Journal of Photochemistry & Photobiology, A: Chemistry 438 (2023) 114535

Contents lists available at ScienceDirect

Journal of Photochemistry & Photobiology, A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Photodynamic inactivation of methicillin-resistant *Staphylococcus aureus* using pyrrolidinium containing Schiff base phthalocyanines

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ARTICLE INFO

Keywords:
Phthalocyanine
Schiff base
Singlet oxygen
Photodynamic Antimicrobial Chemotherapy
Methicillin-resistant *Staphylococcus aureus*

ABSTRACT

New tetra-substituted zinc and indium Schiff base phthalocyanines (ZnPc and InPc, respectively) are synthesized and characterized herein. The ethyl pyrrolidine (**ZnPc-2**, **InPc-2**) and propyl pyrrolidine (**ZnPc-3**, **InPc-3**) substituted Schiff base Pcs were reacted with methyl iodide to form their cationic derivatives (**ZnPc-2Q**, **InPc-2Q**, **ZnPc-3Q**, and **InPc-3Q**, respectively). The photophysical and photochemical properties of the Pcs were studied. The cationic Pcs generated higher singlet oxygen quantum yield in aqueous media than the neutral Pcs. The photoinactivation of Methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin-sensitive *Staphylococcus aureus* (MSSA) strains was evaluated. 5 μM **ZnPc-3Q** and **InPc-3Q** inactivated 100 % of the MSSA and MRSA while 5 μM **ZnPc-2Q** and **InPc-2Q** eradicated 100 % for MSSA and 97.2 % and 98.7 % (respectively) of the MRSA. The photodynamic antimicrobial chemotherapy studies depended on singlet oxygen ability, the charges, and the extension of the alkyl groups.

1. Introduction

The emergence of drug-resistant micro-organisms requires urgent attention [1]. Increased antibiotic consumption and their misuse have exacerbated the prevalence of resistant micro-organisms [2,3]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most commonly found bacteria in hospitals worldwide [4,5]. In 2017, the World Health Organization classified MRSA as a high-priority multi-drug resistant pathogen [5]. Due to the ineffectiveness of conventional antibiotics, an alternative therapeutic approach against infections with multi-resistant bacteria is needed. Over the years, photodynamic antimicrobial chemotherapy (PACT) has been used as a mode of action for the treatment of multi-resistant bacteria [6,7]. This application relies on three components, light, a photosensitizer (PS), and the generation of reactive oxygen species (ROS) such as singlet oxygen, hydrogen peroxide, and superoxides which subsequently cause permanent cellular damage.

Several PSs have been used in the photoinactivation of various micro-organisms, including MRSA [8–11]. One of the most commonly used PSs are phthalocyanines (Pcs). Pcs are 18 π-electron macrocyclic compounds characterized by their ability to efficiently generate singlet oxygen, and they can be fine-tuned by the introduction of different substituents on the aromatic ring and by a change in the central metal [12,13]. Phthalocyanines with one or more cationic groups exhibit high antimicrobial activity [14–19], since cationic phthalocyanines are more effective than neutral and anionic Pcs against most bacteria [20]. Hence, this work employs imine-pyrrolidine phthalocyanines in order to utilize the quaternizable nitrogen groups. Pyrrolidine moiety has been found to be bioactive, exhibiting anticancer and antimycobacterial properties [21,22]. Furthermore, the introduction of diamagnetic (and heavy) central metals such as indium and zinc results in improved intersystem crossing (ISC) from the singlet to the triplet state resulting in increased singlet oxygen quantum yields [23,24]. Schiff base complexes exhibit pharmacological and biological properties such as antitumour, antioxidant, anti-bacterial, antifungal, and anti-inflammatory activities [25,26], hence may enhance the antimicrobial activity of Pcs by synergistic effect. Antioxidant activity of a Schift base substituted phthalocyanine has been reported [27].

Herein, novel neutral and cationic zinc and indium phthalocyanines substituted with pyrrolidine moiety are synthesized. These complexes were evaluated for their photophysical and photochemical properties such as triplet state and singlet oxygen quantum yields. The photodynamic inactivation of MRSA and MSSA (methicillin-sensitive *Staphylococcus aureus)* was investigated and the antibacterial activities were compared. Furthermore, the effect of increasing the hydrocarbon chain was evaluated, and the Pcs' uptake in the bacterial culture is reported.

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https://doi.org/10.1016/j.jphotochem.2022.114535
Received 9 November 2022; Received in revised form 13 December 2022; Accepted 30 December 2022
Available online 31 December 2022