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Synthesis and characterization of biocompatible bimodal *meso*-sulfonamide-perfluorophenylporphyrins

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ABSTRACT

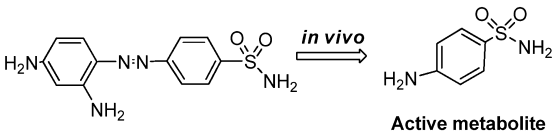
Herein we describe a synthetic strategy for preparing a set of *meso*-aryl sulfonamide-perfluorinated porphyrins by covalent binding in order to obtain new chemical entities that can potentially target bacteria and act both as bacteriostatic and photosensitizing agents. The conditions optimized allow to selectively obtain porphyrins containing the desired number of sulfonamide substituents. The new compounds showed a broad range of 1-octanol/water partition coefficients and singlet oxygen quantum yields from 0.59 to 0.74. Our results demonstrate that sulfonamide-perfluorinated porphyrins are a promising platform for biomedical applications, particularly in aPDT and medical imaging.

1. Introduction

The presence of fluorine atoms in organic compounds with potential application in pharmacology has been increasingly exploited in recent years [1–4]. Notably, nearly 20% of pharmaceutical compounds contain at least one fluorine atom nowadays [5], since it is well established that the replacement of a hydrogen by an electronegative fluorine atom, with C–F bond energy of 105.4 kcal/mol, can significantly influence pharmacological outcomes, metabolic stability, selectivity and physical properties. [6,7,1] Thus, the development and optimization of new organic molecules bearing fluorine atoms in their constitution is an area of increasing interest in medicinal chemistry. In addition, in our previous studies [8–10], we have demonstrated that the presence of fluorine atoms in a sulfonamide-tetrapyrrolic macrocycles originated photosensitizers with ideal PDT photophysical properties and/or remarkable photostability [11–21].

Sulfonamides are celebrated antibacterial agents since 1930, owing to the discovery of Prontosil (Scheme 1) and the recognition that sulfonamides can inhibit the enzyme dihydropteroate synthase [22,23]. Numerous active antibiotics containing this class of compounds have been discovered and marketed [23,24], but they have the major drawback of originating antibiotic-resistant bacteria [25,26]. According to the World Health Organization, National data obtained for *E. coli*, *S.* and *K. pneumoniae*, and *S. aureus* showed that the proportion resistant to commonly used antibacterial drugs exceeded 50% in many settings [27].

The development of new molecular entities capable of promoting the inactivation of bacteria without developing drug resistance depends on finding alternative mechanisms of action for antibiotics. Antimicrobial photodynamic therapy (aPDT) [28,29] is emerging as an alternative to classical antibiotics because aPDT is not associated with the development of microorganism resistance after treatment [30–32]. The most successful photosensitizing agents used in aPDT are porphyrin derivatives. The appropriate design and structural modulation of tetrapyrrolic macrocycles to enhance membrane permeation in all classes of microbial cells, along with appropriate photophysical properties, may drive aPDT to a clinically acceptable alternative to antibiotics.



Scheme 1. *In vivo* metabolism of Prontosil.

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The synthetic difficulties and scarce availability of natural porphyrinoids [29,33,34], led to the use of *meso*-substituted tetrapyrrolic macrocycles, easily obtained by sustainable synthetic methods [12,35–38], as the main choice for the development of new generations of PDT agents [8,9,39]. 5,10,15,20-Tetrakis(pentafluorophenyl)porphyrin (TPFPP) is an interesting template to functionalize *via* nucleophilic substitution reactions [40], making use of nucleophiles such as amines, thiols, alcohols and nitrogen heterocycles [41,42], to improve their avidity for bacteria. However, to the best of our knowledge, the use of sulfonamides as nucleophiles in this functionalization has not yet been described.

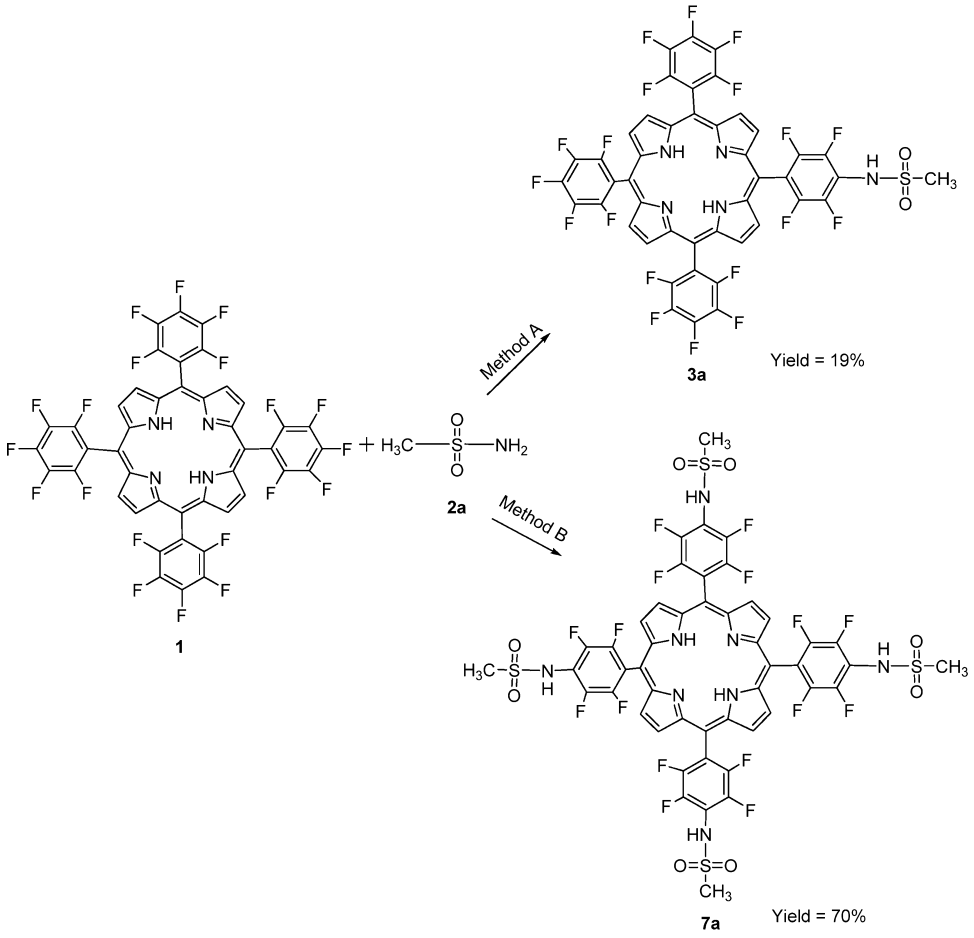
This work presents new methods for the synthesis of bimodal molecules that incorporate sulfonamides and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin in their structure, in order to attain new chemical entities that can potentially target bacteria and act both as bacteriostatic and photosensitizing agents. Additionally, this work presents the fundamental photophysical assessment of the new photosensitizers, namely in terms of their electronic absorptions, singlet oxygen quantum yields and 1-octanol/water partition coefficients. Our results show that sulfonamide TPFPPs are a promising platform for biomedical applications, particularly in aPDT and medical imaging.

2. Results and discussion

In order to prepare *meso*-aryl fluorinated porphyrins containing sulfonamide groups, we first synthesized 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin **1** following our recent improvement of the nitrobenzene synthetic methodology [43]. NaY was used as recoverable Lewis acid catalyst for the condensation of pyrrole with pentafluorobenzaldehyde in an acetic acid/nitrobenzene mixture [35], yielding the desired porphyrin **1** in 9% yield. Next, the studies to selectively prepare the mono or tetra-substituted fluorinated-sulfonamide porphyrins were carried out using the commercially available methanesulfonamide as nucleophile (Scheme 2).

As expected, the concentration of the reactants was crucial to selectively obtain the mono *vs* tetrasubstituted compound. In a typical experiment, the fluorinated porphyrin **1** was dissolved in dioxane (5.1×10^{-3} M), mixed with six equivalents of methanesulfonamide (**2a**) and six equivalents of cesium carbonate (Scheme 2, Method A). Then, the reaction was kept at 100 °C for several hours. After work up the crude was purified by silica gel column chromatography (*n*-hexane:ethyl acetate 2:1), followed by preparative thin layer chromatography, affording the 5-[2′,3′,5′,6′-tetrafluoro-4′-methanesulfamoyl)phenyl]-10,15,20-tri-[(2′,3′,4′,5′,6′-penta-fluoro)phenyl]porphyrin **3a** in 19% yield (entry 1, Table 1).

In order to prepare the tetrasubstituted compound, the reaction conditions were changed by increasing the porphyrin concentration to 1.0×10^{-2} M and the ratio porphyrin:sulfonamide:base to 1:18:12 (Scheme 2, Method B). After 48 h at 100 °C, the initial porphyrin completely disappeared, concomitantly with the formation of a complex mixture of products observed by TLC. In addition, we carried out another reaction, under the same conditions, but increasing the concentration of porphyrin **1** to 1.5×10^{-2} M and, surprisingly, a dark solid precipitated out of the reaction, upon room temperature cooling. After filtration, the solid



Scheme 2. Synthesis of mono and tetra substituted fluorinated-sulfonamide porphyrins. Reaction conditions: Method A – porphyrin/sulfonamide ratio 1:6, $[C] = 5.1 \times 10^{-3}$ M; Method B – porphyrin/sulfonamide ratio 1:18, $[C] = 1.54 \times 10^{-2}$ M.