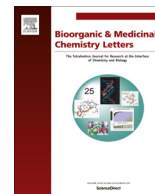




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Novel polycarboxylate porphyrins: Synthesis, characterization, photophysical properties and preliminary antimicrobial study against Gram-positive bacteria

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ABSTRACT

We describe the synthesis, characterization and photophysical properties of two new polycarboxylic photosensitizers. Owing to their structural design, these two compounds show water solubilities larger than natural carboxylic photosensitizers (e.g., protoporphyrin IX, hematoporphyrin, etc.) and also good singlet oxygen quantum yields. These compounds were tested as photo-antimicrobial agents against *Staphylococcus aureus* and *Bacillus cereus* strains. Results reveal that their photocytotoxicities are strongly dependent on their amphiphilic character and more precisely the number and position of the carboxylic acid and mesityl substituents.

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Antimicrobial resistance is a global issue of concern, highlighted by failure of antibiotic treatment of previously treatable infections, additional morbidity and skyrocketing health care costs.¹ Multiresistant strains represent major causes of nosocomial infections, well exemplified by methicillin-resistant *Staphylococcus aureus* (MRSA).² Hence, the urgent need of new and more powerful therapeutic strategies. Photodynamic antimicrobial chemotherapy (PACT) is a promising approach to overcome such stubborn infections.³ PACT relies on the photochemical activation of a photosensitive drug that, in presence of dioxygen, gives rise to reactive oxygen species (ROS) which rapidly react with a variety of biomolecules then leading to cell damaging and eventual death.⁴ So, increasing effort has been recently devoted to the design and synthesis of highly structured artificial porphyrin rings in order to increase their efficiency against bacteria. Owing to their hydrophobicity, tetrapyrrolic macrocycles are prone to form aggregates in aqueous media with a concomitant decrease in the production of ROS.⁵ Covalent grafting of hydrophilic motifs has been used to increase the amphiphilic character of these photosensitizers,⁶ and, hence, their ability to bind and diffuse across bacterial walls and membranes; these motifs can be summarized according to their chemical structure: cation (pyridinium, quaternary ammonium),⁷ anion (sulfonate, carboxylate or phosphonate),⁸ peptides,⁹ carbohydrates,¹⁰ polyethylene glycol,¹¹ polyamine¹² and their derivatives.

Biological results have shown that Gram+ as well as Gram– bacteria prove more sensitive to PACT when photosensitive macrocycle bear positive charges.^{4,13} Nevertheless, natural porphyrins and their derivatives such as Photofrin[®], hematoporphyrin, protoporphyrin IX (Fig. 1), deuteroporphyrin and chlorin e6 which possess anionic charges (carboxylate moieties) have attractive photophysical properties that allow their use in photodynamic therapy of tumors (PDT)¹⁴ and photodynamic antimicrobial chemotherapy (PACT).¹⁵

However, carboxylic acid motif has been less studied than the other water solubilization moieties. Indeed, despite the good results obtained even on highly resistant micro-organisms, only few studies have reported the photophysical and antimicrobial activities of porphyrins bearing carboxylic acid moieties.^{16,17} As shown by recent studies, Gram-positive bacteria such as MRSA have developed resistance to various antibiotics including β -lactams (oxacillin and ampicillin), vancomycin.¹⁸ Thus, in this work, we have focused on the evaluation of antimicrobial activity of anionic photosensitizers against Gram+ bacteria because their cytoplasmic membrane is surrounded by a relative porous layer of peptidoglycan and lipoteichoic acid which allow easier penetration of neutral or anionic photosensitizers. In this paper and in connection with our work on the synthesis of new amphiphilic tetrapyrrolic photosensitizers,^{10,12} we describe the synthesis, characterization and photophysical properties of two new porphyrins bearing six or eight carboxylic functions attached to the macrocycle (Scheme 1). Number and position of these functional groups

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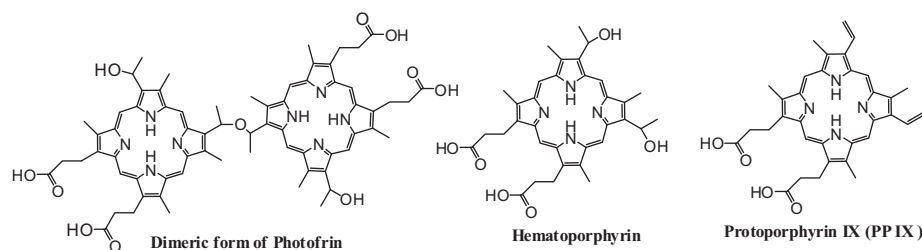
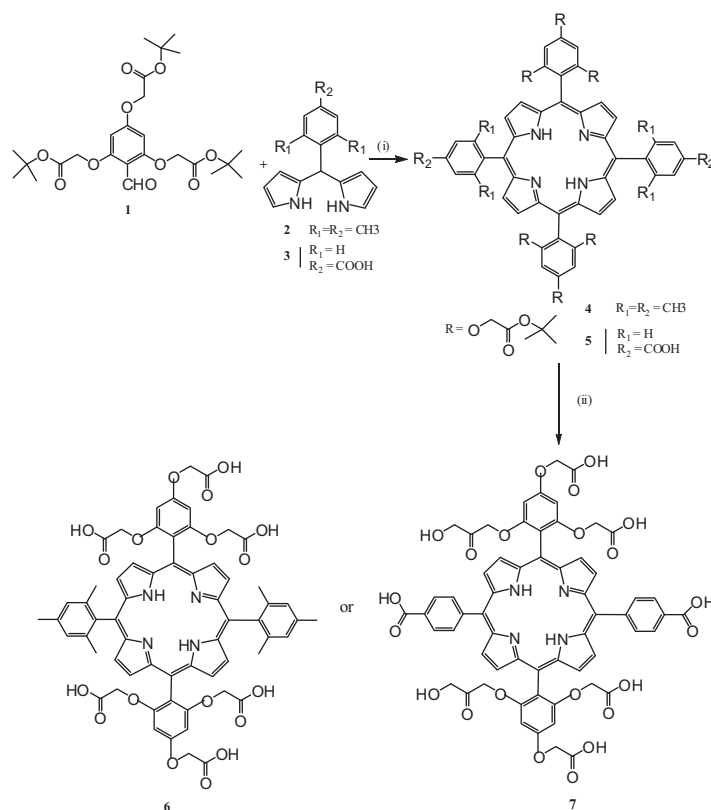


Figure 1. Some example of natural photosensitizers bearing polycarboxylic acid function.



Scheme 1. Synthesis route of porphyrins **6** and **7**. Reagents and conditions: (i) BF_3OEt_2 , $CHCl_3$, 40 min, then DDQ, 1 h, rt; (ii) formic acid, rt, 14 h.

are different in order to study their influence on the amphiphilic character and on the antimicrobial activity against Gram+ bacteria. Moreover, the presence of substituent (methyl or carboxymethoxy groups) should decrease aggregation phenomena of these compounds in aqueous media.

The synthetic route followed for the preparation of carboxylic porphyrin derivatives is depicted in Scheme 1 and the synthesis was performed according to a literature method.^{19,20} In a first time, 2,4,5-tris(*tert*-butoxycarbonylmethoxy)benzaldehyde **1** and *meso*-dipyrromethane **2**, **3** have been synthesized. Aldehyde **1** bearing protected carboxylic acid groups is the key parent molecule for the synthesis of porphyrins **6** and **7**. It was obtained by alkylation of 2,4,6-trihydroxybenzaldehyde with *tert*-butylbromoacetate in the presence of an excess of K_2CO_3 with a yield of 63%. Dipyrromethane **2** and **3** were synthesized by solvation of the corresponding aldehyde in excess pyrrole in presence of TFA; after purification and recrystallization compounds **2** and **3** were obtained with 38% and 50% yields, respectively. In a second part, condensation of aldehyde **1** with dipyrromethane **2** or **3** in anhydrous $CHCl_3$ in presence of 0.1 equiv of BF_3OEt_2 then 0.9 equiv of DDQ gave after purification by flash chromatography, porphyrins **4** in 20% and **5** in 10%

yield, respectively. Acidic hydrolysis of *tert*butyl groups was performed with an excess of formic acid at room temperature for 14 h. After solvent evaporation, carboxylic porphyrin derivatives **6** and **7** were obtained in quantitative yields. The structures of all compounds were assessed by the means of 1H , ^{13}C NMR and by mass spectrometry (MALDI-TOF) (see Supporting information).

Photophysical studies were carried out with all porphyrins. Normalized absorption spectra of compounds **6** and **7** in various solvents (MeOH, H_2O and phosphate buffered saline (PBS, pH = 7)) are displayed in Figure 2. Wavelengths of maximum absorbance (λ) and corresponding molar extinction coefficient (ϵ) values are summarized in Table 1.

Porphyrins **6** and **7** in MeOH show similar absorption spectra which are typical of *etio*-porphyrins.²¹ It is also worth noting that similar absorption features are observed for protected porphyrins **4** and **5** in MeOH. However, compound **7** forms a green solution in distilled water (pH = 6.2, see Supporting information) and exhibits an intense Q_1 band and a broadened red-shifted Soret band. Such kind of spectral behavior has been attributed to the diacid porphyrins obtained by protonation of the central nitrogen core.²² To confirm this hypothesis, UV-visible absorption spectra of **7**

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