SUPPLEMENTARY METHODS

The gut microbiota ellagic acid-derived metabolite urolithin A, and its sulfate conjugate, are substrates for the drug efflux transporter breast cancer resistance protein (ABCG2/BCRP).

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Experimental procedure for the synthesis of Uro-A glucuronide and Uro-A sulfate.

3-*O*-(*tert*-butyl-dimethylsilyl)-8-hydroxy-(6H-(dibenzo [b,d]pyran-6-one)] and 8-*O*-(*tert*-butyl-dimethylsilyl)-3-hydroxy-(6H-(dibenzo[b,d]pyran-6-one)] (1,2). (Numbers of compounds are indicated in Figure 2 of the manuscript)

To a solution of urolithin A (400 mg, 0.964 mmol) in DMF (anhydrous, 4 mL) cooled in an ice-water bath under argon were added sequentially TBDMSOTf (443 μL, 1.92 mmol, 1.10 equiv) and i-Pr^{2}NEt (411 μL, 2.36 mmol, 1.35 equiv). The mixture was allowed to stir for 30 min at 0º C, and TLC (hexane: ethyl acetate 3:1) at that point indicated that the reaction was complete. The pale yellow reaction mixture was diluted with EtOAc (50 mL), introduced into a separatory funnel, washed with water (2x25 mL) and brine (25 mL), and finally the organic phase was dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude that was purified by flash column chromatography (hexane:ethyl acetate, from 10:1 to 3:1) to provide a regioisomeric mixture of **1** and **2** (ratio ~ 1:1, 320 mg, 54%) as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H: 7.69-7.53 (m, 6H, Harom), 7.17 (dd, 1H, J = 2.7 and 8.7 Hz, Harom), 7.08 (dd, 1H, J = 2.4 and 8.7 Hz, Harom), 6.79 (d, J = 2.4 Hz, Harom), 6.66 (dd, 1H, J = 2.4 and 8.7 Hz,

Harom), 6.62-6.60 (m, 2H, Harom), 0.80, 0.79 (2s, 18H, $C(CH_3)_3$ x2), 0.04, 0.03 (2s, 12H, -$Si(CH_3)_2$ x2). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 162.2, 162.1 (C=O), 157.5, 156.9, 156.1, 155.4, 151.5, 151.1, 129.2, 128.5, 128.3, 124.2, 123.4, 123.2, 122.9, 122.8, 121.0, 120.9, 119.6, 119.6, 117.6, 114.9, 113.3, 111.2, 108.5, 104.0, 25.6, 18.3, 18.2 ($C(CH_3)_3$), -4.4 ($Si(CH_3)_2$). HRMS (ES^+) Calcd. for $C_{19}H_{23}O_4Si$ (M+H) 343.1366, Found: 343.1356.

8-Hydroxy-3-*O*-(methyl-2,3,4-tri-O-acetyl-β-D-glucopyranosyluronate)- (6H-(dibenzo[b,d] pyran-6-one)] and 3-hydroxy-8-*O*-(methyl-2,3,4-tri-O-acetyl-β-D-glucopyranosyluronate)-(6H-(dibenzo[b,d]pyran-6-one)] (4,5).

$BF_3.OEt_2$ (13 μL, 0.14 mmol) was added to a solution of trichloroacetimidate **3** (450 mg, 0.943 mmol) and the regioisomer mixture of 3-*O*-(*tert*-butyl-dimethylsilyl)-8-hydroxy-(6H-(dibenzo [b,d]pyran-6-one)] and 8-*O*-(*tert*-butyl-dimethylsilyl)-3-hydroxy-(6H-(dibenzo[b,d]pyran-6-one)] **8** and **9** (320 mg, 0.93 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0ºC. After 1 h, TLC showed a complete consumption of the starting material. The reaction was quenched with NEt_3 and concentrated in vacuo. The resulting residue was purified by flash column chromatography (hexane: ethyl acetate, from 3:1 to 2:3) to provide a regioisomeric mixture of **4** and **5** (ratio ~ 1:1, 503 mg, 83%) as a glassy solid. ^1H-NMR (500 MHz, $CDCl_3$) δ_H: 7.87-7.75 (m, 5H, Harom), 7.69 (d, 1H, J = 2.5 Hz, Harom), 7.39, 7.24 (2 d, 2H, J= 2.5 and 8.5 Hz, Harom), 6.93 (m, 2H, Harom), 6.78 (m, 2H, Harom), 5.41-5.25 (m, 8H, H-1, H-2, H-3, H-4, H-1', H-2', H-3', H-4'), 4.34 (d, 1H, J = 9.5 Hz, H-5), 4.30 (d, 1H, J = 9.5 Hz, H-5'), 3.71, 3.69 (2s, 6H, 2xCH_3O), 2.08-1.99 (m, 18H, CH_3C=O), 0.98, 0.97 (2s, 18H, $C(CH_3)_3$ x2), 0.23, 0.20 (2s, 12H, -$Si(CH_3)_2$ x2). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 170.0, 169.9, 169.3, 169.2, 166.8, 166.7, 160.9, 160.8, 157.4, 157.2, 155.9, 155.8, 151.6, 151.2, 130.7, 128.2, 125.5, 123.3, 123.1, 123.0, 121.5, 121.1, 119.7, 117.5, 115.7, 114.1, 113.6, 111.5, 108.4, 104.9, 98.5, 98.4, 72.5, 72.4, 71.7, 71.1, 71.0, 70.9, 69.0, 68.9, 60.3, 53.0, 52.9, 25.5, 20.9, 20.5, 20.4, 18.2, 18.1, 14.1. HRMS (ES^+) Calcd. for $C_{32}H_{38}O_{13}NaSi$ (M^+) 681.1979, Found: 681.1991.

3-*O*-(β-D-glucopyranosyluronic acid)-8-hydroxy-(6H-(dibenzo [b,d]pyran-6-one)] and 8-*O*-(β-D-glucopyranosyluronic)-3-hydroxy-(6H-(dibenzo[b,d]pyran-6-one)].

A regioisomeric mixture of **11** and **12** (75 mg, 0.114 mmol), KF (13 mg, 0.229 mmol) and K_2CO_3 (32 mg, 0.229 mmol) were dissolved in MeOH-H_2O 5:1 (6 mL). The reaction mixture was stirred at room temperature for 18 h and then the solvent was then removed under vacuo. The crude was purified by RP-C18 (H_2O:CH_3OH, from 100:0 to 50:50). Fractions containing the desired product were concentrated and freeze-dried affording a regioisomeric mixture of glucuronide conjugates (ratio ~ 1:1, 30 mg, 65%) as a yellowish solid. ^{1}H-NMR (500 MHz, D_2O) δ_H: 7.17-7.08 (m, 5H, Harom), 7.02 (d, 1H, J = 9.0 Hz, Harom), 6.78 (d, 1H, J= 8.5 Hz, Harom), 6.71 (s, 1H, Harom), 6.68 (d, 1H, J = 9.0 Hz, Harom), 6.42 (s, 1H, Harom), 6.35 (d, 1H, J = 8.5 Hz, Harom), 5.97 (s, 1H, Harom), 5.02 (d, 2H, H-1, H1'), 3.91 (t, 2H, J = 9.5 Hz, H-3, H-3'), 3.68-3.57 (m, 6H, H-2, H-4, H-2', H-4', H-5, H-5'). ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 175.5, 162.1, 162.0, 156.9, 156.7, 149.2, 148.8, 129.1, 126.0, 123.6, 122.8, 122.5, 118.2, 117.7, 113.5, 112.9, 112.7, 111.7, 108.8, 103.2, 102.2, 99.6, 76.2, 75.2, 72.7, 71.8. MS (ESI$^-$) Calcd. for $C_{19}H_{16}O_{10}$ (M^-) 403.3, Found: 403.1.

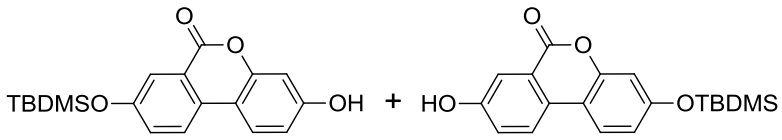
3-*O*-(*Tert*-butyl-dimethylsilyl)-8-sulfate-(6H-(dibenzo[b,d]pyran-6-one)] and 8-*O*-(*tert*-butyl-dimethylsilyl)-3-sulfate-(6H-(dibenzo[b,d]pyran-6-one)] (6,7).

A regioisomeric mixture of compounds **1** and **2** (135 mg, 0.39 mmol) was dissolved in acetonitrile and mixed with $SO_3{\cdot}NMe_3$ as sulfating reagent and NEt_3 as base. Microwave radiation was applied to the reaction mixture at 100 ºC for 20 min. TLC (ethyl acetate:MeOH, 6:1) showed the formation of a major product and complete consumption of the starting material. Solvents were removed and the crude was purified by sephadex LH-20 (CH_2Cl_2:MeOH, 1:1) to afford a regioisomeric mixture of **6** and **7 (**ratio ~ 1:1, 187 mg, 92%) as an oil. ^{1}H-NMR (400 MHz, CD_3OD) δ_H: 8.21-8.08 (m, 5H, Harom), 7.79 (dd, 1H, J = 2.4 and 8.8 Hz, Harom), 7.69 (d, 1H, J = 2.8 Hz, Harom), 7.42 (dd, 1H, J = 2.8 and 8.8 Hz, Harom),

7.35-7.30 (m, 2 H, Harom), 6.91 (dd, 1H, J = 2.4 and 8.8 Hz, Harom), 6.81 (d, 1H, 1H, J = 2.8 Hz, Harom), 3.26-3.18 (m, 12H, NC*H*$_2$CH$_3$), 1.31 (t, 18H, NCH$_2$C*H*$_3$), 1.05 (2s, 18H, C(CH$_3$)$_3$ x2), 0.03, 0.02 (2s, 12H, -Si(CH$_3$)$_2$ x2). ^{13}C NMR (100 MHz, CD$_3$OD) δ_C: 162.2, 162.1 (C=O), 156.3, 153.6, 150.7, 128.8, 128.6, 128.2, 124.0, 123.9, 123.1, 122.9, 121.4, 121.1, 118.8, 117.8, 117.3, 114.5, 109.3, 107.8, 24.7, 17.7, 7.8, -5.8. ESI-HRMS (ES$^-$) Calcd. for $C_{19}H_{21}O_7SiS$ (M-H) 421.0777, Found: 421.0783.

8-Sulfate-(6H-(dibenzo[b,d]pyran-6-one)] and 3-sulfate-(6H-(dibenzo[b,d]pyran-6-one)]. **A** regioisomeric mixture of **6** and **7** (95 mg, 0.181 mmol) was dissolved in MeOH (5 mL) and KF (21 mg, 0.363 mmol) then added. The reaction mixture was stirred at room temperature for 18 h and the solvent was then removed under vacuo. The crude was purified by RP-C18 (H_2O:CH_3OH, from 100:0 to 70:30). Fractions containing the desired product were concentrated and freeze-dried affording a regioisomeric mixture of sulfate conjugates (ratio ~ 1:1, 45 mg, 73%) as a yellow solid. mp >300 ºC. H-NMR (400 MHz, d^6-DMSO) δ_H: 7.96 (d, 2H, J = 8.7 and 9.0 Hz, Harom), 7.77 (d, 1H, J = 2.4Hz, Harom), 7.38 (dd, 1H, J = 2.4 and 8.7 Hz, Harom), 7.32 (d, 1H, J = 2.7 Hz, Harom), 7.12 (dd, 1H, J = 2.7 and 9.0 Hz, Harom), 6.98-6.92 (m, 2H, Harom), 6.60 (dd, 1H, J = 2.4 and 8.7 Hz, Harom), 6.51 (d, J = 2.1 Hz, Harom). ^{13}C NMR (62.5 MHz, d^6-DMSO) δ_C: 161.1, 159.9 (C=O), 158.2, 154.6, 153.2, 151.9, 150.4, 132.9, 130.8, 128.8, 126.7, 124.9, 124.6, 123.4, 123.3, 121.4, 120.0, 117.4, 114.1, 113.7, 109.8, 108.4, 103.4. ESI-HRMS (ES$^-$) Calcd. for $C_{13}H_7O_7S$ (M-H) 306.9912, Found: 306.9913.

^{1}H and ^{13}C NMR spectra of new compounds



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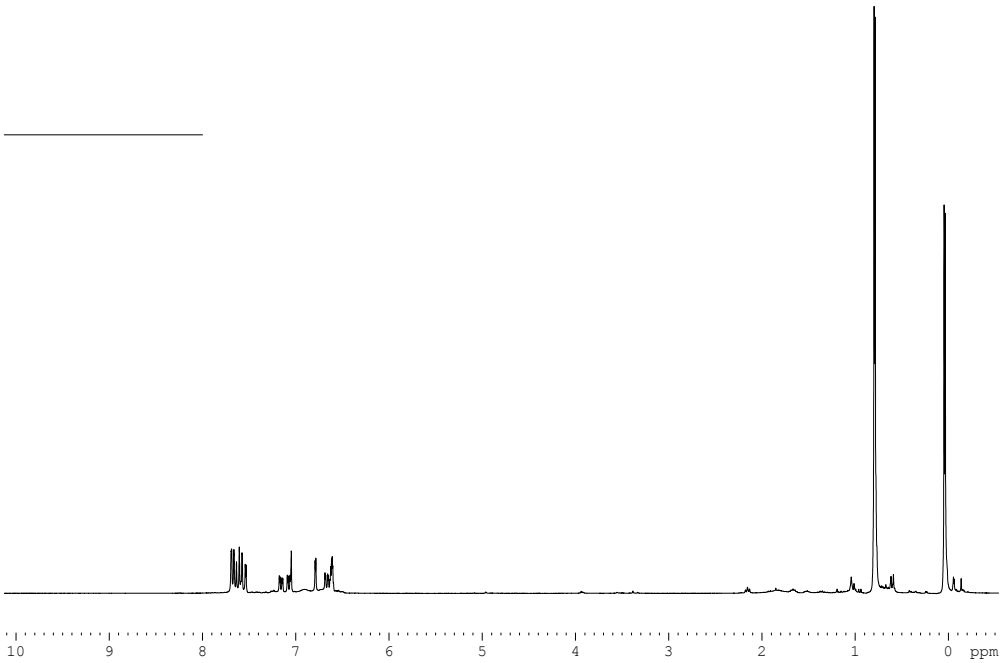

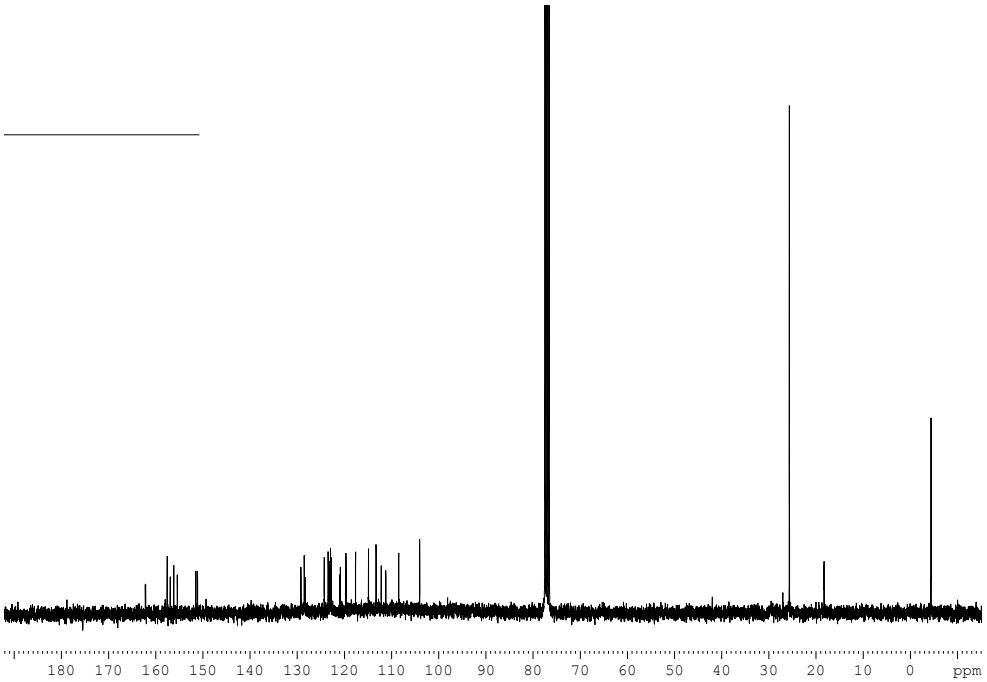

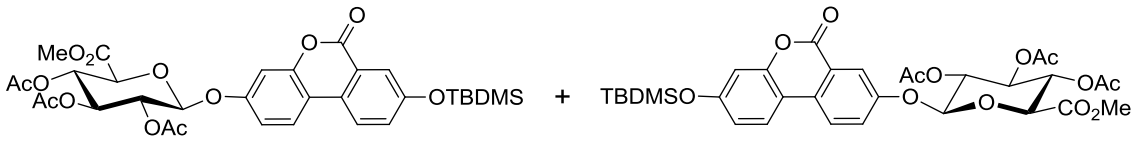
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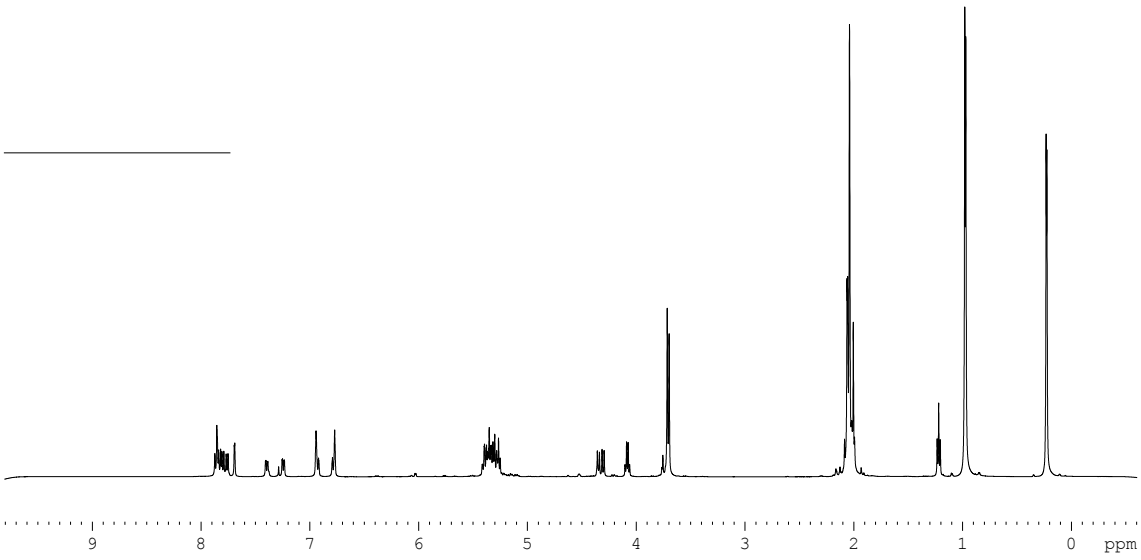
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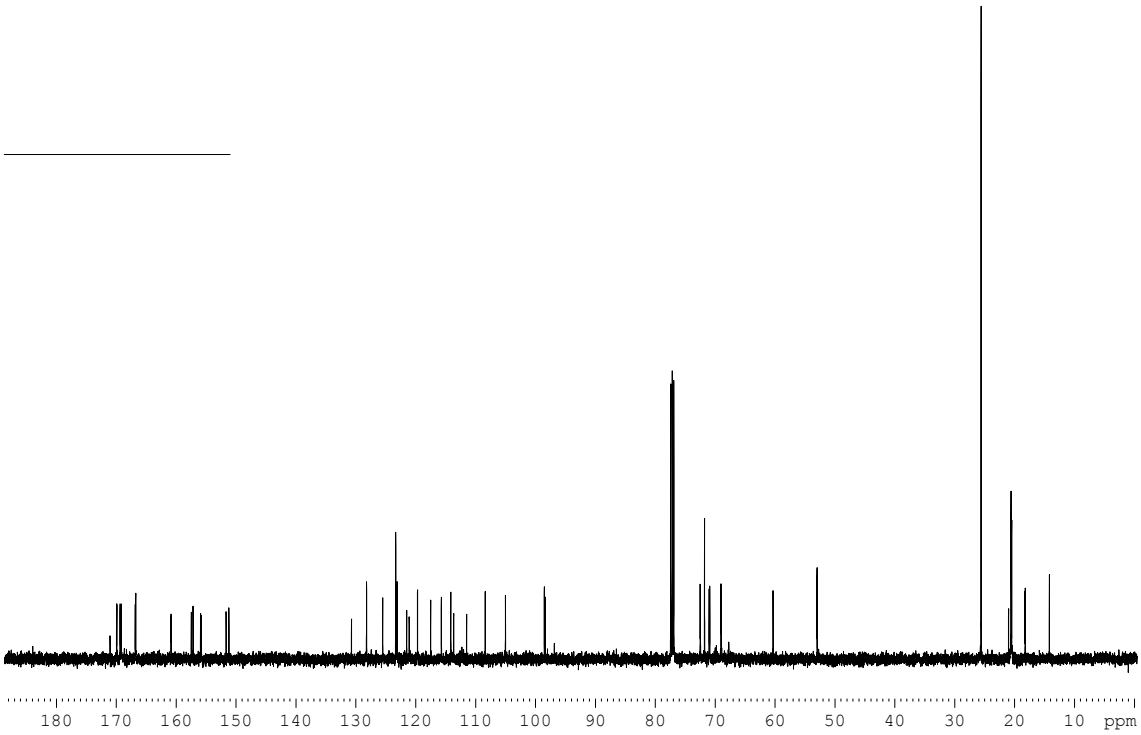
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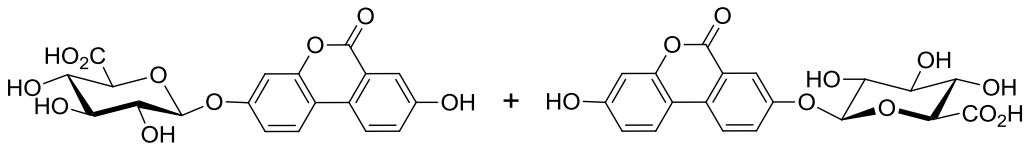
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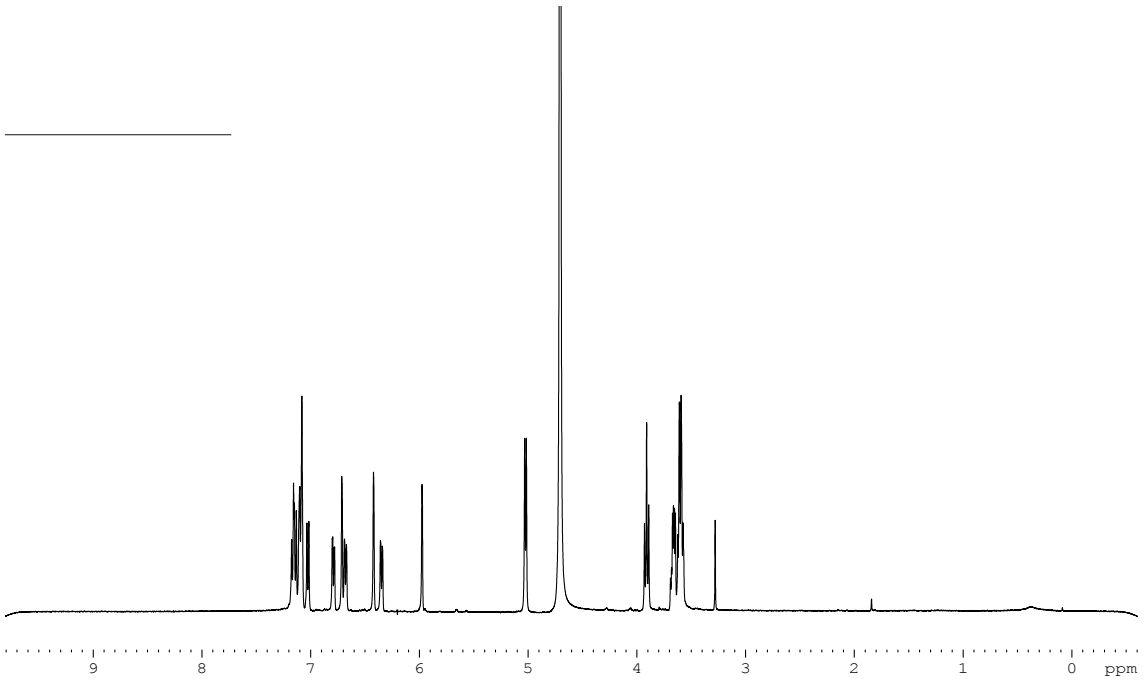
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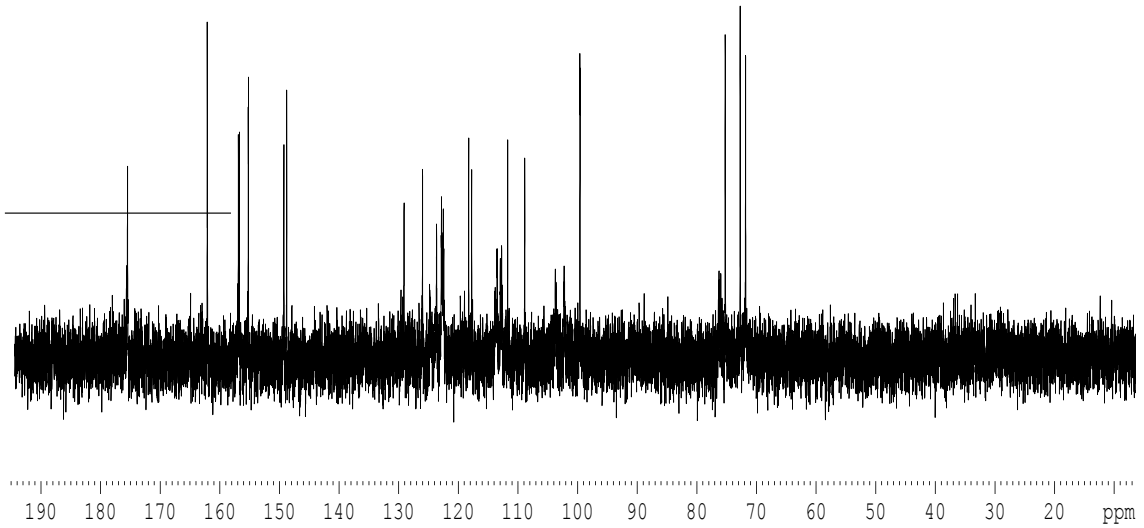
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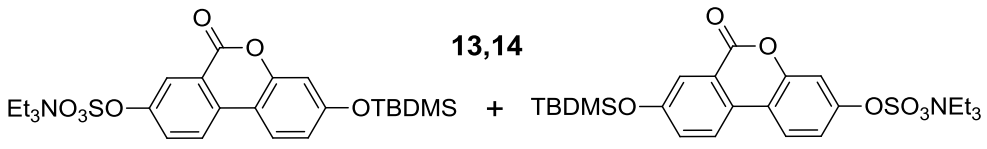
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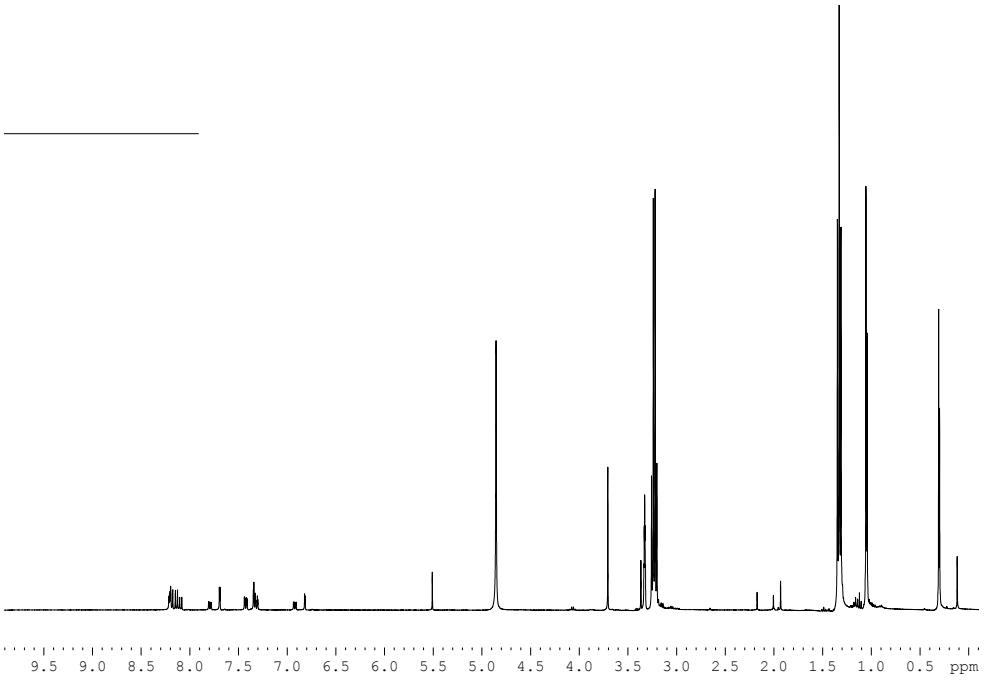
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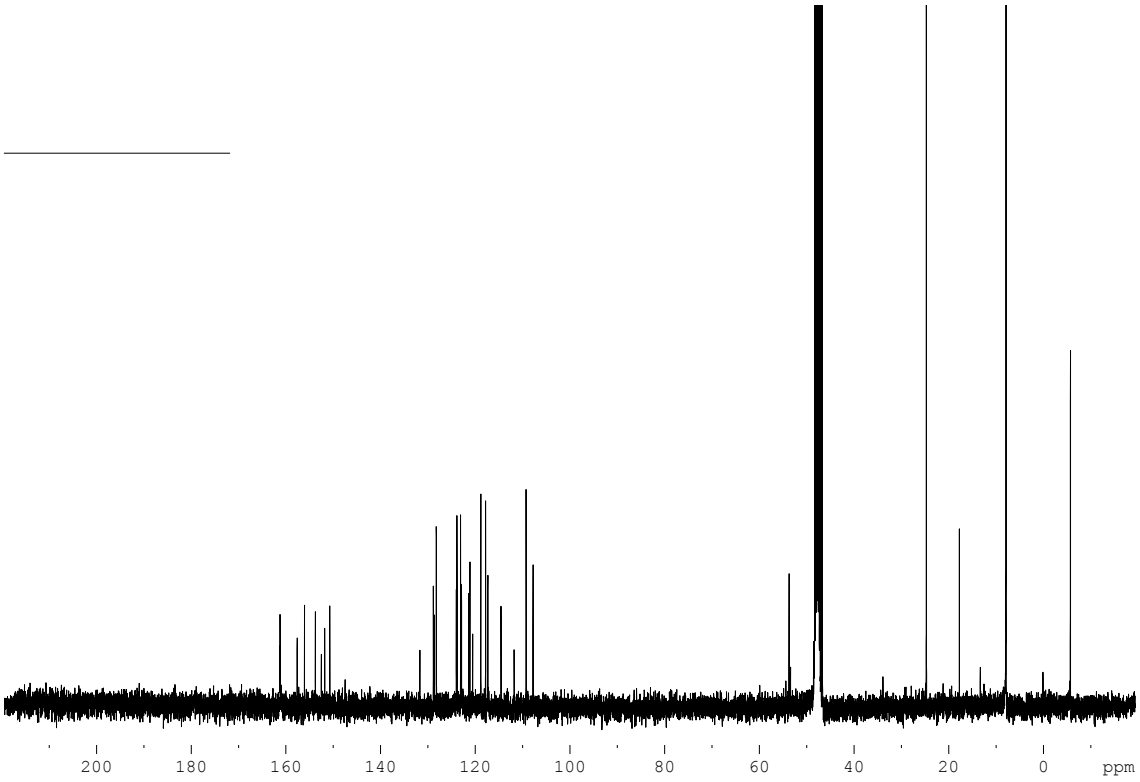
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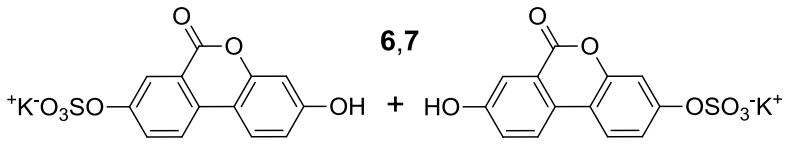
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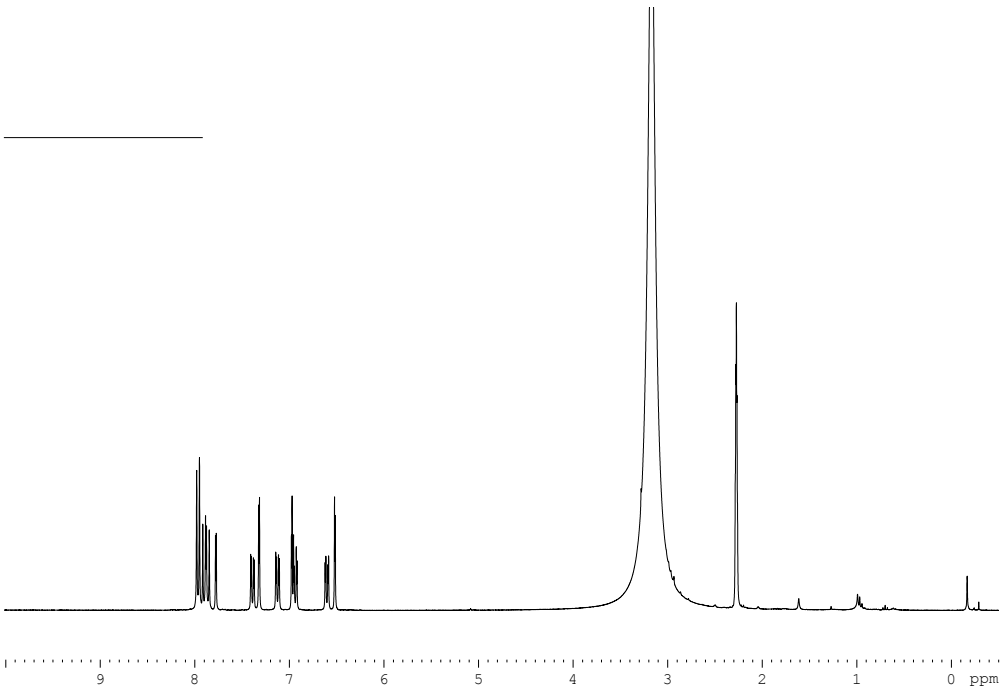
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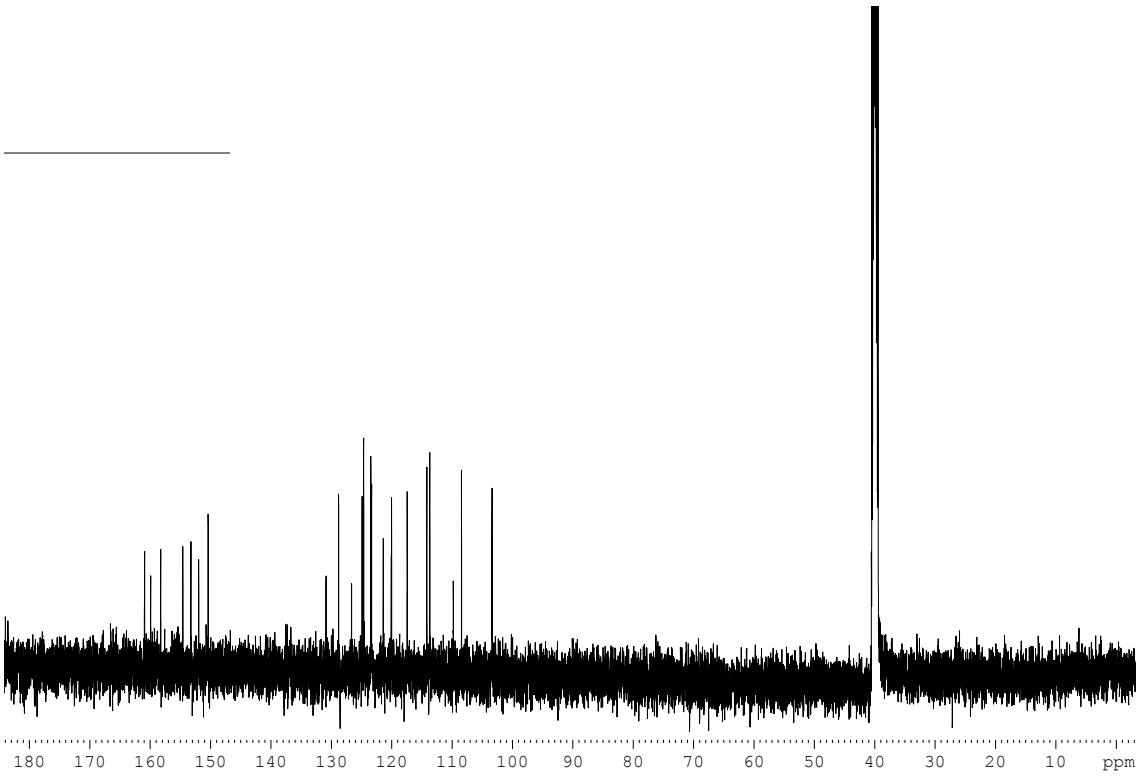
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