Supporting information for:

Synthesis and Evaluation of Artemisinin-based Hybrid and Dimer Derivatives as Antimelanoma Agents.

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Content

SI #1. Stability of compound 11iv by TLC analysis

Compound 11**iv** (10 mg) was dissolved in the cell culture medium (10 mL) under gentle magnetic stirring, and the mixture was left for 48 h at room temperature. Any 6.0 h a sample of the cell culture medium (0.5 mL) was extracted with ethyl acetate (0.5 mL) and the organic phase was analyzed by precoated aluminium silica gel SIL G/UV254 plates (Ma-cherey-Nagel & Co.) using hexane/EtOAc 4:1 as eluent. Commercially available tyrosol and artesunate were used as references.

SI #2. Stability of compound 11iv by HPLC analysis

Compound **11iv** (10 mg) was dissolved in the cell culture medium (10 mL) under gentle magnetic stirring, and the mixture was left for 48 h at room temperature. At the end the cell culture medium (0.5 mL) was extracted with ethyl acetate (0.5 mL) and the organic phase was analyzed by Agilent 1220 Infinity LC system including a degasser, a binary-pump, a thermostated column oven and a UV/vis detector. The column used was a Purospher®STAR RP-18 endcapped (12.5 cm length, 4 mm I.D., 5 µm particle size) from Merck (Germany), 1 mL min^{-1} flowrate with an EtOH:water (5:95, v/v) mixture as mobile phase, in isocratic elution mode. Detection wavelength for signal monitoring was fixed at 280 nm and runtime was set at 60 min. The sample was compared with commercially available tyrosol and original **11iv** as references. As reported in Figure S3 no degradation of **11iv** occurred in the reported experimental conditions.

Figure S1. HPLC analysis of compound 11iv

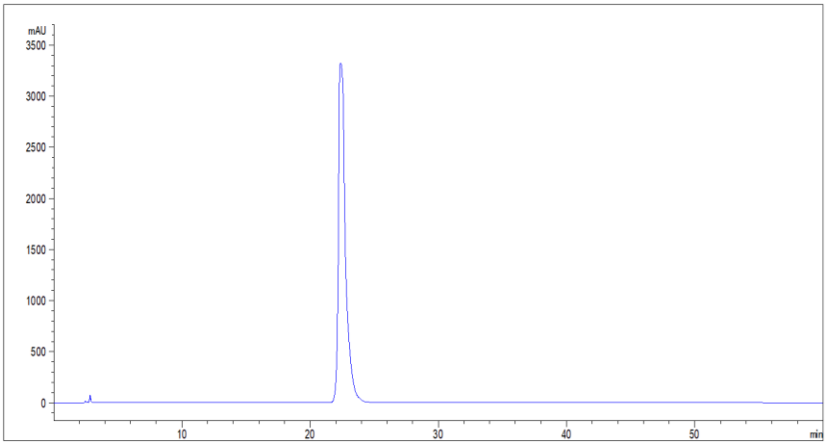


Figure S2. HPLC analysis of tyrosol 8

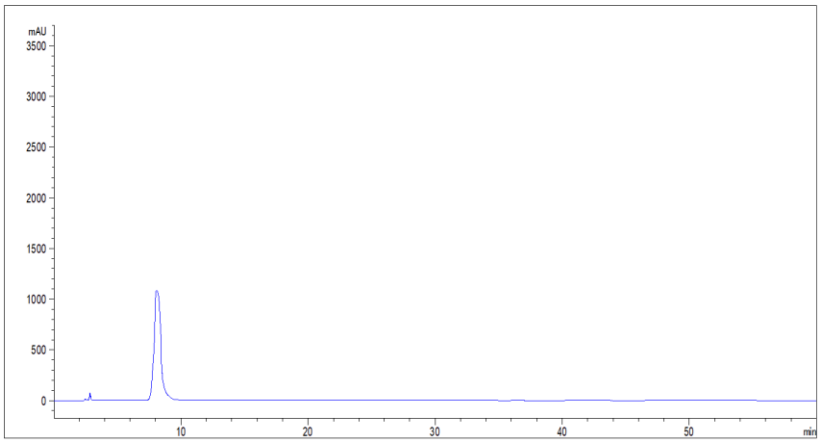
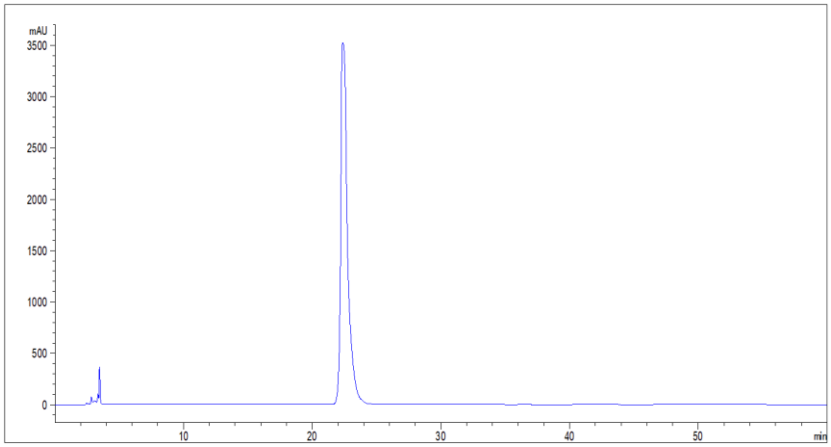


Figure S3. HPLC analysis of compound 11iv after 48h treatment with cell culture medium at room temperature



SI # 3. EPR experiments

Continuous wave (CW) X-band (9 GHz) EPR measurements were carried out with an E580 Elexsys Series spectrometer (Bruker Biospin GmbH, Rheinstetten, Germany) equipped with a Bruker ER 049X microwave bridge and a high sensitivity 4122SHQE/0208 cavity. 0.8x1.0 mm I.D.xO.D. capillaries were used for the EPR room temperature experiments. Samples were prepared in a MeCN/ H_2O (1:1 molar ratio) where the products at a concentration of 60 mM were dissolved with the addition of 2-methyl-2 nitrosopropane (MNP) 70 mM, and at the end, to start the reaction, $Fe(II)SO_4$ 70 mM was added. Experimental conditions are: 0.1mT modulation amplitude, 0.3 mW microwave power, 9.864 GHz microwave frequency. The spectra were recorded at t = 0 (considered after the addition of $Fe(II)SO_4$ to the solution) reaction time and at different times after the reaction was started.

Figure S4. Spectra of compound **11iv** recorded at room temperature CW-EPR in the presence of MNP, iron salt and at different times: a) t=0, b) t=30min, c) t=60min, d) t=90min, e) t=150min.

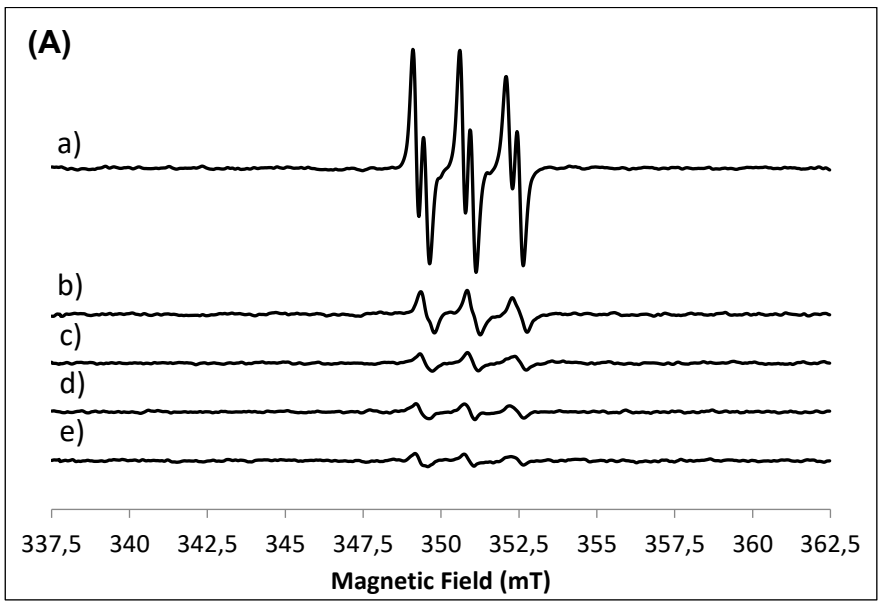


Figure S4. Experimental conditions: ν=9.86GHz, 0.1mT modulation amplitude, 0.63mW microwave power.

Figure S5. Spectra of compound **11iii** recorded at room temperature CW-EPR in the presence of MNP, iron salt and at different times: a) t=0, b) t=30min, c) t=60min, d) t=90min, e) t=150min.

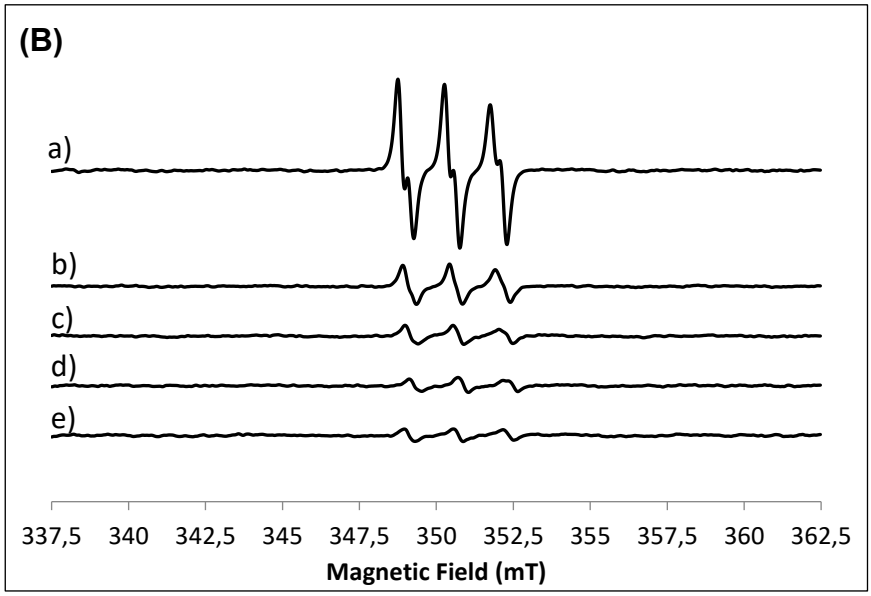


Figure S5. Experimental conditions: ν=9.85GHz, 0.1mT modulation amplitude, 0.63mW microwave power.

Figure S6. Spectra of compound **11ix** recorded at room temperature CW-EPR in the presence of MNP, iron salt and at different times: a) t=0, b) t=30min, c) t=60min, d) t=90min, e) t=150min.

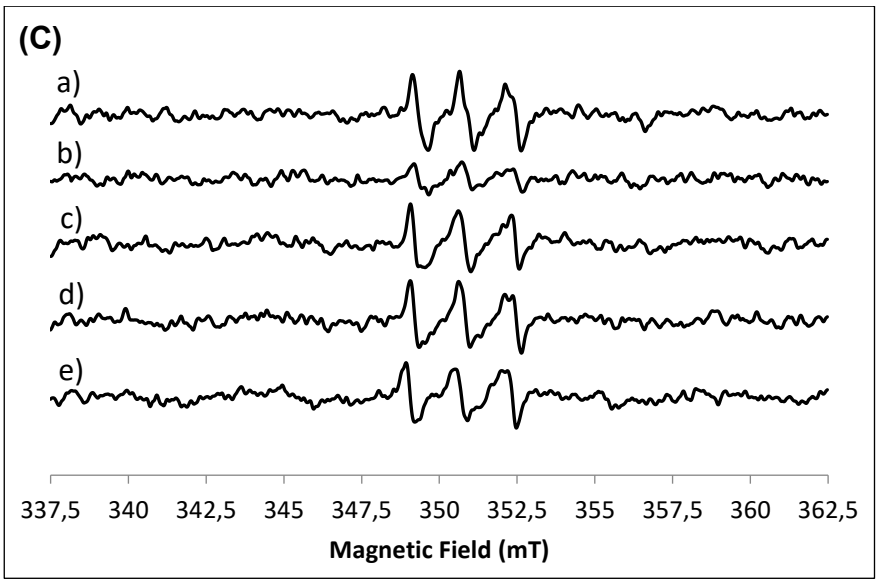


Figure S6. Experimental conditions: ν=9.86GHz, 0.1mT modulation amplitude, 0.63mW microwave power.

Figure S7. Spectra of Artesunate recorded at room temperature CW-EPR in the presence of MNP, iron salt and at different times: a) t=0, b) t=30min, c) t=60min, d) t=90min, e) t=150min.

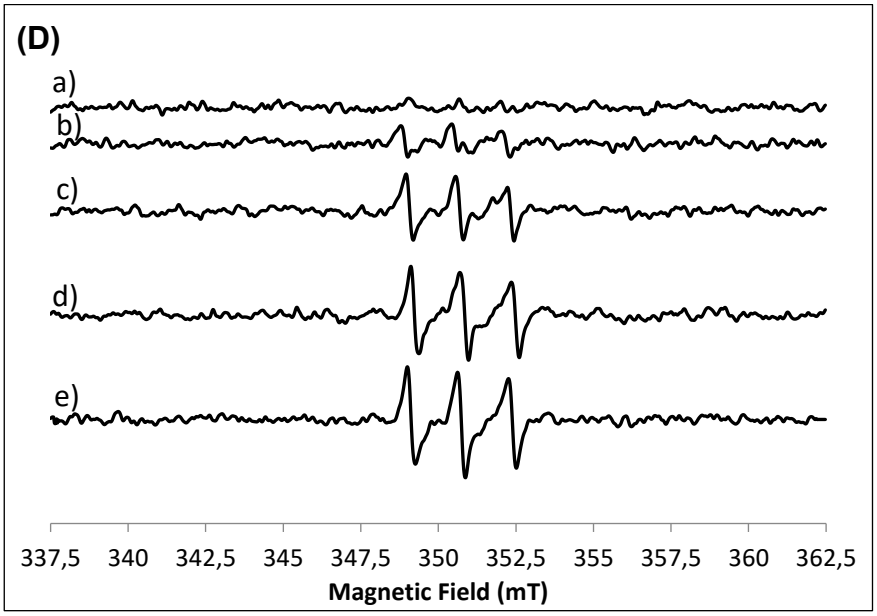


Figure S7. Experimental conditions: ν=9.85GHz, 0.1mT modulation amplitude, 0.63mW microwave power.

Figure S8. Spectra of compound **11viii** recorded at room temperature CW-EPR in the presence of MNP, iron salt and at different times: a) t=0, b) t=15min, c) t=30min, d) t=60min, e) t=90min, f) t=150min.

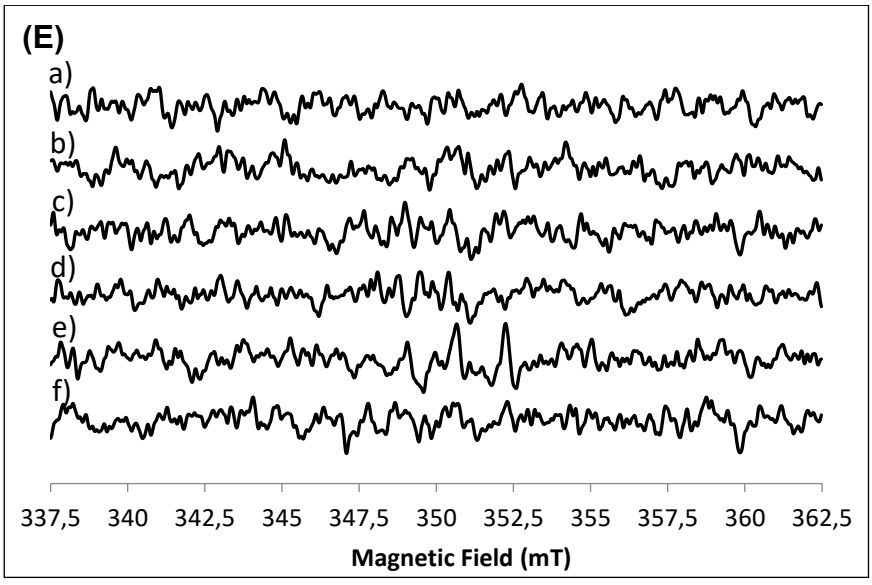


Figure S8. Experimental conditions: ν=9.86GHz, 0.1mT modulation amplitude, 0.63mW microwave power.