



Glycosylated zinc phthalocyanine-gold nanoparticle conjugates for photodynamic therapy: Effect of nanoparticle shape

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ABSTRACT

In this work, we report on the synthesis of tris-[(2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methoxy)-2-(4-benzo[d]thiazol-2-yl)phenoxyphthalocyaninato] zinc(II) (complex **3**) and its linkage to gold nanoparticles (AuNPs) of different shapes through S-Au/N-Au self-assembly. The conjugates of complex **3** (with both gold nanorods (AuNR) and nanospheres (AuNS)), displayed decreased fluorescence quantum yield with corresponding improved triplet and singlet quantum yields compared to complex **3** alone, however **3**-AuNR showed improved properties than **3**-AuNS. Complex **3** showed relatively low *in vitro* dark cytotoxicity against the epithelial breast cancer cells with cell survival $\geq 85\%$ at concentration $\leq 160 \mu\text{g/mL}$ but afforded reduced photodynamic therapy activity which may be due to aggregation. **3**-AuNR afforded superior PDT activity with $<50\%$ viable cells at concentration $\geq 40 \mu\text{g/mL}$ in comparison to **3**-AuNS with $<50\%$ viable cells at concentration $\geq 80 \mu\text{g/mL}$. The superior activity of **3**-AuNR is attributed to the photothermal therapy effect since nanorods absorb more light at 680 nm than nanospheres.

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1. Introduction

Photodynamic therapy (PDT) involves the systemic administration of a suitable photosensitizer (PS), followed by activation of the localized PS in the tumor by light of a specific wavelength. The excited triplet state of the PS then transfers its energy to the ground state molecular oxygen resulting in the production of singlet oxygen which is the main cytotoxic species responsible for the lysis of unhealthy cells [1]. Metallophthalocyanines (MPcs) are a class of dyes used in various fields, such as in nonlinear optics [2], photodynamic therapy (PDT) [3,4], and photodynamic antimicrobial chemotherapy (PACT) [5]. Their ability to efficiently generate singlet oxygen, ease of chemical modification and strong absorption in the near infrared region, make them viable and efficacious photosensitizers (PS) for photodynamic therapy [3].

Despite the many successes recorded for the PDT activity of MPcs, there remain some drawbacks which include lack of selectivity and specificity towards cancer cells in comparison to healthy ones. To address these drawbacks, various approaches such as: encapsulation of the PS in colloidal carriers (liposomes [6,7] or polymeric micelles [8,9]), and conjugation of the PS to antibodies [10,11], synthetic peptides [12–14], nanoparticles [15,16] and carbohydrates [17–22] have been explored.

Glycosylated MPcs are promising PS candidates for use in PDT. Cancer cells are reported to have an increased uptake for sugars and over-

express glucose transporter proteins due to their increased demand for metabolic energy [23–25]. An isopropylidene protected tetra β -glycosylated zinc(II) phthalocyanine was reported to have shown high uptake and photodynamic cytotoxicity in MCF-7 cells [22]. Hence, glycoconjugation of the PSs improves their membrane interaction and uptake by cancer cells, thus increasing tumor selectivity [17,26,27]. Additionally, carbohydrates improve water solubility, an important parameter for cellular uptake of the PSs [17,28].

On the other hand, low symmetry MPcs offer greater advantages over their symmetrically substituted analogue due to possession of specific binding site for attachment to drug delivery agents [29]. The existence of different functional groups in low symmetry Pcs allow for the coexistence of several features in a molecule, and therefore an improvement in the Pc's properties.

Heterocyclic compounds containing sulphur and nitrogen, known as benzothiazole and their derivatives have been shown to possess good photosensitizing as well as anticancer activity [30,31]. In view of the photosensitizing importance of benzothiazoles and glycosylated phthalocyanines, a combination of these functional structures into one is expected to serve as potential PS for PDT. Apart from these, the sulphur and nitrogen in the benzothiazole ring will provide site for the non-covalent interaction of the phthalocyanine to metallic nanoparticles such as Au nanoparticles (AuNPs).

In this work, we report for the first time the synthesis of low symmetry tris-[(2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methoxy)-2-(4-benzo[d]thiazol-2-yl)phenoxyphthalocyaninato] zinc(II) (complex **3**) as well as the

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