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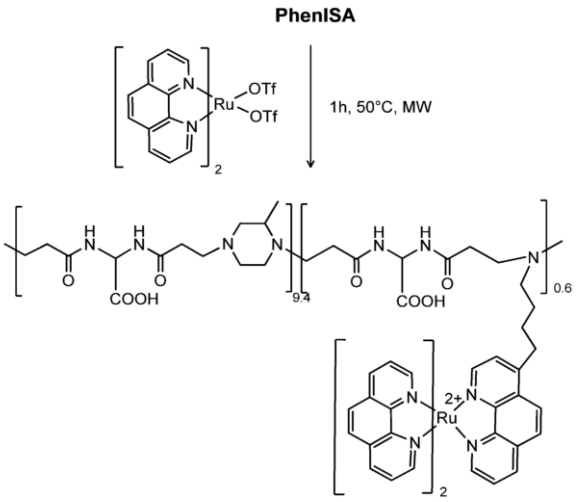
A nucleus-entering ruthenium-based polymeric nanosized photosensitizer for efficient photodynamic therapy

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Abstract

Linear amphoteric polyamidoamines (PAAs) with phenanthroline pendants are water-soluble degradable and biocompatible synthetic polymers capable to self-structure into stable nanoparticles. Due to their multifunctional nature, PAAs can form stable complexes with different heavy metal ions. In this work, we report on the synthesis of three nanostructured ruthenium-trisphenanthroline [$Ru(phen)^{32+}$] complexes and the study of their potential as photosensitizers for photodynamic therapy (PDT), a treatment of solid tumors based on the photoactivation of bioactive compounds that are not harmful in the absence of specific light irradiations. Of these complexes, Ru-PhenISA and Ru-PhenAN, are polymer conjugates containing 6%, on a molar basis, photoactive units. Their performance is compared with that of $Ru(phen)_2BAP^{2+}$ (BAP = 4-(4'-aminobutyl)-1,10-phenanthroline), chosen as a model of the photoactive repeat units. The polymer ligands, PhenISA and PhenAN, are polyamidoamines (PAAs) with different acid base properties. At physiological pH, the former is zwitterionic and the latter moderately cationic. Both are intrinsically cytobiocompatible. Photophysical characterizations show that polymer conjugation does not hinder the $Ru(phen)_3^{2+}$ ability to generate the toxic singlet oxygen by irradiation. The phosphorescence lifetimes and quantum yields are similar in all cases. All tested compounds kill HeLa cells by irradiation with visible light, with relative PDT efficiency: Ru-PhenAN>$Ru(phen)_2BAP^{2+}$>Ru-PhenISA. The same dose of light is harmless for control cells. Flow cytometry demonstrates that the relative cell internalization efficiency of the three complexes governs their PDT efficacy. Intracellular localization studies show that while $Ru(phen)_2BAP^{2+}$ is confined in vesicular structures, the Ru-polymer complexes escape the endolysosomal pathway, a behavior already reported for PAAs of similar structure. Interestingly, Ru-PhenAN proves capable to penetrate into cell nucleus in all treated cells. This explains its superior PDT power and suggests potential for application in gene delivery as a nucleus targeting carrier.

Synthesis of the Ru-PhenISA polymer complex



[a]MW = microwave.

Photograph



Biography

Prof. Elisabetta Ranucci is full professor in Industrial Chemistry at the University of Milan, were she teaches courses of polymer science. Her research interests are in the area of biodegradable and biocompatible polymers for applications in nanomedicine: a) chiral polymers for molecular recongnition; b) self-assembling polymers as drug carriers; c) decoration of inorganic nanoparticles for antitumor therapy; d) as antiviral and antimalarial agents; e) as nanovectors for cellular imaging. Bioinspired polymers with flame-retardant activity; f) nanocomposite hydrogels as scaffolds for tissue regeneration. He published more than 140 papers in peer-reviewed journals.