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for

A Mitochondriotropic Derivative of Quercetin: A Strategy to Increase the Effectiveness of Polyphenols

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Table S1. Chemical shifts (δ) and, enclosed in parenthesis, chemical shift changes (Δδ) of the aromatic protons of quercetin (**1**) and 3-(4-O-chlorobutyl) quercetin (**4**) in [D_6]DMSO for the assignment of the O-alkylation site.

Compound	Chemical shifts (*d*) and chemical shifts changes (Δ*d*)				
	δ(H-6)	δ(H-8)	δ(H-5')	δ(H-6')	δ(H-2')
Quercetin (1)	6.194	6.405	6.887	6.544	7.683
Compound 4	6.189 (-0.005)	6.397 (-0.008)	6.893 (+0.006)	7.436 (+0.892)	7.514 (-0.169)

The data in Table S1 show that while the chemical shift of H-6, H-8, H-5' are very similar in **4** and in **1**, those of H-2' and H-6' differ significantly, thus suggesting that O-alkylation has occurred at C-3. Table S2 shows that similar trends are found for pentaacetylquercetin and 3',4',5,7-tetraacetyl-3-(4-O-chlorobutyl) quercetin (**5**) thus supporting the assignment of C-3 as the site of O-alkylation.

Table S2. Chemical shifts (*d*) and, enclosed in parenthesis, chemical shift changes (Δd) in $CDCl_3$ of the aromatic protons of pentaacetylquercetin and of compound **5**, for the assignment of the O-alkylation site.

Compound	Chemical shifts (δ) and chemical shifts changes (Δδ)				
	δ(H-6)	δ(H-8)	δ(H-5')	δ(H-6')	δ(H-2')
Pentaacetylquercetin	6.876	7.333	7.351	7.717	7.690
Compound 5	6.822 (-0.054)	7.297 (-0.036)	7.346 (-0.005)	7.975 (+0.258)	7.919 (+0.229)

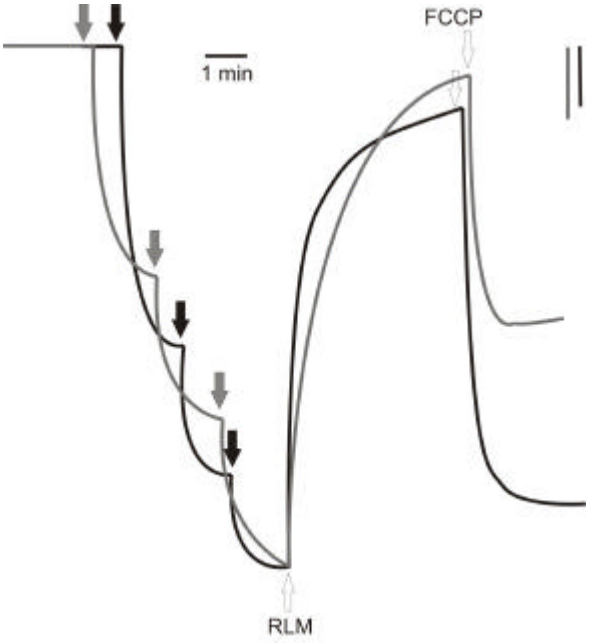


Figure S1. Accumulation of tetraphenylphosphonium (Ph_4P^+) (black) and 3',4',5,7-tetraacetyl-3-(4-O-triphenylphosphoniumbutyl) quercetin iodide (**7**) (gray) by rat liver mitochondria (RLM). Thick arrows indicate the addition of 0.067 µM $Ph_4P^+I^-$ or **7** to the medium (in mM: sucrose 200, HEPES/K^+ 10, succinate/K^+ 5, NaH_2PO_4 1, rotenone $1.25x10^{-3}$; pH 7.4). Addition of RLM (1 mg prot.·mL^{-1}) causes upward deflection of the traces since respiring mitochondria develop a matrix-negative transmembrane potential, and thus take up the positively charged, permeant compounds, which also bind in part to mitochondrial components. Addition of FCCP (in this experiment 0.33 µM), a classic $\Delta\psi_m$-dissipating protonophore (uncoupler), causes extensive release of the compounds. The traces have been normalized to take into account the different response of the electrode in the two cases, which is quantified by the bars in the upper right corner.

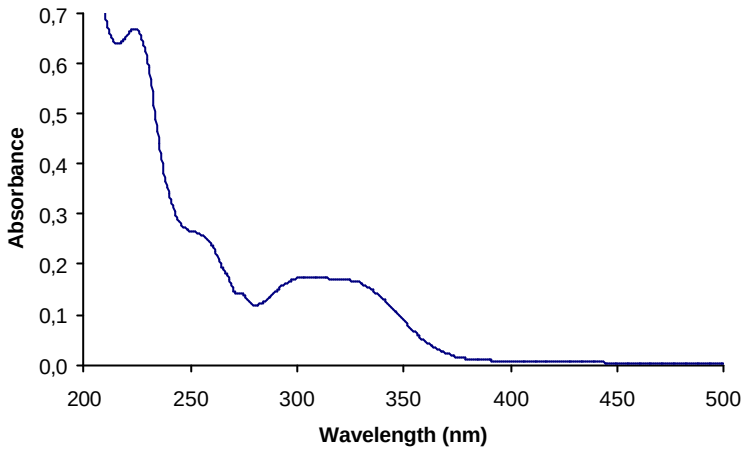


Figure S2. UV/Vis spectrum of **7** (20 µM) in HBSS:CH_3CN 9:1.

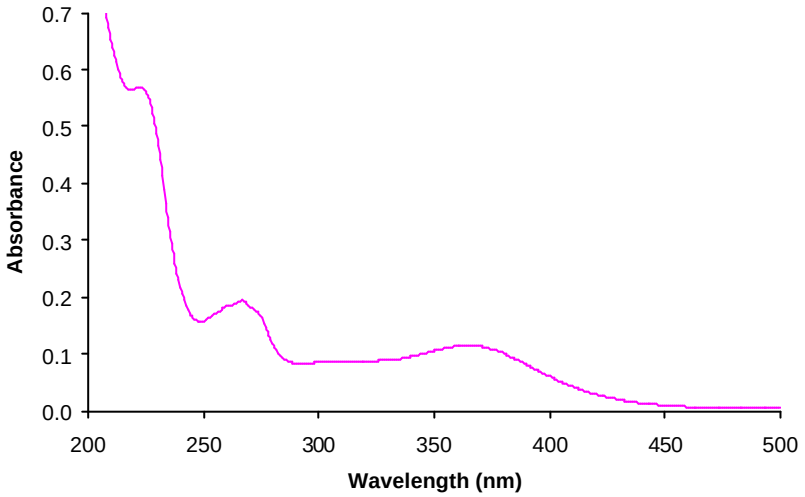


Figure S3. UV/Vis spectrum of 3-(4-O-triphenylphosphoniumbutyl) quercetin iodide (**9**; 10 µM) in HBSS:CH_3CN 9:1.

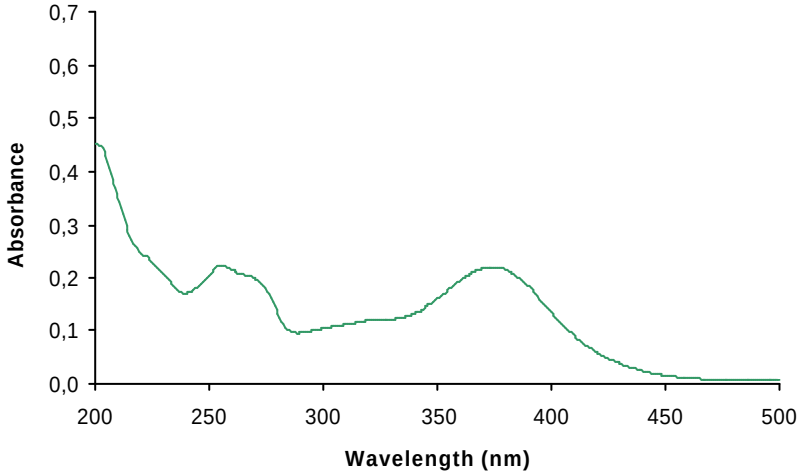


Figure S4. UV-Vis spectrum of quercetin (16 µM) in HBSS:CH_3CN 9:1.

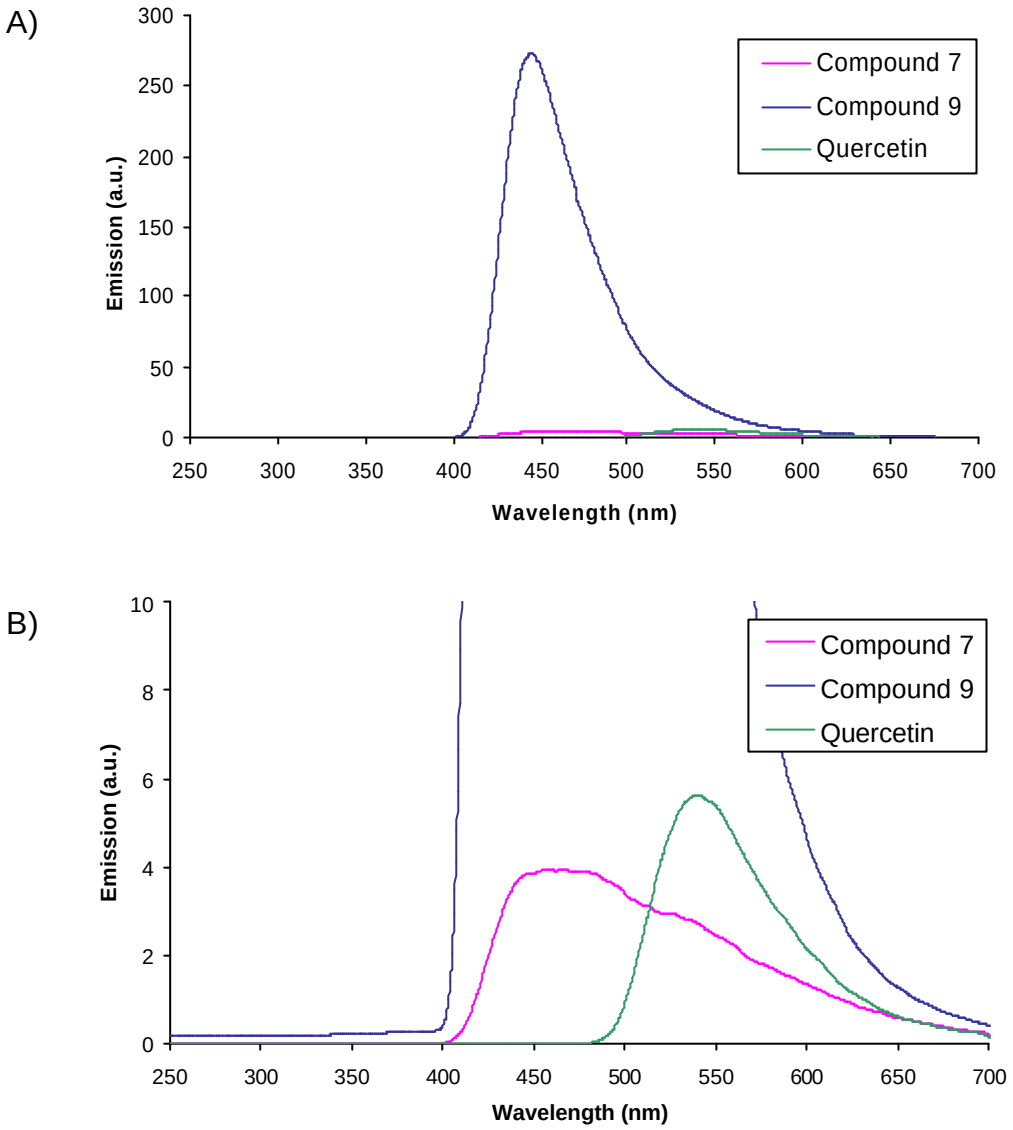
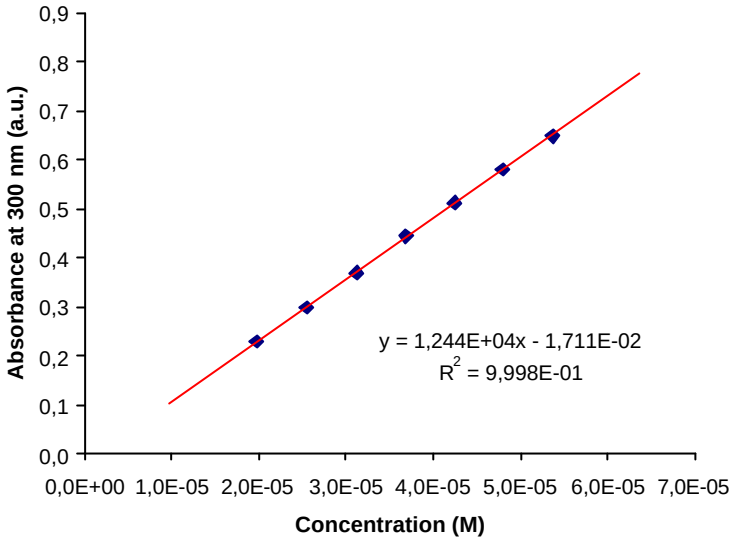


Figure S5. Fluorescence spectra of quercetin, **7** and **9** (2 μM in HBSS containing 0.1% DMSO) at 25°C. The spectra are shown in A and B with different ordinate scales. Compound **7** and quercetin were excited at 380 nm, the wavelength used in microscopy experiments (Figure 4). Compound **9** was excited at 360 nm (its absorption maximum) instead of 380 nm in order to remove a Raman scattering band.



Experimental data	
Concentration (M)	**Absorbance at 300 nm (a.u.)**
$1.97 \cdot 10^{-5}$	0.2291
$2.55 \cdot 10^{-5}$	0.2983
$3.12 \cdot 10^{-5}$	0.3693
$3.68 \cdot 10^{-5}$	0.4453
$4.24 \cdot 10^{-5}$	0.5121
$4.79 \cdot 10^{-5}$	0.5806
$5.37 \cdot 10^{-5}$	0.6485

Figure S6. Calibration curve for the determination of the aqueous solubility of compound **7**.