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Synthesis of mono-, di- and triporphyrin building blocks by click chemistry for photodynamic therapy application

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ABSTRACT

In the present work, we describe a successful strategy centered on the use of click chemistry to synthesize mono-, di- and triporphyrin building blocks named $[ZnTPP]_1$, $[ZnTPP]_2$ and $[ZnTPP]_3$. The number of photosensitizers (ZnTPP unit) coupled to the building blocks does not seem to dramatically modify the photophysical properties of the photosensitizer in terms of fluorescence and singlet oxygen formation, quantum yields and lifetime. These building blocks, obtained in high yield, could be combined with a targeting agent (vector) to create new photosensitizer-vector conjugates to investigate the optimum ratio of photosensitizer needed for maximum photodynamic therapy efficiency.

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1. Introduction

Photodynamic therapy (PDT) is a promising treatment involving the concomitant action of: 1) a photoactivatable molecule, the photosensitizer (PS), 2) light of a suitable wavelength, and 3) oxygen present naturally in the biological medium. After photosensitizer excitation by light, energy transfer to the oxygen allows the generation of reactive oxygen species (ROS), and particularly reactive singlet oxygen, which leads to cell death.[1] This technique has proved to be highly effective for the treatment of some types of diseases in various therapeutic fields such as oncology,[2] vascular cardiology,[3] dermatology,[4] gynecology[5,6] or malaria.[7]

Among the various potential photosensitizers that are available, porphyrins have been extensively studied in the field of photodynamic therapy (PDT).[8] Porphyrinic molecules have an aromatic planar architecture capable of developing attractive photophysical properties for PDT applications (Fig. 1), and several exist in nature.[9] Photofrin®, a mixture of porphyrin oligomers, is the most popular one used clinically in PDT and corresponds to the first generation photosensitizers. However, first generation photosensitizers present several drawbacks such as poor light absorption in the red, cutaneous photosensitivity and lack of tumor specificity. To overcome these disadvantages, second and third generations of photosensitizers were developed, for example such as in oncology, a new porphyrin (Visudyne®), chlorins (Foscan®, Talaporfin® or Photochlor®) and phthalocyanine (Photosens®).[10]

One of the proposed strategies for increasing the photodynamic efficiency of photosensitizers is to combine them with a vector capable of selectively binding to specific receptors overexpressed on tumor cell membranes. The various vectors which have been used by members of our team are, among others, peptides and folic acid (FA).[11] FA is specific for the folate receptor alpha (FRα), which is overexpressed in many human cancers (ovary, brain, kidney, breast, myeloid cells, and lung) while peptides (ATWLPPR and DKPPR)[12,13] were used for targeting vascular endothelial growth factor (VEGF) receptor or its co-receptor neuropilin-1 (NRP-1), both overexpressed by tumor cells. These new PS-vector conjugates developed by our team are depicted in Fig. 2.

In the literature, several strategies to synthesize porphyrin conjugates are described[14] but click chemistry appears to be the most effective method and its use in various fields such as biochemistry, and medicinal or surface chemistry, continues to increase year after year. “Click Chemistry” was an idiom introduced in 2001 by Sharpless to cover all organic reactions that could be

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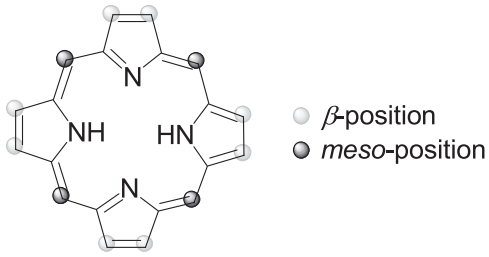


Fig. 1. Typical structure of a porphyrin which can be functionalized at their *β*- and *meso*-positions.

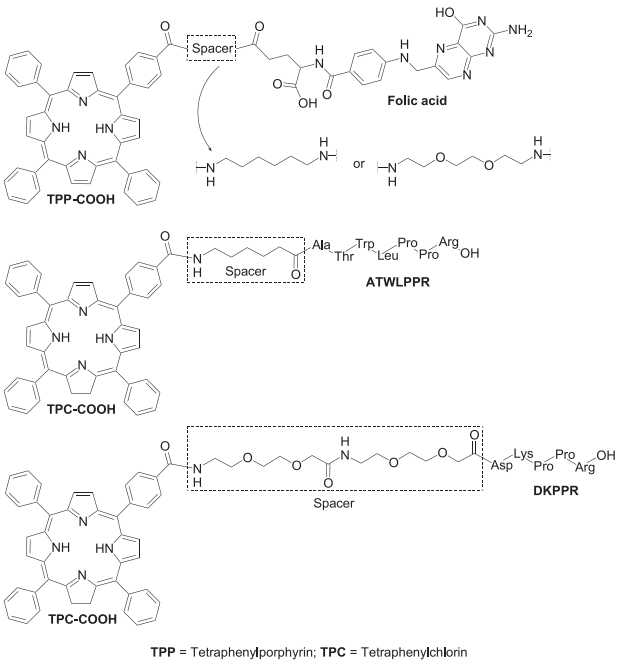


Fig. 2. New PS-vector conjugates developed by our team for PDT applications.

described as modular, wide in scope, high yielding, easy to perform and stereospecific. The reactions must use harmless or easily disposed solvents and have to generate only by-products that can be removed by simple purification techniques.[15]

Among the reactions that are considered as “Click Chemistry”, the most commonly used is the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. The azide-alkyne cycloaddition was first studied by Huisgen et al. in 1968 and the authors' findings showed the slow formation of a mixture of both 1,4- and 1,5-disubstituted 1,2,3-triazole regioisomers (Fig. 3).[16] In 2002, Sharpless and Meldal simultaneously found that the use of the Cu(I) catalyst helps to increase the reaction rate and to obtain only the 1,4-disubstituted regioisomer even at sub-ambient-temperature (Fig. 3).[17,18]

The introduction of the CuAAC reaction has opened up new and

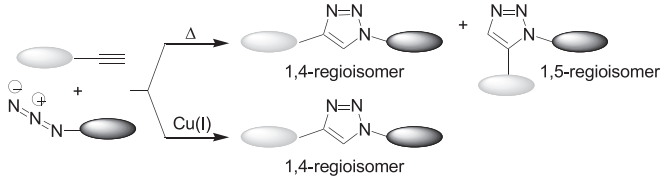


Fig. 3. Huisgen's reaction.

diverse opportunities to combine two building blocks that are difficult to connect by conventional coupling techniques. Recently, the use of a microwave was reported, opening wider applications in the field of click chemistry. In 2015 we published a recapitulative review about the synthesis of porphyrin, chlorine or phthalocyanine conjugates by azide-alkyne click chemistry, and their related applications.[19]

The mild condition of the CuAAC reaction is compatible with the peptidic chemistry and offers the possibility to develop new peptide-based drugs, which could be potentially useful therapeutically.[20] Furthermore, the 1,2,3-triazole ring is highly stable against hydrolysis and could ensure delivery of the conjugated drugs to their targeted receptors.[21]

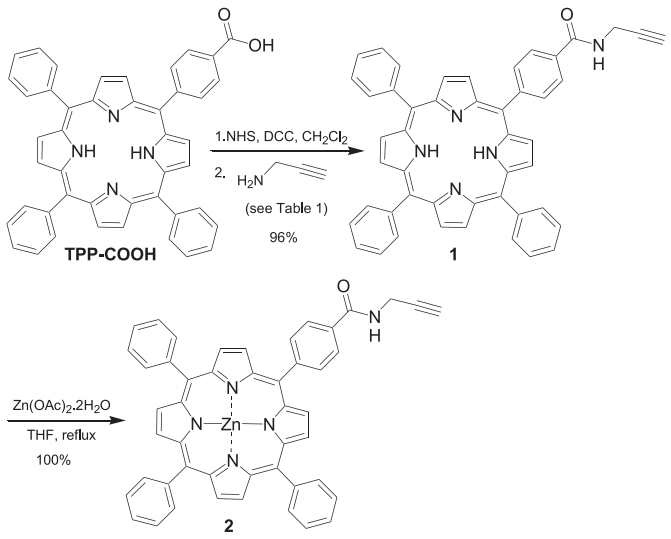
The main goal of this work is to establish a strategy centered on the use of click chemistry to synthesize mono-, di- and tri-porphyrin building blocks abbreviated to $[ZnTPP]_1$, $[ZnTPP]_2$ and $[ZnTPP]_3$ respectively, for easier reading. These building blocks could be combined with a targeting agent (vector) to create new PS-vector conjugates to investigate the optimum ratio of PS needed for maximum PDT efficiency.

2. Results and discussion

2.1. Synthesis of clickable porphyrin scaffold bearing a propargyl group

Our approach was first based on the synthesis of a structurally related derivative of zinc tetraphenylporphyrin (ZnTPP) **2** bearing a propargyl group for linkage upon the CuAAC reaction (Scheme 1), using a protocol similar to that which we reported previously with zinc tetraphenylchlorin (ZnTPC).[22] The metallation of TPP is essential, to avoid copper metallation of the porphyrin ring during the subsequent CuAAC reaction.

5-(4-carbonylphenyl)-10,15,20-triphenyl-21*H*,23*H*-porphyrin (TPP-COOH) was used as starting material and prepared according to the protocol previously described by our team.[23] The TPP-COOH was converted into the propargyl derivative (**1**) in a one-pot two-steps reaction by a classical peptide method (Scheme 1). The first step is the *in situ* activation of the carboxyl group of TPP-COOH by dicyclohexylcarbodiimide (DCC, 1 equivalent) and *N*-hydroxysuccinimide (NHS, 2 equivalents) followed by a coupling reaction with an excess of propargylamine (10 equivalents). Several



Scheme 1. Synthesis of alkyne-functionalized ZnTPP **2.**

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