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

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ABSTRACT

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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 to 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 disease 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 (Figure 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 photosensitizer. 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 photosensitizer were developed, for example such as in oncology, a new porphyrin (Visudyne[®]), chlorins (Foscan[®], Talaporfin[®] or Photochlor[®]) and phthalocyanine (Photosens[®]).¹⁰

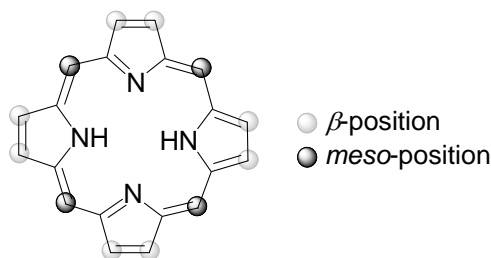


Figure 1. Typical structure of a porphyrin that can be functionalized at β - and *meso*-positions

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, folic acid (FA)¹¹. This is specific for the folate receptor alpha (FR α), which is overexpressed in many human cancers (ovary, brain, kidney, breast, myeloid cells, and lung) and peptides (ATWLPPR and DKPPR)^{12,13} for targeting vascular endothelial growth factor (VEGF) receptor or its co-receptor neuropilin-1 (NRP-1), both over-expressed by tumor cells. These new PS-vector conjugates developed by our team are depicted in Figure 2.

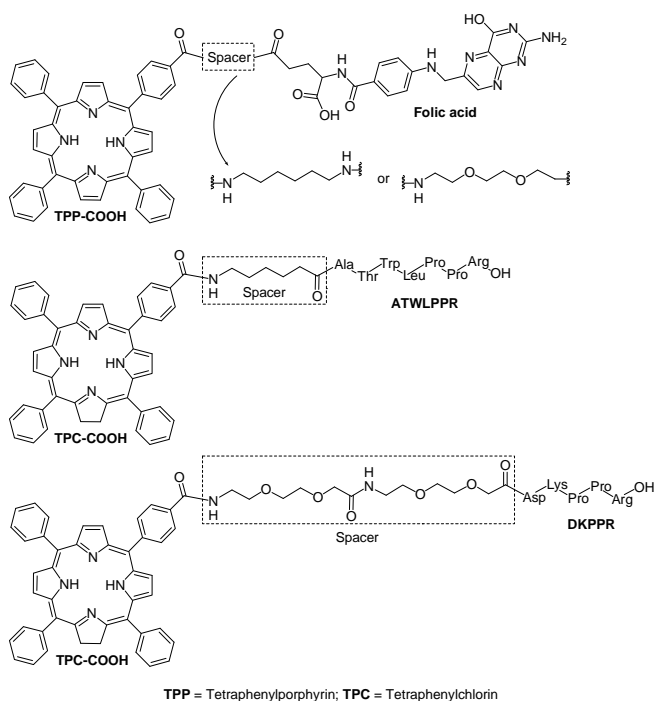


Figure 2. New PS-vector conjugates developed by our team for PDT applications

In the literature, several strategies to synthesize porphyrin conjugates are described¹⁴ 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 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 (Figure 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 regio-isomer even at sub-ambient-temperature (Figure 3).^{17,18}

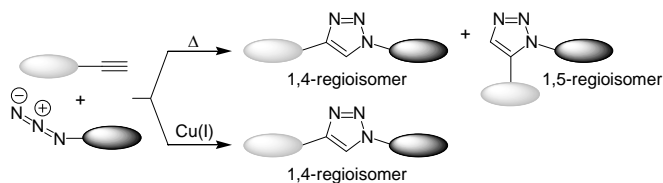


Figure 3. Huisgen’s reaction

The introduction of the CuAAC reaction has opened up new and 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, chlorin or phthalocyanine conjugates by azide-alkyne click chemistry, and their related applications.¹⁹

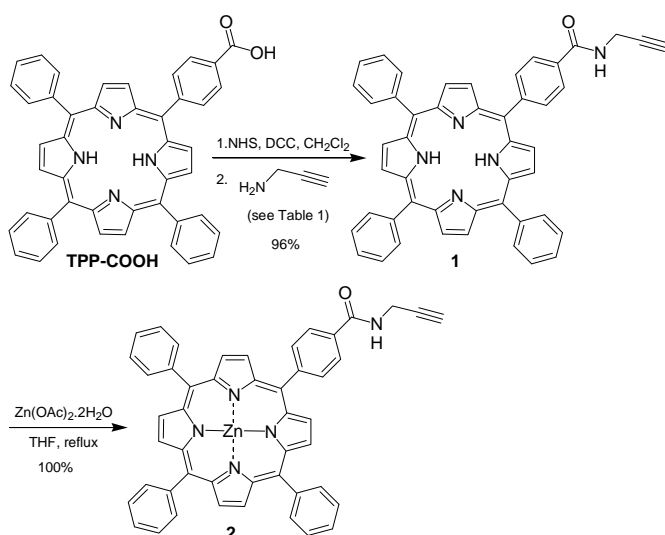
The mild condition of the CuAAC reaction is compatible with the peptidic chemistry and offers the possibility to develop new peptide-based drugs, which could be potentially useful therapeutically.²⁰ Furthermore, the 1,2,3-triazole ring is highly stable against hydrolysis and could ensure delivery of 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 metalization of TPP is essential, to avoid copper metalization of the porphyrin ring during the subsequent CuAAC reaction.



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

5-(4-carbonylphenyl)-10,15,20-triphenyl-21*H*,23*H*-porphyrin (TPP-COOH) (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-step 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 conditions (temperature and reaction time) were tested and those used are summarized in Table 1. The best yield (96%, trial A6) was obtained after one day at 40°C for both activating and coupling steps. Finally, the porphyrin ring of molecule **1** was metalized with Zn(OAc)₂ to provide the alkyne-functionalized ZnTPP **2** in a quantitative yield.

Table 1. Several trials for the one-pot preparation of alkyne-functionalized TPP **1** via Scheme 1

Trial	Step 1 conditions		Step 2 conditions		Yield (%) ^a
	Temperature (°C)	Reaction time (h)	Temperature °C	Reaction time (h)	
A1	rt ^b	4	rt	24	58
A2	rt	24	rt	24	67
A3	rt	24	40	24	68
A4	rt	4	40	24	67
A5	40	4	40	24	69
A6	40	24	40	24	96
A7	40	0.5	40	2.5	66

^aYields calculated after purification by flash chromatography.

^b rt = room temperature

2.2. Synthesis of clickable aromatic scaffolds bearing one, two or three azide groups

To synthesize [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks by the CuAAC reaction, we created platforms bearing one, two or three azide groups. To achieve this goal, we chose to use commercially available hydroxy and polyhydroxy derivatives of methyl benzoate (Figure 4).

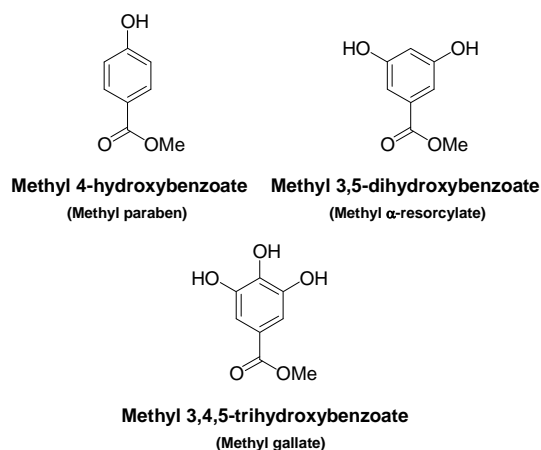
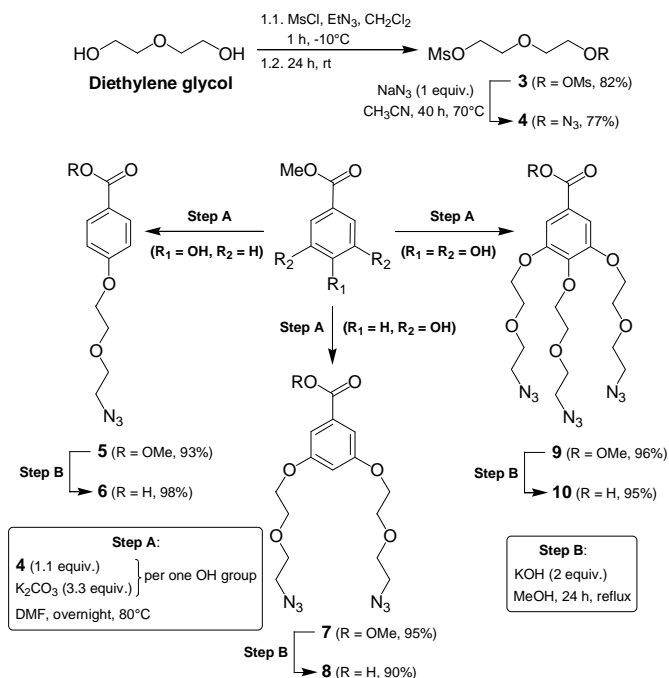


Figure 4. Chemical structures of hydroxy and polyhydroxy derivatives of methyl benzoate used in this work

The methyl benzoate derivatives substituted by 1-3 hydroxy groups (Figure 4) were functionalized through their hydroxy groups with an azide functional group **4** derived from diethylene glycol (Scheme 2). We decided to use diethylene glycol as the spacer unit to improve the hydrophilicity of our clickable aromatic scaffolds **6**, **8** and **10**. 2-(2-azidoethoxy)ethyl methanesulfonate **4** was synthesized in two steps from diethylene glycol with 63% overall yield (Scheme 2). This two-step procedure involved mesylation of both hydroxyl groups using mesyl chloride (4 equivalents) to provide dimesylate intermediate **3**, followed by nucleophilic substitution of one mesylate group of **3** with a sodium azide (1 equivalent). The last step has already been described by Sirion *et al.*²⁴ under similar conditions but we were able to significantly improve the yield (77% instead of 40%).



Scheme 2. Synthesis of clickable aromatic scaffolds **6**, **8** and **10**

The resulting azide- and mesylate-functionalized diethylene glycol **4** was used to elaborate clickable aromatic scaffolds **6**, **8** and **10** bearing one, two or three azide groups and the same two-step approach was adopted for their synthesis (Scheme 2). To achieve this goal, we decided to use experimental conditions similar to those previously employed by Chen *et al.*²⁵ for the synthesis of products **9** and **10**. The first step of this approach is based on the nucleophilic substitution of the mesylate group of product **4** by the hydroxy groups present in the methyl benzoate derivatives represented in Figure 4, to provide the corresponding mono-, di- and triazide derivatives of methyl benzoates **5**, **7** and **9** in high yields (Step A in Scheme 2). Finally, the saponification of the ester group of **5**, **7** and **9** led to clickable aromatic scaffolds **6**, **9** and **10** respectively with yields of up to 90% (Step B in Scheme 2), opening the way for the synthesis of [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks by click chemistry (Figure 5).

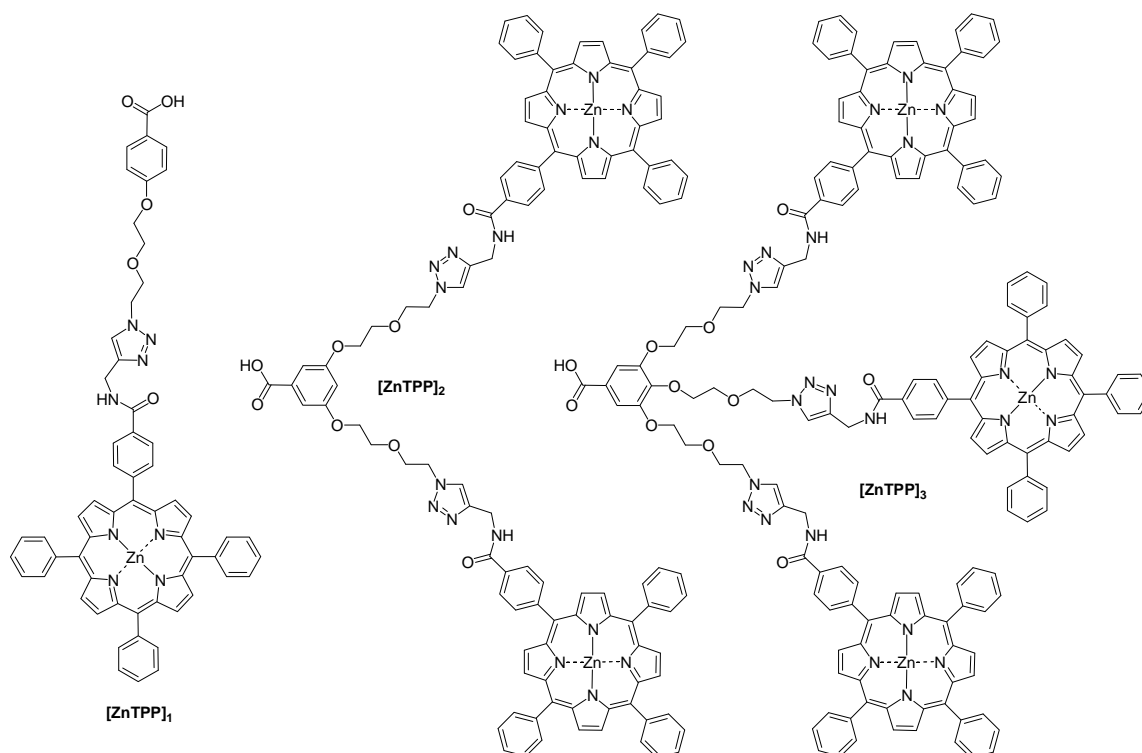


Figure 5. Chemical structures of [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks

2.3. Synthesis of [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks by click chemistry

The last part of this article is dedicated to the conjugation of the alkyne-functionalized ZnTPP **2** to the three azide-functionalized aromatic scaffolds **6**, **8** and **10**, through click chemistry. These various conjugations led to the elaboration of the desired [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks represented in Figure 5.

In the first phase, we investigated the synthesis of the [ZnTPP]₁ building block by appending the alkyne-clickable porphyrin **2** (1 equivalent) onto the monoazide-functionalized aromatic scaffold **6** (1 equivalent) through the CuAAC reaction. The active Cu(I) catalyst, needed to drive the reaction, is generated from CuSO₄·5H₂O (0.1 equivalent) and sodium ascorbate (0.5 equivalent). With the aim of obtaining the best conditions for this reaction, several trials were conducted by changing 5 parameters *i.e.* solvent (DMF or THF/H₂O), method (magnetic stirring or microwave), temperature (rt, 50°C or 80°C), time of reaction and under nitrogen or not. The results of these trials are summarized in Table 2.

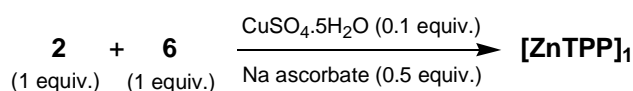
An examination of the results shown in Table 2 demonstrated that the reaction yield is better with the microwave technique than with magnetic stirring, giving higher yields in a shorter time (compare B3/B7 or B4/B8 trials), in THF/H₂O than in DMF (compare B4/B12 or B6/B14 trials), at 80°C than 50°C (compare B10/B11 and B5/B6 trials) and under nitrogen (compare B5/B7 or B6/B8 trials). Moreover, the addition of a second dose of CuSO₄·5H₂O and sodium ascorbate contributes positively to increase the reaction yield (compare B13/B14 or B15/B16 trials). In summary, the [ZnTPP]₁ building block is provided at a very high yield (97%, trials B14 and B16).

Encouraged by these results, we decided to undertake the preparation of the [ZnTPP]₃ building block directly, to examine the steric effects exerted by the triazide-functionalized aromatic scaffold **10** in the triple CuAAC reaction. For the synthesis of the [ZnTPP]₃ building block by the reaction of scaffold **10** with three equivalents of molecule **2**, we chose to use the best result for each of the following conditions: 1) DMF with magnetic stirring (trial B4), 2) DMF with microwave (trial B8), 3) THF/H₂O with magnetic stirring (trial B12) and, 4) THF/H₂O with microwave (trial B14). For the CuAAC reaction, the amount of the catalyst (CuSO₄·5H₂O and sodium ascorbate) is tripled. The results are described in Table 3.

As can be seen from Table 3, none of the four attempts (B4, B8, B12 and B14) were successful. [ZnTPP]₃ is only present in trace amounts and it is impossible to detect it by NMR. However, a weak spot of [ZnTPP]₃ was observed on a TLC plate (CH₂Cl₂/MeOH, 95/5, R_f = 0.21) with a slightly better intensity in the case of the B14 trial. Based on these findings, the result of the B14 trial was placed under a nitrogen atmosphere with magnetic stirring at room temperature for 5 days (named trial B17) and this gave a 77% yield of [ZnTPP]₃. Finally, we carried out a last triple CuAAC reaction (named trial B18) under nitrogen, in THF/H₂O, at room temperature, with magnetic stirring, for 5 days to evaluate whether microwave initiation in trial B17, due to the B14 trial conditions, plays a significant role in the reaction yield. Trial B18 allowed us to obtain [ZnTPP]₃ but at a lower yield (18%) than in trial B17, reflecting the importance of microwave initiation on reaction yield. In short, despite the clear negative impact of the steric hindrance of scaffold **10** in the triple CuAAC reaction (compare trials B14/B17), [ZnTPP]₃ was obtained at a good yield (77%, trial B17).

Concerning the synthesis of the [ZnTPP]₂ building block, we used the same four conditions (trials B4, B8, B12 and B14 of Table 1) as for [ZnTPP]₃ synthesis. The formation of [ZnTPP]₂ requires a double CuAAC reaction between the diazide-functionalized aromatic scaffold **8** and two equivalents of **2**, and this time, by doubling the amount of the catalyst (CuSO₄·5H₂O and sodium ascorbate) compared to the [ZnTPP]₁ synthesis. The results illustrated in Table 4 indicate that the double CuAAC reaction does not occur in THF/H₂O, but in DMF under magnetic stirring (58%, trial B4) and microwave (38%, trial B8). To check whether the negative impact of the steric hindrance of **8** is still present, as previously observed for [ZnTPP]₃ synthesis, the results of trials B4 and B8 were placed separately under magnetic stirring at room temperature until completion (3 days) under a nitrogen atmosphere (named trials B19 and B20 respectively). These conditions enabled us to improve the reaction yield, to reach a maximum of 93% (trial B19).

Table 2. Several trials for the synthesis of [ZnTPP]₁



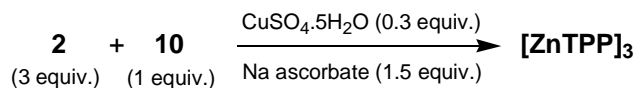
Trial	Solvent	Method	Temperature °C	Reaction time	Nitrogen	Yield (%) ^a
B1	DMF	Magnetic stirring	Rt	Overnight	No	7
B2	DMF	Magnetic stirring	Rt	Overnight	Yes	11
B3	DMF	Magnetic stirring	50	Overnight	Yes	75
B4	DMF	Magnetic stirring	80	Overnight	Yes	75
B5	DMF	Microwave	50	2 rounds ^b of 45 minutes	No	43
B6	DMF	Microwave	80	2 rounds ^b of 45 minutes	No	60
B7	DMF	Microwave	50	2 rounds ^b of 45 minutes	Yes	86
B8	DMF	Microwave	80	2 rounds ^b of 45 minutes	Yes	89
B9	THF/H ₂ O (4:1)	Magnetic stirring	Rt	Overnight	No	10
B10	THF/H ₂ O (4:1)	Magnetic stirring	Rt	Overnight	Yes	20
B11	THF/H ₂ O (4:1)	Magnetic stirring	80	3 hours	Yes	55

B12	THF/H ₂ O (4:1)	Magnetic stirring	80	Overnight	Yes	96
B13	THF/H ₂ O (4:1)	Microwave	80	1 round of 45 minutes	No	88
B14	THF/H₂O (4:1)	Microwave	80	2 rounds^b of 45 minutes	No	97
B15	THF/H ₂ O (4:1)	Microwave	80	1 round of 90 minutes	No	92
B16	THF/H₂O (4:1)	Microwave	80	2 rounds^b of 90 minutes	No	97

^aYields calculated after purification by flash chromatography.

^bCuSO₄·5H₂O (0.1 equiv.) and Na ascorbate (0.5 equiv.) were added again at the end of the first round microwave.

Table 3. Several trials for the synthesis of [ZnTPP]₃



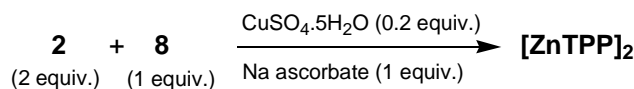
Trial	Solvent	Method	Temperature °C	Reaction time	Nitrogen	Yield (%) ^a
B4	DMF	Magnetic stirring	80	Overnight	Yes	nd ^c
B8	DMF	Microwave	80	2 rounds ^b of 45 minutes	Yes	nd ^c
B12	THF/H ₂ O (4:1)	Magnetic stirring	80	Overnight	Yes	nd ^c
B14	THF/H ₂ O (4:1)	Microwave	80	2 rounds ^b of 45 minutes	No	nd ^c
B17	B14 followed by magnetic stirring at rt for 5 days under nitrogen atmosphere					77
B18	THF/H ₂ O (4:1)	Magnetic stirring	rt	5 days	Yes	18

^aYields calculated after purification by flash chromatography.

^bCuSO₄·5H₂O (0.3 equiv.) and Na ascorbate (1.5 equiv.) were added again at the end of the first round microwave.

^cnd = not determined.

Table 4. Several trials for the synthesis of [ZnTPP]₂

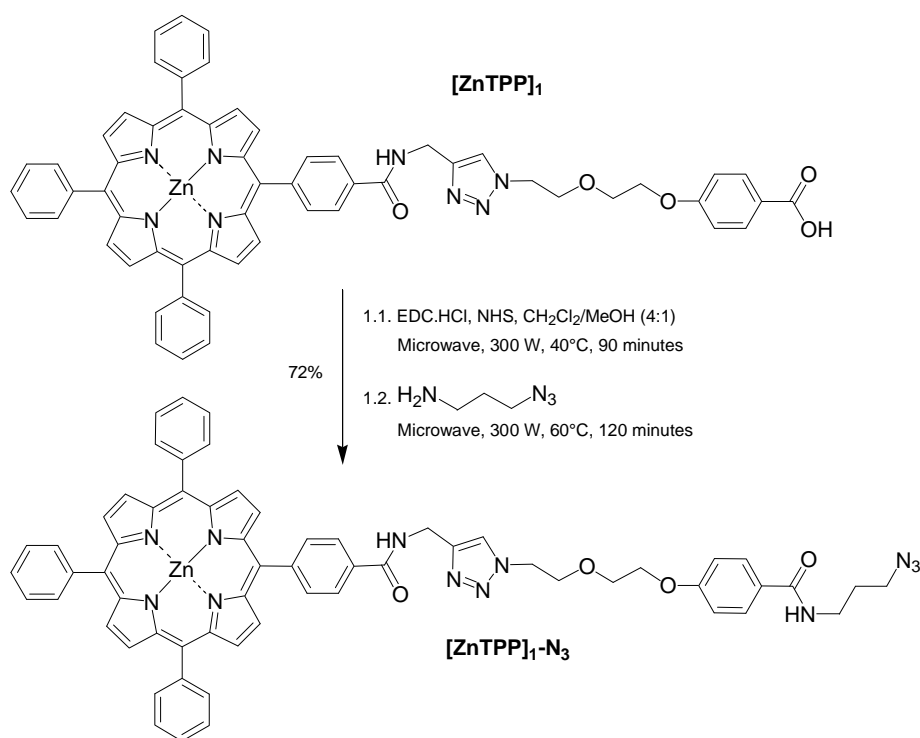


Trial	Solvent	Method	Temperature °C	Reaction time	Nitrogen	Yield (%) ^a
B4	DMF	Magnetic stirring	80	Overnight	Yes	59
B8	DMF	Microwave	80	2 rounds ^b of 45 minutes	Yes	38
B12	THF/H ₂ O (4:1)	Magnetic stirring	80	Overnight	Yes	nd ^c
B14	THF/H ₂ O (4:1)	Microwave	80	2 rounds ^b of 45 minutes	No	nd ^c
B19	B4 followed by magnetic stirring at rt for 3 days under nitrogen atmosphere					93
B20	B8 followed by magnetic stirring at rt for 3 days under nitrogen atmosphere					81

^aYields calculated after purification by flash chromatography.

^bCuSO₄·5H₂O (0.2 equiv.) and Na ascorbate (1 equiv.) were added again at the end of the first round microwave.

The successful synthesis of [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks through the CuAAC reaction paves the way for the development of new PS-vector conjugates. These new conjugates may be synthesized *via* a peptide coupling reaction between the carboxylic acid function of [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks and a targeting agent (vector) such as folic acid or ATLWLPR and DKPPR peptides (Figure 2) to investigate the optimum ratio of PS needed for maximum PDT efficiency. However, to take the best advantage of the click chemistry, it would be interesting to develop new PS-vector conjugates through the CuAAC reaction. To reach that goal, we have shown that it is possible to functionalize the carboxylic acid moiety of our building blocks (only [ZnTPP]₁ is used as an example) with commercially available 3-azido-1-propanamine. The azide-functionalization of [ZnTPP]₁ provides the corresponding [ZnTPP]₁-N₃ in a 72% yield (Scheme 3).



Scheme 3. Azide-functionalization of of [ZnTPP]₁

2.4. Photophysical properties of [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks

Absorption presents a typical porphyrin absorption spectrum with a Soret band at 414 nm and four Q-bands. The fluorescence spectrum is typical of a porphyrin with two maxima at around 650 nm and 720 nm. As we already showed in a previous study²², the addition of Zn induced a shift of 1) the Soret band from 414 nm to 421 nm and 2) the maximum of fluorescence from 650 nm to 610 nm for the first and 720 nm to 660 nm for the second band. It also induced a decrease of the fluorescence lifetime from 10.0 ns to 2.1 ns. Surprisingly, the fluorescence quantum yield did not decrease as has often been described in the literature.^{22,26} DeRosa *et al.* reported that the introduction of Zn into TPP increased the singlet oxygen quantum yield in benzene from 0.63 to 0.83.²⁷ In our case, the introduction of Zn into TPP-propargyl increases the singlet oxygen quantum yield in ethanol from 0.49 to 0.72.

The addition of a Zn-porphyrin to the structure does not seem to modify drastically the photophysical properties of the photosensitizer in terms of fluorescence and singlet oxygen formation quantum yields or lifetime. However, [ZnTPP]₃ presents two different fluorescence lifetimes. This might be due to a dimer formation.

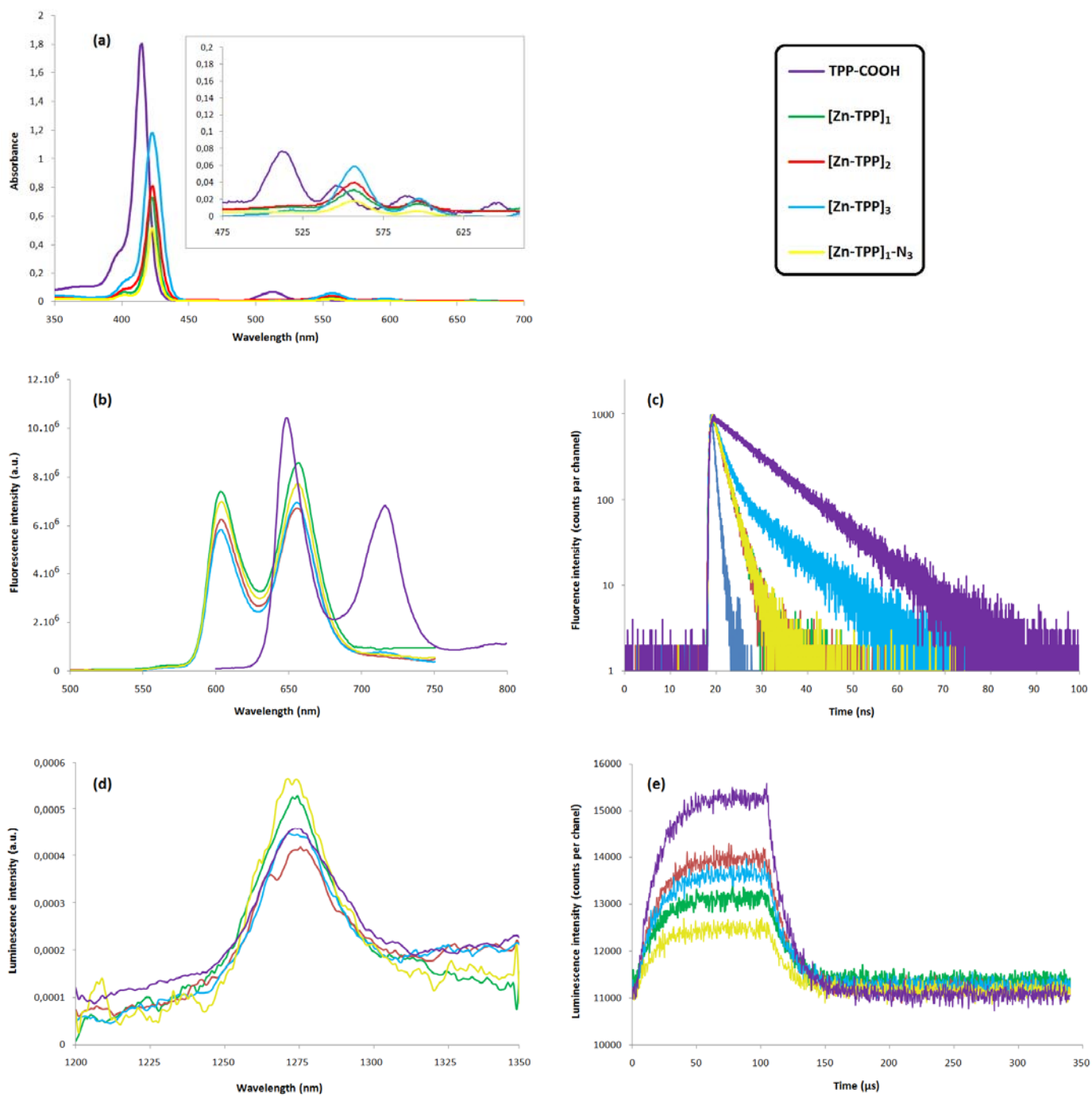


Figure 6. Photophysical properties of TPP-COOH, [ZnTPP]₁, [ZnTPP]₂, [ZnTPP]₃ and [ZnTPP]_{1-N₃}. (a) Absorption spectra at a single concentration of DMSO (1 mg in 1 mL of DMSO) and (b) fluorescence emission spectra at a single concentration of EtOH (equal Soret bands at 0.2 ± 0.05 by dilution). (c) Fluorescence decay, (d) singlet oxygen emission spectra and (e) singlet oxygen decay after excitation ($\lambda_{exc.} = 414$ nm and 421 nm) at a constant EtOH concentration (equal Soret bands at 0.2 ± 0.05 by dilution).

Table 5. Photophysical data for the porphyrin derivatives

Compound	Absorption λ_{\max}^a (nm) (ϵ) ^b - Soret band	ϕ_f^c	ϕ_Δ^d	τ_f^e	τ_Δ^f
TPP-COOH	414 (166993)	0.08	0.60	10.1	16
TPP-propargyl 1	414 (126289)	0.09	0.49	10.0	16
ZnTPP-propargyl 2	421 (290200)	0.07	0.72	2.1	15
[ZnTPP] ₁	421 (211587)	0.08	0.54	1.9	18
[ZnTPP] ₂	421 (226551)	0.07	0.43	1.9	16
[ZnTPP] ₃	421 (329375)	0.06	0.46	2.2-10.6	16
[ZnTPP] ₁ -N ₃	421 (201286)	0.08	0.65	2.0	17

^aMaximum absorption or fluorescence in EtOH.

^b ϵ in L/mol.cm.

^cFluorescence quantum yield determined in EtOH, relative to fluorescence of TPP as standard ($\lambda_{\text{exc.}} = 414$ nm and 421 nm).

^dSinglet oxygen production quantum yield in EtOH, relative to the emission of Rose Bengal ($\lambda_{\text{exc.}} = 414$ nm and 421 nm).

^eFluorescence lifetime (ns).

^fSinglet oxygen lifetime (μ s).

3. Conclusion

Our goal was to synthesize three building blocks named [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ having one, two or three PS units in their structures, respectively. Starting from the use of click chemistry (and more specifically the CuAAC reaction), we described the synthesis of these three building blocks with high yields. The presence of one or more PS units did not seem to result in profound changes in the photophysical properties of the PS (*i.e.* fluorescence and singlet oxygen formation, quantum yields and lifetime). These photophysical results pave the way for the potential conjugation of [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks with a targeting agent (vector) for the elaboration of new PS-vector conjugates to investigate the optimum ratio of PS needed for maximum PDT efficiency.

4. Experimental

4.1. General

Unless other stated, all chemicals were purchased as the highest purity commercially available and were used without further purifications. All reactions involving porphyrin compounds were performed in the dark. All microwave reactions were conducted in oven-dried glass tube using CEM Discover microwave synthesizer (North Carolina, USA). Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed silica gel plates (Macherey-Nagel ALUGRAM[®] SIL >G/UV254). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with a staining solution of phosphomolybdic acid. Product purifications were performing using Silica Gel 60 (230-400 mesh) for column chromatography and Geduran 60 H Silica Gel (63-200 mesh) for flash column chromatography. ¹H NMR spectra were recorded on a Bruker Advance spectrophotometer operating at 300 MHz. The spectra were recorded in CDCl₃ and DMSO-*d*₆ solvents at room temperature (T = 298K) using TMS ($\delta = 0$ ppm) or DMSO residual peak ($\delta = 2.5$ ppm) as internal references respectively. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in hertz (Hz). Multiplicities are reported as follow: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad and Ar. = aromatic. Mass spectra were recorded on a Shimadzu LCMS 2010 EV apparatus (Champs-sur-Marne, France). Absorption spectra were recorded on a Perkin-Elmer Lambda EZ210 (Courtaboeuf, France) double beam UV-visible spectrophotometer. Fluorescence spectra were recorded on a Fluorolog-3 spectrofluorimeter FL3-222 (Horiba Jobin Yvon, Longjumeau, France) with a thermostated cell compartment (25°C) using a 450 W Xenon lamp. Fluorescence quantum yield (ϕ_f) were determined using tetraphenyl porphyrin (TPP) solution in toluene as fluorescence standard ($\phi_f = 0.11$).²⁸ Singlet oxygen quantum yield (ϕ_Δ) were determined by direct measurement of the infrared luminescence using Rose Bengal in EtOH as a reference ($\phi_\Delta = 0.68$).²⁹ The absorbance value at the excitation wavelength of the reference and the sample solutions were set around 0.2.

4.2 Synthesis of clickable porphyrin scaffold bearing a propargyl group (2)

4.2.1. 5-(4-propargylamidocarboxyphenyl)-10,15,20-triphenyl-21H, 23H-porphyrin (1). In the absence of light and under N₂, dicyclohexyl carbodiimide (DCC, 31 mg, 0.15 mmol, 1.0 equiv) and *N*-hydroxysuccinimide (NHS, 35 mg, 0.30 mmol, 2.0 equiv) were added successively to a solution of TPP-COOH (100 mg, 0.15 mmol, 1.0 equiv) in CH₂Cl₂ (20 mL). The mixture was stirred at room temperature during a specified period of time (see Table 1) to afford the succinimide intermediate. An excess of propargylamine (100 μ L, 1.5 mmol, 10 equiv) was then added and the reaction was allowed to continue for several hours (see Table 1). The solvent was evaporated *in vacuo* and the resulting crude material was purified by flash chromatography (CH₂Cl₂/EtOH, 97/3) to afford **1** (101 mg, 0.145 mmol) as purple solid in 96% of maximum yield (Trial A6). TLC (CH₂Cl₂/EtOH, 97/3): R_f = 0.72; ¹H NMR (300 MHz, CDCl₃) δ -2.89 (s, 2H, 2 **NH**), 2.38 (t, *J* = 2.7 Hz, 1H, **CH** alkyne), 4.39 (dd, *J* = 5.1, 2.7 Hz, 2H, **CH**₂), 6.55 (t, *J* = 5.4 Hz, 1H, **NH**), 7.70-7.79 (m, 9H, 9 **CH**), 8.14-8.22 (m, 8H, 8 **CH**), 8.33 (d, *J* = 8.1 Hz m, 2H, 2 **CH**), 8.77 (d, *J* = 4.8 Hz m, 2H, 2 **CH**), 8.83-8.90 (m, 6H, 6 **CH**); MS calculated for C₄₈H₃₃N₅O [M+H]⁺ *m/z* 696.27, found 696.22.

4.2.2. Zinc 5-(4-propargylamidocarboxyphenyl)-10,15,20-triphenyl porphyrin (**2**). In the absence of light and under N₂, zinc acetate dehydrate (114 mg, 0.51 mmol, 3.6 equiv) was added to a solution of **1** (100 mg, 0.14 mmol, 1 equiv) in THF (15 mL) and refluxed for 2 hours. The metallation was monitored by UV-visible spectrometry (350 to 800 nm) and TLC (CH₂Cl₂/EtOH, 97/3). After cooling to room temperature, THF was removed *in vacuo* and the crude material was dissolved in CH₂Cl₂ (50 mL), washed with water (5 x 20 mL) and dried over MgSO₄. After evaporation of CH₂Cl₂, compound **2** was obtained as purple microcrystalline solid in quantitative yield (106 mg, 0.14 mmol). TLC (CH₂Cl₂/EtOH, 97/3): R_f = 0.81; ¹H NMR (300 MHz, CDCl₃) δ 2.39 (t, *J* = 2.7 Hz, 1H, **CH** alkyne), 4.45 (dd, *J* = 5.1, 2.7 Hz, 2H, **CH**₂), 6.59 (t, *J* = 5.4 Hz, 1H, **NH**), 7.71-7.79 (m, 9H, 9 **CH**), 8.16-8.23 (m, 8H, 8 **CH**), 8.31 (d, *J* = 8.1 Hz m, 2H, 2 **CH**), 8.77 (d, *J* = 4.8 Hz m, 2H, 2 **CH**), 8.84-8.88 (m, 6H, 6 **CH**); MS calculated for C₄₈H₃₁N₅OZn [M+H]⁺ *m/z* 758.18, found 758.14.

4.3. Synthesis of azide-terminated diethylene glycol linker (**4**)

4.3.1. 2-(2-methylsulfonyloxyethoxy)ethyl methanesulfonate (**3**). To a solution of diethylene glycol (10.6 g, 100 mmol, 1.0 equiv) in CH₂Cl₂ (200 mL) at -10°C was added Et₃N (22.3 g, 220 mmol, 2.2 equiv) and the mixture was stirred during 1 hour. Methanesulfonyl chloride (34.3 g, 300 mmol, 3.0 equiv) was then added dropwise over a period of 0.5 hour and the resulting mixture was stirred for 24 hours at room temperature under nitrogen atmosphere. The reaction progress was monitored by TLC and after complete disappearance of starting material, the reaction mixture was concentrated under reduced pressure and compound **3** was recrystallized in hot MeOH and white crystals were obtained with a 82% yield (21.5 g, 82 mmol). TLC (CH₂Cl₂/MeOH, 95/5): R_f = 0.67; ¹H NMR (300 MHz, CDCl₃) δ 3.06 (s, 6H, 2 **CH**₃), 3.79 (t, 4H, *J* = 4.5 Hz, 2 **CH**₂-O), 4.37 (t, 4H, *J* = 4.5 Hz, 2 **CH**₂-OMs); MS calculated for C₆H₁₆O₇S₂ [M+H]⁺ *m/z* 265.04, found 264.98.

4.3.2. 2-(2-Azidoethoxy)ethyl methanesulfonate (**4**). To solution of **3** (5.24 g, 20 mmol, 1.0 equiv) in CH₃CN (50 mL) was added NaN₃ (1.30 mg, 20 mmol, 1.0 equiv), and the mixture was stirred at 70 °C for 40 h under nitrogen atmosphere. The precipitate was cooled at room temperature, filtered off, and the filtrate was evaporated and purified by flash column chromatography (EtOAc/petroleum ether, 35/65) to give **4** in 77% yield (3.22 g, 15.4 mmol) as a colorless oil. TLC (CH₂Cl₂/MeOH, 95/5): R_f = 0.69 (visualization by 10% PPh₃ followed by dipping in ninhydrin stain); ¹H NMR (300 MHz, CDCl₃) δ 3.04 (s, 3H, **CH**₃), 3.38 (t, 2H, *J* = 4.8 Hz, **CH**₂-N₃), 3.68 (t, 2H, *J* = 4.8 Hz, **CH**₂-O), 3.76 (t, 2H, *J* = 4.5 Hz, **CH**₂-O), 4.36 (t, 2H, *J* = 4.5 Hz, **CH**₂-OMs); MS calculated for C₅H₁₁N₃O₄S [M+H]⁺ *m/z* 210.05, found 209.97.

4.4. Synthesis of clickable aromatic scaffolds bearing one, two or three azide groups (**6**, **8** and **10**)

4.4.1. General method for nucleophilic substitution reaction (Step A). To a solution of commercially available methyl benzoate derivative (10 mmol, 1.0 equiv) in DMF (40 mL) was added K₂CO₃ (3.3 equiv per hydroxy group) and **4** (1.1 equiv per hydroxyl group) and the mixture was stirred overnight at 80°C. After completion of the reaction as monitored by TLC, the mixture was cooled at room temperature, washed with saturated NaHCO₃ (2 x 50 mL) and dried over MgSO₄. After evaporation of DMF, the resulting crude material was purified by flash column chromatography (EtOAc/petroleum ether, 50/50) to afford the corresponding compound (**5**, **7** or **9**) as light-yellowish oil in yield up to 93%. Compounds **5**, **7** and **9** were characterized as reported below.

4.4.1.1. Methyl 4-[2-(2-Azidoethoxy)-ethoxy]-benzoate (**5**). TLC (EtOAc/petroleum ether, 40/60): R_f = 0.71; ¹H NMR (300 MHz, CDCl₃) δ 3.41 (t, 2H, *J* = 4.8 Hz, **CH**₂-N₃), 3.75 (t, 2H, *J* = 4.8 Hz, **CH**₂-O), 3.88 (s, 3H, **OCH**₃), 3.89 (t, 2H, *J* = 4.8 Hz, **CH**₂-O), 4.20 (t, 2H, *J* = 4.8 Hz, **CH**₂-O-Ar), 6.94 (d, 2H, *J* = 9.0 Hz, 2 **CH**_{meta} Ar), 7.99 (d, 2H, *J* = 9.0 Hz, 2 **CH**_{ortho} Ar); MS calculated for C₁₂H₁₅N₃O₄ [M+H]⁺ *m/z* 266.11, found 266.05.

4.4.1.2. Methyl 3,5-Bis-[2-(2-Azidoethoxy)-ethoxy]-benzoate (**7**). TLC (EtOAc/petroleum ether, 40/60): R_f = 0.60; ¹H NMR (300 MHz, CDCl₃) δ 3.40 (t, 4H, *J* = 4.8 Hz, 2 **CH**₂-N₃), 3.74 (t, 4H, *J* = 4.8 Hz, 2 **CH**₂-O), 3.86 (t, 4H, *J* = 4.8 Hz, 2 **CH**₂-O), 3.88 (s, 3H, **OCH**₃), 4.15 (t, 4H, *J* = 4.8 Hz, 2 **CH**₂-O-Ar), 6.71 (t, 1H, *J* = 2.1 Hz, **CH**_{para} Ar), 7.20 (d, 2H, *J* = 2.1 Hz, 2 **CH**_{ortho} Ar); MS calculated for C₁₆H₂₂N₆O₆ [M+H]⁺ *m/z* 395.16, found 395.12.

4.4.1.3. Methyl 3,4,5-Tris-[2-(2-Azidoethoxy)-ethoxy]-benzoate (**9**). TLC (EtOAc/petroleum ether, 40/60): R_f = 0.58; ¹H NMR (300 MHz, CDCl₃) δ 3.36-3.42 (m, 6H, 3 **CH**₂-N₃), 3.70-3.76 (m, 6H, 3 **CH**₂-O), 3.80-3.89 (m, 9H, 3 **CH**₂-O, **OCH**₃), 4.18-4.26 (m, 6H, 3 **CH**₂-O-Ar), 7.30 (s, 2H, 2 **CH**_{ortho} Ar); MS calculated for C₂₀H₂₉N₉O₈ [M+H]⁺ *m/z* 524.22, found 524.18.

4.4.2. General method for saponification reaction (Step B). To a solution of methyl ester derivative **5**, **7** or **9** (3 mmol, 1.0 equiv) in MeOH (30 mL) was added KOH (6 mmol, 2.0 equiv) and the mixture was refluxed for 24 hours. The crude material was cooled at room temperature, neutralized with Amberlite IR 120 ion exchange resin. The reaction was filtered and the resin was washed with MeOH (3 x 10 mL). The filtrate was concentrated under reduced pressure to give the desired clickable aromatic scaffold (**6**, **8** or **10**) as light-yellowish oil in yield up to 90%. Compounds **6**, **8** and **10** were characterized as reported below.

4.4.2.1. 4-[2-(2-Azidoethoxy)-ethoxy]-benzoic acid (**6**). TLC (EtOAc/petroleum ether, 40/60): R_f = 0.46; ¹H NMR (300 MHz, CDCl₃) δ 3.43 (t, 2H, *J* = 4.8 Hz, **CH**₂-N₃), 3.77 (t, 2H, *J* = 4.8 Hz, **CH**₂-O), 3.91 (t, 2H, *J* = 4.8 Hz, **CH**₂-O), 4.23 (t, 2H, *J* = 4.8 Hz, **CH**₂-O-Ar), 6.98 (d, 2H, *J* = 9.0 Hz, 2 **CH**_{meta} Ar), 8.07 (d, 2H, *J* = 9.0 Hz, 2 **CH**_{ortho} Ar); MS calculated for C₁₁H₁₃N₃O₄ [M+H]⁺ *m/z* 252.09, found 252.04.

4.4.2.2. 3,5-Bis-[2-(2-Azidoethoxy)-ethoxy]-benzoic acid (**8**). TLC (EtOAc/petroleum ether, 40/60): R_f = 0.38; ¹H NMR (300 MHz, CDCl₃) δ 3.42 (t, 4H, *J* = 4.8 Hz, 2 **CH**₂-N₃), 3.76 (t, 4H, *J* = 4.8 Hz, 2 **CH**₂-O), 3.88 (t, 4H, *J* = 4.5 Hz, 2 **CH**₂-O), 4.17 (t, 4H, *J* = 4.5 Hz, 2 **CH**₂-O-Ar), 6.77 (s, 1H, **CH**_{para} Ar), 7.27 (s, 2H, 2 **CH**_{ortho} Ar); MS calculated for C₁₅H₂₀N₆O₆ [M+H]⁺ *m/z* 381.15, found 381.09.

4.4.2.3. 3,4,5-Tris-[2-(2-Azidoethoxy)-ethoxy]-benzoic acid (**10**). TLC (EtOAc/petroleum ether, 40/60): R_f = 0.32; ¹H NMR (300 MHz, CDCl₃) δ 3.37-3.43 (m, 6H, 3 **CH**₂-N₃), 3.73-3.77 (m, 6H, 3 **CH**₂-O), 3.83-3.91 (m, 6H, 3 **CH**₂-O), 4.22-4.30 (m, 6H, 3 **CH**₂-O-Ar), 7.38 (s, 2H, 2 **CH**_{ortho} Ar); MS calculated for C₁₉H₂₇N₉O₈ [M+H]⁺ *m/z* 510.20, found 510.16.

4.5. Synthesis of [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks

4.5.1. Magnetic stirring method (Tables 2-4). To a solution of clickable aromatic scaffold **6**, **8** or **10** (0.1 mmol, 1.0 equiv.) and ZnTPP **2** (1.0 equiv per azide function) in appropriate solvent (5 mL) was added CuSO₄·5H₂O (0.1 equiv per azide function) and Na ascorbate (0.5 equiv per azide function). The mixture was stirred at appropriate temperature for some time under a nitrogen atmosphere or not (see Tables 2-4). At the end of the reaction and after cooling to room temperature, the mixture was washed with water (3 x 20 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography using a stepwise gradient of MeOH in CH₂Cl₂ (2-10%, v/v) to provide the corresponding building block ([ZnTPP]₁, [ZnTPP]₂ or [ZnTPP]₃) as dark purplish powder.

4.5.2. Microwave method (Tables 2-4). Clickable aromatic scaffold **6**, **8** or **10** (0.05 mmol, 1.0 equiv.), ZnTPP **2** (1.0 equiv per azide function), CuSO₄·5H₂O (0.1 equiv per azide function), Na ascorbate (0.5 equiv per azide function) and appropriate solvent (2.5 mL) were mixed in a microwave tube with a magnetic stir bar. The reaction tube was ten fitted with its screw cap, and stirred under a nitrogen atmosphere or not (see Tables 2-4). The reaction was carried out under microwave irradiation at 300 W and appropriate temperature for 45 or 90 minutes per round (see Tables 2-4). After cooling to room temperature, the crude reaction mixture was treated and purified in the same way as magnetic stirring method.

4.5.3. [ZnTPP]₁, [ZnTPP]₂ and [ZnTPP]₃ building blocks were characterized as reported below.

4.5.3.1. [ZnTPP]₁ building block. TLC (CH₂Cl₂/MeOH, 95/5): R_f = 0.38; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.83 (t, 2H, *J* = 5.1 Hz, CH₂-O), 3.94 (t, 2H, *J* = 5.1 Hz, CH₂-O), 4.18 (t, 2H, *J* = 5.1 Hz, CH₂-O-Ar), 4.60 (t, 2H, *J* = 5.1 Hz, O-CH₂-CH₂-triazole), 4.68 (d, 2H, *J* = 5.7 Hz, triazole-CH₂-NH), 7.04 (d, 2H, *J* = 8.7 Hz, 2 CH_{meta} of the benzoic acid unit), 7.78-7.81 (m, 9H, 9 CH), 7.89 (d, 2H, *J* = 8.7 Hz, 2 CH_{ortho} of the benzoic acid unit), 8.16-8.33 (m, 11H, 10 CH, CH triazole ring), 8.74-8.79 (m, 8H, 8 CH), 9.38 (t, 1H, *J* = 5.7 Hz, NH-CH₂-triazole), 12.4 (br s, 1H, CO₂H); MS calculated for C₅₉H₄₄N₈O₅Zn [M+H]⁺, [M+2H]²⁺ and [M+3H]³⁺, *m/z* 1009.28, 505.14 and 337.09 found 1009.30, 505.30 and 337.10.

4.5.3.2. [ZnTPP]₂ building block. TLC (CH₂Cl₂/MeOH, 95/5): R_f = 0.26; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.72 (t, 4H, *J* = 5.1 Hz, 2 CH₂-O), 3.87 (t, 4H, *J* = 5.1 Hz, 2 CH₂-O), 4.09 (t, 4H, *J* = 5.1 Hz, 2 CH₂-O-Ar), 4.53 (t, 4H, *J* = 5.1 Hz, 2 O-CH₂-CH₂-triazole), 4.64 (d, 4H, *J* = 5.7 Hz, 2 triazole-CH₂-NH), 6.72 (br s, 1H, CH_{para} of the benzoic acid unit), 7.08 (br s, 2H, 2 CH_{ortho} of the benzoic acid unit), 7.76-7.80 (m, 18H, 18 CH), 7.95-8.31 (m, 22H, 20 CH, 2 CH triazole ring), 8.72-8.77 (m, 16H, 16 CH), 9.41 (t, 2H, *J* = 5.7 Hz, 2 NH-CH₂-triazole); MS calculated for C₁₁₁H₈₂N₁₆O₈Zn₂ [M+2H]²⁺, [M+3H]³⁺ and [M+4H]⁴⁺, *m/z* 948.26, 632.51 and 474.63 found 948.70, 632.50 and 474.43.

4.5.3.3. [ZnTPP]₃ building block. TLC (CH₂Cl₂/MeOH, 95/5): R_f = 0.21; ¹H NMR (300 MHz, DMSO-*d*₆) δ 3.73-3.84 (m, 6H, 3 CH₂-O), 3.89-3.98 (m, 6H, 3 CH₂-O), 4.08-4.19 (m, 6H, 3 CH₂-O-Ar), 4.53-4.60 (m, 6H, 3 O-CH₂-CH₂-triazole), 4.62-4.69 (m, 6H, 3 triazole-CH₂-NH), 7.25 (s, 2H, 2 CH_{ortho} of the benzoic acid unit), 7.72-7.79 (m, 27H, 27 CH), 8.09-8.30 (m, 33H, 30 CH, 3 CH triazole ring), 8.74-8.77 (m, 24H, 24 CH), 9.36 (t, 3H, *J* = 5.7 Hz, 3 NH-CH₂-triazole); MS calculated for C₁₆₃H₁₂₀N₂₄O₁₁Zn₃ [M+2H]²⁺ and [M+3H]³⁺, *m/z* 1391.38 and 927.92 found 1391.40 and 927.90.

4.6. Azide-functionalization of [ZnTPP]₁ ([ZnTPP]₁-N₃). [ZnTPP]₁ (101 mg, 1.0 equiv, 0.1 mmol), EDC.HCl (38 mg, 2.0 equiv, 0.2 mmol) and NHS (46 mg, 4.0 equiv, 0.4 mmol) were dissolved in 5 mL DCM/methanol (4:1) and microwaved at 300 W, 40°C during 30 minutes. The coupling agents, EDC.HCl (19 mg, 1.0 equiv, 0.1 mmol) and NHS (23 mg, 2.0 equiv, 0.2 mmol), were added in extra and the microwave reaction was continued for 60 minutes. The reaction was monitored by TLC [R_f: 0.65 in DCM/methanol (93/7) for P1-clicked-NHS] and subsequently 3-azido-1-propanamine (50 mg, 5.0 equiv, 0.5 mmol) was added into the reaction vessel and the coupling was also conducted in microwave (300 W, 60°C, 120 minutes). The crude product was washed with 1M HCl (5 mL), saturated NaHCO₃ (5 mL) and water (3 x 5 mL). The crude mixture was dried over MgSO₄ and purified by flash column chromatography (CH₂Cl₂/MeOH, 95/5) to give [ZnTPP]₁-N₃ in 72% yield (79 mg, 0.072 mmol) as a purple powder. TLC (CH₂Cl₂/MeOH, 95/5): R_f = 0.56; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.49-1.56 (m, 2H, CH₂-CH₂-CH₂), 3.21-3.40 (m, 4H, CH₂-CH₂-CH₂-N₃), 3.80 (t, 2H, *J* = 5.1 Hz, CH₂-O), 3.94 (t, 2H, *J* = 5.1 Hz, CH₂-O), 4.16 (t, 2H, *J* = 5.1 Hz, CH₂-O-Ar), 4.60 (t, 2H, *J* = 5.1 Hz, O-CH₂-CH₂-triazole), 4.68 (d, 2H, *J* = 5.7 Hz, triazole-CH₂-NH), 7.02 (d, 2H, *J* = 8.7 Hz, 2 CH_{meta} of the *p*-hydroxybenzamide unit), 7.77-7.84 (m, 11H, 9 CH, 2 CH_{ortho} of the *p*-hydroxybenzamide unit), 8.12-8.35 (m, 12H, 10 CH, CH triazole ring, NH-CH₂-CH₂), 8.75-8.78 (m, 8H, 8 CH), 9.41 (t, 1H, *J* = 5.7 Hz, NH-CH₂-triazole); MS calculated for C₆₂H₅₀N₁₂O₄Zn [M+H]⁺ *m/z* 1091.34, found 1091.38.

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6. Supplementary data

Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2016.xx.xxx.

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