C5), 146.7 (C3), 160.3 (C7), 166.7 (C1), 167.5 (C9). $[\propto]_D^{25}$: -261 (c 0.014, MeOH). **Mp** (°C): 87-89. λ_{max} (nm): 316. ε (L.mol^{-1}.cm^{-1}): 42853. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{19}O_{10}$: 443.0978; found: 443.0978.



Dicaffeoyl-L-tartrate (4b) was synthesized from 3,4-dihydroxybenzaldehyde using GP4. Pale-yellow solid (0.92 g, 29%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 5.68 (s, 2H, H10), 6.37 (d, 2H, *J* = 15.9 Hz, H2), 6.78 (d, 2H, *J* = 8.6 Hz, H8), 7.08 (m, 4H, H5+H9), 7.56 (d, 2H, *J* = 15.9 Hz, H3), 9.20 (s, 1H, H_{phenol}), 9.72 (s, 1H, H_{phenol}), 13.49 (s, 2H, OH_{acid}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 70.7 (C10), 112.4 (C2), 115.3 (C5), 115.9 (C8), 121.8 (C9), 125.3 (C4), 145.7 (C6), 147.1 (C3), 148.9 (C7), 165.6 (C1), 167.6 (C10). $[\propto]_D^{25}$: -228 (c 0.02, MeOH). **Mp** (°C): 84-86. λ_{max} (nm): 334. ε (L.mol^{-1}.cm^{-1}): 31107. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{22}H_{19}O_{12}$: 475.0877; found: 475.0877.



Diferuloyl-L-tartrate (4c) was synthesized from vanillin using GP4. Pale-yellow solid (0.80 g, 24%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 3.83 (s, 6H, H10), 5.71 (s, 2H, H11), 6.59 (d, 2H, *J* = 15.8 Hz, H2), 6.81 (d, 2H, *J* = 8.1 Hz, H8), 7.16 (dd, 2H, *J* = 8.2, 1.9 Hz, H9), 7.41 (d, 2H, *J* = 2.0 Hz, H5), 7.63 (d, 2H, *J* = 15.8 Hz, H3), 9.72 (s, 2H, H_{phenol}), 13.71 (s, 2H, H_{acid}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 55.7 (C10), 70.7 (C11), 111.1 (C5), 112.9 (C2), 115.5 (C8), 124.0 (C9), 125.3 (C4), 147.0 (C3), 148.0 (C7), 149.8 (C6), 165.7 (C1), 167.5 (C12). $[\propto]_D^{25}$: -273 (c 0.024, EtOH). **Mp** (°C): 183-185. λ_{max} (nm): 330. ε (L.mol^{-1}.cm^{-1}): 42480. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{24}H_{23}O_{12}$: 503.1190; found: 503.1189.



Disinapoyl L-tartrate (4d) was synthesized from syringaldehyde using GP4. Light-brown solid (1.08 g, 29%) after purification. **^{1}H NMR** (300 MHz, DMSO-d_6): δ (ppm) 3.81 (s, 12H, H8), 5.73 (s, 2H, H9), 6.65 (d, 2H, *J* = 15.9 Hz, H2), 7.10 (s, 4H, H5), 7.64 (d, 2H, *J* = 15.8 Hz, H3), 9.07 (s, 2H, OH_{phenol}), 13.64 (s, 2H, OH_{acid}). **^{13}C NMR** (75 MHz, DMSO-d_6): δ (ppm) 56.1 (C8), 70.7 (C9), 106.6 (C5), 113.4 (C2), 124.1 (C4), 138.7 (C7), 147.3 (C3), 148.1 (C6), 165.7 (C1), 167.6 (C10). $[\propto]_D^{25}$: -211 (c 0.02, MeOH). **Mp** (°C): 104-106. λ_{max} (nm): 333. ε (L.mol^{-1}.cm^{-1}): 36493. **HRMS** (*m/z*) $[M+H]^+$ calcd for $C_{26}H_{27}O_{14}$: 563.1395; found: 563.1396.

3. Green metrics

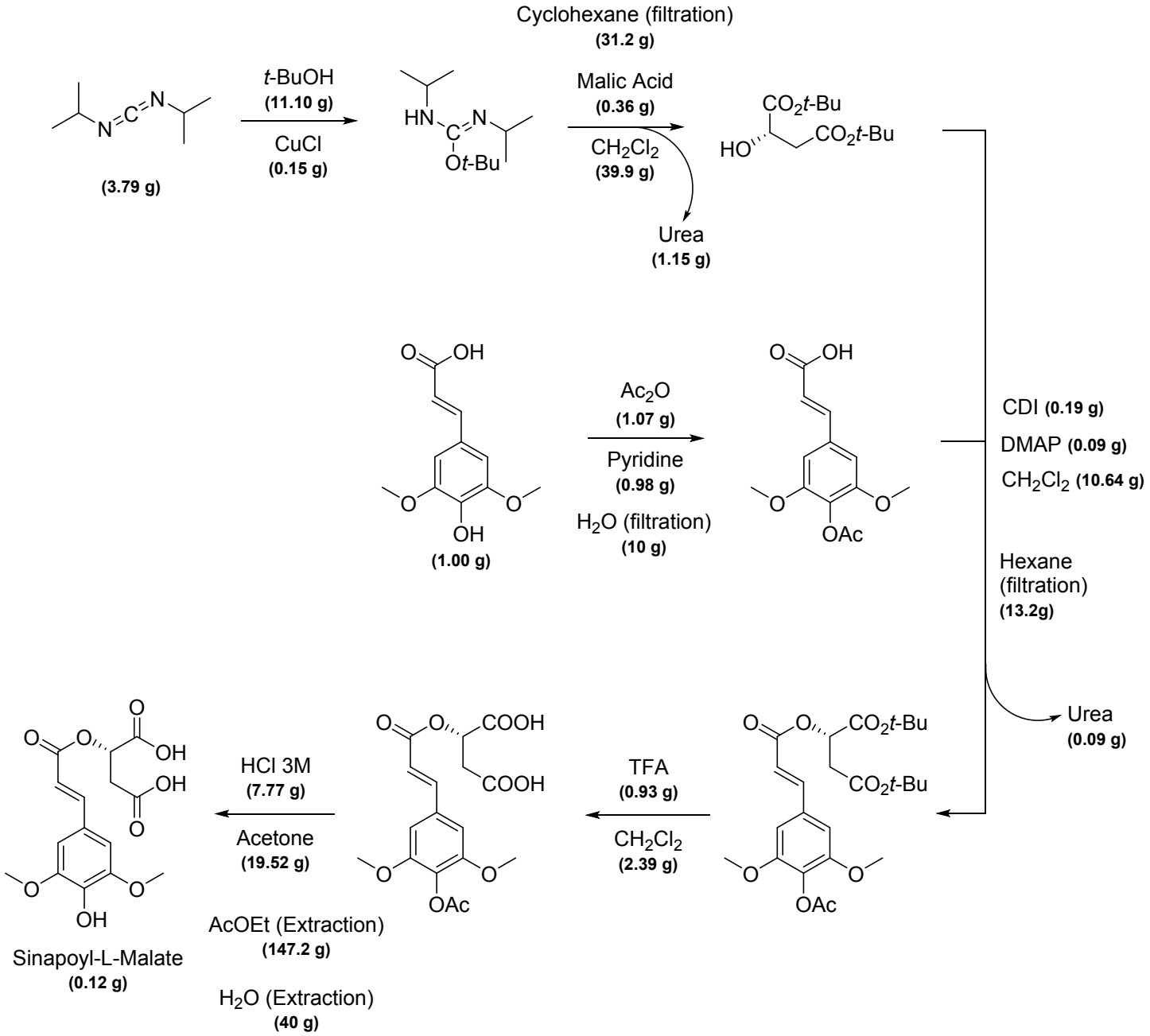
3.1. Equations

$$Atom\ Economy\ (\%) = 100 \times \frac{Mw_{product}}{\sum Mw_{reactants}}$$

$$Process\ Atom\ Economy\ (\%) = 100 \times \frac{m_{product}}{\sum m_{reactants}}$$

$$E - factor\ (g/g\ of\ product) = \frac{\sum m_{reactants} + \sum m_{catalyst} + \sum m_{solvants} + \sum m_{byproducts}}{m_{product}}$$

3.2. Green metrics for the synthetic pathway of *Allais et al.*

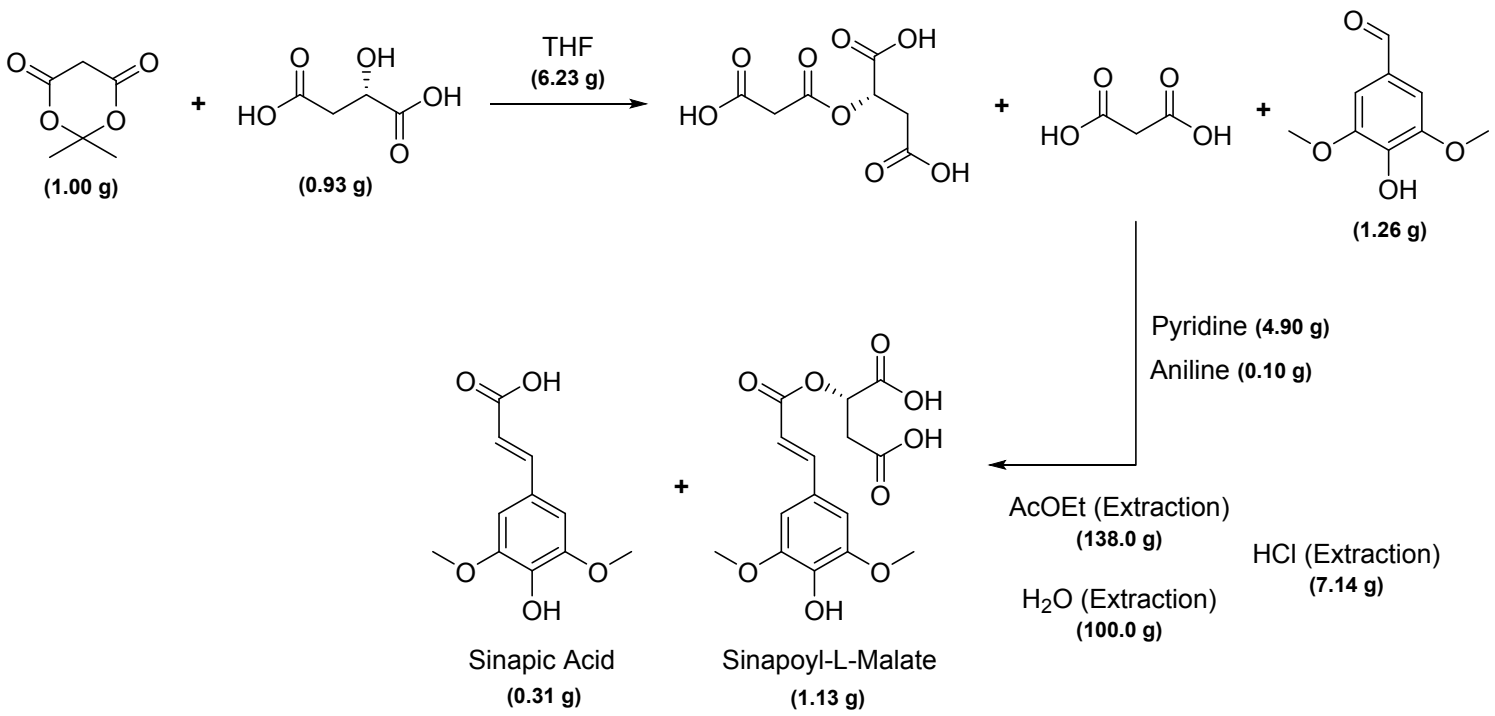


$$Atom\ Economy\ = 100 \times \frac{340.3}{126.2 + 99.0 + 74.1 + 134.1 + 224.2 + 102.1 + 126.2 + 122.3 + 114.0 + 36.5} = 29.4\%$$

$$Process\ Atom\ Economy\ = 100 \times \frac{0.12}{3.79 + 0.15 + 11.10 + 0.36 + 1.00 + 1.07 + 0.93 + 7.77} = 0.5\%$$

$$E-factor = \frac{3.79+0.15+11.10+0.36+39.9+31.2+1.15+1.00+1.07+0.98+10+0.19}{0.12}+\frac{0.09}{}$$
$$= 2809\ g/g\ of\ product$$

3.3. Green metrics for the synthetic pathway of *Peyrot et al.*



$$Atom\ Economy\ = 100 \times \frac{340.3}{144.13+134.1+182.2} = 73.9\%$$

$$Process\ Atom\ Economy\ = 100 \times \frac{1.13}{1.00+0.93+1.26} = 35.5\%$$

$$E-factor = \frac{1.00+0.93+6.23+1.26+4.9+0.10+138+100+7.14+0.31}{1.13} = 230\ g/g\ of\ product$$

4. Life Cycle Assessment (LCA)

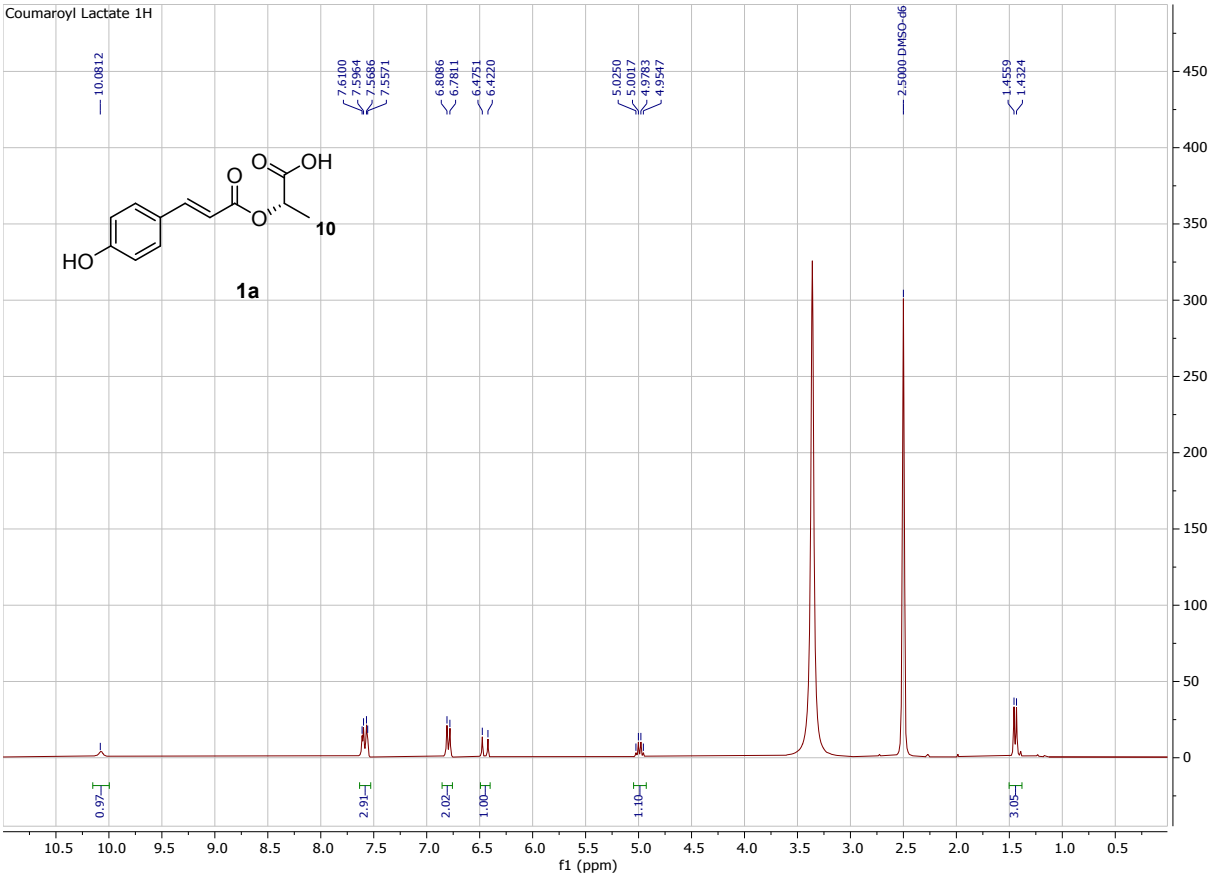
Goal, system description and methodology of feruloyl-L-malate life cycle assessment

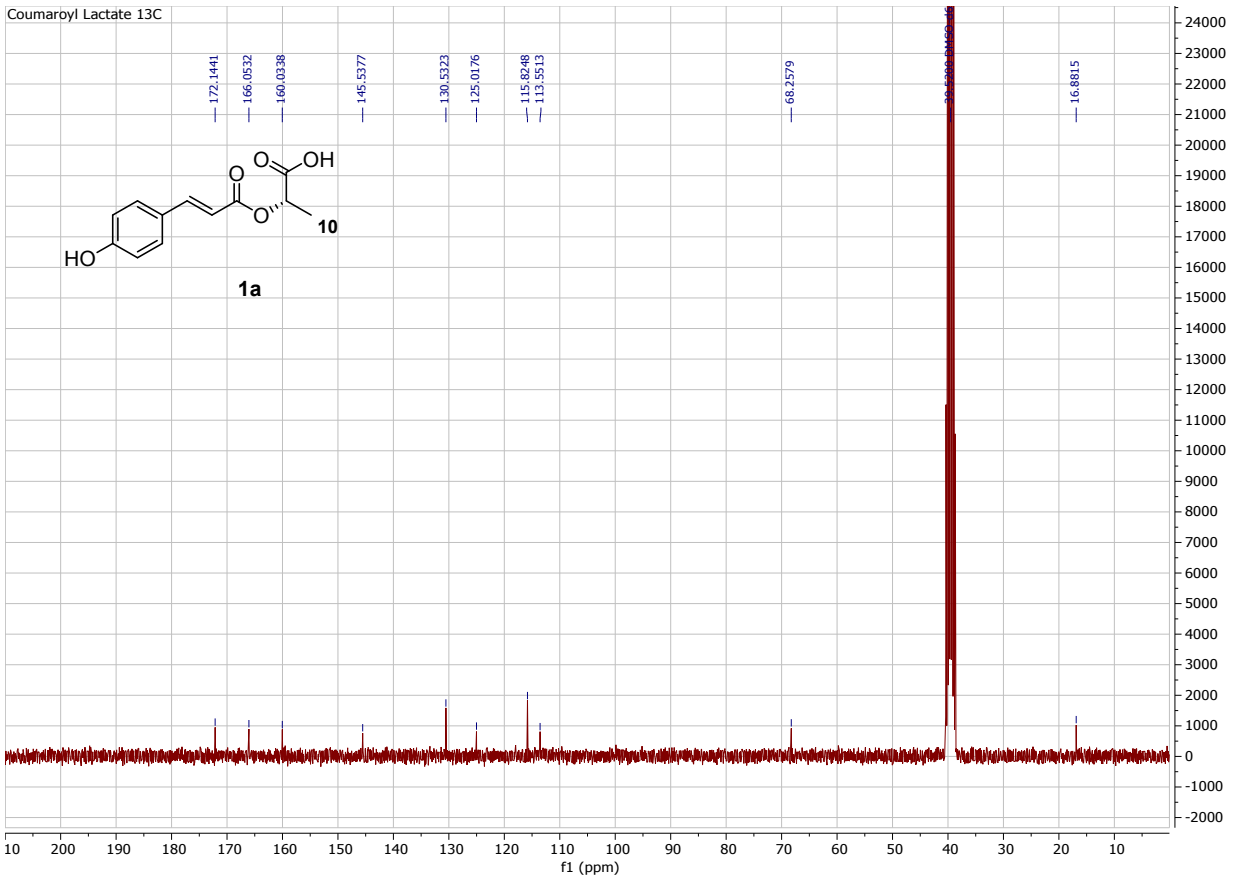
The data collection was carried out using experimental and bibliographic data (from European market of database). An in-depth study was carried out to determine the industrial production methods of the various reagents. In particular for the case of malic acid (from malic anhydride obtained by oxidation of n-butane) and for Meldrum's acid (obtained with malonic acid and acetone). The feruloyl malate LCA has been performed using openLCA software and EcoInvent 3.4 database. Environmental impacts were calculated with CML 2001 (from Leiden University). 4 indicators from baseline database have been selected:

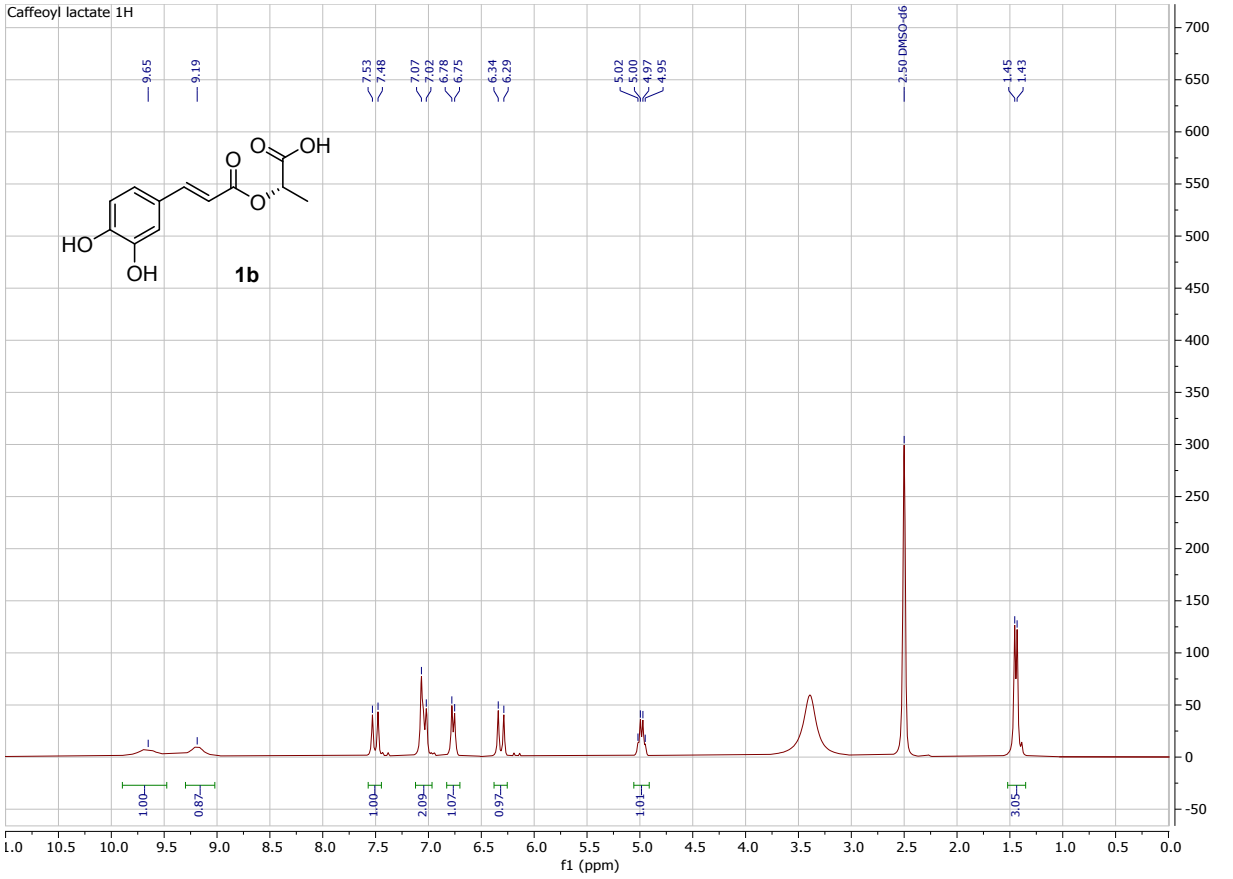
- Climate change: This is the temperature increase in the lower atmosphere and results of greenhouse gases emission such as methane, nitrogen dioxide and carbon dioxide. All these gases are converted in CO_2 equivalent using the global warming potential (GWP) provided by IPCC as conversion factor, expressed in kg of CO_2 equivalent.

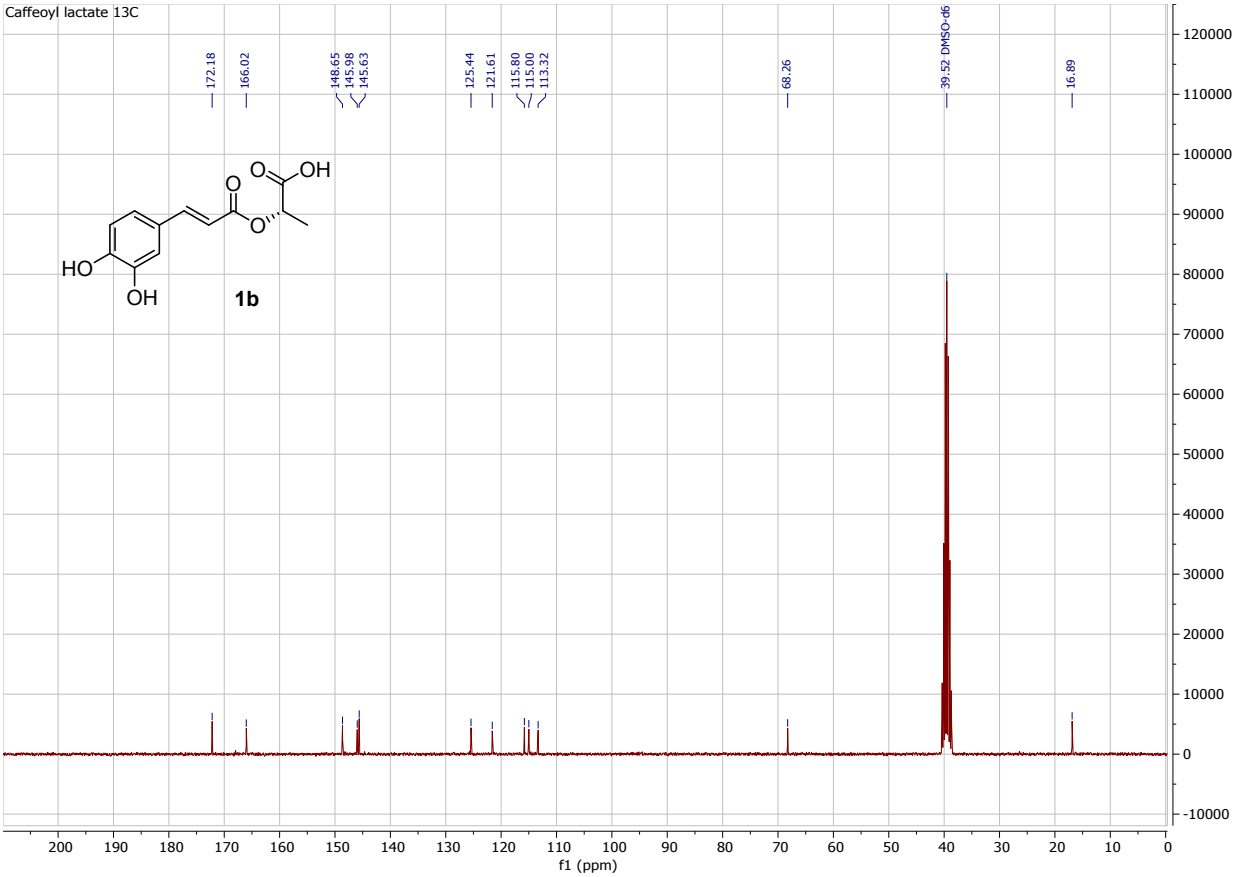
- Human toxicity: This category covers the impact on human health of toxic substances present in the environment. The effect is induced by the dose of pollutant received (inhaled or ingested) by an individual person and not by its concentration in the environment. All pollutants have been converted with Uniform System for the Evaluation of Substances adapted for LCA purposes (USES-LCA) in 1,4-dichlorobenzene (1,4DCB) equivalent.
- Marine aquatic ecotoxicity: This indicator refers to the impact of toxic substances on marine ecosystem, as a result of substance emission to the air, water and soil. This indicator has been calculated with USES-LCA and expressed as 1,4DCB equivalent.
- Terrestrial ecotoxicity: It refers to the impact of toxic substances on terrestrial ecosystem. This indicator has been calculated with USES-LCA and expressed as 1,4DCB equivalent.

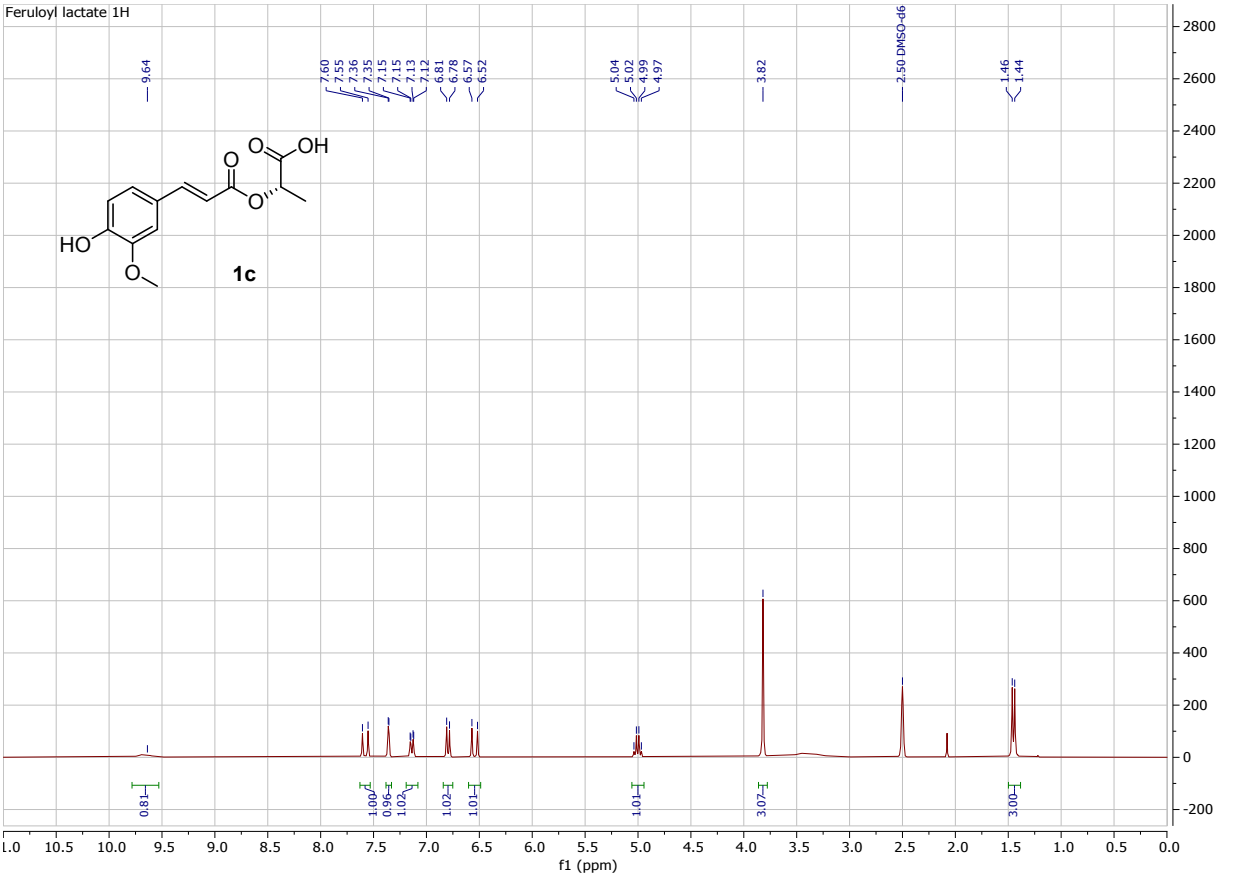
5. ^{1}H & ^{13}C NMR spectra

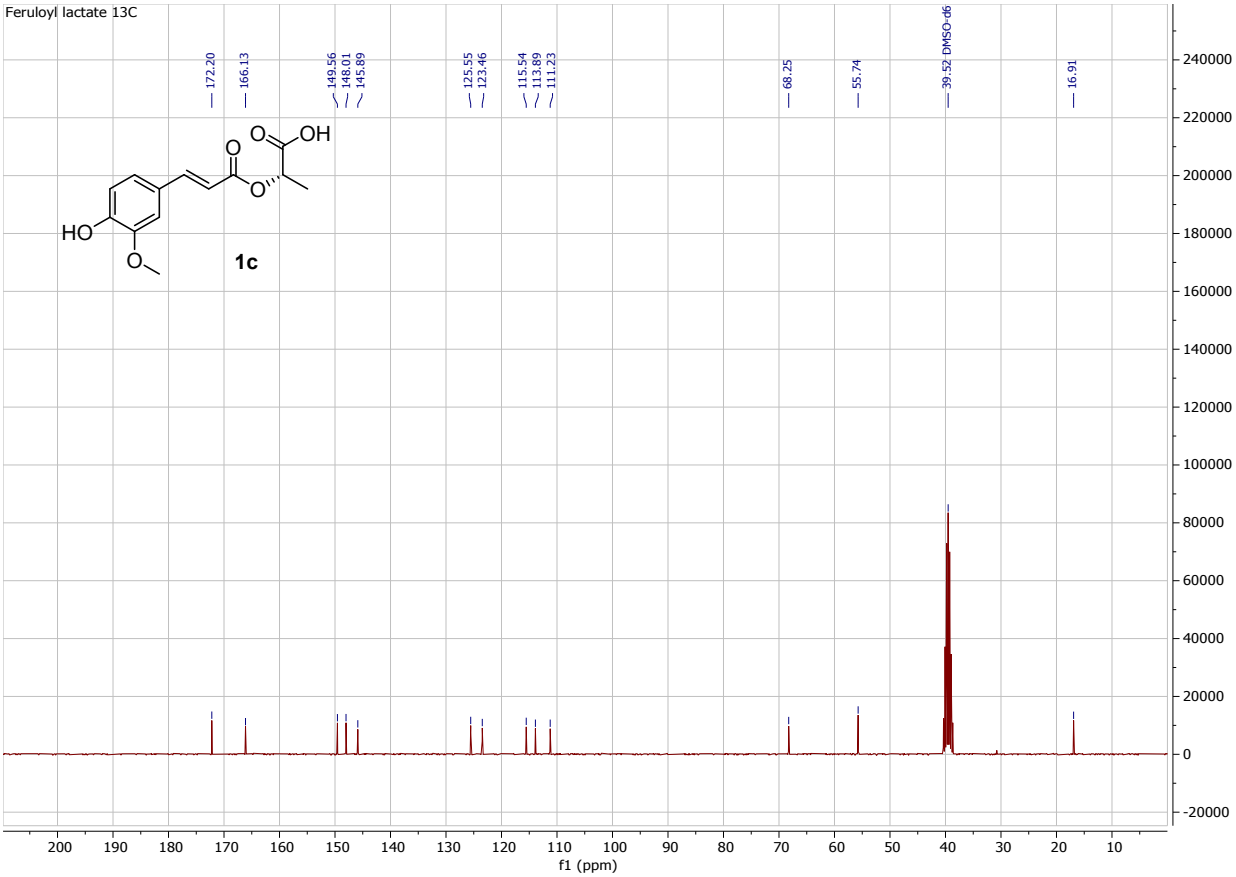


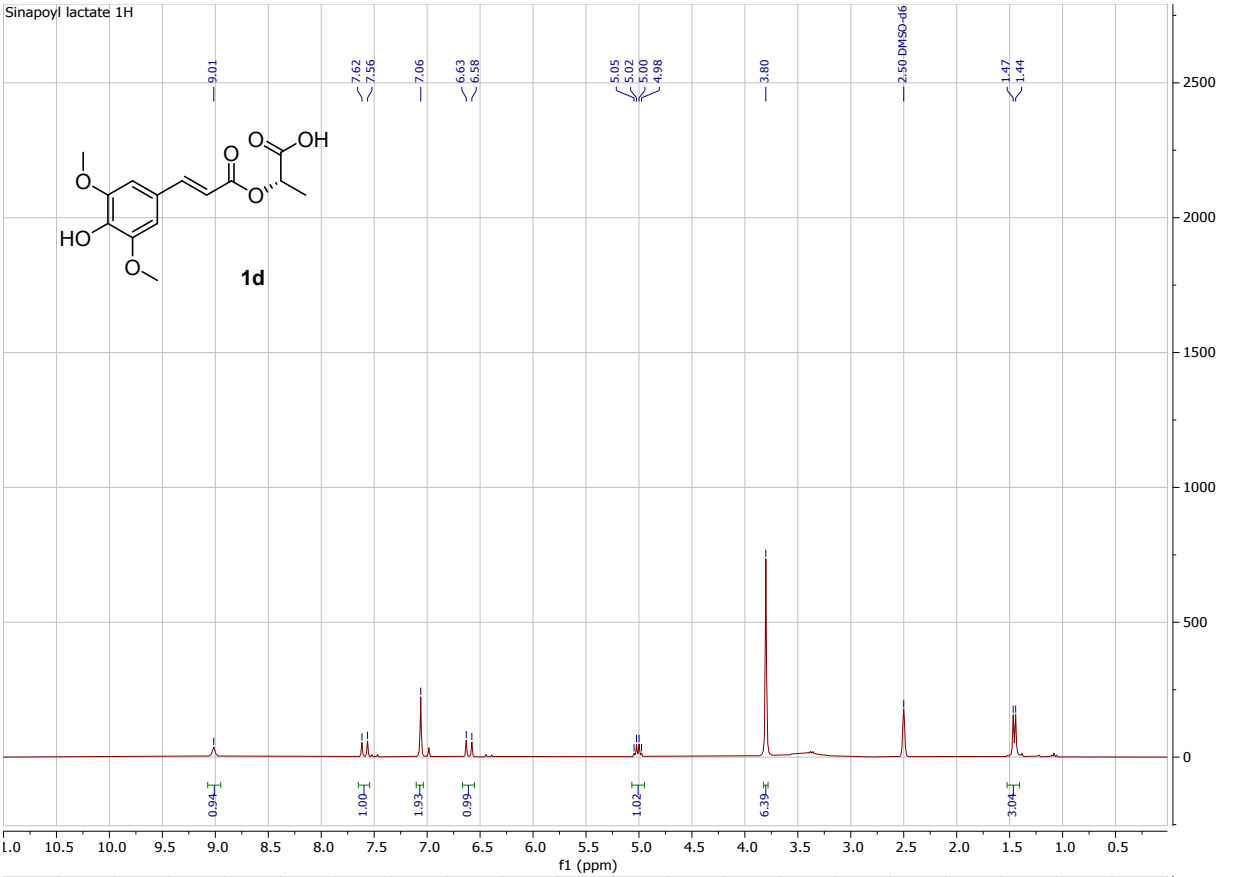

Coumaroyl Lactate 13C
172.1441
166.0532
160.0338
145.5377
130.5323
125.0176
115.8248
113.5513
68.2579
16.8815
HO
O
O
OH
10
1a
f1 (ppm)

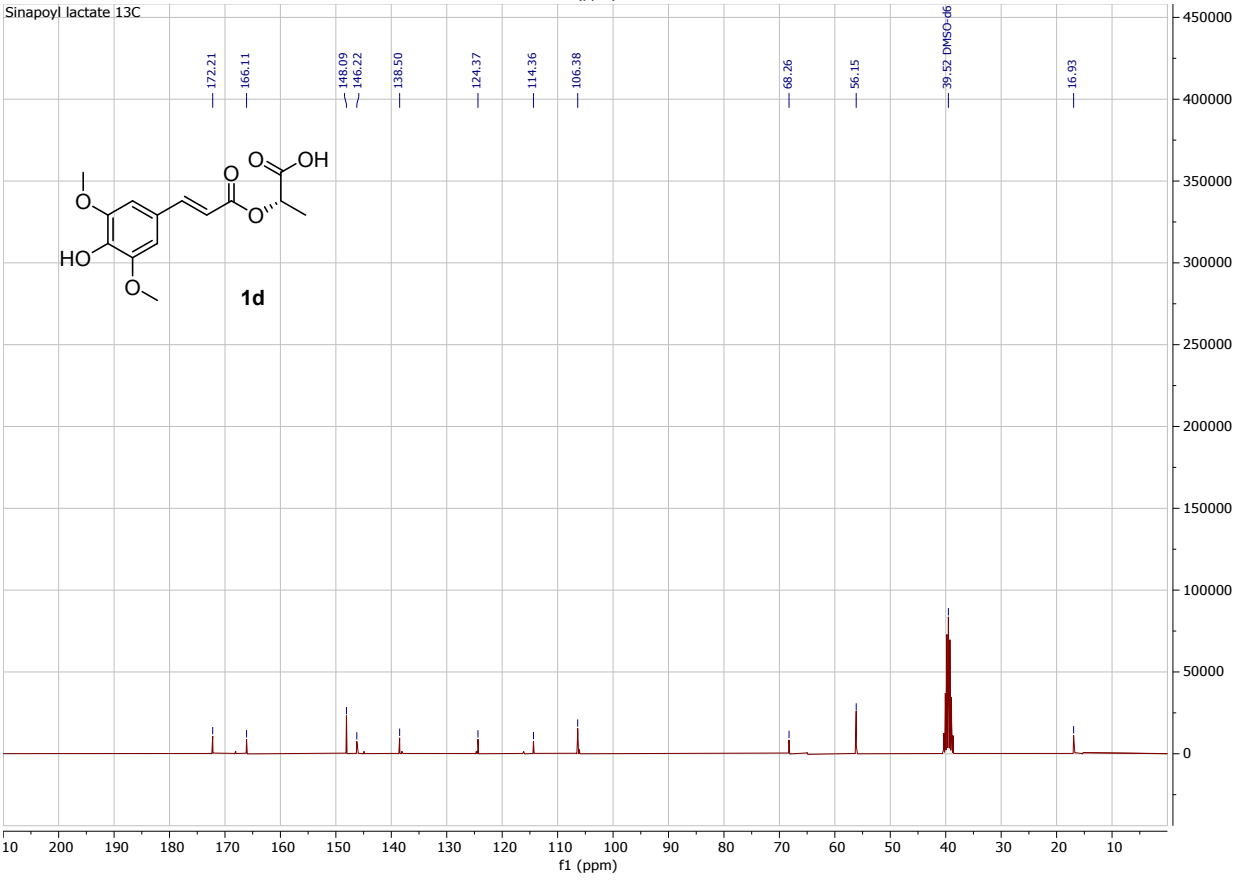

Caffeoyl lactate 1H
9.65
9.19
7.53
7.48
7.07
7.02
6.78
6.75
6.34
6.29
5.02
5.00
4.97
4.95
2.50 DMSO-d6
1.45
1.43
HO
OH
O
O
OH
1b
1.00
0.87
1.00
2.09
1.07
0.97
1.01
3.05
f1 (ppm)

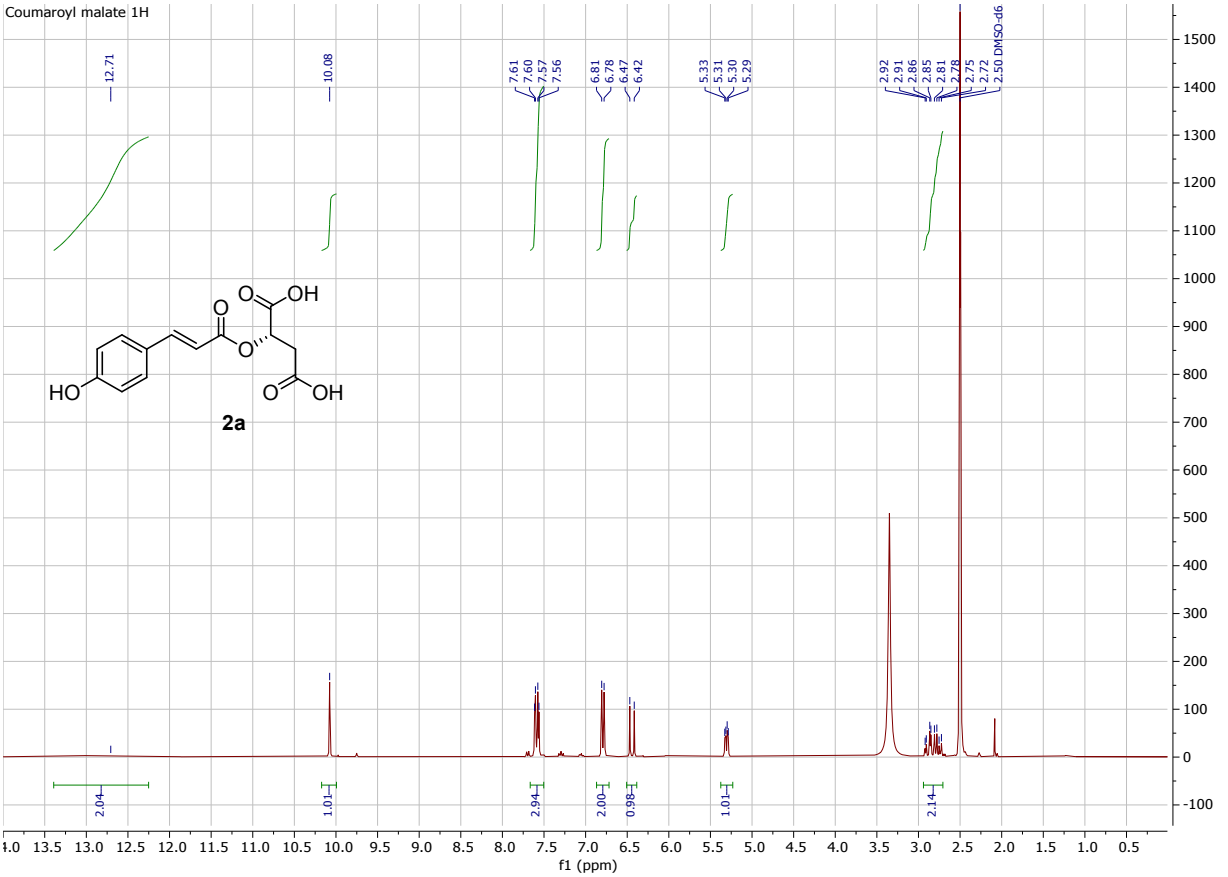

Caffeoyl lactate 13C
172.18
166.02
148.65
145.98
145.63
125.44
121.61
115.80
115.00
113.32
68.26
39.52 DMSO-d6
16.89
HO
OH
O
OH
O
1b
f1 (ppm)

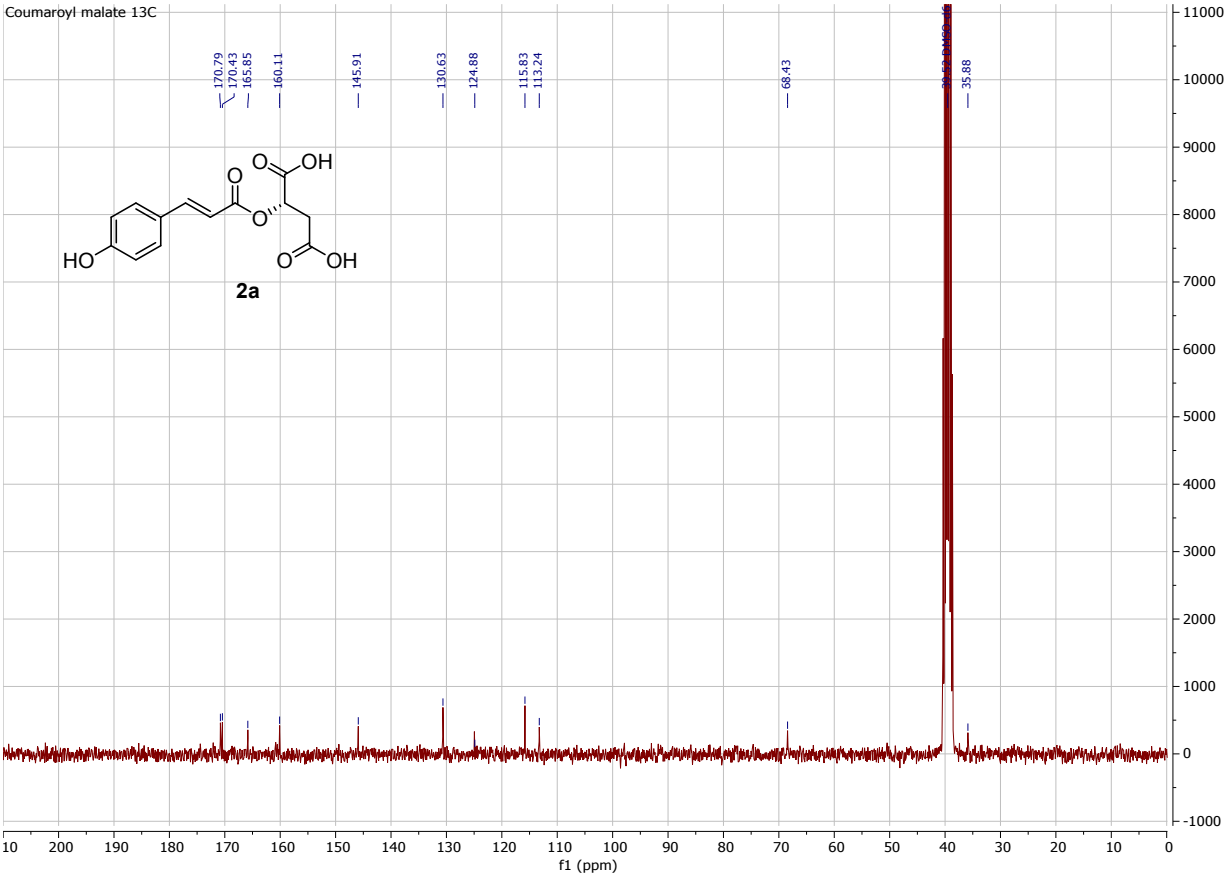

Feruloyl lactate 1H
9.64
7.60
7.55
7.36
7.35
7.15
7.15
7.13
7.12
6.81
6.78
6.57
6.52
5.04
5.02
4.99
4.97
3.82
2.50 DMSO-d6
1.46
1.44
HO
O
OH
O
O
1c
0.81
1.00
0.96
1.02
1.02
1.01
1.01
3.07
3.00
f1 (ppm)

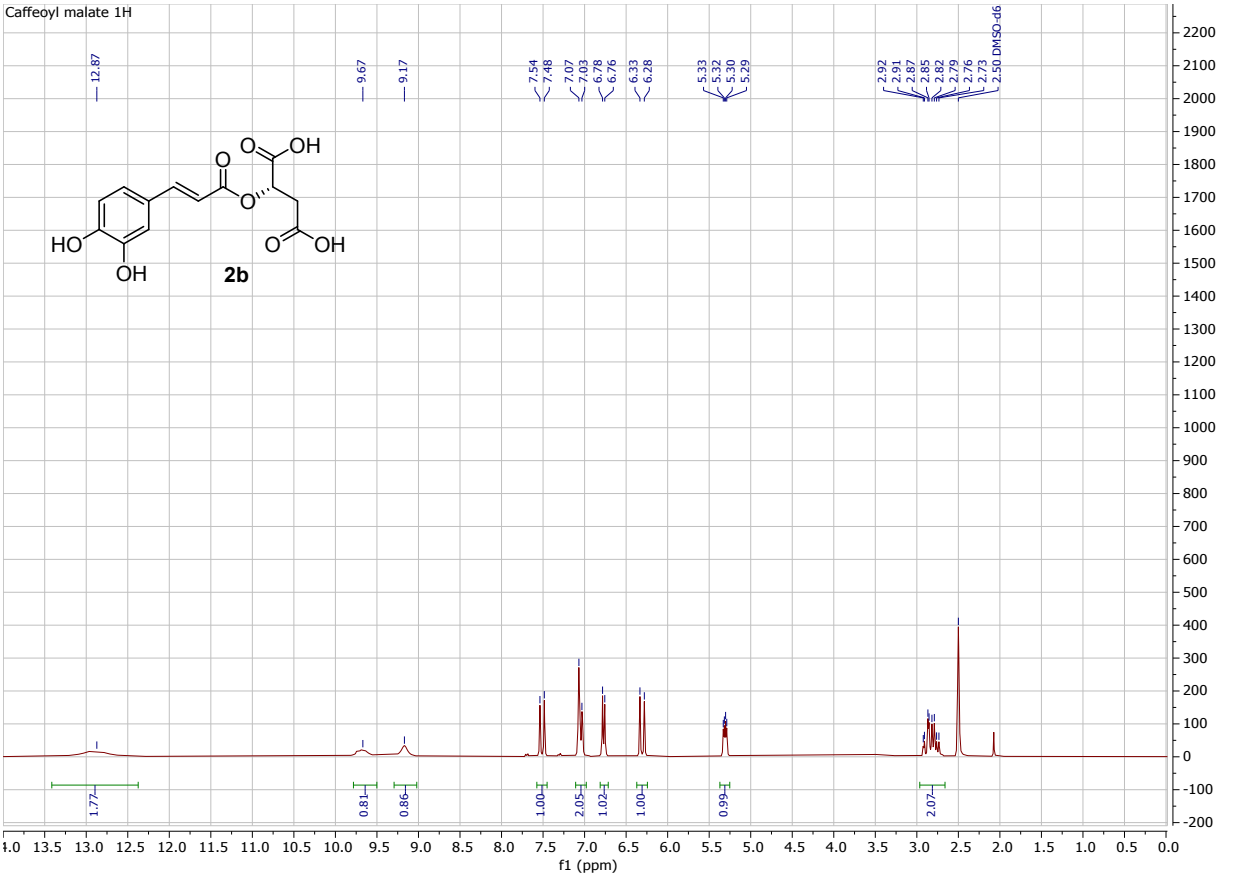

Feruloyl lactate 13C
172.20
166.13
149.56
148.01
145.89
125.55
123.46
115.54
113.89
111.23
68.25
55.74
39.52 DMSO-d6
16.91
O
OH
O
O
HO
O
1c
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

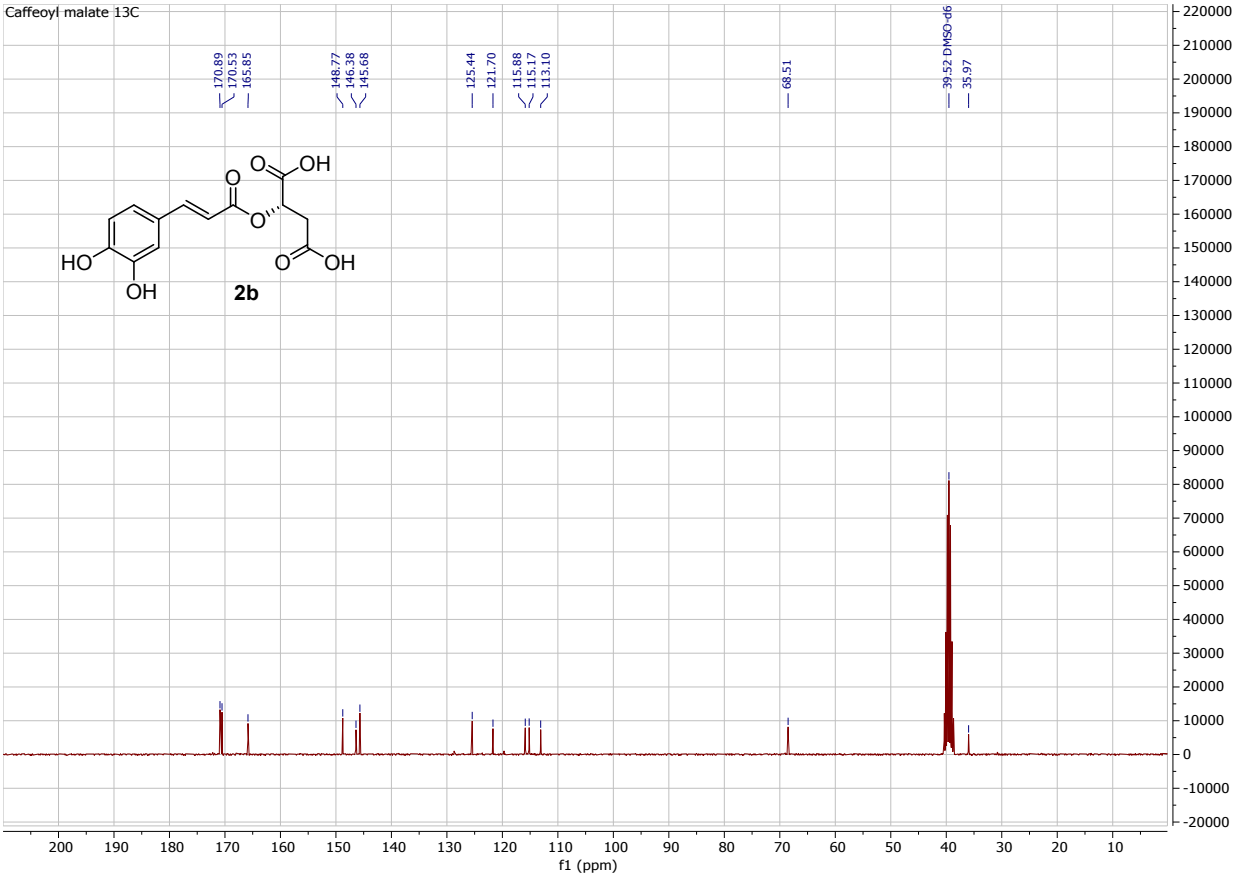

Sinapoyl lactate 1H
9.01
7.62
7.56
7.06
6.63
6.58
5.05
5.02
5.00
4.98
3.80
2.50 DMSO-d6
1.47
1.44
0.94
1.00
1.93
0.99
1.02
6.39
3.04
f1 (ppm)
1d

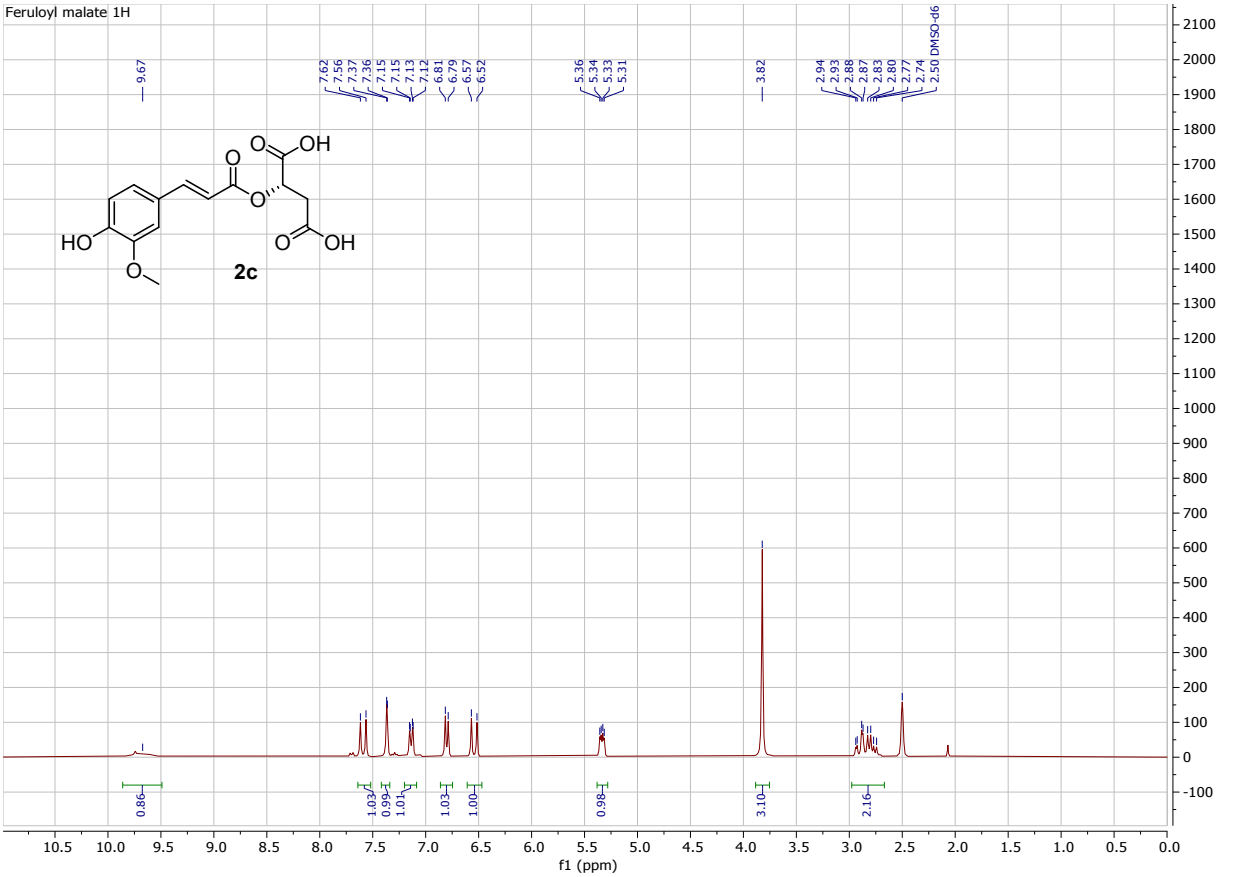

Sinapoyl lactate 13C
172.21
166.11
148.09
146.22
138.50
124.37
114.36
106.38
68.26
56.15
39.52 DMSO-d6
16.93
f1 (ppm)
1d

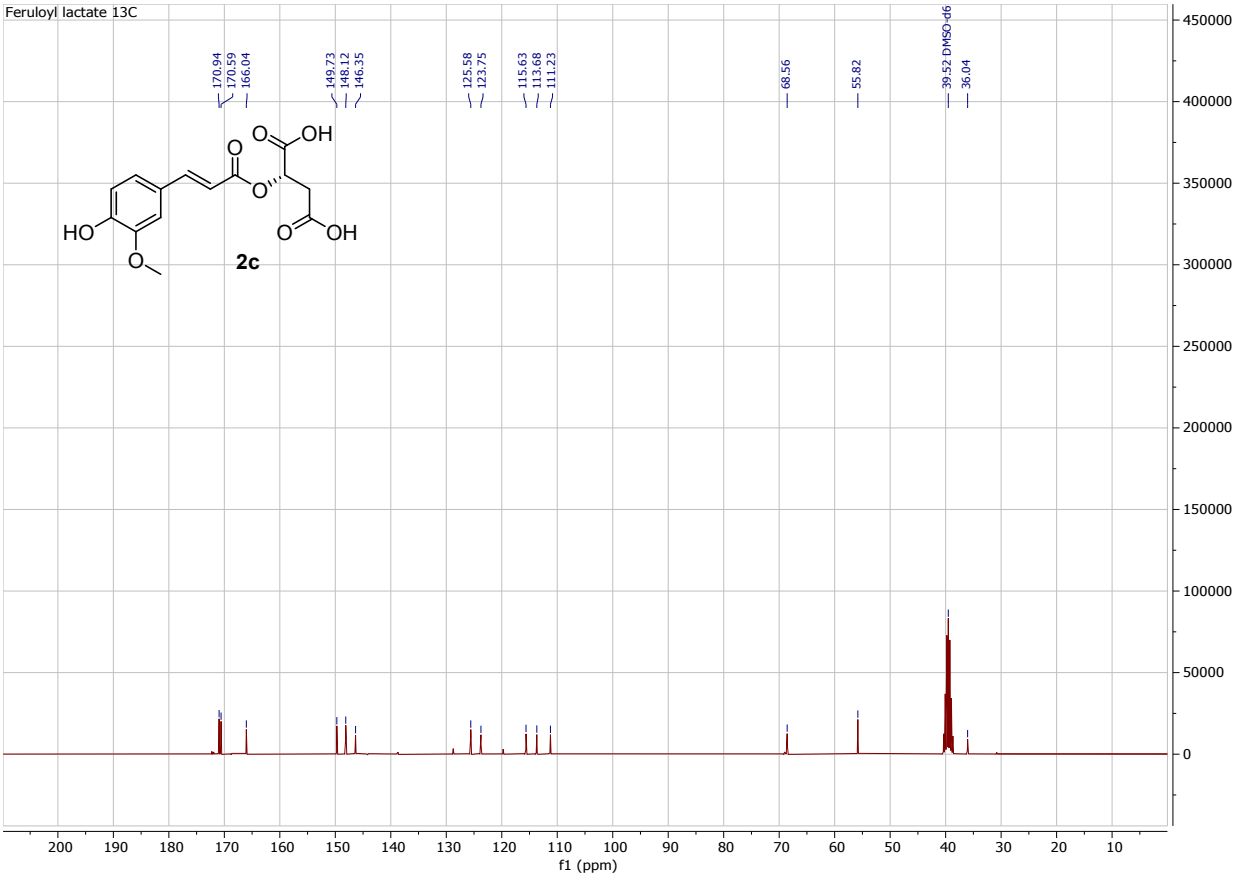

Coumaroyl malate 1H
12.71
10.08
7.61
7.60
7.57
7.56
6.81
6.78
6.47
6.42
5.33
5.31
5.30
5.29
2.92
2.91
2.86
2.85
2.81
2.78
2.75
2.72
2.50 DMSO-d6
HO
O
OH
2a
2.04
1.01
2.94
2.00
0.98
1.01
2.14
f1 (ppm)

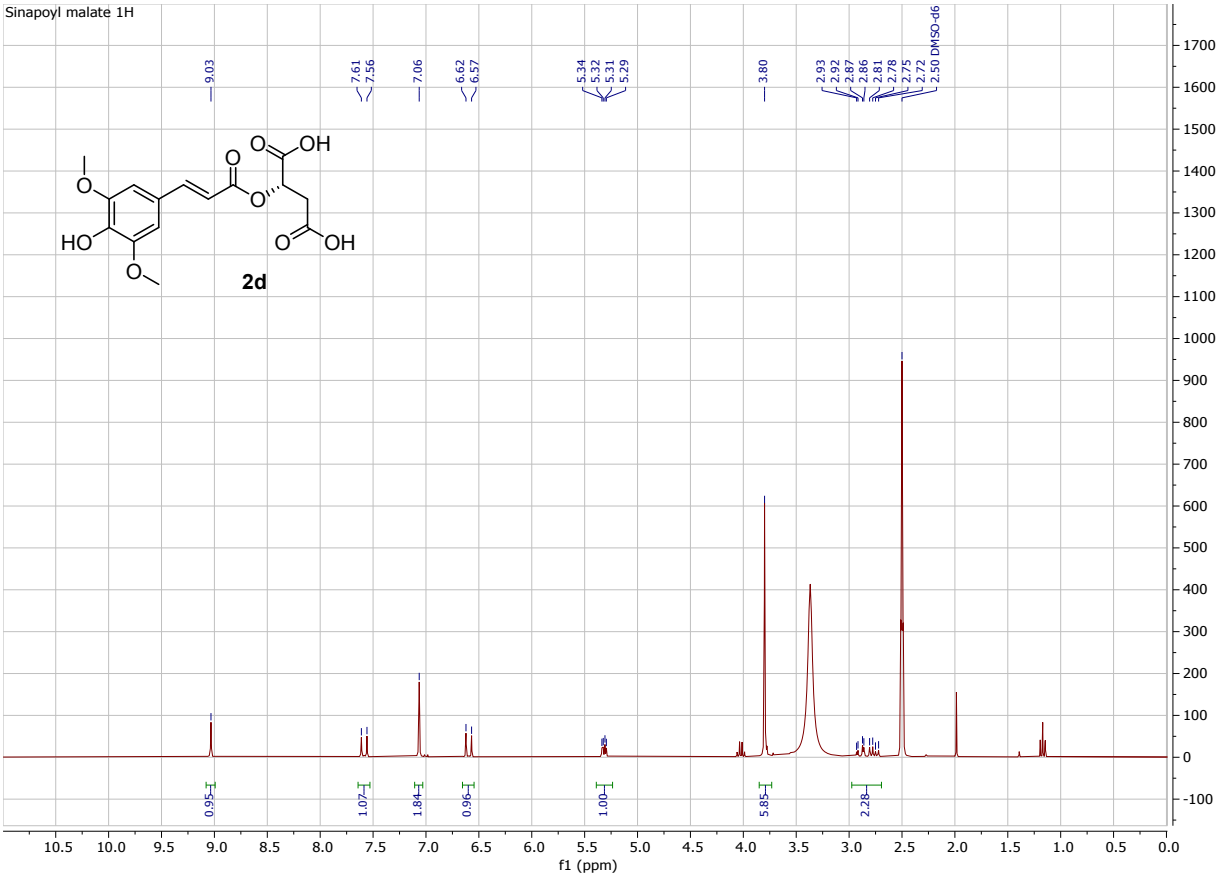

Coumaroyl malate 13C
170.79
170.43
165.85
160.11
145.91
130.63
124.88
115.83
113.24
68.43
35.88
HO
O
OH
2a
f1 (ppm)

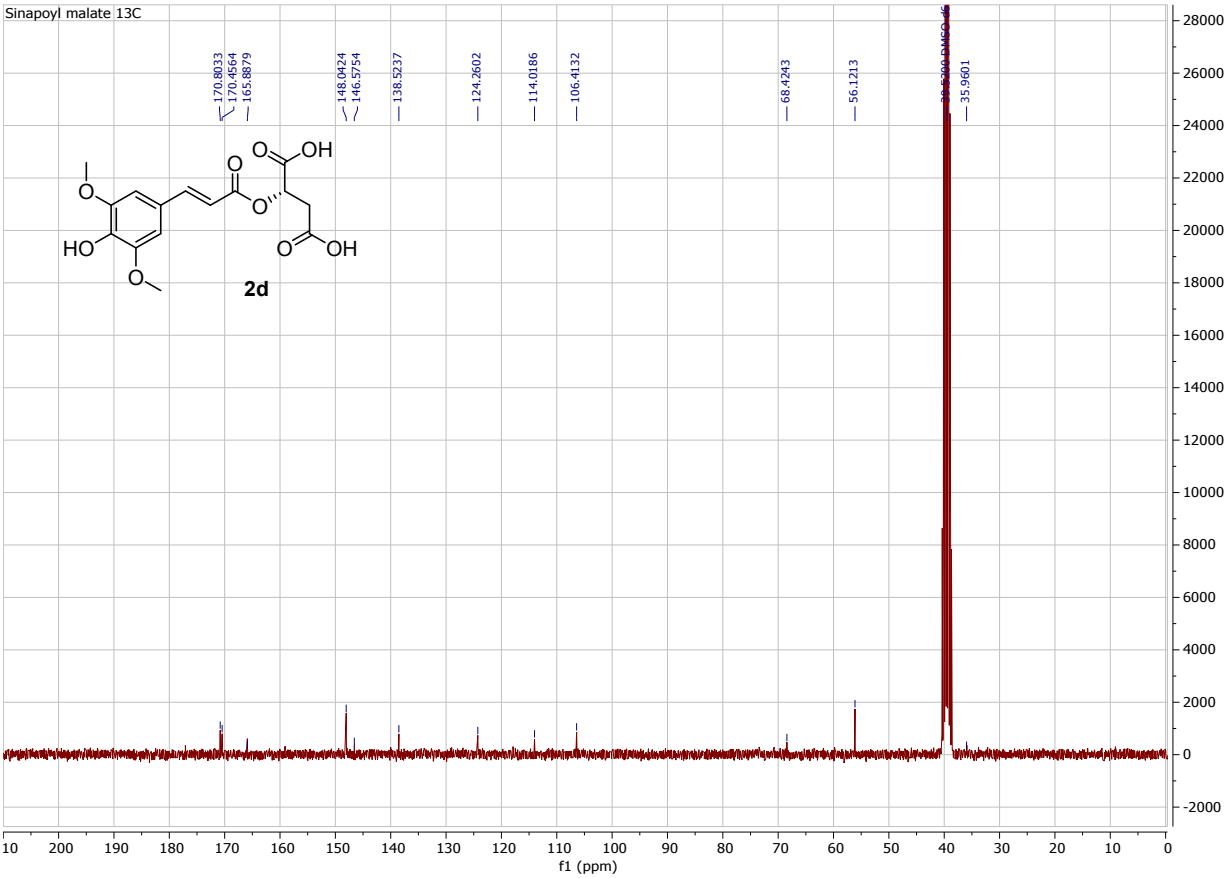

Caffeoyl malate 1H
12.87
9.67
9.17
7.54
7.48
7.07
7.03
6.78
6.76
6.33
6.28
5.33
5.32
5.30
5.29
2.92
2.91
2.87
2.85
2.82
2.79
2.76
2.73
2.50 DMSO-d6
HO
OH
O
OH
O
O
OH
2b
1.77
0.81
0.86
1.00
2.05
1.02
1.00
0.99
2.07
f1 (ppm)

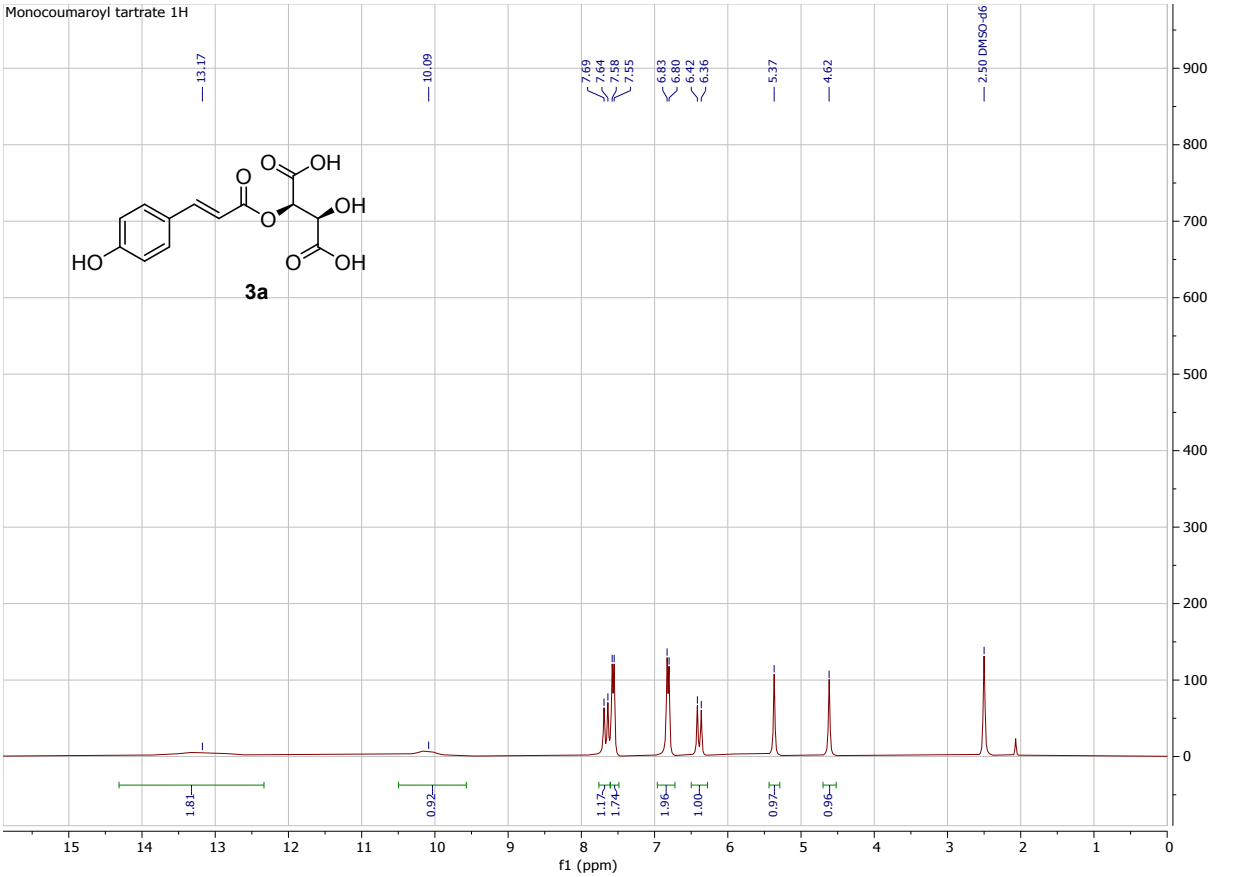

Caffeoyl malate 13C
170.89
170.53
165.85
148.77
146.38
145.68
125.44
121.70
115.88
115.17
113.10
68.51
39.52 DMSO-d6
35.97
HO
OH
O
OH
O
O
OH
2b
f1 (ppm)

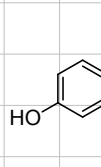

Feruloyl malate 1H
9.67
7.62
7.56
7.37
7.36
7.15
7.15
7.13
7.12
6.81
6.79
6.57
6.52
5.36
5.34
5.33
5.31
3.82
2.94
2.93
2.88
2.87
2.83
2.80
2.77
2.74
2.50 DMSO-d6
HO
O
OH
O
O
O
OH
2c
0.86
1.03
0.99
1.01
1.03
1.00
0.98
3.10
2.16
f1 (ppm)


Feruloyl lactate 13C
170.94
170.59
166.04
149.73
148.12
146.35
125.58
123.75
115.63
113.68
111.23
68.56
55.82
39.52 DMSO-d6
36.04
HO
O
OH
O
O
O
OH
2c
f1 (ppm)


Sinapoyl malate 1H
9.03
7.61
7.56
7.06
6.62
6.57
5.34
5.32
5.31
5.29
3.80
2.93
2.92
2.87
2.86
2.81
2.78
2.75
2.72
2.50 DMSO-d6
2d
0.95
1.07
1.84
0.96
1.00
5.85
2.28
f1 (ppm)

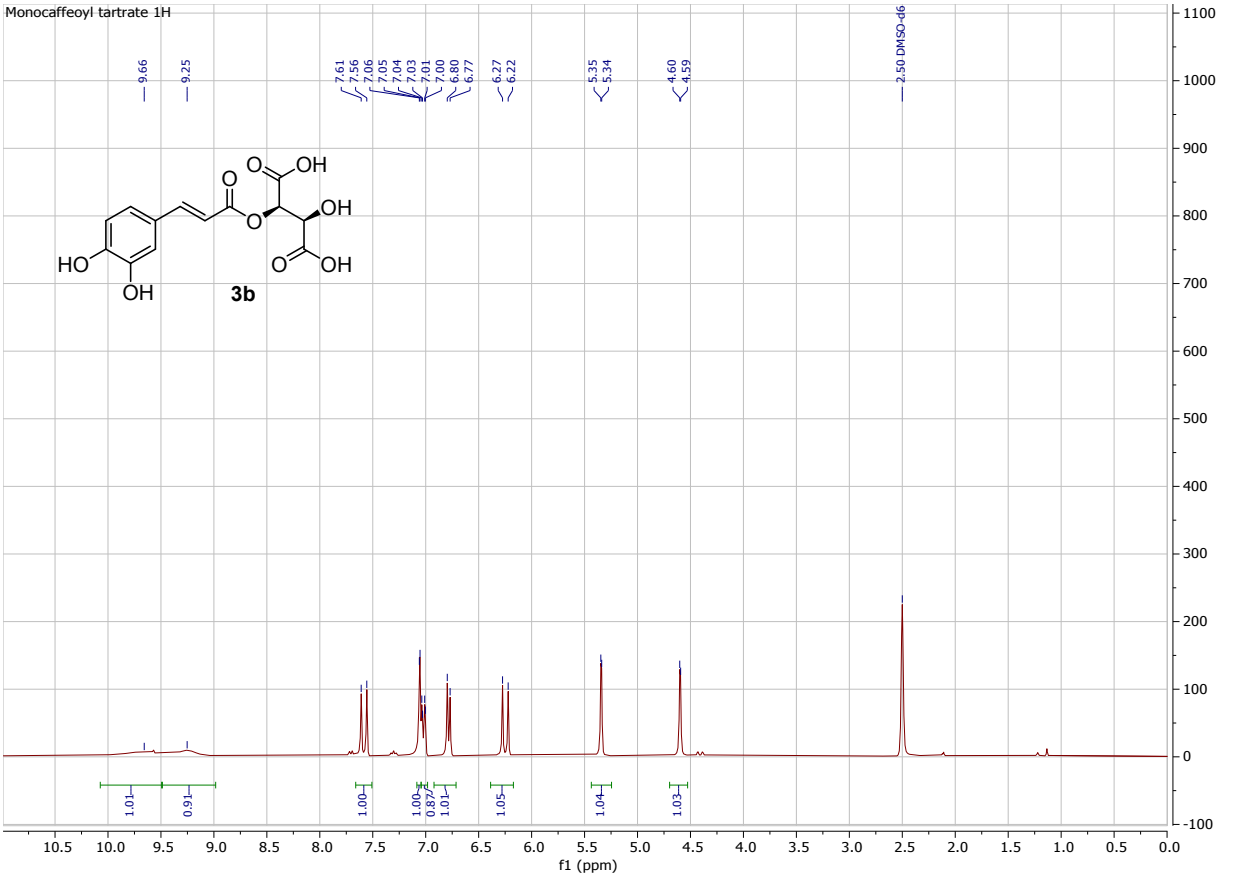

Sinapoyl malate 13C
170.8033
170.4564
165.8879
148.0424
146.5754
138.5237
124.2602
114.0186
106.4132
68.4243
56.1213
39.5200 DMSO-d6
35.9601
2d
f1 (ppm)

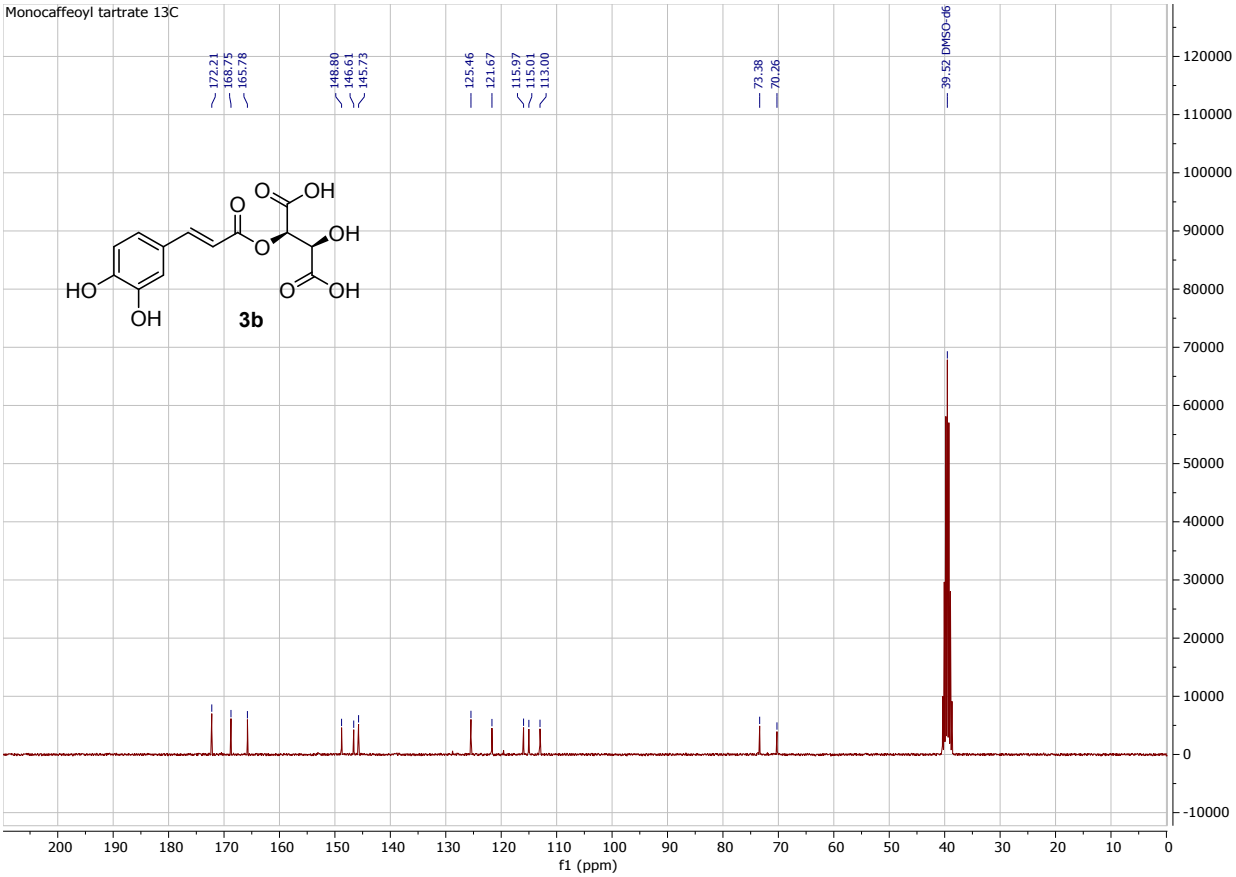

Monocoumaroyl tartrate 1H
13.17
10.09
7.69
7.64
7.58
7.55
6.83
6.80
6.42
6.36
5.37
4.62
2.50 DMSO-d6
1.81
0.92
1.17
1.74
1.96
1.00
0.97
0.96
f1 (ppm)

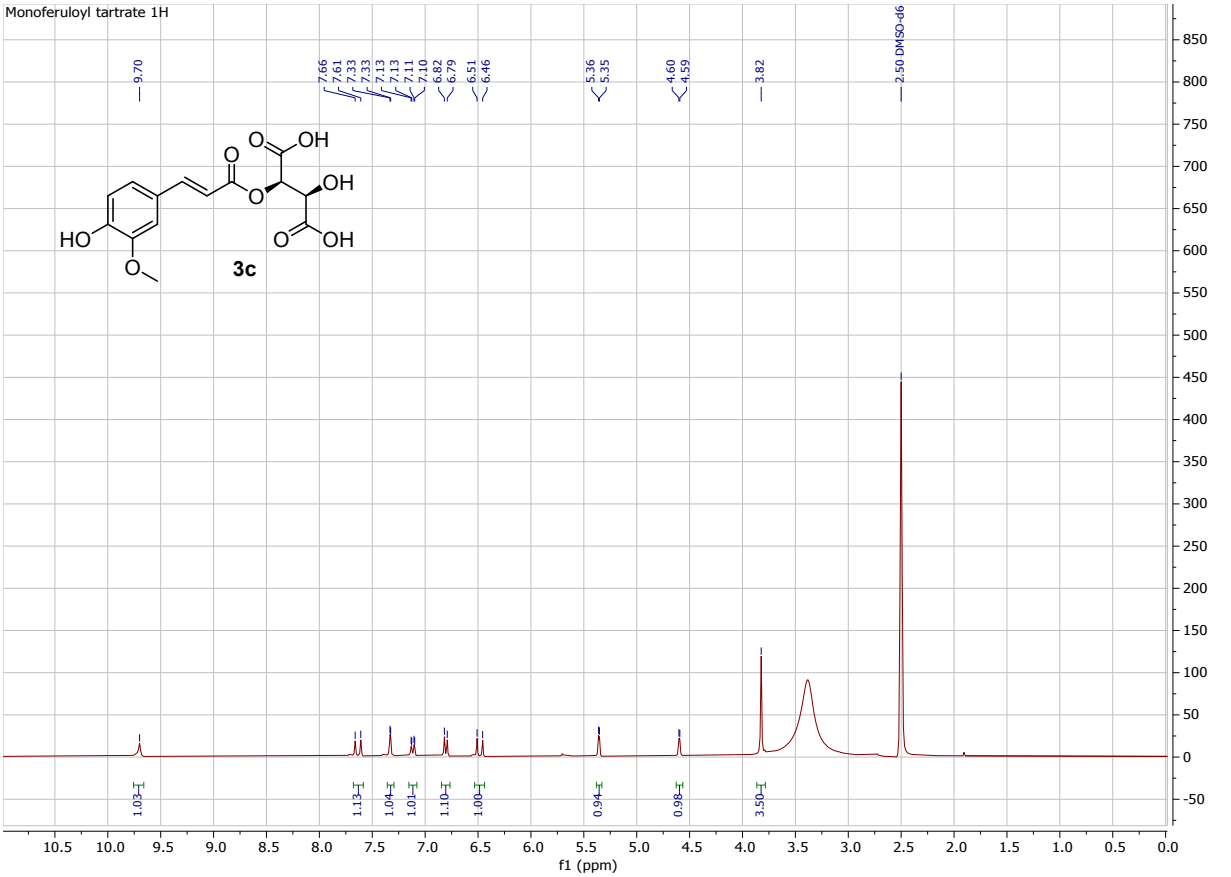

3a

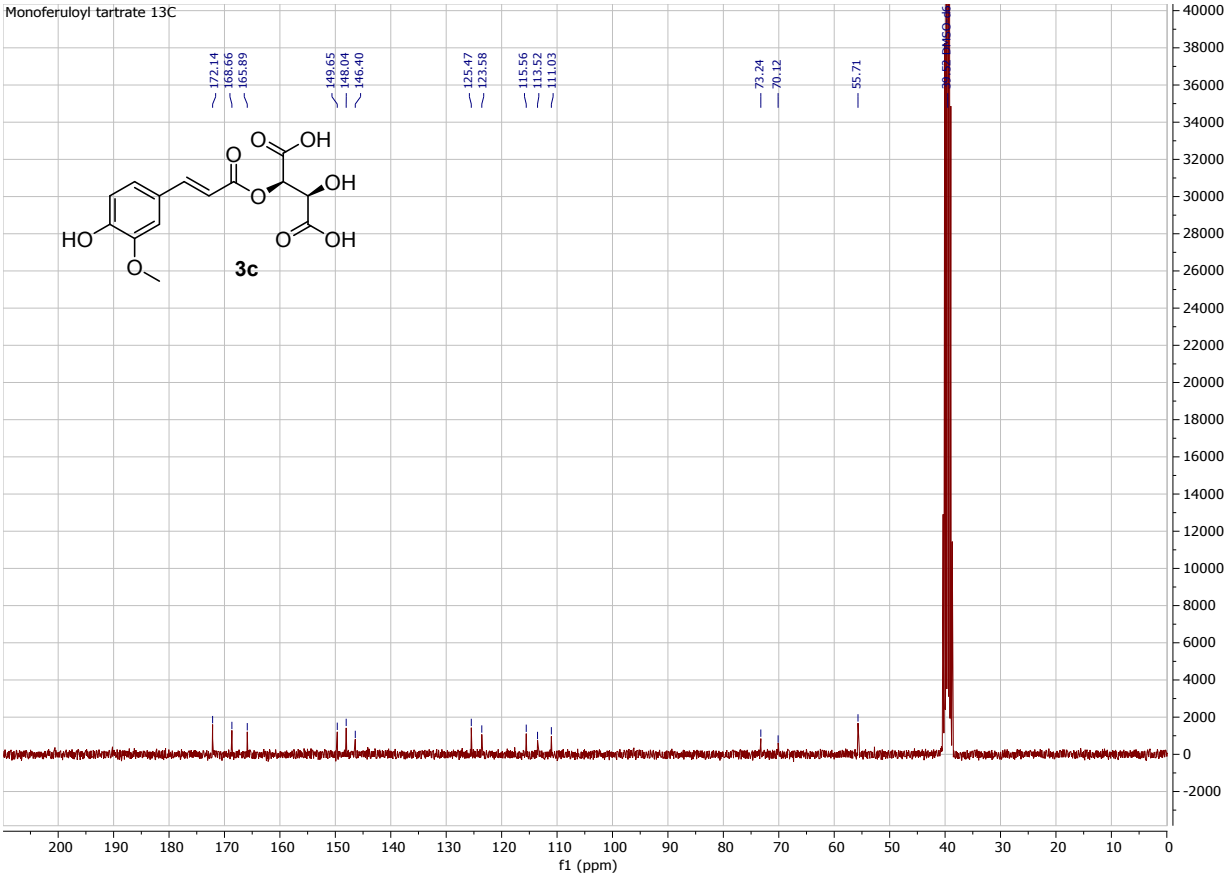
Monocoumaroyl tartrate 13C
172.23
168.76
165.91
160.24
146.24
130.66
125.06
116.03
113.25
73.40
70.25
39.52 DMSO-d6
f1 (ppm)

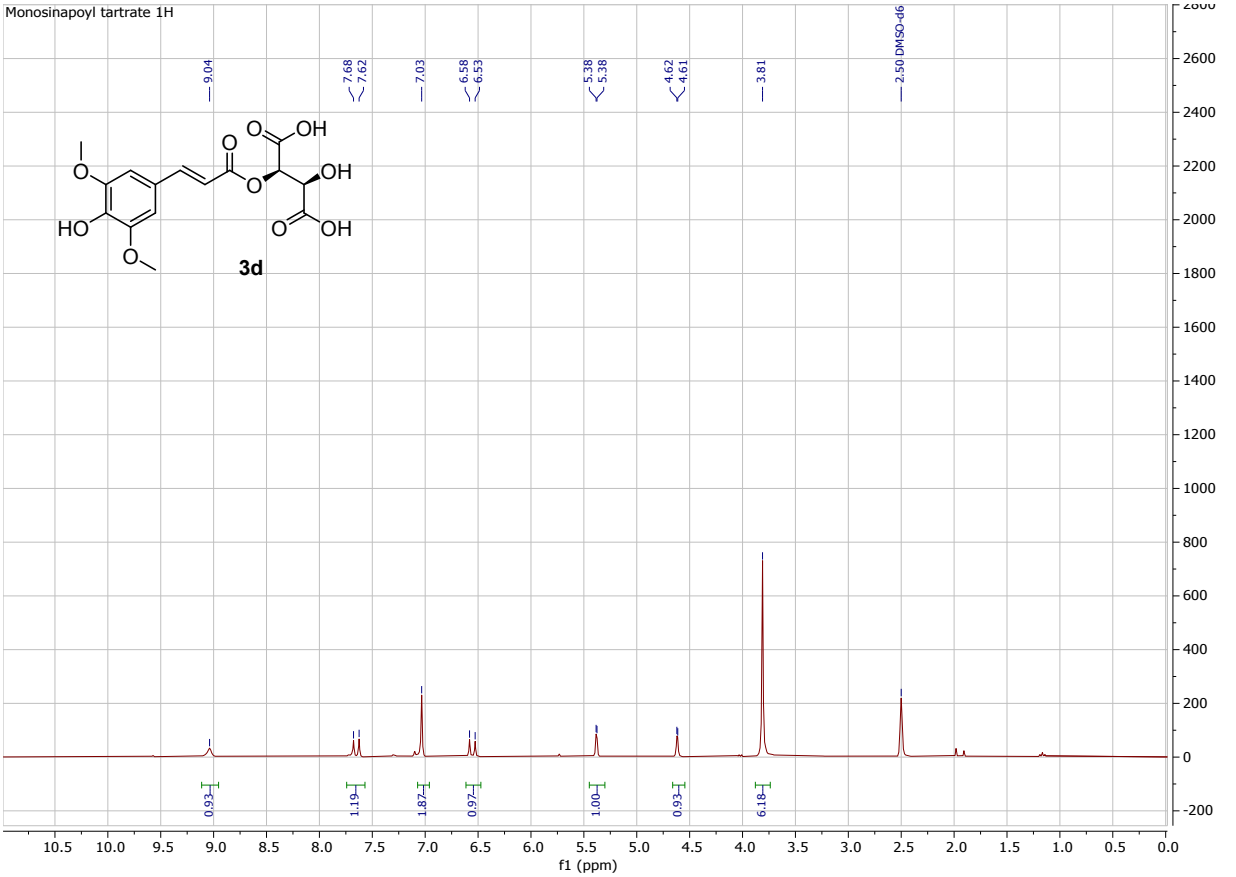
3a

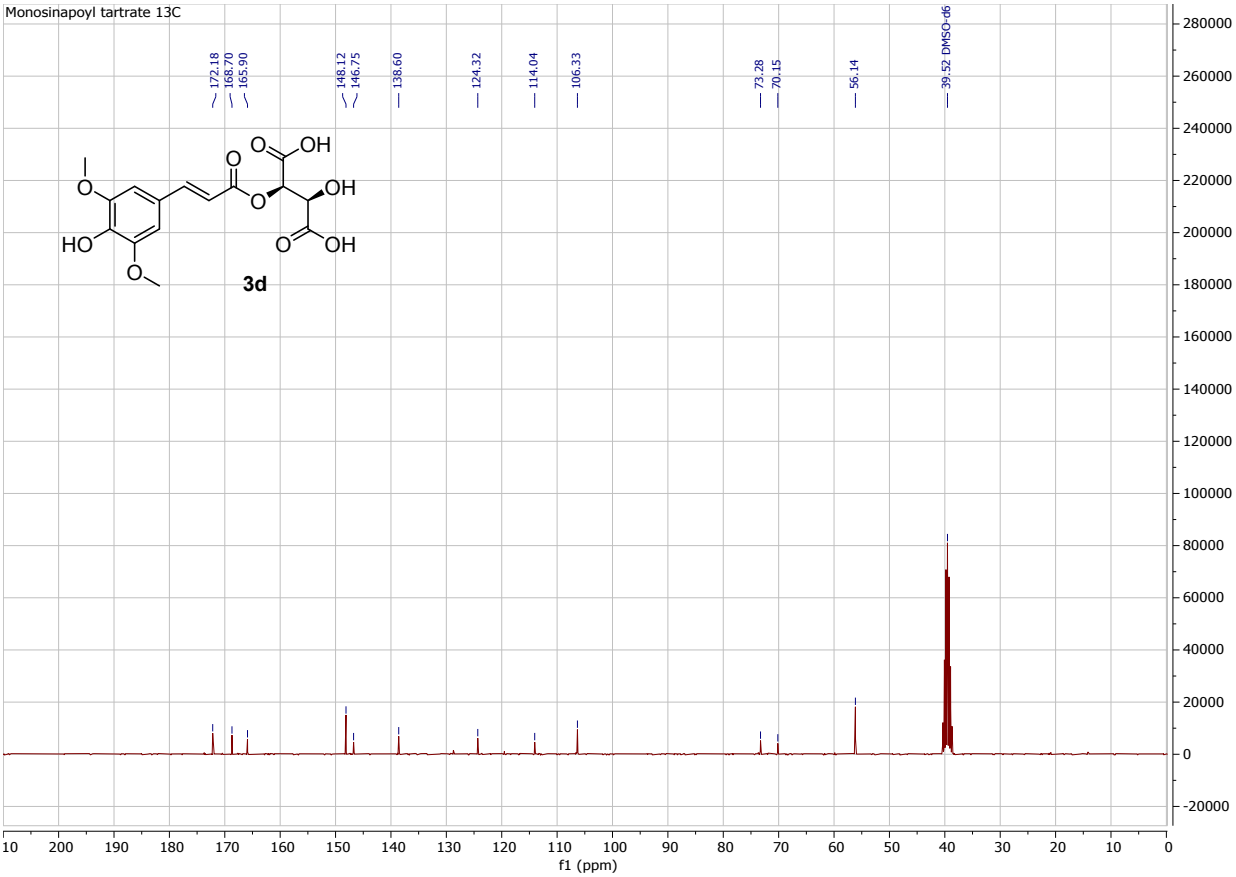

Monocaffeoyl tartrate 1H
9.66
9.25
7.61
7.56
7.06
7.05
7.04
7.03
7.01
7.00
6.80
6.77
6.27
6.22
5.35
5.34
4.60
4.59
2.50 DMSO-d6
3b
1.01
0.91
1.00
1.00
0.87
1.01
1.05
1.04
1.03
f1 (ppm)

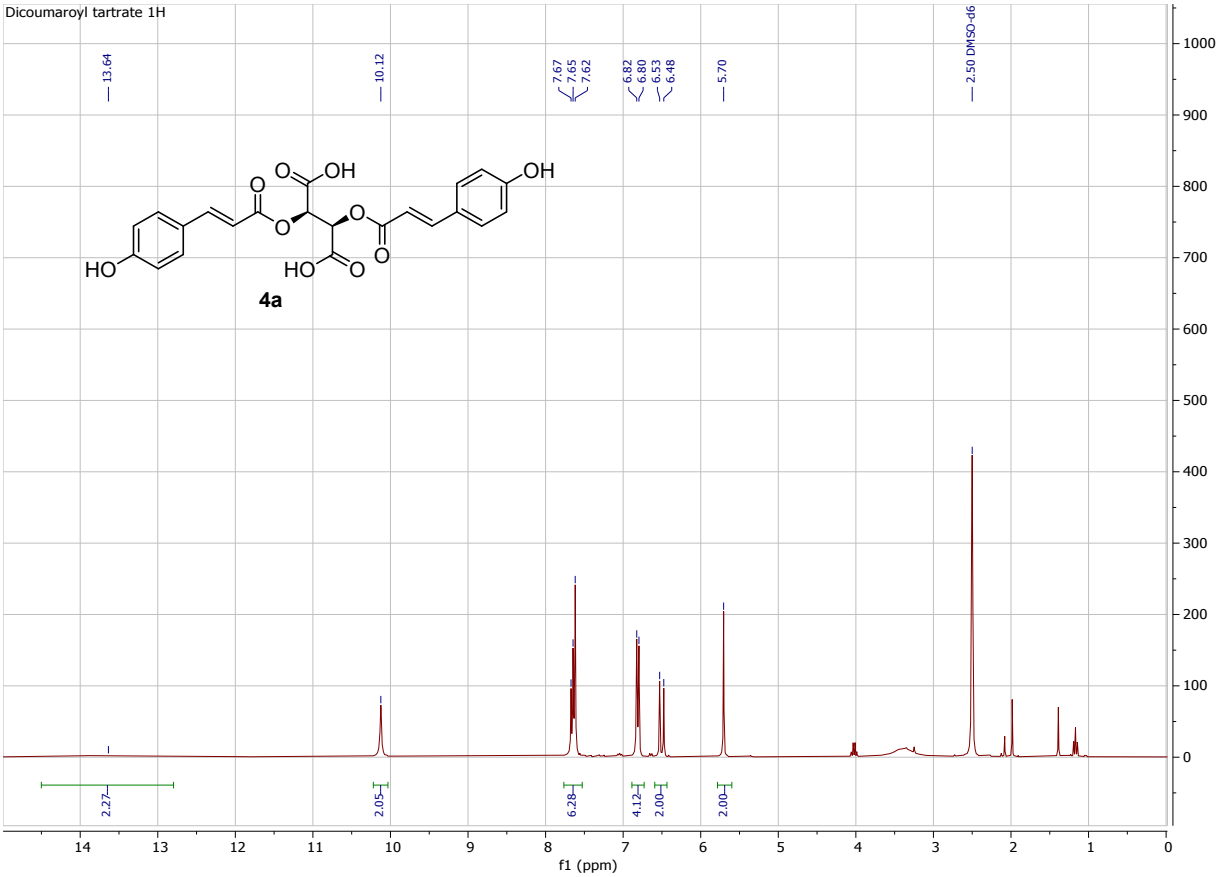

Monocaffeoyl tartrate 13C
172.21
168.75
165.78
148.80
146.61
145.73
125.46
121.67
115.97
115.01
113.00
73.38
70.26
39.52 DMSO-d6
3b
f1 (ppm)

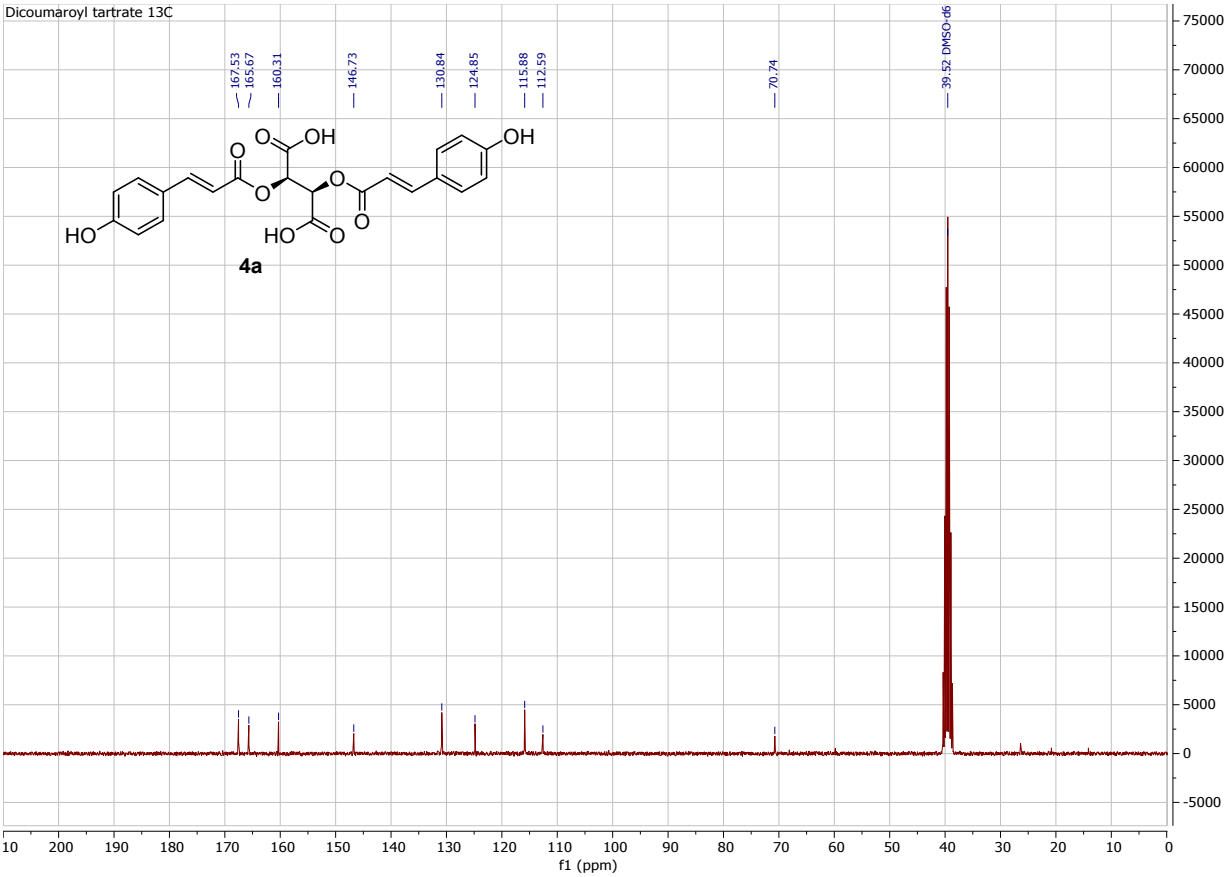

Monoferuloyl tartrate 1H
9.70
7.66
7.61
7.33
7.33
7.13
7.13
7.11
7.10
6.82
6.79
6.51
6.46
5.36
5.35
4.60
4.59
3.82
2.50 DMSO-d6
3c
f1 (ppm)

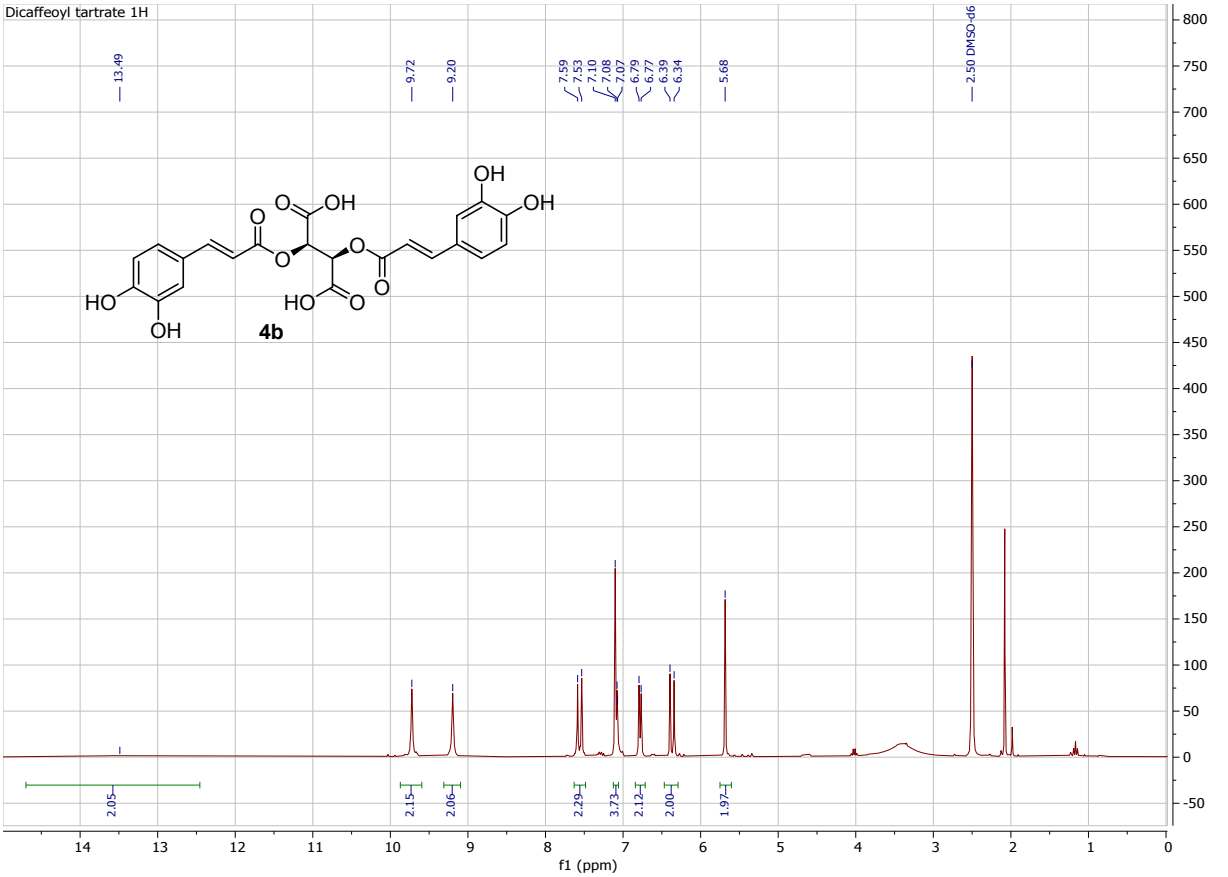

Monoferuloyl tartrate 13C
172.14
168.66
165.89
149.65
148.04
146.40
125.47
123.58
115.56
113.52
111.03
73.24
70.12
55.71
39.52 DMSO-d6
3c
f1 (ppm)

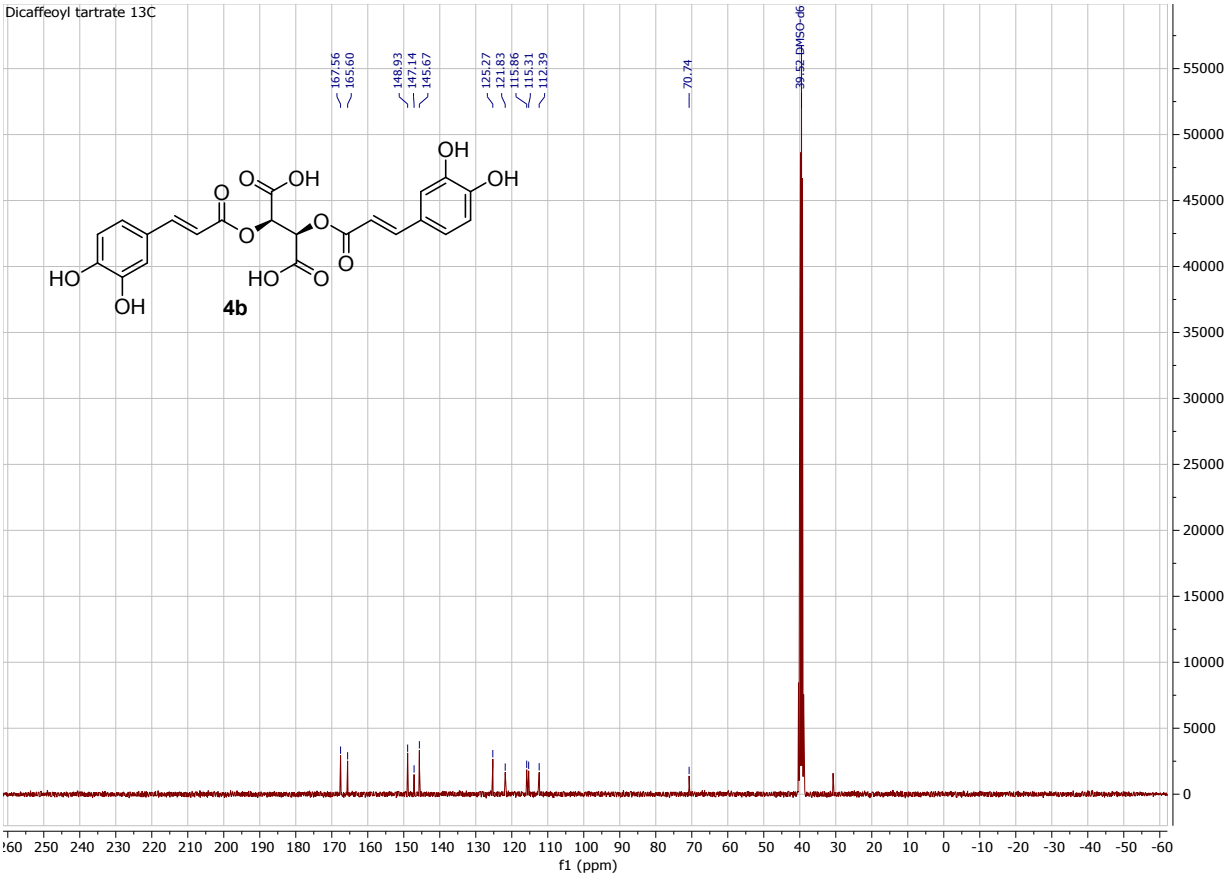

Monosinapoyl tartrate 1H
9.04
7.68
7.62
7.03
6.58
6.53
5.38
5.38
4.62
4.61
3.81
2.50 DMSO-d6
3d
0.93
1.19
1.87
0.97
1.00
0.93
6.18
f1 (ppm)

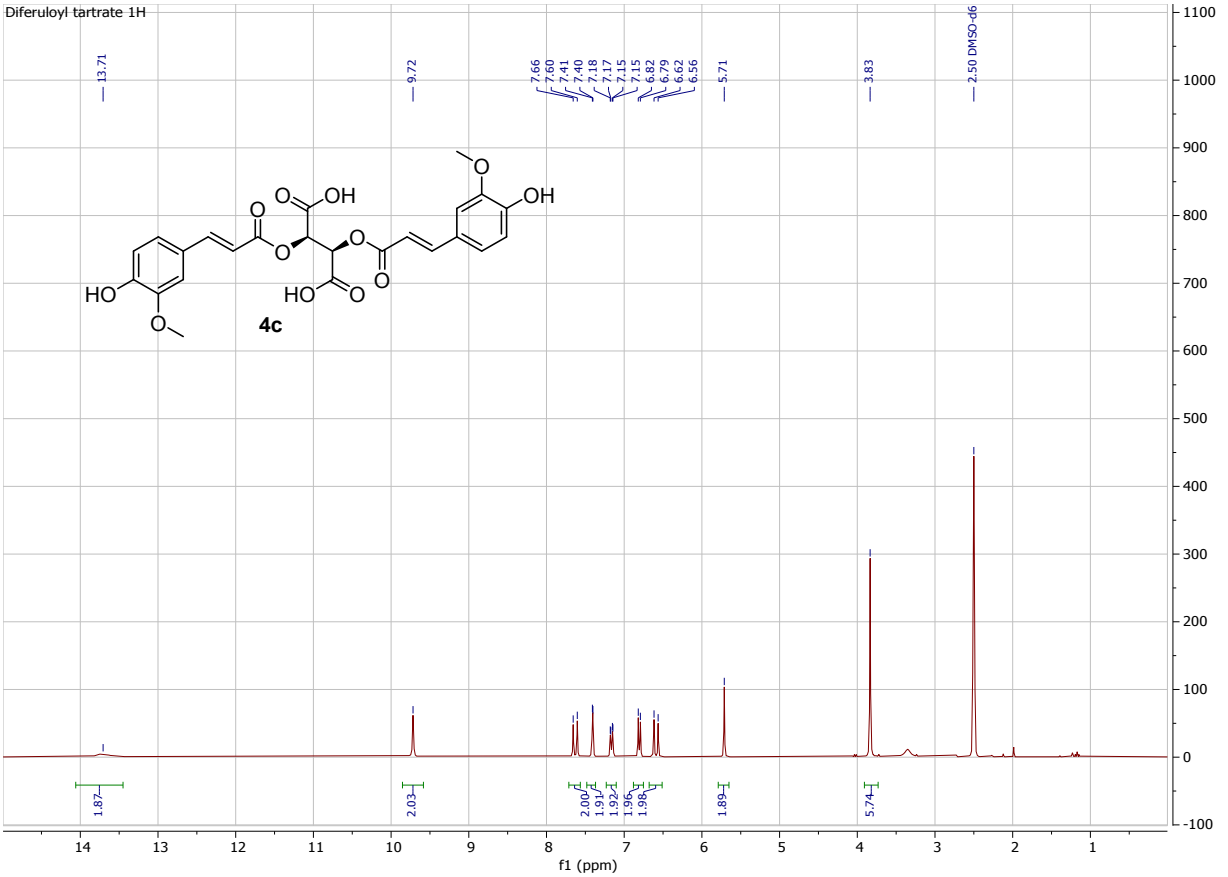

Monosinapoyl tartrate 13C
172.18
168.70
165.90
148.12
146.75
138.60
124.32
114.04
106.33
73.28
70.15
56.14
39.52 DMSO-d6
3d
f1 (ppm)

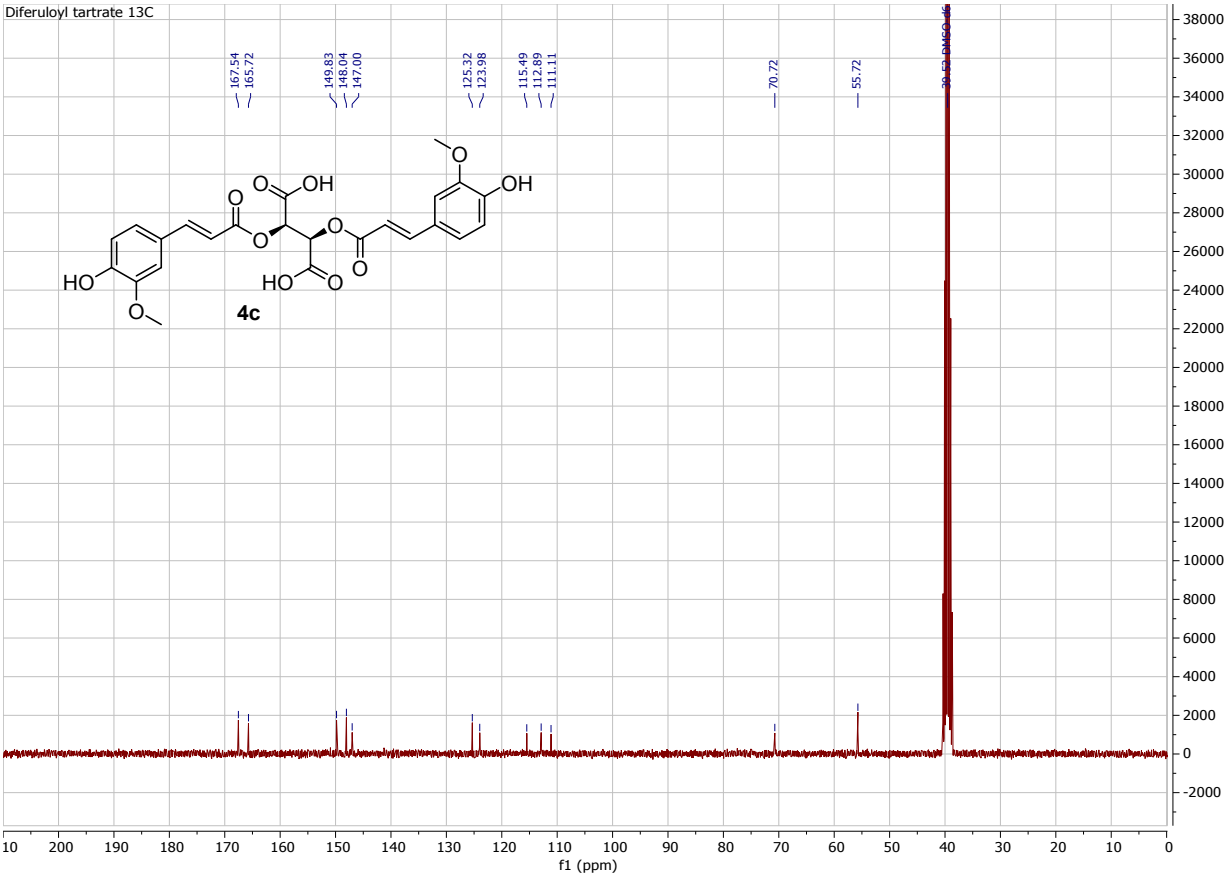

Dicoumaroyl tartrate 1H
13.64
10.12
7.67
7.65
7.62
6.82
6.80
6.53
6.48
5.70
2.50 DMSO-d6
OH
OH
HO
HO
O
O
O
O
O
O
4a
2.27
2.05
6.28
4.12
2.00
2.00
f1 (ppm)

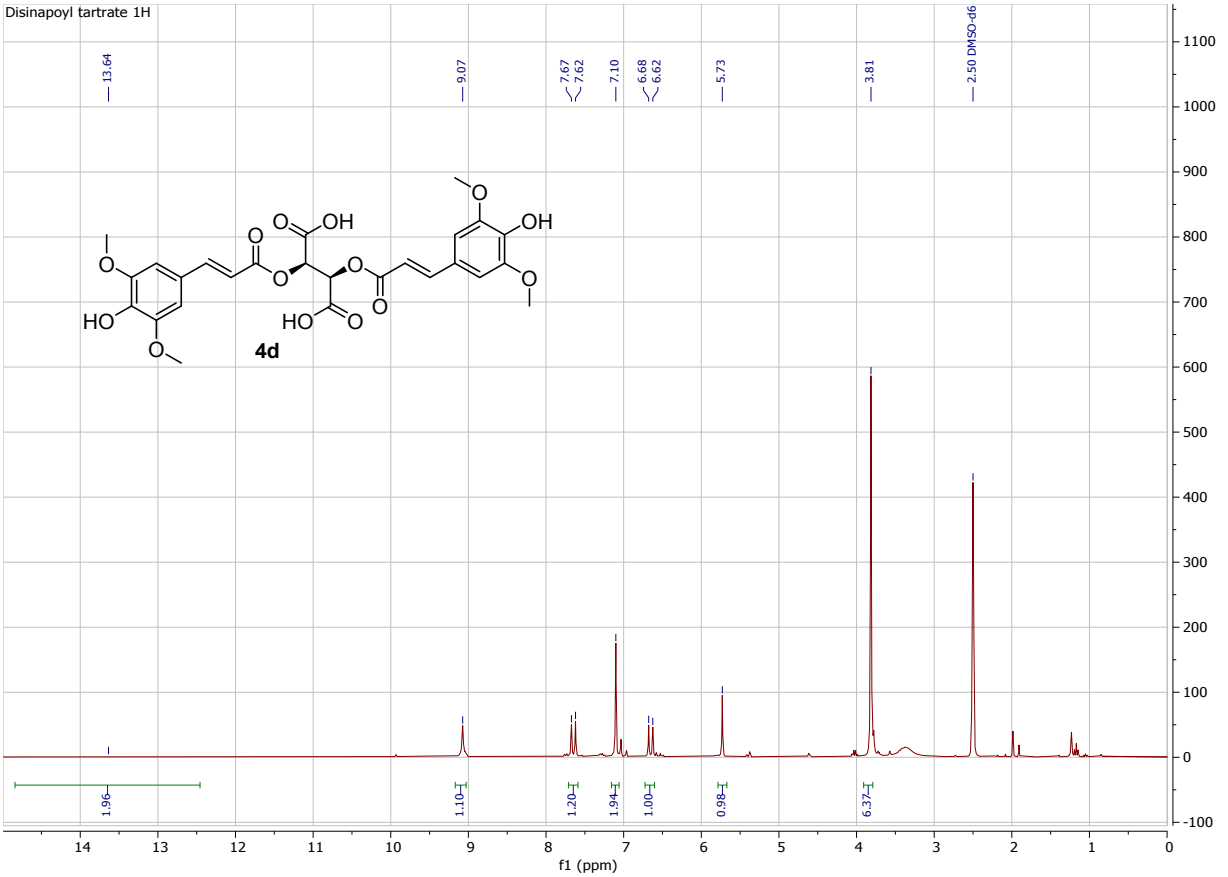

Dicoumaroyl tartrate 13C
167.53
165.67
160.31
146.73
130.84
124.85
115.88
112.59
70.74
39.52 DMSO-d6
OH
OH
HO
HO
O
O
O
O
O
O
4a
f1 (ppm)

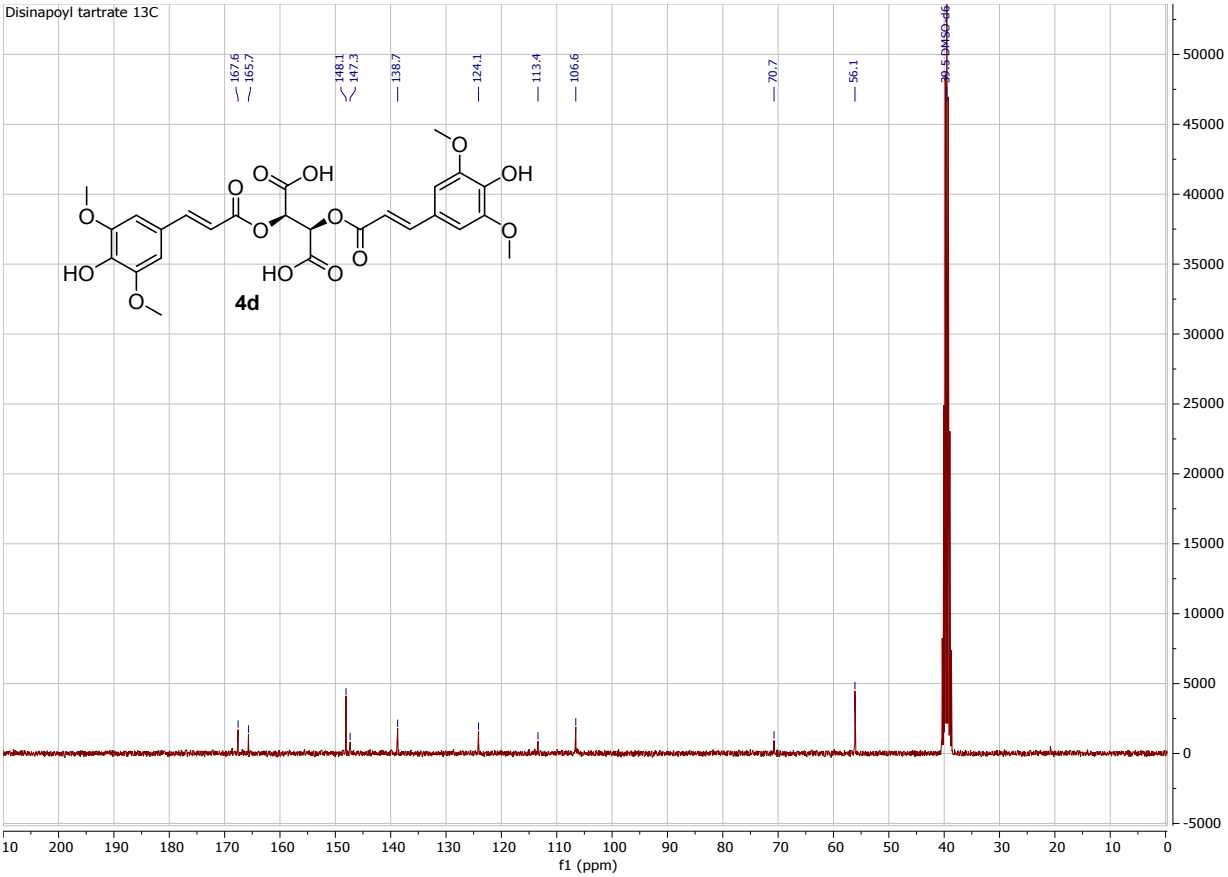

Dicaffeoyl tartrate 1H
13.49
9.72
9.20
7.59
7.53
7.10
7.08
7.07
6.79
6.77
6.39
6.34
5.68
2.50 DMSO-d6
4b
2.05
2.15
2.06
2.29
3.73
2.12
2.00
1.97
f1 (ppm)


Dicaffeoyl tartrate 13C
167.56
165.60
148.93
147.14
145.67
125.27
121.83
115.86
115.31
112.39
70.74
39.52 DMSO-d6
4b
f1 (ppm)

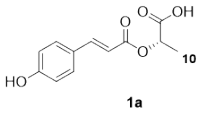

Diferuloyl tartrate 1H
13.71
9.72
7.66
7.60
7.41
7.40
7.18
7.17
7.15
7.15
6.82
6.79
6.62
6.56
5.71
3.83
2.50 DMSO-d6
4c
1.87
2.03
2.00
1.91
1.92
1.96
1.98
1.89
5.74
f1 (ppm)


Diferuloyl tartrate 13C
167.54
165.72
149.83
148.04
147.00
125.32
123.98
115.49
112.89
111.11
70.72
55.72
39.52 DMSO-d6
4c
f1 (ppm)

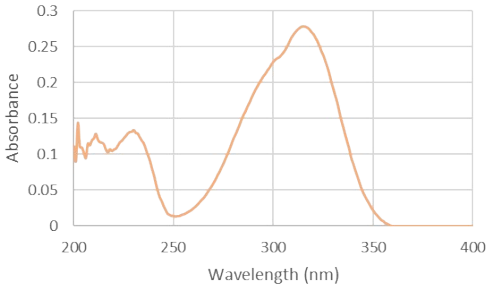

Disinapoyl tartrate 1H
13.64
9.07
7.67
7.62
7.10
6.68
6.62
5.73
3.81
2.50 DMSO-d6
4d
1.96
1.10
1.20
1.94
1.00
0.98
6.37
f1 (ppm)

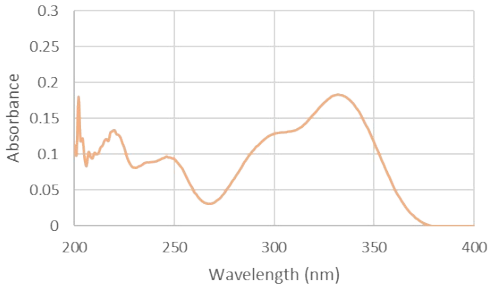

Disinapoyl tartrate 13C
167.6
165.7
148.1
147.3
138.7
124.1
113.4
106.6
70.7
56.1
39.5 DMSO-d6
4d
f1 (ppm)

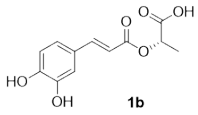
6. UV spectra



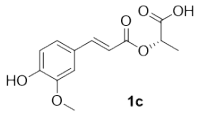
1a



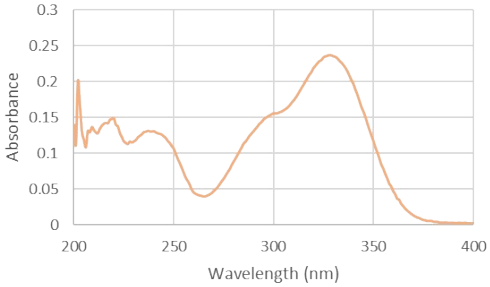


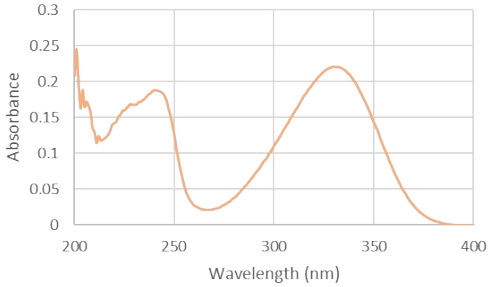


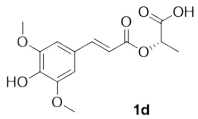
1b



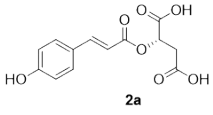
1c



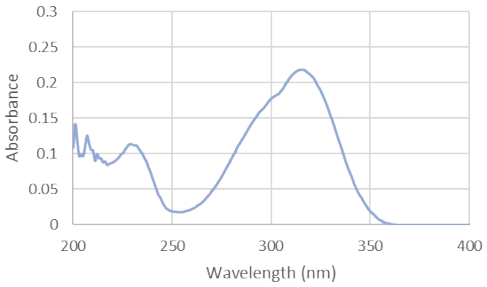


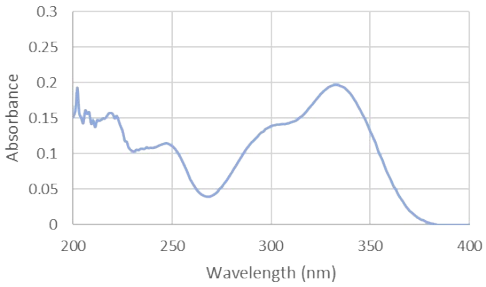


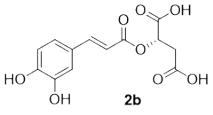
1d



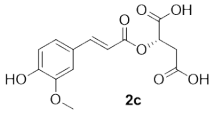
2a



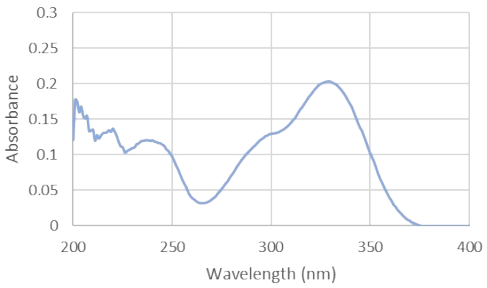


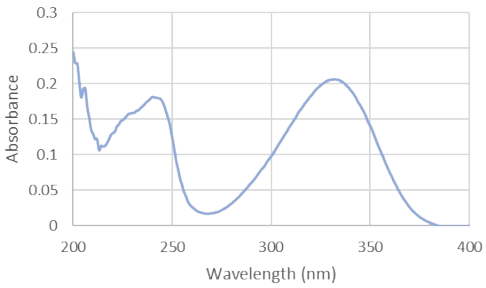


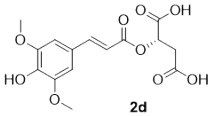
2b



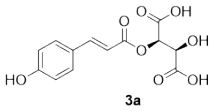
2c

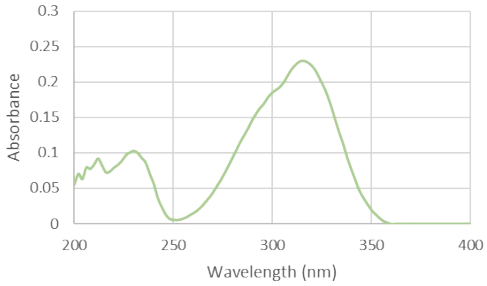


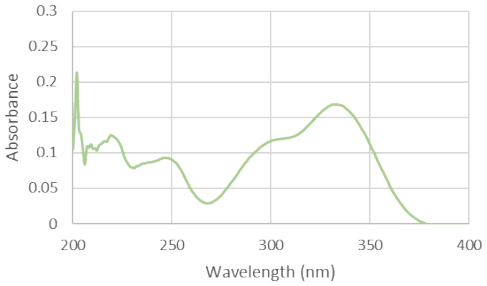


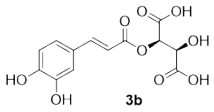


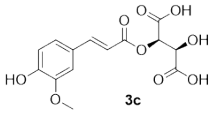
2d

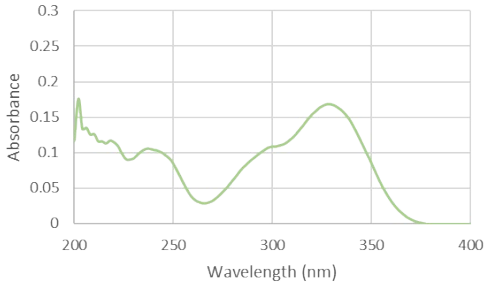

3a

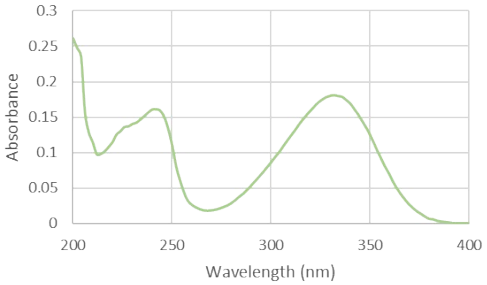

Absorbance
Wavelength (nm)

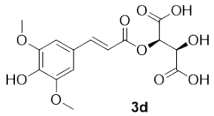

Absorbance
Wavelength (nm)

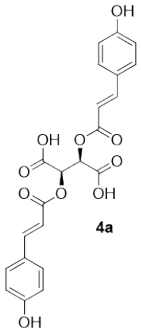

3b

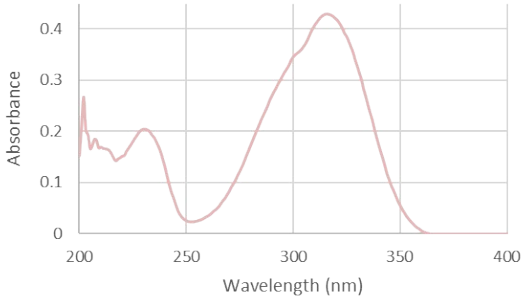

3c

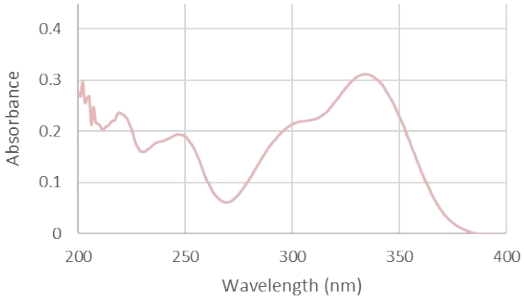

Absorbance
Wavelength (nm)

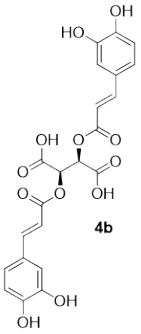

Absorbance
Wavelength (nm)

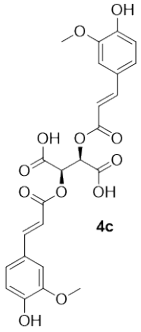

3d

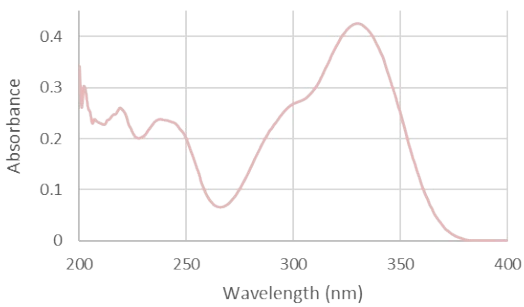

4a

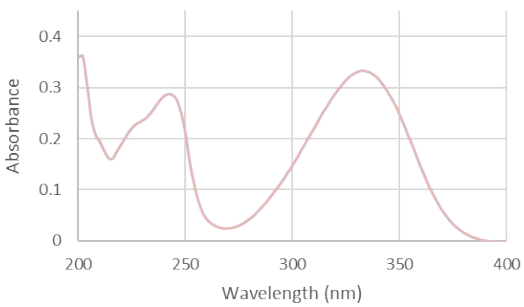

Absorbance
Wavelength (nm)

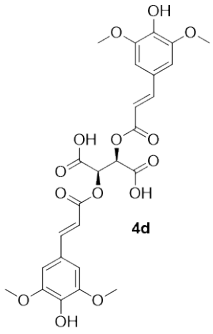

Absorbance
Wavelength (nm)

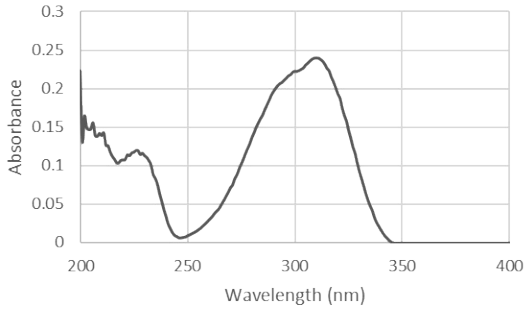

4b

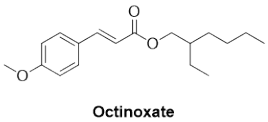

4c


Absorbance
Wavelength (nm)

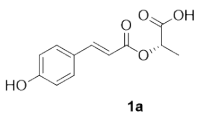

Absorbance
Wavelength (nm)


4d

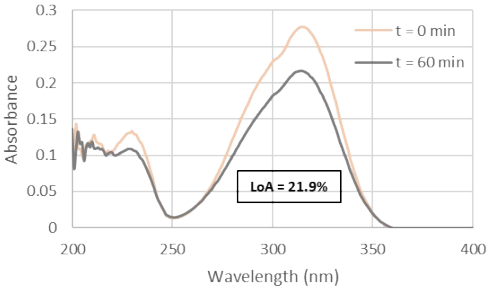

Absorbance
Wavelength (nm)

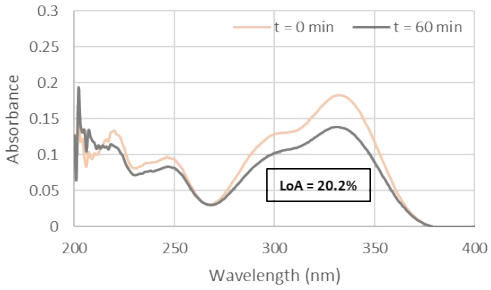

Octinoxate

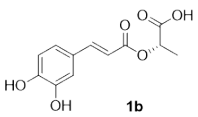
7. Loss of Absorbance (LoA) UV spectra



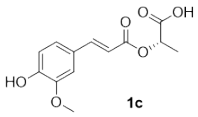
1a



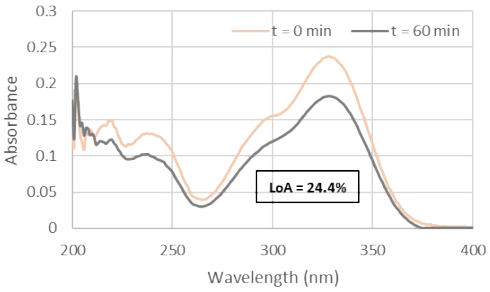


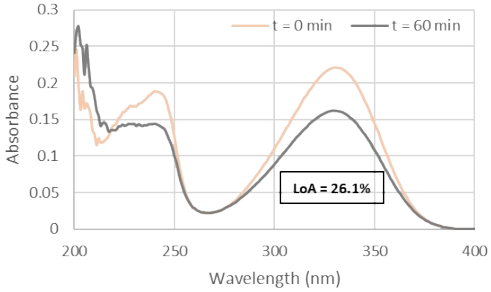


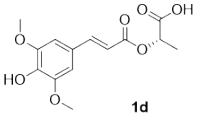
1b



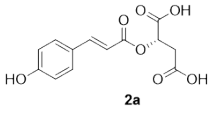
1c



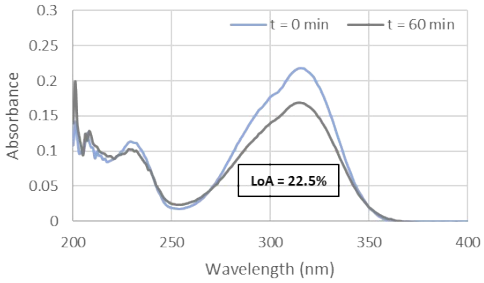


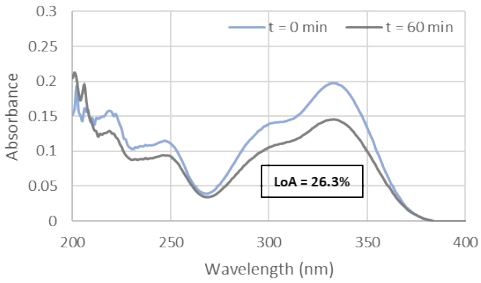


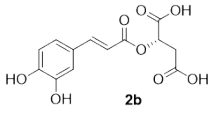
1d



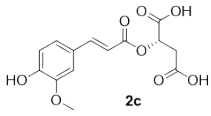
2a



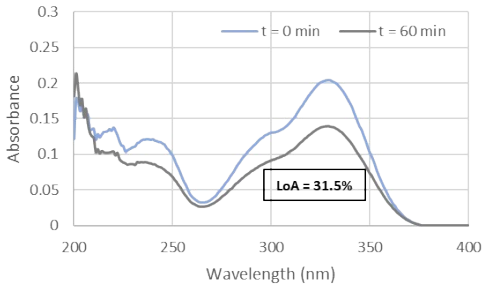


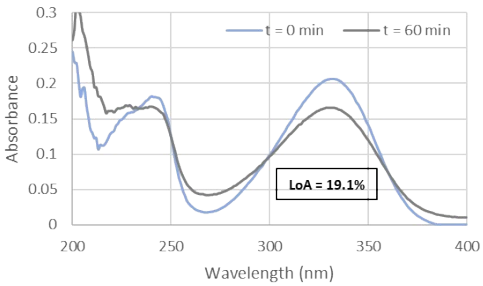


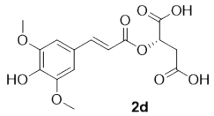
2b



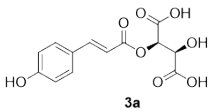
2c



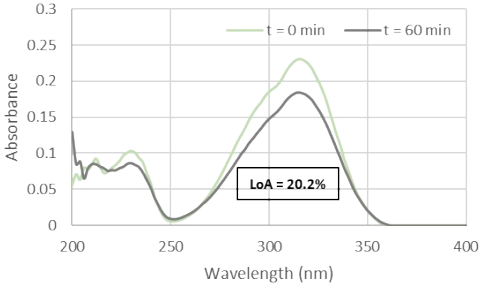


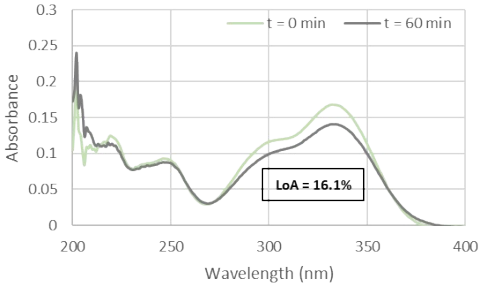


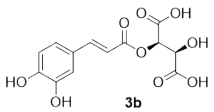
2d



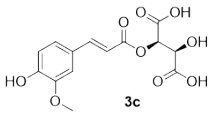
3a



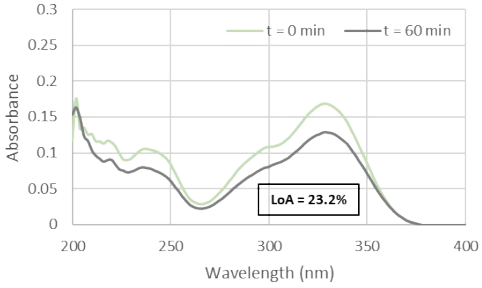


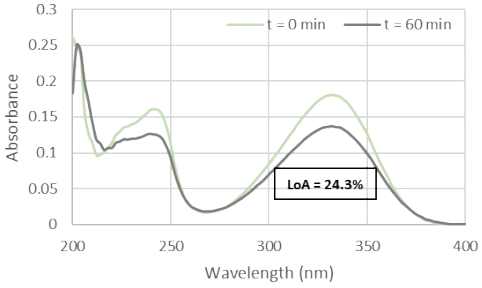


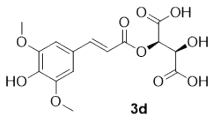
3b



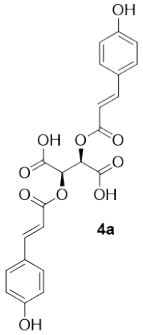
3c



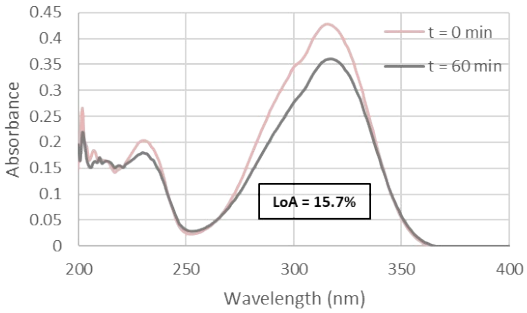


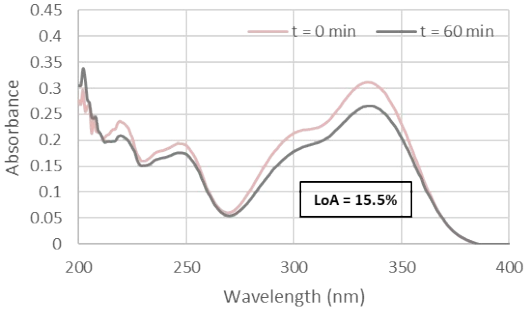


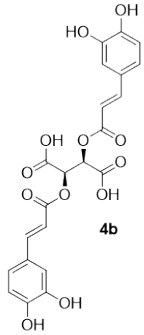
3d



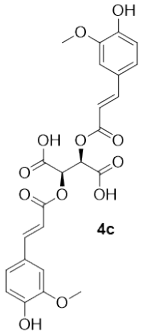
4a



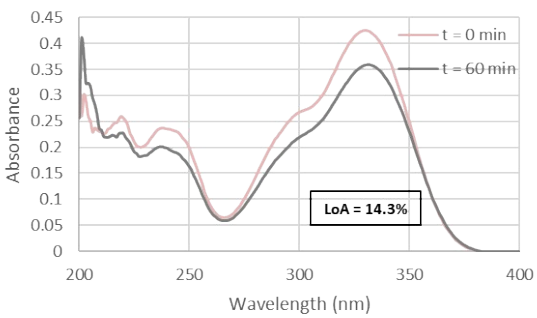


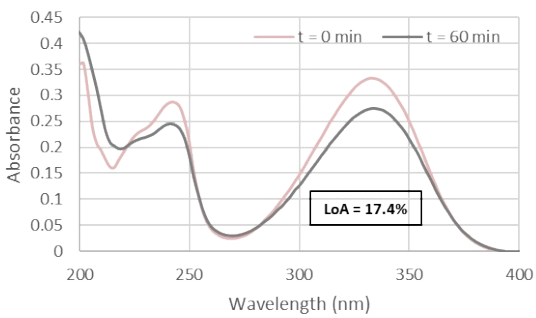


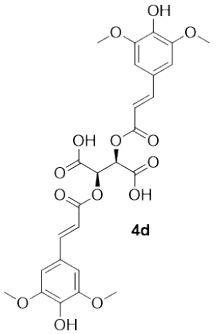
4b



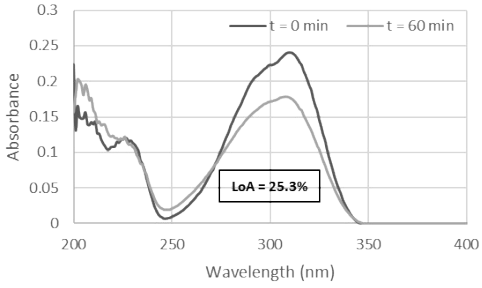
4c

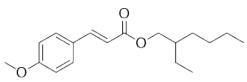






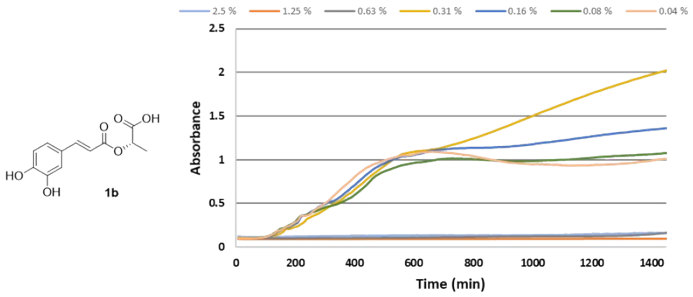
4d



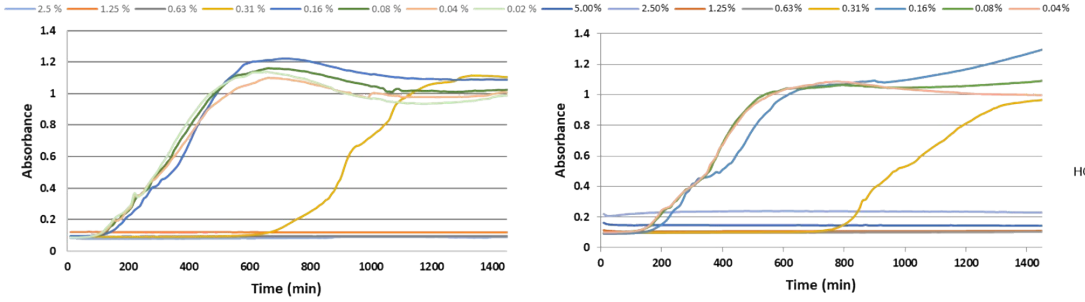


Octinoxate

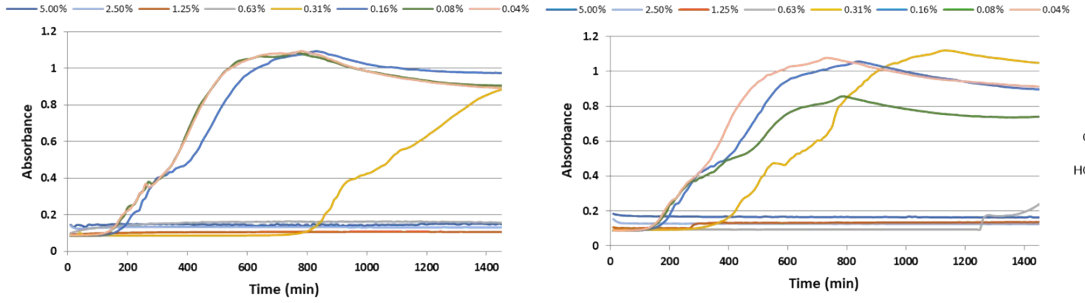
8. Antibacterial assays



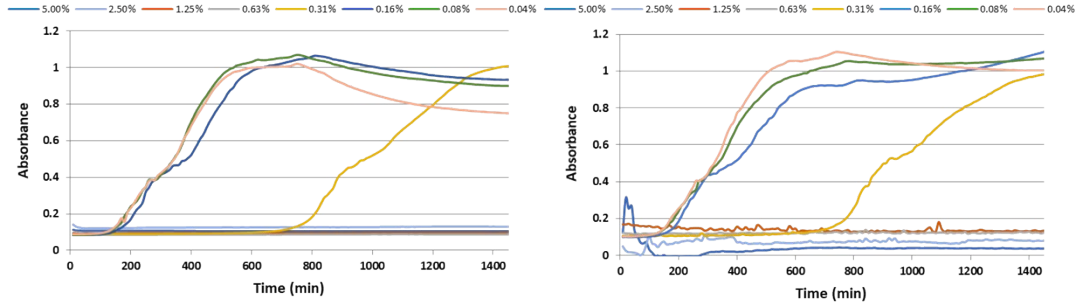
1b



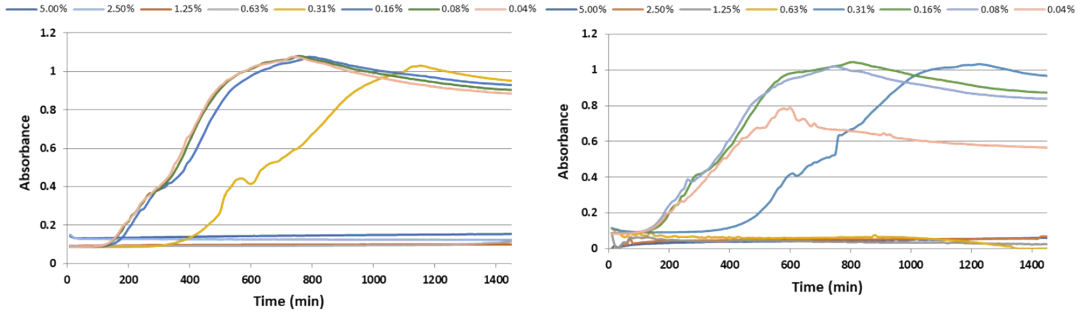
2a 2b



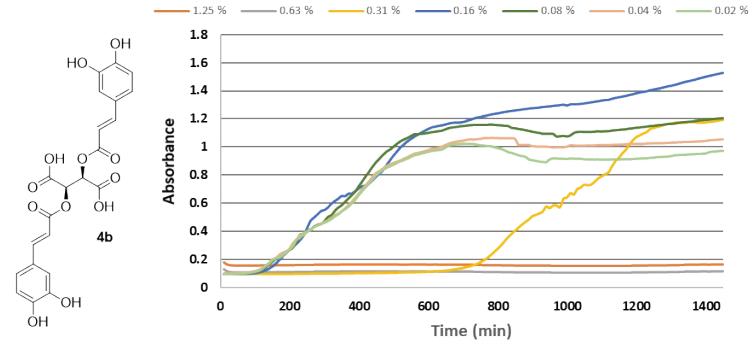
2c 2d

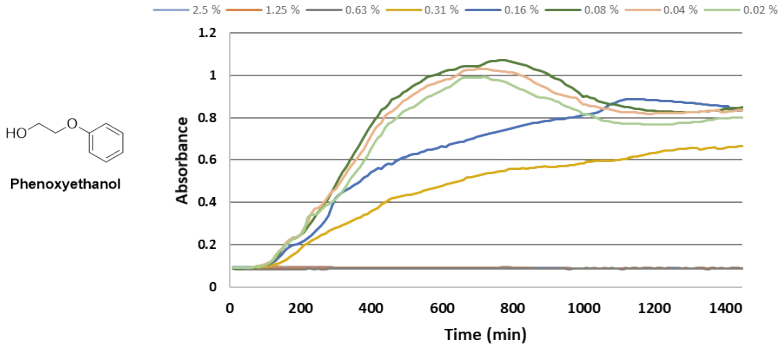


3a 3b

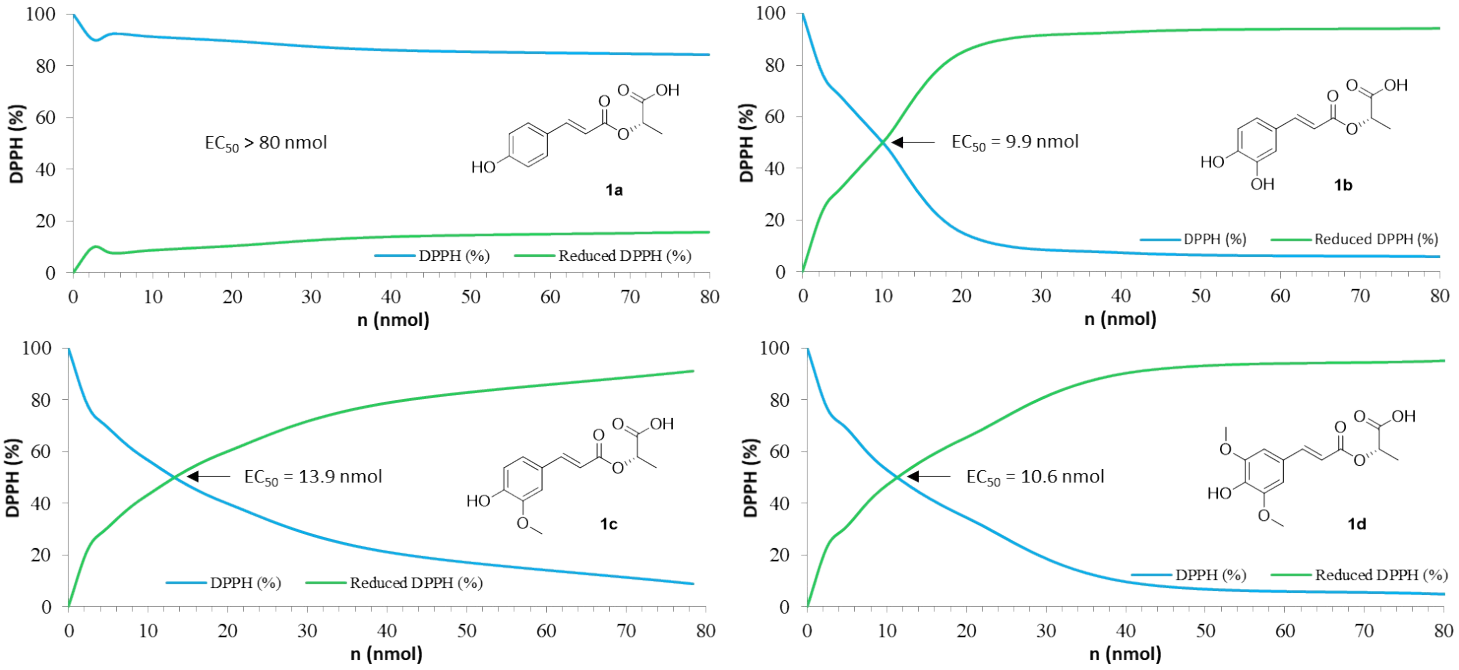


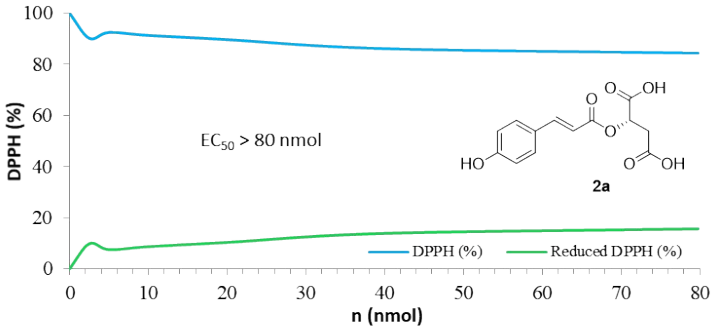
3c 3d

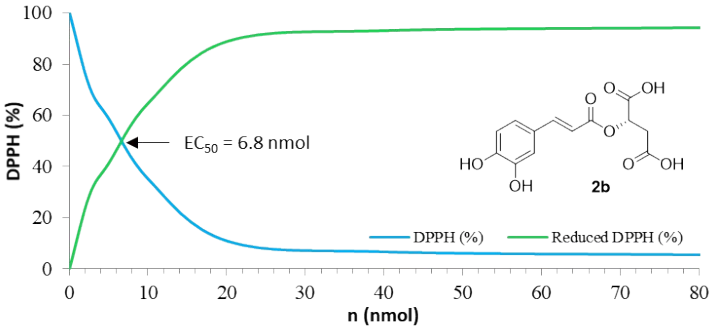


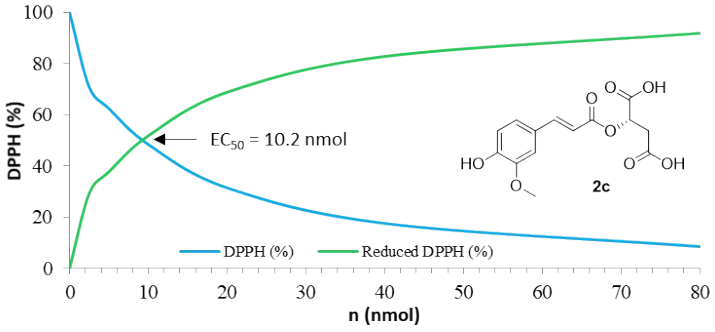


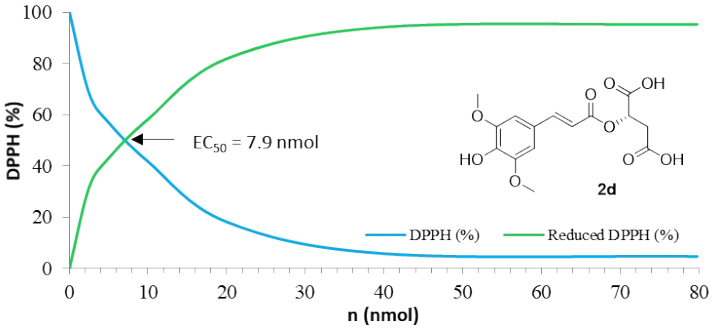
9. DPPH assays

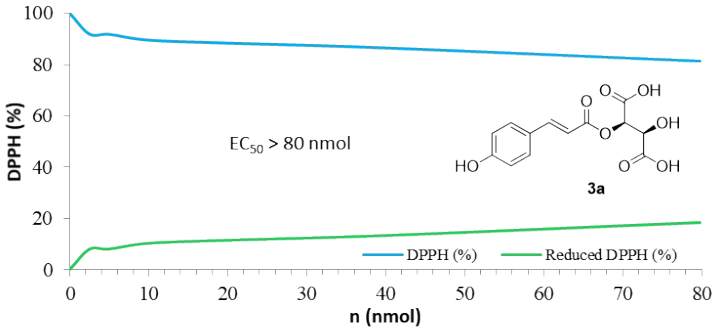


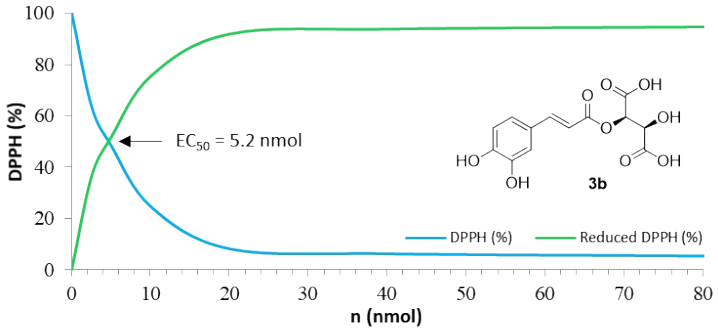

DPPH (%)
n (nmol)
EC50 > 80 nmol
2a
DPPH (%)
Reduced DPPH (%)

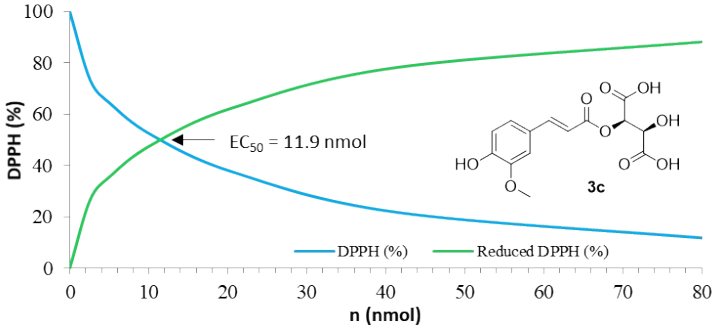

DPPH (%)
n (nmol)
EC50 = 6.8 nmol
2b
DPPH (%)
Reduced DPPH (%)

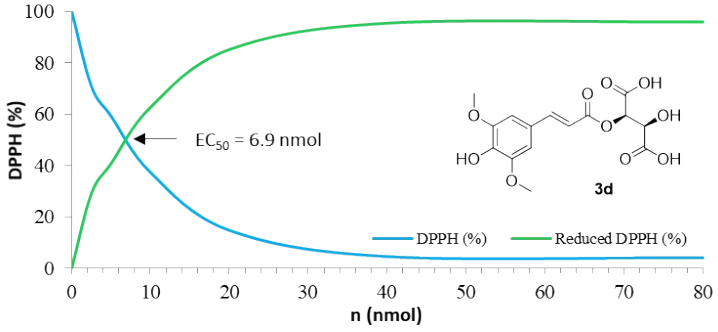

DPPH (%)
n (nmol)
EC50 = 10.2 nmol
2c
DPPH (%)
Reduced DPPH (%)

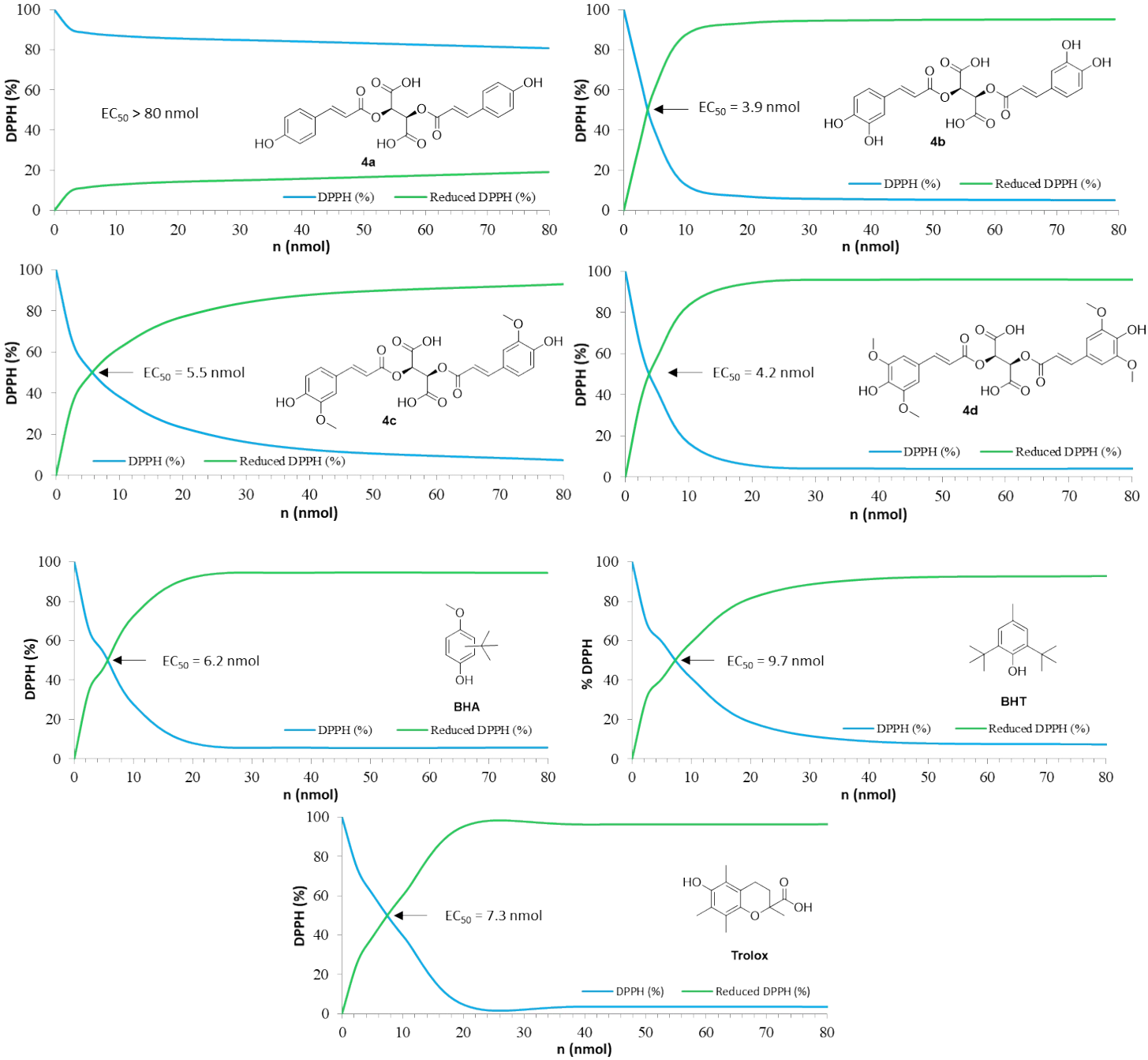

DPPH (%)
n (nmol)
EC50 = 7.9 nmol
2d
DPPH (%)
Reduced DPPH (%)


DPPH (%)
n (nmol)
EC50 > 80 nmol
3a
DPPH (%)
Reduced DPPH (%)


DPPH (%)
n (nmol)
EC50 = 5.2 nmol
3b
DPPH (%)
Reduced DPPH (%)


DPPH (%)
n (nmol)
EC50 = 11.9 nmol
3c
DPPH (%)
Reduced DPPH (%)


DPPH (%)
n (nmol)
EC50 = 6.9 nmol
3d
DPPH (%)
Reduced DPPH (%)



10. References

1. W. Brand-Williams, M. E. Cuvelier and C. Berset, *Food Sci. Technol. (London)*, 1995, **28**, 25-30.
2. V. Delfosse, M. Grimaldi, J.-L. Pons, A. Boulahtouf, A. Le Maire, V. Cavailles, G. Labesse, W. Bourguet and P. Balaguer, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 14930-14935, S14930/14931-S14930/14916.