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# Indium phthalocyanines: Comparative photophysicochemical properties and photodynamic antimicrobial activities against *Staphylococcus aureus* and *Escherichia coli*

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ABSTRACT

In this study, the photodynamic antimicrobial activities of a series of new tetra-substituted indium phthalocyanine (InPc) complexes are assessed. An aldehyde substituted complex (**2**) was initially prepared, which was converted through a condensation reaction to an imine-pyrrolidine substituted complex (**3**), which in turn was quaternized to form a tetracationic species (**4**). Favorable photophysicochemical properties were obtained by incorporating a heavy In(III) ion into the central cavity. Aggregation studies revealed that **2–4** remain non-aggregated in DMSO at concentration below 25 μM. The photodeactivation of *S.aureus* and *E.coli* was studied. Log reduction values > 9.0 were obtained for cationic InPc **4** after 30 min of incubation and exposure to light for 75 min.





## 1. Introduction

The prevention of infectious diseases is the focus of considerable research efforts. For many decades, antibiotics such as penicillin have been developed for use against pathogens. The effect of an antibiotic on a microorganism is explained by binding to a specific target and inhibiting cellular function [1]. However, the widespread and inappropriate use of antibiotics has caused antimicrobial resistance to emerge as a global clinical problem [2]. As antibiotics become ineffective, new research efforts have been developing to deal with this problem. In recent years, photodynamic antimicrobial therapy (PACT) based on the inactivation of microorganisms by oxidative stress has been the focus of considerable interest. This method involves the use of a photoactive compound called a photosensitizer (PS) and visible light to excite the PS. The interaction between the PS and laser light causes molecular oxygen to be converted to singlet oxygen that cause irreversible damage to cell components such as lipids, proteins and DNA, resulting in bacterial death [3]. This method is considered to be a promising alternative for microbial cell deactivation. Key advantages of PACT are that it can cause the death of a wide variety of microbes, such as gram-(+) and gram-(-) bacteria, light-resistant species are unlikely to develop, and PACT kills the microorganisms quickly, while the effect of antibiotics often takes several days [4].

The most studied PS dyes for PACT are based on tetpyrrolic macrocycles, with a particular emphasis on phthalocyanines (Pcs) [5–7]. Cationic phthalocyanines have been found to be the most effective molecules for the inactivation of microorganisms for PACT applications [8–11]. The preference for cationic species can be explained according to the structural differences in the cell walls of bacteria. While gram-(+) bacteria walls are relatively permeable for neutral or anionic Pcs, only positively charged Pc species can readily cross the microbial permeability barrier of gram-(-) bacteria [12,13]. Introducing functional bioactive groups as peripheral substituents can alter the photophysicochemical properties and antibacterial responses of Pc complexes. An imine- pyrrolidone moiety was selected for study (Scheme 1). Pyrrolidone has C=O, C–N and $CH_2$ functional groups, which are nontoxic and biocompatible with human tissue. As is also the case with the imine (C=N) group, pyrrolidone units are known to have biological activities and hence potential for applications in drug development [14,15].

In this study, In(III) has been selected as the central ion since it facilitates axial ligand which can help reduce aggregation and increase solubility in physiological media. Metallo phthalocyanines (MPcs) of heavy diamagnetic elements promote intersystem crossing resulting in high triplet state quantum yields and long-lived

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