Interaction of thiolato-bridged dinuclear arene ruthenium complexes with phospholipids and model membranes

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Thiolato-bridged dinuclear arene ruthenium complexes are highly cytotoxic against various cancer cell lines with IC_{50} values of up to 30 nM [1]. A recent *in vivo* study has demonstrated that these complexes have potential as anticancer drugs, as one complex significantly prolongs the survival of tumor-bearing mice [2]. Interestingly, these complexes are very stable under physiological conditions as well as acidic and basic conditions, and they are particularly inert toward substitution. Only sulfur containing biomolecules such as cysteine and glutathione undergo catalytic oxidation in their presence [3].

Since many aspects of cellular uptake and of the tumor-inhibiting action displayed by these complexes are still largely unknown, we have studied the interactions of three trithiolatho complexes with different degrees of lipophilicity $[(\eta^6\text{-}p\text{-}MeC_6H4Pr^i)_2Ru_2(R^1)_2(R^2)]^+$ (R^1 = SC_6H_4-*m*-Pr^i :**1**; R^2 = SC_6H_4-*m*-Pr^i :**1**; R^1 = SC_6H_4-*p*-OMe :**2**; R^2 = SC_6H_4-*p*-OH :**2**; R^1 = $SCH_2C_6H_4$-OMe :**3**; R^2 = SC_6H_4-*p*-OH :**3**) and of one dithiolato complex $[(\eta^6\text{-}p\text{-}MeC_6H4Pr^i)_2Ru_2(SCH_2C_6H_5)_2Cl_2]$:**4** with lipid membrane models in form of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC) vesicles, 1,2-dihexanoyl-sn-glycero-3-phosphocholine (DHPC) micelles and sodium dodecyl sulfate (SDS) micelles by nuclear magnetic resonance (NMR) spectroscopy and other techniques. 1D ^{1}H NMR spectra, 2D ^{1}H diffusion ordered spectroscopy (DOSY) spectra and T2 (spin-spin) relaxation time measurements together with electrospray ionization mass spectrometry (ESI-MS) suggest noncovalent interaction between the vesicles and the three trithiolato complexes. As expected, the strength of the interaction with the vesicles parallels the lipophilicity of the complexes. The results with the dithiolato complex **4**, on the other hand, suggest that none or only very weak interaction takes place. **1** was further studied with DOPC in presence of the lanthanide shift reagent $PrCl_3$ for estimating if the complex remains at the vesicle surface, is inserted between the fatty acid chains or is localized inside the DOPC vesicle.

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