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Synthesis, photophysics and photochemistry of phthalocyanine-ε-polylysine conjugates in the presence of metal nanoparticles against *Staphylococcus aureus*

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ABSTRACT

This work reports on the photodynamic activity of Zn phthalocyanine-ε-polylysine conjugates in the presence of gold and silver nanoparticles (NPs) towards the inactivation of *Staphylococcus aureus* (*S. aureus*). The conjugates showed high photoinactivation with ~6% growth at a drug dose of 3 μM and fluence of 39.6 mW/cm^2 for 10 min irradiation time in the presence of silver nanoparticles. The presence of silver nanoparticels from the minimal inhibition concentration (MIC_{50}) studies showed remarkable growth inhibition for the tested conjugates even at low concentrations. The MIC_{50} was lowest for the conjugate of **3** with ε-polylysine at concentrations of less than 0.0058 μM in the presence of AgNPs. The lethal photosensitization of microorganisms has emerged as a promising treatment since bacteria have reduced possibilities of developing resistance to photodynamic therapy.

1. Introduction

Phthalocyanine (Pc) derivatives have gained significance in a number of fields including their use as photosensitizers (PSs) in photodynamic therapy (PDT) for cancer treatment [1–5]. The effectiveness of Pc derivatives as PDT agents is caused by their high absorption coefficient ($\varepsilon > 10^5\ M^{-1}\ cm^{-1}$) in the phototherapeutic window (600–800 nm) coupled with a long triplet lifetime to generate cytotoxic singlet oxygen ($^1O_2$) [6–9]. Singlet oxygen is extremely reactive and it destroys biomolecules, while the quantum yield of singlet oxygen production is strongly dependant on the type of photosensitizer used. The need for new phthalocyanine derivatives with improved photophysical characteristics is always high due to the large variety of therapeutic applications [10–12]. The photodynamic activity of Pcs is not only limited to cancer treatment [13], it has also been applied to the inactivation of bacteria [14], viruses [15] and yeasts [16]. Similar to PDT, photodynamic antimicrobial chemotherapy (PACT) involves the use of a non-toxic photodynamically active drug that is activated by visible light of appropriate wavelength to produce reactive oxygen species (ROS) that inactivates microorganisms [17–19]. Although the use of PACT for the treatment of infections is still under investigation, it has potential as a distinct method in case of multidrug-resistant pathogens [20]. Phthalocyanines (Pcs) have been found to inactivate a number of microbial pathogens via photodynamic inactivation [21]. In this study, zinc phthalocyanine (ZnPc)-ε-polylysine (ε-PL) conjugates were synthesized as photodynamic sensitizers for inactivation of *Staphylococcus aureus* (*S. aureus*). This bacterium was chosen due to its permeable outer membrane that allows for the diffusion of agents, as a defence mechanism. Such bacteria tend to develop resistance to antimicrobial agents.

Conjugates of phthalocyanine complexes with polylysine are known for symmetrically substituted (with four COOH groups) Pc derivatives [22]. This work reports, for the first time, on the coordination of a Pc derivative substituted with a single COOH group to ε-PL. A phthalocyanine substituted with a single COOH group will give a more defined coordination on one point on the phthalocyanine ring unlike for Pc containing four COOH groups. However low symmetry substituted phthalocyanines as described in this work are difficult to synthesize hence are very few. The Pc complex is 4-tetrakis-(5-trifluoromethyl-2-pyridyloxy) phthalocyaninato zinc(II), **3**, Scheme 1. The resulting conjugate with ε-PL is represented as **3-ε-PL**. The 5-trifluoromethyl-2-pyridyloxy substituents of complex **3** were chosen for solubility and to prevent aggregation. The inactivation of *S. aureus* is compared to that of $ZnPc(SO_3)_4$ linked to ε-PL after first forming the sulfonyl chloride intermediate (**2**, Scheme 2). The resulting conjugate is represented as **2-ε-PL**. The inactivation of bacteria by **2-ε-PL** and **3-ε-PL** is studied in the absence and presence of Au and Ag nanoparticles.

ε-Polylysine (ε-PL) is a naturally produced, cationic homopolymer that is water soluble and non toxic to humans [23]. It is reported

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