Phototoxic Antitumour properties of Rhenium porphyrin conjugates

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Photodynamic therapy (PDT) is a therapeutic procedure that can exert a selective cytotoxic activity toward malignant cells. As photosensitizing agents (PSs), compounds based on a tetrapyrrole structure, similar to that of the protoporphyrin contained in haemoglobin, are largely used, thanks to their preferential uptake and retention by tumour tissues. An intriguing strategy is the conjugation of peripheral metal fragments to porphyrins for making compounds that might combine the cytotoxicity of the metal moiety to the phototoxicity of the porphyrin chromofore for additive anti-tumour effects. So far very few examples of metal-porphyrin conjugates as potential PSs in PDT are reported, mainly focused on Ruthenium (Schmitt et al., 2008; Gianferrara et al., 2010; Zhang et al., 2012). Among them some Ru(II)-porphyrin conjugates described by us demonstrated a promising phototoxic activity at low doses of visible light (Gianferrara et al., 2010). However, they also exhibited a cytotoxic activity in the dark that could be an unfavourable factor for further evaluations. Therefore, we decided to evaluate other metal fragments, such as Rhenium(I) to obtain, porphyrin conjugates with different and improved features.

Here we describe two new water soluble porphyrins, bearing in peripheral position a diethylenetriamine unit for tridentate coordination **(1)**, or a bipyridyl bidentate chelator connected to the macrocycle through a flexible and hydrophilic linker **(2)**, and of their water-soluble metal conjugates that bear in peripheral position a *fac*-$[Re(I)(CO)_3]^+$ fragment (**3** and **4**, respectively). All compounds show moderate to good singlet oxygen quantum yields, not significantly different from those of the parent porphyrins. Their use as potential PSs was evaluated in the human HeLa cell model of cervical carcinoma. All the porphyrin conjugates affect the *in vitro* growth of the HeLa cells only marginally in the dark, but become cytotoxic after exposure to visible light in the red region of the spectrum, also showing high photostability under the conditions used for the PDT test. The resulting phototoxicity is directly proportional to the total light dose applied and directly related to the ability of the compounds to penetrate cells, a feature favouring **(1)** and **(3)** where the diethylenetriamine ligand is conjugated to an uncharged porphyrin core. These data indicate the Re-porphyrin conjugates as endowed of interesting photosensitizing properties, and extend the knowledge on the metal-porphyrin conjugates as potential agents in PDT.

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