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Study on the synthesis and antimicrobial activity of novel cationic porphyrins

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Abstract

A novel series of quaternary ammonium cationic derivatives based on tetrapyridyl-porphyrin was synthesized. All the compounds were evaluated for their *in vitro* antibacterial activities against *S. aureus*, *E. coli* and *P. aeruginosa*, and antifungal activities against *C. albicans*, where microorganisms were exposed and unexposed to the irradiation. The results revealed that some of these compounds, especially, **3a** and **4a** displayed satisfactory antibacterial activity against Gram-positive bacteria *S. aureus* and moderate antifungal activity against *C. albicans*. Unfortunately, Gram-negative bacteria *P. aeruginasa* was resistant to all compounds. The antimicrobial activity was found to be sensitive to the functional groups attached on the aromatic ring and the complex metal in the porphyrin ring, and decreased with the increase of electron-withdrawing capability of the functional groups. These preliminary results suggested that the remarkable antibacterial efficiency against *S. aureus* makes these substances promising antimicrobial agents.

Keywords: Cationic porphyrin; Synthesis; Antimicrobial activity; Gram-positive bacteria; Gram-negative bacteria; Fungus

Recently, infectious diseases have dramatically increased and become a major threat to public health, despite tremendous progress in medicinal chemistry. The impact is more acute in developing countries due to nonavailability of desired medicines and emergence of widespread drug resistance [1]. Antimicrobial resistance settings have failed to address this essential aspect of drug usage [2], specially, multi-drug-resistant Gram-positive bacteria including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) have emerged as a significant problem in both community and hospital acquired infections [3]. A number of antibiotics that seemed to be efficacious in clinic have been becoming less effective due to development of resistance. Therefore, there is an urgent need for new potent and safe anti-infectives and methods which can treat infectious diseases easily and successfully.

The antimicrobial photodynamic therapy (antimicrobial PDT), a treatment modality that utilizes photosensitizers (PSs) and visible light to induce an oxidative damage to microbial pathogens, could be a useful alternative to systemic medications in treating localized infections, because its multi-target process unlikely induces resistance in

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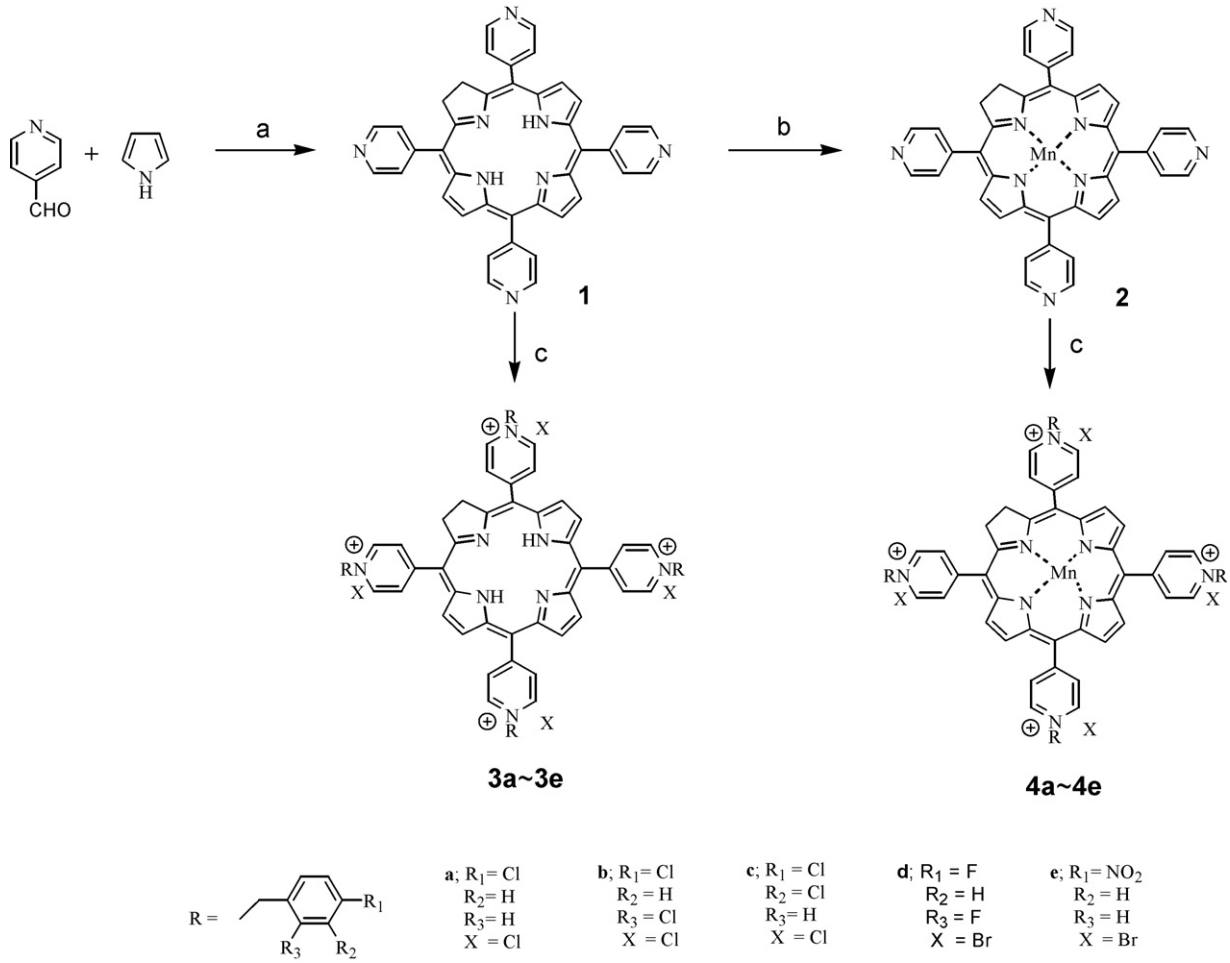

Scheme 1. The synthesis route of target compounds. Reagents: (a) $CH_3CH_2CO_2H$, reflux; (b) $Mn(OAc)_2$, HOAc, reflux, 6 h; (c) benzyl halide, DMF, 100 °C, 30 h.

microorganisms [4]. The marked beginning of photodynamic therapy (PDT) is that the killing of the microorganism paramecia with the combination of acridine and light a little over 100 years ago. Not only the application of PDT in the filed of tumor treatment has proliferated since the first regulatory approval was granted in Canada for the use of PDT in 1993 [5], but also the *in vitro* research on photodynamic antimicrobial agents has attracted many attention [6]. Among all PSs reported, porphyrin-based PSs, which consist basically of porphyrin-like building unit and a suitable linker to modulate the interaction between the recognizing and signaling units, have received great attention due in part to the unique photochemical and biological performances of porphyrin.

In this paper, we wish to report the synthesis of a series of novel porphyrin quaternary ammonium salts and the results for their biological activity evaluation on some normal and resistant bacterial strains.

Based on some reports, cationic porphyrin manifest more unique superiority than anionic or neutral porphyrin in antimicrobial activity [6], and a moderate degree of lipophilicity achieved by the introduction of aromatic hydrocarbon side chains on the pyridyl moieties may improve PSs efficiency [7], we chose to introduce benzyl substituents bearing one or two electron-withdrawing groups, such as fluorine, chlorine and nitro group, on nitrogen of pyridyl groups to obtain quaternary ammonium salts in order to synthesize molecules endowed with increasing lipophilicity and different polarity. We designed these structures owing to a recent PDT report which indicated that the presence of fluorine, chlorine and nitro groups could improve significantly the antitumor activity [8]. On the other hand, in view of our previous works, the metal ion in the porphyrin ring played an important role in the antitumor activities of PSs [9], we synthesized further manganese compounds of aforesaid quaternary ammonium salts to compare the antimicrobial activities between metal porphyrin and free porphyrin.